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Contents

Corrigenda and Addendas

Correction: Linking Dementia Pathology and Alteration in Brain Activation to Complex Daily Functional Decline During the Preclinical Dementia Stages: Protocol for a Prospective Observational Cohort Study (e66438)
Pierfilippo De Sanctis, Jeannette Mahoney, Johanna Wagner, Helena Blumen, Wenzhu Mowrey, Emmeline Ayers, Claudia Schneider, Natasha Orellana, Sophie Molholm, Joe Verghese. . . . 55

Correction: Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study (e57937)
Marta Castillo-Rodenas, Josep Vidal-Alaball, Núria Solanas-Bacardit, Clotilde Farràs-Company, Aïna Fuster-Casanovas, Queralt Miró Catalina, Francesc López Seguí. . . . 5670

Correction: Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study (e58848)
Rupa Rubinstein, Katie Gallagher, John Ho, Julian Bose, Minesh Khashu, Narendra Aladangady. . . . 5672

Correction: Outcomes of Patients With Early and Locally Advanced Lung Cancer: Protocol for the Italian Lung Cancer Observational Study (LUCENT) (e67629)
Luca Bertolaccini, Oriana CIani, Marco Lucchi, Francesco Zaraca, Alessandro Bertani, Roberto Crisci, Lorenzo Spaggiari, LUCENT Study Group. . . . 5674

Correction: Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS)- Protocol for a Pilot Randomized Controlled Trial (e55725)
Philip Kreniske, Olive Namuyaba, Robert Kasumba, Phionah Namatovu, Fred Ssewamala, Gina Wingood, Ying Wei, Michele Ybarra, Charlotte Oloya, Costella Tindyebwa, Christina Ntulo, Vincent Mujune, Larry Chang, Claude Mellins, John Santelli. . . . 6181

Correction: A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial (e55928)
Marianna Masiero, Gea Spada, Virginia Sanchini, Elisabetta Munzone, Ricardo Pietrobon, Lucas Teixeira, Mirtha Valencia, Aline Machiavelli, Elisa Fragale, Massimo Pezzolato, Gabriella Pravettoni. . . . 6183

Correction: The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study (e56085)
Bryony Waters, Martin Orrell, Orii McDermott. . . . 6185

Correction: Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study (e59300)
Yakubu Ibrahim, Nurul Basri, Norshariza Nordin, Amilia Mohd Jamil. . . . 6187

XSL•FO
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Correction: Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial (e58180)
Nicole Wimmesberger, Diana Rau, Florian Schuchardt, Simone Meier, Matthias Herrmann, Ulrike Bergmann, Erik Farin-Glattacker, Jochen Brich. . . . 6189

Correction: Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial (e59383)
Lydia Shrier, Madison O'Connell, Alessandra Torres, Laura Shone, Alexander Fiks, Julia Plumb, Jessica Maturo, Nicholas McCaskill, Donna Harris, Pamela Burke, Thatcher Felt, Marie Murphy, Lon Sherritt, Sion Harris. . . . 6191

Correction: A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study (e60298)
Alla Melman, Min Teng, Danielle Coombs, Qiang Li, Laurent Billot, Thomas Lung, Eileen Rogan, Mona Marabani, Owen Hutchings, Chris Maher, Gustavo Machado, Back@Home Investigators. . . . 6193

Correction: Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study (e63249)
Anandi Sheth, Dazon Dixon Diallo, Celeste Ellison, Deja Er, Adaora Ntukogu, Kelli Komro, Jessica Sales. . . . 6195

Correction: Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study (e60392)
Sara Russo, Rosario Caruso, Gianluca Conte, Arianna Magon, Ida Vangone, Barbara Bascapè, Giulia Maga, Malgorzata Pasek, Cristina Arrigoni. . . . 6197

Correction: Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial (e65322)
Heena Akbar, Madison Contor, Winnie Niumata, Debra Anderson, Danielle Gallegos. . . . 6199

Correction: Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics (e63678)
Gerald Jerome, Lawrence Appel, Linda Bunyard, Arlene Dalcin, Nowella Durkin, Jeanne Charleston, Norma Kanarek, Michael Carducci, Nae-Yuh Wang, Hsin-Chieh Yeh. . . . 6201

Correction: Using Digital Media to Improve Adolescent Resilience and Prevent Mental Health Problems: Protocol for a Scoping Review (e67759)
Riris Rachmayanti, Fatwa Dewi, Diana Setiyawati, Hario Magatsari, Rian Diana, Retno Vinarti. . . . 6204

Correction: Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study (e68647)
Debbie de Graaf, Nienke de Vries, Tessa van de Zande, Janneke Schimmel, Sooyoon Shin, Nathan Kowahl, Poulami Barman, Ritu Kapur, William Marks Jr, Alex van 't Hul, Bastiaan Bloem. . . . 6206

Protocols

Impact of a Mobile App (LoAD Calc) on the Calculation of Maximum Safe Doses of Local Anesthetics: Protocol for a Randomized Controlled Trial (e53679)
Pietro Fubini, Georges Savoldelli, Tal Beckmann, Caroline Samer, Mélanie Suppan. . . . 57

Professional Development to Improve Responsible Beverage Service Training: Formative Research Results and Protocol for a Randomized Controlled Trial (e49680)
W Woodall, David Buller, Robert Saltz, Lila Martinez. . . . 67

XSL•FO
RenderX

Effectiveness of the Wellness Together Canada Portal as a Digital Mental Health Intervention in Canada: Protocol for a Randomized Controlled Trial (e48703)
Syaron Basnet, Michael Chaiton. . . . 83

Role of Chinese Acupuncture in the Treatment for Chemotherapy-Induced Cognitive Impairment in Older Patients With Cancer: Protocol for a Randomized Controlled Trial (e53853)
Sunyan Zhao, Jing Zhang, Haijun Wan, Chenjie Tao, Meng Hu, Wei Liang, Zhi Xu, Bingguo Xu, Jiaying Zhang, Guoxin Wang, Ping Li, Guangmei Lyu, Yongling Gong. . . . 92

Mobile Mindfulness Meditation for Cancer-Related Anxiety and Neuropathy: Protocol for a Randomized Controlled Trial (e47745)
Ariel Orasud, Mai Uchiyama, Ian Pagano, Erin Bantum. . . . 104

Supporting Life Adjustment in Patients With Lung Cancer Through a Comprehensive Care Program: Protocol for a Controlled Before-and-After Trial (e54707)
Wonyoung Jung, Alice Ahn, Genehee Lee, Sunga Kong, Danbee Kang, Dongok Lee, Tae Kim, Young Shim, Hong Kim, Jongho Cho, Juhee Cho, Dong Shin. . . . 113

Efficacy of a Digital Health Preventive Intervention for Adolescents With HIV or Sexually Transmitted Infections and Substance Use Disorder: Protocol for a Randomized Controlled Trial (e47216)
David Cordova, José Bauermeister, Sydni Warner, The Youth Leadership Council, Patricia Wells, Jennifer MacLeod, Torsten Neilands, Frania Mendoza Lua, Jorge Delva, Kathryn Fessler, Versell Smith Jr, Sarah Khreizat, Cherrie Boyer. . . . 122

Mobile Intervention to Address Cannabis Use Disorder Among Black Adults: Protocol for a Randomized Controlled Trial (e52776)
Pamella Nizio, Bryce Clausen, Michael Businelle, Natalia Ponton, Ava Jones, Brooke Redmond, Julia Buckner, Ezemenari Obasi, Michael Zvolensky, Lorra Garey. . . . 136

Family-Based WhatsApp Intervention to Promote Healthy Eating Behaviors Among Amazonian School Children: Protocol for a Randomized Controlled Trial (e54446)
Ana Hovadick, Marly Cardoso. . . . 153

#4Corners4Health Social Media Cancer Prevention Campaign for Emerging Adults: Protocol for a Randomized Stepped-Wedge Trial (e50392)
David Buller, Andrew Sussman, Cynthia Thomson, Deanna Kepka, Douglas Taren, Kimberly Henry, Echo Warner, Barbara Walkosz, W Woodall, Kayla Nuss, Cindy Blair, Dolores Guest, Evelinn Borrayo, Judith Gordon, Jennifer Hatcher, David Wetter, Alishia Kinsey, Christopher Jones, Angela Yung, Kaila Christini, Julia Berteletti, John Torres, Emilia Barraza Perez, Annelise Small. . . . 165

Development of Continuous Assessment of Muscle Quality and Frailty in Older Patients Using Multiparametric Combinations of Ultrasound and Blood Biomarkers: Protocol for the ECOFRAIL Study (e50325)
Naiara Virto, Xabier Río, Garazi Angulo-Garay, Rafael García Molina, Almudena Avendaño Céspedes, Elisa Cortés Zamora, Elena Gómez Jiménez, Ruben Alcantud Córcoles, Leocadio Rodriguez Mañas, Alba Costa-Grille, Ander Matheu, Diego Marcos-Pérez, Uxue Lazcano, Itziar Vergara, Laura Arjona, Morelva Saeteros, Diego Lopez-de-Ipiña, Aitor Coca, Pedro Abizanda Soler, Sergio Sanabria. . . . 187

Effectiveness of a Serious Video Game (MOON) for Attention Deficit Hyperactivity Disorder: Protocol for a Randomized Clinical Trial (e53191)
Marina Martin-Moratinos, Marcos Bella-Fernández, Maria Rodrigo-Yanguas, Carlos González-Tardón, Aaron Sújar, Chao Li, Ping Wang, Ana Royuela, Pilar Lopez-Garcia, Hilario Blasco-Fontecilla. . . . 207

Efficacy of StepAdd, a Personalized mHealth Intervention Based on Social Cognitive Theory to Increase Physical Activity Among Patients With Type 2 Diabetes Mellitus: Protocol for a Randomized Controlled Trial (e53514)
Kayo Waki, Yuya Tsurutani, Hironori Waki, Syunpei Enomoto, Kosuke Kashiwabara, Akira Fujiwara, Kazuki Orime, Sho Kinguchi, Toshimasa Yamauchi, Nobuhito Hirawa, Kouichi Tamura, Yasuo Terauchi, Masaomi Nangaku, Kazuhiko Ohe. . . . 223

XSL•FO
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Decreasing Opioid Addiction and Diversion Using Behavioral Economics Applied Through a Digital Engagement Solution: Protocol for a Randomized Controlled Trial (e52882)
Rubina Rizvi, Jamee Schoephoerster, Sagar Desphande, Michael Usher, Andy Oien, Maya Peters, Matthew Loth, Matthew Bahr, Steffen Ventz, Joseph Koopmeiners, Genevieve Melton. . . . 243

Development of a Multiplatform Tool for the Prevention of Prevalent Mental Health Pathologies in Adults: Protocol for a Randomized Control Trial (e52324)
Nadia Ramos, Felipe Besoain, Natalia Cancino, Ismael Gallardo, Paula Albornoz, Andres Fresno, Rosario Spencer, Soledad Schott, Daniel Núñez, Carolina Salgado, Susana Campos. . . . 254

Promoting Return to Work After Vocational Rehabilitation Using a Work-Related Fitness App: Protocol for a Cluster-Randomized Controlled Trial (e50200)
David Bühne, Jan Elling, Christian Hetzel, Torsten Alles. . . . 264

Telemedicine-Based Risk Program to Prevent Falls Among Older Adults: Protocol for a Randomized Quality Improvement Trial (e54395)
David Rein, Madeleine Hackney, Yara Haddad, Farah Sublett, Briana Moreland, Laurie Imhof, Cora Peterson, Jaswinder Legha, Janice Mark, Camille Vaughan, Theodore Johnson II, Gwen Bergen, Emory STEADI Implementation team. . . . 272

A Digital Platform (Telepalliation) for Patients in Palliative Care and Their Relatives: Protocol for a Multimethod Randomized Controlled Trial (e49946)
Jarl Sigaard, Nanna Henneberg, Cathrine Schacksen, Sissel Kronborg, Laura Petrini, Kristian Kidholm, Una Birgisdóttir, Helle Spindler, Birthe Dinesen. . . . 282

Understanding Physician's Perspectives on AI in Health Care: Protocol for a Sequential Multiple Assignment Randomized Vignette Study (e54787)
Jane Kim, Hyun-Joon Yang, Bohye Kim, Katie Ryan, Laura Roberts. . . . 292

Implementation of an Electronic Clinical Decision Support System for the Early Recognition and Management of Dysglycemia in an Inpatient Mental Health Setting Using CogStack: Protocol for a Pilot Hybrid Type 3 Effectiveness-Implementation Randomized Controlled Cluster Trial (e49548)
Dipen Patel, Yamiko Msosa, Tao Wang, Julie Williams, Omar Mustafa, Siobhan Gee, Barbara Arroyo, Damian Larkin, Trevor Tiedt, Angus Roberts, Richard Dobson, Fiona Gaughran. . . . 300

Telepractice Parent Training of Enhanced Milieu Teaching With Phonological Emphasis (EMT+PE) For Persian-Speaking Toddlers With Nonsyndromic Cleft Palate: Protocol for a Randomized Controlled Trial (e54426)
Neda Tahmasebi, Talieh Zarifian, Atieh Ashtari, Akbar Biglarian. . . . 310

Testing the Effectiveness of an Intervention to Improve Romanian Teachers' LGBT+-Related Attitudes, Cognitions, Behaviors, and Affect: Protocol for a Randomized Controlled Trial (e54254)
Ioana Latu, Nastasia S l gean, Torill Larsen, Andreea Isbasoiu, Florin Sava. . . . 321

An Integrated mHealth App for Smoking Cessation in Black Smokers With HIV: Protocol for a Randomized Controlled Trial (e52090)
Andre Bizier, Arielle Jones, Michael Businelle, Krista Kezbers, Bettina Hoeppner, Thomas Giordano, Jessica Thai, Jacqueline Charles, Audrey Montgomery, Matthew Gallagher, Marshall Cheney, Michael Zvolensky, Lorra Garey. . . . 331

A Hybrid Digital Parenting Program Delivered Within the Malaysian Preschool System: Protocol for a Feasibility Study of a Small-Scale Factorial Cluster Randomized Trial (e55491)
Hal Cooper, Farah Nadzri, Seema Vyas, Rumaya Juhari, Nellie Ismail, Zarinah Arshat, Durgesh Rajandiran, Laurie Markle, Francisco Calderon, Inge Vallance, G Melendez-Torres, Chiara Facciolà, Vanisa Senesathith, Frances Gardner, Jamie Lachman. . . . 354

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Digital Intervention (Keep-On-Keep-Up Nutrition) to Improve Nutrition in Older Adults: Protocol for a Feasibility Randomized Controlled Trial (e50922)
Chloe French, Sorrel Burden, Emma Stanmore. 374

An mHealth Intervention for Gay and Bisexual Men's Mental, Behavioral, and Sexual Health in a High-Stigma, Low-Resource Context (Project Comunic): Protocol for a Randomized Controlled Trial (e52853)
Corina Lelu iu-Weinberger, Mircea Filimon, Donald Hoover, Mihai Lixandru, Lucian Hanu, Bogdan Dogaru, Tudor Kovacs, Cristina Fierbin eanu, Florentina Ionescu, Monica Manu, Alexandra Mari , Elena Pan , Cristian Dorob n escu, Adrian Streinu-Cercel, John Pachankis. 385

Self-Selected Versus Assigned Target to Reduce Smartphone Use and Improve Mental Health: Protocol for a Randomized Controlled Trial (e53756)
Kamal Sharma, Jeeva Somasundaram, Ashish Sachdeva. 402

Efficacy of the iJobs Web-Based Psychoeducational Intervention to Improve Job Search Behavior and Promote Mental Health Among Unemployed People: Protocol for a Waitlist Randomized Controlled Trial (e55374)
Alexandra Bodnaru, Andrei Rusu, Delia Vîrg , Anja Van den Broeck, Roland Blonk, Loredana Tranc , Drago Iliescu. 412

Evaluating and Enhancing an Educational Intervention to Reduce Smallholder Farmers' Exposure to Pesticides in Uganda Through a Digital, Systematic Approach to Behavior Change: Protocol for a Cluster-Randomized Controlled Trial (e55238)
Peter Ssekkadde, Vica Tomberge, Curdin Brugger, Aggrey Atuhaire, Mohamed Dalvie, Hanna-Andrea Rother, Martin Röösli, Jennifer Inauen, Samuel Fuhrimann. 424

An Immersive Virtual Reality Intervention for Preoperative Anxiety and Distress Among Adults Undergoing Oncological Surgery: Protocol for a 3-Phase Development and Feasibility Trial (e55692)
Renée El-Gabalawy, Jordana Sommer, Pamela Hebbard, Kristin Reynolds, Gabrielle Logan, Michael Smith, Thomas Mutter, W Mutch, Natalie Mota, Catherine Proulx, Vincent Gagnon Shaigetz, Jessica Maples-Keller, Rakesh Arora, David Perrin, Jada Benedictson, Eric Jacobsohn. . .
4 4 4

Examining the Effectiveness of Interactive Webtoons for Premature Birth Prevention: Protocol for a Randomized Controlled Trial (e58326)
Sun-Hee Kim, Jennie De Gagne. 459

Patients and Stakeholders' Perspectives Regarding the Privacy, Security, and Confidentiality of Data Collected via Mobile Health Apps in Saudi Arabia: Protocol for a Mixed Method Study (e54933)
Nasser Alhammad, Mohannad Alajlani, Alaa Abd-alrazaq, Theodoros Arvanitis, Gregory Epiphaniou. 472

A Brief Workplace Training Program to Support Help-Seeking for Mental Ill-Health: Protocol for the Helipad Cluster Randomized Controlled Trial (e55529)
Philip Batterham, Amelia Gulliver, Cassandra Heffernan, Alison Calear, Aliza Werner-Seidler, Alyna Turner, Louise Farrer, Mary Chatterton, Cathrine Mihalopoulos, Michael Berk. 483

Mobile Electrocardiograms in the Detection of Subclinical Atrial Fibrillation in High-Risk Outpatient Populations: Protocol for an Observational Study (e52647)
Ajay Mittal, Yasmine Elkaldi, Susana Shih, Riken Nathu, Mark Segal. 500

The Effectiveness of Virtual Reality–Based Training on Cognitive, Social, and Physical Functioning in High-Functioning Older Adults (CoSoPhy FX): 2-Arm, Parallel-Group Randomized Controlled Trial (e53261)
Ewa Szczepocka, Łukasz Mokros, Jakub Kazmierski, Karina Nowakowska, Anna Łucka, Anna Antoszczyk, Javier Oltra-Cucarella, Walter Werzowa, Martin Hellevik, Stavros Skouras, Karsten Bagger. 507

Molecular Detection of SARS-CoV-2 From Throat Swabs Performed With or Without Specimen Collection From the Tonsils: Protocol for a Multicenter Randomized Controlled Trial (e47446)
Benedikte Hartvigsen, Kathrine Jakobsen, Thomas Benfield, Niels Gredal, Annette Ersbøll, Mathias Grønlund, Henning Bundgaard, Mikkel Andersen, Nina Steenhard, Christian von Buchwald, Tobias Todsen. 523

XSL•FO
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Effect of a 12-Week High-Calorie-Expenditure Multimodal Exercise Program on Health Indices in Women With Overweight: Protocol for a Randomized Controlled Trial (e51599)
Mitra Abdollahi Diba, Vahid Sari Sarraf, Ramin Amirsasan, Saeid Dabbagh Nikoukheslat. 531

The Effect of Acupuncture on Brain Iron Deposition and Body Iron Metabolism in Vascular Cognitive Impairment: Protocol for a Randomized Controlled Trial (e56484)
Mingli Wu, Lulu Chen, Yamin Wang, Yunpeng Li, Yuqi An, Ruonan Wu, Yuhan Zhang, Jing Gao, Kaiqi Su, Xiaodong Feng. 545

Web-Based Mindfulness-Based Cognitive Therapy for Adults With a History of Depression: Protocol for a Randomized Controlled Trial (e53966)
Mohammad Hooshmand Zaferanieh, Lu Shi, Meenu Jindal, Liwei Chen, Lingling Zhang, Snehal Lopes, Karyn Jones, Yucheng Wang, Kinsey Meggett, Cari Walker, Grace Falgoust, Heidi Zinzow. 556

Adapting an Efficacious Peer-Delivered Physical Activity Program for Survivors of Breast Cancer for Web Platform Delivery: Protocol for a 2-Phase Study (e52494)
Bernardine Pinto, Ashwin Patel, Danielle Ostendorf, Amy Huebschmann, Shira Dunsiger, Madison Kindred. 569

Effect of Flavored on! Nicotine Pouch Products on Smoking Behaviors: Protocol for a Sequential, Multiple Assignment, Randomized Controlled Trial (e56565)
Hui Cheng, Jed Rose, Joshua Karelitz, David Botts, Tanaia Botts, Perry Willette, Gal Cohen. 588

Web-Based Group Conversational Intervention on Cognitive Function and Comprehensive Functional Status Among Japanese Older Adults: Protocol for a 6-Month Randomized Controlled Trial (e56608)
Kumi Miura, Takashi Kudo, Mihoko Otake-Matsuura. 599

Mindful Self-Compassion Smartphone Intervention for Worker Mental Health in Japan: Protocol for a Randomized Controlled Trial (e53541)
Takumu Kurosawa, Koichiro Adachi, Ryu Takizawa. 609

Piloting a Clinical Decision Support Tool to Identify Patients With Social Needs and Provide Navigation Services and Referral to Community-Based Organizations: Protocol for a Randomized Controlled Trial (e57316)
Elham Hatef, Thomas Richards, Kristin Topel, Sofia Hail, Christopher Kitchen, Katherine Shaw, Talan Zhang, Elyse Lasser, Jonathan Weiner.
6 2 5

Effectiveness of a Mobile Phone Messaging–Based Message Framing Intervention for Improving Maternal Health Service Uptake and Newborn Care Practice in Rural Jimma Zone, Ethiopia: Protocol for a Cluster Randomized Controlled Trial (e52395)
Gebeyehu Bulcha, Hordofa Abdissa, Josef Noll, Demisew Sori, Zewdie Koricha. 637

Design, Develop, and Pilot-Test a Digital Platform to Enhance Student Well-Being: Protocol for a Mixed-Methods Study (e39779)
Ashish Joshi, Kamalpreet Kaur, Ashruti Bhatt, Krishna Surapaneni, Ashoo Grover, Apurva Pandya. 648

Use of Transdermal Alcohol Sensors in Conjunction With Contingency Management to Reduce Alcohol Consumption in People With Alcohol Dependence Attending Alcohol Treatment Services: Protocol for a Pilot Feasibility Randomized Controlled Trial (e57653)
Eileen Brobbin, Paolo Deluca, Stephen Parkin, Colin Drummond. 656

Smartphone-Based Smoking Cessation Intervention (OKquit) for Oklahoma Tobacco Helpline Users: Protocol for a Randomized Controlled Trial (e56827)
Michael Businelle, Jessica Becerra, Carl Witten, Sixia Chen, Krista Kezbers, Laura Beebe, Darla Kendzor. 669

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Improving the Well-Being of People With Advanced Cancer and Their Family Caregivers: Protocol for an Effectiveness-Implementation Trial of a Dyadic Digital Health Intervention (FOCUSau) (e55252)
Peter Hudson, Jill Francis, Joachim Cohen, Suzanne Kapp, Richard De Abreu Lourenco, Lisa Beatty, Kathleen Gray, Michael Jefford, Ilona Juraskova, Laurel Northouse, Aline de Vleminck, Sungwon Chang, Patsy Yates, Sophy Athan, Shaira Baptista, Marlena Klaic, Jennifer Philip. 6 8 1

Evaluating the Efficacy of a Digital Therapeutic (CT-152) as an Adjunct to Antidepressant Treatment in Adults With Major Depressive Disorder: Protocol for the MIRAI Remote Study (e56960)
Brian Rothman, Mary Slomkowski, Austin Speier, A Rush, Madhukar Trivedi, Erica Lawson, Michael Fahmy, Daniel Carpenter, Dalei Chen, Ainslie Forbes. . . . 696

Reducing Alcohol Misuse and Promoting Treatment Initiation Among Veterans Through a Brief Internet-Based Intervention: Protocol for a Randomized Controlled Trial (e59993)
Eric Pedersen, Jordan Davis, Justin Hummer, Kathryn Bouskill, Keegan Buch, Ireland Shute, Reagan Fitzke, Denise Tran, Clayton Neighbors, Shaddy Saba. . . . 710

Effectiveness of a Parent-Based eHealth Intervention for Physical Activity, Dietary Behavior, and Sleep Among Preschoolers: Protocol for a Randomized Controlled Trial (e58344)
Peng Zhou, Huiqi Song, Patrick Lau, Lei Shi, Jingjing Wang. . . . 723

Testing a Consumer Wearables Program to Promote the Use of Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea: Protocol for a Pilot Randomized Controlled Trial (e60769)
Selene Mak, Garrett Ash, Li-Jung Liang, Erin Der-McLeod, Sara Ghadimi, Anjali Kewalramani, Saadia Naeem, Michelle Zeidler, Constance Fung. . . . 738

Testing the Effectiveness of a Mobile Smartphone App Designed to Improve the Mental Health of Junior Physicians: Protocol for a Randomized Controlled Trial (e58288)
Lauren Lai, Samineh Sanatkar, Andrew Mackinnon, Mark Deady, Katherine Petrie, Rosie Lipscomb, Isabelle Counson, Rohan Francis-Taylor, Kimberlie Dean, Samuel Harvey. . . . 750

Chatbot-Led Support Combined With Counselor-Led Support on Smoking Cessation in China: Protocol for a Pilot Randomized Controlled Trial (e58636)
Xue Weng, Hua Yin, Kefeng Liu, Chuyu Song, Jiali Xie, Ningyuan Guo, Man Wang. . . . 764

Ayurvedic Management of Presbycusis (Project TOPMAC): Protocol for an Exploratory Randomized Controlled Trial (e55089)
Krishna V, Sanjeev Thomas, Murugan C Nair, Parvathy Nair, Nisha L, Anuradha S, Arunabh Tripathi, Pallavi Mundada, Babita Yadav, B Rao, Sudhakar D, Srikanth N. . . . 774

Implementation and Evaluation of a Home-Based Pre-Exposure Prophylaxis Monitoring Option: Protocol for a Randomized Controlled Trial (e56587)
Chase Cannon, Katherine Holzhauer, Matthew Golden. . . . 783

Functional Magnetic Resonance Imaging Analysis of the Clinical Effect and Cerebral Mechanism of Tuina in Lumbar Disc Herniation: Protocol for a Randomized Controlled Parallel Group Trial (e63852)
Changzheng Jiang, Hongye Huang, Lechun Chen, Jingjing Jiang, Huanzhen Zhang, Jincheng Chen, Shuijin Chen, Zhigang Lin. . . . 796

Multifaceted Intervention to Improve Graft Outcome Disparities in African American Kidney Transplants (MITIGAAT Study): Protocol for a Randomized Controlled Trial (e57784)
Morgan Overstreet, Hannah Culpepper, Deanna DeHoff, Mulugeta Gebregziabher, Maria Posadas Salas, Zemin Su, Jessica Chandler, Felicia Bartlett, Paige Dunton, Taylor Carcella, David Taber. . . . 809

The Evaluation of a Web-Based Intervention (Deprexis) to Decrease Depression and Restore Functioning in Veterans: Protocol for a Randomized Controlled Trial (e59119)
Rahel Pearson, Christopher Beevers, Joseph Mignogna, Justin Benzer, Paul Pfeiffer, Edward Post, Suzannah Creech. . . . 821

XSL•FO
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A Tailored Postpartum eHealth Physical Activity Intervention for Individuals at High Risk of Postpartum Depression—the POstpartum Wellness Study (POW): Protocol and Data Overview for a Randomized Controlled Trial (e56882)
Maya Ramsey, Nina Oberman, Charles Quesenberry Jr, Elaine Kurtovich, Lizeth Gomez Chavez, Aaloni Chess, Susan Brown, Cheryl Albright, Mibhali Bhalala, Sylvia Badon, Lyndsay Avalos. . . . 836

Efficacy of a Multimodal Digital Behavior Change Intervention on Lifestyle Behavior, Cardiometabolic Biomarkers, and Medical Expenditure: Protocol for a Randomized Controlled Trial (e50378)
Sakeina Howard-Wilson, Jack Ching, Sherri Gentile, Martin Ho, Alex Garcia, Didem Ayturk, Peter Lazar, Nova Hammerquist, David McManus, Bruce Barton, Steven Bird, John Moore, Apurv Soni. . . . 854

The Implementation of the Advocacy Intervention for Midlife and Older Women Who Have Experienced Intimate Partner Violence: Protocol for a Randomized Controlled Trial (e57886)
Lori Weeks, Kathleen Allen, Catherine Holtmann, Joni Leger, Suzanne Dupuis-Blanchard, Colleen MacQuarrie, Marilyn Macdonald, Elaine Moody, Christie Stilwell, Heather Helpard, Danie Gagnon. . . . 869

Scalable Technology for Adolescents and Youth to Reduce Stress in the Treatment of Common Mental Disorders in Jordan: Protocol for a Randomized Controlled Trial (e54585)
Aemal Akhtar, Anne de Graaff, Rand Habashneh, Dharani Keyan, Adnan Abualhaija, Sarah Fanatseh, Muhannad Faroun, Ibrahim Aqel, Latefa Dardas, Chiara Servili, Mark van Ommeren, Richard Bryant, Kenneth Carswell. . . . 884

Study to Evaluate the Comparative Efficacy of Medhya Rasayana (Pharmacological) Versus Nonpharmacological Interventions in Management of Gadget Addiction in Children: Protocol for Parallel, Triple-Arm, Randomized Clinical Trial (e51833)
Prasad Yewale, Renu Rathi, Swapnali Mate. . . . 898

A Personalized Data Dashboard to Improve Compliance with Ecological Momentary Assessments in College Students: Protocol for a Microrandomized Trial (e57664)
Stephanie Lanza, Ashley Linden-Carmichael, Danny Wang, Sandesh Bhandari, Samuel Stull. . . . 909

The Effect of Interventions Based on the Information-Motivation-Behavioral Skills Model on the Human Papillomavirus Vaccination Rate Among 11-13-Year-Old Girls in Central and Western China: Protocol for a Randomized Controlled Trial (e58873)
Shu Jing, Yijin Wu, Zhenwei Dai, Shenglan Tang, Xiaoyou Su, Youlin Qiao. . . . 917

Digital Homework Support Program for Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Protocol for a Randomized Controlled Trial (e44553)
Fanny Gollier-Briant, Laurence Ollivier, Pierre-Hugues Joalland, Stéphane Mouchabac, Philippe Leray, Olivier Bonnot. . . . 930

Improvement of Motor Imagination and Manual Ability Through Virtual Reality and Selective and Nonselective Functional Electrical Stimulation: Protocol for a Randomized Controlled Trial (e63329)
Montserrat Santamaría-Vázquez, J Ortiz-Huerta, Aitor Martín-Odriozola, Olalla Saiz-Vazquez. . . . 939

Essential Coaching for Every Mother Tanzania (ECEM-TZ): Protocol for a Type 1 Hybrid Effectiveness-Implementation Randomized Controlled Trial (e63454)
Justine Dol, Lilian Mselle, Marsha Campbell-Yeo, Columba Mbekenga, Thecla Kohi, Douglas McMillan, Cindy-Lee Dennis, Gail Tomblin Murphy, Megan Aston. . . . 948

Effects of Internet Cognitive Behavioral Therapy for Insomnia and Internet Sleep Hygiene Education on Sleep Quality and Executive Function Among Medical Students in Malaysia: Protocol for a Randomized Controlled Trial (e59288)
Vijandran Mariappan, Firdaus Mukhtar. . . . 959

XSL•FO
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A Remotely Delivered Light-Intensity Physical Activity Intervention for Older Cancer Survivors: Protocol for a Feasibility Randomized Controlled Trial (e59504)
Cindy Blair, Ursa Brown-Glaberman, Scott Walters, Claire Pestak, Tawny Boyce, Laura Barriga, Ellen Burgess, Bernard Tawfik, Cynthia Killough, Anita Kinney, Wendy Demark-Wahnefried, Angela Meisner, Charles Wiggins, V Pankratz, Sally Davis. 974

Examining Share plus—A Continuous Glucose Monitoring Plus Data-Sharing Intervention in Older Adults and Their Care Partners: Protocol for a Randomized Control Study (e60004)
Nancy Allen, Cynthia Berg, Eli Iacob, Bruno Gonzales, Jonathan Butner, Michelle Litchman. 992

Novel Strategy to Assess the Neurotoxicity of Organic Solvents Such as Glycol Ethers: Protocol for Combining In Vitro and In Silico Methods With Human-Controlled Exposure Experiments (e50300)
Nancy Hopf, Laura Suter-Dick, Jörg Huwyler, Myriam Borgatta, Lucie Hegg, David Pamies, Hélène Paschoud, Ramya Puligilla, Elena Reale, Sophie Werner, Marie-Gabrielle Zurich. 1004

Implementation of a Primary Prevention Program for Posttraumatic Stress Disorder in a Cohort of Professional Soldiers (PREPAR): Protocol for a Randomized Controlled Trial (e47175)
Emmanuelle Le Barbenchon, Marion Trousselard, Sonia Pellissier, Mathilde Moisseron-Baudé, Philippine Chachignon, Pierre Bouny, Emma Touré Cuq, Sandrine Jacob, Cécile Vigier, Maud Hidalgo, Damien Claverie, Anais Duffaud. 1021

Investigation of the Association Between e-Cigarette Smoking and Oral Mucosal Health Status Among Young People: Protocol for a Case-Control Trial (e53644)
Siyuan Cheng. 1033

An Individual Music Intervention for Adults With Intellectual Disabilities and Challenging Behavior: Protocol for a Randomized Controlled Trial (e52497)
Gerianne Smeets, Karin Volkers, Erik Scherder, Xavier Moonen. 1039

Survivorship Care for Women Living With Ovarian Cancer: Protocol for a Randomized Controlled Trial (e48069)
Elizabeth Kvale, Farya Phillips, Samiran Ghosh, Jayanthi Lea, Claire Hoppenot, Anthony Costales, Jan Sunde, Hoda Badr, Eberechi Nwogu-Onyemkpa, Nimrah Saleem, Rikki Ward, Bijal Balasubramanian. 1051

Cerebral Mechanism of Tuina on the Descending Pain Inhibitory System in Knee Osteoarthritis: Protocol for a Randomized Controlled Trial (e52820)
Hui Xu, Zheng Wang, Zhen Wang, Hang Zhou, Juan Guo, Wanyu Li, Yunfeng Zhou. 1065

Comparing Repeated (Annual) Couples HIV Testing and Counseling to Individual HIV Testing and Counseling Among Male Couples at High Risk of HIV Infection: Protocol for a Randomized Control Trial (e53023)
Tyrel Starks, Kory Kyre, Juan Castiblanco, Jayelin Parker, Erin Kahle, Rob Stephenson, Demetria Cain. 1077

Pan-Indian Clinical Registry of Invasive Fungal Infections Among Patients in the Intensive Care Unit: Protocol for a Multicentric Prospective Study (e54672)
Anup Ojha, Venencia Albert, Saurabh Sharma, Vinaykumar Hallur, Gagandeep Singh, Umabala Pamidimukkala, Kh Singh, Harleen Kaur, Tadepalli Karuna, Jayanthi Savio, Reema Nath, Immaculata Xess, Prashant Gupta, Anjali Shetty, Madhuchhanda Das. 1089

The Efficacy of Bepotastine Besilate Compared With Hydroxyzine Pamoate for Preventing Infusion Reactions to the First Dose of Rituximab in Patients With Non-Hodgkin Lymphoma: Protocol for a Phase II, Double-Blind, Multicenter Randomized Trial (e54882)
Yumi Kitahiro, Kazuhiro Yamamoto, Kimikazu Yakushijin, Takeshi Ioroi, Masaaki Tanda, Kotaro Itohara, Tomohiro Omura, Hironobu Minami, Ikuko Yano. 1098

Changes in Oral Health and Dental Esthetic in Smokers Switching to Combustion-Free Nicotine Alternatives: Protocol for a Multicenter and Prospective Randomized Controlled Trial (e53222)
Gianluca Conte, Sebastiano Pacino, Salvatore Urso, Doris Greiling, Pasquale Caponnetto, Eugenio Pedullà, Luigi Generali, Ugo Consolo, Vittorio Checchi, Stefan Gospodaru, Gheorghe Bordeniuc, Valeriu Fala, Jan Kowalski, Maciej Nowak, Renata Górska, Amaliya Amaliya, Iain Chapple, Michael Milward, Robert Maclure, Gianna Nardi, Riccardo Polosa. 1108

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Matrix Metalloproteinase-9 Testing of Golden Rice Cookies With Piper Crocatum Active Extract for Preventing Foot Ulcers in Patients With Diabetes: Protocol for a Randomized Controlled Trial (e49940)
Andina Setyawati, Ariyanti Saleh, Takdir Tahir, Saldy Yusuf, Syahrul Syahrul, Aminuddin Aminuddin, Muhammad Raihan, Nuurhidayat Jafar, Hasyrul Hamzah, Nur Arfian. . . . 1126

Improving Health Professional Recognition and Response to Child Maltreatment and Intimate Partner Violence: Protocol for Two Mixed Methods Pilot Randomized Controlled Trials (e50864)
Melissa Kimber, Elizabeth Baker-Sullivan, Donna Stewart, Meredith Vanstone. . . . 1136

Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee): Protocol for an Effectiveness-Implementation Hybrid Randomized Controlled Trial (e54352)
Bryan Tan, Chun Tan, Tong Tan, Su-Yin Yang, Gillian Chew, Siang Tan, Yu Chua, Yew Yan, Derrick Soh, Tong Goh, Pu Ng, Yee Ng, Swee Kuan, Bo Teo, Keng Kong, Michelle Pereira, Hui Ng. . . . 1153

Assessing the Effectiveness of a Multicomponent Intervention on Hand Hygiene and Well-Being in Primary Health Care Centers and Schools Lacking Functional Water Supply in Protracted Conflict Settings: Protocol for a Cluster Randomized Controlled Trial (e52959)
Anaïs Galli, Yaman Ma'ani Abuzahra, Carola Bänziger, Aboubacar Ballo, Max Friedrich, Karin Gross, Miriam Harter, Jan Hattendorf, Maryna Peter, Andrea Tamas, Branwen Owen, Mirko Winkler. . . . 1166

Effectiveness of Sensitization Campaigns in Reducing Leprosy-Related Stigma in Rural Togo: Protocol for a Mixed Methods Cluster Randomized Controlled Trial (e52106)
Dominik Jockers, Akila Bakoubayi, Kate Bärnighausen, P'tanam Bando, Stefanie Pechar, Teresia Maina, Jonas Wachinger, Mark Vetter, Yawovi Djakpa, Bayaki Saka, Piham Gnossike, Nora Schröder, Shuyan Liu, Denis Gadah, Christa Kasang, Till Bärnighausen. . . . 1181

Needs and Experiences With Health Care Providers of Adult Rare Disease Patients and Caregivers of People With Rare Diseases: Protocol for a Qualitative Study (e53362)
Tina erne, Eva Turk, Spela Mirosevic, Danica Rotar Pavli . . . 1192

Marital Self-Disclosure Intervention for the Fear of Cancer Recurrence in Chinese Patients With Gastric Cancer: Protocol for a Quasiexperimental Study (e55102)
Haiyan Zhao, Ye Zhou, Chong Che, Mei Chong, Yu Zheng, Yuzhu Hou, Canjuan Chen, Yantao Zhu. . . . 1201

Motor Effects of Intervention With Transcranial Direct Current Stimulation for Physiotherapy Treatment in Children With Cerebral Palsy: Protocol for a Randomized Clinical Trial (e52922)
Anna Cangussu, Beatriz Lucarini, Igor Melo, Paula Diniz, Marisa Mancini, Bernardo Viana, Marco Romano-Silva, Débora Miranda. . . . 1214

Effect of Rural Trauma Team Development on the Outcomes of Motorcycle Accident–Related Injuries (Motor Registry Project): Protocol for a Multicenter Cluster Randomized Controlled Trial (e55297)
Herman Lule, Micheal Mugerwa, Robinson Ssebuufu, Patrick Kyamanywa, Till Bärnighausen, Jussi Posti, Michael Wilson. . . . 1221

Effectiveness of Gerontechnology Empowerment Program on Awareness and Use of Mobile Apps Among Older Adults for Instrumental Activities of Daily Living: Protocol for a Cluster Randomized Controlled Trial (e53587)
Y Shashidhara, G Raghavendra, Poornima P Kundapur, V Binil. . . . 1238

Effects of Empagliflozin in Type 2 Diabetes With and Without Chronic Kidney Disease and Nondiabetic Chronic Kidney Disease: Protocol for 3 Crossover Randomized Controlled Trials (SiRENA Project) (e56067)
Steffen Nielsen, Camilla Duus, Niels Buus, Jesper Bech, Frank Mose. . . . 1246

The Effects of a Dietary Supplement (PediaFlù) Plus Standard of Care in Children With Acute Tonsillopharyngitis/Rhinopharyngitis: Protocol for a Randomized Controlled Trial (e53703)
Fabio Cardinale, Dionisio Barattini, Federica Sbrocca, Alessandro Centi, Greta Giuntini, Maria Morariu Bordea, Dorina Herteg, Serban Rosu, Cristian Matei. . . . 1260

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Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics (e54126)
Gerald Jerome, Lawrence Appel, Linda Bunyard, Arlene Dalcin, Nowella Durkin, Jeanne Charleston, Norma Kanarek, Michael Carducci, Nae-Yuh Wang, Hsin-Chieh Yeh. . . . 1272

Testing a Biobehavioral Model of Chronic Stress and Weight Gain in Young Children (Family Stress Study): Protocol and Baseline Demographics for a Prospective Observational Study (e48549)
Shannon Pare, Elizabeth Gunn, Katherine Morrison, Alison Miller, Alison Duncan, Andrea Buchholz, David Ma, Paul Tremblay, Lori Vallis, Nicola Mercer, Jess Haines. . . . 1284

Combination of Curcuminoids and Acupressure for Inflammation and Pain in Older People with Osteoarthritis Genu: Protocol for a Randomized Controlled Trial (e54970)
Srinalesti Mahanani, Nyoman Kertia, Ema Madyaningrum. . . . 1300

Evaluation of Staining Propensity of Silver Diamine Fluoride With and Without Potassium Iodide in Children (Project Healthy Smiles): Protocol for a Randomized Controlled Trial (e51087)
Praveena Navaneethan, Imran Mohammed, Rekha Shenoy, Junaid Junaid, Supriya Amanna, Zeyad Alsughier, Shaul Kolarkodi. . . . 1310

Deprescribing as a Way to Reduce Inappropriate Use of Drugs for Overactive Bladder in Primary Care (DROP): Protocol for a Cluster Randomized Controlled Trial With an Embedded Explanatory Sequential Mixed Methods Study (e56277)
Ann Soerensen, Marie Haase Juhl, Marlene Krogh, Mette Grønkjær, Jette Kristensen, Anne Olesen. . . . 1320

Efficacy and Mechanism of Acupoint Catgut Embedding in the Treatment of Chronic Spontaneous Urticaria: Protocol for a Randomized Double-Blind Placebo-Controlled Trial (e54376)
Jianing Bi, Li Liu, Zhu Fan, Shengyuan Qu, Jiao Yang, Chenchen Xu, Bingnan Cui. . . . 1330

Efficacy and Safety of Shi Cervical Rotational Manipulation in Patients With Atlantoaxial Joint Subluxation: Protocol for a Randomized Controlled Trial (e57865)
Deng Zhen, Shang Haibin, Ai Youli, Yuan Weian, Wang Huihao, Zhan Hongsheng, Li Guozhong, Ding Ren, Shen Zhibi. . . . 1342

Effects of Defatted Rice Bran–Fortified Bread on the Gut Microbiota Composition of Healthy Adults With Low Dietary Fiber Intake: Protocol for a Crossover Randomized Controlled Trial (e59227)
Hwei Ng, Jasjot Maggo, Catherine Wall, Simone Bayer, Warren McNabb, Jane Mullaney, Meika Foster, Diana Cabrera, Karl Fraser, Janine Cooney, Tania Trower, Catrin Günther, Chris Frampton, Richard Gearry, Nicole Roy. . . . 1353

Nourishing the Infant Gut Microbiome to Support Immune Health: Protocol of SUN (Seeding Through Feeding) Randomized Controlled Trial (e56772)
Clare Wall, Nicole Roy, Jane Mullaney, Warren McNabb, Olivier Gasser, Karl Fraser, Eric Altermann, Wayne Young, Janine Cooney, Robyn Lawrence, Yannan Jiang, Barbara Galland, Xiaoxi Fu, Jacqueline Tonkie, Nisha Mahawar, Amy Lovell. . . . 1373

Adapting and Evaluating a Brief Advice Tobacco Cessation Intervention in High-reach, Low-resource Settings in India: Protocol for a Cluster Randomized Controlled Trial (e57236)
Sitara Mahtani, Kasisomayajula Viswanath, Himanshu Gupte, Gauri Mandal, Dinesh Jagiasi, Ratandeep Chawla, Marina D'Costa, Ziming Xuan, Sara Minsky, Shoba Ramanadhan. . . . 1385

Dexmedetomidine Versus Midazolam for End-of-Life Sedation and Agitation: Protocol for a Randomized Controlled Trial (The DREAMS Trial) (e55129)
Benjamin Thomas, Greg Barclay, Wing-Shan Lo, Judy Mullan, Kylie Mansfield. . . . 1397

Evaluation of Comparative Efficacy of Levothyroxine Versus Kshar Basti and Kanchanar Guggul in the Treatment of Hypothyroidism: Protocol for a Randomized Controlled Trial (e57287)
Satyajit Kulkarni, Shweta Parwe. . . . 1407

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Examining the Acceptability of Helminth Education Packages “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” and Their Impact on Knowledge, Attitudes, and Practices Among Schoolchildren in the Lower Mekong Basin: Protocol for a Cluster Randomized Controlled Trial (e55290)
Suji O'Connor, Mary Mationg, Matthew Kelly, Gail Williams, Archie Clements, Banchob Sripa, Somphou Sayasone, Virak Khieu, Kinley Wangdi, Donald Stewart, Sirikachorn Tangkawattana, Apiporn Suwannatrai, Vanthanom Savathdy, Visal Khieu, Peter Odermatt, Catherine Gordon, Sangduan Wannachart, Donald McManus, Darren Gray. . . . 1418

Peer Intervention to Link Overdose Survivors to Treatment (PILOT): Protocol for a Multisite, Randomized Controlled Trial Conducted Within the National Institute on Drug Abuse Clinical Trials Network (e60277)
Carrie Papa, Erin McClure, Jenna McCauley, Louise Haynes, Timothy Matheson, Richard Jones, Lindsey Jennings, Tricia Lawdahl, Ralph Ward, Kathleen Brady, Kelly Barth. . . . 1429

Ayurveda Management of Allergic Rhinitis: Protocol for a Randomized Controlled Trial (e56063)
Shweta Mata, Shivshankar Rajput, Isha Tuli, Pallavi Mundada, Bharti Gupta, Narayanam Srikanth, Rabinarayanan Acharya. . . . 1442

Graded Intensity Aerobic Exercise to Improve Cerebrovascular Function and Performance in Older Veterans: Protocol for a Randomized Controlled Trial (e58316)
Medina Bello, Kevin Mammino, Mark Vernon, Daniel Wakeman, Chanse Denmon, Lisa Krishnamurthy, Venkatagiri Krishnamurthy, Keith McGregor, Thomas Novak, Joe Nocera. . . . 1450

Acupuncture as Adjuvant Therapy for Glaucoma: Protocol for a Randomized Controlled Trial (e57888)
Yi-Fang Liao, Yu-Chen Lee, Hui-Ju Lin, Yi-Ching Shao. . . . 1462

Over-the-Counter Hearing Aids Versus Traditional Hearing Aids in Patients With Mild-to-Moderate Hearing Loss: Protocol for a Noninferiority Randomized Controlled Trial (e59894)
Ga-Young Kim, Mini Jo, Young Cho, Il Moon. . . . 1472

High Potassium Diet Rich in Spices and Herbs-Salt Substitution (HPSH-SS) for Blood Pressure Reduction in Older Adults: Protocol for Diet Concept and Randomized Controlled Trial (e56869)
Farapti Farapti, Sheila Putri, Annisaa Furqonia, Purwo Rejeki, Muhammad Miftahussurur. . . . 1481

Impact of Dance or Music and Meditation on the Progression of Parkinson Disease With Mild or Moderate Severity: Protocol for a Pilot Randomized Controlled Trial (e59018)
Bhagyashree Mehrotra, Neha Rai, Rajani MR, Aparna Budhakar, Ritika Aggarwal, Raj Agarbattiwala, Mona Thomas, Sampada Patole, Paresh Doshi. . . . 1493

Influence of Distraction Factors on Performance in Laparoscopic Surgery in Immersive Virtual Reality: Study Protocol of a Cross-Over Trial in Medical Students and Residents—DisLapVR (e59014)
Laura Hanke, Richard Schulte, Christian Boedecker, Florentine Huettl, Patrick Saalfeld, Vuthea Chheang, Marlene Wessels, Christoph von Castell, Heiko Hecht, Christian Hansen, Hauke Lang, Tobias Huber. . . . 1503

Remotely Delivered Video Interaction Guidance for Families of Children With an Intellectual Disability Referred to Specialist Mental Health Services: Protocol for a Feasibility Randomized Controlled Trial (e54619)
Charmaine Kohn, Lauren Turner, Zhixing Yang, Michael Absoud, Angela Casbard, Manuel Gomes, Gemma Grant, Angela Hassiotis, Eilis Kennedy, Sophie Levitt, Rachel McNamara, Elizabeth Randell, Vasiliki Totsika. . . . 1511

Improving Oral Health in Prisons (PriOH): Protocol for a Randomized Controlled Trial (e60817)
Emilie Bryne, Kathrine Bergum, William Gjedrem. . . . 1528

Leveraging Community Health Workers and a Responsive Digital Health System to Improve Vaccination Coverage and Timeliness in Resource-Limited Settings: Protocol for a Cluster Randomized Type 1 Effectiveness-Implementation Hybrid Study (e52523)
Lavanya Vasudevan, Jan Ostermann, Nathan Thielman, Joy Baumgartner, David Solomon, Anna Mosses, Amy Hobbie, Nicole Hair, Chen Liang, Marco van Zwetselaar, Sayoki Mfinanga, Esther Ngadaya. . . . 1538

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Testing an Evidence-Based Self-Help Program for Infertility-Related Distress: Protocol for a Randomized Controlled Trial (e52662)
Jennifer Gordon, Megan Poulter, Ashley Balsom, Tavis Campbell. 1552

Effects of a Powered Ankle-Foot Prosthesis and Physical Therapy on Function for Individuals With Transfemoral Limb Loss: Rationale, Design, and Protocol for a Multisite Clinical Trial (e53412)
Jason Maikos, Alison Pruziner, Brad Hendershot, David Herlihy, John Chomack, Michael Hyre, Samuel Phillips, Alexis Sidiropoulos, Christopher Dearth, Leif Nelson. 1563

Physical Activity Intervention for Urban Black Women With Asthma: Protocol for a Randomized Controlled Efficacy Study (e55700)
Ellen Davis, Elizabeth Townsend, Aero Cavalier, Yi-Fan Chen, Dameka Edwards-Hart, Spyros Kitsiou, Wiktoria Kowalczyk, Iliana Mansur, Ebere Okpara, Karen Powell, Valerie Press, Toni Ramirez, Deborah Salvo, Lisa Sharp, Brittani Wright, Sharmilee Nyenhuis. 1582

Telehealth Behavioral Intervention for Chronic Disease Self-Management in Adults With Physical Disabilities (My Health, My Life, My Way): Protocol for Intervention Fidelity and Dashboard Design for a Randomized Controlled Trial (e53410)
Eric Evans, Ayse Zengul, Tejaswini Subhash Chilke, Amy Knight, Amanda Willig, Andrea Cherrington, Tapan Mehta, Mohanraj Thirumalai. . . 1595

A Digital Intervention to Improve Skin Self-Examination Among Survivors of Melanoma: Protocol for a Type-1 Hybrid Effectiveness-Implementation Randomized Trial (e52689)
Sharon Manne, Carolyn Heckman, Sara Frederick, Alexis Schaefer, Christina Studts, Olga Khavjou, Amanda Honeycutt, Adam Berger, Hao Liu. 1605

Telehealth Movement-to-Music With Arm-Based Sprint-Intensity Interval Training to Improve Cardiometabolic Health and Cardiorespiratory Fitness in Children With Cerebral Palsy: Protocol for a Pilot Randomized Controlled Trial (e56499)
Byron Lai, Robert Oster, Drew Davis, Larsen Bright, Gordon Fisher, Jereme Wilroy, Yumi Kim, Raven Young, Ashley Wright, Tanvee Sinha, James Rimmer. 1627

An mHealth Intervention to Address Depression and Improve Antiretroviral Therapy Adherence Among Youths Living With HIV in Uganda: Protocol for a Pilot Randomized Controlled Trial (e54635)
Proscovia Nabunya, Patricia Cavazos-Rehg, James Mugisha, Erin Kasson, Olive Namuyaba, Claire Najjuuko, Edward Nsubuga, Lindsey Filiatreau, Abel Mwebembezi, Fred Ssewamala. 1643

Improving Quality of ICD-10 (International Statistical Classification of Diseases, Tenth Revision) Coding Using AI: Protocol for a Crossover Randomized Controlled Trial (e54593)
Taridzo Chomutare, Anastasios Lamproudis, Andrius Budrionis, Therese Svenning, Lill Hind, Phuong Ngo, Karl Mikalsen, Hercules Dalianis. . 1656

Integration of an Electronic Screening, Brief Intervention, and Referral to Treatment Program Into an HIV Testing Program to Reduce Substance Use and HIV Risk Behavior Among Men Who Have Sex With Men: Protocol for Intervention Development and a Pilot Randomized Controlled Trial (e56683)
Iván Balán, Ruben Marone, Victoria Barreda, Sylvie Naar, Yuxia Wang. 1667

Providing Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer Adolescents With Nurturance, Trustworthiness, and Safety: Protocol for Pilot Cluster Randomized Controlled Trial Design (e55210)
Robert Coulter, Isabella Mahal, Clarisse Lin, Shari Schneider, Aaryn Mathias, Karuna Baral, Elizabeth Miller, Kaleab Abebe. 1685

A Social Media–Delivered Melanoma Prevention Program for Young Women Engaged in Frequent UV Tanning: Protocol for a Randomized Controlled Trial (e56562)
Jerod Stapleton, Sharon Manne, Sherry Pagoto, Allison Leip, Kathryn Greene, Joel Hillhouse, Allison Merritt, Brent Shelton. 1698

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Efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) in Individuals With Chronic Pain and Opioid Use Disorder: Protocol for a Randomized Clinical Trial of a Digital Cognitive Behavioral Treatment (e54342)
R MacLean, Brett Ankawi, Mary Driscoll, Melissa Gordon, Tami Frankforter, Charla Nich, Sara Szollosy, Jennifer Loya, Larissa Brito, Margaridha Ribeiro, Sara Edmond, William Becker, Steve Martino, Mehmet Sofuoglu, Alicia Heapy. . . . 1716

Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial (e55039)
Lydia Shrier, Madison O'Connell, Alessandra Torres, Laura Shone, Alexander Fiks, Julia Plumb, Jessica Maturo, Nicholas McCaskill, Donna Harris, Pamela Burke, Thatcher Felt, Marie Murphy, Lon Sherritt, Sion Harris. . . . 1740

eHealth-Enhanced Peer Navigation for Substance Use Treatment and HIV Prevention Service Linkage for Young Adults Surveilled by the Criminal Legal System: Protocol for a Pilot Randomized Trial Study (e54815)
Stephanie Creasy, Sheridan Sweet, Janet Myers, Martha Shumway, Marina Tolou-Shams, Nicole McCaffrey, Emily Dauria. . . . 1757

The Feasibility of Using the National PulsePoint Cardiopulmonary Resuscitation Responder Network to Facilitate Overdose Education and Naloxone Distribution: Protocol for a Randomized Controlled Trial (e57280)
Jon Agley, Cris Henderson, Dong-Chul Seo, Maria Parker, Lilian Golzarri-Arroyo, Stephanie Dickinson, David Tidd. . . . 1771

The Effects of an Educational Intervention About Front-of-Package Labeling on Food and Beverage Selection Among Children and Their Caregivers: Protocol for a Randomized Controlled Trial (e54783)
Diana Avila-Montiel, Jenny Vilchis-Gil, América Miranda-Lora, Lubia Velázquez-López, Miguel Klünder-Klünder. . . . 1785

Investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI): Protocol for a Randomized Controlled Trial (e54857)
Bilgin Osmanodja, Zeineb Sassi, Sascha Eickmann, Carla Hansen, Roland Roller, Aljoscha Burchardt, David Samhammer, Peter Dabrock, Sebastian Möller, Klemens Budde, Anne Herrmann. . . . 1792

Combined Motivational Interviewing and Ecological Momentary Intervention to Reduce Hazardous Alcohol Use Among Sexual Minority Cisgender Men and Transgender Individuals: Protocol for a Randomized Controlled Trial (e55166)
Carolyn Lauckner, Bryce Takenaka, Fidelis Sesenu, Jaime Brown, Sally Kirklewski, Erin Nicholson, Kimberly Haney, Reuben Adatorwovor, Donte Boyd, Keisa Fallin-Bennett, Arjee Restar, Trace Kershaw. . . . 1805

Smartphone App–Delivered Mindfulness-Based Intervention for Mild Traumatic Brain Injury in Adolescents: Protocol for a Feasibility Randomized Controlled Trial (e57226)
Andrée-Anne Ledoux, Roger Zemek, Molly Cairncross, Noah Silverberg, Veronik Sicard, Nicholas Barrowman, Gary Goldfield, Clare Gray, Ashley Harris, Natalia Jaworska, Nick Reed, Bechara Saab, Andra Smith, Lisa Walker. . . . 1822

Optimizing Outcomes in Psychotherapy for Anxiety Disorders Using Smartphone-Based and Passive Sensing Features: Protocol for a Randomized Controlled Trial (e42547)
Miriam Müller-Bardorff, Ava Schulz, Christina Paersch, Dominique Recher, Barbara Schlup, Erich Seifritz, Iris Kolassa, Tobias Kowatsch, Aaron Fisher, Isaac Galatzer-Levy, Birgit Kleim. . . . 1843

Mobile Phone–Based Confidential Social Network Referrals for HIV Testing (CONSORT): Protocol for a Randomized Controlled Trial (e55068)
Jan Ostermann, Bernard Njau, Marco van Zwetselaar, Thespina Yamanis, Leah McClimans, Rose Mwangi, Melkiory Beti, Amy Hobbie, Salomé-Joelle Gass, Tara Mtuy, Nathan Thielman. . . . 1852

Standard Versus Family-Based Screening, Brief Intervention, and Referral to Treatment for Adolescent Substance Use in Primary Care: Protocol for a Multisite Randomized Effectiveness Trial (e54486)
Aaron Hogue, Nicole Porter, Timothy Ozechowski, Sara Becker, Megan O'Grady, Molly Bobek, Monica Cerniglia, Kevin Ambrose, Alexandra MacLean, Scott Hadland, Hetty Cunningham, Sarah Bagley, Lon Sherritt, Maddie O'Connell, Lydia Shrier, Sion Harris. . . . 1866

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Assessing the Efficacy of the ARMOR Tool–Based Deprescribing Intervention for Fall Risk Reduction in Older Patients Taking Fall Risk–Increasing Drugs (DeFRID Trial): Protocol for a Randomized Controlled Trial (e55638)
Rekha Priyadarshini, Madhavi Eerike, Sakthivadivel Varatharajan, Gomathi Ramaswamy, Gerard Raj, Jerin Cherian, Priyadharsini Rajendran, Venugopalan Gunasekaran, Shailaja Rao, Venu Konda. . . . 1885

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Improving the Care of Severe, Open Fractures and Postoperative Infections of the Lower Extremities: Protocol for an Interdisciplinary Treatment Approach (e57820)
Steffen Rosslenbroich, Marion Laumann, Joachim Hasebrook, Sibyll Rodde, John Grosser, Wolfgang Greiner, Tobias Hirsch, Stefan Windrich, Michael Raschke. . . . 1981

Implementing and Evaluating a Mobile Phone–Supported and Family-Centered Rehabilitation Program for People With Stroke in Uganda (F@ce 2.0): Protocol for a Randomized Controlled Trial (e60955)
Gunilla Eriksson, Julius Kamwesiga, Uno Fors, Tonny Oyana, Lena von Koch, Charlotte Ytterberg, Susanne Guidetti. . . . 1997

The Effect of Effort During a Resistance Exercise Session on Glycemic Control in Individuals Living With Prediabetes or Type 2 Diabetes: Protocol for a Crossover Randomized Controlled Trial (e63598)
Marissa Ramirez, Maja Gebauer, Christine Mermier, Jonathan Little, Luotao Lin, Gabriel Palley, Yu Hsiao, Roberto Mota Alvidrez, Zach Mang, Fabiano Amorim, Valmor Tricoli, Flavio De Castro Magalhaes. . . . 2011

The Integrating Cultural Aspects Into Diabetes Education (INCLUDE) Study to Prevent Diabetes in Chinese Immigrants: Protocol for a Randomized Controlled Trial (e65455)
Lu Hu, Nelson F Lin, Yun Shi, Jiepin Cao, Mary Sevick, Huilin Li, Jeannette Beasley, Natalie Levy, Kosuke Tamura, Xinyi Xu, Yulin Jiang, Iris Ong, Ximin Yang, Yujie Bai, Liwen Su, Sze Chan, Stella Yi. . . . 2025

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Video Remote Sign Language Interpreting in Health Communication for Deaf People: Protocol for a Randomized Controlled Trial (e64590)
Minerva Rivas Velarde, Laura Izquierdo Martinez, Jyoti Dalal, Angela Martinez-R, Danna Cruz Reyes, Jess Cuculick, Alexie Vallejo-Silva, Jonathan Irreño-Sotomonte, Nora Groce. . . . 2036

Extended Reality Gaming for Exercise and Mindfulness Throughout Pediatric Cancer Rehabilitation: Protocol for a Randomized Controlled Trial (e64879)
Byron Lai, Kelli Chaviano, Joshua Richman, Mahmoud Ahmad, Ashley Wright, Raven Young, Drew Davis, James Rimmer, Avi Madan-Swain, Joseph Chewning. . . . 2044

Exploring Medical Career Choice to Better Inform Swiss Physician Workforce Planning: Protocol for a National Cohort Study (e53138)
Milena Abbiati, Mathieu Nendaz, Bernard Cerutti, Monika Brodmann Mäder, Giatgen Spinas, David Vicente Alvarez, Douglas Teodoro, Georges Savoldelli, Nadia Bajwa. . . . 2055

Participatory Development and Assessment of Audio-Delivered Interventions and Written Material and Their Impact on the Perception, Knowledge, and Attitudes Toward Leprosy in Nigeria: Protocol for a Cluster Randomized Controlled Trial (e53130)
Ngozi Murphy-Okpala, Tahir Dahiru, Anna van 't Noordende, Carolin Gunesch, Joseph Chukwu, Charles Nwafor, Suleiman Abdullahi, Chukwuma Anyaike, Ugochinyere Okereke, Anthony Meka, Chinwe Eze, Okechukwu Ezeakile, Ngozi Ekeke. . . . 2065

Effectiveness of a Nursing Educational Intervention in Adults to Promote Control Behaviors Against Dengue: Protocol for a Randomized Controlled Trial (e54286)
Yolima Llorente Pérez, Alba Rodríguez-Acelas, Rita Mattiello, Wilson Cañon-Montañez. . . . 2076

Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial (e55435)
Heena Akbar, Madison Contor, Winnie Niumata, Debra Anderson, Danielle Gallegos. . . . 2085

Inhibitory Control Training for Anxiety and Math Achievement in Primary School Children: Protocol for a Proof-of-Concept Study (e52929)
Elizabeth Edwards, Khanh Chu, Annemaree Carroll. . . . 2099

The Effectiveness of Brain Injury Family Intervention in Improving the Psychological Well-Being of Caregivers of Patients With Traumatic Brain Injury: Protocol for a Randomized Controlled Trial (e53692)
Siti Omar, Nor Zulkefly, Firdaus Mukhtar. . . . 2106

Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial (e56016)
Angela Starkweather, Wanli Xu, Katherine Gnall, Mariel Emrich, Camille Garnsey, Zachary Magin, Weizi Wu, Joseph Fetta, Erik Groessl, Crystal Park. . . . 2119

A Web-Based Physical Activity Promotion Intervention for Inactive Parent-Child Dyads: Protocol for a Randomized Controlled Trial (e55960)
Daniel Phipps, Weldon Green, Reetta Aho, Eeva Kettunen, Stuart Biddle, Kyra Hamilton, Arto Laukkanen, Kaisa Aunola, Derwin Chan, Nelli Hankonen, Mary Hassandra, Tommi Kärkkäinen, Virpi-Liisa Kykyri, Juho Polet, Ryan Rhodes, Montse Ruiz, Arja Sääkslahti, Jekaterina Schneider, Hanna-Mari Toivonen, Taru Lintunen, Martin Hagger, Keegan Knittle. . . . 2133

Equity-Centered Postdischarge Support for Medicaid-Insured People: Protocol for a Type 1 Hybrid Effectiveness-Implementation Stepped Wedge Cluster Randomized Controlled Trial (e54211)
J Brooks Carthon, Heather Brom, Marsha Grantham-Murrillo, Kathy Sliwinski, Aleigha Mason, Mindi Roeser, Donna Miles, Dianne Garcia, Jovan Bennett, Michael Harhay, Emilia Flores, Kelvin Amenyedor, Rebecca Clark. . . . 2145

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High-Flow Humidified Oxygen as an Early Intervention in Children With Acute Severe Asthma: Protocol for a Feasibility Randomized Controlled Trial (e54081)
Hector Rojas-Anaya, Akshat Kapur, Graham Roberts, Damian Roland, Atul Gupta, Michaela Lazner, Jane Bayreuther, John Pappachan, Christina Jones, Stephen Bremner, Fleur Cantle, Paul Seddon. . . . 2158

Enhancing Psychotherapy Outcomes by Encouraging Patients to Regularly Self-Monitor, Reflect on, and Share Their Affective Responses Toward Their Therapist: Protocol for a Randomized Controlled Trial (e55369)
Alberto Stefana, Eduard Vieta, Paolo Fusar-Poli, Eric Youngstrom. . . . 2176

Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain: Protocol for a Pilot Randomized Controlled Trial (e54406)
Akash Goel, Bhavya Kapoor, Hillary Chan, Karim Ladha, Joel Katz, Hance Clarke, Janneth Pazmino-Canizares, Zaaria Thomas, Kaylyssa Philip, Gabriella Mattina, Paul Ritvo. . . . 2185

Quantifying Bone and Skin Movement in the Residual Limb-Socket Interface of Individuals With Transtibial Limb Loss Using Dynamic Stereo X-Ray: Protocol for a Lower Limb Loss Cadaver and Clinical Study (e57329)
Jason Maikos, John Chomack, David Herlihy, David Paglia, Charlene Wetterstrand, J O'Connor, Michael Hyre, J Loan, Susan D'Andrea. . . . 2195

Social Transfers for Exclusive Breastfeeding (STEB) Intervention in Lao People's Democratic Republic: Protocol for a Randomized Controlled Trial (e54768)
Souliviengkham Sonephet, Sengchanh Kounnavong, Lucienne Zinsstag, Pascale Vonaesch, Somphou Sayasone, Latsamy Siengsounthone, Peter Odermatt, Günther Fink, Jordyn Wallenborn. . . . 2212

The Effect of Prebedtime Behaviors on Sleep Duration and Quality in Children: Protocol for a Randomized Crossover Trial (e63692)
Rosie Jackson, Chao Gu, Jillian Haszard, Kim Meredith-Jones, Barbara Galland, Justine Camp, Deirdre Brown, Rachael Taylor. . . . 2219

Effectiveness of Aerobic Training for Adverse Symptoms Related to Chemotherapy During Treatment: Protocol for a Randomized Controlled Trial With Cost-Effectiveness Assessment (e60828)
William Selles, Gisela Miyamoto, Elinaldo Santos, Cibelle Carmo, Giovanni Moura, Giovanna Santos, Giovanna Lopes, Diego Silva, Leticia Pereira, Adriana Lunardi. . . . 2230

Effectiveness of an mHealth App That Uses Financial Incentives and Gamification to Promote Health Behavior Change in Adolescents and Caregivers: Protocol for a Clinic-Based Randomized Controlled Trial (e63505)
Amy Braddock, Parijat Ghosh, Emma Montgomery, Crystal Lim, Jaya Ghosh, Nicole Henry, Mihail Popescu, Kimberly Kimchi, Congyu Guo, K Bosworth, Richelle Koopman. . . . 2239

Quantification of Urinary Exosomal Prostate-Specific Antigen for the Diagnosis of Prostate Cancer Using Clinical Laboratory–Based Techniques: Protocol for a Case-Control Study (e63551)
Guorong Li, Yannick Tholance, Nora Mallouk, Louis Waeckel, Pascale Flandrin, Bruno Bali, Lionel Badet, Pierre Cornillon. . . . 2250

Effect of Semaglutide on Physical Function, Body Composition, and Biomarkers of Aging in Older Adults With Overweight and Insulin Resistance: Protocol for an Open-Labeled Randomized Controlled Trial (e62667)
Tiffany Cortes, Libia Vasquez, Monica Serra, Ronna Robbins, Allison Stepanenko, Kevin Brown, Hannah Barrus, Annalisa Campos, Sara Espinoza, Nicolas Musi. . . . 2257

Education Program for Enhancing Health Care Students' Attitudes Toward People Living With Dementia: Protocol for a Single-Arm Pre-Post Study (e62654)
Dianis Sari, Haruna Kugai, Ayumi Igarashi, Manami Takaoka, Hiroshige Matsumoto, Haruno Suzuki, Jinyan Wu, Rizki Fitryasari, Ike Nasifah, Eka Has, Noriko Yamamoto-Mitani. . . . 2267

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Effectiveness of a Bullying Intervention (Be-Prox) in Norwegian Early Childhood and Education Care Centers: Protocol for a Cluster Randomized Controlled Trial (e60626)

Ingrid Kvestad, Frode Adolfsen, Renira Angeles, Oda Brandseth, Kyrre Breivik, Janne Evertsen, Irene Foer, Morten Haaland, Birgit Homola, Gro Hoseth, Josefine Jonsson, Egil Kjerstad, Henriette Kyrrestad, Monica Martinussen, Annelene Moberg, Karianne Moberg, Anita Skogstrand, Line Solberg, Merete Aasheim. 2276

Transitional Care Support for Medicaid-Insured Patients With Serious Mental Illness: Protocol for a Type I Hybrid Effectiveness-Implementation Stepped-Wedge Cluster Randomized Controlled Trial (e64575)

J Brooks Carthon, Heather Brom, Kelvin Amenyedor, Michael Harhay, Marsha Grantham-Murillo, Jacqueline Nikpour, Karen Lasater, Daniela Golinelli, Pamela Cacchione, Amanda Bettencourt. 2289

Collaborative Care to Improve Quality of Life for Anxiety and Depression in Posttraumatic Epilepsy (CoCarePTE): Protocol for a Randomized Hybrid Effectiveness-Implementation Trial (e59329)

Heidi Munger Clary, Beverly Snively, Christian Cagle, Richard Kennerly, James Kimball, Halley Alexander, Gretchen Brenes, Justin Moore, Robin Hurley. 2299

Community Versus Facility-Based Services to Improve the Screening of Active Hepatitis C Virus Infection in Cambodia: The ANRS 12384 CAM-C Cluster Randomized Controlled Trial—Protocol for a Mixed Methods Study (e63376)

Emilie Mosnier, Olivier Ségéral, Sansothy Neth, Luis Sagaon-Teyssier, Dyna Khuon, Chan Phoeung, Sovatha Mam, Chhingsrean Chhay, Kimeang Heang, Jean Duclos-Vallée, Vonthanak Saphonn. 2315

Respiratory Strength Training Versus Respiratory Relaxation Training in the Rehabilitation of Physical Impairment, Function, and Return to Participation After Stroke: Protocol for a Randomized Controlled Trial (e59749)

Dorian Rose, Gina Brunetti, Kathryn Cavka, J Hoisington, Hannah Snyder, Wei Xue, Barbara Smith. 2326

Frontal Pole Neuromodulation for Impulsivity and Suicidality in Veterans With Mild Traumatic Brain Injury and Common Co-Occurring Mental Health Conditions: Protocol for a Pilot Randomized Controlled Trial (e58206)

Alyssa Bernanke, Rebecca Hasley, Niki Sabetfakhri, Harriet de Wit, Bridget Smith, Lei Wang, Lisa Brenner, Colleen Hanlon, Noah Philip, Olusola Ajilore, Amy Herrold, Alexandra Aaronson. 2340

Adaptive Intervention to Prevent Respiratory Illness in Cerebral Palsy: Protocol for a Feasibility Pilot Randomized Controlled Trial (e49705)

Alyssa Fleischman, Carlos Lerner, Heidi Kloster, Paul Chung, Thomas Klitzner, Christopher Cushing, Danielle Gerber, Barbara Katz, Gemma Warner, Kristina Singh-Verdeflor, Roxana Delgado-Martinez, Lorena Porras-Javier, Siem Ia, Teresa Wagner, Mary Ehlenbach, Ryan Coller. . .
2 3 6 1

Feasibility, Acceptability, and Preliminary Effectiveness of a Combined Digital Platform and Community Health Worker Intervention for Patients With Heart Failure: Protocol for a Randomized Controlled Trial (e55687)

Jocelyn Carter, Natalia Swack, Eric Isselbacher, Karen Donelan, Anne Thorndike. 2376

Clinical Remote Monitoring of Individuals With Spinal Cord Injury at Risk for Pressure Injury Recurrence Using mHealth: Protocol for a Pilot, Pragmatic, Hybrid Implementation Trial (e51849)

Melissa Morrow, Lynne Hughes, Diane Collins, Tamara Vos-Draper. 2389

Evaluating the Feasibility, Acceptance, and Beneficial Effects of Online Occupational Therapy for Post–COVID-19 Condition: Protocol for a Randomized Controlled Trial (ErgoLoCo Study) (e50230)

Christina Müllenmeister, Andrea Stoelting, Dominik Schröder, Tim Schmachtenberg, Simon Ritter, Iman El-Sayed, Sandra Steffens, Frank Klawonn, Sandra Klawitter, Stefanie Homann, Marie Mikuteit, Christoph Berg, Georg Behrens, Eva Hummers, Aisha Cook, Frank Müller, Alexandra Dopfer-Jablonka, Christine Happle. 2406

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Feasibility and Preliminary Efficacy of α–Calcium Sulfate Hemihydrate in Socket Preservation: Protocol for a Pilot Randomized Controlled Trial (e49922)
Muhammad Ruslin, Nurlindah Hamrun, Andi Tajrin, Andi Yusuf, Rifaat Nurrahma, Diandra Natsir-Kalla, Yossy Ariestiana, Mukhtar Nur Anam, Chung-Ming Liu, Keng-Liang Ou. . . . 2415

Physical Activity Mobile App (CareFit) for Informal Carers of People With Dementia: Protocol for a Feasibility and Adaptation Study (e53727)
Kieren Egan, Bradley Macdonald, William Hodgson, Alison Kirk, Barbara Fawcett, Mark Dunlop, Roma Maguire, Greg Flynn, Joshua Stott, Gill Windle. . . . 2425

Brief Mobile App–Based Mindfulness Intervention for Indonesian Senior High School Teachers: Protocol for a Pilot Randomized Controlled Trial (e56693)
Gede Dantes, Nice Asril, Andrian Liem, Ni Suwastini, Shian-Ling Keng, Ni Mahayanti. . . . 2434

Efficacy and Safety of the Natural Killer T Cell–Stimulatory Glycolipid OCH-NCNP1 for Patients With Relapsing Multiple Sclerosis: Protocol for a Randomized Placebo-Controlled Clinical Trial (e46709)
Tomoko Okamoto, Takami Ishizuka, Reiko Shimizu, Yasuko Asahina, Harumasa Nakamura, Yuko Shimizu, Yoichiro Nishida, Takanori Yokota, Youwei Lin, Wakiro Sato, Takashi Yamamura. . . . 2446

Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep in Individuals With Insomnia Symptoms: Protocol for a Double-Blind Randomized Controlled Trial (e51212)
Lindsey Hildebrand, Alisa Huskey, Natalie Dailey, Samantha Jankowski, Kymberly Henderson-Arredondo, Christopher Trapani, Salma Patel, Allison Chen, Ying-Hui Chou, William Killgore. . . . 2455

Psychostimulant Medications for Physical Function and Spasticity in Children With Cerebral Palsy: Protocol for a Randomized Controlled Trial (e53728)
Mansour Alotaibi, Anwar Almutairi, Saleh Alhirsan, Afrah Alkazemi, Maha Alharbi, Naif Alrashdi, Ahmad Taqi, Bibi Alamiri, Laura Vogtle, Mohammed Alqahtani. . . . 2468

Community Health Workers as Mental Health Paraprofessionals: Protocol for a Mixed-Methods Pilot Feasibility Study (e57343)
Sally Moyce, Cassidy Crawford. . . . 2493

Family-Centered Treatment Program for Problematic Gaming and Excessive Screen Use in a Clinical Child and Youth Population (FAME): Protocol for a Feasibility Pilot Mixed Method Study (e56387)
Marie Werner, Sabina Kapetanovic, Emma Claesdotter-Knutsson. . . . 2500

Effects of Electronic Nicotine Delivery Systems Substitution on Body Weight Status: Protocol for a Systematic Review and Meta-Analysis (e56324)
Giusy La Rosa, Maria Qureshi, Lucia Frittitta, Erika Anastasi, Riccardo Polosa. . . . 2510

Best Practices and Recommendations for Research Using Virtual Real-Time Data Collection: Protocol for Virtual Data Collection Studies (e53790)
Jasmin Sanchez, Amanda Trofholz, Jerica Berge. . . . 2516

Patterns of Use of e-Cigarettes and Their Respiratory Effects: Protocol for an Umbrella Review (e60325)
Giusy La Rosa, Riccardo Polosa, Renée O'Leary. . . . 2524

Epidemiology of Syphilis in Pregnancy and Congenital Syphilis in Brazil and the Risk or Associated Factors: Protocol for a Systematic Review (e50702)
Yago Pinheiro, Janmilli Dantas, Jose Holanda, Ankilma Feitosa, Richardson Augusto Rosendo da Silva. . . . 2533

Blockchain-Based Dynamic Consent and its Applications for Patient-Centric Research and Health Information Sharing: Protocol for an Integrative Review (e50339)
Wendy Charles, Mark van der Waal, Joost Flach, Arno Bisschop, Raymond van der Waal, Hadil Es-Sbai, Christopher McLeod. . . . 2540

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The Effectiveness of Digital Health Lifestyle Interventions on People With Prediabetes: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression (e50340)
Tanja Holm, Flemming Udsen, Kristine Færch, Morten Jensen, Bernt von Scholten, Ole Hejlesen, Stine Hangaard. 2550

Implementation of Chatbot Technology in Health Care: Protocol for a Bibliometric Analysis (e54349)
Zhao Ni, Mary Peng, Vimala Balakrishnan, Vincent Tee, Iskandar Azwa, Rumana Saifi, LaRon Nelson, David Vlahov, Frederick Altice. 2558

Nutritional Interventions for the Prevention of Cognitive Decline in Patients With Mild Cognitive Impairment and Alzheimer Disease: Protocol for a Network Meta-Analysis of Randomized Controlled Trials (e47196)
Qian He, Kevin Wu, Adam Bennett, Jia Zhang, Kei Chan. 2565

The Effectiveness of a Telenutrition Intervention to Improve Dietary Behavior and Physical Activity Among Adolescents With Obesity: Protocol for a Systematic Review (e53282)
Muhammad Ansari, Nurul Kodriati, Ariani Pertiwi, Fatwa Dewi. 2573

Patients' Experiences of Digital Health Interventions for the Self-Management of Chronic Pain: Protocol for a Systematic Review and Thematic Synthesis (e52469)
Ashleigh Main, Haruno McCartney, Maryam Ibrar, Harleen Rai, Fiona Muirhead, Alexandra Mavroeidi, Roma Maguire. 2580

AI as a Medical Device for Ophthalmic Imaging in Europe, Australia, and the United States: Protocol for a Systematic Scoping Review of Regulated Devices (e52602)
Ariel Ong, Henry Hogg, Aditya Kale, Priyal Taribagil, Ashley Kras, Eliot Dow, Trystan Macdonald, Xiaoxuan Liu, Pearse Keane, Alastair Denniston. 2588

Factors Underlying Vaccine Hesitancy and Their Mitigations in Saudi Arabia: Protocol for a Systematic Review (e54680)
Mohammed Kanan, Samar Abdulrahman, Abdulaziz Alshehri, Renad AlSuhaibani, Nawaf Alotaibi, Azhar Alsaleh, Bushra Nasser, Rana Baowaydhan, Ibrahim Alredaini, Taif Khalid, Fatima Almukhtar, Nourah Altoaimi, Almaha Alhneshel, Shouq Alanazi, Shahad Algmaizi. 2595

Applications of Artificial Intelligence in Emergency Departments to Improve Wait Times: Protocol for an Integrative Living Review (e52612)
Bahareh Ahmadzadeh, Christopher Patey, Oliver Hurley, John Knight, Paul Norman, Alison Farrell, Stephen Czarnuch, Shabnam Asghari. . .
2 6 0 4

Effectiveness and Experiences of Quality Improvement Interventions in Older Adult Care: Protocol for a Mixed Methods Systematic Review (e56346)
Md Jabin, Ray Samuriwo, Marcus Chilaka, Emilia Yaroson. 2612

Impact of Digital Interventions on the Treatment Burden of Patients With Chronic Conditions: Protocol for a Systematic Review (e54833)
Manria Polus, Pantea Keikhosrokiani, Olli Korhonen, Woubshet Behutiye, Minna Isomursu. 2620

Family Involvement in the Care of Hospitalized Older Adults: Protocol for a Qualitative Evidence Synthesis (e53255)
Judith Vick, Blair Golden, Sarah Cantrell, Melissa Harris-Gersten, Mollie Selmanoff, Susan Hastings, Tolu Oyesanya, Karen Goldstein, Courtney Van Houtven. 2626

Human-Centered Design and Benefit Realization Management in Digital Health Care Solution Development: Protocol for a Systematic Review (e56125)
Kaisa Kauppinen, Pantea Keikhosrokiani, Sehrish Khan. 2636

Preconception Care Interventions for Adolescents and Young Adults to Prevent Adverse Maternal and Child Health Outcomes: Protocol for an Evidence Gap Map (e56052)
Zahra Padhani, Gizachew Tessema, Jodie Avery, Komal Rahim, Jacqueline Boyle, Salima Meherali, Rehana Salam, Zohra Lassi. 2643

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Evaluation of Artificial Intelligence Algorithms for Diabetic Retinopathy Detection: Protocol for a Systematic Review and Meta-Analysis (e57292)
Jaime Sesgundo III, David Maeng, Jumelle Tukay, Maria Ascano, Justine Suba-Cohen, Virginia Sampang. 2651

The Experience of Cancer-Related Cognitive Impairment Across Common Cancers: Protocol for a Qualitative Systematic Review (e56888)
Maryam Ibrar, Harleen Rai, Ashleigh Main, Haruno McCartney, Roma Maguire, Mario Rodriguez. 2658

Incidence, Risk, and Clinical Course of New-Onset Diabetes in Long COVID: Protocol for a Systematic Review and Meta-Analysis of Cohort Studies (e54853)
Ananya Talanki, Neha Bajaj, Twinkle Trehan, Sathish Thirunavukkarasu. 2664

Multivisceral Oncological Resections Involving the Pancreas: Protocol for a Systematic Review and Meta-Analysis (e54089)
Melina Neuhaus, Juliane Friedrichs, Maurizio Grilli, Jörg Ukkat, Johannes Klose, Ulrich Ronellenfitsch, Jörg Kleeff, Artur Rebelo. 2673

Efficacy and Safety of Remimazolam Versus Etomidate for Induction of General Anesthesia: Protocol for a Systematic Review and Meta-Analysis (e55948)
Li Zhao, Yiping Guo, Xuelei Zhou, Wei Mao, Linlin Chen, Ying Xie, Linji Li. 2681

The Relationship Between Physical Activity and Mental Health Among Individuals With Spinal Cord Injury: Protocol for a Scoping Review (e56081)
Winslet Ong, Noor Omar, Asfarina Zanudin, Muhamad Alias, Lim Hui Wen, Angel Thang Xue Ee, Nor Mohd Nordin, Haidzir Manaf, Basri Husin, Mahadir Ahmad, Hafifi Hisham. 2687

Effects of Lifestyle Interventions on Cardiovascular Disease Risk and Risk Factors Among Individuals at High Risk for Type 2 Diabetes: Protocol for a Systematic Review and Meta-Analysis of Randomized Controlled Trials (e53517)
Getu Demissie, Josephine Birungi, Tilahun Haregu, Sathish Thirunavukkarasu, Brian Oldenburg. 2695

Experiences of Governments and Public Health Agencies Regarding Crisis Communication During the COVID-19 Pandemic in the Digital Age: Protocol for a Systematic Review of Qualitative Studies (e58040)
Tsuyoshi Okuhara, Marina Terada, Hiroko Okada, Takahiro Kiuchi. 2703

Detecting Algorithmic Errors and Patient Harms for AI-Enabled Medical Devices in Randomized Controlled Trials: Protocol for a Systematic Review (e51614)
Aditya Kale, Henry Hogg, Russell Pearson, Ben Glocker, Su Golder, April Coombe, Justin Waring, Xiaoxuan Liu, David Moore, Alastair Denniston. 2710

AI as a Medical Device Adverse Event Reporting in Regulatory Databases: Protocol for a Systematic Review (e48156)
Aditya Kale, Riya Dattani, Ashley Tabansi, Henry Hogg, Russell Pearson, Ben Glocker, Su Golder, Justin Waring, Xiaoxuan Liu, David Moore, Alastair Denniston. 2721

Estimating the Global and Regional Burden of Streptococcus pneumoniae Meningitis in Children: Protocol for a Systematic Review and Meta-Analysis (e50678)
Jay Park, Jakov Tiefenbach, Mohammed Anwar, Sandhya Narayanan, Beatrice Ope, Selene Bin Han, Boni Ale, Davies Adeloye, Igor Rudan.
2 7 3 0

Effectiveness of Mobile App Interventions to Improve Periodontal Health: Protocol for a Systematic Review and Meta-Analysis (e50479)
Reem Musa, Dalia Elamin, Robert Barrie, Faheema Kimmie-Dhansay. 2739

The Effectiveness of Medical Adherence Mobile Health Solutions for Individuals With Epilepsy: Protocol for a Systematic Review (e55123)
Pantea Keikhosrokiani, Manria Polus, Sharon Guardado Medina, Minna Isomursu. 2747

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Engagement With Conversational Agent–Enabled Interventions in Cardiometabolic Disease Management: Protocol for a Systematic Review (e52973)
Nick Kashyap, Ann Sebastian, Chris Lynch, Paul Jansons, Ralph Maddison, Tilman Dingler, Brian Oldenburg. 2753

The Effectiveness of Collaborative Care Interventions for the Management of Patients With Multimorbidity: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression Analysis (e58296)
Anne-Maj Knudsen, Ann-Cathrine Dalgård Dunvald, Stine Hangaard, Ole Hejlesen, Thomas Kronborg. 2762

Training of Community Health Workers in Diabetes Lead to Improved Outcomes for Diabetes Screening and Management in Low- and Middle-Income Countries: Protocol for a Systematic Review (e57313)
Anirudh Gudlavalleti, Giridhara Babu, Sureshkumar Kamalakannan, G Murthy, Nicolaas Schaper, Onno van Schayck. 2771

University Food Environment Assessment Methods and Their Implications: Protocol for a Systematic Review (e54955)
Alicia Dahl, Lilian Ademu, Stacy Fandetti, Ryan Harris. 2779

Electroacupuncture and Transcutaneous Electrical Acupoint Stimulation for Perioperative Neurocognitive Disorder in Older Patients Undergoing Cardiac Surgery: Protocol for Systematic Review and Meta-Analysis (e55996)
Yanbin Peng, Xuqiang Wei, Linxi Sun, Ke Wang, Jia Zhou. 2789

Impact of Biological Sex on Emotional Perception Among Adults With Schizophrenia Spectrum Disorders: Protocol for a Systematic Review (e56977)
Gabrielle Ritchie, Harriet Nwachukwu, Stephen Parker, Frances Dark. 2802

Supporting Carers: Study Protocol of a Meta-Review of Psychosocial Interventions for Carers of People With Cancer (e56403)
Brona Nic Giolla Easpaig, Bronwyn Newman, Judith Johnson, Rebekah Laidsaar-Powell, Ursula Sansom-Daly, Lucy Jones, Lukas Hofstätter, Eden Robertson, Stephen Mears, Kabir Sattarshetty, Reema Harrison. 2810

Metagenomics in the Diagnosis of Pneumonia: Protocol for a Systematic Review (e57334)
Samuel Quarton, Alana Livesey, Charlotte Jeff, Christopher Hatton, Aaron Scott, Dhruv Parekh, David Thickett, Alan McNally, Elizabeth Sapey.
2 8 1 7

Effect of Addition of Metal Oxide Nanoparticles on the Strength of Heat-Cured Denture Base Resins: Protocol for Systematic Review and Meta-Analysis of In Vitro Studies (e59999)
Pragati Kaurani, Amit Hindocha, Amit Porwal, Abhijit Tambe, Carrie Price, Vidhani Goel, Henry Krasner, Jagdish Khubchandani, Kavita Batra.
2 8 2 4

Psychoeducational Burnout Intervention for Nurses: Protocol for a Systematic Review (e58692)
Ili Abdullah Sharin, Norehan Jinah, Pangie Bakit, Izzuan Adnan, Nor Zakaria, Shazwani Mohmad, Siti Ahmad Subki, Nursyahda Zakaria, Kun Lee. 2834

Racial and Ethnic Differences in Traumatic Brain Injury Outcomes From 2009 to 2023: Protocol for a Systematic Review (e58763)
Monique Pappadis, Kelli Talley, Patricia Garcia, Caitlin Aguirre, Chinedu Onwudebe, Michelle Smith, Anthony Lequerica. 2846

A Comparison of Conventional Root Canal Sealers With Ones That Use Green Synthesized Nanoparticles for Antimicrobial Activity: Protocol for a Systematic Review (e51351)
Abubaker Mohamed, Enas Ismail, Razia Adam. 2853

Auricular Therapy to Control Pain in Women With Breast Cancer: Protocol for Systematic Review and Meta-Analysis (e55792)
Ludmila Ruela, Caroline Moura, Bianca Shieu, Yu-Min Cho, Chao Yeh, Franklin Pimentel, Juliana Stefanello. 2863

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Effects of Injury Registry Data on Policy Making, Hospitalizations, and Mortality: Protocol for a Systematic Review and Meta-Analysis (e55029)
Ana Medeiros-de-Souza, Luana Lopes, Bruno de Oliveira, Edna Rother, Lucas Correia. . . . 2870

Effectiveness of Self-Management Programs Among Athletes With Patellofemoral Pain Syndrome: Protocol for a Systematic Review (e58340)
Ameen Masoudi, Nomzamo Chemane, Ushotanefe Useh, Bashir Bello, Nontembiso Magida. . . . 2877

Effectiveness of Computer-Based Psychoeducational Self-Help Platforms for Eating Disorders (With or Without an Associated App): Protocol for a Systematic Review (e60165)
Alessandra Gentile, Yosua Kristian, Erica Cini. . . . 2883

Efficacy of Electroacupuncture in the Treatment of Mild to Moderate Female Stress Urinary Incontinence: Protocol for a Systematic Review and Network Meta-Analysis (e55870)
JiaNi Shi, Peiqi Li, Yifan Wu, Jiawei Li, Yuchen Zhang, Bin Xiao. . . . 2892

Accuracy Standards of Wearable Technologies for Assessment of Soccer Kicking: Protocol for a Systematic Literature Review (e57433)
Luiz Palucci Vieira, Filipe Clemente, Felipe Chang Marquez, Walter Rea Olivares, Kelly Vargas Villafuerte, Felipe Carpes. . . . 2901

Clinical and Biochemical Outcomes in Transgender Individuals Undergoing Hormone Therapy: Protocol for a Systematic Review (e57931)
Emily Sattora, Karen Teelin, Christopher Prendergast, Abigail Smith, James Evans, Aamer Imdad. . . . 2911

Influence of Psychological Stress on the Response to Periodontal Treatment: Protocol for a Systematic Review (e56765)
Kelly Vargas Villafuerte, Luiz Palucci Vieira, Karina Oliveira Santos. . . . 2919

Mental Health Monitoring for Young People Through Mood Apps: Protocol for a Scoping Review and Systematic Search in App Stores (e56400)
Selina Boege, Madison Milne-Ives, Ananya Ananthakrishnan, Cen Cong, Aditya Sharma, David Anderson, Edward Meinert. . . . 2928

Effects of Interprofessional Education on Readiness for Interprofessional Learning in Rehabilitation Science Students From Professional Health Care Programs: Protocol for a Systematic Review (e60830)
Eric Dixon, Jayden Pannu, Kabir Dhaliwal, Rachel Cheng, Gurpal Deol, Sophie Frangos, Emma Tawil, Ana Oliveira, Sarah Wojkowski, Shirley Quach. . . . 2936

Using Artificial Intelligence to Detect Risk of Family Violence: Protocol for a Systematic Review and Meta-Analysis (e54966)
Kathleen de Boer, Jessica Mackelprang, Maja Nedeljkovic, Denny Meyer, Ravi Iyer. . . . 2944

The Relationship Between Self-Compassion and Resilience in the General Population: Protocol for a Systematic Review and Meta-Analysis (e60154)
Xinyi Li, Melina Malli, Theodore Cosco, Guangyu Zhou. . . . 2952

Global and Regional Prevalence of Domestic Violence During the COVID-19 Pandemic and Its Determinants: Protocol for a Systematic Review and Meta-Analysis (e60963)
Razieh Bidhendi-Yarandi, Akbar Biglarian, Farhad Nosrati Nejad, Payam Roshanfekr, Samira Behboudi-Gandevani. . . . 2962

Barriers and Facilitators of International Health Care Students' Well-Being in Higher Education: Protocol for a Systematic Integrative Review (e59927)
Yao Xie, Kayode Fadahunsi, Paul Flynn, Simon Taylor-Robinson, Joseph Gallagher, Walter Cullen, John O'Donoghue. . . . 2969

XSL•FO
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Connecting Actors With the Introduction of Mobile Technology in Health Care Practice Placements (4D Project): Protocol for a Mixed Methods Study (e53284)
Carlos Martínez-Gaitero, Sebastian Dennerlein, Beata Dobrowolska, Angela Fessl, Daniel Moreno-Martínez, Stephanie Herbstreit, Gilbert Peffer, Esther Cabrera, 4D Project Consortium. . . . 2977

Digital Knowledge Translation Tools for Disseminating Sexual and Reproductive Health Information to Adolescents: Protocol for an Evidence Gap Map Review (e55081)
Salima Meherali, Soumyadeep Bhaumik, Sobia Idrees, Megan Kennedy, Zohra Lassi. . . . 2989

Identifying Person-Specific Drivers of Depression in Adolescents: Protocol for a Smartphone-Based Ecological Momentary Assessment and Passive Sensing Study (e43931)
Mei Ng, Jennifer Frederick, Aaron Fisher, Nicholas Allen, Jeremy Pettit, Dana McMakin. . . . 2998

A Digital Communication Intervention to Support Older Adults and Their Care Partners Transitioning Home After Major Surgery: Protocol for a Qualitative Research Study (e59067)
Brian Campos, Emily Cummins, Yves Sonnay, Mary Brindle, Christy Cauley. . . . 3011

Toward a Clinical Decision Support System for Monitoring Therapeutic Antituberculosis Medical Drugs in Tanzania (Project TuberXpert): Protocol for an Algorithm' Development and Implementation (e58720)
Yann Thoma, Annie Cathignol, Yuan Pétermann, Margaretha Sariko, Bibie Said, Chantal Csajka, Monia Guidi, Stellah Mpagama. . . . 3032

The Impact of the Ecosystem on Health Literacy Among Rural Communities in Protected Areas: Protocol for a Mixed Methods Study (e51851)
Nor Abd Kadir, Amirah Azzeri, Hafiz Jaafar, Mohd Mohd Noor, Zurina Kefeli. . . . 3043

Nonspecific Effects of the Bacillus Calmette-Guérin Vaccine in Portuguese Children Under 5 Years of Age: Protocol for a Population-Based Historical Birth Cohort Study (e55332)
Ines Fronteira, Matilde Pacheco, Frederik Schaltz-Buchholzer, Paulo Ferrinho. . . . 3063

Linking Dementia Pathology and Alteration in Brain Activation to Complex Daily Functional Decline During the Preclinical Dementia Stages: Protocol for a Prospective Observational Cohort Study (e56726)
Pierfilippo De Sanctis, Jeannette Mahoney, Johanna Wagner, Helena Blumen, Wenzhu Mowrey, Emmeline Ayers, Claudia Schneider, Natasha Orellana, Sophie Molholm, Joe Verghese. . . . 3073

Communication and Contextual Factors in Robotic-Assisted Surgical Teams: Protocol for Developing a Taxonomy (e54910)
Kyi Nyein, Claire Condron. . . . 3090

Identifying Interventions to Improve Diagnostic Safety in Emergency Departments: Protocol for a Participatory Design Study (e55357)
Woosuk Seo, Sun Park, Zhan Zhang, Hardeep Singh, Kalyan Pasupathy, Prashant Mahajan. . . . 3097

Rehabilitation at Home With the Development of a Sustainable Model Placing the Person's Needs and Environment at Heart: Protocol for a Multimethod Project (e56996)
Marie Elf, Lizette Norin, Louise Meijering, Hélène Pessah-Rasmussen, Riitta Suhonen, Magnus Zingmark, Maya Kylén. . . . 3118

Developing Evidence to Support Policy: Protocol for the StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) (e59830)
Mary Pugh, Jolie Haun, P White, Gerald Cochran, April Mohanty, Lisa McAndrew, Adam Gordon, Richard Nelson, Megan Vanneman, Diana Naranjo, Rachel Benzinger, Audrey Jones, Jacob Kean, Susan Zickmund, Angela Fagerlin. . . . 3128

XSL•FO
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Applying the Multiphase Optimization Strategy for the Development of a Culturally Tailored Resilience-Building Intervention to Facilitate Advance Care Planning Discussions for Chinese Americans: Protocol for a Survey and Qualitative Study (e59343)
Li-Ting Longcoy, Chien-Ching Li, Chun-Yi Tai, Ardith Doorenbos. 3143

Personalized Deep Learning for Substance Use in Hawaii: Protocol for a Passive Sensing and Ecological Momentary Assessment Study (e46493)
Yinan Sun, Ali Kargarandehkordi, Christopher Slade, Aditi Jaiswal, Gerald Busch, Anthony Guerrero, Kristina Phillips, Peter Washington. . . .
3 1 5 2

Digitally Diagnosing Multiple Developmental Delays Using Crowdsourcing Fused With Machine Learning: Protocol for a Human-in-the-Loop Machine Learning Study (e52205)
Aditi Jaiswal, Ruben Kruiper, Abdur Rasool, Aayush Nandkeolyar, Dennis Wall, Peter Washington. 3166

Telehealth-Delivered Program and Accompanying Patients to Enhance the Clinical Condition of Patients Throughout a Liver Transplant: Protocol for a Mixed Methods Study (e54440)
Marie-Pascale Pomey, Enora Le Roux, Nathalie Nadon, Jessie Perron, Angèle Barry, Chantal Bémeur, Thomas Poder, Fernand Duford, Louise Laviolette, Johanne Tétrault-Lassonde, Cécile Vialaron, Manuel Escalona, Louise Normandin, Geneviève Huard, Catherine Girardin, Christopher Rose, Kathy Malas, Denis Ouellet, Catherine Vincent. 3182

Combating Fraudulent Participation in Urban American Indian and Alaska Native Virtual Health Research: Protocol for Increasing Data Integrity in Online Research (PRIOR) (e52281)
Nicole Reed, Sheana Bull, Umit Shrestha, Michelle Sarche, Carol Kaufman. 3198

Recovery and Renewal of Co-Design Approaches in Health: Protocol for a Realist Synthesis (e58318)
Maryam Mallakin, Joe Langley, Gillian Harvey, Sarah Walker, Caylee Raber, Nadia Beyzaei, Luz Paczka Giorgi, Paul Holyoke, Kate Sellen. . .
3 2 0 8

Integrating Social Determinants of Health in Machine Learning–Driven Decision Support for Diabetes Case Management: Protocol for a Sequential Mixed Methods Study (e56049)
Seung-Yup Lee, Leslie Hayes, Bunyamin Ozaydin, Steven Howard, Alison Garretson, Heather Bradley, Andrew Land, Erin DeLaney, Amy Pritchett, Amanda Furr, Ashleigh Allgood, Matthew Wyatt, Allyson Hall, Jane Banaszak-Holl. 3215

Design of a Health Education Program to Manage Chronic Neck Pain: Protocol for a Development Study (e56632)
Milagros Pérez-Muñoz, Isabel Rodríguez-Costa, Gerard Lebrijo-Pérez, Daniel Pecos-Martín, Tomás Gallego-Izquierdo, Yolanda Pérez-Martín.
3 2 2 8

Establishing the Foundations of Emotional Intelligence in Care Companion Robots to Mitigate Agitation Among High-Risk Patients With Dementia: Protocol for an Empathetic Patient-Robot Interaction Study (e55761)
Adeline Nyamathi, Nikil Dutt, Jung-Ah Lee, Amir Rahmani, Mahkameh Rasouli, Donna Krogh, Erik Krogh, David Sultzer, Humayun Rashid, Hamza Liaqat, Riyam Jawad, Farhan Azhar, Ali Ahmad, Bilal Qamar, Taha Bhatti, Chet Khay, Jocelyn Ludlow, Lisa Gibbs, Julie Rousseau, Mahyar Abbasian, Yutong Song, Cheonkam Jeong, Sabine Brunswicker. 3239

Effects of Combined Visual-Motor Response Training on Cognitive Function and Brain Plasticity Mechanisms in Various Populations: Protocol for a Single-Center, Open-Label, Controlled Clinical Trial (e56424)
Wenlong Yu, Jiamin Gao, Ping Zhu. 3258

Combating Antimicrobial Resistance Through a Data-Driven Approach to Optimize Antibiotic Use and Improve Patient Outcomes: Protocol for a Mixed Methods Study (e58116)
Jonathan Mayito, Conrad Tumwine, Ronald Galiwango, Elly Nuwamanya, Suzan Nakasendwa, Mackline Hope, Reuben Kiggundu, Dathan Byonanebye, Flavia Dhikusooka, Vivian Twemanye, Andrew Kambugu, Francis Kakooza. 3267

Using a Device-Free Wi-Fi Sensing System to Assess Daily Activities and Mobility in Low-Income Older Adults: Protocol for a Feasibility Study (e53447)
Jane Chung, Ingrid Pretzer-Aboff, Pamela Parsons, Katherine Falls, Eyuphan Bulut. 3279

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Development of a Mobile App for Occupational Stress Screening Among Female Workers: Protocol for an Exploratory Sequential Design Study (e55874)
Dini Widianti, Zwasta Mahardhika, Robiana Modjo. . . . 3293

N-of-1 Trials of Antimicrobial Stewardship Interventions to Optimize Antibiotic Prescribing for Upper Respiratory Tract Infection in Emergency Departments: Protocol for a Quasi-Experimental Study (e50417)
Hersh Attal, Zhilian Huang, Win Kuan, Yanyi Weng, Hann Tan, Eillyne Seow, Li Peng, Hoon Lim, Angela Chow. . . . 3301

Assessment of the Feasibility of Objective Parameters as Primary End Points for Patients Affected by Knee Osteoarthritis: Protocol for a Pilot, Open Noncontrolled Trial (:SMILE:) (e13642)
Dumitru Dogaru, Serban Rosu, Dionisio Barattini, Simone Guadagna, Luca Barattini, Bogdan Andor. . . . 3319

School Violence Exposure as an Adverse Childhood Experience: Protocol for a Nationwide Study of Secondary Public Schools (e56249)
Sonali Rajan, Navjot Buttar, Zahra Ladhani, Jennifer Caruso, John Allegrante, Charles Branas. . . . 3333

Feuerstein Instrumental Enrichment Program for People With Schizophrenia After the First Episode of Psychosis: Protocol for an Open-Label Intervention Study (e57031)
Ana Fonseca, July Gomes, Rafael Novaes, Cíntia Dias, Maria Rodrigues, Ary Gadelha, Cristiano Noto. . . . 3346

Rethinking Health Systems Responsiveness in Low- and Middle-Income Countries: Validation Study (e59836)
Meesha Iqbal, Cecilia Cazaban, Robert Morgan, Cici Bauer, Sameen Siddiqi. . . . 3356

Advancing Digital Education Technologies by Empowering Nurses With Point-of-Care Ultrasound: Protocol for a Mixed Methods Study (e58030)
Fernanda Gimenes, Angelita Stabile, Rodrigo Bernardes, Vinicius Santos, Mayra Menegueti, Patricia do Prado, Mauricio Ribeiro, Flavia Camerini, Soraia Rabeh. . . . 3368

Differences in Messenger RNA Expression of Fibulin-1, Elastin, Matrix Metalloproteinase-1, Basic Fibroblast Growth Factor, and α-Smooth Muscle Actin Between the Ventral and Dorsal Tunica Dartos in Patients With Hypospadias and Chordee: Protocol for a Prospective Cohort Study (e52282)
Joko Pitoyo, Alvarino, Eryati Darwin, Yanwirasti. . . . 3380

A Real-Life Laboratory Setting for Clinical Practice, Education, and Research in Family Systems Care: Protocol for a Transformational Action Research Study (e53090)
Evelyn Huber, Erika Harju, Elisabeth Stark, André Fringer, Barbara Preusse-Bleuler. . . . 3387

Tracking Implementation Outcomes of an Intensive Case Management Program for HIV: Protocol for a Mixed Methods Study (e57452)
Meron Mengistu, Kris Tom, Liben Gebremikael, Notisha Massaquoi, Obidimma Ezezika. . . . 3399

Health and Well-Being in the Context of Health-Promoting University Initiatives: Protocol for a Mixed Methods Needs Assessment Study at Qatar University (e58860)
Ghadir Al-Jayyousi, Diana Alsayed Hassan, Hanan Abdul Rahim, Manar E Abdel-Rahman, Isabel Ferreira, Banan Mukhalalati, Lily O'Hara, Hanan Khalil, Reema Tayyem, Elham S Abu Alhaija, Randa Abidia, Monica Zolezzi, Alla El-Awaisi, Noor Al-Wattary, Rafif Mahmood Al Saady, Maguy Saffouh El Hajj, Mujahed Shraim, Arpi K Abouhanian, Hatoun Saeb, Mustapha Mohammed, QU Health Youth Wellbeing Research Network Group. . . . 3407

Exploring Shared Implementation Leadership of Point of Care Nursing Leadership Teams on Inpatient Hospital Units: Protocol for a Collective Case Study (e54681)
Sonia Castiglione, Mélanie Lavoie-Tremblay, Kelley Kilpatrick, Wendy Gifford, Sonia Semenic. . . . 3423

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Innovative Design and Development of Personalized Ankle-Foot Orthoses for Survivors of Stroke With Equinovarus Foot: Protocol for a Feasibility and Comparative Trial (e52365)
Rui Silva, Pedro Morouço, Jorge Lains, Paula Amorim, Nuno Alves, António Veloso. 3436

Experimentally Induced Reductions in Alcohol Consumption and Brain, Cognitive, and Clinical Outcomes in Older Persons With and Those Without HIV Infection (30-Day Challenge Study): Protocol for a Nonrandomized Clinical Trial (e53684)
Robert Cook, Veronica Richards, Joseph Gullett, Brenda Lerner, Zhi Zhou, Eric Porges, Yan Wang, Christopher Kahler, Nancy Barnett, Zhigang Li, Suresh Pallikkuth, Emmanuel Thomas, Allan Rodriguez, Kendall Bryant, Smita Ghare, Shirish Barve, Varan Govind, Jessy Dévieux, Ronald Cohen, The 30-Day Challenge Research Team. 3443

Personalized Management of Fatigue in Individuals With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Using a Smart Digital mHealth Solution: Protocol for a Participatory Design Approach (e50157)
Enrique Dorronzoro-Zubiete, Jesús Castro-Marrero, Jorge Ropero, José Sevillano-Ramos, María Dolores Hernández, Ramon Sanmartin Sentañes, Jose Alegre-Martin, Patricia Launois-Obregón, Isabel Martin-Garrido, Asuncion Luque Budia, Juan Lacalle-Remigio, Luis Béjar Prado, Octavio Rivera Romero. 3461

Development and Pilot-Testing of an Optimized Conversational Agent or “Chatbot” for Peruvian Adolescents Living With HIV to Facilitate Mental Health Screening, Education, Self-Help, and Linkage to Care: Protocol for a Mixed Methods, Community-Engaged Study (e55559)
Jerome Galea, Diego Vasquez, Neil Rupani, Moya Gordon, Milagros Tapia, Karah Greene, Lenka Kolevic, Molly Franke, Carmen Contreras. .
3 4 6 9

Reliability and Sensitivity of a Virtual Assessment Developed for Workplace Concussions: Protocol for a Method-Comparison Study (e57663)
Keely Barnes, Heidi Sveistrup, Mark Bayley, Michel Rathbone, Monica Taljaard, Mary Egan, Martin Bilodeau, Motahareh Karimijashni, Shawn Marshall. 3478

Improving Antibiotic Use in Nursing Homes by Infection Prevention and Control and Antibiotic Stewardship (IMAGINE): Protocol for a Before-and-After Intervention and Implementation Study (e60099)
Ana García-Sangenís, Daniela Modena, Jette Jensen, Athina Chalkidou, Valeria Antsupova, Tina Marloth, Anna Theut, Beatriz González López-Valcárcel, Fabiana Raynal, Laura Vallejo-Torres, Jesper Lykkegaard, Malene Hansen, Jens Søndergaard, Jonas Olsen, Anders Munck, András Balint, Ria Benko, Davorina Petek, Nina Sodja, Anna Kowalczyk, Maciej Godycki-Cwirko, Helena Glasová, Jozef Glasa, Ruta Radzeviciene Jurgute, Lina Jaruseviciene, Christos Lionis, Marilena Anastasaki, Agapi Angelaki, Elena Petelos, Laura Alvarez, Marta Ricart, Sergi Briones, Georg Ruppe, Ramon Monfà, Anders Bjerrum, Carl Llor. 3486

Family Support Protocol for Adolescent Internalizing Disorders: Protocol for a Pre-Post Quantitative Treatment Development Study (e64332)
Aaron Hogue, Molly Bobek, Nicole Porter, Alexandra MacLean, Craig Henderson, Amanda Jensen-Doss, Gary Diamond, Michael Southam-Gerow, Jill Ehrenreich-May. 3497

Design of a Tool Capable of Assessing Environmental Sociocultural Physical Factors Influencing Women’s Decisions on When and Where to Toilet Within Real-World Settings: Protocol for the Build and Usability Testing of a Mobile App for Use by Community-Dwelling Women (e54046)
Janis Miller, Jean Wyman, Lawrence An, Haitao Chu, Cynthia Fok, Missy Lavender, Cora Lewis, Alayne Markland, Leslie Rickey, Ying Sheng, Siobhan Sutcliffe, Lisa Low, Elizabeth Mueller, The Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. 3516

Reward Learning as a Potential Mechanism for Improvement in Schizophrenia Spectrum Disorders Following Cognitive Remediation: Protocol for a Clinical, Nonrandomized, Pre-Post Pilot Study (e52505)
Frances Dark, Graham Galloway, Marcus Gray, Matteo Cella, Veronica De Monte, Victoria Gore-Jones, Gabrielle Ritchie. 3526

Education of Patients With Atrial Fibrillation and Evaluation of the Efficacy of a Mobile Virtual Patient Environment: Protocol for a Multicenter Pseudorandomized Controlled Trial (e45946)
Panagiotis Antoniou, Eleni Dafli, George Giannakoulas, Gaukhar Igimbayeva, Olga Visternichan, Serhii Kyselov, Ivetta Lykhasenko, Dmytro Lashkul, Ilia Nadareishvili, Sergo Tabagari, Panagiotis Bamidis. 3538

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Web-Based Intervention to Act for Weight Loss in Adults With Type 2 Diabetes With Obesity (Chance2Act): Protocol for a Nonrandomized Controlled Trial (e48313)
Noraini Mohd Saad, Mariam Mohamad, Aimi Mat Ruzlin. . . . 3550

Compliance of Type 2 Diabetes Applications to International Guidelines: Protocol for a Quantitative App Assessment (e48781)
David Rebus, Andrew Iskander, Felicia Deonarine, Asad Almas, Darren Rattigan, Patrick Henn, Kayode Fadahunsi, John O'Donoghue. . . . 3561

Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study (e52946)
Marta Castillo-Rodenas, Josep Vidal-Alaball, Núria Solanas-Bacardit, Clotilde Farràs-Company, Aïna Fuster-Casanovas, Queralt Miró Catalina, Francesc López Seguí. . . . 3568

Digital Phenotyping for Real-Time Monitoring of Nonsuicidal Self-Injury: Protocol for a Prospective Observational Study (e53597)
Chan-Young Ahn, Jong-Sun Lee. . . . 3577

Adapting and Evaluating an AI-Based Chatbot Through Patient and Stakeholder Engagement to Provide Information for Different Health Conditions: Master Protocol for an Adaptive Platform Trial (the MARVIN Chatbots Study) (e54668)
Yuanchao Ma, Sofiane Achiche, Marie-Pascale Pomey, Jesseca Paquette, Nesrine Adjtoutah, Serge Vicente, Kim Engler, MARVIN chatbots Patient Expert Committee, Moustafa Laymouna, David Lessard, Benoît Lemire, Jamil Asselah, Rachel Therrien, Esli Osmanlliu, Ma'n Zawati, Yann Joly, Bertrand Lebouché. . . . 3587

Development of an App for Symptom Management in Women With Breast Cancer Receiving Maintenance Aromatase Inhibitors: Protocol for a Mixed Methods Feasibility Study (e49549)
Trine Lund-Jacobsen, Peter Schwarz, Gabriella Martino, Helle Pappot, Karin Piil. . . . 3609

A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study (e50146)
Alla Melman, Min Teng, Danielle Coombs, Qiang Li, Laurent Billot, Thomas Lung, Eileen Rogan, Mona Marabani, Owen Hutchings, Chris Maher, Gustavo Machado, Back@Home Investigators. . . . 3624

Investigating Digital Patient-Reported Outcome Measures in Patient-Centered Diabetes Specialist Outpatient Care (DigiDiaS): Protocol for a Multimethod Prospective Observational Study (e52766)
Astrid Torbjørnsen, Ingeborg Spildo, Maria Mollestad, Annesofie Jensen, Tone Singstad, Nina Weldingh, Pål Joranger, Lis Ribu, Heidi Holmen.
3 6 3 5

Effectiveness of Chinese Herbal Medicine as a Complementary Treatment for Neutropenia Prevention and Immunity Modulation During Chemotherapy in Patients With Breast Cancer: Protocol for a Real-World Pragmatic Clinical Trial (e55662)
Kai-Hung Wang, Hsuan-Shu Shen, Sung-Chao Chu, Tso-Fu Wang, Ching-Wei Lin, Wei-Han Huang, Yi-Feng Wu, Ching-Chun Ho, Cheng-Yoong Pang, Chi-Cheng Li. . . . 3652

Navigating Social Cognitive Impairments in Schizophrenia Spectrum Disorders: Protocol for a Pilot Pre-Post Quasi-Experimental Study for Remote Avatar-Assisted Cognitive Remediation Therapy (e54251)
Elisabeth Thibaudeau, Elodie Peyroux, Nicolas Franck, Hannah Carling, Martin Lepage. . . . 3662

Implementing and Evaluating a National Integrated Digital Registry and Clinical Decision Support System in Early Intervention in Psychosis Services (Early Psychosis Informatics Into Care): Co-Designed Protocol (e50177)
Siân Griffiths, Graham Murray, Yanakan Logeswaran, John Ainsworth, Sophie Allan, Niyah Campbell, Richard Drake, Mohammad Katshu, Matthew Machin, Megan Pope, Sarah Sullivan, Justin Waring, Tumelo Bogatsu, Julie Kane, Tyler Weetman, Sonia Johnson, James Kirkbride, Rachel Upthegrove. . . . 3675

XSL•FO
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Examining Parent Mood, Feeding Context, and Feeding Goals as Predictors of Feeding Practices Used by Parents of Preschool Children With Avid Eating Behavior: Protocol for an Ecological Momentary Assessment Study (e55193)
Katie Edwards, Helen Croker, Claire Farrow, Emma Haycraft, Moritz Herle, Clare Llewellyn, Abigail Pickard, Jacqueline Blissett. 3686

Evaluation of the Gonadotoxicity of Cancer Therapies to Improve Counseling of Patients About Fertility and Fertility Preservation Measures: Protocol for a Retrospective Systematic Data Analysis and a Prospective Cohort Study (e51145)
Michael von Wolff, Ariane Germeyer, Bettina Böttcher, Isotta Magaton, Irene Marcu, Janna Pape, Nicole Sänger, Verena Nordhoff, Marie Roumet, Susanna Weidlinger. 3694

Using a Rapid Learning Health System for Stratified Care in Emerging Adult Mental Health Services: Protocol for the Implementation of Patient-Reported Outcome Measures (e51667)
Gina Dimitropoulos, David Lindenbach, Melissa Potestio, Tom Mogan, Amanda Richardson, Alida Anderson, Madison Heintz, Karen Moskovic, Jason Gondziola, Jessica Bradley, Haley LaMonica, Frank Iorfino, Ian Hickie, Scott Patten, Paul Arnold. 3704

Remote Evaluation of Sleep and Circadian Rhythms in Older Adults With Mild Cognitive Impairment and Dementia: Protocol for a Feasibility and Acceptability Mixed Methods Study (e52652)
Victoria Gabb, Jonathan Blackman, Hamish Morrison, Bijetri Biswas, Haoxuan Li, Nicholas Turner, Georgina Russell, Rosemary Greenwood, Amy Jolly, William Trender, Adam Hampshire, Alan Whone, Elizabeth Coulthard. 3719

Benchmarking Mental Health Status Using Passive Sensor Data: Protocol for a Prospective Observational Study (e53857)
Robyn Kilshaw, Abigail Boggins, Olivia Everett, Emma Butner, Feea Leifker, Brian Baucom. 3731

A Global Health Survey of People Who Vape but Never Smoked: Protocol for the VERITAS (Vaping Effects: Real-World International Surveillance) Study (e54236)
Jeffrey Zamora Goicoechea, Allison Boughner, Juan Cirion Lee, Aman Mahajan, Kurt Yeo, Maris Sproga, Tasmin Patel, Claudio Saitta, Christopher Russell, Michael Coughlan, Pasquale Caponnetto, Riccardo Polosa. 3743

Design of a Remote Multiparametric Tool to Assess Mental Well-Being and Distress in Young People (mHealth Methods in Mental Health Research Project): Protocol for an Observational Study (e51298)
Thais Castro Ribeiro, Esther García Pagès, Laura Ballester, Gemma Vilagut, Helena García Mieres, Víctor Suárez Aragonès, Franco Amigo, Raquel Bailón, Philippe Mortier, Víctor Pérez Sola, Antoni Serrano-Blanco, Jordi Alonso, Jordi Aguiló. 3753

National Tunisian Study of Cardiac Implantable Electronic Devices: Design and Protocol for a Nationwide Multicenter Prospective Observational Study (e47525)
Sonia Chabrak, Abdeddayem Haggui, Emna Allouche, Sana Ouali, Afef Ben Halima, Slim Kacem, Salma Krichen, Sonia Marrakchi, Wafa Fehri, Mohamed Mourali, Zeineb Jabbari, Manel Ben Halima, Elyes Neffati, Aymen Heraiech, Mehdi Slim, Salem Kachboura, Habib Gamra, Majed Hassine, Sondes Kraiem, Sofien Kammoun, Leila Bezdah, Gouider Jridi, Hatem Bouraoui, Samir Kammoun, Rania Hammami, Rafik Chettaoui, Youssef Ben Ameur, Fares Azaiez, Rami Tlili, Kais Battikh, Hedi Ben Slima, Rim Chrigui, Samia Fazaa, Islem Sanaa, Yassine Ellouz, Mohamed Mosrati, Sami Milouchi, Soumaya Jarmouni, Wacef Ayadi, Malek Akrout, Rabie Razgallah, Wissal Neffati, Meriem Drissa, Selma Charfeddine, Salem Abdessalem, Leila Abid, Lilia Zakhama. 3768

Preference-Based Implementation of Video Consultations in Urban and Rural Regions in Outpatient Care in Germany: Protocol for a Mixed Methods Study (e50932)
Lara Kleinschmidt, Anke Walendzik, Jürgen Wasem, Klemens Höfer, Beatrice Nauendorf, Matthias Brittner, Paul Brandenburg, André Aeustergerling, Udo Schneider, Anja Wadeck, Stephanie Sehlen, Sebastian Liersch, Katharina Schwarze, Carsten Schwenke, Theresa Hüer. 3775

Participation in Advance Care Planning Among Medically At-Risk Rural Veterans: Protocol for a Personalized Engagement Model (e55080)
Tammy Walkner, Daniel Karr, Sarah Murray, Amanda Heeren, Maresi Berry-Stoelzle. 3785

Fostering Digital Life Skills Through Social Media With Adolescents in 6 German States: Protocol for an Accessibility Study According to the RE-AIM Framework (e51085)
Elizabeth Zimmermann, Samuel Tomczyk. 3796

XSL•FO
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Toward Telemonitoring in Immune-Mediated Inflammatory Diseases: Protocol for a Mixed Attention Model Study (e55829)

Marta Novella-Navarro, Jose Iniesta-Chamorro, Diego Benavent, Javier Bachiller-Corral, Enrique Calvo-Aranda, Helena Borrell, Laura Berbel-Arcobé, Victoria Navarro-Compan, Xabier Michelena, Leticia Lojo-Oliveira, Jaime Arroyo-Palomo, Mariana Diaz-Almiron, Verónica García García, Irene Monjo-Henry, Claudia Gómez González, Enrique Gomez, Alejandro Balsa, Chamaida Plasencia-Rodríguez. 3813

Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study (e52957)

Pasquale Innominato, Jamie Macdonald, Wendy Saxton, Laura Longshaw, Rachel Granger, Iman Naja, Carlo Allocca, Ruth Edwards, Solah Rasheed, Frans Folkvord, Jordi de Batlle, Rohit Ail, Enrico Motta, Catherine Bale, Claire Fuller, Anna Mullard, Christian Subbe, Dawn Griffiths, Nicholas Wreglesworth, Leandro Pecchia, Giuseppe Fico, Alessio Antonini. 3825

KIJANI App to Promote Physical Activity in Children and Adolescents: Protocol for a Mixed Method Evaluation (e55156)

Laura Willinger, Birgit Böhm, Florian Schweizer, Lara Reimer, Stephan Jonas, Daniel Scheller, Renate Oberhoffer-Fritz, Jan Müller. 3841

A Factorial Randomized Controlled Trial to Optimize User Engagement With a Chatbot-Led Parenting Intervention: Protocol for the ParentText Optimisation Trial (e52145)

Maria Ambrosio, Jamie Lachman, Paula Zinzer, Hlengiwe Gwebu, Seema Vyas, Inge Vallance, Francisco Calderon, Frances Gardner, Laurie Markle, David Stern, Chiara Facciola, Anne Schley, Nompumelelo Danisa, Kanyisile Brukwe, GJ Melendez-Torres. 3850

Digital Interventions to Understand and Mitigate Stress Response: Protocol for Process and Content Evaluation of a Cohort Study (e54180)

Josh Martin, Alice Rueda, Gyu Lee, Vanessa Tassone, Haley Park, Martin Ivanov, Benjamin Darnell, Lindsay Beavers, Douglas Campbell, Binh Nguyen, Andrei Torres, Hyejung Jung, Wendy Lou, Anthony Nazarov, Andrea Ashbaugh, Bill Kapralos, Brett Litz, Rakesh Jetly, Adam Dubrowski, Gillian Strudwick, Sridhar Krishnan, Venkat Bhat. 3873

Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study (e55452)

Debbie de Graaf, Nienke de Vries, Tessa van de Zande, Janneke Schimmel, Sooyoon Shin, Nathan Kowahl, Poulami Barman, Ritu Kapur, William Marks Jr, Alex van 't Hul, Bastiaan Bloem. 3887

Effectiveness of Virtual Reality in Reducing Perceived Pain and Anxiety Among Patients Within a Hospital System: Protocol for a Mixed Methods Study (e52649)

Ajay Mittal, Jonathan Wakim, Suhaiba Huq, Tung Wynn. 3900

A Mindfulness-Based App Intervention for Pregnant Women: Protocol for a Pilot Feasibility Study (e53890)

Silvia Rizzi, Stefania Poggianella, Maria Pavesi, Lorenzo Gios, Giorgia Bincoletto, Isabella Scolari, Claudia Paoli, Debora Marroni, Irene Tassinari, Barbara Baietti, Anna Gianatti, Veronica Albertini, Barbara Burlon, Vanda Chiodega, Barbara Endrizzi, Elena Benini, Chiara Guella, Erik Gadotti, Stefano Forti, Fabrizio Taddei. 3906

The Google Health Digital Well-Being Study: Protocol for a Digital Device Use and Well-Being Study (e49189)

Daniel McDuff, Andrew Barakat, Ari Winbush, Allen Jiang, Felicia Cordeiro, Ryann Crowley, Lauren Kahn, John Hernandez, Nicholas Allen. .
3 9 1 9

Grocery Delivery to Support Individuals With Type 2 Diabetes: Protocol for a Pilot Quality Improvement Program (e54043)

Lauren Oshman, Marika Waselewski, Rina Hisamatsu, Noa Kim, Larrea Young, Dina Hafez Griauzde, Tammy Chang. 3929

Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO) in Metropolitan France: Protocol of a Mixed Methods Study and Intervention (e52274)

Albane Aumaitre, Rémi Gagnayre, Aude-Marie Foucaut. 3942

XSL•FO
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Assessing and Optimizing Large Language Models on Spondyloarthritis Multi-Choice Question Answering: Protocol for Enhancement and Assessment (e57001)
Anan Wang, Yunong Wu, Xiaojian Ji, Xiangyang Wang, Jiawen Hu, Fazhan Zhang, Zhanchao Zhang, Dong Pu, Lulu Tang, Shikui Ma, Qiang Liu, Jing Dong, Kunlun He, Kunpeng Li, Da Teng, Tao Li. . . . 3955

Investigating the Efficacy of a Community Support Network Rehabilitation Intervention for Improving Resiliency, Quality of Life, and Neurocognitive Function in Survivors of Intimate Partner Violence–Caused Brain Injury: Protocol for a Feasibility Study (e54605)
Shambhu Adhikari, Tori Stranges, Setareh Tehrani, Shaun Porter, Karen Mason, Paul van Donkelaar. . . . 3968

Daily Time-Use Patterns and Quality of Life in Parents: Protocol for a Pilot Quasi-Experimental, Nonrandomized Controlled Trial Using Ecological Momentary Assessment (e54728)
Laura Altweck, Silke Schmidt, Samuel Tomczyk. . . . 3984

Evaluation of Ambient Sensor Systems for the Early Detection of Heart Failure Decompensation in Older Patients Living at Home Alone: Protocol for a Prospective Cohort Study (e55953)
Benjamin Vögeli, Nisha Arenja, Narayan Schütz, Tobias Nef, Philipp Buluschek, Hugo Saner. . . . 3994

Social Media Promotion of Health Tests With Potential for Overdiagnosis or Overuse: Protocol for a Content Analysis (e56899)
Brooke Nickel, Raffael Heiss, Patti Shih, Emma Gram, Tessa Copp, Melody Taba, Ray Moynihan, Joshua Zadro. . . . 4002

Feasibility of Web-Based Single-Session Empowered Relief in Patients With Chronic Pain Taking Methadone or Buprenorphine: Protocol for a Single-Arm Trial (e53784)
Morgan Klein, Beth Darnall, Dokyoung You. . . . 4011

Technology-Assisted Mental Health Intervention Delivered by Frontline Workers at Community Doorsteps for Reducing Anxiety and Depression in Rural Pakistan: Protocol for the mPareshan Mixed Methods Implementation Trial (e54272)
Fauziah Rabbani, Javeria Nafis, Samina Akhtar, Muhammad Khan, Saleem Sayani, Amna Siddiqui, Sameen Siddiqi, Zul Merali. . . . 4023

Factors Affecting Specialty Training Preference Among UK Medical Students (FAST): Protocol for a National Cross-Sectional Survey (e55155)
Tomas Ferreira, Alexander Collins, Benjamin French, Amelia Fortescue, Arthur Handscomb, Ella Plumb, Emily Bolton, Oliver Feng. . . . 4035

Measuring Relationship Influences on Romantic Couples' Cancer-Related Behaviors During the COVID-19 Pandemic: Protocol for a Longitudinal Online Study of Dyads and Cancer Survivors (e48516)
Jennifer Bowers, Chloe Huelsnitz, Laura Dwyer, Laurel Gibson, Tanya Agurs-Collins, Rebecca Ferrer, Amanda Acevedo. . . . 4044

Effectiveness of a Virtual Reality Open-Air Bath Program in Reducing Loneliness and Improving Brain Function for Dementia Prevention in Older Adults: Protocol for a Prospective Randomized Crossover Study (e57101)
Ayu Imai, Teruyuki Matsuoka, Chikara Nakayama, Nana Hashimoto, Mutsuo Sano, Jin Narumoto. . . . 4058

Evaluating the Population-Based Usage and Benefit of Digitally Collected Patient-Reported Outcomes and Experiences in Patients With Chronic Diseases: The PROMchronic Study Protocol (e56487)
Janis Nikkhah, Viktoria Steinbeck, Thomas Grobe, Thorben Breitkreuz, Christoph Pross, Reinhard Busse. . . . 4067

Development of Automated Triggers in Ambulatory Settings in Brazil: Protocol for a Machine Learning–Based Design Thinking Study (e55466)
Claire Herrera, Fernanda Gimenes, João Herrera, Ricardo Cavalli. . . . 4082

Ameliorating Racial Disparities in HIV Prevention via a Nurse-Led, AI-Enhanced Program for Pre-Exposure Prophylaxis Utilization Among Black Cisgender Women: Protocol for a Mixed Methods Study (e59975)
Chen Zhang, Mitchell Wharton, Yu Liu. . . . 4094

XSL•FO
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Acceptability, Perceptions, and Experiences Regarding Electronic Patient-Reported Outcomes After Laparoscopic Cholecystectomy: Protocol for a Mixed Methods Feasibility Study (e57344)
Kareem Choucair, Mark Corrigan, Adrian O'Sullivan, Sean Barber, Lucja Stankiewicz, Patrick Henn, Oscar Dennehy, Mohd Kayyal, Yong Tan, Kayode Fadahunsi, John O'Donoghue. 4102

Exploring New Models for Implementing Sustainable Integrated Health Access for People in Vulnerable Positions: Protocol for a Mixed Methods Multiple Case Study (e56197)
Sofie Mejsner, Jane Aslaug, Mickael Bech, Viola Burau, Dorte Mark, Kathrine Vixø, Caroline Westergaard, Michael Fehsenfeld. 4110

Evaluating the Implementation of Integrated Proactive Supportive Care Pathways in Oncology: Master Protocol for a Cohort Study (e52841)
Maria Franzoi, Arnaud Pages, Loula Papageorgiou, Antonio Di Meglio, Ariane Laparra, Elise Martin, Aude Barbier, Nathalie Renvoise, Johanna Arvis, Florian Scotte, Ines Vaz-Luis. 4119

Evaluation of the Continuing Education Training “Beratende für Digitale Gesundheitsversorgung” (“Consultant for Digital Healthcare”): Protocol for an Effectiveness Study (e57860)
Bernhard Kraft, Thomas Kuscher, Susann Zawatzki, Sebastian Hofstetter, Patrick Jahn. 4132

Smartphone App for Prehospital ECG Transmission in ST-Elevation Myocardial Infarction Activation: Protocol for a Mixed Methods Study (e55506)
Hassan Mir, Katelyn Cullen, Karen Mosleh, Rafi Setrak, Sanjit Jolly, Michael Tsang, Gregory Rutledge, Quazi Ibrahim, Michelle Welsford, Mathew Mercuri, JD Schwalm, Madhu Natarajan. 4141

Prevention of Recurrent Spontaneous Preterm Delivery Using Probiotics (Clostridium butyricum, Enterococcus faecium, and Bacillus subtilis; PPP Trial): Protocol for a Prospective, Single-Arm, Nonblinded, Multicenter Trial (e59928)
Satoshi Yoneda, Tohru Kobayashi, Kayoko Kikuchi, Shintaro Iwamoto, Tsuyoshi Teramoto, Daisuke Chujo, Katsufumi Otsuki, Akihito Nakai, Shigeru Saito. 4149

Overdose Detection Among High-Risk Opioid Users Via a Wearable Chest Sensor in a Supervised Injecting Facility: Protocol for an Observational Study (e57367)
Basak Tas, Will Lawn, Marianne Jauncey, Mark Bartlett, Paul Dietze, Daniel O'Keefe, Nico Clark, Bruce Henderson, Catriona Cowan, Osian Meredith, John Strang. 4159

Psychological Health and Wellness and the Impact of a Supportive Text Messaging Program (Wellness4MDs) Among Physicians and Medical Learners in Canada: Protocol for a Longitudinal Study (e44368)
Reham Shalaby, Belinda Agyapong, Raquel Dias, Gloria Obuobi-Donkor, Medard Adu, Sharron Spicer, Natalie Yanchar, Vincent Agyapong. .
4 1 7 0

A Digital Intervention for Capturing the Real-Time Health Data Needed for Epilepsy Seizure Forecasting: Protocol for a Formative Co-Design and Usability Study (The ATMOSPHERE Study) (e60129)
Emily Quilter, Samuel Downes, Mairi Deighan, Liz Stuart, Rosie Charles, Phil Tittensor, Leandro Junges, Peter Kissack, Yasser Qureshi, Aravind Kamaraj, Amberly Brigden. 4181

Patterns of Use and Withdrawal Syndrome in Dual Cannabis and Tobacco Users (DuCATA_GAM-CAT): Protocol for a Mixed Methods Study (e58335)
Judith Saura, Ariadna Feliu, Marta Enríquez-Mestre, Marcela Fu, Montse Ballbè, Yolanda Castellano, Margarida Pla, Nathalia Rosa, Petia Radeva, Elena Maestre-González, Carmen Cabezas, Joan Colom, Josep Suelves, Silvia Mondon, Pablo Barrio, Magalí Andreu, Antònia Raich, Jordi Bernabeu, Jordi Vilaplana, Xavier Roca Tutusaus, Joseph Guydish, Esteve Fernández, Cristina Martínez. 4198

Implementation of a Virtual Reality Intervention in Outpatient Physiotherapy for Chronic Pain: Protocol for a Pilot Implementation Study (e58089)
Alexander Elser, Christian Kopkow, Axel Schäfer. 4211

XSL•FO
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Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis With Ambulatory Cognitive Tests: Protocol for the Longitudinal Observational CogDetect-MS Study (e59876)
Anna Kratz, Dawn Ehde, Kevin Alschuler, Kristen Pickup, Keara Ginell, Nora Fritz. . . . 4221

Identifying Gravity-Related Artifacts on Ballistocardiography Signals by Comparing Weightlessness and Normal Gravity Recordings (ARTIFACTS): Protocol for an Observational Study (e63306)
Urs-Vito Albrecht, Annabelle Mielitz, Kazi Rahman, Ulf Kulau. . . . 4237

Development and Evaluation of the Telehealth in Motor Neuron Disease System: The TIME Study Protocol (e57685)
Liam Knox, Elizabeth Coates, Alys Griffiths, Yasmin Ali, Esther Hobson, Christopher McDermott. . . . 4247

Clinical Data Flow in Botswana Clinics: Protocol for a Mixed-Methods Assessment (e52411)
Grey Faulkenberry, Audrey Masizana, Badisa Mosesane, Kagiso Ndlovu. . . . 4258

A Combined Telemedicine and Ambulatory Wound Care Team Intervention for Improving Cross-Sector Outpatient Chronic Wound Management: Protocol for the Mixed Methods TELE-AMBUS Research Project (e55502)
Sindre Høyland, Kari Holte, Olaug Øygarden, Kamrul Islam, Egil Kjerstad, Ragnhild Gjerstad-Sørensen, Synnøve Høyland, Hanne Wærnes, Pascale Carayon, Maureen Fallon, Sarah Bradbury, Marcus Gürgen, Sissel Husebø, Eirin Rødseth. . . . 4266

Development and Implementation of an Online Patient Education Program for Children and Adolescents With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Their Parents, Siblings, and School Personnel: Protocol for the Prospective BAYNET FOR ME/CFS Study (e54679)
Franca Keicher, Julia Thomann, Jana Erlenwein, Mara Schottdorf, Nils Reiter, Nadine Scholz-Schwärzler, Barbara Vogel, Cordula Warlitz, Silvia Stojanov, Silvia Augustin, Lola Goldbrunner, Linda Schanz, Veronika Dodel, Charlotte Zipper, Nicole Schiweck, Robert Jaeschke, Milica Saramandic, Karolina Wiejaczka, Maria Eberhartinger, Kristina Dettmer, Daniel Hattesohl, Stephanie Englbrecht, Uta Behrends, Juliane Spiegler. . . . 4278

mHealth Apps in German Outpatient Mental Health Care: Protocol for a Mixed Methods Approach (e56205)
Klemens Höfer, Felix Plescher, Sarah Schlierenkamp, Stefanie Solar, Silke Neusser, Udo Schneider, Dieter Best, Jürgen Wasem, Carina Abels, Anna Bußmann. . . . 4290

A Gender-Informed Smoking Cessation App for Women: Protocol for an Acceptability and Feasibility Study (e60677)
Osnat Melamed, Kamna Mehra, Roshni Panda, Nadia Minian, Scott Veldhuizen, Laurie Zawertailo, Leslie Buckley, Marta Maslej, Lorraine Greaves, Andreea Brabete, Jonathan Rose, Matt Ratto, Peter Selby. . . . 4299

A Digital Mental Health Solution to Improve Social, Emotional, and Learning Skills for Youth: Protocol for an Efficacy and Usability Study (e59372)
Kayla Taylor, Laurent Garchitorena, Carolina Scaramutti-Gladfelter, Mykayla Wyrick, Katherine Grill, Azizi Seixas. . . . 4311

Virtual Reality–Applied Home-Visit Rehabilitation for Patients With Chronic Pain: Protocol for Single-Arm Pre-Post Comparison Study (e58734)
Hiroki Funao, Ryo Momosaki, Mayumi Tsujikawa, Eiji Kawamoto, Ryo Esumi, Motomu Shimaoka. . . . 4326

Evaluation of the Development, Implementation, Maintenance, and Impact of 3 Digital Surveillance Tools Deployed in Malawi During the COVID-19 Pandemic: Protocol for a Modified Delphi Expert Consensus Study (e58389)
Alanna Denny, Isaach Ndemera, Kingston Chirwa, Joseph Wu, Griphin Chirambo, Simeon Yosefe, Ben Chilima, Matthew Kagoli, Hsin-yi Lee, Kwong Yu, John O'Donoghue. . . . 4336

Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study (e53722)
Yakubu Ibrahim, Nurul Basri, Norshariza Nordin, Amilia Mohd Jamil. . . . 4348

XSL•FO
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Patient Education and Decision Support for Long-Acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing with Ryan White HIV/AIDS Program Medical Case Management Programs in New York (e56892)
Mary Irvine, Rebecca Zimba, Tigran Avoundjian, Meghan Peterson, Connor Emmert, Sarah Kulkarni, Morgan Philbin, Elizabeth Kelvin, Denis Nash. 4356

Global Trends of Medical Misadventures Using International Classification of Diseases, Tenth Revision Cluster Y62-Y69 Comparing Pre–, Intra–, and Post–COVID-19 Pandemic Phases: Protocol for a Retrospective Analysis Using the TriNetX Platform (e54838)
Rosario Caruso, Marco Di Muzio, Emanuele Di Simone, Sara Dionisi, Arianna Magon, Gianluca Conte, Alessandro Stievano, Emanuele Girani, Sara Boveri, Lorenzo Menicanti, Mary Dolansky. 4371

Effectiveness and Cost-Effectiveness of Survivorship Care for Survivors of Hodgkin Lymphoma (INSIGHT Study): Protocol for a Multicenter Retrospective Cohort Study With a Quasi-Experimental Design (e55601)
Eline Lammers, Josée Zijlstra, Valesca Retèl, Berthe Aleman, Flora van Leeuwen, Annelies Nijdam, BETER consortium. 4379

TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) Project: Protocol for an International Longitudinal Multicenter Study (e56262)
Stefanie Bachnick, Maria Unbeck, Maryam Ahmadi Shad, Katja Falta, Nicole Grossmann, Daniela Holle, Jana Bartakova, Sarah Musy, Sarah Hellberg, Pernilla Dillner, Fatemeh Atoof, Mohammadhossein Khorasanizadeh, Paula Kelly-Pettersson, Michael Simon. 4391

Associations Between Stress, Health Behaviors, and Quality of Life in Young Couples During the Transition to Survivorship: Protocol for a Measurement Burst Study (e53307)
Dalnim Cho, Michael Roth, Susan Peterson, Kristofer Jennings, Seokhun Kim, Shiao-Pei Weathers, Sairah Ahmed, J Livingston, Carlos Barcenas, Y You, Kathrin Milbury. 4400

Brief Parent-Child Substance Use Education Intervention for Black Families in Urban Cities in New Jersey: Protocol for a Formative Study Design (e55470)
Ijeoma Opara, Kimberly Pierre, Sandy Cayo, Kammarauche Aneni, Catherine Mwai, Aaron Hogue, Sara Becker. 4411

Assessing Functional Capacity in Directly and Remotely Monitored Home-Based Settings in Individuals With Chronic Respiratory Diseases: Protocol for a Multinational Validation Study (e57404)
Alec Bass, Sarah Géphine, Mickaël Martin, Marianne Belley, Manon Robic, Claudine Fabre, Jean-Marie Grosbois, Geneviève Dion, Didier Saey, Arnaud Chambellan, François Maltais. 4421

Implementation and Impact of Intimate Partner Violence Screening Expansion in the Veterans Health Administration: Protocol for a Mixed Methods Evaluation (e59918)
Galina Portnoy, Mark Relyea, Melissa Dichter, Katherine Iverson, Candice Presseau, Cynthia Brandt, Melissa Skanderson, LeAnn Bruce, Steve Martino. 4437

Transgender-Specific Differentiated HIV Service Delivery Models in the South African Public Primary Health Care System (Jabula Uzibone): Protocol for an Implementation Study (e64373)
Tonia Poteat, Rutendo Bothma, Innocent Maposa, Cheryl Hendrickson, Gesine Meyer-Rath, Naomi Hill, Audrey Pettifor, John Imrie. 4448

Rethinking the Social Determination of Food in Chile Through Practices and Interactions of Actors in Food Environments: Nonexperimental, Cross-Sectional Study (e62765)
Patricia Gálvez Espinoza, Lorena Rodríguez Osiac, Carolina Franch Maggiolo, Daniel Egaña Rojas. 4467

Multicomponent Intervention to Improve Acute Myocardial Infarction Care in Tanzania: Protocol for a Pilot Implementation Trial (e59917)
Julian Hertz, Francis Sakita, Faraan Rahim, Blandina Mmbaga, Frida Shayo, Vivian Kaboigora, Julius Mtui, Gerald Bloomfield, Hayden Bosworth, Janet Bettger, Nathan Thielman. 4480

XSL•FO
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Investigating Exposure and Hazards of Micro- and Nanoplastics During Pregnancy and Early Life (AURORA Project): Protocol for an Interdisciplinary Study (e63176)
Amanda Durkin, Runyu Zou, Justin Boucher, Matthew Boyles, Jeske van Boxel, Mariona Bustamante, Emily Christopher, Payam Dadvand, Hanna Dusza, Majorie van Duursen, Markus Forsberg, Karen Galea, Juliette Legler, Laurens Mandemaker, Florian Meirer, Jane Muncke, Tim Nawrot, Petra P ibylová, Anna Robuck, Nelly Saenen, Barbara Scholz-Böttcher, Kuanliang Shao, Martine Vrijheid, Douglas Walker, Lisa Zimmermann, Laura Zoutendijk, Virissa Lenters, Roel Vermeulen. 4492

Effectiveness of a Person-Centered Interdisciplinary Rehabilitation Treatment of Post–COVID-19 Condition: Protocol for a Single-Case Experimental Design Study (e63951)
Carolina Wiertz, Thijs van Meulenbroek, Cynthia Lamper, Bea Hemmen, Simone Sep, Ivan Huijnen, Marielle Goossens, Jako Burgers, Jeanine Verbunt. 4507

Efficacy and Safety of a Therapy Combining Sintilimab and Chemotherapy With Cryoablation in the First-Line Treatment of Advanced Nonsquamous Non–Small Cell Lung Cancer: Protocol for a Phase II, Pilot, Single-Arm, Single-Center Study (e64950)
Zhiqiang Gao, Jiajun Teng, Rong Qiao, Jialin Qian, Feng Pan, Meili Ma, Jun Lu, Bo Zhang, Tianqing Chu, Hua Zhong. 4520

Exploring the Experiences of Times Without Care and Encounters in Persons With Dementia in the Swiss and German Nursing Home and Domiciliary Care Settings: Protocol for an Ethnographic Multimethods Study (e58190)
Thomas Beer, Julian Hirt, Laura Adlbrecht, Ulrike Lindwedel, Matthias Dammert, Carola Maurer, Matthias Kliegel, Peter König, Helma Bleses.
4 5 2 9

Understanding the Occurrence and Fate of Atmospheric Microplastics and Their Potential Risks to Human Health: Protocol for a Cross-Sectional Analysis (e60289)
Shaikh Hasan, Abdus Salam, Mohammad Moniruzzaman, Md Bari, Nirupam Aich, Farjana Jahan, Mahbubur Rahman, Zubayer Islam, Md Kabir, Md Shaikh, Rubhana Raqib, Sarker Parvez. 4547

Development and Validation of a Novel Tool to Measure Medication Adherence for Noncommunicable Diseases in India: Protocol for an Exploratory Sequential Mixed Methods Multicentric Study (e60805)
Joe Thomas, Maria Jose, Priyanka Rajmohan, Farah Fathima, Hisham Moosan, Nisha Jose, Thekkumkara Anish, Mohan Bairwa, Tulika Goswami Mahanta, Aditi Apte, Jerin Cherian, Praveenlal Kuttichira, Ravi Varma P. 4559

Characterizing Emergency Department Disposition Conversations for Persons Living With Dementia: Protocol for an Ethnographic Study (e65043)
Justine Seidenfeld, Matthew Tucker, Melissa Harris-Gersten, Gemmae Fix, Ivonne Guzman, Nina Sperber, Susan Hastings. 4569

Improving Blood Pressure Control and Tobacco Use Cessation Intervention In Primary Care: Protocol for the Alabama Cardiovascular Cooperative Heart Health Improvement Project (e63685)
Kathryn Foti, Demetria Hubbard, Kimberly Smith, Larry Hearld, Joshua Richman, Trudi Horton, Sharon Parker, Dodey Roughton, Macie Craft, Stephen Clarkson, Elizabeth Jackson, Andrea Cherrington. 4578

The Use of Medical Services for Low-Acuity Emergency Cases in Germany: Protocol for a Multicenter Observational Pilot Study (e54002)
Lara Nau, Gunter Laux, Attila Altiner, Joachim Szecsenyi, Rüdiger Leutgeb. 4592

Development and Testing of an Electronic Diabetes Diary Integrated With a Hospital Information System for Individuals With Type 2 Diabetes Mellitus: Protocol for a Mixed Methods Study (e50732)
Geena Skaria, Bhageerathy Reshmi, Sabu K M, Sahana Shetty, Vani Lakshmi R. 4603

Enhancing the Efficiency of a Radiation Oncology Department Using Electronic Medical Records: Protocol for Preparing Radiotherapy (e51002)
Hao-Shen Cheng, Weir-Chiang You, Ni-Wei Chen, Mu-Chih Hsieh, Che-Fu Tsai, Chia-Jing Ho, Chien-Chih Chen. 4612

Machine Learning Model for Readmission Prediction of Patients With Heart Failure Based on Electronic Health Records: Protocol for a Quasi-Experimental Study for Impact Assessment (e52744)
Monika Nair, Lina Lundgren, Amira Soliman, Petra Dryselius, Ebba Fogelberg, Marcus Petersson, Omar Hamed, Miltiadis Triantafyllou, Jens Nygren. 4619

XSL•FO
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An Approach to Potentially Increasing Adoption of an Artificial Intelligence–Enabled Electronic Medical Record Encounter in Canadian Primary Care: Protocol for a User-Centered Design (e54365)
Krizia Francisco, Catherine Burns. . . . 4628

A Novel Cognitive Behavioral Therapy–Based Generative AI Tool (Socrates 2.0) to Facilitate Socratic Dialogue: Protocol for a Mixed Methods Feasibility Study (e58195)
Philip Held, Sarah Pridgen, Yaozhong Chen, Zuhaib Akhtar, Darpan Amin, Sean Pohorence. . . . 4636

Assessing the Safety, User Acceptability, Dissemination, and Reach of a Comprehensive Web-Based Resource on Medications for Opioid Use Disorder (MOUD Hub): Protocol for a Development and Usability Study (e57065)
Melanie Nicholls, Alexandra Almeida, Justin Castello, David Grelotti, Bianca Daugherty, Donny Gann Jr, Karen Lenyoun, Sharon Trillo-Park, Annick Borquez. . . . 4651

Development of a Web Platform to Facilitate the Implementation and Evaluation of Health Promoting Schools: Protocol for a Double Diamond Design Approach (e52110)
Gemma Bermejo-Martínez, José Julián, Víctor Villanueva-Blasco, Alberto Aibar, Ana Corral-Abós, Alberto Abarca-Sos, Eduardo Generelo, Melania Mur, Manuel Bueno, Elisa Ferrer, Isabel Artero, Luis García-González, Berta Murillo-Pardo, Roberto Ferriz, Susana Menal-Puey, Iva Marques-Lopes, Marta Fajó-Pascual, Eduardo Ibor-Bernalte, Javier Zaragoza Casterad. . . . 4669

The Effects of the Processing of Positive Memories Technique on Posttrauma Affect and Cognitions Among Survivors of Trauma: Protocol for a Daily Diary Study (e51838)
Talya Greene, Ateka Contractor, Sheila Dicker-Oren, Andrea Fentem, Sharon Sznitman. . . . 4683

Microfragmented Fat and Biphasic Calcium Phosphates for Alveolar Cleft Repair: Protocol for a Prospective, Nonblinded, First-in-Human Clinical Study (e42371)
Diandra Natsir Kalla, Salem Alkaabi, Abul Fauzi, Andi Tajrin, Rifaat Nurrahma, Werner Müller, Heinz Schröder, Xiaohong Wang, Tymour Forouzanfar, Marco Helder, Muhammad Ruslin. . . . 4694

Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study (e51820)
Ligia Pires, Cláudia Reis, Ana Mesquita Facão, Armin Moniri, Ana Marreiros, Marta Drummond, Joana Berger-Estilita. . . . 4703

The Impact of Forced Separations Between Women and Their Pets in Domestic Violence Situations and the Effectiveness of Crisis Response: Protocol for a Conceptual Framework (e52067)
Jasmine Montgomery, Janice Lloyd, Zhanming Liang. . . . 4714

Validation of an Anti-Müllerian Hormone Cutoff for Polycystic Ovarian Morphology in the Diagnosis of Polycystic Ovary Syndrome in the HARMONIA Study: Protocol for a Prospective, Noninterventional Study (e48854)
Terhi Piltonen, Deirdre Allegranza, Martin Hund, Katharina Buck, Johanna Sillman, Riikka Arffman. . . . 4723

Let's Agree to Disagree on Operative Versus Nonoperative Treatment for Distal Radius Fractures in Older People: Protocol for a Prospective International Multicenter Cohort Study (e52917)
Nicole van Veelen, Bryan van de Wall, Ruben Hoepelman, Frank IJpma, Björn-Christian Link, Reto Babst, Rolf Groenwold, Detlef van der Velde, Nadine Diwersi, Mark van Heijl, R Houwert, Frank Beeres. . . . 4732

Genomic, Proteomic, and Phenotypic Biomarkers of COVID-19 Severity: Protocol for a Retrospective Observational Study (e50733)
Andrew English, Darren McDaid, Seodhna Lynch, Joseph McLaughlin, Eamonn Cooper, Benjamin Wingfield, Martin Kelly, Manav Bhavsar, Victoria McGilligan, Rachelle Irwin, Magda Bucholc, Shu-Dong Zhang, Priyank Shukla, Taranjit Rai, Anthony Bjourson, Elaine Murray, David Gibson, Colum Walsh. . . . 4740

XSL•FO
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Development and Evaluation of a Community Health Program to Promote Physical Activity Among Vulnerable Community-Dwelling Older Adults: Protocol for a Prospective Cohort Study (e51462)
Tina Auerswald, Katharina Zwingmann, Torsten Schlesinger, Katrin Müller. . . . 4752

Identifying and Validating Alcohol Diagnostics for Injury-Related Trauma in South Africa: Protocol for a Mixed Methods Study (e52949)
Petal Petersen Williams, Megan Prinsloo, Margaret Peden, Ian Neethling, Shibe Mhlongo, Sithombo Maqungo, Charles Parry, Richard Matzopoulos. . . . 4765

Group Acceptance and Commitment Therapy for Recovery From Psychosis: Protocol for a Single-Group Waitlist Trial (e49849)
Marilyn Cugnetto, Eric Morris, Siobain Bonfield, Jesse Gates, Ilona Morrison, Ellie Newman, Julia Nicholls, Lisa Soares, Megan Antonucci, Jacinta Clemente, Claire Garratt, Eliot Goldstone, David Pavone, John Farhall. . . . 4774

Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study (e56293)
Anandi Sheth, Dazon Dixon Diallo, Celeste Ellison, Deja Er, Adaora Ntukogu, Kelli Komro, Jessica Sales. . . . 4787

Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study (e53160)
Rupa Rubinstein, Katie Gallagher, John Ho, Julian Bose, Minesh Khashu, Narendra Aladangady. . . . 4797

Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE): Protocol for a Translational Study (e55723)
Emma Belfrage, Sara Ek, Åsa Johansson, Hanna Brauner, Andreas Sonesson, Kristina Drott. . . . 4808

A Bluetooth-Based Smartphone App for Detecting Peer Proximity: Protocol for Evaluating Functionality and Validity (e50241)
Nancy Barnett, Alexander Sokolovsky, Matthew Meisel, Shannon Forkus, Kristina Jackson. . . . 4817

A Community Needs Assessment and Implementation Planning for a Community Exercise Program for Survivors of Stroke: Protocol for a Pilot Hybrid Type I Clinical Effectiveness and Implementation Study (e55432)
Elizabeth Regan, Pamela Toto, Jennifer Brach. . . . 4833

Health Needs Assessment in Home-Living Older Adults: Protocol for a Pre-Post Study (e55192)
Fifi Kvalsvik, Bente Larsen, Grethe Eilertsen, Helle Falkenberg, Ingvild Dalen, Stine Haaland, Marianne Storm. . . . 4843

Carboplatin in Patients With Metastatic Castration-Resistant Prostate Cancer Harboring Somatic or Germline Homologous Recombination Repair Gene Mutations: Phase II Single-Arm Trial (e54086)
Rishabh Jain, Akash Kumar, Atul Sharma, Ranjit Sahoo, Aparna Sharma, Amlesh Seth, Brusabhanu Nayak, Shamim Shamim, Seema Kaushal, Haresh KP, Chandan Das, Atul Batra. . . . 4855

Investigating SARS-CoV-2 Incidence and Morbidity in Ponce, Puerto Rico: Protocol and Baseline Results From a Community Cohort Study (e53837)
Chelsea Major, Dania Rodríguez, Liliana Sánchez-González, Vanessa Rodríguez-Estrada, Tatiana Morales-Ortíz, Carolina Torres, Nicole Pérez-Rodríguez, Nicole Medina-Lópes, Neal Alexander, David Mabey, Kyle Ryff, Rafael Tosado-Acevedo, Jorge Muñoz-Jordán, Laura Adams, Vanessa Rivera-Amill, Melissa Rolfes, Gabriela Paz-Bailey. . . . 4863

Capturing the Dynamics of Homelessness Through Ethnography and Mobile Technology: Protocol for the Development and Testing of a Smartphone Technology–Supported Intervention (e53022)
Marva Foster, Gemmae Fix, Justeen Hyde, Shawn Dunlap, Thomas Byrne, Naomi Sugie, Randall Kuhn, Sonya Gabrielian, Jill Roncarati, Shibei Zhao, D McInnes. . . . 4878

Supportive Care Needs in Chinese, Vietnamese, and Korean Americans With Metastatic Cancer: Mixed Methods Protocol for the DAWN Study (e50032)
Jacqueline Kim, Marjorie Kagawa Singer, Lisa Bang, Amy Ko, Becky Nguyen, Sandy Chen Stokes, Qian Lu, Annette Stanton. . . . 4887

XSL•FO
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Leveraging AI and Machine Learning to Develop and Evaluate a Contextualized User-Friendly Cough Audio Classifier for Detecting Respiratory Diseases: Protocol for a Diagnostic Study in Rural Tanzania (e54388)
Kahabi Isangula, Rogers Haule. . . . 4898

Exploring the Pathways of Diabetes Foot Complications Treatment and Investigating Experiences From Frontline Health Care Professionals: Protocol for a Mixed Methods Study (e54852)
Elisavet Andrikopoulou, Panagiotis Chatzistergos, Nachiappan Chockalingam. . . . 4911

Real-World Registry on the Pharmacotherapy of Multiple Myeloma and Associated Renal and Pulmonary Impairments in the Greater Gulf Region: Protocol for a Retrospective Real-World Data Study (e49861)
Abdulnaser Nourallah, Abdulrahman Alshehri, Ayman Alhejazi, Binyam Usman, Ghada ElGohary, Hafiz Malhan, Ibraheem Motabi, Khalil Al Farsi, Mohammed Alshuaibi, Mustaqeem Siddiqui, Rasha Ghonema, Ruba Taha, Tarek Abouzeid, Wesam Ahmed, Mohanad Diab, Ahmad Alhuraiji, Magdy Rabea, Mohamed Chouikrat. . . . 4920

Tobacco Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED): Protocol for a Noninterventional Observational Study (e54041)
Davide Campagna, Konstantinos Farsalinos, Giorgio Costantino, Giuseppe Carpinteri, Pasquale Caponnetto, Francesca Cucuzza, Riccardo Polosa, SMOPHED Study Group. . . . 4929

Detection of Urinary Misfolded Proteins for Imminent Prediction of Preeclampsia in Pregnant Women With Suspected Cases: Protocol for a Prospective Noninterventional Study (e54026)
Haiyang Tang, Yijia Tian, Jing Fang, Xiaoying Yuan, Minli Yao, Yujia Wang, Yan Feng, Jia Shu, Yan Ni, Ying Yu, Yuanhe Wang, Ping Liang, Xingmin Li, Xiaoxia Bai. . . . 4937

Gait Features in Different Environments Contributing to Participation in Outdoor Activities in Old Age (GaitAge): Protocol for an Observational Cross-Sectional Study (e52898)
Merja Rantakokko, Emmi Matikainen-Tervola, Eeva Aartolahti, Sanna Sihvonen, Julija Chichaeva, Taija Finni, Neil Cronin. . . . 4946

Patient Partnership Tools to Support Medication Safety in Community-Dwelling Older Adults: Protocol for a Nonrandomized Stepped Wedge Clinical Trial (e57878)
Yan Xiao, Kimberley Fulda, Richard Young, Z Hendrix, Kathryn Daniel, Kay Chen, Yuan Zhou, Jennifer Roye, Ludmila Kosmari, Joshua Wilson, Anna Espinoza, Kathleen Sutcliffe, Samantha Pitts, Alicia Arbaje, Michelle Chui, Somer Blair, Dawn Sloan, Masheika Jackson, Ayse Gurses.
4 9 5 7

A Predictive Noninvasive Single-Nucleotide Variation–Based Biomarker Signature for Resectable Pancreatic Cancer: Protocol for a Prospective Validation Study (e54042)
Nico Seeger, Stefan Gutknecht, Irin Zschokke, Isabella Fleischmann, Nadja Roth, Jürg Metzger, Markus Weber, Stefan Breitenstein, Lukasz Grochola. . . . 4968

Impact of an Automated Population-Level Cirrhosis Screening Program Using Common Pathology Tests on Rates of Cirrhosis Diagnosis and Linkage to Specialist Care (CAPRISE): Protocol for a Pilot Prospective Single-Arm Intervention Study (e56607)
Joan Flores, Christina Trambas, Natasha Jovanovic, Alexander Thompson, Jessica Howell. . . . 4974

Finite Element Analysis of Pelvic Floor Biomechanical Models to Elucidate the Mechanism for Improving Urination and Defecation Dysfunction in Older Adults: Protocol for a Model Development and Validation Study (e56333)
Rui Wang, Guangtian Liu, Liwei Jing, Jing Zhang, Chenyang Li, Lichao Gong. . . . 4982

Detecting and Understanding Social Influence During Drinking Situations: Protocol for a Bluetooth-Based Sensor Feasibility and Acceptability Study (e50650)
Kristina Jackson, Matthew Meisel, Alexander Sokolovsky, Katie Chen, Nancy Barnett. . . . 4994

XSL•FO
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The Daily Experiences of Hispanic and Latinx Dementia Caregivers Study: Protocol for a Fully Remote Daily Diary Observational Cohort Study (e55216)
Sofía Mildrum Chana, Lorelí Álvarez, Abigail Poe, Natashia Bibriescas, Danny Wang, Stephanie DiFiglia, Andrés Azuero, Michael Crowe, Frank Puga. 5010

Erlotinib or Gefitinib for Treating Advanced Epidermal Growth Factor Receptor Mutation–Positive Lung Cancer in Aotearoa New Zealand: Protocol for a National Whole-of-Patient-Population Retrospective Cohort Study and Results of a Validation Substudy (e51381)
Phyu Aye, Joanne Barnes, George Laking, Laird Cameron, Malcolm Anderson, Brendan Luey, Stephen Delany, Dean Harris, Blair McLaren, Elliott Brenman, Jayden Wong, Ross Lawrenson, Michael Arendse, Sandar Tin Tin, Mark Elwood, Philip Hope, Mark McKeage. 5025

Body Composition and Energy Expenditure in Youth With Spina Bifida: Protocol for a Multisite, Cross-Sectional Study (e52779)
Michele Polfuss, Kathryn Smith, Betsy Hopson, Andrea Moosreiner, Chiang-Ching Huang, Michele Ravelli, Dan Ding, Zijian Huang, Brandon Rocque, Rosemary White-Traut, Alexander Van Speybroeck, Kathleen Sawin. 5038

Gender Inequalities of Health and Quality of Life in Informal Caregivers in Spain: Protocol for the Longitudinal and Multicenter CUIDAR-SE Study (e58440)
María Garcia-Calvente, Diana Mora, María Del Río-Lozano. 5056

Effect of Menstrual Cycle and Hormonal Contraception on Musculoskeletal Health and Performance: Protocol for a Prospective Cohort Design and Cross-Sectional Comparison (e50542)
Sarah Myers, Rebecca Knight, Sophie Wardle, Kirsty Waldock, Thomas O'Leary, Richard Jones, Paul Muckelt, Anton Eisenhauer, Jonathan Tang, William Fraser, Julie Greeves. 5068

Childhood Gender Diversity and Mental Health: Protocol for the Longitudinal, Observational Gender Journey Project (e55558)
Marco Hidalgo, Diane Chen, Amy Tishelman, Johanna Olson-Kennedy, Yee-Ming Chan, Robert Garofalo, Hanno Petras, Stephen Rosenthal, Diane Ehrensaft. 5080

Preventing Cognitive Decline in Older Latino Adults With HIV Through a Culturally Tailored Health Promotion Intervention: Protocol for a Single-Arm Pilot Trial (e55507)
Daniel Jimenez, Emily Ross, Elliott Weinstein, Hetta Gouse, Yue Pan, David Martinez Garza, Shanna Burke, Jin Joo, Victoria Behar-Zusman.
5 0 9 1

The Association Between Physical Distancing Behaviors to Avoid COVID-19 and Health-Related Quality of Life in Immunocompromised and Nonimmunocompromised Individuals: Patient-Informed Protocol for the Observational, Cross-Sectional EAGLE Study (e52643)
Paul Williams, Timothy Herring, Renata Yokota, Tiago Maia, Sudhir Venkatesan, James Marcus, Gabriella Settergren, Sofie Arnetorp, Andrew Lloyd, Johan Severens, James Varni, Sharon Dixon, Lweendo Hamusankwa, Philip Powell, Sylvia Taylor, John Ware Jr, Marieke Krol. 5103

Effects of Auditory and Visual White Noise on Oculomotor Inhibition in Children With Attention-Deficit/Hyperactivity Disorder: Protocol for a Crossover Study (e56388)
Erica Jostrup, Marcus Nyström, Pia Tallberg, Göran Söderlund, Peik Gustafsson, Emma Claesdotter-Knutsson. 5119

Effectiveness and Acceptability of Cognitive Behavioral Therapy and Family Therapy for Gaming Disorder: Protocol for a Nonrandomized Intervention Study of a Novel Psychological Treatment (e56315)
Per Bore, Sara Nilsson, Mitchell Andersson, Kajsa Oehm, Joel Attvall, Anders Håkansson, Emma Claesdotter-Knutsson. 5130

EXploring Patterns of Use and Effects of Adult Day Programs to Improve Trajectories of Continuing Care (EXPEDITE): Protocol for a Retrospective Cohort Study (e60896)
Matthias Hoben, Colleen Maxwell, Andrea Ubell, Malcolm Doupe, Zahra Goodarzi, Saleema Allana, Ron Beleno, Whitney Berta, Jennifer Bethell, Tamara Daly, Liane Ginsburg, Atiqur Rahman, Hung Nguyen, Kaitlyn Tate, Kimberlyn McGrail. 5144

Piloting the Inclusion of the Key Populations Unique Identifier Code in the South African Routine Health Information Management System: Protocol for a Multiphased Study (e55092)
Mashudu Rampilo, Edith Phalane, Refilwe Phaswana-Mafuya. 5156

XSL•FO
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Establishing Priorities for Improving Data Collection and Measurement of Mental Health and Well-Being of Adolescents With Special Educational Needs Within Nonmainstream Schools: Protocol for a Delphi Study (e58610)
Mairi Jeffery, Jessica Deighton, Suzet Lereya. . . . 5165

Objective Analysis of Traditional Chinese Medicine Syndrome Differentiation of Patients With Diabetes and Prediabetes: Protocol for a Nonrandomized, Exploratory, Observational Case-Control Study Using Digitalized Traditional Chinese Medicine Diagnostic Tools (e56024)
Hui Ng, Shu Chong, Yi Li, Tong Goh, Ka Pang, Michelle Pereira, Chin-Ming Huang. . . . 5173

Analyzing the Influence of Video Game and Music Engagement on Technical Skills Acquisition in Dental Students in Preclinical Phase: Protocol for a Prospective, Controlled, Longitudinal Study (e55738)
Roselyne Clouet, Alexis Gaudin, Jeanne Tourtelier, Claire Gogendeau, Samuel Serisier, Tony Prud'homme. . . . 5188

Toward Physiological Detection of a “Just-Right” Challenge Level for Motor Learning in Immersive Virtual Reality: Protocol for a Cross-Sectional Study (e55730)
Samory Houzangbe, Martin Lemay, Danielle Levac. . . . 5196

Outcomes of Patients With Early and Locally Advanced Lung Cancer: Protocol for the Italian Lung Cancer Observational Study (LUCENT) (e57183)
Luca Bertolaccini, Oriana Ciani, Marco Lucchi, Francesco Zaraca, Alessandro Bertani, Roberto Crisci, Lorenzo Spaggiari, LUCENT Study Group. . . . 5207

The Rutgers Omnibus Study: Protocol for Quarterly Web-Based Surveys to Promote Rapid Tobacco Research (e58203)
Michelle Bover Manderski, William Young, Ollie Ganz, Cristine Delnevo. . . . 5221

A Self-Administered Eating Behavior Scale for Patients With Heart Failure Living at Home: Protocol for a Mixed Methods Scale Development Study (e60719)
Daisaku Kashiwakura, Akiko Hiyama, Masumi Muramatsu, Atsuko Hinotsu, Michiko Takeda, Norio Suzuki, Sachie Akiyama, Sayuri Kurihara, Keisuke Kida. . . . 5228

Multidimensional School-Based and Family-Involved Interventions to Promote a Healthy and Sustainable Lifestyle (LIVELY) for Childhood Obesity Prevention: Study Protocol (e57509)
Sara Basilico, Maria Conti, Ilaria Ardoino, Chiara Breda, Federica Loperfido, Elena Klaic, Linda Spialtini, Andreana Foresta, Francesca Orsini, Maria Ojeda Fernandez, Stefano Conca Bonizzoni, Elisabetta Modena, Yasamin Tootoonchi Hamedani, Federica Villa, Hellas Cena, Marta Baviera, Carlotta Franchi. . . . 5238

Noninvasive, Multimodal Inflammatory Biomarker Discovery for Systemic Inflammation (NOVA Study): Protocol for a Cross-Sectional Study (e62877)
Jinjoo Shim, Sinziana Muraru, Rucsandra Dobrota, Elgar Fleisch, Oliver Distler, Filipe Barata. . . . 5252

The COSMOS Registry of CytoSorb Hemoadsorption Therapy in Critically Ill Patients: Protocol for an International, Prospective Registry (e55880)
Fabio Taccone, Frank Brunkhorst, Gabriella Bottari, Jorge Hidalgo, Andreas Kribben, Jean-Louis Teboul, Dana Tomescu, Teresa Klaus, Joerg Scheier, Efthymios Deliargyris, Ricard Ferrer. . . . 5263

Effectiveness of Ayush Rasayana A and B on the Quality of Life of Older Adults: Protocol for a Cluster Randomized Controlled Trial (e58186)
Pallavi Mundada, Deepa Makhija, Sunita Mata, Kalpana Kachare, Aparna Manathottathil, Abha Sharma, Bhogavalli Rao, Rakesh Rana, Arunabh Tripathi, Kiran Rana, Vandana Joshi, Ashish Raturi, Anukampa Singh, N Srikanth, Rabinarayan Acharya. . . . 5276

Relatives’ and Intensive Care Unit Personnel’s Perspectives of Care in Organ Donation: Protocol for a Multiple Methods Study (e55643)
Kathe Meyer, Gudrun Rohde, Gro Frivold. . . . 5286

XSL•FO
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Bystander Response and Out-of-Hospital Cardiac Arrest Outcomes (Bro. Study) in 3 Gulf Countries: Protocol for a Prospective, Observational, International Collaboration Study (e58780)
Munawar Farooq, Mahmood Al Jufaili, Faisal Hanjra, Shabbir Ahmad, Emad Dababneh, Omar Al Nahhas, Khalid Bashir. 5297

Methodology for Biological Sample Collection, Processing, and Storage in the Newcastle 1000 Pregnancy Cohort: Protocol for a Longitudinal, Prospective Population-Based Study in Australia (e63562)
Joshua Fisher, Tegan Grace, Nathan Castles, Elizabeth Jones, Sarah Delforce, Alexandra Peters, Gabrielle Crombie, Emily Hoedt, Kirby Warren, Richard Kahl, Jonathan Hirst, Kirsty Pringle, Craig Pennell. 5304

Factors Influencing Outcome After Shoulder Arthroplasty (FINOSA Study): Protocol of a Prospective Longitudinal Study With Randomized Group Allocation (e56522)
Anke Claes, Annelien De Mesel, Thomas Struyf, Olivier Verborgt, Filip Struyf. 5319

Vientiane Multigenerational Birth Cohort Project in Lao People's Democratic Republic: Protocol for Establishing a Longitudinal Multigenerational Birth Cohort to Promote Population Health (e59545)
Jordyn Wallenborn, Miley Sinantha-Hu, Vattahanaphone Ouipoulikoune, Sengchanh Kounnavong, Latsamy Siengsounthone, Nicole Probst-Hensch, Peter Odermatt, Somphou Sayasone, Günther Fink. 5333

Assessment of Health and Well-Being Effects Associated With the Challenging Drinking Water Situation in the Gaza Strip: Protocol for a Cross-Sectional Household Survey Study (e63415)
Curdin Brugger, Dominik Dietler, Bassam Abu Hamad, Tammo van Gastel, Federico Sittaro, Rodolfo Rossi, Branwen Owen, Nicole Probst-Hensch, Mirko Winkler. 5344

Ultrasound-Guided High-Intensity Focused Ultrasound Combined With PD-1 Blockade in Patients With Liver Metastases From Lung Cancer: Protocol for a Single-Arm Phase 2 Trial (e59152)
Chao Hu, Qiang Fu, Fei Gao, Jian Zeng, Wei Xiao, Hui Li, Li Peng, Xi Huang, Li Yang, Wen Chen, Ming Jiang. 5357

Consistent and Correct Use of Condoms With Lubricants and Associated Factors Among Men Who Have Sex With Men from the Ghana Men's Study II: Protocol for a Mixed Methods Study (e63276)
Ratif Abdulai, Edith Phalane, Kyeremeh Atuahene, Refilwe Phaswana-Mafuya. 5366

Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study (e58895)
Sharon White-Lewis, Joseph Lightner, Julia Crowely, Amanda Grimes, Kathleen Spears, Steven Chesnut. 5377

Incentivizing Rural Work Preferences Among Specialist Physicians: Protocol for a Discrete Choice Experiment (e59621)
Anushree Joshi, Jallavi Panchamia, Apurvakumar Pandya. 5385

Evaluating the Impact of Assistive Technologies on Individuals With Disabilities in Benin: Protocol for a Cross-Sectional Study (e60869)
Orthelo Atigossou, Sègbédji Capo-chichi, Penielle Mitcha , Aristide Honado. 5401

SARS-CoV-2 Infections in a Triad of Primary School Learners (Grades 1-7), Their Parents, and Teachers in KwaZulu-Natal, South Africa: Protocol for a Cross-Sectional and Nested Case-Cohort Study (e52713)
Reshmi Dassaye, Terusha Chetty, Brodie Daniels, Zakir Gaffoor, Elizabeth Spooner, Trisha Ramraj, Ncengani Mthethwa, Duduzile Nsibande, Saresha Pillay, Arvin Bhana, Vuyolwethu Magasana, Tarylee Reddy, Khanya Mohlabi, Penelope Moore, Wendy Burgers, Tulio de Oliveira, Nokukhanya Msomi, Ameena Goga. 5409

Examining Caregiver Practices During Adolescent Outpatient Alcohol Use and Co-Occurring Mental Health Treatment: Protocol for a Dyadic Ecological Momentary Assessment Study (e63399)
Samuel Meisel, Aaron Hogue, John Kelly, Elizabeth McQuaid, Robert Miranda Jr. 5424

Spread and Scale of the Integrated Nutrition Pathway for Acute Care Across Canada: Protocol for the Advancing Malnutrition Care Program (e62764)
Katherine Ford, Celia Laur, Rupinder Dhaliwal, Roseann Nasser, Leah Gramlich, Johane Allard, Heather Keller, AMC Core Team. 5444

XSL•FO
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Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study (e51084)
Sara Russo, Rosario Caruso, Gianluca Conte, Arianna Magon, Ida Vangone, Barbara Bascape', Giulia Maga, Malgorzata Pasek, Cristina Arrigoni. . . . 5455

Screen Use Time and Its Association With Mental Health Issues in Young Adults in India: Protocol for a Cross-Sectional Study (e39707)
Swasti Deshpande, Ashmeet Sachdev, Anwesha Maharana, Siddhesh Zadey, Surabhi Dharmadhikari, Swati Ghate, Pawankumar Godatwar, Nisha Ojha, Sanjeev Sharma. . . . 5472

Developing and Validating a Self-Care Self-Efficacy Scale for Oral Anticoagulation Therapy in Patients With Nonvalvular Atrial Fibrillation: Protocol for a Mixed Methods Study (e51489)
Arianna Magon, Jeroen Hendriks, Rosario Caruso. . . . 5480

Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies Using AI (QUADAS-AI): Protocol for a Qualitative Study (e58202)
Ahmad Guni, Viknesh Sounderajah, Penny Whiting, Patrick Bossuyt, Ara Darzi, Hutan Ashrafian. . . . 5490

Evaluating the Appropriateness of Podcasts to Improve the Knowledge and Awareness of Selected Health Topics Among Undergraduate General Nursing Students: Protocol for an International Feasibility Study (e50735)
Alanna Denny, Brian Curtin, Simon Taylor-Robinson, Griphin Chirambo, Liezel Cilliers, Tsung-Shu Wu, Ciara O'Meara, Richard Booth, John O'Donoghue. . . . 5497

Comparison of Spontaneous Pushing and Directed Pushing During the Second Stage of Labor Among Chinese Women Without Epidural Analgesia: Protocol for a Noninferior Feasibility Study (e55701)
Jiasi Yao, Heike Roth, Debra Anderson, Hong Lu, Huijuan Rong, Kathleen Baird. . . . 5505

Evaluating a Remotely Delivered Cardio-Oncology Rehabilitation Intervention for Patients With Breast Cancer (REMOTE-COR-B): Protocol for a Single-Arm Feasibility Trial (e53301)
Camille Short, Jonathan Rawstorn, Tamara Jones, Lara Edbrooke, Sandra Hayes, Ralph Maddison, Sophie Nightingale, Hilmy Ismail, Richard De Boer, Fiona Hegi-Johnson, Aaron Sverdlov, Robyn Bell, Irene Halligan, Linda Denehy. . . . 5516

Assessing and Improving the Care of Patients With Heart Failure in Ghana: Protocol for a Prospective Observational Study and the Ghana Heart Initiative-Heart Failure Registry (e52616)
Felix Awindaogo, Emmanuel Acheamfour-Akowuah, Alfred Doku, Collins Kokuro, Francis Agyekum, Isaac Owusu. . . . 5531

Investigating Rhythmicity in App Usage to Predict Depressive Symptoms: Protocol for Personalized Framework Development and Validation Through a Countrywide Study (e51540)
Md Ahmed, Tanvir Hasan, Salekul Islam, Nova Ahmed. . . . 5543

Lack of Diversity in Research on Females with Ehlers-Danlos Syndromes: Recruitment Protocol for a Quantitative Online Survey (e53646)
Jennifer Glayzer, Bethany Bray, William Kobak, Alana Steffen, Judith Schlaeger. . . . 5560

A Community Mental Health Integrated Disaster Preparedness Intervention for Bushfire Recovery in Rural Australian Communities: Protocol for a Multimethods Feasibility and Acceptability Pilot Study (e53454)
Caitlin Pike, Henriette Dohnt, Phillip Tully, Warren Bartik, Courtney Welton-Mitchell, Clara Murray, Kylie Rice, Suzanne Cosh, Amy Lykins. . . 5 5 7 2

Quality of Life in Patients and Their Spouses and Cohabitating Partners in the Year Following a Cancer Biopsy (the Couples Cope Study): Protocol for a Prospective Observational Study (e52361)
Patricia Moreno, Sarah Worch, Jessica Thomas, Rebecca Nguyen, Heidy Medina, Frank Penedo, Judith Moskowitz, Betina Yanez, Sheetal Kircher, Shilajit Kundu, Sarah Flury, Elaine Cheung. . . . 5582

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Optimizing Response Rates to Examine Health IT Maturity and Nurse Practitioner Care Environments in US Nursing Homes: Mixed Mode Survey Recruitment Protocol (e56170)
Gregory Alexander, Lusine Poghosyan, Yihong Zhao, Mollie Hobensack, Sergey Kisselev, Allison Norful, John McHugh, Keely Wise, M Schrimpf, Ann Kolanowski, Tamanna Bhatia, Sabrina Tasnova. . . . 5592

Feasibility and Acceptability Study of a Culturally Adapted Web-Based Intervention to Reduce Suicidal Ideation for Syrian Asylum Seekers and Refugees in the United Kingdom: Protocol for a Mixed Methods Study (e56957)
Oliver Beuthin, Sadiya Shahid, Ly-Mee Yu, Kamaldeep Bhui. . . . 5602

Parent Education and Counseling (PairEd-C) Intervention to Improve Family-Centered Care: Protocol for a Prospective Acceptability Study Using the Theoretical Framework of Acceptability (e54914)
Leul Deribe, Eshetu Girma, Nataliya Lindström, Abdulkadir Gidey, Solomon Teferra, Adamu Addissie. . . . 5614

Predicting the Transition From Depression to Suicidal Ideation Using Facebook Data Among Indian-Bangladeshi Individuals: Protocol for a Cohort Study (e55511)
Manoshi Turjo, Khushboo Mundada, Nuzhat Haque, Nova Ahmed. . . . 5627

Strengthening Cause of Death Statistics in Selected Districts of 3 States in India: Protocol for an Uncontrolled, Before-After, Mixed Method Study (e51493)
Ashoo Grover, Saritha Nair, Saurabh Sharma, Shefali Gupta, Suyesh Shrivastava, Pushpendra Singh, Srikanta Kanungo, Senthanro Ovung, Charan Singh, Abdul Khan, Sandeep Sharma, Subrata Palo, Tapas Chakma, Anjali Bajaj. . . . 5644

Stepped-Care Web-Based Parent Support Following Congenital Heart Disease: Protocol for a Randomized Controlled Trial (e64216)
Marin Taylor, Bianca Bondi, Brendan Andrade, Stephanie Au-Young, Vann Chau, Ashley Danguecan, Naddley Désiré, Ting Guo, Dragana Ostojic-Aitkens, Shari Wade, Steven Miller, Tricia Williams. . . . 5686

Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis: Protocol for a Phase 1 Clinical Trial to Determine Safety and Identify Side Effects (e50513)
Evan Fogel, Jeffrey Easler, Ying Yuan, Dhiraj Yadav, Darwin Conwell, Santhi Vege, Samuel Han, Walter Park, Vanessa Patrick, Fletcher White. . . . 5716

Benefits, Harms, and Stakeholder Perspectives Regarding Opioid Therapy for Pain in Individuals With Metastatic Cancer: Protocol for a Descriptive Cohort Study (e54953)
Katie Jones, Gretchen White, Antonia Bennett, Hailey Bulls, Paula Escott, Sarah Orris, Elizabeth Escott, Stacy Fischer, Megan Hamm, Tamar Krishnamurti, Risa Wong, Thomas LeBlanc, Jane Liebschutz, Salimah Meghani, Cardinale Smith, Jennifer Temel, Christine Ritchie, Jessica Merlin. . . . 5732

Leveraging Parents and Peer Recovery Supports to Increase Recovery Capital in Emerging Adults With Polysubstance Use: Protocol for a Feasibility, Acceptability, and Appropriateness Study of Launch (e60671)
Tess Drazdowski, Sierra Castedo de Martell, Ashli Sheidow, Jason Chapman, Michael McCart. . . . 5744

Novel Machine Learning HIV Intervention for Sexual and Gender Minority Young People Who Have Sex With Men (uTECH): Protocol for a Randomized Comparison Trial (e58448)
Ian Holloway, Elizabeth Wu, Callisto Boka, Nina Young, Chenglin Hong, Kimberly Fuentes, Kimmo Kärkkäinen, Mehrab Beikzadeh, Alexandra Avendaño, Juan Jauregui, Aileen Zhang, Lalaine Sevillano, Colin Fyfe, Cal Brisbin, Raiza Beltran, Luisita Cordero, Jeffrey Parsons, Majid Sarrafzadeh. . . . 5789

A Microfinance Intervention With or Without Peer Support to Improve Mental Health Among Transgender and Nonbinary Adults (the Creating Access to Resources and Economic Support Study): Protocol for a Randomized Controlled Trial (e63656)
Tonia Poteat, Sari Reisner, Andrea Wirtz, Larissa Mayo-Wilson, Carter Brown, Wiley Kornbluh, Ash Humphrey, Nancy Perrin. . . . 5806

Stimulation Therapy to Induce Mothers: Protocol for a Multicenter Randomized Controlled Trial (e63463)
Danna Tortal, Veronika Shabanova, Sarah Taylor, Xiao Xu, Molly McAdow, Bethany Stetson, Sarah McCollum, Ester Sanchez, Amie Adjakple, Jessica Leventhal, Moeun Son. . . . 5826

XSL•FO
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Feasibility and Acceptability of a Motivational Interviewing–Based Telehealth Intervention for Bacterial Sexually Transmitted Infection Screening: Protocol for a Sequential Explanatory Mixed Methods Study (e64433)
Akshay Sharma, Sara Boyd, Erin Bonar. . . . 5843

Using Systems Engineering and Implementation Science to Design an Implementation Package for Preoperative Comprehensive Geriatric Assessment Among Older Adults Having Major Abdominal Surgery: Protocol for a 3-Phase Study (e59428)
Julia Berian, Margaret Schwarze, Nicole Werner, Jane Mahoney, Manish Shah. . . . 5858

Testing a Conceptual Model of Early Adversity, Neural Function, and Psychopathology: Protocol for a Retrospective Observational Cohort Study (e59636)
Nicolas Murgueitio, Maresa Tate, Lucy Lurie, Zoe Priddy, Sneha Boda, Michelle Shipkova, Micaela Rodriguez, Laura Machlin, Sarah Furlong, Amanda Mitchell, Katie McLaughlin, Margaret Sheridan. . . . 5874

Neural Conversational Agent for Weight Loss Counseling: Protocol for an Implementation and Feasibility Study (e60361)
Alexander Kotov, April Idalski Carcone, Elizabeth Towner. . . . 5903

Examining the Impact of Simultaneous Alcohol and Cannabis Use on Alcohol Consumption and Consequences: Protocol for an Observational Ambulatory Assessment Study in Young Adults (e58685)
Rachel Gunn, Jane Metrik, Nancy Barnett, Kristina Jackson, Sharon Lipperman-Kreda, Robert Miranda Jr, Timothy Trull, Mary Fernandez. . . 5917

Intervention for the Management of Neuropsychiatric Symptoms to Reduce Caregiver Stress: Protocol for the Mindful and Self-Compassion Care Intervention for Caregivers of Persons Living With Dementia (e58356)
Aniyah Travis, Arden O'Donnell, Natalia Giraldo-Santiago, Sarah Stone, Daniel Torres, Shelley Adler, Ana-Maria Vranceanu, Christine Ritchie. 5939

Intervention Development for Tailored Education for Aging and Cognitive Health (TEACH) for Dementia Prevention in Midlife Adults: Protocol for a Randomized Controlled Trial (e60395)
Laura Korthauer, Rochelle Rosen, Geoffrey Tremont, Jennifer Davis. . . . 5949

Structural Influences on Methamphetamine Use Among Black Sexual Minority Men (HISTORY Study): Protocol for a Longitudinal Cohort Study (e63761)
Samuel Opara, Sabriya Linton, Brian Weir, Natalie Crawford, David Holland, Antonio Newman Jr, McKinsey Bullock, Marcus Reed, Srija Dutta, Kamini Doraivelu, Charles Stephens, Justin Smith, Yeeli Mui, Sophia Hussen. . . . 5960

The Young Adult Centered Healthforce Training (YACHT) Program to Increase HIV Testing and Pre-Exposure Prophylaxis Referrals Among Young Sexual Minority Men in Florida: Protocol for a Type 2 Implementation-Effectiveness Hybrid Trial With a Stepped Wedge Design (e63191)
Rebecca Giguere, Maria Fernandez, Jose Bauermeister, Iván Balán, Subhash Aryal, Andrea Cheshure, Sara Green, Willey Lin, Jonathan Morgan, Sylvie Naar. . . . 5992

Impact of Changes in Criminal-Legal Practices During the COVID-19 Pandemic on the HIV Risk Behaviors of Women Who Use Drugs: Protocol for a Multimethods Qualitative Study (e58285)
Amy Smoyer. . . . 6009

Designing, Developing, and Testing a Chatbot for Parents and Caregivers of Children and Young People With Rheumatological Conditions (the IMPACT Study): Protocol for a Co-Designed Proof-of-Concept Study (e57238)
Polly Livermore, Klaudia Kupiec, Lucy Wedderburn, Andrea Knight, Ameenat Solebo, Roz Shafran, Glenn Robert, N Sebire, Faith Gibson, IMPACT Steering Group. . . . 6020

XSL•FO
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Developing and Evaluating a Data-Driven and Systems Approach to Health Promotion Among Vocational Students: Protocol for the Data Health Study (e52571)
Clara Heinze, Rikke Hartmeyer, Anne Sidenius, Lene Ringgaard, Anne-Louise Bjerregaard, Rikke Krølner, Steven Allender, Adrian Bauman, Charlotte Klinker. 6029

Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial (e51683)
Nicole Wimmesberger, Diana Rau, Florian Schuchardt, Simone Meier, Matthias Herrmann, Ulrike Bergmann, Erik Farin-Glattacker, Jochen Brich. 6045

Codevelopment and Deployment of a System for the Telemonitoring of Activities of Daily Living Among Older Adults Receiving Home Care Services: Protocol for an Action Design Research Study (e52284)
Maxime Lussier, Mélanie Couture, Sylvain Giroux, Aline Aboujaoudé, Hubert Ngankam, Hélène Pigot, Sébastien Gaboury, Kevin Bouchard, Carolina Bottari, Patricia Belchior, Guy Paré, Nathalie Bier. 6056

Designing Implementation Strategies for the Inclusion of Lesbian, Gay, Bisexual, Transgender, Intersex, Queer, and Allied and Key Populations' Content in Undergraduate Nursing Curricula in KwaZulu-Natal, South Africa: Protocol for a Multimethods Research Project (e52250)
Celenkosini Nxumalo, Zamasomi Luvuno, Wilbroda Chiya, Silingene Ngcobo, Deshini Naidoo, Sophia Zamudio-Haas, Orlando Harris. 6072

The Durban University of Technology Faculty of Health Sciences Decentralized Clinical Training Project: Protocol for an Implementation Study in KwaZulu-Natal, South Africa (e52243)
Celenkosini Nxumalo, Pavitra Pillay, Gugu Mchunu. 6086

Defining and Risk-Stratifying Immunosuppression (the DESTINIES Study): Protocol for an Electronic Delphi Study (e56271)
Meredith Leston, José Ordóñez-Mena, Mark Joy, Simon de Lusignan, Richard Hobbs, Iain McInnes, Lennard Lee. 6098

Canadian Armed Forces Veterans' Perspectives on the Effects of Exposure to Children in Armed Conflict During Military Service: Protocol for a Qualitative Study (e57146)
Catherine Baillie Abidi, San Patten, Stephanie Houle, Ken Hoffer, Kathryn Reeves, Stéphanie Bélanger, Anthony Nazarov, Samantha Wells. . 6 1 0 6

Rationale, Design, and Baseline Characteristics of Participants in the Health@NUS mHealth Augmented Cohort Study Examining Student-to-Work Life Transition: Protocol for a Prospective Cohort Study (e56749)
Xin Chua, Sarah Edney, Andre Müller, Nicholas Petrunoff, Clare Whitton, Zoey Tay, Claire Goh, Bozhi Chen, Su Park, Salome Rebello, Alicia Low, Janelle Chia, Daphne Koek, Karen Cheong, Rob van Dam, Falk Müller-Riemenschneider. 6118

Evaluating the Preliminary Effectiveness of the Person-Centered Care Assessment Tool (PCC-AT) in Zambian Health Facilities: Protocol for a Mixed Methods Cross-Sectional Study (e54129)
Jessica Posner, Adamson Ndhlovu, Jemmy Musangulule, Malia Duffy, Amy Casella, Caitlin Madevu-Matson, Nicole Davis, Melissa Sharer. . . 6 1 3 4

Capitalizing on Community Groups to Improve Women's Resilience to Maternal and Child Health Challenges: Protocol for a Human-Centered Design Study in Tanzania (e54323)
Kahabi Isangula, Aminieli Usiri, Eunice Pallangyo. 6141

Virtual Hospitals and Patient Experience: Protocol for a Mixed Methods Observational Study (e58683)
Tim Jackson, Kanesha Ward, Shannon Saad, Sarah White, Shila Poudel, Freya Raffan, Sue Amanatidis, Jenna Bartyn, Owen Hutchings, Enrico Coiera, Kevin Chan, Annie Lau. 6150

Fostering Shared Decision-Making Between Patients and Health Care Professionals in Clinical Practice Guidelines: Protocol for a Project to Develop and Test a Tool for Guideline Developers (e57611)
Lena Fischer, Fülöp Scheibler, Corinna Schaefer, Torsten Karge, Thomas Langer, Leon Schewe, Ivan Florez, Andrew Hutchinson, Sheyu Li, Marta Maes-Carballo, Zachary Munn, Lilisbeth Perestelo-Perez, Livia Puljak, Anne Stiggelbout, Dawid Pieper. 6159

XSL•FO
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Real-Time Triage, Position, and Documentation (TriPoD) During Medical Response to Major Incidents: Protocol for an Action Research Study (e57819)
Monica Rådestad, Torkel Kanfjäll, Veronica Lindström. . . . 6172

Model for Doctor of Nursing Practice Projects Based on Cross-Fertilization Between Improvement and Implementation Sciences: Protocol for Quality Improvement and Program Evaluation Studies (e54213)
Azizeh Sowan, Matthew Chinman. . . . 6208

Understanding Employee Voice Behavior Through the Use of Digital Voice Channel in Long-Term Care: Protocol for an Embedded Multiple-Case Study (e48601)
Anja Kepplinger, Alexander Braun, André Fringer, Martina Roes. . . . 6219

Understanding the Acceptability of Broadly Neutralizing Antibodies for HIV Prevention Among At-Risk Populations and Feasibility Considerations for Product Introduction in India: Protocol for a Qualitative Study (e47700)
Joyeeta Mukherjee, Shruta Rawat, Saif ul Hadi, Pritha Aggarwal, Venkatesan Chakrapani, Pratyasha Rath, Pallavi Manchi, Srikrishnan Aylur, Shelly Malhotra, Margaret Keane, Alok Gangaramany. . . . 6233

Lifestyle Medicine Implementation in 8 Health Systems: Protocol for a Multiple Case Study Investigation (e51562)
Meghan Ames, Micaela Karlsen, Samantha Sundermeir, Neve Durrwachter, Tyler Hemmingson, Melissa Reznar, Kara Staffier, Bruce Weeks, Joel Gittelsohn. . . . 6248

Target Product Profile for a Machine Learning–Automated Retinal Imaging Analysis Software for Use in English Diabetic Eye Screening: Protocol for a Mixed Methods Study (e50568)
Trystan Macdonald, Jacqueline Dinnes, Gregory Maniatopoulos, Sian Taylor-Phillips, Bethany Shinkins, Jeffry Hogg, John Dunbar, Ameenat Solebo, Hannah Sutton, John Attwood, Michael Pogose, Rosalind Given-Wilson, Felix Greaves, Carl Macrae, Russell Pearson, Daniel Bamford, Adnan Tufail, Xiaoxuan Liu, Alastair Denniston. . . . 6258

How a National Organization Works in Partnership With People Who Have Lived Experience in Mental Health Improvement Programs: Protocol for an Exploratory Case Study (e51779)
Ciara Robertson, Carina Hibberd, Ashley Shepherd, Gordon Johnston. . . . 6271

Preimplementation Evaluation of a Self-Directed Care Program in a Veterans Health Administration Regional Network: Protocol for a Mixed Methods Study (e57341)
Pranjal Tyagi, Erin Bouldin, Wendy Hathaway, Derek D'Arcy, Samer Nasr, Orna Intrator, Stuti Dang. . . . 6280

Long-Term Post–COVID-19 Health and Psychosocial Effects and Coping Resources Among Survivors of Severe and Critical COVID-19 in Central and Eastern Europe: Protocol for an International Qualitative Study (e57596)
Anna Alexandrova-Karamanova, Anita Lauri Korajlija, Peter Halama, Adriana Baban. . . . 6291

Mapping Respiratory Health Digital Interventions in South and Southeast Asia: Protocol for a Scoping Review (e52517)
Laura Evans, Jay Evans, Monica Fletcher, Adina Abdullah, Zakiuddin Ahmed. . . . 6301

Homestay Hosting Dynamics and Refugee Well-Being: Protocol for a Scoping Review (e56242)
Areej Al-Hamad, Yasin Yasin, Kateryna Metersky, Sepali Guruge, Khadija Mahsud. . . . 6308

Monitoring and Evaluation of Dementia-Friendly Neighborhoods Using a Walkshed Approach: Protocol for a Scoping Review (e50548)
Mark Groulx, Shannon Freeman, Keone Gourlay, Dawn Hemingway, Emma Rossnagel, Habib Chaudhury, Mohammadjavad Nouri. . . . 6315

XSL•FO
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Overview of Retention Strategies for Medical Doctors in Low- and Middle-Income Countries and Their Effectiveness: Protocol for a Scoping Review (e52938)
Norehan Jinah, Ili Abdullah Sharin, Pangie Bakit, Izzuan Adnan, Kun Lee. . . . 6324

Virtual Reality for Developing Patient-Facing Communication Skills in Medical and Graduate Education: Protocol for a Scoping Review (e53901)
Nairy Khodabakhshian, Kyla Gaeul Lee, Tulip Marawi, Maryam Sorkhou, Sobiga Vyravanathan, Nicole Harnett. . . . 6336

Interactive Narrative–Based Digital Health Interventions for Vaccine Communication: Protocol for a Scoping Review (e51137)
Ahmed Haji Said, Kate Winskell, Robert Bednarczyk, Erin Reardon, Lavanya Vasudevan. . . . 6345

Simultaneous Cardiopulmonary Exercise Testing and Echocardiography for Investigation of Cardiopulmonary Dysfunction in Outpatients: Protocol for a Scoping Review (e52076)
Benjamin Gerhardy, Shanthosh Sivapathan, Sam Orde, Lucy Morgan. . . . 6352

Ethical and Quality of Care-Related Challenges of Digital Health Twins in Older Care Settings: Protocol for a Scoping Review (e51153)
Md Jabin, Emillia Yaroson, Adaobi Ilodibe, Tillal Eldabi. . . . 6359

Professional-Facing Digital Health Solutions for the Care of Patients With Chronic Pain: Protocol for a Systematic Scoping Review (e51311)
Haruno McCartney, Ashleigh Main, Maryam Ibrar, Harleen Rai, Natalie Weir, Roma Maguire. . . . 6368

Data Visualization Support for Tumor Boards and Clinical Oncology: Protocol for a Scoping Review (e53627)
Dominik Boehm, Cosima Strantz, Jan Christoph, Hauke Busch, Thomas Ganslandt, Philipp Unberath. . . . 6376

Innovative Solutions for Patients Who Undergo Craniectomy: Protocol for a Scoping Review (e50647)
Laura Fernandez, Dylan Griswold, Isla Khun, Diana Rodriguez De Francisco. . . . 6383

Characteristics of Occupational Therapy Interventions to Promote Healthy Aging: Protocol for a Scoping Review (e55198)
Katrina Bannigan, Nicole Larkan, Emmanuelle Meurgue, Jason Sze. . . . 6388

Analysis of Self-Care Activities in Type 2 Diabetes in Brazil: Protocol for a Scoping Review (e49105)
Marileila Toledo, Edson da Silva, Elizabethe Esteves. . . . 6395

Definitions and Measurements for Atypical Presentations at Risk for Diagnostic Errors in Internal Medicine: Protocol for a Scoping Review (e56933)
Yukinori Harada, Ren Kawamura, Masashi Yokose, Taro Shimizu, Hardeep Singh. . . . 6402

Telehealth Evaluation in the United States: Protocol for a Scoping Review (e55209)
Yunxi Zhang, Yueh-Yun Lin, Lincy Lal, Jennifer Reneker, Elizabeth Hinton, Saurabh Chandra, J Swint. . . . 6409

Digital Health Interventions in Older Adult Populations Living With Chronic Disease in High-Income Countries: Protocol for a Scoping Review (e49130)
Mir Ashraf, Natasha Gallant, Cara Bradley. . . . 6416

Holistic Person-Centered Care in Radiotherapy: Protocol for a Scoping Review (e51338)
Fatima Bhyat, Andrew Makkink, Karien Henrico. . . . 6422

Exploring the Use and Implications of AI in Sexual and Reproductive Health and Rights: Protocol for a Scoping Review (e53888)
Tigest Tamrat, Yu Zhao, Denise Schalet, Shada AlSalamah, Sameer Pujari, Lale Say. . . . 6429

XSL•FO
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The Conceptualization and Measurement of Research Impact in Primary Health Care: Protocol for a Rapid Scoping Review (e55860)
Monica Aggarwal, Brian Hutchison, Kristina Kokorelias, Vivian Ramsden, Noah Ivers, Andrew Pinto, Ross Uphsur, Sabrina Wong, Nick Pimlott, Steve Slade. . . . 6436

Natural Language Processing for Work-Related Stress Detection Among Health Professionals: Protocol for a Scoping Review (e56267)
Jannic Bieri, Catherine Ikae, Souhir Souissi, Thomas Müller, Margarithe Schlunegger, Christoph Golz. . . . 6445

National Public Health Dashboards: Protocol for a Scoping Review (e52843)
Itzhak Yanovitzky, Gretchen Stahlman, Justine Quow, Matthew Ackerman, Yehuda Perry, Miriam Kim. . . . 6452

Application of Machine Learning in Multimorbidity Research: Protocol for a Scoping Review (e53761)
Danny Anthonimuthu, Ole Hejlesen, Ann-Dorthe Zwisler, Flemming Udsen. . . . 6461

Identifying Existing Guidelines, Frameworks, Checklists, and Recommendations for Implementing Patient-Reported Outcome Measures: Protocol for a Scoping Review (e52572)
Randi Jayasinghe, Susannah Ahern, Ashika Maharaj, Lorena Romero, Rasa Ruseckaite. . . . 6469

The Use of Metabolomes in Risk Stratification of Heart Failure Patients: Protocol for a Scoping Review (e53905)
Umar Adamu, Marheb Badianyama, Dineo Mpanya, Muzi Maseko, Nqoba Tsabedze. . . . 6475

Exploring the Distribution of 3D-Printed Simulator Designs Using Open-Source Databases to Facilitate Simulation-Based Learning Through a University and Nonprofit Collaboration: Protocol for a Scoping Review (e53167)
Mithusha Sritharan, Samyah Siraj, Ginny Brunton, Adam Dubrowski. . . . 6482

Impact of Responsible AI on the Occurrence and Resolution of Ethical Issues: Protocol for a Scoping Review (e52349)
Selina Boege, Madison Milne-Ives, Edward Meinert. . . . 6488

Centering Digital Health Equity During Technology Innovation: Protocol for a Comprehensive Scoping Review of Evidence-Based Tools and Approaches (e53855)
Kara Burns, Shoshana Bloom, Cecily Gilbert, Bronwen Merner, Mahima Kalla, Sreshta Sheri, Cleva Villanueva, Amio Matenga Ikihele, Lama Nazer, Raymond Sarmiento, Lindsay Stevens, Ngaree Blow, Wendy Chapman. . . . 6496

In Silico Approaches to Polyherbal Synergy: Protocol for a Scoping Review (e56646)
Anjana Chandhiruthil Sathyan, Pramod Yadav, Prashant Gupta, Arun Mahapathra, Ruknuddin Galib. . . . 6504

Social Factors Associated With Nutrition Risk in Community-Dwelling Older Adults in High-Income Countries: Protocol for a Scoping Review (e56714)
Christine Mills, Liza Boyar, Jessica O'Flaherty, Heather Keller. . . . 6510

Effects of Sound Interventions on the Mental Stress Response in Adults: Protocol for a Scoping Review (e54030)
Marina Saskovets, Zilu Liang, Ian Piumarta, Irina Saponkova. . . . 6520

Nursing Regulation Literature in Canada: Protocol for a Scoping Review (e56163)
Patrick Chiu, Kathleen Leslie, Janice Kung. . . . 6528

Correlates of Mild Behavioral Impairment in Older Adults: Protocol for a Scoping Review (e60009)
Seolah Yoon, Innhee Jeong, Jennifer Kim, Dahye Hong, Bada Kang. . . . 6534

XSL•FO
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Socioemotional Skills in the Teaching-Learning Process Mediated by Medium- and High-Fidelity Clinical Simulation in Nursing Students: Protocol for a Scoping Review (e56436)
Luz Contreras-Ramos, Elveny Laguado Jaimes, Nelly Jaimes Carvajal, Marleny Pico Ferreira, Magda Villamizar-Osorio. 6542

Surgical Residents' Perception of Feedback on Their Education: Protocol for a Scoping Review (e56727)
Carlos Costa, Gabriela Silva, Emerson Santos, Ana Engel, Ana Costa, Taisa da Silva, Washington da Conceição, Helena Cristóvão, Alba Lima, Vânia Brienze, Thaís Bizotto, Antonio Oliani, Júlio André. 6549

Identifications of Similarity Metrics for Patients With Cancer: Protocol for a Scoping Review (e58705)
Iryna Manuilova, Jan Bossenz, Annemarie Weise, Dominik Boehm, Cosima Strantz, Philipp Unberath, Niklas Reimer, Patrick Metzger, Thomas Pauli, Silke Werle, Susann Schulze, Sonja Hiemer, Arsenij Ustjanzew, Hans Kestler, Hauke Busch, Benedikt Brors, Jan Christoph. 6556

Challenges and Facilitation Approaches for the Participatory Design of AI-Based Clinical Decision Support Systems: Protocol for a Scoping Review (e58185)
Tabea Rambach, Patricia Gleim, Sekina Mandelartz, Carolin Heizmann, Christophe Kunze, Philipp Kellmeyer. 6565

Self-Management Systems for Patients and Clinicians in Parkinson Care: Protocol for an Integrated Scoping Review, Product Search, and Evaluation (e58845)
Selina Boege, Madison Milne-Ives, Edward Meinert, Camille Carroll. 6573

The Impact of Digital Technology on the Physical Health of Older Workers: Protocol for a Scoping Review (e59900)
Jeroen Spijker, Hande Barlın, Diana Grad, Yang Gu, Aija Klavina, Nilufer Korkmaz Yaylagul, Gunilla Kulla, Eda Orhun, Anna Šev íková, Brigid Unim, Cristina Tofan. 6582

Factors Influencing Primary Care Access for Common Mental Health Conditions Among Adults in West Africa: Protocol for a Scoping Review (e58890)
Nhyira Adjei-Banuah, Roberta Ayiku, Veronika Reichenberger, David Sasu, Tolib Mirzoev, Adrianna Murphy, Sammy Ohene, Edward Antwi, Irene Agyepong. 6590

Investigating Data Diversity and Model Robustness of AI Applications in Palliative Care and Hospice: Protocol for Scoping Review (e56353)
Selen Bozkurt, Soraya Fereydooni, Irem Kar, Catherine Diop Chalmers, Sharon Leslie, Ravi Pathak, Anne Walling, Charlotta Lindvall, Karl Lorenz, Tammie Quest, Karleen Giannitrapani, Dio Kavalieratos. 6603

Learning Styles of Medical Students, Surgical Residents, Medical Staff, and General Surgery Teachers When Learning Surgery: Protocol for a Scoping Review (e57229)
Gabriela Gouvea Silva, Carlos Costa, Bruno Gonçalves, Luiz Vianney Cidrão Nunes, Emerson dos Santos, Sonia Lopes, Alba Lima, Vânia Brienze, Thaís Bizotto, Júlio André. 6612

Methodology for Measuring Intraoperative Blood Loss: Protocol for a Scoping Review (e58022)
Lätitia Dennin, Jörg Kleeff, Johannes Klose, Ulrich Ronellenfitsch, Artur Rebelo. 6618

Using Digital Media to Improve Adolescent Resilience and Prevent Mental Health Problems: Protocol for a Scoping Review (e58681)
Riris Rachmayanti, Fatwa Dewi, Diana Setiyawati, Hario Megatsari, Rian Diana, Retno Vinarti. 6624

Coproduction in Social Prescribing Initiatives: Protocol for a Scoping Review (e57062)
Madeline Dougherty, Tamara Tompkins, Elaine Zibrowski, Jesse Cram, Maureen Ashe, Le-Tien Bhaskar, Kiffer Card, Christina Godfrey, Paul Hebert, Ron Lacombe, Caitlin Muhl, Kate Mulligan, Gillian Mulvale, Michelle Nelson, Myrna Norman, Bobbi Symes, Gary Teare, Vivian Welch, Anita Kothari. 6632

Development of Leadership Skills in Medical Education: Protocol for a Scoping Review (e62810)
Eliana Chubaci, Carlos Costa, Martins Santos Neto, Emerson dos Santos, Ana Engel, Ana Costa, Taisa Silva, Helena Cristóvão, Alex Quitério, Alba Lima, Vânia Brienze, Fernando Fácio Jr, Júlio André. 6639

XSL•FO
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Current State of Connected Sensor Technologies Used During Rehabilitation Care: Protocol for a Scoping Review (e60496)
Michelle Rauzi, Rachael Akay, Swapna Balakrishnan, Christi Piper, Denise Gobert, Alicia Flach. 6649

Misinformation About Climate Change and Related Environmental Events on Social Media: Protocol for a Scoping Review (e59345)
Maryline Vivion, Valérie Trottier, Ève Bouhêlier, Isabelle Goupil-Sormany, Thierno Diallo. 6659

AI-Supported Digital Microscopy Diagnostics in Primary Health Care Laboratories: Protocol for a Scoping Review (e58149)
Joar von Bahr, Vinod Diwan, Andreas Mårtensson, Nina Linder, Johan Lundin. 6668

Community Health Worker Videoconferencing Interventions for Disease Management and Health Promotion: Protocol for a Scoping Review (e55160)
Sonja France, Amy Dettori, Seda Ekici, Lilian McKinley, Sana Patel, Teresa Jewell, Mary Crocker. 6676

Assistive Technology to Support Dementia Management: Protocol for a Scoping Review of Reviews (e57036)
Chaitali Desai, Erica Dove, Jarshini Nanthakumar, Emilia Main, Heather Colquhoun, Arlene Astell, Alex Mihailidis, Natasha Layton, Amer Burhan, Brian Chan, Rosalie Wang. 6684

Phenotype-Genotype Correlation in Morquio A Syndrome: Protocol for a Meta-Analysis (e56649)
Lorena Diaz-Ordoñez, Paola Duque-Cordoba, Daniel Nieva-Posso, Wilmar Saldarriaga, Juan Gutierrez-Medina, Harry Pachajoa. 6697

Progress of Implementation of World Health Organization Global Antimicrobial Resistance Surveillance System Recommendations on Priority Pathogen-Antibiotic Sensitivity Testing in Africa: Protocol for a Scoping Review (e58140)
Mackline Hope, Reuben Kiggundu, Dathan Byonanebye, Jonathan Mayito, Dickson Tabajjwa, Fahad Lwigale, Conrad Tumwine, Herman Mwanja, Andrew Kambugu, Francis Kakooza. 6704

Barriers and Facilitators Affecting Access to Health Care for People With Syphilis: Protocol for a Scoping Review (e63561)
Rafaela Correia, Rafaela Mourad, Janmilli Dantas, Richardson Silva. 6712

Factors Influencing Domestic Human Trafficking in Africa: Protocol for a Scoping Review (e56392)
Loubna Belaid, Ivan Sarmiento, Anna Dion, Andrés Rojas Cardenas, Anne Cockcroft, Neil Andersson. 6720

Characteristics of Student-Led Clinics in the Allied Health Professions: Protocol for a Scoping Review (e58084)
Sandra Robertson, Katie Thomson, Katrina Bannigan. 6729

Wearables and Smartphones for Tracking Modifiable Risk Factors in Metabolic Health: Protocol for a Scoping Review (e59539)
Victoria Brügger, Tobias Kowatsch, Mia Jovanova. 6736

Evaluation Methods, Indicators, and Outcomes in Learning Health Systems: Protocol for a Jurisdictional Scan (e57929)
Shelley Vanderhout, Marissa Bird, Antonia Giannarakos, Balpreet Panesar, Carly Whitmore. 6744

Sustainability of Interprofessional Education: Protocol for a Scoping Review (e60763)
Nathalia Oliveira, Renata Oliveira, Juliana Soares, Janete Castro. 6751

XSL•FO
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The Use of “Cancer Ratio” in Differentiating Malignant and Tuberculous Pleural Effusions: Protocol for a Prospective Observational Study (e56592)
Sai Chalamalasetty, Preetam Acharya, Thomas Antony, Anand Ramakrishna, Himani Kotian. 6758

Exploring Molecular Genetics Research on Obesity in Malaysia: Protocol for a Scoping Review (e60838)
Liyana Ahmad Zamri, Norhashimah Abu Seman, Nur Zainal Abidin, Siti Hamzah. 6765

Seasonal Malaria Chemoprevention Therapy in Children Up To 9 Years of Age: Protocol for a Cluster-Randomized Trial Study (e51660)
Mahamoudou Toure, Jeffrey Shaffer, Daouda Sanogo, Soumba Keita, Moussa Keita, Fousseyni Kane, Bourama Traore, Djeneba Dabitao, Aissata Kone, Cheick Doumbia, Joseph Keating, Joshua Yukich, Helle Hansson, Alyssa Barry, Mahamadou Diakité, Michael Alifrangis, Seydou Doumbia. 6774

Combining Federated Machine Learning and Qualitative Methods to Investigate Novel Pediatric Asthma Subtypes: Protocol for a Mixed Methods Study (e57981)
Jie Xu, Sankalp Talankar, Jinqian Pan, Ira Harmon, Yonghui Wu, David Fedele, Jennifer Brailsford, Jennifer Fishe. 6782

mHealth-Based Just-in-Time Adaptive Intervention to Improve the Physical Activity Levels of Individuals With Spinal Cord Injury: Protocol for a Randomized Controlled Trial (e57699)
Rachel Carey, Ha Le, Donna Coffman, Inbal Nahum-Shani, Mohanraj Thirumalai, Cole Hagen, Laura Baehr, Mary Schmidt-Read, Marlyn Lamboy, Stephanie Kolakowsky-Hayner, Ralph Marino, Stephen Intille, Shivayogi Hiremath. 6793

Mobile App Promoting Resilience in Stress Management for Adolescents and Young Adults With Cancer: Protocol for a Pilot Randomized Controlled Trial (e57950)
Nancy Lau, Tonya Palermo, Chuan Zhou, Isabel Badillo, Shannon Hong, Homer Aalfs, Joyce Yi-Frazier, Elizabeth McCauley, Eric Chow, Bryan Weiner, Dror Ben-Zeev, Abby Rosenberg. 6810

Improving Neurological Health in Aging Via Neuroplasticity-Based Computerized Exercise: Protocol for a Randomized Controlled Trial (e59705)
Mouna Attarha, Ana de Figueiredo Pelegrino, Paule-Joanne Toussaint, Sarah-Jane Grant, Thomas Van Vleet, Etienne de Villers-Sidani. . . .
6 8 2 0

Protective Assets Reinforced With Integrated Care and Technology (PARITY): Protocol for a Randomized Controlled Trial (e58580)
Elizabeth Mollard, Deirdre Cooper Owens, Christina Bach, Cydney Gaines, Shannon Maloney, Tiffany Moore, Christopher Wichman, Neel Shah, Michele Balas. 6835

An Automated Text Messaging Intervention to Reduce Substance Use Self-Stigma (Project RESTART): Protocol for a Feasibility and Acceptability Pilot Study (e59224)
Adams Sibley, Seth Noar, Kathryn Muessig, Nisha O'Shea, Catherine Paquette, Abby Spears, William Miller, Vivian Go. 6848

Study of Postacute Sequelae of COVID-19 Using Digital Wearables: Protocol for a Prospective Longitudinal Observational Study (e57382)
Sherine El-Toukhy, Phillip Hegeman, Gabrielle Zuckerman, Anirban Das, Nia Moses, James Troendle, Tiffany Powell-Wiley. 6864

Factorial Trial to Optimize an Internet-Delivered Intervention for Sexual Health After Breast Cancer: Protocol for the WF-2202 Sexual Health and Intimacy Enhancement (SHINE) Trial (e57781)
Kelly Shaffer, Jennifer Reese, Emily Dressler, Jillian Glazer, Wendy Cohn, Shayna Showalter, Anita Clayton, Suzanne Danhauer, Michelle Loch, Mai Kadi, Caleigh Smith, Kathryn Weaver, Glenn Lesser, Lee Ritterband. 6881

Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE): Protocol for a Nationwide Hybrid Cohort for Transgender Women in the United States (e59846)
Andrea Wirtz, Tonia Poteat, Annick Borquez, Sabriya Linton, Megan Stevenson, James Case, Carter Brown, Arianna Lint, Marissa Miller, Asa Radix, Keri Althoff, Jason Schneider, J Haw, Andrew Wawrzyniak, Allan Rodriguez, Erin Cooney, Elizabeth Humes, Ceza Pontes, Shannon Seopaul, Camille White, Chris Beyrer, Sari Reisner, ENCORE Study Group. 6899

XSL•FO
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Digitizing Survivorship Care Plans Through the POST-Treatment Health Outcomes of Cancer Survivors (POSTHOC) Mobile App: Protocol for a Phase II Randomized Controlled Trial (e59222)
Kaitlin Chung, Shari Youngblood, Carin Clingan, Dana Deighton, Virginia Jump, Thushini Manuweera, Nicolette McGeorge, Cynthia Renn, Paula Rosenblatt, Aaron Winder, Shijun Zhu, Ian Kleckner, Amber Kleckner. 6919

Serious Gaming for Chemotherapy-Induced Nausea and Vomiting in Older Adults With Cancer: Protocol for a Randomized Clinical Trial (e64673)
Victoria Loerzel, Arsham Alamian, John Clochesy, Patricia Geddie. 6938

Assessing a Couples-Based, Digital HIV Serostatus-Neutral Intervention (Para Ti, Para Mí, Para Nosotros) for Adult Cisgender Sexual Minority Male Couples in Lima, Peru: Protocol for a 6-Month Pilot Randomized Controlled Trial (e63106)
Jason Mitchell, Zoran Bursac, David Diaz, Edward Reyes Diaz, Alfonso Silva-Santisteban, Kelika Konda. 6950

Home-Based Digital Exercise Training Program to Improve Physical Function of Older Sepsis Survivors: Protocol of the HEAL Sepsis Randomized Clinical Trial (e60270)
Rola Zeidan, Margaret Ohama, Natalia Evripidou, Stephen Anton, Laith Hamed, Yi Lin, Christiaan Leeuwenburgh, Faheem Guirguis, Philip Efron, Sheryl Flynn, Barbara Smith, Rhonda Bacher, Naveen Bakarasan, Juan Sarmiento Delgado, Robert Mankowski. 6966

Development and Testing of a Mobile App for Management of Gestational Diabetes in Nepal: Protocol for a User-Centered Design Study and Exploratory Randomized Controlled Trial (e59423)
Lauren Berube, Archana Shrestha, Abha Shrestha, Jean-Francois Daneault, Prabin Shakya, Meghnath Dhimal, Roman Shrestha, Shristi Rawal. 6977

Integrated Online-to-Offline Model of Care for HIV Prevention and Treatment Among Men Who Have Sex With Men in Malaysia: Protocol for an Intervention Development and a Multiphase Trial (e60962)
Antoine Khati, Jeffrey Wickersham, Kamal Gautam, Kiran Paudel, Panyaphon Phiphatkhunarnon, Sin Lim, Kirthana Puniamurthy, Frederick Altice, Nittaya Phanuphak, Iskandar Azwa, Roman Shrestha. 6991

The CHALO! 2.0 mHealth-Based Multilevel Intervention to Promote HIV Testing and Linkage-to-Care Among Men Who Have Sex with Men in Mumbai, India: Protocol for a Randomized Controlled Trial (e59873)
Jatin Chaudary, Shruta Rawat, Alpana Dange, Sarit Golub, Ryung Kim, Venkatesan Chakrapani, Kenneth Mayer, Julia Arnsten, Viraj Patel. . .
7 0 0 3

A Video-Based Communication Intervention for Fecal Ostomy Surgery (CI-oSurg): Protocol for Open Pilot Testing to Improve Intervention Acceptability and Feasibility (e60575)
Christy Cauley, Atziri Rubio, Mary Brindle, Zara Cooper, Ana-Maria Vranceanu, Christine Ritchie. 7017

A Mindfulness-Based Lifestyle Intervention for Dementia Risk Reduction: Protocol for the My Healthy Brain Feasibility Randomized Controlled Trial (e64149)
Ryan Mace, Makenna Law, Joshua Cohen, Christine Ritchie, Olivia Okereke, Bettina Hoeppner, Judson Brewer, Stephen Bartels, Ana-Maria Vranceanu, My Healthy Brain Team. 7027

Efficacy of a Mobile App–Based Behavioral Intervention (DRIVEN) to Help Individuals With Unemployment-Related Emotional Distress Return to Work: Protocol for a Randomized Controlled Trial (e62715)
Elizabeth Danielson, Mystie Saturday, Sarah Leonard, Alexandra Levit, Andrea Graham, Melissa Marquez, Keith Alperin, Stewart Shankman, James Griffith. 7056

Sleep Treatment Education Program for Cancer Survivors: Protocol for an Efficacy Trial (e60762)
Briana Bice, Alexis Michaud, Katherine McCormick, Eva Miklos, Indiana Descombes, Cheryl Medeiros-Nancarrow, Eric Zhou, Christopher Recklitis. 7068

XSL•FO
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A Web-Based Mind-Body Intervention to Improve Resilience Among Patients With Nontraumatic Painful Upper-Extremity Conditions and Comorbid Risky Substance Use: Protocol for a Mixed Methods Study (e64547)
Nadine Levey, Neal Chen, Joseph Ditre, Louisa Sylvia, Chaitanya Mudgal, Abhiram Bhashyam, Rohit Garg, David Ring, Ana-Maria Vranceanu, Jafar Bakhshaie. . . . 7082

Comparing Synchronous and Asynchronous Remotely Delivered Lifestyle Interventions: Protocol for a Randomized Noninferiority Trial (e65323)
Sherry Pagoto, Ran Xu, Richard Bannor, Christie Idiong, Jared Goetz, Denise Fernandes. . . . 7096

Prehabilitation Exercise Training to Target Improved Muscle Strength in Pretransplant Patients Diagnosed With Multiple Myeloma: Protocol for a Pilot Randomized Controlled Trial (e64905)
Amber Normann, Clifton Mo, Rebekah Wilson, Michelle Perez, Corey Cutler, Hajime Uno, LaDora Thompson, Tina Skinner, Paul Richardson, Catherine Marinac, Christina Dieli-Conwright. . . . 7107

Surveillance of Food and Waterborne Pathogens in North-East India: Protocol for a Laboratory-Based Sentinel Surveillance Study (e56469)
Venencia Albert, Thandavarayan Ramamurthy, Madhuchhanda Das, Samaresh Das, Anup Ojha, Pallab Sarmah, Dimpu Gogoi, Karma Dolma, Tapan Majumdar, Indira Sarangthem, Tapan Dutta, Suranjana Hazarika. . . . 7121

Proposals

Personalized AI-Driven Real-Time Models to Predict Stress-Induced Blood Pressure Spikes Using Wearable Devices: Proposal for a Prospective Cohort Study (e55615)
Ali Kargarandehkordi, Christopher Slade, Peter Washington. . . . 1730

Problematic Social Media Use Among Italian Midadolescents: Protocol and Rationale of the SMART Project (e58739)
Valeria Donisi, Laura Salerno, Elisa Delvecchio, Agostino Brugnera. . . . 3019

Meaningful Social Inclusion and Mental Well-Being Among Autistic Adolescents and Emerging Adults: Protocol for a Community-Based Mixed Methods Study (e52658)
Darcy McMaughan, Casey Lewis, Amy McGehee, Dani Noreen, Elliot Parker, Michael Criss. . . . 3055

Suicidal Ideation and Attempts Among Youth With Physical-Mental Comorbidity in Canada: Proposal for an Epidemiological Study (e57103)
Mark Ferro, Christy Chan, Dillon Browne, Ian Colman, Joel Dubin, Laura Duncan. . . . 3107

Assessment of Patient Safety in a Low-Resource Health Care System: Proposal for a Multimethod Study (e50532)
Ghazal Haque, Fozia Asif, Fasih Ahmed, Farwa Ayub, Sabih Syed, Nousheen Pradhan, Malika Hameed, Muhammad Siddiqui, Shafaq Mahmood, Tahani Zaidi, Sameen Siddiqi, Asad Latif. . . . 3308

Digital Gamification Tool (Let's Control Flu) to Increase Vaccination Coverage Rates: Proposal for Algorithm Development (e55613)
Henrique Lopes, Ricardo Baptista-Leite, Catarina Hermenegildo, Rifat Atun. . . . 5653

Quality Indicators for Transition from Pediatric to Adult Care for Youth With Chronic Conditions: Proposal for an Online Modified Delphi Study (e60860)
Alene Toulany, Dmitry Khodyakov, Sarah Mooney, Lisa Stromquist, Katherine Bailey, Claire Barber, Michelle Batthish, Kristin Cleverley, Gina Dimitropoulos, Jan Gorter, Danijela Grahovac, Ruth Grimes, Beverly Guttman, Michèle Hébert, Tomisin John, Lisha Lo, Dorothy Luong, Laura MacGregor, Geetha Mukerji, Jacklynn Pidduck, Vjura Senthilnathan, Rayzel Shulman, Patricia Trbovich, Sarah Munce. . . . 5676

XSL•FO
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Early In-Bed Cycle Ergometry With Critically Ill, Mechanically Ventilated Patients: Statistical Analysis Plan for CYCLE (Critical Care Cycling to Improve Lower Extremity Strength), an International, Multicenter, Randomized Clinical Trial (e54451)
Diane Heels-Ansdell, Laurel Kelly, Heather O'Grady, Christopher Farley, Julie Reid, Sue Berney, Amy Pastva, Karen Burns, Frédérick D'Aragon, Margaret S Herridge, Andrew Seely, Jill Rudkowski, Bram Rochwerg, Alison Fox-Robichaud, Ian Ball, Francois Lamontagne, Erick Duan, Jennifer Tsang, Patrick Archambault, Avelino Verceles, John Muscedere, Sangeeta Mehta, Shane English, Tim Karachi, Karim Serri, Brenda Reeve, Lehana Thabane, Deborah Cook, Michelle Kho. 5700

Development and Evaluation of a Web-Based Platform for Personalized Educational and Professional Assistance for Dementia Caregivers: Proposal for a Mixed Methods Study (e64127)
Logan DuBose, Qiping Fan, Louis Fisher, Minh-Nguyet Hoang, Diana Salha, Shinduk Lee, Marcia Ory, Tokunbo Falohun. 5760

Assessment of Sexual Violence Risk Perception in Men Who Have Sex With Men: Proposal for the Development and Validation of “G-Date” (e57600)
D Angelone, Damon Mitchell, Brooke Wells, Megan Korovich, Alexandra Nicoletti, Dustin Fife. 5775

Prescribing Trends and Associated Outcomes of Antiepileptic Drugs and Other Psychotropic Medications in US Nursing Homes: Proposal for a Mixed Methods Investigation (e64446)
Jonathan Winter, J Kerns, Nicole Brandt, Linda Wastila, Danya Qato, Roy Sabo, Stephen Petterson, YoonKyung Chung, Sarah Reves, Christopher Winter, Katherine Winter, Eposi Elonge, Craig Ewasiuk, Yu-Hua Fu, Adam Funk, Alex Krist, Rebecca Etz. 5887

Neighborhoods, Networks, and HIV Care Among Men Who Have Sex With Men: Proposal for a Longitudinal Study (e64358)
Hong Tieu, Vijay Nandi, José Diaz, Emily Greene, Melonie Walcott, Frank Curriero, Michael Desjardins, Cara Wychgram, Carl Latkin, Andrew Rundle, Victoria Frye, NNHIV Study Team. 5976

Original Papers

Design and Rationale of Prolonged Nightly Fasting for Multiple Myeloma Prevention (PROFAST): Protocol for a Randomized Controlled Pilot Trial (e51368)
David Lee, Elizabeth O'Donnell, Noopur Raje, Cristina Panaroni, Robert Redd, Jennifer Ligibel, Dorothy Sears, Omar Nadeem, Irene Ghobrial, Catherine Marinac. 2480

Content Validity and Psychometric Properties of the German Version of the Holm and Cordoba Urinary Tract Infection Score for Uncomplicated Urinary Tract Infections in Women: Protocol for a Validation Study (e49903)
Katharina Piontek, Sophie Nestler, Anne Holm, John Brodersen, Christian Apfelbacher. 5463

XSL•FO
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Corrigenda and Addenda

Correction: Linking Dementia Pathology and Alteration in Brain Activation to Complex Daily Functional Decline During the Preclinical Dementia Stages: Protocol for a Prospective Observational Cohort Study

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In “Linking Dementia Pathology and Alteration in Brain Activation to Complex Daily Functional Decline During the Preclinical Dementia Stages: Protocol for a Prospective Observational Cohort Study” (JMIR Res Protoc 2024;13:e56726), one error was noted.

In the first paragraph of the “Methods” section and in “Acknowledgments”, the grant number listed as *R01AG036921* has been revised to *R01AG075679*.

The correction will appear in the online version of the paper on the JMIR Publications website on October 21, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Impact of a Mobile App (LoAD Calc) on the Calculation of Maximum Safe Doses of Local Anesthetics: Protocol for a Randomized Controlled Trial

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Abstract

Background: Local anesthetics (LAs) are regularly used to alleviate pain during medical or surgical procedures. Their use is generally considered safe, but exceeding the maximum recommended doses can lead to LA systemic toxicity, a rare but potentially lethal complication. Determining maximum safe doses is therefore mandatory before performing local anesthesia, but rules are often unclear and the factors affecting dose calculation are numerous. Mobile health apps have been shown to help clinical decision-making, but most currently available apps present significant limitations. The Local Anesthetics Dose Calculator (LoAD Calc) app was designed to overcome these limitations by taking all relevant parameters into account. Before deploying this app in a clinical setting, it should be tested to determine its effectiveness and whether clinicians would be willing to use it.

Objective: The primary objective will be to evaluate the effectiveness of the LoAD Calc app through written simulated cases. The secondary objective will be to determine whether physicians find this app easier, faster, and safer than the methods they generally use.

Methods: We describe a parallel-group randomized controlled trial protocol. Anesthesiologists working at the Geneva University Hospitals will be invited to participate. Participants will be asked to compute the maximum dose of LA in 10 simulated clinical cases using 3 different LAs. The maximum safe dose will be determined manually using the same calculation rules that were used to develop LoAD Calc, without using the app itself. An overdose will be considered any dose higher than the correct dose, rounded to the superior integer, while an underdose will be defined as the optimal calculated dose minus 20%, rounded to the inferior integer. Randomization will be stratified according to current position (resident vs registrar). The participants allocated to the LoAD Calc (experimental) group will use the LoAD Calc app to compute the maximum safe LA doses. Those allocated to the control group will be asked to use the method they generally use. The primary outcome will be the overall overdose rate. Secondary outcomes will include the overdose rate according to ideal and actual body weight and to each specific LA, the overall underdose rate, and the time taken to complete these calculations. The app's usability will also be assessed.

Results: A sample size of 46 participants will be needed to detect a difference of 10% with a power of 90%. Thus, a target of 50 participants was set to allow for attrition and exclusion criteria. We expect recruitment to begin during the winter of 2023, data analysis in the spring of 2024, and results by the end of 2024.

Conclusions: This study should determine whether LoAD Calc, a mobile health app designed to compute maximum safe LA doses, is safer and more efficient than traditional LA calculation methods.

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KEYWORDS

dose calculation; drug safety; information systems research; local anesthetic systemic toxicity; local anesthetics; mobile health app; study protocol; toxicity

Introduction

Background

Local anesthetics (LAs) are used daily by physicians to perform minor procedures. While the doses they use are generally limited, anesthesiologists often use higher doses to perform regional anesthesia techniques [1]. While the advantages of such techniques are undeniable, using high LA doses increases the risk of local anesthetic systemic toxicity (LAST), a potentially lethal complication associated with the use of these agents [2]. The actual incidence of LAST is unknown since most minor symptoms are not specific and because LAST awareness varies considerably between practitioners [3,4]. The incidence reported in scientific studies varies from 0.04 to 1.8 per 1000 regional anesthesia procedures but is probably underestimated [5,6]. The main risk factors seem to be inadvertent intravascular injections and inappropriately large doses [7,8].

Prevention of intravascular injection can be achieved by ultrasound guidance and careful aspiration during the procedure, while adequate calculation of the maximum dose of LA before administration is the best way to avoid incorrect doses.

Although different guidelines have been created to help clinicians calculate the maximum safe LA doses, quickly and reliably determining such doses often proves difficult in clinical practice [9]. Many anesthesiologists rely on mental calculation (with or without a pen and paper aid), and some use calculators. These methods are, however, often challenging and inaccurate, especially if LA mixtures are used or when patients present multiple comorbidities [10]. More advanced solutions have been developed to support LA dosage calculation, such as the nomogram created by Williams and Walker [11]. The main limitation of this solution is that the nomogram must always be at hand. Moreover, specificities such as ideal body weight (IBW) calculation and adaptation in the case of relevant comorbidities are indicated but not directly integrated into dose determination.

To facilitate the calculation of safe maximum LA doses, a mobile health (mHealth) app, Local Anesthetics Dose Calculator (LoAD Calc), was developed at the Geneva University Hospitals [12]. This app takes all relevant parameters (IBW and actual weight, height, age, medications, and comorbidities) into account and allows the use of a mixture of 2 different LAs. Since smartphones have widely replaced older paging systems and are therefore always at hand, this mHealth app could be an appropriate solution to enable anesthesiologists to efficiently compute safe maximum LA doses.

Objectives

This study protocol follows the hypothesis that LoAD Calc, an mHealth app designed to help clinicians calculate maximum safe LA doses, is safer and more effective than traditional methods. Thus, the primary objective will be to evaluate the effectiveness of the LoAD Calc app by using it to compute the maximum single doses of LA in written simulated cases. The secondary objective will be to determine whether physicians find this app easier, faster, and safer than the methods they generally use.

Methods

Ethical Considerations

A synopsis of the study protocol was presented to the regional ethics committee (Commission Cantonale d'Ethique de la Recherche [CCER]). This committee confirmed that this project does not fall within the scope of the Swiss Federal Act on Research involving Human Beings and issued a "declaration of no objection" (CCER 2022-01577) [13]. This study protocol does not fall within the scope of the Swiss Federal Act on Research involving Human Beings [13]. It will nevertheless be presented to the regional ethics committee to ascertain that no important or relevant ethical consideration was omitted.

Participants will be told that participation is entirely voluntary, that there will be no consequence if they refuse to participate, and that they will be able to withdraw at any time without explanation. All participants will be asked to sign an electronic consent form immediately after logging in. There is no compensation for participation in the study.

Study Design

This will be a monocentric, parallel-group, randomized controlled trial based on clinical vignettes. The protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Multimedia Appendix 1) [14]. Given its design, the investigators will not be blinded as to the intervention. Nevertheless, participants will not be informed that there are 2 different arms and will not be told the exact outcomes studied, even though they will be provided with general information regarding the study. In addition, the data analyst will be blinded as to participant allocation by renaming the groups before sending data for statistical analysis. Randomization will be stratified according to current position (resident vs registrar).

Results will be reported according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth) guidelines [15]. Relevant elements of the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) will be included since web-based questionnaires will be used in the course of this study [16].

Clinical Vignettes

A total of 10 clinical vignettes will be developed for the purpose of this study. These vignettes will describe clinical cases

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requiring the use of LAs for regional anesthesia. We will include 3 of the most commonly used LAs in these vignettes: lidocaine, levobupivacaine, and ropivacaine. Some vignettes will ask the participant to use LA mixtures, and several will include comorbidities or medications requiring dose adaptations.

For each vignette, 3 authors will be required to determine the maximum dose of LA the simulated patient should receive according to the rules used to develop the LoAD Calc app [12], without using the app. These rules, which are derived from the scientific literature, are summarized in Textbox 1. They were reviewed and approved by clinical pharmacologists and toxicologists [12]. Any disagreement will prompt a review of the vignette. Final vignette approval will only be possible if a consensus can be reached.

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Textbox 1. Dosage elements and app rules used to calculate the maximum safe dose of local anesthetics, adapted from Suppan et al [12].

Dose limit for a single LA (local anesthetic)

- Levobupivacaine: 2 mg/kg (maximum 150 mg/dose)
- Lidocaine: 3 mg/kg (maximum 300 mg/dose)
- Ropivacaine: 3 mg/kg (maximum 225 mg/dose)

Influence of epinephrine on dose limit

- Levobupivacaine: 3 mg/kg (maximum 150 mg/dose)
- Lidocaine: 7 mg/kg (maximum 400 mg/dose)
- Ropivacaine: 3 mg/kg (maximum 225 mg/dose)

Determination of calculation weight (CW)

- Calculation of BMI
- Calculation of ideal body weight (IBW; Devine formula)
- Application of the following algorithm to define CW:
  - weight≤70 kg and BMI<30 and IBW >weight → CW=weight
  - weight≤70 kg and BMI<30 and IBW ≤weight → CW=IBW
  - weight≤70 kg and BMI≥30 → CW=IBW
  - weight>70 kg and IBW>70 → CW=70
  - weight>70 kg and IBW≤70 → CW=IBW

Dose adaptation depending on health conditions and drugs

- Conditions
  - Old age (70 years or older)
  - Renal dysfunction (glomerular filtration rate [GFR]<50 mL/minute)
  - Hepatic insufficiency (prothrombin time <50%)
  - Heart failure (left ventricular ejection fraction≤30%)
  - Pregnancy
  - Drugs decreasing LA metabolism
- List of drugs decreasing LA metabolism
  - Major CYP1A2 inhibitors: ciprofloxacin, norfloxacin, and fluvoxamine
  - Major CYP3A inhibitors: azole antifungals, macrolides, calcium channel blockers, HIV antiretroviral therapy, and tyrosine kinase inhibitors
- If 1 condition is present, the calculator reduces the total maximum dose by 20%
- If 2 or more conditions are present, the calculator reduces the total maximum dose by 30%.

Calculation rule for LA mixtures

- The app performs the following steps
  - Calculation of maximum safe volume for first LA
  - The user enters which volume of first LA is to be used (0–maximum volume)
  - Calculation of corresponding maximum dose of first LA and determination of percentage of total maximum dose
  - Calculation of maximum dose of second LA based on remaining percentage of total maximum dose
  - Calculation of maximum volume of second LA

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Groups and Randomization

There will be 2 study groups: in the control group, participants will be asked to use the method they usually use in their clinical practice to calculate the maximum safe dose of LA; in the LoAD Calc (experiment) group, participants will be required to use the LoAD Calc app, which will be preinstalled on a standard Geneva University Hospitals (HUG) smartphone (Galaxy XCover 4s; Samsung) running on Android 11.

Stata's (StataCorp LLC) replicable balanced randomization mechanism will be used to allocate participants to their study group. Textbox 2 contains the code that will be used.

Textbox 2. Randomization code.

```
set obs #N
egen arm = seq(), to(2)
set seed #S
gen random = uniform()
sort random
```

Wherein "1" will be the control group, and "2" will be the LoAD Calc group.

Since randomization will be stratified according to participant position (either resident or registrar), 2 seeds (#S) will be used (07022023 and 20230207).

A sample size calculation will be used to determine the total number of observations. It will be rounded up to the nearest ten to enhance the study power and take into account attrition and potential exclusions. The stratified number of observations (#N) will be computed according to the proportion of potential participants belonging to both eligible positions (residents vs registrars).

The method used by the participants allocated to the control group to calculate the maximum safe dose of LA will be recorded. There will be no teaching or introductory intervention for any of the participants before the study, and the participants allocated to the LoAD Calc group will therefore discover the app while answering the first vignette.

Web-Based Study Platform

A specific web-based platform will be developed using the Joomla! 4.3 content management system (Open Source Matters). It will be hosted on a Swiss server (Kreativmedia GmbH) and secured by the RSFirewall 3 (RSJoomla) and AdminTools 7 (Akeeba Ltd) components. To ensure participant anonymity, unique usernames and passwords will be created using Manytools' web-based password generator [17]. These credentials will then be imported into Stata and allocated to either study group according to the randomization process described above. Finally, this data will be exported to a CSV file, which will be imported into the web-based study platform using the Import Joomla Users component (version 3.4; Lerus Ltd).

Consents, questionnaires, and vignettes will be managed using Shondalai's Community Surveys 6 and Community Quiz 6 components (Bulasikku Technologies Pvt Ltd). All data will be stored on an encrypted MySQL-compatible database (MariaDB 10, MariaDB Foundation).

Inclusion and Exclusion Criteria

All resident physicians and registrars working in the HUG anesthesiology department will be eligible for inclusion. The only exclusion criteria will be current or previous use of the LoAD Calc app. This criterion will be assessed by a screening question asked after the completion of all study vignettes.

Recruitment

The project will first be presented to the head of the anesthesiology department and then to all consultants. After obtaining their agreement, investigators will recruit potential participants directly in the operating room. These residents and fellows in anesthesiology will be informed that the study will last at most 1 hour and that an investigator will replace them in the operating room while they participate. They will be told that participation is entirely voluntary, that there will be no consequence if they refuse to participate, and that they will be able to withdraw at any time without explanation. No incentive other than advancing scientific knowledge will be given to promote participation. They will be given a paper sheet summarizing the information regarding the study and data protection (Multimedia Appendix 2). Those who agree will be scheduled for participation on the same day. Together with the anesthesiology consultant overseeing the operating room, an investigator will organize replacements to avoid any disruption in the operating program. There will be only 1 slot, and therefore, only 1 participant per hour.

Consent and Study Sequence

Participants will be asked to set their phones to flight mode. This will enable them to access any note, calculator, or app they use to calculate LA doses while avoiding potentially disruptive interruptions. The study itself will take place in a separate, quiet room. There, an investigator will prompt them to pick up a sealed, opaque envelope containing the credentials necessary to log in.

All participants will be asked to sign an electronic consent form immediately after logging in. Those who agree will proceed to a first questionnaire designed to gather demographical data (Textbox 3) and determine whether these participants are currently using LoAD Calc or if they have used this app before (exclusion criterion). After completing this questionnaire, an introductory screen giving information regarding the vignettes they are about to see and specifying the calculation method they are to use (LoAD Calc for the experimental group vs left at the participant's will for the control group) will be displayed. At

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this stage, those allocated to the LoAD Calc group will be given the smartphone preinstalled with the LoAD Calc app.

Textbox 3. First questionnaire.

Page 1: consent

- Consent to participate and to data reuse (multiple-choice questions with only 1 acceptable answer)

Page 2: exclusion criterion

- Has heard of LoAD Calc (multiple-choice questions with only 1 acceptable answer)[a]
- Has installed LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Has used LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions; answering "yes" to either of those questions will lead to participant exclusion)
- Context of LoAD Calc use (multiple-choice question with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Has LoAD Calc still installed (multiple-choice question with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Still uses LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions; answering "yes" to either of those questions will lead to participant exclusion)

Page 3: demographics

- Gender (multiple-choice questions with only 1 acceptable answer)
- Age (free text with regular expression [regex] validation rule)
- Position (multiple-choice questions with only 1 acceptable answer; custom answer accepted)
- Years since graduation (free text with regular expression [regex] validation rule)
- Years of practice in anesthesiology (free text with regular expression [regex] validation rule)
- Specialist diplomas (custom answer accepted; multiple-answer question with more than 1 answer accepted)

After completing the vignettes, the participants allocated to the LoAD Calc group will be asked to complete the French version of the System Usability Scale [18], the translation of which has been validated [19]. Participants allocated to the control group will then be asked which methods they used to calculate LA doses.

Finally, both groups will have to answer a question based on a 10-point Likert scale to assess their confidence as to the method they used to carry out the maximum safe LA dose calculations, from score 1 (absolutely not confident) to score 10 (perfectly confident).

The whole study sequence is summarized in Figure 1.

Figure 1. Study sequence. LoAD Calc: Local Anesthetics Dose Calculator.

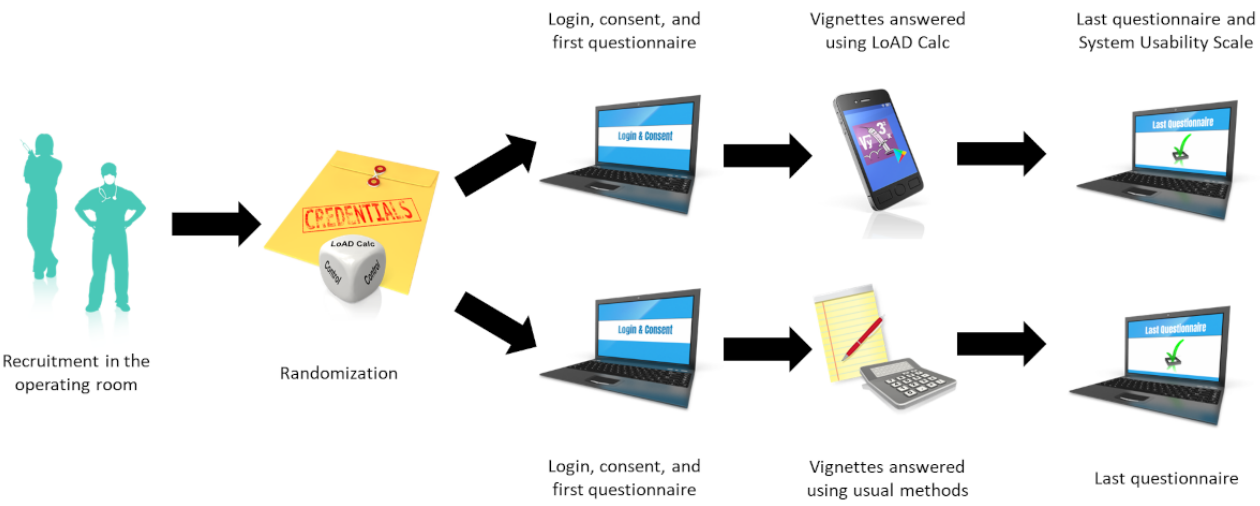

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Outcomes

The primary outcome will be the overall overdose rate, according to the method used. To assess this outcome, the maximum acceptable dose in milligrams, or milliliters, must therefore be established. While this might seem straightforward at first sight, it is actually rather complex. Indeed, although maximum safe doses are calculated in milligrams, anesthetists administer a volume of LA (the concentration of which can vary) rather than a quantity of LA. Therefore, even though toxicity is related to the quantity (in milligrams) of LA administered, it is clinically more relevant to determine the maximum volume (in milliliters) of LA that can be used for a particular patient. Consequently, after applying the rules described in Textbox 1, a quantity in milligrams will be obtained. It will then be converted in milliliters according to the concentration of the LA used in the vignette. This volume will then be rounded to the inferior integer. To be less conservative, 1 mm will be added to this calculated volume, and the total will represent the maximum acceptable volume. An overdose will be considered any dose higher than this maximum acceptable volume or than its corresponding LA quantity in milligrams.

The secondary outcomes will be the overall overdose rate, considering the simulated patient's ideal weight and the simulated patient's actual weight, the overdose rate according to each LA studied, and the overall underdose rate. An underdose will be defined as the maximum acceptable volume minus 20% (or its corresponding LA quantity in milligrams), rounded to the inferior integer. This is an empirical choice since anesthetic underdose can only be determined clinically [20,21].

Other secondary outcomes will be the time taken to complete these calculations, the app's usability, and the physicians' confidence in using the method they were allocated to. The app's usability will be evaluated using the System Usability Scale [18]. Provided that the statistical assumptions are met, factors associated with a higher probability of overdose or underdose will also be assessed.

Statistical Analysis

The sample size calculation and all other statistical analyses will be carried out using Stata (version 17.0 or above). The complete data set will be exported by the webmaster, who will give the study groups codenames before sending the curated data set for statistical analysis. Descriptive statistics will be used to present demographical data. Normality will be assessed graphically, and the Kolmogorov-Smirnov test will be used in cases of doubt. Accordingly, all outcomes will then be computed using either parametric or nonparametric tests. The data acquisition mechanisms will ensure that all data are recorded after each stage. Thus, there should not be any missing data, and there shall be no need for imputation. When LA mixtures are used, participants will be told that 1 anesthetic has already been injected and the dose used has been clearly reported. Thus, they will be asked to determine the maximum safe dose for the second local anesthetic. Multivariable regression will be used to determine an association between specific clinical parameters and the probability of overdose or underdose, provided that all required assumptions are met and that the risk of overfitting is adequately limited. Double-sided P values ($P<.05$) will be considered significant.

Results

The 10 vignettes necessary to carry out the study were successfully created, and the maximum safe doses were determined. These vignettes and the doses were checked and approved by all authors. The 10 vignettes, as well as their English translation, were presented to peer reviewers but are not publicly available to avoid any potential bias. They will nevertheless be published along with the results paper.

The sample size calculation was performed using Stata (version 17.0). It showed that 46 participants (23 in each group) would be needed to detect a 10% difference with a power of 90%, taking into account an SD of 10%. In line with the above methods, a total of 50 anesthesiologists should therefore be recruited. Since there are 62 residents and 52 registrars in the HUG Anesthesiology Department, a participation rate of 44% (50/114) will be necessary. This participation rate seems achievable with the aforementioned recruitment procedure. If this rate cannot be achieved, other Swiss University hospitals will be contacted, and similar recruitment procedures will be carried out to obtain the required sample size.

The study platform has been successfully created and tested by all coauthors [22]. The data extraction mechanisms have also been successfully checked.

The recruitment will take place once this study protocol has been reviewed and accepted for publication to allow for any necessary adjustments before study inception. The current version of the protocol is 0.9 (October 10, 2023). The published version will be 1.0.

It should be possible to start recruitment during the winter of 2023. This would allow data analysis to take place in spring 2024, and results should be submitted for publication in an international peer-reviewed journal by the end of the same year.

Discussion

Overview

This study should allow us to determine whether LoAD Calc, an mHealth app designed to calculate maximum safe LA doses, is safer and more effective than current clinical practice. Previous studies have shown that mHealth apps can enhance dose calculation and potentially improve safety [23], decrease time to drug delivery [23], and lessen stress [24]. Assessing this latter parameter would not make much sense given the design of this study but could prove interesting in future high-fidelity or field trials.

Other solutions have already been proposed for the calculation of the maximum safe LA dose but present significant drawbacks. Some of them, such as the nomogram created by Williams and Walker [11], do not depend on technological devices. This nomogram, which represents a rapid and calculation-free way, must, however, always be within reach. In addition, IBW must first be determined, and there is no dose adaptation based on health conditions or drug interactions. Computer-based solutions

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and mobile apps have also been created, such as MDCalc Local Anesthetic Dosing Calculator [25], The Podiatry Institute's LA Toxic Dose Calculator [26], and SafeLocal by Johns Hopkins Digital [27]. All these solutions lack key elements and do not consider either IBW, comorbidities, or medications. Most allow invalid data to be entered or suggest doses exceeding the maximum safe dose, thereby presenting potential safety issues.

No study can be devoid of limitations, and the one planned according to this protocol is no exception. The first foreseeable limitation is that the LoAD Calc app will be compared to many different methods of LA dose calculation, thereby preventing us from directly comparing this app to a specific method. However, there is no gold standard to calculate the maximum safe LA doses, and the design of the proposed study can be considered pragmatic. Another limitation is that the maximum safe doses will be calculated using the same scientifically grounded rules that were used to develop LoAD Calc [12]. However, some of the calculation rules used by the app are not supported by strong scientific evidence, and there is no gold standard for comprehensive, safe calculation of maximum LA doses. Finally, the results obtained through this study will only apply to the single-dose administration of a limited number of LAs or of LA mixtures. This will not affect the validity of the study's results nor compromise the use of the app since the 3 LAs selected (levobupivacaine, lidocaine, and ropivacaine) are commonly used in clinical practice. Nevertheless, further app developments will be needed to take other LAs and repeated doses into account. Since some LAs, such as lidocaine, are also safe for intravenous use, future versions of the app should enable practitioners to select different injection sites and routes.

Conclusions

Following this protocol should enable us to determine whether LoAD Calc, a mHealth app designed to calculate the maximum safe doses of LA, is both safe and effective. If this hypothesis proves to be true, clinical trials could be considered, and further outcomes, such as the impact of LoAD Calc on cognitive load and physiologic stress, could be considered.

Acknowledgments

The authors of this protocol would like to thank all members of the original LoAD Calc development team for their support throughout its development.

Data Availability

The data sets generated during and/or analyzed during this study will be available in an open access repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 555 KB - resprot_v13i1e53679_app1.pdf]

Multimedia Appendix 2
Study information sheet.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e53679_app2.pdf]

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Abbreviations

CCER: Commission Cantonale d'Ethique de la Recherche
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth
HUG: Geneva University Hospitals
IBW: ideal body weight
LA: local anesthetic
LAST: local anesthetic systemic toxicity

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LoAD Calc: Local Anesthetics Dose Calculator
mHealth: mobile health
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Professional Development to Improve Responsible Beverage Service Training: Formative Research Results and Protocol for a Randomized Controlled Trial

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Abstract

Background: Improved interventions are needed to reduce the rate of driving while intoxicated. Responsible beverage service (RBS) training has reduced service to intoxicated patrons in licensed premises in several studies. Its efficacy might be improved by increasing the proper application and continued use of RBS with a professional development program in the 3 to 5 years between the required RBS retraining.

Objective: This study aims to develop and evaluate a professional development component for an RBS training that aims to improve the effectiveness of the web-based training alone.

Methods: In a 2-phase project, we are creating a professional development component for alcohol servers after completing an RBS training. The first phase involved formative research on the feasibility, acceptability, and potential effectiveness of components. Semistructured interviews with owners and managers of licensed establishments and focus groups and a survey with alcohol servers in New Mexico and Washington State examined support for RBS and the need for ongoing professional development to support RBS. A prototype of a professional development component, *WayToServe Plus*, was produced for delivery in social media posts on advanced RBS skills, support from experienced servers, professionalism, and basic management training. The prototype was evaluated in a usability survey and a field pilot study with alcohol servers in California, New Mexico, and Washington State. The second phase of the project will include full production of the professional development component. It will be delivered in Facebook private groups over 12 months and evaluated with a sample of licensed premises (ie, bars and restaurants) in California, New Mexico, and Washington State (n=180) in a 2-group randomized field trial (*WayToServe* training only vs *WayToServe* training and *WayToServe Plus*). Licensed establishments will be assessed for refusal of sales to apparently intoxicated pseudopatrons at baseline and 12 months after the intervention commences.

Results: Although owners and managers (n=10) and alcohol servers (n=43) were favorable toward RBS, they endorsed the need for ongoing support for RBS for servers and identified topics of interest. A prototype with 50 posts was successfully created. Servers felt that it was highly usable and appropriate for themselves and the premises in the usability survey (n=20) and field pilot test (n=110), with 85% (17/20) and 78% (46/59), respectively, saying they would use it. Servers receiving the professional development component had higher self-efficacy (d=0.30) and response efficacy (d=0.38) for RBS compared with untreated controls.

Conclusions: Owners, managers, and servers believed that an ongoing professional development component on RBS would benefit servers and licensed premises. Servers were interested in using such a program, a large majority engaged with the prototype, and servers receiving it improved on theoretic mediators of RBS. Thus, the professional development component may improve RBS training.

Trial Registration: ClinicalTrials.gov NCT05779774; http://tinyurl.com/4mw6d2vk

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International Registered Report Identifier (IRRID): DERR1-10.2196/49680

(JMIR Res Protoc 2024;13:e49680) doi:10.2196/49680

KEYWORDS

alcohol; driving while intoxicated; responsible beverage service; training; prevention; professional development; social media

Introduction

Background

Driving while intoxicated (DWI) is one of the most preventable public health risks in the United States. However, from 2019 to 2020, there was an increase of 14.3% in DWI deaths, after remaining largely stable from 2015 to 2019 [1]. Although new policies and interventions are needed to reduce the consequences of DWI, gains are possible by increasing the efficacy of existing interventions. Responsible beverage service (RBS) training [2-4] has been effective in some cases [5], but methods of boosting its efficacy are needed. The goal of this research is to develop and evaluate a professional development component for a web-based RBS training program that aims to improve the effectiveness of web-based training. The professional development component will provide ongoing information and instruction in advanced RBS techniques and emphasize professionalism in the hospitality industry. It will be continuously available and easily accessible to alcohol servers via social media after completing the web-based training.

Marketplace approaches to prevent alcohol service that results in intoxication or restrict access to alcohol by persons already intoxicated are an alternative policy approach to deterrence of driving by drinkers considered impaired to decrease DWI [6]. Most US states have laws prohibiting sales of alcohol to visibly intoxicated customers [7]. A complementary intervention is RBS training, which aims to instruct servers on how to prevent intoxication by teaching drink counting techniques, ways to recognize signs of intoxication, and strategies to refuse alcohol sales. This environmental intervention aims to decrease opportunities for risky behavior [8], consistent with harm reduction in a nurturing environment perspective [9]. It is a targeted restriction on alcohol accessibility at the times and places where risk is greatest that does not depend on decision-making by persons considered alcohol impaired, can be applied to all alcohol sales premises, does not depend on house policies of licensees to refuse sales, and reduces intoxicated customers' ability to *shop around* to find premises that will serve.

Research on RBS training presents a mixed picture [5]. Although some studies have failed to show effectiveness [10], reviews in 2000 and 2001 concluded that RBS training can prevent alcohol overservice [11] with strong management support [12]. Recent studies have found RBS training to be associated with increases in refusals of service to apparently intoxicated customers. In addition it was related to decreases in blood alcohol concentration and calls to emergency services [13]. RBS training combined with enforcement reduced alcohol overservice and violent assaults in a trial in Sweden [14-16] but not in Norway [17]. In addition, lower levels of motor vehicle crashes with a high percentage of alcohol involvement were observed in a mandatory RBS training state [18], and another analysis found that states with RBS laws had a reduced number of underage drinking driver fatality crash ratios [19]. Data on self-reported DWI have been mixed, with one study showing no association [20] and another finding a decrease in reported DWI with RBS training [13]. Continued research on RBS training [21] is warranted because (1) positive outcomes have been reported [5,16,22,23]; (2) methodological problems limit existing evidence (eg, lack of randomized trials, clear outcome variables, training fidelity data, and effect size reporting) [5,11,12]; and (3) data are limited on web-based training that can improve training engagement, fidelity, and quality, compared with in-person training [5]. Our team showed that a web-based RBS training program, named *WayToServe*, was effective in premises serving alcohol for onsite consumption (ie, bars and restaurants) [24].

RBS training laws are highly variable across US states [25]. It is legally mandated in 25 US states and incentivized in some fashion in a number of other states [26]. Most states that require training have long periods of 3 to 5 years between required retraining. Consequently, the proper application, monitoring, and continued use of the RBS techniques falls on the shoulders of premises management, so it is not surprising that management commitment to RBS can affect servers' adherence to RBS methods [5,12]. Developing ways to support RBS techniques after training may counter the management's ineffective or limited support for, disinterest in, or outright resistance to RBS.

Objectives

The goal of this study is to develop and evaluate a follow-on professional development component to increase the efficacy of our web-based RBS training, *WayToServe*. Continuing professional development is a widespread practice across a variety of fields including accounting, social work, and medicine [27]. Typically, it focuses on improving knowledge, skills, and performance to help employees stay up-to-date on industry developments, develop and maintain job capabilities, convey professional values and norms, and create communities of practice [27-32]. Although often focused on *high-skill* professional workers (eg, nurses, physicians, lawyers, and architects) [27], the training and certification of community members has improved professionalism [33] and, along with in-service contact, has boosted the success of community prevention programs [34,35]. Vocational education and lifelong learning play essential roles in the hospitality industry. They offer both general knowledge and skills such as communication and customer service as well as job-related knowledge such as understanding laws related to serving alcohol and the ability to recognize signs of intoxication [32,36,37]. Alcohol servers trained in RBS practices should benefit from ongoing professional development by (1) motivating them to implement RBS skills in the face of common barriers, such as pressure to

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sell, low management support, and customers' attempts to continue being served; (2) receiving support for RBS from a *community* of alcohol servers, especially for servers who work in small or unsupportive premises; and (3) preventing the degradation of RBS skills over time.

Methods

Overview

This study is being conducted in 2 phases to create an effective professional development component for alcohol servers who completed state-approved RBS training. The first phase aimed to determine whether a professional development component delivered over social media was feasible, acceptable, and potentially effective for alcohol premises management and servers. The second phase will involve production of the professional development component and testing its efficacy in a randomized controlled trial (RCT).

Phase 1: Formative Research

Overview

A formative research phase in 2022 used both qualitative and quantitative techniques to provide a detailed picture of RBS training and its gaps as well as the feasibility and potential effectiveness of adding a professional development component. It included semistructured interviews with premises managers, focus groups and a survey with alcohol servers, development of a prototype of the professional development component, and usability testing and a field pilot study evaluating the prototype.

Semistructured Interviews With Alcohol Premises Owners and Managers

Owners and managers (n=10) of onsite alcohol premises in New Mexico and Washington State participated in semistructured interviews. Premises had to hold an active state alcohol license and be a bar or restaurant that served alcohol. Managers discussed RBS policies at their premises, support for RBS methods, perceived importance of RBS, quality of RBS methods implemented by their servers, and need for ongoing training and support for RBS among their servers. They also suggested content for a professional development component. The transcripts were coded to identify themes.

Focus Groups and Survey With Alcohol Servers

Alcohol servers working in onsite alcohol sales premises in New Mexico and Washington State were recruited from the roster of *WayToServe* trainees to provide input on experience with RBS methods and interest in ongoing professional development related to RBS methods. To be included, servers had to be aged ≥19 years (by state regulation), serve alcoholic beverages at a licensed premises, have completed the *WayToServe* RBS training, and be proficient in English. Initially, alcohol servers (n=19) were recruited to web-based focus groups; however, when participation lagged, servers (n=24) were recruited instead to complete a web survey. In both the focus groups and survey, servers were asked about their experience with, confidence in, and barriers to RBS methods; support from management and other alcohol servers for RBS; and experience refusing service to customers. They also indicated their interest in and potential utility of receiving ongoing information and activities from *WayToServe* to keep up-to-date and be capable of using RBS methods via a Facebook group. Servers reported whether they were willing to share their RBS experiences or provide feedback on RBS actions with other servers. Focus group transcripts were coded for themes for each question. The survey responses were summarized using descriptive statistics.

Production of a Prototype Professional Development Component

A prototype of the professional development component was produced by the project staff and media developers. Named *WayToServe Plus*, it comprised a series of 50 social media posts. The goal of the messages was to improve servers' professionalism by (1) increasing the confidence and motivation of RBS-trained servers to implement RBS methods, with attention to ways of overcoming common barriers; (2) creating a professional community of servers that supports one another in implementing RBS actions and serves as a resource for advice and strategies to implement RBS (eg, tips and tricks) by encouraging servers to share their personal experiences through comments and posts; and (3) preventing the deterioration of RBS skills and motivation over time by providing refresher instruction. Posts contained text, graphics, web-based learning activities, and videos demonstrating RBS techniques in 4 topic areas derived from the results of the manager interviews and alcohol server focus groups and surveys: advanced RBS skills training (ID checking, cannabis and alcohol, drink counting, and home delivery), experienced servers supporting new servers (eg, tips and tricks to apply RBS and sharing stories on RBS experiences), professionalism (safety and security, security personnel, and handling disruptive customers), and basic management training (content and development of house RBS policies and best practices for RBS). Instructional goals included improving the application of RBS information and skills in realistic settings and circumstances that servers have encountered in their jobs. *WayToServe Plus* was consistent with the transformative approach to continuing professional development by Kennedy [38], combining the transmission of information, skills, and norms and providing coaching or mentoring by striving to create a community of practice among servers with varying levels of experience. Messages in the posts were guided by principles of diffusion of innovation theory (eg, compatibility, simplicity, trialability, and observability) [39] and social cognitive theory (ie, modeling) [40] and written to be relatable, positive, and entertaining. A total of 14 short videos were produced using the TikTok video authoring platform. An interactive quiz activity was taken from the *WayToServe* training and linked to a social media post. *WayToServe Plus* was authored in English because most servers had elected to complete *WayToServe* training in English.

Evaluation of Prototype Professional Development Component

The prototype *WayToServe Plus* component was evaluated for usability, feasibility, acceptability, and engagement through a survey and a field pilot test with alcohol servers recruited from the roster of *WayToServe* trainees.

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Usability Testing

Alcohol servers (n=20) who met the aforementioned inclusion criteria (refer to the *Focus Groups and Survey With Alcohol Servers* section) completed a web survey on prototype acceptability, feasibility, and utility (10 in New Mexico and 10 in Washington State). Ten usability testers can identify 95% of problems [41-43]. In the survey, servers were provided with a description of the *WayToServe Plus* component. Each server was presented with 3 posts and 1 video randomly selected from posts in the prototype. They were then asked to evaluate these items based on their appropriateness for themselves and licensed establishments, their acceptability, and usefulness, using 5-point Likert scales. Servers indicated if they would read or view the post or video, react to it (eg, like, sad, and angry), comment on it, and share it. A description of the interactive activities was provided and rated based on these measures. Next, servers evaluated the *WayToServe Plus* concept on the validated System Usability Scale (SUS) [44-46]. The 10 items were combined using standard techniques, with a score of ≥68 indicating adequate usability. In addition, a single item assessed user-friendliness (1=worst imaginable and 7=best imaginable). Finally, servers indicated whether they would be interested in getting the ongoing information and activities from *WayToServe Plus*, topics that would be of interest to them, and potential reasons for not using it.

Field Pilot Test

A sample of 59 alcohol servers (5 in California, 21 in New Mexico, and 33 in Washington State) participated in a 1-month field pilot test of the prototype, meeting the same inclusion criteria as the focus group and usability testing participants. The study involved a nonrandomized posttest-only 2-group design, in which the treatment group had 2 levels: prototype *WayToServe Plus* program versus no treatment. In the intervention group, 59 servers were recruited and joined a Facebook private group on a rolling basis over 8 weeks. Staff posted prototype *WayToServe Plus* posts (1 per day, Monday to Friday) for the 8-week period. Approximately 24 posts were posted to the private group during any 4-week period in the intervention period. The posts were only viewable to members of the private group and could not be shared outside the private group. Outcomes were assessed in 2 ways at 4 weeks after enrollment. First, servers' engagement with *WayToServe Plus* was measured by recording the number of times posts were viewed, reacted to (eg, liked), and commented on by servers. Second, servers completed a web-based posttest, assessing the prototype on appropriateness, acceptability, and utility for servers and premises and usability on the SUS [44-46] and whether the tone of the prototype aligned with their licensed establishment's atmosphere, using scales similar to those used in the usability survey. Perceived self-efficacy and response efficacy for maintaining community safety by using RBS methods (5-point Likert scales) were measured as proxy outcomes of the effectiveness of the prototype program (ie, dependent variables). Willingness to use the *WayToServe Plus* program in the future and job and demographic characteristics were also measured. The respondents suggested ways to improve the prototype and make it more engaging. A second group of 51 servers was recruited to serve as an untreated control group and completed only a posttest web survey, with the primary purpose being to assess their perceived self-efficacy and response efficacy of RBS methods and compare them with ratings provided by servers who received the prototype.

Phase 2: RCT Protocol for Evaluating the Professional Development Component

The *WayToServe Plus* professional development component will be fully produced and evaluated for effectiveness in an RCT.

Production and Implementation of WayToServe Plus Component

A 12-month version of the *WayToServe Plus* professional development component will be created for evaluation in the trial. Content and format will be developed according to instructional goals, principles from diffusion of innovation theory and social cognitive theory, and insights derived from the formative research findings in phase 1. Posts will contain text, infographics, short videos, and interactive activities based on the *WayToServe* RBS training. Features to elicit user-generated content will be included in posts, such as posing a common situation and asking, for example, RBS strategies; providing polls about RBS methods; and soliciting stories, tips, and tricks from experienced servers for applying RBS. These posts are intended to create sense of community among alcohol servers. An agile iterative production process will be used to author the posts [47]. Approximately 2 months of posts will be prepared before launching the intervention; additional posts will be developed during the intervention, adjusting them for season, current events, and reactions and comments from servers to prior posts.

WayToServe Plus will be administered by a staff member who serves as a community manager. The manager will post 4 posts per week, Monday through Friday, for 12 months (approximately 208 posts in total). In addition, posts selected from the usual-and-customary *WayToServe* Facebook page will be posted once per week. Alcohol servers can comment on and react to posts but cannot share them on their own feed. Orientation to private groups will be self-explanatory. The community manager will stress respect for others; monitor comments; and correct inappropriate, unfavorable, or bullying comments or misinformation [48]. Servers will be compensated US $50 for joining the *WayToServe Plus* Facebook private group.

Randomized Trial Design

The *WayToServe Plus* professional development component will be evaluated with a sample of 180 establishments licensed for sale of alcohol for onsite consumption (ie, liquor by the drink) and their alcohol servers. Premises will be enrolled in a 2-group randomized field trial (*WayToServe* training only [comparison control] vs *WayToServe* training plus *WayToServe Plus* [intervention]) with 2 assessment rounds (baseline and posttest [12 months after intervention commences]), yielding a 2 (treatment)×2 (assessment time) factorial design. Using a custom-written program, the project biostatistician will randomly assign half of the premises (90/180, 50%) to *WayToServe* training plus *WayToServe Plus*, stratified by state (ie,

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independent variables). The remaining half of the premises (90/180, 50%) will receive *WayToServe* training only. All premises will be recruited to have servers complete the *WayToServe* training. Servers in the intervention group will be joined to a *WayToServe Plus* Facebook private group after training to receive the professional development component. To be added to the group, servers will friend the community manager, the manager will invite them to join the group, and servers will accept this invitation. Servers in the control group will be invited to join the usual-and-customary *WayToServe* Facebook page, which is administered by the training company. Premises will be assessed for refusal of alcohol service to visibly intoxicated patrons, the primary outcome or dependent variable and a measure of the impact of *WayToServe Plus* on actual practice [29], using a pseudointoxicated patron (PiP) protocol at baseline and at posttest. The PiP protocol presents a server with the most overt situation in which alcohol service should be refused (ie, when a patron shows clear signs of intoxication), models the behavior of patrons most at risk, and is relatively low cost. The PiP protocol has been used in thousands of alcohol premises [49], including by the research team [50-52]. PiP teams will be blinded to experimental conditions, and premises owners, managers, and alcohol servers will be blinded to PiP assessments.

Selection and Recruitment of Licensed Alcohol Premises

State-licensed onsite alcohol establishments (n=180) in California (n=60), New Mexico (n=60), and Washington State (n=60) were randomly selected from publicly available lists from state alcohol regulation agencies, stratified by location (metro areas [Albuquerque, San Francisco {including Oakland and San Jose}, and Seattle; n=148 premises] vs suburban towns [n=7 towns and 32 premises]). As in the formative research, they had to hold an active state license to sell alcohol and be a bar or restaurant that sold alcoholic beverages. To control travel costs in the large San Francisco and Seattle metropolitan areas, *clusters* of establishments were constructed by randomly selecting seed premises. Next, 14 additional establishments were randomly selected from within the same zip codes of the seed premises. Within each seed area, 5 to 7 establishments were selected at random for PiP visits, with the remaining premises serving as replacements for any deemed ineligible (eg, do not sell alcohol for onsite consumption) or that were closed (either permanently or during evening hours) when visited by PiP teams. In New Mexico, the Albuquerque metropolitan area was much smaller geographically, so we selected premises at random from the state lists.

After the baseline PiP assessment, project staff will contact premises management, describe participation, record the number of alcohol servers, and obtain agreement to participate in the study. Premises will be given a voucher to provide to their servers to access the *WayToServe* training and complete it within 4 weeks from registration. Severs will complete a consent form. For completing the training, servers will receive US $35 and a new server training certificate for their state. *WayToServe* will remain available to the participating premises throughout the trial, and managers will be asked to have newly hired alcohol servers complete it.

PiP Assessment Protocol

The primary outcome (ie, dependent variable) will be refusal of sale of alcoholic beverages to visibly intoxicated patrons assessed using a PiP protocol. Ethnically diverse male and female legal-age individuals (aged ≥ 21 years) will be hired as confederates, chosen for prior acting experience, and trained to feign intoxication when acting as buyers [50-52]. Signs of intoxication (ie, fumbling with keys or cash, swaying, slurred speech, and stumbling) indicate a high level of alcohol intoxication [53], provide a clear unambiguous choice whether to serve, and are signs that alcohol servers are trained to recognize in the *WayToServe* training and *WayToServe Plus* component. In each round (baseline and posttest), assessment will involve 2 PiP buyer visits per premises by the PiP team comprising a buyer and an observer, separated by at least 6 weeks. At each visit, observers will enter the premises before the buyer and position themselves to be able to see the buyer-server interactions. Buyers will enter the premises displaying intoxication signs and order an inexpensive beer. Both buyers and observers will record if alcohol servers agree to serve the buyers the requested alcoholic beverage. Buyers will also record if the drink was served either as requested, with reluctance, with a joke or similar remark, or with a warning that no future drinks will be served.

In addition, buyers will note the type of beverages requested, if their ID was requested, and other responses by the alcohol servers (made statements of risk, enlisted other patrons to support nonsale, offered a nonalcoholic beverage instead, offered food, provided other information [offer of taxi or safe ride, drinking facts, etc], or delayed or ignored service). Observers will record the characteristics of the establishments (state, type, number of staff and patrons, warning signs posted, and cleanliness), rate how busy the establishment is and speed of service, note if staff appear overly familiar with customers, and record the behavior of buyers (type of drink ordered, signs of intoxication displayed, and rating of obviousness of signs of intoxication). Both buyers and observers will record the servers' job at the establishment (bartender, server, manager, bouncer, or other) and apparent sex (male, female, or do not know), Hispanic ethnicity, and race.

Outcome Analysis

The analysis of study outcomes will test the following hypothesis that compared with premises in *WayToServe* RBS training only group, premises assigned to receive *WayToServe* RBS training and *WayToServe Plus* will have higher rates of refusing PiP at posttest.

In our prior research, the uptake of training in alcohol establishments affected refusal rates [54], so we will test whether improvements in refusal rates are associated with uptake of the *WayToServe* training and engagement with the *WayToServe Plus* component. Training uptake will be obtained from the *WayToServe* web-based program database (ie, the number of servers registered, training modules completed, and completion of the training). Engagement with *WayToServe Plus* will be assessed by counting the number of reactions and comments on posts by servers within each premise [55]. We will not be able to count the views of posts because our sample size exceeds

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250 participants; Facebook does not report views of posts in private groups with >250 users. Characteristics of alcohol establishments (type of license, type of business [bar or restaurant], how busy the premises was, and number of staff present during visit), alcohol servers interacting with PiP buyers (sex and ethnicity observed by PiP observers), and PiP buyers (sex and ethnicity) will be analyzed initially as control variables and then in subsequent models as effect modifiers of *WayToServe Plus*.

Interviews of Owners and Managers on WayToServe Plus Feasibility

After posttesting of establishments is completed, 18 owners and managers (6 per state) from premises in the *WayToServe* training and *WayToServe Plus* groups will be selected at random for interviews about *WayToServe Plus*, its compatibility with premises' RBS policies and practices, helpful features, server engagement, suggested improvements, and problems or barriers (compensation=US $75). In addition, alcohol servers in these premises will be surveyed about the same issues and report their engagement with *WayToServe Plus*, whereas servers in the control premises will be surveyed about the *WayToServe* web-based training.

Ethical Considerations

The protocols used in the formative research and randomized trial were reviewed and approved by the WCG institutional review board (#20211770). Participants read and signed an informed consent form (interviews, focus groups, and pilot field trial) or read and acknowledged a consent statement (surveys) approved by the institutional review board that described the purpose of the research, the research procedures, known risks and benefits, and the use and security of the data. Participants were informed that their participation was voluntary and that they could withdraw at any time without penalty. Participants were informed that the data collected from them in the study would be confidential and that their identity would not be disclosed in any public presentation. The participants were compensated as follows: interviews (US $75), focus group discussion (US $50), survey (US $25), usability test (US $50), and field pilot study (US $100).

Results

Phase 1

Owner and Manager Interviews About Professional Development

All owners and managers (n=10; 4 female individuals; 1 African American and 5 Hispanic White individuals) indicated that they supported RBS methods to maintain their establishment's reputation in the community; keep the community safe; and avoid fines, disruptions, and other problems. They supported alcohol servers by addressing RBS methods in mandatory staff meetings and trainings and manager logs. They said that support for RBS was provided by experienced staff. Although most felt the RBS methods were effective at their premises, they did indicate that bartenders have many job tasks and need more help, and some establishments had more difficulty with RBS methods during summers when patrons drank longer and larger quantities of alcohol.

All owners and managers endorsed the need for ongoing training and support for RBS methods and felt that a program could help them support RBS practices. They desired topics such as checking IDs, new recreational marijuana laws, special venues (eg, music venues, wineries, and events), and communication and conflict resolution. They preferred formats such as educational memes, videos, shared experiences and tips and tricks from experienced servers, resource pages, reminders, and work group chats. Owners and managers felt that a variety of staff would benefit from ongoing training. Some of them did not feel confident addressing topics such as marijuana laws, how to handle patrons with children, and how to manage servers' desires to sell alcoholic beverages and make money. All owners and managers would be interested in a program that provided ongoing training and support for RBS if it provided new, relevant content in engaging, easily digestible formats without a large time commitment. They were mostly or very likely to use such a program with their alcohol service staff.

Focus Groups and Survey of Alcohol Servers About Professional Development

Focus Groups

Alcohol servers participating in the focus groups (n=19) were employed in bars, restaurants, and other premises (eg, ski resort, theatre, and market) as bartenders, servers, and other staff. They had worked as servers for 2 months to 6 years.

Most servers had positive experiences applying RBS methods. They reported that owners and managers at their establishment considered RBS methods to be positive, took them seriously, and supported using them. A few servers said that they received very little support, support only from direct supervisors, and support only when they did something incorrectly. They cited management turnover and very large venues as situations that reduced support for RBS. Obstacles to RBS included customers drinking before arriving; pressure to not check IDs or provide heavier pours to regular customers or members of clubs; customers not wanting to hand over ID during COVID-19 social distancing rules; ability to check IDs from different states or military IDs; fake IDs; pressure to sell and fear of losing tips; large, busy events; and potential for negative reactions when refusing sales to intoxicated patrons. Methods to overcome obstacles included observing customers when they arrive; relying on managers, bartenders, and other servers for help; slowing down activities during busy times or slowing service to intoxicated customers; eliminating tips; having support from management; dividing RBS tasks among different staff; serving water to intoxicated customers; and setting limits on the number of drinks served.

All servers saw benefits of continued information, training, and support for RBS methods. The servers also described topics that would be helpful. The perceived benefits of a continuing professional development program included peer support, sense of community, networking among servers, keeping updated on new information, and helping new servers. These included interactive learning activities, prompts, refreshers on laws, IDs,

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recognizing intoxication, drink counting, and refusing service, instruction on how to deal with minors, forums for sharing stories and tips with other servers, help for newer servers, ways of managing difficult customers and de-escalating conflict, polls, infographics, and reminders. Almost all servers indicated that they would be willing to share their experiences and provide feedback on RBS methods in the *WayToServe Plus* Facebook group.

Survey

Table 1 presents the profile of the sample of alcohol servers (n=24) who completed the web survey. Alcohol servers ranged in age from 20 to 40 (mean 28.8, SD 5.4) years; a majority were non-Hispanic White (7/24, 29% Hispanic), and there were slightly more female individuals than male individuals. Most servers worked in restaurants and bars as alcohol servers and bartenders and were a mix of new (7/24, 29% had worked less than 1 year) and experienced (15/24, 63% had worked 3 years or more) servers.

Although most servers were very sure of their ability to apply RBS methods, some encountered problems. A sizable minority were only somewhat sure or unsure that they could verify the validity of IDs (3/24, 12%; mean 4.79 out of 5, SD 0.66), check IDs for age of patron (2/24, 8%; mean 4.83, SD 0.64), count number of drinks to prevent intoxication (6/24, 25%; mean 4.63, SD 0.77), recognize if a patron is intoxicated (6/24, 25%; mean 4.63, SD 0.88), or refuse alcohol service to an intoxicated patron (5/24, 21%; mean 4.75, SD 0.53). The obstacles to RBS methods cited included busy serving environments (10/24, 42%), customer intoxicated before arriving (10/24, 42%), regular customers expecting heavier pours (6/24, 25%), coworker or management pressure to not follow RBS regulations (5/24, 21%), fear of sacrificing tips (3/24, 12%), and checking IDs in a group of customers (2/24, 8%). Servers suggested several ways to overcome these obstacles, such as checking everyone's ID (11/24, 46%), getting support from management to follow rules (5/24, 21%), taking a moment to breathe in busy environments (9/24, 38%), serving water (6/24, 25%) or food (5/24, 21%) to patrons that need to sober up, monitoring patrons for signs of intoxication (13/24, 54%), and involving a manager in handling difficult customers (13/24, 54%).

Almost all servers felt that the management of their establishment was supportive of RBS methods, agreeing that management believes RBS methods are beneficial (22/24, 92%; mean 4.54 out of 5, SD 0.66) and management takes RBS methods seriously (22/24, 92%; mean 4.67, SD 0.64). However, 21% (5/24) reported that management at their establishment provided support for RBS methods only sometimes, rarely, or never. The most common support was help serving when the establishment gets busy (16/20, 80%), answering questions about RBS methods (17/21, 81%), helping servers refuse service to a customer (14/20, 70%), helping check IDs during busy periods (9/20, 45%), and highlighting things to be on alert for before a shift (9/19, 47%).

Servers favorably evaluated the idea of professional development. Overall, 71% (17/24) of servers expressed interest in receiving ongoing information and activities from *WayToServe* to help keep them up-to-date and be able to use the RBS methods. The benefits servers saw from this professional development for themselves would be receiving tips and tricks from other servers, getting refreshers on everyday work practices, helping other servers who need it, and providing a place to vent about poor experiences while serving alcohol (Table 2). Benefits for the establishment included having servers be on the same page when it comes to serving alcohol and remaining in good standing with the state's alcohol licensing agency. Finally, 46% (11/24) of the servers said they were somewhat or very likely to join a Facebook group with the professional development content, and 21% (5/24) might join it. The topics of most interest to servers included refreshers on signs of intoxication, unusual or humorous experiences by another server, quizzes that test knowledge of alcohol serving laws, servers sharing positive or negative on-the-job experiences, stories from other servers about how they used an RBS method, and polls on what the servers believe the community thinks about alcohol serving topics (Table 2). Less popular topics were servers sharing experiences via Facebook Live, refreshers on laws and penalties, information on new state laws, refreshers on ID checking, interactive learning activities, and instruction on using RBS methods.

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Table 1. Profile of alcohol server samples in formative research.

Profile	Server survey (n=24)	Usability testing (n=20)	Field pilot study	
			Prototype group (n=59)	Control group (n=51)
Type of licensed sales, n/N (%)				
On site (by the drink)	—[a]	13/20 (65)	38/59 (64)	39/51 (77)
Off site (package)	—	1/20 (5)	7/59 (12)	8/51 (16)
Both	—	6/20 (30)	13/59 (22)	4/51 (8)
Type of establishment, n/N (%)				
Bar	4/24 (17)	1/20 (5)	—	—
Restaurant	12/24 (50)	14/20 (70)	—	—
Nightclub	0/24 (0)	2/20 (10)	—	—
Brewery	3/24 (12)	2/20 (10)	—	—
Distillery or winery tasting room	0/24 (0)	1/20 (5)	—	—
Other	5/24 (21)	1/20 (5)	—	—
Job type, n/N (%)				
Bartender	8/24 (33)	7/20 (35)	15/59 (25)	13/51 (26)
Server	12/24 (50)	9/20 (45)	27/59 (46)	24/51 (47)
Manager	2/24 (8)	1/20 (5)	7/59 (12)	7/51 (14)
Other	2/24 (8)	3/20 (15)	9/59 (15)	6/51 (12)
Years of experience, n/N (%)				
<1	7/24 (29)	1/20 (5)	14/59 (24)	6/51 (12)
1-2	1/24 (4)	1/20 (5)	14/59 (24)	9/51 (18)
2-5	8/24 (33)	5/20 (25)	10/59 (17)	14/51 (27)
>5	8/24 (33)	13/20 (65)	20/59 (34)	22/51 (43)
Age (y), mean (SD)	28.8 (5.3)	32.2 (4.7)	33.1 (11.5)	34.5 (11.7)
Race or ethnicity, n/N (%)				
African American	0/24 (0)	0/20 (0)	1/51 (2)	0/51 (0)
American Indian or Alaska Native	1/24 (4)	2/20 (10)	2/51 (4)	3/51 (6)
Asian	0/24 (0)	0/20 (0)	1/51 (2)	4/51 (8)
Hispanic	7/24 (29)	8/20 (40)	13/59 (22)	17/51 (33)
Native Hawaiian or other Pacific Islander	2/24 (8)	0/20 (0)	4/51 (8)	0/51 (0)
Non-Hispanic White	11/18 (61)	9/20 (45)	27/48 (56)	30/51 (59)
Sex, n/N (%)				
Male	13/24 (54)	12/19 (63)	41/59 (70)	18/48 (38)
Female	10/24 (42)	7/19 ((37)	17/59 (30)	29/48 (60)
Other	1/24 (4)	0/19 (0)	0/59 (0)	1/48 (2)

[a]Not available.

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Table 2. Topics of interest in continuing professional development identified by alcohol servers (n=23).

Topic	Participants, n (%)
Benefits to servers	
Tips and tricks from other servers	18 (78)
Refreshers on everyday work practices	13 (56)
Providing help to other servers who need it	12 (52)
Having a place to vent about poor experiences while serving alcohol	11 (48)
Benefits to establishments	
Having servers on the same page when it comes to serving alcohol	21 (91)
Remaining in good standing with the state's licensing body	13 (56)
Professional development topics of interest	
Stories from other servers about how they used an RBS[a] method	8 (35)
Unusual or humorous experience by another server	11 (48)
Refreshers on signs of intoxication	12 (52)
Quizzes that test knowledge of alcohol serving laws with prizes	9 (39)
Servers sharing positive or negative on-the-job experiences	9 (39)
Polls on what the server community thinks about alcohol serving topics	8 (35)
Interactive activities that help maintain a skill	7 (30)
Information on new state laws	7 (30)
Question and answer posts	9 (39)
Interactive learning activity for applying an RBS method with feedback	6 (26)
How to use an RBS method	5 (22)
Refreshers on ID checking	5 (22)
Refreshers on laws and penalties pertinent to servers	5 (22)
Servers sharing their experiences via Facebook Live segments	4 (17)

[a]RBS: responsible beverage service.

Survey on Acceptability, Feasibility, and Usability of WayToServe Plus Prototype

Table 1 presents the profile of the sample of alcohol servers in the usability test of the *WayToServe Plus* prototype (n=20). They were aged 25 to 42 (mean 32.2, SD 4.7) years, and the majority were non-Hispanic White (8/20, 40% were Hispanic) and predominately female individuals. Most worked in on-premises alcohol sales establishments, especially restaurants; however, several worked in nightclubs, breweries, and distillery or winery tasting rooms. The main job types were bartender and alcohol server. Most were experienced alcohol servers, with 90% (18/20) working for >2 years as a server.

Alcohol servers rated the posts in *WayToServe Plus* prototype as highly appropriate for themselves and their establishment, very acceptable, and useful (with average ratings of all social media posts and the video being above the scale midpoint; Table 3). They evaluated posts on management and house policy most favorably (means ranged from 3.80 to 4.30), compared with posts on additional training (means ranged from 3.30 to 3.85) and disruptive customers (means ranged from 3.58 to 4.05). The prototype videos were very favorably evaluated in terms of appropriateness, acceptability, and usefulness (means 3.80-4.25). Of the 20 servers, 8 (40%) rated the prototype as usable on the SUS, and 90% (18/20) evaluated it as user-friendly (good, excellent, or best imaginable).

Most servers indicated that they would use *WayToServe Plus* if it was available. Specifically, 60% (12/20) felt that they would like to use it in the future, and 85% (17/20) were interested in getting ongoing information and activities from *WayToServe Plus* to help keep up-to-date and be able to use RBS methods. When considering specific posts, most servers said they would engage with the posts (view, react to, comment, and share), with the number who would read and react to them being especially high. Slightly fewer servers said they would comment on or share their own posts, but ≥45% (9/20) said they would do so. Videos were the most engaging, with >70% (14/20) saying they would read, react, comment on, and share them (Table 3). In addition, 85% (17/20) of the servers would use an interactive learning activity if posted in the *WayToServe Plus* component.

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Table 3. Acceptability and potential engagement with messages in the *WayToServe Plus* prototype usability survey (N=20).

	Social media posts by topic			Videos
	Professionalism	Premises management	Advanced responsible beverage service skills	
Acceptability of posts, mean (SD)				
Appropriate for me	3.70 (1.45)	4.20 (0.83)	3.90 (0.85)	4.15 (1.27)
Appropriate for establishment	3.85 (1.35)	4.25 (0.91)	3.58 (1.17)	3.80 (1.61)
Acceptable to me	3.80 (1.40)	4.30 (0.66)	3.95 (0.89)	4.25 (1.02)
Useful to me	3.30 (1.45)	3.80 (0.95)	4.05 (1.05)	4.05 (1.32)
Potential engagement with posts, n (%)				
Would read post	12 (60)	16 (80)	16 (80)	18 (90)
Would react to post	10 (50)	13 (65)	15 (75)	15 (75)
Would comment on post	12 (60)	10 (50)	10 (50)	15 (75)
Would share post	11 (55)	9 (45)	11 (55)	14 (70)

Field Pilot Test of WayToServe Plus

The profile of the alcohol servers participating in the intervention group (n=59) and control group (n=51) in the pilot test is presented in Table 1. Intervention group participants ranged in age from 18 to 65 (mean 33.1, SD 11.5) years, were mostly non-Hispanic White (13/59, 22% Hispanic), and were predominately female individuals. By job type, most worked in on-premises sales establishments as bartenders or alcohol servers. They were a mix of new and experienced servers (14/59, 24% had worked less than 1 year and 20/59, 34% had worked 5 years or more).

Alcohol servers had high engagement with the *WayToServe Plus* professional development component. Overall, 83% (50/60) viewed at least 1 post, and they viewed an average of 14.85 (SD 12.41) posts over 4 weeks (approximately 24 posts were displayed in any 4-week period). Just under half of the servers (28/60, 47%) reacted (eg, liked) or commented on a post in the *WayToServe Plus* group. Servers on average reacted to 4.17 posts (SD 7.08).

Alcohol servers evaluated the *WayToServe Plus* component as highly usable and its content as appropriate. The mean rating on the SUS scale was 81.10 out of 100, with 88% (52/59) giving it a score of ≥68, a common threshold for usability on this scale. They also gave it high marks on user-friendliness (mean 5.81 out of 7). Many felt that the component (52/59, 88% agreed or strongly agreed; mean 4.42 out of 5, SD 1.19) and its content (50/59, 84%; mean 4.31, SD 1.25) were appropriate for them as alcohol servers and aligned with their establishment's atmosphere (48/59, 81%; mean 4.12, SD 0.79). Most found the posts (49/59, 83%; mean 4.08, SD 0.75) and other servers' comments on the posts (47/59, 80%; mean 4.05, SD 0.78) to be useful. A large majority of the alcohol servers said that they were likely to use *WayToServe Plus* in the future (46/59, 78% somewhat likely or very likely; mean 3.95 out of 5, SD 0.99).

Servers in the control group were similar in characteristics to those in the intervention group (Table 1), although control servers had more years of experience on average. Alcohol servers who received the *WayToServe Plus* prototype were compared with those in the control group in their reported self-efficacy and response efficacy for implementing RBS methods as an indicator of the potential impact of the *WayToServe Plus* program. Given the small sample size, we planned a priori to calculate the effect size estimate, *d*, rather than perform a standard statistical significance test. Ratings on self-efficacy were higher among servers in the prototype group (mean 4.53, SD 0.57) than servers in the control group (mean 4.33, SD 0.77; *d*=0.30). Likewise, ratings on response efficacy were greater in the prototype group (mean 4.68, SD 0.68) than in the control group (mean 4.39; *SD* 0.83; *d*=0.38).

Phase 2

Phase 2 was funded in September 2022. Baseline assessment of licensed alcohol premises (n=179) in California (n=59), New Mexico (n=60), and Washington (n=60) was conducted in 2022-2023 using the pseudopatron protocol, and results are available elsewhere [56]. The recruitment of premises to have servers trained and join the Facebook private group containing the professional development posts is ongoing. Posttest assessment is planned for summer and fall, 2024 with results expected to be published in 2025.

Discussion

Principal Findings

The development of a professional development extension of our RBS training course aims to improve the efficacy of RBS training in the field. The formative research confirmed that owners, managers, and alcohol servers considered a professional development component for RBS to be beneficial, and a large majority would be interested in using such a program. Many owners and managers have already taken steps to help servers implement and maintain their RBS skills, and several of them felt that *WayToServe Plus* would complement and aid in these efforts. A previous study found that managers trained in RBS also trained their staff in cutting off intoxicated patrons and handling fake IDs [57]. Alcohol servers considered the *WayToServe Plus* prototype to be highly appropriate, acceptable, usable, and useful. Many servers followed (ie, viewed a post) and engaged (ie, reacted to or commented on a post) with the

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prototype. These results are consistent with the literature citing education and lifelong learning as essential in the hospitality industry to maintain job competence, be productive, and be valued employees [37]. A formal professional development program, such as *WayToServe Plus*, might help employees improve RBS practice faster than informal training by owners and managers [32]. Continued professional development might also increase employee retention and reduce absenteeism by improving confidence in role, clarifying job expectations, helping to manage stressful situations, and increasing job satisfaction and commitment [29,58].

Formative research identifying the topics of interest to servers likely contributed to creating highly engaging posts in the *WayToServe Plus* prototype. Most servers said that they would be interested in receiving ongoing information and support for RBS methods, and many would enroll in the *WayToServe Plus* component in the future. Moreover, the *WayToServe Plus* prototype appeared to improve theoretic mediators of effective RBS training. Continuing professional development programs should be more effective when personally meaningful to learners [30,59]. Together, these findings suggest that the ongoing professional development in *WayToServe Plus* is likely to improve RBS practices in the upcoming RCT and when disseminated with the *WayToServe* RBS training.

Owners, managers, and servers felt that the professional development content fit with the atmosphere of their licensed establishments. Fit might be further enhanced by providing the information in easily digestible and relatable formats that do not require a large time commitment. Fit is an important innovation characteristic that predicts adoption [39], and continuing professional development programs may be most effective when reflecting the context and experiences of learners [30].

The formative research provided insights into the potentially effective content of a professional development component. Servers and managers wanted skills training on refusing service, handling intoxicated and difficult customers, conflict resolution, communication, drink counting, and recognizing intoxication; serving at special events; ID checking; serving laws and penalties; and prohibited conduct (eg, recreational cannabis, drinking on the job, and firearms). These represent a combination of generic as well as job-specific information and skills for alcohol service, a common combination of skills in the hospitality industry [36,37]. Servers suggested several message features that would promote engagement with the professional development content, including positive messages; relaxed, conversational tone; humor; infographics or charts; articles; videos; questions and answers; resources; reminders; interactive activities; badges or rewards; polls; quizzes; games; weekly discussion topics; tips, stories, and comments from experienced servers; and opportunities to share experiences. Sharing ideas and experiences among servers and creating learning communities where they can work collaboratively should facilitate the success of continuing professional development [59,60]. User-generated content stands out as a key feature of social media platforms and holds significant sway in shaping social norms, particularly through the process of opinion leadership [39]. Managers and servers were interested in developing professionalism, such as understanding the roles of management, building a community in the hospitality environment, and enhancing hospitality careers. Cultivating or enhancing a sense of professionalism among servers could potentially elevate their regard for customer and community safety (ie, fostering professional norms [29]), strengthen their commitment to their roles, and motivate the consistent use of RBS methods.

The findings supported the use of a social media platform to deliver the professional development content. In 2021, most adults used social media (72%), including >80% of those aged 18 to 49 years [61], for information and peer connections that can be influential [62,63]. Web-based learning is common in vocational education and continuing professional development, providing advantages in terms of low cost, time efficiency, media-rich presentations, and interactivity [31,59,60]. Our plan to deliver the professional development content on an ongoing basis should help confer mastery of RBS techniques taught initially in the single, intensive *WayToServe* course by providing time for servers to set goals to improve behavior, assess current performance, and receive timely feedback to make improvements [60]; however, to be effective, servers will need to be self-directed learners with sufficient motivation to engage with the post. Effectiveness and motivation may increase when coupled with in-person instruction and mentoring from managers and experienced servers [31,59,60], rather than replacing this on-the-job support.

We chose to deliver the *WayToServe Plus* over Facebook because (1) the *WayToServe* training had an existing Facebook page with approximately 20,000 followers; (2) despite some decline in its user base [64-66], Facebook still reaches a large majority of adults including more than 70% adults aged 18-49 years by one estimate in 2021 [61]; and (3) Facebook's private group feature will control treatment presentation to prevent contamination when testing the effectiveness of *WayToServe Plus*. Video content appeared to be especially popular, which was not surprising given the popularity of video-dominated social media such as YouTube and TikTok [61,67]. Theoretically, visual depictions should be effective at teaching skills through observational learning [40]. To broaden the appeal of the *WayToServe Plus* component, some posts should be linked to relevant content posted on Instagram, YouTube, and other highly popular social media. Once disseminated, it may be most effective to deliver *WayToServe Plus* messaging through multiple social media platforms.

Limitations

The formative research and upcoming RCT evaluating the *WayToServe Plus* professional development component will be limited by conducting them with servers in only 3 states in the western United States, California, New Mexico, and Washington State, where the *WayToServe* is an approved RBS training provider. However, these states are diverse in population size, history of RBS training requirements (ie, New Mexico and Washington State have required RBS for over 2 decades, whereas California's requirement was new in 2022), and content requirement for RBS training (eg, California requires more content for managers than New Mexico and Washington State).

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The selection method using clustering of establishments in California and Washington State could introduce a design effect, but it was balanced against cost controls and project feasibility. The findings pertain to web-based professional development content, not other forms of support delivered in person or in print, but web delivery creates a high-quality, high-fidelity, engaging learning environment [68]. Uptake of *WayToServe Plus* will undoubtedly vary among servers and across establishments, which could diminish its effectiveness. However, the formative research suggests that many servers will engage with the professional development posts. The upcoming evaluation of *WayToServe Plus* will be strengthened by random selection of the licensed establishments; random assignment to experimental conditions; observational measures of refusal rates; and blinding of PiP teams, establishment management, and alcohol servers.

Conclusions

If successful, this study has the potential to improve the effectiveness of evidence-based RBS training and reduce the negative consequences of DWI. The results will also provide evidence that personnel in regulated industries that affect public health and safety, such as hospitality, can be trained to improve compliance with state policies and regulations. Furthermore, it will show whether professional development can be effective for individuals without specialized professional education. Far from *low-skilled*, alcohol service requires key skills in managing emotions, communication, problem-solving, and flexibility [36] as well as learning and applying the regulations and best practices surrounding responsible alcohol service. It should be amenable to improvement through ongoing professional development between state-required retraining in RBS techniques. The market for RBS training is large; therefore, improvements in this common intervention could have a substantial impact on DWI rates. No RBS training provider currently provides ongoing professional development as extensive as is planned for *WayToServe Plus*, so it should be seen as a value-added component for many licensed establishments, improving its dissemination potential.

Acknowledgments

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Data Availability

The data set generated and analyzed during the pilot study is available in the Inter-university Consortium for Political and Social Research (ICPSR) repository [69].

Authors' Contributions

WGW, DB, and RS conceptualized the study, designed the methods, and secured extramural funding. WGW and DB are supervising project activities. LM is managing day-to-day study activities. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

WGW, DB, and LM receive a salary from Klein Buendel, Inc. DB’s spouse is an owner of Klein Buendel, Inc. WGW and DB are owners of Wedge Communications LLC, the distributor of the *WayToServe* web-based training. An active management plan is in place at Klein Buendel to manage this conflict of interest. RS has no conflicts of interest.

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Abbreviations

DWI: driving while intoxicated
PiP: pseudointoxicated patron
RBS: responsible beverage service
RCT: randomized controlled trial
SUS: System Usability Scale

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Protocol

Effectiveness of the Wellness Together Canada Portal as a Digital Mental Health Intervention in Canada: Protocol for a Randomized Controlled Trial

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Abstract

Background: The Wellness Together Canada (WTC) portal is a digital mental health intervention that was developed in response to an unprecedented rise in mental health and substance use concerns due to the COVID-19 pandemic, with funding from the Government of Canada. It is a mental health and substance use website to support people across Canada providing digital interventions and services at no cost. Two million people have visited the WTC portal over the course of 1 year since launching; however, rigorous evaluation of this potential solution to access to mental health care during and after the COVID-19 pandemic is urgently required.

Objective: This study aims to better understand the effectiveness of the existing digital interventions in improving population mental health in Canada.

Methods: The Let's Act on Mental Health study is designed as a longitudinal fully remote, equally randomized (1:1), double-blind, alternative intervention–controlled, parallel-group randomized controlled trial to be conducted between October 2023 and April 2024 with a prospective follow-up study period of 26 weeks. This trial will evaluate whether a digital intervention such as the WTC improves population mental health trajectories over time.

Results: The study was approved by the research ethics board of CAMH (Centre for Addiction and Mental Health, Toronto, Ontario, Canada). It is ongoing and participant recruitment is underway. As of August 2023, a total of 453 participants in the age group of 18-72 years have participated, of whom 70% (n=359) are female.

Conclusions: This initiative provides a unique opportunity to match people's specific unmet mental health and substance use needs to evidence-based digital interventions.

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KEYWORDS

Wellness Together Portal; randomized trial; COVID-19; mental health; digital health; digital intervention; substance use; portal; effectiveness; well-being

Introduction

Mental health problems are the leading cause of global disability affecting worldwide populations including Canadians. The Bell Let's Talk campaign promotes mental health awareness by engaging Canadians in encouraging people to speak up about mental health. Yet, many Canadians lack access to mental health care services, with equity in access being a key concern for specific groups (eg, gender, race and ethnicity, socioeconomic status, geographic isolation, and immigration status). As a result of the COVID-19 pandemic and preventive measures such as

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social distancing, an "echo pandemic" of declining mental health in the Canadian population has emerged [1]. The COVID-19 pandemic is exacerbating mental health challenges and widening service gaps, especially among those in marginalized groups and those with preexisting mental health issues [2,3]. Research on mental health during the pandemic has found that 40% of Canadians stated that their mental health has declined due to the COVID-19 pandemic, and 48% of individuals felt anxious or worried [4,5]. Even prior to the pandemic, the burden of mental illness was widespread in the population. Worldwide, an estimated 264 million people are affected by depression alone [6]. Mood and anxiety disorders are the most prevalent mental health issues in Canada, occurring among 11.6% of Canadian adults [7]. Our mental health care system is overwhelmed and too underfunded to address the pervasiveness of mental health challenges [8]. At the same time, many people are reluctant to maintain or improve their mental health, with a stigma-based perception that mental health is only an issue for people with a diagnosed mental disorder, rather than being a concern for everyone [9]. The experience of the COVID-19 pandemic demonstrates that it is critical to provide tools to all Canadians, which will improve mental health and provide self-assessment and self-help aids at the population level [10].

The digital intervention for mental health, the Wellness Together Canada (WTC) portal [11], was developed in response to an unprecedented rise in mental health and substance use concerns due to the COVID-19 pandemic, with funding from the Government of Canada. It is a mental health and substance use website to support people across Canada, providing digital interventions and services at no cost. It partners with other digital interventions to be the home portal for access to digital interventions from 1:1 support, peer groups, and self-help tools. WTC is a one-stop, web-based portal, available nationally, which provides all people in Canada with 24/7 free and confidential access to a web-based network of information and psychosocial support services, which comprise triage and self-monitoring tools, mental health promotion information, self-guided apps, coached and peer support programs, mental health counseling, and crisis intervention. Services are readily accessible, available in French and English, and are made available through a variety of digital media (eg, computer and phone) and web-based services (eg, voice, text, web-based chat, and responsive web design). The portal is stigma-free and recovery-oriented, providing a wide range of intervention options, and follows a continuous improvement process based on stakeholder engagement, program data, and user feedback. Two million people have visited the WTC portal over the course of 1 year since launching; however, rigorous evaluation of this potential solution to access to mental health care during and after the COVID-19 pandemic is urgently required.

This initiative provides a unique opportunity to match people's specific unmet mental health and substance use needs to evidence-based digital interventions. Canadians will have a tool that provides valuable information, self-assessment on mental health, access to personalized digital interventions, and an avenue for everyone to participate in better understanding and improving mental health in Canada.

This study aims to evaluate the effectiveness and cost-effectiveness of the WTC portal by conducting a randomized controlled trial. The control group will be referred to the usual care tools available on the CAMH (Centre for Addiction and Mental Health) website. CAMH provides a range of self-care interventions, particularly different mental health programs and resources such as "Game Changers: Self-care information," which is a hub of resources to help start a conversation about health, including a self-help booklet series, a relaxation guide, and free web-based education with a personalized dashboard, which provides an opportunity for the client to self-monitor (symptoms or physiological processes), build awareness, and improve self-efficacy and visualization. Usual care tools such as digital interventions have a self-care and self-help component. Many studies have shown positive outcomes deemed acceptable and feasible with >95% completion rates and a high degree of participation with self-care interventions; some offer significant early benefits of tailored self-care programs [12,13]. A meta-analysis indicates that these interventions can be effective and potentially be future home-based interventions, especially in mental health care such as digital interventions; hence, it has been chosen as a control intervention in this study.

Methods

Trial Design

The Let's Act on Mental Health study is a longitudinal, fully remote, equally randomized (1:1), double-blind, alternative intervention–controlled, parallel-group randomized controlled trial to be conducted between October 2023 and April 2024 with a prospective follow-up for 26 weeks. This trial will evaluate whether digital interventions such as WTC improve population mental health trajectories over time. The trial will consist of 1 baseline assessment at week 0, 13 biweekly short and long follow-ups from week 24, intervention monitoring twice at weeks 6 and 26, and 1 final assessment at the end of the 26-week follow-up period. An overview of the trial process is shown in Figure 1.

The study's overall objective is to evaluate the effectiveness and cost-effectiveness of the WTC portal by conducting a randomized controlled trial. We will use a "Knowledge-to-Action Framework" [14] with extensive stakeholder and cross-sectoral engagement and will incorporate program elements with people with lived experience.

The research questions we seek to answer with this study are the following: (1) how effective is the WTC portal in altering the trajectories of mental health and substance use, primarily anxiety, compared to usual care? (2) What is the benefit of WTC versus usual care in terms of incremental costs, health outcomes, ongoing recruitment, and maintenance costs compared to the cost per quality-adjusted life year (QALY) gained using these interventions? (3) What is the differential impact of WTC by age, sex or gender, race, and socioeconomic status?

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Figure 1. Flow chart showing participation stages and assessments in the Let's Act on Mental Health Survey of 2022.

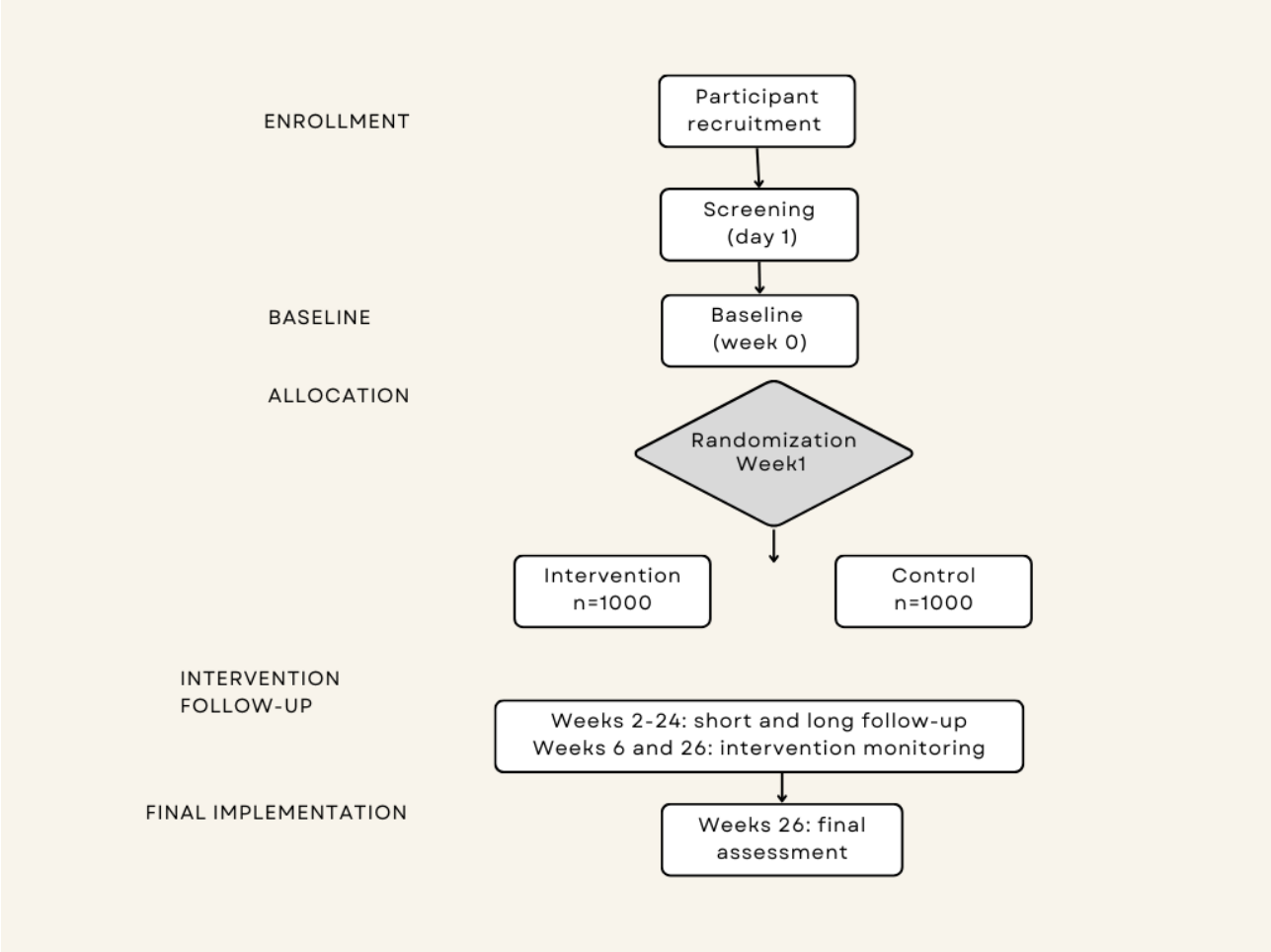

Participants and Recruitment

Adults (N=2000) will be recruited using both paid and free web-based advertisements (social networking sites, Google advertisements, Facebook, Instagram stories, Twitter, etc). The Facebook business account of CAMH will be used to advertise the study and recruit participants. In the case of web-based advertisements, participants will click on a link in the advertisement that will direct them to a REDCap (Research Electronic Data Capture) survey, which will screen them for eligibility (see Textbox 1 for inclusion and exclusion criteria).

The project's social media pages and CAMH's page will be used for advertisements. Further, we will also approach the participants from other ongoing studies at CAMH including the Vaping Research Panel, Smoking Panel, and those who had agreed to be contacted for future studies. We will not cold contact previous participants; we will ensure that initial contact with the participants is made by the research staff who had previously contacted and are known to them. This will help establish trust and compliance for the Let's Act on Mental Health study.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria:

- Adults (≥18 years of age) residing in Canada and speaking English or French
- Ability to complete study assessments in English
- Interest in the use of digital interventions to improve their mental health
- Having internet access

Exclusion criteria:

- People who are at risk for suicide (based on the 9-item Patient Health Questionnaire scores)

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Inclusion Criteria

Inclusion criteria are (1) being aged 18 years or older, (2) residing in Canada and speaking either English or French, (3) able to complete study measures in English, (4) willing or interested to use the digital interventions to improve their mental health, and (5) having internet access. Furthermore, concomitant psychotropic medication use will be allowed.

Exclusion Criteria

The main exclusion criterion was being at risk for suicide (based on the 9-item Patient Health Questionnaire [PHQ-9] score).

Participants who are not eligible for this study after screening will be redirected to a different page, informing them that they are not eligible and thanking them for their time.

Participant Withdrawal Criteria

Participants will not be withdrawn from the study for not wanting to receive the WTC or control intervention. Participants' intention to use and the reason to not use the intervention will be identified through self-assessments. However, they will be withdrawn from the study if suicidal thoughts occur in any of the long-term follow-up assessments at weeks 4, 8, 12, 16, 20, and 24.

Sample Size

The target sample size for the population survey and learning systems sample is 2000. This sample size will also allow for the estimation of the impact of the dashboard and app recommendations on score trajectories of the PHQ-9 and 7-item Generalized Anxiety Disorder Scale (GAD-7). Based on an estimated effect size of Cohen d=0.17 for changes in the PHQ-9 score and Cohen d=0.13 for changes in the GAD-7 score (based on the expected effects of the dashboard) [15], an expected dropout rate of no more than 35% [16], and population mean and SD estimates of PHQ-9 and GAD-7 scores [17,18], we estimate having a power of 0.90 and a type I error rate of 0.05 for detecting improvements in PHQ-9 and GAD-7 scores for subsamples with at least 1000 participants. Therefore, in this study, we will have a sample size of a total 2000 participants, with 1000 randomized to each group.

Randomization

At week 1, after baseline assessments, participants will be randomly allocated through email invitation to intervention or control groups using a simple randomization method equivalent of tossing a coin to ensure double-blinding. Participants deemed eligible after a manual-fraud check will be emailed a personalized URL invitation based on the groups in the study by the research personnel within the study, using the email template attached.

Blinding

Both participants and the research team involved in the trial will be blinded about the groups. The groups will be observed in an identical manner by the study team to ensure randomization. Further, to ensure that the study team is double-blinded, the potential participant receiving the intervention or usual care will be contacted by a research assistant outside the research team. The 2 groups will be followed up for 26 weeks to determine whether there are any differences in outcomes between them. The results and subsequent analysis of the trial will be used to assess the effectiveness of the WTC portal, which is the extent to which the service benefits the patients rather than doing them any harm.

Intervention

The intervention group will be invited to the WTC portal, which provides options for digital interventions. A single-sign on system used by WTC will be used to facilitate ease of transfer.

Control

The control group will be referred to the usual care tools available on the CAMH website, particularly (different mental health programs and resources such as "Game Changers: Self-care information," which is a hub of resources to help start conversations about health, self-help booklet series, relaxation guides, and free web-based education with a personalized dashboard), which provides an opportunity to clients for self-monitoring (symptoms or physiological processes), build awareness, improve self-efficacy, and visualization. The control group will not receive process monitoring assessments at week 6 or 26. Service usage and contamination in the control group will not be monitored.

Duration and Assessments

The expected duration of each participant's involvement in the study is for 6 months with baseline, weekly short follow-ups, intervention monitoring, and final assessments. Participants from the intervention and control groups will be asked to fill 1 baseline assessment at week 0 and 12 biweekly follow-ups from week 2 until week 24 including process monitoring of the intervention at weeks 6 and 26. Lastly, one final assessment will be carried out at week 26, for a total duration of 6 months. Hence, in total, a participant will complete 14 assessments. Participants will be sent weekly reminder emails to complete the assessments for compliance. The study team will track people who are lost to follow-up by communicating with them regularly through weekly emails and will continue to do so until the end of the study. They will be sent emails every week and will be provided an opportunity to complete the assessments when they show up until the end.

Ethical Considerations

This study is approved by the Research Ethics Board (REB) of CAMH (reference <REB#: 037-2022>, version 7.0). The protocol will be reapproved by the REB if it requires amendment. Participants will be screened and provided a unique ID number to protect their personal information. An electronic informed consent form has been prepared in REDCap to remotely obtain consent from the participants prior to enrolling them in the trial. A REDCap survey has also been designed separately for participants' eligibility screening at baseline, biweekly follow-ups, intervention monitoring, and final assessment over the 26-week period. Participants will be allowed to withdraw at any time without penalty.

Participants who meet the eligibility requirements of the initial screening form will be prompted to fill out a contact form with

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their first name and email address. Participants deemed eligible after a manual fraud check will be emailed a personalized URL to the baseline questionnaire by the research staff and those who are deemed ineligible by the fraud check will be sent a notification from REDCap about their ineligibility. The baseline questionnaire is largely composed of questions about age, sex, gender, race and ethnicity, education, and 3 digits of the participants' postal code to later connect it with census data and community-level equity data. Lifetime history of substance use and mental health will be ascertained, including problematic alcohol use (assessed using Alcohol Use Disorders Identification Test item 3 about how often they had 6 or more drinks on 1 occasion in the past year) and drug use (assessed using the modified Drug Use Disorders Identification Test). Finally, we will measure time to completion for data quality reasons, but this variable will not be visible to participants.

This randomized population trial will be compensating thousands of participants (N=2000). We will compensate participants at a rate sufficient to motivate them to comply with the study protocol and to complete all surveys and measures. This will include a CAD $10 (US $7.24) Giftbit [19] e-card after completing the initial baseline survey at week 0, and then CAD $24 (US $17.38) for completing the 12 assessments during biweekly follow-up in weeks 2-24, and finally CAD $10 (US $7.24) for final assessments at week 26. The follow-up payment will be based on completion rate, which, in turn, is based on the number of assessments completed at a rate of CAD $2 (US $1.45) biweekly. Hence, a participant completing 100% of the assessments (N=14) will receive CAD $44 (US $31.87) in total.

Privacy and Confidentiality

The master linking log will be stored in a separate folder than the other data files on the CAMH server. The master linking log will be used to identify contact information in order to send the baseline questionnaire link, follow-up questionnaire, and gift cards; to store status of interest in the qualitative study and future research studies; and to monitor completion of baseline and follow-up surveys. A numerical participant ID number will be used to differentiate participants in an anonymous manner across measures and follow-up questionnaires.

Participants who complete surveys will receive e-gift cards through Giftbit, which allows one to select a gift card of one's choice. Giftbit Incentives is a secure platform that allows bulk and automated sending of e-gift cards, and has been used by the principal investigator (MC) in previous studies at CAMH. Participant information shared with Giftbit will be limited to their first name and email address, in order to allow personalized e-gift card emails.

Safety and Adverse Events

Since the study procedures are not at higher than minimal risk, adverse events (AEs) and serious AEs (SAEs) are not expected. If any unanticipated problems related to the research involving risks to participants or others occur during this study, they will be reported to applicable stakeholders in alignment with institutional policies. AEs that are not serious but are notable and could involve risks to participants will be documented in accordance with institutional documentation requirements.

Outcome Measures

Primary Outcomes

The primary outcomes are the changes in trajectories of mental health, primarily anxiety at baseline (week 0) until final assessments (week 26) between 6 months after invitation to the WTC intervention or usual care. The trajectories are also measured biweekly with short follow-ups at different time points from week 2 until week 26. We will use multilevel modeling to describe within-person differences in anxiety and depression at different time points. We will compare the observed trajectory with those of the control group. Interactions by demographic subgroups (primarily age, gender, race, and socioeconomic status) will be assessed for identification of potential effect modifications.

Secondary Outcomes

An economic analysis will be conducted by comparing incremental costs and health outcomes for the Wellbeing Tracker and WTC compared to within-person expected trajectories using a cost-effectiveness acceptability curve. These costs will be based on the costs associated with the ongoing recruitment and maintenance costs of WTC compared to the cost per QALY gained through the use of these interventions [20]. To be somewhat comparable with World Health Organization's standards for ranking public health interventions, the determination of whether the WTC overall is highly cost-effective will be based on a threshold of CAD $124 (~US $100) per QALY gained [21]. QALYs will be estimated using the SF-6D (Short-Form Six-Dimension), calculated on the basis of the SF-12 (12-item Short Form Survey) [21]. This analysis will provide an empirical basis for the effect of allocation of health care resources in Canada. To aid other countries, we will also base cost-effectiveness calculations based on estimations that incorporate implementation costs of the Wellbeing Tracker and WTC. We will also estimate cost-effectiveness based on clinically Reliable Change Index scores (ie, 5 points on the PHQ-9 [22] and a 6-point change on the GAD-7 [23], as well as employment status. The schedule of the Let's Act on Mental Health study is outlined in Table 1.

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Table 1. Schedule of the Let's Act on Mental Health Survey of 2022.

Procedures	Study period (day 1 to week 26)						
Enrollment	Day 1	Week 0	Week 1	Weeks 2 and 4	Week 6	Weeks 8-24	Week 26
Eligibility screening	✓						
Informed consent	✓						
Screening assessments (PHQ-9[a] item 9)	✓						
Drug use (DUDIT-C modified[b])	✓						✓
Problematic alcohol use (AUDIT-C[c])	✓						✓
Enrollment							
Demographics		✓					
3-Digit postal codes		✓					
Baseline with self-reported questionnaires (GAD-7[d], PHQ-4[e], Current Substance Use, SF-12[f], and WSAS[g])		✓					
Randomization to the WTC[h] intervention or usual care group through an email invitation			✓				
Biweekly short and long follow-up (GAD-7, PHQ-4, Current Substance Use, SF-12, and WSAS)				✓		✓	
WTC and usual care monitoring for contamination and compliance checks					✓		✓
Final assessment (GAD-7, PHQ-4, current substance use, SF-12, and WSAS)							✓

[a]PHQ-9: 9-item Patient Health Questionnaire.

[b]DUDIT-C modified: modified Drug Use Disorders Identification Test.

[c]AUDIT-C: Alcohol Use Disorders Identification Test.

[d]GAD-7: 7-item Generalized Anxiety Disorder Scale.

[e]PHQ-4: 4-item Patient Health Questionnaire.

[f]SF-12: 12-item Short Form Survey.

[g]WSAS: Work and Social Adjustment Scale.

[h]WTC: Wellness Together Canada.

Data Management and Availability

All data will be collected and managed in the REDCap electronic case report forms. This system is maintained on central CAMH servers, with data backed up daily, and is supported by the Research Informatics department. This will strengthen the data's accuracy and maintain data quality. Only authorized personnel will monitor the completion of surveys, sending up to 3 reminder emails to participants who have not completed baseline surveys, up to 3 reminder emails to participants who have not completed follow-up surveys, and up to 3 reminder emails to participants who have not completed 6-month surveys.

The data sets will be stored on the secure CAMH server, and only for the minimum amount of time needed for fraud screening. Only trained research staff will have access to the data sets, and they will only use the merged data set for fraud screening purposes. As participants are screened, they will be entered into the screening log. Those deemed eligible will have their contact information, study ID number, and first name copied by research staff into the master linking log (a separate Excel [Microsoft Corp] file stored in a separate location from the fraud screening data). Once each round of fraud screening is completed, the merged data file will be securely destroyed. The original contact files may remain on the CAMH server to cross-check study IDs with the screening log, in the event that an ineligible individual contacts staff and inquiries about their eligibility.

Statistical Analysis

A statistician who is not affiliated with this study will perform the statistical analyses for Linear random effects modeling—which accounts for repeated measures over time—that will be used to study the intervention's effect [24]. We will also use multilevel modeling to describe within-person differences in anxiety and depression. We will then compare this observed trajectory with the control group's trajectories.

The level of change in anxiety from weeks 0-26 (baseline to final assessment) over the 6 months' time period is the primary trajectory of concern for mental health in this study. We will test the hypothesis that the trajectories are changing over time and the intervention's effects are expected to be observed as

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changes in self-reported mood, which will be measured with the mood scores, cutoff scores, sensitivity, etc, obtained at various time points. Interactions by demographic subgroups (primarily age, gender, race, and socioeconomic status) will be assessed for identifying potential effect modifications.

Analysis will be based on the intention-to-treat principle, as this method allows to draw an unbiased conclusion regarding the effectiveness of an intervention. It also preserves the benefits of randomization, which cannot be assumed when using other methods of analysis [25]. Further, this method is also more effective in accommodating missing data, as missingness is assumed at random.

Results

The study is ongoing and the first wave data collection is complete; we are analyzing data from the baseline and weeks 2-26. The study is ongoing at week 26, we have analyzed the preliminary baseline data and weeks 2 and 4 short and long follow-ups to understand the ongoing trajectory of depression. Until now, 453 individuals in the age group of 18-72 years have responded to the study invitation emails.

The trial is currently in the ethics approval process. Thus far, ethics approval has been granted by the REB of CAMH, and participant recruitment is ongoing. The study will be conducted in accordance with the REB-approved study documents and the determinations (including any limitations) of the REB, and in compliance with the REB's requirements.

Discussion

Anticipated Findings

At baseline, with regard to gender and race, a greater proportion of participants are female (n=359, 75.57%) and White (n=335, 67.95%). We aim to generalize this study to the Canadian population; hence, we have been weighting samples at the census level based on gender and province to make this study representative. Weighing of the sample will help us understand how generalizable the sample and advertisements are and whether they are adequately representative. The SF-12, measuring mental and physical health, has revealed a significant decline in mental health from baseline to short and long follow-ups in this study. It is too early to discuss how this will develop longitudinally, but the preliminary results suggest a larger decline in mental health than in physical health in the Canadian population.

Limitations

The foreseeable factors that could compromise the outcome of this study is the monitoring of WTC usage, which is based on self-reports. However, to mitigate the challenge, the study team will ensure detailed monitoring and contamination of intervention at 1 and 6 months. The study team will continuously explore its potential partners for incorporating artificial intelligence within the digital interventions, such as the WTC, for real-time monitoring of service usage. Service usage and contamination in the control group will not be evaluated.

Digital health interventions for delivering mental health care were relevant even before the COVID-19 pandemic. After the pandemic, it has proven to be a safer alternative to face-to-face treatment [26]. It offers great potential, and there is an urgent need for up-to-date information on the mental health impacts post the COVID-19 pandemic. Especially after pandemic, there is a dire need of population-level mental health interventions to improve access to and the quality of mental health care. The challenges of mental health care are its reach at the population level. Interventions such as WTC have shown great potential in developing interest toward mental health interventions in any population; however, the challenge of consistency remains to be studied.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
CAMH: Centre for Addiction and Mental Health
GAD-7: 7-item Generalized Anxiety Disorder Scale
PHQ-9: 9-item Patient Health Questionnaire
QALY: quality-adjusted life year
REB: Research Ethics Board
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SF-6D: Short-Form Six-Dimension
SF-12: 12-item Short Form Survey
WTC: Wellness Together Canada

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Protocol

Role of Chinese Acupuncture in the Treatment for Chemotherapy-Induced Cognitive Impairment in Older Patients With Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: Older patients with cancer experience cognitive impairment and a series of neurocognitive symptoms known as chemobrain due to chemotherapy. Moreover, older populations are disproportionately affected by chemobrain and heightened negative mental health outcomes after cytotoxic chemical drug therapy. Chinese acupuncture is an emerging therapeutic option for chemotherapy-induced cognitive impairment in older patients with cancer, despite limited supporting evidence.

Objective: Our study aims to directly contribute to the existing knowledge of this novel Chinese medicine mode in older patients with cancer enrolled at the Department of Oncology/Chinese Medicine, Nanjing First Hospital, China, thereby establishing the basis for further research.

Methods: This study involves a 2-arm, prospective, randomized, assessor-blinded clinical trial in older patients with cancer experiencing chemobrain-related stress and treated with Chinese acupuncture from September 30, 2023, to December 31, 2025. We will enroll 168 older patients with cancer with clinically confirmed chemobrain. These participants will be recruited through screening by oncologists for Chinese acupuncture therapy and evaluation. Electroacupuncture will be performed by a registered practitioner of Chinese medicine. The electroacupuncture intervention will take about 30 minutes every session (2 sessions per week over 8 weeks). For the experimental group, the acupuncture points are mainly on the head, limbs, and abdomen, with a total of 6 pairs of electrically charged needles on the head, while for the control group, the acupuncture points are mainly on the head and limbs, with only 1 pair of electrically charged needles on the head.

Results: Eligible participants will be randomized to the control group or the experimental group in 1:1 ratio. The primary outcome of this intervention will be the scores of the Montreal Cognitive Assessment. The secondary outcomes, that is, attentional

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function and working memory will be determined by the Digit Span Test scores. The quality of life of the patients and multiple functional assessments will also be evaluated. These outcomes will be measured at 2, 4, 6, and 8 weeks after the randomization.

Conclusions: This efficacy trial will explore whether Chinese electroacupuncture can prevent chemobrain, alleviate the related symptoms, and improve the quality of life of older patients with cancer who are undergoing or are just going to begin chemotherapy. The safety of this electroacupuncture intervention for such patients will also be evaluated. Data from this study will be used to promote electroacupuncture application in patients undergoing chemotherapy and support the design of further real-world studies.

Trial Registration: ClinicalTrials.gov NCT05876988; https://clinicaltrials.gov/ct2/show/NCT05876988

International Registered Report Identifier (IRRID): DERR1-10.2196/53853

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KEYWORDS

older patients with cancer; cognitive impairment; chemobrain; Chinese medicine; electroacupuncture

Introduction

With the development of new cytotoxic drugs for clinical practice, the clinical curative effects and survival rates of patients with cancer have improved greatly [1]. However, these drugs have considerable adverse side effects that are pernicious, unexpected, and occur at standard doses when administered to older patients with cancer [2]. Studies have shown that older patients with cancer undergoing chemotherapy develop chemotherapy-induced cognitive impairment, known as chemobrain, including a series of neurocognitive symptoms (forgetfulness, trouble concentrating and remembering details, difficulty with multitasking word finding, and taking longer to finish tasks), hospitalizations, and poor quality of life (QoL) [3,4]. In fact, chemobrain-related stress has been reported disproportionately among older individuals with cancer who have undergone chemotherapy [5].

With advances in cancer treatment over the decades, the survival time of older patients with cancer has been gradually extended, and the accompanying symptoms of chemobrain have gradually drawn increasing attention [5]. Recent data have shown that chemobrain-related stress could persist for a long-term period after a systemic therapy, which is particularly relevant to older patients with cancer [6]. These individuals report chemobrain symptoms of anxiety and depressive disorder, and the number of older patients with cancer will increase dramatically in the coming future. Although data on cognitive impairment onset after chemotherapy are lacking for older patients with cancer in China, clinical practitioners have paid constant attention to the health of their constituents, given their propensity for worse physical and mental health outcomes related to chemotherapy [7]. Data suggest that up to two-thirds of older patients with cancer develop chemobrain during or after chemotherapy [8]. Most of these patients experience cognitive impairments for months, but 10%-20% of these individuals experience persistent chemobrain-related stress even after many years of completing chemotherapy. In recent years, the incidence rate of cancer in senile patients has been rising in China [9]. The problem of chemotherapy-induced cognitive dysfunction is becoming increasingly common, and there are growing concerns that chemobrain could become a threat. Therefore, it is crucial to explore an intervention that can effectively prevent and treat chemotherapy-induced cognitive impairment in older patients with tumors.

Pre-existing studies [10] have shown that some neuroprotective factors such as methylphenidate and modafinil are effective for treating chemotherapy-related cognitive impairment; however, most clinical trials on interventions for chemobrain report less access to control groups and less treatment engagement. Combo acupoint stimulation therapy is a new technique based on the theory of traditional Chinese medicine and modern biological principles. With the help of invasive or noninvasive interventions, different stimuli or drug intakes would be administered at acupuncture points, meridians, or related specific body surface sites [11].

Acupuncture has been used for thousands of years in China and other Asian countries to treat various diseases, including sleep disturbance [12]. It is a nonpharmacological therapy that involves inserting needles into acupuncture points and sometimes applying minielectrical current stimulation on acupuncture points via needles or applying acupressure on the surface of points in different parts of the body, including ear and scalp [12]. Electroacupuncture (EA) is an effective family member of combo acupoint stimulation [13]. Lyu et al [14] reported that EA could be effective in alleviating various side effects caused by anticancer drugs, such as pain, vomiting, fever, fatigue, dry mouth, anxiety, depression, and insomnia. In addition, EA could promote the rehabilitation of pathological microstructures in the brain and improve the cognitive ability of patients with cognitive impairment. Clinical trials [14,15] of acupuncture for preventing and managing mild cognitive impairment in older adults show that it can improve the clinical efficacy rate, Mini-Mental State Examination Scale score, Montreal Cognitive Assessment (MoCA) test score, and clock drawing task scores, suggesting that acupuncture can be an effective approach complementary to existing therapies. Evidences [14] from acupuncture in patients after an ischemic stroke support its role in the treatment of neurological deficits through modulation of neuroplasticity. Chemobrain affects cognitive function, in particular, think and memory functions through various mechanisms, including inflammation and oxidative stress, which may lead to neurogenesis and glycogenesis reduction. This pathological process shares some similarities with brain damage after an ischemic stroke [3,16]. Therefore, it is important to investigate if EA is effective in preventing and treating chemobrain in older patients with cancer and for improving the QoL of cancer survivors.

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Emerging chemotherapy-induced cognitive impairments in older patients with cancer are likely to widen without proper early intervention tactics. In this protocol, we propose a 2-arm, prospective, randomized, assessor-blinded trial to examine the efficacy and safety of EA for chemobrain among older patients with cancer who are on or about to receive chemotherapy. The aim of this study directly contributes to the existing knowledge in this area, thereby establishing a basis for further research. Changes in the scores on MoCA [17] and the incidence of adverse events serve as the primary outcome. Scores on the Digit Span Test will be the secondary outcome for attentional function and working memory [18]. The QoL and multiple functional assessments will also be evaluated [19]. Outcomes include the MoCA, Digit Span Test, QoL, and multiple functional assessments at 2, 4, 6, and 8 weeks after randomization. Data from this efficacy trial will determine whether Chinese EA successfully improves the symptoms of chemobrain and whether these improvements could markedly reduce the various side effects caused by cytotoxic chemotherapy drugs. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA within real-world behavioral health and social service settings.

Methods

Ethics Approval

Eligible participants should provide written informed consent after reviewing consent documents with medical staff. To protect participant privacy and confidentiality, questionnaire surveys for the evaluation of cognitive function should be completed by research staff in a secure office in the inpatient ward. Only trained research staff have access to the key that can match participant data to the participant's name. This trial has been approved by the ethics committee of Nanjing First Hospital (approval KY20230310-05-KS-0I), and the collaborator of Jiangsu Health Vocational College provides ongoing oversight. This study was registered in ClinicalTrials.gov (NCT05876988) on April 13, 2023, before the first participant was recruited.

Study Design

We present a protocol for a 2-arm, prospective, randomized, assessor-blinded trial to examine the efficacy and safety of EA for chemobrain among older patients with cancer who are undergoing chemotherapy or those are going to just begin chemotherapy. This study refers to a double-blinded trial in which neither the investigator nor the participant knows the group to which the participant belongs (experimental group or control group), and the analyst usually does not know which group the data being analyzed belong to. This study is designed to eliminate subjective biases and personal preferences that may arise in the consciousness of investigators and participants. Those who report clinically significant cognitive impairment are being recruited and enrolled to participate in a trial on the effects of a novel EA intervention to address negative mood symptoms and reduce chemotherapy-induced adverse reactions. Participants are recruited via community organizations, social media, and internet outlets (eg, hospital classified ads, WeChat). Interested older patients with cancer complete a screener assessment by the medical staff of the Oncology department or a Chinese medicine doctor, and they report the levels of cognitive dysfunction they are experiencing through the Overall Anxiety Severity and Impairment Scale [20] and the Overall Depression Severity and Impairment Scale [21]. Those eligible at the screener complete an enrollment for full eligibility and receive instructions on how to accept EA therapy to complete the baseline assessment. Additionally, eligible participants will be randomly assigned to either an experimental group or a control group at 1:1 ratio. Participants then engage with the assigned intervention for 8 weeks following randomization. Participants complete follow-up assessments at baseline, 2, 4, 6, and 8 weeks after randomization, which include the MoCA, Digit Span Test, QoL, and multiple functional assessments. Additionally, participants are prompted to complete ecological momentary assessments [22] twice weekly throughout the 2-month postrandomization period. The study flow diagram is shown in Figure 1.

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Figure 1. Participant flow diagram in the clinical trial.

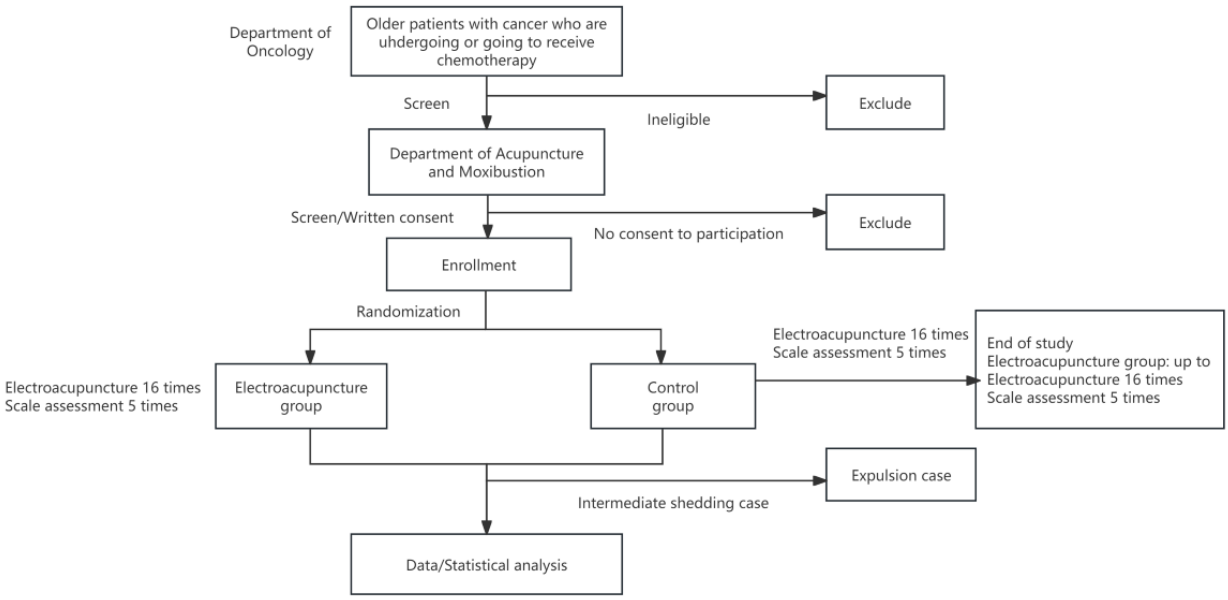

Specific Aims and Hypotheses

Chinese acupuncture is an emerging therapeutic option for chemotherapy-induced cognitive impairment in older patients with cancer, despite limited supporting evidence [23]. This study has 2 specific aims.

1. First, to evaluate the clinical therapeutic response of EA intervention for the treatment of chemobrain in older patients with cancer, a randomized controlled trial is designed to study the effects of EA on chemobrain at baseline, 2, 4, 6, and 8 weeks follow-up. We hypothesize that those assigned to EA will show greater reductions from baseline to follow-ups in MoCA Overall Anxiety Severity and Impairment Scale and Digit Span Test scores and greater reductions in cognitive impairment in daily responsibilities relative to the control group. We also hypothesize that the effectiveness of EA on QoL and multiple functional assessments will be similar across experimental or control groups.
2. Second, our aim is to elucidate the modern biomedical mechanism of EA in the treatment of chemobrain in older patients with cancer. In testing the putative mechanisms of action, we hypothesize that the intervention effects on study outcomes will be mediated by reductions in chemotherapy-induced working memory impairment and the incidence of certain digestive, neurological, and distress-related symptoms.

Participants and Recruitment

This 2-arm, prospective, randomized, assessor-blinded trial will be conducted from September 2023 to December 2025 in the Department of Oncology/Chinese Medicine, Nanjing First Hospital, China. Potentially eligible participants would be screened and recruited through clinical oncologists/Chinese medicine acupuncturists' referral from local hospitals and advertisements. Enrollment to this study began in September 2023 and, as of writing this paper, is in the recruitment phase. Enrollment, randomization, intervention delivery, and assessments are completed by trained research staff. Both study conditions receive the same set of questionnaires at each assessment (see Figure 2) or the full list and timeline of study measures. These questionnaires assess chemobrain symptoms, functional impairment, general and chemotherapy-specific affect constructs, and sociocultural factors. Interested individuals complete an initial screener to assess age, racial/ethnic identity, clinical confirmation of chemobrain, state of residence, and willingness to complete study assessments. During the enrollment, volunteer participants will be asked to sign written informed consent forms and are informed of the purpose, goals, and procedures of the study. All participants will give voluntary, written, and informed consent before entering the trial.

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Figure 2. Schedule of enrollment, interventions, and assessments. T0: baseline; T1-T3: midpoint of main treatment once every 2 weeks; T4: end of the 8-week main treatment.

	Study period					
	Enrollment	Baseline	Main treatment			End of treatment
		T0	T1	T2	T3	T4
Timepoint		0 weeks	2 weeks	4 weeks	6 weeks	8 weeks
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Allocation groups		✓				
Experiment (electroacupuncture) group		◄	—	—	—	►
Control group		◄	—	—	—	►
Assessments						
Montreal Cognitive Assessment	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy-Cognitive function	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy	✓	✓	✓	✓	✓	✓
Functional Assessment of Chronic Illness Therapy-Fatigue	✓	✓	✓	✓	✓	✓
Functional Assessment of Anorexia-Cachexia Therapy	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy-Biologic Response Modifier	✓	✓	✓	✓	✓	✓
European Organization for Research and Treatment of Cancer Quality of Life questionnaire-Core 30	✓	✓	✓	✓	✓	✓

Inclusion and Exclusion Criteria

The participants in this study are 168 older patients with cancer who are further assessed for eligibility and meet the following eligibility criteria: (1) have clinically pathological diagnosis of malignant tumor, (2) aged 60 years or older, and (3) are currently undergoing or just about to commence a comprehensive treatment of chemotherapy. The exclusion criteria are as follows: (1) undergone chemotherapy within the last 2 years; (2) metal device or pacemaker planted in the body, developed epilepsy, and experienced instability; (3) participated in a drug trial within the last 6 months; (4) alcohol or drug abuse history in the past year; and (5) those who are afraid of acupuncture.

Study Procedures

After screening, eligible participants will be enrolled and they will complete baseline assessments. Thereafter, participants will be randomly assigned to either an EA experimental group or a sham control group. EA or sham treatments will be given twice weekly for 8 weeks—a total of 16 sessions. Participants in both groups will receive routine chemotherapy provided by their oncologists, which will include the use of cytotoxic drugs. Participants will be assessed at the following timepoints (see Figure 2): baseline (T0), midpoint of main treatment (T1-T3) once every 2 weeks, and end of the 8-week main treatment (T4). Assessments include MoCA [24] + Functional Assessment of Cancer Therapy-Cognitive function (FACT-Cog) [25] for cognitive performance, FACT/Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) [26] for fatigue, European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30 (EORTC QLQ-C30) [27] for QoL, and Functional Assessment of Anorexia-Cachexia Therapy (FAACT)/FACT-Biologic Response Modifier (FACT-BRM) [28] for chemotherapy-related side effects. Assessments will be done prior to any procedures in that visit, including disease assessment and physician consultation.

Randomization and Allocation Concealment

Older patients with tumors will be screened for eligibility, and enrollment and baseline assessments should be completed thereafter. A random code of simple, complete, and nonsequential numbers could be produced in advance from a computer-generated block randomization with random block sizes. Participants will be randomly assigned to experimental or control groups in a 1:1 ratio. Random information will be sealed in sequentially numbered opaque envelopes.

Blinding

Only the acupuncturist can open the envelope after the participant's completion of baseline assessments. Participants and all other researchers will be blinded to group assignments. Participants are informed that they have a similar chance of allocation to any group and will be blinded to group assignments. A clinical assessor will be arranged to conduct assessments on a day different from the day of acupuncture treatment to avoid cross communications among the assessors,

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acupuncturists, and participants. An eye mask will be used to avoid communications among participants during EA treatment.

Interventions

Potentially eligible patients will be recruited through clinical oncologists' referral from local hospitals and advertisements. Research staff are notified once a participant completes the baseline assessment. The interventions of the experimental and control groups will be performed in the Department of Medical Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China. Registered Chinese medicine acupuncturists at the Division of Chinese Medicine will be recruited who will be responsible for delivering treatment according to STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) [29].

Acupuncture Group

Participants in the experimental group will receive EA treatment. Acupuncture intervention will be conducted for 2 sessions per week over 8 consecutive weeks. Assessments will be conducted at baseline and once biweekly thereafter. For the experimental group, acupuncture points are mainly on the head, limbs, and abdomen, with a total of 6 pairs of electrically charged needles on the head, while for the control group, acupuncture points are mainly on the head and limbs, with only a pair of electrically charged needles on the head. The acupuncture points are as follows: Baihui point, left Shencong point, right Shencong point, bilateral Shuaigu point, bilateral Touwei point, bilateral Toulin point, bilateral Taiyang point, Yintang point, Zhongwan point, Qihai point, bilateral Waiguan point, bilateral Shenmen point, bilateral Hegu point, bilateral Zusanli point, bilateral Fenglong point and bilateral Sanyinjiao point. A total of 6 pairs of electrodes from the electric stimulator (CMNS6-3; 2-5 Hz, continuous wave) will be connected to the end of the needles. The 6 fixed points are Baihui and Yintang, left Shencong and left Toulin, right Shencong and right Toulin, left Shuaigu and right Shuaigu point, left Touwei and right Touwei points, and left Taiyang and right Taiyang (see Figure 3).

Figure 3. Acupoints for electroacupuncture stimulation.

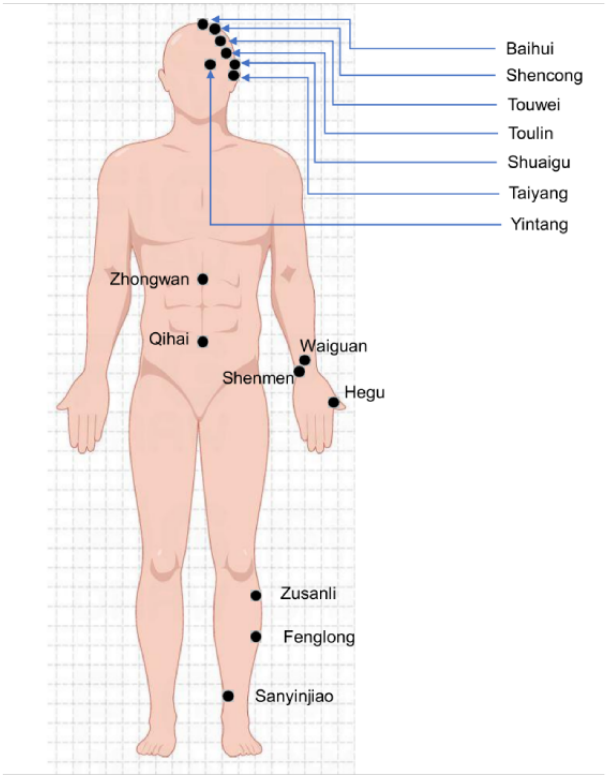

Disposable acupuncture needles (0.30 mm in diameter and 25-40 mm in length) will be inserted at a depth of 10-30 mm perpendicularly or obliquely into the acupoints. Manual manipulation will be performed for all acupoints to evoke needling sensation. Electrical stimulation will be additionally delivered on the 6 pairs of the frontal acupoints. The output peak current and voltage of the machine would be 6 V and 48 mA, respectively, with constant waves at frequencies of 2 Hz and phase duration of 100 μs for 30 minutes. Electrical stimulation will last for 30 minutes. The needles on body acupoints will also be retained for 30 minutes. Upon needle withdrawal, the points will be compressed with iodine volts swabs to prevent bleeding [30].

Control Group

The control treatment procedure is the same as that in the experimental group, except that only a pair of electric needles will be selected for the electrical stimulation on the head. After completing the 8-week acupuncture intervention, patients in the control group will be administered follow-up EA acupuncture free of charge. The same 16 sessions or a total of no more than 8 weeks of acupuncture will be performed as compensation.

Assessments

In this study, therapeutic efficiency will be assessed in terms of the following aspects: cognitive performance, fatigue, QoL, and chemotherapy-induced side effects. The primary outcome

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of this study is to verify whether EA is therapeutically useful for preventing chemobrain and alleviating the related symptoms and the safety of intervention. Cognitive performance will be assessed using MoCA + FACT-Cog. The secondary outcomes are as follows: QoL will be measured using EORTC QLQ-C30, fatigue will be assessed using the FACIT-Fatigue scale, and the manifestation of chemotherapy-induced side effects will be assessed using the Chemotherapy Symptom Rating Scale FAACT + FACT-BRM. All assessment scales will be evaluated by previously trained researchers at the following timepoints (see Figure 2): baseline (T0), midpoint of main treatment (T1-T3) once every 2 weeks, and end of the 8-week main treatment (T4) (a total of 5 timepoints). We will also keep a record of all the shedding cases. This study is a multidisciplinary clinical trial (across oncology and Chinese medicine disciplines) on the role of Chinese acupuncture as therapy for chemotherapy-induced cognitive impairment in older patients with cancer. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA in real-world behavioral health and social service settings.

Questionnaires/Instruments

MoCA Self-Reported Questionnaire

The MoCA self-reported questionnaire is the main method used for assessing cognitive function. To objectively measure the cognitive impairment patterns of the participants, MoCA, a sensitive, time-sparing tool with high diagnostic validity, will be used to measure the degree of chemobrain. We evaluate the utility of MoCA as a chemobrain screening test for older patients with cancer who are undergoing or about to receive chemotherapy. Participants will be instructed to self-report their cognitive functions through MoCA for 5 consecutive timepoints from baseline to the end of the 8-week treatment. Statistical software will be used to analyze participants' cognitive function information recorded in case report forms.

FACT-Cog Questionnaire

FACT-Cog is a subjective measure of chemobrain. The FACT-Cog is a 37-item member of the FACIT suite of questionnaires, which is made up of 4 subscales: perceived cognitive impairments (18 items), perceived cognitive abilities (7 items), impact of perceived cognitive impairment on QoL (4 items), and comments from others on cognitive function (4 items) [24]. FACT-Cog is considered a reliable and valid patient report of chemotherapy-induced cognitive symptoms. Participants are required to report their responses in FACT-Cog just the same as MoCA.

FACT Instrument

FACT is a 37-item self-reported instrument devised to assess the multidimensional health-related QoL in patients with cancer. It consists of 5 subscales, namely, physical, social/family, emotional, functional well-being, and additional concerns for cancer. Each item is scored on a 0 to 4 scale, and the sum of all 5 subscales ranges from 0 to 144. A higher score indicates a better QoL [12].

FACIT-Fatigue Self-Report Questionnaire

The FACIT-Fatigue is a valid self-reported questionnaire for assessing anemia-related fatigue in patients with cancer. This 13-item questionnaire comprises concepts related to the severity and impact of fatigue over the last 7 days, including varied fatigue-related concepts across its 13 items, allowing for a nuanced assessment.

EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 will be used as a self-reported questionnaire for interpreting group-level results in older patients with cancer. The current estimates can be used to better interpret the results of clinical trials in older patients with cancer using the EORTC QLQ-C30 questionnaire.

FAACT Self-Administered Questionnaire

The FAACT is a self-administered questionnaire developed to assess symptoms in patients with cancer with limited food intake and decreased QoL. For FAACT, a cutoff value of ≤24 has been advised to assess anorexia based on the fact that it is the half of the maximum score than can be obtained [31].

FACT-BRM Screening Tool

The FACT-BRM is a brief screening tool designed to assess the QoL in patients treated with BRMs. The FACT-BRM scale will be useful for measuring QoL in older patients with cancer who are receiving treatment with BRMs.

Safety Assessment

Except for the sensation of soreness, numbness, swelling, and heaviness, the EA intervention will not usually cause significant discomfort or serious adverse effects, but some participants may experience pain or subcutaneous ecchymosis. Patients who have acupuncture on an empty stomach are more likely to experience dizziness. Subcutaneous ecchymosis will disappear spontaneously if the participant's blood coagulation is normal. Patients will be reminded to avoid acupuncture on an empty stomach. The condition of each participant will be closely monitored, and if other symptoms or adverse effects occur, the investigator will ensure that the participant is receiving the appropriate treatment and is suitable to continue receiving EA. All participants in the clinical trial will be asked to evaluate the safety of the intervention, and any adverse events experienced during acupuncture treatment will be reported at each visit. The severity of adverse events will be assessed according to the Common Terminology Standard for Adverse Events v5.0 criteria [32], which are useful for determining the causal relationship between acupuncture and adverse reactions. Serious adverse events will be immediately reported to the project investigator and ethics committee. The investigator will also discuss the situation with the participant to plan any temporary discontinuation or withdrawal. The costs will be reimbursed by the investigator's organization.

Sample Size Estimation

A total of 168 older patients with cancer will be recruited, of which 84 will be in the experimental group (EA) and 84 will be in the control group. Sample size calculation:

$$n = [p1 (1 – p1) + p2 (1 – p2)]/(p1 – p2)] \times Cp.power$$

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Cp refers to the process capability index. In the 2-sided test, Cp.power = 10.5 when $P<.05$ is met. n is the number of patients to be recruited in each group, p1 and p2 represent the incidence in each group, and a mean difference with 95% level of significance (α) and 80% power ($1 - \beta$) is set. In older patients with cancer, the incidence of chemobrain after chemotherapy is 30%, and the reduction of chemobrain could be 10%-20% with acupuncture intervention. The sample size for each group is 84 participants, considering a 20% dropout. Therefore, the overall target sample size of 168 will be included.

Statistical Analyses

Cognitive impairment is defined as those with SD>1.5 in the mean scores of MoCA and the QLQ-C30 at baseline for all participants at different timepoints. A time-series test in the Kaplan-Meier survival analysis will be used to compare the incidence of cognitive deficits accumulated after 8 weeks of acupuncture intervention between the 2 groups. Linear mixed-effects modeling will be used to compare participants' cognitive impairment, fatigue, and depression at baseline, during, and after acupuncture intervention, where only those who have completed at least one assessment at baseline and during treatment will be compared. This model will use time and group as categorical fixed factors and random intercepts and use random intercepts in conjunction with a measurement covariance matrix. Participants' age, chemotherapeutic drug dosage, fatigue at baseline, depression, and additional treatments will be considered as covariates in the statistical analyses. A 2-sided *t* test will be used to compare the covariates at each timepoint between the 2 groups. The chi-square test will be used for qualitative information and the *t* test will be used for continuous information at baseline. Statistical significance will be considered at $P<.05$. The study data used will be statistically analyzed using SPSS software (IBM Corp) under the supervision of a statistician. To ensure the privacy of the patients, all relevant study data and personal data will be kept in a locked file cabinet. Electronic data will be stored on an encrypted computer and will not be stored on any external storage device. Each participant will be assigned his or her own ID in the study record, which will be used in lieu of his or her name and personal identifying information. Clinical data from the study will be kept in a separate file from the participant's personal data. The principal investigator will be responsible for all the clinical trial data. During and after the clinical trial, the principal investigator, researchers, and the ethical review committee have the right to view the study data. Participants will have the right to access their personal data and the results of the study. All study data will be stored for a minimum of 3 years after the completion of the trial, after which they will be destroyed in accordance with the rules of the ethics review committee.

Results

This clinical trial was funded by the Jiangsu Health Vocational College and Nanjing First Hospital in January 2023. The ethics review committee approval was finalized in April 2023, and data collection began on September 1, 2023. Investigators have since been engaged in activities associated with study enrollment and data collection, including recruitment, screening, consenting, and enrolling participants; administering EA intervention; timepoint assessing; and monitoring adverse events and resolving problems early. As of October 21, 2023, 11 participants have been recruited into the clinical trial. A total of 168 older patients with cancer who are undergoing or are just about to commence chemotherapy will be enrolled in this clinical trial, and they will be randomly assigned into either the experimental group or the control group of 84 participants each. A total of 16 EA treatments (twice per week) will be administered to each participant for 8 weeks, and the participants will be assessed for cognitive performance, fatigue, and QoL. Concurrently, they will receive conventional chemotherapy. Improvement or even relief of chemobrain symptoms in older patients with cancer undergoing chemotherapy will be expected if the results of the EA intervention are satisfactory.

Discussion

Patients with cancer may have concerns of psychiatric and digestive symptoms while undergoing or just after having recently undergone chemotherapy [3]. The most common clinical manifestations are fatigue, nausea, vomiting, dry mouth, anxiety, depression, and insomnia. More seriously, cognitive impairments with a range of neurocognitive symptoms occur frequently, including visual and verbal memory impairment, forgetfulness, difficulty concentrating, learning difficulties, and organizational and coordination dysfunction [3,4]. Since the 1980s, researchers have been studying chemotherapy-induced cognitive impairment and have given several definitions to this condition, such as postchemotherapy cognitive impairment and chemotherapy-induced cognitive dysfunction. Recently, this condition was termed as chemobrain [3-5].

Chemobrain is a frequent side effect experienced by an increasing number of older patients with cancer, and it has significantly impacted their QoL [4]. Chemobrain can be described as cognitive symptoms reported by patients with cancer in self-reported questionnaires or as cognitive changes evaluated by formal neuropsychological tests [5]. Older patients with cancer will experience cognitive impairment due to chemoradiotherapy, which will lead to a series of neurocognitive symptoms called chemobrain. Older populations have been disproportionately affected by chemobrain and have heightened negative mental health outcomes after cytotoxic chemical drug therapy [3,5,7].

According to available literature [3,14], more than 75% of patients with cancer experience cognitive impairment while undergoing chemotherapy or just after completing chemotherapy, with 15%-30% of these patients experiencing persistent symptoms for up to decades. The prevalence of postchemotherapy cognitive impairment is as high as 50%-75% among older cancer survivors [33]. In some circumstances, the cognitive impairment can be lifelong, affecting the patient's mood, relationships, QoL, career, social activity, and family life. Considering the increasing incidence of cancer, chemobrain is quite complicated, increasingly important, and has far-reaching consequences. As the incidence of cancer survivors rises, the adverse effects of chemobrain will become more

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frequent, thus necessitating the need to effectively prevent and treat chemobrain.

At present, there is no responsive therapy for chemobrain. The current clinical medications are not effective for chemobrain prevention and therapy. Study and research literatures [14,15] suggest that Chinese acupuncture might be effective for relieving various discomforts caused by anticancer drugs, such as pain, vomiting, fever, fatigue, dry mouth, anxiety, depression, and sleep disorders. Several studies [11,13-16,30] have shown the efficacy of EA intervention in various neurological diseases. Compared with acupuncture, EA has reported to produce a higher intensity of stimulation on acupoints and is progressively being widely used for its adjustable strength, frequency, and easy quantification in clinical practice [14]. In addition, EA can promote the rehabilitation of pathological microstructures in the brain and improve the cognitive function of patients with cognitive impairment [16].

Our study aims to explore the feasibility, efficacy, and safety of using EA by involving multiple disciplines (oncology and Chinese Medicine) to treat chemobrain in older patients with cancer. Acupuncture itself has been demonstrated as a safe and effective treatment, and EA is a widely accepted and cost-effective alternative therapy option with low adverse effects for older patients with cancer. The findings of this study will provide useful information on determining a suitable therapy for chemobrain in older patients with cancer. EA may be ready for implementation and dissemination in real-world cognitive function settings consistent with the objectives outlined in this clinical trial's strategic plan. Overall, this proposal has the potential to decrease neurocognitive symptoms among older patients with cancer—populations determined to be most at risk of exacerbated, long-lasting negative health sequelae. EA, if proven to be effective, can be implemented into routine settings to benefit older patients with cancer experiencing chemobrain. We believe that data from this efficacy trial will determine whether Chinese EA successfully alleviates the symptoms of chemobrain and whether these improvements could markedly reduce the various side effects due to cytotoxic chemical drugs.

In conclusion, the goal of this clinical trial is to target and reduce emerging and likely exacerbated cognitive impairments caused by chemotherapy among older patients with cancer. We aim to evaluate this novel Chinese medicine mode of EA in older patients with cancer by developing a therapeutic responsive treatment for chemobrain. By addressing neurocognitive symptoms through an EA intervention that targets underlying pathophysiological and psychological factors, we hope that this EA intervention will reduce the symptoms of chemobrain in older patients with cancer. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA within real-world behavioral health and social service settings.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following the completion of the trial and publication of the main outcomes paper. Deidentified data also will be made available via the Jiangsu Health Vocational College and Nanjing First Hospital.

Authors' Contributions

SZ, JZ, and HW contributed to data curation, formal analysis, investigation, writing the original draft, review, and editing. CT, MH, and WL contributed to conceptualization, data curation, formal analysis, investigation, and methodology. ZX contributed to data curation, formal analysis, writing the review, and editing. BX, JZ, and GW contributed to the electroacupuncture intervention, methodology, and investigation. PL contributed to project administration, writing the review, editing, and supervision. YG contributed to funding acquisition, project administration, writing the review, editing, and supervision. GL contributed to conceptualization, project administration, resources, supervision, writing the original draft, review, and editing. Correspondence may also be sent to Guangmei Lyu 939146961@qq.com and Ping Li Pingli1965@163.com.

Conflicts of Interest

None declared.

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Abbreviations

EA: electroacupuncture
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FAACT: Functional Assessment of Anorexia-Cachexia Therapy
FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue
FACT: Functional Assessment of Cancer Therapy
FACT-BRM: Functional Assessment of Cancer Therapy-Biologic Response Modifier
FACT-Cog: Functional Assessment of Cancer Therapy-Cognitive function
MoCA: Montreal Cognitive Assessment
QoL: quality of life
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture

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Protocol

Mobile Mindfulness Meditation for Cancer-Related Anxiety and Neuropathy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Anxiety- and cancer-related neuropathy are two persistent effects related to treatment for cancer. Mindfulness meditation has been used with substantial impact as a nonpharmacologic intervention to mitigate side and late effects of treatment. Mobile apps are ubiquitous for most of the general population, yet have a particular relevance for cancer survivors, given that physical and geographic limitations can be present.

Objective: This study aims to describe an ongoing trial of the Mindfulness Coach mobile app for cancer survivors.

Methods: In this randomized waitlist controlled trial, cancer survivors experiencing anxiety- or cancer-related neuropathy (200 for neuropathy and 200 for anxiety) and who had finished primary cancer treatment were invited to participate. Data were collected at 3 time points regardless of randomization condition: baseline, 8 weeks, and 16 weeks. Both face-to-face and web-based recruitment strategies were used. The trial was opened for 2 separate primary outcomes (anxiety- or cancer-related neuropathy). The goal was not to compare these groups but to compare treatment and waitlist groups for each condition. In addition to evaluating the impact of mobile mindfulness on reported anxiety- or cancer-related neuropathy, other pain, fatigue, trauma, sleep, and satisfaction with the Mindfulness Coach app will also be assessed.

Results: Outcomes of the study are expected in early 2024.

Conclusions: Mindfulness meditation has become widely practiced, and the use of mobile technology has become ubiquitous. Finding ways to deliver mindfulness meditation to people who have been treated for cancer allows for the intervention to be accessible to a larger number of survivors. The results of this intervention could have implications for further understanding the impact of mindfulness meditation on 2 persistent side and late effects of treatment of cancer, namely anxiety- and cancer-related neuropathy.

Trial Registration: ClinicalTrials.gov NCT03581357; https://ClinicalTrials.gov/study/NCT03581357

International Registered Report Identifier (IRRID): DERR1-10.2196/47745

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KEYWORDS

cancer; cancer survivorship; mindfulness meditation; mHealth; well-being; quality of life; mobile health; coaching; coach; mindfulness; meditation; survivor; survivorship; oncology; mental health; anxiety; neuropathy; survivors; RCT; randomized; clinical trial; clinical trials

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Introduction

Background

The latest report from the American Cancer Society estimates that there are 16.9 million cancer survivors in the United States [1]. A diagnosis of cancer or recurrence of cancer can cause psychological distress, including symptoms of anxiety and depression [2]. For patients receiving treatment for cancer, 10.3% meet the clinical criteria for an anxiety disorder [3], compared with 7% of those in the general population [4]. The prevalence of anxiety disorders is reported to be even higher for those who have been living with cancer for more than 2 years, with 17.9% of survivors meeting diagnostic criteria for anxiety [5]. As cancer treatments have become more effective than in previous decades, there are more cancer survivors living longer with cancer [6], yet also living with side and late effects of treatment.

Anxiety can manifest in both physical and psychological symptoms that negatively impact quality of life and are associated with a substantially increased risk of cancer incidence and cancer-specific mortality [7]. Psychological distress can affect a number of cancer outcomes, including quality of life, adherence to treatment, health behaviors, and potentially disease progression and survival, as well as increased use of health care resources [2].

Neuropathy is another common symptom of either cancer treatment or, less frequently, cancer itself and can be acute or chronic in nature [6]. There are a wide range of ways in which patients describe this experience, although peripheral neuropathy is often described as the sensation of shooting or stabbing pain and tingling or loss of feeling in the affected areas. This can impact many activities, such as walking, balance, and mood [6]. In patients receiving neurotoxic chemotherapy, such as platinum drugs, taxanes, vinca alkaloids, proteasome inhibitors, and immunomodulatory drugs, approximately 30%-40% of patients will develop chemotherapy-induced peripheral neuropathy (CIPN) [8]. CIPN is a common cause of pain and decreased quality of life for patients with cancer undergoing treatment as well as cancer survivors [9]. In approximately 50% of people who experience CIPN, this condition will become chronic [10].

Mindfulness and Mindfulness Meditation

Historically conceptualized in Buddhist spiritual practice with the purpose of cultivating compassion and alleviating suffering, mindfulness meditation has been practiced for thousands of years [11,12]. Mindfulness can be described as bringing nonjudgmental attention or awareness to one's moment-to-moment experience [12]. Mindfulness meditation is the setting aside of time to specifically engage in what is often a seated meditation practice where participants are instructed to close their eyes and are guided through a breathing and focused attention process [13].

The practice of mindfulness with the goal of improving well-being has been described as a universal human capacity that does not involve a particular cultural or religious belief system [11,12]. In recent decades, mindfulness has gained popularity in the United States and has been found to have numerous psychological and physical benefits, with a growing body of research on clinical applications of mindfulness to treat various conditions [2,11,14-20]. Mindfulness has been studied as a therapy to reduce symptoms of depression and anxiety [2], improve outcomes for chronic pain [14], reduce stress and improve attention [15], improve brain function and connectivity [16], and improve immune function [17].

The practice of mindfulness has been shown to improve quality of life and be related to more positive mental health in cancer survivors [18]. Recent studies indicate that mindfulness-based interventions have a positive impact on depression, anxiety, and quality of life in patients with ovarian cancer [2], men living with cancer [19], and patients with metastatic non–small cell lung cancer and their caregivers [20], to name just a few.

Web-Based Behavioral Therapy for Anxiety- and Cancer-Related Neuropathy

While mindfulness is gaining a larger evidence base for applications in the clinical setting, lack of trained personnel, time constraints, reimbursement issues, and patient and provider availability are barriers to delivery and participation in a traditional, face-to-face mindfulness course [21]. Researchers in a recent face-to-face mindfulness-based stress reduction (MBSR) intervention for young adult cancer survivors identified barriers to participation reported by eligible patients who declined to participate in the intervention [22]. Out of the 446 eligible people who declined to participate, the majority reported distance to the intervention site as the main factor (41.5%), followed by time constraints (21.7%). A subset of individuals who declined were asked if they would participate in the course if it were offered in a different location or format. Of those asked, 73.8% stated that they would enroll in an MBSR course offered closer to their home, and 70.8% stated that they would enroll in a online MBSR course. Of the individuals who stated interest in a online MBSR course, 70.9% stated that they would enroll in a self-directed course delivered through educational modules [22]. These barriers to face-to-face mindfulness interventions limit access to care and therefore make face-to-face interventions less likely to be a realistic treatment model [21], but online interventions for mindfulness provide a potential avenue to overcome these barriers and increase accessibility to effective mindfulness interventions.

Advances in technology have allowed for the delivery of effective interventions in the patient's home through a mobile app [23]. When used to effectively disseminate evidence-based interventions, apps have the potential to increase access to evidence-based health care and the use of evidence-based practices by the general population [21,23]. Previous studies have shown that mindfulness-based interventions via the web involving guided meditation audios are feasible and acceptable for cancer survivors [24], who may be too ill or lack the resources to travel to a face-to-face mindfulness intervention. A recent study using the Calm mobile app for mindfulness meditation found that the use of the app for 10 minutes daily for 4 weeks was substantially effective in reducing symptoms of depression and anxiety in patients with myeloproliferative

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neoplasm but did not substantially impact sleep disturbance [25].

The current American Society of Clinical Oncology clinical practice guideline does not recommend any pharmacologic agents in preventing CIPN, and there is limited evidence for the treatment of existing CIPN with pharmacologic agents, with a moderate recommendation for the use of duloxetine [26]. Previous studies suggest that online interventions may have the potential to improve conditions involving chronic pain. A study involving an online, self-guided cognitive- and behaviorally-based pain management intervention for cancer survivors experiencing CIPN had substantially greater improvements in "worst pain" compared with individuals receiving usual care [27].

Mindfulness Coach, an iOS- and Android-based mobile app, is designed to deliver a mobile mindfulness training course designed by researchers from the US Department of Veterans Affairs [21,28]. The senior author of this paper, ER, was part of the team that developed the most recent version of the app. Initially developed among other mobile apps in collaboration with the US Department of Defense [28], Mindfulness Coach is freely available to the general public for both iOS and Android operating systems. A recent study exploring the effects of the app among the general population found that use of the Mindfulness Coach app was feasible, and increased use was strongly correlated with an increase in scores measuring mindfulness characteristics including observing, describing, acting with awareness, nonreactivity to inner experience, and nonjudging of inner experience, as measured by the Five-Facet Mindfulness Questionnaire Short Form (FFMQ-SF) [21,29]. Although mobile health is increasingly being used in research and clinical settings, a recent systematic review and meta-analysis concluded that there is still inconclusive evidence due to small nonsubstantial effects of interventions, as well as concerns regarding study quality [30].

Given the persistent effects of diagnosis and treatment and the limitations of in-person offerings in most places, the Mobile Mindfulness Study was conducted to test the impact on anxiety- and cancer-related neuropathy after 8 weeks of use of the Mindfulness Coach mobile app. The study contains the following secondary aims: evaluate the impact of mobile mindfulness on general pain, fatigue, trauma, and sleep, in addition to evaluating the satisfaction with the Mindfulness Coach mobile app. The goal of this paper is to describe the study design.

Methods

Study Design

The study is being conducted with a randomized waitlist control design, such that participants were randomized through Qualtrics to either begin the intervention immediately or after 8 weeks. In addition, participants were invited to participate with the goal of impacting anxiety- or cancer-related neuropathy as a primary outcome (additional discussion on this below). The goal was to have 200 people complete the 8-week survey measures in each group. Funding was originally garnered to examine anxiety as a primary outcome, with additional seed funding received through the University of Hawai'i Cancer Center to test the same design for cancer-related neuropathy. These groups will not be compared with each other, rather, each treatment group (anxiety- and cancer-related neuropathy, respectively) will be compared with each waitlist control group (anxiety- and cancer-related neuropathy).

Procedure

Recruitment

Recruitment closed for the study in July 2023. The University of Hawai'i (UH) Cancer Center is recognized by the National Cancer Institute as one of their designated cancer centers. The Hawai'i Cancer Consortium, to which all major medical centers on Oahu belong, is led by the UH Cancer Center. Recruitment efforts took place in oncology clinics, via the web, and through organized community events [31]. These included local medical centers and clinical offices, public events (eg, senior fair), and cancer organizations, such as the American Cancer Society and Stupid Cancer, via social media and newsletter unpaid advertisements.

Participants

Cancer survivors experiencing anxiety- or cancer-related neuropathy who had finished primary treatment for cancer were invited to participate in the study. They were first screened and then consented via Qualtrics, where all data were collected, as well. Inclusion criteria were the same for both groups, aside from the different scales used to measure levels of anxiety or neuropathy. Inclusion criteria for both groups include a previous diagnosis of cancer, other than nonmelanoma skin cancer; completion of primary treatment for cancer; not currently practicing meditation for more than 1 hour per week; age older than 21 years; comfortable reading and writing in English; routine access to the internet; and own a smartphone or tablet. There are no exclusion criteria.

For the anxiety group, participants needed to be experiencing cancer-related anxiety, per self-report, as indicated by a score of 22 or higher on the PROMIS (Patient Reported Outcomes Measurement Information System) anxiety short form measure [32]. For the neuropathy group, participants needed to be experiencing CIPN, per self-report, as indicated by a score of 22 points or higher on the Functional Assessment of Cancer Therapy-Cognitive subscale (FACT-GOG-Ntx) CIPN items [33]. The study was powered to examine differences between groups with 200 people in each group (200 total for anxiety, 200 total for neuropathy).

Baseline and Follow-Up Assessments

Figure 1 summarizes the overall timeline for baseline and follow-up data collection. For both the anxiety and neuropathy groups, data on demographics and medical history were collected at baseline. Baseline data collected included cancer status and treatment, past medical conditions, gender, ethnicity, and previous experience with mindfulness. For both the anxiety and neuropathy groups, all 3 surveys include questions about the quality of life (physical well-being, social or family well-being, emotional well-being, and functional well-being),

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anxiety (symptoms of anxiety and whether help was needed due to anxiety symptoms), fatigue (severity of fatigue and the impact of fatigue on daily functioning), pain (sensory, affective or emotional impact, and cognitive evaluation of pain), and mood (anxiety). The anxiety group received additional assessment questions: depression, mindfulness, and posttraumatic stress disorder (PTSD). The neuropathy group received questions about neuropathy: severity and impact of CIPN. Specific measures are listed below for each group.

Figure 1. Timeline for baseline and follow-up data collection.

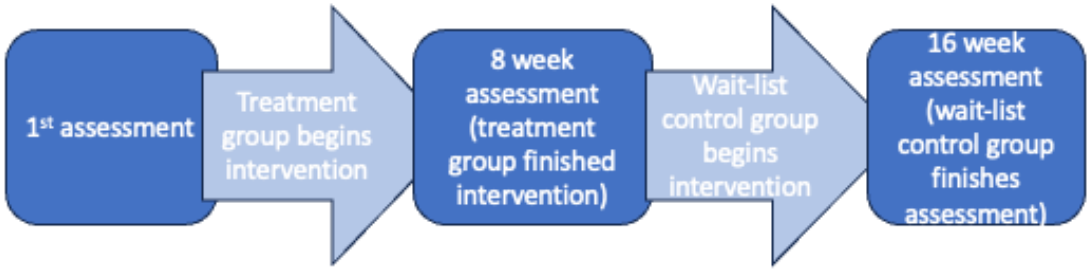

Anxiety Group

Potential participants were screened with the PROMIS anxiety short form measure, an 8-item measure assessing anxiety on a Likert-type scale, with options ranging from “never” to “always” [32]. Pain is measured with the Pain Intensity Enjoyment of Life General Activity Scale, a 3-item measure assessing pain intensity, interference with general activity, and interference with enjoyment of life, with response options ranging from a 0-10 scale, with 0 being “no pain” or “does not interfere” and 10 being “pain as bad as you can imagine” or “completely interferes” [34]. Sleep-related impairment is measured using the PROMIS sleep-related impairment short form, an 8-item measure assessing sleep disturbance and sleep-related impairment [35]. Fatigue is measured with the brief fatigue inventory, a 9-item measure to rate fatigue on a 0-10 scale, with 0 being “no fatigue” or “does not interfere” and 10 being “as bad as you can imagine” or “completely interferes” [36]. Anxiety is measured with the General Anxiety Disorder 7-item measure of anxiety on a 5-point Likert-type scale [37]. Depression is measured with the Patient Health Questionnaire-9, a 9-item measure using 4 response options to assess depressive symptoms and behaviors [38]. PTSD is measured using the PTSD Checklist for DSM-5, a 20-item measure that assesses the 20 *Diagnostic and Statistical Manual of Mental Disorder* symptoms of PTSD [39]. Mindfulness is measured with the FFMQ, a 39-item measure of the 5 facets of mindfulness (observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience), with answer options on a 1-5 scale ranging from “never or rarely true” to “very often or always true” [29]. For the follow-up assessments, the demographic questions are removed. A question regarding how much they have been practicing mindfulness (all groups), and a question about satisfaction with the intervention (for the intervention groups) are added.

Neuropathy Group

Potential participants were screened with the 11-item CIPN measure included in the FACT-GOG-Ntx [33]. The Functional Assessment of Cancer Therapy (FACT) scale is a well-validated quality of life measure with 27 items measuring physical, social or family, emotional, and functional well-being, with the FACT-GOC-Ntx scale including 11 additional items to measure the severity and impact of CIPN [33]. The 11-item FACT-GOG-Ntx data serves as both a screening tool and a baseline measure of CIPN. The rest of the FACT items (27 questions) are included in the baseline questionnaire, with the total measure being included at the 8- and 16-week assessment time points. At each assessment time point, participants are asked about any additional support services (such as support groups or clinical trials that they have been enrolled in, including anything they have done to treat CIPN. In order to assess anxiety, the 8-item PROMIS anxiety short form measure is used [32]. Fatigue is measured using the brief fatigue inventory [36]. The short-form McGill Pain Questionnaire (MPQ) is used as a brief measure of pain [40]. The original MPQ is a self-report questionnaire, consisting of 3 major classes of word descriptors of pain: sensory, affective or emotional impact, and cognitive evaluation of pain. The short-form MPQ was developed to provide an instrument that could be completed in less time than the MPQ but would still reflect both the sensory and affective dimensions of pain and has been shown to have high correlations with the original MPQ [40]. For the follow-up assessments, the demographic questions are removed. For the follow-up assessments, a question regarding how much they have been practicing mindfulness (all groups), and a question about satisfaction with the intervention (for the intervention groups) are added.

Intervention

Mindfulness Coach provides simple written instructions and a brief tutorial that introduces the major features, including a training plan, practice exercises, learning topics, and tracking via the app. Mindfulness exercises are delivered via brief, guided audio mindfulness exercises. This information has been arranged in such an order that it is helpful to have learned the material prior to any given session, although not necessary. The core meditation centers around the seated mindfulness practice, and as the sessions go on, users are asked to sit for longer periods of time, building physical and mental capabilities for meditation. Through this process, participants are instructed to bring nonjudgmental awareness to what they are experiencing in a basic sensorial way (eg, what they are feeling on their skin, hearing in the environment, and experiencing inside their body in regard to physical or emotional sensations or thoughts), with a primary aspect of this involving paying attention to and

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deepening one's breathing. The app delivers 14 sessions (levels) that each include a prerecorded guided audio meditation exercise. The app also provides a mindfulness self-assessment tool through the FFMQ-SF [29], which users are reminded, but not required, to complete at levels 1, 7, and 14. Assessment feedback "quick tips" are provided based on the results of the FFMQ-SF.

The intervention includes 8 weeks of Mindfulness Coach. (see Figure 2 for examples of features included in Mindfulness Coach). This practice is encouraged daily through the app and participants are asked to build the amount of time they are spending daily. There are many other audio recordings that are placed throughout the sessions, including meditations around scanning the body for sensations, awareness, and processing of difficult emotions, eating mindfully, and loving kindness. Participants are asked to use Mindfulness Coach for 8 weeks, either immediately (treatment group) or 8 weeks after the baseline assessment (waitlist control group).

Figure 2. Screenshots of the Mindfulness Coach mobile app.

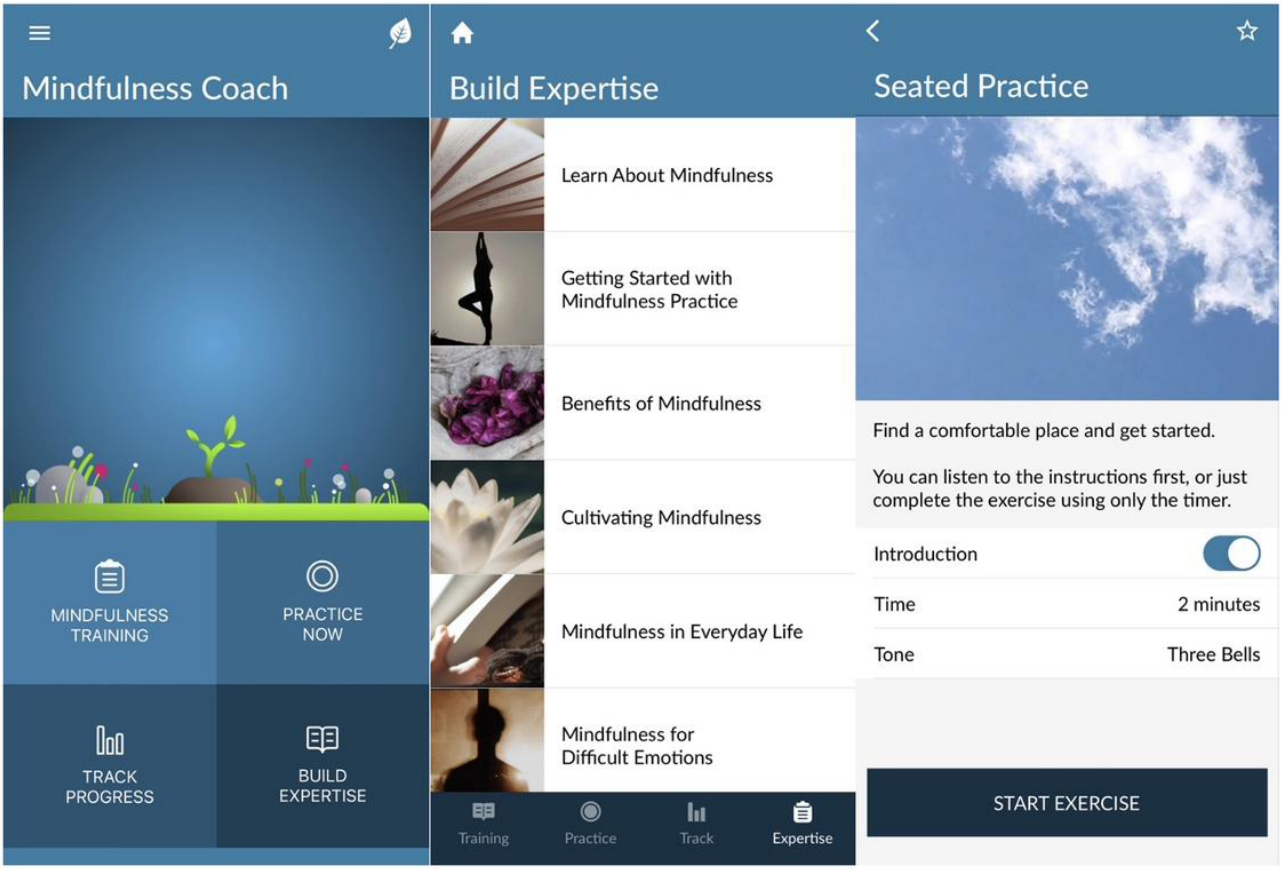

Ethical Considerations

The study was approved by the Western Internal Review Board (20131065). Informed consent was obtained from all participants included in the study. Study data were collected in Qualtrics and only relevant study personnel have access to the data. Participants receive a US $20 gift card after completing each of the 3 surveys, with a total incentive of US $60 for completing all 3 surveys. Reminder emails are sent to participants by a member of the study team.

Results

Overview

We will conduct the primary evaluation of the intervention, comparing changes in multiple outcomes between the treatment and waitlist control groups. Participants were randomized using a simple, open-label (nonblinded) randomization procedure. The intervention was individually guided and conducted electronically. We will follow an intent-to-treat approach, in which individuals are analyzed based on their randomization groups, regardless of adherence. Adherence effects will be examined in a subsequent analysis.

To account for repeated measures, we will run a mixed (both between- and within-subjects variables) linear or logistic model for each outcome. The independent variables are the randomization group (treatment vs waitlist control), time (baseline, 8 weeks, or 16 weeks), and the group by time interaction. The interaction term tests the intervention effect. For all analyses, the assumptions of the models will be checked and remedial measures (eg, transformations and nonparametric tests) will be taken as needed. Logistic models will assess dichotomous outcomes and linear models will assess continuous outcomes. Potential confounders (adherence, age, sex, and race or ethnicity) will be included. Where possible we will run the analyses within subgroups defined by these covariates, providing information on whether the intervention was more effective in certain groups (moderator effects). If there is evidence of nonrandom missing data, such as by differential dropout between groups, we will apply multiple imputation procedures. SAS

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(version 9.4; SAS Institute Inc) will be used to perform all analyses.

Data collection began in 2019 and was completed in 2023. We had very differential rates of recruitment for the differing arms with reaching near the target for the anxiety arm yet not for the cancer related neuropathy arm. This, along with other outcomes of the study will be reported in a separate manuscript.

Power

Assuming a Bonferroni corrected (for 10 outcome measures) 2-tailed type I error rate (α) equal to .005 (0.05/10), 80% power, and 200 participants per group (400 total), a standardized difference (Cohen *d* effect size) of 0.37 will be detectable. Cohen *d* is the standardized difference and can be converted to the original units by multiplying the SD of the original variable.

Discussion

We hope that this study will result in findings that are useful to improving the well-being of cancer survivors experiencing anxiety- and cancer-related neuropathy. If the study shows improvement in symptoms of anxiety or neuropathy in cancer survivors, it will allow for greater accessibility to mindfulness meditation via Mindfulness Coach, which is free, publicly available, and easily accessible through a mobile app. This will allow patients with cancer to access guided mindfulness meditation exercises in the comfort of their own homes and on their own time. This can be helpful for patients who may be too ill, lack resources, or live in a rural area where accessing a face-to-face mindfulness meditation intervention would be difficult or impossible. Results of the study may also be useful for clinicians working alongside patients with cancer or survivors searching for evidence-based, nonpharmacologic interventions to improve anxiety or neuropathy, with mindfulness meditation used alone or along with pharmacologic interventions.

Nonpharmacologic interventions, including exercise, yoga, and mindfulness meditation, have been studied for the treatment of psychological disorders, including anxiety, as a monotherapy or adjunctive therapy [41]. Current evidence supports the use of mindfulness meditation as an adjunctive therapy for people with an anxiety disorder, as there is limited evidence for mindfulness being used as a monotherapy for anxiety [41]. The general health benefits and low risk for harm justify the use of mindfulness as adjunctive therapy for patients with anxiety disorders and other mental health conditions such as depression [41]. At the current time, pharmacologic interventions for neuropathy are not highly effective and are not well tolerated by many patients due to various side effects [42,43]. First-line drugs used to treat neuropathy include antidepressants and anticonvulsants acting at voltage-gated calcium channels, which can have side effects including risk for cardiotoxicity, orthostatic hypotension, dry mouth, nausea, and confusion, among others [43]. In a randomized controlled trial involving 402 patients with neuropathy, 4 drugs commonly used for neuropathy of different drug classes (pregabalin, duloxetine, nortriptyline, and mexiletine) were tested for tolerance and treatment of neuropathic pain. The results of the study found that none of the drugs tested was clearly superior in performance or highly effective for treating neuropathic pain [42]. If results from this study show potential for mindfulness to be used as an alternative intervention to treat neuropathy, a larger number of people, including cancer survivors affected by CIPN, can access effective treatment without the side effects associated with medications commonly used to treat neuropathy.

Mobile apps have large dissemination potential and identifying apps that are found to be related to outcomes of interest is important given the ubiquitous nature of apps. Without identifying apps that are effective, apps that are available yet not effective can easily be reached. Findings from the currently described study will be published as soon as available.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available because it is ongoing. Findings from the currently described study will be published as soon as available.

Authors' Contributions

EB created the design for the study and wrote the proposal to receive funding for the project. ASO and EB conducted the literature review and wrote the main manuscript text. MU edited the manuscript. IP has provided statistical guidance and run power calculations and any relevant statistics for these studies. All authors are team members involved in the research study and reviewed the manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

CIPN: chemotherapy-induced peripheral neuropathy
FACT: Functional Assessment of Cancer Therapy
FACT-GOG-Ntx: Functional Assessment of Cancer Therapy-Cognitive subscale
FFMQ-SF: Five-Facet Mindfulness Questionnaire Short Form
MBSR: mindfulness-based stress reduction
MPQ: McGill Pain Questionnaire
PROMIS: Patient Reported Outcomes Measurement Information System
PTSD: posttraumatic stress disorder
UH: University of Hawai'i

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Protocol

Supporting Life Adjustment in Patients With Lung Cancer Through a Comprehensive Care Program: Protocol for a Controlled Before-and-After Trial

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Abstract

Background: Lung cancer diagnosis affects an individual's quality of life as well as physical and emotional functioning. Information on survivorship care tends to be introduced at the end of treatment, but early intervention may affect posttreatment adjustment. However, to the best of our knowledge, no study has explored the effect of early information intervention on the return to work, family, and societal roles of lung cancer survivors.

Objective: We report the study protocol of a comprehensive care prehabilitation intervention designed to facilitate lung cancer survivors' psychological adjustment after treatment.

Methods: A comprehensive care program was developed based on a literature review and a qualitative study of patients with lung cancer and health professionals. The Lung Cancer Comprehensive Care Program consists of educational videos and follow-up visits by a family medicine physician. To prevent contamination, the control group received routine education, whereas the intervention group received routine care and intervention. Both groups completed questionnaires before surgery (T0) and at 1-month (T1), 6-month (T2), and 1-year (T3) follow-up visits after surgery. The primary outcome was survivors' psychological adjustment to cancer 6 months after pulmonary resection.

Results: The historical control group (n=441) was recruited from September 8, 2021, to April 20, 2022, and the intervention group (n=350) was recruited from April 22, 2022, to October 17, 2022. All statistical analyses will be performed upon completion of the study.

Conclusions: This study examined the effectiveness of an intervention that provided general and tailored informational support to lung cancer survivors, ranging from before to the end of treatment.

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KEYWORDS

comprehensive care; early intervention; adjustment to cancer; return to work; lung cancer; unmet needs; lung; lungs; pulmonary; respiratory; cancer; oncology; prehabilitation; survivor; survivors; survivorship; education; educational

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide and is prevalent in Korea [1,2]. However, advancements in screening and treatment have notably improved lung cancer outcomes. For example, the 5-year conditional recurrence-free survival rate of patients with surgically resected non–small cell lung cancer (NSCLC) in Korea increased from 51.5% to 68.5% in those diagnosed in the 1990s and the 2010s, respectively [3]. Consequently, the growing number of lung cancer survivors underscores the urgent need to address posttreatment needs.

Surviving lung cancer can substantially impact the quality of life and emotional health [4-6]. Many survivors adjust over time; however, persistent fear and the expectation of a rapid return to normal posttreatment life are common [7,8]. While initial postdiagnosis support is robust, survivors often encounter a new spectrum of concerns as they transition to life after cancer, including managing lingering symptoms and comorbidities that can affect overall well-being [8-10]. The commonly reported symptoms among lung cancer survivors include fatigue, pain, dyspnea, and impaired pulmonary function [11-13]. They also experience psychological distress and a fear of cancer recurrence [14,15]. Studies have shown that interventions focusing on physical rehabilitation and psychological adaptations can be effective for cancer survivors [16,17]. These interventions address both the physical and emotional challenges faced during the recovery process.

Despite the abundant information and support available after diagnosis, survivors later find themselves having a different set of questions and concerns related to life after cancer [18]. Our prior qualitative study of patients with lung cancer revealed the need for information on the expected trajectories after treatment. The patients expressed a desire for guidance in managing symptoms, stress, exercise, and nutrition to ease their “new normal” lives [19]. Recently, the importance of integrating oncological and supportive care has been increasing [20], as early interventions designed to provide supportive care for patients with cancer are in demand. Based on the findings of our qualitative interview, we hypothesized that an intervention introduced in the early stages of lung cancer treatment can help survivors return to their new normal lives.

Recognizing the critical need for early supportive interventions, we developed the Lung Cancer Comprehensive Care Program (LC^3P). This program aims to support patients from diagnosis through their adjustment to posttreatment life, encompassing their return to work, family, and societal roles. This study aimed to evaluate the effectiveness of LC^3P in enhancing psychological adjustment to cancer, with the hypothesis that participants receiving the intervention would demonstrate improved adjustment 6 months after surgery.

Methods

Study Setting

We designed a controlled before-and-after trial at the Samsung Comprehensive Cancer Center of the Samsung Medical Center (SMC), a university-affiliated hospital in Seoul, Republic of Korea, to evaluate the impact of LC^3P compared to routine care. This design was selected to minimize the risk of information contamination between the control and intervention groups. This risk is particularly pertinent to educational interventions, in which the exchange of information between participants can confound outcomes.

Eligibility Criteria

The inclusion criteria for the study are (1) age 18 years or older at enrollment, (2) diagnosis of stage I, II, or III NSCLC, and (3) a plan to undergo pulmonary resection. Patients with (1) recurrent lung cancer, (2) multiple sites of primary cancer, and (3) a history of other cancers or those who had received active cancer treatment within the past 3 years were excluded. Participants who canceled their pulmonary resection, received a confirmed diagnosis of stage IV lung cancer, or wished to withdraw from the study were excluded. All participants will be required to provide written informed consent before undergoing baseline assessment.

Intervention

Developing the Intervention

The LC^3P was developed following an extensive literature review [17,21,22], qualitative interviews [19], and cross-sectional studies [15]. These studies aimed to define the informational necessities and challenges faced by lung cancer survivors during their treatment journey. We discovered that the survivors adjusted their postcancer lives by reconciling their expectations with reality [19]. Physical symptoms, psychological challenges, and concerns regarding exercise and nutrition were also examined. Therefore, our intervention delivered timely and stage-specific information from the onset of treatment, primarily through educational videos. This format was selected due to its accessibility, patient friendliness, and potential to alleviate the workload of clinicians.

Content of the Intervention

The LC^3P is a 2-part intervention. The first part of the program comprised 7 educational videos, 4 of which were designed to meet the specific needs of lung cancer survivors. The first video provided general information regarding lung cancer, treatment

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options, and postsurgery challenges such as pain, emphasizing the importance of smoking cessation and exercise. The second video covered postoperative recovery, addressed symptoms such as reduced lung function and fatigue and offered management strategies. The third video was an exercise tutorial for patients, and the fourth video offered nutritional guidance through a sample meal plan. The latter 3 videos provided general information regarding distress management, return to work [23], and fear of cancer recurrence. The second part of the program was the first postsurgical follow-up with a family medicine physician who assessed the patient's unique needs using a study-specific checklist (Figure S1 in Multimedia Appendix 1). This visit focused on personalized care through counseling, medication management, and referrals to specialists as needed.

Delivery of the Intervention

Eligible participants received a brochure containing QR codes linked to educational videos (Figure S2 in Multimedia Appendix 1). We added QR codes for all the videos in a brochure and gave it to participants before surgery so they could preview the videos if they were curious about what to expect and what to work on after surgery. Participants were strongly encouraged to view the first video before surgery. The link to the first video was sent via SMS text message at the time of enrollment to increase patient accessibility. Around the time of discharge, a research assistant visited the intervention group participants to offer them a second copy of the brochure and sent links to each of the 3 videos, reminding them to watch the videos at their convenience. Data on compliance, satisfaction, and feedback on the educational videos were collected during follow-up visits. Measures were taken until the survivors reported watching all 4 videos or at their 1-year follow-up visit.

During the first follow-up visit after discharge, participants in the intervention group were scheduled to visit a family medicine doctor in addition to regular oncology appointments. During their appointment, the participants discussed any physical or psychological difficulties they had experienced after surgery, and the family medicine doctor provided tailored assistance based on the type and depth of their needs. As our intervention was educational, the participants in the intervention group were qualified to receive other concomitant care or additional necessary measures during the study. A flowchart of the study procedure and intervention is shown in Figure 1.

Figure 1. Flowchart of the Lung Cancer Comprehensive Care Program.

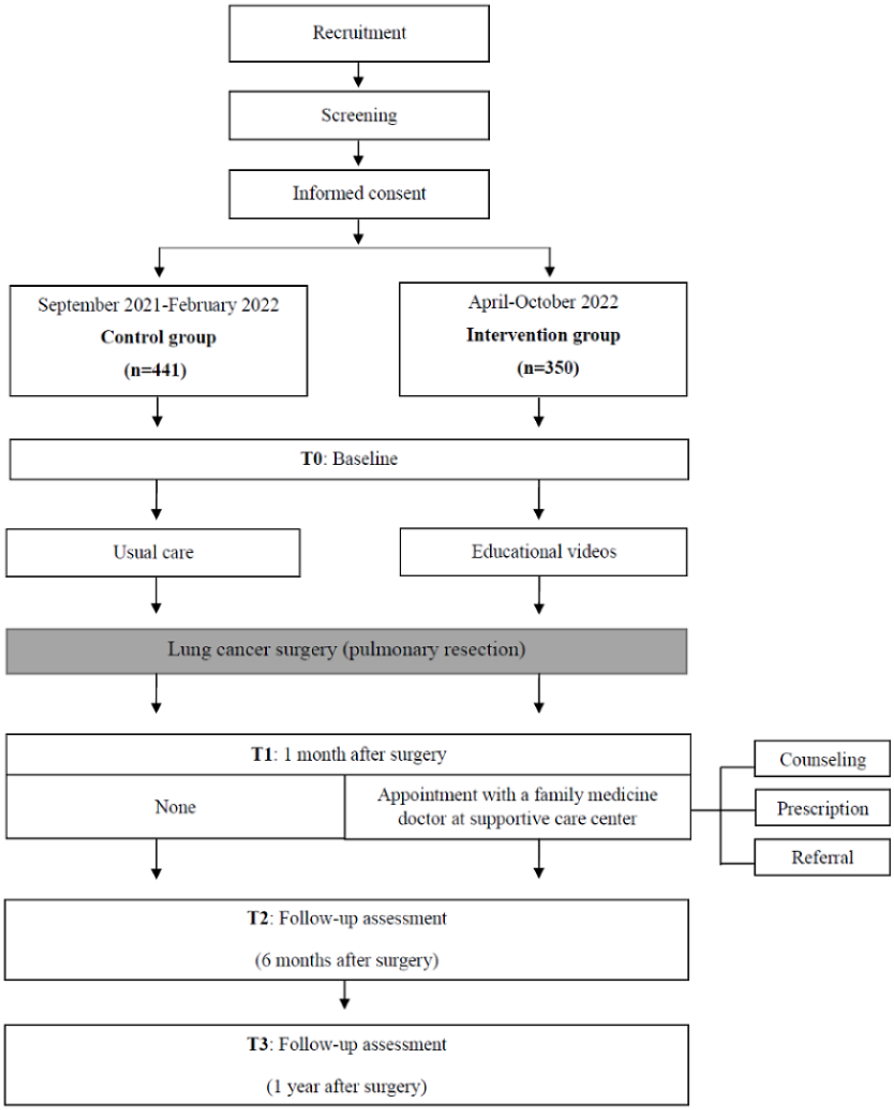

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Control Group

Participants in the control group received routine preoperative and discharge information regarding hospital stay, costs, and postoperative care. They did not have access to educational programs or postoperative educational support.

Outcomes

Primary Outcome Measures

The primary outcome of the study was psychological adjustment for cancer, measured 6 months after pulmonary resection. The Korean version of the Mini-Mental Adjustment to Cancer (Mini-MAC) was used to assess survivors' psychological adjustments to cancer. The Mini-MAC is a 29-item scale scored on a 4-point Likert scale (1=definitely does not apply to me and 4=definitely applies to me) previously validated in Korea [24,25]. The Korean-validated scale consists of the following 4 dimensions: helpless-hopeless (8 items), anxious preoccupation (8 items), cognitive avoidance (4 items), and positive attitude (9 items). The positive attitude dimension contained items identical to those of fighting spirit and fatality from the original Mini-MAC. The total score is the sum of all dimension scores, with higher scores indicating a stronger use of coping strategies. Permission to use the Mini-MAC was obtained from the International Psycho-Oncology Society on May 19, 2021.

Secondary Outcome Measures

The secondary outcomes were unmet informational needs, quality of life, distress, and symptoms. Unmet informational needs were assessed using the information needs scale (3 items) from the Korean version of the Cancer Survivors' Unmet Needs scale [26,27]. Health-related quality of life is measured using the Korean version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 [28]. Distress was assessed using the National Comprehensive Cancer Network Guidelines for Distress Management (version 2.2021) [29]. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer 13 [30], the Chronic Obstructive Pulmonary Disease Assessment Test [31,32], and the modified Medical Research Council dyspnea scale [33] are used to assess the presence and severity of symptoms related to lung cancer.

The Korean version of the International Physical Activity Questionnaire-Short Form is used to identify participants' levels of physical activity [34]. Depending on the level of activity derived from the questionnaire, patients were categorized into high, moderate, or low groups. The Hospital Anxiety and Depression Scale is a measure of depressive mood [35]. The components of each intervention and the hypothesized effects on the primary and secondary outcomes are shown in Figure S3 in Multimedia Appendix 1.

Sociodemographic variables such as age, sex, and level of education were acquired directly from the participants via self-reported questionnaires. Clinical characteristics, such as cancer stage, type of treatment, and postsurgical complications, were obtained from electronic medical records.

Sample Size Calculation

Based on the primary hypothesis that the intervention group would demonstrate a 25% better psychological adjustment to cancer at 6 months after surgery than the control group, initial calculations with an effect size of 0.25 indicated that 252 participants per group would be required. We aimed for a sample size of approximately 300 per group to account for a dropout rate of 16%. However, to increase the robustness of our findings, allow for potential subgroup analyses, and ensure that the study had sufficient power to detect smaller effect sizes, we enrolled 400 participants per group. The sample size significantly exceeded the required number based on our initial estimates, thereby enhancing the statistical power and potential impact on the study's outcomes.

Recruitment

Patients scheduled for pulmonary resection were recruited as controls to prevent contamination. The recruitment and study period for the control group were completed before the start of the intervention to ensure no overlap. Subsequently, recruitment to the intervention group began.

Data Collection

The clinical trial procedure and intervention are outlined in Figure 1, with the outcomes assessed at baseline (T0), 1 month (T1), 6 months (T2), and 1 year (T3) postoperatively. Baseline data will be collected before surgery and immediately after enrollment. To enhance participant retention and adherence, individuals in both groups received a small token of appreciation upon completion of each of the 3 postoperative follow-up assessments (T1-T3). For participants who discontinued or deviated from the intervention protocols, the data collected up to the point of departure were included in the intention-to-treat analysis to maintain the robustness of the trial results and minimize the impact of attrition bias. The data obtained from self-administered questionnaires were coded and stored in password-encrypted Microsoft Excel (Microsoft Corp) files on a secure computer server. The specific variables measured at each time point are listed in Figure 2.

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Figure 2. Schedule of enrollment, intervention, allocation, and assessments. CaSUN-Info: Cancer Survivors' Unmet Needs Measure—Information domain; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; EORTC QLQ LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer 13; HADS: Hospital Anxiety and Depression Scale; IPAQ-7: International Physical Activity Questionnaire-Short Form; Mini-MAC: Mini-Mental Adjustment to Cancer; mMRC: Modified Medical Research Council; T0 is baseline (before surgery); T1 is 1 month after surgery; T2 is 6 months after surgery; T3 is 1 year after surgery. *Primary outcome.

		Study period		
	Enrollment or allocation	Postallocation		Closeout
Time point	T0	T1	T2	T3
Enrollment	O			
Eligibility screen	O			
Informed consent	O			
Allocation	O			
Interventions				
Educational videos	←	→		
Appointment with a family medicine doctor		O		
Outcomes				
Mini-MAC	O	—	O*	O
CaSUN-Info	O	O	O	O
EORTC QLQ C30	O	O	O	O
EORTC QLQ LC13	O	O	O	O
HADS	O	—	O	O
mMRC	O	O	O	O
CAT	O	O	O	O
Distress thermometer and problem list	O	O	O	O
IPAQ-7	O	O	O	O
Smoking and alcohol consumption	O	—	O	O
Sociodemographic characteristics	O	—	—	—
Clinical characteristics	O	—	—	—
Compliance and satisfaction (videos)		O	O	O

Data Monitoring

Although the intervention primarily comprised educational videos and consultations with a family medicine physician, the associated risk to the participants was anticipated to be minimal. Accordingly, the establishment of a formal data-monitoring committee was considered unnecessary. However, procedures for monitoring adverse events and their unintended effects remain in place. The research team regularly reviewed participants' feedback and outcomes to identify potential concerns. Should any adverse events or unintended consequences arise, they will be addressed promptly, with details reported to the overseeing institutional review board (IRB) at the SMC, as per the standard protocol.

Statistical Analysis

To assess the effectiveness of LC^{3}P, we compared the outcomes between the intervention and control groups at multiple time points. The primary analyses involved independent sample 2-tailed *t* tests for continuous variables and chi-square tests for categorical variables to compare baseline characteristics and outcomes between the 2 groups at each follow-up. To account for repeated measures within participants over time and potential within-subject correlations, a mixed-model repeated-measures analysis was used.

In addition to primary analyses, sensitivity analyses probed the robustness of the trial findings under different assumptions regarding missing data and the effects of protocol adherence on treatment outcomes. This included intention-to-treat and per-protocol analyses. Moreover, subgroup analyses were conducted to examine the variability in treatment effects across different patient characteristics such as age, cancer stage, and the presence of comorbid conditions. All tests were 2-tailed, with a significance level of $P<.05$. To address multiple testing concerns, particularly with numerous secondary outcomes, we used Bonferroni correction or other suitable adjustments to preserve the overall type I error rate. All statistical analyses were conducted using STATA/MP (version 16.0; StataCorp).

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Ethical Considerations

This study was approved by the IRB of the SMC (SMC 2021-08-071). If any critical amendments, including but not limited to the eligibility criteria, outcomes, and analyses, become necessary in the future, modifications to the protocol will be shared with all relevant parties, including all investigators, the IRB committee, and the trial registry. A trained research assistant initiated contact with potential participants after screening for eligibility. Written informed consent forms were obtained after the purpose, procedure, and potential harm of participating in the study were explained. Informed consent was obtained from each patient before enrollment in the study. Personal data such as sociodemographic information, clinical characteristics, and outcomes measured at each visit were coded with a unique study identification number in password-encrypted Microsoft Excel files stored on a secure computer server to prevent unauthorized access. Hard copies of the questionnaire were retained for a decade after the completion of the study. Both the primary investigator and coinvestigators had access to the final data set without any contractual regulations.

Results

The historical control group (n=441) was recruited from September 8, 2021, to April 20, 2022, and the intervention group (n=350) was recruited from April 22, 2022, to October 17, 2022. All statistical analyses will be performed upon completion of the study.

As part of a nationally funded study, the results and details of the procedures will be made publicly available upon completion. The findings of this study will be actively shared through publications in peer-reviewed academic journals and at national and international scientific conferences. Regarding the intervention, the content and access to the educational videos will be refined based on the feedback patients provide on their first follow-up visit and will be made available on YouTube and to other health care professionals within the same health care institution, including oncologists and oncology nurses. The full protocol for this study is currently available at the ClinicalTrials.gov (NCT05078918). The raw data for this study will be shared upon request.

Discussion

Principal Findings

In this controlled before-and-after trial, the effectiveness of LC^3P in enhancing psychological adjustment to lung cancer treatment was examined. The LC^3P distinguishes itself by offering informational and personalized support from the initial phases of treatment.

Comparison to Prior Work

Lung cancer is often diagnosed during screening examinations or in the absence of a symptomatic presentation, resulting in a broad spectrum of patient effects upon diagnosis. Unlike previous interventions that typically introduced posttreatment survivorship care, our approach provided support from the outset. The median time for lung cancer survivors to engage in OncoLife and the LIVESTRONG Care Plans, 2 web-based programs providing survivorship care plans, was 1 year after treatment [11]. Similar trends in delivering survivorship care plans at the end of treatment have been reported, with the earliest delivery being within a year [36]. While providing survivorship care at the end of treatment allows survivors to process information relevant to their cancer continuum, some findings suggest that patients want to receive survivorship care plans during earlier stages of treatment [37]. The early engagement of the LC^3P aligns with emerging preferences for immediate survivorship care, as evidenced by patients expressing a desire to receive such information at earlier stages of their treatment trajectory.

In addition to early education, the intervention included general and tailored support. The educational videos offered to patients prior to treatment consisted of general information about the disease and survivorship care and were therefore applicable to all patients with NSCLC who are at stage I to III and who are planning to undergo lung resection. The second half of the intervention is personalized for each patient, as patients discuss their individual needs with their primary care physicians to determine the appropriate intervention to address their concerns. By taking a holistic approach to addressing patients' general and individual concerns about their disease, we expect lung cancer survivors to have a better understanding of their disease and to better adjust by recognizing and accepting the differences between their lives before and after cancer. In addition, the relative simplicity of LC^3P allows for its easy dissemination in routine care. Translating empirical evidence into clinical practice is difficult for several reasons including feasibility and pragmatism [38]. The educational videos that are part of our intervention are available on a web-based, easily accessible platform (eg, YouTube), allowing patients to obtain the information they need at their convenience. Displaying a booklet of QR codes linked to educational videos in outpatient clinics or inpatient wards is another viable option that does not interfere with the primary responsibilities of health care professionals. Furthermore, primary care and family medicine physicians commonly manage the long-term care of cancer survivors [39,40]. Given these considerations, we believe integrating the LC^3P into the routine care of patients with cancer will have fewer barriers.

Limitations

Despite these advantages, this study has some limitations that must be addressed. First, the design of the intervention might be more appealing to participants who are actively seeking ways to adapt to life after cancer, as opposed to those who are less motivated or indifferent about making such adjustments. In addition, although the use of a historical comparison group was intended to minimize the impact of exposure to our intervention in patients with lung cancer, the limitations of using a nonparallel comparison group should not be ignored. Second, socioeconomic and geographic disparities among older patients with cancer could affect accessibility to web-based educational videos. Although disseminating educational videos through web-based platforms allows cancer survivors to access as much information as they need at their convenience, it can be difficult

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for survivors with limited access to technology to access this information. If found to be promising, future studies should address the disparities in accessing web-based educational videos. Finally, the trial was registered after the recruitment commenced. However, there were no changes in the study design, measurement, or analysis methods after receiving the initial ethics approval.

In conclusion, the LC^{3}P represents a proactive, holistic prehabilitation intervention aimed at supporting lung cancer survivors, as they navigate the transition to life after treatment. Our findings highlight the impact of early informational support on patients' psychological adaptation and postdiagnosis stress management. This could potentially establish a new standard for the timing and delivery of survivorship care, emphasizing the benefits of early intervention.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

DWS and Juhee Cho supervised the study as cocorresponding authors. All authors contributed to the study conception and design. The first draft of the paper was written by WJ and AA, and all authors commented on previous versions of the paper. GL, SK, DL, and TEK contributed to material preparation and data collection. DK, YMS, HKK, and Jongho Cho contributed to resources. All authors read and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Figures 1-3.
[DOCX File , 12477 KB - resprot_v13i1e54707_app1.docx]

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Abbreviations

IRB: institutional review board
LC3P: Lung Cancer Comprehensive Care Program
Mini-MAC: Mini-Mental Adjustment to Cancer
NSCLC: non–small cell lung cancer
SMC: Samsung Medical Center

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Protocol

Efficacy of a Digital Health Preventive Intervention for Adolescents With HIV or Sexually Transmitted Infections and Substance Use Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV or sexually transmitted infections remain a significant public health concern in the United States, with adolescents affected disproportionately. Adolescents engage in HIV/STI risk behaviors, including drug use and condomless sex, which increase the risk for HIV/STIs. At-risk adolescents, many of whom are racial minorities, experience HIV/STI disparities. Although at-risk adolescents are disproportionately affected by HIV/STI risk behaviors and infections and although the Centers for Disease Control and Prevention recommends routine HIV/STI testing for adolescents, relatively few adolescents report having ever been tested for HIV/STI. With expected increases in health clinic visits as a result of the Affordable Care Act combined with technological advances, health clinics and mobile health (mHealth), including apps, provide innovative contexts and tools to engage at-risk adolescents in HIV/STI prevention programs. Yet, there is a dearth of efficacious mHealth interventions in health clinics to prevent and reduce both condomless sex and drug use and increase HIV/STI testing for at-risk adolescents.

Objective: To address this gap in knowledge, we developed a theory-driven, culturally congruent mHealth intervention (hereon referred to as S4E [Storytelling 4 Empowerment]) that has demonstrated feasibility and acceptability in a clinical setting. The next step is to examine the preliminary efficacy of S4E on adolescent HIV/STI testing and risk behaviors. This goal will be accomplished by 2 aims: the first aim is to develop a cross-platform and universal version of S4E. The cross-platform and universal version of S4E will be compatible with both iOS and Android operating systems and multiple mobile devices, aimed at providing adolescents with ongoing access to the intervention once they leave the clinic, and the second aim is to evaluate the preliminary efficacy of S4E, relative to usual care control condition, in preventing or reducing drug use and condomless sex and increasing HIV/STI testing in a clinical sample of at-risk adolescents aged 14-21 years living in Southeast Michigan.

Methods: In this study, 100 adolescents recruited from a youth-centered community health clinic will be randomized via blocked randomization with random sequences of block sizes to one of the 2 conditions: S4E mHealth intervention or usual care.

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Theory-driven and culturally congruent, S4E is an mHealth adaptation of face-to-face storytelling for empowerment, which is registered with the Substance Abuse and Mental Health Services Administration's National Registry of Evidence-Based Programs and Practices.

Results: This paper describes the protocol of our study. The recruitment began on May 1, 2018. This study was registered on December 11, 2017, in ClinicalTrials.gov. All participants have been recruited. Data analysis will be complete by the end of March 2024, with study findings available by December 2024.

Conclusions: This study has the potential to improve public health by preventing HIV/STI and substance use disorders.

Trial Registration: ClinicalTrials.gov NCT03368456; https://clinicaltrials.gov/study/NCT03368456

International Registered Report Identifier (IRRID): DERR1-10.2196/47216

(JMIR Res Protoc 2024;13:e47216) doi:10.2196/47216

KEYWORDS

youth; mHealth; HIV; STI; illicit drugs; primary care; prevention; public health; USA; teens; drugs; drug use; sex; racial minority; risk behavior; engagement; tool; substance use disorder

Introduction

Background

HIV infections or sexually transmitted infections (STIs) and drug abuse remain significant public health priorities in the United States, with youths being affected disproportionately. Youths aged 15-24 years constitute only 25% of the sexually experienced population, but account for 46% and 50% of HIV infections and new STIs, respectively [1,2]. National surveillance data indicate that youths disproportionately engage in HIV/STI risk behaviors, including condomless sex [3] and licit and illicit drug use [4], which increase their risk for HIV/STI. Despite the disproportionately high rates of HIV/STI and risk behaviors in youths, less than 14% report having ever been tested for HIV infection [3]. Further, many youths are not routinely screened for asymptomatic STIs as recommended by the Centers for Disease Control and Prevention [5]. In Southeast Michigan (the area targeted in this proposed research), HIV/STI cases are disproportionately high [6,7]. To address these significant public health concerns, we developed an innovative mobile health (mHealth) intervention—the practice and dissemination of public health through mobile devices—for health clinic settings. Using this AIDS-Science Track Award for Research Transition (A-START) mechanism, we propose to examine the preliminary efficacy of our mHealth intervention.

The efficacy rates of mHealth [8-10] and brief interventions delivered in health care settings [11-14] aimed at preventing or reducing condomless sex and drug use in youths have been mixed. We believe our intervention, Storytelling 4 Empowerment (S4E), shows promise for several reasons. First, we developed S4E through a community-university collaboration, integrating community-based participatory research principles [15] with the National Institute on Drug Abuse's prevention guidelines [16]. This process transformed the effective S4E program [17] into an mHealth app [18-22].

S4E is culturally congruent and was adapted in consultation with youths and clinicians from a targeted youth-centered community health clinic. This app is grounded in empowerment [23,24] and ecodevelopmental [22,25-27] theories. S4E uses innovative storytelling scenarios to address key aspects of our intervention's mechanisms of change, including self-efficacy for condom use and drug use refusal skills (hereon referred to as self-efficacy) and improving clinician-youth communication during the health care visit. These elements aim to increase HIV testing and prevent or reduce condomless sex and drug use behaviors among at-risk youths. Our formative research with youths (defined hereon as adolescents and young adults aged 14-21 years) and clinicians demonstrated that youths in the targeted health care clinic (1) routinely visit the clinic for reproductive and other health care, (2) are at increased risk of HIV/STIs, and (3) found S4E to be feasible and acceptable but also want access to S4E outside of the health clinic to continue participating in intervention activities [18-21,28-30].

Youth-centered community health clinics are an ideal setting for delivering and evaluating the efficacy of an mHealth HIV/STI and drug abuse preventive intervention. Many youths do not seek such services in public health clinics or AIDS service organizations [31]. Furthermore, many primary care pediatric practices do not routinely screen youths for HIV/STIs or drug use [32]. Thus, a gap in knowledge persists regarding efficacious mHealth interventions that improve HIV/STI testing and prevent or reduce condomless sex and drug use in at-risk youths in health care settings [10,18,33]. Since S4E has demonstrated feasibility or acceptability [20], the next important step is to develop a more accessible version of S4E and conduct a stage 1 randomized controlled trial (RCT) [34,35] to examine the preliminary efficacy of S4E in at-risk youths.

Aims

The proposed study seeks to accomplish the following 2 aims:

1. The first aim is to develop a cross-platform and universal version of S4E. The cross-platform and universal version of S4E will be compatible with both iOS and Android operating systems and multiple mobile devices aimed at providing adolescents with ongoing access to the intervention once they leave the clinic.
2. The second aim is to evaluate the preliminary efficacy of S4E, relative to usual care, to improve HIV/STI testing and reduce HIV/STI risk behaviors in a clinical sample (N=100) of at-risk youths aged 14-21 years living in Southeast Michigan. We will conduct a stage 1 RCT [34,35] to examine the preliminary efficacy of S4E, relative to usual

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care, in a sample of 100 at-risk youths for 6 months. Our primary outcome is adolescent HIV and STI testing. Secondary outcomes include condomless sex and drug use at 3 months and 6 months postbaseline. As a secondary exploratory aim, we will examine the extent to which our theoretically guided mechanisms of change (ie, self-efficacy, clinician-youth communication) lead to increased HIV and STI testing and prevent or reduce HIV/STI risk behaviors.

The proposed study is innovative, as it is the first to combine mHealth and storytelling to facilitate clinician-youth communication, deliver prevention services, linkage to care, and treatment immediately [27,36,37]. This research program focuses on increasing HIV and STI testing and reducing key risk behaviors such as condomless sex and drug use among at-risk youths. This aligns with the National Institutes of Health HIV/AIDS research priorities [38]. By doing so, it addresses 2 critical goals: (1) preventing and reducing new HIV infections and (2) diminishing HIV-related health disparities. These objectives are among the top 4 priorities outlined in the United States National HIV/AIDS strategy [39].

Significance

HIV/STI risk behaviors among youths remain the major public health concerns. National surveillance data show that 40.9% of the youths reported condomless sex in the last sexual intercourse [3]. Beyond condomless sex, youths engage in drug use behaviors that increase their risk for HIV/STI. National surveillance data indicate that 66% and 49.1% of youths report lifetime licit and illicit drug use, respectively [4]. Alcohol is the most widely used licit drug, with 37.4% and 66% of youths reporting current and lifetime use, respectively [3,4]. Parallel data from Monitoring the Future study indicate that, from 2008 to 2011, youths' lifetime, annual, and 30-day prevalence of any illicit drug use have increased [4]. Marijuana remains the most widely used illicit drug with 21.2% and 44% of adolescents reporting current and lifetime marijuana use, respectively [4]. Although the Centers for Disease Control and Prevention recommends HIV/STI testing among youths as part of routine care, many are only being tested based on their perceived risk [5]. HIV/STI testing has important prevention implications, including linkage to both care (eg, preventing transmission of HIV/STI) and important preventive services to remain HIV/STI-free [5].

Racial or ethnic minority youths experience HIV/STI disparities. Youths aged 15-24 years represent 25% of the sexually experienced population and comprise nearly 46% and 50% of HIV infections and new STIs, respectively [1,2]. In 2014, an estimated 9731 youths were diagnosed with HIV in the United States; 78% of these diagnoses occurred in Black/Latino youths [40]. Although the majority of these infections are among young men who have sex with men [40], African American young women are disproportionately affected by STIs, which increases the risk of HIV infection [41]. Given their needs, our sample will consist of a predominantly racial or ethnic minority sample of adolescents in the age group of 14-21 years. This age group spans a time of limited HIV testing and increased HIV/STI risk-taking [3,4] and thereby permits us to intervene at a developmental moment of increased risk [42,43].

Youth in the targeted clinic, many of whom are racial or ethnic minorities, are at disproportionate risk of HIV/STI. Our research shows that, relative to the general US adolescent population, youths in the targeted clinic are more likely to report condomless sex in the last sexual intercourse (40.9% vs 57.9%) and lifetime alcohol (66.2% vs 71.4%) and marijuana (40.7% vs 46.7%) use, respectively [3,20]. Given that condomless sex and drug use are risk behaviors for HIV/STI, not surprisingly, youths in the targeted clinic experience HIV/STI disparities. In the first quarter of 2016 (January-March), 52% (33/63) of youths who received STI testing services tested positive for an STI compared to 25% of the sexually active US youth population [2].

Self-efficacy and clinician-youth communication are potential mechanisms by which change can occur. Researchers have identified a number of etiological factors that shape youth HIV/STI testing [44-46] and risk behaviors [47-49], including intrapersonal (eg, self-efficacy) and ecological (eg, clinician communication) [42,50]. At the intrapersonal level, for example, higher levels of refusal skills and knowledge of self-efficacy increase HIV/STI testing and prevent HIV risk behaviors in youths [42-45,51,52]. At the ecological level, effective sexual communication can ameliorate HIV/STI testing and risk behaviors. Indeed, higher levels of clinician-patient communication have been shown to yield better health outcomes [53-55]. Drawing from this basic science, the proposed study posits that interventions targeting these potential underlying mechanisms of change (ie, improving refusal skills, knowledge, and HIV communication, which in turn will improve self-efficacy and clinician-youth communication) may increase HIV/STI testing and prevent or reduce HIV and STI risk behaviors. Furthermore, understanding the role of etiological factors on youth HIV/STI testing and risk behaviors should be viewed through a cultural and developmental lens [26,56,57]. Therefore, integrating cultural and developmental perspective into theoretical frameworks is important to improve HIV/STI testing and reduce risk behaviors [26,56-58].

Empowerment and ecodevelopmental theories provide a framework for targeting the theoretical underpinnings of our intervention's mechanisms of change. The empowerment and ecodevelopmental frameworks guide the theoretically driven components of our intervention. The empowerment framework is concerned with linking youths' strengths and proactive behaviors to helping systems [24,25]. Thus, empowerment-informed interventions seek to enhance the knowledge of the risk factors, refusal communication skills, perceptions of self-efficacy, and engage health care clinicians as resources to accomplish these health goals [24,25]. Equally important is to consider ecological factors. The ecodevelopmental theory [59,60] posits that youths are embedded in integrated ecological systems (microsystem, mesosystem, exosystem, and macrosystem), including developmental and social interaction, which influence and are influenced by the youth [59,60]. In the proposed research, we focus on the health clinic microsystem and limit the conversation to that high-impact system. Microsystems are defined as systems in which the youths participate directly [59,60]. Researchers

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have extensively applied the ecodevelopmental theory to the family microsystem aimed at improving parent-youth communication [61-63]. With the passing of the Affordable Care Act, we have an opportunity to apply the ecodevelopmental theory to the health clinic microsystem—a system that will only grow larger and increasingly important as a result of the Affordable Care Act—to understand clinician-youth communication [18-21]. Our formative research supports the use of empowerment and ecodevelopmental theories and provides a robust framework for the proposed research.

Health clinic HIV/STI preventive interventions are needed but limited in availability. A recent review of brief (<60 minutes) health clinic interventions examined 31 trials designed to increase HIV/STI testing and prevent HIV/STI risk behaviors. Of these, only 1 study focused on HIV/STI risk behavior outcomes through clinician-youth communication. Findings suggest that, relative to usual care, an audiotaped risk assessment and education intervention showed an increase in communication with providers on STIs and condom use [64]. Findings on the efficacy of brief interventions in health care settings on youth licit and illicit drug use have been mixed [11,14,65]. For example, a recent review of brief interventions in health care settings with clinician approaches was conducted, with 10 interventions designed to prevent or reduce youth alcohol use examined. Of these, only 3 studies were RCTs: 1 had a primarily racial minority sample and 1 was found to be efficacious in reducing alcohol use [11]. Our community-university approach aims to overcome the limitations of these studies. By engaging the community in the development of our mHealth intervention, we believe we will have a greater impact, given that community-university approaches increase uptake and optimize outcomes of prevention programs [66]. Although federal recommendations highlight the need for clinicians to provide youth HIV/STI and drug use preventive services [67,68], efficacious brief interventions designed to increase HIV/STI testing and prevent or reduce condomless sex and drug use are limited [18,33,64,69]. Our formative research suggests that youths in the targeted clinic routinely show for health care visits, with over 550 monthly visits by youths aged 12-21 years. This provides us with an exciting opportunity to impact HIV/STI testing and behaviors through an innovative and interactive mHealth app.

mHealth apps provide new opportunities for engaging youths in preventive interventions, but research is limited. Advances in technology and increased availability provide novel opportunities for prevention scientists [70,71]. Although mHealth interventions are efficacious for adolescent health behaviors [71-73], relatively few studies on HIV/STI testing and risk behaviors exist. A recent systematic review of mHealth apps aimed at addressing the HIV continuum of care identified only 4 published studies and 14 studies underway [10]. Of these, only 7 studies focused on primary prevention of HIV/STI and 6 studies on HIV/STI testing [10]. A limitation of these studies, however, is that they do not target at-risk youths in health care clinics. Our proposed research aims to harness the widespread use of mobile technology [74] and deliver and evaluate an mHealth HIV/STI intervention among at-risk youths, many of whom are racial minorities, in a health care clinic.

Storytelling for Empowerment (SFE) is an effective face-to-face intervention to translate and test a new mHealth preventive intervention. Registered with Substance Abuse and Mental Health Services Administration's National Registry of Evidence-Based Programs and Practices, SFE aims to increase self-efficacy and communication about HIV risk behaviors and has been shown to prevent or reduce HIV/STI risk behaviors and increase (1) HIV/STI and drug use prevention knowledge, (2) HIV/STI communication, and (3) perception of harm and self-efficacy in refusing drugs [17,75,76]. Adapting SFE into an mHealth version for health care clinics was ideal for several reasons, including SFE has already demonstrated efficacy with other youth populations and the use of storytelling makes it highly flexible and easily transportable into a brief mHealth modality. Based on empowerment [24,25] and ecodevelopmental [22,26,77] frameworks, the mHealth version of SFE, S4E, consists of 3 modules targeting youth: (1) HIV/STI risk assessment, (2) HIV/STI, and (3) alcohol/drugs. The risk assessment assesses youth HIV/STI risk behaviors. Both the HIV/STI and drug modules consist of videos (developed from focus group data on community-specific epidemiology) focused on HIV/STI testing and risk and promotive behaviors, knowledge development, interactive activities, and messaging aimed at increasing clinician-youth communication.

Despite federal guidelines urging clinicians to provide youth HIV and drug use preventative care [67,68], our research [19,20] and that of others [78-80] demonstrate that clinicians' limited HIV/STI communication training and embarrassment to discuss HIV/STI risk pose as challenges to engage youths in these conversations. With funding from the National Institute of Mental Health (R25MH067127), we developed a theory-driven and culturally congruent clinician component to overcome these barriers, which provides clinicians with (1) youth risk assessment scores, (2) tailored HIV/STI communication interviewing toolkits (eg, reflective questioning), and (3) tailored resources to link youths with care. We recognize that youths in health clinics represent one segment of the youth population, but nonetheless an important segment at disproportionate risk of HIV/STI [20,28].

Preliminary Studies

Study 1: Feasibility and Acceptability of S4E

Study Design

Youths (n=30) were recruited from Southeast Michigan and were primarily African Americans (20/30, 67%) and females (22/30, 73%) with a mean age of 16.23 (SD 2.09) years. We used a community-engaged research approach with 3 phases, that is, formative focus groups (n=29), app development, and feasibility testing (n=30). We used agile software development [81]. Formative focus group data collection and app development occurred simultaneously.

Results

We developed a theory-driven and culturally congruent mHealth version of SFE (Figure 1). Both qualitative and quantitative data from the Session Evaluation Form [82] (mean 1.42, SD 0.46) and Client Satisfaction Questionnaire [83] (mean 3.46, SD 0.47) indicate that S4E was acceptable to youths. Data also

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showed that youths regularly visit the clinic (ie, 550 visits per month), visit the clinic multiple times (mean 3 visits), and are at increased risk of HIV/STI risk behaviors. Since we demonstrated the feasibility, the next important step was to conduct a stage 1 preliminary efficacy RCT of S4E on adolescent HIV/STI testing and risk behaviors [18-21].

Figure 1. A theory-driven and culturally congruent mobile health version of Storytelling for Empowerment.

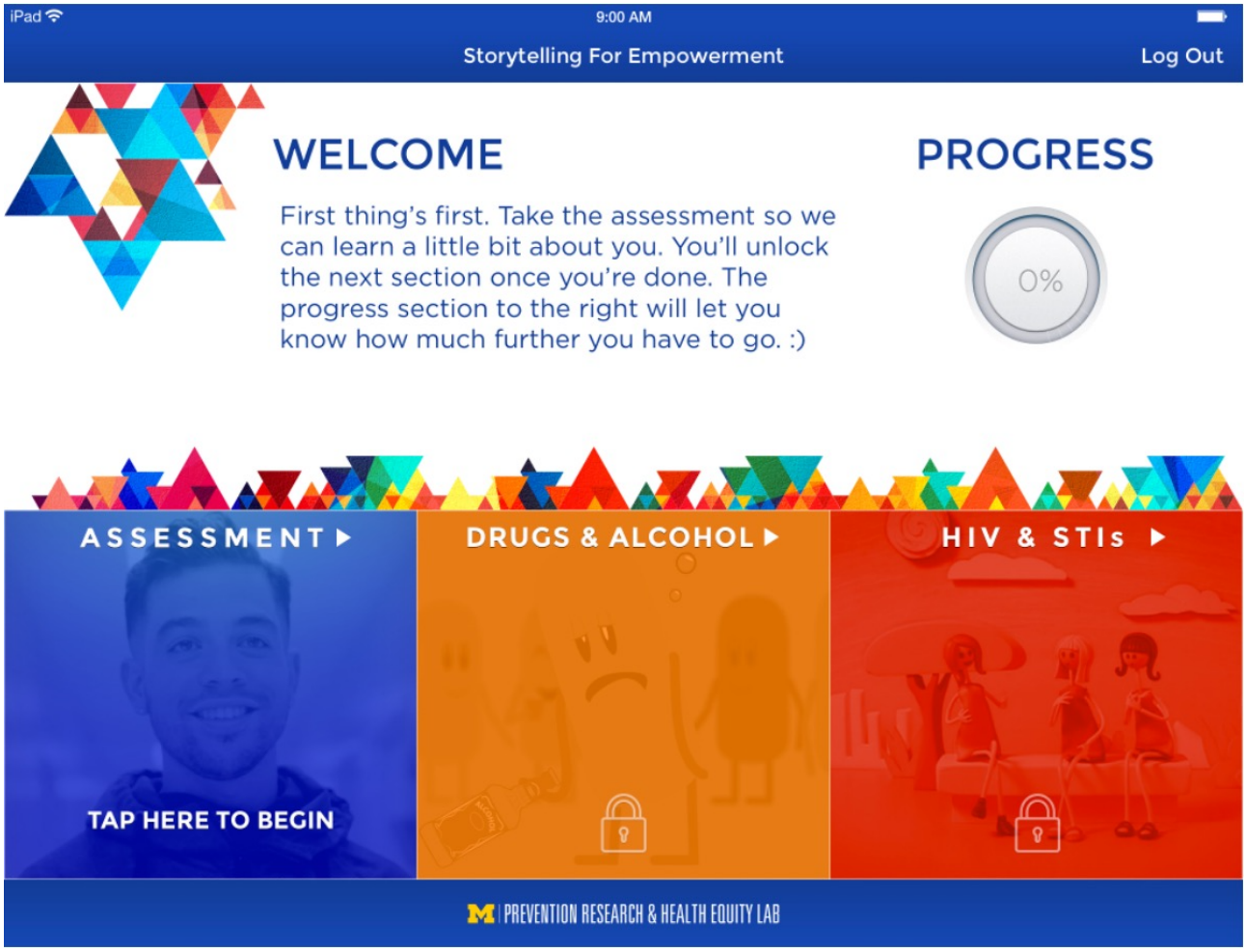

Study 2: Development of S4E Clinician App

Employing Community-Based Participatory Action Research principles, we collaborated with clinicians from the targeted youth-centered community health clinic in Southeast Michigan (NIMH R25MH067127) to inform the development of the clinician components for the S4E app [84]. We used agile software development [81] for the creation of prototype models, obtained rapid feedback from clinicians regarding user interface/experience, and a feedback loop for revisions and to finalize the app. The S4E clinician app provides clinicians with (1) youths' risk assessment scores, (2) tailored HIV/STI communication interviewing toolkit (eg, reflective questioning, positive reinforcement), and (3) tailored resources to link youths with care. Feasibility or acceptability testing is underway and study findings will be incorporated into this proposed A-START research.

Methods

Study Design

The first aim is to develop a cross-platform and universal version of S4E. The purpose of developing a cross-platform and universal version of S4E is to create a more accessible app that is compatible with different operating systems (ie, Android and iOS) and multiple mobile devices, thereby providing youths with ongoing access to the intervention outside of the clinic. Finalizing the universal version of S4E will be streamlined because the app developer, The Annex Group, created S4E for the iOS operating system to use on iPads, which will serve as an existing framework (eg, code, design database). Similar to the methodology employed in our formative research, as part of the iterative process, we will hold weekly meetings with The Annex Group to discuss all aspects of finalizing the app, including framework and user interface or user experience. At the completion of the first aim, we will have finalized S4E, which will be used for our stage 1 preliminary efficacy RCT in the second aim. We will pilot test all study procedures prior to addressing the second aim.

The second aim is to evaluate the preliminary efficacy of S4E to improve HIV/STI testing and reduce HIV/STI risk behaviors in a clinical sample (N=100) of at-risk adolescents aged 14-21 years living in Southeast Michigan. To test the preliminary efficacy of S4E, we will conduct a stage 1 RCT and use a mixed between/within-subjects design with 2 levels of intervention

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(S4E and usual care) as the between-subjects factor and 3 repeated measures assessments (baseline, 3-, and 6-months postbaseline) as the within-subjects factor.

Participants

A clinical sample of 100 youths and clinicians (n=6) will be recruited from Corner Health Center. In 2015, the clinic reported over 5600 visits from individuals aged 12-21 years; therefore, recruiting 100 youths will be feasible. With respect to participant race, ethnicity, and age, we will recruit a sample that is representative of the clinical population. As in our previous studies [28-30], we expect the majority of participants to be racial minority youths and be sexually active (50/70, 71% report past 90-day oral, vaginal, or anal sexual intercourse) [20,28].

Inclusion Criteria

Participants must be female or male youths aged 14-21 years, sexually active, live in Southeast Michigan, and have access to a smartphone or tablet (51/70, 73% report having access to smartphone [85]). Youths must see an enrolled clinician to participate in this study. Exclusion criteria include report of prior psychiatric hospitalization by the adolescent, visible cognitive impairment due to drug use, and adolescent reports (tentative or firm) plans to move out of the Southeast Michigan area during the study.

Recruitment

A multipronged recruitment strategy will be implemented: face-to-face interactions, flyer distribution, engagement in the clinic's waiting area, and informing youths with upcoming clinic appointments at the clinic about the study. Potential participants will be informed about the study by research staff, with details about its voluntary nature and the RCT design. Those interested will be sent a study web-based app link, where they can provide digital consent and screen for eligibility. Participants aged 13-17 years will be given a waiver of parental permission as per Michigan regulations. Following consent, participants will undergo baseline assessment and randomization through the study's web-based app. They will then be informed of their group allocation. Research staff will introduce participants to the app and ensure proper navigation. Participants will be incentivized, receiving a total of US $120: US $30 at baseline, US $40 at the 3-month follow-up, and US $50 at the 6-month follow-up.

Retention

To prevent attrition, we will ask youths to provide the names and contact information of 3 persons who will always know where they can be reached. These names will help maintain contact with the youths in case they move or their telephone lines become disconnected. Youths may choose to provide the names and contact information of individuals they trust, such as a primary caregiver, relative, or significant adult figure. Youths will be informed that if the research team cannot reach them and needs to contact these individuals, the team will only communicate their intention to contact the youths about a health study. Additionally, a sample of 6 clinicians will be recruited. Similar to our formative research, research staff will provide an overview of the study to all clinicians during a staff meeting, and they will be informed that participation is voluntary. To prevent coercion of clinician participation by clinic administration, potential participants will not need to go through nor inform the clinic administration for participation. An initial list of potential clinician participants will be developed, and research staff will follow up with those clinicians who express interest in this study.

Clinicians

Clinicians will be assigned to either S4E or control condition. In lieu of providing each clinician with an incentive for their participation in the study, the clinic will receive US $2000, which will benefit the entire clinic. Randomization will occur after baseline assessment. Three of the 6 clinicians will be assigned to the S4E condition and trained according to research criteria. Clinicians will receive a 1-hour training, encompassing content delivery, app navigation, risk assessment viewing, note-taking within the app, and effective communication strategies for discussing substance use and sexual behaviors. A review training will ensure adherence to the protocols. All clinicians who express interest in this study and do not report (tentative or firm) plans to move out of the region during this study will be eligible to participate.

Experimental and Control Conditions

Participants were assessed at baseline, randomized to intervention (n=50) or control (n=50) groups using block randomization [86], and then reassessed immediately postintervention, at 3 months, and at 6 months. Participants in the S4E condition will initially engage with the intervention by using iPads available in the waiting area. This includes iPads allocated for this study and an additional 10 from the principal investigator's pilot studies. They will also be instructed on how to download the intervention app onto their personal devices, enabling continued participation in intervention activities after leaving the clinic.

S4E Description

Informed by our formative research, the intervention lasts approximately 60 minutes and was found to be feasible and acceptable to youths. Content includes the theoretically driven components of SFE [17,75,76]: (1) storytelling scenarios, (2) drug use and HIV/STI knowledge development, (3) interactive activities, (4) increasing self-efficacy to prevent or reduce sexual risk and drug use behaviors and increase HIV/STI testing, (5) clinician-youth communication, and (6) highlighting prevention principles (Textbox 1 and Textbox 2).

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Textbox 1. Experimental condition of S4E intervention.

Adolescent components

- Risk assessment: Youths complete an HIV/sexually transmitted infection (STI) risk behavior assessment, which include items from the CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble) [87] measure, HIV testing, and sexual and drug use behaviors, and provide opportunity or receptivity to being counselled (1 min to complete).
- HIV/STI module: Youths are exposed to storytelling scenarios, including community-specific HIV/STI epidemiology (eg, risk, protective behaviors). Following the videos, youths operate an app aimed at increasing condom use self-efficacy, HIV/STI knowledge development, and interactive activities aimed at engaging youths and testing knowledge. Additionally, youths receive messaging aimed at facilitating clinician-youth communication and HIV/STI testing (30 min to complete).
- Alcohol/drugs module: Adolescents are exposed to storytelling scenarios, including community-specific alcohol/drug epidemiology (eg, prevalent licit and illicit drugs). Following the videos, adolescents operate an app aimed at increasing drug use refusal self-efficacy, drug use knowledge development, and interactive activities aimed at engaging youths and testing knowledge. Additionally, adolescents receive messaging aimed at facilitating clinician-adolescent communication (30 min to complete).

Clinician components

- Risk assessment scores: Clinicians are provided youth risk assessment scores, identifying at-risk youths, and provided opportunity to reinforce information provided to youths through the modules (above).
- Tailored HIV/STI communication toolkit: Based on empowerment and ecodevelopmental theories, clinicians are provided a communication toolkit, which includes examples of open-ended reflective questioning, positive reinforcement statements, HIV/STI risk probing, and empowerment messaging.
- Tailored resources and referrals: Clinicians are provided tailored community-identified local resources and referrals, including HIV/STI testing and linkage to care.

Textbox 2. Underlying mechanisms of change.

Consistent with empowerment and ecodevelopmental theories, Storytelling 4 Empowerment provides an opportunity to be counselled, which in turn:

- Increases clinician-youth communication
- Increases engagement of health care clinicians as collaborators to address HIV/sexually transmitted infection (STI) and drug use concerns
- Increases clinician-youth sexual risk communication
- Increases HIV/STI knowledge
- Increases condom use
- Increases condomless sex refusal skills
- Increases clinician-youth drug use communication
- Increases drug use knowledge
- Increases refusal skills
- Enables clinicians reinforce prevention strategies and link youths to HIV/STI testing and linkage to care

Control Condition

Participants in usual care (ie, control condition) will not receive the S4E intervention from the study staff. The clinic's usual care includes a standard risk behaviors intake form, pamphlets highlighting resources, and reproductive and health care services.

Measures

Youth HIV/STI Testing and Risk Behaviors

After the intervention, we will assess whether youths requested to receive HIV/STI testing at the clinic, and at 3 months, and 6-months postbaseline (yes/no). Adolescent unsafe sexual behavior will be measured (timepoints 1-3) by using items extracted from the Sexual Behavior Instrument [88]. This gated instrument will assess the adolescent's past 90-day condom use, number of sexual partners, and contraceptive use (not condoms). This measure also assesses the existence of an STI during their lifetime and in the past 90 days. Licit and illicit drug use behaviors will be assessed (timepoints 1-3) using items from the Monitoring the Future study [4]. Youths will be asked whether they have used licit or illicit drugs in their lifetime and in the past 90 days. Youths who report "Yes" to past 90-day sex will be asked to report frequency of drug use prior to sex. These measures have been used in our formative research [18-21].

Potential Mediators: Clinician-Youth Communication and Self-Efficacy

Completed by both the clinicians (α=.70) and youths (α=.69), clinician-youth communication will be assessed (timepoints 1-3) using items adapted from the Matched Pair Instrument (19 items) [89]. The Matched Pair Instrument assesses the process and content of communication, including verbal and

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action-related behaviors performed by clinicians [89]. Responses range from "1=strongly disagree" to "5=strongly agree" on a 5-point Likert scale. A sample statement for clinicians and youths is, "Encouraged the patient/me to express his or her/my thoughts concerning drug use behaviors." Youths' self-efficacy will be assessed (timepoints 1-3) using 2 scales, namely, the Condom Self-Efficacy Scale (19 items, α=.85) [90] and Drug Use Resistance Self-Efficacy (24 items, α=.98) [91]. Responses range from "1=not sure at all" to "4=definitely sure" on a 4-point Likert scale. A sample question for the youth is, "How sure are you that you can refuse if a friend offers you marijuana at a party and you do not want it?" Additionally, youths and clinicians will respond to a demographic survey, wherein they will have to fill in the details of their date of birth, gender identity, sexual orientation, age, ethnicity or race, income, and education.

Intervention Dosage for Both Clinicians and Youths (Not Given to Participants)

S4E includes a login procedure. In addition to the login procedure serving as a mechanism by which the secure access and confidentiality of participants is ensured, it will facilitate the close monitoring of participants' dosage. The login procedure will be used to record whom (ie, participant), when (ie, day/time), how long (eg, dosage), and for what purpose (eg, module). We will assess participants' satisfaction with S4E across platforms (eg, mobile phone) and the use of the intervention once they leave the clinic. Higher frequencies of access and longer durations of app use will indicate higher levels of dosage and engagement with the intervention.

Statistical Analysis

Given the sample size and stage 1 RCT pilot nature of our study, we will not conduct a formal test of efficacy. Researchers affirm [92] that effect size estimates obtained using stage 1 RCT data may not be reliable, given their large variability. Therefore, our primary purpose was to estimate the critical parameters [92] required to inform the potential effects of S4E in a stage 2 RCT. As part of the preliminary efficacy process, we expect the following intervention exposure relative to usual care participants:

1. Hypothesis 1: S4E participants will have increased odds of repeat HIV/STI testing postintervention.
2. Hypothesis 2: S4E participants will have decreased odds of past 90-day condomless sex at 3 months and 6 months postbaseline.
3. Hypothesis 3: S4E participants will have decreased odds of past 90-day licit and illicit drug use at 3 months and 6 months postbaseline.

As a secondary exploratory aim to examine potential mechanisms of change (Figure 2), we also anticipate that S4E participants compared to usual care participants will report (1) higher mean levels of clinician-youth communication and (2) drug use and HIV/STI self-efficacy.

Figure 2. Potential mechanisms of change caused by Storytelling 4 Empowerment. S4E: Storytelling 4 Empowerment; STI: sexually transmitted infection.

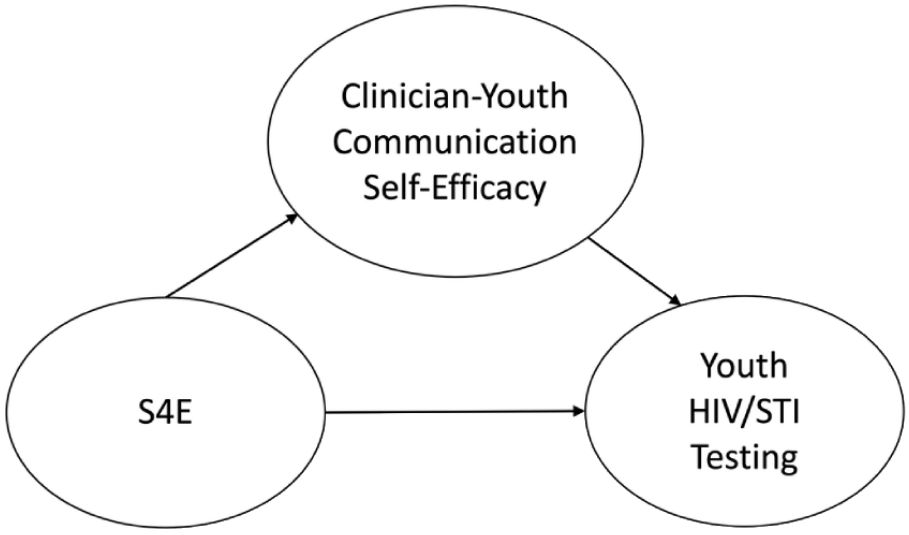

To test differences between conditions postrandomization, we will plot means and proportions by condition over time for descriptive analysis of overall patterns of change across time in the outcomes for the S4E and usual care conditions. We will use linear mixed models (LMMs) for continuous outcomes (eg, clinician-adolescent communication scale scores measured to address exploratory aim) and generalized LMMs (GLMMs) for discrete data (eg, HIV/STI testing measured to address H1) to evaluate the proposed preliminary hypotheses. GLMMs fitted to discrete outcomes (eg, condomless sex) will employ a binomial distribution with a logit link; GLMMs fitted to count outcomes will use the best-fitting distribution from the Poisson family (eg, zero-inflated Poisson) with the log link function [93]. We will assess whether clustering effects associated with clinic physicians must be accounted for in these analyses. All mixed models will be estimated via maximum likelihood estimation and will be fitted to ensure that all requisite information is available in the survey and data to perform the types of analyses typically undertaken in a stage 2 RCT. Similarly, although the modest sample size precludes investigating mediation and moderation formally, we will employ the same LMM and GLMM approaches described above to examine potential mediators (ie, clinician-adolescent

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communication, self-efficacy) and moderators (eg, gender, race) of the S4E intervention.

Power Analyses

Due to the modest sample size, significance testing will be de-emphasized. The purpose of stage 1 RCT is to determine preliminary efficacy rather than to conduct formal hypothesis tests; nevertheless, we conducted power analyses using nQuery Advisor version 7.0 [94] to estimate the magnitude of effect we could observe, given our pilot sample size. With 50 cases per group, we would have 80% power to detect an odds ratio of 3.7 in receiving HIV testing immediately postintervention between the 2 conditions. This would be considered a large effect size [95]. Using GLMM models to compare the 2 groups in terms of trends in the probability of binary outcomes over 6 months (eg, condomless sex), we performed a custom simulation study to estimate the size of the interaction between group × time that we could detect with 80% power when fitting our models (and assuming a within-subject correlation of 0.1 in the binary measures). We would be able to detect percentages of 70% in the intervention group at 3 months and 25% at 6 months as representing a significantly different reduction in the percentage with this outcome over time (ie, a significant group × time interaction) with approximately 80% power, which would again be considered a large effect.

Ethics Approval

The principal investigator (DC) received approval (HUM00158089) from the University of Michigan institutional review board to begin research in February 2017 and was awarded funding from the National Institute on Drug Abuse on February 01, 2017.

Results

This study has been designed to develop an mHealth intervention program (S4E) and evaluate its preliminary efficacy to improve HIV/STI testing and reduce HIV/STI risk behaviors among youth populations. Our study findings will contribute to reducing HIV/STIs and risk behaviors among youths. The development of the intervention has been completed, and recruitment for the preliminary efficacy trial began in May 2018. We completed the trial in August 2020. We recruited 100 participants, data analyses are underway, and the results are expected to be published by December 2024.

Discussion

The overarching goal of this program of research is to move a program of intervention research from efficacy to scale and to examine the extent to which these modules are generalizable to similar youth populations. If found to have preliminary efficacy, the next step in this program of research is to conduct a stage 2 RCT to examine the effects of S4E on youth HIV/STI testing and risk behaviors. We are aware that control group participants may unintentionally receive the experimental group content. Although it might not be possible for youths to see the same clinician at 3 months and 6 months postbaseline, we have the Corner Health's support that youths will only see clinicians in the condition to which they are assigned (ie, S4E or usual care). The proposed age range (14-21 years) may seem wide; however, this is an age group at increased risk for HIV/STI [1,2]. Further, this age range was established in consultation with Corner Health who, in considering both the strengths and limitations, preferred a universal app that was relevant to the clinical population. Our 2-arm, baseline, 3-month, and 6-month postbaseline design was chosen, given the scope of the R03 A-START mechanism.

Our protocol explores the behavioral change practice methods (ie, proposed mechanisms underlying the observed changes), namely, clinician-youth communication and self-efficacy. The use of storytelling scenarios, created by youths through a community-engaged research method grounded in community-based participatory research principles, could offer an innovative strategy for future studies. This approach highlights the importance of the relationship between clinicians and youths as well as the role of self-efficacy.

Our protocol may benefit the society by providing compelling evidence for the preliminary efficacy of an mHealth intervention in promoting HIV and STI testing and reducing sexual and substance use risks among adolescents and young adults. The promising intervention, combined with the proposed recruitment and retention strategies, may provide evidence for larger scale trials. Given the pressing demand for efficacious interventions in this domain, this protocol may have a significant societal impact. Further, this proposed research aligns well with the broader goals of the National Institutes of Health HIV/AIDS research priorities [38], the National HIV/AIDS strategy [4], and the recommendations issued by the US Preventive Services Task Force to reduce youth's HIV and drug use risks by linking them to screening and care services in community health clinic settings [67,68].

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Conflicts of Interest

None declared.

Authors' Contributions

The members of the Youth Leadership Council are: Ian Stewart, Erika Riano-Mojica, Bishop Warford, Franco Machado, Kiristen Hubbard, Maxine Abuelsamid, Sakinah Rahman, Zaki Rahman, Ziara Chestang, and Katheryne Messer.

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Abbreviations

A-START: AIDS-Science Track Award for Research Transition
GLMM: generalized linear mixed model
LMM: linear mixed model
mHealth: mobile health
RCT: randomized controlled trial
S4E: Storytelling 4 Empowerment
SFE: Storytelling for Empowerment
STI: sexually transmitted infection

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Protocol

Mobile Intervention to Address Cannabis Use Disorder Among Black Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: African American or Black (hereafter referred to as Black) adults who use cannabis use it more frequently and are more likely to meet criteria for cannabis use disorder (CUD) than both White and Hispanic or Latin individuals. Black adults may be more apt to use cannabis to cope with distress, which constitutes a false safety behavior (FSB; a behavior designed to reduce psychological distress in the short term). Although FSB engagement can perpetuate the cycle of high rates of CUD among Black individuals, limited work has applied an FSB elimination treatment approach to Black adults with CUD, and no previous work has evaluated FSB reduction or elimination in the context of a culturally tailored and highly accessible treatment developed for Black individuals.

Objective: This study aims to develop and pilot-test a culturally tailored adaptive intervention that integrates FSB reduction or elimination skills for cannabis reduction or cessation among Black adults with probable CUD (Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment [CT-MICART]).

Methods: Black adults with probable CUD (N=50) will complete a web-based screener, enrollment call, baseline assessment, 3 daily ecological momentary assessments (EMAs) for 6 weeks, and a follow-up self-report assessment and qualitative interview at 6 weeks after randomization. Participants will be randomized into 1 out of the 2 conditions after baseline assessment: (1) CT-MICART+EMAs for 6 weeks or (2) EMAs only for 6 weeks.

Results: The enrollment started in June 2023 and ended in November 2023. Data analysis will be completed in March 2024.

Conclusions: No culturally tailored, evidence-based treatment currently caters to the specific needs of Black individuals with CUD. This study will lay the foundation for a new approach to CUD treatment among Black adults that is easily accessible and has the potential to overcome barriers to treatment and reduce practitioner burden in order to support Black individuals who use cannabis with probable CUD.

Trial Registration: ClinicalTrials.gov NCT05566730; https://clinicaltrials.gov/study/NCT05566730

International Registered Report Identifier (IRRID): DERR1-10.2196/52776

(JMIR Res Protoc 2024;13:e52776) doi:10.2196/52776

KEYWORDS

cannabis use; false safety behaviors; mobile health, just-in-time adaptive interventions; Black or African American; mobile phone; African American; Black; cannabis; adults; adult; Hispanic; Latin; adaptive intervention; cannabis reduction; cessation; ecological momentary assessments

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Introduction

Cannabis has been among the most widely used substances for 30 consecutive years in the United States [1], and rates of past-year use have consistently increased in the general population [2,3]. Among individuals who use cannabis, African American or Black (hereafter referred to as Black) individuals exhibit more severe use patterns, including weekly use, and are more likely to meet diagnostic criteria for current cannabis use disorder (CUD) than both White and Hispanic or Latin individuals who use cannabis [4-6]. These data are alarming as CUD is associated with more severe psychosocial risk profiles relative to cannabis users without CUD and nonusers, including poly-substance use, psychiatric problems, and legal trouble [7]. Additionally, although Black individuals who use cannabis are more likely to report being ready to quit and making a recent quit attempt than both Hispanic or Latin and White individuals who use cannabis [8,9], this population is less likely to seek in-person treatment relative to White individuals who use cannabis. Specific individual (eg, beliefs about use) [10], community (eg, neighborhood attitudes about use) [11], and institutional (eg, health care access) [12] factors, as well as institutionalized racism and discrimination (eg, more likely to not be listened to by practitioners) [13], likely contribute to the reluctancy to seek traditional treatments among Black individuals with CUD. Given that treatment involvement has been shown to assist with cannabis use reduction and prolonged abstinence [14], addressing the lack of treatment engagement among this population is imperative to reduce the potential negative health and psychological effects of cannabis use among this group.

Psycho-sociocultural models of substance use posit that Black individuals may use cannabis and continue using it despite cannabis-related problems to manage psychological distress associated with minority-related stress and daily stressors [15-18]. Using cannabis to cope with such distress reflects a false safety behavior (FSB), or a behavior designed to reduce psychological distress in the short term but paradoxically maintains or even exacerbates distress in the long term [19,20]. FSB is more frequent among Black individuals compared to non-Hispanic or Latin White individuals and it is associated with more anxiety, depression, and suicidal thoughts and behaviors among Black individuals [21]. Thus, FSB is an important behavioral vulnerability factor associated with mental health problems among Black individuals. These findings are concerning as problematic cannabis use is higher among those with mental health problems [22], and mental health problems interfere with changing cannabis use [23]. Moreover, the majority of individuals who use cannabis tend to engage in additional FSBs such as avoidance and avoiding social situations when cannabis is unavailable [24], and FSBs may contribute to cannabis-related problems due to tendencies to engage in maladaptive attempts to regulate negative affect [25]. As such, FSB engagement can perpetuate the cycle of high rates of CUD among Black individuals who use cannabis and increase the risk for poor psychosocial outcomes and cannabis-related disparities [24,26,27].

Importantly, transdiagnostic treatments have been developed to eliminate FSBs to improve behavioral health outcomes. Specifically, cognitive-behavioral approaches to FSB elimination treatment that target the identification and elimination of FSBs have been designed and successfully used for use across various anxiety disorders [20]. Furthermore, recent work has explored the potential of FSB elimination integrated with motivation enhancement therapy combined with cognitive behavioral therapy (MET-CBT) to address the co-occurrence among anxiety and CUDs, Integrated Cannabis and Anxiety Reduction Treatment (ICART) [28-30]. In a pilot test of ICART, individuals with CUD were randomized to either in-person ICART or MET-CBT for CUD [28]. Although participants in both study groups reported decreased cannabis use and related problems, patients in the ICART condition were more likely to be abstinent posttreatment than those in the MET-CBT condition. Patients with more severe baseline cannabis use and use-related problems were especially likely to benefit from ICART [31]. These findings suggest that integrating FSB elimination with MET-CBT is at least as efficacious, if not more efficacious, as a gold-standard psychosocial CUD treatment (MET-CBT), especially for patients with more severe cannabis-related pathology.

Despite the potential for FSB reduction or elimination treatments to assist with cannabis use reduction or cessation among individuals with problematic use, this work has been limited by its in-person design and lack of cultural tailoring to Black adults. Indeed, given the cannabis-related and FSB disparities experienced by Black adults [16,21], it may be beneficial to evaluate FSB reduction or elimination integrated with cognitive behavioral therapy (CBT) for CUD in the context of a culturally tailored and highly accessible treatment (ie, a mobile health [mHealth] intervention delivered via a smartphone app) developed for this underserved group.

Extant literature has highlighted existing mHealth work for cannabis use and CUD [32], including mHealth interventions that have been culturally tailored to treat specific populations such as individuals with psychosis [33], as well as individuals with comorbid CUD and cigarette smoking [34]. However, no mHealth interventions for cannabis use and CUD currently target specific psycho-sociocultural factors related to cannabis use and use-related problems among Black individuals who use cannabis with probable CUD. We have therefore developed and are currently pilot-testing a culturally tailored intervention for Black adults with probable CUD through integrated FSB reduction or elimination with CBT for CUD (Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment [CT-MICART]) using an accessible, adaptable, and highly scalable smartphone app. The goal is to examine the effects of CT-MICART on cannabis use, coping motives for cannabis use, and FSB engagement. We hypothesize that participants who are randomized into the CT-MICART condition will report better cannabis outcomes and less FSB compared to those who are randomized into the control condition at the 6-week follow-up. Furthermore, we will examine app engagement indicators and review qualitative data for methods to improve app content.

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Methods

Ethical Considerations

All participants provided written informed consent signed electronically after reviewing consent documents with research staff. To protect participant privacy and confidentiality, all phone and Zoom (Zoom Video Communications) appointments are completed by trained research staff in a secure office. Additionally, participants are assigned an ID number that is used to identify their data throughout the study. Only trained research staff have access to the key that can match the participant data to the participant's name. The key is password-protected on a secure server housed at the University of Houston. Participants are compensated up to US $160 in Amazon electronic gift cards for participating in the study. The institutional review board (IRB) at the University of Houston approved the study (STUDY00003690).

Study Design

A total of 50 Black adults with probable CUD are being recruited through national advertisements across different social media and web-based platforms to participate in this study. Eligible participants are randomized into 1 out of the 2 conditions (ecological momentary assessment [EMA] only vs CT-MICART+EMA). All the participants who consented are asked to complete 3 prompted daily EMAs for 6 weeks. Only participants in the CT-MICART+EMA condition will receive intervention content. Participants are informed during the consent process that they have an equal chance of being assigned to each study condition. Moreover, participants are also informed that one of the study's treatment conditions consists of watching treatment videos and using CT-MICART app features, while the other condition consists only of completing daily EMAs. Following the 6-week intervention period, all participants will complete a follow-up assessment survey in the app and a qualitative interview phone call. See Figure 1 for the study flow.

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Figure 1. Study flowchart. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment; EMA: ecological momentary assessment.

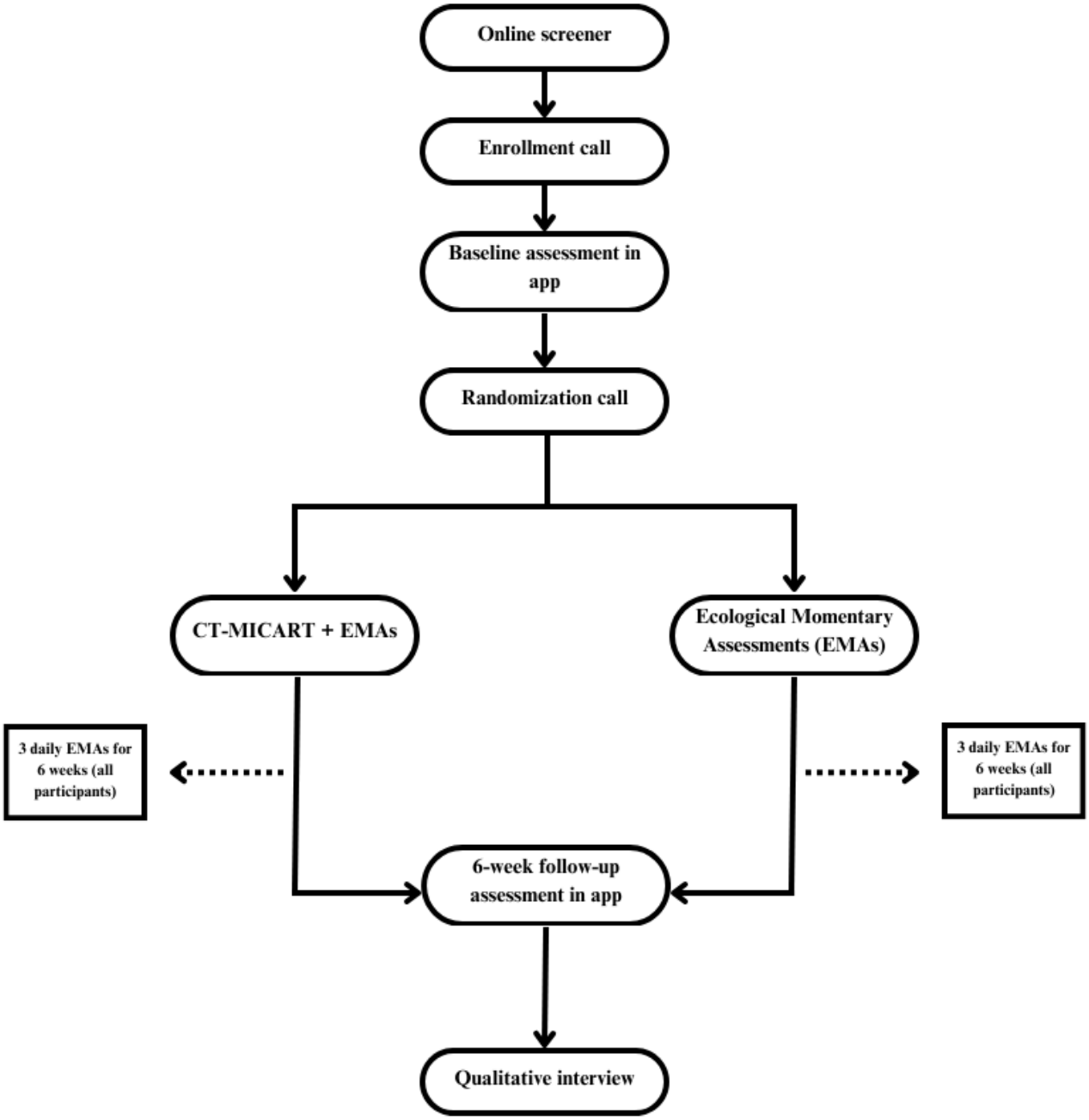

Participants

Participants will include 50 individuals who identify as Black with probable CUD. Participants must meet the following eligibility criteria to participate: (1) at least 18 years of age, (2) self-identify as Black or African American, (3) meet criteria for probable CUD (assessed via the Cannabis Use Disorder Identification Test-Revised [CUDIT-R] with a score of >12) [35], (4) motivated to reduce cannabis (>5 on a 10-point scale), (5) score ≥4 on the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) indicating higher than sixth-grade English reading level [36], (6) own an Android smartphone for EMA completion, and (7) report cannabis use to manage anxiety or stress in the past month. Exclusion criteria include (1) legal mandate of substance misuse treatment; (2) report of current or intended participation in a concurrent substance use treatment, including pharmacotherapy or psychotherapy for CUD not provided by the researchers; (3) ongoing psychotherapy of any duration directed specifically toward the treatment of anxiety or depression; (4) not being fluent in English; (5) pregnant or planning to become pregnant within the next 6 months (assessed via self-report); and (6) inability to provide a photo ID and valid address to verify identity.

Procedures

This study is funded by the National Institute on Minority Health and Health Disparities (U54MD015946) and is registered on

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ClinicalTrials.gov (NCT05566730). The IRB where the study takes place has reviewed and approved all procedures and study materials. Interested participants are asked to complete a web-based self-report screener survey via Qualtrics (Qualtrics International Inc). Those deemed eligible at the screener are then scheduled for an enrollment Zoom call of approximately 30 minutes. During the enrollment Zoom call, participants are given detailed information on the goals, purpose, and procedures of the study; provide informed consent; show their photo ID to the research team; and complete a literacy test to confirm they are at higher than sixth-grade English reading level [37]. Those found eligible during the enrollment Zoom call are asked to download the Insight smartphone app onto their personal smartphone and to complete the 30-minute baseline survey via the app. Eligible participants who complete the baseline survey are then contacted by research staff so they can be randomized into a study condition (ie, CT-MICART vs EMA only). During this randomization call, participants are oriented to app features for their assigned condition by the research team.

Following randomization, participants are prompted by the app to complete 3 EMAs daily. EMAs take approximately 2-3 minutes to complete. The research staff monitors the EMA completion rates of each participant on a weekly basis. When a participant's completion rate falls below 80%, a research staff member contacts the participant via text, phone, or email to remind them of the importance of completing their daily EMAs. Participants are informed that they can contact study staff at any point during the study by pressing the "Call Staff" button at the top of the app screen should they experience technical difficulties. Please see Figure 2 for a screenshot of the CT-MICART features available via the app home screen.

Figure 2. The main menu of CT-MICART features. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

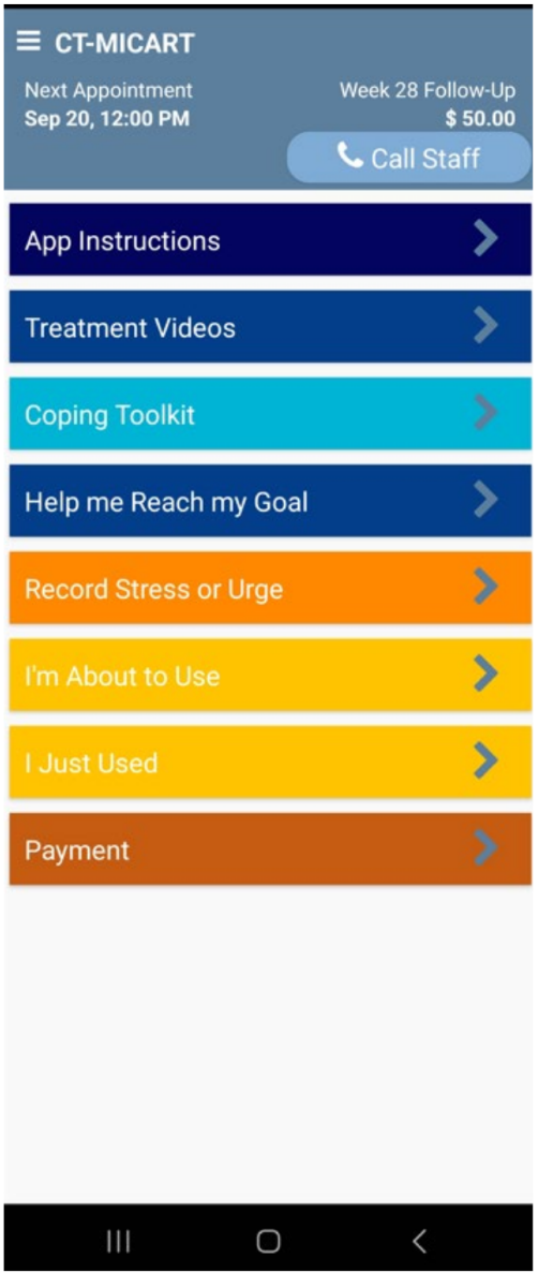

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All participants are also asked to complete a 6-week postrandomization assessment and a qualitative interview. Specifically, at the end of the 6-week EMA period, the follow-up assessment becomes available on the app home screen and takes approximately 30 minutes to complete. The qualitative interview is scheduled with a trained research staff member and focuses on the participant's experiences using the CT-MICART+EMA or EMA-only app features. Participants can earn up to US $160 in Amazon electronic gift cards for their participation. Specifically, eligible participants are compensated with a US $20 gift card for completing the baseline assessment and a US $50 gift card for completing the 6-week follow-up, including the qualitative interview. Ineligible participants are not being compensated for completing the brief baseline Zoom call. In addition to baseline and follow-up compensation, participants are compensated for their EMA completion based on their completion rate. Those who complete 50% to 70% of all EMA assessments during the 6-week study period will receive a US $30 gift card, those who complete 71% to 79% will receive a US $60 gift card, and those who complete 80% or more will receive a US $90 gift card. Thus, if a participant completes 80% or more of the assessment across the entire 6-week trial, they can earn up to US $160 in electronic gift cards across all assessments.

Intervention Conditions

Overview

All participants have access to a "Call Staff" button that enables participants to easily call the study team. In addition, all participants have access to an "App Instructions" button that provides detailed descriptions of each of the app functions. Finally, all participants are informed that they can click the "Payment" button to view an up-to-the-moment accounting of all EMAs prompted and completed and the current compensation based on EMA and assessment completion.

All participants are instructed to complete all smartphone assessments through Insight (TSET Health Promotion Research Center), an encrypted mobile app through which participants receive all study content. Encrypted data will be automatically password protected and saved to the University of Houston's and the University of Oklahoma Health Science Center's institutional server and will only be accessible to the IRB-approved research team members. Moreover, participants are informed during the consent process that they are responsible for any phone service costs related to the study.

Active Condition (CT-MICART+EMAs)

Overview

The CT-MICART+EMA condition consists of access to the CT-MICART content in the Insight app and 3 prompted daily EMAs. The morning EMA is delivered 30 minutes after the preset waking time, the lunch EMA is delivered at 12:15 PM, and the evening EMA is delivered 1 hour and 15 minutes before the participant's preset sleep time. The core components of the CT-MICART condition include FSB elimination training and CBT for CUD with culturally tailored content. The CT-MICART+EMA content includes (1) treatment on a "schedule" that is culturally adapted (ie, 12 different 3- to 5-minute treatment video files); (2) participant-driven, automated, individually tailored treatment messages (eg, tailored to each participant's daily goal of reducing cannabis use, abstaining from cannabis, or no daily goal); (3) "on demand" features (ie, Coping Toolkit and Help Me Reach My Goal); and (4) end-of-day FSB elimination training exercises.

Process to Culturally Adapt Treatment

We followed the Cultural Adaptation Process [38] model of treatment adaption to culturally tailor CT-MICART. All treatment videos include depictions of Black adults and accompanying audio is voiced by Black voice actors who worked closely with our research team. Moreover, all app content was reviewed by a diverse Community Research Advisory Board (CRAB) at the Health Research Institute at the University of Houston. The CRAB was consulted: they provided feedback during the app development process, and appropriate modifications were made based on their feedback.

Treatment on a Schedule

To provide automated intervention content that is tailored to each participant's current goals and delivered in a manner that is best matched to their schedule, the app asks participants if they would like to watch 1 of the 12 different 3- to 5-minute treatment videos (ie, 2 videos per week) over the 6-week intervention period. Scheduled video sessions are cued (ie, the phone rings and vibrates) at the scheduled time and every 15 minutes (up to 2 times) after the scheduled time until the participant acknowledges the cue. Participants have the option to delay or reschedule videos or watch them after the scheduled day or time (ie, the next unwatched video populates [in order] in the app after the previous video is viewed). Videos can be watched as many times as desired. The phone records the date or time when each video is watched (ie, both initiation and completion). The 12 brief (3-5 minutes) CT-MICART videos provide psychoeducation on (1) the nature of cannabis use and negative affect (eg, anxiety and stress) and the FSB model; (2) the emotional processing model of negative affect (and how it relates to cannabis) and cannabis-related coping strategies (eg, avoiding people, places, and things); (3) relations between FSB and racial discrimination, negative affect, and cannabis use; (4) cannabis (and other substance) use as an FSB and understanding cannabis use patterns; (5) countering phobias (ie, exposure to anxiety- and stress-provoking stimuli without engagement in FSB, including cannabis) and coping with cravings; (6) fading other FSBs (eg, checking, reassurance seeking, companions, and avoidance of bodily sensations) and managing thoughts related to cannabis use; (7) fading other FSBs (avoidance) and managing negative moods; (8) fading other FSBs (cognitive avoidance) and seemingly irrelevant decisions; (9) problem-solving; (10) managing social influences (refusal skills and assertiveness); (11) planning for emergencies and coping with lapse; and (12) preventing relapse.

Tailored and Real-Time Treatment Messages

Participants receive personally tailored messages that are based upon each day's cannabis cessation or reduction goal (ie, reduce cannabis use today, abstinent from cannabis today, or no cannabis use goal today). Thus, the app "meets participants where they are" and provides messages that is in line with their

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current goal. On days when the participant has no goal to reduce or abstain from cannabis, the app offers primarily "gain-framed" messages that aim to increase motivation for cannabis cessation or reduction. Importantly, the type of message that is delivered at the end of each EMA is recorded in the database so we may analyze the effect of messages on currently present cannabis use triggers.

On-Demand Features

Hundreds of unique messages were developed for this study to address various use risk triggers and to reduce repetition. Messages are consistent with MET-CBT approaches (including ICART) [31] and address identified cannabis use triggers. On-demand content is available through 2 buttons on the app home screen. First, the Coping Toolkit feature contains a menu of resources that become available once this button is pressed (see Figure 3), including Ways to Cope with Urges; Challenge Unhelpful Thoughts (see Figure 4 for a list of automatic thoughts that can be challenged via the app); I've Slipped, Now What?; How to Cope with Stress; Coping with Discrimination; Coping with others Using Marijuana; Motivate Me to Stay on Track; and Eliminate False Safety Behaviors (see Figure 5 for menu options). Second, the Help me Reach my Goal feature contains a menu of resources that also become available once this button is pressed (see Figure 6), including Benefits of Reducing or Quitting; Harms of Marijuana Use; Relaxation Exercises; Give Me Something to Do; and I'm Bored, Distract Me. Finally, all participants are instructed to click the "Record Stress or Urge," "I'm About to Use," and "I Just Used" buttons (see Figure 2) when appropriate. CT-MICART+EMA participants receive a tailored intervention message at the completion of each participant initiated EMAs.

Figure 3. Coping toolkit CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

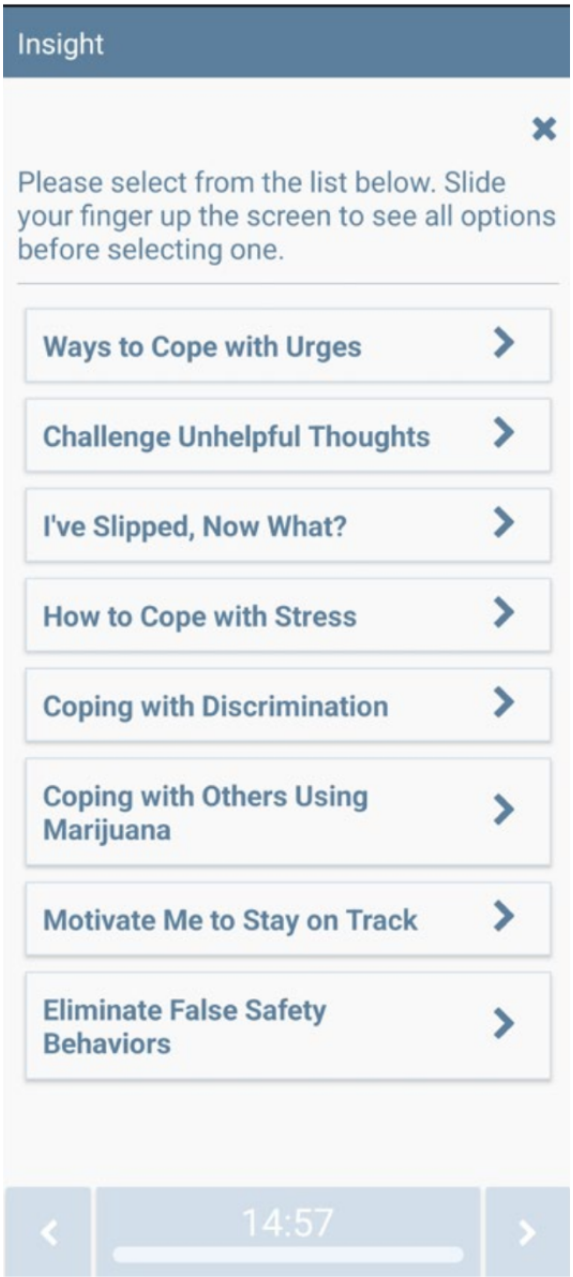

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Figure 4. Challenging unhelpful thoughts CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

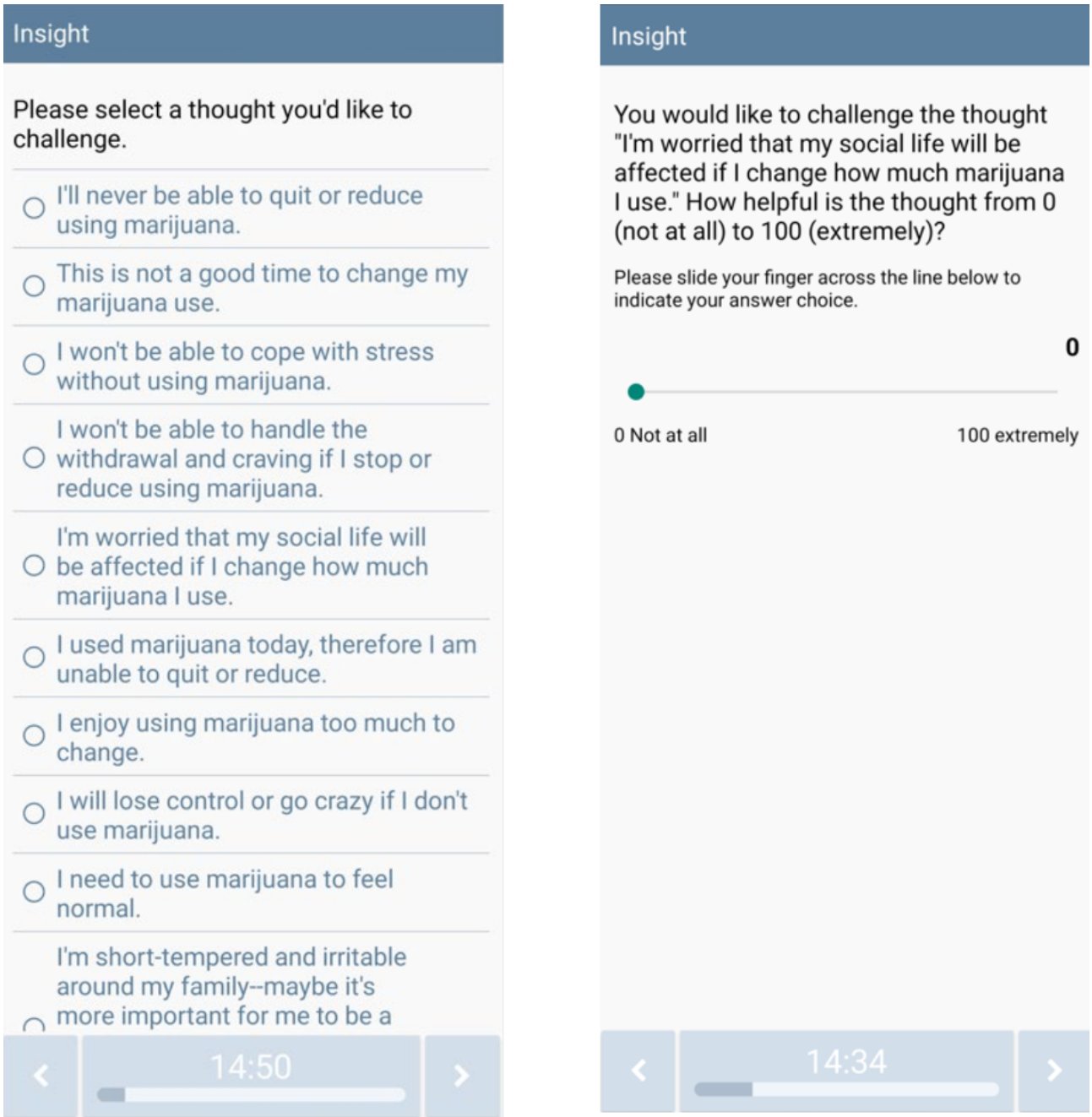

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Figure 5. False safety behavior elimination CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

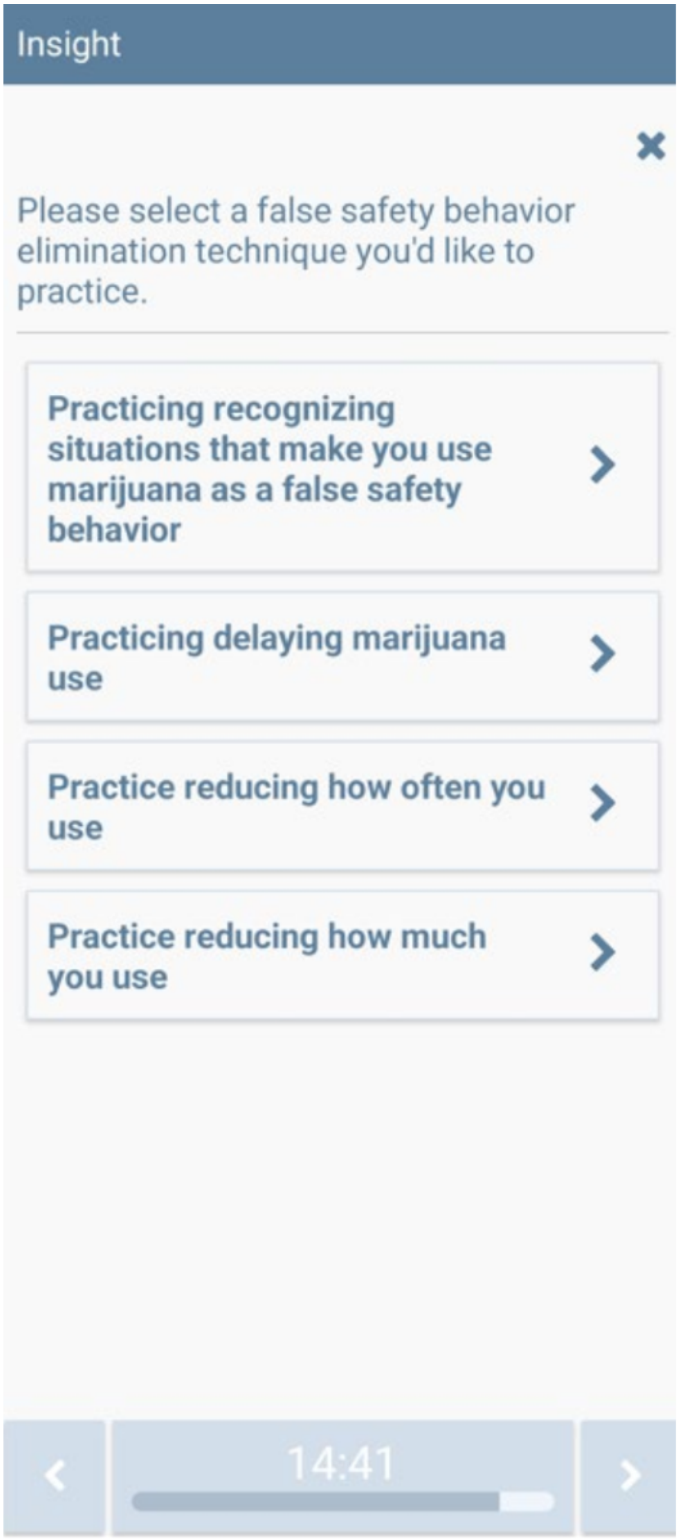

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Figure 6. Help me reach my Goal CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

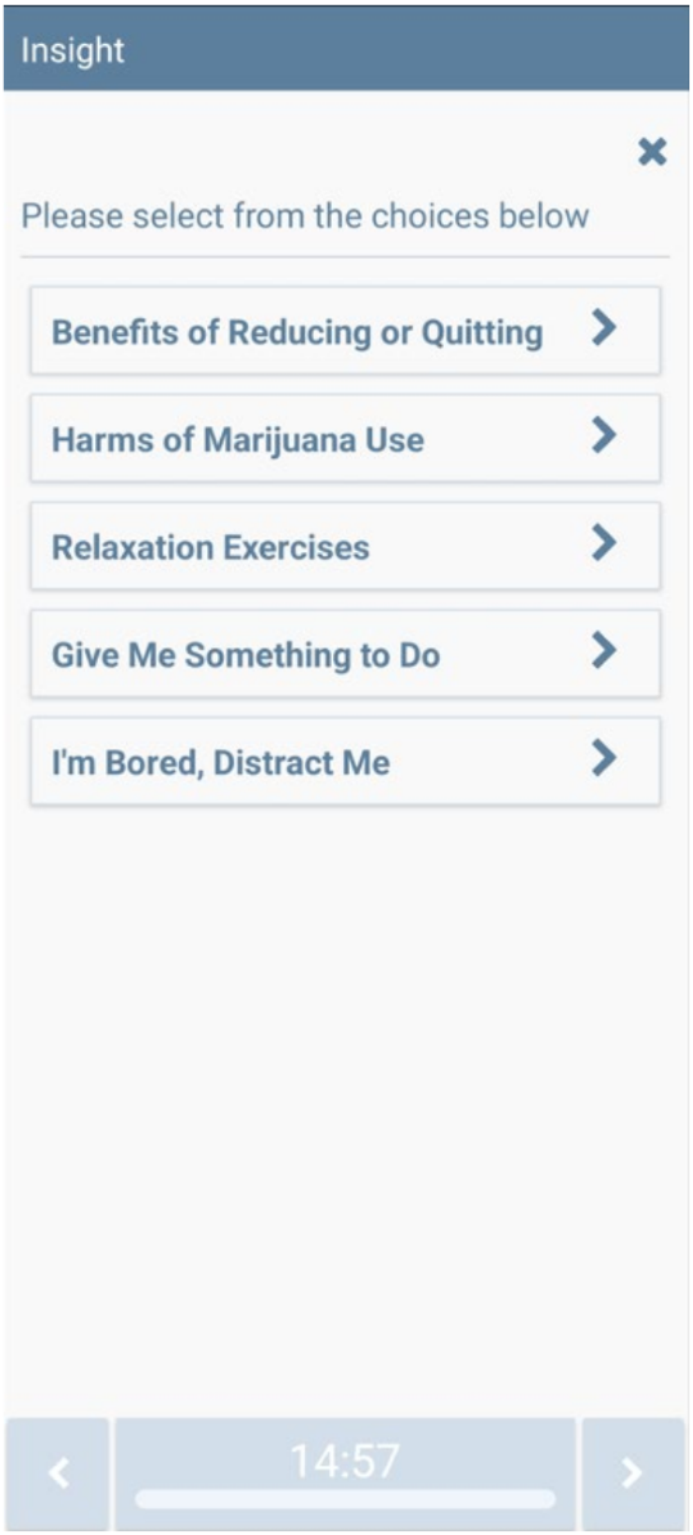

Control Condition (EMAs Only)

Participants randomized to EMA only condition receive the baseline, follow-up, qualitative interview, 3 prompted daily EMAs for 6 weeks, and they have access to the participant-initiated "Record Stress or Urge," "I'm About to Use," and "I Just Used" buttons. However, they do not receive tailored messages or access to the CT-MICART intervention content.

Assessments

Overview

See Table 1 for a schedule of data collection and measures list. All measures have been used among samples of Black adults.

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Table 1. Measures and schedule for data collection.

Measure name	Screener	Baseline	6-week follow-up	EMA[a] items
Demographics or background information	✓			Cannabis use assessment (outcomes)
Motivation to quit cannabis (eligibility)	✓			Alcohol consumption
REALM-SF[b] (eligibility)	✓			Motivation regarding cannabis use
CUDIT-R[c] (eligibility)	✓		✓	Watch treatment videos (CT-MICART[d] condition only)
Legal mandate status (eligibility)	✓			Cannabis use goal assessment (CT-MICART condition only)
Report of cannabis use to manage anxiety or stress in the past month (eligibility)	✓			Negative affect
Assessment of ongoing substance use treatment or anxiety and depression (eligibility)	✓			Confidence in reducing or quitting
Safety Aid Scale (outcome)		✓	✓	Urges or cravings
Qualitative interview (outcome)			✓	Social support and daily interactions
System Usability Scale (outcome)			✓	Coping motives for cannabis and consequences or benefits of using
Credibility or Expectancy questionnaire (outcome)		✓	✓	False safety behavior elimination engagement
Marijuana Motives Measure (outcome)		✓	✓	N/A[e]

[a]EMA: ecological momentary assessment.

[b]REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form.

[c]CUDIT-R: Cannabis Use Disorder Identification Test.

[d]CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

[e]N/A: not applicable.

Study Screening and Demographics Questionnaire

All participants are asked to answer questions related demographic characteristics during the Qualtrics screener (eg, race, ethnicity, age, sex, education, and marital status). In addition, participants answer questions related to previous substance use, discrimination experiences, acculturation, anxiety, depression, motivation to quit or reduce cannabis use (ie, “On a scale from 1 to 10 with 1 being ‘not at all motivated’ and 10 being ‘extremely motivated’ how motivated are you to reduce your marijuana use in the next month?”), legal status to engage in substance use treatment, use of cannabis in the past month to cope with anxiety or stress, and ongoing treatment of substance use, anxiety, or depression.

REALM-SF Assessment

The REALM-SF is designed to determine if participants have at least a sixth-grade literacy level through a 7-item assessment taken with the help of a research assistant [37]. The REALM-SF is used in this study by the research staff to determine if participants can read the EMA items and intervention content.

CUDIT-R Assessment

The CUDIT-R is an 8-item self-report measure designed to identify the likelihood of CUD [35]. The items are rated on a 5-point Likert-type scale where higher scores indicate a higher likelihood of CUD. Scores of 12 or greater indicate probable CUD and it is used as eligibility criteria for this study [35].

Safety Aid Scale

The Safety Aid Scale (SAS) is an 80-item measure that is designed to assess FSBs in participants [24]. Examples of items and FSBs include “Avoid being far from home” and “Fiddling with an object (eg, pen).” The items are rated based on how frequently participants endorse the behavior on a scale from 0 (never or rarely) to 4 (almost always). Items are summed to form a total score of FSB use. This measure has demonstrated excellent internal consistency among Black adults [21]. For this study, item reduction analysis was used to reduce the number of items to 22 [39].

Marijuana Motives Measure

The Marijuana Motives Measure (MMM) is a 25-item questionnaire that assesses 5 motives for cannabis use including enhancement, coping, social, conformity, and expansion regarding motives for, frequency of, and problems associated with cannabis use [40]. Items are rated on a 5-point Likert-type scale where 1=almost never or never, 2=some of the time, 3=half of the time, 4=most of the time, and 5=almost always or always.

System Usability Scale

The System Usability Scale (SUS) is a 10-item questionnaire that is used in this study to evaluate participants’ perceived usability of the app [41]. The SUS includes items related to app engagement, frequency of use, complexity of the app, and thoughts about using the app.

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Credibility or Expectancy Questionnaire

The Credibility or Expectancy Questionnaire (CEQ) is a 6-item measure that assesses treatment expectancy and rationale credibility [42]. It derives 2 predicted factors including cognitively based credibility and affectively based expectancy. In this study, it is used to gauge participants' thoughts on the credibility of the intervention and assessment content assigned to them (CT-MICART+EMA or EMA only), and their expectations regarding the intervention (ie, "How successful do you think this intervention will be in helping you quit or reduce marijuana?").

Daily EMAs

Throughout the 6-week intervention period, participants complete 3 daily EMAs occurring at specific times (one 30 minutes after self-selected wake time, one 60 minutes before the self-selected sleep time, and one at 12:15 PM). Items include questions about cannabis use, duration of being high, urges or cravings, motivation, and confidence to reduce or quit cannabis, negative affect, social support, and other substance use. Each EMA also gauges the CT-MICART+EMA participants' cannabis goal for the day (ie, wanting to avoid using cannabis today, reduce use today, or no cannabis use goal today). All participants are also instructed to access the app's on-demand assessment features, including the "Record Stress or Urge," "I'm About to Use," and "I just used" buttons, when they experience increased stress or an urge to use cannabis as well as anytime they think they might use or after actual cannabis use. Each time participants click these buttons, they are asked to complete a brief set of questions pertaining to their current situation.

Qualitative Interview

After completing the 6-week follow-up assessment in the app, study staff are notified via an encrypted email to contact the participant to complete the qualitative interview phone call. Participants are asked to assess their satisfaction with their assigned app content and ways it could be improved via a semistructured interview. This 30-minute interview assesses participant engagement with the app, and specific thoughts about app features including EMA items, intervention content, and why they did or did not use certain features.

Data Analysis

General Overview

Given this pilot study is likely underpowered to detect statistical significance, conclusions will primarily be based on effect sizes and associated Cis, which will be used to guide future, larger, and fully powered trials of comparative efficacy. Prior to data analysis, we will assess the equivalence of groups on key baseline variables. Variables on which the groups differ will be used as covariates in the final analyses.

Hypothesis Testing

Overview

We will examine treatment effects on cannabis use (derived from EMA data) using multilevel models. We will focus on two cannabis use outcomes: (1) use on a given day and (2) frequency of use within a given day. We will account for baseline covariates and time since the start of the intervention. We will also use appropriate random effects and residual constraints. For coping motives for cannabis and FSB engagement, we will conduct a linear regression analysis wherein we will regress treatment condition on each outcome assessed at the 6-week follow-up while adjusting for baseline scores of the specific outcome and baseline covariates. Triangulation mixed methods quantitative or qualitative data analysis [43] will be used to evaluate quantitative and qualitative data.

Quantitative Data

The app's feasibility and use will be examined by quantifying the use of CT-MICART features (eg, the number of assigned videos that are watched) and by evaluating participant opinions about the helpfulness of CT-MICART features (eg, treatment videos, automated treatment messages that follow EMAs, and exercises). Quantitative data analysis will focus on (1) behavioral markers of engagement with the app; (2) overall evaluations of the app and evaluations of each app feature, including usefulness or helpfulness and likelihood to recommend the app to a friend; and (3) data from the CEQ and SUS [44-46]. Data will be compared across conditions.

Qualitative Data

The week 6 qualitative interviews will prompt information on what participants liked about CT-MICART, how it could be improved, and what barriers currently limit app engagement. Individual interviews will be transcribed following the completion of participant treatment and then reviewed by the research team to ensure data quality. Transcribed interviews will be coded using NVivo (version 12; Lumivero), and decisions regarding the appropriateness of suggested changes to potential future versions of CT-MICART will be evaluated using a team-based approach. Consistent with the systematic and reflexive interviewing and reporting method [47], this approach will help to systematically organize collected qualitative data and thus guide improvements to CT-MICART. Moreover, content analysis will be used to analyze collected qualitative data [48]. Participant responses will be integrated with quantitative usage data to identify inconsistencies in the participant's perceptions and actual engagement with the app [49,50].

Missing Data

Some participant attrition is anticipated to happen during this study. We will assume a missing-at-random mechanism if missing data occurs. This will allow us to increase statistical power and provide more accurate estimates of model parameters and standard errors, as they are the recommended intent-to-treat approach for clinical trials. We will compare this approach and the intent-to-treat approach as a sensitivity check of the influence of missing data on the statistical conclusion.

Results

This study's enrollment started in June 2023 and ended in November 2023. The estimated study completion date is March 2024.

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Discussion

Principal Findings

Black adults evince significant cannabis-related health disparities compared with non-Black populations [13,15,51]. Thus, the primary goal of this study is to develop and pilot-test a culturally adapted mobile app for Black adults with probable CUD to help mitigate these disparities. We have culturally tailored this mobile intervention following the Cultural Accommodation Model [38], incorporating knowledge from the current research team, published literature, expert opinion, and feedback from the CRAB. As a next step, we seek to obtain data on the initial efficacy and qualitative evaluation of the app with the target population (ie, Black adults with probable CUD). To our knowledge, this is the first culturally tailored mHealth intervention to integrate FSB and CBT for CUD for Black adults with a probable CUD. We hypothesize that the culturally tailored mobile app CT-MICART will lead to reduced cannabis use and related problems and reduce the use of FSBs.

Though extant literature has highlighted existing mHealth work for cannabis use and CUD [32], including mHealth interventions tailored to treat specific populations (ie, individuals with psychosis and comorbid substance use) [33,34], this study is the first to target specific psycho-sociocultural factors related to cannabis use and use-related problems among Black cannabis users through a mobile intervention. Should the CT-MICART app prove efficacious in reducing cannabis use, it will provide health care officials and researchers a unique opportunity to further refine and provide low-cost and easily accessible treatment for a historically underrepresented and underserved population. The success of the CT-MICART app would also provide the foundation to further refine and culturally inform better implementation of the app through qualitative interviews of all participants. Overall, the CT-MICART app and its development provide the potential to address the dearth of literature that exists for mobile health development and Black individuals who use cannabis.

Limitations

This study has several limitations which warrant comment. First, this pilot randomized controlled trial (RCT) will only offer intervention content and collect data for 6 weeks. As such, future research should examine the efficacy of similar but longer-term interventions. Second, as the study will only enroll participants that are motivated to quit or reduce their cannabis use, future work should determine if participants who are not currently motivated to quit or reduce their cannabis use can benefit from this type of culturally tailored cannabis cessation or reduction app. Third, only Android smartphone users will be enrolled in this study due to the limitations of the Insight smartphone platform. Future studies will use the updated Insight platform that works on Apple and Android smartphones. Additionally, it is possible that the EMA-only condition will have potentially therapeutic benefits to participants due to self-monitoring of behaviors, although EMA studies on substance use have found such effects to be limited [52-54]. Thus, a waitlist control should be included in future study designs to isolate the effect of CT-MICART beyond the potential influence of behavior monitoring or tracking behavior. Finally, although the sample size will be adequate to achieve study aims or hypotheses, future fully powered studies will be needed to test intervention efficacy and effectiveness.

Conclusions

This study will address a significant gap in the literature. Specifically, this pilot RCT will offer initial insights on the use of an mHealth intervention that is tailored for Black individuals who use cannabis. Smartphone interventions similar to CT-MICART have incredible potential to provide low-cost, scalable treatments to diverse populations. Moreover, the CT-MICART app has the potential to help Black individuals who use cannabis achieve and maintain higher rates of cessation and reduction and help narrow health disparities that have negatively impacted this underserved population.

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Data Availability

The data sets generated and analyzed during this study are not yet publicly available given that data analysis in currently in progress but will be available from the corresponding author on reasonable request.

Conflicts of Interest

MB is the primary inventor of the Insight mobile health platform, which was used in this study. He receives royalties related to its use. EO is the founder and sole owner of HEALTH Equity Empowerment, LLC.

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Abbreviations

CBT: cognitive behavioral therapy
CEQ: Credibility or Expectancy Questionnaire
CRAB: Community Research Advisory Board
CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment
CUD: cannabis use disorder
CUDIT-R: Cannabis Use Disorder Identification Test-Revised
EMA: ecological momentary assessment
FSB: false safety behavior
ICART: Integrated Cannabis and Anxiety Reduction Treatment
IRB: institutional review board
MET-CBT: motivation enhancement therapy combined with cognitive behavioral therapy
mHealth: mobile health
MMM: Marijuana Motives Measure
RCT: randomized controlled trial
REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form
SAS: Safety Aid Scale
SUS: System Usability Scale

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Protocol

Family-Based WhatsApp Intervention to Promote Healthy Eating Behaviors Among Amazonian School Children: Protocol for a Randomized Controlled Trial

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Abstract

Background: Stunting and micronutrient deficiencies have persistently affected children in the Brazilian Amazon for decades. However, in recent years, a notable increase in childhood overweight prevalence has been observed, particularly in the context of heightened food insecurity exacerbated by the COVID-19 pandemic. Despite the limited number of effective solutions proposed to tackle this problem, digital interventions have shown great promise worldwide in preventing obesity and promoting healthy diets.

Objective: This study aims to describe the protocol of a family-based WhatsApp intervention, specifically designed to investigate the efficacy of multimedia messaging in preventing excessive weight gain and improving healthy eating practices among school-aged children in the Amazon region.

Methods: This study protocol outlines a theory-driven randomized controlled trial based on the cognitive theory of multimedia learning and the social cognitive theory. A total of 240 parents or caregivers of children enrolled in the Maternal and Child Health and Nutrition Cohort Study in Acre (MINA-Brazil) will be recruited by phone and social media. The intervention group will receive persuasive multimedia messages through WhatsApp over 19 weeks, while the waitlist control group will remain in the usual care. The primary outcome is a change in children's BMI in *z* score. Secondary outcomes are changes in dietary intake and biochemical indicators of the children. Outcome measures will be assessed at baseline and 5 months after randomization in comparison to usual care. The analysis will use an intent-to-treat approach and will be conducted using the statistical package Stata (version 18.0), with a significance level set at $P<.05$. Paired and unpaired 2-tailed *t* tests will be applied to compare mean changes in the outcomes.

Results: Data collection started in June 2023, and final measurements are scheduled to be completed in December 2023. The results of the main analysis are expected to be available in 2024.

Conclusions: This innovative multimedia message intervention holds significant potential for fostering behavioral changes among Amazonian children.

Trial Registration: Brazilian Clinical Trials Registry RBR-5zdnw6t; https://ensaiosclinicos.gov.br/rg/RBR-5zdnw6t

International Registered Report Identifier (IRRID): DERR1-10.2196/54446

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KEYWORDS

child health; Amazon; dietary intake; mHealth; mobile health; multimedia messaging service; WhatsApp

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Introduction

In recent decades, childhood obesity has emerged as a global epidemic [1]. According to the World Health Organization (WHO), more than 340 million children were overweight or obese in 2016 [2]. In addition, with the emergence of the COVID-19 pandemic in 2019, the situation has been aggravated due to school closures, physical inactivity, dietary changes, and mental health disorders [3].

In Brazil, according to the latest national school anthropometric survey, in 2009, 1 out of 3 children were overweight [4]. However, it is expected that due to the COVID-19 crisis and the absence of national child anthropometric surveys for 15 years, the current prevalence of childhood overweight has likely worsened [5,6]. In this context, the Brazilian Amazon was one of the most affected regions in the country due to its remote location and lack of specialized health assistance [5,7]. Recent studies revealed that approximately 70% of the northern population experience food insecurity [8]. Additionally, 20% experience severe food insecurity, wherein individuals feel hungry but do not have funds to buy food, have only 1 meal a day, or endure entire days without any meals [8].

In this scenario, considering the Brazilian economic crisis paired with the neglected fast growth of the ultraprocessed food (UPF) industry, access to fresh food has become challenging, while UPF has become ubiquitous in most food markets [9,10]. UPF are formulations produced exclusively by the food industry through processing techniques that damage the food matrix (eg, extrusion, refining, and prefrying). Additionally, UPFs are frequently high in calories, harmful fats, sugar, and artificial additives [11]. Many studies in the literature have shown that the consumption of UPF may increase the risk of morbidity and early mortality [12]. Therefore, UPF's high availability and consumption are significantly endorsing a substantial change in Western Brazilian Amazon food patterns, which has placed overweight and obesity as an important public health problem due to the historical rates of stunting and micronutrient deficiencies in the region [13-15]. Although some studies have called attention to the urgent need for early interventions to prevent childhood obesity in the Amazon region, few effective solutions have been proposed to tackle this problem so far [16,17].

Along these lines, digital interventions focused on promoting weight loss and healthy eating behaviors have shown promising results, especially mobile phone interventions (mobile health [mHealth]) [18,19]. MHealth interventions are innovative and have countless advantages. First, it increases the contact between health care professionals and people living in remote areas, such as the Amazon region [20]. Second, it is a low-cost, easy-to-use, and alternative tool that is already widely incorporated into society. Lastly, these interventions can be developed on a large scale, benefiting people in a wide region. Although Amazon is considered a location of poverty and of great inaccessibility, about 80% of the population has access to the internet, and 8 out of 10 adults have a cell phone [21,22].

In this context, multimedia messages have spread rapidly in society in recent years. Since it includes both textual and visual resources, it provides efficient learning due to its greater ability to establish itself in the brain's long-term memory; therefore, it demonstrates great potential to generate changes in health behaviors, especially in populations with low educational levels [23-26]. As far as we know, no studies have evaluated the effects of multimedia messages on children's health behaviors; however, there is plenty of evidence indicating the extensive potential of multimedia resources. Randomized controlled trials based on soap operas, video games, and websites as multimedia components have reported a significant increase in fruit and vegetable consumption and a decrease in sugary drinks and sweets consumption [27-33].

Also, a recent systematic review and meta-analysis showed that childhood obesity risk is significantly influenced by parental weight status [34]. Thus, parent-focused interventions are an important key to promoting efficient and lasting changes in children's eating behaviors. Family-based interventions focusing on children who are overweight that used SMS text messaging lead to a significant reduction in children's adiposity and BMI [35]. Additionally, healthy eating patterns were improved among all family members [36]. These findings support the hypothesis that family-based multimedia messaging interventions have great potential to promote behavioral changes in children.

This study protocol will be the first to assess the effect of mHealth on dietary practices and anthropometric measurements of Amazonian children. We aim to develop a parenting-focused, mobile-based intervention through multimedia messaging to promote healthy eating habits and prevent obesity among Amazonian children. We also intend to support and provide high-quality evidence to guide future public policy regarding childhood obesity, food insecurity, and sustainable food systems.

Methods

Study Aim

The general aim of this study is to evaluate the efficacy of a parent-focused mHealth intervention to change dietary practices and prevent excessive weight gain among school-aged children from the Maternal and Child Health and Nutrition Cohort Study in Acre (MINA-Brazil). Therefore, we hypothesize that children whose parents or caregivers receive nutrition-related multimedia messages will have improvements in BMI in *z* score (BMIz), dietary food intake, and biochemical data.

Overview and Trial Design

This trial will be a parallel randomized controlled trial nested in MINA-Brazil, the first population-based birth cohort based in Cruzeiro do Sul, Acre State, in the Western Brazilian Amazon. The cohort was designed to investigate the determinants of maternal and child health and have as participants children born at the Hospital Estadual da Mulher e da Criança do Jurua, in Cruzeiro do Sul, in the period between July 2015 and June 2016. Participants have been followed up for 5 years, and the last evaluation of health status took place in 2021. This protocol was prospectively registered in the Brazilian Clinical Trials Registry (RBR-5zdnw6t; date of registration: March 30, 2023; UTN code: U1111-1289-0560) and has been described according to the CONSORT-EHEALTH

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checklist (version 1.6.1; Multimedia Appendix 1 [37-47]) [48]. Table 1 shows the timeline of the study activities according to the intervention stage:

Table 1. Timeline of the study activities according to intervention stages.

Stage of intervention	Recruitment	Baseline	Intervention period	Postintervention
Verbal consent for screening	✓			
Eligibility screening verification	✓			
Study invitation	✓			
Face-to-face individual interview		✓		
Written consent from parents and written assent from children		✓		
Sociodemographic and participant information collection		✓		
Anthropometric measures		✓		✓
Food frequency questionnaire administration		✓		✓
Biochemical data collection		✓		✓
Strengths and Difficulties Questionnaire administration		✓		✓
Short version of the Brazilian Food Insecurity Scale administration		✓		✓
Delivery of an educational booklet		✓		
Goals setting for intervention group			✓	
Multimedia messaging for a 19-week follow-up			✓	
Phone call at 1 week to check if caregivers are properly receiving the messages			✓	
Goal achievement assessment for intervention group				✓
Delivery of same intervention to waitlist control group.				✓

Study Population and Setting

We will recruit 300 parents or caregivers of children enrolled in the MINA-Brazil birth cohort (Figure 1). They will be contacted by phone calls made from the Laboratory of Telephone Interviews of the Faculty of Public Health of the University of Sao Paulo. Family phone numbers will be assessed from the MINA-Brazil study database. Trained interviewers will make the calls at different times of the day to maximize the chance of contact with parents or caregivers. Additionally, MINA-Brazil's social media (ie, Facebook and Instagram) will be used to contact families who have changed their phone numbers but have not updated this information in their records. At this first contact, eligibility criteria will be assessed; then, the study's aim will be explained, and the parent or caregiver will be invited to be part of the study. Following this, a face-to-face meeting will be scheduled at a health care center in Cruzeiro do Sul with children and parents or caregivers to collect the consent forms and conduct the initial interview.

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Figure 1. Study flowchart. BMIz: BMI in *z* score; MINA-Brazil: Maternal and Child Health and Nutrition Cohort Study in Acre; MMS: Multimedia Message Service.

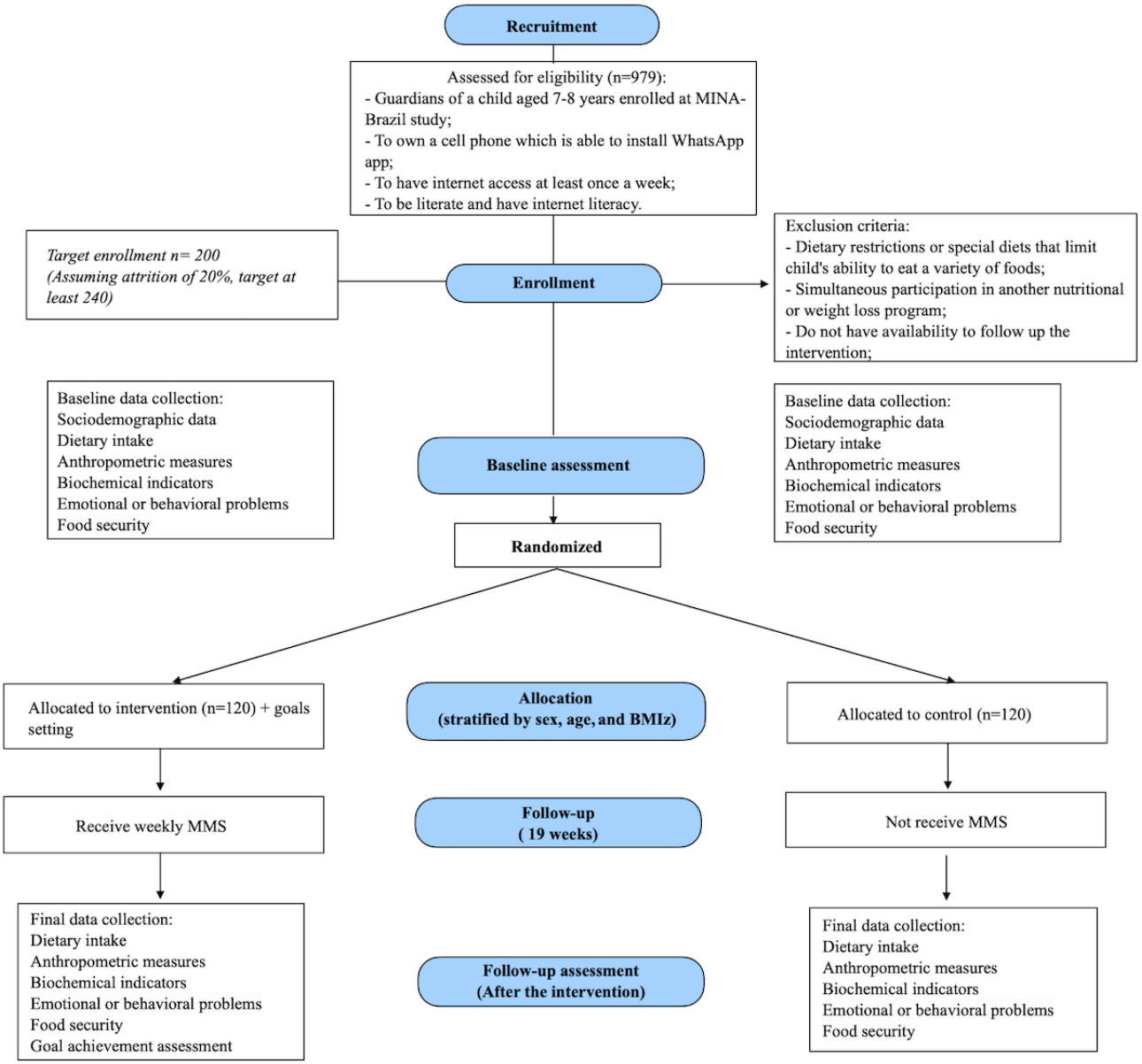

Inclusion criteria for the study include (1) being a guardian of a child aged between 7 and 8 years enrolled in MINA-Brazil, (2) owning a cell phone that can install the WhatsApp app, (3) having internet access at least once a week, and (4) being literate and having internet literacy.

Exclusion criteria include (1) dietary restrictions or special diets that limit a child's ability to eat a variety of foods (eg, children on treatment for any disease that requires a specific diet), (2) simultaneous participation in another nutritional or weight loss program, and (3) not having the availability to follow up on the intervention for the whole period between baseline and final data collection (eg, intending to move out of town).

Power and Sample Size Calculation

The sample size estimation used the expected effect size (E) of at least 10% change for the mean value of BMIz as the main outcome (*z* score=1.5) and SD of 3.5 in a 2-tailed distribution, considering a *P* value of .05, statistical power of 80% (β=20%), and sample size ratio (group 1/group 2) of 1:1. Thus, for the expected E/SD ratio, the minimum sample required must be 100 participants per group [49]. However, assuming a dropout rate and potential losses of 20% during the intervention period, the sample size to be enrolled at baseline will be at least 120 children per study group [49].

Ethical Considerations

The MINA-Brazil birth cohort was approved by the Ethics Committee in Research with Human Beings of the School of Public Health of the University of São Paulo (protocols 872,613 of November 13, 2014, and 872,613 of October 30, 2017). For this trial, a new protocol was submitted and approved by the same Ethics Committee in Research with Human Beings (protocol 5,805,325 of December 9, 2022). Before taking part in the study, consent forms will be collected from parents or caregivers, and assent forms will be collected from children to guarantee the voluntary nature of participation. Additionally, participants will be informed of the minimal anticipated harms

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of the intervention, such as the possibility of discomfort related to interviews with personal questions and venous blood collection, which will involve trained professionals and disposable materials. All participants will receive appropriate information on what to do if they wish to withdraw from the intervention at any time.

Baseline Information and Randomization

Face-to-face individual data collection meetings will take place before the beginning of the intervention to explain the study to parents or caregivers and schedule fasting blood collection at a local laboratory. After recruitment and data collection, participants will be randomly assigned to each experimental group using the R software (R Foundation for Statistical Computing), according to children's sex, age, and BMIz quartile intervals. Additionally, the stratified sortition will consider parents' or caregivers' schooling in years (≤9, 10-12, or ≥13) and wealth index quartiles.

Blinding

Given the nature of the intervention, we cannot guarantee participants will be blinded. However, study participants will not be aware of which group they will be assigned to. All participants will be informed that they will take part in a nutritional program; however, some children will receive the intervention before others. Furthermore, this strategy aims to minimize the chances of contamination bias due to information exchange between participants in the control and intervention groups. Researchers will be aware of participants' allocation, but all analyses will be blind to allocation.

Theoretical Basis

This intervention is grounded in the cognitive theory of multimedia learning (CTML) [50]. The CTML guides the development of efficient multimedia materials and how to implement effective cognitive strategies to amplify learning and promote deep understanding [50]. According to Mayer [50], the use of a dual learning channel activates the verbal and pictorial models of working memory. This activation allows readers to mentally connect visual and textual representations [50,51]. However, to promote effective learning, that is, to reach the individual's long-term memory, the information provided to the reader must be integrated into the working memory in a process called active processing (Figure 2 [50]). To trigger active processing, it is necessary for readers to form a mental representation connecting new knowledge to preexisting knowledge. In this way, readers will be able to make inferences regarding the combination of these contents to establish the understanding itself. Inferences are a central part of the understanding process, and the more inferences individuals make, the greater their active processing [52]. Furthermore, it is important to consider that working memory has a limited capacity. Thus, readers should not be overwhelmed with a large number of new concepts all at once. Therefore, for effective processing of information, the multimedia content should have as few words as possible and reinforce previously discussed concepts [50,52].

Also, social cognitive theory (SCT) was adopted as one of the foundations in the conception of the intervention. This theory claims that the behaviors of individuals are influenced by personal characteristics and the environment around them [53]. Thus, Bandura [53] argues that behavioral changes in health can be more effective if they strengthen individuals' knowledge on the subject, improve environmental factors such as social support, encourage self-efficacy, and, lastly, develop the use of self-regulatory behaviors through modeling of behaviors. Figure 3 shows the framework of the intervention, presenting how multimedia messages will operate to change children's behavior based on both CTML and SCT.

Figure 2. Multimedia information processing system according to the cognitive theory of multimedia learning.

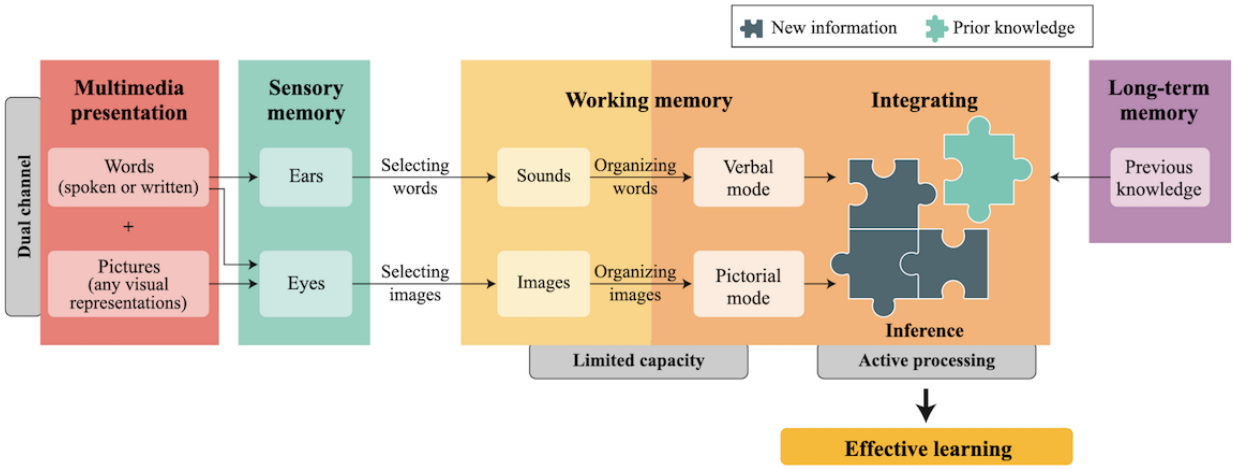

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Figure 3. The framework of the intervention.

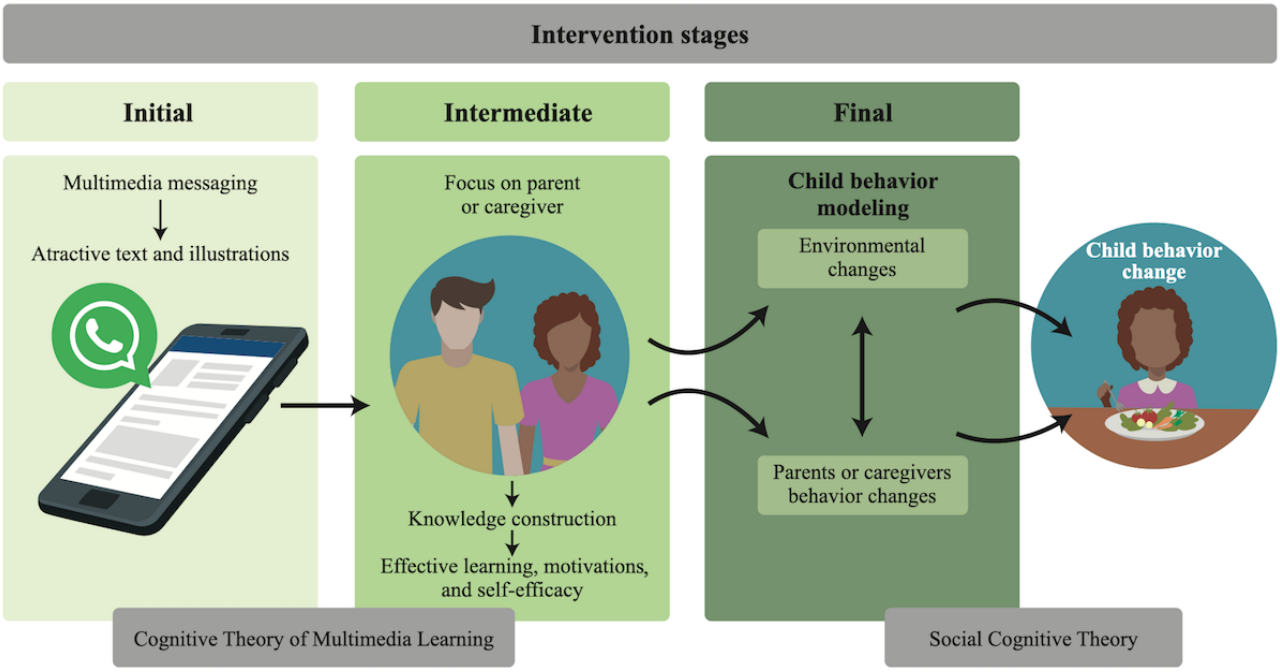

Intervention Plan

Participants allocated to the intervention group will receive individual multimedia messages 3 times a week for 19 weeks [54]. The message-sending system will be programmed using the Python programming language [55]. For individual goal-setting, parent-child or caregiver-child dyad will choose 2 specific, measurable, attainable, realistic, and timely (SMART) goals to focus on during the intervention according to their specific needs [56]. The goals will be chosen according to a preestablished list that will be defined by the topics of the messages that will be sent to parents or caregivers [56,57]. In addition, participants will receive an educational booklet about recommended dietary practices based on the food guide for the Brazilian population [58]. One week after the intervention commences, parents or caregivers will be contacted by phone calls to verify if they are appropriately receiving the messages.

Multimedia Message Content

To elaborate on the textual component of multimedia messages, the following 2 materials will be used as a guide: (1) the food guide for the Brazilian population [58] and (2) the protocol for the use of the food guide for the Brazilian population in the food guidance of children aged between 2 and 10 years [59]. Additionally, to assess the study population's dietary practices, previous results from a 24-hour Dietary Recall and Food Frequency Questionnaire applied to the target population were screened. While structuring the messages, behavior change techniques and persuasive writing strategies were used. Messages were structured according to 5 main topics related to the intervention objective: (1) increase fresh foods consumption, (2) reduce UPF consumption, (3) reduce culinary ingredients consumption (eg, excessive use of salt, sugar, and deep-frying practice), (4) encourage culinary practices, and (5) promote commensality and a healthy relationship with food. For the design of illustrations, we will adopt simple, precise, and easily recognizable images. In addition, persuasive techniques of color combination, typography, and cultural components, among others, will be applied [50,52].

Cross-Cultural Adaptation

To ensure the cultural appropriateness of the messages for the target population, the text component will undergo a 2-step cross-cultural adaptation [60]. The first step will include an expert committee of health professionals with experience in care or research in the Amazon region. In the second step, children's guardians will be invited to participate in formative research to assess the understanding and relevance of the elaborated messages. The formative research will be conducted through a telephone interview using a semistructured questionnaire with 4 exploratory questions for each SMS text message [61]. Then, the answers will be analyzed by 2 researchers, and the necessary adjustments will be made. Parents or caregivers involved in this phase will not be included in the intervention study.

Control Group

The control group will consist of children from the same population as the intervention group to ensure that both groups share similar characteristics, thereby guaranteeing accurate results for the intervention. In this context, the control group will not receive any messages during the intervention period. However, participants allocated to this group will be informed that they are on a waiting list and that the intervention will be carried out in stages, where children will receive the intervention at different times. After the end of the intervention period, the control group will receive the same treatment as the intervention group [35].

Outcome Measures

Participants in both groups will have the following data collected at baseline and immediately post intervention. The data obtained will be compiled onto tablets or computers with the Census and

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Survey Processing System (CSPro) program (US Census Bureau and ICF Macro).

Primary Outcome (BMIz)

Children in both experimental groups will have their weight and height measured by trained study researchers according to the parameters established by the WHO [62]. BMIz and children's anthropometric indices, weight for age and height for age, will be assessed through WHO Anthro-Plus software and will be interpreted as recommended by the WHO [63]. In addition, children's waist circumference (WC) will be measured according to WHO recommendations [64]. Since no WC cutoff points were found in the literature for Brazilian children, to evaluate WC, we will consider that children with WC values above the 90th percentile of the sample have excessive abdominal fat [65,66]. The waist-to-height ratio will also be calculated, in which values above 0.5 will be considered to correspond to the presence of excessive abdominal fat [65,67].

Secondary Outcomes

Dietary Habits

In natural and minimally processed food (fruits, vegetables, grains, tubercles, and cereals) and UPF (chocolate powder, artificial and soft drinks, industrial bread, sweet-filled biscuits, salty crackers, deli products, pre-prepared frozen foods, instant noodles, sweets, and candies, among others), consumption will be assessed through a 1-month validated food frequency questionnaire for Amazonian schoolchildren [68]. Data will be collected by a trained nutritionist, and the frequency of food consumption will comprise the following 8 categories: rarely, 1-3 times a month, 1-3 times a week, 1 time a day, 2-3 times a day, 4-6 times a day, and more than 6 times a day.

Biochemical Indicators

Fasting blood collection will be performed by venipuncture to determine the lipid profile (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and very–low-density lipoprotein cholesterol), insulinemia, and blood glucose in a local clinical analysis laboratory with automated procedures. The lipid profile of the children will be interpreted according to the Brazilian Society of Cardiology, in which values <150 mg/dL for LDL and >45 mg/dL for HDL will be considered acceptable [69]. Blood glucose will be interpreted according to the Brazilian Society of Pediatrics, which establishes adequate values when <100 mg/dL [70]. Additionally, blood glucose and insulinemia will be used to assess peripheral insulin resistance through the Homeostasis Assessment Model-Insulin Resistance Index [71]. Results above the 90th percentile of the sample will indicate the presence of insulin resistance [71].

Other Measures

Sociodemographic and Participant Information

At baseline, only children's sex, age, and who is their primary caregiver will be assessed. For caregivers, the level of education and wealth index will be measured.

Emotional or Behavioral Problems

To screen 'children's mental health problems, the Strengths and Difficulties Questionnaire (SDQ) will be completed by the children's parents or caregivers [72]. SQD has 25 items divided between 5 scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior [72]. Total difficulty score will be calculated from the summary of the scale results (except prosocial behavior), and the final score will be classified into 3 categories: normal (0-13), borderline (14-16), and abnormal (17-40). For the assessment of prosocial behavior, a higher score will indicate better performance on this scale.

Food Security

To assess the food security of the study population, the short version of the Brazilian Food Insecurity Scale [73], with 5 questions, will be used. Study participants will be classified as food secure (0 points) or food insecure (>0 points) [73].

Data Analysis

The analysis will use an intent-to-treat approach to test the efficacy of the intervention. Tablets programmed with CSPro (US Census Bureau, ICF International) will be used for data entry. Descriptive statistics will be calculated for parents or caregivers and children. Paired and unpaired 2-tailed *t* tests will be applied when comparing mean changes of the outcome variables from pre- to post intervention when examining within-group changes in exploratory data analysis. For skewed distribution data, the Mann-Whitney test will be used to assess differences between groups. Multiple imputation methods will be used to deal with missing data. All analyses will be performed with the statistical package Stata 18.0 or higher (StataCorp), at a significant level of $P<.05$.

Results

Data collection started in June 2023, and 266 children were enrolled at baseline. Final measurements are scheduled to be completed in December 2023. The results of the main analysis will be conducted in 2024 and are expected to be available in 2024 and 2025.

Discussion

Overview

This is the first mHealth intervention focused on Amazonian children and also the first one, as far as we know, that investigates the efficacy of multimedia messages on children's dietary habits and excessive weight gain. Furthermore, it is novel because it translates policy-level recommendations from the food guide for the Brazilian population to a hard-to-reach and vulnerable population.

Furthermore, due to both food insecurity increases and large consumption of UPF, nutritionally adequate and environmentally sustainable food patterns from local Amazonian communities have been compromised, which may greatly influence global environmental changes [74,75]. Diets based on large consumption of UPF cause higher greenhouse gas emissions

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through the need for large deforestation areas for monoculture farms and industrial processes. This contributes to biodiversity loss, land degradation, and intensification of climate change [74].

Conclusion

This trial is expected to better understand the efficacy, challenges, and limitations of the use of technologies in healthy eating promotion, particularly in regions characterized by high social vulnerability and limited access to health care, as is the case in the Western Amazon. We hypothesize that children whose parents or caregivers receive multimedia messages related to nutrition will demonstrate improvements in BMIz, dietary food intake, and biochemical data. Furthermore, we expect that the data produced by this trial will contribute to the development and strengthening of innovative public health policies aimed at preventing childhood obesity.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[DOCX File , 50 KB - resprot_v13i1e54446_app1.docx]

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Abbreviations

BMIz: BMI in z score
CSPro: Census and Survey Processing System
CTML: cognitive theory of multimedia learning
E: effect size
HDL: high-density lipoprotein
LDL: low-density lipoprotein
mHealth: mobile health
MINA-Brazil: Maternal and Child Health and Nutrition Cohort Study in Acre
SCT: social cognitive theory
SDQ: Strengths and Difficulties Questionnaire
SMART: specific, measurable, attainable, realistic, and timely
UPF: ultraprocessed food
WC: waist circumference
WHO: World Health Organization

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Protocol

#4Corners4Health Social Media Cancer Prevention Campaign for Emerging Adults: Protocol for a Randomized Stepped-Wedge Trial

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Abstract

Background: Many emerging adults (EAs) are prone to making unhealthy choices, which increase their risk of premature cancer morbidity and mortality. In the era of social media, rigorous research on interventions to promote health behaviors for cancer risk reduction among EAs delivered over social media is limited. Cancer prevention information and recommendations may reach EAs more effectively over social media than in settings such as health care, schools, and workplaces, particularly for EAs residing in rural areas.

Objective: This pragmatic randomized trial aims to evaluate a multirisk factor intervention using a social media campaign designed with community advisers aimed at decreasing cancer risk factors among EAs. The trial will target EAs from diverse backgrounds living in rural counties in the *Four Corners* states of Arizona, Colorado, New Mexico, and Utah.

Methods: We will recruit a sample of EAs (n=1000) aged 18 to 26 years residing in rural counties (Rural-Urban Continuum Codes 4 to 9) in the Four Corners states from the Qualtrics' research panel and enroll them in a randomized stepped-wedge, quasi-experimental design. The inclusion criteria include English proficiency and regular social media engagement. A social

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media intervention will promote guideline-related goals for increased physical activity, healthy eating, and human papillomavirus vaccination and reduced nicotine product use, alcohol intake, and solar UV radiation exposure. Campaign posts will cover digital and media literacy skills, responses to misinformation, communication with family and friends, and referral to community resources. The intervention will be delivered over 12 months in Facebook private groups and will be guided by advisory groups of community stakeholders and EAs and focus groups with EAs. The EAs will complete assessments at baseline and at 12, 26, 39, 52, and 104 weeks after randomization. Assessments will measure 6 cancer risk behaviors, theoretical mediators, and participants' engagement with the social media campaign.

Results: The trial is in its start-up phase. It is being led by a steering committee. Team members are working in 3 subcommittees to optimize community engagement, the social media intervention, and the measures to be used. The Stakeholder Organization Advisory Board and Emerging Adult Advisory Board were formed and provided initial input on the priority of cancer risk factors to target, social media use by EAs, and community resources available. A framework for the social media campaign with topics, format, and theoretical mediators has been created, along with protocols for campaign management.

Conclusions: Social media can be used as a platform to counter misinformation and improve reliable health information to promote health behaviors that reduce cancer risks among EAs. Because of the popularity of web-based information sources among EAs, an innovative, multirisk factor intervention using a social media campaign has the potential to reduce their cancer risk behaviors.

Trial Registration: ClinicalTrials.gov NCT05618158; https://classic.clinicaltrials.gov/ct2/show/NCT05618158

International Registered Report Identifier (IRRID): PRR1-10.2196/50392

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KEYWORDS

cancer prevention; young adults; rural; social media; physical activity; diet; alcohol; tobacco control; sunburn; human papillomavirus; HPV vaccination

Introduction

Background

Emerging adulthood is an important habit-forming period of life. The lives of emerging adults aged 18 to 26 years are in flux [1], as they experience lifestyle transitions and increased autonomy while taking on adult-related responsibilities (eg, financial, residential, and employment). It is an important time for health behaviors because with increased autonomy, numerous emerging adults are at risk of making unhealthy choices [2,3].

Health-compromising behaviors that increase cancer risk later in life are especially prevalent among emerging adults [4] and are linked to future cancer morbidity and mortality [5]. Many emerging adults have reduced physical activity and unhealthy eating patterns that do not meet the 2020 American Cancer Society guidelines [6] (are overweight, eat fast food [7,8], and have low self-efficacy for making healthy food choices) [9-13]. Emerging adults' use of nicotine products [9-12,14] and multiple combustible and noncombustible products [15,16] and their alcohol use and heavy drinking (bingeing) are high [17,18]. Emerging adults are also more prone to intentional UV exposure (solar and artificial tanning) [19]; sporadic sun safety practices [20-23]; and a lack of human papillomavirus (HPV) knowledge [24,25], resulting in incomplete vaccination rates [26,27]. These modifiable cancer risk behaviors are important targets of primary prevention for emerging adults by promoting moderate to vigorous physical activity (MVPA) and dietary and sun safety skills, supporting the use of brief interventions for tobacco or alcohol use, and encouraging emerging adults to make their own health care decisions such as HPV vaccination. However, there is a lack of rigorous research on interventions for emerging adults, and information on their cancer risk behaviors is limited [28].

In the United States, rural populations have substantially higher rates of cancer [29] related to unhealthy eating [30,31], high rates of smoking and alcohol use, exposure to UV radiation and radon (riskier for smokers) [32,33], and persistent HPV infection compared with urban populations. Rural cancer disparities are exacerbated by a lack of health insurance and preventive care [34,35], low socioeconomic status [36,37], poor health literacy [36,38], fatalistic beliefs and ambiguous health information [25], and pervasive barriers to preventive health care [37,39,40].

Social media may offer a superior intervention channel for reaching and influencing emerging adults compared with health care, schools, and workplaces, including in rural areas. Emerging adults (90%) are the most engaged age group on the internet [41], and the internet is a preferred channel for health information among rural and urban emerging adults [40,42]. Rural adults use the internet (85%), as do most Hispanic (86%) and African American (85%) individuals [42]. Social media platforms are very popular with emerging adults [41,43]. Social media provide flexible, responsive, accessible, and low-cost platforms for distributing cancer information to the public from trusted voices [44]. Social media can improve information dissemination, credibility, and relevance and are often used to detect and respond to emerging issues [45] and promote engagement with personalized and impactful user-generated content [46]. Although use varies across platforms, there is growing evidence that interventions delivered using social media can improve physical activity, diet, nicotine product use, skin cancer prevention, and HPV vaccination outcomes among young adults [47-57]. By contrast, it can be challenging to implement a cancer prevention intervention in health care organizations,

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schools, and workplaces in low-resourced rural communities. Interventions in these channels also may not reach many emerging adults who have low preventive health care use, school enrollment, or employment. However, social media platforms also circulate inaccurate, misleading, and harmful information [58,59]. For instance, social media has spread misinformation on tobacco products [60], breast cancer prevention [61], the efficacy of cannabidiol for cancer care [62], cancer-related nutrition [63], and the mistrust of HPV vaccines [64,65], which can undermine cancer prevention efforts. Thus, interventions also need strategies to correct misinformation and provide digital and media literacy skills [66-70].

In summary, emerging adulthood is an important period for establishing cancer prevention. Many rural emerging adults experience several cancer risk factors, but successful interventions for them are lacking. With the popularity of web-based resources for emerging adults, an innovative multirisk factor intervention over social media has the potential to reach this underserved population and reduce emerging adults' cancer risks. The goal of this trial is to modify cancer risk factors among emerging adults aged 18 to 26 years living in rural counties in the Four Corners states of Arizona, Colorado, New Mexico, and Utah using a unique, theory-based social media campaign designed with community advisers that delivers relevant, credible, and timely content on reducing multiple cancer risks to emerging adults. A multirisk factor approach [71,72] is adopted because (1) emerging adults vary in cancer risk profiles, (2) several risks cooccur and are affected by similar mechanisms [73-76], and (3) coverage of a variety of topics in the campaign will be engaging. Furthermore, the Four Corners region has a relatively high burden of poverty [77,78], significant population diversity with large Hispanic and American Indian populations [79], and low population density where distance and transportation are health care access barriers [37,80], providing a rich environment to test the efficacy of a multibehavior health promotion intervention.

Objectives

Our proposed intervention will aim to aid rural emerging adults in making informed decisions to reduce cancer risks related to infrequent physical activity, unhealthy diet, alcohol intake (per 2020 American Cancer Society guidelines [6]), nicotine product use, UV exposure, and lack of HPV vaccination uptake. In addition, it will help them critically evaluate and resist misinformation and marketing that promote cancer and other health risk behaviors and support emerging adults to be media literate when using digital media. The trial will test the following hypotheses:

- Hypothesis 1: emerging adults will increase MVPA and healthy eating patterns, reduce nicotine product and alcohol use and sunburns, and increase HPV vaccine uptake from baseline to final assessment when receiving the social media intervention.
- Hypothesis 2: the positive impact of the social media campaign on cancer risk factors among emerging adults will be mediated by improved cancer risk knowledge and beliefs (ie, self-efficacy and response efficacy, norms, social support, and vaccine antecedents), digital and media literacy skills, misinformation identification, and family communication.

Analyses will also explore whether the impact of the campaign differs according to (1) the level of emerging adults' engagement with it, (2) cancer risk factors, and (3) the biological sex of the participants. The prospective randomized quasi-experimental design and its large sample will provide a rigorous evaluation of the social media campaign compared with many previous studies on social media that have used less rigorous nonrandomized controlled trial designs and small samples [81-86].

Methods

We will test a social media campaign to reduce cancer risk factors among emerging adults in rural counties in the Four Corners states using a randomized stepped-wedge trial design.

Target Population and Recruitment Procedures

Emerging adults (N=1000) aged 18 to 26 years residing in rural counties in the states of Arizona, Colorado, New Mexico, and Utah will be enrolled in the study (refer to Textbox 1 for the inclusion and exclusion criteria). Many emerging adults will report ≥1 cancer risk behavior and will be residing in a variety of living arrangements, from multigenerational families to roommates to spouses or partners to alone. In the Four Corners states, 99 counties are rural (ie, Rural-Urban Continuum Codes [RUCC] 4 to 9 [87]), with >2 million residents (176,737 residents aged 19 to 25 years; annual income) [88]. Pregnant individuals will be excluded because the intervention will not provide individualized counseling and could lead to behavioral changes in diet or exercise that might be contraindicated during pregnancy.

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Textbox 1. Inclusion and exclusion criteria for the sample of emerging adults.

Inclusion criteria

- Member of the Qualtrics survey panel in year 2
- Aged 18 to 26 years
- Resides in a county coded as Rural-Urban Continuum Codes 4 to 9 in Arizona, Colorado, New Mexico, or Utah
- Able to speak and read English
- Has regular social media engagement
- Accepts screening call from the study staff
- Provides consent to participate

Exclusion criteria

- Participated in community engagement activities
- Cannot speak and read English
- Has low or no social media engagement
- Does not accept a screening call from the study staff
- Does not provide consent to participate
- Does not give permission for engagement data to be extracted from the Facebook private groups
- If biologically female, currently pregnant

Emerging adults will be recruited from Qualtrics' research panel, built from multiple providers that use by-invitation or double opt-in methods. Qualtrics will select adults aged 18 to 26 years residing in counties designated as RUCC 4 to 9 in the 4 selected states [87], balanced on gender, and refer emerging adults to the project's registration website to complete a consent form. Fake, duplicate, and unqualified respondents will be screened out, and steps will be taken to ensure that they participate only once. The project staff will contact the consented emerging adults by telephone and confirm their eligibility. To avoid clustering, only 1 emerging adult per household will be enrolled. If recruitment lags, we will add Mountain West states with similar populations (ie, Idaho, Montana, Nevada, and Wyoming). We will use quotas so that the sample matches the education and the race and ethnicity of the counties. Although research panel members are required to have internet access, selection bias will be reduced as most US adults (90%), including emerging adults (100%) and rural adults (85%), have access to the internet [42]. We will confirm that the emerging adults have regular social media use (post ≥1 time per week) to allow them to engage with our campaign. We acknowledge that this criterion may impact generalizability, but social media influence those who view them regularly [89,90]. The escalating compensation schedule is designed to achieve retention for postintervention assessments.

Randomized Stepped-Wedge Trial Design

The cancer prevention social media campaign will be tested using a randomized stepped-wedge design (Figure 1).

Figure 1. Randomized stepped-wedge trial design.

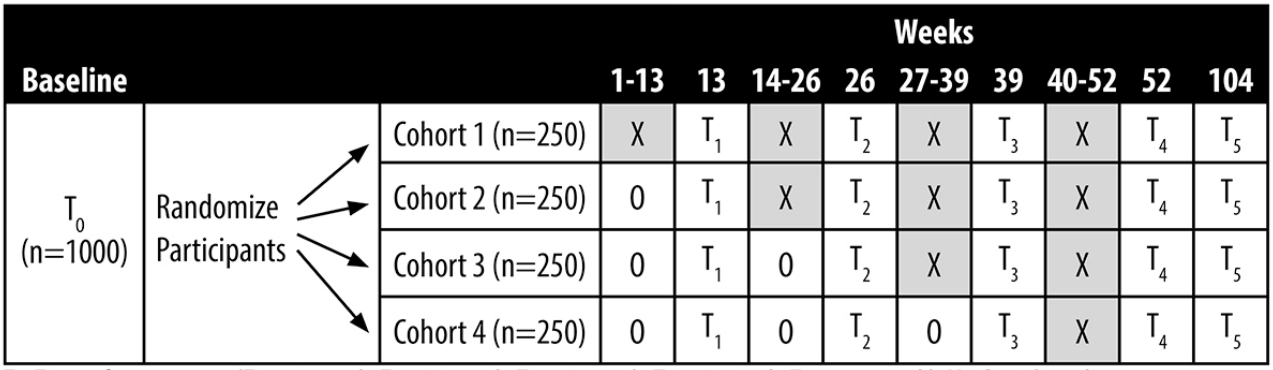

Following baseline assessment (T_0), emerging adults will be stratified by state, ethnicity (racial and ethnic minority individuals vs non-Hispanic White individuals), and biological sex (male vs female) and randomly assigned to 1 of 4 cohorts differing in intervention duration by the project biostatistician. All cohorts will complete postintervention assessments at weeks

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13 (T_1), 26 (T_2), 39 (T_3), 52 (T_4), and 104 (T_5). All data collection will be conducted using the secure web-based REDCap (Research Electronic Data Capture; Vanderbilt University) application. The primary outcomes measured at all assessment times will be MVPA, healthy eating patterns, nicotine product use, alcohol intake, sunburn, and HPV vaccination.

The social media campaign will be conducted over 12 months in 4 separate Facebook private groups. The intervention will start in each cohort at successive 13-week intervals, so cohorts will receive varying doses of campaign exposure (ie, 180 posts per 13-week interval) via stepped entry. Specifically, cohort 1 (250/1000, 25%) will start the social media campaign at week 1, receiving approximately 720 posts in 52 weeks. Cohort 2 (250/1000, 25%) will start the campaign at week 13 (approximately 540 posts), cohort 3 (250/1000, 25%) at week 26 (approximately 360 posts), and cohort 4 (250/1000, 25%) at week 39 (approximately 180 posts). Emerging adults will be told to read, react to, and comment on posts as often as they like. Exposure to cancer risk information and misinformation from other sources will be controlled by randomization.

The stepped-wedge quasi-experimental design was selected because it has several methodological advantages [91]. First, it allows for the random assignment of participants to 1 of the 4 cohorts, ensuring that potential confounding factors are evenly distributed across the groups. Each cohort is assigned to start the intervention at different times, creating a staggered, time-sequenced implementation schedule across the cohorts that creates the controlled nature of our trial. This design element allows for the within-study comparison of outcomes across different cohorts, with each cohort serving as a control for the others before they receive the intervention. Specifically, the control condition is represented by the periods when the cohorts have not yet started the intervention. For example, cohort 2 serves as a control group for cohort 1 before they commence their intervention in week 13. Second, the design also allows for comparisons between cohorts that have received the intervention for different durations. Third, by collecting data at multiple time points (T_1-T_5), the design facilitates the assessment of outcomes over an extended period that allows for the evaluation of trends and changes in outcomes over time within each cohort as well as comparisons between cohorts. The multiple baseline measures in cohorts 2, 3, and 4 will permit the examination of any trends or patterns before the intervention is introduced and will control threats to validity [92], as we can account for potential confounding factors, such as time-related effects or external factors, and compare cohorts at different stages of intervention exposure. This strengthens the internal validity of the study. Fourth, the design optimizes study resources by focusing on recruiting and retaining a longitudinal sample. This approach differs from securing a sample where half remain untreated, mitigating problems associated with control groups such as loss to follow-up, demoralization, disengagement, or noncomparability. It adheres to ethical standards by having all participants eventually receive the intervention but still preserves the controlled trial's integrity.

Cancer Prevention Social Media Campaign

The social media campaign will deliver 2 posts per day (n=approximately 720 posts) over 12 months, addressing cancer risk reduction, teaching digital and media literacy, encouraging family and friend communication, responding to misinformation, and highlighting community resources. The diverse content should be engaging and should avoid fatigue, but we will assess information overload and compare varying intervention durations (ie, 13, 26, 36, and 52 weeks).

Theoretical Approach to Social Media Intervention

We will adopt a multitheoretical approach to influencing rural emerging adults' health behaviors. Social cognitive theory (SCT) [93] and self-determination theory (SDT) [94] will provide a framework and guide message development and measures of theoretical mediators, including cancer risk perceptions, self-efficacy and response efficacy, norms, social support, relatedness, autonomy, and motivation. SCT constructs address the environment (eg, environmental risks [UV exposure] and settings [health care access]), situation (eg, social norms of risk behaviors), behavior (eg, risk-reduction knowledge and skills), expectations (eg, good health outcomes), observational learning (eg, behavioral modeling), and self-efficacy (eg, confidence to perform prevention) [95]. Three needs must be satisfied when using SDT to foster well-being [94]: (1) competence—ability to control outcomes and feel self-efficacy, (2) relatedness—innate desire to interact with others, and (3) autonomy—need to be in charge of one's life. Effective interventions implement techniques and strategies that support these 3 basic psychological needs. In need-supportive environments and contexts, extrinsic motivation can be transformed into higher-quality, intrinsic motivation, which is linked to positive health behavior change [96].

Posts will also include engagement strategies to encourage user-generated content and incorporate testimonials. The diffusion of innovations theory (DIT) and social network principles [97] explain that social media are uniquely influential because (1) user activity increases dissemination [98] and (2) information spread among social media communities, notably by knowledgeable peers, reduces uncertainty; makes sentiments dominant [65,99]; and motivates collective action [97,100] via social comparison [97,101] and collective identity that stabilizes actions [101]. Social media's influence is further clarified by transportation theory [102]. According to this theory, personal stories can be more influential than didactic messages and expert advice [103] partly because of the audience's identification with the characters [104]. Users often share stories on social media.

Digital and media literacy principles, including "active inquiry and critical thinking about mediated messages" [105], will be addressed in the campaign because many emerging adults are not critical media consumers [106]. Strategies to help emerging adults navigate the media landscape, combat echo chambers of misinformation, counterargue critical information, and develop trust in public health voices are imperative [107,108]. Fact-checking and corrections are important strategies for the campaign, but counternarratives, peer correction, factual elaboration, coherence and credibility appeals, media literacy [109-113], eHealth literacy [114], and advice on safe content

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sharing are also essential for the posts [69,115]. Media literacy interventions have helped health-related decisions and provided skills to combat unhealthy messages across health topics [116-120], suggesting they will make emerging adults "better prepared and willing to take preventive actions recommended by health professionals" [121]. We will convey how to identify media sources, their intentions, and misinformation; conduct web searches; overcome discomfort of new behaviors; converse with others about cancer risks (skills acquisition); highlight benefits to self, family, and friends (positive outcome expectations); and reinforce that they can reduce risks (self-efficacy). We will measure digital and media literacy skills and the level of misinformation (ie, holding inaccurate beliefs) about cancer prevention as mediators.

Social Media Posts

Social media posts will contain text with images, infographics, videos, and links to websites or other social media platforms (eg, Instagram and YouTube) from government, health care, news media, and trusted sources. Preferred health content for emerging adults of any gender and various social groups (eg, race, ethnicity, income, education, and living circumstances) will be identified through community engagement methods. Messages will address SCT [93], SDT [94], DIT [97], and media literacy principles [122] described earlier. The posts will be positive, at the seventh-grade reading level, and in English. The posts will cover 5 content areas:

- Cancer prevention: posts will address 6 cancer risk factors and various methods to improve them including behavioral skills for risk reduction, benefits of engaging in such behaviors, social support for these efforts, and strategies to minimize the social and financial costs associated with cancer risk reduction. In addition, advice from health care providers will be shared to help individuals overcome barriers to adopting healthier behaviors. Risk-reducing behaviors will be targeted by the posts include increasing MVPA and healthy eating behavior (more vegetables, fruits, and whole grains and less red and processed meats, sugar-sweetened beverages, highly processed foods, and refined grains); decreasing nicotine product use, alcohol intake, and UV exposure (sunburn); and increasing HPV vaccination. Posts will seek to improve several theoretical mediators, including self-efficacy and response efficacy and perceived risk, and to link cancer prevention to personal goals, including compatibility with values, observable benefits, and simplicity. Posts will also address cost of cancer prevention, present descriptive norms related to healthy and unhealthy behaviors, and highlight social support from family, friends, and partners. They will also promote emerging adults autonomy for their own health and decisions to adopt healthy behaviors. Posts will highlight the cancer prevention benefits of these behaviors and other benefits that may motivate emerging adults to adopt risk-reduction behaviors, including appearance (eg, avoiding skin aging), social (eg, reducing alcohol-induced partner violence), financial (eg, cost savings from quitting nicotine products), and disease prevention (eg, cardiovascular health) benefits. We will use a rotation pattern that covers the 6 cancer risk factors in at least 1 post per week and highlights 1 cancer risk factor in a series of posts each week to provide an in-depth intervention.
- Digital and media literacy skills: media literacy posts will focus on critical thinking, skill acquisition, and misinformation correction. Posts will aim to improve emerging adults' digital and media literacy competencies related to (1) access, (2) analysis, (3) creation, (4) reflection, and (5) action [122]. Posts will focus on assessing message credibility and quality (eg, authorship [eg, bots], purpose [eg, marketing], construction, and algorithms) and validity (eg, original source identification, images, deep fake videos, and scientific evidence). Differences in storytelling and scientific evidence will be discussed. Marketing messages will be addressed because advertisers (eg, tobacco, alcohol, and tanning industries) reach emerging adults through social media promotions [41]. Even brief exposure to these marketing messages can instill positive attitudes toward the products [123].
- Responding to misinformation: we will use our best practices to respond to misinformation [124], that is, messages in conflict with scientific and medical information and advice. Misinformation will be identified by monitoring users' reactions and comments, auditing the media landscape, and responding immediately [125] to forestall it from going viral. We will respond both proactively in the feed and reactively in replies to the comments. Responses will show empathic engagement and acknowledge users' uncertainty, confusion, or motivations to prevent defensiveness and maintain trust [125]. Posts will then debunk misinformation by fact-checking, providing factual elaboration and coherence appeals with evidence-based sources [110,111], reframing information to fit existing beliefs, using resistance-to-persuasion tactics (2-sided appeals [126,127] and inoculation [128-130]), telling stories that offer personalized advice, presenting credible statistics and science [111,112,131,132], highlighting prevention actions by resistant groups [132], and depicting patient-provider interactions [132].
- Family and friend communication: emerging adults are expected to reside in several living arrangements, often with other adults, so posts will present prompts to talk with family (eg, parents, siblings, and partners) and friends about cancer prevention (and content from the campaign posts). Posts will focus on skills for active listening, self-disclosure, support, and conflict management.
- Referral to community resources: a website will be created that contains links to web-based tools and brief interventions to help emerging adults alter cancer risk behaviors, especially those that may be unknown to emerging adults. Examples include quit-smoking services, portals to state vaccination records, tools for managing the multidose HPV vaccination schedule, and fact sheets and guidelines from health authorities. Resources will be identified by the community advisers and maintained by the investigators. A link to this website and its relevant resources will be included regularly in posts.

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Development of Cancer Prevention Posts

An agile, just-in-time process will be used to create and adapt posts to be responsive to emerging adults and to reflect current events [133]. Investigators will prepare a campaign framework for developing posts, identifying target behaviors for each cancer risk factor and key theoretical principles. Project staff will continuously audit cancer prevention information and misinformation in (1) published literature, government reports, and national surveys; (2) participant comments on posts; (3) quarterly web-based emerging adult focus groups; and (4) advisory board input. The investigators and media developers will revise posts, add emerging themes, and tailor posts to key subgroups. Initially, 3 months of campaign posts will be prepared, with additional posts developed during the campaign, creating a planned adaptive campaign. Social media posts will be written in English because rural emerging adults are the primary target group, with Hispanic and American Indian emerging adults comprising a minority of them. English continues to be the most common language on the internet, especially in the United States [134,135]. Nearly all young adults in the United States are proficient in English, even most foreign-born young adults [136].

To ensure campaign exposure, posts must regularly engage users because the Facebook algorithm presents posts from the private groups more frequently and prominently in participants' newsfeeds when they engage more with the group's posts. To achieve high visibility and engagement, we will post twice per day and (1) provide novel, high-interest, useful, and current-event content; (2) adjust for season; (3) link to content from other emerging adults to create descriptive norms; (4) address age differences and cultural barriers and facilitators; (5) use ethnically diverse emerging adult images that can improve health communication [137]; and (6) use formats such as stories, polls, questions and answers, videos, and visuals, and invite comments [58,98,138-141].

The campaign will be pilot-tested with rural emerging adults (N=25) meeting the inclusion and exclusion criteria displayed in Textbox 1 (13/25, 52% female individuals and ethnically diverse). It will contain a feed of 56 campaign posts (2 per day) over 4 weeks, and participants will provide feedback in focus group discussions.

Implementation of Social Media Campaign

The social media campaign will be implemented through Facebook private groups. A staff person will serve as the community manager and schedule posts twice a day on all 7 days of the week (1 message in the morning and 1 in the afternoon) to achieve reach [142,143]. In each cohort, emerging adults will receive welcome posts on purpose and ground rules (eg, respect for others) and then receive the ongoing feed delivered in their separate private group so that posts are identical across cohorts, timely, linked to current events and news stories, relevant for seasons, and engaging. We will not start each cohort at the beginning of the feed because it would require adjusting earlier posts to be current, making them dissimilar across cohorts. The community manager will monitor reactions and comments from emerging adults, answer questions, address uncertainty, and correct misinformation [58,124,133]. The community manager will promote peer influence by, for example, (1) recruiting high-frequency emerging adult users to be guest moderators for up to 3 days to schedule posts and reply to comments and (2) hosting Facebook Live events with emerging adult experts (eg, an emerging adult dietitian). If any bullying arises, the community manager will de-escalate it by (1) highlighting empathy and (2) sending direct messages to stop it. If participants leave a group, they will be contacted to see why. Project staff, except the community manager and the project coordinator, will be blinded to the cohort membership.

Facebook's private group function possesses unique features not found in other social media platforms. These distinctive qualities offer practical methodological advantages and enhance experimental rigor. Facebook remains one of the most popular social media platforms for emerging adults, used by 70% of the population nationally (among which 70% use it daily), with the majority reporting use in nearly all demographic groups, including by age, rurality, race, ethnicity, and income [43]. Thus, nearly all emerging adults will have existing accounts and be familiar with its interface. Other social media place limits on content delivery that would restrict cancer prevention messaging, including by restricting format (eg, YouTube and Instagram mainly use video and images), length (Snapchat and TikTok deliver short videos), and permanence (Snapchat posts last for 24 hours after posting), and they all restrict the ability to link to other web content more than Facebook. Facebook's private group function will also help ensure that posts appear in users' feed and will limit access to posts to group members (posts cannot be shared on other social media) to avoid contamination. Finally, Facebook has superior data analytics for tracking exposure to content compared with other platforms.

Community Engagement Methods

Community-based participatory research methods will inform the study and cancer prevention campaign. Partnership processes aligned with the model by Sandoval et al [144] will provide a framework for the study: (1) knowledge of *contexts* that inform catchment area needs; (2) culturally informed *partnership processes* guiding engagement; (3) *intervention and research* protocols responsive to rural, low-income, and underserved conditions; and (4) participatory *outcomes* disseminated to partners. The research team will draw on the community networks of the Four Corners Cancer Centers Collaborative through each cancer center's Community Outreach and Engagement program [145] to convene 2 community advisory boards for the project—an Emerging Adult Advisory Board (EAAB) and a Stakeholder Organization Advisory Board (SOAB). Up to 16 emerging adults from rural counties in the Four Corners states, diverse in gender and ethnicity, will be recruited to serve on the EAAB. The EAAB will meet quarterly with investigators in years 2 and 3 and biannually in years 1, 4, and 5. Members provide input on the social media campaign and implementation protocols (year 1) and review proposed posts (years 2 to 3), with attention to the relevance of posts for the circumstances experienced by rural emerging adults, especially the challenges experienced by low-income and marginalized emerging adults. Up to 4 stakeholder organizations that provide health promotion and cancer prevention services to rural emerging adults in each of the 4 states will be recruited

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for the SOAB. The SOAB will meet twice annually to review messaging, identify local resources, and plan dissemination efforts. Both advisory boards will advise on trial findings and dissemination efforts in years 4 to 5.

A series of focus groups with up to 8 rural emerging adults per group, meeting the inclusion and exclusion criteria (Textbox 1), will be conducted during the project to help develop the social media campaign. Discussions will cover cancer risk behaviors, social media use, health information seeking, misinformation, the context of health behaviors, and current issues and trends. Emerging adults will review social media posts and suggest how to engage rural emerging adults and reflect local contexts and issues. The results will be summarized and used to adapt posts to be responsive, timely, and engaging for emerging adults and targeted to key subgroups.

Measures

Primary Outcomes: Cancer Risk Behavior Outcome Measures

We will use validated self-report measures of each cancer risk behavior in the T_0-T_5 surveys presented in Table 1.

Table 1. Primary and secondary cancer risk behavior outcome measures.

Cancer risk behavior	Measure	Metric
Physical activity	• Primary and secondary: Global Physical Activity Questionnaire [146]	• Minutes per week of MVPA[a] (primary) • Meet 150 minutes per week goal (secondary)
Diet	• Primary: Dietary Screener Questionnaire [147,148] • Secondary: other meal behaviors [149-152]	• Intake per day of fruits, vegetables, whole grains or fiber, added sugars (from sugar-sweetened beverages), and red or processed meats • Frequency of eating meals and snacks, fast food, and skipping meals
Nicotine product use	• Primary: 30-day prolonged tobacco or nicotine product abstinence [153] • Secondary: 7-day point prevalence of smoking [153] • Secondary: readiness to quit [154]	• Use in the past 30 days (every day, some days, and not at all) • Use in the past 7 days (every day, some days, and not at all) • 10-point rating (1=no thought of quitting and 10=taking action to quit)
Alcohol intake	• Primary: consumption of alcoholic drinks [155] • Secondary: binge drinking (male individuals: 5 drinks per sitting and female individuals: 3 drinks per sitting)	• Number of days in the past 30 days; number of drinks per occasion • Number of times in the past 30 days
UV exposure	• Primary: sunburn prevalence [156] • Secondary: sun protection behavior [157]	• Number of sunburns • Percentage of sun exposure days using sun protection
HPV[b] vaccination	• Primary: any dose of HPV vaccine [158] • Secondary: completion of vaccine series	• Received 1 or more doses • Received 2 or 3 doses as recommended for age

[a]MVPA: moderate to vigorous physical activity.

[b]HPV: human papillomavirus.

Self-report measures are most practical for this pragmatic trial, with the large sample of emerging adults in 4 geographically large states (approximately 1,100,700 sq km), web-based recruitment, and a multirisk factor approach that makes clinical and observational measures infeasible. The recall period for nicotine abstinence, alcohol use, and sunburn prevalence measures will be 30 days, which improves reliability [156]. Physical activity and other meal behaviors will be measured for the past 7 days, and HPV vaccination will be measured from baseline.

The primary outcome measures of physical activity, diet, and nicotine abstinence will be validated in subsamples of emerging adult participants at baseline and at the 52-week posttest stage. Physical activity and diet self-report measures will be verified with (1) accelerometry (ActiGraph GT9X) [159,160] and (2) 24-hour recalls (for 3 random days; 2 weekdays and 1 weekend day) [161] in a subsample of emerging adults (139/1000, 13.9%) at baseline and repeated at 52 weeks. Nicotine abstinence self-report measures will be verified via saliva cotinine assays (Salimetrics assay) on a subsample of 15% emerging adults reporting abstinence at 52 weeks [153]. Objective measurement of alcohol use, sunburn, and HPV vaccination is infeasible within the scope of the trial.

Mediators

Mediators will be assessed in all surveys. These include theoretical antecedents—cancer risk (SCT; severity and susceptibility: 6 items); self-efficacy and response efficacy (SCT) [162]; cost of cancer prevention [162]; descriptive norms (SCT; 2 items; prevalence among people you know and 5 people you know best) [163]; social support from family, friends, and partners (SCT); relatedness (SDT; 4 items) [164]; autonomy and motivation (SDT; 10-point contemplation ladder) [154,165]—family and friend communication about cancer prevention (SDT and DIT; if emerging adults shared information from feed with family and friends) [166]; and vaccine antecedents (ie, confidence, constraints, complacency,

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calculation, and collective responsibility [167]). Digital and media literacy will be assessed with 3 competency measures—self-perceived media literacy (4 items) [168], perceived social media literacy (6 items) [169], and eHealth literacy (8 items) [170]—along with cancer prevention misinformation (8 accurate and 8 inaccurate Likert statements recoded for belief in misinformation).

Potential Covariates

The following variables, measured at baseline, will be assessed as covariates:

- Participant characteristics: race, Hispanic ethnicity, gender identity, biological sex, RUCC codes (4 to 9), age, education, employment, and emerging adults' height and weight for BMI (treated as a covariate because of stability at this age) [171]
- Household features: marital status, parenting status (children at home), household composition, food insufficiency [149], and use of government nutrition assistance programs [155]
- Health care use: insurance status [172] and prior visit to a physician for routine preventive care
- Cancer history: personal and family history of cancer
- Cancer messaging: exposure to cancer information (ie, topics and sources [health care provider, social media, website, news media, and conversations]) [64] and perceived credibility of various media [133]
- Social desirability: a socially desirable response set 5-item measure [173] to account for socially favorable response bias.

Social Media Campaign Engagement Measures

Behavioral and experiential measures of campaign engagement [174,175] will be collected, guided by the model of engagement by Perski et al [176]. Behavioral measures will be (1) staff records of posts; (2) counts of emerging adults' views, reactions (eg, like or sad), and comments extracted in identified format using our custom-written app and coded for content and pro, anti, or neutral sentiment by 2 trained research assistants [113]; and (3) use of resources on the project website recorded by the web server. Experiential measures will be collected in each postintervention test, including time spent and frequency of reading posts, flow experience (ie, social interaction, enjoyment, and concentration) [177], cancer information overload [178], and sharing post content with others.

Statistical Analysis Plan

Hypothesis Testing

We plan to use advanced statistical methods suitable for stepped-wedge designs to compare outcomes between different cohorts and time points, which will account for both time effects and intervention effects. This includes using mixed-effects models or generalized estimating equations that can adjust for time-related trends and cohort effects. In addition, by comparing cohorts that start the intervention at different times, we will isolate the effect of our campaign from other external factors and assess whether changes in the cancer risk behaviors are more pronounced or accelerated following the introduction of our intervention compared with the periods before the intervention. In addition, our analysis will adjust for potential confounding factors that might influence cancer risk behaviors, such as age, sex, ethnicity, and other relevant sociodemographic factors. This approach ensures that the control aspects of the design are rigorously analyzed.

Specifically, the 2 hypotheses and exploratory research questions will be tested using R (R Foundation for Statistical Computing) [179] and Mplus, V8.2 (Munthén & Munthén) [180], a structural equation modeling program that allows for growth models and latent constructs (to model measurement error appropriately), repeated measures, direct and indirect effects, and moderators using interaction terms and multiple group analysis [181]. Mplus will handle missing data via full information maximum likelihood. All tests will be intent to treat. To mitigate false discovery (type I error), an α of .008 will be used (ie, the traditional α=.05÷6 [number of cancer risk factors considered]) [182]. Once the full sample is recruited, baseline data will be described and plotted, measurement models will be assessed, and transformations for normality will be examined and applied.

The effect of the treatment on each of the primary outcomes will be examined using a linear mixed-effects model for a stepped-wedge design, as outlined by Hussey and Hughes [183] and Li et al [184]. Repeated measures (6 per individual—T_0, T_1, T_2, T_3, T_4, and T_5 in Figure 1) will be regressed on time since the start of the study ("calendar time") and time since the start of message exposure ("exposure time"), both of which are expressed as categorical variables via dummy codes. Any mediators found to be significantly impacted by the treatment will be subsequently examined as mediators of the treatment effect on the outcomes via formal mediation models. Multilevel mediation models will be fit as described by Preacher [185] using the structural equation modeling program. As moderation tests require a vastly larger sample than tests of main effects [186], we will examine them without conducting null hypothesis significance tests [187]. We will estimate each model, evaluate the effect magnitude as a function of the moderator, construct bootstrap CIs to illustrate uncertainty, and use false discovery rate controls [182,187]. Linear mixed-effects models for hypothesis 1 will be extended to consider effect modification because of cancer risk behaviors, campaign exposure variables, biological sex, and the time of year of data collection (to control for seasonal fluctuations in UV levels, food availability, and alcohol intake).

Finally, behavioral and experiential engagement will be tested for campaign dose response (ie, duration of the campaign) related to cancer risk behaviors. In addition, behavioral engagement with posts (ie, views, reactions, and comments) on certain topics (eg, risk behaviors, media literacy, or family communication) and formats (eg, text, video, or interactive features such as polls) will be examined to determine if they have an impact on campaign effectiveness.

Power Analysis

To determine the appropriate sample size for the stepped-wedge design, we used the Shiny Cluster Randomized Trial calculator [188], setting α at .008 and assuming, conservatively, that the within-person correlation of the repeated measures is 0.5. Power

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analysis focused on the main effect on outcomes at the 104-week posttest score being significantly better than preintervention scores (ie, the time-averaged intervention effect). We considered a mean standardized difference between pre- and postexposure measure of 0.2 for a continuous outcome and a difference in pre- versus postexposure prevalence of 0.40 versus 0.48 for a binary outcome. These are conservative and relatively small effects based on our past assessment of a social media campaign [166,189] and the expectation that emerging adults are unlikely to see all posts. We will achieve a power of 0.80 with 115 people per cohort for a continuous outcome and 175 per cohort for a binary outcome. We have planned for a 30% (300/1000) dropout rate, so we will enroll 1000 emerging adult participants and expect to finish the trial with approximately 175 individuals in each cohort. We will use full information maximum likelihood methods for estimation; thus, even incomplete cases will be retained.

Ethical Considerations

The WCG Institutional Review Board reviewed and approved the protocols for the research (study #20223673). Participation will be voluntary, and participants will read and sign an informed consent form approved by the institutional review board. The consent form will present the purpose of the research, the procedures, known risks and benefits, and the use and security of the data. All data collected in the study will be confidential, and participant identity will not be disclosed publicly. Emerging adults that participate in a focus group discussion will be compensated US $40. In the stepped-wedge design, participants will be paid US $30 for baseline, US $15 for 13-week, US $15 for 26-week, US $15 for 39-week, US $30 for 52-week, and US $30 for 104-week postintervention tests (US $135 in total). Those who are selected for the verification of outcome measures via accelerometry, 24-hour dietary recalls, and saliva cotinine assays will receive US $25 compensation for each measure.

Results

Project Initiation and Administration

The study commenced in September 2022. It is supervised by a steering committee comprising the project principal investigators (D Buller and A Sussman) and coinvestigators from each site. The steering committee is meeting once a month to make design and administration decisions, plan activities, track progress, troubleshoot problems, maintain consistency in actions, implement quality controls, and communicate with the funding agency and institutional review board. In addition, the project staff at each site meet monthly with the coordinating center lead staff to ensure timely and regular communication and timeline adherence.

Project activities are being conducted by 3 subcommittees of investigators and project staff, meeting bimonthly (Figure 2). The Community Engagement Subcommittee is managing the partnerships with emerging adults and key stakeholder organizations in the rural counties of the Four Corners states. Advisory boards with members of these 2 groups have been convened and meet regularly with the research team. The Social Media Campaign Subcommittee is developing campaign content and implementation procedures. It has created a framework and procedures for creating social media posts and protocols for the community manager and responding to misinformation. The Measurement Subcommittee has identified assessment instruments, is piloting the measures with samples of emerging adults, and is developing data collection and retention procedures. A subcommittee guiding statistical analysis will be created in the future once the trial commences. The steering committee is functioning as a working group on trial recruitment issues and procedures.

Figure 2. Steering committee and subcommittees for project management.

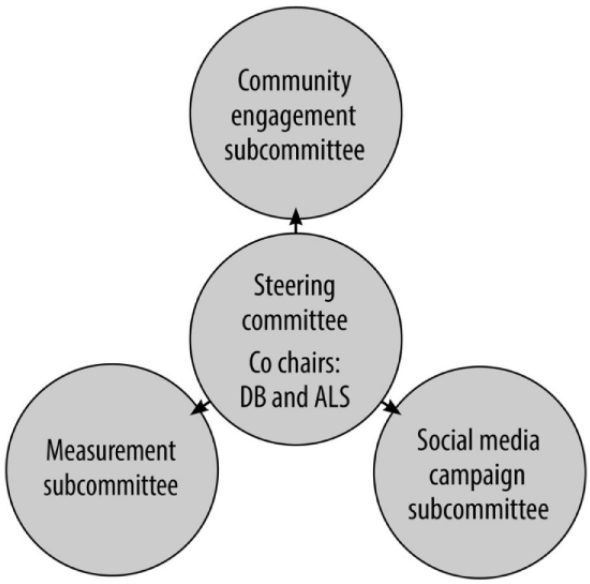

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Project Advisory Boards Meetings

The EAAB and SOAB have been formed with members recruited from each of the 4 states and met with the project investigators and staff in 2023. The EAAB members (3/8, 38% from Arizona, 2/8, 25% from Colorado, 1/8, 12% from New Mexico, and 2/8, 25% from Utah) are diverse in gender (6/8, 75% women and 2/8, 25% men), race and ethnicity (4/8, 50% White, 3/8, 38% American Indian, and 3/8, 38% Hispanic), and age (mean 22.4 years, SD 2.0; range 19-25 years). Nearly all (7/8, 88%) are students (only 1/8, 12% was employed for wages), but 62% (5/8) of the EAAB members have ≥4 years of college education. In addition, 12% (1/8) of the members live alone, 25% (2/8) of the members live with parents, 38% (3/8) of the members live with other people (not with family), and 25% (2/8) of the members live in a college dormitory. The SOAB members represent a diversity of organizations serving the health and education needs of rural counties, specifically emerging adults. Advisers self-identify as female and White (2/14, 20% were Hispanic) and have a mean age of 49.9, SD 9.1 (range 41-63) years, and all completed some college education, with most having a ≥4-year degree education. Advisory boards will meet twice a year (with the EAAB meeting quarterly during project years 2 and 3) and also communicate through Facebook groups to provide ongoing input.

The initial advisory board meeting agendas focused on introducing the project and discussing important health issues for emerging adults, social media use, misinformation on social media, and community resources for emerging adults (SOAB only). In the EAAB, participants identified nicotine product use, healthy eating, and alcohol intake as the most important health priority areas for emerging adults. The emerging adults described a passive approach to reviewing health information on social media, noting that they do not routinely initiate a search but instead encounter a high volume of posts. Furthermore, members of the EAAB were generally confident in their ability to discern the trustworthiness of the posted health information. The EAAB reviewed initially created posts on cancer risk factor reduction, providing input on text, visuals, and links to outside sources. The SOAB cited the importance of HPV vaccination, alcohol intake, and healthy eating as major health priorities for emerging adults among the 6 cancer risk factors. Most organizations represented on the SOAB use social media to reach emerging adults. The SOAB members expressed a higher degree of concern compared with emerging adults in determining the trustworthiness of posted health information. Finally, most SOAB members indicated that there are not enough community resources to address the complete list of risk factors included in our study. Subsequent EAAB and SOAB meetings will deepen the exploration of these issues.

Social Media Campaign Framework Development

A framework has been created to guide the development of social media posts. It contains information that will be used to track messages by topic, primary and secondary outcomes, theoretical mediators, communication mediators, media literacy mediators, message design features, and engagement techniques. The message text, corresponding link, and image or video used in the post will also be tracked. In addition, the date and time the post is published to the Facebook feed and the Facebook link for the message will be recorded. Investigators with content expertise in each of the 6 cancer risk behaviors have identified key precursor behaviors and effective past interventions, especially with young adults, to incorporate into the framework. In addition, specific protocols were developed for the community manager, who will administer the social media campaign, the process of responding to misinformation during the campaign, and the process for the research team to review messages before posting to the social media feed. A style guide for the post content is also in development.

Discussion

Principal Findings

Emerging adulthood is an important period for the promotion and sustainment of guideline-recommended cancer prevention behaviors. Many rural emerging adults experience several cancer risk factors, but successful interventions for them are lacking. Emerging adults in the rural areas of the Four Corners states may be at a particularly high risk of adopting unhealthy cancer-preventive behaviors. With the popularity of web-based resources for emerging adults, an innovative multirisk factor intervention over social media should be able to reach this underserved population and reduce emerging adults' cancer risk behaviors. Web-based health programs have been effective in past research [46,64,190-197]. In particular, social media has influenced cancer risk behaviors in some past studies [47-57], although studies evaluating social media with only emerging adults are uncommon, as are prospective randomized study designs [83,198-203].

Strengths and Limitations

The planned trial has several methodological strengths, including the unique multi-institutional team of investigators with expertise in each of the health behaviors of interest as well as cancer prevention and control; a diverse, rural population; an understudied age group; extensive community engagement; a multirisk factor approach; the use of social media; a rigorous study design; and high dissemination potential. The stepped-wedge design will provide experimental control, reduce error variance, avoid problems with control groups, model campaign dose, and efficiently use resources to recruit and retain the sample. We will recruit from an internet panel rather than from the community to obtain a large sample from the sparsely populated Mountain West. The social media campaign will be based on theories of health behavior change and social media influence. The stepped-wedge design and a multifaceted analysis of campaign engagement will be used to assess campaign dose effects.

Several design decisions were made to avoid or reduce potential weaknesses. Using a research panel to improve sample diversity is appropriate for a field experiment that does not aim to estimate population prevalence [204]. Research panel members may participate in multiple studies, but this does not appear to cause low-quality results [205]. Social media advertising was considered for delivering the intervention, but it is difficult to achieve advertising exposure [206] and control contamination, and any test would require a very large sample. Emerging adults

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with a history of cancer will be included because (1) their numbers are small [207], (2) many engage in cancer risk behaviors [208] and can benefit, and (3) excluding them would reduce generalizability. Self-report measures can contain errors; however, given the large geography and virtual environment, they are practical. We have selected validated self-report measures and will verify physical activity, diet, and nicotine abstinence measures using a subgroup validation cohort that provides more rigorously measured health behavior data. The primary evaluation will test the impact of the overall social media campaign, not the individual message strategies. To obtain insights on which strategies impact outcomes, we will examine campaign engagement measures, theoretical mediators, and the association of message topic and format with changes in cancer risk behaviors and theoretical mediators. Although most emerging adults engage with a variety of social media platforms, we have chosen to use the Facebook platform for delivering our social media campaign. This decision is based on its practicality and widespread use among emerging adults as well as its features that enhance experimental rigor.

Conclusions

New strategies are needed to improve public health information dissemination, correct misinformation [66-68], and promote skills to help emerging adults judge the veracity of web-based content to promote cancer risk reduction. The study will provide this innovation in several ways. A unique, theory-based social media campaign will be created that delivers relevant, credible, and timely content on reducing multiple cancer risks among emerging adults and can be translated to emerging adults in other rural regions. It promotes the reduction of cancer risk behaviors in the diverse (based on ethnicity and education) emerging adult population in the Four Corners area, which has been largely overlooked in past research. This will be one of the first studies using participatory strategies to focus an intervention on behavioral and environmental cancer risk factors and health disparities in an emerging adult population. Emerging strategies will be used to correct misinformation about cancer risk behaviors on social media, along with promoting digital and media literacy skills to emerging adults. The study should have a major impact on emerging adults' cancer risk behavior decisions and the consumption of accurate cancer information. Finally, the findings should be applicable to other cancer communications and disease prevention efforts for rural emerging adults.

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Data Availability

The data collected in this study will be made available in a publicly accessible data repository at the conclusion of the research.

Authors' Contributions

DBB, ALS, CAT, DK, DT, KLH, ELW, BJW, WGW, KN, CKB, DDG, EAB, JSG, JH, and DW conceptualized the study, designed methods, and secured extramural funding. DBB, ALS, CAT, DK, and DT are supervising project activities. AK, DDG, AKY, CFJ, KC, JB, JAT, EYBP, and AS are managing day-to-day study activities. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

DBB, BJW, WGW, KN, JB, AS, and AK receive a salary from Klein Buendel, Inc. DBB's spouse is an owner of Klein Buendel, Inc. DK is a consultant for Merck and has received 2 Merck Investigator Studies Program research awards. All other authors declare no other conflicts of interest.

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Abbreviations

DIT: diffusion of innovations theory
EAAB: Emerging Adult Advisory Board
HPV: human papillomavirus
MVPA: moderate to vigorous physical activity
REDCap: Research Electronic Data Capture
RUCC: Rural-Urban Continuum Codes
SCT: social cognitive theory
SDT: self-determination theory
SOAB: Stakeholder Organization Advisory Board

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Protocol

Development of Continuous Assessment of Muscle Quality and Frailty in Older Patients Using Multiparametric Combinations of Ultrasound and Blood Biomarkers: Protocol for the ECOFRAIL Study

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Abstract

Background: Frailty resulting from the loss of muscle quality can potentially be delayed through early detection and physical exercise interventions. There is a demand for cost-effective tools for the objective evaluation of muscle quality, in both cross-sectional and longitudinal assessments. Literature suggests that quantitative analysis of ultrasound data captures morphometric, compositional, and microstructural muscle properties, while biological assays derived from blood samples are associated with functional information.

Objective: This study aims to assess multiparametric combinations of ultrasound and blood-based biomarkers to offer a cross-sectional evaluation of the patient frailty phenotype and to track changes in muscle quality associated with supervised exercise programs.

Methods: This prospective observational multicenter study will include patients aged 70 years and older who are capable of providing informed consent. We aim to recruit 100 patients from hospital environments and 100 from primary care facilities. Each patient will undergo at least two examinations (baseline and follow-up), totaling a minimum of 400 examinations. In hospital

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environments, 50 patients will be measured before/after a 16-week individualized and supervised exercise program, while another 50 patients will be followed up after the same period without intervention. Primary care patients will undergo a 1-year follow-up evaluation. The primary objective is to compare cross-sectional evaluations of physical performance, functional capacity, body composition, and derived scales of sarcopenia and frailty with biomarker combinations obtained from muscle ultrasound and blood-based assays. We will analyze ultrasound raw data obtained with a point-of-care device, along with a set of biomarkers previously associated with frailty, using quantitative real-time polymerase chain reaction and enzyme-linked immunosorbent assay. Additionally, we will examine the sensitivity of these biomarkers to detect short-term muscle quality changes and functional improvement after a supervised exercise intervention compared with usual care.

Results: At the time of manuscript submission, the enrollment of volunteers is ongoing. Recruitment started on March 1, 2022, and ends on June 30, 2024.

Conclusions: The outlined study protocol will integrate portable technologies, using quantitative muscle ultrasound and blood biomarkers, to facilitate an objective cross-sectional assessment of muscle quality in both hospital and primary care settings. The primary objective is to generate data that can be used to explore associations between biomarker combinations and the cross-sectional clinical assessment of frailty and sarcopenia. Additionally, the study aims to investigate musculoskeletal changes following multicomponent physical exercise programs.

Trial Registration: ClinicalTrials.gov NCT05294757; https://clinicaltrials.gov/ct2/show/NCT05294757

International Registered Report Identifier (IRRID): DERR1-10.2196/50325

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KEYWORDS

muscle; ultrasound; blood-based biomarkers; sarcopenia; frailty; older adults

Introduction

Aging is associated with a gradual decline in muscle mass and function, contributing to an increased incidence and prevalence of chronic diseases [1,2]. This, in turn, often leads to situations of multimorbidity [3] and adversely affects functional autonomy [4]. The most severe manifestation of this condition is frailty, described as “a progressive decline in physiological systems that leads to decreased reserves of intrinsic capacity. This confers extreme vulnerability to stressors and increases the risk of various adverse health outcomes” [5]. Frailty is linked to dependency, hospitalization, institutionalization, falls, poor quality of life, and mortality [6-10], along with elevated health care costs [11,12]. While standardized diagnostic criteria are not universally established, the 2 most widely accepted ones [13,14] are rooted in the phenotype construct [4]. According to this construct, frailty is diagnosed when 3 or more of the following criteria are met: unintentional weight loss, self-reported exhaustion, reduced grip strength, slow gait speed, and low levels of physical activity. Moreover, the Cumulative Deficit Model—Frailty Index encompasses cognitive, functional, emotional, and nutritional status [15,16].

The frailty phenotype, as outlined by Fried et al [4], centers around muscle dysfunction [17]. Considering that weakness, slowness, and impairment of the muscular system are characteristic features of frailty, sarcopenia is likely a crucial physiopathological contributor [13,18]. Sarcopenia is a progressive skeletal muscle disease, and its prevalence tends to increase with age. Estimates suggest that sarcopenia affects between 6% and 19% of the general population aged 60 years and older, with variations depending on the applied definition [19]. Currently, the most widely used definitions come from the European Working Group on Sarcopenia in Older People 2 (EWGSOP-2) [20], the Definition and Outcomes Consortium (DOCS) [21], and the National Institute of Health Foundation (NIHF) [22]. According to the EWGSOP-2, reduced muscle strength serves as the initial criterion for probable sarcopenia, and the diagnosis is confirmed by reduced muscle mass and quality. Furthermore, when low physical performance is identified, sarcopenia is categorized as severe [20]. The DOCS supports the inclusion of both weakness (defined by low grip strength) and slowness (defined by low usual gait speed) in the definition of sarcopenia [21]. The NIHF defines sarcopenia as a loss of strength diagnosed by low grip strength, accompanied by low muscle mass [22].

In clinical care, the assessment of muscle mass and quality involves a semiquantitative evaluation using 2D images through dual-energy X-ray absorptiometry (DXA) and a body composition estimate through bioelectrical impedance analysis (BIA) [20]. It is worth noting that these techniques can be influenced by other variables, such as skeletal mass and a high BMI [23]. Radiological imaging enables comprehensive 3D mapping of muscle composition and microstructure. The proposed methods are magnetic resonance imaging (MRI) and computed tomography (CT) sequences, allowing the assessment of adipose fraction and fibrous microstructure, among other parameters [24-26]. However, because of their high cost and the potential for patient complications, these imaging methods are presently limited to research applications or as supplementary examinations for different primary indications [27].

Sarcopenia and frailty, although connected and associated with aging, are distinct conditions. Sarcopenia primarily centers around the musculoskeletal system, while frailty is a more multifactorial condition [28,29]. Various studies indicate that the prevalence of sarcopenia among older adults with frailty is higher than the prevalence of frailty among those with sarcopenia [28,30-32]. Adverse outcomes linked to muscular

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decline can be mitigated, delayed, or even reversed through early detection and interventions, including nutritional support and physical exercise programs [13,18,33]. Nonetheless, there exists a need for straightforward and dependable tools that facilitate the assessment of muscle quality and its implications for frailty [28,34].

Ultrasound, as a fast, noninvasive, and cost-effective imaging modality, is gaining rapid prominence for musculoskeletal examination [35,36]. Currently, clinical ultrasound images (B-mode) enable the assessment of muscle mass and morphology, encompassing measures such as muscle thickness, pennation angle, cross-sectional area, echo intensity, and fascicle length [37-39]. Despite ongoing efforts for standardization, these measurements remain highly reliant on the expertise and skills of the operator, and they do not provide definitive results for the early staging of muscle quality loss [37,40]. Ultrasound morphometric measurements of sarcopenia in older adults have demonstrated mild to moderate associations with frailty [41]. More recently, various quantitative ultrasound techniques have surfaced, involving the analysis of echogenicity, texture parameters, elastography, and acoustic wave properties. However, their translation to clinical practice is still limited [42-51]. Artificial intelligence is presenting new opportunities to objectify musculoskeletal ultrasound, with recent studies showcasing automatic muscle segmentation, fiber angle detection, and textural discrimination of muscle microstructures [52-55].

Biological biomarkers serve as valuable tools in diagnosing and stratifying patients, as well as in comprehending the underlying pathophysiology of diseases. Oxidative stress, a proinflammatory state, and immune aging play significant roles in the connection between nonspecific biomarkers and specific biological systems related to frailty and sarcopenia [56-59]. Recent studies have delved into the intricate interrelationships among various systems that underlie frailty through multi-omics approaches [60]. As an example, the FRAILOMIC initiative used blood samples to delineate a collection of biological biomarkers, encompassing both protective and risk factors. Notably, oxidative stress, vitamin D, and the cardiovascular system were found to be associated with frailty [61]. Despite these advancements, the currently available biomarkers exhibit weak individual associations with the clinical outcomes of sarcopenia and frailty. Furthermore, their ability to detect changes after physical intervention remains largely unknown.

A limited number of studies have explored the combination of ultrasound and blood-based biomarkers. In one study, changes in circulating biomarkers corresponding to a short-term resistance exercise intervention in older adults were identified. These changes were found to be significantly related to ultrasound leg cross-sectional area [62]. Associations were discovered between combined genetic and methylation scores and ultrasound-derived skeletal muscle morphometry in older women [63]. In another cross-sectional study, ultrasound characteristics of the quadriceps femoris in patients with sarcopenia were correlated with blood and urinary biomarkers [64].

In summary, there is a lack of simple and objective screening tools for diagnosing frailty and sarcopenia [28,34]. While clinical standardization of B-mode images is essential, there is also a requirement for advancements in ultrasound technology to develop quantitative indicators for assessing muscle quality [65,66]. This study is designed to assess objective methods for evaluating muscle quality using quantitative analysis techniques based on the analysis of ultrasound raw data combined with blood-based biomarkers. Additionally, the study aims to investigate the capability of these biomarkers to detect changes in muscle quality resulting from a physical exercise intervention program in older individuals with frailty.

The primary aim of this study is to assess the feasibility of combining point-of-care quantitative ultrasound parameters with blood-based assays for evaluating muscle quality and frailty in older adults. This evaluation will encompass both hospital settings and community care, with a focus on comparing the findings with traditional clinical evaluations.

Methods

Study Setting

This study is designed as a prospective, experimental, multicenter, 3-cohort investigation. The research will be performed at Albacete University Hospital Complex, Spain (with the coordinating Clinical Research Ethics Committee; hospital 1); Getafe University Hospital, Spain (hospital 2); and primary care units of Donostialdea, Osakidetza, Spain (primary care units). The primary health care units involved in the study will be located in 2 districts/regions of Gipuzkoa: the region of Donostialdea and the region of Tolosaldea. The design of this study protocol, characterized as exploratory, adheres to the SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials; Multimedia Appendix 1) 2013 guidelines, as depicted in Figures 1 and 2.

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Figure 1. SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials) figure.

	STUDY PERIOD						
	Enrolment	Allocation	Intervention Period			Close out	
TIMEPOINT	0 week	0 week	0 week	1-16 weeks	1 year	17 weeks (Hospital exercise and control cohort)	1 year (Primary care cohort)
Enrolment:							
Eligibility screen (Inclusion and exclusion criteria)	X						
Informed consent	X						
Allocation		X					
Interventions:							
Hospital exercise cohort (1)				1			
Hospital control cohort (2)				2			
Primary care cohort (3)					3		
Assessments:							
Body composition			1-2-3			1-2	3
GDS			1-2-3			1-2	3
Charlson Comorbidity index.			1-2-3			1-2	3
Barthel index			1-2-3			1-2	3
Lawton and Brody index			1-2-3			1-2	3
SPPB			1-2-3			1-2	3
SARC-F			1-2-3			1-2	3
FRAIL			1-2-3			1-2	3
Frailty phenotype of frailty			1-2-3			1-2	3
MNA-SF			1-2-3			1-2	3
IPAQ			1-2-3			1-2	3
EQ 5D-5L			1-2-3			1-2	3
Gait speed test			1-2-3			1-2	3
Grip strength			1-2-3			1-2	3
Ultrasound			1-2-3			1-2	3
Blood sample testing			1-2-3			1-2	3
Dropout reasons						1-2	3
Adverse events						1-2	3

Figure 2. Flow diagram of the study protocol.

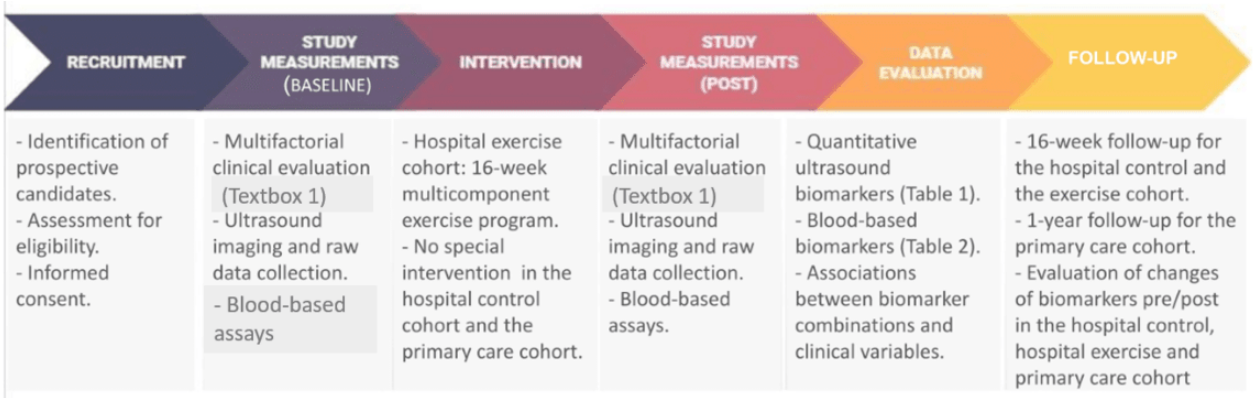

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Study Population Recruitment

Hospital Exercise Cohort

Participants will be consecutively recruited from the scheduled patient list of the falls unit and the outpatient clinics of hospital 1. Upon obtaining informed consent, patients will undergo a baseline clinical evaluation. Subsequently, ultrasound measurements and a DXA scan will be conducted, and blood samples will be collected, processed, and stored. These patients will then be enrolled in a 16-week multicomponent physical exercise program (discussed later). Following the completion of the exercise program, at the 16-week follow-up, a repetition of clinical evaluation, ultrasound, DXA, and blood-sample testing will be performed.

Hospital Control Cohort

Participants will be consecutively recruited from the scheduled patient list of the frailty unit, day hospital, and the outpatient clinic of the Geriatrics Department of hospital 2. Upon obtaining informed consent, baseline study variables will be collected. These patients will be followed up for 16 weeks under usual care. After the follow-up period, a repetition of the baseline evaluation will be conducted.

Primary Care Cohort

Participants will be consecutively recruited from the scheduled patient list of the primary care units. Upon obtaining informed consent, baseline study variables will be collected. These patients will be followed up for 1 year under usual care. After the 1-year follow-up, a repetition of the baseline evaluation will be conducted.

Recruitment is conducted by the study coordinator staff at each site, under the overall supervision of the clinical principal investigator at each site. Participants will sign the informed consent at the beginning of the first visit. The professional overseeing the assessment will provide an explanation of the project, and the participant will sign both the information sheet and the informed consent to participate. The principal investigator at each site will be responsible for collecting and monitoring the documentation related to informed consent. The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion, exclusion, and termination criteria.

1. Inclusion criteria

- Age of at least 70 years.
- Either gender.
- Ability to provide informed consent.
- Ability to perform all the functional tests.
- In the hospital exercise cohort, the ability to participate in the physical exercise program.

2. Exclusion criteria

- Expected survival of <1 year.
- Barthel Scale score <70.
- Moderate-to-severe cognitive impairment.
- Refusal to participate.
- Medical conditions that may compromise or impede follow-up assessments.
- Older adults already enrolled in regular physical exercise programs will be excluded from participating in the hospital exercise cohort.

3. Termination criteria

- Refusal to continue participation.
- Complications during or in between examinations and intervention.

Allocation

The allocation sequence in this multicentric study is institution-based. Patients recruited at the Department of Geriatrics of the Complejo Hospitalario Universitario de Albacete will be automatically allocated to the supervised exercise program by default. By contrast, patients recruited at the Geriatrics Department of the University Hospital of Getafe will not be assigned to any specific interventions. Similar sociodemographic characteristics are anticipated for both patient populations. At each institution, patients will be recruited from the falls unit, outpatient clinics, and day hospital. Within each acquisition site, patient selection will be conducted based on the clinical agenda until the recruitment goals are met.

The allocation sequence is sequential, aligned with the clinical agenda, and overseen by the clinical principal investigator at each site. Any deviations from the recruitment plan outlined in the clinical agenda must be thoroughly justified and meticulously documented.

Interventions

In the hospital exercise cohort, a 16-week supervised multicomponent physical exercise program will be implemented. The individualized exercise intervention, tailored to each

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individual's functional capacity, comorbidities, and previous experience, will consist of 2 supervised sessions per week, each lasting 45 minutes. These sessions will be conducted in small groups, with 4-6 older adults per group. The sessions are divided into warm-up, main part (strength, power, and coordination exercises), and cool down (flexibility and stretching). The main part of the exercise program comprises 8 exercises targeting the major muscle groups. The progression starts with low-intensity and high-volume sessions, gradually advancing to higher intensities and lower volumes. Depending on the stage, participants will complete 2-4 sets, consisting of 4-15 repetitions, with a 30-second rest between sets and exercises. For each exercise, loads and intensities will be adjusted to achieve a total of 30 repetitions. All exercise sessions are to be conducted in the gym of the Geriatrics Department of the hospital. Participants will be encouraged to incorporate additional 90-minute walks per week into their routine. It is important to note that the exercise program is aligned with the guidelines of the VIVIFRAIL program [67], which specifically aims to prevent weakness and reduce the risk of falls.

In the hospital control and primary care cohorts, no specific intervention will be implemented.

Retention

In alignment with the VIVIFRAIL program guidelines, our intervention program is designed to prevent weakness and reduce the risk of falls. Patients will be informed about the program's benefits during recruitment and follow-up. Within the supervised exercise program, interventions and patient progress will be personalized and monitored, taking into account functional capacity, comorbidities, and the individual's previous experiences. The sessions will be closely monitored at the gym of the Geriatrics Department of the hospital. The individualized sessions will enable discussions on progress with the patient throughout the intervention, fostering motivation for retention and completing the follow-up. Participants will also be encouraged to adopt healthy habits, such as incorporating an additional 90-minute walk per week. In case participants require medical care that may interfere with the ongoing study procedures, they will be managed according to the clinical routine and subsequently excluded from the study. In these cases, the data collected during the baseline examination will be used for a cross-sectional clinical evaluation of frailty and sarcopenia. However, musculoskeletal changes following the multicomponent exercise program will not be assessed.

Safety Monitoring

Each principal investigator at every data acquisition center will oversee the monitoring and follow-up of participants included in their respective cohorts under usual care. They will make decisions regarding patient exclusion and assignment to interventions, and monitor termination criteria as deemed necessary. Additionally, participation in an exercise program is generally associated with a low risk (–1%) of adverse events [68], most of which are typically low-grade responses to exercise, such as muscle soreness [69]. However, in the event of adverse events or serious adverse events, they will be promptly reported to the Clinical Research Ethics Committees.

Randomization and Blinding

Data analysis will be conducted independently of cohort recruitment and follow-up. The evaluation of data will take place at the Deusto Institute of Technology (Ultrasound Data Evaluation Center) and Biodonostia (Blood-based Assays Evaluation Center). Initially, only anonymized data, including ultrasound images, raw data, and blood-based assays, will be transmitted to the data evaluation centers. In the case of combination models, a training set of clinical variables will also be transferred to the data evaluation centers. Reserved data sets will be kept at the clinical acquisition centers for independent testing. This includes data from various sites and information obtained during follow-up examinations.

Sample Size

A population of 200 participants will be recruited, with 100 participants in the primary care cohort, 50 participants in the hospital exercise cohort, and 50 participants in the hospital control cohort (2:1:1 ratio). Patient selection within each acquisition site will be conducted based on the clinical agenda until the recruitment goals are met. Each participant will undergo 2 examinations (baseline and follow-up), resulting in a minimum total of 400 examinations.

An estimated distribution of 85% of patients with frailty to 15% of healthy participants is anticipated in the hospital cohorts, while a distribution of 15% of patients with frailty to 85% of healthy participants is expected in the primary care cohort. Consequently, an accrual of 139 robust participants and 86 patients with frailty is projected. It is assumed that up to 10% of the participants may be excluded in data evaluation as a result of failed measurements or logistical challenges in collecting all variables. In cases where follow-up measurements are not feasible for patients, the baseline measurement will still be included in the evaluation of the primary outcomes. With 80% power, the planned population will enable the detection of a biomarker medium effect size of E/S=0.39, considering a 2-sided α level of .05. For the secondary goal, our sample size of 100 provides 80% power to detect a biomarker with a medium effect size (E/S=0.284) at a 2-sided α level of .05. The sample size was calculated using RiskCalc (Moody's Analytics) [70].

Outcomes

Primary Outcomes

Investigating the association between quantitative ultrasound biomarkers related to muscle mass and quality (thickness [mm], cross-sectional area [cm^2], perimeter [mm], pennation angle [degrees]) extracted from raw data and blood-based biomarkers, as well as their combinations with clinical variables. These clinical variables encompass frailty (FRAIL [short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight] scale ranging from 0 to 5, with 0 indicating robustness and 5 indicating frailty, and Frailty phenotype by Fried et al [4], ranging from 0 [robust] to 5 [frail]), sarcopenia (SARC-F [Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls] scale scores ranging from 0 [robust] to 10 [sarcopenic]), physical function (Short Physical Performance Battery [SPPB] Scale score ranging from 0 to 12, where 0 indicates the lowest physical performance and 12

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indicates the highest performance), International Physical Activity Questionnaire scores ranging from 0 (lowest) to 3 (highest), Gait Speed Test in seconds, grip strength measured by Jamar dynamometer in kilogram, disability (Global Deterioration Scale, consisting of 7 stages), Barthel Index (ranging from 0 [total dependent] to 100 [independent]), Lawton and Brody Index (scores from 0 [dependent] to 8 [independent]), nutritional status (Mini Nutritional Assessment—Short Form), body composition (DXA), and quality of life (EQ-5D-5L) within 3 cohorts of older adults: hospital control cohort, hospital exercise cohort, and primary care cohort.

Secondary Outcomes

- In the hospital exercise cohort, we will assess changes in quantitative ultrasound and blood-based biomarkers, as well as clinical variables, following a 16-week multicomponent physical exercise program. Additionally, exploring associations between ultrasound and blood-based biomarkers and the remaining clinical variables both before and after the exercise program.
- In the hospital control cohort, we will examine changes in quantitative ultrasound and blood-based biomarkers, along with clinical variables, following a 16-week follow-up period without intervention. Furthermore, we will explore associations between quantitative ultrasound and blood-based biomarkers and the remaining clinical variables after the 16-week follow-up period.
- In the primary care cohort, we will assess changes in quantitative ultrasound and blood-based biomarkers, along with clinical variables, following a 1-year follow-up period without intervention. Additionally, we will explore associations between quantitative ultrasound and blood-based biomarkers and the remaining clinical variables after the 1-year follow-up.
- We will evaluate differences in the changes of all measurements among the 3 cohorts. A direct comparison will be made between the 2 hospital cohorts, while the primary care cohort will serve as a reference for understanding changes in nonhospital populations.

Outcome Measurements

The list of clinical variables collected at baseline and follow-up assessments is included in Textbox 2.

Textbox 2. Clinical variables in baseline and follow-up examination.

- Global Deterioration Scale of Reisberg for assessment of cognitive function.
- Charlson Comorbidity Index.
- Barthel Index of independence to perform basic activities of daily living.
- Lawton and Brody Index of independence to perform instrumental activities of daily living.
- Short Physical Performance Battery for Physical Function Assessment.
- SARC-F (Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls) scale of sarcopenia screening.
- FRAIL (short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight) scale of frailty evaluation.
- Frailty phenotype of frailty proposed and validated by Fried et al [4].
- Mini Nutritional Assessment—Short Form for nutritional screening.
- International Physical Activity Questionnaire for physical activity levels.
- EQ-5D-5L for health-related quality of life assessment.
- Gait Speed Test for Physical Function Assessment.
- Grip strength with Jamar dynamometer.
- Population characteristics: age, sex, and BMI.
- Body composition (dual-energy X-ray absorptiometry; total muscle mass, appendicular lean soft tissue mass [ALM], dual-energy X-ray absorptiometry [ALM/h^2 or ALM divided by height squared], total fat, and fat percentage)

Ultrasound Imaging and Raw Data Acquisition

The ultrasound equipment used in this study is the L7 HD3 portable linear scanner (Clarius Mobile Health Corp.). Specifically designed for point-of-care ultrasound examinations, the probe of this device boasts a frequency range of 4-13 MHz with a center frequency of 7 MHz. To facilitate seamless data transfer, anonymized digital ultrasound data are transmitted from the scanner through a customized Wi-Fi network to a smart device, enabling real-time B-mode navigation and data storage. The important feature of the scanner is an integrated image processing package designed to optimize B-mode musculoskeletal image quality. This technology enhances the clarity and quality of musculoskeletal imaging during examinations. Additionally, the scanner is equipped with a research package designed to capture raw beamformed backscattering ultrasound data after the beamformer. These raw data are presented in an in-phase/quadrature complex baseband representation, commonly referred to as IQ data. The IQ data serve as the foundation for the implementation of tailored quantitative ultrasound algorithms [71].

All examinations will be conducted within a depth range of 0-60 mm, using 50% of the maximum acoustic output offered by the scanner. During measurements, efforts will be made to minimize skin-probe compression to maintain acceptable image

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quality. Following each examination, the acquired data will be uploaded to a HIPAA (Health Insurance Portability and Accountability Act)-compliant cloud service, offered by the scanner's manufacturer, enabling the centralization of data (Figure 3).

Figure 3. Ultrasound data flow and management from clinical acquisition centers to ultrasound data evaluation center.

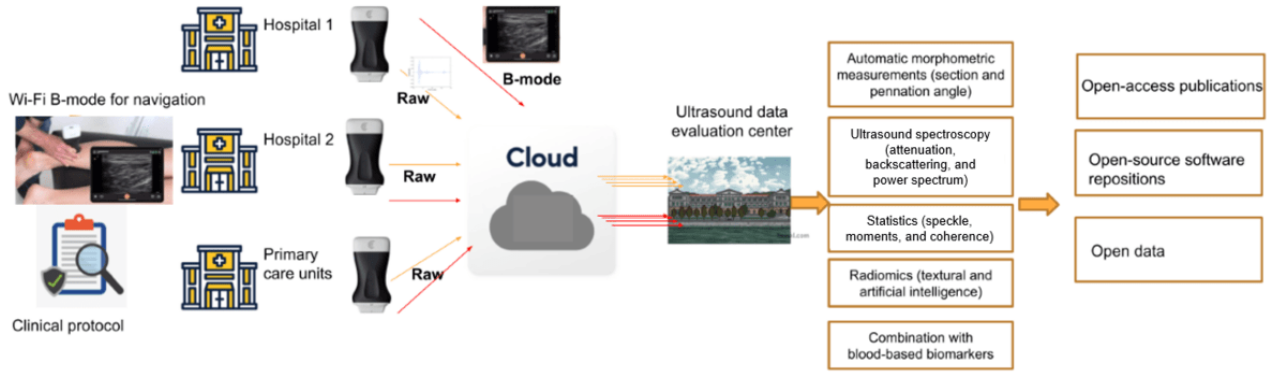

Ultrasound Examination Protocol

The midpoint of the thigh will be determined and marked as the half-distance between the superior border of the patella and the anterior-superior iliac crest. Using the femur as a guide in the transverse view, the midpoint of each thigh will be located, and the various components of the quadriceps muscles (rectus femoris, vastus intermedius, vastus medialis, and vastus lateralis) will be identified (Figure 4).

Figure 4. Echographic B-mode appearance of mid-thigh in the (A) transverse and (B) longitudinal views.

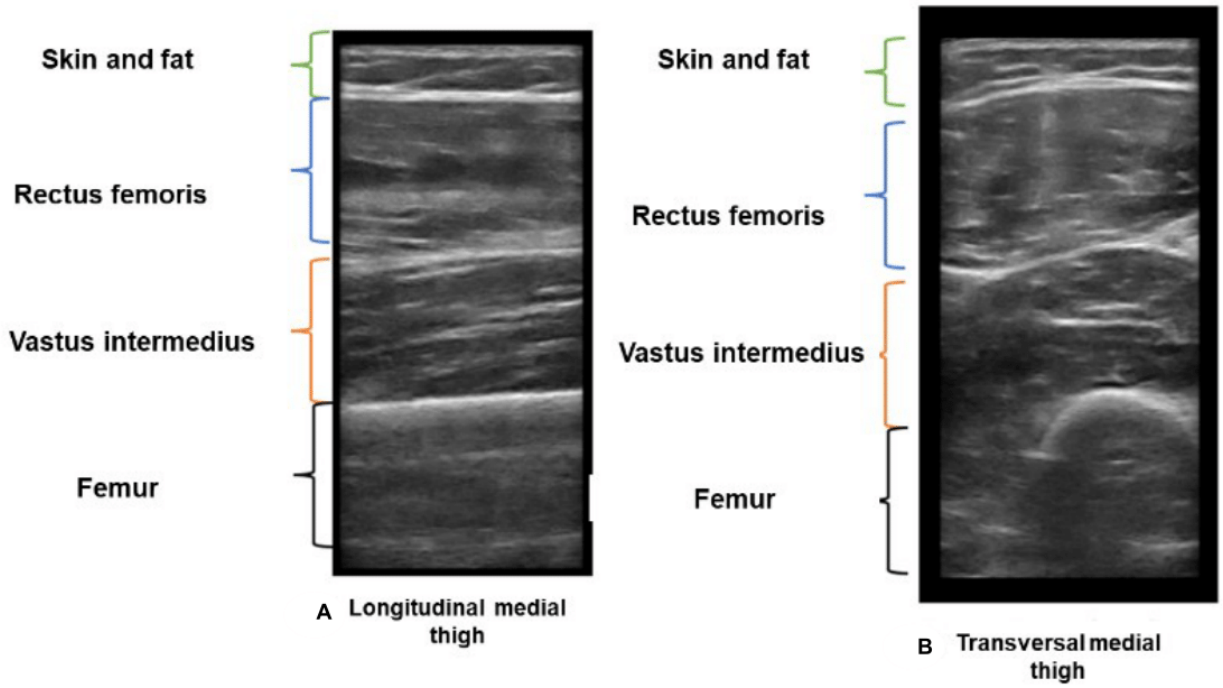

In each examination, a minimum of 12 coregistered B-scan and raw data frames will be obtained. This will include 3 transverse and 3 longitudinal views for both thighs. The longitudinal examination will be conducted in a plane where fasciculations are visible, ensuring comprehensive coverage and detailed assessment of the musculoskeletal structures.

Evaluation of Quantitative Ultrasound Biomarkers

Morphometric Ultrasound Measures

Throughout the examination, the sonographer will record morphometric ultrasound measurements using the online ultrasound scanner's interface (Figure 5). This includes capturing the thickness of the rectus femoris in the transverse view at the midsection point, measuring the perimeter and cross-sectional area of the rectus femoris in the transverse view, and determining the pennation angle in the longitudinal view.

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Figure 5. Morphometric ultrasound measurements. (A) Rectus femoris thickness, cross-sectional surface, and perimeter (transverse view). (B) Pennation angle (longitudinal view).

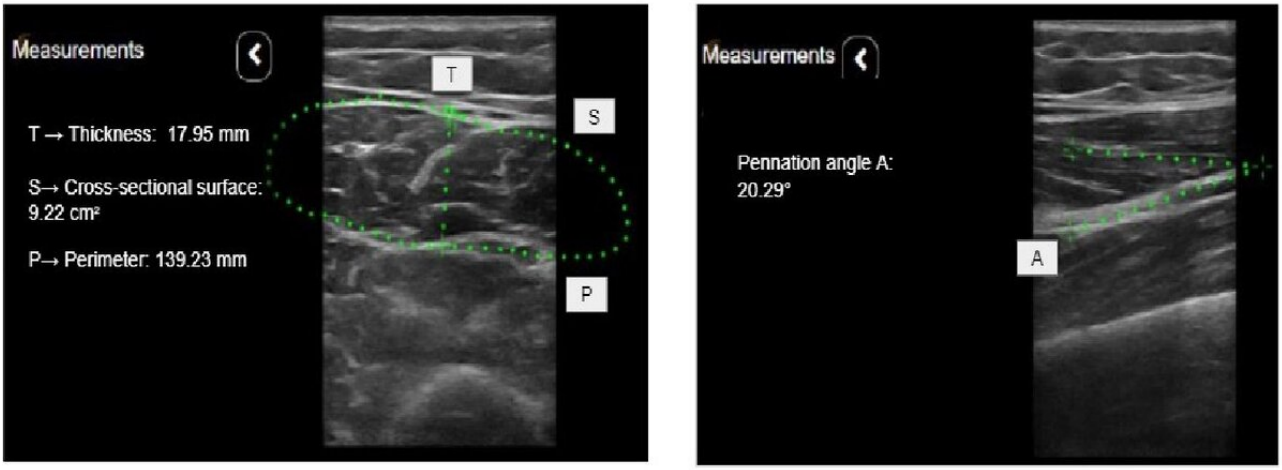

Raw Data Evaluation

Quantitative ultrasound biomarkers will be assessed offline using the acquired raw IQ data. Regions of interest encompassing the rectus femoris will be delineated in the raw data domain by automatically generating B-mode images from the raw data. This process will use the coregistered clinical B-mode images and sonographer annotations as a reference for the definition of the accurate region of interest. Table 1 presents a list of state-of-the-art quantitative ultrasound biomarkers, the hyperparameters of which will be systematically adjusted through experimental adaptation for musculoskeletal examinations. These adjustments will be made and subsequently evaluated using the raw data obtained from the ultrasound probes during the study.

Table 1. Quantitative ultrasound biomarkers based on raw data.

Biomarker	Description	Literature references
Automatic morphometric measurements	Automatic muscle morphometric analysis based on neural network segmentation models trained with respect to sonographer annotations of rectus femoris cross section, and 2D Fourier analysis of pennation angle.	[72,73]
Attenuation coefficient	Measurement of loss of signal intensity with depth.	[47,48,50]
Backscattering coefficient	Measurement of tissue reflectivity after attenuation compensation.	[74,75]
Power spectrum (Lizzi-Feleppa parameters)	Spectroscopy measurement of backscattered signal variation with frequency, including parametrizations such as spectral slope, spectral intercept, and midband fit	[49]
Speckle statistics	Fitting of raw envelope signal to speckle statistical distribution models, including Rayleigh, Nakagami, and homodyned K-distribution. Estimation of scatterer concentration, spacing, and coherence from fitted model parameters.	[49,76,77]
Statistical moments	Nonparametric statistical moments capturing scatterer distribution and concentration, such as entropy, kurtosis, skewness, variance, anisotropy, and signal-to-noise ratio.	[78,79]
Coherence and speed of sound	Generalized spectrum analysis and estimation of coherence, mean scatterer spacing, and speed-of-sound in muscle.	[80,81]
Textural radiomics	First- and second-order texture features extracted from both B-mode (eg, based on gray-scale co-occurrence matrices) and raw data (eg, based on wavelet and Laplacian transformations) and combined with machine learning models trained with respect to clinical outcomes.	[51,53,54]
Artificial intelligence radiomics	Radiofrequency data and B-mode features extracted automatically with end-to-end neural network models trained with respect to clinical outcomes	[52,82-84]

Evaluation of Blood-Based Biomarkers

During both basal and follow-up acquisitions, venipuncture will be performed to collect one 10-mL serum blood tube and two 5-mL ethylenediaminetetraacetic acid (EDTA) blood tubes. The serum sample will undergo centrifugation and will be stored in 4 aliquots. One of the EDTA samples will be promptly frozen and stored at –80°C, while the other will be subjected to centrifugation for plasma and buffy coat extraction. These samples will be stored at –80°C at the clinical sites until transportation, which will be carried out with dry ice to the Blood-Assay Evaluation Center for subsequent processing and storage (Figure 6).

The expression of previously described biomarkers, including vitamin D, lutein zeaxanthin, troponin T, pro-brain natriuretic peptide, soluble receptor for advanced glycation end products

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(sRAGE) [85], and microRNAs, along with those associated with relevant pathways related to frailty such as inflammation (interleukin 6) and senescence (p16INK4A and p21CIP [56]), will be assessed in cells obtained from a blood sample. This evaluation will be conducted in a subsample of patients in baseline conditions and after intervention at both the transcriptional and protein levels, as outlined in Table 2. Erythrocytes will be lysed using Buffer EL (Qiagen), and total RNA from leukocytes will be isolated using the miRNeasy Mini Kit (Qiagen). Initially, RNA samples will undergo purification with the RNeasy Kit (Qiagen). Subsequently, the RNA will be retro-transcribed, and gene expressions will be quantified through quantitative polymerase chain reaction (PCR) using specific primers or probes and the ABI Prism SDS 7300 Real-Time PCR System (Applied Biosystems). Expression levels will be normalized to the expression of the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [86]. Furthermore, protein levels will be assessed in serum samples using Quantikine enzyme-linked immunosorbent assays and Luminex, as previously outlined [87].

Figure 6. Biomarkers data flow and management from clinical centers to blood-essay evaluation center. ELISA: enzyme-linked immunosorbent assay; qRT-PCR: real-time quantitative reverse transcription polymerase chain reaction.

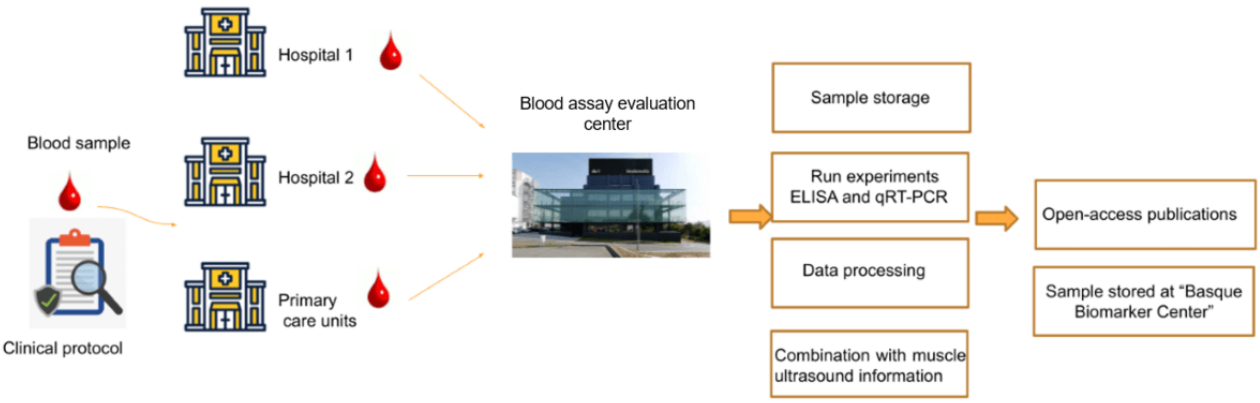

Table 2. Blood-based biomarkers.

Biomarker	Method of measurement
Vitamin D	ELISA[a]
Lutein zeaxanthin	ELISA
Troponin T	ELISA
Pro-brain natriuretic peptide	ELISA
Soluble receptor for advanced glycation end products	ELISA
MicroRNA 125	qRT-PCR[b]
MicroRNA 194	qRT-PCR
MicroRNA 454	qRT-PCR
Interleukin-6	ELISA and Luminex
$P16^{INK4A}$	qRT-PCR
$P21^{CIP}$	qRT-PCR
New unpublished	qRT-PCR and ELISA

[a]ELISA: enzyme-linked immunosorbent assay.

[b]qRT-PCR: real-time quantitative reverse transcription polymerase chain reaction.

Statistical Analysis

The study population will be characterized based on demographic and clinical attributes. Categorical data will be summarized with frequency and percentage representations. Continuous data will be described using mean, SD, median, and the 25th and 75th percentiles. Furthermore, the distribution of ultrasound parameters with respect to the primary endpoint will be depicted using graphical techniques. The correlation of quantitative biomarkers will be evaluated for each multifactorial clinical evaluation parameter using the Pearson correlation coefficient for continuous variables and the Spearman correlation coefficient for categorical variables [88]. Unpaired tests, such as the Student *t* test, will be used for comparing means of biomarkers among various acquired patient cohorts and for stratified patient subgroups based on the frailty scales outlined in Textbox 1. To manage the extensive array of ultrasound and blood biomarkers, a robust statistical analysis

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plan will be implemented. This plan will incorporate correction methods to address the risk of type I errors associated with multiple comparisons. Specifically, for the primary outcome concerning biomarker-clinical associations, we will use Lasso regression. This technique automates the selection of relevant variables, reducing the necessity for extensive corrections and improving interpretability. Paired statistics will be applied in the statistical analysis for longitudinal monitoring, encompassing both interventions and clinical follow-up. The monitoring period in hospital and primary care environments will differ to accommodate the distinct follow-up workflows in each setting. The duration of primary care follow-up aligns with established norms [89,90]. To account for differences in follow-up duration among cohorts over time, our data analysis will incorporate appropriate statistical methods, potentially enabling adjustments for these variations. For the secondary objective, the impact of physical intervention in 50 patients will be compared with 50 patients with no intervention. With 80% power, the planned population size will enable the detection of a biomarker with a medium effect size of E/S=0.284 at a 2-sided α level of .05.

In the context of multiparametric data science models, unsupervised learning techniques will be assessed to cluster patient populations based on biomarker expression. Moreover, supervised multi-omics models will be trained using a training set of clinical variables. Stratified cross-validation will be used to derive model performance statistics, ensuring separate patient data in the training and validation folds and maintaining a balanced distribution of health participants and those with frailty in both training and validation sets. Consecutively, sample imputation will be used to address missing data in the training set, while missing reference variables will be excluded during validation and testing. Sensitivity analyses will be conducted to evaluate the impact of the imputation method on the robustness of our results. Reserve data sets, comprising data from various sites and follow-up examinations, will be used for model testing.

Biomarker reproducibility will be evaluated using the interclass correlation coefficient and the Bland-Altmann method, taking into account repeated measurements within an examination. Subgroup analyses will be conducted to explore variations across patient subpopulations, and regression models will be used to examine the influence of covariates, thereby enhancing methodological precision.

Ethical Considerations

This study protocol received approval from the Research Ethics Committee of Albacete (Spain) with reference CEIm-2021-51. The study will be conducted in adherence to the principles outlined in the Declaration of Helsinki [91]. Before participation, written informed consent will be obtained from all participants, and their data will be handled in accordance with HIPAA guidelines. Additionally, consent will be sought for the review of participants' medical records and for the collection of blood samples to assess biomarkers. In the event of necessary modifications to this protocol during the clinical research, the changes will undergo review by the hospital ethics committee and will be implemented only after obtaining approval. The trial results will be communicated to participants via email by the investigators. Participants involved in this study will not receive any form of compensation for their participation.

The study information will be stored in Microsoft Excel 365 within an electronic database. This database will comprehensively capture individual data, including baseline characteristics, pre- and postassessment data, and any potential adverse events. Notably, no personally identifiable patient information, apart from the unique trial identification number, will be included in the metadata associated with the recorded ultrasound and biomarker data. Ultrasound and biomarker data will be uploaded to a HIPAA-compliant cloud service provided by the ultrasound system manufacturer, enabling centralized evaluation by team members. As outlined in the reference manuscript, upon completion of the study, digitized data sets encompassing ultrasound data, biomarkers, digitized blood-based biomarkers, and anonymized multifactorial clinical evaluations will be published in open-access repositories, such as Zenodo (CERN). Biological samples will be securely stored in the Basque Biomarker Center (Biobanco). Additionally, software models derived from ultrasound raw data will be made accessible through open-source software repositories (eg, GitLab).

Results

The initial analysis results indicate a correlation between ultrasound morphometric parameters and clinical variables (Table 3). This table examines the correlations of ultrasound geometric parameters with clinical variables. The clinical data considered in this analysis are derived from a subset of the hospital cohort, comprising a total of 66 participants. Specifically, correlations between clinical variables and ultrasound parameters during the basal examination have been included in the table.

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Table 3. Preliminary correlations at baseline visit for the hospital cohort (n=66).

Correlations	Thickness run average, *r* (*P* value)	Area run average, *r* (*P* value)	Angle run average, *r* (*P* value)
Age	–0.023 (.82)	0.002 (.98)	–0.072 (.47)
BMI	0.269 (.009)[a,b]	–0.016 (.88)	0.167 (.09)
Charlson	–0.180 (.09)	–0.213 (.04)[a,b]	–0.018 (.85)
Barthel Index	0.058 (.58)	0.176 (.09)	0.224 (.02)[a,b]
Lawton and Brody Index	–0.002 (.98)	–0.056 (.60)	0.220 (.02)[a,b]
Mini Nutritional Assessment—Short Form	0.183 (.08)	0.036 (.74)	0.210 (.03)[a,b]
SARC-F[c]	–0.098 (.35)	–0.236 (.02)[a,b]	–0.158 (.11)
Grip strength	0.240 (.02)[a,b]	0.372 (<.001)[a,b]	0.105 (.32)
Short Physical Performance Battery total	0.288 (.005)[a,b]	0.355 (.001)[a,b]	0.197 (.04)[a,b]
Gait speed	0.168 (.11)	0.327 (.002)[a,b]	0.241 (.01)[a,b]
Frailty phenotype (Fried et al [4])	–0.101 (.34)	–0.211 (.04)[a,b]	–0.044 (.68)
FRAIL[d]	–0.125 (.24)	–0.284 (.006)[a,b]	–0.034 (.73)
DXA[e] total muscle mass	0.473 (<.001)[b,f]	0.498 (<.001)[b,f]	0.143 (.28)
DXA ALM[g]	0.440 (<.001)[b,f]	0.539 (<.001)[b,f]	0.100 (.45)
DXA ALM/h^2	0.529 (<.001)[b,f]	0.493 (<.001)[b,f]	0.115 (.38)
DXA total fat	0.271 (.04)[a,b]	0.29 (.83)	0.130 (.32)
DXA fat percentage	0.132 (.31)	–0.239 (.07)	0.064 (.63)

[a]Significant weak correlations (r<0.4).

[b]Significant correlations (P<.05).

[c]SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls.

[d]FRAIL: short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight.

[e]DXA: dual-energy X-ray absorptiometry.

[f]Significant moderate and strong correlations (r>0.4).

[g]ALM: appendicular lean soft tissue mass.

The analysis revealed significant moderate correlations between muscle cross-section and thickness and DXA parameters (Table 3). Notably, the highest correlation (r=0.539, P<.001) was observed between DXA appendicular mass and muscle cross section. Additionally, significant weak correlations were identified between functional variables (such as gait speed, grip strength, and SPPB) and ultrasound morphometric parameters (including muscle section, thickness, and pennation angle; indicated in Table 3 in rows 7, 8, and 9, respectively). The frailty scale (FRAIL, Fried et al [4]) and the sarcopenia scale (SARC-F) exhibited weak but significant associations with muscle cross section as illustrated in row 2 of Table 3. Additionally, significant weak correlations were identified between pennation angle and measures of independence (Barthel and Lawton Index) as well as nutritional assessment (Mini Nutritional Assessment—Short Form) as detailed in Table 3. Notably, age did not demonstrate a significant association with ultrasound morphometric variables (r=–0.023, P=.82; r=0.002, P=.98; and r=–0.072, P=.47, respectively). However, a weak correlation was observed between BMI and muscle thickness.

Discussion

Principal Findings

The anticipated outcomes of this study are the identification of associations and the development of combination models between quantitative ultrasound and blood-based assays with multifactorial clinical assessments, specifically focusing on muscle quality and frailty. The use of noninvasive portable technologies facilitates the implementation of the clinical protocol in both hospital and primary care environments [92].

The primary findings concerning the correlations of ultrasound geometric variables with clinical and functional variables align with existing clinical literature [17,35,36,41]. These preliminary results are encouraging, demonstrating robust correlations between echo geometric parameters, measured in a standardized manner, and various clinical parameters. Notably, moderate correlations are observed between ultrasound geometrical parameters and muscle mass (DXA), while functional parameters and global scales of sarcopenia and frailty exhibit weak yet significant associations. These results serve as a

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foundational baseline for the development of advanced models based on raw data (Table 1) and blood biomarkers. It is anticipated that these advanced models will exhibit superior correlations with basal characteristics and enhanced sensitivity to changes in muscle quality.

Comparison With Prior Work

Recent literature indicates that impaired mobility associated with aging is not solely attributed to changes in skeletal muscle mass; other factors contributing to muscle quality also play a crucial role. Notably, alterations in muscle tissue composition, characterized by elevated levels of intramuscular adipose tissue and intramyocellular lipids, have been identified as factors that negatively impact muscle functional capacity [17,65,93]. Our hypothesis suggests that quantitative ultrasound biomarkers derived from raw data may exhibit superior discriminative performance, greater reproducibility, and enhanced ease of use compared with the current state-of-the-art assessments based on B-mode images. B-mode morphological ultrasound parameters are primarily linked to muscle mass and demonstrate limited sensitivity in the diagnosis of sarcopenia. Quantitative ultrasound biomarkers derived from raw data have consistently demonstrated their ability to capture both tissue composition and microstructural properties. Furthermore, they have exhibited a greater capacity to encode richer information content compared with ultrasound B-mode images in artificial intelligence models, as highlighted in prior research [52,54,83,84]. Ultrasound spectroscopy parameters and tissue acoustic properties, such as speed of sound and attenuation, have been associated with tissue composition [47] and viscoelastic changes in muscle [49] among older individuals with sarcopenia. Specifically, speed of sound has demonstrated correlations with MRI adiposity estimates in the calf muscles [94], CT assessment of the psoas muscle [95], and short-term changes in muscle due to immobilization [96]. The ultrasound statistical analysis of the envelope signal in soft tissues has been correlated with the concentration, spacing, and directionality of microstructural scatterers [78]. Additionally, texture features derived from radiomics analysis capture musculoskeletal composition and microstructure. This approach has been successfully applied to differentiate various musculoskeletal conditions, including muscle spasticity, dynapenia, myositis, fibromyalgia, Duchenne muscular dystrophy, and exercise-induced muscle damage [55,97]. Being acquired at the early stages of ultrasound image formation, ultrasound raw data may play a crucial role in minimizing equipment- and operator-dependent bias. Additionally, they have the potential to provide data-based guidance for examiners with limited sonographic acquisition expertise.

Molecular biomarkers obtained from blood assays are linked to functional changes between healthy individuals and those with frailty. However, the absence of single established predictor biomarkers is primarily attributed to several factors. These include the heterogeneity and limitations of the scales or indices used to detect sarcopenia and frailty; variations in age, sex, and characteristics across different populations; small sample sizes; limited longitudinal clinical studies; a lack of characterization on interventions to assess their potential reversibility; and differences in techniques and cut-offs used for biomarker measurement. In this study, we incorporate a panel of biomarkers rather than assessing individual molecules. This approach is aimed at providing a more comprehensive reflection of the accumulation of damage associated with age-related syndromes [98]. Additionally, the potential of these biomarkers to assess reversibility, a critical characteristic of frailty, will be evaluated upon completion of an intervention based on an exercise program, followed by a 16-week follow-up.

Sarcopenia and frailty, although related, are distinct aging phenotypes. Notably, the prevalence of sarcopenia is higher among older individuals with frailty than the prevalence of frailty among those with sarcopenia [28-32]. As part of our exploratory outcomes, we will consider the coexistence of sarcopenia and frailty, redefining the frailty prognosis based on the presence or absence of sarcopenia.

To the best of our knowledge, this cohort study stands out as one of the few that integrates raw data ultrasound measurements with blood samples to extract noninvasive biomarkers of frailty and sarcopenia in older adults. Notably, this study represents the first of its kind to establish a connection between quantitative ultrasound and blood biomarkers with the cross-sectional evaluation of frailty and sarcopenia in both hospital and primary care environments. The utilization of point-of-care ultrasound devices presents an opportunity to introduce ultrasound quantitative technology across various clinical settings. Notably, this study marks the pioneering effort to combine quantitative ultrasound with blood-based biomarkers to evaluate musculoskeletal changes following multicomponent physical exercise programs.

Limitations

The study does have certain limitations, notably the absence of access to a gold standard for muscle quality assessment. Established radiological techniques such as CT and MRI serve as references for muscle composition and microstructure but come with patient complications and are not widely accessible in the clinical environments under investigation. Instead, we rely on a multifactorial clinical assessment, patient stratification, and carefully controlled interventions to evaluate changes in muscle quality. The exploration of ultrasound technology is limited to backscattering ultrasound data derived from beamformed raw data. Other ultrasound quantitative technologies, such as shear wave elastography [43] and blood flow measurements based on Doppler sequences [99], are excluded from the scope because of their lack of routine availability in point-of-care ultrasound devices and the added complexity they introduce to the protocol execution. The disparate monitoring periods in hospital (16 weeks) and primary care environments (1 year) are designed to accommodate the distinct follow-up workflows in both settings. We also acknowledge that the randomization of populations in the secondary goal is conducted on an institutional basis, which could introduce statistical bias if the populations in the 2 institutions differ. To address this potential bias, we will perform a *post hoc* analysis to examine the characteristics of the populations in the various recruitment centers. The dimensioning of the primary care follow-up aligns with periods established in previous studies for the general population [89,90].

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Conclusions

In summary, the outlined study protocol aims to integrate portable technologies, leveraging quantitative muscle ultrasound and blood-based biomarkers, for an objective cross-sectional assessment of muscle quality in both hospital and primary care environments. The study endeavors to yield data that will facilitate the exploration of associations between biomarker combinations and the cross-sectional clinical evaluation of frailty and sarcopenia, alongside an examination of musculoskeletal changes following multicomponent physical exercise programs.

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Availability of Data and Materials

The outcomes of this study will be disseminated through publication in an academic journal. Additionally, we plan to organize at least two interdisciplinary workshops involving geriatrics and imaging specialists. To promote transparency and encourage further research, digitalized data sets, comprising ultrasound data and biomarkers, digitized blood-based biomarkers, and multifactorial clinical evaluations, will be published in open-access repositories such as Zenodo. Biological samples will be securely stored at the Basque Biomarker Center (Biobanco). Furthermore, software models derived from ultrasound raw data will be made accessible through open-source software repositories such as GitLab.

Authors' Contributions

SJS and A Coca contributed to the study conceptualization. XR, NV, A Coca, and SJS contributed to the writing of the original draft. XR, NV, RGM, A Coca, RAC, A Costa-Grille, UL, MS, LA, DLI, and SJS contributed to the manuscript review and revisions. PAS, LRM, IV, DLI, A Coca, and SJS contributed to the project administration. XR, NV, GA, RGM, AAC, RAC, EBCZ, EGJ, PAS, LRM, A Coca, DM-P, AM, IV, A Costa-Grille, and SJS contributed to the methodology, investigation, and data acquisition. RG, AAC, EBCZ, and EGJ contributed to the data curation. PAS, LRM, A Coca, DLI, and SJS contributed to the study supervision. All authors have read, provided feedback, and agreed to the final version of the manuscript for publication. Authorship will be decided before publication depending on the researchers' contributions to the specific manuscripts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 315 KB - resprot_v13i1e50325_app1.pdf]

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Abbreviations

CT: computed tomography
DOCS: Definition and Outcomes Consortium
DXA: dual-energy X-ray absorptiometry
EDTA: ethylenediaminetetraacetic acid
EWGSOP-2: European Working Group on Sarcopenia in Older People 2
FRAIL: short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
HIPAA: Health Insurance Portability and Accountability Act
MRI: magnetic resonance imaging
NIHF: National Institute of Health Foundation
PCR: polymerase chain reaction
SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls
SPIRIT: Standard Protocol Items of the Recommendations for Interventional Trials
SPPB: Short Physical Performance Battery
sRAGE: soluble receptor for advanced glycation end products (sRAGE)

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Protocol

Effectiveness of a Serious Video Game (MOON) for Attention Deficit Hyperactivity Disorder: Protocol for a Randomized Clinical Trial

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood and adolescence, with a prevalence of 5% and associated difficulties and worse prognosis if undetected. Multimodal treatment is the treatment of choice. However, sometimes treatment can be insufficient or have drawbacks.

Objective: This study protocol aims to demonstrate the effectiveness of cognitive training through the serious video game The Secret Trail of Moon (MOON) in improving emotional regulation in people with ADHD.

Methods: This is a prospective, unicenter, randomized, unblinded, pre- and postintervention study. The groups will be randomized (MOON vs control) via an electronic case report form. The MOON intervention will be performed 2 times per week for 10 weeks (30 minutes per session). The first 5 weeks (10 sessions) will be conducted face-to-face at the Puerta de Hierro University Hospital, and the remaining weeks will be conducted via the internet at the participants' homes. The total sample consists of 152 patients aged between 7 and 18 years. All participants have a clinical diagnosis of ADHD under pharmacological treatment. Data collection will be used to obtain demographic and clinical data. The data will be recorded using REDCap. Measures will be made through clinical scales for parents and objective tests of cognitive functioning in patients. Additional information on academic performance will be collected. The study has a power greater than 80% to detect differences. Student *t* test, 2-factor analysis of variance (ANOVA), and Mann-Whitney analyses will be performed according to each variable's characteristics.

Results: The study was approved by the Research Ethics Committee of the Puerta de Hierro University Hospital on December 14, 2022. As of September 26, 2023, we have enrolled 62 participants, and 31 participants have completed the study. This clinical trial was funded by the Comunidad de Madrid (IND2020/BMD-17544). The approximate completion date is March 2024.

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Conclusions: Serious video games such as MOON can be motivational tools that complement multimodal treatment for ADHD.

Trial Registration: ClinicalTrials.gov; NCT06006871; https://clinicaltrials.gov/study/NCT06006871

International Registered Report Identifier (IRRID): DERR1-10.2196/53191

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KEYWORDS

attention deficit hyperactivity disorder; ADHD; emotional dysregulation; serious video games; virtual reality; cognitive training; music; chess; attention deficit hyperactivity disorder; video game; video games; children; child; adolescents; adolescent; teen; teens; emotional regulation; neurodevelopmental disorder; multimodal treatment; intervention; motivational tools

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder diagnosed in childhood and adolescence, affecting about 5% of people worldwide [1]. In addition to the classical clinical triad of ADHD (inattention, hyperactivity, and impulsivity) [2], the existence of comorbidity, executive dysfunction, or emotional dysregulation can complicate the prognosis [3]. A greater severity of ADHD symptoms is correlated with greater emotional dysregulation in both children [4] and adults [5]. Emotion regulation involves intrinsic and extrinsic processes responsible for managing the appraisal and control of emotional reactions, emotion intensity, temporality, and goal orientation [6]. Emotional dysregulation has a severe impact on social skills, academic performance, and adaptive skills, leading to a higher rate of usage of treatment services [4]. This impact on emotional regulation manifests diversely across broad age ranges in ADHD from children to adults [7-9]. Emotional regulation issues, even in patients aged 5 years and younger, predict inattention later on [10]. Guidelines recommend that emotional dysregulation be treated before the age of 7 years [11]. ADHD is considered a chronic disorder with a high economic cost [12,13], high accident rate, and increased risk of mortality [14].

Multimodal treatment is the most effective treatment for ADHD, and it encompasses pharmacological treatment, psychological treatment, and psychoeducation for parents and teachers. Pharmacological treatment is the treatment of choice in children and adolescents with severe ADHD [15] and the most common treatment in high-income countries [16]. Approximately 70% of patients observe a positive change in symptoms in the short term due to stimulants [17]. However, some drawbacks such as the side effects of pharmacological treatment (insomnia, appetite suppression, and growth retardation) make some parents reluctant [18]. Moreover, medication is more effective for the core symptoms of ADHD than for the bottom-up mechanisms associated with emotional regulation [19]. Cognitive behavioral therapy can help with social skills and problem-solving [20]. However, motivational difficulties in ADHD [3] and low adherence to treatment [18] have led to the development of additional interventions complementing multimodal treatments. Some studies show promising results with cognitive training [21], metacognitive interventions [22], music [23], and video games [24]. However, the overall results show small effect sizes and difficulties in maintaining long-term benefits and transferability to daily life (generalizability and transferability) [25]. More evidence is needed with greater control of risk biases.

Video games provide immersive and engaging entertainment experiences. They have been extended as tools in the field of health (eg, promoting physical exercise through exergames) to others for cognitive training, as discussed in the reviews by Peñuelas-Calvo et al [24] and Rodrigo-Yanguas et al [26]. In particular, a recent systematic review [27] showed the potential use of video games in improving emotional regulation. Using video games for ADHD treatment may be beneficial for several reasons, including their attractiveness, customization to suit the player's tastes, and immediate reinforcement [28]. Children and adolescents with ADHD have difficulties associated with poor verbal working memory (poor internal language), which can make it difficult for them to perform tasks. In addition, they may be more dependent on external stimuli (ie, they may have low intrinsic motivation), causing them to become bored earlier [3]. Therapeutic interventions based on gamification and video games can be a good strategy to decrease treatment dropout rates by encouraging patients to perform tasks as games.

The Secret Trail of Moon (MOON) is a serious video game based on cognitive training for people with ADHD. It comprises a set of different mini-games focused on enhancing the most affected cognitive abilities in ADHD according to the Executive Functions and Behavioral Inhibition Model [3,29,30]. The games progressively increase in difficulty according to the patient's needs. MOON was designed by a multidisciplinary team following a user-centered model (usability study) and an iterative redesign process [28,31]. Prior to this clinical trial, we completed another clinical trial. In that prospective, single-center, randomized clinical trial with 3 arms, MOON was tested in clinically stable patients with ADHD (on medication) aged 12 to 22 years (NCT04355065) for 3 months. The 105 patients were randomly assigned to the 3 groups: (1) cognitive training (12 sessions) with face-to-face MOON (n=31; 30); (2) cognitive training with online therapeutic chess (n=24; 23); and (3) control group with telephone monitoring (n=34; 32%). Contrary to our expectations, we did not find any statistically significant improvement in executive functioning, which was the primary outcome. However, we found some improvements in secondary outcomes, such as emotional intelligence, emotional regulation, and performance in the school context in both self-reports and parent reports [32]. Following these encouraging results, we designed the present clinical trial (NCT06006871) with the limitations of the previous clinical trial in mind, namely: (1) increasing sample size; (2) increasing the number of cognitive "doses" (20 sessions) and the access to the platform using virtual reality (VR) and computer interfaces; (3) improving some aspects of the MOON video

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game, particularly emotional regulation, such as the aesthetics of the virtual environment, the introduction of music [23], rhythm-based gameplay, and motivational elements such as the reward system; and (4) simplifying the design (2 arms, case versus control, instead of 3 arms). The main objective is to test the efficacy of MOON in improving emotional regulation in patients aged 7 to 18 years with a clinical diagnosis of ADHD.

Methods

Ethical Considerations

This study was approved by the Research Ethics Committee of the Puerta de Hierro University Hospital on December 14, 2022 (PI 106/22). Authorization from the Spanish Agency of Medicines and Health Products was granted on February 14, 2023 (1061/22/EC-R). Informed consent will be requested from legal guardians and minors protecting their personal data to the provisions of the Organic Law (3/2018) passed on December 5, 2018, regarding personal data protection and guarantee of digital rights.

The Spanish Agency of Medicines and Medical Devices (AEMPS) authorized the clinical research with medical devices lacking Conformité Européenne (CE) marking on February 14, 2023 (1061/22/EC-R). The version approved by both entities was version 4 in the protocol, data collection, and recruitment material. The investigator's brochure was approved in version 3. The ethics committee requested the elimination of the rhythm-based game because it has not been previously tested in patients with ADHD. Monitoring of the clinical trial was deemed necessary.

Study Design

This is a prospective, unicentric, randomized, unblinded, pre- and postintervention study with a concealed randomization sequence. The groups will be randomized (MOON vs control) via an electronic case report form (CRF). The interventional study model is a parallel assignment. The allocation ratio will be equal in both groups.

Procedure

All participants will be recruited from the child and adolescent psychiatry outpatient clinics of Hospital Universitario Puerta de Hierro Majadahonda. The number of visits varies in each group—the MOON group will have 12 face-to-face visits, while the control group will have only 2 presential visits. The total duration of the research will be 90 days in total (3 months for each participant: 12 weeks including both the pre- and postevaluation periods; Figure 1). Table 1 summarizes all the visits.

Figure 1. Duration of the research. MOON: The Secret Trail of Moon; SDQ: Strengths and Difficulties Questionnaire.

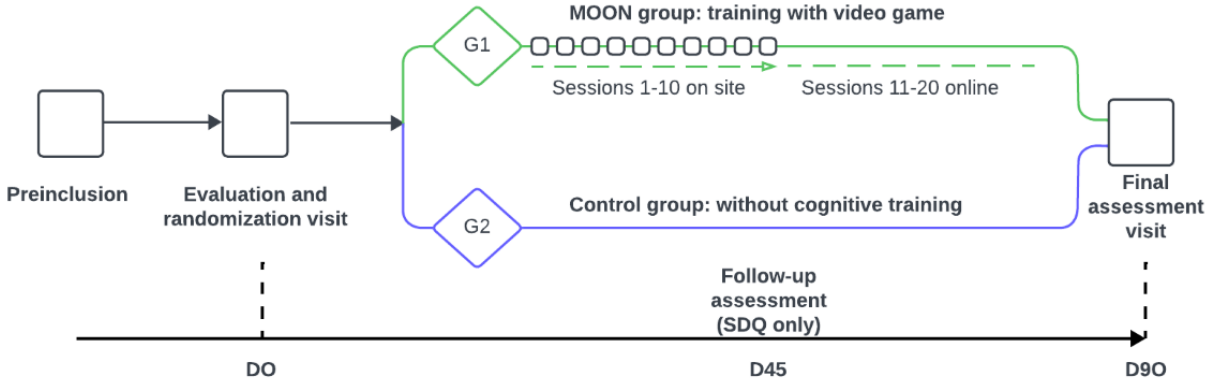

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Table 1. Study flow.

Visit and day	Preinclusion (D1)	Inclusion (D0)	Training (D1-D90)	Final (D90)
Explanation protocol	✓			
CGI[a] (clinical)	✓			
Randomization		✓		
Informed consent		✓		
Data collection note		✓		
CGI (parents)		✓		✓
SDQ[b] (parents)		✓	✓	✓
CPRS-HI[c] (parents)		✓		✓
SNAP-IV[d] (parents)		✓		✓
SDSC[e] (parents)		✓		✓
BRIEF-2[f] (parents)		✓		✓
CPT-3[g] (patients)		✓		✓
Corsi cubes (patients)		✓		✓
CTMT-2[h] (patients)		✓		✓
GASA[i] (patients)		✓		✓
Academic mark		✓		✓
UKU[j] (patients)			✓	
Satisfaction questionnaire				✓

[a]CGI: Clinical Global Impression Scale.
[b]SDQ: Strengths and Difficulties Questionnaire.
[c]CPRS-HI: Conners Abbreviated Symptom Questionnaire.
[d]SNAP-IV: Swanson, Nolan, and Pelham Rating Scale.
[e]SDSC: Sleep Disturbance Scale for Children for Parents
[f]BRIEF-2: Behavior Rating Inventory Executive Function, Version 2.
[g]CPT-3: Conners Continuous Performance Test, Third Edition.
[h]CTMT-2: Comprehensive Trail-Making Test, Second Edition.
[i]GASA: Game Addiction Scale for Adolescents.
[j]UKU: Udvalg für Kliniske Undersolgester.

For the MOON group, the total number of sessions with the video game will be 20 (twice a week, adjusted according to the availability of the participants). Participants in the MOON group aged 12 years and over will perform the video game sessions in VR, while those under 12 years will perform the video game sessions on a computer. All participants in the MOON group will perform the cognitive training with MOON following the same order of the games reflected in Table 2. Each session will have a maximum duration of 30 minutes (approximately 20 minutes of MOON gameplay). The first 10 sessions will be held in person at the hospital. For participants over 12 years of age, the researchers will help to manually calibrate the eye distance of the VR headset to adjust the quality of vision. For those under 12 years of age, researchers will perform computer-based support to ensure proper use and understanding of the video game tasks. The researcher will explain the task, adapting the instructions to each participant's age. Once the researcher is assured of the understanding of the task, the difficulty level will be raised in a personalized way for each participant. Progress is signaled to the player by leveling up, parameters (eg, hits, errors, time taken), and stars earned (0 star=poor performance, must repeat the level; 1 star=acceptable performance; 2 stars=good performance; 3 stars=excellent) (Figures 2 and 3).

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Table 2. Gameplay order by sessions.

Mode	Onsite at the hospital										At participants' homes									
Sessions	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Games																				
Smasher		1	2				1		2			1			2		1		2	
Kuburi		2		1		2			1	2				1		1		2		
Teka-Teki	1			2		1		2			1	2							1	2
Enigma	2				1		2			1			2		1	2				1
Chess			1		2			1			2		1	2			2	1		

Figure 2. The Secret Trail of Moon (MOON) progress.

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Figure 3. The star system in The Secret Trail of Moon (MOON).

Parents in session 10 will receive a flash drive with the video game and training on how to use it at home. The last 10 sessions will take place at the participants' homes on their computers and will be monitored via the internet by the researchers. Data collected in the game (eg, completed levels, hits, errors, or reaction times) will be automatically sent to the PlayFab (Microsoft Corp) data server. The parents of MOON group participants will be asked in advance to provide their consent for the collection of these data.

For the control group, participants will be followed up with weekly calls to parents during this period. During this follow-up, psychoeducational support about ADHD will be provided to the parents.

Hypothesis

Our main hypothesis is that patients with ADHD using MOON will improve their emotional regulation more than the control group. The efficacy will be evaluated by measuring the change produced from the baseline evaluation (day 0) and the final evaluation visit (day 90), aiming for a decrease of 3 to 4 points in the global score of the Strengths and Difficulties Questionnaire (SDQ) filled by the patient's parents.

As secondary hypotheses, the difference with the control group in measures such as ADHD core symptomatology, cognitive abilities, and academic performance will be assessed. Our secondary hypotheses are listed in Textbox 1.

Textbox 1. Secondary hypotheses of the study.

- H2: Patients with Attention deficit hyperactivity disorder (ADHD) using The Secret Trail of Moon (MOON) video game will improve in core ADHD symptoms compared with the control group.
- H3: Patients with ADHD using MOON will improve their cognitive functioning compared to the control group.
- H4: Patients with ADHD using MOON will improve in academic performance with respect to the control group.
- H5: A change in platform (face-to-face, internet) will not entail differences in emotional regulation.
- H6: There will be no clinically meaningful side effects associated with the video game.

Participants

Sample

A total of 152 patients (76 cases versus 76 controls) with a clinical diagnosis of ADHD according to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) will be enrolled. All participants will have a clinical diagnosis of ADHD, take ADHD medication, be clinically stable, and have a Clinical Global Impression (CGI) score between 3 and 6 before entering the trial. Medication will not change during the investigation unless changes are required for clinical reasons. A 15% loss rate is expected. The inclusion and exclusion criteria are summarized in Textbox 2.

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Textbox 2. Participant inclusion and exclusion criteria.

Inclusion criteria:

- Age 7 to 17 years (may turn 18 during the study)
- Clinical diagnosis of attention deficit hyperactivity disorder (ADHD) in any presentation
- Taking pharmacological treatment for ADHD
- Ability to follow verbal instructions
- Ability to play a video game (not necessary to play regularly)
- Clinically stable, with ADHD symptomatology severity based on a clinician-assessed Clinical Global Impression (CGI) score between 3 and 6

Exclusion criteria:

- Patients with severe symptoms (> or equal to 5 CGI) or very mild symptoms (CGI < or equal to 1)
- Patient at risk of suicide (according to the clinical judgment of the professional in charge of the patient)
- Motor difficulties that prevent playing the video game
- Participation in other similar studies
- Intention to initiate any psychotherapeutic treatment (including cognitive-behavioral therapy) in the next 3 months of the course of participation in the clinical trial

Randomization and Masking

To warrant clinical trial randomization, a random block sequence of 76 “1” (experimental) and 76 “2” (control) in 4 blocks of 38 numbers (19 “1” and 19 “2”) will be generated using the R program (R Foundation for Statistical Computing) by author MBF [33]. The sequence will be unknown to the recruiters [34].

In the preinclusion phase, patients will be informed about the research by the principal investigator (author HBF) and their suitability will be assessed according to the inclusion and exclusion criteria (Textbox 2). Subsequently, another author (MMM) will explain the research procedure in detail and summon the prerecruited participants. Once the consent form is signed, they will be randomly assigned by blocks using the electronic CRF with a ratio of 1:1. Randomization of the groups (MOON vs control) will be performed by the electronic CRF REDCap.

Materials

Hardware

Materials to be used for this study include the video game (MOON) itself, VR goggles, PlayStation 4 (Sony Group Corp) controllers, test consoles, monitor screens, and headsets. The VR software runs on a PlayStation 4 test device (Figure 4). A computer with an internet connection will also be used in this study to ensure the proper transmission of game data to the PlayFab server.

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Figure 4. User playing The Secret Trail of Moon (MOON).

Software: Video Game

MOON has been designed to be a therapeutic cognitive training video game for patients with ADHD. This serious video game can be used both on a computer and s PlayStation 4 VR console. The use of VR allows a more focused approach to the task and a greater impact on the participants' motivation. The use of a computer allows more accessibility. The game is set in a natural environment, potentially beneficial for people with ADHD with animals that accompany the player throughout the training session [25]. Various games or tasks are incorporated into the game design with the purpose of training the most affected cognitive functions in ADHD. MOON has 5 game mechanics. These are as follows: (1) SMASHER (sustained attention and inhibitory control) is a task based on the Continuous Performance Test, Third Version (CPT-3) [35], with a 2-item sequence similar to Sustained Attention Task in Childhood Test (CSAT) [36]; (2) in TEKATEKI (planning), the participant is asked to perform a minimum number of possible movements (based on the *Tower of Hanoi*); (3) in ENIGMA (working memory), the *span* of items to remember increases according to the difficulty curve [37]; (4) KUBURI (visuospatial ability) is a 3D cube rotation task; and (5) CHESS (reasoning) consists of tasks related to the rules of chess.

Psychometric Assessments

Preinclusion

CGI Scale for Clinicians

Symptom severity will be measured with the CGI scale [38] (approximately 1-minute duration). ADHD symptomatology severity based on clinician-assessed CGI score (between 3 and 6) for the inclusion criteria.

Clinical Anamnesis

The clinical anamnesis includes demographic, clinical, school, and medical history data.

SDQ For Parents

The SDQ has 25 items (approximately a 5-minute duration) [39]. It measures (1) emotional symptoms, (2) behavioral challenges, (3) hyperactivity, (4) conflicts/issues with peers, and (5) prosocial behavior. A decrease of 3 to 4 points in the postassessment visit (D70) concerning the preassessment visit (D0) will be considered an improvement in emotional regulation.

The Swanson, Nolan, and Pelham Rating Scale for Parents

The main ADHD symptomatology (inattention, hyperactivity, impulsivity) will be measured using subjective scales for parents. The Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) is an 18-item questionnaire for assessing ADHD symptoms [40,41]. It has a Likert scale ranging from 0 to 4 (approximately 5 minutes long), among which 9 items assess attention deficit

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and the other 9 items assess hyperactive impulsive component. The cut-off point for attention deficit is 1.78 for parents. For hyperactivity-impulsivity, the cut-off point is 1.44 for parents.

The Conners Abbreviated Symptom Questionnaire for Parents

The Conners Abbreviated Symptom Questionnaire (CPRS-HI) helps assess patients with ADHD [42,43]. It is a 10-item questionnaire with a Likert scale of 0 to 3 (approximately 2 minutes long). This revised and abbreviated version of the Conners scale is designed to be answered by parents of children aged 6 to 18 years. It contains Likert-type responses (0= not true at all/never; 1= just a little true/occasionally; 2= Pretty much true/often; 3=very much true/very often). The cut-off points are divided by sex. For boys, a score above 16 is suspected ADHD, while for girls, a suspected diagnosis of ADHD is above 12 points.

CGI for Parents

Symptom severity will be measured with the CGI adapted for parents (approximately 1-minute duration) consisting of a "thermometer" with a Likert scale ranging between 1 and 10 [44].

Behavior Rating Inventory Executive Function 2 Questionnaire for Parents

The Behavior Rating Inventory Executive Function, Version 2 (BRIEF-2) is a questionnaire designed to evaluate executive functions in children and adolescents [45]. It consists of 63 items with 3 answer options (never, sometimes, and frequently). Its correction provides 4 general indices: emotional regulation, cognitive regulation, behavioral regulation, and global index of executive function. It also provides 2 second-order factors and a general index.

CPT-3 for Patients with ADHD

The CPT-3 is a screening task for ADHD in addition to measuring sustained attention, impulse control, and processing speed [35]. It is a computerized, standardized, and validated application test for different age and gender groups. The task consists of pressing a button each time a letter (target) appears on the screen, except for the letter X (nontarget), which must not be pressed. The duration is 14 minutes, and the presentation interval between letters varies (1, 2, and 4 seconds). The test provides results on hits, errors of omission (undetected target) or commission (reacted nontarget), which are considered a measure of impulsivity. In addition, CPT3-3 provides information on hit mean reaction time and variability.

Sleep Disturbance Scale for Children for Parents

The Sleep Disturbance Scale for Children (SDSC) is a 26-item questionnaire with a Likert scale ranging between 1 and 5 (1: never; 5: always). It has an approximate duration of 5 minutes [46].

Corsi Cubes for Patients With ADHD

Corsi cubes are used to measure visuospatial working memory [37,47].

Comprehensive Trail-Making Test, Second Edition for Patients With ADHD

The Comprehensive Trail-Making Test, Second Edition (CTMT-2) is used to measure cognitive flexibility, with 3 indexes: inhibitory control, task switching, and total index (Figure 5) [48].

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Figure 5. Psychometric assessments: Corsi Cubes, Continuous Performance Test, Third Version (CPT-3), and Comprehensive Trail-Making Test, Second Edition (CTMT-2).

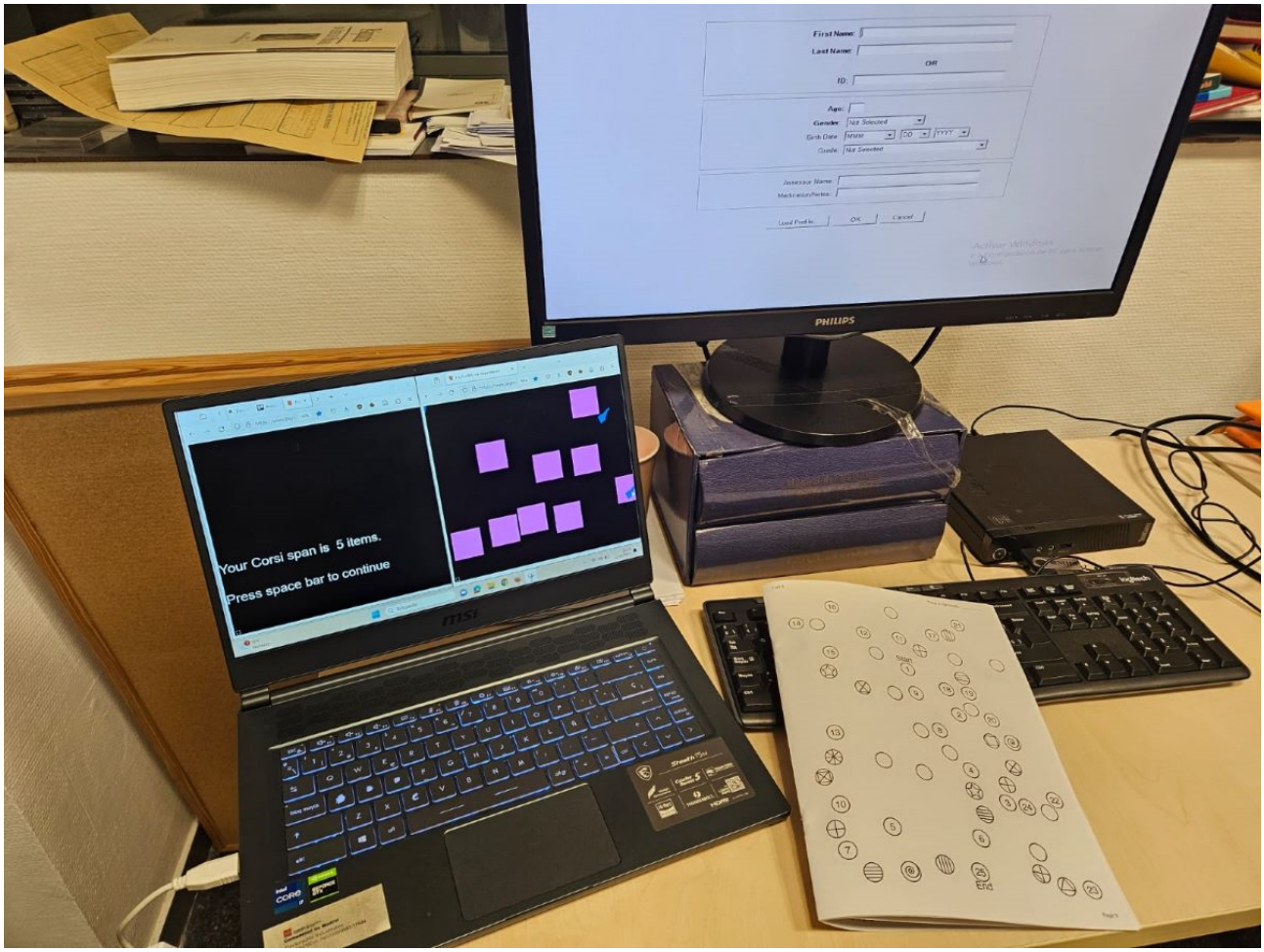

Udvalg für Kliniske Undersogelser for Patients With ADHD

Udvalg für Kliniske Undersogelser (UKU) is a tool designed to evaluate possible secondary symptoms that happen during the week [49]. This scale is not included in the assessment phases. Only the participants playing VR will have to complete the scale after each cognitive training session.

Game Addiction Scale for Adolescents

The Game Addiction Scale for Adolescents (GASA) is a 7-item questionnaire to assess video game addiction [50,51].

Academic Performance

Information about academic performance will be obtained via the patients' grades.

Interventions

After the initial evaluation, 2 groups randomized by blocks will be formed. Group 1 (MOON) will receive personalized cognitive training with a video game in person and via the internet. Psychoeducational support on ADHD to parents will be provided during the research (n=76; 50%).

Group 2 (control) will receive the usual pharmacological treatment (without cognitive training intervention). Psychoeducational support on ADHD will be provided to the parents during the research (n=76; 50%).

Analyses

Sample Size Calculation

Based on similar investigations with hypotheses that are centered around the administration of the SDQ [52], our sample size calculation shows the need to perform the study on approximately 152 participants with a diagnosis of ADHD to cover most of the possibilities with a Cronbach α of 0.05 and a statistical power of 80%, taking into account a 15% dropout rate. We performed the sample size calculation to contrast a mean in the control group of 11 points on the SDQ global score versus a 2-point mean drop (symptomatologic improvement) in the experimental group with a pooled SD of 4. This estimate covers other less conservative situations, such as a difference of up to 4 points.

Study Population

The intention-to-treat (ITT) analysis population is defined as participants who are randomized and receive at least 10 sessions, and the per-protocol population is defined as participants who will complete 100% of the training. All analyses will be performed on the premise of the ITT analysis.

A 2-way analysis of variance (ANOVA) will be performed, with time (pre and post) and group (experimental vs control)

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as factors and each measure as dependent variable. The difference between the study groups will be considered significant when P<.05.

Demographic and Baseline Characteristics

A data collection notebook will be used to obtain demographic and clinical data. The data will be recorded with electronic CRF (REDCap). Measures to answer the hypotheses will be made through clinical scales for parents and objective tests of cognitive abilities in patients. Additional information on academic performance will be collected.

Primary End Point Analysis

The main objective is to test the efficacy of the cognitive training treatment (MOON) in improving emotional regulation in patients aged 7 to 18 years who have a clinical diagnosis of ADHD. The effectiveness is evaluated by measuring the change produced between the baseline evaluation (day 0) and the final evaluation visit (day 90) in the decrease of 3 to 4 points in the global SDQ score evaluated by the parents. A decrease of 3 to 4 points on the postassessment visit (D70) concerning the preassessment visit (D0) will be considered an improvement in emotional regulation based on other similar studies [52].

Subsequently, 3 parent SDQ measures will be assessed: initial assessment (D0), midterm assessment (D45), and final assessment (D90) to evaluate hypothesis 5 (switching from face-to-face to web-based methods does not lead to differences in emotional regulation).

Secondary End Point Analysis

Two subjective scales will be used to assess hypothesis 2 (patients with ADHD using MOON will improve in ADHD symptomatology relative to the control group). The main ADHD symptomatology (inattention, hyperactivity, and impulsivity) will be measured with (1) SNAP, an 18-item questionnaire with a Likert scale ranging between 0 and 4 (approximately 5 minutes long) and (2) CPRS-HI, a 10-item questionnaire with a Likert scale ranging between 0 and 3 (approximately 2 minutes long). Symptom severity will be measured with the CGI adapted for parents (approximately 1-minute duration) consisting of a "thermometer" with a Likert scale ranging between 1 and 10.

Relative to hypothesis 3 (Patients with ADHD using MOON will improve their cognitive abilities more than the control group), executive dysfunction will be evaluated through subjective scales for parents and objective tests for patients. The subjective test for parents will be performed with the BRIEF-2 questionnaire. There will be three objective tests for the patients: (1) CPT-3, which is usually used to screen for ADHD in addition to measuring sustained attention, impulse control, and processing speed; (2) Corsi cubes, which are used to measure visuospatial working memory; and (3) CTMT-2, which is used to measure cognitive flexibility using 3 indexes, namely, inhibitory control, task switching, and total index.

Regarding hypothesis 4 (patients with ADHD using MOON will improve in academic performance relative to the control group), grades will be collected for each subject on the quarterly school report card immediately preceding (pre) and following (post) treatment.

Safety and Adherence Analysis

Additional measures have been taken concerning the previous clinical trial [32] to assess the occurrence of side effects. Hypothesis 6 (there will be no side effects associated with the video game) is related to this aspect. To mitigate the possibility of motion sickness due to VR use, the UKU test will be used. In the previous clinical trial, nonsignificant effects related to sleep were observed; therefore, in this clinical trial, the SDSC scale will be used to assess this symptomatology in depth. Since people with ADHD are more prone to addictive behaviors related to video games [53], two main precautions will be taken: (1) adapting the game design so as not to encourage addictive behaviors [28] and (2) collecting additional information with the GASA test.

Results

The clinical trial is funded by the Community of Madrid (2020 Industrial Doctorates IND2020/BMD-17544). The expected date of data collection was between May 2023 and January 2024. The approximate completion date is March 2024. As of September 26, 2023, we have enrolled 62 participants. A total of 31 (20%) participants completed the study. The analysis of the total results is expected to be published in May 2024.

Discussion

ADHD is a neurodevelopmental disorder with great variability. Some authors associate the symptoms of inattention with a disorder of "cool" executive function (dorsolateral prefrontal cortex pathway), while the symptoms of hyperactivity and impulsivity are associated with deficits of "hot" executive function (orbital and medial prefrontal cortex pathway) [54]. According to Gross [55,56], emotional regulation is a process whereby people modulate their emotions using strategies such as suppression, strategy modulation, or reappraisal. This process requires an interaction of executive functions with emotional regulation. In relation to these intrinsic-extrinsic processes, children with ADHD compared with typically developing children tend to overestimate their performance in different domains (social, school, and behavioral). Some authors call this term "positive illusory bias" (PIB), with consequent disparity between children's self-reports and parents' assessments [22,57].

The MOON video game was developed as a form of cognitive training to improve cognitive abilities, such as sustained attention, inhibitory control, working memory, visuospatial ability, reasoning, and planning [30,31]. However, after conducting the first clinical trial, our main hypothesis of improving executive functions measured with the BRIEF-2 test was not fulfilled [32]. Nevertheless, we did find improvements in emotional domains compared to the control group both in self-reports and parent reports (the most relevant being emotional intelligence, emotional regulation, and performance in the school context). Accordingly, in this second clinical trial, we wanted to replicate and extend our previous positive findings on different measures of emotion regulation. The global SDQ scale we used includes measurements of emotional symptoms, behavioral problems, hyperactivity, problems with peers, and prosocial behavior [39,52].

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We believe that any improvement found in measures should be transferred or generalized to daily life. Thus, in this study, we will measure academic performance to assess whether the improvement in cognitive domains includes a transfer to other domains such as arithmetic or reading.

Additional measures have been adopted. Improvements have been added to make the video game more attractive (music, aesthetics, and rewards). To avoid the presence of PIB causing questionnaires to be completed by ”bad informants,” objective tasks, including CPT-3 [35], Corsi cubes [37], and CTMT-2 [48], were proposed for participants in this second clinical trial. To mitigate THE possible excessive use of video games or addiction, the video game design was controlled [28], and the GASA test will be incorporated [50,51].

However, this clinical trial has important limitations. First, a blinded study is not possible. Second, cognitive domains are difficult to measure in the absence of unified questionnaires; in fact, some laboratory measures related to executive function are moderately related to the main symptoms of ADHD and their impact on daily life. As for the video game, it was not possible to incorporate all the improvements designed. Despite the incorporation of children under 12 years of age into this clinical trial, it is possible that some difficulty levels are not well adjusted due to not having been able to perform a usability study prior to this new clinical trial. Moreover, typical of ADHD symptomatology, the decay of the video game sessions—especially those sessions conducted at home without researcher supervision—may occur. Participants could lose motivation for the treatment as the same game is played for a long time [58].

Video games can be a potential tool to improve different skills, such as emotional regulation [27]. In people with ADHD, it is especially important to incorporate motivational tools complementary to multimodal treatment that can facilitate treatment adherence.

Acknowledgments

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Authors' Contributions

MMM, MBF, and HBF carried out the research. MMM and HBF will recruit the patients. MMM and MBF will perform the data collection. MMM will monitor the Calendly appointments and The Secret Trail of Moon (MOON) home training data collection via PlayFab. MMM designed the electronic case report form (REDCap) and MBF will enter the data into the program. MMM, MRY, CGT, and HBF designed the video game. AS made programming enhancements to this version of MOON. CL and PW provided research design ideas and statistical input. The sample size calculation was carried out by AR. MBF, HBF, MMM, and AR will perform the statistical analyses. PLG and HBF supervised the study.

Conflicts of Interest

Author HBF has received lecture fees from Takeda Pharmaceuticals, and the laboratories BIAL, Rubio, and Rovi. He has also been granted 3 prizes for developing the serious video to treat attention deficit hyperactivity disorder (ADHD): the Shibuya Prize by Takeda, the first prize from the College of Psychologists of Madrid, and a prize for the best innovative health initiative within the Health Start campaign. He is the principal investigator of predoctoral contracts for training in health research (IFI16/00039), the coprincipal investigator of a Ministry of Economy, Trade and Enterprise research grant (RTI2018-101857-B-I00), and the principal investigator of a Sincronia research, funded by the Start-up Bitsphi. Moreover, he is the recipient of (1) a Foundation for Innovation and Foresight in Health in Spain grant and (2) a Puerta de Hierro Segovia de Arana Institute of Health Research intensification grant and is involved in 2 clinical trials (Mensia Koala, Newrofeed study; ESKETSUI2002). He is also a cofounder of Haglaia Solutions and an employee and member of the advisory board of ITA Salud Mental (Korian).

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Abbreviations

ADHD: attention deficit hyperactivity disorder
BRIEF-2: Behavior Rating Inventory Executive Function, Version 2
CGI: Clinical Global Impression
CPRS-HI: Conners Abbreviated Symptom Questionnaire
CPT-3: Continuous Performance Test, Third Edition
CRF: case report form
CSAT: Sustained Attention Task in Childhood Test
CTMT-2: Comprehensive Trail-Making Test, Second Edition
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ITT: intention to treat
MOON: The Secret Trail of Moon
PIB: positive illusory bias
SDQ: Strengths and Difficulties Questionnaire
SNAP-IV: Swanson, Nolan, and Pelham Rating Scale
VR: virtual reality

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Protocol

Efficacy of StepAdd, a Personalized mHealth Intervention Based on Social Cognitive Theory to Increase Physical Activity Among Patients With Type 2 Diabetes Mellitus: Protocol for a Randomized Controlled Trial

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Abstract

Background: Increasing physical activity improves glycemic control in patients with type 2 diabetes (T2D). Mobile health (mHealth) interventions have been proven to increase exercise, but engagement often fades with time. As the use of health behavior theory in mHealth design can increase effectiveness, we developed StepAdd, an mHealth intervention based on the constructs of social cognitive theory (SCT). StepAdd improves exercise behavior self-efficacy and self-regulation through the use of goal-setting, barrier-identifying, and barrier-coping strategies, as well as automatic feedback functions. A single-arm pilot study of StepAdd among 33 patients with T2D showed a large increase in step count (mean change of 4714, SD 3638 daily steps or +86.7%), along with strong improvements in BMI (mean change of −0.3 kg/m^2) and hemoglobin A_{1c} level (mean change of −0.79 percentage points).

Objective: In this study, we aim to investigate the efficacy and safety of StepAdd, an mHealth exercise support system for patients with T2D, via a large, long, and controlled follow-up to the pilot study.

Methods: This is a randomized, open-label, multicenter study targeting 160 patients with T2D from 5 institutions in Japan with a 24-week intervention. The intervention group will record daily step counts, body weight, and blood pressure using the SCT-based mobile app, StepAdd, and receive feedback about these measurements. In addition, they will set weekly step count goals, identify

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personal barriers to walking, and define strategies to overcome these barriers. The control group will record daily step counts, body weight, and blood pressure using a non–SCT-based placebo app. Both groups will receive monthly consultations with a physician who will advise patients regarding lifestyle modifications and use of the app. The 24-week intervention period will be followed by a 12-week observational period to investigate the sustainability of the intervention's effects. The primary outcome is between-group difference in the change in hemoglobin A_{1c} values at 24 weeks. The secondary outcomes include other health measures, measurements of steps, measurements of other behavior changes, and assessments of app use. The trial began in January 2023 and is intended to be completed in December 2025.

Results: As of September 5, 2023, we had recruited 44 patients. We expect the trial to be completed by October 8, 2025, with the follow-up observation period being completed by December 31, 2025.

Conclusions: This trial will provide important evidence about the efficacy of an SCT-based mHealth intervention in improving physical activities and glycemic control in patients with T2D. If this study proves the intervention to be effective and safe, it could be a key step toward the integration of mHealth as part of the standard treatment received by patients with T2D in Japan.

Trial Registration: Japan Registry of Clinical Trials (JRCT) jRCT2032220603; https://rctportal.niph.go.jp/en/detail?trial_id=jRCT2032220603

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KEYWORDS

digital therapeutics; behavior change; social cognitive theory; exercise; type 2 diabetes mellitus; mobile app; randomized controlled trial; mobile phone

Introduction

Background

Worldwide, approximately 537 million people aged between 20 and 79 years have type 2 diabetes (T2D) [1]. T2D is a serious public health concern with a considerable impact on health expenditures and human life, causing 4.2 million deaths per year [2,3]. T2D is a disease that is difficult to cure once it develops, and if left untreated, it causes complications such as cardiovascular disease and microvascular complications [4].

Exercise has been proven to improve glycemic control and other metabolic parameters, including low-density lipoprotein cholesterol, visceral adipose tissue, and blood pressure (BP) [5]. Patients with T2D are recommended to commit to a minimum of 150 minutes of moderate to vigorous physical activity per week. As walking has been rated as the most favored form of physical activity by sedentary groups, it is a suitable form of exercise for patients with T2D, who typically have low physical activity [6,7]. The recommended 150 minutes of activity translates into taking at least 7500 steps per day, of which 3000 steps should be at moderate to vigorous intensity [8]. Although physical exercise has been proven to be effective in improving blood glucose levels, reducing cardiovascular risk factors, and improving cardiorespiratory fitness in patients with T2D, lack of motivation has been reported to be a barrier [9]. It is difficult for patients to change their current exercise behavior by themselves [9]. It has also been reported that adherence to physical activities is lower than adherence to medication regimens [10].

Mobile health (mHealth) interventions such as mobile phone apps that support self-management have proven to be effective in increasing physical activity of patients [11,12] and improving glycemic control [13,14]. According to the American College of Sports Medicine, web-based fitness programs, exercise-related digital services, and use of mobile phones are becoming increasingly popular in the worldwide exercise community [15]. Recent meta-analyses found a moderate to large positive effect in daily step changes owing to the use of smartphone apps that focus on physical activities [16,17]. Although mHealth is effective, patients lose motivation to engage with the intervention after some time [18,19]. Personalization of intervention components has been shown to increase patient motivation and engagement in using the app [20]. Several studies have found that tailored interventions are more effective in changing health behavior than nontailored interventions [21,22].

Although several studies evaluating the effectiveness of personalized interventions have reported an increase in the physical activity levels of users [23,24], so far, studies generally do not use a theory-based framework with mHealth. In particular, social cognitive theory (SCT), with a human agency model in which individuals proactively self-reflect, self-regulate, and self-organize, offers a powerful framework that could support improved mHealth interventions [25,26]. SCT has been used to understand behaviors relating to physical activity owing to its emphasis on the dynamic interactions between the individual, environment, and behavior [27]. SCT-based interventions were found to be effective in changing physical activity behaviors among people with prediabetes [28].

To address this research gap, we developed a personalized smartphone-based mHealth intervention, StepAdd, to improve physical activity levels and T2D control among patients with T2D by using the SCT framework. In 2021, we conducted a pilot study of StepAdd among 33 patients with T2D attending Mitsui Memorial Hospital in Japan, using a pre-post evaluation design over 12 weeks. The results show very high retention (97%), very large increase in mean daily steps (from 5436 to 10,150 steps per day; 86.7% increase), and positive changes in BMI (mean change of −0.3 kg/m^2) and hemoglobin A_{1c} (HbA_{1c})

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levels (mean change of −0.79 percentage points) [29]. Growth in step count continued throughout the intervention, as did growth in step count goals. The step goal achievement rate remained steady and high throughout the intervention period. With strong positive impacts and strong ongoing engagement in this pilot study, we concluded that StepAdd warranted a deep study.

This trial aims to investigate the efficacy of StepAdd, also known as diabetic kidney disease–exercise therapy, in a long (24 weeks), randomized controlled trial. The specific research objectives and hypotheses are as follows.

Objective 1

The first objective is to investigate the efficacy of StepAdd in improving physical activity levels, as measured using daily step count.

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant increase in daily step count relative to the counts of the control group.

Objective 2

The second objective is to investigate the efficacy of StepAdd in reducing HbA_{1c} levels.

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant reduction in the primary outcome, HbA_{1c} levels, relative to the HbA_{1c} levels in the control group.

Objective 3

The third objective is to assess the effect of StepAdd in improving 7 self-care behaviors (walking duration, adherence to T2D self-care, self-management behavior to enhance and maintain physical activity, self-regulation of physical activity, self-efficacy to achieve targeted daily steps, self-efficacy to deal with barriers to achieving the targeted daily steps, and self-efficacy for health-promoting behaviors) and 10 health indicators (fasting blood glucose, estimated glomerular filtration rate, BMI, BP, high-density lipoprotein, low-density lipoprotein, triglyceride, locomotive syndrome, T2D-related emotional distress, and T2D-dependent quality of life).

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant improvement in the 7 self-care behaviors and 10 health indicators.

Methods

Study Design

This study is an open-label, multicenter (Textbox 1), confirmatory, 2-armed, randomized controlled trial to study the efficacy of an mHealth intervention, StepAdd, in promoting exercise behavior among patients with T2D. The conduct and reporting of the trial will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines. This study (Figure 1) begins with recruitment, a baseline measurement period (nominally 2 weeks, but at least 7 days), and randomized assignment to the intervention and control groups. The patients in the intervention group will use the SCT-based StepAdd smartphone app to measure body weight (BW), BP, and daily steps; receive personalized feedback; and develop updated step goals. The patients in the control group will use a placebo smartphone app that simply measures and reports BW, BP, and daily steps. Both groups will receive monthly consultations with their physician. The intervention will last for 24 weeks and will be followed by a 12-week observational period. This study will be conducted over 3 years, from January 1, 2023, to December 31, 2025.

Textbox 1. Participating institutions—5 medical centers within Japan.

- University of Tokyo Hospital
- Akita University Hospital
- Yokohama City University Hospital
- Yokohama City University Medical Center
- Yokohama Rosai Hospital

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Figure 1. Overview of study timeline—at least 1 week of baselining, 24 weeks of intervention, and 12 weeks of observation.

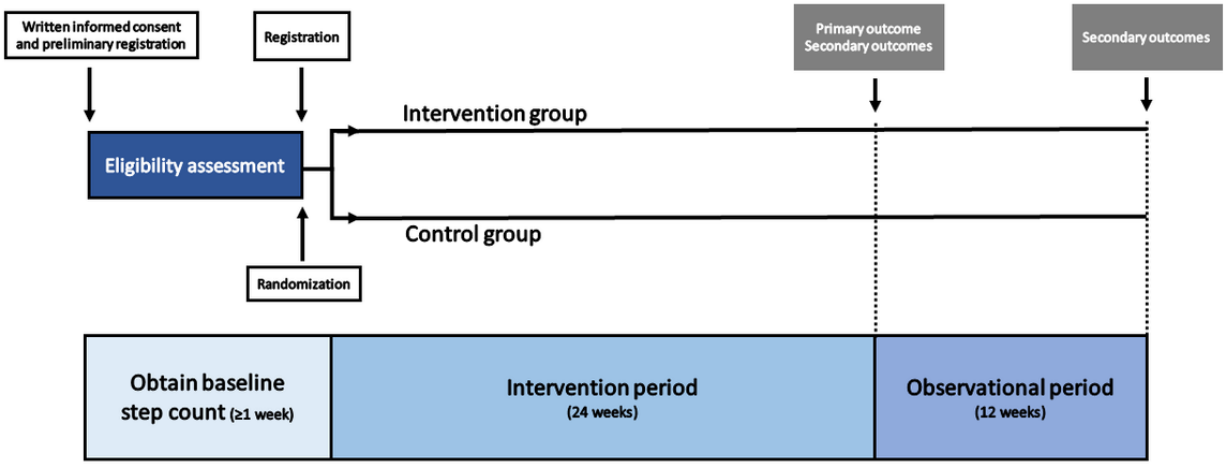

Intervention Design

This mHealth intervention uses a pedometer; a body weighing scale; a BP monitor; and a smartphone with an mHealth app, StepAdd. The app is an iOS app on an iPhone that communicates with the StepAdd server. An administrative screen is used by a medical professional (either a physician or a clinical research coordinator who is overseen by a physician). Pedometer count, BP, and BW are measured at home. The pedometer count is synchronized with the app continuously during the day, and the BP and BW are synchronized with the app daily when patients open the app at the time of measurement. The app interacts with the patient to establish personalized goals, provide personalized feedback, and define and assess the efficacy of patient-specific coping skills (Figure 2 [29]). This app was developed in collaboration with foo.log Co Ltd, a software development company. The control group uses a placebo app supporting the same measurements but without personalized goals and feedback (Table 1).

Figure 2. StepAdd's process for implementing social cognitive theory (SCT)–based personalization on daily, weekly, and monthly timelines (adapted from Wei Thing Sze et al [29], Copyright 2023, used with permission from Elsevier).

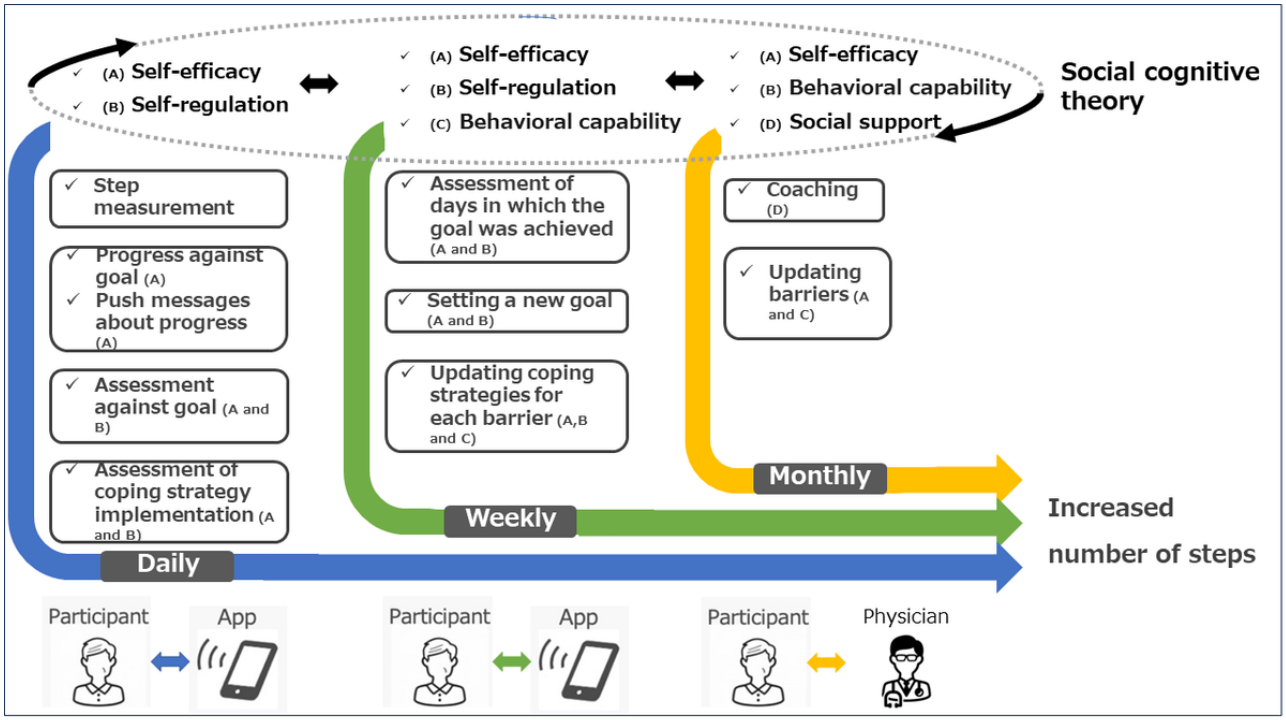

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Table 1. Features of the trial's StepAdd and placebo apps and additional features provided to the intervention group.

Features	StepAdd app	Placebo app
Display, record, and upload step count, BW[a], and BP[b]	Yes	Yes
Reminders to measure BW and BP and to carry pedometer	Yes	Limited reminders to carry pedometer
Review of step count, BW, and BP	Yes	No
Exercise instructions	Yes	No
Goal setting	Yes	No
Coping strategies to overcome barriers to achieving step goals	Yes	No
Reminders about coping strategies	Yes	No
Display of recorded health data that were registered by physicians from the administrative screen	Yes	No
Daily reflection assistance	Yes	No
Weekly reflection assistance	Yes	No
Record about whether the tasks agreed with the health care professional are completed	Yes	No
Personalized feedback	Yes	No

[a]BW: body weight.

[b]BP: blood pressure.

The intervention uses the framework of SCT [25,26]. The intervention incorporates the SCT constructs that are most used in physical activity research: self-efficacy, self-regulation, behavioral capability, and social support [30]. Self-efficacy is an individual's belief in their ability to perform a particular behavior successfully. Individuals are less likely to engage in a behavior if they do not believe they are capable of producing the desired effects. Sources of self-efficacy include mastery experience (the successful accomplishment and mastering of a desired behavior) and verbal persuasion (receiving verbal encouragement from others for performing a behavior). Self-regulation, one of the constituent concepts of SCT that is closely linked with behavior change, is a dynamic feedback loop in which an individual sets a target goal and, by comparing this goal with their present state, is motivated to change their behavior to achieve the goal [31]. Motivation does not originate from the goals themselves but from the individual analyzing their own behavior with reference to their goal [32]. Self-regulation includes behaviors such as setting personal goals and planning courses of action to achieve them, and it is often motivated by expected positive outcomes. Behavioral capability is a person's actual ability to perform a behavior through essential knowledge and skills. Social support involves identifying others who will provide encouragement in the form of moral support, participation in the behavior, and accountability [33].

SCT constructs integrated in this app focused on a self-regulated walking habit using goal setting and perceived self-efficacy [34]. Users set small, progressive, and realistic goals for daily step counts (self-efficacy and goal setting), track and monitor daily step count performance (self-observation), and evaluate their own progress against the goals (self-judgment). The belief that one's progress is acceptable, along with the anticipated satisfaction of meeting a goal, enhances self-efficacy and motivation (self-reaction) [34]. The intervention provides social support through monthly meetings with a physician who examines the use of the app and provides advice, verbal encouragement, and support regarding the participants' exercise behavior (behavioral capability and social support).

The app proposes the target number of daily steps for the following week according to the achievement of the current week's step count against goals. Our algorithm [29] increases, maintains, or decreases the suggested goal based on the number of days in the previous week in which the user achieved their goal. Increases are either 300 or 500 steps, depending on past goal achievement levels. The patient may choose to decrease their goal by decrements of 200 steps if they are not confident in being able to complete the goal for ≥5 days. In this way, the app recommends goal adjustments according to the user's self-efficacy in goal achievement. Personalized goal setting also enhances self-regulation through forethought (setting a goal and deciding on goal strategies), performance control (using goal-directed actions and monitoring performance), and self-reflection (evaluating one's goal progress and adjusting the strategies to ensure success) [35].

The app provides automated feedback with individualized advice. Status against the daily goal is available continuously on the app. Self-regulation is enhanced as patients are able to self-monitor their behavior through the personalized feedback. The feedback also enhances self-efficacy as it acts as a means of verbal persuasion, which is a source of self-efficacy [25,26]. The app automatically communicates with the patients through push notifications 4 times a day (at 11 AM, 1 PM, 4 PM, and 6 PM) to communicate the achievement against the step goals. For example, if the target number of steps have not been reached at 11 AM, the message "The number of steps registered by 11 o'clock is [participants' registered number of steps]. The additional number of steps required is [target number of steps minus current number of steps] to achieve your goal" appears on the app. The day's achievement against the goal is shown at 6 PM. If the participant has reached the target step goal, the

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message “Today’s steps have significantly exceeded your goal! Congratulations. You’re in good shape tomorrow. Don’t get tired” appears on the app. At the end of the week, the app provides feedback by displaying the number of days in the week that the step goals were achieved (Figure 3).

Individualized coping planning enhances self-regulation by allowing patients to evaluate the possible barriers to achieving their step goals. Each week, participants select or input 1 to 3 barriers that prevented them from achieving the targeted number of steps, and for each barrier, they suggest a coping strategy that could be useful to overcome the barrier (Figure 4). The coping strategies can be selected from a literature-based list of solutions to common barriers to walking [36-39] or can be freely described by the participants. At the end of each day, participants use the app to report about how many coping strategies they implemented that day. At the end of each week, the app provides feedback about the coping strategy use by displaying the average number implemented per day.

Figure 3. Example of end-of-week feedback (with English translation) showing daily and weekly performance against goals.

Figure 4. Example of personalized coping planning strategy on the app (with English translation) showing how patients select the strategy to use for the upcoming week.

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Patient Recruitment

Patients will be recruited at 5 medical institutions in Japan: University of Tokyo Hospital, Akita University Hospital, Yokohama City University Hospital, Yokohama City University Medical Center, and Yokohama Rosai Hospital. Recruitment will be conducted by attending physicians during patients' regular consultations at outpatient clinics. Recruitment will be conducted over 2 years, starting from January 1, 2023, and ending on December 31, 2024.

To detect 0.35% difference in the primary outcome (change in HbA_{1c} level), assuming an SD of 0.74% as seen in a previous study [40], and to achieve a 2-sided significance level of .05 and a statistical power of 80%, the minimum sample size is 72 patients per group [41]. On the basis of an assumed dropout rate of 10%, we are targeting to recruit a total sample of 160 patients (n=80, 50% in the intervention group; n=80, 50% in the control group).

All participants will receive a thorough written and verbal explanation about participation. We will subsequently obtain written informed consent from all study participants before screening for eligibility to participate in the study. If findings regarding efficacy and safety that may affect patient consent are discovered at any points during the trial, we will swiftly disclose this information to participants and acquire their renewed consent.

To focus on patients who are likely to benefit and likely to be capable of participating, we will recruit patients who meet all the inclusion criteria (Textbox 2). To ensure that patients can safely and effectively participate in the intervention, we will recruit patients who do not meet any of the exclusion criteria (Textbox 3). We will use a transtheoretical model (TTM) questionnaire to categorize the participants who are currently at the contemplation stage (willing to change health behavior within the next 6 months), preparation stage (willing to change health behavior within the next month), or action stage (has made modifications to health behavior) [42]. In our previous study, patients who were in the contemplation and preparation stages of TTM were more likely to prefer to use smartphone-based self-management tools than those in the precontemplative stage [43]. Therefore, we targeted patients who are in the contemplation, preparation, or action stages of achieving the target goal of 10,000 steps a day.

We will provisionally register patients who meet the eligibility criteria. We will then provide them with a step-counting device and a smartphone with just the step-counting part of the placebo app. We will ask patients to record their daily step count for a baseline period (nominally 2 weeks, but at least 7 days), and then, we will measure their HbA_{1c} level at the end of the screening period. We will enroll patients who were able to measure their step count for ≥7 days during the baseline period (to ensure that we study patients who are able to adequately participate in the study) and who continue to have an HbA_{1c} level ≥7.5% (to ensure that patients continue to have high HbA_{1c} level after the screening period). We believe that the 2-week trial will have no significant effect on outcomes. We will then use the electronic data records to randomize eligible participants in 1:1 ratio to either the intervention group or the control group using the covariate-adaptive randomization by minimization method to ensure covariance balance for age (<65 years and ≥65 years), sex, HbA_{1c} level (<8.5% and ≥8.5%), and institution [44].

Textbox 2. Inclusion criteria of the study, focusing on patients who are likely to benefit from the intervention and are likely to be capable of participating.

Inclusion criteria

- Diagnosed with type 2 diabetes mellitus
- Being in the contemplation, preparation, or action stages of the transtheoretical model to achieve the target step count of 10,000 steps per day
- Hemoglobin A_{1c} level ≥7.5% and ≤10% at the time of consent acquisition
- No change in antidiabetic medication within 8 weeks before the time of consent acquisition
- Aged ≥18 years
- Systolic blood pressure <180 mm Hg and diastolic blood pressure <110 mm Hg at the time of consent acquisition
- eGFR ≥45 mL/min/1.73 m_2 recorded at least once in the 12 weeks before the time of initial registration (V0)
- Urine albumin-creatinine ratio is <300 mg/gCr on at least 1 occasion in the past year (52 weeks) before V0
- BMI ≥22 kg/m_2
- No incidences of severe hypoglycemic attacks where assistance by others was required in the 12 weeks before V0
- No symptoms of a possible hypoglycemic attack (including palpitations, tremors, dizziness, lightheadedness, anxiousness, loss of consciousness, sweating, pale face, tachycardia, headache, drowsiness, blurred vision, and convulsion) observed in the 12 weeks before V0
- Able to attend consultations at designated times during the trial
- Fully informed about participation in this study and has given free and voluntary written consent based on thorough understanding of the study

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Textbox 3. Exclusion criteria, focusing on patients who may not be able to participate safely or whose participation may interfere with the effectiveness of the study.

Exclusion criteria

- Walked an average of ≥10,000 steps a day in the 4 weeks before V0 (must be verifiable by pedometer, etc)
- Wearing a pacemaker
- Using continuous glucose monitoring (but do not exclude if self-monitoring of blood glucose level or intermittently scanned continuous glucose monitoring was conducted ≥8 weeks before V0)
- Diagnosed with hyperthyroidism and have received treatment other than thyroid hormone replacement in the year before V0
- Diagnosed with a moderate to severe heart condition that requires exercise restriction as assessed by a physician
- Require exercise treatment restrictions as assessed by a physician at V0—decision made with reference to "Cases in which exercise therapy should be prohibited or restricted" in the Guidelines for Diabetes Treatment (Japan Diabetes Society; 2022-2023)
- Hemoglobin <10 g/dL in the 12 weeks before V0
- Serum albumin ≤3 g/dL in the 12 weeks before V0
- Diagnosed with preproliferative retinopathy or retinopathy of a later stage within the year before V0
- Cannot undergo exercise treatment
- Pregnancy, including any possibility or intention of pregnancy
- Participation in other trials at the time of initial registration (V0)
- Impaired cognitive function, as determined by the investigator or subinvestigator
- Any other reason that the patient is classified as unfit for participation by the investigator or subinvestigator (a record must be maintained about the reason the patient was determined to be ineligible)

Intervention Process

The study (Table 2) includes 10 events (V0-V9), a 24-week continuous measurement phase (M), and a 12-week follow-up observation phase. Initial measurements will be made at event V0. At V0, we will provide each participant with a near field communication–enabled pedometer (A&D; UW-204NFC) and an iPhone (iPhone 8 with iOS 16) prepared with the placebo app configured for step count only. We will direct the participants to wear the pedometer throughout the day except during sleep. We will use the step count gathered during V1 to confirm eligibility and to set a step count baseline.

The surveys that will be used in this study are listed in Textbox 4.

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Table 2. Study events—1 measurement period and 10 visits spanning approximately 37 weeks.

Event	Focus	Time	Key activities
V0	Physical baseline assessments and initial registration	Enrollment—≥7 days before the beginning of the intervention	• Collect consent • Collect demographic information: date of birth, sex, smoking and drinking status, medical history, diet and exercise habit, household living condition, employment, use of smartphones, habit of step count measurement, and stage of behavior change according to the transtheoretical model of change regarding walking 10,000 steps a day • Collect physical data: blood tests to measure HbA_{1c}[a], FBG[b], LDL[c] cholesterol, HDL[d] cholesterol, TG[e], and eGFR[f]; urinalysis; and height, body weight, and BP[g] measurements • Collect medication and combination therapy status • Assess health literacy • Conduct surveys (Textbox 4) • Distribute pedometer and placebo-equipped phone
V1	Step count baseline	From V0 to the day before V2 (at least 7 days)	• Patients record daily steps and determine step count baseline
V2	Registration, allocation, and beginning of the intervention	Beginning of the intervention (end of week 0)	• Measure HbA_{1c} level • Finalize registration and allocation • Distribute BP monitor and scale • Activate all placebo and StepAdd features • Collect medication and combination therapy status • Check for adverse events
M	Ongoing measurement	From V2 to V8	• Daily measurements via app • Intervention only: daily feedback, weekly feedback, and weekly personalized goal setting via app • Check for defects
V3	Hospital visit 1	End of week 4	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V4	Hospital visit 2	End of week 8	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V5	Interim hospital visit	End of week 12	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status • Conduct surveys (Textbox 4)
V6	Hospital visit 4	End of week 16	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V7	Hospital visit 5	End of week 20	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status

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Event	Focus	Time	Key activities
V8	End of the intervention	End of week 24	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Collect medication and combination therapy status • Check for adverse events • Conduct surveys (Textbox 4) • Assess usefulness and usability
V9	End of follow-up	End of week 36	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Collect medication and combination therapy status • Check for adverse events • Conduct surveys (Textbox 4)

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]FBG: fasting blood glucose.

[c]LDL: low-density lipoprotein.

[d]HDL: high-density lipoprotein.

[e]TG: triglyceride.

[f]eGFR: estimated glomerular filtration rate.

[g]BP: blood pressure.

Textbox 4. Surveys—9 surveys assessing type 2 diabetes–related behaviors and outcomes.

Problem Areas in Diabetes

- 20 items to assess type 2 diabetes–related emotional distress [45]

Locomo 25

- 25-question risk assessment to evaluate musculoskeletal disorders such as walking disability, difficulty in daily living, or pain in the body [46]

Evaluation Scale for Self-Management Behavior Related to Physical Activity of Type 2 Diabetic Patients

- Assessments of the following:
  - Self-management behavior to enhance daily physical activity
  - Self-management behavior to maintain the level of physical activity [47]

Steps achieved

- Self-Efficacy Scale relative to achieving the targeted daily steps [48]

Dealing with barriers to achieving the targeted daily steps

- Self-Efficacy Scale relative to dealing with barriers to achieving the targeted daily steps [49]

Physical Activity Self-Regulation Scale–12; Japanese version

- Addresses self-monitoring, goal setting, eliciting social support, reinforcement, time management, and relapse prevention
- Rated from 1 (never use strategy) to 5 (use strategy very often)
- Scores are the sum of the 2 individual item scores and summed self-regulation subscale scores for a measure of overall self-regulation [50]

The Summary of Diabetes Self-Care Activities Measure; Japanese version

- Assesses type 2 diabetes self-care activities [51]

Health behavior "active coping behavior with disease"

- Self-Efficacy Scale for health behavior "active coping behavior with disease" subscale [52]

Audit of Diabetes-Dependent Quality of Life; Japanese version

- Assesses type 2 diabetes–dependent quality of life [53]

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Following randomization, we will begin the intervention. We will provide participants a Bluetooth-enabled sphygmomanometer (A&D; UA-651BLE Plus) and a Bluetooth-enabled weighing scale (A&D; UC-352BLE; in addition to the already provided pedometer and phone). For the control group, we will enable BP and BW measurement functions in the placebo app. For the intervention group, we will replace the placebo app with StepAdd and define the initial goals and barriers. Both the intervention and control groups will watch a video regarding lifestyle modification, self-management of T2D, and effect of exercise on glycemic control.

The main part of the intervention is the daily measurement by all patients throughout phase M. We will direct participants to measure their BW and BP daily upon awakening and wear the pedometer throughout the day except during sleep. All the participants will log the measurement data by syncing the recording devices (weighing scale, sphygmomanometer, and pedometer) to the app, rather than by manually inputting the data. These data are then uploaded to the server and made visible to health care professionals via the administrative screen. Intervention group participants receive personalized feedback about their step count performance 4 times a day. At the end of each week, intervention group participants review their weekly step count performance on the app, determine their personal barriers to achieving the step goals, and identify the possible coping strategies. StepAdd then provides a personalized step goal recommendation for the following week.

Every 4 weeks (events V3-V7), both groups will meet with a physician who will advise patients regarding lifestyle modifications and use of the app and, for the intervention group only, help with goals and coping strategies. Baseline measurements (other than collection of some background information) are repeated at the interim (V5), at the end of the intervention (V8), and at the end of the follow-up observation period (V9). We will collect the equipment at V8, before the follow-up observation period. The purpose of the observational period is to assess whether the intervention-induced effects are maintained after the end of the intervention.

During the study, we will not restrict the use of supplements and drinks that can affect blood glucose level and BP. In both the intervention and control groups, T2D treatment details, such as changes or additions of oral T2D medications, insulin, and glucagon-like peptide–1 receptor agonists and changes in medication dosage, can be changed at the discretion of the attending physician.

If patients discontinue the trial or stop using the app, we will define this as discontinuation, and we will collect the measurements within 7 days of this discontinuation. If participation in the study is discontinued during the intervention period, we will collect the V8 measurement items. If participation in the study is discontinued during the observation period, we will collect the V9 measurements items, except for urinalysis.

Monitoring, Quality Control, and Data Management

An auditor who is independent from the departments involved in the trial, including those responsible for monitoring, will inspect the medical institution and other facilities involved to ensure that the trial is conducted appropriately.

Ethical Considerations

This trial will be conducted in compliance with the Declaration of Helsinki, Pharmaceutical and Medical Device Act, Ministerial Ordinance on Good Clinical Practice for Medical Devices, and all other guidelines in relation to these regulations (jRCT2032220603). This study was approved by the institutional review board of the University of Tokyo School of Medicine (approval number 2022012-11DY). We will obtain written informed consent from all study participants. All patient data will be anonymized. Patients will be compensated JPY 7000 (approximately US $50) for each visit to the hospital.

Outcome Measures

Primary Outcome

The primary outcome of this study is the between-group differences in the change of HbA_{1c} value between baseline (V2) and either the end of the intervention period (week 24 [V8]) or, for patients who discontinue before V8, the point of discontinuation. Reduction of HbA_{1c} level by 0.35 percentage points is considered to be clinically significant [54,55].

Secondary Outcomes

Secondary outcomes (Table 3) include health measures, measurements of steps, measurements of other behavior changes, and assessments of app use. We will also assess safety outcomes such as hypertension requiring medical assistance (assessed from the system records), subjective hypoglycemia, pain in the lower back and lower extremities (tarsus, thighs, knees, calves, shins, ankles, and feet), and any other adverse events (all assessed through patient interviews).

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Table 3. Secondary outcomes investigated in the study—22 areas spanning health outcomes, exercise outcomes, other behavior changes, and app assessments.

Categories and item numbers	Outcomes
Health outcomes	

1	• HbA_{1c}[a] level (%)
	  • Change in HbA_{1c} level[b]
	  • Proportion of patients with HbA_{1c} level <7%[c]

2[d]	• FBG[e] (mg/dL) >5 hours after a meal
3[d]	• eGFR[f] (L/min/1.73m2)
4[d]	• BMI (kg/m2)
5[g]	• Body weight measured at home (kg)

6	• Systolic and diastolic BP[h] (mm Hg)
	  • BP measured at hospital[d]
	  • BP measured at home[g]

7[d]	• HDL[i] (mg/dL), LDL[j] (mg/dL), and TG[k] (mg/dL)

8[l]	• Concomitant medication intake (type of medication and daily dosage or weekly dosage for weekly formulation)
	  • Change in type 2 diabetes medication intake (either increased, unchanged, or reduced)
	  • Introduction of new medications to treat type 2 diabetes, hypertension, or dyslipidemia

9[d]	• Type 2 diabetes–related emotional distress (assessed using Problem Areas in Diabetes) [45]
10[d]	• Type 2 diabetes–dependent quality of life (assessed using Audit of Diabetes-Dependent Quality of Life) [53]
Exercise outcomes	
11[g]	• Daily step count
12[d]	• Walking duration
Other behavior changes	
13[d]	• Locomotive syndrome (assessed using Locomo 25) [46]
14[d]	• Type 2 diabetes self-care, assessed using the Japanese version of the Summary of Diabetes Self-Care Activities Measure [51]
15[d]	• Self-management behaviors related to physical activity, assessed using Evaluation Scale for Self-Management Behavior Related to Physical Activity of Type 2 Diabetic Patients [47]
16[d]	• Self-regulation of physical activity, assessed using the Japanese version of Physical Activity Self-Regulation Scale–12 [50]

17[d]	• Changes in walking self-efficacy:
	  • Self-efficacy for achieving the targeted daily steps [48]
	  • Self-efficacy for dealing with barriers to achieving the targeted daily steps (assessed using Self-Efficacy Scale of Walking Behavior) [49]

18[d]	• Changes in self-efficacy in health-promoting behavior, assessed using Positive Coping Behavior Towards Illness subscale within Self-Efficacy Scale for Health Promoting Behaviors [52]
19[m]	• Health literacy, assessed using Health Literacy Scale 14 [56]
App assessments	

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Categories and item numbers	Outcomes

20[n]	• App use is assessed through the following:
	  • Recording rate of body weight, step count, and BP and its change[o]
	  • Goal achievement rate[p]
	  • Goal increment rate[q]
	  • Goal reduction rate[r]
	  • Average number of coping planning strategies implemented per day[s]
	  • Number of barrier identifications[t]

21[u]	• System feasibility and usability (only for the intervention group)
22[v]	• Number of emails, SMSs, and calls to encourage registration

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]Includes both differences between week 0 (registration at V2) and week 12 (V5; or point of discontinuation, if earlier) and between week 0 (registration at V2) and week 36 (V9; or point of discontinuation, if earlier), which are compared within group and between groups, and includes the difference between week 0 (registration at V2) and week 24 (V8; or point of discontinuation, if earlier), which are compared within group.

[c]Includes all 3 proportions that are compared between groups: latest HbA_{1c} level up to week 12 (V5; or point of discontinuation, if earlier) <7%, latest HbA_{1c} level up to week 24 (V8; or point of discontinuation, if earlier) <7%, and latest HbA_{1c} level up to week 36 (V9; or point of discontinuation, if earlier) <7%.

[d]Includes all 3 differences: between provisional registration (V0) and week 24 (V8; or point of discontinuation, if earlier), between provisional registration (V0) and week 12 (V5; or point of discontinuation, if earlier), and between provisional registration (V0) and week 36 (V9; or point of discontinuation, if earlier), which are compared between groups.

[e]FBG: fasting blood glucose.

[f]eGFR: estimated glomerular filtration rate.

[g]Includes differences between the beginning of the intervention (V2; or from baseline period [V1] for steps) and week 4 (V3) and differences between each visit and each subsequent visit, which are compared between groups. In addition, they include measurements at each period (between visits), which are to be compared between groups. Item 11 also includes difference between baseline (V1) and 2 weeks before week 12 (V5; or point of discontinuation, if earlier) and week 24 (V8; or point of discontinuation, if earlier), which are compared within group and between groups.

[h]BP: blood pressure.

[i]HDL: high-density lipoprotein.

[j]LDL: low-density lipoprotein.

[k]TG: triglyceride.

[l]Includes assessment at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier), respectively, and it will be compared between groups.

[m]Will be assessed at provisional registration (V0).

[n]Includes comparisons of the differences over the first period of the intervention (from week 0 [V2] to week 4 [V3]) and differences over each subsequent period (between subsequent visits), which are compared between groups (only the recording rate of body weight, step count, and BP and its change) and within group (all assessments).

[o]Formula: (number of days in which measurements for BW, step count, and BP are recorded/total number of days) × 100.

[p]Formula: (number of days in which step goal was achieved/total number of days) × 100; examined only for the intervention group.

[q]Formula: (number of days in which step goal was increased/total number of reset times) × 100; examined only for the intervention group.

[r]Formula: (number of days in which step goal was reduced/total number of reset times) × 100; examined only for the intervention group.

[s]Formula: total number of coping strategies implemented over the period/total number of days; examined only for the intervention group.

[t]Number of barriers identified every 4 weeks; examined only for the intervention group.

[u]Will be assessed for the intervention group only, at week 24 (V8; or point of discontinuation, if earlier).

[v]Will be assessed at week 24 (V8; or point of discontinuation, if earlier).

Statistical Analysis

In this study, we define 3 analysis populations: full analysis set (FAS), per protocol set (PPS), and safety analysis set (SAS). FAS is the set of all patients whose data were obtained at least once after randomization. We will follow the intention-to-treat principle and analyze data based on the assigned group in the FAS analysis. PPS is the FAS population with the exclusion of patients who were found to have violated the eligibility criteria after randomization or who did not use the app over a 3-week period. SAS is the set of all patients who used the StepAdd app or the placebo app at least once after randomization. In the safety analysis using SAS, we will analyze data based on the apps actually used by the patients, regardless of allocation. AS will be the primary analysis population, and PPS will provide supportive results. All safety analyses will be conducted in SAS.

Data about patients' characteristics will be presented as mean, SD, minimum, 25th percentile, median, 75th percentile, and

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maximum for continuous variables and as frequency and proportion for categorical variables.

In the primary analysis, we will perform between-group comparison of the change in HbA_{1c} level from week 0 (V2) to week 24 (V8; or point of discontinuation, if earlier) using analysis of covariance, including baseline HbA_{1c} level (ie, HbA_{1c} level at week 0 [V2]) as a covariate in FAS. If participants discontinue the study, the latest measurement of HbA_{1c} level before V8 will be used.

We will also conduct 2 subgroup analyses with one classification by HbA_{1c} level at week 0 (V2; either <8.5% or ≥8.5%) and the other classification by BMI at the time of initial registration (V0; either <25 kg/m^2 or ≥25 kg/m^2). We will conduct subgroup analysis on the primary outcome in each analysis set to investigate whether the efficacy of StepAdd is consistent between these subgroups.

In the secondary analysis, the change in HbA_{1c} level at week 12 (V5) and week 36 (V9) will be analyzed as in the primary analysis. The proportion of patients with HbA_{1c} level <7% at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be compared between the groups using Fisher exact test. The change from baseline in the step counts, various laboratory test values, and questionnaire scores at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be analyzed as the primary end point. Changes in T2D medications, classified as weakened, unchanged, or strengthened, will be compared between groups using the Cochran-Mantel-Haenszel test. The proportion of new medications added will be compared between groups using Fisher exact test. Change in app data (step counts, BW, and BP) and their recording rates will be evaluated between each visit based on the week-0 (V2) to week-4 (V3) period and compared between groups using 2-tailed *t* tests. The McNemar test will be used for within-group comparison of the proportion of people who walked ≥10,000 steps in the 2 weeks before the intervention and the 2 weeks before week 24 (V8). A paired *t* test will be used for within-group comparison over the week-0 (V2) to week-4 (V3) period for goal achievement rate, goal increment rate, goal reduction rate, average number of coping planning strategies implemented per day, and number of barrier identifications.

As an exploratory analysis, we will use linear regression to investigate the relationship between the average number of coping strategies implemented per day and improvement in HbA_{1c} level in the intervention group. The analysis will use the average number of coping strategies implemented per day and baseline HbA_{1c} level as explanatory variables and the change in HbA_{1c} level as the response variable. The change from baseline to week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be evaluated.

We will conduct statistical analysis of safety outcomes. We will compare the proportion of incidences of hypoglycemia, joint pain, significantly elevated BP (≥145/95 mm Hg), and exacerbations of joint pain between groups using Fisher exact test. Other adverse events will be recorded using the Japanese version of the Medical Dictionary for Regulatory Activities categories for Preferred Term and System Organ Class, and their incidence proportions will be compared between groups using Fisher exact test. The severity of each incidence will be categorized into 3 grades (low, moderate, and high), and their between-group comparison will be conducted using the Cochran-Mantel-Haenszel test.

Results

Recruitment began on January 1, 2023. As of September 5, 2023, we have recruited 44 patients. We expect the trial to be completed by October 8, 2025, with the follow-up observation period being completed by December 31, 2025. We anticipate completing the analysis by March 30, 2026.

Discussion

Expected Outcomes

We have designed this study based on the foundational concept that this is a behavior change intervention, albeit one where we are measuring medical outcomes. We base the intervention on a specific theory of behavioral change, in this case SCT, to give a framework to the intervention, ensuring clarity about the targets of the intervention and keeping the focus on these targets to avoid scatter-shot ideas about how and where to intervene. We identified a specific and actionable target behavior, walking more, and designed a measurement and feedback system around this focused behavior. This focused approach brings clarity to the researchers and to the patients. The focus lets us determine if this specific intervention increases walking behavior while also assessing any resulting changes in physical parameters such as BMI and ultimately assessing changes in health. It is not sufficient to show that some behavior intervention leads to HbA_{1c} level improvement—we need to understand the steps in between, in particular, the behavior response, to fine-tune the intervention to expand on the aspects that work and eliminate the aspects that do not. We have designed this trial to provide evidence about the intermediate stages.

Our study uses objectively measured data for all primary and many secondary outcomes. The intervention uses wireless technology that allows step count, BW, and BP measurements to be synced automatically to the app. These simple, passive features make for easy-to-use objective measurements, especially for older patients. Daily monitoring of blood glucose level has been shown to have low measurement rates and to not be preferred by patients; therefore, we have not included it in this intervention [57].

We chose HbA_{1c} level as our primary outcome, as it is regarded as both a global standard for measuring glycemic control and an appropriate indicator of the effectiveness of T2D treatment [58]. According to The Japan Diabetes Society's treatment guideline, patients with T2D should aim to reduce their HbA_{1c} level to <7% to prevent the development of any complications [59]. Therefore, we decided to study the proportion of patients who achieved an HbA_{1c} level <7% in addition to studying the absolute change in HbA_{1c} levels.

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In this study, we have elected to use a "formidable" control [60] using a fairly high-functioning placebo app. We have initial confirmation of proof of concept from the pilot, and now, we want to show whether our specific behavior change intervention methods are superior to simply giving patients access to their step count, BW, and BP. There is evidence suggesting that simply giving patients a pedometer increases their activity level [61]; thus, there is some risk that the study will induce a response in the control group, which may prevent statistical proof of any superiority of the StepAdd intervention. Most people who want a pedometer already have access to one in their smartphone, and we think this risk is modest. By giving the placebo group a functional app, albeit one lacking StepAdd's functionality, we have designed the study to give strong proof of the success of StepAdd, if in truth, it is effective.

Many behavior interventions show solid, short-term gains that fade later [62]. Our StepAdd pilot [29] showed results that continued to improve throughout the study, with no sign of fading. This study expands the trial time to 24 weeks with a 12-week observation period to examine whether the pilot results hold true over a long period. Behavior change maintenance is theorized as an outcome of active and ongoing self-regulation, and habit development follows a period of successful self-regulation of a new behavior [63]. Our objective is to change behavior in a sustainable way, such that the new pattern of behavior becomes a habit that can be sustained over the long haul.

A key to our approach is ensuring that the patients receive a strong introduction to the mechanics of the intervention and the StepAdd app. Patients have busy lives, and we work to make it clear and easy for them to meet the demands of the intervention. By providing training regarding the intervention and the app and by ensuring that all messaging in the intervention is simple and focused, we maximize the likelihood that the patients will use the tools of the intervention just as we intend them to.

Another key part of the approach is focusing first on the patients whom the intervention will serve. We designed the intervention for a specific target set, not all patients, and customized the intervention to meet their needs and accommodate their preferences. We have found that it is essential to design with cultural background and patient preference in mind, as we did in the StepAdd pilot [29]. Another key aspect of our approach is applying it only to patients who are already motivated to change their behavior. We filter based on TTM stages, and we have found this approach to be highly effective [29,43]. Our intervention is designed for high-motivation patients who are in need of some help in implementing their desired behavior—low-motivation patients are in need of an entirely different intervention focused on improving their motivation. We have found that large proportions of patients with T2D in Japan have high motivation, with a study showing that 92% are in the contemplation-through-action stages of TTM [64]. There is a very large pool of patients who would benefit from this targeted intervention. Exercise has been shown to improve health in patients with chronic kidney disease [65], and a recent meta-analysis confirms that exercise and diet programs improve the health of patients with T2D who are obese, including improving BMI and HbA_{1c} level [66]. This study is a multicenter randomized controlled trial, and this increases the generalizability of the findings to patients with T2D throughout Japan. Our techniques are general, and there is every reason to believe that these methods could be applied to increase exercise for patients with other diseases and in countries throughout the world.

Limitations

The study has limitations. The results of our trial may be specific to the population studied and may not be fully generalizable to other populations. Our participants will likely be older people of Japanese ethnicity. There are differences between Japanese and other populations in lifestyles and in the pathophysiology of T2D. The study is limited to patients who are able to use mobile phones; therefore, there may be biases owing to users' digital literacy. In contrast, results may differ with a young population [67], as it has been reported that young populations are able to complete tasks more successfully on mHealth apps [68] and have high satisfaction compared with their older counterparts [69]. Participants will not be blinded to randomization; therefore, social desirability bias may affect the results. We do not engage on or control for dietary changes, and changes in dietary behavior during the study may affect our results. Baseline step count is measured using pedometers provided to participants, and the resulting measurements may be higher than the true prestudy step count, as studies have found that providing a pedometer increases step count by >2000 steps [63], at least in the short term. This effect is mitigated by our 2-arm trial and the length of our trial, but it may lead us to underestimate the increases in step count and, therefore, overestimate the per-step impact on health outcomes.

This trial will provide important evidence about the efficacy of an SCT-based mHealth intervention in improving physical activities and glycemic control in patients with T2D. If this study proves the intervention to be effective and safe, it could be a key step toward the integration of mHealth as part of the standard treatment received by patients with T2D in Japan. Our findings will inform future studies of using theory-based behavior change techniques and may lead to practical use by exercise professionals in the real world [70].

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Data Availability

Aggregate data analyzed in this study may be made available upon reasonable request by contacting the corresponding author via the email address provided.

Conflicts of Interest

The study was supported by Raxi Co Ltd. The patent that resulted from this study is issued to Raxi Co Ltd and The University of Tokyo. KW received support from Raxi Co., ltd. as a PI to conduct the study, and HW is their spouse.

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Abbreviations

BP: blood pressure
BW: body weight
CONSORT: Consolidated Standards of Reporting Trials
FAS: full analysis set
HbA_{1c}: hemoglobin A_{1c}
mHealth: mobile health
PPS: per protocol set
SAS: safety analysis set
SCT: social cognitive theory
TTM: transtheoretical model
T2D: type 2 diabetes

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Protocol

Decreasing Opioid Addiction and Diversion Using Behavioral Economics Applied Through a Digital Engagement Solution: Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite strong and growing interest in ending the ongoing opioid health crisis, there has been limited success in reducing the prevalence of opioid addiction and the number of deaths associated with opioid overdoses. Further, 1 explanation for this is that existing interventions target those who are opiate-dependent but do not prevent opioid-naïve patients from becoming addicted.

Objective: Leveraging behavioral economics at the patient level could help patients successfully use, discontinue, and dispose of their opioid medications in an acute pain setting. The primary goal of this project is to evaluate the effect of the 3 versions of the Opioid Management for You (OPY) tool on measures of opioid use relative to the standard of care by leveraging a pragmatic randomized controlled trial (RCT).

Methods: A team of researchers from the Center for Learning Health System Sciences (CLHSS) at the University of Minnesota partnered with M Health Fairview to design, build, and test the 3 versions of the OPY tool: social influence, precommitment, and testimonial version. The tool is being built using the Epic Care Companion (Epic Inc) platform and interacts with the patient through their existing MyChart (Epic Systems Corporation) personal health record account, and Epic patient portal, accessed through a phone app or the MyChart website. We have demonstrated feasibility with pilot data of the social influence version of the OPY app by targeting our pilot to a specific cohort of patients undergoing upper-extremity procedures. This study will use a group sequential RCT design to test the impact of this important health system initiative. Patients who meet OPY inclusion criteria will be stratified into low, intermediate, and high risk of opiate use based on their type of surgery.

Results: This study is being funded and supported by the CLHSS Rapid Prospective Evaluation and Digital Technology Innovation Programs, and M Health Fairview. Support and coordination provided by CLHSS include the structure of engagement,

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survey development, data collection, statistical analysis, and dissemination. The project was initially started in August 2022. The pilot was launched in February 2023 and is still running, with the data last counted in August 2023. The actual RCT is planned to start by early 2024.

Conclusions: Through this RCT, we will test our hypothesis that patient opioid use and diverted prescription opioid availability can both be improved by information delivery applied through a behavioral economics lens via sending nudges directly to the opioid users through their personal health record.

Trial Registration: ClinicalTrials.gov NCT06124079; https://clinicaltrials.gov/study/NCT06124079

International Registered Report Identifier (IRRID): PRR1-10.2196/52882

(JMIR Res Protoc 2024;13:e52882) doi:10.2196/52882

KEYWORDS

opioid abuse; opioid naïve patients; opioid addiction; behavioral economics; nudges; MyChart; personal health record; post-operative care; opioid; opioid use; randomized controlled trial; RCT; behavioral economics; digital engagement; health crisis; overdose; acute pain; pain; tool; tools; phone app; website; application

Introduction

Opioid-related overdose and death rates continue to soar in all age groups [1-3]. Today, it is the leading cause of unintentional, injury-related death in the United States [4]. As of 2020, prescription opioid-related deaths totaled more than 16,000 [5]. Even in 2021, despite opiate prescribing reaching a low point, opiate deaths continue to rise [6]. Further, 1 hypothesis to explain this is that existing interventions target those who are opiate-dependent but do not prevent opioid-naïve patients from becoming addicted [7-9]. Once a patient acquires and fills a prescription, they are free to use it however they choose. The continued skyrocketing trajectory of opioid deaths as well as the persistent conundrum of opioid use demonstrates the insufficiency of exclusively relying on prescriber-directed strategies. This highlights the critical need to directly empower individual patients to responsibly manage their use, weaning, discontinuation, and disposal of opioid medications.

Continuous perioperative interventions centered on opioid management and coming from many different angles could contribute to a solution. Evidence has shown that less than 10% of unused opioids are properly disposed of after surgery, suggesting that excess opioids remaining in the home after surgery is a widespread but targetable problem [10]. Diversion of opioids, which is defined as illegal distribution or abuse of opioids for purposes not intended by the prescriber, could be intentional (for example, sharing or selling of medications) or unintentional (for example, theft or ingestion by a child).

Behavioral economics is a field of study within human decision-making where the goal is to predictably influence human behavior and encourage people to do something without forcing, coercing, or penalizing them [11,12]. Several behavioral economics interventions have been leveraged to influence human behaviors but do not guarantee an improvement in the target population's target behavior. Nudging is a way to manipulate people's choices to lead them to make specific decisions. Nudging has previously been used to influence smoking, alcohol consumption, diet, and physical activity to improve population health and reduce health inequalities [13]. More recently, nudging has been used to improve medication compliance among patients with various medical conditions, for example, cardiac [14], kidney transplant recipients [15], patients with diabetes [16], HIV [17], and mental illness [18]. Behavioral economics also offers an opportunity to help individuals make choices consistent with responsibly using and disposing of their opioid medications [19].

The primary goal of this project is to evaluate the effect of the 3 versions of the Opioid Management for You (OPY) tool described in the methods section on measures of opioid use relative to the standard of care (SOC) leveraging a pragmatic randomized controlled trial (RCT). We hypothesize that appropriate patient opioid use and diverted prescription opioid availability can both be improved by information delivery applied through a behavioral economics lens via sending nudges directly to the opioid users, that is, patients. We anticipate not only better management of opioid use and its safe disposal but also expect to obtain a better understanding of the unresolved questions regarding how pain medication is used in acute perioperative settings. In the future, we could further optimize the OPY tool, integrating artificial intelligence and other machine learning models for a more enhanced patient experience.

Methods

OPY Tool

Overview

A team of researchers from the Center for Learning Health System Sciences (CLHSS) at the University of Minnesota partnered with M Health Fairview (MHFV) to design, build, and test the 3 versions of the OPY tool. Based on a literature review of current popular nudging theories implemented in various delivery modes, we incorporated 3 nudging tactics into the workflow of Care Companion to improve patient self-management, medication adherence, and overall health. Tactics were based on the following behavioral economic principles: social influence, precommitment, and testimonial version. Other forms of interventions, including reminders, feedback, and loss-framing, will also be partially incorporated as a component of the design but will not be considered as major guidelines.

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The tool is being built using the Epic Care Companion platform and interacts with the patient through their existing MyChart personal health record account and Epic patient portal, accessed through their phone app or the MyChart website. As patients communicate their pill usage, pain scores, or other concerns, the intervention will communicate timely and relevant information regarding opioid use and addiction while also offering encouraging feedback to help patients successfully wean and safely dispose of their opioids. OPY saves the data that a patient enters and based on their responses, the care team is alerted to important issues through an in-basket message system. The alerts or flags are selected and color-coded based on the urgency of action required after discussion with the patient education specialist team.

Each of the 3 OPY versions will deliver the same instructions and information about pain management recommendations and collect the same information about patient pain experience and side effects; however, the behavioral economics techniques used to influence weaning and disposal are different across the 3 versions. The 3 versions will correspond to different treatment arms of the RCT.

Version 1, Social Influence and Commitment

Social influence refers to how individuals change their ideas and behaviors to meet the needs in a social environment [20]. Studies have found that social influence has proved effective for physical activity promotion when applied to mobile apps and is also promising in helping manage chronic diseases, including diabetes.

Patients are provided with text that communicates a social norm or expresses an expectation to the patient meant to decrease the average time it takes for patients to begin weaning. Textbox 1 provides an example of social influence text shown to patients.

Textbox 1. Example of social influence text shown to patients.

Opioid overdoses are at an all-time high. You can help us end this opioid epidemic! When you're ready, we'll help you wean as quickly as possible – and then get rid of your leftover medicine safely.

Version 2, Precommitment

Precommitment refers to a commitment we make in advance to ensure our future actions align with our current preferences and eventually reach the goal we set for ourselves [21]. Studies have shown that precommitment effectively ameliorates self-control problems by encouraging healthy diets, less smoking, and reducing temporary drinking. Being cost-effective in many cases [22], precommitment could have positive implications for chronic disease control and prevention [23].

Patients are given the same suggestions as in other versions but are asked to check a box next to the suggestions they are planning to try. Textbox 2 provides an example of precommitment options provided to patients.

Textbox 2. Example of precommitment options given to patients.

Let's try to reduce your opioid pain medicine. Set a goal to use one of the options below — and be sure to tell a friend or family member about your goal.

- Try taking a dose every X+2 hours (instead of X hours).
- For every other dose, take just half the dose.
- Try skipping a dose.

Version 3, Testimonial

Emerging evidence suggests that storytelling, or narrative communication, influences listeners by actively engaging them in a story, causing them to identify themselves with the storyteller and picture themselves taking part in the action. This approach of leveraging testimonials offers a unique opportunity to promote evidence-based choices in a culturally appropriate context. Stories and storytelling have been previously used as mechanisms to improve patient medication compliance for both hypertension [24] and diabetes [25], as well as improve other health education and literacy programs.

In this approach, instead of text-based nudges or setting goals, the patient receives short videos communicating risks and benefits through narrative storytelling. The videos use voice actors to depict patients who have experienced complications related to opioid use after surgery. A video clip of a person is presented to represent the patient sharing their personal story. Textbox 3 provides an example of testimonial audio presented to patients.

To ensure that videos and their content meet the current in-place requirements of the organization, we worked closely with the patient education team and followed their requirements. We also made sure that the videos were relatable to patients from diverse demographic backgrounds (ie, race, ethnicity, gender, and age) after judicious selection of individual stock video clips from University of Minnesota stock image resources [26] and collecting voice-over audio recordings from our team members who volunteered to read and record the scripts. We will collaborate with the IT team at our implementation sites to create reports on when each patient watched the video and if they watched the full video or left without finishing it. If patients do not complete the video, the task will be flagged to ensure the patient can see and come back later to finish watching the given video.

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Textbox 3. Example of testimonial audio presented to patients.

> After having my appendix removed, I took opioids to help with the pain. But, even on the Vicodin my doctor prescribed, I didn't feel great. When my doctor suggested that I start reducing how much I was taking, I didn't want to do that. I wasn't feeling totally better yet. When day 5 came and I hadn't reduced the number of pain pills, I had another problem: constipation. Turns out the pain of going to the bathroom was much worse than the actual pain resulting from surgery. After taking stool softeners along with gradually reducing the dose, I started feeling better in a week. I wish I had started weaning sooner.

OPY Functional Description

OPY appears as a task within MyChart. The first OPY tasks present welcome text for first-time users that describes what OPY is and how to use it. OPY asks users if they want to use OPY or if they want to opt out. OPY tasks and questions will not appear again for people who opt out. OPY then asks patients about their comfort with filling out medical forms and their safety taking ibuprofen or acetaminophen. The medical form information is used to stratify results in our analysis, and the medication question is used to customize pain management suggestions on subsequent days. OPY users must complete these questions before receiving other content from OPY. OPY presents customized messages and questions based on the duration of time since surgery and the responses of the patient. On day 0 (the day of surgery), only the questions described will be asked. OPY patients will not know which version of OPY they are using, or that other versions exist. After day 0, a patient who has opted in will receive several questions every day offered in this order: OPY asks about side effects with prespecified suggestions for what to do for each side effect that they check, pain levels, and the number and frequency of pills they took in the last 24 hours (Figure 1).

Responses are then customized based on the number of days since surgery, patient pain level, and patient pill intake. Depending on their responses, patients receive some combination of pain management advice, including recommendations to take ibuprofen or acetaminophen if able and other standard nonmedication strategies, weaning advice on when and how to start, and disposal advice, including instructions on how and where to dispose of opioids.

At the end of the pathway, all patients will receive a patient satisfaction survey which is standard and exists as an important element of all Epic Care Companion protocols.

Once OPY patients indicate they are taking 0 opioids per day, they will be asked at most 5 times to dispose of the opioids over a span of at most 25 days. OPY will become inactive after 15 consecutive days of no response counted either from day 0 or the last response submitted. Figure 2 summarizes the flow of events that a patient encounters once they are enrolled in the OPY journey.

As per randomization strategy, patients would be assigned one of the following paths: null pathway, pathway 1, pathway 2, or pathway 3. The details are explained in Figure 3.

Figure 1. Epic Systems Corporation 2024 screenshots of OPY screen displaying questions and their responses for (A) social influence and (B) precommitment. OPY: Opioid Management for You.

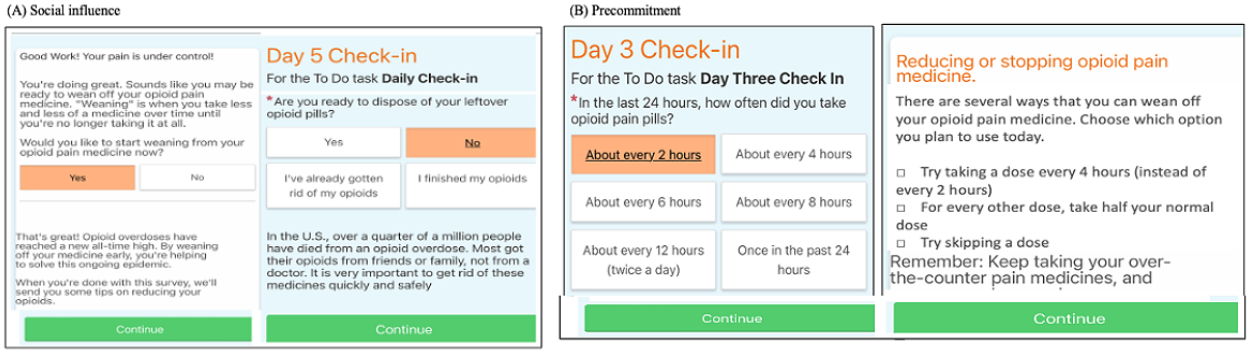

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Figure 2. Flow of events once patients are enrolled in OPY. AVS is given to patients after medical appointments to summarize their health and guide future care. OPY: Opioid Management for You.

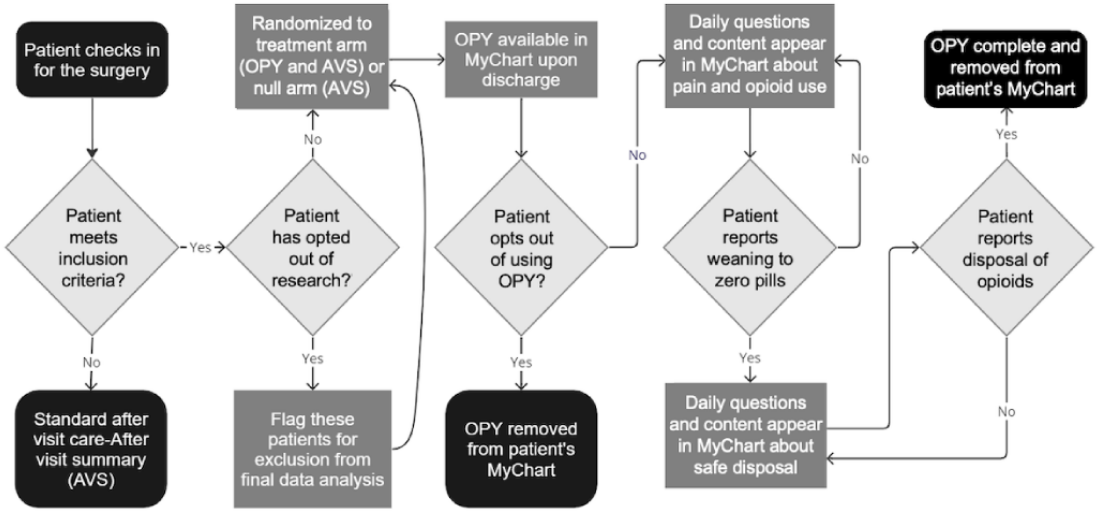

Figure 3. Randomization strategy. Standard care: null pathway; pathway 1: social influence; pathway 2: precommitment; and pathway 3: testimonial. First question patients receive: welcome to the Opioid Program for You! (OPY), Your care team has enrolled you in a digital opioid management program, "OPY," … Do you want to take part in OPY? Click Yes to continue. Click No to stop getting these messages (yes or no). The number of available OPY versions will change over time, which will change the randomization ratio (eg, 1 version available=1:1, standard care versus standard care + pathway 1; 2 versions available=1:1:1, standard care versus standard care + pathway 1 versus standard care + pathway 2). We will leverage an existing random number generator that is embedded within the NAÏVE tool platform which will in turn assign a designated OPY pathway based on the ratio prescription from the statistical team. Rx: doctor's prescription.

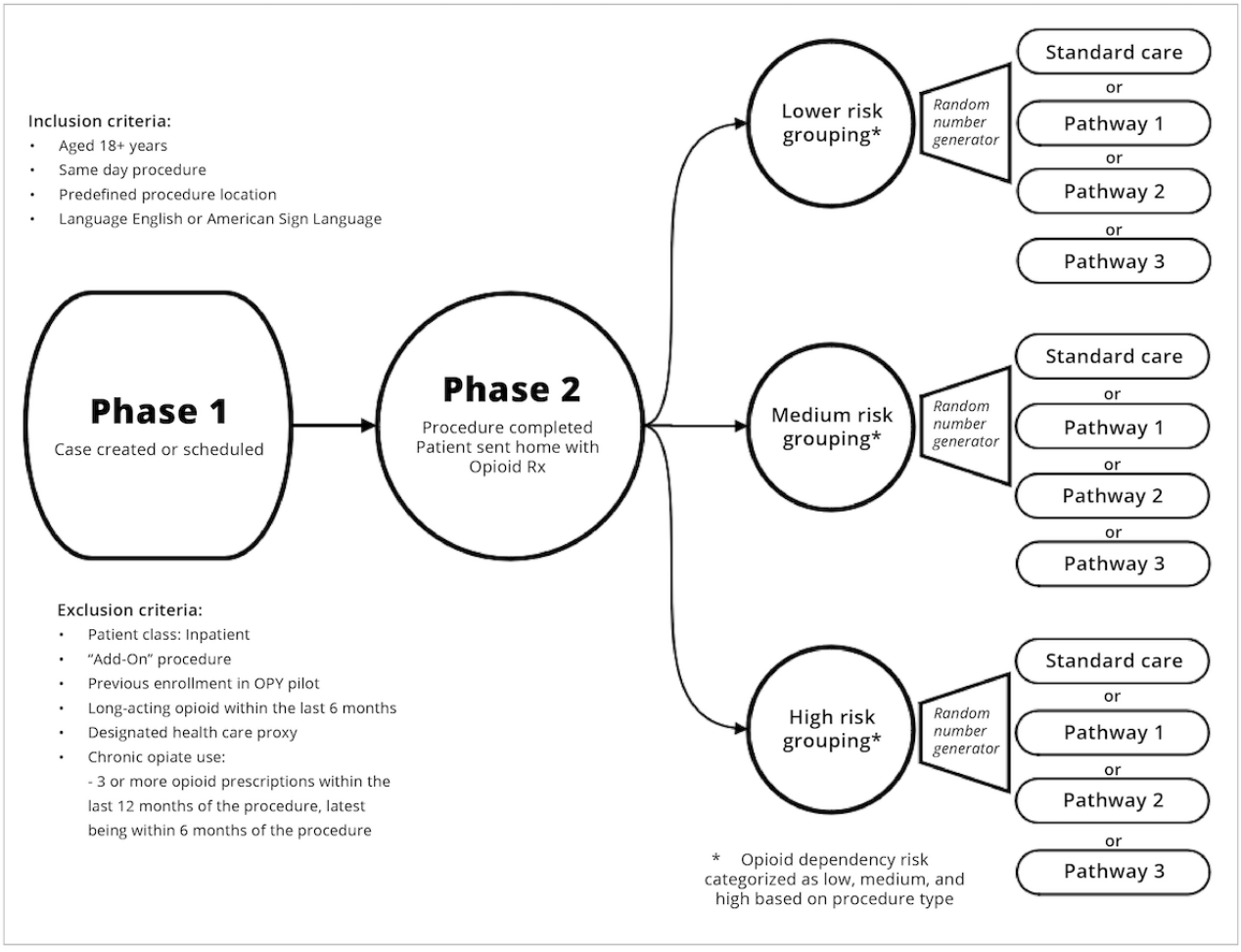

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Preliminary Data From the Pilot

We have demonstrated feasibility with pilot data of the OPY app (Pathway 1) by targeting our pilot to a specific cohort of patients undergoing upper-extremity procedures. About 13% of opioid-naïve patients continue to fill opioid prescriptions 90 days after hand surgery, signaling that this patient population could benefit from tools to help manage opioid use [27]. Another population that we included in the pilot is breast surgery patients, specifically opioid-naïve patients undergoing lumpectomy, mastectomy, mastopexy, and reduction mammaplasty. In total, 10% of opioid-naïve women continued to fill their prescriptions 3 months after breast reconstruction surgery [28]. Over the initial 15 weeks from August of the pilot, 100 patients were eligible to use OPY. In total, 47 (44%) of eligible patients did not interact with OPY to either opt-in or opt-out. Further, 26 (26%) patients opted out of participating in OPY and 27 (27%) opted into using OPY. There is also evidence of persistent engagement with the OPY app, with 24 (65%) of opted-in patients using the tool at least once in the first 4 days after surgery, and 16 (33%) of opted-in patients using the tool at least twice in the first 4 days after surgery as of August 10, 2023.

The preliminary data from the pilot indicates low patient engagement in continuous use. To identify the exact reason why patients were not using the OPY tool as we expected them to, we reached out to patients, their families, and even perioperative nurses. We found a few reasons, the most prominent one being introducing patients and their families to a new tool such as OPY on the day of surgery which was not considered as an effective approach. Patients are already stressed, under the influence of anesthesia, and are overwhelmed with new information. To ensure that we address those concerns, we came up with certain strategies to improve patient compliance, for example, introducing OPY during preop clinic visits, sending epic care companion messages 3 days before surgery sharing what OPY is all about, and also considering options where a nurse (who normally call on postop day 1 to ask about patient progress or pain) to remind them about OPY tool and its benefits.

Study Design

This study will use a group-sequential RCT design to test the impact of this important health system initiative. Patients who meet OPY inclusion criteria will be stratified into low, intermediate, and high risk of opiate use based on their type of surgery. We used preliminary data to categorize surgery types according to their risk of opiate use. We ranked surgery types according to their opiate use rates at 14 days and categorized surgery types with use rates belonging to the lower 60 percentile, 60-75 percentile, and upper 25 percentile into low, intermediate, and high-risk opioid use groups (surgical risk groups in Multimedia Appendix 1). We estimate the prevalence of these subgroups to be approximately 49%, 34%, and 17%. Randomization will be stratified by baseline risk group, and, within a group, participants will be randomized equally to the SOC (the control group or nonintervention arm) or SOC plus one of the available OPY versions.

Participant Characteristics, Sample Size, and Recruitment Strategies

Inclusion Criteria

We will enroll opioid-naïve patients, aged 18 years or older, including pregnant women, prisoners, and underserved populations who can read and understand English and are undergoing surgery at the MHFV Clinics and Surgery Center—Maple Grove (Maple Grove) or MHFV Clinics and Surgery Center—Minneapolis. Currently, only outpatient surgeries are performed at MHFV Clinics and Surgery Center—Minneapolis and MHFV Clinics and Surgery Center—Maple Grove. Any patient on active opioid prescription (prescribed between 30 days before surgery and until the day of surgery) who was not previously randomized or exposed to OPY would be included. All patients with cancer would be included.

Exclusion Criteria

We will exclude patients aged younger than 18 years; those with chronic opioid use, defined as 3 or more opioid dispensing events in the last 12 months with at least 1 of these events in the last 6 months; patients with any long-acting opioid prescription in the last 6 months; patients with a health proxy (legal guardian) designated in Epic; patients who have opted out of clinical research; and patients with an active palliative care referral.

Children are excluded due to complexities in postoperative care and communication.

Sample Size

The study will enroll up to 3500 participants (approximately 1715, 1190, and 595 enrollments to the low, intermediate, and high-risk groups, respectively) in each OPY version.

Recruitment

We will recruit patients who are undergoing surgery with participating providers at the 2 predetermined locations, that is, MHFV Clinics and Surgery Center in Minneapolis and the Maple Grove locations. Patients who opt out of clinical research or for whom opt-out status is missing will be excluded. The patient is given a choice to consent or opt out of the OPY journey during their first postoperative interaction with the OPY questionnaire distributed through Epic Care Companion. The final decision to participate or not in the OPY journey would be collected from the patient on the day of the surgery (end of the day) through the OPY questionnaire distributed through Epic Care Companion leveraging MyChart.

Study Duration and Data Management

We anticipate that the pragmatic trial will be implemented over 24 months. Our trial will continue enrollments until we reach our 3500 patients enrollment goal. We rely entirely on collaboration with MHFV for data collection within the CLHSS and Fairview data specialist teams. This is because these efforts require the creation of new data fields that leverage a learning health system platform. Unless specified, we will use naturally collected NAÏVE data (including OPY usage) to assess process fidelity, patient safety, and impact on outcomes.

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This project will use the existing CLHSS or Center for Quality Outcomes, Discovery, and Evaluation database covered by the institutional review board (IRB) under 597 Protocol (STUDY00014481). The research database lives within Fairview IT. At Fairview, IT access is facilitated by Fairview Research. Please see the data governance processes described in IRB 597 Protocol (STUDY00014481) for further details. This study will rely on the surgical data mart for data acquisition outside of (1) the data primarily generated through the patients' clinical participation in the OPY tool and (2) follow-up surveys.

Data will not be shared publicly. Access is regulated by the CLHSS and Fairview Data stewards. Additional sharing beyond the focus of this study would require additional IRB approval.

Data Collection

Patients meeting OPY inclusion criteria will receive a MyChart message notifying them of access to a specific OPY app. Each patient, regardless of assignment to an OPY version, will receive SOC information via the after-visit summary regarding the appropriate use and disposal of opiates and how to contact their care team if pain persists or worsens. Implementation of each app is primarily driven by the health system. The research team will assist with the allocation approach and subsequent analysis. OPY will collect and send data via the Epic care companion platform leveraging MyChart. Data generated through patient interactions with the OPY tool will live in the Epic environment while the patient is interacting with the tool. This includes data such as daily pain scores, daily opiate usage, daily deferrals of weaning, use of nonopiate medications, "red flag" triggers, and disposal of excess medication. Data generated through interaction with the tool will subsequently be transferred to an Academic Health Center Information Exchange–compliant server as described above. Data on various stakeholder (patients and clinicians) perspectives about their experience with the OPY tool or program would be collected periodically using surveys and or interviews.

Primary and Secondary Study Outcomes

Our primary outcome is the persistent use of opiates as measured by continued use at 14 days. Secondary end points we will seek to evaluate include the number of days between initiation of opioid therapy and opioid-free pain control; the interval time between opioid doses; daily pain scores; number and cause of patient-initiated outreach events (from the care companion app); the number of MyChart messages within the first 30 days postoperative; the number of phone notes in the first 30 days postoperative; 90-day hospitalization rates and hospital length of stay; repeat surgery rates; outpatient encounter rates; referral and completion of referral of pain management rates; 90- and 120-day opiate use rates; OPY usage at 1, 3, 7, 14, and 30 days, 90 days all-cause mortality; metrics around patients' reported disposal of remaining pills, for example, time to disposal and preferred disposal route.

Outcome data will be extracted from natural electronic health record data, common to pragmatic trials. Specific measures including tool usage, opioid prescribing rates, and the existence of comorbidities, are all validated as a part of quality reporting (opioid reduction optimal care map). Each measure is validated at the time of variable construction and immediately before statistical analysis.

Data Analysis

The analysis of the primary and secondary end points will be completed following the intention-to-treat principle. Participant data will be analyzed according to the randomly assigned treatment group. We will ensure that only records of patients who have agreed to have their information used for research are included in the analysis. We will include all patients who opted into the OPY experiment whether they ever used the OPY tool or not.

The baseline opioid use rate of patients varied substantially between the low, intermediate, and high-risk groups. Moreover, preliminary data suggested that our new tool's effectiveness may vary strongly across subgroups. Therefore, we opted out of pooled analyses including all 3 subgroups. Instead, we will conduct 3 prespecified subgroup analyses and each will use a 5% type I error level.

Efficacy Analysis

The study will enroll up to 3500 participants (approximately 1715, 1190, and 595 enrollments to the low, intermediate, and high-risk groups) in each OPY version. Interim and final analyses efficacy analyses will be conducted every 3 months, separately for each surgery risk group, using an O'Brien-Fleming type error-spending function approach to account for the multiple interim and final analyses. Risk-group-specific group-sequential hypothesis tests will use a 1-sided 5% type I error level, to control the overall type I error for each of the 3 interventions at a 15% type I error level.

Futility Interim Analyses

Futility interim analysis will be conducted every 3 months separately in each risk group. The study will stop testing an OPY version in a subgroup if, at the interim analysis, the predicted probability of a positive study outcome (predicted power) in this subgroup drops below 15%.

Power Analysis

Based on our initial estimates of the 14-day opioid use rates (0.03, 0.07, and 0.16) for the SOC in each of the 3 subgroups and an odds-ratio treatment effect of 2.0 (opioid use rates 0.015, 0.037, and 0.087), the group-sequential design has 64%, 82%, and 85% power to detect positive treatment effects in the low, intermediate, and high-risk subgroups.

Study Risks

In this minimal-risk study, there is a very low risk to participants. This risk extends to providers involved in the study or family members of participants. Breach of confidentiality is unlikely but remains a possibility. Data will be maintained in a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant environment.

Ethical Considerations

This study protocol is submitted to the University of Minnesota IRB and given the initial determination of "Not human subjects research." All patients will be e-consented to the study before

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data collection. This will be verified by study staff before data collection and analysis. No data from patients outside the study group will be transmitted into the study database. The study obtained IRB approval on 31 August, 2023 (STUDY00019820). The trial was registered in ClinicalTrials.gov (NCT06124079).

Results

This study was originally started in August 2022 and is being supported by the Rapid Prospective Evaluation and Digital Technology Innovation programs at CLHSS. The implementation of this intervention has been fully resourced by MHFV. The structure of engagement, survey development, data collection, statistical analysis, and dissemination will be coordinated by the Rapid Prospective Evaluation Program and funded entirely. The pilot was launched in February 2023 and is still running. Preliminary data from the pilot collected in August 2023 is reported in the section Methods: Preliminary Data From the Pilot. The RCT is planned to start by the end of August 2023.

Discussion

Principal Results

In this paper, we present the protocol for the OPY study, a group-sequential pragmatic RCT design of patient-facing digital tools deployed using their existing chart personal health record platform. The purpose of this innovative tool is to effectively manage opioid use, weaning, and disposal among postoperative patients by directly interacting at patient levels leveraging behavioral economics principles. To our knowledge, this is one of the first-ever pragmatic clinical trials to study the impact of introducing behavioral economics techniques into a patient-facing, innovative digital technology on opioid management, leveraging the learning health system. The trial is set up as a hybrid implementation-effectiveness trial with strategies informed by behavioral economics theory.

The efficacy of artificial intelligence chatbots in promoting healthy lifestyles, smoking cessation, treatment or medication adherence, and reduction in substance misuse has been tested earlier; however, there were mixed results regarding feasibility, acceptability, and usability [17]. OPY is a novel solution to aid with weaning and disposal of opioids in opioid-naïve people and acts uniquely in a preventative manner. By using an OPY tool, equivalent to an archetype of a chatbot, we could integrate a natural language interface, delivering the pertinent information to the postoperative patients around opioid use at the relevant times and reporting graded alerts or flags to clinical staff to initiate a patient or provider communication if necessary. Earlier evidence has shown that patient characteristics (such as age and gender) play a pivotal role in determining the probability of filling an opioid prescription [3,18,19]. With the implementation of this patient-facing OPY tool, we could help postoperative, naïve patients who are at risk of addiction to more effectively manage these medicines.

By combining the OPY tool, a preliminary version of a chatbot, with behavioral economics, we can use social influence (social norms), precommitment, and testimonial-based “nudges” to encourage patients toward more responsible opioid usage. Future nudges may include social norms, loss aversion, salience effect, and IKEA effect to encourage patients [20]. In the future, we could include infographics showing harm from inappropriate opioid storage and disposal and create charts for patients on opioid use to reinforce patient decisions.

There is some evidence that the effect of behavioral economics nudges on human behavior is not guaranteed to have the desired effects. Introducing behavioral nudges in some instances, has induced the opposite behavior than desired [29-31]. For example, precommitment can unintentionally telegraph to the patient that the behavior has low urgency, decreasing their motivation to accomplish the task. Another well-established mechanism for influencing target behaviors is communicating social norms that support the intended behavior. Social norm nudges are generally accepted to operate by creating some amount of discomfort within the patient, by demonstrating that they are not doing what is typically done by others, to encourage the intended behavior [32]. Our study will help clarify if the behavioral economics techniques we have incorporated can inspire early weaning and disposal or not.

Limitations

A limitation of this study is that the app is currently only available in English, and we will only include patients who can read and write basic English. We are also excluding patients lacking the capacity to consent, as well as children, due to their inability to functionally and meaningfully interact with the app. We will only limit the enrollment to patients undergoing same-day surgery across 2 locations and not system-wide at this time. This limits the operational lift to execute this project and the number of staff needing new training on the OPY technology and care pathway. We do plan to expand to outpatient surgery at the hospital and then to inpatients. Further, in the testimonial version of OPY, the images or voices over the image are generic and the current technology does not have the capability of matching with the patient’s actual demographics.

Conclusions

In summary, by implementing OPY in opioid-naïve patients, we will be able to help prescribers remotely manage new opioid prescriptions. Given the significant limitation in physical proximity with the care team, we must empower patients with a practical tool to assist in weaning off and disposing of opioid medications that are available to them 24/7. Implementation of 3 versions of OPY, all designed to promote weaning from opioids and legal disposal in opioid-naïve patients, will produce generalizable evidence about the impact of behavioral economics on patient prescription behavior. If successful, OPY will advance the understanding and effectiveness of electronic health record–based strategies with patient interaction to improve the delivery of evidence-based care to patients at high risk for opioid addiction.

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Acknowledgments

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Authors' Contributions

The authors confirm contributions to this paper as follows: study conception and design were by SSD, RFR, MU, JSK, and GBM; data collection and analysis plan was done by SV, JSK, RFR, MSL, MWB, and MMP; draft paper preparation was performed by RFR, JAS, MSL, SSD, MMP, MWB, and AEO. All authors reviewed the results and approved the final version of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Ranking of surgery types according to their opiate use rates at 14 days. Surgeries are listed from lowest to highest rates of opiate use. Surgery types are additionally categorized by use rates into lower 60 percentile (low-risk opioid use group), 60-75 percentile (medium-risk opioid use group), and upper 24 percentile (high-risk opioid use group).

[XLSX File (Microsoft Excel File), 64 KB - resprot_v13i1e52882_app1.xlsx]

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Abbreviations

CLHSS: Center for Learning Health System Sciences
HIPAA: Health Insurance Portability and Accountability Act

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IRB: institutional review board
MHFV: M Health Fairview
OPY: Opioid Management for You
RCT: randomized controlled trial
SOC: standard of care

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Protocol

Development of a Multiplatform Tool for the Prevention of Prevalent Mental Health Pathologies in Adults: Protocol for a Randomized Control Trial

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Abstract

Background: The prevalence of depression and anxiety has increased in recent years, with many individuals having trouble accessing mental health support. Smartphones have become an integral part of modern life, with apps offering new ways to deliver evidence-based self-help strategies to cope with common mental health symptoms. However, most of them do not have empirical evidence of their overall effectiveness or the effectiveness of their components, which could pose a risk for users.

Objective: The aim of this study is to evaluate the effectiveness of the modules of evaluation, psychoeducation, and emotional regulation strategies in a multiplatform self-help mental health mobile app in the Maule region of Chile.

Methods: A sample of 196 adults will be selected, who will be randomly assigned to different components of the app for a fixed period to assess its ability to reduce symptomatology.

Results: The trial is not yet recruiting and is expected to end in October 2024. The first results are expected in April 2024.

Conclusions: This is the first study in Chile to develop and test the effectiveness of a mobile app to manage anxiety and depression symptoms in adults. The intervention proposed is based on evidence suggesting that the internet or remote intervention tools and self-management of prevalent symptomatology could be the future of mental health care systems in the digital era. If the effects of the intervention are positive, wide implementation in Chile and other Spanish-speaking countries could be possible in the future.

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KEYWORDS

adults; anxiety; depression; eHealth; mental health; mobile app; RCT

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Introduction

Background and Rationale

Mental health disorders are common in the general population. In Chile, depression and anxiety are the most frequently observed psychopathologies, with a prevalence of 5% for depression and 6.5% for any form of anxiety [1]. However, the population affected by depression or anxiety symptoms may be greater, with 49.2% of Chileans reporting some level of depression symptoms [2]. These prevalences have become a significant issue in public health settings, where waitlists in public mental health services in Chile are mostly stagnant [3], and in the past 2 years have become extensive due to the COVID-19 pandemic. Thus, it becomes necessary to find alternatives that allow providers to respond to this need for mental health access [4].

In this context, the use of remote self-guided psychological interventions, such as those found in mental health mobile apps, has gained popularity [5]. It has been reported that this remote modality improves access, reduces waiting times for appointments, saves time, and reduces the effect of attitudinal barriers in patients seeking psychological support [6]. Studies indicate a high effectiveness rate of web-based care, with smartphone-based psychological interventions reducing user anxiety [7] and depression [8,9]. Accordingly, there has been an increased number of mental health mobile apps available to users. However, many of them do not have sufficient theoretical support for their effectiveness. In 2015, a total of 447 apps related to cognitive behavioral therapy (CBT) were found available in any App Store [10]. Conversely, 9 studies regarding the use of smartphones in cognitive-behavioral interventions were found, of which only 2 had readily available apps in the market [10]. Moreover, 10% of those who say they use cognitive behavioral interventions as a theoretical basis were not evidence-based [11]. It has been suggested that, without empirical support, these apps can be potentially harmful to users [12].

Among the small portion of mobile apps that have empirical support for their tools, 3 specific components or modules have the highest rates of applicability and effectiveness for reducing depression and anxiety: assessment, education, and self-regulation digital tools [13]. The assessment component allows for the recognition of the current symptomatic state of the user, while the constant evaluation helps the monitoring and the development of awareness of the process of change in the symptomatology [14]. The psychoeducation process allows users to be informed about what they are experiencing. Although psychoeducation alone is an effective strategy for the improvement of some anxiety and depression symptoms [15,16], its effectiveness increases when it is accompanied by other strategies [17]. The final component, the use of self-regulation tools, demonstrates a series of brief, easy-to-use self-guided activities that attempt to regulate, express, or otherwise manage psychological distress, low mood, and symptoms of anxiety.

The presentation of these modules normally follows the theoretical framework of CBT. This treatment model can be easily adapted to non–face-to-face environments and has been repeatedly tested in web-based modalities [18,19]. Moreover, other approaches theoretically derived from CBT, such as behavioral activation therapy or mindfulness-based behavioral therapy, also exhibit evidence of their effectiveness in non–face-to-face settings [20]. The behavioral activation treatment for depression attempts to regulate depression symptoms through the programming of pleasurable activities [21], while mindfulness-based CBT focuses primarily on breathing techniques, relaxation, self-compassion, and mindfulness abilities [22], aimed at regulating anxiety states.

According to the literature, there are no mobile apps with scientific support to address depression and anxiety symptoms in the adult population in Chile. The regular and widespread use of such apps could help provide self-care tools to individuals who are reticent about therapy.

Aims

The main aim of this study is to develop a multiplatform self-help mental health mobile app for adults and to test the effectiveness of its assessment, psychoeducation, and emotional regulation strategy modules post intervention and at 1-month follow-up. We hypothesize that the combination of psychoeducation and any self-regulatory strategies will prove more effective than the evaluation and psychoeducation components alone in decreasing symptomatology.

Trial Design

This is a protocol for a double-blind, 4-armed randomized controlled trial (ClinicalTrials.gov NCT05997849) evaluating changes in primary and secondary outcomes (symptomatology and well-being variables) post intervention and at follow-up. The 4 arms will be group 1 (control): the participants will have access only to the monitoring and psychoeducation module for 30 days; group 2: participants will have access to the monitoring module, psychoeducation, and mindfulness strategies for 30 days; group 3: participants will have access to the monitoring module, psychoeducation, and behavioral activation strategies for 30 days; and group 4: participants will have access to the monitoring, psychoeducation, and cognitive strategies module for 30 days. Additionally, 1 focus group per condition will be carried out to qualitatively assess the user experience with the app and its overall usability.

Methods

Study Setting

Participants will be adults (18 years of age and older) in the Maule Region of Chile and mixed-sex. We expect to recruit 49 participants per arm, configuring 196 participants in total.

Eligibility Criteria

Adult Chilean citizens, 18 years of age or older, with access to a computer, tablet, or smartphone (Android or iOS) with internet, and no untreated mental health diagnosis, will be included in the study. The mental health diagnosis and current treatment will be assessed solely by the participant's self-report.

Individuals who self-report substance abuse problems or any current serious mental health disorder and participants reporting

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scores greater than 1 on question 9 (suicidal ideation) on the Patient Health Questionnaire–9 (PHQ-9) will be excluded from the study.

Ethical Considerations

This study and all associated documents were approved by the Scientific Ethics Committee of the University of Talca (14/2022). Informed consent will be obtained from all participants through web-based forms before the allocation process begins. The collected data are completely deidentified and stored in secure servers (see Data Management section). Participants will not receive any type of compensation for their participation in the study.

Recruitment and Informed Consent

For recruitment, invitations will be made through the social networks of the Center for Applied Psychology and the Faculty of Psychology of the University of Talca. In addition, the educational and health services of 4 districts in the region will be contacted to disseminate the multiplatform application Cuidandome to adults. The call for participation will include an explanatory video and an informed consent form, which will be available on and collected through the project website (under development). Participants will be recruited through convenience sampling and will be randomly assigned to 1 of the 4 groups by means of simple randomization (through the PHP: Hypertext Preprocessor rand() function).

Interventions

Description of Interventions

Cuidandome is a multiplatform self-help mental health app that does not constitute a psychological treatment. The mobile app will be available for iOS and Android operating systems, and it is composed of 3 modules: monitoring, psychoeducation, and strategies for people to learn to manage their emotional states and their depression or anxiety symptoms.

The modules of the app are given below.

Monitoring (M) Module

The aim of this assessment module is to acquire information on the symptoms and well-being of the participants in the process of using the app and their satisfaction with the strategies. This transversal component is composed of a weekly assessment and a brief daily mood assessment so that the person can monitor their own mood.

Psychoeducation (P) Module

The aim of this module is to provide information to the user about different aspects of mental health care, understanding depression and anxiety symptoms, and the fundamentals of the app and how to get the most out of it. Several studies have shown the relevance of psychoeducation in mental health care.

Regulation Strategies (RS) Module

This module is based on cognitive behavioral change techniques and strategies originating from the basic principles of CBT for the treatment of depression and generalized anxiety, behavioral activation therapy for depression, and mindfulness strategies for managing anxiety and depression. The module is organized into 3 types of strategies: cognitive (strategies to help modify cognitions that cause discomfort), behavioral activation (strategies focused on modifying behavior that causes discomfort), and mindfulness (strategies to help stay in the present moment and decrease activation of the sympathetic nervous system). Each of the strategies will be developed sequentially through 3 tasks: understanding, learning, and practicing; providing activities to understand why the strategy works and how it should be done; and finally, putting the strategy into practice. Figure 1 shows the overview of the dashboards.

Figure 1. Main dashboard (left) and regulation strategies: square breathing dashboard (right).

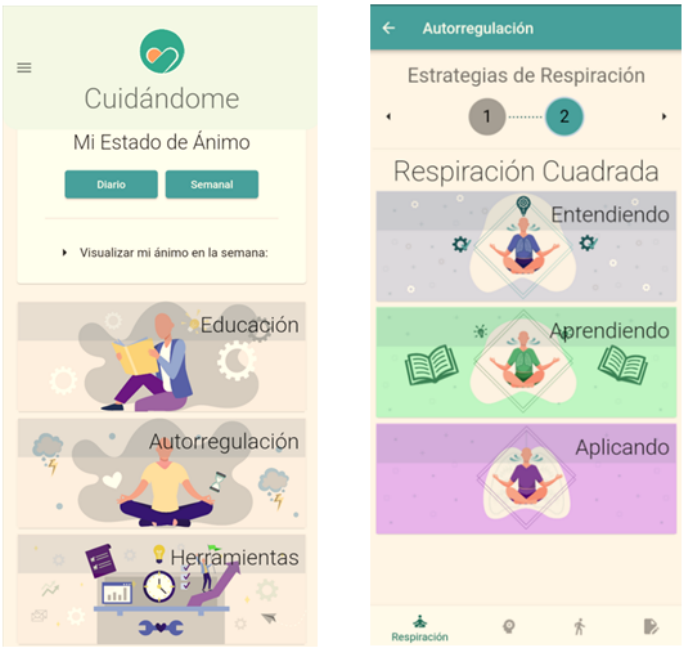

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Criteria for Discontinuing or Modifying Allocated Interventions

Participants in any group can leave the study at any time if they wish without any consequences; this means that their information and collected data will not be analyzed.

Strategies to Improve Adherence to Interventions

No group will be monitored regarding adherence, as the app is essentially self-guided. However, the app sends daily messages to participants to remind them to access the app and complete at least 1 activity.

Outcomes

Primary Outcomes

Anxiety symptom is 1 of the 2 primary outcomes, and it will be measured by the Generalized Anxiety Disorder–7 Scale (GAD-7). It consists of 7 items that the person assesses on a scale of 0-3 according to the frequency with which each symptom has disturbed them during the past 2 weeks [23]. It shows high reliability in Chilean samples (Cronbach α=0.86 [24]).

Depression symptoms will be measured by the PHQ-9 depression scale, which consists of 9 items that evaluate the presence of depression symptoms present in the past 2 weeks, with a response scale of 0=never, 1=some days, 2=more than half the days, and 3=almost every day. With a Cronbach α of 0.83, its reliability is high in Chilean samples [25]. Additionally, depression and anxiety symptoms in the past week will be assessed through the Patient Health Questionnaire–4 (PHQ-4) [26].

Primary and secondary outcomes will be assessed at 3 time points: preintervention (baseline), immediately post intervention (30 days post intervention), and 1-month follow-up in all groups.

Secondary Outcomes

Well-Being

Perceived psychological and overall well-being is measured by the Pemberton Happiness Index scale (PHI), a 21-item instrument evaluated in 2 subscales: psychological well-being (experienced 5 positive and 5 negative experiences) and subjective well-being (remembered). The scale is Likert-type, with scores per item from 0 to 10 [27].

Resilience

Perceived resilience is measured by the Brief Resilience Scale (BRS), a 6-item instrument on a Likert scale from 1 to 5. It has 3 inverted items, and the rating results from the average of the scores obtained [28].

Ruminative Thoughts

Rumination and ruminative thoughts are assessed by the Ruminative Response Scale (RRS, short version), consisting of 10 items that measure ruminant thoughts in 2 dimensions: reflection and restlessness. It has a high level of internal consistency (Cronbach α=0.85). Each item is scored on a 4-point Likert scale from 1 (almost never) to 4 (almost always) [29].

Emotional Regulation

Emotional regulation is assessed by the Emotional Regulation Questionnaire (ERQ), a 10-item questionnaire designed to measure respondents' tendency to regulate their emotions in 2 ways: (1) cognitive reappraisal (1, 3, 5, 7, 8, and 10) and (2) expressive suppression (2, 4, 6, and 9) [30].

Mindfulness Skills

Mindfulness skills are assessed with the Mindfulness Attention Awareness Scale (MAAS), an instrument composed of 14 items on a Likert scale from 1 to 6. The scores obtained are added, and the higher the score, the greater the ability to pay attention fully and consciously. The average scores of the nonclinical participants are 65 points out of a total of 84 [31].

Participant Timeline

See Table 1 for the participant timeline.

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Table 1. Participant timeline.

Time point	2023					2024								
	Enrollment			Allocation		Post allocation					Close-up			
	September	October	November	December	January	February	March	April	May	June	July	August	September	October
Enrollment														
Contact with health centers and prospects	✓	✓												
Eligibility screen		✓	✓	✓										
Allocation				✓	✓									
Informed consent					✓	✓								
Interventions														
Intervention all arms							✓							
Assessment														
Baseline variables						✓								
Outcome variables							✓	✓	✓					
Dissemination														
Analyses										✓	✓	✓		
Results presentation and publication													✓	✓

Sample Size

To achieve the aims of the study, we have considered 4 arms. To obtain a statistical power of 0.80, a minimum sample size of 36 participants is required for each of the 4 arms. Controlling for a dropout rate of 26%, as shown by the literature on behavioral experiments linked to mobile apps for symptoms related to mood and anxiety [32,33], a final sample size of 49 participants per group is required. The sample size approximation was made based on the literature on statistical power and sample sizes in clinical and social science research [34], while the estimate to reduce the effects of the percentage of abandonment in the experimental conditions was calculated based on Wang and Ji [33]. Thus, an estimate of 196 participants sufficiently obeys such parameters. In addition to the quantitative data collection, a qualitative collection of information will be carried out through focus groups. Regarding the number of focus groups, a total of 4 have been established, 1 for each study group. The size of the focus groups, following the recommendations in the literature [35], is estimated at a total of 32 participants (reaching an estimate of the saturation point), that is, 8 participants per focus group.

Recruitment

The strategies for achieving adequate participant enrollment to reach the target sample size will include contacting and presenting the study to municipality authorities, who are expected to help establish contact with public health authorities. Interested individuals can sign up to participate through the QR code available in pamphlets delivered to primary health clinics in the Maule area. Health staff in the selected public clinics will also encourage patients to participate in the study.

Assignment of Interventions: Allocation

Sequence Generation

Participants will be randomly assigned to any group with a 1:1 allocation through a website. The web system will generate randomization based on the rand() function of the PHP language. Through this function, a random number between 0 and 3 is generated and subsequently assigned to the participants upon recruitment.

Concealment Mechanism

After the randomization and allocation, participants will not receive information regarding the group they belong to. Instead, they will be instructed to access the app and complete the emotional regulation activities, regardless of the type. The participants will only have access to a version of the app that includes the strategies that correspond with their assigned group. Additionally, this information will not be disclosed to the assessment research team (outcome evaluators) to keep the participant allocation blind.

Allocation Implementation

Participants will be randomly assigned to any group with a 1:1 allocation through a website. The web system will generate randomization based on the rand() function of the PHP language. Through this function, a random number between 0 and 3 is generated and subsequently assigned to the participants upon recruitment. Depending on the random number assigned, a QR code will be sent to the participants, which will allow them to download a version of the app that contains the strategies pertinent to their study group.

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Assignment of Interventions: Blinding

Who Will Be Blinded?

This is a double-blinded trial, blinded to the participants and the research team. A data analyst will work with the final data set, where the group condition will be masked.

Procedure of Unblinding If Needed

Unblinding will not occur in this study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Self-report questionnaires assessing primary and secondary outcomes will be administered at baseline (immediately before intervention), post intervention, and follow-up. Primary outcomes will be assessed through the website and the app, and secondary outcomes will be measured only on the website.

Plans to Promote Participant Retention and Complete Follow-Up

Participants will receive extensive information about the study setup and requirements during the recruitment. This information will include and stress the importance of completion of the follow-up.

Data Management

After the participants have completed the web-based questionnaires both on the website and on the app, we will enter the confidential data into a secure platform without identifying information, as each participant will be assigned an encrypted ID number. Only the lead investigator, the research assistants in charge of partial data entry, and the statistician will have access to the complete database. All people with access to the data set will need to sign a confidential agreement to assure the commitment to not reveal identifying information.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

We will use descriptive statistics to assess balance across groups at baseline. The primary between-group analysis will be carried out on an intention-to-treat basis for GAD-7 and PHQ-9 scores. We will use a linear mixed model for repeated measures (MMRM) analyses to compare all the intervention and control groups regarding the change in all outcome measures from baseline to post intervention and at follow-up. All the models will be adjusted for sex, age, educational level, and concurrent psychological or psychiatric treatment. Analysis will be carried out with SPSS 26 (IBM Corp) and Stata 15.01 (StataCorp).

Statistical Methods for Additional Analyses

Secondary analyses will mainly explore the complex associations between all outcomes. To this end, correlation analyses will be carried out between symptomatic and other psychological variables. Multiple regression analyses and logistic regression analyses among all variables, particularly between mindfulness skills and anxiety symptoms, rumination and depression symptoms, and gender and symptomatology variables will be carried out. Lastly, group comparisons by gender and hours of app use will also be performed. The analysis will be carried out with SPSS 26.

Interim Analyses

There will not be interim analyses because the data will be analyzed at the end of the trial.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Primary outcomes will be assessed using an intention-to-treat analysis. Missing data will be reduced to a minimum by (1) rendering it impossible to advance on the app if a questionnaire is not completed in full, and (2) using the appropriate measures to encourage participants to fill out the follow-up questionnaires. Multiple imputations will be used to handle any missing data in the analyses.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

The data set produced during the study will be available upon reasonable request from the lead researcher NR.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

Daily support for the trial will be provided by the lead investigator, who supervises the trial. Additionally, the study coordinator helps with trial registration and will coordinate and oversee the study visits and reports while organizing data collection and assuring data quality. The data analyst will handle the database and carry out all primary and secondary analyses once all data are collected. Lastly, the app developer will design and implement all content of the app, ensuring the proper functioning of fundamental features such as the randomization of participants, completeness of data collected, automatic creation of the database, etc. The main study team will meet weekly during the duration of the study and monthly with a secondary group of expert collaborators. There is no trial steering committee, stakeholder, or public involvement group. The Ethical Scientific Committee of the Universidad de Talca will check the completeness of the investigation.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

A monitor from the Ethical Scientific Committee of the Universidad de Talca will check once a year the presence and completeness of the investigation. This committee is independent of the sponsor and has no competing interests. For further details, please contact cec@utalca.cl.

Adverse Event Reporting and Harms

The intervention does not cause any harm to the participants. However, if participants experience emotional distress upon using the app, they can contact the lead investigator at any time, who can provide them with options for referral to other public mental health services available. This procedure is explained in detail in the informed consent and initial training videos.

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Frequency and Plans for Auditing Trial Conduct

A monitor from the Ethical Scientific Committee will check annually the presence and completeness of the investigation files, such as informed consent, inclusion and exclusion criteria, and data collection and storage.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethical Committees)

All substantial amendments will be notified to the Ethics Committee of the Universidad de Talca. In case amendments concern or affect participants in any way, they will be informed about the changes. If needed, additional consent will be requested and registered. Additionally, web-based trial registries will be updated accordingly.

Dissemination Plans

All results of this research will be disclosed completely in international peer-reviewed journals. Executive summaries of the results will be given to government authorities and public entities acting as stakeholders. Lastly, preliminary relevant results will be presented at an international internet-based mental health seminar organized by the research team, to take place in mid-2024. The full protocol will be made publicly available on the original registry's website when the study is completed. Publications resulting from this protocol will consider the principal investigators and any participating analyst as authors.

Results

The trial is not yet recruiting and is expected to end in October 2024. The first results are expected in late April 2024.

Discussion

Overview

This study aims to develop a multiplatform self-help mental health mobile app for adults and test the effectiveness of its modules post intervention and at 1-month follow-up. This is the first study in Chile to develop and test the effectiveness of a mobile app to manage anxiety and depression symptoms in adults. The intervention proposed is based on evidence suggesting that the internet or remote intervention tools and self-management of prevalent symptomatology could be the future of mental health care systems in the digital era. If the effects of the intervention are positive, wide implementation in Chile and other Spanish-speaking countries could be possible in the future.

However, this project faces some challenges regarding feasibility and adoption of the intervention, where dropout rates could potentially hinder the results of the experimental procedure, even when accounted for [36]. Additionally, probable limitations are the exclusion of part of the clinical population from the study sample (ie, individuals not currently in treatment or at suicide risk) and the difficulty of controlling the effects of therapy on the primary outcomes in individuals simultaneously undergoing psychotherapy.

Conclusion

Implementing this research protocol, we expect to provide evidence for the effectiveness of a mental health mobile app in reducing depression and anxiety symptoms in Chilean adults. Moreover, we expect to provide evidence on the associations of these symptom variables and other risk or protective factors for mental health in adults in the context of digital platforms and interventions for health. The potential clinical and research implications derived from this study could help the mental health and well-being of the Chilean population significantly.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

NR conceived, designed, and applied for funding for the study. FB designed the mobile technology. NC contributed to the methodological design and reviewed the app content. IG contributed to the methodological design. PA created the media and content for the app and coordinated the project. AF, RS, SS, DN, and CS acted as theoretical and methodological advisors and reviewed app content. SC created content for the mobile app and wrote the protocol. Funder and committees did not have a role in study design, data management, or other areas.

Conflicts of Interest

None declared.

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Abbreviations

BRS: Brief Resilience Scale
CBT: cognitive behavioral therapy
ERQ: Emotional Regulation Questionnaire
GAD-7: Generalized Anxiety Disorder-7 scale
MAAS: Mindfulness attention awareness scale
MMRM: mixed model for repeated measures
PHI: Pemberton Happiness Index scale
PHQ-4: Patient Health Questionnaire-4
PHQ-9: Patient Health Questionnaire-9
RRS: Ruminative Response Scale

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Protocol

Promoting Return to Work After Vocational Rehabilitation Using a Work-Related Fitness App: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: Retraining programs in vocational rehabilitation are often characterized by a low level of physical activity, even when targeting jobs with primarily physical demands. They might therefore be accompanied by a decline in functional capacity if the lack of physical activity is not compensated by increased activity during leisure time. The implementation of a work-related exercise app might be a promising approach to promoting a return to work in vocational rehabilitation. We developed the "WORKout-app" which provides exercise plans based on a comparison of the physical demands of the retraining profession and the current functional capacity.

Objective: The aim of this study is to examine the effects of app-based exercise during vocational rehabilitation on perceived work ability (primary outcome), occupational self-efficacy, days of sick leave, and return to work (secondary outcomes).

Methods: We conducted a cluster-randomized controlled trial with 2 arms (intervention: WORKout-app vs control: treatment as usual) in 4 cohorts of 5 vocational rehabilitation centers in Germany. Participants are nested within retraining classes per vocational rehabilitation center and per cohort assigned to either the intervention condition or the control condition. The target sample size at the participant level is 598. Measurement time points include baseline, the end of rehabilitation, 3 months after the end of rehabilitation, and 6 months after the end of rehabilitation. Linear and generalized linear mixed-effects models are performed to test for treatment differences in outcomes.

Results: This study is funded by the German Federal Pension Insurance. The trial is registered with the German Clinical Trials Register (DRKS00030775) and approved by the Ethics Committee of the German Sport University Cologne (145/2022).

Conclusions: The findings of the study will inform researchers and practitioners about the effectiveness of an exercise app developed to counteract the effects of physical inactivity during vocational rehabilitation.

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KEYWORDS

digital health; eHealth; physical activity; profile comparison; vocational rehabilitation

Introduction

In 2020, more than 125,000 services for participation in working life were provided by the German Pension Insurance. Of these, 27% among women and 17% among men were educational services. A total of 6 months after finishing, nearly 1 in 2 individuals was either on long-term sick leave (12%), unemployed (22%), receiving further services to promote the participation of disabled people in working life (5%), or receiving a disability pension (4%) [1]. The demands of retraining programs, usually carried out over a period of 12-24 months, are often largely mental in nature, even when targeting jobs with primarily physical work demands. Overall, they are

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therefore characterized by a low level of physical activity. A lack of physical activity in turn is associated with increased morbidity [2], mortality [3], and low physical capacity [4,5]. Among college students, an association was found between inactivity and self-reported depression, self-harm, and suicidal attempts [6]. A negative perception of the health condition increases the likelihood of failure to return to work [7,8]. These negative effects are not limited to individuals in professions with high physical demands. Even among white-collar workers, higher physical activity is associated with better work ability [9].

Unfortunately, there is no evidence in vocational rehabilitation that a lack of physical activity is commonly compensated by increased activity during leisure time, for example, by using the exercise and sports programs that are offered within the facilities. In contrast, rehabilitants frequently report low levels of physical activity [10]. An increased risk can be assumed for the period of exam preparation in particular. Among college students, physical activity is found to decline significantly in the graduation year [11]. Furthermore, the overall negative impact of the COVID-19 pandemic on physical activity likely amplified this issue [12].

The implementation of work-related functional capacity training, as successfully established in work-related medical rehabilitation, might be a promising approach to promoting a successful return to work. Being a key component of these measures, the demonstrated positive effects of work-related medical rehabilitation on return to work, self-rated work ability [13], and days of sick leave [14] are in large part attributable to the work-related functional capacity training. However, an implementation within vocational rehabilitation would fail as personnel and spatial preconditions are not given. Exercise apps can be considered the opposite in this context. The low personnel and spatial requirements, as well as the possibility of access at any time, constitute their utility and attractiveness. A positive effect on physical activity levels has already been demonstrated meta-analytically for app-based fitness programs [15]. However, there are currently no exercise apps available that are focused on the critical physical demands of work.

The aim of this study is to examine whether providing an app-based exercise intervention focused on the critical physical demands of work can improve the conditions for successful reintegration among individuals in vocational rehabilitation. A cluster-randomized controlled trial is conducted to avoid contamination effects. We hypothesize that participants receiving the job-related exercise app (“WORKout-app”) will report better work ability at the end of rehabilitation as well as 3 and 6 months thereafter compared to participants in the control condition. A further beneficial effect is expected for secondary outcomes, which include occupational self-efficacy, days of sick leave within the follow-up period, and return to work. We hypothesize that these effects are primarily manifested among participants who use the app regularly during the period between the start of the intervention and the end of rehabilitation. Regular use is defined as 12 or more workouts completed in the app.

Methods

Study Design

A 9-month cluster-randomized controlled trial with 2 arms (intervention condition vs control condition) is conducted in 5 vocational rehabilitation centers in Germany. In those centers, referral diagnoses are dominated by diseases of the musculoskeletal system and connective tissue, as well as mental and behavioral disorders. The majority of participants are aged between 30 and 49 years and are mostly male candidates [7].

A flowchart of the study design is presented in Figure 1. Participants in the intervention condition receive an exercise app (“WORKout-app”). Access to the app is provided between 6 and 3 months before the regular end of rehabilitation and ends 6 months after the termination of rehabilitation. Participants in the control condition receive treatment as usual. Participants in both conditions are asked to answer a total of 4 questionnaires. The first questionnaire is distributed at baseline (T0), that is, approximately 3-6 months before the end of rehabilitation. Follow-up questionnaires are distributed at the end of rehabilitation (T1), 3 months post end of rehabilitation (T2), and 6 months post end of rehabilitation. The participating vocational rehabilitation centers (“Berufsförderungswerke”) are located in Berlin/Brandenburg, Cologne, Dortmund, Munich, and Oberhausen.

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Figure 1. Study design overview.

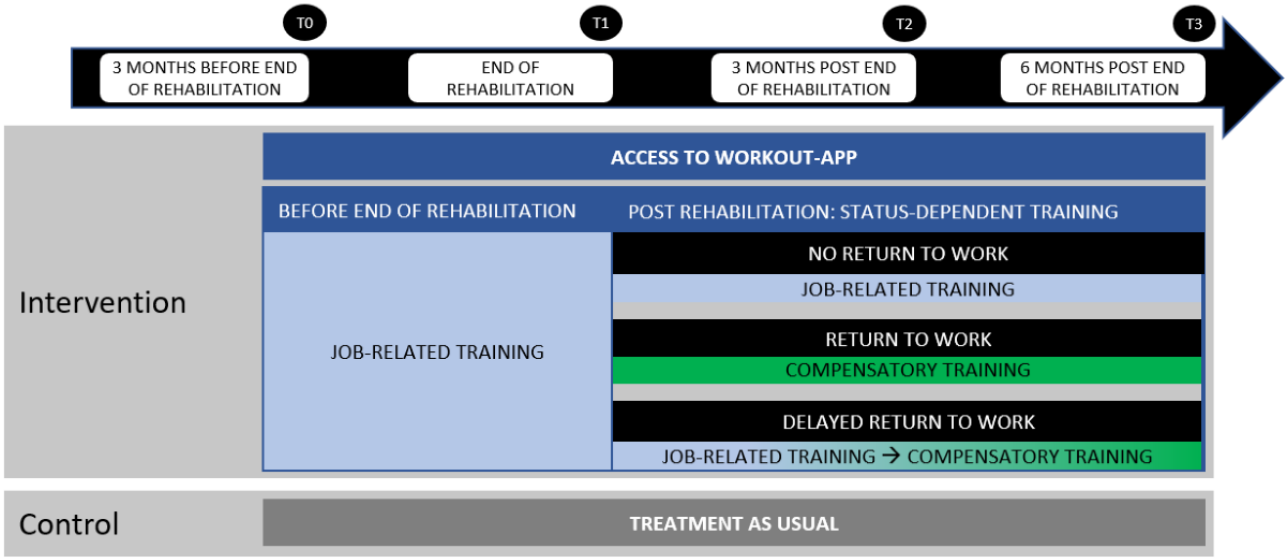

Study Sample and Recruitment

We intend to include about 598 participants in total, which provides 80% power (α=.05) to detect a small effect (d=0.25) assuming a design effect of 1.18 (intracluster correlation coefficient=0.02) and a medium cluster size of 10. The sample size was calculated with G*Power (Erdfelder, Faul, and Buchner) [16]. An exclusion criterion at the participant level is a limited ability to exercise safely due to health problems.

Randomization

Randomization is conducted at the cluster level. Vocational rehabilitation centers in Germany are divided into classes based on the retraining occupations pursued by the rehabilitants. These classes serve as clusters in this study. Whole classes at each vocational rehabilitation center are allocated in a 1:1 ratio to either the intervention or control condition.

Block randomization is carried out within 5 groups of professions that have a similar level of physical work demands. This means that within each group, the classes are randomly assigned to either the intervention or control condition. This procedure is repeated in 4 cohorts per center.

Measures

Primary Outcome

An overview of all constructs and their measurement points is provided in Multimedia Appendix 1. The primary outcome of this study is the perceived work ability, as assessed by the Work Ability Score [17]. This is an 11-point scale used to estimate the current work ability compared to the lifetime best (“Assume that your work ability at its best has a value of 10 points. How many points would you give your current work ability?”).

Secondary Outcomes

Secondary outcomes include occupational self-efficacy, days of sick leave within the last 3 months, and return to work (ie, the current employment status). Occupational self-efficacy is assessed using a 6-item scale (eg, “I face difficulties in my job calmly, because I can trust my abilities”), rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree) [18].

Characteristics and Covariates

Sociodemographic characteristics include age, gender, migration background, highest school degree, highest vocational qualification, relationship status, and income in the last regularly performed job. Moreover, the county of residence is assessed to determine the regional unemployment rate [19].

The employment biography is assessed by years of employment throughout the entire working life, periods of unemployment as well as periods of sick leave in the 2 years before the start of retraining, and the type of work demand (psychologically demanding, physically demanding, and physically and psychologically demanding) in the last regularly performed job. The retraining profession is divided into 4 categories (commercial and administrative professions, professions in technology and industry, social professions, and electrical and IT professions).

Rehabilitation-related characteristics include the retraining profession, the housing situation (resident of the boarding school vs commuter), and the sponsor of the retraining (German Pension Insurance, Federal Employment Agency, and others). Health-related characteristics include BMI, work ability in relation to physical and mental job demands [17], the type of condition underlying the retraining approval (predominantly physical factors, predominantly psychological factors, physical and psychological factors, and others), general health perception (1=poor to 5=excellent), 5 items of the “Functionality in everyday life” scale of the Indicators of the Rehabilitation Status-24 Questionnaire [20], and the 4-item Patient Health Questionnaire [21]. Furthermore, with regard to the last 3 months, participants are asked whether new health impairments have arisen that have limited their sporting activities.

Physical activity-related characteristics include sports preference (eg, sports disinterested and recreational athletes), sports activity per week, locomotion by bike or on foot in everyday life, as well as the adoption of new exercise or sport habits within the

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past 3 months. Furthermore, participants' motives for physical activity are assessed by a selection of items of the Attitude Toward Physical Activity Scales [22,23]. The following motives are assessed: social experience ("…want to be with others"), ascetic experience ("…want to overcome myself"), pursuit of vertigo ("…need excitement and thrill"), health and fitness ("…want to keep myself healthy and fit"), aesthetic experience ("…enjoy aesthetic movements"), and catharsis ("…want to relax"). The items are rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Variables concerning physical activity apps include app experience (eg, "How many physical activity apps have you downloaded so far?"), motives for app use (eg, "I expect a physical activity app to help me reduce or maintain my weight"), the perceived usefulness of physical activity apps ("I consider the use of a physical activity app helpful in achieving my health goals"), the perceived ease-of-use of physical activity apps ("I find it easy to learn how to use a physical activity app"), the social influence regarding the use of physical activity apps ("People whose opinions matter to me would approve of me using a physical activity app"), the behavioral intention to use a physical activity app ("I intend to use a physical activity app in the future"), and technology competence beliefs ("I find dealing with new technology difficult—I just cannot do it most of the time"; eg, [24] and [25]). The items are rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree). The usability of the WORKout-app is assessed by the System Usability Scale [26]. Furthermore, an overall grade for the WORKout-app is measured on a scale ranging from 1 (very bad) to 10 (very good).

Usage behavior is evaluated based on the number of workouts, exercise plans, and self-tests completed. Cut-off values are used to sort out activities in which participants did not actually perform the behavior in question but only clicked through the app (eg, a workout must last at least 10 minutes; otherwise, it does not count). Furthermore, at the completion of each workout, the perceived exertion ("How strenuous did you find this workout?") is surveyed on a 5-point scale ranging from 1 (too easy) to 5 (too difficult).

With the exception of app usage behavior, all measures are self-reported by respondents.

Data Analysis

Statistical analyses are performed using R (R Core Team). Descriptive statistics are used to describe the study sample in terms of sociodemographic, vocational, and health characteristics. The primary outcome (ie, work ability) is assessed by linear mixed-effects models. The effect is estimated as the coefficient of the study condition adjusted for the baseline measure, with the follow-up measure as the dependent variable. Random intercepts for the cluster are included. Age, general health perception, retraining profession, and termination of rehabilitation with graduation are included as additional covariates [8]. Participants are nested within retraining classes per vocational rehabilitation center and per cohort assigned to either the intervention condition or the control condition.

Secondary outcomes are assessed in a similar manner, using linear or generalized linear mixed-effects models as appropriate. In the analyses of return to work and days of sick leave, the baseline measures are not included as covariates because there are no baseline measures for these variables. Covariates in the analyses of return to work and days of sick leave include age, general health perception, retraining profession, termination of rehabilitation with graduation [8], regional unemployment rate [19], and periods of unemployment or periods of sick leave in the 2 years before the start of retraining. Covariates in the analysis of occupational self-efficacy include the baseline measure, age, general health perception, retraining profession, termination of rehabilitation with graduation, and the type of condition underlying the retraining approval.

Discontinuation of app use among intervention participants is analyzed by 2 generalized linear mixed-effects models. The first model includes sociodemographic predictors, and the second model additionally includes motives for app use, the system usability scale, and the overall grade.

Introductory Session and Telephone Support

A joint introductory session (approximately 1-2 hours) led by sports scientists or health psychologists is held as the official start of the intervention in each cluster of the intervention condition. The introductory session begins with an educational part that includes information about the dose-response relationship between physical activity and mortality, the beneficial effects of physical activity on physical and mental health, as well as the recommendations of the World Health Organization regarding physical activity. This educational part aims to raise participants' awareness and initiate reflection on their own physical activity and the health benefits that can be achieved through increased physical activity. The second and main part of the session is to become familiar with the app and learn how to use its various features in order to enhance participants' attitudes toward the app and increase their self-efficacy in using it. The session ends with an action planning section, which consists of setting a specific, measurable, attractive, realistic, and time-bound (SMART) goal for training with the app and forming implementation intentions for barriers to training with the app.

During the intervention period, participants are offered weekly opportunities to contact sports scientists within a 2-hour time slot to discuss difficulties and uncertainties in using and training with the app. Participants will be able to get in touch during these time slots by telephone as well as videotelephony on Microsoft Teams (Microsoft Corporation).

WORKout-App

The WORKout-app is a web app that was created with Blazor (ie, a Microsoft web application framework). Screenshots of the web app are presented in Figure 2. The app contains various exercises that are grouped into workouts, which are in turn integrated into training plans. The primary characteristic of the WORKout-app is that the training is specifically focused on those physical demands of work that could potentially limit return to work in the individual case. The underlying concept is a profile comparison, a comparison of physical abilities and

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the individual physical demands of the retraining profession. A total of seven characteristics are thereby distinguished: (1) sitting, (2) standing, (3) trunk movements and compulsory trunk postures, (4) demands regarding upper extremities, (5) demands regarding lower extremities including locomotion and endurance, (6) load handling, and (7) balance.

Figure 2. Screens of the WORKout-app used for the intervention.

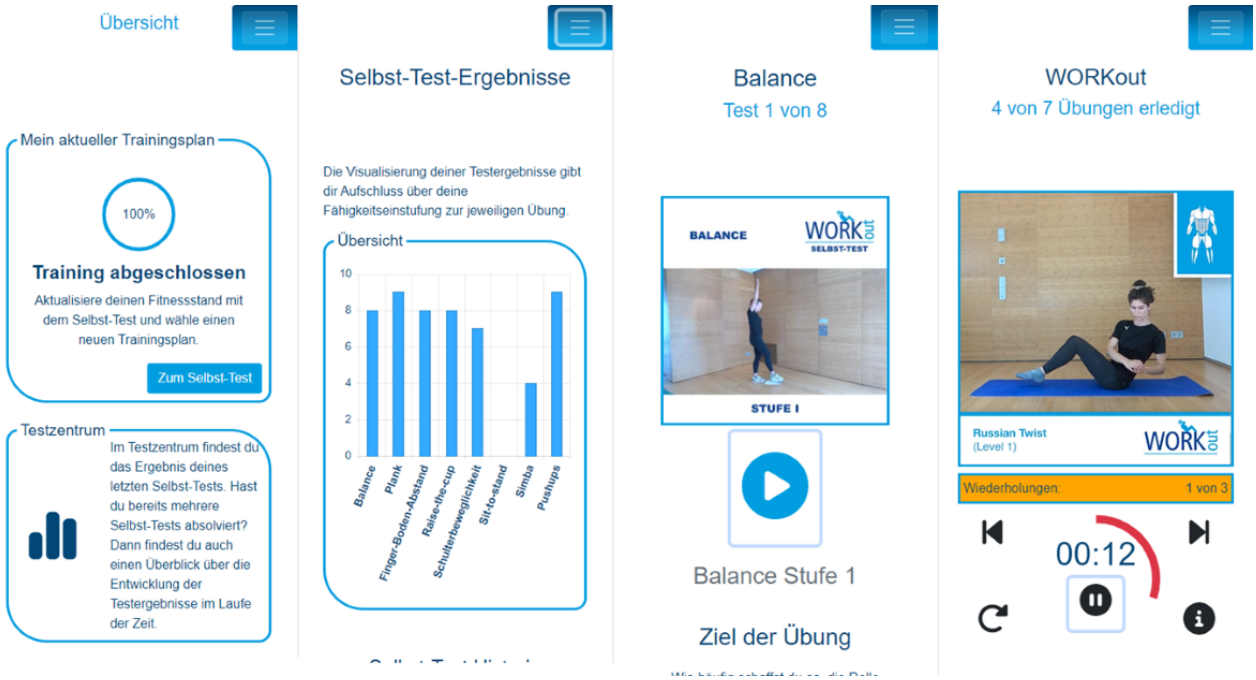

Classification of Physical Demands of Work

Before the development of the app, the physical demands of work were estimated for all retraining professions according to the 7 characteristics mentioned above. A 6-point scale based on the "Integration von Menschen mit Behinderung in die Arbeitswelt" method [27] was used for this purpose (1=very low demands and 6=demands that require at least above-average abilities).

The individual retraining profession must be specified when setting up the app, which allows for assigning an individual level of physical capacity that should be reached in order to be able to cope with the physical demands of work. Tax clerks, for example, only require a roughly average capacity for sitting, while the other 6 characteristics are weakly pronounced. In the case of in-house technicians, on the other hand, low demands are only given in terms of sitting.

Physical Capacity Examination

The app contains a self-test with 5 motor tests designed to estimate the ability to cope with the aforementioned physical demands of work. The motor tests include static strength endurance of the trunk (reference for work demands 1 to 3), static strength endurance of the upper extremities (4), physical endurance (5), weight handling (6), and balance (7). The convergent validity of the motor tests was evaluated in advance. The tests for weight handling and balance were strongly correlated with the results of a Functional Capacity Evaluation test [28]. In contrast, only moderate correlations were observed for the remaining motor tests. Given the limited convergent validity, self-ratings are therefore additionally included. A 6-point scale is used for the 5 self-ratings, which are weighted equally with the motor test results.

Work-Related Training

With regard to all exercises, workouts, and training plans, a distinction is made regarding the expected effect on coping with the physical demands of the work mentioned above. Furthermore, 3 levels of intensity (low, medium, and high) are distinguished. After the completion of the self-test, an automated profile comparison is performed. Depending on the result of this profile comparison, training plans are provided that address those abilities that are below the level required in the profession and that also correspond to the individual's physical capacity. This profile comparison is the key characteristic of the app, characterized by a demand-related orientation toward the individual physical requirements of work. For example, if the profile comparison indicates excessive demands in the characteristic “trunk movements and compulsory trunk postures” and the subject performed roughly average in the self-test, the training plan includes exercises such as back extensions in a lying position and good mornings. If an additional overload were to be expected with regard to the characteristic weight handling, exercises such as curl to press and rowing from a high plank position would also be included. In addition, the training is aimed at those abilities that are poorly manifested (a score of less than 3).

With the transition into work—directly after finishing vocational rehabilitation or in a further course—the workouts turn into compensatory training (Figure 1). The focus shifts to avoiding potential muscle imbalances resulting from the demands of the job. In podiatrists, for example, who are confronted with prolonged sitting as well as stress on the lower back muscles,

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compensatory training is focused on dynamic exercises of the lower extremities as well as the abdominal muscles.

The information on perceived exertion following completed workouts is used to identify inappropriate training intensities. If participants report twice in a row that a workout was too hard or too easy, they are advised to end the training plan prematurely, after which the training intensity is automatically adjusted.

Behavior Change Techniques Integrated in the App

The behavior change techniques (BCTs) are described according to the taxonomy of Michie et al [29]. Only the BCTs integrated in the app are described here; the introductory session is described in detail above. The app includes extensive instructions for all exercises in the workouts as well as for all tests of the self-test (BCTs: provide instruction on how to perform the behavior and model or demonstrate the behavior). The instructions are presented in the form of videos in which people perform the exercises or tests (Figure 2), and the execution is explained in detail through voice-over. In the videos of the tests, on-screen text is used sparingly to highlight important issues. In the videos of the exercises, the trained muscle groups are marked in a pictogram of the body. After each completed self-test, the performance in the individual tests is displayed in a graph (Figure 2; BCT: provide feedback on performance). The progress over time can be viewed in separate graphs per test that show the results of the last 5 self-tests. Moreover, a fun feature is implemented in which participants can earn virtual badges for completing workouts and self-tests, as well as for exercising for several weeks in a row (BCT: provide rewards contingent on successful behavior). The app also includes a knowledge section with 12 health- and physical activity-related videos, as well as daily tips and trivia with motivational or scientific content (BCT: provide information on the consequences of behavior in general).

Ethical Considerations

The trial is registered with the German Clinical Trials Register (DRKS00030775) and approved by the ethics committee of the German Sport University Cologne (145/2022). All participants need to provide written, informed consent to participate.

Results

This study is funded by the German Federal Pension Insurance. Patient recruitment takes place between March 2023 and July 2024. Considering the follow-up period of 6 months post end of rehabilitation, results are expected to be published in the first quarter of 2026.

Discussion

The study aims to evaluate the effectiveness of a work-related physical activity intervention through a web app to promote self-reported work ability in vocational rehabilitation. The rationale for the development of the intervention lies in the primarily mental demands of retraining, which favor a decrease in physical performance and thus in the chance of a successful return to work, unless the low demands of retraining are compensated by increased physical activity in leisure time.

User motivation is crucial in digital physical activity interventions [15]. In this study, the timing of receiving the intervention may be a barrier to continued participation. Access to the app is given between 3 and 6 months before the regular end of retraining. This is the period of exam preparation, which has been associated with a decline in physical activity among college students [11]. The focus on the physical demands of work does not necessarily have a positive effect on individual motivation, despite the physiological meaningfulness, if, for example, rehabilitants seek a distance from occupational issues in their leisure time due to a high stress load.

This study underlines the opportunity of adopting holistic approaches in rehabilitation, where physical activity is integrated with innovative digital interventions. Such an approach aligns with the evolving landscape of digitalization. The insights derived from this research are particularly relevant for practitioners and policy makers in the field of vocational rehabilitation. Moreover, the findings may be relevant for digital health interventions in related fields, such as regular vocational training, higher education, or use in aftercare.

Acknowledgments

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Data Availability

Data sharing is not applicable to this research protocol as no data sets were generated or analyzed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of constructs and corresponding measurement points.
[DOCX File , 25 KB - resprot_v13i1e50200_app1.docx]

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Abbreviations

BCT: behavior change technique
SMART: specific, measurable, attractive, realistic, and time-bound

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Protocol

Telemedicine-Based Risk Program to Prevent Falls Among Older Adults: Protocol for a Randomized Quality Improvement Trial

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Abstract

Background: The Center for Disease Control and Prevention's Stopping Elderly Accidents, Deaths, and Injuries (STEADI) initiative offers health care providers tools and resources to assist with fall risk screening and multifactorial fall risk assessment and interventions. Its effectiveness has never been evaluated in a randomized trial.

Objective: This study aims to describe the protocol for the STEADI Options Randomized Quality Improvement Trial (RQIT), which was designed to evaluate the impact on falls and all-cause health expenditures of a telemedicine-based form of STEADI implemented among older adults aged 65 years and older, within a primary care setting.

Methods: STEADI Options was a pragmatic RQIT implemented within a health system comparing a telemedicine version of the STEADI fall risk assessment to the standard of care (SOC). Before screening, we randomized all eligible patients in participating clinics into the STEADI arm or SOC arm based on their scheduled provider. All received the Stay Independent screener (SIS) to determine fall risk. Patients were considered at risk for falls if they scored 4 or more on the SIS or answered affirmatively to any 1 of the 3 key questions within the SIS. Patients screened at risk for falls and randomized to the STEADI arm were offered a registered nurse (RN)–led STEADI assessment through telemedicine; the RN provided assessment results and recommendations to the providers, who were advised to discuss fall-prevention strategies with their patients. Patients screened at risk for falls and randomized to the SOC arm were asked to participate in study data collection only. Data on recruitment, STEADI assessments, use of recommended prevention services, medications, and fall occurrences were collected using electronic health records and patient surveys. Using staff time diaries and administrative records, the study prospectively collected data on STEADI implementation costs and all-cause outpatient and inpatient charges incurred over the year following enrollment.

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Results: The study enrolled 720 patients (n=307, 42.6% STEADI arm; n=353, 49% SOC arm; and n=60, 8.3% discontinued arm) from September 2020 to December 2021. Follow-up data collection was completed in January 2023. As of February 2024, data analysis is complete, and results are expected to be published by the end of 2025.

Conclusions: The STEADI RQIT evaluates the impact of a telemedicine-based, STEADI-based fall risk assessment on falls and all-cause health expenditures and can provide information on the intervention's effectiveness and cost-effectiveness.

Trial Registration: ClinicalTrials.gov NCT05390736, http://clinicaltrials.gov/ct2/show/NCT05390736

International Registered Report Identifier (IRRID): RR1-10.2196/54395

(JMIR Res Protoc 2024;13:e54395) doi:10.2196/54395

KEYWORDS

aging; cost-effectiveness; elderly; fall risk screening; fall risk; falls; medication management; older adults; physical therapy; prevention; public health; telemedicine

Introduction

Falls were the leading cause of nonfatal injuries and the leading cause of unintentional injury-related deaths among older adults (aged ≥65 years) in the United States in 2020, resulting in approximately 37,000 deaths, 3 million emergency department visits, and 1 million hospitalizations [1]. Falls among older adults are expensive, resulting in US medical costs of US $50 billion in 2015 [2]. With the aging population, the burden of falls on health care systems will continue to rise if fall prevention efforts are not expanded in clinical settings [3]. In a systematic review, Gillespie et al [4] found that multifactorial interventions significantly reduced the rate of falling among community-dwelling older adults. In more recent years, digital and telehealth programs for older adults have been implemented to evaluate their effectiveness in improving overall health and fall prevention [5-7].

The Stopping Elderly Accidents, Deaths, and Injuries (STEADI) initiative, developed by the US Centers for Disease Control and Prevention (CDC), offers health care providers tools and resources to assist with fall risk screening and multifactorial fall risk assessment and interventions [8]. The core components of STEADI are to screen, assess, and intervene: (1) screen older adults for fall risk using the 3 key questions (Have you fallen in the past year? Do you feel unsteady when walking or standing? and Do you have a fear of falling?) or the CDC's Stay Independent screener (SIS) to identify patients at risk of falls [9]; (2) assess those who screened at risk for modifiable risk factors including gait and balance disturbances, medication risk, home hazards, orthostatic blood pressure, vision changes, concerns about feet and footwear, need for vitamin D supplementation, and comorbidities that increase fall risk [10]; and (3) intervene with evidence-based clinical and community strategies to reduce fall risk by addressing modifiable risk factors identified during the assessment [11,12]. STEADI has been implemented in full in primary care settings and in abbreviated versions in pharmacy and inpatient settings [9,13,14].

Evaluations of STEADI's impact on outcomes has been limited. In a previous implementation of abbreviated STEADI in community pharmacies, Blalock et al [13] conducted a randomized controlled trial that compared the fall reduction impact of a pharmacist-led abbreviated medication management assessment implemented in 65 community pharmacies in North Carolina and usual care. The intervention successfully identified medication risks but found no statistically significant differences between the intervention and usual care groups in subsequent prescribing or fall outcomes during the observation period.

A recent multicenter clinical fall prevention study, the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE), implemented a cluster-randomized trial of a nurse-administered multifactorial intervention in 86 primary care practices. The study compared the effects of a multifactorial intervention targeting modifiable risk factors to enhanced usual care [15]. They found that the intervention resulted in a significantly lower rate of a first self-reported fall injury compared to enhanced usual care, but no significant differences in rates of a first adjudicated serious fall injury, hospitalization, or death were found between the 2 groups [15]. Additional efforts are needed to evaluate the impact of clinical fall prevention on various health outcomes in clinical settings, including through telemedicine.

This paper describes the implementation protocol of the STEADI Options Randomized Quality Improvement Trial (RQIT) as implemented through telemedicine in primary care clinics to reduce falls among community-dwelling older adults. We designed the STEADI Options RQIT to estimate the effectiveness and cost-effectiveness of the STEADI assessment when pragmatically implemented through telemedicine.

Methods

Study Design

The STEADI Options RQIT was implemented in 5 primary care clinics between September 1, 2020, and December 31, 2021. The RQIT used a randomized design to compare patients at risk for falls who were assigned to receive a one-time telemedicine fall prevention assessment to a control group of patients at risk for falls who received the standard of care (SOC) of general disease state management. Due to the COVID-19 pandemic, screening was conducted through SMS text messaging–initiated surveys and phone calls, and we adapted the STEADI fall assessment to be implemented through phone- or video-supported telemedicine encounters conducted by a designated RN. Primary care providers were sent assessment information that they could access during the patient's scheduled visit. We collected patient-level data on recruitment,

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assessments, health service use, prescriptions, fall events, implementation costs, and all-cause outpatient and inpatient costs incurred over one year using administrative and electronic health records (EHRs) and patient surveys. The following sections describe the study's implementation and procedures (Figure 1).

The STEADI Options RQIT was a quality improvement initiative supported by health system leadership. Team members obtained verbal consent from study participants to share contact information with an evaluation partner outside the institution for the purpose of surveying (National Opinion Research Center [NORC] at the University of Chicago). Willingness to participate in the evaluation phase did not impact whether the patient received the STEADI evaluation as part of the quality improvement program.

Figure 1. Clinical workflow of the Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial: recruitment, screening, STEADI assessment, and intervention recommendation (Emory Health Services, 2020-2021). Those who screened at risk for falls but were assigned to the standard of care arm did not complete steps 5, 6, and 8. CRI: clinical research interviewers; RN: research nurses.

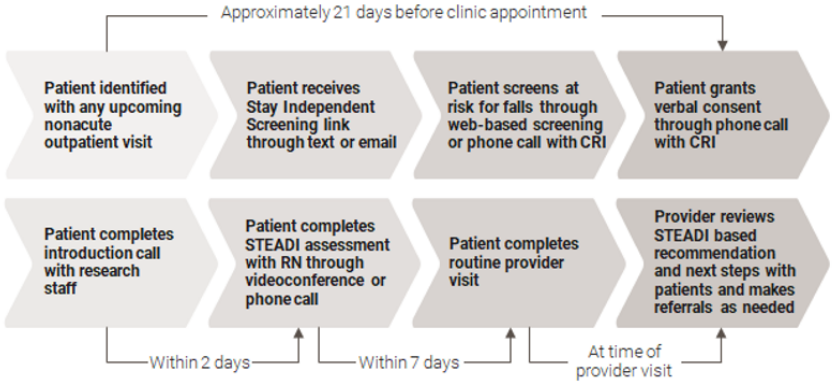

Ethical Considerations

The study protocol was reviewed and approved by the US Office of Management and Budget to assure its compliance with the Paperwork Reduction Act (Office of Management and Budget control number, 0920-1281). Evaluation aspects of the RQIT deemed to be human subjects research (patient surveys) were reviewed by the Emory Institutional Review Board to assure the safety and ethical treatment of human subjects (00111996), and the RQIT was registered (ClinicalTrials.gov NCT05390736).

Study Setting and Staffing

We selected 5 primary care clinics based on the willingness of clinic leadership to participate, clinic patient population diversity, and the number of older adults served. The research team included representatives from CDC's Division of Injury Prevention, NORC at the University of Chicago, and the Emory School of Medicine and Emory Healthcare primary care clinicians and staff. The Division of Injury Prevention was responsible for project oversight and fall prevention expertise, NORC designed the study protocol and data collection instruments and managed the project, and Emory was responsible for clinical implementation. Emory hired clinical research interviewers (CRIs), a clinical research coordinator, and RNs to conduct recruitment, coordination, and assessments. CRIs were responsible for screening patients for fall risk, recruiting and enrolling those at risk, scheduling STEADI assessments, and conducting preassessment coordination calls. The clinical research coordinator managed the workloads of the CRIs. The RN was responsible for conducting assessments, providing patient education, creating recommendations based on assessment information, and disseminating those recommendations to the patient's provider. Providers were responsible for determining whether to act on recommendations through the creation of clinical referrals to services or by managing medications. Emory implementation staff participated in monthly calls with the research team to discuss recruitment and implementation. Emory additionally convened monthly meetings between Emory implementation staff and primary care clinic staff to communicate the study design, intent, and responsibilities.

Information Technology Infrastructure

Before the implementation, Emory integrated the SIS into Tonic (Tonic Solutions), an electronic platform used to administer previsit screening. Through Tonic, patients were able to take the SIS on a web-based device before their appointment using a phone, tablet, or computer, with the results automatically populating the patients' EHR. The research team used REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, internally hosted web-based application, to capture STEADI assessment results. The RN sent conclusions and recommendations to the provider using the EHR messaging center.

Study Eligibility

Patients aged 65 years or older with a nonacute outpatient visit scheduled at participating primary care clinics were eligible for screening. Patients completed the SIS, and those with an SIS score of 4 or higher or those who answered "Yes" to any of the statements used as proxy to the 3 key questions within the SIS were eligible for enrollment (Textbox 1) [9]. Patients needed to be cognitively able to participate in the assessment, be able to converse in English, and have access to an able-bodied person to help with or respond to an emergency during the STEADI gait and balance assessments conducted by telemedicine (Textbox 1). Patients without valid phone numbers and those who opted out of receiving health system text messaging were excluded.

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Textbox 1. Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options trial patient eligibility criteria, Emory Health Services, 2020-2021.

Patients aged 65 years or older with a qualifying (ie, nonacute) visit scheduled at 1 of the 5 designated Emory clinic implementation sites and:

- Identified as high risk for falls through the Stay Independent screener by scoring 4 or more or answering affirmatively to any of the following statements in the Stay Independent screener as proxy to the 3 key questions:
  - Sometimes I feel unsteady when I am walking.
  - I am worried about falling.
  - I have fallen in the past year.
- Able to participate in the STEADI assessments:
  - Cognitively able to answer screening questions and participate in assessment.
  - English-speaking.
  - Have a computer, tablet, phone with internet and a webcam, or telephone.
  - Have an able-bodied helper who can be available to help or called for help during the STEADI gait and balance assessment (in case of unsteadiness or a fall).

Randomization

Providers were randomized each week 1:1 to either the STEADI or SOC arms based on a dice roll, and their scheduled patients were assigned to study arms based on the provider's assignment. Providers were rerandomized each week; however, patient assignment remained the same even if they rescheduled an appointment to another week. During 3 weeks in the summer of 2021 when the RN was unavailable, all providers and their patients were assigned to the SOC arm. Over the subsequent 6 weeks, providers and their patients were assigned to the STEADI arm on a 2:1 basis to restore assignment balance, after which the study returned to 1:1 assignment. A total of 2 additional study arms with modified STEADI assessments were discontinued early in the study due to low overall enrollment.

Screening, Recruitment, and Enrollment

Before their scheduled primary care visit, all eligible patients received a web-based or text link to a web-based SIS to complete. CRIs attempted to contact patients who had not completed the SIS on the web up to 3 times and completed the screener with them by phone if they were reached. Patients who screened at risk through the web-based SIS or through CRI contact and were randomized to the STEADI arm depending on the provider they were seeing were asked if they had (1) a computer, tablet, or phone with a camera and internet—if not, if they could participate by phone; (2) a clear hallway and corner in their home with space to assess gait or balance; and (3) someone nearby they could call upon for help if needed during the assessment. Those patients who answered yes to all 3 questions were then asked to provide informed consent to participate in the study. Patients who consented were asked if they had a blood pressure cuff at home (if not, the CRI ordered a cuff to be sent to their address), scheduled for a preassessment technology and home set-up call, and scheduled for a STEADI assessment before the primary care visit. Patients received an email with study information and instructions outlining the assessment process. Patients who were reached but did not consent to study inclusion were offered and provided STEADI assessments, although their data were not transmitted to the analytic team and were not included in analyses. Patients who were not reached were not included in analyses.

Preassessment Technology and Home Set-Up Call

A total of 2 days before the STEADI assessment, CRIs called each patient and provided setup instructions based on a script. CRIs confirmed the patient had a stable internet connection and was able to start the videoconferencing software (Zoom; Zoom Video Communications). They asked the patient to use tape to mark 5 feet of space from their video call device for the visual acuity test and to mark a 10-foot path for the Timed Up and Go (TUG) physical therapy assessment. CRIs also had patients choose a safe corner of their homes for the modified 4-Stage Balance physical therapy assessment and ensured that the patient had an appropriate chair and wall space to set the chair against for the 30-Second Chair Stand physical therapy assessment. CRIs presented demonstration videos of STEADI's 3 physical therapy assessments and helped patients adjust camera angles. Those patients scheduled for phone assessments were reminded of the scheduled assessment visit and given information regarding what to expect.

STEADI Assessments

Overview

During the subsequent assessment call, the RN conducted 6 standardized assessments to identify the patient's risk factors for falls. The protocol prioritized video calls but allowed for phone assessments for those unable or unwilling to participate in video assessments. Summaries of each assessment component, possible component findings, intended recommendations and interventions, and adaptations for phone assessments are described below and in table form (Multimedia Appendix 1).

Comorbidity Review

Before the assessment, the RN reviewed the patient's EHR problem list for diagnoses of 6 comorbidities (Multimedia Appendix 2) associated with fall risk: cognition problems, Parkinson disease, cardiac arrhythmia, depression, or urinary incontinence [16,17]. Comorbidities were shared with providers in the RN's recommendation statement.

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Medication Review

Before the assessment, the RN reviewed the patient's EHR medication list for any prescriptions from 10 classes of medications known to increase fall risk based on the Beers criteria (Multimedia Appendix 3) [18]. The RN additionally checked for polypharmacy, most commonly defined as prescriptions for 5 or more medications [19]. During the assessment, the RN confirmed with the patient the accuracy of the prescriptions listed in the EHR. The RN reported medication-related fall risk in her or his report for the provider and provided medication management educational materials to the patient (Multimedia Appendix 4). The RN also shared a recommendation to assess and adjust medications considered to increase risk of falls with providers.

Falls History

The RN asked how many times the patient had fallen in the past 12 months. If the patient reported a fall within the past 12 months, the RN asked if the patient sought medical attention for any fall or experienced loss of consciousness or broken or fractured bone or bones resulting from a fall. Fall history information was added to the provider report to increase the salience of fall prevention information.

Assessment of Feet or Footwear and Diabetes Assessment

The RN observed (through video) or asked about the patient's current footwear, asked about foot pain or loss of sensation, and when applicable noted a diabetes diagnosis. Patient reports of foot pain, loss of sensation, or diabetes resulted in a RN note to the provider to examine the patient's feet and the potential need for a referral to podiatry. The RN also reviewed a safe footwear handout (Multimedia Appendix 4) with all patients and emailed it to patients following the call.

Assessment of Visual Acuity

The RN projected the Banner eye chart on Zoom for the patient to read with their contact lenses or eyeglasses from five feet away (the distance was marked during the technology set up call) for both eyes together and each eye individually [20]. Phone patients were asked to self-report any vision problems. If the video screening or self-report indicated vision problems, the RN noted the result and recommended an eye health referral.

Gait and Balance

For video patients, the RN conducted the 30-Second Chair Stand test, the TUG, and the first three stages of CDC's 4-Stage Balance Test [21-23]. During the 30-Second Chair Stand test, the RN counted the number of times in 30 seconds the patient rose to a full standing position from sitting in a chair without using their hands. For the TUG test, the RN timed how long it took a patient to stand up from their chair, walk 10 feet, turn around, walk back to their chair, and sit down. During the balance test, the RN observed the patient in 3 progressively difficult standing positions: (1) feet side-by-side, (2) one foot touching the big toe of the other foot, and (3) one foot in front of the other, heel touching toe. Patients assessed by phone without video were asked 10 questions (Multimedia Appendix 1) that corresponded with the physical domains tested by the 30 Second Chair Test, TUG, and the first three stages of 4-Stage Balance Test.

If a patient failed any of the mobility tests, exhibited signs of unstable gait, or reported difficulties, the RN discontinued gait and balance assessments and recommended physical therapy referral through the provider messaging center. With the increased popularity of fitness programs for older adults [24], the RN recommended a web-based tai chi for arthritis program (Multimedia Appendix 4) for patients that passed all 3 tests, as all patients were still considered to be at risk for falls based on the SIS [25].

Orthostatic Hypotension

The RNs evaluated observed changes in systolic blood pressure by measuring sit-to-standing blood pressure. Sit-to-standing was chosen over a supine-to-standing test to increase feasibility for in-home assessment [26]. The patient measured their blood pressure using their own cuff or one provided by the study and sat for at least 2 minutes before standing. Patients experiencing a systolic blood pressure drop of more than 15 mm Hg when standing from their chair were given STEADI-based educational materials on managing orthostatic hypotension (Multimedia Appendix 4), and the RN reported the finding to the provider for management [27]. The RN also asked the patient about dizziness and relayed any reports of dizziness to the provider.

Home Safety Risks

The RN reviewed the CDC brochure *Check for Safety: A Home Fall Prevention Checklist for Older Adults* (Multimedia Appendix 4) with each patient [28]. *Check for Safety* asks 17 questions about the home's floors, stairs and steps, kitchen, bathrooms, and bedrooms and suggests ideas for removing or reducing fall hazards. The RN communicated home safety risks and a recommendation for occupational therapy to the provider for indicated patients.

Vitamin D Deficiency

Vitamin D deficiency is common and often underdiagnosed among older adults, although recommendations on supplementation are mixed [29]. The RN asked the patient if they usually take a vitamin D supplement with their other medications. If the patient did not take a vitamin D supplement, the RN recommended the provider check vitamin D levels and consider supplementation if vitamin D levels were less than 20 ng/ml.

RN Recommendations and Provider Action

The RN reviewed health education materials with the patient and sent these materials in an email follow up. RNs compiled assessment results, the educational materials presented to the patient, and their recommendations for referrals and care management and entered them into the patient's EHR and sent assessment results and recommendations to the provider using the EHR messaging center. Providers in each participating clinic were informed about the study protocol, communication methods, and actions they could take to act on information contained in the RN report. Provider actions included ordering patient referrals to physical therapy, optometry, podiatry, the neurovestibular clinic (ie, dizzy clinic), and occupational

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therapy; reviewing and changing patient medications when indicated; and testing patients for vitamin D levels. Providers acted on RN recommendations at their clinical discretion (Multimedia Appendix 5). For example, at the patient's upcoming primary care visit, providers would evaluate whether the medications identified by the RN should be adjusted or if a referral to Emory's Dizziness and Balance Center and providing the Epley maneuver home exercise handout was warranted [30].

Data Collection

To evaluate the intervention, we collected screening and assessment records, self-reported patient survey data, EHR health records, administrative medical cost information, implementation cost information through cost diaries, and qualitative interview data. Screening and assessment information was collected using a REDCap template. This included tracking compliance for the STEADI arm by recording whether each patient's planned STEADI assessment occurred. Self-reported surveys were administered in 4 waves through web and phone follow up. We administered a baseline survey within 1 month of enrollment, and 3 follow-up surveys were administered at 4, 8, and 12 months after enrollment. The baseline survey collected patient information on fall perceptions, fall history, health status, and self-reported service and prescription use. Follow-up surveys collected information on fall events and on patient adherence to recommended treatments and STEADI-related service use (eg, physical therapy and occupational therapy). Survey respondents initially received a token of appreciation of US $3 in US postage stamps after completing each wave of the survey. After 13 months of implementation, we added a US $2 cash pre-incentive and a study-branded glasses cleaning cloth to increase response rates.

We extracted EHR and cost information from Emory records for each enrolled patient for the period of the participant's enrollment date through 365 days of follow up. We also collected retrospective EHR and cost data for the 365 days before enrollment. We used time diaries completed by the CRI and RN to estimate implementation costs. We collected qualitative data from 45-minute phone interviews with the project RN and CRI and a sample of providers drawn from the Emory clinics implementing the study. All interviews were recorded and transcribed before being uploaded and coded in NVivo (Lumivero). A written summary of findings to contextualize quantitative data was developed.

Evaluation

We will analyze process outcomes, short- and long-term outcomes, costs, and cost-effectiveness of the implementation (Multimedia Appendix 6). Process analyses will evaluate the extent to which assessments were conducted through phone or Zoom calls, evaluated intended risk factors, and identified risks among participants who were assessed. Qualitative interviews with providers will be thematically analyzed to provide details on whether the intervention was implemented as intended and provide additional information on intervention feasibility, communication between implementation staff, perceived efficacy, and patient engagement.

Using an intent-to-treat approach, we will evaluate sample balance and assess short- and long-term outcomes comparing the STEADI and SOC arms. We will use survey and EHR data to evaluate differences between the arms in the short-term outcomes of (1) STEADI-indicated service use (eg, physical therapy and occupational therapy) and (2) prescriptions for medications that increase fall risks. For the long-term outcomes of (1) medically treated and self-reported falls and (2) all-cause health care costs from the Emory Healthcare system, we will use EHR data and administrative cost data. We will use the *International Classification Definition, 10th Revision, Clinical Modification* (ICD-10-CM) codes (Multimedia Appendix 2) and chart text notes to identify medically treated falls at Emory. Preliminary analyses indicate that ICD-10-CM codes without text note review are insufficient to differentiate individual fall episodes or determine fall severity. Therefore, we will also use self-report of falling with treatment at Emory to guide additional text note reviews for fall events that may not have been coded in the EHR. Falls will be coded as EHR-confirmed, self-reported medically treated falls outside the Emory system (EHR not confirmed), and self-reported and not medically treated to support analyses. We will additionally evaluate the impact of STEADI using a per protocol approach using a 2-stage residual inclusion approach.

For cost and cost-effectiveness, using time diaries and programmatic records, we will estimate the total implementation cost of the intervention per person. Cost will be assessed both based on an intent-to-treat perspective per person and based on the per-protocol cost of implementation per person associated with full compliance with the study protocol. Using estimates of the implementation costs per person assessed and the intervention effect (if any) on falls and all-cause health expenditures, we will estimate the incremental cost-effectiveness of STEADI from the health care perspective. This will be compared to the SOC over one year using an incremental net benefit framework anchored to the willingness to pay to prevent 1 fall.

Sample Size Estimation

We estimated a sample size based on the sample size required to detect a difference in the relative risk (RR) of falling at least once during the year between the STEADI arm and SOC arm. We assumed an absolute risk of any fall in the control group of 0.5 and a design effect of 1.05. We assumed a 50% risk of falling based on the expected performance of a screening tool to detect fall risk [31] and assumed a relatively small design effect under the assumption that individuals assessed were largely independent of each other in behavior given the telemedicine implementation. The results indicated that a sample of 500 in each arm would have 80% power of detecting an RR of 0.82, a sample of 350 would have 80% power of detecting an RR of 0.78, and a sample of 250 would have 80% power of detecting an RR of 0.75. Based on this, we sought to recruit at least 250 people in each arm with a recruitment goal of 500 per arm.

Statistical Procedures

We will impute missing values in the survey data using multiple imputations by chained equations. Imputation will be conducted

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using logistic models for categorical variables and predictive mean matching for continuous and count variables. Analyses using imputed data will use methods that appropriately estimate standard errors for multiply imputed data. Quantitative analyses will include bivariate and multivariable logistic, Poisson, and linear regression models estimating the intent-to-treat effect of the STEADI initiative on fall outcomes. We will use prespecified multivariable statistical models to control for unbalanced covariates and reduce residual variance. Per-protocol estimates of the effect of STEADI on outcomes will be estimated using treatment assignment as an instrument for the STEADI risk screening and assessment. Finally, 2-part models [32] will be used to estimate health expenditures.

Results

From September 1, 2020, to December 31, 2021, the study enrolled 720 patients, of whom 307 (42.6%) were assigned to the STEADI arm, 353 (49%) were assigned to the SOC arm, and 60 (8.3%) were assigned to arms that were discontinued. Process and implementation cost data were collected. Follow-up data collection was completed in January 2023. As of February 2024, data analysis is complete, and results are expected to be published in the end of 2025.

Discussion

Overview

The primary purpose of the CDC's STEADI Options RQIT was to evaluate the impact of a telemedicine-based form of the STEADI fall risk screening and assessment on falls and all-cause health expenditures among older adults when implemented within a primary care setting. We hypothesize that intervention patients will experience fewer fall-related outcomes compared to the control group; however, this relationship may be challenging to detect. For example, the STRIDE study found that a multifactorial intervention was associated with an 8% reduction in the rate of a first adjudicated serious fall compared to an enhanced usual care, but this result was not statistically significant [33]. The STRIDE study considered fall injuries but not falls without injuries in their outcomes and required one source of independent adjudication to determine the primary outcome.

This study includes patient self-reports of falls that did not require medical attention and falls that resulted in medical attention obtained outside the Emory health care system. Sustaining a serious injury from a fall requiring medical care or serious injury requiring hospitalization or prolonged care is likely dependent on individual health and functional characteristics. Therefore, detecting differences in all falls, including those that did not require medical intervention, is important in understanding the potential impact of a fall prevention intervention. Further, our survey captures falls that required medical attention but were treated outside the Emory Healthcare System because patients may turn to alternative settings such as urgent care centers to treat injuries.

This study collects detailed data on the STEADI risk screening and assessment process, allowing us to measure implementation fidelity. We are also collecting data on short-term outcomes of service use and prescriptions for medications that increase fall risk. Having this level of detail will allow us to evaluate whether the intervention translated into patient use of preventive health services with the potential to prevent falls, even if no difference in falls is detected. Additionally, we collected time diary data on STEADI implementation to estimate the costs of replicating the intervention and the cost-effectiveness of the intervention.

Limitations

Several factors limit this study. First, the COVID-19 pandemic required us to adapt STEADI from primary care, in-person risk screening, and assessment to telemedicine. As initially conceptualized, it was intended that all participants assigned to the intervention group would receive in-home video assessments through the Zoom platform. However, not all patients were able or willing to conduct assessments over video, so we adjusted the protocol to allow for some participants to be assessed by phone. We hypothesize that phone evaluations are less effective than video assessments because they replaced visual assessments of gait and balance, footwear, and vision problems with patient self-reported values likely underestimating risk. Ideally, the study design would have assigned patients to phone or Zoom assessments to compare outcomes by assessment type. However, the randomization of participants to phone or video calls was infeasible.

Second, conditions of the COVID-19 pandemic may have impacted the intervention's effectiveness if patients avoided encounters with the health care system for social distancing reasons. Avoiding health care encounters would reduce use of fall preventive services and might result in a lower number of medically treated falls if patients deferred medical care for falls they would have sought care for in the absence of COVID-19. This limitation is likely to bias our results toward the null hypothesis of no intervention effect.

Third, the instance of the Emory EHR deployed at the time of the study did not track referrals. Therefore, if patients did not access services indicated by the assessment, we are unable to determine if this was due to a lack of provider referrals or low patient adherence. Further, a change in Emory's EHR vendor resulted in a loss of approximately 6 weeks of follow-up data from 80 enrolled patients, a limitation we are adjusting for in statistical models. Fourth, not all patients completed each wave of the patient survey due to survey nonresponse. We will attempt to mitigate this limitation by using poststratification weights or imputation methods. Fifth, preliminary analyses have indicated that fall-related diagnosis codes in the EHR by themselves are limited in their ability to detect medically treated falls and differentiate unique fall events. We will attempt to mitigate this limitation using chart reviews but will likely miss some medically treated falls, biasing results toward the null. Sixth, because providers were randomized into STEADI and SOC arms by week, possible contamination in favor of fall-related interventions may have been introduced during the weeks providers were assigned to SOC, a limitation which would also bias results toward the null.

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Conclusion

Many older adult falls are preventable. The CDC's STEADI initiative [10] offers tools and resources for health care providers to conduct clinical fall prevention efforts with their older patients. We designed this study to capture detailed information on the implementation, short-term outcomes, and long-term outcomes of STEADI fall risk assessment and screening when implemented through telemedicine through a pragmatic design in collaboration with a primary care setting. The main advantage of this study is the collection of self-reported fall outcomes and health service use information from the entire sample of participants. This study can provide evidence to support future implementations and adaptations of multifactorial fall prevention interventions such as STEADI.

Acknowledgments

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Conflicts of Interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors declare no conflicts of interest in this work.

Multimedia Appendix 1
Protocol for assessment of Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial, Emory Health Services, 2020-2021.
[DOCX File , 21 KB - resprot_v13i1e54395_app1.docx]

Multimedia Appendix 2
International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes indicating potential fall occurrences and comorbidities.
[DOCX File , 14 KB - resprot_v13i1e54395_app2.docx]

Multimedia Appendix 3
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial electronic record medication flag list for medication management assessment component.
[DOCX File , 17 KB - resprot_v13i1e54395_app3.docx]

Multimedia Appendix 4
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial educational materials distributed and reviewed to patients during assessment.
[DOCX File , 16 KB - resprot_v13i1e54395_app4.docx]

Multimedia Appendix 5
Collaboration between clinical research nurse (RN) and provider in the Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial, Emory Health Services, 2020-2021.
[DOCX File , 21 KB - resprot_v13i1e54395_app5.docx]

Multimedia Appendix 6
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial evaluation design, Emory Health Services, 2020-2021.
[DOCX File , 16 KB - resprot_v13i1e54395_app6.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CRI: clinical research interviewer
EHR: electronic health record
ICD-10-CM: International Classification Definition, 10th Revision, Clinical Modification
NORC: National Opinion Research Center
REDCap: Research Electronic Data Capture
RN: registered nurse
RQIT: Randomized Quality Improvement Trial
RR: relative risk
SIS: Stay Independent screener
SOC: standard of care
STEADI: Stopping Elderly Accidents, Deaths, and Injuries
STRIDE: Strategies to Reduce Injuries and Develop Confidence in Elders
TUG: Timed Up and Go

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Protocol

A Digital Platform (Telepalliation) for Patients in Palliative Care and Their Relatives: Protocol for a Multimethod Randomized Controlled Trial

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Abstract

Background: The World Health Organization defines end-of-life palliative care as “prevention and relief of suffering, by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.” Over 20 million people worldwide are in need of palliative care. In Denmark, palliative care is given at a general and a specialist level. The general level comprises health care professionals (HCPs) who do not perform palliative care full-time. The specialist level comprises specialized palliative care (SPC), where HCPs perform palliative care full-time. In total, 20%-30% of patients who need palliative care are referred to SPC. Challenges with SPC include a short time span from referral to end of life, patients who are very ill and may therefore find it hard to travel to an outpatient clinic, and the SPC unit having a relatively small staff. The need for SPC is expected to rise, as the number of patients dying from terminal diseases is increasing. Telehealth has been successfully implemented in different home care settings, including palliative care.

Objective: The aim of the study is to present the research design of the clinical testing of a telepalliation program by the use of a digital platform for patients in palliative care and their relatives.

Methods: The telepalliation program will be conducted as a multimethod randomized controlled trial. The intervention group will follow the telepalliation program, while the control group will follow the traditional standard of care program for palliative care. The primary outcome of the study is increased quality of life. Secondary outcomes include enhanced sense of security; reduced experience of pain; satisfactory experiences of patients and relatives with the TelePal platform and degree of satisfaction in being a part of the program; experiences with the use of the TelePal platform on the part of HCPs and the professionals’ experiences of being a part of the program; the use of a cross-sector communication platform and the telepalliation program by patients, relatives, and HCPs; and the projected lower cost of health care services. These outcomes will be assessed using questionnaires, data generated by digital technologies, and semistructured interviews.

Results: The collection of data began in May 2021 and will be completed in August 2024. The results of the study will be published in peer-reviewed journals and presented at international conferences. Results from the telepalliation program are expected to be published by fall 2024.

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Conclusions: The expected outcomes of the study are increased quality of life and increased sense of security. We also expect that the study will have a clinical impact on future telepalliation for those patients who are referred to a palliative team.

Trial Registration: ClinicalTrials.gov NCT04995848; https://clinicaltrials.gov/study/NCT04995848

International Registered Report Identifier (IRRID): DERR1-10.2196/49946

(JMIR Res Protoc 2024;13:e49946) doi:10.2196/49946

KEYWORDS

palliative care; digital health; quality of life; telehealth; interdisciplinary research; randomized controlled trial

Introduction

The World Health Organization defines end-of-life palliative care as "prevention and relief of suffering, by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. The aim of palliative care is to provide relief from pain and other distressing symptoms offered by health care professionals (HCPs) at a general or specialist level, with a focus on addressing the needs of patients and their families [1,2]. More than 20 million people worldwide are estimated to be in need of end-of-life palliative care, equivalent to 377 adults in a population of 100,000, the majority of these being adults aged 60 years and older [2].

In Denmark, as in most other Western European countries, palliative care is provided at 2 different levels, a general and a specialist. The general level comprises HCPs, such as general practitioners (GPs) and primary care nurses, who do not perform palliative care on a full-time basis. The specialist level comprises specialized palliative care (SPC), where HCPs perform palliative care on a full-time basis at a specialist level [3]. It is expected that the basic level palliative care can address around 70%-80% of the patients in need of palliative care. The remaining 20%-30% of patients, having more complex problems, need SPC. SPC consists of specialized palliative care teams (SPCTs) placed at large hospitals serving a wider geographical area with home visits and cross-sector communication with patients, relatives, and other HCPs capable of caring for the patients.

Among patients receiving SPC, more than 90% are diagnosed with cancer [4], with the remaining cases divided among patients diagnosed with terminal cardiac insufficiency, terminal chronic obstructive pulmonary disease, and terminal neurological disorders [2,4].

There are several challenges associated with SPC, such as the very short time span from referral to the end of the patient's life [4] and the fact that patients are very ill and may therefore find it hard to travel to an outpatient clinic and that SPC unit often has a relatively small staff [2,5-7]. The need for SPC is expected to rise in the future, as the number of patients dying from life-threatening diseases, including cancer, is increasing [5,8]. As an increasing number of these patients prefer to be cared for at home, the demand for SPC is expected to increase [5,8].

The use of telehealth has been introduced in different settings and at different levels of home care and has also been used with success in palliative care [8,9]. Demand for telehealth solutions in palliative care has also increased due to the COVID-19 pandemic [10,11]. The use of information and communication technologies within palliative care can be defined as "telepalliation."

The overall purpose of the telepalliation study is to test, implement, analyze, and evaluate a telepalliation program for patients receiving palliative care. To accomplish this goal, we combine clinical, psychosocial, interorganizational, and health economic approaches. The telepalliation study will be implemented and evaluated in a randomized controlled trial (RCT). The aim of this paper is to describe the research design of the telepalliation study, the data collection methods used, and the outcome measures.

Methods

Research Design

The telepalliation program will be conducted as a multimethod RCT using qualitative and quantitative data collection techniques [12,13]. The intervention group will take part in the telepalliation program, while the control group will follow a traditional palliation program at Southwest Jutland Hospital, Esbjerg, Denmark. Enrollment of patients began in May 2021, and the RCT will end in August 2024. The study will be reported following the SQUIRE (Standards for Quality Improvement Reporting Excellence) guidelines [14].

The purpose of the telepalliation study is to test, implement, and evaluate a telepalliation program for patients receiving SPC at the Hospital of Southwest Jutland, Esbjerg, Denmark. To accomplish this goal, we combine clinical, psychosocial, interorganizational, and health economic approaches. This will be done by collecting data on symptom scores over time, patients scoring their feeling of security over time, and interviews with patients, their families, HCPs of the specialist team, and primary HCPs. Interviews will focus on the use of the TelePal platform but also on the interorganizational perspective of the communication between primary and secondary health systems. Evaluation of overall economic implications will be done separately at the end of the study. The telepalliation study will be implemented and evaluated in an RCT.

The TelePal Platform

The telepalliation program and platform have been developed through a participatory design process [15], involving patients who have received SPC and their relatives, HCPs working in palliative care, district nurses, GPs, and an interdisciplinary research team.

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The study uses a TelePal platform, a communication platform that is shared among the patient, his or her relatives, and related HCPs. The platform can be used to communicate between patients, their families, and HCPs in primary and secondary health care. The patients must give their written consent as to whom they want to share their data. All information will be available and presented in the same way to all participating parties. The HCPs and researchers have extra tools with which to administer care, gain an overview of the patient's condition, and monitor multiple patients at the same time. The digital platform is not an electronic patient record but a platform for coordination and communication across sectors between patients, relatives, and HCPs.

All the measured values are stored on a secure database at Aalborg University (AAU). The TelePal web portal (Figure 1) is a web-based platform that encompasses multiple features that have been selected and developed through user-driven innovation [16]. Facilities and entered data (symptom scores, etc) of the specific patient are available to the persons, to whom the patient allows access to the platform. The features are described in Textbox 1.

Figure 1. Overview of the TelePal platform.

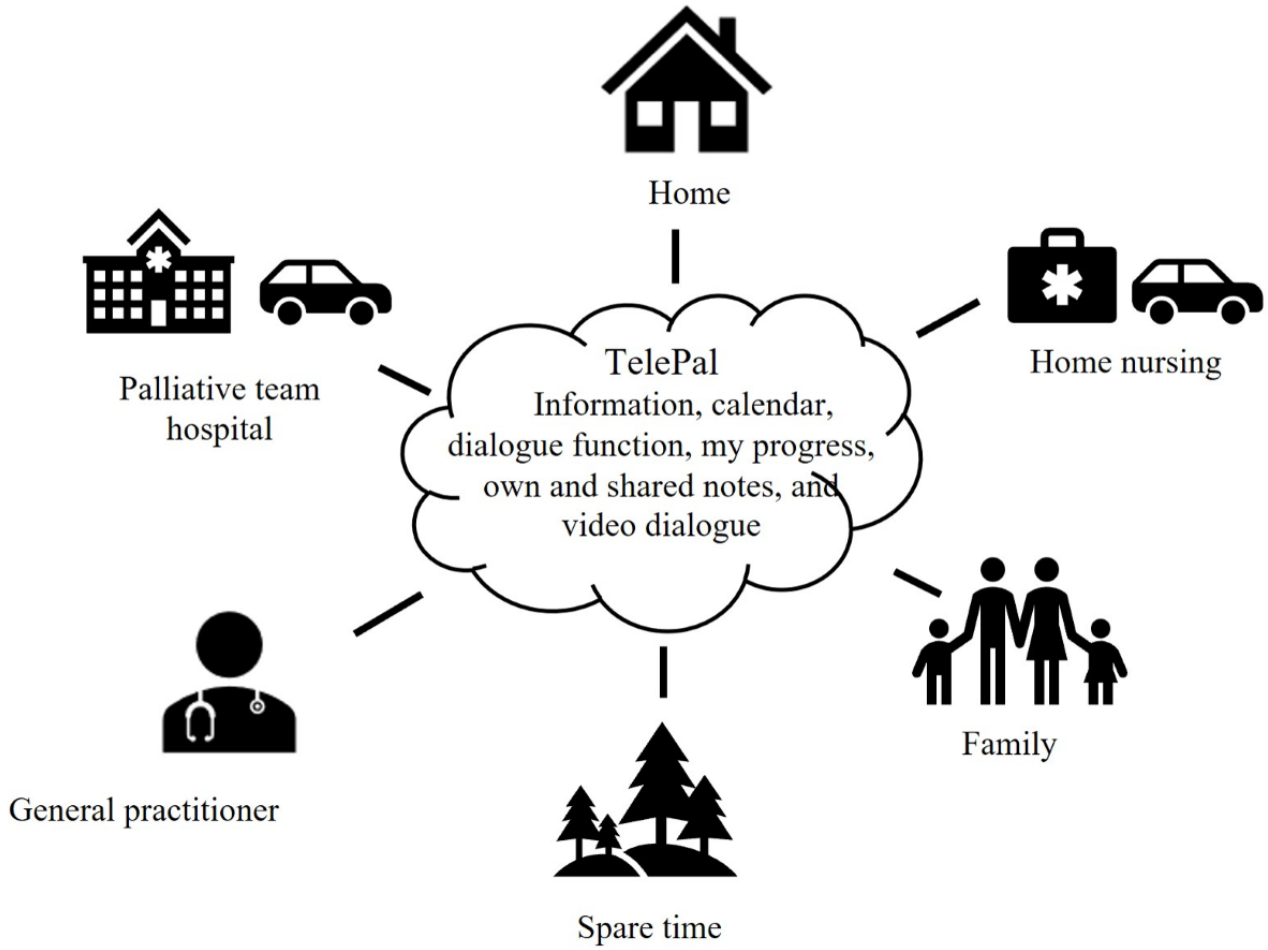

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Textbox 1. Features of the TelePal web portal.

My page/front page (*Min side* in Danish); used to give the patient an overall overview of the different features)

- New messages
- Video consultations (the patient can have video conversations with the palliative team, district nurses, and GPs via TelePal. However, only the HCPs can book meetings with patients and their relatives)
- Questionnaires for patients to fill out

My treatment (*Mit forløb* in Danish)

- Dialogue function (here, the patients can send and reply to messages to the palliative team and the district nurses; if the patient so desires, an SMS function can be used to inform the patient about new messages on TelePal)
- Calendar (gives the patient the opportunity to register coming appointments with the palliative team or any other activity for an overview)
- Joint notes (notes related to the patient's treatment are written here by either the palliative team, the home nurse, or GPs)
- Own notes (these are the patient's own notes, thoughts, questions, and reflections, if they want to use this function)

My status (this site provides the patient with an overview of the results from all the questionnaires they have filled out)

- The data from the questionnaires are visible to the patient's relatives and HCPs, if the patient has allowed them to see and follow their data on TelePal.
- Patients may decide themselves whether they want to allow up to 2 relatives to have access to their TelePal platform. It is also the patient who defines what relatives should have access.

Data and Network Security

The TelePal platform is web-based. It is possible to access the platform from any internet-enabled device, for example, a PC or Mac computer or a tablet, via any modern browser. The most optimal experience and resolution will appear when using an iPad or tablet. All communication and data are secured based with SSL and a 2-factor log-in. The portal will be kept at AAU on servers provided by AAU IT services.

Eligibility Criteria

All participants will be recruited by 2 project nurses at the palliative team at Southwest Jutland Hospital, Esbjerg, Denmark. Recruitment will take place by personal contact and by a recruitment letter. Enrollment will proceed if the participant fits the inclusion and exclusion criteria. Inclusion criteria for participants are that they must be patients under SPC at the Hospital of Southwest Jutland; be aged 18 years or older; live in Esbjerg, Varde, Billund, Fanø, or Vejen municipalities; have cancer, heart failure, chronic obstructive pulmonary disease, or motor neuron disease; and have basic computer skills or have a relative who is able to help them. The exclusion criteria are delirium at enrollment based on the Confusion Assessment Method score; an active psychiatric history other than depression or anxiety related to the main diagnosis, which refers to the reason for palliative care; and a lack of cooperation. Enrollment will take place at the patient's home, where a doctor and a nurse from the palliative team will take the inclusion and exclusion criteria into consideration. Patients who are moribund are not assessed for participation in the study. The patient will be given complete information about the project, and the palliative team will obtain informed consent. The project nurse will then proceed to explain to the patient how to use the equipment and the TelePal portal. If the patient meets the inclusion criteria and agrees to be included, randomization to either the intervention group or standard care will be made.

Details on the RCT

The randomization is performed randomly by a digital tool. The randomization was designed as a block with equal numbers for the intervention and control groups. Only 1 person was blinded. The intervention group participated in the telepalliation program, and the control group received standard SPC [1,3] that was individualized for each patient.

Sample Size

The sample size of the telepalliation study was determined to be 91 patients in both the intervention and the control groups when calculating values based on Ramsenthaler et al [17]. This was done using a 95% CI, an 80% power, an SD of 20.5, a mean quality-of-life score of 59.5 determined by the European Organisation for Research and Treatment of Cancer, and a mean quality-of-life score of 68.43 determined by the European Organisation for Research and Treatment of Cancer when operating with a 15% change in quality of life (QoL).

Theoretical Framework

The theoretical framework is applied as lenses in qualitative analysis.

Psychosocial

In recent years, increasing attention has been paid to the importance of psychosocial factors in palliative care and how these factors can play a crucial role for good end-of-life care in terms of alleviating pain and other distressing symptoms [18]. The World Health Organization [1,19] stated that control of pain, psychological disorders like anxiety and depression, and social and spiritual problems is paramount in palliative care.

Research shows that an intervention focused on the assessment of pain and psychosocial symptoms, establishment of goals of care, assistance with decision-making regarding treatment, and individualized coordination of care can all significantly improve

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patient QoL. Patients reported less depression and physical symptom burden and lived an average of 2.7 months longer than the usual care group, despite receiving less aggressive care [20].

Interorganizational Theory

Collaboration across sectors in the telepalliation program will be studied through the lenses of interorganizational theory by Alter and Hage [21]. The network approach facilitates an exploration of the interplay, communication, collaboration, and dynamics between the HCPs, for example, palliative team, district nurses, and GPs across borders and sectors when developing and implementing the telepalliation program. Alter and Hage [21] define a network as follows: "Networks constitute the basic social form that permits inter-organizational interactions of exchange, converted action, and joint production. Networks are unbounded or bounded clusters of organizations that, by definition, are non-hierarchical collectives of legally separate units."

Ethical Considerations

This study was approved by the ethical committee in Northern Jutland (N-202000094) and registered at ClinicalTrials.gov (NCT04995848). This study will be conducted according to the Declaration of Helsinki. Patients in palliative care and their relatives are a vulnerable group and will be informed thoroughly about the purpose of the study. Accordingly, it is specified that the patient can withdraw their consent at any given time in the study without having any consequences for their treatment. Individuals will be considered as participants in the trial, whereas their relatives will not be considered as participants. However, they are invited to voluntarily participate in the use of the digital platform TelePal. To clarify and ensure that all relatives are fully informed about the study and feel safe about their participation, a written letter of information was sent to all relatives. Patients are enrolled in the study for a maximum of 6 months or until (1) they stop being followed by the palliative team due to lack of symptoms or (2) they are diagnosed with delirium based upon the Confusion Assessment Method score [22,23]. Patients who develop cognitive impairment will be dismissed from the study, and patients who develop delirium will also be dismissed, and data collection will end immediately.

Baseline Data

Baseline data on demographics and diagnosis will be collected for both the intervention and the control groups. Questionnaires regarding QoL, sense of security, pain assessment, and quality-adjusted life years (QALYs) will be combined in questionnaire packages matching the time of measurement illustrated in Table 1. The intervention and the control group will be asked to fill in identical questionnaire packages at the same point in time. All years will be answered by both the intervention and the control group, thereby meaning that both groups obtain identical questions and the same number of questionnaires. All questionnaires will be filled out on TelePal. However, the control group can choose to complete the questionnaires on paper if they desire.

Table 1. Primary and secondary outcome measures.

Outcomes	Time of measurement	Group	
		Intervention	Control
Primary			
Quality of life	Once weekly	✓	✓
Secondary			
Changes in medicine	Weekly for 6 months	✓	✓
Pain assessment	Weekly	✓	✓
Feeling of security	Twice a week	✓	✓
Patients' experiences	Interviews will be conducted after 4 weeks	✓	
Relatives' experiences	Interviews will be conducted after 4 weeks and after 3 months	✓	
Health care professionals' experiences	Interviews will be conducted at 6 and 12 months		
Use of the TelePal platform and telepalliation program	Analysis at the end of the project	✓	✓
Cost of health care services	Week 1 and week 4, and analysis at the end of the project	✓	✓
Quality of life associated with cost of health care services	Week 1 and week 4, and analysis at the end of the project	✓	✓

Outcome Measures

Overview

Primary and secondary outcome measures will be collected as shown in Table 1. The data collection process is described in the following sections.

Quality of Life

The EORTC QLQ-C15-PAL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care) [24] questionnaire will be used to measure QoL as the primary outcome. The EORTC QLQ-C15-PAL was developed by the European Organization for Research and Treatment of Cancer to measure the QoL for

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patients in palliative care. It is a briefer version of the EORTC QLQ-C30-PAL I, as this patient group is often not able to complete extensive self-report measures. It consists of 15 items, of which, all but one (global QoL) is self-rated on a 4-point Likert scale (1=not at all to 4=very much), whereas global QoL is rated on a 7-point Likert scale (1=very poor to 7=excellent). In this study, we did not use the global QoL item. Items are used to calculate scores on 2 multi-item functional scales (emotional and physical), 2 multi-item symptom scales (fatigue and pain), and finally, they contribute to 5 single-item symptom scales (nausea or vomiting, lack of appetite, shortness of breath, constipation, and sleeping difficulties). The EORTC QLQ-C15-PAL is considered to have good content validity [24], and a recent study comparing measures of QoL in palliative care found acceptable internal consistency and test-retest reliability as well as sensitivity of the EORTC QLQ-C15-PAL, while overall results indicated that no other QoL measure is superior to use in this patient group [25].

In addition, the EQ-5D health questionnaire was used to determine QALY to support our analysis on the cost of health care services, as no other QoL measure is validated for this purpose. Hence, we incorporated EQ-5D, the EQ Visual Analog Scale from the EQ-5D, which records the patient's self-rated health on a vertical visual analog scale using the end points, the best health you can imagine and the worst health you can imagine. This scale can be used as a quantitative measure of health outcomes that reflect the patient's own judgment [26]. Studies have shown good construct validity and responsiveness in palliative care [27], and a recent systematic review finds that the EQ-5D has excellent psychometric properties across a broad range of populations [28].

Changes in Medicine

Information on medicine for both groups will be collected at enrollment and every week from the electronic patient record during a 6-month period. Changes in medicine over time will be analyzed.

Pain Assessment

In line with the recommendations for supplementing the EORTC QLQ-C15-PAL with focused measures, if more information on a specific content area is warranted [29], and in accordance with the Expert Working Group of the European Association for Palliative Care [30], we incorporated the Brief Pain Inventory Short Form, a pain measurement tool [31]. The Brief Pain Inventory rapidly assesses the severity of pain and its impact on the patient's functioning. In this study, we incorporated the 11-point numeric rating scale (0-10) for pain intensity as well as 7 items focusing on the impact of pain on functioning in relation to activity, mood, ability to walk, work, relation to other people, sleep, and general joy of life rated on an 11-point numeric rating scale (0=no impact to 10=full impact). The internal consistency of the Brief Pain Inventory (Cronbach α) ranges from .77 to .91, and more specifically, for the pain intensity scale, Cronbach α ranges from .78 to .96 [32].

Sense of Security

To evaluate the patient's sense of security using the TelePal platform, we developed a single item ("Overall, how would you rate your sense of security over the past 24 hours?"), rated on a 5-point scale (1=very unsafe to 5=very safe), to be used in this study.

Use of TelePal Platform and Experiences Using the TelePal Platform

Qualitative exploration of the patients', their relatives', and the HCPs' experiences using the TelePal platform will be collected during semistructured interviews inspired by Brinkmann and Kvale [33]. Patients will be selected randomly to participate in interviews. Interviews with patients and relatives will be conducted after 4, 8, and 12 weeks. Interviews with HCPs will be conducted after 6 and 12 months. All interviews with patients, relatives, and HCPs will be conducted until data saturation has been reached. To analyze which parts of the TelePal platform are being used and for how long, time log files for log-in and log-out of patients, relatives, and HCPs will be analyzed at the end of the project. Consent for the extraction of log files from the database will be received from patients, relatives, and HCPs.

Evaluation of Cost of Health Care Services

The data used to determine QALYs will come from the EQ Visual Analog Scale of the EQ-5D questionnaire [26] (see description in the Quality of Life section). Patients will be asked to answer the EQ-5D health questionnaire twice, first in week 1 of the study and then in week 4, in order to determine QALYs [26]. The questionnaire will be completed by the intervention group on TelePal, and the control group will complete the questionnaire on TelePal or on paper. Furthermore, a cost-effectiveness analysis will be conducted by calculating the differences in clinical efficacy and differences in average cost per patient [34,35]. The cost parameters are numbers of phone or video calls from the palliative team, equipment used, driving distance, personal use in palliative care, visits from GPs, outpatient clinic visits, numbers of hospitalizations, readmissions, length of stay, and visits from the palliative team.

Adverse Events and Dropouts

All adverse events, deaths, dropouts, or withdrawals from the study will be recorded and documented. If the patients no longer want to participate in the study, they can withdraw their consent at any time without having to give a reason. After withdrawing they will be given standard care treatment. The patient's reason for withdrawal, if any is given, will be documented. In this case, the project team will collect the equipment upon request. Patients who do not participate actively in the intervention will still be included in the study and analyzed according to the intention-to-treat approach. These patients will be allowed to use the project equipment as long as they want. Technical problems with the equipment will be recorded and documented.

Statistical Analysis

The applied statistical methods will be used to investigate differences between patients in the intervention group and the control group. Statistical analyses will be used to explore the normal distribution of the sample, the SD, the hypothesis tests, and the *P* values. Nevertheless, a 2-tailed *t* test between the intervention and control groups will be performed in order to compare baseline data between the 2 groups, and a 2-way ANOVA with repeated measures will also be performed to

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compare the 2 groups in relation to their outcomes. All the statistical analyses will be performed using SPSS Statistics (version 25; IBM Corp). Data will be analyzed for gender differences in both primary and secondary outcomes. If there is any missing data, it will be analyzed based on the data received from the questionnaires. If there is too much data missing, a sensitivity test will be performed based on the demographic data.

Qualitative Analysis

All interviews will be transcribed into Word (Microsoft Corp) files. The data will be coded in NVivo (version 12.0; QSR International) inspired by methods developed by Brinkmann and Kvale [33]. Two researchers (JVAS and BD) will conduct the interviews and analysis of the data. The data will be presented in themes, findings, and with citations.

Results

Results from the RCT will be analyzed in spring 2024, published in peer-reviewed journals in the fields of palliative care and telepalliation, and presented at relevant international conferences by fall 2024.

Discussion

Principal Findings

The aim of the telepalliation study is to test, implement, and evaluate the telepalliation program for patients receiving palliative care. The study is carried out using combined clinical, psychosocial, interorganizational, and health economic approaches.

A scoping review by Steindal et al [36] has shown that the use of telehealth in palliative homecare improves access to HCPs at home and enhances patients' sense of security and safety. The review indicated that there are contradicting results as to whether the use of telehealth will improve burdensome symptoms and QoL [36]. A study by Caraceni et al [11] has shown that telemedicine facilitates patient-clinician interaction, but the investigation of clinical impact should be better documented.

The TelePal platform and program have been developed in a participatory design process, and an important part of the study is to explore how patients in palliative care and their relatives experience the TelePal program and use the digital platform. Important questions to explore are whether the patients have the resources to use the technology, and if so, what functions are they and their relatives using and what value do they attribute to these functions. Another important question revolves around the ethical issues of using a digital platform in the collaboration between patients in palliative care and HCPs. Steindal et al [36] stated that there is a need for increased knowledge about these issues. We hope that the platform can help increase the feeling of security for the patients and relatives and ease communication, collaboration, and coordination among the HCPs across sectors.

In palliative settings, video has been used for conferences between patient's homes and between rural health professionals and specialist centers to support patients and their relatives at home [8]. The use of video can increase the collaboration between SPCTs and GPs [6] and fit the practice of home-based palliative care, thus resulting in a more empathetic patient-professional relationship [37]. In the TelePal study, we will explore how the platform will affect the patient care process and interorganizational collaboration among the HCPs across sectors. We have not identified other studies using a telepalliation platform and a program.

What are the health economy costs of running a telepalliation program? Caraceni et al [11] highlighted the lack of cost-effectiveness studies within telepalliation. In the TelePal study, we will conduct a cost-effectiveness evaluation to show that it will be cost-effective, reduce the cost for transportation, and reduce patients' travel to the hospitals.

Limitations

A limitation of this study is that it is a 1-center study and therefore reflects the findings of only a single SPCT. The fact that it has been conducted only in Denmark means that it reflects findings within a Danish context. These findings may not necessarily be applicable to other settings and in different contexts.

Conclusions

The expected outcomes are increased QoL and increased sense of security for patients in the intervention group. We expect that the study will have a clinical impact on future telepalliation for patients who are referred to a palliative team.

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Conflicts of Interest

None declared.

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Abbreviations

AAU: Aalborg University
EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care
GP: general practitioner
HCP: health care professional
QALY: quality-adjusted life year
QoL: quality of life
RCT: randomized controlled trial
SPC: specialized palliative care
SPCT: specialized palliative care team
SQUIRE: Standards for Quality Improvement Reporting Excellence

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Protocol

Understanding Physician's Perspectives on AI in Health Care: Protocol for a Sequential Multiple Assignment Randomized Vignette Study

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Abstract

Background: As the availability and performance of artificial intelligence (AI)–based clinical decision support (CDS) systems improve, physicians and other care providers poised to be on the front lines will be increasingly tasked with using these tools in patient care and incorporating their outputs into clinical decision-making processes. Vignette studies provide a means to explore emerging hypotheses regarding how context-specific factors, such as clinical risk, the amount of information provided about the AI, and the AI result, may impact physician acceptance and use of AI-based CDS tools. To best anticipate how such factors influence the decision-making of frontline physicians in clinical scenarios involving AI decision-support tools, hypothesis-driven research is needed that enables scenario testing before the implementation and deployment of these tools.

Objective: This study's objectives are to (1) design an original, web-based vignette-based survey that features hypothetical scenarios based on emerging or real-world applications of AI-based CDS systems that will vary systematically by features related to clinical risk, the amount of information provided about the AI, and the AI result; and (2) test and determine causal effects of specific factors on the judgments and perceptions salient to physicians' clinical decision-making.

Methods: US-based physicians with specialties in family or internal medicine will be recruited through email and mail (target n=420). Through a web-based survey, participants will be randomized to a 3-part "sequential multiple assignment randomization trial (SMART) vignette" detailing a hypothetical clinical scenario involving an AI decision support tool. The SMART vignette design is similar to the SMART design but adapted to a survey design. Each respondent will be randomly assigned to 1 of the possible vignette variations of the factors we are testing at each stage, which include the level of clinical risk, the amount of information provided about the AI, and the certainty of the AI output. Respondents will be given questions regarding their hypothetical decision-making in response to the hypothetical scenarios.

Results: The study is currently in progress and data collection is anticipated to be completed in 2024.

Conclusions: The web-based vignette study will provide information on how contextual factors such as clinical risk, the amount of information provided about an AI tool, and the AI result influence physicians' reactions to hypothetical scenarios that are based on emerging applications of AI in frontline health care settings. Our newly proposed "SMART vignette" design offers several benefits not afforded by the extensively used traditional vignette design, due to the 2 aforementioned features. These advantages are (1) increased validity of analyses targeted at understanding the impact of a factor on the decision outcome, given previous outcomes and other contextual factors; and (2) balanced sample sizes across groups. This study will generate a better understanding of physician decision-making within this context.

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KEYWORDS

AI-based clinical decision support; decision-making; hypothetical vignettes; physician perspective; web-based survey; hypothesis-driven research; ethics; stakeholder attitudes

Introduction

The implementation of artificial intelligence (AI) in health care is recognized as a promising means to advance medicine by providing timelier diagnoses, reducing administrative burden, and predicting outcomes with higher accuracy. As the availability and performance of AI-based clinical decision support (CDS) systems improve, physicians and other care providers poised to be on the front lines will be increasingly tasked with using these tools in patient care and incorporating their outputs into clinical decision-making processes. Due to the few instances of CDS systems in current use by frontline physicians, there is limited empirical research studying how these tools and the specific characteristics of these tools influence physicians' engagement with AI and their clinical decision-making.

Previous research has identified factors that may influence physicians' use and decision-making in the context of AI-based CDS systems, including clinical risk, explainability, as well as trust and transparency [1,2]. While the role of trust and transparency in clinician acceptance has been emphasized in the literature in recent years, findings supporting the claim that transparency about AI can actually support clinical decision-making are mixed [3-5]. Jussupow et al [6] used vignette-based experiments with physicians to understand how AI influences their decision-making, finding that the timing of the presentation of the AI result, whether or not the AI result aligns with the physician's opinion, and the experience level of the physician may all be factors that influence the decision-making of a physician who is tasked with incorporating an AI-based CDS system in their diagnostic care. Such knowledge is critical to ensuring successful implementation of AI in health care, but due to the many differences in the types of applications of AI, subspecialties, and health care systems, there is a high degree of heterogeneity in physician attitudes regarding acceptance, and factors influential to their decision-making are likely to be context specific.

Experimental vignette studies such as Jussupow et al [6] provide an effective means to explore emerging hypotheses regarding how context-specific factors may impact physician acceptance and use of AI-based CDS tools or to generate new hypotheses regarding how individuals may react to specific scenarios involving new applications where much is unknown. Vignettes are narrative representations of real-world scenarios, providing context-specific stimuli and characteristics with which respondents may practice decision-making without actual exposure to such scenarios [7-9]. Experimental vignette studies have been used to understand reactions toward algorithmic errors [10], physician liability while using AI [11], and physician diagnostic accuracy in the context of AI [12].

In this study, we use a novel vignette survey design—"sequential multiple assignment randomization trial (SMART) vignettes," proposed by JP Kim and HJ Yang (unpublished data)—which uses the SMART design developed by Murphy [13] in a web-based vignette survey. The novelty of this survey design is that it features 2 design elements previously not seen in conventional designs: sequential randomization and adaptive allocation. In experimental vignette studies, hypothetical characteristics (factors) are varied according to levels. Each respondent is randomly assigned to 1 vignette characterized by a specific realization of each factor in order to test how the factors influence responses. In conventional vignette studies, this randomization typically occurs once before the study is administered at baseline, followed by a complete set of questions. Sequential randomization, on the other hand, involves randomly assigning respondents to vignettes multiple times throughout the survey, with each randomization point followed by a subset of questions pertaining to the factor being tested. This latter approach allows inferences about the final response based on previous factors and responses. In contrast, baseline randomization in traditional designs is limited to inferences on how likely each combination of responses is based on given factors. Adaptive allocation is a way to adjust randomization probabilities to encourage more balanced groups for such inference. While these 2 concepts are not novel in and of themselves—the former appears in the field of SMARTs [13,14] and the latter is from Efron [15]—the application of such concepts in the context of vignette survey methodology is novel, to the best of our knowledge.

To best anticipate the decision-making of frontline physicians in scenarios involving AI CDS tools, a hypothesis-driven approach that enables scenario testing in advance of clinical implementation of these tools is urgently needed. As such, we propose to undertake an empirical study engaging frontline physicians in order to better understand the causal effects of specific contextual and algorithmic features on their clinical judgments and perspectives. For our approach, we will conduct a "SMART vignette" web-based survey that features hypothetical scenarios based on emerging or real-world applications of AI-based CDS systems. These scenarios will vary systematically by features related to clinical risk, the amount of information provided about the AI, and the AI result in order to test and determine the causal effects of specific factors on the judgments and perceptions salient to physicians' clinical decision-making.

Methods

Overview

The purpose of this study is to better understand the impact of algorithm-related features on physician acceptance and attitudes related to clinical decision-making in the context of AI CDS tools. US-based physicians with specialties in the family or internal medicine (ie, those most poised to be on the "front lines" of nonemergency patient care) who are listed in the most recent version of the American Medical Association (AMA) Physician Masterfile (PMF) will be recruited through email and

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mail (target n=420). Through a web-based survey, participants will respond to baseline questionnaires regarding their demographics, professional experience, and attitudes toward and experience with AI or machine learning (ML) in medicine. They will then be randomly assigned to a 3-part "SMART vignette" detailing a hypothetical clinical scenario involving an AI decision support tool. Each respondent will progress through the multistage vignette survey, and at each stage, they will be randomly assigned to one of the possible vignette variations. The 3 randomization points will vary in regard to the level of clinical risk (higher risk vs lower risk), the amount of information provided about the AI (more information vs less information), and the certainty of the AI output (higher certainty vs lower certainty). After each randomization point, participants will be asked to respond to questions regarding their hypothetical decision-making as it relates to these factors.

This study is part of a broader project studying stakeholder views regarding the development and use of AI and ML in medicine (National Center for Advancing Translational Sciences R01-TR-003505). It is built upon findings from the first phase of the broader project, in which AI and ML researchers and physicians were interviewed regarding ethical considerations they have encountered or anticipated in the development, refinement, and application of AI and ML in medicine [16,17]. Insights from this phase of research were used to create hypothetical but realistic scenarios for this study and to inform the development of questions assessing physician decision-making in these scenarios.

Recruitment

US-based physicians who are listed in the most recent version of the AMA PMF as specializing in family medicine or internal medicine will be eligible to participate in this study. The PMF is a comprehensive database of US physicians used for verifying professional credentials. Through the AMA-approved third-party vendor Medical Marketing Services, Inc, we will obtain the email and mailing addresses of a sampling frame of 10,000 physicians who meet our inclusion criteria. Physicians who are identified in this sampling frame will be contacted with invitations to participate in our web-based survey.

Through the third-party vendor Medical Marketing Services, Inc, we will send up to 4 email invitations to each physician in the sampling frame. Each email will provide a short description of our study and a web link to the web-based survey. Based on previous studies of this method of recruitment, we anticipate a 1.5% response rate [18]. If the target recruitment goal of 420 is not reached after 4 email invitations are sent, we will send a follow-up invitation by mail to any physicians in the original sampling frame who have not yet responded to the survey. Each mailed invitation will briefly describe our study and will contain a web address for the web-based survey.

Ethical Considerations

This project has received human participant research ethics approval from the Stanford University Institutional Review Board (65168). Upon navigating to the web-based survey, potential participants will be presented with a web-based informed consent form that details the content of the survey and the anticipated risks and benefits of participation. Participants will only proceed to the web-based vignette survey if they provide consent. Participation will be voluntary, and all responses will be anonymous. All participants will be compensated for their time and effort with a US $10 Amazon gift code at the completion of the survey.

Hypotheses and Outcome Variables

Our hypotheses are the following:

1. Hypothesis 1: higher degrees of clinical risk associated with the algorithm will influence lower levels of physician agreement with the effectiveness of and confidence in using the algorithm to help guide treatment decisions.
2. Hypothesis 2: disclosure of details of the algorithm will impact physicians' attitudes of confidence and efficacy, depending on their previous exposure to AI (ie, education, training, and clinical experience). We hypothesize that greater disclosure will influence positive attitudes among physicians with greater exposure but will have a negative or no impact on physicians with less exposure.

The primary outcome variables will be physicians' ratings, on a Likert scale, of perceived confidence in the AI algorithm in helping the physician make the best treatment recommendation for their patient (eg, "The AI result improved the confidence I have in my final decision"; from 1="strongly disagree" to 5="strongly agree"), as well as the perceived effectiveness of the use of the AI algorithm (eg, "Overall, the AI improved the care that I was able to provide to the patient"; rated on a 5-point scale from 1="strongly disagree" to 5="strongly agree").

Survey Design

Survey Instruments

Demographic characteristics (age, gender, educational level, race, and ethnicity) and professional characteristics (specialty type and years of experience) will be assessed through a baseline demographics questionnaire (13 questions). Experience with and attitudes toward AI and ML applications in medicine will be assessed using adapted measures (7-10 questions assessing experience and 11 questions assessing attitudes) [19,20]. A 3-part sequentially randomized vignette detailing a clinical scenario involving a CDS system will be presented to each participant; follow-up questions will assess participant attitudes and decision-making in the context of the vignette scenario (21 questions).

Vignette Development and Design

The vignettes used in this study were developed based on scenarios encountered by researchers and clinicians, as told in interviews in the first phase of this project [16]. Based on these findings, the dimensions in which the vignettes are systematically varied include the context of the decision-making scenario (higher risk vs lower risk), the amount of information provided regarding the algorithm (more information vs less information), and the certainty of the AI output (higher certainty vs lower certainty). The full content of the vignettes is available in Multimedia Appendix 1.

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SMART Design

We have harnessed a design element that originates from clinical trial design: SMART [13,21,22]. JP Kim and HJ Yang (unpublished data) report the design. First, we use randomization probabilities to assign the subsequent vignette, which allows for tailoring the sequence of assigned vignettes to the individual instead of predetermined assignments of combinations of vignettes. The web-based survey format is particularly amenable to the design in which the subsequent questions are randomized. To the best of our knowledge, the SMART design has not yet been applied in the area of survey designs. SMART designs have been used in the evaluation of treatment algorithms for several psychiatric disorders (eg, depression in the Sequenced Treatment Alternatives to Relieve Depression and Clinical Antipsychotic Trials of Intervention Effectiveness studies) and for the treatment of advanced prostate cancer [23,24].

As shown by Figure 1 (adapted from JP Kim and HJ Yang—unpublished data), we configured our SMART vignette to have 3 dimensions, each with 2 levels: patient risk (higher risk vs lower risk), information on AI (more information vs less information), and certainty of AI output (higher certainty vs lower certainty), respectively. Corresponding vignette scenarios and question sets were input for each combination of randomization sequences. One question from every question set was flagged to serve as a primary question, the response for which was used to adaptively allocate the participants [16,17]. For 5-point Likert scale primary questions, participants who respond from "1" to "3" are assigned to response group 0, while those who respond with "4" to "5" are assigned to response group 1. For yes or no questions, "yes" corresponds to response group 1 and "no" to response group 0. The probability of Efron's [15] biased coin was prespecified to be 0.667.

Figure 1. Study design for the web-based vignette survey featuring sequential randomization. Yellow boxes indicate a randomization point, blue boxes indicate vignette content, and orange boxes indicate responses. Respondents will be physicians in family medicine or internal medicine across the United States. ADHD: attention-deficit/hyperactivity disorder; AI: artificial intelligence; SSRI: selective serotonin reuptake inhibitors.

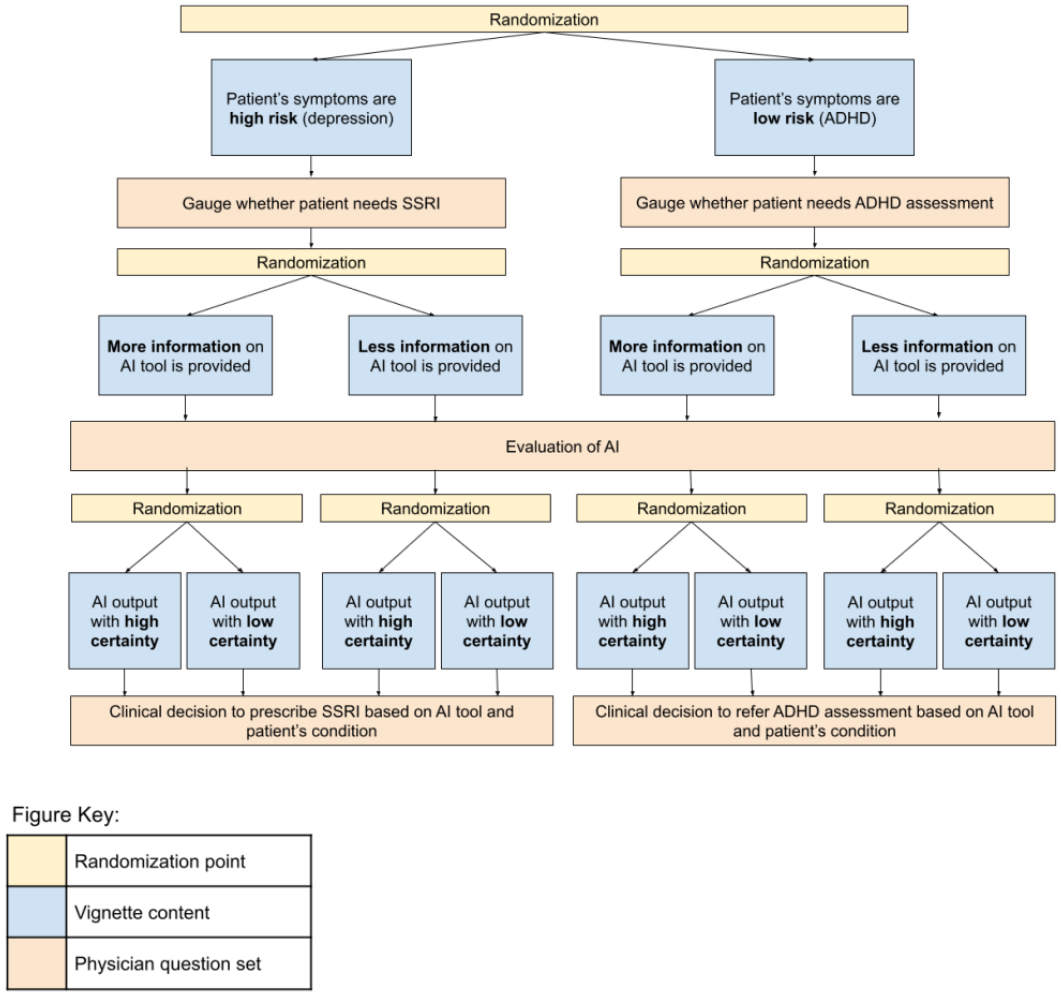

Power Analysis

We performed a sample size estimation for determining the best embedded dynamic treatment regime using the approach outlined in Artman et al [25] for power analysis in a SMART design. Using the R package *smartsizer* (R Foundation for Statistical Computing) that implements Monte Carlo simulations in Artman et al [25], we calculated that the number of individuals needed to enroll in the vignette experiment is 420 to guarantee at least 80% power to detect an effect size of 0.15.

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Survey Implementation

The SMART vignette survey will be administered on the internet using a web application created by our research team and hosted by Stanford University [26]. The application was developed using Python Flask and deployed using Amazon Beanstalk and Elastic File System, with survey responses stored on a secure SQLite database. This platform allows sequential randomization and adaptive allocation, which are features not yet offered by other survey software such as Qualtrics or Research Electronic Data Capture (REDCap; Vanderbilt University).

The study survey went through a round of internal testing before its launch. Dummy responses were created to ensure data were being properly parsed and stored. The research team tested the application on various devices to identify errors and provide feedback on the user experience and user interface. After a few rounds of internal testing, all study responses and parameters were reset for launch.

Unique user IDs were generated for each potential participant. As part of the recruitment emails and letters, participants will be asked to log into the SMART vignette survey using their assigned user ID and a provided study ID. Respondents have the option to exit and return to the survey at any time. Once a respondent has submitted a complete response, a US $10 Amazon gift card code will be claimed and displayed. The study will remain open to responses until the target number of responses is reached.

Statistical Analysis

Regression models will be used to determine the causal effects of contextual dimensions on clinician judgments, where confidence is an outcome and the assignment indicator, age, gender, and race are variables. We will estimate "conditional vignette effects" on physicians' judgments (ie, the effect of the vignette context within subgroups defined by strata of the baseline variables).

Results

This study was funded in September 2020 by the National Center for Advancing Translational Sciences. After the completion of internal testing, the survey was officially launched on May 16, 2023. Email recruitment occurred between May 16 and August 18 and resulted in 35 complete responses. Mail recruitment began on October 1, 2023, and will continue until the target number of 420 participants is reached. It is anticipated that we will reach this number by 2024. The survey will be closed, and data analysis will begin immediately after the target number of responses is reached.

Discussion

As AI technologies in medicine continue to advance, AI-based CDS tools are expected to be increasingly integrated into frontline care, and physicians will be faced with incorporating these tools to inform the evaluation and management of large numbers of patients with diverse needs. This web-based SMART vignette study will generate a better understanding of frontline physician decision-making in the context of AI-based CDS systems and will provide information on how specific factors, such as the level of clinical risk, the amount of information provided to the physician about the AI, and the certainty of the AI output, may influence physician decision-making and related attitudes.

The clinical and algorithmic factors tested in this project will expand on insights from previous research. In at least 1 previous study, risk perception was indicated to influence physicians' willingness to adopt AI-based tools in clinical practice [27]. By testing this factor in controlled scenarios involving moderately varied levels of clinical risk, our study will offer the opportunity to fine-tune our understanding regarding the effect of risk on physician decision-making involving AI. Additionally, while previous studies have demonstrated physician's preferences for greater explainability, this has not had a demonstrated effect on their overall clinical decision-making [1]. As a possible alternative to explainable AI, our study will examine whether simply providing more information about an AI affects frontline physicians' attitudes and their related decision-making. Finally, the analysis of physician decision-making in the context of varied AI output certainties will expand on Jussupow et al [6] by allowing us to identify the individual and context-specific factors that may contribute to a physician's overall acceptance of an AI output.

To empirically test these factors, this study uses a novel vignette study method, "SMART vignettes," an adaptation of the SMART design developed by Murphy [13], applied to web-based survey designs. Further details on the methodology can be found in JP Kim and HJ Yang (unpublished data). This novel method leverages 2 new design characteristics, namely sequential randomization and adaptive allocation. Our newly proposed "SMART vignette" design offers several benefits not afforded by the extensively used traditional vignette design, due to the 2 aforementioned features. These advantages are (1) increased validity of analyses targeted at understanding the impact of a factor on the decision outcome, given previous outcomes and other contextual factors; and (2) balanced sample sizes across groups.

Strengths of the proposed survey include the use of the sequential randomization design feature, which will allow the presentation of vignettes to be tailored to the individual. Our design offers an advantage above a "rule-based, branching logic approach," the predominant approach used in web-based surveys, in which a particular response determines the subsequent question to be the same across all respondents [28,29], as well as a single-time baseline randomization in conventional vignette studies. The use of sequential randomization in this web-based survey will enable assessments of the causal effects of contextual information in the algorithms on the judgments of physicians entrusted with applying and implementing the use of the algorithms. In addition, the adaptive quality of the survey may allow for a greater sense of interactivity from the perspective of the survey respondent. Potential limitations of this study include a low response rate, as previously documented in the literature regarding physicians, as well as possible response fatigue, as is commonly experienced in survey studies. Another limitation is that the novel design features we presented are not yet widely available on existing

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survey platforms (eg, REDCap and Qualtrics) and thus may limit the reproducibility of this particular method. This represents an area of future research.

AI-augmented tools have the potential to improve physicians' decision-making and productivity by automating referrals and triage, augmenting in-person and between-visit treatment, and assisting with minimally invasive procedures. Given this potential, there is a need to better anticipate decision-making in AI-augmented settings as well as identify potential vulnerabilities that may compromise decision-making [30]. Our proposed study comes from the approach of "stakeholder research," the work of seeking perspectives from individuals impacted by the situation at hand, and fills a missing gap in the literature. As Rahwan et al [31] noted in their study, "machine behavior...cannot be fully understood without the integrated study of algorithms and the social environments in which algorithms operate." Such work is needed to understand the range of physician decisions and the causal impact of attributes of AI-embedded care, particularly in high-stakes settings, and vignettes are well suited to address this need.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Vignettes.
[DOCX File , 15 KB - resprot_v13i1e54787_app1.docx]

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Abbreviations

AI: artificial intelligence
AMA: American Medical Association
CDS: clinical decision support
ML: machine learning
PMF: Physician Masterfile
REDCap: Research Electronic Data Capture
SMART: sequential multiple assignment randomization trial

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Protocol

Implementation of an Electronic Clinical Decision Support System for the Early Recognition and Management of Dysglycemia in an Inpatient Mental Health Setting Using CogStack: Protocol for a Pilot Hybrid Type 3 Effectiveness-Implementation Randomized Controlled Cluster Trial

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Abstract

Background: Severe mental illnesses (SMIs), including schizophrenia, bipolar affective disorder, and major depressive disorder, are associated with an increased risk of physical health comorbidities and premature mortality from conditions including cardiovascular disease and diabetes. Digital technologies such as electronic clinical decision support systems (eCDSSs) could play a crucial role in improving the clinician-led management of conditions such as dysglycemia (deranged blood sugar levels) and associated conditions such as diabetes in people with a diagnosis of SMI in mental health settings.

Objective: We have developed a real-time eCDSS using CogStack, an information retrieval and extraction platform, to automatically alert clinicians with National Health Service Trust–approved, guideline-based recommendations for dysglycemia monitoring and management in secondary mental health care. This novel system aims to improve the management of dysglycemia and associated conditions, such as diabetes, in SMI. This protocol describes a pilot study to explore the acceptability, feasibility, and evaluation of its implementation in a mental health inpatient setting.

Methods: This will be a pilot hybrid type 3 effectiveness-implementation randomized controlled cluster trial in inpatient mental health wards. A ward will be the unit of recruitment, where it will be randomly allocated to receive either access to the eCDSS plus usual care or usual care alone over a 4-month period. We will measure implementation outcomes, including the feasibility and acceptability of the eCDSS to clinicians, as primary outcomes, alongside secondary outcomes relating to the process of care

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measures such as dysglycemia screening rates. An evaluation of other implementation outcomes relating to the eCDSS will be conducted, identifying facilitators and barriers based on established implementation science frameworks.

Results: Enrollment of wards began in April 2022, after which clinical staff were recruited to take part in surveys and interviews. The intervention period of the trial began in February 2023, and subsequent data collection was completed in August 2023. Data are currently being analyzed, and results are expected to be available in June 2024.

Conclusions: An eCDSS can have the potential to improve clinician-led management of dysglycemia in inpatient mental health settings. If found to be feasible and acceptable, then, in combination with the results of the implementation evaluation, the system can be refined and improved to support future successful implementation. A larger and more definitive effectiveness trial should then be conducted to assess its impact on clinical outcomes and to inform scalability and application to other conditions in wider mental health care settings.

Trial Registration: ClinicalTrials.gov NCT04792268; https://clinicaltrials.gov/study/NCT04792268

International Registered Report Identifier (IRRID): DERR1-10.2196/49548

(JMIR Res Protoc 2024;13:e49548) doi:10.2196/49548

KEYWORDS

blood sugar; CDSS; clinical decision support system; decision support; diabetes; diabetic; dysglycemia; electronic clinical decision support; hyperglycemia; hypoglycemia; implementation; medical informatics; mental health; mental healthcare; mental illness; metabolic health; randomized controlled trial; RCT

Introduction

Overview

People with severe mental illnesses (SMIs) such as schizophrenia, bipolar affective disorder, and schizoaffective disorders have a significantly reduced life expectancy in comparison with the general population. These groups have higher rates of cardiovascular disease (CVD) risk factors such as central obesity, high blood pressure, raised cholesterol levels, and raised blood sugar levels compared with the general population [1,2].

Improvements to the primary prevention of diabetes in the general population have not been replicated to the same degree in people with SMI [3]. Diabetes refers to a group of metabolic disorders characterized by a high blood sugar level (dysglycemia) over an extended period of time [4]. If unrecognized, untreated, or poorly managed, diabetes can lead to long-term health complications, including CVD, stroke, chronic kidney disease, foot ulcers, retinopathy, and peripheral neuropathy [4,5].

Diabetes accounts for approximately 10% of health care resources in the United Kingdom, and this is set to rise to 17%, with total costs of GBP 39.8 (US $50.7) billion estimated by 2035, when direct health care costs and indirect costs on productivity are taken into account [6]. Recorded rates of diabetes among ethnically diverse middle-aged people with a diagnosis of established psychosis in South London reach 20%, with a further 30% evidencing raised blood sugar levels (dysglycemia) [7]. Likewise, the prevalence of both diabetes and dysglycemia is higher in inpatient psychiatric settings than in the general community [8]. Furthermore, rates of dysglycemia double in the first year after a first psychotic episode, creating a unique window for prevention strategies to address these risks as early as possible [9].

Diabetes outcomes are poor in SMI groups, with people with schizophrenia and cooccurring diabetes having an increased risk of excess mortality, including postcomplication mortality [10]. A key inequality affecting people with SMI is the less than–adequate assessment and management of physical health conditions such as diabetes. In order to target the physical health care of people with SMI and close the life expectancy gap, a number of evidence-based clinical guidelines and policies have been published over the past decade [11-13].

Unfortunately, there remains significant variation in the implementation of these guidelines and recommendations in mental health care services, as outlined by the National Audit of Schizophrenia [14]. A retrospective audit of people diagnosed with schizophrenia or schizoaffective disorder revealed that among those with dysglycemia, only 53.5% were recorded as receiving an appropriate intervention, and among those with dyslipidemia, this was only 19.9% [15]. Another study found that people with SMI and diabetes were not receiving the expected standards of care in glucose monitoring or access to specialist diabetes services when admitted to a psychiatric unit [16].

Globally, studies evaluating the provision of care by clinicians reveal a suboptimal uptake of clinical guidelines into practice. The underlying reasons for this are complex and noted to occur at a combination of patient, clinician, and wider systemic levels [17]. There is therefore a need for more targeted and clinically informed interventions that improve the standard of physical health care screening and interventions offered to people with SMI across both primary and secondary care settings.

Digital health solutions have the potential to improve the delivery of care through tools such as clinical decision support systems [18]. An electronic clinical decision support system (eCDSS) consists of digital-enabled tools and interventions [19,20] that can be “based on a software algorithm designed to aid directly in clinical decision-making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration” [19]. An eCDSS has the potential to overcome problems associated with the use and

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implementation of traditional paper-based guidelines. Interventions involving clinical decision support systems appear to achieve small to moderate improvements in targeted processes of care in acute physical health care settings [21]. However, the evidence base for eCDSSs in mental health care settings remains sparse.

Given the high disease burden of diabetes in SMI and the deficits in providing evidence-based care for diabetes prevention and treatment, there is a pressing need to identify novel systems-focused solutions. The adoption of digital technology to improve physical health in people with a diagnosis of SMI presents a unique opportunity but requires evidence of acceptability, feasibility, and effectiveness.

Digital systems that are not accepted by their users cannot be expected to contribute to improving the quality of care; hence, facilitators, barriers, and other unintended consequences need to be understood for the successful implementation of novel digital tools and could also serve as a basis for future system reengineering. Hence, there is a call for research to include evaluating its implementation to improve the chances of successful future scalability [22].

Given that patients with SMI have a high risk of CVD factors, including dysglycemia and diabetes, and that there is typically a suboptimal uptake of clinical guidelines, there is a need for more targeted and clinically informed interventions that improve the standard of physical health care screening and interventions offered to people with SMI. Assessing the physical health of patients with SMI when they are admitted under mental health services offers an opportunity to identify risk factors for developing conditions such as CVD or diabetes and provide advice and support to their care teams on services that can be accessed in hospitals and in the community.

We have previously reported on the design and development of a novel eCDSS built using the information retrieval and extraction platform CogStack, deployed at the South London and Maudsley National Health Service (NHS) Foundation Trust, UK (CogStack@Maudsley), comprising a real-time computerized alerting and clinical decision support system for dysglycemia management that has been previously validated for use in secondary mental health care [23].

Objectives

The primary objective of this study is to establish the acceptability, feasibility, and other implementation challenges of the eCDSS (CogStack@Maudsley), comprising a real-time computerized alerting and clinical decision support system, in supporting dysglycemia management in an inpatient secondary mental health care setting.

Our secondary objective is to assess the change in rates of guideline-indicated tests or interventions for dysglycemia on the test wards before and after the introduction of the eCDSS, compared to comparator wards without access to the eCDSS.

This will be measured using pseudonymized group observational data gathered from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre's Clinical Records Interactive Search (CRIS) system. Since 2006, the South London and Maudsley NHS Trust has operated fully electronic health records. The CRIS system, established in 2008, is an ethically approved electronic health records interface system that allows researchers to access deidentified electronic health records from this trust for research purposes [24-26].

Data gathered from this study will allow us to refine the system, address potential challenges with future successful implementation, and inform a larger and more definitive effectiveness trial that will examine for hypothesized improvements in (1) rates of clinician-delivered, evidence-based interventions for patients with dysglycemia and (2) clinical outcomes relating to diabetes care.

Methods

Study Design

We will conduct a pilot hybrid type 3 effectiveness-implementation randomized controlled cluster trial in inpatient mental health ward settings [27]. This specific study design was chosen as the primary aim is focused on implementation outcomes, while the secondary aims relate to effectiveness outcomes. Wards will be the unit of recruitment and will be assigned to deliver care with either the eCDSS platform alongside usual care processes (treatment as usual [TAU]) or to follow TAU alone. The trial will last for a period of 4 months. Qualitative implementation outcome data will be obtained from participating clinicians on all recruited wards using implementation pre- and poststudy surveys and individual semistructured interviews. Quantitative indicative effectiveness data to inform future work will be gathered using pseudonymized group data, including rates of adherence to dysglycemia guidelines and process of care measures.

Setting

The study will be conducted with clinicians in 5 general adult psychiatry inpatient wards at South London and Maudsley NHS Foundation Trust in the United Kingdom.

Recruitment and Eligibility

Screening for dysglycemia is indicated in all people admitted to general adult inpatient wards at the host NHS Trust hospital. All general adult inpatient wards in the hospital will be eligible for inclusion in the study, with the study publicized at consultant continuing professional development meetings and to senior management of all wards at the trust. Managers of wards who show an initial interest will be approached and their wards invited to participate until a total of 5 participating wards is reached. All clinicians on participating wards who are routinely involved in dysglycemia management, including consultant psychiatrists, medical doctors, ward pharmacists, and the ward nursing team, will be eligible and invited to consent to participate in the preintervention surveys and interviews and postintervention surveys and interviews if they were on an intervention ward at the end of the study.

Processes of care in each participating ward will be obtained using the available pseudonymized observational data of all people receiving inpatient care in participating wards during the trial period. Individual patient outcomes will not be recorded.

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Randomization

Wards will be the unit of recruitment and will be assigned randomly to either the intervention or TAU group to receive either the eCDSS platform alongside usual care or to follow usual care processes only for a period of 4 months. We will recruit and randomly allocate 2 wards to the intervention arm and 3 wards to the comparator arm using fixed block randomization. Random allocation of the wards will be done by an independent trial manager who is outside of the research team to ensure there is no bias in allocations.

Sample Size

The primary end points of this study are implementation outcomes rather than direct measures of intervention effects on clinical outcomes. Hence, power analyses for intervention outcomes have not been undertaken in advance. A total of 5 wards will be recruited in total, which will be a large enough sample of wards to recruit enough staff to take part in preintervention qualitative work, and to inform the practicalities of implementing the system and collecting sufficient outcome data.

Intervention

We previously developed an eCDSS for dysglycemia hosted within CogStack@Maudsley [23]. The eCDSS is designed to alert clinicians automatically when patients are admitted under their care regarding the need for screening for, or management of, dysglycemia. Prompts are triggered by the presence of new, old, or absent HbA_{1c} pathology reports in the electronic health record.

Digital-enabled clinical decision support is provided as a combination of visual prompts on a dashboard embedded within an existing electronic platform used at the NHS Trust and email supplements sent to NHS Trust email accounts of participating wards. The eCDSS was designed to integrate as easily as possible within existing workflows by building it into the existing NHS Trust electronic systems that clinicians use in inpatient wards.

The alerts in this study will include NHS Trust "Quality Centre"–approved, guideline-based recommendations for clinician-led monitoring and management of dysglycemia and known diabetes, tailored to the individual patient's reported HbA_{1c} values. The eCDSS algorithm is based on gold-standard clinical management guidelines, which were developed and agreed upon by the NHS Trust [23].

Clinicians on intervention wards will be able to view priority-tagged prompts in the EHR system, corresponding to guideline-based recommended actions they can access for further patient-specific guidance with regard to their care. Clinicians are already familiar with the platform for other uses, but a demonstration of the system will be given to users before the intervention period, so they are aware of how the system is accessed and used. Access to the system will be restricted to the intervention wards only, but access to it can be expanded in the future to more wards and teams.

The research team will be available to provide support to clinicians participating in the study to ensure that any technical queries relating to the eCDSS are dealt with appropriately. The research team will also work closely with the host trust IT department so that any potential technical issues are responded to quickly.

Study Procedure

Ward managers of the selected wards will notify ward staff of the study and the opportunity to participate in interviews and surveys as part of this study. All clinical staff working on recruited wards who express an initial interest to their ward manager will be approached by members of the research team and given a participant information leaflet and an opportunity to ask and discuss any further questions regarding the study. They will be invited to take part in an initial survey and an individual interview with a member of the research team at the start of the study, and then again at the end of the trial, should their ward be randomized to the intervention arm.

Consented participants will be invited to complete an initial survey and to take part in an individual interview lasting approximately 30 minutes. The interview will follow a semistructured interview topic guide with key prompts to direct the discussion, but researchers will be able to direct further questions if additional themes or content arise during the course of the interview. The survey and interview aim to scope the experiences of clinicians in managing diabetes and related physical health conditions in secondary mental health care settings and to explore their attitudes toward the use of novel digital technology as a means of improving physical health care provision in secondary mental health care settings.

Participants in the intervention arm of the study will be invited, a minimum of 4 months from the start of the study, to complete a follow-up survey and individual interview lasting approximately 30 minutes, which will aim to scope their experiences and attitudes toward using the eCDSS and their perceptions of its impact upon diabetes and dysglycemia care. The interview will again follow a semistructured interview topic guide with key prompts to direct the discussion, but researchers will be able to direct further questions if additional themes or content arise during the course of the interview.

Service-level process of care outcome data will be collected at the level of participating wards using pseudonymized observational group-level data from the CRIS system [25]. Approvals for the acquisition of relevant deidentified data through the CRIS system will be applied for through the CRIS oversight committee.

Ethical Considerations

This study was reviewed and approved by the NHS Health Research Authority and Health and Care Research Wales (reference 285509). The eCDSS has received NHS digital clinical safety sign-off by the host trust, and any immediate patient safety issues will be reported in line with the digital safety policy at the host NHS Trust. The eCDSS is built within existing IT systems at the trust; therefore, data do not leave the firewall of the existing systems.

Each participant will be given an identification number. All information collected will be kept confidential; all identifiable

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data will be securely stored; and forms with identifiable data, such as consent forms, will be kept separate from the outcome data in a locked cupboard. All data generated will be stored securely, such that participants can only be identified by their unique study identifier, and all stored electronic data will be password-protected.

Outcomes and Data Collection

As this is a feasibility study, the primary outcome relates to acceptability, feasibility, and other implementation outcomes relating to the intervention (Table 1). Secondary outcomes relate to the process of care measures (ie, screening rates for dysglycemia, documentation of interventions relating to dysglycemia and diabetes care, and documentation of communication to other relevant care professionals regarding follow-up). The study is not powered to detect impacts on clinical outcomes. As this is a pilot study, the primary outcomes will be used to inform further work to refine the system before progressing to a full trial.

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Table 1. Outcome measures.

Outcomes	Definition	Data collection
Primary outcomes (implementation outcomes)		
Acceptability	• Extent to which eCDSS[a] is perceived by clinical users to be acceptable in prompting evidence-based dysglycemia management, and an effective system for improving dysglycemia and, where applicable, diabetes care. 1. Experience of the system 2. Effect on workload 3. Barriers and facilitators to its use 4. Impact on clinicians' time compared to usual care 5. Perceived effectiveness of the system 6. Intention to continue to use the system	• Qualitative: pre- and postsurvey and semistructured individual interviews
Feasibility	• Ability to recruit wards and clinicians to the study. • Retention and participation of clinicians on recruited wards through to the end of the study. • Usefulness and limitations of CRIS to collect process of care outcome measures	• Quantitative and qualitative: survey and semistructured individual interviews
Adoption	• Individual clinicians and the wider system's intention to adopt and use the system for dysglycemia management.	• Qualitative: survey and semistructured individual interview
Reach	• Number of clinicians who make use of the system as a proportion of the total number of clinicians expected to use the system	• Qualitative: survey and semistructured individual interview • Quantitative: audit trail on eCDSS platform
Appropriateness	• Extent to which the novel system is perceived to be fit and relevant for dysglycemia management by users	• Qualitative: survey and semistructured individual interview
Fidelity of Delivery	• Extent to which the eCDSS system alerts are delivered as intended.	• Qualitative: survey and semistructured individual interview • Quantitative: eCDSS platform
Sustainability	• Facilitators and barriers to sustained use of the system. • Clinician attitudes toward the system.	• Qualitative: survey and semistructured individual interview
Contextual Factors	• Facilitators and barriers to the implementation of the system	• Qualitative: survey and semistructured individual interview
Maintenance	• Satisfaction of, and intention to use eCDSS, by clinicians	• Qualitative: survey and semistructured individual interview
Secondary outcomes (processes of care)		
HbA_{1c}[b] testing	• Rates of HbA_{1c} testing on inpatients	• Quantitative
Documentation of dysglycemia or diabetes in clinical notes	• Documentation of diabetes or prediabetes diagnosis in case notes during inpatient stay (where indicated)	• Quantitative
Documentation of discussion with patient regarding exercise, diet, and smoking cessation	• Documentation of advice by clinician given to the patient regarding lifestyle changes—exercise, diet, and smoking cessation in patients with dysglycemia	• Quantitative
Documentation of diabetes-related screening interventions	• Documentation of completed foot check for patients with diabetes	• Quantitative
Delivery of evidence-based pharmacological interventions for diabetes or prediabetes where clinically indicated	• Documentation of discussion regarding diabetes-related medication changes post alerting where clinically indicated: • Initiation of diabetes-related medication • Intensification of medication (dose change or introduction of new agent in accordance with guidance)	• Quantitative

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Outcomes	Definition	Data collection
Communication with general practitioner or community mental health team regarding diabetes or dysglycemia follow-up	• Documentation to relevant community teams and GP[c] regarding follow-up plans for dysglycemia management post discharge where indicated	• Quantitative

[a]eCDSS: electronic clinical decision support system.

[b]HbA_{1c}: glycated hemoglobin.

[c]GP: general practitioner.

A process evaluation of the implementation of the intervention will be conducted to identify factors that inhibit or facilitate implementation. A mixed methods approach will be adopted to establish feasibility, acceptability, and other implementation outcomes.

Details of the study were first shared among ward managers and consultants in January 2022, and formal enrollment of eligible wards began in April 2022. Clinical staff on recruited wards were then individually recruited to take part in surveys and interviews starting in June 2022. The intervention period of the trial began in February 2023, and qualitative data collection was completed in August 2023. All interviews were recorded and subsequently transcribed verbatim.

Baseline Measurements

We will collect the following sociodemographic data on participating clinicians from recruited wards: age, gender, years of clinical experience, specialty or profession, and grade.

No identifiable data will be collected on patients on the recruited wards. However, a separate application will be made to the CRIS oversight committee to gather the following pseudonymized information at a ward or group level: age, gender, ethnicity, HbA_{1c} levels, recorded history of diabetes, International Classification of Diseases-10th revision (ICD-10) mental disorder diagnosis, and history of referral to diabetes specialist teams.

Analysis

Mixed methods will be used to analyze the outcome data generated.

Qualitative analysis of data generated through semistructured interviews and surveys of clinician users will be used to evaluate the primary outcome measures relating to implementation. A thematic analysis of interview transcripts will be conducted. We will then use a qualitative process evaluation, grounded within established implementation science frameworks, to analyze and report on the implementation outcomes generated [28-30].

We will compare changes in the process of care measures between intervention and control groups to evaluate the eCDSS impact on the process of care measures by analyzing group-level pseudonymized observational data through the CRIS platform. Descriptive statistics will be used to report on these results.

Key stakeholders will be informed of the outcomes of the study through internal report and the presentation of the study results at local meetings. It is planned that the methods and findings of the study will be incorporated into an original research paper that can be widely shared, following peer review in a journal.

Results

As this paper is a study protocol, no results are currently available. Enrollment of wards began in April 2022, after which clinical staff were recruited to take part in preintervention surveys and interviews. The intervention period of the trial began in February 2023, and subsequent data collection for postintervention interviews and surveys was completed in August 2023. Data are currently being analyzed, and results are expected to be available in June 2024.

Discussion

Overview

To our knowledge, this will be the first-ever trial of an eCDSS comprising an automated electronic physical health monitoring and alerting platform developed for use in a secondary care mental health setting, which aims to improve the clinician-led management of dysglycemia and diabetes care to patients with SMI. eCDSS has the potential to radically improve the standards of physical health care offered to patients with SMI and may be a crucial step in reducing the morbidity and mortality associated with chronic physical health conditions in SMI.

Implementation of eCDSS for use in clinical settings has previously been shown to be time-consuming, and its complexity can result in slow adoption into practice [20]. To bridge this gap, we have adopted a stepwise approach, starting with technical development and in silico evaluation [23], and progressing to this pilot, with the aim of informing further refinement, development, and engineering of the eCDSS, to enable its longer-term successful adoption in clinical practice.

Integration of eCDSS into existing clinical workflows is not simple, and digital health systems that are not wholly accepted by their users cannot be expected to contribute to improving care, hence the need for research into facilitators and barriers to adoption. These need to be well understood to support the successful implementation of novel digital tools, with calls for research to include evaluating eCDSS implementation for successful future scalability [22].

Gaining a good understanding of the factors that affect the adoption and integration of digital health tools into routine practice could also serve as a basis for creating frameworks for delivering future impactful digital tools. For this reason, we have included implementation outcomes alongside other

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measures of effectiveness, to inform further work that aims to facilitate smoother implementation of digital technologies into clinical settings. This knowledge can then be used to apply and scale the eCDSS for other physical health conditions in SMI, such as atrial fibrillation, hypertension, and hypercholesterolemia.

This study does have some limitations. Recruitment is limited to 1 NHS Trust, with 2 wards allocated to the intervention arm from 1 site, thus limiting the extent to which broader conclusions can be made as the findings are not generalizable. There could be a self-selection bias in regard to staff who agree to participate in interviews and surveys, as it is possible that they are more likely to be interested in or accustomed to novel digital technologies. All staff will be encouraged to ask the research team about any concerns they may have so that they can be addressed with a view to reducing the risk of this. It is possible that different data might be generated if it were conducted in settings across multiple sites. Given the study design, there is also the possibility of the Hawthorne effect, which is well documented in research, when participants may knowingly or unknowingly alter their behaviors as a result of being observed as part of the study [28]. Nonetheless, this pilot study still serves as a useful basis for preliminary research in a setting that has not been explored in depth previously.

We have previously demonstrated that it is technically feasible to design and deploy a functional monitoring and alerting eCDSS for dysglycemia in a secondary care setting for mental health [23]. This pilot feasibility trial seeks to further improve our understanding of the implementation challenges of implementing a new digital system that aims to improve physical health care provision to patients in mental health settings and inform a further, more comprehensive evaluation of the eCDSS. Key implementation outcomes, including acceptability and feasibility, will be evaluated alongside outcomes relating to impacts on care processes and based on established implementation science methods [29-31].

Conclusion

An eCDSS can have the potential to improve clinician-led management of dysglycemia in inpatient mental health settings. If found to be feasible and acceptable in this study, then, in combination with the results of the implementation evaluation, the system can be refined and improved to support future successful implementation. A larger and more definitive effectiveness trial should then be conducted to assess its impact on clinical outcomes over a longer period of time and to guide its scalability and application to other conditions in wider mental health care settings.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

RJBD is the Co-founder and director of CogStack Ltd. FG has received honoraria for talks from Boehringer Ingelheim, Lundbeck, Otsuka and Sunovion. FG is in part supported by the National Institute for Health Research's (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Abbreviations

CRIS: Clinical Records Interactive Search
CVD: cardiovascular disease
eCDSS: electronic clinical decision support system
ICD-10: International Classification of Disease-10th revision
NHS: National Health Service
SMI: severe mental illness
TAU: treatment as usual

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Protocol

Telepractice Parent Training of Enhanced Milieu Teaching With Phonological Emphasis (EMT+PE) For Persian-Speaking Toddlers With Nonsyndromic Cleft Palate: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children born with a cleft palate with or without a cleft lip (CP/L) are at increased risk for delayed language development and speech sound disorders. Enhanced Milieu Teaching with Phonological Emphasis (EMT+PE) is a recommended naturalistic intervention for toddlers with CP/L. The parents' role in providing naturalistic interventions is critical and they need training based on learning principles to implement these interventions. Telepractice is an appropriate method for training parents and children with various speech-related disorders.

Objective: This study aims to determine and compare the effectiveness of telepractice and the parent-implemented EMT+PE intervention on language and speech measures in toddlers with CP/L with usual interventions and determine the effectiveness maintenance of the intervention.

Methods: A randomized controlled trial (RCT) will assess the efficacy of telepractice and the parent-implemented EMT+PE intervention in enhancing speech and language measures in toddlers with CP/L. Eligible participants will be randomly assigned to one of 2 groups: the conventional intervention group and the EMT+PE intervention group. Participants' speech and language measures will be evaluated remotely by trained raters before and after the intervention and 2 months after the intervention. Parents of participants in the intervention group will receive 3 months of training in speech and language supportive strategies from trained therapists using telehealth fidelity scales. Parents of participants in the control group will receive the conventional speech and language intervention by cleft team therapists. Study outcomes will include language variables (mean length of utterance) and speech production variables (percent correct consonants).

Results: The protocol was approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences in February 2022. The selection process of participants, as well as training therapists and raters, commenced in January 2022, the therapy and follow-up period ended in June 2023, and pre- and postintervention assessments have been conducted. Data analysis is ongoing, and we expect to publish our results by the summer of 2024. Funding is yet to be received.

Conclusions: The results of this study may help us develop a speech and language intervention with a different delivery model for toddlers with CP/L, and the cleft team care can use these results in service delivery. Consistent with our hypothesis, speech and language measures are expected to improve.

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KEYWORDS

telepractice; cleft palate; language intervention; parent training; Phonological Emphasis; Enhanced Milieu Teaching; Persian-speaking toddlers; toddler; toddlers; children; child; cleft lip; language development; speech sound disorders; speech sound disorder; effectiveness; parent-based; intervention; speech; therapy

Introduction

Background

Cleft palate with or without cleft lip (CP/L) frequently leads to difficulties with speech and language [1-5]. Previous studies have reported that children with CP/L have limited consonant inventory, which leads to decreased expressive vocabularies [6-8]. Thus, trained and experienced speech-language pathologists (SLPs) in cleft and craniofacial teams often provide speech-language therapy services for these children. Team-based cleft care for this population follows particular intervention protocols. However, due to limited cleft teams in some countries or regions, especially in low-income and transitional countries, and the long distance between the cleft teams and families' residences, many of these children are unable to receive appropriate speech-language therapy services. Parent training and telepractice therapy sessions could help fill this gap [9-12].

Training and coaching for parent-implemented interventions have been known as practical methods to prevent or improve speech-language disorders in children [9-14]. Parents are considered the first teachers of their children's speech and language development since they spend considerable time with their children in a natural environment, which provides them many opportunities to teach their children through daily routines. Intervention approaches in speech-language pathology have highlighted the crucial role of parents in these approaches. Parents are trained to use supportive language and speech strategies while interacting with their children [14]. Training strategies parents use in a child's environment also facilitate the transfer of therapy from clinical settings to the child's natural environment [15-17]. A systematic review of 18 studies [18] analyzing parent-implemented interventions revealed that parents who received training increased their responsiveness, usage of language models, and rate of communication with their children—in addition to the use of language-supportive strategies—had positive impacts on expressive language in preschool children with or without language impairments.

Language and motor intervention approaches have been used for children with CP/L. A systematic review [19] comparing the benefits of linguistic and phonological versus motor phonetics approaches revealed that although all the studies reported significant findings, they did not report a more effective intervention approach. Other studies [8] showed that both approaches improved consonant inventory; however, the linguistic and phonological approach was more effective in improving speech outcomes. Most of these studies have been conducted with children older than 4 years. It seems that the naturalistic-based approach is more effective in and applicable to younger children [20]. Enhanced Milieu Teaching (EMT) is one of the approaches of the naturalistic approach. It is a conversation-based naturalistic model for early language intervention that uses children's interests and initiations as opportunities to model and encourage language use in daily routines [15]. EMT with Phonological Emphasis (EMT+PE) extends the prompting strategies of EMT to include Phonological Emphasis (PE). PE or speech recasts are a subset of recasts that target correct phonological production in response to the child's incorrect productions [5,11,12,21]. Studies have reported positive effects of EMT+PE on language and speech outcomes including the percentage of correct consonants (PCC), consonant inventory, word production speed, compensatory errors, expressive vocabulary, and receptive language [5,21,22]. EMT+PE delivery methods are flexible for children with CP/L. Two pilot studies have demonstrated the effectiveness of the EMT+PE intervention via telepractice [11,12].

Telepractice refers to services delivered over long distances using videoconferencing or other technologies. Also, it is a service delivery model for different purposes in specific populations with communication disorders [13,23]. Telepractice is used to train parents in parent-implemented approaches [11,12,24]. Parent training via telepractice is implemented through different media such as videoconferences, YouTube videos, and web-based modules. The type of media for service delivery depends on the media facilities [24,25]. Previous research has indicated that treatment outcomes are comparable for both in-person and telepractice service delivery, and these methods are used as alternatives or as a hybrid approach [26].

The prevalence of cleft lip and palate (CLP) in Iran has been reported as 1.24 per 1000 births, with an incidence rate of 1 in 1000 births [27,28] There are 6 active cleft teams in Iran, all located in the center of major provinces. Iran, with a population of over 80 million individuals, of which 26% live in rural areas and 74% in cities, most families with a child with CLP are likely to face significant challenges in accessing team services or may not have the opportunity to use them due to their living conditions. According to various studies [26,29], telepractice service delivery can largely address the problems of health care services and provide timely access to services for children and families; therefore, our objective is to develop a protocol to evaluate the effect of a parent-based telepractice EMT+PE intervention on speech and language outcomes in Persian-speaking toddlers with nonsyndromic cleft palate, and compare this intervention to conventional, usual-care interventions.

Aims

Primary Objectives

Our primary objective is to determine the effectiveness of a parent-based telepractice EMT+PE intervention on language and speech outcomes in toddlers with CP/L.

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Secondary Objectives

Our secondary objectives are to compare the effectiveness of this parent-based telepractice EMT+PE intervention with usual-care interventions and determine the effectiveness of the intervention in the follow-up period.

Methods

Study Design

This is a single-blind, 2-arm, parallel randomized controlled trial (RCT).

Study Population and Setting

The study will enroll 32 children with different types of oral cleft including unilateral cleft lip and palate, bilateral cleft lip and palate, and isolated cleft palate (Figure 1).

Participants will be recruited through local cleft palate teams in 3 major provinces (Esfahan, Tehran, and Shiraz), social media support groups, and local speech and language centers. All child-parent dyads will be required to meet the inclusion criteria.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart showing the flow of participants in both groups.

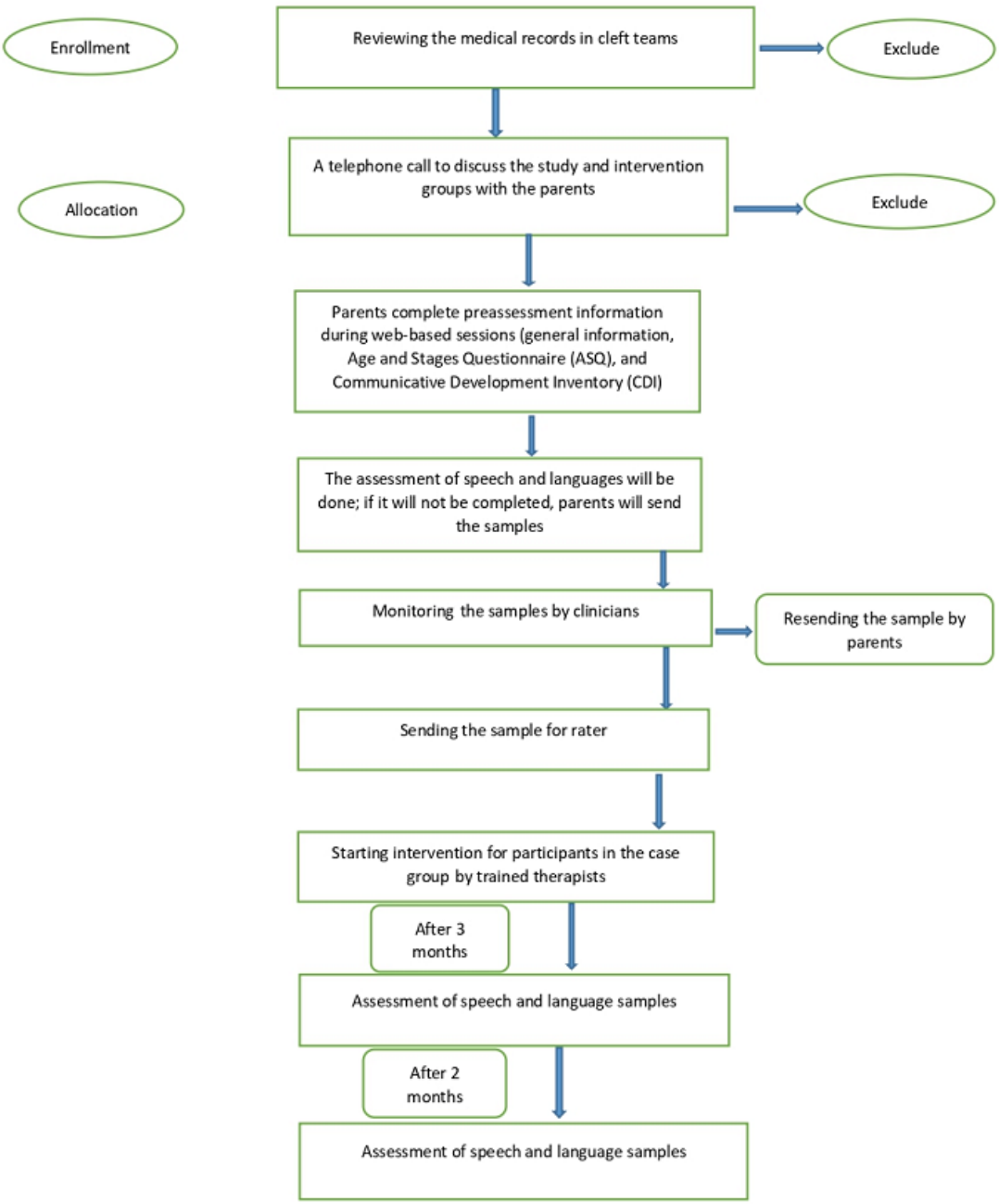

Inclusion and Exclusion Criteria

Eligible participants including children, their parents, and SLPs will be recruited through a rigorous review of the literature in this field [4,11,12,21].

Inclusion Criteria

Children

The inclusion criteria for children are as follows: (1) Persian-speaking children with CP/L aged between 18 and 36

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months before the intervention, (2) lack of a diagnosis of a syndrome by a geneticist and by referring medical records to cleft care teams, (3) undergoing primary palate repair by the age of 15 months, (4) absence of sensorineural hearing loss or a sound field hearing threshold greater than 30 dB HL (decibels in hearing level), (5) preintervention assessment of typically developing children wherein scores on the Age and Stages Questionnaire in all domains (communication, fine motor, gross motor, personal and social, and problem-solving skills) are within the normal range (±1 SD from the cutoff points in each domain), (6) the child's sufficient joint attention with the parent during the collection of play-based language samples, (7) at least 1 type of compensatory error throughout the speech sample, and (8) the child can produce at least 5 different words as measured using the Macarthur-Bates Communicative Development Inventory (MCDI).

Parents

The inclusion criteria for parents are as follows: (1) having literacy skills at least at the level of elementary school education, (2) being interested in participating in the assessment and telepractice training sessions, and (3) being able to use a cell phone containing apps that will be used in the intervention.

SLPs

The inclusion criteria for SLPs are as follows: (1) having at least 5 years of experience in providing treatment approaches for children with speech-language disorders, (2) not currently delivering EMT+PE and not previously trained in the interventional approach, and (3) having experience in treating children with various speech-language disorders via telepractice.

Exclusion Criteria

Children

Children will be excluded from the study if they (1) are bilingual or do not speak Persian, (2) have other dysmorphic features that affect speech (fistula in the palate), (3) have been receiving either therapy in the last 6 months or speech therapy in private clinics, or (4) are participating in another research study involving an intervention or multiple assessments.

Parents

Parents will be excluded from the study if they are (1) unable to properly implement speech- and language-supportive strategies or (2) unwilling to continue with the intervention process.

SLPs

SLPs will be excluded from the study if they are unable to provide weekly family therapy sessions.

Randomization and Blinding

Overview

After preassessments, participants will be allocated to either of 2 intervention groups to eliminate selection bias and control for any extraneous variables: EMT+PE or the usual-care intervention. Block randomized trials will be conducted for each age group using the blockrand package in R software (version 4.1.3; The R Foundation). Randomization will be based on age (3 age groups) and the 2 interventions. The flow of participants through the study is illustrated using the CONSORT (Consolidated Standards of Reporting Trials) flowchart in Figure 1.

Blinding of Raters and Reliability of the Data

Trained and experienced raters who are blinded to the grouping of participants will transcribe audio and video samples of speech and language. The samples will be collected from the parents at home as they are interacting with their children using toys and pictures, using the Profiles of Early Expressive Phonological Skills (PEEPS) assessment.

Intervention

EMT+PE Intervention

The EMT+PE intervention consists of implementing supportive speech and language strategies by parents in their interaction with their children. All parents will be trained in accordance with the Teach-Model-Coach-Review (TMCR) instructional model that has been adapted for the telepractice environment [9,30]. The Teach component of the instructional approach involves introducing targeted supportive strategies. The Model component includes the implementation of strategies by a clinician when interacting with a child—we will implement this component by showing recorded video examples of strategies. The Coaching aspect entails parents using strategies during their interaction with their children. The Review component includes monitoring and evaluating the entire session and planning for the next session at the end of every session. EMT+PE treatment principles for the intervention group are illustrated in Figure 2.

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Figure 2. Principles of the EMT+PE (Enhanced Milieu Teaching with Phonological Emphasis) intervention. EMT: Enhanced Milieu Teaching.

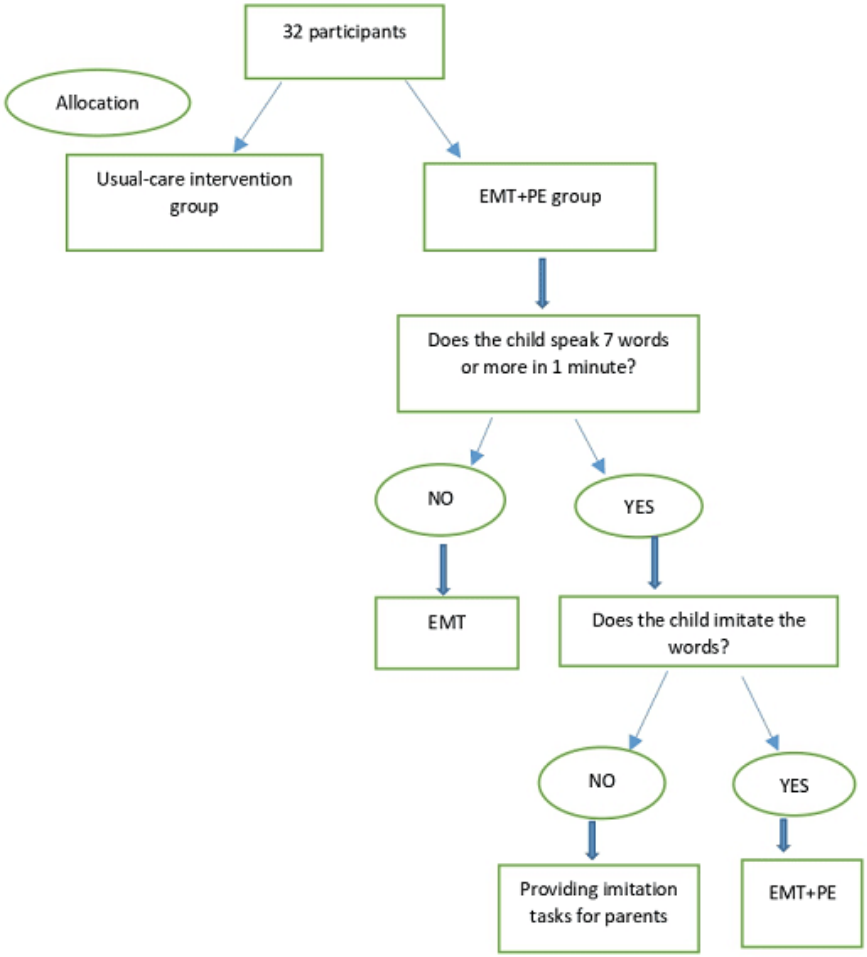

Speech Target Selection

Speech targets for each child are determined by analyzing the errors produced in their speech sounds during the PEEPS assessment. A list of sample words will be created from the speech sound errors observed in the children's PEEPS assessment. To select the target speech sounds, developmental norms and the frequency of speech sound errors related to cleft palate, including high-pressure and fricative consonants in words with the syllabic consonant-vowel-consonant-vowel structure, are taken into account. For each child, place, and manner of articulation, pre- and postvocalic voicing are considered. Once a participant can produce 7-10 words per minute, a speech recast strategy is integrated into the intervention process.

Usual-Care Intervention

Children assigned to the usual-care intervention (control) group will be assessed twice before and after the 3-month intervention. If they are not, they will be enrolled in cleft teams. They will receive speech and language therapy there in accordance with a specific protocol. Regular evaluations administrated every 3-6 months, are part of the usual speech and language intervention for children aged up to 3 years undergoing team care. Based on each child's evaluation, early counseling is provided to parents in person or remotely. Parents are expected to apply the recommendations provided until the next visit. The EMT+PE will not be administered to participants in the control group throughout the experimental intervention period.

Procedure

Therapist Training

We will recruit 3 eligible SLPs based on the study inclusion criteria. The process of implementing the protocol will be explained to them by the first author; if they are responsible for implementing it, they will participate in training sessions. They will receive training regarding the study methodology, participants, EMT+PE intervention, strategies, and fidelity of implementation for therapists and parents. SLPs will receive at least 3 in-person training sessions in accordance with the TMCR instructional model. For the Teach component, the research team will introduce speech and language strategies and their rationale. For the Model component, video examples related to the implementation of strategies by professional therapists in interacting with a child with a language disorder will be shown [12]. In the Coach component, therapists will implement strategies through role-playing. Thereafter, for the Review component, all training sessions will be monitored by researchers and therapists, and questions related to session content will be discussed and answered. For the competency-based assessment according to telehealth fidelity scales, each therapist will train a parent of a child with CP/L on the telegram platform so that the groups will consist of a therapist, a parent, and the main researcher. Then, the therapist

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will train the parent in at least 1 language strategy during offline and web-based sessions, and the parent will send a video of using the trained strategy when interacting with her child. Two independent experts will observe the skills-based assessment sessions and rate the therapists' performance using telehealth fidelity scales.

Parent Training

Parents will receive training on specific strategies and apply them while interacting with their children at home. The competency-based assessment of parents will be defined using fidelity scales that are based on the trained strategies. The therapist will connect with parents twice a week for 3 months during the intervention course. The training sessions will be held in both offline and web-based modes. The therapist will share the material with the parents during offline sessions to teach them the strategies. For the model component, the therapist will send video examples of the strategies to the parents. Parents will be provided sufficient time to study the documents and view the video examples of the strategies. At the next stage of the administration process, the therapist will schedule a video call with the parents and they will discuss the content of the documents and video examples that would be sent, and talk about how to apply the strategies when interacting with their child. After the discussion, the parents will submit a video that shows them implementing the taught strategy. The therapist will review the videos sent. Next, the weaknesses and strengths of the video will be described on the basis of a fidelity checklist through a video call. Trainees will learn 7 supportive speech and language strategies that are arranged hierarchically from easy to difficult, including environment arrangement, match turns, modeling, prompting, time delay, expansion, and recasting [12,22]. The environment arrangement strategy aims to enhance the child's engagement with the physical setup by selecting, arranging, and managing materials. In the matched turns strategy, parents are encouraged to match their turns of conversation with those of their child and carry out language mapping, in which parents are encouraged to mirror their child's actions during play and incorporate language into the shared actions. Modeling involves a verbal model by the parent in which the child is encouraged to imitate. In the prompting strategy, the parent encourages the child to use an utterance at the target level in a conversational interaction. In the time delay strategy, parents encourage their child to promote initiation by providing nonverbal cues rather than relying on verbal models and commands; this includes assistance, pause in routine action (when the parent is interacting with their child), visual selection, and inadequate portion (ie, parents must ensure that the toys or equipment that they provide to their children are complete and ready to use; for example, if a doll is in a box, the child may require assistance in unboxing it and starting to play with it). In the expansion strategy, the parents repeat their child's utterance and add a word or phrase to complete its utterance. Speech recasting involves repeating a child's phrases with modified grammar or speech production (or both).

Rater Training

The child's speech and language samples are transcribed by 4 experienced and trained raters who are blinded to the child's group allocation (intervention or control). Before transcribing the samples, they will be provided instructions on how to rate the samples. To assess the reliability of the data, 25% of each rater's samples will be scored by an independent expert. In case of inadequate agreement (ie, <85%) differences will be identified, and the samples will be reevaluated.

Fidelity Assessment

Fidelity of Implementation for Therapists

Therapist fidelity will be assessed using an observational checklist with Likert scales. This checklist is designed in accordance with the components of the TMCR instructional model and the telepractice environment (Kaiser Telehealth Fidelity Scale). The checklist includes 5 sections: teach, model, coach, review, and overall interaction. Each section has several statements to measure implementation quality by the therapist. After training sessions with the therapists and before starting the intervention, they will be assessed using the fidelity checklist while delivering the intervention to a parent. The reliability of each therapist will be assessed (Multimedia Appendix 1).

Fidelity of Implementation for Parents

Parents' ability to implement the trained EMT+PE strategies with procedural fidelity will be determined through formative visual analysis based on established learning criteria. To ensure fidelity, therapists and an independent expert will assess parents' use of each strategy during 8 monthly sessions, using a checklist. The criteria for the strategies are as follows: environment arrangement (80%), language mapping (75%), match turns (75%), expansions (50%), modeling (40%), child's target level (50%), prompt (80%), delay (80%), and speech recast (40%). The reliability of parents' fidelity will be measured during the intervention [12,13] (Multimedia Appendix 2).

Data Collection

In total, 32 children with CP/L in different provinces of Iran (Isfahan, Tehran, and Shiraz) who meet the primary inclusion criteria will be recruited. Next, the first author will call the parents and explain the process and the study's terms of acceptance. Then, she will schedule a web-based session to complete the assessment. Parents will complete demographic information forms followed by the Age and Stages Questionnaire for their children's developmental screening. Parents will collect speech and language samples before and after the intervention for their child in the naturalistic environment (Multimedia Appendix 3).

Primary Outcomes

Speech Outcome Measures

The early phonological development of Persian-speaking monolingual children with CP/L is assessed using the Persian adaptation of the PEEPS assessment, which focuses on early acquired vocabulary [31]. The PEEPS assessment consists of 60 words that are expected to be expressed by Persian-speaking monolingual children aged 18-36 months. When administering the PEEPS assessment, an assessor first presents a picture or toy to the child as a target word; at this stage, the child is expected to respond independently. If the child does not respond,

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the assessor asks a question that requires the child to cue a specific word (eg, "What is this?"). If the child fails to respond again, the assessor utters a sentence that the child must complete with the target word (eg, "The baby has..."). Finally, if the child cannot produce the target word despite these cues, the assessor provides a direct command (eg, "Say..."). If the child still cannot produce the target word in response to the final command, it is marked as having provided no response.

In this study, the PEEPS assessment will be administered to assess consonant inventory based on the word-initial and word-final consonants. Also, the accuracy of speech production will be assessed by determining the total PCC, PCC stops, whole structure match, and whole-word accuracy match by an expert during a web-based session [32,33]. The evaluation session will be recorded. If the child does not participate actively in the web-based PEEPS assessment session, the parent will follow the assessor's instructions to record their child's responses to the speech sample and send them to the assessor.

The second version of MCDI provides parents with a categorized vocabulary list and asks them to indicate whether their children can express each word or phrase. The scale has 2 sections and assesses 680 expressive vocabulary items in 22 semantic categories among young children aged 16-30 months [34].

Language Outcome Measures

During the assessment, parents will engage in play sessions with their children using various toys. A 15-minute language sample will be collected remotely to determine the child's number of different words, number of total words, and language complexity measured by mean length utterances. The assessment session will be video recorded. If the child does not engage during the web-based assessment session to collect language samples, the parent will follow the assessor's instructions for recording the child's responses and send the video recording to the assessor.

Secondary Outcomes

Speech intelligibility will be measured using the Intelligibility in Context Scale, which is a parent-reported social validity tool [35]. The intelligibility rating is determined by the average response on a 5-point rating scale over 7 questions [36].

>Parents will be required to complete a postintervention satisfaction survey. The questionnaire aims to measure parent satisfaction with the telepractice EMT+PE intervention and parent training sessions (Multimedia Appendix 3).

Statistical Analysis

Analysis

The analysis will be carried out using descriptive and analytical statistics. Descriptive statistics appropriate for summarizing demographic information and assessment data will be used. Preintervention differences between groups will also be estimated. The data analysis will be carried out using the SPSS (version 19; IBM Corp). The study's outcomes will be presented as an estimation of the difference between groups, with a 95% CI and its associated *P* value. The statistical significance level will be set at α=.05. We will use analysis of covariance, an efficient statistical test that provides impartial estimations of an intervention's effects, assuming random treatment assignment; this test is more powerful than other alternative statistical strategies. We will also carry out a paired samples *t* test, which compares the means of 2 variables within a single group; it estimates the differences between the values of 2 variables for each case and tests whether their average is significantly different from 0. Additionally, data from all randomized participants will be included in the intention-to-treat analysis.

Intended Sample Size

Based on comparable studies with a 95% confidence level, 80% power of the test, variance of 0.0036 units, and an accuracy (improvement) of 0.06 units in the PCC, each group requires a maximum sample size of 16 participants.

Ethical Considerations

Participants' safety risk will not be increased by participating in this trial. Each participant's information will be stored under a unique number, and the coded information will be appropriately stored. When the research is completed, the results will be presented at scientific conferences or published in scientific journals, and the identities of study participants will remain confidential. The parents will be required to complete the informed consent form before participating in the study, and both the researcher and the participant must sign the document, with a copy provided to the participant. This study has been approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences, Iran (IR.USWR.REC.1400.310).

Results

The protocol was approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences in February 2022. The selection process of participants, training therapists, and raters, commenced in January 2022, the therapy and follow-up periods ended in June 2023, and pre- and postintervention assessments have been conducted. Data analysis is ongoing, and we expect to publish our results by the summer of 2024. Funding is yet to be obtained.

Discussion

This study is the first RCT with follow-up, which aims to develop a protocol to evaluate the effect of parent-based EMT+PE through telepractice in Persian-speaking toddlers with nonsyndromic cleft palate.

In this study, the impact of the interventions will be evaluated by language and speech outcomes as primary outcome measures. Language outcomes include a vocabulary inventory, collected using the MCDI, mean length utterances, number of total words, and number of different words, collected through language samples and during the parent-child interaction. Speech outcomes including PCC, consonant inventory, whole-word accuracy match, and whole structure match will be collected during the PEEPS assessment. The effect of interventions will be examined for 12 weeks, with an additional 8-week follow-up

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period for the EMT+PE group to exclude any temporary effects that may have limited clinical value. Our results will provide information about the efficacy of the parent-implemented EMT+PE telepractice intervention in enhancing speech skills while also promoting speech production and language measures and its stability over a prolonged period. In addition, we will obtain parents' satisfaction and score on the Intelligibility in Context Scale before and after delivering interventions as secondary outcome measures. Improvement of speech intelligibility is a long-term target of most speech therapy interventions.

The study's limitations include its small sample size for each age group. To address the effects of such interventions, a larger-scale clinical trial is necessary. Additionally, the intervention and follow-up periods are limited in demonstrating effects. It is important to note that toddlers are in different age ranges and may require more time to develop their language and speech skills.

In summary, we anticipate demonstrable effects of the parent-implemented EMT+PE telepractice intervention on language and speech outcomes in toddlers with CP/L; these should specifically include not only an extended vocabulary inventory but also an improved consonant inventory and speech intelligibility. This study's results may help develop a specific intervention with a different delivery model for toddlers. Parent training through telepractice has multiple benefits for families, including providing therapy for children with speech-language disorders, reduced costs, unrestricted access to therapy services for people living in rural areas, and saving time and expenses [24-26]; therefore, cleft care teams can harness our results in service delivery.

Acknowledgments

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Data Availability

The research team will retain all the data obtained from the study. In compliance with applicable legal and statutory obligations, the coordinating principal investigator will archive all study-related documents for 5 years upon completion of the study.

Authors' Contributions

All authors contributed to the protocol's design, construction, and writing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Telehealth Fidelity Scales.
[PDF File (Adobe PDF File), 314 KB - resprot_v13i1e54426_app1.pdf]

Multimedia Appendix 2
EMT+PE Fidelity Rating Form. EMT+PE: Enhanced Milieu Teaching with Phonological Emphasis.
[PDF File (Adobe PDF File), 157 KB - resprot_v13i1e54426_app2.pdf]

Multimedia Appendix 3
Study timeline.
[DOCX File , 24 KB - resprot_v13i1e54426_app3.docx]

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Abbreviations

CLP: cleft lip and palate
CONSORT: Consolidated Standards of Reporting Trials
CP/L: cleft palate with or without cleft lip
dB HL: decibels in hearing level
EMT: Enhanced Milieu Teaching
EMT+PE: Enhanced Milieu Teaching with Phonological Emphasis
MCDI: Macarthur-Bates Communicative Development Inventory
PCC: percentage of correct consonants
PE: Phonological Emphasis
PEEPS: Profiles Of Early Expressive Phonological Skills
RCT: randomized controlled trial
SLP: speech-language pathologist
TMCR: Teach-Model-Coach-Review

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Protocol

Testing the Effectiveness of an Intervention to Improve Romanian Teachers' LGBT+-Related Attitudes, Cognitions, Behaviors, and Affect: Protocol for a Randomized Controlled Trial

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Abstract

Background: Repeated stigmatization due to group membership constitutes a recurrent stressor with negative impact on physical and mental health (minority stress model). Among European countries, Romania ranks low on LGBT+ (lesbian, gay, bisexual, and transgender people. The "+" represents individuals whose identities do not fit typical binary notions of male and female [nonbinary]) inclusion, with 45% of Romanian LGBT+ respondents reporting discrimination in at least 1 area of life in the year preceding the survey. Importantly, while all LGBT+ people might experience minority stress, younger sexual minority individuals are more prone to the detrimental impacts of stigma on their mental and physical health. As such, interventions are necessary to improve the inclusion climate within schools, where young people spend most of their time. Until now, most interventions addressing this topic have been conducted on undergraduate students in Western countries, with no studies conducted in countries that have widespread anti-LGBT+ attitudes.

Objective: This paper describes the research protocol for a randomized controlled trial investigating whether LGBT+ stigma and bias among Romanian school teachers can be reduced using an internet-based intervention focusing on education and contact as primary training elements.

Methods: A sample of 175 school teachers will be randomly assigned to either the control or experimental group. The experimental group participants will receive the intervention first and then complete the outcome measures, whereas the control group will complete the outcome measures first and then receive the intervention. The 1-hour multimedia intervention is developed for internet-based delivery under controlled conditions. It includes 2 interactive exercises, 2 recorded presentations, animations, and testimonies from LGBT+ individuals. Data for attitudinal, behavioral, cognitive, and affective measures will be collected during the same session (before or after the intervention, depending on the condition). We also plan to conduct a brief mixed methods follow-up study at 6 to 8 months post participation to investigate potential long-term effects of training. However, due to attrition and lack of experimental control (all participants will have completed the intervention, regardless of the condition), these data will be analyzed and reported separately using a mixed methods approach.

Results: This paper details the protocol for the teacher intervention study. Data collection began in December 2022 and was completed by February 2023. Data analysis will be performed upon protocol acceptance. Follow-up measures will be completed in 2024. Results are expected to be submitted for publication following analysis in the spring of 2024.

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Conclusions: The findings of this study will establish the effectiveness of an internet-based intervention intended to lessen anti-LGBT stigma and sentiment in a nation where these views have long been prevalent. If successful, the intervention could end up serving as a resource for Romanian teachers and guidance counselors in high schools.

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KEYWORDS

discrimination; intervention; school; lesbian, gay, bisexual, and transgender; attitude; behavior; cognition; stigma; stigmatization; negative impact; physical health; mental health; minority stress model; European; Europe; Romania; stress; young; student; students; undergraduate; bias; data analysis; online intervention; lesbian, gay, bisexual, and transgender stigma; sentiment

Introduction

Overview

The experience of stigmatization based on group membership can lead to negative effects on physical and mental health via repeated experiences of stress which, in the long term, accumulate to impact health negatively (minority stress model) [1]. Stigmatization can occur based on membership in any group that is discriminated against. In this research, we focus on LGBT+ (lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female [nonbinary]) stigmatization and its reduction in Romania.

Among European countries, Romania tends to fare poorly when it comes to LGBT+ inclusion. A recent survey [2] showed that 45% of Romanian LGBT+ respondents felt discriminated against in at least 1 area of life during the year before the survey. Similarly, 43% of respondents experienced harassment due to being LGBT+, a rate that ranks second among all European countries. Much of this discrimination and harassment happens in schools for young people, with 44% of LGBT+ students (15-17 years of age) in Romania saying they are hiding being LGBT+ at school, a rate that is 3 to 4 times higher than in countries such as Luxembourg (11%), the Netherlands (16%), or Malta (17%). Indeed, schools seem to be a fertile ground for LGBT+ harassment, with 51% of incidents involving perpetrators from schools [2], a finding reinforced by a UNESCO (The United Nations Educational, Scientific and Cultural Organization) report on school violence [3].

Such high rates of LGBT+ discrimination among Romanian students are concerning, because stigma impacts young LGBT+ people's mental and physical health. A meta-analysis [4] including 35 studies of over 2 million heterosexual young people and over 100,000 LGBT+ young individuals (age range 12-20 years) showed that suicide risk was higher for LGBT+ young people compared to those who were not LGBT+. For every heterosexual young person, the chance of suicide was 3.71 higher for gay and lesbian young people, 4.87 higher for bisexual youth, and 5.87 higher for young transgender people. This risk is paired with a higher likelihood for sexual minority youth to experience mental health issues such as anxiety and depression but also impaired academic performance [5]. The findings for sexual minority youth are consistent with sexual minority individuals in general—a systematic review showed that the majority of studies revealed a higher risk for mental health issues, substance abuse, and suicide risk for sexual minorities [6]. LGBT+ people are also more likely to endure physical health issues due to minority stress, including an increased risk for cancer, cardiovascular disease, and chronic conditions such as asthma and diabetes [7].

Importantly, although minority stress can affect all LGBT+ people, younger sexual minority individuals seem to be most vulnerable to the negative effects of stigma on their mental and physical health. A meta-analysis indicated age as a significant moderator, such that youth younger than 17 years of age experienced higher negative outcomes due to LGBT-related victimization compared to those older than 17 years of age [8].

Together, these findings indicate a strong need to implement effective interventions to reduce LGBT+ stigma and bias in Romanian schools, to improve the mental and physical health of LGBT+ students in Romania. These interventions may be most efficient particularly among teachers, as they can impact their students' experiences either directly or indirectly, via establishing inclusivity norms in the classroom.

To be effective, interventions should not only focus on reducing teachers' biases toward LGBT+ students, but also on learning, implementing, and modeling behaviors that would equip them to intervene when students experience LGBT+-related victimization. A meta-analysis [9] showed that interventions can be moderately successful in reducing sexual prejudice, resulting in changes ranging from one-third to one-half of an SD in size. Moreover, the meta-analysis specified the most effective strategies in reducing different outcomes—educational interventions, contact with LGBT+ individuals, and interventions combining education with contact. A more careful analysis reveals that most intervention studies have been conducted on undergraduate students in Western countries and none in Eastern Europe or other countries with strong antigay attitudes. Although more recent research has started to test interventions in other countries such as Jamaica [10] or Brazil [11], no such adaptation exists in Romania (or Eastern Europe), particularly for teachers. Adapting interventions to the cultural and institutional context seems vital, given that a recent qualitative analysis suggests that participants tend to criticize many interventions for their mismatch with the context in which they are conducted, possibly as a rationale for resisting change [12].

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The primary goal of this research line is to design and test an intervention that is geared toward Romanian teachers. Importantly, we plan to achieve this goal by deliberately taking into account specific cultural and institutional characteristics, rather than indiscriminately applying previous intervention strategies. More specifically, although we plan to use education and contact as primary training elements, consistent with meta-analytic findings [9], we plan to design the educational components to respond to the needs of our particular target group. For example, we drew from recent research conducted in Russia [13], a country with a similar culture and history regarding LGBT+ attitudes. Building on these findings, we propose that the educational component should include information regarding the biological (vs social) causes of homosexuality, given that attributions of causality are related to perceived threat, and subsequently lead to biased outcomes. In addition, given the importance of threat in predicting antigay bias, and consistent with intergroup threat theory [14], education should explicitly address potential feelings or perceptions of threat (for example, the perception that exposure to LGBT+ people will "make" children gay).

A second novel aspect is that the intervention will aim not only to improve attitudes and knowledge as an outcome but also target behavioral change by imparting tools that teachers can use to address LGBT+-related victimization in schools. This strategy has been used successfully in the past in a web-based intervention program for Brazilian health practitioners [11]. As a result, we are likely to increase the impact of the intervention of LGBT+ students, not only by improving the inclusion climate within the schools but also by improving teachers' actual behavioral intentions and skills that may improve LGBT+ students' outcomes.

Aims and Hypotheses

In this research, we design and report the protocol of a randomized controlled trial (RCT) intervention and evaluation. The intervention is based on existing evidence about the efficacy of strategies identified in Bartoş et al's [9] meta-analysis. According to their results, the most effective strategies in reducing LGBT+ stigma combine educational elements with contact with LGBT+ people. We also add elements that were found to be useful in other bias-reducing interventions such as perspective taking [15] and self-efficacy [16,17], and which we deem culturally appropriate. A summary of intervention components, subcomponents, and contents is presented in Table 1. For each element, we include the supporting reference, as an evidence base for their efficiency in reducing bias.

Using an RCT in which teachers are randomly assigned to complete the intervention before assessing outcomes (experimental) or after assessing outcomes (control), we predict that the intervention will have a positive effect on attitudinal, cognitive, behavioral, and affective measures of LGBT+ bias among teachers. Specifically, we predict that teachers randomly assigned to the experimental condition, compared to those randomly assigned to the control condition will experience (1) more positive attitudes toward LGBT+ individuals, (2) more factual knowledge about LGBT+ issues, (3) stronger behavioral intentions and self-efficacy about addressing LGBT+ issues in the classroom, and (4) more positive affect toward LGBT+ individuals.

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Table 1. Training elements for the randomized controlled trial intervention designed to improve Romanian teachers' LGBT+[a] related attitudes, cognitions, behaviors, and affect[b].

Intervention component and subcomponent	Duration and timestamps	Content and supporting references
Introduction	• Duration: 02 minutes 50 seconds • Timestamps: 00.00-02.50	Introduction from academic research team, highlighting the goals and the evidence-based nature of the intervention
Education [9]		
Definition of terms	• Duration: 05 minutes 40 seconds • Timestamps: 02.50-08.30	• Definition of LGBT+ terms • Definition of sexual orientation • Differentiation between sex versus gender • Definition of intersex • Description of gender identity and transgender
Threat reduction	• Duration: 03 minutes 40 seconds • Timestamps: 08.30-12.10	• LGBT+ children and their families: meta-analysis on children raised by LGBT+ families • Sexuality and sexual orientation in humans and animals. • Normalizing varied sexual orientations across species • The function of same-sex sexual behavior in ensuring survival
Effects of stigma to understand minority stress [1]	• Duration: 05 minutes 35 seconds • Timestamps: 12.10-17.45	• Suicide rates of LGBT+ youth • The role of stress from exposure to prejudice, ridicule, physical, and verbal aggression in understanding mental health outcomes • The role of social support and family or school acceptance in improving mental health and the danger of conversion therapy • Bullying as a special case of discrimination, types of bullying, the role of sexual orientation
Behavioral tools [11]	• Duration: 04 minutes 00 second • Timestamps: 24.45-28.45	• Presentation of tools that can be used by teachers, including the following: • Romania's new antibullying law and bullying protocol in schools • Lesson plans to discuss and combat bullying in the classroom • UNICEF[c] intervention model for bullying • Procedure to report bullying and harassment with the Romanian National Council for Combating Discrimination • Support groups for LGBT+ students in Romania • For all resources links were shared in the presentation and then sent in PDF format to all participants
Perspective taking [15]		
Writing exercise, 7 minutes	• Duration: 07 minutes 00 second • Timestamps: 17.45-24.45	• Writing prompt: "Imagine a day in the life of a gay student—write a few paragraphs about what this student is living and feeling on a school day. What are his/her thoughts and feelings that day? Please write down your answers."
Contact [9,10]		

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Intervention component and subcomponent	Duration and timestamps	Content and supporting references
Indirect contact via recorded testimonials	• Duration: 15 minutes 00 second • Timestamps: 28.45-43:45	• Video testimonials of 3 university students (1 gay man, 1 bisexual woman, and a lesbian woman) and 1 teacher (lesbian woman). • Testimonial prompts for students included the following: • Tell us about yourself • When did you come out? What were your barriers during this process • How was your experience in school? Were there teachers who supported you? • What would you have needed when you were a high school student? • What would you say to teachers to help them support their LGBT+ students? • Testimonial prompts for the teacher included the following: • Tell us about yourself • How do you see LGBT+ students' experiences in schools currently? • What is missing from our educational system in supporting LGBT+ students? • What would you say to teachers to help them support their LGBT+ students?
Self-efficacy		
Writing exercise, 5 minutes	• Duration: 5 minutes 00 second • Timestamps: 43.45-48:45	• Writing prompt: "Imagine now that, as a teacher, you are interacting with the student you previously imagined. For example, the student asks for your help in a discussion after class. Knowing what you know now about the LGBT+ community and how we can help LGBT+ students, please imagine this interaction in which you offer suggestions and support. What would you say to this student? Please write down your answers."
Conclusion	• Duration: 1 minutes 10 seconds • Timestamps: 48.45-49:55	• Acknowledging the advisory board representatives from the LGBT+ community for their input and feedback

[a]LGBT+: lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female (nonbinary).

[b]All intervention elements are drawn from empirical evidence. We present timestamps and specific content which is included in the multimedia intervention resource.

[c]UNICEF: United Nations Children's Fund.

Methods

Participants and Recruitment

We plan to collect data exclusively from teachers or counselors working in Romanian public schools. All participants will be required to speak Romanian because of the language used in the intervention and measures. Participants who complete the intervention will be sent a participation certificate which could be used for continuing education credits and are given the option to enter a raffle where they can win a 500 RON (equivalent to US $110) gift certificate.

Our recruitment strategy is to ask the local Center for Educational Resources and Assistance to distribute a message nationally, to all their members who are teachers or counselors employed in Romanian schools. If interested, they have the opportunity to sign up for 1 of the several sessions depending on their availability. The sessions are capped at 30, with an average of 25 participants signing up for each (range 24-27). We will advertise a total of 17 sessions across 3 months at different times during the day.

Study Design

This intervention's experimental design is an RCT. We use a 2-group random assignment design, such that participants are randomly assigned to either the experimental condition in which they receive the intervention first and then complete the outcome measures, or to a control condition in which they complete the outcome measures first and then receive the intervention. From an ethical perspective, we chose this design so that all participants will receive the intervention and associated resources by the end of their participation. From a validity perspective, the outcome measures of those in the control condition are not affected by the intervention, thus serving as an appropriate control comparison to participants in the experimental condition.

Participants will join sessions in groups of up to 30 participants, depending on their availability. Cluster randomization will be

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done at the session level, such that each session will be randomly assigned to either experimental or control conditions. Individual randomization within the session is not possible given that the intervention will be presented to all participants at the same time. Sessions will be scheduled across different times and days outside typical working hours, so we do not anticipate any systematic biases arising from participants' session choices. To ensure experimental control, each session will be led by 2 researchers who deliver scripted instructions, answer questions, and ensure all participants complete the study at a similar pace and with minimal distraction.

Intervention

The intervention is designed for internet-based delivery and is multimedia, containing a recorded presentation, animations, testimonials of LGBT+ people, as well as 2 exercises. Whereas the intervention is rooted in empirical evidence, we also ensured cultural sensitivity by collaborating with local LGBT+ educational and advocacy nongovernmental organizations who offered feedback on intervention components. A detailed summary of the evidence-based components, as well as timestamps and duration for each subcomponent, are included in Table 1.

Ethical Considerations

Ethics approval was obtained from the West University of Timisoara, Romania, ethical panel (74505/10.11.2022), based on an application containing the procedure, measures, and materials used. Upon being presented with detailed information regarding the study, informed consent will be obtained from all participants before starting their participation. All data will be anonymously collected, with no personal or identifiable information being recorded. All fully anonymous data will be stored on password-protected computers and servers. Compensation consists of a participation certificate which could be used for continuing education credits and the option to enter a raffle where they can win a 500 RON (equivalent to US $110) gift certificate. There is no identification of individual participants in any images within the paper.

Outcomes

Overview

With 1 exception (the factual knowledge variable), we will use validated scales to measure intervention outcomes. Where possible, we will use previously translated and validated scales in Romanian, selected from ResearchCentral repository, a free internet-based platform dedicated to the development of Romanian psychology by providing researchers with free, validated assessment tools. Where translations did not previously exist, 2 Romanian researchers, who are fluent in English, translated and then back-translated the scales to ensure accuracy. For all scales, before computing a final score, we will ensure sufficient reliability by computing Cronbach α, with a cutoff minimal score of 0.70.

Attitudinal

Overview

Given the wide divergence in the definition of antigay bias or homophobia, several scales have been developed across time [18] and will be used in this research.

Attitudes Toward Lesbians and Gay Men Scale

This 10-item scale measures beliefs and attitudes toward gay men and lesbians ("Sex between two men is just plain wrong" and "Female homosexuality is a perversion") [19]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse coding 4 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Homophobia Scale

This 25-item scale measures attitudes but also social avoidance and aggression toward gay people ("If I discovered a friend was gay I would end the friendship" and "I tease and make jokes about gay people") [20]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) on a Likert scale. After reverse coding 9 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Attitudes Toward Homosexuals Scale

This 12-item scale measures attitudes toward gay people ("Homosexuality is disgusting in the eyes of God" and "If I can, I prefer to not be in the company of homosexuals") [21]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) Likert scale. After reverse coding 5 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Behavioral

Behavioral Intentions

This 16-item scale measures intentions for supportive professional behaviors that teachers would perform in the classroom ("I would talk with a student about questions regarding sexual orientation" and "I would have books about gay and lesbian issues in my classroom") [22,23]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scores will be averaged into a final score with higher values denoting more willingness to engage in LGBT+ supportive behaviors in the classroom.

Self-Efficacy

This 10-item scale adapted the original scale to working with LGBT+ students in the school context ("If I try hard, I can solve difficult issues related to LGBT+ students" and "I can deal with unexpected situations that arise with LGBT+ students") [24]. Items were rated from 1 (Not at all true for me) to 4 (Perfectly true for me). Scores will be averaged into a final score with higher values denoting more self-efficacy in dealing with LGBT+-related behaviors in the classroom.

Cognitive: Factual Knowledge About LGBT+ Issues

We constructed 7 items based on training content to assess participants' knowledge about LGBT+ issues ("Gender is a biological construct, unrelated to cultural associations" and "Heterosexual youth are 1.5 to 3 times more likely to attempt

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suicide compared to LGBT+ youth"). Items are rated as true or false, and a final score will be computed by adding up the number of correct responses, with higher scores denoting more knowledge about LGBT+ issues.

Affective

Feeling Thermometer (1 Item Each for Gay, Lesbian, and Bisexual)

We will use a feeling thermometer [25] to assess participants' feelings toward gay, lesbian, and bisexual people by asking them to rate how they feel about each group using a slider thermometer scale from 0 (very negative feeling) to 100 (very positive feeling).

Perspective Taking

This 5-item measure assesses the extent to which participants take the perspective of LGBT+ people ("Can you imagine how an LGBT+ person feels?" and "Do you have an understanding of issues that are important for LGBT+ people") on a scale from 1 (Never) to 5 (All the time) [26]. Scores will be computed by averaging the 5 items, with higher final scores denoting more perspective-taking.

Intergroup Disgust Sensitivity

We adapted this 7-item scale to measure repulsion toward LGBT+ groups ("I feel disgusted when people with a different sexual orientation invade my personal space" and "After shaking hands with someone who has a different sexual orientation, even if their hands were clean, I would want to wash my hands.") [27]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) on a Likert scale. After reverse scoring 1 item, scores will be averaged into a final score with higher values denoting more disgust toward LGBT+ outgroups.

Intergroup Anxiety

This 10-item scale measures anxiety-related emotions when interacting with people of another sexual orientation by asking them to rate their likelihood of feeling several emotions (embarrassed, unsure, irritated, suspicious, etc) on a scale from 1 (not at all) to 10 (extremely) [28]. A total of 2 scores will be computed, 1 for positive emotions and another for negative emotions.

Toronto Empathy Questionnaire

This 16-item scale measures the general tendency to empathize with other people ("It upsets me to see someone being treated disrespectfully" and "I find that I am 'in tune' with other people's moods") [29,30]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse scoring 7 items, scores will be averaged into a final score with higher values denoting more empathy.

Demographic and Control Variables

Demographics

It consists of age, gender, and sexual orientation.

Contact With LGBT+ People

We will ask participants how often they have contact (eg, talk) with a gay man, a lesbian woman, a bisexual woman or man, or a transgender person on a scale from 1 (almost daily) to 6 (never).

Religiosity

Religiosity (Duke University Religion Index) [31] is a 5-item scale measure of religious involvement, measuring organizational religious activity, nonorganizational religious activity, and intrinsic religiosity (or subjective religiosity). Responses are averaged in 1 single score with higher scores denoting more religiosity.

Ideology

Ideology was measured by asking people to indicate their political orientation on a 100-point sliding scale from 0 (very conservative) to 50 (center) to 100 (very liberal or progressive).

Statistical Analysis

Power

To determine our sample size, we conducted a power analysis using an average effect size of d=0.66 computed from Bartoş et al's [9] meta-analysis to ensure a statistical power of 0.80. The analysis indicated a sample of 122, but we aim to overrecruit, if possible, up to 200 participants given multiple outcomes. We do not have a stopping rule—we will recruit until all interested participants are given the chance to participate within 1 of the 17 sessions posted.

Data Exclusion

We will use data from all participants who completed their participation in the study, without any exclusions. Before computing final scores for each outcome variable, we will ensure sufficient reliability using Cronbach α, using a threshold of 0.70. To test our hypotheses, we will perform a series of 1-way between-subjects ANOVAs to compare attitudinal, cognitive, behavioral, and affective outcomes between the participants in the experimental and control conditions. For the effective measures we will perform the analyses (1) while controlling for contact with LBGT+ individuals and (2) separately by LGBT+ status (given the nature of the measures). We will report F test and P values, as well as all descriptive statistics (n, mean, and SD). We will also compute Cohen d for estimating the effect size, using means and SDs. Violin plots in R ggplot2 will also be included to visually represent means, CIs, as well as score distributions for each outcome.

Results

This paper details the protocol for the teacher intervention study. Data collection began in December 2022 and was completed by February 2023. Data analysis will be performed upon protocol acceptance. Follow-up measures will be completed in 2024. Results are expected to be submitted for publication following analysis in the spring of 2024.

Discussion

This paper describes the research protocol design and planned evaluation of an RCT aimed at improving attitudinal, cognitive, behavioral, and affective outcomes in Romanian teachers regarding LGBT+ inclusion. Strengths of the intervention

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include its evidence-based nature—all components included were derived from research showing positive outcomes on LGBT+ or other bias reduction. All elements were, however, adapted to be appropriate and sensitive to the Romanian cultural system and educational context. The intervention was also engaging and multimedia, thus increasing engagement. Importantly, it offers evidence-based tools to further address LGBT+ biases and bullying in schools, thus, potentially leading to stronger behavioral effects.

Limitations include the fact that outcomes will be assessed immediately after the intervention, so we are unsure about the long-term effects, as well as whether potential positive effects further impact LGBT+ students' lives. Further studies should investigate the effects on a larger sample of teachers, with a wider range of initial attitudes toward LGBT+ inclusion.

If successful, however, the intervention has the potential of becoming a valuable, nationally available resource for teachers and high school counselors across Romania. The materials developed, especially those around education, perspective-taking, and self-efficacy can be further used to educate students about LGBT+ issues and increase their willingness and capacity to support LGBT+ peers. The findings resulting from this protocol are important, as they are the first to test the effectiveness of an evidence-based intervention in improving LGBT+ stigma in Romanian schools.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be published in anonymous form on Open Science Framework and the European Commission Funded Research (OpenAire) community platform. This will be done after the successful publication of the results.

Conflicts of Interest

None declared.

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Abbreviations

LGBT+: lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female (nonbinary)
RCT: randomized controlled trial
UNESCO: The United Nations Educational, Scientific and Cultural Organization

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Protocol

An Integrated mHealth App for Smoking Cessation in Black Smokers With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Black adults who smoke and have HIV experience immense stressors (eg, racial discrimination and HIV stigma) that impede smoking cessation success and perpetuate smoking-related health disparities. These stressors also place Black adults who smoke and have HIV at an increased risk of elevated interoceptive stress (eg, anxiety and uncomfortable bodily sensations) and smoking to manage symptoms. In turn, this population is more likely to smoke to manage interoceptive stress, which contributes to worse HIV-related outcomes in this group. However, no specialized treatment exists to address smoking cessation, interoceptive stress, and HIV management for Black smokers with HIV.

Objective: This study aims to test a culturally adapted and novel mobile intervention that targets combustible cigarette smoking, HIV treatment engagement and adherence, and anxiety sensitivity (a proxy for difficulty and responsivity to interoceptive stress) among Black smokers with HIV (ie, Mobile Anxiety Sensitivity Program for Smoking and HIV [MASP+]). Various culturally tailored components of the app are being evaluated for their ability to help users quit smoking, manage physiological stress, and improve health care management.

Methods: This study is a pilot randomized controlled trial in which Black combustible cigarette smokers with HIV (N=72) are being recruited and randomly assigned to use either (1) the National Cancer Institute's QuitGuide app or (2) MASP+. Study procedures include a web-based prescreener; active intervention period for 6 weeks; smartphone-based assessments, including daily app-based ecological momentary assessments for 6 weeks (4 ecological momentary assessments each day); a video-based qualitative interview using Zoom Video Communications software at week 6 for participants in all study conditions; and smartphone-based follow-up assessments at 0, 1, 2 (quit date), 3, 4, 5, 6, and 28 weeks postbaseline (26 weeks postquitting date).

Results: Primary outcomes include biochemically verified 7-day point prevalence of abstinence, HIV-related quality of life, use of antiretroviral therapy, and HIV care appointment adherence at 26 weeks postquitting date. Qualitative data are also being collected and assessed to obtain feedback that will guide further tailoring of app content and evaluation of efficacy.

Conclusions: The results of this study will determine whether the MASP+ app serves as a successful aid for combustible cigarette smoking cessation, HIV treatment engagement, and physiological stress outcomes among Black people with HIV

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infection. If successful, this study will provide evidence for the efficacy of a new means of addressing major mental and physical health difficulties for this high-risk population. If the results are promising, the data from this study will be used to update and tailor the MASP+ app for testing in a fully powered randomized controlled trial that will evaluate its efficacy in real-world behavioral health and social service settings.

Trial Registration: ClinicalTrials.gov NCT05709002; https://clinicaltrials.gov/study/NCT05709002

International Registered Report Identifier (IRRID): PRR1-10.2196/52090

(JMIR Res Protoc 2024;13:e52090) doi:10.2196/52090

KEYWORDS

smoking cessation; Black; HIV; anxiety sensitivity; mobile health; mHealth; just-in-time adaptive intervention; mobile phone

Introduction

Background

People with HIV/AIDS smoke at a rate 3 times higher (33.6% vs 12.5%) than that of the general population [1,2]. This group is also less likely to quit smoking and is more susceptible to the harmful effects of smoking (eg, increased risk for cancer and lung disease) [1,3,4], likely due to the combined impact of several social determinants of health, including behavioral risk factors, limited resources, and diminished access to health care, as well as immune system dysfunction and chronic inflammation caused by HIV [5-10]. Indeed, cigarette smoking is a leading risk factor for HIV-related and non–HIV-related morbidity and mortality among people with HIV/AIDS [11,12], even among those taking antiretroviral medications [13], and contributes to more life-years lost than HIV-related complications among those effectively treated with antiretroviral therapy (ART) [13-15]. Furthermore, people with HIV/AIDS who smoke are less adherent to ART than nonsmokers and experience poorer viral and immunologic responses to ART [16,17], a greater risk of virologic rebound, and more frequent immunologic failure [18].

Among people with HIV/AIDS who smoke, those who identify as members of a racial minority group are at an elevated risk for negative health consequences of smoking and poorer HIV-related outcomes. Evidence suggests that Black adults with HIV, in particular, experience high rates of discrimination and stigma that lead to the onset and maintenance of maladaptive coping, including smoking [19,20]. Consistent with these data, Black adults with HIV are more likely to smoke [4], less likely to quit [4,21-24], and experience greater quit difficulty when attempting to quit than White smokers or smokers without HIV [21]. Black adults with HIV also have lower rates of compliance with routine HIV care (ie, ART adherence), retention in long-term care, and are less likely to be virally suppressed relative to other groups [25-28]. This is a public health problem because Black adults account for the highest proportion (42%) of new HIV diagnoses and experience higher mortality than White adults with HIV [25,27,28]. From an intersectional stigma and discrimination perspective and socioecological models of social determinants of health [29,30], Black adults who smoke and have HIV may be at elevated risk for worse HIV disease management and smoking outcomes and ultimately experience increased health disparities [6].

Emotional models of coping suggest that Black adults with HIV may smoke and continue to smoke despite health problems to manage interoceptive stress and uncomfortable physiological arousal associated with minority status stressors such as racial discrimination and HIV-related stigma. Anxiety sensitivity (AS) is one of the most noteworthy constructs related to physiological distress and manifestations of elevated internal distress, including psychopathologies. AS refers to the fear of anxiety or anxiety-related symptoms [31]. AS amplifies negative mood states via enhanced threat perception (eg anxiety) [32,33], contributing to the development of anxiety and depressive problems [34]. Notably, anxiety and depression contribute to an increased likelihood of poor ART adherence [35]. Among people with HIV/AIDS, AS is related to more severe social anxiety symptoms, anxious arousal symptoms, HIV-related stigma, and HIV symptom distress [36,37]. AS has also been implicated as a contributing factor in smoking initiation, maintenance, and relapse [38,39]. Emerging data indicate that AS is elevated in both Black adults who smoke and people with HIV/AIDS who smoke [40], placing this group at greater odds of early lapse and relapse [41,42]. Without appropriate interventions to address susceptibility to the negative impact of interoceptive stress, Black adults with HIV who smoke and have elevated AS may be inclined to return to smoking to alleviate abstinence-induced increases in anxiety and to manage uncomfortable HIV-related bodily symptoms that may increase with smoking cessation.

Although smoking cessation treatments that target AS exist, they are limited in their reach, adaptability, and potential for adoption and do not consider critical barriers to smoking cessation or HIV treatment engagement and adherence. For example, current combined AS and smoking treatments focus primarily on multisession, intensive treatments, particularly those that rely on in-person, clinician-administered psychosocial protocols [43-46]. Participation in these treatments often requires notable time commitments, practical limitations, and expense [47]. Such burdens are barriers to treatment and may contribute to the low treatment participation rates [47]. An additional limitation of current treatments is that no readily available smoking cessation treatments that target AS integrate information to improve HIV treatment engagement and adherence. Given the robust evidence that targeting AS and promoting smoking cessation may lead to improved HIV outcomes, this is a major limitation. Finally, the required human resources, specialized training, and financial support that are needed to administer currently available combined AS and

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smoking treatments discourage the adoption of these treatments in communities most in need, such as those that serve Black adults with HIV who smoke. Therefore, it is essential to develop a digital AS intervention that can be culturally adapted for this population.

Objectives

On the basis of our prior work [48], we modified our previously developed and tested novel, integrated, smartphone-delivered intervention for AS reduction and smoking (ie, Mobile Anxiety Sensitivity Program [MASP]) [49] for Black people with HIV/AIDS who smoke, integrating HIV information and care support that is culturally tailored to create the new smartphone-based app: Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+). MASP+ contains features and content designed to aid Black adults with combustible smoking cessation, HIV care adherence, and AS reduction. The initial efficacy of MASP+ relative to an established control intervention, the National Cancer Institute's (NCI) QuitGuide app, on combustible cigarette smoking cessation, HIV-related outcomes, and AS reduction is currently being tested in a pilot randomized controlled trial (RCT). We expect that MASP+ participants will report greater biochemically confirmed smoking abstinence at 26 weeks postquitting date relative to the QuitGuide group. In addition, we hypothesize that MASP+ participants will report greater HIV-specific quality of life, ART adherence, and HIV treatment engagement at 26 weeks postquitting date relative to the QuitGuide group. Finally, we expect that improvement in AS will mediate the relationship between treatment and (1) smoking abstinence and (2) HIV-related outcomes and that daily experiences of discrimination (race and HIV) will moderate these relationships. We will also examine qualitative and quantitative data to guide the refinement and further adaptation of MASP+ and support the development of a high-quality, culturally relevant, and scalable intervention.

Methods

Ethical Consideration

The Institutional Review Board at the University of Houston (UH) approved the protocol presented in this study under STUDY00003811, whereas the University of Oklahoma Health Sciences Center and Baylor College of Medicine relied on the UH Institutional Review Board. This trial has been registered at ClinicalTrials.gov (NCT05709002; protocol ID: QKWEF8XLMTT3).

Study Eligibility

The study eligibility criteria included being aged ≥18 years, having HIV, self-identification as Black or African American, providing a current picture of their cigarette package to verify smoking status [48], possessing at least a grade 6 reading level (≥4 on the Rapid Estimate of Adult Literacy in Medicine [REALM]) [50], experiencing elevated AS (ie, Short Scale Anxiety Sensitivity Index [SSASI] score of ≥5) [51], reporting daily smoking with a minimum of 10 cigarettes per day for at least 2 years, being motivated to quit smoking (>5 on a 10-point scale) [52], willingness to complete all study surveys or assessments, agreeing to use nicotine replacement medications (nicotine replacement therapy [NRT]; nicotine patch and lozenges), and agreeing to attempt to quit smoking 2 weeks after the date of randomization. Exclusion criteria included not being fluent in English; high blood pressure that is not under control (eg, medicated); experiencing a heart attack (myocardial infarction) within the past 2 weeks; use of any pharmacotherapy targeting smoking cessation beyond what is provided by this study; legal status that would interfere with participation (eg, incarceration with restricted access to mobile devices); cognitive impairment (assessed via the 6-item Cognitive Impairment Test) [53]; and being non-Black, pregnant, or younger than 18 years.

Recruitment and Procedures

Participants are recruited via web-based advertisement materials, as well as physical materials placed throughout the city of Houston. Study materials provide contact information for UH if a potential participant has questions about the study. Study advertisements also include a QR code linked to a REDCap (Research Electronic Data Capture; Vanderbilt University) prescreener survey. Those who complete the prescreening are deemed either ineligible or pre-eligible. For those recruited from Thomas Street at Quentin Mease Health Center, a clinic in Houston that provides routine medical care to ≥5000 people with HIV/AIDS study team members at Thomas Street perform a chart review to confirm HIV status. Pre-eligible participants are then contacted to complete an enrollment call wherein they provide informed consent and complete the final eligibility screening for the study (refer to Figure 1 for the participant enrollment flowchart).

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Figure 1. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) participant enrollment flowchart. Note: after initial eligibility screening, participants will complete an enrollment call, baseline survey, randomization call, postrandomization survey, 6-week ecological momentary assessment (EMA) period, monthly check-ins for 5 months, and a final survey and week of EMAs at week 28. iCO: iCarbon Monoxide.

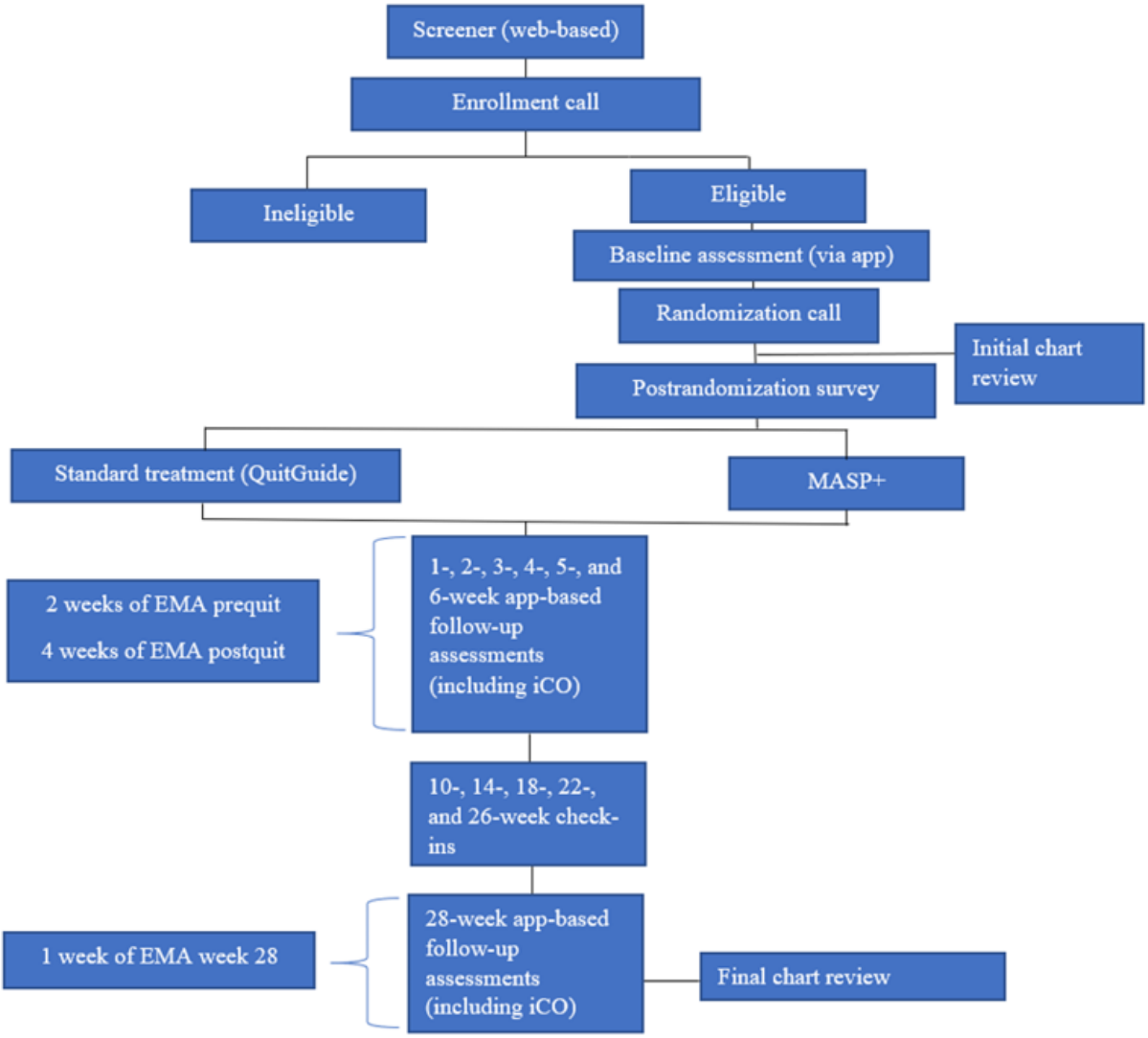

Persons deemed eligible at the enrollment call download the Insight app onto their personal smartphone or study phone. The Insight app houses the MASP+ content and is used to administer smartphone-based surveys and ecological momentary assessments (EMAs) to all participants. The study smartphones are provided to those without a smartphone and those with a smartphone that is incompatible with the Insight platform. Insight is supported on most Android smartphones (Android versions 6.0-14.0). Participants with a personal phone that is incompatible with Insight are sent a study phone. For those using their personal smartphone, the study staff instruct participants on how to download the app onto their personal phone. Insight adjusts according to the font size selected by participants on their phones. Participants who experience issues reading text in the app due to font size are instructed to increase font size in the phone settings. Once Insight is downloaded, participants are given a unique single-use code that enables them to use the app to complete the baseline assessment, which must be completed within 6 days after inputting the code. If participants do not complete the baseline survey within 6 days, they are no longer eligible to participate in the study. All participants are mailed a baseline package that includes a Bedfont iCO (iCarbon Monoxide) quit smokerlyzer, a Greenphire Mastercard, and NRT. The Bedfont iCO is used to biochemically verify self-reported abstinence at follow-ups.

Upon completion of the baseline survey and receipt of the baseline package, the participants complete a randomization call with the study staff. During the randomization call, the participants are randomized to receive the MASP+ or QuitGuide interventions based on the randomization chart developed by the study statistician (MWG). Block randomization was used and stratified according to binary sex (assigned at birth). Variable-sized permuted block randomization (block sizes vary from 4 to 12) is used. Before data analyses, the balance of randomization will be checked and controlled for imbalanced factors by including any factors that differ between groups as covariates. The participants are provided with a unique code to access the app to which they are randomized. MASP+ participants have access to all MASP+ features (ie, Treatment Videos, Coping Toolkit, Quit Tips, and Stress Management Trainings) through the Insight platform. Participants randomized

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to the control intervention (ie, QuitGuide) have access to limited features (ie, App Instructions, Payment Tracking, Call Staff, and Record Stress) through the Insight platform and receive intervention content (ie, Track My Craving, Manage My Mood, and Learn To Quit) through the QuitGuide app. Participants assigned to the control intervention receive assistance with downloading the QuitGuide app through the Google Play Store. Both intervention groups use the Insight app to complete the study assessments, which include the baseline survey, weekly follow-ups, the 28-week follow-up, and EMAs. Once the code is entered, the research staff orients the participant to the app features and the iCO carbon monoxide (CO) breath testing device. Participants have access to MASP+ or QuitGuide content through the final follow-up (ie, the 28-week follow-up). At the end of the randomization call, participants are directed to take a brief postrandomization survey, which must be completed within 6 days after the randomization call. Failure to complete the postrandomization survey within 6 days does not affect participants' status in the study.

Following randomization, the participants complete 4 daily EMAs for 6 weeks. Participants also complete app-based follow-up surveys each week of the treatment period (ie, weeks 1-6) and at 26 weeks postquitting date (28 weeks postbaseline). Between weeks 6 and 28, all participants are prompted to complete a brief check-in survey each month, which reminds them about available app features and assesses their current smoking status. The participants complete a final series of EMAs (4 per day) for 7 days before the 28-week follow-up assessment. The Insight app prompts daily EMAs and follow-up assessments for both treatment groups. In addition, participants complete a Zoom-based qualitative interview to assess their experience with the app and capture recommendations for improving app features and content at 6 weeks postrandomization. Participants who received loaned study smartphones are required to return them after their final follow-up assessment at week 28.

Compensation

Each participant who enrolls receives a Greenphire Mastercard gift card that is loaded with compensation for survey completion. Participants receive all compensation in USD. Participants receive US $30 for completing the baseline assessment and US $10 for completing the postrandomization survey. Participants receive US $10 for completing each weekly follow-up assessment at weeks 1, 2 (quit date), 3, 4, and 5 as well as 6 weeks postbaseline (including the app-based survey, iCO breath test, and Zoom-based qualitative interview at week 6 only). Participants receive US $50 for completing the 28-week follow-up assessment (via Insight) and iCO breath test. Participants are compensated at the end of week 6 for EMA completion during weeks 1 to 6 and at the end of week 28 for EMAs completed during week 28. Specifically, participants receive a total of US $60 for completing 50% to 74% of the brief EMAs (4 per day×7 days=28 weekly EMAs) prompted during weeks 1 to 6, US $90 for completing 75% to 89% of EMAs, or US $120 for completing ≥90% of EMAs. For week 28, participants will receive US $10 for completing 50% to 74% of the brief EMAs, US $15 for completing 75% to 89% of EMAs, or US $20 for completing ≥90% of EMAs. Participants can use the "Payment" and "Weekly Survey Payment" buttons on the app's home screen whenever desired to view an up-to-the-moment summary of EMAs presented and their current completion rate. Payments for completed EMAs are loaded onto participants' Greenphire cards following week 6 and week 28.

Study Conditions

Both Conditions

Given that clinical guidelines recommend that all smokers attempting to quit should receive and use pharmacotherapy [54], both MASP+ and QuitGuide participants are sent NRT with their baseline package. Transdermal nicotine patches and nicotine lozenges are provided for use during the first 4 weeks postquitting date, and each participant is given the option order up to 4 weeks of additional NRT. For those in the MASP+ condition, an additional NRT can be ordered by clicking a button on the app home screen, which sends an encrypted email to the study team informing them of NRT requests. For those in the QuitGuide condition, NRT orders are placed by calling the number provided to participants and speaking with a member of the study team (Figure 2). In a prior study, 66% of enrolled participants used a similar app button or feature to place NRT orders [55]. Patches and lozenges were chosen for use in this study because of their safety and effectiveness (especially in combination with NRT), ease of use, and relatively benign side effects compared to other forms of NRT [56,57].

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Figure 2. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) app home screen. Note: app features include App Instructions, Treatment Videos, Coping Toolkit, Quit Tips, Stress Management Trainings, Order Patches/Lozenges, Record Stress, Record Cigarette About to Smoke, Record Cigarette I Already Smoked, Payment, and Weekly Survey Payment.

NCI QuitGuide Condition

The NCI's QuitGuide app (available for free by request from the NCI Smokefree [58] server, on Google Play, or from the Google Play Store) is a free smartphone app that complies with many of the clinical practice guidelines for quitting smoking [54]. QuitGuide aims to orient smokers to their own smoking patterns and support users in developing the skills needed to quit smoking. Participants with a compatible smartphone who are randomly assigned to use QuitGuide are directed to download the app to their personal devices. Those who do not own a compatible device receive a study smartphone and are directed to download the QuitGuide app during the randomization call. Information explaining how to use the QuitGuide app is shared and reviewed during the randomization phone call. QuitGuide participants also download and use a modified version of the Insight EMA app with all MASP+ intervention features removed, which allows participants to receive EMAs and baseline or follow-up assessments. Refer to Table 1 for a list of QuitGuide features.

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Table 1. Comparison of treatment conditions[a].

App components	MASP+[b]	QuitGuide
EMA[c]	✓	✓ (add on for this study)
Set a quit date	Quit date is set to 2 weeks after randomization	Quit date is set to 2 weeks after randomization
Share quit information on social media		✓
Smoking cessation psychoeducation	✓	✓
Content specific to Black smokers with HIV	✓	
NRT[d] tips and use advice	✓	
AS[e] psychoeducation	✓	
On-demand tips and exercises		
Coping with cravings	✓	✓
Coping with mood	✓	✓
Coping with stress	✓	
Coping with HIV stigma	✓	
HIV care management	✓	
Inspirational messages	✓	✓
Scheduled tips		✓
Treatment messages tailored to currently present smoking lapse triggers	✓	
Coping toolkit	✓	
Guided relaxation and mindfulness exercises	✓	
Challenging automatic thoughts	✓	
Tips for coping with stress	✓	
Interoceptive exposure	✓	
Resources to help distract participants if they experience elevated distress	✓	
Individualized quit plan		✓
Document smoking triggers		✓
List reasons for quitting		✓
Savings from smoking fewer cigarettes		✓
Create journal entries		✓

[a]Some treatment components will be available to all participants regardless of group or app assignment during randomization (eg, smoking cessation psychoeducation and inspirational messages). Other components will be exclusive to either the MASP + condition (eg, content specific to Black smokers with HIV and guidance for challenging automatic thoughts) or the QuitGuide condition (eg, scheduled tips and individualized quit plan).

[b]MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV.

[c]EMA: ecological momentary assessment.

[d]NRT: nicotine replacement therapy.

[e]AS: anxiety sensitivity.

MASP+ Condition

The MASP+ app was adapted from MASP materials and focuses on smoking cessation, HIV treatment engagement or adherence, and AS reduction among Black smokers with HIV [59,60]. Specifically, treatment video scripts were updated from MASP to reflect language and life experiences particular to those with HIV (eg, “Smoking can cause infections, slow down healing, and make it harder for HIV medications to keep your immune system strong.”). EMA messages underwent similar tailoring (eg, “Thinking about the stress of HIV treatment can sometimes feel overwhelming. Relieve your stress by doing one of the relaxation exercises in the app’s Coping Toolkit.”), and 2 new features were added to the app: “How to Improve my Treatment Outcomes” and “Tips on Living with a Chronic Disease.”

Within a culturally adapted framework, MASP+ integrates both standard cognitive behavioral therapy practices for smoking cessation (in accordance with clinical practice guidelines) and

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transdiagnostic treatment for AS reduction [54]. MASP+ provides participants with (1) scheduled treatment content, (2) participant-initiated and scheduled stress exposure sessions, (3) personalized messages following each completed EMA (both pre- and postquit), and (4) numerous "on-demand" features (eg, Quit Tips and Coping Toolkit; both pre- and postquit). Culturally tailored components (eg, educational content related to menthol tobacco products in the Black community, the history of tobacco marketing directly to Black people, HIV treatment management and HIV disparities, and the impact of discrimination and racism on smoking and stress) are featured throughout MASP+. To support cultural tailoring, subject matter experts, including coinvestigators specializing in health disparities and HIV research and members of a Community Research Advisory Board, provided feedback on the cultural tailoring of the study materials for Black participants with HIV.

MASP+ App Features

Treatment on a Schedule

MASP+ includes 17 videos that are 4 to 6 minutes long. These videos provide psychoeducation on topics such as nicotine withdrawal, unhelpful thinking, coping with others smoking nearby, managing uncomfortable sensations, chronic stress and HIV, myths about smoking, strategies for cessation and relapse prevention, smoking as a temporary coping mechanism to avoid experiencing negative emotions, thinking flexibly, stress management, stress and smoking, interoceptive exposure techniques, and the importance of using NRT. All videos were based on those deployed in the MASP study; however, scripts and content were updated to reflect the life experiences of Black adults with HIV (eg, smoking can cause infections, slow down healing, and make it harder for HIV medications to keep your immune system strong). In addition, 1 video was split into 2 videos to reduce the length of individual videos and thereby reduce participant burden. Two new videos become available each day for the first 8 days of the intervention. Participants are able to watch videos as they become available or later by clicking on the on-demand "Treatment Videos" button (Figure 2). There is no limit on how frequently each video can be viewed. The app records date-, time-, and location-stamped information each time a video is watched. This process occurs at both initiation and completion.

Exposure Sessions

Empirical studies demonstrate that internet-based stress exposure is well tolerated, acceptable, and effective [61,62]. The MASP+ treatment videos introduce graduated exposure to anxiety- and distress-provoking situations and response prevention to target AS. Originally, these exposure exercises were created for the MASP pilot study (that is, straw breathing, running in place, head rush, overbreathing, and chair spinning) [49]. Participants are instructed to press the "Stress Management Trainings" button to initiate a stress exposure session (Figure 2). The MASP+ app randomly selects 1 of the 5 exercises each time a participant presses the Stress Management Trainings button. The participants are then guided through stress exposures: the app explains to the participant the purpose of the assigned activity and how to perform it, normalizes the physiological symptoms experienced during the exercise, and relates this experience to their quit attempt. As in the MASP pilot [49], when the participant is ready to begin, the app assesses their level of distress (0-100 scale), displays a countdown timer while the exercise is being completed, and then assesses their level of distress again (0-100 scale) following the expiration of the countdown. The app suggests repeating the exercise up to 3 additional times if the participant's current reported distress is >50 on a 1 to 100 scale. The aim of this strategy is to increase habituation to feared physiological sensations. Participants in the MASP pilot study accessed the Stress Management Training exercises on 6 out of 13 days before their quit date [63]. A recent review of phone-delivered interventions for anxiety and depression showed that treatments involving interoceptive exposure were safe and effective for participants [61,62,64].

EMAs With Tailored Real-Time Treatment Messages

During the prequit date period (ie, a participant's first 2 weeks in the study), the MASP+ app delivers a message at the end of each EMA (4 per day) intended to increase motivation and provide information about quitting (eg, "Everyone experiences negative emotions, such as stress. These emotions do not last forever, but they can lead to relapse. Make a specific plan to cope with such feelings."). During the postquitting date period (weeks 3-6 postbaseline), participants receive tailored messages following each EMA. These messages are based upon their responses to the EMA items they answered, which assess constructs such as ART adherence (eg, "Did you miss a dose of your HIV medication yesterday?") and reported the likelihood of smoking today (ie, 0%-100%). HIV-related EMA messages were specifically developed for the MASP+ study. When participants report that they missed a dose of medication, they are prompted to select the reason that they missed their medication (eg, "Simply forgot" or "Away from home"). On the basis of the response or responses they provide, a tailored message is shared with the participant. For example, selecting that a dose was missed due to forgetting leads the app to display 1 of several possible messages to encourage participants to take their medication as prescribed (eg, "Taking your medications every day is a step toward improving your health!"). The type of message (eg, motivational, coping with urges or stress, and tips for HIV care management) that is delivered following each EMA is recorded and uploaded to our server for future analyses that examine the effects of messages on targeted smoking lapse triggers, HIV outcomes, and anxiety or depression in future EMAs. In addition, participants are instructed to review and practice stress management exercises (ie, interoceptive exposure exercises) to normalize and learn to manage symptoms of anxiety and withdrawal. These exposure exercises have been deployed without incident in the MASP study [49].

On-Demand Features

On-demand features including Quit Tips (Figure 3) and Coping Toolkit (Figure 4) are available to participants via buttons found on the MASP+ home screen. Each of the available icons provides a specific message related to the content area or an activity to support participants in that moment. The research team has developed hundreds of unique messages that address various triggers for smoking relapse [55,65]; the large message bank is intended to reduce repetition. Two new on-demand

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features were developed for this study: How to Improve My Treatment Outcomes and Tips on Living with a Chronic Disease. When selected, these features provide on-demand tips and messages of support regarding managing HIV care (eg, "Set reminders on your phone to help you remember appointments and when to take your medication.") and coping with health stress (eg, "Going on a daily walk, even if just for a few minutes, can help you relax and sort through your thoughts!"), respectively. LG and MB led the development of these messages and activities.

Figure 3. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) quit tips feature. Note: the Quit Tips button will bring participants to a screen where they can select to receive advice on the following topics: Nicotine Medication Tips; General Help for Quitting; Benefits of Quitting; Ways to Cope with Urges; Managing Stress/Mood; Motivate Me to Stay Quit; I've Slipped, Now What?; Harms of Smoking; and Coping with Others Smoking.

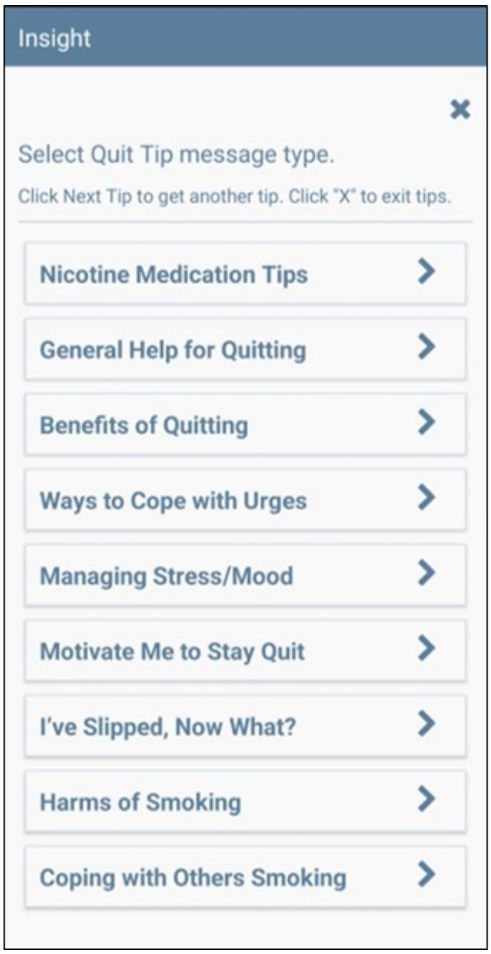

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Figure 4. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) coping toolkit feature. Note: the Coping Toolkit button will bring participants to a screen where they can select to receive help with the following topics: Relaxation Exercises; Challenge Unhelpful Thoughts; How to Cope With Stress; I'm Bored, Distract Me; Coping With Discrimination; How to Improve My Treatment Outcomes; and Tips on Living With a Chronic Disease.

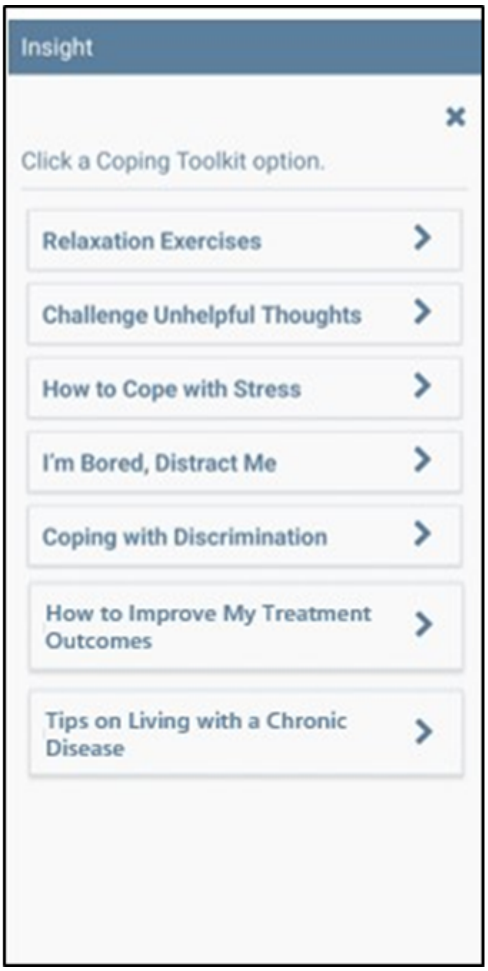

Measures

Overview

To reduce the potential for data entry errors and the need to retain paper copies of raw data, baseline and follow-up data are collected via smartphone using the Insight mHealth platform app software [66]. Questions appear on the phone screen, and answers are provided via touch screen. Tables 2-4 provides the schedule for when each measure is administered. The baseline survey takes approximately 30 minutes to complete; the postrandomization survey takes approximately 10 minutes to complete, the EMAs take approximately 2 to 4 minutes to complete, and the follow-up assessments take up to 15 minutes to complete.

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Table 2. Table of measures[a].

Survey measures	Total number of items, n	Screener, n	Baseline, n	Postrandomization, n	Week 1 to week 6, n	Week 28, n
Screener Survey	41	41	—[b]	—	—	—
6-Item Cognitive Impairment Test (cognitive screener; eligibility)	7	7	—	—	—	—
Rapid Estimate of Adult Literacy in Medicine-Short Form [50] (eligibility)	9	9	—	—	—	—
Demographics or background information	19	—	19	—	—	—
MacArthur Scale of Subjective Social Status	2	—	2	—	2	2
Everyday Discrimination Scale	10	—	10	—	—	—
HIV adherence and treatment	17	—	—	17	—	17
Qualitative interview	24 (MASP+[c]); 20 (QG[d])	—	—	—	24 (MASP+ week 6); 20 (QG)	—
ART[e] adherence	6	—	6	—	6 (week 6)	6
AIDS Clinical Trials Group Adherence Questionnaire	24	—	24	—	19 (week 6)	19
Index of Engagement in HIV Care	10	—	10	—	10 (week 6)	10
WHO[f] Quality of Life-HIV	36	—	36	—	8 (week 6)	8
Carbon Monoxide Analysis (Phone Bedfont iCO[g])	1	—	1	—	1	1
SSASI[h] (eligibility)	5	5	5	—	5	5
System Usability Scale	10	—	—	—	10 (week 6)	—

[a]Various measures will be deployed during the eligibility screener, baseline and randomization surveys, weekly surveys, and daily EMAs. Daily EMAs will include items assessing sleep quality, HIV medication adherence, and discrimination, whereas random and event EMAs will include items assessing social interactions and smoking availability.

[b]Not available.

[c]MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV.

[d]QG: QuitGuide.

[e]ART: antiretroviral therapy.

[f]WHO: World Health Organization.

[g]iCO: iCarbon Monoxide.

[h]SSASI: Short Scale Anxiety Sensitivity Index.

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Table 3. Daily diary ecological momentary assessment.

Survey measures	Items	Prequit morning	Prequit evening	Postquit morning	Postquit evening
Smoking behavior	3	1	1	3	2
Sleep quality	2	2	—[a]	2	—
Distress levels	2	2	—	2	—
HIV adherence	2	2	—	2	—
Other substance or medication use	4	2	2	2	2
General health or quality of life	2	—	2	—	2
Discrimination	2	—	2	—	2
Motivation levels	2	—	1	1	2
NRT[b] use and side effects	8	—	—	8	—
Watch a brief video	1	1	1	—	—
Confidence levels	4	—	—	3	4
Single-item anxiety assessment	1	—	—	1	1
Single-item depression assessment	1	—	—	1	1
Location	1	—	—	1	1
Take lozenge now	1	—	—	1	1

[a]Not available.

[b]NRT: nicotine replacement therapy.

Table 4. Random and event sampling ecological momentary assessment.

Survey measures	Items	Prequit	Postquit
Smoking behavior and availability	3	3	3
Stress and coping	2	2	2
Social interactions	1	1	1
Motivation levels	1	1	1
Other substance or medication use	1	1	1
Confidence levels	3	3	3
Single-item anxiety assessment	1	1	1
Single-item depression assessment	1	1	1
Location	1	1	1
Coping toolkit	1	1	1
Take lozenge now	1	—[a]	1

[a]Not available.

Screening

The prescreener includes a demographic questionnaire that assesses demographics (eg, sex, age, race, and ethnicity), smoking history, motivation to quit, and smartphone and data plan details. The REALM-Short Form was used to assess literacy (>grade 6 English literacy level is required to complete EMAs) [50]. Participants read the REALM words from their phone screen back to the research assistant during the enrollment call. If a participant has trouble reading the words due to vision issues, they have the option to use their phone settings to enlarge the font. The 6-item Cognitive Impairment Test is used to assess impairment in cognitive function (participants with scores <8 will be excluded) [53]. After participants recruited from Thomas Street Clinic complete the prescreener, a team member at Thomas Street Clinic performs a chart review to verify HIV status and record relevant details of health history, including history of respiratory illnesses related to smoking (eg, chronic obstructive pulmonary disease; COPD), height or weight, and number of missed appointments in preceding months. All other participants progress without a chart review.

Smoking Outcomes

During each weekly follow-up survey, smoking status is biochemically confirmed using the Insight platform and the Bedfont Scientific iCO smokerlyzer device. Biochemically

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confirmed 7-day point prevalence abstinence (PPA) at 26 weeks postquitting date is the primary study outcome. This is consistent with best practices as well as most published smoking cessation RCTs (refer to the clinical practice guidelines) [54,67]. In their baseline package, participants receive the Bedfont iCO smokerlyzer, which they use to verify smoking status at each weekly follow-up assessment (weeks 1-6 and week 26 postquitting date). At the end of each assessment, the participants are directed by the Insight app to connect the iCO device to the smartphone (simply by pressing the power button on the device) and complete the iCO test. The date and time of completion are collected and saved to our server along with the test results. Our CO criteria are informed by numerous studies that have used CO cutoffs of <7 ppm [68-74]. The CO level is a validated indicator of smoking status and outcomes and is strongly correlated with cotinine and other biochemical measures that have longer detection windows [75-77].

HIV Outcomes

HIV outcomes are assessed using several measures. HIV-specific quality of life is assessed using the World Health Organization Quality of Life-HIV [78], a questionnaire comprising 36 items related to the quality of life in individuals with HIV. The items assess psychological well-being, functional limitations resulting from HIV status, pain, and the impact of HIV status on interpersonal relationships. ART adherence is assessed using 2 measures: the ART Adherence Scale [79], which consists of 7 items that assess adherence to ART medication regimens and attendance of HIV-specific medical appointments, and the AIDS Clinical Trial Group Adherence Baseline Questionnaire [80], which assesses ART adherence and reasons for missed medication, and nonadherence across 20 items. HIV treatment engagement is assessed using the Index of Engagement in HIV Care [81], a 10-item scale that asks participants about their experience of HIV care.

Discrimination

Race-based and HIV status–based discrimination is assessed using the Everyday Discrimination Scale [82]. This 5-item measure allows participants to report how often they face various forms of discrimination. Consistent with past work [83], the 5 items were adapted to assess both race-based and HIV status–based discrimination for a total of 10 items.

Anxiety Sensitivity

We assess AS using the SSASI [51]. The SSASI is derived from the ASI-3 and consists of 5 items that measure AS using a 5-point Likert-type scale (0=very little to 4=very much) [31].

MASP+ Feedback

We assess the perceived utility of MASP+ using the standardized System Usability Scale (a participant-completed, reliable, and valid metric for measuring usability and acceptability of technologies), which is administered during a 6-week follow-up survey [84-86]. Using a 5-point Likert-type scale (1=strongly agree to 5=strongly disagree), participants indicate their level of agreement with statements about the app's usefulness (eg, "I thought the smoking cessation app was easy to use").

MASP+ Feedback: Qualitative Interviews

Participant experience is assessed via a Zoom-based qualitative interview conducted at the end of treatment (week 6). The semistructured qualitative interview is conducted by trained members of the research team and audio recorded. These interviews focus on the ease of interacting with the app, the usefulness of app features, how the app can be improved, how sociocultural factors that affect Black smokers with HIV could be further woven into the intervention, and their willingness to refer the app to a friend. As participants in both study arms use the Insight app to complete EMAs and receive intervention content via the Insight app or QuitGuide app, the qualitative interview questions primarily concern participants' experiences with Insight (MASP+ and EMA, or EMA only) and QuitGuide (intervention content). During the qualitative interviews, participants provide details about the features of the different apps that they did and did not like (eg, "What did you like about the app?"), how app features impacted relevant study outcomes (eg, "Which, if any, app features helped you manage your HIV better?"), and how the app or apps they used could be improved (eg, "How can we make the app fit better with your life experiences?"). Combined with the primary outcomes and other quantitative data, qualitative interview data will be used to refine MASP+, which will then be tested in a large-scale RCT.

Ecological Momentary Assessments

Overview

At present, EMAs are the most accurate way to measure phenomena in real-time, natural settings [87,88]. EMA items are less biased than traditional in-person assessments and identify fluctuations in key variables related to the study outcomes. EMA data are used to tailor the MASP+ treatment content and identify both treatment mechanisms and moments of high risk for smoking lapse.

The EMA methodology used in this study mimics that used in our previous studies and by other researchers [49,55,65,87,89-95]. The EMA items assess multiple constructs hypothesized to be related to HIV care and smoking lapse. Three types of EMAs are used in this study: daily diary, random sampling, and event sampling. Random and daily diary EMAs are prompted and initiated by the app. The phone audibly and visually notifies the participants of these EMAs for 30 seconds. If participants do not respond after 5 prompts, the assessment is recorded as "missed. All assessments are date and time stamped for future analyses.

Daily Diary

Each morning during weeks 1 to 6 and week 28, participants complete a daily diary EMA, for which they receive a notification 30 minutes after waking. Likewise, participants receive a notification to complete their evening daily diary 75 minutes before their reported bedtime. Questions from the morning daily diary ask about thoughts, experiences, feelings, and behaviors from both the previous day and the present (eg, "Did you miss a dose of your HIV medication yesterday?" and "Today, how long ago did you last smoke a cigarette?"). The participants are also asked about smoking cessation medication use, ART adherence, and sleep quality from the previous day.

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During evening daily diaries, participants are asked about thoughts, experiences, feelings, and behaviors from the same day (eg, "How is your health in general today?" and "How would you rate your quality of life today?").

Random Sampling

Twice each day during weeks 1 to 6 and week 28, participants are prompted to complete EMAs that are scheduled to occur randomly during each participant's normal waking hours. Participants rate their affect by indicating their level of agreement with several statements on a 5-point scale from "strongly disagree" to "strongly agree" (eg, "I feel stressed"). In addition, participants are asked about smoking triggers (eg, "I have an urge to smoke"), current depression level ("Rate your current level of depression [feeling sad]"), and anxiety level ("Rate your current level of anxiety [feeling nervous]"). Participants are also asked to describe their current environment (eg, home and work) and social setting.

Event Sampling

Throughout the treatment period, participants are asked to initiate Smoking Assessments (prequit date), Lapse Assessments (postquitting date), and Stress Assessments (pre- and postquitting date).

Before their quit date, participants are instructed to click a Record Cigarette button every time they feel they are about to smoke or have already smoked a cigarette. In addition, 10% of the time, this triggers a brief survey asking participants about their affect, stress, and experiences while smoking (eg, "Smoking improved my mood" and "Smoking was pleasurable"). These smoking assessments are date, time, and location stamped for future analyses.

Participants are instructed to press the Record Cigarette I Am About to Slip or the I Already Slipped button and complete a lapse assessment each time they smoke after their quitting date. Items on these assessments are similar to those presented in the random and smoking assessments and worded to separately assess the participants' responses immediately before and after the lapse.

Participants are instructed to press the Report Stress button and complete the resulting assessment each time they "experience a significant increase in stress."

Importantly, each MASP+ pre- and postquitting date EMA is followed by a treatment message that is tailored to the participant's responses and current situation. Those assigned to the QuitGuide group complete EMAs identical to the MASP+ group, although they do not receive tailored intervention messages after completion.

EMA Alert Settings

During the enrollment call, the participants' sleep-wake times for each day of the week are recorded and stored (Note: these sleep-wake times can be changed by calling the study team). This practice is intended to prevent or reduce the chance of the phone ringing while participants are asleep. When an EMA is prompted, participants can delay ("snooze") EMAs by up to 30 minutes by clicking the Snooze Assessment option on the smartphone screen.

Data Loss Prevention

To avoid potential data loss as a result of participants losing their phones, each device is programmed to synchronize and upload encrypted data with our secure server multiple times each day (Note: in most studies, <1% of phones have been lost) [48]. These procedures prevent the collected EMA data from being lost, allow the researchers to remotely monitor participants' EMA completion rates, and identify when participants need to be contacted for low survey completion. Notably, EMA data are encrypted and password protected on each study phone. Therefore, the study data are only accessible to the research team. The lost phones are wiped remotely. Participants who lose their phones are provided up to 1 replacement.

The Insight Platform

Overview

The Insight mHealth platform was developed by the mHealth Shared Resource at the University of Oklahoma Health Sciences Center and the Stephenson Cancer Center. This platform offers resources to help researchers build, test, and launch technology-based assessment and intervention tools [66]. The mHealth resource uses a sizeable team that includes 1 program manager, 4 project coordinators, and 4.5 computer scientists or engineers. Together, they develop and maintain web and mobile apps and relational databases. These apps are developed using cutting-edge, cross-platform design tools.

Smartphone Training

Our team has developed and implemented a brief user-friendly training protocol to aid those with limited smartphone experience. During the randomization call, all participants, depending on condition assignment, receive training on how to use either the MASP+ app or the EMA-only Insight app and the QuitGuide app. Both versions of the Insight app (MASP+ and EMA only) contain an "App Instructions" button to remind participants of how each app feature functions (Figure 2). In previous studies, similar protocols have resulted in high EMA compliance rates (eg, 82%-87% of all EMAs completed) in samples of socioeconomically disadvantaged and nondisadvantaged adults [55,65,95,96]. All smartphones used in this study automatically collect data on intervention delivery (eg, number of times features are used and number of minutes treatment videos are watched).

Data Analyses

Overview

To test the hypothesis that MASP+ produces higher rates of smoking abstinence compared to the NCI QuitGuide app, a biochemically verified measure of 7-day PPA that is collected during weekly assessments via Bedfont iCO will be used. PPA is defined as no smoking, not even a puff, in the 7 days before follow-up assessments and biochemical verification of smoking abstinence (ie, CO levels <7 ppm according to an iCO test). We will calculate odds ratio effect sizes (with 95% CI) to estimate between-group differences for PPA at each follow-up assessment. The effect size for the comparison between conditions at the 26-week postquitting date assessment will

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serve as the primary analysis of the impact of treatment condition on smoking cessation.

We will then conduct a series of conditional latent growth curve models (LGM) to examine the impact of treatment condition on abstinence trajectories. First, an LGM will be specified using CO breath tests at 2 (quit date), 3, 4, 5, 6, and 28 weeks. The intercept of these models will be centered on the baseline assessment and will be specified to model linear change across the major assessments. A dummy code representing the treatment condition will be specified as a predictor of the intercept and slope factors to quantify the effect of MASP+ on the longitudinal course of abstinence.

The impact of treatment conditions on HIV quality of life, ART adherence, and HIV treatment engagement (hypothesis 2) will be examined using the same sequence of analyses: between-condition effect sizes followed by conditional LGM. We will then conduct univariate LGM to explore changes in AS a function of treatment (hypothesis 3), followed by a series of parallel process LGM to examine how changes in AS relate to changes in smoking and HIV outcomes. The indirect effects of treatment via AS will be evaluated by calculating bootstrapped CIs of the indirect effect using the MODEL INDIRECT command in MPlus.

Mixed Methodology

Triangulation mixed methods quantitative and qualitative data analysis will be used to evaluate quantitative and qualitative data [97]. Using an explanatory sequential mixed methods design, qualitative data collection and analysis will increase the investigators' understanding of participant experiences of the tailored material for both cultural relevance and relevance to living with HIV.

Quantitative Data

Quantitative data analysis will focus on (1) behavioral markers of engagement with the app (ie, completion of >75% of all assigned videos and completion of >75% of all assigned exercises); (2) self-report evaluations of the app including ease of interacting with the app (ie, >75% of all participants agreeing that MASP+ is easy to use based on a rating of ≥3 on the scale), that the MASP+ features (eg, automated treatment messages that follow EMA and treatment videos) are useful and helpful on a similar scale, and that at least 75% of participants would be likely to recommend the app to a friend; and (3) data from the System Usability Scale [98-100]. Low engagement and evaluation of MASP+ will be discussed with each participant during the qualitative interview.

Qualitative Data

Qualitative data analysis will focus on participants' experiences with the app and incorporating their feedback to improve the app interface and features. Individual interviews will be transcribed following completion of participant treatment and then reviewed by the research team to monitor data quality. The transcribed interviews will be coded using NVivo (version 12; Lumivero). Following a first reading of the transcripts, the interviews will be coded using 2 coding passes [101]. The first coding pass will be use focused [102], with initial codes developed from the question path questions and additional codes based on responses to the System Usability Scale. The qualitative researcher (MKC) will code the interviews, and the coding will be reviewed by a second member of the research team trained in qualitative methods. The coding disagreements will then be discussed and resolved. Memos and notes will be reviewed and discussed. A second coding pass will then be conducted based on additional codes identified during the discussion, which may be process based or theoretically based, depending on what emerges from the first round of coding. Following the review of both coding passes, the research team will conduct a thematic analysis in several steps, beginning with the MASP+ participants, where themes will be identified both within and between codes. The team will then create data displays and review the patterns of responses between related sets of codes [103]. Points of integration between the MASP+ qualitative and quantitative data will be identified, a joint analysis will be conducted, and joint displays will be created [104]. Following the joint analysis, the transcripts will be read again for additional confirming and disconfirming evidence of themes [103], and representative quotes will then be selected. The QuitGuide responses will then be analyzed and compared to the MASP+ responses.

Sample Size Determination

As this is the first empirical evaluation of the MASP+ intervention in this population, our focus is on determining the feasibility of the new intervention and obtaining preliminary estimates of effect sizes on smoking and HIV outcomes and the hypothesized mechanism of change, rather than conducting a full-scale and statistically powered examination of comparative efficacy. We expect that MASP+ will be superior to the NCI QuitGuide on all outcomes examined, but that the effects of MASP+ may vary and be larger for smoking outcomes than for HIV outcomes. On the basis of power calculations conducted using Repeated Measures and Sample Size and simulation studies identifying the sample sizes necessary to detect indirect effects [105,106], a target sample size of 72 would provide sufficient statistical power to detect a medium to large effect (Cohen $d \geq 0.6$) and an indirect effect for H3 if the treatment effect on AS is large (Cohen $d=0.8$) and the effect of AS on outcomes is medium to large (Cohen $d=0.5$). Our conclusions will primarily be based on effect sizes and associated CIs, and the effect size estimates (and associated CIs) from this trial will be used to guide future larger trials of comparative efficacy.

Qualitative interviews are conducted with all MASP+ and QuitGuide participants. The recommended minimum size for any subgroup is 20 interviews [107]. However, based on our prior work [48], interviews vary substantially in the content provided, so interviews will be conducted with all enrolled study participants in MASP+ and QuitGuide to meet the saturation of key study questions. Interviewing all MASP+ participants should be sufficient for the saturation of key study questions. The QuitGuide interviews will be used as a comparative group following the analysis of the MASP+ content, based on our prior work.

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Results

This study received IRB approval on November 29, 2022, under STUDY00003811 and began data collection on October 16, 2023. As of manuscript submission, a total of 9 participants have been fully enrolled in this trial. Data enrollment is scheduled to be completed by June 2024, and data collection is scheduled to be completed by December 2024. Data analysis will begin February 2025 and results will be published March 2024.

Discussion

Expected Findings

Data collection is currently underway. Results are expected to indicate that MASP+, relative to QuitGuide, will lead to improved biochemically verified 7-day PPA, increased adherence to ART, and improved attendance at HIV-related health appointments at 26 weeks postquitting date. Qualitative interviews will be integrated with quantitative data to further refine and adapt MASP+ and support the development of an iterative intervention that is high quality, culturally relevant, scalable, and ready for rigorous testing as part of an R01-level grant.

Study Implications

This study is the first to culturally tailor a smoking cessation smartphone-delivered intervention that is integrated with AS reduction skills for Black people with HIV/AIDS who smoke and elevated AS. Smartphone interventions such as MASP+ have the potential to provide low-cost, scalable treatments to diverse populations who may not be as likely to have access to in-person treatment or may not have health insurance to cover costs. A 2021 survey found that 85% of US adults reported owning a smartphone [108], and other studies have found that smartphone ownership is high among minoritized populations (83% among Black adults) as well as individuals with low socioeconomic status (76% among those earning <US $30,000/y) [108]. Given the widespread ownership of smartphones, MASP+ has the potential to overcome traditional barriers to care and enhance the accessibility and reach of culturally appropriate, clinical-grade care for hard-to-reach populations.

Clinically, the cultural tailoring and integration of AS reduction skills within MASP+ represents a groundbreaking approach. Experiences of AS and related mental health factors (eg, anxiety, depression, and drug withdrawal or craving) can vary over time and among individuals [109]. By assessing these factors throughout the day and providing support as these symptoms arise, MASP+ constitutes a just-in-time tailored intervention for smoking cessation, AS, and HIV management. Such an approach may serve as a potential solution to address the documented health disparities experienced by Black people with HIV/AIDS who smoke [6,110]. MASP+ is also distinguished by the specificity with which it can respond to the unique stressors, needs, and challenges experienced by Black smokers with HIV and AS. This underscores the potential for MASP+ to serve as a stand-alone or adjunctive treatment for smoking cessation. Indeed, MASP+ offers personalized care to address factors that impede successful behavioral change in a culturally appropriate and person-centered manner, which may have strong implications for mitigating health disparities for Black smokers with HIV.

Understanding the role of AS in the process of quitting cigarettes and better managing HIV among Black adults with HIV has several theoretical implications. First, this work bridges together disparate yet complementary work on AS, smoking, and HIV [111,112]. Thus, findings from this trial may provide a holistic understanding of how these constructs relate to and influence one another. This greatly advances the current models for the role of interoceptive distress as a risk factor for worse smoking cessation and HIV-related outcomes [113-116]. Second, several models related to minority stress indicate the need for culturally tailored interventions, particularly those targeting smoking cessation [117-119]. Expanding these efforts to produce tailored interventions for Black smokers with HIV that focus on a mechanism implicated in worse health outcomes among this group (ie, AS) allows providers and researchers to address documented health disparities among this population in a culturally specific manner [120]. Further studies of the mechanisms underlying quit success among Black smokers with HIV and AS will guide future efforts to tailor smoking cessation interventions for this population. This study will provide insights about which risk factors to target during smoking cessation treatment among this group, the ideal timing of intervention efforts, and the preferred content of intervention messages.

Anticipated Limitations

This study has several limitations. Daily EMAs can be disruptive as they are prompted throughout the day rather than clustered in a single study appointment. This could potentially discourage participation in the daily EMA component of this study. In addition, some study measures rely on self-reporting, and participants may not respond in real time. In addition, recruiting a population as specific as Black people with HIV/AIDS who smoke only combustible cigarettes may prove challenging for the study team. Finally, although participants will be responding to items while navigating daily life, thereby increasing ecological validity, this comes at the expense of depriving experimenters of a high degree of control over participants' environmental conditions.

Conclusions

This study may provide insights into precision medicine treatment that is not otherwise available by providing a smoking cessation and HIV management intervention with tailored treatment content based on the psychological and environmental context in real time. Pending tests of its efficacy, an intervention that is automated, scalable, and culturally informed could be easily incorporated into other real-world settings and aid in the reduction of health disparities. This novel mobile intervention has the potential to address the mental and physical barriers to smoking cessation and treatment engagement that are unique to Black people with HIV/AIDS. Despite any potential difficulties in recruiting such a specific group or capturing EMA data, the benefits of this study far outweigh any drawbacks.

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Additional work is essential for the successful translation and cultural adaption of effective in-person smoking cessation interventions into mobile, remotely delivered treatments such as MASP+. Compared to current treatment options, mobile interventions have the potential to produce even greater cessation outcomes and provide wider access for historically oppressed and underserved populations such as Black smokers with HIV and high AS. In light of prior studies that demonstrate the feasibility of mobile smoking cessation technology [49,55,121], mobile treatments that integrate AS constitute a vital "next step" for addressing tobacco-related health disparities among Black smokers with HIV. This study will extend our work in this area as well as in the wider field of smoking–emotional disorder comorbidity by adapting and testing a fully automated, culturally tailored, mobile AS smoking cessation intervention for Black smokers with HIV. Future work will focus on testing the MASP+ app in a larger, fully powered efficacy trial; national dissemination of intervention materials; and implementation across diverse health care settings.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

MB is an inventor of the Insight mobile health platform and receives royalties related to the use of this platform by investigators external to the University of Oklahoma Health Sciences Center. As MB is one of multiple principal investigators in this study, he did not receive royalties for the use of the platform to create the Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) app.

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Abbreviations

ART: antiretroviral therapy

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AS: anxiety sensitivity
CO: carbon monoxide
EMA: ecological momentary assessment
MASP: Mobile Anxiety Sensitivity Program
MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV
NCI: National Cancer Institute
NRT: nicotine replacement therapy
PPA: point prevalence abstinence
RCT: randomized controlled trial
REALM: Rapid Estimate of Adult Literacy in Medicine
REDCap: Research Electronic Data Capture
SSASI: short scale anxiety sensitivity index
UH: University of Houston

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Protocol

A Hybrid Digital Parenting Program Delivered Within the Malaysian Preschool System: Protocol for a Feasibility Study of a Small-Scale Factorial Cluster Randomized Trial

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Abstract

Background: The United Nations' Sustainable Development Goal 4, and particularly target 4.2, which seeks to ensure that, by 2030, all children have access to quality early childhood development, care, and preprimary education so that they are ready for primary education, is far from being achieved. The COVID-19 pandemic compromised progress by disrupting education, reducing access to well-being resources, and increasing family violence. Evidence from low- and middle-income countries suggests that in-person parenting interventions are effective at improving child learning and preventing family violence. However, scaling up these programs is challenging because of resource constraints. Integrating digital and human-delivered intervention components is a potential solution to these challenges. There is a need to understand the feasibility and effectiveness of such interventions in low-resource settings.

Objective: This study aims to determine the feasibility and effectiveness of a digital parenting program (called Naungan Kasih in Bahasa Melayu [Protection through Love]) delivered in Malaysia, with varying combinations of 2 components included to encourage engagement. The study is framed around the following objectives: (1) to determine the recruitment, retention, and engagement rates in each intervention condition; (2) to document implementation fidelity; (3) to explore program acceptability among key stakeholders; (4) to estimate intervention costs; and (5) to provide indications of the effectiveness of the 2 components.

Methods: This 10-week factorial cluster randomized trial compares *ParentText*, a chatbot that delivers parenting and family violence prevention content to caregivers of preschool-aged children in combination with 2 engagement components: (1) a WhatsApp support group and (2) either 1 or 2 in-person sessions. The trial aims to recruit 160 primary and 160 secondary caregivers of children aged 4-6 years from 8 schools split equally across 2 locations: Kuala Lumpur and Negeri Sembilan. The primary outcomes concern the feasibility and acceptability of the intervention and its components, including recruitment, retention, and engagement. The effectiveness outcomes include caregiver parenting practices, mental health and relationship quality, and child development. The evaluation involves mixed methods: quantitative caregiver surveys, digitally tracked engagement data of caregivers' use of the digital intervention components, direct assessments of children, and focus group discussions with caregivers and key stakeholders.

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Results: Overall, 208 parents were recruited at baseline December 2023: 151 (72.6%) primary caregivers and 57 (27.4%) secondary caregivers. In January 2024, of these 208 parents, 168 (80.8%) enrolled in the program, which was completed in February. Postintervention data collection was completed in March 2024. Findings will be reported in the second half of 2024.

Conclusions: This is the first factorial cluster randomized trial to assess the feasibility of a hybrid human-digital playful parenting program in Southeast Asia. The results will inform a large-scale optimization trial to establish the most effective, cost-effective, and scalable version of the intervention.

Trial Registration: OSF Registries; https://osf.io/f32ky

International Registered Report Identifier (IRRID): DERR1-10.2196/55491

(JMIR Res Protoc 2024;13:e55491) doi:10.2196/55491

KEYWORDS

parenting intervention; chatbot-led public health intervention; engagement; implementation science; feasibility; evidence-based program

Introduction

Background

Globally, while gains have been made in promoting access to education, the United Nations' Sustainable Development Goal 4 and, in particular target 4.2, to ensure that, by 2030, all girls and boys have access to quality early childhood development, care, and preprimary education so that they are ready for primary education, is far from being achieved [1]. Before the COVID-19 pandemic, 43% of children in low- and middle-income countries (LMICs) were at risk of not achieving their developmental potential [2]. The COVID-19 pandemic has exacerbated this risk; between March 2020 and February 2021, an estimated 167 million preprimary-aged children had no access to early childhood education and care [3] at an age that represents a sensitive period in children's educational development. Early childhood experiences and skills predict future academic achievement [4], with the strongest predictors being school entry–level mathematics, reading, and attention skills [5]. Furthermore, children who enter school with a knowledge of letters and numbers are likely to have achieved this because of parental instruction [6]. Thus, the *home learning environment*—the availability of educational resources (eg, books) and the quality of parenting activities (eg, reading to children and playing number games) [7]—is important for the development of foundational skills, including literacy and numeracy [8].

A World Bank review in 2023 of preschool education in Malaysia reported that preschools in the country aim to develop children's "school readiness" for entry into compulsory primary school at age 7 years [9]. Malaysia endured one of the region's longest periods of school closure because of the COVID-19 pandemic. Consequently, many children were poorly prepared to start primary school because of learning loss that had particularly impacted early literacy [9]. Other dimensions of children's development, such as socioemotional and psychomotor development, were also adversely affected. Households with low incomes were disproportionately affected because state-funded preschools, that is, those in the Jabatan Kemajuan Masyarakat (Department of Community Development in Bahasa Melayu [KEMAS]), which is part of the Ministry of Rural and Regional Development) system, were closed longer than private preschools, and children from households with low incomes were less likely to have engaged in web-based schooling activities.

In addition to improving access to, and the quality of, public preschool education in Malaysia, the World Bank report recommends supporting parents' improved involvement in preschool-aged children's education and learning at home [9]. A national health survey in 2016 found that just 25% of children in Malaysia receive early learning stimulation at home [10]. Research has shown parenting interventions to be effective in supporting children's learning. A meta-analysis of 14 studies in high-income countries found that parenting interventions (such as training parents to share books with their children) improved the reading development of children aged 4 to 8 years [11]. These findings have also been obtained in LMICs; for example, a randomized controlled trial of children aged 3 to 5 years in the Philippines found that, compared to the control group, children whose parents had received 1 of 3 types of training—dialogic reading coaching, early literacy skills development coaching, and numeracy skills development coaching—improved significantly in several dimensions of their development, including preliteracy skills (eg, phonological awareness and letter name knowledge) and numeracy skills [12]. This evidence reinforces the World Bank's recommendation that parents should be supported in promoting their preschool children's learning and development.

Preschools in Malaysia are an essential component of the country's education system. Formal education in Malaysia typically commences at age 4 years; however, it is not compulsory. Nevertheless, most children aged <6 years are enrolled in preschool to prepare them for formal schooling and to lay the foundation for their future academic and personal development. Several agencies are involved in providing preschool education in Malaysia, including the Ministry of Education, public entities (eg, Tabika Perpaduan [Unity Kindergarten] and Taman Bimbingan Kanak-Kanak (Children's Guidance Park [TABIKA]) KEMAS), state government–supervised institutions (eg, Majlis Agama Islam Wilayah Persekutuan [Islamic Religious Council of the Federal Territory] Islamic kindergartens and Jabatan Agama Islam Selangor [Selangor Islamic Religious Department] preschools), and private kindergartens. The early childhood education

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program TABIKA, organized by KEMAS, provides early education opportunities for children aged 4 to 6 years. TABIKA KEMAS preschools use a *learning through play* pedagogical approach, which aligns with children's natural drive to play, be curious, and experiment [13].

Learning through play is essential for child development and refers to the process by which children acquire knowledge, develop skills, and explore their world through play activities. Play is a natural and instinctive behavior for children, and it serves as a powerful tool for their cognitive, social, emotional, and physical development. Positive parenting emphasizes building a strong, supportive, and nurturing relationship between parents and children. Parents can facilitate learning through play with positive parenting by providing safe and stimulating environments and play materials, allowing children to take the lead during playtime [14], and encouraging opportunities for social interactions for playing to facilitate learning [15].

Despite compelling evidence of the benefits of playful and nurturing parenting for improved learning and educational outcomes, there are significant challenges to the uptake of in-person interventions aimed at promoting such parenting [16]. In addition, local governments and service providers face multiple challenges implementing face-to-face or in-person parenting programs [17-20]. Parenting programs are often too expensive to deliver effectively at scale in low-resource settings due to their complexity, intensity, and length [21]. In Malaysia, barriers to the scale-up of in-person parenting programs include limited financing and resource allocation for such programs, and those that are implemented are usually one-off workshops with a limited or no evidence base [22].

In response to the COVID-19 pandemic and the need to create cost-effective and scalable interventions, remote-delivered parenting programs have been tested by several researchers [23]. A recent systematic review suggests positive impacts on parenting skills and childhood outcomes, although the effect may not be as great when compared to in-person–delivered programs [24]. The main barrier to implementation is difficulty in contacting parents by telephone. However, a study that used a combination of methods (SMS text messaging and group meetings) to address the restrictions associated with remote-only delivery showed an improvement in the effectiveness of the program [25].

In Malaysia, a feasibility pilot study of an in-person program highlighted the demand from parents for flexible delivery modalities [26]. Thus, a collaboration among Universiti Putra Malaysia (UPM), the University of Oxford, United Nations Children's Fund (UNICEF) Malaysia, Malaysian government ministries, and civil society organizations has identified the need for digital and hybrid solutions to address such challenges in the scale-up of parenting programs. Web-based and hybrid delivery of such interventions has the advantage of lower costs compared to in-person–only programs, which is central to ensuring scale-up, and can potentially improve accessibility for parents who would otherwise not participate, or who have difficulty participating, in in-person programs, such as male caregivers, migrant families, and people living with disabilities.

In addition to improved learning and educational outcomes, evidence has shown parenting interventions to be effective in reducing violence against children and promoting child well-being more generally in LMICs [21,27-31]. These interventions aim to improve caregiver-child relationships through positive parenting and support parents in controlling their children's behavioral issues with age-appropriate and effective nonviolent discipline methods. These dimensions of children's development and welfare are particularly important in Malaysia and must also be considered. A review of the prevalence of child abuse and neglect in Malaysia reports evidence of 53% of children experiencing physical parental maltreatment, 20% experiencing emotional abuse, and 21.3% experiencing sexual abuse [32]. The impact of multitype childhood abuse is associated with negative effects on children's psychological status (depression, anxiety, and stress) when they grow into adults [33].

In Malaysia, the Naungan Kasih (Protection through Love) Positive Parenting Program was developed in collaboration with the Malaysian government's National Population and Family Development Board, UPM, UNICEF Malaysia, the Malaysian Association of Social Workers, Maestral International, and Parenting for Lifelong Health. National Population and Family Development Board staff members were trained to deliver the program in person to parents. Despite challenges to uptake, the intervention was effective in providing support to caregivers, improving parent-child relationships, and significantly reducing child maltreatment [26].

This study, conducted within the TABIKA KEMAS program, will assess the feasibility, acceptability, and effectiveness of ParentText delivered (1) with a WhatsApp support group and (2) with 1 or 2 in-person sessions. The results will inform a full optimization trial to determine the most effective and cost-effective version of the program, which is planned to take place across Malaysia with 800 families in the second half of 2024.

Aims and Objectives

The primary aims of this pilot factorial cluster randomized trial are two-fold: (1) to determine the feasibility of the intervention and (2) to examine preliminary indications of the relative effectiveness of a multicomponent human-digital hybrid playful parenting intervention (ParentText combined with a WhatsApp support group and either 1 or 2 in-person sessions) at government-run preschools in Malaysia.

The objectives are as follows:

1. To determine the recruitment, retention, and engagement rates in all 4 intervention conditions and explore reasons for these rates
2. To document the extent to which the intervention was implemented in line with the program model (fidelity) in rural and periurban school settings
3. To explore the acceptability of the parenting program among caregivers, facilitators, supervisors, and members of the KEMAS leadership team
4. To estimate the costs of delivering the different intervention components

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5. To provide preliminary indications of the relative effectiveness and cost-effectiveness of the different intervention components on the intended intervention outcomes, including proximal outcomes (ie, positive parenting, child physical and emotional abuse, and parent mental health and stress) and distal outcomes (ie, child learning [namely literacy, numeracy, and socioemotional development], child behavior, intimate partner relationships, financial stress, and parent quality of life).

Methods

Study Setting

The study will take place within the preschool system in 2 locations in Malaysia: the federal territory of Kuala Lumpur and Negeri Sembilan. Kuala Lumpur is a periurban location, while Negeri Sembilan is more rural. This contrast will provide comprehensive information pertaining to the feasibility and acceptability of the program across different contexts.

Trial Design

This feasibility pilot is a 2×2 factorial cluster randomized trial that compares ParentText (chatbot-led parenting program) delivered to all participants, with different combinations of two engagement components: (1) a WhatsApp support group (yes or no) and (2) either 1 or 2 in-person sessions (Table 1). This study will adopt a parallel design using a 1:1:1:1 allocation ratio (each cluster at each study site exposed to 1 experimental condition).

Table 1. Experimental conditions from 2×2 factorial design (n=8 clusters; n=160 families).

Condition	Clusters (schools; n=8), n (%)	Caregivers (primary, n=160; primary and secondary, n=320), n (%)	Children (n=160), n (%)	Facilitators (n=8), n (%)	ParentText	WhatsApp support group (yes or no)	In-person sessions, n
1	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	No	1
2	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	Yes	1
3	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	No	2
4	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	Yes	2

Eligibility Criteria

Study participants include caregivers, children, program facilitators, KEMAS supervisors, and members of the KEMAS leadership team. Participants must provide informed consent (parents, caregivers, program facilitators, program supervisors, and KEMAS leadership team members) or verbal assent (children) to participate in the study and before any study procedures take place.

Inclusion Criteria

Caregivers eligible for the trial must be aged ≥18 years, be responsible for a child aged between 4 and 6 years who is registered with a KEMAS preschool, live in the same household with the child for at least 4 nights a month, and have access to a mobile phone compatible with WhatsApp.

Children eligible for the trial must be aged between 4 and 6 years, be enrolled in a KEMAS preschool, and have parental consent to participate in the study.

Teachers and facilitators of the program must be aged ≥18 years, be registered employees of a KEMAS preschool, have a diploma or certificate in early childhood education or equivalent, have participated in a facilitator training workshop, and be available to deliver the intervention package.

KEMAS supervisors must be aged ≥18 years, be registered supervisors with KEMAS, have a diploma or certificate in early childhood education or equivalent, have participated in 2 intervention program trainings (facilitator training workshop [for new facilitators to deliver the program] and training of trainers workshop [supervisors who completed the facilitator training workshop were trained to deliver training to new facilitators]).

KEMAS leadership team members must be aged ≥18 years and be federal or state administrative staff members of the Division of Early Childhood Education within KEMAS.

Schools

Preschools from the 2 study sites were eligible for inclusion if they had sufficiently sized classes (20-25 children aged 4-6 years/class). Eight preschools were selected from a list of eligible preschools (provided by KEMAS; Multimedia Appendix 1) in Kuala Lumpur and Negeri Sembilan (4 schools per study site). Within each selected preschool, 1 class will be selected (randomly if >1 class) from which 20 families will be invited to participate in the study. Teachers of the selected classes will act as facilitators and contact the families of the children and invite 2 caregivers to participate in the study. Four children in each cluster (ie, 32 in total) will be randomly selected to participate in direct assessments.

Intervention

The intervention is a hybrid human-digital playful parenting program Naungan Kasih, which consists of a chatbot-led parenting program (ParentText 2.0) delivered to all participants and two intervention engagement components: (1) a WhatsApp support group (yes or no) and (2) either 1 or 2 in-person sessions.

ParentText

ParentText is a chatbot-led parenting intervention that delivers personalized, gamified, scheduled, and on-demand messages through WhatsApp, audio, and visual messages to caregivers of children at different developmental stages, that is, from ages 0 to 23 months, 2 to 9 years, and 10 to 17 years. It was developed by the UK-based charities Parenting for Lifelong

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Health and IDEMS International. The version targeting caregivers of children aged 2 to 9 years is used in this trial, with additional content specifically relevant for caregivers of children aged 4 to 6 years.

The ParentText version used for this intervention was adapted in response to key findings from previous research in Malaysia by project partners; for example, a pre-post evaluation of the in-person version of Naungan Kasih delivered in 2 communities with low-income status between November 2018 and April 2019 found promising intervention effects on some caregiver self-reports (n=74), including reductions in overall child maltreatment, physical abuse, emotional abuse, attitudes supporting corporal punishment, and child behavior problems, as well as improvements in early childhood involvement [26]. However, no effects were found on positive parenting, harsh parenting, parental mental health, and marital satisfaction; nor were there any significant intervention effects on child (aged 10 to 17 years) reports (n=26). Qualitative findings highlighted tangible benefits for female program recipients, such as reduced use of harsh physical and verbal punishment toward their child and lower stress associated with parenting, as well as improved communications with partners [26]. However, program facilitators reported that the traveling required to facilitate in-person sessions on top of their daily work left them feeling overburdened and highlighted the potential of digital modalities.

ParentChat, a digital parenting program delivered through WhatsApp, was piloted in 2021 in Malaysia. The study found a 23% reduction in parenting stress, a 24% reduction in parental report of child behavior problems, a 15% increase in parental self-efficacy to prevent sexual abuse, and a 39% increase in intimate partner respect [34]. Caregiver attendance during the 8-week program was high; on average, parents attended 81% of the 16 sessions. In addition, a pilot of ParentText with 82 caregivers in Malaysia showed a 68% enrollment rate, with average engagement of 13 days in the chatbot. Topics most frequently accessed were *Keeping Calm*, *One-on-One Time*, and *Helping Your Children Learn*. When parents interacted with a WhatsApp message, they requested additional content provided within the chatbot 78.8% of the time. Exploratory analyses of program effects found significant improvements in positive parenting behavior. Pilot tests across Malaysia, Jamaica, the Philippines, and South Africa between 2021 and 2022 highlighted five principal areas for attention in improving ParentText [34]: (1) structural issues leading to participant dropout, (2) multimedia being insufficiently engaging, (3) the need for more and improved personalization features, (4) the need for mechanisms to promote re-engagement, and (5) issues with ease of use.

As such, the ParentText program designed for this study has been streamlined, and the goals have broadened to include those more relevant to the Malaysian preschool context; for example, content has been developed to specifically target improving learning through play and child educational outcomes. ParentText is structured around 6 goals, each with several modules (28 modules in total; Textbox 1) that take approximately 5 minutes to complete.

At program onset, caregivers choose which goal they want to start with, and each day, receive a prompt asking them whether they can complete a module related to this goal. On completion of this goal, they choose which one they would like to start next. Caregivers will have 33 days between starting and finishing the program, a time frame that allows 1 day for each module (28 days) plus 5 days to catch up on the days on which they were unable to complete a module.

Although the self-guided nature of ParentText is advantageous in terms of scalability, engagement boosters (such as social networking tools) are commonly used in parenting programs and in digital interventions more broadly to support participation [35-38]. There is evidence for the effectiveness of such engagement boosters; for example, parents taking part in a web-based version of the Triple P parenting intervention who received telephone-delivered support from practitioners engaged more with the program and reported greater program satisfaction than parents who did not receive phone support [39]. However, such improvements in engagement are not always found, as other parenting studies have documented [40]. Another option is to supplement digital interventions with in-person sessions where participants interact with program facilitators (eg, clinicians or counselors), which has been found to improve program adherence [41,42]. However, in-person sessions accrue costs associated with facilitator training [43]. This study seeks to establish whether the use of WhatsApp support groups and in-person sessions promotes engagement, satisfaction, and the effectiveness of the ParentText intervention.

Textbox 1. Overview of ParentText content and number of modules.

Goal and number of modules

- Improve My Relationship with My Child: 5
- Support My Child's Development: 3
- Prepare My Child for Success in School: 6
- Give My Child Structure: 5
- Support Positive Child Behavior: 4
- Keep My Child Safe and Healthy: 5

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Component 1: WhatsApp Support Group (Yes or No)

WhatsApp support groups will be facilitated by the preschool teachers (facilitators). Each week, the teacher (facilitator) will share preformulated content on the WhatsApp group using a share button on a facilitator app. Caregivers can use the group to interact with each other and share tips, thoughts, and feelings. Facilitators will not moderate WhatsApp groups; they will only intervene if the content discussed goes against positive parenting practices.

Component 2: In-Person Sessions (1 or 2)

This study aims to investigate rates of engagement and acceptability for the program when participants attend 1 or 2 in-person sessions that are facilitated by preschool teachers. All participants receive the first session, which will comprise an introduction to the program and an onboarding to ParentText. Half of the participants will attend an additional second session at the end of the program, in which they will review content, role-play examples of practices they have learned, and receive a certificate of completion. It is hypothesized that this session will improve the acceptability of the program to caregivers, improve outcomes related to the content of the program thanks to the review and practice, and improve engagement by motivating parents to complete the program and receive a certificate.

Outcomes

Overview

Recruitment, retention, and engagement rates (objective 1) will be measured by the indicators presented in Textbox 2.

Program fidelity (objective 2) is defined as the completion of at least 80% of facilitator-delivered components of the program. This is measured via a checklist that facilitators will complete using a dedicated app in which they will report whether they carried out planned in-person activities and whether they sent weekly WhatsApp support group messages (for those delivering this component of the intervention).

Program acceptability (objective 3) will be assessed using qualitative focus group and interview data, which will gather information from caregivers and facilitators on their views and experiences of the intervention, including what they perceive to be barriers and enablers to using it (among caregivers) and to implementing it (among facilitators). Program acceptability will also be assessed via 2 parent self-report quantitative measures (Textbox 3).

Figure 1 shows the hypothesized association among intervention components, process outcomes, and the intended primary intervention outcomes. Findings relevant to the aforementioned objectives will inform an understanding of the relationship between the intervention components and the process outcomes. Furthermore, these findings will facilitate an understanding of the relationship between process outcomes and the proximal outcome of positive parenting.

The cost of implementation (objective 4) will be measured from the provider perspective and will consider all resource inputs required for intervention. Cost indicators estimated will include the total cost of the intervention (set-up and operation), cost for each intervention component, and the average cost per participant enrolled (unit cost). Costs will be estimated from data gathered on actual expenditures (financial costs) and the market value of all donated and subsidized resource inputs (economic costs).

Preliminary intervention effects (objective 5) will be assessed for the main outcomes of interest, which are described in the following subsections.

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Textbox 2. Outcomes and indicators to measure recruitment, retention, and engagement rates (objective 1).

Outcomes and indicators

- Recruitment
  - Number of eligible primary caregivers invited to participate and consented
  - Number of eligible secondary caregivers invited to participate and consented
  - Number of baseline assessments completed with primary caregivers
  - Number of baseline assessments completed with secondary caregivers
  - Number of child direct assessments completed at baseline
- Retention
  - Number of posttest assessments completed with primary caregivers
  - Number of posttest assessments completed with secondary caregivers
  - Number of child direct posttest assessments completed
- Engagement
  - Number of ParentText modules completed by primary caregivers
  - Number of ParentText modules completed by secondary caregivers
  - Number of primary caregivers who attended in-person sessions
  - Number of secondary caregivers who attended in-person sessions
  - Number of primary caregivers who participated in WhatsApp support groups
  - Number of secondary caregivers who participated in WhatsApp support groups

Textbox 3. Caregiver outcomes and measures related to program acceptability (objective 3).

Outcomes and measures

- Partner participation in program (postintervention assessment only)
- 8 items adapted from previous studies of Parenting for Lifelong Health interventions
- Program satisfaction (postintervention assessment only)
- 4 items adapted from previous studies of Parenting for Lifelong Health interventions

Figure 1. The hypothesized association among intervention components, process outcomes, and the intended primary intervention outcomes based on the theory of change conceptual model.

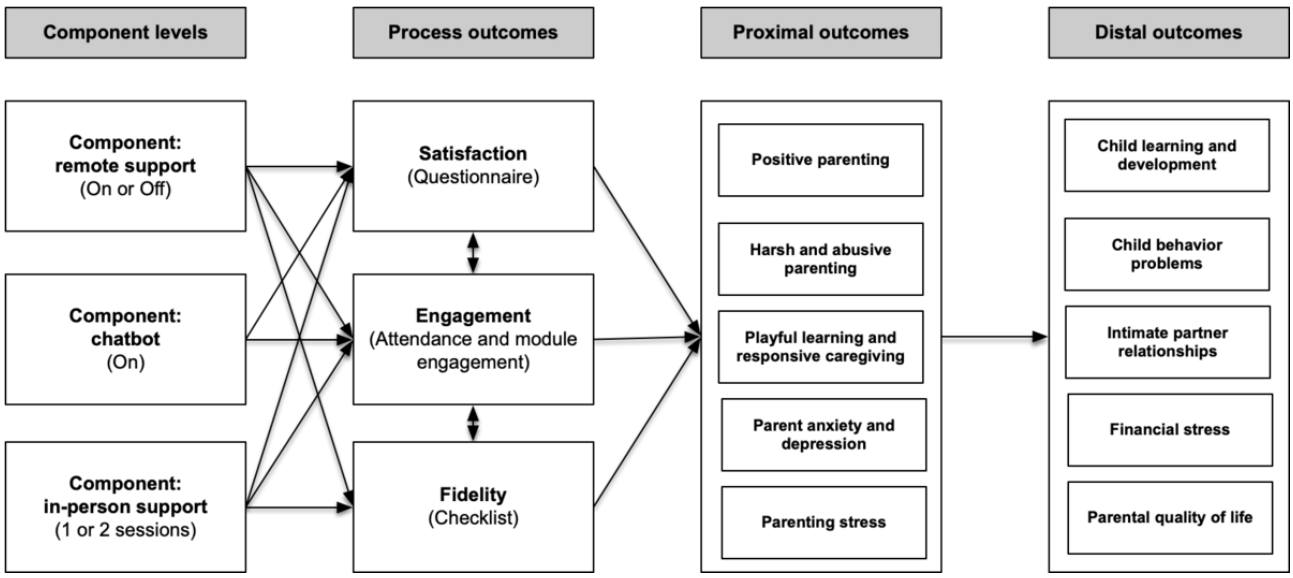

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Proximal Outcomes

Harsh and Abusive Parenting

Two indicators of harsh and abusive parenting (physical and emotional abuse) will be measured using items from the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool–Parent version [44]. Each item measures responses on 9-point count scales, asking the number of times a behavior occurred in the previous 2 weeks (ranging from 0=0 times to 8=8 or more times).

Child physical abuse will be measured using 4 items from the physical abuse subscale that ask questions regarding the frequency of the parents disciplining their children physically (eg, "In the last 2 weeks, how often did you discipline your child by slapping, spanking, or hitting with your hand?").

Child emotional abuse will be measured using 5 items from the emotional abuse subscale that ask questions regarding the frequency of the parents disciplining their children emotionally (eg, "In the last 2 weeks, how often did you shout, yell, or scream at your child in an aggressive manner?").

Parent-child playful learning or responsive caregiving

This will be measured using the UNICEF Multiple Indicator Cluster Surveys child development module and family care indicators [45]. The module consists of 4 items that ask parents to state the frequency of a series of learning activities on a scale ranging from 0 to 8 (eg, "How many times in the past 2 weeks (14 days) did you play with your child?").

Positive Parenting

This will be measured using 2 subscales from the Parenting Young Children Scale [46], with 7 items in each scale. Parents will be asked about the frequency of these parenting practices on a scale ranging from 0=not at all to 6=most of the time during the last 2 weeks (last 14 days). The first subscale is *supporting positive behavior* (eg, "Were you able to spend time with your child in ways that were fun for both of you?"). The second subscale is *setting limits* (eg, "Were you able to stick to your rules and not change your mind?").

Parent Anxiety and Depression

This will be measured using the Patient Health Questionnaire-4 [47]. This comprises 4 items relating to anxiety and depression, such as "Over the last 2 weeks, how often have you been bothered by the following problems? Feeling nervous, anxious, or on edge?" Parents are asked to respond on a 4-point Likert scale (ranging from 0=not at all to 3=nearly every day) that addresses parents' perception of the frequency of the problems.

Parenting Stress

This will be measured using the Parenting Stress Scale [48], which comprises 6 items, such as "The major source of stress in my life is my child(ren)," and responses are on a 5-point Likert scale (ranging from 0=strongly disagree to 4=strongly agree) that will address the extent of agreement with the items.

Distal Outcomes

Child Learning and Development

Parent Report

Child learning or *child development* will be measured using the Measure of Development and Early Learning, a module from the Measuring Early Learning Quality and Outcomes (MELQO) framework [49]. The survey consists of 38 items asking caregivers about their child's development across four dimensions: (1) literacy (5 items), (2) mathematics (10 items), (3) socioemotional development (21 items), and (4) executive function (2 items). Examples of items include (1) "Can [name] write his/her own name?" (literacy development), (2) "Can [name] add 3 and 2 together?" (mathematics), (3) "Does [name] share with his/her peers?" (socioemotional development), and (4) "When asked to do several things, how often does [name] remember all the instructions?" (executive function).

Direct Child Assessment

A subset of items from the International Development and Early Learning Assessment (IDELA) [50] will be used to measure 3 dimensions of children's learning and development: emergent literacy (3 items), emergent numeracy (3 items), and socioemotional awareness (2 items); for example, for emergent literacy, the assessor will ask the child to identify letters in a chart; for emergent numeracy, the child will be asked to perform simple addition and subtraction tasks; and for socioemotional awareness, the child will be asked to identify the emotion being experienced by a cartoon girl who is crying.

The items chosen make up 6 of the items from the IDELA *short form*, with 2 questions related to motor skills removed, and 1 question each related to emergent literacy and emergent numeracy added. This was decided because of the ParentText intervention's greater prioritization of these dimensions of children's early learning with respect to motor skills.

Child Behavior

Externalizing problems of the child will be measured using the Child and Adolescent Behavior Inventory [51]. The scale consists of 12 items asking parents about their child's behavior, such as physical aggression, defiance, theft, and vandalism, in the past 2 weeks. Examples of items are "He/she is quick-tempered and has fits of anger" and "He/she destroys things." Responses are based on a 3-point Likert scale (ranging from 0=not true to 2=very true).

Intimate Partner Relationships

Gender-Equitable Behaviors

Four items will assess the frequency of a selection of gender-equitable behaviors; for example, "In the past 2 weeks, how often did you and your partner share housework and caregiving tasks equally?" Responses are based on a 5-point Likert scale (ranging from 1=never to 5=most of the time).

Marital Health Quality

The Marital Health Scale [52] will be used to assess the marital health of the parents. The 5-item scale will ask parents about the extent of agreement in regard to 5 questions about their marriage. Each item will include a similar theme (in parentheses)

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for the parents to consider when providing answers regarding their marriage (eg, "My marriage is satisfactory" [content, fulfilled, gratified]). Responses will be based on a 5-point Likert scale (ranging from 1=strongly disagree to 5=strongly agree).

Financial Stress

This will be measured using the Financial Self-Efficacy Scale [53], which consists of 6 items that ask about financial behavior (eg, "It is hard to stick to my spending plan when unexpected expenses arise" and "I lack confidence in my ability to manage my finances"). Responses are based on a 4-point Likert scale.

Parents' Health-Related Quality of Life

The Assessment of Quality of Life-4D instrument [54] will be used to evaluate the parents' health-related quality of life, which will be measured to facilitate an economic evaluation of the program's impact on quality-adjusted life years. There are 12 items that ask questions related to dimensions such as sleep, relationships, and pain, and responses are chosen on a 4-point Likert scale (eg, "Because of your health, your relationships [for example: with your friends, partner or parents] generally: [responses range from] Are very close and warm [to] I have no close and warm relationships").

Partner Participation in Program

This will be measured at postintervention assessment only. Primary caregivers will be asked 8 questions about their partner's participation or nonparticipation in the program (eg, "If your partner or spouse participated in the program, did s/he share with you what they had learnt in the training?"). Items will be measured on a 3-point Likert scale.

Program Satisfaction

This will be measured after the intervention only. Caregivers will be asked 4 questions related to their satisfaction with the program on a 5-point Likert scale (eg, "Would you recommend the program to a friend or relative?" Responses range from 1=strongly not recommend to 5=strongly recommend).

Textbox 4 presents a summary of the intervention effectiveness outcomes, along with measures and number of items.

Textbox 4. Summary of intervention effectiveness outcomes.

Outcomes and measures

- Proximal outcomes
- Child physical abuse: International Society for the Prevention of Child Abuse and Neglect (ISPCAN) Child Abuse Screening Tool–Trial, physical abuse subscale (4 items)
    - Child emotional abuse: ISPCAN Child Abuse Screening Tool–Parent version, emotional abuse subscale (5 items)
    - Playful learning: United Nations Children's Fund Multiple Indicator Cluster Surveys child development module and family care indicators (4 items)
    - Parenting: Parenting Young Children Scale (supporting positive behavior, and setting limits; 14 items)
    - Parent mental health: Patient Health Questionnaire-4 (4 items)
    - Parenting stress: Parenting Stress Scale (6 items)
- Distal outcomes
- Child learning and development: MELQO framework's Measure of Development and Early Learning module teacher or caregiver report item (38 items); IDELA (8 overarching items, total 21 subitems)
- Child behavior—externalizing problems: Child and Adolescent Behavior Inventory, externalizing subscale (12 items)
- Gender-equitable behaviors: adapted from questionnaires used in previous violence prevention studies (4 items)
- Marital health or quality: Marital Health Scale (5 items)
- Financial stress: Financial Self-Efficacy Scale (5 items)
- Quality of life: Assessment of Quality of Life-4D (12 items)

Demographic Information

Caregiver and child demographic information will be collected at baseline and include caregiver age, marital status, employment, educational attainment, literacy, and household socioeconomic status; child age; family health (eg, parent and child disability) and family vulnerabilities (eg, substance abuse by household member); child's relationship to caregiver; presence of child's biological parents and other child in the house; and presence of another person who shares the responsibility of child rearing and their relationship with the caregiver.

Intervention Effectiveness

Findings related to intervention effectiveness will inform the extent to which intervention components and their related process outcomes are associated with the primary proximal outcome of positive parenting, the primary distal outcome of child development, and other outcomes, namely child maltreatment, child behavior problems, and parent mental health.

Overall, findings related to the 5 study objectives will inform decision-making regarding whether to include intervention components or which level of intervention component to include in future evaluations of the optimized version of the Naungan Kasih program. This is illustrated in Figure 2. Thus, if a

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component level is both effective and cost-effective, it will not be included in a subsequent optimization trial. If it is effective but not cost-effective, it will be evaluated in a subsequent optimization trial. If it is not effective but is feasible (ie, there is engagement, it is acceptable, and it is implemented with fidelity), it will be included in a subsequent optimization trial. If it is not effective and not feasible but can be improved, the improved version will be evaluated in a subsequent optimization trial. If it is not effective, not feasible, and cannot be improved, then it will not be included in a subsequent optimization trial.

Figure 2. Decision-making model to determine the inclusion of intervention components in a full trial. N/A: not applicable.

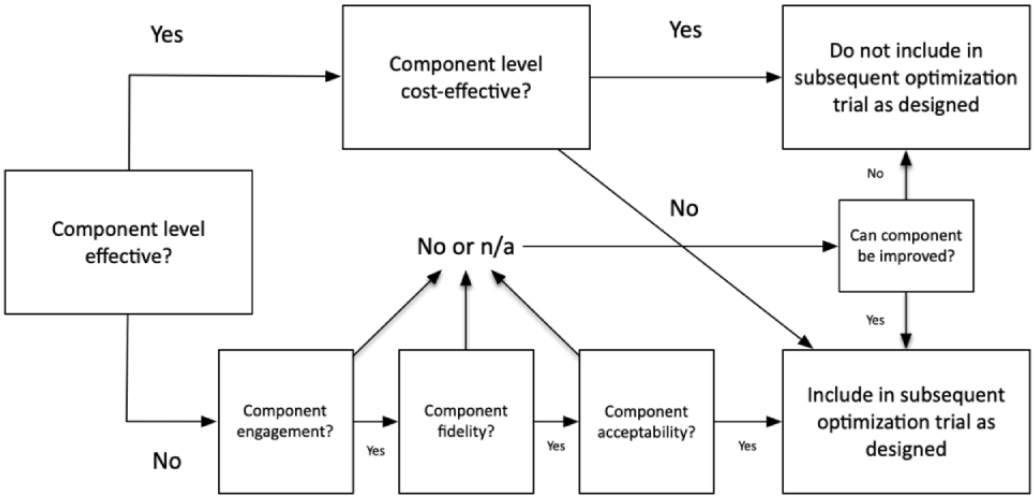

Participant Timeline

The participant timeline is summarized in Table 2. Parents invited to participate by facilitators will be asked to attend an in-person session that will include (1) eligibility screening, (2) informed consent, and (3) baseline assessment. The baseline sessions took place in schools from December 6 to 16, 2023. Schools were then randomly allocated to the 4 treatment conditions. The intervention began with onboarding sessions that took place in schools from January 4 to 6, 2024. The intervention ran until February 7, 2024. Qualitative assessments with facilitators, supervisors, and KEMAS leadership team members were conducted between February 5 and 16, 2024. Posttest data collection was carried out with parents and children between February 24 and March 12, 2024.

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Table 2. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule for participant enrollment, intervention, and assessments. FGD: focus group discussion; KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development).

	Study period			
	Enrollment and baseline (time point 1)	Allocation	After allocation (intervention)	After the intervention (time point 1)
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Condition 1			✓	
Condition 2			✓	
Condition 3			✓	
Condition 4			✓	
Assessments				
Recruitment	✓			✓
Retention				
Adherence			✓	
Engagement			✓	
Parent survey				
Recruitment	✓			✓
Demographics	✓			
Child physical abuse	✓			✓
Child emotional abuse	✓			✓
Playful learning	✓			✓
Child learning and development (parent report)	✓			✓
Child behavior—externalizing problems	✓			✓
Parenting	✓			✓
Parent mental health	✓			✓
Parenting stress	✓			✓
Gender-equitable behaviors	✓			✓
Marital health	✓			✓
Financial stress	✓			✓
Quality of life	✓			✓
Partner participation in program	✓			✓
Program satisfaction	✓			✓
Child development and learning (child direct assessment)	✓			✓
Costs			✓	
Qualitative assessments				
Parent FGDs[a]				✓

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	Study period			
	Enrollment and baseline (time point 1)	Allocation	After allocation (intervention)	After the intervention (time point 1)
Facilitator interviews				✓
Supervisor FGD				✓
KEMAS[b] leadership FGD				✓

[a]FGD: focus group discussion.

[b]KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development).

Sample Size

A formal sample size calculation was not used for this feasibility pilot study. It is anticipated that the sample size of 160 families (160 primary caregivers and up to 160 secondary caregivers, as well as 160 children from the same households) split equally across 8 preschools (4 at each study site) will provide sufficient information on the study objectives to inform a future main trial. In 20% (32/160) of the families at each preschool, direct assessments will be conducted with the child. The 8 project facilitators will be invited to participate in interviews. Five supervisors will be invited to participate in a focus group discussion (FGD). Finally, 5 KEMAS leadership team members will be invited to participate in an FGD.

Recruitment

Recruitment of KEMAS leadership team members, supervisors, and facilitators took place between July 4 and September 15, 2023. Supervisors and facilitators took part in the Naungan Kasih training during the second week of November 2023.

KEMAS Leadership Team Members

UPM used existing contacts with KEMAS to invite members to participate in the study. KEMAS leadership team members were sent an information sheet and consent form via email.

KEMAS Supervisors

Members of the KEMAS leadership team identified and invited school supervisors in the KEMAS system to confirm their willingness to participate in a training of trainers session.

Facilitators

Members from the KEMAS leadership team identified and invited teachers at the selected preschools to confirm their willingness to participate as program facilitators.

Caregivers

Facilitators (class teachers) informed parents at the selected preschools about the study in mid-November 2023, after the training program. Two parents from each household have been invited to attend the registration and baseline data collection session. During the in-person data collection session, research assistants will screen the attendees to confirm their eligibility and establish which parent is the primary caregiver and which one the secondary caregiver. The research assistants will then ask parents to provide full written consent and complete the baseline assessment. Caregivers who do not attend the in-person data collection session but who indicated their interest in participating will be contacted by UPM researchers in the 2 weeks after the in-person session. The researcher will screen each caregiver to confirm their eligibility and establish which parent is the primary caregiver and which one the secondary caregiver. The researcher will then ask them to provide full verbal consent and carry out the baseline survey with them verbally over the telephone. Parents who provide consent and who complete the baseline assessment will be invited to participate in the first in-person session of the intervention, the onboarding session.

Children

A random subsample of 4 children from each cluster will be selected to participate in direct assessments. Primary caregivers attending the in-person baseline data collection session will be asked to provide written consent to their child's participation. The parent will then select a bead from a bag to determine the random selection of the child. For the children selected, the assessment will take place at the school during the 2 weeks after the parents' in-person informed consent and baseline data collection session. The children selected will be asked to provide verbal assent.

Assignment of the Intervention

Allocation

Sequence Generation

Within each study site, schools will be randomly allocated in a 1:1:1:1 ratio to 1 of the 4 treatment conditions (described in the Trial Design subsection) using a computerized random number function in Microsoft Excel. The list of schools will be sorted in Excel by study site (strata) and then by random number, and within each stratum, schools will be manually assigned to the 4 experimental conditions: the school with the lowest random number will be assigned to experimental condition 1, the school with the second lowest random number to experimental condition 2, and so on.

Allocation-Concealment Mechanism

Randomization will be conducted after the final baseline data collection session. Data collectors, facilitators, and participants will be concealed to allocation until the start of the intervention. The onboarding session will take place between the final data collection session and the start of the intervention, at which point the facilitators and the intervention recipients will be informed about condition allocation. Condition allocation will remain concealed throughout the study for data collectors. Those involved in analysis will remain blinded until main analyses

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have been conducted; however, they may become aware of condition allocation when analyzing FGD data because of particular questions and answers related to components of the study relevant to the intervention conditions.

Implementation

Before randomization, a list of recruited schools will be sent to the University of Oxford by UPM researchers. The data manager, based at the University of Oxford, will then randomly assign schools to the experimental conditions. The randomization sequence will be in a password-protected file and accessed on a need-to-know basis. After randomization, the allocation of each school will be forwarded to UPM researchers, who will share this with the implementing facilitators at the relevant schools.

Blinding

During baseline assessment, UPM researchers and intervention participants will be blinded to condition allocation and will not be informed about the range of conditions and the allocation status of other schools to reduce the risk of contamination. During the intervention onboarding process, participants will be exposed to information pertaining to the condition to which they are assigned. Blinding will not be possible for the facilitators because of their involvement in program implementation. UPM research assistants will be blinded to the allocation of schools during the postintervention assessments. FGDs will take place after the collection of postintervention data. It is expected that research assistants will learn about the allocation of clusters, as will the teacher-facilitators, during the FGDs. Statisticians will be blinded to cluster and participant allocation when carrying out quantitative analyses.

Data Collection, Management, and Analysis

Data Collection

This feasibility pilot study will use a mixed methods approach using both quantitative and qualitative data.

Quantitative Data

These data will include digitally tracked engagement data, facilitator administrative data and self-reports on program implementation, caregiver baseline and posttest surveys, and direct assessments of children.

Digitally tracked data on parent engagement with the chatbot will be collected automatically through parent interactions with ParentText. These data will be linked to the individual participant ID. Facilitator administrative data will include a register of caregivers invited to participate in the intervention and whether they consented to participate. Facilitators will record caregiver participation in the WhatsApp support groups via the facilitator app. Information recorded will include whether caregivers sent a message (participated or did not participate) in the WhatsApp group over the week during which facilitation content messages were sent. Finally, facilitators will also complete checklists on the activities they carried out in in-person sessions and whether they shared program content on the WhatsApp support groups.

Caregiver self-completion assessments will be administered at 2 time points: baseline and after the intervention. A longer survey will be administered to primary caregivers, and a shorter version will be administered to secondary caregivers. Baseline data were collected between December 6 and 16, 2023. Postintervention data will be collected from all participants 3 weeks after the second in-person session (for participants receiving 2 in-person sessions); all other participants (those receiving only 1 in-person session) will be invited to the school to complete the assessment. All assessment data will be collected using Open Data Kit (ODK; Get ODK Inc). UPM researchers will provide assistance to caregivers with low digital literacy. Caregivers consenting to participate in ParentText but who are unable to attend the in-person session will be contacted by UPM researchers who will administer the survey over the telephone after informed consent and enter responses using ODK on tablet computers.

Direct assessments of a subsample of children (32/160, 20%) will be undertaken at baseline and after the intervention by 2 UPM researchers from the field of child development who will enter scores on the observational measure into ODK on tablet computers.

Qualitative Data

These data will include FGDs with caregivers, KEMAS supervisors, and KEMAS leadership team members as well as individual interviews with facilitators. All FGDs and interviews will be conducted by qualitative researchers from UPM. Participants will be asked for their consent to the discussions and interviews being audio recorded. If any participants decline, notes will be taken instead.

FGDs among caregivers will be conducted at 4 randomly selected schools, and each school will represent 1 condition. Caregivers from the selected schools will be invited to participate with other caregivers from the same school. Two FGDs for each class (1 FGD with male participants and 1 FGD with female participants) will be conducted, resulting in 8 FGDs.

In-depth interviews with 8 facilitators will be held in the 2 weeks after caregivers' completion of the intervention. Interviews will be conducted via web-based videoconferencing.

KEMAS supervisors will participate in an FGD that will be held via web-based video conferencing. KEMAS leadership team members will also participate in an FGD that will be held via web-based videoconferencing. These 2 FGDs will be held during the week after the interviews with the teacher-facilitators.

Data Management

Survey data collection will be carried out through computer-assisted self-interviews using tablet computers, which will be stored in a locked cabinet at the UPM research office and accessed only by authorized personnel on data collection dates. All data collected on tablet computers and exported to ODK will be encrypted as soon as the survey is completed by the interviewer and will be accessible only to senior research personnel on a need-to-know basis. Each tablet computer will have a GPS tracking application that will permit remote deletion of stored information in the event of theft.

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Paper-based surveys will be used in cases where tablet computers malfunction. These surveys will also be stored in a locked cabinet at the UPM research office. They will be destroyed once data have been transferred to ODK via tablet computers and verified for accuracy by the research team.

Quantitative data from the baseline and postintervention assessments will be anonymized and stored in a password-protected University of Oxford secure server. Data on this server will be managed by the University of Oxford central IT team and the Global Parenting Initiative (GPI) data management team, with support from the Department of Social Policy and Intervention IT office. Access, which will be managed by the GPI data management team, will be restricted to study team members or partner organizations involved in the research. Engagement data from ParentText will be stored using end-to-end encryption on the UNICEF server. Participants will be assigned a unique ID number during data collection that will enable linkage of the data across data sets.

Audio recorders will be used for in-person FGDs. Web-based FGDs and interviews will be recorded using the Google Meet audio recording function. Audio recordings from the FGDs and interviews will be transcribed verbatim and stored on password-protected devices, then securely uploaded and backed up on the University of Oxford server. Subsequently, all audio files will be deleted from the recording devices. Transcripts will be anonymized and verified, after which audio recordings will be permanently deleted from the databases.

All electronic documents will be named following a standard format, including the date as version control. Access to anonymized transcripts will be granted only by the GPI data manager via OneDrive for Business (Microsoft Corp) at the University of Oxford. Anonymized data sets will be stored securely for perpetuity and use per UK Data Archive guidance [55]. Raw data will be owned by the University of Oxford and UPM and stored by the University of Oxford. External access to the data will require approval from both principal investigators.

Data cleaning will be conducted during data collection to monitor data quality. Individual raw data sets from the baseline and postintervention evaluations will be stored separately from the final merged data set so that data reference points are available in the data validation process. All electronic documents and data, including quantitative data and transcripts of qualitative data, will be stored on at least 2 servers with access granted individually on a need-to-know basis. Thus, data will be protected from both server failure and confidentiality breaches.

Statistical Methods

All statistical analyses will be performed using Stata (StataCorp LLC) or R statistical software (R Foundation for Statistical Computing). Summary statistics will be used to describe all variables of interest. Descriptive analysis will be conducted to analyze recruitment, retention, adherence, and engagement data (objective 1), and all statistical tests will be 2-tailed with α=.05.

Intervention effects on primary and secondary outcomes (objective 5) will be represented by point estimates and their SEs. The main effect for each intervention component on primary and secondary outcomes will be estimated using multilevel models (including mixed models where outcomes are continuous, Poisson models where outcomes are counts or count distributed, and logistic models where outcomes are binary). Each model will specify 3 levels to account for the longitudinal and clustered nature of the data: repeated measures are nested within individuals, which are, in turn, nested within schools. Level 1 will include a term for categorical time (before and after the intervention) and for the interaction between time and intervention status; level 2 will include terms for individual sociodemographics such as age (parent and child) and gender (parent) and other individual-level covariates, centered at the sample mean; and level 3 will include terms for the intervention components and the stratifying factor. Robust SEs will be estimated to adjust for clustering. This study will report the direction and magnitude of standardized betas, incidence risk ratios, and odds ratios at a significance level of P<.10 with 90% CIs. Two-tailed tests will be conducted across all analyses.

Intervention costs (objective 4) will be estimated from the provider perspective. Resource inputs valued to estimate costs will include facilitator costs, such as those associated with their training to deliver ParentText (captured as their time spent attending training sessions) and with preparing and delivering specific intervention components; physical space used to deliver in-person sessions, which will be audited and valued; and travel and supplies (such as internet data and mobile phones). Local researchers and coordinators will collect resource use data in real time (ie, alongside the full study trial) via the completion of weekly ODK-based surveys. Costs related to the development of ParentText and content adaptation and translation will be included as a capital start-up cost. As the cost analyses will be conducted from the provider perspective, costs incurred by participants (travel expenditure and opportunity costs) will be excluded. While the implementing organization's program monitoring and evaluation costs will be included in the cost estimates, broader research activity costs will be excluded. Program implementation costs and outcomes data will be recorded and analyzed in Excel. The total cost for each intervention condition will then be compared against the number of participants who completed all ParentText modules and for the positive parenting outcome.

Regarding qualitative data, the audio recordings from the interviews and FGDs will be transcribed by UPM researchers. Qualitative data will be analyzed in Bahasa Melayu using NVivo (Lumivero) and Microsoft Word using framework analysis. The analysis will include five stages: (1) familiarization, (2) the identification of themes, (3) indexing, (4) charting and summarization, and (5) interpretation and mapping. Researchers will begin by familiarizing themselves with the transcripts and identifying emerging themes. A code will then be assigned to each theme and subtheme at the indexing stage. After themes are indexed, they will be charted and summarized. Finally, interpretation and mapping will be used to develop a deeper understanding of the findings.

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Data Monitoring

UPM and University of Oxford research teams will oversee the study procedures, including implementation, participant safety, and study conduct. The research teams will also monitor data management throughout its duration, including baseline and postintervention data collection, cleaning, and storage and analysis, and ensure the quality and rigor of the study conduct. A survey monitoring checklist will be created to keep track of errors in data quality checks, such as incorrectly entered names in the participant ID list and duplicates in the data.

Harms

This pilot study will carry out safeguarding strategies developed from universal principles of ethics, respect, beneficence, and justice. The local UPM research team will be trained on the safety protocol for this study. UPM also has its own guidelines on protection from sexual exploitation and abuse (PSEA) under the policy of zero tolerance toward sexual harassment. The guidelines define UPM's commitment to PSEA with regard to adults and children considered vulnerable. The PSEA guidelines fulfill the requirements of the United Nations in ensuring adequate safeguards and action related to PSEA.

Caregivers will be informed of any risks related to their participation in the study. They will have the right to decline any assessment and participation at any time. Caregivers can opt out of ParentText at any time by typing "STOP MESSAGES" in the ParentText WhatsApp chat. Any withdrawal from the study will not affect participants' rights to other services or result in any penalty.

Ethical Considerations

Ethics approval for this study was granted by the University of Oxford Research Ethics Committee (R88954/RE001) on September 18, 2023, and by the UPM Ethics Committee for Research Involving Human Subjects (JKEUPM-2023-1226) on October 15, 2023.

Consent or Assent

Caregivers and Children

Trained program facilitators will collect informed consent from adults and informed assent from children before baseline assessment at local schools in the communities where the study is taking place. Informed consent and assent forms will include clear descriptions of the intervention; study objectives; the use of, and protection measures for, participant data; and participants' rights to refuse to respond to survey questions or withdraw at any point from the study. Children's participation will be conditional on their parents providing consent and their providing verbal assent. Adults who agree to participate in the intervention will be invited to sign a paper-based informed consent form to indicate their consent.

KEMAS Leadership Team Members

UPM researchers will contact potential participants by telephone and read out the information sheet and consent form. If they agree to participate, they will be asked to sign the consent form and email it to the UPM research coordinator, who will print and securely store the form and delete the email.

KEMAS Supervisors

UPM researchers will obtain informed consent from supervisors after they attend an in-person training of trainers session. UPM researchers will read out the study information and respond to any questions or concerns that participants raise. Supervisors who agree to participate will be asked to sign a paper-based informed consent form. Those who sign will be invited to participate in an FGD after the completion of the program.

Facilitators

UPM researchers will obtain informed consent from teachers after they attend the Naungan Kasih training session. UPM researchers will read out the study information and respond to any questions or concerns that participants raise. Teachers who agree to participate will be asked to sign a paper-based informed consent form. Those who sign will be invited to participate in a qualitative interview after the completion of the program.

Privacy and Confidentiality

Anonymized baseline and postintervention data sets will be stored in a password-protected server at the University of Oxford. Access will be controlled and only granted to members of the study team or partner institutions that aided in the research project. Audio recordings of the interviews and FGDs will be transcribed verbatim and stored in password-protected devices and will then be securely uploaded and backed up at the University of Oxford server. Once uploaded to the server, the audio files will be deleted from the recording devices. After the transcripts have been anonymized and verified, the audio recordings will be permanently deleted from data repositories. All Excel and Word files will be named following a standardized protocol, including the download date, to ease version control. Deidentified interview transcripts and data sets will only be shared by the GPI data manager by granting access to specific files through OneDrive for Business at the University of Oxford. Deidentified data sets will be stored securely for perpetuity and use per UK Data Archive guidance. Raw baseline and postintervention data collected will be owned by UPM and the University of Oxford.

Data captured from ParentText is stored in an encrypted anonymous database managed by UNICEF Malaysia. Personally identifiable information, such as the user's telephone number, is never stored. Data captured from the facilitator app are also anonymous and stored in an encrypted server hosted by IDEMS International. Both the application and chatbot are General Data Protection Regulation compliant.

Compensation

Parents will receive compensation for their participation at 3 stages of the research: survey completion at baseline data collection, survey completion at postintervention data collection, and participation in FGDs at postintervention data collection. They will receive MYR 50 (US $10.5) for their participation at each stage. They can therefore receive up to MYR 150 (US $31.5) for participation in the study.

Access to Data

Only the University of Oxford and UPM will have access to the raw research data. Access to clean and pseudoanonymized

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data sets and interview transcripts will be managed by the GPI data manager and evaluated on a need-to-know basis. UNICEF and the Malaysian Association of Social Workers, the implementing partners, will also have access to these data sets to assist with data quality checks.

Ancillary and Posttrial Care

Safeguarding procedures will be used to mitigate risks to participants. The informed consent form for study participants indicates that if the participant feels anxious or worried during their involvement in the trial, they will be offered support such as counseling.

Results

Recruitment began on December 6, 2023, and as of December 29, 2023, a total of 208 caregivers had been recruited into the trial. The intervention was completed on February 7, 2024. Follow-up data collection was completed on March 12, 2024. Data management is still in progress; therefore, data analysis has yet to be performed. Results are expected to be published in the second half of 2024.

Discussion

Summary

This factorial cluster randomized trial is the first to evaluate the feasibility of a hybrid human-digital playful parenting program in Southeast Asia. It explores this in 2 contrasting contexts in Malaysia—an urban setting in Kuala Lumpur and a rural setting in Negeri Sembilan—which aims to maximize the generalizability of its results. The findings from this study will contribute to understanding the viability for such a hybrid program to be scaled up in similar contexts to Malaysia. By examining the feasibility, acceptability, and effectiveness of ParentText, which is delivered along with a WhatsApp support group and 1 or 2 in-person sessions, the study will provide important insights into the optimal combination of intervention components. The findings may identify versions of the intervention that are considerably more or less feasible than others, which could inform their inclusion or exclusion in future evaluations of the program.

In addition to this trial, other trials of different versions of ParentText are currently underway that will further contribute to the evidence base on the feasibility and effectiveness of hybrid parenting programs. In South Africa and Tanzania, cluster randomized controlled trials are being conducted among caregivers of adolescent girls (in South Africa) [56] and caregivers of adolescents (in Tanzania) [36,57].

Limitations

This study has 2 main limitations. First, because the aim of the study is primarily to evaluate feasibility and not effectiveness, the sample size is likely too small to have the statistical power to detect significant differences in outcomes among the different program versions. Second, the study will not provide information on the reasons for nonparticipation of those who did not enroll. Given that this study aims to investigate the acceptability of the program, understanding barriers to participation would inform potential adaptations to its content and delivery in preparation for future testing to maximize recruitment and engagement.

Acknowledgments

This study is part of the Global Parenting Initiative, which is funded by the LEGO Foundation, the Oak Foundation, the World Childhood Foundation, The Human Safety Net, and the UK Research and Innovation Global Challenges Research Fund (ES/S008101/1). The study sponsors and funders had no role or influence in the conceptualization and design of this trial. They will not have any role in implementation, analysis, the interpretation of data, or the dissemination of results.

Data Availability

The data sets generated during and analyzed during this study will be available in the OSF repository [58].

Authors' Contributions

UPM and University of Oxford team members led the conceptualization and writing of this protocol. All authors contributed to the conceptualization, development, and writing of this manuscript. RJ and JML are the principal investigators on the study. HC, IV, NI, FZMD, ZA, FC, FG, and SV provided critical input in the selection of the quantitative measures in this study. HC and RJ led the development of qualitative measurements. SV, GJMT, and JML contributed to the proposed research design and statistical analysis. LM, CF, HC, and DR developed the content for the chatbot. All authors provided critical feedback and revised sections of the manuscript and approved the final manuscript.

Conflicts of Interest

ParentText was developed by members of the research team. JML is the chief executive officer of Parenting for Lifelong Health (PLH), which holds the intellectual property rights of the intervention content. HC, FG, IV, SV, FC, LM, DR, VS, and RJ work for or with PLH, and the University of Oxford receives research grants to support this work. All other authors declare no other conflicts of interest. The investigators will not benefit financially from the implementation and dissemination of the intervention.

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Multimedia Appendix 1
List of Jabatan Kemajuan Masyarakat (Department of Community Development; KEMAS) preschools for the feasibility pilot study.
[DOCX File , 25 KB - resprot_v13i1e55491_app1.docx]

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Abbreviations

FGD: focus group discussion
GPI: Global Parenting Initiative
KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development)
LMIC: low- and middle-income country
ODK: Open Data Kit
PSEA: protection from sexual exploitation and abuse
TABIKA: Taman Bimbingan Kanak-Kanak (Children's Guidance Park)
UNICEF: United Nations Children's Fund
UPM: Universiti Putra Malaysia

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Protocol

Digital Intervention (Keep-On-Keep-Up Nutrition) to Improve Nutrition in Older Adults: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Digital health tools can support behavior change and allow interventions to be scalable at a minimal cost. Keep-on-Keep-up Nutrition (KOKU-Nut) is a free, tablet-based app that focuses on increasing physical activity and improving the dietary intake of older adults based on UK guidelines. The intervention targets an important research area identified as a research priority reported by the James Lind Alliance priority setting partnership for malnutrition.

Objective: This study aims to assess the feasibility of using the digital health tool KOKU-Nut among community-dwelling older adults to inform a future randomized controlled trial. The secondary aims are to determine the acceptability, usability, preliminary effect sizes, and safety of the study and the intervention (KOKU-Nut).

Methods: This is a feasibility randomized controlled trial. We plan to recruit a total of 36 community-dwelling older adults using purposive sampling. Participants will be randomized 1:1 to either the intervention or the control group. The intervention group will be asked to engage with KOKU-Nut 3 times a week for 12 weeks. Participants in the control group will receive a leaflet promoting a healthy lifestyle. All study participants will complete questionnaires at baseline and the end of the 12 weeks. A sample of participants will be asked to participate in an optional interview. The study will collect a range of data including anthropometry (height and weight), dietary intake (3-day food diary), physical function (grip strength and 5-times sit-to-stand), perceived quality of life (EQ-5D), usability (System Usability Scale), and safety (adverse events).

Results: Data collection commenced in March 2024, and the results will be ready for publication by January 2025. Feasibility will be determined on the basis of participants' self-reported engagement with the intervention, and recruitment and retention rates and will be summarized descriptively. We will also consider the amount of missing data and assess how outcomes are related to group assignment. Acceptability will be measured using the modified treatment evaluation inventory and one-to-one semistructured interviews. Transcripts from the interviews will be analyzed using NVivo (version 12; QSR International) software using framework analysis to understand any barriers to the recruitment process, the suitability of the assessment measures, and the acceptability of the intervention and study design.

Conclusions: The study aligns with guidelines developed by the Medical Research Council for developing a complex intervention by using qualitative and quantitative research to examine the barriers of the intervention and identify potential challenges around recruitment and retention. We anticipate that these results will inform the development of a future powered randomized controlled design trial to test the true effectiveness of KOKU-Nut.

Trial Registration: ClinicalTrials.gov NCT05943366; https://classic.clinicaltrials.gov/ct2/show/NCT05943366

International Registered Report Identifier (IRRID): PRR1-10.2196/50922

(JMIR Res Protoc 2024;13:e50922) doi:10.2196/50922

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KEYWORDS

feasibility; usability; digital health; diet; gerontology; geriatric; geriatrics; older adult; older adults; elder; elderly; older person; older people; ageing; aging; dietary; nutrition; hydration; community dwelling; RCT; randomized; controlled trial; controlled trials

Introduction

It is well established that progressive resistance training combined with strength and balance exercises are safe and effective for improving muscle mass, hip and lumbar spine bone mineral density, and muscle strength and function [1] and for reducing the risk of falls [2], hospitalizations, fractures [3], and mortality. Furthermore, diet has a fundamental role in the health of older adults [4], and meta-analyses have found that nutritional interventions in addition to physical activity lead to greater improvements in physical function, body composition, and strength in frail and pre-frail older adults [5-7].

Advancements in technology have provided the opportunity for digital platforms to remotely deliver, monitor, and complement patient care. Digital platforms can complement traditional face-to-face programs or provide an alternative option based on the individual's preference and financial situation [8]. Furthermore, digital interventions can be scalable so they can maximize outreach at a minimum cost. Mobile apps are increasingly being used to support dietary change [9] and increase physical activity [10]; however, most are not designed for the older adult population. A recent systematic review identified that apps can be effective at increasing physical activity levels in community-dwelling older adults [8]; however, there has been little research investigating the effectiveness of apps to prevent malnutrition in this population [11].

Keep-on-Keep-up (KOKU) is a free, tablet-based gamified strength and balance exercise app that was soft launched in 2020 [12]. KOKU is approved by the National Health Service and Organization for the Review of Care and Health Apps as a lifestyle app and has been viewed positively by older adults after 6 weeks of independent use [13]. Anonymized Google analytics data show that there are more than 1000 users in the United Kingdom and users averaged 2.2 sessions per week, with an average weekly engagement of 1 hour 51 minutes. KOKU has a collection of health literacy games, and studies internationally found that engagement with the app led to increased exercise frequency and qualitative feedback found that the gamification was engaging and motivating [13]. Keep-on-Keep-up-Nutrition (KOKU-Nut) is a development of this gamification platform and includes an educational and interactive game based on the UK dietary guidelines to nudge older adults to improve their diet [14,15]. The game requires the user to choose a pair of cards to reveal food items, with the aim of finding matching food items. The user is presented with information about the different food items, and upon finding all the matching pairs, the user is provided with important tips to improve their diet and reduce their risk of malnutrition.

The intervention is based on qualitative work with 33 older adults to understand their determinants of dietary intake and barriers to healthy eating. Initial prototypes were tested on a diverse group of end users and health care professionals to facilitate co-design and ensure that the needs of the user were taken into consideration.

This study aims to assess the feasibility of conducting a randomized controlled trial (RCT) using KOKU-Nut to improve the dietary intake of community-dwelling older adults. The secondary aims are to determine the acceptability, usability, preliminary effect sizes, and safety of the study and the intervention (KOKU-Nut). These aims are in line with the Medical Research Council Framework that advocates conducting a feasibility study as part of the development and evaluation of complex interventions to assess the study design and the intervention itself [16].

Methods

Study Setting

This is a feasibility parallel group RCT study design using 1:1 randomization using both quantitative and qualitative methods to explore the feasibility and acceptability of KOKU-Nut (a digital service that aims to improve nutritional and fluid intake in community-dwelling older adults). Data will be collected from community-dwelling older adults living in Greater Manchester in the United Kingdom. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement and CONSORT (Consolidated Standards of Reporting Trials) statement extended to randomized pilot and feasibility trials and associated checklist were used in the design and reporting of this study [17,18] (Multimedia Appendix 1). Version 3 of the protocol was last updated on February 5, 2024.

Eligibility Criteria

Participants will be included in the study if they are aged 65 years or older, living independently in the community, have access to the internet, and are willing to use an iPad or tablet (their own or one provided) for the duration of the study. Participants will be excluded if they are unable to communicate in English or have a known cognitive impairment.

Interventions

Participants in the intervention group will be helped to download KOKU-Nut onto their iPad or tablet during the baseline visit. The researcher (CF) will demonstrate the features and assist with any technical queries. In cases where participants do not have the necessary devices or data to join the intervention, a tablet with KOKU-Nut installed will be provided for the duration of the intervention. Participants will be asked to engage with KOKU-Nut at least 3 times a week throughout the 12-week period. This will involve carrying out strength and balance exercises and engaging with the gamification features relating to bone health and healthy eating. A crib sheet and contact details for the research team will be available if participants require additional support to help with technical issues.

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Participants assigned to the control group will continue with usual care and receive a leaflet developed by Age UK about the importance of a healthy lifestyle including information on the importance of staying active and nutrition [19]. This will allow the comparison of a more traditional way to provide lifestyle advice compared to the digital health tool.

Outcomes

Primary outcomes will be related to feasibility and will assess engagement with the intervention, recruitment and retention rates, and acceptability of the intervention and study design. These findings are important to inform the development of a large-scale RCT in community-dwelling older adults to compare the effectiveness of KOKU-Nut to an information booklet about healthy living. Recruitment rates will be assessed as cumulative recruitment against the target rate each month. Retention rates will be calculated as the number of participants who completed the study divided by the number of participants randomized. Engagement with the intervention will be based on self-reported use of KOKU-Nut at the end of the 12 weeks (every day, 3-4 times a week, 1-2 times a week, and once or twice a month). A questionnaire previously developed and used by the research team for the KOKU app will assess the acceptability of KOKU-Nut [13]. Intervention acceptability will also be assessed using the 11-item, 7-point, modified Treatment Evaluation Inventory [20]. Higher scores indicate higher acceptability, with a score of 44 indicating moderate acceptability. Interviews will explore the acceptability of the intervention and the perceived impact of taking part in the study. Interviews will also consider the participant's experience of the recruitment process, the assessment tools used, and their experience and motivation for participating in the study (positive and negative).

Secondary outcomes will consider the usability and safety of the intervention and the practicality of collecting and assessing the effectiveness of KOKU-Nut compared to an information booklet about healthy living. The perceived usability of KOKU-Nut will be assessed using the validated 10-item system usability scale. Responses are measured on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). A score >68 is considered above-average usability and >80 is considered high usability such that participants are likely to recommend the product to peers. The safety of the intervention will be based on the number of adverse events that occurred as a result of participation in the study. We will consider the practicality of collecting effectiveness data by documenting the amount and rationale for any missing data. Changes in means and SDs will be compared to consider the preliminary effectiveness of the intervention and to calculate sample sizes for a future trial. The study will be assessed against progression criteria based on Shanyinde et al [21] to determine progression to a powered RCT. Figure 1 shows the schedule of the intervention and assessment according to the SPIRIT statement.

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Figure 1. Schedule of enrollment, interventions, and assessments.

Sample Size

As this is a feasibility study that is not designed to detect statistically significant differences in measures, no formal power calculation has been conducted to determine the sample size. Lancaster et al [22] recommend a sample size of 36 participants for feasibility and pilot studies, so after accounting for potential dropout (at 20%), we aim to recruit 18 participants in each arm.

Recruitment

Men and women aged 65 years and older living independently in the community will be recruited through purposive sampling via local age UK groups, assisted living facilities, and university networks. We plan to recruit a mixture of participants with and without access to a tablet computer to explore differences in the outcomes and the experiences between those with and without prior experience with tablets or iPads.

The study will be advertised using social media, posters, and through current collaborations with sheltered housing facilities,

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local charities, and community-based organizations across Greater Manchester. Staff at assisted living facilities, charities, and community organizations will act as gatekeepers and will offer potential participants flyers about the study and participant information sheets. Older adults who are interested in participating can agree to have their details passed over to the research team (CF) and will complete the consent to contact form. The research team will follow up with participants who are interested in joining the study and screen potential participants. Alternatively, potential participants may contact the research team directly following the study advertisement in posters and on social media to find out more information and check their eligibility. An existing research database will also be used where older adults have previously consented to be contacted about future research. Participants on the research database will be contacted directly by the research team with the participant information sheet and summary of the research according to their preferred choice (via email, telephone, or letter). The research team will then arrange to conduct an initial telephone screening over the phone to determine eligibility, provide further information about the study, and answer any questions.

Recruitment for the qualitative interviews will be done purposefully, to recruit a demographically representative group of participants. To do this, the sample frame will be divided into a number of smaller groups, namely the treatment group, age, gender, and prior ownership of a tablet or iPad. Individuals will then be drawn at random from each of these groups. We also plan to contact any dropouts to understand their rationale for dropping out to optimize the retention of participants if continuing to a full RCT. Researchers will use the concept of information power [23] to determine the number of interviews, but we anticipate sufficient data will be obtained from interviewing 20% of participants recruited for the study. Figure 2 represents the overall flowchart of participants through the study.

Participants who meet the screening criteria and are interested in taking part will provide informed written consent (Multimedia Appendix 1) before being formally enrolled in the study. During the screening phone call, the researcher (CF) will arrange a date and time suitable for the participant to conduct the initial baseline assessment. Prior to completing baseline measures, participants will be randomized in a 1:1 ratio to receive the intervention (KOKU-Nut) or to the control group and receive usual care.

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Figure 2. Flowchart of participants from screening to follow-up.

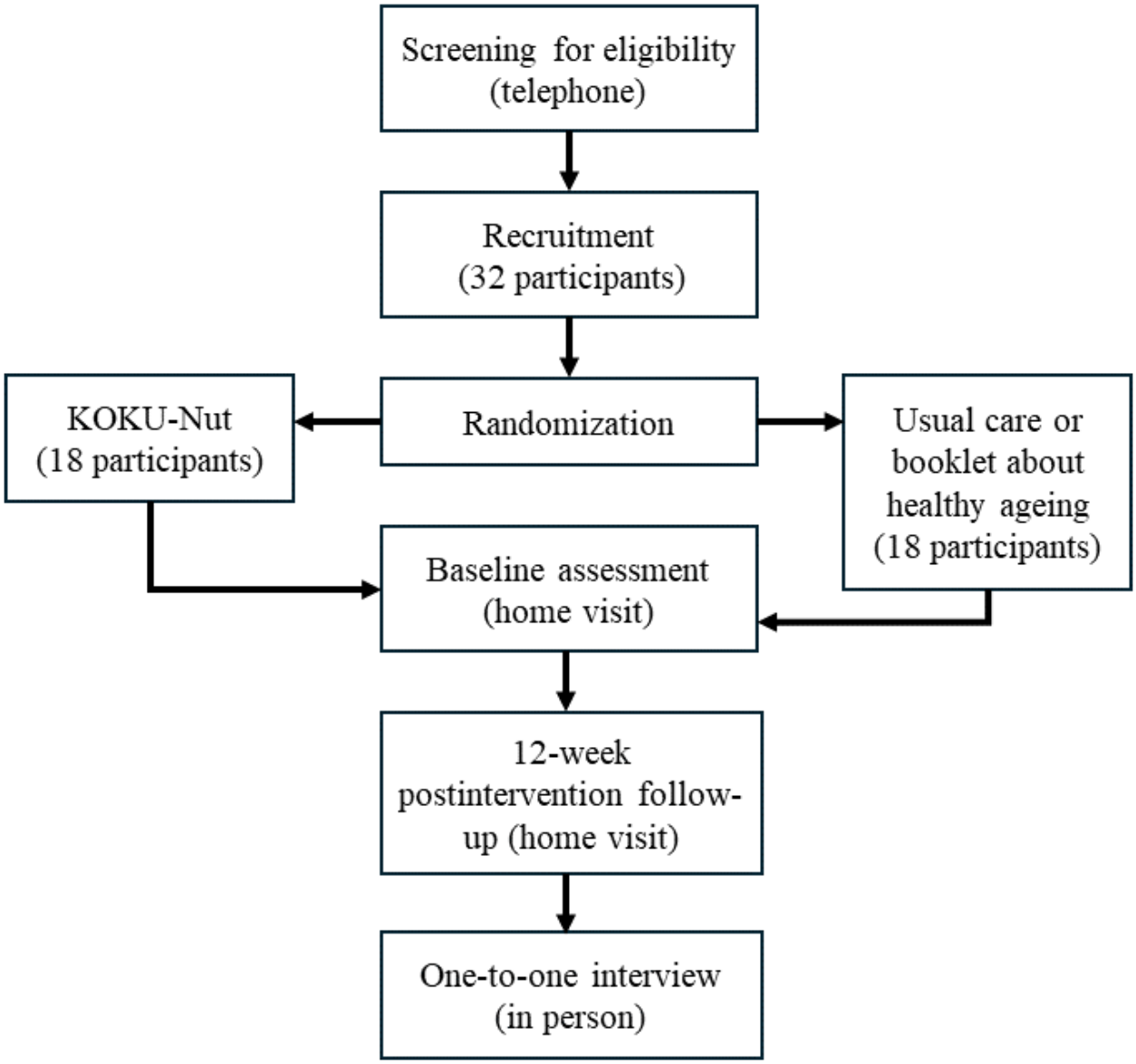

Allocation

Randomization will be undertaken by a separate member of the research team using the Sealed Envelope randomization service [24], and participants will be stratified by age group (65-75 years and 76 years and older), gender, and prior experience of using a tablet or iPad. Given the nature of the intervention, participants and researchers will be unblinded.

Data Collection Methods

Overview

All participants will receive in the post a baseline case report file to be completed before the baseline assessment to collect sociodemographic information including age, gender, ethnicity, marital status, occupation, use of digital technology, shopping, and cooking habits. Participants will also be asked to complete a 3-day food diary using Intake24 prior to the baseline visit [25]. This web-based dietary assessment tool is compliant with the general data protection regulations (2018), and participants will be sent a unique number that will enable the researcher to identify the digital dietary records. Data collected will be used to assess the consumption of different food groups to identify adherence to the Eatwell guide [14]. During the home visit, the researcher (CF) will collect baseline measurements to assess anthropometry, dietary intake, physical function, quality of life, mood, and frailty. All measurements are responsive to change, appropriate for use in this population, and easily assessed in a community setting.

At the end of the 12-week intervention period, all baseline measures will be repeated, and participants will complete a follow-up case report file to collect feasibility outcome data. The researcher will conduct one-to-one semistructured interviews with a selected group of participants from both the intervention and the control group. Interviews will be conducted in person or over the phone depending on the preference of the participant. Interviews will last approximately 60 minutes, will be audio-recorded, and then transcribed verbatim by the research

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team. Additional consent will be collected prior to conducting the interview. A topic guide developed for the study will be used flexibly to guide the interviews.

Anthropometry

A member of the research team will measure height to the nearest centimeter using a stadiometer (Harpenden pocket stadiometer Practical Metrology) and body weight to the nearest 0.1 kg (TANITA, Arlington Heights). BMI will be calculated and categorized according to standard cutoffs [26].

Dietary Assessment

A researcher (CF) who is also a registered nutritionist will use the malnutrition universal screening tool as recommended by the European Society for Clinical Nutrition and Metabolism to assess the risk of malnutrition [27].

Physical Function

Participants will be asked to complete the 5-times sit-to-stand physical function test. The 5-times sit-to-stand requires participants to rise from a chair 5 times as quickly as possible with arms folded across their chest and the researcher will record the time taken to complete the task. The researcher will then calculate lower limb muscle power using the validated equation developed by Kirk et al [28] and Alcazar et al [29]. Grip strength will be assessed on a Takei 5001 analog hand grip dynamometer (Takei Scientific Instruments Co, Ltd) 3 times on each hand with the best score used for analysis.

Quality of Life

The participants' perceived state of health and quality of life will be assessed using the validated EQ-5D questionnaire in combination with the EQ-5D-5L [30]. The EQ-5D questionnaire comprises 5 questions assessing mobility, self-care, usual activities, pain or discomfort, and anxiety or depression to produce an overall score representing the participant's health profile. The score will range from 1 (full health) to 0 (state of health equitable to death), with the option to have negative values representing a state of health considered to be worse than death [31]. The EQ-5D-5L is a visual scale ranging from 0 (worst health imaginable) to 100 (best health imaginable), where participants indicate how they perceive their current health status both on a number line and numerically [31].

Mood

Participants will complete the 4-item Geriatric depression scale as part of the baseline questionnaire, given that mood can affect motivation and may affect the use of KOKU-Nut.

Frailty

The researcher will assess frailty status based on the descriptions and pictographs included in the clinical frailty scale, which has been well validated and is frequently used in adults aged 65 years and older [32,33].

Data Monitoring and Management

All digital and physical data will be stored securely at the University of Manchester and securely destroyed at the end of the data retention period as stated in the data management plan. Digital data will be stored on a backup drive on the university's central server accessible by the research team. On enrollment to the study, all participants will be assigned a unique identification number with all subsequent data stored against this pseudonymized number. Identifiable information (such as name and contact details) will be stored separately and will only be linked to study-collected data through a recruitment log which will be password protected and file access will be limited to researchers working on the study. All printed documentation including consent forms and participants' case files will be stored in a locked storage cabinet in a designated location at the University of Manchester. Interviews will be recorded on an encrypted Dictaphone. Audio recordings will be securely destroyed (digitally shredded) from the Dictaphone after being transcribed and validated by a member of the research team.

Statistical Analysis

All quantitative data will be analyzed in STATA (version 15; StataCorp). The primary outcome will be calculated with regard to the indicators of feasibility to investigate engagement with the intervention, recruitment and retention rates, and acceptability of the intervention and study design. These will be summarized appropriately using descriptive statistics including percentages, mean with SDs, and ranges. Pre-post intervention changes in health measures will be analyzed in an exploratory fashion to gain preliminary insights into the number of valid versus missing data and to assess how outcomes are associated with group assignment and intervention engagement. Effect sizes will be determined using Cohen *d* to calculate sample sizes for a powered RCT.

Qualitative interview transcripts will be managed using NVivo software (version 12; QSR International Pty Ltd) and analyzed using an inductive approach with the 5 stages of framework analysis [34,35] to understand any barriers to the recruitment process, the suitability of the assessment measures, and the practicality of using the KOKU-Nut intervention. The first stage of framework analysis involves familiarization of the data from the transcripts and audio-recordings. The second stage involves classifying the data into codes and identifying a thematic framework from the key themes identified. The third stage involves systematically indexing the data using the framework identified. The fourth stage involves charting and synthesizing the data to categorize and capture key concepts and themes. The final stage involves the mapping and interpretation of the data [34]. All stages of the analysis process will be discussed and reviewed with at least 2 researchers (ES and SB) to ensure rigor [36].

Ethical Considerations

Ethics approval was obtained from The University of Manchester Research Ethics Committee on August 18, 2023 (2023-17372-30569) to ensure that adequate safeguards are in place to protect the privacy of participants and to maintain the confidentiality of data. This study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and the Declaration of Helsinki guidelines. Prior to data collection, all the participants who agreed to participate in the study will sign a consent form, which includes a description of the study, its objectives, and participants' involvement and rights (Multimedia Appendix 1). Participation

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in the study is entirely voluntary and participants can withdraw at any time. Participants will not receive financial compensation for their contribution to the study. Any deviations from the protocol will be put through the appropriate ethical amendment process. It is not anticipated that the study will be stopped prior to its intended end date. However, the study will be halted if safety issues arise regarding the intervention or resources to conduct the study are no longer available. Outcomes will be disseminated through conference presentations and publications in peer-reviewed journals in deidentified form. The findings will also be shared through presentations with digital inclusion teams and community stakeholders.

Results

We anticipate recruitment will commence in March 2024 and will continue until enrollment is complete (N=36). The analysis is expected to be completed by November 2024, and the results will be published by January 2025.

Discussion

Principal Findings

The intervention (KOKU-Nut) involves educating users about how and why to make lifestyle changes, encouraging participation in regular and progressive strength and balance activities, and nudging older adults to improve their dietary intake. These features are underpinned by behavior change theories and have been co-designed with end users.

In comparison to many physical activity digital health tools such as Nymbl and Standing Tall, KOKU-Nut incorporates a nutritional component with a focus on dietary protein and fluid intake, given their low intakes among older adults [37,38] and their role in health [39,40]. The impact of diet is well established and can help older adults maintain health status and physical function [41]. Furthermore, it is estimated that one-quarter of Europeans older than the age of 65 years are at a high risk of malnutrition [42], and this can increase the risk of frailty, musculoskeletal conditions, and mortality [43-45]. In addition to the high prevalence of malnutrition, a recent James Lind Alliance priority setting partnership identified early intervention in vulnerable groups as a top priority [46].

There has been a rapid development in the number and quality of mobile health apps, and there is a growing acceptance among older adults. These tools have many benefits including that they can increase motivation through notifications and tracking of progress and provide personalized feedback to the user and increase engagement through gamification. However, there are still many challenges around introducing new digital health apps to this population. The usability of digital technology is important to ensure sustained use and to allow users to engage with the product for its intended purpose. Acceptability refers to the extent to which users consider the digital technology appropriate. Mobile apps are more likely to be usable and acceptable to older adults if they are codeveloped with them using principles of human-centered design [47,48]. KOKU-Nut was co-designed with end users and health care professionals, and we hope this will maximize the usability and usefulness of the interface and content.

This study will provide information on the feasibility and usability of the mobile health app KOKU-Nut. To our knowledge, this is the first digital health app in the United Kingdom designed to empower community-dwelling older adults to increase their activity levels and improve their diet and fluid intake so that they can stay active and healthy for longer.

Study Limitations

This study has a number of limitations. We plan to recruit participants using purposive sampling from across Greater Manchester and thus this limits the generalizability of the results to the rest of the United Kingdom and internationally. However, this is a feasibility study that aims to inform a powered RCT that would then enable conclusions to be drawn. Furthermore, many of the study outcomes including dietary assessment and assessments of feasibility are self-reported and so prone to recall bias. Questionnaires will be checked for completeness and Intake24 appears to report similar data to intakes reported in interviewer-led dietary recall [49] and the gold standard assessment of energy intake using doubly labeled water [50].

Conclusions

To our knowledge, this will be the first RCT to evaluate a digital health tool that nudges community-dwelling older adults living in the United Kingdom to improve their dietary intake and reduce the risk of malnutrition. The study aligns with guidelines developed by the Medical Research Council for developing a complex intervention by using qualitative and quantitative research to examine the barriers to intervention from the perspective of users and identify potential challenges around recruitment and retention [51].

Acknowledgments

CF receives financial support from the Medical Research Council (CASE Entry: /R015767/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data Availability

We plan to write up the findings for publication, which will include an overview of the anonymized data. The data sets generated and analyzed during this study are not publicly available in accordance with the data management plan but are available from the corresponding author on reasonable request.

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Authors' Contributions

CF was involved in the study design and writing the manuscript. ES and SB were involved in the study design and editing of the manuscript.

Conflicts of Interest

ES is the Director of Keep-On-Keep-Up Health Community Interest Company. CF and SB declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Multimedia Appendix 1
Supplementary material to demonstrate SPIRIT checklist (S1), CONSORT checklist (S2) and Consent form (S3).
[DOCX File , 40 KB - resprot_v13i1e50922_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
KOKU: Keep-on-Keep-up
KOKU-Nut: Keep-on-Keep-up Nutrition
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

An mHealth Intervention for Gay and Bisexual Men's Mental, Behavioral, and Sexual Health in a High-Stigma, Low-Resource Context (Project Comunic): Protocol for a Randomized Controlled Trial

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Abstract

Background: The World Health Organization reported that 80% of new HIV diagnoses in Europe in 2014 occurred in Central and Eastern Europe. Romania has a particularly high HIV incidence, AIDS prevalence, and number of related deaths. HIV incidence in Romania is largely attributed to sexual contact among gay and bisexual men. However, homophobic stigma in Romania serves as a risk factor for HIV infection for gay and bisexual men. The Comunică intervention aims to provide a much-needed HIV risk reduction strategy, and it entails the delivery of motivational interviewing and cognitive behavioral therapy skills across 8 live text-based counseling sessions on a mobile platform to gay and bisexual men at risk of HIV. The intervention is based on the information-motivation-behavior and minority stress models. There is preliminary evidence suggesting that Comunică holds promise for reducing gay and bisexual men's co-occurring sexual (eg, HIV transmission risk behavior), behavioral (eg, heavy alcohol use), and mental (eg, depression) health risks in Romania.

Objective: This paper describes the protocol for a randomized controlled trial designed to test the efficacy of Comunică in a national trial.

Methods: To test Comunică's efficacy, 305 gay and bisexual men were randomized to receive Comunică or a content-matched education attention control condition. The control condition consisted of 8 time-matched educational modules that present information regarding gay and bisexual men's identity development, information about HIV transmission and prevention, the importance of HIV and sexually transmitted infection testing and treatment, heavy alcohol use and its associations with HIV

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transmission risk behavior, sexual health communication, finding social support, and creating sexual health goals. Participants undergo rapid HIV and syphilis testing and 3-site chlamydia and gonorrhea testing at baseline and the 12-month follow-up. Outcomes are measured before the intervention (baseline) and at the 4-, 8-, and 12-month follow-ups.

Results: The study was funded in September 2018, and data collection began in May 2019. The last participant follow-up was in January 2024. Currently, the data analyst is cleaning data sets in preparation for data analyses, which are scheduled to begin in April 2024. Data analysis meetings are scheduled regularly to establish timelines and examine the results as analyses are gradually being conducted. Upon completion, a list of manuscripts will be reviewed and prioritized, and the team will begin preparing them for publication.

Conclusions: This study is the first to test the efficacy of an intervention with the potential to simultaneously support the sexual, behavioral, and mental health of gay and bisexual men in Central and Eastern Europe using motivational interviewing support and sensitivity to the high-stigma context of the region. If efficacious, Comunică presents a scalable platform to provide support to gay and bisexual men living in Romania and similar high-stigma, low-resource countries.

Trial Registration: ClinicalTrials.gov NCT03912753; https://clinicaltrials.gov/study/NCT03912753

International Registered Report Identifier (IRRID): DERR1-10.2196/52853

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KEYWORDS

gay and bisexual men; HIV prevention; heavy alcohol use; stigma; mental health; behavioral intervention; mobile phone

Introduction

Background

The World Health Organization reported that 80% of new HIV diagnoses in Europe in 2014 occurred in Central and Eastern Europe (CEE) [1]. Of the 15 surveyed European countries, Romania had the second-highest HIV incidence and AIDS prevalence and the highest number of AIDS-related deaths between 2005 and 2014 [1]. After the first wave of the HIV epidemic in Romania, which occurred in children via nosocomial infection in the 1980s [2-6], a new wave, largely attributed to male-to-male sexual contact, has emerged and is increasing [1,7,8]. The increased exposure of gay and bisexual men to HIV and other sexually transmitted infections (STIs) in the past 2 decades has purportedly resulted from more frequent travel to and from areas of high HIV prevalence outside Romania, including many European Union (EU) states in Western Europe [9]; lack of sexual education in Romania in general [10-12] and specifically sexual education that responds to gay and bisexual men's distinct sexual health needs [13]; and pervasive stigma against gay and bisexual men [14].

Despite these co-occurring threats resulting in increased HIV transmission risk, gay and bisexual men remain underprioritized in Romanian public health [2]. Furthermore, reporting of epidemiologic data might be unreliable in Romania due to ineffective surveillance systems and gay and bisexual men's anticipated stigma and normative identity concealment [15]. As a result, HIV transmission among gay and bisexual men is frequently underreported or misclassified as heterosexual [1,16,17]. For instance, an independent European survey found that the number of HIV diagnoses self-reported by Romanian gay and bisexual men respondents was 2.7 times the official national notification rate [17], suggesting that a significant proportion of HIV infections occurring among the gay and bisexual men community might be attributed to heterosexual transmission, thus yielding inaccurate guidance for national HIV-related priorities.

The best available evidence suggests that HIV prevalence among Romanian gay and bisexual men increased from <10% in 2009 to approximately 20% in 2014 [18-20]. An international biobehavioral survey of gay and bisexual men found that Romania had the highest rate of unrecognized HIV infections across all included European countries [19-22]. Untreated STIs represent a primary risk factor for HIV transmission [23], yet gay and bisexual men–sensitive screening for STIs is rare in Romania. For example, of 629 gay and bisexual men who sought an STI test over 1 year in the capital city of Bucharest, only 6.4% received both an anal swab and penile examination (compared to 72.4% in Amsterdam)—the lowest rate in all 40 cities participating in a European survey of gay and bisexual men (N=174,209). Furthermore, fewer than one-third of Romanian gay and bisexual men had been screened for STIs in the previous year, and fewer than half knew where they could access STI testing [20,24].

Insufficient sexual health knowledge specific to gay and bisexual men in Romania has direct implications for HIV transmission. A 2017 survey of 50 European and contiguous countries found that, of 2002 Romanian gay and bisexual men respondents, only 0.4% had ever used pre-exposure prophylaxis (PrEP) and 1.1% had ever used postexposure prophylaxis, whereas 62% were unaware of PrEP and only 56% were knowledgeable regarding *undetectable=untransmissible*. A total of 13% of respondents reported having at least 2 steady sex partners in the previous year with whom they did not use condoms (the third highest rate among the 50 surveyed countries); 32% reported having condomless sex due to lack of access to condoms (the seventh highest rate among the 50 surveyed countries) [25]. Of those who had never been tested for HIV (approximately 50% in the Romanian sample), half (51%) did not know where to get tested (the fifth highest rate among the 50 countries) [25].

In terms of mental and behavioral health needs that can co-occur with HIV transmission risk among gay and bisexual men [26,27], European surveys indicate that 12% of Romanian gay and bisexual men reported severe anxiety and depression during

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the previous 2 weeks, 21% had thoughts of self-harm [25], and 14% met criteria for alcohol dependency. Homophobic stigma is also a risk factor for HIV transmission and co-occurring mental and behavioral health risks as it keeps most Romanian gay and bisexual men hidden and out of reach of official HIV and STI surveillance and the few available prevention services. Depression, anxiety, heavy alcohol use, and homophobic stigma combine to create a syndemic affecting gay and bisexual men [28-30].

Despite gains in some rights for lesbian, gay, bisexual, transgender, and queer (LGBTQ) individuals (eg, decriminalization of homosexuality) over the past 2 decades, Romania remains one of the most structurally homophobic countries in Europe [31,32], with structural homophobia being associated with low life satisfaction, poor mental health, social isolation, internalized homonegativity, and high degrees of identity concealment among gay and bisexual men [15,31,33]. Identifying as an ethnic minority group (eg, Roma) may further amplify the odds of encountering hate speech and harassment [34], and there might be intersectional challenges for ethnic minority gay and bisexual men in Romania [35]. A recent report by the EU Agency for Fundamental Rights found significant physical or sexual attacks against LGBTQ people in Romania (15%) [34]. Of 28 EU member states, Romania was among the top 3 countries in terms of the prevalence of hate-motivated physical or sexual attacks against LGBTQ people [34]. Perhaps as a further manifestation of structural stigma toward gay and bisexual men, no governmental funds are currently allocated for HIV and STI prevention among gay and bisexual men in Romania despite the clear and increasing need for such prevention, as outlined previously [2,18,22,36].

Evidence-based HIV prevention interventions for gay and bisexual men are not widely available in Romania and are rare in the CEE region, where most HIV-related interventions have been developed for people who inject drugs [37]. A systematic review in 2015 identified only 24 HIV prevention interventions for gay and bisexual men in Europe [38], none of which appeared to have been implemented in Romania. To address this gap and respond to the interlocking challenges facing gay and bisexual men in Romania that contribute to their increasing HIV transmission risk behavior, our team sought to adapt a promising intervention created for gay and bisexual men in the United States [39], which was recently pilot-tested in Romania, under the name of Comunică, to support this population's unmet needs of [40].

Comunică Intervention Background and Pilot

Comunică is based on the information–motivation–behavioral skills (IMB) model of health behavior change [41], which postulates that individuals must possess the requisite information for enacting sexual health; motivation to address their HIV transmission risk behavior, alcohol use, and mental health; and behavioral skills necessary for reducing risk behaviors. The Comunică intervention is guided by motivational interviewing (MI) principles and techniques [42] to provide accurate information about HIV transmission, heavy alcohol use, and local gay and bisexual men–affirmative health resources (eg, HIV-testing sites) and build motivation to improve behavioral skills via cognitive behavioral skill training (CBST) [43]. MI is an evidence-based form of person-centered therapeutic communication that privileges client values and preferences for change to help individuals resolve ambivalence and move toward their valued goals [41,44]. For individuals who attain a high degree of motivation for change [45], CBST is used to promote awareness of contextual triggers and unhealthy behavioral patterns and teach coping skills to reduce personal risk [46]. Given the stigmatizing context of Romania, the CBST skills in Comunică are presented in a manner that acknowledges the barriers posed by social stigma to gay and bisexual men's health while empowering them to circumvent these barriers by building self-efficacy, learning effective communication, and implementing planful problem-solving [47-49]. In this way, Comunică also draws on minority stress theory recognizing that stigmatizing societal contexts represent the ultimate source of health disparities affecting gay and bisexual men [50]. Minority stress content informs the context in which the aforementioned psychoeducational information is presented, such as through a focus on identity development in the context of stigma and the ways in which minority stress affects mental, behavioral, and sexual health.

The Comunică intervention is delivered across 8 sessions by a trained counselor via synchronous (ie, live) text-based chat on a mobile-optimized website that also contains features for weekly tracking of HIV transmission risk behavior, heavy drinking, and mood. The study platform allows gay and bisexual men randomized to the Comunică intervention to track their weekly number of condomless sex acts, number of partners, number of heavy alcohol use days, and positive and negative moods [51]. A review of this information with counselors during sessions is intended to support motivation and create contextually informed behavior change goals. Previous research has shown that mobile tools are the primary means for Romanian gay and bisexual men to form and navigate social and sexual networks, especially given normative identity concealment [31], offering an ideal intervention platform [40]. While session content is driven by participant-selected priorities, they are discussed within the general theoretical and counseling frameworks of the Comunică intervention.

The feasibility, acceptability, and preliminary efficacy of Comunică was established between 2014-2016 in an open-trial pilot study with 43 young gay and bisexual men in Romania (mean age 23.2, SD 3.6; range 17-29 years) who reported condomless anal sex (CAS) acts with a male partner and at least 5 days of heavy drinking (≥5 drinks on one occasion) in the previous 3 months [40]. Specifically, gay and bisexual men who received Comunică reported, from baseline to a 3-month follow-up, significantly reduced depression, anxiety, and heavy alcohol use (P=.005) and increased condom use self-efficacy (P=.01), HIV-related knowledge (P=.001), and HIV testing (P=.05) [40]. While reductions in CAS trended in the expected direction from baseline to postintervention follow-up (mean 14.7 vs mean 10.8), the analyses were not sufficiently powered to detect significant differences. The Comunică intervention was created through in-depth consultation with 22 Romanian gay and bisexual men and 6 community stakeholders (eg, gay and bisexual men advocates and service providers) and was

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based on a chat-based MI intervention established in the United States [39].

Study Objectives

This study aims to test the efficacy of Comunică in reducing HIV transmission risk behavior (ie, number of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days) in a randomized controlled trial of 305 Romanian gay and bisexual men. The secondary outcomes include depression, heavy alcohol use, and HIV and STI testing. The control condition consists of 8 time-matched educational modules that present information regarding gay and bisexual men identity development, HIV and STI prevention, heavy alcohol use and its associations with HIV transmission risk behavior, sexual health communication, and the importance of social support created in consultation with Romanian gay and bisexual men community members and advocates. The educational modules for the control condition are hosted on the same study website as the Comunică intervention but without access to counseling or behavioral and mood-tracking features.

This study also tests two sets of mechanisms of intervention efficacy: (1) motivational mechanisms derived from the IMB model [41,44,52] (eg, knowledge of sexual health and alcohol use effects, motivation to reduce HIV risk and heavy alcohol use, and self-efficacy for safer sex and reductions in alcohol use) and (2) minority stress mechanisms derived from minority stress theory (eg, rejection sensitivity, stigma consciousness, and identity concealment) [53]. If shown to be efficacious in this trial, Comunică will constitute a unique mental, behavioral, and sexual health intervention that can be implemented in Romania and other high-stigma, low-resource national contexts in the future.

Methods

Design

In this randomized controlled trial, Comunică is compared to a content-matched education attention control (EAC) condition in changing (1) the primary outcome (frequency of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or viral suppression) and (2) secondary outcomes (depression, anxiety, suicidal thoughts, heavy alcohol use, and HIV and STI testing). Both the intervention and control groups received 8 one-hour intervention sessions or educational modules, respectively, to be completed over the course of 4 months. Outcomes are measured before the intervention (baseline) and at the 4-, 8-, and 12-month follow-ups. All participants self-administer at-home rapid testing for HIV and syphilis, and self-collect sampling (urethral, pharyngeal, and rectal) for chlamydia and gonorrhea sent to a laboratory at baseline and the 12-month follow-up. The CONSORT (Consolidated Standards of Reporting Trials) diagram in Figure 1 outlines the flow of participants throughout the study as of September 12, 2023.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. *As of September 16, 2020, mental health screening questions are no longer part of eligibility criteria. **These participants admitted to providing false condomless anal sex (CAS) or heavy drinking days (HDD) data at baseline assessment. EAC: education attention control; HD: heavy drinking; PrEP: pre-exposure prophylaxis.

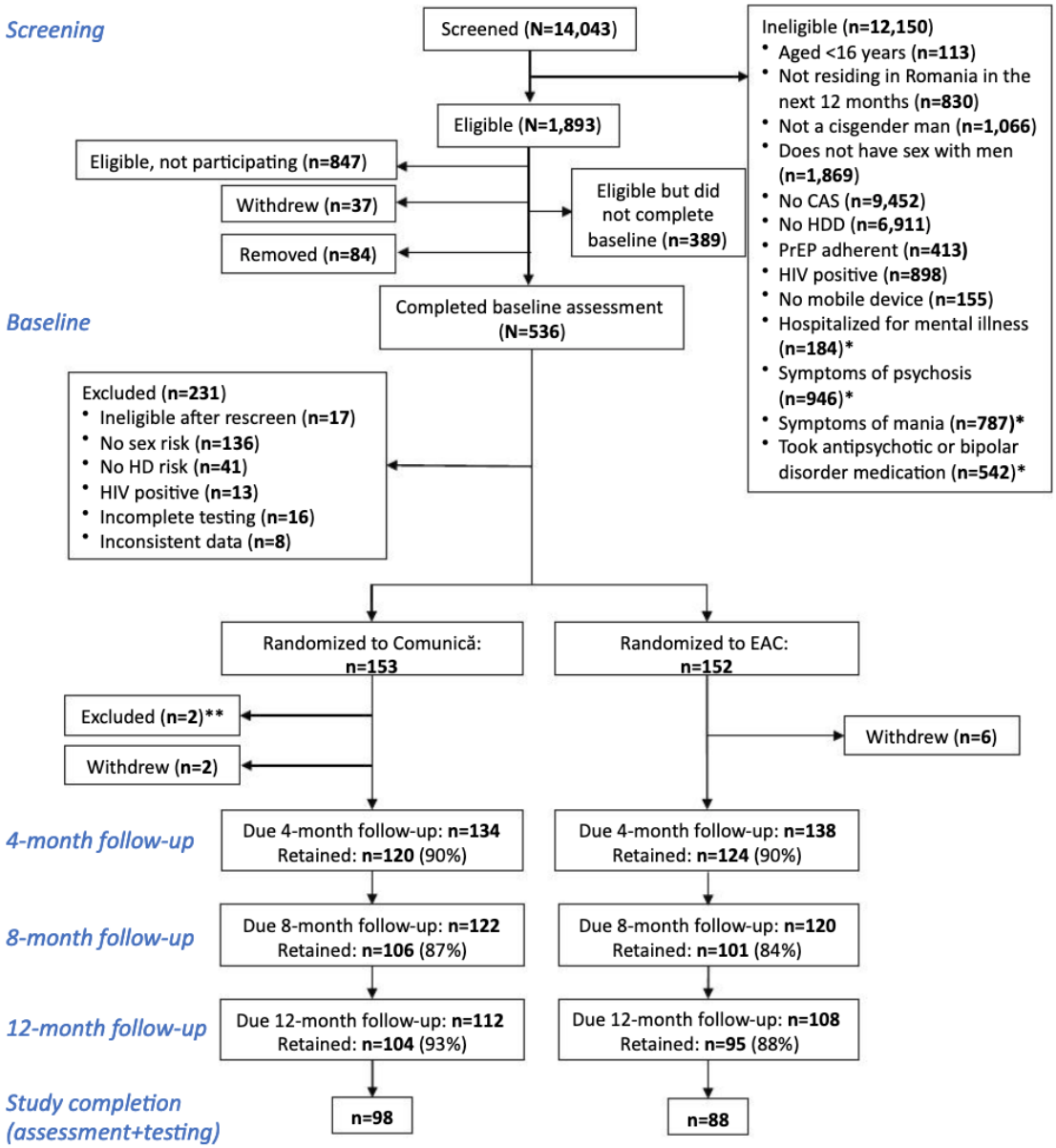

Recruitment

Recruitment and enrollment for the study ended in January 2023, with follow-up completion in January 2024. Gay and bisexual men living in or within 40 miles of 10 cities (ie, Bucure ti, Bra ov, Timi oara, Cluj-Napoca, Ia i, Constan a, Suceava, Craiova, Gala i, and Satu Mare) were recruited and screened. By selecting these cities, this study covers all regions of the country [54]. Collaborating LGBTQ advocacy organizations posted study advertisements on their websites, subscriber lists, and key virtual venues (eg, Grindr, Facebook, and Instagram). Study recruitment also relied on word of mouth; for instance, recruiters approached men in gay and bisexual men–prevalent venues (bars, events, and public cruising areas). Finally, enrolled participants were encouraged to share study information with their peers. Nevertheless, 44.9% (137/305) of participants were recruited on Grindr, and 41% (125/305) were recruited on Facebook.

Eligibility

Inclusion Criteria

Gay and bisexual men were eligible if they reported (1) male sex at birth and current male identity, (2) age of ≥16 years, (3) ≥1 act of CAS with an HIV-positive or status-unknown male partner in the previous 30 days, (4) ≥1 heavy drinking day in the previous 30 days (ie, ≥5 standard alcoholic drinks on 1 occasion per month [55,56]), (5) owning a mobile device (smartphone, tablet, or laptop), (6) residence in Romania for the duration of study participation (12 months), and (7) nonadherence to PrEP and (8) were confirmed to be HIV negative upon testing at baseline.

Exclusion Criteria

Participants were excluded if they demonstrated active suicidality, psychosis, or mania.

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Screening

Potential participants completed an eligibility screener on Qualtrics (Qualtrics International Inc), a research-designated secure Health Insurance Portability and Accountability Act–compliant web-based software [57]. Eligible gay and bisexual men had the option to provide contact information at the end of the screener in a separate survey for research staff to later contact them to review the study in more detail and assess consent.

Consent

A research staff member contacted eligible participants via phone to review the consent form and verify their age. Points of confusion were clarified, and individuals still interested in participating submitted an electronic consent form via Qualtrics [57]. The research staff outlined the steps to take place immediately following consent, namely, that participants would receive a link to the baseline assessment and a numerical study identification number to be used for the duration of the study for confidentiality purposes, undergo HIV and STI testing, and be randomized to one of the study conditions. Participants were able to use any mobile device (smartphone, tablet, or laptop) to complete the sessions.

Randomization

After baseline, participants were randomized to the Comunică or EAC condition based on a list of random numbers generated by the study biostatistician. A blocked stratified randomization scheme was used, with 150 participants each being randomized 1:1 to each arm within the following four strata based on past 3-month self-reported baseline number of HIV transmission risk behavior sex acts and heavy alcohol use days as follows: (1) lower CAS acts (≤2 acts) and lower alcohol use (≤5 drinks); (2) lower CAS acts (≤2 acts) and higher alcohol use (>5 drinks); (3) higher CAS acts (>2 acts) and lower alcohol use (≤5 drinks); and (4) higher CAS acts (>2 acts) and higher alcohol use (>5 drinks). The 150 persons within each stratum were randomized using 15 blocks of size 4 and 15 blocks of size 6, with the order of the 30 total blocks being randomly permuted.

Counselors contacted participants assigned to the Comunică condition to schedule the first session, at which point they both logged onto the study platform. Group assignment was not masked from study staff given that all assessments were self-administered.

EAC Condition

The EAC condition consisted of 8 educational modules based on the team's experience with HIV prevention education with gay and bisexual men in the United States and Romania [15,39,40,48,58,59] and included the following topics: (1) gay and bisexual men identity, (2) "HIV 101" (eg, transmission risks, prevention, and treatment), (3) the importance of HIV and STI testing and treatment, (4) alcohol and the body, (5) the role of alcohol in HIV transmission risk behavior, (6) HIV status disclosure and sexual health communication, (7) finding social supports and safety, and (8) creating and reaching sexual health goals. The content was finalized in collaboration with staff of Romanian LGBTQ-supportive organizations. To maximize participant engagement and learning, each module contained a 5-item quiz (with correct answers subsequently provided) and exercises and vignettes prompting participants to provide answers based on their understanding of the topics and their own experience.

To minimize contamination, counselors who administered Comunică did not interact with EAC participants, and Comunică and EAC materials were only accessible through unique log-in credentials known only to participants.

Counselor Training and Fidelity Monitoring

In 2019, before trial commencement, 5 psychologists living in Romania completed a 2-day training on the intervention. Of these psychologists, 2 delivered the Comunică intervention in the pilot study [40], and 3 were recruited from a pool of 54 mental health professionals whom the principal investigators (PIs) had previously engaged in a separate study [60]. The training included didactic and experiential components; a review of MI, CBST, the IMB model, and minority stress theory; unique facets of delivering the intervention via text; and reviewing vignettes from the pilot study. The counselors practiced delivering each session on the intervention platform, taking turns being a mock participant and counselor, and receiving biweekly remote video supervision from a clinical supervisor. At the start of the trial, the team reviewed all session transcripts. Once intervention fidelity was attained, the team randomly selected slightly over half of the subsequent sessions to verify fidelity to the intervention content and adherence to MI principles and techniques. As in the pilot study, the counselors translated each session transcript into English for the clinical team's review.

Study Assessments

Participants provided assessment data at baseline and at 4-, 8-, and 12-month follow-up appointments, self-administered via Qualtrics [57] and a web-based platform designed specifically for this study to capture past–30-day sexual and alcohol use behaviors in a self-administered calendar review. Participants also completed biological testing for HIV, syphilis, gonorrhea, and chlamydia at the baseline and 12-month follow-up appointments. Finally, all retained participants completed an exit survey after their 12-month follow-up that assessed the acceptability of the intervention. Based on each completed portion of the study, participants were compensated in Romanian RON equivalent to US $20, US $25, US $30, and US $40 for the baseline, 4-, 8-, and 12-month assessments, respectively, and US $10 per session based on each completed portion of the study. The measures are described in the following sections.

Demographics

At baseline, as shown in Table 1, participants indicated their age, sexual orientation, sex assigned at birth, current gender identification, income, residence (rural vs urban), ethnicity, and educational level. Participants also indicated the age at which they attained sexual orientation developmental milestones (eg, age of awareness of attraction to men) [61].

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Table 1. Baseline characteristics of the enrolled participants (N=305).

Characteristic	Participants, n (%)
Age (y)	
16-29	232 (76.1)
30-39	56 (18.4)
40-49	16 (5.2)
≥50	1 (0.3)
Sexual identity	
Gay	205 (67.2)
Bisexual	92 (30.2)
Queer	2 (0.7)
Pansexual	2 (0.7)
Uncertain	4 (1.3)
Educational level	
High school or lower	78 (25.6)
Vocational studies	9 (3)
Some college	108 (35.4)
College degree	57 (18.7)
Graduate degree	53 (17.4)
Relationship status	
Single and not dating	97 (31.8)
Dating	98 (32.1)
In a serious relationship	110 (36.1)
Ethnicity	
Romanian	279 (91.5)
Hungarian	22 (7.2)
Roma	3 (1)
Other	1 (0.3)
Employment	
Full time	149 (48.9)
Part time	18 (5.9)
Unemployed	15 (4.9)
Student	121 (39.7)
On disability	2 (0.7)
High school location	
Small town	161 (52.8)
Medium to large town or city	144 (47.2)
Age of awareness of attraction to men (y)	
4-14	230 (75.4)
15-25	72 (23.6)
26-34	3 (1)

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Primary Outcome

This study's primary outcome, HIV transmission risk behavior, is the frequency of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days. The partner's adherence to PrEP use was verified by the participant having witnessed their partner taking their medication daily. The partner's viral suppression in the past 30 days was verified by the participant having seen current test results or witnessing that partner taking antiretroviral therapy. To report past–30-day sexual behavior, participants completed a self-administered web-based Timeline Followback (TLFB) interview [62,63]. For each sexual act on each day, participants reported partner type (eg, primary or casual), partner gender, partner HIV status and known viral suppression (if applicable), type of sexual behavior (eg, insertive anal sex), condom use, PrEP use by themselves or their partner, and whether they were under the influence of alcohol during reported sex. TLFB collects retrospective day-level data and has been validated for electronic self-administration [62]. TLFB has good test-retest reliability, convergent validity, and agreement with collateral reports for sexual behavior [64,65] and alcohol use [66]. In this study, we developed a mobile-optimized web-based platform for the TLFB and iteratively improved it during a usability testing phase with local gay and bisexual men community members.

Secondary Outcomes

Heavy Alcohol Use

TLFB also asks participants to report their past–30-day heavy alcohol use, including whether it took place before or during sex. Participants also complete the 3-item Alcohol Use Disorders Identification Test–Consumption scale (AUDIT-C) [67], a standardized measure of alcohol-related problems.

Mental Health

Participants complete the Center for Epidemiologic Studies Depression Scale (CES-D) as a measure of depression symptoms [68], the Beck Anxiety Inventory (BAI) as a measure of anxiety symptoms [69], and the Suicidal Ideation Attributes Scale (SIDAS) [70] as a measure of suicidal ideation.

Potential Intervention Mediators

IMB Model

As informed by the IMB model, knowledge acquisition and motivation to reduce HIV transmission risk behavior and heavy alcohol use will be assessed as potential mechanisms of intervention efficacy. Information is measured using the Sexual Health Knowledge Questionnaire [71] and the Alcohol Attitudes Questionnaire [72]; motivation to reduce CAS and alcohol use is measured using the University of Rhode Island Change Assessment Scale [73] and the Stages of Change Readiness and Treatment Eagerness Scale [74], respectively; and behavioral self-efficacy to reduce HIV transmission risk behavior and heavy alcohol use is measured using the Safer Sex Efficacy Questionnaire [75] and Confidence in Reducing Alcohol Use Questionnaire [76], respectively.

Minority Stress Pathways

We measured potential mechanisms suggested by minority stress theory [77], including sexual orientation concealment using the concealment motivation subscale of the Lesbian, Gay, and Bisexual Identity Scale (LGBIS) [78]; rejection sensitivity using the acceptance concerns subscale of the LGBIS [78]; internalized stigma using the internalized homonegativity subscale of the LGBIS [78]; assertiveness using the Rathus Assertiveness Schedule [79]; and social support using the Multidimensional Scale of Perceived Social Support [80].

The protocol was also approved by the Bioethics Committee of the National Institute for Infectious Diseases the European Men-Who-Have-Sex-With-Men Internet Survey [21], participants indicate the frequency of their HIV or STI testing. Participants are asked whether they provided a blood sample to test for any STIs; whether their penis and anus were examined and swabbed as part of any STI testing in the previous 4 months; and whether and, if so, when (eg, past 7 days or 4 weeks) they were diagnosed with chlamydia, gonorrhea, genital warts, herpes, syphilis, hepatitis B or C, or urethritis.

HIV and STI Testing, Counseling, and Linkage to Services

Participants complete HIV and STI testing after providing consent and completing the baseline and 12-month follow-up assessments. Specifically, a testing counselor affiliated with the study and based at a Romanian nongovernmental organization specialized in HIV and STI prevention and treatment for gay and bisexual men and other marginalized populations contacts the participant to provide two options: (1) mail an HIV and STI test kit to their home or (2) have the participant pick up the test at their offices. Participants receive a self-testing kit containing a rapid HIV and syphilis test and swabs and a urine collection container for pharyngeal, rectal, and urethral testing of chlamydia and gonorrhea. The testing counselor guides participants through the testing steps [81,82]. The HIV and syphilis test results are available within 20 minutes of testing. Participants are required to take a photograph of the results (marked with their study ID) and upload it to a study platform. The chlamydia and gonorrhea self-collected samples are mailed back to the organization, which mails them for analysis to a laboratory. Upon receiving results for chlamydia and gonorrhea testing (usually within 1 week of laboratory receipt), the testing counselor communicates the results to the participant. For positive or inconclusive test results, the testing counselor provides participants with the name and contact information of the study-affiliated infectious disease care provider in their area for confirmatory testing and treatment, as appropriate, and offers to assist with this linkage. Finally, participants are asked to complete a satisfaction survey at the 12-month follow-up [83].

Ethical Considerations

Ethics Approval and Consent to Participate

This research was conducted in accordance with the Declaration of Helsinki, and all methods were carried out in accordance with relevant guidelines and regulations within the United States and Romania. This study was approved by the Columbia University Institutional Review Board (FWA0000263; protocol

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AAAU2518), Yale University Institutional Review Board (FWA00002571; protocol 2000024286), and Rutgers University Institutional Review Board (FWA00003913; protocol Pro2018000725). The protocol was also approved by the Bioethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Bal " in Bucharest, Romania (FWA00013199). All enrolled participants provided informed consent to take part in this study.

Overall Assessment of Risk

Participants are at minimal risk of harm associated with study participation. Although unlikely, the risks of this study are potential emotional discomfort from completing the assessments or the intervention sessions and breaches of confidentiality. In addition, participants may experience discomfort during HIV and STI testing or emotional distress when receiving positive test results. All possible steps are taken to minimize such risks through our carefully designed protocols, staff training, and fidelity monitoring. All study staff are trained in and follow study clinical protocols to protect against risks. Risks are being monitored and addressed (as outlined in the following sections) during assessments (via direct real-time triggers signaling emotional distress) and counseling sessions and in between assessment points (via communication from participants in both arms with study staff).

Risk of Emotional Discomfort

Participants may experience emotional distress associated with the study content. The consent document indicates that participants do not have to respond to any questions they do not wish to answer and may discontinue their participation at any time while being compensated for the portions of the study they completed.

At each assessment point, participants complete the SIDAS, with a score of ≥21 triggering an email to the project staff, who immediately alert the study counselors, who contact the participant to assess their well-being and potential need for immediate intervention in case of severe distress. All counseling resources are available to participants regardless of their ability to pay.

Should participants experience discomfort during assessments or sessions, they are contacted as described previously to assess their mental state, need for referral or immediate intervention, and capacity to continue in the study. On the basis of the counselors' determination, the participant may continue with the study (if there is no concern about imminent harm or lack of capacity to consent) or be referred to local in-person or telehealth LGBTQ-affirmative counseling services. For any person judged to be a danger to themselves or others or in imminent need of medical or mental health services, the project staff contacts local emergency services to intervene.

Risk of Physical Discomfort

Biological testing for HIV, syphilis, chlamydia, and gonorrhea may be associated with physical discomfort from the finger prick or incorrect swabbing, of which participants are informed during the consent process. Information on appropriate testing procedures and risk reduction counseling is provided to all participants at the time of testing at baseline and the 12-month follow-up. Staff are available via phone and email to answer questions that participants may have about performing biological testing. These tests are routinely conducted, and therefore, potential risks are no greater than those encountered during routine medical examinations. At the start of the study, we trained 10 infectious disease physicians from the 10 study cities of Bucure ti, Bra ov, Timi oara, Cluj-Napoca, Ia i, Constan a, Suceava, Craiova, Gala i, and Satu Mare. These physicians agreed to provide confirmatory testing and treatment to participants who test positive for HIV or other STIs during the study.

Risk of Breach of Confidentiality

Before any assessments, all participants are assigned a study ID number. The name-ID link is kept under electronic password and firewall protection in one of the PIs' offices at the Columbia University research space. Electronically signed consent forms are kept in a database separate from the data under password protection. Records are kept confidential, and information provided by study participants is not released to outside sources unless written consent is provided by the study participant or it is required by law (eg, suspicion of child or elder abuse and threat of imminent action on suicidal or homicidal ideation) or to protect participant well-being (eg, in the event that immediate local intervention is required following a safety assessment). The web-based intervention platform is only accessible to study staff and participants, whose log-in information is not linked to any identifying information. All participants are required, as part of the consent process, to upload to REDCap (Research Electronic Data Capture; Vanderbilt University) a photograph of their HIV and syphilis test paddle showing the results and label marked with their unique study ID. Finally, all procedures are being monitored by the Human Subjects Protection Programs at Columbia University and the study's Data and Safety Monitoring Board (DSMB).

Risk Versus Benefit

Given the public health significance addressed by this first study of its kind in CEE, the social, psychological, and physical risks reviewed previously are likely to be outweighed by the new knowledge gained regarding the efficacy of this highly scalable and portable approach to reducing gay and bisexual men's HIV transmission risk behavior and increasing their well-being. Preventing the further spread of HIV presents clear public health implications, especially in high-stigma, low-resource contexts such as Romania and other CEE countries. By participating in this study, participants may gain insight into their sexual, behavioral, and mental health that could lead to sustained behavior change. In addition, study participants may reduce their risk of acquiring HIV and STIs through involvement in our counseling or education sessions and behavioral risk tracking. Of note, participants are the first to be involved in at-home STI testing in Romania, a procedure they may adopt routinely in their lives beyond the study, both reducing their personal health risk and potentially promoting these protective practices within their networks.

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Data Safety Monitoring Plan

Any unexpected or serious adverse events (eg, hospitalization) that occur during the course of the study will be reported by the contact PI and to the Committee on Human Research (Institutional Review Board) at Columbia University in accordance with current guidelines for reporting adverse events. The PIs meet biweekly with the team to discuss study progress and address participant safety immediately as issues arise (eg, reported suicidal ideation).

DSMB Function

A 5-member monitoring committee has been convened to determine safe and effective conduct and recommend the conclusion of the study if significant risks develop or if the trial is unlikely to be concluded successfully. On May 6, 2019, the team held the first DSMB meeting and has been convening annually since. The 5 members have reviewed and approved the study design and procedures and a plan for monitoring study data and interim outcomes. Starting in year 2 and annually thereafter, the study statistician has prepared and presented to the DSMB both open (pooled) and closed (stratified and with treatment arm unidentified) reports on the following data by arm: suicidality, HIV and STI test results, depression, heavy alcohol use, and HIV transmission risk behavior. Upon review of study progress, the DSMB provides a determination about study continuation to the PIs, who share it with the Institutional Review Board and National Institute of Mental Health in their annual progress report.

Data Analyses

Primary and Secondary Outcomes

It is hypothesized that participants randomized to the Comunică intervention, compared to those randomized to the EAC condition, will report significantly greater decreases in the primary (HIV transmission risk behavior defined as CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days) and secondary (depressive and anxiety symptoms, suicidality, heavy alcohol use, and HIV and STI testing outside of study testing) outcomes at the 4-, 8-, and 12-month follow-up visits.

Sample Size Justification

As we approached the end of study recruitment, three factors were considered for estimation of power: (1) while 305 participants were finally enrolled, we had estimated that we would likely only be able to recruit 288 participants by December 31, 2022 (our date of termination of recruitment), and therefore, we re-estimated power based on this number; (2) the overall participation rate for all 3 postintervention visits was 85.9% (262/305), with a high proportion of the remaining sample completing 2 postintervention assessments; (3) we had normative distributions of the study outcomes that could be used in establishing a study design and metrics for powering the primary outcome. To that end, we re-estimated the study power as described in the following paragraphs. This new estimate was approved by the DSMB and our program officer at the National Institute of Mental Health.

In the original proposal, repeated-measures mixed linear model (or generalized estimating equations [GEE]) using all 4 study visits (baseline and 4-, 8-, and 12-month follow-ups) was planned. However, the distribution of our primary outcomes (HIV transmission risk behavior) based on collected data was problematic for fitting this type of model, which is based on a central limit theorem assumption that may not manifest. Namely, there were two issues to consider: (1) at each follow-up visit, >50% of participants manifested no HIV transmission risk behavior, creating a large point mass at the lower limit of 0.2; and (2) on the other hand, the distribution of HIV transmission risk behavior acts was very skewed, with numbers of acts of >50 leading to a skewness of >3, which again contradicts normality-based methods.

Although generally accepted approaches for power estimates for this situation do not readily exist, we found one approach that will satisfy assumptions for standard normal methods and that is also amenable to conducting a power estimation. This approach is to take the average behavior over all 3 follow-up time points (4-, 8-, and 12-month assessments) as a single within-person outcome rather than evaluating the repeated measures at the 4-, 8-, and 12-month follow-ups as separate within-person outcomes. For example, if a person reported 0, 1, and 2 high-risk acts at the 4-, 8-, and 12-month follow-up visits, respectively, these would be summed together (0 + 1 + 2 = 3) and averaged over the 3 visits (3/3=1) as a single outcome of 1 high-risk sex act over the previous 30 days per follow-up period. The details of what transpired when we examined this outcome in our (still unblinded to intervention condition) data follow in the next paragraphs.

When we took the average of HIV transmission risk behavior acts of all 3 follow-up time points (ie, during the previous 4 months), only 23.9% (73/305) of participants had no HIV transmission risk behavior acts over the entire 12-month period (ie, the point mass at 0), which, given our projected sample size of 288 (or 246 evaluable participants assuming 246/288, 85.4% or a 15% loss of data as we have been observing), is low enough to treat this average as a continuous variable in a normal approximation. However, due to a few individuals reporting very high numbers of risk acts (ie, >50), this variable was still skewed (>3), so we capped (ie, Winsorized) the maximum number of average per-assessment HIV transmission risk behavior acts at 15, the upper 97th percentile of HIV transmission risk behavior. When this was done, the HIV transmission risk behavior outcome was close enough to normal (ie, skewness=1.5) for the central limit theorem to apply to the linear model presented in the following paragraph.

The power estimation approach assumes that a linear model will fit $Y = a + bX + cT + \varepsilon$, where Y is the averaged (during the previous 4 months) previous–30-day high-risk sex behavior over the 12-month behavior; a is the intercept; X is the number of baseline previous–30-day HIV transmission risk behavior acts; T is 0 for control and 1 for the intervention; ε is the random error with a mean of 0 and constant variance; and a, b, and c are unknown parameters that are estimated in the model fit. The null hypothesis c=0 will be tested with an overall 2-sided type-1 error of 0.05.

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Importantly for power estimation, the correlation between the baseline and the average 12-month HIV transmission risk behavior acts was 0.37, which means that, after adjustment for the preintervention behavior, the SD of the postintervention behavior would be the square root of $1 - 0.37^2 = 0.93$ of the unadjusted outcome. On the basis of this, and with 288 participants, 86.1% (248/288) of whom participated in all 3 visits, as we have been observing will happen (or, conservatively, 123/288, 42.7% in each treatment arm), there is 80% power to detect an effect size of 0.33, slightly greater than our originally estimated effect size of 0.25 to 0.27 and at the upper end of the range of effect sizes found for behavioral interventions addressing multiple health outcomes among sexual minority men [84]. We believe that 0.33 represents a plausible effect size to detect in this trial given the strong distinction between the 2 intervention conditions, with one involving an active therapist-guided intervention and the other consisting of self-guided psychoeducation only. The SD of the (Winsorized) averaged outcome over 12 months of per-assessment HIV transmission risk behavior acts was 3.46 acts. Multiplying this SD by the effect size of 0.33 gives 1.14 HIV transmission risk behavior acts. This means that the study will have 80% power to detect an overall mean reduction of 1.14 HIV transmission risk behavior acts in the previous 30 days per assessment period in the intervention compared to the control condition.

It should be noted that our final analysis will most likely incorporate the partial information from men with only 1 or 2 postintervention follow-up visits through imputations, or more exactly, adjustment of the partial information for the number of follow-up periods reported; if so, this would increase power, albeit by a very modest amount.

Data Preparation

Skewed variables will be recoded for analytic symmetry using appropriate log, square root, or other nonlinear transformations. Should we fail to be able to find a transformation that achieves sufficient linearized normality, then robust GEE (ie, with logit or log link function) will be fitted to dichotomized or count outcomes. We will also examine variable distributions, which may suggest dichotomous and multinomial recoding relevant to our primary research questions and would increase the statistical power of our models. Dependent and independent variable values will be cross-plotted as a function of time in study and summarized using parametric and nonparametric modeling methods such as loess curves. In addition to detecting trends and temporal patterns, graphic representations of time-series data will provide knowledge of within- and between-individual variability of measurements. The results will be used to construct more complex cross-group or time analytic models.

Analytic Plan

The analysis of the primary and secondary outcomes will use intent to treat, with participants analyzed according to their original treatment assignment. The SAS (version 9.4; SAS Institute), SPSS (version 26.0; IBM Corp), Stata (StataCorp), and R (R Foundation for Statistical Computing) software will be used for all analyses.

Comparability of Treatment Groups

Differences in baseline demographic characteristics between the 2 treatment arms will be assessed using appropriate graphical and statistical methods, including summary statistics and *P* values from exact, rank, chi-square, and 2-tailed *t* tests, and ANOVAs. Of note, as the analyses progress, we will control for variables related to the study outcome in the analyses. We will also investigate whether the randomization scheme was compromised.

For the HIV transmission risk behavior primary outcome (number of CAS acts in the past 30 days with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load) analyses, the statistical significance threshold for an intervention (vs control) arm effect will be a 2-sided *P* value of ≤.05. The primary outcome will be evaluated between the 2 arms at the 4-, 8-, and 12-month follow-ups combined in a repeated-measures analysis that adjusts for baseline behavior. This will be analyzed using negative binomial regression with the baseline and the 4-, 8-, and 12-month time points clustered within the same person. The main effect terms for 4, 8, and 12 months after the baseline (each time point vs baseline) will be included in the model. A single interaction term between the 4-, 8-, and 12-month measures and the intervention arm will be included in the model to test for pooled postbaseline treatment arm differences. The relative number of HIV transmission risk behavior acts with a 95% CI will quantify intervention effect. GEE with person as the cluster will be used to account for within-person repeated-measure collinearity. As a sensitivity analysis, this will be repeated including all baseline covariates that are statistically associated ($P<.05$ to enter and $P\geq.10$ to leave in a stepwise selection) with HIV transmission risk behavior in negative binomial GEE models with person as the cluster and adjusting for time of visit (eg, 4, 8, and 12 months each vs baseline). If there are excess zeros at each postbaseline visit, we will consider using a zero-inflated negative binomial model instead. However, this approach will split the intervention effect parameter into 2 models and, thus, may dampen the power to detect statistical significance for an intervention that affects both parts. Thus, in this setting, we will more likely use the sensitivity analysis approach described in the following paragraph.

As a further sensitivity analysis, averaged HIV transmission risk behavior over all 3 follow-up visits (or 2 postbaseline visits if 1 visit is missing) will be used as the outcome in an analysis of covariance linear regression model that adjusts for baseline HIV transmission risk behavior as a predictor and includes treatment arm assignment as a covariate. For those who are missing 1 follow-up visit, indicator variables as to which visit is missing will be included. The mean difference in HIV transmission risk behavior acts with a 95% CI will quantify intervention effect. This will be repeated including all baseline covariates that are statistically associated ($P<.05$) with HIV transmission risk behavior in stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave) in the aforementioned model. Should the negative binomial model described previously fail to converge, this will become the primary analysis. The statistical significance

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threshold for the new (vs control) intervention arm effect will again be a 2-sided *P* value of ≤.05.

The secondary outcomes of interest (all of these assessed at baseline and at the 4-, 8-, and 12-month follow-up visits) are depression and anxiety symptoms, suicidality, and heavy alcohol use. Depression, as measured using the CES-D, will be examined as a continuous and a binary variable using a cutoff of ≥16 (indicating clinical depression). Anxiety, as measured using the BAI, will be examined as a continuous variable and using a cutoff of ≥16 (indicating potentially concerning levels of anxiety). Suicidality, as measured using the SIDAS, will be examined as a continuous variable and as a binary outcome using a cutoff of ≥21 (indicating high risk of suicidality) as well as any score >0. Heavy alcohol use, as measured using the AUDIT-C, will be examined as a continuous variable and as a binary outcome using a cutoff of ≥4. The percentage of heavy drinking days in the previous 30 days before the visit, as measured using TLFB, will be examined as a continuous variable. Due to multiple comparison issues, these will each be tested individually using a 2-sided type-1 error of 0.01 and quantified using 99% CIs. The levels of these measures at the 4-, 8-, and 12-month follow-ups will be compared (adjusting for the level at the baseline visit) between the Comunică intervention and the EAC condition in repeated-measures analyses, as described in the following paragraph.

For continuous outcomes that are heavily skewed to the right and without an excessive point mass at 0 for the 4-, 8-, and 12-month follow-ups (eg, the BAI or number of heavy drinking days), a similar approach to that described for the primary outcome analyses will be used. For continuous outcomes that are not heavily skewed to the right at the 4-, 8-, and 12-month follow-ups (eg, CES-D or AUDIT-C), repeated-measure linear regression mixed models will be fitted for outcomes at baseline and the 4-, 8-, and 12-month follow-ups with participant intercept as a fixed effect; main effects for the 4-, 8-, and 12-month follow-ups; and the single interaction term between treatment arm assignment and the time point being follow-up. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($P<.05$) with the outcome in models using stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave). The mean postintervention difference in the outcome between the treatment arms with 99% CIs will quantify intervention effect. Binary outcomes (eg, >0 HIV transmission risk behaviors, CES-D score of ≥16, SIDAS score of ≥21, SIDAS score of ≥0, and AUDIT-C score of ≥4) will be analyzed in repeated-measures models using the baseline visit and follow-up visits at 4, 8, and 12 months. Repeated-measures GEE will be fit about individual as a cluster using a logit link function. The visit number (ie, 4, 8, and 12 months vs baseline) and treatment arm assignment will be included as main effects, as will the baseline level of the outcome being modeled. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($P<.05$) with the outcome in models using stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave). The intervention effect will be quantified using odds ratios with 99% CIs. Finally, we will also use exact tests to compare treatment arms for having ever been diagnosed with HIV, syphilis, chlamydia, and gonorrhea during a single time point (the 12-month study follow-up).

Mediation Analyses

In our mediation analyses, we will examine whether changes in the proposed mediators (eg, self-efficacy for condom use or heavy alcohol use prevention, identity concealment, and internalized homophobia) precede and statistically mediate intervention effects consistent with our IMB and minority stress models. We will use path analysis or structural equation modeling to model and assess the size of the indirect effect of intervention condition on 12-month outcomes through mediators assessed at 4 and 8 months controlling for the baseline effects of these mediators.

Results

The study was funded in September 2018, and data collection began in May 2019. The last participant follow-up was in January 2024. Currently, the data analyst is cleaning data sets for each assessment point, verifying the accuracy of scale calculations, and examining patterns of missing data in preparation for data analyses for the primary and secondary outcomes as a first step. Data analyses are scheduled to begin in April 2024. Data analysis meetings are scheduled regularly to establish timelines and examine the results as analyses are gradually being conducted. Upon completion, a list of manuscripts will be reviewed and prioritized, and the team will begin preparing them for publication.

Discussion

This study is the first to test the efficacy of an intervention with the potential to simultaneously support the sexual (eg, HIV transmission risk behavior), behavioral (eg, heavy alcohol use), and mental (eg, depression) health of gay and bisexual men in CEE using MI support and sensitivity to the high-stigma context of the region [39,40]. This study has some potential limitations. This study is only focused on cisgender men, whereas additional groups (eg, transgender and gender-expansive individuals) may present high HIV risk and could benefit from tailored interventions. Should this intervention be efficacious, future research should consider adaptations to apply this intervention to other groups at risk of HIV and associated comorbidities, such as heavy alcohol use. In addition, this study takes place in only 1 country, potentially limiting generalizability, including to other settings where this intervention might also be beneficial. Finally, this study includes only 1 comparison condition and takes place in the context of a controlled trial rather than a real-world context suitable to test the intervention's effectiveness. As such, pending this intervention's efficacy confirmation in this trial, future research ought to consider expansion to other target groups and countries and implementation in real-world settings in an effectiveness trial. The resulting intervention holds promise for building a bridge from initial web-based counseling support to on-the-ground service use. If efficacious and cost-effective, the Comunică intervention presents a scalable platform to address HIV and STI risk and provide behavioral and mental health support to gay and bisexual men in other high-stigma, low-resource areas

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in the region (eg, Ukraine and Poland) and the United States (eg, rural areas). This study will also generate intervention content and protocols that can be replicated by international service providers who do not operate in a research capacity.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CL-W and JEP led the development of this protocol. CL-W prepared the initial manuscript draft, JEP provided substantive feedback on the manuscript, and DH drafted the data analytic sections and provided substantive feedback on the manuscript. MLF provided substantive feedback on the manuscript. All authors were involved in developing or implementing the study protocol. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test–Consumption scale
BAI: Beck Anxiety Inventory
CAS: condomless anal sex
CBST: cognitive behavioral skill training
CEE: Central and Eastern Europe
CES-D: Center for Epidemiologic Studies Depression Scale
CONSORT: Consolidated Standards of Reporting Trials
DSMB: Data and Safety Monitoring Board
EAC: education attention control
EU: European Union
GEE: generalized estimating equations
IMB: information–motivation–behavioral skills
LGBIS: Lesbian, Gay, and Bisexual Identity Scale
LGBTQ: lesbian, gay, bisexual, transgender, and queer
MI: motivational interviewing
PI: principal investigator
PrEP: pre-exposure prophylaxis
SIDAS: Suicidal Ideation Attributes Scale
STI: sexually transmitted infection
TLFB: Timeline Followback

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Protocol

Self-Selected Versus Assigned Target to Reduce Smartphone Use and Improve Mental Health: Protocol for a Randomized Controlled Trial

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Abstract

Background: Smartphones have become integral to people's lives, with a noticeable increase in the average screen time, both on a global scale and, notably, in India. Existing research links mobile consumption to sleep problems, poor physical and mental health, and lower subjective well-being. The comparative effectiveness of monetary incentives given for self-selected versus assigned targets on reducing screen time and thereby improving mental health remains unanswered.

Objective: This study aims to assess the impact of monetary incentives and target selection on mobile screen time reduction and mental health.

Methods: We designed a 3-armed randomized controlled trial conducted with employees and students at an educational institution in India. The study is conducted digitally over 12 weeks, including baseline (2 weeks), randomization (1 week), intervention (5 weeks), and postintervention (4 week) periods. We emailed the employees and students to inquire about their interest in participation. Those who expressed interest received detailed study information and consent forms. After securing consent, participants were asked to complete the initial survey and provide their mobile screen time during the baseline period. At the beginning of the intervention period, the participants were randomly allocated into 1 of 3 study groups in a 2:2:1 ratio (self-selected vs assigned vs control). Participants in the self-selected group were presented with 3 target options: 10%, 20%, and 30%, and they were asked to self-select a target to reduce their mobile screen time from their baseline average mobile screen time. Participants in the assigned group were given a target to reduce their mobile screen time from their baseline average mobile screen time. The assigned target was set as the average of the targets selected by participants in the self-selected group. During the intervention period, participants in the self-selected and assigned group were eligible to receive a monetary incentive of INR (Indian Rupee) 50 (US $0.61) per day for successfully attaining their target. Participants in the control group neither received nor selected a target for reducing their mobile screen time and did not receive any monetary incentives during the intervention period. All participants received information regarding the advantages of reducing mobile screen time. As an incentive, all participants would receive INR 500 (US $6.06) upon completion of the study and a chance to win 1 of 2 lotteries valued at INR 5000 (US $60.55) for consistently sharing their mobile screen time data.

Results: Currently, the study intervention is being rolled out. Enrollment occurred between August 21, 2023, and September 2, 2023; data collection concluded in November 2023. We expect that results will be available by early 2024.

Conclusions: The monetary incentives and self-selected versus assigned targets might be effective interventions in reducing mobile screen time among working professionals and students.

Trial Registration: AsPredicted 142497; https://aspredicted.org/hr3nn.pdf

International Registered Report Identifier (IRRID): DERR1-10.2196/53756

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(JMIR Res Protoc 2024;13:e53756) doi:10.2196/53756

KEYWORDS

screen time; monetary incentives; target selection; mental health; mobile phone

Introduction

Smartphones have become ubiquitous in people's lives. The global average for daily screen time is 6 hours and 37 minutes [1]. In 2021, India had a mobile subscriber count of 1.2 billion, and around 750 million of them were using smartphones [2]. The average screen time for Indians has increased to 7.3 hours [3]. As of 2019, the leading mental disorders are depression and anxiety, which affect 280 million and 301 million people worldwide, respectively [4]. Estimates suggest that over 197 million Indians, approximately 15% of our population, experience mental disorders. Of these, approximately 85 million experience depression- and anxiety-related disorders [5]. Existing research links excessive screen time to lower subjective well-being, depression, anxiety, sleep disorders, and poor physical health [6-13].

Numerous correlational studies have explored the relationship between digital media use and well-being, with many of them indicating that screen time and mobile consumption are negatively linked to subjective well-being [6-10,14]. For instance, Przybylski and Weinstein [15] explored the effect of digital media use on the well-being of adolescents, providing support for the Goldilocks hypothesis—individuals with moderate use have higher well-being than those with lower and higher use.

On the other hand, Twenge and Campbell [14] showed that although light users of digital media had higher well-being than people who abstain, moderate and heavy users had lower well-being than light users. Twenge and Martin [7] demonstrated that the associations between greater digital media use and psychological well-being are greater for female than male individuals. In their correlational study, Twenge and Campbell [14] found that individuals with moderate and heavy digital media use (smartphones, social media, and others) had lower well-being than those with lighter media use, especially individuals with greater than 5 hours of digital media use per day. Orben and Przybylski [16] used specification curve analysis to understand if there is any correlational relationship between digital media use and well-being among adolescents. They found a negative but small association, explaining at most 0.4% of the variation in well-being [16].

In addition, existing research has also shown that temporary monetary incentives and targets can be used to inculcate behavioral change in domains such as gym attendance [17], smoking, work behavior [18], alcohol abuse [19], and weight loss [20]. Research studies suggest that temporary monetary incentives and specific targets can effectively reduce social media use and allow people to limit their screen time [21].

However, the current body of research does not provide evidence regarding whether self-selected targets or externally imposed targets are more effective in promoting and maintaining behavioral change, especially in the context of smartphone use, thereby improving mental health. Reducing smartphone screen time is essential for maintaining a healthy and productive lifestyle.

In this study, we aim to nudge people to reduce their screen time by providing temporary monetary incentives and targets. Target is defined as the minimum percentage reduction in daily mobile screen time from the daily average mobile screen time during the baseline period.

The objectives of the study are as follows:

1. To estimate the impact of monetary incentives and targets on reducing mobile screen time during the treatment and posttreatment period.
2. To evaluate the efficacy of self-selected versus assigned targets in reducing mobile screen time.
3. To estimate the impact of screen time reduction on mental health. Mental health will be assessed using measures such as Generalized Anxiety Disorder–7 (GAD-7) for anxiety, Patient Health Questionnaire–9 (PHQ-9) for depression, daily mood survey for mood, and well-being scores for general well-being.

Methods

Study Design and Setting

To achieve the study objectives, we are conducting a pragmatic, 3-arm, parallel-group, randomized controlled trial involving students and employees of the Indian School of Business (ISB). The ISB operates across 2 campuses located in the states of Punjab and Telangana, India. The randomized controlled trial spans a 12-week duration, comprising 2 weeks of baseline, 1 week for randomization, 5 weeks of intervention, and 4 weeks of the postintervention period.

Participants and Eligibility Criteria

Current employees and students at both ISB campuses who had Android-operated mobile phones and were available throughout the 12-week study period were eligible to participate in the study. The study excluded employees affiliated with the implementing department, Max Institute of Healthcare Management, ISB, as they previously participated in the study's pilot.

Recruitment

The study was conducted entirely through digital communication, avoiding the need for in-person interaction between the researchers and the participants. We initiated the study by sending an email through the Head of Student Affairs and Human Resources to both employees and students of ISB to their official email addresses. The email included a link to a form that allowed participants to express their interest in the study. This email was sent 3 times. Recruitment took place for 2 weeks, the preregistration period, to gather expressions of interest. Potential participants who expressed interest were

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subsequently provided with study details and consent forms. Three email reminders were sent to the potential participants to provide consent. The participants who provided consent were asked to complete the baseline survey and provide their mobile screen time data during the baseline period.

Randomization and Blinding

After obtaining the baseline mobile screen time data, participants were randomly assigned to 1 of 3 groups in a 1:2:2 (control vs self-selected vs assigned) ratio. This assignment was carried out using a stratified randomized permuted block design with a block size of 5 using the *ralloc* command on Stata 17 software (StataCrop LLC). The allocation was stratified based on 2 variables: status in the institute (employee or student) and the quartile of baseline average mobile screen time. Following randomization, the research team became aware of the allocation groups. Blinding at the participant level was not possible due to the nature of the intervention. Participants were informed about their group before the start of the intervention period. They were not told about other groups or the groups of other participants. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study is provided in Figure 1.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study.

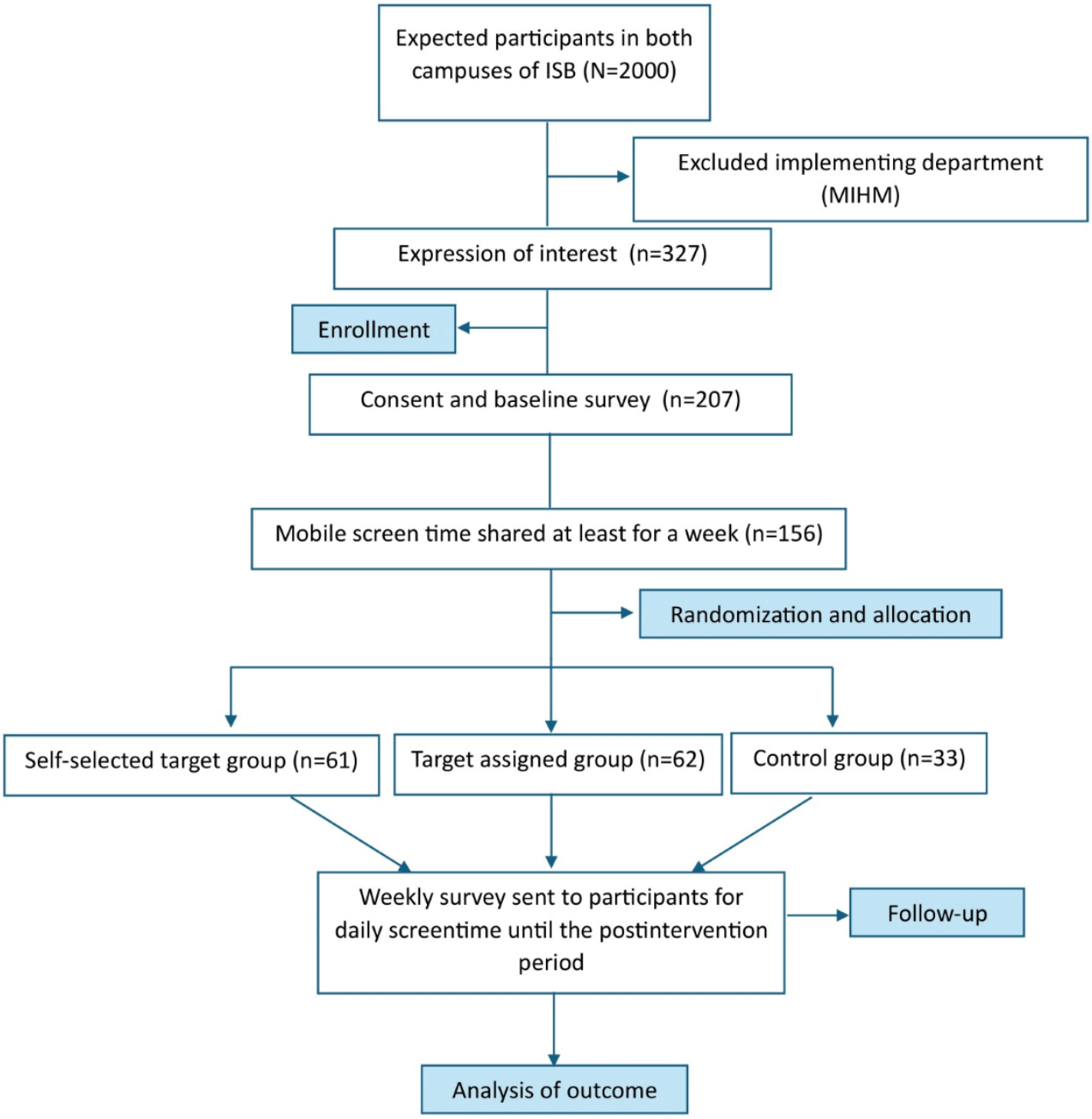

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Sample Size

The target sample was 300 participants, assuming a conservative effect size (*d*) of 0.12 for the difference between self-selected and assigned conditions and 0.15 for the difference between the intervention group and control conditions, with 80% power and an α of .05. The effect size was estimated based on past studies in this domain [22,23].

Interventions

At the end of the baseline period, the participants were randomized into 3 groups: the control group and 2 intervention groups.

Intervention-1 (Self-Selected Group)

In this group, participants were asked to select a target to reduce their mobile screen time from their baseline average mobile screen time. They were presented with 3 target options (10%, 20%, and 30%) and were asked to select one of the targets. The target options were chosen such that none of the targets is unreasonably high, ensuring that there are at least some participants who chose the target. Additionally, we want to ensure that the targets are sufficiently different so that participants are not indifferent between them. During the intervention period, participants in this group were eligible to receive a monetary incentive of INR (Indian Rupee) 50 (US $0.61) per day for successfully achieving the target they selected.

Intervention-2 (Assigned Group)

In this group, participants were assigned a target to reduce their mobile screen time from their baseline average. This target was determined after the participants in the self-selected group chose their respective targets. The assigned target was determined as the average of the targets selected by participants in the self-selected group. This was done such that both groups have the same average screen time reduction target, and thereby we can compare the average screen time reduction between the groups. This makes the intervention arms on average only differ in whether they chose or were assigned a screen time reduction target. During the intervention period, participants in this group were eligible to receive a monetary incentive of INR 50 (US $0.61) per day for successfully achieving the assigned target.

Control Group

Control group participants were neither assigned nor asked to select a target for reducing their mobile screen. They were provided with standard information regarding the advantages of reducing their mobile screen time and received reminders to do so. They will not receive any monetary incentives for reducing their mobile screen time.

All participants, including the control group, received identical information regarding the advantages of reducing mobile screen time. All participants were informed that they would receive a fixed amount of INR 500 (US $6.06) upon completing the study. Additionally, participants in the study who report their mobile screen time every week will have the opportunity to win 1 of 2 lotteries, worth INR 5000 (US $60.55) each.

Study Procedures and Stages

The study has 5 stages: preregistration, baseline, group allocation, intervention, and postintervention, as presented in Figure 2.

Figure 2. An overview of the study.

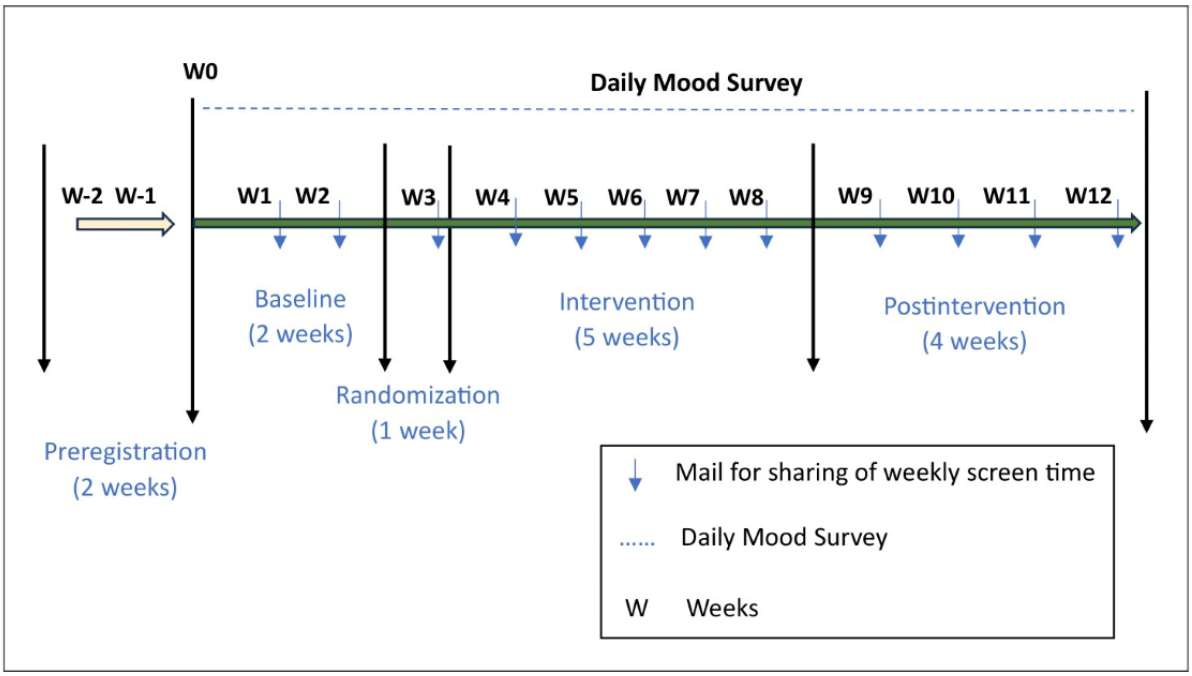

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Preregistration

Over 2 weeks, we conducted preregistration to gather expressions of interest. A total of 327 individuals expressed interest in the study. The individuals who displayed interest in the study were requested to complete the baseline survey, which included information regarding demographics, daily mobile phone time, past attempts to reduce screen time, willingness to reduce screen time, and GAD-7 and PHQ-9 for assessing anxiety and depression (a list of collected data is summarized in Table 1). Participants were also asked to report their daily mobile screen time and upload screenshots of the digital well-being app for the week before preregistration.

The digital well-being tools offer a daily overview of a person's phone use: the number of times the user checks their phone and the screen time. The screen time measures the total and app-wise time of the phone use. Participants share their mobile screen time through a weekly survey asking them to fill in the total time in hours and minutes of screen time for each day as displayed in the digital well-being app. As proof, the participants were asked to upload a screenshot of the digital well-being app for that week. A screenshot of the digital well-being app is shown in Figure 3. The study team checks whether the screen time in the survey matched with the screenshot. The study team provided step-by-step visual instructions for the process of uploading the screenshot from the digital well-being app. Of the 327 individuals interested in the study, 207 provided consent and completed the baseline survey.

Table 1. Data collection at various stages of the study.

Data category	Expression of interest	Baseline[a,b]	End of intervention[a,b]	End of postintervention[a,b]
Basic information and contact details	✓	✓	✓	✓
Demographic		✓		
Information on willingness, difficulty, and magnitude in reducing mobile screentime		✓		
Information about mobile use		✓		✓
Phone addiction scale	✓	✓		✓
Generalized Anxiety Disorder–7		✓	✓	✓
Patient Health Questionnaire–9		✓	✓	✓

[a]Daily mobile screen time use: participants share their daily screen time and upload screenshots of their screen time by using the digital well-being feature on their Android mobile phones through self-administered weekly surveys.

[b]Daily mood survey: mood data are collected daily through WhatsApp messages, using a 1-10 scale that is sent at varied times of the day.

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Figure 3. A screenshot of the digital well-being app.

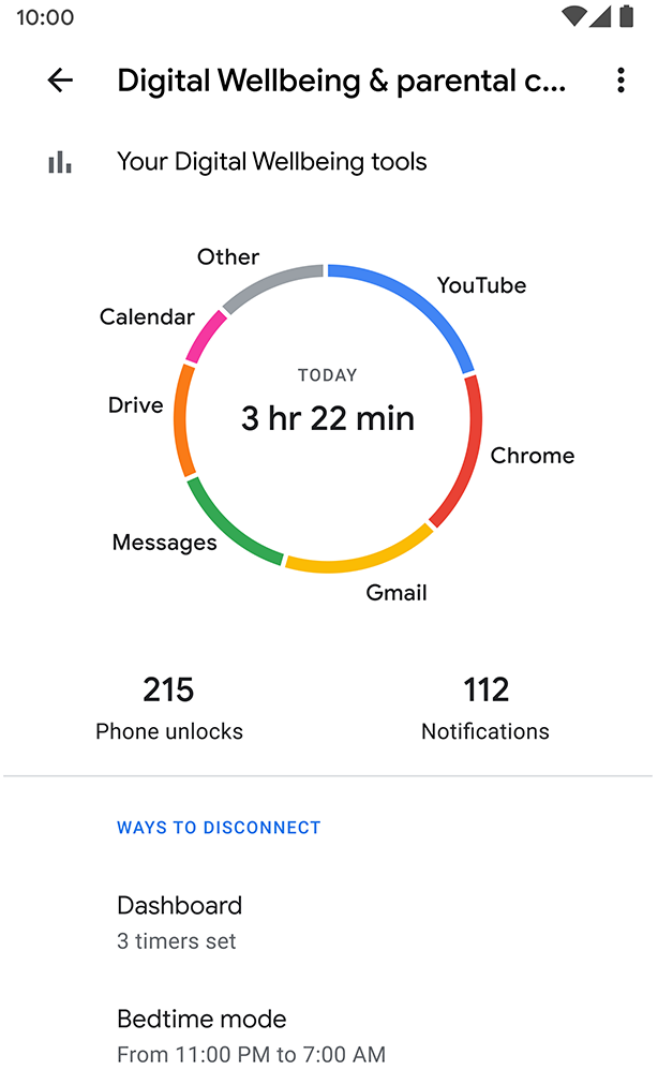

Baseline (Mobile Screen Time)

The 2-week period following the preregistration was the baseline period. Every Sunday during this period, we emailed participants who had completed the baseline survey. They were instructed to provide their daily mobile screen time for the preceding week and upload a screenshot of the digital well-being app on their phones. Two reminder emails were sent to those who did not respond. Additionally, participants received a daily mood survey via WhatsApp (Meta) every day. Throughout the 2-week baseline period, 156 participants shared their mobile screen time for at least 1 week, while those who did not respond were excluded from the study.

Group Allocation

The 1-week period after the baseline was the group allocation period. During this period, the 156 participants who shared their mobile screen data were randomly assigned to 1 of 3 study groups. Initially, participants in the self-selected group were given information regarding their baseline average daily mobile screen time and asked to choose a target for reducing their mobile screen time based on this average. After the participants in the self-selected group had made their specific target choices, an email was sent to participants in the assigned group informing them about their given target.

All participants, including the control groups, received an email about the benefits of reducing mobile screen time and their baseline average daily mobile screen time.

Intervention Period

The period of 5 weeks following the group allocation is the intervention period. During this, the participants will receive an email every Sunday asking them to report their mobile screen time for the preceding week and provide a screenshot. Two reminder emails will be sent to those who do not respond. Additionally, participants will continue to receive a daily mood survey through WhatsApp. Every Wednesday, we will send out reminders to all groups via WhatsApp with information about the benefits of reducing mobile screen time and details about 2 lotteries. Participants in both intervention groups will also receive email reminders for their chosen and assigned targets. Participants in the intervention groups will receive a daily incentive of INR 50 (US $0.61) for successfully meeting their daily target. These incentives will be transferred to the participants via the Unified Payments Interface after the intervention period. At the end of the intervention, an

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end-of-intervention survey will be administered to all participants.

Postintervention Period

The 4-week period following the intervention period is the postintervention period. During this, the participants will continue to receive an email requesting them to report their mobile screen time for the previous week and provide a screenshot. Two reminder emails will be sent to the participants who do not respond. Participants will also continue to receive a daily mood survey through WhatsApp. The participants will not receive monetary incentives for achieving their targets during this phase. After the postintervention period, an end-of-postintervention survey will be conducted.

Data Collection and Management

The following data are collected during various stages of the study (Table 1). Detailed survey instruments are presented in Multimedia Appendix 1.

We collect data through a web-based survey link shared over an email. All survey instruments are created using Qualtrics (Qualtrics International Inc), a secure web-based survey and database administration application. Data privacy is maintained with password protection for access to the Qualtrics platform. Only members of the research team have access to the database. We use the user-friendly WhatsApp platform for the daily mood survey to gather mood ratings on a scale. Upon concluding the study, the mood survey data will be extracted from WhatsApp and integrated with other data for subsequent analysis.

A pilot study was conducted with the implementing department (Max Institute of Healthcare Management) employees to evaluate and refine the study procedures and the survey tools.

Statistical Analysis

We will estimate the effects of mobile screen time, target achievement rate, GAD-7, PHQ-9, and daily mood scores by comparing variables of interest between the intervention and baseline and between the postintervention and baseline periods. To perform this analysis, we will use Stata 17 and R (version 4.2.2; Free Open-Source Software). The unadjusted effects will be calculated as differences in the means and conducting a 2-tailed Student *t* test for significance. For adjusted effects, we will use simple ordinary least square regression adjusting for participant-level covariates: age, gender, and employee or student. We assume errors to be correlated within each participant but uncorrelated across participants. A separate equation will be used for each dependent variable. The regression equations are provided in Multimedia Appendix 1. For mobile screen time, we will estimate a difference-in-difference ordinary least square regression. To account for the impact of the intervention and the postintervention period, we will incorporate dummy variables for the period. Specifically, assessing the effect on mobile screen time and target achievement rate postintervention will provide valuable insights into habit formation. Multilevel or hierarchical linear modeling will also be used to allow differential relationships between mood and screen time at the individual level.

Ethical Considerations

Ethical approval for this study was granted by the institutional review board of the ISB, Hyderabad, India (reference ISB-IRB2023-18; dated July 26, 2023).

Results

We started the recruitment process on August 21, 2023. We randomized 156 participants, and at the original submission of the protocol, we completed 3 weeks of the intervention period. The results are expected to be published in early 2024. The study results will be published in academic journals. These published findings have the potential to guide policy makers in establishing guidelines for monitoring and limiting excessive mobile screen exposure among both working professionals and students.

Discussion

Principal Findings

The study focuses on the impact of monetary incentives and self-selected versus assigned targets on reducing mobile screen time and thereby improving mental health and well-being during the intervention and postintervention periods.

Previous studies mainly focused on providing correlational evidence. For example, Mosquera et al [24] found that deactivating Facebook for 1 week made people less depressed and led them to engage in healthier activities. Allcott et al [25] found that deactivating Facebook for 4 weeks before the 2018 US election caused small but significant improvements in well-being, self-reported happiness, life satisfaction, depression, and anxiety. However, they did not find an effect on other well-being measures. In a follow-up paper, Allcott et al [21] monetarily incentivized people to reduce social media (Facebook, Instagram, Twitter, Snapchat, web browsers, and YouTube). The group that was monetarily incentivized over a period reduced their screen time by 56 minutes during the treatment period of 3 weeks. However, they found statistically insignificant changes in measures of happiness, life satisfaction, anxiety, and depression [21].

Compared with existing studies that have incentivized reduction over a period, this study offers everyday incentives and targets for people to reduce their overall smartphone use. While there is only 1 study that has used daily incentives, the focus of the study is on rational addiction and does not test the effects on anxiety and depression [22]. In addition, none of the studies have examined self-chosen targets versus given targets on the reduction, target achievement, and impact on well-being. Moreover. the existing studies do not study the effect of reduction on PHQ-9, GAD-7, and daily moods. Although Alcott et al [25] measured daily happiness, they did not have daily use data to understand the impact of daily use on happiness [25].

In this study, we expect the screentime reduction target to vary at the individual level. There might be cases when the average target is higher than the individual reduction that some individuals will prefer to achieve, while for some others there might be cases when the target is less than the individual

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reduction they will aim to achieve. In the former case, the participants may not be able to achieve the average target, while in the latter case, they will achieve it. Other psychological factors, such as cognitive dissonance, support the idea that the self-selected condition is likely to outperform the assigned target condition. This is because participants are motivated to follow through on their personally chosen targets. So overall the reduction in exogenous (assigned group) condition could be lower due to this reason as well.

Through rigorous research design and a comprehensive examination of various factors, the results from the study make a substantial contribution to enhancing the comprehension of how self-selected versus assigned targets may potentially reduce mobile screen use and thereby improve mental health.

Strengths

The primary strength of the study is its intervention, which involves the use of monetary incentives and self-selected versus assigned to reduce mobile screen time and assess improvements in mental health through measures such as the GAD-7, PHQ-9, daily mood scores, and well-being scores. We will have daily mobile screen use data and therefore assess the impact of daily targets and incentives on daily screen use. Another strength advantage is that the study is conducted using digital communication, which removes the requirement for physical contact with participants.

Limitations

One of the potential limitations of the study is that the analyses in the study may lack sufficient power to detect the anticipated effects due to low enrollment. Another limitation is requesting the weekly submission of screen time through a mobile app, which might increase overall mobile screen time. However, this task only demands 4-5 minutes of weekly effort and will not impact the results, as the same procedure was also used at the baseline. The daily mood score was collected through a messaging app, WhatsApp, which is another limitation of the study.

Conclusions

The results of the study might add a significant layer of depth to the existing knowledge, guiding both researchers and policy practitioners toward more about monetary incentives, as well as self-selected versus assigned targets that might be effective interventions in changing health behavior including mobile screen use and thereby improving mental health for working professional and students.

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The authors extend thanks for the active involvement of Indian School of Business (ISB) employees and students. The authors also value the contributions made by Akash Raj and Barsha Saha in tool development and study procedures, as well as the support from the administrative teams at the Max Institute of Healthcare Management and ISB. The study is funded by the Max Institute of Healthcare Management, ISB.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request. The data collected for this study will be stored in the central repository of the Indian Schools of Business.

Authors' Contributions

AS and JS had the original idea for the study and designed the study together. KKS is implementing the study and wrote the first draft of the manuscript. AS and JS reviewed the manuscript, and all authors approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Surveys, weekly reminders and emails, and statistical analysis.
[DOCX File , 69 KB - resprot_v13i1e53756_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder–7
ISB: Indian School of Business
INR: Indian Rupee
PHQ-9: Patient Health Questionnaire–9

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Protocol

Efficacy of the iJobs Web-Based Psychoeducational Intervention to Improve Job Search Behavior and Promote Mental Health Among Unemployed People: Protocol for a Waitlist Randomized Controlled Trial

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Abstract

Background: Unemployment affects millions of people worldwide and, beyond its economic impact, has severe implications for people's well-being and mental health. Different programs have been developed in response to this phenomenon, but to date, job-search interventions have proved to be most effective, especially the JOBS II program. The JOBS II program proved not only to be effective for re-employment but also has a positive impact on beneficiaries' mental health (ie, reduces anxiety or depression). However, by now, this evidence-based program has been delivered only on site in the various countries where it was implemented. In the digital era, web-based alternatives to such programs are highly needed because they have the advantages of scalability and cost-effectiveness.

Objective: In this context, we aim to investigate the efficacy of iJobs, the web-based adaptation of the JOBS II program, on job-search intensity and effort, the quality of job-search behaviors, and job-search self-efficacy. Further, 1 month after the intervention, we will also assess the employment status and the satisfaction with the job (if applicable). This study will also investigate the effect of iJobs on well-being and mental health (ie, anxiety and depression).

Methods: This study is a 2-arm randomized controlled trial. The 2 independent groups (intervention vs waiting list control group) will be crossed with 3 measurement times (ie, baseline, the postintervention time point, and 1-month follow-up). The design will be a 2 (intervention vs control) × 3 (baseline, the postintervention time point, and 1-month follow-up) factorial design. iJobs is a 2-week intervention consisting of 6 modules: an introductive module and 5 modules adapted from the original JOBS II program to the web-based setting and Romanian population. The web-based intervention also has a human component, as beneficiaries receive personalized written feedback after each module on the platform from a team of psychologists involved in the project.

Results: The enrollment of study participants started in June 2023 and is expected to end in May 2024. The data collection is expected to be completed by July 2024. The results are expected to be submitted for publication in the summer of 2024.

Conclusions: This study is the first large-scale randomized controlled trial aiming to test the efficacy of a web-based adaptation of the JOBS II program. If our results support the efficacy of iJobs, they will offer the premise for it to become an evidence-based, accessible alternative for unemployed people in Romania and might be implemented in other countries.

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Trial Registration: ClinicalTrials.gov NCT05962554; https://clinicaltrials.gov/study/NCT05962554
International Registered Report Identifier (IRRID): PRR1-10.2196/55374

(JMIR Res Protoc 2024;13:e55374) doi:10.2196/55374

KEYWORDS

iJobs; JOBS II program; employability; internet intervention; randomized-controlled trial

Introduction

Background

Losing a job or not being able to find a job after finishing studies is a stressful life event—unemployed people struggle not only with financial strain but also with the stigma around it. Unemployment has become a vicious spiral that negatively affects individuals' lives. As time passes, the motivation of unemployed people declines, which affects the intensity of the job-search process [1]. Hence, the chances of gaining re-employment decrease, and the well-being of unemployed people worsens. This can finally lead to mental health impairment (eg, depression and anxiety), and an essential moderator in this relationship is the duration of unemployment [2]. The alarming aspect of this phenomenon is not only how bad the impact of unemployment is at the individual level but also how many people are experiencing it worldwide.

In 2022, the unemployment rate was 6.1% in the European Union, but it is spread differently between countries, and more importantly, it is distributed asymmetrically within the same country regions. In Romania, the lowest percentage of unemployment is registered in the North-West and West regions (3.1% and 3.7%), whereas the highest rates range from 6.6% to 8.8% in the North-East and South regions [3]. From an economic perspective, the youth unemployment rate (people aged between 15 and 29 years) is more concerning. Romania's Central and South regions register youth unemployment rates above 14.7%, and the European Union rate is 11.3% [3].

Various national programs and strategies are being developed to fight this phenomenon. However, the need for alternative solutions that promote employment (shortly after job loss) and well-being among unemployed people is evident. Efficient alternatives to classic governmental programs are job-search interventions. The JOBS II intervention [4] is one of them. JOBS is a job-search intervention intended to promote re-employment and mental health that differentiates itself from others by being studied in and adopted by many countries over the years, such as Finland [5], China [6], Ireland [7], Netherlands, Sweden, and South Korea [8], South Africa [9], or Germany [10].

Existing theories emphasize that unemployment is a cause of distress because unemployed people lose an essential social role (ie, status) and lack psychological basic needs fulfilled by one's job (eg, time structure, social contact, activity, and financial security) [2]. Unsuccessful attempts to gain re-employment reduce the motivation of job seekers and affect their sense of competency and positive self-evaluations. In time, this can lead to mental health issues (ie, anxiety and depression). According to the results of a recent systematic review [11], JOBS improved participants' self-esteem, self-efficacy (ie, job-search self-efficacy; JSSE), and ability to deal with setbacks (ie, inoculation against setbacks), which improved their well-being and mental health (on both the short and long term). Additionally, these coping mechanisms and job-search skills promoted and enhanced by JOBS are crucial for obtaining re-employment in a shorter period and obtaining a more qualitative job. Employment success and quality are predicted by job-search intensity and effort and job-search quality [12]. JOBS promotes job-search behaviors (JSBs; eg, beneficiaries make their job-search schedule) and the quality of those behaviors (eg, networking and practicing interviews).

The program's effectiveness and popularity are based on its structure. It is a short-term intervention of 5 group sessions, encompassing almost all the components proven effective for job-search interventions [13]: *active learning*, *job-search skills*, *inoculation against setbacks*, *social support*, and *referent power*. During JOBS, participants learn the tasks they have to perform from the role of a job seeker and improve the necessary skills through group discussions, case studies, and role-playing exercises. They discover how to overcome potential setbacks in the re-employment process by brainstorming coping strategies, practicing their problem-solving skills, and receiving continuous social support from the trainers and beneficiaries.

However, JOBS is an on-site intervention that requires many resources to be delivered. This format restricts the number of beneficiaries and implies costs for both the organizers (eg, trainers and materials) and unemployed people to participate (eg, transportation fees). In the digitalization era and in the recent context of the COVID-19 pandemic that drastically changed the way we work and learn, it would be worthwhile to explore the efficacy of this intervention in a web-based format. An internet-delivered intervention can be an immediate solution at hand for those who just lost their jobs and could address more people at a time. Some possible advantages of such an alternative may also be the reduced costs and increased flexibility (ie, it is asynchronous).

iJobs is the first web-based adaptation of the JOBS II intervention, which was previously studied in a feasibility and acceptability trial [14]. The results were promising in terms of satisfaction with iJobs, so a further study testing its' efficacy is worthwhile because it can provide information regarding the program's impact on relevant outcomes.

Specific Objectives

This study aims to investigate the efficacy of iJobs on job-search intensity and effort, the quality of JSBs, and JSSE. We will also assess the employment status and satisfaction with the job (for those who will be employed) 1 month after the intervention. This study will also investigate the effect of iJobs on well-being and mental health.

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As a secondary objective, we will evaluate the moderating effects on re-employment of factors such as age, educational level, unemployment period, financial strain, and the mediating effects of job-search intensity, job-search quality, and self-efficacy on re-employment.

Since this is the first large-scale study on a web-based adaptation of the JOBS II program, as stated in the feasibility study [14], we will also evaluate the satisfaction with the intervention, the system usability, and the treatment adherence for the intervention groups.

Specifically, we will test the following hypotheses:

- H1: iJobs will increase the job-search intensity (H1a) and job-search effort (H1b) in the intervention group compared to the control group.
- H2: iJobs will increase the quality of job-search behaviors in the intervention group compared to the control group.
- H3: iJobs will increase job-search self-efficacy in the intervention group compared to the control group.
- H4: iJobs will increase self-esteem (H4a), inoculation against setbacks (H4b), and psychological capital (H4c) in the intervention group compared to the control group.
- H5: iJobs will decrease future career anxiety (FCA; H5a), depression (H5b), anxiety (H5c), and mental health complaints (H5d) in the intervention group compared to the control group.
- H6: The job-search intensity (H6a), job-search quality (H6b), and JSSE (H6c) will mediate the effect of iJobs on re-employment.
- H7: Age (H7a), educational level (H7b), unemployment period (H7c), and financial strain (H7d) will moderate the effect of iJobs on re-employment. iJobs will have stronger effects on re-employment for younger participants, participants with higher educational levels, participants with a shorter period of unemployment, and participants with lower levels of financial strain.

Methods

Ethical Considerations

Ethical approval regarding human subject research was obtained from the West University of Timi oara's Scientific Council in May 2023 based on an application containing this study's aim, procedure, measures, and materials (32005/17.05.2023). This study was registered as a clinical trial on ClinicalTrials.gov (NCT05962554). Participants will give their informed consent and, as per the European Union's regulations, accept the General Data Protection Regulation statement when enrolling in the program: all the data from the questionnaires completed during and after the intervention is anonymous, their identity on the iJobs platform is protected by a random identification code that serves as the username, and they can withdraw from this study at any point. Participants who complete the follow-up measurements will be included in a raffle and can win either a backpack or an insulated bottle.

Trial Design

This study is a 2-arm randomized controlled trial (RCT) that will test the efficacy of a web-based adaptation of iJobs. Participants will be randomly assigned (1:1 allocation) to either the intervention group, which benefits from the iJobs program, or a waiting list control group that will also receive the iJobs intervention 2 weeks after the intervention group finishes it. The 2 independent groups (intervention vs waiting list control group) will be crossed with 3 measurement times (ie, baseline, the postintervention time point, and 1-month follow-up). Hence, the design will be a 2 (intervention vs control) × 3 (baseline, the postintervention time point, and 1-month follow-up) factorial design.

Participants and Recruitment

Eligible participants are unemployed Romanian adults. We will include in this study participants who (1) are unemployed and looking for a job, (2) work as volunteers and are looking for a paid job, (3) are aged between 18 and 60 years, and (4) have a PC or a laptop and basic digital skills. We will exclude the participants who do not have internet access or are lacking in availability during the 2-week program period.

Our recruitment strategy is to post an overview of iJobs on social media (ie, Facebook and LinkedIn), using paid advertising targeting job seekers, and on web-based newspapers. We will also promote iJobs on Employment Force Agencies and Recruitment Agencies across Romania.

Intervention

iJobs is a web-based adaptation of the JOBS II program: *a manual for teaching people successful job-search strategies* [4]. iJobs is a 2-week intervention with 6 modules: an introductive module and 5 modules adapted from the original JOBS II program. iJobs will be delivered via TalentLMS (Epignosis), a web-based, cloud-based learning management system. iJobs' visual interface is depicted in Figure 1. The intervention was previously tested in a feasibility and acceptability open-label trial using a different platform [14]. A brief description of iJobs modules can be found in Textbox 1. The program's content is audio and text based, but the participants will answer in writing to all of the exercises.

iJobs is an asynchronous program, so the component of mutual social support between beneficiaries is absent. Compared to the JOBS II program, the participants interact via messages only with the counselors involved in the feedback process. The counselors were previously instructed about iJobs' aim, content, and feedback process.

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Figure 1. iJobs' interface samples. From authentication to the main app dashboard, a preview of video material, and completing of an exercise on the platform.

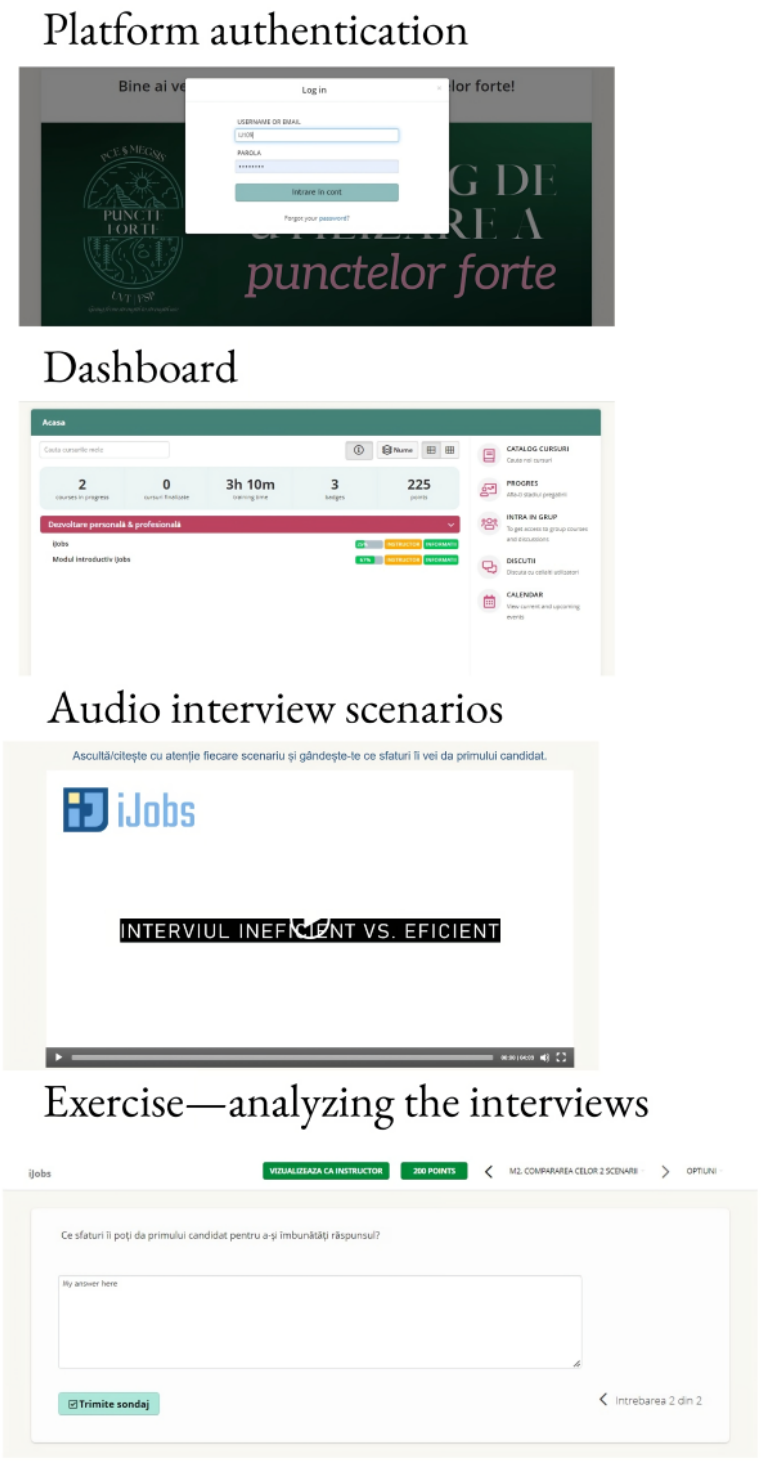

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Textbox 1. Overview of iJobs modules. Brief description of each module's content.

Introductive module

- Participants will watch a short video explaining the platform's main features (eg, how to complete exercises during the program and send messages to the counselors). At the end of the module, the participants must complete a questionnaire (eg, the pretest measures for the intervention group) to be enrolled in the intervention.

Discovering your job skills

- Participants will identify their strengths and learn how to demonstrate them during interviews from audio case studies that illustrate effective versus ineffective interviews.

Dealing with obstacles to employment

- Participants will identify possible obstacles and challenges in the employment process and explore how they can address them during interviews.

Finding job openings

- Participants will learn about networking and how their extended network can help identify job opportunities (eg, they complete an informational interview exercise).

Resumes, contacts, and interviewing

- The fourth module focuses on resumes (participants will analyze a resume and then create their curriculum vitae) and includes interview exercises from both the role of the candidate and the employer.

Complete interview and planning for setbacks

- Participants will integrate the information learned during the program into a complete interview. Ultimately, they will anticipate obstacles and prepare strategies for overcoming them in the re-employment process.

Procedure

The study procedure is presented in Figure 2. In the enrollment phase, an overview of the program and a link to open the iJobs presentation website [15] will be posted on social media (ie, paid advertising on Facebook and LinkedIn, web-based newspapers, and employment agency sites). Those who want to participate will have to complete a registration form, give their informed consent, and accept the General Data Protection Regulation statement. Eligible participants will be randomly allocated to either the intervention or the waiting list control group (1:1 allocation).

Figure 2. Study design and procedure overview. t0: 2-3 weeks before iJobs; t1: randomization within 1 week before iJobs and pretest assessments for both groups; t2: posttest assessments within 1 week after iJobs for both groups; the control group starts now iJobs; t3: follow-up screening 1 month after iJobs for the intervention group; posttest assessments for the control group at the end of iJobs; t4: follow-up screening 1 month after iJobs for the waiting list group.

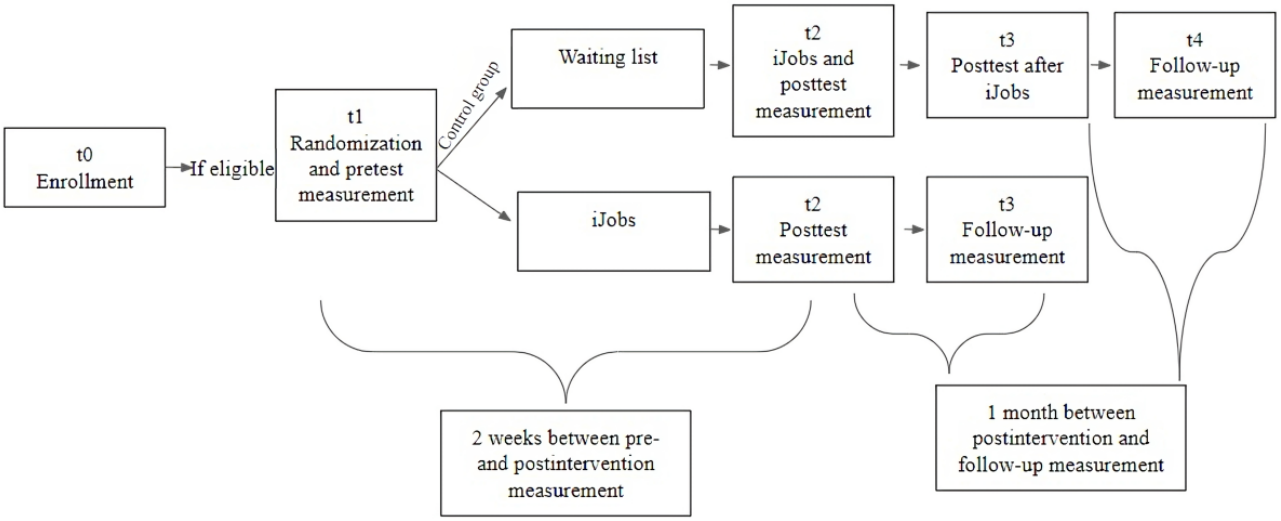

The participants from the intervention group will receive an email with the iJobs calendar and brief instructions. Afterward, they will receive an email with the platform login information. The username will be a random combination of digits (eg, IJ105) to ensure participants' anonymity during the program. The account password is generated automatically by the platform. Once participants access their accounts, an introductive module containing the baseline measures questionnaire will be available

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on the platform. Meanwhile, the waiting list control group participants will receive an email with the iJobs period and a link to the baseline questionnaire.

On the iJobs' platform, each module will be available for completion for 27 hours. After participants receive personalized written feedback on the platform from the team of counselors involved in the program, the following module will become automatically available for completion. After the last module, the posttest questionnaires will be available on the platform for 48 hours.

Further, 2 weeks after the intervention group finishes iJobs, the control group will start the intervention and go through the abovementioned steps. The questionnaire from the introductive module is the posttest measure for the control group.

Additionally, 1 month after the intervention, the participants who complete the posttest measures will be contacted to complete a brief questionnaire that evaluates their employment status and JSBs.

An overview of this study's period is presented in Table 1.

Table 1. Study timeline. Time points and outcome assessments for the intervention group and waiting list group from enrollment to follow-up.

	Time point[a]				
	Enrollment (t0)	Randomization and pretest measurement (t1)	Posttest measurement (t2)	Follow-up intervention group (t3)	Follow-up control group (t4)
Enrollment	✓				
Eligibility screen	✓				
Informed consent	✓				
Randomization		✓			
Intervention group		✓	✓		
iJobs (intervention group)		✓			
Waiting list control group		✓	✓		
iJobs (control group)			✓		
Assessments[b]					
Job-search intensity and effort		✓	✓	✓	✓
Job-search quality		✓	✓	✓	✓
Job-search self-efficacy		✓	✓	✓	✓
Self-esteem		✓	✓		
Inoculation against setbacks		✓	✓		
Psychological capital		✓	✓		
Future career anxiety		✓	✓		
Depression		✓	✓		
Anxiety		✓	✓		
Mental health complaints		✓	✓		
Physical health	✓				
Financial strain	✓				
Sociodemographics	✓				
Treatment adherence			✓	✓	
Treatment satisfaction			✓	✓	
System usability			✓	✓	
Employment status	✓			✓	✓
Job quality (if applicable)				✓	✓

[a]t0: 2-3 weeks before iJobs; t1: randomization within 1 week before iJobs and pretest assessments for both groups; t2: posttest assessments within 1 week after iJobs for both groups; the control group starts iJobs; t3: follow-up screening 1 month after iJobs for the intervention group; posttest assessments for the control group at the end of iJobs; t4: follow-up screening 1 month after iJobs for the waiting list group.

[b]For a detailed description, see the *Outcomes* section.

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Outcomes

Primary Outcomes

Job-Search Intensity and Effort

We will use a contemporary version of Blau's JSB scale, adapted to the Romanian context [16], to assess the frequency and intensity of participants' job-search activities during the past 2 weeks. The scale consists of 16 items on a 5-point scale (1=never; 5=very frequent). Thus, 13 items measure job-search intensity (eg, "How often did you send your CV to potential employers?"), with a total score between 13 and 65, and 3 items measure job-search effort (eg, "You dedicated much of your time to job search."), with a total score between 3 and 15. A higher score means a better outcome. JSBs will be measured at baseline, the postintervention time point, and follow-up.

Job-Search Quality

We will use the Job Search Quality scale [17] to assess the quality of the job-search process, with precisely 4 components: goal establishment and planning, preparation and alignment, emotion regulation and persistence, and learning and improvement. The scale has 20 items on a 5-point scale (1=not at all applicable to me; 5=fully applicable to me). Goal establishment (ie, job-search goals and planning are clear, specific, and systematic) is measured with 7 items (eg, "I was determined to find a job."); the total score ranges between 7 and 35. Preparation and alignment (ie, preparation of job-search activities in alignment with what the organizations are looking for in their applicants) is measured with 5 items (eg, "I carefully studied the website of organizations where I was going to apply."); the total score ranges between 5 and 25. Emotion regulation (ie, self-control facilitating persistence in the job-seeking process; eg, "I persisted in my job search, even though it was unpleasant at times.") and learning (ie, reflection on the job search and ways to improve it; eg, "I thought about other ways to find a job beyond those I had already tried.") are measured with 4 items; the total score ranges between 4 and 20. A higher score means a better outcome. Job-search quality will be calculated at baseline, the postintervention time point, and follow-up.

About JSSE

The JSSE [18] will be used to assess participants' perception of their ability to gain employment. The scale has 20 items (eg, "I believe my job search will be successful") on a 5-point scale (1=a little; 5=a great deal), with a total score between 20 and 100. A higher score means a better outcome. JSSE will be measured at baseline, the postintervention time point, and follow-up.

Secondary Outcomes Measures

Inoculation Against Setbacks

Inoculation against setbacks will be assessed using 2 items (eg, "Do you have an action plan for potential setbacks in the re-employment process?"), on a 5-point Likert scale (1=completely disagree; 5=completely agree), retrieved from Vuori and Vinokur [5], aiming to measure the participants' ability to deal with setbacks in the job-seeking process. The minimum score is 5, and the maximum is 10. A higher score means a better outcome. Inoculation against setbacks will be measured at baseline and the postintervention time point.

Self-Esteem

Rosenberg's [19] Self-Esteem Scale will be used to assess global self-worth by measuring both positive and negative feelings about the self. The scale has 10 items (eg, "I believe I have many qualities.") on a 4-point scale (1=completely disagree; 4=completely agree). The minimum score is 10, and the maximum is 40. A higher score means a better outcome. Self-esteem will be measured at baseline and the postintervention time point.

About FCA

The FCA scale [20] will be used to assess participants' anxiety regarding their future jobs. The scale has 5 items (eg, "I worry about future employment because of fierce competition in the job market.") on a 5-point scale (1=completely disagree; 5=completely agree), with scores between 5 and 25. A higher score means a worse outcome. FCA will be measured at baseline and the postintervention time point.

Anxiety

The Generalized Anxiety Disorder–7 assessment [21] will be used to assess the severity of anxiety symptoms in the past 2 weeks, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria. The scale has 7 items (eg, "Over the past two weeks, how often you had trouble relaxing?") on a 4-point scale (0=not at all; 3=nearly daily), with scores between 0 and 21. A higher score means a worse outcome. Anxiety will be measured at baseline and the postintervention time point.

Depression

Patient Health Questionnaire–9 [22] will be used to measure participants' severity of depression symptoms in the past 2 weeks, according to *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. The scale has 9 items (eg, "Over the last two weeks, how often you had little interest or pleasure in doing things?") on a 4-point scale (0=not at all; 3=nearly daily). The minimum score is 0, and the highest one is 27. A higher score means a worse outcome. Depression will be measured at baseline and the postintervention time point.

Mental Health Complaints

We will use the Mental Health Complaints Scale [23], a 5-item instrument (eg, "In the past two weeks, how often were you happy?") with a 6-point scale (1=not at all; 6=all the time). The minimum score is 6 and the maximum is 30. A higher score means a worse outcome. Mental health complaints will be measured at baseline and the postintervention time point.

Psychological Capital

The Compound Psychological Capital Scale [24] will be used to measure participants' psychological capital. The scale has 12 items (eg, "Right now, I see myself as being pretty successful.") on a 6-point Likert scale (1=completely disagree; 6=completely agree), with a minimum score of 12 and a maximum of 72. A higher score means a better outcome. Psychological capital will be measured at baseline and the postintervention time point.

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Other Measures

Physical Health

A short version of Ware's Physical Health Complaints Scale [25] will be used to assess participants' physical health. The scale has 4 items (eg, "I get sick easier than other people.") on a 5-point scale (1=completely disagree; 5=completely agree). The minimum score is 5 and the maximum is 25. A higher score means a worse outcome. Physical health will be measured only at baseline.

Sociodemographics

At baseline, participants will fill in their age, gender, residential area, educational level, average monthly income, unemployment period, work experience, and targeted professional field.

Treatment Adherence Measures

We will assess the dropout rate, the number of completed modules, and the quality of the completed assignments. Two independent experts will rate the degree of completeness and depth of the answer for each assignment based on an a priori grid (eg, "The participant understood the assignments."). Treatment adherence will be measured at the postintervention time point.

Satisfaction With the Intervention

Satisfaction with the intervention will be measured using 21 items. The scale consists of 5 items (eg, "My trainer is competent.") retrieved from a questionnaire used for measuring the alliance between trainers and trainees in a face-to-face JOBS intervention [26], and 9 items (eg, "Overall, how satisfied are you with the program?") and 7 open-ended questions retrieved from Richards et al [27] and previously used in questionnaires evaluating the satisfaction with interventions delivered on e-cbt [28], the platform we previously used to provide the program. Satisfaction with the intervention will be measured at postintervention time point.

Usability

The System Usability Scale [29] will be used to measure participants' satisfaction with TalentLMS, the web-based platform we will use for program delivery. The scale has 10 items on a 5-point scale (eg, "I think I would like to use this platform frequently"; 1=completely disagree and 5=completely agree); the calculation formula suggested by Brooke [30] generates a score between 0 and 100. A higher score means a better outcome. Usability will be measured at the postintervention time point.

Employment Status

We will assess the self-reported employment status with a dichotomous question at follow-up (ie, "Do you currently have a paid job?").

Job Quality

The job quality will be measured at follow-up only for the participants who found employment, with 4 questions (a dichotomous question and 3 questions on a 10-point Likert scale; eg, "How much do you like your current job?"; 1=not at all and 10=very much). Specifically, we will assess the satisfaction with the professional domain, overall tasks, and salary.

Statistical Analysis

Power

The sample size estimation in GPower (Heinrich-Heine-Universität Düsseldorf) for a mixed factorial design aiming for a .80 statistical power is 132 participants. Based on our previous results from a feasibility and acceptability trial on iJobs, we can anticipate a possible dropout rate of about 36% (n=48). Thus, the final sample aimed for enrollment will be 180 eligible participants (see Figure 3 for the flowchart).

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Figure 3. CONSORT flow diagram with the estimated number of participants aimed by the end of data collection and the current status of enrolled participants. CONSORT: Consolidated Standards of Reporting Trials.

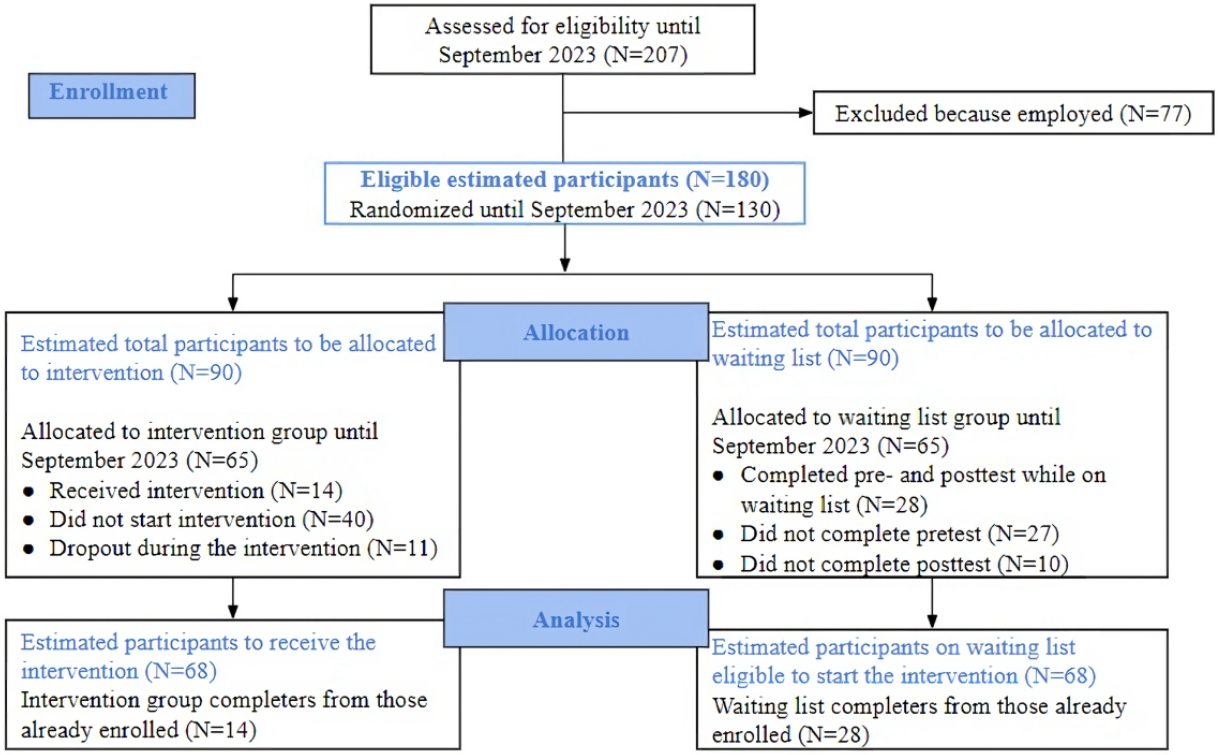

Data Analysis

We will use data from all the participants eligible for this study who completed the pretest measures. The data will be analyzed using the intent-to-treat framework with linear mixed model procedures. Intention-to-treat is based on the principle "once randomized, always analyzed." It is a pragmatic approach to avoid bias in estimating the effect of treatment assignment in RCTs. We will use the linear mixed model approach without ad hoc imputations because it is more powerful than other options for studies with a high percentage of missing data [31].

For all the outcomes, time (baseline vs the postintervention time point) will be set as the within-group factor, and trial condition (intervention vs waiting list control group) will be used as the between-groups factor. We will analyze these 2 variables together with the entire set of outcomes (baseline vs postintervention comparison for the primary and secondary outcomes) to estimate the intervention's effect size. Baseline to 1-month follow-up comparisons will be made to test how much the primary outcomes are preserved in time. We will also conduct separate analyses for each outcome with group, time, and group-by-time interaction as fixed effects and a random intercept for subjects with an identity covariance structure. The group-by-time interactions express the mean outcome change between the 2 trial groups from baseline to posttreatment.

Results

The enrollment of study participants started in June 2023 and is expected to end in May 2024. Until September 2023, we organized 2 iJobs sessions. Out of the 130 randomized participants, we collected complete data (ie, pre- and postintervention) from 42 participants ($n_{\text{intervention group}}$=14, $n_{\text{control group}}$=28). The dropout rate from pretest to posttest in the intervention group was 44% (11/25) and 26% (10/38) in the waiting list control group (see Figure 3 for a flowchart). The data collection is expected to be completed by July 2024. The results are expected to be submitted for publication in the summer of 2024.

Discussion

Summary

This study aims to test the efficacy of iJobs, a web-based alternative to the JOBS II program, in the Romanian context and population. To our knowledge, this is the first large-scale RCT testing of the program's efficacy as a web-based intervention. iJobs intends to increase re-employment and prevent mental health issues among its beneficiaries. Such an alternative for people experiencing unemployment is highly needed, mainly because, at the moment, there seem to be no available effective digital mental health interventions tailored to them [32]. Moreover, a web-based intervention should be easily accessible and cost-reduced, so that many unemployed people could benefit from it shortly after losing their jobs. This aspect is essential since the longer the unemployment period is, the worse the impact on an individual's well-being [2].

Limitations

Even if the web-based format of iJobs has some advantages, it also has some limitations. Social support is one of the most critical components of the JOBS II program. In the web-based format, mutual social support between beneficiaries is absent, while the support from the trainers comes only through written

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feedback messages. Immediate feedback for some types of exercises (eg, practice interviews) might be more valuable for participants. In addition, the solution for substituting social support constrains the participants to stick to specific timeframes while completing iJobs.

Another significant limitation is this study's design. The waiting list control group also completes iJobs, so we cannot compare the groups regarding employment at the follow-up. The relatively high dropout rate is also a concerning factor. The recruitment strategy should be reconsidered to reduce the number of iJobs sessions taken and simultaneously increase the number of participants who benefit from them. By now, the program has been promoted on social media (ie, Facebook) through paid advertising. For further iJobs sessions, we are considering promoting the program also via web-based newspapers, recruiting agencies, and labor force agencies.

Conclusions

If our results confirm iJobs' efficacy, the intervention will have the perspective of becoming an accessible, evidence-based web-based solution for unemployed people in Romania. Moreover, it might be of interest to implement iJobs in other countries.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available yet because the data collection is still ongoing, but preliminary data sets are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CV: curriculum vitae
FCA: future career anxiety
JSB: job-search behavior
JSSE: job-search self-efficacy
RCT: randomized controlled trial

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Protocol

Evaluating and Enhancing an Educational Intervention to Reduce Smallholder Farmers' Exposure to Pesticides in Uganda Through a Digital, Systematic Approach to Behavior Change: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: Smallholder farmers receive educational interventions on safe pesticide handling by governmental agencies, industries, or nongovernmental organizations to reduce exposure risks. However, existing educational interventions have limited effects on changing behaviors. Targeting psychosocial determinants of behavior change in educational interventions through theory- and evidence-based approaches may enhance their effectiveness.

Objective: We aim at describing the intervention development and study design of a 3-arm cluster-randomized controlled trial to assess the effects in improving safe pesticide handling and reducing pesticide exposure of (1) an existing educational intervention and (2) a newly developed SMS text messaging intervention based on the Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS) behavior change approach.

Methods: We enrolled 539 Ugandan smallholder farmers in 12 clusters (subcounties). The clusters, each with 45 farmers, were randomly allocated to one of the three arms: (1) educational intervention, (2) educational intervention+RANAS-based SMS text messages, or (3) control group. The educational intervention comprised a 2-day workshop that targeted multiple aspects of safe pesticide handling, whereas the SMS text messages targeted the use of personal protective equipment (PPE) and were based on the RANAS approach. For intervention development in this study, this approach includes identifying psychosocial determinants of PPE use at baseline and selecting behavior change techniques to target them in SMS text messages. The primary outcomes of the study are (1) pesticide knowledge, attitude, and practice scores indicating performance throughout the educational intervention; and (2) frequency of PPE use. Secondary outcomes are the RANAS-based behavioral determinants of PPE use, the frequency of glove use, algorithm-based pesticide exposure intensity scores, and signs and symptoms of pesticide poisoning. The outcomes were assessed in structured interviews before the intervention (baseline) and at the 12-month follow-up. The effect of the interventions among the arms will be analyzed using the intervention arms and baseline measures as predictors and the follow-up measures as outcomes in linear multivariable mixed models including the clusters as random effects. The mediating psychosocial determinants of the interventions will be assessed in multiple mediation models.

Results: The study was conducted from 2020 to 2021—baseline interviews were conducted in October 2020, and the educational intervention was delivered in November 2020. The RANAS-based SMS text messages were developed based on the baseline

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data for relevant behavioral determinants of PPE use and sent between February 2021 and September 2021. Follow-up interviews were conducted in October 2021. Overall, 539 farmers were enrolled in the study at baseline; 8.3% (45/539) were lost to follow-up by the end of the study.

Conclusions: This study will contribute to a better understanding of the effectiveness and behavior change mechanisms of educational interventions by using an experimental, cluster-randomized study design to improve pesticide handling among smallholder farmers.

Trial Registration: International Standard Randomised Controlled Trial Number (ISRCTN) 18237656; https://doi.org/10.1186/ISRCTN18237656

International Registered Report Identifier (IRRID): DERR1-10.2196/55238

(JMIR Res Protoc 2024;13:e55238) doi:10.2196/55238

KEYWORDS

smallholder farmers; knowledge; attitude; practice; behavior change; psychosocial determinants of behavior; health; education; pesticide exposure; SMS text messages

Introduction

Background

Agricultural pesticide use has almost doubled worldwide in the past 3 decades, with a particular increase in low- and middle-income countries (LMICs) [1]. For example, in Uganda, there was a 12-fold increase in pesticide import value between 2000 (US $9.4 million) and 2020 (US $108.5 million) [2]. The increase in pesticide use results from many factors, such as the intensification of agricultural systems, changing land use patterns due to climate change [3], pesticide resistance, or increasing pest pressure [4]. In most LMICs, smallholder farmers dominate agricultural production [5], mainly relying on pesticides as their primary and often their only pest control strategy [6,7]. However, smallholder farmers often have insufficient knowledge, attitude, and practice (KAP) along the pesticide-handling chain, for example, limited knowledge of hazard information present on pesticide labels [8], low risk perception of the product [6,9], and limited use of recommended personal protective equipment (PPE) [6]. Hence, these gaps in the KAP of pesticide handling may risk farmers' health [10,11].

The agricultural extension service system that ought to provide technical advice to improve farmers' skills in pest control [12] and on safe pesticide handling [13] is often constrained by low staffing in LMICs. Therefore, it does not effectively reach out to farmers [4]. Consequently, smallholder farmers obtain most of their pesticide use information from their counterparts and agro-dealers [6]. However, agro-dealers often lack sufficient legal and technical qualifications to guide farmers on safe pesticide handling in LMICs [10,14]. Alongside these information channels, interventions promoting safe pesticide handling by smallholder farmers are rolled out by governmental agencies, industries, or nongovernmental organizations (NGOs) worldwide [15]. These interventions can be classified as educational or behavioral [16], technological or engineering-based, legislation- or enforcement-focused, incentive-based, and multifaceted interventions [15]. They range from creating awareness to promoting the use of PPE, adherence to manufacturers' instructions, use of low-toxicity–class pesticides and other pest control strategies, and policy advocacy. By 2022, a total of 3 intervention studies had been systematically assessed for their impacts in reducing pesticide exposure in Africa [17]. Of these studies, 2 provided insight into the importance of farmer field schools in promoting integrated pest management (IPM) and, consequently, reducing pesticide use among smallholder farmers [18,19]. The other study provided evidence that training health care workers improves their knowledge and skill in handling acute pesticide poisoning cases [20].

In Uganda, educational interventions on pest management and safe pesticide use are mainly conducted by NGOs or industries [21]. These educational interventions, for example, reduced pesticide application frequency, increased PPE use, and introduced IPM strategies [18]. Similar findings are reported in other LMICs. For example, in Bolivia, trained farmers that adhered to safe pesticide use practices had considerably lower urinary pesticide metabolite levels after pesticide application than the untrained farmers [22]. Similarly, in Costa Rica, lower self-reported pesticide exposure intensity scores (EISs) among farmers were observed in farmers who had attended training in safe pesticide handling [23]. In summary, the existing literature on pesticide intervention evaluations in LMICs is limited by (1) cross-sectional study designs; (2) no comparative assessment of the impact on KAP; and (3) no systematic approach to targeting and assessing behavioral determinants of pesticide handling, such as farmers' psychosocial cognitions [24].

One way to systematically change behavior is the Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS) framework [25]. The RANAS approach is an established tool that suggests different steps for designing and evaluating evidence- and theory-based behavior change interventions based on proposed psychosocial behavioral determinants [26]. This study protocol showcases the study design of a randomized controlled trial to evaluate and an enhance existing educational interventions using the RANAS approach for systematic behavior change [25] to promote safe pesticide handling among smallholder farmers in Uganda. This study is part of the African Pesticide Intervention Project, which seeks to promote and improve intervention studies on pesticide handling in LMICs [27].

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Aims and Specific Objectives of the Study

There are two main aims to this study (Figure 1): o evaluate the effectiveness of an existing educational intervention on pesticide-related KAP, PPE use, exposure, and health risks of pesticide handling; and (2) to evaluate whether the effect of the educational intervention can be enhanced by sending tailored RANAS-based SMS text messages targeting behavioral determinants of PPE use among smallholder farmers in Uganda. In relation to the first aim, the following outcomes are addressed:

1. To investigate the effect of the educational intervention on pesticide-related KAP along the educational curriculum compared to the control.
2. To assess the effect of the educational intervention on pesticide exposure intensity compared to controls.
3. To assess the effect of the educational intervention on health signs and symptoms associated with acute pesticide poisoning compared to controls.

In relation to aim 2, the specific research questions are as follows:

1. To test whether SMS text messages that targeted behavioral determinants based on the RANAS approach for behavior change have an additional, increased effect on PPE use compared to the educational intervention alone.
2. To understand which behavioral determinants specified by the RANAS approach were enhanced by the intervention and explain behavior change regarding PPE use.

Figure 1. Conceptual framework showcasing the 5 objectives and their outcome measures to evaluate the existing educational intervention (2-day workshop) and the newly designed Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS)–based SMS text messaging intervention on safe pesticide handling among smallholder farmers in Uganda. PPE: personal protective equipment.

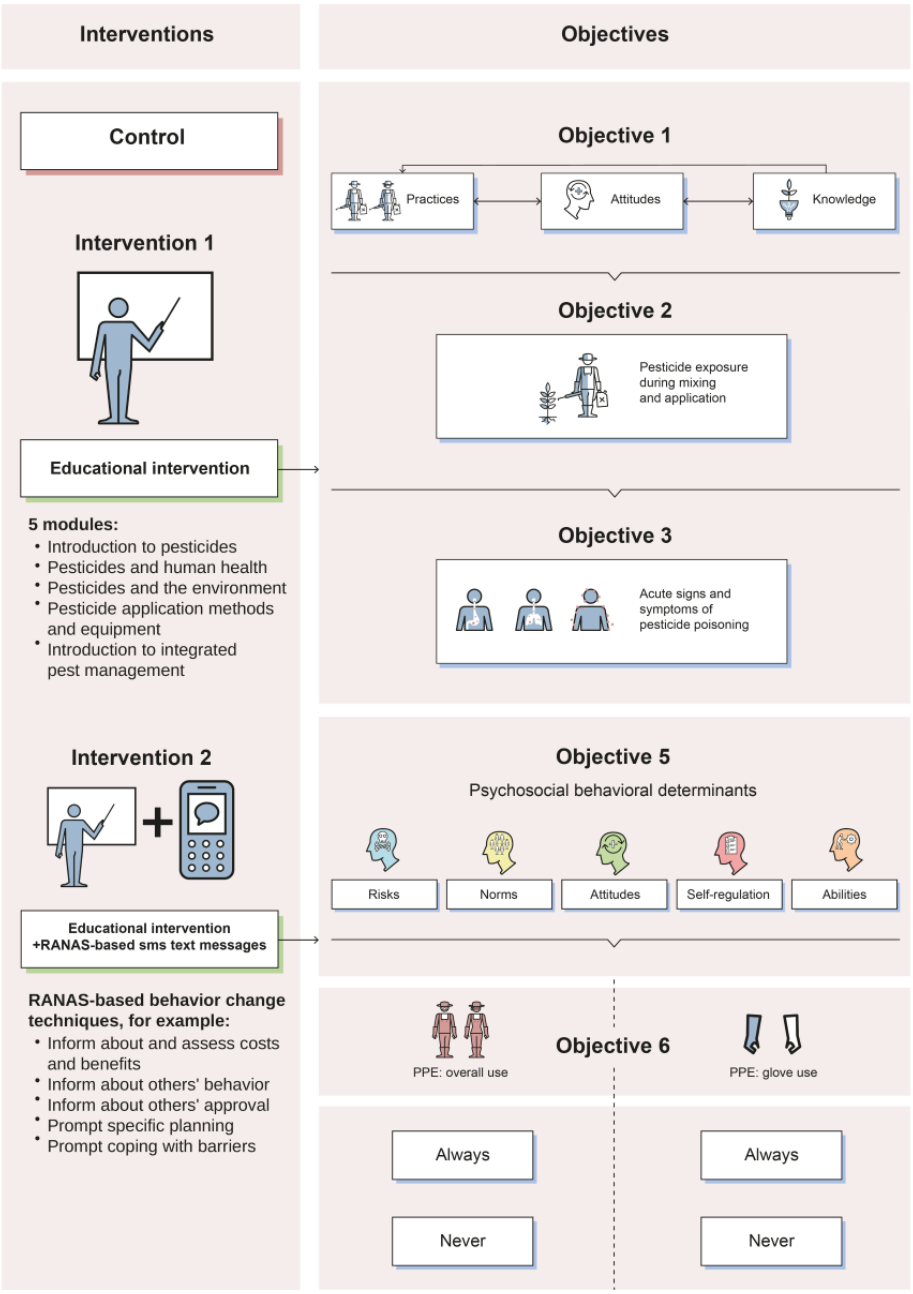

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Methods

Study Design

A cluster-randomized controlled trial with 3 arms—educational intervention, educational intervention and RANAS-based SMS text messages, and a control arm (received no intervention; Figure 2)—was conducted in the Kumi and Sembabule districts of Uganda between October 2020 and October 2021. A video describing the study can be found in Multimedia Appendix 1. A total of 12 subcounties (6 from either district), which are geographical administrative units of lower local government, formed the clusters for the study.

Figure 2. (A) Study design of the 3-arm cluster-randomized controlled trial to evaluate the educational intervention (2-day workshop) and the newly designed Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS)–based SMS text messaging intervention on safe pesticide handling. (B) Timeline of the 3-arm cluster-randomized controlled trial.

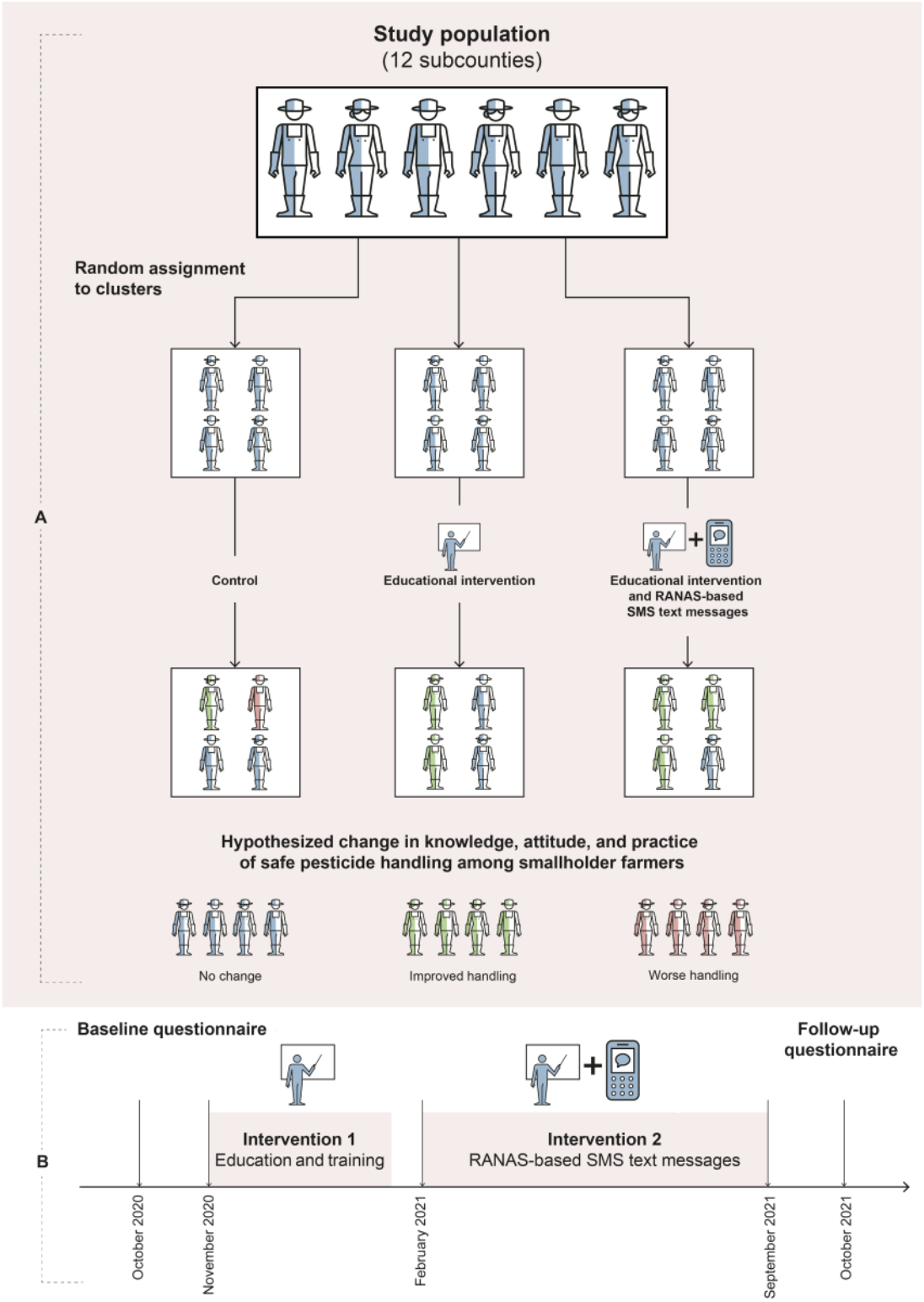

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Study Area

Sembabule District is located in the central region of Uganda and has 6 subcounties and 2 town councils. Kumi District, on the other hand, is situated in the eastern region and subdivided into 6 subcounties and 1 municipality (Figure 3). The 6 subcounties from each district were selected based on their rural setting associated with ongoing agricultural activities. Both districts have pesticide-intensive crop (eg, watermelon, tomato, cabbage, and passion fruit) and livestock (eg, cattle, goats, and sheep) production systems, which constitute major economic activities.

Figure 3. A map of Uganda showing the 2 study districts and intervention allocation of the subcounties. RANAS: Risks, Attitudes, Norms, Abilities, and Self-regulation.

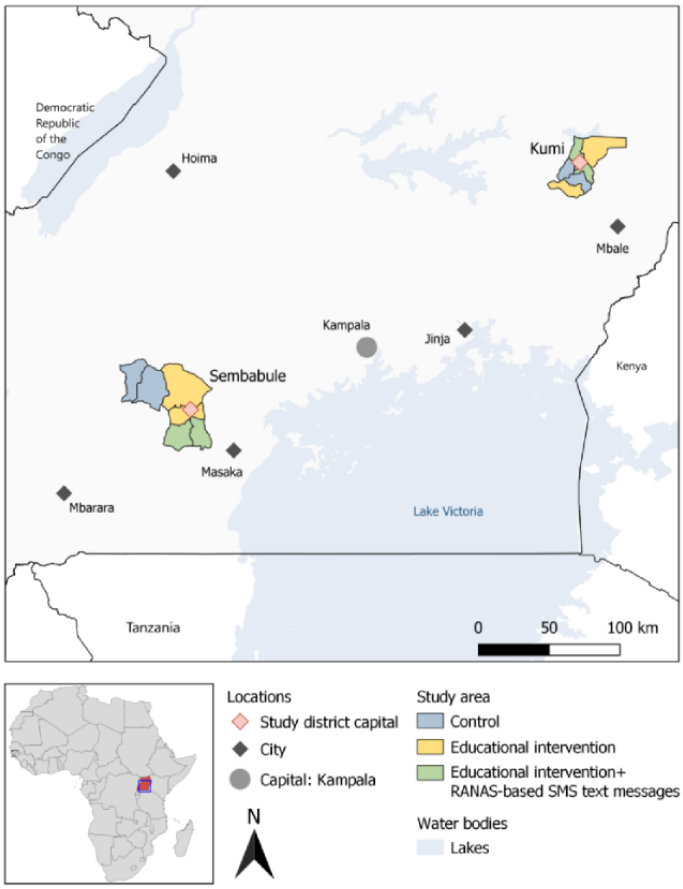

Participants

The District Farmers' Associations (DFAs)—the Sembabule DFA and the Kumi DFA—provided lists of farmers who (1) grew at least one of the crops (watermelon, tomato, cabbage, and passion fruit) that are locally associated with frequent pesticide use, (2) had been actively involved in pesticide application in the previous 12 months, (3) were aged ≥18 years, (4) were able to read and write in English or the local language, (5) belonged to a household with at least one active mobile phone, and (6) had not directly participated in previous Uganda National Association of Community and Occupational Health (UNACOH)–led trainings in the area. Each of the DFAs provided a list each comprising 300 smallholder farmer names and contacts from their database, providing a total of 600 eligible participants, 50 from each subcounty. The research assistants contacted the farmers and interviewed (at baseline and 12 months afterward) those available and obtained consent until 45 farmers per subcounty were enrolled. The interviews took place at the farmers' homes or fields depending on the farmers' location at that time.

Ethical Considerations

Ethics approval for the study was secured from the Higher Degrees, Research, and Ethics Committee at Makerere University in Uganda (reference 846). In addition, the study was registered on the ISRCTN clinical trial registry (ISRCTN 18237656), and written informed consent was obtained from all study participants before the baseline interview.

Randomization and Blinding

After the baseline survey in October 2020, a total of 4 clusters each with 45 farmers were randomly assigned to one of the three arms, comprising 180 farmers per arm (Figure 1): (1) educational intervention, (2) educational intervention+RANAS-based SMS text messages, or (3) control group. One of the Swiss investigators who had no previous knowledge of the subcounties used Microsoft Excel (Microsoft Corp) random numbers to randomize the clusters to the arms. The allocation of the clusters was concealed from the participants. The participants were also blinded with regard to which arm other farmers had been assigned to. The investigators and facilitators knew which arm the farmers had been assigned

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to, and at the follow-up interviews, the research assistants could know which arm the farmers had been assigned to.

Sample Size Calculation

We estimated a sample size of 540 farmers that assumed a statistical power of 80% based on the estimated observed differences between the EISs of an average pesticide application between smallholder farmers who received training in pesticide handling and those who did not receive it in a recent survey in Uganda [23]. The trained group had a mean EIS of 0.47 (SD 0.10), and the untrained group had a mean EIS of 0.55 (SD 0.18). We assumed that the 2 planned intervention arms would show a similar effect distribution. Hence, we based our sample size calculation on the 2-sample means test assuming a cluster-randomized design, a total of 12 clusters equally distributed between the control and intervention groups, and an intraclass correlation coefficient of 0.4. The package *power two means* in the statistical software Stata (version 15; StataCorp) resulted in a cluster size of 40 farmers and a total of 480 farmers, which would reach a power of 80% at a significance level of 5%. To account for a possible dropout rate of 13% at follow-up based on a previous study in a similar setting [23], in each cluster, an additional 5 farmers were enrolled, hence constituting a total sample size of 540.

Description of the Interventions

Educational Intervention

The investigated educational intervention is an existing training curriculum (Multimedia Appendix 2) designed by the UNACOH to reduce pesticide exposure and associated human and environmental health effects in Uganda between 2010 and 2020 [28]. It includes 5 modules: introduction to synthetic pesticides, pesticides and human health, pesticides and the environment, pesticide application equipment, and IPM. The main objective of the intervention was to improve pesticide handling through enhancing the KAP of smallholder farmers. Furthermore, the intervention is hypothesized to reduce pesticide exposure and the negative associated health symptoms.

The intervention was developed under the Pesticide Use Health and Environment (PHE) project and implemented in 3 phases by the UNACOH in collaboration with Diálogos, a Danish NGO. The project's interventions included 3 thematic areas: evidence gathering or documentation, training or knowledge dissemination, and policy influence or lobbying and advocacy. Among the several project trainees were smallholder farmers, agro-dealers, extension workers, village health personnel, and health workers on topics such as responsible pesticide handling; IPM; and acute pesticide poisoning diagnosis, management, and reporting.

The educational materials used by the PHE project in its first phase (2010-2013) were originally adapted from a sister project, *Proyecto De Desarrollo Comunitario*, implemented in Bolivia with support from the same partner, "Dialogos." A series of 7 small booklets or modular training guides was developed and used to facilitate training in the first 2 phases (2010-2013 and 2013-2017), and at the start of the third phase (2017-2020), they were revised and merged into 1 training manual or curriculum in technical partnership with and with approval from the Agricultural Chemicals Control Board; Department of Crop Protection; and Ministry of Agriculture, Animal Industry, and Fisheries of Uganda. Copies of this 5-module manual, titled "Responsible pesticide use and handling: A guide for sustainable pest management," were widely disseminated by the Ministry of Agriculture, Animal Industry, and Fisheries through its structures.

RANAS-Based Text Messages

Overview

In addition to being delivered the educational training manual, one arm received mobile phone SMS text message reminders. The SMS text message intervention was based on the RANAS approach, a systematic approach for behavior change (see Multimedia Appendix 3 for detailed wordings of the messages). The RANAS approach is an established tool that suggests different steps for designing and evaluating evidence- and theory-based behavior change interventions, most importantly by informing intervention development through a baseline assessment (see step 1). Figure 4 outlines the 5 steps suggested by the RANAS approach and how these steps were applied to design the SMS text messages in this study. All steps have been successfully executed (see the ticked boxes in Figure 4) except for the evaluation phase, which will be reported in forthcoming papers. Thus, we promoted farmers' PPE use as one behavior to substantially reduce pesticide exposure [23].

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Figure 4. Development and evaluation guide for the SMS text messaging intervention based on the steps to systematic behavior change from the Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS) approach [25] for this study. BCT: behavior change technique; PPE: personal protective equipment.

Step 1 of RANAS-Based Intervention Development: Identifying Psychosocial Determinants of PPE Use at Baseline

The core concept of the RANAS approach is that behavior change is driven by various psychosocial determinants that need to be in favor of new behavior [26,29]. On the basis of a synthesis of behavior change theories (eg, the health belief model [30] and the theory of planned behavior [31]), the RANAS approach describes 17 psychosocial determinants that are of potential relevance to change behavior. These are grouped into 5 categories of determinants (risks, attitudes, norms, abilities, and self-regulation). Table 1 outlines sample items for all determinants proposed by the RANAS approach, which can help understand their definition.

1. Risks comprise health knowledge, perceived vulnerability (estimates regarding the personal likelihood of catching a disease related to pesticides), and severity (estimates regarding the seriousness of a pesticide-related disease and its consequences).
2. Attitudes include feelings (emotions arising when thinking of or practicing PPE use or thinking about its consequences, eg, being proud of using PPE) as well as beliefs about cost benefits, such as monetary and nonmonetary (eg, farmers' perception of the fit of PPE and expenditure of time related to PPE use) costs and benefits of a behavior. These beliefs may also include response efficacy, which is the belief of successfully averting threats by using PPE.
3. Norms include perception of descriptive norm (others' behavior, ie, observation and awareness of PPE use practiced by others) and injunctive norm (perception of to what extent PPE use is typically approved or disapproved of by significant others and institutional norms), as well as personal importance (farmers' belief of what the farmer should [not] do).
4. Abilities include how-to knowledge (knowledge of how to obtain access to PPE) and confidence (perceived ability to execute and continue PPE use and recover from setbacks of not using PPE).
5. Self-regulation includes action planning (attempts to plan for PPE use, eg, when, where, and how to buy or wear PPE), action control (attempts to self-monitor PPE use and correcting it toward a behavioral goal), barrier planning (attempts to plan to overcome barriers that would impede PPE use), commitment (the obligation that a farmer feels), and effort to practice PPE use.

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Table 1. Baseline results to identify relevant psychosocial determinants of personal protective equipment (PPE) use based on the Risks, Attitudes, Norms, Abilities, and Self-regulation approach—(1) intention to buy PPE, (2) intention to use PPE, (3) amount of PPE items owned, and (4) frequency of PPE use.

Predictor	Sample item	Amount of PPE items owned, β (SE)	Frequency of PPE use, β (SE)	Intention to buy PPE, β (SE)	Intention to use PPE, β (SE)
Intercept	N/A[a]	.47 (0.09)[b]	.27 (.08)[b]	.06 (.11)[b]	.34 (.07)[b]
Intention to buy PPE	How strong is your intention to buy all the recommended PPE items for your personal use?	.05 (.04)	.04 (.03)	N/A	N/A
Intention to use PPE	How strong is your intention to always wear all the recommended PPE items when handling pesticides in the future?	–.01 (.05)	–.04 (.05)	—	—
Vulnerability	How likely do you think it is that you will experience acute symptoms from using pesticides if you do not wear all the recommended PPE items?	–.00 (.05)	.01 (.04)	.15 (.06)[c]	.01 (.04)
Severity	Imagine you are experiencing acute symptoms of pesticide use, how severe do you rate the consequences for your own health?	.02 (.05)	–.03 (.05)	–.17 (.07)[c]	–.06 (.05)
Response efficacy	To what extent do you think that wearing all the recommended PPE items when handling pesticides can protect you from getting sick?	–.04 (.05)	.01 (.04)	.11 (.06)	.20 (.04)[b]
Attitude: costs	How expensive do you consider it to buy all the recommended PPE items?	–.09 (.04)[c]	–.08 (.04)[c]	–.01 (.05)	.02 (.03)
Attitude: fitting clothes	How fitting is the recommended PPE for you (eg, size and cut)?	.05 (.04)	.03 (.04)	.04 (.05)	–.01 (.04)
Attitude: time consuming	How time consuming do you think it is to put on all the recommended PPE items when handling pesticides?	.02 (.03)	.01 (.03)	.12 (.04)[d]	–.00 (.03)
Feeling: uncomfortable	To what extent do you feel that it is uncomfortable to always wear all the recommended PPE items when handling pesticides? (recoded)	.04 (.03)	.04 (.03)	.06 (.04)	–.01 (.03)
Feeling: proud	How proud would you feel if you wore all the recommended PPE items when handling pesticides?	.03 (.05)	.04 (.04)	.17 (.06)[d]	–.01 (.04)
Feeling: weak	To what extent would others think you are weak when wearing all the recommended PPE items? (recoded)	–.04 (.02)	–.03 (.02)	–.02 (.03)	.02 (.02)
Overall rate of benefit	Now, considering the potential disadvantages of wearing all the recommended PPE items against its advantages, how advantageous do you evaluate the use of PPE as recommended?	–.03 (.06)	.04 (.06)	.00 (.08)	.08 (.05)
Descriptive norm (others' behavior)	How many farmers in neighboring farms are using all the recommended PPE items when handling pesticides?	.40 (.06)[b]	.36 (.05)[b]	–0.12 (.07)	.04 (.05)
Injunctive norm (others' approval)	To what extent do you think that your wife (or partner) wants you to wear all the recommended PPE items when handling pesticides?	–.01 (.04)	.00 (.04)	.13 (.05)[c]	.01 (.04)
Personal norm	How important is it for you to wear all the recommended PPE items when handling pesticides?	–.01 (.07)	.02 (.07)	.15 (.09)	.07 (.06)

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Predictor	Sample item	Amount of PPE items owned, β (SE)	Frequency of PPE use, β (SE)	Intention to buy PPE, β (SE)	Intention to use PPE, β (SE)
Action knowledge	Where would you go to buy all this equipment?	.05 (.02)[d]	.04 (.02)[c]	.01 (.02)	–.00 (.02)
Confidence	How confident are you that you can remember to wear all the recommended PPE items when handling pesticides?	.00 (.04)	–.01 (.04)	.08 (.06)	.04 (.04)
Action plan to buy PPE	Do you have a plan for how to buy all the PPE items to cover all body parts?	.06 (.05)	.03 (.04)	.23 (.06)[b]	.01 (.04)
Action plan to wear PPE	Imagine you have all the PPE items, do you have a plan to make sure you always wear them?	.05 (.04)	.10 (.04)[c]	.09 (.05)	.04 (.04)
Barrier planning	Do you have a plan for how to overcome these difficulties (that hinder you from wearing PPE)?	–.31 (.06)[b]	–.28 (.05)[b]	–.06 (.07)	–.01 (.05)
Commitment	How strongly do you feel committed to wearing the PPE items you have when handling pesticides?	.02 (.05)	.08 (.04)	–.04 (.06)	.06 (.04)
Effort	To what extent do you make a conscious effort to always wear all the recommended PPE items?	–.00 (.03)	.01 (.03)	.09 (.04)[c]	.18 (.03)[b]

[a]N/A: not applicable.

[b]$P<.001$.

[c]$P<.05$.

[d]$P<.01$.

Step 2 of RANAS-Based Intervention Development: Identifying Behavioral Determinants of PPE-Related Intentions and Behaviors at Baseline

Different contexts, behaviors, and persons may presuppose the expression of different psychosocial behavioral determinants, which need to be identified in a baseline assessment (step 2). To identify the determinants that are relevant when promoting PPE use among Ugandan smallholder farmers, we assessed all psychosocial determinants described by the RANAS approach at baseline (see the Outcome Measures section; ie, psychosocial determinants related to pursuing PPE use and using PPE). Multiple regression analyses were then computed to identify which determinants were related to higher behavior and intention to pursue PPE use and use PPE. In total, 4 regression models were calculated using the following dependent variables: intention to buy PPE, intention to use PPE, number of PPE items owned, and frequency of PPE use.

The baseline analyses of all 3 study groups before the interventions revealed that farmers owned PPE to cover an average of 4 (out of 8; SD 1.6) body parts. The accumulated frequency of using PPE to cover all body parts was 4.1 (SD 2.8), with a possible range of 0 (never covering any body part) to 40 (always covering all body parts). This mean corresponds to 10% (SD 7%) of full body, consistent use (always covering all body parts with PPE=100%). The regression analyses (Table 1) indicated the following:

1. Farmers' intention to buy PPE was higher when they considered themselves more vulnerable to health risks, perceived the health risks of pesticides to be less severe, perceived wearing PPE as more time consuming, felt proud of using PPE, perceived other people to approve of PPE use more, and had an action plan for where to buy PPE, as well as when they were more committed to using PPE.
2. Farmers' intention to buy PPE was higher when they perceived higher response efficacy and were more committed to using PPE.
3. Farmers owned more PPE items when they perceived the costs to be lower, perceived other farmers to use PPE, had an action plan for where to buy PPE, and had a coping plan in the sense of overcoming arising barriers to using PEE and pursuing more PPE.
4. Farmers used PPE more frequently when they perceived the costs to be lower, perceived other farmers to use PPE, had an action plan for where to buy PPE, and had a coping plan in the sense of overcoming arising barriers to using PPE pursued more PPE.

Step 3 of RANAS-Based Intervention Development: Selecting Behavior Change Techniques and Designing Behavior Change Strategies

After identifying relevant psychosocial determinants of the healthy behavior (in this case, PPE use) at baseline, the RANAS approach suggests selecting behavior change techniques to promote the identified psychosocial determinants. In this way, farmers who are not yet adopting the behavior may be enabled to do so. Behavior change techniques are components of an intervention designed to enable behavior change by targeting psychosocial determinants that facilitate behavior change [32,33]. The RANAS catalog proposes which behavior change techniques to select to target each RANAS-based psychosocial

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determinant. The behavior change techniques that were used, as well as detailed wording of the developed SMS text messages, can be found in Multimedia Appendix 3.

Procedures of Educational Intervention

A 2-day workshop was held in the DFAs' training facilities and delivered the curriculum based on the 5 modules (see Multimedia Appendix 4 for a summary of activities per module as well as coded behavior change techniques). The training was facilitated by the study coordinator, the author of the educational curriculum, who has >10 years of field experience facilitating similar trainings under the PHE project. In total, 2 local extension workers supported the coordinator. Delivery methods for the educational intervention included short videos, practical demonstrations, visual aids (pesticide labels, PPE, and spraying equipment), farmer experience sharing, breakout group exercises, and take-home infographic posters.

Step 4 of RANAS-Based Intervention Development: Procedures of RANAS-Based Text Messages

After the educational intervention was implemented, 20 SMS text messages were sent in increasing intervals from mid-February 2021 to September 2021 to the farmers assigned to 1 of the 2 arms that received the educational intervention. Figure 5 illustrates the procedure, targeted psychosocial determinants of behavior, and behavior change techniques. The first phase was implemented from February 2021 to March 2021 and aimed at motivating farmers to buy PPE (A1: action plan to buy PPE; A2: others' behavior; call 1: action plan+monitoring of PPE purchase; B1: others' behavior; B2: response efficacy, as indicated in the figure). The second phase was carried out from April 2021 to September 2021 with an emphasis on the use of PPE while handling pesticides during the spraying season (calls 2 and 3: monitoring of PPE use; B3: others' behavior; B4: response efficacy; C1: others' behavior; C2: overcoming barriers). The SMS text messages were automatically sent to the farmers' phones according to the following timeline. In the first intensive week, we sent daily SMS text messages to refresh the RANAS framework and 2 KAP-related details that had been identified as relevant in the baseline assessments. These targeted beliefs about costs and benefits, descriptive and injunctive norm, attitudes toward pesticide toxicity (KAP), feelings (proud, not weak), knowledge of the best weather in which to use PPE (KAP), action knowledge, and action planning. Gradually decreasing the frequency of reminders, we then sent weekly; biweekly; and, finally, monthly SMS text messages. These alternatively targeted descriptive norm (others' behavior), response efficacy, and barrier planning regarding PPE use. As one of the most relevant determinants was descriptive norm we wished to send real information about other farmers' behavior to the participants, particularly other farmers' extent of owning and using PPE. For this purpose, the participants were called 3 times during the SMS text messaging period to assess to what extent they owned and used PPE to later on share this information in SMS text messages with other farmers.

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Figure 5. Procedures for the Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS)–based SMS text messaging intervention for smallholder farmers in Uganda. KAP: knowledge, attitude, and practice; PPE: personal protective equipment.

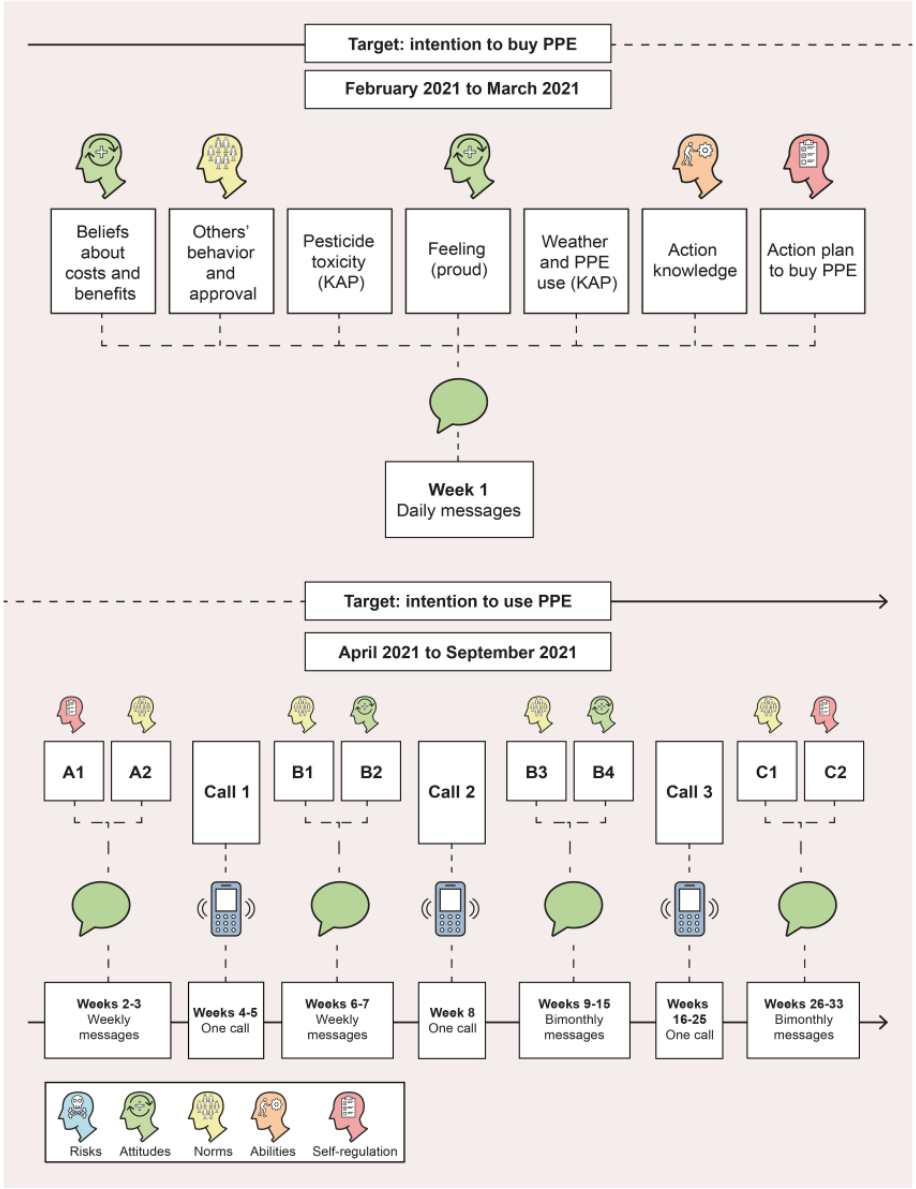

Outcome Measures

Overview

The coprimary outcomes of the study are (1) pesticide KAP scores indicating performance along the educational curriculum and (2) PPE use (to cover all body parts). Secondary outcomes are the psychosocial determinants based on the RANAS framework regarding PPE use, frequency of using gloves when handling pesticides, algorithm-based pesticide EISs, and frequency of health signs and symptoms associated with pesticide poisoning. All measures were self-reported. The full questionnaire, programmed to be used in Open Data Kit (ODK; Get ODK Inc), can be found in Multimedia Appendix 5. Items using Likert scales had 5 answer options and were augmented with a visual 5-dot scale to increase participants' understanding, as has been shown to be helpful in other studies to support responding populations with low literacy [26]. The outcomes are summarized in Textbox 1.

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Textbox 1. Summary of the objectives and outcomes of the study.

Objective 1: knowledge, attitude, and practice on pesticide handling

- Knowledge mean scores
- Attitude mean scores
- Practice mean scores

Objective 2: pesticide exposure

- Personal protective equipment (PPE) use exposure scores
- Change scores
- Changing cloths (CHANGE) exposure scores
- Exposure intensity scores (EIS)
- Yearly pesticide application days
- Yearly pesticide exposure (EIS^{Year})

Objective 3: health signs and symptoms associated with pesticide poisoning

- Sum of health signs and symptoms
- Category of symptoms (low and high based on the baseline median)

Objective 4: effect on PPE use

- Mean frequency of using 8 PPE items to cover the whole body [23,34]
- Mean frequency of using gloves [23,34]

Objective 4: determinants of behavior change regarding PPE use

- Mean score of the following [29,35]:
  - Intention to buy PPE
  - Intention to use PPE
  - Vulnerability
  - Severity
  - Response efficacy
  - Attitude: costs
  - Attitude: fitting clothes
  - Attitude: time consuming
  - Feeling: uncomfortable
  - Feeling: proud
  - Feeling: weak
  - Overall rate of benefit
  - Descriptive norm (others' behavior)
  - Injunctive norm (others' approval)
  - Personal norm
  - Action knowledge
  - Confidence
  - Action plan to buy PPE
  - Action plan to wear PPE
  - Barrier planning
  - Effort
  - Commitment

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KAP Assessment

Overview

KAP scores were assessed based on 16 items grouped around a similar training module separately for KAP (the full list of questions can be found in Multimedia Appendix 6). The KAP items were developed based on previous KAP assessments in the Pesticide Use in Tropical Settings survey [21] and another study [36] and adapted to assess KAP for 4 out of the 5 modules of the educational intervention curriculum on pesticide handling. The fifth module on IPM was not considered for the KAP scores as it was mainly related to pesticide product use and is captured in the exposure frequency under objective 2.

Example KAP Scoring

Knowledge questions were binary (eg, "The name of the plant protection product active ingredients can be found on the label of the product" [*true*, *false*, or *not sure*]). For every correct answer, 1 point was added to the knowledge score, resulting in final scores ranging between 0 and 16. The higher the score, the more knowledge the farmer had on safe pesticide handling. The "Not sure" responses were treated as "False."

Attitude was measured using a 5-point Likert scale (eg, "It is important for me to know the active ingredients in a given plant protection product" [*agree not at all*=1; *agree a little*=2; *somewhat agree*=3; *rather agree*=4; *strongly agree*=5; *do not have an opinion*=coded as missing]).

Practice was also measured using a 5-point Likert scale (eg, "I look for the name of the active ingredients when buying or using a given pesticide product" [*never*, 0%=1; *rarely*, 25%=2; *sometimes*, 50%=3; *often*, 75%=4; *always*, 100%=5; *do not have an opinion*=coded as missing]).

Pesticide Exposure

The pesticide EIS (ranging from 0 to 13) during an average application day was based on a semiquantitative exposure algorithm specifically modified [23], applied, and validated for smallholder farmers who use handheld knapsack sprayers in LMICs as described in recent studies [37-39]. Concisely, EIS estimates are derived from a comprehensive evaluation involving 5 key factors. These factors are (1) mixing pesticides (MIX; score of 5); (2) the application of pesticides using a knapsack (APPLICATION; score of 8); (3) the type of PPE used, protecting different body parts, and accounting for differences in application frequency (PPE; score of 0.14-1); (4) the time taken to change clothing after pesticide handling (CHANGE; score of 0.7-1); and (5) the postapplication bathing routine (SHOWER; score of 0.7-1), as illustrated in equation 1. Mixing and application of pesticides are expected to increase exposure, whereas use of PPE, changing clothes, and showering after an application reduce exposure.

$$EIS = (MIX + APPLICATION) \times PPE \times CHANGE \times SHOWER \quad \textbf{(1)}$$

Yearly pesticide exposure was assessed using [23] (1) the yearly pesticide application days over the previous 12 months and (2) the EIS during an average application day, as indicated in equation 2. The pesticide application days were captured using a spreadsheet that included the pesticide products used by the farmer in the previous 12 months and the number of days each product was applied [39.

$$EIS^{Year} = EIS \times \text{Yearly pesticide application days} \quad \textbf{(2)}$$

Health Signs and Symptoms Associated With Acute Pesticide Poisoning

Farmers' health was assessed using a checklist of 31 symptoms associated with acute poisoning (eg, dizziness, anxiousness, nausea, vomiting, sleeping difficulties, weakness of the limbs, and changes in taste and smell [40]). Participants were asked whether they presented the symptoms (yes or no) and, if they did, the frequency with which they experienced them (once a year, once a month, once a week, or more than once a week) and whether they experienced them after spraying pesticides. The sum of the symptoms experienced by the farmers after pesticide application will be calculated and further dichotomized based on the baseline median distribution of the signs and symptoms.

Frequency of PPE Use and its Psychosocial Determinants

Using PPE to cover all body parts was assessed using behavioral frequency measures as is common in behavioral science [34]. Participants were shown pictures of 15 PPE items to cover the whole body and were asked about the frequency of using these items in the previous 12 months, with answer options ranging from *always*=1 to *never*=5. These items were reverse coded as infrequent use (1) and frequent use (5) and categorized into 8 means for the covered body parts: "eyes, mouth, hands, arms, legs, feet, trunk, and head" [23]. To create the total frequency of PPE use to cover all body parts, a sum of all categories' means was calculated (ie, frequency of PPE use = mean [frequency of using items to cover the hands] + mean [frequency of using items to cover the mouth] + ... + mean [frequency of using items to cover the feet).

Frequency of using gloves. In addition, as the hands are the most exposed body part during pesticide handling [23], we assessed the mean frequency of using PPE to cover the hands through common behavioral frequency assessment [34]. Participants were asked about the frequency of using PPE to cover their hands (using any kind of gloves).

Exposure modified by PPE use was assessed using the modifying PPE variable from the pesticide exposure scores [23]. This can account for the material of the PPE being used and the exposure risk of different body parts. For example, the hands account for 40% of pesticide exposure, whereas the eyes-only account for 10% of exposure.

Psychosocial determinants of PPE use (RANAS factors) were assessed using the measurements proposed by the RANAS model [29,35]. All items were pretested in an unpublished pilot study in Uganda. The items assessed the 17 psychosocial determinants proposed by the RANAS approach asking participants how much they agreed with certain RANAS-based questions (see Table 1 in the *Description of the Interventions* section for sample items) using a 5-point Likert scale (*not at all*=1; *very much*=5). For each scale, multiple items were averaged. Beliefs about cost benefits in the attitude category

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were assessed using single rather than averaged items given their low internal consistency at baseline.

Sociodemographic characteristics included age, educational level, marital status, number of children, smoking status, drug and alcohol use, main occupation, and monthly income. Farming characteristics included farm size, main farming objective, number of farm workers, major crops grown, main pest management practices, debut age for working on farms, age when they started mixing and applying pesticides, who mixes the pesticides, disposal of pesticide containers, who washes the pesticide application equipment, field re-entry after pesticide application, sources of farming and pesticide use information, training in pesticide use, knowledge of routes of exposure, and negative consequences of pesticide use.

Data Collection and Management

The study data were collected using an electronic questionnaire developed using ODK. The research assistants were trained before the baseline interviews on the objectives of the study, ethical aspects, and the use of the ODK. They collected pretest data in a pilot study from 20 smallholder farmers from another district that was not part of our study. The research assistants visited the farmers either in their homes or on the fields and administered the computer-assisted interviews in either 3 local dialects (Luganda, Runyankore, or Ateso) or English. At the end of each day, the data were uploaded to a secure server. A data quality management team inspected the data regularly for any inconsistencies or errors, and where found, the responsible research assistants were contacted, and appropriate resolutions were reached. The data were securely stored in a password-protected database with restricted access.

Statistical Analyses

Statistical analyses will be conducted using Stata (version 15; StataCorp) and R (version 4.3.1; The R Foundation). The outcomes will be based on intention-to-treat analyses, and missing data values will be computed using the multivariate imputation chained equations R package. The effect of the interventions on the 3 arms will be analyzed using the intervention arms as dummy-coded predictors and the follow-up measures as outcomes in multivariate mixed models with the cluster (subcounty) as the random effect. Sensitivity analyses are planned to control for differences in sex, age, educational level, previous training, and annual pesticide use days. For objective 2, subanalyses of factor scores (type of PPE, time taken to change clothing after pesticide handling, postapplication bathing routine, mixing pesticides, and application of pesticides using a knapsack) used to compute the exposure algorithms will be made to test their variation resulting from the interventions. Intervention effects on KAP, PPE use (frequency of using PPE for all body parts, frequency of using gloves, and exposure modified by pesticide use), algorithm-based pesticide EIS, and health signs and symptoms associated with acute pesticide poisoning will be analyzed in a model testing the control group (0) against the educational intervention (1) and against the educational intervention+RANAS-based SMS text messages (1). For the intervention effects on PPE and glove use (objective 4), all arms will be compared by testing the educational intervention against the educational intervention+RANAS-based SMS text messages (0) in an additional model.

To understand the psychosocial mechanisms of the interventions (objective 5), we will perform 2 mediation models with multiple psychosocial behavioral determinants as mediators, one testing the educational intervention group (1) against the control group (0) and one testing the educational intervention+RANAS-based text message group (1) against the educational intervention (0). The mediation analyses will use the change scores (follow-up value – baseline value) for all RANAS-based psychosocial determinants as mediators and PPE use as the outcome, operationalized as the frequency of using PPE to cover all body parts and using gloves.

Results

The study received approval from Makerere University's Higher Degrees, Research, and Ethics Committee in Uganda (reference 846) and was additionally registered in the ISRCTN clinical trial registry (ISRCTN 18237656). It was conducted between October 2020 and October 2021, and 539 farmers in 12 clusters were enrolled. Data were collected from October 5 to 30, 2020, for the baseline assessment, and for the follow-up, data collection occurred from October 1 to 26, 2021.

A total of 91.7% (494/539) of the farmers consented to participate at follow-up (Figure 6). During implementation, 91.1% (164/180) of the farmers attended both days of the educational intervention, whereas 7.8% (14/180) of the farmers were not available to attend both days. Although 91.1% (163/179) of the farmers received the educational intervention and RANAS-based SMS text messages, 8.4% (15/179) of the farmers could not receive the messages as their phones were turned off during the intervention. Preliminary results show that 84.6% (456/539) of respondents were male and 31.9% (172/539) of the farmers had received training in pesticide use before the baseline survey. The average age was 41.1 (SD 12.0) years, and 46.8% (252/539) of the farmers had attained at least secondary education. The preliminary findings are expected to be published in autumn 2024.

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Figure 6. African Pesticide Intervention Project (APSENT) consent flowchart showing participant recruitment and inclusion and exclusion from the educational and SMS text messaging interventions. ITT: intention to treat; RANAS: Risks, Attitudes, Norms, Abilities, and Self-regulation.

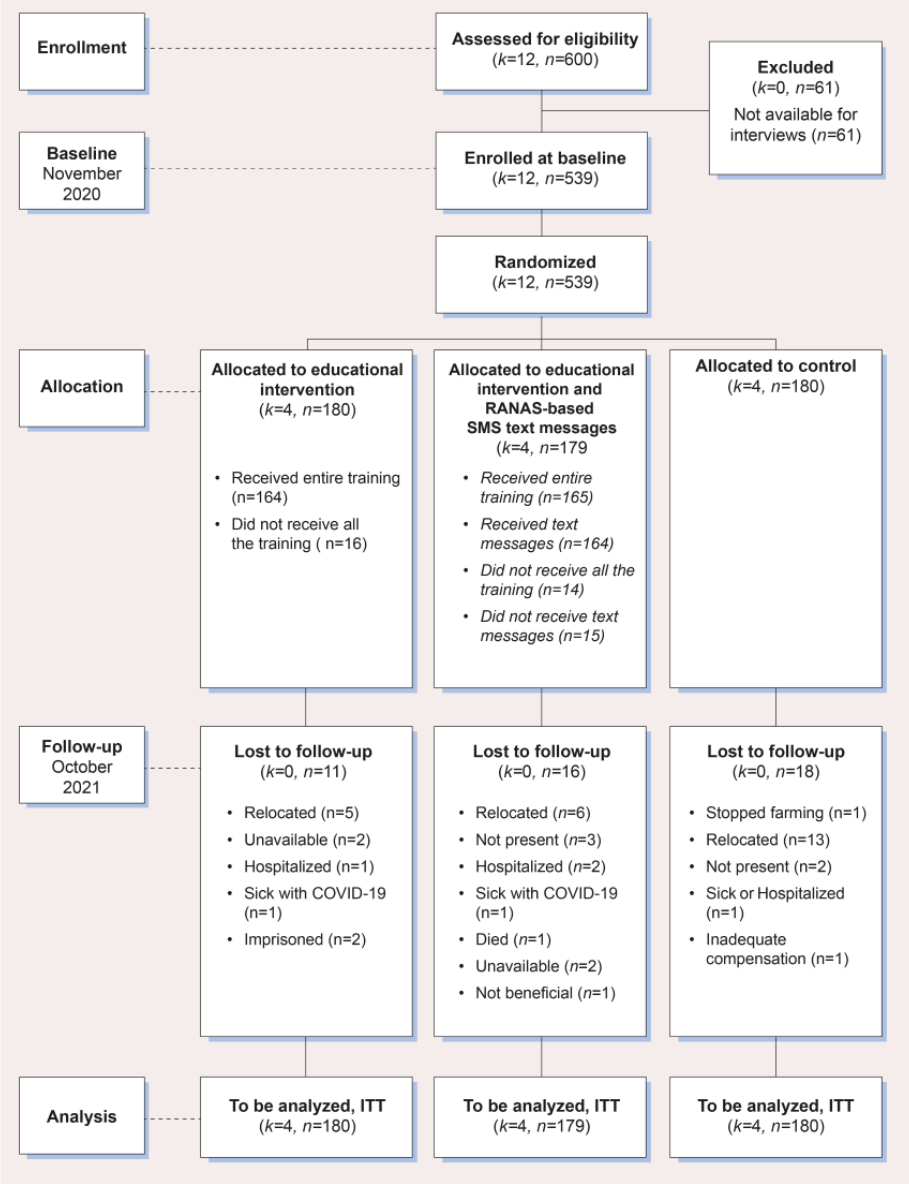

Discussion

Expected Findings

Interventions are part of the strategies for reducing pesticide exposure and the associated health consequences [17] in addition to other strategies such as using less toxic alternatives and improving the comprehensibility of hazard communication via pesticide labels [41]. This is useful especially in LMICs, where pesticide regulation enforcement is weak [42] and public extension service systems are not well supported [19]. Educational interventions aim at enlightening agricultural workers on the occupational health and environmental risks associated with pesticides and equipping them with skills with the intent to influence them to adopt safe pesticide-handling practices [15,41].

This study has several strengths, but there are also some limitations and avenues for future research. The UNACOH NGO developed their educational training curriculum over the years and is widely sensitized to the Ugandan public. This study is the first to objectively evaluate the effectiveness of these efforts through a cluster-randomized trial, assessing their ability to improve farmers' adherence to safety precautions and the ultimate reduction in the undesirable health effects of pesticides. The holistic perspective evaluating effects on knowledge, attitudes and other psychosocial determinants, behavior, exposure, and health can be considered a strength. The results can provide evidence-based recommendations to heighten the possibilities of scalability of the UNACOH training.

Moreover, we will assess the effectiveness of an additional, more intensive approach: RANAS-based SMS text messages that target 1 behavior (PPE use) specifically. This will, on the one hand, inform about the effectiveness of such reminders and allow for first recommendations on whether targeting psychosocial determinants of behavior change can increase PPE use more than targeting farmers' education. In addition, this study will be the first to examine the psychosocial mechanisms of interventions for safe pesticide handling. Analyzing

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psychosocial determinants that lead to behavior change as part of an intervention can provide essential insights into how an intervention works and can be improved. Overall, the findings of this study will support us in identifying the most efficient intervention approach.

As a further strength, the training intervention curriculum used was developed by a local NGO based on context-specific experience gained from working with local pesticide stakeholders in the country. In addition, the RANAS-based SMS text messaging intervention was developed building on previous local use experience by the same NGO, further refined by occupational health, pesticide safety, and behavior change experts and practitioners. Therefore, the intervention package used is culturally adapted to promote responsible pesticide handling among smallholder farmers in Uganda. These materials can now be used and adapted for further evidence-based educational and behavior change campaigns in similar settings (ie, other LMICs).

It is important to note that PPE use is the least effective strategy for reducing exposure, as illustrated by the hierarchy of controls, with elimination being the most effective [43]. However, PPE use remains one important focus of trainings. Given that, for the correct PPE to be used on a regular basis when applying pesticides, farmers must use the right PPE every time, this study provides valuable insights on the amount and type of training required.

Limitations

As a limitation in sampling, it is noted that this trial only included smallholder farmers who were directly responsible for pesticide application. Significant exposure to pesticides is also expected from re-entry activities (ie, hoeing, weeding, planting, and harvesting in fields that have been treated with pesticides) and washing contaminated clothing and equipment [44]. This work is predominantly undertaken by women and girls, who face exacerbated risks because of low education and access to training on safe pesticide handling or other resources [45]. Future intervention studies urgently need to target safe pesticide practices such as PPE use during re-entry work or when handling contaminated items and explicitly target gender-equal access to training.

Our study design does not allow us to estimate whether the potentially increased effects in the SMS text messaging intervention are due to being reminded via SMS text message to handle pesticides safely and having a longer intervention than the education-only arm or to the promotion of behavioral determinants. We may partly target this limitation by investigating whether a greater number of psychosocial determinants targeted by the RANAS approach achieve intervention effects, but ideally, future intervention studies should compare educational SMS text messages with RANAS-based SMS text messages.

Finally, all our measures were self-reported, which can lead to bias regarding subjectivity and socially desirable answers. While assessments of knowledge, attitude, and other psychosocial determinants (ie, RANAS factors) are typically self-reported, there are potential ways for future studies to more objectively assess behavior and pesticide exposure. For example, they may assess (correct) PPE use through field observations or demonstrations by farmers and pesticide exposure through biomarkers in hair or urine samples. However, collecting and analyzing such data is often costly.

Conclusions

This research will contribute to a better understanding of the effectiveness and mechanisms of educational and theory-based behavior change SMS text messaging interventions for reducing pesticide exposure among smallholder farmers. The insights from this study could be used to strategically improve and implement context-specific interventions to reduce pesticide-related risks to human and environmental health in different LMICs.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

PS, VMJT, CB, AA, JI, SF, and MR contributed to the conceptualization of the study, methodology, investigation, data curation, writing—original draft, visualization, and project administration. AA, SF, MR, and JI contributed to supervision, while SF, MR, and JI contributed to funding acquisition. JI, MAD, and HAR contributed to writing—review, with JI also providing editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Baseline data collection in Uganda and intervention description, African Pesticide Intervention Project.
[MP4 File (MP4 Video), 81356 KB - resprot_v13i1e55238_app1.mp4]

Multimedia Appendix 2
Educational intervention curriculum for farmers covering 5 broad topics on safe pesticide handling.
[DOCX File , 20 KB - resprot_v13i1e55238_app2.docx]

Multimedia Appendix 3
Psychosocial determinants and behavior change techniques based on Risks, Attitudes, Norms, Abilities, and Self-regulation targeted in text messages sent to farmers.
[DOC File , 31 KB - resprot_v13i1e55238_app3.doc]

Multimedia Appendix 4
Risks, Attitudes, Norms, Abilities, and Self-regulation behavior change techniques and expected psychosocial determinants derived from the educational curriculum on safe pesticide handling.
[DOC File , 21 KB - resprot_v13i1e55238_app4.doc]

Multimedia Appendix 5
Questionnaire.
[PDF File (Adobe PDF File), 6871 KB - resprot_v13i1e55238_app5.pdf]

Multimedia Appendix 6
Knowledge, attitude and practice questions along the four modules of the education curriculum on safe pesticide handling.
[DOCX File , 21 KB - resprot_v13i1e55238_app6.docx]

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Abbreviations

DFA: District Farmers' Association
EIS: exposure intensity score
IPM: integrated pest management
KAP: knowledge, attitude, and practice
LMIC: low- and middle-income country
NGO: nongovernmental organization
ODK: Open Data Kit
PHE: Pesticide Use Health and Environment
PPE: personal protective equipment
RANAS: Risks, Attitudes, Norms, Abilities, and Self-regulation
UNACOH: Uganda National Association of Community and Occupational Health

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Protocol

An Immersive Virtual Reality Intervention for Preoperative Anxiety and Distress Among Adults Undergoing Oncological Surgery: Protocol for a 3-Phase Development and Feasibility Trial

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Abstract

Background: Preoperative state anxiety (PSA) is distress and anxiety directly associated with perioperative events. PSA is associated with negative postoperative outcomes such as longer hospital length of stay, increased pain and opioid use, and higher rates of rehospitalization. Psychological prehabilitation, such as education, exposure to hospital environments, and relaxation strategies, has been shown to mitigate PSA; however, there are limited skilled personnel to deliver such interventions in clinical practice. Immersive virtual reality (VR) has the potential for greater accessibility and enhanced integration into an immersive and interactive experience. VR is rarely used in the preoperative setting, but similar forms of stress inoculation training involving exposure to stressful events have improved psychological preparation in contexts such as military deployment.

Objective: This study seeks to develop and investigate a targeted PSA intervention in patients undergoing oncological surgery using a single preoperative VR exposure. The primary objectives are to (1) develop a novel VR program for patients undergoing oncological surgery with general anesthesia; (2) assess the feasibility, including acceptability, of a single exposure to this intervention; (3) assess the feasibility, including acceptability, of outcome measures of PSA; and (4) use these results to refine the VR content and outcome measures for a larger trial. A secondary objective is to preliminarily assess the clinical utility of the intervention for PSA.

Methods: This study comprises 3 phases. Phase 1 (completed) involved the development of a VR prototype targeting PSA, using multidisciplinary iterative input. Phase 2 (data collection completed) involves examining the feasibility aspects of the VR intervention. This randomized feasibility trial involves assessing the novel VR preoperative intervention compared to a VR control (ie, nature trek) condition and a treatment-as-usual group among patients undergoing breast cancer surgery. Phase 3 will involve refining the prototype based on feasibility findings and input from people with lived experience for a future clinical trial, using focus groups with participants from phase 2.

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Results: This study was funded in March 2019. Phase 1 was completed in April 2020. Phase 2 data collection was completed in January 2024 and data analysis is ongoing. Focus groups were completed in February 2024. Both the feasibility study and focus groups will contribute to further refinement of the initial VR prototype (phase 3), with the final simulation to be completed by mid-2024.

Conclusions: The findings from this work will contribute to the limited body of research examining feasible and broadly accessible interventions for PSA. Knowledge gained from this research will contribute to the final development of a novel VR intervention to be tested in a large population of patients with cancer before surgery in a randomized clinical trial.

Trial Registration: ClinicalTrials.gov NCT04544618; https://www.clinicaltrials.gov/study/NCT04544618

International Registered Report Identifier (IRRID): DERR1-10.2196/55692

(JMIR Res Protoc 2024;13:e55692) doi:10.2196/55692

KEYWORDS

virtual reality; preoperative anxiety and distress; perioperative mental health; breast cancer; oncological surgery

Introduction

Background

Overview

There is increasing recognition of the detrimental effects of anxiety and distress in medical populations. The National Comprehensive Cancer Network (NCCN) has advocated for psychological distress to be the sixth vital sign [1]. Both the aging demographic and overall population are increasing in Canada, which confers an elevation in the overall cases of cancer and those requiring surgery [2]. The patients' lived experience of anxiety and distress before surgery is a near-universal and often overlooked aspect of the perioperative journey. In a study of >15,000 patients undergoing nonobstetric surgery in the United Kingdom, anxiety was rated by patients as the *worst* aspect of the perioperative experience [3]. Preoperative anxiety and distress have been shown to significantly affect negative perioperative outcomes (eg, increased hospital length of stay, pain, opioid use, and rehospitalization) [4]. However, few feasible preoperative interventions exist to mitigate preoperative anxiety and distress (hereinafter termed preoperative state anxiety [PSA]) [5].

PSA Risk and Defining Features

Rates of psychiatric disorders (eg, anxiety disorders and depression) are elevated across surgical samples, with particularly high rates among patients undergoing breast cancer surgery [6]. These psychiatric disorders are associated with a range of poor postoperative health outcomes [7], including increased mortality [8,9]. The presence of a psychiatric disorder at the preoperative stage is also associated with significantly greater health care costs incurred among patients undergoing breast cancer surgery [6]. A history of psychiatric disorders also increases the risk of acute PSA in elective surgery [10], although PSA can also occur outside the context of threshold psychiatric disorders. PSA is defined by anticipatory distress or anxiety related specifically to perioperative factors such as pain, loss of independence, the surgery itself, anesthesia, and death [11,12], but it can also relate to unfamiliar environments, such as the operating room (OR) and encounters with health professionals (G Klar, unpublished data, February 2024) [13]. PSA tends to be transient in nature based on a current stressor (eg, upcoming surgery); however, it can be clinically significant and debilitating in approximately 40% of patients undergoing surgery [14]. PSA is often impacted by unfamiliarity and uncertainty regarding the surgical process [15]. Research by our group and others (G Klar, unpublished data, February 2024) [12] demonstrates that PSA relates to several OR environmental stimuli, including exposure to, and placement of, the anesthetic face mask; intravenous cannula insertion; limb restraint application; and inadequate information about the intraoperative process across surgical groups. Patients undergoing oncological surgery experience elevated rates of preoperative distress, ranging from 23% to 77% in recent research [16-18]. PSA in this population has been found to relate to uncertainties of what the surgeon might find and operative procedures or regarding the effects of surgery itself [10]. The experiences with PSA of patients undergoing oncological surgery have been associated with increased postoperative pain, nausea, discomfort, fatigue, and analgesic consumption (G Klar, unpublished data, February 2024) [10-13], highlighting the significance of PSA and raising the question of whether reducing PSA can impact postoperative outcomes.

Interventions Targeting PSA

It is well understood that psychological states and disorders are highly responsive to a range of empirically supported targeted psychological and behavioral treatments. In light of this, there is a growing body of literature examining preoperative psychological interventions to reduce negative postoperative sequelae, with some promising but mixed results. A Cochrane review by Powell et al [19] examined the evidence on psychological preparation before surgery using general anesthesia on a range of postoperative outcomes. The authors concluded that there were significant positive effects for a range of interventions, but overall, the quality of evidence was low, which in part related to the heterogeneity of the data and the methodologies used. The interventions with the most empirical support across a range of outcomes used relaxation strategies at the preoperative stage. In oncological surgeries specifically, systematic reviews have demonstrated that preoperative psychological interventions are associated with improved outcomes, particularly patient-reported outcomes such as mood and anxiety, quality of life, fatigue, and somatic symptoms [20,21]. However, many psychological interventions, such as cognitive behavioral therapy, are high-resource approaches

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requiring expert administration and are not feasible to be implemented for the large and growing number of surgical interventions. This is particularly true in publicly funded and often (already) overwhelmed health care systems. Although digital technology options have addressed some of these challenges (eg, cost and accessibility), these tend to be focused on more general cognitive behavioral therapy. Formal mobile-based cognitive behavioral therapy interventions still require greater and longer patient engagement and often mental health professional support [22]. In addition, cognitive behavioral therapy is most often used to address trait anxiety or mental disorder symptomatology by dealing with maladaptive thoughts and behaviors over time [23], rather than the more transient nature of PSA, which is a psychological state directly related to the stressor [24]. Thus, virtual reality (VR) may be optimally suited to address PSA because it requires less time commitment and may be undergone at any point in the weeks leading up to surgery, providing greater flexibility. The VR technology can reduce the need for direct health care provider support and has the potential for at-home use.

The vast majority of existing studies examining nonbehavioral interventions for PSA have focused on preoperative education with mixed results and often smaller effect sizes [25]. Educational interventions typically take the form of patient reading material (eg, informational brochures), which are often underused, lack important information, are provider directed rather than patient directed, and require a higher level of health literacy [25]. Successful educational initiatives for mitigating PSA, which also translate to decreased perioperative pain and increased functioning, often include poorly feasible, high-resource initiatives such as preoperative classes led by anesthesiologists and surgeons [26]. Researchers have also examined the impact on PSA levels by enabling patients to tour the OR before surgery [27] because the OR environment is an anxiety-inducing trigger for patients undergoing surgery [12,13,28]. Although this approach has been associated with reductions in PSA levels [27], it has limited feasibility to be administered broadly due to the infrequent availability of ORs and limited resources and personnel to implement this intervention. The feasibility of such an approach is even further reduced in the context of COVID-19 and future pandemics, where hospital accessibility is restricted and maintaining sterility in patient areas such as the OR is of the utmost importance.

With respect to the use of medications for PSA, the use of anxiolytics at the preoperative stage is a somewhat controversial practice. A survey was conducted among 3661 anesthesiologists from the American Society of Anesthesiologists to determine whether anesthesiologists ask their adult patients about preoperative anxiety and what methods they use to reduce it [29]. They found that >60% of the anesthesiologists reported asking their patients about anxiety and that 91.6% of these anesthesiologists prescribed anxiety medication (most commonly, the benzodiazepine Midazolam) [29]. In the preoperative environment, benzodiazepines may be used for relaxation, sedation, ease of administering anesthesia, or the suppression of seizure activity. Although there are reasons for the use of benzodiazepines outside of PSA, they are not without risk and not ideal in all populations. Specifically, benzodiazepines can be associated with adverse outcomes such as impaired motor and cognitive functioning, delirium, and respiratory depression [30]. Benzodiazepines are also not recommended for use in older adults aged >65 years because they are at increased risk for cognitive impairment and delirium [30]. Furthermore, the use of benzodiazepines for anxiety reduction in the acute preoperative period is not associated with any differences in patient satisfaction as assessed on the day after surgery, suggesting the lack of clinical benefit for patients [31]. Other anxiolytics, such as selective serotonin reuptake inhibitors, are not suitable for PSA and are more commonly prescribed for chronic mental disorders. Pharmacological interventions also do not target the cause of anxiety experienced by patients before surgery, such as a lack of perioperative information and fear of the OR environment, nor do they provide foundational exposure (ie, exposing patients to a feared environment to reduce avoidance and promote habituation) and relaxation paradigms proven to be effective for PSA in other contexts.

VR Interventions

VR is a computer-generated 3D environment in which a user may be immersed through visualization and interactions. VR can be used to approximate reality to achieve ecological validity for a targeted environment and can yield affective responses [32]. VR represents a potentially novel targeted modality for PSA because it enables the integration of several effective intervention techniques, such as exposure to hospital environments, education, and relaxation strategies. VR interventions have been shown to significantly reduce anxiety and other psychiatric symptoms in other contexts (eg, fear of flying, injection phobia, and fear of heights) and are used as a predeployment prehabilitative intervention to prepare military personnel for anticipated exposure to acute stress during combat (ie, stress inoculation training [33]). Evidence suggests that prehabilitative VR interventions may be associated with reductions in psychological distress, both before [34,35] and after [36] deployment. Recently, researchers evaluated whether preoperative VR simulations that expose patients to the OR can mitigate PSA [37,38]. Preliminary research in pediatric populations has found that preoperative exposure in a VR simulation to the OR environment reduces PSA and increases compliance during the induction of anesthesia [38], and it is regarded positively and accepted by patients [39]. In recent years, some targeted VR interventions have also been developed for adult populations. Systematic reviews by Yu et al [40] and Mbewe and Smith [41] identified 5 previous studies using VR to reduce perioperative anxiety in adult patients. Yu et al [40] included studies examining both perioperative and periprocedural anxiety, and the eligibility criterion was limited to VR interventions focused on OR tours specifically. The interventions were all in video format, with the VR experiences ranging from first- [42] to third-person points of view [37,43], some of which also provided 360° visuals [44,45]. Each intervention was meant to educate the participant on the surgical procedural process and expose them to the OR environment. Results varied, with some studies reporting no differences in anxiety levels between the VR intervention and control groups, [43,44] while others found anxiety to be significantly decreased

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with the VR intervention [37,42,45]. Importantly, VR interventions were also found to improve patients' procedural understanding and increase patient satisfaction and preparedness [37,45]. Mbewe and Smith [41] included 3 additional studies in their meta-analysis because they were focused on surgical cases and did not restrict VR interventions to OR tours, thus including other VR interventions (eg, nature scenes). The alternative VR interventions included a training video focused on educating patients on wide-ranging aspects of the surgical process [46], a 360° nature video with relaxing music and birdsong [47], and an audio narration of a progressive muscle relaxation technique showing a beach scene [48]. The results of the meta-analysis demonstrated that VR interventions have greater positive impacts on preoperative anxiety compared to the standard of care; however, the effect size was relatively small [41].

The impact of these VR interventions may have been limited because they lacked relevant perioperative information or exposure and only displayed re-enactments or simply exposed patients to features of the surgical process as opposed to an immersive patient-directed VR experience. Immersive patient-directed VR refers to environmental fluidity changes with head movement, which facilitates presence and immersion and deepens engagement [49]. Displaying videos offers a limited sense of presence and immersion because the user cannot directly interact with the environment, and therefore ecological validity is reduced [50]. The importance of immersion and interactivity on agency and embodied learning has been supported in prior research [51]; for example, when using VR exposure to treat anxiety disorders, first-person body experiences and other features that enhance immersion, such as movement tracking and audio and tactile exposure, have been found to be important components of effective VR interventions [52]. A sense of immersion is not only positively related to feelings of anxiety (which is a necessary component of exposure-based paradigms), but it may also enhance the effectiveness of the intervention in facilitating behavior change [52,53]. In addition, the immersive aspect of VR is biologically supported with studies demonstrating that immersing patients in a stressful VR environment can alter biomarkers of stress [54]. This initial research is promising and provides preliminary support for the utility of immersive VR to mitigate PSA, which ultimately may improve perioperative outcomes. However, one way in which this body of literature is limited is that very few, if any, studies have examined the feasibility of this type of intervention, which is a critical step given its novelty in the perioperative setting.

Study Overview and Objectives

On the basis of these gaps in the literature and the importance of developing practically implemented, low-resource interventions for PSA, we designed and are evaluating the feasibility of a novel immersive VR intervention, first targeting PSA among patients undergoing breast cancer surgery. Patients undergoing cancer surgery were identified as the first target group given their high rates of PSA [16-18] and the large volume of cases (nearly 50% of patients with cancer undergo surgery), which are scheduled as elective surgeries. The use of VR is particularly advantageous for elective procedures, given that it provides the opportunity for preoperative interventions in the weeks before surgery. The development of the intervention is an iterative and collaborative process using multidisciplinary health professional input and later using focus groups of patients with lived experience. The use of both qualitative and quantitative methods promotes our ability to hear the patient voice and to make relevant adaptations to the application as directed by our analysis based on the feasibility and focus group findings. This will be achieved in 3 phases as depicted in Figure 1, developed in line with international guidelines established by the Virtual Reality Clinical Outcomes Research Experts (VR-CORE) committee for VR trials in health care [55]. Phase 1 (completed; in line with the framework from the VR-CORE guideline's VR1 phase) involved the development of an initial VR prototype that was developed in conjunction with health care professionals working in the OR and engineers (authors MSDS, CP, and VGS) at the National Research Council of Canada [56]. This prototype comprises an immersive VR representation of the OR and patient induction process for an individual undergoing breast cancer surgery with general anesthesia. Phase 2 (underway; in line with the framework from the VR-CORE guideline's VR2 phase) uses a randomized design (VR intervention vs VR control [ie, Nature Treks VR] vs treatment as usual [TAU]) to assess feasibility on a sample of patients undergoing breast cancer surgery. The feasibility study used quantitative scales to understand the recruitment and randomization capability, acceptability, and feasibility of the study design, along with preliminary utility for reducing PSA. In phase 3 (underway; also in line with the VR-CORE guideline's framework VR1 phase because we are collecting user-testing feedback to improve the VR content), we are conducting focus groups with select participants from the feasibility trial, and the results based on the focus groups, along with the feasibility findings, will inform continued refinements of the prototype for a future randomized clinical trial (in line with the framework from the VR-CORE guideline's VR3 phase). An effective PSA-reducing intervention has the potential to mitigate poor perioperative mental and physical health outcomes in patients undergoing oncological surgery and yield significant cost savings to the overall health care system. An initial successful VR platform could be modified and applied to other surgical populations in the future.

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Figure 1. Flowchart of the 3-phase development. VR: virtual reality.

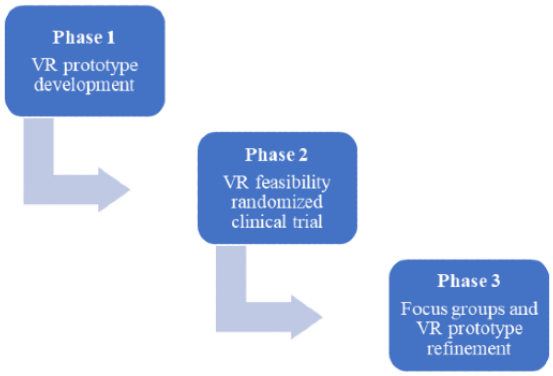

Methods

Phase 1 (Complete)

VR Development

Phase 1 involved the development of the initial VR prototype, developed in the Unity game engine (Unity Technologies) and deployed using the Oculus Rift S headset (Meta). We aimed to develop the initial VR prototype to simulate an OR and anesthetic induction at the Health Sciences Centre (HSC) in Winnipeg, Manitoba, Canada, a tertiary care university-affiliated hospital connected to a provincially mandated cancer agency. With institutional approval, several photographs and videos were taken of the OR, and 1 live induction process was audio and video recorded (refer to the *Ethical Considerations* section for consent details). Furthermore, an email was sent to all attending anesthesiologists at the HSC requesting them to provide their standard patient *induction and safety scripts*. We received 4 scripts that were compared, and consistent elements across the scripts were amalgamated into a *standard script* to be integrated into the VR simulation.

An iterative and collaborative development process was used to create the VR environment and simulation. The initial prototype was based on all elements included in an induction sequence on a real patient, which was filmed. On the basis of input and feedback from coauthors and OR professionals at the HSC in addition to consultations between coauthors and the VR development team at the National Research Council, further elements to be implemented (equipment, personnel, narrations, animations, etc) were identified and prototypes were developed. In the interest of having a prototype to test in a timely manner and to reserve the bulk of the grant funds to commit to the development of the intervention after patient feedback via the feasibility trial and focus groups, specific decisions were made to animate aspects in the OR that have been reported by patients to be the most anxiety provoking (G Klar, unpublished data, February 2024). Prototypes were trialed regularly by coauthors and feedback incorporated in the next round of refinement. Phase 1 commenced in November 2019 and was completed by April 2020 (refer to Figure 2 for screenshots of the immersive VR OR environment and Figure 3 for the administration setup). A manuscript detailing the technical aspects of the VR creation is in development.

Figure 2. Screenshots of the immersive virtual reality operating room environment.

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Figure 3. Virtual reality administration and setup.

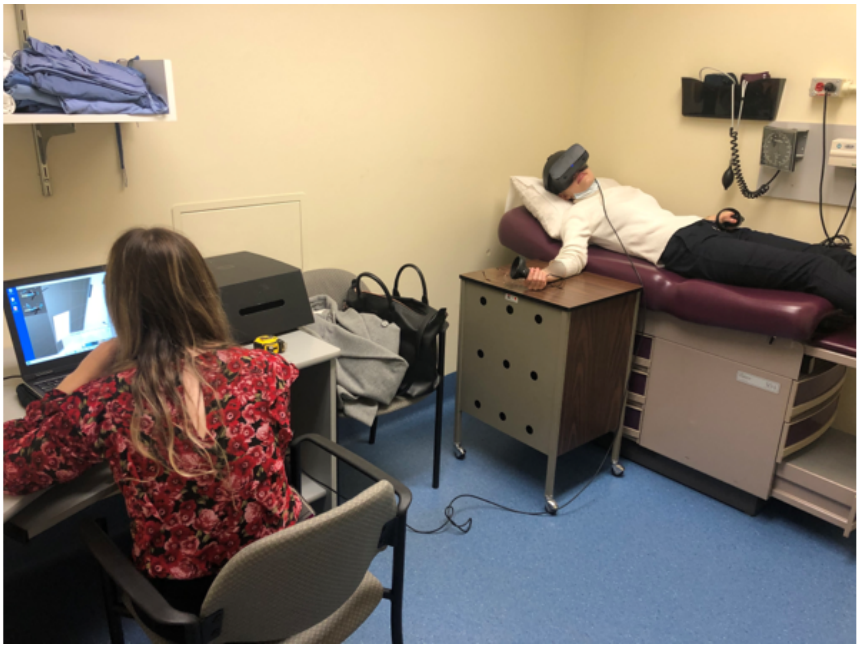

Components of the Initial VR Prototype

The user starts the simulation seated on a virtual operating table in the OR. The user is provided a minimum duration of 5 minutes to visually *explore* the environment, which includes surgical (eg, instruments, lights, medical devices, sterile items, and x-ray images) and anesthetic (eg, medications and anesthetic monitors) items. The environment also includes background noises (eg, a beeping monitor) and lighting consistent with the OR environment. Several health care personnel (ie, an anesthetist, a surgeon, and 2 nurses), including a woman and a racial and ethnic minority person, are present in the room. After at least 5 minutes of exploration, an induction narrative simulation commences. The patient is instructed to lie supine (on the virtual OR table) and is taken through a mock anesthetic induction process from a first-person perspective. For the initial prototype, the patient's avatar was developed as White and gender neutral. One of the virtual nurses and the virtual anesthetist speak to the patient and walk them through the steps while the procedures are being performed. The narrative component includes describing surgical procedures such as attaching electrocardiogram stickers, attaching a pulse oximeter, completing a safety briefing, and placing an oxygen mask over the patient's face. The additional steps of attaching a blood pressure cuff, attaching an intravenous line to the cannula on the hand, and injecting antibiotics and anesthesia are described but not animated in the VR. As mentioned previously, the animation of these steps was not included due to time and funding constraints, along with the desire to have the final simulation (including the animated components) be patient informed. At the point in the virtual induction where the patient would be falling asleep, the VR screen fades to black, and the simulation ends. To further encourage immersion, the induction script includes periods of patient engagement, including having the patient place their right arm correctly for the nurse and specifying their name, date of birth, type of surgery, and whether they have any allergies (as would be done as part of the mandatory World Health Organization surgical safety briefing). All this is done in real time. The OR induction process is controlled by a combination of autoadvancement methods, based on the detection of certain physical positioning requirements, and input from research personnel who progress the patient through each phase of information delivery and patient engagement (eg, responding to questions). However, haptic feedback to participants was not provided because this was beyond the scope of the study objectives, and the resources available at the time were insufficient.

Phase 2 (Completed)

Study Design

This study used a single-center feasibility and pilot randomized clinical trial with 3 arms. The study was registered on ClinicalTrials.gov (NCT04544618) on September 10, 2020 [57].

Overview

Phase 2 assessed the feasibility and preliminary outcomes of the VR OR prototype among patients undergoing breast cancer surgery. Specifically, with respect to the feasibility of this intervention, this study evaluated (1) recruitment capability and the characteristics of the resulting sample, (2) data collection procedures and selection of an appropriate outcome measure of PSA, and (3) participant acceptability and suitability of the VR OR intervention (ie, the active intervention) as well as the inclusion and acceptability of a VR control group (Nature Treks VR; ie, a non-OR immersive VR nature environment) and a TAU group. In addition, as a final aim, this study (4) pilot-tests the preliminary impact of the active intervention on PSA.

This study aimed to recruit 45 participants (n=15, 33% randomized to each arm [ie, active intervention, VR control, and TAU]). This target sample size is consistent with recommended guidelines for determining the sample size of a feasibility study and previous studies of this nature [58,59]. Furthermore, as an aim of this feasibility study, we are evaluating the extent to which we are able to recruit participants within the target population, which will inform modifications

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to the recruitment method as well as the expected duration of the upcoming randomized controlled trial (RCT).

Inclusion and Exclusion Criteria

The inclusion criteria for participation are as follows: (1) being aged ≥18 years, (2) able to speak and read English, (3) having a breast cancer diagnosis, and (4) scheduled or being scheduled to undergo breast cancer surgery under general anesthesia at the HSC. Those who do not meet these criteria, are not competent to provide informed consent (eg, due to cognitive impairment), or are unable to participate in a VR intervention (eg, due to significant visual or auditory impairments) are excluded.

Recruitment

Patients undergoing oncological surgery are recruited from the HSC via posters, patient surgical oncology appointment, or preoperative education class at the Shared Health Breast Health Centre (ie, a public health breast center that coordinates clinical assessment, diagnostic tests, treatment, education, and support) or the Breast & Gyne Cancer Centre of Hope (ie, resource center). A staff person or physician at the Breast Health Centre or Breast & Gyne Cancer Center of Hope (or research coordinator) briefly describes the study, and the contact information of interested patients is recorded. Recruitment posters with study staff's contact information are posted at the Breast Health Centre, Breast & Gyne Cancer Center of Hope, the HSC, and on the web for any potential participants not identified at the time of their surgical oncology appointment or the preoperative education class.

Protocol

Phase 2 used a single-blind randomized design (1:1:1 randomization; stratified according to surgery type [with vs without reconstruction] and whether neoadjuvant chemotherapy was received; stratification enables equal proportions of participants with these characteristics across each of the 3 study groups), using quantitative and qualitative methodologies. This was done to assess the feasibility of, and pilot-test, the VR simulation to expose patients undergoing breast cancer surgery to the OR and induction process (ie, VR OR) compared to a non–surgery-related VR simulation (ie, VR control) and TAU. All participants complete self-report measures approximately 2 weeks before surgery (ie, baseline; for VR groups, this will occur on the day of the VR visit as well as before and after testing the intervention), on the day of surgery (preoperative period), 5 days after surgery (acute postoperative period), and 30 days after surgery (30-day postoperative follow-up).

Randomization is carried out using a web-based random number generator (details of how these random numbers are generated are available on the website) [60]. A master file was created in Excel (Microsoft Corp) by author JS, which consisted of 4 different stratification groups to correspond to the number of possible combinations: no chemotherapy and no reconstruction; no chemotherapy, with reconstruction; chemotherapy, no reconstruction; and chemotherapy and reconstruction. Using the web-based number generator, each stratification group was populated with equal proportions of the randomly ordered numbers (1, 2, or 3) that corresponded to the intervention groups to which a participant could be assigned (1: OR intervention; 2: Nature Treks VR intervention, and 3: TAU). Only research personnel who randomized the participants had access to the file. Due to the nature of this study, only partial blinding was possible. Specifically, those in the TAU group received no VR intervention, but those randomized to VR control versus the VR active intervention were blinded. Participants randomized to either the active intervention or VR control group schedule a meeting date to undergo the VR intervention, approximately 2 weeks before their surgery, during their telephone call with the study coordinator. On the day of the intervention meeting, participants complete baseline questionnaires before the intervention and additional questionnaires after the intervention (detailed in the *Measures* section). Those randomized to TAU are either emailed a link to complete the baseline measures using Qualtrics software (Qualtrics International Inc) or are mailed a hard copy, depending on their preference, 2 weeks before their surgery (baseline). On the day of surgery (preoperative period), participants again complete the measures assessing PSA that had been assessed at baseline. Five days after surgery (acute postoperative period), participants will complete the PSA measures, in addition to the other initial baseline measures. Finally, all baseline measures are readministered at the 30-day postoperative follow-up. For both postoperative follow-ups, participants have the option to receive hard copies of the measures via mail (to complete within 72 hours) or a survey link to complete the measures on the web.

For the active intervention group, the VR simulation begins with the patient sitting on a hospital bed, wearing the VR headset, and holding the controllers. The details of the final prototype are described in the *Phase 1 (Complete)* section and represented in Figure 2. For the exploration component, the patient is instructed to explore the VR OR for a minimum of 5 minutes, although the exploration period can last longer (the total duration engaged in the simulation is tracked for each participant). After the exploration period, the scripted portion of the simulation begins. As detailed previously, the simulation ends after the virtual oxygen mask is placed on the patient's mouth, and the screen darkens. The scripted portion of the simulation is approximately 3 minutes long (ie, participants will spend a minimum of 8 minutes engaged in the VR intervention).

Participants randomized to the control intervention have the opportunity to explore a non–surgery-related VR simulation preprogrammed in the VR goggles (ie, Nature Treks VR experience). Participants are instructed to explore a selected nature environment for a minimum of 10 minutes, and their total duration engaged with the simulation is tracked. Participants in the TAU group receive the standard of care; they receive no additional intervention and have the option to receive information at their surgical oncology appointment and attend preoperative education classes, which all patients have the opportunity to attend. After the completion of the study, all participants are provided with a debriefing form that explains the purposes of the study.

Measures

A variety of self-report measures are administered to participants across 4 time points of this study (ie, baseline or VR visit,

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preoperative period, acute postoperative period, and 30-day postoperative follow-up). Baseline measures are administered approximately 2 weeks before surgery (at the VR intervention visit for the intervention groups or via mail or web-based for the TAU group). These measures include a background sociodemographic questionnaire (eg, assessing age, marital status, diagnosis, type of surgery, previous history of surgeries, and mental health diagnoses); the Preoperative Intrusive Thoughts Inventory (PITI) [61]; the Amsterdam Preoperative Anxiety Information Scale (APAIS) [62]; the NCCN Distress Thermometer (a visual analog scale; also adapted for anxiety) [63,64]; the Peritraumatic Distress Inventory [65]; the Primary Care Screen for Posttraumatic Stress Disorder Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [66]; the Brief Resilient Coping Scale (BRCS) [67]; and the Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety [68], depression [68], global health [69], fatigue [70], and emotional support scales [71]. The sociodemographic data collected were informed by the methodology used in a previous study by Grocott et al [72] that itself informed the current methodological approach. All mental health symptom scales are empirically validated self-report measures in various health populations, languages, and cultures. During the VR simulation, we also monitor participants' skin conductance (using eSense Skin Response [Mindfield Biosystems Ltd]) and heart rate (using a Fitbit device [Google LLC]) while engaged in the VR simulation; participants are asked to report their level of distress and anxiety (using the NCCN Distress and Anxiety Thermometer scale ranging from 0 to 10) during the intervention (approximately 7 min from the start time). Throughout the simulation, research personnel complete a standardized behavioral observation form recording any notable verbal or nonverbal indications while in the intervention. After the simulation, the intervention groups complete the Igroup Presence Questionnaire [73] and a patient acceptability questionnaire (developed by the research team and including both closed-ended and open-ended items for participants to describe their impressions of the intervention). The patient acceptability questionnaire contains questions pertaining to rating the extent (on a scale ranging from 0% to 100%) to which the participant agrees to 13 statements about the VR intervention (eg, "I found the VR intervention was helpful" and "The VR intervention worsened my anxiety/concerns about my surgery"), open-ended and closed-ended questions about motion sickness, open-ended questions about what the participant liked and disliked and what they found helpful about the VR (if applicable), open-ended and closed-ended questions about whether the VR intervention was worthwhile, and a closed-ended question about other elements that should be included in the VR OR simulation.

On the day of surgery, all participants are asked to complete the PITI, the APAIS, and the NCCN Distress and Anxiety Thermometer either while they are in the waiting room or in the preoperative holding area (depending on when is most convenient and the timings of surgeries). Furthermore, we again monitor participants' skin conductance and heart rate at this time. Participants are also asked to provide an additional rating for the NCCN Distress or Anxiety Thermometer while in the OR; instead of using the paper copy in the OR, the study coordinator or anesthesiologist asks participants to verbally indicate their current level of distress and anxiety (ie, on a scale ranging from 0 to 10). Five days after surgery, participants are asked to complete the NCCN Distress and Anxiety Thermometers; the PROMIS anxiety, depression, global health, fatigue, and pain intensity scales; a visual analog anxiety and distress graph; a postoperative summary form (to capture length of hospital stay and impressions of the various preoperative anxiety and distress measures); the BRCS; and the Peritraumatic Distress Inventory. Those in the active intervention group also receive open-ended questions requesting feedback to inform modifications that should be made to the second model of the simulation (in phase 3). Finally, 30 days after surgery, participants are asked to complete the NCCN Distress and Anxiety Thermometers; the PROMIS anxiety, depression, global health, fatigue, and pain intensity scales; the BRCS; and the Primary Care Screen for Posttraumatic Stress Disorder Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

As will be detailed in the feasibility manuscript, although a number of self-report and objective measurements were obtained, the primary measures relate to feasibility (eg, recruitment and dropout rate as well as VR impressions and feedback). This feasibility study will also evaluate the extent to which these measures are completed as instructed and best represent PSA and whether preliminary trends support decreases in PSA across the study duration. The primary outcome measure for the larger future clinical trial will be determined based on this study. The proposed primary outcome measures of interest include the PITI, the APAIS, and the NCCN Distress and Anxiety Thermometers.

Data Analysis

Quantitative data will first be analyzed descriptively: the recruitment, engagement, and attrition rates will be calculated; sample characteristics will be summarized (both across the total sample and within each group); and mean scores on measures will be reported (within each group). The assessment of acceptability will be based on open-ended qualitative feedback regarding impressions of the VR intervention, which will be analyzed using content analysis with NVivo 12 (Lumivero), which was designed to assist with qualitative data organization. We will also determine acceptability based on the developed Likert scale questions. Means or medians will be reported depending on the distribution of the data. A triangulation approach will be used to amalgamate data sources and comprehensively assess acceptability. Paired samples *t* tests (1-tailed) and repeated measures ANOVAs will assess whether there are changes in participant-reported symptoms across the duration of the study within the active intervention group. If power permits, independent samples *t* tests (or an ANOVA, followed by post hoc pairwise comparisons) will assess whether there are mean differences in PSA scores between (1) the active and control intervention groups and (2) the active intervention group and TAU (this will be examined descriptively if underpowered). We will also examine changes in physiological arousal (an objective indicator of distress), assessed via skin conductance and heart rate, between and within (ie, during VR intervention vs within OR) intervention groups, and we will

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assess whether self-reported distress and anxiety scores are correlated with the indices of physiological arousal. Physiological data will also be integrated in the VR technological paper (in development) to understand whether physiological indices change during the VR experience (indicative of immersion). Finally, if power permits, independent samples *t* tests and ANOVAs will assess whether there are mean differences in patient-reported symptoms according to certain sample characteristics (eg, age, clinically significant anxiety, history of previous surgery, and type of surgery), both within the active intervention group and within the complete sample.

Phase 3 (Underway)

Focus Groups

The focus groups are being led by 4 authors (RE, KR, GSL, and JB). The first focus group consisted of individuals randomized to the VR intervention (ie, those who received the VR OR intervention before surgery) and took place over Zoom (Zoom Video Communications, Inc). A second focus group was then conducted with individuals randomized to the TAU group or the VR control group (ie, those who did not receive the VR intervention). This focus group took place in person at the HSC and commenced with each participant trialing the VR OR prototype. Due to scheduling conflicts, we held an additional focus group for TAU participants in December 2023, and an additional focus group with VR intervention participants in February 2024. It is important to note, as we discuss in the *Results* and the *Limitations* sections, that the VR control group (ie, Nature Treks VR experience) ended up being dropped due to slow recruitment; thus, we only ran the control focus groups with individuals randomized to TAU.

The focus groups commence by reviewing the purpose of the feasibility study and the VR prototype. A semistructured question guide was developed by the research team, including several open-ended questions regarding patients' experiences with the VR prototype, whether they believe it impacted their surgical experience, and recommendations for further development. After open-ended questions are asked, more specific questions regarding feedback on potential adaptation of the prototype are explored. The focus groups are audio recorded and transcribed using Trint software (Trint Limited). Qualitative data will be analyzed using reflexive thematic analysis [74-76], examining themes identified by the authors across participants.

VR Refinement

On the basis of the results of phase 2 and the focus groups, additional modifications and changes are being made to the VR prototype. As part of the feasibility study, participants from phase 2 were asked about any additional elements to be included in the VR simulation. In addition, a coinvestigator meeting was held in April 2023 where preliminary results from a case series proof-of-concept study (first 7 participants of the feasibility trial) were presented. The expert coinvestigators provided additional input on modifications based on these initial case series findings. On the basis of the findings from the feasibility trial, expert input, and focus groups, a list of additional elements to be integrated into the VR will be developed (eg, artificial intelligence integration, educational component, guided relaxation strategies, and exposure to the waiting room or recovery environments). People engaging with the VR OR will also be provided with the opportunity to customize their avatar to be more representative of themselves. This means participants will be able to change the avatar's skin color and height to enhance embodiment. Efforts will also be undertaken to improve the diversity of the VR OR staff.

On the basis of the results from the feasibility study, focus groups, and expert input consensus, we will aim to complete the final prototype by mid-2024 for testing in a future randomized clinical trial.

Ethical Considerations

Phase 1

No patient participants were involved in the development of the initial VR prototype; therefore, ethics approval was not required. However, for the audio and video recording of a live anesthetic induction process at the HSC, we obtained signed patient consent (of note, we excluded any visual of the patient).

Phase 2

We received ethics approval from the University of Manitoba Health Research Ethics Board on June 30, 2020 (HS23957). Ethics amendments were approved in January 2021, September 2021, April 2022, and November 2022 (Multimedia Appendix 1). Participants first gave verbal consent to be contacted for research purposes after being briefly told about the study at the individual's surgical oncology appointment or at a preoperative education class. Alternatively, if learning about the study from a poster, patients contact our research team directly (as described in the *Recruitment* section). Participants are randomized during the recruitment call if they provide verbal consent to participate. Furthermore, we obtain verbal consent over the telephone from participants in the screening period and written informed consent before their participation in the study (via mail or email). All data are stored deidentified. Participants received a $25 CAD honorarium for participating in the feasibility trial.

Phase 3

In June 2023, we received ethics approval to conduct the focus groups from the University of Manitoba Health Research Ethics Board (HS26054) to recruit participants from phase 2 who indicated on their consent form that they would be willing to serve as a patient partner or adviser for future development of the VR program. For those indicating *yes*, a research assistant followed up via telephone to assess continued interest in involvement. All focus group transcript data are deidentified. All focus group participants received a $20 CAD honorarium for participating in the focus groups.

Results

This study was funded by the Government of Canada's New Frontiers in Research Fund, an operational research grant program supporting high-risk and high-reward transformative research, awarded to author RE as principal investigator in March 2019. Two extensions were provided on funding related to COVID-19 delays and parental leave of the principal

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investigator (RE). Author JS led a component of the feasibility trial for the purposes of her doctoral dissertation and, given the novelty of this area, analyzed data from the first 7 participants in a proof-of-concept case series format [77]. Phase 1 was completed in November 2021, and recruitment for phase 2 commenced in December 2021 and was completed in December 2023. On the basis of some of the initial challenges with recruitment, such as institutionally mandated shutdowns of clinical research, there were a few amendments to the initial protocol (Multimedia Appendix 1). The 2 major changes to the protocol were initiated because of challenges with recruitment, which were related to the COVID-19 pandemic restrictions, including university-wide research shutdowns, and changes to the formats of the Breast Health Centre's educational sessions (classes became virtual). We opted to exclude the VR control arm for the purposes of feasibility and proceeded with a 2-armed trial (ie, VR intervention vs TAU). We also expanded recruitment to all major oncological surgeries (instead of restricting it to breast cancer surgeries) in November 2022. However, as of August 2023, no patients undergoing non–breast cancer surgery have been recruited. We conducted the first 2 focus groups in August and September 2023, and the final focus group was completed in February 2024. We will submit full feasibility results and results of the focus groups for publication after the completion of data analysis in summer 2024. After the final development of the VR program, we will apply for additional funding in winter 2024 to conduct an RCT of the final VR simulation in 2025. We will develop a separate protocol outlining the details of the final prototype and subsequent RCT.

Discussion

Summary

Despite the high prevalence of PSA and the significant health-related impact of PSA on perioperative outcomes, little research has examined feasible and accessible interventions. Empirically supported treatments for generalized anxiety, such as cognitive behavioral therapy, are not obtainable before surgery for most patients in Canada due to limited access to mental health professionals and limited time before surgery. To the best of our knowledge, there has not been any comprehensive immersive VR simulation to be implemented before surgery. An easily accessible simulation using VR has the potential to reduce PSA for a large number of Canadians, which may yield better postoperative health outcomes as well as cost savings to the health care system as a whole. The final novel VR intervention that we are developing is intended to be able to be used by patients independently (including in the comfort of their own homes), but it could also be offered in hospital settings (including preanesthesia clinics) and be able to be easily customized for different surgical procedures under general anesthesia. The integration of VR in health care shows tremendous growth and promise [78]. Headsets are now commercially available at low cost, and advances in the technology create growing opportunities for easy implementation (eg, stand-alone wireless VR headsets). It is expected that the release of the Apple Vision Pro, the company's first augmented and VR headset that was unveiled in June 2023, will further increase awareness, demand, and accessibility of VR.

Limitations

The development of this research took place during the peak of the COVID-19 pandemic, and therefore, there were unanticipated recruitment challenges and overall delays in development. First, lockdown orders initially slowed the development and refinement of the VR OR prototype itself due to work-from-home orders. Once the prototype was completed, there were further issues due to surgery delays, along with advisories against *unnecessary* hospital visits, and changes to how patients were initially approached for their interest in participating (the Breast Health Centre changed the format of education classes from in-person to virtual sessions, and eventually some classes were canceled altogether). Ultimately, from December 2021 to December 2022, only 8 participants were recruited. Of note, during this time, there were also intermittent periods where no clinical research could be conducted. However, from January to September 2023, an additional 15 participants were recruited. This increase in recruitment may relate to changes in societal and health care practices (eg, vaccinations, reduced COVID-19 hospitalizations, and the removal of public health mandates) and will be explored further in the feasibility analysis.

Although feasibility and pilot studies are critical in the development of new interventions, the generalizability of the findings is limited. Therefore, when published, the results of the feasibility trial will need to be interpreted with caution. Relatedly, the focus of these 3 initial phases has been on patients undergoing oncological surgery, namely patients undergoing breast cancer surgery, which may differ in important ways from other noncancer surgical samples. In addition, within the VR program itself, there was 1 variation of the patient avatar, and it does not reflect differences in gender, body type, or ethnicity, which may potentially decrease patient embodiment within the VR intervention and the ecological validity on the day of surgery. Furthermore, we did not ask background questions related to ethnicity, sexual orientation, or disability and, therefore, are limited in understanding feasibility aspects across diverse populations. The sample size is also underpowered to reliably detect effects but will be able to inform future RCTs in terms of design and implementation. Furthermore, preliminary trends in the data will increase confidence in the potential utility of the intervention. Relatedly, the exclusion of the VR control group (ie, non-OR VR) as per our amendment limits our ability to understand preliminary effects of the VR intervention. It is possible that any anxiety-reduction trends for the VR intervention group compared to TAU may relate to a factor other than the effect of the intervention itself (eg, an additional appointment before surgery and the opportunity to discuss fears). It will be particularly important for future RCTs to include a comparable comparison group to elucidate potential mechanisms. A future RCT is planned to test the final iteration of the VR OR, and we intend to compare it to a mobile phone–based intervention using the same components of the simulation as well as TAU. This will allow us to disentangle the potential additive effect of immersion that exists only in VR applications. Finally, recent research by our group [72] and

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others demonstrates that PSA for oncological surgery relates to a range of factors, including uncertainty of the health trajectory, recovery [79,80], and the psychosocial implications of surgery. Our prototype intervention only targets 1 component of PSA (ie, exposure to the OR and information regarding induction), which may not result in meaningful reductions among those with PSA related to other factors. However, the results from these 3 phases will allow us to refine the VR intervention to best meet patients' needs and integrate all possible features to further ameliorate PSA (eg, relaxation strategies). Future versions of the simulation may also include advanced VR features, such as relevant haptic feedback, as the technology develops further.

Conclusions

We are developing, testing, and refining a novel VR intervention aimed to reduce PSA before major oncological surgery using a general anesthetic. The development of the VR simulation is guided by both experts in the field and people with lived experience. VR is a promising tool, given its ability to be broadly disseminated. This study will lay the groundwork for a promising intervention to reduce PSA before major oncological surgery, and future iterations could be easily adapted to other forms of surgery. This ultimately may have significant positive effects on patient health postoperative outcomes and patient experience, along with cost savings for health care systems in the future.

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Authors' Contributions

RE, JLS, PH, KR, TCM, WAM, NM, JLMK, RCA, DP, and EJ were responsible for study conception and design. RE, JLS, WAM, TCM, MSDS, CP, and VGS developed the prototype. JLS, GSL, and JB were responsible for data collection. JLS, RE, GSL, JB, and KR conducted the analysis. RE, JLS, PH, KR, TCM, WAM, NM, JLMK, RCA, DP, and EJ interpreted the results. RE, JLS, PH, KR, GSL, MSDS, TCM, WAM, NM, CP, VGS, JLMK, RCA, DP, JB, and EJ prepared the draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

RE is the external advisory chair of the Center for Perioperative Mental Health at Washington University and receives an honorarium related to her service. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Virtual reality study ethics amendment submission details.
[DOCX File , 14 KB - resprot_v13i1e55692_app1.docx]

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Abbreviations

APAIS: Amsterdam Preoperative Anxiety Information Scale
BRCS: Brief Resilient Coping Scale
HSC: Health Sciences Centre
NCCN: National Comprehensive Cancer Network
OR: operating room
PITI: Preoperative Intrusive Thoughts Inventory
PROMIS: Patient-Reported Outcomes Measurement Information System
PSA: preoperative state anxiety
RCT: randomized controlled trial
TAU: treatment as usual
VR: virtual reality
VR-CORE: Virtual Reality Clinical Outcomes Research Experts

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Protocol

Examining the Effectiveness of Interactive Webtoons for Premature Birth Prevention: Protocol for a Randomized Controlled Trial

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Abstract

Background: Premature birth poses significant health challenges globally, impacting infants, families, and society. Despite recognition of its contributing factors, efforts to reduce its incidence have seen limited success. A notable gap exists in the awareness among women of childbearing age (WCA) regarding both the risks of premature birth and the preventative measures they can take. Research suggests that enhancing health beliefs and self-management efficacy in WCA could foster preventive health behaviors. Interactive webtoons offer an innovative, cost-effective avenue for delivering engaging, accessible health education aimed at preventing premature birth.

Objective: This protocol describes a randomized controlled trial to assess the effectiveness and feasibility of a novel, self-guided, web-based intervention—Pregnancy Story I Didn't Know in Interactive Webtoon Series (PSIDK-iWebtoons)—designed to enhance self-management efficacy and promote behaviors preventing premature birth in WCA.

Methods: Using an explanatory sequential mixed methods design, this study first conducts a quantitative analysis followed by a qualitative inquiry to evaluate outcomes and feasibility. Participants are randomly assigned to 2 groups: one accessing the PSIDK-iWebtoons and the other receiving Pregnancy Story I Didn't Know in Text-Based Information (PSIDK-Texts) over 3 weeks. We measure primary efficacy through the self-management self-efficacy scale for premature birth prevention (PBP), alongside secondary outcomes including perceptions of susceptibility, severity, benefits, and barriers based on the health belief model for PBP and PBP intention. Additional participant-reported outcomes are assessed at baseline, the postintervention time point, and the 4-week follow-up. The feasibility of the intervention is assessed after the end of the 3-week intervention period. Outcome analysis uses repeated measures ANOVA for quantitative data, while qualitative data are explored through content analysis of interviews with 30 participants.

Results: The study received funding in June 2021 and institutional review board approval in October 2023. Both the PSIDK-iWebtoons and PSIDK-Texts interventions have been developed and pilot-tested from July to November 2023, with the main phase of quantitative data collection running from November 2023 to March 2024. Qualitative data collection commenced in February 2024 and will conclude in May 2024. Ongoing analyses include process evaluation and data interpretation.

Conclusions: This trial will lay foundational insights into the nexus of interactive web-based interventions and the improvement of knowledge and practices related to PBP among WCA. By demonstrating the efficacy and feasibility of a web-based, interactive educational tool, this study will contribute essential evidence to the discourse on accessible and scientifically robust digital platforms. Positive findings will underscore the importance of such interventions in fostering preventive health behaviors, thereby supporting community-wide efforts to mitigate the risk of premature births through informed self-management practices.

Trial Registration: Korea Disease Control and Prevention Agency (KDCA) KCT0008931; https://cris.nih.go.kr/cris/search/detailSearch.do?seq=25857

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KEYWORDS

cartoon; cartoons; webtoon; webtoons; story; stories; storytelling; preterm; infant; infants; infancy; baby; babies; neonate; neonates; neonatal; newborn; newborns; perception; perceptions; web-based; satisfaction; client satisfaction; clinical trial protocol; education; health belief model; web-based intervention; premature birth; prevention and control; prevention; premature; maternal; pregnant; pregnancy; randomized controlled feasibility trials; self-efficacy; women; randomized; controlled trial; controlled trials; birth; mobile phone

Introduction

Background

Premature birth is defined as a live birth that occurs before 37 weeks of pregnancy. The estimated global premature birth rate per 100 live births was 9.9% (13.4 million premature births) in 2020 [1]. It poses a serious health issue for children, their families, and society worldwide [2], with complications from premature birth being the primary contributors to childhood mortality. This accounts for 35% of all deaths during the neonatal period and 18% of all deaths in children younger than 5 years [3]. Premature birth is also associated with short-term and long-term morbidity, developmental loss in children, adult-onset diseases, and negative impacts on human capital, such as lower education and income levels and reduced social success [2].

A variety of community, societal, maternal, and fetal health factors affecting premature birth before and during pregnancy have been identified [2]. Interventions including medication, surgical procedures, cervical devices, targeted diets, physical exercise, smoking cessation programs, nutritional supplementation, education, and various special tests or investigations have been developed with reported effectiveness [4,5]. However, despite efforts to reduce its prevalence over the past several decades, the rate of premature birth has not significantly changed, showing a slight increase of 0.14% per year on average from 2010 to 2020 [1]. Women of childbearing age (WCA) still lack awareness about premature birth and the necessary health behaviors to prevent it [6,7]. Research has predominantly focused on the effects of trials with single-pronged interventions targeting narrow aspects, unable to address the complexity of premature birth's multifactorial etiological network of risk factors [2]. Moreover, step-by-step, long-term interventions are recommended for women both before and during pregnancy, with most intervention development concentrating on pregnant women and neglecting WCA in prepregnancy stages [7].

To prevent premature birth, it is crucial for women to be aware of its risks and to cultivate preventive health behaviors. The health belief model highlights the importance of strengthening health beliefs, which include perceived susceptibility, severity, benefits, and barriers, alongside self-efficacy and behavioral intention, in promoting health behaviors [8]. Studies have shown that health beliefs significantly influence prepregnant [9] and pregnant women [10-13], predicting health behavior. Self-efficacy is a key factor in WCA's health behaviors before [7,9] and during pregnancy [13]. Thus, enhancing health beliefs and self-efficacy regarding premature birth prevention (PBP) could lead to an increase in preventive health behaviors.

WCA have shown a preference for web-based education for its accessibility and convenience [7]. Systematic reviews have indicated the effectiveness of web-based education programs for WCA both before [14] and during pregnancy [15,16], suggesting web-based interventions as practical and potentially more effective educational tools. Such interventions, adaptable across devices, offer personalized and interactive educational experiences [16]. Moreover, WCA have expressed a preference for case-based education using visuals over text [7].

Webtoons, digital comics, or graphic novels presented in a vertical, scrollable format designed for easy reading on computers and mobile devices contain narrative, image, metaphor, and characterization elements. They are an effective educational method that increases understanding and awareness, easily creates empathy, and engages readers through interactive storytelling [17]. Webtoons have been shown to enhance learners' interest, concentration, critical thinking, participation, and sharing [17,18]. Their effectiveness in educational interventions, particularly in the context of women's pregnancy health, has been demonstrated through improvements in actual and perceived knowledge, risk perception, affective assessment, self-efficacy, intention to take protective behaviors, subsequent information-seeking behavior [19], environmental health perceptions, and behaviors during pregnancy [20]. Additionally, webtoons have been effective in increasing self-efficacy and knowledge regarding preventive health management of premature labor among WCA [21]. Therefore, to prepare a new intervention plan that is highly accessible, increases interest and concentration, and allows for participation and sharing to prevent premature birth in WCA, we propose to develop a web-based intervention using webtoons and aim to validate its effectiveness.

Objectives

This study is designed to evaluate the efficacy and feasibility of "Pregnancy Story I Didn't Know in Interactive Webtoon Series (PSIDK-iWebtoons)," an interactive web program aimed at preventing premature birth. The efficacy of the intervention will be assessed by comparing self-reported self-management self-efficacy for premature birth prevention (SMSE-PBP), health belief model scale for premature birth prevention (HBM-PBP), and premature birth prevention intention (PBPI) among WCA who receive the PSIDK-iWebtoons intervention to those who receive the text-based version, "Pregnancy Story I Didn't Know in Text-based Information (PSIDK-Texts)." To explore the

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feasibility of PSIDK-iWebtoons, we will examine participants' satisfaction using the Client Satisfaction Questionnaire-8 (CSQ-8) and evaluate the quality of the website, comparing responses between the 2 groups. Additionally, insights into the intervention's effects and feasibility will be further drawn from a qualitative content analysis based on interviews with participants conducted after the second postintervention period (T2) and from usage data of the intervention recorded through web activity tracking.

Methods

Study Design

This study uses an explanatory sequential mixed methods design [22]. Initially, a quantitative study (phase 1) will assess the intervention's effects and feasibility through a 1:1 parallel-group, superiority, double-blind, randomized controlled trial. Subsequently, phase 2 will involve one-to-one and semistructured interviews to provide deeper qualitative insights.

Setting

The study will be hosted on a dedicated website titled "Pregnancy Story I Didn't Know" (Korean: 내가 몰랐던 임신 이야기), with the program referred to as PSIDK-iWebtoons. This platform will be accessible exclusively to invited participants from any region of South Korea, ensuring privacy and control over the study's environment. A few screenshots of the program displayed on mobile devices are included in Multimedia Appendix 1.

Inclusion and Exclusion Criteria

Participants will be selected based on the criteria presented in Textbox 1. Participants in this study are WCA who intend to give birth on their own in the future, plan to become pregnant, or are currently in the first trimester of pregnancy, regardless of whether they have high-risk factors for premature birth. Interview participants will be drawn from both the experimental and control groups, focusing on those showing significant changes in main effect variable scores. Approximately 30 participants will be selected for interviews to further explore the intervention's impact and practicality.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Women of childbearing age, ranging from 19 to 49 years
- Women who express intentions to conceive in the foreseeable future, are actively planning for pregnancy, or are currently in the first trimester of pregnancy
- Being able to read and write in Korean
- Having access to an intern-capable device (smartphone, tablet, laptop, or desktop)
- Possessing a valid phone number and email for website account creation
- Active user of mobile instant messaging apps or social media, with readiness to use these for study participation
- Willingness to engage in a self-help web program for 3 weeks and provide written consent for participation

Exclusion criteria

- Having a previous experience of premature birth
- Having a career in a childbirth facility as a health care provider

Intervention

Overview

Participants in both the experimental and comparative groups will access their designated web programs using personal internet devices, such as smartphones, tablets, laptops, or desktops. Over a 3-week period, they will independently register by clicking on a provided link, at their convenience, without set limits on duration or frequency of participation. The approach encourages self-guided engagement with the web programs, adhering to principles of minimal contact.

Three days prior to the intervention's start, participants will receive an SMS text message on their mobile phone from a research assistant, outlining details about the commencement and procedures for participation. On the morning of the start date, an additional message will provide specific information, including the website address, the participation time frame, account creation instructions, an introduction to the program, learning methodologies, reflection writing guidelines, and a note to prevent account sharing. Further, reminder messages will be sent twice a week (Monday and Thursday) after the intervention begins. Participants found engaging in activities not related to the intervention's objectives, such as marketing promotions or violating digital etiquette and civility standards, will be subject to removal by the administrator according to the established discontinuation criteria.

Experimental Group

Overview

Participants in the experimental group will engage with the PSIDK-iWebtoons intervention through the website. Designed as a responsive web application, it aims to improve accessibility across different operating systems and devices, catering to a wide range of users. The intervention includes 7 webtoon series coupled with professional information, and it encourages

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participants to make comments or provide feedback by writing about their reflections on the webtoon series.

Webtoon Series Learning and Repeated Learning

The webtoon series features the stories of 7 women, 6 of whom have high-risk factors for premature birth, spanning from prepregnancy to pregnancy phases, with each story culminating in 3-4 different endings. Participants in the experimental group begin by creating personal accounts and completing questionnaires to identify high-risk factors for premature birth (Textbox 2). Based on the questionnaire responses, a personalized list of recommended webtoon series is generated and prioritized at the top of the web page for easy selection.

Textbox 2. Questionnaires on high-risk factors for premature birth.

Please respond with "yes" if applicable, "no" if not applicable, or "not sure" by checking the appropriate box next to each of the following risk factors for premature birth.

- Are you able to manage your pregnancy health effectively on your own?
- Have you undergone prepregnancy health checkups? Or do you intend to do so?
- Is your current age or planned age at the time of pregnancy 36 years or older?
- Were all your pregnancies planned, or do you intend for future pregnancies to be planned?
- Do you currently smoke?
- Do you handle stress well, or do you have difficulty managing stress?
- Do you have many responsibilities, such as work, childcare, and caregiving?
- Have you had difficulty with nutritional intake or been underweight currently or before pregnancy?
- Are you currently overweight or obese currently or before pregnancy?
- Have you experienced premature labor in the past?
- Have you been trying to conceive for over a year without success, experiencing infertility?
- Do you currently have high blood pressure, or did you have hypertension during a past pregnancy?
- Have you been diagnosed with diabetes or gestational diabetes currently or in the past?
- Do you currently have or have you ever had amniotic fluid leak before 37 weeks of pregnancy?
- Have you had cervical surgery currently or in the past?
- Have you experienced early separation of the placenta before childbirth, causing bleeding?
- Do you currently have excess amniotic fluid, or did you have it in the past?
- Are you currently pregnant with twins, or have you had a twin or more pregnancies in the past?
- Are you frequently exposed to chemicals or pesticides?
- Do you have uterine fibroids (myomas)?

Participants are then guided through an introduction to the program's objectives and how to navigate the website efficiently. This includes accessing the PBP education page to choose and read from the series recommended to them or from the entire list of webtoon series available. Each story is designed with key learning outcomes in mind and incorporates 2 or 3 decision-making user interfaces that allow participants to direct the actions of the protagonist. The choices made at these decision points alter the course of the story, leading to various endings. Each webtoon series is structured to have 3 or 4 possible outcomes, enriching the learning experience by illustrating the consequences of different health decisions and behaviors.

Participants are unrestricted in their choice of webtoon series from the list, with no limits on viewings, fostering repeated engagement. After finishing a story ending, they are taken to the webtoon list on their "my page," now updated with a badge marking completion and the completion date. The "my page" learning record will then list the series engaged with, showing high-resolution, clear images for endings they have completed. Conversely, endings that remain unexplored are indicated by blurred images, marked "Incomplete." These blurred images visually cue participants about content that awaits their attention. An indicator of learning progress is also displayed as a percentage for each ending, allowing for a review of choices made and the option to continue from the last decision point, enhancing the interactive and personalized learning experience.

Professional Information Review

Participants in the experimental group have access to detailed professional information linked to the learning content of the webtoons. This information is succinctly summarized and available in 2 formats: "Learn All" and "Learn Selectively." "Learn Selectively" allows participants to delve into health information pertinent to each individual series upon its completion, while "Learn All" offers comprehensive insights across all series, accessible at any point during the intervention. This structured approach enables participants to either broaden their knowledge base or focus on specific topics of interest.

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Writing and Sharing Reflections

Following the exploration of each webtoon series, participants are encouraged to write reflections. These reflections prompt them to answer semistructured questions on various aspects, including the main narrative, the most impactful content, learned health behaviors for PBP, strategies for coping with PBP, and areas of confusion or curiosity. Reflections are to be concise, with a length requirement of 30-300 Korean characters (roughly equivalent to 20-200 English words), ensuring focused and meaningful contributions. At least one reflection must be shared publicly, fostering an interactive community environment. Participants can then view and engage with others' reflections, leaving comments and expressing appreciation through "hearts" (emoticons), further enhancing the communal learning experience.

Comparative Group

To maintain the integrity of the study through blinding, a specialized website was developed exclusively for the comparative group. This platform, hosted on TISTORY—a blogging service by Kakao Corp—mimics the layout of conventional websites, featuring primarily text-based content. This choice leverages the ubiquity of KakaoTalk (Kakao Corp), a messaging service dominating 98% of messaging app usage time in Korea, to ensure familiarity and accessibility for participants [23].

Participants in this group will be introduced to the PSIDK-Texts intervention. Unlike their counterparts in the experimental group, who interact with the webtoon series, the comparative group will engage with 7 text-based fictional cases. These narratives mirror the webtoon content available to the experimental group, ensuring content parity across groups. Additionally, they will have access to the same professional information, available in both "Learn Selectively" and "Learn All" formats, aligning with the educational material provided to the experimental group.

The engagement process for the comparative group involves creating a personal account on the TISTORY platform. From there, participants will navigate the intervention autonomously, reading through the case studies and accompanying professional information. They are also encouraged to reflect on their learning by writing and sharing at least one reflection on the platform, mimicking the reflective exercise of the experimental group but within a text-centric learning environment.

Upon the conclusion of the final survey, participants in the comparative group will be granted access to the same educational program that was provided to the experimental group. They will receive the URL, enabling them to benefit from the program at their convenience, thereby ensuring equitable access to the intervention resources after trial.

Outcomes

Primary Outcome: SMSE-PBP

The primary quantitative outcome is measured by the SMSE-PBP, encompassing 3 dimensions across 10 subscales with a total of 60 items, validated for reliability [24]. The SMSE-PBP spans prepregnancy (dimension 1) with a 3-factor scale of 13 items, pregnancy (dimension 2) with a 5-factor scale of 32 items, and hospital stay (dimension 3) with a 2-factor scale of 15 items [24]. This scale was selected due to the absence of existing measures for behaviors related to PBP and the critical role of self-efficacy in health behavior [25]. Responses are gauged on a 5-point Likert scale from 1=I can hardly do it to 5=I can do it very well, with the mean of the total item scores ranging from 1 to 5. Scores for prepregnancy, pregnancy, and hospital phases indicate respective levels of self-management self-efficacy, with higher scores reflecting greater efficacy. At the time of development, Cronbach α was reported as 0.88 for dimension 1, 0.96 for dimension 2, and 0.96 for dimension 3 [24].

Secondary Outcomes

Health Belief Model Scale for Premature Birth Prevention

This scale assesses perceived susceptibility, severity, benefits, and barriers regarding premature birth, featuring 4 dimensions across 15 subscales with 96 items, validated for reliability [26]. The number of items in the 4 dimensions of the HBM-PBP is as follows: perceived susceptibility (21 items), severity (26 items), benefits (27 items), and barriers (22 items).

Each item on this scale is rated using a 5-point Likert scale that ranges from 1=not likely at all to 5=very likely. The scores for each dimension are computed as the mean of the total item scores, ranging from 1 to 5. Higher scores across these dimensions indicate stronger health beliefs and perceptions concerning the susceptibility, severity, benefits, and barriers of premature birth. At the time these measures were developed, the Cronbach α values were established as 0.87 for perceived susceptibility, 0.94 for perceived severity, 0.94 for perceived benefits, and 0.92 for perceived barriers [26].

Premature Birth Prevention Intention

The PBPI score assesses participants' intentions toward preventing premature birth. This instrument was specifically developed for this trial, drawing upon previous research on prevention intention. Participants respond to 3 statements: "I intend to do something to prevent premature birth," "I plan to do something to prevent premature birth," and "I will try to do something to prevent premature birth." Responses are captured on a 7-point Likert scale from 7=strongly agree to 1=strongly disagree. The mean of the total item scores, ranging from 1 to 7, reflects the intensity of the participant's prevention intention, with higher scores indicating stronger intentions toward preventing premature birth.

Feasibility Outcomes

Client Satisfaction Questionnaire-8

Participant satisfaction with the web-based education program will be measured using the CSQ-8, developed by Attkisson and Zwick [27], which consists of 8 items rated on a 1- to 4-point Likert scale; higher aggregate scores indicate greater satisfaction. Criterion validity was tested, and Cronbach α was reported as 0.93 [27].

Quality of the Website

The quality of the website used for the study will be assessed with a scale developed by Kang et al [28] and modified by Choi

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[29], featuring 20 items also rated on a 1- to 4-point Likert scale. A higher score on this scale reflects a more positive evaluation of the website's quality by users. Content validity was evaluated by experts [28,29] and reported a Cronbach α of 0.82 [29].

Use of the Web-Based Intervention

In the experimental group, the use of the web-based intervention will be assessed based on the number of logins during the intervention period, the number of completed series to the end, the number of endings collected for each series, the user's activities (reflections and comments), and messages to be left in the inquiry. The use of the intervention in the comparison group will be assessed based on users' reflections on the educational program in the guestbook.

Qualitative Outcome

This study will gather qualitative insights using a semistructured interview to complement the quantitative data. The primary qualitative outcome will center on an open-ended question that explores participants' perceived changes in self-efficacy for self-management of PBP before and after engaging with the education program. Secondary outcomes will delve into participants' perceptions of susceptibility, severity, benefits, and barriers related to PBP, as framed by HBM-PBP, both pre- and postparticipation. Additionally, open-ended questions concerning satisfaction with the education program and the quality of the website will be posed to assess feasibility outcomes (Multimedia Appendix 2). Follow-up questions will be tailored based on participants' initial responses to these open-ended inquiries.

Demographic Characteristics and Pregnancy- and Birth-Related Characteristics

Demographic characteristics encompass age, education level, occupation, marital status, monthly income, and area of residence. Additionally, pregnancy- and birth-related characteristics data comprise childbirth experience, number of children, diagnosed health problems, prenatal education, self-perceived likelihood of premature birth, level of intention to give birth in the future, and high-risk factors for premature birth.

Participant Timeline

Recruitment and intervention delivery for participants are structured over 5 cycles. Each recruitment phase spans 2 weeks, during which interested individuals can sign up and immediately complete a preintervention digital survey. After this period, followed by another 2 weeks, an intervention link is sent via SMS text message 3 days prior to commencement (typically on Friday), signaling the start of a 3-week engagement phase according to each participant's schedule. Throughout the intervention, SMS text messages from research assistant A are sent twice a week (on days 1, 4, 8, 11, 15, and 18) to encourage ongoing participation. The notification schedule is designed to avoid weekends and provide notifications in the middle of the day. A postintervention survey (T1) invitation is sent via text shortly after the intervention ends, with participants expected to complete this survey autonomously within the following week. After a 4-week washout period, a second postintervention survey (T2) follows a similar process. Subsequently, participants are invited to partake in one-on-one qualitative interviews, conducted on the web by 2 researchers. Each recruitment cycle initiates after the completion of the preceding 2-week recruitment phase. A detailed timeline of enrollment, interventions, assessments, and interviews is illustrated in Figure 1.

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Figure 1. Time schedule of enrollment, interventions, assessments, and interviews for participants.

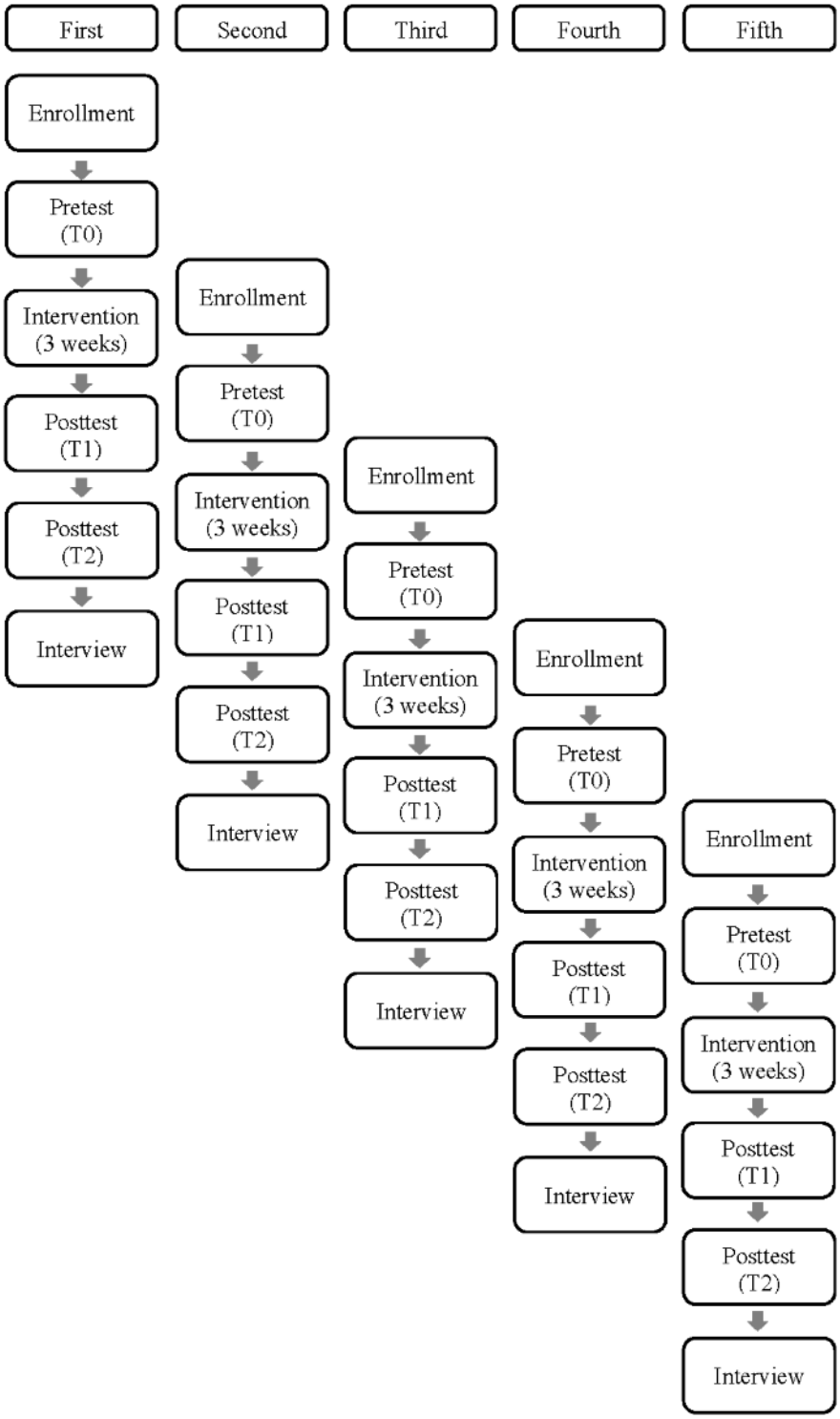

Sample Size

The sample size was calculated using G*Power software (Heinrich Heine University) [30], considering the absence of identical measurement tools and programs for an independent *t* test. A medium effect size of 0.50, a 1-sided significance level of 0.025, a power of 0.80, and an equal allocation ratio (1:1) for the 2 groups were assumed. This analysis determined that a total of 128 participants are required. Given the dropout rates of 20%-40% reported in previous web education program research [31,32], we anticipate a 30% dropout rate. To accommodate this, the study aims to enroll a total of 182 participants, allocating 91 participants to both the experimental and comparative groups, respectively.

Recruitment

The recruitment strategy includes using social media platforms such as Twitter, digital forums related to pregnancy or marriage, Kakao open chat rooms, and lifestyle information apps like Daangn Market Inc. Interested individuals will follow the

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provided web link to read the study details and consent form. The eligibility screening will include questions about gender, age, childbearing intentions, experience with premature birth, and experience working in obstetric clinical settings. Eligible participants will then complete a preintervention survey.

Allocation

Upon consenting to participate, individuals will receive an alphanumeric identification code from research assistant B, who will also stratify participants by childbirth experience. Allocation sequences will be generated using the "randombetween (1,6)" formula in Microsoft Excel (Microsoft Corp) with 4-block randomization, assigning participants to 1 of 2 groups. Two days before the intervention starts, research assistant A will inform participants of their group's specific URL. Participants will remain unaware of their group allocation on the first day of the intervention, with the allocation process being managed by research assistant B.

Blinding

Participants will be informed at the onset that they will be randomly assigned to 1 of 2 web-based interventions, with the design making it challenging for them to discern their assigned intervention. This ensures participants are blinded to their group allocation throughout the intervention, postintervention surveys, and interviews. The comparative group will only be unblinded after completing the interview phase, at which point they will be offered the intervention provided to the experimental group. Research assistant B will be temporarily hired solely for participant allocation, and the other researchers, including research assistant A, will not participate in the allocation process.

Data Collection Methods

Survey Data

Outcomes and demographic and pregnancy- and birth-related characteristics data collection will be managed on the web by research assistant A, using survey URLs sent to participants. To ensure comprehensive data collection, during the posttest phases T1 and T2, participants will receive reminder SMS text messages on the first, third, and sixth days (for nonrespondents), prompting completion of the survey. Additionally, use data will be systematically gathered from the web program's administrative interface. These data will be requested at regular intervals throughout the study to ensure comprehensive coverage and accuracy in our analysis of participant engagement.

Interview Data

To enrich the quantitative findings and delve into barriers to intervention participation, qualitative interviews will be conducted with 30 participants, selected purposefully to represent diverse experiences across both experimental and comparison groups and varying outcomes. These semistructured interviews will be carried out by the research team via Zoom (Zoom Video Communications, Inc) or KakaoTalk, aiming for an insightful blend of video and voice meetings. Immediate transcription will follow each recorded interview, with data analysis facilitated by NVivo software (version 14 for Windows; Lumivero). Prior to interviews, investigators will familiarize themselves with participants' demographic, baseline, and both T1 and T2 data. Training for interviewers will emphasize techniques for fostering a comfortable atmosphere, building rapport, maintaining neutrality, and eliciting detailed responses. The research team will hold weekly debriefing sessions to discuss any new findings or issues encountered during data collection.

Data Management

To safeguard participant confidentiality, unique identification numbers will anonymize all data, which will be encrypted and stored in a nonidentifiable format. These data, alongside automatically generated identification codes, will be kept on a dedicated USB storage device and secured in locked filing cabinets, accessible solely to the designated data analyst. In line with Daegu Catholic University's research data management policy, all data will be retained by the principal researcher (SHK) for 3 years after study completion. Subsequent to this period, all documents will be destroyed, and digital files permanently erased to ensure irretrievability.

Data Analysis

Quantitative Data Analysis

The quantitative data collected will be processed using SPSS Statistics (version 25.0; IBM Corp). Descriptive statistics, including frequency, percentage, mean, and SD, will evaluate demographic and pregnancy- and birth-related characteristics. The analysis of primary, secondary, and feasibility outcomes will also include mean, SD, and tests for normal distribution. To compare the homogeneity of characteristics and outcomes (T0) between experimental and comparative groups, chi-square tests and 2-tailed *t* tests will be applied. Depending on the homogeneity of baseline characteristics and initial SMSE-PBP scores, either repeated measures ANOVA or repeated measures analysis of covariance will be used. For nonnormally distributed data, generalized estimating equations will be used. Subgroup analyses based on demographic and pregnancy- and birth-related characteristics (eg, age and education level) will be conducted using linear or logistic regression. The use of the web-based intervention (the number of logins during the intervention period, the number of series completed to the end, and the number of endings collected for each series) in the experimental group will be assessed for primary, secondary, and feasibility outcomes using linear regression analysis. The reliability of measurement tools will be assessed using Cronbach α coefficient, and missing data will be addressed through multiple imputation.

Qualitative Data Analysis

Interview data will be explored starting with the frameworks of SMSE-PBP, HBM-PBP, CSQ-8, and website quality evaluation. Using the qualitative content analysis method by Hsieh and Shannon [33], the process begins with enhancing sensitivity to the data through repeated listening to recordings and reviewing transcriptions. Follow-up interviews may clarify ambiguities, with field notes enhancing content accuracy. Familiarization with the transcribed content aims to deeply understand participant experiences and gain insights into the intervention's impact. Initial coding involves identifying

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keywords and phrases from the text, generating preliminary codes from the first few participants, and iteratively integrating new and overlapping codes as the participant pool expands. Codes will be organized into categories, examining their interrelations and distinctions, with themes emerging to represent recurring concepts or latent ideas. To validate the analysis methods and findings, discussions among researchers, reviews by 2 professors, and feedback from 5 experienced qualitative researchers will ensure the derived data and themes are meaningful and accurately represented. For the validation and reliability of the qualitative components of our study, the research team will develop a reference framework. This framework will be based on the subcategories identified within the SMSE-PBP, HBM-PBP, CSQ-8, and website quality evaluations. To ensure the accuracy of our coding process, data from 1 interview will be coded independently by different researchers. Subsequently, the interpretations of each coding will be discussed collectively among the research team to harmonize understanding and finalize the coding schema. Furthermore, to reinforce the credibility of our findings, transcripts of the interviews will be sent to all participants within 1-3 days following their interview. Participants will be asked to review the content for accuracy and provide any necessary feedback. This member check process is designed to confirm and validate the data captured during the interviews.

Data Monitoring

The integrity and completeness of data collection will be diligently overseen by research assistant A, with an additional layer of verification provided by the principal researcher. Efforts will be made to address any missing data throughout each survey period, ensuring follow-up does not cause undue distress to participants. As mandated, findings will be systematically reported to the institutional review board of Daegu Catholic University. It is important to note that all aspects of data collection and analysis will be conducted independently of the National Research Foundation of Korea, the sponsoring body. Given the nature of web-based interventions, adverse events are not commonly anticipated. However, should participants experience any unintended effects, they are encouraged to promptly communicate these to the research team for appropriate adjustments. The autonomous participation model of the web-based intervention negates the necessity for regular audit frequencies and procedures by the research team, emphasizing participant-led engagement within the study framework.

Ethical Considerations

This study protocol has received ethics approval from the institutional review board of Daegu Catholic University (CUIRB-2023-0050). Comprehensive written information about the study will be provided to all participants, from whom informed consent will be obtained prior to their participation. Participation in this study is entirely voluntary and incurs no cost to the participants. All procedures outlined in this protocol will adhere strictly to applicable guidelines and regulations to ensure ethical compliance and participant safety. Addressed within the application were several potential ethical considerations. First, although no adverse effects are anticipated from the web-based intervention itself, it is acknowledged that prolonged screen use may lead to eye fatigue, and participants may incur internet data costs. To mitigate these issues, the research materials will include advice on using a Wi-Fi connection where possible and recommendations against extended continuous screen use. Second, the importance of maintaining participant privacy, especially when using web-based communication for intervention delivery, has been paramount [34]. To safeguard privacy, participants will interact with the study platform using anonymous, auto-generated identification codes. Secure web-based interfaces will be used for all interactions, with only private SMS text messages used for sending reminders to participants. The results of the feasibility study and the broader research findings will be disseminated through various channels to ensure wide reach. These include social networking services, a dedicated project website, and publications in academic journals. This multifaceted approach aims to engage a diverse audience, spanning practitioners, researchers, and the public to maximize the impact of the study's findings.

Results

Development of the Intervention Program

The creation of the PSIDK-iWebtoons website involved a 23-month process that included the writing of scenarios, the production of webtoons, and the development of the website itself. The scenario for PSIDK-iWebtoons was developed by an author who brings a unique blend of expertise: professional experience in nursing care specifically tailored to high-risk pregnant women coupled with a background in scenario writing. This combination ensured the educational content was both medically accurate and engagingly presented. The webtoons were crafted by student interns specializing in webtoon creation, enrolled at Korean universities that offer a major in webtoon studies. The development of the website was managed by a professional company, ensuring both innovative content from emerging artists and a high standard of technical execution. All educational content, including 7 scenarios and webtoon series, underwent 1-2 rounds of expert review by nurses, doctors, and nursing professors. Feedback from WCA was also solicited to refine the scenarios, webtoon series, and website. The intervention scenarios were initially created using insights derived from qualitative interviews with women who have experienced premature births. These initial versions were further refined based on qualitative feedback from 3 WCAs. Additionally, the complete webtoon series and the accompanying website were extensively reviewed by 7 WCAs, who provided both qualitative and quantitative feedback, leading to further revisions.

Trial Status

The study received funding in June 2021 and institutional review board approval in October 2023. The development of PSIDK-iWebtoons commenced on February 7, 2022, and concluded on November 19, 2023, incorporating enhancements based on pilot testing feedback. The pilot intervention took place from September 4 to 24, 2023, with quantitative data collection occurring from July 17 to October 29, 2023. Qualitative data collection followed from October 30 to

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November 5, 2023, targeting WCA at high risk for premature birth.

The main quantitative data collection phase started on November 6, 2023, and concluded on March 31, 2024, targeting a broader demographic of WCA. Qualitative data collection for process evaluation commenced in February 2024 and will be completed in May 2024, with analyses and interpretation of these data ongoing. The analysis is expected to be completed by October 2024, and the results will be published by March 2025.

Discussion

Expected Findings

This study aims to explore the impact of the PSIDK-iWebtoons intervention, delivered on the web as a self-help tool, on WCA. Anticipated outcomes include improved SMSE-PBP and HBM-PBP, leading to increased engagement in PBP behaviors. Such improvements could contribute to a reduction in premature birth rates. Previous research has highlighted the effectiveness of webtoon educational programs in fostering preventive behaviors to mitigate disease risk [21], suggesting potential benefits for WCA. This research also seeks to evaluate the feasibility of a responsive web program, aiming to expand the knowledge base on interventions effective in preventing premature birth. Given that many WCA are initially unaware of premature birth risks until after giving birth [35], emphasizing preventive measures is crucial. Demonstrating the effectiveness and feasibility of web-based interventions could enhance the accessibility of preventive measures without the constraints of time, location, or direct medical interaction.

Potential Challenges

Several limitations are anticipated in this study. First, the nature of self-help web-based interventions may result in higher dropout rates. To mitigate this, establishing a notification system that offers personalized content and promotes participant interaction is vital. Due to budget constraints, this study will use manual notifications instead of an automated system. Second, the instruments for measuring primary and secondary outcomes are newly developed. While their psychometric properties have been evaluated, their novelty may influence result validity, necessitating cautious interpretation and the potential use of qualitative data to enrich findings. Third, accurately assessing PBP behaviors presents challenges, and reliance on measures such as SMSE-PBP, HBM-PBP, and PBPI to predict these behaviors has its limitations. Fourth, an unexpected finding that may arise from the intervention is a decrease in the intention to give birth. Research suggests that negative experiences during pregnancy and childbirth can lead some women to reconsider future pregnancies [36]. The webtoon series, designed to realistically portray scenarios involving premature birth, might inadvertently heighten fears associated with such outcomes. This potential influence on WCAs who view the webtoon could lead them to feel apprehensive about the risks of premature birth, impacting their future pregnancy intentions. Fifth, although the comparative group receives a text-based web intervention to compare the effectiveness of story-incorporated cartoons, the scarcity of PBP interventions for WCA may still yield positive outcomes from the text-based approach alone. Additionally, the learning effects across 3 measurements underscore the need for a research design that includes a control group for comparison.

Conclusions

Preventing premature birth is critical for the health and well-being of children, families, and society at large. Despite the underrecognized importance of PBP, the PSIDK-iWebtoons intervention is designed to raise awareness and underscore the significance of proactive engagement in PBP. By conducting this clinical trial on the web, the study not only assesses the efficacy of the PSIDK-iWebtoons intervention but also highlights its potential to make a positive impact on maternal and child health outcomes.

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Authors' Contributions

SHK contributed to the design of the intervention and conceptualized the website. SHK and JCDG drafted the original version of the manuscript and wrote the protocol manuscript. All the authors have critically reviewed the entire manuscript and have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshots of the webtoon program displayed on mobile devices.

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[PDF File (Adobe PDF File), 429 KB - resprot_v13i1e58326_app1.pdf]

Multimedia Appendix 2
List of the interview questions.
[DOCX File , 28 KB - resprot_v13i1e58326_app2.docx]

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Abbreviations

CSQ-8: Client Satisfaction Questionnaire-8
HBM-PBP: health belief model scale for premature birth prevention
PBP: premature birth prevention
PBPI: premature birth prevention intention
PSIDK-iWebtoons: Pregnancy Story I Didn't Know in Interactive Webtoon Series
PSIDK-Texts: Pregnancy Story I Didn't Know in Text-Based Information
SMSE-PBP: self-management self-efficacy for premature birth prevention
WCA: women of childbearing age

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Protocol

Patients and Stakeholders' Perspectives Regarding the Privacy, Security, and Confidentiality of Data Collected via Mobile Health Apps in Saudi Arabia: Protocol for a Mixed Method Study

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Abstract

Background: There is data paucity regarding users' awareness of privacy concerns and the resulting impact on the acceptance of mobile health (mHealth) apps, especially in the Saudi context. Such information is pertinent in addressing users' needs in the Kingdom of Saudi Arabia (KSA).

Objective: This article presents a study protocol for a mixed method study to assess the perspectives of patients and stakeholders regarding the privacy, security, and confidentiality of data collected via mHealth apps in the KSA and the factors affecting the adoption of mHealth apps.

Methods: A mixed method study design will be used. In the quantitative phase, patients and end users of mHealth apps will be randomly recruited from various provinces in Saudi Arabia with a high population of mHealth users. The research instrument will be developed based on the emerging themes and findings from the interview conducted among stakeholders, app developers, health care professionals, and users of mHealth apps (n=25). The survey will focus on (1) how to improve patients' awareness of data security, privacy, and confidentiality; (2) feedback on the current mHealth apps in terms of data security, privacy, and confidentiality; and (3) the features that might improve data security, privacy, and confidentiality of mHealth apps. Meanwhile, specific sections of the questionnaire will focus on patients' awareness, privacy concerns, confidentiality concerns, security concerns, perceived usefulness, perceived ease of use, and behavioral intention. Qualitative data will be analyzed thematically using NVivo version 12. Descriptive statistics, regression analysis, and structural equation modeling will be performed using SPSS and partial least squares structural equation modeling.

Results: The ethical approval for this research has been obtained from the Biomedical and Scientific Research Ethics Committee, University of Warwick, and the Medical Research and Ethics Committee Ministry of Health in the KSA. The qualitative phase is ongoing and 15 participants have been interviewed. The interviews for the remaining 10 participants will be completed by November 25, 2023. Preliminary thematic analysis is still ongoing. Meanwhile, the quantitative phase will commence by December 10, 2023, with 150 participants providing signed and informed consent to participate in the study.

Conclusions: The mixed methods study will elucidate the antecedents of patients' awareness and concerns regarding the privacy, security, and confidentiality of data collected via mHealth apps in the KSA. Furthermore, pertinent findings on the perspectives of stakeholders and health care professionals toward the aforementioned issues will be gleaned. The results will assist policy makers in developing strategies to improve Saudi users'/patients' adoption of mHealth apps and addressing the concerns raised to benefit significantly from these advanced health care modalities.

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KEYWORDS

awareness; data privacy; confidentiality; security; health care; patients; Saudi Arabia; mHealth; mobile apps

Introduction

Background

In recent years, the utilization of mobile health (mHealth) apps by both the public and health care professionals (HCPs) has significantly increased, driven by the widespread adoption of smartphones [1], as well as the growing interest in health care industry and research field [2]. The COVID-19 pandemic has further expedited the reliance on digital health [3]. mHealth apps serve various purposes, including disease management, self-monitoring, health information gathering, facilitating behavioral changes, fitness management, and medication and rehabilitation schedule reminders [4]. From the perspective of HCPs, these apps aid in health record management, offer convenient access to health records, and enable mobile consultations and remote monitoring during and after treatment [5].

HCPs, particularly physicians, constitute the second largest stakeholders in the health care field, following patients. Therefore, mHealth apps integrated with clinical information systems (CISs) enable HCPs to access patients' databases [6]. One of the primary drivers behind the adoption of mHealth apps among HCPs is to facilitate timely consultation and decision-making at the point of care, necessitating various resources, particularly clinical data from CISs. CISs are integral components of hospital information systems, directly connected to both inpatient and outpatient care. These systems offer a significant advantage in that they can integrate with other subsystems within a hospital, including various departments and laboratories [7]. Clinicians depend on these systems when making decisions regarding their patients' health. Consequently, patients are encouraged to engage with CISs, particularly in cases where health care providers exclusively offer care through mHealth apps. Although linking CISs with mHealth apps streamlines hospital workflows, it also presents new challenges, such as ensuring data confidentiality and security. Concerns about data confidentiality, privacy, security, and regulatory oversight of the apps are recognized barriers that impede mHealth adoption in the health care field [8].

Confidentiality entails the obligation of entities acquiring data/information (such as app providers) to safeguard the privacy concerns of the individuals to whom the information pertains (consumers) [8]. Meanwhile, as defined by the National Committee on Vital and Health Statistics, privacy denotes an individual's legal right or freedom to control the protection or disclosure of their health information, while security encompasses the personal, mechanical, or administrative protective measures used to shield health information from unauthorized access or disclosure. Security, conversely, is described as the physical, mechanical, or legislative mechanisms or tools used to safeguard personal health information from unauthorized disclosure [8]. Numerous reasons underscore the importance of data protection in mHealth apps, including the vulnerability of keyed-in information and the attractiveness of mobile apps to attackers or hackers [7]. Furthermore, factors such as data management and storage, data privacy disclosure, data integration, data encryption, app operability, and authentication are recognized as established contributors to data breaches [7].

Numerous studies have underscored the correlation between patients' awareness and the risk of data breaches [7-9]. End users bear responsibility for the security and privacy of their data, which must be upheld [4,10]. As the primary stakeholders in the health care system, patients have a contractual relationship with health care providers, who are entrusted with ensuring the safety and confidentiality of patients' health information. While mHealth providers are cognizant of the security measures, privacy, and confidentiality related to patients' health data, the latter seems to lag in these crucial aspects [4,10].

In the context of Saudi Arabia, the health care economy is experiencing rapid growth as a result of the digitization of the sector [11]. This progress in health care service delivery is closely linked to the nation's high penetration rate of smartphones, internet usage, and social networking in the Arabian Gulf region. Recent statistics suggest that the number of smartphone and mobile phone users in the Kingdom of Saudi Arabia (KSA) is projected to rise from 21.87 and 23.77 million in 2018 to 24.02 and 30.0 million in 2025, respectively [11]. To align with the growing population of smartphone users, Saudi Arabia has introduced numerous mHealth apps in accordance with its Vision 2030 objectives [12]. As part of the nation's initiatives, the implementation of a digital transformation plan for both private and public health care sectors began in 2017 [13]. The Saudi Ministry of Health has developed several mobile apps aimed at streamlining administrative procedures for users and patients, enabling them to access medical consultations and update their medication information [12,14].

However, the adoption of mHealth apps in Saudi Arabia has not yet reached the anticipated benchmark [13]. Recent studies have highlighted concerns regarding the safety, privacy, and confidentiality of information exchanged via mHealth apps connected to CISs [11,15]. These challenges could be contributing factors to the low adoption rates among end users and patients. However, a thorough understanding of their awareness regarding these issues is necessary to confirm this. For instance, previous studies have reported significant security and privacy issues that could potentially result in data breaches with severe social, legal, and financial repercussions [11,15]. Aljedaani et al [15] provided empirical evidence indicating that the majority of end users of mHealth apps were unaware of the existing security features. Furthermore, a recent study conducted

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within the context of mHealth apps in Saudi Arabia revealed that only a small number of participants were aware of adverse drug reactions, and many denied receiving prior education or attending events related to such mHealth apps [16].

Another noteworthy issue concerning the existing literature on mHealth apps in the KSA is the predominant focus on HCPs, with limited attention given to patients' perspectives [15]. It is essential to balance both developers' and users' viewpoints to ensure that mHealth apps fulfill their intended objectives in enhancing health care service delivery. Nevertheless, there has been no qualitative analysis conducted on users' awareness and perspectives regarding data privacy, confidentiality, and security in Saudi Arabia. Furthermore, there is a scarcity of data regarding users' awareness of privacy concerns and how they impact the acceptance of mHealth apps, particularly in the Saudi context. Such information is crucial for addressing users' needs and developing patient-friendly mHealth apps in the KSA. This article presents a study protocol for conducting a mixed method analysis of patients' and stakeholders' perspectives on the privacy, confidentiality, and security of data collected through mHealth apps in Saudi Arabia. We will outline its scope, theoretical background, and research hypotheses in the following sections.

Scope

The scope of this study is focused on examining end users' awareness of security, privacy, and confidentiality aspects related to clinical mHealth apps, including patient management systems that handle highly sensitive health-critical data and personal information. This study specifically centers on end users' perspectives regarding their awareness of the security, privacy, and confidentiality of information collected via mHealth apps. The study aims to offer an in-depth understanding of end users' security awareness by assessing their existing knowledge of the security features provided by mHealth apps available in the country. Furthermore, it seeks to explore the relationship between end users'/patients' security awareness and their sociodemographic characteristics. In addition, the study aims to identify specific security features that may enhance end users' confidence in using mHealth apps. The findings of this study will contribute to benchmarking the effectiveness of security features in mHealth apps, providing valuable insights for developers in Saudi Arabia. These insights can inform the engineering of both existing and next-generation mHealth apps, with the aim of improving their security features. Ultimately, this may lead to enhanced adoption of mHealth apps within the health care management landscape in Saudi Arabia.

Theoretical Framework

A review of the current literature reveals the widespread use of various technology acceptance theories in understanding the adoption of advanced health care systems. These theories include the Technology Acceptance Model (TAM), the Theory of Reasoned Action (TRA), and theories related to health information management and ethical behavior in information assurance and security [17]. The TAM is widely recognized as a valuable model for investigating technology acceptance in information systems, including health care systems, owing to its simplicity and ease of understanding [18]. Proponents of the TAM argue that the key to promoting use lies in increasing acceptance of information technology, which can be measured based on an individual's intention to use it in the future [19].

Closely related to the TAM is the TRA, which adopts a psychological approach to understanding how individuals' belief systems influence human behavior. TRA suggests that an individual's behavioral intention (BI) to use a system is influenced by their subjective norms and attitudes associated with the behavior [19]. Fernández-Alemán et al [20] evaluated the psychosociocultural framework along with several sociodemographic features such as gender, age, and experience in their research. They advocated for improved security awareness training to foster better security practices.

In a previous study, another approach used was the combination of the Protection Motivation Theory and the Theory of Planned Behavior [21]. These theories were used to ascertain whether security practices were influenced by security awareness, experience, and information policy. The Theory of Planned Behavior relies on subjective norms, attitudes, and perceived behaviors to predict human behavior [22] while the Protection Motivation Theory emphasizes the individual's ability to protect themselves from threats. This is based on factors such as the perceived likelihood of occurrence or vulnerability, perceived severity of a threat, perceived self-efficacy, and the effectiveness of recommended preventive measures [21].

Hence, various theories could be used to assess security practices and user perspectives on eHealth and mHealth in the Saudi context. Recognizing that sociodemographic characteristics influence health care security practices and psychological factors, this study proposes the adoption of the psychosociocultural framework to facilitate a comprehensive approach to elucidating users' characteristics and determining factors for using mHealth apps in Saudi Arabia. Furthermore, it aims to explore their perspectives on data privacy, security, and confidentiality. As we will assess users' acceptance levels, awareness, and antecedents, the TAM will be considered in developing the conceptual framework.

Research Hypotheses

This study proposes that awareness of data privacy, security, and confidentiality serves as a predictor of BI toward using mHealth apps among the Saudi population. Existing literature suggests that users' awareness of data privacy makes them cautious about adopting technology and sharing their personal information [4,6]. Users' perspectives and concerns about the privacy of health information may influence their avoidance of using specific health care services, particularly mHealth in the present context [9]. Previous research has shown that failure to address customers' privacy concerns can severely impact their behavior and attitude toward health care services [23,24]. Mukherjee and Nath [23] also discovered that the combination of security and privacy, along with shared values, positively influenced customers' BI. This study aligns with the argument that concerns about privacy, security, and confidentiality are associated with end users' or patients' reluctance to rely on mHealth apps, particularly regarding the sharing of their personal data. Hence, based on the aforementioned arguments, the following hypotheses are proposed:

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- H1(a): BI to use mHealth apps connected to CISs is associated with users' awareness level of data privacy, security, and confidentiality issues.
- H1(b): Sociodemographic factors (ie, gender, age, job type, income level, location, and educational qualification) are associated with users' awareness level of data privacy, security, and confidentiality issues.

In examining the acceptance of mHealth apps among the Saudi population, this study aims to use the TAM in formulating the research hypotheses. The 2 primary components of the TAM, perceived ease of use (PEOU) and perceived usefulness (PU), are believed to influence users' BIs [24]. Despite extensive research on data privacy and security in various environments and contexts, only a few studies have examined the effects of privacy concerns on PU and PEOU [25]. In fact, no study in the literature has focused on these aspects in users' or patients' adoption of mHealth apps. A study reported that higher privacy and security concerns played a negative mediating role in the association between users' perceived risk and attitude [25]. Therefore, it is reasonable to predict that patients or end users will not perceive technology as useful if they perceive a high risk of privacy invasion. Individuals are more likely to invest more effort into monitoring, especially when they perceive their data privacy to be at risk while using any service. Consequently, privacy and security concerns may diminish an individual's PEOU and the usefulness of any service, including the use of mHealth apps. Based on these arguments, the following hypotheses are proposed:

- H2(a): Privacy, security, and confidentiality concerns are negatively associated with the PU of using mHealth apps.
- H2(b): Privacy, security, and confidentiality concerns are negatively associated with the PEOU of mHealth apps.

Research Objectives

The following are the research objectives:

- To explore patients' and stakeholders' awareness levels and perspectives on issues relating to the privacy, security, and confidentiality of data collected via mHealth apps in Saudi Arabia.
- To determine the association between BI to use mHealth apps and users' awareness level of data privacy, security, and confidentiality issues.
- To determine the association between patients' sociodemographic factors and concerns regarding data privacy, security, and confidentiality issues.
- To determine the association between patients' PU of mHealth apps and concerns regarding data privacy, security, and confidentiality.
- To determine the association between patients' PEOU of mHealth apps and concerns regarding data privacy, security, and confidentiality.
- To propose initiatives for the Saudi government to improve Saudi users'/patients' adoption of mHealth apps and address the concerns relating to data privacy, security, and confidentiality.

Research Questions

In line with the research objectives, this study aims to answer the following questions:

- What is the patients' awareness level of data confidentiality, privacy, and security issues concerning mHealth apps in Saudi Arabia?
- Is there any relationship between BI to use mHealth apps and users' awareness level of data privacy, security, and confidentiality issues?
- Is there any relationship between patients' sociodemographic factors and concerns regarding data privacy, security, and confidentiality issues?
- Is there any relationship between patients' PU of mHealth apps and concerns regarding data privacy, security, and confidentiality?
- Is there any relationship between patients' PEOU of mHealth apps and concerns regarding data privacy, security, and confidentiality?
- What are the perspectives of patients and stakeholders regarding the privacy, security, and confidentiality of data collected via mHealth apps?

Methods

Study Area and Study Design

There are a total of 13 provinces in Saudi Arabia, namely, Riyadh, Madinah, Mecca, Tabuk, Najran, Hall, Northern, Eastern, Al Jouf, Asir, Qassim, Jazan, and Al Baha. However, this study will concentrate on regions housing hospitals with state-of-the-art facilities that are presently using mHealth apps for patient management. mHealth users from the identified provinces will be included in the recruitment process, regardless of their current place of work or occupation. Therefore, mHealth users from the health care, service, educational, and industrial sectors will be recruited into the study as long as they meet the inclusion criteria. These study sites were chosen because they represent Saudi Arabia's fastest-growing medical complexes and have implemented mHealth apps that directly connect patients to CISs. With the high number of patients and users of mHealth apps in the aforementioned provinces, as well as the availability of experienced clinicians and health care providers using mHealth apps connected to CISs, these study sites provide an ideal environment for gathering the necessary data to accomplish the research objectives.

A mixed method approach incorporating both qualitative and quantitative methods will be used in this study. Given the scarcity of data on the aforementioned research topics in the Saudi context, this study will be exploratory in nature. Therefore, the mixed method approach will allow the researchers to explore a wide breadth of the topic. By combining qualitative and quantitative methods, the study ensures convergence and correspondence of results drawn from different methodologies [26,27].

Qualitative data will be collected through structured interviews with stakeholders of mHealth apps in Saudi Arabia. Meanwhile, the quantitative phase will involve patients who are either currently using mHealth apps or seeking health services from

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health care facilities in Saudi Arabia. For the quantitative phase, a structured survey (questionnaire) will be developed, validated, and pilot tested before conducting the actual survey. Hence, the first to fifth research questions will be addressed in the quantitative phase, while qualitative data will be collected to answer the sixth research question. As different participants will be involved in the quantitative and qualitative parts, both phases will be conducted concurrently.

Study Population

The study population and unit of analysis in this study include all patients and other stakeholders who meet the inclusion criteria. The target population will be mHealth app users who are actively seeking health services from health care institutions, as well as other stakeholders such as app developers, HCPs, and policy makers in Saudi Arabia's health sector.

Inclusion and Exclusion Criteria

Certain inclusion and exclusion criteria will be considered for respondent recruitment in this study. The target participants will be mHealth app users and stakeholders aged 18 years and above. Patients must be actively seeking health services, currently visiting any hospital in any province of Saudi Arabia, and must have a basic understanding of the functions of mHealth apps. Meanwhile, individuals under 18 years old, those lacking basic knowledge of mHealth apps, and those not currently visiting any hospitals in the provinces will be excluded from this study. Stakeholders must be either HCPs, mHealth app developers, or policy makers with experience in mHealth apps. Indeed, such knowledge will aid the researchers in elucidating patients' and stakeholders' perspectives regarding data confidentiality, privacy, and security issues in the usage of mHealth apps.

Sample Size Calculation and Sampling Technique

The sample size for the quantitative phase will be estimated based on factors such as the estimated total population of mHealth app users in the study locations, a CI of 95%, a precision error of 5%, and estimates from previous related studies on the adoption rate of mHealth apps in Saudi Arabia and other countries in the Middle East. Specifically, the sample size will be estimated using the following formula for analytical and cohort studies:

where n is the sample size; $Z_{1-\alpha/2}$ is the Z statistic for 95% confidence level, with a value of 1.96; $Z_{1-\beta}$ is the Z statistic for 90% power, with a value of 1.28; P_1 is the proportion of participants with satisfactory accessibility and receptiveness levels toward counseling in the first group; and P_2 is the proportion of participants with satisfactory accessibility and receptiveness levels toward counseling in the second group.

P_1 and P_2, representing the proportions of participants adopting mHealth apps or being aware of data privacy, security, or confidentiality issues, will be obtained from previous studies conducted in Saudi Arabia or other countries in the Middle East. These values will then be substituted into the equation to calculate the required sample size (n). A nonresponse rate of 20% will be taken into account when determining the final sample size. Moreover, the probability proportionate to size method will be applied to allocate the sample size for each selected province. This approach ensures a proportionate distribution of patients and users of mHealth apps across the different provinces, thereby enhancing the representativeness of the sample. Following that, a convenience sampling technique will be used to obtain the necessary number of participants from each region. Meanwhile, purposive sampling will be used to select the provinces as outlined in the study design and study area.

Qualitative Phase: Study Instrument and Interview Session

In the qualitative phase, a semistructured interview will be designed. The interview session will include patients, developers of mHealth apps, and HCPs. Questions for the interview session will be synthesized based on an in-depth review of previous literature and discussions among the researchers. Previous studies that used interviews or focus group discussions will be reviewed [4,24], followed by the selection and modification of topics relevant to this study and the Saudi context. The questions will primarily focus on 3 main areas: (1) strategies to enhance patients' awareness of data security, privacy, and confidentiality; (2) feedback on the current mHealth apps regarding data security, privacy, and confidentiality; and (3) features that could enhance the data security, privacy, and confidentiality of mHealth apps connected to CISs. The interview guide will facilitate participants in sharing their experiences of using mHealth apps and expressing their concerns regarding data security, privacy, and confidentiality.

The interview will be carried out by a trained enumerator and conducted in either English or Arabic, depending on the participant's preference. The interview is expected to last for 10-20 minutes, and for patients, it will take place in hospitals, while stakeholders will be interviewed at their preferred locations. The relevant authorities and personnel in the hospitals will be contacted, and they will be briefed about the research objectives and methodology. Once approval is obtained from the hospitals, potential participants will be approached during their visits, and their consent to participate in the study will be sought. The same method will be used to recruit stakeholders from their respective industries. In addition, a snowball method will be used, where participants will be asked to nominate other potential patients or stakeholders willing to participate in the study. With participants' permission, a voice recorder will be available during the interview session. Different participants will be recruited for the qualitative and quantitative phases of the study.

Quantitative Phase: Instrument Development and Administration

Questionnaire development involves designing, directing, and compiling the items to assess or measure various constructs in a given survey [28]. In this study, a multidimensional approach was used to develop the instrument. This approach included

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gathering insights from previous related research, modifying instruments used in prior studies, and engaging in discussions among the researchers. The structured questionnaire was designed in 2 broad parts: part 1 and part 2. Part 1 included demographic details such as age, gender, marital status, occupation, income level, education level, current health app usage, and frequency of mobile app use. As discussed in the previous section, participants' sociodemographic factors are crucial in understanding the adoption of new health care technology such as mHealth apps. These sociodemographic factors were selected for this study based on previous research demonstrating their relevance in the adoption of mHealth and their association with security and privacy issues in the Saudi context [15]. The second part of the questionnaire (part 2) consists of 6 sections. The first section was designed to gather information on patients' awareness of mHealth apps connected to CISs. A total of 5 items (Q1-Q5) were adopted from previous research conducted by Aljedaani et al [15], with slight modifications to suit this study's context. The questions emphasize patients' awareness of access to their personal data, installation of trackers, and their self-reported awareness level of data privacy and security.

The second section focuses on patients' privacy concerns about mHealth apps. A total of 8 items (Q6-Q13) were used in this section, as described by Dhagarra et al [24], with slight modifications. The initial 3 items seek patients' concerns regarding the extent of information requested and those collected by health centers. Meanwhile, the remaining items emphasize concerns relating to access from authorized persons, nonaccurate storage of patient data, and measures taken to ensure data privacy.

The third section is designed to assess patients' concerns about data confidentiality in mHealth apps. A total of 6 items (Q14-Q19) are used in this section, as described by Aljedaani et al [15]. The first and second items seek patients' concerns relating to sharing confidential data, whereas the remaining 3 items focus on actions taken to ensure the confidentiality of data shared via mHealth apps.

The fourth section focuses on data security, comprising 8 items (Q20-Q27). These items were adopted from studies conducted by Aljedaani et al [15], Zhou et al [29], and Zhou et al [4]. Similarly, the items include actions to ensure data security, such as password settings, security policies and settings, encryption functions, and user authentication.

The PU/utility of mHealth apps was investigated in the fifth section, comprising 4 items (Q28-31) to document patients' responses to the expected effects of mHealth apps on productivity, performance, effectiveness, and accessibility to health care services. Meanwhile, PEOU was evaluated in the sixth section using 6 items (Q32-Q37) adopted from the sources reported for perceived utility. The last section contains 3 items (Q38-Q40) adapted from Dhagarra et al [24] to assess patients' BIs.

Finally, the questionnaire will be translated from English to Arabic by 2 experienced translators. After completing the translation process, both versions of the questionnaire will undergo pilot testing to assess the validity and reliability of the instrument. Findings from experts' opinions and pilot testing will be used to mitigate potential ceiling and floor effects from the questionnaire items that may impact accurate data interpretation. The developed questionnaire (see Multimedia Appendix 1) will be distributed either online (ie, Google Forms [Google LLC] and Qualtrics [Silver Lake Technology Management, L.L.C.]) or self-administered to selected patients and users of mHealth apps in Saudi Arabia. The method of administering the questionnaire will depend on the participants' preferences. Data obtained from both quantitative and qualitative approaches will be combined to provide a more robust assessment of the study.

Ethical Consideration

Ethical approval is vital for this study as the researchers will be recruiting patients and users of mHealth apps. The ethical approval for this research has been obtained from the Biomedical and Scientific Research Ethics Committee, University of Warwick (Reference number: BSREC 03/22-23), and the Medical Research and Ethics Committee, Ministry of Health in the KSA. Participation will be anonymous to ensure the confidentiality of participants throughout the research. No identifying details will be obtained from the participants during the research process. The researchers will also ensure the confidentiality of all information provided by the participants. The participants will be informed that they can decide to withdraw from the study at any time without any penalty. All collected data will be stored on a personal computer with a secure password and will only be accessible to authorized parties, including the supervisory team and the researchers.

Management and Quality Control Measures

Participants' anonymity will be protected in this research, and all data will be kept confidential without revealing the participants' identities. When submitting the results to sponsors or regulatory institutions, all participants' clinical records will be represented using a coding system, accessible only to the researchers. Each participant will be given 2 copies of consent forms signed by both parties. All data files will be stored in a single folder in a secured location.

This study does not expose participants to any risks, and no personal expenses will be incurred during the interview or survey completion. In addition, participation is not associated with any financial gain or incentives. All expenses will be covered by the research budget. Participation is voluntary, and there are no implications for the participants' health if they decide not to take part in the study. Participants can also request to terminate their participation at any time, regardless of the stage of the study, without any consequences to their care at the hospitals. The research findings will be published in journal articles and presented at conferences or meetings; however, participants' identities will remain confidential.

Several methodological resources, including a mixed method study design, inclusion criteria, and random sampling, will be used to ensure quality control and reduce bias during data gathering. Trained enumerators will conduct the interviews and perform data collection during the quantitative phase. Quality control will be further ensured by periodically assessing the

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enumerators to ensure adherence to the survey protocol. The retrieved questionnaire will be assessed in terms of data completeness and quality.

Data Analysis

The qualitative data will be transcribed, coded, and analyzed thematically using NVivo (version 12; QSR International), leading to the emergence of themes and subthemes. A reliability analysis based on Cronbach α will be performed to assess the internal consistency of the questionnaire. Items with a minimum Cronbach α value of .70 will be considered reliable and acceptable. We will use descriptive statistics to summarize the participants' background information. For questionnaire items measured on a scale, we will assess normality using the Smirnov-Kolmogorov test. The results will be presented as mean (SD) or median (interquartile range) based on the normality assessment. The statistical association between variables will be assessed using simple and multiple linear regression models. Both SPSS version 25 (IBM, Inc.) and SmartPLS (SmartPLS GmbH) will be used accordingly. In line with the study's objectives, measurement and structural models will be developed in partial least squares structural equation modeling (PLS-SEM) to evaluate the research hypotheses. PLS-SEM is selected because of its alignment with the predictive-oriented goals of this study.

Timeline

Participants for the qualitative study have been recruited, and interviews are scheduled to conclude by November 2023. Currently, participant recruitment for the quantitative phase is ongoing and anticipated to finish by May 2024. Data analysis is projected to be conducted by June 2024, with the research expected to be fully completed by August 2024.

Results

Ethical approval for this research has been granted by the Biomedical and Scientific Research Ethics Committee at the University of Warwick (Reference number: BSREC 03/22-23) and the Medical Research and Ethics Committee at the Ministry of Health, Saudi Arabia. In the qualitative phase, 15 participants have been interviewed, and interviews with the remaining 10 participants are scheduled to be concluded by November 25, 2023. Preliminary thematic analysis is currently ongoing. Concurrently, the quantitative phase is underway, with 150 participants providing signed informed consent to participate. Data collection for the quantitative segment is expected to conclude by May 2024, followed by data analysis in June 2024. The research is slated for completion by August 2024.

Discussion

Expected Findings

The research has demonstrated that patients' awareness of mHealth apps significantly predicts their adoption of the technology for health management [4,30]. Nevertheless, there remains a lack of research specifically addressing patients' concerns regarding data privacy and security, and how these concerns impact mHealth app usage. Consequently, the primary objective of this study is to empirically evaluate patients' awareness and perception of issues pertaining to the privacy, security, and confidentiality of data collected through mHealth apps in Saudi Arabia.

The results of this study will provide valuable insights to relevant stakeholders in pinpointing the factors contributing to low levels of awareness regarding data security and privacy, as well as identifying areas that require the highest level of attention. In addition, given that this study incorporates qualitative assessment, the analysis will uncover the underlying events that lead to discordant perspectives on mHealth apps. For instance, users who possess a heightened awareness of mHealth apps, understand the involvement of health care providers in data collection, and recognize the criticality of using collected patient data solely for medical purposes may exhibit greater concerns regarding data security and privacy.

Saudi Arabia's government has escalated its efforts to enhance the adoption and use of eHealth and telemedicine modalities through awareness campaigns and investments in the health care sector [12]. These strategies have the potential to positively impact stakeholders and influence the intention to use advanced health technologies. Nonetheless, no specific approaches have been taken to explore the perspectives of users and HCPs regarding the security and privacy of data collected via such apps. The results from this study will elucidate these aforementioned gaps in knowledge.

In this study, 4 overarching research hypotheses will be examined, drawing upon constructs from the TAM, including PEOU, PU, and BI, alongside patients' awareness and concerns regarding data privacy, security, and confidentiality. Previous research has indicated that users' awareness of data privacy stimulates their intention to adopt technology and share personal information [4,31]. Users' perspectives and concerns regarding the privacy of health information may influence the use of specific health care services, including mHealth [9]. However, many of these studies have been empirical in nature and lacked support from theoretical frameworks.

In this study, we hypothesize that PU and PEOU will directly influence users' concerns about data security, privacy, and confidentiality. PEOU refers to the ease of operating the technology, understanding its features, and the support available to address any difficulties encountered. We anticipate that at least one or more of these hypotheses will be supported, indicating that users' PU or ease of use of mHealth apps will increase once their concerns about data security, privacy, and confidentiality are addressed. Indeed, an effective approach to address users' concerns regarding data security is to ensure that they can easily navigate the technology and access its security features. These anticipated findings align with reports from previous studies that have identified various approaches to enhance the adoption and uptake of mHealth apps [32,33].

The qualitative phase of our study will reveal specific themes and subthemes that will be integrated with the empirical findings obtained from the quantitative data. Consequently, our research will help illuminate the factors that influence participants' concerns regarding data privacy, security, and confidentiality. By encompassing stakeholders, HCPs, and patients, our study

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will capture diverse perspectives, providing a comprehensive understanding of the issue. Previous research has shown that failure to address issues related to data security and privacy violations can have significant consequences on users' behavior and attitudes toward health care services [23,24]. Similarly, a recent review by Nurgalieva et al [34] highlighted that low levels of security and privacy are key factors contributing to the declining uptake of mHealth apps among the target audience. The expected themes in this study may also encompass negative perceptions, fear of data breaches, and the failure to address issues related to data security and privacy violations.

In addition, we aim to explore the association between participants' demographic attributes and their concerns regarding the privacy and security of mHealth apps. Previous research has indicated that married patients tend to exhibit higher levels of concern regarding information security and privacy, and they may desire more stringent security protection compared with single patients [4]. Furthermore, users earning less than US $10,000 annually demonstrated the weakest concerns about the privacy and security provided by mHealth apps. In addition to income, attributes such as age and educational background are anticipated to influence concerns regarding the privacy and security of mHealth apps within the context of Saudi Arabia. For example, individuals with higher levels of education are more likely to comprehend and stay updated on data security features within mHealth apps. This demographic is also more inclined to report any issues concerning data privacy or confidentiality to the app developer. Conversely, younger patients or users, who are often the primary users of numerous social media platforms with security notifications and authentication, may face an increased risk of exposure to events related to data breaches. In addition, younger individuals tend to spend more time on their smartphones compared with the older population. This increased usage may lead to greater exposure to potential security risks and, consequently, heightened concerns regarding the data privacy and security of mHealth apps.

Implications

This study holds significant implications for mHealth app developers, end users, and the health care system in Saudi Arabia. Strengthening the security and adoption of mHealth systems can be achieved more effectively when the perspectives of both developers and patients regarding mHealth apps are aligned [35]. The research findings can enable mHealth developers to pinpoint specific security features that urgently require adjustment to ensure the safety of patient health information, facilitate efficient health care service delivery, and maintain a balance between security and usability. Importantly, developers will directly gain insights from the primary stakeholders in mHealth apps: patients and end users. By contrast, patients will have the opportunity to express their perspectives on the security, privacy, and confidentiality of sharing their health data via mHealth apps. This feedback could lead to essential adjustments that can enhance both the security and the usability of such apps, as well as capitalize on the numerous advantages associated with integrating mHealth apps with CISs.

Saudi Arabia has introduced several mHealth apps to enhance health care service delivery, aligning with its Vision 2030 goals [12]. The findings from this study will shed light on underlying issues related to patients' and users' awareness of security and privacy features provided in mHealth apps implemented by the Saudi government. Therefore, the research outcomes may uncover certain factors contributing to the currently low adoption rate of mHealth apps among the population. Necessary adjustments in terms of decision-making, policies, and investments could be made to ensure that mHealth apps align with Vision 2030 goals, particularly in the realm of public health.

Limitations

Despite using a mixed method approach in this study, it is important to acknowledge certain methodological limitations. The inclusion and exclusion criteria used to select study participants may inadvertently exclude potential cases that could provide relevant information on the research topics. In addition, recruiting only patients for the survey and relying on survey instruments have inherent limitations, such as the potential for response bias. Furthermore, respondents may be hesitant to provide in-depth information during the interview process, which could impact the depth of data collected. These limitations may affect the generalizability of the results. Lastly, it is essential to note that this study uses a cross-sectional design, meaning that the findings will only depict associations between the studied variables, including PEOU, PU, and BI to use mHealth apps, as well as awareness and concerns regarding data privacy, security, and confidentiality. Therefore, no causal relationships can be inferred from the findings. Despite these limitations, the strengths of this study lie in addressing the scarcity of information on the research topic within the context of Saudi Arabia. Moreover, the study contributes to filling the gap in knowledge by using a mixed methods approach, which is relatively rare in existing literature.

Conclusions

The accumulation of evidence underscores the existence of a significant knowledge gap concerning the factors influencing patients' awareness and concerns regarding the privacy, security, and confidentiality of data collected via mHealth apps in Saudi Arabia. Similarly, the perspectives of stakeholders and HCPs on these issues remain incompletely understood. Given the increasing prevalence of smartphone usage, significant investments in mHealth apps, and efforts to promote the adoption of advanced health care systems in Saudi Arabia, this research holds relevance in uncovering a crucial aspect that could impede the attainment of these targeted goals. Policy makers and relevant bodies can use the findings to implement a model aimed at enhancing the adoption of mHealth apps and addressing issues related to the privacy, security, and confidentiality of data collected via such apps.

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Data Availability

Upon completing this study, the important data underlying the findings will be described in the paper at the time of publication. Additional data will also be provided in a supporting document.

Authors' Contributions

All authors have made substantial contributions to the work presented in this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire survey.
[PDF File (Adobe PDF File), 330 KB - resprot_v13i1e54933_app1.pdf]

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Abbreviations

BI: behavioral intention
CIS: clinical information system
HCP: health care professional
KSA: Kingdom of Saudi Arabia
mHealth: mobile health
PEOU: perceived ease of use
PLS-SEM: partial least squares structural equation modeling

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PU: perceived usefulness
TAM: Technology Acceptance Model
TRA: Theory of Reasoned Action

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Protocol

A Brief Workplace Training Program to Support Help-Seeking for Mental Ill-Health: Protocol for the Helipad Cluster Randomized Controlled Trial

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Abstract

Background: Most people with mental health problems do not seek help, with delays of even decades in seeking professional help. Lack of engagement with professional mental health services can lead to poor outcomes and functional impairment. However, few effective interventions have been identified to improve help-seeking in adults, and those that exist are not widely implemented to deliver public health impact. Co-designing interventions with people with lived experience of mental ill-health and other relevant stakeholders is critical to increase the likelihood of uptake and engagement with these programs.

Objective: This study aims to (1) test the effectiveness of a co-designed help-seeking program on increasing professional help-seeking intentions in employees in a workplace setting; (2) determine whether the program reduces mental illness stigma and improves help-seeking intentions and behavior, mental health literacy, mental health symptoms, and work and activity functioning relative to the control condition; (3) explore factors that facilitate broader implementation of the co-designed program; and (4) explore the cost-effectiveness of the co-designed program compared to the control condition over 6 months.

Methods: A 2-arm cluster randomized controlled trial will be conducted (target sample: N=900 from 30 to 36 workplaces, with n=25 to 35 participants per workplace). The trial will compare the relative effectiveness of an enhanced interactive program (intervention condition) with a standard psychoeducation-alone program (active control condition) on the primary outcome of professional help-seeking intentions as measured by the General Help-Seeking Questionnaire. Secondary outcomes include the impact on mental illness stigma; mental health literacy; help-seeking attitudes and behavior; work and activity functioning; quality of life; and symptoms of mental ill-health including depression, anxiety, and general psychological distress.

Results: Facilitators of and risks to the trial are identified and addressed in this protocol. Recruitment of workplaces is scheduled to commence in the first quarter of 2024.

Conclusions: If effective, the program has the potential to be ready for rapid dissemination throughout Australia, with the potential to increase appropriate and efficient service use across the spectrum of evidence-based services.

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Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12623000270617p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=385376

International Registered Report Identifier (IRRID): PRR1-10.2196/55529

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KEYWORDS

help seeking; mental health; workplace; employee; implementation; internet; psychiatry; psychology; mobile phone

Introduction

Background

In a 12-month period, 16.8% of Australian adults will experience an anxiety disorder and 4.6% will experience a major depressive episode [1]. Despite the high prevalence of common mental disorders, most people with a mental health problem will not seek help from a health professional [1]. Among those who seek help, delays of years or decades to seeking professional help are common [2,3]. The lack of engagement with professional services may lead to poorer outcomes in both mental health symptoms and functional impairment [4] and productivity loss [5-8]. While structural factors such as service accessibility impact help-seeking, we also know that individual factors such as the stigma of mental illness, the stigma of help-seeking, poor mental health literacy, and high self-reliance reduce the likelihood of an individual seeking help when experiencing symptoms of mental ill-health [9,10].

Mental Health Promotion Programs

Promotion programs that are universally delivered (ie, provided to all people in a population, regardless of risk or symptom level) have the potential to improve mental health. Such programs often involve targeting key barriers to help-seeking, such as knowledge or mental health literacy (including how, where, and when to seek help), and reducing stigmatizing attitudes toward help-seeking [11]. Facilitating pathways to professional help is critical, as treatment delays from the onset of symptoms can be as long as 8 years for depression and up to 23 years for anxiety disorders, leading to potentially significant and avoidable disability [3]. Mental disorders such as depression and anxiety can follow a chronic and treatment-resistant course in the absence of early intervention [12]. Therefore, there is increasing recognition of the need for promotion and prevention approaches.

Much of the evidence for the effectiveness of universal prevention programs on knowledge and mental health outcomes comes from adolescent settings [13,14], typically showing modest effects that may have a significant impact when delivered at scale. However, >50% of anxiety disorders and 75% of mood disorders emerge in adulthood [15], and they have high rates of relapse [16]. Workplaces offer an ideal environment to deliver prevention programs due to the significant proportion of adults in paid employment and the motivation among employers to ensure their employees remain well and productive. Prevention programs for adults delivered in the workplace typically focus on reducing emerging or subthreshold symptoms of depression, anxiety, or distress, with very modest effects for universally delivered programs [17]. A promising alternative approach is to promote help-seeking for distress by increasing knowledge about mental health and pathways into care, along with reducing stigmatizing attitudes about mental ill-health [18,19]. However, very few help-seeking promotion programs have been evaluated in general adult populations, with just 2 focusing on workplaces [20] and neither being implemented broadly. Consequently, there may be untapped opportunities for developing and implementing evidence-based mental health promotion programs within workplaces that ultimately lead to greater support for adults who experience mental distress.

Co-Design and Online Delivery Modes

The COVID-19 pandemic has dramatically accelerated the need for mental health programs [21], particularly those delivered distally [22]. However, few effective programs have been identified for improving help-seeking in adults [23], and existing interventions are not widely implemented to deliver public health impact [19,24]. Web-based mental health interventions are cost-effective [25] and can be widely disseminated [26], but they can have high dropout rates, increasing the need for co-design to improve acceptability [27]. There is increasing recognition of the expertise of people with lived experience of mental health problems in research, and the important insights end users of a product or service can bring to the research process, by improving translation, real-world impact, and responsive practice [28]. Co-design involves partnering with end users during all stages of designing and developing a product or service. Using this method enhances the potential that the service can be tailored to the target population, creating a strong potential to foster a sense of empowerment and ownership, which in turn may improve the uptake of and engagement with the service [27].

This Study

Programs that promote help-seeking intentions and behaviors can reach large proportions of people when delivered at scale within workplaces. This paper is a protocol for a cluster randomized controlled trial (RCT) that will provide a robust evaluation of the effectiveness and cost-effectiveness of a novel co-designed program for improving help-seeking in workplaces. Furthermore, this study examines potential factors that may impede or enhance the subsequent delivery and implementation of the program.

Aims

The aims of this study are as follows:

1. To test the effectiveness of a co-designed help-seeking program (the Helipad program) on increasing professional help-seeking intentions (primary outcome) in employees

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in a workplace setting at posttest (primary end point) and the 6-month follow-up
2. To determine whether the program reduces mental illness stigma and improves help-seeking attitudes and behavior, mental health literacy, mental health symptoms, quality of life, and functioning (secondary outcomes) relative to the control condition at the 6-month follow-up
3. To explore factors that facilitate broader implementation of the co-designed program
4. To explore the cost-effectiveness of the co-designed program compared to the active control condition from the health sector and societal perspectives at the 6-month follow-up

Hypotheses

To investigate the abovementioned aims, we propose the following hypotheses.

Primary Hypothesis (Aim 1)

- Hypothesis 1: Help-seeking intentions will be higher in the Helipad co-designed interactive program condition relative to the control condition (standard psychoeducation only) at posttest.

Secondary Hypotheses (Aim 2)

- Hypothesis 2: Mental illness stigma will be lower and mental health literacy and help-seeking attitudes will be higher in the Helipad co-designed interactive program condition relative to the control condition (standard psychoeducation only) at posttest.
- Hypothesis 3: Help-seeking behavior will be greater in the Helipad co-designed interactive program condition among people with elevated symptoms of depression or anxiety relative to the control condition (standard psychoeducation only) at the 6-month follow-up.
- Hypothesis 4: Symptoms of mental ill-health will be lower and quality of life and functioning will be higher in the Helipad co-designed interactive program condition relative to the control condition (standard psychoeducation only) at the 6-month follow-up.

Exploratory Hypotheses (Aim 3)

We do not have any specific hypotheses for factors that facilitate broader implementation of the program as this is exploratory; furthermore, we will use interviews with participants to explore this aim.

Exploratory Hypotheses (Aim 4)

The Helipad program will be cost-effective relative to the active control (psychoeducation) at the 6-month follow-up from health sector and societal perspectives relative to the willingness-to-pay thresholds identified by the Productivity Commission report on mental health [29].

Methods

Trial Design

A 2-arm cluster RCT will test whether the Helipad co-designed interactive program increases help-seeking intentions in employees in workplaces more than the standard psychoeducation-alone program. Workplaces will be randomly allocated using minimization processes to either (1) the active intervention condition comprising the Helipad program or (2) an active control condition (a web-based time-matched standard psychoeducation program). Help-seeking intentions will be assessed at the individual level accounting for clustering by workplace. Self-report assessments will be conducted on the web at preintervention, immediately postintervention, and at the 6-month follow-up. This study protocol addresses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [30].

The flow of participants through the study is presented in Figure 1.

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Figure 1. Cluster randomized controlled trial flowchart for the Helipad brief workplace training program to support help seeking for mental ill-health.

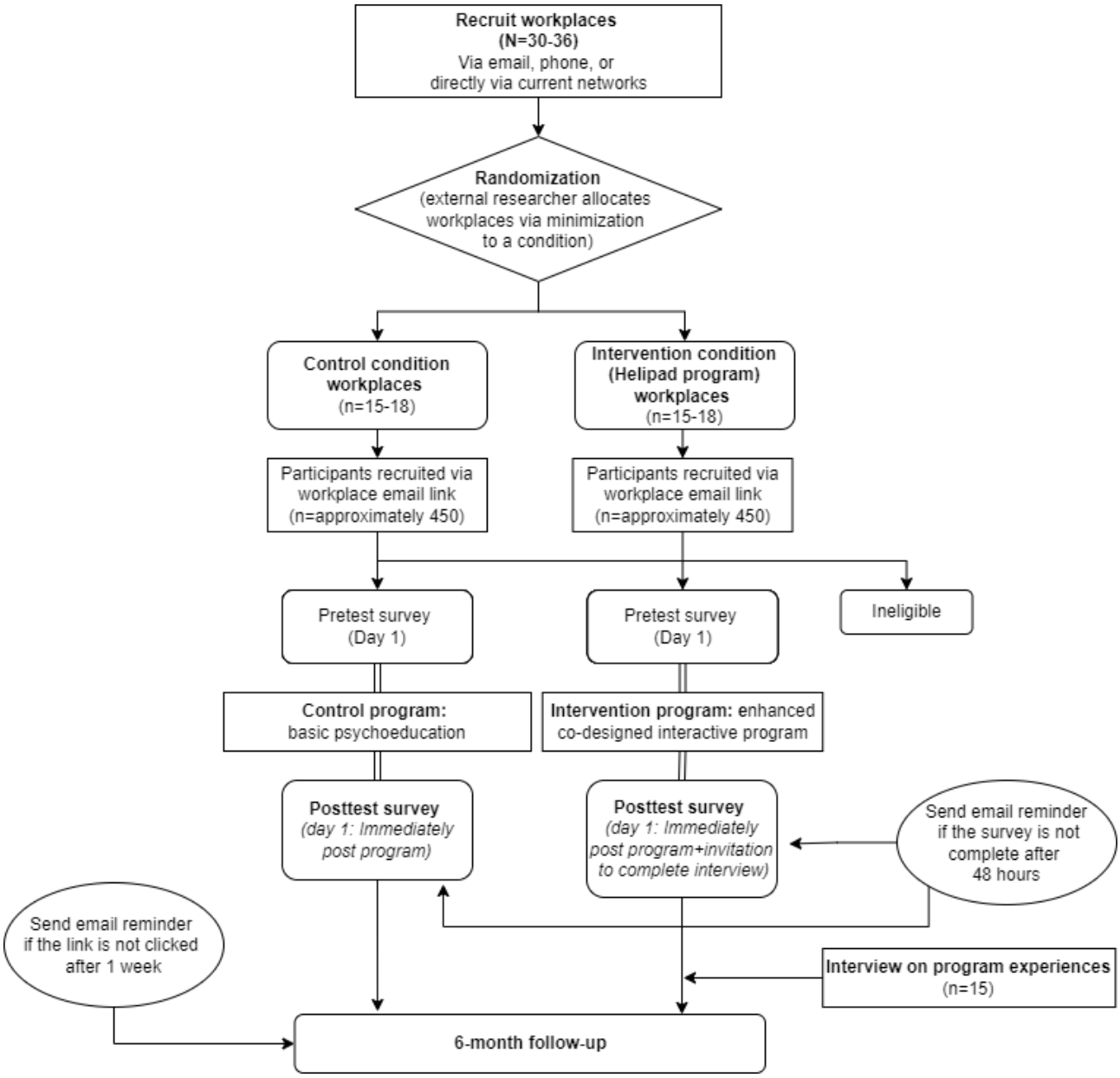

Interventions

The Helipad Program

A co-design working group was convened to develop the program from May to October 2023. Two authors, who identify as lived experience researchers (AG and CH), facilitated and led the co-design working group. The program was developed using principles of community-based co-design research, which are particularly appropriate in implementation research that focuses on the relevance and uptake of interventions within and across organizations [31]. The co-design group comprised 9 team members from the community. In addition, 2 web development team members were consulted during the later stages of the co-design working group's activities. All 9 community co-design team members were currently employed, and almost all identified as belonging to >1 group (consumers: 6/9, 67%; carers: 5/9, 56%; managers: 2/9, 22%; human resources staff: 2/9, 22%; and clinician: 1/9, 11%). The co-design process is outlined in detail in a separate paper (Gulliver et al, forthcoming).

The resulting co-designed program, called Helipad, is brief and takes approximately 20 minutes to complete. Brevity was essential to ensure that the information provided could be easily digestible and did not form a barrier to completing the program.

The Helipad program consists of 5 interactive modules addressing the core issues described by the co-design group as being important to facilitating help-seeking in workplaces (Textbox 1). The modules have been designed to be highly interactive, including clickable diagrams, videos of health professionals and people with lived experience, and interactive quizzes.

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Textbox 1. Interactive modules of the Helipad program.

Modules

1. Recognizing symptoms: explores signs and symptoms via a traffic light model (red, orange, and green indicators) of mental health. This module comprises an interactive map of the body that explains how we can recognize signs, symptoms, or indicators in our minds and bodies that tell us we might need to pay attention to our mental health and suggests what we can do about it.
2. Seeking support: answers questions regarding how, where, and from which health professionals to seek help for mental health and how each provides assistance. Moreover, it demystifies the process of seeking help by providing a specific example pathway (ie, accessing a psychologist with or without a referral from a general practitioner [GP]) and 3 videos of health professionals (Employee Assistance Program, psychologist, and GP) explaining what they do to support people's mental health.
3. Treatment options: provides information regarding evidence-based treatment options including psychological treatment, medication, exercise, and lifestyle treatments for common mental health problems, such as depression and anxiety. The psychological strategies were focused primarily on strategies approved by the Australian Government Medicare Benefits Schedule (MBS [32]), which are the most accessible evidence-based treatments available through the MBS, such as cognitive behavioral therapy (CBT), with medical and lifestyle treatments suggested by members from the co-design group. Furthermore, this module contains a practical example of a specific CBT strategy called "cognitive restructuring," works and an exercise on identifying people who may support them during challenging times.
4. Helping others: explores how to help others in the workplace who may disclose their experiences of mental ill-health and provides some examples about how different responses to this disclosure can affect the outcome for the person experiencing a mental health issue. In addition, this module contains a video of a manager discussing their experience of an employee who disclosed their mental health issue.
5. Supportive workplaces: addresses stigmatizing attitudes toward mental ill-health, help-seeking, and disclosure in the workplace. This module contains 3 videos of peers describing their experiences of disclosing in the workplace, myth-busting information in the form of a quiz on common mental disorders of depression and anxiety, and information targeting concerns about disclosure of mental ill-health in the workplace.

Active Control Program

The active control condition was chosen to maximize participant and organizational engagement in the trial and provide a strong test of the efficacy of the active ingredients of the Helipad program. The program comprises 5 time-matched standard written psychoeducation modules about mental health and well-being. The modules comprise written content from the National Institutes of Health News in Health newsletters [33] that was minimally edited by the research team (eg, to combine content from separate papers on the same topic). Written content focused on education on signs and symptoms of common mental health conditions of depression and anxiety disorders and how aspects of our lives (ie, sleep, exercise, relationships, and stress) impact our mental health. However, this program did not contain detailed information regarding treatment options, content explicitly targeting stigma reduction (eg, contact via peer stories), or how or where to seek help from health professionals. Furthermore, the content was not co-designed, is minimally interactive, and does not provide targeted information about help-seeking processes. Psychoeducation has been shown to increase mental health literacy and may have modest effects on reducing stigma but does not typically translate into changes in behavioral intentions such as help-seeking [24].

The modules are as follows:

1. Sleep and well-being: contains information regarding sleep, including sleep stages, sleep quality and duration, and how lack of sleep affects our overall health and well-being.

2. Exercise and physical health: provides information on how exercise is beneficial for health and well-being and tips on how to increase overall physical activity.

3. Mental health: provides information on depression and anxiety disorders, including signs and symptoms and how they can be treated.

4. Social relationships and health: explores how social relationships affect our health in both positive and negative ways and how social support may buffer stress.

5. Stress and health: provides information regarding stress, including the impact of stress on our physical and mental health and how we can reduce stress in daily life.

Recruitment Procedures and Randomization

Workplace Recruitment

Recruitment of workplaces is expected to be conducted using our existing networks through the The Mental Health Australia General Clinical Trials Network. We plan to recruit approximately 30 to 36 workplaces, with 25 to 35 participants per workplace to meet our total sample size target of 900 adult participants. Workplaces will be eligible if they (1) report having at least 50 employees to ensure that each cluster is viable and (2) have an Employee Assistance Program (EAP) available for their staff to ensure that employees experiencing mental health concerns can access effective and immediate care. Any industry of work is eligible for inclusion. A mixture of general and high-risk workplaces (ie, those likely to be exposed to situations that may impact mental health, such as health care settings) initially in the Australian Capital Territory, New South Wales, and Victoria are being targeted. Recruitment is highly feasible based on previous public health trials conducted by the team (N=849 to 2773 [34-36]), and our universal cluster-based trials have typically recruited high numbers (eg, N=1477 [37] and N=1633 [38]).

We will invite workplaces through multiple channels, including directly via an email invitation addressed to the "key representatives" from a workplace such as managers or staff in charge of human resources, via telephone calls, and via invitation emails to employees in our existing networks. We will contact the workplace key representatives who express

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interest to determine organization characteristics and eligibility for the study.

Randomization

Given the cluster design, we will use a minimization approach to randomization [39]. Minimization is a type of randomization where the first participant (or cluster) is randomized and subsequent selections are allocated in a way that minimizes the imbalance on specific factors between groups. This method is helpful for a design with few participants (or clusters) and has the advantage of making each condition more closely matched on key factors across the trial. To implement this, we will use a preprogrammed computer algorithm that will assign each new workplace recruited into the trial into a condition. This process will aim to balance across conditions on the following key workplace characteristics: (1) workplace type (office-based vs non–office based), (2) organization size (<200 vs >200 employees), and (3) location (Australian Capital Territory or New South Wales or Victoria vs other Australian state or territory). Once a workplace has been allocated a condition, we will discuss with their key representative what participation in the trial involves and provide them with an email or SMS text message (depending on their preferred communication with employees) with an embedded link to their assigned study recruitment website. We expect the text to read as follows:

> *Would you like to participate in a research study testing a new resource for supporting employee wellbeing? Learn more about your mental health and wellbeing by completing a survey and a brief online program today: <link>.*

We will ask the workplaces to send invitations to all their employees themselves, with each workplace determining who from within their organization will send this invitation. This process is designed to increase ecological validity, as the goal for the program is for it to be delivered by workplaces, we expect this to be a minimal burden (ie, 1 or 2 SMS text messages or emails) on the workplace administration staff tasked with sending invitations.

Participant Recruitment and Informed Consent

Participants will be recruited on the web through participating workplaces. To be eligible for the trial, potential participants must fulfill the following criteria:

- Be an employee in a participating Australian workplace
- Be aged ≥18 years, living in Australia, and fluent in reading and understanding English
- Have access to a device (eg, desktop, laptop, tablet, or smartphone) and a reliable internet connection

If participants complete the abovementioned screening criteria and are not eligible, they will be informed and provided with a list of relevant help-seeking resources.

After being assigned a condition, the workplace will send a brief email or SMS text message to their employees inviting them to participate in the trial (refer to the Randomization section for an example). The email or SMS text message will contain a link to the web page containing information about the study. Then, the employees who click the link provided by their employers will be taken to the information and consent web-based page, where they will be invited to read the information that the study and provide their consent to participate in the study on the web. This process will be confidential, and their work organization will not be informed of who among their employees has consented to participate in the trial. Participants can complete the preintervention, program, and postintervention survey in a single session. Furthermore, participants can save their progress at the bottom of the screen if they wish and re-enter the survey or program at the last point they left off by reaccessing the link from their email or SMS text message. In addition, they will be sent reminders to complete the program if they have not done so within the expected time frames (Figure 1).

Outcomes

Estimand

In workplace employees, what is the between-group difference for the Helipad co-designed web-based program compared with the standard psychoeducation web-based program as measured by change from preintervention to immediately postintervention on help-seeking intentions on the General Help-Seeking Questionnaire (GHSQ)?

Primary Outcome

Help-seeking intentions (hypothesis 1) will be assessed based on increased intentions to seek help on the GHSQ completed at posttest.

Secondary Outcomes

Effectiveness will be compared between the Helipad co-designed interactive program condition and the standard psychoeducation web-based program condition for mental illness stigma, mental health literacy, and help-seeking attitudes (hypothesis 2), which will be assessed, respectively, based on reduced mental health stigma (Stigma and Self-Stigma Scales [40]), increased mental health literacy (Anxiety Literacy Questionnaire [A-Lit] and Depression Literacy Questionnaire [D-Lit] composite measure [41,42]), and increased help-seeking attitudes (Attitudes Toward Seeking Professional Psychological Help Scale-short form [43]) over time relative to the control condition.

In addition, we will examine the comparative effectiveness of the Helipad co-designed interactive program condition and the standard psychoeducation web-based program condition on reducing symptoms of mental ill-health and increasing quality of life and functioning (hypothesis 4). This will be determined based on reduced symptoms over time of depression (Patient-Reported Outcomes Measurement Information System [PROMIS] Depression short form scale [44]), anxiety (PROMIS Anxiety short form scale [44]), and general psychological distress (Distress Questionnaire-5 [DQ5] [45]) and increased scores on the Recovering Quality of Life (ReQoL-10) Questionnaire [46] and increased work and activity functioning (Work Productivity and Activity Impairment [WPAI] questionnaire [47]).

Finally, the relative effects of the program on increasing help-seeking behavior (hypothesis 3) will be assessed by the proportion of participants who reported seeking help from a

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professional source (defined as a psychologist or counselor, a psychiatrist, a family doctor or general practitioner [GP], or an EAP) in the past 6 months. We anticipate that this will be greater in the Helipad co-designed interactive program group among people with elevated symptoms of depression or anxiety relative to the control condition (standard psychoeducation only).

The primary end point for changes in mental health literacy is the posttest assessment, while for the other secondary outcomes, the 6-month follow-up assessment will be the primary end point as these outcomes take longer to elicit change.

Data Analysis

An intention-to-treat approach to account for missing data of the mixed model repeated measures ANOVA (continuous data) or mixed effects logistic regression (binary data) will be used, adjusting for intraclass correlation to account for clustering effects within each site. Mixed models include all available data and account for within-individual variability, including those participants with missing data points, under the missing-at-random assumption [48].

Exploratory analyses will examine evidence for moderators or mediators of outcome and will be reported separately from the primary and secondary outcomes. Implementation outcomes at 6 months will be separately examined using description statistics, including *t* tests (2-tailed). The economic analysis will examine cost-effectiveness from the health sector and societal perspectives. The cost of the Helipad intervention and the active control program will be estimated using microcosting methods. Service use data will be limited in this study to health care professional visits or services accessed (internet program and helpline) specifically for mental health. The additional costs of health care resource use will be operationalized as the number of contacts with health professionals collected on the Actual Help-Seeking Questionnaire [49] (psychologist or counselor, psychiatrist, family doctor or GP, EAP, phone helpline, and internet-based treatment program). Lost productivity will also be evaluated in societal perspective costs as assessed through the WPAI questionnaire [47] and valued using the human capital approach. The ReQoL-10 Questionnaire [46] will be used to calculate utility values and quality-adjusted life years (QALYs) using the area under the curve method. Differences in costs between trial groups will be compared to the differences in QALYs through an incremental cost-effectiveness ratio (ICER) because of the inherent value-for-money connotations associated with cost-effectiveness ratios using QALYs. Additional ICERs using secondary outcomes will be calculated where the Helipad intervention is found to have an effect. Nonparametric bootstrapping will be used to determine CIs for ICERs.

In addition, we will report proportions of participants who improve, decline, and do not change on outcome measures. Automatically collected aggregate use data will also be analyzed, including information on how many participants access each page, location, average time on each page, video view count data, and clicks to external links.

Trial Delivery

The trial will be delivered using a custom-designed website that will contain the 2 web-based programs. This website will allow self-report assessments, intervention materials, and email reminders to be delivered seamlessly to the participants. Furthermore, the website will collect and securely house the survey data collected. To streamline access and reduce the need for participants to create log-ins while maintaining security and confidentiality, participants will only need to provide an email to access the program.

If surveys or the program are discontinued, participants will be emailed a single reminder (at 48 hours if they discontinue any part of the preintervention, program, and postintervention survey and 1 week for the 6-month follow-up survey) with a unique link to access the program from their email account to continue from where they left to complete that part of the study. We expect most participants will complete the preintervention, program, and postintervention surveys in one 40-minute sitting. As such, we do not anticipate that these reminders will be needed frequently; however, given that people could discontinue the program or surveys, we have a method to reconnect them with the study.

Data Collection

Overview

Participants who agree to participate in the trial by clicking the link will be asked to provide an email address and complete a brief 10-minute baseline questionnaire. Following completion of the baseline questionnaire, participants will immediately be given access to the web-based program (approximately 20 minutes), which will be followed immediately by the 10-minute posttest questionnaire survey. The 10-minute follow-up survey link will be sent to participants via email 6 months after completion of their allocated condition.

Assessments and Blinding

Table 1 presents the trial measures and assessment time points. Assessments will occur at baseline (pretest), posttest, and 6 months after the program is completed. The trial will be triple blinded. Participants will be blinded as far as possible to the condition; they will only be informed that their workplace has been randomized to receive one of two programs: (1) an enhanced interactive mental health education program or (2) a standard written psychoeducation program. We will not provide participants with information about which program is expected to be the most effective. The statistician who will perform the analyses will be blinded to condition allocation (triple blind). Finally, assessments will also be blinded, as they rely on participants independently completing self-report measures on the web.

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Table 1. Assessment time points for the Helipad cluster randomized controlled trial of a brief workplace training program to support help-seeking for mental ill-health.

Construct	Measure	Presurvey	Postsurvey	6-month follow-up survey
Gender	What is your gender?	✓		
Age	What is your age?	✓		
Language spoken at home	What language do you usually speak at home?	✓		
Ethnicity	How would you describe your ethnicity?	✓		
Education	What is the highest level of education that you have completed?	✓		
Employment status	What is your current employment status?	✓		
Industry	What industry are you employed in?	✓		
Help-seeking intentions	GHSQ[a]	✓	✓	✓
Help-seeking attitudes	ATSPPH-SF[b]	✓	✓	✓
Help-seeking behavior: service use type and quantity	AHSQ[c]	✓		✓
Mental illness stigma	(SASS[d]-modified)	✓	✓	✓
Mental health literacy	D-Lit[e] or A-Lit[f] composite	✓	✓	✓
Depression symptoms	PROMIS[g] Depression-Short Form	✓		✓
Anxiety symptoms	PROMIS Anxiety-Short Form	✓		✓
General psychological distress	DQ5[h]	✓		✓
Work and activity impairment	WPAI[i]	✓		✓
Quality of life	ReQoL-10[j]	✓		✓
Adverse events	Did you have any unexpected or negative experiences that might be related to completing this program?		✓	✓
Intervention acceptability	AIM[k]		✓	
Intervention appropriateness	IAM[l]		✓	
Intervention feasibility	FIM[m]		✓	
Debriefing	Explanation of study			✓
Interview	Interest in an interview		✓	

[a]GHSQ: General Help-Seeking Questionnaire.

[b]ATSPPH-SF: Attitudes Toward Seeking Professional Psychological Help Scale-short form.

[c]AHSQ: Actual Help-Seeking Questionnaire.

[d]SASS: Stigma and Self-Stigma Scales.

[e]D-Lit: Depression Literacy Questionnaire.

[f]A-Lit: Anxiety Literacy Questionnaire.

[g]PROMIS: Patient-Reported Outcomes Measurement Information System.

[h]DQ5: Distress Questionnaire-5.

[i]WPAI: Work Productivity and Activity Impairment.

[j]ReQoL-10: Recovering Quality of Life-10.

[k]AIM: Acceptability of Intervention Measure.

[l]IAM: Intervention Appropriateness Measure.

[m]FIM: Feasibility of Intervention Measure.

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Measures

Demographic Characteristics

These demographic characteristics are planned for assessment at preintervention: gender (male, female, nonbinary, different term, or other), age (18 to 25, 26 to 35, 36 to 45, 46 to 55, 56 to 65, or >66 years), ethnicity (open ended: "how would you describe your ethnicity"), language spoken at home (English only, English and another language, or another language only), level of education (primary school, some secondary school or year 10 equivalent, year 12, Certificate level I-IV, Diploma or Associate degree, Bachelor degree, Graduate Diploma or Graduate Certificate, Master degree, or Doctoral degree), employment status (eg, full time, part time or casual, unemployed, or not currently working due to studying or maternity leave), and work industry (business, consultancy, or management; accountancy, banking, or finance; charity and voluntary work; creative arts or design; energy and utilities; engineering or manufacturing; environment or agriculture; health or social care; hospitality or events; computing or Information Technology; law; law enforcement and security; leisure, sport, or tourism; marketing, advertising, or public relations; media or digital; property or construction; public services or administration; recruitment or human resources; retail or sales; science or pharmaceuticals; teacher training or education; and transport, logistics, or other).

Help-Seeking Intentions (Primary Outcome)

Help-seeking intentions will be measured by the intentions scale of the GHSQ [50]. The scale is an index, which for this study comprised 11 items measuring intentions to seek help "if you were having a personal or emotional" problem. Consistent with the GHSQ as a flexible index of help-seeking sources, we modified the scale to group nonprofessional informal sources together, that is, "partner, friend, parent, other relative/family member." Furthermore, we added "Employee Assistance Programs," and "internet-based treatment programs" to the potential sources of help and separated mental health professionals (ie, psychologists or counselors vs psychiatrists) to allow for economic analysis. Each source of help is rated on a 7-point Likert-type scale ranging from 1 (extremely unlikely) to 7 (extremely likely), with a midpoint at "unsure." Item scores range from 1 to 7, with higher scores indicating greater intentions to seek help from that particular source.

Help-Seeking Attitudes

The help-seeking attitudes of participants will be measured using a 5-item updated version [51] of the Attitudes Toward Seeking Professional Psychological Help Scale-short form [43]. The 5 items retained were the positively-worded items of 1, 3, 5,6, and 7 and were selected based on factor loadings [52,53]. The scale asks respondents to indicate on a 4-point Likert-type scale (0=disagree and 3=agree) to what extent they agree with statements regarding psychological treatment (eg, "If I was having personal or emotional problems, the first thing I would do is seek professional help"). Scores are summed to produce a possible range of 0 to 15, with higher scores indicating more positive attitudes toward seeking professional help. Both the 5-item modified short form (Cronbach α=0.72) [52] and the 10-item scale have demonstrated sound psychometric properties [43,51,54].

Help-Seeking Behavior

Help-seeking behavior will be assessed by the proportion of participants reporting seeking help from a professional help-seeking source in the past 6 months on the Actual Help-Seeking Questionnaire [49]. This questionnaire consists of 10 items measuring self-reported help-seeking behavior. Participants are provided a list of help-seeking sources (matched to the abovementioned list for the intentions scale) and asked to indicate where, if any, they have "gone to for advice or help in the past 6 months for a mental health problem." Furthermore, participants can indicate if they had seen someone else not listed, that they had not spoken with anyone about their problems, or that they had not experienced any problems. The number of visits to each health professional (psychologist or counselor, psychiatrist, family doctor or GP, and EAP) or the number of times a service was accessed (internet program and helpline) will also be assessed. Items from this scale specifying the number of contacts with each health professional or service will be used for the economic analysis.

Mental Health Literacy

Mental health literacy will be assessed using a bespoke measure generated by combining items from the D-Lit [41] and A-Lit [42]. The scale comprises 11 items (5 from the D-Lit questionnaire, 5 from the A-Lit, and 1 new item) that ask respondents to indicate their knowledge on a scale of true, false, or do not know for statements regarding the symptoms and treatment of depression and anxiety. Example items include "Depression does not affect your memory and concentration" (false) and "Generalized anxiety disorder is a common cause of workplace disability" (true). The new item added for this study was "Avoiding professional help for my mental health is unlikely to have an effect on my health long-term" (false). The original scales have good internal consistency and reliability, and scores on the bespoke measure will range from 0 to 11 (correct response=1 point), with higher scores indicating higher literacy [41,42].

Mental Illness Stigma

To measure stigma, we adapted the "stigma to others" scale from the Stigma and Self-Stigma Scales for attitudes toward mental health problems [40]. We generated a bespoke 4-item scale by retaining 4 of the 6 original items and slightly altering the wording (eg, changing mental disorder to "mental illness" for clarity and removing the word "suffering"). One item was removed due to a low factor loading of 0.32, and another item was double barreled and duplicated another item; therefore, we retained the item with the higher factor loading, leaving 4 items rated on a 5-point scale from 0=strongly disagree to 4=strongly agree: "Employees with a mental illness are less reliable than other employees," "People with a mental illness are weak," "People with a mental illness should just "snap out of it," and "People with a mental illness are not really ill." The original stigma to others scale demonstrated good validity and internal consistency (Cronbach α=0.71) [40]. Scores range from 0 to

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16, with higher scores indicating higher stigmatizing attitudes toward mental illness.

Depression and Anxiety Symptoms

Depression and anxiety symptoms will be assessed using the PROMIS depression and anxiety [44] short form scales. They both comprise 8 items, each assessing the frequency of symptoms of depression or anxiety, respectively, during the past 7 days. The depression scale focuses on negative mood (eg, feeling unhappy), decrease in positive affect (eg, nothing to look forward to), and negative views of the self (eg, feeling helpless and worthless). The anxiety scale focuses on fear (eg, fearfulness), anxious misery (eg, worry), and hyperarousal (eg, tension and nervousness). Items are rated on a 5-point scale ranging from 1=never to 5=always, and the item scores are summed to produce an overall score ranging from 8 to 40, with higher scores indicating higher symptom severity. Both short forms correlate highly with the original scales (r=0.96) and demonstrate validity, with the depression scale correlating with the Center for Epidemiological Studies-Depression Scale (r=0.81) [44] and the anxiety scale correlating with the Mood and Anxiety Symptom Questionnaire (r=0.80) [44].

General Psychological Distress

We will measure general psychological distress on the DQ5 [45]. The DQ5 comprises 5 items that ask the respondents to indicate the frequency with which they have experienced a range of distressing situations, thoughts, and feelings over the previous 30 days. The scale assesses these statements on a 5-point Likert scale ranging from 1=*never* to 5=*always*. Items include “My worries overwhelmed me,” “I felt hopeless,” and “I found social situations upsetting.” Scores are summed to produce a total score (range 5-25), with higher scores indicating more severe levels of psychological distress. The DQ5 has demonstrated high internal consistency (Cronbach α=0.86) and validity in previous studies [45,55].

Quality of Life

To measure the impact of the program on quality of life and for the economic evaluation, we will use the ReQoL-10 Questionnaire [46], which is a validated measure and highly suitable for measuring recovery and quality of life in the mental health context. The ReQoL-10 comprises 11 items, including 10 focused on mental health and 1 focused on physical health. The mental health items assess the frequency experienced over the last week of the thoughts, feelings, or activities mentioned, such as “I could do the things I wanted to do” and “I felt lonely,” assessed on a scale from 0=none of the time to 4=most or all of the time. Negatively worded items are reverse scored. The 11th item assesses the severity of physical health problems, including “problems with pain, mobility, difficulties caring for yourself or feeling physically unwell” experienced on a 5-point scale from 4=no problems to 0=very severe problems. The scale has been validated, with Cronbach α ranging from 0.87 to 0.92 [46,56], and has been used in economic evaluations of mental health interventions [57]. A UK-derived value set will be used to calculate utility values at each time point. The area under the curve method will be used to calculate QALYs from utility values.

Work and Activity Functioning

The WPAI questionnaire will be used to measure the effect of health problems on the ability of the participants to work and perform daily activities, and it will also be used for economic evaluation purposes. We altered the original WPAI questionnaire to assess days (as opposed to hours) during the past month (30 days). The original WPAI questionnaire comprises 6 questions; we will omit the first question which asks if the respondent is employed given our target group, retaining the 5 questions targeting (Question 1, Q1) the number of days missed due to health problems, (Q2) the number of days missed for other reasons, (Q3) the number of days worked, and (Q4) degree health problems affected productivity while working on 0 to 10 Visual Analogue Scale (VAS); (Q5) degree that health problems affected productivity in regular unpaid activities on 0 to 10 VAS [47]. We will derive percentage scores for absenteeism, presenteeism, work productivity loss, and activity impairment based on the predefined scoring methods [58]. Previous studies have provided support for the validity of the original scale [59].

Implementation Measures: Acceptability, Appropriateness, and Feasibility

To provide information regarding implementation outcomes, we will use the 3 measures designed by Weiner et al [60] that assess the acceptability, appropriateness, and feasibility of the intervention. Each of the 3 scales has 4 items assessing the acceptability (eg, “the intervention is appealing to me”), the appropriateness (eg, “the intervention seems suitable”), or the feasibility (eg, “the intervention seems easy to use”) of the program. The items are responded to on a scale ranging from 1 to 5, where 1=completely disagree and 5=strongly agree. Total scores on each scale can range from 4 to 20, with lower scores indicating a lack of each construct (acceptability, appropriateness, and feasibility). The scales demonstrate good validity, and the internal consistency is high for the 4-item scales, with Cronbach α ranging from 0.85 to 0.91 [60]. In addition, we will examine adherence levels (intervention completion), attrition, and factors associated with these indicators of engagement. Follow-up interviews (described in the Quality Assurance and Monitoring section) will also be used to inform the future implementation of the intervention in workplaces.

Power and Recruitment

Our study’s power and sample size estimations were informed by the primary outcome measure: the level of intention to seek help from professional sources, as measured by the GHSQ. Using data from the MATES in Construction workplace trial [61], a conservative intraclass correlation of 0.02 was assumed to estimate the design effect. An RCT [62] exploring the potential effectiveness of a web-based program designed to increase help-seeking intentions for social anxiety disorder informed the anticipated difference between pre- and posttest GHSQ scores (standardized mean difference=0.2). Because the size of the workplace clusters could not be anticipated ahead of time, a conservative average cluster size ranging from 25 to 35 was assumed. We assumed 15% attrition in participant numbers from pre- to postintervention, a conservative assumption based on previous workplace trials [63] and accounting for the

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single-session nature of the intervention. To detect an effect size of Cohen *d*=0.2 between the intervention and comparison arms with 80% power, using a 2-tailed type I error level of 0.05, we need to recruit between 30 and 36 workplaces (assuming each workplace has 25 to 35 participants), resulting in a minimum of 900 employees.

Quality Assurance and Monitoring

Overview

The project manager and research officer will be responsible for the day-to-day administration of the research. They will meet regularly (fortnightly to monthly, depending on the trial needs) with the primary investigator (PJB) to discuss the research progress. Other investigators will attend these meetings as needed, and full team meetings will be conducted several times per year throughout the project. Recruitment of trial sites and tracking of participant numbers will be monitored closely.

Follow-Up Interview

In the follow-up survey, participants in the active intervention condition will be asked to indicate their willingness to be interviewed regarding their experience using the program by a member of the research team after the 6-month trial period ends. Interviews will explore experiences using the program and ideas to facilitate implementation. We expect that up to 15 interviews will be required to obtain a breadth of different experiences from participants from different workplaces, work levels (eg, management and employees), ages, and genders on their experiences and views on the co-designed program. Interview participants will be selected based on this diversity. The interview will be recorded on Zoom (Zoom Video Communications, Inc) or audio recorded over the telephone for accuracy, with the audio recording only stored on secure Australian National University (ANU) IT servers. The recordings will be transcribed for analysis by a professional external transcription company. Any references to the participants' name or workplace will be removed in transcription to reduce the chance of identification in any publications. Consent for participating in interviews, recording of interviews, and using interview data for publication will be obtained separately for the trial. Participants will be emailed an Aus $50 (US $33) e-gift card to remunerate for their time and effort participating in an interview. Participants will receive an e-gift card if they commence the interview, regardless of whether they finish it or not.

Ethical Considerations

Overview

The ethical aspects of this study have been approved by the ANU Human Research Ethics Committee (protocol number 2023/053). Participants will be presented with comprehensive information regarding the study before providing informed consent on the web. Participants will not be provided with compensation for participating in the study.

Ethical issues in the literature relevant to this study relate predominantly to the potential for coercion; the use of internet-based programs; and workplace confidentiality, health, and safety concerns. These concerns include the web-based storage of data, managing privacy of personal information, obtaining consent to participate, providing opportunities to withdraw from the study, and ensuring any distressed participants in the study are provided with appropriate assistance. These issues are addressed in the following sections.

Data Availability, Storage, and Privacy

The major ethical issue relates to ensuring the privacy of web-based data collected and stored in password-protected computers and a secure web portal for web-based data collection and delivery of the web-based program. The website that houses the data will be assessed by ANU via a Privacy Impact Assessment to ensure it meets the privacy standards outlined in the Australian Privacy Act. Survey data will be initially stored on the custom-built secure website. After downloading it from this portal, any potentially identifying information (ie, email addresses) will be removed from the main data file and stored in a separate file. These will be linked by an ID code that will not contain any individually identifying information. We will explain to participants this is primarily so that if they wish to withdraw from the study, we can relink their data across the 2 files using this unique code and delete it.

Audio recordings and transcripts for the qualitative interviews will be stored on a secure server with access restricted to the researchers involved in the study and the IT support staff. Their interview and transcript data will be identified by a code we assign them, which will be unique to each participant but contain no identifying details (ie, a number). The audio recordings and transcripts will not be linked with the survey data and will be stored separately from the data we collected from the surveys.

We will protect the privacy of web-based data collected after downloading by storing it on secure university servers with access restricted to authorized personnel only (the project team and IT support staff responsible for managing the server). Any identifiable data associated with this project (eg, contact emails) will be deleted after the first publication is submitted. Following this, deidentified data will be retained and stored in web-based data repositories for data aggregation purposes (eg, meta-analyses) and data sharing.

The information collected from the RCT will be presented as group summaries (in aggregate form) for the purpose of publication in relevant academic journals and conference presentations. Findings will be presented with no reference to individuals. For the interview data, during the publication of results, we expect to refer to individual quotes from participants; these will be identified by broad demographic data (ie, age range, gender, and workplace type or industry only). Furthermore, individual workplaces will not be identified in any publications.

Participant Withdrawal and Distress

Participants will be informed that they can withdraw from the study at any time. Participants will only need to contact the researchers to withdraw if they have provided their email. If a participant requests to have their data removed from the study by sending an email to the researchers, the principal investigator (PJB) will action this request. Participants will be able to withdraw from the study at any time until the first publication

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is submitted, which is expected to be in early 2025. After this, we will be deleting emails and will be unable to identify an individual's specific data. We will only recruit workplaces that have an EAP to ensure that employees experiencing mental health concerns can access effective and immediate care. We will encourage any participants who are experiencing discomfort to contact their EAP or another crisis service (eg, Lifeline). In addition, given that the purpose of the trial is to encourage help-seeking, the intervention itself will contain explicit encouragement to seek help throughout their participation in the project if they are experiencing any distress. As the program aims to improve help-seeking, our invitation letter to workplaces will clearly outline potential outcomes (such as increased utilization of EAP services) and benefits (such as enhanced mental health awareness among employees) that their participation in the trial may bring to their workplace.

Coercion and Informed Consent

Given that the trial will be conducted in workplaces, a critical issue is perceived coercion and pressure to participate in the study, whether explicit or implicit. Therefore, it is essential that it is made clear to the workplace key representatives, who will be coordinating the sending of invitation emails, and to the potential participants, who will be employees of the organizations, that their participation is entirely voluntary. Participants will be informed that those sending invitations to employees (eg, human resource staff and managers) will not have access to the participants' data. In addition, workplaces will not be able to determine which of their employees have participated in the study, unless the employee wishes to tell them. We will emphasize the voluntary nature of the trial in the information and consent web-based forms for participants and explain this clearly in all communication with the workplace key representatives. Furthermore, we will discuss with each individual workplace their potential involvement in the trial and work collaboratively with them to assist them in meeting any workplace health and safety requirements relevant to participation both before and during the conduct of the trial. In addition, the workplace key representatives will be advised that we will inform our ethics committee (ANU Human Research Ethics Committee) of the details of each workplace recruited for the study to assist them in managing and supporting workplaces if any ethical concerns are raised.

Participants will be provided with a PDF version of the participant information sheet that they can save or print. The informed consent form will be provided through an information web page. The web-based consent process will require participants to answer a question indicating that yes, they wish to consent to participate in the study. Participants who do not consent can close the web page and will not proceed any further.

Work Health and Safety Regulations

We will engage in discussions with key representatives from workplaces regarding their potential participation in the trial. During these discussions, we will address any relevant Work Health and Safety regulations that may apply, which we will bring up when we approach workplaces to gauge their interest in participating in the trial. Furthermore, we will provide ongoing support to workplaces in navigating any potential Work Health and Safety regulation issues relevant to the trial while it is being conducted. Our letter to the key representatives in potential workplaces will explain that we will provide this support but that workplace's will to seek their own advice on workplace health and safety requirements, as well as what may happen because of their workplace's participation (eg, a potential increase in those seeking help from EAP services).

Results

Recruitment of workplaces is planned to commence in April 2024. The primary and secondary outcomes, predictors of outcome, and economic analyses will be published separately after 6-month data collection is complete, which is anticipated to occur in 2025.

Discussion

Principal Findings

This protocol describes a cluster RCT of a new interactive co-designed on the web delivered program to increase help-seeking among adults in Australian workplaces. We expect the program will be beneficial primarily for those who experience or are at risk of experiencing symptoms of common mental health problems, such as depression and anxiety, by improving help-seeking to health services. However, it may also provide preventive education to those who may experience such problems in the future or to those who support staff experiencing mental distress. This study protocol outlines how we will test the effectiveness, acceptability, and feasibility of the intervention to increase help-seeking intentions. However, there are several potential limitations or risks that could impact the outcome of the trial, and consequent risk mitigation strategies are addressed in the following section.

Limitations and Risks

A potential but omnipresent risk in trials is that of recruitment; this risk involves recruiting insufficient participants to enable statistical power to detect intervention effects. We expect this risk to be moderate given that the Helipad trial is situated within a large clinical trials network (Mental Health Australis General Clinical Trials Network [64]), which will provide recruitment support through an extensive network and by directly providing contacts in workplaces. In addition, based on previous trials we have conducted, we have found that recruitment is typically highly successful in web-based trials, where we have previously engaged comparable number of participants [34-36], including in cluster-based universal web-based trials [37]. It may be challenging to retain the participants; however, given the instantaneous pre- and posttest design, attrition between these 2 time points may be less likely than in previous trials. Furthermore, as outlined in our data analysis plan, this risk is somewhat mitigated by conducting statistical analyses that account for all available data (ie, mixed effects models).

Moreover, there is an ethical risk that the intervention may provide information to participants that leads them to think they may be experiencing symptoms of common mental health problems (ie, psychological distress, anxiety, or depression). We intend to measure adverse events in our postintervention

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and 6-month follow-up surveys, which may capture these data. However, this forms a key part of the intervention, in that it is expected to prompt those who may not know they are experiencing symptoms of a common mental disorder to seek help. There is potential that such an experience may cause distress to a small proportion of people. We expect this risk to be low, as approximately 20% (180/900) of the participants are expected to have elevated symptoms, and this is unlikely to be surprising for many of these people. Given that the intervention is specifically designed to support this group, we will be providing specific resources, including how and where to seek treatment, to equip participants to access appropriate sources of help if this occurs.

We created the Helipad web-based program with a small group of co-designers. Because the intervention was modeled around the specific views of this group, it is possible that this intervention may not be suited to all workplaces or be effective for improving help-seeking intentions in employees. The program was deliberately designed to be brief to increase engagement and uptake; however, there may be other key effective tools that could have been included but were not due to the required brevity of the program. The program as developed by the co-design group inadvertently included many aspects of other evidence-based programs for reducing stigma and increasing help-seeking [18,19,24], potentially increasing the probability the program will be found to be effective.

Co-design is a methodology that aims to actively involve people with lived experience to better align health care programs with the needs of service users [65], and funders increasingly expect that co-design principles are incorporated into research funding applications [66]. Incorporating lived experience and other stakeholder perspectives into the development of interventions and services may increase engagement and improve outcomes [67]. However, co-design is not the only solution to creating and implementing more effective interventions, and no study has compared co-designed to non–co-designed interventions head-to-head [67]. This study will test a co-designed intervention and will provide new data on the use of co-design, although the intervention contains other features that may differentiate it from the control condition, such as greater interactivity.

Conclusions

Workplaces are ideal settings to deliver web-based mental health promotion programs to adults; however, no evidence-based programs are currently implemented widely. This study provides a significant opportunity to fill this gap by providing a rigorous test of the effectiveness of a new co-designed program in real-world settings, identifying potential barriers to and enablers of implementation, and exploring the potential economic impact of the program. If the Helipad program is found to be effective, given the web-based format and existing platform, it can be rapidly upscaled for dissemination across Australia. Furthermore, this program also provides significant potential to work with employers, insurers, and health providers to ensure all Australian workers are better equipped to seek help across the spectrum of mental health services.

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Data Availability

Deidentified data will be retained for data aggregation purposes (eg, meta-analyses) and data sharing. To advance science, medicine, and public health, we may share deidentified data with any current and future funders, research projects, medical journals, or data research repositories. Some of these organizations may be located overseas. Any deidentified data that we send overseas is not protected by the Australian laws and regulations. Data will be archived for use in any related or unrelated future research with permission from the principal investigator (PJB) or his nominated delegate. Data will be shared upon reasonable request to the principal investigator (PJB) or his nominated delegate. The deidentified data will be made available for research purposes through data repositories including Health Studies Australian National Data Asset and Australian National University Data Commons [68].

Authors' Contributions

PJB led the design of the study and contributed to the drafting of the manuscript. AG assisted with the drafting of the manuscript. CM and MLC contributed to the design of the economic evaluation. All authors critically reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

A-Lit: Anxiety Literacy Questionnaire
ANU: Australian National University
D-Lit: Depression Literacy Questionnaire
DQ5: Distress Questionnaire-5
EAP: Employee Assistance Program
GHSQ: General Help-Seeking Questionnaire
GP: general practitioner
ICER: incremental cost-effectiveness ratio
PROMIS: Patient-Reported Outcomes Measurement Information System
QALY: quality-adjusted life year
RCT: randomized controlled trial
ReQoL-10: Recovering Quality of Life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WPAI: Work Productivity and Activity Impairment

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Protocol

Mobile Electrocardiograms in the Detection of Subclinical Atrial Fibrillation in High-Risk Outpatient Populations: Protocol for an Observational Study

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Abstract

Background: Single-lead, smartphone-based mobile electrocardiograms (ECGs) have the potential to provide a noninvasive, rapid, and cost-effective means of screening for atrial fibrillation (AFib) in outpatient settings. AFib has been associated with various comorbid diseases that prompt further investigation and screening methodologies for at-risk populations. A simple 30-second sinus rhythm strip from the KardiaMobile ECG (AliveCor) can provide an effective screen for cardiac rhythm abnormalities.

Objective: The aim of this study is to demonstrate the feasibility of performing Kardia-enabled ECG recordings routinely in outpatient settings in high-risk populations and its potential use in uncovering previous undiagnosed cases of AFib. Specific aim 1 is to determine the feasibility and accuracy of performing routine cardiac rhythm sampling in patients deemed at high risk for AFib. Specific aim 2 is to determine whether routine rhythm sampling in outpatient clinics with high-risk patients can be used cost-effectively in an outpatient clinic without increasing the time it takes for the patient to be seen by a physician.

Methods: Participants were recruited across 6 clinic sites across the University of Florida Health Network: University of Florida Health Nephrology, Sleep Center, Ophthalmology, Urology, Neurology, and Pre-Surgical. Participants, aged 18-99 years, who agreed to partake in the study were given a consent form and completed a questionnaire regarding their past medical history and risk factors for cardiovascular disease. Single-lead, 30-second ECGs were taken by the KardiaMobile ECG device. If patients are found to have newly diagnosed AFib, the attending physician is notified, and a 12-lead ECG or standard ECG equivalent will be ordered.

Results: As of March 1, 2024, a total of 2339 participants have been enrolled. Of the data collected thus far, the KardiaMobile rhythm strip reported 381 abnormal readings, which are pending analysis from a cardiologist. A total of 78 readings were labeled as possible AFib, 159 readings were labeled unclassified, and 49 were unreadable. Of note, the average age of participants was 61 (SD 10.25) years, and the average self-reported weight was 194 (SD 14.26) pounds. Additionally, 1572 (67.25%) participants report not regularly seeing a cardiologist. Regarding feasibility, the average length of enrolling a patient into the study was 3:30 (SD 0.5) minutes after informed consent was completed, and medical staff across clinic sites (n=25) reported 9 of 10 level of satisfaction with the impact of the screening on clinic flow.

Conclusions: Preliminary data show promise regarding the feasibility of using KardiaMobile ECGs for the screening of AFib and prevention of cardiological disease in vulnerable outpatient populations. The use of a single-lead mobile ECG strip can serve as a low-cost, effective AFib screen for implementation across free clinics attempting to provide increased health care accessibility.

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KEYWORDS

mobile ECG; digital health; cardiology; ECG; electrocardiogram; atrial fibrillation; outpatient; randomized; controlled trial; controlled trials; smartphone; mobile health; app; apps; feasibility; effectiveness; KardiaMobile single-lead ECGs; mobile phone

Introduction

Addressing the Use of Sinus Rhythm Screening

Cardiovascular disease is the leading cause of death in the United States [1]. It is estimated that by 2030, 43.9% of US adults will have at least 1 type of cardiovascular disease [2]. Atrial fibrillation (AFib) is the most common sustained arrhythmia diagnosed in clinical practice [3,4]. It reduces a patient's quality of life and increases morbidity and mortality rates, which may lead to an increased risk of heart failure [5].

The prevalence of AFib is 2.3% in people older than 40 years and 5.9% in those older than 65 years, and about 70% of individuals with AFib are between 65 and 85 years of age [6]. The prevalence of AFib increases with age, and considering the present aging population, an epidemic is expected to occur within the next 10-20 years [4]. Patients with chronic kidney disease show a higher prevalence of AFib, with ranges estimating from 16% to 21% for patients not on dialysis and 15%-40% for patients on dialysis [4,7]. Currently, about 2.7-6.2 million people in the United States have AFib, but as the population continues to age, an estimated 6-12 million people in the United States will be affected [4,7]. However, since AFib can be asymptomatic, it may remain undiagnosed until or after complications occur. Waiting for these complications to arise may be detrimental, as AFib has a 5-fold increased risk of stroke [8,9]. Developing a low-cost and efficient screening protocol for primary care and outpatient clinics may help to improve the detection of AFib and may help prevent the risk of stroke. In fact, implementing proper treatment, such as the use of oral anticoagulants after a diagnosis of AFib, can decrease the risk of stroke by 60% [5].

To diagnose AFib, an electrocardiogram (ECG) reading must show irregular R-wave intervals without distinct P waves [10,11]. Standard 12-lead ECGs are costly and time-consuming devices that are used to detect AFib [12,13]. The development of new devices like the single-lead portable, phone-based KardiaMobile device (AliveCor) may be an efficient and cost-effective alternative to the standard 12-lead ECGs that can potentially offer feasible mass screenings for AFib [14,15]. The standardization of mass screenings for AFib in primary and outpatient clinics can thus help improve the implementation of prevention strategies for cardiovascular diseases [16]. Costs, availability, and time required to use ECG machines are prohibitive factors for conducting regular ECGs [17,18].

Timely identification of AFib plays a crucial role in reducing mortality rates, allowing for an opportunity to cardiovert the patient, start the patient on anticoagulant therapy, and apply catheter ablation techniques [19,20]. AFib is often asymptomatic; thus, many cases may go undiagnosed without any screening mechanisms in place. A retrospective modeling study published in 2018 discovered that 1.3% of older patients and 0.9% of working-age adults went undiagnosed for AFib [8,21]. To decrease this gap of undiagnosed cases and improve the health care of patients, it is primordial to implement feasible screening and prevention strategies. A 2018 study published in the *Journal of Arrhythmias* reviewed portable out-of-hospital ECG devices [22,23]. Of the devices that they reviewed, AliveCor's KardiaMobile device was determined to be accurate in measuring QTC wave intervals on ECG and was found to have a sensitivity of 98.5% and a specificity of 91.4% in pharmacy patients older than 65 years [24,25].

Specific Aims

The aim of this study is to demonstrate the feasibility of performing Kardia-enabled ECG recordings routinely in outpatient settings in high-risk populations and its potential use in uncovering previously undiagnosed cases of AFib. Specific aim 1 is to determine the feasibility and accuracy of performing routine cardiac rhythm sampling in patients deemed at high risk for AFib. Specific aim 2 is to determine whether routine rhythm sampling in outpatient clinics with high-risk patients can be used cost-effectively in an outpatient clinic without increasing the time it takes for the patient to be seen by a physician.

Methods

Participants

For this study, we will recruit approximately 655 participants from each of the selected University of Florida (UF) outpatient specialty clinics. This sample size was specifically chosen as a result of statistical analysis that suggests this study population would indicate a powered study. There is no control group, as this was an observational study. Due to the nature of our enrollment process, which does not require a follow-up visit, we expect a <1% attrition rate, reaching a desired ~655 samples per site based on our power analysis. Study participants will be between the ages of 18 and 99 years.

Eligible participants are any patient visiting the UF Nephrology Clinic, UF Sleep Clinic, UF Neurology Clinic, UF Ophthalmology Clinic, UF Urology Clinic, and UF Pre-Surgical Center. Patients with a history of AFib will not be excluded from the study, as they provide valuable data on potential risk factors and may be prone to AFib recurrence. Participants were only excluded if they were younger than 18 years of age, a leg or hand amputee, a paralyzed person, unable to consent, or unable to read and comprehend English.

Recruitment

Participants will be recruited for the study under the title "Mobile ECGs in Detection of Subclinical AFib in High-Risk Outpatient Populations." Study participants will be approached by a research assistant trained in informed consent and will be asked if they are interested in learning more information about this study. If they are interested, the research assistant will discuss the goals of the study as well as potential risks. If the participant agrees to participate in the study, the research assistant will provide them with informed consent and a

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questionnaire for them to fill out that aims to reveal any risk factors for cardiovascular disease.

Participants enrolled in the study will receive a standardized data collection code in the format of "NEP," the number of weeks, and the number of participants enrolled that week. For example, NEP0101 will indicate the first participant enrolled during the first week of the study. This will allow for participant data to remain confidential during the data analysis portion of the study. A master sheet of the collection codes and the associated participant study data will be stored on an institutional review board (IRB)–approved, secure study Dropbox.

Procedure

Upon obtaining informed consent, research assistants will use the KardiaMobile single-lead ECG by AliveCor to obtain an ECG reading. Before conducting the examination or filling out a cardiovascular-specific screening survey, participants will have to consent to the study. Any questions regarding the survey will be answered by study personnel present in the room. The Mobile ECG recording by the KardiaMobile device will take place in the patient waiting room for approximately 30 seconds.

The smartphone single-lead attachment is compatible with the KardiaMobile app, a HIPAA (Health Insurance Portability and Accountability Act)-compliant smartphone phone app that can temporarily save these ECGs. Each ECG recorded from a participant will be saved on the UF Dropbox using a randomly generated number that corresponds with the participants' medical record numbers.

The UF Dropbox cloud-hosting service will only be accessible to study personnel who require viewing the ECGs in order to assess them. Access to the UF Dropbox requires logging into the UF Health VPN and accessing the site via a password combination containing uppercase letters, lowercase letters, numbers, and punctuation. The KardiaMobile smartphone app requires either a 6-digit password login, fingerprint scan, or face ID to access. ECG recordings will not be permanently stored on the device hosting the recording and will be immediately transferred from the smartphone to the UF Dropbox.

Mobile ECGs will not contain any protected health information, and participants who volunteer to be a part of this research will only be identified by a number that corresponds to the number of persons the study is recruiting. For example, the first study volunteer will have their images labeled as "01" as well as "UF Health Clinic" and will have no personal health identifiers attached to their Mobile ECG recording.

The paper files collected will be stored in a secured holding unit after completion by study participants in accordance with the UF's IRB guidelines. Upon notification of an irregular finding from the KardiaMobile single-lead device, the treating physician for the participant will be informed by research assistants. If the participant does not have a past medical history of arrhythmia, the physician will decide to order a 12-lead ECG to confirm any suspicion of cardiovascular disease.

The number of patients who were screened as having AFib and had an abnormal ECG reading will be compared by using the participant's medical record on Epic Systems. The number of positive screens versus negative screens will also be compared to assess the sensitivity and specificity of testing in the given population.

Procedure Flow Diagram

The procedure flow diagram is shown in Textbox 1.

Textbox 1. Assessing the accuracy of the KardiaMobile smartphone–based electrocardiogram (ECG) system for atrial fibrillation pathology.

1. Approach the patient with informed consent at the University of Florida Health Clinic:
   - Yes: Proceed with smartphone-based ECG screen
   - No: Do not perform smartphone-based ECG screen
2. Clinic-specific screening survey
3. Smartphone-based ECG screen
4. Cardiologist interprets ECG readings and order confirmatory 12-lead ECG if indicated

Outcome Measures

Overview

The following measures will be collected for all participants. All data will be stored via a secured, university-affiliated Dropbox account approved by the IRB, a HIPAA-compliant and university-supported app used for data capture and storage.

Primary Measures

Detection Accuracy

The researchers will measure the accuracy of the KardiaMobile ECG device by comparing the resulting ECG phenotype (normal, possible AF, unreadable, unclassified, tachycardia, or bradycardia) to the patients' actual heart health as determined by the standard 12-lead ECG.

Feasibility

Staff members from the different clinic sites will be asked how the incorporation of the mobile ECG device impacted the flow of the clinic. This will provide researchers with information on whether or not this study impacts the length of time it takes for patients to be seen by their physicians, informing us on the feasibility of implementing this device in a clinical setting.

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Secondary Measures

Demographics

Patient demographics including age, gender, weight, height, blood pressure (if known), and race will be collected through a self-reported questionnaire.

Symptoms

Study staff will ask patients in both groups about their symptoms using the following question: "Have you experienced any of these conditions in the last two weeks?" and the following response choices: chest pain, fainting, shortness of breath, palpitations, and weakness.

Risk Factors

The patient's medical history will be assessed using the following question: "Do any of the following apply to your medical history?" and the following response choices: diabetes, overweight or obese, high blood pressure, high cholesterol, family history of heart disease, and smoking.

Site-Specific Health

Depending on the UF Health specialty clinic that the patient is visiting, this section of the questionnaire will be slightly different. Conditions relevant to that site will be listed, and the patient will select the ones that apply to them. Then, they will be asked to state how long, in years, they have experienced those conditions.

Heart Health

The final section of the questionnaire focuses on the patients' cardiac health and their experience with a cardiologist. The questions and response choices are as follows:

- "Have you personally ever been diagnosed with any of the following cardiac conditions?"
  - Atrial fibrillation, cardiomyopathy, heart stents, congestive heart failure, heart attack, coronary artery disease, hypertension, stroke, and pacemaker or defibrillator
- "Are you currently being seen by a cardiologist?"
  - Yes: When is your next scheduled appointment? (eg, 03/2030)
  - No: When is your next scheduled appointment with a primary care physician?

Statistical Analysis

The information collected from the study is categorical data: accurate versus inaccurate. We will be performing an interrater reliability test using Cohen κ coefficient for each of the individuals making a preliminary diagnosis. This will give us a level of agreement. All tests will be 2-sided, and *P* values <.001 will be considered statistically significant.

The number of participants required to achieve statistical significance for this study was calculated to be 655 after completing a power analysis for a 2×2 contingency table design. The probability of a positive diagnosis was .84 and .82 for KardiaMobile and standard ECG, respectively, after applying published literature findings on the efficacy of both methods. Applying Cohen κ statistic, we are looking at the agreement between the 2 metrics to see if KardiaMobile is an effective prescreen. Additional statistical methods include direct comparison, noninferiority, superiority, qualitative comparison, sensitivity, and specificity.

Ethical Considerations

This study, which includes human participant research, was approved by the IRB of the Florida Department of Health (IRB201900697). The informed consent forms, used in this study, provide participants with a description of the study, its qualitative and quantitative measures, potential risks and discomforts, and explicitly ask the patient to voluntarily agree to participate and allow their data to be collected. Study data are deidentified, as all participants are assigned a numerical code. This code follows the format of OC001. Anonymity of all study participants is ensured. No compensation of any sort is offered to human participants. This is stated in the informed consent form. No identification of individual participants is present in any images of this manuscript or in any supplemental material.

Results

As of March 1, 2024, a total of 2339 participants have been enrolled. Of the 6 UF Health specialty clinics, 335 were from the UF Health Nephrology Clinic, 466 from the UF Health Sleep Clinic, 597 from the UF Health Ophthalmology Clinic, 526 from the UF Health Urology Clinic, 231 from the UF Health Neurology Clinic, and 184 from the UF Health Pre-Surgical Clinic. The participants' ages ranged from 18 to 99 years, with an average age of 61 (SD 10.25) years. The average weight of all participants is 194 (SD 14.26) lbs. The race distribution was reported to be 266 (11.42%) African American, 51 (2.18%) Asian, 124 (5.30%) Latino, 1818 (77.73%) White, and 80 (2.61%) others.

The KardiaMobile rhythm strip reported 381 abnormal readings, which are pending analysis from a cardiologist. A total of 78 readings were labeled as possible AFib, 159 readings were labeled unclassified, and 49 were unreadable. Additionally, 1573 (67.25%) of participants report not regularly seeing a cardiologist.

Discussion

A total of 2339 participants across 6 different medical specialty clinics were enrolled in this study. Preliminary findings of the feasibility and accuracy of performing routine cardiac rhythm sampling in patients deemed at high risk for AFib were encouraging, with the average length of patient enrollment being 3:30 (SD 0.5) minutes after informed consent was completed. This time included the participant filling out the site-specific questionnaire. The average length of the single-lead mobile ECG data collection was just 30 (SD 2.5) seconds. Furthermore, when considering feasibility, there were no reports from clinical staff regarding the patient enrollment effort impacting the flow of clinic operations, and 9 of 10 reported satisfaction with the study on clinic operations per medical staff (n=25). Regarding accuracy, the study demonstrated KardiaMobile to have a

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sensitivity and specificity of 95% and 97%, respectively, for detecting previously undiagnosed AFib. The relatively short time to collect the single-lead ECG along with the accuracy of the technology in detecting AFib suggests that the implementation of routine rhythm sampling with high-risk patients can be used cost-effectively in an outpatient clinic without increasing the time it takes for the patient to be seen by a physician.

The use of a single-lead mobile ECG strip can serve as a low-cost, effective AFib screen for implementation across outpatient clinics attempting to provide increased health care accessibility. A study published in 2022 suggested an "incremental cost-effectiveness ratio of US $57,894 per quality-adjusted life year, meeting the acceptability threshold of US $100,000 per quality-adjusted life year" regarding the cost-effectiveness of single-lead mobile ECGs [26,27]. Additionally, patients can easily purchase this device on their own and measure their ECG signal from the comfort of their own homes. This may allow for more immediate feedback on their heart health and a reduction in costs from clinic visits.

Limitations to the study include the fact that the study was not designed to measure the impact of potential moderators on the outcomes. Additionally, there were limitations related to the relatively high rates of unclassified or unreadable ECG outputs that have been included in the abnormal findings data. Furthermore, the participants were not asked to return for another reading, as these outputs are representative of the device's effectiveness.

Overall, this study indicates that the use of a mobile ECG at an outpatient clinic to screen for AFib is acceptable, feasible, and, with preliminary measures, a cost-effective means for detecting previously undetected AFib without impeding clinical operations. These findings have broader public health implications, as an effective screening protocol for AFib can provide earlier access to care through the use of relatively low-cost technologies, which could lead to fewer instances of stroke and more timely initiation of medical therapy.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AFib: atrial fibrillation
ECG: electrocardiogram
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
UF: University of Florida

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Protocol

The Effectiveness of Virtual Reality–Based Training on Cognitive, Social, and Physical Functioning in High-Functioning Older Adults (CoSoPhy FX): 2-Arm, Parallel-Group Randomized Controlled Trial

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Abstract

Background: Virtual reality (VR) has emerged as a promising technology for enhancing the health care of older individuals, particularly in the domains of cognition, physical activity, and social engagement. However, existing VR products and services have limited availability and affordability; hence, there is a need for a scientifically validated and personalized VR service to be used by older adults in their homes, which can improve their overall physical, cognitive, and social well-being.

Objective: The main purpose of the CoSoPhy FX (Cognitive, Social, and Physical Effects) study was to analyze the effects of a VR-based digital therapeutics app on the cognitive, social, and physical performance abilities of healthy (high-functioning) older adults. This paper presents the study protocol and the results from the recruitment phase.

Methods: A group of 188 healthy older adults aged 65-85 years, recruited at the Medical University of Lodz, Poland, were randomly allocated to the experimental group (VR dual-task training program) or to the control group (using a VR headset app showing nature videos). A total of 3 cognitive exercises were performed in various 360° nature environments delivered via a VR head-mounted display; the participants listened to their preferred music genre. Each patient received 3 sessions of 12 minutes per week for 12 weeks, totaling a minimum of 36 sessions per participant. Attention and working memory (Central Nervous System Vital Signs computerized cognitive battery) were used as primary outcomes, while other cognitive domains in the Central Nervous System Vital Signs battery, quality of life (World Health Organization–5 Well-Being Index), health-related quality of life (EQ-5D-5L), and anxiety (General Anxiety Disorder 7-item questionnaire) were the secondary outcomes. The group-by-time interaction was determined using linear mixed models with participants' individual slopes.

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Results: In total, 122 (39%) of the initial 310 participants failed to meet the inclusion criteria, resulting in a recruitment rate of 61% (188/310). Among the participants, 68 successfully completed the intervention and 62 completed the control treatment. The data are currently being analyzed, and we plan to publish the results by the end of September 2024.

Conclusions: VR interventions have significant potential among healthy older individuals. VR can address various aspects of well-being by stimulating cognitive functions, promoting physical activity, and facilitating social interaction. However, challenges such as physical discomfort, technology acceptance, safety concerns, and cost must be considered when implementing them for older adults. Further research is needed to determine the long-term effects of VR-based interventions, optimal intervention designs, and the specific populations that would benefit most.

Trial Registration: ClinicalTrials.gov NCT05369897; https://clinicaltrials.gov/study/NCT05369897

International Registered Report Identifier (IRRID): DERR1-10.2196/53261

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KEYWORDS

cognitive functions; head-mounted-display; healthy seniors; virtual reality; well-being; mobile phone

Introduction

Background or Aims

The global demographic shift toward an aging population presents a pressing need to enhance the quality and effectiveness of health care [1]. Aging is typically associated with cognitive inactivity and, thus, cognitive impairment, resulting in escalating care demands and health care costs [2] and reducing daily functioning and quality of life among older adults [3]. As such, there is a need for effective interventions aimed at enhancing cognitive functions, which can mitigate their decline and promote healthy aging [4].

A promising tool with significant potential across various fields is virtual reality (VR), which has been found to be effective in caring for older individuals, both with and without cognitive impairment [5]. By offering immersive digital experiences, VR can provide varying levels of immersion and high immersion can be provided by head-mounted displays (HMDs), which can stimulate multiple sensory modalities [6]. Such heightened immersion enhances the sense of presence, yielding more pronounced behavioral responses [7].

In addition to the general cognitive function, VR-based training programs have shown promise in improving specific cognitive domains, such as short-term memory, orientation, attention, comprehension, naming, constructions, memory, and judgment [8]. Indeed, VR interventions have been found to significantly improve executive function and verbal memory in older adults [9], whereas traditional cognitive training methods may be limited in terms of accessibility, motivation, and ecological validity [10]. VR technology offers a unique opportunity to create immersive and engaging 3D experiences that simulate real-world scenarios and involve multiple sensory modalities [11,12]. Indeed, studies indicate that VR interventions can enhance the effectiveness and engagement of cognitive interventions, resulting in better outcomes among older patients [13]. VR-based training may also have a beneficial influence on physical activity, with research suggesting it can improve balance performance and functional mobility [14]. Additionally, the potential of VR interventions to promote social engagement and combat social isolation has also been studied among older adults [15].

Research has shown that music has many positive effects on human health, including reducing stress and anxiety [16], enhancing mood [7], improving sleep [17], and relieving pain [18], and it can be an excellent motivator for physical activity [19]. Music has previously been integrated into VR experiences among older adults [11] to increase motivation [11], improve mental well-being [20], and support rehabilitation [21].

While studies have examined the use of VR in health care settings, particularly in mental health [22], its application in healthy older adults who can use VR at home is still an emerging area of research [11]. Understanding the benefits and potential limitations of home-based VR interventions is crucial for developing evidence-based strategies to support healthy aging [4]. Further research is still needed to assess the impact of VR interventions on specific cognitive, physical, and social domains and to identify the optimal protocols for therapeutic use.

Currently, existing VR products and services are prohibitively expensive for many home end users, and their use is typically limited to clinics, nursing homes, and rehabilitation centers [23]. However, the most effective strategy for ensuring maintainable health care in the face of aging populations is prevention. As such, there is a need to provide a home-based service that offers scientifically validated, safe, engaging, and personalized content for older adults to enhance their cognitive, physical, and social abilities.

Objective

The main aim of the study is to determine the effects of using a VR-based digital therapeutics app to improve the cognitive, social, and physical performance abilities of healthy (high-functioning) older adults.

Experimental Hypotheses

It is expected that significant relationships will be found between the 2 factors (group × time) for each of the tested cognitive, physical, and social performance scores. Specifically, cognitive, social, and physical performance scores are expected to significantly improve throughout the VR training intervention compared with the start, but only for the experimental group. No such change is expected to be observed for the control group.

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Methods

Trial Design

The Cognitive, Social, and Physical Effects (CoSoPhy FX) study was designed as a randomized, parallel-group, 2-arm, superiority study with an aimed 1:1 allocation ratio. The protocol was registered with ClinicalTrials.gov (NCT05369897) on June 30, 2022.

Participants

Recruitment

In total, 200 high-functioning older adults aged 65-85 years from a community-dwelling setting were recruited for the study. All recruitment was performed by the Medical University of Lodz (MUL), Poland. High-functioning older adults were defined as those who were older than 65 years of age and maintained their functional independence concerning activities of daily living, including the ability to go on a long walk and to interact with standard modern technology (eg, using a smartphone to send a message).

The recruitment strategy included the following: (1) promotional materials such as posters, flyers, press announcements, and posts on social media groups devoted to older adults were used to raise awareness in the local community and inform older adults about the project; (2) a dedicated phone line operating during working hours was set up to answer inquiries regarding participation in the study; and (3) study visits were carefully planned and scheduled to work around holiday breaks.

The enrollment period lasted over 12 months. The allocated research team member screened the potential participants according to the eligibility criteria, given in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Individuals aged 65-85 years
- Stable medical condition (eg, well-controlled diabetes or hypertension)
- Undisturbed locomotion
- Independent in everyday functioning
- Capable of going on long walks without assistance
- Able to use standard modern technology

Exclusion criteria

- Neuropsychiatric disorders (Montreal Cognitive Assessment<26 points)
- Abuse or addiction to alcohol, drugs, and tranquilizers (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*)
- Blurred vision that cannot be corrected with lenses or glasses
- Auditory pathologies causing significant hearing loss
- High sensitivity to motion sickness
- Migraines
- Epilepsy
- Obesity (BMI>30)
- Deemed unsuitable for participation by the investigator

The clinical and demographic data that were collected during the screening were age, sex, educational level, marital status, socioeconomic status, data on chronic diseases, and medications. A clinical assessment was conducted using the Montreal Cognitive Assessment (MoCA) test [24,25] to exclude participants with suspected cognitive impairment (ie, achieving a total MoCA score lower than 26 points). After qualification, the participants were randomly allocated to either the experimental or the control group. These participants were invited for a second visit, during which they completed a battery of tests for neuropsychological and psychosocial assessment and were trained on how to use the VR-HMD on their own.

Randomization

After the participants had been screened for eligibility, the research team produced a list of eligible participants. Participants were randomly allocated to an experimental or control group with a 1:1 allocation using a computerized random number generator [26]. A simple randomization method was adopted. One author (ES) generated sequences of numbers from 1 to 200 and assigned them to the intervention based on the assumption that 1-100=experimental group and 101-200=control group. Another author (AA) assigned the participants to either the experimental or control group according to the list of randomized numbers. To ensure that the researchers were blinded, the list was kept by an independent research team member (JK) who did not participate in the participant recruitment process. No other stratification was used.

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Ethical Considerations

The protocol and the informed consent form (Multimedia Appendix 1) received approval from the Bioethical Committee of the MUL, Poland (RNN/222/21/KE). Each participant was introduced to the study by a research team member, who performed an initial demonstration of the equipment. The participants were given time to ask any remaining questions. Following this, if they agreed to take part, they signed a form giving their written informed consent (Multimedia Appendix 1).

All data collected during the study will be entered into a secure, password-protected electronic database (internal cloud service and protected from external access). The data set for statistical analysis was fully anonymized. Participants' paper files will be stored in numerical order and in a secure place and manner. A coding system will be developed to ensure uniformity and consistency in categorizing variables. Each variable will be assigned a unique code that will be used throughout the study for data entry and analysis. Access to the data will be restricted to authorized personnel only. Data will be stored on a secure server with regular backups to prevent data loss. Personally identifiable information will be stored separately from the research data to maintain participant confidentiality.

In the conduct of this research, all human participants participated voluntarily and without the promise or receipt of financial compensation or any other form of remuneration.

Intervention

Overview

The intervention was delivered using a VR-HMD worn by the older adults—a Pico Neo 3 Pro (Pico Interactive) in the experimental group and a Pico G2 in the control group. The content shown in the VR-HMD consists of 2 key components.

Base Content

The base consent comprises high-quality 360° photographs and videos from natural environments in the real world, such as a relaxing environment with a mountain view. Initially, 80 different base content environments were used.

Graphical Overlay

Overview

The base content has a graphical overlay that has 2 key components.

Hands

The user's hands and their position are shown inside the VR environment as virtual hands, moving in real time. This requires the user to hold a controller in each hand. The user's hands and their positions are displayed within the VR environment as digital hands that move in real time. This setup requires the user to hold a controller in each hand.

Graphical Objects

Graphical objects are, for example, balloons, that users can touch using their virtual hands. These appear inside the VR environment and move in prespecified trajectories. Graphical objects, such as balloons, can be touched by users through their digital hands. These objects appear in the VR environment and follow predetermined trajectories. The intentions of this design were (1) to perform physical exercises (moving the arms and upper body to touch the graphical objects) and (2) to perform cognitive exercises (using the arms to touch graphical objects according to specific rules for each cognitive task).

While performing the physical and cognitive exercises, the participants could also listen to a selection of musical pieces from the HealthTunes database. The music was played in stereo (48 kHz 24-bit WAV files, –15 dB LUFS) on the Pico G2 and Pico Neo 3 Pro VR-HMDs. All tracks were organized by HealthTunes [27]; none had any drastic tempo changes that could adversely entrain participants or any drastic dynamic changes that could interfere with the experience. The levels of the audio frequency bands were also adjusted to optimize the music to the older adults' hearing. The selection of musical pieces is presented in Multimedia Appendix 2. Participants were provided with a choice of music spanning 4 genres—classical, ambient, electronic, and jazz, with the option to select rock music. This diverse selection was intended to accommodate individual preferences and enhance the personalization of the VR experience. Classical music was the most popular choice among participants, featuring a variety of operas and symphonies or concerti from renowned composers, offering a rich tapestry of auditory stimuli conducive to cognitive stimulation and relaxation. The cognitive exercises that were implemented within the VR app are as follows:

1. Warm-up: a simple exercise to familiarize the participant with each task, in which participants must select the graphical objects that match the color of their hands. The warm-up introduction is presented in Figure 1 and a warm-up exercise is presented in Figure 2.
2. Focus: an exercise of focused attention in which participants must select the graphical objects that match the color of their hands and avoid those that do not. The focus introduction is presented in Figure 3 and a focus exercise is presented in Figure 4.
3. Switch: an exercise for alternating attention in which participants must reach alternately for the shapes of the graphical objects with the matching hand color. The switch introduction is presented in Figure 5 and a switch exercise is presented in Figure 6.
4. Memory: an exercise of working memory based on the n-back task, in which participants must tap a graphical object if it is the same color as the one that appeared 2 graphical objects earlier. The memory introduction is presented in Figure 7 and the memory exercise is presented in Figure 8.

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Figure 1. Warm-up introduction.

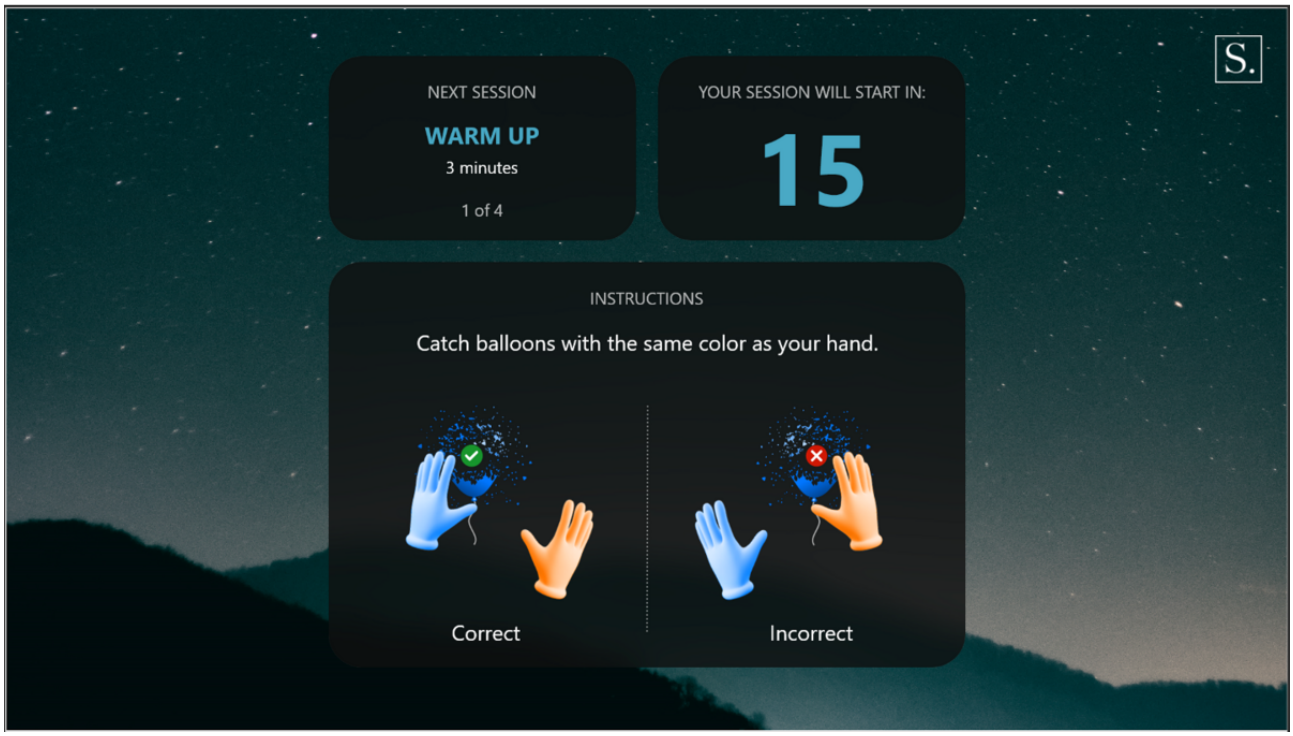

Figure 2. Warm-up exercise.

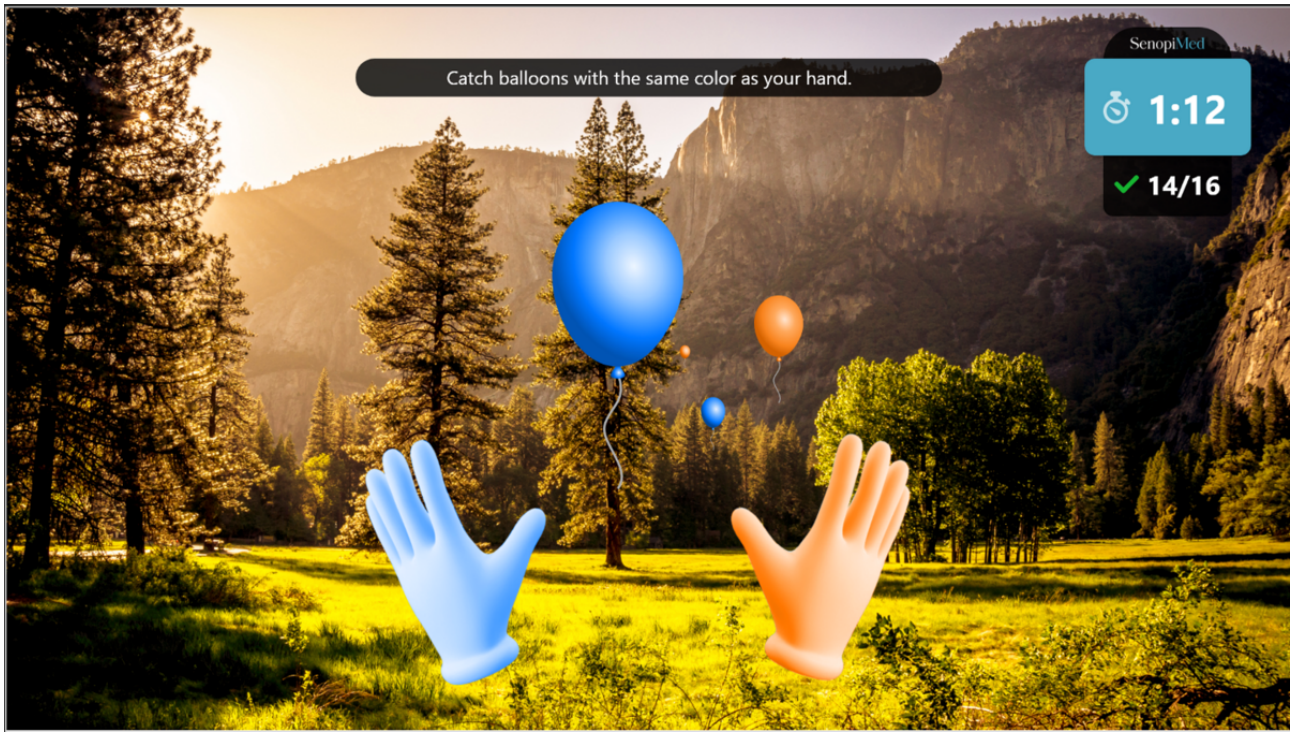

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Figure 3. Focus introduction.

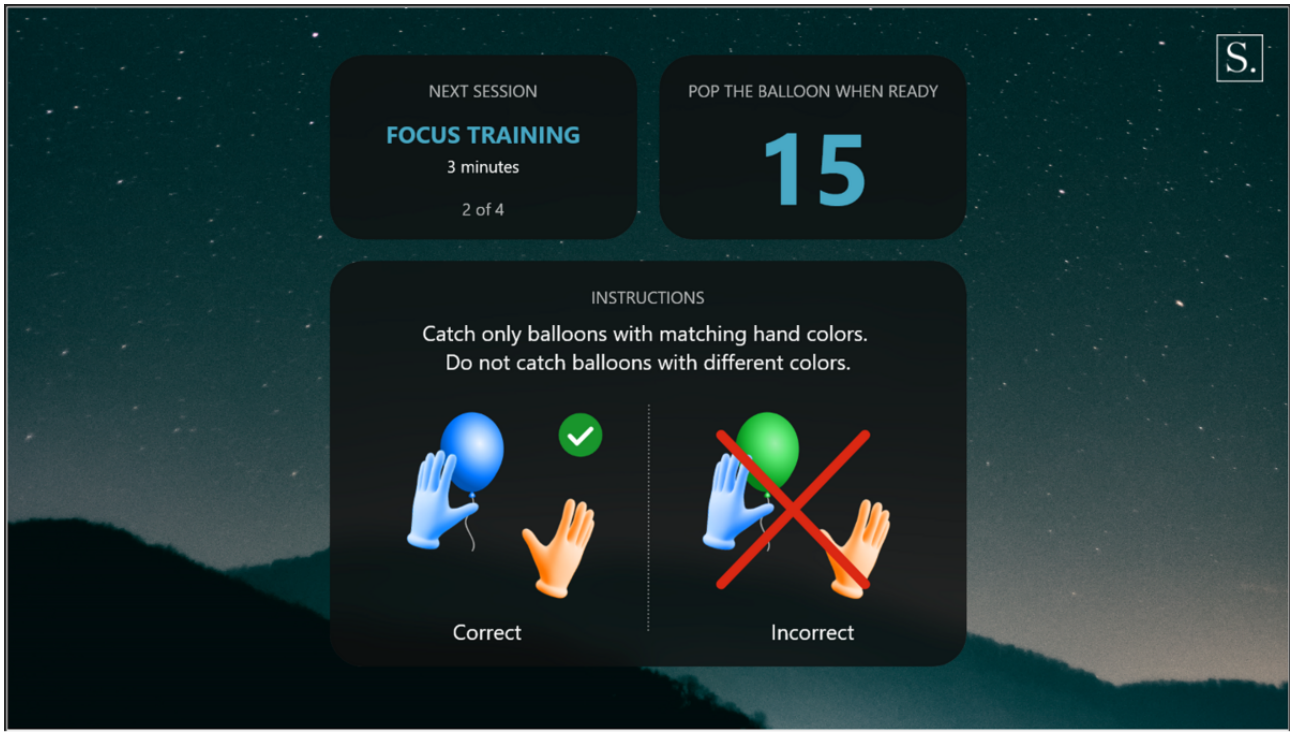

Figure 4. Focus exercise.

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Figure 5. Switch introduction.

Figure 6. Switch exercise.

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Figure 7. Memory introduction.

Figure 8. Memory exercise.

The targeted sample size was 200 participants, equally divided between the experimental and the control groups. Both groups were balanced regarding sex.

The experimental group members underwent a 3-month computerized VR dual-task training program, as described. The control group passively experienced 360° photographs and videos from natural environments without dual-task physical and cognitive training. This technique is frequently used in cognitive studies, offering a passive experience devoid of cognitive challenges [28]. In both groups, the participants were encouraged to use the VR-HMD for a minimum of 3 sessions of 12 minutes per week for 3 months, that is, for at least 36 sessions in total.

The first training session occurred at the MUL, where the participants were trained on how to use the VR-HMD. At the end of the session, the participants took the VR-HMD to their homes to use them according to the schedule described.

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The adverse effects of using VR headsets, often referred to as cybersickness, have been reported to include eye strain, dizziness, nausea, and vomiting [29]. However, these side effects are most often due to suboptimal use of the technology, for example, by using VR content with quick changes of position, low image resolution, and low display refresh rates. The VR app used in the study was designed specifically for older adults and avoided any such drastic camera movements.

The app used in the control group had previously been tested by older adults in 15 older adult care homes in Switzerland and Finland. The first version of the app, containing cognitive training, used in the experimental group was tested by 30 older adults in usability studies by terzStiftung in Switzerland between September 2021 and January 2022. After 8 workshops, the feedback was used to develop updated versions of the app. The resulting cognitive training program, image quality, and usability were rated as high by the participants [30]. The results confirm that VR-HMDs are safe for use by high-functioning healthy older adults at home without substantial risks or side effects. Nevertheless, participants received explicit instructions to discontinue the VR intervention and contact the researchers if they experienced any side effects. Moreover, in the case of suspected side effects, the participants would be withdrawn from the study, and this would be reported as an adverse event. Any side effects could be reported through a software app running on their mobile phone, tablet, or computer. At the end of the intervention, an open-ended questionnaire was used to collect feedback, including information on perceived side effects.

To acquire reliable and comprehensive outcome data, strategies were used to promote participant retention and ensure follow-up completion (Textbox 2). If participants discontinued the intervention or deviated from the protocol, information regarding their decision was collected with various self-reported outcome data related to their experience, expectations, perceived benefits, and any changes observed during their participation.

Textbox 2. Promoting participant retention and ensuring follow-up completion.

Clear expectations

- The study requirements, including the duration of the intervention, the frequency of sessions, and any follow-up assessments, will be communicated. A comprehensive overview of the study timeline should be provided to participants, and their continued participation should be emphasized.

The informed consent process

- During the informed consent process, efforts will be made to ensure that participants fully understand the study's goals, procedures, and potential benefits. Concerns expressed by participants will be addressed and their questions will be answered to foster their commitment to the study.

Flexible scheduling

- Participants' schedules and preferences will be considered when planning pre- and postintervention assessments. Flexibility in scheduling will be offered to accommodate their availability, facilitating the completion of the required sessions.

Reminders and communication

- Periodic reminders about upcoming sessions or assessments will be sent to participants via SMS text messages and phone calls. Clear instructions, directions, and any necessary materials or equipment for the virtual reality –based training will be provided to participants.

Supportive staff

- A dedicated research team that is easily accessible to participants will be established. Staff members will be trained to provide emotional support and address participants' questions or concerns during the study.

Compliance and performance were monitored through a web-based platform. The researchers contacted participants who did not perform the VR training at least 3 times per week to check whether they faced difficulties using the VR app or wished to discontinue participation. Throughout the intervention, the participants were expected to avoid participating in any other trials, especially those related to cognitive functions or mental states. The participants were covered by health insurance throughout their participation in the study, concerning any potential harm, according to a standard clinical study insurance policy.

Outcome Measures

Neuropsychological assessment was performed at baseline and after the intervention. The primary outcomes of the initial study comprised the cognitive, social, and physical performance abilities of healthy (high-functioning) older adults. The parameters that were selected are (1) a wide range of cognitive domains: composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, simple attention, and motor speed (Central Nervous System Vital Signs [CNS-VS] battery) [31]; (2) physical performance across 6 subcomponents: lower body strength, upper body strength, aerobic endurance, lower body flexibility, upper body flexibility, and dynamic balance or agility (Senior Fitness Test); (3) standard grip strength (using a dynamometer); (4) the sense of loneliness (De Jong Gierveld Loneliness Short Form); (5) the quality of life and perceived well-being (World Health Organization [WHO]–5 Well-Being Index); (6) the health-related quality of life (EQ-5D-5L); (7) satisfaction with participation in social roles and ability to participate in social roles and activities (Patient-Reported Outcomes Measurement Information System Short Form 8a); and (8) the severity of

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anxiety symptoms (General Anxiety Disorder 7-item questionnaire [GAD-7]) [32].

The CNS-VS is a computerized neurocognitive test battery developed as a routine clinical screening instrument. It comprises 7 tests—verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention, and the continuous performance test. The result includes neurocognitive clinical evaluation domains—composite memory, verbal memory, visual memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, simple attention, and motor speed [31]. The CNS-VS clinical battery is sensitive to subtle cognitive deficits and progressive decline or improvement. Previous research has shown it is validated, reliable, and easy to use [33].

The WHO-5 Well-Being Index is a 5-item measure of well-being with high internal consistency, evidence of a 1D factor structure, and high convergent associations with other measures of well-being [34,35]. The respondent is asked about their well-being in the last 14 days. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time). The raw score ranges from 0 (absence of well-being) to 25 (maximal well-being) [36].

The EQ-5D-5L is a questionnaire used to assess health-related quality of life. It measures the problems experienced in 5 domains, which are, mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The questionnaire also includes an overall health scale where individuals rate their health condition from 1 to 100, with 100 representing the best imaginable health. Previous research has found the EQ-5D-5L to be reliable and valid [37].

The GAD-7 was used to measure the severity of anxiety symptoms. Each item considers different anxiety symptoms and is answered on a 4-point Likert-like scale. The total score ranges from 0 to 21, and a rise in the score indicates more severe anxiety. The tool is sensitive to anxiety in nonclinical samples and to changes in the severity of anxiety symptoms.

Grip strength was assessed with a hand-held dynamometer. The method is a reliable measure of the strength of muscles in older adults when using a standardized protocol and instructions [38]. The resulting grip strength data have been reported to predict general muscle strength and physical functioning in the older adult population [39,40].

Challenges

On September 21, 2021, KB, SS, JK, LM, ES, KN, MMH, and WW prepared the original version of the protocol (version 1.0). During the further development of the VR-based digital therapeutics app, it was decided to eliminate the physical and social aspects of the intervention. On January 10, 2022, the protocol concerning outcome measures was amended (version 2.0); the primary outcomes were redefined as attention and working memory. Secondary outcomes comprised other cognitive domains, quality of life, well-being, anxiety, and standard grip strength. The same authors were involved in making the amendment, and all the changes to the protocol and outcomes were made before participant recruitment. All relevant parties (including the institutional review board and investigators) were informed about the protocol amendments and outcomes. This decision was prompted by several limitations experienced when using the solution at home, such as insufficiently fast internet, which was needed for trouble-free operation, difficulties in connecting to Wi-Fi, a complex setup process, and the risk of falling.

Statistical Methodology

An a priori computation of the required sample size based on the type of test, the expected effect size, the type I and type II error rates, the number of groups, and the number of measurements were performed according to Lu et al [41]. The statistical power analysis was conducted for a mixed model of repeated measures for 2 groups, 1 measure at a time (corresponding to the main cognitive performance scores detailed) with a 0.7 pre-post correlation, a 20% dropout rate, a medium effect size (0.5), a significance level of α=.05, and a statistical power of 1–β=.80. The necessary sample size for these parameters was 77 (n=154) participants per group.

The MUL stored the personal data of the interested and eligible participants on an internal cloud service, protected from external access. The data set for statistical analysis was fully anonymized. All data storage and processing comply with the General Data Protection Regulation (GDPR) and other applicable regulations. Where possible, fully anonymized data may be made publicly available through open-access repositories supporting the Open Science Initiative.

Results

Participant Flow

The project received funds from June 1, 2021, to October 31, 2023. The study's design, management, analysis, and reporting are independent of the funder. The study, from recruitment to completion of follow-up, was planned to take place from January 2022 to May 2023. The recruitment phase was performed from January 2022 to mid-January 2023. As shown in Figure 9, a total of 310 participants were tested for eligibility and 122 were excluded because of not meeting the inclusion criteria. The most common cause of exclusion was the MoCA score being below 26 points, suggesting the presence of objective cognitive impairment. The recruitment rate (61%, 188/310) was acceptable. Following this, 188 participants were allocated to an experimental group (n=100, 53.2%) or a control group (n=88, 46.8%), with an allocation ratio of 1:0.88.

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Figure 9. CoSoPhy FX (Cognitive, Social, and Physical Effects) study flowchart. Study design: a randomized, parallel-group, 2-arm, superiority study; allocation ratio: 1:0.88; population: individuals aged 65-85 years; location: Poland; time frame: 3 months.

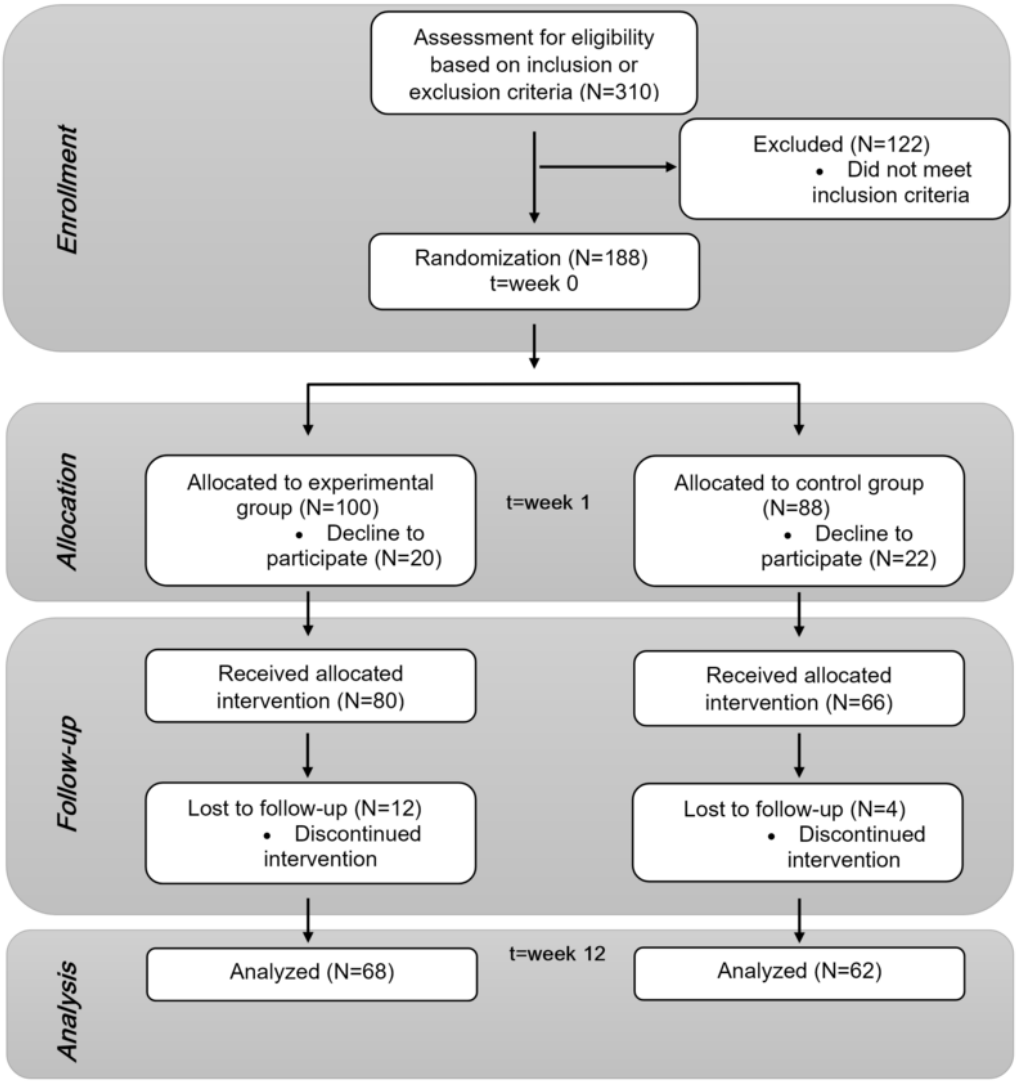

In the experimental group, 20 participants declined to participate before the start of the intervention and withdrew their consent without giving a reason. A total of 12 participants withdrew because they reported somatic and mental health problems unrelated to the intervention. In the experimental group, 68 participants completed the intervention.

In the control group, 22 participants declined to participate before the start of the intervention and withdrew their consent without giving a reason. A total of 4 participants withdrew because they reported somatic and mental health problems unrelated to the intervention. In the control group, 62 participants completed the intervention. There were no missing data.

The data are currently being analyzed, and we plan to publish the results by the end of September 2024.

Dissemination

The study results will be published in scientific journals and presented at appropriate scientific conferences. All materials and papers will be written by the researchers. No services of external copywriters will be used. The study protocol was registered and published on ClinicalTrials.gov.

Discussion

Potential Benefits

VR-based interventions can significantly improve the quality of life for healthy older individuals in several ways. First, VR offers a means of mental stimulation and cognitive engagement. By immersing the user in various environments, tasks, and games, VR can delay cognitive decline by enhancing various cognitive abilities such as memory, attention, and problem-solving skills [42,43]. Second, VR interventions can be used to support physical activity and rehabilitation by providing a safe environment for older adults to improve their balance and flexibility and reduce the risk of falls and injuries [14]. Third, VR provides opportunities for social interaction and connectivity, thus combating the isolation and loneliness often experienced by older people. VR meetings and games can promote engagement with family and peers, and exploring VR worlds can offer a sense of adventure and travel without physical limitations [15]. Finally, VR apps can be used to manage anxiety

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and stress, promote general well-being, and provide leisure opportunities, thus positively impacting quality of life [44].

Potential Risks and Challenges

Several potential risks and challenges are associated with using VR interventions in the older adult population, and these should be taken into consideration to maximize their benefits and minimize any potential harm. First, suboptimal and prolonged use may be associated with physical discomfort or cybersickness, comprising symptoms such as nausea, disorientation, or eyestrain [29]. Second, there can be a significant learning curve for older adults unfamiliar with the technology, and some individuals may find the technology intimidating or stressful, leading to rejection or noncompliance [45]. Third, if the person is unaware of their real-world surroundings while immersed in the VR environment, they may be at risk of falls or accidents. Finally, while the cost of VR hardware has decreased, it can still be expensive, especially for high-quality systems.

Limitations

One limitation of this study is that it did not determine the degree of function of the participants by an appropriate objective tool; instead, it was evaluated by a research team based on a medical interview during the screening process. While this approach provided some insight into the participants' functional independence in activities of daily living, it may have introduced subjectivity and potential bias. Objective tools, such as standardized assessments or performance-based measures, could have provided more reliable and valid measures of older adults' functioning. For instance, widely recognized tools such as the Timed Up and Go (TUG) [46] test for mobility and the Instrumental Activities of Daily Living (IADL) scale [47] for more complex tasks could offer standardized and quantifiable metrics. Future studies should consider incorporating these objective tools to obtain a more comprehensive and accurate assessment of functional ability.

Another potential limitation of the study relates to the occurrence of cybersickness among participants engaging with VR interventions. Cybersickness, a condition characterized by symptoms such as dizziness, nausea, and headache, mirrors the symptoms of motion sickness but is induced by immersive VR environments. The incidence of cybersickness varies among individuals and can significantly impact the user's ability to engage with VR-based interventions over time [29]. This limitation is particularly relevant as it may affect the participant's adherence to the intervention, potentially skewing the study's outcomes. Future research should aim to identify strategies to minimize cybersickness, possibly through the adaptation of VR content, the duration of sessions, or the inclusion of breaks, to enhance the comfort and participation of all users.

Furthermore, the study faced challenges associated with Wi-Fi connectivity, which represents another significant limitation. A reliable Wi-Fi connection is crucial for the seamless delivery of VR content and the uninterrupted participation of subjects in the study. Issues with Wi-Fi connectivity, such as signal instability or bandwidth limitations, can disrupt the VR experience, leading to fragmented sessions or the inability of participants to complete the intervention as planned. This technological constraint not only affects the consistency and quality of the intervention delivery but also potentially impacts the engagement and satisfaction of participants. Addressing Wi-Fi connectivity issues is essential for ensuring the fidelity of VR-based interventions, and future studies may need to consider alternative solutions or backup options to mitigate these challenges, ensuring a smooth and effective implementation of VR technology in research settings.

Conclusions

Previous research found that VR therapy can improve the well-being of older adults in long-term care, rehabilitation hospitals, and older adult care residences, who often experience cognitive decline, reduced mobility, and isolation [22]. We intend to publish our findings in a future study, and we believe that they will provide further information on the effect of immersive VR therapy among healthy, community-dwelling older adults regarding their cognitive performance, tolerance, and technology acceptance. Even so, further research is needed to explore the long-term effects, optimal intervention designs, and specific populations that may benefit most from VR-based interventions.

Acknowledgments

This project is cofunded by the Active and Assisted Living (AAL) Programme, the European Union (EU) Commission, the Swiss Innovation Agency Innosuisse, the Research Council of Norway, the Polish National Centre for Research and Development, and the Austrian Research Promotion Agency, under the AAL project CoSoPhy_FX (AAL-2020-7-215-CP). The project received funds from June 1, 2021, to October 31, 2023. The study's design, management, analysis, and reporting are entirely independent of the funder. In the preparation of this paper, generative artificial intelligence (AI) tools were used to assist in the identification and selection of relevant academic papers. Specifically, scite.ai [48] and elicit.com [49] were used to facilitate the literature search process. Each identified resource was subsequently reviewed and verified by the authors to ensure relevance and accuracy in supporting the research presented. This use of generative AI tools was confined to the initial stages of literature search and did not extend to the generation of paper content. Author LM has moved to a new institution since completing the research. His new affiliation is the Second Department of Psychiatry, Institute of Psychiatry and Neurology in Warsaw, Poland.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

KB and SS conceived the study. KB, SS, JK, LM, ES, KN, MMH, and WW initiated the study design, and JOC helped to adapt the final study design. JK, LM, ES, KN, AA, and AL implemented the study. LM, ES, KN, AL, and AA collected the data and drafted the paper. JOC conducted the preliminary statistical analysis. All authors contributed to refining the study protocol and approved the final paper. KB and SS led the acquisition of grant funding for the project, designed the software architecture for the VR solutions, and led the software development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent.
[DOCX File , 22 KB - resprot_v13i1e53261_app1.docx]

Multimedia Appendix 2
Music selection.
[DOCX File , 19 KB - resprot_v13i1e53261_app2.docx]

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Abbreviations

CNS-VS: Central Nervous System Vital Signs
CoSoPhy FX: Cognitive, Social, and Physical Effects
GAD-7: General Anxiety Disorder 7-item questionnaire
GDPR: General Data Protection Regulation
HMD: head-mounted display
IADL: Instrumental Activities of Daily Living
MoCA: Montreal Cognitive Assessment
MUL: Medical University of Lodz
TUG: Timed Up and Go
VR: virtual reality
WHO: World Health Organization

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Protocol

Molecular Detection of SARS-CoV-2 From Throat Swabs Performed With or Without Specimen Collection From the Tonsils: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Testing for SARS-CoV-2 is essential to provide early COVID-19 treatment for people at high risk of severe illness and to limit the spread of infection in society. Proper upper respiratory specimen collection is the most critical step in the diagnosis of the SARS-CoV-2 virus in public settings, and throat swabs were the preferred specimens used for mass testing in many countries during the COVID-19 pandemic. However, there is still a discussion about whether throat swabs have a high enough sensitivity for SARS-CoV-2 diagnostic testing, as previous studies have reported a large variability in the sensitivity from 52% to 100%. Many previous studies exploring the diagnostic accuracy of throat swabs lack a detailed description of the sampling technique, which makes it difficult to compare the different diagnostic accuracy results. Some studies perform a throat swab by only collecting specimens from the posterior oropharyngeal wall, while others also include a swab of the palatine tonsils for SARS-CoV-2 testing. However, studies suggest that the palatine tonsils could have a tissue tropism for SARS-CoV-2 that may improve the SARS-CoV-2 detection during sampling. This may explain the variation of sensitivity reported, but no clinical studies have yet explored the differences in sensitivity and patient discomfort whether the palatine tonsils are included during the throat swab or not.

Objective: The objective of this study is to examine the sensitivity and patient discomfort of a throat swab including the palatine tonsils compared to only swabbing the posterior oropharyngeal wall in molecular testing for SARS-CoV-2.

Methods: We will conduct a randomized controlled study to compare the molecular detection rate of SARS-CoV-2 by a throat swab performed from the posterior oropharyngeal wall and the palatine tonsils (intervention group) or the posterior oropharyngeal wall only (control group). Participants will be randomized in a 1:1 ratio. All participants fill out a baseline questionnaire upon

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enrollment in the trial, examining their reason for being tested, symptoms, and previous tonsillectomy. A follow-up questionnaire will be sent to participants to explore the development of symptoms after testing.

Results: A total of 2315 participants were enrolled in this study between November 10, 2022, and December 22, 2022. The results from the follow-up questionnaire are expected to be completed at the beginning of 2024.

Conclusions: This randomized clinical trial will provide us with information about whether throat swabs including specimens from the palatine tonsils will improve the diagnostic sensitivity for SARS-CoV-2 molecular detection. These results can, therefore, be used to improve future testing recommendations and provide additional information about tissue tropism for SARS-CoV-2.

Trial Registration: ClinicalTrials.gov NCT05611203; https://clinicaltrials.gov/study/NCT05611203

International Registered Report Identifier (IRRID): DERR1-10.2196/47446

(JMIR Res Protoc 2024;13:e47446) doi:10.2196/47446

KEYWORDS

SARS-CoV-2; COVID-19; pandemic; oropharyngeal sampling; diagnostic accuracy; PCR; polymerase chain reaction; PCR analysis; swab; diagnostic; oropharyngeal; virology; testing; detection; molecular biology; microbiology; laboratory; palatine tonsil; COVID-19 detection; COVID-19 testing; tonsil; swabs; oropharyngeal swabs; oropharyngeal swab; nasal swab; nasal swabs; molecular detection; tool; diagnostic technique; diagnostic procedure; clinical laboratory techniques

Introduction

Background and Rationale

Testing for SARS-CoV-2 has been essential in limiting the spread of infection in society during the COVID-19 pandemic, where billions of tests have been performed worldwide [1]. Further, sensitive tests for SARS-CoV-2 are also important to provide early COVID-19 treatment for people at high risk of severe illness. Proper upper respiratory specimen collection is the most critical step in diagnosing COVID-19, and standard sample guidelines are recommended [2]. A throat swab, alone or combined with a nasal swab, is a frequently used sample method in many countries [3-5]. However, there is considerable variability in the reported diagnostic accuracy of throat swabs, with a 95% CI from 52% to 100% reported in systematic reviews [6,7]. Several studies have found that throat swabs have significantly lower sensitivity than other respiratory specimens [8,9] and the Infectious Diseases Society of America, therefore, does not recommend throat swabs for SARS-CoV-2 testing [10]. In contrast, an experimental study with volunteers inoculated with SARS-CoV-2 intranasally to assess virus kinetics found that SARS-CoV-2 molecular testing of throat swabs was positive before nasal swabs during the asymptomatic infectious stage [11]. Many of the previous studies performing throat swabs also lack a detailed description of the sampling technique, which makes it difficult to compare the different diagnostic accuracy results. Some studies perform a throat swab by only collecting specimens from the posterior oropharyngeal wall [12,13], while others also include a swab of the palatine tonsils for SARS-CoV-2 testing [14,15]. However, recent studies suggest that throat swabs, including the palatine tonsils, have a higher sensitivity for SARS-CoV-2 detection than nasal and nasopharyngeal swabs in asymptomatic and early infectious stages [16,17]. SARS-CoV-2 primarily uses the tissue-specific proteases TMPRSS2, TMPRSS4, and TMPRSS11D as cellular entry factors via angiotensin-converting enzyme 2 channels, which are richly expressed in the tonsil crypts [18,19]. This may explain why SARS-CoV-2 can be detected in throat swabs before nasal swabs, underlining timing as a crucial factor for test results [20]. Many factors may contribute to the variation of sensitivity reported, but no clinical studies have explored the clinical role of the palatine tonsils in diagnostic testing for SARS-CoV-2 in community settings. We will, therefore, conduct a randomized clinical trial to compare the diagnostic sensitivity of a throat swab with or without the palatine tonsils.

Research Question

The question of this research is, in a cohort of individuals tested for COVID-19 at a public test center, what is the sensitivity of a throat swab including the palatine tonsils compared to only swabbing the posterior oropharyngeal wall in molecular detection of SARS-CoV-2?

Methods

Overview

We will conduct a randomized controlled trial to compare the molecular detection rate of SARS-CoV-2 by a throat swab performed from the posterior oropharyngeal wall and the palatine tonsils (intervention group) or the posterior oropharyngeal wall only (control group).

Study Setting

Participants will be enrolled in a free public COVID-19 test center in Valby and Hillerød, Capital Region, Denmark starting from November 10, 2022, until December 22, 2023. All samples will be sent for molecular testing at Statens Serum Institut and data analysis will be performed at Rigshospitalet.

Only specially trained health care workers (HCWs) at Valby and Hillerød test center will collect specimens from the participants enrolled in the study. Before enrollment, all HWCs will receive training and a competency-based assessment of their skills [21] (see Multimedia Appendix 1 for details).

Follow-up data will be collected from study enrollment until 3 months post enrollment by an electronic questionnaire sent via REDCap (Vanderbilt University).

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Eligibility Criteria

Individuals with or without symptoms of upper respiratory tract infection, aged 18 years or older, who visit Valby or Hillerød test center for reverse transcriptase–polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 will be offered participation in the study.

The exclusion criteria are individuals with a tracheostomy, laryngectomy, or prior oropharyngeal cancer surgery that would make the throat swab difficult. Further, individuals without a Danish civil registration number will be excluded from participating. Individuals who are not included in the study will have the standard oropharyngeal swab performed in the test center.

An individual will only be allowed to participate in the study once. If a participant is enrolled in the study more than once, only the first enrollment (or the first positive test case) will be included. The following test results will be excluded from the statistical analysis by the statistician who will remove any duplicates of the civil registration numbers.

Randomization to Intervention and Control Group

After enrollment, the participants will be randomized in a 1:1 ratio either having the throat swab performed including the posterior oropharyngeal wall and both palatine tonsils (intervention group) or only including the posterior oropharyngeal wall and avoiding the palatine tonsils (control group; see Figure 1).

Figure 1. (A) Anatomic visualization of the posterior oropharyngeal wall (green) and palatine tonsils (pink). (B) Throat swab including the posterior oropharyngeal wall and palatine tonsils. (C) Throat swab including the posterior oropharyngeal wall but avoiding the palatine tonsils. %: no swabbing was performed from the palatine tonsils.

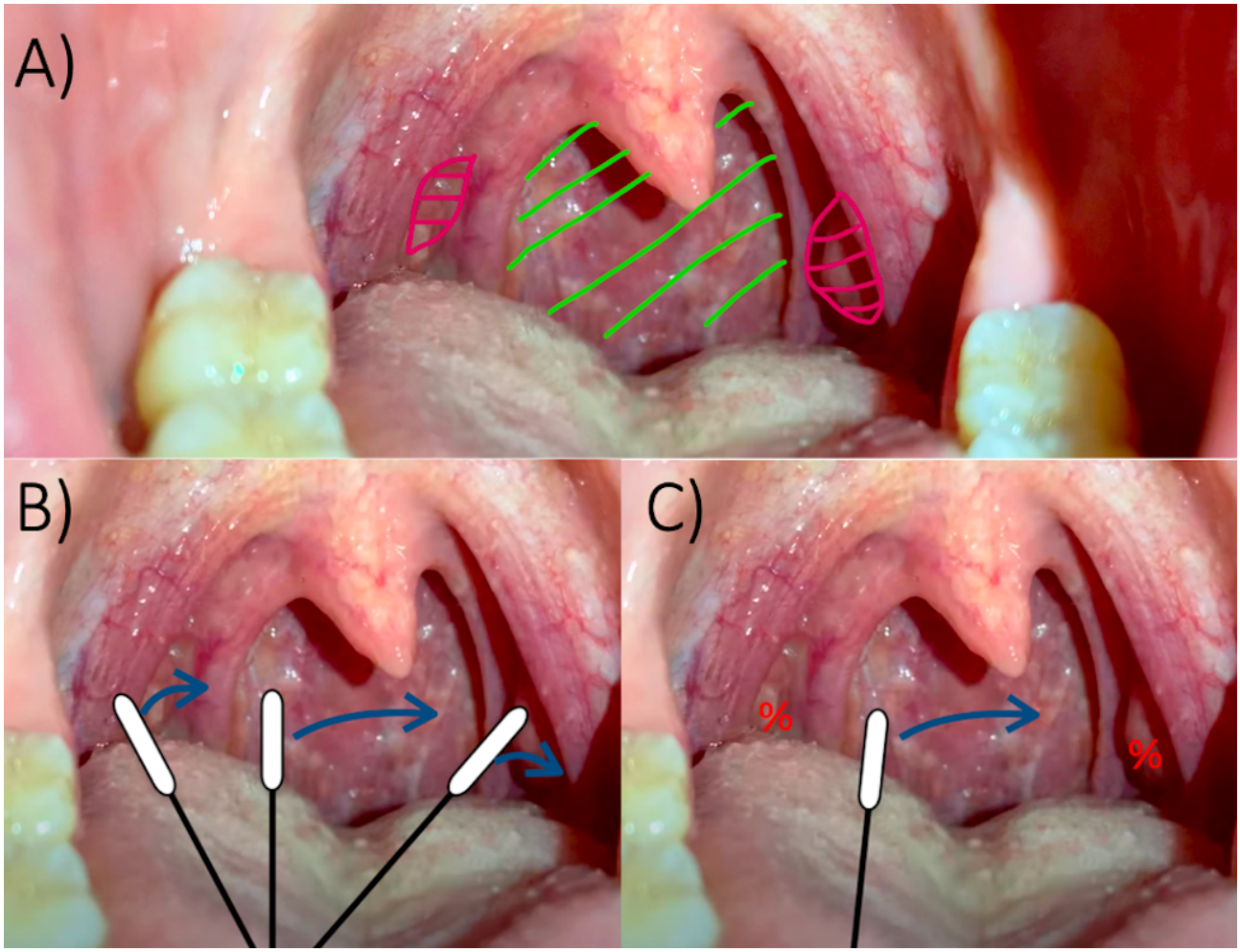

A block randomization list was generated by author TT using the online randomization software Sealed Envelope [22] and afterward uploaded to REDCap. The randomization group will be disclosed in connection with trial registration in REDCap using the REDCap “randomize” function. The throat swab will afterward be performed by the trained HWCs with or without swabbing of the palatine tonsils depending on the randomization to either the intervention or control group, see Figure 2.

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Figure 2. Study flowchart of the randomized controlled trial study design including volunteer participants from 2 public SARS-CoV-2 test centers in Copenhagen Municipality between November 2022 and March 2023. NRS: numerical rating scale; RT-PCR: reverse transcriptase-polymerase chain reaction.

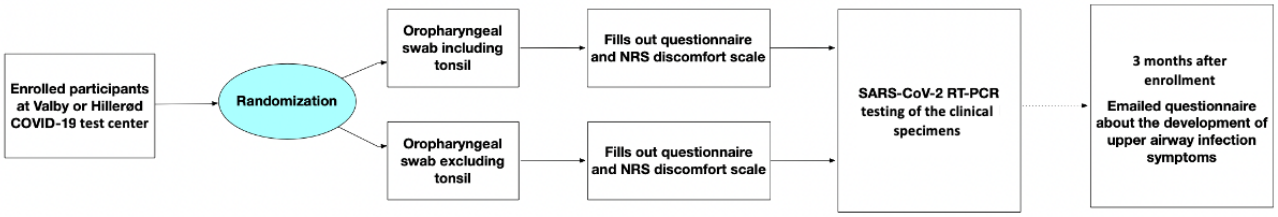

The swabs will be placed in separate dry tubes and sent to the Statens Serum Institute, Copenhagen, Denmark, for detection of SARS-CoV-2 by single-target RT-PCR. Samples with viral cycle threshold (Ct) values below 38 are considered positive, 38-40 inconclusive, and above 40 negative [23].

All participants are required to fill out a baseline survey on site about their reason for being tested, prior COVID-19 infections, vaccination status, symptoms, and if any prior tonsillectomy has been performed (Multimedia Appendix 1).

All HCWs participating in the data collection have been given a unique ID that will be registered for each throat swab performed in the study. Further, the HCW will also be asked to rate the Mallampati score of the participants included in the study (Multimedia Appendix 1). All data will be documented on site in a secure web database (REDCap; Multimedia Appendix 1).

Outcomes

The primary outcome will be reported as SARS-CoV-2 RNA by RT-PCR test result (positive, negative, and inconclusive). The secondary outcome will be reported as (1) SARS-CoV-2 RT-PCR Ct value, (2) test discomfort on an 11-point numerical rating scale (NRS), (3) development of COVID-19 disease after testing, (4) SARS-CoV-2 detection rate for each HCW, and (5) Mallampati score of participants being tested.

Sample Size

Based on a SARS-CoV-2 test positive proportion of 13% in the Danish capital region in the last week of October 2022, we expected the proportion of positive tests to increase to about 20% during the following study period [24]. The power calculation was based on an expected improvement in diagnostic accuracy of 25% by including the palatine tonsils in the throat swab compared to a sample without the tonsils. Using the ClinCalc [25] sample size calculator, we, therefore, estimated that a sample of 2188 participants would provide the trial with 80% power at a 5% significance level with an expected test-positive proportion of 20% equal to 438 individuals positive for SARS-CoV-2 among the participants tested. As we expect about 219 (10%) participants missing due to dropout and missing data, we aim to include 2407 participants in the study. All individuals entering the testing facility who meet the eligibility criteria are offered to participate in the study. We expect about 300-700 tests performed at both COVID-19 test centers each day and an assumed participation of 10%-30%. We, therefore, expect to complete the enrollment within 3 months.

Statistical Analysis

A study participant is considered to have a SARS-CoV-2 infection if the throat swab is RT-PCR positive (reference standard). Participants with an inconclusive RT-PCR test result will be included in the analyses as a negative test result following an intention-to-diagnose approach [26]. Differences in the proportion of SARS-CoV-2–positive tests between the intervention and the control group will be compared using binary logistic regression using the test center as a fixed effect and a generalized estimating equation to adjust for clustering of data within the HCWs performing the sample (see the statistical analysis plan in Multimedia Appendix 1 for further details). The difference in SARS-CoV-2 detection rate between HCWs will also be reported separately to estimate the potential difference in sampling efficacy. The Ct values from positive RT-PCR samples and the NRS discomfort scores will be compared using a general linear model with mixed effects (Ct) and generalized estimating equation (GEE) models (NRS discomfort). The 95% CI will be presented. Categorical data will be summarized with numbers and percentages, while continuous data will be summarized by mean and SD. We will not perform tests of statistical significance for baseline characteristics. A significance level of 5% was applied. Statistical analysis software (version 9.4; SAS Institute) will be used for the statistical analyses.

Planned Subgroup Analyses

We planned to do a sensitivity analysis using a lower Ct<30 for positive SARS-CoV-2 definition to explore the consequences of a higher test specificity for the SARS-CoV-2 detection rate between specimen types. Further, we plan to do subgroup analyses exploring the distribution of positive test results for participants stratified by symptoms, age, sex, tonsillectomy, chronic diseases or conditions, smokers, previous COVID-19 infection, vaccination status, prior tonsillectomy, and Mallampati score. To explore a potential bias from the distribution of the inconclusive test results, we excluded the inconclusive results in the subgroup analyses.

Quality Assurance

All the HCWs, who will be including participants in this study, will be trained and have at least 3 months prior experience performing throat swabs. Further, they will complete a special standardized training and certification program taught by a board-certified otorhinolaryngologist to ensure all HCWs perform the same technique on the participants in the intervention and control group [21]. A 2-hour long training session will cover the theoretical and practical part of throat swab sample techniques and the study design with the elements

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(1) a walk-through of the practical study setup, how participants are enrolled, and how diagnostic interventions are performed; (2) theory on throat swabbing including upper airway anatomy, anatomical variations, and Mallampati score; and (3) practical exercises in throat swab technique with and without tonsils.

Checklists outlining the 2 different sampling techniques for throat swabs with and without palatine tonsils, respectively, will be used to assess the swab performance of all the HCWs by a board-certified otolaryngologist or specially trained nurse before study enrollment (see Multimedia Appendix 1). An on-site health care professional (NTG) will be in charge of internal daily quality assurance.

The test center in Denmark's PCR laboratory at Statens Serum Institut, which performs the PCR analyses for this study, is ISO/IEC 17025 accredited.

Follow-Up

The participants enrolled in the study will receive an online questionnaire 3 months after enrollment to follow up on the number and length of symptoms after they were tested (see Multimedia Appendix 1).

Ethical Considerations

This trial was reported to the Regional Ethics Committee of the Capital Region of Denmark which considered it exempted from further processing (H-22022937). All participants received oral and written information (Multimedia Appendix 1) before signing a consent form (Multimedia Appendix 1) upon enrollment in the trial, and no financial compensation was made to participants in the study. All data have been collected, anonymized, analyzed, and stored in accordance with Danish General Data Protection Regulation legislation. This trial is approved by the data responsible institute in the Capital Region of Denmark (P-2022-803). The protocol was registered with the ClinicalTrials.gov database (NCT05611203). No generative artificial intelligence was used in any portion of the paper writing. Participation is voluntary and participants are required to provide oral and written consent to participate before entering the study (Multimedia Appendix 1).

Results

A total of 2315 participants were enrolled in the study between November 10, 2022, and December 22, 2022. By March 22, 2023, follow-up data collection was completed. The research group is currently finalizing the statistical analyses and preparing the paper for publication aiming to publish primo 2024.

Discussion

Principal Findings

This randomized clinical trial will provide us with information about whether throat swabs including specimens from the palatine tonsils will improve the diagnostic sensitivity for SARS-CoV-2 molecular detection. These results can, therefore, be used to improve future testing recommendations, as well as it will provide additional information about the tissue tropism for SARS-CoV-2.

Study Design

The scope of our study is to compare the diagnostic accuracy of 2 different techniques for throat swabs—with or without swabbing the palatine tonsils. We, therefore, aimed to conduct the study in a way that SARS-CoV-2 testing is currently performed in clinical practice with as little as possible of change. The HCW performing the throat swab was, therefore, instructed to do as usual and only focus on performing the swab including the posterior oropharyngeal wall and both palatine tonsils (intervention group) or only including the posterior oropharyngeal wall (control group), depending on randomization (see Figure 1). This setup has several strengths. First, the participant only needs 1 swab which is expected to make enrollment easier. Second, the HCW performing the test has to make only minimal changes to their usual routine. This ensures a high degree of familiarity with the test setting minimizing the risk of human error and optimizing time consumption. Finally, all samples in the study are handled the same way as any normal sample which ensures that our test analyses are comparable to those not participating in the study.

However, another study design where each participant was swabbed twice from the tonsil and posterior oropharyngeal wall, respectively, could have provided a more direct comparison of the presence of SARS-CoV-2 detection from each anatomical location. However, such a design would also have several drawbacks. First, recruiting participants would likely prove more difficult as throat swabs are associated with discomfort and more people would volunteer to participate if only a single swab was performed. Next, this setup would require considerably more time per participant, which would be difficult to prioritize in a busy test center. Finally, it would also double the cost of swabs and molecular tests, increasing the overall cost of the study substantially.

However, another study design where each participant was swabbed twice from the tonsil and posterior oropharyngeal wall, respectively, could have provided a more direct comparison of the presence of SARS-CoV-2 detection from each anatomical location. Furthermore, this way of testing is not comparable to the way tests are performed in the test centers, and results, therefore, would not be directly transferrable to clinical practice.

Study Setting

We chose to enroll participants from public COVID-19 test centers, as it gave us the opportunity to enroll a high volume of participants in a standardized test setting with HCWs specially trained for the research project. By recruiting 2 test centers geographically separated from one another and with different staff teams, we ensure a broader spectrum of HCWs performing the tests, improving the generalizability of our study results.

Limitations

As we will enroll participants from public COVID-19 test centers during a mass-testing strategy, many of our participants will be tested for screening and not diagnostic purposes. Therefore, our study population will not be the same as the typical patients requiring a SARS-CoV-2 for diagnostic reasons in a future postpandemic period. However, in our study, we will both include participants being tested for diagnostic and

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screening reasons and we will, therefore, also have a unique insight into the virus detection during the asymptotic infectious phase.

Conclusions

In conclusion, this study will be the first study to explore the role of collecting a palatine tonsil specimen in throat swabbing for SARS-CoV-2 molecular testing. As SARS-CoV-2 continues to infect people around the globe it seems relevant to have a deeper understanding of how to improve testing for this disease. Furthermore, the generalizability of performing a throat swab to test for upper respiratory virus may mean that the results of this study can be applied in test settings regarding other upper respiratory viruses.

Acknowledgments

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Data Availability

The data generated during this study are not publicly available but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Training and competency-based assessment of the skills of health care workers.
[DOCX File , 462 KB - resprot_v13i1e47446_app1.docx]

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Abbreviations

Ct: cycle threshold
GEE: generalized estimating equation
HCW: health care worker
NRS: numerical rating scale
RT-PCR: reverse transcriptase–polymerase chain reaction

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Protocol

Effect of a 12-Week High-Calorie-Expenditure Multimodal Exercise Program on Health Indices in Women With Overweight: Protocol for a Randomized Controlled Trial

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Abstract

Background: High-calorie-expenditure training is common among endurance athletes and is an effective strategy for weight loss. Although many training protocols include walking, running, cycling, and swimming according to a target heart rate, there is limited research on high-calorie-expenditure interventions with multimodal training programs using quantitative methods.

Objective: The aims of this research protocol are to (1) develop a high-calorie-expenditure training program to cover target calorie expenditure according to the trainability of women classified as overweight (according to a BMI of 25-29.9 kg/m^2); (2) determine the effect of high-calorie-expenditure workouts on conditioning, glycemic variables, and body composition; and (3) evaluate the implementation of the intervention and results in comparison with outcomes obtained under a standard-calorie-expenditure training program.

Methods: This is a randomized controlled trial with a pretest-posttest design. Participants include 33 women with a BMI in the overweight range (25-29.9) allocated to three groups: two intervention groups and one control group. The intervention will be conducted for 12 weeks. Participants in the first group will be assigned an exercise program with high energy expenditure of approximately 3000-3500 kilocalories/week in the form of 5 sessions per week with an intensity of 50%-75% maximum oxygen rate (VO_2 max) and 60%-80% target heart rate. The second group will be assigned an exercise program with a standard energy expenditure of approximately 1200-1500 kilocalories/week with 3 sessions per week at an intensity of 60%-75% VO_2 max, according to The American College of Sports Medicine guideline. The effects of the multimodal training program with daily tasks will be compared to those of the standard-calorie-expenditure and control (no exercise) conditions with respect to changes in glycemic indices and body composition. Daily calories will be calculated through the International Physical Activity Questionnaire and using Nutrition 4 software.

Results: Preliminary results show significant weight loss in both the high- and standard-calorie-expenditure groups (P=.003). Significant improvements were also found in muscle percentage (P=.05) and BMI (P=.05) for the high-calorie-expenditure group. Analyses are ongoing for glycemic indices, inflammation factors, and blood parameters.

Conclusions: High-calorie-expenditure training can cause further weight loss than standard exercise, which can eventually lead to greater fat mass reduction and improvement in glycemic indices. These results demonstrate that, in some cases, it may be necessary to increase the activity of women and use multimodal exercise programs with increased volume and intensity to increase the expenditure of exercise and daily activity. We found a net effect of exercise and daily activity at the individual level, whereas the daily lifestyle and physical behaviors of the participants remained constant.

Trial Registration: Iranian Registry of Clinical Trials IRCT20220202053916N1; https://tinyurl.com/c8jxfw36

International Registered Report Identifier (IRRID): DERR1-10.2196/51599

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(JMIR Res Protoc 2024;13:e51599) doi:10.2196/51599

KEYWORDS

high-calorie expenditure; multimodal exercise; International Physical Activity Questionnaire; IPAQ; body composition; metabolic health

Introduction

Obesity affects more than 650 million people worldwide [1]. The prevalence of obesity is estimated to have nearly tripled since 1975; it is predicted that by 2030, 1 in 5 women and 1 in 7 men globally, equating to more than 1 billion people, will be living with obesity [2]. This increase is consistent across sex and age groups, with more than half of women of reproductive age being classified as overweight (defined by a BMI≥25 kg/m^2) or obese (BMI≥30 kg/m^2) [3]. Overweight and obesity are significant risk factors for many noncommunicable diseases (NCDs), including hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, and some cancers [1,3]. The World Health Organization classifies risk factors for NCDs into changeable behavioral factors and metabolic risk factors [4]. Modifiable behavioral risk factors include smoking, excess salt/sodium in the diet, harmful drinking, and insufficient physical activity. Metabolic risk factors include hypertension, overweight and obesity, hyperglycemia, and hyperlipidemia [5].

Exercise has many benefits, including improving the condition and sensitivity of the body and brain, enhancing mental health, improving heart function, increasing immunity, reducing anxiety, and preventing osteoporosis. Female obesity is associated with several adverse pregnancy outcomes, including miscarriage, hypertension, preeclampsia, and diabetes [6], leading to reduced fertility, mainly due to anovulation [2]. However, other factors also vary between women with obesity and those with a body weight in the optimal range, including having a harder time conceiving, even in the case of regular menstruation. The current cultural context of valuing speed, including a tendency toward fast food, fast communication, and working within the virtual space, challenges the long-term patience of modern humans, and this desire for instant pleasure is evident in all facets of life worldwide. This issue is also emerging in terms of physical activity and exercise, in which the general public seeks to reach the desired goal in the shortest possible time; this results in increasing caloric expenditure with increased physical activities along with greater nutritional restrictions [3].

The most popular training methods at present for improving maximal oxygen consumption (VO_2 max) are circuit training (CT) and high-intensity interval training (HIIT), which are commonly adopted by the general population, health and fitness professionals, and physiologists [7]. CT is typically performed at a moderate or high intensity over a period of 30-50 minutes and involves a range of aerobic, body weight, and resistance exercises with minimal rest [8]. Low-volume HIIT is defined as “short intermittent bursts of vigorous activity, interspersed with periods of rest or low-intensity exercise” [7], which is usually prescribed at a workout intensity of 80% to 100% of the maximum heart rate [9].

Whole-body CT and low-volume HIIT consisting of 8- to 12-minute interval episodes, interspersed with similar recovery time, have been shown to improve cardiometabolic health and cardiorespiratory fitness. The American College of Sports Medicine (ACSM) recommends that individuals perform moderate exercise 5 times per week, vigorous exercise 3 times per week, or a combination of moderate and vigorous exercise 3-5 times per week [10]. However, the optimal exercise type for improving overall health remains unclear [11]. Caloric expenditure is a common measure that can be used to compare different implementation systems. However, there are still no adequate doses for the workout tailored to specific populations [7].

The ACSM also identified the top 20 fitness trends for Australia, Brazil, Europe, Mexico, Portugal, Spain, and the United States, featuring individual fitness trends, including weight loss and unique health goals [9]. The new guidelines for adults specify a target range of 150-300 minutes of moderate-intensity physical activity and 75-150 minutes of vigorous-intensity physical activity, which differs from the previous guidelines that focused on achieving at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week. This change acknowledges that there is a range of physical activity that maximizes risk reduction for health outcomes; in the case of older adults, multicomponent physical activity is recommended that focuses on functional balance and strength training to increase functional capacity and prevent falls [12].

Designing an exercise program above the standard level of calorie expenditure, especially for sedentary people, can be challenging. High-caloric exercises could act as a double-edged sword; on the one hand, a reduction of adipose tissue brings benefits of reducing metabolic syndrome, while on the other hand, high-intensity activity can be accompanied by increased inflammation. The restriction of energy intake below the amount necessary to maintain weight, known as caloric restriction (CR), can extend the lifespan even for people with normal weight. CR significantly extended lifespan in various preclinical studies with animal models; moreover, CR of approximately 30% was shown to increase life expectancy in humans by 1-5 years [13]. Thus, individuals with higher metabolic rates tend to have shorter lifetimes [14].

The development of this hypothesis stems from the inverse association observed between the rate of metabolism of mammals (by body weight and per day) and lifespan [15]. Mechanistically, the rate of life theory is supported by the free radical theory of aging [16], which postulates that 1%-3% of the oxygen consumed in mitochondrial ATP production produces reactive oxygen species (ie, oxidative stress) [17]. Therefore, with more energy expended as a function of time

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(ie, with aging) or because of a high metabolic rate, there is a greater likelihood of oxidative damage to the cells and tissues [18]. Oxidative stress also disrupts many molecular and cellular structures and functions. Low physical activity exacerbates this mechanism by reducing mitochondrial function and oxidation capacity in cells and tissues. Physically, caloric excess and low physical activity increase the fat mass and cause declines in skeletal muscle mass, strength, and physical fitness [19]. During a 6-month pilot study at Pennington Biomedical, participants in both CR groups lost 10% of their body weight [20] with a 25% reduction in total fat mass and a 27% reduction in visceral fat [11], the fat deposit type most closely linked to the development of metabolic diseases [16].

Similarly, participants in a study conducted at the University of Washington achieved a 20% energy deficit by exercising or losing comparable weight, total fat mass, and a visceral fat mass [13]. Although short-term CR resulted in no change in low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol, 2 years of CR induced significant and persistent declines in LDL cholesterol and triglycerides, increases in HDL cholesterol, and a decreased ratio of HDL to total cholesterol; decreases in systolic and diastolic blood pressure and mean blood pressure were also observed [14]. After 1 year, CR improved left ventricular function in healthy older adults, an advantage typically observed with exercise [9]. Furthermore, the level of systemic inflammation, as measured by the concentrations of interleukin-6, tumor necrosis factor-α, and C-reactive protein, appears to have strong correlations with survival and is an important determinant of longevity in centenarians [12].

Although loss of bone mineral density is common with weight loss, regardless of the method, CR did not affect total bone mineral content in young individuals with type 2 diabetes and was deemed to be a suitable approach for weight loss in the general population [11]. However, another study showed that bone mass decreased at clinically important sites of osteoporotic fractures, such as the hip, femoral neck, and lumbar spine, after the age of 16 years [15]. These reductions were only partially proportional to changes in nutrition, physical activity, or body composition (10%-31% association in a regression analysis). This intraindividual variability in bone loss emphasizes a need for regular, close monitoring of bone health for individuals consuming a CR-based diet [16].

At present, the most popular health trend in Iran is strength training with free weights, which occupies a high proportion of the fitness industry for 2024. Specifically, eight trends related to fitness activities have emerged, including strength training with free weights, low-cost gyms, dance-based workouts, outdoor activities, Pilates, body weight training, core training, and water sports. Weight loss exercise and training methods under group-training formats ranked among the top 10 most popular health and fitness trends nationwide. There is no association between the type of training method and comfort with modern technology. Health was ranked as one of the top 20 attractive goals across the country, which is also reflected in the increased interest in aerobic sports, body weight bearing, and step training among Iranian women [17]. Furthermore, reductions in fat-free mass were associated with older age, male sex, less activity-related energy expenditure, and higher baseline BMI, and were not influenced by protein intake (normalized to body weight) [21]. Despite the greater effects of CR on fat-free mass in men, CR was found to only influence aerobic capacity and leg strength in women [19]. However, it remains unclear how specific exercise programs might affect inflammatory, oxidative, and muscle damage variables in the body in women over 35 years old who are overweight. Therefore, in this study, we aimed to evaluate whether standard- and high-calorie-expenditure exercises that are applicable to women with a BMI falling in the overweight category (ie, 25-29.9 kg/m^2) who have not previously exercised will induce different types of changes and if there is a training capacity for 12 weeks of high-calorie-expenditure training for these women, which constitutes a form of CR.

Methods

Study Design

This study was designed to assess the effect of a 12-week multimodal exercise program intervention under two different calorie-expenditure conditions (high=3000 calories/week vs standard=1200 calories/week) and a no-exercise waitlist control group. The study was conducted at the University of Tabriz in the southeastern region of Azerbaijan, Iran. This study was registered in the Iranian Registry of Clinical Trials (IRCT20220202053916N1).

Figure 1 summarizes the proposed 12-week training plan. Participants will be allocated to three groups: a high-calorie-expenditure group, standard-calorie-expenditure group, and control group. In the high-calorie-expenditure group, participants will engage in 3 sessions of exercise per week for 45 minutes with an estimated expenditure of 650-900 calories per week for weeks 1 and 2. In the third week, they will also have 3 sessions per week with a training duration of 50 minutes per session at an estimated calorie expenditure of 750-1200 per week. In the fourth week, the duration of the exercise will be increased to 60 minutes with 3 sessions per week, thereby increasing the calorie expenditure of the exercise by approximately 1200-1300 per week. In the fifth and sixth weeks, the training time will increase to 70 minutes and the number of training sessions will also increase to 4 sessions per week, resulting in calorie expenditure of approximately 1800-1500 and 1600-2000 calories per week, respectively. In week 7, the training duration will increase to 4 sessions of 80 minutes each with estimated weekly calorie expenditure of 1800-2200. In weeks 8 and 9, the training duration will increase to 90 minutes with expenditure of 1900-2500 calories/week. In the last 3 weeks, the number of sessions will reach 5 with weekly sessions of 95, 100, 110, 110, and 110 minutes, respectively accounting for 2700-3100, 3000-3500, and 3300-3700 calories consumed in week 10, 11, and 12, respectively.

The standard-calorie-expenditure group will receive a 12-week exercise program in the form of 3 training sessions. In weeks 1 to 4, each session will comprise 40 minutes of exercise with 650-900 calories consumed per week; in weeks 5 to 8, sessions will last 60 minutes with 1000-1200 calories consumed per week; and weeks 9 to 12 will involve an increase in the training

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time to 80 minutes with expenditure of 1200-1500 calories per week.

The control group will not undergo exercise training, but will undergo the same blood tests, body composition measurements, appetite measurements, and nutrition and physical activity records as performed in the other two groups.

The schedule of data collection for the main outcome measures is presented in Table 1. Primary and secondary outcomes are measured 2 weeks prior to commencing the exercise training (baseline) and 2 days after completing the 12-week exercise or control period. We are also assessing the effectiveness of different types of exercise programs in mediating the risk of metabolic syndrome, including blood pressure disorders, increased blood lipids, uncontrolled blood sugar, obesity, and insulin resistance, with the goal of gaining a better understanding of the mechanism linking exercise to metabolic control. This is assessed by validating relevant formulas and other variables such as cardiovascular fitness and functional tests. Moreover, since high-calorie-expenditure exercise is associated with a goal of weight loss, there is a possibility that such a program will induce eating disorders, which is an issue that is more common in women. Therefore, two sessions were held for the participants to familiarize themselves with recording of daily food calories with the Eating Attitude Test-26 (EAT-26) questionnaire, including questions related to diet and appetite, in the 3 groups at 3 stages: before and during the course and at the end of the course. Body composition parameters were measured in the two training groups once every 2 weeks and in the control group before, in the middle, and at the end of the intervention. Blood parameters were also measured before and after the intervention to compare appetite levels. Performance tests were conducted before, during, and after the training period, and the calories consumed and physical activity were measured on a weekly basis.

Figure 1. Study design and a summary of the proposed 12-week training programs for the two intervention groups and the control group. CG: control group; HC: high-calorie-expediture exercise; SC: standard-calorie-expenditure exercise.

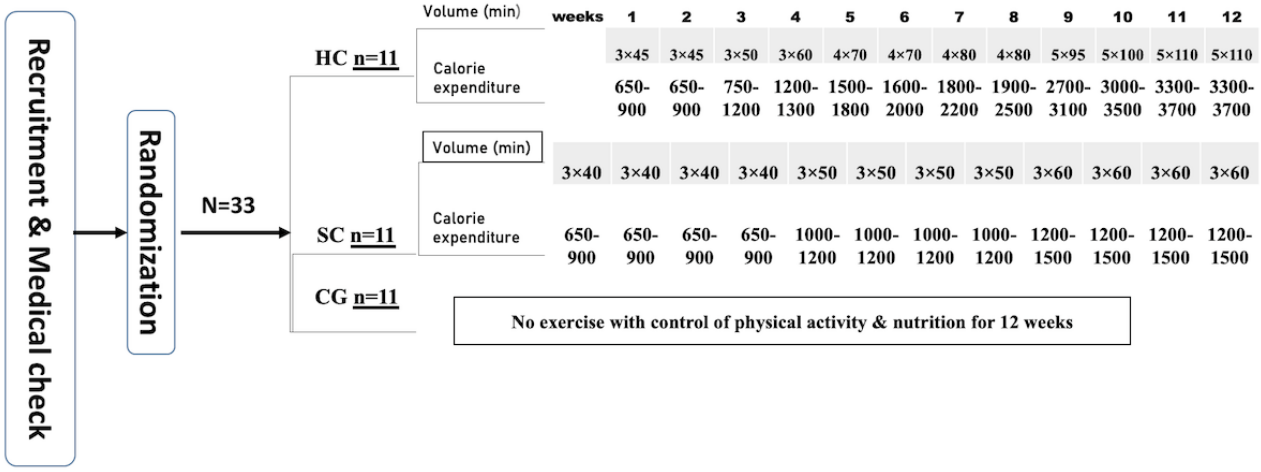

Table 1. Schedule of tests and measures for the primary and secondary outcomes.

Tests	Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Blood sample	✓											✓
Functional test	✓					✓						✓
Appetite	✓					✓						✓
Body composition	✓		✓			✓			✓			✓
Physical activity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nutrition	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study Population

The program was designed for women who are classified as overweight (BMI=25-29.9 kg/m^2) without an athletic background. Participants were recruited as a result of local media coverage related to fitness and health. To be considered eligible for this study, individuals had to be of female sex and aged between 35 and 50 years; informed written consent was required prior to the baseline measures and sample collection. The specific inclusion criteria are listed in Textbox 1.

Exclusion criteria are the onset of menopause during training, disruption of the menstruation cycle, and failure to participate in exercises in more than 30% of the sessions.

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Textbox 1. Inclusion criteria for study participation.

1. In good health without a history of specific diseases
   - physical diseases such as diseases and problems of the joints and bones or any type of physical and orthopedic injury to the extent that it would interfere with the implementation of exercises;
   - endocrine and metabolic diseases (eg, type 1 or type 2 diabetes, kidney and liver thyroid diseases);
   - cardiovascular diseases (eg, high blood pressure, coronary artery disease, atherosclerosis, peripheral vascular disease, heart disease);
   - mental and psychological diseases (eg, depression, schizophrenia, mania);
   - epilepsy;
   - anemia;
   - cancer;
   - any infectious and inflammatory diseases.
2. BMI of 25-29.9 kg/m^2, leading to a classification of overweight.
3. Inactive; participated in sports/fitness activities less than 3 times a week for less than 20 minutes in the past year and did not participate in organized activities in the past year.
4. Premenopausal with a relatively regular menstrual cycle.
5. Not taking any drugs that affect heart rate, metabolism, and body weight (such as drugs related to diabetes or thyroid diseases), antidepressants, nonsteroidal anti-inflammatory drugs, reproductive hormones, supplements, and vitamins.
6. Have not consumed turmeric, caffeine, or alcohol 48 hours prior to each blood sample collection.
7. Completed and signed the consent and engagement forms as well as medical history forms.

Ethical Considerations

The study protocol has been approved by the ethics committee of Tabriz University (code IR.TABRIZU.REC.1402026). All data will remain confidential and only the researchers have access to the data. Initial examinations were performed by a specialist doctor in compliance with ethical protocols, and all entrance tests were conducted with the permission of the participants and in a completely confidential manner. All participants provide informed consent before inclusion, and it is explained to them that they can withdraw from the project at any time. The participants are also assured that their information will remain strictly confidential with the research group and that the study data are completely anonymous.

All medical tests, counseling and educational services, familiarization classes with the calorimeter, and other services are provided to the participants completely free of charge. We have also insured our gym for 1 year and all safety points are guaranteed. In particular, given the outbreak of viruses such as COVID-19 and influenza, we implemented all health protocols and repeatedly announced health principles to all athletes using the gym. Before starting the research project, all participants were examined by the research team's specialist and underwent cardiovascular tests such as echocardiography, blood pressure control, blood oxygen, and sports performance tests. Finally, all participants were provided with insurance in the case of exercise-related injuries by the research team for 1 year.

Blinding

During the data collection, physical fitness and blood tests as well as anthropometric measurements will be performed in the test center, and the laboratory analysts will not have information about the group allocation of the samples or participants.

Intervention Fidelity

There are two instructors per class who will administer the intervention in all cases. At random intervals, an independent assessor will observe all classes and monitor them for content consistency using a checklist based on the explicit components of the exercise intervention protocol. In addition, instructors will maintain a log of activities in each class and these logs will also be reviewed by the independent assessor to confirm intervention fidelity.

Sample Size and Group Allocation

The sample size was determined by a power calculation to detect group differences in the primary outcomes. Previous randomized controlled trials of exercise interventions have demonstrated effect sizes between 0.24 and 1.17 in similar populations for cognitive performance measures following aerobic interventions. To obtain 80% statistical power with an α level of .05, using an *F*-test for three independent groups and an effect size of 0.6, the sample size required was determined to be 30 participants using G*Power version 3.1. Among 60 applicants, a total of 33 participants have been recruited after primary evaluations, including height, weight, fat percentage, waist circumference, BMI, confirmation of the activities performed in the last year, and the lack of medical restriction to participate in the exercise training.

Following written informed consent of all participants and an explanation of the risks and benefits of the research, participants were randomized into the three groups: high-calorie-expenditure (n=11), standard-calorie-expenditure (n=11), and control (n=11) groups.

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Outcome Measures

Baseline Measures

Before starting the training, the participants undergo a 2-week familiarization period with the physical tests and training protocol. Participants' anthropometric characteristics such as height, weight, and body composition variables (determined at 220 Hz with the device) are measured prior to randomization.

Physical Activity

The baseline physical activity of the participants will be assessed with the International Physical Activity Questionnaire (IPAQ) short form (7 items) and long form (IPAQ-L, 27 items) considering a reference period of the past 7 days. The IPAQ-L is a widely used tool that queries 5 activity domains independently and provides specific details on physical activity intensity levels, differentiating between usual weekdays and weekend days by measuring sitting time [20].

Calorie Expenditure

Apple Watch Series 6 (Apple Inc) was used to measure the energy expenditure in each exercise session. Apple Watch is an accelerometer-based device that provides estimates of heart rate, distance traveled, calories burned, minutes of activity, and standing time. When using the associated Workout app, the Apple Watch continuously measures heart rate during exercise, and the heart rate sensor is designed to compensate for low signal levels by increasing both the light-emitting diode brightness and the sampling rate. Calories burned represent both active calories and total calories. Energy expenditure during exercise will be determined based on the VO_2 max measurement in milliliters and body weight, and thus evaluated according to each participant's individual characteristics [22]. The Apple Watch was selected for all monitoring periods and all types of training. Raw data are exported to Microsoft Excel via Apple Health [23]. The Apple Watch monitors physical activity by entering and updating information such as height, weight, and wrist circumference, and then outputs the energy consumption of the exercise [22]. The Apple Watch data will be validated using the following formulas of the ACSM for females [24]:

> Calories/minute = [–20.4022 + (0.4472 × heart rate) – (0.1263 × body weight in kg) + (0.074 × age)]/4.184

> Calories burned per minute = (METs × 3.5 × body weight in kg)/200

In this formula, METs refers to metabolic equivalents as a measurement of exercise intensity, where 1 MET=3.5 mL/kg/min based on completion of the 3-min exercise stage, and METs=8.975–0.065 (age in years) [22]. The energy expenditure during the day and night is then computed as follows [25]. First, the activities performed over 24 hours are calculated to obtain the approximate energy consumption for different physical activities in relation to the resting energy expenditure (REE) [26]. The value is presented for activity per hour for a healthy body and sleep, where REE×1 indicates general activities, REE×1.5 indicates light activities, REE×5.2 indicates moderate activities, and REE×5 and REE×7 indicate heavy activities. Second, the activity factor is multiplied by the duration of the activity. Third, the energy consumption for REE and physical activity is calculated as the average activity factor×exercise period×REE. Finally, the total energy consumption is calculated by multiplying the number obtained in the previous step, which is equivalent to the thermal effect of food.

Borg Rating of Perceived Exertion

Perceived exertion was measured according to the Borg Rating of Perceived Exertion scale [27] in each exercise with a score ranging from 6 to 20.

Maximum Oxygen

A respiratory gas analysis device, or metabolic gas analyzer device, is used to measure the maximum oxygen consumption during the physical activity on a treadmill or bicycle at different intensities. Queen's step test was used to calculate the VO_2 max (for females) according to the following formula [28]:

> VO_2 max (ml/kg/min) = 65.81 – [0.1847 × pulse rate beats (for 15 seconds)/min]

Muscle Preparation Test

Before the daily muscle preparation test, participants were guided through a 5-minute dynamic warm-up. The warm-up session began with a short walk to an indoor track or open gym. Next, a series of active movements targeting the pectoral, deltoid, and trapezius muscles was completed. Muscle tests included those indicated in the ACSM Health-Related Fitness Assessment Guide [29], such as the plank test (in seconds), the number of correct push-ups performed within 1 minute, and the wall squat test (how long the participant remains in squat position until fatigue). The participant is instructed to rate the pain intensity in their legs on a 0-10 numerical rating scale, with 0 defined as "no pain" and 10 as "the worst imaginable pain" [30].

Balance of Energy Expenditure and Energy Intake

Energy intake was recorded for each participant with daily energy intake obtained using the dietary analysis software Nutrition 4, version 1 [31].

Metabolic Syndrome

The siMS score was calculated as a measure of metabolic syndrome according to the following formula [32]:

> siMS score = [(2 × waist circumference)/height] + glucose/reference value + triglycerides/reference value + systolic blood pressure/reference value – HDL/reference value

The siMS risk score was calculated as an expansion of the siMS score using the following formula:

> siMS score × (age/50) × (family history of cardio- or cerebrovascular event=1.2, else=1)

Appetite and Nutrition

To assess subjective appetite sensations, the visual analog scale (VAS) is used. A VAS is typically composed of lines (of varying length) with words anchored at each end describing the extremes (ie, "I have never been hungrier" to "I am not hungry at all").

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Participants are then asked to make a mark across the line corresponding to their feelings [33].

Nutrition attitude will be measured using the EAT-26 tool, a 26-item scale that assesses the symptoms and characteristics of eating disorders and yields an overall score. This questionnaire asks about the frequency of thinking and feeling about food, eating, and their body in disordered ways. Items are rated on a 6-point Likert scale, ranging from "always" to "never." The three least symptomatic responses (never, rarely, and sometimes) are given a value of 0. A Cronbach α of 0.94 was reported for the EAT-26 in a sample of women [34]. A score of 20 or higher is considered to indicate the likelihood of having an eating disorder. EAT-26 has been validated by factor analysis in an Iranian population, which is based on three response options (never, rarely, and sometimes), and the Cronbach α was reported to be 0.86 [35].

Standard-Calorie-Expenditure Training Protocol

According to the ACSM fitness guidelines [36], the standard-calorie-expenditure program includes 15 minutes of walking or running on a treadmill and 24 minutes of whole-body exercises in the first 4 weeks, followed by 25 minutes of walking and running and 39 minutes of whole-body exercises in the last 4 weeks. Specifically, this program involves 12 weeks of multimodal training starting with 3 weekly sessions of 30 minutes of compound training at a moderate intensity of 60%-75% VO_2 max with 900 kilocalories of energy expenditure per week. By the end of the exercise period, the energy expenditure increases to 1200 kilocalories per week, with the exercise period increasing to 75 minutes with an intensity of 75% VO_2 max. The details of the program are outlined in Table 2.

Table 2. Exercise protocol in the standard-calorie-expenditure group on a weekly and session basis (3 sessions/week).

Parameter	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Total time (min)	120	120	120	120	155	155	155	155	190	190	190	190
EXE[a] (min)	15	15	15	15	20	20	20	20	25	25	25	25
MHR[b], %	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85
Whole-body exercises: 10 movements[c]												
EXE time (min)	24	24	24	24	31.5	31.5	31.5	31.5	39	39	39	39
Sets (rest), seconds	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)	3 (30)
Work (rest), seconds	30 (15)	30 (15)	30 (15)	30 (15)	40 (20)	40 (20)	40 (20)	40 (20)	50 (25)	50 (25)	50 (25)	50 (25)
RPE[d]	13-15	14-16	13-15	1416	13-15	14-16	13-15	14-16	13-15	14-16	13-15	14-16
Calories/session	220-280	230-290	260-300	260-320	320-390	330-410	350-420	360-440	370-480	375-490	370-480	400-500
Total calories/week	650-850	700-900	780-900	800-950	920-1185	950-1200	100-1300	110-1340	115-1440	120-1470	115-1440	120-1500

[a]EXE: aerobic exercise.

[b]MHR: maximum heart rate.

[c]In the whole-body section, 10 movements are performed in 3 sets, which increases based on the addition of long-term load and training volume, including a change in resting interval intensity (active recovery and low intensity/recovery such as jogging). Based on the timing of the table, in the range between each set, there is a constant passive recovery period of 30 seconds.

[d]RPE: rate of perceived exertion; calculated as the maximal effort movement for each subject in 30 seconds based on a minimum of 6 when at rest and 20 at the maximum heart rate. During the initial session, we determined the RPE to range from 13 to 15.

High-Calorie-Expenditure Training Protocol

Compared to the standard program, the exercise prescription for the high-calorie-expenditure group has a longer duration (45-110 vs 40-65 minutes per session), lower intensity (50%-75% vs 60%-85% VO_2 max), and more frequent exercise (5 vs 3 times a week). Walking and running are the preferred forms of exercise to maximize calorie burning in comparison to weight training (cycling or rowing), which burns fewer calories. In the high-calorie-expenditure group, the goal of exercise expenditure is 3000-3500 kilocalories per week [30], which is achieved after 2-4 weeks of gradual lengthening of the exercise periods. The training protocol also lasts for 12 weeks, with 45 minutes of whole-body training at 65%-85% VO_2 max consuming 1200 kilocalories per week; based on the principle of gradual overload with increasing weight, the energy expenditure at the end of the training period will be 3500 kilocalories. The calories increase per week [37] and the training time increases to 112 minutes. The main element of training is the same as that of the standard protocol, which starts with 3 sessions per week and gradually increases to 5 sessions per week, although the duration of each training session will be twice that for the standard-calorie-expenditure program in each step (Table 3).

In addition, the participants will be taught how to measure their heart rate in 10 seconds using the two index and middle fingers to find the pulse of the carotid artery of the neck and the pulse

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of the wrist. Participants will report their heart rate during aerobic exercise when requested by the investigator [38]. After 1 minute of active rest, each participant will begin a full-body exercise.

Table 3. High-calorie-expenditure training protocol on a weekly and session basis (3 sessions/week).

Parameter	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Total time (min)	135	135	150	150	246	280	340	340	475	525	530	530
EXE[a] (min)	20	20	20	30	30	30	40	40	40	50	50	50
MHR[b], %	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85	65-75	70-85
Whole-body exercises: 10 movements[c]												
EXE time (min)	25	25	30	30	40	40	45	45	55	55	60	60
Sets (rest, seconds)	3 (30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)	3(30)
Work (rest), seconds	30 (15)	30 (15)	40 (20)	40 (20)	50 (25)	50 (25)	60 (30)	60 (30)	70 (35)	70 (35)	80 (40)	80 (40)
RPE[d]	13-15	14-16	13-15	14-16	13-15	14-16	13-15	14-16	13-15	14-16	13-15	14-16
Calories/session	250-370	320-400	390-400	400-500	450-560	500-580	580-660	600-680	620-700	250-370	320-400	390-400
Total calories/week	750-1100	950-1200	1170-1200	1200-1500	1800-2000	2000-2200	2300-2600	2400-2700	3000-3200	3200-3500	3700-3900	3800-4000

[a]EXO: aerobic exercise.

[b]MHR: maximum heart rate.

[c]In the whole-body section, 10 movements are performed in 3 sets, which increases based on the addition of long-term load and training volume, including a change in resting interval intensity (active recovery and low intensity/recovery such as jogging). Based on the timing of the table, in the range between each set, there is a constant passive recovery period of 30 seconds.

[d]RPE: rate of perceived exertion; calculated as the maximal effort movement for each subject in 30 seconds based on a minimum of 6 when at rest and 20 at the maximum heart rate. During the initial session, we determined the RPE to range from 13 to 15.

Training Exercise or Multimodal Program for One Session

In both groups, participants report their weekly exercise with an exercise physiologist to estimate caloric intake and ensure compliance. After 1 minute of rest after completing the aerobic exercises, whole-body exercises are performed, consisting of 10 repetitions of the movement, in such a way as to replace the energy expenditure specified in the program and prevent repetition of the exercises. The body weight training pattern shows the energy expenditure during exercise, and the calories burned for the warm-up and cool-down periods are also calculated from the smartwatch and verified from the ACSM formula [39]. To avoid fatigue and repetition of movements during the training period, the movements are changed in a variety of ways every week, as shown in Figure 2.

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Figure 2. Specific exercises and drills applied in the program. In the aerobic part, participants can choose from the exercises of the first row. In the whole-body section, participants can choose 2 movements from the exercises of the 2nd row and 4 movements from the exercises of the 5th row to prevent the repetition of exercises in each session.

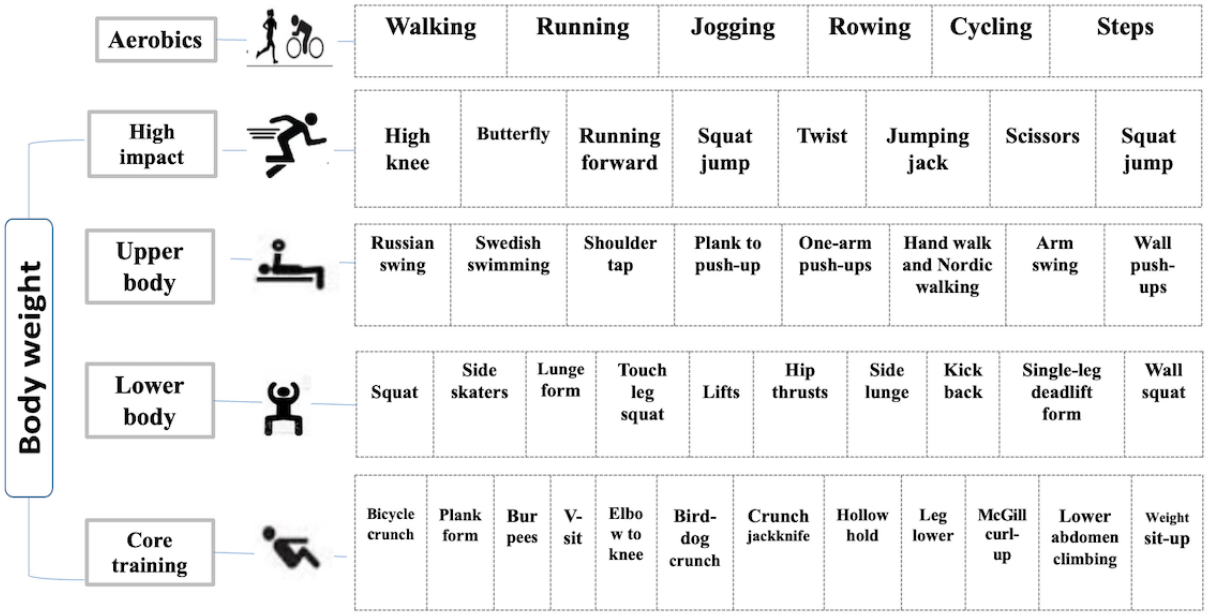

Results

Preliminary results show that the high-calorie-expenditure training program more than doubled weight loss and reduced fat mass, along with a further decrease in waist circumference. Figure 3 shows the changes in the body composition of the three groups. The overall goal of increasing exercise energy consumption was achieved, with an increase in energy consumption in physical activity of more than 3500 calories per week in the high-calorie-expenditure group and up to 1200 calories per week in the standard-calorie-expenditure group. Preliminary statistical analyses indicate significant differences between the stages and in the interaction of time and group. Additional analyses of functional parameters, lipid profiles, inflammatory factors, and blood indicators are ongoing.

Figure 3. Changes in BMI, weight, fat content, and muscle in the the three groups. CG: control group (no exercise); HC: high-calorie-expenditure group; SC: standard-calorie-expenditure group.

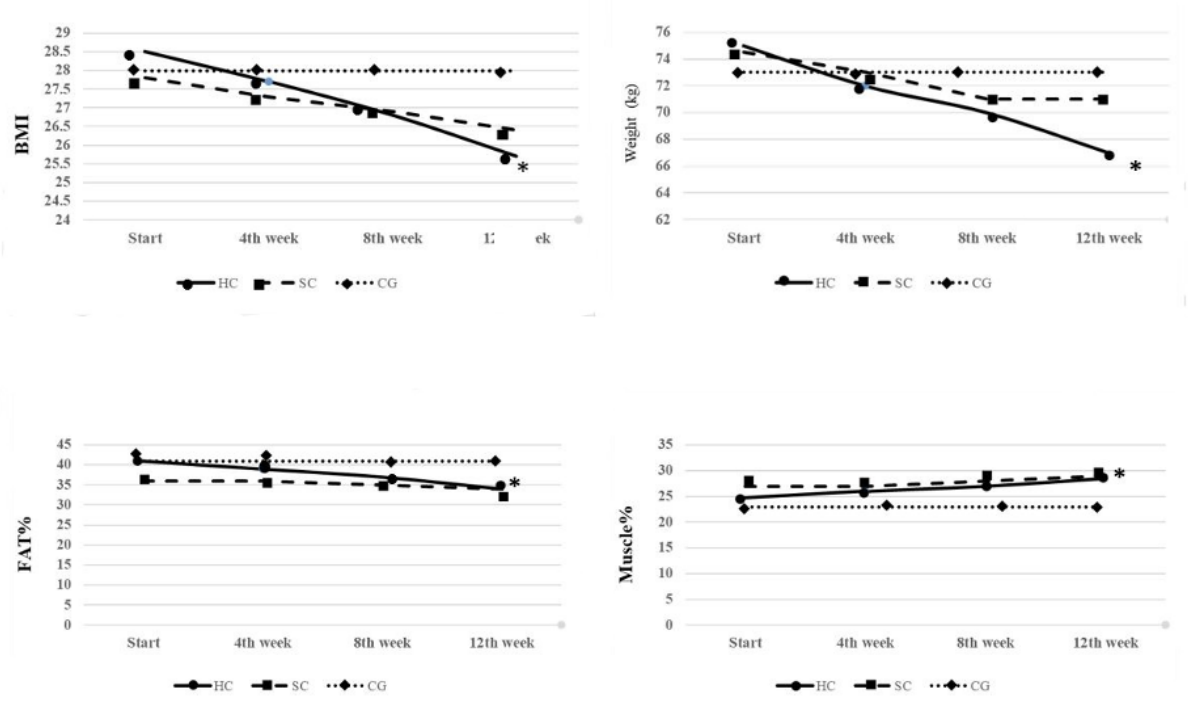

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Discussion

Principal Findings

The primary results of this study show that high-calorie-expenditure exercise is superior to regular exercise in terms of achieving weight loss in women with overweight. Our results demonstrate that both types of exercise (high and standard calorie expenditure) led to significant weight loss (P=.003). Significant changes were also observed in muscle percentage (P=.05) and BMI (P=.05) of the high-calorie-expenditure group after 12 weeks. The functional tests also showed that both exercise programs had a positive effect on the participants.

Comparison With Prior Studies

In the case of severe and acute illnesses such as COVID-19, the effects of the disease not only decrease physical activity but also cause obesity problems in women [40]. Consequently, living an active lifestyle and monitoring one's diet by counting daily calories can be a helpful approach to lose weight. The preliminary results of this study show that the average calorie expenditure of group-based mixed high-calorie-expenditure exercise (including the warm-up and cool-down periods) was 800 kilocalories, as estimated by the Apple Watch calorimeter. By contrast, the energy consumption per session for the standard-calorie-expenditure group was only 450 kilocalories. Results from a limited number of studies measuring energy expenditure with caloric intake have been mixed. Overall, participants performing high- and standard-calorie-expenditure exercises burned 3700 and 1350 calories, respectively. Brisebois [41] showed that 30 adults (19-60 years old, 50% women) had an average energy expenditure of 7.5 kilocalories/minute in a 60-minute CrossFit session. In a 2018 study [42], a 10-month implementation of an integrated neuromuscular circuit-type training program in small groups resulted in (1) an increase in daily energy expenditure relative to energy intake, leading to a decrease in body mass and fat; (2) an increase in strength and cardiovascular performance; and (3) a high adherence rate. Exercise-induced gains were reduced but not lost after a 5-month no-exercise period. The exercise program involved noninjury HIIT using resistance exercises of the whole body and cardiovascular activities with a limited time commitment and organized in a small group, resulting in favorable adaptation in the body and fat mass of people with overweight and obesity. Circuit-type neuromuscular exercise training protocols using only body-weight exercises could reduce body mass and fat and improve strength and endurance performance in women. These changes were attributed to an increased resting metabolic rate and lean mass, leading to increased energy expenditure. Weight/fat recovery from nonexercise was limited, suggesting that this type of exercise training may promote the long-term maintenance of weight loss in adults with overweight [42]. Willis et al [43] recorded the energy expenditure of 20 men and women during a 40-minute training session delivered by video. The findings indicated that the participants burned an average of 392 kilocalories per session (9.8 kilocalories per minute). Differences in the type and intensity of exercise throughout the session can explain the differences in the results of our study and those of previous studies. In addition, Willis et al [43] found a significant difference in energy expenditure between men and women of ~134 kilocalories per session (3 kilocalories/minute). This previous study compared the traditional exercise method with other methods. Therefore, it was not based on whole-body training and the sessions all involved steady-state exercise at the same intensity. Weight training is usually performed at high intensity for short periods with longer periods in between, which is expected. In this study, the timing of the training protocols was modified, but the protocol was similar to that of resistance training.

Monteiro et al [44] indicated that CT requires the consumption of more calories than resistance training. CT, resistance training, and combined exercises such as using a treadmill or bicycle have not been compared. Skelly et al [45] compared single sessions of two cycling protocols, HIIT and moderate steady-state endurance exercises, with a constant caloric-expenditure protocol, showing that oxygen consumption was higher in the steady-state protocol than in the HIIT protocol. However, the steady-state protocol was of a much longer duration (50 vs 20 minutes). Therefore, it can be assumed that if the duration of the two sessions were equal, the HIIT protocol would burn more calories [45]. A 6-month pilot study conducted at Pennington Biomedical Research Center [46] compared 25% CR achieved through (1) dietary restriction alone and (2) a combination of dietary restriction and exercise. Compared to the free control group, CR and exercise led to an increase in energy expenditure by 12.5%. The primary hypothesis was that CR would attenuate primary aging processes, as represented by the presence of metabolic adaptation, which is a reduction in the rate of energy expenditure beyond what would be expected on the basis of body size. In support of the hypothesis, they found that the mass-adjusted sleeping energy expenditure was reduced after 6 months of CR and CR+exercise, indicating metabolic adaptation and perhaps a delay of primary aging [46].

Among the multifaceted combined exercises highlighted above, body weight and aerobics exercises are highly valuable and can provide powerful results for middle-aged individuals. In particular, these exercises have been shown to improve cardiovascular performance and respiratory health, reduce weight, reduce body fat and increase muscle mass, improve blood circulation, improve bone and skeleton conditions, and finally improve the quality of life of middle-aged people [47,48]. In addition, in line with the prominent health-related effects of a multimodal exercise program, Batrakoulis et al [49] showed that combined aerobic and resistance exercise was the most effective method and hybrid exercise was the second most effective method for cardiometabolic health outcomes in adults with overweight and obesity, indicating higher efficacy for multicomponent exercise interventions compared to single-component methods such as continuous endurance training as a periodic exercise. Subgroup analysis of resistance training further showed that the effects of different types of training were mediated by gender [49]. This study also supports recent findings and exercise guidelines for individuals with overweight/obesity, highlighting the importance of a multicomponent exercise approach to improving cardiometabolic health. Accordingly, physicians and health care professionals should prescribe multicomponent exercise interventions for

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adults with overweight and obesity to maximize clinical outcomes [48]. In the present protocol, ACSM guidelines were suggested with some changes to increase the caloric expenditure of the exercise. Although HIIT exercises can also be effective, according to international guidelines for physical activity and exercise and guidelines for sedentary behavior, obesity, and type 2 diabetes, it is suggested that before starting HIIT exercise protocols, individuals should achieve a baseline level of physical fitness. Participating in a preliminary training program before using HIIT can help to reduce the risk of musculoskeletal injury while ensuring a positive training experience from the outset [50]. A gender difference in outcomes is anticipated because of variabilities in body weight and the higher rate of weight loss in men than in women.

Limitations

This study has several limitations. The physical activity levels of the participants obtained with the IPAQ were not installed in the software and mobile phones of each participant. However, the results were determined to be satisfactory after answering the questionnaire. In addition, because this investigation started immediately after the lifting of restrictions related to the COVID-19 pandemic to conform with health protocols, it is possible that this long period of isolation had mental and psychological consequences on the participants.

When developing a target exercise interval, it is important to consider relevant variables to ensure that energy expenditure is at the level necessary for the health of all people. Further research is needed to confirm our results and determine the optimal group-based workouts that maximize caloric burn while increasing adaptation. In this study, we have confirmed the applicability of 5 high-calorie-expenditure training sessions in women over 35 years old, with benefits of weight loss, fat mass reduction, and muscle mass increase. In addition, our initial analyses suggest benefits with respect to inflammation and the lipid profile. However, the effects of these exercises on the immune system, bone conditions, reproduction, and other health facets remain unclear. It will also be valuable to examine the effect of this type of exercise over the longer term for 6 months to 1 year.

Conclusion

Multimodal exercises with high calorie expenditure have a significant effect on body composition and glycemic and health indicators, and these exercises can be performed by people who are overweight, including those with type 2 diabetes. Our study only focused on women over 35 years of age with a sedentary lifestyle and a body weight in the overweight range. Future work could focus on the impact of this program on both men and women with obesity and overweight. In addition, tools and machines can be incorporated into the programs in future research. Several studies have shown that multimodal exercises may offer a means of repairing and recharging metabolism for middle-aged people with inactive lifestyles. Training programs using the ACSM's minimum protocols for exercise have shown significant improvements in strength and endurance. The ACSM guidelines seem appropriate for a large proportion of the adult population who are seeking to gain muscle and lose fat. Research suggests that aerobic and total body exercise may play an important role in fitness and health, particularly with regard to body composition, glucose utilization, resting blood pressure, blood lipid profile, vascular status, and gastrointestinal transport, along with positive impacts on bone mineral density, heart function, back pain, arthritis, depression, metabolic syndrome, cardiovascular disease, and all-cause mortality. Therefore, it is recommended to include multimodal methods in weight loss and health promotion programs.

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Authors' Contributions

SDN was responsible for project ideation, article editing, exercise design and study design, statistical analysis, study concept, and the literature search. VSS and RA were responsible for revision of the protocol and the manuscript. MAD implemented the plan, coached the participants, obtained the measurements, and wrote the article.

Conflicts of Interest

None declared.

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Abbreviations

ACSM: American College of Sports Medicine
CR: calorie restriction
CT: circuit training
EAT-26: Eating Attitude Test-26
HDL: high-density lipoprotein
HIIT: high-intensity interval training
IPAQ: International Physical Activity Questionnaire
IPAQ-L: International Physical Activity Questionnaire long form
LDL: low-density lipoprotein
MET: metabolic equivalent
NCD: noncommunicable disease
REE: resting energy expenditure
VAS: visual analog scale
VO_2 max: maximum oxygen rate

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Protocol

The Effect of Acupuncture on Brain Iron Deposition and Body Iron Metabolism in Vascular Cognitive Impairment: Protocol for a Randomized Controlled Trial

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Abstract

Background: Vascular cognitive impairment (VCI) persistently impairs cognition and the ability to perform activities of daily living, seriously compromising patients' quality of life. Previous studies have reported that disorders of serum iron metabolism and iron deposition in the brain can lead to inflammation, abnormal protein aggregation and degeneration, and massive neuronal apoptosis in the central nervous system, which in turn leads to a progressive decline in cognitive processes. Our previous clinical studies have found acupuncture to be a safe and effective intervention for treating VCI, but the specific mechanisms require further exploration.

Objective: The objective of the trial is to evaluate the clinical efficacy of Tongdu Xingshen acupuncture and to investigate whether it can improve VCI by regulating brain iron deposition and body iron metabolism.

Methods: In total, 42 patients with VCI and 21 healthy individuals will participate in this clinical trial. The 42 patients with VCI will be randomized into acupuncture and control groups, while the 21 healthy individuals will be in the healthy control group. Both the control and acupuncture groups will receive conventional medical treatment and cognitive rehabilitation training. In addition, the acupuncture group will receive electroacupuncture treatment with Tongdu Xingshen for 30 minutes each time, 6 times a week for 4 weeks. Meanwhile, the healthy control group will not receive any intervention. All 3 groups will undergo baseline assessments of brain iron deposition, serum iron metabolism, and neuropsychological tests after enrollment. The acupuncture and control groups will be evaluated again at the end of 4 weeks of treatment, as described earlier. By comparing neuropsychological test scores between groups, we will examine the efficacy of Tongdu Xingshen acupuncture in treating VCI. Additionally, we will test the correlations between neuropsychological test scores, brain iron deposition, and body iron metabolism indexes to explore the possible mechanisms of Tongdu Xingshen acupuncture in treating VCI.

Results: Participants are currently being recruited. The first participant was enrolled in June 2023, which marked the official start of the experiment. As of the submission of the paper, there were 23 participants. The recruitment process is expected to continue until June 2025, at which point the processing and analysis of data will begin. As of May 15, 2024, up to 30 people have been enrolled in this clinical trial.

Conclusions: This study will provide data on the effects of Tongdu Xingshen acupuncture on cerebral iron deposition as well as somatic iron metabolism in patients with VCI. These results will help to prove whether Tongdu Xingshen acupuncture can improve VCI by regulating brain iron deposition and body iron metabolism, which will provide the clinical and theoretical basis for the wide application of acupuncture therapy in VCI rehabilitation.

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KEYWORDS

acupuncture; vascular cognitive impairment; iron metabolism; mechanisms explored; clinical trial; needling technique; dry needling; acupunctures; activities of daily living; iron; prevalence; cerebrovascular diseases; vascular dementia; vascular; traditional Chinese method; Chinese methods

Introduction

Vascular cognitive impairment (VCI) is a series of clinical syndromes that encompasses mild cognitive impairment to severe vascular dementia (VD) caused by cerebrovascular disease and its risk factors [1]. VCI accounts for 15% to 20% of all patients with dementia in North America and Europe, and up to 30% of patients with dementia in Asia, making it the second most prevalent type of dementia after Alzheimer disease [2]. The persistent and progressive decline of higher brain functions, such as learning, memory, and executive functions, caused by VCI is a difficult problem in clinical rehabilitation, which seriously affects patients' quality of life and involves a severe burden for families and society. Although donepezil and memantine may slow the progression of VCI, there are currently no effective clinical drug options for VCI from a clinical perspective [3,4]. Although nonpharmacological treatments such as aerobic exercise and cognitive rehabilitation training, as well as early control of risk factors such as blood pressure, lipids, and blood glucose, have been reported to have positive effects on the prevention and treatment of VCI, a range of issues limit the effective treatment of VCI, including a lack of clinical research, low compliance, lengthy interventions, and variable efficacy [5-8]. Therefore, it is important to find safe, effective, and widely applicable treatment methods for the clinical treatment and development of VCI.

Numerous studies have indicated that traditional Chinese medicine (TCM) can play an important role in the treatment of VCI [9,10]. In particular, acupuncture has the unique advantages of simplicity, convenience, safety, and effectiveness in the treatment of VCI [11]. According to the understanding of VCI in Chinese medicine, in which the "brain" and "governor vessel" play key roles in regulating the "vital spirit" and brain function, the "deficiency of the medulla oblongata and loss of the use of the spiritual mechanism" is considered to be the fundamental pathogenesis of VCI, leading to the development of the Tongdu Xingshen treatment principle. Several prior clinical studies in our laboratory and meta-analyses published by other researchers have demonstrated that acupuncture is effective in improving cognitive function and enhancing overall outcomes in patients with a history of stroke [12-14]. However, the in-depth mechanisms of Tongdu Xingshen acupuncture treatment for VCI require further validation and exploration.

The pathogenesis of VCI is complex. Previous studies of the pathogenesis of VCI have mainly focused on blood-brain barrier disruption, secondary inflammation, excitatory amino acid toxicity, cell autophagy, and apoptosis [15,16]. With the discovery of ferroptosis and the in-depth study of its mechanism of occurrence, more and more scholars believe that it plays an important role in central nervous system diseases [17,18]. By exploring the relationship between serum iron metabolism, brain iron deposition, and cognitive impairment, researchers in various countries, including China, have found that iron deposition can lead to the development of inflammation, abnormal protein aggregation, and degeneration in the central nervous system, which in turn causes a progressive decline in cognitive function [19,20].

Quantitative susceptibility mapping (QSM) is a postprocessing technique developed in recent years on the basis of sensitivity-weighted imaging (SWI), which enables to quantify the magnetic susceptibility properties of tissues in vivo [21,22]. The ability to measure brain iron content, which is quantified by the magnetization rate values obtained from QSM calculations, raises the possibility of investigating ferroptosis in VCI.

Therefore, the proposed study will examine brain iron deposition and body iron metabolism as entry points and use a clinical randomized controlled study design to investigate the clinical efficacy and possible mechanism of action of Tongdu Xingshen acupuncture to treat VCI with a view to providing a scientific basis for the clinical application of acupuncture.

Methods

Research Objectives

The primary objectives of this randomized controlled trial will be twofold: (1) to observe the clinical efficacy of Tongdu Xingshen acupuncture in patients with VCI and provide feasible and affordable acupuncture treatment for patients with VCI and (2) to investigate whether Tongdu Xingshen acupuncture improves the clinical performance of patients with VCI by affecting brain iron deposition and body iron metabolism and reveal the potential central and peripheral mechanisms of acupuncture in the treatment of vascular cognitive disorder.

Trial Design and Setting

The proposed protocol involves a randomized controlled clinical trial to investigate whether Tongdu Xingshen acupuncture can improve the clinical performance of patients with VCI by regulating brain iron deposition and body iron metabolism. In total, 42 patients with VCI hospitalized at the First Affiliated Hospital of Henan University of Traditional Chinese Medicine from May 2023 to December 2025 and 21 healthy participants will be included in the study. Participants will be divided into acupuncture, conventional treatment, and healthy control groups according to a ratio of 1:1:1, with 21 participants in each group.

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The control group (n=21) will receive conventional medical and cognitive rehabilitation treatment, the acupuncture group (n=21) will receive professional acupuncture treatment by a professional acupuncturist on the basis of the conventional treatment, and the healthy control group (n=21) will not receive any intervention. All of the above treatments will be performed for 4 weeks, 6 times per week. Brain iron deposition and serum iron metabolism will be measured at week 0 (baseline) and week 4 of treatment using SWI and blood biochemistry. In parallel, a neuropsychological test battery including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Clinical Dementia Rating will be administered to evaluate comprehensive cognitive function and clinical symptoms. Details of the proposed study process are presented in Figure 1 and Table 1.

Figure 1. Flowchart of the trial. CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; SWI: sensitivity-weighted imaging; VCI: vascular cognitive impairment.

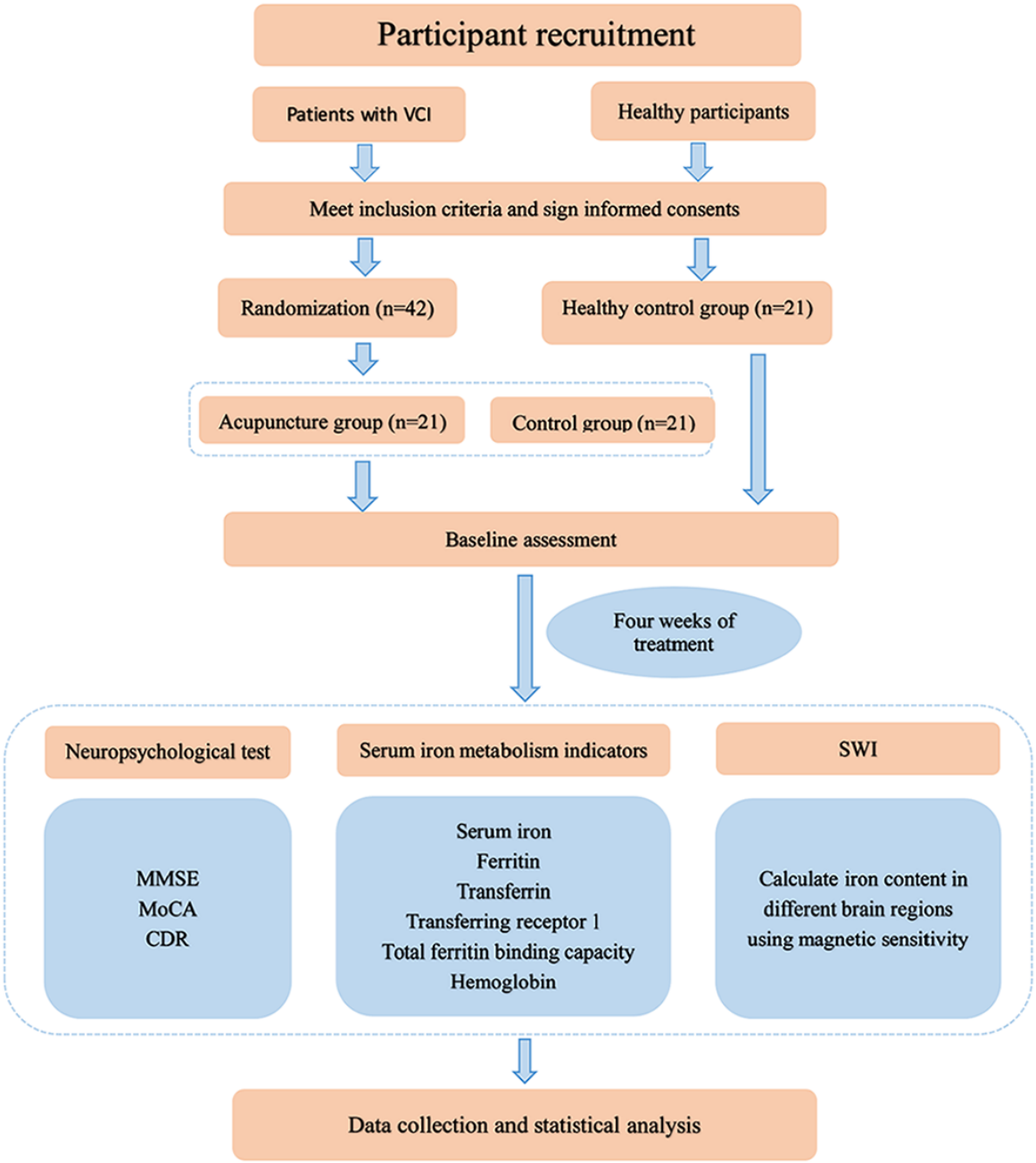

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Table 1. Timing of treatment assessments and data collection.

Time point	Enrollment (week –1)	Baseline assessment (week 0)	Treatment phase (weeks 1-4)	Assessment of efficacy (week 5)
Sign informed consent	✓			
Demographic information	✓			
Medical history	✓			
Disease history	✓			
Randomization	✓			
Interventions				
Acupuncture plus routine treatment		✓	✓	
Routine treatment		✓	✓	
Assessments		✓		
Cognitive function assessments				
MMSE[a]		✓		✓
MoCA[b]		✓		✓
CDR[c]		✓		✓
Blood detection				
Serum iron metabolism indicators		✓		✓
SWI[d] scanning				
Brain iron content		✓		✓
Safety evaluation		✓	✓	
Adverse event		✓	✓	

[a]MMSE: Mini-Mental State Examination.

[b]MoCA: Montreal Cognitive Assessment.

[c]CDR: Clinical Dementia Rating.

[d]SWI: sensitivity-weighted imaging.

Participants and Recruitment Strategy

Participants in this study will be recruited mainly through the inpatient system of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, and we will also use the hospital's website and WeChat public number platform for promotion and recruitment. Patients with VCI and healthy participants who are interested and whose initial screening meets our recruitment needs will be fully informed of the entire study procedure, benefits, and risks. We will conduct this recruitment with full respect for each participant's individual wishes. We also guarantee that the right of each participant to withdraw from the study will be respected at all stages of the clinical trial.

Inclusion and Exclusion Criteria

Inclusion Criteria

Inclusion criteria are as follows: (1) aged 18-75 years, male or female; (2) patient or informant reports of memory loss or other cognitive impairment lasting for at least 3 months and not using any medication to improve cognitive function prior to enrollment; (3) diagnostic criteria for VCI are met (Western medical diagnostic criteria refer to the *2019 Chinese Guidelines for the Diagnosis and Treatment of Vascular Cognitive Disorder* and Chinese medical diagnostic criteria refer to the *Diagnostic, Identification and Efficacy Determination Criteria for Vascular Dementia*); (4) imaging evidence (computed tomography or magnetic resonance imaging) to support cerebrovascular disease; (5) clear cognitive dysfunction, as assessed by the MMSE (no education: MMSE score≤17, primary school: MMSE score≤20, or junior school or above: MMSE score≤24) and MoCA (MoCA score < 26 points); and (6) consciousness and stable vital signs.

Exclusion Criteria

Exclusion criteria are as follows: (1) occurrence of other brain diseases that affect cognitive function, such as intracranial occupying lesions, traumatic brain injury, arteriovenous aneurysms, and intracranial infections; (2) cognitive impairment caused by hemorrhagic stroke; (3) diseases that seriously affect the cognitive examination such as abnormal visual and auditory functions, and psychiatric abnormalities; (4) history of significant cognitive decline or dementia prior to current onset; (5) other serious diseases such as immune diseases, endocrine diseases, abnormal liver, and kidney function; (6) pregnant and lactating women; and (7) coagulation disorders and treatment site infections.

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Rejection Criteria

Rejection criteria are as follows: (1) individuals who were mistakenly included without a diagnosis of VCI; (2) individuals who did not complete the treatment cycle in the enrolled study cases; (3) serious adverse events or complications that make it inappropriate to continue the experiment; (4) participants spontaneously shed, miss visits, or die during observation; and (5) receiving medications and treatments that have a significant effect on outcomes during the trial.

Sample Size

Previous clinical studies on patients with VCI treated with acupuncture reported that the scores on the MoCA scale of acupuncture-treated and base-treated patients with VCI at 4 weeks were mean 26.13 (SD 5.33) and mean 22.66 (SD 5.38), respectively. We set the significance level at .05 and calculated the sample size as follows:

$$N = 2\,[(Z_{\alpha/2} + Z_{\beta})\,\sigma / \delta]^2$$

N is the sample size in each group, and σ and δ represent the larger SD and mean difference between the 2 groups with values of 5.38 and 3.47, respectively. When α=.05 and β=.1, checking the table shows that $Z_{\alpha/2}$=1.96 and Z_{β}=1.282. Substituting the above data into the formula, a minimum of 64 patients in the randomized acupuncture group or control group will be required, considering a 20% shedding rate.

A review of relevant studies indicates that in magnetic resonance imaging–based studies of cognitive impairment, statistical significance can be achieved with 12 or more cases [23,24]. Because of limitations in the experimental conditions (high scanning cost of magnetic resonance imaging and the need for high levels of participant cooperation during scanning), we estimate that approximately one-third of the estimated sample of patients with VCI will be included as study participants, and finally, 42 patients with VCI and 21 healthy controls will be included.

Randomization

To ensure balanced comparability between groups, we will use SPSS software (version 25.0; IBM Corp) to generate a random sequence, and 42 participants with VCI who meet the inclusion criteria will be randomly assigned to the acupuncture and control groups at a ratio of 1:1. In addition, the 42 numbered random sequences as well as the grouping scheme will be placed independently in sealed opaque envelopes, which will be opened only when a patient with VCI is enrolled. The randomization and concealment processes described earlier will be carried out by an independent third-party statistician who is not involved in any subsequent parts of this study.

Blinding

Because of the limitations of the protocol and the specific nature of acupuncture treatment, it will not be possible to blind the participants and the acupuncturists. However, to improve the quality and reliability of this study, the researchers will be blinded during the efficacy assessment, data collection and management, and statistical analysis of the results. Thus, the efficacy assessors, data collection and management personnel, and outcome analysis personnel will not be aware of the grouping of the trial and will not be allowed to communicate with each other or with the participants about the treatment. In addition, to prevent bias in the results by nonblinded participants or researchers, this study will only involve individuals who do not have a conflict of interest or preconceived position.

Intervention

Overview

Different groups will receive different interventions: the acupuncture group will receive acupuncture in addition to conventional medical treatment and cognitive rehabilitation training, the control group will receive conventional medical treatment and cognitive rehabilitation training only, and healthy participants will not receive any treatment. All of the above treatments will be performed by physicians and therapists who are certified and have more than 5 years of clinical experience. Below we describe the specific interventions for the 2 intervention groups.

Acupuncture Group

On the basis of conventional medical treatment and cognitive rehabilitation training, we will use Shenting and Baihui for electroacupuncture treatment. The specific acupuncture point positioning standards refer to *Acupuncture and Moxibustion* (“14th Five-Year Plan” National Higher Education Planning Textbook for the Chinese Medicine Industry). The specific method is as follows: the patient is placed in a supine position, and after routine disinfection of the Shenting and Baihui points with 75% alcohol cotton balls, the patient is stabbed backward with Hua Tuo brand (0.25 mm×25 mm) acupuncture needles in a flat direction (needle body and skin surface layer 15 degrees) of Baihui 0.8 to 1.0 inch and Shenting 0.5 inch. The electroacupuncture therapy instrument (SDZ-II; Jiangsu Medical Supplies Co) is connected to acupuncture needles after the patient gets qi (local soreness), and the waveform is continuous for the first 15 minutes, at an intensity that is tolerated by the patient, and then changes to a sparse waveform after 15 minutes to prevent electrical adaptation. After 30 minutes of electroacupuncture, the electroacupuncture instrument is removed; the needles are not removed and are retained for 1 hour. Cognitive function training is performed during the retention period, and the needles are twisted once at the beginning and once at 30 minutes, until the end of cognitive function training. The acupuncture needles are then removed. The electroacupuncture treatment will be performed once a day, 6 times a week, for 4 weeks.

Control Group

The control group will receive only conventional medical treatment as well as cognitive rehabilitation training. Specific treatment will include symptomatic treatment for the patient’s underlying diseases, such as controlling blood pressure, blood sugar, and blood lipids, antiplatelet aggregation, and nourishing brain cells. At the same time, according to the patient’s condition, a combination of manual training and computer training will be used to perform conventional cognitive function training such as category classification, rule (response) inhibition, plan analysis, reasoning and comprehension, working

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memory, and synthesis ability, for 1 hour per session, 6 times a week, for 4 weeks.

Healthy Control Group

The healthy control group will receive no intervention.

Outcome Measurements

Overview

The 3 main areas of assessment will include neuropsychological tests, SWI, and serum iron metabolism. Researchers who are blinded to the treatment allocation will carry out all treatment evaluations.

Neuropsychological Tests

Cognitive function will be assessed at baseline and after 4 weeks of treatment by a professional evaluator using neuropsychological tests, and the evaluator will not be aware of the current grouping. The following are the neuropsychological test scales that will be used in this experiment.

MMSE Scale

The MMSE scale consists of 30 questions (1 point per question) in 7 areas: temporal orientation, place orientation, immediate memory, attention and calculation, delayed memory, language, and visuospatial ability [25]. Scores on this scale are closely related to literacy level, and it is generally accepted that people with illiteracy (≤17), primary school education (≤20), and junior high school and above education (≤24) have different degrees of cognitive dysfunction. Because of its simplicity, time-saving features, convenience of administration, and wide range of applications, the MMSE scale is used for the initial screening of different types of cognitive impairment and dementia.

MoCA Scale

The MoCA scale was developed by Tsai et al [26] in 2004 for rapid screening of mild cognitive impairment and has better sensitivity than the MMSE. The MoCA scale assesses cognitive domains including attention and concentration, executive function, memory, language, visual-structural skills, abstract thinking, numeracy, and orientation, with a total scale score of 30, and test results showing a normal value of ≥26.

Clinical Dementia Rating

In Clinical Dementia Rating, the physician obtains information by talking to the patient and family to quickly complete an assessment of the patient's level of cognitive impairment [27]. The scale's assessment domains include memory, orientation, judgment and problem-solving, work and social interaction, family life and personal hobbies, and independent living skills. Each of the above 6 functions was evaluated at 5 levels, from no impairment to severe impairment. The 6 abilities were combined into a total score that is based on the overall scoring criteria, with the results expressed as 0, 0.5, 1, 2, or 3, which are considered to represent normal, suspicious, mild, moderate, and severe dementia, respectively.

Serum Iron Metabolism–Related Indicators

A total of 4 mL of blood will be collected from patients in the morning on an empty stomach. The supernatant will then be extracted after centrifugation at 3000 revolution/min for 15 minutes at 4 °C. The levels of iron, ferritin, transferrin, transferrin receptor 1, total iron binding capacity, and hemoglobin will be measured using enzyme-linked immunosorbent assay.

High-Resolution Magnetically SWI

All participants will undergo SWI, and the data will be postprocessed and analyzed using Susceptibility Mapping and Phase Artifacts Removal Toolbox software (The Math Works Inc) to obtain QSM images. Signal processing in Nuclear Magnetic Resonance software (Philips Healthcare Netherlands Ltd) will then be used to detect and quantitate the corrected phase value in the region of interest, including bilateral parietal cortex, frontal white matter, caudate nucleus, putamen, globus pallidus, thalamus, red nucleus, substantia nigra, hippocampus, and dentate nucleus [21,22,28]. Care will be taken to avoid blood vessels, calcifications, and visible lesions during the measurements. Each site will be measured twice, and the average of the 2 measurements will be taken. The magnitude of magnetization will be used to indicate the level of iron content of the tissue.

Safety Evaluation and Adverse Events

We will minimize the occurrence of adverse events in this clinical trial to ensure the safety of each participant. A comprehensive physical safety examination will be performed on all volunteers before and after treatment, including vital signs (heart rate, blood pressure, and respiration), routine blood and urine tests, biochemical function tests, electrocardiography, and liver and kidney function tests. Possible adverse reactions in this study include pain during acupuncture, fainting, and skin breakage or other injury caused by improper handling. If the patient experiences acupuncture fainting because of weakness or excessive stress, the acupuncture treatment will be stopped immediately, and the patient will be placed in a comfortable position and given warm water until they recover. In addition, if pain or systemic adverse reactions are caused by excessive current and voltage intensity, the electroacupuncture instrument will be turned off immediately. After confirming that the patient has no adverse reactions, the electroacupuncture instrument will be properly connected and used correctly according to the operational requirements. We will not only record the occurrence of any of the abovementioned adverse events in the case report book but will also actively deal with them.

Data Collection and Management

All participants' information will be recorded in the case report form in a true, complete, accurate, and timely manner, and data entry will be performed using the Clinical Monitor Data Manager (Microsoft Corp) after completion of at least 5 case report forms. We will use a data entry program that is prepared by computer software for the double entry of data, which keeps the participant's personal information strictly confidential during the entry process. To prevent data leakage and loss, these data will be stored by our data researchers on servers with passwords

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and access restrictions and will not be shared with third parties outside of the data recorders and data administrators without the express permission of the research team leader. The quality control team will regularly review the accuracy and reliability of our data, and if there is no objection to these data, we will lock the data. No further changes will be allowed to the locked data file, and the database will be handed over to the statistical analysts for statistical analysis as required by the statistical plan. All of the above data collectors and managers will be involved in this clinical trial only after passing a standardized training and assessment, and more importantly, an agreement will be signed with the data collectors and managers to ensure that they will not disclose any personal information of the participants.

Statistical Analysis

All data will be statistically analyzed by professional statisticians using SPSS software (version 25.0). If the data involved satisfy the characteristic properties of a normal distribution with uniform variance, we will use the mean and SD to describe them; conversely, if the data are not normally distributed, we will use the median and IQR to describe them. All statistical results will be considered statistically significant at $P<.05$.

Neuropsychological scale scores, iron metabolism–related indicators, and brain iron deposition are all measurement data. Normally distributed data with uniform variance among 3 groups will be analyzed using 1-way ANOVA, followed by multiple comparisons using the least significant difference test, whereas those with nonnormal distributions will be compared using the Kruskal-Wallis test followed by the Mann-Whitney *U* test with Bonferroni correction. Correlations between neuropsychological scale scores and serum iron metabolism indexes and brain iron deposition in patients with VCI will be assessed using Pearson correlation analysis.

Quality Control

To ensure the quality of the proposed experiment, we will conduct unified and standardized training for the researchers in each role before the start of this study. Researchers will then be tested, and only competent researchers will participate in this study. Additionally, to improve participant compliance, we will conduct regular health education activities, enhance humane care, and develop a long-term follow-up plan. Finally, with reference to the requirements in the Specifications for Quality Control and Quality Assurance of Clinical Research in Chinese Medicine, a 4-level quality monitoring system will be established to monitor the clinically collected data on a regular monthly basis to ensure the authenticity and reliability of the study results.

Ethical Considerations

This study will adhere to the principles outlined in the Declaration of Helsinki, ensuring that no additional harm or risks are imposed on the participants. Ethics approval has already been granted by the ethics committee of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine on May 6, 2023 (ethics reference 2023HL-141-01). Prior to the start of the clinical trial, all participants will be fully informed of the purpose of the trial, the procedures involved, the expected duration, and the potential risks and benefits and will voluntarily provide written informed consent. To protect the privacy of participants, their real names will not appear in the case reports, and they have the right to opt out of any section of the experiment. In addition, all participants will receive a Chinese medicine gift pack valued at US $30.

Results

Participants are currently being recruited. The first participant was enrolled in June 2023, which marked the official start of the experiment. As of the submission of the paper, there were 23 participants. The recruitment process is expected to continue until June 2025, at which point the processing and analysis of data will begin. As of May 15, 2024, up to 30 people have been enrolled in this clinical trial.

Discussion

Overview

With the aging of society and the increasing prevalence of cerebrovascular diseases, the number of patients with VCI is increasing. If VCI is not effectively controlled at an early stage, patients may exhibit further deterioration and eventually develop VD [1]. More seriously, there is currently no effective conventional medical treatment for cognitive decline. However, as a simple, convenient, inexpensive, and effective traditional Chinese medical method, acupuncture is widely recognized in medical science for its effectiveness in treating various diseases, particularly a needling technique for restoring cognition, which has been widely used for patients with VCI, giving hope for the treatment of VCI [29,30].

Chinese medicine classifies VCI as “forgetfulness” and “dullness” and considers the condition to be located in the brain. The governor meridian oversees all of the yang and has the ability to regulate both yin and yang, replenish qi and blood, fill the marrow, awaken the mind, and open the orifices. Therefore, the governor meridian is preferred for the treatment of brain diseases [31,32]. Our group’s previous clinical research revealed that electroacupuncture head acupuncture points can effectively improve cognitive dysfunction after stroke, improve patients’ ability to take care of themselves in daily life, and improve the rehabilitation of patients’ limb motor function [14,33]. More importantly, we are now committed to studying the possible mechanisms of TCM in treating diseases from the perspective of modern medicine.

Iron is essential for many biological processes in the central nervous system, including oxygen transport, myelin production, and neurotransmitter synthesis and metabolism [34]. A number of studies have suggested that disorders of iron metabolism may be an important pathophysiological factor in VCI [35-38]. Clinical studies have reported not only a significant increase in serum iron ions in patients with a history of stroke but also a significant increase in iron deposition in brain tissue, as observed using imaging methods [28,39]. Animal experiments have revealed the presence of iron accumulation in the affected brain regions of experimental animals with cerebral ischemia or reperfusion injury [40]. Another clinical study found brain iron accumulation in patients with subcortical ischemic VD and its

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correlation with the severity of cognitive impairment [41]. Therefore, regulation of brain iron deposition and somatic iron metabolism is expected to provide a new target for the treatment of VCI. Based on this, we propose a randomized controlled trial to verify whether the improvement of cognitive function in patients with VD by Tongdu Xingshen acupuncture is associated with the modulation of cerebral iron deposition and body iron metabolism.

Innovations and Limitations

This is the first clinical randomized experimental protocol of our team to use iron metabolism as an entry point to explore the potential mechanisms of acupuncture for VCI using modern medicine. This trial will be conducted using rigorous methods, for example, the patients with VCI will be randomly assigned to 2 groups; the data will undergo blind statistical analysis; and the interventionists, efficacy evaluators, and statisticians will be separated. However, due to the specificity of acupuncture, this experimental protocol could not be double blinded. Moreover, we could not avoid gender bias during the random allocation process. Therefore, to ensure the reliability of the data, we still need to further expand the sample size.

Conclusions

This study will provide data on the effects of Tongdu Xingshen acupuncture on cerebral iron deposition as well as somatic iron metabolism in patients with VCI. More importantly, if the hypothesis of this study is confirmed, the results would provide evidence supporting TCM acupuncture as an alternative treatment modality for VCI and lay the scientific basis for the clinical application of Tongdu Xingshen acupuncture for VCI, which may have important socioeconomic benefits.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

MW and XF proposed the concept for this trial and designed the study. MW, LC, and YW contributed equally to draft the manuscript. JG and KS participated in the revision and editing of this manuscript. YL, YA, RW, and YZ contributed to finding the literature and patient recruitment. All authors contributed to the final version and approved to submit it.

Conflicts of Interest

None declared.

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Abbreviations

MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
QSM: quantitative susceptibility mapping
SWI: sensitivity-weighted imaging
TCM: traditional Chinese medicine
VCI: vascular cognitive impairment
VD: vascular dementia

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Protocol

Web-Based Mindfulness-Based Cognitive Therapy for Adults With a History of Depression: Protocol for a Randomized Controlled Trial

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Abstract

Background: Depression poses a major threat to public health with an increasing prevalence in the United States. Mindfulness-based interventions, such as mindfulness-based cognitive therapy (MBCT), are effective methods for managing depression symptoms and may help fortify existing efforts to address the current disease burden. The in-person group format of MBCT, however, incurs barriers to care such as expenses, childcare needs, and transportation issues. Alternate delivery modalities such as MBCT delivered via the web can be investigated for their capacity to overcome these barriers and still reduce symptoms of depression with adequate feasibility and efficacy.

Objective: This study protocol aims to examine the feasibility and efficacy of MBCT delivered via the web for the treatment of depression.

Methods: To attain study aims, 2 phases will be implemented using a waitlist control design. A total of 128 eligible participants will be randomized into either an 8-week MBCT intervention group plus treatment as usual (MBCT + TAU; group 1) or an 8-week waitlist control group (group 2). In phase I (8 weeks), group 1 will complete the intervention and group 2 will proceed with TAU. In phase II (8 weeks), group 2 will complete the intervention and group 1 will continue with TAU until reaching an 8-week follow-up. TAU may consist of receiving psychotherapy, pharmacotherapy, or combined treatment. Data collection will be completed at baseline, 8 weeks (postintervention for group 1 and preintervention for group 2), and 16 weeks (follow-up for group 1, postintervention for group 2). The primary outcomes will include (1) current, residual, or chronic depression symptoms and (2) psychiatric distress. Secondary outcomes will include perceived stress and facets of mindfulness. The feasibility will be measured by assessing protocol adherence, retention, attendance, and engagement. Finally, the extent of mindfulness self-practice and executive functioning skills will be assessed as mediators of intervention outcomes.

Results: This study began screening and recruitment in December 2022. Data collection from the first cohort occurred in January 2023. By November 2023, a total of 30 participants were enrolled out of 224 who received screening. Data analysis began in February 2024, with an approximate publication of results by August 2024. Institutional review board approval took place on September 11, 2019.

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Conclusions: This trial will contribute to examining mindfulness-based interventions, delivered via the web, for improving current, residual, or chronic depression symptoms. It will (1) address the feasibility of MBCT delivered via the web; (2) contribute evidence regarding MBCT's efficacy in reducing depression symptoms and psychiatric distress; and (3) assess the impact of MBCT on several important secondary outcomes. Findings from this study will develop the understanding of the causal pathways between MBCT delivered via the web and depression symptoms further, elucidating the potential for future larger-scale designs.

Trial Registration: ClinicalTrials.gov NCT05347719; https://www.clinicaltrials.gov/ct2/show/NCT05347719

International Registered Report Identifier (IRRID): DERR1-10.2196/53966

(JMIR Res Protoc 2024;13:e53966) doi:10.2196/53966

KEYWORDS

mindfulness-based cognitive therapy; MBCT; mindfulness-based interventions; depression; depressive symptoms; virtual delivery; mindfulness; mental health; depressive; distress; stress; remote; randomized; controlled trial; controlled trials; RCT; psychotherapy; cognitive therapy

Introduction

Major depressive disorder (MDD) is a serious threat to health in the United States and other middle and high-income countries [1], with a lifetime prevalence rate close to 20% [2]. Those with MDD have both the symptoms of depression and impairments in quality of life [3]. Moreover, MDD can place economic burdens on families and society at large [4]. The average annual costs per depression case can range from US $1000 to $2500 for direct costs, from US $2000 to $3700 for morbidity costs, and from US $200 to $400 for mortality costs [5].

To address chronic challenges to community health such as depression, public health stakeholders seek out programs that can be easily delivered in a web-based setting [6]. Mindfulness-based interventions (MBIs) have been increasingly recognized as efficacious [7] and cost-effective [8] in addressing chronic issues in mental health and substance misuse. Originating from Eastern meditation and yoga traditions, MBIs are designed to foster greater awareness of present-moment experiences [9]. Recent evaluations found that MBIs with a standardized protocol saved health care expenditures for patients with various physical or mental health issues [10,11]. With their consistent benefit on mental health, substance misuse, and physical fitness outcomes [7,12-14], MBIs represent a promising strategy for community organizations dedicated to improving the health of their residents.

Particularly, mindfulness-based cognitive therapy (MBCT) has been shown to be an effective method of reducing symptoms of depression [15-20]. MBCT has also been shown to decrease depression symptoms in individuals with chronic and treatment-resistant depression, as well as residual symptoms of recurrent depression [21-23]. MBCT is an 8-session group intervention program designed to increase awareness of internal reactions that may lead to symptoms of depression. These internal processes may include depression-related rumination and persistent negative thoughts. By equipping individuals with techniques to detach from these dysfunctional cognitive patterns, MBCT has the potential to redirect attention to the current, present-moment experiences [20]. Additionally, MBCT has been associated with several mechanisms of change purported to impact depressive symptoms, including increases in mindfulness and self-compassion in addition to decreases in cognitive reactivity to negative, ruminative thinking [24-26].

Further, 1 challenge surrounding in-person MBCT is the financial barrier that may prevent at-risk populations from accessing the care that they need. The average cost for an 8-session program ranges from US $100 to $250 per session, making it inaccessible for individuals with limited financial resources. What is particularly striking is that individuals with lower incomes are at an increased risk for depression [27] as well as other mental health disorders [28]. This points to the importance of investigating what role MBCT delivered via the web may play for at-risk populations.

A benefit commonly associated with web-based adaptation is decreased cost [29-32]. A web-based format can reduce or eliminate expenses like facilities, food, and traveling fees [33]. Decreased costs enable the interventions to be accessible to a wider range of participants, companies, and researchers at a lower price, allowing for broader dissemination and increased study size. Technology-based delivery also addresses many issues pertinent to administering interventions, such as reaching groups who live in remote locations or who lack adequate transportation [30,34,35]. Web-based platforms enable participants to complete evidence-based intervention sessions in the privacy of their own homes, potentially protecting anonymity and reducing the stigma associated with taking part in a mental health intervention [36,37]. Finally, technology-based administration also eliminates the need to travel to sessions or arrange for childcare, increasing convenience and reducing time commitment for participants [38,39].

However, despite the numerous benefits associated with formats delivered via the web, there are challenges associated with adapting interventions originally designed for in-person delivery. Further, 1 reason for concern is that adaptations that remove fidelity, or key elements of an intervention, harm the efficacy of the intervention [40]. In addition to the potential loss of fidelity of the MBCT program, MBCT delivered via the web also presents challenges in retaining participant attention, maintaining the quality of group discussion, and combating "zoom fatigue."

Our study will take steps to address these concerns, testing the feasibility of the web-based, or online-delivery model of MBCT.

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Such steps will include making recommendations to participants to keep their video on during the intervention session, remaining in a quiet area, making prior arrangements to minimize interruptions, regular check-ins during the session to stimulate participant response to exercises and questions, using headphones if available, having water and a blanket nearby in case needed, and finally, ensuring that a device charger is at hand. In addition to addressing feasibility concerns, we aim to contribute to the evidence base regarding MBCT's efficacy in reducing depressive symptoms. Finally, we hope to add to the understanding of the causal mechanisms and factors that moderate treatment outcomes of MBCT for depressive symptoms.

Methods

Study Design

Our study plans to examine how MBCT delivered via the web may affect primary and secondary outcomes for individuals with a history of depression. It will also assess mediators, moderators, and the sustainability of the intervention. The following hypotheses will be assessed among program participants in the intervention group as compared to a waitlist control group, and within groups compared from pre- to postintervention.

- The MBCT intervention group will show a greater reduction in depressive symptoms from TI to TII, compared to the waitlist group.
- The MBCT intervention group will show a greater reduction in psychiatric distress symptoms from TI to TII compared to the waitlist group.
- The MBCT intervention group will sustain gains through the 8-week follow-up period at TIII.
- The MBCT intervention will improve secondary outcomes, such as:
  - perceived stress
  - facets of mindfulness
- The MBCT intervention will improve the skills associated with mechanisms of change for individuals with a history of depression, and these skills will act as mediators between MBCT and primary and secondary outcomes:
  - extent of mindfulness self-practice
  - executive functioning skills
- The format delivered via the web will meet feasibility aims measured by adherence, retention, attendance, and engagement.

Trial Design

Using a waitlist control design, this trial will randomize 128 eligible participants into 2 groups. In the first phase lasting 8 weeks, group 1 will partake in the MBCT intervention plus treatment as usual (MBCT + TAU) while group 2 will remain as waitlist control following TAU. In the second phase lasting 8 weeks, group 2 will begin completing the MBCT intervention, and group 1 will enter a follow-up phase, continuing with TAU. TAU will be comprised of psychotherapy, pharmacotherapy, or a combination of both. Data collection will be completed at baseline, 8 weeks (postintervention for group 1 and preintervention for group 2), and 16 weeks (follow-up for group 1 and postintervention for group 2). In this manner, our study design will ensure that both trial arms are treated fairly, and that group 1 can be followed up for 8 weeks to assess the sustainability of the intervention. Figure 1 outlines the flow of this study. The registration of this trial took place on April 22, 2022.

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Figure 1. Study flow. MBCT: mindfulness-based cognitive therapy; T: timepoint.

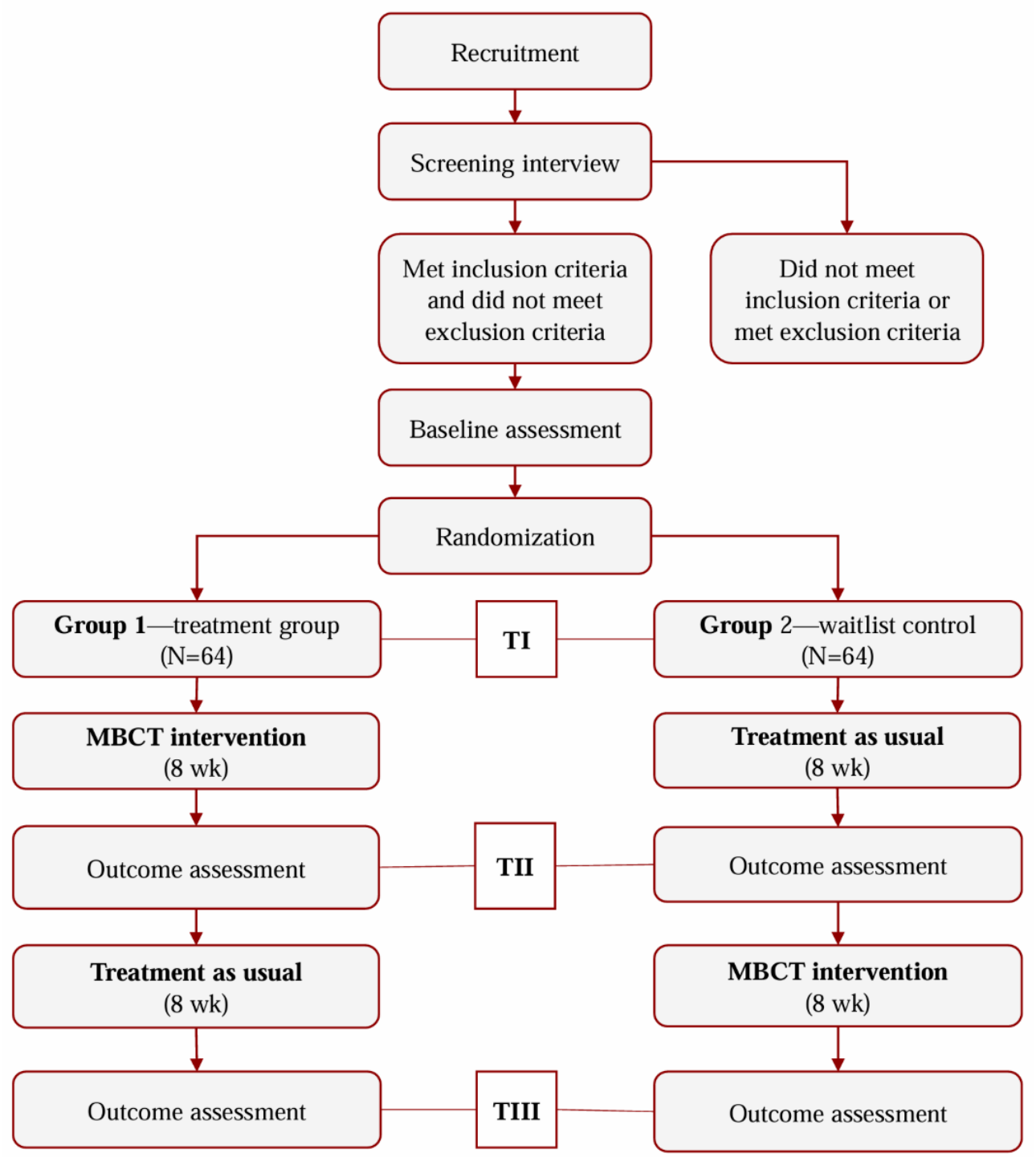

Participants and Procedure

Setting

This study will be led by Prisma Healthcare System and Clemson University, in collaboration with the Prisma Health-Upstate Internal Medicine Clinic. The clinic is a branch of the Prisma Health System that provides community-based primary care and acts as an academic tertiary care site. As part of their goal to address the chronic disease burden, health care providers at the clinic screen approximately 700 patients monthly for depression.

Eligibility Criteria

Participants in this study must (1) be aged 18 years at a minimum, (2) speak English fluently, (3) have sixth grade and above literacy, (4) be willing to share contact information (home address, phone number, or email), (5) have no current mindfulness practice, (6) be Greenville residents or persons who are patients of the partnering organizations in our study, and (7) have current or a lifetime history of any major depressive episode. Study exclusion criteria include (1) current psychosis, dementia, moderate to severe traumatic brain injury, pregnancy, or active suicidality; (2) persistent antisocial behavior; (3) persistent self-injury requiring clinical management; (4) an

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acute episode of a substance use disorder episode (met 2 or more substance use disorders criteria in the past 2 weeks); (5) previously completed or currently attending an MBI; and (6) are currently younger than 18 years, are non–English speakers, or have a literacy lower than sixth grade.

Recruitment and Screening Procedure

Participants will be recruited from the Prisma Health-Upstate Internal Medicine Clinic who currently have or have had a lifetime history of any major depressive episode. Health care providers at the clinic will identify patients using the *ICD-11* (*International Classification of Diseases, 11th Revision*) codes [41] from the patients' electronic medical records. Researchers will contact eligible participants and ask for verbal consent before participation in an in-person screening interview with a member of the research team. At this time, the Patient Health Questionnaire (PHQ-9) [42] is to ascertain any current depression symptoms. PHQ-9 scores of 5, 10, 15, and 20 will represent mild, moderate, moderately severe, and severe depression, respectively. If no depression symptoms are currently present, this will also be noted. Participants who meet eligibility criteria will be asked to provide written informed consent before enrolling in this study. Recruitment began in December 2022.

Intervention Procedures

The intervention will be delivered by 3 Licensed Clinical Social Workers who have previously undergone MBCT teacher training and become certified instructors. The intervention will consist of 8 weekly 2-hour group therapy sessions. All sessions will be delivered to a group of up to 12 participants and will take place over Zoom (Zoom Video Communications, Inc). The minimum number of participants needed to proceed with each intervention program is 7 individuals. Certified instructors will follow the standardized MBCT protocol developed by Segal et al [43] (see Textbox 1 for the outline of each session).

Textbox 1. Mindfulness-based cognitive therapy program outline per Segal et al [43].

Session 1: Awareness and automatic pilot
Session 2: Living in our heads
Session 3: Gathering the scattered mind
Session 4: Recognizing aversion
Session 5: Allowing or letting be
Session 6: Thoughts are not facts
Session 7: How can I best take care of myself?
Session 8: Maintaining and extending new learning

MBCT integrates training in mindfulness meditation and cognitive-behavioral methods. It teaches skills designed to increase awareness of internal reactions that trigger depressive symptoms, such as depression-related rumination and negative thoughts, and provides techniques to detach from these dysfunctional cognitive processes [19]. In the first half of the program, participants will focus on learning the principal tenets of mindfulness. They will explore central themes about the tendencies of the mind to habitually engage with thoughts, which produces an array of feelings and emotions. In the latter half of the program, participants will begin the practice of becoming aware of thoughts as they arise, thereby witnessing habitual patterns that may lead to unpleasant feelings or emotions [43]. Outside of the sessions, participants will be assigned daily homework exercises and given handouts as well as audio recordings to use in their mindfulness practice. Participants who miss a session will be contacted by the research team to determine if they would benefit from medical or psychiatric assistance and to assess any barriers to upcoming sessions.

Study Fidelity

The intervention's fidelity will be evaluated using the MBCT Assessment Scale [44]. Weekly session audio recordings will be archived for access by 2 members of the research team who shall conduct the assessment. They will each use the MBCT Assessment Scale to code a random selection of half of the sessions. To achieve reliability, they will conduct 10 practice assessments which will be vetted by the research team. To prevent drift, frequent recalibration meetings will be scheduled. Additionally, group facilitators will convene weekly in the presence of the licensed clinical psychologist for supervision.

Study Withdrawal

Participants will not be permitted to continue in this study if uncooperative behavior is displayed threatening group cohesion, or if participants undergo severe psychological or medical symptoms that warrant professional treatment. If a participant does not attend an intervention session, the research team will follow up with that individual. A record will be maintained of contact information for participants' usual providers and other emergency contact persons, and these individuals will be contacted if the participant cannot be reached. If following 5 weekly attempts to reach a participant no response is obtained, the participant will be considered lost to follow-up. Those who wish to voluntarily discontinue participation in this study will be asked the reasoning behind their decision.

Assessment Procedures

This study will conduct data collection at 3 different time points: TI—baseline, TII—postintervention for group 1 and preintervention for group 2 (8 weeks), and TIII—follow-up for group 1 and postintervention for group 2 (16 weeks). Participants will complete web-based self-reported surveys administered via Qualtrics (Qualtrics). If the participant prefers, paper surveys will be administered. Figure 2 lists study measures and assessment points.

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Figure 2. Schedule of enrollment, interventions, and assessments.

	Study period					
	Enrollment	Allocation	Postallocation			Close-out
Timepoint**	$-t_1$	0	t_1	t_2	t_3	t_x
Enrollment:						
Eligibility screen	✓					
Informed consent	✓					
Allocation		✓				
Interventions:						
[Group 1]			◆—	——		
[Group 2]				◆—	——	
Assessments: Demographic and lifestyle information						
[Age]			✓			
[Gender]			✓			
[Race]			✓			
[Ethnicity]			✓			
[Marital status]			✓			
[Language spoken]			✓			
[Highest level of education completed]			✓			
[Annual household income level]			✓			
[Health insurance status]			✓			
[Current smoking status]			✓			
Assessments: Medical history						
[Use of psychotropic medication (what type, how much, for how long)]			✓			
[Current receipt of mental health treatment, including type and frequency]			✓			
[Treatment history]			✓			
[Trauma history]			✓			
Assessments: Primary outcomes						
[Depression severity]			✓	✓	✓	✓
[Psychiatric distress]			✓	✓	✓	✓
[Perceived stress]			✓	✓	✓	✓
[Facets of mindfulness]			✓	✓	✓	✓
[Extent of mindfulness self-practice]				✓	✓	✓
[Executive functioning skills]			✓	✓	✓	✓
[Satisfaction with treatment]					✓	✓

Primary Outcome Measures

Depression Symptoms

Depression symptoms will be assessed with the PHQ-9 [42].

Psychiatric Distress

Psychiatric distress will be measured using the depression and anxiety subscales of the Brief Symptom Inventory [45].

Secondary Outcome Measures

Perceived Stress

Using the Perceived Stress Scale-4 [46], perceived stress will be investigated.

Facets of Mindfulness

The Five Facet Mindfulness Questionnaire [47] will be used to assess self-reported mindfulness. In total, the 5 subscales include

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(1) nonreactivity, (2) observing, (3) describing, (4) nonjudgment, and (5) acting with awareness.

Possible Mediators

Extent of Mindfulness Self-Practice

Participants will be asked the following questions: "Besides the sessions you may have attended as part of this study, on your own, 'Did you engage in mindfulness meditation or other mindfulness practices in the past two months (8 weeks)?' 'How many days per week did you engage in mindfulness meditation or other mindfulness practices?' 'How long in minutes did you meditate per session of mindfulness meditation?' 'Describe your practice of mindfulness (what exercises/activities/techniques did you practice?).'" For quantitative analyses, we will use the variable representing the number of days of mindfulness practice per week.

Executive Functioning

The 20-item self-reported Deficits in Executive Functioning Scale, Short Form will be used [48].

Participant Characteristics and Possible Moderators

Demographics

We will assess age, gender, race, ethnicity, marital status, language spoken, educational attainment, employment status, annual household income, health insurance status, and current smoking status.

Treatment History

Mental health treatment history will be assessed using the Adult Service Use Schedule [49-51].

Trauma History

Adverse life events and trauma history will be assessed with the Adverse Childhood Experiences Questionnaire [52] and Life Events Checklist for the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [53].

Baseline Depression Symptoms

The PHQ-9 [42] will be used to assess baseline depression symptoms. Participants will be subdivided into mild depression (scores less than or equal to 10) or moderate to severe depression (scores greater than 10) for subgroup comparisons.

Feasibility Outcomes

Retention and Attendance

Retention and attendance will be assessed via the number of sessions attended and the percentage of participants who completed all sessions.

Engagement

Engagement will be measured per the items described above that assess the frequency and extent of mindfulness practice.

Satisfaction With Treatment

Treatment satisfaction and perceived utility of treatment will be assessed with the Treatment Satisfaction Survey [54] adapted for our study. This version will reflect how participants are satisfied with and respond to the MBCT intervention.

Format Delivered via the Web

To determine the feasibility of the web-based format, participants will be asked about strengths, weaknesses, and areas for improvement.

Sample Size

The total sample size of our trial is expected to be 128 individuals with 64 participants placed into each group. This was estimated by a 2-tailed *t* test using GPower 3.1 (Informer Technologies, Inc) software. Our calculation of sample size depended on (1) the level of significance (α error probability), which was set as .05 based on Ronald A Fisher's suggestion [55]; (2) the expected effect size, which was set as d=0.5, according to Cohen classification that "a medium effect of .5 is visible to the naked eye of a careful observer" [56]; (3) the expected power of this study (1–β error probability), which was set as 0.8 based on Cohen theory [57] because we failed to obtain support from previous similar studies; and (4) the allocation ratio (N2/N1), for which we expect number of participant in treatment group and control group to be the same.

Randomization

Consenting participants will be randomized 1:1 to either group 1 or group 2 via the randomization function found in Qualtrics. This will be conducted by the principal investigator (PI). Once the number of participants has reached 7-12 individuals for both group 1 and group 2, this study will commence. This will proceed continuously until the expected sample size of 128 individuals is reached, or 4 years have elapsed. The implementation of this process will be overseen by the clinical research team.

Blinding

Blinding in this type of study is not possible, as knowledge of the group assignment to the participants and providers will be evident. However, to minimize bias in this study, the investigators as well as data analysts will be masked from the respective assignments of the intervention group and TAU group. Blinding will only be terminated after all data collection and analysis have been completed.

Statistical Methods

Primary Outcomes

An intent-to-treat method will be used to conduct the primary analyses. By comparing the baseline and demographic variables between groups, the randomization success will be determined. With a random intercept for a cluster of individuals, generalized linear mixed effects models (GLMMs) will be used [58] to assess the effects of MBCT on depression and psychiatric distress symptoms (hypothesis 1). Week 8 will be the primary end point for this assessment. The covariates measured at TI that are relevant but not balanced between group 1 and group 2 will be incorporated into all models. Additionally, all analysis models will include clinical site level as a fixed effect. GLMMs will be used to test the association between MBCT psychiatric distress (hypothesis 2), in addition to gains sustained at an 8-week follow-up (hypothesis 3).

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Secondary Outcomes, Moderators, and Mediators

GLMMs will be used to assess the association between MBCT and the secondary outcomes of perceived stress and mindfulness skills (hypothesis 4). Potential moderators of the effect of MBCT, namely treatment history, traumatic life events history, baseline depression, and their interaction with MBCT, will be looked at in their own GLMMs. Using regression coefficients, the role of moderators that these variables may play will be assessed.

Using the PROCESS macro [59] in SAS (SAS Institute), the mediators, extent of mindfulness self-practice, and executive functioning skills (hypothesis 5), will be examined via the product of the coefficient method. This will be limited to the first phase of this study lasting 8 weeks. Further, 2 separate GLMMs will be used to assess how the primary and secondary outcomes may be indirectly influenced by MBCT. By regressing the mediator and outcome, respectively, on MBCT, and controlling for the mediators as well as applicable covariates, the indirect effects of MBCT on outcomes will be examined. Parallel multiple mediator models in addition to serial multiple mediator models will be used to conduct sensitivity analysis. To examine if MBCT effects will be sustained through 8 weeks postintervention (hypothesis 3), linear mixed-effects models will be used with main effects consisting of treatment group, time, group × time interaction, and nested random effects for subjects and cluster. A regression parameter associated with group × time interaction at 0 will be the null hypothesis. This acts as an equivalent for assessing the carryover effect [60]. If rejected, there is support that the effects of the intervention remain after 8 weeks have elapsed. An imputation method will be used to address any data that are missing.

Potential Bias

It is possible that participants who choose to participate in this study could be more motivated than those who choose not to participate. Participants who are lost to follow-up after randomization could also affect the comparability of the groups.

Ethical Considerations

This study was approved by the Institutional Review Boards (IRBs) at Greenville Health System and Clemson University (1852922; Pro00092709). All participants will provide written informed consent before participating in this study. This will be collected and safely stored by one of the clinical data collection team members.

Dissemination

The IRB at Clemson University and Prisma Healthcare System have approved this study. Some of the topics we will discuss are personal and may be upsetting to some participants. If participants experience distress and need treatment, a licensed clinical psychologist or psychiatrist will be contacted immediately. If required, we will provide a list of referral sources for participants who need additional treatment. In the event of physical injury, we will follow emergency procedures for the facility from which the participants are recruited. If an adverse event occurs, a member of the research team will reach out to the affected participant within 24 hours. Subsequently, a meeting will be convened by the research team to discuss the cause of the adverse event and if any modification to this study needs to be made. If any modification needs to be made to the trial protocol, a formal amendment will be submitted to the IRB for approval.

Data Monitoring Plan

By the National Institutes of Health Office of Human Research Protection, the research team has constructed the Data and Safety Monitoring Plan, safeguarding the well-being and privacy of study participants. Recruitment and safety data will be regularly reviewed by the monitoring board comprised of members from Prisma Health System and Clemson University. Using a personal code that is only accessible by the PI, each participant's demographic data, and outcome measures will be linked and stored for data analysis. No other identifying data relating to the participant will be linked to these codes. If there are data that are missing, these will also be a component of the monitoring plan for statistical analyses. Every quarter, the board will convene to assess any adverse effects, and on an annual basis, the board will discuss the audition of trial conduct. If the trial needs to be halted, and after consulting the data monitoring committee, the PI will make the final decision to stop all trial proceedings.

Data Collection and Management

The clinical data collection team will receive training from a licensed clinical psychologist on appropriately gathering data from the PHQ-9 [42] forms to ensure the validity and reliability of trial data. All data collected will be stored electronically and encrypted to ensure confidentiality. This will be done at the clinical facility at which the data are collected. The PI will have full access to the trial data set. To promote the retention of participants, intervention facilitators will encourage continued participation in MBCT sessions, providing the stage to voice any concerns that may have arisen. If concerns arise regarding participation, a member of the research team will reach out to that participant to encourage them to remain.

Data Reporting Guidelines

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [61] were used in the editing of this paper.

Results

This study began screening and recruitment in December 2022. Data collection from the first cohort occurred in January 2023. As of November 2023, a total of 30 participants have been enrolled out of 224 who received screening. Data analysis is expected to begin in December 2023, with an approximate publication of results by June 2024. IRB approval took place on September 11, 2019.

Discussion

Principal Findings

A core aim of this study is to supply the field of research concerning the effect of MBIs on depressive symptoms. To achieve this, we will first address the feasibility and efficacy of

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delivering MBCT to adults with depressive symptoms via a model delivered via the web. Our unique method of implementation will be tested via a randomized controlled trial with objective markers of depressive symptoms, an adequate overall sample size, and the assessment of adherence and feasibility. Additionally, we will be able to continue postintervention follow-up for 8 weeks, adding to the literature on whether gains can be sustained over time. It is important to assess the capability of MBIs to exert similar effects via web-based formats, as the ability to deliver web-based interventions improves accessibility and affordability of treatment. As such, these interventions may have a broader reach and be used in complement to formal mental health treatment.

Next, we will contribute to the evidence base regarding MBCT's efficacy in reducing depression symptoms and psychiatric distress. Although pharmacotherapy is widely used and upholds its role in the management of depression, it can be accompanied by medication side effects, delayed onset of therapeutic effects, a lessened impact on milder forms of depression, and an inability to show efficacy in treatment-resistant depression [62]. Furthermore, improper discontinuation of antidepressive medications runs the risk of medicine withdrawal symptoms, and even in the presence of proper medication cessation, there may be a risk of rebound or relapse in depression after discontinuation of antidepressants [63]. Consequently, more evidence supporting MBCT's role as an adjunct or primary therapy in depression management will be imperative for both clinicians and patients.

We also hope to examine the impact of MBCT on secondary outcomes, including perceived stress and facets of mindfulness. There is increasing evidence in support of perceived stress being positively correlated with the risk of developing depression [64,65]. This may be due to increased activity in the superior frontal gyrus which plays an important role in emotional regulation and cognitive control, with higher spontaneous activity in this region being possibly associated with psychopathologies such as MDD, posttraumatic stress disorder, and social anxiety disorder [66]. If MBCT has a positive impact on perceived stress, this study will add to the understanding of the causal pathway between MBCT, perceived stress, and depressive symptoms. Similarly, given that facets of mindfulness are inversely correlated with components of depression [67], this study can add to the evidence supporting the role that MBCT may play on that causal pathway also.

Through measurement of the extent of mindfulness self-practice and executive function, we hope to better understand the causal pathways between MBCT and depression symptoms. The positive effects of mindfulness practice have been purported to follow a dose-dependent pattern. This may be due to increased functional connectivity within various brain regions [68]. As such, it would be important to assess the role of mindfulness self-practice outside of the dedicated intervention time and its effects on depression. Finally, executive functioning has been shown to have an important influence on emotional regulation abilities [69,70]. The application of MBIs has been shown to be a viable means of improving certain aspects of executive function [71]. Thus, examining executive functioning could provide important insight into MBCT's ability to influence emotional regulation and depression symptoms.

We will also be able to look at moderators and correlates of intervention outcomes, such as intervention adherence and mental health history, to determine factors that could improve or detract from intervention success.

Overall, this study will generate valuable insights elucidating the possibility of future studies with larger scopes and more elaborate study designs. These may consist of multiple evidence-based comparisons and longer postintervention follow-ups.

Trial Status

Recruitment for the trial began in December 2022 and will last approximately until the sample size of 128 individuals is reached or 4 years have elapsed (September 2026).

Acknowledgments

The authors thank FUNDER for sponsoring this intervention among people with a history of depression in Greenville County, South Carolina, United States. We thank Greenville Mental Health and Prisma Health-Upstate Internal Medicine Clinic for collaborating on the intervention delivery. This study is to be conducted as part of the Mindful Greenville Project which is funded through the Greenville Health Authority (GHA) Healthy Greenville 2018 Grant Award Initiative. The funding body had no role in the design of this study and will not be involved in data collection, analysis, or interpretation.

Data Availability

Data gathered from this trial will be available to the public and research community. The research team will convene before the end of the trial to select the appropriate method to disseminate the data collected.

Authors' Contributions

HZ and LS conceived this study. MHZ and GF drafted the protocol with oversight from MJ, LZ, KJ, LC, HZ, and LS. Insights on clarity, consistency, and grammar were provided by CBW, KM, SL, and YW. All research team members listed in this protocol contributed to the design, conduct, writing, and editing of this protocol, and have fulfilled authorship criteria. The PI and data manager was LS. Preparation of protocol and revisions was by LS, SL, and MHZ. The steering committee and data monitoring

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committee consisted of LS, HZ, and MJ. The trial management committee held MJ and HZ. The recruitment committee was KM and CBW.

Conflicts of Interest

None declared.

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
GLMM: generalized linear mixed effects model
ICD-11: International Classification of Diseases, 11th Revision
IRB: institutional review board
MBCT: mindfulness-based cognitive therapy
MBI: mindfulness-based intervention
MDD: major depressive disorder
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual

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Protocol

Adapting an Efficacious Peer-Delivered Physical Activity Program for Survivors of Breast Cancer for Web Platform Delivery: Protocol for a 2-Phase Study

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Abstract

Background: Interventions promoting physical activity (PA) among survivors of cancer improve their functioning, reduce fatigue, and offer other benefits in cancer recovery and risk reduction for future cancer. There is a need for interventions that can be implemented on a wider scale than that is possible in research settings. We have previously demonstrated that a 3-month peer-delivered PA program (Moving Forward Together [MFT]) significantly increased the moderate to vigorous PA (MVPA) of survivors of breast cancer.

Objective: Our goal is to scale up the MFT program by adapting an existing peer mentoring web platform, Mentor1to1. InquistHealth's web platform (Mentor1to1) has demonstrated efficacy in peer mentoring for chronic disease management. We will partner with InquisitHealth to adapt their web platform for MFT. The adaptation will allow for automating key resource-intensive components such as matching survivors with a coach via the web-based peer mentoring platform and collecting key indexes to prepare for large-scale implementation. The aim is to streamline intervention delivery, assure fidelity, and improve survivor outcomes.

Methods: In phase 1 of this 2-phase study, we will interview 4 peer mentors or coaches with experience in delivering MFT and use their feedback to create Mentor1to1 web platform adapted for MFT (webMFT). Next, another 4 coaches will participate in rapid, iterative user-centered testing of webMFT. In phase 2, we will conduct a randomized controlled trial by recruiting and training 10 to 12 coaches from cancer organizations to deliver webMFT to 56 survivors of breast cancer, who will be assigned to receive either webMFT or MVPA tracking (control) for 3 months. We will assess effectiveness with survivors' accelerometer-measured MVPA and self-reported psychosocial well-being at baseline and 3 months. We will assess implementation outcomes, including acceptability, feasibility, and program costs from the perspective of survivors, coaches, and collaborating organizations, as guided by the expanded Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework.

Results: As of September 2023, phase 1 of the study was completed, and 61 survivors were enrolled in phase 2. Using newer technologies for enhanced intervention delivery, program management, and automated data collection has the exciting promise of facilitating effective implementation by organizations with limited resources. Adapting evidence-based MFT to a customized web platform and collecting data at multiple levels (coaches, survivors, and organizations) along with costs will provide a strong foundation for a robust multisite implementation trial to increase MVPA and its benefits among many more survivors of breast cancer.

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Conclusions: The quantitative and qualitative data collected from survivors of cancer, coaches, and organizations will be analyzed to inform a future larger-scale trial of peer mentoring for PA delivered by cancer care organizations to survivors.

Trial Registration: ClinicalTrials.gov NCT05409664; https://clinicaltrials.gov/study/NCT05409664

International Registered Report Identifier (IRRID): DERR1-10.2196/52494

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KEYWORDS

physical activity adoption; web platform; breast cancer survivors; design; implementation; cost-effectiveness; mobile phone

Introduction

Background

The 5-year survival rates for female survivors of breast cancer have increased from 63% in the 1960s to 90% currently, with >3.6 million survivors of breast cancer in the United States today [1]. There is a large body of evidence on the benefits of aerobic exercise to alleviate sequelae of cancer treatments when conducted with onsite supervision, as well as home-based programs [2-6]. Hence, the American College of Sports Medicine [7] and the American Cancer Society (ACS) [8] recommend that survivors participate in aerobic exercise at moderate to vigorous intensity for at least 150 minutes per week. However, only 24% to 44% of survivors meet these guidelines [8].

The literature suggests that leveraging peer support may help improve moderate to vigorous physical activity (MVPA) adoption among survivors of breast cancer [9]. Sociocultural and communication theories suggest that people are more receptive to assistance when it is delivered by someone perceived as similar to oneself (eg, of comparable age and life experiences) [10]. Peer support for health is used to maximize impact, sustainability, and scale-up of successful interventions while facing limited resources and contextual constraints. With the growing evidence of the key role that physical activity (PA) can play in cancer recovery, we are one of the first teams to extend these research findings into the "real world" by training community volunteers to encourage survivors to adopt MVPA [11-13].

We chose to test the dissemination potential at the ACS, a not-for-profit community-based organization. Specifically, ACS' Reach to Recovery peer mentors provide emotional support and information to patients with cancer. Hence, it was a "natural fit" to test the effects of these peer coaches encouraging sedentary survivors to become more physically active to enhance their recovery from cancer treatment. Our prior randomized controlled trial (RCT) showed that this peer-delivered intervention (Moving Forward Together [MFT]) was effective in increasing survivors' MVPA [12]. Coaches who were trained and supervised to provide MVPA counseling via telephone calls to other survivors of breast cancer effectively helped them significantly increase their MVPA to a mean of 129 minutes per week at 12 weeks (P<.05).

The telephone counseling component of our evidence-based MVPA intervention is based on the Transtheoretical Model (TTM) [14,15] and Social Cognitive Theory (SCT) [16] of behavior change that have been applied to exercise behavior. Key constructs from the TTM (motivational readiness) and SCT (self-efficacy and beliefs about the importance of MVPA in reducing fatigue etc) underlie the telephone counseling that coaches delivered to survivors in our prior work [12]. We plan to extend these individual-level theories with frameworks from the field of dissemination and implementation science to assess contextual and organizational-level factors that are critical to planning for large-scale implementation of our evidence-based intervention. We will use the expanded Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework of implementation outcome dimensions that includes a model of key contextual determinants of successful implementation, that is, the Practical, Robust Implementation and Sustainability Model (PRISM) [17,18]. RE-AIM has been in use since 1999 and has been applied widely to plan and evaluate the translation of many interventions in primary care and community settings, including smoking cessation interventions, diabetes management, and MVPA promotion [19,20]). As PRISM operationalizes the organizational staff and survivor domains that influence implementation success, we will use PRISM to identify contextual and organizational factors that influence RE-AIM outcomes [18].

Objective

To address the gap in the literature of limited real-world translation of MVPA promotion among survivors of cancer, our study objective is to develop and test the implementation of Mentor1to1 web platform adapted for MFT (webMFT) as a scalable intervention to effectively increase MVPA among survivors of breast cancer. The study has 2 phases: phase 1, which includes aims 1 and 2, and phase 2 which includes aim 3.

Phase 1

In phase 1, we will work with peer coaches who have prior experience in delivering MFT to adapt an existing web platform, Mentor1to1 developed by InquisitHealth Inc (a technology company that offers peer mentoring for chronic disease management via a web platform). In aim 1, we will conduct semistructured interviews with 3 to 4 peer coaches who have already delivered MFT in our prior work to obtain their feedback on how to adapt Mentor1to1 for MFT. In aim 2, we will use the interview data and use rapid, iterative user-centered design principles with another 3 to 4 peer coaches (with prior experience with MFT) to create webMFT.

Phase 2

For phase 2, the study aims are as follows:

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- Aim 3a: conduct an RCT wherein 10 to 12 peer coaches will be trained to deliver webMFT to 56 survivors of breast cancer, who will be randomly assigned to receive either webMFT or MVPA tracking. We will collect quantitative and qualitative data on the acceptability and feasibility of webMFT (eg, number and duration of calls delivered and barriers experienced) and suggestions for improvement from the coaches.
- Aim 3b: obtain data on survivor outcomes at 12 weeks from accelerometer-measured MVPA (primary outcome) and self-reported quality of life (QOL), physical functioning, mood, and fatigue to help estimate effect sizes for a larger trial to test the impact of webMFT versus MVPA tracking on survivor effectiveness outcomes. We expect that at the postintervention time point, survivors randomized to webMFT will increase MVPA; improve QOL, physical functioning and mood; and decrease fatigue significantly more than survivors randomized to MVPA tracking.
- Aim 3c: assess organizational-level factors (eg, the barriers and facilitators for implementation, setting and contextual factors, resources required, and alignment of webMFT with workflow and mission) using the RE-AIM and PRISM models [18] by interviewing key multilevel stakeholders at the collaborating organizations.
- Aim 3d: collect detailed cost, time, and resource information to conduct cost-effectiveness analyses from the perspectives of the survivors, coaches, and cancer care organizations.
- Aim 3e: develop a guide on how to recruit and build collaborations with other organizations that offer peer mentor programs with which webMFT can be integrated. The long-term goal of this work is to use these data to inform a robust, large-scale pragmatic trial with several cancer care organizations to deliver webMFT to survivors of breast cancer across the country.

Methods

Study Design

The study will consist of 2 phases: phase 1 will involve the adaptation and user-centered testing of Mentor1to1 for MFT. We will recruit coaches from past studies who have previously delivered the MFT program. These coaches have experience with intervention content and delivery and thus will be able to provide informed feedback. In phase 2, we will test webMFT using a randomized controlled design.

Phase 1

Recruitment of Coaches

Peer mentors who participated as coaches for the MFT program in a prior RCT [13] will be invited to participate. The eligibility criteria are that the participants must: (1) be aged ≥21 years, (2) currently have an email address and telephone access, and (c) have access to a tablet or computer with internet. We anticipate recruiting 6 to 8 coaches.

Adaptation of the Web Platform (Mentor1to1) for MFT

This includes (1) customizing coach-survivor matching criteria; (2) defining the MFT program path in terms of call frequency and counseling content; (3) counseling questions that coaches will ask survivors during each call; (4) counseling questions to structure data entry for coaches via the web platform, and (5) integration of a Fitbit tracker (Fitbit Inc) to autocapture MVPA, heart rate, and step data. The coach-survivor's matching criteria, progression in the 12-week program, counseling content, and review of the survivor's weekly MVPA data are based on our prior studies [12,13] and interview data collected during the principal investigator's participation in the National Cancer Institute's Speeding Research-Tested Interventions program.

The steps involved in the development process is as follows: the web platform will be rapidly and iteratively tested by (1) InquisitHealth's team to ensure navigational ease and functionality robustness and (2) our research team to ensure accuracy regarding our design intentions and completeness and fidelity to the content and process of MVPA counseling within MFT. (3) InquisitHealth will conduct interviews via Zoom with 3 to 4 coaches who will complete usability tasks (eg, creating an account in webMFT). (4) After incorporating all available feedback, an additional 3 to 4 coaches (with prior MFT experience) will review the entire system and provide qualitative and quantitative feedback. Quantitative feedback will include the System Usability Scale, which consists of 10 items where coaches will rate the usability of webMFT using a Likert scale (1=strongly disagree; 5=strongly agree) [21]. System Usability Scale has been shown to be reliable and valid. On the basis of recommendations from the coaches, the InquisitHealth team will refine webMFT. Hence, we will adhere to well-established iterative user-centered design principles in adapting Mentor1to1 for evidence-based MFT [22-24]. Coaches will receive a US $100 gift card for their participation.

Phase 2

Phase 2 will be an RCT of webMFT wherein 10 to 12 coaches (naive to the MFT program, across the collaborating cancer care organizations that have peer mentoring programs) will be trained to deliver webMFT to survivors of breast cancer. We will recruit 56 survivors of breast cancer and randomize them to webMFT (assigned a coach to deliver intervention via the web platform) or an MVPA tracking group (independent MVPA tracking; refer to Figure 1). We will use multiple methods to examine the acceptability and feasibility of the coaches using webMFT and to gather data on the implementation and effects of webMFT on survivors' MVPA (primary outcome), mood, QOL, physical functioning, and fatigue at baseline and 12 weeks. Finally, we will conduct individual interviews with multilevel stakeholders at the collaborating organizations to collect data, based on RE-AIM outcome dimensions and PRISM domains, to guide the implementation of webMFT on a larger scale.

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Figure 1. Study design (phase 2). MVPA: moderate to vigorous physical activity; webMFT: Mentor1to1 web platform adapted for Moving Forward Together.

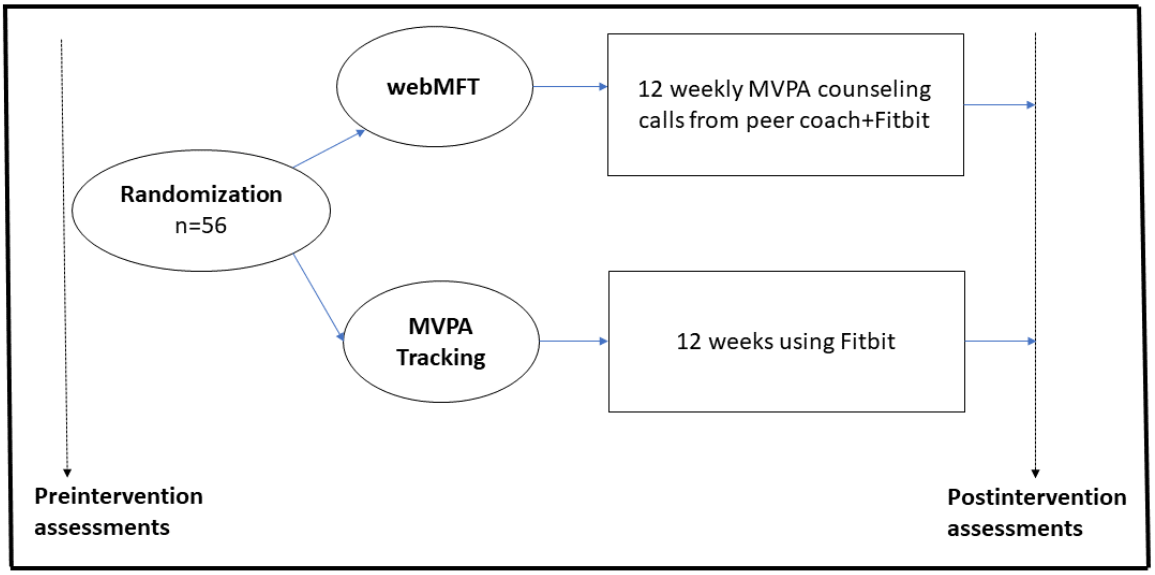

Description of webMFT

Mentor1to1 is a web-based platform for coach and survivor enrollment; survivor-to-coach matching; one-on-one remote coach mentoring via phone, text, and smartphone messaging; automated MVPA tracking via Fitbit; and administrator oversight and support. Access to the system by both the coach and staff is password protected. Within the webMFT, the coach will be able to review information from prior calls (eg, a survivor's MVPA recorded by a Fitbit activity tracker) and review information for the upcoming call (eg, counseling questions). When ready for a call to a webMFT participant, the coach will click a button on the computer to initiate the call. The system calls the survivor and connects the coach and survivor for a one-on-one telephone conversation. This avoids the need to exchange contact information. All calls are generated from a secure server, allowing the tracking of call frequency, length, and recording for quality control, safety, and training purposes, while respecting Health Insurance Portability and Accountability Act (HIPAA)–mandated security and privacy requirements. During the call, coaches will be expected to document their discussion for each specified counseling question; additional notes can be taken throughout the call within the platform. At the end of each call, coaches will collaboratively set MVPA goals with the participants, discuss strategies to achieve those goals in the upcoming week, and schedule the next call. As needed, the platform will assist with scheduling time zone differences between the coach and the participant. The system will send email or text reminders to the coach and the participant about their upcoming call.

Recruitment of Coaches

We will work with cancer care organizations (eg, Cancer Hope Network and Pink Lemonade Project) to recruit coaches and survivors. In total, we will recruit 10 to 12 coaches across the organizations to be trained to deliver webMFT. Each coach will be asked to work with 4 to 5 survivors over the study duration. As in our prior work [12,13], the organizations will mail or email informational letters and brochures to peer mentors, offering them the opportunity to become a coach and receive training in the delivery of webMFT.

Eligibility criteria for coaches include that they must (1) be a current peer mentor (at least 1 year) at the organization; (2) have an email address, telephone access, and access to a tablet or computer with internet to use the web platform; (3) be willing to participate in group training via videoconference; (4) be willing to have calls recorded and reviewed; (5) be willing to be supervised; (6) have a baseline level of digital literacy for this health technology (ie, sufficient internet speed and proficient in typing); and (7) currently exercise for at least 60 minutes per week.

Survivor Recruitment

The collaborating cancer care organizations will be asked to send informational mailings or emails about the study to their lists consisting of survivors of breast cancer. Other recruitment avenues will include informational mailings from oncology practices, tumor registries, and community events. Interested survivors will be asked to contact the study's research assistant who will explain the study and obtain verbal informed consent to conduct a telephone screen for eligibility. If eligible, the staff will send the survivor an informed consent document through REDCap (Research Electronic Data Capture; Vanderbilt University) [25,26]; once signed, participants will be sent a copy for their records. Participants will be mailed a physician consent form for their participation in the study. After the consent forms are obtained, all survivors will be mailed an Actigraph (GT3X; Actigraph LLC) accelerometer to monitor MVPA with instructions and a stamped envelope to return the Actigraph. In addition, they will receive instructions on completing baseline questionnaires within REDCap. After the baseline assessments are completed and the Actigraph has been reviewed for wear time and confirmation of a sedentary lifestyle, participants will be mailed a Fitbit Inspire 2 tracker. Participants will also receive a Fitbit manual and a study username and password to log in to the Fitbit app on their phone. Survivors randomized to the MVPA tracking arm will receive an identical

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Fitbit in the mail; their data will be tracked directly via the Fitbit Application Programming Interface.

Eligibility criteria for survivors include the following: (1) women aged >21 years; (2) diagnosis in the past 5 years with stage 0 to stage 3 breast cancer (completed surgery, radiation, or chemotherapy, and those currently receiving hormone therapy; physician consent for all study survivors will be obtained); (3) ability to read and speak English; (4) those with sedentary lifestyle (ie, <30 minutes per week of vigorous exercise or <90 minutes per week of moderate intensity exercise for the past 6 months); (5) ability to walk unassisted; and (6) access to a smartphone with Bluetooth and internet access. Women with more advanced disease (stage 4) and medical or psychiatric problems (eg, coronary artery disease, peripheral vascular disease, diabetes, and orthopedic problems) that may interfere with protocol adherence will not be included. These inclusion and exclusion criteria are similar to those used in our prior work [12,13]. Survivors will be asked to provide consent for medical chart review to extract disease and treatment history.

Ethical Considerations

Phase 1 of the study was deemed exempt by the institutional review board of the University of South Carolina (Pro00117242), and phase 2 of the study was approved by the same institutional review board. All study participants and coaches will provide written informed consent to participate in the study.

Study data will be deidentified before analyses and dissemination.

Coaches taking part in phase 1 of the study will be provided with US $100 as an incentive. Coaches taking part in phase 2 will be paid US $30 upon completion of training. In addition, coaches will be provided US $25 on delivering the intervention to their first participant and US $25 during the holiday season. Study participants (survivors) in phase 2 will be paid US $25 for completing baseline assessments and US $25 for assessments at the postintervention time point.

Sample Size

Power calculations were based on data from our prior work with MFT [27], and data from the study by Cadmus-Bertram et al [28], who compared web-based tracking+Fitbit to pedometer alone among postmenopausal women. Comparing the effects of coach counseling [27] to web-based tracking+Fitbit [28] on changes from baseline in MVPA would yield a medium effect size, d=0.60. Assuming similar effect sizes and a 2-sided α=.05, we would have more than sufficient power to test intervention effects on changes in MVPA (minutes per week) at the end of intervention with 20 survivors per arm. However, given the risk of powering on pilot studies, we have conservatively inflated the sample size to 25 survivors per arm. On the basis of our prior work, we expect attrition to be ≤10% at 12 weeks, so we will recruit a total of 56 women (n=28 survivors per arm) to obtain complete data from 50 survivors.

Study Implementation

Survivor Enrollment

Each survivor will be asked to obtain medical consent from her oncologist to enroll. Providers will be allowed to exclude patients if the MVPA goal would be unsafe for the patient. Intervention delivery will begin after informed consent, medical consent, and baseline data are obtained.

Random Assignment

Survivors will be randomly assigned to a group after informed consent and baseline data are obtained. Consistent with prior work, the sample will be stratified for 2 variables that may affect MVPA outcomes (age: <60 years or >60 years; and treatment: received or not received chemotherapy). The randomization scheme will be generated using the R (the R Foundation for Statistical Computing), based on a permuted block randomized procedure with small, random-size blocks so that equal numbers of survivors are randomized to webMFT or MVPA tracking by age and treatment. The project director will contact the survivor and disclose the group assignment from a sealed envelope.

Matching

The coach-survivor matching criteria for survivors randomized to webMFT will include mandatory and preference-driven criteria. The mandatory criterion is overlapping times on their respective schedules. The preference-driven criteria include age (+10 years or −10 years), type of cancer treatment (eg, radiation), race, and ethnicity. If >1 matching coach exists, preference-driven criteria will be used to identify an appropriate coach. Following matching, the first call between a coach and a survivor will be scheduled. The coach will receive an alert (email and text, depending on preference) that a new survivor has been added to the queue.

The webMFT Group

Survivors randomized to webMFT will receive the evidence-based MFT program for MVPA promotion [29] that consists of MVPA counseling matched to patients' motivational readiness and self-monitoring of MVPA (Fitbit activity tracker).

Exercise Counseling

Coaches will be asked to contact survivors using the web platform and make 12 calls (1 call per week over 12 weeks). Each call will take approximately 15 to 20 minutes. The purpose of the calls is to build a supportive relationship with the survivor, assess motivational readiness, review MVPA participation (participant Fitbit data viewed on the web platform), identify any health concerns, assist the survivor to identify relevant barriers to MVPA, and help her to problem solve such barriers and set MVPA goals. In addition, the coach will provide feedback and reinforce and encourage efforts to start being active and stay active. The counseling will be matched to the survivor's motivational readiness assessed at the start of each call. For example, women in the precontemplation stage will be given information to increase their awareness of the benefits of MVPA after cancer treatments (eg, improved physical functioning). The goal, as in prior work, will be to gradually increase the amount of moderate intensity aerobic exercise that is performed to the current national recommendations of at least

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150 minutes of MVPA per week [7]. Coaches will be trained not to provide medical advice but to encourage patients to contact their oncologist for medical care and health issues. If patients report symptoms such as chest pain or difficulty breathing, participation will be temporarily halted, and they will be referred to their oncologist.

Self-Monitoring of MVPA

Survivors will be asked to self-monitor MVPA participation (frequency, duration, steps, and heart rate during MVPA) by wearing the Fitbit activity tracker each day. These data will be automatically uploaded to the webMFT platform via the Fitbit Application Programming Interface integrated into the Mentor1to1 platform. Participants will be encouraged to sync their Fitbit daily via Bluetooth. Automated reminders to sync the tracker will be sent from the web platform. Coaches will be able to email or text the participant their Fitbit data (chiefly, active minutes) as shown on the web platform. Coaches will review their survivor's weekly MVPA during calls and enter these data into the web platform.

MVPA Tracking Group

These survivors will be asked to self-monitor MVPA participation (frequency, duration, and heart rate during MVPA) by wearing the Fitbit device each day over 12 weeks (3 months). They will be able to see the feedback that the tracker provides on the app dashboard (eg, daily MVPA minutes) and can access other Fitbit features. They will receive weekly text reminders from the research staff members to sync the tracker. The research staff members will review Fitbit data through the Fitbit dashboard to ensure that the device is worn and routinely synced. This group will be provided with the same 12 tip sheets as those provided to webMFT group and the procedures to follow in the event of any injury. This comparison arm thus constitutes a real-world, low-cost intervention.

Training Coaches

Before beginning training, coaches will receive a training manual. On the basis of prior work, we will develop recorded training modules that provide information on the benefits of exercise for survivors of cancer; TTM and SCT; training on counseling techniques (eg, empathy and reflective listening); working with human participants and HIPAA regulations; and emergency protocols. In addition, trainers will offer 1 live internet-based group training session during which coaches will practice role plays and receive feedback through videoconferencing. Coaches will complete a second live internet-based individual training session to ensure that they can deliver the intervention while using the platform, using screen sharing capabilities between the coach and research staff. Coaches will be trained to query patients at each call about health symptoms and notify the research staff immediately if survivors endorse any symptoms that are potentially indicative of a serious problem. In these cases, study participation will be temporarily halted until the medical issue has been resolved. Coaches will receive a supervision call every other week from research staff members through the web platform.

Measures

Overview

In phase 2, we will collect RE-AIM outcome measures from survivors, coaches, and organizational staff members as well as key contextual and organizational factors that influence RE-AIM outcomes using PRISM (Tables 1-3). Quantitative and qualitative data will be collected. Perspectives from the survivors, coaches, and organizational staff members will be obtained through semistructured interviews. Interview guides will be developed based on the RE-AIM outcome dimensions and PRISM domains of contextual influence. The RE-AIM outcome dimensions assessed include Effectiveness, as well as the implementation outcomes of Reach, Adoption, Implementation, and Maintenance. The PRISM domains include: (1) perspective of the intervention at the level of the survivor, coach and organization; (2) organizational characteristics; (3) external environment; and (4) implementation and sustainability infrastructure [17,18].

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Table 1. Quantitative data collection for effectiveness outcomes.

Effectiveness outcome	Measure	Participant level	Time point	
		Survivors	Baseline	12 weeks
MVPA[a]	Accelerometer (Actigraph GT3X) worn over 7-d period	✓	✓	✓
QOL[b]	36-item Short Form Health Survey	✓	✓	✓
Physical functioning	FACT-B[c]	✓	✓	✓
Fatigue	FACT-F[d]	✓	✓	✓
Mood	POMS[e]	✓	✓	✓
Stages of change	Stage of Readiness for Exercise	✓	✓	✓
Self-efficacy for exercise	Exercise Self-Efficacy Scale	✓	✓	✓

[a]MVPA: moderate to vigorous physical activity.

[b]QOL: quality of life.

[c]FACT-B: Functional Assessment of Cancer Therapy Scale-Breast.

[d]FACT-F: Functional Assessment of Cancer Therapy Scale-Fatigue.

[e]POMS: Profile of Mood States.

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Table 2. Quantitative data collection for reach, adoption, and implementation outcomes.

RE-AIM[a] dimension and PRISM[b] domain outcome	Measure	Participant level			Time point	
		Survivor	Coach	Organization	Baseline	12 weeks
Reach						
Total potential survivors in participating organizations	• Count	✓			✓	
Number of survivors eligible to participate (meet study eligibility criteria)	• Count, % of total	✓			✓	
Number of survivors excluded by the investigator due to not meeting eligibility criteria for study	• Count, % of total	✓			✓	
Reasons survivors excluded by the investigator	• Descriptive data tracked by the study team	✓			✓	
Number of eligible survivors who agree to enroll	• Count, % of eligible	✓			✓	
Number of eligible survivors who decline	• Count, % of eligible	✓			✓	
Reasons eligible survivors decline	• Tracked by study team	✓			✓	
Adoption						
Total number of potential settings	• Count			✓	✓	
Number of settings eligible (based on organizational readiness criteria)	• Count, % of total			✓	✓	
Number of settings excluded by investigator (based on organizational readiness criteria)	• Count, % of total			✓	✓	
Reasons settings excluded by the investigator	• Settings score <4 on ORIC[c] questions or <4 on single-item organizational readiness survey or informed study team not ready or PI[d] discretion			✓	✓	
Number of eligible settings that agree to participate in MFT[e]	• Count, % of eligible			✓	✓	
Number of eligible settings that decline to participate in MFT	• Count, % of eligible			✓	✓	
Reasons eligible settings choose to agree to participate or decline to participate in MFT	• Open-ended item at the end of ORIC survey			✓	✓	
Number of eligible settings not contacted or other	• Count, % of eligible			✓	✓	
Setting: characteristics of adopters vs nonadopters	• Number of employees, location, etc			✓	✓	
Within each site, number of coaches who agree to participate in MFT	• Count, % within a participating setting		✓		✓	

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RE-AIM[a] dimension and PRISM[b] domain outcome	Measure	Participant level			Time point	
		Survivor	Coach	Organization	Baseline	12 weeks
Within each site, number of coaches who decline to participate in MFT	• Count, % within a participating setting		✓		✓	
Reasons coaches choose to decline to participate in MFT	• Tracked by the study team		✓		✓	
Coaches: characteristics of adopters vs nonadopters	• Age, sex, race, ethnicity, and baseline activity levels		✓		✓	
Implementation						
Perspective of webMFT[f] intervention[g]						
Acceptability of webMFT	• Study-specific questionnaire • IAM[h] (4-items) • NPS[i]	✓	✓			✓
Feasibility of webMFT	• FIM[j]; 2-items: is webMFT easy to use? Doable?	✓	✓			✓
Adaptations[k]	• FRAME[l]		✓			✓
Costs[k]	• Cost tracking form	✓	✓			✓
Fidelity[k]	• Auditing of coach-delivered calls		✓			✓
Patient characteristics						
Patient demographics	• Age, race, ethnicity, baseline level of MVPA[m], cancer treatment status, and home address	✓			✓	
Organizational characteristics						
Organizational readiness	• ORIC			✓	✓	

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance

[b]PRISM: Practical, Robust Implementation and Sustainability Model

[c]ORIC: Organizational Readiness for Implementing Change.

[d] PI: principal investigator.

[e]MFT: Moving Forward Together.

[f]webMFT: Mentor1to1 web platform adapted for Moving Forward Together.

[g]Practical, Robust Implementation and Sustainability Model (PRISM) domains.

[h]IAM: Intervention Appropriateness Measure.

[i]NPS: Net Promoter Score.

[j]FIM: Feasibility of Intervention Measure.

[k]These measures will be tracked continuously throughout the study.

[l]FRAME: Framework for Reporting Adaptations and Modifications-Enhanced.

[m]MVPA: moderate to vigorous physical activity.

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Table 3. Qualitative data collection for Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) and Practical, Robust Implementation and Sustainability Model (PRISM).

RE-AIM dimension, PRISM domain, and outcome	Description (interview[a] questions)	Participant type		
		Survivors	Coaches	Organizational staff
Reach				
Perspective of webMFT[b] intervention, survivor characteristics				
Motivation	• What factors did you consider when you agreed to participate in webMFT? What motivated you, if anything, to stay in the intervention for the full 12 weeks? If you withdrew, why?	✓		
Effectiveness				
Perspective of webMFT intervention				
Program value	• How did webMFT impact health and well-being of the survivors? What have you learned from participating in webMFT? How might webMFT benefit you?	✓	✓	
Adoption				
Perspective of webMFT intervention, Organizational Characteristics				
Motivation	• What factors did you consider when you agreed to participate in webMFT? What motivated you to continue volunteering with webMFT?		✓	✓
Implementation				
Perspective of webMFT intervention				
Acceptability of webMFT	• Is webMFT acceptable? Did you like the intervention? What went well? What did not go well?	✓	✓	✓
Feasibility of implementing webMFT	• Was webMFT feasible? What went well? What didn't go well? Suggestions for improvements	✓	✓	✓
Patient centeredness	• How did the intervention align (or not align) with the needs?	✓	✓	✓
Adaptations	• What changes were made to webMFT during implementation?		✓	✓
Organizational readiness	• How ready were you to implement webMFT?		✓	✓
Burden	• Time and costs of implementation, unintended effects from webMFT	✓	✓	✓
Program fit	• How does webMFT fit with your values and mission?			✓
Organizational characteristics				
Climate and culture	• Shared goals with webMFT; alignment with mission		✓	✓
__[c]	• Data and decision support; workflow		✓	✓

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RE-AIM dimension, PRISM domain, and outcome	Description (interview[a] questions)	Participant type		
		Survivors	Coaches	Organizational staff
Organizational readiness	• Capacity to partner; What factored into your decision to partner to implement webMFT? What would have made it easier or harder to partner?			✓
External environment				
—	• Community resources, apps, local policies, access to safe places to recreate, urban or rural, access to Wi-Fi, insurance reimbursement, etc	✓	✓	✓
Implementation infrastructure				
Implementation strategies	• Coach training and support, resources, tools or skills • Inclusion of webMFT roles into job descriptions and performance evals		✓	✓
Maintenance				
Sustainability infrastructure				
Potential for sustainability	• Intention to maintain webMFT; factors that would make it more sustainable (cost of delivery)		✓	✓
Motivation to sustain webMFT	• Intention to continue, discontinue, or adapt webMFT delivery (coaches and staff); motivation to continue exercise behavior (survivors)	✓	✓	✓

[a]Interviews will last approximately 45 to 60 minutes.

[b]webMFT: Mentor1to1 web platform adapted for Moving Forward Together.

[c]Not applicable.

Effectiveness

Intervention effectiveness, operationalized as changes in survivors' MVPA (primary outcome), will be assessed at the postintervention time point (3 months; Table 1).

Postintervention assessments will follow the same procedures as at baseline: the questionnaires will be completed via REDCap and staff members conducting assessments will be blinded to the survivors' group assignments. Staff members will mail the accelerometer to the patients. When the units are returned by mail and web-based questionnaires completed, survivors will receive a US $25 gift card (US $25×2 assessments=US $50). The assessments are described in Tables 1 and 3 and include the following:

1. Accelerometer: we will use the Actigraph accelerometer (GT3X) as a device-based and gold standard measure of MVPA. Survivors will be asked to wear the unit around their waist during all waking hours over a 7-day period. The Actigraph will be worn at baseline and the postintervention time point. The Freedson cut points [30] will be used to score the data; data will be collected in 10-second epochs. A valid accelerometer day is defined as >10 hours per day; participants are required to have 4 valid days of wear.
2. QOL, physical functioning, fatigue and mood will be assessed using validated and standardized questionnaires that have been used by patients with breast cancer. Survivors will be asked to complete the following standardized questionnaires via REDCap: Functional Assessment of Cancer Therapy Scale-Breast [31], a 36-item Short Form Health Survey that includes a Physical Functioning subscale [32], Functional Assessment of Cancer Therapy Scale-Fatigue [33], and the Profile of Mood States [34]. In addition, the following questionnaires will be used to assess the constructs relevant to the TTM and SCT: Stage of Readiness for Exercise [35] and Exercise Self-Efficacy [36].
3. Program value will be assessed during semistructured interviews at the study end with survivors to understand how webMFT impacted the health and well-being of the survivors (Table 3).

RE-AIM Implementation Outcomes

Reach

Reach will be assessed at the level of the survivor and will include the number of survivors eligible to participate out of the total potential survivors at participating organizations as well as the number of survivors excluded [18,37]. Furthermore, survivors will be asked about factors that influenced their motivation to join the program during semistructured interviews

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conducted at the postintervention time point (refer to Tables 2 and 3 for additional details).

Adoption

Adoption will be assessed at the level of the organization and the level of the coach and will include the total number of eligible organizations out of the total number of potential organizations, the percentage of eligible organizations that agree to participate in the study, as well as the percentage of eligible coaches who agree to participate to deliver webMFT [18,37]. In addition, coaches and organizational staff will be asked about factors that influenced their decision to participate in the study during semistructured interviews (refer to Tables 2 and 3 for additional details).

Implementation

On the basis of RE-AIM, the implementation dimension includes measures of the costs of delivering webMFT, as well as the fidelity of delivery and adaptations needed to feasibly deliver the program in an acceptable way to end users [18]. Accordingly, we have also grouped our assessment of feasibility and acceptability outcomes in this RE-AIM dimension, as well as the assessment of organizational readiness that relates to the feasibility of program delivery.

Implementation outcome measures of acceptability and feasibility of webMFT will be assessed at the postintervention time point (3 months). In addition, we will track adaptations to webMFT, costs of delivering webMFT, and fidelity to the program throughout the implementation of webMFT. Organizational readiness will be assessed at the level of the organization. Finally, we will collect several qualitative assessments of additional implementation outcomes based on the PRISM domains [18], through semistructured interviews with survivors, coaches and organizational staff members (Table 3). These assessments are described in Tables 2 and 3 and include the following:

1. Acceptability and feasibility: at 12 weeks, the survivors randomized to webMFT group and the coaches will evaluate the intervention components (eg, usefulness of calls and satisfaction) via a REDCap questionnaire [29,38] and during semistructured interviews. At the end of their study participation, all coaches will complete an evaluation (using REDCap) of the components of webMFT using a feedback questionnaire similar to the one used in prior trials, with additional items that focus on the web platform. Coaches will complete evaluations (on a 1-4 rating scale, 1=not at all satisfied; 4=very satisfied) of satisfaction and acceptability of each webMFT component (eg, viewing patient's MVPA) in REDCap. We will also evaluate the number and duration of the calls delivered (tracked by the web platform) and barriers identified by the coaches on the feedback questionnaire. Furthermore, both survivors and coaches will complete additional quantitative measures including the 4 items from the Intervention Appropriateness Measure [39], 2 items from the Feasibility of Intervention Measure—is the intervention (1) easy to use and (2) doable? [39]—and the Net Promoter Score [40,41]. During intervention delivery, coaches will be interviewed to explore their experiences with webMFT and to elicit suggestions for improvements. These data will be used to modify webMFT at the end of the study.
2. Adaptations: adaptations to webMFT will be assessed at the level of the coach and the level of the organizational staff. We will track adaptations throughout the duration of the implementation of webMFT based on a survey adapted from the Framework for Reporting Adaptations and Modifications-Enhanced (FRAME; Table 2) [42] and using qualitative methods (Table 3).
3. Costs: we will assess patient costs as in prior studies [27] to capture out-of-pocket expenses and any health care costs related to MVPA. We will also assess the costs for coach training or intervention delivery, using established time-based activity costing techniques [43]. We will use the quantitative data to inform the development of debrief questions and recontact a subgroup of webMFT survivors (n=20, randomly selected) and conduct interviews to understand the patient perspective of webMFT and elicit suggestions for improvements, based on RE-AIM dimensions and PRISM domains. The time taken by the coaches to deliver webMFT (ie, for preparation, delivery, and follow-up of calls) will be tracked on the web platform and during biweekly calls with the project director. These data along with the time spent in training and supervision will allow us to estimate costs to the coaches, a key issue in designing for dissemination [44].
4. Fidelity: intervention fidelity will be assessed using auditing of the coach-delivered calls as has been done in prior work [11-13]. The principal investigator will audit 10% of completed coach calls throughout the duration of implementation of webMFT.
5. Organizational readiness: we will conduct brief surveys (assessing demographics and prior experience with research collaborations) and telephone-based interviews with key individuals in each partner organization. Each potential organization will also be asked to complete the Organizational Readiness for Implementing Change questionnaire [45]. We anticipate interviewing 4 to 6 individuals (1-2 per organization) such as the peer supervisor. Semistructured interviews will be scheduled at a time that is convenient for the interviewee, will last approximately 45 to 60 minutes, and will be audio recorded. A research team member will conduct the interviews and use a semistructured interview guide to ensure that each interviewee is asked the same core questions, based on PRISM domains.

Maintenance

Potential for sustainability and motivation to sustain webMFT will be assessed during the semistructured interviews with survivors, coaches, and organizational staff (Table 3).

Data Analyses

Overview

We will examine RE-AIM dimensions (Tables 1-3) to guide us in assessing the potential for larger-scale implementation of webMFT. We will conduct descriptive analyses of reach, adoption, and implementation outcomes including acceptability and feasibility of webMFT (eg, the number and mean duration

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of calls, barriers, and perceived feasibility of intervention delivery as judged by coaches). According to the current recommendations [46], we will consider webMFT feasible if >75% of the scheduled calls are delivered and survivor and coach and acceptability or satisfaction exceed 80% on rating scales (ratings of "moderately" to "very satisfied/acceptable"). Feedback from coaches and survivor debrief interviews will be used to revise and update webMFT for a larger-scale implementation trial.

We will assess potential between-group differences (webMFT vs MVPA tracking) in baseline variables (eg, age and medical history) using graphical methods, nonparametric and parametric tests as appropriate (eg, Wilcoxon rank-sum test for skewed data, 2-tailed *t* tests for normally distributed continuous data, and chi-squared tests for categorical data). Any variables not balanced by randomization will be controlled for as covariates in subsequent analyses, provided they are significantly associated with the outcome under consideration (at a modest $P<.10$ level).

We will assess effectiveness by examining the effects of webMFT versus MVPA tracking on the change in survivors' MVPA in minutes per week (accelerometer data) at 12 weeks (3 months) using a mixed effects regression model, in which we will regress MVPA at 12 weeks on baseline MVPA, randomized group, wear time, and any variables not balanced by randomization. Models will include random intercepts to adjust for repeated measures within the participant over time. We will use a similar approach to estimate the effects of group on mood, QOL, physical function, and fatigue at 12 weeks. The interest is in estimating effect sizes and CIs. Analyses will be conducted on the intent-to-treat sample with all randomized participants included. Mixed effects models use a likelihood-based approach to estimation and do not require any direct imputation of missing outcomes.

Analyses of Qualitative Data

The audio-recorded interviews will be transcribed, and each transcript will be coded using a preliminary coding schedule. The coding scheme will be refined through an iterative process but will begin with the codes developed as a function of a priori research questions based on RE-AIM dimensions and PRISM domains. We will use NVivo software (Lumivero) to facilitate data coding and analyses. After data coding, we will identify themes across interviews [47] to develop a guide for future partnerships with organizations.

We will compare the relative cost-effectiveness of each arm in increasing survivors' weekly MVPA minutes. Data collection following best practices for pragmatic measures will include tracking of the time, cost, and resources required to (1) recruit, train, and manage coaches; (2) recruit and enroll survivors; and (3) deliver the intervention. We will track Fitbit cost and delivery and Mentor1to1 technology–related costs [48]. Research-related activities and developmental costs will be excluded. Administrative time in (1)-(3) will be tracked automatically on Mentor1to1, reducing tracking time and administrative burden. We will assess costs to survivors, coaches, and organizations at the end of the study and conduct 3 separate analyses from the perspective of survivors, coaches, and organizations, respectively, to help prepare for implementation.

Results

As of September 2023, phase 1 of the study was completed, and 61 survivors were enrolled in phase 2. We expect that using newer technologies for enhanced intervention delivery, program management, and automated data collection may facilitate effective implementation by organizations with limited resources. Adapting evidence-based MFT to a customized web platform and collecting data from coaches, survivors, and organizations along with costs will provide the basis for an implementation trial to increase MVPA and its benefits among many more survivors of breast cancer.

Discussion

Principal Findings

The 2 phases of this work address the adaptation of a web platform for an effective MVPA intervention (webMFT) followed by an RCT to test the effectiveness of webMFT as well as the RE-AIM outcomes of Reach, Adoption, Implementation and Maintenance that will inform future approaches to scale up this intervention. By adapting an existing peer mentoring web-based platform, Mentor1to1 for MFT, an intervention that was proven effective when delivered by phone, we expect to be able to scale up our intervention with fidelity and reduce the costs of intervention delivery. The benefits of this web-based platform include an efficient infrastructure to support coaches to deliver all aspects of the webMFT intervention, including key process steps to accept coaching requests, initiate secure phone calls, send text messages, and view survivor data. Administrative staff will use the web platform to manage the entire program (eg, make coach-survivor matches, review call recordings, and track Fitbit data). By using webMFT, we expect that coaches can reach many more survivors to become physically active, with potential health and psychosocial benefits [7,49,50].

This work is innovative because peer mentoring is relatively new in the PA literature, and to the best of our knowledge, our work in training cancer peer mentors (coaches) to support MVPA adoption in cancer survivors is unique. We plan to use user-centered iterative design for the adaptation and creation of webMFT, while retaining the same established principles and theories used in our previous work with additional technology-based enhancements. The updated web platform will streamline survivor and coach enrollment and will allow staff members to use real-time, multivariate matching between coaches and survivors. The current matching approach is manual, which is time-consuming and expensive. Our web platform–based intervention allows for the delivery of a multichannel (phone, SMS text messaging, and smartphone) peer mentoring approach in what we expect will be scalable, flexible, and low cost. All interactions will be recorded and tracked automatically through the platform, providing full oversight, detailed reports, and tracking of each coach's time and effort. Finally, we expect that the web platform will integrate with a Fitbit activity tracker to provide automated

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MVPA data for the coach to review with the survivor during weekly calls. We expect that these features will reduce the need for investment in personnel to coordinate and collect data as well as facilitate intervention delivery.

Adapting our intervention to a web platform will require changes in the training program that we have provided the coaches. Our prior training required 4 in-person or videoconferencing group training sessions, each lasting about 2.5 hours. We will revise our training program extensively to include recorded training modules, a live internet-based group training focusing on training coaches to deliver the counseling content, and an individual training session to familiarize the coach with navigating the web platform while delivering the PA counseling. During the study implementation, we will also track any additional training and time spent by the research team to provide guidance and solve issues related to using the web platform. Careful attention to the changes required and adaptations in our training and supervision will allow the evidence-based intervention to be reliably implemented by cancer care organizations that have peer mentoring programs.

There is a large body of evidence to support the promotion of PA to facilitate the recovery and functioning of survivors of cancers, and numerous PA interventions (onsite, offsite, and hybrid) have been developed. Yet, these interventions have had limited applicability outside of research efforts. Much of the focus in implementing national PA guidelines for survivors of cancers [51-53] has been in health care settings. While there is considerable variation in the needs and challenges faced by survivors of cancers in adopting PA, there is a huge scope for community-based programs to meet the needs of those survivors who can safely become active outside of specialty care (eg, physical therapy and occupational therapy). There are numerous, well-established cancer support organizations in the United States focused on meeting the needs of their communities, especially patients or survivors, family members, and caregivers. Many of these organizations offer peer support programs. Our focus is to leverage the existing resources in these organizations, especially those which recognize the importance of PA in cancer recovery and make MFT more accessible to survivors.

To translate our research and build the capacity to improve survivors' recovery, we do need to understand multilevel stakeholders' perspectives on this partnership. By applying user-centered design principles and dissemination and implementation frameworks, we believe that we can design webMFT with dissemination and sustainability in mind from the beginning, thus improving the potential for adoption and sustainment. Key constructs measured with guidance from our expanded RE-AIM framework will inform future implementation efforts and improve our understanding of contextual factors at the levels of survivors, coaches, and organizations, which may influence future the adoption and maintenance of webMFT. Overall, these results will provide rich preliminary data to inform a future, large-scale pragmatic trial to involve multiple cancer care organizations in the delivery of webMFT to survivors of breast cancer across the country.

Limitations

We have restricted the survivor sample to those who have smartphones. The use of smartphones has increased over time. We are designing for the future when the prevalence of communication technology will be higher; therefore, we anticipate that access will improve.

Timeline

See Table 4 for the timeline and associated tasks.

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Table 4. Study timeline.

Months	Study activity
1-48	• Conduct weekly meetings with consultants (as needed) and research staff to plan, implement, problem solve, and review progress of the study • Conduct weekly meetings with research staff to track progress, discuss and resolve problems, and plan all study activities
Phase 1	
1-3	• Hire study staff • Obtain IRB[a] approval
4-6	• Recruit 6-8 coaches from prior studies
7-12	• InquistHealth will adapt the web platform Mentor1to1 for MFT[b] • InquistHealth staff will work with coaches and obtain their feedback on webMFT[c] • Data collected (webMFT platform notes) and any written documentation will be stored at InquistHealth offices and their secure servers • InquistHealth will modify and make changes in webMFT in response to feedback from coaches in an iterative approach
Phase 2	
13-16	• Work with collaborating organizations to recruit new coaches and survivors for the RCT[d] to test webMFT
16-18	• Train new coaches (n=10-12) via videoconferencing • Conduct posttraining evaluation of coaches
17-30	• Survivor recruitment and baseline assessments
20-33	• Intervention delivery
24-33	• Postintervention assessments of survivors
34-36	• Interviews with stakeholders at the collaborating cancer care organizations • End of study interviews with coaches
37-40	• Transcription, coding, and thematic analyses of interview data (survivors, coaches, and stakeholder interviews)
41-44	• Develop a guide for developing and sustaining partnerships with cancer care organizations that have peer mentoring programs
16-36	• On-going data entry
36-40	• Quantitative analyses of data collected from coaches and survivors
45-48	• Manuscript preparation and begin plans for large-scale, pragmatic implementation trial

[a]IRB: Institutional Review Board.

[b]MFT: Moving Forward Together.

[c]webMFT: Mentor1to1 web platform adapted for Moving Forward Together.

[d]RCT: randomized controlled trial.

Dissemination Plan

The study goals are to gather data to prepare for a larger-scale implementation trial of webMFT in several cancer care organizations that have peer mentoring programs. On a local and regional level, the work will be disseminated at the University of South Carolina–sponsored conferences, journal clubs, and community-based cancer support groups and local hospitals that have oncology programs. In addition, the results will be disseminated via presentations at regional, national, and international scientific meetings. A summary of the study results will be shared with the stakeholders at the organizations that have collaborated on the trial so that they can use the study results to inform their own staff, volunteers, cancer survivors, and potential funders.

Conclusions

Survivors' MVPA data from the RCT along with quantitative and qualitative data from coaches, survivors, and cancer organizations will provide the foundation for a large-scale implementation trial of the MFT program.

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The analysis plan was registered before beginning data collection at ClinicalTrials.gov (Pro00117242).

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

BMP, AGH, and MMK have no conflicts to declare. AP is an employee and owns stocks in InquistHealth. SID is a consultant on the study and received financial payment for her role. DMO was supported by this grant to travel to present preliminary research findings from this project at the AcademyHealth's Annual Conference on Dissemination and Implementation Science in December 2022.

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Abbreviations

ACS: American Cancer Society
FRAME: Framework for Reporting Adaptations and Modifications-Enhanced
HIPAA: Health Insurance Portability and Accountability Act
MFT: Moving Forward Together
MVPA: moderate to vigorous physical activity
PA: physical activity
PRISM: Practical, Robust Implementation and Sustainability Model
QOL: quality of life
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
REDCap: Research Electronic Data Capture
SCT: Social Cognitive Theory
TTM: Transtheoretical Model
webMFT: Mentor1to1 web platform adapted for Moving Forward Together

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Protocol

Effect of Flavored on! Nicotine Pouch Products on Smoking Behaviors: Protocol for a Sequential, Multiple Assignment, Randomized Controlled Trial

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Abstract

Background: Cigarette smoking is a leading cause of morbidity and mortality. For adults who smoke cigarettes and cannot or will not quit smoking, smoke-free products, such as nicotine pouches, have been recognized as a potential alternative to smoking combusted cigarettes to reduce harm due to cigarette smoking. The role of flavors in these smoke-free products in tobacco harm reduction has not been fully understood.

Objective: This study evaluates the effect of flavors in *on!* nicotine pouch products (research products) in the reduction of cigarette smoking among adults who smoke cigarettes in their natural environment.

Methods: This study uses a sequential, multiple assignment, randomized trial design. Approximately 400 eligible adults who smoke cigarettes will be enrolled and randomized to have access to either the Original (unflavored) *on!* nicotine pouch product only or a complete flavor profile (ie, Berry, Cinnamon, Citrus, Coffee, Mint, Original, and Wintergreen) of *on!* nicotine pouch products. After 3 weeks, participants in the Original-only arm will be randomized again, with half remaining in the Original-only arm and half having access to the complete flavor profile for another 3 weeks. Primary outcomes are expired-air carbon monoxide (CO) levels. Secondary outcomes are self-reported cigarette consumption and CO-verified cigarette abstinence.

Results: Recruitment and data collection started in September 2023 and is projected to last until March 2025. We anticipate completing the data analysis in 2025. As of May 2024, we have enrolled 314 participants.

Conclusions: This study will provide empirical evidence about the effect that flavor availability in smoke-free products may have in reducing cigarette smoking.

Trial Registration: ClinicalTrials.gov NCT06072547; https://clinicaltrials.gov/study/NCT06072547

International Registered Report Identifier (IRRID): DERR1-10.2196/56565

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KEYWORDS

nicotine pouches; flavored products; smoking reduction; tobacco harm reduction; randomized controlled trial

Introduction

Smoking tobacco cigarettes is the leading cause of preventable morbidity and mortality in the United States, with approximately half a million attributable deaths each year [1,2]. The vast majority of smoking-related diseases are caused by inhaling harmful and potentially harmful constituents (HPHCs) present in tobacco smoke as a result of combustion [3,4]. While not entirely risk free, nicotine is not directly responsible for most of the harm caused by smoke exposure from combusted tobacco products [5]. The US Food and Drug Administration (FDA) and public health experts acknowledge that nicotine and tobacco

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products exist along a continuum of risk, ranging from combusted products posing the highest risk and noncombusted products at the lower end [5-8]. Complete tobacco cessation is the best option for reducing smoking-related morbidity and mortality for the 28.3 million adults who smoke cigarettes in the United States [9]. Nonetheless, tobacco cessation is often a protracted process that can span over multiple years for many adults who smoke cigarettes [10]. For adults who smoke cigarettes who cannot or are unwilling to stop smoking cigarettes, switching completely or replacing most of their combusted cigarettes with smoke-free nicotine products may be a viable harm-reduction option [11].

Oral tobacco-derived nicotine products are a relatively new category among the growing field of smoke-free nicotine products. Within this growing category are nicotine pouches (NPs), which contain pharmaceutical-grade nicotine derived from tobacco (but are tobacco-leaf free) along with flavors and other food-grade ingredients [12]. These products are commercially available in the United States in a wide variety of flavors (eg, mint, fruit, tobacco, coffee, and unflavored), with nicotine levels typically ranging 1.5-8.0 mg (with some brands offering levels up to 50 mg) [12-14]. NPs typically contain significantly lower levels of HPHCs than cigarette smoke [15,16], and switching from combusted cigarettes to these products has been shown to significantly reduce HPHC exposure to the user [17], positioning these products to serve as a potential reduced-harm option for adults who smoke cigarettes. Among the few studies assessing the longitudinal use of NPs among adults who smoke cigarettes, initial evidence suggests that adults who smoke cigarettes may switch to these smoke-free products or use them to help reduce cigarette consumption.

To date, we are aware of only 2 published studies of switching behavior or smoking reduction over time among adults who smoke cigarettes provided with NPs [13,18]. Campbell et al [18] provided participants with free choice among NPs in 2 flavors—mint or citrus—in a single nicotine level (4 mg) to use ad libitum for 6 weeks. At the end of the study, the majority of participants (79/97, 82%) reduced cigarette consumption, with 16% (15/97) reducing by ≥50% and 3.1% (3/97) self-reporting stopping smoking. No switching behavior outcomes were reported. This pilot study was intended to refine procedures and was not adequately powered to detect significant effects of using the research product on smoking reduction outcomes. Becker et al [13] examined longitudinal ad libitum use of NPs over 6 weeks among adults who smoke cigarettes (n=399). When provided with NPs in 7 flavors (ie, cinnamon, citrus, coffee, berry, mint, original, and Wintergreen) and 5 nicotine levels (ie, 1.5, 3, 3.5, 4, and 8 mg), 27% of adults who smoke cigarettes completely switched from cigarettes to NPs. Additionally, 39% reduced cigarette consumption by ≥50%, and 24% reduced their consumption by up to 49%. Interestingly, Becker et al [13] reported a positive association between the number of flavors used and the magnitude of cigarette reduction. Overall, these studies provide strong initial evidence that, in the context of free product provision, adults who smoke cigarettes are willing to switch to NPs, and those who do not completely switch can have meaningful reductions in their cigarette consumption when using NPs. Although they provided some initial insights about the potential role of flavors, the observational nature of these studies (eg, uncontrolled, no comparator groups, and no randomization) preclude the inference of causal relationships between NP use (regardless of flavor) and cigarette reduction.

The examination of available NP sales data shows that flavored varieties (eg, mint and fruit) consistently outsell nonflavored or "Original" varieties [19]. However, these data do not provide information on consumers' concomitant use of other tobacco products (ie, switching or cigarette reduction). We designed this protocol to fill the knowledge gap and provide important information on the role of NP flavors on switching behavior and cigarette reduction among adults who smoke cigarettes (ClinicalTrials.gov NCT06072547). Specifically, this study uses a sequential, multiple assignment, randomized trial (SMART) design [20,21] to assess the effect of the availability of flavored (vs unflavored) *on!* brand NPs—holding nicotine level constant at 4 mg per pouch—on the smoking behavior of adults who smoke cigarettes over 6 weeks. Our purpose in this paper is to describe the protocol for a SMART study involving sequential randomization of adults who smoke cigarettes to provide evidence from an experimental study to advance the understanding of the role of NP flavors in smoking reduction. Our study objectives are to assess the following:

1. The overall effect of the availability of a complete flavor profile of the research products on smoking reduction among adults who smoke cigarettes.
2. The effect of the availability of the complete flavor profile of the research products on smoking reduction maintenance among participants who reduce their cigarette consumption ≥50% at week 3 (ie, responders).
3. The effect of the availability of the complete flavor profile of the research products on the smoking reduction at week 6 among participants who did not reduce their cigarette consumption ≥50% at week 3 (ie, nonresponders).
4. The effect of early versus delayed availability of complete flavor profile of the research products on smoking reduction.

We hypothesize that access to a complete profile of flavored NP products will result in greater reduction, including greater persistence of reduction, in exposure to a smoking-related toxicant (ie, carbon monoxide [CO]) and cigarette consumption. With objectives 1-3, we intend to assess the hypothesis from 3 different angles (ie, overall effect, maintenance of reduction among responders, and additional reduction among nonresponders). With objective 4, we seek to explore the potential effect of a delayed access to flavored products, which may have regulatory implications for the speed of decision-making on flavored products. We consider objective 4 to be exploratory because it is difficult to simulate such a scenario in a trial context with limited follow-up time.

Methods

Study Design

Overview

This study will use an open-label randomized controlled trial design to evaluate the impact of availability of flavored versus nonflavored (ie, Original) *on!* 4-mg NP products on cigarette

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smoking among adults who smoke cigarettes. This study involves a remote screening visit, a baseline assessment period (3-7 days), 6 weeks of at-home product use, and a 6-month posttrial follow-up survey. Figure 1 provides a depiction of the study design (baseline assessment prior to week 1 and 6-month follow-up are not shown).

Figure 1. Depiction of study design. Responders are participants who have a ≥50% reduction in cigarette consumption at week 3 (relative to baseline assessment); nonresponders are participants who have a <50% reduction in cigarette consumption at week 3 (relative to baseline assessment). R: random assignment.

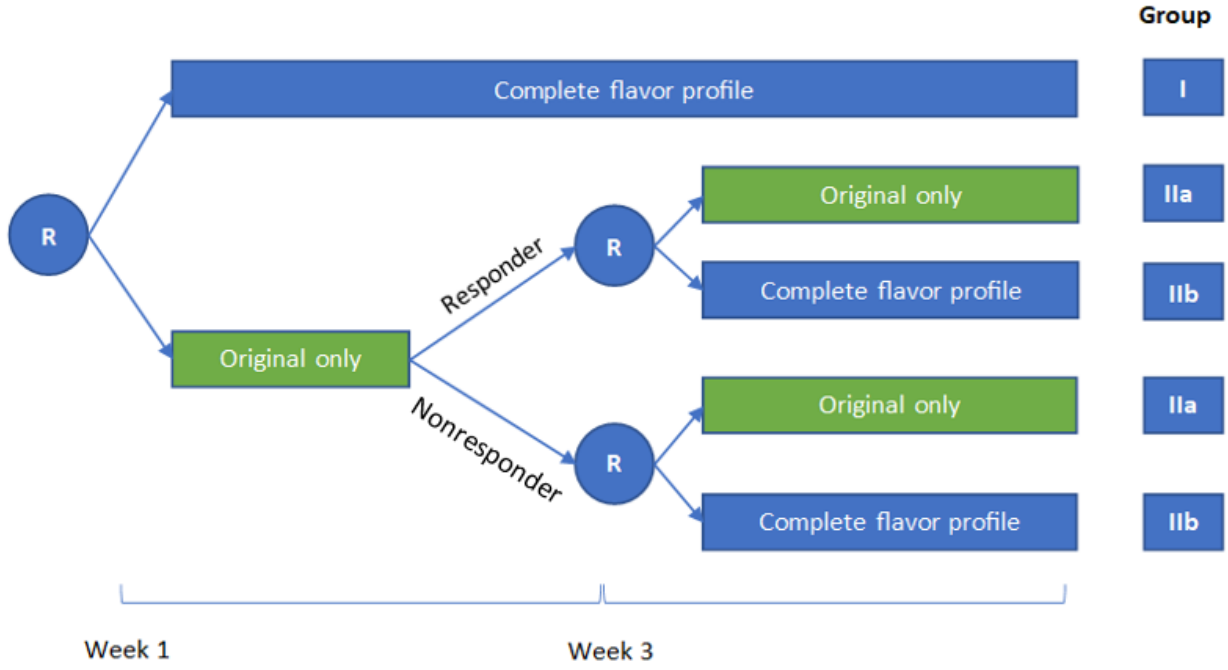

Randomization

Approximately 400 participants will be recruited over an approximately 7-month period. After confirming eligibility and obtaining informed consent, participants will be randomized into 3 groups varying only by the availability of research product flavors. Group I (n=150) will have access to the complete flavor profile of the research products (ie, Berry, Citrus, Cinnamon, Wintergreen, Mint, Coffee, and Original). Group IIa (n=125) will have access to only the Original variety for the entire 6-week trial period. Group IIb (n=125) will have access to only the Original variety for the first 3-week period and will be provided access to the complete flavor profile for the second 3-week period. We chose to randomize participants to these 3 groups at study onset rather than have sequential randomizations (ie, first randomize to the full flavor profile or Original-only arm, then rerandomize those in the Original-only arm to either the full flavor profile or remain with the Original-only arm) to simplify the logistics of randomization.

Baseline Assessment

After randomization and prior to week 1, participants will be asked to track their daily cigarette consumption via a web-based daily diary and provide ≥2 biometrically verified expired-air CO readings via Bluetooth-enabled remote CO monitor (iCOquit Smokerlyzer, Bedfont Scientific) over a period of 3-7 days. These initial data will serve as baseline cigarette consumption and CO for subsequent comparisons.

Weeks 1-6

In week 1, participants randomized into Group I will enter a 7-day period, during which they will receive 7 packs (20 pouches per pack) of research product (1 of each flavor) and instructed to try each flavor. This trial period is intended to allow participants to identify their preferred flavor(s) to use over the remainder of the study. After the trial period in week 1, Group I participants will complete 5 additional weeks of ad libitum product trial of research products (ie, weeks 2-6) with free choice of all flavors (up to 7 packs per week in any flavor combination of their choosing).

Likewise, following the baseline assessment, participants randomized into Group IIa and Group IIb will be provided with the Original variety of research products to use ad libitum for weeks 1-3 (up to 7 packs per week). At the end of week 3, participants in Group IIa will continue with the Original variety of research product for the remaining 3 weeks of the study (ie, weeks 4-6), and those in Group IIb will be provided access to all flavors of the research product. In week 4, Group IIb will have a 7-day trial period, during which they will receive 7 packs of research product (1 of each flavor) and instructed to try each flavor. As with Group I, this trial period is intended to allow Group IIb participants to identify their preferred flavor(s) to use over the remainder of the study. After the week-4 trial period, Group IIb will complete 2 weeks of ad libitum product trial of research products with free choice among all flavors (up to 7 packs of any combination per week).

Participants will be invited to complete a 6-month follow-up survey to gain insights about their tobacco use and related

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factors after the end of the product trial. This study will involve approximately 7 weeks (including the baseline period) of study participation in a home use test with daily surveys, weekly surveys, and a 6-month follow-up survey after the trial period.

Inclusion and Exclusion Criteria

The study sample will include approximately 400 adults who smoke cigarettes, between 22 and 65 years of age who have smoked an average of at least 5 commercial brand cigarettes per day for 12 months prior to signing consent. Specific inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Has signed the informed consent form (ICF) and is able to read and understand the information provided in the ICF.
- Healthy adults who smoke cigarettes and are 22-65 years of age at screening.
- Smokes an average of at least 5 cigarettes per day for the last 12 months.
- Does not intend to use a Food and Drug Administration–approved treatment for nicotine dependence within the next 60 days (as assessed at screening).
- Responds "Yes" to "Are you interested in replacing combustible cigarettes with a smoke-free tobacco product?" when asked at screening.
- Willing and able to comply with the requirements of the study.
- Owns a smartphone with SMS text messaging and data capabilities compatible with necessary surveys.

Exclusion criteria

- Participant enrollment numbers met (in subgroup or entire study).
- Participant, or their first-degree relative (eg, parent, sibling, child, or spouse) or household member, is a current or former employee of the tobacco or e-vapor industry.
- Participant, or their first-degree relative (eg, parent, sibling, child, or spouse) or household member, is a named party or class representative in litigation involving a tobacco or e-vapor company.
- Participant, or their first-degree relative (eg, parent, sibling, child, or spouse) or household member, is a current or former employee of a marketing consultant, market research firm, advertising or promotions agency, TV or radio station, magazine or newspaper, government regulatory agency or public policy advocacy group, or law firm or legal department of a company.
- Participant self-reports being "in poor health."
- Participants of childbearing potential (CBP) who have a positive pregnancy test (as assessed at screening) or are nursing or planning to become pregnant during their participation.
- Participant has an allergy or sensitivity to menthol or menthol-containing products or phenylalanine.
- Participant has any other self-reported health restrictions.
- Participant self-reports cardiovascular disease, cancer, or diabetes or is being treated for high blood pressure.
- Participant self-reports periodontal disease, gum disease or bleeding, open mouth sores, or ulcers.
- Participant self-reports as wanting to stop using tobacco products in the next 60 days.
- Participant has participated in 1 tobacco research study in the past 30 days or a tobacco research study lasting 2 weeks or longer in the past 90 days.
- Participant is unable to read, speak, or understand English.
- Participants who ever used at least a pack of nicotine pouch products or currently uses nicotine pouch products.
- Participant who smokes marijuana more than once a week.
- Heterosexually active participants of CBP (not sterilized by tubal ligation, oophorectomy, hysterectomy, or other surgical methods, or postmenopausal) who do not agree to practice medically appropriate methods of birth control (or remain abstinent) during the course of the trial and for 30 days after the last use of research product. Medically acceptable methods of birth control include vasectomy, vaginal diaphragm with spermicide, intrauterine device, hormonal birth control (oral, injected, patch, or implanted), condom with spermicide, or sponge with spermicide.
- Taking psychoactive medications (eg, antipsychotics or mood stabilizers).
- Cannot participate in the study for any reason (eg, medical, psychiatric, or social reason) as judged by the investigator or designated medical staff based on all available information from the screening period.

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Ethical Considerations

The study protocol and informed consent form (ICF) has been approved by Advarra Institutional Review Board (IRB; Pro00072765). Study conduct will follow the principles set forth by the Belmont Report and, where applicable, guidelines established under 21 Code of Federal Regulations (CFR) § 50 and 56. In addition, study conduct will be in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the US FDA as described in 21 CFR 50 and 56, applicable laws, and the IRB requirements.

Informed consent will be obtained from all participants remotely through an electronic consent process. Participants will be required to verify that they understand each section of the ICF by checking a box. They will provide their consent at the end of the document by checking a box after reading the consent statement. Electronic copies of the ICF are made available for the participants to download and reference at any time. Participants will be informed that their participation is completely voluntary, and they may discontinue their participation at any time for any reason.

After providing consent, participants will be asked to upload a copy of their government-issued ID for verification. We will use a multistep process for age verification, validation of the uploaded government-issued identification, and to ensure that the person matches the photo on the ID. This process will be conducted by software and research staff. Software will initially determine whether the uploaded ID is valid, verify the individual's age, and compare previously submitted information against what is detected on the uploaded ID. Any discrepancies at this point will be reviewed by research staff. If the uploaded ID is expired, blurred, or otherwise not valid, the potential participant will be given the opportunity to resubmit and continue the screening process. For those who pass the initial software-level review, research staff will verify that the face on the ID matches the individual who joins the telemedicine session. We rely on human review for this final step for the safety of minors and due to limitations in currently available software.

Recruitment

Participants will be recruited through IRB-approved, study-specific recruitment advertisements or from the Rose Research Center volunteer database, an Advarra IRB-approved generic volunteer database. Participants will be contacted with IRB-approved materials. These documents will include a brief description of the study and information on how to prescreen for participation. This study will recruit remotely across the United States in North Carolina, Ohio, Georgia, Florida, Michigan, South Carolina, Tennessee, and Pennsylvania. Participant recruitment will be guided by the distribution of demographic characteristics shown in Table 1.

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Table 1. Demographic distribution of adults who smoke cigarettes based on National Survey on Drug Use and Health (NSDUH) 2021 data.

Demographic subgroup	Prevalence in US adult smoker population, %[a]	Corresponding average expected cell size given (n=400), n
Sex and age (years)		
Male	53.9	216
21-34	11.0	44
35-44	13.2	53
45-49	6.1	24
50-64	23.6	94
Female	46.1	184
21-34	9.6	38
35-44	12.1	48
45-49	5.8	23
50-64	18.7	75
Race or ethnicity		
White non-Hispanic	77.7	311
Black non-Hispanic	8.1	32
Other non-Hispanic	6.3	25
Hispanic	7.9	32
Education		
Less than College	60.4	242
Some college	30.20	121
College+	9.40	38
Menthol preference		
Menthol	36.20	145
Nonmenthol	63.80	255

[a]Estimates were based on weighted proportions.

Study Procedure

This study involves a multistep screening process, a baseline assessment period (3-7 days), 6 weeks of at-home product use, and a 6-month posttrial follow-up survey. During recruitment, participants will sign the ICF, upload a picture of their government-issued ID, complete web-based screening surveys, and download eResearch Advance Science from Home to their smartphones.

All who pass the initial web-based screening will have a CO monitor sent to their home address. At this point, male participants are able to schedule their baseline telehealth session and continue the screening process. Female participants are sent a urine pregnancy test with instructions for completing and uploading results, which are reviewed and confirmed by study staff. Those with confirmed negative pregnancy test results are then able to schedule the baseline telehealth session.

At the baseline telehealth session, participants will be further assessed for eligibility with additional inclusion or exclusion criteria, including a biometrically verified expired-air CO reading. If eligible, they will be randomized to Group I or Group IIa/IIb. During the 3- to 7-day baseline assessment period, participants will provide CO readings every other day and record their cigarette consumption in web-based daily diary survey. Upon the completion of the baseline assessment period, participants will begin week 1 when they receive the research product to use in their natural environment, following group configurations shown in Figure 1. During weeks 1-6, participants will respond to daily diary surveys to report their use of the research product (by flavor, if applicable), cigarette consumption, and use of other tobacco products. They will request and receive research products weekly. They will also be alerted to provide pseudorandom biometrically verified CO readings once every 3 days. At the end of week 3, female participants of childbearing potential will be asked to provide urine pregnancy test results; those with positive results (ie, pregnant) will be discontinued from the study and referred to their primary care provider. Six months after the study ends, participants will be recontacted to complete a follow-up survey with questions related to tobacco-use behaviors (including cigarette smoking and *on!* NP use), reasons to use or not use *on!* NPs, risk perceptions of use of a variety of tobacco products at the category level (eg, cigarettes, smokeless tobacco, and NPs), and respiratory symptoms. The main purpose of the 6-month follow-up survey is to collect information on

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participants' posttrial tobacco use behaviors when they are no longer provided with *on!* NPs. None of our research questions rely on the 6-month follow-up survey.

Participants will be presented with the following debriefing statement at the conclusion of the study (ie, at the end of Week 6) or upon discontinuation of participation (ie, withdrawal from the study):

> *We would like to emphasize that in conducting this research, we were not trying to market, sell or promote a tobacco or nicotine product to you. Finally, oral tobacco-derived nicotine products should never be viewed as an alternative to quitting all tobacco products.*

Research will be conducted in the context of participants' natural environment (ie, home use test). Research products will be shipped to participants weekly.

Participants will receive compensation after successful completion of each study milestone, including the completion of each daily survey, weekly survey, and CO measurement collection throughout the study. An end-of-study bonus will be awarded if the participant completes the entire study.

Outcome Measures

Primary outcomes of this study are (1) at least 50% reduction in expired-air CO readings from baseline (yes or no) and (2) expired-air CO as a continuous variable (averaged across the week of interest).

Secondary outcomes include (1) at least 50% reduction in self-reported cigarette consumption from baseline (yes or no), (2) CO-verified smoking abstinence (ie, self-reporting no cigarettes smoked in past 7 days and CO<6ppm [22]), and (3) self-reported number of cigarettes smoked (averaged across the week of interest).

Participants who meet the ≥50% cigarette reduction (based on self-reported cigarette consumption) threshold will be identified as "Responders"; those unable to meet this threshold will be identified as "non-Responders."

We chose to use expired-air CO values in primary outcomes because it is an objective measure not susceptible to recall bias, demand characteristics, or prevarication. Further, expired-air CO closely reflects actual smoke exposure and would not lead to an erroneous conclusion of reduced exposure that results from more intensive smoking of fewer cigarettes as compared to self-reported cigarette consumption. Nonetheless, expired-air CO measures are not without limitation. Factors other than cigarette smoking, such as exposure to environmental pollutants, second-hand smoke, vehicle exhaust, etc, can contribute to elevated expired-air CO, and vigorous exercise can lead to lower expired-air CO. In this study, we include both expired-air CO (taken twice a week) and self-reported cigarette consumption (daily) to provide robust assessments of smoking behavior.

Analytic Plan

A description of recruitment will be reported, including the number of participants who are recruited, pass screening, are randomized, complete weeks 1-3, enter week 4, complete the trial (ie, weeks 1-6), and complete the 6-month follow-up.

We will use descriptive statistics to characterize the distribution of demographic variables, tobacco use history (ie, cigarettes per day, use of other tobacco products, and menthol cigarette preference), and CO at baseline. We will examine the aforementioned demographic variables and tobacco use history variables among responders and nonresponders for potential imbalance. If such imbalance is discovered, respective variables will be adjusted in the analysis as covariates.

The analysis will be conducted on an intention-to-treat basis. Primary outcome variables include a binary (yes or no) variable indicating at least 50% reduction in CO readings from baseline and a numeric variable for expired-air CO. For individuals who drop out of the study prematurely, they will be assumed not achieving at least 50% reduction in CO readings, and their numeric CO reading variable after those last reported will be replaced with their baseline CO readings.

To compare incidence proportions of at least 50% reduction in CO readings between study groups at each time point (week 3 or week 6, depending on the objective), generalized linear regression models with a log link will be used to generate incidence ratios and their 95% CIs. To compare numeric CO readings between study groups at each time point (week 3 or week 6, depending on the objective), linear regression will be used to compare group-level differences in CO readings and their 95% CIs when adjusting for baseline CO reading. We chose to use linear regression adjusting for baseline CO reading over ANOVA for change in CO readings from baseline because the adjustment approach properly corrects for "regression to the mean," provides greater statistical power, and produces unbiased estimates [23-25].

Similarly, we will use generalized linear regression with a log link for binary secondary outcomes (ie, at least 50% reduction in cigarette consumption based on self-report and CO-verified smoking abstinence). Generalized estimating equations will be used to analyze cigarette consumption based on the daily diary, with cigarette consumption at baseline as a covariate. Specific comparisons are as follows: (1) for objective 1, comparison will be made between (a) Group I and combined Groups II at Week 3 and (b) Group I and Group IIa at Week 6; (2) for objective 2, comparison will be made between Group IIa and Group IIb at week 6 among nonresponders at week 3; (3) for objective 3, comparison will be made between Group IIa and Group IIb at Week 6 among responders at week 3; and (4) for objective 4, comparison will be made between Group I and Group IIb at week 6.

Power

Sample size calculation was based on the primary outcomes of the study: at least 50% reduction in expired-air CO readings from the baseline numeric CO readings. Because the Original variety is included in the complete flavors, we do not expect the occurrence of the main outcome to be lower in the complete flavor arms compared to the Original arms, so we will use 1-sided tests with an α level of 0.05 and power of 0.80. Sample size calculation was conducted using Stata 16 (StataCorp).

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For objective 1, we assumed an incidence of at least 50% reduction in CO readings of 60% in Group I and 45% in the Original arm at week 3, and incidence of the main outcome among 80% in Group I and 60% in Group IIa at week 6. Based on these values, it was estimated that 136 participants and 64 participants per arm will be needed, respectively. Numeric CO readings will be analyzed as a continuous variable, which typically has higher levels of statistical power [26]. Assuming a mean CO of 6 ppm in Group I and SD of 5 [27], a sample size of 136 per arm will be able to detect a difference of 1.7 between study groups.

For objective 2, we assumed an incidence of at least 50% reduction in CO readings for 70% of those in Group IIb and 45% among the Group IIa at week 6 among the nonresponders in Group II (ie, those who did not reduce cigarette consumption by ≥50% at week 3). Based on these values, we estimated that 48 participants per group will be needed. Assuming 55% of participants in Group II will be nonresponders at week 3; we estimated that a total of 175 participants will be needed in Group II at baseline.

For objective 3, we assumed that 85% in Group IIb and 60% in Group IIa will maintain their responder status at week 6 among responders in Group II (ie, those who reduce cigarette consumption by ≥50% at week 3). Based on these values, it was estimated that 39 participants per group will be needed. Assuming 45% of participants in Group II will be responders at week 3, a total of 174 participants will be needed in Group II at baseline.

Based on these calculations, we will randomly assign 150 participants to Group I and 250 participants to Group II at baseline.

Objective 4 is considered exploratory in nature. Given the above sample size, 125 participants per group will be able to detect a difference between 80% and 67% of at least 50% of CO reduction comparing immediate versus delayed access to complete flavor profile.

Results

This study was approved by Advarra IRB (Pro00072765) in July 2023. Recruitment and data collection began in September 2023. Recruitment for the trial is projected to end in July 2024 and the entire study in March 2025 (with the 6-month follow-ups). We anticipate publishing study results in 2025. As of May 2024, we have enrolled 314 participants.

Discussion

Expected Findings

This study seeks to provide empirical evidence about the causal relationships between availability of flavored smoke-free NP products and the reduction or complete cessation of combusted cigarette smoking, a critical knowledge gap in the literature. In addition to the use of an experimental design, this study was designed to include several features intended to enhance internal and external validity. First, using a SMART design can provide multiple insights about the potential role of flavors in smoking reduction that would not be possible with traditional experimental designs (eg, randomized controlled trials). In other words, using a single study design, we will be able to assess the role of flavors in smoking reduction, maintenance of smoking reduction (among responders), potential added benefit of flavors among nonresponders (ie, the rescue), and the effect of timing (ie, immediate versus delayed access to flavors).

Second, we will remotely collect expired-air CO values. This noninvasive measure provides a validated, objective assessment of recent smoke exposure, not subject to potential bias when relying solely on self-reported cigarette consumption. This is especially relevant when blinding is not feasible as in this study [28,29].

Third, we include the unflavored or Original *on!* NP variety in the complete profile arm to assess the potentially additional effect of flavored products beyond the unflavored or Original variety. This will provide direct evidence from a counterfactual scenario whether there will be any loss of benefit from smoking reduction if a flavor ban was to be implemented for new smoke-free tobacco products, in which case only unflavored or Original products would be allowed in the market. We realize that another scenario relevant to the flavor ban is the removal of all nontobacco flavored smoke-free tobacco products from the market. In this scenario, adults who smoke cigarettes who have replaced their cigarettes with nontobacco flavored smoke-free tobacco products may relapse to smoking or choose to use tobacco-flavored or nonflavored smoke-free products instead. Our study will not provide evidence for this scenario due to considerations of resources and logistics. Future studies with a "constricting" arm where participants have access to the complete profile of smoke-free tobacco products during phase 1 and then only to tobacco-flavored or nonflavored products during phase 2 will provide direct evidence for this scenario.

Last, participants will be instructed to use the research products ad libitum in their natural environment and are allowed to use other tobacco products as they wish. This is intended to enhance external validity relative to studies that may restrict use of research or other tobacco product use or be conducted in a highly controlled laboratory environment.

Limitations

One potential study limitation is that blinding is not feasible. Consequently, participants are aware of their group assignment. We use expired-air CO as our primary outcome to minimize potential biases in participants' self-reported cigarette consumption. Another possible limitation is the relatively short study duration (ie, a total of 6 weeks). This study design aspect was a result of balancing feasibility and available resources while also providing sufficient time for participants to achieve a meaningful reduction in their cigarette consumption. Due to the relatively short study duration, we chose at least a 50% reduction in CO values as one of our primary outcomes—and abstinence as one of our secondary outcomes—considering we may not be able to observe the full course of smoking cessation. Previous studies using the same research products have shown measurable changes in smoking behavior in a similar timeframe [13]. Finally, this study uses a nonprobability sample, a common challenge of clinical trials. We try to mitigate these limitations

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by setting population quotas to align the sample with the adults who smoke cigarettes population in key demographic characteristics.

Acknowledgments

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Authors' Contributions

HGC, JER, and GC conceptualized the study. All authors contributed to the design of the study. All authors wrote, reviewed, and approved the manuscript before submission.

Conflicts of Interest

HGC and JLK are employees of Altria Client Services, LLC, an affiliate of tobacco manufacturers. As partial owners of Rose Research Center, LLC, JER, TLB, and DRB disclose recent research support from Foundation for a Smoke-Free World; Philip Morris International; Altria Client Services, LLC; Swedish Match North America; Otsuka Pharmaceutical; National Institutes of Health; and JUUL Labs. JER also discloses consulting for Philip Morris International and JT International and patent purchase agreement with Philip Morris International for nicotine inhalation system patents, final payment 2014. PNW and GC are employees of Rose Research Center, LLC. GC was previously a principal scientist at JUUL Labs and was previously employed by its predecessor companies. He holds stock in Qnovia and JUUL Labs. Only Altria Client Services had financial interest in the technology that was the subject of this study.

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Abbreviations

CO: carbon monoxide
CFR: Code of Federal Regulations
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HPHC: harmful and potentially harmful constituent
ICF: informed consent form
IRB: institutional review board
NP: nicotine pouch
SMART: sequential, multiple assignment, randomized trial

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Protocol

Web-Based Group Conversational Intervention on Cognitive Function and Comprehensive Functional Status Among Japanese Older Adults: Protocol for a 6-Month Randomized Controlled Trial

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Abstract

Background: Social communication is a key factor in maintaining cognitive function and contributes to well-being in later life.

Objective: This study will examine the effects of "Photo-Integrated Conversation Moderated by Application version 2" (PICMOA-2), which is a web-based conversational intervention, on cognitive performance, frailty, and social and psychological indicators among community-dwelling older adults.

Methods: This study is a randomized controlled trial with an open-label, 2-parallel group trial and 1:1 allocation design. Community dwellers aged 65 years and older were enrolled in the trial and divided into the intervention and control groups. The intervention group receives the PICMOA-2 program, a web-based group conversation, once every 2 weeks for 6 months. The primary outcome is verbal fluency, including phonemic and semantic fluency. The secondary outcomes are other neuropsychiatric batteries, including the Mini-Mental State Examination, Logical Memory (immediate and delay), verbal paired associates, and comprehensive functional status evaluated by questionnaires, including frailty, social status, and well-being. The effect of the intervention will be examined using a mixed linear model. As a secondary aim, we will test whether the intervention effects vary with the covariates at baseline to examine the effective target attributes.

Results: Recruitment was completed in July 2023. A total of 66 participants were randomly allocated to intervention or control groups. As of January 1, 2024, the intervention is ongoing. Participants are expected to complete the intervention at the end of February 2024, and the postintervention evaluation will be conducted in March 2024.

Conclusions: This protocol outlines the randomized controlled trial study design evaluating the effect of a 6-month intervention with PICMOA-2. This study will provide evidence on the effectiveness of social interventions on cognitive function and identify effective target images for remote social intervention.

Trial Registration: UMIN Clinical Trials UMIN000050877; https://tinyurl.com/5eahsy66

International Registered Report Identifier (IRRID): DERR1-10.2196/56608

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KEYWORDS

randomized controlled trial; web-based intervention; communication technology; cognitive health; neural blood markers; social isolation; well-being

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Introduction

Remote intervention, which allows interventions to be conducted remotely through communication technology with participants, may benefit health and convenience. Remote interventions enable people with low accessibility to interventions due to disability, illness, location, or pandemic to participate in interventions and provide equitable health service. In particular, there has been increased attention to internet-based social interventions that alleviate social isolation since the COVID-19 pandemic [1-3] because of increased social isolation reported [4].

Social isolation is a major public health concern and determinant of healthy longevity. According to Lancet Reports from the *Lancet* Commission on Dementia, social isolation has been identified as one of the single potentially modifiable risk factors for dementia [5]. A growing body of literature has reported a link between social interactions and the risk of dementia [6-9]. Recent longitudinal meta-analyses [10] have demonstrated the integrated risks of poor social interaction and greater loneliness with the occurrence of dementia. This meta-analysis suggests that the strength of this association is comparable to other well-established risk factors, such as low education, depression in later life, and poor physical activity.

Psychological, behavioral, and biological pathways may link social interactions to health. Social interaction may play a significant role in maintaining mental health [11,12] and could be an important contributing factor to dementia [13] by providing a sense of connection with others and buffering perceived stress. Social interactions may also have behavioral effects. Interacting with others may promote appropriate health behaviors [14,15] by providing access to health information and social support. Biological mechanisms may also be mediated by physiological processes involved in cardiovascular, immune, and neuroendocrine functions [16-18].

In addition, communication, the basis of social interaction, is an intellectual activity. Communication requires multiple cognitive processes. Furthermore, the multifaceted brain processes nonverbal information, such as the other person's voice [19], facial expressions [20], and emotions [21], as well as a variety of verbal information during communication. Such cognitive stimulation through social and conversational activities can contribute to the maintenance of the cognitive abilities of an individual.

Based on the evidence, we hypothesized that social communication-based interventions would be effective in maintaining cognitive function. Consequently, a series of our previous randomized controlled trials (RCTs) examined the effect of structural face-to-face group conversation intervention and consistently observed some positive effects on verbal fluency [22,23]. Our explanatory investigation using multimodal magnetic resonance imaging identified the brain network, brain regions, and brain structure that could benefit from the intervention. Despite the significant limitation regarding the lack of preintervention data, we observed higher resting-state functional connectivity between the left inferior frontal gyrus as a seed region and the temporal pole and middle frontal gyrus, which may reflect the brain network involved in the intervention effects [24]. Our voxel-based morphometric analysis also identified the candidate brain regions involved in the intervention mechanism, including the lateral prefrontal cortex [25]. Further, analysis using diffusion tensor imaging metrics suggested that left frontal white matter structures were candidates for white matter microstructural changes effected by the intervention [26]. Building on these findings, we have inferred that our conversational intervention may stimulate language-related function in the prefrontal lobe, serving as a potential mechanism underlying the observed effects.

We recently focused on remote social intervention to address the challenges of the COVID-19 pandemic and clinical face-to-face interventions in which functional decline reduces accessibility to interventions. We developed a remote smartphone-based group conversation intervention program called "Photo-Integrated Conversation Moderated by Application" (PICMOA) and conducted a 12-week RCT to determine the effectiveness of the program [27]. The PICMOA trial showed a positive intervention effect on semantic fluency for those who were good at using smartphones before the intervention. On the other hand, potential issues for PICMOA intervention were also suggested, such as the difficulty of operating a small smartphone for older people, the psychological burden of using smartphones and apps for older adults, the possibility that the stimulation of visual social interaction is small due to the small smartphone screen, and the short intervention period.

To address these challenges of smartphone-based interventions for older adults in a past trial, we developed Photo-Integrated Conversation Moderated by Application version 2 (PICMOA-2), a remote conversational intervention for PC tablets. By adapting the intervention to a PC tablet, a larger screen is expected to improve operability for older people and increase cognitive stimulation through recognition of the speaker's face.

The primary aim of this study is to evaluate the effect of a 6-month intervention with PICMOA-2 on cognitive function in community-dwelling older adults. In addition to investigating the intervention's effects on cognitive function, this study also evaluates its impact on frailty and social and psychological indicators. We hypothesized that this intervention may have secondary effects, potentially contributing to the physical, mental, and social well-being of participants. These possible secondary effects could arise from the maintenance of cognitive function through our intervention or via other pathways such as stress buffering, behavioral changes, and physiological processes owing to the enhanced social interaction by the intervention. Furthermore, this study will address whether target attributes modify the intervention effects as a secondary objective, as it remains unclear whether web-based conversational intervention is effective for a broad population or only for a specific population.

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Methods

Study Design

The PICMOA-2 trial is an open-label, 6-month RCT with 2 parallel groups, including 1 intervention group and 1 passive control group. The overall timeline of the procedure is shown as a SPIRIT flow in Table 1. The main and secondary outcomes will be assessed at baseline and after a 6-month intervention period.

Table 1. Overall timeline of the procedure of the PICMOA-2 trial.

Time point	Enrollment	Allocation	Post allocation		Evaluation
	$-t_1$	0	t_1	t_2	t_3
Enrollment					
Eligibility screening	✓	—[a]	—	—	—
Informed consent	✓	—	—	—	—
Allocation	—	✓	—	—	—
Interventions					
Practice using equipment and test session	—	—	✓	—	—
Interventions	—	—	—	✓	—
Assessments					
List of baseline variables					
Demographic and socioeconomic information	✓	—	—	—	—
Lubben Social Network Scale-6	✓	—	—	—	—
Familiarity with using devices	✓	—	—	—	—
List of outcome variables					
Mini-Mental State Examination	✓	—	—	—	✓
Verbal fluency tests	✓	—	—	—	✓
Logical Memory I and II	✓	—	—	—	✓
Verbal paired associates I and II	✓	—	—	—	✓
Kihon checklist	✓	—	—	—	✓
UCLA[b] Loneliness Scale 10-item version	✓	—	—	—	✓
The 5-item World Health Organization Well-Being Index	✓	—	—	—	✓
Health Utility Index Mark 3	✓	—	—	—	✓
S-A creativity test	✓	—	—	—	✓
List of other variables					
Blood-based biomarkers	—	—	✓	—	✓
Face scale	—	—	—	✓	—

[a]Not applicable.

[b]UCLA: University of California, Los Angeles.

Participants

We recruited community-dwelling older adults aged 65 years and older without cognitive decline living in Kishiwada city, Osaka Prefecture, Japan, near a metropolitan area with a population of 188,129 as of December 2023 [28]. This study's design is illustrated in Figure 1. This procedure included eligibility screening, informed consent, outcome assessments, randomization, and 6 months of web-based conversational intervention. The inclusion criteria are as follows: a Mini-Mental State Examination (MMSE) score ≥ 24, available to provide written consent, and able to undergo the required tests and interventions on specified dates. We screened medical conditions and medication use and excluded patients with dementia; those with a history of disease or previous medications that could affect the central nervous system, such as neurological impairment, serious complicating disorders, and a history of serious head injury; and those certified as having a long-term care condition ("care needs levels" or "support need levels") by the national public long-term care insurance system in Japan.

Participants were recruited by sending recruitment letters and flyers to community-dwelling older adults from the municipal government and posting announcements for enrollment in a new community paper. We mailed 3000 recruitment letters to

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randomly selected older adults without certificates of long-term care in 4 living areas of Kishiwada city. Some flyers were also distributed to the public and in collaboration with organizations. Once potential participants expressed interest in participating in the trial, they were screened for eligibility. Participants in both groups will receive cash compensation.

Figure 1. Participant flow of the PICMOA-2 trial. MMSE: Mini-Mental State Examination; PICMOA-2: Photo-Integrated Conversation Moderated by Application version 2.

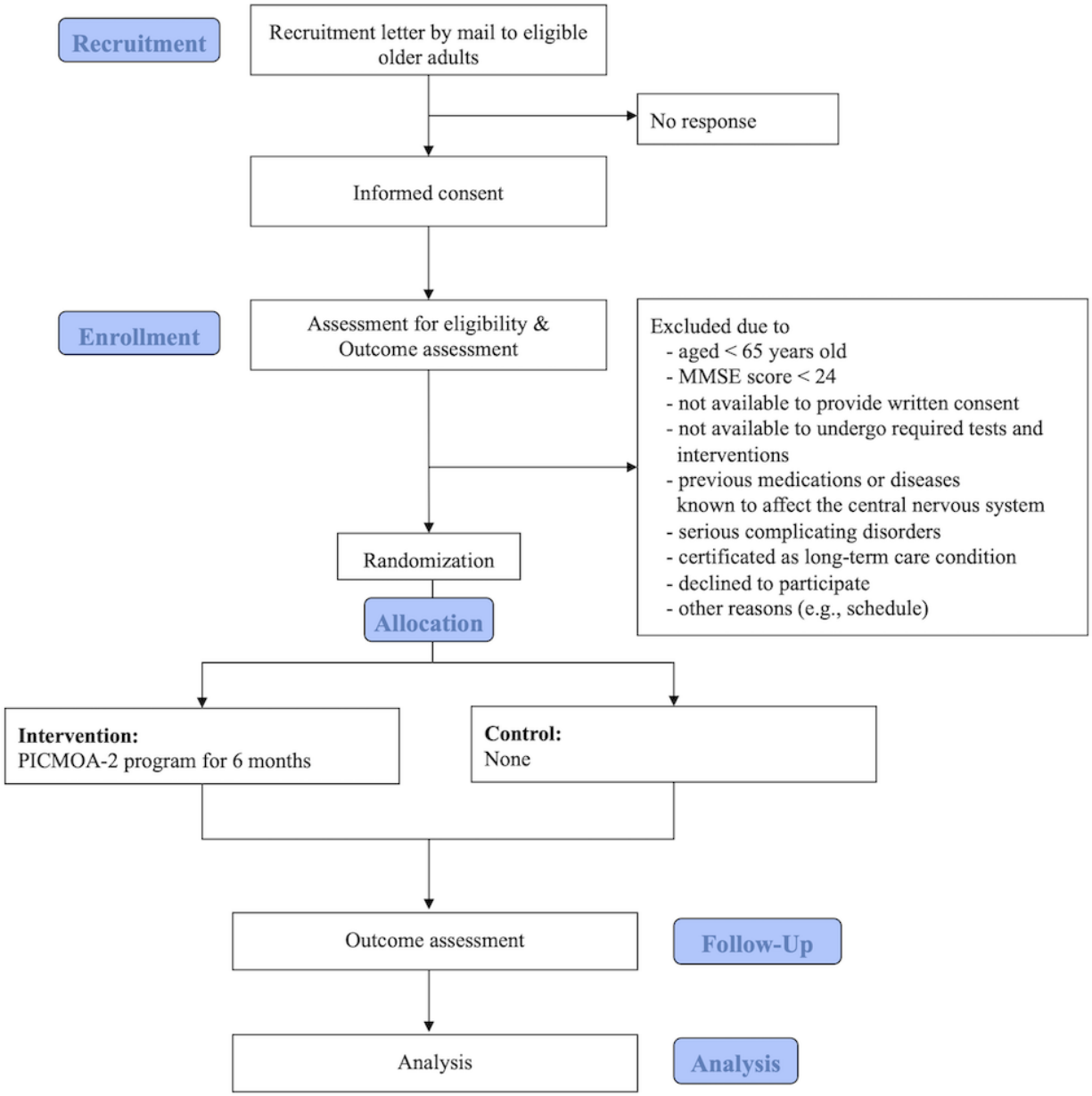

Intervention

The intervention program is PICMOA-2, a web-based conversational intervention that uses a PC tablet at the participant's home. Participants are instructed to take photos in their daily lives as much as possible according to the specific 12 themes during the 6-month intervention period and join conversational intervention based on PICMOA-2 once every 2 weeks for 6 months. Figure 2 describes the intervention structure of PICMOA-2. Participants are required to upload to the web system using a smartphone app that we originally developed before the intervention session, join the group conversational intervention session, and have a presentation and discussion about the photos that participants took during the session.

In the conversational session, each participant in a designated group of 4 gives a 1-minute speech about the 2 photos they took in their daily lives. Other participants then ask questions related to the photos, and the presenter answers the questions in the context of a natural conversation for 2 minutes for each photo. Research staff administer intervention using the PICMOA-2 system and support participants' PC operations through remote access.

In the case of dropouts, substitutes are included in the group conversation to maintain the intensity of the intervention since different numbers of group members can lead to quantitative differences in the amount and duration of speaking, potentially impacting the effect sizes.

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Smartphones for taking photos and PC tablets (Surface Go; Microsoft Corp) for conversational sessions with an internet connection were prepared for all participants.

Figure 2. The intervention architecture. PICMOA-2: Photo-Integrated Conversation Moderated by Application version 2.

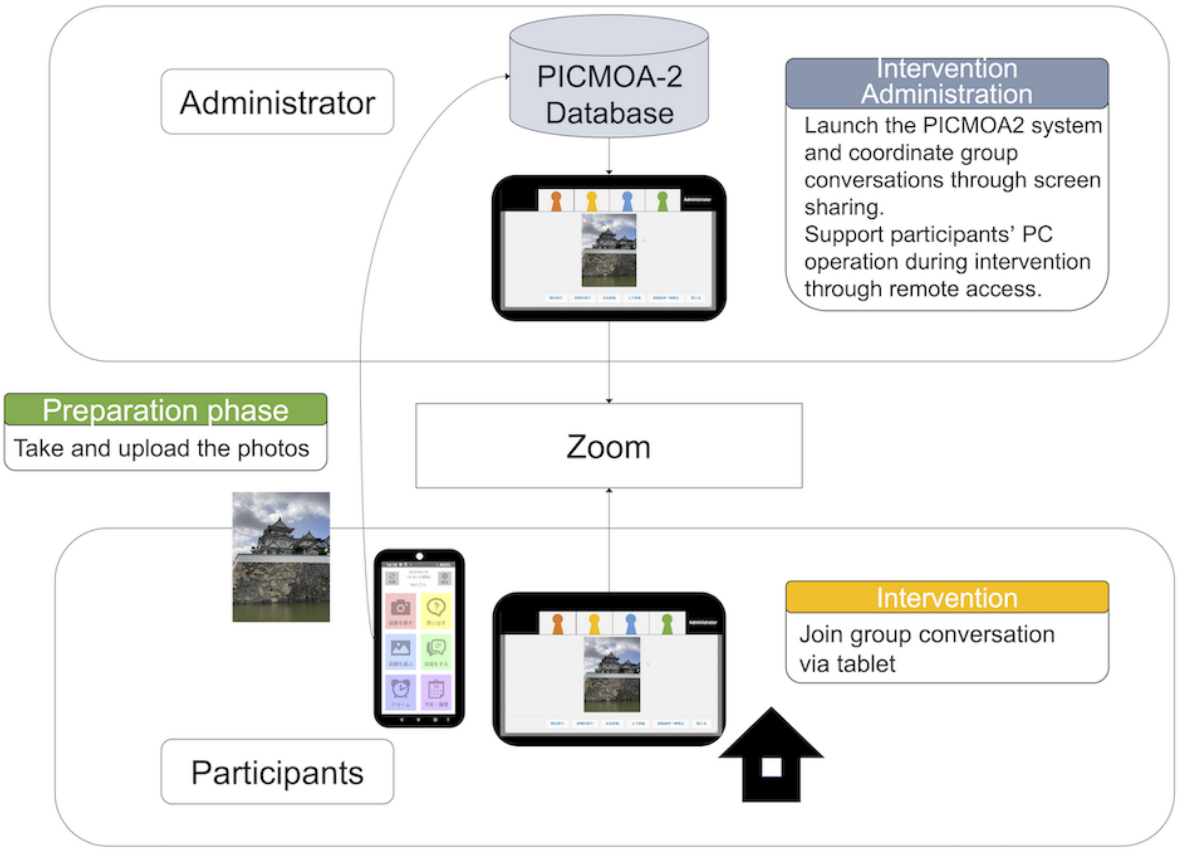

Outcomes

Overview

Table 2 shows the overall outcome measurements.

Table 2. The construction of outcome measurements.

Construction	Outcomes
Cognitive function	MMSE[a], verbal fluency tests, Logical Memory I and II, and verbal paired associates I and II
Frailty	Kihon checklist
Loneliness	UCLA-LS 10[b]
Well-being	WHO-5[c]
Health-related quality of life	HUI3[d]
Divergent thinking	S-A creativity test

[a]MMSE: Mini-Mental State Examination.

[b]UCLA-LS 10: The University of California, Los Angeles Loneliness Scale-10 item version.

[c]WHO-5: 5-item World Health Organization Well-Being Index.

[d]HUI3: Health Utilities Index Mark 3.

Cognitive Functions

The main outcome measure is cognitive function. Specifically, we hypothesized that the PICMOA-2 may stimulate linguistic and executive functions through fundamental conversation activities based on the results of previous RCTs [22,23,27] and mechanistic hypothesis based on the explanatory investigation using multimodal magnetic resonance imaging [24-26]. Thus, we will specifically focus on verbal fluency as the primary outcome, which may reflect linguistic and executive functions. Well-trained clinical psychologists administered standardized

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neuropsychiatric tests to evaluate the effects of the intervention on cognitive function.

MMSE [29] is used to evaluate global cognitive function and screen for cognitive decline. The MMSE consists of 11 question sets and the total score is calculated. Verbal fluency tests, including 3 tasks each for semantic and phonemic fluency, are administered to assess linguistic and memory retrieval abilities, which may reflect executive control. A semantic fluency test is required to produce the names of animals, sports, and jobs, while the phonemic fluency test is required to generate the words that begin with the letter "a," "ka," and "si" in Japanese within 1 minute each. To evaluate episodic memory, Logical Memory I and II and the Verbal paired associates from the Wechsler Memory Scale-Revised [30] are introduced. Logical Memory is a story recall subtest. Logical Memory I assesses immediate recall and is required to immediately reproduce each of the 2 stories read out by the examiner, whereas Logical Memory II is required to reproduce stories approximately 30 (±5) minutes later to assess delayed recall. Verbally paired associates are paired-associate learning subtests. Participants are required to learn 4 pairs of related and unrelated words and test their memory of word pairs. Verbal Paired Association I assesses immediate recall, while Verbal Paired Association II assesses delayed recall approximately 30 (±5) minutes later.

Frailty

The Kihon checklist (KCL) [31] is used to assess frailty. The KCL is a self-report scale for frailty that has shown high validity in Japanese community-dwelling older adults. The KCL is commonly used in Japan, as municipalities across Japan have used it to determine high-risk populations to invite or evaluate intervention programs. The KCL includes 7 domains: daily life, physical strength, nutritional status, oral function, extent of house boundedness, cognitive function, and risk of depression. The total KCL scores and the occurrence and recovery of comprehensive or domain frailty will be assessed.

Social and Psychological Factors

Loneliness, well-being, health-related quality of life (HRQOL), and divergent thinking are introduced to evaluate the effects of conversational interventions on social and psychological aspects.

The University of California, Los Angeles Loneliness Scale-10 item version (UCLA-LS 10) [32] is used to assess loneliness. A total UCLA-LS score of 10 is calculated from the sum of each item (10-40 points). Higher scores on the UCLA-LS 10 indicate severe loneliness. The 5-item World Health Organization Well-Being Index [33] is introduced to evaluate well-being. The percentage score of WHO-5 is calculated (0-100 points) according to the manual. The Health Utilities Index Mark 3 [34] is used to assess HRQOL, and the multi-attribute utility score (–0.36 to 1.00) is calculated using the formula. Higher 5-item World Health Organization Well-Being Index and Health Utilities Index Mark 3 reflect better well-being and HRQOL. An item fluency test from the S-A creativity test [35], which is a divergent thinking assessment tool, is also introduced. While the S-A creativity test has 3 kinds of tasks that correspond to the 3 tasks of the Torrance test of creative thinking [36], including unusual use, product improvement, and just suppose, we only perform an unusual use task, which is an item fluency test to evaluate the flexibility of thought and divergent thinking, due to the balance between our study interest and time limitation. The 2 questions in the unusual use task ask participants to generate as many ideas as possible for the alternative uses of typical objects in unique ways in 5 minutes. The scoring of the S-A test is calculated using the formula by Tokyo Shinri Corporation.

Covariates

The covariates from the questionnaire include the following variables to describe participants' demographics: age, sex, educational attainment, social isolation (the Lubben Social Network Scale-6) [37], and familiarity with devices such as smartphones, PCs, and email. Blood samples are also collected, with the measurement of blood-based biomarkers, including plasma neurofilament light chain (NfL), plasma tau, and tau in neuron-derived extracellular vesicles from plasma, which may reflect neuronal condition.

Sample Size

We used G*power [38] to calculate the sample size, assuming the following conditions: 2-sided hypothesis test; medium effect size (f=0.25); 95% power; an analysis of variance model between groups over time; and 5% α level. Therefore, 65 participants are required, with a 20% dropout rate.

Randomization and Blinding

Stratified block randomization, a block design (2, 4, and 6 block sizes) with a 1:1 allocation, was performed using the University Hospital Medical Information Network Internet Data and Information System for Clinical and Epidemiological Research Cloud version [39]. The participants were allocated to either the intervention or the control group. Sex (male or female) and MMSE scores (28 or higher and 27 or lower) at baseline were used for stratification. KWM is responsible for the randomization. As this study uses an open-label design, we aim to prevent potential assessment bias by blinding the assessors.

Statistical Analysis

This study evaluates the effects of the PICMOA-2 intervention on outcome measurements. Linear mixed models with random intercepts for outcome measurements will be used to estimate the intervention effects. Our model will include the group assignment factor, time factor, and group × time interaction term and evaluate the intervention effect from the interaction term. As a secondary aim, we will test whether the intervention effects varied with the covariates at baseline to examine the effective target attributes.

All analyses will be conducted using the R software (The R Foundation). Statistical significance will be set at $P<.05$.

Ethical Considerations

This trial was approved by the Ethics Committee of RIKEN (RIKEN-W1-2022-063) and was registered in the University Hospital Medical Information Network clinical trial registry (UMIN000050877).

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Results

Recruitment began in April 2023 and ended in July 2023. In total, 66 participants were enrolled and randomly allocated to intervention or control groups. As of January 1, 2024, the intervention is ongoing. Participants are expected to complete the intervention at the end of February 2024; the postintervention evaluation will be conducted in March 2024.

Discussion

Findings and Strength

This protocol aimed to evaluate the effect of a 6-month PICMOA-2 intervention, a web-based group conversational intervention, on cognitive function, frailty, and social and psychological indicators to determine the effectiveness of a web-based remote conversational intervention that we originally developed.

This study has several strengths. First, it may have clinical significance by accumulating evidence on the effectiveness of social interventions on cognitive function and digital health practices. Although large-scale observational studies have demonstrated a link between social interaction and cognitive health [2-7], whether social interventions can slow cognitive decline remains unknown. Since there is low evidence of social intervention and there are no clear clinical guidelines, this study may add knowledge on the effectiveness of social intervention. Second, this study examined whether there are differences in intervention effects depending on attributes by collecting subjective and laboratory data. A previous study in a completed clinical trial on mild Alzheimer disease suggested that baseline plasma NfL, which is a neurological biomarker, holds independent information on short-term cognitive decline [40]. Our previous RCT of a face-to-face conversational intervention program also found a positive intervention effect in the group with lower levels of NfL [23]. In addition, our previous PICMOA trial using smartphones suggested that familiarity with digital devices causes differences in the intervention effect [27]. This research may contribute to the search for clues to effective target images for remote social intervention by examining effective targets. Finally, this study directly recruited community-dwelling older adults mainly via mail in cooperation with the municipal government. This method can eliminate selection bias and enhance generalizability to real community intervention settings compared with recruiting from specific organizations or surveys.

Limitations

This study uses an open-label trial design. Although the assessors are blinded to avoid assessment bias, blinding the research staff and participants is not possible for such behavioral interventions. In addition, the sample size was designed with a minimum of 65 participants for feasibility considerations. Large-scale validation is required to examine the effectiveness of the intervention.

Conclusions

This protocol outlines the design of an RCT study that evaluates the effect of a 6-month intervention with PICMOA-2 on cognitive function, frailty, and social and psychological indicators. Though examining the effect of the PICMOA-2 program, this study will provide evidence of the effectiveness of social interventions on cognitive function and identify effective target images for remote social intervention.

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Conflicts of Interest

None declared.

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Abbreviations

HRQOL: health-related quality of life
KCL: Kihon checklist
MMSE: Mini-Mental State Examination
NfL: neurofilament light chain
PICMOA: Photo-Integrated Conversation Moderated by Application
PICMOA-2: Photo-Integrated Conversation Moderated by Application version 2
RCT: randomized controlled trial
UCLA-LS 10: University of California, Los Angeles Loneliness Scale-10 item version

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Protocol

Mindful Self-Compassion Smartphone Intervention for Worker Mental Health in Japan: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mental health problems among workers cause enormous losses to companies in Japan. However, workers have been considered to have limited access to psychological support because of time constraints, which makes it difficult for them to engage in face-to-face psychological support interventions.

Objective: This study aimed to present an intervention protocol that describes a randomized controlled trial to examine whether brief guided mindfulness meditation (MM) or self-compassion meditation (SCM) provided by a smartphone app is effective for mental health and work-related outcomes among workers.

Methods: This is an open-label, 3-arm randomized controlled trial. The participants will be recruited through an open call on relevant websites with the following inclusion criteria: (1) employees who are working more than 20 hours per week, (2) between the ages of 18 and 54 years, (3) not on a leave of absence, (4) not business owners or students, and (5) not currently diagnosed with a mental disorder and have a Kessler Psychological Distress Scale-6 score below 13 points. We will include 200 participants and randomly assign them to an SCM course (n=67), an MM course (n=67), and a waitlist group (n=66). The intervention groups (SCM and MM) will be instructed to engage in daily guided self-help, self-compassion, and MMs lasting 6-12 minutes per day over 4 weeks. Primary outcomes will include psychological distress and job performance, and secondary outcomes will include somatic symptoms, cognitive flexibility, self-esteem, self-compassion, perceived stress, well-being, emotion regulation, work engagement, anger, psychological safety, and creativity. All procedures were approved by the ethics committee of the University of Tokyo (22-326). All participants will be informed of the study via the websites, and written informed consent will be collected via web-based forms.

Results: The recruitment of participants began in December 2022, and the intervention began in January 2023. As of September 2023, a total of 375 participants have been enrolled. The intervention and data collection were completed in late October 2023.

Conclusions: This study will contribute to the development of effective self-care intervention content that will improve mental health, work performance, and related outcomes and promote mindful and self-compassionate attitudes when faced with distress.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000049466; https://tinyurl.com/23x8m8nf

International Registered Report Identifier (IRRID): DERR1-10.2196/53541

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KEYWORDS

self-compassion; mindfulness; smartphone apps; preventive intervention; mental health; work performance; smartphone intervention; workers; psychological support; mindfulness meditation; meditation; work-related outcomes; mobile phone

Introduction

Background and Rationale

Worker health issues significantly influence corporate management due to productivity losses and worsening employee retention. This has led to a social problem in Japan, where the working-age population is decreasing [1]. Mental health problems such as depression, anxiety, and emotional disorders have been reported to cause personal wage loss [2]. All levels of depression are associated with impaired work productivity, and even mild levels of depression have been reported to decrease work performance [3]. The World Health Organization [4] defines mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community." This indicates that being productive is also an essential element of personal well-being. Thus, preventive support for mental health problems is beneficial not only for workers' mental health but also for their well-being and work performance.

Mindfulness and Self-Compassion for Workers

Mindfulness and self-compassion have been of particular interest in providing psychological support to workers because of their potential positive effects on work-related outcomes [5]. Mindfulness is defined as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment" [6]. Mindfulness is also a widespread self-care practice among workers in the United States, with more than 13% reporting that they practice mindfulness [7]. Evidence from previous studies has confirmed that mindfulness interventions have beneficial effects on mental and physical health, including anxiety, depression, chronic pain, and immunity [8,9]. A growing body of evidence demonstrates the effectiveness of mindfulness-based interventions for workers in improving positive indicators, such as work engagement, personal accomplishment, good sleep quality, and relaxation, and reducing negative indicators, such as emotional exhaustion, occupational stress, and anxiety [10,11]. Some researchers have shown that mindfulness training improves key workplace outcomes, such as performance and relationships [12,13]. Mindfulness affects attention and, through attention, influences major domains of human functioning, including cognition, emotion, behavior, and physiology, resulting in improved workplace outcomes such as performance and creativity [13].

Compassion is another area of growing interest in psychotherapy research [14]. Kirby [15] identified at least 8 types of compassion-based therapies that cultivate compassion (eg, compassion-focused therapy, mindful self-compassion, and compassion and loving-kindness meditation). Self-compassion refers to kindness toward oneself in compassion. Neff [16] defined self-compassion as comprising three main components: (1) self-kindness, (2) common humanity, and (3) mindfulness. These elements are described as follows: (1) self-kindness: being kind and understanding toward oneself in instances of pain or failure rather than being harshly self-critical, (2) common humanity: perceiving one's experiences as part of the larger human experience rather than seeing them as separating and isolating, and (3) mindfulness: holding painful thoughts and feelings in balanced awareness rather than overidentifying with them [16]. Meta-analyses of compassion-based interventions have found strong to moderate effect sizes in reducing depression, anxiety, and psychological distress and increasing well-being among participants compared with active controls [17]. Similarly, a systematic review of self-compassion interventions for workers indicated improvements not only in self-compassion but also in outcomes such as quality of life, well-being, and resilience as well as reduced stress and burnout [18]. Therefore, self-compassion is expected to improve workplace outcomes through mechanisms similar to those of mindfulness [13]. However, only a few randomized controlled trials (RCTs) have shown that self-compassion is effective in improving work-related outcomes; thus, a body of methodologically robust evidence is needed [18].

Both mindfulness and self-compassion training are centered on meditation practices and share the same emphasis on mindful states with acceptance, where events are experienced fully, as they are, without defensiveness [19]. Self-compassion further adds to the components of self-kindness and common humanity, which in turn contribute to mental health [20]. For low-intensity and short-period interventions, it is also important to select only effective content. Therefore, a comparative study of mindfulness and self-compassion practices, which are similar in terms of methods but may differ in effectiveness, is required.

Challenges of Mindfulness and Self-Compassion

Traditional mindfulness and self-compassion programs are 8-week programs that include group sessions of approximately 2-3 hours each week, and participants are required to practice daily at home [8,21]. However, many employees have difficulty participating in formal programs due to strict work hours and the need to balance work and family life [22]. Web-based interventions can be a solution to the problem of supporting workers with time constraints. A growing body of research indicates that the use of digital technologies, such as smartphone apps and web-based platforms, may help overcome these barriers. For example, digitally assisted mindfulness interventions have been shown to effectively help participants develop a wide range of cognitive, emotional, and behavioral self-regulation skills, which has led to satisfying psychological needs and consequently enhancing mental wellness [23]. Mindfulness interventions that use state-of-the-art digital technology, such as virtual reality, an artificially created virtual space, are highly effective in overcoming barriers for people who have traditionally faced difficulties participating in mindfulness training [24]. According to Li et al [22], compared to traditional forms of intervention, web-based interventions are particularly suitable for employees. It has been shown that

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the essential skills of acceptance, mindfulness, and self-compassion can be acquired through low-intensity interventions delivered via smartphone apps [25]. Moreover, these app-based interventions have been found to reduce distress and job strain and improve workers' well-being [5,26]. Although assistance with mobile health apps has been regarded as an effective tool for mental health support, little evidence of the effectiveness of smartphone app interventions in RCT designs exists, thus necessitating further research in rigorous designs [27]. Indeed, evidence is accumulating that self-care interventions using apps aimed at learning mindfulness and self-compassion principles reduce stress and improve attention and self-compassion [5]. When providing support to workers who are healthy enough to work, it is important to consider the effects on work-related outcomes and mental health. However, few studies have examined the impact of such app-based interventions on diverse work-related (eg, work performance) and mental health outcomes among workers.

The American Psychological Association has stated that the COVID-19 pandemic and the widespread adoption of remote work have affected the provision of psychological support for workers, and easy-to-access web-based psychological support is urgently required [28]. Thus, the need for remote web-based support, especially via highly convenient smartphone apps, has been recognized. Among other things, there is a need to develop a self-care app for workers to learn mindfulness and self-compassion meditation (SCM) methods and to evaluate the effectiveness of such an app using various indicators.

Virgili [29] has stated that a comprehensive understanding of the effectiveness of mindfulness-based interventions (MBIs) requires complementing self-reported psychological measures with objective physiological measures (eg, heart rate [HR] and HR variability [HRV]). HR and HRV are biomarkers indicating mental health status [30]. The normal regulation of HRV is dominated by parasympathetic activation; however, during stressful situations, sympathetic activation increases the HR. Low HRV can reflect autonomic nervous system inflexibility and has been considered a marker for unfavorable health outcomes [30]. It has been suggested that work stress might be associated with not only mental health deterioration but also increased HR and decreased HRV [31]. Although several studies have a high risk of bias, some reviews have shown that MBIs could reduce HR and increase HRV [32,33]. Furthermore, there is a need to examine the effects of MBI using objective and subjective indicators. Subjective indicators that request individuals to provide accounts of their experience depend on the individuals' practice and experience in interrogating their minds, which is a skill that varies according to MBI [34]. However, most of the previous studies have focused on acute changes in HR and HRV effects during 1-session MBI or chronic changes measured before and after multiple-session MBI. Few studies have distinguished acute and chronic changes in multiple sessions [35]. This study uses a daily assessment approach. Daily intervention studies can be easily combined with a daily assessment approach to analyze within-person processes and individual differences in these processes [36]. Daily assessments have the following advantages: first, data are collected in real-world environments, as participants go about their lives [37]. HR and HRV may be particularly sensitive to circumstances. Second, the mechanism of intervention effects can be examined from daily fluctuations in physiological indicators [36]. Therefore, this study will examine the effects of the intervention from a physiological perspective by measuring HR and HRV, which can be measured non–face-to-face daily.

Objectives

This study aims to develop a self-care app for mindfulness and SCM and examine its efficacy using mental health and work-related indicators. This study will use a 3-arm RCT design that divides the app-based intervention group into 2—the SCM group and the mindfulness meditation (MM) group—and includes a waitlist group. This study will adopt low-intensity intervention content to target busy workers who have had difficulty participating in traditional intervention forms. In addition, the intervention effects will be evaluated from a broad perspective by measuring mental health conditions and work-related outcomes such as work performance and physiological indicators. Thus, to gain insight into the mechanism of the effects, this study will examine effectiveness by not only collecting data on subjective measures but also measuring HR and HRV as objective physiological measures.

Methods

Participants

Recruitment began in December 2022 and ended in October 2023. Japanese-speaking participants were recruited from a broad Japanese worker community through an open call on Japanese websites, including a recruitment website for psychological experiments and our laboratory website in Japan. Contact information was provided in the recruitment guide, and participants could contact the research team directly.

The participants comprise young to middle-aged workers in Japan, working either full- or part-time. The inclusion criteria are employees who are (1) working more than 20 hours per week, (2) between the ages of 18 and 54 years, (3) not on a leave of absence, (4) not business owners or students, and (5) not currently diagnosed with a mental disorder and have a Kessler Psychological Distress Scale-6 (K6) score below 13 points. All these criteria will be assessed after informed consent is obtained, and participants who do not provide informed consent will be excluded. The smartphone app used in this study can only be used with an Apple iPhone (iOS); therefore, the participants are limited to iPhone users. The participants will not be informed that our study focuses on work performance or on the cutoff values for inclusion (ie, K6 score<13). Participants who meet the exclusion criteria according to their K6 cutoff scores will be informed by email that they are not eligible to participate. However, we will not provide specific reasons but only notify participants that they are not eligible to participate due to research reasons. In addition, participants who meet the exclusion criteria according to their K6 cutoff scores will receive an email with information about public psychological support services and health centers.

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Interested candidates can read the experiment description posted on the website. Workers who are willing to participate can provide informed consent via the website. They will then be asked to confirm their consent to participate in this study and complete a screening questionnaire via a web form. The screening questionnaire consists of the K6 (screening for depression) and items regarding the inclusion criteria (participant attributes).

Trial Design

This study will comprise an open-label randomized trial comparing an SCM course (n=67), an MM course (n=67), and a waitlist group (n=66). Based on the power analysis (see the *Sample Size* section), 37 participants are required in each active group (SCM and MM).

The included participants will not be informed which arm they are allocated to but would be part of one of the intervention groups when the interventions commence. The waitlist group will be randomly assigned to either the SCM or MM group after a 1-month waiting period. Figure 1 presents the intervention flowchart.

Figure 1. Intervention flowchart. MM: mindfulness meditation; SCM: self-compassion meditation.

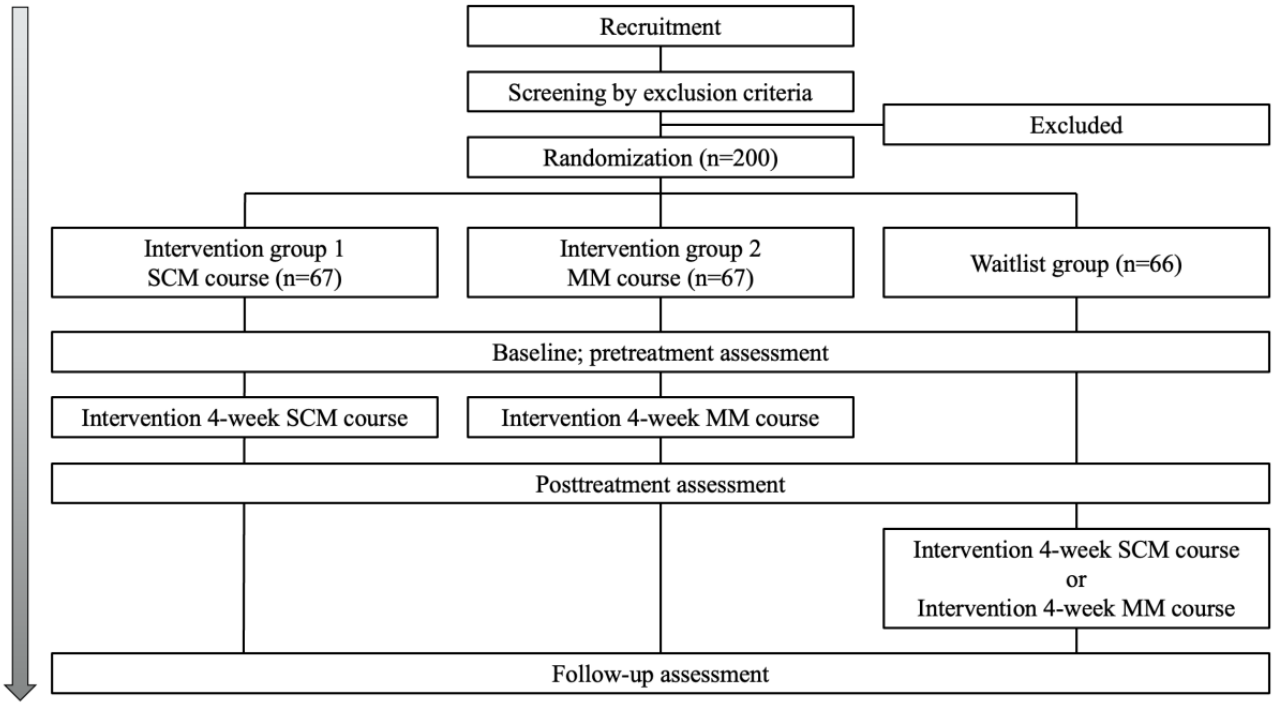

Interventions

SCM and MM were set as the intervention conditions and waitlist as the control condition, and the 3 groups were compared. Participants assigned to the SCM and MM groups will use a smartphone app to engage in guided meditation on their own once a day (Multimedia Appendix 1). The duration of all intervention conditions is 4 weeks. Both SCM and MM interventions contain elements of mindfulness. The difference between SCM and MM is the content of meditation in weeks 3 and 4: in SCM, participants will engage in loving-kindness meditation in weeks 3 and 4, whereas in MM, they will participate in a breath, sound, and body meditation. The duration of guided meditation is the same in both groups. Participants assigned to the waitlist group will receive no intervention during the 4-week waiting period; after the waiting period, they will be randomly assigned to either the SCM course or MM course to engage in 4 weeks of guided meditation.

The SCM and MM courses will be delivered via a smartphone app developed by the authors' research team. Each course will offer 3 modules of guided self-help meditations. The modules in the SCM and MM courses will be structured as psychoeducation and guided meditation. The audio script for guided meditation is a Japanese version available from the University of California, Los Angeles Mindful Awareness Research Center [38], and audio instructions will be given before and after the meditation. The contents of psychoeducation include stress and stress responses and the theory of mindfulness and self-compassion. Both courses will involve the same guided meditations in weeks 1 and 2. The guided meditations contained in each week's module are as follows (Table 1): week 1 (SCM and MM courses): a breathing meditation (7 minutes); week 2 (SCM and MM courses): a short body scan (6 minutes); and weeks 3-4: (SCM course): a loving-kindness meditation (12 minutes), including the contents of self-kindness and common humanity, and (MM course): a breath, sound, body meditation (12 minutes). Participants will receive weekly reminders via email to encourage involvement; however, there will be no minimum time commitment to participate.

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Table 1. Schedule of procedures.

Process or assessment	Screening period	Pretreatment assessment (baseline)	Intervention period				Posttreatment assessment	Waitlist intervention period				Follow-up assessment
			Wk 1	Wk 2	Wk 3	Wk 4		Wk 1	Wk 2	Wk 3	Wk 4	
Enrollment												
Eligibility screen	✓											
Informed consent	✓											
Allocation	✓											
Assessment												
Demographic information		✓					✓					✓
K6[a]		✓					✓					✓
WHO-HPQ[b]		✓					✓					✓
SPS[c]		✓					✓					✓
SSS-8[d]		✓					✓					✓
CFS[e]		✓					✓					✓
RSES[f]		✓					✓					✓
SCS[g]		✓					✓					✓
PSS-14[h]		✓					✓					✓
SWLS[i]		✓					✓					✓
CERQ[j]		✓					✓					✓
UWES-9[k]		✓					✓					✓
STAXI-2[l]		✓					✓					✓
PSS[m]		✓					✓					✓
Creativity scale		✓					✓					✓
Weekly assessment												
Affect Grid			✓[n]	✓[n]	✓[n]	✓[n]		✓[o]	✓[o]	✓[o]	✓[o]	
PANAS[p]			✓[n]	✓[n]	✓[n]	✓[n]		✓[o]	✓[o]	✓[o]	✓[o]	
Daily assessment												
HR[q] or HRV[r]			✓[n]	✓[n]	✓[n]	✓[n]		✓[o]	✓[o]	✓[o]	✓[o]	
Relaxation scale			✓[n]	✓[n]	✓[n]	✓[n]		✓[o]	✓[o]	✓[o]	✓[o]	
Interventions												
Breathing meditation			✓[n]					✓[o]				
Short body scan				✓[n]					✓[o]			
Loving-kindness meditation					✓[s]	✓[s]				✓[t]	✓[t]	
Breath, sound, body meditation					✓[u]	✓[u]				✓[v]	✓[v]	

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[a]K6: Kessler Psychological Distress Scale-6.
[b]WHO-HPQ: World Health Organization Health and Work Performance Questionnaire.
[c]SPS: Stanford Presenteeism Scale.
[d]SSS-8: Somatic Symptom Scale-8.
[e]CFS: Cognitive Flexibility Scale.
[f]RSES: Rosenberg Self-Esteem Scale.
[g]SCS: Self-Compassion Scale.
[h]PSS-14: Perceived Stress Scale-14.
[i]SWLS: Satisfaction With Life Scale.
[j]CERQ: Cognitive Emotion Regulation Questionnaire.
[k]UWES-9: Utrecht Work Engagement Scale-9.
[l]STAXI-2: State-Trait Anger Expression Inventory.
[m]PSS: Psychological Safety Scale.
[n]Self-compassion meditation and mindfulness meditation.
[o]Waitlist.
[p]PANAS: Positive and Negative Affect Schedule.
[q]HR: heart rate.
[r]HRV: heart rate variability.
[s]Self-compassion meditation.
[t]Waitlist self-compassion meditation.
[u]Mindfulness meditation.
[v]Waitlist mindfulness meditation.

Criteria for Discontinuing or Modifying Allocated Interventions

In this study, only participants with psychological distress below a certain level will be included; thus, the risks associated with the intervention are likely to be minimal. However, we will provide information on support groups or mental health services that participants can contact in case they experience any distress. Participants can discontinue the trial at any time without providing further explanation.

Strategies to Improve Adherence to Interventions

The smartphone app includes a reminder. Participants will receive a reminder once a day at a time of their own choice. Reminder notifications are not mandatory. Prior research has shown that reminders are a promising engagement strategy for encouraging adherence to web-based mindfulness programs [39].

Provisions for Posttrial Care

All participants, including those assigned to the waitlist group, will attend a 4-week course in SCM or MM. Information on the mental health services operated by public institutions will be posted on a questionnaire. Participants will have access to mental health services as needed. If a participant makes an inquiry, we will introduce a similar application**.**

Outcomes: Primary Outcome Measures

Psychological Distress

Psychological distress will be assessed using the Japanese version of K6 [40,41]. All items are rated on a scale ranging from 0=never to 4=always over the past 30 days. It has been designed to assess nonspecific psychological distress (depressive mood and anxiety) using 6 items. The reliability and validity of the Japanese version have been reported to be equal to those of the original English version [41]. A previous study suggested a cutoff point of 12 or 13 for K6 scores to screen for severe depressive symptoms [42]. Considering the possibility of a high psychological burden for participants with severe depressive symptoms, we set an exclusion criterion of a K6 cutoff value of 13 or higher, from an ethical point of view.

Work Performance

Presenteeism will be measured using the World Health Organization Health and Work Performance Questionnaire (WHO-HPQ) [43]. The Harvard Medical School stated that presenteeism is conceptualized as a measure of actual performance in relation to possible performance [44]. However, some studies have defined presenteeism as attending work while ill and have confirmed that it is associated with poor job performance [45]. This study follows the definition of Harvard Medical School, which developed the WHO-HPQ [44]. The WHO-HPQ provides 2 scores: the absolute presenteeism score, obtained by multiplying the self-reported single question to rate respondents' overall work performance over the past 28 days by 10, and the relative presenteeism score, obtained by dividing the evaluation of others' work by the self-reported single question score described earlier. In this study, absolute presenteeism scores will be used as an indicator of presenteeism. Absolute presenteeism scores range from 0=worst to 100=best. Additionally, regarding presenteeism scoring, the Harvard Medical School states that, unlike absenteeism, a higher score indicates a lower amount of lost performance [44]. Therefore, higher absolute presenteeism scores indicate higher work performance. Previous studies have confirmed the reliability and validity of the Japanese version of the scale [46,47]. Kessler et al [43] reported a close relationship between self-reported scores on the WHO-HPQ and the performance ratings by supervisors and peers.

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Additionally, the work impairment score included in the Stanford Presenteeism Scale [48,49] will be used to assess work inefficiency. Work inefficiency is the state of one's cognition, emotions, and behaviors that affect their ability to complete work and avoid distraction [50]. The subsequent studies follow this definition of work inefficiency by Turpin et al [50]. The work impairment score is measured using the responses given to the 10 Stanford Presenteeism Scale items on a 5-point scale where 1=always and 5=never. The validity and reliability of the Japanese version have been reported in a study on Japanese female workers [51].

Outcomes: Secondary Outcome Measures

Somatic Symptom

The Somatic Symptom Scale-8 [52] can assess the somatic symptom burden during the previous 7 days. This scale includes 8 items rated on a 5-point Likert scale (0=not at all to 4=very much) with no reverse-coded items. The total score, ranging from 0 to 32, is the sum of all item scores, with a higher score indicating more severe somatic symptoms. The Japanese version of the Somatic Symptom Scale-8 has demonstrated acceptable reliability in a sample of Japanese individuals aged 20-64 years [53].

Cognitive Flexibility

The Cognitive Flexibility Scale (CFS) [54] is used to measure cognitive flexibility and considers an individual's ability to produce diverse ideas, conceive response alternatives, and modify behaviors to adapt to changes in circumstances [55]. The CFS is a 12-item self-report questionnaire using a Likert-type scale ranging from 1=strongly disagree to 6=strongly agree. Each item in this questionnaire contains a sentence regarding beliefs and feelings about the respondent's behavior. Total scores range from 12 to 72, with higher scores indicating greater cognitive flexibility. A previous study has confirmed the reliability and validity of the Japanese version of CFS among a sample of Japanese individuals [56].

Self-Esteem

Self-esteem will be measured using the Rosenberg Self-Esteem Scale [57], which consists of 10 items, such as "On the whole, I am satisfied with myself." and "At times, I think I am not good at all." Responses to these items are rated on a 4-point Likert scale (1=strongly disagree to 4=strongly agree). Mimura and Griffiths [58] have confirmed the reliability of the Japanese version.

Self-Compassion

The Self-Compassion Scale [16] is a 26-item assessment of the levels of self-compassion across 6 subscales (self-kindness, self-judgment, common humanity, isolation, mindfulness, and overidentification). Participants will be asked to rate the frequency of certain behaviors corresponding to each subscale. Responses range from 1=almost never to 5=almost always. The Self-Compassion Scale has good internal consistency, and its total score exhibits high convergent and discriminant validity [16]. The Japanese version of this inventory has high reliability and validity [59].

Perceived Stress

The Perceived Stress Scale-14 (PSS-14) is a self-report questionnaire intended to measure the degree of stress perceived by an individual in their life within the past month [60,61]. The PSS-14 consists of 14 items measuring how unpredictable, uncontrollable, and overloaded individuals feel about their circumstances. Participants rate each item on a 5-point Likert-type scale ranging from 0=never to 4=very often. Scores are obtained by reverse scoring the positively stated items and then summing the scores across all 14 items. The scores range from 0 to 56, with higher scores representing more significant perceived stress. Sumi [62] translated the Japanese version of the PSS-14 and confirmed its reliability and validity.

Well-Being

Life satisfaction will be assessed using the 5-item Satisfaction With Life Scale (SWLS) [63]. The SWLS items are rated on a 7-point Likert scale from 1=strongly disagree to 7=strongly agree, with higher scores indicating greater satisfaction with regard to one's well-being. Its reliability and validity were substantiated by Pavot et al [64]. The Japanese version of the SWLS has been used in cross-cultural studies [65].

Emotion Regulation

The Cognitive Emotion Regulation Questionnaire is a 36-item scale measuring cognitive emotion regulation strategies to cope with the experience of threatening or stressful events or situations [66]. It evaluates 9 facets of cognitive handling strategies: positive reappraisal, putting into perspective, rumination or focus on thoughts, acceptance, self-blame, positive refocusing, other blame, catastrophizing, and refocus on planning. A 5-point Likert scale ranging from 1=almost never to 5=almost always is used to evaluate cognitive emotion regulation strategies. A validated Japanese version of the questionnaire will be used in this study [67].

Work Engagement

The Japanese version of the 9-item Utrecht Work Engagement Scale-9 can assess work engagement, which is defined as "a positive, fulfilling, work-related state of mind that is characterized by vigor, dedication, and absorption" [68-70]. Work engagement is assumed to be negatively correlated with burnout, and the 2 can be considered "opposites," in that they represent a positive and a negative aspect of work-related well-being [70]. This scale includes measures of vigor, dedication, and absorption on a 7-point Likert scale from 0=never to 6=all the time. Each subscale comprises 3 items, and the scores of all are summed to determine the work engagement scores. The Utrecht Work Engagement Scale-9 has been translated into Japanese with adequate internal consistency and factorial validity [70].

Trait Anger

The State-Trait Anger Expression Inventory-2 is a 57-item questionnaire developed to measure the characteristic styles of coping with anger arousal using 5 components [71]. The 5 subscales include state anger, trait anger, anger-in, anger-out, and anger control. In this study, the participants will rate 10 items of the trait anger domain on a 4-point Likert scale ranging

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from 1=I strongly disagree to 4=I strongly agree to assess their degree of anger.

Psychological Safety

Psychological safety will be measured using the 7-item Psychological Safety Scale [72,73]. Psychological safety is defined as "being able to show and employ one's self without fear of negative consequences to the self-image, status or career" [74]. Participants rate the items on a 7-point Likert-type scale ranging from 1=not at all to 7=strongly agree.

Creativity (Self-Perceived Creativity Scale)

The idea generation aspect of creativity in the workplace is assessed using 3 items from George and Zhou's [75] scale modified for a self-report instrument by Dul et al [76]. This scale has been translated into Japanese and is used with the original authors' permission. It includes the following 3 items for measuring employee creativity, which are scored on a 7-point Likert scale ranging from 1=do not agree to 7=agree: "In my work, I often have new and innovative ideas," "In my work, I often come up with creative solutions to problems," and "In my work, I often suggest new ways of performing work tasks."

Outcomes: Weekly Measures

Affect

The Affect Grid [77], which is used to assess emotional aspects, is a single-item scale designed as a quick means of assessing respondents' affect along the dimensions of pleasure-displeasure and arousal-sleepiness. This scale evaluates the affect in a 2D structure consisting of 9×9 squares, with pleasure-displeasure on the horizontal axis and arousal-sleepiness on the vertical axis. The pleasure scores range from 1=unpleasurable to 9=highly pleasurable, and the arousal scores also range from 1=sleepy to 9=highly aroused.

Positive and Negative Emotions

The Positive and Negative Affect Schedule (PANAS) is used to measure the degree to which participants experienced positive and negative emotions within the past week [78]. The PANAS includes 20 items (10 positive and 10 negative emotions) that are rated on a 5-point Likert scale ranging from 1=not at all to 5=extremely. The Japanese version of this scale has demonstrated high reliability and validity [79].

Outcomes: Daily Measures

Subjective psychological indices (relaxation) and physiological indices (HR and HRV) will be measured before and after daily meditation. The rating scale of relaxation will be used to assess the degree of participants' relaxation [80]. This scale comprises 4 items, each of which is rated on a 10-point scale. Participants are required to "[select] the number from 1 to 10 that best describes [their] current state." The 4 items are as follows: 1=feeling high to 10=stable, 1=tense to 10=relaxing, 1=anxiety to 10=relief, and 1=restrictive to 10=free. Nedate and Agari [80] used the average of the 4 scores as the relaxation score, which will be calculated similarly in this study as well (for more information on HR and HRV measurements, see the *Data Collection and Management* section).

Participant Timeline

Participants who agree to participate in the study with informed consent and meet the inclusion criteria are assigned to the SCM, MM, or waitlist group. Participants are not notified as to which group they are assigned. All participants will then receive a web-based pretreatment assessment questionnaire at baseline via email and will be asked to complete it. Simultaneously, the participants assigned to the active arm (SCN and MM) will be asked via email to download and start using the smartphone app used for the intervention. Four weeks after the start of app use, participants will be sent a web-based posttreatment questionnaire by email and asked to complete it. Participants in the waitlist group will receive a web-based posttreatment questionnaire 4 weeks after they respond to the initial baseline questionnaire. Participants in the waitlist group will be asked to download and start using the smartphone app via email, distributed with the posttreatment questionnaire. All the participants in the waitlist group will be randomly assigned to the SCM and MM groups. During the 4-week intervention, all participants will be asked to respond to daily and weekly assessments of the smartphone app. Table 1 presents the schedule of procedures.

Sample Size

The sample size is determined based on an a priori analysis of group-specific intervention effects. This analysis is modeled as the interaction of the within-subject factor of time (preintervention vs postintervention assessment) and the between-subject factor of the group (SCM vs MM vs control). Power analysis is conducted using the G*Power software app developed by Heinrich-Heine-Universität Düsseldorf Institut für Experimentelle Psychologie to estimate how much power would be required to find small interaction effects. In this study, the intervention effect size is assumed to have weak interaction effects (Cohen F=0.15) based on previous research [81]. Repeated measures scores are also expected to have a moderate to strong correlation of 0.5. To achieve 80% power, 37 participants are required in each arm (SCM, MM, and control). Expecting approximately 40% attrition based on similar previous studies [82,83], we will include 200 participants and assign 67 participants to each of the 3 arms.

Recruitment

Recruitment will be conducted via a recruitment website for psychology experiments and through the website of our laboratory. Information about the study is available via posters on those websites. The posters also contain contact information for the research team, who can be contacted directly.

Assignment of Interventions: Allocation

Randomization will be performed after obtaining informed consent and screening the participants. It will be computerized and independently carried out by research staff using a blocked randomization scheme (block size 15) to ensure the seamless participation of those who apply to participate in the study. Eligible participants will be randomized into the SCM, MM, or waitlist group in a ratio of 1:1:1.

Participants are assigned to either the intervention (SCM or MM) or control (waitlist) condition immediately after randomization. The intervention will begin approximately 1

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week after allocation. No specific instructions are given to the waitlist group, and they will be asked to wait for 4 weeks.

Interested candidates will be asked to confirm their consent to participate in this study and complete a screening questionnaire via web forms. The screening questionnaire consists of the K6 and items based on the inclusion criteria. Participants who meet the inclusion criteria are immediately included in the blocked randomization scheme and assigned by the research staff. After the participants have been assigned, they will receive an email with instructions to participate or wait.

Assignment of Interventions: Blinding

It is practically impossible to blind the allocation in this study because the participants engage in the meditation independently, following a guide. Therefore, this study will be an open-label RCT. Once a participant is assigned to a condition, there will be no further interaction with the research staff, except when the participant contacts the research staff. To minimize interaction between the participants and research staff, notifications and instructions will be sent to the participants via automated emails. Participants can infer which group they have been allocated to, based on the instructions, but they are not explicitly informed about the groups to which they are assigned.

Data Collection and Management

The participants will be assessed for outcome measures via web forms at baseline (pretreatment assessment) and 1 month and 2 months after the course starts (posttreatment assessment and follow-up assessment, respectively). Additionally, the participants will complete weekly and daily assessments during their courses. As mentioned earlier, the weekly measures consist of 1 question from the Affect Grid [77] and 20 questions from the PANAS [78,79]. The daily assessment involves the degree of participants' relaxation [80] and objective physiological measures (HR and HRV) on the smartphone app. Participants will be asked to perform daily assessments using the smartphone app before and after daily meditation. The weekly assessment will be measured via web-based forms once a week immediately after the 7-day meditations, and participants will receive an email requesting them to respond to the questionnaire and a reminder to use the self-care app. The web-based survey to be conducted in this study is designed with reference to the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist to ensure a complete description of web-based surveys (Multimedia Appendix 2) [84]. When reporting the results, we will provide a detailed report of what is described in CHERRIES.

HR and HRV measurements will be taken on the smartphone app used for the intervention. Participants will be provided a sample and instructed to gently press their index finger against their smartphone's camera for 30 seconds. At this time, the smartphone's flash will turn on. By capturing the finger illuminated by the flash with the smartphone camera, HR and HRV will be measured. The procedure was set up based on a study that used HR and HRV measurements to evaluate the effectiveness of psychological interventions similar to this study [81]. HR and HRV will be measured using contact photoplethysmography, which is a noninvasive and convenient optical biomonitoring technique used to detect pulsatile changes in blood volume that appear in the microvascular bed of tissues [85]. The contact photoplethysmography method uses a white LED flashlight built into a smartphone and a rear camera to illuminate the skin for 30 seconds and detect light absorption due to arterial pulsation in the finger pad (Multimedia Appendix 3). For measuring HRV, the root mean square of successive differences—a measure of the square root of the mean squared difference between consecutive normal heartbeats—is used. The average HR measured in beats per minute is analyzed for HR.

When participants do not answer a questionnaire (baseline, preintervention assessment, and postintervention assessment), they will receive automatic reminders via email 6 days later. Participants who do not respond at baseline and preintervention assessment will receive further reminders after 13 days. If the participants are found not to respond to the questionnaire, they will be considered dropped by 14 days at baseline and preintervention assessment and by 7 days at postintervention assessment.

The data collected through the web-based forms are stored on a secure server with restricted access at the University of Tokyo. After data collection, this study will use a study-generated identification for data management, analysis, and publication. The list linking identifications to the participants' personal information is stored on a hard disk disconnected from the internet, and the hard disk is kept in a locked cabinet.

This study will be conducted according to the protocol approved by the ethics committee of the institution to which the research team belongs. Identifications are used only for data management, and collected data and personal information are stored separately. Participants are informed that their personal information will remain confidential if they provide informed consent.

Statistical Methods

Primary Outcome

The intention-to-treat approach involving participants who have completed pretreatment and posttreatment assessments will be used to test the effectiveness of the active arms compared to the waitlist group. To examine preintervention and postintervention changes and pre-post differences between the groups, the results of the assessment questionnaires will be analyzed using repeated measures ANOVA. The statistical significance level is set at $P<.05$ for all statistics. Analyses will be performed using SPSS (IBM Corp) and R (R Foundation for Statistical Computing).

Secondary Outcomes

Descriptive statistics of the study participant characteristics at baseline and questionnaire responses will include means, SDs, frequencies, and percentages according to the type of variable (continuous or categorical). The fit of quantitative variables to the normal distribution will be confirmed by the Shapiro-Wilk test. Differences in demographic information at baseline between groups will be analyzed using the chi-square test for categorical variables and ANOVA or the 2-tailed *t* test for continuous variables (ie, age, sex, employment status, educational

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attainment, previous meditation experience, and psychological distress at baseline).

Other Analyses

An interim analysis will be conducted once half of the planned number of participants have completed the intervention period. The interim analysis will primarily examine the feasibility, including dropout rates, and the trial may be discontinued if the dropout rate is higher than expected. Multivariate analysis will be conducted to test the effects of the interventions, adjusting for estimated predictors or confounding variables, and multilevel linear regression will be performed.

Following the intention-to-treat principle, the analyses will include data from all participants. Web-based self-care interventions are often associated with higher dropout rates and lower rates of continued implementation [86]. In their study, Farvolden et al [87] reported that only 12 of 1161 participants (approximately 1%) completed a 12-week web-based panic disorder self-help program in its entirety. Similarly, Hasselberg and Rönnlund [83] conducted a 2-week web-based program targeting mindfulness and self-compassion and reported that 33% of the participants stayed in the program until the end. Therefore, even if self-care app activities are minimal, participants will be considered to have completed the course and will be included in the analysis if each questionnaire is answered. The patterns of missing values will be examined and, when applicable, replaced with suitable statistical methods.

Adverse Event Reporting and Harms

The participants in this study comprise a nonclinical population with lower than a certain level of psychological distress and no diagnosed mental disorders. Therefore, the risk associated with psychological interventions is assumed to be low. Participants may interrupt a trial without disclosing the reason and will be able to contact the research staff via email or web-based forms, if necessary. Participants can also obtain information on mental health services operated by public institutions on web-based forms and receive mental health care as needed.

Dissemination Plans

The findings of this study will be disseminated through presentations at national and international conferences and publications in international journals. The results of this research will adhere to the CONSORT (Consolidated Standards of Reporting Trials) statement [88].

Ethical Considerations

The study protocol used in this study and all procedures were approved by the Life Science Research Ethics and Safety Committee of the University of Tokyo (22-326). Data collected in this study will be anonymized and managed. Written informed consent to participate will be obtained from all participants via a web form. Participants are given the option to opt out at any time. Participants will also be rewarded with a gift card worth up to JP ¥10,000 (JP ¥137.09=US $1 as of December 1, 2022), depending on their level of participation.

Results

Recruitment of participants began in December 2022, and the intervention began in January 2023. A total of 375 participants have been enrolled as of September 2023. The intervention and data collection will be completed by late October 2023.

Discussion

Principal Findings

The purpose of this study is to develop a self-care app for MM and SCM and examine its effectiveness using various indicators such as work performance. The study will adopt an RCT design comparing the SCM and MM intervention groups and a waitlist group. This study will focus on accessibility and availability and will use a low-intensity self-care program delivered via a smartphone app. This will allow us to examine the possibility of supporting busy workers who have had difficulty participating in traditional intervention formats. It is expected that by developing accessible self-care smartphone apps and examining the effectiveness of the intervention, it will be possible to propose efficient and feasible solutions for improving workers' mental health and work performance. In the field of worker assistance, where methodologically robust evidence is scarce [18], this study can contribute to the body of findings by examining the effectiveness of assistance through an RCT design.

In recent years, health support technologies using mobile digital devices, such as smartphones, have been developed, and their effectiveness has been examined; however, comparability between studies has been considered difficult [5]. Using consistent guidelines—such as the mobile health evidence reporting and assessment checklist [89]—when reporting the results of this study ensure that the findings from this study provide synthesizable evidence and promote comparability between studies.

Strengths and Limitations

The study has several notable strengths. First, this study will adopt brief self-care interventions for preventive health care in healthy workers. Traditional self-compassion and mindfulness interventions are long-term face-to-face programs [8,21], thus presenting difficulties related to worker participation and dissemination [22]. For interventions aimed at treatment, evidence-based, structured programs for well-experienced instructors are essential. However, even a brief intervention with an app may be sufficient to facilitate preventive health care for healthy workers.

Second, this study will examine the intervention effects not only on mental health conditions but also on work-related outcomes and objective physiological measures, such as HR and HRV. Examining work-related outcomes can provide a broad perspective of the effects of interventions. Measuring objective physiological outcomes may provide insights into the mechanisms underlying these effects.

Third, this RCT design compares 2 types of interventions in the intervention group: SCM and MM. They are similar but have

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different background theories. This study on preventive health care for healthy workers has the potential to provide suggestive findings for the development of accessible, available, and more effective intervention content that can improve mental health and work-related outcomes.

This study has several limitations. First, the duration of the intervention is shorter, and the intensity is lower than that of traditional self-compassion and mindfulness interventions. Second, the intervention is conducted in a self-care format, which may result in a lack of sufficient skill acquisition and limited intervention effectiveness. Third, because the target population is limited to healthy workers, the intervention effect may be too small and not be fully confirmed. Furthermore, a trait mindfulness scale is not included in this study's secondary outcomes. Measuring both, a self-compassion measure and a trait mindfulness scale would have provided a better understanding of each intervention's effects and allowed us to determine any differences in the constructs being targeted. However, this is not possible in this study. Therefore, future research should use both a self-compassion measure and a trait mindfulness scale to better understand the intervention effects.

Conclusions

The intervention protocol in this study has described an RCT to examine whether brief guided MM or SCM interventions provided by a smartphone app are effective for mental health and work-related outcomes among workers. The authors' research team at the University of Tokyo, Japan, planned to begin the RCT in December 2022. There is a great need for preventive interventions for mental health and work-related problems such as presenteeism in the working population because of inadequate support. We expect that this study will contribute to the evaluation of effective self-care intervention content that will improve mental health, work performance, and related outcomes and promote mindful and self-compassionate attitudes when faced with distress.

Acknowledgments

The authors would like to thank all the participants of this study. The authors also thank Mr Kei Minoura for technical assistance with data collection through smartphone apps. RT is supported in part by JSPS Grants-in-Aid for Scientific Research (16H05653, 19K03278, 22H01091, and 22K18582), and The Royal Society and The British Academy (Newton International Fellowship Alumni follow-on funding; AL150003), and The University of Tokyo Social Cooperation Program "Fulfillment through Work". The sponsors played no part in the design or execution of the study, the analysis or interpretation of data, or the writing of the paper and the decision to submit it for publication.

Data Availability

The data sets generated and analyzed during this study are not publicly available because data sharing in publicly available repositories was not included in the informed consent. However, the data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

TK, KA, and RT (principal investigator) developed the study design and designed the trial protocol, and TK and RT wrote the first draft of the manuscript. All authors revised and commented on the manuscript and read and approved the final manuscript. TK (kurosawa@p.u-tokyo.ac.jp) and RT (takizawar-tky@umin.ac.jp) are cocorresponding authors of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
App screenshot 1.
[PNG File , 78 KB - resprot_v13i1e53541_app1.png]

Multimedia Appendix 2
The CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist.
[DOCX File , 24 KB - resprot_v13i1e53541_app2.docx]

Multimedia Appendix 3
App screenshot 2.
[PNG File , 337 KB - resprot_v13i1e53541_app3.png]

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Abbreviations

CFS: Cognitive Flexibility Scale
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT: Consolidated Standards of Reporting Trials
HR: heart rate
HRV: heart rate variability
K6: Kessler Psychological Distress Scale-6
MBI: mindfulness-based intervention
MM: mindfulness meditation
PANAS: Positive and Negative Affect Schedule
PSS-14: Perceived Stress Scale-14
RCT: randomized controlled trial
SCM: self-compassion meditation
SWLS: Satisfaction With Life Scale
WHO-HPQ: World Health Organization Health and Work Performance Questionnaire

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Protocol

Piloting a Clinical Decision Support Tool to Identify Patients With Social Needs and Provide Navigation Services and Referral to Community-Based Organizations: Protocol for a Randomized Controlled Trial

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Abstract

Background: Social needs and social determinants of health (SDOH) significantly outrank medical care when considering the impact on a person's length and quality of life, resulting in poor health outcomes and worsening life expectancy. Integrating social needs and SDOH data along with clinical risk information within operational clinical decision support (CDS) systems built into electronic health records (EHRs) is an effective approach to addressing health-related social needs. To achieve this goal, applied research is needed to develop EHR-integrated CDS tools and closed-loop referral systems and implement and test them in the digital and clinical workflows at health care systems and collaborating community-based organizations (CBOs).

Objective: This study aims to describe the protocol for a mixed methods study including a randomized controlled trial and a qualitative phase assessing the feasibility, acceptability, and effectiveness of an EHR-integrated digital platform to identify patients with social needs and provide navigation services and closed-loop referrals to CBOs to address their social needs.

Methods: The randomized controlled trial will enroll and randomize adult patients living in socioeconomically challenged neighborhoods in Baltimore City receiving care at a single academic health care institution in the 3-month intervention (using the digital platform) or the 3-month control (standard-of-care assessment and addressing of social needs) arms (n=295 per arm). To evaluate the feasibility and acceptability of the digital platform and its impact on the clinical and digital workflow and patient care, we will conduct focus groups with the care teams in the health care system (eg, clinical providers, social workers, and care managers) and collaborating CBOs. The outcomes will be the acceptability, feasibility, and effectiveness of the CDS tool and closed-loop referral system.

Results: This clinical trial opened to enrollment in June 2023 and will be completed in March 2025. Initial results are expected to be published in spring 2025. We will report feasibility outcome measures as weekly use rates of the digital platform. The acceptability outcome measure will be the provider's and patient's responses to the truthfulness of a statement indicating a willingness to use the platform in the future. Effectiveness will be measured by tracking a 3-month change in identified social needs and provided navigation services as well as clinical outcomes such as hospitalization and emergency department visits.

Conclusions: The results of this investigation are expected to contribute to our understanding of the use of digital interventions and the implementation of such interventions in digital and clinical workflows to enhance the health care system and CBO ability

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related to social needs assessment and intervention. These results may inform the construction of a future multi-institutional trial designed to test the effectiveness of this intervention across different health care systems and care settings.

Trial Registration: ClinicalTrials.gov NCT05574699; https://clinicaltrials.gov/study/NCT05574699

International Registered Report Identifier (IRRID): DERR1-10.2196/57316

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KEYWORDS

social needs; social determinants of health; clinical decision support tool; electronic health records; randomized controlled trial

Introduction

Background

Social needs and social determinants of health (SDOH) significantly outrank medical care when considering the impact on a person's length and quality of life [1]. Rising health care costs and worsening life expectancy in the United States are, in large part, the direct result of these unmet social needs and SDOH challenges [2-6]. Challenges related to social needs and SDOH disproportionately impact racial and ethnic minority populations and those with low income and are critical factors in explaining many health-related disparities, ultimately leading to higher mortality rates in these populations [7].

Currently, many sources of data on social needs and SDOH challenges can be found within a typical electronic health record (EHR) and some vendors have started adding specific data fields for collecting information on social needs and SDOH challenges. However, no universally accepted or standardized format exists for documenting social needs and SDOH information [8-13]. Furthermore, delivery systems can now take advantage of recent health IT advances in offering automated integration of new sources of relevant social needs and SDOH information [8,14,15]. The development of cross-provider regional health information exchanges, such as Maryland Health Information Exchange (known as CRISP), also offers the opportunity to connect social needs and SDOH data from multiple clinical organizations and to share information across medical and social sectors (eg, primary care practices and community-based organizations [CBOs]) [16].

The extensive range of available social needs and SDOH data will offer a better understanding of how individual and neighborhood challenges could impact a patient's social needs and SDOH and increased risk of adverse health outcomes [17-22]. However, many technical and organizational challenges must be surmounted before social needs–integrated health IT solutions can be implemented on a wide scale. For example, the literature provides evidence of existing gaps in the development of best practices for integrating social needs and SDOH data into the clinical workflow and the clinicians' core clinical decision support (CDS) tools [23] and data sharing with CBOs [24].

Also, multiple practical gaps exist in addressing social needs and SDOH in underlying care management tools. Over the past decade, the new generation of "value-based" health insurance plans and integrated delivery systems (eg, Patient-Centered Medical Homes, and Accountable Health Organizations) have fully embraced available Health IT systems to implement clinically oriented risk identification and stratification CDS tools addressing the needs of medically underserved patients [25]. These mechanisms are commonly used to identify and refer the subset of patients who are high-risk or high-cost (ie, with serious and multiple chronic conditions) who need care management services [25]. Today, more providers are placed at financial risk for a wider range of nontraditional performance-based target indicators (eg, neighborhood health indicators) and more diverse populations. Hence, there is a rapidly growing gap regarding the use of social needs and SDOH risk information, relative to clinical or morbidity risk factors, within current case finding and risk stratification methodologies. Such a gap is critical for the large proportion of patients, especially among minority populations, who, in addition to having high clinical needs, concomitantly face behavioral, socioeconomic, and community-resource challenges [26].

Some health plans and provider systems have started to address the social needs of their patients by implementing EHR-based survey assessment tools and navigation services in their clinical and digital workflows [27-31]. Moreover, a growing body of evidence such as the Accountable Health Communities model by the Centers for Medicare & Medicaid Services provides support for the implementation of such services in the health care settings and their impact on improving the care process and health outcomes [30,32,33]. However, automated and standardized social needs and SDOH risk identification metrics and data collection and curation processes are sorely lacking. To avoid burdensome and inefficient social needs assessment (data collection from all patients at each visit), it will be essential to develop automated screening tools using EHR or community databases to help identify the subset of patients who would most benefit from EHR-integrated social needs assessment and data collection [34]. Also, currently in most health systems, the referral to CBOs is based on clinic staff's one-off attempt to identify available CBOs and to make referral arrangements. And, in cases where an automated directory of services is used, information is rarely exchanged that might benefit the patient [24,29,30]. The disconnect between health systems and CBOs and the lack of established data-sharing mechanisms have many negative implications for the patient and the system. For example, it is difficult for the providers to identify whether the social needs of their patients were addressed [8,28,35]. From a system perspective, such disconnect makes it difficult to evaluate the impact of identification, assessment, and referral of social needs on health outcomes and health care use, as well as to evaluate the efforts of health systems to address disparate access to medical and social services [28].

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Thus, integrating data on social needs and SDOH challenges along with clinical risk information within operational CDS systems built into EHRs is an effective approach to addressing health-related social needs. To achieve this goal applied research is needed to (1) identify optimal solutions for the effective collection and application of social needs and SDOH information within EHRs; (2) develop EHR-integrated CDS tools and closed-loop referral systems; and (3) implement the CDS tools and closed-loop referral systems in the digital and clinical workflows at health care systems and collaborating CBOs.

Primary Objective

The objective of this mixed methods study including a randomized controlled trial (RCT) and a qualitative phase is to address the current gaps in the EHR-based social needs assessment and navigation services. Thus, we plan to assess the feasibility, acceptability, and effectiveness of an EHR-integrated digital platform to identify patients with social needs and provide navigation services including CBO referrals. The digital platform includes a CDS tool and a closed-loop CBO referral. The CDS tool contains a social risk score and an overview of different risk factors and comorbidities contributing to the patient's social risk score. The CDS tool also provides recommendations on assessment for social needs based on the social risk score and other available information (refer to Multimedia Appendix 1 for an explanation and overview of the CDS tool).

Using both patient- and population-level data, we developed a social predictive risk score based entirely on electronic information readily available within most health care delivery systems. We also validated the model using multiple denominators to ensure generalizability and retrained and tested the model for each subpopulation of interest (eg, individuals aged 65 years or older, racial and ethnic minority populations, and those living in the most and least disadvantaged neighborhoods) [34]. The predictive risk score helps providers systematically identify patients at risk of having social needs based on their demographic characteristics, clinical comorbidities, previous social needs, and clinical outcomes such as hospitalization and emergency department visits. Those patients represent likely targets for further assessment of their social needs and ultimately potential referral to CBOs to address such needs. Using this systematic electronic case-finding screening approach helps the health care system avoid burdensome and inefficient social needs assessment (eg, primary data collection from every patient at every visit).

Hypothesis

Building on the current evidence on the experience of patients, providers, and health care systems with the EHR-based social needs assessment and navigation services [32] as well as the impact of such systems on care process and health outcomes [33], we plan to test the central hypothesis that implementing the digital platform for social needs identification and providing navigation services will (1) be feasible in digital and clinical workflows of primary care ambulatory clinics and CBOs; (2) be acceptable by patients, clinical providers, and CBO staff; and (3) demonstrate effectiveness in improving care process and ultimately the clinical outcomes.

Methods

Study Overview and Design

We will apply an RCT design to compare selected outcomes between the intervention (digital platform) and control (standard of care) groups during their primary care ambulatory visits. The RCT will take place in 5 primary care ambulatory clinics at Johns Hopkins Health System (JHHS) and 5 CBOs in Baltimore City. The CBOs are specialized in providing services related to different categories of social needs including residential instability (ie, homelessness, housing insecurity, and poor-quality housing), food insecurity, and transportation. We will identify a clinical provider champion in each pilot primary care clinic who will serve as the liaison between the study team and the clinic. The provider champion will help the research team with the implementation of the platform in the digital and clinical workflow and will advocate for the study among other providers. Figure 1 describes the RCT's procedural flow.

We will identify eligible patients via EHR in the JHHS pilot primary care clinics. A research project manager will contact patients after obtaining their permission via mail, email, and patient portal communications. After verifying eligibility and introducing the study, interested patients will complete consent processes. We will randomize the patients to the intervention or control arm for a 3-month study period. The patients in the intervention group will be contacted by staff at Hopkins Community Connection (HCC; a team of trained social workers and care managers, serving as a hub at JHHS providing standardized social needs assessment and navigation services) within 48 weekday hours of enrollment and receive social needs assessment and navigation services based on their social risk score and other information available in the CDS tool. The patients in the control group will receive the standard of care consisting of provider assessment, assessing, and addressing social needs on an as-needed basis based on the information provided during the visit. The patients in the intervention group will complete an exit interview via phone 3 months after the intervention, assessing their experience with the digital and clinical work process. For patients in the control group, we will retrieve any information on social needs assessment and referral services provided as a standard of care from their EHR.

To evaluate the feasibility and acceptability of the digital platform and its impact on the clinical and digital workflow and patient care we will conduct focus groups with the care teams at various pilot primary care clinics (eg, clinical providers), HCC staff, and CBO staff to determine satisfaction of users and identify any facilitators or barriers to using the digital platform.

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Figure 1. An overview of a randomized controlled clinical trial to identify patients with social needs and provide navigation services. *In the screening phase, the HCC team (a team of trained social workers and care managers, serving as a hub at Johns Hopkins Health System providing standardized social needs assessment and navigation services) uses the social risk score available in the CDS tool for the intervention arm to decide the social risk of the patient and the need for further assessment. CBO: community-based organization; CDS: clinical decision support; EHR: electronic health record; F/U: follow-up; HCC: Hopkins Community Connection.

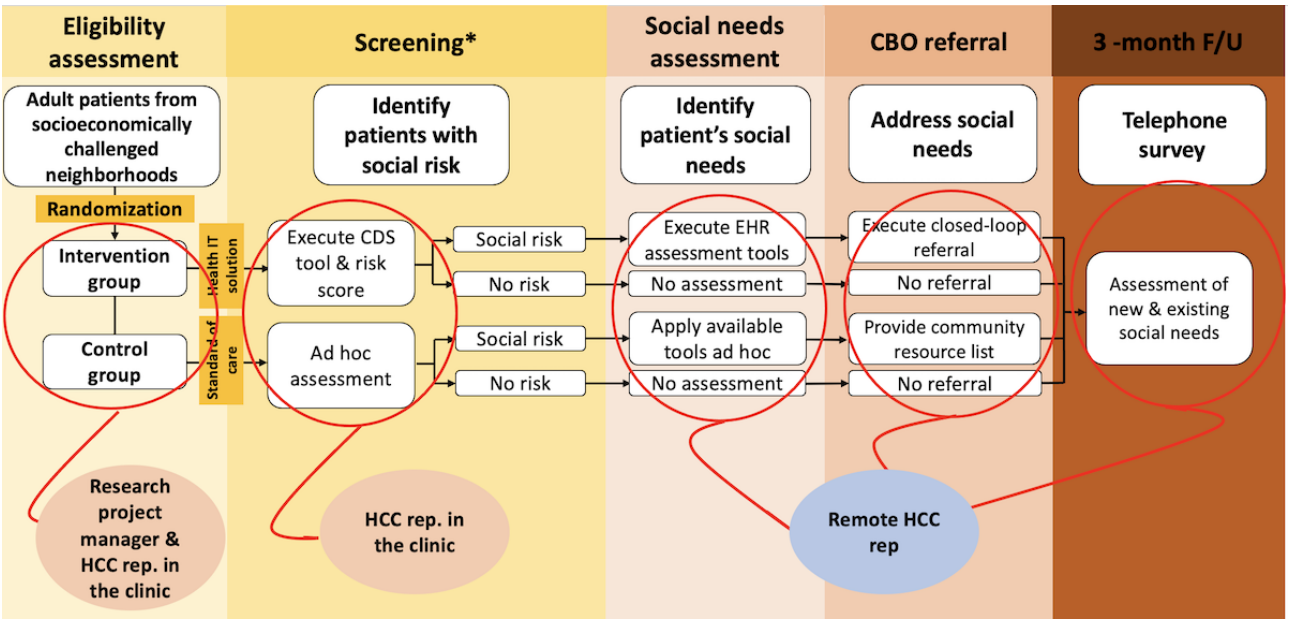

Randomized Controlled Trial

Patient Enrollment—Identifying Eligible Patients

To identify eligible patients, we will use the following inclusion or exclusion criteria: adult (18+ years of age) patients living in socioeconomically challenged neighborhoods. First-generation immigrants who may be non–English speakers will be eligible for enrollment. The JHHS-EHR does not contain data on patients' income. Therefore, we will consider enrollment in Medicaid and living in a neighborhood with a high poverty level and socioeconomic challenges as proxies for low income. We will use the patient's address in the EHR to identify his or her neighborhood of residence and use the area deprivation index [36], a population-level composite measure ranking the neighborhoods based on their poverty level, using data from the US Census Bureau American Community Survey. We will consider area deprivation index at the 75th percentile as a proxy for the most deprived neighborhoods. We will consider children, individuals with high levels of income, and patients who already have an HCC care team member assigned to them with a start date within the last 90 days and no end date as noneligible to enroll in the study.

Every week, our data analyst will use the abovementioned inclusion or exclusion criteria to identify eligible patients with a primary care appointment in 3 weeks in one of the pilot primary care clinics at JHHS. The data analyst also will update the list of eligible patients to add patients with a newly scheduled appointment within 3 weeks of their appointment. We will use the JHHS-EHR patient portal (EPIC MyChart) to send automated messages to eligible patients, inform them about the study, and provide background information on the project. If patients agree to participate in the study, the research project manager will contact them to complete the consent process. The research project manager will also reach out to patients via email and paper mail to ask permission to contact them by phone. The research project manager will contact patients who will not opt out of future communications with the study team to inform them of the study, provide information, and obtain consent. We will also distribute flyers, containing a 1-page graphic document summarizing the study process, in the pilot primary care clinics to inform patients of the ongoing study and provide contact information for them to get connected to the research project manager (refer to Multimedia Appendix 2).

Moreover, we will contact the providers via the EHR secure messaging before an eligible patient visits and inform them about the patient's eligibility for our study. The providers inform the patients about the study and if the patients agree to participate, they will communicate this information with the research project manager via secure messaging. This process will be completed using an EHR SmartPhrase to populate a prefilled form containing a 1-page summary of the project along with the contact information of the research project manager and add it to the visit summary. This document will be printed at the clinic or sent via email or patient portal to the patient.

Patient Enrollment—Consenting and Randomization

We will use both teleconsent via DocuSign and in-person consenting in the clinic when possible to obtain informed consent from eligible patients. We will use the DocuSign 21 CFR Part 11-compliant software (DocuSign, Inc) to obtain a secure electronic signature [37]. The consent discussion will take place via phone or videoconference (eg, Zoom; Zoom Video Communications) and patients will be given adequate time to consider the research study and ask questions before signing the consent form. For patients unable to use the DocuSign to complete the consent process the HCC staff will approach the patients in the clinic on the day of their visit and obtain the consent after providing information about the study,

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answering their questions, and giving them adequate time to read through the consent form.

We will use stratified blocked sampling through REDCap (Research Electronic Data Capture) with each pilot primary care clinic serving as a stratum to generate the randomization list. Each pilot primary care clinic will have blocks of different sizes (eg, 4, 6, and 8), which will be randomly distributed (eg, one clinic may have blocks of 4,6, 8, 6, 4, 8, …. and another one may have blocks of 6,8, 4, 4, 8, 6, …). Each block will contain an equal number of intervention and control assignments with different orders. This strategy helps ensure an equal number of patients in the 2 arms of the study at any time point during the enrollment and ensures complete masking of the randomization process, with no chance to predict the next randomization assignment in a clinic. The randomization will be completed for each patient after they complete the consent process. On the day of an eligible patient's visit, the research project manager will monitor the patient's arrival in the clinic through EHR, and when the patient gets to the clinic, they will use the REDCap randomization list to receive the randomization assignment for each patient and to record the patient's name and ID with their assigned group (ie, intervention or control arm). They will communicate the randomization assignment with the HCC staff in the clinic through EHR secure messaging.

Planned Intervention

Once consented to and randomized into the intervention or the control arms, the patients will be seen at their regularly scheduled appointment in the primary care clinic.

Intervention Arm

For patients in the intervention arm the HCC staff in each clinic will use the CDS tool to review their social risk score. If the patient is identified as with medium to high social risk based on their risk score and other information provided in the CDS tool, the HCC staff will perform further assessment of their social needs using available standard social needs assessment tools in the EHR [38,39]. For patients with low risk, the HCC staff will review the social needs history and other information depicted in the tool and decide whether to perform further assessment. A summary sheet will be provided to the HCC staff as a guide to all the details depicted in the CDS tool to help with their decision-making (refer to Multimedia Appendix 1). If the HCC staff decides to screen the patient for social needs, they will leave a secure message for the clinical provider in the EHR, informing them about the risk score and the decision regarding the assessment. The clinical provider will have the option of checking the risk score on the CDS tool, the summary of patients' previous social needs, and other factors contributing to the social risk score.

To perform further assessment of the social needs the HCC staff will reach out to the patients over the phone and will perform the assessment. If any social needs are identified and the patient agrees to address those needs the HCC staff will work with the patient to set goals for different identified social needs and provide navigation services including CBO closed-loop referral to achieve those goals. The HCC staff will use FindHelp [40], a Health Insurance Portability and Accountability Act–compliant database and referral platform for social needs assessment, documentation, and referral to CBOs. FindHelp also provides the opportunity for real-time communications between clinical providers and CBOs.

After an assessment of the social needs and providing available navigation services at JHHS the HCC staff will generate a summary report through FindHelp and alert the CBOs about the referred patients. CBOs will have access to FindHelp and can review patients' social needs assessment and summary reports. After meeting with the referred patient and identifying resources to address their social needs, CBOs generate a summary report, which will be accessible to the HCC staff and clinical provider teams.

Control Arm

For patients in the control arm the standard-of-care assessment and addressing of social needs will be provided. The assessment will not be automated with precollected information as is designed in our CDS tool. The assessment will be on an ad hoc basis, which may include completing currently available social needs assessment tools in the clinics and providing information to the patients about available community-based resources.

Follow-up

For patients in the intervention arm of the study who get screened by the HCC, after their case has been closed (approximately 3 months after enrollment), the HCC staff will conduct a telephone survey with the patients to assess any changes in their social needs, the degree of which the social needs were met, and patient's satisfaction with the process for social needs assessment and navigation services as well as the services they received. For patients in the control group, we will retrieve any information on social needs assessment and referral services provided as a standard of care from their EHR. Moreover, for all patients in the study, we will conduct a secondary data analysis to assess the impact of the CDS tool and navigation services on selected clinical outcomes such as hospitalization and emergency department visits (refer to Multimedia Appendix 3 for an overview of the clinic workflow).

Sample Size

We plan to enroll approximately 295 patients in each study arm. The sample size calculation is based on addressing the primary outcome of the study namely the effectiveness of the proposed digital process and its impact on process measures. The primary outcome is defined as the change in the number of social needs identified during the visit at the 3-month follow-up telephone survey versus the baseline visit comparing the intervention and control arms. Such a sample will provide 80% power in 2-sided tests with a type I error rate of 5% to detect standardized small effect sizes (Cohen d=0.17-0.20 as is estimated in similar studies of social needs assessment and navigation services [30]). Sample size estimates conservatively account for a 20% loss to follow-up.

Data Collection and Measures

We will collect demographic data (ie, age, gender, race, insurance type, language preference, and need for interpreter), clinical comorbidities (using the Johns Hopkins Adjusted

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Clinical Groups [41], one of the world's most widely used population-based predictive modeling and case-finding methodologies), previous social needs, and health outcomes (ie, hospitalization and emergency department visits) from the JHHS-EHR. The information related to the assessment for social needs, and navigation services including referral to CBOs, and their 3-month follow-up interview will be documented in the FindHelp platform [40]. We will also obtain information on the randomization assignment for each patient through REDCap and collect the information on the social risk score at the time of randomization from our CDS tool. The data generated through the CDS tool will be stored in the Health Insurance Portability and Accountability Act–compliant JHHS enterprise data warehouse.

Qualitative Assessment—Focus Groups

Participant Enrollment

We will evaluate the EHR-integrated digital platform (the CDS tool and the CBO closed-loop referral) from the health system and community organization perspectives. Thus, we will conduct focus groups with provider teams such as physicians, nurses, social workers, care managers, community program coordinators or patient navigators in the clinics and at HCC, and staff of CBOs to determine the satisfaction of the users with the digital platform, determine whether there are any facilitators or barriers to using the platform, and generate ideas on who to improve the platform and the digital process. The research project manager will identify individuals who interacted with the platform in each pilot clinic, HCC, and CBOs and invite them to join the focus groups. We will work with the provider champion at each clinic site to inform other provider teams about the focus groups and invite them to the study. We will also work with the HCC program manager and the CBO staff to identify qualified individuals for the focus groups. We will use a convenience sampling method to select and enroll qualified individuals.

Conducting Focus Groups

The focus groups will be 90 minutes each. Participants will be invited via email to join a focus group at a convenient date and time for their schedule and will consent to this part of the study on the day of the meeting. The email will provide a summary of the study and the purpose of the focus group; the date, time, and duration of the focus group; and the contact information of the study principal investigator (PI) to answer any questions of the potential participants before they agree to participate. The focus groups will be conducted under the supervision of the study PIs and study coinvestigators with expertise in qualitative research. Participants in the focus groups will be asked a variety of questions on their interaction with the digital platform, their perception of how it fits within the clinic and CBO digital and clinical workflow, their satisfaction with the platform, and how it can be improved. Focus groups will be recorded in Zoom and transcribed using the Zoom-automated service. We will review the transcripts to address any inconsistency in the automated Zoom transcripts, deidentify, and upload them into MAXQDA (VERBI Software) [42] for data management and analyses.

Sample Size

We aim to enroll and engage a variety of clinical providers, HCC, and CBO staff. We will attempt to conduct six 90-minute meetings for 6 months to collect input on the potential challenges in the implementation and use of the digital platform. We plan to have 6-10 individuals at each meeting for a total of 36-60 individuals from a variety of positions within the health system and CBOs.

Outcome Assessment

We will assess whether the EHR-integrated digital platform is superior to the standard of care and more feasible and acceptable. Thus, we will track the outcomes of feasibility, acceptability, and effectiveness through the RCT and qualitative study components (Table 1). We will report feasibility outcome measures as weekly use rates of the digital platform (the CDS tool and closed-loop CBO referral). The acceptability outcome measure will be the provider's responses to the truthfulness of a statement indicating a willingness to use the digital platform in the future. Effectiveness (ie, the primary outcomes) will be measured by tracking the 3-month process and clinical outcomes versus the baseline visits comparing the intervention and control arms.

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Table 1. Outcome measures for digitally enabled social needs assessment and intervention.

Selected measure	Data source and collection method	Timing
Outcome category: feasibility		
Use of the EHR[a]-integrated digital platform—quantitative measures—including weekly rates of log into the CDS[b] tool and closed-loop CBO[c] referral	JHHS[d]-EDW[e] FindHelp Data	Enrollment to 3-month follow-up
Types of use—qualitative measures—including checking the risk score and reviewing the summary report of contributing factors to social risk	Focus group transcript	During and after completion of the RCT[f]
Types of use—quantitative and qualitative measures—including performing social needs assessment, setting goals for the patients and follow-up with patients and CBOs, and performing follow-up interviews	JHHS-EDW, FindHelp data, and focus group transcript	During and after completion of the RCT
Outcome category: acceptability		
Willingness to reuse—quantitative and qualitative measures	Provider focus group transcript	During and after completion of the RCT
Willingness to use the EHR-integrated digital platform again	Patient follow-up interview	3-month follow-up
Outcome category: effectiveness		
Impact on process measures—quantitative measures—including change in the number of identified social needs from enrollment to follow-up, comparing intervention and control arms, and change in the number of navigation services and CBO closed-loop referrals from enrollment to follow-up, comparing intervention and control arms	JHHS-EDW and FindHelp data	Enrollment and 3-month follow-up
Impact on clinical outcomes—quantitative measures—including change in the hospitalization rates from enrollment to follow-up, comparing intervention and control arms, and change in the emergency department visit rates from enrollment to follow-up, comparing intervention and control arms	JHHS-EDW	Enrollment and 3-month follow-up

[a]EHR: electronic health record.

[b]CDS: clinical decision support.

[c]CBO: community-based organizations.

[d]JHHS: Johns Hopkins Health System.

[e]EDW: enterprise data warehouse.

[f]RCT: randomized controlled trial.

Analysis Plan

We will adhere to the standards for trial design, analysis, and reporting per the CONSORT (Consolidated Standards of Reporting Trials) [43]. We will perform univariate analysis including demographic characteristics, clinical comorbidities, previous social needs, and clinical outcomes such as hospitalization and emergency department visits among all patients as well as in the intervention and control arms. We will use frequencies, means, and standard deviations related to feasibility and acceptability outcomes. For the effectiveness outcomes, we will use the change in the number of identified social needs and provided navigation services from baseline to 3-month follow-up and proportion with any hospitalization and emergency department visits comparing the 2 study arms using *t* test and Pearson chi-square tests. We will also use a logistic regression model to include other potential predictors of the outcome to improve the precision of the estimate. All trial procedures will also be in concordance with ClinicalTrials.gov regulations (NCT05574699).

For focus groups, we will deidentify the transcripts and upload them into MAXQDA [42] for data management and analyses. We will deductively develop an initial codebook from the interview guide and apply the deductive codes to the first few interview transcripts. In addition, we will inductively identify emergent subcodes for each parent code, resulting in several subcodes. This initial coding process will be conducted by the PI and coinvestigators with expertise in qualitative research. We will discuss the disagreements in coding and reach a consensus by mutual agreement. One coder will then code the remainder of the interview data and both reviewers will discuss emergent findings and modifications to the coding framework. We will engage in a process of constant comparison of emergent findings throughout the analytic process, and when no new codes can be identified, we will consider thematic saturation to have been achieved.

Ethical Considerations

This study protocol was approved by the Johns Hopkins University, School of Medicine's institutional review board (IRB; #IRB00354803).

Data Management Plan

We will convene a data and safety monitoring board (DSMB) to safeguard the interests of study patients, ensure safety and adherence to human subjects' protection policies, and monitor the overall conduct of the study. The DSMB will be an

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independent advisory group to the project PI. Communication with DSMB members will be primarily through the PI. It is expected that other study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls. The DSMB will meet twice annually throughout the study, when the DSMB will review the progress of the study (accrual rate, protocol deviations, and interim study analyses, if recommended) and make recommendations.

Privacy and Confidentiality

To safeguard participant information data will be deidentified for analysis and reporting of the results.

Compensation Details

Patients who participate in the RCT will receive services based on their social needs. After completion of the 3-month follow-up interview, patients will receive a $20 gift card for their participation in the study. There are no monetary tokens or compensation directly to the participants in the focus groups.

Plan for Reporting Unanticipated Problems or Study Deviations

It is anticipated that patients will experience more benefits than risks from their participation in the trial. There are only minimal risks associated with this study including the risk of unintended consequences, such as social risk profiling that could lead to bias and stereotyping in the delivery of care to patients. To address this risk, the study team will incorporate patients' preferences into the design and use of the EHR-integrated digital platform and will provide training for the clinic, HCC, and CBO staff on how to use the information available in the CDS tool in their communications with patients. There might also be some ethical concerns about identifying social needs beyond the major categories we have specified in this study (ie, residential instability, food insecurity, and transportation) without addressing them. We refer to such events as alerts and have well-developed procedures for their management. All alerts are reported to the DSMB on a biannual basis. However, the reporting of alerts to the IRB is not required. Details about specific alerts and actions taken are shown in Table 2.

If a serious adverse event happens the DSMB will be notified by the PI within 48 hours of initial notification to the project team. All members of the DSMB will receive copies of all safety reports at the time of submission to the IRB. In addition, a listing of all adverse events and their attribution (eg, study-related, intervention-related, or unrelated to study or treatment) will be provided to the DSMB monthly.

Table 2. Specific alerts and actions taken for reporting unanticipated problems or study deviations in the randomized controlled trial to identify patients with social needs and provide navigation services.

Alert	Action taken
Suicidal ideation, threats to hurt self	If an HCC[a] staff encounters a situation in which the person threatens to hurt themself immediately, then the physician at the clinic site is informed and the person is referred to the emergency department for observation and psychiatry consult. If the person is not an immediate threat to self, then the physician at the clinic site is informed and the person is actively encouraged to make a psychiatry appointment and the contact is made for the person if they choose. The HCC staff also informs the person that a member of the team will be contacting him or her shortly to follow up. Immediately after the visit, the PI[b] will be notified of the situation. The PI will complete the alert form and give the form to the study project manager for filing.
Evidence of abuse and intimate partner violence	Evidence of physical abuse is as follows: (1) patient states to the HCC staff that abuse occurs and (2) the HCC staff observes physical evidence (eg, black eye, black and blue marks on arms or legs). The HCC staff informs the physician at the clinic site. The physician obtains further information from the patient and will contact Adult Protective Services. Immediately after the visit, the PI will be notified of the situation. The PI will complete the alert form and give the form to the study project manager for filing. Note: The possibility of informing an agency about an abusive situation is stated in the informed consent.

[a]HCC: Hopkins Community Connection.

[b]PI: principal investigator.

Dissemination Plan

We will disseminate the study results regardless of effect direction and size through publications in peer-reviewed journals and presentations at conferences. Moreover, we will develop guidelines and algorithms to support other health care systems wishing to apply our methods and tools. These will include logic flow for an EHR-integrated digital platform containing the risk assessment process, the navigation services, and the referral process. In addition, we will provide information on challenges surrounding data sharing between primary care practice sites and CBOs. Our recommendations will suggest how to address the variabilities in information technology infrastructure across different CBOs. We will also develop recommendations for how best to scale the implementation of the EHR-integrated digital platform, across the entire JHHS, regionally, and nationally. Finally, we will vigorously disseminate our findings and methods to major provider networks, technology vendors, policy makers, and other stakeholders.

Results

We started enrollment in June 2023 and will complete it in January 2025. The analysis is expected to be completed by March 2025 with results published in spring of 2025. We plan to perform an interim analysis when the enrollment reaches 50% of the planned sample size.

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Discussion

This study will provide evidence on the best approaches to create and implement a digital workflow for social needs assessment and navigation services and assess whether the implementation of the EHR-integrated digital platform and process is feasible in a health care system and in CBOs, acceptable among the frontline providers and CBOs staff, and effective in impacting health-related outcomes. If the planned intervention demonstrates greater improvements in 1 or more study outcomes, these findings can be tested and spread through future implementation research and processes. We acknowledge that the inadequate available resources in the community may limit the ability of the CBOs to address identified social needs, which may impact the effectiveness of the digital platform.

Importantly, the application of mixed methodology and the addition of focus groups with clinical and social stakeholders are unique aspects of this study. This approach will help identify barriers and facilitators to future implementation of the digital platform and potential needed modifications to the digital platform and workflow to ensure the sustainable use of the platform in clinical settings. Such modifications will facilitate future uptake of the digital platform should it prove effective. Our methodology can be used to examine the effects of similar EHR-integrated digital platforms to address unmet social needs in the health care systems and collaboration with community-based organizations.

Acknowledgments

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Conflicts of Interest

Johns Hopkins University (JHU) holds the copyright to the Adjusted Clinical Groups (ACG) System and receives royalties from the global distribution of the ACG system. This revenue supports a portion of the authors' salary. The authors are members of a group of researchers who develop and maintain the ACG System with support from JHU. The authors report no other conflicts of interest in this work.

Multimedia Appendix 1
Randomized controlled clinical trial to identify patients with social needs and provide navigation services—clinical decision support tool explanation sheet.
[DOCX File , 454 KB - resprot_v13i1e57316_app1.docx]

Multimedia Appendix 2
Randomized controlled clinical trial to identify patients with social needs and provide navigation services—clinic flyer.
[DOCX File , 537 KB - resprot_v13i1e57316_app2.docx]

Multimedia Appendix 3
Randomized controlled trial to identify patients with social needs and provide navigation services—clinic workflow.
[DOCX File , 417 KB - resprot_v13i1e57316_app3.docx]

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Abbreviations

CBO: community-based organization
CDS: clinical decision support
CONSORT: Consolidated Standards of Reporting Trials
DSMB: data and safety monitoring board
EHR: electronic health record
HCC: Hopkins Community Connection
IRB: institutional review board
JHHS: Johns Hopkins Health System
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDOH: social determinants of health

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Protocol

Effectiveness of a Mobile Phone Messaging–Based Message Framing Intervention for Improving Maternal Health Service Uptake and Newborn Care Practice in Rural Jimma Zone, Ethiopia: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Ethiopia has high rates of maternal and neonatal mortality. In 2019 and 2020, the maternal and newborn mortality rates were estimated at 412 per 1,000,000 births and 30 per 10,000 births, respectively. While mobile health interventions to improve maternal and neonatal health management have shown promising results, there are still insufficient scientific studies to assess the effectiveness of mobile phone messaging–based message framing for maternal and newborn health.

Objective: This research aims to examine the effectiveness of mobile phone messaging–based message framing for improving the use of maternal and newborn health services in the Jimma Zone, Ethiopia.

Methods: A 3-arm cluster-randomized trial design was used to evaluate the effects of mobile phone–based intervention on maternal and newborn health service usage. The trial arms were (1) gain-framed messages (2) loss-framed messages, and (3) usual care. A total of 21 health posts were randomized, and 588 pregnant women who had a gestational age of 16-20 weeks, irrespective of their antenatal care status, were randomly assigned to the trial arms. The intervention consisted of a series of messages dispatched from the date of enrolment until 6-8 months. The control group received existing care without messages. The primary outcomes were maternal health service usage and newborn care practice, while knowledge, attitude, self-efficacy, iron supplementation, and neonatal and maternal morbidity were secondary outcomes. The outcomes will be analyzed using a generalized linear mixed model and the findings will be reported according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth) statement for randomized controlled trials.

Results: Recruitment of participants was conducted and the baseline survey was administered in March 2023. The intervention was rolled out from May 2023 till December 2023. The end-line assessment was conducted in February 2024.

Conclusions: This trial was carried out to understand how mobile phone–based messaging can improve maternal and newborn health service usage. It provides evidence for policy guidelines around mobile health strategies to improve maternal and newborn health.

Trial Registration: Pan African Clinical Trials Registry PACTR202201753436676; https://tinyurl.com/ykhnpc49

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KEYWORDS

message framing; mHealth; digital health; SMS; maternal health; newborn health; cluster randomized controlled trials; RCT; Ethiopia; mobile phone; effectiveness; SMS-based interventions; text messaging; maternal; newborn care practice; randomized; controlled trial; controlled trials; mobile phone messaging; phone-based intervention

Background

Ethiopia has one of the highest maternal and neonatal mortality ratios worldwide, with a maternal mortality ratio of 401 per 100,000 live births and a neonatal mortality rate of 33 per 1000 live births [1]. The risk of death due to complications during pregnancy, labor and delivery, and the postnatal period is believed to be reduced with bundles of antenatal care, institutional delivery, and postnatal care (PNC) [2]. However, in Ethiopia, the proportion of women attending at least 4 antenatal visits, delivered at health facilities, and had early PNC service was 43%, 48%, and 35%, respectively [3], indicating there are missed opportunities for almost half of the women who were not able to seek the recommended antenatal visits, institutional delivery, and PNC in the country.

Innovative strategies are required to reduce maternal mortality by improving the use of antenatal care (ANC) services to achieve Sustainable Development Goal 3 by 2030—reducing maternal mortality to fewer than 70 per 100,000 births. Improving child survival also remains a matter of urgent global support. A clear and accessible strategy to achieve this goal is to take advantage of the potential of simple mobile phones to increase the number of ANC visits for prenatal women [4]. Recently, mobile phones have been introduced to disseminate health information and interventions (eg, mobile health [mHealth] interventions) in low- and middle-income countries (LMICs). mHealth is recognized as an important area in implementing global strategies for women's and children's health. Although mHealth interventions are promising, there is insufficient scientific research to assess their effects [5]. As of 2022, the number of mobile phone users, including smartphones and feature phones, was 7.26 billion, representing 91.54% of global mobile phone ownership [6]. mHealth has the potential to improve tens of thousands of lives each year. The ubiquity and penetration of mobile phones provide a unique opportunity to leverage mHealth for maternal and newborn care [7]. According to the International Telecommunication Union, mobile phone coverage has increased to 90% of the world's population and 80% of the rural population [8].

Digital health, or the use of digital technologies for health, has become a prominent field of practice for using routine and innovative forms of information and communications technology to address health needs and improve health knowledge, including in rural areas of LMICs [9,10]. Mobile technology is creating new opportunities to permit safe, accessible, coordinated, and effective maternal and child health care in these regions [11]. Introducing mHealth as a new strategy for health care delivery is seen as a suitable option for reducing the high rates of maternal and child mortality in low-income countries [12,13]. mHealth, a subset of eHealth, is defined as "the use of mobile wireless technologies for health" [9]. SMS is text messaging following mobile network standards. It has been suggested that mobile phone messaging interventions can improve self-management of diabetes, weight loss, physical activity, quitting smoking, and adherence to medication in antiretroviral therapy [14,15]. The use of SMS has also indicated promising outcomes in the promotion of maternal and child health care services [16-20]. However, to date, few studies have evaluated the effect of SMS-based interventions on maternal and newborn health among pregnant and postpartum women in transitioning countries [16,20]. While evidence for SMS-based interventions is well described, the effect of SMS-based message framing intervention for improving maternal and newborn health is limited.

Message framing is the presentation of information in a way that affects the perception, attitude, or behavior of the person receiving it. It is how a message is worded, structured, or framed to impact the target audience's perception and persuade them to take action [21,22]. There are 2 primary forms of message framing: gain-framing and loss-framing. Gain-framing highlights the advantages or positive results of a decision or action, while loss-framing focuses on the potential negative consequences or losses that could result. The type of framing used depends on the context and objectives of the message, as it can be used to either encourage or discourage specific actions [23,24]. Scholars have been reporting that gain-framed information is more persuasive for disease prevention behaviors as it encourages risk aversion and thus engages in safe disease prevention behaviors. Conversely, loss-framed information is suggested for disease detection behaviors, as it makes people willing to take risks and engage in relatively risky disease detection behaviors [25,26].

The literature on health message framing is extensive and has shown promising effects on health outcomes, including maternal and child health [27,28]. A study by Divdar et al [28] showed significant improvements in oral health knowledge, attitude, intention, efficacy, and practice among the intervention group as compared to the control group, although no significant difference was observed between gain and loss-framed messages. Both gain and loss-framed messages significantly improved breastfeeding self-efficacy in a study conducted in Iran [29]. Another 3-arm intervention has shown significant improvements in complementary feeding knowledge, attitude, self-efficacy, and practice among interventions, with the loss-framed group showing higher improvement than the gain-framed group [30]. However, Frew et al [31] found is no improvement in maternal influenza immunization in their intervention evaluating message framing. These findings indicate

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inconsistent results regarding which framing method improves maternal and child health care practices [29-31]. Moreover, the evidence on the impact of message framing on maternal and newborn care practice is still unclear in LMICs and needs further assessment [32]. Therefore, to foster our understanding of framing effects and determine which way of information framing has a strong persuasive effect on maternal and newborn health, we need further confirmation.

Although various studies have reported that digital health interventions are effective in improving health service uptake, including maternal and child health services, none, to our knowledge, have considered message framing as a strategy to persuade, change opinions, and encourage the adoption of new behaviors. The main objective of this study is to evaluate the effects of mobile phone messaging-based gain or loss-framed messages on improving maternal health care usage and newborn care practice in the rural Jimma zone.

Methods

Setting

The study is being conducted in Manna, Shebe-Sombo, and Dedo districts of Jimma Zone, Oromia, Ethiopia. The districts were selected from 21 districts in the zone after confirming the unavailability of interventions aiming to improve maternal and newborn health services in each of them. Jimma Zone is characterized by weak health infrastructure, high health workers to the population ratio (1:329), only 9 health facilities offering comprehensive emergency obstetric and newborn care and a high maternal mortality ratio (412 per 100,000 live births).

Study Design

A 3-arm, cluster-randomized trial design with a 1:1 allocation ratio was used.

Intervention Components

The participants in the intervention were assigned to 3 arms: gain-framed, loss-framed, and control. The detailed description of each arm is presented as follows:

Gain-Framed Message

Women in this arm received an automated gain-framed message. The gain-framed SMS text messages, which were tailored based on individual women's gestational age (GA), expected delivery time, and postnatal period, were sent from the time of enrolment during ANC until the end of the postnatal period to the established list of participants' phone numbers. Women in this group also received the existing maternal care provided at the health facility.

Loss-Framed Messages

Women in this arm received automated, loss-framed messages. The loss-framed SMS text messages, which were tailored based on individual women's GA, expected delivery time, and postnatal period, were sent from the time of enrolment during ANC until the end of the postnatal period to the established list of participants' phone numbers. Women in this group also received the existing maternal care provided at the health facilities.

Control Group

Participants in the control group received existing ANC and PNC services provided at health facilities. According to the recent ANC guidelines, pregnant mothers are expected to have 8 ANC and 3 PNC contacts. In addition to these cares, counseling services is recommended on the following topics during ANC visits: (1) lifestyle modification, (2) danger signs and symptoms, (3) birth preparedness and complication readiness, and (4) other issues such as family planning, cord care, bathing, breastfeeding, child immunization, and screening for cervical cancer [33].

Intervention Packages

The intervention messages and the messaging system, which automatically dispatches these messages, were developed. These messages were developed based on the concept of message framing, with half of them developed in the form of a gain frame—emphasizing the benefits of maternal and newborn health care practices (eg, choosing to put your new baby to the breast in the first hour he or she is born will increase a baby's protection from many diseases and illnesses). The other half of the messages were developed as a loss frame—emphasizing loss as a result of not using maternal health services and practicing newborn care (eg, failing to put your new baby to the breast in the first hour he or she is born will lower a baby's protection from many diseases and illnesses). Multimedia Appendix 1 provides more examples of both gain- and loss-framed messages.

The content of the messages was evaluated by mothers and experts before it was used in the intervention. Initially, 120 (60 for each form) English version messages were drafted within the character count of 160, based on the Ethiopian Ministry of Health's guidelines and the World Health Organization's recommendations. After discussing with the research team, 32 (16 from each form) messages were discarded. The remaining 88 messages were translated into the Afan Oromo language and used for content evaluation. Mothers evaluated the content of these 88 messages through a card sorting activity, and 10 messages (5 from each form) that were not well understood by mothers were discarded. Following the card sorting activity, 8 experts evaluated the retained 78 messages (39 for each form) using 10 statements. The experts suggested modifications for 14 messages (13 loss-framed and 1 gain-framed), and all of these messages were modified and refined based on the suggestions.

Finally, 39 messages for each message form were retained under 10 thematic areas: nutrition, lifestyle modification, danger signs, birth preparedness, complication readiness, breastfeeding practice, labor, newborn care, immunization, and antenatal and PNC usage. These messages were dispatched using locally developed software that manages the schedule and sends the messages automatically. To facilitate this, a domain, layer 3 VPN, and short code were purchased from Ethio-telecom Company. The software program includes an interface to enter the participant's name, gestational week, mobile phone number, message type, message category, language option, report generation, and feedback options.

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Eligibility Criteria for Clusters and Participants

Clusters (Kebeles) with good mobile network coverage in 3 of the selected districts were eligible for randomization. Pregnant women with a GA of 16-20 weeks who either owned a mobile phone themselves or had a family member who owned one, lived in the selected cluster for at least 6 months, provided consent to participate in the intervention, and shared their phone number were eligible for the trial. Pregnant mothers who were unable to read mobile phone messages and had plans to relocate from the study cluster during the follow-up period were excluded from the intervention.

Sample Size Determination

Sample Size for the ANC Visit

The method suggested by Hooper et al [34] for cluster randomized trials with repeated cross-sections was used for the calculations. This method requires calculating 2 design effects, which are then used to inflate the sample size for individual randomization to account for the within-period intracluster correlation coefficient (ICC) and the between-period ICC. A sequence of steps has been followed to get the final sample size for the current 3-arm cluster randomized trials with repeated cross-sections. For ANC, we first calculated the individual randomization trial using the following assumptions: P1—the proportion of women attending ANC for more than 4 visits among the control group 23.27% [35], power=80%, 2-sided α=0.025, effect size=15%, and Zα/2 adjusted for multiple comparisons using a Bonferroni correction of 2.24. Individual randomization sample size (n) is calculated as follows:

Next, the design effect (d_c) due to cluster randomization was calculated as $d_c = 1 + (m - 1)\rho$. Here, the following parameters were considered: the within-period ICC(p) was assumed to be 0.003 [36], and the cluster size (m) was assumed to be 28. The calculation yielded a design effect due to cluster randomization $dc = 1 + (m - 1)\rho = 1.08$. Additionally, the design effect due to repeated assessment was calculated as $d_r=(1–r^2)$, where r is the correlation between samples from the same cluster at different times and determined as . Based on this, d_r was calculated using assumptions: within-period ICC=0.003, autocorrelation coefficient (π) of 0.8 (to allow for a 20% decay of the correlation from within to between different periods) [37], and m=28 and =0.062. Thus, the design effect due to repeated assessment was $d_r=(1–r^2)=0.996$.

To arrive at the final sample size per arm, the sample size for individual randomization is multiplied by both design effects, resulting in $(n\times d_c\times d_r)=188$. Considering a 4% loss to follow-up, the final sample size for each arm is 196 and this gives a total sample size of 588 when ANC was used as the primary outcome of the intervention.

Sample Size for Newborn Practice

For newborn care practice, the same procedure described earlier was used. First, the individual randomization sample size was calculated to be 118 based on the following assumptions: P1—the proportion of exclusive breast feeding among the control group of 74.8% [38], power=80%, 2-sided α of 0.025, effect size=15%, and Zα/2 adjusted for multiple comparisons using a Bonferroni correction=2.24. Then, the design effect (d_c) due to cluster randomization was calculated as $d_c = 1 + (m – 1)\rho = 1.35$ by considering the following parameters: within-period p of 0.013 [39] and cluster size assumed to be 28. The design effect due to repeated assessment was calculated as $d_r=(1–r^2)=0.953$, where the correlation between samples from the same cluster at different times r=0.251 by using assumptions: within-period ICC=0.013 [39], autocorrelation coefficient (π) of 0.8 (to allow for a 20% decay of the correlation from within to between different periods) [37], and m=28. By inflating the sample size under individual randomization with the 2 design effects as $(n\times d_c\times d_r)=152$. Considering a 4% loss to follow-up, the total sample size was 475.

Therefore, the sample calculated for ANC was larger (588) and was the final sample size of the trial to arrive at 21 clusters (7 per arm) and an average of 28 eligible pregnant mothers.

Recruitment

Following the randomization of the clusters, lists of pregnant women in the randomized kebeles were obtained from the health extension worker's registration book. Midwives then identified eligible pregnant women using 2 strategies: the last menstruation period (LMP) and the fundal height measurement technique (in the case of an unknown LMP) to determine the GA of mothers. The data collector provided a detailed explanation of the inclusion criteria and overall intervention procedure to eligible mothers by using the information sheet. Eligible pregnant mothers were enrolled in the intervention after obtaining informed consent regarding their willingness to give their phone number for the intervention and their approval to receive text messages to their own or their family's phone during the intervention period. The recruitment was done after randomly selecting 28 participants from a list of eligible pregnant mothers in each cluster. After recruitment, information, such as the participant's name, mobile phone number, and GA, was gathered during the baseline assessment. This information was then entered into the software to dispatch the messages according to the GA of those assigned to the intervention arm.

Randomization, Allocation Concealment, and Blinding

A total of 6 primary health care units, 2 from each district, were randomly selected, and kebeles in these primary health care units were used as units of randomization for the trial. A simple randomization with a 1:1 allocation was used to randomize the clusters (kebeles). After listing 30 kebeles that fulfilled the eligibility criteria, 21 of them were randomly selected for randomization. To assign the clusters to the intervention groups (gain-framed group, loss-framed group, and control group), the following steps were followed. First, the 21 clusters were alphabetically listed and labeled 1 to 21. Next, random numbers were generated using Excel 2019 (Microsoft Corp), and the generated values were copied and pasted as values next to the list of clusters. The list was then sorted in ascending order based on the generated random number. Finally, the first 7 clusters in

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the sorted list were assigned to the gain-framed group, the next 7 to the loss-framed group, and the last 7 to the control group. After the randomization, eligible pregnant women with a GA of 16-20 weeks were identified from the selected cluster by midwives. The midwives used 2 strategies: the LMP and the fundal height measurement technique in the case of an unknown LMP to determine the GA of mothers (Multimedia Appendix 2).

The allocation process was done by a person who was not involved in the implementation of the trial, and it was masked from the researcher involved in the implementation of the intervention. The interviewers who collected the data were blind to the intervention assignment. It is not possible to blind participants due to the nature of the intervention.

Outcomes

The primary and secondary outcomes are provided in Textbox 1.

Textbox 1. Primary and secondary outcomes.

Primary outcomes

- Maternal health service usage
- Newborn care practice

Secondary outcomes

- Knowledge about maternal health services
- Knowledge of danger signs (during pregnancy, labor and delivery, and the postnatal period)
- Knowledge of newborn care practice
- Knowledge about newborn danger signs
- Attitude toward maternal health services
- Attitude toward newborn care
- Self-efficacy toward maternal health service usage
- Self-efficacy toward newborn care practice
- Iron supplementation
- Maternal morbidity
- Neonatal morbidity

Operational Definitions

Operational definitions are as follows:

- Maternal health service usage:
  when mothers receive at least 8 ANC follow-up visits, give birth in a health facility, and visit a health facility for PNC follow-up contact from health professionals within 7 days of delivery.
- Newborn care practice:
  this refers to the care provided to the baby from birth to 28 days of age by the mothers, including early initiation of breastfeeding, exclusive breastfeeding, feeding colostrum, thermal care, hygienic cord care, and seeking care for an ill newborn. If a mother feeds colostrum, initiates breastfeeding within 1 hour after birth, feeds a newborn only breast milk, practices thermal and hygienic cord care, and seeks care for her ill newborn, she is considered to be practicing newborn care, and if she misses one of them, she is considered to be not practicing newborn care.
- Knowledge about maternal health services:
  participants were asked to mention the recommended newborn care practice using 16 questions. All the responses were counted, and the higher score indicates a higher knowledge of newborn care practice.
- Knowledge of maternal danger signs:
  this was measured by 7 items related to maternal danger signs during pregnancy, labor & delivery, and the postnatal period such that yes=1 for correct statements and no=0 for incorrect statements. The scores of correct answers were summed, and a higher score was interpreted as a higher level of knowledge of maternal danger signs.
- Knowledge of newborn danger signs:
  this was measured by 12 items related to neonatal danger signs, such that yes=1 for correct statements and no=0 for incorrect statements. The scores of correct answers were summed, and a higher score was interpreted as a higher level of knowledge of newborn danger signs.
- Knowledge of newborn care practice:
  participants were asked to mention the recommended newborn care practice using 7 questions. All the responses were counted, and the higher score indicates a higher knowledge of newborn care practice.
- Attitude toward maternal health services:
  this refers to mothers' feelings toward maternal care practice. Attitude toward maternal care practice was measured by 10 items on a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree. The cumulative scores were used in the analysis once negatively phrased items were reverse-coded. A higher composite

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score indicated a more favorable attitude toward maternal care practice.

- Attitude toward newborn care practice:
this refers to mothers' feelings toward newborn care practices. It was measured by 16 items, which are designed in a 5-point Likert scale format ranging from 1=strongly disagree to 5=strongly agree. The sum score was used in the analysis after reverse coding the negatively worded items. The higher composite score was interpreted as a favorable attitude toward newborn care practice.
- Self-efficacy to practice maternal health service usage:
self-efficacy in practicing maternal care is an individual belief in mothers' ability to perform maternal care practices. It was measured by 10 items designed on a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree. Once negatively worded items were reverse-coded, the sum score was used in the analysis. A score with a high value indicated greater self-efficacy in practicing maternal care.
- Self-efficacy to practice maternal and newborn care:
this refers to an individual belief in one's ability to perform maternal and newborn care practice. It was measured by 9 items, which are designed in a 5-point Likert scale format ranging from 1=strongly disagree to 5=strongly agree. The sum score was used in the analysis after reverse coding the negatively worded items. A score with a high value indicates higher self-efficacy toward practicing newborn care.

Data Collection Procedures and Tools

The baseline survey was conducted in March 2023, while the end-line survey was conducted in February, 2024. Trained interviewers collected data for both the baseline and end-line surveys through face-to-face interviews using a structured questionnaire. The questionnaire addressed various domains, including sociodemographic factors, socioeconomic factors, obstetric history, maternal health service usage, newborn care practice, knowledge about maternal health services, knowledge about maternal danger signs, knowledge about newborn danger signs, knowledge about newborn care practices, attitude toward maternal health services, attitude toward newborn care practice, self-efficacy toward maternal health services, self-efficacy toward newborn care practice, iron supplementation, and maternal and neonatal morbidity. Participants who were lost to follow-up were recorded, along with their reasons for discontinuation and the outcome of their pregnancy. The data were checked for inconsistencies and errors during the data collection period by dedicated supervisors and submitted to the central data management unit.

A total of 10 data collectors and 2 supervisors were recruited during each data collection period. A 2-day training was given for data collectors and supervisors on the questionnaire content, measurements, ethical issues, and how to use the ODK app (during end-line assessment), and they were kept uninformed about cluster allocation.

Data Management

The collected data during the baseline and end-line was checked for completeness at the time of data collection by supervisors, and questionnaires with missing items were communicated with data collectors for correction. Double entry was done for baseline data to identify and manage mistakes during the data entry, while the end-line data were retrieved from KoBo Toolbox. Data cleaning was done to identify the duplicate records and missing and outlier values; to verify that the values were in the proper format and expected range; and to correct the errors. Only the study team has access to the intervention data sets. Information about clusters and participants was not shared with any third party, both during and after the intervention. Moreover, all personal identifiers were removed from the database, and paper-based filled questionnaires were stored in a locked cabinet. Data were stored in a database on a password-protected computer, and only the research team could access it.

Data Analysis Plan

Double-data entry was accomplished using Epi-data (version 4.6, released in 2020; the EpiData Association) and exported to the SPSS (version 25; IBM Corp) for analysis. The report of this study will be made according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth) standards for reporting randomized controlled trials. Exploratory subgroup analysis was done to identify whether the effects of intervention vary with sociodemographic characteristics, socioeconomic characteristics, obstetric history, and psychological factors. To assess the characteristics of the study population through the lenses of different variables, selected data were tabulated by study arms; this helped us to identify variations and similarities among study arms. The summary statistics used for categorical variables were frequencies and percentages. For continuous variables, the mean and standard deviation will be presented.

To observe the effectiveness of mobile phone messaging-based message framing interventions for improving maternal and newborn health service usage, we will use an intention-to-treat approach where all randomized participants will be included in the statistical analysis, regardless of whether they received the intervention or not. A generalized linear mixed model will be used to adjust for both the clustering effect and the participant-level intracluster correction. The outcome variables are assumed to have a multivariable normal distribution. The odds ratio will be used to measure the effectiveness of the intervention on the outcome variable with a 95% CI.

Ethical Considerations

Ethical approval was received from the Jimma University Institutional Review Board (ref no JUIH/IRB/358/23). Participating in this trial was completely voluntary, and women can opt out of receiving the messages by sending "stop" to the domain. Informed consent was obtained for taking part in the intervention, baseline, and end-line assessments. The interviewer read the contents of the informed consent form and outlined the purpose of the study, the institutions and researchers involved, the expectations of women, and the risks and benefits associated with the trial using the local language. Women also get an explanation about their rights as participants and have their questions answered before enrollment.

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Women's phone numbers were kept encrypted, and no one could access them without a server technician and researcher. Codes were assigned to each enrolled woman to ensure confidentiality; mobile numbers were entered into the dashboard anonymously. Data were shared with the research team after removing participants' names. No compensation was provided to participants for taking part in this trial.

Monitoring

Monthly monitoring of intervention implementation was conducted by collecting data through face-to-face interviews using a predefined questionnaire. Participants were asked the number of maternal and newborn information they have received through SMS, the number of messages read, the service they have used following the received message, and any pregnancy outcomes. They were also asked about any barriers that they have faced to receive the messages and the usage of services after receiving messages. Moreover, the functionality and stability of the messaging system were monitored continuously for the duration of the project. Data about the SMSs being sent and delivered were also automatically recorded by the messaging system and checked weekly.

Results

The recruitment of 588 intervention participants and the baseline survey were carried out in March 2023. The intervention was rolled out starting in May 2023 and ending in December 2023. The end-line assessments were conducted in February 2024. We are working on data management, and we expect the analysis to be completed by May 30, 2024. The publication of the results is anticipated in August, 2024.

Discussion

Major Findings

This study aims to evaluate the effectiveness of mobile phone messaging–based message framing interventions for improving maternal and newborn health practices. We hypothesize that increased usage of maternal and newborn care services in the intervention group exposed to mobile-based message framing (gain-framed and loss-framed messages) was comparable to that in the control arm. This trial is designed with the assumption of achieving improvements in key indicators such as 8-time antenatal care visits, increased health facility deliveries, increased postpartum attendance, and improved newborn care practice. Previous studies indicate that mobile phone interventions during pregnancy have a positive effect on maternal health outcomes. For instance, text messaging interventions have shown potential for informing, motivating, and reminding pregnant and postpartum women about timely health care usage, which leads to positive maternal and child health outcomes [40-43].

Our intervention focuses on message framing for the early enrollment of pregnant women on the continuum of care. Pregnant mothers with a GA of 16-20 weeks are preferred based on the World Health Organization's recommendations for early antenatal care initiation. Previous studies evaluating the effectiveness of SMS-based interventions to improve maternal and neonatal health selected pregnant women who had already started antenatal care visits and used health facilities [12,44-46].

Strengths and Limitations

This study uses a cluster randomized controlled trial (CRCT) design to address shortcomings in prior observational and pseudo-experimental studies. This study attempts to minimize contamination by cluster randomization at the health post level. Many previous studies were observational and pseudo-experimental in nature, which have inherent biases because they lack randomization, which leads to inference problems and difficulty in group comparability. This suggests that there is a methodological gap that requires generating more reliable information by using stronger designs such as CRCTs [47-50].

To reduce the risk of incomplete or inconsistent data, supervision of field-based data collection is sustained throughout the entire data collection period. The use of mediation analysis examines the intricate relationship between participants' adherence to the mobile messaging intervention and the observed changes in maternal health service uptake and newborn care practices, offering a comprehensive understanding of its impact. Subgroup analysis is performed to investigate differences in results among various clusters, considering unique contextual factors that may influence the intervention's impact on clusters.

The intervention could have some limitations that should be acknowledged. One limitation is that the study included only pregnant mothers who have mobile phones. Consequently, the findings may not be generalized to all pregnant mothers. Focusing on pregnant mothers who own mobile phones is the drawback of this study, as it has the potential to marginalize those who do not have mobile phones. Another limitation of the study is the failure to assess the cost-effectiveness of the interventions, which is essential for informing resource allocation decisions and promoting their adoption in low-resource settings.

Future research directions could involve scaling up the mobile phone messaging intervention to reach a larger population or exploring additional strategies to complement its effects. Integrating mobile phone messaging interventions within broader health care frameworks could enhance their effectiveness in promoting maternal health service uptake. To ensure the sustainability and long-term impact of mobile phone messaging interventions, it is crucial to integrate them into existing health care systems. This could involve collaborating with local health authorities to develop policies and guidelines for the use of mobile health interventions in maternal and newborn care. Conducting long-term follow-up studies can provide valuable insights into the sustained impact of mobile phone messaging interventions on maternal health service uptake and newborn care practices. Assessing the cost-effectiveness of mobile phone messaging interventions is essential for informing resource allocation decisions and promoting their adoption in low-resource settings.

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Dissemination Plan

The dissemination plan involves publishing results in peer-reviewed journals, presenting the findings at conferences, engaging with local health authorities, and collaborating with community organizations for implementation.

Conclusions

To the best of our knowledge, this study is the first CRCT to evaluate the effectiveness of a mobile phone messaging-based message framing intervention in improving maternal health service uptake and newborn care practice in Ethiopia. The evidence from this study will be crucial for policy makers to scale up as a strategy to reduce maternal and neonatal mortality rates.

Authors' Contributions

GB and HG conceptualized the study and designed the protocol and first draft of the manuscript. ZB, DA, and JN guided the technical design of the protocol. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example gain and loss message types from ten thematic areas.
[DOCX File , 15 KB - resprot_v13i1e52395_app1.docx]

Multimedia Appendix 2
The flow of participants through each stage of the randomized trial, including enrollment, allocation, follow-up, and analysis.
[DOCX File , 35 KB - resprot_v13i1e52395_app2.docx]

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Abbreviations

ANC: antenatal care
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth
CRCT: cluster randomized controlled trial
GA: gestational age
ICC: intracluster correlation coefficient
LMIC: low- and middle-income country
LMP: last menstruation period
mHealth: mobile health
PNC: postnatal care

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Protocol

Design, Develop, and Pilot-Test a Digital Platform to Enhance Student Well-Being: Protocol for a Mixed-Methods Study

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Abstract

Background: Well-being is a multidimensional concept and has been extended to many areas. Student well-being has garnered attention over the last decade due to concerns that have been raised. Digital health interventions have the potential to enhance and improve student well-being.

Objective: The objective of the study is to design, develop, and pilot-test a digital health platform to enhance student well-being.

Methods: A sample size of 5000 participants will be recruited across Gujarat and Tamil Nadu, India. Students will be enrolled from Parul University in Vadodara, Gujarat, as well as Panimalar Medical College Hospital and Research Institute, Panimalar Engineering College, Panimalar Institute of Technology, and Panimalar College of Nursing in Chennai, Tamil Nadu. Current undergraduate and graduate students consenting to participate will be recruited using convenience sampling from these institutes. The study will collect baseline data to construct the student well-being index. Based on the risk profile, a random subset of the population will be provided access to the digital health intervention, which will deliver tailored interactive messages addressing the various dimensions of well-being among undergraduate and graduate students. The eligible study participants will be aged 18 years and older, enrolled in these institutes, and willing to give their consent to participate in the study.

Results: The proposed research is an unfunded study. The enrollment of the individuals in the study began in October 2022. Data gathered will be analyzed using SAS (version 9.3; SAS Institute) and results will be reported as 95% CIs and *P* values.

Conclusions: The proposed study will help to determine the factors affecting well-being among college students and help in designing digital health interventions to improve the well-being of undergraduate and graduate students.

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KEYWORDS

well-being; students; digital interventions; social support; family demands; mental well-being

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Introduction

Background and Rationale

Well-being is a multifaceted concept that encompasses 3 dimensions: mental, social, and physical [1]. According to the World Health Organization, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [2]. Therefore, well-being can be summarized as a positive outcome that constitutes physical, mental, and social stability. It comprises the presence of positive emotions such as happiness and resilience and the absence of negative emotions such as anxiety and depression [3].

Over the last decade, there has been an increased interest in student well-being [4]. The transitional period from school to university puts forward many new challenges and changes for students, such as academic demands, facing new people, making independent choices, and being away from home and social networks. These shifts or changes act as potent stressors in the lives of students [5].

In a survey conducted by the World Health Organization in 21 countries to assess the associations of mental disorders with college entry and attrition, it was found that anxiety disorders were the most prevalent class of disorders, followed by mood disorders, substance disorders, and behavioral disorders [6]. Another cross-sectional study conducted across 30 low- and middle-income countries drew similar conclusions [7]. A study of undergraduate students at a South African university reported minimal to mild symptoms of depression in 87.7% of students and moderate to severe symptoms in 11.2% of students. Similarly, low anxiety was prevalent in 84.2% of students, and moderate to severe anxiety was present in 5.8% of students [8]. Additional studies in Nigeria and Kenya also reported that moderate to severe depression was prevalent among university students [9,10].

For medical education students, the components of a stressful environment include on-call responsibilities, high workload, competitive training, peer pressure, a large volume of content to study, and financial burdens [11]. A meta-analysis reported depression in approximately one-third of medical students globally [12], which may contribute to anxiety, burnout, suicidal thoughts, and substance abuse [11].

In a local context, a survey to assess the perceived stress and psychological well-being of 281 college students from 6 states in India showed a negative effect of perceived stress on their psychological well-being. A higher level of internet addiction negatively affected psychological well-being, whereas perceived social support from friends, family, and significant others was positively associated with well-being among college students [13]. Female students reported a higher level of well-being even though their stress levels were similar to male students [14].

In a study conducted by Jeyaraj et al [15] among college students in Maharashtra, India, stress was observed in 24.4% of students. Moderate to severe stress was experienced by 14.4% of students. Academic factors and lifestyle were significantly associated predictors of stress among college students. Another large survey study in India highlighted that more than 80% of medical students experienced burnout and were at higher risk of mental disorders and lower well-being [16]. This was also corroborated by additional studies that reported high psychological distress, burnout [17], perceived stress [18], poor well-being, stress, and depression in Indian medical students [19,20].

In India, mental health problems are prevalent in the young adult population, and since India is home to the world's largest population of young people, it has become a matter of critical concern [21]. The World Health Organization reported that 8% of the Indian population has common mental disorders, of which 4.5% and 3.5% experience depression and anxiety, respectively [16].

However, conventional evidence-based psychological treatments have certain limitations associated with them, such as lack of access, stigma, and difficulty in affording the services [22]. Additionally, the limited availability of mental health professionals exacerbates the situation [23]. In this scenario, digital health interventions have the potential to address these challenges as they can reach a larger audience, are more cost-effective, and avoid the risk of stigma [24]. Targeted use of technology can be more effective in the health and well-being domain [25]. Various digital interventions, including computer-based [26,27], web-based [28,29], mobile-based (SMS text message–based and app-based), and virtual reality–based [30-32] interventions have been used for depression, anxiety, stress, sleep quality, psychological well-being, and mindfulness.

There is limited research available on digital health interventions in enhancing overall well-being among college students in India [33]. Further studies have shown that use of the health belief model (HBM) for student well-being is effective [34]. Hence, this study aims to explore factors affecting the well-being of students and develop and design a tailored, internet- and mobile-enabled digital health intervention based on the HBM to enhance well-being among college students in Indian settings.

Study Objective

The objective of the study is to design, develop and pilot-test a digital health platform to enhance student well-being. The study aims are (1) to identify multiple determinants and factors impacting well-being among undergraduate and graduate students; (2) to design and develop a digital health intervention based on the HBM, incorporating the findings of aim 1 to address the well-being issues among undergraduate and graduate students; (3) to evaluate the feasibility and acceptance of the proposed digital health intervention; and (4) to evaluate the role of the digital health intervention, as well as the roles of adherence to and engagement with it, in enhancing the well-being of undergraduate and graduate students.

Methods

Study Design and Population

For aim 1, a cross-sectional study will be conducted to identify multiple determinants affecting the well-being of the students. Five thousand participants will be recruited across Gujarat and Tamil Nadu, India. Current undergraduates and graduates will be recruited from Parul University in Vadodara, Gujarat, as well as Panimalar Medical College Hospital and Research Institute,

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Panimalar Engineering College, Panimalar Institute of Technology, and Panimalar College of Nursing in Chennai, Tamil Nadu, using a convenience sampling approach. The participants will be recruited from their respective institutes with prior permission from their departments. The survey will be filled out by the students using their mobile devices or from the computer labs of the institutes. The survey will consist of validated tools, which are described in Multimedia Appendix 1 [35-37].

For aim 2, we will use a mixed methods approach and a quasi-experimental research design to gather data. Baseline data will be collected from aim 1 using predefined questionnaires and validated tools. Additionally, 3 focus group discussions (FGDs) will be conducted at each study site to identify the barriers that students face to manage their well-being. Two focus groups at each site is considered to be ideal [38]. Consenting participants from the baseline survey will be invited via an email to participate in the FGDs; they will then be given access to the mobile- and web-based platform to generate their initial user profiles. The data gathered from user profiles and FGDs will be used to formulate a student well-being index and also used to design and develop a tailored and context-specific digital health intervention (based on the principle of a human-centered approach) to address the well-being issues of the students. The quantitative data collected from the baseline survey and the qualitative factors will help in identifying causal factors in the environment of the students affecting their well-being [39]. The digital intervention will be based on a human-centered approach and will be designed after understanding an analysis of responses generated from the baseline survey and FGDs. The digital health intervention will be designed as per the needs identified from the FGDs and the baseline survey with population health informatics.

For aim 3 and aim 4, we will perform a randomized controlled trial. Based on the well-being index generated, high-risk individuals will be divided randomly into an intervention group and a control group. The digital health intervention will be a mobile- and web-based platform for students designed to provide tailored well-being–related education and awareness. A human-centered approach will be used to design and develop the intervention by incorporating the students' needs and preferences to ensure an optimal technology-enabled intervention [40]. The study will also use the HBM in designing the digital health intervention, where HBM will be used as a framework to aid in the factors that influence implementation and the persistence of students in maintaining well-being. The HBM is one of the most widely used theoretical frameworks for understanding behavioral change. The model holds that an individual's likelihood of adopting and maintaining a new behavior is heavily influenced by their perceptions of the health threat and the behavior being proposed to address that threat [41]. The intervention will include modules for the physical, social, and mental well-being of the students. The study participants will be able to access the personalized, human-centered digital health intervention through their computers or mobile phones depending on the technology platform available to them. The intervention will be tailored and will be delivered via interactive messages addressing the various dimensions of well-being among undergraduates and graduate students. Study participants in the control group will be provided with an educational booklet addressing health information related to student well-being. Pre- and postevaluation of the individuals in the intervention and control groups will be conducted to assess the impact of the digital health intervention. The feasibility, adherence, engagement, and acceptability of the system will be assessed.

Study Eligibility

The eligible study participants will be aged 18 years or older; be enrolled in Parul University, Panimalar Medical College Hospital and Research Institute, Panimalar Engineering College, Panimalar Institute of Technology, or the Panimalar College Of Nursing; have access to a Wi-Fi or internet-enabled device; and consent to participate in the study. Participants younger than 18 years, not enrolled in these institutes, or not providing consent will be excluded from the study.

Data Collection, Data Entry, and Quality Assurance

To ensure efficiency and high-quality data collection and processing, we will (1) use a well-trained team of field-workers, (2) use a clearly defined study manual, (3) conduct weekly meetings with the research team, and (4) maintain logs of all patient contacts. Confidentiality of the information obtained from the participants will be ensured. The information will be accessible to members of the research team only.

Variable Assessment

Sociodemographic Profile

Data will be gathered from the participants on age, gender, income level, education level, region of residence, marital status, children, and religion. The socioeconomic status of the participants' families will be evaluated with an updated version of the original Kuppuswamy Scale [42].

Health Status Profile

The height and weight of the participants will be measured to calculate BMI, as Sarwer and Polonsky [43] suggested that BMI has an impact on well-being. Any self-reported disability will be assessed. Predefined questionnaires will be used to gather the data.

Familiarity With Technology

We will gather data on access to desktop or laptop computers, tablets, and mobile phones, as well as the type of phone possessed, knowledge of texting, and access to and familiarity with the internet. Predefined questionnaires will be used to gather the data.

Health Behavior

Health behavior data will include the consumption of tobacco, use of alcohol, smoking, and sleep duration. Predefined questionnaires will be used to gather the data.

College Profile

Data will be collected on the residential status and prior education of the students (within the city or outside the city). Predefined questionnaires will be used to gather the data.

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Data Security and Privacy

Data security will be maintained by frequent backup in password-protected computers locked in the principal investigator's office. The information will be accessed by the research team only. Locked data will be stored for 5 years from the point of study completion, at which time they will be destroyed [44].

Outcomes

The study will help to identify multiple determinants affecting the students' well-being. Additionally, it will explore the role of digital health interventions in enhancing good health and well-being among the students. The study will also help in designing and developing individualized, tailored, and interactive internet-enabled digital health interventions to manage the well-being of undergraduate and graduate students.

Outcome Variables

The outcomes will be assessed with the tools described in this section.

General Well-Being

The General Well-Being Schedule will be used to gather data. The scale covers 6 dimensions, including anxiety, depression, general health, positive well-being, self-control, and vitality, to measure mental and physical well-being [45].

Perceived Social Support

The Multi-Dimensional Scale of Perceived Social Support will be used to collect the data. It includes subscales for support from family, friends, and significant others to assess perceived social support [46].

Mental Well-Being

Two components will be measured to assess mental wellness: stress and depression. Depression will be measured via the 8-item Patient Health Questionnaire [47] on a 4-point Likert scale that ranges from 0 ("not at all") to 3 ("nearly every day"). Stress will be measured through the 10-item Perceived Stress Scale [48], which ranges from "never" to "very often" on a 5-point Likert scale.

Family Demands

Family demands are measured through a work-family conflict scale. It has 5 items on a Likert scale, from 1 ("strongly disagree") to 7 ("strongly agree") [49].

System Acceptability

System acceptability will be evaluated through the Client Satisfaction Questionnaire–8 to assess the acceptability of the digital health intervention [35].

General Self-Efficacy

General self-efficacy will be evaluated through the General Self-Efficacy Scale [36]. It is a 10-item scale to assess the ability to cope with daily challenging demands or situations in life.

Stigma

The Stigma Scale will be used to assess stigma. It has 42 statements on a 5-point Likert scale, ranging from "strongly agree" to "strongly disagree" [37].

Perceived Ease of Use

The Perceived Ease of Use questionnaire will be used to assess the feasibility of the digital health intervention [50].

Diet and Behavior Scale

A 29-item questionnaire called the Diet and Behavior Scale is used to gauge people's intake of typical dietary components. The Diet and Behavior Scale's first component focuses on the respondent's typical frequency of consumption of common foods and beverages. The answers to the questions are given on a scale of 1 to 5, with 1 being "never," 2 "once a month," 3 "once or twice a week," 4 "most days," and 5 "every day." The second segment is open ended and looks into the normal serving sizes for 11 popular foods and beverages [51].

Other Tools, Follow-Up, and Engagement

Tools other than the Perceived Ease of Use questionnaire and Client Satisfaction Questionnaire–8 will be used before and after the digital health intervention to assess its usefulness. Individuals will be followed up for a period of 3 months at regular intervals to assess adherence to the well-being modules provided in the digital health intervention. Engagement with the digital health intervention will be assessed by monitoring the number of weekly logins, completion of tasks in a timely manner, and submission of regular data.

Data Analysis

The baseline data for generating the well-being profile include sociodemographic profile, college profile, health status profile, familiarity with technology, and health behavior. Outcome variables will be assessed using the General Well-Being Schedule, Multidimensional Scale of Perceived Social Support, Personal Health Questionnaire Depression Scale, Perceived Stress Scale, Work-Family Conflict Scale, Client Satisfaction Questionnaire–8, Perceived Ease of Use questionnaire, General Self-Efficacy Scale, Nutrition Behavior Scale, and Stigma Scale. A descriptive analysis will be carried out using the baseline data; also, cross tabulation of sociodemographic factors with variables gathered from the instruments will be done. Two FGDs will be conducted per site to assess the perception of students on how their well-being can be addressed. Thematic analysis will be done in accordance with AMEE Guide No. 131 for qualitative data collected through FGDs [52]. For continuous variables, means and SDs will be reported, and for categorical variables, frequencies will be calculated. All statistical analysis will be performed using SAS (version 9.3; SAS Institute), and results will be reported as *P* values and 95% CIs.

Project Timeline and Milestones

A detailed study timeline is presented in Table 1.

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Table 1. Scheduled timeline of tasks in the student well-being study.

Task	Months									
	1-2	3	4	5	6-7	8-10	11-13	14-15	16-19	20-24
Development of study protocol and ethical approval	✓									
Baseline data collection		✓	✓	✓						
Focus group discussions and development of intervention					✓	✓				
Deployment of the well-being intervention and recruitment of the target sample into intervention and control groups							✓			
Follow-up data collection							✓	✓		
Postdeployment assessment of intervention								✓		
Review of collected data by the research team								✓	✓	
Data analysis									✓	
Scientific publication										✓
Dissemination (report writing and presentations)										✓

Ethical Considerations

The study, bearing protocol number PMCHRI-IHEC-071, gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration; ECR/1399/Inst/TN/2020) in January 2021 (PMCH&RI/IHEC/2021/078, dated December 13, 2021). Results of the study will be disseminated through national and international conference presentations and peer-reviewed publications. Findings of the study will also be disseminated to local and state officials and policy makers for data-driven, evidence-based decision-making.

The institutional review board–approved informed consent form will be collected from the eligible study participants by the research team. The consent form will include information on the study, the duration of the study, and the benefits of the study results for the participants. Participants who are willing to participate will be enrolled in the study via email. Study participants can withdraw from the study at any time. All data, including withdrawals, will be reported in the final analysis. No monetary compensation will be given for participation in the study.

Results

The proposed research is an unfunded study. The enrollment of the individuals in the study began in October 2022. Data gathered will be analyzed using SAS and the results will be reported as 95% CIs and *P* values. Thematic analysis will be done of the qualitative data from the FGDs. The proposed research study will help in identifying determinants of well-being among college students. It will also help in designing tailored, internet-based, interactive, digital health interventions to enhance student well-being.

Discussion

The research project will help in assessing the factors affecting the well-being of undergraduate students. It will also aid in developing and implementing data-driven, human-centered, interactive interventions to improve overall well-being among undergraduate and graduate students. It will explore the role of digital health interventions in enhancing the good health and well-being of students. Additionally, considering the barriers related to delivery of digital interventions for mental health and the unique needs of Indian college students, it is imperative to fill the research gap and implement research studies to design, develop, and assess the usability, acceptability, and feasibility of digital interventions tailored to students' needs [51,53]. The study will provide an outline of the well-being and also the potential academic stress of college students in India [54].

Data Availability

The data sets generated during and/or analyzed during the current study will be made available by the corresponding author on reasonable request.

Authors' Contributions

All authors have contributed to the design of the study, development of the questionnaire, preparation of the manuscript, and have approved the manuscript for publication.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Full text of instruments used in the study.
[DOCX File , 89 KB - resprot_v13i1e39779_app1.docx]

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Abbreviations

FGD: focus group discussion
HBM: health belief model

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Protocol

Use of Transdermal Alcohol Sensors in Conjunction With Contingency Management to Reduce Alcohol Consumption in People With Alcohol Dependence Attending Alcohol Treatment Services: Protocol for a Pilot Feasibility Randomized Controlled Trial

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Abstract

Background: Wearable technology for objective, continuous, and reliable alcohol monitoring has been developed. These are known as transdermal alcohol sensors (TASs). They can be worn on the wrist or ankle with the sensor pressed against the skin and can measure sweat vapors being emitted from the skin, to record transdermal alcohol concentration (TAC). Previous studies have investigated the accuracy and acceptability of the available TAS brands, but there has been little research into their use in people with alcohol use disorders (AUD).

Objective: This feasibility randomized controlled trial aims to explore the feasibility, strengths, and limitations of using a TAS to monitor alcohol consumption in individuals in treatment for AUD with or without contingency management (CM) to promote abstinence or low-level alcohol consumption.

Methods: The target sample size is 30 (15 randomized to each group). Participants will be recruited through poster adverts at alcohol services. Both groups (control and CM) will wear the TAS (BACtrack Skyn) for 2 weeks in the context of their usual treatment, meeting with the researcher every other weekday. In the last meeting, the participants will complete a postwear survey on their experience of wearing the TAS. The CM group will also receive small financial incentives for low or no alcohol consumption, as measured by the TAS. On days where the TAC peak is below a set threshold (<115.660 g/L), CM group participants will be rewarded with a £5 (US $6.38) voucher. There are financial bonuses if this target is achieved on consecutive days. The researcher will monitor TAC for each day of the study at each research visit and allocate financial incentives to participants according to a set reinforcement schedule.

Results: The first participant was enrolled in June 2023, and the last in December 2023. Data analysis is underway and is estimated to be completed by June 2024. A total of 32 participants were enrolled.

Conclusions: Most TAS brands have had limited application in clinical settings, and most studies have included healthy adults rather than people with AUD. TAS has the potential to enhance treatment outcomes in clinical alcohol treatment. The accuracy, acceptability, and feasibility of TAS for people with AUD in clinical settings need to be investigated. This is the first study to use TAS in specialized alcohol services with diagnosed AUD individuals currently receiving treatment from a south London alcohol service.

Trial Registration: ISRCTN Registry ISRCTN46845361; https://www.isrctn.com/ISRCTN46845361

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KEYWORDS

accuracy; addiction; alcohol; alcohol monitoring; alcohol treatment; contingency management; transdermal alcohol sensors; wearables; mobile phone; transdermal; TAS; wearable technology; alcohol use disorders; AUD; RCT; randomized controlled trial; abstinence; community-based; residential rehabilitation; consumption; alcohol consumption; low-risk consumption

Introduction

Background

Many individuals require specialist alcohol treatment for their alcohol dependence, with the main aim being abstinence, although some may be able to aim for a goal of moderate or low-level alcohol consumption [1,2]. Specialist community alcohol services are free services provided by the National Health Service (NHS), delivered in the community (ie, not residential), offering a range of drug and alcohol treatments. The NHS is the publicly funded health care system in the United Kingdom. Following service engagement and assessment, the first step of specialist alcohol treatment will typically be medically assisted alcohol withdrawal. For people with more severe alcohol dependence, an in-patient withdrawal may be required [3,4]. After this, the treatment will be focused on reducing the risk of relapse, which can include psychosocial or pharmacological interventions and dealing with co-occurring issues that mediate alcohol consumption. These intervention options can include, but are not limited to, individual therapy, group sessions, community-based or residential rehabilitation programs, medications, network therapy, and promoting social support and the 12-step facilitation [5]. In addition to alcohol-specific treatment, individuals may also be diagnosed with other mental health disorders that will require treatment, for example, depression and anxiety [1,6-8]. The treatment options that can be delivered by each service providing specialist alcohol treatment will differ from service to service and will also be influenced by funding and resources [5]. An underlying factor of the alcohol treatment options available is the focus on reducing alcohol consumption and maintaining abstinence by increasing the individual's motivation to achieve this [9-11].

Common tools used by staff to establish a typical drinking pattern include timeline follow back (TLFB) [12] or breathalyzer measurements. However, these methods have limitations. The TLFB is limited in recall bias [13,14], and the breathalyzer is limited in the period it can cover, most likely only detecting if alcohol has been consumed in the past 24 hours or less before test administration. Outside of clinical services, another tool that can be used are other digital forms of alcohol management, such as smartphone apps. These have been identified with the potential to reduce alcohol consumption by tracking and providing feedback on the individuals' behavior toward their goals [15]. However, they are limited by relying on self-report.

Now, transdermal alcohol sensors (TAS) are being developed and tested. These devices can measure alcohol consumption through sweat vapors on the skin and are similar in appearance to a health watch or tracker. TAS could be used to support alcohol treatment interventions, improve patient motivation, and reliably monitor alcohol consumption to provide an accurate and reliable regular data record for an extended period of time. TASs appear to have potential in clinical settings [16-20]. One brand (SCRAM [secure continuous remote alcohol monitoring]) has also been used effectively in the criminal justice system for alcohol-related offenses [21-25]. The SCRAM has been used in the criminal justice system in the United States since 2004 [24] and in England and Wales since 2020 [23].

Interest in TASs as a clinical tool is because they can address the limitations of current tools used to measure alcohol consumption. TAS can record alcohol consumption continuously as transdermal alcohol concentration (TAC) when worn appropriately, which could lead to weeks or months of detailed alcohol monitoring data. TASs have potential benefits and uses at different stages of treatment to provide detailed and accurate data for staff, tangible information to discuss with clients to consider drinking triggers and events, to monitor abstinence from alcohol during detoxification, as well as to enhance motivation for alcohol reduction or abstinence. However, there is currently no way of converting TAC to blood alcohol concentration (BAC) with the BACtrack Skyn [26].

A previous study our research team conducted, using TAS with alcohol-dependent individuals accessing treatment, suggests that patients find TAS acceptable to wear in their day-to-day lives without interference with their usual activities [27,28]. While that study had no aim to reduce alcohol consumption, in the interview, many patients stated that simply seeing the TAS on their wrist made them think about their alcohol consumption. Another study by Alessi et al [29] asked participants to complete a postwear survey after using SCRAM and found that 81% reported that the TAS helped them reduce drinking and that 75% would wear it for longer. The most common suggestions and concerns Alessi et al [29] found were related to the size and side effects of SCRAM. This was less commonly reported in our previous study, but the BACtrack Skyn is much smaller than SCRAM. Other studies looking at the acceptability and feasibility of the BACtrack Skyn support its use as an objective alcohol measurement tool [30] and for assessing alcohol use over an extended time frame (28 days) [31].

Another potential use of TAS in alcohol treatment is to use them as a method of delivering contingency management (CM). CM is an established treatment, recommended by the National Institute of Health and Care Excellence [32], and is effective for a range of substance use treatments [33-36]. However, although initially developed for use with alcohol use disorder (AUD) treatment, it has had limited adoption in routine clinical practice [37,38]. This is due to the nature of alcohol metabolism and its low detectability within the body. After alcohol consumption, the body rapidly metabolizes it, with the majority

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being eliminated by the liver. The other 2%-5% is eliminated through breath, urine, and sweat [39]. This means that alcohol is only detectable in the body for a short period. Currently used methods to detect alcohol in breath, blood, and urine have a relatively short time frame to detect alcohol. Thus, up until recently, to accurately implement CM in alcohol treatment, the individual would require frequent and multiple breath, blood, or urine tests daily to prove reduction or abstinence and correctly achieve CM rewards [36,38,40,41]. The implementation of this is not feasible with staff time and resources, and multiple daily visits would increase the burden on both patients and staff, as well as being potentially invasive. However, with the development of TAS, there is now the possibility to objectively monitor alcohol consumption 24/7 without these barriers [19,20,42-47].

Previous literature has started to explore TAS use to implement CM [19,20,42-47]. These studies found TAS successful in implementing the CM procedure and found that the CM intervention was able to significantly reduce alcohol consumption [19,20,43,44]. Of these studies, none involved alcohol-dependent participants. In total, 2 used recent drinking while intoxicated offenders with differing criteria on alcohol consumption, one AUDIT (alcohol use disorder identification test) score of 4+ [45] and the other AUDIT score of 8+ [42], 2 used human immunodeficiency virus-diagnosed individuals drinking higher levels of alcohol consumption [46,47], and the other 4 were classified as risky or heavy drinks with varying ways to define this [19,20,43,44]. The length of the TAS wear periods and CM length ranged from 1 to 4 months. Previous literature implementing CM with a TAS has used the SCRAM, which measures TAC at 30-minute intervals. The BACtrack Skyn measures every 20 seconds, allowing for a larger amount of data to be used when considering CM rewards and within the statistical analysis.

Including individuals with a current alcohol dependence diagnosis is important because this population may differ in several aspects from populations who drink alcohol but are not clinically dependent. Our study may provide insight into other considerations that laboratory or shorter duration studies do not. For example, participant compliance, motivation, and experience of wearing the TAS over a longer period. This study will explore the feasibility of using a TAS and providing CM to people attending community alcohol treatment services. The design was consistent with a previous study conducted by the same research team [27]. This previous study found that most participants were willing to wear the TAS for longer and that staff believe that to be used in alcohol treatment, it would be more clinically useful to have patients wear the TAS for longer than 1 week. Therefore, we have extended the wear time to 2 weeks in this study.

Objectives and Hypothesis

The primary objective is to explore the feasibility, strengths, and limitations of using a TAS to monitor alcohol consumption in individuals in treatment for AUD with or without CM to promote low-risk consumption or abstinence.

The secondary objectives are to assess the acceptability of the TAS for individuals in treatment for AUD; to compare the accuracy of TAS compared to self-reported TLFB over a 2-week period in an alcohol-dependent clinical population; and to assess the implementation of CM to incentivize alcohol reduction or abstinence.

We will use a randomized controlled trial (RCT) trial design, randomizing participants into the CM or control group (1:1), to investigate this.

Methods

Trial Design

This is a RCT with a 1:1 allocation ratio to control and CM group.

Participants, Eligibility Criteria, and Settings

The site participating in this study is South London and Maudsley (SLaM) NHS alcohol services, from June to December 2023. Specifically, 3 alcohol services: Wandsworth Community Drug and Alcohol Service, Pier Road Project, and the Alcohol Assertive Outreach Team from SLaM. Treatment staff in all services are specialists in the treatment of addiction behavior.

Individuals will be able to participate if they are attending one of the participating services and meet the following inclusion criteria: (1) receiving alcohol treatment for an alcohol use disorder in one of the participating South London alcohol services, (2) aged 18 years or older, (3) speaking English competently, (4) able to meet throughout the study period, (5) not currently participating in any other research trials, and (6) willing to provide informed consent to participate. Individuals will be excluded from participating if they meet any of the following exclusion criteria: (1) current use (past 4 weeks) of any illegal or addictive substances (excluding marijuana and tobacco and nicotine smoking), (2) under 18 years old, and (3) cannot speak English. This study focuses on adults in treatment for AUD; however, it was recognized and advised by staff consultation that if the exclusion criteria included all illegal drugs, including cannabis, this would reduce the number of potential participants within each service significantly. Therefore, it was decided to exclude the current use of any other illegal or addictive substance other than cannabis and tobacco and nicotine smoking.

Ethical Considerations

This study was approved by the Cornwall and Plymouth research ethics committee (REC; reference 23/SW/0066). All participants provided written informed consent after reviewing consent documents with the research staff. Participants will be given a unique study ID that will be used to identify their data throughout the study. Only trained research staff will have access to the key that matches the participants' ID. The key is password-protected and stored on a secure server at King's College London. All participants will provide informed consent and will be aware that they can stop their participation at any point in the study without having to provide a reason to the researcher. All data will be password-protected and hardcopy files will be stored in a locked cabinet at King's College London.

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Intervention

Both groups (control and CM groups) will wear the TAS for the same length of time, meeting with the researcher every other weekday. The TAS is not the intervention being measured but will be used to track participants' alcohol use behavior to determine whether or not they have met the criteria for the CM rewards. The CM rewards are for abstinence or low drinking.

The CM group will be provided with vouchers if this target behavior occurs and is recorded by the TAS. The target behavior is very low drinking or abstinence, as measured by the TAS. The threshold for achieving the target behavior is below 115.660 TAC g/L (air). From here onwards, target behavior will be referred to as low or no drinking (defined as TAC below the set threshold of 115.660). This limit was chosen based on our previous research [48]. We decided to have the target behavior of low or no drinking as the typical amounts of alcohol being consumed by service users are much higher than this amount, and therefore, we considered a reduction to this amount still as an achievement for the service users.

For each day that the target behavior (low or no drinking) occurs, the CM group participants will be rewarded with a £5 (US $6.38) voucher. If target behavior occurs over consecutive days, they will be rewarded with bonus vouchers. If the target behavior occurs every single day for the study period, then they will be rewarded with another additional bonus voucher. In total, the participants could be provided with up to £180 (US $229.72) in CM rewards. The participant will not be eligible for the CM rewards if they remove the TAS for longer than 1 hour. The CM procedure is shown in Table 1.

In this example, day 1 is a Monday. If a participant was recruited on a Wednesday or Friday, the meetings would still occur on a similar schedule, always occurring on Mondays, Wednesdays, and Fridays only. This is to account for Skyn data storage.

All participants (control and CM groups) will additionally be compensated with a £5 (US $6.38) Love2Shop voucher at each meeting for their time and travel expenses reimbursed. All participants will also be given an additional £10 ($1=£0.79 GBP) Love2Shop voucher for returning the TAS at the end of participation to incentivize TAS return.

If the participant wishes to stop wearing the TAS, they will be told to contact the researcher and arrange a meeting to return the TAS. It will be clear that withdrawal will not interfere with their treatment or care at their service.

Table 1. Contingency management (CM) payment procedure plan (total: £180).

Day	Day of the week	CM for low or no drinking per day (£)	CM bonus for consecutive low or no drinking days (£5[a] per day; £)	CM bonus for 14 days low or no drinking (£35 for 14 days; £)
1	Monday	5 (First meeting)	(First meeting)	—[b]
2	Tuesday	5	—	—
3	Wednesday	5 (Second meeting)	10 (Second meeting)	—
4	Thursday	5	—	—
5	Friday	5 (Third meeting)	10 (Third meeting)	—
6	Saturday	5	—	—
7	Sunday	5	—	—
8	Monday	5 (Fourth meeting)	15 (Fourth meeting)	—
9	Tuesday	5	—	—
10	Wednesday	5 (Fifth meeting)	10 (Fifth meeting)	—
11	Thursday	5	—	—
12	Friday	5 (Sixth meeting)	10 (Sixth meeting)	—
13	Saturday	5	—	—
14	Sunday	5	—	—
15	Monday	5 (Seventh meeting)	15 (Seventh meeting)	35 (Seventh meeting)
Sum	—	75	70	35

[a]£1=US $1.28.

[b]Not applicable.

Procedure

Figure 1 shows a flow chart of the study procedure. Participants will be recruited from the 3 SLaM alcohol services and approached by the researcher or service staff. Staff will be aware of the study and inclusion criteria and have participant information sheets to provide to individuals. The research team will then speak to the individual directly, answer any questions, and arrange a meeting if the individual meets the inclusion criteria and is willing to participate. The researcher will also attend group meetings at each service and be able to talk to service users directly if they are willing to be approached, describe the study, and provide participant information sheets.

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Randomization will take place at the first meeting after informed consent is provided. The participant will be enrolled as part of the control or CM group. Both groups will follow the same study procedure, conduct research visits, and wear the TAS. The difference is that the CM group could be provided with additional CM rewards when the target behavior occurs. At the first meeting, the participants will be trained on how to wear the TAS. The research visits occur every other weekday, a total of 7 times; for example, if starting on a Monday, they will meet Monday, Wednesday, Friday, Monday, Wednesday, Friday, and Monday. If the first meeting is on a Wednesday or Friday, the schedule will shift as needed, with meetings only occurring on Mondays, Wednesdays, and Fridays. At each meeting, the next meeting will be arranged, and a reminder text will be sent the day before. This is due to the storage capacity of the BACtrack Skyn TAS. It can store data for approximately 72 hours before data starts to be overwritten. Therefore, meetings must occur regularly to avoid data being overwritten. The TLFB will also be completed at each meeting (meetings 2-7) to record the past 2-3 days since the last meeting. An image of the BACtrack Skyn is shown in Figure 2. In the last meeting, the TAS will be returned, and a postwear survey will be completed. For the CM group, this will include questions on their experience with the CM rewards. The TAS recorded data will be analyzed by the research team and descriptive of missing data, removals (defined as skin temperature <30 degrees Celsius for longer than 2 minutes), and participant TAS adjustments.

Figure 1. Flow chart of the study. Participants will be randomized into the control or CM group at the first research visit. The following research visits will occur every other weekday. In this example, the first research visit would occur on a Monday.

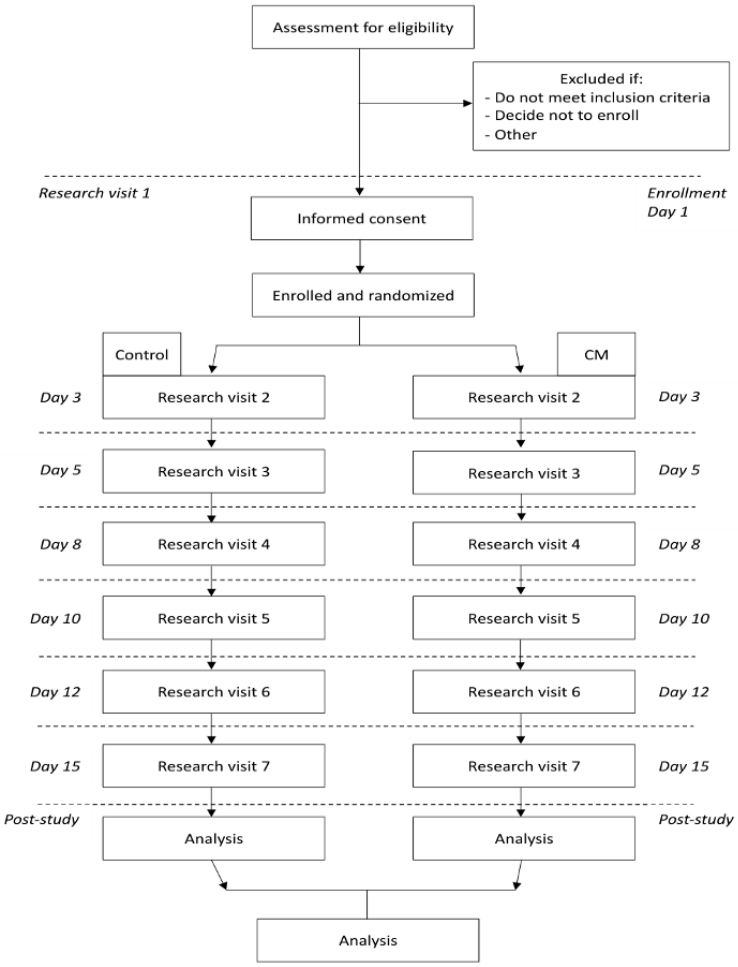

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Figure 2. Image of the BACtrack Skyn (https://skyn.bactrack.com).

Outcomes

For the analysis of assessing the feasibility, strengths, and limitations of using a TAS to monitor alcohol consumption with or without CM to promote low-risk consumption of abstinence, both groups will have feasibility outcomes defined as follows: enrollment (recruitment rate, willingness of participants to enroll, willingness of clinicians to recruit participants); participation (enrolled participants who completed the intervention, attendance rate, response rate, compliance); tampering and malfunction rates (removal without replacement, tampering (turning it off), TAS malfunction, battery issues, number of times a participant had a query that required an extra contact or meeting with the researcher, and number of TAS returned); and the feasibility of using a TAS to measure CM target behavior and the acceptability of delivering CM to patients.

To assess acceptability, both groups will complete a postwear survey on wearing TAS, and those in the CM group will also complete a survey on their experience of receiving CM; these surveys are adapted from Alessi et al [29] and Miguel et al [49], respectively. Finally, to determine TAS accuracy, the TAC data recorded will be compared to the self-reported TLFB.

Measures

BACtrack Skyn

The TAS that will be used is the BACtrack Skyn. It will be worn on the participant's preferred wrist, but they will be allowed to change which wrist they wear it on during the study period. The Skyn will continuously measure the TAC while being worn, as well as skin temperature (Celsius). Output will be viewed at 1-minute intervals. The participants can remove the TAS at any time if they do not wish to wear it and will be required to remove it for bathing as it is not waterproof. The CM group will be told they can remove it once a day for up to 60 consecutive minutes to bathe and still be eligible for their CM reward. If removed for longer than an hour, then they will no longer be able to receive the CM reward, even if the other data suggest no alcohol consumption. If they wear the TAS according to this and the TAC does not increase above our set threshold of 115.660, they will be eligible for the CM reward for that day. We will explore various TAC criteria when defining a drinking event: TAS 15 (TAC>15, >15 minutes), TAS 60 (TAC>15, >60 minutes), and TAS 90 (TAC>15, >90 minutes).

To note, an alcohol drinking day defined by TAC is different from the CM intervention criteria, which allows for a low amount of drinking and has a higher TAC criterion. There are 2 distinctions: those in the CM group at each meeting will have their data examined for meeting the CM rewards criteria, and then in the analysis at the end after all data collection, all participants will have an accuracy analysis conducted where participant days will be defined as alcohol-drinking days (according to TAC/minute criteria) or nonalcohol drinking days.

TLFB

A TLFB will be completed at meetings 2-7 to assess self-reported alcohol consumption and compare it against the TAC data. The TLFB is a calendar-based measure to record self-reported substance use. Each date of the study period was completed at the following meeting. Any reported alcohol consumption on the TLFB will define that day as an alcohol-drinking day. Days will be recorded as 12 AM to 11:59 PM.

Postwear Surveys

Participants will complete a postwear survey on their experience of wearing the Skyn at their last meeting. This survey was adapted from Alessi et al [29]. If they were randomized to the CM group, they would also complete a survey on their CM experience. This study was adapted from Miguel et al [49].

Feasibility

Feasibility is defined by enrolment, participation, device tampering, removals, adjustments, malfunction rates, and the number of TAS returned (Textbox 1).

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Textbox 1. Feasibility outcome definitions.

Enrolment

- Recruitment rate, willingness of participants to enroll, and willingness of clinicians or services to recruit participants.

Participation

- Enrolled participants who attended meetings or intervention, follow-up rate, response rate, compliance, reasons for incomplete participant data (meeting nonattendance, data overwritten, and technical fault).

Tampering

- Tampering with the transdermal alcohol sensor (TAS) to hide alcohol consumption or to stop its recording.

Removals

- Removal (more than 2 minutes where the temperature was <30 °C).

Malfunction

- Device error, missing data due to technical fault, charging issues, and syncing issues.

TAS return

- Number of TAS successfully returned intact.

Sample Size

The target is to recruit 30 participants within 6 months. This sample size was influenced by budget and time constraints and the number of participants considered suitable for meeting and carrying out the study's aims of feasibility, as recommended for pilot studies by Lancaster et al and Browne [50-53].

Randomization

This is a nonblinded study. Participants will be individually randomized into either the control group or the CM group (1:1 ratio). The randomization will be remote and overseen by an independent statistician using a sealed envelope randomization technique. The statistician (an independent researcher not involved in the study) generated a random list with Stata, with each allocation on a piece of A4 paper printed and sealed in the appropriate envelope (numbered 1-30). When a participant is enrolled, the researcher will then open the corresponding envelope to the participant's study ID for group allocation. Therefore, no member of the research team is aware of the group allocation until a participant enrolls on their first research visit.

Recruitment

To achieve adequate participant enrollment and reach the target sample size, we plan to have regular communication with each participating service. We will attend each service regularly to inform staff of the ongoing recruitment and attend service user groups to discuss the research with eligible individuals.

Data Collection and Management

In this study, there are 3 sources of alcohol measurement data collection.

The first is the TAS (BACtrack Skyn model T15). The TAS will collect TAC at 20-second intervals and average the appropriate 3 measurements to provide data at 1-minute intervals. This will be checked by the researcher at each research visit. For the CM group, these data will determine if they meet the criteria for the additional CM rewards. It will be checked to see if any TAC is above the low or no drinking threshold as well as for any removals. If the TAS is removed for periods of longer than 1 hour, then the participant will not be eligible for the CM rewards.

The second is the self-reported TLFB [12]. This will be used in the analysis to compare TAS accuracy to the TLFB.

The third potential alcohol collection method will be a breathalyzer. This study uses the Lion Alcometer SD-400 (Lion) with a fuel cell sensor (standard version) with a measuring range of 0.02-2.0 mg/L BrAC, an operating range of –5 to +45 C, and is calibrated 1 week before recruitment starts. The breathalyzer will only be used if the TAS malfunctions or does not record any data. We do not expect the TAS to malfunction, but if the TAS, for any reason, does not record hours of TAC data, we do not want this to impair the participants' chance of meeting the criteria for the CM vouchers. If the TAS has not recorded the data, we will first ask the participant for a TLFB and if they have consumed alcohol in the past 2 days. If they respond "Yes, I have consumed alcohol," then it will be marked as an alcohol-drinking day. If they say "No, I have not consumed alcohol," we will ask them to do a breathalyzer to confirm low BrAC data. If the BrAC is below the United Kingdom drink drive limit, they will still be able to meet the criteria for the CM vouchers.

The data from each participant will be entered and coded as it is collected and will start after the first participant is enrolled. Personal data will be regarded as strictly confidential. Any data leaving the site will identify participants by their initials and unique identification code only. The study will comply with the Data Protection Act, 1988. The data custodian for this study is King's College London. This data will be collected by EB.

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Statistical Analysis

Baseline and demographic variables will have descriptive statistics reported. Outcome measures will be conducted by intervention groups (control and CM) and then compared between the groups.

We will report on the feasibility measures stated earlier. Descriptive data from the postwear survey will be reported, and statistical comparisons of the postwear survey responses between groups will be performed using 2-tailed *t* tests. In instances where the data are ordinal or the assumptions of the paired samples *t* test are not met, the nonparametric alternative to the paired samples *t* test will be used, the Mann-Whitney *U* test. Given the small sample size and nature of this pilot study, the primary purpose of these results will be to inform the potential barriers and limitations and challenges faced in implementing CM for future work.

To assess TAS accuracy, the TAC data will be compared against the TLFB to address the secondary outcomes of accuracy. The analysis will focus on the sensitivity, specificity, positive predictive value, and negative predictive value of TAC compared to TLFB as the gold standard. Sensitivity in detecting alcohol events and specificity in classifying an alcohol-drinking day versus a nonalcohol-drinking day will be assessed. Recorded drinking and abstinent days will be analyzed using Spearman Rank correlations comparing different alcohol-drinking day TAC criteria. All statistical analyses will be conducted using SPSS (version 28; IBM Corp).

Adverse Event Protocol

A data monitoring committee was not required for this study because it was a small pilot study. A data monitoring committee was not required in the ethical approval process.

Some previous literature reports slight irritation from wearing the TAS in certain activities, which the participant will be made aware of. There are no other expected medical complications. In the previous study conducted with the same design (minus CM) over 1 week instead of 2, there were no serious adverse events (SAE) reported by participants. The TASs are low risk for medical complications. There were side effects reported by 6 participants, which included rash and irritation of the skin from wearing the TAS. All participants were made aware that if the TAS remained uncomfortable, they could remove it. All participants said that after a day, irritation reduced and no further action was needed. Any SAE occurring during the study will be reported. In the case of a SAE that is related to the study or unexpected, the chief investigator will email the REC using the nonclinical trial of an investigation medicinal product safety report to the REC form. This would be sent within 15 days of the chief investigator becoming aware of the event. The research team includes supervision from a medical doctor.

Results

This study has been designed to explore the feasibility, strengths, and limitations of using a TAS to monitor alcohol consumption in individuals in treatment for AUD with or without CM to promote low-risk consumption or abstinence. Our findings will contribute to the growing TAS literature on TAS implementing CM, expanding the literature to include the investigation of the BACtrack Skyn used to deliver CM in South London alcohol services. We completed the trial in December 2023; we recruited 32 participants; data analysis is underway; and the results are expected to be published by December 2024.

Discussion

We hypothesize that TAS-delivered CM will be feasible to deliver and will be well-liked by participants. We anticipate that the TAS will be acceptable to wear for a 2-week period, with little to no challenge or side effects experienced. Side effects could possibly be related to the strap irritation against the wrist. In addition, we predict that the TAS will be more accurate in recording alcohol drinking days compared to self-reported drinking days.

Previous literature has started to investigate the accuracy, feasibility, and acceptability of TAS use and how TAS could be used to implement CM [19,20,42-46,54]. While previous evidence supports TAS accuracy, feasibility, and CM implementation with populations that range from social to heavy drinkers as defined by AUDIT scores and the NIAAA [55], there is yet to be a TAS study conducted in specialist alcohol services, particularly in the United Kingdom. To our knowledge, this is the first trial to establish the feasibility of TAS implementing CM, with clinically diagnosed alcohol-dependent individuals accessing treatment in the United Kingdom. The previous literature with TAS and CM has used the SCRAM [19,20,42-46,54]. This study will be the first to use the BACtrack Skyn for this purpose. There are 2 main differences between using SCRAM and BACtrack to deliver CM. The first is that SCRAM has longer data storage and can be downloaded remotely using a home phone landline or modem, allowing these studies to have weekly or less frequent research meetings but still check the data daily to deliver CM. The second is that SCRAM has an established alcohol event detection system to alert the researcher if there has been alcohol consumption. The BACtrack does not have this, and we had to determine a threshold for low drinking to use as CM eligibility for this study. These 2 SCRAM features may make it more feasible and less time-consuming and resource-intensive to deliver CM. However, the SCRAM is far bigger, bulkier, less stylish, and worn on the ankle, with a similar appearance to a house arrest monitor. This makes the SCRAM less suitable for use within clinical settings than a wrist-worn TAS, such as the BACtrack Skyn. Therefore, it will be useful to see how Skyn compares to the SCRAM to deliver CM and if this TAS brand too is feasible for this purpose.

Previous work by this research team demonstrated the acceptability of the BACtrack Skyn over 1 week with adults accessing treatment for alcohol dependence and a high correlation between the TAS and self-report [27,28]. This present protocol follows a similar design but over a slightly longer time (2 weeks rather than 1) and with the addition of the CM component. Therefore, due to the promising results of previous studies, we predict a similar high recruitment, attendance, and compliance among participants.

Our results will be of high relevance due to the increase in interest in the TAS field. Most of the TAS literature is being

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conducted in the United States with individuals without an alcohol dependence diagnosis. Therefore, this study will be highly important in determining whether the successful data shown in other literature translates to this population. It addresses a gap in the literature. Specifically, this pilot feasibility RCT will offer initial insights into the use of a wrist-worn TAS to monitor alcohol consumption and deliver CM for low or no drinking with an AUD population who are accessing treatment. Earlier studies have shown that the SCRAM ankle-worn TAS was feasible to implement CM, but the key difference in the removability of the BACtrack needs to be investigated. TASs provide a potential option to address the current barriers to implementing CM for alcohol treatment. TAS also has the potential to help adults accessing alcohol treatment to monitor, motivate, and reduce their alcohol consumption and maintain rates of abstinence.

This study will aim to determine the feasibility of conducting this study on a larger scale and any facilitating or barrier factors that should be considered in a larger study. For patient care, if shown to be effective, it will be important to consider future implementation within alcohol services as an option for treatment, with the necessary further investigation.

Strengths

This study aims to demonstrate the feasible use of BACtrack Skyn over 2 weeks with individuals currently diagnosed with alcohol dependence and receiving alcohol treatment. Participants will wear the TAS in their natural settings, unsupervised. While the objective of this study is to assess the feasibility of a larger trial, the data collected will be able to provide more evidence of how this population wears, uses, and experiences a TAS. The study findings collected indicate high meeting attendance and TAS return rates, and no participants needing additional training for using the TAS after the baseline. This study's results suggest continued support for the use of TAS within the population.

Limitations

Participants will only be recruited if they are willing to wear the TAS from the start of the study period, but if during the study they change their mind, they can remove or stop wearing it. This means that no participants will be recruited who are not willing to attempt wearing the TAS. While this is not a limitation in some considerations, as TAS would be a voluntary treatment option for service users if implemented in services, it does mean that the postwear survey findings may be skewed more positively. Only those who were interested and willing to wear the TAS have the chance to complete the postwear survey at the end of the 2 weeks. However, participants being willing to wear the TAS for the study does not necessarily mean they are positive about the technology or that they will have a good experience wearing it. Therefore, while we note that the study design does exclude those who are not initially willing to attempt wearing a TAS, this may reflect a truer view of service users who would try wearing the TAS as part of alcohol treatment if TAS were to be implemented in clinical settings.

This trial hopes to add clinically relevant information about the use of a wrist-worn TAS to deliver CM to adults accessing alcohol treatment and determine the feasibility of this design for a future, larger trial. Of importance, this trial will be the first to use BACtrack Skyn to deliver CM and to deliver CM with a TAS within South London alcohol services.

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Data Availability

The research team, EB, PD, SP, and CD, only have access to the final trial data set. The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

EB was involved in conceptualization (equal), methodology (equal), analysis (lead), investigation (lead), resources (lead), data curation (lead), visualization (lead), project administration (lead), and writing (lead) and revising the article (lead); PD was involved in conceptualization (equal), methodology (equal), supervision (equal), and revising the article (equal); SP was involved in conceptualization (equal), methodology (equal), supervision (equal), and revising the article (equal); CD was involved in conceptualization (equal), methodology (equal), supervision (equal), and revising the article (equal).

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 275 KB - resprot_v13i1e57653_app1.pdf]

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Abbreviations

AUD: alcohol use disorder
AUDIT: alcohol use disorder identification test
BAC: blood alcohol concentration
CM: contingency management
NHS: National Health Service
RCT: randomized controlled trial
REC: research ethics committee
SAE: serious adverse event
SCRAM: secure continuous remote alcohol monitoring
SLaM: South London and Maudsley
TAC: transdermal alcohol concentration
TAS: transdermal alcohol sensor
TLFB: timeline follow back

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Protocol

Smartphone-Based Smoking Cessation Intervention (OKquit) for Oklahoma Tobacco Helpline Users: Protocol for a Randomized Controlled Trial

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Abstract

Background: Tobacco quitlines provide effective resources (eg, nicotine replacement therapy, smoking cessation counseling, and text and web-based support) for those who want to quit smoking in the United States. However, quitlines reach approximately only 1%-3% of people who smoke each year. Novel, smartphone-based, and low-burden interventions that offer 24/7 access to smoking cessation resources that are tailored to current readiness to quit may increase appeal, reach, and effectiveness of smoking cessation interventions.

Objective: This study will examine the efficacy of OKquit, a low-burden smartphone-based app for smoking cessation.

Methods: Approximately 500 people who smoke cigarettes and access the Oklahoma Tobacco Helpline (OTH) will be randomized to receive standard OTH care (SC) or SC plus the novel OKquit smartphone app for smoking cessation (OKquit). All participants will use a smartphone app to complete study surveys (ie, baseline, 27 weekly surveys, brief daily check-ins, and 27-week follow-up). Upon completion of daily check-ins and weekly surveys, participants will receive either trivia type messages (SC) or messages that are tailored to current readiness to quit smoking and currently experienced lapse triggers (OKquit). In addition, those assigned to receive the OKquit app will have access to on-demand smoking cessation content (eg, quit tips, smoking cessation medication tips). It is hypothesized that participants assigned to OKquit will be more likely to achieve biochemically verified 7-day point prevalence abstinence than those assigned to SC at 27 weeks post enrollment. In addition, participants who use more OTH resources (eg, more cessation coaching sessions completed) or more OKquit resources (eg, access more quit tips) will have greater biochemically verified smoking cessation rates.

Results: Data collection began in September 2022 and final follow-ups are expected to be completed by May 2025.

Conclusions: Data from this randomized controlled trial will determine whether the OKquit smartphone app combined with OTH care will increase smoking cessation rates over standard OTH care alone. If successful, OKquit could provide tailored intervention content at a fraction of the cost of traditional interventions. Furthermore, this type of low-burden intervention may offer a way to reach underserved populations of adults who smoke and want to quit.

Trial Registration: ClinicalTrials.gov NCT05539209; https://clinicaltrials.gov/study/NCT05539209

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International Registered Report Identifier (IRRID): DERR1-10.2196/56827

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KEYWORDS

smoking cessation; helpline; just-in-time adaptive intervention; mobile application; smartphone-based; mobile health; tobacco

Introduction

Cigarette smoking continues to be the leading cause of preventable disease and death in the United States [1]. Recent estimates indicate that approximately 11.5% of adults in the United States smoke cigarettes [2]. According to the Centers for Disease Control and Prevention, smoking-related mortality accounts for as many as 480,000 deaths annually in the United States [3]. In 2004, the National Cancer Institute and the Centers for Disease Control and Prevention collaborated to establish a national telephonic portal for tobacco cessation quitlines using a toll-free number, 1-800-QUIT-NOW. This portal works by connecting callers directly with their appropriate state quitline. The effectiveness of tobacco quitlines has been well established in the literature [4-7]. In fact, both the 2008 US Public Health Service Clinical Practice Guideline and the 2020 Smoking Cessation Report of the Surgeon General endorsed state quitlines as an evidence-based method for tobacco cessation [1,8].

The Oklahoma Tobacco Helpline (OTH) was launched in 2003 to provide telephone-based tobacco cessation services to Oklahomans who want to quit smoking. The helpline is primarily funded by the Oklahoma Tobacco Settlement Endowment Trust to offer free, statewide services. OTH offers a variety of cessation services including phone counseling, automated email and text-based support, and nicotine replacement therapy (NRT, ie, nicotine patches and lozenges or gum) [9]. Over the past 2 decades, more than 490,000 Oklahoma tobacco users have received services from the program [10]. The North American Quitline Consortium has repeatedly ranked OTH as a leader in state-supported tobacco quitlines. In fact, between 2019 and 2022, the OTH had the highest reach of any US state quitline [11]. Despite its impressive ranking compared with other quitlines, OTH reaches only 3.1% of all Oklahomans who smoke annually, which leaves a large majority of Oklahomans who smoke unreached by OTH services [12].

It has been suggested that smoking cessation interventions should focus on particular difficulties that smokers are likely to encounter as they transition from being not ready to quit in the next 30 days to maintaining a successful quit attempt (eg, see Transtheoretical Model [13-15]). The Transtheoretical Model has stimulated a tremendous amount of addiction research; however, some limitations have constrained its use [16]. More recently, the Phase-Based Model (PBM) of cessation treatment has been proposed which includes four cessation phases: (1) motivation, (2) precessation, (3) cessation, and (4) maintenance [17]. The PBM suggests that specific challenges and opportunities present themselves in each phase of a quit attempt and treatments should be “phase tuned” to address these challenges and opportunities.

Smartphone-based ecological momentary assessments (EMA) are used to capture an individual’s behaviors and experiences in their natural environments [18]. EMA data have been used to tailor health behavior change interventions to an individual’s needs in real time [19-22]. For example, EMA data have been used to develop a smoking lapse risk estimator that identified 80% of all smoking lapses within 4 hours of the first lapse [23]. The Smart-Treatment (Smart-T) app offered on-demand features and used this lapse risk estimator to tailor smoking cessation messages to the current needs of socioeconomically disadvantaged adults in real time [19,20]. Research has indicated that urges to smoke, stress, and easy access to cigarettes were significantly reduced after tailored messages were delivered via the Smart-T app [24].

This randomized controlled trial aims to examine the impact of an adjunctive smartphone-based smoking cessation intervention (OKquit) combined with standard care (SC) by the OTH versus OTH care alone on biochemically verified smoking abstinence 27 weeks after study enrollment. This randomized controlled trial will also examine the impacts of OTH service engagement and use of OKquit intervention content on smoking abstinence and key lapse risk factors. To our knowledge, no study has examined whether low-burden app-based adjunctive interventions can improve state-based smoking cessation quitline quit rates.

Methods

Ethical Considerations

The University of Oklahoma Health Sciences Center institutional review board approved the protocol presented in this paper (reference number 14792). This trial is registered at ClinicalTrials.gov (NCT05539209). All participants provide informed consent, are notified that they can earn up to US $225 for completing study measures, and that they can withdraw from the study at any time without consequence. Data sets are deidentified via a subject identification number.

Study Eligibility

Participants will include approximately 500 adults who smoke cigarettes and access the OTH (ie, phone or web) seeking smoking cessation treatment. Participants are eligible for the study if they meet the following criteria: (1) demonstrate interest in participating in this study by giving approval to the OTH provider to share contact details with the study research team, (2) provide proof of a valid Oklahoma residential address (eg, sending a text message of their photo ID or a photo ID along with a piece of stamped mail that was sent to them), (3) score 4 or higher on the Rapid Estimate of Adult Literacy in Medicine—Short Form (REALM-SF) [25] indicating greater than sixth-grade English literacy level, (4) are willing to quit smoking within 21 days after the randomization phone call, (5)

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currently smoke 5 or more cigarettes per day, (6) agree to complete daily 10- to 30-second app-prompted check-ins and 27 weekly 3- to 5-minute surveys on their personal smartphone, (7) own an active Android smartphone that is compatible with the Insight platform [26], (8) agree to install the Insight application onto their personal phone, (9) are 18 years of age and older (participant age has ranged from 18 to 80 years in similar trials with most participants reporting that they are 40-50 years of age), and (10) agree to complete the 27-week postrandomization follow-up assessment (which includes biochemical verification for those who report smoking abstinence).

Procedure

Individuals who contact the OTH for smoking cessation services via the phone or web are asked whether they are interested in participating in a smoking cessation research study. Contact information for interested individuals is shared with OKquit research team members who then send a web-based Research Electronic Data Capture (REDCap) study screener link to these individuals. Those who complete the 5-minute REDCap screener and meet the initial study inclusion criteria then complete an enrollment call, which includes the informed consent process and a full study eligibility assessment. Those who enroll in the study receive instructions about how to download the Insight app onto their personal smartphone, and they are given 7 days to complete the 30-minute app-based baseline survey. Following completion of the baseline survey, research staff contact participants to randomize them into an intervention group. Randomization is stratified based on self-reported race and ethnicity (non-Hispanic White vs minoritized race and ethnicity), biological sex at birth (male vs female), and number of cigarettes smoked per day (20 vs ≥20). During the randomization call, all participants are asked to use the app to select a quit date within the next 21 days, are given instructions on how to access intervention content, and are instructed on how to complete the prompted daily check-ins and weekly surveys. Following randomization, participants interact with their assigned intervention for the 27-week study duration. Those who report abstinence from smoking during the 26th weekly survey are mailed a Bedfont carbon monoxide monitor that pairs with the Insight app by pressing the power button on the device, and they are asked to submit a breath sample for abstinence verification. Participants are also prompted to complete a 27-week follow-up assessment via the Insight app. The study flow is shown in Figure 1.

During the randomization call, research staff review the "App Instructions" button, which explains all app features (see Figure 2), walk participants through the schedule of daily check-ins and weekly surveys, and explain that participants will receive a US $5 for completing each weekly survey. The US $5 weekly survey is available on Saturdays via a button in the app and via app prompts. When participants do not complete the weekly survey, research staff contact them via text, call, or email to check in and remind them of the importance of completing the daily check-ins and weekly surveys. The day after randomization, the app begins to prompt a brief daily check-in 30 minutes after waking, and participants select up to 5 additional brief check-ins they would like to receive for that day. All participants are prompted to complete the daily check-ins for the entire 27-week study duration.

Figure 1. Participant flow through the OKquit study. OTH: Oklahoma Tobacco Helpline; REDCap: Research Electronic Data Capture.

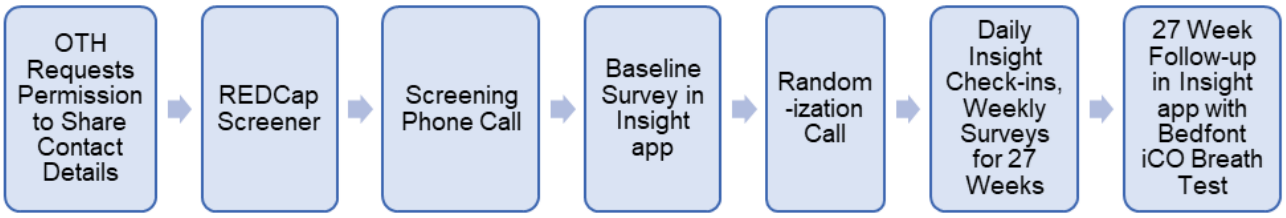

Figure 2. OKquit app home screen by Quit Phase. The red boxes indicate app features that are available only to the OKquit group. Features not in red boxes are available to all participants.

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After initial randomization into the study and after clicking the "Set New Quit Date" button during the 27-week study period, all participants move to the Pre-–Quit Phase. Participants remain in the Pre–Quit Phase for up to 21 days (this duration is determined by the participants when they set their quit date). After setting a new quit date, the participants gain access to an app home screen that provides free smoking cessation resources including a one-click call to the OTH (both groups) and additional OKquit app resources (OKquit group only; see Figure 2). Instructions for phase-specific features are available for review at any time via the "App Instructions" button on the app home screen. During the Post–Quit Phase, the participants continue to have access to the free smoking cessation resources and additional OKquit app features through the Post–Quit Phase home screen (see Figure 2). On the morning of the quit date, the participants are prompted to complete a quit date assessment and are provided instructions about the Post–Quit Phase app features. In this phase, the participants complete up to 6 brief daily check-ins, a weekly survey, and are asked to complete slip assessments if or when they lapse. During the weekly survey, participants are asked whether they have smoked in the past 7 days. Their response to this item determines what phase they will move to next. If the participants report they have not smoked, they are asked, "How LIKELY is it that you will NOT smoke in the NEXT MONTH?" If they respond less than 8 on a 1-10 scale, they remain in the Post–Quit Phase. If they respond 8 or more, they move to the Maintenance Phase. If they report that they have returned to smoking, they are asked, "Right NOW, are you ready to get back on the wagon and set a new quit date within the next 21 days?" If they answer no to this question, they are moved to the Motivation Phase.

During the Maintenance Phase, the participants complete daily check-ins, weekly surveys, and are asked to complete slip assessments if or when they lapse. After reporting a lapse, the participants are asked whether they want to continue the quit attempt. Participants who choose to end their quit attempt are moved to the Motivation Phase. Those that choose to continue the quit attempt remain in the Maintenance Phase. In addition, all participants can click the "Set New Quit Date" button on the app home screen to change their quit date or set a new quit date at any time. Finally, during the weekly survey, the participants are asked whether they smoked within the past 7 days. If they indicate that they have smoked, they are asked whether they are ready to set a new quit date. Participants who choose a new quit date are moved back into the Pre–Quit Phase or the Post–Quit Phase. Participants move into the Motivation Phase when they report a lapse and want to end their quit attempt. Motivation Phase participants who use the "Set New Quit Date" button to set a quit date move to the Pre–Quit Phase or the Post–Quit Phase.

Study Conditions

Those who are eligible and enroll in the study are randomly assigned to 1 of 2 conditions: Standard OTH Care (SC) or SC plus the OKquit intervention.

Standard OTH Care (SC) Condition

Standard OTH services, including NRT (eg, nicotine patches, gum, and lozenges), phone-based counseling, and web-based intervention services are available to all participants. SC participants are prompted to complete brief daily check-ins and weekly surveys through the Insight app. In addition, SC participants have access to an on-demand one-click "Call Oklahoma Helpline" feature in their app. SC participants are able to advance through the 4 PBM phases (ie, Motivation, Pre–Quit, Post–Quit, and Maintenance); however, they do not receive tailored messages after each weekly survey or daily check-in. Instead, SC participants receive "factoid" or trivia-type messages at the completion of each check-in or weekly survey. These factoid messages serve as an attention control (see Table 1).

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Table 1. Message types and examples.

Message level	Phase/group	Example
1	Motivation (OKquit)	First name, after quitting smoking, ex-smokers report lower levels of stress than when they were smokers.
2	Pre-Quit (OKquit)	First name, after you quit smoking, you will be tempted to lapse. Reduce temptation by removing ashtrays, lighters, matches, and cigarette butts. These items can trigger cravings and reduce motivation for staying quit.
3	Post-Quit: Low Risk for Imminent Lapse (OKquit)	First name, sometimes people save a pack of cigarettes (or even a few cigarettes) "just in case" or to prove they have the willpower to not smoke. DON'T! This just makes it easier to start smoking again!
4a: Stress	Post-Quit/Maintenance: High Risk for Imminent Lapse (OKquit)	First name, right now, it may feel like smoking would be enjoyable. However, you will feel worse later on if you do smoke now. You can get through this time without smoking.
4b: Urge	Post-Quit/Maintenance: High Risk for Imminent Lapse (OKquit)	First name, when you crave a cigarette, focus on a happy memory and get away from it all for a moment. Concentrate on that memory and nothing else.
4c: Cigarette Availability	Post-Quit/Maintenance: High Risk for Imminent Lapse (OKquit)	First name, you may be tempted to smoke when you see someone smoking or smell smoke. Do something to keep your mind off smoking. Listen to music, read, call a supportive friend, or take a walk.
4d: Cessation Motivation	Post-Quit/Maintenance: High Risk for Imminent Lapse (OKquit)	First name, you are setting a great example for children and others in your life! Congratulations on quitting smoking!
5	Maintenance: Low Risk for Imminent Lapse (OKquit)	First name, bored? Consider going to the movies or the mall—smoking is forbidden in most indoor places.
6	Post-Quit Recently Lapsed (OKquit)	First name, most smokers try to quit multiple times before they kick the habit for good, keep on trying!
7	SC[a]	It would take almost 23 million ping pong balls to fill a 747.

[a]SC: standard care.

OKquit Condition

OKquit participants have access to all SC intervention features and app content and complete the same daily check-ins and weekly surveys as the SC group. However, OKquit participants have access to several additional features (see details in the Automated Messages and On-Demand Content sections).

Automated Messages

During each of the daily check-ins and weekly surveys, OKquit participants receive intervention content that is tailored to their current quitting phase (ie, Motivation, Pre-Quit, Post-Quit, and Maintenance; see Figure 2 for screenshots of the OKquit app by study phase), current level of risk for imminent lapse (ie, Cessation and Maintenance Phases only), and currently reported smoking lapse risk factors (ie, Cessation and Maintenance Phases only).

More than 900 unique messages have been embedded into the OKquit app. Messages were taken from a message bank that was developed by this research team and have been evaluated by 6 tobacco experts [27]. Table 1 provides a summary of the various message types, the phases that messages are available or used, along with example messages. All messages begin with the participant's first name. One message is delivered at the end of each check-in and weekly survey (up to 6 per day). Level 1 messages are presented during the Motivation phase. These messages aim to increase motivation and readiness to quit smoking. Level 2 messages are presented during the Pre–Quit Phase. These messages consist of content that aims to prepare the participants for their upcoming quit attempt. During the Post–Quit and Maintenance Phases, the participants receive personalized automated messages based upon their current risk of imminent smoking (a complete description of the lapse risk estimator is presented elsewhere [23]). When participant responses indicate a low degree of risk for smoking lapse during the Post–Quit Phase, level 3 messages are presented. Level 3 messages provide general coping strategies for lapse triggers that are commonly encountered early in quit attempts. When participants report that they smoked the day prior, or they indicate that they have more than 0% likelihood of smoking that day, level 4 messages are delivered. Level 4 messages provide suggestions on ways participants could cope with 1 of 4 currently experienced smoking lapse triggers (ie, easy access to cigarettes, high stress, high urge, or low motivation for cessation). Level 5 messages are delivered during the Maintenance Phase when the app algorithms indicate low risk for imminent lapse. Level 5 messages provide general advice on sustaining longer-term abstinence. If a participant reports multiple current triggers, 1 message is delivered in this order of priority: easy access to cigarettes, high stress, high urge, or low motivation for cessation. This order is based on findings from our previous research [19,20,23,24]. Specifically, variables that are better at indicating high risk for imminent lapse are given higher priority than variables that are less strongly linked with imminent lapse. When a participant initiates a Slip assessment, a level 6 message is presented at the completion of the assessment. Level 6 messages focus on encouraging participants to resume smoking abstinence.

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On-Demand Content

OKquit participants have access to various on-demand features available through the smartphone app home screen. The following features are accessible 24 hours a day for 27 study weeks and include (1) the "Quit Tips" button that offers a menu of treatment-related messages, relaxation exercises, and distraction videos, (2) the "Medication Tips" button that provides information about common smoking cessation medications (eg, nicotine gum, patch, and lozenges), such as medication use tips and common medication side effects, and (3) the "Additional Resources" button that provides helpful information and website links to useful resources (eg, COVID-19 tests, food, housing, and job placement resources). When a participant clicks the "Quit Tips" or "Medication Tips" buttons, a menu of options appears (see Figure 3 for menus and example messages).

Figure 3. Quit Tips and Medication Tips Menus and examples available in the OKquit app.

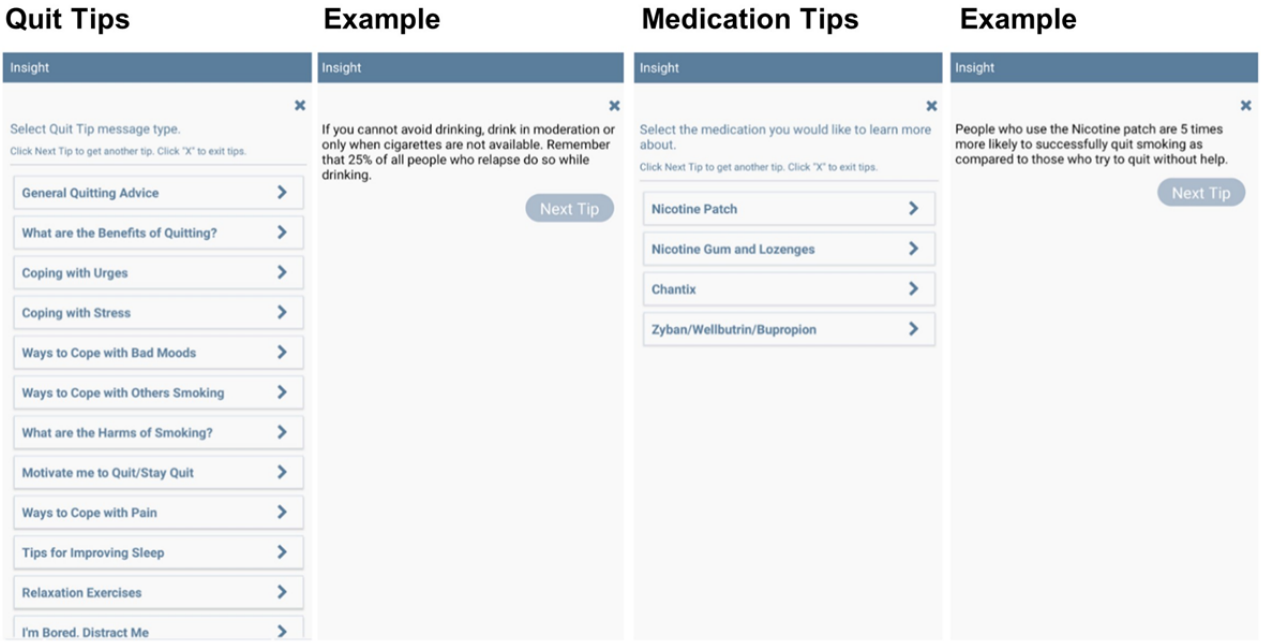

Measures

Overview

The initial prescreener survey is completed via REDCap. The screener collects individual contact information and demographic information (eg, age, race, and biological sex at birth), average cigarettes smoked per day, and level of desire to quit smoking. The baseline assessment (30 minutes), weekly surveys (3-5 minutes each), daily check-ins (10-30 seconds), and 27-week follow-up assessment (20 minutes) are collected via the Insight app. See Table 2 for study assessments and administration schedule. For daily check-ins and weekly surveys, the phone rings and vibrates to prompt the participant to complete the assessment. If the participant does not respond after 5 prompts, the check-in/survey is automatically rescheduled up to 3 times 15 minutes later. Assessments collect information about several factors related to smoking, smoking lapse, and health. Participants are instructed to self-initiate "About to Slip" and "Already Slipped" assessments and to initiate the "Set New Quit Date" assessments when they want to set a new quit date. Each check-in and survey are date-, time-, and geolocation-stamped for future examination.

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Table 2. List and timeline of study measures.

Measure	Screener	Baseline	Follow-up
Screening Questionnaire	✓		
Phone Call Screener	✓		
Rapid Estimate of Adult Literacy in Medicine—SF (REALM) [25]	✓		
Tobacco History Questionnaire		✓	✓
Heaviness of Smoking Index [28]		✓	✓
Self-Efficacy Scale/Confidence [29]		✓	✓
Demographic/Background Information Questionnaire		✓	
MacArthur Scale of Subjective Social Status [30]		✓	✓
Overall Anxiety Severity and Impairment Scale (OASIS) [31]		✓	✓
Overall Depression Severity and Impairment Scale (ODSIS) [32]		✓	✓
The Patient Health Questionnaire-4 (PHQ-4) [33]		✓	✓
Financial Strain Questionnaire [34]		✓	
Perceived Stress Scale [35]		✓	✓
The Everyday Discrimination Scale (Brief version) [36]		✓	
The Pandemic Stress Index		✓	
Perceived Social Support Questionnaire [37]		✓	
Religious Participation [38,39]		✓	✓
Self-Rated health [40]		✓	✓
Health Related Quality of Life [41]		✓	✓
Alcohol Use Disorders Identification Test (AUDIT-C) [42]		✓	✓
Marijuana/Cannabis Use Behavior		✓	✓
BRFSS Inadequate Sleep [43]		✓	✓
Short Scale of Anxiety Sensitivity Index (SSASI) [44]		✓	✓
Cannabis Use Disorder Identification Test Short Form [45]		✓	✓
Weekly EMA[a] items		✓	✓
Smoking Status items			✓
System Usability Scale [46]			✓
Treatment Quality and Satisfaction Survey			✓

[a]EMA: ecological momentary assessments.

Check-Ins

Thirty minutes after the preset wake time, participants are prompted by the app to complete a morning check-in. The app welcomes participants in each condition with a different message. The SC group is told that the check-in should take less than 30 seconds to complete and given no further instructions. The OKquit group is told that the check-in should take less than 30 seconds and that their answers to the check-in questions will help the app tailor messages to their current needs. All participants are then asked, “How many cigarettes did you smoke yesterday?” OKquit participants in the Post–Quit and Maintenance Phases receive a message reminding them how many days they have been smoke-free and how much money they have saved to date by not smoking. All participants are then asked, “Which of the following apply to you RIGHT NOW? (Check all that apply).” Answer responses include the following: I could easily get cigarettes within 5-10 minutes; someone is currently smoking near me; I feel stressed; I have an urge to smoke; my motivation to quit smoking is low; I drank alcohol in the last hour; and none of the above. Next, participants are asked, “How likely is it that you will smoke between now and the end of the day?” Answer responses range from 0% to 100%. Participants are then asked, “Which of the following brief (30 seconds) check-ins would you like to schedule for today?” with the following responses: 10:00 AM, 12:00 PM, 4:00 PM, 6:00 PM, 1 hour before your usual bedtime, and None of the above. After these questions are completed, SC participants receive a level 7 (ie, factoid) message, and OKquit participants receive a message tailored to their current PBM stage and their current situation. Participants are prompted at the specified times to complete the additional check-ins that they selected for that day.

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Weekly Survey

All participants are prompted to complete the weekly survey on Saturdays for 27 weeks. The weekly survey includes all items from the morning check-in and additional items about smoking status, current thoughts about quitting, whether they have attempted to quit smoking during the past 7 days, motivation and desire to quit smoking, cessation fatigue, alcohol and drug use, social support, and several additional items. After these questions are completed, SC participants receive a level 7 (ie, factoid) message, and OKquit participants receive a message tailored to their current PBM stage and their current situation.

Biochemical Verification of Smoking Status

Participants who report smoking abstinence 26 weeks after enrollment are mailed a Bedfont iCO Smokerlyzer to complete a breath test and verify their smoking status. Step-by-step instructions are presented on the smartphone screen on how to complete an iCO test. All test results are date- and time-stamped and saved for future analysis.

OTH Data

OTH will provide the research team with data on all interactions with study participants. In particular, the dates and number of OTH coaching sessions completed will be extracted, along with the dates and amounts of NRT ordered.

Compensation

Participants receive compensation for completing the baseline assessment (US $20), weekly surveys (US $5 each), and the 27-week follow-up assessment (US $50) via a reloadable GreenPhire Mastercard. Participants are not compensated for completing or accessing treatment components including daily check-ins, on-demand assessments, or intervention content. Participants who report 7-day smoking abstinence at 26 weeks post enrollment (via weekly survey) and provide a breath sample are paid an additional US $20 regardless of their actual smoking status. Thus, participants may receive up to US $225 for completing all study measures. Participants can click the “Payment” button on the app home screen to review their compensation summary.

Smartphone Programming

The mHealth Shared Resource at the NCI Designated Stephenson Cancer Center provided the smartphone app programming services for this project. This resource employs 9.5 team members including 5.5 computer scientists and engineers who develop and maintain web and mobile apps and relational databases. To date, this resource has supported 94 research studies.

Statistical Analysis

Descriptive statistics for continuous variables will include mean, SD, and quantiles, and categorical variables will be summarized as percentages and counts. We hypothesize that participants randomly assigned to the OKquit group will have significantly higher rates of biochemically verified 7-day point prevalence smoking abstinence than those assigned to SC at 27 weeks post randomization. We will use a chi-square test or Fisher exact test to compare the proportion of participants in the treatment conditions (ie, OKquit and SC) who are biochemically verified as abstinent (ie, iCO <7 ppm, and self-reports show no smoking in the past 7 days) 27 weeks after randomization. We will conduct the analysis using the intention-to-treat assumption wherein participants who are lost to follow-up or fail to complete the iCO evaluation will be classified as not abstinent. Prior to analyzing the data, we will examine the missing rate and patterns of missing data. If the missing rate is high, then we will explore sequential multiple imputation with at least 20 imputed data files as described by Raghunathan et al [47]. The analysis results from sequential multiple imputation data will be compared with those from the available data and intention-to-treat analyses. Based upon previous studies [48], we expect that 9% of those receiving the SC intervention will be biochemically confirmed abstinent at the 27-week post–quit follow-up, and based upon our pilot work, we expect that 18% of those receiving the OKquit treatment will be abstinent at the 27-week postquit follow-up visit [19,20]. With alpha values of .05 and 250 participants in each group, we have 84% power to detect a 9% difference in biochemically confirmed 7-day point prevalence abstinence at 27 weeks (ie, 45/250, 18% abstinent in the OKquit group vs 22/250, 9% abstinent in the SC group) by using Pearson chi-square test. In addition to the chi-square test or Fisher exact analysis, we will perform logistic regression analyses to determine whether the odds of abstinence vary by other baseline characteristics (eg, sex, race, and ethnicity). Finally, we will examine interactions between treatment condition and sex and race (separately) to identify potential differential effects on abstinence.

We will examine secondary outcome measures from the collected data, including 30-day point prevalence abstinence, days to first lapse, and longest period of abstinence, which will be compared across treatment conditions. We will use the chi-square test or Fisher exact test and logistic regression models to examine 30-day point prevalence abstinence. For time to first lapse, Kaplan Meier and Cox regression modeling methods will be used. For the longest period of abstinence, *t* test or Wilcoxon rank sum test and linear regression methods will be used. Finally, we will use generalized linear mixed model regression analysis to compare abstinence rates between groups over time.

We hypothesize that OTH service engagement and use of OKquit intervention content will predict biochemically verified 7-day point prevalence smoking abstinence 27 weeks post randomization. Logistic regression models will be used to examine whether total number of OTH coaching sessions completed and OTH NRT shipments predict 27-week biochemically confirmed 7-day point prevalence abstinence. We will also examine whether the number and type of interactions with the OKquit app (eg, messages viewed) predict 27-week abstinence. Baseline characteristics such as race and sex will be considered as potential covariates during the modeling process.

Results

The smartphone app was developed and initial data collection began in September 2022. As of July 2024, 345 participants have been enrolled. We expect to complete data collection by

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September 2025 and to prepare a paper describing the main outcomes by December 2025.

Discussion

Principal Results

This study will determine whether the OKquit app improves biochemically confirmed smoking cessation rates for OTH service users 27 weeks after enrollment. This study will also examine the effects of engagement with OTH services and OKquit intervention content on smoking abstinence and key lapse risk factors. To our knowledge, this will be the first study to examine the effects of a low-burden app-based adjunctive intervention on smoking cessation quitline quit rates.

Quitline services are evidence-based [1,8]; however, only 1%-3% of people who smoke register for quitline services each year [12,49]. Early versions of quitline services included phone counseling supplemented with mailed cessation materials. Over time, as technology has advanced, quitlines have expanded their offerings to include NRT (eg, nicotine patches, nicotine gum), web-based counseling, and mobile communications via text and email [9,10,50,51]. Adjunctive smartphone-based cessation apps such as OKquit could increase convenience, appeal, reach, and effectiveness of quitline services. Given that nearly all people in the United States own a smartphone [52], low-burden smartphone-based interventions may offer a novel way to administer empirically validated smoking cessation interventions. If using the OKquit app with and without use of standard helpline services increases biochemically verified smoking abstinence, then this type of intervention could help in the fight against smoking for individuals who might not otherwise have the means to take part in intensive smoking cessation programs. OKquit's low-burden design includes brief daily check-ins that prompt thinking about cessation and provide useful cessation advice on how to cope with currently experienced lapse triggers. Furthermore, OKquit enables participants to access smoking cessation materials on demand and reinitiation of cessation attempts after lapse or relapse.

Limitations

Study participants are required to use their personal Android smartphone. Individuals whose Android phone does not meet app requirements, those unwilling to install the app on their personal smartphones, those without a smartphone, and iPhone users are unable to participate. Future interventions will use a new version of the Insight platform that works with all phone types. Another limitation is that the sample will focus solely on OTH users. Finally, this study will not examine the efficacy of OKquit as a stand-alone intervention for quitline users.

Future Work

Based upon the results of this study, future work should examine ways to improve and refine the OKquit intervention. Furthermore, future dissemination and implementation studies should examine the effectiveness of the OKquit intervention with those seeking services from smoking cessation helplines across the United States and beyond. In addition, studies should compare the effectiveness of the OKquit intervention versus standard quitline services. Finally, future work should examine the cost-effectiveness of this type of smartphone app–based intervention.

Acknowledgments

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Authors' Contributions

All authors contributed to the conceptualization of the study and assisted in the drafting and editing of the paper. MB led the conceptualization, methodology, project administration, writing—original draft, and writing—review and editing. JB contributed to the writing of original draft and writing—review and editing. CW contributed to the project administration and writing—review and editing. SC contributed to writing—review and editing, formal analyses, and data curation. KK contributed to the project administration, writing—review and editing, and data curation. LAB contributed to writing—conceptualization, writing—review and editing. DEK contributed to the conceptualization and writing—review and editing.

Conflicts of Interest

MB and DEK are inventors of the Insight mHealth Platform and receive royalties related to use of this platform. Since MB is the principal investigator on this study, they did not receive royalties in this case.

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Abbreviations

EMA: ecological momentary assessment
NRT: nicotine replacement theory
OTH: Oklahoma Tobacco Helpline
PBM: Phase-Based Model
REALM-SF: Rapid Estimate of Adult Literacy in Medicine—Short Form
REDCap: Research Electronic Data Capture
SC: standard care
Smart-T: Smart-Treatment

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Protocol

Improving the Well-Being of People With Advanced Cancer and Their Family Caregivers: Protocol for an Effectiveness-Implementation Trial of a Dyadic Digital Health Intervention (FOCUSau)

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Abstract

Background: Advanced cancer significantly impacts patients' and family caregivers' quality of life. When patients and caregivers are supported concurrently as a dyad, the well-being of each person is optimized. Family, Outlook, Communication, Uncertainty, Symptom management (FOCUS) is a dyadic, psychoeducational intervention developed in the United States, shown to improve the well-being and quality of life of patients with advanced cancer and their primary caregivers. Originally, a nurse-delivered in-person intervention, FOCUS has been adapted into a self-administered web-based intervention for European delivery.

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Objective: The aims of this study are to (1) adapt FOCUS to the Australian context (FOCUSau); (2) evaluate the effectiveness of FOCUSau in improving the emotional well-being and self-efficacy of patients with advanced cancer and their primary caregiver relative to usual care control group; (3) compare health care use between the intervention and control groups; and (4) assess the acceptability, feasibility, and scalability of FOCUSau in order to inform future maintainable implementation of the intervention within the Australian health care system.

Methods: FOCUS will be adapted prior to trial commencement, using an iterative stakeholder feedback process to create FOCUSau. To examine the efficacy and cost-effectiveness of FOCUSau and assess its acceptability, feasibility, and scalability, we will undertake a hybrid type 1 implementation study consisting of a phase 3 (clinical effectiveness) trial along with an observational implementation study. Participants will include patients with cancer who are older than 18 years, able to access the internet, and able to identify a primary support person or caregiver who can also be approached for participation. The sample size consists of 173 dyads in each arm (ie, 346 dyads in total). Patient-caregiver dyad data will be collected at 3 time points—baseline (T_0) completed prerandomization; first follow-up (T_1; N=346) at 12 weeks post baseline; and second follow-up (T_2) at 24 weeks post baseline.

Results: The study was funded in March 2022. Recruitment commenced in July 2024.

Conclusions: If shown to be effective, this intervention will improve the well-being of patients with advanced cancer and their family caregivers, regardless of their location or current level of health care support.

Trial Registration: ClinicalTrials.gov NCT06082128; https://clinicaltrials.gov/study/NCT06082128

International Registered Report Identifier (IRRID): PRR1-10.2196/55252

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KEYWORDS

advanced cancer; clinical trial; digital health intervention; palliative care; health economics; implementation science; wellbeing; well-being; cancer; family caregiver; family caregivers; caregivers; caregiver; digital health; quality of life; dyad; self-administered; web-based intervention; web-based; Australian; Australia; efficacy; cost-effectiveness; psychoeducation

Introduction

Overview

Advanced cancer is a "family affair" significantly affecting the well-being of the person with cancer and their family [1]. Family caregivers are at the core of patient care; they are typically unpaid laypeople, comprising close family members or friends or others who provide a significant level of support (practical, social, or emotional) to the person with cancer. Additionally, their contributions alleviate some of the burden on the Australian health care system, resulting in significant cost savings [2]. As a result, addressing the needs of both patients and their family caregivers is a priority in many countries, with established standards, policies, and guidelines [3-5].

Furthermore, the World Health Organization advocates that palliative care should be "family centered," enhancing the quality of life (QoL) of the patient and their family caregivers [6], and includes supporting those still receiving curative treatment in addition to those receiving end-of-life (EoL) care [7]. Palliative care, when effectively delivered, can restore choice regarding options for care [8], improve patients' and caregivers' sense of control, self-efficacy, coping ability, communication about the illness, and reduce emotional distress [9]. Research has shown the benefits of early access to palliative care for patients, their family caregivers, and the health care system; there has been an increased and proactive approach to early integration of palliative care to improve QoL and symptom management of patients and family caregivers [7]. Hence, intervening earlier in the disease trajectory to assist the family unit in preparing for and responding to the implications of life-threatening illness constitutes best practice.

Despite the policy, clinical and research evidence advocating a family approach to palliative care, systemic inadequacies such as the inability of many family caregivers to access health professional support and fragmented, inconsistent, variable palliative care services, along with the lack of preparation for death have impeded family-centered care [10]. Patients may undergo potentially unnecessary treatment, report high levels of pain, difficulty coping, poor physical and emotional health, and their EoL wishes not always upheld [10]. This translates to many caregivers reporting high emotional distress, unmet needs, and difficulties with providing complex home-based care, especially during the advanced stages of illness and EoL [11]. Around 40% of caregivers are reported to experience psychological distress [12] which is typically underrecognized [13]. Furthermore; these impacts may be more pronounced in underserved groups.

The overwhelming majority of Australians would prefer to die at home [14], yet Australian acute hospitals provide EoL care to approximately 50% of people who die [15]. Comprehensive family support is a key factor in determining whether the preference for home care and death can be realized [16]. Yet, effective systematically applied psychosocial support for family caregivers in the EoL context is still underdeveloped [16,17].

Patients and family caregivers experience illness together, with 1 person's ability to cope affecting the other's [18]. In a longitudinal study of dyads including people with advanced cancer and their caregivers, caregiver mental health at baseline significantly influenced patient mental health 3 months later [11], while in a study of dyads affected by brain cancer, greater caregiver competence in the caregiver role predicted longer patient survival [19]. Dyadic interventions, targeting the patient

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and family caregiver together, are more likely to result in better outcomes for both parties than single-target interventions and may be more cost-effective [18,20,21]. Consequently, dyadic interventions focusing on the QoL of both the patient and caregiver from the point of advanced disease diagnosis are necessary to promote well-being and cost-effective care.

Historically, much of the psychological and psychoeducational palliative care intervention research has been delivered in person, with demonstrated improvements in patient QoL [22] and family caregiver well-being, sense of preparedness, reduction of unmet needs, and more favorable bereavement outcomes [21,23-25]. While these in-person delivered interventions produce promising results, they can be time and resource-intensive. These resource requirements constitute a major barrier to longer-term implementation and integration of these interventions into the health care system, particularly in the context of current shortages of staff and other resources.

Digital health interventions offer an innovative modality for the delivery of health care services [26]. They provide considerable resource advantages to in-person interventions [27] such as improving, information-sharing, decision-making, and communication [26,28,29]. Advantages for users also include lower cost of delivery, greater reach (including for rural and remote areas), convenience, less travel time, reduced risk of infections due to reduced exposure associated with face-to-face consultations, and recipients feeling more empowered [27,29]. A meta-analysis of internet therapy studies has provided strong support for the adoption of internet-based psychological interventions [30] and the increasing use of digital health has ushered in a new era of patient-centered cancer care that moves beyond the traditional in-person care model [31].

Digital health within the context of palliative care should not be considered a replacement for, but complementary to, in-person care in this con (which has numerous benefits) [29]. Indications are that digital health communication in this context may result in patients and caregivers receiving more reliable information; it can be more feasibly applied; and at organizational and societal levels, digital health may contribute to more efficient and equitable use of resources [29]. Furthermore, disseminating dyadic interventions via the internet and other technologies may be more scalable from a health systems perspective [18]. Reduced labor costs, as well as lower ongoing program charges, suggest that the longer-term cost-effectiveness of digital health interventions compares favorably with traditional in-person care [18]. However, compared to the rapid increase of digital health interventions in other areas of health care, there is limited application of digital health interventions within advanced cancer and palliative care settings. No rigorously tested interventions applied systematically in Australia have targeted the psychosocial well-being of the patient-caregiver dyad [26,29]. There is an urgent need, therefore, to develop evidence-based, dyadic digital health approaches that are meaningful, accessible, and maintainable for integration into the Australian health system.

Focus Intervention Background

The Family, Outlook, Communication, Uncertainty, Symptom management (FOCUS) intervention has been developed in accordance with guidelines for complex interventions [32-36]. Co-designed with consumers, patients, and family caregivers, the intervention consists of five core components underpinning the FOCUS acronym and they are (1) supporting *Family* involvement, (2) supporting *Outlook* and meaning, (3) increasing *Coping* effectiveness, (4) reducing *Uncertainty*, and (5) *Symptom* management. The original in-person FOCUS program was developed in the United States as a nurse-delivered in-person intervention, being multicomponent and psychoeducational in its framework, and providing tailored informational and emotional support to patients with advanced cancer and their family caregivers [32]. The efficacy of this in-person FOCUS intervention was demonstrated in 3 randomized control trials and 2 pilot effectiveness studies conducted in the United States [32-35,37], with the patient-caregiver dyads reporting significantly improved QoL and well-being, less negative appraisal of illness and caregiving, reduced uncertainty and hopelessness, improved communication, and enhanced self-efficacy. To make the FOCUS (United States) intervention more accessible, the main component (family involvement) of this in-person intervention was then adapted into a tailored, digital or web-based format [38]. Significant intervention effects were found in a pre-post study on dyads' QoL, emotional distress, perceived benefits of illness or caregiving, and caregivers' self-efficacy [38].

The strong empirical base and use of the FOCUS (United States) intervention have been acknowledged by the European Union (EU) through successful grant funding awarded to test European-adapted versions of both programs (in-person [FOCUS+] and digital [iFOCUS] in a phase 3 trial, currently being conducted across 6 countries (England, Ireland, Belgium, Denmark, the Netherlands, and Italy) [39-41].

For this study, we aim to test the FOCUS EU digital version (iFOCUS) for the Australian setting ("FOCUSau"), given the need to reach regional and rural areas and address the cost-effectiveness and maintainability issues that arise for in-person interventions.

Research Aim and Hypotheses

We seek to determine the effectiveness and maintainability of a digital health intervention (iFOCUS) aimed at improving the well-being of patients with advanced cancer and their primary family caregivers. Our objectives are to (1) adapt iFOCUS to the Australian context to create FOCUSau; (2) examine the effectiveness of FOCUSau in improving the well-being (primary outcomes are emotional well-being and self-efficacy) of patients with advanced cancer and their primary family caregiver, compared to the control group (usual care); (3) compare the types and costs of health services used by participants in the intervention and control group; and (4) assess the acceptability, feasibility, and scalability of FOCUSau in order to inform the maintainable implementation of the intervention within the Australian health care system.

Our hypotheses are that compared to the control group, patent-caregiver dyads in the intervention group (who receive the intervention in addition to usual care) will, at 12 weeks follow-up, report (1) higher levels of emotional well-being and self-efficacy (ie, confidence in managing illness; primary

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outcomes) and (2) higher QoL, less negative appraisal of illness or caregiving, better communication about the illness, and improved coping ability (secondary outcomes). In addition, FOCUSau will be cost-effective compared with the control group in terms of the incremental cost (change in health care use) per additional participant with a meaningful change in (1) emotional well-being and (2) self-efficacy.

Methods

The study addresses the objectives in 3 stages.

Stage 1: Adaptation of iFOCUS to the Australian Health Care Setting (Objective 1)

The adaptation of iFOCUS to create FOCUSau will involve appraisal of the intervention by consumer representatives and research team participants along with detailed feedback to inform modifications. The process will be underpinned by the ADAPT process [42] whereby we will also evaluate the quality, acceptability, appropriateness, comprehensibility, accessibility, and feasibility of the intervention before and after adaptation. We have concurrently reviewed the compatibility of the intervention software with Australian digital health infrastructure and ensured alignment with Australian standards for digital accessibility, security, privacy, and shareability of personal data, and capacity to interoperate with other systems.

Consumer representatives and research team participants (n=16) viewed the iFOCUS intervention and provided detailed feedback to inform the modifications. Participants also completed the Adapted Mobile Application Rating Scale [43] and the Theoretical Framework of Acceptability questionnaire [44] and commented on the quality, acceptability, appropriateness, comprehensibility, accessibility, and feasibility of the intervention before and after adaptation. We collected data using REDCap (Research Electronic Data Capture; Vanderbilt University) [45] and analyzed data using descriptive statistics, thematic analysis [46], and content analysis [47]. Data analysis led to suggestions for modifications to the intervention which were voted favorably by participants. The full method and results of the adaptation study will be reported elsewhere.

Stage 2: Pragmatic Phase 3 Hybrid Effectiveness-Implementation Trial of FOCUSau (Objectives 2 and 3)

Design

We chose to conduct a Hybrid type 1 implementation study that included a Phase 3 effectiveness component and an observational implementation study [48]. This integrated research design includes digital health evaluation [49] to account for the interaction between conventional health effects and human-computer engagement [50]. This includes (1) randomization of participating dyads to the intervention versus standard care (control group), to examine FOCUSau effectiveness in relation to clinical outcomes and health service use, while simultaneously (2) exploring acceptability, feasibility, maintainability, and scalability of the intervention—that are recognized in both implementation science methods [48] and digital health evaluation methods [51]. Hybrid designs have a dual focus—a priori assessment of clinical effectiveness and implementation [48]. These pragmatic designs offer novel ways of testing intervention effectiveness and potential uptake and are recommended for multisite psychosocial-related interventions in cancer care [52].

Participants

Patient inclusion criteria are diagnosis of advanced cancer; older than 18 years of age; able to comprehend written or spoken English; no visual, hearing, or cognitive impairment that would preclude participation; can commit to research participation requirements (including data collection and completion of the FOCUSau intervention if randomized to that group); able to access the internet (on their own desktop computer, laptop computer, or tablet device); and able to identify a primary support person or caregiver, who is an unpaid individual (not necessarily a partner or family member) who is providing them with physical, social, or emotional support. The patient exclusion criterion is involvement in an advanced cancer nondrug trial that focuses on improving QoL. Family caregiver inclusion criteria are identified by the patient as their primary support person who is related to them biologically, legally, or emotionally, and is willing to accept this support role; aged older than 18 years; no visual, hearing, or cognitive impairment that would preclude participation; commits to research participation requirements; and is able to access the internet. Dyad inclusion criterion is the capacity to effectively use the internet (as determined through a short practical internet-based exercise as part of the screening and consent process).

The FOCUSau Intervention

Aim and Core Features

The overall aim is to enhance dyads' emotional well-being and self-efficacy, addressed by 5 core components of the intervention [32]. The transactional model of stress and coping underpins the intervention [53].

Delivery Mode, Dose, and Timeline

The intervention is self-administered, completed autonomously via the internet by the patient and caregiver dyads. It encompasses 4 prescribed consecutive sessions (with 3 weeks between each session) over a period of 12 weeks that collectively cover the 5 core components; the core content of which is outlined in Figure 1. The sessions are completed simultaneously by the patient and family caregiver, together at a computer. At the beginning of each session, a computer prompt (wizard) explains how dyads can navigate through the sessions. Access to the 4 sessions is provided via an automated link sent by an email. The content of the sessions is written at a lower secondary education reading level, using principles of plain language. Audio instead of text provision of material is also available to allow for participation by those with visual impairment. Written content is complemented by images and videos of patients and caregivers reflecting on their advanced cancer experience which is linked to 5 core components.

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Figure 1. Intervention overview.

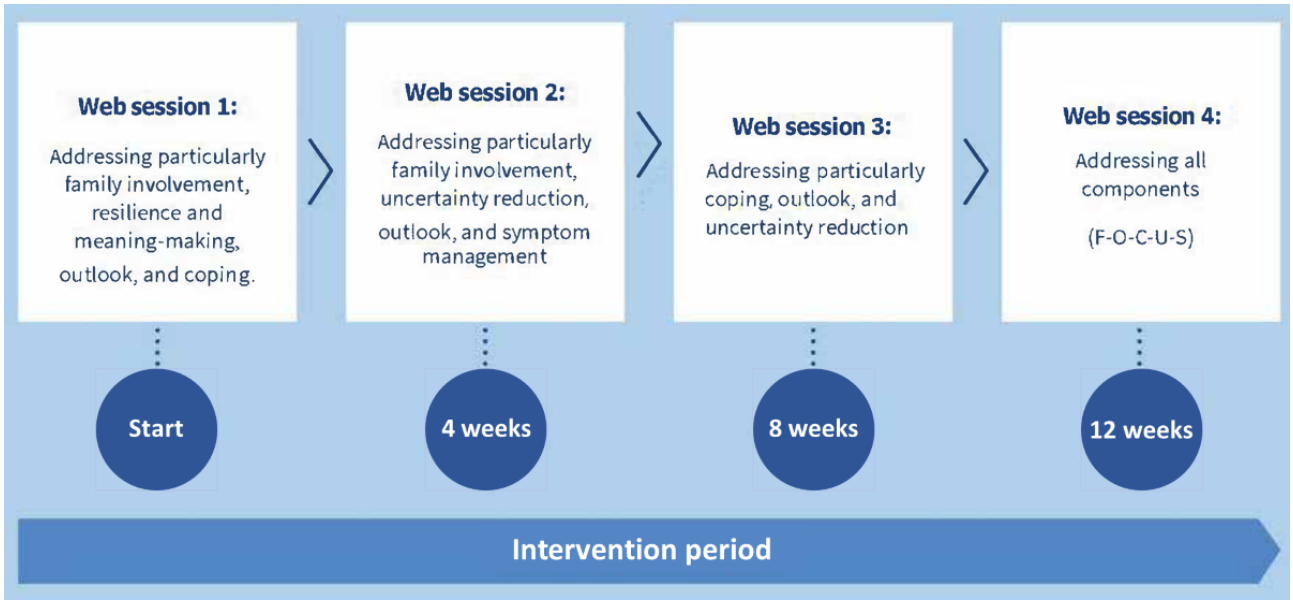

Additional Resources

Dyads are provided with an internet-based personal workbook containing information tailored to their responses to questions completed during the internet sessions. Any information sheets that the dyad indicated as "of interest to them" during the internet sessions are included as a hyperlink in their personal workbook which also contains evidence-based local advanced cancer-related resources. Assistance via a helpdesk (via email or telephone) is available to resolve any technical difficulties with accessing the internet-based materials.

Tailoring of the Intervention

Tailoring enhances the intervention's efficacy by providing dyads with information personally relevant to them. Three types of tailoring strategies are used—personalization, tailored feedback, and content matching [54]. Participants receive tailored individual and dyadic messages according to their own demographic characteristics (age, sex, and dyadic relationship) provided at study enrollment and their responses to questions within the sessions.

The Control—Usual Care

Participants in the control group will receive usual care. Usual care in advanced cancer care is known to be heterogeneous. Nonetheless, we will collect relevant health services usage data (see below) to describe and compare the control and intervention arms.

Setting and Recruitment Procedures

The patient-caregiver dyads will be recruited via two methods that are (1) referral from hospitals or (2) self-referral. For method 1, approximately 6 hospitals and cancer centers (metropolitan and regional) across several states of Australia will be selected. The specific selection of institutions will be undertaken by the Cancer Symptoms Trials (CST) group (a national cooperative trials group) as the trial coordinating center. The CST will undertake a feasibility assessment process to ensure institutions are selected on their ability to demonstrate that they have the internal resources and patient population to refer sufficient dyads to achieve the site-specific sample size and broad coverage of services across Australia. As part of the CST site selection process, participating institutions will identify multidisciplinary staff in relevant departments to undertake an initial eligibility screen. The study will be verbally explained to eligible patients who receive a brief written project summary. With their permission, the contact details of patients interested in the study will be submitted to the project website by the relevant referring clinician. Thereafter the patient will be contacted by a research officer who will undertake the screening and consenting process incorporating obtaining permission to contact the patient's primary family caregiver to seek their interest in participating, then scheduling a video meeting with the dyad which will also serve as a further check of their capacity to engage in an internet intervention. If all inclusion criteria are met, electronic consent via standard ethical requirements will be undertaken.

For the self-referral recruitment method, patients who have been made aware of the project (but have not been officially screened by a clinician) may self-refer via a form on the project website. These patients will be made aware via consumer, caregiver, cancer advocacy groups, or social media advertisements. A research officer will then review the self-referral form and liaise directly with the patient to advise if they meet the criteria and if so, recruiting and consent procedures will be undertaken as per method 1. There will be a second videoconference arranged (after consent and subsequent randomization) to explain to the dyad which group they have been allocated to and brief orientation to the FOCUSau platform and the associated data collection methods.

Allocation and Blinding

Following informed consent and completion of baseline measures, block randomization will occur via an embedded randomizer within the FOCUSau platform to create the randomization table based on blocks of multiplicators of 2 and blocks of 4, 6, and 8. The block randomization method is designed to randomize subjects into groups to ensure a balance

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in sample size across groups over time. A research officer will initiate the randomization process which will involve logging into the FOCUSau platform, entering relevant participant details and then block randomization will occur. Due to the nature of the intervention, the patient-caregiver dyads cannot be blinded to allocation. Data collection will occur electronically and the research team will remain blind to which trial arm the dyads were randomized until the end of the final data-collection point. The first 10 consented dyads who are allocated to the intervention group will additionally be invited to participate in the final step of the aforementioned intervention adaptation process and be provided with a specific (additional) participant information sheet and consent form.

Data Collection: Primary and Secondary Psychosocial Outcomes

Patient-caregiver dyad data will be collected at 3 time points—baseline (T_0) completed prerandomization, first follow-up (T_1) at 12 weeks post baseline, and second follow-up (T_2) at 24 weeks post baseline. All data will be completed by the dyads (regardless of allocation) using the FOCUSau software platform, whereby they will complete a suite of internet-based questionnaires. The platform enables the application of data validation rules to ensure that required data are entered or that an annotation is provided to explain any missing data. The FOCUSau platform automatically generates a unique ID number used by the dyad to log into the platform. Data collection will be completed separately by the patient and caregiver (regardless of allocation). The data collection points, outcomes, and measures have been selected in accordance with those used in the aforementioned EU trial to enhance international comparison and potential generalizability [39].

The list of variables and associated measures to be completed by the dyad are summarized in Table 1 and are as follows, for the primary outcomes—emotional well-being (10 items describing emotional functioning from the European Organization for Research and Treatment of Cancer (EORTC) The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30) [55,56] and self-efficacy (The Lewis' Cancer self-efficacy scale [57]); for the secondary outcomes—QoL of patients—EORTC QLQ-palliative care [58], 2 social functioning items (#26, 27) plus 1 item about overall health (#29) from the EORTC QLQ-C30, social well-being scale from Functional Assessment of Cancer Therapy-General (FACT-G)—and family caregivers (The Caregiver Quality of Life Index-Cancer [59]), appraisal of illness (Benefits of illness scale [60]), coping (Brief cope [61]), and dyad communication (Ways of giving support questionnaire [62] plus 1 item from the Dyadic Coping Inventory).

In addition, we will administer a sociodemographic questionnaire at baseline (T_0) and a modified version of the Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment [63] (response option 5 "death" removed as not relevant for this study).

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Table 1. Trial data collection measures.

Objective and outcome or variable	Instrument	Timing		
		T_0: Before randomization	T_1:T_0 + 12 weeks	T_2: T_0 + 24 weeks
Outcome measures used for the primary outcomes				
Psychosocial effectiveness				
Emotional well-being	• For patients: EORTC[a] QLQ-C30[b] emotional function items (10 items) • For caregivers: EORTC QLQ-C30 item emotional function scale (10 items)	✓	✓	✓
Self-efficacy	• For patients and caregivers: the Lewis' Cancer self-efficacy scale (17 items)	✓	✓	✓
Outcome measures used for the secondary outcomes				
Psychosocial effectiveness				
Quality of life	• For patients: EORTC QLQ-C15-PAL (23 items) + 2 social function items + 2 items about overall health from EORTC QLQ-C30; social well-being scale from the FACT-G[c] (6 items) • For caregivers: the Caregiver Quality of Life Index-Cancer (CQOLC; 35 items)	✓	✓	✓
Appraisal of illness	• For patients and caregivers: benefits of illness scale (5 items)	✓	✓	✓
Coping	• For patients and caregivers: a shortened version of Brief Cope (20 items)	✓	✓	✓
Communication	• For patients and caregivers: the "Active engagement scale" (5 items) from the "Ways of giving support questionnaire." Three scales (10 items) from the "Dyadic Coping Inventory": "Stress communication by oneself," "Stress communication by partner," and "Evaluation of dyadic coping"	✓	✓	✓
Level of functioning	• For patients (4 items): modified version of Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment (item 5 "death" removed)	✓	✓	✓
Cost-effectiveness				
Health economic measures	• For patients (23 items) 17 and for caregivers (14 items): client Services Receipt Inventory (CSRI) including use of hospital versus in-patient palliative EoL[d] care and the use of informal care or services provided outside of the health care system (to be completed by caregivers) and modified to reduce overlap with Medicare data	✓	✓	✓
Primary outcome expressed as cost per participant with a meaningful change in well-being or self-efficacy for the intervention compared with control	• For patients and caregivers: EQ-5D and EQ-5D-5L (5 items)	✓	✓	✓
Secondary outcomes expressed as cost per quality adjusted life year for the intervention compared with control	• For patients and caregivers: Services Australia data—use of outpatient medical and pharmaceutical services	✓	✓	✓
Implementability				
Acceptability	• For patients and for caregivers (intervention group): Theoretical Framework of Acceptability (TFA) survey (9 items)—perceptions based on info provided and actual after completion	✓	✓	✓

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Objective and outcome or variable	Instrument	Timing		
		T_0: Before randomization	T_1:T_0 + 12 weeks	T_2: T_0 + 24 weeks
Acceptability	• For patients and for caregivers (control group) 1: Theoretical Framework of Acceptability (TFA) survey (9 items) perceptions based on info provided only	✓		
Acceptability	• For patients and for caregivers (intervention group only): qualitative (interviews) to explore acceptability and barriers and enablers to uptake of FOCUSau by dyads, the latter informed by the Theoretical Domains Framework of behavior		✓	
Satisfaction with intervention	• For patients and for caregivers (intervention group): FOCUS items asking about experience and satisfaction with the intervention (intervention group only) • For patients (12 items) • For caregivers (12 items)		✓	✓
Uptake	• Study log: recruitment data including reasons for accepting or declining participation, sociodemographic profile of invited dyads, and capacity to reach vulnerable populations (with lower socioeconomic status, cultural minorities, and from rural or remote locations)	✓	✓	✓
Intervention fidelity	• Study log: communication between trial managers and participants, whether for technical problem-solving or for other reasons. Aspects of adherence (intervention as received) are built into the FOCUSau intervention. Completion rates of individual FOCUSau sessions	✓	✓	✓
Technical feasibility	• Interviews or focus groups with health IT experts: data and infrastructure standards adherence, system architecture for interoperability or integration with electronic patient records, and extensibility and scalability potential	✓	✓	✓
Other characteristics				
Sociodemographic characteristics	• For patients (14 items) and for caregivers (15 items): sex, age, relationship status, living situation, children, educational level, employment status, income, financial difficulties, medical insurance, ethnicity, and dyad's relationship	✓		
Patient level of functioning	• For patients (1 item): modified version of Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment (response option 5 "death" removed as not relevant)	✓	✓	✓

[a]EORTC: European Organization for Research and Treatment of Cancer.

[b]QLQ-C30: The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire.

[c]FACT-G: Functional Assessment of Cancer Therapy-General.

[d]EoL: end of life.

Data Collection: Health Services Use

The impact on health care costs of FOCUSau will be determined by analyzing patterns and costs of health care use, including the costs of administering the intervention. Information will be collected on the time required to administer FOCUSau (per patient and overall). The impact of FOCUSau and usual care on health care services' use will be assessed by consenting participants for access to their Medicare (Australian Government health services) data (to obtain information on the use of outpatient medical and pharmaceutical services) and using the Client Services Receipt Inventory (CSRI) [64]; modified to reduce overlap with Medicare data. The CSRI will also allow us to explore the use of hospital versus inpatient palliative EoL care, and the use of informal care or services provided outside of the health care system (to be completed by caregivers).

Data Collection: Implementability

Table 1 also outlines data to be collected to measure factors related to implementability of the intervention. This will include piloting and administering a new acceptability questionnaire [44]. Interview topic guides (1 for patients; a parallel guide for caregivers) will be informed by the Theoretical Domains Framework (TDF) of behavior change [65].

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Sample Size

A predetermined strict fixed sequence (FS) procedure defines prospectively hierarchical ordering of the primary end points; (1) emotional well-being and (2) self-efficacy. Testing of null hypotheses proceeds according to their hierarchical order; that is, H(1)0 is tested first at a significance level of 5%, and if H(1)0 is rejected then H(2)0 is tested at the same significance level, otherwise H(2)0 is not tested at all. The strict FS approach has the highest power for testing the first hypothesis (outcome: emotional well-being) compared to the other methods, as it does not save any portion of α for testing the later hypothesis. The reference mean value from EORTC for all patients with cancer, stage III-IV is 71.5 (SD 23.8). To maintain rigorous control over type I errors due to multiple comparisons, the α level is set at .025 instead of the more common .05. This adjustment accounts for the multiple comparisons required in the study, including comparisons between a control group and 2 participant groups (patients and caregivers). We set the statistical power at 0.80. The expected difference between the control group and the intervention arm in the primary outcomes is SD 0.375 at T_1 (12 weeks). With these parameters, 173 dyads are needed in each arm (ie, 346 dyads in total). Anticipating a maximum 80% retention rate at T_1 (US FOCUS retention was 86% [38]) we will require approximately 433 dyads to be recruited. An enrollment rate of 55% of those eligible was achieved in a prior digital health FOCUS study from 2014 [38]; however, we anticipate this will be higher for FOCUSaus (estimating 70%) given the internet is much more widely available now and our digital recruitment approach, meaning that we will need to identify approximately 618 dyads who meet eligibility criteria. Evidence also suggests that recruitment rates can increase when a digital health intervention is offered [18]. To meet these targets the CTS has calculated that approximately 6 referral sites will be required complemented by our aforementioned self-referral strategy.

Data Analysis

The effectiveness of FOCUSau will be compared with the standard care (control group) for each participant population (patients or caregivers). Our hypotheses will be tested using a mixed model (per participant population) with the T_1 measurement values for emotional well-being and self-efficacy as primary outcomes using a significance level of α=.025. These mixed models will be implemented using SPSS (IBM Corp) for Windows (version 27.0; Microsoft Corp) and R (R Core Team) with the recruitment centers treated as a random effect and the randomization groups as predictor variables. As per the FS procedure, the null hypotheses of the second primary end point (self-efficacy) will only be tested if a significant result is found for the first primary end point (emotional well-being). Additionally, we will incorporate other factors identified in the literature as potentially predictive by including them as covariates in the mixed models. We will perform analyses on both "intention-to-treat" and per-protocol principles. To interpret the magnitude of the effects for the different outcomes, we will estimate effect sizes (Cohen *d*). Our analysis will encompass all primary and secondary outcomes. Primary end points, including emotional well-being and self-efficacy measured at T_1, will be analyzed first. Following that, secondary end points, comprising outcomes measured at T_1 that are not primary end points, as well as all outcomes measured at T_2 (occurring 24 weeks from T_0), will be assessed. This approach allows for a comprehensive evaluation, including the examination of longer-term effects.

The robustness and validity of the results will be explored using sensitivity analyses by varying the parameter inputs (including sensitivity to the use of values for missing observations). The analysis will be conducted within trial period; the potential to extrapolate results over the longer term will be assessed based on the proportion of patients alive at the end of follow-up.

For the cost-effectiveness analysis, costs will be reported as the mean costs of care per dyad in each arm of the study. Costs applied to health care service use will be as per Australian standard fees (eg, via the Medicare Benefits Schedule). If a difference in outcomes is observed, as hypothesized, the incremental cost-effectiveness of FOCUSau compared with control will be estimated in terms of the (1) cost per additional patient with a meaningful improvement in emotional well-being (as assessed using the EORTC QLQ-C30 emotional well-being scale) and separately, and (2) cost per additional caregiver with a meaningful change in self-efficacy (as assessed using the Lewis' Cancer self-efficacy scale). The base case analysis of cost-effectiveness will be conducted from a health care system perspective. Subsequent sensitivity analyses will modify the assessment of costs to adopt a societal perspective to capture the impact of informal care costs, as well as test the robustness of the analysis results to variations in other parameter inputs.

Missing data for costs and outcomes will be described and summarized. Where missing data can be regarded as missing at random, likelihood (interpolation) methods will be used for the analysis of those data as appropriate.

Stage 3: Acceptability, Feasibility, and Scalability of FOCUSau (Objective 4)

Our approach is underpinned by a conceptual framework that highlights the link between acceptability, fidelity and feasibility, and potential implementability [66]. An investigation of fidelity will also inform internal validity and thus our interpretation of the effectiveness findings. If prospective acceptability, uptake and engagement with the intervention are moderate (based on conventional cutoff scores of 50%) [67,68], then FOCUSau is feasible to deliver in other settings; if participants receive and comprehend FOCUSau as designed (ie, fidelity is high), then the effectiveness findings will represent a valid test of the intervention; if participant retention and retrospective acceptability are high, then FOCUSau is likely to be maintainable; and if FOCUSau is cost-effective and additional workforce requirements are minimal, then the intervention is likely to be scalable. Acceptability is "the extent to which people receiving FOCUSau consider it to be appropriate, based on anticipated (prospective) or experienced (retrospective) cognitive and emotional responses to the intervention" [69]. Informed by a new and influential theoretical framework of acceptability [69], we will pilot test a questionnaire [44] to be administered at baseline and follow-up (T_0 and T_2). As acceptability is ideally

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assessed both quantitatively and qualitatively [36], a diverse subsample of participants (~30 dyads) will be recruited from the intervention group and be interviewed via videoconference immediately following the completion of FOCUSau (T_1), to gain a greater insight into intervention acceptability, including potential for further enhancements. As for the uptake, we will document the recruitment process, including reasons for accepting or declining participation and examine the sociodemographic profile of dyads invited to participate in the trial, capturing our capacity to reach relevant populations (with lower socioeconomic status, cultural minorities, and from rural or remote locations). We will also use the aforementioned T_1 interviews to explore barriers and enablers to uptake by dyads. Interview topic guides (1 for patients; a parallel guide for caregivers) will be informed by the TDF of behavior change [65]. Intervention fidelity encompasses whether the intervention is delivered and received as planned [70]. We will document communication between trial managers and participants, whether for technical problem-solving or for other reasons, to assess whether components have been added to FOCUSau as designed. Aspects of adherence (intervention as received) are built into the FOCUSau internet module and include a readily accessible "help" function. Dyads who experience problems with onboarding for the FOCUSau sessions will receive help from the trial manager via phone; they will confirm their presence and indicate whether they are using the computer or phone; dyads who exit an FOCUSau session before completion will be sent a reminder email or text message. Completion rates of individual FOCUSau sessions will be monitored.

The audiotaped semistructured interviews with dyads to assess FOCUSau acceptability will be transcribed verbatim and thematically analyzed using the Framework method [46]. To ensure methodological rigor, the analysis will follow (1) a step-by-step guide outlined by Gale et al [71] and (2) criteria for trustworthiness [72]. The deductive analysis will be informed by the theoretical framework of acceptability (component constructs—affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy) ascertaining whether particular elements of FOCUSau were experienced as positive or negative and will include themes from previous intervention evaluations. Coding of established themes and subthemes will be computer-assisted using NVivo software (Lumivero). Statistical descriptions of the quantitative data from the intervention checklist and routine monitoring will be used to describe fidelity, using conventional cutoff points for acceptable intervention adherence.

For technical aspects of implementability we will consider key factors in the scalability, that is "the ability of a health intervention shown to be efficacious on a small scale or under controlled conditions, to be expanded under real-world conditions to reach a greater proportion of the eligible population, while retaining effectiveness" [73]. This study will follow the previous stages and will be the subject of additional human research ethics approval. It will use health IT expert consensus methods, to determine the technical feasibility of implementing and operating the FOCUSau program as an ongoing service at each site that is participating in the clinical trial, as well as at other potential hosting sites for the program that are identified during the clinical trial. The assessment of this aspect of implementability [66] will entail either semistructured interviews or focus groups with health IT stakeholders who may include trial managers, software proprietors, digital health specialists in health service management and governance roles, and experts in the deployment of software in routine clinical care. The interview or focus group schedule will use two probes which are (1) a technical specification of the software as it has been adapted for use in the trial, based on work done by the proprietor with the research computing services group and (2) a summary of the intervention's clinical and socioeconomic value proposition, based on preliminary findings of project studies up to this point. The interview or focus group schedule will collect and thematically analyze data, based on stakeholders' knowledge of current local, national and international best practice approaches to digital health implementation planning [74,75], including the Australian Digital Health Agency technical standards and specifications.

Data Management, Monitoring, and Risk Management

CST has a suite of standard operating procedures that will be used in support for the management of study data including electronic data handling, case report forms, archiving of research materials, and record destruction. Referral and recruiting reviews will be undertaken via monthly trial management video calls and ongoing oversight by the lead investigator. Monitoring will be conducted remotely, including data quality, protocol deviations or violations, adverse event reporting, participant consent, and eligibility. We will also monitor recruitment status and target achievement, review any adverse events or serious adverse events (suspected or actual), and review participant withdrawals and mortality.

Ethical Considerations

This research protocol was approved by the Human Research Ethics Committee of St Vincents Hospital Melbourne (ERM ID 84479, SAGE Project ID 2022/PID06577, and SVHM Local Ref ID 262/22). FOCUSau is noninvasive with no known risk of protocol-related injury. As a psychoeducational intervention focused on the provision of information we anticipate the risk of any adverse events to be low. Nevertheless, information is available in FOCUSau about where participants may access additional medical and psychosocial support. Our project team is experienced in leading complex psychosocial interventions involving the recruitment of patients with advanced disease and their family caregivers. If necessary, any adverse events will be reported to the CTS Ethical and Data Monitoring Committee. Due to the nature of the study population, some deaths due to advanced disease progress are expected. A protocol for liaising with the caregiver of the deceased has been developed for these situations. This includes advising caregivers allocated to the intervention arm that they will not be required to continue with the study.

Results

This study was funded in March 2022 and recruitment commenced in July 2024.

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Discussion

Anticipated Principal Findings

Australia's capacity to meet its national palliative care standards has been challenged [10]. This project will examine the clinical and health economic impacts of FOCUSau and gauge its potential for maintainability. If shown to be effective, this intervention will improve the emotional well-being of patients with advanced cancer and their family caregivers, regardless of their location or current level of health care support. Empirical findings as described above will inform an implementation and maintainability strategy. The strategy will describe a pathway and recommended steps for longer-term systematic delivery of FOCUSau across Australia, linking where possible with existing nationally supported cancer and palliative care programs.

Comparison With Prior Research

Historically, much of the psychological and psychoeducational palliative care intervention research has been delivered in person focusing on either the patient or their family caregivers [21,23-25]. However, trials of dyadic interventions, which focus on the patient and family caregiver together, have shown favorable outcomes for both parties [18,20,21]. Furthermore, digital health interventions offer an innovative modality and may provide considerable resource advantages to in-person interventions [26,27]. Hence, our trial will advance knowledge in these areas.

Limitations

We acknowledge some of the limitations associated with our control arm, including that control participants will not have access to FOCUSau after the final data collection point. Unfortunately, we do not have the funding and resources required to support this. We will, however, report on the number of participants who withdraw because they have not been allocated to the intervention arm.

Conclusions

Advanced cancer is a "family affair" significantly affecting the well-being of the person with cancer and their family [1]. We seek to determine the effectiveness and maintainability of a digital health intervention (FOCUSau) aimed at improving the well-being of patients with advanced cancer and their primary family caregivers.

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Data Availability

The data that support this study will be shared upon reasonable request to the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

CSRI: Client Services Receipt Inventory
CST: Cancer Symptoms Trials
ECOG: Eastern Cooperative Oncology Group
EoL: end of life
EORTC: European Organization for Research and Treatment of Cancer
EU: European Union
FACT-G: Functional Assessment of Cancer Therapy-General
FOCUS: Family, Outlook, Communication, Uncertainty, Symptom management
FOCUSau: Family, Outlook, Communication, Uncertainty, Symptom management in the Australian context
FS: fixed sequence
iFOCUS: digital Family, Outlook, Communication, Uncertainty, Symptom management
QLQ-C30: The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
QoL: quality of life
REDCap: Research Electronic Data Capture
TDF: Theoretical Domains Framework

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Protocol

Evaluating the Efficacy of a Digital Therapeutic (CT-152) as an Adjunct to Antidepressant Treatment in Adults With Major Depressive Disorder: Protocol for the MIRAI Remote Study

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Abstract

Background: Major depressive disorder (MDD) is common worldwide and can be highly disabling. People with MDD face many barriers to treatment and may not experience full symptom relief even when treated. Therefore, new treatment modalities are needed for MDD. Digital therapeutics (DTx) may provide people with MDD an additional treatment option.

Objective: This study aimed to describe a phase 3 remote, multicenter, randomized, masked, sham-controlled trial evaluating the efficacy of a smartphone app–based DTx (CT-152) in adult participants diagnosed with MDD, used as an adjunct to antidepressant therapy (ADT).

Methods: Participants aged 22-64 years with a current primary diagnosis of MDD and an inadequate response to ADT were included. Participants were randomized 1:1 to CT-152 or a sham DTx. CT-152 is a smartphone app–based DTx that delivers a cognitive-emotional and behavioral therapeutic intervention. The core components of CT-152 are the Emotional Faces Memory Task exercises, brief lessons to learn and apply key therapeutic skills, and SMS text messaging to reinforce lessons and encourage engagement with the app. The sham DTx is a digital working memory exercise with emotionally neutral stimuli designed to match CT-152 for time and attention. Participants took part in the trial for up to 13 weeks. The trial included a screening period of up to 3 weeks, a treatment period of 6 weeks, and an extension period of 4 weeks to assess the durability of the effect. Sites and participants had the option of an in-person or remote screening visit; the remaining trial visits were remote. Efficacy was evaluated using the Montgomery-Åsberg Depression Rating Scale, the Generalized Anxiety Disorder-7, Clinical Global Impression–Severity scale, the Patient Health Questionnaire-9, and the World Health Organization Disability Assessment Schedule 2.0. The durability of the effect was evaluated with the Montgomery-Åsberg Depression Rating Scale and Generalized Anxiety Disorder-7 scale. Adverse events were also assessed. Satisfaction, measured by the Participant and Healthcare Professional Satisfaction Scales, and health status, measured by the EQ-5D-5L, were summarized using descriptive statistics.

Results: This study was initiated in February 2021 and had a primary completion date in October 2022.

Conclusions: This represents the methodological design for the first evaluation of CT-152 as an adjunct to ADT. This study protocol is methodologically robust and incorporates many aspects of conventional pivotal pharmaceutical phase 3 trial design, such as randomization and safety end points. Novel considerations included the use of a sham comparator, masking considerations

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for visible app content, and outcome measures relevant to DTx. The rigor of this methodology will provide a more comprehensive understanding of the effectiveness of CT-152.

Trial Registration: ClinicalTrials.gov NCT04770285; https://clinicaltrials.gov/study/NCT04770285

International Registered Report Identifier (IRRID): RR1-10.2196/56960

(JMIR Res Protoc 2024;13:e56960) doi:10.2196/56960

KEYWORDS

adherence; digital placebo; sham control; cognitive-emotional training; Emotional Faces Memory Task; mobile phone

Introduction

Depression is a disabling and common disorder that affected 279.6 million people (5% of adults) worldwide in 2019 [1-3]. Major depressive disorder (MDD) accounted for 32.8 million years lived with disability globally in 2017, a 12.6% increase from 2007, and is predicted to be the leading global cause of disability by 2030 [4,5].

Early effective treatment of MDD is associated with better outcomes, and decreasing the duration of the depressive episode can reduce symptoms, improve clinical and functional outcomes, and increase the chance of full symptom relief [6-8]. However, people with MDD face many barriers to antidepressant therapy (ADT) and psychotherapy treatment, including access to mental health care professionals (HCPs) [9,10], logistical challenges such as long wait times for appointment scheduling and limited schedules due to work and family demands [11], and the stigma associated with mental illness [12]. In 2022, only 61.5% of US adults with a major depressive episode (MDE) in the past year received treatment for depression [13]. Global treatment rates are lower, with only 34.8% of people with depression receiving treatment annually [14].

Even when people with MDD can access treatment, it is not always successful. Many people with MDD do not respond to or achieve remission with ADT alone [15]. In the foundational Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only 48.6% and 36.8% of participants showed treatment response and achieved remission after first-line ADT, respectively, with lower percentages responding and remitting at each subsequent treatment step [15]. Psychotherapy may also not be effective for all patients; a meta-analysis of 193 studies of psychotherapy for the treatment of depression found a response rate of 41% at a 2-month follow-up [16]. Although ADT and psychotherapy alone may not work for all patients, data support that combining the 2 approaches is more effective for treating MDD symptoms than either approach alone [17-19].

Current treatment options may be difficult to access and are not effective for all people with MDD; therefore, new approaches for treating MDD are needed. One approach that may address this unmet need is the use of digital therapeutics (DTx), a subset of digital health [20-24]. DTx are software programs that deliver evidence-based interventions for medical conditions [25]. DTx may address a medical condition, manage, prevent, or treat a medical disorder or disease, or optimize medication [25]. When used to treat mental disorders, DTx may help overcome some barriers to treatment [26]. These software programs can be accessed remotely, allowing people with MDD more options than what may be available locally, and to access treatment on their own schedule [27-29]. Remote access to treatment can also ease stigma concerns and allow for more privacy [30]. DTx may offer an additional option for nonpharmacological treatment, expanding patient choice [31]. However, there are different types of digital health products in the United States that require different levels of regulatory oversight. Products that claim a treatment benefit must be cleared by the US Food and Drug Administration (FDA) and may require a prescription [25,32,33].

Otsuka Pharmaceutical Development & Commercialization, Inc, in collaboration with Click Therapeutics, Inc, has developed a smartphone app–based DTx, CT-152, for depression, used as an adjunct to ADT with the goal of reducing symptoms of depression. The core components of CT-152 are evidence-based training exercises (Emotional Faces Memory Task [EFMT]), brief lessons and activities to learn and apply key therapeutic skills, and supportive SMS text messaging to reinforce lessons and encourage engagement with the app. Although there are no comparable FDA-authorized digital therapeutics for MDD in the United States, there are some digital tools designed to support patients with MDD in addition to standard treatment that are available under FDA enforcement discretion (software that meets the regulatory definition of a device but pose minimal risk to patients, which can be obtained without a prescription). These tools have psychotherapy-based components but do not have training exercises [34]. The EFMT component of CT-152 was developed to adjust the connectivity in the affective network and regions of the cognitive control network that provide cognitive control over emotions [35,36].

A growing body of research has linked MDD with impaired cognitive control of emotionally salient information [37,38]. Impaired cognitive control is believed to manifest in perseverative thinking patterns (eg, rumination) [39]; these patterns serve to maintain or exacerbate the sad or depressed mood component in MDD [37-39]. Cognitive-emotional training, such as EFMT, has been shown to enhance cognitive control over emotions in people with MDD [40].

The goal of the EFMT exercises is to modify connectivity between the amygdala and dorsolateral prefrontal cortex by simultaneous emotion recognition and working memory tasks [36,37]. In 2 randomized controlled trials (RCTs), an improvement in depression symptoms was found to be statistically significant for participants with MDD who completed a digital EFMT regimen (4 and 6 weeks, respectively) compared with control participants who were not being treated with ADT or cognitive behavioral therapy (CBT) [36]. A

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follow-up study with participants who completed the 6-week EFMT regimen indicated that EFMT use altered connectivity between the amygdala with the right dorsolateral prefrontal cortex and bilateral dorsal anterior cingulate cortex; these altered connections correlated with improved symptoms [40].

The MIRAI trial (ClinicalTrials.gov NCT04770285) was designed to measure the effectiveness and safety of CT-152 for reducing depressive symptoms in patients diagnosed with MDD who were on ADT monotherapy for the treatment of depression. Data from MIRAI supported the FDA application for this product to be cleared as a prescription DTx for the treatment of people with MDD. There is also the potential to use these data to support regulatory approvals in other global markets.

MIRAI had design components reflecting conventional phase 3 pharmaceutical trials and novel components designed for DTx evaluation specifically. Conventional components included a control group and the evaluation of both effectiveness and safety. Effectiveness end points were established from gold-standard scales that are acceptable to the FDA [41-43]. Safety was evaluated by the frequency and severity of adverse events (AEs). Novel considerations in MIRAI included a sham comparator. The sham DTx consisted of a digital working memory exercise with emotionally neutral stimuli and was matched to CT-152 for time, attention, and expectation of benefit. The sham DTx also had an SMS text message component. Another consideration was treatment masking, which is important when designing studies for DTx [44]. Both participants and sites were masked to the treatment assignment. In DTx trials, a participant can spontaneously speak to an investigator, clinical raters, or study site staff about the exercises on the app (eg, participants reporting having difficulty with recognizing emotions on faces), leading to unmasking treatment assignment and introducing bias. Thus, additional masking considerations are required for both participants and investigators; steps taken in the MIRAI trial are listed in the Methods section. Finally, MIRAI incorporated outcomes that are relevant to DTx, including participant satisfaction with the treatment and adherence metrics.

There is a growing body of literature calling for DTx to be held to the same evidentiary standards as pharmacotherapy [45-50]. It is critical that the effectiveness and safety of these novel DTx are evaluated in RCTs with adequate sample sizes and clinically meaningful end points [51-53]. This trial will extend the findings from earlier EFMT studies and provide data on the efficacy and safety of this DTx. If shown to be effective, CT-152 may be considered a novel nonpharmacological option for people diagnosed with MDD to use as an adjunct to ADT. Here, we review the rationale and study design for the MIRAI trial, including procedures to enable a methodologically rigorous investigation of the new treatment options offered with DTx.

Methods

Overview

This was a phase 3 multicenter, randomized, masked, sham-controlled trial to evaluate the efficacy of CT-152 in adult participants diagnosed with MDD who were taking ADT. Participants took part in the trial for up to 13 weeks. The trial included a screening period of up to 3 weeks, a treatment period of 6 weeks, and an extension period of 4 weeks to assess the durability of the effect (Figure 1). Given the COVID-19 pandemic and the advantages of remote trials, especially for a DTx, MIRAI was run as a remote study. Except the screening visit, all visits took place remotely; the screening visit had an in-person or remote option per investigator and patient preference. Due to the DTx nature of this trial, participants needed routine access to their smartphones in their work and home life.

Figure 1. MIRAI Trial design.

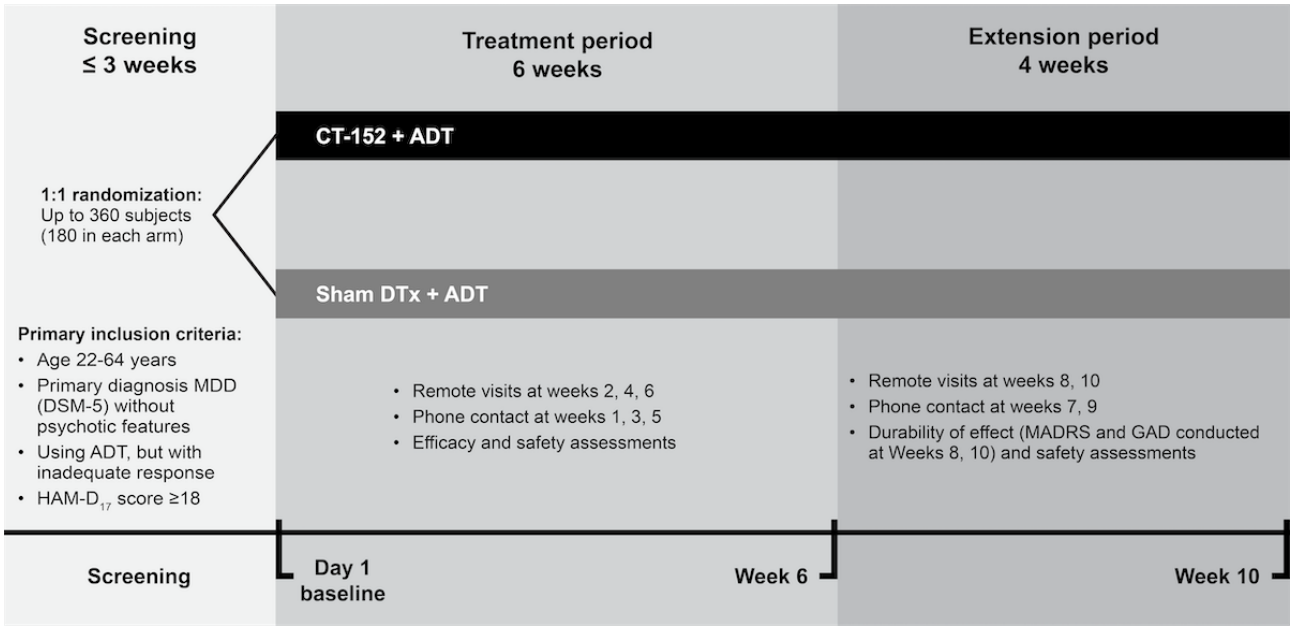

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Study Participants

Key participant inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Key inclusion and exclusion criteria for participation.

Inclusion criteria

- Aged 22 to 64 years at the time of informed consent.
- Fluent in written and spoken English.
- Taking antidepressant therapy (ADT) monotherapy with a current primary diagnosis of major depressive disorder (MDD) based on the criteria in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]), single or recurrent episode, without psychotic features, and did not meet the criteria for MDD with mixed features subtype.
- Had a score for the Hamilton Rating Scale for Depression, 17-item of ≥18 at screening and the baseline visit (day 1).
- Had a reported history of inadequate response to an adequate trial of ADT in the current episode.
  - Inadequate response was defined as a reduction in depression symptom severity <50% per the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ).
  - An adequate trial was defined as at least 6 weeks at a minimum therapeutic dose (or higher), according to the MGH-ATRQ.
- Were willing to maintain their current ADT at the current dose for the duration of their participation in the trial.
- Were currently using a smartphone not shared with anyone else, with an Android operating system 9.0 or greater capabilities or with iPhone Operating System 13.0 (Apple, Inc) or greater capabilities and agreed to download and use the smartphone app as required by the protocol.
- Had completed the onboarding module in the smartphone app during the screening period, continued consent to participate in the trial, and understood how to use the app at the baseline visit.

Exclusion criteria

- Had a reported inadequate response to >1 adequate trial of ADT (as defined in the inclusion criteria) for the current major depressive episode (MDE).
- Had been treated with psychopharmacological augmentation (eg, lithium, triiodothyronine, antipsychotics added to ADT, and multiple ADT) for any past episode or the current episode.
- Had received psychotherapy within 90 days before screening.
- Had significant suicidal ideation within the last year, suicidal behavior within the past 2 years, or presented a serious risk of suicide (in the opinion of the investigator).
- Had been treated with electroconvulsive therapy or neuromodulation devices (ie, transcranial magnetic stimulation, vagus nerve stimulation, or transcranial direct current stimulation) for MDD in the past.
- Were currently using a computer, web, or smartphone software–based application or equivalent for mental health or MDD; participants could enroll if this app was discontinued before the baseline visit.
- Had been in a current MDE lasting longer than 2 years.
- Were considered resistant or refractory to treatment by history and per investigator judgment.
- Had a lifetime diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorder, bipolar I or II disorder, or current posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder.
- Had been diagnosed with any DSM-5 personality disorder.
- Had MDD due to a general medical condition or a neurologic disorder.

Ethical Considerations

This trial was conducted in accordance with local laws, the International Conference on Harmonization Good Clinical Practice guidelines, and the Declaration of Helsinki. The protocol was reviewed and approved by the governing institutional review board (IRB) for each investigational site. Of the 54 study sites, IRB services were provided by Advarra (approval number 00000971) for 53 sites, and WCG IRB (approval number 1-1377994-1) for 1 site. IRB approvals were granted between November 2020 and January 2021. All participants were asked to provide consent to participate in this study before enrollment and agree to its privacy policy and terms of service required for the remote collection of their information. All information collected in the trial was considered confidential and was only used in accordance with the protocol. Participants were identified only by a unique identification number in eSource. However, regulatory officials or sponsor personnel could be allowed access to records, consistent with local requirements. Participants could withdraw from the trial at any time without justification. Participants received a stipend to help cover the costs associated with being in the study. Participants also had the option to have their ADT provided to them by the sponsor at no charge for the length of the study.

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Intervention

CT-152 is a smartphone app–based DTx that delivers a proprietary interactive cognitive-emotional and behavioral intervention, intended for use as an adjunct to ADT. The core components of CT-152 are the EFMT exercises; brief CBT-based lessons, each paired with an out-of-app activity or guided audio psychotherapy exercise targeting the most common MDD symptoms; and SMS text messaging to reinforce the CBT-based lessons and encourage engagement with the app. Each treatment session consisted of an EFMT exercise and a brief lesson with an activity. During the EFMT exercises, participants were presented with a series of pictures of faces, tasked with identifying the emotions they observed and remembering the sequence of emotions [35]. Using an N-back working memory training paradigm, for each face observed, participants indicated whether the emotion is the same as the emotion N faces back [35]. To date, CT-152 has only been developed in English.

A sham DTx served as a control and provided a cognitive training exercise designed to retain user interest while minimizing therapeutic effects. Each sham session consisted of a Shapes Memory Task (SMT) exercise. The SMT is a working memory task that provides users with an analogous structure, matched for time and attention, to the cognitive-emotional training exercise (EFMT) in CT-152. The sham DTx did not include EFMT exercises or lessons to retain its intended nontherapeutic nature. Participants in the control group also received supportive SMS text messages related to maintaining engagement with study treatment. The SMT exercise has been previously used in EFMT pilot studies as the control condition [35,36].

In order to be eligible to participate, during the screening period, participants had to complete an N-back working memory task simulating basic features of CT-152 to ensure they had the necessary skills to use it. This also confirmed their interest in participating in the study. After eligibility was confirmed, participants were randomized 1:1 to either CT-152 or sham DTx at the baseline visit (day 1). The participants progressed through a treatment schedule of 18 sessions at a rate of 3 sessions per week over the 6-week treatment period (day 1 to week 6). Participants had a remote study visit at weeks 2, 4, and 6 and were contacted by telephone at weeks 1, 3, and 5.

After week 6, participants continued in the trial during the extension period (weeks 7 to 10) to assess the durability of the effect. In the extension period, the smartphone app remained installed for each group; no new therapeutic content was introduced, and EFMT and SMT exercises were not available. The 2 groups each received brief supportive SMS text messages in the extension period with content related to the previously completed exercises. Participants had a remote study visit at weeks 8 and 10 and were contacted by the trial site by telephone at weeks 7 and 9.

A dedicated call center was available to support the participants and the trial sites on the initial downloading of and access to the smartphone app, as well as any technical issues with the app throughout the trial.

Outcomes and Assessments

The primary objective of the trial was to evaluate the efficacy of CT-152 in improving depressive symptoms versus the sham DTx, which served as a control. The primary efficacy end point was the change from baseline to week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Other efficacy end points included assessment of the MADRS at weeks 2 and 4; Generalized Anxiety Disorder-7 (GAD-7) scores at weeks 2, 4, and 6; the Clinical Global Impression–Severity scale scores (CGI-S) at weeks 2, 4, and 6; and the Patient Health Questionnaire-9 (PHQ-9) scores at weeks 4 and 6. Functional outcomes were assessed by World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores and quality of life by EQ-5D-5L scores at week 6. To evaluate the durability of the effect of the DTx, the change from baseline in MADRS and GAD-7 total score as well as MADRS response and remission rates were evaluated at weeks 8 and 10. The MADRS was conducted by trained and calibrated independent raters. Trial site staff administered the CGI-S. Participants completed the GAD-7, PHQ-9, WHODAS 2.0, and EQ-5D-5L (for scale descriptions, refer to Table 1).

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Table 1. Scales used for study assessments.

Scales	Description
MGH-ATRQ[a]	A 6-item, participant self-reported scale to evaluate treatment-resistant depression [54,55]
HAM-D_{17}[b]	A 17-item, observer-reported scale to evaluate depression severity and response to treatment [56]
MADRS[c]	A 10-item, HCP[d]-reported scale to evaluate depression severity [57]
CGI-S[e]	A single-item, observer-reported scale to evaluate the severity of mental illness over the past week [58]
PHQ-9[f]	A 9-item, participant self-reported scale to screen for and assess depression severity [56]
GAD-7[g]	A 7-item, participant self-reported scale to screen for and assess the severity of general anxiety disorder [59]
WHODAS 2.0[h]	A 36-item, participant self-reported scale to assess the impact of a health condition on functioning [60]
Participant satisfaction scale	A 9-item, participant self-reported scale designed for the MIRAI trial to assess participants' satisfaction with their DTx[i] assignment for the trial
HCP satisfaction scale	A 2-item, HCP self-reported scale designed for the MIRAI trial to assess HCP satisfaction with delivering the DTx used by their patients during the trial
EQ-5D-5L	A 5-item, participant self-reported scale to measure overall health status. It includes a vertical visual analog scale for participants to indicate their perception of their overall health [61]
C-SSRS[j]	A 6-item, participant self-reported scale to assess suicide risk, severity of risk, and support needed [62]

[a]MGH-ATRQ: Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire.

[b]HAM-D_{17}: Hamilton Rating Scale for Depression, 17-item.

[c]MADRS: Montgomery-Åsberg Depression Rating Scale.

[d]HCP: health care professional.

[e]CGI-S: Clinical Global Impressions-Severity.

[f]PHQ-9: Patient Health Questionnaire-9.

[g]GAD-7: Generalized Anxiety Disorder-7.

[h]WHODAS: World Health Organization Disability Assessment Schedule.

[i]DTx: digital therapeutics.

[j]C-SSRS: Columbia-Suicide Severity Rating Scale.

The safety objective was to assess the safety of CT-152 in adult participants with MDD who were concurrently taking ADT. Safety was evaluated by the frequency and severity of AEs, serious AEs, and discontinuations from the trial due to AEs. AEs related to smartphone use may include dizziness, fatigue, or headache and were anticipated as potential AEs reported by the participants [63,64]. Previous research did not assess AEs related to EFMT use [35,36]. Participants were required to be on ADT monotherapy, and the safety profile of ADTs used for MDD is well understood. Based on the known risks of ADT and smartphone use and a preliminary understanding of the risks of EFMT use, no additional risks were anticipated as related to CT-152 use. All participants were assessed weekly for both anticipated and unanticipated AEs; any participants reporting serious AEs were monitored.

Participant adherence was monitored weekly. Furthermore, the number of CT-152 or sham sessions completed over the entire trial course was recorded.

Masking Considerations

In addition to masking the participants and trial sites for the treatment assignment, masked independent raters conducted the MADRS assessment by telephone. The independent raters had no access to trial procedures, treatment assignment, trial data, or clinical information other than what was solicited for the assessment. In addition, both independent raters and participants were instructed to avoid discussion of the DTx content and other aspects of the trial.

To minimize potential bias, trial sites had designated administrators of the other efficacy assessments. Administrators had limited contact with the participants and did not perform adherence checks. Participants completed self-reported outcomes independently and remotely.

The hypothesis of this trial—CT-152 would lead to greater improvement in MDD symptoms versus the sham DTx—was masked, and participants were informed that either DTx may be effective. This approach was intended to optimize adherence in both arms and limit the risk of participant unmasking and associated expectation biases. At the end of the study, participants were informed of the trial hypothesis, but were not informed of which DTx they had received.

CT-152 meets the definition of a nonsignificant risk device per 21 Code of Federal Regulations § 812.3(m) and a low- to

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moderate-risk device per Software as a Medical Device [65,66]. The masking approaches used in this trial were only used because (1) CT-152 posed minimal risks, (2) masking did not adversely affect the participants, and (3) the trial could only be conducted by withholding the information on participant treatment assignment.

Sample Size Calculation

The initial sample size was calculated to detect a 3-unit difference between the CT-152 plus ADT and sham DTx plus ADT in the change from baseline in MADRS total score, with 85% power at a 2-sided α=.05 level. The resulting sample size was 324 evaluable participants in total (162 in each arm). The full analysis set was defined as all randomized participants who received at least 1 CT-152 or sham DTx session and had at least 2 MADRS total score assessments, 1 of which was at baseline. To compensate for participants who failed to have evaluable assessments of MADRS total score in the full analysis set sample (estimated at up to 10% of all participants), a total of approximately 360 participants (180 in each arm) were planned to be randomized. The trial randomized eligible participants 1:1 across 54 sites. The sample size at any single trial site was capped at approximately 15% of the total number of randomized participants. Randomization was stratified by the trial site.

Due to the limitations of applying assumptions on the treatment effect size, and to ensure adequate power of the trial, an unmasked interim analysis was conducted by a data monitoring committee, whose members recommended continuing the trial with the planned sample size of 360 participants (actual enrollment included 386 participants).

Statistical Methods

Baseline and demographic characteristics, including age, sex, race, and ethnicity, were summarized using descriptive statistics.

End Points and Assessments

The primary efficacy analysis was based on the mixed-model repeated measurements method and the change from baseline score to week 6 for the MADRS. The MADRS score change from baseline to weeks 2 and 4 was also assessed. Additional efficacy analyses included changes from baseline to predetermined end points for the GAD-7, CGI-S, WHODAS 2.0, and PHQ-9. MADRS partial and full response rates (≥30% to <50% from baseline and ≥50% reduction from baseline, respectively) at weeks 2, 4, and 6 were analyzed; MADRS response rates were also analyzed during weeks 8 and 10 of the extension period. All efficacy end points were based on the full analysis set.

The durability of the treatment effect was assessed based on MADRS and GAD-7 scores during the extension period. The SAS Enterprise Guide version 8.3 (SAS Institute Inc.) was used for statistical analyses.

Plan for Missing Data in Efficacy End Points

All data collected during the trial treatment period and extension period were used for statistical analysis. The mixed-model repeated measurements method assumed data were missing at random, which is a reasonable assumption for longitudinal clinical trials in MDD [67]. However, the possibility of missing not at random data was also considered. As sensitivity analyses, pattern-mixture models were used to explore data missing mechanisms of missing not at random and investigate the response profile of participants by dropout reason.

Exploratory End Points

MADRS remission rates at weeks 2, 4, and 6 were analyzed. Remission was defined as a MADRS total score of ≤10 and a decrease of 50% or more of the total score from baseline. Satisfaction, measured by the Participant and Healthcare Professional Satisfaction Scales, and health status, measured by the EQ-5D-5L, were summarized using descriptive statistics.

Safety End Points

All AEs were coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA)-preferred term. The incidence of the following events was summarized by treatment group: (1) AEs that are potentially causally related to the treatment or sham DTx, (2) AEs with an outcome of death, serious AEs, and (3) AEs leading to discontinuation from the trial.

Adherence

Adherence was evaluated for all participants as the percentage of sessions completed over the course of the trial.

Results

The MIRAI study was funded in September 2020. It was initiated in February 2021, with a primary completion date of October 2022. As of study completion, 386 participants were enrolled. The primary data analysis is complete and expected to be published in the fall of 2024.

Discussion

Principal Findings

This was the first investigation of CT-152 as an adjunct to ADT for the treatment of depression. CT-152 has both cognitive-emotional training and behavioral intervention components, which is a novel combination compared with other digital tools designed to support patients with MDD currently available under FDA enforcement discretion [34]. This protocol incorporated aspects of conventional phase 3 pharmaceutical trials, including using a randomized controlled design and gold-standard scales for evaluating effectiveness. In addition, the safety analyses were intended to evaluate if CT-152, designed to provide a clinical intervention, had a low safety risk and was well tolerated by participants. MIRAI also considered factors that are not typical for DTx study design. The use of a sham DTx comparator minimized the potential that any changes between groups were because of CT-152 and not due to the demand characteristics of using a DTx. Bias related to knowledge of study treatment assignment was managed through robust masking procedures. Adherence was evaluated for both CT-152 and the sham DTx arms.

Safety

Although DTx for mental disorders may be less likely to lead to AEs than pharmacotherapy, AEs, such as dizziness, fatigue,

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and headache, that are associated with mobile device use may also be associated with DTx [63,64,68]. Therefore, it is important to assess the safety of DTx. Other current clinical trials for DTx for MDD do not assess safety outcomes [69]. Among 11 protocols for clinical trials assessing DTx for MDD published recently, only 1 mentions assessing AEs along with suicide risk [70]; 5 others assess suicide risk only [71-75]. Unlike the pivotal trials for current FDA-cleared DTx for mental disorders, the MIRAI trial assessed safety outcomes [76-79]. CT-152 was expected to be well tolerated due to the digital delivery of therapy and the mechanisms of action of its core therapeutic modules.

Sham Comparator

In trials for pharmacological treatments, masking is typically achieved through a placebo that resembles the treatment being tested. In RCTs for DTx, having a placebo that allows for masking can be challenging [50]. Of 11 clinical trial protocols published in the past few years that evaluated digital interventions for MDD, only 5 involved masking; 1 of the 5 trials masked both participants and interviewers [80]. When a participant is waitlisted or given treatment as usual during a trial of digital intervention, they may become aware of not receiving the treatment under study, which could impact their involvement and expectations [81]. In conclusion, there are masking advantages to using a sham comparator.

The variability in comparator arms in DTx trials can lead to challenges in understanding the effects of digital treatments as a class and relative to one another. In total, 3 meta-analyses of digital interventions for depression found lower effect sizes in studies of smartphone interventions that included comparators that controlled for time and attention but did not provide therapeutic intervention, compared with those studies with inactive comparators or waitlist controls [81-83]. This suggests that smartphone use alone may confer psychological benefits [46,81-84]. Using a digital comparator may raise the evidentiary standard for evaluating a digital treatment [83,84]. Given these recent findings and the potential confounding factors when using a nondigital comparator for the control group (eg, waitlist or treatment as usual), a digital comparator is important for a more unbiased and accurate understanding of the effectiveness of a DTx [81-83].

The MIRAI trial design is innovative because it included a sham DTx as the comparator, which helps to ensure that the comparison reflected a true change in symptoms (if any), rather than a nonspecific benefit related to digital interventions more broadly [46,81,82]. The sham DTx more easily allowed for masking, with less risk of participants and investigators becoming unmasked.

Outcomes Important for DTx

An important consideration for any treatment is understanding the relationship between improvement in patient symptoms and increased patient adherence to the treatment; this is a novel consideration for digital interventions [85,86]. For MDD specifically, among 11 study protocols involving DTx for MDD, 9 protocols described adherence assessments [80]. While data on adherence were collected, none of the protocols defined adherence or how it would be evaluated.

A systematic literature review on adherence and engagement with digital interventions for MDD defined adherence as the percentage of sessions completed (the number of sessions completed divided by the total number of sessions) and found that only 38 out of 94 studies reviewed had this information available [80]. Their findings highlight the importance of establishing a standardized metric for adherence to digital interventions to better compare results across studies and different types of interventions [80]. The MIRAI study was designed to collect data that can be used to measure the percentage of sessions completed, which will contribute to the body of literature measuring adherence to digital interventions in a way that can be compared across studies.

Another novel consideration for DTx that does not often apply to pharmacological treatments is the consideration of patient satisfaction with and the ability to easily use the intervention. This can include features such as an easy onboarding practice, personalizing app content, and text reminders for patients [87]. CT-152 includes text messages to remind participants of what they learned and to engage them with treatment. In addition, MIRAI had both a participant and an HCP satisfaction survey to gain further insights into how easy CT-152 was to use and how satisfied participants were with their experience.

Limitations

While this study design addressed many common concerns about trials for digital interventions, it had limitations, such as not including adults younger than 22 years or older than 65 years. Therefore, potential benefits for these populations will need to be explored in future research [88]. The inclusion criterion for MDD severity was a Hamilton Rating Scale for Depression, 17-item score of ≥18, potentially excluding participants with milder MDD. A further limitation is that the MIRAI trial assessed CT-152 as an adjunct to ADT, and thus the results cannot be generalized to using the digital intervention without ADT.

There were also potential limitations related to remote trials and digital interventions, such as limited access to technology or low digital literacy. In this study, participants were required to own a smartphone and had to complete an onboarding module to show they had an interest in study participation and the skills necessary to use CT-152 or the sham DTx. These requirements limited the potential for low digital access or literacy to impact participation.

In addition, a common occurrence in trials for digital interventions or that use remote data collection is participant attrition [89,90]. Although most clinical trials have some participants discontinue or be unresponsive to follow-up, this is more likely to happen in studies involving DTx [89,90]. Participant attrition was evaluated after the trial but was expected to be similar to what is seen in the literature. Participant engagement and adherence to digital interventions were also concerns [80]. Both CT-152 and the sham DTx had text messages designed to encourage participant adherence and engagement throughout the study. To encourage overall

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continued adherence to the study program, participants were informed before enrolling that remote visits would be required, and they reviewed the visit schedule with trial site staff once randomized to a treatment arm. Adherence checks were also performed during the treatment period and adherence was monitored remotely through the DTx. Any signs of nonadherence were addressed by the investigator to remind and encourage participants to continue adhering to the study program.

Conclusions

DTx has the potential to address many barriers to MDD treatment, including increasing access to more treatment options, allowing for remote access, easily fitting into a patient's schedule, and easing stigma concerns [26-28,30]. However, it is important that the effectiveness and safety of DTx are evaluated in RCTs with rigorous study design [51-53].

Many considerations in conventional phase 3 trial design, such as safety end points, adherence, and the use of a sham comparator, have been incorporated into this protocol to assess the efficacy of CT-152 for MDD, although the way these considerations are assessed is often different for pharmacological treatment. Incorporating safety and adherence considerations, along with participant masking to the treatment, are not yet typical for DTx evaluation. Moreover, rigorous assessments of these outcomes will provide a more comprehensive understanding of the effectiveness of CT-152.

Acknowledgments

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Authors' Contributions

BR, MS, AS, EL, MF, DC, D Chen, and AF made a significant contribution to the conception, study design, execution, acquisition of data, analysis, and interpretation of the work reported. AJR and MHT made a significant contribution to the conception, study design, and interpretation of the work reported. BR, MS, AS, AJR, MHT, EL, MF, DC, D Chen, and AF took part in drafting, revising, and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Conflicts of Interest

BR, MS, EL, MF, D Chen, and AF are employees of Otsuka Pharmaceutical Development & Commercialization, Inc, and DC is an employee of Otsuka Precision Health, Inc. AS is an employee of Click Therapeutics, Inc. MHT is a consultant for Otsuka Pharmaceutical Development & Commercialization, Inc. AJR has received consulting fees from Compass Inc., Curbstone Consultant LLC, Emmes Corp., Evecxia Therapeutics, Inc, Holmusk Technologies, Inc, ICON, PLC, Johnson & Johnson (Janssen), Liva-Nova, MindStreet, Inc, Neurocrine Biosciences Inc, Otsuka-US; speaking fees from Liva-Nova, Johnson & Johnson (Janssen); and royalties from Wolters Kluwer Health, Guilford Press, and the University of Texas Southwestern Medical Center, Dallas, TX.

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Abbreviations

ADT: antidepressant therapy
AE: adverse event
CBT: cognitive behavioral therapy
CGI-S: Clinical Global Impression–Severity scale
DTx: digital therapeutics
EFMT: Emotional Faces Memory Task
FDA: US Food and Drug Administration
GAD-7: General Anxiety Disorder-7 scale
HCP: health care professional
IRB: institutional review board
MADRS: Montgomery-Åsberg Depression Rating Scale
MDD: major depressive disorder
MDE: major depressive episode
MedDRA: Medical Dictionary for Regulatory Activities
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
SMT: Shapes Memory Task
STAR*D: Sequenced Treatment Alternatives to Relieve Depression
WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0

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Protocol

Reducing Alcohol Misuse and Promoting Treatment Initiation Among Veterans Through a Brief Internet-Based Intervention: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young adult veterans who served after the September 11 attacks on the United States in 2001 (ie, post-9/11) are at heightened risk for experiencing behavioral health distress and disorders including hazardous drinking, posttraumatic stress disorder, and depression. These veterans often face significant barriers to behavioral health treatment, and reaching them through brief mobile phone–based interventions may help reduce drinking and promote treatment engagement.

Objective: Following a successful pilot study, this randomized controlled trial (RCT) aims to further test the efficacy of a brief (ie, single session) mobile phone–delivered personalized normative feedback intervention enhanced with content to promote treatment engagement.

Methods: We will conduct an RCT with 800 post-9/11 young adult veterans (aged 18 to 40 years) with potentially hazardous drinking and who have not recently received treatment for any behavioral health problems. Participants will be randomly assigned to the personalized intervention or a control condition with resources for seeking care. The personalized normative feedback module in the intervention focuses on the correction of misperceived norms of peer alcohol use and uses empirically informed approaches to increase motivation to address alcohol use and co-occurring behavioral health problems. Past 30-day drinking, alcohol-related consequences, and treatment-seeking behaviors will be assessed at baseline and 3, 6, 9, and 12 months post intervention. Sex, barriers to care, posttraumatic stress disorder, depression, and severity of alcohol use disorder symptoms will be explored as potential moderators of outcomes.

Results: We expect recruitment to be completed within 6 months, with data collection taking 12 months for each enrolled participant. Analyses will begin within 3 months of the final data collection point (ie, 12 months follow-up).

Conclusions: This RCT will evaluate the efficacy of a novel intervention for non–treatment-seeking veterans who struggle with hazardous drinking and possible co-occurring behavioral health problems. This intervention has the potential to improve veteran health outcomes and overcome significant barriers to treatment.

Trial Registration: ClinicalTrials.gov NCT04244461; https://clinicaltrials.gov/study/NCT04244461

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KEYWORDS

military; mental health; substance use; mobile; PTSD; posttraumatic stress disorder; drinking; mobile intervention; digital intervention; alcohol; alcohol misuse; veterans; young adults; depression; alcohol use; veteran health; veteran

Introduction

Background

Americans who served in the US military during or after September 11, 2001, and have since been discharged (post-9/11 veterans) experience concerning rates of mental health disorders, with an estimated prevalence of depression and posttraumatic stress disorder (PTSD) ranging from 10% to 30%, respectively [1-5], and often co-occurring [6]. Alcohol use disorder (AUD) is the most common substance use disorder among veterans [7-10] and it, too, often co-occurs among veterans with depression or PTSD [11-14]. Approximately 1 in 10 post-9/11 veterans who are seeking any care within the Veterans Health Administration meet the criteria for an AUD [9], and studies show that upwards of 40% of these veterans drink alcohol at levels that place them at risk for negative alcohol-related consequences (ie, hazardous drinking) [10,15-18]. Veterans younger than 40 years old drink more heavily than older veterans [9,10] and may be at heightened risk for developing an AUD later in life, making early intervention and prevention efforts for younger adult veterans essential.

Despite the availability of evidence-based behavioral health care (ie, care for mental health or substance use disorders) through Veterans Affairs (VA) and in private care settings [19-22], not all veterans with behavioral health needs use these services. Estimates suggest that over 50% of post-9/11 veterans meet screening criteria for a mental health disorder (including AUD), but less than half receive care [23-29]. Those who do often receive inadequate care to address their needs, such as seeing a mental health provider only once or twice for an intake without follow-up or not completing a doctor's full planned prescription for psychotropic medications [30-32]. Veterans who engage in heavy drinking and have a co-occurring PTSD and depression diagnosis have particularly difficult barriers to seeking care [33]. It is important to target heavy alcohol use early after discharge and in young adulthood so both alcohol use and co-occurring mental health problems do not become chronic or more difficult to treat.

Veterans may not receive needed care for a variety of reasons. Barriers to care include perceived stigma from others (eg, a belief that colleagues, family, and friends would respect them less), fear of repercussions or career harm (eg, concerns that their career would not progress if they seek treatment), beliefs that their drinking behavior is normative among other veterans and not in need of change, lack of awareness of treatment options, concerns about high costs, limited access due to residency in rural areas, and beliefs that they can handle their problems on their own or that available treatments are not effective [27,29,34-38]. Women and racial or ethnic minority veterans may have additional barriers related to childcare responsibilities, apprehension about using VA facilities, discomfort and mistrust of providers, and discrimination within health care systems [39].

Internet and mobile phone–based treatment approaches represent a potentially important avenue through which to help veterans overcome barriers to accessing the care they may not otherwise pursue. Existing outreach efforts target veterans already seeking services at the VA (eg, care for physical injuries) through public media campaigns and announcements in primary care clinics. However, these efforts do little for the largely neglected population of veterans who have not received care from the VA or for those who may prefer to seek care elsewhere but are either unaware of or disinterested in their options [33,40]. In addition, stand-alone internet-based alcohol interventions for veterans are lengthy and characterized by high attrition [41-45].

In an effort to reach veterans outside of VA settings, we designed and pilot-tested a single-session intervention [46] for a cohort of young adult veterans (ie, aged 18 to 34 years) who were recruited on social media websites. In the intervention, which targeted veteran drinkers who were not necessarily seeking treatment for alcohol-related concerns, veteran participants were shown normative data of their sex-specific veteran peers (ie, other male veterans and other female veterans) [47,48] to correct their overestimations of peer veteran drinking behavior and to provide a comparative reference for their drinking behavior (ie, to demonstrate that their veteran peers likely drink less than an individual may think other veterans drink, or less than they, in fact, do). In this pilot randomized controlled trial (RCT; ClinicalTrials.gov NCT02187887), we found small but significant intervention effects favoring the intervention 1 month post intervention on all prespecified drinking outcomes: past 30-day drinks per week (d=0.47), average number of drinks per occasion (d=0.17), binge drinking days (defined at 5 drinks in a row for males and 4 drinks in a row for females; d=0.18), and alcohol-related consequences (d=0.17) compared to control [49].

As concluded in a recent review of brief internet-based interventions for young adult alcohol misuse [50], from a public health perspective, being able to reach a large number of individuals and provide them with interventions that lead to even modest effects is beneficial at a societal level. Such modest effects from a single-session program may be important as an individual begins to evaluate one's personal alcohol use and considers making a change, which may include seeking out formal assessment and more intensive treatment. The personalized normative feedback (PNF) approach offers a reference point for an individual's personal drinking habits compared to peers, and similar to a checkup model [41,51], allows one to consider making a change to their drinking. Though PNF interventions are efficacious, these effects are often small and short-lived [52]. Thus, there is room for PNF interventions to expand beyond short-term effects on drinking and be used as a vehicle to connect those who have never received an intervention before with more intensive services. For veterans engaging in heavier problem drinking, sustained changes in drinking may be better obtained through in-person individual or group interventions, as opposed to a one-time brief

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intervention. For veterans who use alcohol to cope with or manage PTSD or depression symptoms, more intensive co-occurring disorder treatment may be indicated, whereby they can learn more adaptive techniques to cope with negative affect. In our pilot study, we found that almost twice as many PNF condition participants as control participants reported increases in motivation and likelihood to seek AUD treatment simply after viewing the PNF [53], alluding to the promise of the approach in targeting treatment initiation among the group of veterans who have not engaged in care or have had substantial barriers or challenges doing so. If the brief intervention prompted veterans to think more about making a change to their drinking, it may be a tool to reach those who may not have otherwise considered change and to connect them with services.

This Study

To build upon the pilot trial, we designed this study to test the longer-term effects (ie, 12-month outcomes) of a brief PNF intervention on drinking and treatment (ie, motivation and preparation for; actual initiation) outcomes. For this larger study, we expand upon the original pilot intervention content, which primarily focused on correcting misperceived norms of veteran peer alcohol use, to include empirically informed approaches to increase motivation to address one's alcohol use and co-occurring behavioral mental health problems (eg, depression, anxiety, and PTSD) in more formal care settings (ie, those beyond a one-time brief intervention such as care with a provider at a VA). In doing so, we will evaluate intervention effects on readiness to initiate behavioral health care, preparatory behaviors toward seeking that care, and any actual care initiation in the postintervention period. To evaluate the impact of the intervention on these outcomes, we intend to enroll and randomize 800 participants into either the PNF intervention (n=400) or a resources-only control condition focused on providing information related to care services (n=400). In the protocol that follows, we describe our recruitment methods and target sample, list our measures for outcomes and moderators of intervention effects, discuss the intervention content in detail, and lay out the proposed analytic plan to examine the efficacy of the brief internet-based intervention on alcohol use and treatment initiation outcomes.

Methods

Trial Design Overview

This RCT (ClinicalTrials.gov NCT04244461) was designed to test the efficacy of a single-session brief mobile phone–based intervention with young adult veterans. The intervention will be a mix of narrated video, audio, text, and graphics that contain personalized content emphasizing the veteran's values, their goals for treatment initiation, and resources to help them connect with behavioral health care. Veteran participants aged 18 to 40 years will complete a baseline survey, be randomized to the intervention or a control condition, and then complete four follow-up surveys at 3, 6, 9, and 12 months post baseline. At each follow-up period, all participants will be emailed a list of resources to help connect them to behavioral health services, as well as a link to the intervention website after each follow-up assessment. The intervention is named Project BRAVE (Building Resilience and Agency through Veteran Engagement), with an accompanying logo, to help veterans recognize the study during recruitment and reminder correspondence (Figure 1).

Figure 1. Flow of proposed randomized controlled trial. BRAVE: Building Resilience and Agency through Veteran Engagement.

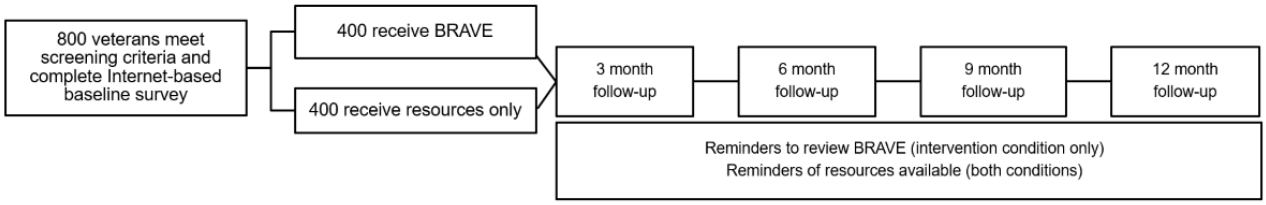

Specific Aims and Hypotheses

For the first aim, we intend to conduct an RCT of the BRAVE intervention by randomly assigning veterans with potentially hazardous drinking patterns, but who have not received recent treatment for drinking or any other behavioral health problem, to receive either the BRAVE intervention or a resources-only control condition. We hypothesize that BRAVE participants will drink less (fewer days per week, fewer drinks per occasion, and fewer binge drinking days), experience fewer negative alcohol-related consequences, and report more treatment readiness, preparatory behaviors, and initiation behaviors at 3, 6, 9, and 12 months post intervention, relative to control participants. For the second aim, we will determine for which subgroups the intervention works best. We hypothesize BRAVE participants who report more baseline barriers to care (eg, perceived public stigma beliefs that others would view them negatively for seeking care, not having time due to work or family responsibilities), baseline high levels of PTSD or depression symptoms, and higher baseline problematic alcohol use will benefit most from the intervention in terms of drinking reductions and treatment initiation outcomes. Sex (male and female) will be examined as an exploratory moderator, which expands on veteran work that traditionally examines male veterans only, which is important considering unique female-specific factors that affect treatment engagement [39].

Participant Recruitment and Eligibility

The BRAVE intervention is designed for mobile phones with internet capabilities and is targeted toward young adult veterans. Though the intervention is designed for use on mobile phones, it can be accessed through computers and tablets. Given the focus on a younger veteran cohort, eligibility criteria include (1) US veteran who has been discharged or separated from the Air Force, Army, Navy, Marine Corps, or Coast Guard (participants could have also been in the reserves or guard units,

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but not on active duty), (2) between the ages of 18 and 40 years, (3) a score on the 10-item Alcohol Use Disorders Identification Test (AUDIT [54]) of 4 or greater (men) or 3 or greater (women), which represents cutoff scores to identify those who may benefit from interventions to reduce alcohol misuse, (4) no upcoming appointments at the VA or elsewhere to receive treatment for a behavioral health concern (such as depression, PTSD, or alcohol use concerns), and (5) no appointments in the past six months for behavioral health treatment at a VA or elsewhere. The purpose of these latter 2 criteria is to reach participants outside of traditional care settings (ie, those who may need care but who are not receiving it) and to measure the effect of the intervention on treatment initiation. Participants also need access to the internet via a computer, tablet, or phone; a working email address; and the ability to read and understand English. Based on these criteria, we will recruit 800 participants who will be randomly assigned to the BRAVE intervention (n=400) or a resources-only control condition (n=400) that presents resources for care seeking (eg, location of local VA and links for connecting with local veteran service organizations) without any personalized content.

Procedures

Participants will be recruited with the aid of a recruitment platform, BuildClinical, which uses machine learning and data mining procedures to target internet ads to recruit the sample population from a variety of general internet and social media sources (eg, Instagram, Facebook, Google, and health websites). BuildClinical uses targeted ad imagery and text to ensure we meet the recruitment needs of the study, including aiming for 10%-15% women veterans to match the growing number of post-9/11 women veterans. The pilot intervention study successfully enrolled 18% of women veterans [49]. Participants will click on ads displayed and be directed to a website with a description of the study. If interested, they can fill out a web-based screening form to assess eligibility and answer questions to help determine that they are not falsifying responses to gain access to the offered incentives. We have developed procedures to identify and exclude nonveterans from enrollment, which includes asking about first-hand knowledge through questions that must be consistent across responses (eg, branch, rank, pay grade, and job in the military must all make sense when considered together) and ensuring responses are identical when asked variations of the same question at different times throughout the survey. Once participants pass through the initial validation checks, we will call each potential participant to verify the information they provided (eg, ensuring phone responses match survey responses to items such as branch and rank). If the individual's responses are deemed credible and they remain interested in participation, the individual will be enrolled as a participant following a discussion of the study procedures and consent document. Once enrolled, participants will fill out a baseline survey and then be randomized to one of two conditions: the BRAVE intervention or a resources-only control condition.

BRAVE Intervention Condition

The intervention was designed to build upon the piloted PNF intervention with veterans from our prior work [49]. Similar to other young adult groups, veterans misperceive the drinking behavior of their peers and these misperceptions are associated with their drinking behavior [48]. PNF is one of the most frequently used efficacious drinking interventions for young adults [52] and we have shown promise in the stand-alone approach for young veterans [49]. In the PNF, individuals are presented with normative data that challenges their beliefs that similar peers drink as heavily as the individual perceives they do. Using graphics and descriptions of norms theory (eg, we pay attention to patterns outside the norm and come to believe those deviations are more normative than they are), individuals can see that their perceptions about others may be incorrect and that they may be drinking more than their peers. In BRAVE, participants are presented with PNF approximately midway through the larger, multicomponent intervention. First, participants are asked about their drinking behavior and the behavior of their peers in the past 30 days. Participants indicate how many drinks they consumed on a typical drinking day and how many drinks they think other male and female veterans drank on a typical drinking day. They then indicate how many days in the past 30 days they drank 4 (for females) or 5 (for males) drinks on an occasion (ie, binge drinking) and how many days they think male and female veterans drank these amounts. PNF is then displayed for both male and female drinking norms to all participants so veterans can see that heavy drinking is not the norm among both sexes (see example in Figure 2). Norms for drinking were derived from our prior work with 1230 veterans [55].

We expanded the PNF intervention to include content designed to encourage veterans who were not currently seeking care for alcohol or mental health concerns to more strongly consider and actually seek care. The intervention includes a mix of videos, audio, text, graphics, and text-based components. There are 2 veteran peers as narrators (one male and one female) who walk veterans through a 20- to 30-minute personalized intervention. Veteran peers were selected for the program given prior work showing the importance of peers in helping change attitudes and behaviors in health interventions [56], particularly among veterans with mental health and substance use concerns [57,58].

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Figure 2. Sample of drinking personalized normative feedback.

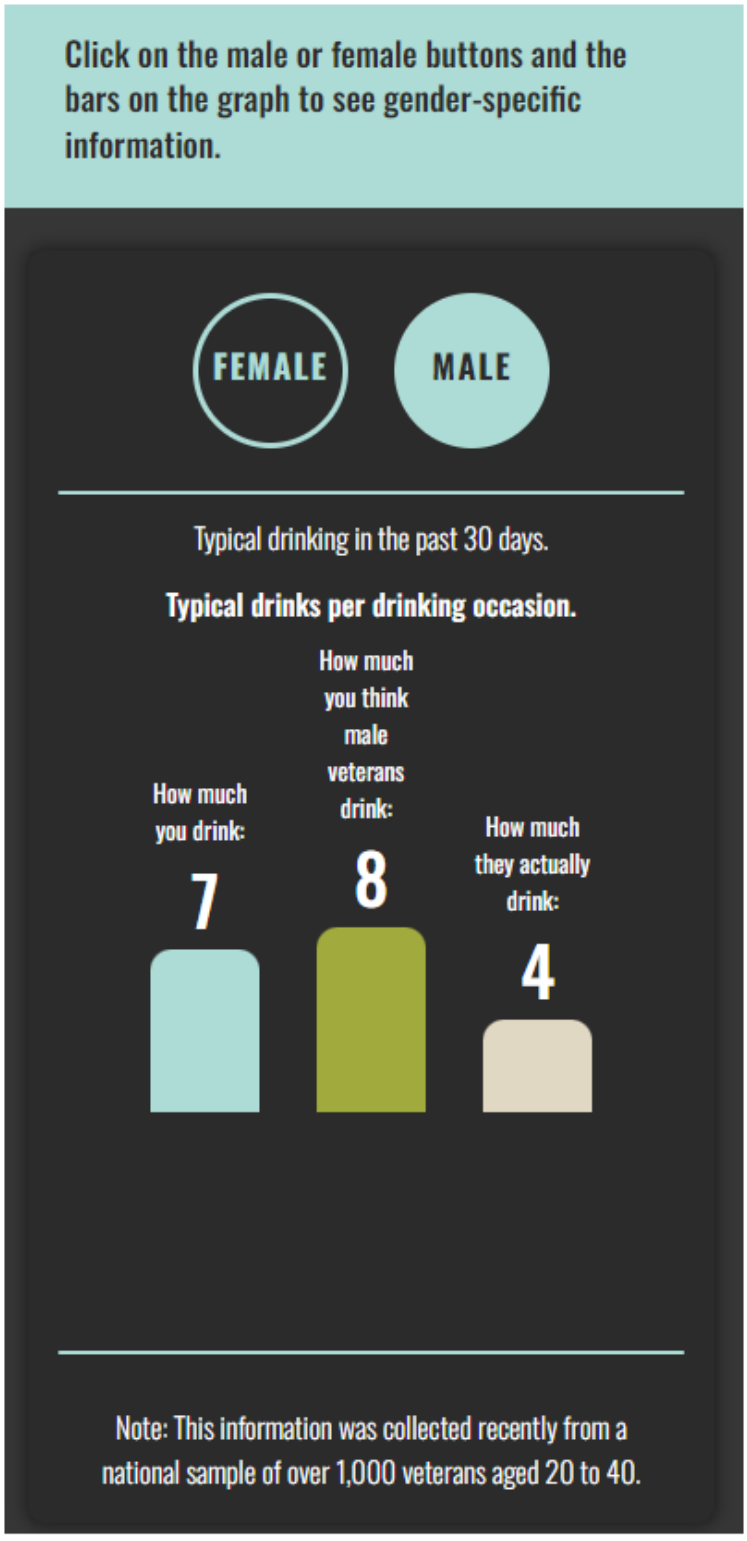

BRAVE begins with the clarification of personal values, with the selection of values and related content that highlights the ways in which veterans live according to those values. Veterans are given a set of 16 values and asked to select which resonates with them. Examples of values presented include Honor ("To adhere to what is right with great respect"), Self-control ("To be disciplined in my own actions"), Courage ("To be brave and strong in the face of fear, threat, or difficulty"), and Empathy ("To try and understand the perspective of others and what they are feeling"). They are also given the option to indicate their own values not included in the sample list. This component is based on the "values card sort" exercise originally created as a tool in Motivational Interviewing [59], and used heavily in Acceptance and Commitment Therapy [60]. The purpose of using these intervention components is to help veterans identify and reflect on what is most meaningful and important to them in their lives; this may include seeking care for any mental health concerns they may have. Clarifying values will then help

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a veteran move forward on important committed actions, defined as actions in the direction of what someone cares about even in the presence of obstacles (eg, addressing problematic alcohol use or seeking care) [61]. Values clarification is followed by content to help veterans overcome identified barriers to care, such as challenging unhelpful beliefs about treatment (eg, "I can handle my problems on my own," "Providers will force me to take medication," and "My symptoms are not severe enough to deserve care") by providing information about what to expect when seeking care, with practical resources for where to seek help. Four main topic areas are presented to veterans, where they can click to learn more about each area: "What is mental health treatment like?" "What is the format of mental health treatment?" "How much of a commitment is mental health treatment?" and "Where can I get mental health treatment?" PNF is reviewed for alcohol use as described above, followed by normative feedback that helps to challenge the perceived public stigma that many veterans have about seeking care [62]. For example, the narrators describe studies that show that other veterans would not see someone as weak for seeking care; in fact, they would encourage those who need help to get the help they need. Preliminary work shows the promise of showing individuals information that corrects their misperceptions about perceived public stigma (eg, informing them that most people think that having a mental health problem is nothing to be embarrassed about [63]). Within the intervention, veterans are prompted to identify their personal values; these values are repeatedly referred to throughout the content of the intervention, including when veterans make goals for themselves about seeking care or making a positive change in their lives (eg, the intervention prompts them to mindfully consider what changes they can make to live more in accordance with their values [64]). Veterans are asked about some reasons for seeking behavioral health care that resonates with them, such as "My family life may improve," "I may gain personal insight and awareness," and "I may feel more motivated to do the things I want to do." These reasons for seeking care are presented alongside their values and veterans are asked to consider if seeking care would help them live more in line with their values. Informed by Cognitive Behavioral Therapy [65] and Motivational Interviewing [51,66] theory and practice, content is presented in a nonjudgmental way, with veterans able to make their own choices about making a change to their drinking or pursuit of behavioral health care.

In the penultimate section of the program, veterans are asked to make immediate, short-term, and long-term goals, with encouragement from the narrators to work toward those goals in the next few months [67]. Veterans type in their goals related to any area of their life where they want to make a change (eg, "I want to drink less," "I want to address my anxiety and reduce stress," and "I want to improve my relationship with my kids") and are asked to make sure these goals align with their values. Prompts for immediate (ie, something small and simple that they can easily accomplish within the next 24 hours), short-term (ie, things they can do in the service of their values-based goal within the next few days and weeks), and long-term (ie, actions that will move them closer to their values-based goal over the next few months and years) goals are provided.

The intervention concludes with a summary of the content reviewed, as well as personalized resources, including where to get help (eg, the location of nearest care centers based on the participant's ZIP code and crisis assistance) and information about local peer support groups and veterans service organizations. In the RCT, participants will receive a login for the intervention and can return to it at any time during the study. At each follow-up survey, they will be sent the link to the intervention with their login information and encouraged to review the content again.

Control Condition

Participants assigned to the control condition will receive a link to a website with resources similar to those provided at the end of the BRAVE intervention. On the site, veterans are able to find care centers, peer support groups, and veterans service organizations by clicking through the organized content. Participants will be asked to explore the content on the website for about 20 to 30 minutes, to match the length of the BRAVE intervention. They can return to the website at any time. After each follow-up survey, the control participants will be sent the link to these resources again to have it easily accessible.

Measures

Overview

Measures will be collected at screening, baseline, and all follow-up time points through confidential web-based surveys. After completing the screening survey and becoming enrolled, participants will receive a US $20 gift card for each survey they complete (a total of US $100 for all surveys).

Demographics and Background

Participants will fill out several demographic items that will be used to describe the sample. These include age, sex at birth, gender, race, ethnicity, income level, military branch, military rank and pay grade at discharge, number and location of deployments, education level, marital status, and number of children. Participants will also complete a measure of combat exposure to assess for presence and severity of combat experiences while in the military [27].

Primary Outcomes

Primary outcomes are drinking behavior (past 30-day frequency, quantity, and number of binge-drinking days), negative alcohol-related consequences, and treatment initiation. Three past 30-day drinking outcomes will be assessed through single-item self-reports: drinking days, average drinks per occasion, and binge drinking days. Alcohol-related consequences in the past 30 days will be assessed with the Short Inventory of Problems [68], which is modified from the Drinker Inventory of Consequences [69]. The treatment outcome will be measured as treatment initiation in the time period after the intervention (ie, post baseline). Treatment initiation is assessed with an item asking participants to indicate if they have seen a provider at a VA or non-VA care setting for therapy, counseling, support groups, hospitalization, or medications for any concerns related to alcohol or substance use (eg, if they sought help to drink less, or attended groups to stay abstinent from cannabis or other drugs) or mental health concerns (eg, to help with stress,

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anxiety, depression, nightmares) in the past 6 months (at baseline) and past 3 months (follow-ups). Providers are defined for participants as a mental health or behavioral health provider (eg, psychiatrist, psychologist, social worker, mental or behavioral health nurse, or other providers), a general medical provider (eg, primary care doctor, physician assistant, and nurse practitioner), or an addiction specialist (eg, addiction counselor). Care is specified as either in-person or via telehealth.

Secondary Outcomes

The decision to seek care and then actual receipt of care can be a lengthy process. Given that participants may not receive any care during the 12 months of follow-up, we will also assess their readiness to receive care in the future and if they made preparations to receive that care. Preparatory behaviors will be specified as 6 behaviors participants would definitely do, probably do, probably not do, or definitely not do in the next 30 days to prepare for treatment (ie, looking at options on the internet; discussing with a partner, family member, or friend the options available; talking with a partner, family member, or friend about their experiences with treatment; contacting a provider to learn more about the options; contacting the insurance provider to see what options are available; and contacting a provider to make an appointment). Two readiness rulers will also assess participants' readiness to seek care in the next 30 days in order to reduce their drinking and to address any mental health concerns they have from 0 (not ready at all) to 10 (absolutely ready).

Moderators

To examine the characteristics of participants for whom the intervention is most efficacious, we will include measures at baseline of perceived barriers to treatment, PTSD symptoms, depression symptoms, and AUD severity. Perceived barriers are assessed with the 15-item RAND Barriers to Mental Health Care item bank [70]. Items are rated on a scale from 1 (not at all) to 5 (very much) and reflect barriers of perceived stigma (eg, seeking care would be viewed as a sign of personal failure, others would lose respect for the person, and other veterans would see them as weak), fears about confidentiality (eg, people might find out about it), beliefs that treatment does not work, and difficulties finding time for treatment due to other responsibilities (eg, because of work or family). These items can be summed to receive a baseline severity of barriers score. PTSD symptoms will be assessed with the 20-item PTSD Checklist (PCL-5), a widely used measure for military and veteran populations with adequate reliability and validity for young adult military samples [71]. Depression symptoms will be assessed with the Patient Health Questionnaire 8-item (PHQ-8), a reliable and valid measure of depression used in research and practice for military and veterans [72-74]. The severity of AUD will be assessed with the AUDIT [54], a 10-item alcohol screen that identifies individuals who had probable AUD in the past year. The PCL-5, PHQ-8, and AUDIT can each be summed to create baseline symptom severity scores for each.

Analytic Plan

Overview

Prior to the main aims analyses, we will assess for multivariate normality. The maximum likelihood estimator will be used if data are approximately normal and robust maximum likelihood will be used if the data are not multivariate normal. Missing data will be assumed to be missing at random and handled using direct maximum likelihood techniques. We will assess for differences in baseline demographics and military characteristics between the intervention (BRAVE) and control conditions. Any characteristic significantly different between groups will be controlled for in analyses.

To assess the effects of the intervention on continuous primary outcomes (drinking days, average drinks per occasion, binge drinking days, negative alcohol-related consequences, and treatment initiation) and secondary outcomes (preparatory behaviors, readiness to seek care ruler for alcohol, readiness to seek care ruler for mental health), a taxonomy of latent growth models will be estimated [75]. The primary outcome time point for this trial will be the baseline to first follow-up (ie, 3 months post baseline); however, we are interested in the past 30-day changes from baseline to each of the 3 additional follow-up timepoints (ie, baseline to 6, 9, and 12 months post baseline). To assess between-group differences in the intercept and growth factors, we will regress each on a dummy variable representing the intervention (BRAVE=1) and control (control=0) groups. For any count variables, negative binomial or Poisson distributions will be explored for better model fit. To understand the change in treatment initiation (binary outcome), we will use latent growth models with categorical outcomes, as well as estimate simple logistic regression at each time point. To understand the practical significance, we will calculate standardized mean differences (Cohen *d*) at all 4 follow-up time points for both between group and within group.

We will test for significant effect moderation by the following variables: barriers to care, PTSD, depression, and severity of AUD symptoms. To explore moderation, we will use simple linear regression models for primary outcomes at each time point. We will include an interaction term between each potential moderator and the intervention indicator (BRAVE vs control). Significant interactions between the intervention group and these moderators will be plotted with appropriate values and interpreted. Simple slopes will be calculated for all significant interactions. Given our prior work and the large sample size, we expect to have adequate numbers of participants in each cell for moderation analyses and will use established cutoff scores on the PCL-5 (score 33 or higher vs under 33), PHQ-8 (scores 10 or higher vs under 10), and the AUDIT (scores 8 or higher vs under 8). We hypothesize that those with greater barriers, PTSD, depression, and severity of AUD symptoms will benefit most from the intervention. Sex (male or female) will be included as an exploratory moderator.

Power Analysis

Given this study design (and standard $P<.05$; 2-tailed testing), we will have 80% power to detect small treatment effects between the groups; specifically, effects of d=0.22 at 3- and

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6-month follow-ups and d=0.23 at 9- and 12-month follow-ups. For reference, our observed intervention effect sizes at 1 month post intervention in the pilot study were *d*=0.17 for average drinks, *d*=0.18 for binge days per month, and *d*=0.19 for consequences [49]. We have similarly found small effect sizes over 2 years of follow-up in other large-scale PNF studies [76-78]. We expect effect sizes to be small, though slightly larger than those in our prior work given we include a sample screening positive for hazardous alcohol use that could benefit from treatment, whereas prior work targeted general college students and young veterans drinking at less severe levels. As noted, given that this intervention targets those who may never have received care otherwise, small effects seen in brief interventions, such as this, are potentially clinically significant.

Our prior work evaluating treatment-seeking behaviors has found rates of preparatory and actual treatment-seeking by service members to increase by double following brief phone-based feedback [79]. Other work has similarly found rates of substance use treatment initiation to increase to upwards of 50% following in-person feedback–based approaches [80]; thus, we hypothesize that upwards of 50% of participants who receive the enhanced PNF will report actual treatment initiation at some point during the 12-month follow-up period. We will examine preparatory behaviors (ie, steps along the way to actual initiation) and motivation to seek care.

Ethical Considerations

The internal review board at the University of Southern California approved all procedures for this study (HS-19-00532). All participants will review and sign an informed consent form prior to participation. Participants "opt-in" for this study and can remove themselves from participation at any time. Incentives for participation are specified above and will be made clear to participants at the time of recruitment. All collected data are confidential.

Results

Data on primary and secondary outcomes will be collected as specified in the Methods section. We expect recruitment to be completed within 6 months, with data collection taking 12 months for each enrolled participant. Analyses will be conducted as specified in the Analytic Plan section above and begin within 3 months of the final data collection point (ie, 12-month follow-up).

Discussion

Principal Findings

The brief intervention we designed is intended to reach younger veterans who may have never otherwise considered seeking care for alcohol misuse or co-occurring mental health problems. BRAVE was designed to expand upon our prior pilot intervention study [46] that showed a PNF intervention yielded small intervention effects 1 month post intervention [49]. Given the ability of the internet recruitment method to access this difficult-to-reach population, combined with the intervention's ability to prevent alcohol misuse and consequences among a population with high rates of co-occurring mental health symptoms, we included values clarification, goal setting, and content to address barriers to care to expand on the theoretical and empirical basis of PNF interventions, including theories of normative influence [81,82] and aspects of Motivational interviewing [66], to encourage veterans to consider making changes to their drinking behaviors early, either by reducing on their own or seeking formal treatment, before their alcohol use transitions to a more problematic AUD.

Should BRAVE demonstrate efficacy in reducing drinking and improving treatment engagement among veteran participants, there is the potential to reach large numbers of veterans given the ubiquity of mobile technology [83] and the potentially low cost and burden of accessing mobile health interventions [84]. There may be challenges associated with disseminating such an intervention more broadly, given that the target population involves veterans not engaged in treatment who therefore are not in contact with those who would traditionally recommend such an intervention (ie, care systems and providers).

Moderation analyses of this study could allow for the further tailoring of our treatment approach and better targeting of specific subgroups of veterans. That is, should our analyses reveal that veterans with specific clinical or demographic characteristics are more likely to evidence reductions in drinking and treatment-seeking behaviors, this could justify targeted dissemination of PNF interventions, like ours, to such veterans. On the other hand, should a subgroup of veterans be less responsive to BRAVE, researchers could consider further adapting such interventions to better target relevant symptom processes or demographic groups. Hypothetically, such an intervention could be tailored to better meet the needs of female or male veterans or could include modules specific to PTSD or depression symptomology.

Limitations and Considerations

As the sample will involve relatively younger post-9/11 US veterans, it is unclear whether results will generalize to broader veteran samples, and in particular, veterans who are less comfortable with technology may have challenges engaging with an intervention such as BRAVE. Additionally, should the intervention demonstrate efficacy for reducing drinking and treatment-related outcomes, it will not be possible to disentangle whether it was the intervention as a whole or specific aspects of the intervention that were efficacious. Further dismantling studies of BRAVE may be necessary.

Conclusions

The BRAVE intervention has much potential to provide intervention to a traditionally difficult-to-reach population. It leverages mobile technology and combines several intervention strategies to fit the needs of the specific clinical presentation and needs of the population. While we anticipate BRAVE to be efficacious, reaching veterans outside of research studies will be an essential next step for our team and for intervention developers more broadly. Dissemination and implementation of evidence-based mobile and internet-based interventions is a key component of continuing to improve behavioral health care access for veterans and other groups in need.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author (ERP) upon reasonable request.

Authors' Contributions

ERP is the lead author and drafted the first version of this manuscript. ERP conceptualized the study and obtained funding along with JPD, JFH, KB, and CN. KDB is the project manager for this study and assisted with drafting sections of this manuscript, as well as providing formatting for the journal. JPD, JFH, KB, CN, KDB, IMS, REF, DDT, and SS contributed equally when providing edits to the first and final drafts of the manuscript. All authors approved this final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUD: alcohol use disorder
AUDIT: Alcohol Use Disorders Identification Test
BRAVE: Building Resilience and Agency through Veteran Engagement
PCL: posttraumatic stress disorder checklist
PHQ-8: Patient Health Questionnaire 8-item
PNF: personalized normative feedback
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
VA: Veterans Affairs

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Protocol

Effectiveness of a Parent-Based eHealth Intervention for Physical Activity, Dietary Behavior, and Sleep Among Preschoolers: Protocol for a Randomized Controlled Trial

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Abstract

Background: Preschoolers' lifestyles have become physically inactive and sedentary, their eating habits have become unhealthy, and their sleep routines have become increasingly disturbed. Parent-based interventions have shown promise to improve physical activity (PA), improve dietary behavior (DB), and reduce sleep problems among preschoolers. However, because of the recognized obstacles of face-to-face approaches (eg, travel costs and time commitment), easy access and lower costs make eHealth interventions appealing. Previous studies that examined the effectiveness of parent-based eHealth for preschoolers' PA, DB, and sleep have either emphasized 1 variable or failed to balance PA, DB, and sleep modules and consider the intervention sequence during the intervention period. There is an acknowledged gap in parent-based eHealth interventions that target preschoolers raised in Chinese cultural contexts.

Objective: This study aims to investigate the effectiveness of a parent-based eHealth intervention for PA, DB, and sleep problems among Chinese preschoolers.

Methods: This 2-arm, parallel, randomized controlled trial comprises a 12-week intervention with a 12-week follow-up. A total of 206 parent-child dyads will be randomized to either an eHealth intervention group or a control group. Participants allocated to the eHealth intervention group will receive 12 interactive modules on PA, DB, and sleep, with each module delivered on a weekly basis to reduce the sequence effect on variable outcomes. The intervention is grounded in social cognitive theory. It will be delivered through social media, where parents can obtain valid and updated educational information, have a social rapport, and interact with other group members and facilitators. Participants in the control group will receive weekly brochures on PA, DB, and sleep recommendations from kindergarten teachers, but they will not receive any interactive components. Data will be collected at baseline, 3 months, and 6 months. The primary outcome will be preschoolers' PA. The secondary outcomes will be preschoolers' DB, preschoolers' sleep duration, preschoolers' sleep problems, parents' PA, parenting style, and parental feeding style.

Results: Parent-child dyads were recruited in September 2023. Baseline and posttest data collection occurred from October 2023 to March 2024. The follow-up data will be obtained in June 2024. The results of the study are expected to be published in 2025.

Conclusions: The parent-based eHealth intervention has the potential to overcome the barriers of face-to-face interventions and will offer a novel approach for promoting a healthy lifestyle among preschoolers. If this intervention is found to be efficacious,

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the prevalence of unhealthy lifestyles among preschoolers may be alleviated at a low cost, which not only has a positive influence on the health of individuals and the well-being of the family but also reduces the financial pressure on society to treat diseases caused by poor lifestyle habits.

Trial Registration: ClinicalTrials.gov NCT06025019; https://clinicaltrials.gov/study/NCT06025019

International Registered Report Identifier (IRRID): DERR1-10.2196/58344

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KEYWORDS

physical activity; dietary behavior; sleep; electronic health; eHealth; preschoolers; parenting

Introduction

Background

People's lifestyles affect their health and well-being [1]. The main lifestyle dimensions of physical activity (PA), dietary behavior (DB), and sleep have played pivotal roles in decreasing cardiovascular risk [2], improving brain growth velocity [3], preventing mental disorders [4], improving social interactions [5], and improving the central nervous system [6]. These dimensions appear to be interrelated. PA brings about substantial benefits in not only reducing high-fat calorie consumption [1] but also improving sleep patterns and increasing sleep duration [7]. A longer nighttime sleep duration was shown to be associated with a less frequent intake of fast foods and sugar-sweetened beverages [8], and people with sufficient sleep quality were more likely to form active lifestyles [9]. In the past few decades, individuals' lifestyles have become physically inactive and sedentary [10], their eating habits have become unhealthy [11], and their sleep routines have become increasingly disturbed [12]. These changes have led to an ever-increasing prevalence of noncommunicable diseases such as diabetes and obesity [13]. Therefore, an effective intervention is needed to reverse this negative trend. A previous study indicated that children of preschool age may respond better to treatment as the lifestyle behaviors in this period are malleable and less entrenched [14]. Lifestyles formed in the early years of life can extend throughout the lifetime and influence lifelong health trajectories [15].

Parents have a profound impact on the healthy lifestyle of preschoolers and are the key agents of behavioral modification [16]. Parents provide an overwhelming majority of cues for PA, diet, and sleep routines and are responsible for role modeling these behaviors among their children [17]. Preschoolers are particularly dependent on their parents since younger children have limited autonomy and rely on parental supervision [18]. A longitudinal study demonstrated that parents' influence on children's lifestyle may be attenuated as children age because peer interaction gradually becomes their preferred activity when they grow up [19].

Despite the importance of parental involvement, previous parent-based interventions involving home visits and in-person education have been associated with high attrition rates, with many relying on self-reported assessments, failing to use a randomized controlled study design [20], and showing lower recruitment [21]. Other limitations of delivering interventions face-to-face within the home are related to the associated time commitment for participants [21], the need for childcare for other siblings [22], stigma, parental denial [23], the need to travel [24], and associated costs [23], which have hindered intervention adoption and adherence and have ultimately decreased the effectiveness of these programs. In response, eHealth, which is defined as the cost-effective and secure use of information and communication technologies in support of health, including health care services, health surveillance, health literature, health education, health knowledge, and health research [25], has the potential to address these barriers [26], providing convenience and flexibility for parents and enabling parents to participate regardless of their geographic location [27]. Moreover, personalized information and feedback delivered via eHealth interventions may augment behavioral change strategies [28].

Efficacy trials assessing the effectiveness of parent-based eHealth for preschoolers' PA, diet, and sleep have been conducted in 12 studies [29-40]. Although these 12 studies demonstrated that participants engaging in eHealth interventions had significant improvements in their healthy lifestyles, 7 studies [29,33,35-38,40] only concentrated on 1 variable, with 2 studies focusing on sleep, 3 focusing on fruit and vegetable intake, and 2 focusing on PA. A study by Ling et al [34] reported that disclosed intervention content between 2 groups may result in insignificant group-by-time changes in PA and diet. The remaining 4 studies [30-32,39] found a significant group-by-time difference in diet, but this effect was not found in PA and sleep. Possible reasons for this may be that these 4 studies involved more diet modules compared to PA and sleep modules. Overall, previous studies that examined the effectiveness of parent-based eHealth on preschoolers' PA, diet, and sleep have either emphasized 1 variable or failed to balance PA, diet, and sleep modules and consider the intervention sequence during the intervention period. Specifically, more exposure to diet modules relative to fewer PA modules may yield outcomes favoring diet variables. When the posttest was conducted, parent-child dyads may have been more familiar with the modules distributed at the end of the intervention period, thus producing favorable outcomes regarding the content of these modules compared to others.

Empirical relationships obtained in one culture may be a product of its milieu and may not be generalizable to other countries [41]. Very little is currently known about whether parent-based eHealth can effectively improve preschoolers' PA and diet and reduce sleep problems in China. In the past decade, the prevalence of physical inactivity, unhealthy diet patterns, and sleep problems among Chinese children has increased. Around

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70.1% of preschoolers do not meet the PA guidelines recommended by the World Health Organization (WHO) (ie, over 180 minutes of PA daily, including at least 60 minutes of moderate-to-vigorous PA) [42]. The total energy consumption involving fat and sodium exceeds the Chinese Recommended Nutrient Intakes by 10% and 56%, respectively [43]. Over 61% of Chinese preschoolers experienced or are experiencing insufficient sleep and sleep problems (eg, sleep onset latency) [44]. China has the largest population in the world, and the implementation of a traditional face-to-face intervention to improve the unhealthy lifestyles of preschoolers would pose a heavy financial burden on society [44]. An effective and feasible intervention strategy is imperative to tackle these growing health problems.

Currently, the number of smartphone and internet users in China is 1.64 billion and 1028.74 million, respectively [45]. eHealth interventions addressing unhealthy lifestyles could be cost-effective and easily scaled up [46]. Furthermore, affected by Confucianism, Chinese parents emphasize "training" (Guan), which refers to parents' control and demands [47]. "Guan," a typical characteristic of Chinese parenting, may generate a profound impact on determining a child's lifestyle behaviors, including PA, diet, and sleep [48]. Considering the shortcomings revealed in the study design of previous eHealth studies, high-quality robustly designed research studies that balance the intervention content and sequence are needed to determine the effectiveness of eHealth interventions to support behavior change in Chinese preschoolers, with parents being agents of change.

Research Objective

This study aims to investigate the effectiveness of parent-based eHealth interventions for PA, DB, and sleep among Chinese preschoolers.

Methods

Study Design

This study is a 2-arm, parallel, single-blinded, randomized controlled trial designed to promote preschoolers' PA, DB, and sleep by providing parents with relevant health information through an eHealth modality. The first arm involves an eHealth intervention, which will deliver evidence-based information and interactive components via social media (ie, WeChat, similar to WhatsApp; and TikTok or Douyin, similar to YouTube). The interactive components include push notifications, social rapport, influence agents, goal setting, and personalized feedback. The second arm involves a control intervention, which consists of printed evidence-based educational materials on standard recommendations for PA, diet, and sleep, without interactive components. The primary outcome will be preschoolers' PA. The secondary outcomes will be preschoolers' DB, preschoolers' sleep duration and sleep problems, parents' PA, parenting style, and parental feeding style. The intervention will last 12 weeks, with a 12-week follow-up. Based on the results of a previous systematic review, the duration of parent-based eHealth interventions varied from 8 weeks to 2 years, with over half of the studies being shorter than 12 weeks [49]. In this case, the 12-week intervention duration, which roughly coincides with the length of a school semester in the Chinese educational system of kindergarten (ie, two 3-month semesters in an academic year), is considered sufficient for behavioral modification. The proposed study design is shown in Figure 1. The study will follow the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials Statement for Randomized Trials: Improving and Standardizing Evaluation Reports of Web-Based and Mobile Health Interventions) guidelines [50].

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Figure 1. Study design.

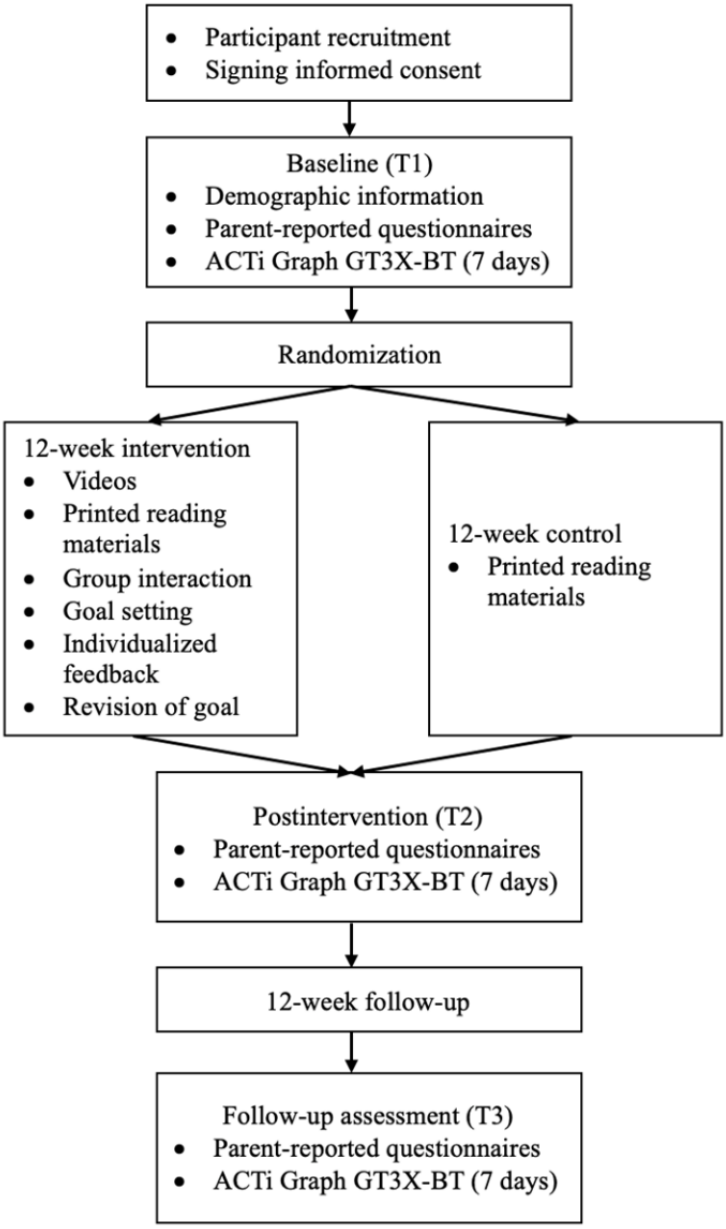

Ethical Considerations

The study has been approved by the Hong Kong Baptist University Research Ethics Committee (reference number: SOSC-SPEH-2022-23_115). This study has been prospectively registered at the ClinicalTrials.gov Protocol Registration and Results System (PRS) (NCT06025019). Written informed consent will be obtained from all participants or their legal guardians. Personal data (ie, gender, age, and marital status); preschoolers' PA, diet, and sleep behaviors; and family information (family economic status, parents' education level, and family structure) will be collected. No other information related to participant identity will be recorded or disclosed. The data collected by the researchers will be destroyed after the project is completed and published (within 7 years). In case of withdrawal, the data will be deleted from the data file immediately. Incentives (honorary certificates) will be offered to families judged to be more active and healthier.

Participant Recruitment and Eligibility Criteria

Parent-child dyads will be recruited from kindergartens in Guiyang, Guizhou Province, China, with the support of Sun Yat-sen University and Guiyang Preschooler Education College. The entire recruitment process will be school-based. Kindergarten teachers will be asked to send a message to the parents in their respective WeChat class group. The message will briefly introduce the objectives and significance of the study. Parents will respond "yes" or "no" regarding their intention or willingness to participate. Face-to-face meetings will be held to provide more details to those parents who agree to participate in the study, especially on measurements, and to clarify the benefits that parents will receive after the study. Parents will be asked to add the researcher's WeChat and sign the informed consent at the end of parent meetings. The inclusion criteria are as follows: (1) parents are older than 21 years and have children aged 3-6 years (the age range from 3 to 6 years has been found to be a strong predictor of future

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health) [51], (2) parental commitment to participate in the overall 6-month intervention, (3) parents have access to mobile technology, (4) parents and children are healthy (referring to a state of physical, mental, social, intellectual, and emotional well-being and the absence of disease) based on a health assessment performed by the kindergarten on the commencement day of a new semester, and (5) parents reside with participating children for at least 4 days a week in order to adequately expose the children to the parent-based intervention.

Randomization

Once participants are recruited and baseline measurements are collected, participants will be randomly allocated to either an intervention group (eHealth group) or a control group (traditional group) in a 1:1 ratio through a computer-generated list, using the statistical software SPSS (IBM SPSS 27, IBM Corp). The randomization will be conducted by a researcher who is blinded to the intervention recruitment and delivery. Random allocation to either the eHealth group or the control group will not be informed to parents.

Theoretical Foundation

The intervention is grounded upon social cognitive theory (SCT), which considers learning as a social phenomenon that comes from a person's interaction with others through watching and observing [52]. Moreover, it considers the evidence that eHealth implemented directly to preschoolers may have adverse impacts on preschoolers' healthy lifestyles (eg, disturbed sleep, myopia, and increased screen time). Thus, a key component of this intervention is to involve parents in modeling health-promoting behaviors among their preschool-aged children. Figure 2 depicts how the intervention will be conducted. First, SCT proposes that an individual's behavioral modification can be influenced by personal, environmental, and behavioral factors [53]. These 3 factors describe what intervention content should be involved to induce behavioral modification:

- Personal factors refer to an individual's self-efficacy to carry out a behavior, which is dependent on personality, knowledge, beliefs, self-perceptions, and expectations. Knowledge and beliefs of the importance of PA, DB, and sleep for preschoolers will be addressed through the topic content of the eHealth intervention (videos and reading materials).
- Environmental factors refer to supportive environments that help an individual to conduct a behavior. Interaction with others by posting photos, videos, and ideas concerning a healthy lifestyle will provide participants with vicarious learning. Communication, feedback, and reinforcement from other parents through social media platforms and from research staff through personalized interaction can provide parents with opportunities to practice the skills, potentially contributing to behavioral modification.
- Behavioral factors refer to the responses by the individual once they have practiced carrying out a behavior. The parent will put the skills and behaviors into practice after goal setting and action plans. Positive reinforcement will be gained by monitoring progress with the goals and action plans and the personal benefits experienced.

Additionally, the 4 processes for behavior change involved in SCT are attention, retention, reproduction, and motivation. If any one of these steps is missing, the learning and adaptation of new behaviors will not take place. These 4 steps describe what intervention sequence should be followed to induce behavioral modification:

- Attention, which is matched with personal factors, represents that individuals cannot learn unless they pay attention to what is happening around them. Therefore, attention is tackled by providing printed educational materials and TikTok videos delivered through WeChat [54].
- Retention, which is matched with environmental factors, represents that individuals must not only recognize the observed behaviors but also remember these behaviors at some later time. Therefore, retention is addressed by interactions with other participants through the WeChat group to support parents in remembering the content of videos and educational material. Moreover, each week, parents will receive 4 push notifications to remind them about the information of each interactive component (ie, video or printed material, communication, goal setting, and feedback).
- Reproduction, which is matched with behavioral factors, represents that individuals must be physically and mentally capable of producing the observed behaviors. Therefore, reproduction will be achieved through goal setting based on the SMART (Specific, Measurable, Achievable, Relevant, and Time-bound) goal framework, action plans, and solutions to barriers.
- Motivation, which is matched with behavioral factors, relates to the interests and achievements of individuals regarding the tasks and activities being put in place. Therefore, motivation is addressed by creating cognitive dissonance with parents describing current behaviors and asking parents to identify the positive consequences and expectations as a result of performing the planned behaviors.

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Figure 2. SCT-based eHealth intervention. DB: dietary behavior; PA: physical activity; SCT: social cognitive theory; SMART: Specific, Measurable, Achievable, Relevant, and Time-bound; WHO: World Health Organization.

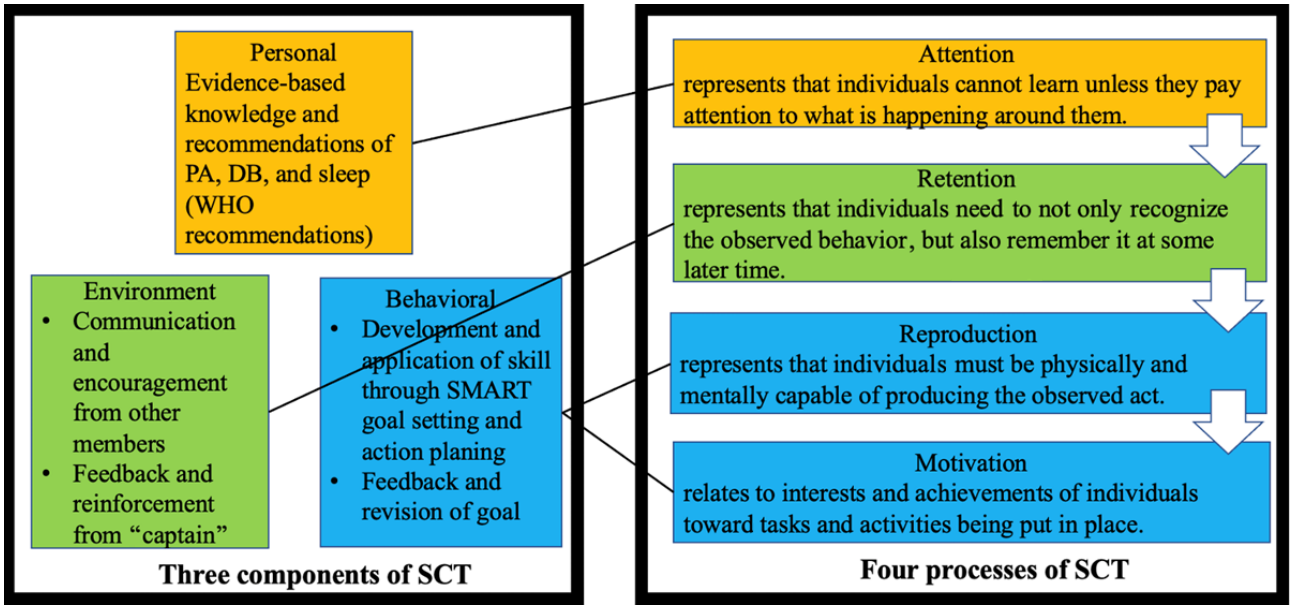

Intervention Procedure

The eHealth intervention comprises 12 interaction modules, including PA (n=4), DB (n=4), and sleep (n=4). Each module will be rotated weekly to reduce the order effect on the outcome variables during the 12-week intervention period (ie, PA, diet, sleep, PA, diet…). Given that previous social media studies have indicated that 5 to 9 members in a group will produce the desirable group interactive effect [55], the participants will be grouped into 26 WeChat groups (8 members involved in each WeChat group) by the researchers according to the sample size calculation. Given that a facilitator has been found to be important to potentially make the intervention more individualized and may be successful in behavioral change [56], a teacher with expertise in PA, DB, and sleep who is working in the kindergarten will act as a facilitator, also known as a "captain," in each WeChat group. Facilitators will be trained in a 5-hour workshop before the intervention and will be blinded to the study objectives. They will be responsible for sending videos; facilitating group interactions; responding to questions from parents; helping parents establish PA, diet, and sleep goals for their children; and providing feedback. Parents in each WeChat group will receive 2 self-monitoring text messages, and they will be required to provide a "yes" or "no" response. The first message will be sent as a feedback message to evaluate the progress toward the child's weekly goal in the middle of the week. An "N" response may elicit a skill-building response to adjust the goal or adopt alternatives to achieve the goal (eg, try offering the same vegetable many times in different ways). If the parent responds "Y," the facilitator will generate a message to reinforce positive behaviors, such as "Be proud of yourself, you're getting your child off to a healthy start!" The second self-monitoring message will be sent on the weekend to assess goal attainment for the weekly target behavior before the new weekly theme is introduced. Figure 3 illustrates the intervention process of each module [57,58]. Multimedia Appendix 1 indicates what specific content will be shared.

Consistent with SCT [52], the content of each module will follow 4 steps (Figure 2 illustrates the intervention process of each module) as follows:

1. Attention (read educational material and watch a TikTok or Douyin 3-minute video): Each video involves behavior change techniques, which are mapped onto SCT and are critical for promoting behavior change [59-61]. It will be sent to parents at the beginning of each week, with each video containing information related to goal setting, action plan, feedback, monitoring, shaping knowledge, natural consequences, repetition and substitution, comparison of outcomes, reward and threat, antecedents, identity, and self-belief [54,59].

2. Retention (parent interaction): A meta-analysis assessing the psychological architecture and adherence factors of online interventions indicated that intervention adherence is more likely to be influenced by push factors, peer communications, and personal contact [62]. Parents will receive regular messages to remind them to watch videos and read text. Facilitators and researchers will regularly share questions and images related to the week's topic, aiming to stimulate discussion among parents [30]. For example, "What is your child's current PA pattern?" and "Do you read the ingredient label of food when buying?" It was anticipated that parents would gain the most benefit from actively participating (posting information or commenting) based on findings from previous studies on online health discussion groups, which have indicated that parents who wrote posts, commented, asked questions, and provided support to others achieved greater benefits than passive parents [63,64]. If there are parents in the WeChat group who do not post or share, they will receive a reminder message sent by the facilitator via WeChat privately.

3. Reproduction (set goals and conduct behaviors): The facilitator of each WeChat group will help parents set goals related to the weekly topic based on SMART principles [65]. Goals should be individualized and can be adjusted along with the child's and parent's progress in behavior changes. The

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facilitator of each WeChat group will inform the parents via private text messages on how to employ goal setting to help their children set PA, DB, and sleep goals. It is encouraged to share goal achievements with other members in the WeChat group or with the facilitator privately. Throughout the intervention period, parents will be offered the possibility to interact with the facilitator on a regular basis by means of WeChat in order to discuss problems and raise questions regarding the promotion of PA, a healthy diet, and sleep for their children.

4. Motivation (feedback and making changes): Feedback and subsequent revision of goals have been shown to be positively related to successful interventions of behavioral modification [66,67]. Tailored feedback will be provided by a research assistant with expertise in lifestyle (PA, DB, and sleep) based on the goal, barrier identification, and solution. The research assistant will assist parents to revise their weekly theme-related goal following the SMART framework [68].

Figure 3. Intervention mapping process of each module based on the 4 steps of social cognitive theory. PA: physical activity; SMART: Specific, Measurable, Achievable, Relevant, and Time-bound.

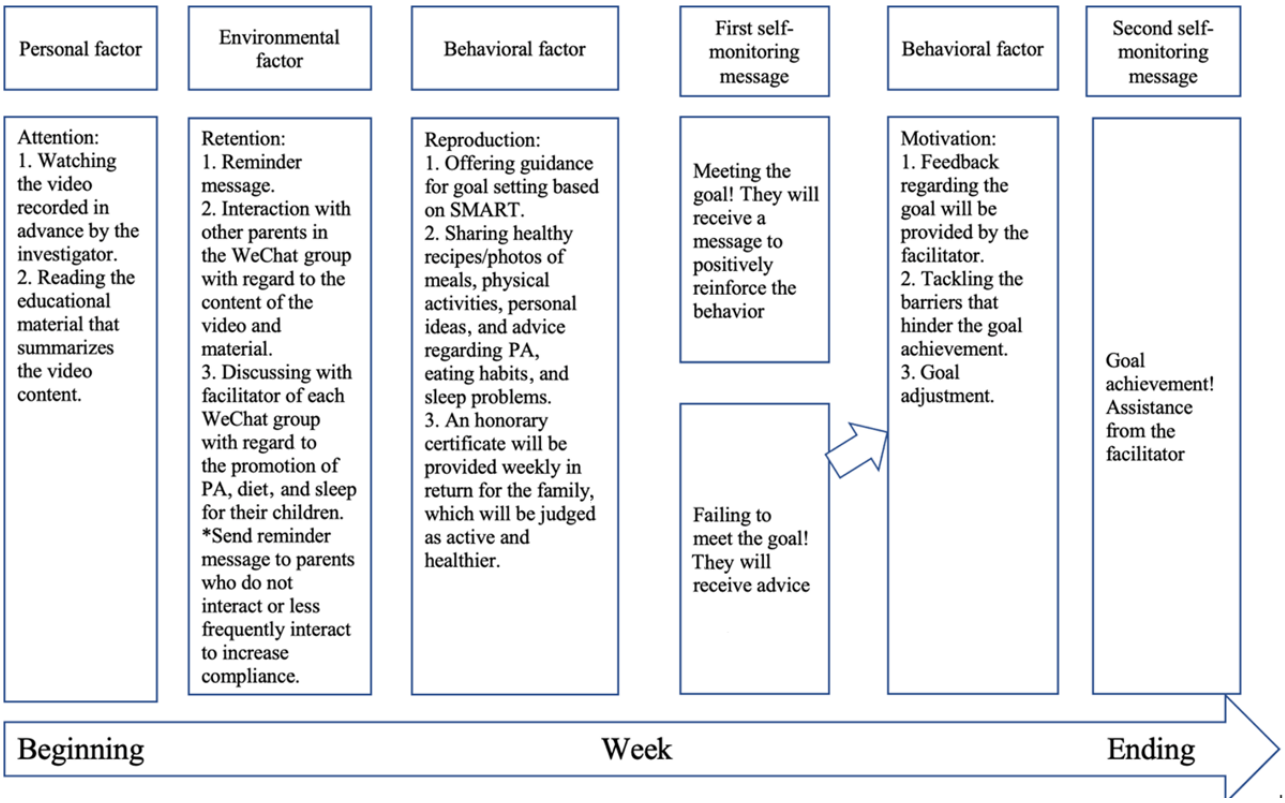

Control Group

Parent-child dyads assigned to this group will receive a weekly pamphlet on PA, DB, and sleep recommendations via the child, but they will not receive interactive components.

Sample Size

A recent systematic review and meta-analysis indicated a small but significant effect size for interventions to improve the PA of children aged younger than 5 years [69]. Interventions that aimed to enhance DB and reduce sleep problems among preschoolers had small to medium effect sizes [9,70]. Based on the information, a priori analysis will be conducted using G*power 3.1.9.6 [71]. A minimum sample size of 82 parent-child dyads in the intervention and control groups separately is required to detect a small effect size (*d*) of 0.3 with a power of 0.80 under the condition of an α level of .05. Considering a 20% potential attrition rate, 206 parent-child dyads in total are needed.

Outcomes

Data collection will be conducted at baseline (1 week before the intervention; T1), 12 weeks postintervention (at the end of the intervention; T2), and at the end of the 12-week follow-up period (T3).

Demographic Information

The following demographic information will be collected from parents: socioeconomic status (range of income, educational level, and occupational status), age, gender, and marital status.

The following demographic information will be collected from preschoolers: sex, age, weight, height, and BMI. Preschoolers' weight will be measured with standard practices to the nearest 0.1 kg using calibrated measurement scales (Salter) and height will be measured using a stadiometer (SECA) to the nearest 0.1 cm. BMI will be calculated with height and weight measurements. As sibship size has been observed to influence parenting behaviors, the number of children in the household will be collected.

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Primary Outcome

Preschoolers' PA

The PA level and sedentary time will be objectively monitored using a triaxial accelerometer ActiGraph GT3X-BT (ActiGraph). The ActiGraph accelerometer has been found to be valid and reliable to objectively measure PA levels in preschoolers [72]. The kindergarten teachers and parents will receive written and video instructions for the use of the accelerometer. In addition, parents will be asked to register an activity diary for both wear and nonwear times. The accelerometer wear will be checked by teachers on each school day. An accelerometer will be affixed to the participant's right wrist to monitor all activities for a period of 7 continuous days, except during periods of water-related activities or situations involving the risk of damage to the device, such as contact sports or self-defense. Data will be downloaded and initialized using the ActiLife software (version 6.13) and analyzed in 1-second epochs. Valid wear time will be considered at least 16 hours of wear time over at least 3 days (2 weekdays and 1 weekend day) [73]. Nonwear time will be defined by 60 consecutive minutes of 0 counts per minute (CPM), using ActiLife standard approaches. The accelerometer's activity counts will be categorized into different intensities (ie, sedentary behavior, light PA, moderate PA, and vigorous PA) by using cutoff points as follows: sedentary, <819 CPM; light, 820-3907 CPM; moderate, 3908-6111 CPM; and vigorous, ≥6112 CPM.

Secondary Outcomes

Preschoolers' DB

Preschoolers' DB will be assessed using the Children's Eating Behavior Questionnaire (CEBQ), which has been shown to be valid in Chinese preschool-age children [74]. Parents will rate the frequency of their children's eating behaviors on a 5-point scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=always) in terms of 8 domains (35 items): satiety responsiveness (eg, My child gets full before the meal is finished), slowness in eating (eg, My child finishes the meal quickly), food fussiness (eg, My child enjoys tasting new foods), food responsiveness (eg, If allowed, my child would eat too much), enjoyment of food (eg, My child enjoys eating), desire to drink (eg, If given the chance, my child would always be having a drink), emotional undereating (eg, My child eats more when happy), and emotional overeating (eg, My child eats more when there is nothing else to do). The scale has high internal consistency and reliability (overall Cronbach α >.7).

Preschoolers' Sleep Duration and Problems

The ActiGraph accelerometer will be used to examine children's sleep duration in conjunction with a parent-reported log sheet and nap schedule provided by kindergartens. Bedtime and wakeup time will be identified based on the algorithm by Sadeh et al [75], and periods of sleep will be estimated using the algorithm by Tudor-Locke et al [76]. The nighttime sleep and daytime nap durations, bedtime, and wakeup time will be assessed using ActiLife software (version 6.13) in 60-second epochs and matched with the nap schedule filled out by kindergarten teachers and log sheets finished by parents. The total duration of sleep per day will be the sum of nighttime and daytime sleep.

The Chinese version of the Children's Sleep Habits Questionnaire (CSHQ) [77], a parent survey regularly used to track kids between the ages of 4 and 10 years, will be used to assess preschoolers' sleep problems. It contains 33 items from 8 domains: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnia, sleep-disordered breathing, and daytime sleepiness. Each scored question is rated on a 3-point scale as follows: 3="usually if something occurs 5 or more times in a week," 2="sometimes if something occurs 2-4 times in a week," and 1="rarely if something occurs never or 1 time during a week." Higher scores represent greater sleep problems. This survey has shown good reliability (Cronbach α=.73) and validity.

Preschoolers' Screen Time

Parents will be asked to answer questions that estimate the usual amount of screen time for their children on a typical weekday and weekend to determine the average screen time per week. Questions also involve the availability of screens and rules about screen entertainment. This questionnaire has been used in a previous study [23].

Parents' PA

Parents' PA will be assessed using the Chinese version of the International Physical Activity Questionnaire-Short Form (IPAQ-SF). The questionnaire will ask about the time spent being physically active in the last 7 days through 7 questions. The obtained data will be converted to metabolic equivalent task (MET) scores for each dimension or intensity of PA. To calculate the weekly PA (MET-min/week), the number of total minutes dedicated to each activity class is multiplied by the specific MET score for the activity, with 3.3 METs for walking, 4 METs for moderate PA, 6 METs for cycling, and 8 METs for vigorous PA. This questionnaire has been shown to be a reliable and validated measure for assessing PA levels in Chinese cities (overall Cronbach α=.788) [78].

Parenting Style

The Parenting Style & Dimension Questionnaire, a self-report instrument designed to measure authoritarian (eg, I yell when I disapprove of my child's behavior), authoritative (eg, I am responsive to my child's feelings and needs), and permissive (eg, I find it difficult to discipline my child) parenting styles of the parents of children aged 4-12 years, will be used to evaluate the parenting styles. This scale comprises 32 items, with each item of the scale evaluated using a 5-point Likert scale ("never," "once in a while," "about half of the time," "very often," and "always"). The overall Cronbach α is .87 [79].

Parental Feeding Style

The parental feeding style will be assessed using the Chinese version of the Parent Feeding Style Questionnaire, which consists of 4 parts: instrumental feeding (4 items), emotional feeding (5 items), prompting or encouragement to eat (8 items), and control over eating (10 items). Respondents will be asked to choose responses on a 5-point Likert scale (ranging from "never" to "always"). For example, "I allow my child to choose

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which food to have for meals, I encourage my child to look forward to the meal." The average score on each scale will be calculated, and a higher score will be considered to indicate a greater tendency for parents to feed their children in that style [80]. The overall Cronbach α is .75.

Parents' Self-efficacy

Parents' self-efficacy will be assessed using a previously used questionnaire [23], which has been translated back-to-back into simplified Chinese language. This questionnaire consists of 11 questions related to a child's PA (4 items), DB (6 items), and sleep (1 item). For example, "How confident are you that you can promote healthy eating habits for your child?" Respondents will be asked to select from a 10-point Likert scale (ranging from "not at all" to "to a very high degree"). A higher score for the sum of the 11 questions will be considered to indicate a higher self-efficacy of parents regarding their children's PA, DB, and sleep.

Statistical Analysis

All statistical analyses will be conducted using IBM SPSS 27 (IBM Corp), and a 2-sided *P* value <.05 will be considered statistically significant. Baseline characteristics between the intervention group and control group will be compared using the chi-square test for categorical variables and ANOVA for continuous variables. A mixed model, which accounts for missing repeated measures, will be adopted with a 2-level between-group factor (intervention and control) and 2-level within-group factor (postintervention and follow-up assessment) repeated measures analysis of covariance (RM ANCOVA) to examine whether the eHealth-based parenting intervention improves preschoolers' PA, DB, and sleep compared to the findings in the control group.

Results

Parent-child dyads were recruited in September 2023. Baseline and posttest data collection occurred from October 2023 to March 2024. The follow-up data will be obtained in June 2024. The research team has completed data collection for 238 parent-child dyads and is currently analyzing the outcomes. The results of the study are expected to be published in 2025.

Discussion

Low compliance with a healthy lifestyle (eg, PA, healthy dietary patterns, and sufficient sleep) exacerbates the likelihood of noncommunicable diseases such as obesity [81]. Focusing preventive efforts on early childhood growth trajectories provides an opportunity to address unhealthy lifestyles before individuals' lifestyles are entrenched [82]. Chinese parents have high standards and a tendency to control their children, and these strong parenting influences may affect the early life behaviors of Chinese children [83]. Given the current economic climate, time constraints are likely to intensify for parents, making face-to-face interventions more problematic. The intervention in this study will be delivered in an easy-access setting (ie, WeChat; monthly active users have reached 1.26 billion, accounting for 77% of internet users aged from 16 to 64 years). Moreover, 70.2% of Chinese people rank Douyin, known as TikTok in Western countries, as the second favorite social media platform [84] on which parents are already engaged and are likely to share what they learn through peer communication. Unfortunately, proven parent-based eHealth interventions against preschoolers' unhealthy lifestyles are not being practiced routinely in China. Therefore, the objective of this study is to assess the effectiveness of an eHealth intervention for promoting Chinese preschoolers' PA, DB, and sleep, where parents are the agents of change. This study draws on the success of previous studies. A randomized controlled trial remains the gold standard for evidence of the effectiveness of eHealth interventions [85]. Previous studies have indicated that a longer intervention is more effective than a shorter intervention, possibly because a longer intervention duration allows program content to be repeated and allows participants to internalize program materials [10,86]. According to a previous systematic review, the intervention duration varied from 8 weeks to 2 years, with over half of the studies being shorter than 12 weeks [49]. In China, preschoolers attend kindergarten for 2 semesters over 1 year, with each semester lasting around 12 weeks. Gardner et al [87] indicated that behavioral modification needs at least 2 to 3 months. As such, the 12-week intervention duration in this study, which fits well in the semester time, may be acceptable and feasible for parents and preschoolers. The waitlist control group is identified as having "no intervention," which is likely to be unacceptable to participants and can contribute to poor retention and follow-up, thus compromising the study's integrity [88]. A follow-up test can help assess whether any behavioral changes resulting from the parent-based eHealth intervention are sustained over time [89]. Considering that different educational levels (ie, lower literacy vs better literacy) are associated with a poorer understanding of the health information provided, the use of video in this study may be beneficial for parents with lower educational backgrounds [90]. Some new delivery modes via smartphones include infographics (used to provide additional support for different topics), text messages (used to offer feedback messages), and social media discussions (ie, parents have the opportunity to communicate with members of the cohorts as well as experts in the WeChat group), which can be promising ways to provide parents with knowledge, goals, and advice to directly influence their children's healthy lifestyles [30,54]. The primary outcome of this proposed study is preschoolers' PA. PA has been considered dispensable and trivial because Chinese parents have subscribed to the concept that any activities, including PA, that compromise academic success and examination results should be eliminated [83]. This study may not only provide parents with the knowledge, skills, and confidence to create an environment for their children in which healthy behaviors (eg, PA, DB, and sleep) are developed and flourished, but also correct misleading concepts about PA. Parents' PA, parenting style, and feeding practices are involved in secondary outcomes for several reasons. First, previous studies have indicated that preschoolers with parents who were regularly engaged in PA were more than 5 times more likely to be active than peers whose parents were not physically active, suggesting parents' PA may be positively related to improved preschoolers' PA [91]. Second, parenting style (ie, authoritative, authoritarian, permissive, and disengaged) is an important factor that potentially affects the

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lifestyle of young children. For example, an authoritative parental style was shown to be effective in improving healthy behaviors (ie, PA, diet, and less sedentary behaviors) [92]. Tyler et al [93] found that an authoritarian parental style was positively associated with preschoolers' sleep problems. Third, parental feeding practices were associated with child eating patterns [94] because preschoolers' food preferences and patterns have been shown to be influenced by the foods parents provide at a young age and food persistence in children's meals [95].

This study has several strengths, including a randomized controlled trial design, calculation of sample size that ensures adequate statistical power, and objective and valid data collection methods for outcome measurements. Multiple lifestyle-related behaviors (ie, PA, diet, and sleep) are targeted in the intervention. The intervention delivery is grounded upon 4 behavioral modification steps included in SCT. A 3-month follow-up will determine whether the behavioral changes made during the intervention can be maintained. This study addresses many limitations summarized from previous studies, such as failure to either consider the imbalance of the intervention dose to bias the results or consider the sequence of the intervention contents to bias the results.

There are some limitations that need to be considered. The parent-child dyads that will be allocated to either the intervention or control group may be from the same school, and it is therefore possible that the intervention content may be contaminated. Thus, the outcome of this intervention may not be generalizable to preschoolers living in other cities in China. Owing to subjective measurements for the questionnaires, there is potential for parents to intentionally or unintentionally misreport; however, this is common in all free-living studies examining behavioral measures [96].

This study will make an important contribution to the literature on the application and verification of eHealth interventions (eg, social media) for cultivating healthy lifestyles (ie, PA, DB, and sleep) among Chinese preschoolers, where parents are the agents of change. By applying a theory-based (SCT) intervention with eHealth technology, a new perspective for future scientific health promotion will be obtained. As China has a large population, the implementation of a traditional face-to-face intervention to improve the unhealthy lifestyles of preschoolers would pose a heavy financial burden on society. According to the China Internet Network Information Center, as of December 2023, around 78% of Chinese people are connected to mobile devices with access to the internet (including those living in rural and remote regions), potentially enabling widespread access regardless of geographic location. This intervention has the potential to achieve a broad reach as it addresses many obstacles associated with the face-to-face delivery method. If the intervention is found to be efficacious, the prevalence of unhealthy lifestyles among preschoolers may be alleviated at a low cost, which not only has a positive influence on the health of individuals and the well-being of the family, but also reduces the financial pressure on society to treat diseases caused by poor lifestyle habits.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention content of each module.
[DOCX File , 34 KB - resprot_v13i1e58344_app1.docx]

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Abbreviations

CPM: counts per minute
DB: dietary behavior
MET: metabolic equivalent task
PA: physical activity
SCT: social cognitive theory
SMART: Specific, Measurable, Achievable, Relevant, and Time-bound

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Protocol

Testing a Consumer Wearables Program to Promote the Use of Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Although positive airway pressure (PAP) therapy is considered first-line treatment for obstructive sleep apnea (OSA), nonadherence is common. Numerous factors influence PAP use, including a belief that the therapy is important and effective. In theory, providing information to patients about their blood oxygen levels during sleep (which may be low when PAP is not used), juxtaposed to information about their PAP use, may influence a patient's beliefs about therapy and increase PAP use. With the advent of consumer wearable smartwatches' blood oxygen saturation monitoring capability (and the existing routine availability of PAP use data transmitted via modem to clinical dashboards), there is an opportunity to provide this combination of information to patients.

Objective: This study aims to test the feasibility, acceptability, and preliminary efficacy of the Chronic Care Management With Wearable Devices in Patients Prescribed Positive Airway Pressure Therapy (mPAP), a program that augments current PAP therapy data with consumer-grade wearable device to promote self-management of PAP therapy for OSA in a pilot randomized waitlist-controlled clinical trial.

Methods: This is a single-blinded randomized controlled trial. We will randomize 50 individuals with a history of OSA, who receive care from a Department of Veterans Affairs medical center in the Los Angeles area and are nonadherent to prescribed PAP therapy, into either an immediate intervention group or a waitlist control group. During a 28-day intervention, the participants will wear a study-provided consumer wearable device and complete a weekly survey about their OSA symptoms. A report that summarizes consumer wearable–provided oxygen saturation values, PAP use derived from modem data, and patient-reported OSA symptoms will be prepared weekly and shared with the patient. The immediate intervention group will begin intervention immediately after randomization (T1). Assessments will occur at week 5 (T3; 1 week after treatment for the immediate intervention group and repeat baseline for the waitlist control group) and week 11 (T5; follow-up for the immediate intervention group and 1 week after treatment for the waitlist control group). The primary outcome will be the change in 7-day PAP adherence (average minutes per night) from T1 to T3. The primary analysis will be a comparison of the primary outcome between the immediate intervention and the waitlist control groups (intention-to-treat design), using a 2-sample, 2-sided *t* test on change scores (unadjusted).

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Results: Recruitment began in October 2023. Data analysis is expected to begin in October 2024 when all follow-ups are complete, and a manuscript summarizing trial results will be submitted following completion of data analysis.

Conclusions: Findings from the study may provide additional insights on how patients with OSA might use patient-generated health data collected by consumer wearables to inform self-management of OSA and possibly increase their use of PAP therapy.

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KEYWORDS

sleep apnea; consumer wearables; adherence; self-management; mobile phone

Introduction

Background

Obstructive sleep apnea (OSA) is prevalent and affects more veterans who obtain care in Veterans Health Administration facilities than any other sleep disorder (20%) [1]. Characterized by repetitive blockage in the airway during sleep that causes breathing to stop or get very shallow and that may cause transient hypoxemia, OSA disrupts sleep and contributes to symptoms of excessive daytime sleepiness; decreased quality of life; and increased risk of health conditions such as depression, cardiovascular disease, erectile dysfunction, and dementia [1]. OSA is also associated with work disability [2] and increased risk of motor vehicle crashes [1].

OSA is a chronic disease that requires long-term management [3]. Positive airway pressure (PAP) devices, which deliver air under pressure into the airway to stent the airways open, are considered the gold standard treatment for OSA. The success of this treatment is quantified by hourly and nightly adherence plus changes to symptoms (eg, daytime sleepiness) and reduction in the number of times per hour airflow ceases or is reduced, as well as improvement in sleep-related oxygen levels [4,5]. Adherence to treatment can improve sleep quality, reduce the risk of OSA-related comorbidities, and improve quality of life [6]. However, low PAP adherence is a common issue [7].

Among a number of important factors that influence whether a patient uses prescribed therapy is the belief that the therapy is important and effective [2]. Through clinical experience and a prior project that have focused on patients' decision-making about their OSA and treatment, we found that providing information to patients about their blood oxygen levels (eg, lowest blood oxygen level) during sleep is very powerful as a tool for engaging them in their OSA management. Studies have shown that data visualizations may be associated with positive effects on decision-making due to the decreased cognitive and intellectual burden of interpreting data [8,9]. With the advent of consumer wearable smartwatches' (hereafter smartwatch) blood oxygen saturation (SpO_2) monitoring capability, there is both an opportunity and an impending need to optimize the manner in which this information is used in patients' daily lives and in routine sleep clinic care so that the information enhances patients' experience with care.

Increased affordability and relative convenience of putting a device on the wrist to continuously collect physiological data (eg, steps and heart rate) have popularized smartwatches for everyday use. Manufacturers have also developed proprietary algorithms using data collected with various sensors to estimate sleep-related metrics such as sleep time, wake time, and sleep stages. The result is a great deal of data available to the consumer that may appear medically relevant, particularly against the backdrop of beautifully designed interfaces and eye-catching graphics. However, these watches are designed to be consumer-facing products, such that the data presented should not be used to replace clinical screening or diagnosis of sleep disorders such as OSA, even if they have features to detect signs of moderate to severe OSA [10]. While there is limited evidence to the reliability [11] and validity [12-14] of the data for clinical purposes, there may be benefits to tracking health behaviors for self-monitoring purposes [15].

Newer models of consumer-facing smartwatches (eg, Fitbit) are providing SpO_2 measurements in minute-by-minute intervals [16]. Although these wearables are not intended for medical purposes such as diagnosing OSA, they are currently used by patients for self-monitoring oxygen levels, which can drop to low levels in some patients when they are not using PAP therapy. Theoretically, patients who use their PAP therapy inconsistently may have patterns in consumer wearable data that correlate with PAP use. Given the high prevalence of OSA and the growing use of smartwatches, inevitably a subset of patients with OSA will use smartwatches for self-monitoring their oxygen levels during sleep and will present to their sleep clinicians with questions about their wearable oxygen levels. A conundrum is how best to incorporate the vast amount of sleep data from consumer technology into the chronic care management of patients with sleep disorders such as OSA.

Although the PAP devices include airflow sensors that can provide physiologic data feedback [17], additional feedback about oxygen levels may influence behavior. The proposed research study will incorporate the use of a wearable collecting SpO_2 data during sleep and provide a weekly report that will not only depict the physiological consequences of nonadherence as a timely behavioral reinforcement strategy, but also highlight day-to-day relationships of adherence and possible barriers (eg, lower adherence on nights of greater pain). In conjunction with PAP device data and patient-reported outcomes (eg, daytime sleepiness and alertness), the wearable data represent an opportunity to augment current strategies for increasing use of PAP therapy.

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The Health Beliefs Model provides a framework for incorporating wearable data (specifically oxygen saturation data) in a PAP therapy program [18]. The model suggests that the desire to get well if already ill (eg, improve OSA) and the belief that a specific health action will cure illness, together, influence health behavior (eg, use PAP for OSA), and the patient's course of action often depends upon the patient's perceptions of the benefits and barriers related to that health behavior (eg, PAP use). The perceptions influencing PAP use may include (1) perceived susceptibility—if levels of oxygen saturation collected during sleep are intermittently low, (2) perceived severity—if oxygen levels are lower than normal values, and (3) perceived benefits—if oxygen levels during sleep are different on days PAP used versus not used. Cues to action (eg, PAP use) may be feedback showing wearable oxygen saturation data combined with PAP use and patient-reported outcomes.

The goal of the Chronic Care Management With Wearable Devices in Patients Prescribed Positive Airway Pressure Therapy (mPAP) project is to assess the impact and acceptability of augmenting current PAP therapy data with consumer-grade wearable device data to promote self-management of PAP therapy for OSA. To isolate the impact of the augmentation by the wearable device, the comparator intervention is receiving current PAP therapy data while on a waitlist to add the wearable device data.

Study Aims and Hypotheses

The specific aims and hypotheses are as follows:

- Specific aim 1: to measure the effect of the consumer grade wearable–augmented program on PAP use.
  - Primary hypothesis: compared to participants in the waitlist control group, participants in the immediate intervention group will have greater improvement in PAP adherence (change in average minutes per night from baseline [T1] to posttreatment assessment [T3]).
  - Secondary hypothesis: PAP adherence (average minutes per night) from delayed baseline (T4) to delayed posttreatment assessment (T5) will improve among participants in the waitlist control group after receiving the delayed wearable intervention.
  - Exploratory hypotheses: the effect of the program will be maintained at T5 for the immediate intervention group.
- Specific aim 2: to assess the acceptability of the program.

Methods

Study Design

This study is a randomized parallel 2-group waitlist-controlled trial with 1:1 allocation evaluating the efficacy of a consumer wearable–augmented self-monitoring program on PAP adherence compared to a standard self-monitoring program on PAP adherence among patients with OSA prescribed PAP therapy. In addition, following the primary end point, the control group will crossover to the intervention condition and be compared to their time in the control condition (ie, single-group nonrandomized crossover design). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement was used to report standard protocol items for clinical trials [19].

Study Site

The study will be conducted at Veterans Affairs Greater Los Angeles Healthcare System in Los Angeles, California.

Participants: Inclusion and Exclusion Criteria

Inclusion criteria were as follows: aged ≥21 years, prescribed PAP therapy from the sleep center for >1 week, have an active profile in our Center's ResMed AirView (ResMed) or Respironics Care Orchestrator (Philips Respironics) accounts for >1 week, willing to continue using current PAP device for 28 days continuously, nonadherent to PAP therapy (ie, not using their PAP for 4 or more hours per night on 70% of nights during a consecutive 30-day period) [20], and have a smartphone compatible with the wearable app.

Exclusion criteria were as follows: conditions that may cause nocturnal hypoxemia unrelated to OSA (ie, heart failure, chronic lung disease, and home oxygen use); conditions that may limit individual's ability to follow study procedures such as wear Fitbit, attempt to use their PAP, participate in interviews with research team, and complete web-based surveys (ie, dementia, active substance use disorder, unstable medical or psychiatric illness, concurrent participation in another clinical trial that would interfere with study procedures, planned nonuse of PAP therapy, and planned surgery or hospitalization during study period that would limit PAP use); planned extensive travel during study period; and history of repeated nonattendance at clinic visits. Textbox 1 provides details on how we will operationalize the exclusion criteria.

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Textbox 1. Operationalizing exclusion criteria.

Exclusion criteria

- Conditions that may cause nocturnal hypoxemia unrelated to obstructive sleep apnea
  - Heart failure: heart failure diagnosis listed in the electronic health record problem list
  - Chronic lung disease: lung conditions that can cause hypoxemia including asthma, chronic obstructive lung disease, and restrictive lung disease
  - Home oxygen use: evidence in the electronic health record or patient report of prescription for home oxygen
- Conditions that may interfere with the protocol
  - Dementia: dementia reported by patient and/or caregiver or listed in the electronic health record
  - Active substance use disorder interfering with the protocol (investigator discretion)
  - Unstable medical or psychiatric illness interfering with the protocol (investigator discretion)
  - Planned surgery or hospitalization during study period interfering with the protocol (positive airway pressure [PAP] access or investigator discretion)
  - Planned extensive travel during study period interrupting electricity, cellular and/or internet service, or the protocol (investigator discretion)
  - History of repeated nonattendance at clinic visits
- Refusal to engage in any PAP therapy
  - No future intention of resuming PAP use

Procedures

Recruitment and Screening

Recruitment strategies will include (1) mailing letters to patients with active modem accounts, (2) posting flyers or posters in the clinic areas and enclosing flyers with PAP equipment distributed to patients, and (3) notifying sleep center staff about the study. Participants will undergo an initial telephone screen to assess for eligibility and to collect demographic data (age, gender, race, and ethnicity). Research staff will perform a brief medical chart review to verify eligibility and OSA history (diagnosis date, severity [apnea-hypopnea index], and PAP settings [fixed vs auto]). We will verify that the patient has a PAP modem profile on the clinic's AirView or Care Orchestrator account. The research team will meet weekly to review eligibility requirements for each individual after completing baseline assessment and 1-night oximetry to determine whether the individual is eligible for randomization in the clinical trial.

We increased the number of letters mailed each week to patients meeting the inclusion criteria to help us achieve adequate participant enrollment to reach target sample size. Another strategy used was to present this study to the Greater Los Angeles Veteran Engagement Team (CIN 13-417) in December 2023 for feedback on our recruitment strategy. The Greater Los Angeles Veteran Engagement Team is composed of a diverse team of local veterans whose mission is to partner as active stakeholders with the Greater Los Angeles research community and impart veteran-based knowledge and perspectives on research and other improvement efforts. Some of their suggestions include posting flyers in additional locations with more foot traffic.

Assessments

Baseline Assessment

Participants in both arms will undergo a baseline assessment (T1 for the immediate intervention group; T3 for the waitlist control group), where current 7-day and 30-day PAP adherence will be collected from modem data. One-night oximetry using a United States Food and Drug Administration–approved wrist-worn pulse oximeter (Nonin) will be conducted. Other measures such as determinants of PAP compliance (ie, self-efficacy, knowledge, stages of change, and decisional balance index) [21], sleep disturbance, sleep quality, daytime function, comorbidities, and health literacy will be collected through an electronic survey using the Qualtrics platform. A baseline assessment appointment with a research team member will be conducted, where the research team member will review the survey and administer any items that were unintentionally left incomplete.

Follow-Up Assessment

The immediate intervention group will undergo posttreatment assessment at T3 and follow-up assessment at T5. The waitlist control group will complete the posttreatment assessment at T5. Participants will also undergo an intervention program evaluation upon completion of the intervention (either T3 or T5, depending upon group assignment). At T3 and T5, 7-day and 30-day PAP adherence data will be abstracted from modem data, regardless of whether participants wear the watch or view the reports.

Randomization

Eligible participants will be randomized to 1 of the 2 study arms: an immediate intervention and waitlist control, using a 1:1 ratio. Randomization will be performed using a random permuted block design with varying block size generated by

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the study statistician. Opaque sequentially numbered envelopes were prepared by a researcher who was not involved in any part of our study, thus implementing the random allocation sequence that randomized each successive eligible participant.

Blinding

The primary and secondary outcomes at follow-up (ie, T3—week 5 and T5—week 11) will be assessed by research team members who are blinded to study arm assignment. The portion of the assessment covering program evaluation will be administered by an unblinded team member. Participants will not specifically be informed that they are in the immediate versus waitlist group; rather, they will be informed of the expected date of beginning the program.

Device Selection

We selected the Fitbit Charge 5 (Google Inc), a smartwatch with a sensor that can sample SpO_2 in minute-by-minute intervals. There were three considerations:

1. Whether the device had the sensor capable of collecting SpO_2 data. The Fitbit Charge 5 has "red and infrared light sensors on the back of the device. [These] sensors shine red and infrared light onto skin and blood vessels and use the reflected light that bounces back to estimate how much oxygen is in the blood. Machine learning is used to estimate the SpO_2 value and to ensure a high confidence level in the blood oxygen reading" [22].
2. Whether we would get data suitable for our purposes. Unlike manufacturers that provide a 15- or 30-minute average SpO_2 value, or present "high" or "low" variation in oxygen, none of which are useful for self-management of OSA, the Fitbit Charge 5 sampled SpO_2 in minute-by-minute intervals. For purposes of self-monitoring SpO_2 while sleeping, it is critical that the data are sampled at sufficiently small intervals to allow for appropriate characterization of abnormal oxygen saturation (eg, SpO_2<93%).
3. Whether participants would wear the device night after night. Although there are other devices, such as an oximeter, that could provide similar data, we chose a smartwatch because it is more likely that an individual would keep wearing a smartwatch over putting on the oximeter sensor night after night. As participants get to keep the smartwatch after the trial, we hope that many will continue to use the device for its convenience and myriad of features, tracking SpO_2 or otherwise.

Intervention

Immediate Intervention: Consumer-Grade Wearable-Augmented PAP Adherence Intervention Program

Immediately following randomization (day 0), each eligible participant assigned to the immediate intervention group will receive a consumer-grade wearable , which records minute-by-minute SpO_2 data (Fitbit Charge 5), on day 1, along with instructions on how to use it. They will be asked to wear the wearable nightly, even if not using treatment device. Participants will be oriented to using their wearable for the self-monitoring program, including a feature that includes viewing their personal reports on demand. Participants who are not available for an in-person visit will be sent the device and scheduled for a telehealth visit with the research team. Participants will share data with project team via a third-party platform (Fitabase) and will be sent a weekly survey about OSA-related symptoms. The weekly survey about each 7-day period will be sent the morning of day 7, 14, 21, and 28. An automated reminder will be sent after 12 hours if the participant has not completed the survey. We will track the percentage of surveys completed as part of monitoring adherence to intervention protocols.

Data shared by participants will be used to generate customized reports that emphasize the amount of time participant had SpO_2 values in the various oxygen range categories (eg, minutes spent >92% SpO_2), PAP use modem data, and responses from the participant about their OSA-related symptoms. The juxtaposition of these 3 different types of information (SpO_2, PAP use, and symptoms) is intended to help participants identify patterns of association between PAP use and objective (SpO_2) and subjective (symptoms) data. Within 1 to 2 days of the first report delivery (or scheduled for delivery) to the participant, the participant will meet with a member of the research team, who will review the report and the meaning of the information presented using a structured session guide. The participants will continue to complete an OSA-related symptoms survey weekly until day 28 so that weekly customized reports can be delivered to the participant (also using the Qualtrics platform). The report is presented as an embedded image in the Qualtrics survey that participants can view and download.

The allocated intervention may be modified or discontinued at the participant's request or by the study team in cases where the intervention (ie, charts) causes severe anxiety or distress or PAP treatment causes harms (eg, dermatitis that is persistent despite changing interfaces). Permitted concomitant care and interventions include those recommended and provided by the participant's provider within the sleep center (eg, mask fitting, psychoeducation, and PAP desensitization).

Waitlist Control

Participants assigned to waitlist control will receive usual care from the sleep center, which includes clinic visit every 6 to 12 months on average, with access to durable medical equipment such as PAP interfaces on an as-needed basis. Participants will also have walk-in access to sleep technologists and respiratory therapists who can answer questions about PAP device issues and can fit patients with a new PAP mask. Each device can be paired with a self-monitoring app by the manufacturer so that patients can monitor adherence (eg, myAir [ResMed] and DreamMapper [Philips Respironics Inc]), and patients also receive feedback about their PAP use on the device display. These participants will receive instructions on the wearable at time point T4 and be offered the same intervention as the immediate group until T5 (28 days).

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Program Evaluation

We will conduct a semistructured interview with participants at the completion of the program to obtain feedback from participants about the program and to elucidate opportunities to improve the trial design. Research staff with experience conducting program evaluation interviews will conduct these interviews using a semistructured interview guide with questions such as “What did you think about the reports?” or “What did you think about using a Fitbit to collect pulse oximetry data while you slept?” The staff will ask the participants how many of the reports they viewed and if they had any technical difficulties opening or viewing them. Those who choose not to view any reports will still be interviewed for their impressions of the process and concept. We will record and transcribe interviews for analysis.

Participant Timeline

Participants are enrolled on a rolling basis. After baseline assessment (T1), participants are randomized into either the immediate intervention group or the waitlist control group. Participants in the immediate intervention group start the 28-day program immediately (T2). After 7 days, at T3, the participants in the immediate intervention group undergo posttreatment assessment, and participants in the waitlist control group complete delayed baseline assessment. At T4, 7 days after T3, waitlist control participants start the intervention for 28 days. At T5, 7 days after intervention completion, participants in the waitlist control group undergo posttreatment assessment and participants in the immediate intervention group complete follow-up assessment.

Measures

Sample Characteristics

Participants will be asked to provide demographic characteristics, such as age, gender, race, ethnicity, marital status, and education level. We will also abstract from the medical record OSA history (severity and PAP settings). Comorbidities will be summarized by the Self-Administered Comorbidity questionnaire (convergent validity with Charlson Comorbidity index r=0.55) [23]. Participants' overnight oxygen desaturation, based on clinical overnight oximetry, will be summarized by the amount of time spent at various oxygen saturation levels.

Primary Outcome Measure

The primary outcome measure will be the change in PAP adherence (average minutes per night over a 7-day period) from T1 to T3. PAP adherence, defined as the use of the device for 4 or more hours per night on 70% of nights during a consecutive 30-day period [20], is measured continuously and is recorded by the participant’s PAP machine and transmitted to the participant’s PAP account (eg, AirView and Care Orchestrator) through a cellular modem that is embedded in the device [24]. PAP devices can distinguish between periods when the mask is on versus off the face (by detecting flow).

Secondary Outcome Measures

Additional PAP adherence metrics will be abstracted from the participant’s PAP modem report: Percentage of days used for 4 or more hours, number of days used out of 7 days, and average residual apnea-hypopnea index on therapy.

Participant acceptability will be assessed [25]. We will review the data and evaluate the proportion of nights participants used the wearable overall and while on treatment to ascertain feasibility and acceptability of using a wearable to collect SpO_2 data. We will further assess intervention feasibility, acceptability, and appropriateness with items developed by Weiner et al [25]. The postprogram survey will be followed by an interview with patients about their experience using the wearable with treatment, including opinions about the wearable program and intention to continue using the wearable.

Other Measures

Sleep disturbance and sleep-related impairment will be measured by the 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and 8-item Sleep-Related Impairment [26]. Scores are presented as t scores, with an average of 50 and SD of 10. Scores >60 are considered elevated. Internal consistency has previously been very high (Cronbach α>0.94) [27].

Hypersomnolence will be assessed with the 8-item Epworth Sleepiness Scale [28]. Score ranges from 0 to 24 (internal consistency Cronbach α=0.82) [29].

Determinants of PAP compliance subscales (self-efficacy, 5 items; knowledge, 12 items) and transtheoretical model (decision balance, 11 items; stages of change, 1 item), chosen from constructs of social cognitive theory, will measure factors that are commonly associated with PAP use (subscale Cronbach α=0.66-0.93) [21].

Graph literacy will be evaluated using a 4-item Short Graph Literacy Scale [30] that presents data in the form of a chart and queries the respondent’s comprehension, with the number of correct answers out of 4 indicating graph literacy. This short scale has convergent validity with both the Long Graph Literacy Scale (r=0.90) and a detailed verbal query of how well the participant comprehended the graph (r=0.44).

The impact of OSA on biopsychosocial aspects (eg, mood and/or psychosocial outcomes) will be assessed using the Symptoms, Tiredness, Alertness, Mood, and Psychosocial questionnaire [31]. It is a 12-item questionnaire that is scored on a 6-point scale (internal consistency Cronbach α=0.91).

Statistical Analysis

An intention-to-treat approach will be used. Demographic and clinical characteristics, as well as all outcome measures at baseline, will be summarized using descriptive statistics by study arm to assess baseline comparability. If the distribution of the continuous variable is skewed, an appropriate variable transformation will be made before the comparison. Multiple imputation will be implemented to account for missing data using software for regression models developed by Belin et al [32], Liu et al [33], and Schafer [34].

Changes in sleep-related outcome measures will be analyzed to assess the “success” (effect) of the wearable intervention. The primary sleep-related outcome is change in average minutes

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per night of PAP use from T1 to T3. Our primary hypothesis is that the proposed intervention program will improve PAP adherence among participants who receive the program immediately compared to a waitlist control group. The primary analysis will be a comparison of mean change in PAP use between the immediate intervention group and the waitlist control group using a 2-sample, 2-sided *t* test (unadjusted). Next, we will construct an analysis of covariance regression model that includes baseline PAP adherence score, study arm (intervention vs control), demographic characteristics (eg, age), and preselected clinical characteristics (eg, determinants of PAP compliance score, OSA severity, and PAP setting) to examine whether the effect of the wearable intervention on PAP adherence, where the change score is the primary outcome, is significant. Because this is a single-site pilot, we have no plans to conduct any interim analyses that would be used to determine termination of trial.

Secondary analyses will compare secondary outcomes, such as the percentage of days used for ≥4 hours out of 28 days and the percentage of days used out of 28 days, between study arms. These comparisons will use generalized linear mixed-effects models with appropriate link functions, such as logit for binary outcomes and log for count outcomes. Each regression model will include the fixed effects of interest (study arm, time, and a 2-way study arm-by-time interaction term) and participant-level random effects to account for dependency of repeated observation within participants. Similar to the primary analysis, adjusted analyses of secondary outcomes with preselected factors will be performed. In addition, a generalized linear mixed-effects model will be used to compare change scores before and after the wearable intervention within the waitlist control group to estimate whether the difference in change scores before and after is significant (secondary hypothesis). This analysis will include the PAP adherence measurements from T1 to T5 for all the waitlist control participants. A similar modeling approach will be used to evaluate whether the effect of the 28-day wearable intervention is maintained at the end of the study (exploratory analysis).

Participant acceptability will be measured and analyzed to assess acceptability. We will summarize acceptability measures (frequency, mean, etc). For interview data, we will summarize interview content thematically using Veterans Affairs (VA)–approved qualitative data analysis software (eg, ATLAS.ti) and identify ways to improve the protocol for a future full-scale trial.

Power and Sample Size Considerations

A sample size of 25 participants per study arm will provide at least 80% power to detect a standardized effect size (Cohen *d*) of 0.72 using a 2-group test with a .05 two-sided significance when comparing mean changes in primary outcome between study arms. We anticipate a relatively larger effect size because the study time point is in a shorter time frame after treatment. The effect size estimated from this pilot study will be used to plan a future full-scale, multiyear trial.

Ethical Considerations

Institutional Review Board Approval

The study procedures were reviewed and approved by the VA Greater Los Angeles (VAGLA) institutional review board (IRB; approval 1754210) and University of California, Los Angeles, and the full trial was registered through ClinicalTrials.gov (NCT06039865). Any modifications to the protocol related to deviation of study aim, study design, patient populations, or study procedures will not be implemented until the formal amendment to the protocol is approved by the IRB.

Privacy and Informed Consent

A Health Insurance Portability and Accountability Act waiver will be requested for the chart review. Patients who are eligible based on preliminary telephone screening will be invited to participate in an informed consent appointment where the risks and benefits of the study will be presented. After written informed consent (either paper or electronic) is obtained, participants will undergo a baseline assessment. Data will be deidentified.

Data Management

Electronic data will be stored behind a VA firewall on a secure research server, with access limited to the research team. Paper charts will be secured in locked filing cabinets in locked research offices with access limited to the research team. PAP modem reports will be downloaded and data extracted and converted to data files using an automated process. Random files (10%) will be manually extracted, and these manually extracted data will be compared to the automated process. Data will be cleaned over the course of the study. All personal information about potential and enrolled participants will only be accessible to study team members before, during, and after the trial to protect confidentiality. We will retain and dispose of records in compliance with VA Record Control Schedules [20].

Monitoring and Auditing

A data and safety monitoring board will not be needed for this study because our study is a single-site clinical trial involving the use of PAP machines that is considered standard of care for patients with OSA. We will be pairing the use of PAP machines with a consumer-grade wearable device but using both together should pose minimal risk to the patient because none of the data collected will be used for diagnosing purposes. We will conduct a check-in visit with patients to ask about their experience with the program, which will include questions about adverse events related to study participation. We will follow VA reporting requirements to our IRB for adverse events and serious adverse events.

VAGLA Compliance conducts monthly audits to ensure compliance with procedures for informed consent. This process is independent from investigators.

Results

Amendments were approved by VAGLA IRB in October 2023 and in March 2024. Primary reason for the March 2024 protocol amendment was as follows: protocol updates included addition

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of nonadherence to PAP therapy (use of PAP device for 4 or more hours per night on 70% of nights during a consecutive 30-day period) as inclusion criteria; changed collection of 3 nights oximetry at baseline assessment to 1 night of oximetry if no prior overnight oximetry results available; added PROMIS Sleep Disturbance Short Form and Sleep-Related Impairment Short Form and removed Pittsburg Sleep Quality Index and Insomnia Severity Index as baseline assessment instruments; and clarified that Symptoms, Tiredness, Alertness, Mood, and Psychosocial, PROMIS Sleep Disturbance Short Form, Sleep-Related Impairment Short Form, and determinants of nasal continuous PAP compliance would be asked at T3 and T5 and that the Acceptability of Intervention Measures, Intervention Appropriateness Measures, and Feasibility of Intervention Measures would be collected from participants after they complete the intervention program. Primary reason for A2 protocol amendment included protocol updated by adding VA DocuSign as a method of obtaining written consent during VA telehealth consent visit.

Recruitment began in October 2023 and should be completed by September 2024. Results will be disseminated through conferences and peer-reviewed journals in the sleep, digital health, and health services fields.

Discussion

Anticipated Findings

The proposed pilot study will examine the impact and acceptability of augmenting current PAP therapy data with a consumer-grade wearable device to promote self-management of PAP therapy for OSA. Using SpO_2 data collected by a consumer-grade wearable represents an opportunity to support self-management of OSA to increase the use of PAP therapy and promote dialogue between patients and their sleep clinicians about OSA treatment. This pilot trial will provide important information regarding the acceptability of the consumer wearable intervention.

Underuse of PAP therapy is common among patients with OSA. Improving adherence to PAP therapy remains a formidable task, and new approaches that can be used alone or in combination with existing programs to improve adherence are needed. The growing use of consumer wearables provides a new opportunity to increase and optimize the use of PAP therapy. Including a consumer-grade wearable device to collect pulse oximetry data nightly and discussing the data presented in a customized report with a clinician as part of the patient's OSA therapy represents a new approach. The self-monitoring program provides participants with the support they might need between clinic visits, agency to manage their own treatment, and self-awareness. The intervention was designed to maximize accessibility by incorporating internet-based modalities such as e-surveys and video visits to allow participants who live further away from the sleep clinic to participate in the study, thus ensuring access to care and tools for these patients who may experience greater barriers to attending follow-up visits.

Limitations

There may be data limitations to using pulse oximetry data collected by a consumer-grade wearable device. We may encounter instances where there are missing data from part of the night when a participant was asleep, which could be due to the position of the wearable while sleeping. Anticipating this issue, we have established a procedure to notify the participant that no data had been collected for the previous night and to remind them to wear the device on their nondominant wrist. In addition, we do make it clear that the report will be based on available data only, which is adequate for the purposes of self-monitoring. There may also be situations where the smartwatch fails to sync and does not transmit to the third-party platform for the research team to download. For these instances, we will check syncing weekly and call participants who do not have a sync in the past 24 hours.

As our inclusion criteria will allow for either use of Respironics or ResMed device, there could be potential discrepancies in PAP use reports due to manufacturer algorithm differences. A study by Nolan et al [35] compared adherence to an older Respironics versus older ResMed device versus Breas and found no significant difference between the Respironics versus ResMed device (there was significant difference for the Breas, but our sleep center has never used Breas). Although Isetta et al [36,37] reported differences in the algorithms between Respironics and ResMed device, noncompliance is multifactorial such that the device algorithm could be just one factor among many other non–pressure-related factors. Moreover, larger studies comparing fixed versus flexible pressure settings identified no difference in adherence for new users [7]. We will attempt to perform stratified subanalyses for patients prescribed ResMed versus Respironics devices if we end up enrolling participants using CPAP devices by different manufacturers.

Some participants may have difficulty understanding and applying information from the charts [38]. To increase the utility of the weekly report displaying nightly oxygen saturation data and patient-reported outcomes on sleep quality, mood, and functioning, our study will include a check-in video visit on day 7 to orient the participant to the weekly report, which may promote participant engagement [39]. We will explore the effect of these sessions as well as participant experience with the intervention with semistructured interviews conducted at the end of the research study.

Some studies have suggested that knowing there will be a delay in receiving the intervention may influence a participant's behavior such that it is no longer an accurate portrayal of their natural behavior while awaiting treatment [40]. Some participants may in fact put less effort in their current treatment, potentially exacerbating their symptoms. This could result in an inflated estimated effect of the intervention if waitlist control participants improve "significantly" once in treatment. However, our trial's wait time is brief (6 weeks), which is not very different from other delays participants may have encountered in receiving sleep equipment due to recent device recalls [41]. We will not use the term "waitlist," which may carry negative connotations, for participants who will start the intervention after an initial waiting period.

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Finally, we may encounter a selection bias due to participants who may not be comfortable with video visits or using a wearable device declining participation. This is a common issue with trials involving technology. In a future large-scale trial, we could work with patients who decline due to discomfort with technology before randomization and give them more time to acclimate to using video visits or a wearable device.

Possible Implications

This study will provide an opportunity to explore SpO_2 as a use case of patient-generated health data for OSA self-management and to assess the effect of sharing these data with patients on PAP adherence. In the proposed trial, nightly SpO_2 data will be visualized to show the amount of time in normal and abnormal oxygen saturation while sleeping along with sleep-related patient-reported outcomes (eg, daytime sleepiness) over a 7-day period. To our knowledge, SpO_2 data have not been visualized in this manner.

This intervention will also pair the weekly report with a discussion with a research team member after week 1 so the patient can learn to interpret the figure and apply insights for OSA self-management. Findings from the study may provide additional insights on how patients with OSA might use patient-generated health data collected by consumer wearables to inform self-management of OSA and possibly increase their use of PAP therapy. When patients are provided with meaningful data, in the form of oxygen saturation and their symptoms, and they are able to identify patterns and relationships between these data points, this may help increase patient awareness of their condition and lead to better decision-making about their treatment [42]. We will be examining the utility of the curated data visualizations delivered weekly to further our understanding of how to deploy this type of intervention to improve use of PAP therapy and promote patient engagement in their own care.

Promoting engagement with one's care is vital to management of OSA. Our study will examine the effect of providing support to patients with OSA with a self-monitoring program between clinic visits. The intervention will provide patients with curated data visualizations and will also assist patients with interpreting these weekly reports. Findings from examining the acceptability and efficacy of augmenting current PAP therapy with wearable oxygen data will enable us to optimize implementation of patient-generated health data as an enhancer of daily living and routine clinic care. Findings will contribute additional knowledge regarding the implementation of interventions aimed at increasing OSA self-management practices.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SM participated in conceptualization, methodology, data curation, validation, supervision, and original draft preparation. GA participated in conceptualization, methodology, data curation, validation, and reviewing and editing the draft. LJL participated in methodology, validation, formal analysis, and reviewing and editing the draft. EDM participated in data curation, project administration, and reviewing and editing the draft. SG participated in data curation, project administration, and reviewing and editing the draft. AK was involved in data curation and reviewing and editing the draft. SN was involved in data curation and reviewing and editing the draft. MZ participated in conceptualization, methodology, data curation, validation, and reviewing and editing the draft. CF participated in conceptualization, methodology, data curation, validation, supervision, and original draft preparation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 118 KB - resprot_v13i1e60769_app1.pdf]

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Abbreviations

IRB: institutional review board
mPAP: Chronic Care Management With Wearable Devices in Patients Prescribed Positive Airway Pressure Therapy
OSA: obstructive sleep apnea

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PAP: positive airway pressure
PROMIS: Patient-Reported Outcomes Measurement Information System
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SpO2: blood oxygen saturation
VA: Veterans Affairs
VAGLA: Veterans Affairs Greater Los Angeles

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Protocol

Testing the Effectiveness of a Mobile Smartphone App Designed to Improve the Mental Health of Junior Physicians: Protocol for a Randomized Controlled Trial

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Abstract

Background: Shift (Black Dog Institute) is the first mobile health smartphone app created to support the mental health of junior physicians. Junior physicians experience demanding work conditions, leading to high levels of psychological distress and burnout. However, they are often concerned about the potential career impacts of seeking mental health support. The confidentiality and ease of access of digital interventions may be particularly suited to address these concerns. The Shift app provides therapeutic and psychoeducational content and strategies contextualized for the specific needs of physicians in training. App content includes information on mental health, help seeking, mindfulness, and common workplace-related concerns of junior physicians.

Objective: This study aims to test, at scale, the effectiveness of Shift among junior physicians working in Australia using a randomized controlled trial design. The primary aim is to examine whether junior physicians using Shift experience a reduction in depressive symptoms compared with a waitlist control group. The secondary aim is to examine whether the app intervention group experiences improvements in anxiety, work and social functioning, help seeking, quality of life, and burnout compared with the control group.

Methods: A total of 778 junior physicians were recruited over the internet through government and nongovernment medical organizations across Australia, as well as through paid social media advertisements. They were randomly allocated to one of 2 groups: (1) the intervention group, who were asked to use the Shift app for a period of 30 days, or (2) the waitlist control group, who were placed on a waitlist and were asked to use the app after 3 months. Participants completed psychometric measures for self-assessing mental health and wellbeing outcomes, with assessments occurring at baseline, 1 month after completing the baseline period, and 3 months after completing the baseline period. Participants in the waitlist control group were asked to complete an additional web-based questionnaire 1 month after receiving access to the app or 4 months after completing the baseline survey. Participants took part in the study on the internet; the study was completely automated.

Results: The study was funded from November 2022 to December 2024 by the New South Wales Ministry of Health. Data collection for the study occurred between January and August 2024, with 780 participants enrolling in the study during this time. Data analysis is underway; the effectiveness of the intervention will be estimated on an intention-to-treat basis using a mixed-model, repeated measures analysis. Results are expected to be submitted for publication in 2025.

Conclusions: To the best of our knowledge, this is the first randomized controlled trial to examine the effectiveness of a mobile health smartphone app specifically designed to support the mental health of junior physicians.

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International Registered Report Identifier (IRRID): DERR1-10.2196/58288

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KEYWORDS

junior physicians; digital mental health; smartphone app; depression; mobile phone

Introduction

Background

The mental health and wellbeing of junior physicians is of increasing concern, with the term *junior physician* applying to physicians who have worked for 5 to 11 years or more after they enter the workforce [1]. As they navigate the transition from medical school to the workforce, junior physicians experience high work demands. Junior physicians must balance highly demanding working conditions and expectations of high performance with the completion of examinations, long working hours, often unsupportive work environments, and relative inexperience in clinical practice [1].

These stressors can place junior physicians at a heightened risk of mental and physical ill-health, which can be particularly impactful at a time that is critical for establishing future health, life goals, and career progression [2-4]. A comprehensive 2013 study of physicians in Australia found that junior physicians showed higher levels of psychological distress, burnout, and thoughts of suicide compared with more experienced physicians [5]. Psychological distress in junior physicians remains high in the post–COVID-19 era; a 2022 study of UK-based junior physicians reported poor mental health in those sampled (429/456, 94.1% total participants), with 45.2% (194/429) of the participants scoring highly on depression symptoms and 63.2% (271/429) scoring highly on anxiety symptoms [6]. The high prevalence of mental health problems is compounded by the physicians' low rates of seeking help for suicidal thoughts and mental health concerns [7]. A range of barriers to seeking help exist for physicians, including self-stigmatization, concerns about being reported to medical regulators, and subsequent negative career repercussions [8].

Mobile health smartphone apps (mHealth apps) have the potential to provide free, 24×7, confidential support by providing educational content and skills training. They can aid in the prevention and early intervention of mental illness by providing easily accessible evidence-based information, such as exercises teaching the basics of cognitive behavioral therapy and acceptance and commitment therapy. Furthermore, they can provide avenues, including clinical services, for users to seek mental health support for those with more severe psychological distress. Presenting this information in the form of an app may circumvent the common barriers to seeking help and avoid the impact of stigma. This is because mental health information and support can be provided in a confidential manner that is unrelated to users' places of work. Previous studies have found mHealth apps to increase resilience and decrease symptoms of depression in other high-risk workplace populations such as ex-soldiers and male-dominated industries including agriculture and mining [9,10]. While there have been a few efforts to develop mHealth apps for health care workers more generally [11,12], specific digital support options for the junior physician population remain lacking.

The Shift app was funded by and developed as part of a 10-step plan by the local Australian state government, the New South Wales (NSW) Ministry of Health, to improve the wellbeing and support available for junior physicians. As part of the scoping assessment for the app, the research team conducted interviews with 12 junior physicians to examine the acceptability of an mHealth app for mental health in this population. The majority of participants surveyed were "very or somewhat interested" in an mHealth app specifically designed to support the mental health and wellbeing of physicians who are early in their careers [13]. They agreed that the main barrier to app use was a lack of time and concerns about confidentiality [13].

Therefore, the Shift app was purposely created to target the unique circumstances of junior physicians. The app specifically incorporates modules and content aimed at the relevant stressors of this group such as shift work, long working hours, dealing with consultations, and where to seek help as a medical professional. Each module includes a scenario of a junior physician facing an emotional or a professional problem, with solutions geared toward these physicians in training. It is hoped that covering a wide range of common problems faced by junior physicians will help to meet the varying needs of individual users, including tools to stay mentally healthy, greater education and awareness of mental health management, and encouraging the users to actively seek mental health help.

To ensure that the preferences and needs of junior physicians were met, the Shift app was developed in multiple phases, with a user-centric design process. An overview of the multiphase design process can be seen in Textbox 1. An in-depth report of phases 1 to 4 can be found in Counson et al [13]; phase 5 is detailed in Sanatkar et al [14]. Notably, a 2020 uncontrolled evaluation of the Shift app with 222 junior physicians across NSW found significant reductions in symptoms of depression and anxiety after 1 month of app use [14]. While preliminary findings are promising, a nationwide randomized controlled trial (RCT) with junior physician participants is required to reliably establish the app's effectiveness.

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Textbox 1. A summary of the different phases that were completed in the process of designing the Shift app.

Phase 1: qualitative interviews

- Needs assessment through qualitative interviews with 12 junior physicians in New South Wales (NSW). Topics surveyed included attitudes toward an app, desired app contents, and barriers to app use.

Phase 2: prototype development

- A prototype of the app was developed, with content written on the basis of recommendations from Phase 1 and in line with evidence from recent literature.

Phase 3: pilot-testing

- The app prototype was pilot-tested with 22 junior physicians who were recruited from one rural and one metropolitan hospital in NSW. Results revealed issues with the organization of the app content, but overall usability ratings were high.

Phase 4: app redevelopment

- The app was redeveloped to increase user engagement, with changes made to improve layout and design, increase personalization, update the clinical contents, and adopt more meaningful and relatable wording. This phase was informed by three user consultation workshops with 51 junior physicians in NSW.

Phase 5: uncontrolled evaluation study

- An uncontrolled evaluation study of the Shift was conducted in 222 junior physicians working in NSW during the COVID-19 pandemic. Depressive and anxiety symptoms significantly decreased after one month of app use.

Phase 6: naturalistic evaluation

- The Shift app was made freely available to the public, with a reduced research component where participants were able to opt-out of data collection. This enabled further interpretation of the effectiveness of the app in a naturalistic setting and to inform future improvements and Shift's ongoing safety and quality.

Phase 7: minor redesign

- A minor redesign of the app was performed in preparation for a nationwide rollout of the app in a randomized controlled trial, including updating the content to be relevant to a nationwide audience, and design changes to increase usability. For further detail, see the Intervention section of this paper.

Outcomes

This study is a national RCT with junior physicians to test the effectiveness of the Shift app. Specifically, we will investigate whether junior physicians who are allocated to the intervention group experience a significantly greater reduction in the symptoms of depression than those who were allocated to the control group (Primary and Secondary Outcomes: Depression section) after a period of 30 days. We will also compare intergroup differences in anxiety symptoms, work and social functioning, quality of life, burnout, and help-seeking intentions and behaviors (Primary and Secondary Outcomes section). Finally, we will assess the suitability of the app and its contents using feedback from junior physicians.

Methods

Study Design

The study is a 2-arm parallel RCT. Randomization is not stratified and will automatically occur when a participant completes the baseline questionnaire. The study will be carried out entirely on the internet and will not be blinded due to the nature of the intervention.

Junior physicians will be randomly allocated to one of two groups, namely, (1) the intervention group or (2) the control group. The intervention group will be provided with a link to download the Shift mHealth app; the participants in this group will be asked to use the app for a period of 30 days. The control group will be placed on a waitlist and will be asked to use the app after 3 months. Participants allocated to the control group are provided with a factsheet that lists several mental health support services, which they are encouraged to contact for further support. These participants will gain access to Shift after 3 months and will be asked to use the app for 30 days.

Primary and secondary outcomes will be measured through self-assessment using questionnaires at 3 time points: the first distributed as part of the baseline assessment, the second distributed 30 days after the baseline assessment, and the third distributed 3 months after the baseline assessment. Waitlist control participants will be further asked to respond to a questionnaire measuring primary and secondary outcomes after 4 months following the baseline assessment or 1 month after they gain access to the app. This will enable us to compare the 30-day app use patterns of the control group with those of the intervention group who used the app in the first month of the trial.

Study Setting and Recruitment

Data collection will occur between January and August 2024; recruitment will occur using 3 strategies. Firstly, participants will be recruited through the Black Dog Institute's web-based

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and social media channels including webpages on the Black Dog Institute website and targeted social media advertisements on Facebook (Meta Platforms, Inc) and Instagram (Meta Platforms, Inc). Secondly, the NSW Ministry of Health will disseminate study information through NSW Health public health systems. NSW is the state in which the greatest proportion of junior physicians in Australia are employed, primarily through public hospitals. Thirdly, the research team will partner with private medical colleges and other medical specialist organizations based in Australia to disseminate study information on medical platforms. Promotional materials may include the logos of the Black Dog Institute, the University of NSW Sydney, and NSW Health.

The inclusion criteria for participants taking part in this study include the following: (1) The participant must be currently working as a junior physician (ie, intern, hospital medical officer, resident medical officer, nonaccredited trainee, postgraduate trainee, principal house officer, registrar, or specialist trainee) in Australia. (2) The participant must own an internet-enabled smartphone that has an iOS (Apple) or Android (Google) operating system. (3) The participant must provide consent to participate.

Candidates who do not meet all the 3 eligibility criteria will be excluded from participation. Instead, they will be provided with mental health support options and information on other current research projects run by the Black Dog Institute.

The study is conducted remotely and occurs entirely on the web for all participants. This means that there is no direct contact with the research team unless a participant voluntarily contacts the team using contact details in the participant information statement and consent form.

Intervention

The Shift modules include content covering topics related to mental health, getting support, lifestyle, and work. Other components of the Shift app include a tracking function for monitoring mood, physical activity, work-life balance, and sleep. The contents of the app are delivered through video, audio, graphical representation, and text displays. The module content was developed by the Black Dog Institute and was informed by recognized, evidence-based psychological approaches including cognitive behavioral therapy, acceptance and commitment therapy, mindfulness, and stress management. Thus, the app provides therapeutic, psychoeducational content and strategies contextualized for the specific needs of junior physicians. Examples of the most recent Shift app design and contents can be seen in Figure 1.

During the onboarding phase, the participants are encouraged to complete 2 to 5 activities per week, with each activity requiring 2 to 10 minutes from start to finish. However, participating junior physicians are free to decide how much they engage with the app and which modules they complete. Modules do not need to be completed in a fixed order, and a user can complete one module multiple times. At the onboarding phase, the participants are presented with the option to enable daily push notifications to use the app. They also have the option to change the time of the notifications or turn the notifications off at any time in the “settings” section of the app.

Several updates have been made to the Shift app since the uncontrolled trial of the app in 2020 [14]. This means that the Shift app available for the current RCT is version 2.0. Three new modules were added addressing financial difficulties, academic pressure, and common stigmatizing beliefs about physicians with mental health concerns. The app content was also modified to suit physicians working in all Australian states and in a postpandemic working environment. Changes were also made to enhance the user experience based on previous user feedback. For example, aesthetic updates were made to streamline the content, and in-app personalization was increased. A quality assurance phase by the development team ensured that these changes did not impact the quality or functionality of the app.

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Figure 1. Visual examples of content in the Shift mobile health smartphone app for junior physicians.

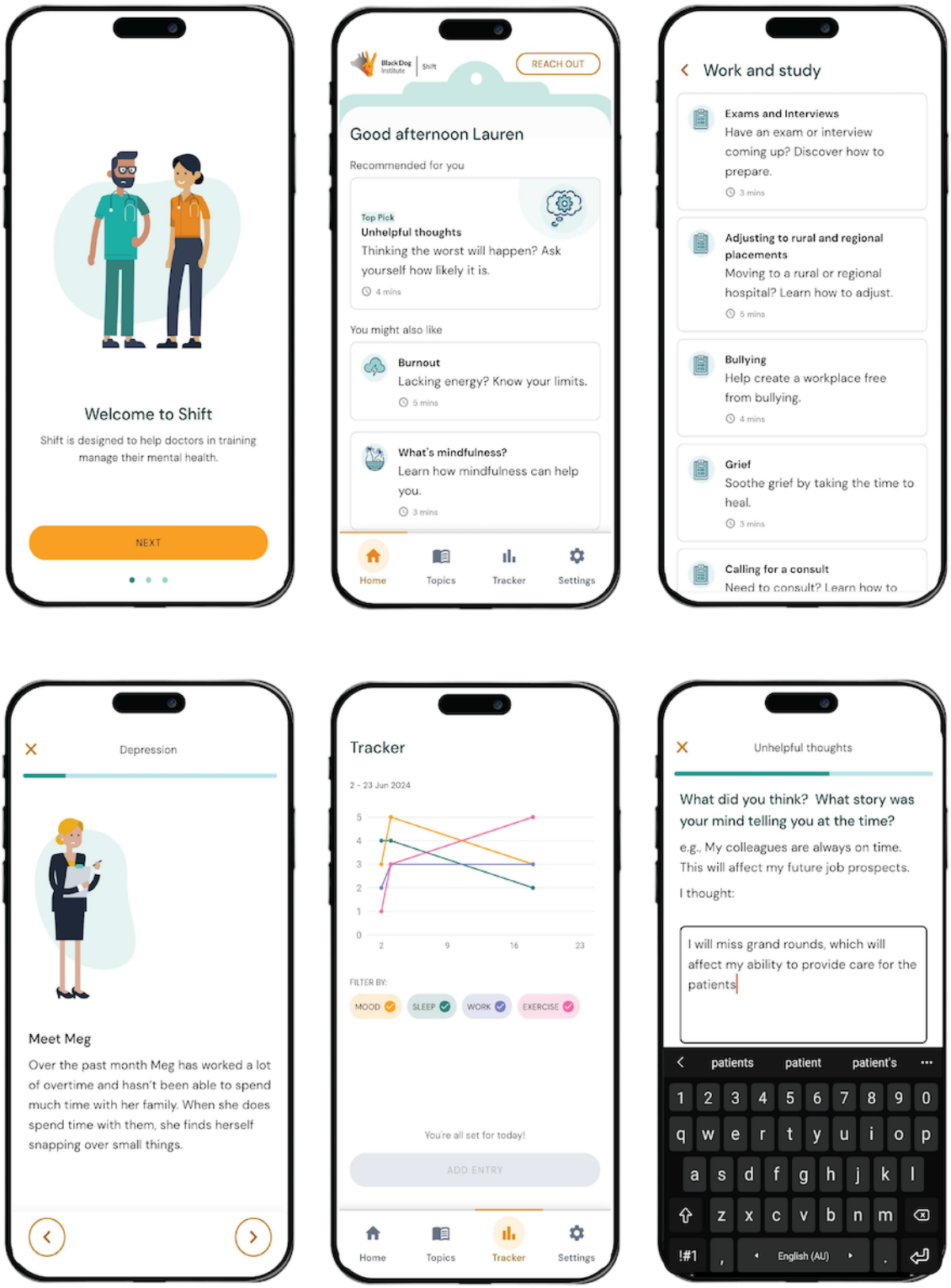

Primary and Secondary Outcomes

Depression

The primary outcome of the study, *depression*, will be measured using the Patient Health Questionnaire-9 (PHQ-9), a reliable and valid 9-item screening tool for assessing depression severity during the past fortnight [15]. On a scale ranging from 0 (not at all) to 3 (nearly every day), respondents indicate their agreement with items describing common symptoms observed in major depressive disorder. Sum scores range from 0 to 27, with scores of 10 or higher indicative of a possible major depressive disorder. The PHQ-9 also includes a single item assessing the level of difficulty in daily functioning due to depressive symptoms. The validity and reliability of the PHQ-9 have been verified, and the measure has been used in physician populations [15,16].

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Anxiety

The secondary outcome *anxiety* will be measured using the Generalized Anxiety Disorder-7 (GAD-7) Scale. The GAD-7 is a reliable and valid 7-item screener for generalized anxiety symptoms [17]. On a scale ranging from 0 (not at all) to 3 (nearly every day), respondents indicate their agreement with items describing common symptoms observed in general anxiety disorder. Overall scores range from 0 to 21, with scores of 10 or higher indicative of a possible general anxiety disorder. GAD-7 also includes a single item assessing the level of difficulty in daily functioning due to anxiety-related symptoms. The validity and reliability of GAD-7 have been confirmed, and the measure has been used in physician populations [17-19].

Work and Social Functioning

The secondary outcome *work and social functioning* will be measured using the 6-item Work and Social Adjustment Scale. The Work and Social Adjustment Scale is a valid and reliable tool used to measure functional impairment in private and professional areas of life [20]. On a scale ranging from 0 (not at all) to 8 (very severely), respondents indicate to what degree their ability to perform in social and work domains is impaired due to their mental health problems. Higher scores indicate a greater level of impairment in respondents' ability to perform in their usual capacity.

Help Seeking

The secondary outcome *help seeking* will be measured using a brief 2-item assessment modeled after the General Help Seeking Questionnaire. The measure will assess the participants' willingness to seek help for mental health concerns and will assess whether they recently sought help for mental health-related issues [21]. The respondents indicate their willingness to seek help on a Likert-type response scale ranging from 1 (*extremely unlikely*) to 7 (*extremely likely*) and indicate whether they sought help from a mental health professional in the previous month (using a simple *yes* or *no* response scale).

Quality of Life

The secondary outcome *quality of life* will be measured using the 5-item Linear Analog Scale Assessment. The Linear Analog Scale Assessment is a reliable and valid tool to measure the quality of life with respect to a number of domains (physical, emotional, spiritual, intellectual, and overall) [22]. On a scale ranging from 1 (as bad as it can be) to 10 (as good as it can be), the respondents are asked to rate their wellbeing during the past week.

Burnout

The secondary outcome *burnout* will be measured using the 16-item Oldenburg Burnout Inventory. The Oldenburg Burnout Inventory is a valid and reliable tool to measure the 2 main dimensions of burnout: exhaustion and disengagement from work [23]. Respondents use a 4-point Likert-type scale to indicate their degree of agreement with a number of questions relating to their level of burnout at work. Higher scores indicate a higher level of burnout.

App Acceptability

After using the app for 30 days, the participants will be asked to respond to 12 open- and closed-ended questions to rate the degree of satisfaction with the app components and identify areas of possible improvement in functionality and design. Seven items use a 5-point Likert-type scale. Using these items, the participant are asked to indicate how easy the app was to use, how helpful various components of the app were, whether they would use the app in the future, and whether they would recommend the app to other physicians in training. Furthermore, 4 open-ended questions assess which activities the participants found most and least helpful and whether the participants have general suggestions or the additional features they would like in the app. One final closed-ended question clarifies why the participants stopped using the app, if this was the case. Additionally, 1 optional item will seek clarification on the reasons why the participants chose to take part in the Shift study.

App Use

The app will automatically record use data such as the number of logins, time spent on app contents, and how many times the tracker function was used (to track mood, exercise, sleep, and work-life balance).

A timeline of all points of measurement for these outcomes is outlined in Table 1.

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Table 1. Constructs and information assessed using web-based surveys and app data collection.

Outcomes	Time point 1: baseline survey	Time point 2: follow-up survey 1	Time point 3: follow-up survey 2	Time point 4: follow-up survey 3[c]	In-app data collection
Demographics	✓[a]	N/A[b]	N/A	N/A	N/A
Depression (PHQ-9[c])	✓	✓	✓	—[d]	N/A
General anxiety disorder (GAD-7[e])	✓	✓	✓	—	N/A
Work and social functioning (WSAS[f])	✓	✓	✓	—	N/A
Help seeking (self-generated questions)	✓	✓	✓	—	N/A
Quality of life (LASA[g])	✓	✓	✓	—	N/A
Burnout (OLBI[h])	✓	✓	✓	—	N/A
App use and study-related questions (self-generated questions)	N/A	X[i]	N/A	—	N/A
App use data	N/A	N/A	N/A	N/A	✓

[a]For intervention and control group.

[b]N/A: not applicable

[c]PHQ-9: Patient Health Questionnaire-9.

[d]For control group only.

[e]GAD-7: Generalized Anxiety Disorder-7 Scale.

[f]WSAS: Work and Social Adjustment Scale.

[g]LASA: Life Linear Analog Scale Assessment.

[h]OLBI: Oldenburg Burnout Inventory.

[i]For intervention group only.

Procedure

The procedure for the Shift RCT is depicted in Figure 2. At the study sign-up, candidates will be invited to visit a study-specific website [24]. Through the website, they will be presented a brief overview of the study purpose and the full participant information statement and consent form. The candidates who are willing to participate will be able to self-screen for eligibility. All the eligible participants will then be presented with a registration page in which they will be asked to input their first name, email address, mobile number, and password.

Following registration, the participants will be asked to complete a survey assessing the primary outcome (depression) and secondary outcomes (anxiety, work and social functioning, quality of life, burnout, and help-seeking intentions and behaviors). After completing the baseline survey, the participants will be randomly assigned to (1) the intervention group (in which a link will be provided through which they can download and use the app, immediately after registration) or (2) the waitlist control group (the members of will be added to a waitlist to use the app). The participants in the waitlist control group are provided with a factsheet listing contact details for several mental health support services and are encouraged to reach out if they would like further support. After the 3-month study period, the participants in the control group will also gain access to the app and will be asked to use it for 30 days. After the participants are provided with a link to download the Shift app on their smartphone, they will be able to use the app free-of-cost.

The primary and secondary outcomes will be measured in both the control group and the intervention group at a number of time points: at baseline and registration (time point 1), 30 days after registration (time point 2), and 3 months after registration (time point 3). These outcomes will also be measured among participants in the control group after 4 months following registration (time point 4), that is, once the participant has had access to the app for 30 days. At each follow-up measurement time point, the participants will receive an initial email reminder to complete the study. This will be followed by an email, a text reminder after 2 days and a text reminder after 9 days.

The study will run for a total of approximately 8 months, between January and August 2024. For participants in the intervention condition, the duration of the study period is 12 to 14 weeks. The duration of the study period for waitlist control participants is 16 to 18 weeks.

After the study is completed, participants can continue to use the app for as long as they wish. The participants can remove the app at any time by uninstalling it from their smartphone. In future, the app may be removed from the app store for development purposes; during this time, all users will be notified and will lose access to the app.

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Figure 2. Flowchart describing how individual participants will progress through the phases of the research.

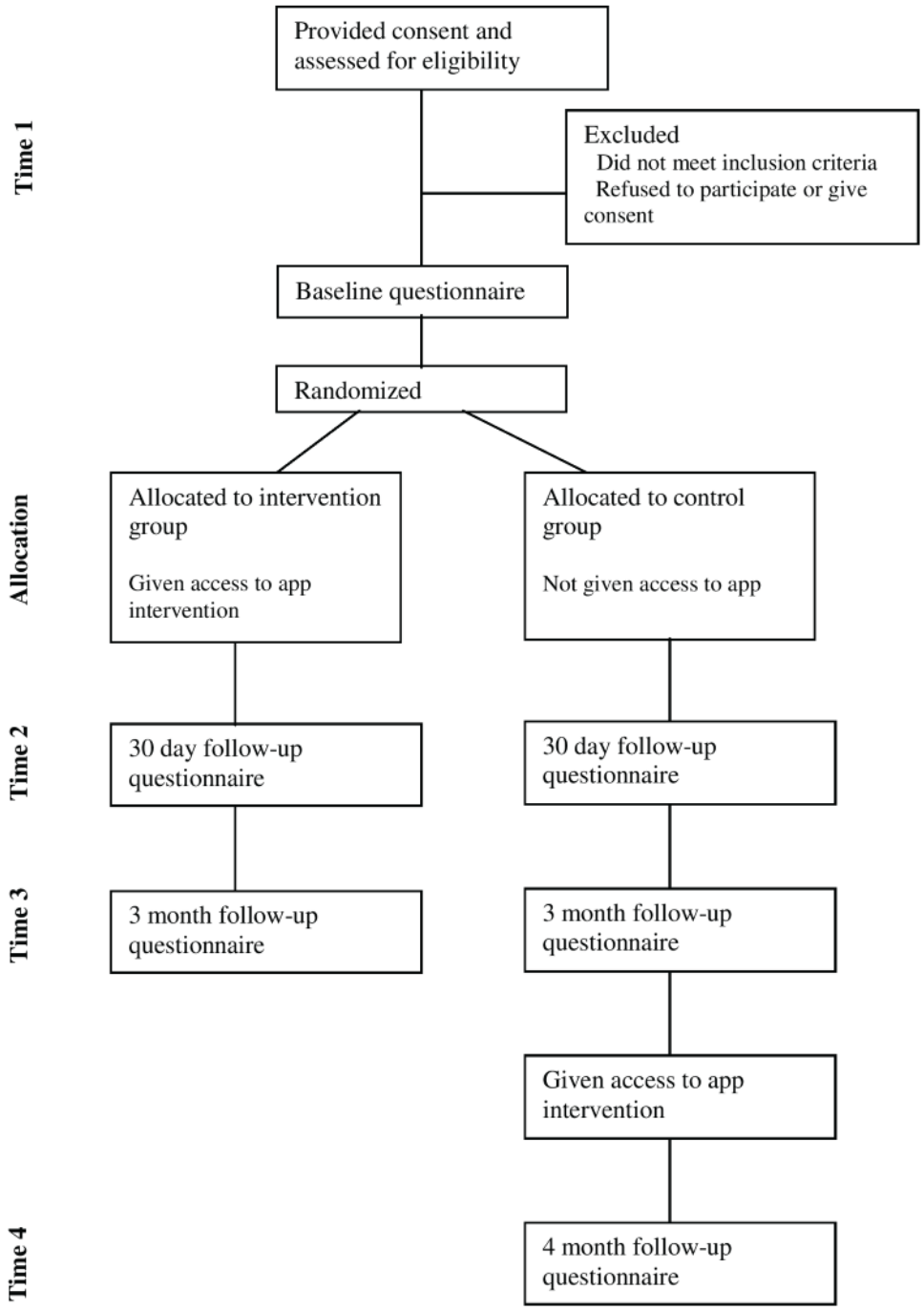

Data Management

Data Management and Monitoring

All study data will be collected and recorded electronically through the Black Dog Institute Research Engine. The servers are hosted in a secure environment (Amazon Web Services) managed by the University of NSW Sydney.

The raw data contain identifiable information (ie, first name, private email address, and mobile phone number) from the registration section at baseline as well as an individual identifier code, which is automatically generated by the system for each participant. Direct individual identifiers will be removed during the transcription process before data preparation and analysis.

Every week, the research team will manually back up all data during the data collection phase; the team will also check that the data are properly archived during every quarter. The backups will be stored in a secure and password-protected University of NSW OneDrive (Microsoft Corporation) folder.

Only the research team approved by our ethics boards (University of NSW Human Research Ethics Committee and Sydney Local Health District Ethics Review Committee) and the designated Black Dog Institute technical staff can access the data. The data will be retained for a minimum of 15 years after the publication of the research findings.

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Trial Harms and Risk Management

Because the study addresses common mental health concerns and challenges associated with being a junior physician, there is a possibility that a few participants may find it distressing to engage with this content. We do not, however, expect the app itself to result in more serious harm, and there were no adverse or serious adverse events registered in the preceding app trials [14]. We define adverse events as any event in which a participant contacts the Shift research team with the indication that the app has had a harmful effect on their health, including any level of psychological distress. The principal investigator will keep a record of all adverse events and inform both the approving ethics committees (the University of NSW Human Research Ethics Committee and the Sydney Local Health District Ethics Review Committee) within 24 business hours following an adverse event. A data safety monitoring board will review the safety protocol and risk management plan. If any risks or adverse events emerge during the trial, the board will meet to review the continuing safety of the study. The board will consist of 3 reviewers who are not associated with the RCT and have a clinical background. If a serious adverse event or reaction is reported, or several adverse events or reactions, the study's data safety monitoring board will review the impact of the study on the participants, and the study may be terminated if the board determines the study is harmful to participants.

When participants initially access the study website, they are presented with the participant information statement and consent form in which the study risks are outlined and emergency helpline contact details are provided. In this form, participants are also provided with the contact details of the research team. If participants contact the research team expressing any level of psychological distress or requesting further support, the team will arrange a callback from the Black Dog Institute's Clinical Services to ensure that appropriate care is being offered to the participant.

On every page of the study website, including the web-based questionnaires, a banner with emergency-contact details is presented at the bottom of the page. These details can be used by the participants if they are experiencing psychological distress. Furthermore, the participants who have medium or high scores (suggesting medium or severe ranges for depression and anxiety) or indicate having suicidal thoughts while responding to the depression measure will see a pop-up window that informs them of their scoring result along with suggestions on how to seek help through a designated helpline. They are also advised to consider making an appointment with their general practitioner or a mental health professional if their symptoms increase or persist.

The app features an in-built "reach out" button at the top right-hand corner of the home screen to support participants who may become distressed while using the app. This button takes users directly to contact details for mental health services and 24×7 telephone helpline numbers. Furthermore, the participants who score poorly on the daily mood checkups (those who select the response options "worse than usual" or "slightly worse than usual") are provided with suggestions to access mental health support options.

Data Analysis

Estimands and Statistical Analysis

Estimands

The primary estimand [25] will reflect intention-to-treat principles and will be based on all participants in the group to which they were randomized regardless of actual receipt, uptake of the intervention, alternative support or interventions received, and withdrawal from the study. A mixed-model, repeated measures analysis will be used for the primary outcome and continuously scaled secondary outcome variables to estimate and compare the change in mean PHQ-9 score in each intervention arm from time point 1 to time points 2, 3, and 4 (if applicable). This form of analysis assumes that unobserved outcome data are missing at random.

As substantial attrition is expected given the distal, universal nature of the intervention, a sensitivity analysis of the primary outcome will be undertaken if the outcome of the intention-to-treat is statistically significant. The "jump-to-reference" approach will be used [26]. This approach assumes that the participants who withdraw or have no postbaseline data have the same trajectories as participants in the control condition. This will yield a robust, conservative lower bound estimate of the intention-to-treat effect in the presence of missing outcome data.

Secondary estimands will estimate the treatment effect in participants who have engaged with the Shift app to various extents. Given that app users are free to choose the modules they use and to access them as often as desired, the concept of full compliance is not applicable. One estimate will involve participants who complete the recommended 8 or more modules during the intervention. The second estimate will broaden engagement to participants who have completed at least 4 modules. This reflects the levels of engagement more commonly observed in the previous version of the app [14]. The complier average causal effect comparing *compliers* in the intervention group to *would-be compliers* in the control group will be estimated using latent variable methods [27]. A conventional per-protocol analysis, including only participants allocated to the intervention group who have downloaded the app, will also be conducted.

Primary Outcome

The change in mean depressive symptoms will be assessed by a planned comparison of the difference between groups in the change of PHQ-9 scores from baseline to postintervention using a linear mixed model for repeated measures. This test will be undertaken with an α of .05. Models will include factors of intervention arm (intervention or control group), occasion of measurement (time points 1, 2, and 3), and their interaction. An unstructured residual variance-covariance matrix will accommodate within-participant dependency. Tests of significance will use the Kenward-Roger method of df adjustment based on the observed information matrix. Where necessary, transformation of the outcome variable will be undertaken to ensure the distributional assumptions of the model are met.

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Depression caseness will be estimated using the established threshold for moderate depressive symptoms using the PHQ-9 total score (a score of 10 or greater). Odds ratios and predicted probabilities will be obtained from a generalized logistic mixed model, which will include random participant intercepts and the factors used in linear models. This will allow us to determine the app's effectiveness in reducing symptomatic status in participants who are likely to have depression, as well as investigate whether the participants who are mentally healthy were able to stay well after the app use.

Secondary Outcomes

Group differences on secondary outcomes on the GAD-7, Work and Social Adjustment Scale, Linear Analog Scale Assessment, and Oldenburg Burnout Inventory scales will follow the same analysis strategy that is used for the primary outcome. For the categorical secondary outcome measure (modified General Help Seeking Questionnaire), analogous generalized mixed models will be used.

Secondary analyses will also include changes in the primary and other outcome variables from baseline (time point 1) to follow-up (time point 3) to establish retention of any benefit. The waitlist group will be provided with access to the intervention after follow-up at time point 3. Postintervention outcomes in the waitlist group (time point 4) will be compared with the intervention group's postintervention (time point 2) scores to estimate changes after they have accessed the intervention. Subject to qualifications arising due to attrition and any natural drift with the passage of time, this analysis will stand as a quasi-replication of the primary outcome of the trial.

As participant sample size allows, a priori defined subgroup analyses (focusing on age, sex, specialty, training level, and location) will be conducted to explore how the primary and secondary outcomes are affected by app use, baseline symptoms patterns (severity of depression and anxiety symptoms), and related factors (eg, self-reported wellbeing status) across all examined time points to inspect group and subgroup trajectories.

Qualitative, open-ended feedback responses will be examined to aid subsequent app changes and future study design considerations. Individual data collected in the questionnaires will be assessed using a structured tabular thematic analysis approach for brief texts, as outlined in Robinson [28].

Sample Size

We determined a total sample size of 778 research participants. Power calculations were based on a recent systematic review and meta-analysis quantifying the efficacy of digital prevention interventions for depression [29]. Hence, an estimated Cohen *d* effect size of 0.25, an α value of .05, a power of 0.8, and a correlation coefficient of 0.6 yielded the required sample size of 404, without any participant dropouts.

A systematic review and meta-analysis examining dropout rates during clinical trials of smartphone apps for depressive symptoms found a pooled dropout rate of 48% [30]. Therefore, we expect to randomize a total of 777 participants (N=404+373) to the 2 trial conditions to conduct a sufficiently powered analysis. To allow for evenly sized groups, this number was rounded off to 778 participants.

Data Exclusion

The participants who withdraw and do not wish for their data to be used will be removed from the analysis.

Ethical Considerations

The trial is registered in the Australian and New Zealand Clinical Trials Register (ACTRN12623000664640) and was approved by the University of NSW Human Research Ethics Committee (HC230355) and the Sydney Local Health District Ethics Review Committee (RPAH Zone, X23-0424). Two ethical approvals were obtained to enable the research team to recruit through nongovernment and government organizations. This is because recruitment through hospitals in Australia requires ethics approval with a government-run human research ethics council such as the Sydney Local Health District Ethics Review Committee.

All candidates will be required to provide informed consent to participate in the study. This is done by digitally signing a web-based participant information statement and consent form before commencing participation in the trial. Candidates are free to withdraw their consent at any time during or after their participation in the trial. Furthermore, all data used in the study analysis will be deidentified.

After the completion of each of the follow-up questionnaires, the participating junior physicians will have the option of participating in a draw to win 1 of 7 eGift vouchers worth Aus $100 (US $68.06) or Aus $200 (US $136.11).

Results

Overview

The study was funded from November 2022 to December 2024 by the NSW Ministry of Health. Data collection ran from January to August 2024, during which time 780 participants enrolled in the study. As of September 2024, data analysis was underway, with results expected to be submitted for publication in 2025.

Dissemination

Results will be disseminated through open-access, peer-reviewed journal articles, professional and media publications, and presentations at scientific conferences. Results may be shared with specialist bodies and forums related to junior physicians and may be included in training materials for physicians. A summary of the results and a copy of any publications from the study will also be made available to participants on request. Participating individuals will not be identified when disseminating the study findings.

Discussion

Summary

Workplace stressors contribute to poor mental health outcomes in junior physicians. These risk factors include long working hours, high work demands, unsupportive work environments, and reluctance to seek help due to concerns regarding confidentiality and potential professional repercussions [1-4]. In light of this, the Shift smartphone app was created to support

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the mental health of junior physicians in a manner that is entirely confidential, easily accessible, and available 24×7. This paper describes the protocol for an RCT to test the effectiveness of the Shift app in reducing symptoms of depression and other mental health outcomes among junior physicians who used the app. While previous studies have found that mHealth apps can reduce depression and provide evidence-based mental health support for other workforces who are at risk [9,10,31], to the best of our knowledge, the effectiveness of a mHealth app for junior physicians has not yet been evaluated in a randomized controlled design.

Strengths

The Shift app specifically targets common problems and concerns faced by junior physicians. During the design phase of the app, qualitative interviews with 12 junior physicians showed that there was a lack of information and support for the unique issues faced at the early stages of a physician's medical career, including navigating professional hierarchies, occupational stress, and the high amount of emotional labor [32]. Therefore, the Shift app's content was designed to be specific to junior physicians, with modules incorporating stories of various junior physicians facing work-related or emotional problems. This was validated by a rigorous codesign process to ensure that the design, wording, and the information presented were suitable and relatable for junior physicians who use the app. Furthermore, the app was designed to address the common barriers to engaging with mental health support tools, as identified by junior physicians [13]. Because junior physicians are time restricted and required to work irregular hours, these barriers include confidentiality, ease of use and ease of access.

Furthermore, as the participants were asked to use the app freely within the 30-day intervention period, we do not expect significant variations between app use patterns in the RCT compared with app use patterns outside of an RCT setting.

Limitations

One limitation of this study is that the study participants will not be blinded with regard to their respective group allocation (intervention or control); nor will they be blinded to the suspected outcomes. This is for feasibility and transparency reasons; however, the potential for bias must be recognized. It is possible that knowledge of group allocation and outcomes is subjected to demand characteristics. While this is an important limitation of the research design, this approach aligns with the self-guided nature of the Shift app in real-world settings.

It is possible that the app will be mostly beneficial to a subset of participants with a low-to-medium level of mental health knowledge, due to the universal nature of the intervention and content. External validity concerns may be further exacerbated by potentially high rates of study attrition. This is because junior physicians typically have limited time to engage with nonessential tasks and, thus, may not return to complete all follow-up assessments or engage with the app on a regular basis or with enough frequency or duration to obtain the intended benefit. Furthermore, because participants will use the app intervention without further direction after the initial in-app onboarding, app use will not be standardized. It was found in the pilot testing phase of the Shift app that our target audience (junior physicians) disliked the highly structured design of the app and preferred to complete the modules that interested them personally [13]. Therefore, while this open app design is suited to physicians' preferences, we expect considerable variation in the app contents that participating junior physicians engage with and how frequently the app is used during the trial phase.

It must also be noted that although the trial does not screen candidates on the basis of their mental health symptom severity, it is possible that not all levels of symptom severity will be represented in the final sample. For example, it is possible that physicians who are already seeking support for mental health problems are more inclined to sign up for this research. Consequently, any inferences drawn will be limited to the mental health spectrum represented in the study sample and may not be generalizable to junior physicians based in Australia as a whole.

Finally, many challenges faced by junior physicians are related to poor workplace factors, such as long work hours and hierarchical work environments. Participants' individual organizational cultures, existing mentoring structures, and sets of occupational risk factors will constitute important institutional influences on physicians' mental health and wellbeing. Qualitative interviews with junior physicians revealed that the main factors impacting their mental health were (1) professional hierarchies, (2) occupational stress, (3) emotional labor, and (4) continuation of worry and rumination at home [32]. While the current intervention is targeted at addressing the influence of workplace stressors on mental health experiences and reducing worry and rumination, the app is largely focused on individual-level strategies and on how to seek mental health support through professional and private avenues. Systematic, organizational-level workplace change is likely required in conjunction with self-guided digital interventions to create a lasting improvement in mental health outcomes for junior physicians.

Conclusions

The Shift app is the first intervention of its kind created to support the mental health of junior physicians. If the app is found to be effective and suitable for junior physicians, it will pave the way to providing a widely accessible tool to increase help-seeking behaviors and serve as a preventative tool in the high-stress work environment in which junior physicians operate. However, the intervention must undergo rigorous trials, given that many digital interventions currently available for mental health are recommended without testing and may be ineffective [33].

In the current postpandemic era, the medical workforce has been placed under increasingly heightened levels of stress. An efficacious mHealth app tool would act as a first step toward increasing awareness about mental health and promoting avenues through which users can seek help, fostering a more open and informed environment for junior physicians.

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Acknowledgments

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LL and RL were responsible for the investigation and project administration. LL, AM, and RL were responsible for writing the original draft. SS, AM, MD, RF-T, and SH were responsible for conceptualization. SS was responsible for data curation and investigation. LL, SS, MD, KP, and IC were responsible for methodology. SS, MD, KP, IC, RF-T, and KD were responsible for writing (review and editing). AM was responsible for the formal analysis. KD and SH were responsible for the funding acquisition. SH was responsible for supervision.

Conflicts of Interest

Intellectual property for the Shift app is owned by the Black Dog Institute. However, the Shift app does not currently produce any income; the authors do not receive any financial gain from this intellectual property.

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Abbreviations

GAD-7: Generalized Anxiety Disorder-7 Scale
mHealth app: mobile health smartphone app

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NSW: New South Wales
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial

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Protocol

Chatbot-Led Support Combined With Counselor-Led Support on Smoking Cessation in China: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: China has a large population of smokers, with half of them dependent on tobacco and in need of cessation assistance, indicating the need for mobile health (mHealth) to provide cessation support.

Objective: The study aims to assess the feasibility and preliminary effectiveness of combining chatbot-led support with counselor-led support for smoking cessation among community smokers in China.

Methods: This is a 2-arm, parallel, assessor-blinded, pilot randomized controlled trial nested in a smoke-free campus campaign in Zhuhai, China. All participants will receive brief face-to-face cessation advice and group cessation support led by a chatbot embedded in WeChat. In addition, participants in the intervention group will receive personalized WeChat-based counseling from trained counselors. Follow-up will occur at 1, 3, and 6 months after treatment initiation. The primary smoking outcome is bioverified abstinence (exhaled carbon monoxide <4 parts per million or salivary cotinine <30 ng/mL) at 6 months. Secondary outcomes include self-reported 7-day point prevalence of abstinence, smoking reduction rate, and quit attempts. Feasibility outcomes include eligibility rate, consent rate, intervention engagement, and retention rate. An intention-to-treat approach and regression models will be used for primary analyses.

Results: Participant recruitment began in March 2023, and the intervention began in April 2023. The data collection was completed in June 2024. The results of the study will be published in peer-reviewed journals and presented at international conferences.

Conclusions: This study will provide novel insights into the feasibility and preliminary effectiveness of a chatbot-led intervention for smoking cessation in China. The findings of this study will inform the development and optimization of mHealth interventions for smoking cessation in China and other low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT05777005; https://clinicaltrials.gov/study/NCT05777005

International Registered Report Identifier (IRRID): DERR1-10.2196/58636

(JMIR Res Protoc 2024;13:e58636) doi:10.2196/58636

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KEYWORDS

chatbot; smoking cessation; mHealth; mobile phone; campus; China

Introduction

China has the world's largest population of tobacco users, with more than 300 million current smokers [1]. Approximately half of these smokers are dependent on tobacco and require cessation assistance [2]. Traditional smoking cessation programs, including pharmacotherapy and behavioral counseling [3], have shown efficacy but face challenges such as limited accessibility and high costs in China [4,5], highlighting the need for innovative and scalable interventions.

Mobile health (mHealth) interventions have proven effective in increasing smoking abstinence [6] by enhancing perceived behavioral and psychosocial support for quitting [7]. However, most current mHealth studies rely on fixed-schedule text messages [8-10], which may limit personalization and engagement [11]. Mobile instant messaging (IM) apps (eg, WeChat or WhatsApp) offer more tailored and interactive behavioral and psychosocial support between smokers and smoking cessation counselors. Our previous trials in China found that personalized cessation support via IM, combined with a brief intervention, significantly increased both smoking cessation service utilization and smoking cessation rates [12]. Our pilot trial indicated the feasibility and preliminary efficacy of integrating personalized counselor support via IM with pharmacotherapy [13]. Other trials in China have corroborated these findings, showing the efficacy of IM-based cessation support in increasing abstinence rates [14-16].

Nonetheless, high attrition rates remain a challenge in mHealth interventions. A meta-analysis found a 40%-50% dropout rate in mHealth interventions [17], and our studies observed suboptimal adherence to real-time counselor support, with only about 17% of participants engaging in real-time communication with counselors [12,18]. This limited engagement may be attributed to counselors being available only during working hours, thereby reducing the timeliness and convenience of the support.

Chatbots, automated conversational agents that leverage artificial intelligence and natural language processing to simulate human-like conversations [19], offer a novel opportunity for delivering personalized and interactive cessation support at scale. Unlike human counselor support, chatbots are available 24/7, providing personalized and instant feedback and facilitating psychosocial support [20]. Prior research on chatbot interventions for smoking cessation has shown promise, particularly in enhancing user engagement and adherence to cessation programs [21]. However, our previous trial, which integrated chatbot support with pharmacotherapy and real-time counselor support, did not significantly improve abstinence rates compared with general health messages [22]. The evidence of the effectiveness of chatbots for smoking cessation is not conclusive, with generally small effect sizes [20]. More research is needed on chatbot interventions to determine their efficacy in smoking cessation, particularly in combination with other support modalities in real-world settings.

This study aims to evaluate the integration of chatbot-led support with counselor-led support in promoting smoking cessation among Chinese smokers. The specific objectives of the study are to (1) assess the feasibility of a chatbot-led support intervention for smokers in China, and (2) compare the preliminary efficacy of chatbot-led support combined with counselor-led support versus chatbot-led support alone.

Methods

Study Design

This is a 2-arm, assessor-blinded, pilot randomized controlled trial nested in a smoke-free campus campaign in Zhuhai, China. The campaign is jointly organized by the Youth League and the Staff Union of the Beijing Normal University, Zhuhai, and aims to promote smoking cessation and health education among students and staff [23]. The campaign includes a series of activities, including a "Health for the Future" Smoke-free Promotion Competition that allows students to design publicity materials, a "Smoke-free Ambassador" Competition in which smoke-free volunteers can receive training and recognition, and a "Smoke-free Campus" Smoking Cessation Contest that motivates smokers to quit. The design adheres to the CONSORT (Consolidated Standards of Reporting Trials) statement recommendations (Figure 1) [24].

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

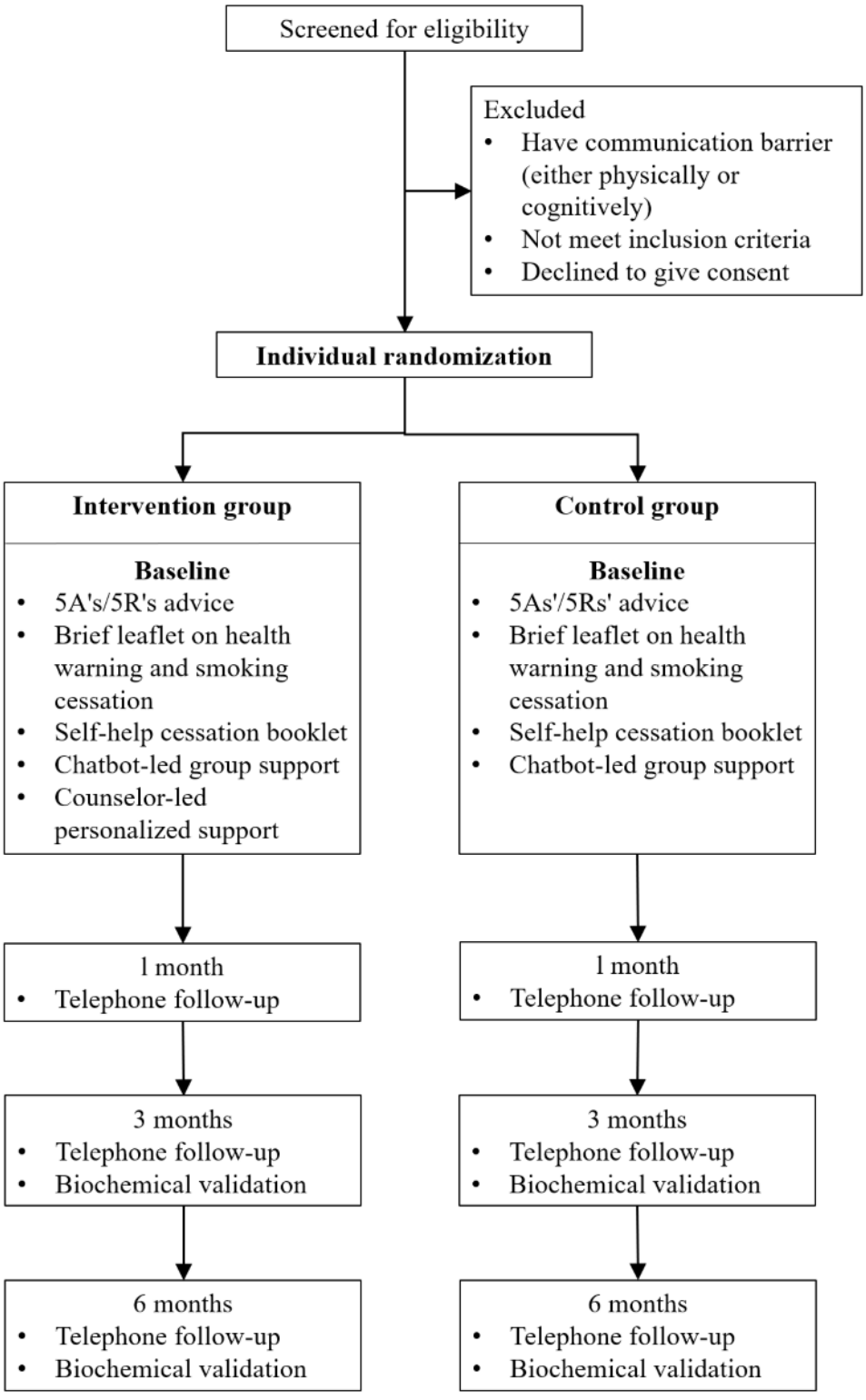

Lay Counselor Recruitment and Eligibility

Similar to our previous trials [25-27], university students will be recruited and trained as lay counselors to provide brief cessation advice to community smokers. Recruitment will be advertised through the website and WeChat official account of the university's volunteer organizations. Eligibility criteria for the lay counselors are as follows: (1) current university students aged 18 years and older; (2) the time and commitment to attend the training sessions and pass the posttraining assessments; and (3) the ability to provide informed consent.

Participant Recruitment and Eligibility

Web-based promotional strategies will be used to recruit participants through the social media websites of student associations, posters and flyers, and referrals. On-site recruitment activities will be conducted in high-traffic areas on campuses, such as the campus canteen and dormitories. Trained

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counselors will proactively approach smokers using the "foot-in-the-door" approach [28]. This approach has been extensively used in our previous community trials [25-27] and involves engaging smokers, explaining the study, and inviting them to join the study. The counselors will provide detailed information about the study and the benefits of quitting and the incentives offered. Participants will receive a cash incentive of RMB 100 (approximately US $14) for passing the biochemical validation at 3 and 6 months.

Participant eligibility criteria are intended to be inclusive to maximize generalizability and reach. Eligibility criteria include age of 18 years and older; daily smokers, defined as those smoking ≥1 cigarette per day in the past 3 months; exhaling carbon monoxide ≥4 ppm, indicating active smoking; having a smartphone with WeChat installed; and being motivated to quit smoking or reduce smoking, as assessed using the Transtheoretical Model. Smokers with physical or cognitive communication difficulties or those in other smoking cessation programs will be excluded. All eligible smokers willing to participate will sign a written informed consent form.

Smokers will be informed that the intervention involves a baseline assessment of their exhaled carbon monoxide level, brief questions on past smoking behaviors (baseline questionnaire), and further telephone interviews (follow‐up questionnaires at 1, 2, 3, and 6 months).

Randomization and Blinding

Participants will be individually randomized in a 1:1 ratio to the intervention or control group. The allocation of participants to the intervention and control groups will be conducted using a computer-generated randomization list. To ensure balance, a randomized blocking schema with block sizes of 2, 4, or 6 will be implemented. Blinding is not possible for the interventionists and participants due to the nature of the intervention. Outcome assessors and statistical analysts will remain masked until the predefined analyses are completed.

Sample Size

There is no fixed rule for calculating sample size for a pilot study [29]. Prior research on the estimation of sample sizes for pilot studies indicates that a sample of 50 participants per group should be sufficient to achieve 80% power to detect differences between groups [30] on the assumption of a 5% significance level and a 10% attrition rate. Therefore, a total of 150 participants will be recruited for this study.

Interventionist Training and Supervision

All lay counselors will be required to attend a workshop before participant recruitment. The training covers three key domains: (1) an overview of the intervention content including the 5A/5R advice, chat-led support and counselor-led support, with a demonstration of recruitment strategies such as the foot-in-the-door approach, and the use of exhaled carbon monoxide tests; (2) detailed knowledge of the harms of smoking and the benefits of quitting; and (3) smoking cessation methods and counseling techniques. A pre- and posttest survey will evaluate changes in counselors' knowledge, attitudes, and practices related to smoking cessation, with only those passing the posttraining assessment qualifying for participant recruitment.

Experienced research staff will provide supervision and assistance at each recruitment session. Counselor performance will be monitored through regular supervision sessions, participant feedback, and periodic reviews of brief counseling by experienced supervisors. Eligible smokers who decline to participate will be asked to provide their reasons for refusal. Information on the number of approached smokers will be gathered, and smokers' reasons for declining will be recorded verbatim by the smoking cessation counselors. Weekly group supervision will be conducted to review all active cases.

Interventions

Brief Cessation Advice

All participants will receive 5A/5R cessation advice delivered by well-trained cessation counselors on site. The 5A/5R model consists of 5 steps: ask, advise, assess, assist, and arrange for those who are willing to quit in 30 days and relevance, risks, rewards, roadblocks, and repetition for those who are unwilling to quit in 30 days. The participants will also receive a leaflet and a booklet that contain information and tips to help them quit smoking. The leaflet highlights the absolute risk of death due to smoking, diseases caused by active and passive smoking, explicit pictorial health warnings, the benefits of quitting, and motivational messages. The booklet was designed by the Chinese Center for Disease Control and Prevention and includes topics such as benefits and methods of quitting, relapse prevention strategies, and common myths and facts about smoking.

Chatbot-Led Group Support

All participants will join a WeChat group led by a chatbot called the "BNU Cessation Assistant." The chatbot will greet each participant by name and introduce its functions when the participants join the group. The chatbot will engage the participants in interactive conversations by presenting them with a choice of fixed conversations that will cover topics such as the harms of smoking, benefits and methods of quitting, withdrawal symptoms, cessation medications, and quitting self-efficacy. The chatbot will also provide open-ended conversations using natural language processing techniques and will be accessible at any time. The chatbot will deliver announcements and reminders and prompt the participants to share their stories, difficulties, and achievements with other group members. The participants can also communicate with each other for mutual support and encouragement.

The participants can participate in a smoke-free punch-in activity in the group every day to show their commitment and determination to quit smoking. The punch-in activity asks participants to report their smoking status on that day. If a participant reports being smoke-free, he or she will receive encouragement from the chatbot along with the participant's number of smoke-free days and ranking among other group members. The aim of the punch-in activity is to motivate the participants to quit smoking by increasing their self-efficacy and providing social support.

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Counselor-Led Personalized Support

Participants in the intervention group will receive 3-month, counselor-led, personalized support through the WeChat platform. This support consists of 2 main components: individualized counseling and prescheduled messages. First, individualized counseling will be provided through one-on-one sessions with trained counselors proficient in behavior change techniques [31]. The counseling is designed to be both proactive and responsive, with counselors initiating regular check-ins and providing tailored advice via text messages. Participants can also initiate contact with counselors as needed. The counselors will respond promptly to any cessation-related queries within working hours (weekdays from 9 AM to 6 PM). Second, participants will receive 24 prescheduled messages over the 3-month period that match their readiness to quit. These messages are delivered on a tapering schedule: 3 messages per week in the first month, 2 messages per week in the second month, and 1 message per week in the third month. The content of these messages includes education on the harms of smoking, the benefits and methods of quitting, techniques for managing cravings, and information on available cessation services. The messages are designed to initiate conversation, and participants are invited to respond.

Procedures

The participants will be assessed at baseline and 1, 3, and 6 months after treatment initiation (Figure 2). The baseline questionnaire will measure the participants' smoking behavior (eg, daily cigarette consumption, age when starting smoking, time of first cigarette upon waking up in the morning, and quit attempts), readiness to quit, reasons for quitting, social support, perceived self-efficacy of quitting (importance, difficulties and confidence), depression and anxiety, alcohol consumption, and sociodemographic characteristics. The participants will be informed that they may withdraw from the study at any time without giving a reason. The participants will be followed up at 1, 3, and 6 months by trained smoking cessation counselors with a maximum of 7 telephone calls at different times. All data will be stored in a secure, password-protected database. Only authorized research staff will have access to the data. All personal identifiers will be removed from the data set before analysis to ensure confidentiality. Participants who self-report abstinence for more than 7 days at 3 and 6 months will be invited for biochemical validation. Exhaled carbon monoxide samples will be collected by research staff with a piCO Smokerlyzer (Bedfont Scientific Ltd), and saliva cotinine samples will be measured using a test strip (Shanghai Yuduo Biotechnology Co, Ltd). To increase participation, participants will receive a cash incentive of RMB 100 (≈US $14) for passing the biochemical validation at 3 and 6 months.

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Figure 2. Schedule of enrollment, baseline, and follow-up assessments.

TIMEPOINT	Study period				
	Enrolment	Baseline	1-month follow-up	3-month follow-up	6-month follow-up
Enrolment					
Eligibility screen	✓				
Informed consent	✓				
Randomization and allocation	✓				
Interventions					
Chatbot-led group support		✓	✓	✓	
Counselor-led personalized support		✓	✓	✓	
Assessments					
Sociodemographic characteristics*		✓			
Smoking history		✓			
FTND**		✓			
Prior quit attempts		✓			
Readiness to quit		✓			
Reasons for quitting		✓			
Smoking status		✓	✓	✓	✓
Social support		✓	✓	✓	✓
Smoking behavior		✓	✓	✓	✓
Quit attempts		✓	✓	✓	✓
Self-efficacy of quitting		✓		✓	✓
Withdrawal symptoms				✓	✓
Depression and anxiety		✓		✓	✓
Alcohol consumption		✓		✓	✓
Exhaled carbon monoxide test		✓		✓	✓
Biochemically validated abstinence***				✓	✓
Qualitative evaluation					✓

* Sociodemographic characteristics include age, sex, education level, occupation, marital status, residence with minors, education and household income.

** FTND, Fagerström test for nicotine dependence.

*** Only for participants with self-reported smoking abstinence for more than 7 days.

Outcomes

Smoking Outcomes

The primary smoking cessation outcome is biochemically validated 7-day point prevalence abstinence at 6 months, defined as not smoking (even a puff) in the previous 7 days, confirmed using exhaled carbon monoxide concentrations of <4 ppm or salivary cotinine concentrations of <30 ng/mL. Secondary outcomes include biochemically validated abstinence at 3 months, 7-day point prevalence abstinence, and smoking reduction, defined as at least a 50% reduction in baseline cigarette consumption.

Feasibility Outcomes

Feasibility will include the following measures: eligibility rate (the percentage of eligible smokers out of the total number of smokers screened), consent rate (the percentage of eligible smokers who agree to participate out of the total number of

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eligible smokers), intervention engagement (the percentage of participants who actively engage with the WeChat-based chatbot group, join the smoke-free punch-in activity, read text messages, and chat with counselors), and retention rate (the percentage of participants who remain in the study out of the total number of participants randomized). In addition, participants who engage with the intervention will be asked to rate its effectiveness in increasing their motivation to quit smoking on a scale from 0 (not effective at all) to 10 (very effective).

Statistical Analyses

Descriptive statistics will be used to summarize the baseline characteristics and outcomes of the participants. Differences between the intervention and control groups will be assessed using chi-square tests for categorical variables and independent *t* tests for continuous variables. The intervention effect on primary and secondary cessation-related outcomes will be analyzed using regression models with and with no adjustment for imbalanced baseline characteristics. Sensitivity to missing data will be examined using multiple imputation by chained equations assuming that the data will be missing at random [32]. The intervention effect by subgroups will be assessed, including age group, sex, education level, household income, previous quit attempts, cigarette dependence, and intention to quit.

Qualitative interview data related to the process and outcomes of the intervention will be analyzed using the thematic framework [33]. The framework will be based on topics specified in the interview guide and emerging themes identified through a process of familiarization with the transcripts. All interviews will be audio-recorded and transcribed verbatim. Up to 10 smoking cessation counselors and 20 participants will be included, depending on data saturation.

Ethical Considerations

This study was approved by the institutional review board of the University of Beijing Normal University (SSDPP-HSC-20230012). All participants gave their informed consent before taking part in the study. To ensure privacy, all data were anonymized, with unique identifiers removed during processing and only aggregate data used in analysis. Safeguards, including encrypted storage and restricted access, were in place to protect confidentiality. Participants received a cash incentive of RMB 100 (≈US $14) after passing biochemical validation at 3 and 6 months as appreciation for their time and contributions to the research.

Results

Data collection for the study started in March 2023 and will be completed in June 2024. Findings are expected to be published in high-impact peer-reviewed journals and presented at local, national, and international conferences after November 2024.

Discussion

This pilot randomized controlled trial aims to examine the feasibility and preliminary effectiveness of a combined chatbot-led smoking cessation intervention in community settings in China. We hypothesize that integrating chatbot support with personalized counselor-led support will improve smoking cessation outcomes. If proven effective, this intervention could offer a scalable, cost-effective, and accessible approach to smoking cessation, addressing the high prevalence of smoking in China. The anticipated findings will contribute to the growing body of evidence on the use of Artificial intelligence–powered chatbots for health promotions and inform the development of a full-scale trial and provide insights for developing more engaging and effective mHealth interventions. The results will also offer valuable strategies for optimizing the use of chatbot interventions, in combination with other support modalities, to enhance smoking cessation outcomes.

This trial is important and innovative for several reasons. First, this trial is being conducted in China, a country with a large number of smokers [1] and regional disparities in access to smoking cessation services [4,14]. Furthermore, most available smoking cessation services are hospital-based [5], which may pose barriers of accessibility and convenience for community smokers. We aim to develop a low-cost, sustainable, and scalable mHealth intervention that can extend cessation services so that community smokers can access them more easily and conveniently. Second, the intervention design built on our previous mHealth trials in China [12,18,27], which showed the effectiveness of real-time counselor support on smoking cessation. By integrating chatbot support, which can provide instant, personalized, and interactive feedback to smokers, we aim to increase mHealth intervention engagement. Third, the study uses a proactive recruitment method by applying the "foot-in-the-door" approach [28], which can recruit a more representative sample of community smokers.

This study has several limitations that should be acknowledged. First, the sample size in this study can assess only the preliminary effectiveness of the intervention. Thus, all results should be treated as preliminary, and conclusive results await a fully powered trial. Second, the absence of a control group without a chatbot-led intervention limits the comparison of the intervention outcomes, potentially confounding the interpretation of the intervention's true efficacy. Third, this study will assess only the short-term and midterm effectiveness of the intervention (ie, 3 months and 6 months after treatment initiation), which precludes the evaluation of long-term smoking abstinence (eg, 12 months) and relapse rates. Finally, the study is conducted in a campus setting, where participants are primarily students who are well educated and may be more responsive to mHealth interventions, limiting the generalizability of the findings to other populations.

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Data Availability

Data of this study will be available from the corresponding author upon reasonable request after the main results of the study have been published.

Authors' Contributions

XW conceived and designed the study. CS and JX coordinated the recruitment and data collection. XW wrote the first draft of the manuscript. XW and NG performed the statistical analysis and interpretation. HY, KL, and MPW reviewed and revised the manuscript. All authors provided final approval for publication submission.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
IM: Instant messaging
mHealth: Mobile health

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Protocol

Ayurvedic Management of Presbycusis (Project TOPMAC): Protocol for an Exploratory Randomized Controlled Trial

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Abstract

Background: Presbycusis is characterized by sensorineural hearing loss in both ears at high frequencies, which affects more than half of the older adults by the age of 75 years and is often accompanied by tinnitus and cognitive deterioration. Unfortunately, there are no treatments available to restore hearing loss. Treatment mainly focuses on improving the quality of life and communication with hearing aids. Traditional medicine like Ayurveda also explains ailments of a similar nature as Badhirya and advises using drugs with antiaging and neuroprotective activity for treatment. In Ayurveda, Badhirya and Karnanada (senile deafness with tinnitus) are due to vitiation of Vata Dosha. Treatments such as topical oil pooling (Karnapurana) are usually advised to counter Vata, improve hearing capacity, and reduce tinnitus. Kshirabala Taila, a medicated oil formulation prepared with *Sida cordifolia* Linnaeus, is one of the most preferred oils for topical oil pooling in such conditions, as it has a definitive indication for sensory dysfunctions. Drugs like *Withania somnifera* (L.) Dunal (Ashwagandha) are also used, as they ameliorate neurodegeneration and help to improve cognitive dysfunction.

Objective: We propose an exploratory randomized controlled trial study for evaluating the efficacy of TOPMAC (Topical Oil Pooling with Kshirabala Taila and Supplementation of Ashwagandha Churna) in tinnitus suppression and hearing and cognitive function protection in patients aged 60-75 years with mild to moderate presbycusis.

Methods: A parallel, 2-group, exploratory randomized controlled trial will be conducted in an Indian Ayurvedic research center at its outpatient service. Participants (N=60) with mild to moderate presbycusis will be recruited by screening. Participants will be randomized (computer-generated 1:1) to receive either basic treatment and health education (BTHE) or BTHE+TOPMAC for 24 weeks. The primary objective is to compare the efficacy of TOPMAC with that of BTHE in the protection of hearing function. The secondary objective is to compare the efficacy of TOPMAC with that of BTHE in tinnitus suppression and cognitive function protection.

Results: This project was funded in January 2023. The institutional ethics committees at National Ayurveda Research Institute for Panchakarma (3/1/2020/NARIP/Tech/2036) and Institute for Communicative and Cognitive Neuro Sciences (IEC006) approved this study. The first patient was enrolled in September 2023; 22 participants were enrolled as of August 2024. The data analysis is yet to start, and the results are expected to be published by January 2025.

Conclusions: If this exploratory trial is proven effective, it will steer the setting of a definitive randomized controlled trial to test whether the TOPMAC intervention can be incorporated as a cost-effective integrative approach for managing presbycusis. The Indian government has already launched a National Program for Prevention and Control of Deafness to benefit the deaf population. TOPMAC may later be considered for integration with the national program.

Trial Registration: Clinical Trials Registry India CTRI/2023/04/051485; https://tinyurl.com/2h2hry3n

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KEYWORDS

presbycusis; Karnapurana; Kshirabala Taila; Rasayana; Withania somnifera (L.) Dunal; age-related hearing loss; hearing loss; sensorineural; auditory information; older adults; older adult; geriatrics; tinnitus; population-based; cognitive deterioration; topical oil pooling; efficacy; TOPMAC; intervention; hearing status; effectiveness; Ayurveda

Introduction

Presbycusis (age-related hearing loss) is characterized by sensorineural hearing loss at high frequencies in both ears, delayed central processing of auditory information, and problems understanding speech in loud environments [1]. It is usually associated with an audiogram that reveals the greatest hearing loss at higher frequencies. It affects over half of the older adults by the age of 75 years and nearly all older than 90 years [2]. Hearing loss is often accompanied by tinnitus. Many extensive population-based longitudinal studies have recommended that presbycusis is independently connected with cognitive deterioration.

The issues and effects of presbycusis are exacerbated in older adults due to additional degenerative processes in the central nervous system, which can lead to loss of neuroplasticity, cognitive ability, and other sensory modes, particularly vision [3]. Age-related hearing loss has an impact on both psychological well-being and physical ability. Some recent studies have established independent associations of hearing loss with driving ability, walking difficulty, social isolation, functional decline, and falls [4]. Social isolation causes emotions of incarceration and anxiety, which reduce higher cognitive performance, potentially increasing the economic and societal burden of age-related hearing loss [5]. The risk factors include age, male sex, diabetes mellitus, hypertension, and hereditary hearing loss [6]. Diabetes or hypertension, if not appropriately controlled, may also cause hearing problems through chronic arteriosclerosis. These are common chronic diseases in the aged population, leading to reduced blood flow in the inner ear [6]. Presbycusis is a serious but primarily neglected condition in India. The Indian government has started the National Program for Prevention and Control of Deafness to benefit the deaf population. The aims of this program include medically rehabilitating deaf persons of all age groups and fortifying the existing intersectoral linkages to maintain the rehabilitation program [7].

Unfortunately, there are no treatments available to restore lost hearing. Research on restoring hearing is a growing scientific field [8]. Treatment in most persons includes suitable hearing aids, but it is a limited solution, with some drawbacks. Studies have shown that people who would benefit from hearing aids are hesitant to use them due to cost, fit and comfort, maintenance, attitude, device factors, fiscal factors, psychosocial/situational factors, ear problems, and appearance. More precisely, these causes include the hearing aid's ineffectiveness in loud environments, low benefit or low sound quality, and incompatibility with the type of hearing loss. Factors affecting hearing aid fit and comfort include the need for assistance in inserting and removing the hearing aid, feeling uncomfortable, or experiencing adverse effects (eg, rashes, itching) [9]. The treatment of tinnitus is also challenging [10]. Tinnitus should be managed using neurophysiological methods such as tinnitus retraining therapy—a combination of cognitive directive counseling and sound therapy, hearing aids, and white-noise generators. However, this retraining therapy also fails in 30%-40% of the patients [11]. A recent systematic review recommended that incorporating conventional or complementary and alternative therapies for treating mild cognitive impairment will be beneficial [12]. All functions of the nervous system in the human body are represented through Vata in Ayurveda. A subtype of Vata, Prana Vata, is situated in the head and controls intellectual functions, cardiovascular functions, sense organs, psychological activities, respiration, and reflex activities such as sneezing, belching, and deglutition [13]. Since presbycusis is a sensory dysfunction with cognitive decline, it is evident that the Prana Vata is impaired here. Ayurveda mentions similar ailments as Badhirya and Karnanada (senile deafness with tinnitus) [14]. The diseases Badhirya and Karnanada occur in the ears primarily by Vata Dosha vitiation. Topical oil pooling (Karnapurana) is a commonly employed treatment in such conditions, as it does the Vatashamana, improves hearing capacity, and reduces tinnitus. No mechanistic studies show the exact mechanism of action of Karnapurana. However, although histologically, the tympanic membrane is impermeable, a recent study [15] has discovered the possibility of a biological mechanism of active transport through the tympanic membrane to the middle ear. This way, the topically pooled medicine might be absorbed to impart its action in the inner ear. Ayurveda recommends a class of drugs termed as Rasayana, which possess antiaging properties that can be beneficial in these conditions. They can exhibit neuroprotective effects in the inner ear and brain tissue. Kshirabala Taila, a medicated oil prepared with *Sida cordifolia* Linnaeus, is preferred as the drug of choice, as it has definitive indications for sensory dysfunctions [16]. An animal study has also demonstrated that the aqueous root extract of *S. cordifolia* Linn has a neuroprotective effect due to its antioxidative properties and validated the Rasayana claim of *S. cordifolia* Linn in neurodegenerative diseases [17]. *Withania somnifera* (L.) Dunal (Ashwagandha) is another medicine commonly used, as it can regenerate damaged nerve cells and thereby improve nerve function [18]. Recent reviews have shown Ashwagandha as a potent medicine for cognitive function protection [19]. A randomized controlled trial has shown that Ashwagandha effectively enhanced immediate and general memory in individuals with mild cognitive impairment and improved attention, executive function, and information processing speed [20]. The administration of the water extract from Ashwagandha

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(100 mg/kg/d) with drinking water for 8 months has shown to be safe and showed no toxicity in rats [21]. Ashwagandha may operate as a gamma-aminobutyric acid mimetic, cholinomimetic, and agonist for α-7 nicotinic receptors for cognitive function protection [22]. However, no clinical trials or documented data are available on the efficacy of these drugs for presbycusis treatment, despite being widely used in clinics. The only available data is a case report recommending an Ayurveda treatment protocol to effectively improve hearing mechanisms in presbycusis with no side effects [23].

Hence, we propose an exploratory randomized controlled trial for evaluating the efficacy of TOPMAC (Topical Oil Pooling with Kshirabala Taila and Supplementation of Ashwagandha Churna) in tinnitus suppression and hearing and cognitive function protection in individuals aged 60-75 years with mild to moderate presbycusis and comparing this intervention with basic treatment and health education (BTHE) for presbycusis. BTHE includes treatment for diabetes mellitus, hypertension, and dyslipidemia and counsel related to lifestyle modification and avoiding alcohol and cigarette use. The primary objective is to compare the efficacy of TOPMAC with that of BTHE in the protection of hearing function. The secondary objective is to compare the efficacy of TOPMAC with that of BTHE in tinnitus suppression and cognitive function protection.

Methods

Trial Design

This is a multicenter, parallel, 2-group, exploratory, randomized (1:1) controlled trial. The plan of enrollment, interventions, and assessments is given in Table 1.

Table 1. Schedule of enrollment, interventions, and assessments for the TOPMAC (Topical Oil Pooling with Kshirabala Taila and Supplementation of Ashwagandha Churna) study.

	Screening	Baseline	Intervention period					End of treatment
Timepoint		Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169
Potential participant identification and screening	✓							
Provision of participant information sheet	✓							
Eligibility assessment	✓							
Informed consent	✓							
Interventions								
Ashwagandha Churna days 1-168		✓	✓	✓	✓	✓	✓	
Karnapurana: weeks 1,5,9,13,17,21		✓	✓	✓	✓	✓	✓	
Basic treatment and health education		✓	✓	✓	✓	✓	✓	
Assessments								
Demographics		✓						
Tympanometry	✓							
Pure tone average	✓				✓			✓
Speech recognition threshold	✓				✓			✓
Speech discrimination score	✓				✓			✓
Laboratory investigations	✓				✓			✓
Brainstem Evoked Response Audiometry		✓			✓			✓
Tinnitus Functional Index		✓			✓			✓
Montreal Cognitive Assessment		✓			✓			✓
Drug compliance (%)			✓	✓	✓	✓	✓	✓
Concomitant medication			✓	✓	✓	✓	✓	✓
Rescue medication			✓	✓	✓	✓	✓	✓
Adverse reactions			✓	✓	✓	✓	✓	✓

Setting

Likely eligible participants would be identified at the outpatient department of the National Ayurveda Research Institute for Panchakarma (NARIP). They will be sent for screening at the Institute for Communicative and Cognitive Neuro Sciences (ICCONS). NARIP is an Ayurvedic research hospital, and ICCONS is a medical hospital in rural Kerala, India.

Eligibility Criteria

The intended population is adults aged 60-75 years diagnosed with mild to moderate presbycusis. Pure tone audiometry (PTA)

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will be performed for octave frequencies between 0.25 and 8 kHz, and the pure tone average will be calculated for 500 Hz, 1 kHz, and 2 kHz. The patients with a pure tone average of 26-55 dB hearing loss will be included. The other eligibility criteria are shown in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Patients aged 60-75 years diagnosed with mild to moderate presbycusis

Exclusion criteria

- Conductive hearing loss and abnormal middle ear
- Current hearing aid user (>3 months)
- Patients with features of dementia
- Uncontrolled hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg)
- Uncontrolled diabetes (hemoglobin A_{1c}>8%).
- Patients with very high dyslipidemia (total cholesterol >240 mg/dL, low-density lipoprotein >190 mg/dL, high-density lipoprotein >60 mg/dL, triglycerides >500 mg/dL) National Cholesterol Education Program Adult Treatment Panel III classification
- Patients with aspartate amino transferase and alanine amino transferase >2 times the upper normal limit
- Patients with serum creatinine >the upper limits of the normal
- History of malignancy within 5 years
- History of cerebrovascular accident within 1 year
- History of use of ototoxic, psychiatric, and nervous system drugs
- History of hypersensitivity to the trial drug or any of its ingredients
- Continuing addiction to smoking and usage of tobacco in any form
- Individuals simultaneously or previously (within 30 days before the investigation starts) participating in a clinical investigation using experimental drugs or devices

Participant Identification

Screening

Individuals attending the outpatient department of NARIP identified as likely eligible to participate in the study will be given a participant information sheet. A trial team member will check initial eligibility if interested in participating. If the person is likely eligible, the researcher will send them to ICCONS for further screening.

Eligibility Confirmation

Eligibility confirmation will be done at ICCONS by an experienced audiologist and neurologist. This assessment will include tympanometry, PTA, and Montreal Cognitive Assessment (MoCA). Only patients with a pure tone average of 26-55 dB hearing loss will be included.

Consent

Written informed consent would be obtained before starting trial-related procedures or data collection. A suitably qualified and experienced person delegated by the principal investigator will get the consent. We have pilot tested the readability and comprehension level of the consent materials. For participants with literacy challenges and visual impairment, the bystander of the participant will help in the informed consent process.

Randomization, Blinding, and Allocation Concealment

After giving consent, participants would be randomly chosen to receive either BTHE for 24 weeks or BTHE+TOPMAC in a 1:1 ratio using the serially numbered opaque sealed envelope provided by the Central Council for Research in Ayurvedic Sciences (CCRAS) headquarters. It is impossible to blind the participants or the investigators due to the trial design. The principal investigator enrolled the participants and assigned the intervention. However, the investigator conducting the audiometric evaluation is blinded. The statistician analyzing the collected data will also not be blinded to allocation.

Interventions

Comparator

In BTHE, participants will receive treatment for diabetes mellitus, hypertension, and dyslipidemia and counsel related to lifestyle modification and avoiding alcohol and cigarette use. Advice on optimizing individual acoustic environments is provided, including reducing background noise and engaging in face-to-face conversations to maximize exposure to nonverbal communication cues. Lip reading classes will also be offered. This ancillary care is provided within the scope of this trial.

TOPMAC Intervention

The topical oil pooling will be done on weeks 1, 5, 9, 13, 17, and 21. The preparatory procedure includes temporal region massage with processed gingelly oil (Murchita Tila Taila)

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followed by sudation therapy. The main therapeutic procedure is to instill 5 mL of Kshirabala Taila in each auditory canal for 15-20 minutes in the morning. The therapy procedure includes massaging the ear base, and after 15-20 minutes, the oil will be wiped with dry cotton. Ashwagandha Churna will be supplemented with a dose of 6 grams at bedtime with 10 mL of cow's ghee for 24 weeks. Participants in both groups are covered under clinical trial insurance.

Study Training

A trained Panchakarma therapist will perform the topical oil pooling per the institute's standard operating procedure (SOP). Trained technicians from ICCONS would perform all the audiometry evaluations. The investigator's brochure and SOPs developed for the project are communicated to all the investigators. Further intermittent meetings of the investigators are planned. The reorientation/interaction with the study staff is repeated periodically during the investigators' meeting.

Concurrent Health Care for All Participants

All participants would be instructed to access routine health care, including medicines and consultations, with other health professionals. The details of the cointerventions would be noted at the assessments on day 29, day 57, day 85, day 113, and day 141.

Primary Outcomes

The primary outcomes include differences in the average 500 Hz, 1 kHz, and 2 kHz in PTA from baseline and after the 24th week of intervention. PTA is the gold standard for measuring sensitivity and identifying the presence and degree of hearing loss. PTA (isolated frequency) over a range of frequencies critical for everyday listening can determine the degree, configuration, and type of hearing loss in a manner detailed enough to assist the health care team in determining the etiology and prognosis for the hearing loss as well as the optimal treatment strategy [24]. Pure-tone evaluation is typically performed in a sound-treated booth to reduce the impact of external sounds, with the booth environment and electroacoustic equipment calibrated to American National Standards Institute standards to optimize intertest and intratest reliability. Primary outcomes also include Brainstem Evoked Response Audiometry (BERA) changes and differences in speech recognition threshold and speech discrimination score.

Secondary Outcomes

The secondary outcomes consist of differences in the tinnitus functional index (TFI) from baseline and after the 24th week of intervention. The secondary outcome also includes the MoCA score difference. TFI is considered the gold standard for measuring tinnitus severity. It is a 25-item questionnaire that identifies the tinnitus severity of the patient by calculating the overall TFI score. The 8 subscales address 8 critical domains of negative tinnitus impact: I, intrusive (unpleasantness, intrusiveness, persistence); SC, sense of control (reduced sense of control); C, cognitive (cognitive interference); SL, sleep (sleep disturbance); A, auditory (auditory difficulties attributed to tinnitus); R, relaxation (interference with relaxation); Q, quality of life (quality of life reduced); and E, emotional (emotional distress). In this way, the TFI score and subscore will measure the improvement in subjective well-being and quality of life related to tinnitus.

Adverse Events

Any adverse event or adverse drug reaction, if seen during the trial period, will be documented suitably, and timely management would be performed, and the same would be reported to the ethics committee and the sponsor(s) at the earliest. Considering the participant's age and the character of the intervention, predictable adverse events include gastrointestinal side effects (nausea, vomiting, and diarrhea), dizziness, fatigue, ear pain, itching in the ears, and fullness in the ears. Safety reporting would begin from the point of randomization and finish when the participant has finished their 169th-day assessment.

Sample Size Determination

A previously published report on the administration of topical oil pooling in patients with presbycusis showed that the average hearing level for the frequency of 500 Hz, 1 kHz, and 2 kHz after treatment was 53 dB (for air conduction defect of the right and left ears) [11]. We based our sample size calculation on the assumption that the average hearing level at these 3 frequencies will be 50 dB in the TOPMAC+BTHE group, while it will be 60 dB in the BTHE group. A difference of 10 dB after treatment between both groups has been considered clinically meaningful. With a standard deviation of 12 dB, 80% power, and a confidence interval of 95%, the calculated sample size for each arm is 23. The sample size becomes 28.75, rounded to 30 per arm, adding an attrition rate of 25%. Therefore, 60 participants must be enrolled in the trial (30 in each arm). The attrition rate was based on the clinical experience in treatment compliance. Moreover, in a previous study [25] on Ayurveda interventions among older participants, such attrition had occurred. An interim analysis will be performed after 25% of the participants complete the study duration, and then the reassessment of the attrition rate will be considered along with the original sample size.

Data Collection

Baseline Assessment

Baseline assessments include demographic data and Ayurveda parameters. It also includes assessing BERA, TFI, and MoCA score (Table 1).

Treatment Logs

For BTHE and TOPMAC intervention sessions, the drug compliance reports will record the date, clinician details, day of intervention, mode of delivery, and drugs issued.

Follow-Up Assessment

All participants will attend on day 29, day 57, day 85, day 113, day 141, and day 169 for follow-up. Drug compliance (%), concomitant medication, and rescue medication will be assessed at all visits. In addition to that, PTA, BERA, laboratory investigations, TFI, and MoCA score will be repeated on day 85 and day 169 (Table 1).

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Early Discontinuation/Withdrawal of Participants

During the study, participants can withdraw at any time. Moreover, the investigator may discontinue a participant from the study if they judge it indispensable for any reason, that is, if the patient is not ready to continue or is noncompliant with the study procedure (at least 80% compliance is crucial to continue in the study); if the patient develops a life-threatening crisis or any other severe sickness due to other pathology, which requires emergency treatment or making it necessary to introduce new treatment during the study period; or if the patient experiences any adverse event or adverse reaction requiring hospitalization. The decision to withdraw a participant from the study will be made only by the investigator, who will provide a thorough justification and indicate further management if needed. The sponsor and the ethics committee will be informed within 2 working days.

Data Management

Data would be collected using paper case record forms (CRFs) and electronic CRFs and maintained by the principal investigator. Regularly monitoring data entry and data collection processes will be executed during the project. The electronic CRF for data entry will also be used to check data accuracy and validity. The modeling imputation technique will impute any outlier or missing data. The parameters having follow-ups will be imputed through the time series modeling, and those with single-point observations will be imputed with the population's average or median depending on the variable's distribution. The data will be collected and entered in the CRFs identified by the enrollment IDs only. The consent document and the screening and baseline information containing the participants' names or identities will be secured more cautiously. The electronic format will be locked by password, and access to this data set will be restricted to authorized persons only. The shared data file will be locked with a separate code that can be accessed after the code is disclosed on request. The statistician at the CCRAS headquarters will analyze the data. After completion of the study, the data will be stored for at least 5 years.

Statistical Methods

Data will be managed through SPSS software (version 29.0; IBM Corp). The data would be individually analyzed for central tendencies (mean, median), range, standard error, standard deviation, and 95% CIs for each intervention arm in each of the groups in the study. Data will be tabulated and graphically shown using a standard format, Microsoft Excel, and other software programs. For nonparametric values, the Wilcoxon signed-rank test and Mann-Whitney *U* test will be performed, and for parametric values, a paired 2-sided *t* test and Student *t* test will be done. Further, multivariable regression and Cox regression analyses will be used if any confounding factor or censored data are found during the analysis. Bayesian analysis may also be performed if any necessity arises after the initial phase of data analysis. This study will assess patients with mild to moderate presbycusis based on impairment. Clinically, it is established that participants with moderate impairment have a lesser chance of cure and persons with mild impairment have a higher chance of cure, which is the available information before the study starts. Therefore, we use this information as prior distribution to calculate the later treatment response of the participants. Further, Bayesian analysis gives another angle to explore the outcome and reduce the researcher's dependency on *P* values.

Regression analysis will control the diversity during analysis and stratify results by demographic factors such as sex, socioeconomic status, and comorbidities. The analysis will be done by stratifying these factors to estimate the effect of the intervention as accurately as possible. The regression analysis will consider these factors to determine the intervention's adjusted effect. In the case of dichotomous or multinomial type of data, a separate analysis will be performed for each stratum, or logistic regression analysis will be used.

Data Monitoring

This study will be monitored by the Data and Safety Monitoring Board of the TOPMAC project at NARIP, Cheruthuruthy. A particular quality control program would be initiated to secure an agreement with the present approved protocol, good clinical practice, related regulations, and SOPs of NARIP. The principal investigator will develop data management and monitoring plans and manage the trial's daily activities. The Data and Safety Monitoring Board team will perform quality assurance checks to ensure the integrity of randomization, study entry procedures, and data collection. The Data and Safety Monitoring Board team will conduct at least one e-Clinical Research Form inspection once a year. Additionally, the sponsor may monitor or audit the study per the approved protocol, good clinical practice, relevant regulations, and SOPs.

Ethics Approval and Dissemination

The institutional ethics committees at NARIP (3/1/2020/NARIP/Tech/2036 dated January 31, 2023) and ICCONS (IEC006 dated March 21, 2023) approved this study (protocol-1 dated February 3, 2023). This study was registered on April 11, 2023 (CTRI/2023/04/051485). This protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [26] (completed SPIRIT checklist: Multimedia Appendix 1). Results would be published in a peer-reviewed journal with authorship eligibility according to the criteria of the International Committee of Medical Journal Editors.

Results

This project was funded in January 2023. The institutional ethics committees at NARIP (3/1/2020/NARIP/Tech/2036 dated January 31, 2023) and ICCONS (IEC006 dated March 21, 2023) approved this study. The first patient was enrolled in September 2023; 22 participants were enrolled as of August 2024. The data analysis is yet to start, and the results are expected to be published by January 2025.

Discussion

This randomized exploratory trial is proposed to assess the efficacy of TOPMAC intervention in improving the hearing status of adults aged 60-75 years with mild to moderate presbycusis.

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Strength

The TOPMAC intervention was methodically developed, amalgamating existing best and anecdotal shreds of evidence, and is the first trial to evaluate the effectiveness of Ayurveda intervention in presbycusis as an add-on to BTHE. The quantitative outcome measures included in this trial will give valid data about the possibility of performing a definitive randomized controlled trial of the TOPMAC intervention.

Limitations

This study has limitations, as only effectiveness outcomes are included and not feasibility outcomes. This trial design has no follow-up period. The lasting effects of the treatment on presbycusis and associated symptoms may need to be assessed. Nevertheless, a case study has been reported, wherein the treatment effect of Ayurvedic medicines in presbycusis was sustained for a follow-up period of 6 months when no treatment was administered [23]. This study will apply only to Asian countries where Ayurveda is practiced. Nonetheless, the applicability of this protocol is limited in other continents. However, they could also replicate this model if there is accessibility of trained Panchakarma therapists to perform the Karnapurana procedure and if they have regulatory permissions to use Ashwagandha.

Another limitation is the absence of subjective Ayurvedic diagnostics in the research design, which might influence the broader integration of Ayurvedic treatments into conventional medical practice. However, Badhirya and Karnanada are described in Ayurveda and can be correlated with various symptoms of presbycusis. Although the standardized or validated assessment criteria for severity are not available in Ayurveda terminology, the outcome measures/tools for the assessment of presbycusis are conceptually applicable to inferring the results for Badhirya. Further, this protocol evaluates the patient's prakriti (psychosomatic constitution) by using the standardized Ayur Prakriti web portal developed by CCRAS [27]. Prakriti is considered an essential part of Ayurvedic diagnostics [28]. Although TFI is a robust tool for assessing tinnitus impact, the absence of a broader quality of life measure for other dimensions possibly affected by the treatment is yet another limitation of this protocol. These limitations will be considered in the future definitive randomized controlled trial.

Conclusion

If this exploratory trial is proven effective, it will steer the setting of a definitive randomized controlled trial, which will incorporate the limitations as described above, to test whether the TOPMAC intervention can be incorporated as a cost-effective integrative approach for managing presbycusis.

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Authors' Contributions

KKV, the principal investigator, conceived and designed the study and drafted the manuscript. SVT, MCN, PGN, NML, AS, PM, BY, BCSR, SD, and SN contributed to the study design, provided specific content, and edited the trial protocol and manuscript. AT provided statistical oversight. KKV acts as a guarantor. All authors have reviewed and approved the final manuscript.

Conflicts of Interest

KKV, PGN, AT, PM, BY, BCSR, SD, and SN work in the sponsor organization. However, the trial medicines are not proprietary drugs manufactured or marketed by the sponsor. These are Ayurveda medicines mentioned in the classical texts. There are no personal financial interests related to the subject matters discussed in the manuscript. The other authors declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 223 KB - resprot_v13i1e55089_app1.pdf]

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Abbreviations

BERA: Brainstem Evoked Response Audiometry
BTHE: basic treatment and health education
CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: case record form
ICCONS: Institute for Communicative and Cognitive Neuro Sciences
MoCA: Montreal Cognitive Assessment
NARIP: National Ayurveda Research Institute for Panchakarma
PTA: pure tone audiometry
SOP: standard operating procedure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TOPMAC: Topical Oil Pooling with Kshirabala Taila and Supplementation of Ashwagandha Churna

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Protocol

Implementation and Evaluation of a Home-Based Pre-Exposure Prophylaxis Monitoring Option: Protocol for a Randomized Controlled Trial

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Abstract

Background: HIV prevention is a public health priority. Despite progress in recent years, pre-exposure prophylaxis (PrEP) use remains suboptimal especially among groups disproportionately impacted by new HIV diagnoses such as gender and sexual minorities of color. Multiple barriers including a lack of PrEP providers and challenges with attending quarterly monitoring visits contribute to low PrEP uptake and retention. Home-based PrEP (HB-PrEP) services could reduce stigma, increase convenience, expand health system capacity for PrEP care, and improve PrEP retention.

Objective: Home Option Testing for PrEP (HOT4PrEP) is a hybrid randomized controlled trial (RCT) that aims to examine whether HB-PrEP care is acceptable to PrEP users, feasible to implement in a sexual health clinic setting, and impacts PrEP retention.

Methods: The RCT will recruit 458 persons currently taking or soon to initiate PrEP at a sexual health clinic in Seattle, Washington, and randomize them to continue the standard of care or have the option to use HB-PrEP for 2 of 3 triannual PrEP follow-up visits. Participants in the intervention arm will be sent home kits containing gonorrhea and chlamydia swabs and Tasso devices for blood self-collection. The primary outcome is PrEP retention between groups at 20 months; secondary outcomes include user satisfaction and acceptability, feasibility, self-reported PrEP adherence, and sexually transmitted infection (STI) incidence. Interviews with PrEP users and clinic staff will elucidate barriers and facilitators of implementation.

Results: The HOT4PrEP RCT began enrolling in March 2022, was on hold during the height of the US mpox epidemic, then resumed enrollment in December 2022. Of the first 100 enrollees, the median age is 34 years, and most are cisgender gay men (89/100, 89%) with at least some college education (91/100, 91%). Among the 49 participants randomized to the HB-PrEP option, 33 (67%) chose to self-collect samples at home at least once, of whom 27 (82%) successfully returned test kits for HIV and STI testing. Primary PrEP retention and qualitative analyses are ongoing.

Conclusions: Implementation of HB-PrEP into a high-volume sexual health clinic seems to be feasible and acceptable to early RCT enrollees. This strategy has the potential to address individual and systemic barriers associated with initiating and persisting on PrEP, such as increasing sexual health agency and expanding clinical capacity to serve greater numbers of PrEP users.

Trial Registration: ClinicalTrials.gov NCT05856942; https://clinicaltrials.gov/study/NCT05856942

International Registered Report Identifier (IRRID): DERR1-10.2196/56587

(JMIR Res Protoc 2024;13:e56587) doi:10.2196/56587

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KEYWORDS

pre-exposure prophylaxis, self-collection, telehealth, sexually transmitted infections; implementation; evaluation; HIV prevention; HIV; PrEP; home-based pre-exposure prophylaxis; HB-PrEP; stigma; home option testing; sexual health; impact; gender; sexual minorities; race; human immunodeficiency virus; United States; sexual minority men; SMM; barriers; barrier; clinical monitoring; monitoring

Introduction

Background

In 2021, the majority of new HIV infections in the United States occurred in sexual minority men [1]. The US federal government targeted resources toward the goal of reducing new HIV infections by 75% by the year 2025 through the "Ending the HIV Epidemic" initiative [2] and highlights the prevention of new infections as a key component of the plan. While pre-exposure prophylaxis (PrEP) has been proven to reduce new HIV diagnoses at the population level [3,4], it remains an underused intervention. Preliminary evidence suggests that only 36% of people in the United States with an indication for PrEP received a prescription in 2022, up only slightly from 30% in 2021 [5]. Though PrEP coverage among sexual minority men at greatest risk for HIV in Seattle-King County, Washington approached 65% in 2021 [6], PrEP use remains low among younger people and some sexual minority men of color [4,6]. As part of its Ending the HIV Epidemic initiative, Public Health-Seattle and King County (PHSKC) aims to achieve ≥70% PrEP coverage among sexual minority men and transgender persons, with equal use among all racial and ethnic groups.

Structural barriers such as lack of access to PrEP medical providers and the burden of quarterly clinical monitoring visits have stymied PrEP scale-up in the United States for years [7-9]. PrEP retention (defined as maintaining all aspects of PrEP care, including attending follow-up visits and obtaining monitoring tests every 3 months according to US guidelines [10]) represents a substantial gap in the PrEP care continuum [11,12]. Studies on national PrEP retention rates suggest only 56% of individuals who initiate PrEP remain on PrEP for at least 1 year, and only 41% persist through year 2 [13]. Younger age, Black race, and unstable or lower income are each associated with discontinuations and being lost to follow-up [14]. We have observed similar levels of PrEP retention in the PHSKC Sexual Health Clinic (SHC), with 40% of PrEP users discontinuing the intervention at least once within 12 months [15]. The COVID-19 pandemic created dramatic reductions in sexual health service capacity [16] that only further exacerbated and continues to impact existing structural barriers that lead to lower PrEP access and higher numbers of discontinuations [17-19]. Among sexual minority men newly diagnosed with HIV in King County, previous PrEP use and discontinuations are common and underscore the urgent need to develop and implement novel targeted strategies to minimize barriers and provide individuals with more options to stay on PrEP [20].

Home-based PrEP (HB-PrEP), whereby an individual self-collects PrEP monitoring specimens at home, mails them into a laboratory for testing, and follows up with a provider remotely to renew PrEP prescriptions, has the potential to decrease PrEP access barriers and increase PrEP continuation rates. Studies confirm that patients are comfortable self-collecting bacterial sexually transmitted infection (STI) screening specimens [21] and that HB-PrEP monitoring is acceptable and often preferable to in-person care [11,22,23]. Configuring PrEP programs to users' needs can optimize both uptake and delivery [24]. Particularly for young sexual minority men, programs that are convenient, discreet, and provide them with agency over PrEP use and monitoring may reduce the stigma associated with PrEP use, and increase PrEP uptake and retention [11,23]. Furthermore, HB-PrEP may decongest high-volume clinical sites and create additional capacity to grow PrEP programs.

Several direct-to-consumer companies [25] and fewer research or clinic-based PrEP programs provide PrEP services completely from home [22,23,26]. However, opportunities to adequately screen for newly acquired syphilis and HIV in the home setting are often limited. Given that STI incidence is high among people on PrEP, [27] the US Centers for Disease Control and Prevention guidelines recommend PrEP users be screened for STI quarterly, specifically for syphilis and HIV using assays with narrow windows from infection to test positivity [12]. Syphilis is highly associated with HIV acquisition in PrEP users; [28] thus, it is important that PrEP monitoring include tests that can distinguish new from old syphilis, such as with the quantitative rapid plasma reagin (RPR). Approximately 40% of PHSKC PrEP users have a history of syphilis, of which 25% are serofast (have a persistently positive RPR despite treatment in the past) and require a quantitative RPR for syphilis screening [29]. Although previous HB-PrEP studies used procedures that allowed PrEP users to collect all specimens (gonorrhea and chlamydia [GC and CT] swabs and blood samples) from home [22,26], nearly all require fingerstick specimens to perform a less accurate rapid HIV antibody test and collected insufficient blood volume to perform RPR titers, limiting the ability to determine whether titers were stable or indicative of newly acquired syphilis. We previously conducted a pilot study [29] that showed the acceptability and feasibility of using a novel blood self-collection device (formerly Tasso OnDemand, second-generation larger volume device Tasso+) [30] to obtain samples suitable for HIV antigen and antibody and quantitative RPR testing. However, whether these devices could be used successfully within a dedicated program for serial PrEP monitoring remains unknown.

Objectives

Through a hybrid [31] randomized controlled trial (RCT), we aim to simultaneously evaluate the effectiveness of HB-PrEP as a strategy for improving PrEP retention and its implementation into an urban SHC's existing PrEP program.

The specific aims of our study are to: (1) evaluate the impact of HB-PrEP on PrEP retention rates among groups assigned to either home-based monitoring or routine care and (2) assess the

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program's reach and define the factors that influence HB-PrEP implementation.

Methods

Study Overview

The HOT4PrEP (Home Option Testing for PrEP) project is a series of interrelated studies designed to implement and evaluate an HB-PrEP monitoring system that includes the option for biological specimen self-collection at home and remote clinical follow-up in Seattle-King County, Washington. A detailed description of Tasso device use and results of preimplementation acceptability and feasibility analyses are published elsewhere [29]. The current phase of the HOT4PrEP project is an explanatory sequential mixed methods study consisting of 2 components, that are (1) a hybrid RCT wherein we evaluate HB-PrEP as an implementation strategy and its effect on PrEP retention over time along with other secondary outcomes, and (2) semistructured interviews with study participants and clinic staff to explore individual and system-level barriers and facilitators to HB-PrEP implementation.

For the first study component, we will enroll 458 participants from the PHSKC SHC and randomly assign participants 1:1 to either continue the PrEP standard of care ([SOC], control group) or to have an HB-PrEP monitoring option (intervention). Participants in both arms will complete serial web-based surveys and receive PrEP follow-up through telehealth or at the clinic (Textbox 1). At the time of trial conception, monitoring intervals were initially set at every 3 months; however, these changed to every 4 months in March 2023 following the SHC PrEP program's shift to reduce the total number of required annual visits. HB-PrEP participants receive mailed sampling kits containing instructions and materials to collect extragenital (pharyngeal and rectal) GC and CT swabs and 2 devices to self-collect capillary blood from the upper arm into microtainer tubes. Participants mail kits through United Parcel Service to the PHSKC laboratory for creatinine, quantitative syphilis serologies, and fourth-generation HIV antigen/antibody testing. Secondary outcomes include reach (number of kits requested and used per participant), user satisfaction with the assigned PrEP monitoring program, STI incidence, and time from resulting of abnormal laboratory values to participant notification. Participation in this first RCT component is not incentivized.

For the second component of the study, we will use quantitative data from surveys to inform semistructured interview guides. In-depth interviews will take place with study participants, staff, and administrative personnel to determine factors associated with the program's implementation.

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Textbox 1. Study procedures for the home option testing for pre-exposure prophylaxis randomized controlled trial.

The home option testing for pre-exposure prophylaxis trial is a hybrid implementation study that randomizes new or current HIV pre-exposure prophylaxis (PrEP) patients at the Sexual Health Clinic in Seattle, Washington, to have the option of home-based monitoring with self-collection of samples for HIV, syphilis, gonorrhea, chlamydia, and creatinine and telehealth follow-up vs standard care including in-clinic visits and monitoring. Trial enrollment began in March 2022 and the primary outcome is pre-exposure prophylaxis retention at 20 months.

Baseline visit (in-person visit required)

- Intervention arm: Home-based pre-exposure prophylaxis (HB-PrEP) participants
  - Complete informed consent and enrollment.
  - Confirm baseline laboratory tests are complete (hepatitis A total b, hepatitis B sAb and sAg).
  - Ensure interval monitoring laboratory tests are collected (HIV Ag and Ab enzyme immunoassay (EIA), serum creatinine, quantitative vs quantitative rapid plasma reagin (RPR) based on history of previous syphilis).
  - Participant completes web-based survey.
  - Provide 30-day PrEP supply with 3 refills.
  - Perform home kit teaching.
- Standard of care (SOC) arm: Routine care participants
  - Complete informed consent, enrollment.
  - Confirm baseline laboratory tests are complete (hepatitis A total b, hepatitis B sAb and sAg).
  - Ensure interval monitoring laboratory tests are collected (HIV Ag and Ab EIA, serum creatinine, quantitative versus quantitative RPR based on history of previous syphilis).
  - Participant completes web-based survey.
  - Provide 30-day PrEP supply with 3 refills.

2-4 days later

- Review laboratory results: if HIV or HBsAg is positive, bring the participant to the sexual health clinic for clinical evaluation.

Month 4, 8, and 16 visits

- Intervention arm: HB-PrEP participants (Follow-up by telehealth)
  - Study staff (PrEP disease research intervention specialist or other trained staff)
    - Assess adherence.
    - Confirm no symptoms of acute HIV or contact with sexually transmitted infection (STI).
    - Routine PrEP counseling.
    - Order applicable PrEP laboratory tests (HIV Ag and Ab EIA, RPR qual or quant, gonorrhea and chlamydia [GC and CT], creatinine).
    - Troubleshoot home kit issues.
    - Reminder to return kit with self-collected samples.
    - Reminder to complete web-based survey.
    - Provide 30-day PrEP supply with 3 refills.
    - Schedule or give reminder for next visit.
- SOC arm: Routine care participants
  - Study staff (PrEP disease and intervention specialists [DRISs] or other trained staff)
    - Confirm no signs or symptoms of acute HIV and STI or known sexual contact with a person diagnosed with an STI.
    - If STI contact or concern for acute HIV and STI: notify the clinician, principal investigator (PI), and research coordinator and arrange an in-person evaluation.
    - Draw blood; participant self-collects GC and CT specimens at exposed sites (pharyngeal, vaginal, and rectal).
    - Order and process specimens for HIV Ag and Ab EIA, GC/CT, RPR qual or quant, creatinine (month 6 only). Provide 30-day PrEP supply with 3 refills.
    - Participant completes web-based survey.

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- Schedule or give reminder for next visit.

Month 12 visit (in-person visit required)

- PrEP DRIS
  - Confirm no signs or symptoms of acute HIV and STI or known sexual contact to a person diagnosed with an STI.
  - If STI contact or concern for acute HIV and STI - notify clinician, PI and research coordinator and arrange in-person evaluation.
  - Draw blood; participant self-collects GC and CT specimens at exposed sites (pharyngeal, vaginal and rectal).
  - Order & process specimens for HIV Ag and Ab EIA, GC and CT, RPR qual or quant, creatinine (may defer if already done within last 3 months).
  - Provide 30-day PrEP supply with 3 refills.
  - Participant completes web-based survey.
  - Schedule or give reminder for next visit.
  - For HB-PrEP or intervention arm enrollees: Troubleshoot home kit issues, provide kit for next visit if desired.
- Clinician
  - Assess adherence, side effects, willingness to continue PrEP.
  - Address any participant concerns about PrEP. If issues are related to the study, refer to the research coordinator or PI directly.
  - Complete hepatitis A or B or other vaccines (eg, HPV) if indicated.
  - Provide 30-day PrEP supply with 3 refills.

Month 20 study exit visit (in-person visit required)

- PrEP DRIS
  - Confirm no signs or symptoms of acute HIV and STI or known sexual contact with a person diagnosed with an STI.
  - If STI contact or concern for acute HIV or STI: notify the clinician, PI, and research coordinator and arrange an in-person evaluation.
  - Draw blood; participant self-collects GC and CT specimens at exposed sites (pharyngeal, vaginal, and rectal).
  - Order and process specimens for HIV Ag and Ab EIA, GC and CT, RPR qual or quant, creatinine (may defer if already done within previous 4 months).
  - Provide 30-day PrEP supply with 3 refills.
- Exit assessment: participant will either complete web-based exit survey or may be selected to participate in exit interview with the research coordinator or PI.

Study Setting and Staff

The PHSKC SHC provides direct medical services related to sexual health and STI to over 6500 patients each year and is the largest single diagnosing site for HIV infection in the Pacific Northwest region of the US. Of all patients seen annually in the SHC, approximately 41% identify as sexual minority men and 42% as racial or ethnic minorities. Disease and research intervention specialists (DRIS), who are nonclinical public health staff trained in HIV and STI prevention and to provide partner services, currently serve as PrEP navigators and conduct all PrEP initiation and nonclinical monitoring visits in the SHC [32]. They will continue to fulfill this role during the study, augmenting their current work to manage HB-PrEP, and along with the lead research coordinator will help with eligibility screening, recruitment, and retention efforts.

Primary RCT

Eligibility Criteria and Exclusions

All patients in the SHC meet both PrEP use criteria according to the US Centers for Disease Control and Prevention's 2021 clinical practice guidelines [12] and at least one of three PHSKC PrEP criteria: (1) HIV-negative cisgender man, transgender or nonbinary person who has sex with men; (2) person who has a sex partner with unsuppressed HIV; or (3) person who injects drugs or engages in exchange sex [32]. Prospective participants for the trial, in addition, must meet the following study-specific criteria (Textbox 2).

Persons with active hepatitis B or a creatinine clearance <50 mL/minute are not excluded; however, they will receive counseling about the risk of hepatitis B infection worsening if PrEP medications are discontinued and be encouraged to follow up with medical providers outside of the study for management of comorbid conditions.

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Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years.
- Resident of Washington State.
- Can speak, understand, read and write in English or Spanish.
- Current pre-exposure prophylaxis user or interested in starting or restarting pre-exposure prophylaxis.
- Willingness to be randomized to home-based pre-exposure prophylaxis and adhere to specified procedures.
- Willingness to provide primary and alternate contact information.

Exclusion criteria

- Recent (<4 weeks) "high risk" HIV exposure while off pre-exposure prophylaxis or symptoms of acute HIV infection.
- No mailing address to receive packages or sampling kits.
- No stable, working telephone number.
- No smartphone or electronic device with internet access.
- History of bleeding disorder, current or recent (≤7 days) use of anticoagulant medications (warfarin and rivaroxaban).
- Pregnancy.

Screening, Recruitment, and Enrollment

Existing Patients

DRIS or the research staff review patients scheduled for routine PrEP visits at the SHC and offer enrollment in person to eligible patients. Enrollees are randomized to continue SOC (attend the PHSKC SHC every 4 months for a visit with DRIS, have blood samples collected for PrEP monitoring, and perform self-collection of GC and CT swabs) or have the option to do HB-PrEP monitoring. Those assigned to HB-PrEP (intervention arm) are eligible to participate in home-based monitoring immediately after receiving instruction from study staff on how to use the Tasso devices, procedures for mailing kits back to the PHSKC laboratory, and how to complete web-based surveys after returning kits. DRIS or research staff facilitate training on the use of the Tasso devices. This includes a review of the test kit components, the importance of warming the upper arm, aseptic technique, and proper use of the device. After the overview, participants were also asked to watch the training video provided by Tasso (Tasso Inc) [30].

New and Former ("Lost to Follow-Up") PHSKC PrEP Patients

Prospective and former PrEP patients who are eligible for the study may be recruited at their initial visit. Those randomized to the control arm will adhere to the usual SHC PrEP clinical protocols [32]. Persons randomized to HB-PrEP receive instruction from DRIS or study staff about self-collection procedures as above and are eligible to return their first kit for the month 4 monitoring cycle. Persons initiating PrEP (or reinitiating after a prolonged discontinuation) must be evaluated in person by a clinician and have blood collected by clinic staff for HIV screening, renal function, viral hepatitis serologies, and so on; thus, these individuals will become eligible to use home kits at their first tri-annual follow-up (ie, 120 days after PrEP initiation). Follow-up time in the study for all participants begins immediately after enrollment.

Randomization and Study Procedures

Sample Size and Power Considerations

Sample size calculations for the primary Kaplan-Meier survival analysis were based on standard methods [33]. Assuming that 2.5% of individuals discontinue PrEP per month in the control arm, we expect 45% of SOC participants to discontinue PrEP (55% retention) over the 20-month study period. In the intervention arm, we estimate that 70% will adopt HB-PrEP. We assume a relative risk of discontinuation of 0.6 among participants assigned to receive HB-PrEP leading to a 32% discontinuation rate (68% retention) in the HB-PrEP arm. We also allowed for an overall dropout rate in both groups of 6% [15]. Thus, a sample size of 458 participants should yield 80% power to detect a 13% point difference in PrEP retention. All eligible participants are assigned through simple 1:1 randomization to either the intervention arm (n=229) or SOC arm (n=229) and followed for 20 months. RCT procedures are detailed in Textbox 1.

Surveys

Participants in both arms are asked to complete web-based surveys using REDCap (Research Electronic Data Capture) [34]—a secure, web-based platform that participants used successfully in the preimplementation pilot study. The initial enrollment survey collects basic demographic and contact information including valid mailing address and phone number for the participant and an approved alternative contact, sexual orientation and gender identity items, and PrEP monitoring preferences. Subsequent interval surveys focus on evaluating self-reported PrEP adherence, number of sex partners, type and frequency of sex, frequency of drug or condom use, and measures of satisfaction with the assigned monitoring program.

Home Specimen Tracking

Participants in the HB-PrEP arm are contacted by study staff approximately 1 month before their visit (months 4, 8, and 16) to confirm whether they would prefer to come into the clinic or

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use a home sampling kit. Participants who opt for home sampling are sent a kit at that time to allow for samples to be received and results to be finalized before or near the date of their remote follow-up visit. Home sampling kits contain instruction sheets in English or Spanish, specimen labels, 2 swabs (Hologic Aptima 2 Combo, San Diego, California) for extragenital (or vaginal, if applicable) GC and CT testing, and 2 Tasso devices. The SHC's protocol is not to offer men who have sex with men routine urine or urethral screening for GC and CT given that asymptomatic positivity at this anatomic site among men who have sex with men in our clinic is relatively rare and not felt to justify the cost of additional testing. Thus, consistent with our existing clinical protocols for in-person SOC, urine or urethral screening is not included in the home kits. Mailing and tracking of kits are managed through Tasso's confidential kit delivery portal. Study staff enter participant information into the portal, at which point kits are assembled and mailed directly to the participant's specified address. Tracking numbers allow staff to track the location of packages when they are received at the home, and when the participant arranges for pick-up to return specimens to the clinic. An automated text or email is then generated to notify participants that kits have been shipped and a reminder is sent 7 days after delivery if kits have not yet been returned.

Telehealth Visits and Interim Follow-Up

Participants in the HB-PrEP arm have 2 options for completing scheduled telehealth follow-ups: (1) through a telephone call with DRIS or (2) through a HIPAA (Health Insurance Portability and Accountability Act)-compliant Zoom conference call through the SHC electronic medical record. In addition, participants can reach study staff through WelTel—a secure and health information-compliant, 2-way message support program already in use by DRIS in our clinic for contacting PrEP patients [35]. Scheduled check-in visits for both arms consist of routine PrEP adherence counseling, screening for new HIV or STI symptoms, and PrEP prescription renewal if indicated. Per SHC protocols, participants with symptoms compatible with acute HIV or any STI must be evaluated in person in lieu of receiving a home sampling kit.

Specimen Processing and Laboratory Evaluations

Individuals randomized to HB-PrEP are mailed sampling kits to their preferred address and return self-collected samples through prepaid express postal mail to the PHSKC laboratory for processing within 48 hours. Participants are advised to refrigerate any sample that cannot be shipped and received in the clinic within 2 days (eg, over weekend days). Upon receipt in the clinic, the study staff and PI conduct a brief quality assessment of specimens, place laboratory orders in the electronic health record, and send samples to the PHSKC laboratory for testing per standard clinic protocol. Additional processing and testing procedures for HIV, syphilis, RPR, and creatinine have been described elsewhere [29].

Outcomes and Analyses

Primary Outcome Measures

Effectiveness will be evaluated with a survival analysis using PrEP nonretention as the event of interest. Observation time for all participants begins at the time of randomization and continues until either loss-to-follow-up or study end at 20 months. Consistent with previous studies [36,37], we define participants in either arm as "retained" on PrEP if they complete monitoring tests and visits with a clinician or DRIS at each 4-month interval to receive a renewed PrEP prescription. Kaplan-Meier curves will compare PrEP retention rates between the intervention and control arms at 20 months. We will use Cox proportional-hazards regression models to examine individual-level correlates (age, race and ethnicity, income range, and education status) of PrEP retention.

Secondary Outcome Measures

Reach is defined as the proportion of individuals assigned to the HB-PrEP study arm who choose to send in self-collected specimens from home for at least half of tri-annual PrEP visits over the study period. As we are interested in the real-world uptake of HB-PrEP, we are tracking and will report the total number of PrEP patients approached about the study, the number who declined participation and reasons for declination, and the proportion of individuals assigned to the intervention arm who choose at any time to transition to the SOC arm and reasons for doing so. To mitigate potential sampling (self-selection) bias, we explain in the screening process that even if randomized to the intervention arm, the use of HB-PrEP is optional, and patients in the intervention arm can always continue with standard in-clinic monitoring for some or all of the PrEP follow-up visits.

Acceptability or patient satisfaction with HB-PrEP will be evaluated using tri-annual web-based participant surveys including 5-point Likert scale questions adapted from questionnaires of similar PrEP trials. Additional items will inquire about the ease or difficulty of self-sampling device use, issues with receiving kits, and any other challenges with the home monitoring process. Specific validated psychometric tools to assess PrEP user satisfaction are limited overall and, to our knowledge, none exist that are designed to evaluate HB-PrEP services.

Study surveys inquire about PrEP use strategy (event-driven or "2-1-1" vs daily) over the preceding 4 months and adherence questions are tailored to the reported use strategy. Based on data that taking ≥4 doses/week confers a 96% reduction in HIV risk [38], self-reported PrEP adherence is measured using validated question items asking the percent of PrEP taken in the previous 4 weeks [39]. The percentage of PrEP adherence will be compared between arms and analyzed using linear mixed models to account for repeated measures on each participant.

We will measure the time from receipt of monitoring and STI results into the SHC electronic health record to the time study staff notify the participant of abnormal results.

We will also track new syphilis and GC or CT infections for each group per tri-annual interval to estimate a composite asymptomatic STI positivity incident rate.

Qualitative Data

Semistructured interviews will be conducted with HB-PrEP participants (n=24) beginning at month 4 and occur at triannual intervals thereafter, until recruitment goals are reached. The

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focus of these HB-PrEP participant interviews will be understanding specific barriers and facilitators of PrEP retention, identifying unanticipated negative effects or issues with the delivery of the intervention, determining whether HB-PrEP is preferred to SOC, and how future iterations of the program might be improved. Interview guides will be adjusted based on preliminary data from patient surveys to further explore any issues HB-PrEP participants identify. Clinic staff, including DRIS and administrators (n=3), will also be invited to participate in semistructured interviews at 12 and 20 months to understand operational barriers and facilitators of program implementation. Study participants and staff will be offered their choice of an in-person or virtual interview. Interviews will be audio recorded; transcripts will be independently reviewed by 2 study staff members and evaluated using thematic coding and a mix of inductive and deductive coding.

Ethical Considerations

The study is considered human subjects research. All study procedures were reviewed and approved by the University of Washington institutional review board (IRB; STUDY00013871) and considered not to pose any more than minimal risk to study participants. Informed consent forms describing all study procedures, potential risks, compensation (if applicable), and contact information for the IRB and study staff were available in English and Spanish. Participation in the first study component (home-based monitoring vs SOC with web-based surveys) is not compensated. Patients and staff who participate in interviews for the qualitative study component will receive US $25 compensation.

All study staff are required to uphold strict confidentiality in accordance with the HIPAA. Only the information necessary to conduct the clinical trial or coordinate clinical care with providers will be viewed or used by authorized study staff. Home kits are in nonlabeled, plain boxes with no external information to identify study participants. Identifiable data is kept on an approved and password-locked database and only linked with indirect identifiers. Contributions in qualitative interviews will be deidentified and only general information used to derive themes for analysis.

Results

Overview

The HOT4PrEP trial is a hybrid implementation study that randomizes new or current HIV PrEP patients at the Sexual Health Clinic in Seattle, Washington, to have the option of home-based monitoring with self-collection of samples for HIV, syphilis, gonorrhea, chlamydia and creatinine and telehealth follow-up versus standard care including in-clinic visits and monitoring. The primary outcome is PrEP retention at 20 months.

Enrollment for the trial began in March 2022 and continued through May 2022 when all research was halted in the SHC to focus on the emerging mpox outbreak. Study enrollment then resumed in December 2022 and is ongoing.

From March 2022 to May 2023, a total of 161 PrEP patients were screened to enroll the first 100 participants into the intervention arm (49/100, 49%) or standard care arm (51/100, 51%). In total, 2 PrEP patients (1.2%) were deemed ineligible to enroll, 55 (34%) declined to participate, and staff were not able to discuss enrollment with 4 (2.5%) patients. Common reasons for declining to participate included preferring to come into the clinic or having an aversion to seeing blood during the self-collection process.

Table 1 describes demographics and other baseline characteristics participants self-reported upon enrollment. The baseline survey completion rate was 96% for both trial arms. Median age was 34 (IQR 28-39, range 19-67) years. Of the participants who elected to provide sex and gender information, all were assigned male sex at birth (47/47, 100%). Most identified as cisgender men (41/47, 87%), gay (42/47, 89%), and their race and ethnicity as non-Hispanic White (n=36, 38%) or Asian (n=23, 24%). Most participants reported an annual income of US $30,000 or more (75%) and at least some college education (91%).

All participants in the intervention arm were contacted before their 4-month follow-up visit to ask if they would prefer to come into clinic or receive home kits. Of the 49 participants contacted, 33 (67%) opted to collect samples at home and follow up through telehealth, 14 (29%) opted to come in person to the clinic, and 2 (4%) canceled their appointments. Of those who opted for home sample collection and telehealth follow up, 27 (82%) returned test kits with samples for HIV and STI testing, 5 (15%) came in person to the clinic for their visit, and 1 (3%) canceled their appointment.

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Table 1. Baseline characteristics of the first 100 home option testing for pre-exposure prophylaxis trial enrollees, March 2022-May 2023.

Characteristics	Values
Age (years), median (IQR)	34 (28-39)
Male sex assigned at birth, n (%)	47 (47)
Current gender identity, n (%)	
Cisgender man	41 (87)
Transgender, nonbinary, genderqueer, etc	6 (11)
Race and ethnicity, n (%)	
NH[a] Black	10 (11)
Hispanic or Latinx	15 (16)
NH[a] White	36 (38)
Asian	23 (24)
American Indian or Alaska native, mixed race, or other	8 (9)
Sexual orientation, n (%)	
Gay	42 (89)
Straight, pansexual, bisexual, or queer	5 (11)
Annual income (US$), n (%)	
14,999 or less	5 (11)
15,000-29,999	6 (14)
30,000-49,999	11 (25)
50,000-99,999	11 (25)
100,000 or more	11 (25)
Highest level of education, n (%)	
Grade or high school	4 (8)
Some college, associate, or technical degree	11 (23)
Bachelor's degree	17 (35)
Some graduate school	5 (11)
Graduate degree	11 (23)
Medical insurance (excluding PrEP[b] care), n (%)	
None	17 (37)
Private insurance	24 (52)
Medicaid	2 (4)
Other insurance type	3 (7)
Ever diagnosed with STI[c], n (%)	
Yes	33 (70)
No	14 (30)
PrEP[b] use status, n (%)	
Currently taking PrEP[b]	42 (89)
Planning to start soon	5 (11)
Duration of current PrEP[b] use, n (%)	
<3 months	3 (7)
3-6 months	8 (20)
6-12 months	6 (14)

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Characteristics	Values
1-2 years	8 (20)
>2 years	16 (39)
Substance use in the past 12 months[d], n (%)	
Alcohol	37 (37)
Stimulants (cocaine or meth)	9 (9)
Hallucinogens (LSD or mushrooms)	6 (6)
Marijuana	25 (25)
None	5 (5)

[a]NH: non-Hispanic.

[b]PrEP: pre-exposure prophylaxis.

[c]STI: sexually transmitted infections.

[d]Total percentages may not sum to 100% as participants could select multiple answer choices.

Discussion

Principal Findings

Preliminary data from the first 100 participants of this hybrid RCT suggest that thus far, the implementation strategy of HB-PrEP monitoring, consisting of self-collected GC and CT swabs, blood specimens obtained using the Tasso device, and telehealth follow-up, is acceptable to users and feasible to incorporate into a busy PrEP clinic. Though results are preliminary, reach appears to be high among participants randomized to the intervention arm. Two-thirds of participants who were offered the option of HB-PrEP chose to use it, and of those who received kits, 27 (82%) successfully returned kits containing samples sufficient to complete their requisite PrEP monitoring laboratory tests.

Our initial pilot study undertaken during the COVID-19 pandemic (2020-2021) found that 98 (80%) of surveyed patients in our clinic preferred home-based services over coming into the clinic. Some studies conducted in the prepandemic era [22,23,40] and another completed more recently among men who have sex with men in a Dutch sexual health center [41] came to similar conclusions about the preference for home-based sampling. However, at least 1 other study conducted in a real-world pharmacy-based PrEP program found that less than half of participants used home kits when offered them [26]. Factors affecting a participants' decision to do home sampling over coming to the clinic may be variable and depend on one's self-efficacy and assessments of potential risks (eg, breach of privacy) versus benefits (eg, increased convenience and saved time) [26]. While our preliminary results of home kit uptake are promising, it remains to be seen if stated preference or intention to self-collect samples at home will equate to consistent use over time. Survey data and interviews of participants will aim to identify reasons motivating choice over time.

Our trial faces a few challenges and limitations. Interpretation of preliminary results remains limited given that enrollment in the randomized portion of the trial is ongoing. Study staff are recruiting for the qualitative component of the study, and analyses of preliminary PrEP retention rates at 4 and 8 months and secondary outcomes are also underway. While the initial cohort is diverse from a racial and ethnic standpoint, other demographics and characteristics may not represent groups of PrEP patients in other settings. Our clinic is large, serves an urban population, and is fairly well-resourced; thus, results may not be generalizable to smaller clinics in less populous or less well-resourced areas. We will not be able to verify that returned samples came from the enrolled participant, but we do not anticipate this to be a significant problem since abnormal or positive test results will require an in-person clinic visit for confirmatory retesting and treatment. Finally, the first component of our RCT is not incentivized which may be associated with decreasing engagement over time with study procedures (eg, survey completion). However, this trial was designed to be pragmatic with study procedures that could be reproducible for similar clinics where routine PrEP care is not incentivized in the real world. Despite these challenges, we feel the study seeks to answer important questions and will yield useful information about the utility, barriers, and facilitators of this implementation strategy for expanding PrEP access locally and beyond.

While not every person may choose to use a home-based option for every PrEP follow-up visit, HB-PrEP holds promise as a strategy to decrease barriers for staying on PrEP, increase patient autonomy and accessibility, and expand the capacity of clinics to initiate and maintain a greater number of people on PrEP. In turn, if successful even for a proportion of users, HB-PrEP has the potential to contribute to larger efforts to end the HIV epidemic by increasing PrEP uptake and retention. Our results will provide important information about the feasibility and value of implementing HB-PrEP into growing programs seeking to strike a balance between expanding PrEP access, maintaining capacity for in-person services, and facilitating patient choice and convenience.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available as study enrollment is ongoing and requires the collection of data involving protected health information about notifiable conditions. Unidentified data are available from the corresponding author on reasonable request.

Conflicts of Interest

Self-sampling devices and shipping services for this RCT are provided in kind by Tasso, Inc. MG has received research support from Hologic, Speedx, and GSK.

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Abbreviations

CT: chlamydia
DRIS: disease and research intervention specialist
GC: gonorrhea
HB-PrEP: home-based pre-exposure prophylaxis
HIPAA: Health Insurance Portability and Accountability Act
HOT4PrEP: home option testing for pre-exposure prophylaxis
IRB: institutional review board
PHSKC: Public Health-Seattle and King County
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPR: rapid plasma reagin
SOC: standard of care
SHC: sexual health clinic
STI: sexually transmitted infection

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Protocol

Functional Magnetic Resonance Imaging Analysis of the Clinical Effect and Cerebral Mechanism of Tuina in Lumbar Disc Herniation: Protocol for a Randomized Controlled Parallel Group Trial

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Abstract

Background: Lumbar disc herniation (LDH) has become a serious public health and socioeconomic problem. Tuina is a Chinese medicine treatment method based on meridian acupuncture theory and modern anatomy. Tuina can relieve pain and muscle tension and improve functional disorders; this massage is performed by pressing, kneading, pushing, pulling, and shaking the skin, muscles, and bones. However, the mechanism of action and the effect of Tuina as an external treatment on the activities of the central nervous system to relieve LDH pain is unclear. Therefore, we performed functional magnetic resonance imaging (fMRI), which is widely used in pain-related research, as it can detect the effects of different types of pain on brain activity.

Objective: Our randomized controlled parallel-group trial aims to compare the effects of Tuina with those of transcutaneous electrical nerve stimulation (TENS) with traction in patients with LDH.

Methods: This trial will be conducted between May 2024 and April 2025 in the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine. Seventy-six participants with LDH will be enrolled for this trial and randomly assigned to 2 groups: Tuina intervention group and TENS with traction intervention group. Participants in both groups will receive treatment for 14 days. fMRI will be performed for the main pain measurements by assessing the effect of the intervention on brain activity before and after the end of the intervention. Short-Form McGill Pain Questionnaire, pressure pain thresholds, and the Oswestry disability index will be used to reflect the degree of pain and lumbar dysfunction, and the results will be used as secondary outcome measurements.

Results: The study protocol has been approved by the ethics review committee of The Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine. This study was registered on May 1, 2024, with the Chinese Clinical Trial Registry. Data collection began on May 2024 and is expected to end on April 2025. Currently, data from this trial are in the collection phase, and no data analysis has been performed. As of July 1, 2024, we have collected data from 21 patients. The results of this trial are expected to be submitted for publication in September 2025.

Conclusions: This clinical trial will compare the effectiveness of Tuina with that of TENS with traction in the treatment of patients with LDH and will show the cerebral mechanism of Tuina in LDH treatment by using fMRI. The results of our trial will be helpful in clarifying the cerebral mechanism of Tuina in the treatment of LDH and provide a solid foundation for Tuina therapy research.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400083784; https://www.chictr.org.cn/showproj.html?proj=225157

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KEYWORDS

fMRI; functional magnetic resonance imaging; lumbar disc herniation; Tuina; traction; transcutaneous electrical nerve stimulation; cerebral mechanism

Introduction

Lumbar disc herniation (LDH) is a common clinical disease, which is caused by the rupture of the annulus fibrosus of the lumbar intervertebral disc, herniation of nucleus pulposus, and stimulation and compression of the dural sac and nerve root, leading to a series of symptoms such as low back pain, lower limb radiation pain, and numbness [1]. LDH is more prevalent among individuals aged 30-50 years, and the lifetime risk for symptomatic LDH is 1%-3%. In contemporary society, due to poor lifestyles and lack of exercise, the incidence of LDH is increasing every year and is frequently reported among younger male populations; therefore, LDH has become a serious public health and socioeconomic problem [2].

The pathogenesis of pain caused by LDH is complex, mainly involving the central and peripheral nervous systems. The peripheral mechanism is usually attributed to mechanical compression or local inflammation of the nerve roots caused by LDH [3]. For example, larger protrusions lead to lumbar spinal nerve root damage and induce changes in nerve fibers, and inflammatory response–related factors result in local inflammation in the microenvironment, leading to LDH pain. At the same time, related inflammatory mediators in LDH, such as interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor-α, and interferon γ, can also synchronously stimulate peripheral nerve endings and receptors and lead to LDH pain [4,5]. However, the peripheral mechanism alone is not enough to explain the complex clinical symptoms caused by LDH, such as pain sensitization, anxiety, and depression, which are often observed in patients with LDH [6,7]. Therefore, the central mechanism is considered to play a key role in the etiology of LDH.

Functional magnetic resonance imaging (fMRI) is an imaging technique that depicts the neural activity in the brain in real time based on the changes in local oxygen consumption and cerebral blood flow [8]. fMRI is widely used in pain-related research, and it can detect the effects of different types of pain on brain activity. A number of studies have shown that structural and functional changes can occur in the brains of patients with LDH [9]. Among them, a prospective study found that the volume of gray matter volume in the right anterolateral prefrontal cortex, right temporal lobe, left premotor cortex, right caudate nucleus, and the right cerebellum decreased significantly, while the volume of the right dorsal anterior cingulate cortex, left precuneal cortex, left fusiform gyrus, and the right brainstem increased in patients with LDH, suggesting that LDH can cause specific local changes in the brain structure [10]. In patients with LDH, the amplitude of low-frequency fluctuations (ALFF) increased in the right lingual gyri in the conventional band and in the left Cerebelum_Crus1 in the slow-4 band [11]. In addition, patients with LDH also have impaired excitability of the somatosensory and motor cortex, decreased homogeneity of the default mode network, and dysfunction of functional connectivity (FC) [12]. These findings suggest that brain structural remodeling and functional changes may be the cerebral mechanism of the pathogenesis of LDH.

At present, the treatment of LDH mainly includes conservative treatment, interventional therapy, and surgical treatment [13]. Tuina is a massage therapy guided by traditional Chinese medicine theory, which has a long history. Recently, several randomized controlled trials have confirmed the positive effects of Tuina treatment [14-16]. For example, Tuina has a good therapeutic effect on diseases such as LDH, chronic neck pain, and knee osteoarthritis. A meta-analysis of 13,075 patients also showed that Tuina is more effective than traction and Chinese herbal medicine in the treatment of LDH [17]. However, the mechanism of Tuina in the treatment of pain in LDH has not been fully elucidated, and the potential cerebral mechanism of Tuina analgesia is a hot topic of interest.

Recently, some scholars have used fMRI technology to study the central mechanism of Tuina in the treatment of LDH pain and obtained some positive results. For example, Zhou et al [18] found that patients with LDH showed abnormal brain ALFF and regional homogeneity (ReHo) values, which were altered after Tuina manipulation. Patients with LDH showed decreased ReHo in the left orbital part of the middle frontal gyrus, decreased dynamic FC (dFC) variance between the left orbital part of the middle frontal gyrus and the left fusiform, and increased dFC variance in the left orbital inferior frontal gyrus and left precuneus. Tuina therapy positively altered the ReHo and dFC values, making the brain activities in patients with LDH similar to those in healthy controls [12].

In recent years, although many studies [12,19] have provided evidence on the central brain mechanism of Tuina analgesia by using fMRI technology, relatively few studies have explored the central mechanism of Tuina in the treatment of LDH. Therefore, we designed a randomized controlled trial to explore the potential cerebral mechanism of Tuina analgesia by using fMRI.

Methods

Trial Design

This is a single-center randomized controlled trial with 2 parallel arms: the Tuina intervention group and traction with transcutaneous electrical nerve stimulation (TENS) intervention group. A total of 76 eligible patients with LDH will be recruited for this trial, and patients with LDH will be randomly assigned to the groups in 1:1 ratio. All patients will provide written informed consent. Outcome evaluation and statistical analysis

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will be performed by 2 researchers who do not know the specific groups. The trial design flowchart is shown in Figure 1, and the study schedule is shown in Figure 2. This study will be conducted in the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine. This study follows the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Multimedia Appendix 1).

Figure 1. Flowchart of this trial. fMRI: functional magnetic resonance imaging; ODI: Oswestry disability index; PPT: pressure pain threshold; SF-MPQ: Short-Form McGill Pain Questionnaire; TENS: transcutaneous electrical nerve stimulation.

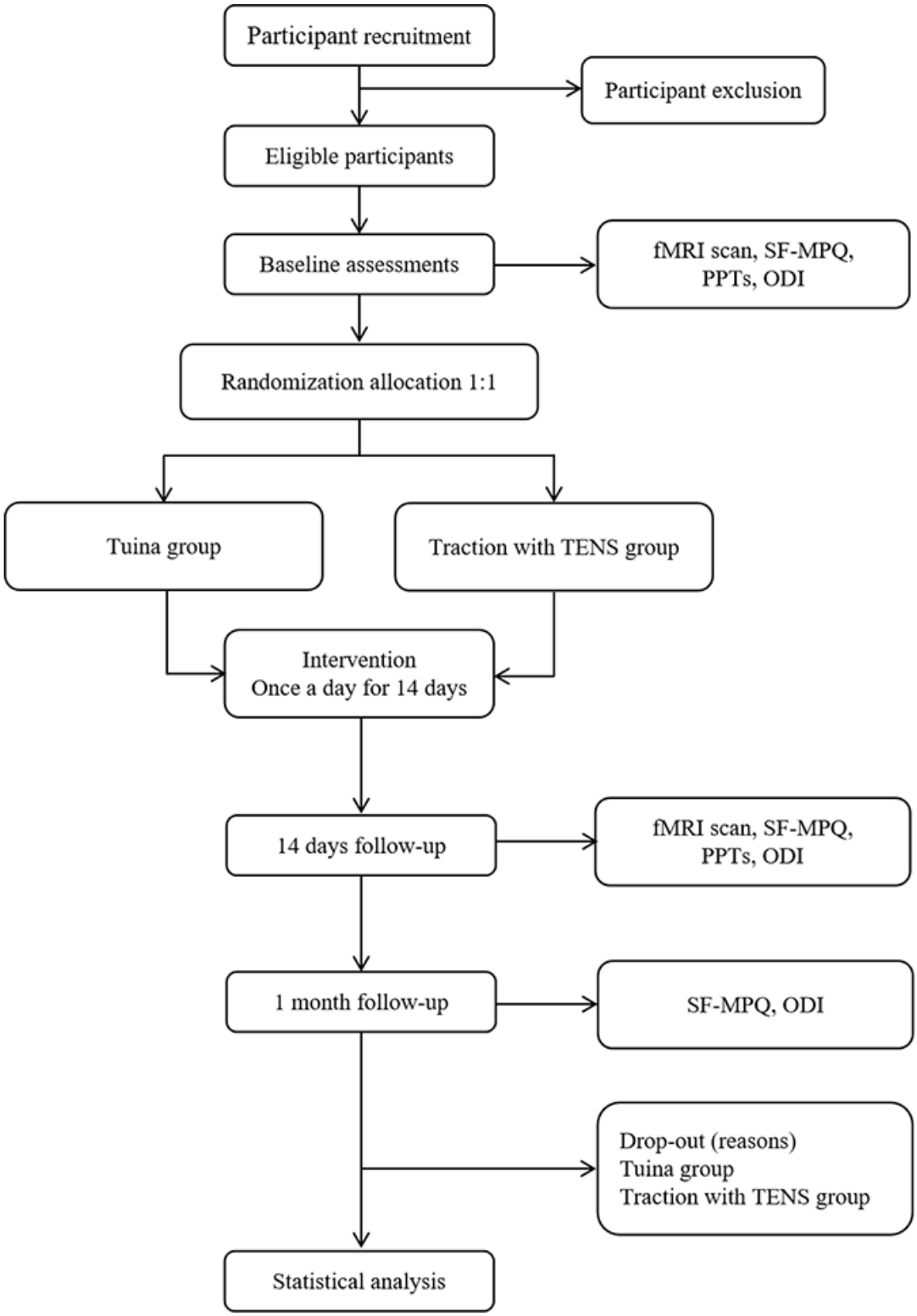

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Figure 2. Flow diagram of this study. –3 to 0 days: within 3 days prior to treatment; 0 day: day 0 of treatment; 1 day: day 1 of treatment; 7 days: day 7 of treatment; 10 days: day 10 of treatment; 14 days: day 14 of treatment; 1 month: 1 month after treatment; fMRI: functional magnetic resonance imaging; ODI: Oswestry disability index; PPT: pressure pain threshold; SF-MPQ: Short-Form McGill Pain Questionnaire; TENS: transcutaneous electrical nerve stimulation.

	Study period						
	Enrollment	Allocation	Intervention (days)				Follow-up
Timepoint	–3 to 0 days	0 day	1 d	7 d	10 d	14 d	1 month
Eligibility screening	✓						
Informed consent		✓					
Randomization		✓					
Allocation		✓					
Intervention							
Tuina			◄	—	—	►	
Traction with TENS			◄	—	—	►	
Outcome measurements							
fMRI		✓				✓	
SF-MPQ		✓	✓	✓	✓	✓	✓
ODI		✓	✓	✓	✓	✓	✓
PPT		✓	✓	✓	✓	✓	
Safety evaluation							
Adverse event			◄	—	—	►	

Ethics Approval

The study protocol has been approved by the ethics review committee of The Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine (project 2024KY-008-02). This study was registered on May 1, 2024, with the Chinese Clinical Trial Registry (ChiCTR2400083784).

Participants and Recruitment

We will recruit participants in the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine. All participants need to meet the LDH diagnostic criteria in the guidelines for clinical diagnosis and treatment (Orthopedic Bundle Separation) [20]. In addition, we will recruit potential patients through posters and internet platforms. Clinical trial communicators will fully explain the trial to patients before the trial begins to ensure that all the patients participate voluntarily and sign an informed consent form.

Inclusion Criteria

The inclusion criteria for the participants are as follows: (1) right-handed; (2) age between 18 and 60 years; (3) computed tomography or magnetic resonance imaging examination show L4-L5 or L5-S1 disc herniation; (4) the main manifestation is nerve root pain, and the imaging is consistent with the nerve localization; (5) the neuropathic pain rating scale (Douleur Neuropathique 4 questions) score is ≥4; (6) patients who did not take painkillers or nutritional neurodrugs for nearly 1 month and did not receive systematic treatment; and (7) patients who voluntarily want to participate in clinical trials and sign informed consent forms.

Exclusion Criteria

The exclusion criteria are as follows: (1) patients with progressive neurological deficit or cauda equina syndrome; (2) patients with LDH combined with other major lumbar diseases such as tumor, tuberculosis, and severe osteoporosis; (3) patients with trauma, acute lumbar injury caused by surgery pain, and lower limb nerve injury; (4) patients with any other condition causing lower limb neuropathy (diabetes or neurological diseases); (5) patients with cardiovascular, pulmonary, renal, hematopoietic system, and other major diseases; (6) patients with mental health issues; (7) pregnant or lactating women; and (8) patients with contraindications for fMRI.

Dropout Criteria

Participants who were unable to complete the trial for the following reasons will be considered to have dropped out: (1) patients are not treated by the regulations, and the curative effect cannot be judged; (2) incomplete data that affect the judgment of efficacy or safety; or (3) accidents occur in the course of treatment and participants are unable to adhere to treatment.

Comprehensive Suspension Criteria

The comprehensive suspension criteria are as follows: (1) participants in the study have serious adverse effects due to a poor treatment plan, (2) participants experience severe complications or disease deterioration during the study period,

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and (3) if the test termination conditions are met after the doctor follows the standard operating procedure treatment, they shall be terminated immediately.

Randomization

An independent technician will use the SPSS statistical software (version 26.0; IBM Corp) to generate random sequence numbers, and participants will be randomly divided into the Tuina intervention group or the traction with TENS intervention group in 1:1 ratio. Random sequence numbers will be sealed in opaque envelopes. The envelopes will be opened in a numerical order to determine the allocation for the participants.

Blinding

In this study, blindness will be implemented for outcome evaluators and data statisticians. Due to the particularity of the treatment method in this trial, the therapists and patients will not be blinded for their grouping. This blinded process will continue until the end of the trial data analysis.

Interventions

Participants will receive treatment once a day for 14 days. Tuina treatment will be performed by a professionally trained Tuina therapist, and a senior attending physician will perform TENS and traction. Before the trial, both operators should pass the relevant clinical tests to ensure the operation's consistency. Other related treatments such as medicines, acupuncture, and physiotherapy will not be allowed during the treatment period.

Tuina Intervention Group

The standard Tuina procedure will be based on Tuina therapy described in [21]. The specific therapy will be performed as follows (Figure 3).

1. The Tuina therapist will guide the patient to lie in the prone position and gently press the bladder meridian on both sides of the patient's waist and buttocks as well as the posterior lateral side of the affected lower limb for 10 minutes of operation.
2. Thereafter, the Tuina therapist will rhythmically press the acupoints of Shenshu (BL23), Dachangshu (BL25), Huantiao (GB30), Chengfu (BL36), Weizhong (BL40), Chengshan (BL57), and Kunlun (BL60) with their fingers at a frequency of 120 times per minute for 10 minutes of operation.
3. Then, the Tuina therapist will guide the patient to lie on their side by using the waist oblique pull method once on the left and once on the right.
4. Finally, the patient is placed in a supine position, and the lower limb on the affected side is raised. The operation is similar to a straight leg lift test, and this process will be repeated several times.

Figure 3. Operation in the Tuina intervention group.

TENS With Traction Intervention Group

Step 1: TENS

The patient lies in the prone position on the treatment bed. In order to treat the patients, the therapist places 2 electrodes of the TENS therapeutic apparatus (WOND2000F0, SUNJAVA) on the Ashi acupoint on the patient's back and lower limbs. The therapist then changes the stimulation parameters, setting the frequency to 25 Hz and the pulse width to 280 μs. The therapist chooses the maximum intensity based on the patient's condition and the level that the patient can tolerate. TENS is performed once a day for 20 minutes, and the treatment will be continued for 14 days.

Step 2: Traction

Traction will be performed after 10 minutes of TENS. The patient lies on the spine traction bed (TC-30S, MINATO). Once

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the therapist assists the patient in putting on the traction strap, they determine the traction amount based on the patient's weight. Initially, the therapist sets the traction volume at 25% of the patient's body weight, gradually increasing it by 2 kg/time as the patient's condition changes until it reaches 40%-50% of the patient's body weight. The therapist allows the patient to lie down and rest for 5 minutes after each traction session. The patient will receive traction once a day, with a duration of 20 minutes each time. The treatment will last for 14 days.

Outcome Measurements

We will present the trial results by using both objective and subjective indicators. fMRI will be used for the main measurements, reflecting the changes in the participants' brain structure and functional changes. Short-Form McGill Pain Questionnaire (SF-MPQ), pressure pain thresholds (PPTs), and the Oswestry disability index (ODI) will indicate the degree of pain and lumbar dysfunction and will be used for secondary outcome measurements.

Primary Outcome Measurement

The fMRI examination will be performed in the Imaging Department of the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine. The first fMRI scan will be performed 1 day before the start of treatment, and the second fMRI scan will be performed within 6 hours after the last intervention. The fMRI data will be collected by a 3.0 Tesla magnetic resonance scanner (MAGNETOM Prisma 3.0T, Siemens) with 64-channel phase-array head coils. During the acquisition process, participants will be required to close their eyes, relax, stay awake, keep their heads fixed as far as possible, and not perform thinking activities. We will perform fMRI at the beginning and end of the experiment.

To acquire the structural images, we will use the following parameters. The T1-weighted imaging scan parameters are as follows: time of repeat=2200 ms, time of echo=2.48 ms, flip angle=8°, field of view=230 mm×230 mm, matrix=256×256, resolution=0.98×0.98×1 mm^3, slice number=160, and slice thickness=1.0 mm. The functional images will be acquired using the following parameters: time of repeat=2000 ms, time of echo=30 ms, flip angle=90°, field of view=230 mm, matrix=64×64, resolution=3.6×3.6×3.6 mm^3, slice number=37, slice thickness=3.6 mm, and scan time=10 minutes for 300 timepoints.

Secondary Outcome Measurements

SF-MPQ Indicators

We will translate the SF-MPQ into Chinese to assess pain perception. This questionnaire consists of 5 indicators [22]: sensory pain rating index, affective pain rating index, total pain rating index, visual analog scale (which assesses the overall intensity of the total pain experience), and present pain index. The sensory pain rating index consists of 11 items describing sensory pain, and the affective pain rating index consists of 4 items describing emotional pain, with scores of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The total pain rating index is the sum of the sensory pain rating index and affective pain rating index. The overall intensity assessment of total pain experience consists of a visual analog scale ranging from 0 to 10, with 0 indicating no pain and 10 indicating the most severe pain imaginable [23]. In addition, 6 levels appear in the present pain index to describe the patient's pain level: no pain, mild, uncomfortable, painful, terrible, and unbearable expressed as 0, 1, 2, 3, 4, and 5 points, respectively, for each participant. We will ask participants to indicate the score that best matches their level of pain.

PPT Test

PPT is a quantitative sensory test that can effectively describe the intensity of pain [24]. When the patient lies in the prone position, the estimator first locates the Dachangshu (BL25), Guanyuanshu (BL26), and Xiaochangshu (BL27) on the patient's erector spinae muscles and Zhibian (BL54) and Huantiao (GB30) on the gluteus maximus muscles and uses them as test points (Figure 4). Then, the estimator will use the handheld tenderness tester (FTX50, Wagner) to press the test points at a uniform speed, lock it immediately when the patient feels pain, and then record the pressure value. The PPT will be measured every 5 minutes; a total of 3 measurements will be recorded, and the average will be taken to indicate the PPTs.

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Figure 4. Test points used to measure the pressure pain threshold. BL25: Dachangshu; BL26: Guanyuanshu; BL27: Xiaochangshu; BL54: Zhibian; GB30: Huantiao.

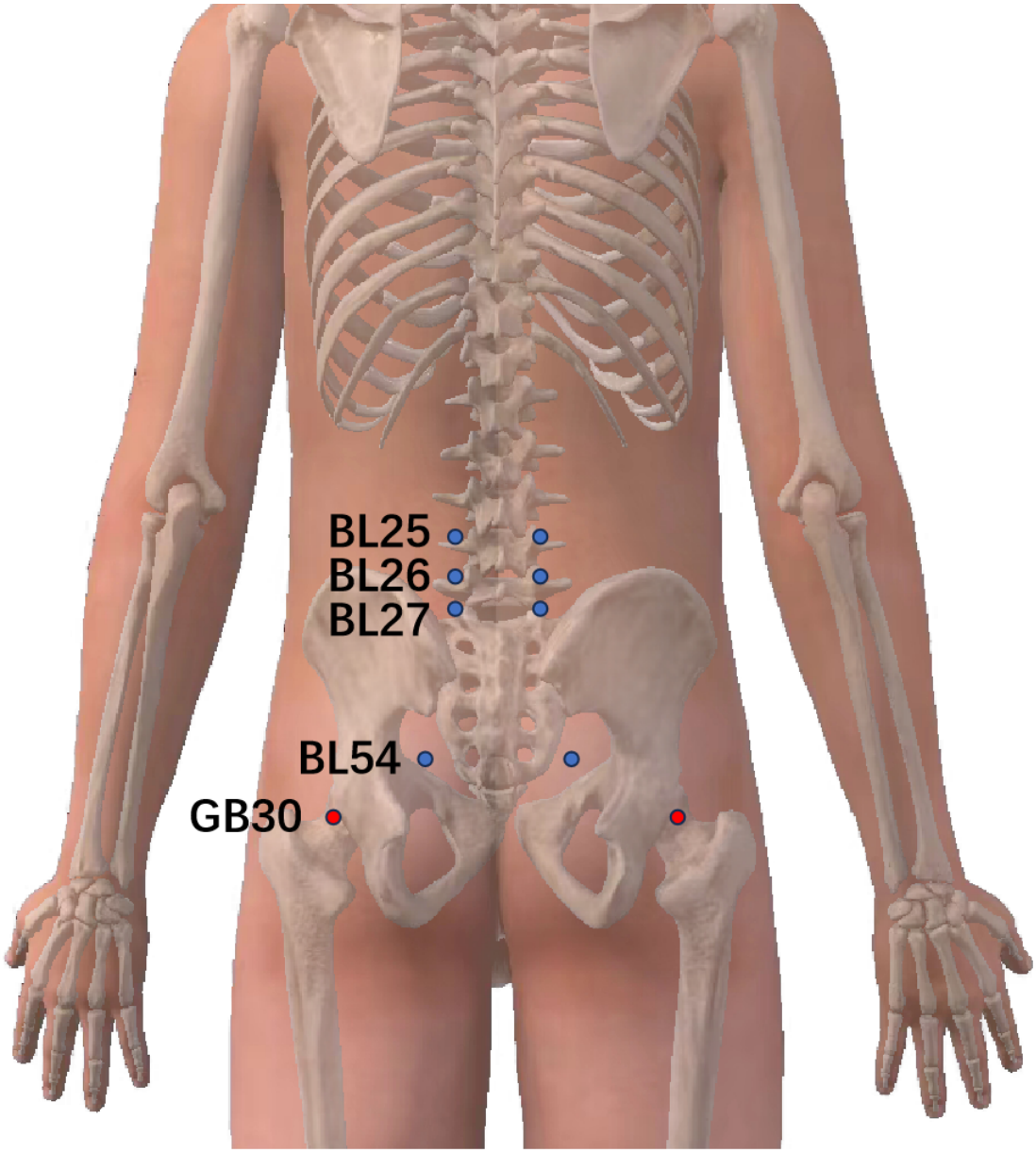

ODI Questionnaire

The ODI is a commonly used questionnaire for self-quantification of dysfunction in patients with LDH, and it has good reliability and sensitivity in patients with LDH [25]. This questionnaire consists of 10 questions. The score for each question ranges from 0 to 5. The maximum total score is 45 points. ODI score = [actual score/(5×number of actual answered questions)]×100%. The higher the score, the more severe the dysfunction.

Safety Evaluation

The investigators will assess the adverse events, defined as unexpected or adverse reactions occurring during or after treatment. In this experiment, adverse events [26] will be defined as (1) syncope, (2) ecchymosis, (3) increased pain, (4) fracture, and (5) skin allergy. The investigator will assess and solve the adverse events during the study, reporting them to the appropriate departments and ethics committees. Following that, they will monitor all the adverse events until the event resolves or the participant's condition becomes chronic or stable, and they will make every effort to ensure their safety and record the relevant information in case report forms.

Follow-Up

To evaluate the efficacy and safety of the intervention, we will follow up with the participants for 1 month after the end of the treatment. A month after the treatment ends, the results evaluator will call the participants to investigate the recurrence of their symptoms. Participants can also inform evaluators of their clinical symptoms face-to-face or via email, text message, or WeChat at the relevant timepoint.

Data Collection and Monitoring

The outcome assessors will record the detailed information in case report forms, including the evaluation of treatment effectiveness, adverse events, questionnaire data, and fMRI data. Two data administrators outside the team will use the

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Excel database for data entry and management, and these data administrators must complete rigorous training in data monitoring. To ensure the accuracy of the data, 2 data administrators will enter the information independently and proofread it, and they will enter the real-time data into the China Clinical Trial Registration Center. During the trial, the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine will review the conduct of the trial.

fMRI Data Preprocessing

First, MRIConvert 2.0 software (Lewis Center for Neuroimaging) converts the DICOM format of the fMRI images into a Neuroimaging Informatics Technology Initiative format file for data analysis. Next, we apply the default preprocessing pipeline in the Statistical Parametric Mapping–based CONN 2.0b toolbox of the MATLAB 2022b (The MathWorks, Inc) platform to preprocess all the nuclear magnetic data.

fMRI Data Processing

ALFF Analysis

The ALFF analysis will be performed using the AFNI (Analysis of Functional NeuroImages) software [27]. The fast Fourier transform transforms the filtered time series to the frequency domain (parameters: taper=0%, fast Fourier transform length=shortest) to obtain the power spectrum. Since the power of a given frequency is proportional to the square of the magnitude of this frequency component in the original time series, the square root is calculated at each frequency of the power spectrum, and the average square root ranges from 0.01 Hz to 0.08 Hz at each voxel. This average square root is considered as the ALFF.

ReHo Analysis

The Kendall coefficient of concordance is used to measure the local synchronization of the time series of its nearest neighbor voxels as [28], where W is the Kendall coefficient of concordance among given voxels, ranging from 0 to 1; Ri is the sum rank of the ith timepoint; R (n+1) K/2 is the mean of Ri; K is the number of time series within a measured cluster (K=7, 19, and 27; K=27 is used in this study); and n is the number of ranks (here n=60). The Kendall coefficient of concordance program is coded in MATLAB [29]. Thus, an individual ReHo map is generated for each data set.

FC Analysis

Differential brain regions obtained by ALFF or ReHo analysis, regions of interest, and differential brain regions will be selected, and FC will be calculated. An FC plot for each participant will be obtained by DynamicBC using the sliding window method. We will select a window length of 50 times of repeat (time of repeat: 100 seconds) with a window overlap of 98% (step size of 1 time of repeat) to calculate the FC for each participant. The FC plots for each participant will be calculated within each window to generate a series of FC plots. The coefficient of variation of the FC map is calculated to measure the temporal variability of intrinsic brain activity. Finally, the FC variability of all the participants will be transformed into standardized *z* scores to enhance the normality of the data by subtracting the mean of each voxel and dividing by the standard deviation [30].

Statistical Analysis

Statistical analysis will be conducted using SPSS 26.0 statistical software. Count data will involve the ratio of the sex and age variables compared between the 2 groups via the χ^2 test of the 4-fold table or the Fisher test. The SF-MPQ scores, PPTs, and ODI scores are the rank data. Therefore, the Mann-Whitney *U* test will be used for the intergroup comparison, and the Wilcoxon symbolic test will be applied for the intragroup comparison. Paired 2-sided *t* test will be used to assess the difference in ALFF and ReHo between the 2 groups. In addition, Pearson correlation coefficients will be used to estimate the connection between the seed region and all of the voxels within the whole brain separately based on the patients. Statistical significance will be set at $P<.05$ (2-sided).

Sample Size Calculation

There is still no consensus on sample size estimates for fMRI studies. Desmond and Glover's [31] empirical research results indicate that to achieve 80% test power at the single voxel level in magnetic resonance imaging data with a multiple comparison correction threshold of 0.05, at least 24 participants are required. We also referred to similar studies investigating neuroimaging mechanisms related to LDH and combined them with the research design for this topic [12,18]. The visual analog scale was selected as an important indicator of LDH pain level [32]. According to literature [33], patients with LDH had a score of 4.28 (SD 1.16) points after Tuina intervention and a score of 5.68 (SD 1.26) points after traction intervention. We used G*Power 3.1 software to calculate the sample size based on the mean, wherein α is .05 and power is .85. Each of the 2 groups require 30 cases. With 20% dropout, 38 cases are required for each group for a total of 72 cases.

Quality Control

Quality Control of the Evaluation Methods

Before the implementation of this study, we conducted centralized and unified training for all participants to achieve consistency in their understanding and mastery of the criteria (diagnosis, inclusion, exclusion, elimination, termination criteria, etc), the operating procedures of intervention measures, observation index collection and scoring criteria; formulation of a detailed research plan and schedule; assessment indicators; and strict and consistent implementation of the study plan.

Quality Control of the Research Participants

Before the study begins, we will provide each participant with details about the operability and precautions of the intervention method, prohibit other treatment methods during the intervention, and provide free health counseling throughout the study. With the informed consent of the participants, the corresponding test contents can be included and conducted voluntarily. If the pain fails to be relieved during the intervention, the project team must be informed in time and relevant drugs must be given if necessary; if the symptoms cannot be relieved, comprehensive treatment should be given immediately. If there is an accident or adverse event during a

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treatment event, the record form should be filled accurately, providing details such as the adverse event type, occurrence time, severity, duration, measures taken, and other reports.

Quality Control of Data Management

The case observation form should be as complete and accurate as required, avoiding random alteration. The same person should conduct the observation records of the same participant, ensure consistency between the recorded data in the computer database and the original data, and correctly select the statistical analysis method.

Quality Control of Tuina

Tuina will be performed by a physician with more than 2 years of clinical experience in Tuina therapy, who has received specialized Tuina therapy training and passed relevant tests. The physician is required to perform specific Tuina operations according to the operating instructions and maintain consistency in the Tuina operations.

Results

This trial was approved by the ethics committee of the Rehabilitation Hospital affiliated to Fujian University of Traditional Chinese Medicine (project 2024KY-008-02). This trial is in the participant recruitment and intervention phase. Participant enrollment began in May 2024, and data collection is expected to end on April 30, 2025. As of July 1, 2024, we have collected data from 21 cases. The results of this trial are expected to be submitted for publication in September 2025.

Discussion

Overview

This randomized controlled trial investigates the clinical efficacy and potential mechanism of Tuina in treating LDH. The results of this trial will be helpful in clarifying the cerebral mechanism of Tuina in the treatment of LDH. LDH occurs when the annulus fibrosus of the lumbar intervertebral disc tears, the nucleus pulposus herniates, and the dural sac and nerve root are stimulated and compressed [1]. This causes a wide range of symptoms, including low back pain, radiation pain in the lower limbs, and numbness. Pain, the primary symptom of LDH, is usually the main reason for patients to seek medical treatment [34].

Tuina is a traditional Chinese medicine treatment method based on meridian acupoint theory and modern anatomy [35]. A therapist manipulates the patient's skin, muscles, and bones with both hands, including pressing, kneading, pushing, pulling, and shaking. Tuina is widely used for the treatment of LDH in China because of its proved effectiveness in relieving pain and muscle tension and improving dysfunction [35,36]. Traction is a technique used for stretching soft tissue and separating joint surfaces or bones to achieve the treatment goal [37]. Through electrodes placed on the skin, TENS creates pulsed alternating current. This can help relieve pain by activating the central nervous system's endogenous inhibition mechanism [38-40]. The *Chinese Journal of Evidence-Based Medicine* published the "Evidence-based practice guide for nonoperative treatment of LDH" in 2024, listing Tuina, traction, and TENS as routine treatments and interventions for LDH [41].

Pain is considered to be an unpleasant and emotional feeling related to actual or potential histopathology [42]; therefore, changes in pain perception should include subjective and objective indicators. This study will use subjective SF-MPQ and ODI scores to assess changes in pain perception and dysfunction, while the objective index of tenderness threshold will demonstrate changes in pain symptoms. The combination of subjective and objective indicators can comprehensively reflect the changes in the symptoms of patients with LDH, reducing the occurrence of potential bias and improving the quality of clinical evidence.

In addition, we add neuroimaging observations based on objective indicators. Previous neuroimaging studies have shown that patients with LDH can show changes in brain structure and function. Liu et al [43] found that compared with the control group, patients with LDH had considerably longer typical path lengths in the brain network, as well as worse clustering coefficients, global efficiency, and local efficiency. Another systematic review [44] noted that in patients with LDH, the medial prefrontal cortex, cingulate cortex, amygdala, and insular lobe are more active. Pain-relief areas are less active, and the FC in pain-related areas is changed. Mei et al [45] reported that LDH may involve altered FC in several brain regions as well as decreased excitability in sensory motor areas during tasks and increased activity in the sensory-motor network during resting states. Therefore, brain structural changes and dysfunction caused by long-term pain afferent signals may be the key factors for pain associated with LDH.

Neuroimaging technology also provides an objective basis for Tuina's cerebral mechanism in treating LDH. Li et al [46] found that after receiving Tuina treatment, the hypothalamus, left nucleus accumbens, and left amygdaloid of patients with LDH were excited, while the left anterior cingulated gyrus was inhibited. Yuan et al [47] discovered that after Tuina treatment, the brain functional activity in patients with LDH was mainly inhibited and the inhibited areas were located in the right side of the prefrontal cortex and cerebellum and that Tuina has the ability to alter the default mode network's functionality in patients with LDH, which may help explain some of the intervention's analgesic effects [12]. The above findings suggest that brain function regulation may be an important factor affecting Tuina's effect on pain regulation. Therefore, we designed this study as a clinical randomized controlled trial to compare the effectiveness of Tuina with that of traction combined with TENS in patients with LDH and to investigate the cerebral mechanism of Tuina in LDH treatment by using fMRI. The results of this trial will provide a visual basis for the clinical application of Tuina in the treatment of LDH and provide a solid foundation for Tuina therapy research.

Study Limitations

In the course of operation, due to the differences in the form of treatment between Tuina and traction combined with TENS, it is impossible for participants and operators to be blinded. For this limitation, we will perform quality control on the blindness of the questionnaire and magnetic resonance imaging data

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analysis to improve the credibility of the questionnaire measurement, which is composed of outcome assessors, data administrators, and data analysts.

Conclusions

This trial aims to investigate the cerebral mechanism of Tuina in the treatment of LDH. We used TENS combined with traction as a control intervention. We expect that Tuina can relieve pain symptoms in patients with LDH and that this pain relief mechanism is related to the activation or inhibition of pain-related regions in the brain.

Acknowledgments

This trial will be supported by the National Natural Science Foundation of China (project 82174523, 82105039, 82205305), Natural Science Foundation of Fujian, China (project 2023J06037), and Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare. The funding sources played no role in the design or conduct of the trial.

Data Availability

The data sets used and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[DOC File , 197 KB - resprot_v13i1e63852_app1.doc]

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Abbreviations

AFNI: Analysis of Functional NeuroImages
ALFF: amplitude of low-frequency fluctuations
CONSORT: Consolidated Standards of Reporting Trials
dFC: dynamic functional connectivity
FC: functional connectivity
fMRI: functional magnetic resonance imaging
LDH: lumbar disc herniation
ODI: Oswestry disability index
PPT: pressure pain threshold
ReHo: regional homogeneity
SF-MPQ: Short-Form McGill Pain Questionnaire
TENS: transcutaneous electrical nerve stimulation

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Protocol

Multifaceted Intervention to Improve Graft Outcome Disparities in African American Kidney Transplants (MITIGAAT Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: The outcome disparities for African American recipients of kidney transplant is a public health issue that has plagued the field of transplant since its inception. Based on national data, African American recipients have nearly twice the risk of graft loss at 5 years after transplant, when compared with White recipients. Evidence demonstrates that medication nonadherence and high tacrolimus variability substantially impact graft outcomes and racial disparities, most notably late (>2 years) after the transplant. Nonadherence is a leading cause of graft loss. Prospective multicenter data demonstrate that one-third of all graft loss are directly attributed to nonadherence. We have spent 10 years of focused research to develop a comprehensive model explaining the predominant risk factors leading to disparities in African American kidney recipients. However, there are still gaps in patient-level data that hinder the deeper understanding of the disparities. Lack of data from the patient often lead to provider biases, which will be addressed with this intervention. Culturally competent, pharmacist-led interventions in medication therapy management will also address therapeutic inertia. Pharmacist interventions will mitigate medication access barriers as well (cost and insurance denials). Thus, this multidimensional intervention addresses patient, provider, and structural factors that drive racial disparities in African American kidney recipients.

Objective: This prospective, randomized controlled trial aimed to determine the impact of multimodal health services intervention on health outcomes disparities in African American recipients of kidney transplant. The aims of this study are to improve adherence and control of late clinical issues, which are predominant factors for racial disparities in kidney recipients, through a technology-enabled, telehealth-delivered, 4-level intervention.

Methods: The Multifaceted Intervention to Improve Graft Outcome Disparities in African American Kidney Transplants (MITIGAAT) study is a 24-month, 2-arm, single-center (Medical University of South Carolina), 1:1 randomized controlled trial involving 190 participants (95 in each arm), measuring the impact on adherence and control of late clinical issues for racial disparities in kidney recipients, through a technology-enabled, telehealth-delivered, 4-level intervention. The key clinical issues for this study include tacrolimus variability, blood pressure, and glucose control (in those with diabetes mellitus). We will also assess the impact of the intervention on health care use (hospitalizations and emergency department visits) and conduct a cost-benefit analysis. Finally, we will assess the impact of the intervention on acute rejection and graft survival rates as compared with a large contemporary national cohort.

Results: This study was funded in July 2023. Enrolled began in April 2024 and is expected to be complete in 2026. All patients will complete the study by the end of 2028.

Conclusions: In this protocol, we describe the study design, methods, aims, and outcome measures that will be used in the ongoing MITIGAAT clinical trials.

Trial Registration: ClinicalTrials.gov NCT06023615; https://www.clinicaltrials.gov/study/NCT06023615

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International Registered Report Identifier (IRRID): PRR1-10.2196/57784

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KEYWORDS

kidney transplant; mobile health; medication adherence; mHealth; nephrology; transplant surgery; postoperative monitoring; telemedicine; eHealth

Introduction

Background

Racial disparities in kidney transplants is a public health issue that has persisted for more than 50 years. As compared with White kidney recipients, African American kidney recipients have nearly twice the risk of graft loss at 5 years after transplant. Despite recent data demonstrating modest improvements in this disparity, a kidney transplanted today is still expected to function about half as long in African American people [1-3]. Marginal improvements in African American recipients are due to improved access to transplants, stemming from organ allocation policy changes and reductions in early acute rejection through a better understanding of immunological risk and the use of potent immunosuppression [4-6]. However, recent studies from our team and others demonstrate that posttransplant outcome disparities in African American people can predominately be explained by issues that arise late (≥2 years) after transplant [7-9]. These issues include late medication nonadherence leading to high tacrolimus variability and rejection and poor control of diabetes and hypertension [7-13]. In models adjusting for these late issues, the risk of graft loss in African American recipients was reduced by up to 75%, as compared with non–African American recipients. [7-11].

For the past decade, our research team has focused on improving posttransplant outcomes and reducing disparities in African American kidney recipients by developing and using mobile health (mHealth) and telehealth interventions [14-20]. Our mHealth app and intervention are founded on the self-determination theory and are designed to improve patient autonomy, competence, and relatedness [21-23]. This is coupled with the use of pharmacist-led motivational interviewing (MI) delivered during televisits, which is designed to improve care and identify and address barriers preventing optimal adherence and comorbidity management, including medication costs [24-27]. Our mHealth-based telehealth intervention improves access to care through remote patient monitoring and medication therapy management, addressing structural barriers, racial bias, and therapeutic inertia that induce disparities [28-30]. Through robust preliminary research, we developed, refined, and tested the functionality, acceptance, and durability of our intervention [14-17]. We completed a 60-patient (39/60, 65% African American) pilot study (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] K23DK099440), demonstrating significant improvements in the control of diabetes and hypertension through our mHealth intervention; improvements in hypertension control were more substantial in African American recipients [16]. In 2020, we completed a 12-month randomized controlled trial (RCT; Agency for Healthcare Research and Quality [AHRQ] R18HS023754) in 136 patients (87/136, 64% African American) that used our mHealth, remote patient monitoring, pharmacist-led telehealth intervention to improve medication adherence and reduce hospital readmissions and costs by over 40% [14,20]. These 2 clinical trials demonstrated that our intervention is highly accepted in African American people; 55% of our kidney transplant population is African American, while 65% (88/136) of study participants were African American. Dropout rates were 3% [16,20]. An economic analysis demonstrated that the intervention provided a net cost savings of US $368,839 through reduced hospitalizations and had a return of investment of US $4.30 for every dollar spent [31].

Objectives

The next clear step in our research trajectory is to conduct a long-term, large-scale study and assess whether this 4-component health services intervention can improve health outcome disparities in African American recipients of kidney transplant. Thus, we propose an RCT to use this system to deliberately address posttransplant disparities in African American people entitled the “Multifaceted Intervention to Improve Graft Outcome Disparities in African American Kidney Transplants (MITIGAAT)” study. The overarching hypothesis for the MITIGAAT study is that late nonadherence and suboptimal control of diabetes and hypertension are more common in African American recipients of kidney transplant and are major contributors to health disparities. A multimodal intervention that addresses these issues will significantly reduce health care disparities among African American recipients of kidney transplant.

Methods

Study Design

This is a single-center, 24-month, 2-arm, 1:1 RCT involving 190 participants (95 in each arm), with roughly 55% (100 participants) being African American. All patients will be recruited from the Medical University of South Carolina (MUSC), in Charleston, South Carolina (ClinicalTrial.gov NCT06023615). This study was funded by the National Institute of Health’s (NIH) NIDDK. We will also conduct a retrospective longitudinal cohort study, comparing a large contemporary national cohort of adult veteran kidney recipients transplanted between 2015 and 2021 with our RCT intervention arm. This study meets all guidelines set by ClinicalTrials.gov and has been approved by the local Institutional Review Board. The statistician conducting the analyses will be blinded to the treatment arm (semiblind). The randomization will occur through computer-generated random numbers, with no stratification, in blocks of 10. REDCap (Research Electronic Data Capture; Vanderbilt University) will be used for

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computerized randomization and arm assignment, which will be done by a study team member.

Aims

The primary outcome of this study is to determine the impact of multilevel health services intervention on achieving improved adherence to tacrolimus. In addition, we will determine the impact of multilevel health services intervention on blood pressure (BP) and glucose control (in those with diabetes). We will conduct a cost-benefit analysis, assessing the estimated costs of hospitalizations and emergency department (ED) visits compared with the cost to deliver interventions. Finally, we will track the incidence of acute rejection, graft loss, and death in the intervention patients; compare our data with a large national cohort of veteran patients of kidney transplant; and assess for racial disparities for these health outcomes. We will enroll both African American and non–African American people to allow us to directly compare these groups across treatment arms to assess disparities.

Recruitment, Screening, and Enrollment Procedures

Patients will be recruited from the MUSC kidney transplant roster. Adult (≥18 years old at the time of transplant) recipients of kidney transplant having a posttransplant period of more than 2 years who meet the eligibility criteria will be approached by researchers for consideration of participation. After discussing the details of the study, providing time, and gaining informed consent, patients will be randomized in a 1:1 fashion (blocks of 10) to either the enhanced control group (usual care and attention control) or the intervention group (usual care and 4-level intervention [Table 1]). For the aim-4 cohort study, we will include all adult solitary kidney recipients transplanted between 2015 and 2021, with more than 2 years of follow-up, to match the RCT. Complete discussion of this follow-up cohort study is beyond the scope of this RCT methodology paper.

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Table 1. Overview of the objectives for each visit at each timepoint.

Months and telehealth visit number	Techniques used and topics covered
1-2	
1	Teach patient how to use app, home BP[a], and glucometer
2	Review technology with patient, troubleshoot any issues
3-4	
3	Using MI[b], discuss current control of hypertension and barriers to optimal control
4	Educate on importance of hypertension control and implement strategies to improve self-monitoring and management
5-6	
5	Using MI, discuss current control of DM[c] and barriers to optimal control
6	Educate on importance of DM control and implement strategies to improve self-monitoring and management
7-8	
7	Using MI, discuss current control of anemia and barriers to optimal control
8	Educate on importance of anemia control and implement strategies to improve management
9-10	
9	Using MI, discuss adherence to immunosuppression and barriers to optimal adherence
10	Educate on importance of medication adherence and implement strategies to optimize adherence
11-12	
11	Educate importance of staying active and implement strategies to improve staying active and exercising
12	Educate importance of smart dietary choices and implement strategies to choose wisely
13-14	
13	Review current hypertension control and using MI, identify barriers to optimal control
14	Implement additional strategies to improve hypertension control
15-16	
15	Review current DM control and using MI, identify barriers to optimal control
16	Implement additional strategies to improve DM control
17-18	
17	Review current anemia control and using MI, identify barriers to optimal control
18	Implement additional strategies to improve anemia control
19-20	
19	Review medication adherence and implement strategies to improve if not optimal
21-22	
20	Discuss any ongoing issues with patient precluding optimal management of comorbidities and adherence
23-24	
21	Study close-out session. Conduct surveys and implement plan for continued engagement

[a]BP: blood pressure.

[b]MI: motivational interviewing.

[c]DM: diabetes mellitus.

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Eligibility

Inclusion

Participants must be adult (≥18 years of age at the time of enrollment) recipients of kidney transplant at least 2 years after their kidney transplant.

Exclusion

We will exclude patients who are recipients of multiorgan transplants or those patients who received a transplant of an organ that is not a kidney (liver, lung, heart, intestine, pancreas, and bone marrow). Any patients who are not capable of measuring their own BP and glucose (if applicable); using mHealth apps after adequate training; and speaking, reading, and hearing English will be excluded.

Data Capture and Management

Data capture will be accomplished using electronic extraction, manual chart abstraction, and through direct patient interviews (when necessary) by a study coordinator. Data will be collected by conducting a thorough review of the patient's medical records with patient phone calls at 3-month intervals. Data collection will include all baseline donor or recipient demographics and transplant characteristics as well as medications, laboratory data, pathology, and clinical events that occur during the study. Data will also be captured through the web-based portal and linked to abstracted data within the research database. The REDCap system will be used for data management. REDCap is a secure, web-based application designed exclusively to support data capture for research studies, which we have used in our previous clinical trials. REDCap provides (1) an intuitive interface for data entry (with data validation); (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages (SPSS [IBM], SAS [SAS Institute], Stata [StataCorp], and R [R Development Core Team]); (4) procedures for importing data from external sources; and (5) advanced features, such as branching logic and calculated fields.

Sample Size and Power

This study is powered to detect clinically meaningful and statistically significant improvements in medication adherence (aim 1), systolic BP (SBP) control (aim 2), diabetes mellitus (DM) control (aim 3), and graft survival (aim 4) while also demonstrating significant reductions in African American disparities for these end points (overarching aim). The analyses take full advantage of all measurements captured during the entire 2-year study using repeated measures methodology. For tacrolimus variability (aim 1), there will be 9 assessments (baseline and every 3 months), aligning with when laboratories are measured. Over the 2-year study, a 5% trajectory difference between arms for tacrolimus variability is considered clinically meaningful and is feasibly achievable given our pilot data (time×treatment). Tacrolimus concentration coefficient of variation (tac CV) has an expected SD of 8.5 with an approximate Gaussian distribution; thus, meeting normality assumptions. A sample size of 87 per group (N=174) achieves >0.999 power, assuming both arms start with a tac CV of 35% and change over the 2-year study to 32% in the control arm and 27% in the treatment arm. The study is powered at 0.800 to specifically test for reductions in racial disparities between the intervention and control arms, using a 3-way interaction term in the model (time×treatment×race). For BP and glucose control (aim 2), we will capture all home- and ambulatory-based measures aggregated into monthly assessments, totaling 25 (baseline and once monthly for 24 periods). We have 0.998 power to detect a difference in SBP changes between arms, assuming a mean SBP of 135 mm Hg in both arms at baseline and a 5 mm Hg reduction in the treatment arm, using 25 repeated measures (monthly). SBP has an expected SD of 9 with a Gaussian distribution; thus, meeting normality assumptions. We have 0.800 power to test for reductions in racial disparities between the arms for SBP, using the time×treatment×race 3-way interaction term. We have 0.998 power to detect a difference between arms for glucose changes, assuming a mean baseline glucose of 160 mg/dL in both arms, 50% (87/174) of patients having DM at the time of randomization, and a trajectory difference in glucose of 24 mg/dL between arms (25 repeated measures). We have 0.803 power to test for significant reductions in racial disparities between the 2 arms for glucose control, modeled using the time×treatment×race interaction term. Mean glucose has an expected SD of 10.8 and distribution approximates Gaussian; thus, meeting normality assumptions. To account for dropouts and censoring events, we will increase each arm sample size to 95, totaling 190 participants. This is an inflation of approximately 10%, which is significantly above the expected totals for dropouts (estimated to be between 2% and 3%), and power reductions due to censoring events.

For aim 4, this study has adequate power to detect a statistically significant difference between the intervention arm and the national contemporary Veterans Affairs (VA) cohort for graft survival. Based on our previous research using the national VA database, we expect to identify roughly 8500 kidney transplants from the VA transplanted between 2015 and 2021, representing a contemporary cohort (33% of which are expected to be African American). Annual graft loss attrition rates are expected to be 5% in the VA cohort (with a mean of 7-year follow-up time) and 3% in the RCT treatment arm (with 2-year follow-up time). Given these, we will have 0.780 power to detect a significant difference in graft survival between the VA national cohort and our intervention patients. To assess if the intervention reduced racial disparities in graft loss, we would compare the African American persons in the RCT treatment arm to the roughly 2800 African American persons in the national VA cohort. We expect annual graft attrition rates to be 7% in the VA cohort (7-year mean follow-up) and 4% in the treatment arm (2-year follow-up). Given these estimates, we have 0.812 power to assess if the treatment intervention significantly reduced racial disparities for graft survival, as compared with the national contemporary VA cohort. These power analyses are valid across different data distribution assumptions (Gaussian and log-transformed). Power analyses were conducted using SAS 9.4 (SAS Proc GLMPower for aims 1-2; SAS Proc Power; two-sample survival test=log rank for aim 4; [SAS Institute]).

Intervention

Patients randomized to the intervention arm will be provided the same usual care as the control group. In addition, these participants will receive comprehensive supplemental remote

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monitoring and follow-up by using our smartphone-enabled mHealth app and dashboard, integrated with home-based monitoring of BPs and glucoses, and pharmacist-led scheduled televisits Figure 1. Participants in this group will be provided with a smartphone and data plan if they are not current owners of a device that is compatible with the mHealth app (iOS [Apple Inc] or Android [Google]). All will also be provided with a Bluetooth-enabled, automated, cuff-style bicep home BP monitor. Those with diabetes will be provided a Bluetooth-enabled glucometer with testing supplies. On the mobile device, our mHealth app will be installed which displays the patient's medication list and alerts them when it is time to take each medication, requiring them to respond by a push button when they have taken the specified medications, providing a time stamp of intake as part of a multi-method adherence tracking system [14]. The intervention will include pharmacist-led telemonitoring of patient adherence to medications, appointments, BP measures, glucose readings in DMs, and electronic health record (EHR) information (tacrolimus variability, appointments, and insurance status) and 21 scheduled telehealth visits with patients that cover specific topics.

Figure 1. Flow of study procedures.

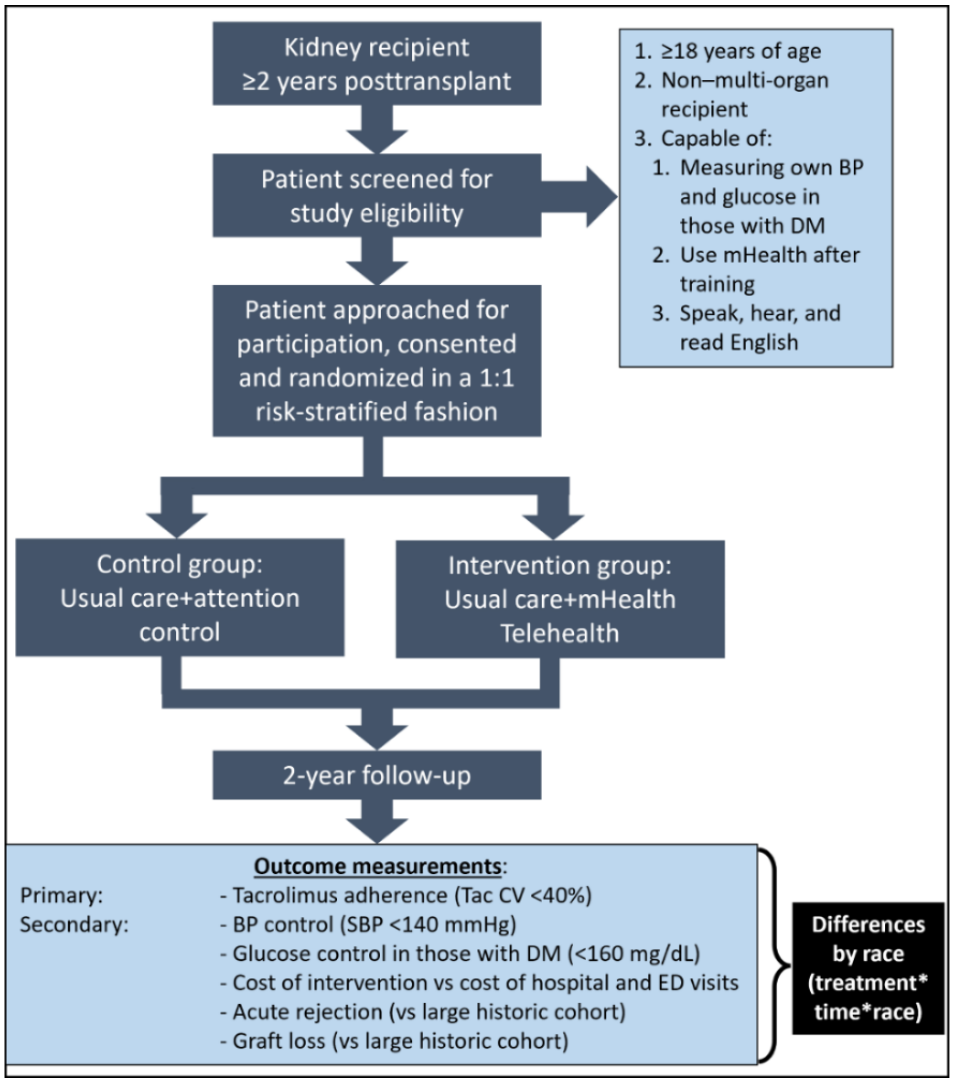

Telehealth Visits, Activities, and Schedule

We have a detailed plan that we developed from previous work, which we will use for televisits in this study [14,20]. The pharmacists will first introduce themselves and provide a synopsis regarding the call rationale. Following this, they will conduct medication reconciliation, discuss lifestyle and diet, and review home measures to determine causes of suboptimal adherence and BP and DM control, if applicable. MI will be used to develop and implement a patient-centered plan to address identified issues leading to suboptimal control of BP, DM, and medication nonadherence. The MI follows a six-step process: (1) establishing rapport; (2) assessing knowledge, health literacy, motivation, and confidence; (3) defining barriers, concerns, and positive self-motivational statements about their behaviors; (4) summarizing "pros" and "cons" of proposed interventions to address behaviors; (5) providing options to help with adherence; and (6) giving a summary of the session, having the patient repeat back key details. During calls, the pharmacist will implement agreed-upon changes to medications and monitoring plans. This process was purposely developed so that it can be entirely conducted during televisits [24-27]. Each televisit will have a predominant theme, such as BP management, DM management, adherence, lifestyle, etc. During these 21 visits

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(Table 1), we will consistently use MI to better understand patient's ambivalence toward specific issues and their intrinsic motivations and values to resolve these self-contradictory factors. Culturally competent MI will be used to work collaboratively toward goals and as a means toward improved overall well-being and health. MI is well-known to our investigator team, as we have used these in our formative research and demonstrated successful outcomes [14,16,20]. The already developed and tested mHealth and remote monitoring dashboard are supplemental technology-enabled tools that will help reinforce the telehealth sessions and provide the patient and the team with objective comprehensive data to gauge successes and continued barriers. All encounters will be documented in the EHR [14,20]. As this intervention is intense, we will also track and report back intervention delivery fidelity, call adherence, and dropout rates.

Smartphone mHealth App

Through an iterative, patient-centered process, we developed, tested, and validated an mHealth app that will be used within this study [14-18]. This app was used for a recently completed RCT demonstrating efficacy in reducing medication errors and improving adherence (NCT03247322) [20]. The app performed well and the feedback from enrollees is that it was well received and is useful to help with medication adherence and comorbidity self-monitoring and regulation [20]. A brief description of the app and function is further described. After a patient logs into the app using a HIPAA (Health Insurance Portability and Accountability Act)–compliant PIN (personal identification number), they are taken to their home screen. From here, they can record and review medications, BPs, glucoses, and medication side effects. They can also directly call the transplant center, study coordinator, or pharmacy for refills and send real-time email alerts to the clinician if they need to document a medication change, a visit to the ED, or admission to the hospital. When the patient taps the medications button, they can review their complete medication list, which is automatically updated from the EHR. Patients can review their medication regimen scheduled times and select which medications they are taking to document adherence. If the patient wants to document medication side effects, they tap the "Side Effects?" button, which brings them to the survey to document the incidence and severity of side effects. To review and automatically upload (using Bluetooth) BPs and blood glucoses, the patient taps the appropriate button, which brings them to the BP or glucose page. The data from Bluetooth-connected home monitoring is automatically synced to the mHealth app, encrypted, and transmitted to the web-based portal. The mHealth app also provides several important and timely push notifications to patients, including when it is time to take their medications, check their BP or glucose, and take a survey. The push notifications have a snooze function as well (every 30 minutes, up to 3 snoozes). The app provides daily individualized motivational text messages to patients, based on the self-determination theory and a comprehensive survey the patient completes at initiation [18]. These messages are automated based on how well the patient is adhering to the medication regimen and monitoring. We will enhance the app by making it compatible on Android (currently only on iOS), improve the medication data from the EHR to make it real-time (currently on an overnight delay), and add surveys.

Remote Monitoring Dashboard

We will also use a web-based dashboard portal that was developed as part of the aforementioned RCT [20]. The system curates data from the EHR and app and presents it in summary form on a single screen, where the clinician user can efficiently review patients (each row is a single patient), sort relevant measures (each column), and identify and triage at-risk patients. Each patient row is color-coded based on risk factors. Blue demonstrates a patient with all measures within goal, yellow demonstrates a patient with 1 measure out of range, while red indicates 2 or more measures outside targets. The thresholds for out-of-range values were set based on validated levels from previous research [7-9,11]. From this portal, the clinician can also edit patient contact information, change the passwords or login credentials for the app, update the medication regimen timing, update the timing of notifications to check home measurements, and directly text patients. Several different reporting capabilities are available through the system; reports display trends in BPs, glucoses, and medication adherence. These data can be downloaded as raw values into a spreadsheet and shared with patients or outside providers.

Enhanced Usual Care Control Arm

The standard care that is provided to all kidney transplant recipients will continue to be provided to both arms in this study. The structure and processes involved within this care model are well established, as evidenced by our institution's ranking among the top-performing US transplant centers for length of stay, readmissions, and outcomes. Our kidney program was bestowed the American Society of Health-System Pharmacists Foundation Award for Excellence in Medication-Use Safety for demonstrating improvements in outcomes through a pharmacist-led, comprehensive multidisciplinary quality improvement initiative. As part of this initiative, specific protocols, which delineate immunosuppressant regimens, laboratory evaluations and timing, follow-up clinic schedules, and the treatment of comorbidities (hypertension, diabetes, and hyperlipidemia), will continue to be used. During the long-term ambulatory care phase, patients are followed with serial laboratories and clinic visits as follows. From months 6 to 12 after transplant, patients have laboratories every month with clinic visits every 3 months. From year 1 to 3 after transplant, patients are seen every 6 months with laboratories every 2 to 3 months. After year 3, patients are seen annually with laboratories every 3 months. For the enhanced usual care arm, to ensure we have home BP and glucose measure results to compare between arms, patients will be given access to the app to use in a passive mode, meaning that data will be collected, but no interventions will be delivered. Within this usual care arm, no alerts or alarms will be set within the app. If a patient does not have a compatible smartphone and data plan, one will be provided. All will be provided a Bluetooth-enabled BP device and glucometer (for DMs) and supplies. To minimize attention control bias, we will provide enhanced attention control as participants in the control group will receive SMS text messages every 7 days on general health-related topics. These SMS text messages include healthy

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lifestyle tips related to physical activity, dietary intake, nonexposure to first- or second-hand smoke, and limited alcohol intake.

Safety Monitoring

The data safety monitoring plan (DSMP) will include the use of a safety officer and the MUSC Institutional Review Board to monitor study-related safety, clinical outcomes, and potential adverse events. In addition, the DSMP will use the study statistician to review the data generated by the MITIGAAT study, ensure data integrity, and assess the potential for futility. Summaries of adverse event reports and safety concerns raised by the safety officer will be made to the NIH in yearly progress reports unless the nature of a particular event is such that it bears reporting to the NIH immediately. The designated safety officer for the MITIGAAT study is a well-experienced transplant physician who is not directly involved in the intervention component of the study. The designated statistician responsible for data oversight and creating the reports needed for the DSMP meetings is an experienced biostatistician with knowledge in monitoring clinical research data integrity. Both the safety officer and the biostatistician will coordinate data review and analysis and communicate with the study principal investigator and the coinvestigators. The functions of the designated safety officer are to (1) provide scientific oversight, (2) review all serious adverse effects or complications related to the study, (3) monitor accrual, (4) review summary reports relating to compliance with protocol requirements, and (5) provide advice on resource allocation.

Ethical Considerations

This study was submitted to the MUSC Institutional Review Board (IRB) for a full board review. The IRB reviewed and approved the protocol and reviewed consent forms to ensured protection of patient privacy and safety. The study was approved on April 18, 2023, under ID Pro00127666. Potential participants provide informed consent before participation and can opt out at any time. In order to protect participants against any risk regarding loss of personal information, all obligations under the HIPPA will be met. Any data or information shared for dissemination will be deidentified and the confidentiality of all participants will be strictly maintained. The only persons with access to protected health information will include study investigators, research coordinators, and those approved by the IRB of record. All data will be secured on university servers, behind firewalls, with passwords protecting entry in these systems. All protected health information will be obtained and managed in accordance with the HIPAA Privacy Rule (45 CFR Parts 160 and 164).

All participants will be compensated US $120 for their data use.

Statistical Analysis Plan

For the primary outcome (aim 1, tacrolimus variability), repeated measures analyses will be conducted using generalized linear mixed modeling (GLMM). We will assess for tac CV distribution and use the appropriate link function and data transformation, if necessary, to ensure model assumptions are not violated. GLMM is the ideal model to use for this clinical trial as it provides robust estimates, takes full advantage of longitudinal data captured during the entire 2-year study, and accounts for a wide array of continuous data distribution types (eg, Gaussian, log-normal, exponential, and gamma) and discrete data distribution types for secondary outcomes (eg, Poisson, binomial, and negative binomial). Assessments for tacrolimus variability will be made every 3 months, aligning with when laboratories are typically drawn. For treatment effect estimates, both unadjusted (raw) and multivariable adjusted modeling will be conducted in an iterative manner. The time×treatment interaction term will serve as the primary measure of efficacy, which estimates the longitudinal trajectory difference between arms over the entire 2-year study. A time×treatment×race 3-way interaction term will be used to assess for changes in racial disparities, as this term estimates if the longitudinal trajectory changes between arms differ by race. Statistical significance for this term indicates that the treatment effect significantly differs by race (African American vs non–African American).

For secondary outcomes, which include BP and glucose (in those with diabetes), data will be aggregated into 25 repeated measure assessments (baseline and monthly for 2-year study). GLMM methodology will also be used for these outcome analyses. The primary efficacy measure for all secondary outcomes will be the time×treatment interaction term estimates (measure of difference in the slope between arms) from GLMM models. To specifically test for the impact of the intervention on racial disparities, the 3-way (time×treatment×race) interaction term will again be used. For both the primary and secondary outcomes, graft loss and death will be considered censoring events, and analyses will include patient data accrued up until these events occurred. To assess for differences in infection rates by treatment arm and race, Poisson or negative binomial modeling will be conducted. Model estimates for rate ratios and 95% CI will be reported. Acute rejection, graft loss, and death will be reported using Kaplan-Meier survival curves and compared using the Log Rank test. Multivariable modeling will be used to adjust for confounders, using frailty Cox regression analysis. Hazard ratios and 95% CIs will be reported. The proportional hazards assumption is tested using Schoenfeld residual plots, log (−log) plots, and *ASSESS PH* in SAS.

Missing Data Assessment

Given we are capturing a large amount of patient-generated data, missingness may be an issue and we have devised a comprehensive plan to assess and address this. First, we will have all patients in both arms use a smartphone enabled with our mHealth app to capture and automatically send home-based, patient-generated data (BPs, glucoses, and adherence). If the patient fails to send this data, the study coordinator will reach out to the patient and facilitate capture. Second, we will use the study coordinator to conduct manual chart abstraction to reduce missing data for key baseline variables and outcomes (graft loss, death, and acute rejection). Following this, if missing data for any variable is >5%, we will conduct multiple imputation and maximum likelihood methods to address missingness. We will use fully conditional multiple imputation regression, with 20 imputations for each missing value. For outcome assessments in all aims, both unadjusted and adjusted modeling will be performed on each imputation and *PROC MIANALYZE* will be used for pooling model outputs to obtain estimates, 95% CIs,

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and *P* values. We will compare estimates generated from complete-case and multiple imputation analysis. To assess for missing not at random, we will implement sensitivity analysis using the missing not at random tool of *PROC* multiple imputation. We will report both sets of results (complete case and imputation results) in papers with implications addressed in the discussion [32].

Outcomes and Definitions

The aims of this study are to improve adherence and control of late clinical issues that are predominant factors for racial disparities in kidney recipients, through a technology-enabled, telehealth-delivered, 4-level intervention. The key clinical issues for this study include tacrolimus variability, BP, and glucose control (in those with DM). We will also assess the impact on the intervention on health care use (hospitalizations and ED visits) and conduct a cost-benefit analysis. Finally, we will assess the impact of the intervention on acute rejection and graft survival rates versus a large contemporary national cohort. The study design and intervention were developed using our formative research, providing insights into interventions that change behaviors, improve access, and address provider bias and structural racism, while being highly acceptable to patients [7-9,11-21].

Study End Points

Primary Outcome, Aim 1: Tacrolimus Variability

It is defined as the intrapatient tac CV; SD divided by the mean for each patient. All outpatient true trough tacrolimus levels drawn will be used to calculate the tac CV. We will assess every 3 months, which aligns with the minimum laboratory draw schedule for recipients of kidney transplant at out center. This is the sole primary outcome and will be analyzed using repeated measures methodology, estimating efficacy effect size using the time×treatment interaction term and disparity using the time×treatment×race interaction term.

Secondary Outcome, Aim 1

Time in Therapeutic Range

Time in therapeutic range (TITR) is defined as the proportion of time the tacrolimus levels for a given patient are within desired therapeutic range, typically 6-10 mg/mL. Goal ranges may vary by patient but is well documented in the medical record. TITR will be calculated using a modified version of the linear extrapolation Rosendaal method, as proposed by Reiffel [33]. All outpatient trough tacrolimus levels will be used to calculate the TITR. We will aggregate these and assess every 3 months; analyzing using repeated measures.

Medication Adherence Survey

It is defined based on a self-reported questionnaire administered to patients in both arms through the app every 3 months (9 total, including baseline). The Identification of Medication Adherence Barriers Questionnaire (IMAB-Q)-10 will be used; it is a validated, easy to administer, 10-question instrument. A score of <20 (range 10 to 50) indicates medication adherence.

Secondary Outcome, Aim 2

BP Assessments

It is defined as the mean of all SBPs checked by patients at home and the transplant center (ambulatory measures). Patients with a mean of SBP ≤140 mm Hg will be considered controlled. All patients will use the same home-based device for these measures and be taught proper techniques.

Glucose Assessments

This will only be assessed in those with a diagnosis of diabetes, estimated to be in more than 50% of the study population. Glucose control will be defined as the mean measure of all glucoses (random or fasting). Only those with diabetes will be included in this outcome. Those with DM and a mean random glucose ≤160 mg/dL will be considered as controlled. All patients will use the same meter and strips for these measures.

Secondary Outcome, Aim 3

Health Care Use

It is defined as any hospitalization or ED visit that occurs during the study period. Assessments will be analyzed using count data modeled using Poisson or negative binomial link. Total length of stay will also be assessed.

Hospitalizations

It is defined as any admission to a hospital with at least 1 overnight stay. Hospitalizations that occur outside the study institution will be gathered at the end of the study by querying the South Carolina Revenue and Fiscal Affairs Office, which tracks all hospitalizations for South Carolinians, regardless of payer.

ED Visits

It is defined as any visit to the ED with a documented encounter during the study period. ED visits that occur outside the study institution will be gathered at the end of the study by querying the South Carolina Revenue and Fiscal Affairs Office, which tracks all ED visits.

Aim 4

Acute Rejection

It is defined as a renal allograft biopsy showing at least grade 1A rejection by Banff criteria [34,35]. As per usual care practices, all patients are required to have biopsy confirmation of rejection episodes within 24 hours of onset of treatment for acute rejection. It is standard care that all kidney allograft biopsies performed for recipients of transplant occur at the transplant center (study institution). Biopsies will be read by a blinded local pathologist, as usual care. This will be assessed using time to event analyses.

Graft Failure and Death

Graft failure will be defined as return to chronic dialysis, nephrectomy, retransplant, or death. The timing and cause of each graft loss will be recorded for comparative analysis. Patient death will also be captured, with timing and cause. These will be analyzed using time to event methodology. For primary and secondary outcomes, graft loss and death will be considered

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censoring events; data accrued until these events will be used in analyses.

Results

This study was funded in July 2023. The first patient was enrolled in April 2024, and the study is 25% (49/190) enrolled. We expect to complete enrollment in 2026. All patients will complete the study by the end of 2028, and results can be expected shortly after.

Discussion

We propose an RCT to use this system to deliberately address posttransplant disparities in African American people, entitled the MITIGAAT study. The overarching hypothesis for the MITIGAAT study is that late nonadherence and suboptimal control of diabetes and hypertension are more common in African American kidney recipients and are major contributors to health disparities. A multimodal intervention that addresses these issues should significantly reduce health care disparities among African American recipients of kidney transplant.

Conflicts of Interest

DT has received research grants from Veloxis Pharmaceuticals, Inc; Merck; Sharp & Dohme; Takeda Pharmaceuticals U.S.A., Inc; and CareDx, Inc.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
BP: blood pressure
DM: diabetes mellitus
DSMP: data safety monitoring plan
ED: emergency department
EHR: electronic health record
GLMM: generalized linear mixed modeling
HIPAA: Health Insurance Portability and Accountability Act
IMAB-Q: Identification of Medication Adherence Barriers Questionnaire
IRB: Institutional Review Board
mHealth: mobile health
MI: motivational interviewing
MITIGAAT: Multifaceted Intervention to Improve Graft Outcome Disparities in African American Kidney Transplants
MUSC: Medical University of South Carolina
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIH: National Institute of Health
PIN: personal identification number
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SBP: systolic blood pressure
tac CV: tacrolimus concentration coefficient of variation
TITR: time in therapeutic range
VA: Veterans Affairs

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Protocol

The Evaluation of a Web-Based Intervention (Deprexis) to Decrease Depression and Restore Functioning in Veterans: Protocol for a Randomized Controlled Trial

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Abstract

Background: Depressive symptoms are common in veterans, and the presence of these symptoms increases disability as well as suicidal thoughts and behaviors. However, there is evidence that these symptoms often go untreated. Intervening before symptoms become severe and entrenched is related to better long-term outcomes, including improved functioning and less disease chronicity. Computer-delivered interventions may be especially appropriate for those veterans with mild to moderate depressive symptoms, because these interventions can require fewer resources and have lower barriers to access and thus have potential for wider reach. Despite this potential, there is a dearth of research examining computerized interventions for depressive symptoms in veteran samples.

Objective: The aim of this study is to evaluate the efficacy of Deprexis (GAIA AG), a computerized intervention for depressive symptoms and related functional impairment.

Methods: Veterans will be recruited through the US Department of Veterans Affairs electronic medical record and through primary care and specialty clinics. First, qualitative interviews will be completed with a small subset of veterans (n=16-20) to assess the acceptability of treatment procedures. Next, veterans (n=132) with mild to moderate depressive symptoms will be randomly assigned to the fully automated Deprexis intervention or a treatment-as-usual control group. The primary outcomes will be self-reported depressive symptoms and various dimensions of psychosocial functioning.

Results: This project was funded in May 2024, and data collection will be conducted between October 2024 and April 2029. Overall, 4 participants have been recruited as of the submission of the manuscript, and data analysis is expected in June 2029, with initial results expected in November 2029.

Conclusions: This study will provide initial evidence for the efficacy of self-guided, computerized interventions for depressive symptoms and functional impairment in veterans. If effective, these types of interventions could improve veteran access to low-resource psychosocial treatments.

Trial Registration: ClinicalTrials.gov NCT06217198; https://www.clinicaltrials.gov/study/NCT06217198

International Registered Report Identifier (IRRID): PRR1-10.2196/59119

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KEYWORDS

depression; eHealth; mental health; randomized controlled trial; RCT; mobile phone

Introduction

Background and Rationale

Depression is the leading cause of disability worldwide [1], and those diagnosed with major depressive disorder (MDD) are up to 7.6 times more likely to die by suicide compared to the general population [2]. Depressive symptoms are associated with severe and chronic impairment in occupational and social domains [3], decreased quality of life [4], and adverse physical health outcomes [5]. Depression is a significant problem for US military veterans, with 13% of post-9/11 war veterans meeting criteria for current MDD [6] and 46.5% of female veterans and 36.3% of male veterans meeting criteria for lifetime MDD [7]. The high prevalence of depressive symptoms in veterans not only has negative ramifications for social and interpersonal functioning, occupational participation, and quality of life [8] but also markedly increases the risk for suicide. On average, 543 veterans die by suicide each month [9], and MDD is the second most important predictor of veteran suicide among all recorded mental health diagnoses [10]. Depressive comorbidity among veterans with posttraumatic stress disorder (PTSD) compared to PTSD alone is also associated with elevated rates of disability in cognitive (Cohen *d*=1.03) and mental health (Cohen *d*=1.49) domains. Veterans with comorbid PTSD and MDD also reported decreases in quality of life (Cohen *d*=0.84) and a 2-fold risk of suicide compared to those with PTSD alone [11]. Given the functional impairments and elevated suicidal risk associated with depressive symptoms, it is essential to provide veterans with timely and appropriate intervention.

Addressing depression before the symptoms become severe and entrenched could substantially improve outcomes. Even mild to moderate and subthreshold depressive symptoms are associated with significant disease burden, including increases in disability and mortality and decreases in quality of life [12]. The rates of transition to MDD for individuals with subthreshold depressive symptoms are exceedingly high both in the short term [13] and long term [14]. When subthreshold symptoms progress to MDD, symptoms become chronic in the vast majority of cases, with 85% of individuals with MDD experiencing recurrent episodes even after receiving specialty mental health treatment [15]. Evidence suggests that interventions targeted at individuals with mild to moderate symptoms, including those with subthreshold symptoms of MDD, are effective in restoring functioning and preventing the progression to severe disease [16].

Although depressive symptoms often go undetected at mild to moderate or subthreshold levels in community settings [17], depression symptom screenings are routinely performed on a population level at US Department of Veterans Affairs (VA) facilities. This provides a key opportunity to identify veterans with depressive symptoms, even before these symptoms reach the diagnostic threshold, allowing for rapid and high-quality intervention. Patient preference studies indicate that individuals with depressive symptoms prefer to receive psychotherapy over medication [18]. Although the VA has made significant strides in improving access to psychotherapy, including through the expansion of primary care–mental health integration [19], many veterans still struggle to access adequate psychotherapy. Research shows that the majority of veterans (61%) with diagnosed mental health disorders only attend 1 session of psychotherapy [20]. Shame and stigma around depressive symptoms and seeking mental health treatment, as well as difficulties attending mental health treatments due to a lack of time or transportation, are known barriers to adequate and timely intervention and care [21]. Although the expansion of virtual mental health care (ie, telehealth) within VA facilities is effective at overcoming certain logistical barriers to treatment, telehealth is as resource intensive as traditional face-to-face psychotherapy, and access is dependent on provider availability. Furthermore, VA telehealth services might be less appropriate for individuals with mild to moderate symptoms, whose symptom severity level might not merit individual psychotherapy, but who would nonetheless benefit from help. Thus, despite increased detection of depressive symptoms and an identified need for intervention, a significant treatment gap exists.

Internet-delivered interventions are well positioned to fill this treatment gap because these interventions are low cost, easily accessible, and scalable. When compared to telehealth or traditional face-to-face mental health care, internet-delivered interventions could alleviate veterans' stigma concerns and provide increased flexibility of access in the presence of competing demands of work and childcare. Positive experiences with internet-delivered interventions could also facilitate the eventual transition to traditional mental health care if needed [22]. Meta-analyses of results from community samples provide evidence for the effectiveness of internet-delivered interventions for depressive symptoms, including acceptance and commitment therapy [23], cognitive behavioral therapy [24,25], and mindfulness-based approaches [26].

Deprexis (GAIA AG) [27,28] is an internet-delivered intervention that integrates acceptance and commitment therapy, cognitive behavioral therapy, and psychodynamic and mindfulness-based approaches. The program consists of 10 core modules targeting depressive symptoms and associated functional impairment. Engagement with content is completely self-guided, and the program is accessed remotely. A randomized controlled trial (RCT) of Deprexis in a general population sample found that it was effective in reducing depressive symptoms, improving well-being, and decreasing disability [29]. Despite these positive results in the general population, it is unknown whether Deprexis is an effective treatment for veterans with depressive symptoms, given the unique composition of the veteran population in terms of gender ratio, barriers to treatment, the severity of comorbid conditions,

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and sociodemographic characteristics. Furthermore, there is a need to understand whether this low-intensity, internet-delivered treatment for depression also addresses functional impairments in veterans. A critical gap in the field is testing the effects of evidence-based mental health interventions on recovery outcomes. The primary goal in previous trials was to test the effect of Deprexis on depressive symptoms. Although improvements in functional domains after Deprexis treatment have been reported [29], the conducted assessments did not span the full range of functional outcomes. There is a need to centralize the assessment of psychosocial functioning in mental health delivery research generally and the study of Deprexis specifically.

Aims

Deprexis has not yet been rigorously evaluated with a veteran population in a VA medical center setting. This study aims to fill this critical gap in the literature by testing whether Deprexis is acceptable and effectively decreases depressive symptoms and improves functional outcomes in veterans (N=152) presenting for VA health care with mild to moderate depressive symptoms. The objective of aim 1 is to assess perceptions, needs, and preferences as they relate to Deprexis through conducting posttreatment assessment interviews with veterans (n=16-20) and identify the components that improve veterans' experience and uptake of Deprexis. The results obtained in aim 1 will be used to inform the rollout of RCT procedures under aim 2. Aim 2a involves completing an RCT comparing an 8-week course of Deprexis to a treatment-as-usual (TAU) control condition. We hypothesize that veterans engaged in Deprexis will show improvements on measures of functioning and decreases in depressive symptoms compared to the TAU control group. To generate hypotheses for future study, the objective of exploratory aim 2b will be to examine whether demographic variables, baseline psychopathology, credibility, and Deprexis use moderate treatment effects on the primary outcomes.

Methods

Trial Design

This study is an individually randomized, parallel, 2-group therapy trial. A total of 132 veterans will be randomized in a 1:1 fashion to either a Deprexis intervention or a TAU control group.

Study Setting

Recruitment will take place within the VA Central Texas Healthcare System. All assessment and intervention components will be completed remotely through Qualtrics (Qualtrics International Inc) [30] and the Deprexis website, respectively.

Eligibility Criteria

Potential participants include all veterans irrespective of sex or gender and of all ages and races and ethnicities who (1) are able to comprehend and sign the informed consent form; (2) have reliable access to the internet and a computer, tablet device, or smartphone; (3) exhibit mild to moderate (not very severe) levels of depression (Quick Inventory of Depressive Symptomatology–Self-Report [QIDS-SR] [31] score between 6 and 20 at the time of screening); and (4) are stable on psychotropic medications (defined as no medication change in the 30 days before study entry). The last criterion is included to ensure that the symptoms evaluated during the pretreatment assessment are due to underlying psychiatric conditions and not because of starting or stopping medications. Veterans will be excluded from study participation if they (1) endorse any positive symptoms of a psychotic disorder (assessed via the Psychiatric Diagnostic Screening Questionnaire [PDSQ] [32]), (2) screen positive for bipolar I disorder (assessed via the Mood Disorder Questionnaire [33]), or (3) report current suicidal risk (assessed via Beck Depression Inventory–Second Edition [BDI-II] item 9 [34]).

Recruitment

For this study, veterans presenting with mild to moderate symptoms of depression will be recruited. Recruitment letters, including a link to the Qualtrics survey, will be sent out by US mail to veterans identified through the medical record who screen positive on the Patient Health Questionnaire (PHQ)-2 clinical reminder screen (a score of ≥3). The initial eligibility criterion is purposefully broad (ie, a positive PHQ-2 screen vs a positive PHQ-9 screen) because we do not want to exclude treatment-receptive veterans with mild depressive symptoms. Veterans' telephone numbers will be obtained from the medical record, and a research technician will contact veterans by telephone to ensure that they have received their letters, answer any questions, and provide them with a link to the Qualtrics survey if needed. Flyers at VA primary care and medical specialty clinics will also be posted and distributed, and information about the study and participant inclusion and exclusion criteria will be provided to VA primary care providers.

Intervention Description

Deprexis is an internet-delivered treatment for depressive symptoms and related functional impairment. The intervention draws from various theoretical frameworks and consists of 12 modules: 10 core content modules, an introductory module, and a summary module. Deprexis, which is designed to be interactive involves answering questions and learning techniques and concepts through instruction and examples. Deprexis uses a software technology (Broca) that tailors content dynamically to the users' responses, resulting in a simulated conversational flow. To increase motivation, Deprexis features symptom tracking, with accompanying graphical and text feedback, worksheets and summaries in printable format, audio recordings, and illustrations. The content focuses on improving depressive symptoms (eg, cognitive restructuring of depressogenic thoughts) and decreasing functional deficits associated with depressive symptoms (eg, behavioral activation, interpersonal skills, and healthy lifestyle choices). The program is self-paced, and every module takes between 10 and 60 minutes to complete. Participants are provided a free Deprexis voucher and will access the intervention through the Deprexis website. Textbox 1 [27] presents an overview of session content, while Figure 1 depicts a Deprexis sample presentation.

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Textbox 1. Deprexis module content.

Introduction

- Overview of the Deprexis program; psycho-education about the relationships among thoughts, feelings, and behaviors; observing and accepting thoughts and feelings; mindfulness exercise; a worksheet to encourage regular program use

Behavioral activation

- Exploring the relationship between activity and depressive symptoms; psycho-education on basic psychological needs (eg, need for competence and social relatedness); selecting and scheduling activities that satisfy basic psychological needs using a checklist and log; exploring and problem-solving barriers to completing activities

Cognitive modification

- Psycho-education on automatic thoughts; exploring antecedents and consequences of automatic thoughts; common cognitive distortions; strategies for correcting cognitive distortions (eg, birds-eye view and a scientist's perspective)

Relaxation, physical exercise, and lifestyle modification

- Relationship between lifestyle habits (eg, sleep, exercise, and diet) and depression; instruction and practice of various relaxation exercises to help mitigate stress (eg, diaphragmatic breathing and visual imagery)

Acceptance and mindfulness

- Illustrate the difficulty of controlling thoughts and feelings and the alternative of calmly accepting unwanted thoughts and feelings using metaphors and exercises; mindfulness exercises that promote acceptance (eg, leaves on a stream); clarifying values and taking value-consistent action

Problem solving

- Strengthening problem-solving skills by defining problems in concrete rather than vague terms, setting achievable goals, generating a variety of potential solutions, evaluating solutions, implementing the chosen solution, and evaluating outcomes

Childhood experiences

- Exploring difficult childhood memories and using coping skills such as expressive writing, acceptance, forming new positive memories, and forgiveness

Interpersonal skills

- Psycho-education about the relationship between interpersonal functioning and depression; exploring different communication styles (eg, assertive, passive-aggressive, aggressive, and nonverbal communication); practicing communication techniques (eg, nonblaming communication)

Positive psychology

- Psycho-education about positive psychology; focusing on strengths instead of deficits; fostering happiness by savoring positive experiences and identifying and fostering talents

Dreamwork and an emotion-focused intervention (optional)

- Coping with distressing dreams (eg, keeping a dream journal and rewriting the ending of dreams); reconceptualizing dreams as a way for our brain to help us problem solve

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Figure 1. Deprexis sample presentation.

Veterans randomized to the control condition will have access to standard VA treatment resources, including mental health treatment (they will be provided with a list of available resources).

Criteria for Discontinuing or Modifying Allocated Interventions

Veterans can choose to discontinue study involvement at any time without facing any consequences. We will actively monitor for any serious adverse events occurring during their study involvement. Modifications to intervention components or procedures may be made at the discretion of the principal investigator (PI; RP), pending approval from the institutional review board (IRB) and other relevant stakeholders.

Strategies to Improve Adherence to Intervention Protocols

Adherence will be optimized using strategies from previous Deprexis trials. All veterans will be sent brief SMS text messages to increase engagement. These SMS text messages will target behavioral and cognitive processes that are known to maintain depressive symptoms and will include reminders to use the Deprexis program. Research staff will also have access to veterans' real-time Deprexis use data, and based on this use data, short encouraging emails will be sent to them by research staff. These emails will range from acknowledging the veterans' use of the Deprexis program to encouraging further engagement and addressing feelings of discouragement. Research staff will also reach out to veterans who have not activated their free Deprexis vouchers to provide technical support if needed. Study staff will initiate contact with veterans if there is no engagement with Deprexis over a 2-week period.

Relevant Concomitant Care and Interventions That Are Permitted or Prohibited During the Trial

To participate, veterans need to be stable (no changes in the last 30 days) on medications prescribed for a mental health disorder. Veterans randomized to either treatment group are allowed to start or continue any nonstudy treatment resources, including mental health treatment, during their participation in the trial.

Participant Timeline

Figure 2 shows the participant timeline in detail.

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Figure 2. Participant timeline.

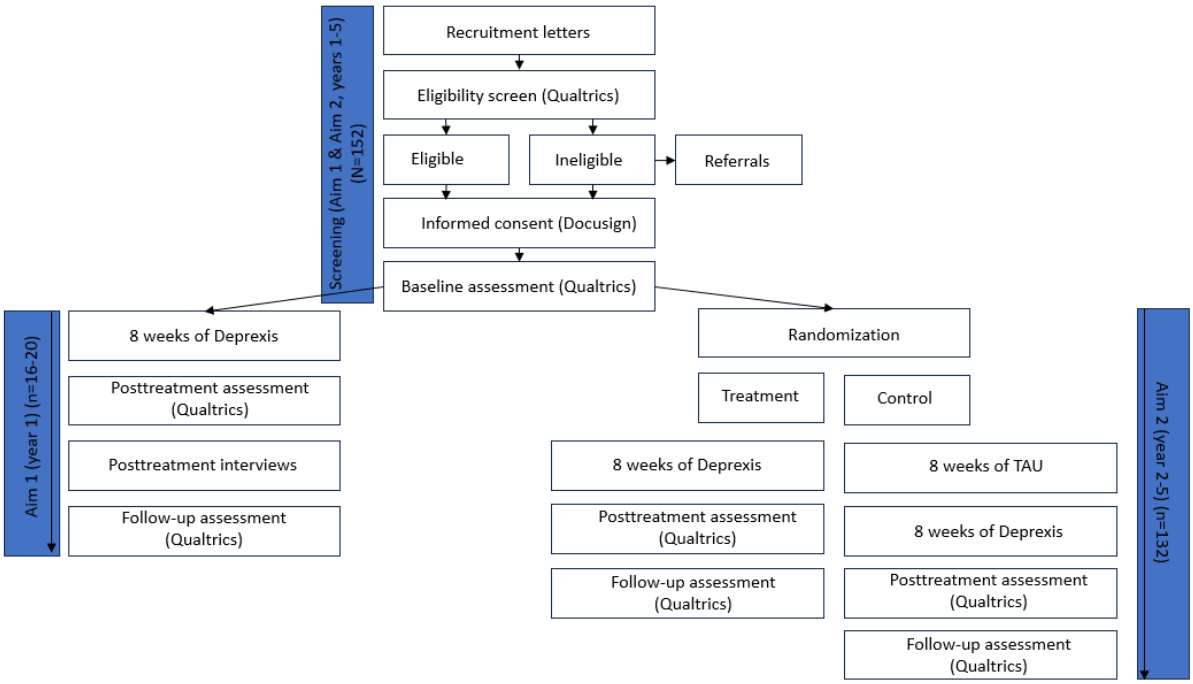

Outcomes

In aim 1, qualitative veteran feedback on the Deprexis intervention and study procedures will be obtained; no quantitative analyses will be completed. Broadly, the posttreatment interview questions will cover the following content areas: (1) motivation toward, and barriers to, treatment and participation in the study; (2) Deprexis content, presentation, adherence, and usability; (3) perceptions of study procedures; and (4) changes experienced in mood, behavioral engagement, or interpersonal interactions after Deprexis treatment.

In aim 2a, we will test whether Deprexis is effective for decreasing depressive symptoms and improving functional outcomes in veterans presenting for VA health care with mild to moderate depressive symptoms. The primary outcomes for this aim are depressive symptoms (assessed with the QIDS-SR-16) and functioning (assessed with the World Health Organization Disability Assessment Schedule II [WHODAS-II] and the Sheehan Disability Scale [SDS]). The secondary outcomes are other psychopathology (assessed with the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [PCL-5] and the PDSQ), social functioning (assessed with the Interpersonal Support Evaluation List–Short Form [ISEL-SF] and the Inventory of Interpersonal Problems–Short Circumplex Form [IIP-SC]), and quality of life (assessed with the Quality of Life Scale [QLS]).

Exploratory analyses in aim 2b will examine whether demographic variables (sex, gender, age, race, ethnicity, and education), PTSD symptom severity (assessed with the PCL-5), comorbidity (assessed with the PDSQ), treatment credibility (assessed with the Credibility and Expectancy Questionnaire), frequency of study support, and Deprexis use moderate treatment effects.

Measures

The following primary outcomes (assessed at all time points) are administered through Qualtrics:

The QIDS-SR-16 [31] is a 16-item self-report measure of depressive symptom severity. This measure takes 5 to 7 minutes to complete and assesses the 9 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-V), symptom criterion domains for depression (eg, “There is no change in my usual appetite”) and has been shown to be highly internally consistent (Cronbach α=0.86). The QIDS-SR-16 demonstrates concurrent validity with measures assessing similar outcomes (r=0.86-0.65) and is sensitive to symptom change [31]. Scores of >6 are indicative of meaningful depressive symptoms. The QIDS-SR-16 will serve as a primary eligibility criterion, specifically a QIDS-SR-16 score between 6 and 20. To verify the duration of depressive symptoms, we will include an item adapted from the Clinical Interview Schedule–Revised, which will assess the duration of depressive symptoms on a 6-point scale.

The WHODAS-II [35] is a 36-item self-report questionnaire, which takes 5 to 20 minutes to complete. The measure assesses functional disability across 7 domains: understanding and communicating, getting around, getting along with people, life activities, work, participation in society, and self-care (eg, “In the last 30 days, how much difficulty did you have in concentrating and doing something for 10 minutes?”). The WHODAS-II total score is scaled from 0 to 100, with higher scores indicating greater disability. The WHODAS-II has high test-retest reliability (r=0.98) and moderate to good concurrent validity with measures assessing similar outcomes (r=0.45-0.65), and it is sensitive to change in functional disability after treatment [35].

The SDS [36] is a 3-item self-report measure of symptom-related disability (eg, “The symptoms have disrupted your work/school

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life") that has been used in previous Deprexis trials. The SDS takes approximately 5 minutes to complete, and items are summed (range 0-30), with higher scores indicating greater disability. The SDS was developed as a global measure of the impact of mental illness on work and school activities, family relationships, and social functioning. The SDS is highly internally consistent (Cronbach α=0.89) and has good reliability (*r*=0.73and high construct validity [37]; in addition, it is sensitive to treatment effects [38].

The secondary outcomes listed in the following sections are assessed at all time points.

The PDSQ [32] is a 125-item questionnaire containing 13 subscales (eg, MDD, anxiety disorders, and alcohol and drug abuse and dependence) that is used to screen for symptoms of mental health disorders. The PDSQ takes 15 to 20 minutes to complete, with scoring and cutoffs varying by individual scale [34]. This scale shows high internal consistency (Cronbach α=0.82); high test-retest reliability (*r*=0.84); and good discriminant, convergent (mean *r*=0.17), and concurrent (mean *r*=0.72) validity [32].

The BDI-II [34] is a 21-item self-report measure assessing depression symptom severity, completed in approximately 10 minutes. Items are scored on a 4-point scale (range 0-63), with higher scores reflecting increased endorsement of depressive symptoms. A score of ≥15 indicates the presence of clinically significant depressive symptoms [39]. The BDI-II has high internal consistency (Cronbach α=0.90), good to high test-retest reliability (*r*=0.73-0.96), and it correlates highly with interview-based measures of depression (*r*=0.66-0.75) [40]. The BDI-II will be used as a secondary measure of depression and to assess the suicidal ideation exclusion criteria.

The IIP-SC [41] is a 32-item self-report measure assessing the interference of depressive thoughts, behaviors, and symptoms across various psychosocial domains (eg, "It is hard for me to join in on groups"). The measure takes 10 to 15 minutes to complete. It consists of 8 scales consisting of 4 items each. Scores are averaged (range 0-4), with higher scores indicating greater interpersonal problems. The IIP-SC is sensitive to treatment effects and has demonstrated good to high internal consistency (Cronbach α=0.64-0.87) and good to high test-retest reliability (*r*=0.56-0.81) [42].

The ISEL-SF [43] is a 12-item self-report measure assessing perceived social support across four subscales: (1) appraisal support (the perceived availability of someone to discuss issues of personal importance), (2) tangible assets support (the perceived availability of material aid), (3) belonging support (the perceived availability of others to interact with socially), and (4) self-esteem support (the perceived availability of others with whom one compares favorably). The measure takes approximately 5 minutes to complete, with higher scores indicating the presence of increased social support. There is evidence that perceived social support improves after internet-delivered interventions for depression [44]. The ISEL-SF has been found to be highly internally consistent (Cronbach α=0.83) and has demonstrated moderate convergent construct validity with other measures of social support (*r*=0.45) [45].

The QLS [46] is a 16-item self-report measure of quality of life across various domains, including material and physical well-being; relationships; social, community, recreational, and civic activities; personal development; and fulfillment and independence. Ratings for domains (eg, "Health, being physically fit, and vigorous") are assigned on a 7-point scale from "delighted" to "terrible" (range 12-116), with higher scores indicating a better quality of life. The measure takes approximately 10 minutes to complete. The QLS has high to excellent internal consistency (Cronbach α=0.82-0.92) and high test-retest reliability (*r*=0.78-0.84), and it has demonstrated good convergent validity with similar measures (*r*=0.67-0.75) [47]. Furthermore, the QLS is able to discriminate between populations with expected differences in quality of life (ie, those with chronic illness and those without) [48].

The PCL-5 [49] will be used to identify whether PTSD is a potential moderator of symptom change and to examine whether Deprexis produces meaningful changes in PTSD symptoms. The version of the PCL-5 used (PCL-5 with Criterion A) will include an assessment of the presence of a traumatic event meeting criterion A (the first criterion for diagnosing PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). If no traumatic event is endorsed, veterans will not complete the remaining PCL-5 questions. Veterans who endorse exposure to a criterion A traumatic event will complete the 20-item PCL-5, which assesses PTSD symptom severity on a 5-point scale (eg, "In the past month, how much were you bothered by 'Repeated, disturbing, and unwanted memories of the stressful experience?'"). Scores range from 0 to 80, with scores of >31 being indicative of probable PTSD (ref). The measure takes approximately 10 minutes to complete. The measure has excellent internal consistency (Cronbach α=0.94), high test-retest reliability (*r*=0.82) [49], and moderate convergent and discriminant validity (*r*=0.31-0.60) [49]. The PCL-5 is as sensitive to clinical change that occurs between pre- and posttreatment assessments as gold standard interview-based measures of PTSD symptoms (alerting convergent validity: *r*=0.94 and contrast converting validity: *r*=0.92) [50].

The following moderators and covariates are measured at baseline:

1. The Credibility and Expectancy Questionnaire [51] is a 6-item self-report survey used to measure participants' perceived treatment expectancy and the credibility of clinical outcome studies (eg, "At this point, how logical does the course offered to you seem?"). The measure takes approximately 5 minutes to complete, with higher scores indicating increased treatment credibility. Treatment credibility predicts therapy outcome [52] and was an important predictor of Deprexis treatment response in the general population RCT [53]. The measure has high internal consistency (Cronbach α=0.84) and high test-retest reliability (*r*=0.83) [52].
2. The Client Satisfaction Questionnaire-8 [54] will be administered after treatment to assess the quality of services, treatment satisfaction, and willingness to recommend the treatment to others (eg, "How would you rate the quality of service that you received?"). The self-report measure

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takes approximately 5 minutes to complete and consists of 8 items scored on a 4-point scale (range 4-32), with higher scores representing greater acceptability. The measure has high internal consistency (Cronbach α=0.91), and it has been shown to correlate with treatment attendance (r=0.54) and outcomes (r=–0.35) [55].

3. Participants will self-report on demographic variables, including sex, gender, race, age, ethnicity, marital status, employment, and income. The demographic questionnaire will take approximately 10 minutes to complete.

Sample Size

Aim 1

In determining the sample size for qualitative studies, the key goals are to develop case-oriented perspectives, select participants with a range of characteristics and perspectives, and achieve saturation (ie, the point at which subsequent interviews fail to produce new themes) [56]. Research indicates that typically, saturation is reached with 12 to 16 interviews. As we are also obtaining qualitative data on veterans who did not adhere to the treatment (approximately 23% of the sample), we increased our recruitment target slightly to 16 to 20 veterans to allow for a sufficient sample of veterans who completed Deprexis treatment, as well as those who terminated treatment early (ie, did not complete the posttreatment or follow-up questionnaires).

Aim 2

Effect sizes in the general population Deprexis RCT for participants with mild to moderate depression (QIDS-SR-16 score <21) ranged from Cohen d=0.65 to Cohen d=0.90. Some evidence suggests that effect sizes for psychological interventions may be smaller for veterans [57]; therefore, we estimate that effect sizes are at least medium (Cohen d=0.50) for measures of functioning and large (Cohen d=0.80) for depressive symptoms. To achieve 0.8 power at an α of .05, a total of 102 participants need to be recruited. Accounting for 23% attrition over time, we will randomize 132 participants at baseline. In the general population trial, approximately 57% (n=213) of the randomized participants were high engagers (>90 min), and effect sizes were slightly higher in the high engager group (Cohen d>0.67) than in the overall sample. Thus, we expect to be adequately powered for analysis in this subgroup.

Assignment of Intervention: Allocation and Blinding

Allocation Sequence Generation

Computer-generated stratified block randomization with block sizes of 4 and 8 will be performed by the research technician using a web-based application. As depression severity has previously been associated with Deprexis treatment response, randomization will be stratified by depression severity, consisting of 3 categories: mild=QIDS-SR-16 score 6-10, mild to moderate=QIDS-SR-16 score 11-15, and moderate=QIDS-SR-16 score <16-20. Stratification was limited to depression severity because minimizing the number of strata is recommended in trials that enroll relatively few participants.

Who Will Be Blinded?

The use of a TAU control condition precludes the blinding of participants and research staff. Confounds due to research staff not being blinded will be minimal because all assessment and intervention components will be completed remotely without research staff support. Given that we only use self-report measures, the involvement of research staff in responses will be very limited, and rater effects are unlikely.

Data Collection, Management, and Analysis

Plans to Promote Participant Retention

Participants will receive SMS text and email reminders with embedded links to their Qualtrics follow-up assessments. Research technicians will attempt to make telephone contact with veterans who fail to complete follow-up assessments within the designated time frame.

Data Management

Various steps will be taken to ensure data quality. First, questionnaire data will be directly downloaded from Qualtrics into a Microsoft Excel file. Statistical software code will then be used to score the questionnaires. Two different research technicians will double score the questionnaires, and any discrepancies will be reviewed by the study PI. All identifying participant data will be stored behind a VA firewall to ensure data security.

Statistical Methods

Aim 1 preliminary analyses will be conducted using established methods for qualitative research [58]. Debriefings will occur after each interview through a structured audio review and matrix displays. The debriefing format will highlight the content and key findings from each interview, enabling the study team to determine when saturation has been reached. The findings from these debriefings will be categorized into “rapid codes” on a matrix display signifying the key areas of the interview agenda they represent (eg, barriers to treatment, Deprexis content, and changes experienced in mood and functioning). Matrix displays create a visual representation of responses to key codes from each participant by lining up each primary response to a question side by side in a single row of a spreadsheet. Rapid codes are summarized into themes, revised continually, and used to determine saturation and inform intervention content areas. Subsequently, during formal analyses, all interviews will be recorded, transcribed verbatim, deidentified, and reviewed for accuracy against the recordings. Drawing from the literature, the interview agenda will be used to develop an initial coding structure that captures participant responses. An iterative process of transcript review will generate additional codes that will be added to the coding structure. The final coding structure will then be used by the research team to code and review all transcripts for concordance. The final codes will be entered into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH) [59], a qualitative data management software tool, for review using applied thematic analysis. Applied thematic analysis is a systematic approach to coding, organizing, and interpreting qualitative data to best capture meaning via themes across participants’ responses; for example, within any given code, this approach captures the breadth of

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responses to create an overall theme. In accordance with the purpose of aim 1—to improve the further study and uptake of Deprexis in the RCT—we will look carefully for themes that describe the intended needs and desires of veterans, the perceived utility of Deprexis, changes noted in mood and functional domains, and other emergent themes. These themes will be used to identify several potentially modifiable components of Deprexis, which can be used to guide current and future study efforts.

For aim 2, linear mixed effects regression [60] with restricted maximum likelihood estimation will be used to model continuous outcomes (eg, changes in psychosocial functioning outcomes and depressive symptoms), and logistic models will be used to model changes in dichotomous outcomes (eg, significant change: ≥50% improvement in scores) over time. Linear mixed effects regression models will initially be fit using an interactive model (eg, treatment condition+time+treatment condition×time) and compared to an additive model (eg, treatment condition+time) using a likelihood ratio test. This nested comparison serves as a significance test of the treatment×time interaction and will be reported as such in the analyses [61]. *Condition* (treatment or TAU), *time* (before treatment, after treatment, and follow-up), and their interaction will be entered as fixed effects, and *participant* will be entered as a random effect (ie, random intercepts). Cohen *d* for the treatment×time interaction will be calculated using an effect size derived from the mean pretreatment-to-posttreatment and follow-up change in the treatment condition minus the mean pretreatment-to-posttreatment and follow-up change in the TAU control divided by the pooled pretreatment SD [62]. Simulations suggested that this effect size estimate was the most stable and robust for these types of treatment designs [63]. When comparisons are made within a time period, Welch 1-tailed *t* tests will be performed because they are ideal when the 2 samples have unequal variances or unequal sample sizes [64]. When comparisons are made within a treatment condition over time (repeated measures), a paired samples *t* test will be performed. As participants can engage in nonstudy mental health treatment, nonstudy treatment use will be included as a covariate in all analyses.

Methods for Additional Analyses

In an exploratory and hypothesis-generating mode, potential moderators for Deprexis treatment effects will be examined. Generalized linear mixed models with robust maximum likelihood estimation will be used to model continuous outcomes (eg, changes in psychosocial functioning outcomes and depressive symptoms), and logistic models will be used to model changes in dichotomous outcomes (eg, significant change: ≥50% improvement in scores) over time. *Participant* will be entered as a random effect (ie, random intercepts). Each potential moderator will be examined in a separate model for changes in primary outcomes (QIDS-SR-16, WHODAS-II, and SDS). Each model will include main effects for the potential moderator and time (before treatment, after treatment, and follow-up), 2-way interactions (moderator×time and time×treatment condition), and a 3-way interaction (moderator×time×treatment condition). To prevent spurious associations, the α value will be Bonferroni corrected [65]. A variable will be considered a moderator of treament effects if there is a significant 3-way interaction (moderator×time×treatment condition) after treatment or at 8-week follow-up.

Definition of Analysis Population Relating to Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Consistent with CONSORT (Consolidated Standards of Reporting Trials) recommendations [66], aim 2 analyses will be conducted across four groups: (1) the intention-to-treat group, which includes data from all randomized participants, regardless of treatment adherence or attrition; (2) the per-protocol group, which consists of participants who are considered treatment adherent, defined as ≥60 minutes of Deprexis use (which is consistent with previous research [29]); (3) the high-engagement group, which consists of participants who demonstrated strong treatment uptake, defined as ≥90 minutes of Deprexis use (this cutoff is approximately 1 SD below the mean for the treatment-adherent group in the general population Deprexis RCT); and (4) the completer group, which consists of participants who complete both baseline and posttreatment assessments. In the intent-to-treat group, the *Amelia II* (version 1.8.2) package in R [67] will be used to impute missing data with an expectation-maximization and bootstrapping algorithm. All available variables will be used to impute missing data, and the number of imputed datasets will be based on the proportion of missing data.

Dissemination of Results

Several manuscripts are planned to align with the various study aims. In addition, results will be presented at research conferences, and summaries will be drafted for media releases. Author eligibility and order will be determined by the study PI.

Oversight and Monitoring

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

The data safety monitoring board (DSMB) will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the clinical trial [68]. The DSMB will provide recommendations about stopping or continuing the clinical trial. To contribute to enhancing the integrity of the trial, the DSMB may formulate recommendations relating to the selection, recruitment, and retention of participants; their management; improving adherence to protocol-specified regiments; and procedures for data management and quality control. The DSMB will consist of at least 3 members, all of whom are independent of the trial. Any protocol deviations or unanticipated problems involving risks to participants or others will be reported to the DSMB within 5 days, as well as to the IRB, and summarized in the study progress report and submitted during continuing review.

Interim Analyses

No interim analyses are planned.

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Adverse Event Reporting and Harms

In cases of unanticipated problems involving risks to participants or others or apparent serious or continuing noncompliance with federal regulations for the protection of research participants or the requirements or determinations of the IRB, a written report will be prepared for submission to the central IRB and DSMB within 5 business days of notification. The report will include a brief narrative summary of the event as well as a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent should be revised because of the event, and whether all enrolled participants should be notified of the event. All team meetings will begin by asking whether any such events have occurred.

Frequency and Procedures for Auditing Trial Conduct

Yearly auditing will be conducted by an IRB member who is independent of the study and its investigators. This is to ensure that the study is compliant with the protocol and is meeting the standards of human participant research.

Ethical Considerations

The protocol has been approved by the Central Texas Veterans Affairs Healthcare System IRB (protocol 2024-001). Any changes to the study protocol will be promptly communicated to relevant stakeholders.

A waiver of informed consent will be obtained for the completion of the eligibility screen. Informed consent will be obtained for the remainder of the study procedures. A watermarked paper copy of the informed consent will be included with the study recruitment letter. An electronic version of the consent form will be included in the Qualtrics eligibility survey. Veterans will be asked to review the consent form, and they will be asked whether they have any questions or concerns. Veterans who indicate that they have questions or concerns will be contacted by telephone by the research technician. Once all questions and concerns are responded to, the research technician will verbally ask whether the veteran is still interested in the study and if the veteran answers in the affirmative will send a link to DocuSign consent via encrypted email. Veterans who indicate that they do not have questions or concerns will be asked in the Qualtrics eligibility screen whether they are interested in participating in the study. If they answer in the affirmative, they will be sent a link to DocuSignconsent via encrypted email.

No participant data will be released in any form unless the investigators or study personnel are mandated to do so by law (eg, because of risk to self or others). All study data will be kept in accordance with VA guidelines, which require that electronic and paper data be kept for the duration of the study and for 6 fiscal years thereafter (for details on data storage and disposition, refer to VA Records Control Schedule 10-1 [69]). Participants will be assigned a study ID, which is linked to identifying information in a password-protected spreadsheet, which is stored behind the VA firewall. Study personnel who have access to study data will receive training in confidentiality policies and procedures.

All IRB-approved study team members may have access to participant-level data pending approval from the study PI. The full protocol will be available at the discretion of the study PI.

Results

This study was funded in May 2024. Data collection is anticipated to take place between October 2024 and April 2029. Currently, 4 participants have been recruited into this study. The results are expected in November 2029.

Discussion

Summary

Research examining computer-delivered interventions in veterans lags behind that conducted in general population samples. This study will gather the qualitative experiences of veterans with a computerized intervention and will be the first RCT of a self-guided, computerized intervention for depressive symptoms and functional impairment in veterans. The results from the described study will demonstrate whether the positive results in general population trials of computerized interventions generalize to the veteran population. Furthermore, we broaden the target population of these types of interventions by including veterans with subthreshold symptoms of depression. The described trial has an explicit focus on functional outcomes because there is evidence that symptomatic recovery and functional improvements do not consistently improve in tandem after mental health interventions. Deprexis has previously been associated with significant improvement in disability and well-being; however, these were secondary outcomes. This study centralizes and significantly expands the assessment of psychosocial functioning across domains.

Depressive symptoms, independent of comorbid trauma symptoms, are an important driver of functional impairment and suicidality in veterans. When depressive symptoms co-occur with PTSD, these symptoms often persist after trauma-focused treatments. Thus, depressive symptoms should be an urgent target of intervention in veterans, even in the context of complex comorbid conditions. There is evidence that the depression treatment gap commonly described in community samples also exists for veterans who receive their care at VA facilities [20]. Various reasons for the existence of this treatment gap have been suggested, and it seems likely that multiple individual, logistical, and institutional barriers may prevent veterans with depressive symptoms from receiving appropriate care. Cost-effective, accessible computerized interventions would broaden the reach of depressive treatments available within the VA system.

Importantly, the VA system is an appropriate site for testing an intervention such as Deprexis. The broad screening for depressive symptoms that occurs at all VA clinics (ie, outside of specialty mental health clinics) and the integrated mental health record allow for the timely identification of veterans presenting with relatively mild depressive symptoms. There is an opportunity to prevent chronicity and disease progression by focusing treatment on mild to moderate depressive symptoms. There is evidence that Deprexis may be especially effective for

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individuals with lower depressive symptom severity [53]. Our long-term vision is that brief, computerized interventions such as Deprexis can be integrated in a stepped-care approach, providing rapid intervention for veterans with mild to moderate depressive symptoms, while reserving resource-intensive treatments such as face-to-face psychotherapy for individuals with severe symptomatology.

Alongside the aforementioned strengths, this study has several limitations. The choice of a TAU control group is a relatively weak comparator. Follow-up studies comparing Deprexis to active treatment conditions would provide further evidence for the relative impact of the intervention. All assessments administered in this study are self-report questionnaires, which are prone to certain types of bias (eg, desirability bias). If the efficacy of Deprexis is supported in this trial, examining whether change also generalizes to other assessments, such as ecological momentary assessment or tracking, may be merited. Relatedly, because no clinical interviews are conducted, we are not able to assess the presence or absence of clinical diagnoses. Finally, use will be closely monitored in this trial, which may not be feasible in clinical settings. Automating use reminders may be an important step to promote successful uptake in the VA system.

Conclusions

Despite the aforementioned limitations, we believe that the described study will provide much needed initial evidence for the effectiveness of computerized interventions broadly and Deprexis specifically for veterans presenting with depressive symptoms and functional impairment. The results obtained in this study could inform the rollout of targeted computer-delivered interventions that address common barriers to mental health care in veterans. This is especially pertinent given that demand for VA behavioral health care outpaces supply, resulting in increased outsourcing of behavioral health care in the form of community care referrals [70]. Building a diverse arsenal of psychosocial interventions, including computerized interventions, potentially allows more veterans to receive behavioral health care within the VA system. Furthermore, giving veterans additional mental health care options could improve overall engagement with treatment [71]. We believe that the results of this study could potentially extend and advance routine care for veterans with depressive symptoms, which is an essential step toward closing the treatment gap and providing the highest quality care for veterans with complex mental health needs.

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Disclaimer

The contents of this manuscript do not represent the views of the US Department of Veterans Affairs or the United States government. As RP, JM, JB, PNP, EP, and SKC are employees of the US government and contributed to this paper as part of their official duties, the work is not subject to US copyright.

Data Availability

A deidentified participant-level dataset may be available to the scientific community pending appropriate approvals. The full statistical code will be available at the discretion of the principal investigator.

Conflicts of Interest

None declared.

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Abbreviations

BDI-II: Beck Depression Inventory–Second Edition
CONSORT: Consolidated Standards of Reporting Trials
DSMB: data safety monitoring board
IIP-SC: Inventory of Interpersonal Problems–Short Circumplex Form

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IRB: institutional review board
ISEL-SF: Interpersonal Support Evaluation List–Short Form
MDD: major depressive disorder
PCL-5: posttraumatic stress disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
PDSQ: Psychiatric Diagnostic Screening Questionnaire
PHQ: Patient Health Questionnaire
PI: principal investigator
PTSD: posttraumatic stress disorder
QIDS-SR: Quick Inventory of Depressive Symptomatology–Self-Report
QLS: Quality of Life Scale
RCT: randomized controlled trial
SDS: Sheehan Disability Scale
TAU: treatment-as-usual
VA: US Department of Veterans Affairs
WHODAS-II: World Health Organization Disability Assessment Schedule II

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Protocol

A Tailored Postpartum eHealth Physical Activity Intervention for Individuals at High Risk of Postpartum Depression—the POstpartum Wellness Study (POW): Protocol and Data Overview for a Randomized Controlled Trial

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Abstract

Background: Postpartum depression (PPD) is associated with significant health consequences for the parent and child. Current recommendations for PPD prevention require intense health care system resources. Evidence-based interventions for PPD prevention that do not further burden the health care system are needed. Evidence suggests that physical activity (PA) can generally reduce depressive symptoms. Technology-based interventions may help decrease common barriers to PA.

Objective: This study aims to report the protocol and provide a data overview of the POstpartum Wellness study (POW)—an effectiveness trial evaluating whether an eHealth PA intervention tailored for postpartum individuals increased PA and decreased depressive symptoms among individuals at high PPD risk.

Methods: This remote parallel-group randomized controlled trial included postpartum individuals with a history of depression or at least moderate current depressive symptoms not meeting the PPD diagnostic threshold and with low PA levels from an integrated health care delivery system. Participants were randomized to an eHealth PA intervention or usual care. The intervention group received access to a library of web-based workout videos designed for postpartum individuals, which included interaction with their infants. At baseline and follow-up (3 and 6 months), PA was measured using questionnaires and a wrist-worn accelerometer. Depressive symptoms were measured using the Patient Health Questionnaire-8 (PHQ-8). Data were collected to assess exploratory outcomes of sleep, perceived stress, anxiety, parent-infant bonding, and infant development.

Results: The study was funded in January 2020. Participants were enrolled via REDCap (Research Electronic Data Capture) or telephonically between November 2020 and September 2022; data collection ended in April 2023. Randomized participants (N=99) were 4 months post partum at baseline with moderately severe depressive symptoms (mean PHQ-8 score 12.6, SD 2.2). Intervention (n=50) and usual care (n=49) groups had similar sociodemographic characteristics, months post partum, baseline depressive symptoms, number of children at home, and prepregnancy PA levels. Retention in assessments was ≥66% for questionnaires and ≥48% for accelerometry, with modest differences by group. At 3-month follow-up, 73 of 99 (74%) participants (intervention: 35/50, 70%; usual care: 38/49, 78%) completed questionnaires; 53 of 99 (54%) wore the accelerometer for 7 days (27 of 50 (54%) intervention, 26 of 49 (53%) usual care). At 6-month follow-up, 66 of 99 (67%) participants (30 of 50 (60%) intervention, 36 of 49 (73%) usual care) completed questionnaires and 43 of 99 (43%) wore the accelerometer for 7 days (21 of 50 (42%) intervention, 22 of 49 (45%) usual care). Data analysis is completed, and a manuscript with these findings is currently under review for publication.

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Conclusions: The POW trial evaluates the effectiveness of an eHealth PA intervention for improving depressive symptoms and increasing PA among postpartum individuals at high PPD risk. Results have implications for the design and delivery of behavioral interventions among vulnerable patients.

Trial Registration: ClinicalTrials.gov NCT04414696; https://clinicaltrials.gov/ct2/show/NCT04414696

International Registered Report Identifier (IRRID): DERR1-10.2196/56882

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KEYWORDS

postpartum depression; depression; eHealth; online workout videos; exercise videos; physical activity; wellness; health promotion; digital interventions

Introduction

Postpartum depression (PPD) is a debilitating and costly condition that affects over 22% of birthing parents and is associated with significant health consequences for them [1-5] and their children [6-12]. In 2019, the US Preventive Services Task Force issued a recommendation stating that postpartum women at increased risk of PPD (ie, women with a history of depression prior to pregnancy or at least moderate postpartum depressive symptoms that do not meet the diagnostic threshold for PPD) [13,14] should receive counseling interventions [15]. We have previously [16] highlighted the significant pressure this will place on the demands of health care systems already struggling with a shortage of mental health care providers. Thus, effective, evidence-based interventions to prevent PPD among those at risk—that can be easily integrated into health care systems, yet do not involve intensive health care system resources—are urgently needed.

Strong evidence in general populations suggests physical activity (PA) can reduce depression risk by half [17-21]. While national guidelines and professional organizations, including the American College of Obstetricians and Gynecologists, recommend at least 150 minutes per week of moderate to vigorous intensity PA for postpartum women [22,23], 70% of postpartum women do not meet these guidelines [24-29]. Common barriers to participating in postpartum PA include parental responsibilities and childcare, limited time, and limited availability and awareness of existing PA resources for postpartum individuals [30]. Technology-based (eHealth) interventions are a promising approach since they can address these common barriers and have been shown to effectively increase PA in the general population [31,32]. However, there are few eHealth PA interventions tailored specifically for postpartum women, and it is unclear if such interventions are effective in reducing PPD risk.

The POstpartum Wellness study (POW) is an effectiveness randomized controlled trial (RCT) to evaluate whether an eHealth PA intervention tailored for postpartum individuals was effective at increasing PA and decreasing depressive symptoms among postpartum individuals at increased risk of PPD and with low PA. Here, we provide a detailed overview of the trial protocol following the CONSORT (Consolidated Standards of Reporting Trials) guidelines, and present baseline data and retention in trial follow-up assessments.

Methods

Study Setting

This trial was conducted in Kaiser Permanente Northern California (KPNC), an integrated health care delivery system that provides care for over 4.6 million members (over 66,000 pregnant and postpartum individuals annually). KPNC health plan members are covered by employer-sponsored insurance plans, the California Insurance Exchange, Medicare, and Medicaid. Coverage is provided for approximately 47% of the Northern California population and is similar demographically, ethnically, and socioeconomically to the underlying population except with respect to income, where members underrepresent the very poor and the very wealthy [33,34]. As part of standard perinatal care, women are screened for PPD using the validated Patient Health Questionnaire-9 (PHQ-9) screening tool [35,36] at their 4- to 6-week postpartum visit [37,38]. Additionally, postpartum parents are screened for PPD using the Patient Health Questionnaire-2 (PHQ-2) [39] at each well-baby visit. All screening scores are captured in the KPNC's comprehensive electronic health records (EHR).

Study Design Overview

POW is a 2-arm parallel RCT comparing an eHealth PA intervention tailored for postpartum women to usual postpartum care in women at high risk of PPD with low PA levels. Potential participants were identified via PPD screening scores captured in KPNC's EHR databases or clinician referral. Enrolled participants completed assessments at baseline before randomization, and at follow-ups at 3 months and 6 months post randomization. Primary outcomes were depressive symptoms and device-based PA at 3-month follow-up. Secondary outcomes were depressive symptoms and device-based PA at 6-month follow-up and self-reported PA (3-month follow-up and 6-month follow-up). Additional outcomes ascertained included self-reported sleep, anxiety, stress, parent-infant bonding, and parent-reported infant development. See Table 1 for a list of data collected at each time point. Recruitment began on November 19, 2020. The trial protocol was modified 3 times to improve trial implementation (Modification 1 in January 2021, Modification 2 in July 2021, and Modification 3 in February 2022), as described below and in Table 2.

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Table 1. Data collection and time points.

Measures	Instrument	Recruitment screener	Baseline	3 months post baseline	6 months post baseline	12 months post partum
Primary and Secondary Outcomes[a]						
Depressive symptoms	Patient Health Questionnaire-8 (PHQ-8) [40]	X		X	X	
Moderate/vigorous intensity physical activity	ActiGraph GT3X+ (7 days); Pregnancy Physical Activity Questionnaire (PPAQ) [41]		X	X	X	
Additional Outcomes						
Perceived stress	Perceived Stress Scale (PSS-10) [42]		X	X	X	
Anxiety symptoms	Generalized Anxiety Disorder (GAD-7) [43]		X	X	X	
Sleep quality and duration	Pittsburg Sleep Quality Index (PSQI) [44]		X	X	X	
Mother and infant bonding	Mother-to-Infant Bonding Scale (MIBS) [45]		X	X		
Infant development at 12 months	Ages and Stages Questionnaire (ASQ-3) [46]					X
Participant satisfaction				X		
Potential Mediators for Physical Activity (PA)						
Self-efficacy	Modified self-efficacy to overcome barriers to PA Scale [47]		X	X		
Perceived barriers	Modified barriers to being physically active scale [47]		X	X		
Potential Effect Modifiers						
Physical activity before pregnancy	Stanford Leisure-Time Activity Categorical Item (L-Cat) [48], modified to reflect year before pregnancy		X			
Physical activity during pregnancy	Stanford L-Cat, modified to reflect pregnancy		X			
Covariates and Confounders						
Demographic characteristics (survey-based: number of children and ages, race/ethnicity, education, income, employment, marital status; electronic health record–based: maternal age)	N/A[b]		X			
Baseline infant development	Mobility and behavior questions		X			
Social support for PA	Modified family or friend support for participation in exercise scale [47,49]		X			
COVID-19 stress and coping mechanisms	N/A		X			
Health behaviors (smoking, alcohol, breastfeeding)	N/A		X	X	X	
Adverse Event Reporting						
Injuries or illness related to exercise	N/A			X	X	

[a]Primary outcomes were depressive symptoms and device-based physical activity (PA) measured at the 3-month follow-up. Secondary outcomes were depressive symptoms and device-based PA at the 6-month follow-up and self-reported PA at the 3- and 6-month follow-ups.

[b]Not applicable.

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Table 2. Electronic health record (EHR) identification of potentially eligible participants, study inclusion and exclusion eligibility criteria, recruitment and retention strategies and their modifications over the study period.

	Original Protocol—November 2020	Modification 1—January 2021	Modification 2—July 2021	Modification 3—February 2022
Identification of potentially eligible participants via the EHR	• 2-6 months post partum AND • No current depression diagnosis AND • Postpartum PHQ-9 score between 10 and 19 OR • Postpartum PHQ-2 score ≥3	N/A[a]	• 2-6 months post partum AND • No current depression diagnosis AND • Postpartum PHQ-9[b] score (10-19) OR • Postpartum PHQ-2[c] score ≥3 OR • History of depression diagnosis or antidepressant medication use	N/A
Inclusion criteria Ascertained via eligibility screener	• PHQ-8[d] score between 10 and 19 • Engages in <30 minutes of regular, moderate/vigorous intensity physical activity per week	• PHQ-8 score between 10-19 • Engages in <90 minutes per week of regular, moderate/vigorous intensity physical activity per week	• Clarification of what is meant by moderate/vigorous intensity physical activity in eligibility screener	N/A
Exclusion Criteria Ascertained via eligibility screener	• Not current Kaiser Permanente member • <18 years of age • Does not own a smartphone, computer, or TV with internet access • Has a heart condition and a physician recommending medically supervised physical activity • Has chest pain during physical activity or chest pain within the prior month • Takes medication for hypertension or a heart condition • Diagnosed with depression or received treatment for depression (eg, taken antidepressant medications or received psychotherapy) since giving birth • Tendency to fall due to syncope or dizziness • Has orthopedic problems that might be aggravated by physical activity • Has exercise-induced asthma • Is currently pregnant or is planning to become pregnant in the next 3 months • Baby weighs outside 11-22 lbs • Baby has a chronic illness/disorder that prevent them from being held or lifted up	N/A	N/A	N/A

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	Original Protocol—November 2020	Modification 1—January 2021	Modification 2—July 2021	Modification 3—February 2022
Recruitment	• Recruitment email followed up by recruitment phone call to provide opportunity to discuss the study • DOB[e] authentication by participants to enter survey • Study hotline and email to respond to participant communication	N/A	• Recruitment letter mailed first • Recruitment email • Recruitment phone calls made when recruiter time available • Removed DOB authentication due to technical issues—recruiter confirms identity over phone • Study website	N/A
Retention	• Reminder phone calls to wear and send back activity monitor • Financial incentive for completion of each assessment (US $70.00 in total) • Recognizable logo and culturally competent and sensitive material	N/A	• Information added to email for participants emphasizing the importance of contributions and survey completion for all participants, regardless of study group • Study gift - Notepad with logo sent at 3 months • Study newsletters with information on postpartum topics between study surveys • Reminder emails/texts about follow-up surveys • One reminder email/text 1 week after randomization to log in to MomZing in intervention group	• Shorter, limited surveys, only including primary outcomes were available • Additional reminders (text/email) were sent to intervention group for using MomZing

[a]N/A: not applicable.

[b]PHQ-9: Patient Health Questionnaire-9.

[c]PHQ-2: Patient Health Questionnaire-2.

[d]PHQ-8: Patient Health Questionnaire-8.

[e]DOB: Date of birth.

EHR Identification of Potential Participants

The EHR was used as an efficient way to identify potentially eligible individuals to invite to participate. Recruitment began on November 19, 2020, and ended on September 2, 2022. Individuals who were 2-6 months post partum, did not have a current depression diagnosis and were at high risk for PPD (PHQ-9 score of 10-19 [35,36] or PHQ-2 score of ≥3 [39]) were identified in the EHR for potential recruitment. However, KPNC's PPD screening rates were severely impacted by COVID-19's effects on health care delivery. As a result, the number of potentially eligible participants identified was much lower than originally anticipated. Thus, in July 2021 we expanded our approach to include participants with a history of depression diagnosis or antidepressant medication use prior to the delivery date (Modification 2, see Table 2).

Individuals identified through the EHR were sent a recruitment email that included a link to the eligibility screener using email addresses registered in the EHR. Starting a week later, nonresponders were contacted by phone. Those meeting the eligibility criteria were invited to enroll.

Clinician Identification of Potential Participants

As a secondary recruitment strategy, health system clinicians were encouraged to identify potential participants from their patient panel. Clinicians shared information about the trial with such patients and shared contact information with the study team. If the participant met the identification criteria, a study team member then reached out to the individual to screen for eligibility.

Eligibility Criteria

Eligibility criteria are outlined in Table 2. Potential participants were screened for depressive symptoms using the validated Patient Health Questionnaire-8 (PHQ-8) [40]. The PHQ-8 is a validated instrument for assessing depressive symptoms similar to the PHQ-9 but does not assess suicidal ideation [50]. Scores between 10 and 19 (indicating high risk for PPD) were considered eligible. Low physical activity during postpartum was defined as not engaging in regular, moderate or vigorous intensity physical activity for 30 minutes or more per week. "High" physical activity (ie, 30 minutes or more per week) was the most common reason for ineligibility in the first few months of recruitment. On January 13, 2021 (Modification 1), the current low PA during postpartum criterion was modified to "not engaging in regular, moderate or vigorous intensity physical

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activity for 90 minutes or more per week" to match the American College of Sports Medicine's definition of not participating in regular exercise [51].

Recruitment

For individuals identified through the EHR, we sought approval to recruit from their obstetric provider (if a provider did not respond within 14 days, it was considered an approval to proceed) via email to contact the individual. Individuals were emailed recruitment materials with information about the trial, a link to the eligibility screener, and a link to the trial website [52]. Individuals were sent 1 recruitment email with a link to the eligibility screener requiring login using date of birth, followed by phone call recruitment if there was no response to the email. The recruitment protocol was modified (Modification 2, July 13, 2021) to first send a recruitment letter by postal mail followed by the original protocol. The date of birth authentication was also removed due to technical issues preventing participants from accessing the screener. Recruiters attempted to reach potential participants, (prioritizing PHQ-9 scores of 10-19) by phone at least once as recruiters' time allowed. All recruitment efforts stopped once a patient reached 6 months post partum.

Baseline Data Collection

Eligible participants completed Informed eConsent through REDCap (Research Electronic Data Capture) and were emailed a copy of the signed consent form. Next, the participant completed baseline surveys through REDCap. After baseline survey completion and mailing address confirmation, an accelerometer (Actigraph GT3X+) was mailed to the participant. Participants were asked to wear it for 24 hours for 7 consecutive days, complete a wear log for the activity monitor, and mail the activity monitor and log back. Once baseline surveys were completed and the activity monitor was returned, participants were then randomized into the intervention or usual care group.

Randomization and Blinding

Participants were randomized using the minimization randomization technique as implemented via the QMinim software program [53,54], which was generated by the project manager [53,54]. Factors included in the block randomization included: parity (1 vs 2+), racial and ethnic category (Asian or Pacific Islander, Hispanic, non-Hispanic Black, non-Hispanic White, or Other), baseline PHQ-8 severity (scores of 10-14 and 15-19), and physical activity level prior to pregnancy (below vs at or above recommendations). Information on these factors was obtained from the eligibility screening and baseline trial questionnaires. The data analyst and investigators were blinded.

Follow-Up Data Collection

Follow up data collection occurred at 3 and 6 months after randomization (Figure 1). An additional assessment occurred when the participant's child was 12 months old; for some participants, this occurred simultaneously with the 6-month follow-up. At 3 and 6 months after randomization, participants were emailed links to web-based surveys via REDCap. After completion of the surveys at each timepoint, participants were sent an accelerometer (ActiGraph GT3X+), asked to wear it for 24 hours for 7 consecutive days, complete an activity monitor wear log, and mail back the activity monitor and wear log. When the participant's child was 12 months old, participants were emailed the link to the web-based Ages and Stages Questionnaire (ASQ-3). Occasionally, the 6-month survey would fall around the time when the child was 12 months old. In these cases, the 6-month survey and ASQ-3 were sent together.

Figure 1. Final protocol. POW: POstpartum Wellness study.

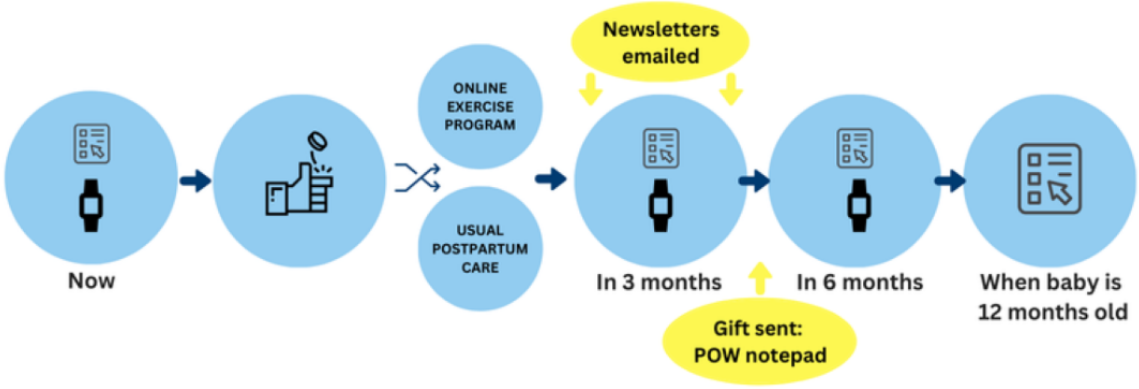

To increase retention and ascertainment of the primary outcomes (depression symptoms and PA) partway through the trial (Modification 3, February 2022), a limited survey was sent to participants nearing the end of the follow-up period and who had not completed their surveys.

Retention Strategies

Strategies implemented mid-way through the trial to increase retention included newsletters, a gift, and text or email reminders (Table 2, Figure 1). Once implemented, participants received a newsletter halfway between randomization and the 3-month follow-up and then again halfway between the 3- and 6-month data collection points. The newsletters contained fun facts, tips for things such as bedtime and baby development, additional resources (unrelated to PA or depressive symptoms), and contact information for the study team. A week before each follow-up, participants would receive a notification text or email to expect their survey within a week. As a gift, participants received a notepad with the trial logo included with the 3-month follow-up activity monitor.

Usual Care

Participants randomized to the usual care group received usual postpartum care for women at increased risk of depression,

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which typically is a brief discussion about their depression symptoms with their obstetric provider.

Intervention

Participants randomized to the intervention group received usual care plus access to MomZing (Figure 2) [55], a web-based library of tailored exercise videos [56] that was developed based on postpartum individuals' preferences for exercise videos that (1) guided them on how to exercise safely with their baby based on the infant's weight and developmental stage; (2) did not require exercise equipment or a substantial time commitment per video (eg, maximum time per video of 10 minutes); (3) provided different types of physical activities (yoga, strengthening, cardio) and intensity levels (light, moderate, hard); and finally, (4) featured women in the exercise demonstrations who were "real" postpartum individuals (not fitness instructors) exercising with their own infant. Users could either select individual videos, combine up to 3 videos to create a longer workout, or choose a "Ready Made" workout lasting 10, 20, or 30 minutes. The website also included an activity tracker that logged exercise videos watched and allowed users to input outside workouts to track daily and weekly total physical activity. Participants randomized to the intervention group were provided individual login information for the website.

Figure 2. Screenshot of MomZing program.

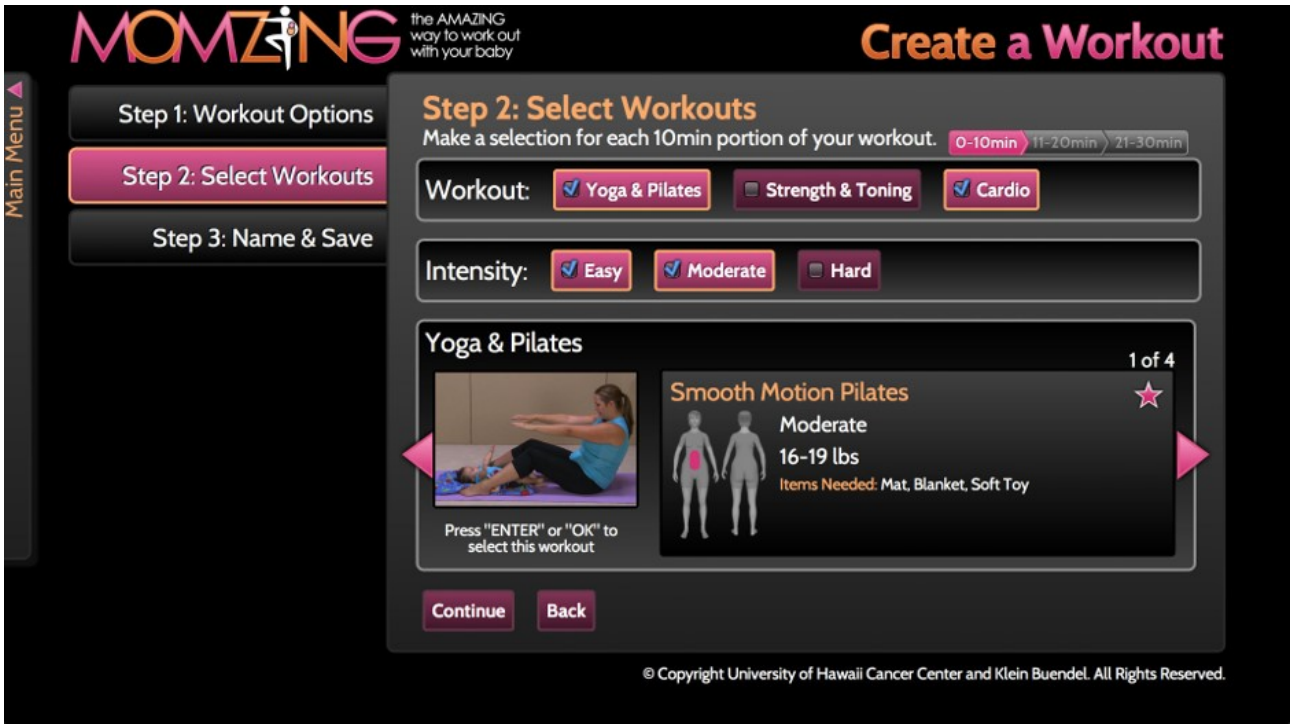

Adherence and engagement with the intervention were assessed using website analytics to track logins and videos watched. The 3-month follow-up survey for participants in the intervention group included additional questions on intervention satisfaction.

To increase adherence to the intervention, after Modification 2, participants randomized to the intervention group received 1 text or email reminder (depending on participants' preference) 1 week after randomization to log into the MomZing website. After Modification 3, additional text reminders were sent to participants in the intervention group between randomization and 3-month follow-up, reminding them to log in to the MomZing website in an effort to increase use of the intervention. Participants could receive up to 5 additional reminder texts at the discretion of research staff.

Outcomes

Primary and Secondary Outcomes

Primary outcomes were depressive symptoms and device-based PA measured at the 3-month follow-up. Secondary outcomes were depressive symptoms and device-based PA at the 6-month follow-up and self-reported PA at the 3- and 6-month follow-ups.

Depressive Symptoms

Depressive symptoms were measured at baseline (eligibility screening), 3-month, and 6-month follow-up using the PHQ-8 [40]. The PHQ-8 has been validated in many studies as an instrument for screening for depression with high sensitivity (>88%) and specificity (>88%) in obstetric patients. The PHQ-8 is also a valid tool to establish depression severity and outcome [40]. The 8-question screener scores range from 0 to 24. A score of 1-4 suggests minimal depression; 5-9, mild depression; 10-14, moderate depression; 15-19, moderately severe depression; and 20-24, severe depression.

Device-Measured Moderate or Vigorous Intensity PA

Device-measured moderate or vigorous intensity PA (dm-MVPA) was measured using accelerometry at baseline, 3-month, and 6-month follow-up. The Choi algorithm [57-59], Tracy algorithm [60], and the Hibbing two-regression model, which was developed for wrist-worn accelerometer data [61], were used to identify wear time, bedrest, and PA intensity,

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respectively. Average moderate or vigorous intensity PA duration was calculated across valid days.

Self-Reported Moderate or Vigorous PA

Self-reported moderate or vigorous intensity PA (sr-MVPA) was assessed using the sports or exercise domain of the Pregnancy Physical Activity Questionnaire [41], a valid and reliable instrument developed for perinatal populations.

Additional Outcomes

Sleep

The 19-item Pittsburgh Sleep Quality Index (PSQI) [44] was used to measure sleep during the past month. A global score, ranging from 0 to 21, is calculated using 7 components of sleep. Higher scores indicate poorer sleep quality.

Anxiety

The Generalized Anxiety Disorder Scale (GAD-7) has been validated in prenatal [62] and racially diverse populations [63,64] and was used to measure anxiety symptoms. Scores range from 0 to 21 and scores of 10-21 were categorized as clinically significant anxiety symptoms [43].

Perceived Stress

The Perceived Stress Scale (PSS-10) [42] is the most widely used psychological instrument for measuring the perception of stress and has been validated in diverse populations and in perinatal women [65]. Scores range from 0 to 40 with 14 or greater signifying moderate-to-severe perceived stress.

Parent-Infant Bonding

The Mother-to-Infant Bonding Scale (MIBS) [45] is an 8-item questionnaire designed to assess feelings of the birthing parent toward their baby. The MIBS has demonstrated acceptability and has good internal reliability. Scores range from 0 to 24, with lower scores indicating better parent-infant bonding.

Infant Neurodevelopment

Infant neurodevelopment at 12 months was assessed using the validated ASQ-3 [46], a high-quality tool to screen for developmental delays in children [46,66]. The ASQ-3 screens for delays in child development in 5 domains: communication, gross motor, fine motor, problem-solving, and personal adaptive skills. Scores will be calculated based on the ASQ-3 scoring guide with scores above the cut-off point indicating typical development categorized as “on schedule” and scores in the zones indicating the need for monitoring or the need for further assessment categorized as “not on schedule.”

Sample Size

Original sample size calculations were based on a planned sample size of 100 participants per group. With our achieved sample size of 99 participants (50 in the intervention group, 49 in the control group), 80% power, and 5% type I error rate, the minimum detectable difference in mean depressive symptom scores and accelerometer-measured duration of moderate or vigorous intensity PA was 0.57 standard deviation units, which is considered a “medium” effect size [67].

Data Analysis

Demographic characteristics for those invited to participate in the trial and those enrolled and randomized are presented in Table 3 and baseline characteristics of the intervention and control groups are presented in Table 4. Intention-to-treat will be used for primary data analysis. We will use linear regression models for estimation of mean differences in outcomes between the intervention and control group, adjusting for all variables included in the randomization scheme.

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Table 3. Participant characteristics for postpartum individuals invited and those randomized.

Characteristic	Invited (n=12,269)	Randomized (n=99)
Age (years), mean (SD)	31.5 (5.4)	32.1 (4.8)
Months post partum at recruitment letter sent, mean (SD)	2.36 (0.66)	2.43 (0.78)
Race/ethnicity, n (%)		
Asian or Pacific Islander	2141 (17)	10 (10)
Hispanic	3615 (29)	31 (31)
Multiracial	416 (3.4)	5 (5.1)
Native American	55 (0.4)	1 (1.0)
Non-Hispanic Black	1075 (8.8)	7 (7.1)
Non-Hispanic White	4738 (39)	44 (44)
Other or unknown	229 (1.9)	1 (1.0)
Parity, n (%)		
0	4690 (38)	40 (40)
1+	6917 (56)	55 (56)
Unknown	662 (5.4)	4 (4.0)
Marital Status, n (%)		
Married, registered domestic partner, or common law	7477 (61)	65 (66)
Separated or divorced	194 (1.6)	1 (1.0)
Single or never married	4223 (34)	33 (33)
Widowed or Other	72 (0.6)	0 (0)
Unknown	303 (2.5)	0 (0)
Medicaid insurance, n (%)	1842 (16)	10 (10)
PHQ-2[a] Score, mean (SD)	3.72 (0.91)	3.65 (0.74)
PHQ-9[b] Score, mean (SD)	12.71 (2.49)	12.18 (2.30)

[a]PHQ-2: Patient Health Questionnaire-2.

[b]PHQ-9: Patient Health Questionnaire-9.

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Table 4. Baseline participant sociodemographic characteristics by randomization arm.

Characteristic	Control (n=49)	Intervention (n=50)
Baseline PHQ-8[a] score[b], mean (SD)	12.6 (2.2)	12.6 (2.2)
Age at randomization (years), mean (SD)	32.7 (4.5)	31.9 (5.1)
Months post partum at randomization, mean (SD)	4.0 (1.0)	4.1 (1.2)
Race and ethnicity[b], n (%)		
Asian or Pacific Islander	4 (8.2)	6 (12)
Hispanic	12 (24)	10 (20)
Non-Hispanic Black	3 (6.1)	3 (6.0)
Non-Hispanic White	18 (37)	19 (38)
Other[c]	12 (24)	12 (24)
Highest level of education, n (%)		
High School or less	8 (16)	11 (22)
College	29 (59)	31 (62)
Graduate School	12 (24)	7 (14)
Unknown	0 (0)	1 (2.0)
Annual household income (US $), n (%)		
Less than 65,000 per year	13 (27)	13 (26)
65,000 to 99,999 per year	9 (18)	14 (28)
100,000 and greater per year	23 (47)	17 (34)
Unknown	4 (8.2)	6 (12)
Employment status, n (%)		
Currently working	15 (31)	11 (22)
Not currently working	34 (69)	39 (78)
Marital status, n (%)		
Married, civil union, or living with a partner	44 (90)	41 (82)
Single or divorced	5 (10)	9 (18)
Number of children at home[b], n (%)		
>1	28 (57)	30 (60)
1	21 (43)	20 (40)
Prepregnancy activity level[b], n (%)		
At or above recommendations[d]	18 (37)	21 (42)
Below recommendations	31 (63)	29 (58)

[a]PHQ-8: Patient Health Questionnaire-8.

[b]Variable included in randomization schema.

[c]Other includes Multiracial, Native American, and unknown.

[d]Moderate or higher intensity physical activity ≥5 times per week for ≥30 minutes a time.

Ethical Considerations

The study protocol was approved by the Kaiser Permanente Northern California Institutional Review Board (#1548855). All participants provided documented informed consent. It was explained to them that they could withdraw from the project at any time for any reason without any repercussions. Confidentiality of participation was maintained, with data access exclusively limited to the research team members. Participants' personal identity was not revealed during data collection, analysis, presentations, and publications. Participants received gift cards after completing each assessment: US $20 after the baseline and 3-month assessments and US $30 after the 6-month assessment (including the 12-month infant ASQ screener), for a total of US $70.

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Results

The study was funded in January 2020. During 22 months of recruitment (November 2020-September 2022), 12,269 postpartum KPNC members were invited to participate in this trial (Table 3). The recruited sample was representative of all participants invited to participate in the trial with regard to several sociodemographic characteristics and depressive symptoms captured in the EHR with the exception of race and ethnicity (Table 3). A smaller percentage of Asian or Pacific Islander individuals were randomized compared to those invited (10% vs 17%) and a larger percentage of Non-Hispanic White participants were recruited compared to invited (44% vs 39%). Of the 2872 postpartum individuals assessed for eligibility, 2773 were not eligible, 124 declined to participate, and 99 were randomized (50 to intervention and 49 to usual care; Figure 3).

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. ASQ-3: Ages and Stages Questionnaire, Third Edition.

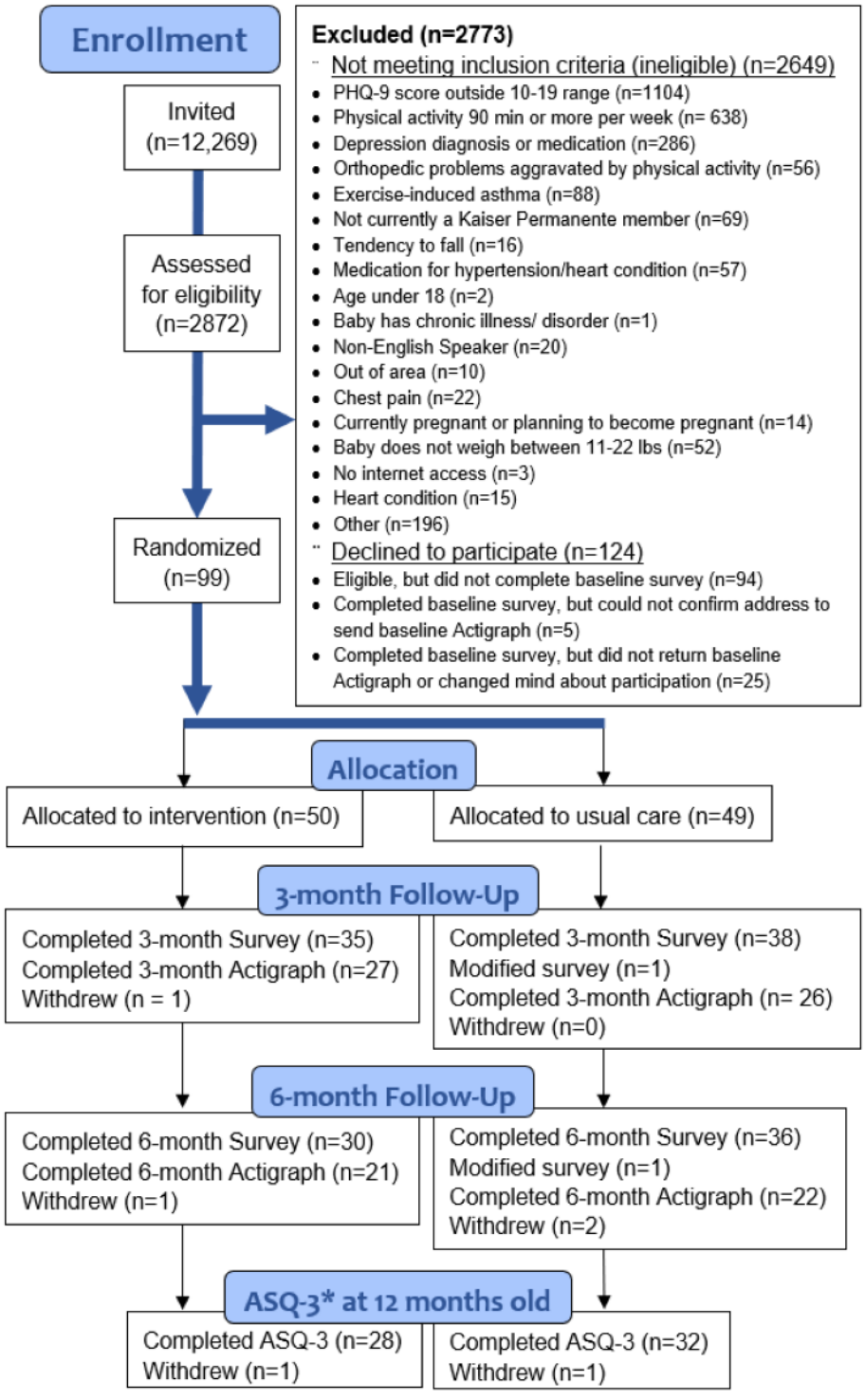

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Baseline Characteristics

The randomized sample included 55 (56%) participants from racial and ethnic backgrounds other than non-Hispanic White (Table 4). Participants were 4.0 (SD 1.0) months post partum on average at baseline with moderately severe depressive symptoms (mean PHQ-8 score 12.6, SD 2.2). The intervention and usual care groups were similar regarding sociodemographic characteristics, months post partum, baseline depressive symptoms, number of children at home, and prepregnancy PA level.

Retention

Follow-up data collection ended in April 2023. At the 3-month follow-up, 73 out of 99 (74%) participants (35/50, 70% in the intervention group and 38/49, 78% in the usual care group) completed questionnaires; 53 out of 99 (54%) returned the accelerometer after wearing it for 7 days (27/50, 54% in the intervention group and 26/49, 53% in the usual care group). At the 6-month follow-up, 66 out of 99 (67%) participants (30/50, 60% in the intervention group and 36/49, 73% in the usual care group) completed questionnaires and 43 out of 99 (43%) returned the accelerometer after wearing it for 7 days (21/50, 42% in the intervention group and 22/49, 45% in the usual care group). A total of 60 out of 99 (61%) participants completed the ASQ-3 when their child was 12 months old (28/50, 56% in intervention group and 32/49, 65% in the usual care group).

Impact of Modifications on Recruitment and Retention

Modification 1 reduced the number of participants ineligible due to “high” PA (21/59, 36% before vs 689/2813, 25% after); however, the overall eligibility rate only changed slightly (7/59, 12% before vs 216/2813, 8% after) as many participants remained ineligible due to PHQ-8 scores outside of the eligible range (15/59, 25% before vs 1089/2813, 39% after).

Modification 2 increased the monthly recruitment rate (4.2 participants per month before vs 6.2 participants per month after) and the proportion of participants recruited by email (3/30, 10% before vs 39/69, 56% after), added postal recruitment (25 participants) and decreased the proportion of participants recruited by phone (27/39, 90% vs 5/69, 7%). Retention rates decreased for the 3-month follow-up survey after Modification 2 (20/21, 95% before vs 53/78, 68% after). Retention increased for the 6-month follow-up survey after Modification 2 (2/4, 50% before vs 64/93, 69% after).

Modification 3 increased the proportion of participants in the intervention group that logged into the MomZing website (11/18, 61% before vs 29/32, 91% after) and decreased the mean time between randomization and first login (22 days before vs 8 days after). Analysis of the effectiveness of the MomZing intervention has been completed, and a manuscript with these findings is currently under review.

Discussion

Background

Interventions to prevent PPD that are feasible in the clinical setting and do not involve intensive health care system resources are urgently needed. The POW trial was designed to evaluate the effectiveness of an eHealth PA intervention for improving depressive symptoms and increasing PA among postpartum individuals at high risk for PPD. In addition to possible effects of the intervention on depressive symptoms and PA, the POW trial data can also be used to evaluate the effect of the eHealth PA intervention on postpartum sleep, perceived stress, anxiety symptoms, parent-infant bonding, and infant development. Given that the intervention tested here does not require intense health system resources, it has the potential for being adopted into clinical practice if found effective in decreasing PPD symptoms and increasing PA.

Recruitment and Retention Strategies

Over the course of recruitment, we modified our protocol at several points in an attempt to increase recruitment, retention, and adherence to the intervention. Successful strategies included adding a recruitment letter sent via postal mail before sending the same letter via email and removing authentication to access surveys, which increased monthly recruitment rate and email recruitment and decreased staff time spent on phone recruitment, and adding reminders to log in to the MomZing website in the intervention group, which increased initial login rates and decreased time to first login from randomization. However, our modifications to the low PA eligibility criterion did not have the intended impact on eligibility rates. Although the ineligibility rate due to high physical activity decreased, most participants remained ineligible due to PHQ-8 scores outside of the eligible range. After modifications addressing retention (adding information emphasizing importance of survey completion for all participants, study gift, newsletters, and reminders about follow-up surveys) were implemented, retention rates did not improve for the 3-month follow-up and increased for the 6-month follow-up. Recent studies of retention strategies for RCTs suggest that study gifts and electronic or text reminders are effective retention strategies [68,69]. However, these may be less effective during postpartum in those with high risk of PPD, especially during a global pandemic.

Our retention rates ranged from 60% (30/50) to 78% (38/49) for questionnaire completion and 42% (21/50) to 54% (27/50) for accelerometer return, with retention rates decreasing from the 3-month to the 6-month follow-up. Compared to a previous RCT of a home-based eHealth PA intervention conducted among postpartum individuals at high risk of PPD [70], our retention rates are lower for questionnaire completion (70% (35/50) to 78% (38/49) versus 80%-97%) and higher for accelerometer data (53% (26/49) to 54% (27/50) versus 27%-47%) at 3-month follow-up. In an RCT of a team-based eHealth PA intervention in the general postpartum population, retention rates similarly decreased from 6 weeks to 6 months follow-up [71]. In our study, both the 3-month and 6-month follow-up retention rates for questionnaire completion were higher in the usual care arm than the intervention arm, while retention rates for accelerometer return were similar in both arms. A similar pattern was observed previously in an RCT of a mobile app targeting PA in postpartum [72]; however, other RCTs have observed the opposite pattern. In a previous RCT of a home-based eHealth PA intervention conducted among postpartum individuals at high risk of PPD [70] and an RCT of a team-based eHealth PA intervention in the general postpartum population [71], retention

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rates were higher in the intervention group than in the control group.

Additional strategies to improve recruitment, retention, and adherence outcomes that could be used in future studies include consultation with diverse stakeholders during the design study phase [72]; larger financial incentives [73]; trial orientation sessions [74]; and methodological infographics that convey the scientific importance of high, nondifferential trial retention [75].

Strengths

Strengths of our trial include recruitment of individuals within an integrated health care delivery system with universal PPD screening, allowing for efficient identification of patients within the KPNC health care system who meet the criteria for high risk of PPD to participate in this trial; recruitment of a representative sample of postpartum individuals at high risk of PPD; use of an eHealth PA intervention for postpartum individuals that was developed with key stakeholder input, resulting in a tailored intervention for postpartum individuals; inclusion of several important potential confounders in our randomization scheme to ensure that randomized groups are balanced; and assessment of multiple behaviors, mental health outcomes, and infant development at multiple timepoints, which will allow for assessment of longitudinal effects of the intervention across postpartum. Finally, 80% of participants randomized to the intervention group logged into the MomZing website; however, additional metrics of engagement will be considered to determine the impact of adherence and engagement with the intervention on results. Results will be published in the peer-reviewed scientific literature.

Limitations

Although the research team worked diligently to monitor trial implementation, remain flexible [76], include a diverse and sensitive research staff [76], and introduce new strategies in an effort to improve recruitment, retention, and adherence outcomes throughout the trial, we acknowledge a few limitations with our trial. The challenges we encountered are common in clinical trials [77]. While over 50% of our study sample was from a racial and ethnic minority group, the sample was not completely reflective of the racial and ethnic demographics of our target population and we had difficulty meeting our original recruitment goal. We noted differential follow-up rates by randomization arm, with predominately higher rates in the usual care arm which may result in biased estimates if there are differences between participants who completed the trial and those who were lost to follow-up. We will carefully consider loss-to-follow-up in our analyses and apply appropriate statistical methods to mitigate some of these concerns.

Conclusions

In summary, the POW trial is designed to expand our understanding of the effectiveness of an eHealth PA intervention to reduce PPD symptoms and increase PA. The rigorous evaluation of this technology-based intervention that requires few resources from the health care system is designed to produce generalizable results to inform clinical practice. Throughout the study, we used flexible solutions to address challenges related to recruitment and retention, which are common in RCTs. Successful strategies included multiple modes of contact for recruitment (postal mailing, email, and phone calls) and reminders in the intervention group to log in to the intervention website. Differential follow-up rates will be addressed using appropriate statistical techniques to mitigate potential bias. Future studies of eHealth PA interventions in postpartum populations at high risk for PPD should monitor recruitment and retention frequently and be flexible in implementing strategies to increase recruitment, retention, and adherence to interventions.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LAA and SEB were responsible for study concept, study design, funding acquisition, statistical analysis, and revision of the manuscript. MR was involved in data collection, supervision of the study team, study design modification, and drafting and revising the manuscript. NO designed the study tracking system, collected data, conducted statistical analysis, and critically reviewed the manuscript for important intellectual content. LGC and AC participated in data collection and drafting and revising the manuscript. EK was involved in supervision of the study team and revision of the manuscript. CPQ consulted the investigators regarding study design and statistical analysis and reviewed the manuscript for important intellectual content. CLA designed the eHealth intervention (MomZing) and reviewed the manuscript. SDB and MB contributed to study design and critically reviewed the manuscript for important intellectual content.

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Conflicts of Interest

None declared.

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Abbreviations

ASQ-3: Ages and Stages Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
dm-MVPA: device-measured moderate/vigorous intensity PA
EHR: electronic health record
GAD-7: Generalized Anxiety Disorder Scale
KPNC: Kaiser Permanente Northern California
MIBS: Mother-to-Infant Bonding Scale
PA: physical activity
PHQ-2: Patient Health Questionnaire-2
PHQ-8: Patient Health Questionnaire-8
PHQ-9: Patient Health Questionnaire-9
POW: POstpartum Wellness study
PPD: postpartum depression
PSQI: Pittsburgh Sleep Quality Index
PSS-10: Perceived Stress Scale
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
sr-MVPA: self-reported moderate or vigorous intensity physical activity

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Protocol

Efficacy of a Multimodal Digital Behavior Change Intervention on Lifestyle Behavior, Cardiometabolic Biomarkers, and Medical Expenditure: Protocol for a Randomized Controlled Trial

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Abstract

Background: The US Preventive Services Task Force recommends providers offer individualized healthy behavior interventions for all adults, independent of their risk of cardiovascular disease. While strong evidence exists to support disease-specific programs designed to improve multiple lifestyle behaviors, approaches to adapting these interventions for a broader population are not well established. Digital behavior change interventions (DBCIs) hold promise as a more generalizable and scalable approach to overcome the resource and time limitations that traditional behavioral intervention programs face, especially within an occupational setting.

Objective: We aimed to evaluate the efficacy of a multimodal DBCI on (1) self-reported behaviors of physical activity, nutrition, sleep, and mindfulness; (2) cardiometabolic biomarkers; and (3) chronic disease–related medical expenditure.

Methods: We conducted a 2-arm randomized controlled trial for 12 months among employees of an academic health care facility in the United States. The intervention arm received a scale, a smartphone app, an activity tracker, a video library for healthy behavior recommendations, and an on-demand health coach. The control arm received standard employer-provided health and wellness benefits. The primary outcomes of the study included changes in self-reported lifestyle behaviors, cardiometabolic biomarkers, and chronic disease–related medical expenditure. We collected health behavior data via baseline and quarterly web-based surveys, biometric measures via clinic visits at baseline and 12 months, and identified relevant costs through claims datasets.

Results: A total of 603 participants were enrolled and randomized to the intervention (n=300, 49.8%) and control arms (n=303, 50.2%). The average age was 46.7 (SD 11.2) years, and the majority of participants were female (80.3%, n=484), White (85.4%, n=504), and non-Hispanic (90.7%, n=547), with no systematic differences in baseline characteristics observed between the study arms. We observed retention rates of 86.1% (n=519) for completing the final survey and 77.9% (n=490) for attending the exit visit.

Conclusions: This study represents the largest and most comprehensive evaluation of DBCIs among participants who were not selected based on their underlying condition to assess its impact on behavior, cardiometabolic biomarkers, and medical expenditure.

Trial Registration: ClinicalTrials.gov NCT04712383; https://clinicaltrials.gov/study/NCT04712383

International Registered Report Identifier (IRRID): RR1-10.2196/50378

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KEYWORDS

health behavior; fitness; digital devices; lifestyle change; cardiovascular disease; chronic disease; physical activity; nutrition; sleep; mindfulness

Introduction

In July 2022, the US Preventive Services Task Force (USPSTF) recommended that providers offer personalized health behavior interventions for improving diet and physical activity to all adults in the United States, independent of an individual's underlying risk for cardiovascular disease [1]. Tacit within this recommendation is a recognition that Americans, generally speaking, have suboptimal lifestyle behaviors [2,3] and have an increased risk of cardiovascular disease. Less than half of all Americans engage in the recommended 150 minutes per week of moderate-intensity aerobic activity or 75 minutes/week of vigorous physical activity, and only 12.3% and 10% of 294,566 surveyed adults in the United States meet the recommended daily intake of fruit or vegetables, respectively [4,5]. It is estimated that half of all American adults (117 million individuals) have at least 1 or more chronic diseases [4,6] and cardiovascular disease is the number 1 cause of death and disability [7,8]. Evidence suggests that chronic disease incidence and progression are accelerated by suboptimal health behaviors [9-12]; conversely, improving lifestyle behaviors can prevent the onset of chronic disease or modify its trajectory [13-18].

Strong evidence for the ability of an intervention to improve multiple lifestyle behaviors and prevent or delay disease onset comes from the literature surrounding the Diabetes Prevention Program, which focuses interventions among the population with prediabetes and has demonstrated as much as 30% to 60% reduction in the incidence of diabetes [19-21]. Additionally, scaling up the Diabetes Prevention Program required significant support from the Centers for Disease Control and Prevention, including increasing workforce expansion to implement the program cost-effectively, standardizing program implementation to assure quality, providing infrastructure resources to build sites that can provide the program, and developing a network to increase referrals for use of the prevention program [20,21]. However, the translation of these effects for a more generalized population is not well established [20,21]. Certainly, extending this model to all adults, independent of their risk of chronic disease, would require a huge financial and logistical undertaking, which may not be feasible.

Digital behavior change interventions (DBCIs) use mobile apps, wearables, computer programs, or websites to prevent disease through health behavior promotion and hold promise to overcome resource and time limitations that traditional behavioral interventions programs face [22-24]. Indeed, digitization of the Diabetes Prevention Program has demonstrated similar treatment effects [25-27]. Efforts to evaluate the feasibility of implementation and maintenance of in-person and digital diabetes prevention program are underway and will provide critical insight for scaling up implementation of digital approaches [28,29]. Whether the success of a digital Diabetes Prevention Program translates to the general population, that is, with and without prediabetes, remains unknown. Thus, rigorous evaluation of a holistic DBCI in the general population is needed in light of the USPSTF's recommendation. However, investigating the effects of multimodal intervention on a diverse set of behaviors is difficult, and recruitment, retention, and DBCI adherence pose a challenge for conducting these types of studies in populations that are not recruited from clinics or on the basis of their underlying conditions.

Occupational settings provide a unique opportunity to engage a large proportion of the adult population in lifestyle behavior intervention and have been endorsed by the American Heart Association [30]. In addition to promoting healthy behavior among adults, wellness programs in the workplace can boost morale and improve productivity [31,32]. Additionally, DBCI programs are less likely to be disruptive in an occupational setting in comparison to traditional programs and, therefore, more likely to experience higher engagement and adherence. However, the availability of resources such as in-person coaching, room and space availability, and time off from work responsibilities constrain the ability to scale behavioral interventions.

To address these issues, we present a framework for a DBCI that integrates the Health Belief Model with proposed mechanisms of lifestyle interventions' effect on chronic conditions as a precursor to subsequent research that will describe the primary outcomes of our innovative study. In this paper, we describe the design of the UMass Fitbit Care Study, which evaluates a multimodal DBCI provided by Fitbit among health care employees in Central Massachusetts. The primary objectives of the UMass Fitbit Care study were to evaluate the efficacy of intervention on the following (Textbox 1):

Our hypothesis is that self-reported lifestyle behaviors are going to be a proximal outcome affected by the intervention and likely to show the strongest treatment effect; cardiometabolic biomarkers will be more distal and show a modest treatment effect; and medical expenditure will be the most distal outcome and demonstrate a minimal treatment effect during the study period but may reveal a trend towards reduced expenditure among the intervention group.

The secondary objectives of the UMass Fitbit Care study were to characterize the following (Textbox 2):

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Textbox 1. Primary objectives of the UMass Fitbit Care study.

- Change in self-reported lifestyle behaviors on physical activity, nutrition, sleep, and mindfulness among participants
- Cardiometabolic biomarkers over a 12-month period
- Chronic disease–related medical expenditure

Textbox 2. Secondary objectives of the UMass Fitbit Care study.

- Trajectories of intervention engagement over a 12-month period
- Differential engagement of the Fitbit intervention in relation to baseline behavior and comorbidities
- Differential efficacy of interventions based on engagement

Methods

Study Design

The UMass Fitbit Care Study is a dual-arm, unblinded randomized clinical trial with a 12-month study period. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines were used in the development of this protocol and fulfilled the SPIRIT checklist [33]. Recruitment began in December of 2020. Participants were randomized to the intervention or control arm using a permuted block randomization that stratified based on age (40 vs ≥40) and sex to achieve a balance for those 2 demographic variables between the intervention and control groups (Figure 1). Participants were randomized 1:1 to a control arm, where participants only received their standard health and wellness benefits during the study period, or an intervention arm, where participants received their standard health and wellness benefits as provided by their employer, plus a digital behavioral change intervention through Fitbit at no cost for 1 year. The Fitbit DBCI included 5 components: a wearable health and fitness device (participant choice of Fitbit Inspire 2 tracker or Versa 3 smartwatch), a wireless weight scale (Fitbit Aria Air), the Fitbit app (provided basic tracking and goal setting functionalities), Fitbit Premium (provided additional advanced metrics and rich video content through the Fitbit app), and an on-demand human health coach (provided goal setting, action planning, and accountability support through secure, asynchronous, in-app messaging).

Figure 1. UMass Fitbit Care Study design: health behavior data were collected through baseline and quarterly web-based surveys, while biometric measurements were obtained during clinic visits at baseline and at the 12-month follow-up. The exit screening phase concluded in January 2022. *US dollars.

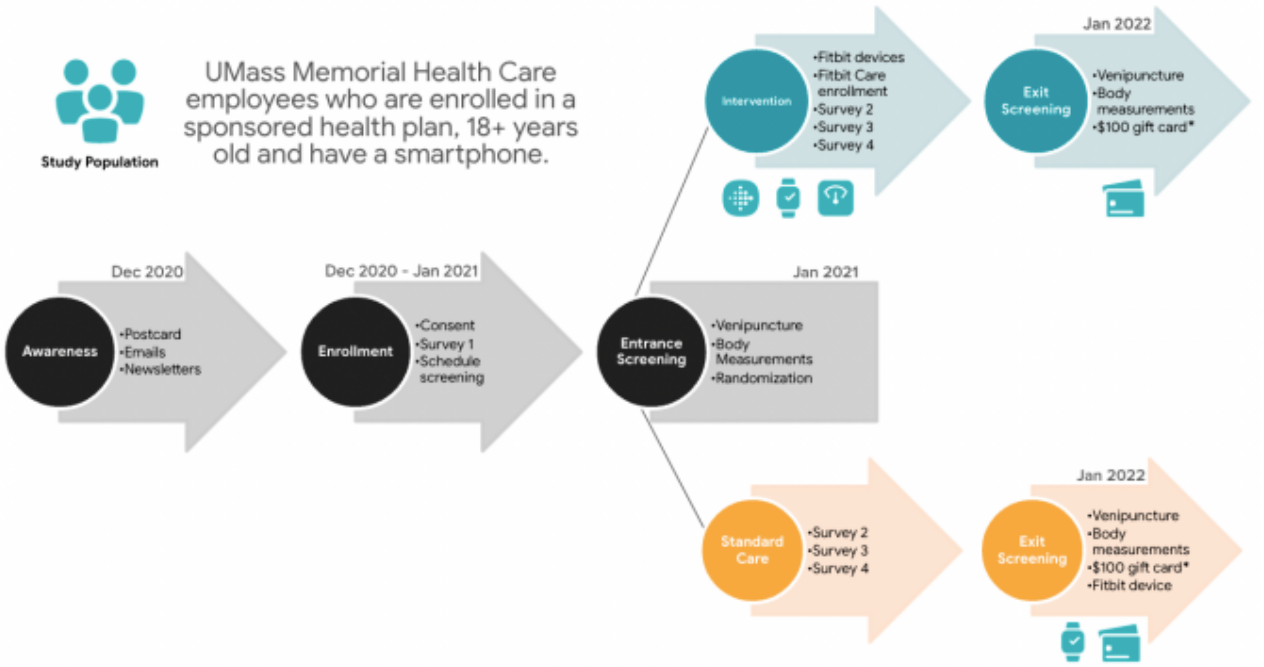

Study Setting and Participants

This study was conducted in Worcester, Massachusetts, with employees of UMass Memorial Health (UMMH). To be eligible, participants must have been enrolled on a UMMH-sponsored health plan, had to own a smartphone, had to be 18 years of age or older, and agreed to consent to the study (Figure 1). Participants who were pregnant at the time of enrollment, did not speak English, or were incarcerated were excluded from the study. The study had an a priori enrollment goal of up to 700 employees, which represents roughly 7.5% of the entire eligible population. The sample size for this study was derived based

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on the pragmatics of resource availability. All eligible employees were invited to participate in the study through electronic communication and a home mailer. To be enrolled in the study, participants had to electronically sign informed consent, fill out a baseline survey and demographics, use a self-scheduling service to pick an appointment for their initial biometric screening, and then complete said screening in person. Participants were then randomized to either the intervention arm or the control arm. Randomization was conducted using a random number generator to provide a random number of 1 or 2 for each of the study participants. A permuted block design with random block sizes was used to generate the randomization sequence. That sequence was loaded into a randomization module using a free, secure, and robust data collection platform called REDCap (Research Electronic Data Capture; developed at Vanderbilt University) so that it was readily available during the in-person screening process. Participants were asked to schedule an exit biometric screening at the end of the 12-month study period. Because this intervention being investigated is designed to help users improve their health behaviors in alignment with the advice of their health care providers and not to make medical decisions, the risk of harm to health is low. Participants were free to withdraw from the study at any time.

Ethical Considerations

A trial steering committee consisting of 2 principal investigators, JM and SB, met biweekly to provide supervision of the study, ensure progress milestones were met, and communicate important protocol updates to relevant parties. The study was reviewed and approved by the University of Massachusetts Chan Medical School (UMass Chan) Institutional Review Board (approval #H00021669) and registered on ClinicalTrials.gov (NCT04712383) on January 13, 2021. All participants had to electronically sign an informed consent to participate in the study. Entrance and exit biometric exam data were collected in person; held by Quest Diagnostics; and electronically transferred to UMass Chan, where it was stored on an encrypted server approved for data containing personal health information and personal identifying information. The medical claims data from Conifer were also transferred to the same server for analysis. Participants who completed both the entrance and exit biometric screenings were provided a US $100 incentive via a Visa e-gift card. Additionally, participants assigned to the intervention arm were able to keep the Fitbit wearable device and weight scale received during the study, and those assigned to the control arm received a Fitbit wearable device at their exit screening appointment.

Intervention

Participants in the intervention group were provided with a Fitbit tracker and scale and received assistance in creating a Fitbit account in the Fitbit app, syncing their devices, and enrolling into the study experience in the Fitbit app. Enrolling into the study experience gave each participant access to Fitbit Premium and Health Coaching.

Fitbit DBCI Components

Wearable Health and Fitness Device

Intervention participants had a choice of a Fitbit Inspire 2 tracker or a Fitbit Versa 3 smartwatch. Both devices provided comparable health and fitness tracking features and capabilities, including steps, distance, energy burn, exercise, heart rate, active zone minutes (AZM; measure of moderate-to-vigorous physical activity based on the Physical Activity Guidelines for Americans), and sleep. The Fitbit Inspire 2 had a smaller, bracelet-like form factor and longer battery life (~10 days), while the Fitbit Versa 3 had a watch form factor, additional smartwatch features (built-in GPS, apps, etc.), and a shorter battery life (~6 days).

Wireless Scale

The Fitbit Aria Air scale provided intervention participants with a simple wireless (Bluetooth) scale that integrated with the Fitbit app for ease of weight trend tracking.

Fitbit App

The Fitbit app provided intervention participants with features to enhance tracking and goal setting for each of the health and fitness measures tracked by their wearable device. For example, the AZM feature in the app allowed users to see graphs of their trends in moderate-to-vigorous physical activity over time (daily, weekly, monthly, etc.) and to set personal goals for the number of AZMs to achieve in a day and a week. As another example, the sleep tracking feature allowed them to see their sleep duration, bedtime and wake-up time consistency, and time spent in different sleep stages and to see trends in these measures over time, as well as set goals for sleep duration, bedtime, and wake-up time.

Fitbit Premium

Participants assigned to the intervention arm also received Fitbit Premium. Fitbit Premium is a subscription membership service that provides advanced scores and rich content within the Fitbit app to enhance the participant experience. The advanced scores, included in both the sleep score and stress management score, provide additional feedback and insights to users on these dimensions of their wellness. The rich content includes hundreds of workout videos and mindfulness audio sessions, as well as healthy recipes, all designed to help users improve their health behaviors (Figure 2).

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Figure 2. Sample screenshots of Fitbit Premium features: rich video content including meditation videos (left) and advanced analytics including sleep score (right).

On-Demand Human Health Coach

Each intervention participant was paired with a personal, human health coach that provided goal setting, action planning, and accountability support for health behavior improvement across activity, nutrition, sleep, and mindfulness, with emphasis on the domains desired by the participant at any moment in time. The health coaches sent a secure, asynchronous, in-app SMS text message within a day of enrollment to each participant to start the process of creating a goal and an action plan for improving the behaviors when the participant's motivation and confidence were greatest. For example, there might be an exchange of a few messages to determine that a particular user wanted to focus on improving sleep. The coach might help that user set a goal about a regular sleep schedule and an action plan for doing a mindfulness session before bed and not bringing electronic devices to bed (Figure 3).

The health coach then sent a message every day or every other day for the first few weeks to encourage the participant to stick with the plan and to provide support for follow-through or adjustment of the plan. The health coaches monitored core Fitbit data from the users (steps, AZMs, sleep, etc) via a dashboard to help tailor their support. The frequency of messages decreased as the participant gained self-efficacy; however, the option to increase messaging remained if the participant wanted extra support. Each participant was free to use any of the software features of the Fitbit app and Fitbit Premium as desired throughout the course of the intervention, although the health coach made recommendations on features such as workout videos, mindfulness sessions, etc that might be most helpful based on the participant's goals, action plan, and device data. If participants were unresponsive for several weeks or requested to discontinue coaching, the health coaches archived their profiles in their dashboard and ceased sending them messages unless the participant proactively re-engaged by sending the coach a message.

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Figure 3. Sample screenshot of on-demand health coaching features. The participant and coach collaboratively create an action plan for stress management. The user can click on the coach's profile to learn more about their background or click on the messaging button to chat securely and asynchronously.

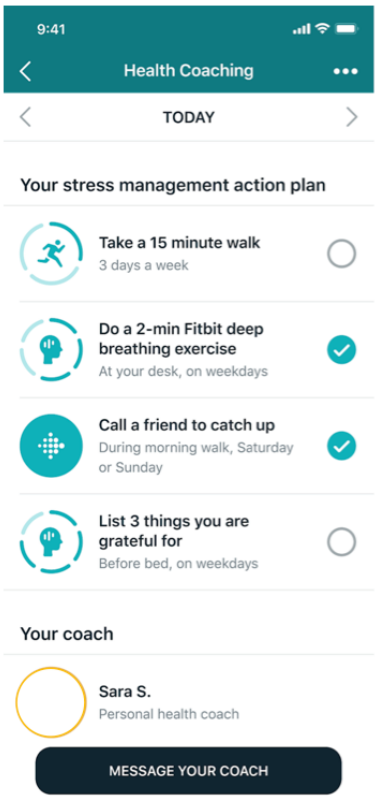

Data Collection and Management

There were four forms of data collected: (1) survey data through baseline surveys and scheduled quarterly surveys for all participants; (2) Fitbit-tracked data for those participants assigned to the intervention arm; (3) biometric data for all participants, which include anthropometric and vital sign measurements and laboratory investigations performed by Quest Diagnostics; and (4) total medical expenditure claims data abstracted by Conifer Health Solutions for all participants. Table 1 describes all the data collected as part of this study. An initial invitation to participate in the study was sent via email to a list of predetermined eligible employees. Interested participants signed up for the study by entering their email address, signing the consent form, and filling out their baseline survey and demographics and presented at an in-person biometric screening appointment performed by Quest Diagnostics staff. At this first visit for the biometric screening, participants in both the control group and intervention group were randomized and scheduled for the 4 follow-up quarterly surveys to study trends in perceptions, motivation, and confidence around improvements in health behaviors. An email was sent to participants each quarter with a link to the quarterly survey in UMass REDCap. Up to 2 reminder emails were sent to participants who did complete the survey. An additional email to all participants was sent in September 2021 to re-engage participants at the three-quarters point of the study. All survey data collection was performed using the REDCap data collection platform. SAS (SAS Institute) was used for all analyses. The final trial dataset, which consists of survey questionnaire data, Fitbit device data, Quest biometric data, and Conifer claims data, is only available to partners within the UMass Chan Department of Population and Quantitative Health Sciences who were responsible for the analysis.

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Table 1. Data collection schedule.

Events and procedures	Study period (January-December 2021)						Poststudy period
	Enrollment	Allocation	Postallocation			Close-out	
	Visit 0	Visit 1	3 months	6 months	9 months	12 months or visit 2	
Enrollment							
Informed consent	✓						
Demographics	✓						
Eligibility confirmation	✓						
Allocation		✓					
Assessment							
Biometric screening (height, weight, waist circumference, blood pressure, etc)—Quest Diagnostics		✓				✓	
Baseline survey (nutrition, exercise, sleep, and mindfulness habits)—REDCap[a]	✓						
Quarterly survey (nutrition, exercise, sleep, and mindfulness habits)—REDCap			✓	✓	✓	✓	
Two years of total medical expenditure claims data—Conifer Health Solutions							✓
Intervention							
Onboarding survey for coaching component		✓					
Engagement data for each component of intervention		• Continuous collection of device wear duration • Event-based collection of app-open events, feature usage (including Fitbit Premium features), secure messages with coach, etc	• Continuous collection of device wear duration • Event-based collection of app-open events, feature usage (including Fitbit Premium features), secure messages with coach, etc	• Continuous collection of device wear duration • Event-based collection of app-open events, feature usage (including Fitbit Premium features), secure messages with coach, etc	• Continuous collection of device wear duration • Event-based collection of app-open events, feature usage (including Fitbit Premium features), secure messages with coach, etc	• Continuous collection of device wear duration • Event-based collection of app-open events, feature usage (including Fitbit Premium features), secure messages with coach, etc	

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Events and procedures	Study period (January-December 2021)					Poststudy period
	Enrollment	Allocation	Postallocation		Close-out	
	Visit 0	Visit 1	3 months	6 months	9 months	12 months or visit 2	
Wearable device and weight scale data		• Continuous collection of wearable device data (steps, resting heart rate, sleep metrics, etc) • Event-based collection of weight data	• Continuous collection of wearable device data (steps, resting heart rate, sleep metrics, etc) • Event-based collection of weight data	• Continuous collection of wearable device data (steps, resting heart rate, sleep metrics, etc) • Event-based collection of weight data	• Continuous collection of wearable device data (steps, resting heart rate, sleep metrics, etc) • Event-based collection of weight data	• Continuous collection of wearable device data (steps, resting heart rate, sleep metrics, etc) • Event-based collection of weight data	

[a]REDCap: Research Electronic Data Capture.

Statistical Analysis

In this paper, we present descriptive statistics for baseline characteristics and overall engagement among the participants assigned to the intervention group using proportions and the mean for the distribution of categorical and continuous variables, respectively. The study will evaluate its primary objectives using intention-to-treat analysis. A 2-tailed Student *t* test for independent samples will be used to compare the mean of continuous variables, and a chi-square or Fisher exact test will be used to compare categorical variables between the intervention and control groups. Secondary objectives will be evaluated using group-based trajectory modeling to identify distinct trajectories of engagement and adherence, the association of distinct trajectories with baseline behavior and comorbidities, and performing an intervention-only analysis where the treatment effect of the intervention is evaluated across different trajectories of engagement. Additional exploratory analyses will consider accounting for possible contamination based on the self-reported use of wearable health and fitness devices among the control group participants. There are no plans to use biological specimens in ancillary studies. Data collection questionnaires can be provided upon request.

Results

Baseline Characteristics

A total of 13,391 employees were eligible to enroll in the UMass Fitbit Care Study and received an email or home mailer about participating in the study. Of those invited, 758 completed consent to participate in less than 24 hours and scheduled an appointment for initial biometric screening. The follow-up rate was 75.7%, with 603 individuals attending the biometric screening and getting randomized to the intervention (n=300, 49.8%) or control group (n=303, 50.2%). Baseline characteristics of these 2 groups are provided in Table 2, and no systematic differences were observed between the 2 groups. On average, participants were 46.7 (SD 11.2) years of age. The majority of the participants were female (80.3%, n=484), White (85.4%, n=504), and non-Hispanic (90.7%, n=547). More than half (74.8%, n=440) of the participants had a baseline BMI that classified them as overweight or obese.

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Table 2. Baseline participant characteristics.

Characteristics	Intervention (n=300)	Control (n=303)	*P* value
Age (years), mean (SD)	46.3 (11.0)	47.2 (11.4)	.34
Sex, n (%)			.50
Female	241 (80.3)	243 (80.2)	
Race (intervention: n=295; control: n=295), n (%)			.80
White	254 (86.1)	250 (84.8)	
Black or African American	11 (3.7)	9 (3.1)	
Asian	20 (6.8)	22 (7.5)	
Other	10 (3.4)	14 (4.8)	
Ethnicity, n (%)			.34
Hispanic	16 (5.3)	25 (8.3)	
Non-Hispanic	277 (92.3)	270 (89.1)	
No answer	7 (2.3)	8 (2.6)	
BMI classification (intervention: n=297; control: n=291), n (%)			.56
Underweight	3 (1.0)	2 (0.7)	
Normal	65 (21.9)	78 (26.8)	
Overweight	100 (33.7)	91 (31.3)	
Obese	129 (43.4)	120 (41.2)	
Biometric measurements, mean (SD)			
Weight (lb; intervention: n=297; control: n=292)	185.5 (46.9)	178.4 (43.7)	.06
Height (in; intervention: n=297; control: n=291)	65.5 (3.5)	65.2 (3.3)	.26
BMI (kg/m^2; intervention: n=297; control: n=291)	30.4 (7.1)	29.5 (6.7)	.12
Waist circumference (in; intervention: n=294; control: n=289)	37.6 (6.5)	36.4 (6.0)	.02
Systolic BP[a] (mm Hg; intervention: n=297; control: n=291)	121.0 (9.6)	119.2 (10.2)	.03
Diastolic BP (mm Hg; intervention: n=297; control: n=291)	75.2 (8.0)	74.3 (7.9)	.17
HbA_{1c}[b] (%; intervention: n=297; control: n=292)	5.2 (0.6)	5.2 (0.5)	.47
Total cholesterol (mmol/L; intervention: n=296; control: n=291)	190.6 (38.7)	196.8 (38.0)	.05
HDL-C[c] (mmol/L; intervention: n=296; control: n=292)	58.0 (14.5)	59.3 (14.7)	.29
LDL-C[d] (mmol/L; intervention: n=296; control: n=292)	118.7 (34.5)	123.5 (34.6)	.10
TC/HDL ratio[e] (intervention: n=296; control: n=292)	3.5 (1.0)	3.5 (1.2)	.57

[a]BP: blood pressure.

[b]HBA_{1c}: hemoglobin A_{1c}.

[c]HDL-C: high-density lipoprotein cholesterol.

[d]LDL-C: low-density lipoprotein cholesterol.

[e]TC/HDL ratio: total cholesterol/high-density lipoprotein cholesterol ratio.

Intervention Engagement and Participant Retention

To approximate real-world scenarios, this study did not have a specific plan to promote participant engagement with the intervention or retention of participants in the study beyond ensuring that their Fitbit device was synced with the mobile app and initial communication with their personal health coach occurred. The median wear time for Fitbit was observed to be 325 (IQR 154-372) days, and 264 (88%) participants used health coaching at least once. Of the 603 participants who completed entrance screening and thus were included in the study, 8 (1.3%) withdrew, 519 (86.1%; intervention: n=251; control: n=268) completed exit surveys, and 469 (77.8%; intervention: n=227; control: n=243) completed exit biometric screening (Figure 4).

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Figure 4. UMass Fitbit Care Study participant flow: flow of participants through the UMass Fitbit Care study, showcased by the CONSORT (Consolidated Standards of Reporting Trials) diagram. UMMHC: UMass Memorial Health Center.

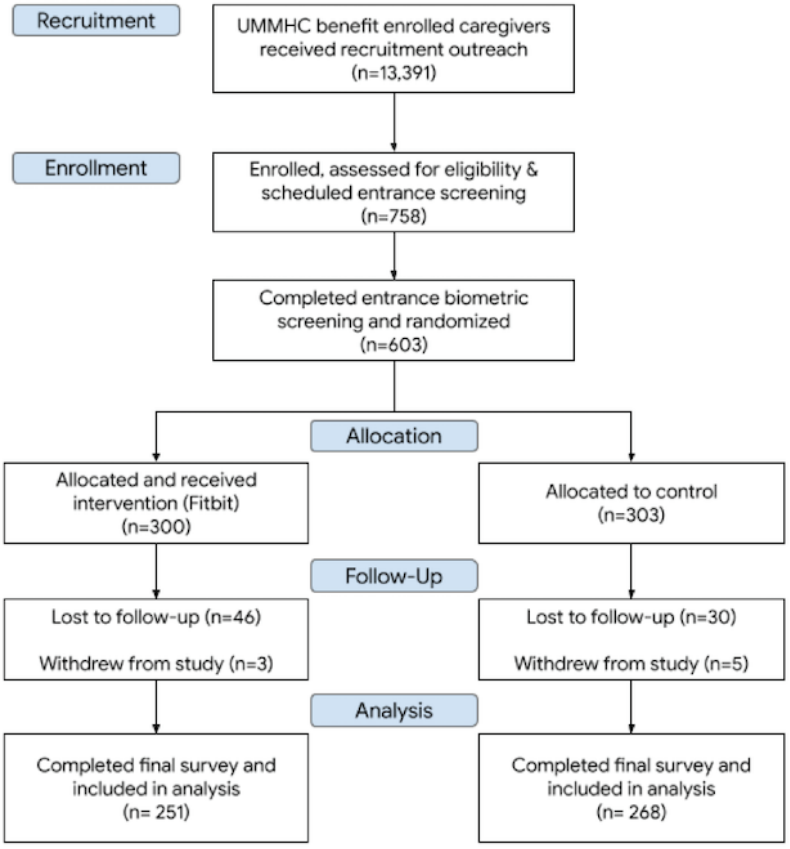

Discussion

Overview

We describe the design, rationale, and baseline characteristics of a randomized control trial of a multimodal DBCI from Fitbit on improving lifestyle behaviors and cardiometabolic health in a general, rather than disease-specific, population. The high retention rate and balanced distribution of baseline characteristics, paired with a comprehensive assessment of the intervention's impact on behavioral, cardiometabolic biomarkers, and medical expenditure, will allow for detailed evaluation of the intervention for primary and secondary endpoints.

Comparison With Prior Work

Research on the effectiveness of DBCIs for chronic disease prevention has yielded mixed results with regard to behavioral change and cardiometabolic outcomes. One randomized controlled trial led by Toro-Ramos et al [34] assessed the effectiveness of a lifestyle app in individuals with prediabetes, in which significant weight loss was observed in the intervention group, but there was no significant difference in hemoglobin A_{1c} levels between the intervention and control groups at 1 year (mean difference 0.006%; n=103; *P*=.93) [35]. Likewise, another study investigating a mobile diabetes prevention program found a 1.9% (n=163) decrease in hemoglobin A_{1c} among intervention participants compared to the control group, but there were no improvements in patient-reported behaviors such as mood after 12 months [36]. Additionally, such interventions have often focused on evaluating behaviors within disease-specific populations [34,37-40].

Future Aims

Therefore, we aim to adopt a more holistic approach to behavior change intervention research by evaluating the effectiveness of a DBCI intervention in a broader, real-world population and assessing changes in behavior across 4 key areas: physical activity, nutrition, sleep, and mindfulness. Additionally, we will conduct comprehensive biometric evaluations using both digital and laboratory biomarkers, which will contribute valuable insights to the existing literature.

There are several potential mechanisms through which Fitbit DBCI can affect healthy behavior changes, which lie upstream of factors that impact the onset and progression of chronic diseases. The Lifestyle Medicine Research Summit proposed that promotion of healthy lifestyle behavior can interrupt the pathogenesis of chronic diseases and possibly reverse it [41-44]. The Health Belief Model is a well-established theory to explain an individual's decision-making for a behavioral change [45]. We propose that an integration of these 2 frameworks, as described in Figure 5 [43], can provide theoretical underpinning for the impact of the Fitbit DBCI on chronic diseases. Fitbit DBCI's ability to pair tracking of behavior with nudges and coaching that can be delivered through telecommunications and motivational messaging can act on lifestyle behaviors that lie upstream of factors that lead to chronic diseases [37,46-50]. Support for individual goal setting and self-monitoring through alerts based on certain patterns of inactivity or pushing

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motivational messages based on the accomplishment of healthy behaviors can motivate individuals, promote self-efficacy, and provide cues for action [51-53]. It offers a holistic approach to improving lifestyle behaviors and is responsive to the USPSTF's recommendation for tailoring behavioral intervention to individuals' needs.

In our study, we observed a high adherence to wearable devices, with a median wear time of 325 (IQR 154-372) days. We had an 86.1% (n=519) retention rate for exit surveys that evaluated self-reported behavioral outcomes and a 77.9% (n=490) retention rate for exit visits that measured cardiometabolic biomarkers. Our results are consistent with findings from prior research on DBCIs for diabetes and hypertension prevention [26,39].

Further secondary analysis of the data from this study can inform the feasibility and acceptance of providing multimodal DBCIs for employees in a workplace setting. Additionally, through the collection of data over the course of the year from the Fitbit intervention, we will be able to perform secondary data analysis that characterizes the intensity of the coaching intervention, which is likely to be a key determinant of its efficacy. A 3-year study showed that individualized biweekly counseling decreased sedentary time and promoted healthy behavior [41,42]. However, it is unlikely that all users of the program require an intervention of this intensity. We will be able to perform analysis to understand factors associated with goal setting and the self-efficacy of participants for affecting behavioral change as measured through standardized questionnaires. Thus, our findings will inform optimal intervention practices for implementing DBCI programs at scale, where participant-reported outcomes can be used to facilitate tailored behavioral counseling for participants and align DBCI programs with USPSTF recommendations for individualizing interventions.

Figure 5. Conceptual framework of Fitbit's multimodal digital behavior change intervention (DBCI) for improving healthy behaviors and cardiometabolic outcomes. Components of Fitbit's DBCI are depicted in blue boxes. The framework represents a combination of the Health Belief Model and the framework proposed by Bodai et al.

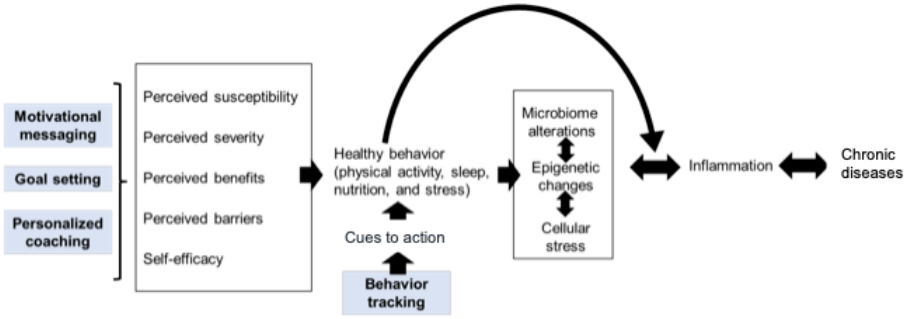

Strengths and Limitations

Several aspects of the study represent methodological strengths, which include the use of a randomized design, rigorous and standardized outcome evaluation, and robust adherence to the protocol. However, the study's limitations should also be noted when interpreting the results from this study. Our study lacks an active control and therefore we cannot estimate treatment effects of activity tracking and DBCI separately. However, the intended use of Fitbit health coaching is as a combination, and therefore, this study estimates the combined treatment effect of this multimodal intervention. Our study sample underrepresents Black or African American, Hispanic, and Asian staff, suggesting a need for future studies to implement robust recruitment strategies to target underrepresented groups. Moreover, our study sample was selected from employees at an urban academic medical center, which may suggest that these participants are already engaging in healthy behaviors given their health backgrounds. Our study sample included individuals who volunteered to participate in digital health research. Our baseline characteristics suggest that there is skewness in demographic representation such that individuals more likely to participate in these studies are enrolled in this study, which may account for our high adherence and retention rates. While that limits the generalizability of the study findings, the randomized assignment of interventions balances any possible bias that may emerge from early responders to the invitation. Lifestyle behavior was measured using standardized surveys with high face validity, but these were not validated instruments, such as the Pittsburgh Sleep Quality Index, 24-hour food recall, perceived stress scale, etc, which limits the external generalizability of the findings; however, differences between groups in these measures are unlikely to be affected by them.

Conclusions

To our knowledge, this is one of the largest evaluations of a multimodal DCBI's impact on physical activity, nutrition, sleep, and mindfulness among participants who were recruited independent of their underlying disease status. It is also among the only studies that comprehensively evaluates the impact of the DBCI on the sequelae of healthy behavior by measuring cardiometabolic biomarkers and abstracting medical expenditure data. Finally, data from this study can help understand adherence to DBCIs over the period of 1 year and elucidate the association between intensity of coaching, self-reported motivation for changing behavior, and objective measurement of health behavior trajectories from wearable health and fitness devices and wirelessly connected scales. Taken together, the findings from this study have the promise to provide useful insights for individualizing the Fitbit intervention among otherwise healthy people, as recommended by the 2022 USPSTF.

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Acknowledgments

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Data Availability

The datasets analyzed during this study are available from the corresponding author on reasonable request. Due to the collection of participant health information, we do not have plans for granting public access to participant-level datasets.

Authors' Contributions

SHW and AS wrote the manuscript. JM developed the concept and design of the study. JC, MH, and BB provided critical revisions for important intellectual content. PL, DA, and BB performed the statistical analysis for the manuscript. Supervision provided by AS, JM, and DM. Logistical support provided by PL, SG, and NH. All authors reviewed the final manuscript and are in agreement with authorship contributions. We used the generative AI tool ChatGPT by OpenAI for editing purposes on April 22, 2024.

Conflicts of Interest

The following authors declare no competing financial or nonfinancial interests: SHW, SG, DA, PL, DM, BB, SB, and AS. The following authors declare no competing nonfinancial interests but the following competing financial interests: JC, MH, AG, NH, and JM are Google employees and own stock at Alphabet.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 42 KB - resprot_v13i1e50378_app1.docx]

Multimedia Appendix 2
CONSORT-EHEALTH (V 1.6.1) checklist.
[PDF File (Adobe PDF File), 1156 KB - resprot_v13i1e50378_app2.pdf]

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Abbreviations

AZM: active zone minutes
CONSORT: Consolidated Standards of Reporting Trials
DBCI: digital behavior change intervention
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UMass Chan: University of Massachusetts Chan Medical School
UMMH: UMass Memorial Health
USPSTF: US Preventive Services Task Force

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Protocol

The Implementation of the Advocacy Intervention for Midlife and Older Women Who Have Experienced Intimate Partner Violence: Protocol for a Randomized Controlled Trial

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Abstract

Background: Midlife and older women who experience intimate partner violence (IPV) often have less access to supports and services than younger women. There is far less focus on research and supports for midlife and older women compared to younger women experiencing IPV, and often, neither elder abuse nor IPV services meet their needs. Few interventions are available to meet the needs of midlife and older women.

Objective: The goal of this randomized controlled trial is to test the effectiveness of an advocacy intervention for midlife and older women who experience IPV and to learn from the experiences of those who implement and participate in the program.

Methods: This trial is a 2-arm, unblinded, parallel, pragmatic randomized controlled trial with a qualitative component. Eligible participants will be women who live in the Maritime provinces of Canada (New Brunswick, Nova Scotia, and Prince Edward Island), who are in midlife and older (aged approximately ≥50 years), and who are currently in a relationship with an abusive partner or have recently left an abusive partner. Facilitators will be trained to deliver the intervention. The intervention will be entirely virtual and will consist of 2 components: (1) an empowerment component, which will involve sharing resources and information with the women; and (2) a social support component, which will include providing support and encouragement to women for 12 weeks. Quantitative effectiveness data will be collected from all trial participants at baseline, 3 months after the intervention, and 9 months after the intervention about the incidence and severity of IPV, physical and mental health, and safety behaviors and strategies. Qualitative interviews will be conducted with the facilitators and intervention group participants. Control group participants will receive a static, nontailored version of the advocacy intervention for midlife and older women (AIM) intervention materials after baseline data collection.

Results: A total of 12 facilitators have been trained to deliver the AIM intervention to trial participants. Participant recruitment and data collection will be completed in January 2025. Data analysis will continue throughout the data collection period, and the results will be disseminated by December 2025.

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Conclusions: This research will result in the adaptation and testing of a program to support and empower midlife and older women in the Maritime provinces of Canada who experience IPV.

Trial Registration: International Standard Randomized Controlled Trial Registry ISRCTN30646991; https://doi.org/10.1186/ISRCTN30646991

International Registered Report Identifier (IRRID): DERR1-10.2196/57886

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KEYWORDS

intimate partner violence; intervention; virtual; midlife; aging

Introduction

Background and Rationale

Intimate partner violence (IPV) is widely recognized as a major public health concern globally [1] and in Canada, with 1 in every 10 adults aged ≥65 years experiencing some form of abuse each year [2]. We use the term IPV to refer to any type of abusive behavior (eg, emotional, verbal, physical, sexual, or financial) that occurs between intimate partners, such as spouses, those living in a common-law relationship, or in a dating relationship. While our knowledge is far less complete on IPV among older versus younger women, a mistaken assumption is that IPV ceases with age [3]. Prevalence studies have shown that between 15% and 30% of older women report IPV at some point in their lives [4-7]. Incidence studies have shown that 8.6% of women currently in partnerships experienced IPV since reaching the age of 55 years [8]; 3.5% of women aged ≥65 years experienced IPV in the past 5 years, with 2.2% in the past year [4]; and 5.5% of women aged between 50 and 64 years experienced IPV in the past 2 years [9]. In a study of coroners' files of homicide by individuals aged ≥65 years, 89% of homicide survivors were female, and of these, 93% were current or former spouses of male perpetrators [10]. It is generally recognized that IPV among older women is underestimated.

There is far less focus on research and supports for midlife and older women compared to younger women experiencing IPV, and often, neither elder abuse nor IPV services address their unique needs. Researchers define midlife as a pivotal time in the life span, representing the transition from earlier to later periods of life during which individuals are balancing multiple roles, life transitions, and opportunities and challenges [11]. Midlife is generally viewed as spanning from the ages of 40 to 60 years [11]. Midlife is viewed as a bridge between generations and can involve multiple caregiving responsibilities (eg, grandchildren, adult children, and aging parents), career development and retirement planning, changes in family leadership, and changes in health status (eg, developing chronic illnesses) [11]. During midlife, women often juggle multiple demands. People providing elder abuse services often are not equipped to support women from a gendered and relational lens [12], and those providing family violence services often focus on meeting the needs of girls, young women, and women with dependent children [13]. Thus, the needs of midlife and older women who experience IPV may not be met by the assistance of those working in elder abuse or IPV services. In addition, initiatives that offer IPV support and services to older women in Canada do not necessarily implement formal program evaluations, and therefore, information about the effectiveness of these initiatives is lacking [14].

Women have unique needs and experiences and require individualized help to receive the support they need. In a recent research study conducted by our team, we interviewed midlife and older women and found many groups of women, including francophone women, new immigrants (eg, from Arabic-speaking countries), Black women, and people living in rural places with limited access to services, have unique needs [15]. Research suggests that other populations considered vulnerable in Canada are also at increased risk of experiencing IPV, such as Indigenous women, gender and sexual minority groups, and people living with disabilities [16]. Women considered vulnerable and women with multiple vulnerable identities are at an increased risk of experiencing IPV due to them being exposed to multiple forms of systemic oppression (eg, racism, agism, and ableism), making it difficult to break the cycle of violence [17].

Given that many existing services are not appropriate to meet the unique needs of older women, there is an emergent emphasis on supports that do address the unique preferences and situations, or "victim-centered supports" [18,19]. There are few published studies about initiatives focused specifically on IPV and older women [14]. While a feminist lens is often used in research and with practitioners working with abused women and girls, gender-based analysis is often neglected by scholars and practitioners working with or for abused midlife and older women. In this research, we will use an intersectional approach to consider how various social factors (eg, age, gender, language, race, ethnicity, culture, and geographic region) intersect to impact women's risk of IPV exposure and their experiences of violence, their ability to seek help and access services, as well as their overall health and quality of life [20].

Objectives

The goal of this randomized controlled trial (RCT) with a qualitative component is to test the effectiveness of the 2 components of an advocacy intervention for midlife and older women (AIM) that has been adapted to support midlife and older women who have experienced IPV and to learn from the experiences of those who will implement and participate in the program. This research will support the adaptation, scale-up, and spread of the program to support and empower women in Canada in midlife and older who experience IPV to improve their health and quality of life.

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Methods

Trial Design

This trial is a 2-arm, unblinded, parallel, pragmatic RCT [21] registered in the International Standard Randomized Controlled Trial Registry (ISRCTN30646991). This protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [22]. The intervention has been modeled using the Template for Intervention Description and Replication checklist [23], and the results will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement for RCTs [24]. Figure 1 displays the CONSORT flow diagram for this RCT.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

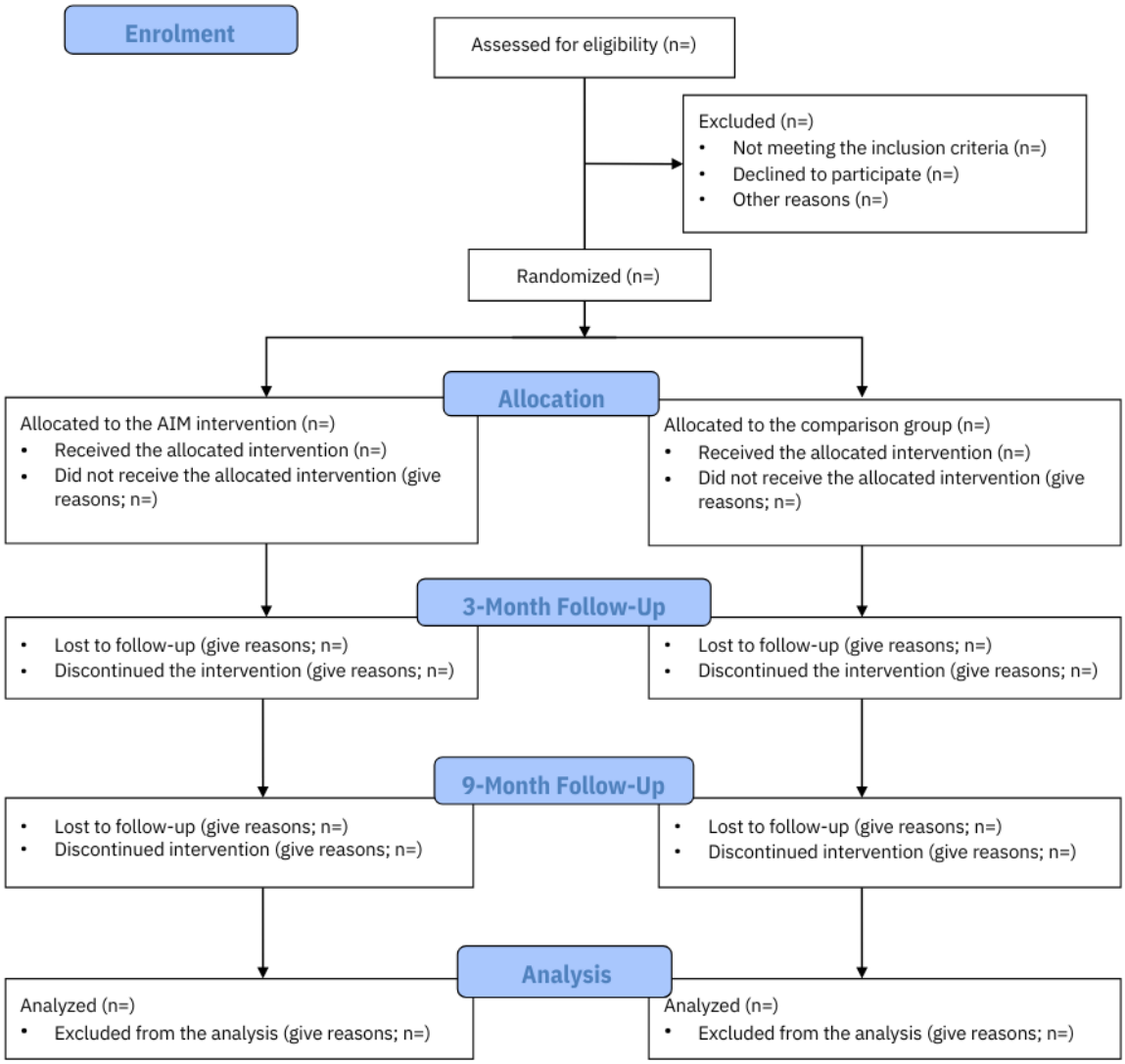

Study Setting

Participants will be recruited from the 3 Maritime provinces of Canada (New Brunswick, Nova Scotia, and Prince Edward Island). As the program will be delivered virtually, we are not restricted to a certain number of sites. Our rationale for including the Maritime provinces for this study is that the members of our research team are located within the Maritime provinces, and we have extensive professional and personal networks that will help to support the success of the research. The Maritime provinces are among the Canadian provinces with the highest proportion of adults aged ≥65 years [25]. In addition, New Brunswick is the only Canadian province that is officially bilingual and represents a unique opportunity to include both anglophone and francophone participants from the same geographic region [26].

Eligibility Criteria

The following inclusion criteria will be used to determine if women are eligible to be enrolled in the trial. The potential participants are those who self-identify as a woman; are in midlife and older (aged approximately ≥50 years); are currently living in the Maritime provinces; can participate in an interview in either English or French; and are currently in a relationship with an abusive partner or have recently left an abusive partner within the last year, including a same-sex partner.

In a recent systematic review [27], our team used the theoretical concepts of reclaiming self-theory and the four levels of

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prevention [28-31] to classify IPV interventions into the categories of (1) preventing IPV, (2) identifying and documenting IPV, (3) supporting women while living with or leaving an abusive partner, and (4) supporting women after leaving an abusive partner. The intervention used in this trial will target women in category 3 as it is designed to empower women to make decisions and take action related to the abuse they are experiencing or have recently experienced.

The dynamics of abusive relationships are such that leaving an abusive partner is often a process that involves leaving and returning multiple times [32]. During this process, the woman may reach out to available services, such as outreach services, or live in a transition house or other form of safe housing. Thus, the participants may have already contacted IPV services and may be using various forms of services or initiatives during the course of this study. Given that our research team will not be interfering with the supports and services that the participants are already using during their participation in the study, this study aligns with the tenets of a pragmatic trial [33]. Our team has had success recruiting older women experiencing IPV who had already accessed services, but we have had challenges recruiting older women in the region who have never contacted an organization for support [14]. The intervention is designed to provide information about other resources and supports available to women and to encourage women to use these services; therefore, it is not a concern that the women access and use other supports during our study.

AIM Intervention

Overview

After completing a recent systematic review focused on the IPV interventions relevant to women during the COVID-19 pandemic, including research evidence from 4 systematic reviews and 20 individual studies [27], our team identified an advocacy health promotion program [34] that was ideal to adapt, implement, and test in this RCT. Given that the advocacy health promotion program is not a proprietary program, permission was not required to adapt it for our research. The intervention reported by Tiwari et al [34] has been selected to be adapted for this trial because the researchers reported that it significantly reduced depression and psychological aggression scores and improved perceived social support and the use of safety-promoting behaviors. Other interventions that we examined in our systematic review either did not result in positive outcomes for the health and safety needs of women or the results did not reach statistical significance. We also found that providing highly tailored interventions can contribute to positive outcomes [35,36], and the intervention reported by Tiwari et al [34] could be tailored as needed. This study will pay particular attention to ensuring that those who are trained to deliver the intervention provide individualized and person-centered support.

An innovative aspect of this research is the adaptation of the intervention to meet the needs of midlife and older women that can often be different from those of younger women. For example, leaving one's home, property, and community may not be a priority for older women experiencing IPV [19], and therefore, the women will be provided support to empower them to identify their own goals and strategies for achieving those goals. The intervention has also been adapted to meet the needs of women who reside in the Maritime provinces of Canada. Information on local IPV services and resources will be provided to the participants. The format will also be adapted to meet the preferences of the women to use whatever form of technology they prefer for the social support component of the study. In addition, those trained to deliver the program will use a person-centered perspective to support the unique needs of the participants, such as for participants who are francophone, living in a rural place, or a new immigrant to Canada.

We have chosen to name the program the Advocacy Intervention for Women in Midlife and Older, and we will use the acronym AIM to refer to the intervention. The AIM intervention has 2 components: an empowerment component and a social support component. These components are theoretically congruous with the framework we are using based on the empowerment model by Dutton [37] and the social support theory by Cohen [38]. We expect that the combination of the empowerment and social support components will be highly effective.

Components of AIM

The empowerment component is derived from the empowerment model by Dutton [37] to increase women's safety. This component will involve the facilitator providing a 1-hour-long individual one-on-one information-sharing session with the participants that will be delivered virtually by telephone or video call. These sessions will include providing information on recognizing increased danger and how to use an individualized safety plan adapted for older women, providing information about cycles of violence, providing community and legal resources, and developing goals and strategies for the future. In addition to discussing this information, print materials will be provided electronically (via email) or in hard copy (via postal mail). Thus, this component clearly contributes to awareness raising and also empowers the women to develop changes in the future.

The social support component is based on the social support theory by Cohen [38] that involves tangible and perceived social support to contribute to health and well-being. This component will involve the facilitator scheduling weekly telephone or video calls over a course of 12 weeks at a time that is convenient to the participant. The duration of calls is variable and would average approximately 20 minutes per call. The calls are intended to provide encouragement and support and to answer questions the participant may have about using or applying the resources provided in the empowerment component. There are no specific or scheduled topics that are planned for each session. These are very individualized and based on the women's needs and questions that each woman may wish to discuss. For example, facilitators will be prepared to help women with recognizing their past abuse and processing the abuse as well as providing support to women who are undergoing court proceedings and legal issues. The social support provided through the weekly contact is a key component of the intervention in addition to the topics discussed.

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Comparison Group

The comparison group will receive a static, nontailored version of the AIM intervention materials after baseline data collection. They will be asked if they prefer to receive these materials via email or postal mail. The document will include a condensed version of the empowerment component and information about the dynamics of abusive relationship, warning signs of abuse for older adults, materials on safety planning and digital safety, local and national IPV resources, and guidance for setting goals for the future. The participants in the comparison group will not receive any further contact from the research team or facilitators to discuss these materials. Textbox 1 outlines the features (ie, information and support) that participants will receive depending on what group they are randomly assigned to.

Textbox 1. Features of the advocacy intervention for midlife and older women (AIM) intervention group and comparison group.

AIM intervention group

- Receives the information package
- Participates in 1-hour-long information-sharing session with the program facilitator
- Participates in 12 weekly social support sessions with the program facilitator

Comparison group

- Receives the information package

Sample Size

For the quantitative portion of the study (ie, the RCT), we determined an appropriate sample size that would be sufficient to contribute to the evidence base. We reviewed the sample sizes analyzed in the systematic review we conducted, the sample sizes of the studies focused on women experiencing IPV in midlife and older, and the sample size calculations in the study from which we have adapted the program [34]. We used our prior experience in recruiting midlife and older women as well as the resources available to conduct this research. We then concluded that recruiting 30 participants per arm is sufficient, that is, 30 women randomized into the intervention arm and 30 women randomized into the control arm. To account for a 15% attrition rate identified in a similar study [39], we will recruit 70 women, with 35 randomized to each group.

Participant Recruitment

The facilitators were asked to recruit participants within their organization. Facilitators were encouraged to distribute the recruitment poster for the study to potentially eligible participants in the following formats: (1) through email, phone call, social media (eg, Facebook), or in-person visit or (2) through a poster placed in a central location (eg, a lobby of a building) or a handout given to potential participants. Potentially eligible women will be assured that choosing not to participate in the study will not negatively affect their access to other services. They will be asked whether they are comfortable with the facilitator providing the research team with their names and contact information, or alternatively, whether they would prefer to contact the research team on their own. Facilitators were asked to distribute the study's recruitment poster throughout their region. This included sending email requests to organizations and distributing the poster to community bulletin boards.

Once a potential participant reaches out to the research team by phone or email or is referred by a facilitator, research staff (eg, research coordinator or research assistant) will respond and arrange a time to communicate with them by telephone. Research staff will provide an overview of the study details with each potential participant and answer any questions they have, ensure that they meet the study inclusion criteria, and review the informed consent forms. Once these first steps are complete, the research team will contact the participant to schedule a time to collect the baseline survey data.

We will include any woman who fulfills the eligibility criteria, and there are no quotas for women with specific characteristics, but we will try to include women from diverse backgrounds, including francophone women, new immigrants, women from visible and racialized minority groups, women living in rural places with limited access to services, and women in same-sex relationships. We will try to recruit women from diverse backgrounds by contacting organizations that offer services to women from marginalized or diverse backgrounds in the Maritime provinces and asking them to take part in a research partnership. Given that the professionals working in these organizations (eg, transition houses, outreach programs, and women's centers) have the expertise in working with these populations, they will be instrumental in helping us to reach and recruit diverse women into the study. In this study, our definition of rural is informed by the rural and small-town definition, which includes towns with population <10,000 inhabitants and people who live outside the commuting zone of a large urban center (eg, >40 minutes) [40,41].

Partnerships With Community-Based Organizations

Overview

The facilitators were recruited by the research coordinator with the support of the study coinvestigators and study partners. The study team developed a contact list of potential organizations throughout the Maritime provinces that deliver services for older adults experiencing abuse and those who work with women experiencing IPV. The organizations included transition houses, IPV outreach services, women's shelters, women's centers, and other service providers for women (eg, sexual health centers and addiction services). The research coordinator contacted the organizations via email to inquire about forming

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a partnership with the research team. The organizations were asked if they would be willing to collaborate with the study team by agreeing to 1 of the 2 research partnerships we offered. Organizations that expressed interest in partnering upon our initial email were requested to meet with the research team virtually to discuss the study and answer any questions.

Partnership 1

Organizations were asked if they would be interested in partnering with the study by appointing a staff member who could serve as a facilitator on the project. Organizations were notified that the facilitators would need to take part in a 2-hour training session on how to deliver the intervention and would be assigned the tasks of recruiting potential participants and delivering the intervention to any participants that they recruited within their organization. Organizations were informed that they would receive a stipend of CAD $2500 (CAD $1=US $0.74) for agreeing to partnership 1 and having a staff member take part in the training and recruiting and delivering the intervention to 1 to 5 participants. An additional CAD $2500 stipend will be offered to any organization that has a facilitator who recruits and delivers the intervention to ≥6 participants, given the increased time and resources this would take. A technology fee of CAD $1000 will be provided to each partnering organization for overhead costs and the use of their equipment (ie, laptops and phones) to deliver the intervention. Organizations were notified that staff members need to meet the following criteria to be eligible to become a facilitator: (1) at least 2 years of experience working in the IPV service delivery field and (2) completion of a postsecondary education program (eg, social work, health professions, human services, counseling, health promotion, or social sciences).

The research team also hired staff facilitators throughout the Maritime provinces to deliver the intervention to participants that were not recruited from within community-based organizations. The staff facilitators will be completing the same tasks but will be working independently (ie, not with an organization). All staff facilitators need to meet the minimum educational and experience requirements.

Partnership 2

We offered a CAD $500 honorarium to organizations that were willing to help us out with participant recruitment only. The research team asked partnering organizations if they could help with recruitment by distributing the recruitment poster to potential participants and completing 1 of the following tasks: (1) asking potential participants within their organizations for permission for a member of the research team to contact them and (2) share information about the study with potential participants who can contact the research team directly if they wish to do so.

Training for Facilitators

All facilitators will take part in a virtual training session individually or in a group. The content of the AIM intervention was developed by LW, CM, and HH. A slideshow was developed by LW and provided to the rest of the study team for review. The slides were then translated to French to provide the training to francophone facilitators. Given that New Brunswick is a bilingual province, the research team wanted to ensure that we could recruit both anglophone and francophone participants in all regions in the province. The research coordinator scheduled the training sessions and provided a copy of the slides to the trainees before their scheduled training session. Textbox 2 provides an overview of the content that was included in the training slideshow.

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Textbox 2. Facilitator training content.

Section 1: an overview of the advocacy intervention for midlife and older women (AIM) study

- Study rationale
- Study goal and research questions
- Empowerment component
- Social support component
- Tasks to be completed
- Eligibility criteria for participants
- Study timeline
- Research team members

Section 2: diverse midlife and older women and intimate partner violence

- Applying an intersectional lens to violence against midlife and older women
- Intersectionality wheel
- Using a trauma-informed approach
- Wheels of power and control
- Warning signs that an older adult may be in an unhealthy relationship
- Working with rural women who are in midlife and older
- Working with Black women who are in midlife and older
- Working with midlife and older women who are immigrants
- Working with midlife and older women who are francophone

Section 3: safety planning for older women

- Safety planning toolkit
- Digital safety strategies: computer safety
- Digital safety strategies: cell phone safety

Section 4: local community and legal resources

- National resources
- New Brunswick resources
- Nova Scotia resources
- Prince Edward Island resources

Section 5: supporting midlife and older women to develop goals and strategies for the future

- Using specific, measurable, achievable, relevant, time-bound (SMART) goals

Section 6: documenting the delivery of the AIM program

- Plans for documenting sessions with participants on the study's OneDrive

LW will be delivering the training session along with the research coordinator who will be present to answer any questions about the study procedures. The research coordinator will be responsible for communicating with the facilitators for the duration of the study. The training session was not designed to be a lecture but rather to share information and to have an open dialogue with the service providers who already have a great deal of experience providing services to clients. The training session was used to ensure that facilitators were informed on how to deliver the components of the AIM intervention in a highly individualized way. Facilitators were also encouraged to contribute to the list of resources provided if they had knowledge of other resources in their region that were not listed. Facilitators were informed that they could begin recruiting participants upon completion of the training session.

Random Assignment of Interventions

REDCap (Research Electronic Data Capture; Vanderbilt University) software will be used to store and manage the data collected from participants. REDCap is a web-based software application that securely stores research data [42]. The random allocation sequence was generated using REDCap [42]. The

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research coordinator developed an allocation table that included each option for random assignment that was stratified by the province of residence. This involved creating an Excel (Microsoft Corp) table with each intervention option (ie, intervention and control) in one column and province of residence (ie, New Brunswick, Nova Scotia, and Prince Edward Island) in another column. We wanted to ensure that an equal number of participants were randomized to the intervention and control group within each province in a balanced manner. Therefore, there were 6 study options uploaded to the software. Once the allocation table was uploaded to REDCap, it was locked and could not be modified.

REDCap will be used to randomize the participants. After a participant has completed the baseline surveys, the researcher will press the "randomize" button to determine the participant's group allocation. While assignment to the groups is random, once assigned, participants are not blinded to their group. The researcher will inform each participant of the group they are allocated to at the end of the baseline interview. The research staff (research coordinator and research assistant) will be responsible for screening, consenting, enrolling, and using Recap's randomization module to allocate participants to their study group.

Outcomes Measured

Research staff will collect quantitative effectiveness data from participants by telephone or video call at 3 time points: baseline, 3 months, and 9 months. Research staff will schedule a meeting by telephone or Zoom (Zoom Video Communications) to collect the survey responses from participants verbally. Table 1 details the survey information to be collected directly from participants.

Table 1. Quantitative measures.

Quantitative measure collected	Time point for data collection			Explanation
	Baseline	3 months	9 months	
Screening questions	✓			Age, province of residence, and description of the stage of their relationship with their abusive partner
Demographic information	✓			Education, marital status, and diversity characteristics (eg, immigrant status, francophone status, ethnic status, and rural status)
WEB[a]	✓	✓	✓	To measure women's experiences of feeling fearful and controlled by their abusive partner [43]
DCS[b]	✓	✓	✓	To measure the conflict (ie, difficulty) that women endure in making decisions about leaving their abusive relationship [44]
IPV[c] strategies index	✓	✓	✓	To measure the different types of IPV strategies that women are using to keep themselves safe in their abusive relationship [45]
SF-12v2[d]	✓	✓	✓	To measure quality of life [46]
CES-D[e]	✓	✓	✓	To measure depressive symptoms [47]
ISEL[f]	✓	✓	✓	To measure perceived social support [48]

[a]WEB: Women's Experiences of Battery Scale.

[b]DCS: Decisional Conflict Scale.

[c]IPV: intimate partner violence.

[d]SF-12v2: Short Form Health Survey.

[e]CES-D: The Center for Epidemiologic Studies Depression Scale.

[f]ISEL: The Interpersonal Support Evaluation List.

Primary outcomes include (1) physical and mental health, (2) knowledge about IPV, and (3) safety strategies. Physical and mental health will be assessed using the following scales: Short Form Health Survey [46], Centre for Epidemiologic Studies Depression Scale [47], and Interpersonal Support Evaluation List [48]. Knowledge about IPV and safety strategies will be measured using the following scales: the Women's Experiences of Battery Scale [43], Decisional Conflict Scale [44], and Intimate Partner Violence Strategies Index [45].

Participant Involvement by Group

Participant recruitment began in October 2023 and is expected to continue until July 2024. Participants will complete the screening and informed consent process with research staff and will be randomized upon completion of their baseline surveys. Participants that have been randomized to the intervention group will be matched with a facilitator in their region. The facilitators will follow up after randomization and schedule the 1-hour-long information-sharing session (ie, empowerment component) and then continue to follow up with the weekly calls for 12 weeks (ie, social support component). Quantitative survey data will be collected from all the participants at 3- and 9-month follow-ups. Follow-ups with participants in the AIM intervention group will take place 3 and 9 months after their final social support session. For participants randomized to the comparison group, follow-ups will take place 3 and 9 months after they have completed the baseline surveys. We estimate the total time commitment for participants to be 11 hours for those randomized to the AIM intervention group and 4 hours for those in the comparison group. Table 2 breaks down the estimated time commitment for each study activity.

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Table 2. Participant involvement by group.

Study activity	Time commitment for participants in the AIM[a] intervention group (hours)	Time commitment for participants in the comparison group (hours)
Informed consent process	0.5	0.5
Baseline data collection	1.5	1.5
Empowerment component	1	—[b]
Social support component	6	—
3-month follow-up	1	1
9-month follow-up	1	1
Total time commitment	11	4

[a]AIM: advocacy intervention for midlife and older women.

[b]Did not participate.

Data Management

REDCap software will be used to store and manage the study data [42]. The only individuals with access to the REDCap data will be the research coordinator and the research assistants. The research coordinator and the research assistants will enter the participants survey responses directly into the REDCap forms at baseline and 3- and 9-month follow-ups.

Statistical Analysis

Quantitative data will be exported from REDCap as a spreadsheet and then uploaded into SPSS (IBM Corp) for quantitative analysis. Participants in the AIM intervention group need to complete the empowerment component and attend at least 10 out of 12 weekly calls of the social support component for their quantitative data to be included in the analysis.

Descriptive statistics will provide a profile of study participants, including demographics for the whole sample and for those in each of the 2 groups. The provisional effect of the intervention will be tested using a prospective chi-square test of independence between the 2 groups for categorical data (Fisher exact test) at 3 and 9 months. Repeated measures analysis of variance will measure mean differences between the groups on continuous variables at 3 and 9 months.

Qualitative Component

We will conduct interviews with approximately 12 participants of the AIM intervention group. This sample size is sufficient when using a qualitative descriptive approach to generate rich, detailed descriptions and meaningful data [49,50]. In these interviews, we will use maximum variation sampling to include women who have specific characteristics (eg, francophone, new immigrant, and rural) and ask them about their perceptions of the program and their recommendations for further program development. We will also invite any intervention group participants who did not complete the AIM program to participate in an interview to learn about their experiences in the program and ask for any recommendations they may have to help improve the program. All facilitators who deliver the AIM intervention to trial participants will be invited by telephone or email by the research coordinator to complete a qualitative interview. While all will be invited, we hope that at least 4 to 5 will volunteer to participate in the interview.

At the 9-month follow-up data collection point, the research coordinator will invite women from the AIM intervention group to take part in a virtual interview. To be eligible to be invited for the interview, participants must have completed the empowerment component and at least 10 out of 12 social support sessions. In these interviews, the research coordinator will try to recruit a diverse sample of women who represent the characteristics of the participants and ask them about their perceptions of the program and their recommendations for further refinement of the program to meet the needs of diverse midlife and older women. The informed consent form will be shared by email or by postal mail.

The research team will also conduct an exploratory qualitative analysis on the data recorded by the program facilitators. Facilitators will be instructed to record the date and length of each session and take notes. The notes will detail the topics discussed with participants, the support and resources offered to participants, and any questions or concerns raised by the participants. The analysis of this exploratory data will summarize what topics are discussed and what supports are provided to participants.

All qualitative data will be analyzed using thematic analysis [51]. This is a form of pattern recognition allowed for inductive coding [52] and is particularly useful in understanding the influences and motivations related to how people respond to events [53]. The data coding process will involve generating initial codes, searching for themes, reviewing themes, and defining and naming themes that result in thematic codes representing patterned responses within the dataset [51]. Qualitative interview data from the participants of the intervention group will provide important insights about further refinement of the program to meet the needs of diverse women. Qualitative interview data from facilitators will provide important insights about the training program they participated in, delivery methods and content of the program to consider in further development, and scale-up and spread of the program.

Ethical Considerations

Overview

This trial required research ethics approval from the institutions where the investigators are located, which included Dalhousie

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University, the University of New Brunswick, St. Francis Xavier University, the University of Prince Edward Island, and the Université de Moncton (Table 3). To facilitate this process, the application was first submitted and approved by Dalhousie University's Social Sciences and Humanities Research Ethics Board and then subsequently submitted to the other research ethics boards. The trial was deemed more than minimal risk and, therefore, underwent a full, rigorous review at 4 of the 5 institutions. St. Francis Xavier University conducted an expedited review because the trial was previously approved by Dalhousie University.

Table 3. Institutional review board approvals.

Institutional ethics review board	Date of approval	REB[a] file number
Dalhousie University Health Sciences Research Ethics Board	July 11, 2023	2023-6548
St. Francis Xavier University Research Ethics Board	August 23, 2023	26598
Université de Moncton Ethics Committee for Research Involving Human Beings	September 6, 2023	2324-005
University of New Brunswick Research Ethics Board	September 23, 2023	2023-110
University of Prince Edward Island Research Ethics Board	October 6, 2023	6012156

[a]REB: research ethics board.

Informed Consent Process

All potential participants will be provided with information about the study and will receive either an electronic or a mailed copy of the informed consent form and will be given an opportunity to review it and ask questions before deciding whether they wish to volunteer to participate. The consent form will be reviewed verbally with the potential participant, and verbal consent will be obtained before beginning data collection. The person collecting the data will electronically record that consent was obtained before the first data collection point and before the 2 follow-up data collection points. After consenting to take part in the study, the participants and research staff will agree on a time to conduct the baseline interview by telephone or video call. At the beginning of each follow-up interview, key components of the consent form will be reviewed, and any questions raised will be responded to before the interview proceeding.

Participants can choose to withdraw by canceling the scheduled data collection session, withdrawing at the beginning of the session, or withdrawing after the data collection session begins. Participants can withdraw their data up to 7 days after a data collection session. This information is included in the consent form, and this will be emphasized during the review of the consent form before data collection begins.

Confidentiality and Anonymity

All study data will be kept confidential, and the participants' identity (eg, names and identifying information) will not be made known in any reports of the results. A participant ID number will be used for any quotes in reporting qualitative results. Qualitative interviews will be recorded on the research coordinator's secure laptop. The transcription function in Microsoft Word will be used to create a draft transcript that will then be edited by the research team members. Once a transcript is checked and edited by a research team member, the interview transcripts and the quantitative data will be shared among the team members using OneDrive, a secure, password-protected file-sharing system hosted by Dalhousie University. No hard copies of any study documents that could identify a participant will be retained.

The digital recordings will be kept only until the transcript is prepared, and then, the recording will be destroyed. Qualitative data, numerical key codes, and contact information of the participants will be retained by the co–principal investigators on a password-protected computer and on the OneDrive systems at Dalhousie University and the University of New Brunswick. These data will be destroyed 5 years after the publication of study results. Each participant will be given the option of allowing the co-principal investigators to retain the deidentified quantitative data indefinitely to be used in potential future research studies or for teaching purposes (eg, in a course with content on family violence). Providing this consent is not required for inclusion in the study.

This study focuses on midlife and older women who are currently experiencing IPV and are either living with an abusive partner or are in the process of leaving an abusive partner. There are different laws regarding the duty to report elder abuse in different provinces where we will be collecting data, and we will follow the procedure in each province. However, the issues about when to report typically are focused on the situations in which people do not have the physical or mental capacity to protect themselves or make their own decisions. If in the process of conducting data collection, the abuse of a child or an adult in need of protection is disclosed, the facilitator will contact the appropriate child protection or adult protection services in the location where the data are being collected.

The participants could be clients of an agency the facilitators work for. The participants will be assured that whether they choose to participate in the AIM study or not, there will be no negative repercussions on other services they access.

Compensation

All participants in the quantitative study will be provided with an honorarium of CAD $125 after completion of their baseline surveys. The honorarium is provided for agreeing to take part in the study and is not provided as an incentive. An additional CAD $20 honorarium will be provided to those who participate

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in a qualitative interview. All facilitators will receive an honorarium of CAD $45 if they participate in a qualitative interview. All participants will be given the option of receiving a physical gift card sent in the mail or a digital gift card sent via email.

Potential Harms to Participants

For participants living at home with the perpetrator, the participant may be at risk if the perpetrator finds out they are participating in the study. We will ensure personal safety of the participants in various ways at each stage of the research, including participant recruitment. The participants are welcome to participate virtually at a time and location that is chosen by them. If they need to end participation at any time, they are welcome to do so, and the facilitator will follow up at a time that is suitable and safe for them. As both the empowerment and social support components are delivered individually to participants, we can be very flexible about when the intervention is delivered.

The facilitators will teach the participants about ensuring digital security (eg, clearing browser history) during the empowerment component of the intervention. The participants will also be provided with information about local resources and services that are available. If the participant is in immediate danger during the time the facilitator is talking with them, they will instruct the participant to call 911, and if that is not possible, they will call 911 on the participant's behalf.

Data Monitoring

This pragmatic RCT does not have a data monitoring committee. Participant safety will be monitored through the research coordinator's regular communications (eg, biweekly communication when the facilitators are delivering the intervention) about any potential harm to the participants. However, we do not expect that the intervention will cause harm to the participants. The main potential risk that we identified is for the participants currently experiencing abuse and potentially living at home with the perpetrator. The perpetrator may find out about the study and may be against participation. The participants can leave the study at any time, and they have been provided with information about local resources and services that are available.

Access to Data

The data from this trial will not be publicly available due to the risk of compromising the privacy of the research participants.

Dissemination of Results

The findings of this study will be disseminated in several ways. We will submit a journal article to a peer-reviewed journal (eg, *Journal of Women and Aging* and *Violence Against Women*). We will ensure that the article is open access to ensure accessibility. We will deliver conference presentations at academic and professional conferences (eg, Canadian Association on Gerontology Annual Conference and Canadian Domestic Violence Conference). The intended audience will be researchers, practitioners, students, trainees, and policy makers. We will also develop and disseminate other research outputs that are required by the funders (eg, plain language summary, brief video, and infographic) in English and French. These accessible documents will be important for all our team members to share with their networks.

If the AIM intervention is determined to be effective, we will use the feedback we receive from the qualitative interviews with staff and participants to refine the staff training program and make it publicly available in both French and English. The final program materials will be distributed to service providers who work with victims of IPV and elder abuse in the Maritime provinces. In addition, the final program will be made freely available to anyone interested in supporting midlife and older women experiencing IPV and will be posted and publicized in the resources section of the Muriel McQueen Fergusson Centre for Family Violence Research website. The program will also be posted and distributed through the resource hub of the Canadian Network for the Prevention of Elder Abuse.

Results

The funding from the Public Health Agency of Canada for this study began in January 2023. From January to June 2023, the initial ethics proposal was drafted and research staff were hired. Research ethics applications were submitted to each university from July to October 2023. Table 2 provides the research ethics board approval numbers for each institution. Recruitment of facilitators began in July 2023 and continued till May 2024. The principal researcher conducted 5 AIM training sessions with 12 facilitators from the Maritime provinces. Four of the training sessions were conducted in English only, and 1 training session was provided to a francophone facilitator via Zoom using simultaneous translators. Participant recruitment and data collection will be carried out from November 2023 to January 2025. Data analysis will continue throughout the data collection period, and results will be disseminated by December 2025.

Discussion

Anticipated Principal Findings

We anticipate that the quantitative data will reveal positive outcomes for participants in the intervention arm on our primary outcome measures of (1) physical and mental health, (2) knowledge about IPV, and (3) safety strategies. Given that the participants in the control arm will receive a static, nontailored version of the AIM intervention materials after baseline data collection, we expect that there could be some positive outcomes on items such as knowledge about IPV and safety strategies but to a lesser extent than for the participants in the intervention arm.

We anticipate that the qualitative data will reveal the value of offering the AIM intervention to midlife and older women who have experienced IPV. We expect that the qualitative findings will reveal how the content and delivery of the program can be improved for both the participants and the facilitators.

Limitations

The results of this trial may not be generalizable to the larger Canadian context given the smaller, predominantly rural,

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population in the Maritime provinces. Another limitation to this study is that it relies on self-reported data from the participants.

Comparison With Prior Work

This study represents a novel intervention that is urgently needed to support midlife and older women who experience IPV in the Maritime provinces of Canada. Our previous research indicated that initiatives focused specifically on supporting older women who experience IPV are lacking [14], and diverse older women who experience IPV need additional supports [15]. The AIM study is novel in the following ways: (1) the AIM intervention was adapted to focus on the specific needs of diverse midlife and older women that experience IPV whose needs are often ignored by service providers and (2) the intervention is entirely virtual, which will reduce barriers to participation.

Directions for Future Research

Future research is needed to examine the implementation of the AIM intervention after adaptations are made, based on the findings of this RCT, preferably in a pan-Canadian study.

Conclusions

This research will result in the adaptation and testing of a program to support and empower diverse midlife and older women who experience IPV. This research will significantly enhance our understanding of a population that has been historically understudied and underserved. The quantitative findings from this RCT will provide preliminary evidence about the effectiveness of the intervention. Interview data from the participants in the intervention group will provide important insights about further refinement of the program to meet the needs of diverse midlife and older women. Interview data from facilitators will provide important insights about the training program they participated in, delivery methods and content of the program to consider in further development, and scale-up and spread of the program.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to the sensitive nature of this research and the participants not providing consent for their data to be shared publicly.

Authors' Contributions

LW and CH designed the study and drafted the study proposal to acquire funding from the Public Health Agency of Canada. LW, CH, SD-B, CM, MM, and EM developed the study measures and methodology. LW, KA, JL, and DG were responsible for project administration and for carrying out the investigation. LW, JL, and DG were responsible for supervising research staff. Data analysis will be carried out by LW and KA. All authors were involved in regular project discussions and study validation. LW and KA drafted the manuscript and CH, SD-B, MM, EM, HH, and CS reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AIM: advocacy intervention for midlife and older women
CONSORT: Consolidated Standards of Reporting Trials
IPV: intimate partner violence
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Scalable Technology for Adolescents and Youth to Reduce Stress in the Treatment of Common Mental Disorders in Jordan: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young people in low- and middle-income countries encounter significant barriers to accessing mental health support due to various factors, including a substantial treatment gap and limited health care budgets allocated to mental health. Using innovative strategies, such as scalable digital self-help psychological interventions, offers a potential solution for improving access to mental health support. However, digital mental health interventions come with their own set of challenges, including issues related to low user engagement. Chatbots, with their interactive and engaging nature, may present a promising avenue for the delivery of these interventions.

Objective: This study aims to explore the effectiveness of a newly developed World Health Organization (WHO) digital mental health intervention, titled Scalable Technology for Adolescents and Youth to Reduce Stress (STARS).

Methods: A single-blind, 2-arm randomized controlled trial will be conducted nationally across Jordan. Participants will include 344 young adults, aged 18-21 years, currently residing in Jordan. Inclusion criteria are heightened levels of psychological distress as determined through the 10-item Kessler Psychological Distress Scale (≥20). Assessment measures will be conducted at baseline, 1-week post intervention, and 3-month follow-up. Following baseline assessments, eligible participants will be randomized to receive STARS or enhanced usual care. The primary outcomes are the reduction of symptoms of depression and anxiety (Hopkins Symptom Checklist, 25 subscales) at 3-month follow-up. Secondary outcomes include general functioning (WHO Disability Assessment Schedule 2.0), well-being (WHO-5 Well-Being Index), personal problems (Psychological Outcomes Profile), and agency (State Hope Scale subscale).

Results: The study was funded in January 2020 by the Research for Health in Humanitarian Crises Programme (Elhra) and recruitment for the trial started on July 16, 2023. As of November 15, 2023, we randomized 228 participants.

Conclusions: This trial intends to contribute to the growing digital mental health evidence base by exploring technological solutions to address global public health challenges. Given the widespread use of technology globally, even in resource-constrained settings, and the high adoption rates among adolescents and young individuals, digital initiatives such as STARS present promising opportunities for the future of mental health care in low- and middle-income countries.

Trial Registration: ISRCTN Registry ISRCTN10152961; https://www.isrctn.com/ISRCTN10152961

International Registered Report Identifier (IRRID): DERR1-10.2196/54585

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(JMIR Res Protoc 2024;13:e54585) doi:10.2196/54585

KEYWORDS

mHealth; psychosocial intervention; youths; depression; anxiety; minimally guided digital intervention; low- and middle-income countries; barriers; access; mental health; digital self-help; chatbots; conversational agents; effectiveness; Scalable Technology for Adolescents and Youth to Reduce Stress; randomized controlled trial; Jordan; psychological distress; mental disorders; disability

Introduction

Mental disorders are one of the leading causes of disability worldwide, with an estimated 284 million and 264 million people affected by anxiety and depression, respectively [1]. The majority of mental disorders emerge between childhood and young adulthood, before the age of 25 years [2], with a median age of onset at 18 years [3]. The proportion of people with any anxiety disorder and the proportion of those with major depressive disorder that started before the age of 25 years is 7 out of 10 and 4 out of 10, respectively [3].

Although there exists a high prevalence of mental disorders, there remains an equally high treatment gap, with estimates of between 76% to 85% of people—in countries classified by the World Bank's Development Indicators as "less developed" receiving no treatment [4]. This treatment gap is exacerbated by low expenditure on mental health services, with countries allocating on average less than 2% of their health care budgets to mental health. Compared to adults, young people are less likely to access mental health services due to reasons such as perceived stigma and limited knowledge about mental health [5]. Additionally, treatment is often designed for adults and may not be appropriate for younger adults [6]. There is a need for innovative approaches to increase access to mental health care. This need may be more pressing for conflict-affected populations, where the World Health Organization (WHO) estimates suggest around 1 in 5 people affected by conflict in the previous 10 years currently experience a mental disorder [7].

Research on the delivery of psychological interventions by nonspecialists, using task shifting, shows promising results [8]. Yet, while the evidence for the effectiveness of these interventions for youths is growing, difficulties remain in accessing evidence-based interventions, particularly in low- and middle-income countries (LMICs) [9,10]. This highlights the need for evidence-based psychological interventions that can be used in settings that are resource-pressured [11]. Such interventions should be suitable for scale-up, as well as being appropriate for diverse sociocultural groups. A number of these interventions have been developed for adult populations, with meta-analytical evidence suggesting their effectiveness [12]. However, there are fewer interventions that have been developed and trialed for younger populations with the resulting evidence being less concrete [9]. Digital solutions may be one way to mitigate some of the access and resource challenges for young people [8].

Digital mental health (also called e-mental health) interventions refer in part to the use of electronic devices such as smartphones to support the provision of mental health care. In high-income settings, some guided self-help interventions have been found to be as effective as face-to-face interventions in adults [13,14]. Additionally, these interventions have been shown to reduce symptoms of mental disorders in routine care [15]. Similar delivery models have also been shown to be effective in more resource-constrained, middle-income countries and with conflict-affected populations [16-18]. This compelling evidence has led to the inclusion of digital mental health interventions in a number of countries' national mental health strategies and treatment guidelines [19]. In addition, WHO guidelines on mental health promotive and preventive interventions for adolescents and youths recommend the use of digital mental health interventions [20].

While the existing evidence for digital mental health interventions for youths suggests such interventions may be beneficial [21-23], the public availability of evidence-based interventions remains limited [9,24,25]. Additionally, while research on the efficacy of internet-delivered interventions is developing [21,26,27], studies beyond high-income English-speaking countries remain sparse, with the exception of China, where some studies have been completed [22,23]. However, digital mental health interventions may be a useful approach for increasing access to treatment because the use of electronic devices, internet, and social media continues to rise in LMICs, especially among youths [28-30]. This suggests the importance of developing, adapting, and determining the effectiveness of these types of interventions for younger populations, particularly in low- and middle-income and conflict-affected settings.

Implementation of digital mental health approaches is not without its challenges, as they introduce particular complexities associated with the use of digital platforms, such as the complexity and cost of building and maintaining some smartphone apps, which may lead to barriers in scale-up attempts [31]. A potential way to address these barriers is to explore the benefits of different delivery systems for online interventions. One such delivery method is using conversational agents, more commonly known as chatbots. Chatbots may provide a potential alternative and highly engaging method to deliver such interventions. Chatbots are text-based automated conversational agents that give the impression of speaking to a human, although the user is aware beforehand, that they are speaking with a computer program. They may use machine learning and respond to user inputs or use a decision tree format with users following a defined path. Preliminary studies exploring the effectiveness of chatbots on mental health outcomes are promising [32,33] and suggest they may be a practical way of providing mental health care as they can (1) use existing and widely available software infrastructures, and

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(2) may increase engagement due to the conversational nature of delivery.

For these reasons, the WHO has designed and developed a chatbot based on decision tree logic for youths, entitled Scalable Technology for Adolescents and Youth to Reduce Stress (STARS) [34]. This protocol outlines the first randomized controlled trial (RCT) aiming to test the effectiveness of STARS, a guided self-help mental health chatbot intervention among youths residing in Jordan, including Syrian refugees. This study builds and adds to the current literature as it aims to test a chatbot as an innovative delivery approach that may overcome some of the barriers and challenges involved in digital mental health interventions, within a middle-income, Arabic-speaking country, where specialist care for mental health is particularly limited and there is a high proportion of refugees per capita. Testing in this setting will demonstrate whether such an intervention aimed at youths may be a feasible model for scaling up much-needed services. This trial follows preliminary work on the development of the STARS intervention, including the cultural adaptation of STARS to the Jordanian context (not yet published), and a completed pilot trial to determine cultural acceptance and appropriate research methods. The primary aim of this study is to determine the effectiveness of the STARS intervention in alleviating symptoms of depression and anxiety among individuals aged 18-21 years residing in Jordan, compared to enhanced usual care (EUC). Secondary aims include assessing the effectiveness of STARS in improving levels of psychological distress, self-defined problems, general functioning, agency, and subjective well-being.

Methods

Design

We will conduct a 2-arm, single-blind, superiority RCT comparing the STARS intervention to EUC in 344 study participants. Multimedia Appendix 1 presents the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist and Multimedia Appendix 2 presents the trial registration data.

Setting

The project will take place at a national level in Jordan. Jordan is a middle-income country with limited resources allocated to mental health care. Specialist care for mental health problems is especially limited, with 1.04 psychiatrists, 2.97 mental health nurses, 0.11 psychologists, and 0.01 occupational therapists available per 100,000 people [35]. In addition, Jordan hosts the second most refugees per capita, globally, with the majority originating from Syria [36], further straining available mental health care. The majority of people residing in Jordan have access to the internet, with the World Bank reporting 83% of the population able to access the internet in 2021 [37] ensuring that a digital mental health intervention would be both accessible and scalable. The study will be implemented by the Institute for Family Health (IFH), a nongovernmental organization operating across Jordan.

Participants and Recruitment

Participants will include youths aged 18 to 21 years residing in Jordan. Recruitment will be conducted through various means, including online advertisements and social media channels, adverts, and posters hosted in community centers, primary health care facilities, universities, and other areas frequented by this age group. During the recruitment process, potential participants will be able to access the study through either a QR code or a web link. Inclusion criteria for potential participants are (1) youths aged 18 to 21 years; (2) living in Jordan; (3) scores 20 or higher on the Kessler Psychological Distress Scale, 10-item version (K10) [38], indicative of moderate levels of psychological distress; and (4) having access to a device for intervention delivery or willingness to use one at a participating center. Exclusion criteria are (1) persons not between the ages of 18 and 21 years, and (2) imminent risk of suicide.

Ethical Considerations

The RCT has been approved locally by the research committee of the School of Nursing, University of Jordan (PF.22.9 on March 23, 2022) and by the WHO ethics review committee (ERC; ERC.0003729 on July 1, 2022). Informed consent for participation in the trial will be taken prior to screening. Upon initially accessing the STARS website through the recruitment material, participants will receive information regarding the purpose of the study, an explanation of the assessments and study procedures, and information on the 2 interventions being trialed; STARS and EUC. This written information is additionally provided in a short, 3.5-minute animated video. They will subsequently be invited to complete the screening assessment. Participants will be remunerated JOD 4 (US $5.64) upon completion of the postassessment and again following the 3-month follow-up assessment.

Study Procedures

Figure 1 presents a study flowchart outlining the study procedure. Prior to the commencement of the trial, STARS underwent a rigorous cultural adaption to ensure that the translation and material contained in STARS were relevant to the Jordanian context. This culturally adapted version of STARS was subsequently piloted in a feasibility RCT to ensure the safety, acceptability, and feasibility of the proposed research methodology (not yet published).

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Figure 1. Study flowchart. K10: Kessler Psychological Distress Scale, 10-item version; STARS: Scalable Technology for Adolescents and Youth to Reduce Stress.

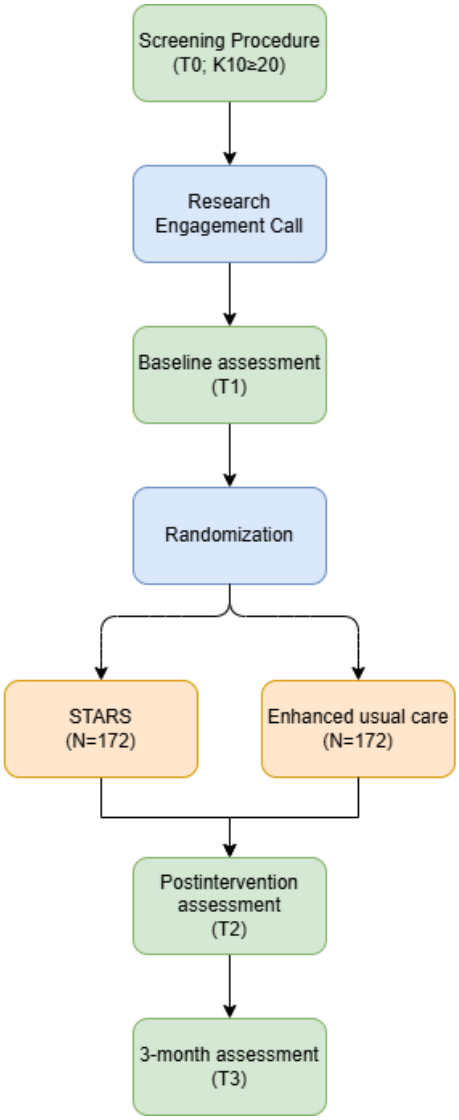

Participants will be directed to take part in the screening procedure after accessing the online software tool, Qualtrics, through the research project's website and reading through the study information outlined earlier. As part of the screening procedure, participants will first be asked their country of residence and age, administered the K10, and administered the screening questions for imminent risk of suicide. Participants outside of Jordan, not between the ages 18-21 years, or screening negative on the K10 will be informed that they are not eligible for participation and will be invited to contact the implementing team if they have any questions or would like to receive information on psychosocial services available close to them. If participants are excluded due to screening positive for imminent risk of suicide, a message will appear that they may need additional mental health support along with signposting to a nationally recognized helpline.

If participants meet all inclusion criteria, they will be invited to provide their contact information (phone number and/or email address). Immediately after having completed the screening or on the next working day, participants will be contacted by a member of the research team to answer any questions regarding the study. Participants will then receive a personalized link to the baseline questionnaires.

All subsequent assessments will also be completed remotely by participants either on their own private devices, or devices that will be made available in private rooms at the IFH health care centers. The baseline assessment will include the following instruments: Hopkins Symptoms Checklist, 25 (HSCL-25) [39], WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) [40], WHO-5 Well-Being Index (WHO-5) [41], Psychological Outcomes Profile (PSYCHLOPS) [42], and the agency subscale of the State Hope Scale (SHS-A) [43]. In addition, participants will be asked about their previous mental health care use both related to services and prescribed medicines. Following the baseline assessment, participants will be randomized to either receive STARS or EUC.

The postintervention assessment is scheduled to take place at 8 weeks following baseline assessment completion for all participants. The postintervention assessment will include the HSCL-25, K-10, WHODAS 2.0, WHO-5, PSYCHLOPS, SHS-A, the Client Satisfaction Questionnaire adapted to internet-based interventions [44], and questions about whether

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they accessed mental health care during the trial. The final assessment will be conducted in 3 months following the postassessment, or 20 weeks after the baseline assessment, and will include the HSCL-25, K-10, WHODAS 2.0, WHO-5, PSYCHLOPS, SHS-A, and questions pertaining to any mental health services received between the postintervention assessment and the time of the 3-month assessment. Participants will receive up to 3 reminder messages and/or phone calls spread out over 2 weeks including their personalized link to the assessment. Participants will be remunerated JOD 4 (US $5.64) upon completion of the postassessment and again following the 3-month follow-up assessment. Table 1 presents a SPIRIT diagram outlining the assessment and intervention time points of the trial.

Table 1. SPIRIT[a]: Schedule of enrollment, interventions, and assessments for the STARS[b] trial.

	Measures	Enrollment (–T1)	Screening (T0)	Baseline (T1)	Intervention	Postassessment (T2; 8 weeks)	3-month follow-up (T3; 20 weeks)
Enrollment							
Informed consent		✓					
Eligibility screen			✓				
Allocation				✓			
Interventions							
STARS				✓	✓	✓	
ETAU[c]				✓	✓	✓	
Assessments							
Psychological distress	K10[d]		✓			✓	✓
Depression symptoms	HSCL-25[e]			✓		✓	✓
Depression symptoms	PHQ-2[f]				✓		
Anxiety symptoms	HSCL-25			✓		✓	✓
Functioning	WHODAS 2.0[g]			✓		✓	✓
Subjective well-being	WHO-5[h]			✓		✓	✓
Perceived problems	PSYCHLOPS[i]			✓		✓	✓
Agency	SHS-A[j]			✓		✓	✓
User satisfaction	CSQ-I[k]					✓	
Mental health care use	2 items			✓		✓	✓

[a]SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials.

[b]STARS: Scalable Technology for Adolescents and Youth to Reduce Stress.

[c]ETAU: enhanced treatment as usual.

[d]K10: Kessler Psychological Distress Scale, 10-item version.

[e]HSCL-25: Hopkins Symptoms Checklist, 25 subscales.

[f]PHQ-2: Patient Health Questionnaire, 2-item version.

[g]WHODAS 2.0: WHO Disability Assessment Schedule 2.0.

[h]WHO-5: WHO-5 Well-Being Index.

[i]PSYCHLOPS: Psychological Outcomes Profile.

[j]SHS-A: State Hope Scale, agency subscale.

[k]CSQ-I: Client Satisfaction Questionnaire adapted to internet-based interventions.

Randomization and Blinding

Participants will be randomized to receive either STARS or EUC at a 1:1 allocation ratio following the baseline assessment. The randomization sequence will be developed through Qualtrics software and will be automated and embedded in the baseline questionnaire, with participants having their group allocation conveyed to them immediately upon completion of the

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assessment. Given the high proportion of Syrian refugees and other populations residing in Jordan, randomization will be stratified on a 1:1 ratio (Jordanian or Palestinian vs Syrian or other nationalities). Given that questionnaires are self-administered online, the outcome assessments will not be blinded.

Interventions

Scalable Technology for Adolescents and Youth to Reduce Stress

The STARS intervention has been described in detail elsewhere [34]. The intervention is guided, brief, and consists of 10 chatbot sessions that have been developed from evidence-based techniques to address emotional distress experienced by youths. Participants are encouraged to complete 2 chatbot sessions a week spread out over 5 weeks, with each session taking approximately 20-25 minutes to complete. Upon completion of a chatbot session, the next chatbot session is unlocked immediately. During initial registration, participants will be able to opt-in to receive push notifications to receive reminders to complete prior chatbot sessions, to be alerted when a new session is available, and yet to be started, or when they have not accessed the intervention for some time. There are several notifications to improve engagement of participants with the chatbot. These notifications are described in Multimedia Appendix 3. The STARS intervention is being delivered using the OpenDialog automated conversation system.

Prior to use in this study, a cultural adaptation of the intervention took place to ensure that the chatbot was relevant to the Jordanian context (not yet published). As part of the cultural adaptation procedures, a prior iteration of the chatbot was translated from English to Arabic. This was then tested with youths using commonly used adaptation procedures outlined by WHO and detailed in a recently released manual [45]. These include techniques such as "cognitive interviewing," a process that explores how relevant, understandable and acceptable an intervention is. Additionally, focus groups were used to understand the context and how to maximize the reach of STARS in Jordan. After the development of an updated STARS, there was an additional round of user testing to further refine the included content, with a focus on the wording and presentation of the content. The adapted version, called SALAM, will be used in this trial.

STARS was based on a cognitive behavioral therapy framework to deliver psychological content aimed at addressing the broad mental health needs reported by adolescents and youths. Cognitive behavioral therapy is recommended as an evidence-based mental health treatment for youths with emotional disorders according to WHO guidelines [20]. Lesson 1 ("Let's get started") provides participants with an overview of the intervention and an explanation of privacy and confidentiality. Lesson 2 ("Emotions are not our enemies") provides participants with psychoeducation about emotions. Lessons 3 and 4 ("Breathe to relax"—parts 1 and 2) teach participants emotion regulation techniques, such as slow breathing. Lessons 5 and 6 ("What we do can change how we feel"—parts 1 and 2) focuses on behavioral activation. Session 7 ("Managing problems") focuses on problem management techniques. Lessons 8 and 9 ("Talking kindly to yourself"—parts 1 and 2) teach participants about thought challenging. Finally, lesson 10 ("Put your skills together") is focused on consolidating learnings and relapse prevention [34]. The techniques are taught by SALAM that sends brief text messages to which participants can respond using predefined response options consisting of prewritten text and emojis. The use of the response buttons is "practiced" during the first lesson. In some lessons, there is an opportunity to give a free-text response, for example, when participants are asked to specify a goal for the intervention that has not been predefined by the chatbot. Additionally, useful tools such as audio and video demonstrations (eg, breathing techniques, problem management) and practice quizzes will be available for use anytime, as will the ability to go back to a previous session. This can be done by navigating to the "session menu" where participants can select the lesson they would like to repeat. Throughout the intervention, users will be encouraged to practice and apply these skills in their day-to-day lives.

The training and materials for the guided component of the chatbot intervention are based on a guided self-help approach developed by WHO and used in several studies [17,18,46]. It consists of 5 weekly telephone calls by trained, nonspecialist e-helpers. The support calls last approximately 15 minutes each to provide participants with support and guidance to implement the STARS intervention techniques and to use the STARS intervention chatbot. E-helper support is strongly protocolized and outlined session-by-session for each support phone call in an e-helper manual. E-helpers are trained on the STARS intervention and research protocols during a 5-day training delivered by IFH. The training includes knowledge about psychological distress and other mental health problems, communication skills, providing support, responding to distress, and procedures for adverse events (AEs) including referral procedures. E-helpers can monitor their participants' progress through the OpenDialog system and can view some of the participants' responses. These are limited to specific parts that are relevant for the e-helper, such as responses to the mood check, the goal a participant selected, and free-text fields. Free-text responses will be monitored on a daily basis for any indications that the participant is unsafe (eg, in case a participant expresses suicidal ideation in a free-text field or suggests a harmful goal to work on in the intervention). E-helpers will be supervised on a weekly basis by a clinical supervisor based at IFH, with additional support to the project team from WHO. Clinical group supervision will ensure fidelity of the e-helper support calls, discussion of challenging situations when providing telephone support, and e-helper self-care. The clinical supervisor will also listen to 5% of e-helper support calls to provide feedback on the delivery of the support calls.

To evaluate treatment fidelity, a random sample (5%) of e-helper support calls will be audio recorded. Participants will be asked for verbal consent prior to recording. Recordings will be evaluated according to a treatment fidelity checklist. This information has also been added to the consent form.

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Enhanced Usual Care

The EUC intervention will include basic psychoeducation regarding depression and anxiety, as well as resources on available evidence-based care available in Jordan. This will be delivered through a website where participants register to gain access. The information provided to those in EUC will also be provided during the psychoeducation session to those enrolled in the STARS intervention. Available resources will include a list of organizations that offer evidence-based mental health and psychosocial support in Jordan—as this study is taking place at a national level, a list has been created of the resources available across the country so that those in need can access services close to their physical location.

Measures

All assessments will take place remotely and be hosted through Qualtrics, a secure data collection online platform.

Screening Measures

The screening assessment consists of the K10 to assess levels of psychological distress [38] and screening questions to determine the imminent risk of suicide informed by the WHO mhGAP Intervention Guide 2.0 [47]. The K10 assesses general psychological distress and consists of 10 items corresponding to symptoms of depression and anxiety experienced in the preceding 30 days. Items are rated on a 5-point Likert scale ranging from 1=none of the time to 5=all of the time, with scores determined through the sum of the items (range 10-50). Higher scores are indicative of higher levels of distress; a cutoff score of 20 will be used to determine inclusion as it has been previously shown to indicate moderate to significant levels of distress [48]. The K10 will also be used as a secondary outcome measure. The imminent risk of suicide, as defined by the WHO Mental Health GAP program, will be screened through 3 questions [47]. Participants will be asked to indicate whether they have had thoughts of suicide in the preceding 30 days and if a positive response is recorded, follow-up questions regarding prior attempts or future plans will be asked. Participants who indicate imminent risk as determined by the follow-up questions will be excluded from the study and provided with on-screen information directing them to support services.

Primary Outcome

The primary outcome will be levels of depression and anxiety as determined through the HSCL-25 [39]. The HSCL-25 is a 25-item questionnaire consisting of 2 subscales assessing symptoms of depression and anxiety; 15 items correspond to symptoms of depression and 10 correspond to symptoms of anxiety. The validity and psychometric properties of the questionnaire have been well established in both adults and youths or adolescents [49,50]. Additionally, an Arabic version of the HSCL-25 has been previously validated [51] and has been used successfully among adults in Jordan during a previous study determining the effectiveness of a scalable psychological intervention [52].

Secondary Outcomes

The WHODAS 2.0 will be used to assess levels of impaired functioning [40]. The measure assesses general disability people experience in their daily lives over the prior 30 days across 6 domains: self-care, getting along with others, cognition, mobility, participation, and life activities. The 12-item version will be used, which includes 2 contributing items from each domain. Difficulties are scored on a 5-point scale ranging from 0=none to 4=extreme, with total scores ranging from 0 to 48. The measure has been widely validated globally, with specific psychometric studies taking place in youth populations [53] and on the Arabic version [40,54].

The PSYCHLOPS measure will be used to understand participants' primary problems and how they impact daily functioning, and to track improvements of these problems over the course of the study [42]. The measure includes 4 items spanning 3 domains: problems, functioning, and well-being. Free-text responses are provided for the problem and functioning domains, with impacts on daily life being scored on a 6-point ordinal scale. Posttreatment and follow-up versions of the measure include an overall valuation question to determine the improvement of these problems. The PSYCHLOPS has been validated in a number of contexts [55,56].

Psychological well-being and quality of life will be assessed through the WHO-5 [41]. The WHO-5 measures subjective positive well-being across 5 items scored on a 6-point Likert scale, with responses ranging from 0=at no time to 5=all of the time. Total scores range from 0 to 25, with higher scores indicating higher levels of well-being. The WHO-5 has been used globally in research and across a number of clinical settings [41] and has previously been validated in an Arabic sample [57].

The SHS-A will be used to assess perceived agency [43]. The agency subscale consists of 3 items observing perceived levels of goal-directed energy measured on an 8-point Likert scale ranging from 1=definitely false to 8=definitely true. The potential mediation effect of agency on treatment outcomes will be explored in the secondary analysis.

Other Measures

To capture any mental health services that participants received prior to or during the study period, 2 items will be included in postassessments to capture information on the use of psychological or counseling services and medications (each item answered with yes or no).

Those randomized into the STARS intervention will complete the Patient Health Questionnaire, 2-item version (PHQ-2) [58] during every other session. The PHQ-2 has been shown to allow for the detection and monitoring of depression over time and will allow the research team to identify potential worsening of symptoms in participants during the intervention phase [58]. The measure inquiries about symptoms of depression over the past 2 weeks, with items scored on a 4-point Likert scale ranging from 0=not at all to 3=nearly every day, with scores ranging from 0 to 6.

Finally, user satisfaction of the STARS intervention will be assessed through a version of the Client Satisfaction Questionnaire, a scale intended to measure client satisfaction with health services, adapted specifically for web-based health interventions [44]. The questionnaire includes 8 items scored

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on a 4-point Likert scale ranging from 1=does not apply to me to 4=does totally apply to me. The assessment will be offered to participants during the post-intervention assessment as an optional additional questionnaire.

Sample Size

A total of 344 participants will be included in the RCT. This sample size calculation was based on the results of prior trials exploring the effectiveness of comparable digital interventions which report effect sizes (Cohen *d*) ranging from 0.48 to 0.56 [17,18,59]. In addition, a similar effect size was used to determine the sample size for a similar RCT observing the effectiveness of a WHO-developed digital health intervention, based on a conservative, yet clinically significant effect size of 0.5 [60]. Assuming an effect size of 0.5 at a 3-month follow-up (power=90%; α=0.05, 2-sided), the trial would require 172 participants (STARS=86 and EUC=86). Given the high attrition rates reported in digital intervention studies, a conservative attrition rate of 50% was assumed. This attrition rate was informed by the results of the feasibility RCT and comparisons with protocols for similarly designed studies.

Statistical Analysis

To measure baseline differences between the 2 treatment arms, 2-tailed *t* tests will be conducted for continuous variables and chi-square tests for categorical data. To determine the effectiveness of the STARS intervention, intention-to-treat analysis will be conducted to compare the mean difference between STARS and EUC at baseline, post intervention, and 3-month follow-up. Differential change over time between treatment arms will be assessed using linear mixed models that accommodate missing data at subsequent assessments and provide differential slopes of trajectories between conditions. Hierarchical linear models study treatment effects because this allows the number of observations to vary between participants and handles missing data by using maximum likelihood estimation methods. Missing data will be assumed to be random if participants retained and not retained at 3 months do not differ on baseline characteristics. Fixed (intervention and time of assessment) effects and their interactions will be entered in unstructured models to yield indices of the relative effects of the treatments; time of assessment included baseline, post treatment, and 3-month follow-up. Analyses will focus on the primary outcome and secondary measures, with the main outcome time point being the 3-month follow-up relative to baseline. A subsequent per protocol completers analysis will be conducted, only including those who completed the 3-month follow-up, in order to assess the robustness of the primary analysis.

In addition to these analyses, the role of potential moderators and mediators, such as agency, on outcomes will be explored independently using the PROCESS macro. Two-tailed tests with a significance level of $P<.05$ will be reported for all analyses.

Data Management, Trial Monitoring, and AE Reporting

All assessment data will be collected electronically in Qualtrics. Participants will receive personalized Qualtrics links for their baseline, post-, and 3-month follow-up assessments so that assessments can be linked to each other. Only the research team will have access to the data in Qualtrics. Deidentified data stored from the STARS intervention (eg, PHQ-2 scores, free-text responses, session completion date) are available to e-helpers and the research team through the OpenDialog website. Data collected online will be held securely and separately from study data, according to the relevant data protection laws. Data will be deidentified and stored confidentially at the University of New South Wales after transferring to an SPSS database.

An identifying key list (a list connecting names to numbers) will be kept by the project manager at IFH. All downloaded electronic data will be pseudonymized and stored on password-protected computers. Hardcopy files of the study, such as supervision notes, will be stored in locked cabinets at IFH. No identifiable data will be used in publications or presentations. Trial monitoring will be done by WHO staff on a biweekly basis to ensure the accuracy of data storage and output.

AEs or serious AEs (SAEs) refer to any undesirable experience of a participant during the trial, whether or not considered related to the trial procedures or to the STARS or EUC interventions. All AEs or SAEs reported spontaneously by participants or observed by the research team or e-helpers will be reported to the IFH clinical supervisor for immediate action and resolution where required. All SAEs will be reported to the local ERC within 24 hours of being informed about the event, and a summary of AEs will be reported to the local ERC every three months. The local ERC will review any SAEs as soon as possible and the summary of AEs during their regular meetings. They will determine any appropriate action with respect to ongoing study conduct. Additionally, all SAEs will be reported to the WHO ERC. As STARS is nonpharmacological and there exists a broad evidence base for the safe use of e-interventions and therefore a low risk for adverse effects, no Data Monitoring Safety Board will be installed for this study. Adverse events will be monitored and reported to the local ethics committee.

Any modifications to the protocol that may impact the conduct of the study, the potential benefit of the participant, or may affect participant safety will require a formal amendment to the protocol. Such amendment will be reviewed and approved by the local ethics committee of the University of Jordan and by the WHO ERC prior to implementation. Administrative changes are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be documented in a memorandum and communicated to the WHO ERC.

Safety Considerations

The therapeutic techniques included across the 10 lessons are evidence-based, and therefore, it is unlikely that participants in the intervention will experience an increase in psychological distress. The PHQ-2 will be administered in the STARS intervention once a week (every other lesson) and will be monitored by e-helpers to track participants' levels of distress during the intervention phase of the trial.

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The development of the STARS intervention was intended to minimize the risk of potential adverse events. Of particular focus was to minimize the loss of privacy or confidentiality of intervention participants. Preliminary work revealed that participants may use shared devices to access the intervention, which led to STARS being developed on a website as opposed to an app, that would require a log-in each time the intervention is accessed. Additionally, during the guided components of the interventions, participants are asked to indicate a codeword during their onboarding that could be used by the e-helpers to ensure that the person on the other end of the line is those accessing STARS. Furthermore, the chatbot is transparent throughout each lesson that they are a program and not a person. Lastly, e-helpers check digital reports on session use, which include responses to open text fields; responses are analyzed to identify responses that may indicate concern for participants' well-being and allow for the AE or SAE procedures to be followed. The e-helpers and research staff will be trained in the AE or SAE procedures and subsequent referral pathways prior to the start of the trial.

Scalability of STARS

STARS was developed with potential scalability in mind for future implementation initiatives if the intervention is found to be effective. The chatbot uses a decision tree format which leads users on a defined path through the lessons. The choice to use a decision tree chatbot was in part informed by the technical feasibility of scaling up the intervention across a range of contexts in the future, as it does not require the development or maintenance of a bespoke website or app and can be used on many existing widely available platforms. WHO aims to release the STARS decision tree script and content as open access on the basis of pooled positive results from 2 trials, meaning that STARS could be adapted and implemented on different software platforms and in different contexts. Furthermore, having defined lessons, and a decision tree format will allow for easier reproducibility. Together these design features may be more cost-efficient and support more rapid uptake and sustained use of the intervention over time, compared to a bespoke website or app which may require additional maintenance and support.

Results

The study was funded by the Research for Health in Humanitarian Crises Programme (47467) in January 2020. Recruitment for the trial commenced on July 16, 2023, and as of November 15, 2023, a total of 228 participants have been randomized. The expected end date of data collection is July 2024. To date, no data analysis has been conducted.

Discussion

Brief Summary

Given the immense mental health treatment gap that exists globally, which is more pronounced in LMICs, scalable psychological interventions that can alleviate psychological distress and symptoms of mental health conditions are needed. This is particularly critical for youths, as they often face reduced access to mental health services due to the stigma associated with seeking help and the fact that many existing services are primarily designed for adults.

Digital health solutions can be particularly useful in bridging this gap. This study intends to contribute to the ongoing efforts of developing and evaluating potentially effective digital mental health solutions to minimize the mental health treatment gap by exploring the effectiveness of a novel digital mental health intervention in the form of a chatbot. The goal of this trial is to conduct a single-blind, 2-armed RCT among 344 young adults aged 18-21 years with heightened psychological distress in Jordan to evaluate the effectiveness of a newly developed WHO digital mental health intervention (STARS) in reducing symptoms of depression and anxiety versus EUC. STARS uses an engaging format to provide education and techniques to help reduce psychological distress, such as symptoms of depression and anxiety experienced by youths and adolescents. Recruitment for the trial began on July 16, 2023. Should the intervention demonstrate a decrease in symptoms of depression and anxiety at 3-month follow-up, it would support the potential for implementation of this new scalable psychological intervention for young people. Results from this trial are expected to expand the current range of available scalable psychological interventions.

Limitations

Limitations to this study will be the potentially high attrition rates that are a common challenge in eMental health research [32] and the lack of long-term follow-up assessments (ie, beyond 3-month follow-up) to evaluate long-term outcomes of the intervention. Both interventions (STARS and EUC) require participants to have access to a device for intervention delivery (or to be willing to use one at a participating center), which may limit the generalizability of findings.

Conclusions

If the intervention is found to be effective through this trial and an upcoming secondary trial, the WHO aims to release its contents through open-access channels. This will help toward realizing the scalability of the intervention and will provide implementers with access to evidence-based content that can be further adapted and tested in novel contexts. Furthermore, by providing evidence of the effectiveness of this chatbot-based intervention, this study can pave the way for a more diverse range of options for those seeking mental health support. Collectively, this study aims to further develop the evidence base concerning the effectiveness of digital and self-help tools among adolescents and youths. If effective, it is expected to potentially have a substantial impact on shaping future policy decisions regarding the availability of resources for mental health care, ultimately leading to more inclusive and efficient mental health services for those in need.

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Acknowledgments

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Data Availability

Data generated during this study will be available following the completion and publication of the trial from RB (r.bryant@unsw.edu.au) upon reasonable request.

Authors' Contributions

A Akhtar, AMDG, RH, DK, LD, MVO, RB, and KC were responsible for the development of the study design and protocol. A Akhtar wrote the first draft of the manuscript. AMDG, RH, DK, A Abualhaija, SF, MF, LD, RB, and KC critically revised the manuscript. All authors approved the final manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Checklist.
[DOCX File , 61 KB - resprot_v13i1e54585_app1.docx]

Multimedia Appendix 2
The World Health Organization Trial Registration Data Set.
[DOCX File , 24 KB - resprot_v13i1e54585_app2.docx]

Multimedia Appendix 3
Overview of notifications used to improve user engagement.
[DOCX File , 20 KB - resprot_v13i1e54585_app3.docx]

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Abbreviations

AE: adverse event
ERC: ethics review committee
EUC: enhanced usual care
HSCL-25: Hopkins Symptoms Checklist, 25 subscales
IFH: Institute for Family Health
K10: Kessler Psychological Distress Scale, 10-item version
LMIC: low- and middle-income country
PHQ-2: Patient Health Questionnaire, 2-item version
PSYCHLOPS: Psychological Outcomes Profile
RCT: randomized controlled trial
SAE: serious adverse event
SHS-A: State Hope Scale, agency subscale
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
STARS: Scalable Technology for Adolescents and Youth to Reduce Stress
WHO: World Health Organization
WHO-5: WHO-5 Well-Being Index
WHODAS 2.0: WHO Disability Assessment Schedule 2.0

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Protocol

Study to Evaluate the Comparative Efficacy of Medhya Rasayana (Pharmacological) Versus Nonpharmacological Interventions in Management of Gadget Addiction in Children: Protocol for Parallel, Triple-Arm, Randomized Clinical Trial

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Abstract

Background: Gadget addiction is a common behavioral problem among children. It is known to hamper social and academic life as well as adversely affect the lives of children. Ayurveda offers many therapeutic modalities and Ayurvedic medicines that can be used in the management of gadget addiction in children. The purpose of this study is to evaluate and compare the effectiveness of nonpharmacological therapies and the pharmaceutical intervention Medhya Rasayana in treating childhood gadget addiction.

Objective: This study aims to provide a detailed description of the study methodology that will be used to compare the efficacy of nonpharmacological versus pharmaceutical interventions in the treatment of children's gadget addiction.

Methods: A randomized, parallel, triple-arm interventional study will be conducted on diagnosed participants of gadget addiction with an age group of 6- to 16-year-old children, which will be selected and equally distributed in 2 groups. Group P will be given Medhya Rasayana (pharmacological intervention), group N will be nonpharmacological Ayurveda intervention, and group C (cognitive behavioral therapy) will be an external group. The Study duration is 180 days with assessment at baseline, midpoint, and endpoint Appropriate statistical techniques, such as ANOVA and regression analysis, will be used to examine the data and evaluate the efficacy of the 3 groups' interventions. We will perform subgroup analysis according to initial addiction severity, gender, and age. Primary outcome measures include a reduction in gadget addiction and changes in the psychosocial well-being of participants. Standardized questionnaires and instruments will be used to collect data.

Results: In December 2023, the randomized controlled study got underway. Since participants may begin at any time, our goal is for everyone to be finished by December 2024.

Conclusions: This research will provide crucial new information about the relative effectiveness of Ayurveda nonpharmacological therapies and Medhya Rasayana in treating children's gadget addiction. The results will guide evidence-based treatments aimed at reducing the negative impact of excessive gadget use on this susceptible population's psychosocial development. In the end, the findings are meant to help policy makers and medical professionals create sensible plans to deal with the rising issue of childhood gadget addiction.

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KEYWORDS

addiction; Ayurveda; gadget addiction; children; Kaumarbhritya; Medhya Rasayana; yoga; complementary and alternative medicine

Introduction

Overview

In the modern era, technology has affected life in various ways. One of the evolutions in the world of technology is electronic gadgets, which are used for entertainment, communication, information, education, and business. Moderate use of electronic gadgets improves the quality of life, but they also have the potential to be misused and cause gadget addiction. In general, addiction terminology was only associated with addiction to drugs, alcohol, and tobacco, but in the recent era, addiction may be defined as a process whereby a behavior that can function both to produce pleasure and to provide relief from internal discomfort is used in a pattern characterized by recurrent failure to control the behavior and continuation of the behavior despite significant negative consequences (unmanageability) [1]. Gadget addiction is a broad term that includes excessive use of mobile devices, internet games, internet-based gambling, excessive surfing on the internet, and excessive use of social media [2]. Gadget addiction is adversely associated with psychosocial disorders among children in the adolescent age group [3], as well as musculoskeletal problems and visual disturbance [4]. Gadget addiction leads to a reduction in physical activities, which results in fat deposition at an early age [5]. Research reveals that stressful environmental conditions promote human addiction [6]. Gadget addiction is a type of behavioral addiction; these addictions are similar to drug addiction except that in the case of gadget addiction, the person is not addicted to the substance but to the behavior or feeling brought about by the use of a gadget [7]. The mesolimbic brain circuit plays a significant role in behavior due to addiction [8]. All addictive substances increase the feeling of joy and this trend leads to their repeated use.

Previous studies by Ayurveda scholars reveal only the prevalence and side effects of gadget addiction but it lacking in proven and published cost-effective, promising, and convenient Ayurveda therapy for gadget-addicted children. Are search gap exists with special reference to the use of Ayurvedic interventions for the management of gadget addiction in children.

The Ayurveda concepts of Asatmeindriyartha Samyoga [9] (inadequate association of senses with their organs of perception) and Pradnyaparadh (misuse of intellect) go much further to today's gadget addiction. Rather, it helps stimulate gadget addiction. The word Pradnyaparadha [10] is a combination of 2 words, that are Pradnya and Aparadh. Pradnya encompasses Dhee (intellect), Dhruti (control), and Smriti (memory), and Aparadh means misdemeanor. In addiction (could be of any type), the mental ability of the affected person is compromised, affecting their decision-making power. The mind needs controlling power to make decisions. According to Ayurveda, Dhee is the factor that governs the action of the mind [11]. Satva, Raja, and Tama Manas Guna also play an important role in the decision-making power and emotions of a person. Many features of gadget addiction are similar to the clinical features of Raja and Tama Guna's predominance [12]. Hence, to achieve a normal mental equilibrium in a person, we need to increase satva guna and decrease Tama and Raja Guna. This can be achieved by adequate counseling, assurance, Sadvritta Palana (Ayurveda rules to prevent mental and physical disorders), Dhyana (meditation), and the use of the Medhya Rasayana [13]. Medhya Rasayana means the drugs that promote Medha, which has Dhee (intellect), Dhruti (control on mind), and Smriti (memory) as its components [14]. Medhya Rasayana enhances the Sadhaka pitta, which is responsible for Nischayatmaka Buddhi [15] that is the decision-making power to opt for the right thing over wrong.

Gadget addiction is a behavioral disorder. There is research evidence of the use of antidepressants and antianxiolytic drugs for the management of gadget addiction [16]. The antidepressant and anxiolytic effects of Medhya drugs have proven efficacy, as reflected in various previous studies [17]. Medhya Rasayana acts on the hypothalamus-pituitary-adrenal axis and normalizes the secretion of serotonin and acetylcholine, thereby improving mental function [18]. The classical texts of Ayurveda describe Satvavajaya Chikitsa (subjugation of mind) for the management and prevention of behavioral, psychogenic, and lifestyle-related disorders [19]. Satvavajaya (subjugation of mind) helps a person to control the mind and restrain it from unwholesome objects by playing a significant role in maintaining a harmonious state between intellect, memory, and patience, leading to a healthy mental condition. Practical approaches of Satvavajaya Chikitsa are Ashwasana (reassurance and explanation), Pratidwanda Chikitsa (replacement of emotions), Chintya (presumption), Dhyeya (correction of objectives and ideas), Sankalpa (proper guidance and advice for taking the right decision), Dhriti (proper control of patience), Suhritvakya (guidance and suggestion), Dharmarthavakya (education of individual and family), Santwana (rehabilitation and assurance) [20]. Applying the above methods could change children's thinking and restrain them from unwholesome things. It could be beneficial in the management of Gadget addiction. Changing the thinking power of a patient is very important in the case of any addiction; this will happen with the help of Satvavajaya Chikitsa. Sadvritta helps in maintaining physical and mental fitness [21]. This helps improve the quality and longevity of life by secreting happy hormones [22]. It supports an increase in the Satvik guna of mind. Nonpharmacological measures like Sattwavajaya Chikitsa (subjugation of mind) dealing with manonigraha (control over unwanted thoughts and desires of mind) and proper counseling of patients, along with improvising the patient's self-confidence. Along with this, yogic (postures and meditation) therapy and lifestyle modifications are very beneficial to keep the body and mind healthy and calm. Yoga enables the person to restrain from addiction by promoting self-regulation. Yoga has the potential to detoxify our mind and body and it is also capable of controlling emotions. This phenomenon is useful in addiction

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craving, compulsive behavior, tolerance, and relapse conditions [23]. Yoga induces dopamine homeostasis, leading to long-term benefits for various addictive behaviors [24].

Protocol

Study Objectives

Evaluation of comparative efficacy of Medhya Rasayana (pharmacological) intervention versus Ayurveda nonpharmacological interventions and cognitive behavioral therapy in gadget addiction in children of the age group of 6 to 16 years.

The objectives of this study are listed in Textbox 1.

Textbox 1. Primary and secondary objective.

Primary objectives

- To evaluate the efficacy of Medhya Rasayana in gadget addiction with an internet addiction test scale, a digital addiction scale, and *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]).
- To evaluate the efficacy of Ayurveda nonpharmacological interventions in gadget addiction with an Internet addiction test scale, a digital addiction scale, and *DSM-5*.
- To assess the comparative efficacy of 3 therapeutic modalities in the management of gadget addiction by Internet addiction test scale and *DSM-5*.

Secondary objectives

- To evaluate the association of gadget addiction with Deha and Manas Prakriti (physical and mental constitution) of the participant with the help of Ayusoft software. Manufactured by C-DAC (Centre for Development of Advanced Computing) To assess the impact of gadget addiction on social relationships and behaviors in the *DSM-5* scale.

Hypothesis

Null Hypothesis (H0)

Any intervention among the Medhya Rasayana and Ayurveda nonpharmacological intervention are not as effective as the control group in reducing gadget addiction in children.

Alternative Hypothesis (H1)

At least 1 intervention among the Medhya Rasayana and Ayurveda nonpharmacological intervention are more effective than the control group in reducing gadget addiction in children.

The purpose of this hypothesis is to determine whether the 3 interventions under comparison in the study differ in their efficacy. If statistically significant differences exist in the outcomes, researchers can ascertain them by testing the null hypothesis against the data gathered during the randomized controlled trial.

Methods

Study Design

A 3-arm superiority randomized controlled trial will be performed. The study flow is depicted in Figure 1. Patients with gadget addiction will be selected from the Kaumarbhritya Outpatient Department of MGACHRC Salod, Wardha as per inclusion criteria mentioned in Textbox 2. During the first visit, Parents will be asked whether they would like to deaddict their child from gadget addiction if they are willing then written informed assent will be obtained from the participants' guardian. Participants will then complete questionnaires on the internet addiction test scale and digital addiction scale. Furthermore, participants' social behavior and Prakruti (physical and mental constitution) will be assessed. As well as age, gender, socioeconomic status, and type of gadget he or she is using frequently, and the purpose of gadget use will be assessed. After this period, participants will be randomly allocated to both intervention groups in a 1:1 allocation ratio. After this, Medhya Rasayana will be prescribed to participants in group I according to age-wise doses at a frequency of twice a day for a period of 90 days as mentioned in Table 1. Participants allocated to group II will be counseled regarding the adverse effects of gadget addiction on physical and mental health and advised to follow the following routine daily for a period of 90 days, details of nonpharmacological interventions are described in Tables 1 and 2. Yoga (sun salutations, meditation), Targeted reduction in Gadget use time Padanshik krama, that is, reduce gadget use time by one-fourth part each week. Reduced time will be used for adventure, bravery, cognitive skill-oriented things, sports, and yoga. Patients will be counseled to play indoor and outdoor games daily. Encouragement toward attending social programs whenever required and feasible, encouragement of parent-child relationship by advising parents to spend a minimum of 2 hours of quality time daily with children and to give a reward for not using mobile with encouraging children to learn new things, participate in group activities with peers and teach etiquette. Initial training in sun salutation and the method of meditation will be given to participants and their parents at the time of enrollment. Children will be asked to do the proposed sun salutation and meditation on the assessment day. Participants not responding or not following instructions will be eliminated from the study. Group III will be the external group due to the fact that cognitive behavioral therapy requires trained professionals and there are time and financial constraints as well. Hence, in this published data of previously conducted clinical trials, cognitive behavioral therapy intervention in the management of gadgets or internet addiction will be used for comparison with Medhya Rasayana and Ayurveda nonpharmacological interventions. On the 30th, 60th, and 90th days of treatment, participants will be evaluated using the internet addiction test scale and the *DSM-5* (*Diagnostic and*

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Statistical Manual of Mental Disorders, Fifth Edition) scale for social behavior. A follow-up will be conducted on the 180th day to determine whether the intervention's possible effects are lasting.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

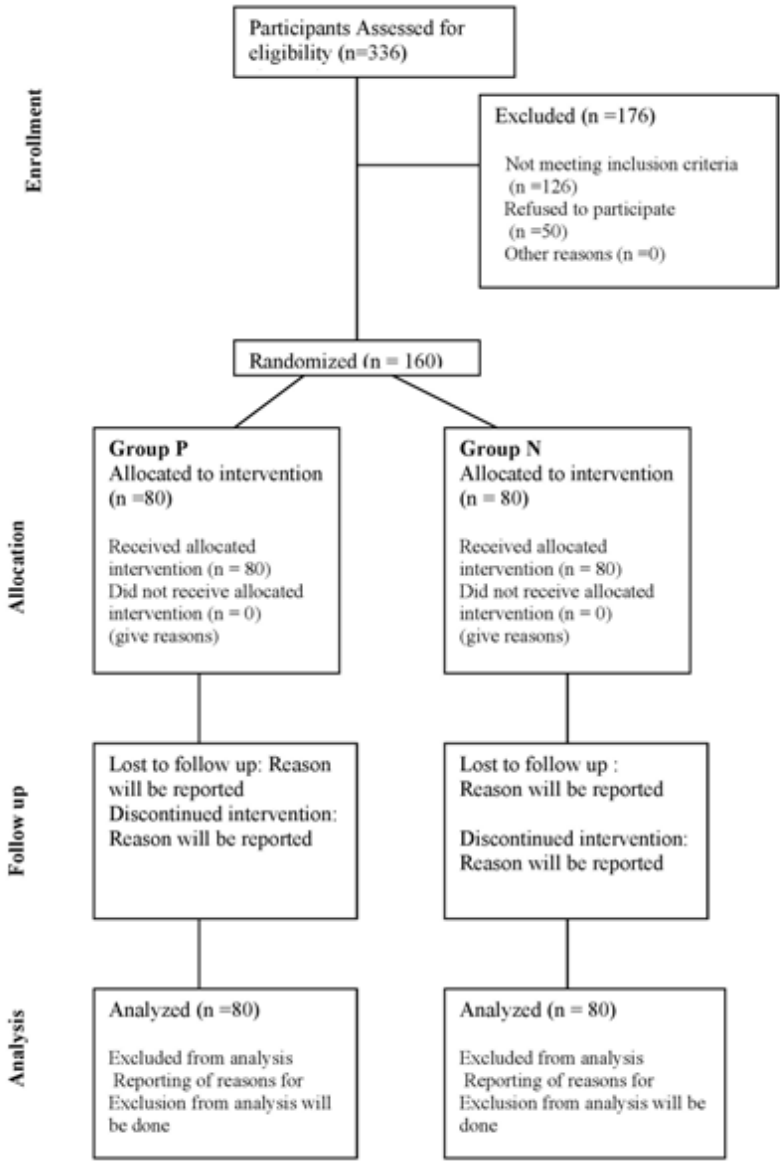

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Participants irrespective of gender, religion, and socioeconomic status.
- Participants affected with gadget addiction as per case definition, that is internet addiction test score: 31-79.
- Age group between 6-16 years with signs and symptoms of gadget addictions as per *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) or 11 as follows.
- Parents who are willing to provide written informed consent for their children to be included in the study.

Exclusion criteria

- Internet addiction test score >80.
- Children aged <6 years and those aged >16 years.
- Parents who are not willing to provide written informed consent for their children to be included in the study.
- Children experiencing from behavioral diseases, locomotor diseases, genetic diseases, and systemic disorders.

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Table 1. Overview of interventions.

	Group P	Group N	Group C
Participants, n	80	80	External group
Name of medication	Medhya Rasayana	Nonpharmacological	Cognitive behavioral therapy
Dosage form	Young's formula	As per schedule	__[a]
Duration	90 days	90 days	—
Assessment with IAT[b] scale	0, 30, 60, and 90 days	0, 30, 60, and 90 days	—
Follow up with the IAT scale, digital addiction scale, and *DSM-5*[c] scale	180th day	180th day	—
Route or mode of administration	Oral	—	—
Anupana	Lukewarm water	—	—

[a]Not applicable.

[b]IAT: internet addiction test.

[c]*DSM-5*: *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

Table 2. Overview of Ayurveda nonpharmacological intervention.

Intervention	Details of method	Duration and frequency
Counseling (Satvavajaya)	Counseling about hazardous effects of mobile and benefits of mobile deaddiction	Fortnight 1 session with parents and child separately
Yoga therapy	Surya Namaskar, Dhyana	Daily
Encouragement for indoor and outdoor games	Patients will be counseled to play indoor and outdoor games daily	Daily for1hour
Encouragement towards attending social programs	Parents will be guided for engagement of children in learning new things, in group activities with peers, etiquette	"Si-opus sit" Whenever required and feasible
Encouragement of parent-child relationship	Parents are advised to spend time with their children. And advised to give a reward for not using mobile to child.	Minimum 2 hours of quality time daily by parents
Targeted reduction in Gadget use time	Reduced time will be used for adventure, bravery cognitive skill-oriented things, sports, and yoga.	By Padanshik karma reduces gadget use time by one-fourth part each week

Participants

The required sample size was calculated by using the following formula.

To evaluate the effectiveness of the therapeutic modalities for managing internet addiction, several key parameters are defined. The type I error rate () is set at 5% and the type II error rate (β) is set at 20%. The true proportion difference, represented by ε, is assumed to be 0. δ denotes the clinically relevant difference at 20% superiority. Initially, the proportion of individuals with internet addiction (P1) is 62.22% (0.622). After the intervention (P2), this proportion decreased to 36.2% (0.362). To determine the appropriate sample size for the study, a clinically accepted difference of 20% is used. The sample size is calculated according to the formula N=(1.64+0.84)2(0.622)(1–0.622) +0.362(1–0.362)/(0.20)2. Based on this formula, the required sample size is 72 individuals per group. To account for a 10% dropout rate, the sample size is increased to 80 per group.

Therefore, 80 participants will be recruited after randomization in each group from the Kaumarbhritya OPD of Mahatma Gandhi Ayurved College Hospital and specialty camps held in peripheral villages of Wardha city. A computer-generated random number table will be used to avoid selection bias in the study. The principal investigator will carry out the process of randomization and enroll the participants. To be eligible for participation, participants should fulfill the inclusion criteria as mentioned in Textbox 2. Patients having any characteristics of exclusion criteria will be excluded from participation in the study.

Preparation of Medhya Avaleha

Medhya Rasayana Avaleha is the polyherbal combination of Centella asiatica, Convolvulus prostratus, Tinospora cordifolia, and Glycyrrhiza glabra mentioned in Table 3. Drugs required for the preparation of Medhya Avaleha will be collected from local markets or herbal gardens and identified in the Dravyaguna Department. Preparation of Medhya Rasayana Avaleha will be done as per classical reference [25] in Rasashastra and Bhaishyajya Kalpana Department of MGACHRC, Salod Wardha.

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Table 3. Overview of contents of Medhya Rasayana Avaleha [26].

Contents	Parts used	Proportion	Maximum dose
Centella asiatica (Linn.); family: Apiaceae; Ayurveda name: Manduk-parni	Leaves	1 part	1. mg/kg [27]
Convolvulus prostratus (chois); family: Convolvulaceae; Ayurveda name: Shankhpushpi	Leaves, roots, barks, flowers,	1 part	1. mg/kg [28]
Tinospora cordifolia (Willd Miers); family: Menispermaceae; Ayurveda name: Guduchi	Barks	1 part	Extracts 120 mg/kg [29]
Glycyrrhizaglabra (Linn.); family: Fabaceae; Ayurveda name: Yash-timadhu	Roots	1 part	50 gm/day [30]

Yoga Pose

For yoga poses refer to Figures 2-4.

Figure 2. Yoga pose 1.

Figure 3. Yoga pose 2.

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Figure 4. Yoga pose 3.

Assessment of Participants

All participants will be assessed for level of addiction, social behavior, and Prakruti (physical and mental constitution) before initiating the intervention during the study at 0, 30, 60, and 90 days, and on the follow-up day at180 days at Mahatma Gandhi Ayurved Hospital Salod (H). For the assessment of gadget addiction, an internet addiction test scale [31] questionnaire and a digital addiction scale [32] will be used. There are 20 statements on this questionnaire. After carefully reading each statement, participants have to choose the response (0, 1, 2, 3, 4, or 5) that best describes him or her using the 5-point Likert scale. Select the option that most accurately reflects how participants have been spending their time over the past month if 2 options seem to fit equally well. Along with participants, their parents or caretakers will be asked the following question regarding the gadget-addicted behavior of their children and the mean of both scores will be calculated to avoid bias in the study. The social behavior of the patient will be assessed by *DSM-5* [33] criteria on the proposed day Prakruti examination will conducted on the day of initiation of intervention by Ayusoft software [34].

Data Quality Assessment

The researchers will oversee and direct the process of gathering data. Since this study is a component of a postgraduate doctoral degree project, no committee was specifically tasked with overseeing or monitoring the data trials. However, the study progress will be discussed monthly with the supervisor.

Statistical Analysis

The data collection phase will be concluded with statistical analysis. Repeated measures ANOVA test, and chi-square test, will be used for statistical interpretation. A statistician consultation will be considered for the selection of the proper statistical method.

Dropout

If participants choose to stop the intervention, a detailed interview of the participant will be conducted to rule out the reason for the dropout. But no force will be exerted on them to continue the intervention. Common reasons for dropping out of the study will be enlisted and measures will be taken to manage them if feasible within the limits of the researcher.

Informed Consent

Before the study begins, all participants must give written informed consent (ie, during the first visit to the hospital). Every participant will get information regarding the study's design, objectives, data confidentiality, and the freedom to withdraw from the study at any moment without giving a reason. The original informed consent or approval from the institutional review board explicitly permits secondary analyses of the research data without necessitating additional consent.

Adverse Effects

Adverse consequences are characterized as unfavorable results resulting from study involvement. This study's potential side effects may include injury while doing yoga or Gastrointestinal system disturbances due to Medhya Rasayana avaleha. Adverse effects that occur will be noted and assessed for both the intervention and control groups.

Data Storage

Every piece of information regarding the study will be stored on a central disk space on a password-protected computer. Data access will be restricted to members of the research team only.

Incentive

Participation in the study is completely voluntary; hence, no incentive will be provided to students.

Ethical Considerations

The Mahatma Gandhi Ayurved College Hospital and Research Center's (MGACHRC) Institutional Ethics Committee approved this study (registration number MGACHRC/IEC/Oct-2022/614), and it was also registered with the Clinical Trial Registry of India (registration number CTRI/2021/10/037211). We will get assent from each participant's parents. During data analysis, measures will be taken to protect participants' privacy. The original informed assent or approval from the institutional review board explicitly permits secondary analyses of the research data without necessitating additional assent.

Results

In December 2023, the randomized controlled study got underway. Since participants may be in the study at any time, our goal is to complete the research by December 2024. Any

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significant changes to the protocol will be posted on clinicaltrials.gov. The study's findings will be disseminated through publications.

Discussion

Principal Findings

Compulsive conduct is one of the symptoms of addiction that can substantially impede a person's ability to receive therapy. Gadgets negatively affect the social life, health, and cognition of the child [35]. Hence, it is necessary to diagnose and treat gadget addiction in children as early as possible. The Medhya Rasayana avaleha was selected in this study as a pharmacological intervention. Medhya Rasayana has been popularly used as a proven therapy for the improvement of the intellect of children in India for centuries. As per Ayurveda, cognition is called Medha and it is not only related to the memory of a person but also consists of 3 components, that are Dhee (intellect), Dhruti (control of mind), and Smriti (memory). Among these 3 components, Dhruti is responsible for governing features and prevents the person from consuming destructive or nonbeneficial substances [36]. Consumption of Medhya Rasayana on a daily basis could enhance the control of the mind along with intellect and memory, which is beneficial in the management of addiction.

The nonpharmacological arm selected in this study is Satvavajaya (Ayurveda psychotherapy). It is the psycho-spiritual method and is intended for use with the mind and its associated qualities. It is mainly used as an important therapeutic to control the mind, which is heading toward unwholesome objects. Satvavajaya has multiple domains along with them, we are choosing the Vijnana (educative approach), Dhairya (supportive approach and development of coping ability), and Samadhi (psychophilosophical approach) [37]. Vijana (educative approach) and Dhairya (supportive approach and development of coping ability) are achieved in this treatment through proper counseling, which will include the adverse effects of gadget addiction on physical and mental health in a simple language that the child can understand. As well, Padanshika karma is preferred over sudden stoppage of treatment, which is part of Dhairya (supportive approach and development of coping ability). Samadhi (psychophilosophical approach) is a stage of unwavering concentration and minimizing mental fluctuations one could be distracted from unwholesome things and thoughts. This is achieved by regular meditation and yogic practices. Child externalization behavior and psychological factors like anxiety and depression are associated with gadget addiction [38,39]. The Ayurveda interventions, Medhya Rasayana and Satvavajaya have proven therapeutic effects on psychological factors [40-46]. As well as the impaired cognition in gadget addiction [47], both pharmacological and nonpharmacological interventions are beneficial in improving cognition [48].

Gadget addiction in children is one of the serious issues of concern in today's era so, there is a need to deaddict children to maintain proper growth and development of the child. Gadget addiction in children is associated with many behavioral diseases and no cost-effective convenient therapy is available for it this study can fill the gap.

While conducting the study, the investigator may face difficulties at the level of overdiagnosis of gadget addiction in children due to overconscious parents. Another difficulty we may face in the Ayurveda nonpharmacological intervention group is the failure to follow lifestyle modifications and yogic practices. This is the first study in the Ayurveda domain using pharmacological and nonpharmacological interventions for gadget addiction. Hence the small sample size and lack of a proven Ayurvedic control group are the main limitations of this study.

Conclusion

This research will provide crucial new information about the relative effectiveness of Ayurveda nonpharmacological therapies and Medhya Rasayana in treating children's gadget addiction. The results will guide evidence-based treatments aimed at reducing the negative impact of excessive gadget use on this susceptible population's psychosocial development. In the end, the findings are meant to help policy makers and medical professionals create sensible plans to deal with the rising issue of childhood gadget addiction.

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Data Availability

The datasets that will be generated and/or analyzed during this study will be available from the corresponding author upon reasonable request.

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Authors' Contributions

PY contributed to conceptualization, methodology, data collection, data curation, statistical analysis, writing–original draft, review, and editing. RR managed conceptualization, methodology, data collection, writing–original draft, review, and editing. SM performed methodology, conceptualization, writing of original draft, review, and editing.

Conflicts of Interest

None declared.

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Abbreviations

C-DAC: Centre for Development of Advanced Computing
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)
MGACHRC: Mahatma Gandhi Ayurved College Hospital and Research Center

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Protocol

A Personalized Data Dashboard to Improve Compliance with Ecological Momentary Assessments in College Students: Protocol for a Microrandomized Trial

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Abstract

Background: Ecological momentary assessments (EMA) are ideal for capturing the dynamic nature of young adult substance use behavior in daily life and identifying contextual risk factors that signal higher-risk episodes. These methods could provide a signal to trigger real-time intervention delivery. Study compliance and engagement are common barriers to participation but may be improved by personalizing messages. This study compares compliance outcomes between one group of young adults receiving standard (generic) prompts at each assessment and another group that received additional personalization and an updated data dashboard (DD) showing study progress to date at 1 randomly selected prompt per day.

Objective: The primary objectives are to (1) develop a real-time DD for giving participants personalized updates on their progress in the study and (2) examine its preliminary overall effects on study compliance and experiences. Secondary objectives are to identify person-, day-, and moment-level characteristics associated with study compliance and person-level characteristics associated with perceived usefulness of the DD.

Methods: This is a protocol for Project ENGAGE, a 2-arm randomized controlled trial. Arm 1 (EMA group) is engaged in a standard EMA protocol, and arm 2 (EMA+DD group) is engaged in the same study but with additional personalization and feedback. Inclusion criteria are (1) previous participation in a recent college student survey about health behavior and mental health who indicated willingness to participate in future research studies and (2) indicated past-month alcohol use; lifetime marijuana, hashish, or Delta-8-tetrahydrocannabinol (THC) use; or some combination of these on that survey. All participants in this study completed a baseline survey; EMA at 11 AM, 2 PM, 5 PM, and 8 PM each day for 21 days; and an exit survey. Participants in arm 2 engaged in a microrandomized trial, receiving a personalized DD at 1 randomly selected prompt per day. Primary outcomes include whether a survey was completed, time to complete a survey, and subjective experiences in the study. Primary analyses will compare groups on overall study compliance and, for arm 2, use marginal models to assess the momentary effect of receiving 1 updated DD per day.

Results: Approval was granted by the university's institutional review board on February 8, 2023. Recruitment via direct email occurred on March 30 and April 6, 2023; data collection was completed by April 29, 2023. A total of 91 individuals participated in the study. Results have been accepted for publication in *JMIR Formative Research.*

Conclusions: Results from the evaluation of this study will indicate whether providing (at randomly selected prompts) real-time, personalized feedback on a participant's progress in an EMA study improves study compliance. Overall, this study will inform whether a simple, automated DD presenting study compliance and incentives earned to date may improve young adults' compliance and engagement in intensive longitudinal studies.

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KEYWORDS

ecological momentary assessments; data dashboard; study compliance; microrandomized trial; intensive longitudinal data; EMA; adolescents; substance use; wearables

Introduction

Overview

The prevalence of alcohol and cannabis use peaks in young adulthood (age range approximately 18-25 years), with 31% of young adults reporting recent heavy episodic drinking (5+ drinks in a row) and 11% reporting daily or near-daily cannabis use [1]. Heavy and frequent use in this age group can be linked with risk for alcohol use disorders, cannabis use disorders, or combined alcohol and cannabis use disorders, with 16.4% of young adults meeting criteria for a past-year alcohol use disorder and 16.5% meeting criteria for a past-year cannabis use disorder [2]. Far more common are the numerous acute substance-related harms that young adults experience from heavier alcohol use, cannabis use, or combined alcohol and cannabis use episodes in daily life, such as social-interpersonal issues, physical effects, and memory impairments [3].

Real-time data capture, as in daily diary studies or ecological momentary assessment (EMA) studies, is ideal and widely used for identifying antecedents and consequences of days and moments of highest alcohol- and cannabis-related risk [4]. Such intensive longitudinal data methods can be used to distinguish between- and within-person effects by asking questions such as “Are individuals who experience more stress more likely to report binge drinking?” (between-person) and “Are individuals more likely to report binge drinking on days when they experience more than their usual stress?” (within-person). Such methods are also ideal for capturing the dynamic nature of substance use behavior in daily life and identifying contextual risk factors that signal higher-risk episodes. Using such methods could ultimately provide a signal to trigger real-time intervention delivery.

However, compliance—particularly in substance use studies—can be a major concern for several reasons. First, young adults are less likely to complete reports on weekends when substance use is more likely to occur [5,6] and thus most critical to assess. Second, particular types of substance use behaviors, such as combining alcohol and cannabis, occurs somewhat rarely [7]. These behaviors can only be captured with many days of assessment, but participant compliance and motivation to participate in the study protocol may wane over time. Third, to assess behavior in optimal windows and provide timely intervention content, in some cases it is critical to assess behavior *in the moment when risk factors are higher*. However, engagement in the study protocol has the potential to interfere with participants’ daily lives. If young adults feel burdened by intensive longitudinal data collection, they may be less likely to provide complete data. A meta-analysis by Jones et al [8] concludes that overall, EMA compliance is only approximately 75% among individuals who use substances. Few studies have examined ways to improve participant compliance during intensive longitudinal data collection, yet recent work suggests that personalizing messages to young adults may increase compliance [9].

Mobile health apps have been developed in efforts to improve symptoms related to mental health, substance use, and a variety of other chronic health conditions and health behaviors. Many of these apps have shown no efficacy and/or modest clinical effects [10]. Poor engagement and related factors (eg, compliance, retention, and dropout) likely contribute to these findings because poor engagement with intervention content greatly weakens therapeutic effects. Only recently have studies of mobile health apps included measures of engagement as important outcomes; some even include aspects of engagement as the focus of interventions [11,12]. Among a wide variety of mobile health apps for managing chronic conditions (eg, mental well-being and HIV medication adherence), a meta-analysis estimated that the pooled dropout rate across apps was 43%, though the duration (range: 2 weeks to 1 year) and characteristics of study design varied considerably [13]. In another meta-analysis of apps addressing mental health problems, the dropout rate was approximately 36% after 8 weeks [11].

One way to improve young adult compliance may be to provide personalized, updated progress reports throughout their study participation, such as a data dashboard (DD) with real-time feedback on their progress in a study or aspects of the participant’s current or recent characteristics or behaviors. Personalization may be particularly useful because it can provide timely information unique to the person. Personalization may be operationalized in a variety of ways and may include content that serves self-interest or prosocial goals. For example, Carpenter et al [14] implemented a trial in which participants received biweekly messages about accrued reward points for a chance to win a prize for themselves (self-interest messages) or a chance to win a prize to donate to a charity (prosocial messages) and compared compliance rates. Interestingly, self-interest messages were more effective for compliance early in the study, and prosocial messages were more effective later in the study [14]. Thus, providing personalized data-driven feedback, particularly with the goal of improving compliance, is an understudied but particularly useful area of investigation.

To better understand study engagement and begin to address limitations in prior research, we enrolled young adults in a 2-arm randomized controlled trial called Project ENGAGE. Both groups participated in a 21-day EMA study that included 4 survey prompts per day (up to 84 prompts total). Participants were randomized to either participate in a traditional EMA study, where standard text prompts with links to a survey were received 4 times per day (EMA group), or an augmented study condition in which the text prompt was accompanied by a DD for 1 randomly selected survey per day throughout the EMA protocol (EMA+DD group). This 2-group design allows us to examine the overall effect of receiving 1 DD per day on overall

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study compliance and engagement. Individuals assigned to the EMA+DD group participated in a microrandomized trial (MRT) [15], which allows us to examine the short-term effects of the DD on momentary study compliance and inform the development of a just-in-time intervention that could be deployed to maximize study compliance within individuals.

Aims and Objectives

Primary Objectives

The primary objectives of Project ENGAGE are to (1) develop a platform or delivery system for providing real-time, personalized updates on progress in the study and (2) examine the preliminary overall effects of embedding this real-time DD on study compliance and experiences. Intervention group differences will be examined in terms of the overall number of completed surveys (out of 84 prompts), average time to submit completed surveys, and subjective experiences with the study protocol. For the second aim, primary outcomes include participants' overall compliance with the 84 surveys, mean time to complete a survey after receiving a prompt, and user experiences with the DD system.

Secondary Objectives

Secondary outcomes are to identify person-, day-, and moment-level characteristics associated with study compliance and person-level characteristics associated with perceived usefulness of the DD:

1. The following person-level characteristics will be examined in relation to study compliance overall and as moderated by the treatment group: baseline characteristics (gender, first and second vs third and fourth year in college, and history of substance use) and weekly app use.
2. We will estimate differences in compliance outcomes (did or did not complete all 4 surveys that day and mean time to complete surveys that day) as a function of day in study (days 1-21) and whether it was a weekday or weekend.
3. We will compare differences in momentary compliance and time to respond to a prompt across the following moment-level characteristics: whether the participant reported using their phone at the time they received the prompt, and (for the EMA+DD group) time of day on which the DD was received.

This study will yield didactic information for the broader research community on how to deploy a real-time DD or messaging system in a smartphone-based EMA study to improve ongoing participant compliance. Additionally, this study will demonstrate how to collect and analyze data from a study that uses an MRT embedded within a 2-arm randomized controlled trial.

Methods

Participants and Trial Design

Participants were drawn from a sample of undergraduate college students at a large public university who previously participated in a large, campus-wide cross-sectional survey in Spring 2023 and agreed to be contacted for future research. Participants who indicated past-month alcohol use or lifetime marijuana, hashish, or Δ-8-tetrahydrocannabinol (THC) use or some combination thereof were sent an email inviting them to participate in this study. Individuals interested in participating contacted the study team for more information or moved directly to the screener questionnaire using unique REDCap (Research Electronic Data Capture; Vanderbilt University) survey links provided in their emails.

Individuals were eligible to continue into the study if their responses to the screener questionnaire indicated that they were 18-25 years of age, used alcohol and cannabis in the past 30 days, and used an iPhone with an iOS version of 12 or more recent. The iPhone eligibility requirement was added to overcome technical challenges and additional confounding elements related to variations in how REDCap surveys and visual messages are displayed in iOS versus Android systems. Previous work by the study team has shown that students in the current institution are overwhelmingly iPhone users.

Eligible participants who consented to participate in this study were randomized into either the EMA group or the EMA+DD group and directed to the baseline survey. The randomization was performed automatically such that each participant had a 50% chance of being assigned to either of the 2 groups. The team planned to collect data from at least 40 individuals in each study condition. Study team members were able to see participants' group assignment but had no contact with participants at any time to avoid introducing interview bias. After completing the baseline survey, participants were automatically enrolled in the 21-day portion of the study, with day 1 starting on the first Thursday after baseline completion. During the 21-day portion of the study, the participants received text-based prompts with a personalized REDCap link to a web survey.

Each prompt was sent at 4 equally spaced times per day (11 AM, 2 PM, 5 PM, and 8 PM) for 21 days, for a total of 84 prompts for each participant. Assessment timing was fixed to ensure data collection protocol as identical between both groups, to allow time in between assessments or avoid stacking of assessments, and to accommodate typical sleeping schedules and timing of substance use among our sample of college students who use substances. At each prompt, participants reported their substance use since the last prompt, psychosocial factors, and whether they were using their phone at the exact moment of receiving each prompt. Participants were instructed to complete each survey within 60 minutes of receiving the link, at which point the link would expire. At the conclusion of the 21-day portion of the study, participants completed an exit survey to provide feedback on their experiences in the study, including the acceptability and usefulness of a DD (for the EMA+DD group) or their openness to receiving a DD (for the EMA group).

Real-Time Data Dashboard Intervention: an MRT Design

For individuals in the EMA+DD group, 1 of the 4 prompts on each day included a DD component plus a personalized message, whereas the other 3 prompts simply presented the standard text with a link to the survey. Within each day, the prompt at which the DD would be delivered was selected at random. Figure 1

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depicts the data collection schedule and corresponding compliance, as experienced by 5 random participants in each condition.

Figure 1. Data collection schedule and corresponding compliance data from 10 random study participants: 5 in the EMA+DD group (top panel) and 5 in the EMA group (bottom panel). Each row represents 1 participant, and each cell represents 1 day. Cell shading indicates EMA completion by the participant (blue=completed, gray=missing), and dots indicate display of the DD to the participant (black=DD without completion bonus progress ring, red=DD with completion bonus progress ring). DD: data dashboard; EMA: ecological momentary assessment.

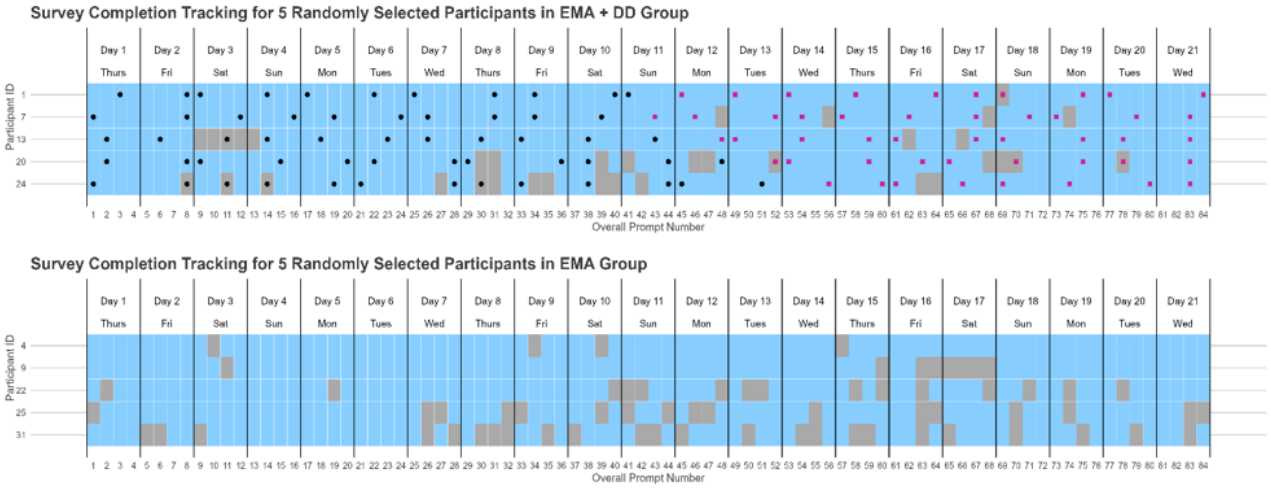

Our DD included several features to convey a participant's study compliance. The visual image for the DD was partly inspired by the progress charts or exercise rings commonly found on wearable smart devices and fitness trackers (eg, Apple Watch and Garmin devices). Multiple iterations of the DD were tested internally by the study team to confirm accuracy and ensure that the information was user-friendly. The DD comprised 2 separate rings in the form of concentric circles. The outer ring (blue) represented the number of surveys that have been completed; the inner ring (red) represented the number of days (out of 21) completed. The colored parts (nongray areas) of the ring provided a visual representation of study compliance to date and were labeled with a count of the prompts and days completed to that point. Once participants completed at least 50% of their daily surveys, a portion of the outer ring turned yellow. The yellow portion indicated the number of surveys remaining before the participant reached a high completion bonus; the number of remaining surveys also was shown in the yellow portion of the ring. Color-matched text below the visual image provided a key to interpret the rings, with blue text showing the number of surveys completed, red text showing the number of days left in the study, and yellow text showing the number of surveys left before achieving the bonus (only when the bonus event activated, as described above). The center of the rings represented a "bank," displaying the total amount of incentive money the participant had earned to that point in the study. The participant's name also was generated on each DD as a form of personalization (eg, "[Name's] progress so far!"). Colors for the rings were selected from a color palate that is more distinguishable for individuals with colorblindness.

Figure 2 shows a hypothetical example of the real-time, personalized DD that accompanied 1 randomly selected prompt per day among individuals randomized to the EMA+DD group. This example shows data for a hypothetical individual on day 15 who had completed 42 prompts, conveying the participant's progress in the study to date. Specifically, the DD shows the number of prompts completed so far, the number of days remaining in the study, the number of surveys remaining until they earn the high completion bonus, and the total amount of incentives earned to date.

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Figure 2. Example of a data dashboard that accompanied a text prompt to complete an ecological momentary assessment survey for a hypothetical participant who had completed 15 days of the study, provided data in response to 42 prompts to date, was 18 prompts away from reaching the high compliance bonus, and had earned US $21 in incentives.

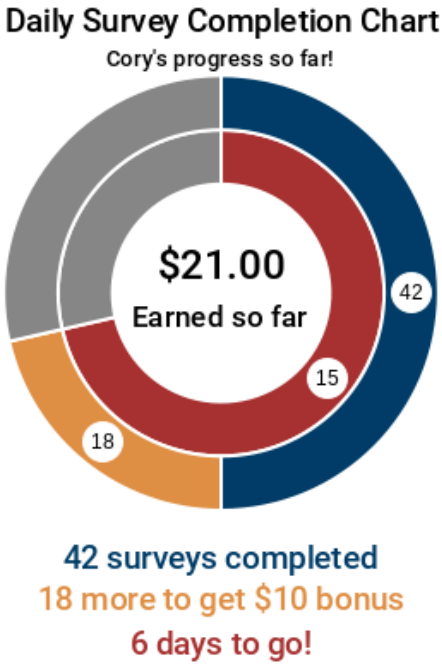

Study Implementation

The entirety of the study was conducted in REDCap, which is a free survey platform that allows researchers to create and manage surveys to collect data securely. The complex study was designed and implemented in a way that was fully automated.

Specifically, we created a project consisting of multiple surveys: a screener, a baseline survey, 4 momentary surveys (1 for each time of day: 11 AM, 2 PM, 5 PM, and 8 PM) for the EMA portion of the study, and an exit survey. Surveys were used to store participants' contact information separately from the rest of the data. These surveys were uploaded by the research team for all potential participants. This triggered the automated survey invitations for these individuals to go out at a scheduled date and time. At each prompt, these automated invitations provided unique participant links to the screener survey.

The screener survey contained the consent form, as well as several eligibility-related questions. Once a participant clicked on the link and completed the screener, they were told whether they were eligible to continue. The survey ended for participants who were not eligible to continue, but they were provided with study team contact information if they had further questions.

Participants who were eligible after the screener survey were automatically forwarded to the baseline survey. After completing the baseline survey, each participant was redirected to a server maintained by the institution's survey research center. This server randomly assigned each participant to the EMA or the EMA+DD condition and scheduled all 84 prompt invitations via texts using Twilio's Multimedia Messaging service. For the EMA group, all 84 invitations would simply include the text "It's time to complete your next survey:" with a link to the EMA survey in REDCap corresponding to that time of day.

For the EMA+DD group, on each of the 21 study days, the server would randomly select 1 of 4 prompts at which to deliver the DD. At the other 3 prompts during that day, participants would receive the standard message that was used for all prompts in the EMA group. Just before each prompt, if a participant was randomly determined to receive a DD at that prompt, the server used JavaScript libraries to calculate the compliance data for each participant and then generated a visual image showing their progress to date in the study, to be delivered at that prompt.

Participants were given 1 hour to complete each survey after receiving the invitation via text. The invitation links in the text messages took the participant to the server and forwarded them to the relevant REDCap survey only if the link was clicked within the designated timeframe and the participant had not already completed that prompt.

At 11 AM on the day following the 21st day of the EMA study, all participants in both groups received a link to an exit survey, which assessed their experiences while participating in the study. Participants had 7 days to complete the exit survey.

Outcome Measures

Primary Outcomes

This study focused on 2 objective measures of compliance and a set of quantitative and qualitative measures of subjective experiences. Primary outcomes included the following:

1. Overall compliance: overall compliance was derived from a moment-level binary measure of compliance (ie, an indicator of whether the participant completed the survey within 60 minutes of a particular prompt), summed across 84 prompts within an individual. This was used to address the question: "Did individuals who received a daily DD

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complete a greater number of surveys, on average, compared to those who did not?"

2. Average time of survey response: average time was derived from the length of time between the survey prompt and survey completion (among completed surveys), averaged across up to 84 prompts. This outcome was used to address the question: "Did participants who received the DD complete surveys more quickly, on average, compared to those who did not?"
3. Subjective experiences of the study protocol: subjective experiences were assessed in the exit survey and were compared across groups. This comparison relied on both quantitative and qualitative measures of experiences.

Secondary Outcomes

1. Total number of surveys completed within each week, to compare whether participants were more likely to comply to the EMA protocol during week 1, 2, or 3, and whether the intervention effect varied across weeks.
2. Mean time to complete surveys (among completed surveys) within each week.
3. Total number of surveys completed within each day, to compare whether participants were more likely to comply to the EMA protocol across days 1 through 21, and whether they were more likely to comply on weekdays versus weekends. These differences also were examined to see whether the intervention effect varied across days or types of days.
4. Mean time to complete surveys (among completed surveys) within each day.
5. The moment-level binary indicator of compliance and moment-level length of time to complete each survey will be used as outcomes in multilevel models examining moment-level predictors of compliance (eg, time of day and whether they completed last survey) and moment-level predictors of time to complete surveys (eg, whether currently using phone, stress, positive affect, and negative affect). Group assignment will be included as a moderator to see whether the intervention effect varies across types of moments.
6. (For the EMA+DD group only) The moment-level binary indicator of compliance and moment-level length of time to complete each survey will be examined in relation to whether the DD was included at that prompt.

Ethical Considerations

The institutional review board at the Pennsylvania State University approved all study procedures (#00021945). Participants provided informed consent before completing the baseline and daily diaries. Study data are deidentified. Participants could earn up to US $67 via an e-gift card for full participation in the study. Specifically, participants were compensated US $10 for the baseline survey, US $0.50/daily survey, a US $10 bonus if they completed 70+ of the 84 surveys, and US $5 for completing a brief exit survey.

Results

Recruitment invitations were sent via direct email to 411 individuals. Of these, 92 (22%) completed the consent form, completed the baseline survey, and were randomized to either the EMA group or the EMA+DD group. Among these individuals, 91 (99%) ultimately participated in the EMA survey (ie, provided data at 1 or more EMA prompt), thus determining our final sample size. Data were collected during March and April 2023.

Participants were predominantly White (92%), non-Hispanic (89%), and female (67%), with a mean age of 20.3 (SD 1.18) years. Among the 91 participants, 43 (47%) were randomized to the EMA group and 48 (53%) were randomized to the EMA+DD group. Overall study compliance was very good, with a mean of 64.3 (14.6) out of 84 (76.5%) prompts completed, resulting in a total of 5896 (out of a possible 7644) person-moments of data.

Discussion

Results from our evaluation of the MRT will provide evidence about whether providing real-time and personalized feedback on a participant's progress in an EMA study improves compliance across multiple metrics. MRTs have a high potential for informing the development of effective just-in-time interventions focused on higher-risk substance use behavior. Information about the use of personalized dashboards to improve compliance will be a critical finding from this study, as compliance is a critical first step toward greater overall study engagement. Evaluating the effect of receiving a DD on speed of completing that particular survey will also be useful, as it reflects a state of investment or energy and cognitive energies, key components of engagement [16].

Further, REDCap and similar data collection tools are ubiquitous in most university settings. Thus, our automated approach could be deployed at many institutions with existing technology. This approach circumvents the often tedious or slow process of gaining approval for use of a third-party service to deploy such studies. Although REDCap does not natively support EMA data collection, there are relatively straightforward workarounds to automate a tailored process such as in this study. Because of the nearly universal adoption of these software packages, a wealth of information including community forums also exists online to troubleshoot issues and develop new techniques.

This study necessitated a specialized system to implement the generation of the DD based on real-time information of the participant. Through a collaboration with the institution's survey research center, expert staff were able to connect the REDCap system to a server in which custom code was used to determine the timing of deployment, calculate data for inclusion, and generate the DD for each individual at appropriate times.

This feasibility study was limited in sample size and thus may be underpowered to evaluate the effectiveness of the DD. Further, generalizability to the broader population of young adults may be limited given that all participants were currently attending college at a large, predominantly White, public

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university in the Northeast region of the United States. Additionally, the system designed for this study was specific for iPhone users; additional modifications would be necessary to adapt the study for Android phone users.

Overall, this study will inform whether a simple, automated DD that presents study compliance and incentives earned to date could improve ongoing compliance and overall engagement in intensive longitudinal studies. Future research could expand this scope by varying the frequency of presenting a DD (including providing one at every assessment point) and adding additional information to the graphical presentation of data. Additionally, real-time data such as biofeedback data from wearable devices could be integrated in future studies to further personalize messaging. For example, a heart rate monitor could be used to tailor messaging that corresponds to a DD, such as "Your heart rate was really high this afternoon. You said you like to meditate—might be a good idea to try it now." Such personalization could help researchers to better understand and improve on the effects of providing a personalized DD and use it to trigger tailored intervention content. Alternatively, future studies might take into consideration relevant, passively detected contextual features such as current weather to determine whether they moderate the effect of receiving a DD.

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Data Availability

Data from this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

DD: data dashboard
EMA: ecological momentary assessment
MRT: microrandomized trial
REDCap: Research Electronic Data Capture
THC: Δ-8-tetrahydrocannabinol

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Protocol

The Effect of Interventions Based on the Information-Motivation-Behavioral Skills Model on the Human Papillomavirus Vaccination Rate Among 11-13-Year-Old Girls in Central and Western China: Protocol for a Randomized Controlled Trial

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Abstract

Background: Persistent infection of high-risk human papillomavirus (HPV) can lead to cervical intraepithelial neoplasia, cervical cancer, and even death. HPV vaccination for girls aged 9-14 years can effectively prevent the occurrence of cervical cancer. Some Chinese provinces and cities have launched free HPV vaccination programs for school-age girls; however, due to the lack of supportive government policies, the high price and supply shortage of HPV vaccines, and vaccine hesitancy, some parents refuse to vaccinate their daughters.

Objective: This protocol reports the design of a randomized controlled trial (RCT) aiming to explore the efficacy of a digital HPV vaccination education intervention based on the information-motivation-behavioral skills (IMB) model in improving the HPV vaccination rate among 11-13-year-old girls in central and western China.

Methods: A multicenter intervention study based on an online applet will be conducted in December 2024, and about 750 eligible parents of 11-13-year-old girls will be assigned in a 1:1 ratio to an intervention group receiving 7-day digital HPV vaccination education based on the IMB model or a control group using non-HPV publicity materials. Free HPV vaccination pilot projects will be carried out among this population by our research team in central and western China (some parents might refuse to vaccinate their daughters). All participants will be asked to complete online questionnaires at baseline; postintervention; and 1 week, 1 month, and 3 months after the intervention.

Results: The primary outcome of this study will be receipt of the first HPV vaccination within 3 months. Data will be analyzed based on an intention-to-treat approach, and Stata 16.0 will be used for statistical analysis.

Conclusions: This study aims to improve the HPV vaccination rate among 11-13-year-old girls and will examine the impact of a digital HPV vaccination education intervention based on the IMB model. The findings of this study may offer promising intervention measures for HPV vaccine hesitancy in low-health-resource areas in the future.

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Trial Registration: Chinese Clinical Trial Registry, ChiCTR2300067402; https://tinyurl.com/v5zt4hc9
International Registered Report Identifier (IRRID): PRR1-10.2196/58873

(JMIR Res Protoc 2024;13:e58873) doi:10.2196/58873

KEYWORDS

human papillomavirus; HPV; HPV vaccine; vaccine hesitancy; information-motivation-behavioral skills model; HPV vaccination rate; randomized controlled trial; vaccination rate; China

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections that can cause various genital diseases among women [1]. Persistent high-risk HPV infection is closely associated with the occurrence of cervical and other cancers [2]. According to the worldwide cancer statistics released by the International Agency for Research on Cancer, there were 604,000 new cases of cervical cancer and 342,000 deaths due to cervical cancer in 2020 worldwide [3]. The incidence of cervical cancer ranked third among malignant tumors, and the estimated death toll ranked second among deaths due to malignant tumors in Chinese women aged 15-44 years in 2020 [3]. In the past decade, the incidence and mortality of cervical cancer in China have shown an upward trend year on year [4]. Overall high-risk HPV infection rates in mainland Chinese women are about 19.0%, with subtypes 16, 52, 58, 53, and 18 being the most common infections [5].

Cervical cancer is considered near completely preventable through the primary and secondary prevention measures of HPV vaccination and screening [6]. In November 2020, the World Health Organization (WHO) released the *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem* [4]. The WHO position paper recommended that young adolescent girls aged 9-14 years be the primary target group for HPV vaccination [7]. Relevant clinical trials and cohort studies have verified the safety and efficacy of HPV vaccines among this population [8]. In some high-income countries, the incidence of cervical cancer apparently decreased 10-12 years after widespread HPV vaccination [9,10]. However, effective prevention strategies were not applied adequately, with only 15% of girls of the target age vaccinated with the full course of HPV vaccines in 2019 [11]. In China, the HPV vaccination rate among girls aged 9-14 years was less than 1% in 2020, which is lower than the current world average of 20% [12,13]. As a result, improving the HPV vaccination rate among girls is an urgent need in China.

Chinese authorities approved HPV vaccines in 2016 [14]. Since 2020, some provinces and cities in China, especially those with good financial status, such as Guangdong Province and Fujian City, have launched free HPV vaccination programs for school-age girls [15]. However, without supportive government policies, the high price and supply shortage of HPV vaccines have impacted accessibility and affordability in the central and western regions of China [16,17]. In addition to the financial considerations and accessibility issues, vaccine hesitancy is also a major barrier to vaccine coverage [18]. Vaccine hesitancy is defined as the refusal or delay of vaccination when immunization services are available, which means low vaccine acceptance despite the availability of vaccination services [16]. Given the young age of the HPV vaccine target population, this study will focus on HPV vaccine hesitancy among the parents of girls aged 9-14 years. A recent study in mainland China reported that 53.9% of the guardians of secondary school girls aged 12-19 years were HPV vaccine hesitant, mainly because of a lack of knowledge of HPV vaccines and insufficient communication from reliable sources of information [19]. Previous studies have demonstrated that health interventions targeting parents can effectively improve vaccine coverage among girls. In 2018, an intervention using health education manuals and reminder letters was implemented among parents of 11-12-year-old girls in New York State, which increased the HPV vaccination rate from 24.1% to 75% [20]. Research on East African immigrant mothers conducted 10 HPV vaccine–related health education forums to increase HPV vaccine–related knowledge, improve attitude, and increase the intention to vaccinate adolescent children. Results from this study showed that mothers who attended the forums showed a more positive attitude and an intention to getting their daughters vaccinated [21]. Therefore, vaccine hesitancy has been shown to be a major obstacle to HPV vaccination among targeted girls.

In 2023, our research team initiated a free HPV vaccination pilot project among low-health-resource areas in China, which may last for at least 2 years, aiming to provide girls aged 11-13 years with HPV vaccines. Considering the possible HPV vaccine hesitancy among parents, this study will use an intervention for parents to improve their vaccination intention and increase the vaccination rate among their daughters, guided by the information-motivation-behavioral skills (IMB) model. The IMB model is a validated approach to predicting and promoting health behavior performance by providing relevant information, personal and social motivation, and behavioral skills [22,23]. It has been widely used in behavior interventions over the past decade among different populations, such as HIV prevention among Indian truck drivers, improvement of maternal breastfeeding efficiency in pregnant women with hepatitis B virus (HBV) infection, and antiretroviral therapy (ART) adherence improvement among HIV-positive patients in southwestern China [24-26]. In terms of HPV vaccine interventions in China, the IMB model has been proven to effectively increase the willingness of HPV vaccination, when combined with an online program [27]. This study will use the IMB model, which asserts that information related to HPV infection and cervical cancer prevention, HPV vaccination motivation, and behavioral skills are fundamental determinants of HPV vaccination (Figure 1) [28].

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Figure 1. Framework of the IMB model used in the study. HPV: human papillomavirus; IMB: information-motivation-behavioral skills.

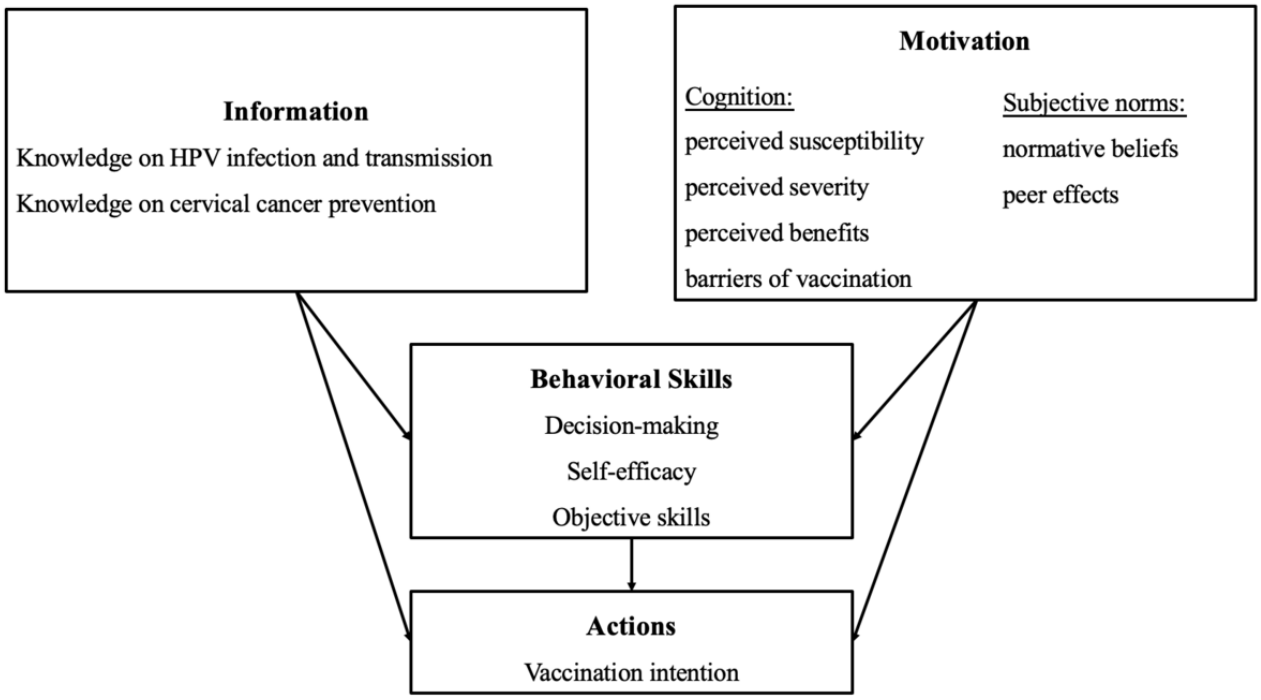

We hypothesize that a digital HPV vaccination education intervention based on the IMB model will motivate parents to vaccinate their children against HPV, thus significantly improving the local HPV vaccination rate among 11-13-year-old girls (who are in the senior grade of primary school). Therefore, the primary objective of this study is to improve the HPV vaccination rate among 11-13-year-old girls in central and western China. Through this study, we aim to explore the potential influencing factors and mechanisms of parents' hesitancy to vaccinate their daughters against HPV. In addition, we will discuss the intervention effects of 7-day digital HPV vaccination education based on the IMB model on the parents. The ultimate goal is to evaluate the efficacy of such intervention measures against HPV vaccine hesitancy in order to help improve the HPV vaccination rate among 11-13-year-old girls in China in the future.

Methods

Trial Design

This will be a double-blind randomized controlled trial (RCT) of an intervention based on an online applet. Before the intervention, the research team will carry out free HPV vaccination pilot projects for 11-13-year-old girls in 4-5 study sites in low-health-resource areas in China. After the first stage of the HPV vaccination program is completed, 11-13-year-old girls' parents who choose not to vaccinate their daughters will be invited to our intervention study, and those who are willing to participate will be guided to register and log on to the "Yi Yan Health" mini applet (Figure 2), which was independently developed by our research team and can be used for mobile app–based education and questionnaire collection. Next, all participants will be randomly divided into 2 groups: (1) an intervention group, which will receive a baseline questionnaire, 7-day digital HPV vaccination education based on the IMB model (with a sample shown in Figure 3), and follow-up right after the intervention period and 1 week, 1 month, and 3 months after the intervention, and (2) a control group, which will only receive popular science education that is not related to HPV vaccines; these non-HPV publicity materials will be uploaded at the same time every day as the intervention group to maintain parents' interest in the control group. Meanwhile, participants in the control group will also need to complete questionnaires simultaneously with the intervention group. After the intervention trial, we will provide the control group with the same IMB-based HPV vaccine intervention materials free of charge for ethical considerations. Our free HPV vaccination pilot program will also continue until at least half a year after the intervention to ensure that all 11-13-year-old girls whose parents are willing to vaccinate their daughters can receive the first HPV vaccination during or after the intervention.

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Figure 2. Interface of the "Yi Yan Health" mini applet. IYH: Yi Yan Health mini-program.

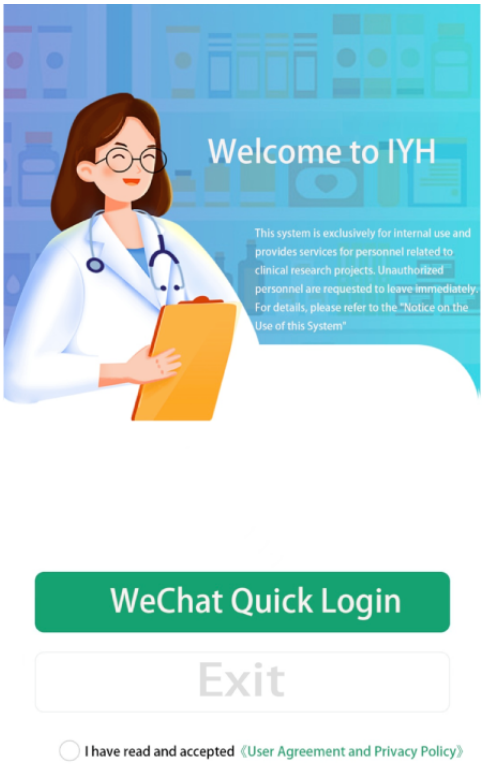

Figure 3. Mobile app intervention material sample.

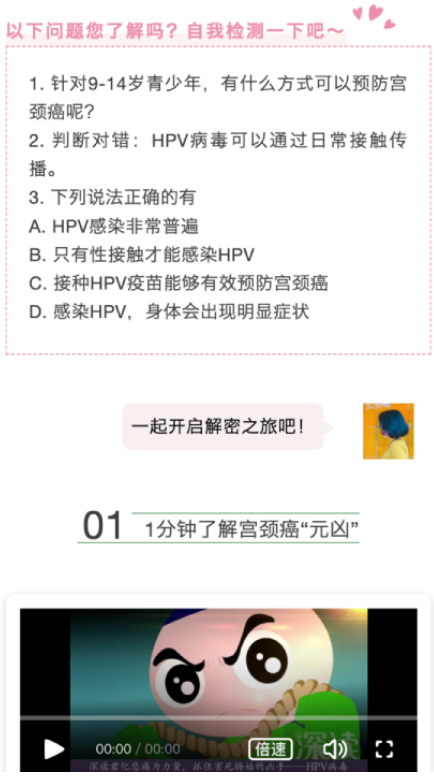

Settings

Our research team will conveniently select 5 cities or counties in central and western China as research sites. Local hospitals or medical schools will provide assistance in the recruitment of participants and other implementation issues of the project. All researchers in this study were required to have a professional background in medicine or public health and received unified training conducted by the research team before the start of the study. This study is scheduled to start in September 2024 and is expected to last for about 12 months. This study was registered on the Chinese Clinical Trial Registry (ChiCTR 2300067402, registration date January 6, 2023).

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Ethical Considerations

The subjects of this study are 11-13-year-old girls' parents who do not choose to get their daughters vaccinated against HPV. Due to the fact that HPV vaccination for children in China requires parental informed consent, we will only recruit parents instead of their daughters in this study.

In adherence to normative documents, including the Declaration of Helsinki (revised by the World Medical Association in October 2013) and the "Approach to the Ethical Review of Biomedical Research Involving Humans" issued by the National Health Commission of the People's Republic of China, Research Ethics Committee, Chinese Academy of Medical Sciences & Peking Union Medical College, approved this research (ID: CAMS&PUMC-IEC-2022-077) on November 30, 2022, following thorough review and discussion. Informed consent will be obtained from all participants, with a clear explanation of the project, including confidentiality agreements and conditions for opting out at any time.

If parents accept the free HPV vaccination for their daughter, they will need to pay a Chinese yuan (CNY) 20 (~US $3) injection fee to the local health facility, which is the same as the injection fee for other vaccines. Participants will incur no additional costs by participating in this study. Additionally, they will benefit from learning about HPV, HPV vaccines, and cervical cancer prevention. Participants can choose to vaccinate their daughters with free HPV vaccines offered by the government or decline. This project aims to improve HPV vaccine coverage among girls aged 11-13 years in low-health-resource areas in China, provide valuable insights into promoting HPV vaccination nationwide, and, ultimately, contribute to reducing and potentially eliminating cervical cancer in China.

Patient and Public Involvement

After project introductions by the researchers, those who are interested in this study will be recruited. Once participants sign the informed consent form, the researchers will complete eligibility checklists, and those who fail to meet the inclusion criteria will be removed. All information will be stored on an encrypted laptop. Participants will also have the right to freely obtain more information at any time and will be allowed to freely withdraw from the study without restrictions at any research stage.

Sample Size

According to the purpose of intervention effect evaluation, the comparison formula of 2 independent rates is used to calculate the required sample size. To date, there are no studies on the effects of a mobile app–based intervention for 11-13-year- old girls in central and western China to improve the HPV vaccination rate. For this reason, the anticipated effect size is largely based on findings of similar studies derived from the relevant literature in other countries. In this study, according to the literature review and the results of our research team's free HPV vaccination campaign conducted in Ordos City, Inner Mongolia Autonomous Region, China, in 2020, about 30% of parents in the control group refused to vaccinate their daughter (Pc), while parents in the intervention group who refused are expected to be 20% lower than those in the control group (Pt): α=.05 (2-sided), β=.2 [29-31]. Considering the possible dropout (20%), the intervention and control groups need 74 effective samples each, totaling 148, and each project site needs to recruit about 150 participants. There will be 750 participants in 5 project sites, 375 (50%) in the intervention group and 375 (50%) in the control group.

Eligibility Criteria

The inclusion criteria are as follows:

- Parents who have refused to vaccinate their 11-13-year-old daughters against HPV after being offered the first dose of vaccination
- Parents who have the local household registration of the research site
- Parents who have an electronic device with internet access, such as a smartphone, a tablet, or a laptop
- Parents who are able to read and understand the questionnaire
- Parents who understand the vaccination procedure and volunteer to participate in this study

The exclusion criteria are as follows:

- Parents whose daughters have contraindications for HPV vaccination or other physical conditions that are not suitable for HPV vaccination
- Parents who have participated in similar research in the past 6 months

Recruitment

In 5 regions with free HPV vaccination pilot projects, parents who refuse to vaccinate their daughters and who meet the inclusion criteria will be enrolled into this study. After providing informed consent, all participants will register and log on to the mini applet, and they will then be randomly assigned to the intervention group or the control group in a 1:1 ratio using the randomization algorithm embedded in the mini applet.

Intervention

Intervention Group

All participants in the intervention group will need to log on to the mini applet through a computer or a smart phone and will receive 7-day digital HPV vaccination education based on the IMB model. Our research team has developed intervention materials after reviewing the relevant literature and conducting multiple rounds of panel discussions with a group of experts, including 1 cancer epidemiologist, 1 infectious disease epidemiologist, 1 researcher from the project center, and 1 senior manager from a media company. This 7-day digital HPV vaccination education intervention was previously applied by our research team in a project on HPV vaccination willingness of Chinese female college students and achieved positive results [14,32]. However, since digital education aims to target different participants in this study, the researchers have worked with the expert panel to adjust and optimize the previous content to better

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meet the needs of the parents of 11-13-year-old girls before the start of intervention.

According to the IMB model, digital HPV vaccination education is divided into 3 modules and 6 themes, with each module containing 2 themes. The first module is information, which is the initial prerequisite for promoting healthy behaviors. Module 1 has 2 themes: (1) HPV infection and related diseases and (2) high-risk factors of HPV infection and how to prevent HPV infection. The second module is motivation, which mainly refers to personal attitudes toward health behavior and related social motivation. Personal attitudes include the understanding of HPV susceptibility, the expectation of costs and benefits of taking preventive actions, and the experience and willingness to take actions; social motivation includes social support and social values. Module 2 has 2 themes: (3) introduce the benefits of HPV vaccines so as to encourage parents to vaccinate their daughters and (4) describe the harm and susceptibility of HPV infection through a true story to motivate parents to take action to prevent their daughters from contracting HPV infection. The third module is behavioral skills, which mainly emphasizes the improvement of personal objective skills and self-efficacy. Module 3 has 2 themes: (5) how to use personal objective skills to make firm decisions and communicate effectively with family members to obtain understanding and support for daughters' HPV vaccination and (6) the concept and function of self-efficacy and ways to improve self-efficacy and promote the transformation of motivation into behaviors.

Each of the 6 thematic courses will be uploaded to the mini applet and will take participants about 10-15 minutes to read and learn. In addition, the mobile app–based HPV vaccination education contains a high level of interactivity with the following learning forms: reading text, viewing pictures, small videos pictures watching, and taking quizzes. The intervention will last for 1 week, and data will be collected at baseline (1 week before the intervention); postintervention; and 1 week, 1 month, and 3 months after the intervention. All the data will be obtained for statistical analysis.

Control Group

The control group will receive health promotion materials unrelated to HPV vaccines, and the researchers will distribute the questionnaire to both intervention and control groups simultaneously through the same mini applet. After 3 months of follow-up, participants in the control group will receive the same health education about HPV vaccines as the intervention group, free of charge for ethical considerations.

Adherence

The intervention will be stopped at the participants' request if they find anything harmful about it, and participants have the right to refuse to answer some sensitive questions in the questionnaire or to withdraw from the study at any time.

Before the intervention, the researchers will introduce the importance and expected benefits of this study. During the intervention, once the course is uploaded, the mini applet will automatically send a text message to participants every day to remind them to learn until they have completed the course. The researchers can also supervise participants by their learning duration, which will be automatically recorded by the backend database of the mini applet. During follow-up, similarly, the mini applet will automatically send a text message to participants every day before they complete the questionnaire, and the number of completed questionnaires will be used to evaluate the adherence of participants to the entire trial process. Finally, we will express our gratitude to all participants for their involvement and encourage them to complete the study through nonmaterial incentives, such as by answering their questions related to HPV or cervical cancer during the research.

Measures

Outcome Measurements

The questionnaire in this study is divided into 4 sections: general demographic data, current HPV vaccination status, parents' hesitancy and attitudes toward HPV vaccines, and potential factors related to HPV vaccine hesitancy. The questionnaire in the study is designed in Chinese to ensure that participants can understand and respond to the questions.

Primary Outcome: HPV Vaccination Status

The ultimate goal of this study is to improve the HPV vaccination rate among 11-13-year-old girls. This indicator will be measured by the proportion of parents who choose to vaccinate their daughters against HPV within 3 months after the intervention. To ensure the authenticity of HPV vaccination, the vaccination status will be checked by the registration history in the information systems of local health agencies, which have already collaborated with us, rather than being self-reported by participants. The HPV vaccination behaviors will be strictly verified by our researchers, and those who are just "willing" to be vaccinated will not be included in the positive results.

Secondary Outcomes: Parents' Hesitancy and Attitudes Toward HPV Vaccines

We will measure parents' hesitancy and attitudes toward HPV vaccines in 3 parts. The first part is about general vaccination attitudes, which will be used to investigate participants' attitudes toward other common vaccines recommended by the Chinese government. The second part is about HPV vaccine hesitancy, which will be used to assess the degree of HPV vaccine hesitancy among parents. The third part is about vaccine confidence used, which will be to investigate participants' confidence in HPV vaccines.

Other Outcomes: Potential Factors Related to HPV Vaccine Hesitancy

To explore the potential factors associated with HPV vaccine hesitancy, our research team has designed a section based on the IMB theoretical framework to assess parents' HPV-related information, vaccination motivation, and behavioral skills to further explore the factors associated with HPV vaccine hesitancy. We will also directly ask participants what factors can affect their daughters' HPV vaccination, thereby investigating the reasons for their vaccine hesitancy.

Blinding

Although participants will not be blinded because of the nature of the intervention, blinded evaluation will be adopted in our

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study. In this study, all researchers involved in outcome assessments will be blinded to the group allocation. During the intervention, only unblinded research assistants in each center will be aware of the allocation and will be in contact with participants. In addition, all data analysis will be completed by personnel who are blinded to the intervention assignment. Participants will be unblinded after the follow-up survey.

Data Collection, Management, and Monitoring

The questionnaire will be distributed via the mini applet, and all completed questionnaires will be automatically saved into the read-only web-based database to ensure authenticity of the data. Moreover, our researchers will promptly check the collected data after each questionnaire survey. Regarding integrity of the data, all questions will be self-administered and set as mandatory to ensure that all submitted questionnaires have no missing data.

Statistical Analysis

Stata 16.0 will be used for statistical analysis. The distribution of categorical variables will be described by frequencies and percentages, and continuous variables conforming to normal distribution will be described by means (SDs). Chi-square tests will be performed to compare the differences between different groups. The *t* test or 1-way ANOVA will be performed to compare the mean scores between groups on the same continuous and dependent variables. Logistic regression will be conducted to analyze the factors associated with HPV vaccine hesitancy. Repeated measurement data at baseline; postintervention; and 1 week, 1 month, and 3 months after the intervention will be analyzed using generalized estimation equations (GEEs). Significant variables will be included in baseline chi-square analysis, and we will also assess group (intervention and control), time (baseline; immediately after the intervention; and 1 week, 1 month, and 3 months after the intervention), and time×group interactions, with the interaction indicating a differential change by group from baseline to the end of the trial. Statistical significance will be set at $P<.05$ (2-sided).

Results

This study protocol is reported following SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines. Table S1 in Multimedia Appendix 1 shows the SPIRIT diagram for the schedule of enrollment, intervention, and assessment.

Figure 4 shows the flowchart of the protocol. See Table 1 for the structure design of the questionnaire and Table 2 for the structure design of the 7-day mobile app–based education intervention on HPV vaccines.

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Figure 4. Flowchart of the protocol. HPV: human papillomavirus.

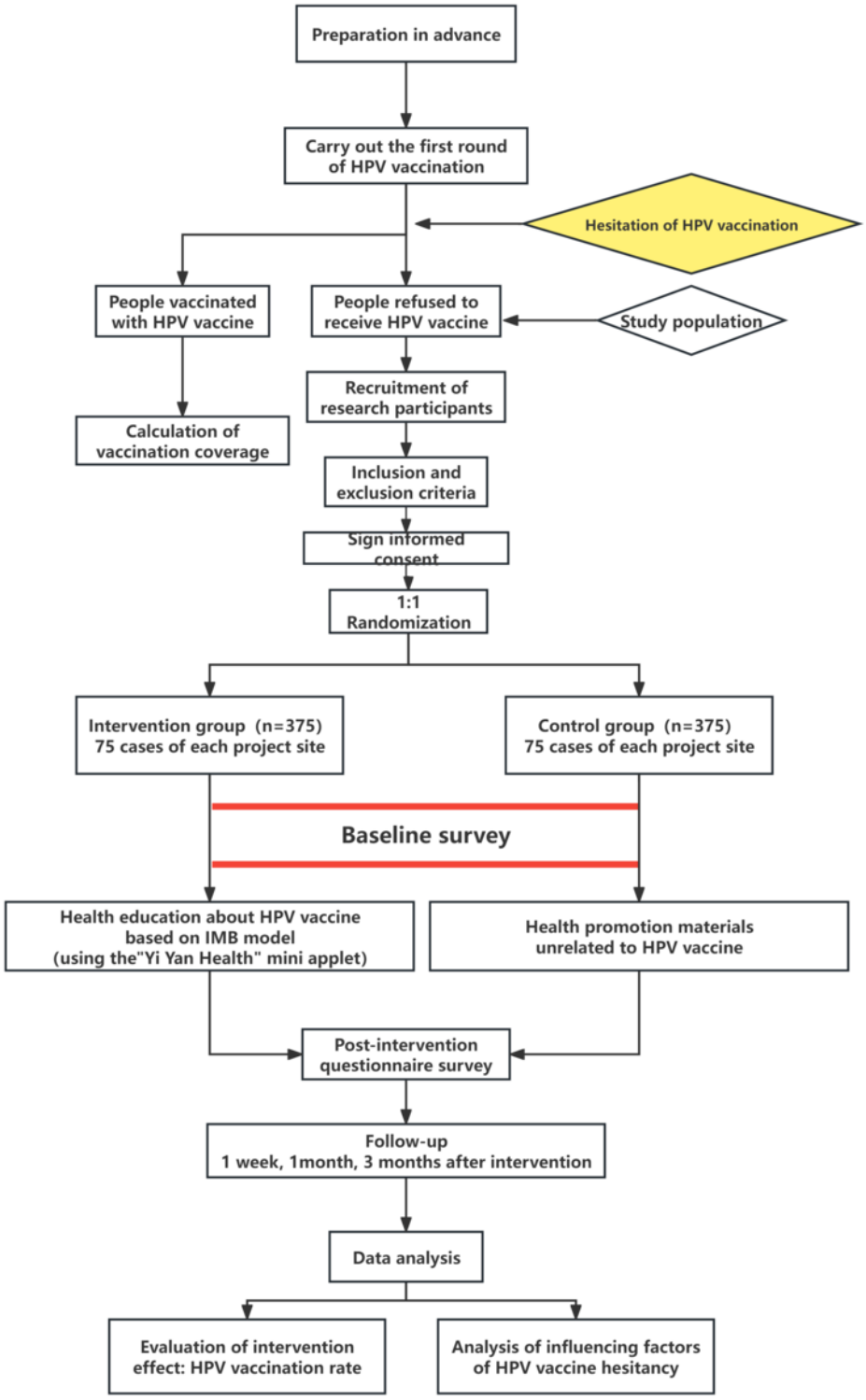

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Table 1. Structure design of the 7-day digital education intervention on HPV[a] vaccines.

Day	Content
1	Information about HPV infection
2	Information about HPV vaccines
3	Cherishing your health, actively preventing and controlling cervical cancer
4	Cervical cancer, a threat to women's health
5	Introduction to effective decision-making and communication skills
6	Small tips to action promotion
7	Invitation to HPV vaccination

[a]HPV: human papillomavirus.

Table 2. Structure design of the questionnaire.

Section	Content or part
General social demographic data survey	Age, nationality, religious belief, permanent residence, parents' education level, family monthly income (CNY[a]/month), whether any of the relatives has cancer, etc
HPV[b] vaccination status	Whether parents chose to vaccinate their daughters against HPV within 3 months after the intervention or whether they took an appointment for HPV vaccination within 3 months
Vaccine hesitancy survey	• General vaccination attitude survey • HPV vaccine hesitancy survey • Vaccine confidence survey
Factors resulting in HPV vaccine hesitancy	• Parents' HPV-related information, vaccination motivation, and behavioral skills (based on the IMB[c] model) • What factors can affect their daughters' HPV vaccination?

[a]CNY: Chinese yuan.

[b]HPV: human papillomavirus.

[c]IMB: information-motivation-behavioral skills.

At the time of manuscript submission in October 2024, study recruitment was pending and was expected to start in November 2024. The expected results will be analyzed and prepared for publication in 2025.

Discussion

Summary

This multicenter RCT based on an online mini applet aims to reduce vaccine hesitancy among parents of 11-13-year-old girls in central and western China by using digital education measures based on the IMB model. By reducing vaccine hesitancy, the intervention will encourage parents to vaccinate their daughters against HPV, improve the coverage of HPV vaccines in China, and promote the elimination of cervical cancer in China. To the best of our knowledge, this study will be the first to evaluate whether the mobile app–based education intervention designed according to the IMB model can improve the HPV vaccination rate among 11-13-year-old girls in central and western China. In addition, this study will also explore the factors associated with parents' HPV vaccine hesitancy, which may provide a much clearer reference for formulating an HPV vaccination policy and subsequent HPV vaccination rate intervention studies in China.

Our study will focus on girls in central and western China because the distribution of health resources in China is still not completely balanced, and the central and western regions have relatively fewer resources than the east [33,34]. Due to relatively scarce health resources, 11-13-year-old girls in central and western China are less knowledgeable about HPV and HPV vaccines [35]. In addition, compared to some eastern provinces of China, such as Guangdong, Fujian, and Shandong Provinces, which have launched free HPV vaccination campaigns for 11-13-year-old girls, it is much more difficult for girls in central and western China to obtain HPV vaccines. Therefore, it is more urgent and significant to carry out vaccination campaigns and intervention studies in central and western China to realize the target of eliminating cervical cancer in the country.

Previous studies have revealed that HPV vaccination can significantly reduce the risk of cervical cancer in women aged 9-45 years, and the earlier the vaccination, the better the preventative effect obtained [10]. At present, Finland, the United Kingdom, and other countries have implemented HPV vaccination plans for 11-13-year-old girls, and their current vaccination rates are high [36-38]. For example, more than 80% of 13-year-old girls in England have completed 2 doses of HPV vaccination, and similar high statistics are reported in other countries [38]. However, in China, HPV vaccines have been on the market for only a few years, and some parents remain

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skeptical or even hesitant of the vaccine, leading to an unsatisfactory coverage rate, especially among 11-13-year-old girls who are still studying in primary school [39]. A cross-sectional study conducted in Weihai, Shandong Province, China, about HPV vaccination willingness of parents of girls aged 9-17 years showed that only 19.32% of parents were willing to vaccinate their girls against HPV. These results suggest that Chinese parents have a high degree of HPV vaccine hesitancy and that relevant action is needed to change this attitude [40]. Additionally, an RCT conducted in the United States had parents of adolescents aged 11-17 years watch HPV vaccine health education videos in outpatient clinics, and 2 weeks later, the HPV vaccination rate among adolescents whose parents watched the videos was 3 times higher than among those whose parents did not watch the videos [41], which shows that health interventions targeting parents could effectively improve vaccine coverage among children and teenagers. Based on the aforementioned domestic and foreign evidence, it is necessary to explore effective strategies against HPV vaccine hesitancy among parents of 11-13-year-old girls in central and western China.

Evidence suggests that a change in behavior is the result of knowledge, psychology, and social factors, which indicates that the design of health education activities could be based on appropriate theories of behavior change [42,43]. The health intervention materials in this study are based on the IMB model, which improves the logicality and scientific integrity of the intervention. Our research team had previously used similar health education materials in an intervention for HPV vaccination willingness among female college students in mainland China, and the results revealed that the proportion of participants willing to receive HPV vaccines increased from 52.5% before the intervention to 59% after the intervention, while the proportion in the control group did not change [44]. These results indicate that the 7-day digital HPV vaccine education interventions based on the IMB model can improve the willingness of participants to receive HPV vaccines, which proves the effectiveness of mobile app–based education in female college students. Such effectiveness may be extended to other groups, such as parents of 11-13-year-old girls.

To the best of our knowledge, there is no research using the theory-based digital education method to improve the HPV vaccination rate among 11-13-year-old girls in central and western China. Regarding the study design, this double-blind RCT with the actual vaccine coverage rate as the main outcome may provide more innovative suggestions for the promotion of HPV vaccines. At present, because of the efforts of the Chinese government in infrastructure construction, mobile devices have become an integral part of daily life among the majority of Chinese people, including in central and western China. Additionally, mobile app–based interventions could be free from time and space constraints, greatly improving the efficiency and flexibility of interventions and reducing the cost, which can benefit more people. If this study proves that the 7-day digital HPV vaccine education intervention based on the IMB model can effectively improve the HPV vaccination rate, this convenient, low-cost, and easy-to-popularize intervention can be implemented among a wider range of people.

Limitations

This study has several limitations. First, since HPV vaccines were approved to be used in China in 2016 and have not yet been covered by the National Immunization Program, the sample size cannot be accurately calculated due to the lack of the exact HPV vaccination rate or the HPV vaccine hesitancy rate in central and western China. Second, HPV vaccines need to be administered 2 or 3 times, but the follow-up period may not fully capture the entire vaccination process. As a result, it will be impossible to collect comprehensive data on the frequency and extent of vaccine hesitancy. Third, due to the nature of the intervention, participants in our study will not be blinded and contamination may occur. However, investigators and data analysts will all be blinded to the randomized allocation, and only the research assistants in each center will be aware of the allocation. Fourth, the research sites will be selected by convenience sampling, which would cause selection bias. Although this method is necessary, considering local cooperation and feasibility, it may limit the generalizability of our findings to other regions. Future studies could consider random sampling to enhance representativeness and reduce potential biases.

Conclusion

To sum up, this will be the first study based on the IMB model for improving the HPV vaccination rate among 11-13-year-old girls in central and western China. This multicenter RCT can perhaps offer promising intervention actions for HPV vaccine hesitancy in the future. Future studies could focus on evaluating the effectiveness of HPV vaccination promotion materials across different geographical regions. Additionally, research could compare the impact of various intervention strategies to identify the most effective methods for increasing vaccine uptake.

Acknowledgments

The authors would like to thank the National Health Commission of the People's Republic of China, Research Ethics Committee, Chinese Academy of Medical Sciences & Peking Union Medical College, for approving this study. We also extend our gratitude to Dr Youlin Qiao and Dr Xiaoyou Su for their invaluable guidance and supervision throughout the study. Lastly, we appreciate the efforts and cooperation of all the staff members at the study sites who will contribute to the smooth execution of this research.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

YQ and XS were responsible for the conceptualization and methodology of the study; ST, XS, and YQ provided overall guidance and supervised research activities; XS, SJ, and YW prepared the original draft; and SJ, YW, and ZD were responsible for the questionnaire design.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram for the schedule of enrollment, interventions, and assessments.
[DOCX File , 22 KB - resprot_v13i1e58873_app1.docx]

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Abbreviations

CNY: Chinese yuan
HPV: human papillomavirus
IMB: information-motivation-behavioral skills
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Digital Homework Support Program for Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) affects 4% to 5% of the general population. Homework sessions are frequent conflictual moments characterized by increased anxiety in children and stress in their parents, contributing to a lower family quality of life. Children with ADHD experience more severe homework problems than typically developing peers. Poor academic performance in individuals with ADHD is partly attributed to challenging homework. Psychoeducational and school-based approaches are time-consuming and not fully accessible to professionals. Digital tools, such as smartphone and tablet apps, might offer an interesting alternative. We present our digital homework support program for children and adolescents, known as "Programme d'Aide Numérique aux Devoirs pour Enfant avec TDA-H" (PANDAH), along with the study protocol of our ongoing randomized controlled trial.

Objective: This study aims to test PANDAH's efficacy in improving homework performance and family quality of life.

Methods: Individuals aged 9-16 years with an ADHD diagnosis and no comorbid psychiatric disorders are included. This is a multicenter study involving 9 reference centers for ADHD in France. The study comprises (1) a 3-month period with a randomized controlled trial design, where participants are divided into 2 parallel groups (group 1: care as usual or waiting list; group 2: PANDAH app), followed by (2) an extension period of 3 months (months 3-6), during which all participants will have access to the app. This second phase serves as a crucial incentive for patients initially randomly assigned to group 1. Assessments will be conducted at baseline, month 3, and month 6 for each patient by trained psychologists. The primary end point will be the global Homework Performance Questionnaire (HPQ), Parent version score at 6 months. The main analysis will adhere to the "intent-to-treat principle" (all patient data will be analyzed according to their initial group determined by randomization). We expect (1) HPQ score improvement in individuals using the app during the first 3-month period compared to individuals not using the app; (2) greater HPQ score improvement for individuals using the app for 6 months compared to those using the app for 3 months only; and (3) adherence to the PANDAH program, measured with in-app metrics.

Results: Recruitment began in January 2024, and the trial is ongoing.

Conclusions: This study contributes to the digital transformation of health care. The use of smartphone apps in self-care and self-management is a societal phenomenon, and its implementation in the field of psychiatry is of particular interest. The app

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might serve as both valuable support for patients and an opportunity for parents to distance themselves from conflict-laden homework sessions. Since the market for smartphone apps in the health care and well-being sector is primarily industry driven, it is crucial to have an academic conception and evaluation of such digital tools.

Trial Registration: ClinicalTrials.gov NCT04857788; https://clinicaltrials.gov/ct2/show/NCT04857788

International Registered Report Identifier (IRRID): PRR1-10.2196/44553

(JMIR Res Protoc 2024;13:e44553) doi:10.2196/44553

KEYWORDS

attention-deficit/hyperactivity disorder; mobile app; assisted homework session; digital mental health; e-health; smartphone; psychiatry; neurodeveloppemental disorders

Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects 4% to 5% of the general population [1,2]. Elementary school children with ADHD face severe academic challenges characterized by reduced seatwork completion, seatwork accuracy, on-task behavior, and homework performance compared to their peers [3,4]. Homework sessions are often tense moments marked by increased anxiety in children and stress in their parents, undeniably contributing to decreased family quality of life. Children with ADHD experience more severe homework difficulties than typically developing peers [5,6]. Longitudinal studies also indicate that homework performance during elementary school serves as a key predictor of later academic success for individuals with ADHD [7].

These issues persist into later school years, with middle and high school students with ADHD exhibiting poorer organizational skills, lower grades, increased truancy, and higher rates of suspension and grade retention compared to their peers [8-11]. Moreover, significantly fewer individuals with ADHD graduate from high school (68% vs 100% of controls) [11] or enroll in 4-year colleges and universities compared to controls (29.5% vs 76.8% of controls) [12]. In summary, academic underachievement is strongly associated with ADHD [13-19], and homework sessions could be a critical area of intervention to prevent this outcome.

To address this issue, several health care interventions are available, such as classroom management and behavioral consultations in school settings [20-22]. Although classroom management procedures and interventions have demonstrated short-term improvements in classroom behavior and seatwork completion and accuracy among children with ADHD in classroom and analog classroom settings [23-25], it is potentially beneficial to explore additional interventions targeting the academic functioning of children with ADHD, both at home and the parenting level. Research indicates a positive relationship between homework and achievement, with a stronger link observed in middle and high school [26].

Among the various behavioral parent training (BPT) programs for children with ADHD, two programs have focused on homework functioning: (1) the Family School Success Program [27] and (2) Parents and Teachers Helping Kids Organize [28]. Both programs incorporate effective components of BPT, such as consistent responses, time-out, goal setting, rewards, and positive attention. They have demonstrated efficacy in improving parent-reported problematic behaviors during homework time, with moderate to large effect sizes ranging from 0.52 to 1.51 [28,29]. Furthermore, these academically focused BPTs have improved self-reported parenting strategies, teacher-reported homework problems, and parent- and teacher-reported organizational skills. Interestingly, children on stimulant medication who received BPT showed greater improvement in parent-reported homework management than their unmedicated peers [29]. However, none of these programs have incorporated new technologies thus far.

Over the past 4 years, we have been developing a smartphone app to assist in homework management within therapeutic groups, aiming to help both parents and patients improve their homework sessions and concentration. However, the real and perceived use of an app significantly impacts its usefulness [30]. Therefore, to be efficient and reduce attrition, a digital tool needs a specific design; an intuitive user interface; and the addition of an artificial intelligence module to create an algorithm that can analyze, predict, and provide suitable personalized advice. As a result, we developed *Programme d'Aide Numérique aux Devoirs pour Enfant avec TDA-H* (PANDAH; "a digital program to help children with ADHD during homework sessions" in French) to support children with ADHD during their homework sessions with minimal or no parental assistance.

This study aims to investigate the impact of PANDAH on children and adolescents aged 9 to 16 years with ADHD over a 6-month period, focusing on homework performance and well-being.

Methods

Recruitment

This multicenter study involves 9 reference centers for ADHD in France, which are specialized centers covering specific geographic areas with multidisciplinary teams experienced in ADHD diagnosis and treatment. We plan to include a total of 360 patients with ADHD from waiting lists of reference centers (median waiting time in France is 9 months) [31]. The inclusion and exclusion criteria are shown in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients aged 9-16 years, currently on the waiting list of one of the participating centers
- Consensus diagnosis of attention-deficit/hyperactivity disorder (ADHD) by 2 mental health care professionals
- Written informed consent provided by patients and their parents

Exclusion criteria

- Patients with severe psychiatric conditions such as schizophrenia, bipolar disorder, or autism spectrum disorders, along with suicidal ideation or behavior (assessed by the Child Behavior Checklist Scale)
- Patients with no access to a smartphone or limited smartphone access (eg, patients in social facilities or those with low economic status)
- Patients with mild to severe mental retardation or deemed clinically unable to use the app
- Patients participating in special programs beyond standard care received while on the waiting list
- Patients not attending school (no homework)
- Patients in the titration period of methylphenidate or those with unstable doses over the past 3 months

Study Design

The primary investigator's center is the Department of Child and Adolescent Psychiatry at Nantes University Hospital Centre, which includes a clinical research unit in psychiatry, addictology, and child and adolescent psychiatry. The study will consist of a 3-month period with a randomized controlled trial design, where participants are divided into 2 parallel groups (group 1: care as usual or waiting list; group 2: PANDAH app). This is followed by a 3-month extension period (month 3 [M3] to month 6 [M6]), during which all participants will have access to the app (Figure 1). This second phase serves as an incentive for patients initially randomized into group 1. Assessments will be conducted at baseline (M0), M3, and M6 for each patient. Baseline evaluations will be performed by trained psychologists at inclusion and will include age, sex, school grade, treatment history, Child Behavior Checklist, Hamilton Anxiety Scale, ADHD Rating Scale, and Homework Performance Questionnaire (HPQ) [32] with parents. Interviews will last approximately 2 hours and 30 minutes, including instructions for using the app for group 2. Evaluations at M3 and M6 will be similar (2 hours and 30 minutes), allowing the assessment of the maintenance of effects and efficacy.

Figure 1. Study design of PANDAH protocol. ADHD: attention-deficit/hyperactivity disorder; ASQ: Abbreviated Symptom Questionnaire; CDRS: Children's Depression Rating Scale–Revised in Adolescents; HPC: Homework Problem Checklist; HPQ: Homework Performance Questionnaire; M: month; PANDAH: Programme d'Aide Numérique aux Devoirs pour Enfant avec TDA-H; PedsQL: Pediatric Quality of Life Inventory.

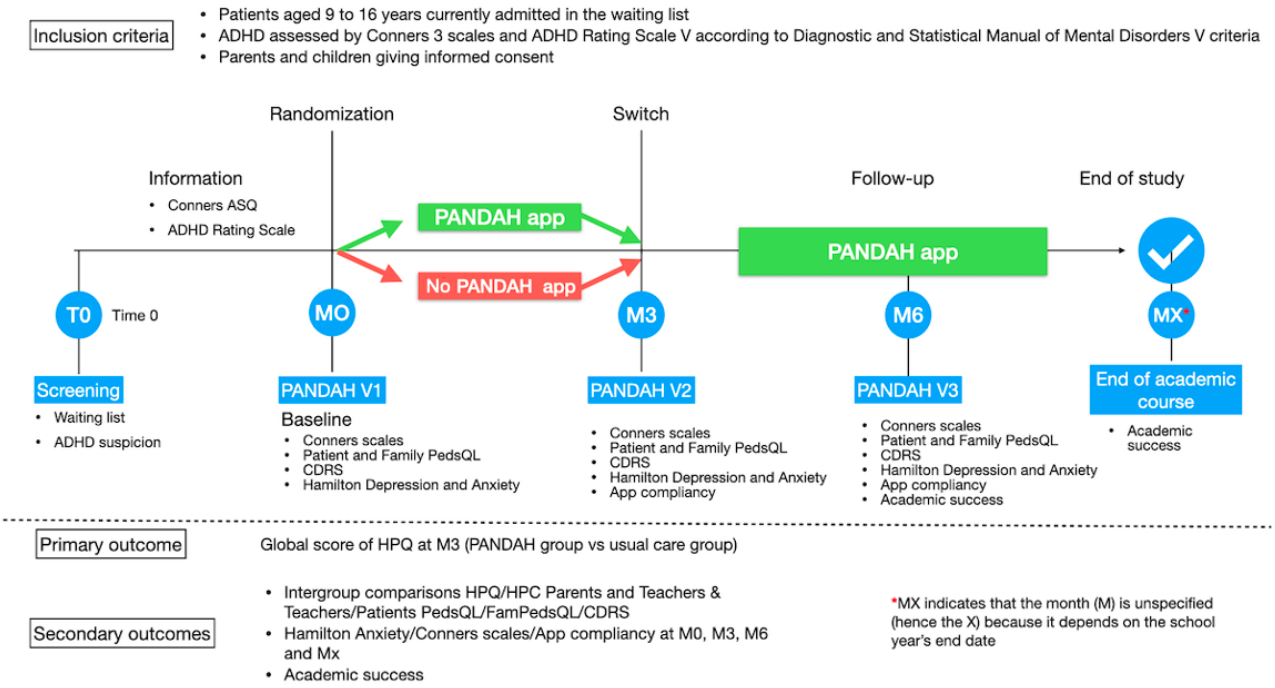

A screening visit will be scheduled for patients provisionally diagnosed with ADHD based on the psychologist's interpretation of *Conners 3rd Edition* parents' and teachers' scales and ADHD Rating Scale V. The screening visit will involve evaluation by

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2 health care professionals who will reach a consensus on the diagnosis. If the ADHD diagnosis is confirmed and the inclusion and exclusion criteria are met, participants will be fully informed about the study, their questions will be addressed, and consent (from both parents and children) will be obtained. For group 2 participants, the investigator will assist with setting up the app (15-20 minutes). Technical support will be provided remotely by each center from 8:00 AM to 6:00 PM via phone or email.

Given the unique attributes of our app, a traditional randomized controlled trial design proved unfeasible. Instead, we adopted a crossover design to facilitate a comparison between our app and a null intervention scenario. While this approach is likely to yield positive results, it may not definitively establish the specific efficacy of our intervention. Subsequent analysis will encompass the entire cohort, allowing for a comparison between those who used the app for 3 months and those who used it for 6 months. Any noticeable disparities may serve as an indicator of our intervention's efficacy.

Intervention

The intervention is based on the PANDAH app, which engages patients in understanding their grades, homework location, surrounding environment, habits, schedules (including sports and therapy), and expectations. PANDAH guides students throughout their homework sessions, from ensuring they have everything they need to create a comfortable workspace to packing for the next day. During sessions, patients receive positive feedback and reinforcement when appropriate. The app also provides personalized artificial intelligence–enhanced advice, such as suggesting students tackle challenging subjects first to reduce anxiety and avoid extended sessions. PANDAH is used independently at home but is complemented by real-life sessions (3 times a year during the school term) to familiarize children and adolescents with the app and address any questions (Figure 2).

Usage during the study will be monitored in terms of time, frequency, and schedule, with in-app data securely transferred to the principal investigator for analysis.

Figure 2. Screenshots and general concept of the PANDAH app. ADHD: attention-deficit/hyperactivity disorder; PANDAH: Programme d'Aide Numérique aux Devoirs pour Enfant avec TDA-H.

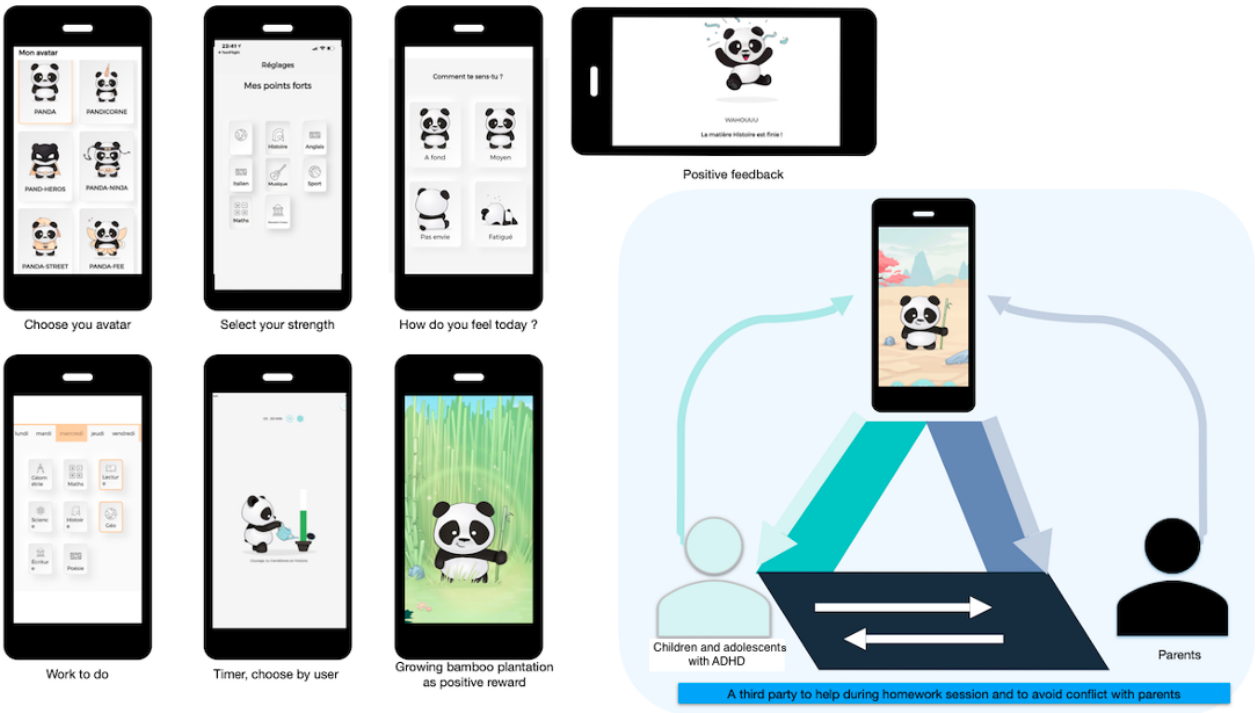

Primary End Point

The primary end point will be the global score on the HPQ, Parent version (HPQ-P) [32]. This 12-item questionnaire, developed in partnership with parents using focus groups and interviews, uses a 4-point scale.

Secondary End Points

The secondary end points include (1) global and domain scores of HPQ-P at M6 [32]; (2) global and domain scores of HPQ, Teacher version at M3 and M6 [32]; (3) Patient Pediatric Quality of Life Inventory and Pediatric Quality of Life Inventory Family Impact Module at M3 and M6 [33,34]; (4) global score of Homework Problem Checklist for Parents at M3 and M6 [35,36]; (5) Inattention and Hyperactivity scores from Conners 3 at M3 and M6 ; (6) in-app scores for fill rate and number of complete app sessions during the M0-M3-M6 period; (7) Children's Depression Rating Scale–Revised in Adolescents and Hamilton Anxiety Scale at M3 and M6; and (8) Likert scale for teachers at M3, M6, and end of the academic year (Mx) regarding changes in students' academic levels: "Degraded/Slightly Degraded/Slightly Improved/Improved" [37].

Secondary criterion 6 will further allow us to assess the actual usage of the app by estimating the time the app is open and the

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time of interaction (using fingers) with the app. This way, we can evaluate whether the child is not solely focused on the app but engaged in other activities as well.

Safety

Data security is a crucial aspect of digital tools. Most data will be stored on the user's smartphone and inaccessible to unauthorized individuals without the user's personal code. Notably, the app does not require an internet connection to function. Patients included in the research will transfer data securely to investigators using a multistep process, ensuring encryption and secure handling. The data will be decrypted and analyzed only by the principal investigator. Data will be securely stored and analyzed in a Microsoft Excel spreadsheet.

Statistical Analysis

The primary analysis will adhere to the "intent to treat principle," analyzing all patient data based on their initial group determined by randomization.

Descriptive statistical analyses will be conducted for categorical data (number and percentage) and continuous data (range, mean, median, and IQR).

Confirmatory factor analysis will be applied preliminarily to the HPQ-P and HPQ, Teacher version questionnaires to assess construct validity. Adequate fit will be considered if the Comparative Fit Index≥0.90 and the root mean square error of approximation≤0.08. Meaningful differences between well-fitting models will be assessed using Δ Comparative Fit Index>+0.01. Reliability will also be assessed using Cronbach α, considered satisfactory if above 0.7.

Cross-sectional comparisons (eg, M3) of continuous and categorical data will use linear or logistic regression, adjusting for M0 if appropriate based on the data collection schedule.

Longitudinal data will be analyzed and compared between the 2 groups using linear mixed models with random effects to account for repeated measurements within patients. Different models, including random intercept or slope models, will be assessed based on the Akaike information criterion, and normality and homoscedasticity of residuals will be examined. A dummy variable reflecting the switch at M3 from the control group to the PANDAH app group will be included in the models (M0 to M6).

Assuming a mean difference of 0.4 on the global score of the HPQ-P at M3 between the 2 groups, with a common SD of 0.9, a total of 264 patients (n=132, 50% in each group) is required to detect this difference with a 5% type I error and 95% power in a 2-tailed *t* test. Assuming 0 attrition (no loss to follow-up) due to proximal assessments at M3, saturation of the child psychiatrist network, and no removal or relocation of families shortly after the school year begins, our aim is to include precisely 264 patients in the PANDAH trial.

Ethical Considerations

Ethical approval was obtained on June 15, 2021, from the Comité de Protection des Personnes—Est V of CHU de Strasbourg, France, with reference: 21/19/SI 21.02.01.49939. Written informed consent was obtained from the patients and their parents. All personal data from the PANDAH app are fully encrypted and anonymous. There was no compensation for participants

Expected Findings

We expect (1) improvements in HPQ score in individuals with ADHD using the app during the first 3-month period compared to individuals not using the app; (2) greater improvements in HPQ score for individuals using the app for 6 months compared to those using the app for 3 months only; and (3) adherence to the PANDAH program, measured with in-app metrics.

Results

Recruitment began in January 2024, and the trial is ongoing.

Discussion

Overview

This study aligns with the digital transformation of health care, leveraging smartphone apps for self-care and self-management, which is particularly relevant for children and adolescents who are digital natives. Collecting data through smartphones, known as ecological momentary assessment, and using this data for ecological momentary intervention with algorithm-driven personalized patient feedback and advice is a burgeoning trend [38-42]. While there are existing apps for ADHD, they tend to lack intuitiveness and interactivity and focus mainly on treatment management, comorbid symptoms, or psychotherapy. Currently, there is only 1 Food and Drug Administration–approved therapeutic app for ADHD, primarily based on cognitive therapy.

The PANDAH app focuses on homework sessions and helps with planning and organization, providing a potentially more engaging and effective approach compared to adult supervision. It addresses the limitations of medication, which may have side effects and limited duration, especially during after-school hours. The most widely used evidence-based treatment for children with ADHD [43], psychostimulants, may not yield long-term academic gains [44,45]. Therefore, there is a need for psychosocial and psychoeducational methods to enhance educational outcomes for these children. Digital tools offer a promising alternative and may reduce the need for medication.

In summary, our aim is to evaluate the efficacy of a digital-only program, which could be a cost-effective complement to traditional ADHD care, especially considering the societal trend toward increasing use of health care apps. However, it is important to address technology access issues for low-income families who may not have smartphones.

Conclusions

This study envisions that smartphone-based digital tools could be highly effective for the youth population due to several synergistic reasons: (1) daily care support that is more engaging than adult supervision; (2) personalized advice with positive reinforcement; (3) addressing organizational and time management skills; and (4) the strong connection between youth and smartphones. If proven effective, this digital-only program

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could enhance the academic achievement of patients with ADHD and pave the way for the digital transformation of ADHD health care protocols. However, it is crucial to address economic challenges related to technology access for low-income families in future health care plans.

Acknowledgments

The authors extend their acknowledgments to Maelle Leray for administrative coordination and Jean Christophe Guilbaud for additional English editing. The study protocol was approved by the Ministry of Health of the French Government and has undergone peer review by the funding body. Proof of approval is included as Multimedia Appendix 1. The study received funding from the French Government Grant (Ministry of Health), Programme Hospitalier de Recherche Clinique, PHRC N 2019-0026. Details of the grant can be found at PHRC-N 2019. This grant funded the development of the digital tool and the study costs.

Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study. All data will be provided as supplementary material at the end of the study.

Authors' Contributions

FGB, LO, and OB drafted the initial article, while SM, PHJ and PL, conducted a complete rewrite and editing. The latter authors were also responsible for the successful grant application, with contributions from FGB, OB, LO, and SM. PHJ and PL developed the smartphone app based on an idea from FGB, LO, SM, and OB. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethics committee approval letter.
[PDF File (Adobe PDF File), 472 KB - resprot_v13i1e44553_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
BPT: behavioral parent training
HPQ: Homework Performance Questionnaire
HPQ-P: Homework Performance Questionnaire, Parent version
M0: baseline
M3: month 3
M6: month 6
Mx: end of the academic year
PANDAH: Programme d'Aide Numérique aux Devoirs pour Enfant avec TDA-H

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Protocol

Improvement of Motor Imagination and Manual Ability Through Virtual Reality and Selective and Nonselective Functional Electrical Stimulation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Motor imagery (MI) is a cognitive process that has been shown to be useful in the rehabilitation process after brain injury. Moreover, functional electrical stimulation (FES) and virtual reality (VR) have also been shown to be effective interventions in many parameters, and there is some evidence of their contribution to the improvement of MI capacity.

Objective: This study aimed to compare the improvements in MI parameters, grip strength, and manual dexterity obtained using VR, FES, and selective FES based on multifield electrodes in healthy people.

Methods: This clinical randomized controlled trial (RCT)with 4 branches will involve 80 healthy university students, with blinded third-party assessment. Participants will be divided into 4 groups: control (no intervention), selective FES (Fesia Grasp), traditional FES (Globus Elite), and Virtual Rehab Hands (Leap Motion sensor). Each group will receive 5 daily sessions, and assessments will be conducted at baseline, postintervention, and follow-up. The Movement Imagery Questionnaire-Revised (MIQ-RS) and chronometry will be used to assess MI, strength will be measured with a digital dynamometer, and manual dexterity will be evaluated with the Nine Hole Peg Test (NHPT) and the Box and Block Test (BBT). Statistical analyses will include 2-way repeated-measures ANOVA with post hoc Bonferroni correction to compare group differences over time, with nonparametric tests (eg, Kruskal-Wallis) being used if normality or variance assumptions are violated. The study will be organized into 3 phases: preparation, data collection, and analysis. The preparation phase will involve finalizing project protocols and obtaining ethical approvals. The data collection phase will consist of recruiting participants, randomizing them into 4 intervention groups, and conducting baseline assessments, followed by intervention sessions. Finally, the analysis phase will focus on evaluating the data collected from all groups and compiling the results for presentation.

Results: The study received approval in July 2023, with recruitment and data collection starting in September 2023. The recruitment phase was expected to conclude by July 2024, and the entire study, including the 2-week follow-up, was set to finish in September 2024. As of July 2024, we had enrolled 100% of the sample (N=80 students). We plan to publish the study findings by the end of 2024.

Conclusions: Improvements in MI and upper limb functionality are expected, particularly in the selective FES group. This RCT will identify which intervention is most effective in enhancing these skills, with potential benefits for patients with neurological motor disorders.

Trial Registration: ClinicalTrials.gov NCT06109025; https://clinicaltrials.gov/study/NCT06109025

International Registered Report Identifier (IRRID): DERR1-10.2196/63329

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KEYWORDS

electric stimulation therapy; motor imagery; virtual reality exposure therapy; hand strength; hand injuries

Introduction

Motor imagery (MI) is defined as the cognitive process of imagining the movement of one's own body part without actually moving it [1]. The procedure of testing MI via electroencephalography mainly consists of 5 phases: signal data acquisition, data preprocessing, feature extraction, feature classification, and device control interface [2]. The data acquisition phase includes MI signal collection, signal digitization, and data storage. The data preprocessing phase involves filtering, cleaning, and transforming the data. The feature extraction phase extracts discriminative features containing useful information from electroencephalogram signal data. The feature classification phase uses the extracted features as input to train machine learning models. Finally, in the device control interface phase, the categorized signals are translated into commands to control devices, such as robots, home appliances, and wheelchairs [3].

MI can help people with disabilities and older adults to perform specific tasks through imagination without physically performing any limb movement [1]. Considering this, different techniques have been proposed in recent years that could improve MI in individuals with neurological pathologies. Among the most used techniques are mirror therapy, virtual reality (VR), and augmented reality [4]. Although studied less, electrical stimulation has also been shown to help improve MI parameters in such type of pathologies [5].

Neuromuscular stimulation is an application of electrical stimulation used in movement rehabilitation [6]. Functional electrical stimulation (FES) is a subtype of neuromuscular stimulation in which the stimulation assists functional and purposeful movements [7]. Electrical currents are applied to motor nerves, producing muscle contractions in a sequence that allows the patient to perform different tasks. Examples might include grasping a key, holding a toothbrush, standing up, cycling, or walking [8].

FES was developed in the 1960s, emphasizing its potential as an assistive technology [9]. Since then, FES has evolved into an important therapeutic intervention that clinicians can use to help people with neurological diseases to regain motor abilities [10].

FES device technology has traditionally relied on conventional electrodes. However, multifield surface electrodes have emerged, consisting of groups of several small conducting fields, which can be activated/deactivated and configured independently [11].

The Fesia Grasp (Fesia Technology) [12] is the only commercial FES hand rehabilitation device based on multifield electrodes (32 cathodes and 8 anodes). It delivers trains of biphasic pulses to different electrode fields in an asynchronous manner to generate contractions of the forearm muscles (it can trigger at least 8 different flexion and extension movements of the wrist and fingers) in order to restore motor function in persons with neurological injuries [11].

Hand rehabilitation is sometimes a lengthy process, and motivation is crucial to the patient's outcome. Moreover, the outcome of the treatment depends not only on the rehabilitation process of the practitioner but also on the patient's motivation to engage in the training [13]. One of the ways to make rehabilitation more attractive is to incorporate game-based protocols, such as 2D games, 3D games, VR games [14], and augmented reality games [15].

Notably, the use of VR in game-based training protocols meets both the physiological and the psychological needs of patients [13]. VR creates a dynamic and motivating environment by merging touch, hearing, and vision, which makes patients more engaged in clinical or home training [14]. This technology could also be useful when improving MI.

The objective of this study was to compare the improvements in MI parameters, strength, and manual dexterity obtained using VR, traditional FES, and selective FES based on multifield electrodes in people without neurological pathologies.

Methods

Study Design

This will be a parallel-group, clinical randomized controlled trial (RCT). It will be a single-center study, with blinded third-party assessment (the researchers conducting the evaluations will not be involved in the recruitment or randomization of the sample or in the implementation of the interventions). As the study sample, 4 parallel groups, each comprising 20 university students, are planned (N=80). The Spanish version of OxMaR software (Oxford Medical Simulation) will be used to randomize the study sample. The study design followed SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 recommendations (Multimedia Appendix 1) and CONSORT (Consolidated Standards of Reporting Trails) 2010 guidelines (Multimedia Appendix 2) for clinical trial protocols.

The first group will receive an intervention based on multifield FES with the Fesia Grasp device (selective FES multifield), the second group will receive traditional FES using the Globus Elite electrostimulation device (based on conventional electrodes), the third group will receive an intervention based on VR, and, finally, the control group will not receive any treatment.

Study Population

As this will be a feasibility study, with a short intervention (5 sessions in the same week), the selected study population is healthy students. Paravlic et al [16] analyzed numerous studies measuring the strength and MI in healthy populations, both

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variables in this work, and we have chosen to replicate the same population of previous works.

Student recruitment will be conducted in 2 ways: First, the study will be presented to all students of the Faculty of Health Sciences via email, outlining the objectives and the most relevant information. In the second stage, the snowball method will be used, allowing recruited students to invite other peers or students from other faculties. Sample size calculation was performed using power analysis with SPSS version 28 software. With a significance level of α=.05, a statistical power of 0.80, and an expected effect size of P<.05 based on previous studies, it was determined that at least 18 participants per group would be necessary to detect statistically significant differences. This calculation ensures that the study will have sufficient power to avoid type II errors.

Participants will be included according to these inclusion criteria: (1) be of legal age and provide signed informed consent; (2) not have any pathology in the upper limb, such as tendinitis, edema, or fracture; and (3) have intact skin (without breaks, scratches, cuts, and other types of superficial or deep lesions) on the nondominant arm, where the devices will be placed, if applicable. Exclusion criteria include (1) severe medical problems, (2) use of a pacemaker, (3) pregnancy, (4) peripheral neuropathies, or (5) the presence of other neuromuscular pathologies.

Participants may leave the study in the following cases: at their own request, without providing reasons; if any adverse events occur that prevent them from continuing the study; failure to complete the treatment; or failure to complete the sessions within the schedule established for each one. The reason for withdrawal will be recorded in the database.

Procedure

There will be 3 phases of the project: preparation, data collection, and a final phase of analysis and reporting (Figure 1). The preparation phase will include drafting the project, obtaining ethics committee approval, and starting sample collection. This phase will last for 2 months. During sample collection, participants will be randomized and assigned to different groups.

The data collection phase will be the longest phase of all and will be spread over 13 weeks. During this period, preintervention assessments, interventions, and postintervention and follow-up assessments 2 weeks after the intervention will be conducted by blind evaluators who will neither know the assigned groups nor participate in the intervention sessions. Each participant will receive the intervention in the nondominant arm.

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Figure 1. Phases of the project.

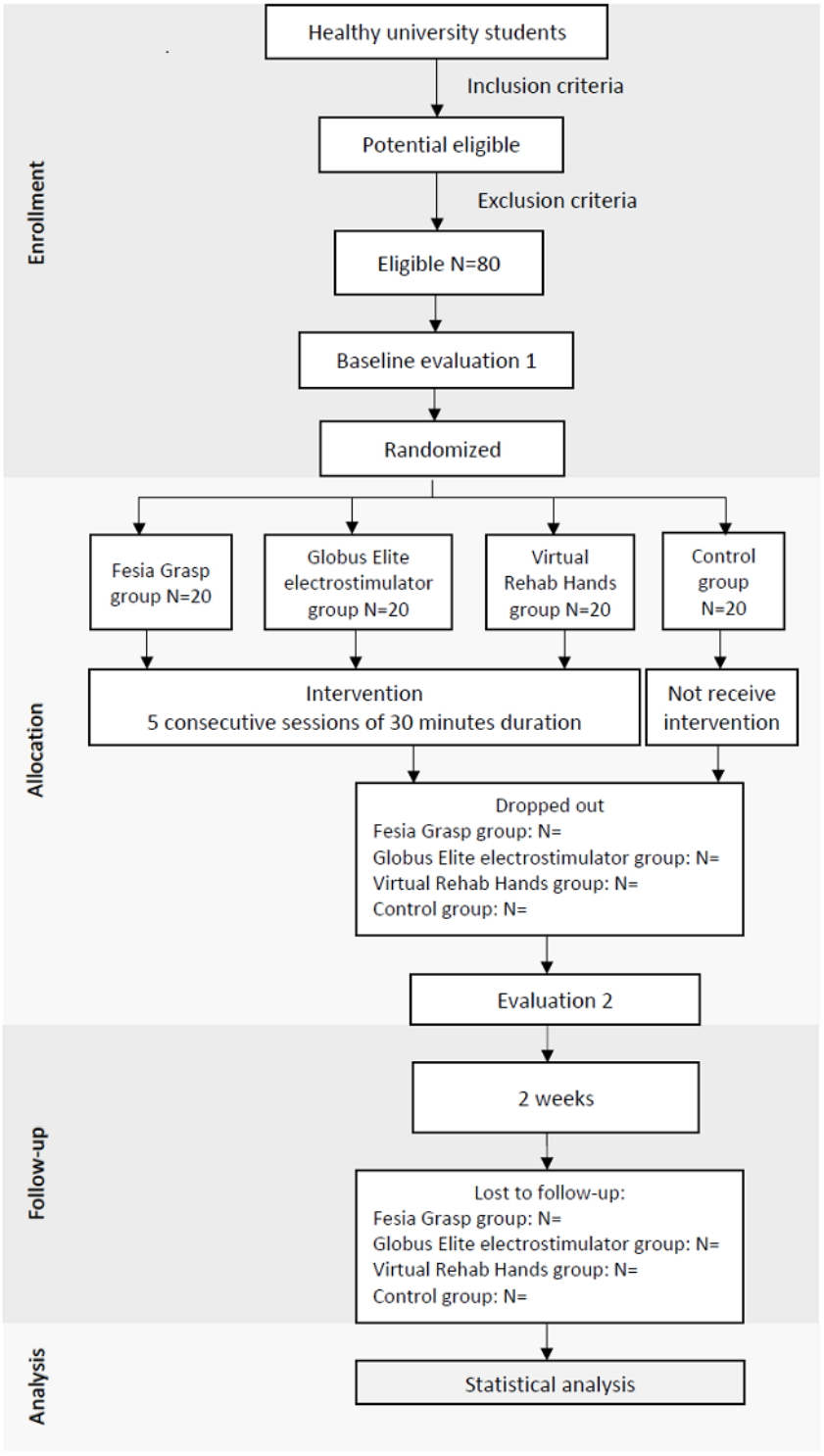

Control Group

This group will not receive any type of intervention, and participants will continue with their usual routine. They will be asked to commit to not start any physical activity other than their usual routine during the study period.

Selective FES (Fesia Grasp) Group

For this group, 5 sessions of 30 minutes each will be carried out on consecutive days, and 2 available protocols will be used: habituation and repetitive task training. The habituation protocol will be used during the first half of the first session to allow the participants to adapt to the sensation of electrical stimulation by means of an automatic sweep of electrical stimulation. The repetitive task training will be used in sessions 1-5. First, the device will be configured, selecting cathode combinations that generate the clearest flexion and extension movements of the wrist, thumb, index, and fingers 3-5. If the motor threshold for any of the movements is not found in any of the users, or stimulating any of these movements may be considered harmful or not beneficial, it will not be selected. It will be important to

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carry out this configuration thoroughly in the first session, and small variations will be made in subsequent sessions. The therapy will then be initiated (to be adjusted according to the progress of the patients).

Sessions 1-3

Selective contractions of the forearm muscle groups will be performed. The proposed progression for the sessions is as follows: beginning (5 minutes), which will involve placing the device and checking that the previous configuration is correct. In the first part (5 minutes), selective contractions of the different muscle groups will be performed using FES. In the second part (10-15 minutes), voluntary selective contractions will be performed by the patient, guided by the therapist.

Sessions 4-5

These sessions will include training in activities of daily living with the help of FES. The general development proposed is as follows: beginning (5 minutes), which will involve setting up the device and checking that the previous configuration is correct. In the first part (5 minutes), selective contractions of the different muscle groups will be performed using FES. In the second part (10-15 minutes), the previously activated functional movements will be included in functional actions using FES to grasp objects of different sizes.

Traditional FES (Globus Elite Electrostimulator) Group

For this group, 5 sessions of 30 minutes each will be carried out on consecutive days. The device will be applied, adjusted according to the progress of the patients.

Sessions 1-3

These sessions will consist of general repetitive contractions of the muscle groups of the forearm. The general sequence is, again, as follows: beginning (5 minutes), which will involve setting up the device and checking that the configuration is correct. In the first part (5 minutes), general contractions of the different muscle groups will be performed using FES, while in the second part (10-15 minutes), the patient will perform general voluntary contractions, guided by the therapist.

Sessions 4-5

These sessions will also include training in activities of daily living using FES. The general development proposed for the sessions is as follows: beginning (5 minutes), which will involve setting up the device and checking that the configuration is correct. In the first part (5 minutes), general contractions of the different muscle groups will be performed using FES, while in the second part (10-15 minutes), the previously activated functional movements will be included in functional actions using FES to grasp objects of different sizes.

The electroparameters selected will be the same in both FES groups (frequency: 25 Hz; pulse width: 250 µs). Therapy times will vary according to the patient's fatigue, as measured by the Borg scale. The Borg scale score should not exceed 3 points out of 10 one minute after the end of the exercise. If the perception of fatigue is higher, first the intensity (eg, frequency of movements) and then the duration of therapy will be adjusted.

Virtual Rehab Hands Group

The group will play for 5 sessions of 30 minutes each on consecutive days. The Virtual Rehab Hands device includes fine motor games. There is an ergonomic support to rest the arm, and the user is able to perform the exercises more comfortably with the Leap Motion sensor, which accurately detects movements of the hands, fingers, and wrists. Each session will be divided into 3 phases: warm-up, effort, and cooldown. In the warm-up phase, we will play "wrist flexion and extension bird," "flexion and extension candy," "ulnar-radial deviation frog," and "ulnar-radial deviation frog." In the effort phase, we will play "digital piano," "balloon tongs," and "finger abduction." Finally, in the cooldown (return-to-bed) phase, we will play "frog flexion-extension" and "wrist flexion and extension bird."

Measurement Tools

Different assessment tools have been developed that assess hand dexterity, strength, and MI. The Nine Hole Peg Test (NHPT) will be included for the assessment of manual dexterity. The NHPT [17] is a manual test, in which the subject must place 9 pegs into corresponding holes and then remove them, the variable measured being the total time taken to complete the process. Less time implies better manual dexterity.

The Box and Block Test (BBT) consists of a rectangular wooden box with a base 53.7 cm wide and 25.4 cm long, which is divided into 2 square compartments of 25.4 cm on each side, separated by a 15.2-cm-high separator. The test contains 150 cube-shaped wooden blocks of 2.5 cm on each side. The number of blocks the subject has carried from one compartment to another with each hand in 1 minute is recorded. Higher scores indicate better manipulative skills. The hand grip strength (Jamar hand dynamometer) is used to measure grip strength in the hand, allowing the force exerted by the subject to be converted into a numerical reading. The subject is asked to grip the device and perform the maximum sustained contraction. The force is recorded in kilograms. The timing assessment of MI ability requires at least 2 tests. Chronometry measures the temporal congruence between an executed motor act and the same imagined act. In this case, the NHPT itself is proposed as the executed motor act. So, once administered to obtain the test variable (time taken to perform), each participant is asked to imagine the performance of the test, which is timed. Both measurements are taken in seconds to calculate the chronometric ratio (CR) according to the following formula [18]: CR = (time motor act executed – time motor act imagined)/time motor act executed.

Finally, the revised Movement Imagery Questionnaire-Revised (MIQ-RS) [19] consists of 2 subscales, one visual and the other kinesthetic. Each subscale has 7 items, and each item is scored on a 7-point Likert scale (the higher the score, the greater the ease of imagining). For all items, the user is asked to perform a certain motor act (only once), to return to the starting position, and then to imagine it. When scoring the visual scale, the participant is asked to generate an image "as if they could see themselves" doing the gesture, while the kinesthetic scale asks them to "recall the sensation of the movement." The minimum value is 14, and the maximum value is 98 (minimum 7 and

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maximum 49 for the subscales). The Spanish version of the MIQ-RS was validated by Cantalejo - Fernández et al [20] in a sample of university students, achieving Cronbach α values of .90 and a 2-factor structure.

In this study, several devices will be used to carry out the intervention. The Fesia Grasp device bases its operation on superficial electrical stimulation of the antebrachial musculature to generate flexion and extension movements of the wrist, thumb, index finger, and fingers 3-5. The device is Conformité Européenne (CE) marked. The main feature of this device is its multifield electrode, which allows a greater number of movements to be selected, to do so quickly and selectively, and to combine the movements with one another. This is a matrix electrode designed to cover a large portion of the forearm surface in order to stimulate the muscles of the neuromuscular groups of the radial, ulnar, and median nerves. The electrode comprises 32 cathodes (output fields) and 8 anodes (return fields), which can be activated independently or in combination, allowing the electrode to be adapted to the anthropometry of different patients.

Globus Elite 4-channel electrostimulation is a traditional electrical stimulation, which allows up to 8 electrodes to be activated at the same time (4 channels). The device, which is CE marked, allows the use of different types of electrical currents, which are selected according to the desired therapeutic objectives and the evolutionary phase of the patient. Among the currents that can be applied are those also emitted by the Fesia Grasp device. These currents are biphasic and symmetrical rectangular.

Lastly, Virtual Rehab Hands is a therapeutic tool that uses VR for the rehabilitation of a patient with neurological or musculoskeletal disorders. The device provides a wide range of activities designed to improve mobility, coordination, and strength. This tool is based on the idea of gamification in rehabilitation, where patients participate in virtual games that require physical movements to complete challenges. These games are tailored to the individual needs and abilities of each patient, allowing for personalized rehabilitation. Virtual Rehab Hands allows for (1) a comprehensive assessment, (2) personalized treatment planning, and (3) monitoring and tracking of the patient's progress. This tool has different fine motor games, including 8 video games for fine motor training that can be customized to the needs of each patient.

Ethical Considerations

This study was approved by the Ethic Committee of Burgos University (IO 2/2023). It will adhere to the Declaration of Helsinki and the requirements established in Spanish legislation. All participants will be provided all relevant information about the study prior to their participation, and signed informed consent will be obtained from them before the evaluation. Data will be anonymized. Once the participants have signed the informed consent form, they will be assigned an alphanumeric code, which only the researcher in charge of anonymizing the data will be able to link. In the database, the alphanumeric code will appear with the rest of the data collected. The linking document between personal data and the assigned code will be stored with a password to limit access. Participants will not receive any compensation for their participation in the study.

This study has been registered with ClinicalTrials (NCT06109025).

Dissemination Plan

Once the study is completed, we plan to publish the results in high-impact journals, preferably in open access. In addition, we will participate in at least 2 specialized congresses through oral communications or posters.

Statistical Analysis

IBM SPSS version 28 software will be used for all analyses.

General Analysis

Comparative analyses between the 4 groups will be carried out to verify that there are no differences between groups at the beginning of the different interventions (ANOVA for baseline). In addition, descriptive analysis of the sample will be carried out.

Inferential Analysis

Two-way repeated-measures ANOVA (group×time) will be used with post hoc Bonferroni correction to test the hypotheses, although the sample does not meet the normality criteria [21]. If the data do not meet the assumptions of homogeneity of variances, the Levene test can also be used to validate this assumption. The use of parametric tests in a nonnormal distribution can be justified in certain cases. In this study, the use of parametric tests has been considered for different reasons, such as their robustness, their greater statistical power, and the homogeneity of variances that exists in the dependent variables of the study. In case the assumptions of normality or equality of variances are not met, nonparametric tests can be used. In this case, the nonparametric equivalent to ANOVA would be the Kruskal-Wallis test, which does not assume normality of data and is appropriate when there are independent groups.

Repeated-measures ANOVA will also be performed, as the use of repeated measures provides a more effective control of extraneous sources of variation associated with individual characteristics (ie, a reduction in error variance is achieved) [22].

Results

The study received approval in July 2023, with recruitment and data collection starting in September 2023. The recruitment phase was expected to conclude by July 2024, and the entire study, including the 2-week follow-up, was set to finish in September 2024. As of July 2024, we had enrolled 100% of the sample (N=80 students). We plan to publish the study findings by the end of 2024.

As a result of the proposed interventions, an improvement in visual and kinesthetic MI capacity is expected in the groups receiving FES treatment, with a more significant improvement anticipated in the selective FES group. We also expect improvements in the rest of the variables studied: improvement in manual dexterity and manipulative skills and improvement

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in grip strength. The improvement related to MI is expected to be maintained in the follow-up evaluation. However, regarding the other variables (manual dexterity, manipulative skills, and grip strength), differences are expected between time 1 and time 2 in all of them compared to the control group, with the possibility that these changes may not be maintained over time due to, among other factors, the short intervention period.

Discussion

Summary

This study aims to compare the effectiveness of selective FES training, traditional FES training, and VR in improving MI parameters, strength, and manual dexterity in the upper extremities of healthy subjects. For this, 4 groups will be created (selective FES, traditional FES, VR, and control), and the following pre- and posttreatment measurements will be carried out: the NHPT, the BBT, hand grip strength, and the MIQ-RS.

One of the most common sequelae after stroke or other neurological diseases is the limitation or loss of functional capacity of the upper extremities [23]. Around 65% of affected individuals are unable to use their impaired limb in activities of daily living 6 months following the impairment [24], and this loss of functionality directly affects their quality of life, often leading to dependency [25].

MI is a crucial factor in rehabilitating the affected limb, enabling training even when the limb's motor skills are nearly nonexistent [16]. To carry out interventions based on MI, it is necessary that the person who is going to receive the treatment has a certain facility to imagine these motor acts. This is not always the case, and it is necessary to improve their MI skills so that they can benefit as much as possible from MI-based treatment. Although there are various techniques that have demonstrated good results with regard to improving MI (mirror therapy, for example) [26], more effective and easy-to-use techniques are necessary.

On the one hand, VR has been shown to effectively increase patient motivation and enhance adherence to treatment [27]. If the results in terms of MI improvement are also positive, it could become a technique of choice in people with severely affected limbs in whom following traditional MI treatment is complicated because of a lack of usability.

On the other hand, electrical stimulation is among the therapies with the highest level of evidence for motor rehabilitation of the upper extremities in individuals with neurological conditions [28]. However, its effect on MI parameters is still unknown, as there are few studies in this regard. However, the findings in neuroplasticity parameters suggest that it could be an interesting technique for this [27].

Furthermore, if this FES is applied selectively using multifield electrodes, the effects may be enhanced by concentrating sensory input (both central and peripheral) on the affected muscles and brain or spinal areas, providing the minimal stimulus needed for executing certain motor tasks [29]. In addition to increasing clinical effectiveness, the use of multifield electrodes has been shown to increase the usability of FES systems [30], which could also have an effect on patient motivation and treatment adherence. Should the study demonstrate that FES interventions improve MI, it could present a valuable alternative for enhancing this skill prior to initiating imagination-based treatments, while also improving related skills, such as strength and manual dexterity.

Limitations

The study has several limitations. First, the subjects may change their physical activity during the week of their participation, and this change may contaminate the data; to avoid this, the contract method has been proposed, so in the informed consent form the participants sign, in addition to their agreement to participate in the study, a commitment not to vary their physical activity is included. However, since the sample comprises healthy subjects, specifically university students, in the event that the results are positive, it is not clear whether they can be extrapolated to healthy older subjects or to persons with neurological pathologies, such as stroke. In both cases, it is more than likely that the number of intervention sessions would have to be increased to find any positive results in the variables studied.

Conclusion

If the study yields positive results, it would be valuable to test these techniques in individuals with neurological impairments, such as stroke or spinal cord injury, to assess their effectiveness for inclusion in treatment protocols for patients with motor disorders caused by neurological diseases and to support further cost-effectiveness studies.

Acknowledgments

The authors would like to thank Fesia Technology for temporarily lending the device to carry out the interventions.

Conflicts of Interest

AM-O works for Fesia Technology, from which they receive financial compensation. Fesia Technology has participated in the development of the device used in the study. The rest of the authors declare that they have no conflicts of interest.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.
[PDF File (Adobe PDF File), 124 KB - resprot_v13i1e63329_app1.pdf]

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Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trails) 2010 checklist.
[PDF File (Adobe PDF File), 160 KB - resprot_v13i1e63329_app2.pdf]

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Abbreviations

CR: chronometric ratio
BBT: Box and Block Test
FES: functional electrical stimulation
MI: motor imagery
MIQ-RS: Movement Imagery Questionnaire-Revised
NHPT: Nine Hole Peg Test
RCT: randomized controlled trial
VR: virtual reality

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Protocol

Essential Coaching for Every Mother Tanzania (ECEM-TZ): Protocol for a Type 1 Hybrid Effectiveness-Implementation Randomized Controlled Trial

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Abstract

Background: Despite global goals to improve maternal, newborn, and child health outcomes, mortality and morbidity continue to be a concern, particularly during the postnatal period in low- and middle-income countries. While mothers have the responsibility of providing ongoing care for newborns at home, they often receive insufficient newborn care education in Tanzania. Mobile health via text messaging is an ever-growing approach that may address this gap and provide timely education.

Objective: We aim to evaluate a text message intervention called Essential Coaching for Every Mother Tanzania (ECEM-TZ) to improve maternal access to essential newborn care education during the immediate 6-week postnatal period.

Methods: ECEM-TZ consists of standardized text messages from birth to 6 weeks post partum that provide evidence-based information on caring for their newborn and recognizing danger signs. Messages were developed and then reviewed by Tanzanian mothers and nurse midwives before implementation. A hybrid type 1 randomized controlled trial will compare ECEM-TZ to standard care among mothers (n=124) recruited from 2 hospitals in Dar es Salaam. The effectiveness outcomes include newborn care knowledge, maternal self-efficacy, breastfeeding self-efficacy, maternal mental health, attendance at the 6-week postnatal checkup, and newborn morbidity and mortality. The implementation outcomes include the reach and quality of implementation of the ECEM-TZ intervention.

Results: Recruitment for this study occurred between June 13, 2024, and July 22, 2024. A total of 143 participants were recruited, 71 in the control and 72 in the intervention. The 6-week follow-up data collection began on July 30, 2024, and was completed on September 21, 2024.

Conclusions: This study will generate evidence about the effectiveness of implementing text messaging during the early postnatal period and the feasibility of doing so in 2 hospitals in Dar es Salaam. The intervention has been designed in collaboration with mothers and nurse midwives in Tanzania.

Trial Registration: ClinicalTrials.gov NCT05362305; https://clinicaltrials.gov/study/NCT05362305

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International Registered Report Identifier (IRRID): DERR1-10.2196/63454

(JMIR Res Protoc 2024;13:e63454) doi:10.2196/63454

KEYWORDS

mobile health; maternal health; randomized controlled trial; parenting self-efficacy; self-efficacy; maternal; RCT; mother; text message; coaching; postnatal; newborn; child; low-income country; middle-income country; Africa; newborn care education; nurse midwife; Tanzania

Introduction

Background

The postnatal period during the first 6 weeks of life is a critical time point for newborns and mothers in Tanzania, which has a neonatal mortality ratio of 20 per 1000 live births [1] and a maternal mortality ratio of 104 per 100,000 live births [2]. Neonatal and maternal mortality is highest in the first week post partum [3,4]. Despite the high number of deaths that occur postnatally, most mothers and their newborns receive insufficient care during this period, especially in low- and middle-income countries (LMICs) [5]. There is a significant need to develop and evaluate innovative approaches to reach mothers during this period to ensure they are knowledgeable and confident in caring for their newborns at home.

While most Tanzanian women (90%) have at least 1 antenatal care contact, only half (51%) of the women and 54% of the infants receive postnatal care within 2 days after giving birth [2]. Further, health facilities are often unable to provide individualized education based on maternal needs due to staff shortages and resource constraints [6-8]. Across Tanzania, mothers receive little education about how to care for their newborns before hospital discharge due to significant health system challenges [6,8,9].

One innovative strategy that can be used to provide postnatal education directly to parents is mobile health (mHealth) [10]. The goal of mHealth interventions delivered postnatally is not to replace the need for in-person follow-up but to complement existing care and fill knowledge gaps by providing timely, standardized, relevant, and evidence-based information on newborns' care at home. The use of mobile phones to reach mothers is supported by the World Health Organization recommendations, which state that traditional postnatal contact can be enhanced through mobile phone–based contact between mothers and the health system [11].

Due to the severe shortage of health care providers and the low rate of in-person postnatal contacts in Tanzania [12], Essential Coaching for Every Mother Tanzania (ECEM-TZ) is poised to bridge this gap without adding a significant burden to the health system. The goal of the ECEM-TZ intervention is to improve maternal access to knowledge during the immediate 6-week postnatal period, and to increase maternal self-efficacy and improve mental health outcomes.

Effectiveness Objectives

The objective is to compare mothers who receive ECEM-TZ to mothers who receive standard care on newborn care knowledge, maternal parenting self-efficacy, breastfeeding self-efficacy, postpartum depression symptoms, anxiety symptoms, postnatal care attendance, newborn morbidity, and newborn mortality at 6 weeks post partum.

Effectiveness Hypotheses

Mothers who receive ECEM-TZ will have higher levels of newborn care knowledge, maternal parenting self-efficacy, breastfeeding self-efficacy, and postnatal care attendance and lower rates of postpartum depression symptoms, anxiety symptoms, and newborn morbidity and mortality at 6 weeks post partum in comparison to those who received standard postpartum care.

Implementation Objectives

The objective is to explore the implementation extent and quality of ECEM-TZ. Using process evaluation guidelines [13,14], the specific questions for ECEM-TZ are as follows:

1. *Recruitment effectiveness*: was this study able to recruit the desired number of participants in the time frame? Is there a difference in recruitment based on hospital level? What is the recruitment rate (ie, approached vs randomized)?
2. *Implementation extent*: what was delivered, including the quality (fidelity), dose delivered (completeness), dose received (exposure), satisfaction, reach (participation rate), and recruitment?
3. *Implementation quality*: what were the barriers and facilitators in implementing behavior change based on ECEM-TZ content? What is the level of satisfaction of ECEM-TZ?

Methods

Study Design

This is a 2-arm, parallel-group, hybrid type 1 randomized controlled trial (RCT). Participants will be randomized to receive a 6-week postpartum text message program called ECEM-TZ or standard care (no messages) with a 1:1 allocation.

A hybrid type 1 RCT study focuses on evaluating clinical outcomes while also seeking to understand the context for future implementation through a process evaluation [15,16]. For this protocol, a hybrid type 1 RCT study was selected as ECEM-TZ is a new digital health solution and thus, exploring whether the intervention improves clinical outcomes is the key focus. However, it is also important to explore the implementation factors related to extent and quality as well as recruitment effectiveness to ensure that the intervention effectiveness outcomes are not put at risk or misinterpreted if the digital health solution is not able to be implemented as intended.

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Intervention

ECEM-TZ Development (Pre-RCT Phase)

To create a standardized, evidence-based approach to the content, the initial messages were developed using the World Health Organization guidelines for postnatal care [11]. There were 54 unique messages initially developed: 6 related to the research study, 6 on postnatal care, 7 on feeding, 3 on handwashing, 3 on cord care, and 4 on thermal care. For messages related to danger signs, 5 each were on fever and breathing with 3 each on feeding, no movement, jaundice, cord infection, and convulsions. ECEM-TZ messages were designed to be tailored to each participant in that all mothers will receive the same content but may include the name of the mother or child. All text messages were developed in English and then translated into Kiswahili using standardized forward-backward translation processes [17] before testing.

All messages mapped onto the social cognitive theory of behavior change [18,19] and included four types: (1) educational, (2) reminders, (3) social support, and (4) interactivity (two-way), all to reinforce positive behaviors associated with newborn care. Educational messages provided one-way information about essential newborn care to encourage action, such as exclusive breastfeeding and hygiene cord care. Reminder messages consisted of one-way messages about upcoming postnatal contacts and returning to a clinic if they recognize a danger sign. Social support messages included messages from other fictional mothers encouraging them to provide evidence-based care. Finally, interactivity (two-way) messages included options for mothers to respond to inquiries, such as checking into whether they visited a postnatal clinic within the past seven days.

To ensure that the content of ECEM-TZ was appropriate and acceptable, the messages underwent two rounds of iterative testing with Tanzanian mothers and nurse midwives. Mothers were eligible for inclusion if they met the following criteria: (1) had recently given birth within the hospital; (2) were aged older than 18 years; and (3) spoke and read English or Kiswahili. Mothers were excluded if (1) their newborn died or was expected to die before leaving the hospital or (2) they were experiencing major postnatal complications expected to impact their ability to provide informed consent (eg, major postpartum hemorrhage or seizures). Nurse midwives were eligible to participate in this study if they (1) worked in a hospital on a labor or postnatal ward for at least three months to ensure that they had experience providing care to this population, (2) were currently involved in providing maternal and newborn care either on the labor ward or postnatal unit, and (3) could speak and read English or Kiswahili. Nurse midwives were excluded if they were not on duty during the data collection period.

On recruitment and before starting the interview, oral and written consent was obtained for this study's purpose, as well as consent for the use of a voice recorder by all participants. Interviews were conducted by a research assistant at the hospital in a comfortable location as suggested by the participant. Participants were shown messages based on the topic area and asked: "What do you think this phrase is saying? Does anything come to mind when you read this? Are there any words that you did not understand? Was anything in this unacceptable or offensive? Are there any words you would suggest that could be used instead? If so, which one conforms best to your usual language?" Mothers were also asked to review and complete the Karitane Parent Confidence Scale [20], which was translated into Kiswahili. Interviews were transcribed verbatim and translated into English by a Tanzanian research assistant to facilitate analysis. A summary of concerns for both the Karitane Parent Confidence Scale and ECEM-TZ was created during each round of testing. Changes were made to the text messages based on participant feedback and any revisions were retranslated in Kiswahili. Final messages were translated back into English for backward translation to ensure the message remained intact and evidence-based [17].

In total, 10 mothers and 7 nurse midwives participated in the validation. In round 1, three mothers and 3 nurse midwives provided feedback, and in round 2, seven mothers and 4 nurse midwives provided feedback. Mothers were on average aged 27.4 (SD 5.1) years and had 1 (SD 1.4, range 0-4) other child. Nurse midwives were on average aged 37.4 (SD 8.9) years and had 10.8 (SD 6.9, range 1-19) years of clinical experience.

Final Intervention

ECEM-TZ is a one-way text message program sent from the third day after birth until 6 weeks postnatally. Messages are sent once per day in the morning. After 2 rounds of testing, the ECEM-TZ was finalized with a total of 44 messages that covered the following topics: 4 related to the research study, 7 on feeding, 6 on postnatal care follow-up, 4 on normal development, 3 each on thermal care and maternal care, and 2 each on cord care and handwashing. For messages related to danger signs, 3 each were on fever, no movement, or convulsions; 2 each were on poor feeding, jaundice, and breathing; and 1 was on cord infection. Given participant feedback during the pretesting, social support and two-way messages were removed due to reported poor participant acceptance and perceived clarity. Thus, only educational and reminder messages were included. No changes in care or education will be implemented, with mothers in the intervention group receiving standard in-hospital education as provided to all women delivering at that hospital before discharge from the postpartum unit. Mothers will be able to message "acha" (stop in Kiswahili) to withdraw from this study at any time and will stop receiving messages.

Control Group

No changes in care or education will be implemented, with mothers in the control group receiving standard in-person education as provided to all women delivering at that hospital before discharge from the postpartum unit. Mothers will not receive any text messages from the program.

Procedure (RCT)

Mothers will be recruited by a research assistant after giving birth at a health care facility and before discharge. Mothers will be approached and informed about this study. If interested, mothers will be screened against eligibility criteria. Eligible and consenting mothers will complete a baseline questionnaire

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(T1) and are then randomized into a study group. All participants will be followed up at six weeks postnatally (T2) via telephone.

Randomization, Allocation, and Blinding

Using a 1:1 allocation, participants will be randomized into either the intervention or control group using a computer-generated stratified block randomization with blocks varying between 4 to 8 via REDCap (Research Electronic Data Capture; Vanderbilt University). Stratification based on the site of recruitment will be implemented. Due to the nature of ECEM-TZ, blinding will not be possible for mothers (ie, mothers will know if they receive text messages or not). To minimize bias at the participant level, all mothers will receive the same in-hospital care. Due to the nature of the intervention, mothers in the control group will not be exposed to the intervention text messages. Hospital staff (nurse midwives, physicians, and other health care providers) will be blind to participant group allocation to ensure both groups receive the standard discharge education. The researchers will be aware of participant allocation but will not be involved in data collection from participants or the randomization process. The research assistants will be blinded to allocation at baseline (T1) but not at T2.

Setting

This study is being conducted in Dar es Salaam, Tanzania, which is in East Africa. Participants will be recruited from the Mwananyamala Regional Hospital and Sinza Palestina Hospital. The Mwananyamala Regional Hospital is a large government-run hospital that has 70 to 90 deliveries per day. The Sinza Palestina Hospital is a governmental, public hospital that has up to 50 deliveries per day.

Inclusion Criteria

Mothers are eligible if they meet the following criteria: (1) have given birth within the past 48 hours, (2) have daily access to a mobile phone with text messaging capabilities, (3) are aged older than 18 years, and (4) speak and read English or Swahili. Participants will be excluded if (1) newborns die or are expected to die before leaving the hospital; (2) they have no access to a mobile phone, either personal or shared; (3) they are unwilling to receive SMS messages; (4) decline to participate; (5) are experiencing major postnatal complications expected to impact learning or ability to consent while in the hospital (eg, postpartum hemorrhage or seizures); or (6) participated in ECEM-TZ development phase.

Ethical Considerations

Ethics approval has been received from Dalhousie University (REB#2018-4538), Muhimbili University of Health and Allied Science (REB#MUHAS-REC-7-2019-010), and National Medical Institute of Research (REB#NIMR/HQ/R.8c/Vol.I/2457). All participants will be provided with written and verbal information and will complete a written consent form before enrollment in the study. To maintain confidentiality, all study data will be identified using a study number unique to each participant on all questionnaires and surveys. All data will be entered into REDCap by a research assistant in Tanzania with the first author having access to the data. REDCap is a secure web application for building and managing online surveys and databases [21]. All participants will receive the equivalent of honorarium (TZS 10,000; approximately US $4) in phone vouchers to their airtime provider of choice.

Outcome Measures

Baseline data will be collected in person in the hospital while follow-up data at 6 weeks post partum will be collected by telephone. Research assistants will attempt to contact participants until 10 weeks post partum to obtain complete follow-up data. Table 1 shows the outcome assessment time points.

Table 1. Outcome assessment time points.

Outcome	Baseline (T1[a])	6-Week follow-up (T2)
Eligibility screen	✓	
Informed consent	✓	
Randomization	✓	
Demographics	✓	
Newborn care knowledge	✓	✓
Parenting self-efficacy	✓	✓
Breastfeeding self-efficacy	✓	✓
Postpartum anxiety	✓	✓
Postpartum depression	✓	✓
Neonatal morbidity and mortality		✓
Postnatal clinic attendance		✓
Implementation quality—evaluation survey		✓
Implementation extent	✓	✓

[a]T: time point.

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Effectiveness Outcomes

To measure the effectiveness of ECEM-TZ, the following will be assessed:

1. Newborn care knowledge: Knowledge will be assessed using a modified questionnaire developed by McConnell and colleagues [22] assessing newborn care knowledge. The questions determine whether mothers can identify danger signs, handwashing practices, cord care, newborn thermal care, and breastfeeding. A total sum of the number of items mothers can identify will be created. Additionally, binary variables will be created to determine whether mothers can identify three or more newborn danger signs, two or more best practice hand washing, two or more cord care practices, three or more thermal care practices, and two or more breastfeeding practices. Based on these variables, a summative score will be created ranging from 0 to 5, with a higher score representing increased newborn care knowledge.
2. Maternal self-efficacy: Parenting self-efficacy will be measured using the Karitane Parenting Confidence Scale [20]. This 15-item scale was developed to assess the perceived self-efficacy of mothers of newborns from birth to aged twelve months and has acceptable internal consistency (Cronbach α=0.81) and test-retest reliability (r=0.88) [20]. A cutoff score of 39 or less (out of a possible 45) was determined to be a clinically low perceived parenting self-efficacy [20]. The Kiswahili version was piloted as part of the development phase.
3. Breastfeeding self-efficacy: Breastfeeding self-efficacy will be measured using the Breastfeeding Self-Efficacy Scale—Short Form [23]. This 14-item tool was developed originally in Canada and has been translated into Kiswahili and determined to be valid and reliable [24]. Higher scores indicate higher breastfeeding self-efficacy.
4. Postpartum depression: Depression will be measured using the Edinburgh Postnatal Depression Scale (EPDS) [25]. The EPDS is a self-report screening scale with 10 items that can indicate if a respondent has symptoms related to perinatal depression [25,26]. The EPDS is valid for assessing depressive symptoms across the perinatal period with a score >12 considered as high symptoms of depression. The EPDS has been used in a variety of African countries to measure perinatal depression [27-29]. The EPDS has already been translated into Kiswahili and has been modified for contextual differences [30].
5. Postpartum anxiety: Anxiety will be measured using the Generalized Anxiety Disorder (GAD)-7 [31], which is a 7-item scale used to assess GAD. The scale ranges between 0 and 21, with scores of 10 or greater indicative of generalized anxiety at a moderate or severe level. The GAD-7 has already been translated into Kiswahili [32] and has been widely used to measure perinatal anxiety in African countries, including in Tanzania [33,34].
6. Newborn morbidity and mortality: The 6-week follow-up survey will collect information on morbidity (eg, diarrhea, jaundice, or infection), need for readmission due to illness, and mortality.
7. Postnatal clinic attendance at six weeks: The 6-week follow-up survey will collect information on the number and date of postnatal contacts.

Implementation Outcomes

To measure the implementation of ECEM-TZ, 3 measurement tools will be used.

1. Data related to recruitment will be collected, such as the number of women approached at each site and the number of women randomized.
2. Output data available through the Twilio and TextIt platforms will be collected per participant, including the number of messages sent, messages delivered, error messages, opt-out rates, and response rates.
3. At the final follow-up at 6 weeks post partum, mothers in the intervention group will evaluate the program and be asked about the number of messages they recall receiving, user experience, perspectives on the frequency and timing of messages, and what they liked and did not like about ECEM-TZ.

Sample Size

The sample size was calculated based on the outcome of newborn care knowledge. While previous studies on postnatal education knowledge are significantly varied and no studies to date have reported on maternal postnatal education knowledge in Tanzania, we considered a binary summative score of 100% as the goal at 6 weeks post partum. Using a power of 80%, α of .05 (2-tailed), and assuming 90% of the intervention group and 70% of the control group will score 100% at 6 weeks, a total sample size of 124 is required. This is in line with our implementation sample size approach: recruiting across two hospitals to determine the feasibility of recruitment at these sites. We will aim for approximately similar numbers of participants at each site, recruiting for six weeks. Assuming two research assistants are recruiting five days per week at each hospital and each research assistant can recruit a minimum of 2 participants per day, this would be approximately 20 participants per week. Over six weeks, this would be 120 participants we anticipate recruiting. If recruitment is higher than anticipated, it will be limited to a maximum of 200 across both sites.

Statistical Analysis

Data will be analyzed on an intention-to-treat (ITT) analysis basis as well as per protocol analysis (excluding women who requested to stop the program or were lost to follow-up). Data will be analyzed using SPSS (version 29, IBM SPSS Statistics, IBM Corporation). Demographic characteristics will be expressed in means, SDs, and percentages, as applicable, based on group allocation. Any significant differences in baseline characteristics, examined through a chi-square analysis or Mann-Whitney test, will be adjusted for in the analyses. A P value of .05 will be considered significant for all outcomes. For all analyses, unadjusted and adjusted models will be reported.

For the effectiveness outcomes, total and summative scores will be reported using means, SDs, and percentages, as appropriate. Analysis of covariance will be used to measure whether scores

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differ between the two groups, adjusted for the pretest scores and any significant baseline characteristics. For newborn care knowledge, newborn morbidity, newborn mortality, and attendance at postnatal care six-week contact, binary variables will be created, and data will be analyzed using logistic regression.

For the implementation outcomes, descriptive statistics will be used to describe mothers' experience with ECEM-TZ and outcomes will be reported using means, SDs, and percentages, as applicable. Open-ended questions will be analyzed using thematic analysis [35]. Responses will be transcribed verbatim and translated into English for analysis.

Results

Recruitment for this study occurred between June 13, 2024, and July 22, 2024. A total of 143 participants were recruited, 71 in the control and 72 in the intervention. The 6-week follow-up data collection began on July 30, 2024, and was completed on September 21, 2024. Figure 1 outlines the CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Figure 1. CONSORT flow diagram. CONSORT: Consolidated Standards of Reporting Trials. As data analysis has not yet been completed, the final numbers for analysis has not yet been confirmed. The completed CONSORT will be available once the results are published.

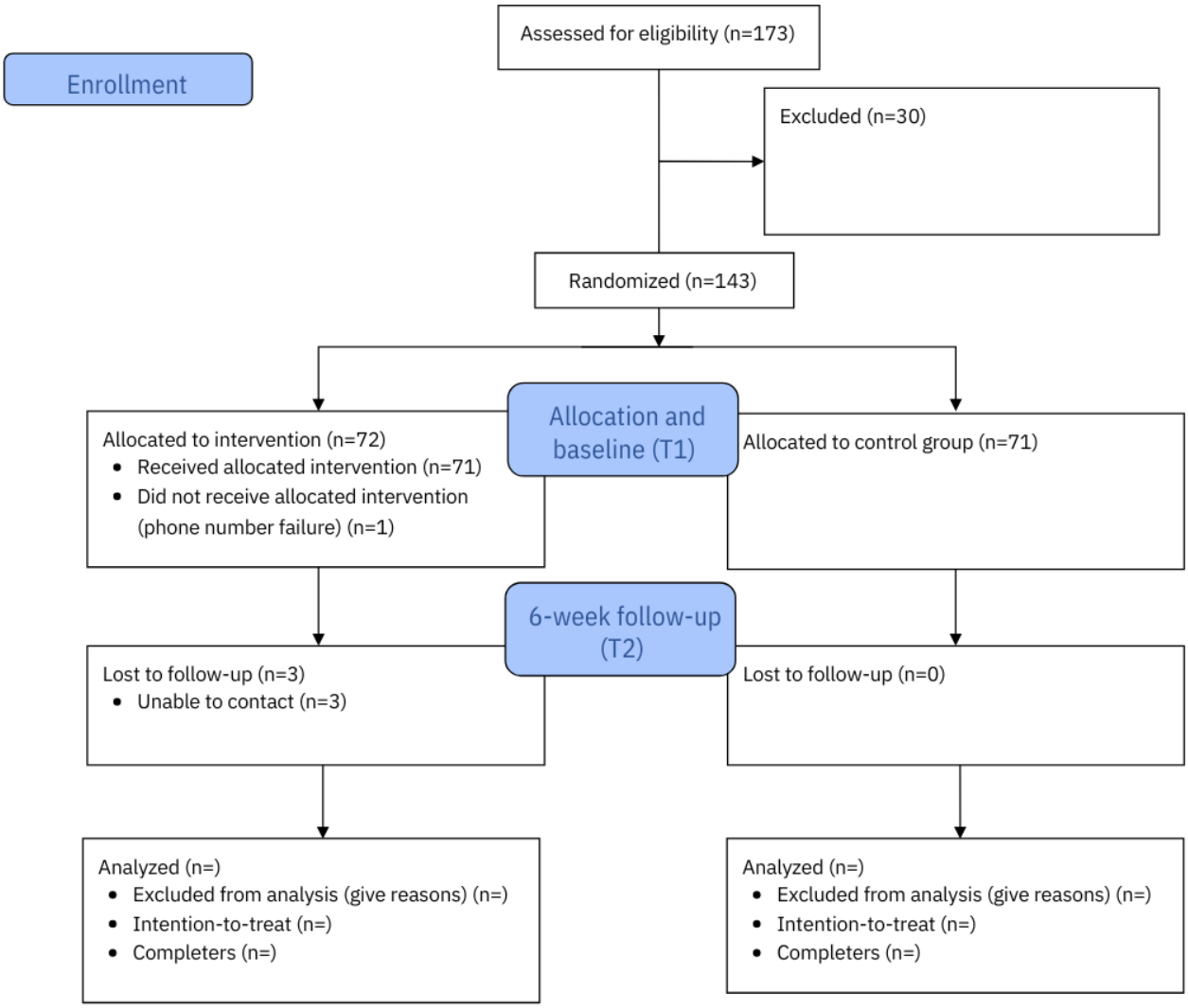

Discussion

Anticipated Findings or Significance

We anticipate the mothers who receive ECEM-TZ will report a significant increase in newborn care knowledge compared to those who only receive standard care. We also anticipate mothers in the intervention group will have higher self-efficacy, be more likely to attend their 6-week follow-up postnatal clinic visit, and have lower depression and anxiety symptoms and fewer newborn mortality and morbidity outcomes at 6 weeks post partum. These results, if present, suggest that providing mothers additional newborn care knowledge to complement in-hospital postnatal education through text messages during the first 6 weeks after birth can improve maternal and newborn outcomes for mothers in Tanzania.

Comparison to Prior Work

Providing text message support to mothers in Tanzania is not new. For example, in 2012, *Wazazi Nipendeni* ("Love me, parents" in Kiswahili) was an initiative in Tanzania that sought to improve maternal health outcomes by sharing

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health-promoting messages through radio, television shows, print advertisements, and billboards [36]. It was developed by the Johns Hopkins Bloomberg School of Public Health Center for Communication Programs and led by the Ministry of Health and Social Welfare [37]. As a subcomponent of *Wazazi Nipendeni*, the text message component of Healthy Pregnancy, Healthy Baby had the objective of sharing antenatal and nutrition information to mothers and their partners, friends, and relatives (as requested) via text message between pregnancy and 16 weeks post partum [38,39]. Mothers were sent three to four text messages per week on topics including preventing mother-to-child transmission of HIV/AIDS, antenatal and postnatal care, family planning, malaria prevention, nutrition, and danger signs, all of which were developed and approved by the Government of Tanzania's Ministry of Health and Social Welfare, targeted toward the gestational age of the newborn [38]. However, during the evaluation, only 8.8% of women recalled exposure through text messages [36].

Wired Mothers is another example of an mHealth intervention that was developed and evaluated in Zanzibar, a semiautonomous island off the coast of Tanzania, through collaboration with University of Copenhagen, Zanzibar's Ministry of Health and Social Welfare, and the Danida Health Sector Programme Support [40]. Targeting pregnant mothers (recruited at their first antenatal care contact) to 42 days post partum, a cluster RCT was conducted with 2550 women [41]. The *Wired Mothers* intervention had two components: unidirectional, automatic text messages to mothers with registered numbers and a voucher system to allow for two-way communication between mothers and their health care providers [41]. The text messages contained health information related to pregnancy, skilled delivery, and postnatal care as well as reminders to attend antenatal care contacts according to the gestational age of the newborn [41]. The *Wired Mothers* intervention significantly improved the likelihood of women having more antenatal contacts, delivering with a skilled birth attendant for urban women, and reducing perinatal mortality risk [41,42].

However, these text message interventions were developed and evaluated over a decade ago (2012-2014), and neither focus on maternal newborn care knowledge, self-efficacy, or other mental health outcomes such as depression and anxiety. Thus, there is a need to evaluate ECEM-TZ as a potential to improve maternal outcomes in these dimensions. In a recent systematic review of mHealth interventions targeting the perinatal period in LMICs, it was found that only a few studies reported on self-efficacy and knowledge outcomes [10]. Furthermore, a recent study in Tanzania found that in the immediate postpartum period, 25% of women experienced depression symptoms and 37% experienced anxiety symptoms [43]. This indicates that exploring the potential of mHealth interventions that target psychosocial and mental health outcomes in LMICs is needed to improve maternal psychosocial and mental health outcomes.

Strengths and Limitations

This protocol has several strengths that should be acknowledged. First, mothers and nurse midwives in Tanzania were involved in providing feedback on the content of the messages before implementation. The messages were also designed using the World Health Organization guidelines for postnatal care [11] and mapped onto the social cognitive theory of behavior change [18,19]. Second, implementation outcomes were identified, which is important per understanding the "black box" of interventions [44] that will hopefully be able to add information to explain the effectiveness outcome findings.

Despite the strengths of this protocol, there are some limitations to acknowledge. The first limitation of our protocol is that women were recruited immediately after they gave birth. An antenatal recruitment process was also considered; however, due to the late arrival of many women in labor to the hospital wards, this was deemed not feasible by the nurse-midwives hired as research assistants for recruitment. In addition, earlier recruitment in the antenatal period (ie, before labor) was deemed not feasible as the messages are based on the date of the infant's birth, thus would require the mother to inform this study when they had given birth. As a one-way intervention, this two-way contact was not feasible. This limitation may influence which women participate; however, the research assistants hired for recruitment were nurse midwives and thus were familiar with the clinical setting. They will be able to encourage participants to take breaks during the verbal interview and participants will be encouraged to continue baby care through the interview.

A second limitation of our study is that we are unable to collect information on participants who declined to participate. This will limit the ability to evaluate the recruitment process and representativity of our sample.

A third limitation of our study is that TextIt and Twilio do not report on the "read" or "unread" status of the messages. While it does report on the number of messages sent, delivered, or undelivered (error), whether the messages were read by participants and when is unknown. This may influence the implementation evaluation as the results will be unable to be controlled for this implementation variable. However, as part of the implementation evaluation, women are asked to recall how many messages they remember receiving per day and over how many days. Feedback on their perception of the messages is also requested, which will provide insight into what mothers recall.

A fourth limitation is that ECEM-TZ is not monitored in real time, and it is only a one-way intervention and thus, cannot be used as a clinical care tool. It will be made clear to participants that ECEM-TZ is not able to respond to clinical care questions as well as an automatic message is programmed to be sent to the mothers telling them to seek care if participants engage with the text messages. Nevertheless, despite these limitations, ECEM-TZ has a strong potential to improve outcomes for mothers in Tanzania while reducing the burden on health care providers.

Future Directions

To expand this work, it will be important to explore potential challenges related to rural versus urban locale. This study recruited from Dar es Salaam, the commercial capital of Tanzania. For broad-scale expansion, exploring potential challenges in nonurban areas will be important. In considering

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postnatal care use in Tanzania more broadly, several studies have attributed higher use of postnatal care to higher maternal education [45,46], living in an urban area [45-47], receiving counseling from a health care provider to attend [45-47], higher socioeconomic status [46,47], and having trust in the health system [45]. Thus, expanding ECEM-TZ to other areas of Tanzania, including rural and remote areas, will need further research to understand how best to implement the program.

Future work should also consider including other caregivers such as fathers and grandparents in receiving such an mHealth intervention. Other caregivers have been found to play an important role in seeking postnatal care due to cultural norms [48]. Additionally, fathers in Tanzania have been found to struggle with psychosocial and mental health concerns during the perinatal and early childhood period [49]. Thus, an mHealth intervention that targets mothers as well as other caregivers is a warranted future direction.

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Data Availability

Data sharing does not apply to this paper, as the trial is ongoing.

Authors' Contributions

JD handled the conceptualization, methodology, writing of the original draft, review and editing of the writing, project administration, and funding acquisition. MC-Y did the conceptualization, methodology, writing of the original draft, review and editing of the writing, project administration, funding acquisition, and supervision. LTM worked on the conceptualization, methodology, review and editing of the writing, and project administration. CM carried out the conceptualization, methodology, review and editing of the writing, project administration, and funding acquisition. TK conducted the conceptualization, methodology, review and editing of the writing, and funding acquisition. DM put effort into the conceptualization, methodology, and review and editing of the writing. CLD performed on the methodology and review and editing of the writing. GTM was responsible for conceptualization, methodology, and review and editing of the writing. MA was involved in conceptualization, methodology, and review and editing of the writing.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

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ECEM-TZ: Essential Coaching for Every Mother—Tanzania
EPDS: Edinburgh Postnatal Depression Scale
GAD: Generalized Anxiety Disorder
ITT: intention-to-treat analysis
LMIC: low- and middle-income country
mHealth: mobile health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Effects of Internet Cognitive Behavioral Therapy for Insomnia and Internet Sleep Hygiene Education on Sleep Quality and Executive Function Among Medical Students in Malaysia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Medical students are frequently affected by poor sleep quality. Since poor sleep quality has negative physiological and psychological consequences such as on executive function, there is an opportunity to improve sleep quality and executive functions using non-pharmacological intervention such as cognitive behavioural therapy.

Objective: The aim of this study therefore is to determine if improving sleep quality could improve executive functions in medical students with poor sleep quality by comparing cognitive behavioural therapy for insomnia (CBT-I) with sleep hygiene education (SHE) in a randomized controlled trial (RCT).

Methods: A parallel group, RCT with a target sample of 120 medical students recruited from government-based medical universities in Malaysia. Eligible participants will be randomized to internet group CBT-I or internet group SHE in a 1:1 ratio. Assessments will be performed at baseline, post-intervention, 1 month, 3-months, and 6-months. The primary outcome is between-group differences in sleep quality and executive function post-baseline. The secondary outcomes include pre-sleep worry, attitude about sleep, sleep hygiene and sleep parameters.

Results: This study received approval from the Research Ethics Committee in Universiti Putra Malaysia (JKEUPM-2023-1446) and Universiti Kebangsaan Malaysia (JEP-2024-669). The clinical trial was also registered in Australian New Zealand Clinical Trial Registry (ACTRN1264000243516). As of June 2024, the recruitment process is ongoing and a total of 48 and 49 students have been enrolled from the universities into the CBT-I and ISHE groups, respectively. All the participants provided signed and informed consent to participate in the study. Data collection has been completed for the baseline (pre-treatment assessment), and follow-up assessments for T1 and T2 for all the participants in both groups, while T3 and T4 assessments will be completed by July 2025. Data analysis will be performed by August 2025 and the research will be completed by December 2025.

Conclusions: This study is the first attempt to design a CBT intervention to ameliorate poor sleep quality and its related negative effects among medical students. This research is also the first large-scale exploring the relationship between health status and CBT-mediated sleep improvement among medical students.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000243516; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=387030

International Registered Report Identifier (IRRID): PRR1-10.2196/59288

(JMIR Res Protoc 2024;13:e59288) doi:10.2196/59288

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KEYWORDS

sleep quality; cognitive behavioral therapy; sleep hygiene; medical students; executive function; Malaysia; insomnia

Introduction

Background

It is scientifically acknowledged that sleep and executive functions undergo changes in prefrontal circuits that underlie executive functioning as part of healthy aging [1]. According to the model proposed by Harrison and Horne [2] and recent findings, selective sleep loss affects prefrontal cortex (PFC) circuitry, leading to changes in brain metabolism and impairing executive function in healthy adults [3-5]. Based on these findings, several studies have debated the vulnerability of the PFC to sleep loss [6,7]. A study investigating sleep problems and executive function among university students found a significant relationship between poor sleep quality (SQ) and impaired executive function [8]. Medical students, in particular, are frequently affected by poor SQ during their time in medical school [9].

Medical students from various countries have shown differing prevalence rates of poor SQ, including 44.2% in Nepal, 41% in Iran, 51% in the United States [10], 59% in Lithuania [11], 90% in China, 70.0% in Hong Kong, 32.5% in Nigeria, 37% in Saudi Arabia [12], and 62.0% in Ethiopia [13]. Recently, in Malaysia, a prevalence of 59.6% was reported among clinical students at International Islamic University Malaysia [14].

Sleep-related problems can result in substantial medical costs and human burden [15,16]. Sleep disorders such as insomnia affect approximately 25 million people in the United States annually, contributing to an estimated health care cost of US $100 billion [17]. Therefore, improving SQ among medical students through nonpharmacological interventions may help prevent or minimize the consequences of poor sleep, such as burnout.

To date, only a few effective nonpharmacological interventions are known to treat sleep-related issues such as poor SQ [18]. In a systematic review of nonpharmacological interventions aimed at improving sleep among university students (including 11% of medical students), cognitive behavioral therapy (CBT) accounted for 33.3% of the interventions, followed by sleep hygiene at 33.1%; relaxation, mindfulness, and hypnotherapy at 22.2%; and Gestalt therapy or imagery rehearsal therapy at 11.1%. The researchers concluded that CBT was effective in treating sleep disorders among university students. Additionally, other outcome variables, such as sleep duration, SQ, sleep onset latency (SOL), sleep hygiene, and dysfunctional beliefs about sleep, were examined [19]. Based on these findings, CBT and sleep hygiene education (SHE) were identified as the most commonly used interventions to improve SQ.

CBT for insomnia (CBT-I) is a nonpharmacological intervention recommended as the first line of treatment for improving SQ [20] and is considered the gold standard for insomnia treatment [21,22]. CBT-I was developed based on the Spielman behavioral model of insomnia [23] and is an extension of the stimulus control theory of insomnia [24]. It is a multicomponent psychotherapy, comprising elements such as sleep education, stimulus control therapy, sleep restriction therapy, cognitive therapy, sleep hygiene, and relaxation training [25,26].

CBT-I focuses on dysfunctional cognition and maladaptive behaviors that contribute to sleep problems. However, access to CBT-I is limited due to the shortage of trained personnel and the high cost of treatment [27-30]. Internet-based CBT-I (ICBT-I), with or without therapist guidance, has been successfully used for managing chronic insomnia [27,28]. Similarly, SHE has been reported to be equally effective in improving SQ among individuals aged 12 years and older [29]. However, SHE is a single educational intervention that focuses on sleep hygiene, whereas CBT-I is a multicomponent intervention. Therefore, CBT-I is considered a potentially more effective intervention for improving SQ and executive function among individuals, but evidence-based data to support this claim are lacking. Furthermore, studies comparing the effectiveness of CBT-I and SHE interventions are scarce. Despite recognizing SQ as a foundation of a healthy lifestyle, there is limited emphasis on sleep hygiene and sleep education in medical schools. Hence, this study protocol outlines the methodology of a randomized controlled trial (RCT) designed to examine the effectiveness of CBT-I and SHE on SQ and executive function among medical students. The secondary outcomes to be investigated include presleep worry, attitudes toward sleep, sleep hygiene, and sleep parameters.

Conceptual Framework

This study will use several theories, namely, the cognitive models of insomnia, the hyperarousal models of insomnia, and the PFC circuitry model, to develop the theoretical framework for the interventions to be investigated. First, according to the cognitive model of insomnia (Figure 1), individuals with sleep problems often experience excessive worry, which prevents them from falling asleep and consequently leads to poor SQ [30]. As a result of this worry, individuals with sleep problems tend to focus on sleep-related internal threats (eg, bodily sensations) and external threats (eg, environmental noises). This selective focus causes them to become hyperaware of minor cues (previously unnoticed), which leads to excessive worry and anxiety. Additionally, individuals with sleep problems develop negative cognitions that further increase their cognitive and arousal activity, preventing them from falling asleep [30]. The model also suggests that individuals with sleep problems often engage in safety behaviors, such as napping or consuming alcohol, to relieve this arousal. However, these safety behaviors eventually worsen the worry and prevent individuals from challenging their negative sleep beliefs [30].

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Figure 1. The cognitive model of insomnia.

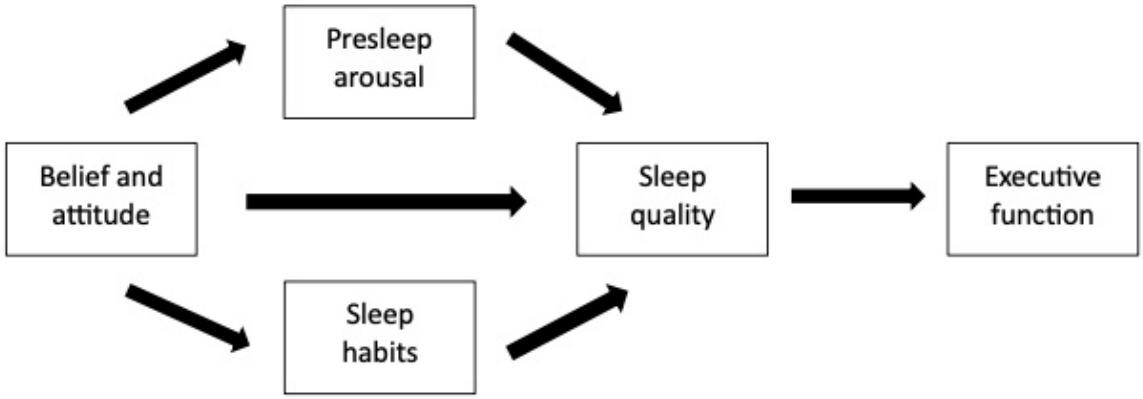

Second, the hyperarousal model of insomnia incorporates both the cognitive and behavioral models of insomnia, while integrating principles of classical conditioning [24,25]. This model posits that conditioned arousal is a key factor in perpetuating sleep problems. It further explains that repeated associations between poor sleep and the bed can increase conditioned arousal, with the bed and sleep environment becoming stimuli for heightened arousal [31]. Cognitively, individuals with increased sleep arousal begin to perceive "learned sleep–preventing associations," thereby perpetuating their sleep problems [25].

Third, it is scientifically acknowledged that sleep and executive functions undergo alterations in prefrontal circuits that support executive function as part of healthy aging [1]. According to the model proposed by Harrison and Horne [2] and recent findings [3-5], selective sleep loss affects PFC circuitry, potentially leading to changes in brain metabolism that impact executive function in healthy adults. Building on these findings, several studies have debated the vulnerability of the PFC to sleep loss [6,7]. In this study, improvements in SQ may affect the PFC circuitry, particularly executive function. Consistent with this, our study aims to use ICBT-I to alleviate poor SQ and enhance executive function among medical students. The delivery of ICBT-I overcomes common limitations associated with traditional face-to-face administration, such as the lack of trained personnel, high costs, and limited treatment availability due to time constraints [30].

Research Aim and Hypotheses

This study aims to elucidate the effects of improved SQ on executive function. The following hypotheses will be investigated in the trial:

- ICBT-I will lead to a significant improvement in SQ compared with the SHE intervention at 1 month (T2), 3 months (T3), and 6 months (T4) postintervention.
- ICBT-I will lead to a significant improvement in executive functioning compared with the SHE intervention at 1 month (T2), 3 months (T3), and 6 months (T4) postintervention.
- ICBT-I will lead to a significant improvement in total sleep time (TST), SOL, number of awakenings (NOA), wake time after sleep onset (WASO), and sleep efficiency (SE) compared with the SHE intervention at 1 month (T2), 3 months (T3), and 6 months (T4) postintervention.
- Dysfunctional beliefs, attitudes about sleep, presleep worry, and sleep hygiene will significantly mediate the between-group differences in study outcomes at 1 month (T2), 3 months (T3), and 6 months (T4) postintervention.

Methods

Trial Design

A 2-arm, parallel-group RCT will be conducted, comparing ICBT-I with internet-delivered SHE (ISHE). The trial design is summarized in Figure 2. The study population will consist of preclinical medical students who meet the established criteria for poor SQ, as indicated by self-report assessments, which are internationally recognized as standardized instruments. The medical students will be randomly assigned in a 1:1 ratio to either the ISHE or ICBT-I group. All interventions will be conducted online using a paid Zoom (Zoom Video Communications/Qumu Corporation) platform. As shown in Figure 2, participants will receive an electronic document containing the participant information statement, screening instruments, informed consent form, and randomized allocation to the intervention groups. Both baseline and follow-up assessments will be conducted either online or via mobile platforms. Participants will be able to print the participant information statement, and contact details (phone numbers and emails) will be provided for participants to reach the researchers before consenting and during the data collection process.

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Figure 2. The trial design. dTMT: Digital Trail Making Test; ICBT-I: internet-based cognitive behavioral therapy for insomnia; ISHE: internet-based sleep hygiene education; PSQI: Pittsburgh Sleep Quality Index; UKM: Universiti Kebangsaan Malaysia; UPM: Universiti Putra Malaysia.

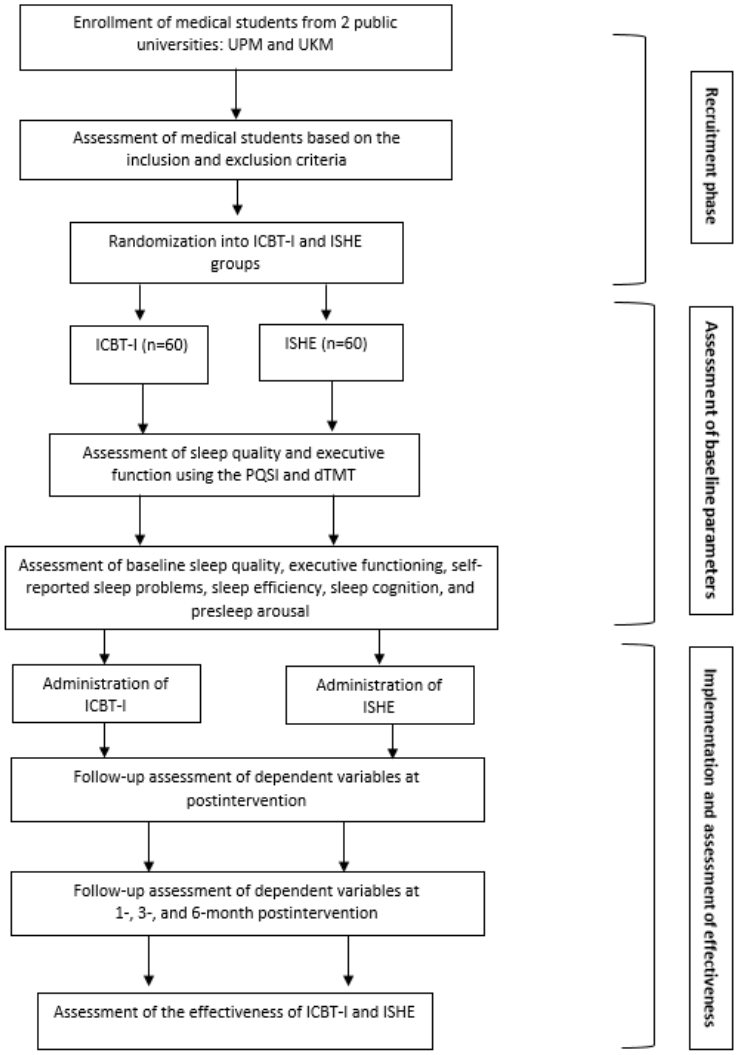

Ethics and Dissemination

Ethical approval for this study was obtained from the Human Ethics Committees at Universiti Putra Malaysia (UPM; JKEUPM-2023-1446) and Universiti Kebangsaan Malaysia (UKM; JEP-2024-669). Informed consent will be obtained from each potential participant before their recruitment into the study. They will be briefed on their right to participate or decline, as well as their right to opt out of the study without penalty. Regarding privacy and confidentiality, data will be fully anonymized, and no detailed information about participants will be recorded. No incentives will be provided for participation in this study.

The RCT protocol aligns with the SPIRIT (Standard Protocol Items for Randomized Trials) guidelines [32], as shown in the recruitment and assessment procedures in Figure 2. The uploaded SPIRIT checklist can be found in Multimedia Appendix 1. Multimedia Appendix 2 presents the protocol approval obtained from the Australian New Zealand Clinical Trials Registry (ANZCTR; ACTRN12624000243516). Upon completion of the study, all data will be stored in the institutional database for a specified duration before being destroyed. The findings will be published as a research article in a journal, with no information that could reveal the participants' identities.

Sample Size Estimation

As shown in Figure 3, the sample size for the RCT was calculated using G*Power software (Heinrich-Heine-Universität Düsseldorf), selecting the *F* tests for analysis of variance: repeated measures, within-between interaction. The calculation was based on a precision level of 0.05, a study power of 95%, an effect size of 0.20, and a correlation coefficient of 0.5 among the outcome measures. Therefore, the minimum required sample size for each group is 56. A low effect size of 0.20 was chosen based on previous interventions addressing SQ [33]. After adjusting for a 10% dropout rate, the sample size was increased to 60 medical students per group. Given that this is a 2-arm RCT, a total of 120 medical students will be required to complete the study.

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Figure 3. Statistical test used in computing the required sample size in G*Power software.

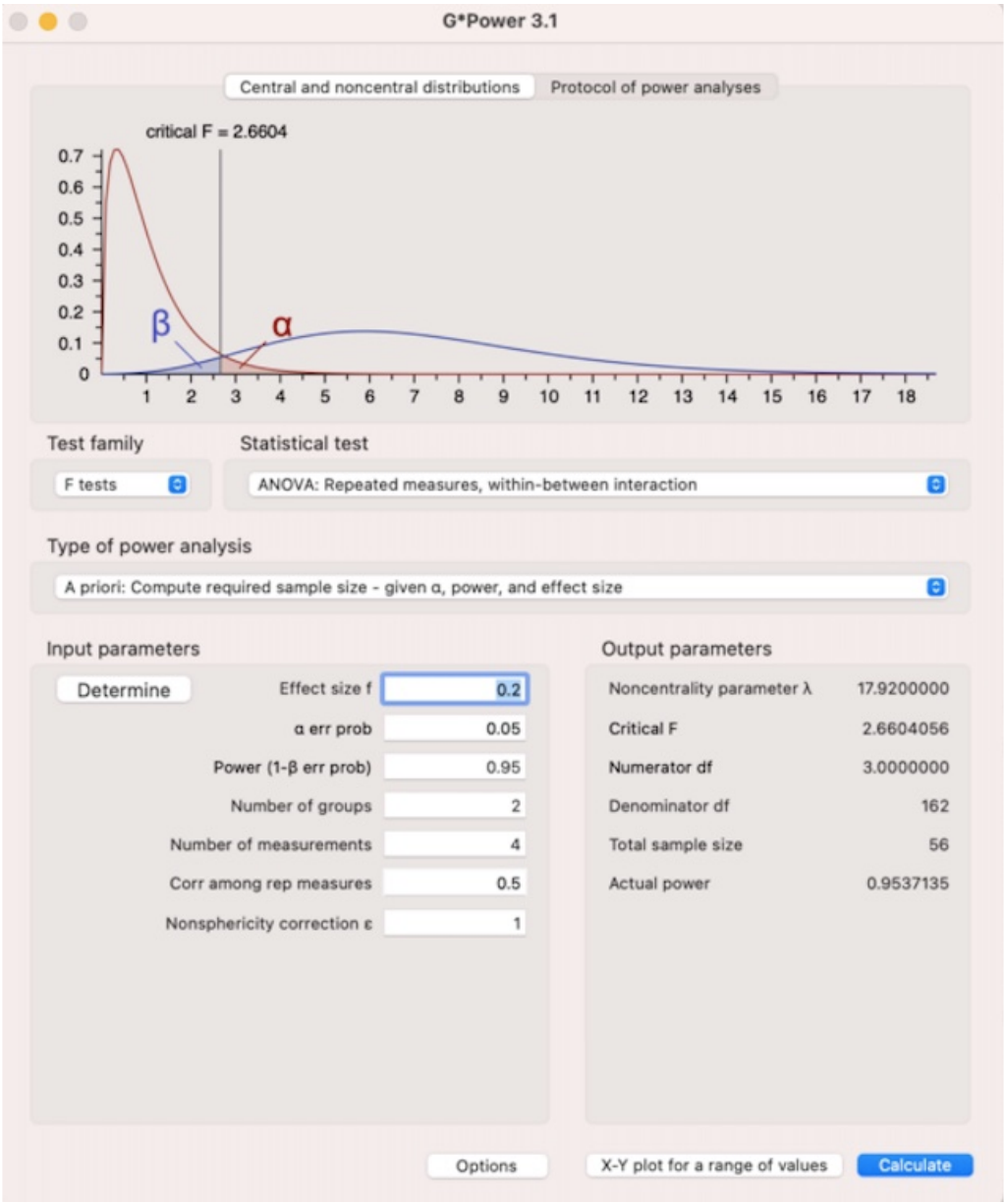

Participants and Recruitment

The RCT will involve 120 medical students from 2 government-based medical universities: UPM and UKM. These institutions were selected for their convenience and proximity to the researchers. The inclusion of both universities is also intended to account for potential differences in medical curricula and academic schedules between government-based and private medical institutions. Participants will consist of volunteers, specifically undergraduate medical students in the preclinical years (ie, years 1-3). A list of potential participants will be compiled with permission from the dean. Recruitment advertisements will be posted across various platforms, including social media, campus spaces, and noticeboards, to facilitate participant engagement. Before the initial assessment, each participant will be required to complete the consent form and information sheet. Potential participants will undergo a screening process to assess their eligibility before being randomized into either the ISHE or ICBT-I group.

Randomization and Allocation Concealment

As participants will be recruited from 2 different universities, a stratified randomization method will be used to ensure balance between the groups from each university. Eligible students will be grouped by university and gender before random selection. Gender will serve as a matching factor during the stratified randomization process to ensure a comparable number of female and male students are recruited from both universities.

Data will be collected from volunteer medical students, and the researchers will have no influence on the randomization process or access to future allocations. Each participant will be assigned an identification number and listed before being randomized into either the ISHE or ICBT-I group using online randomization software [34]. A total of 60 students will be allocated to each group.

Study Location

The initial assessment and experiment will be conducted using a paid Zoom platform. Participants will be interviewed by the

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researcher using a semistructured questionnaire to determine their eligibility based on the inclusion and exclusion criteria before randomization.

Eligibility

Upon expressing interest in participating in the RCT, medical students will be directed to a website with general information about the study and its procedures. They will then access the screening assessment document and consent form to complete the eligibility process. After providing informed consent and meeting the inclusion criteria, potential participants will be contacted by phone. During the call, the investigator will confirm the participant's understanding of the RCT and the provisions for the internet-based interventions being investigated.

The inclusion criteria in Textbox 1 will be considered before recruiting a medical student for this study.

The criteria listed in Textbox 2 will be used to exclude individuals from this study.

Textbox 1. Study inclusion criteria.

- Participants must be aged 18 years or older.
- Participants must currently be enrolled as medical students in Klang Valley, Selangor, Malaysia.
- Participants must be willing and able to provide written informed consent.
- Participants must be able to read and understand English.
- Participants must have access to reliable internet service, either at university or at home.
- Participants must be proficient in basic computer and internet operational skills, such as completing self-report questionnaires and online assessments.

Textbox 2. Exclusion criteria.

1. Individuals currently suffering from a sleep disorder, such as restless legs syndrome or obstructive sleep apnea [35].
2. Individuals who have previously participated in sleep hygiene programs or undergone cognitive behavioral therapy for insomnia (CBT-I) treatment.
3. Individuals who currently consume alcohol.
4. Individuals with a history or present medical condition that may affect the use of CBT-I, such as recent cardiac surgery, epilepsy (self-reported) within the last 12 months, or currently experiencing an attack of multiple sclerosis.
5. Individuals with tight work schedules, such as night shifts, that may interfere with the completion of the online assessments.
6. Pregnant medical students.
7. Individuals unable to modify their sleep pattern or with limited opportunities to sleep as usual, such as those caring for an infant or having an infant at home.
8. Individuals currently being treated for insomnia and registered in 1 or more trial centers.
9. Individuals suffering from a severe physical health issue requiring surgery or with less than 6 months of prognosis for reassessment.
10. Individuals who have taken prescribed sleeping medication or pills for more than 2 nights in the last 14 days before recruitment into the study.
11. Individuals with suicidal intentions. No other mental or physical health problems will lead to exclusion from this study.

Blinding

Single blinding will be implemented in this trial. As an online self-report assessment will be conducted, the researchers will remain blinded to the outcomes during the RCT. An automated email will inform the participants of the randomization results, so the medical students will know which group they are assigned to. Limited contact will be maintained between the researchers and participants to prevent any bias in the allocation process or influence on the subsequent assessments. The assessors will remain blinded even after participants contact the research team and reveal their allocation. A researcher (VM; University Putra Malaysia), who has access to all data, will perform the statistical analyses.

Assessment Points

Participants in both groups will be assessed at baseline (week 0 or pretreatment assessment), week 6, 1 month, 3 months, and 6 months after the intervention. T0 represents the pretreatment assessment, while the subsequent 4 assessment points are designated as T1, T2, T3, and T4, respectively.

Planned Interventions

The Internet Group (CBT-I)

A total of 6 modules focusing on the circadian and homeostatic mechanisms of human sleep regulation and their daytime consequences will comprise the CBT-I, as shown in Table 1. These modules outline the rationale for the key CBT-I interventions: (1) sleep restriction, which involves reducing time in bed to the average self-reported sleep duration from a 1-week sleep diary, plus 30 minutes, with a minimum of 6 hours

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of sleep and waking up at the same time daily, regardless of sleep duration; (2) stimulus control, which entails not going to bed unless feeling sleepy and not staying in bed unless asleep within 20 minutes; (3) discouraging napping; and (4) cognitive techniques, which involve restructuring dysfunctional beliefs, such as those about the consequences of sleep loss, and targeting unrealistic sleep perceptions or beliefs. A 10-minute video will be used to present the information.

Table 1. The structure and contents of the interventions.

Module	ICBT-I[a] content	ISHE[b] content
Module 1	• Medical students will be introduced to the structure of the intervention and motivation for the therapy. • Informing the participants that the treatment of choice for poor sleep quality and sleep disorders is the ICBT-I. • Psychoeducation: information about sleep hygiene and regulation.	• Medical students will be introduced to the structure of the intervention and motivation for the therapy. • Informing the participants that the treatment of choice for poor sleep quality and sleep disorders is the ISHE. • Psychoeducation: information about sleep hygiene and regulation.
Module 2	• Sleep restriction: reducing time spent in bed, specifically to a minimum of 6 hours, in a stepwise manner. Using the sleep diary completed by the participants since the module to improve sleep pressure. Participants can increase the time spent in bed by 15 minutes if their sleep efficiency is greater than 85%.	• Sleep hygiene I (sound, light, and temperature)
Module 3	• Sleep hygiene and stimulus control: information on sleep-wake-rhythm, sleep-inhibiting substances, evening rituals, and physical exercise, as well as information on stimulus-control principles aimed at reassociating the bed with sleep.	• Sleep hygiene II (food, exercise, and nicotine/alcohol/caffeine)
Module 4	• PMR[c] based on Jacobson [36] with downloadable written instructions and audio.	• PMR based on Jacobson with downloadable written instructions and audio tape.
Module 5	• Cognitive restructuring: identifying, reexamining, and modifying dysfunctional thoughts and beliefs about sleep and the consequences of poor sleep quality.	• Stress management and sleep.
Module 6	• Relapse prevention: actions to be taken to prevent poor sleep quality or relapse in sleep perturbations, including when it is appropriate to seek medical assistance and identify the conditions of safe pharmacotherapy.	• Treatment evaluation and maintenance.

[a]ICBT-I: internet-based cognitive behavioral therapy for insomnia.

[b]ISHE: internet-delivered sleep hygiene education.

[c]PMR: progressive muscle relaxation.

The program includes a sleep diary in which medical students record their wake time, bedtime, sleep latency, night awakenings, and TST. Graphs will be generated based on the data entered by participants into the sleep diary. Additionally, various exercises will be included to ensure participants practice what they have learned. Participants will have the opportunity to repeat, internalize, and apply the modules, exercises, and examples to their daily lives at their own pace. Behavioral instructions will be provided to guide participants in completing the instruments, sleep diary, and responses during the program's interactive phase.

Based on the preferred wake-up time and the average TST from the previous week, a sleep window will be proposed. To avoid excessive tiredness, a more flexible minimum time in bed of 6 hours has been chosen for this study. Participants are encouraged to extend their sleep window gradually. Once the sleep diary indicates an SE of 85% or greater over the past week, participants will be advised to add 15 minutes to their sleep window. However, if the recommended SE of 85% is not achieved, participants will be advised to reduce their sleep window based on their preferred average total sleep and wake-up times during the observation period. For those with an SE between 80% and 85%, the sleep window will remain unchanged, but it can be extended by 15 minutes if the efficiency is lower than 85%.

Besides the overall recommendations on sleep hygiene, the medical students will be encouraged to focus on specific behaviors that received the highest scores in the Sleep Hygiene Index (SHI; ie, reducing coffee or alcohol consumption just before bedtime if the participant reports frequent use). They will also be guided by the Dysfunctional Beliefs and Attitudes About Sleep-16 (DBAS-16), particularly for participants who score highly on the item "feel irritable, depressed, or anxious during the day, mostly because I did not sleep well the night

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before." This reflects a strong belief in the negative impacts of poor SQ. Such participants will be advised to explore whether there are any underlying reasons for their anxiety and depression, aside from insomnia.

The internet program will serve as the primary medium for delivering all intervention materials, with participants engaging with the materials independently. They will also have the opportunity to consult a clinical psychologist (see the "Withdrawal and Crisis Management Procedure" section). Additionally, participants are strongly encouraged to use the feedback form to contact a specialist, particularly if they are newly recruited into the RCT, experiencing negative effects from the ICBT-I or ISHE interventions, or encountering methodological or technical difficulties with the program. The content of the intervention is entirely based on the well-established ICBT-I, which has been validated and tested in previous studies [37].

Each module will be completed with a homework report, which participants will fill out and submit to their therapists. The therapist will review the report, worksheets, and sleep diary data. Written feedback will be provided within 48 hours, and the therapist will grant the medical student access to the subsequent module. Meanwhile, if the participant is inactive for 1 week, the therapist will be alerted via a mobile phone SMS text message, serving as a reminder and encouragement. If necessary, another SMS text message will be sent, followed by emails, with phone calls as the final step. The therapist (FM) in this study is a licensed clinical psychologist with expertise in poor SQ and insomnia-related CBT.

The Internet-Based SHE

The ISHE modules provide psychoeducation on sleep, insomnia, and goal setting for treatment. The modules cover various topics including sleep hygiene I (light, sound, and temperature), sleep hygiene II (exercise, food, and alcohol/nicotine/caffeine), stress management, applied relaxation, mindfulness, and treatment evaluation and maintenance.

At the end of each module, participants will use a homework report checklist to review their assignments. The research team recommends daily entries in the sleep diary, encouraging participants to explore factors and patterns that affect their sleep. Participants are also encouraged to write comments in the discussion forum for each module and submit a post on a specific theme. While some content in the ISHE overlaps with the CBT-I, it does not include components such as stimulus control, sleep restriction, and cognitive restructuring.

Treatment Adherence

Treatment adherence will be ensured through a standardized approach to delivering the intervention. The treatment manual outlines the key therapeutic information provided to the medical students, minimizing the influence of individual therapists. Additionally, the use of a therapist manual and supervision will further support adherence to the treatment in both groups.

Outcome Measures

Overview

An email will be sent to participants requesting them to complete the online assessment in a secure online environment [38]. A consistent order of assessments will be followed by each participant at all time points. Participants who fail to complete the outcome measures within 2 days will receive follow-up email reminders. The research instruments consist of 56 items, including the Digital Trail Making Test (dTMT), and should take approximately 20-30 minutes to complete. A recent study demonstrated that online databases can effectively be used for data collection [37]. Participants' demographic characteristics will be collected only at baseline, including descriptive data on alcohol use and smoking.

The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is an instrument used to assess sleep over the previous month, and it is completed at the beginning of 2 study periods. This validated tool, based on polysomnographic research, consists of 19 self-reported items that evaluate 7 components: subjective SQ, sleep duration, sleep disturbance, sleep latency, habitual SE, use of sleeping medications, and issues related to sleep dysfunction. The instrument provides an index score ranging from 0 to 21 points. Scores greater than 5 indicate significant sleep problems, while lower scores reflect high or acceptable SQ [39].

Digital Trail Making Test

Executive functioning will be assessed using a self-reported online version of the dTMT, which includes TMT-A and TMT-B. In TMT-A, participants are required to connect a sequence of numbers in order. In TMT-B, participants must alternately connect numbers enclosed in circles and squares, following the sequence while ensuring that the pen remains in contact with the paper throughout the process. Participants' executive functioning will be evaluated based on the time taken to complete the entire test and the accuracy of the number connections [40].

In this study, the dTMT will be used to assess medical students' executive functioning. The TMTs are widely used in neuropsychological assessments due to their sensitivity to various neurological disorders. The test consists of 2 conditions (A and B) [41]. In part A, medical students will be instructed to draw a line sequentially connecting a total of 26 numbered circles as quickly as possible. In part B, each student will be asked to connect a series of 26 circles containing either a number or a letter, alternating between them. Both conditions will be scored based on the total time taken to complete the tasks and the frequency of errors made.

Other Sleep Measures

Average sleep parameters, including SOL, TST, NOA, WASO, SQ, and SE (calculated as TST/time in bed × 100), will be derived using the PSQI [42]. Inclusion criteria will be assessed using the baseline sleep diary. Participants will be instructed to document information about their SOL, WASO, NOA, early morning awakenings, number of nocturnal awakenings, TST,

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and SE for 10 days before the intervention (out of the previous 14 consecutive days) [43].

Dysfunctional Beliefs and Attitudes About Sleep-16

The DBAS-16 contains 16 items designed to measure sleep-related beliefs and attitudes [44]. A 10-point Likert scale is used to rate the items, ranging from 1=strongly disagree to 10=strongly agree. The minimum and maximum mean scores for the variables range from 1 to 10. Higher scores indicate a greater endorsement of dysfunctional beliefs about sleep. A previous study demonstrated that the instrument has an acceptable test-retest reliability of 0.83 and an internal consistency of 0.79, indicating its suitability for measuring dysfunctional beliefs and attitudes about sleep [45].

Pre-Sleep Arousal Scale

Sleep arousal among medical students will be assessed using the Pre-Sleep Arousal Scale (PSAS), which consists of 8 items each for measuring somatic and cognitive arousal [46]. A 5-point Likert scale is used to present items depicting symptoms of arousal at bedtime [46,47]. Higher scores reflect higher presleep arousal. The minimum and maximum scores for both types of arousal range from 8 to 40. The instrument demonstrates internal consistency, with Cronbach α of 0.82 for the cognitive scale and 0.79 for the somatic scale [47].

Sleep Hygiene Index

The SHI is a 13-item self-report instrument used to assess behaviors that may compromise sleep hygiene [48]. Poor sleep hygiene has been significantly associated with poor SQ [49-51]. Scores range from 0 to 52, with higher scores indicating behaviors that compromise sleep. The scores can also be analyzed using percentile ranks, where scores below 26 indicate good sleep hygiene, scores between 27 and 34 represent normal sleep hygiene, and scores of 35 and above indicate poor sleep hygiene [48]. The SHI has an internal consistency reliability coefficient of 0.66 [48].

Assessment of Participants' Safety

The risk of severe or serious adverse events in this study is low, as no such events have been reported in previous studies using CBT-I for the management of insomnia [49].

Nevertheless, studies have shown that sleep restriction therapy, one of the components of CBT-I, may increase levels of vigilance impairment and daytime sleepiness among participants, potentially leading to adverse situations such as suicide attempts, incidents, and formal complaints about the online intervention [49]. As both the intervention and assessment will be conducted online, the researcher may not be made aware of all such events. The researcher will, however, instruct participants to complete a feedback form to report any self-reported adverse effects [50].

Withdrawal and Crisis Management Procedure

Participants can withdraw from the RCT at any time without penalty and are not required to provide reasons for their decision. In terms of crisis management, emergency psychiatric services will be available at UPM Teaching Hospital to assist participants in cases of crisis or distress that exacerbate their symptoms or lead to significant deterioration in functioning. All clinic attendees will have access to this service. The investigators will be notified if any medical student utilizes the emergency service, at which point a decision will be made regarding the RCT and whether the crisis qualifies as an adverse event related to the trial.

Data Collection Procedures

The primary researcher (VM) will collect all data under the supervision of a registered and licensed clinical psychologist (FM). The researcher holds a master's degree in clinical psychology and meets the minimum qualifications to administer all questionnaires to participants. Online assessments will be conducted by the clinical psychologist, using an instrument with Yes or No responses to items related to the inclusion and exclusion criteria. All clinical interviews will be audio-recorded to enable subsequent reliability assessments (see Multimedia Appendices 3 and 4 for the study information sheet and consent form, respectively). Participants who are willing to participate will be provided with a consent form. Their consent will be confirmed once they sign the form. Participants who meet the inclusion criteria and have PSQI scores greater than 5 will be grouped and asked to complete the online Trail Making Test, DBAS-16, PSAS, and SHI.

Monitoring of Intervention and Follow-Up Assessment

The flowchart for the research activities is summarized in Figure 2. An SMS text message reminder will be sent by the Zoom administrator 1 day prior to and 30 minutes before the intervention. Follow-up assessments will be conducted at 1-month, 3-month, and 6-month intervals after the postintervention to reassess participants' SQ, executive functioning, self-reported sleep problems, SE, sleep cognition, and presleep arousal. The same instruments described in the previous section will be used for the assessments. All participants will be monitored for adherence to the intervention, and potential dropouts will be identified and addressed accordingly.

Data Analysis

Data will be analyzed using SPSS version 29 (IBM Corp.). Descriptive statistics will be used to obtain information on dropout rates, recruitment, and completeness. All participants will be included in the intention-to-treat analysis for assessing the main efficacy of the intervention, with no planned interim analysis for efficacy or futility. The baseline characteristics of participants will be presented according to their randomized group, with no inferential statistical tests performed at this stage.

For the RCT design, outcome measures will be assessed for normality and presented as either means with SD or medians with IQR, depending on the data distribution. Participants' characteristics will be summarized using descriptive statistics, with categorical data presented as frequencies and percentages, and continuous data presented as means (SD) or medians (IQR). Normality will be tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Changes in all outcome measures (ie, SOL, TST, NOA, WASO, SQ, SE, dysfunctional beliefs about sleep, presleep arousal, and SHI) from pretreatment (T0) to the first (T1), second (T2), and

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third (T3) time points will be assessed for treatment effects using repeated measures analysis of variance. Both treatment and time interaction effects will be examined. Paired samples *t* tests will then be conducted within each condition to evaluate possible simple or main effects. Significant findings and statistical trends will be further analyzed using Cohen *d* effect size, which accounts for the correlation between pre- and posttreatment values.

Potential confounding factors, particularly class year and gender, will be addressed and analyzed as variables that may influence the research outcomes. These factors will be incorporated into the analysis through both univariate and multivariate linear regression analyses, allowing for the isolation of each factor and its association with the outcomes of interest.

Regarding the fourth hypothesis, mediation analyses will be conducted to explore whether changes in the outcome measures from pretreatment to posttreatment are significantly mediated by dysfunctional beliefs and attitudes about sleep, sleep hygiene, and presleep worry. The analysis will follow the traditional mediation model, where the direct, indirect, and total effects are defined in terms of the linear regression coefficients [51]. For example, when the mediation effect size is medium (ie, SM) and the intraclass correlation coefficient is 0.2, with 4 repeated measures, the Sobel method would require 191 participants to achieve 80% power. By contrast, the product-of-coefficients and bootstrap methods would require 188 and 185 participants, respectively, to achieve the same power [52]. This study will adopt the bootstrap method for mediation analysis due to its flexibility in terms of sample size requirements.

Dissemination Policy

The results of this trial will be published in academic journals and presented at international and national conferences or clinical scientific meetings. Depending on the journal's policies, the results will be made accessible online to interested readers.

Results

Ethical approval for this research has been granted by the Ethics Approval Committee of UPM and UKM. As of June 20, 2024, the recruitment process is ongoing, with 48 students enrolled in the CBT-I group and 49 students in the ISHE group. All participants have provided signed informed consent to participate in the study. Data collection has been completed for the baseline (pretreatment assessment) and follow-up assessments at T1 and T2 for all participants in both groups. The T3 and T4 assessments will be completed by July 2025. Data analysis is scheduled for completion by August 2025, and the research is expected to conclude by December 2025.

Discussion

Expected Findings and Implications

CBT has long been established as the first-line treatment for individuals suffering from chronic insomnia, demonstrating positive effects and sustained improvements in sleep-related outcomes, as measured by both sleep diaries and objective indices of SQ [19-21]. A recent RCT with a well-defined placebo-controlled group found that dCBT produced effect sizes comparable to those of traditional face-to-face therapy [53]. However, it remains unclear whether CBT-I has a significant causal relationship with improving executive function among medical students compared with an SHE intervention. This knowledge gap has persisted for some time, and an investigation among medical students is therefore necessary. This study represents the first attempt to specifically examine SQ and executive function by comparing 2 established sleep interventions in this vulnerable group. The findings will be relevant to the care of medical students experiencing persistent SQ issues, particularly during their preclinical years. In particular, the results may highlight the potential for improving SQ as a novel therapeutic target, with benefits extending to generalized health outcomes and enhanced executive function. Furthermore, as an ICBT-I approach will be used in this trial, the study will demonstrate that addressing SQ among medical students is measurable, feasible, and effective.

Given the negative psychological and physiological consequences of poor SQ, such as burnout, suicidal ideation, and reduced empathy toward patients, this trial provides an opportunity to explore a nonpharmacological intervention for improving SQ and executive function among medical students. The findings will help bridge the important research gap identified in previous studies on CBT-I across diverse populations. These studies rarely focus on specific groups such as health professionals or young adults (eg, medical students). If poor SQ causally alters executive function, it is plausible to hypothesize that (1) CBT-I will improve both SQ and executive functioning and (2) the pathway through improved SQ will facilitate the treatment effects on executive functioning [54]. Furthermore, this trial provides a unique opportunity to expand existing knowledge, as only a few RCTs have investigated the roles of hyperarousal mediators (eg, presleep worry), cognitive mediators (eg, dysfunctional beliefs and attitudes about sleep), and behavioral mediators (eg, sleep hygiene) in CBT-I [20].

Strengths and Limitations

This study will be the first RCT in Malaysia to investigate SQ and executive function using a dTMT among medical students. Additionally, it is the first to examine potential mediators, such as presleep worry and sleep hygiene, in the relationship between beliefs about sleep and SQ in this population. A representative sample will be recruited through a simple random sampling technique, allowing the findings to be extrapolated to public medical students in Malaysia and potentially other countries with similar educational demographics.

Nevertheless, this study has important limitations. The sample will be drawn only from medical students at UPM and UKM, meaning it may not be representative of all government-based undergraduate medical students in Malaysia. Additionally, the risk of response biases cannot be ruled out, particularly regarding subjective sleep experiences, which may influence the findings. Participants may also be inclined to provide socially desirable answers. Studies on Asian cultures have shown that, due to the cultural emphasis on modesty, Asians are likely to suppress the expression of positive emotions, which could impact the accuracy of self-reported data [55]. This study will

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use only a quantitative research approach, which may limit a comprehensive understanding of medical students' perspectives and views on poor SQ symptoms and the strategies they use to address the issue. Additionally, there is a risk that participants may provide socially desirable answers when responding to the research instruments.

Conclusions

This study is the first attempt to design a CBT intervention aimed at ameliorating poor SQ and its associated negative effects among medical students. It is also the first study to explore the relationship between improvements in SQ and executive function among medical students using CBT-I.

CBT-I focuses on addressing dysfunctional cognition and maladaptive behaviors that contribute to sleep problems. However, access to CBT-I is limited due to a shortage of trained professionals and the high cost of treatment [27-30]. ICBT-I, with or without therapist guidance, has proven effective in managing chronic insomnia [27,28]. Similarly, SHE has also been shown to improve SQ among individuals aged 12 years and older [29]. However, SHE is a single educational intervention that focuses on sleep hygiene, whereas CBT-I is a multicomponent intervention. Therefore, CBT-I is considered a potentially more effective intervention for improving SQ and executive function. However, evidence-based data to support this claim are lacking. Additionally, studies comparing the effectiveness of CBT-I and SHE are scarce. Despite recognizing SQ as a foundation of a healthy lifestyle, there is limited emphasis on sleep hygiene and sleep education in medical schools. Consequently, this study protocol outlines the methodology of an RCT aimed at evaluating the effectiveness of CBT-I and SHE on SQ and executive function among medical students.

Acknowledgments

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Data Availability

Important data underlying the results will be described in the manuscript once it is accepted for publication, with additional data provided in a supporting document.

Authors' Contributions

VM prepared the study proposal, obtained ethical approval from Universiti Putra Malaysia and Universiti Kebangsaan Malaysia, drafted the manuscript, and will execute the study. FM contributed to the conceptual framework and planning of the research activities, supervised and guided the execution of the study, and reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items for Randomized Trials) checklist.
[PDF File (Adobe PDF File), 78 KB - resprot_v13i1e59288_app1.pdf]

Multimedia Appendix 2
Protocol registration and approval.
[PNG File , 84 KB - resprot_v13i1e59288_app2.png]

Multimedia Appendix 3
Study information sheet.
[DOCX File , 29 KB - resprot_v13i1e59288_app3.docx]

Multimedia Appendix 4
Study consent form.
[DOCX File , 23 KB - resprot_v13i1e59288_app4.docx]

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Abbreviations

ANZCTR: Australian New Zealand Clinical Trials Registry
CBT: cognitive behavioral therapy
CBT-I: cognitive behavioral therapy for insomnia
DBAS-16: 16-item Dysfunctional Beliefs and Attitudes
dTMT: Digital Trail Making Test
ICBT-I: internet-based cognitive behavioral therapy for insomnia
ISHE: internet-based sleep hygiene education
NOA: number of awakenings
PSAS: Pre-Sleep Arousal Scale
PSQI: Pittsburgh Sleep Quality Index
RCT: randomized controlled trial
SE: sleep efficiency
SHE: sleep hygiene education
SOL: sleep onset latency
SPIRIT: Standard Protocol Items for Randomized Trials
SQ: sleep quality
TST: total sleep time
UKM: Universiti Kebangsaan Malaysia
UPM: Universiti Putra Malaysia
WASO: wake time after sleep onset

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Protocol

A Remotely Delivered Light-Intensity Physical Activity Intervention for Older Cancer Survivors: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Older cancer survivors face age- and treatment-related comorbidities, including physical functional impairment, which are exacerbated by physical inactivity and sedentary behavior. Regular physical activity can reduce this risk, yet less than 30% of older cancer survivors meet the recommended guidelines for physical activity.

Objective: This study aims to describe the design, methods, and rationale for a remotely delivered intervention that uses a whole-of-day approach to physical activity in older cancer survivors. This approach focuses on the accumulation of intermittent bouts of light-intensity activity throughout the entire day by disrupting and reducing sedentary activity. The intervention was guided by social cognitive and self-determination theories and incorporated motivational interviewing.

Methods: The 12-week Move for Your Health trial randomly assigned 64 older cancer survivors to a theory-based physical activity intervention or a waitlist control. A Fitbit (Google) activity tracker and smartphone app were used to promote awareness of activity levels and enable self-monitoring of both activity and inactivity in tandem with health coaching phone calls. Motivational interviewing was used to engage participants and tailor strategies to achieve goals during the 12-week intervention. Data were collected at baseline, immediately after the intervention, and at longer-term follow-up (3 months thereafter). Feasibility outcomes included recruitment, retention, adherence, adverse events, and acceptability. Other outcomes included obtaining the parameter estimates for changes in physical function, physical performance, physical activity, sedentary behavior, and quality of life.

Results: Recruitment for the Move for Your Health randomized controlled trial was completed in June 2023. Data collection was completed in March 2024. Data analyses are ongoing.

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Conclusions: The results of this trial will provide information on the feasibility of implementing this intervention in the target patient population, as well as data that will provide information about the potential impact of the intervention on the outcomes. Both of these outcomes will inform the design of a larger randomized controlled trial to more fully test a physical activity intervention in an older cancer survivor population.

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International Registered Report Identifier (IRRID): DERR1-10.2196/59504

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KEYWORDS

cancer survivor; physical performance; physical activity; physical function; older adults; activity tracker; mobile phone

Introduction

Background

The unprecedented growth of the number of individuals in the United States who are 65 years and older, combined with the cancer burden in this age group (>55% of diagnoses) and the high survivability of cancer (currently >65%) [1,2], is resulting in a rapidly expanding high-need population of older cancer survivors. Compared with the general population, older cancer survivors are at higher risk for physical function decline and other comorbidities (eg, cardiovascular disease, osteoporosis, fracture, etc), which further exacerbate the risk for functional limitations [3-6]. Given the adverse consequences of functional impairment, including mobility limitations, increased number of falls, hospital or skilled nursing facility admissions, diminished quality of life, premature death, and substantial financial costs [7-10], the importance of implementing strategies to delay or mitigate these effects is crucial. Despite comprising the majority of cancer survivors, few health behavior change interventions are conducted in older survivors with comorbidities [11].

Regular physical activity has been shown to reduce the risk of comorbid conditions [12-14], yet less than 30% of cancer survivors meet the recommended goal (≥150 minutes per week of moderate-intensity physical activity or ≥75 minutes per week of vigorous-intensity physical activity; eg, fast walking or aerobics) [13-17]. Compounding the effects of physical inactivity are the adverse physiologic distinct effects of sedentary behavior [18,19], defined as sitting, lying, or reclining with minimal energy expenditure during waking hours (ie, excludes sleep) [20]. Sedentary behavior is associated with an increased risk of cardiovascular disease [21-24], premature mortality [25,26], and decreased physical function [27,28], even among individuals who meet recommended activity guidelines.

The predominant focus in physical activity research has been on moderate- to vigorous-intensity physical activity (MVPA) since this intensity level is associated with the greatest health benefits [12]. However, older cancer survivors with functional impairment may have different needs, preferences, and barriers to being physically active and thus may require a different approach. Light-intensity physical activity (LPA), such as leisurely walking, is associated with better physical health [29-34], including physical function [35-39] and emotional well-being [29,33,34,40], independent of MVPA. These associations may only be apparent or appear stronger in adults who are older, less physically active, or with impaired lower extremity function [25,30,36,41,42]; that is, the effect sizes are larger or only reach statistical significance when stratified by these categories. Changing the focus from MVPA to LPA may represent a more achievable and sustainable target for vulnerable populations such as older survivors with comorbidities. Despite evidence of the health benefits of LPA, few randomized controlled trials (RCTs) have been conducted to evaluate the effects of LPA on health outcomes.

The majority of physical activity studies have been clinic or center based, focused on common cancers (breast, prostate, and colorectal), and targeted behavior (ie, physical activity) as the primary outcome [43,44]. Few studies have focused on medically underserved survivor populations (older adults, racial and ethnic minority groups, and rural dwellers) and targeted outcomes meaningful to survivors (eg, patient-reported outcomes) [43]. Thus, there is a critical need for lifestyle activity interventions that are effective, low-cost, and accessible to older cancer survivors from diverse backgrounds, designed to be feasible, relevant, and meaningful for them. A distance- and technology-based approach (in both intervention delivery and outcomes assessment) would expand the reach of interventions to underserved and underrepresented minority survivor populations.

Consumer wearable activity trackers are a low-cost, easily accessible, and potentially scalable strategy to promote behavior change and facilitate remote intervention delivery. Many trackers, along with their phone applications, use multiple behavior change techniques associated with improving physical activity, such as incremental goal setting, review of behavioral goals, self-monitoring of behavior, and feedback on behavior. These devices can measure progress, provide feedback in real-time, and even deliver prompts or cues to action. Several well-designed pilot or feasibility studies have evaluated wearable activity trackers as an intervention tool to increase physical activity [45-49], interrupt and replace sedentary behavior [50,51], or both [52-54]. These studies have primarily enrolled breast, prostate, or colorectal cancer survivors and focused on brisk walking as a form of MVPA. In contrast, there have been few studies using trackers that have also focused on LPA as the prescription.

A challenge of distance-based trials is the availability of low-resource assessments of objective data, such as physical performance (eg, the Timed Up and Go test and the chair stand test [55-57]). Before the COVID-19 pandemic, physical

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performance testing for objective measurement of physical functioning was primarily assessed in person, which may have excluded rural, older, or other individuals unwilling or unable to travel. Low-cost, valid, and reliable methods to remotely conduct such testing in the home setting were limited. We designed a study to evaluate the validity, reliability, acceptability, and, most importantly, safety of using videoconferencing to remotely assess tests of functional mobility and strength among older cancer survivors in their own homes [58]. The COVID-19 pandemic has accelerated the use of videoconferencing to remotely deliver physical performance testing [59-61], potentially expanding the reach, scalability, and dissemination of interventions to cancer survivors who may not otherwise have access, especially those residing in rural areas [58].

Objectives

To address these research gaps, we designed the Move for Your Health (MY Health) study, a 12-week RCT to determine the feasibility of using a whole-of-day approach to physical activity to improve physical function among older cancer survivors. The whole-of-day approach focuses on the accumulation of intermittent, short bouts of activity (stepping) throughout the entire day by disrupting sedentary activity. The specific aims are to (1) determine the feasibility and acceptability of a remotely delivered lifestyle activity intervention by assessing recruitment, retention, adherence rates, and participant satisfaction and monitoring adverse events; (2) estimate effect sizes for primary and secondary end points for the adoption (baseline to after the intervention) and maintenance (3 months after the intervention) of the intervention; and (3) conduct a process evaluation using mailed surveys and intervention fidelity assessments to inform a larger definitive trial with broader dissemination.

Methods

Study Design and Setting

MY Health is a waitlist RCT that examined the feasibility of an intervention to promote LPA and disrupt sedentary activity using a whole-of-day approach in 64 older cancer survivors. Data collection occurred at baseline, immediately after the intervention, and at longer-term follow-up (3 months after the intervention; Figure 1). Both intervention delivery and data collection were conducted remotely in participants' homes.

Figure 1. Study flow diagram.

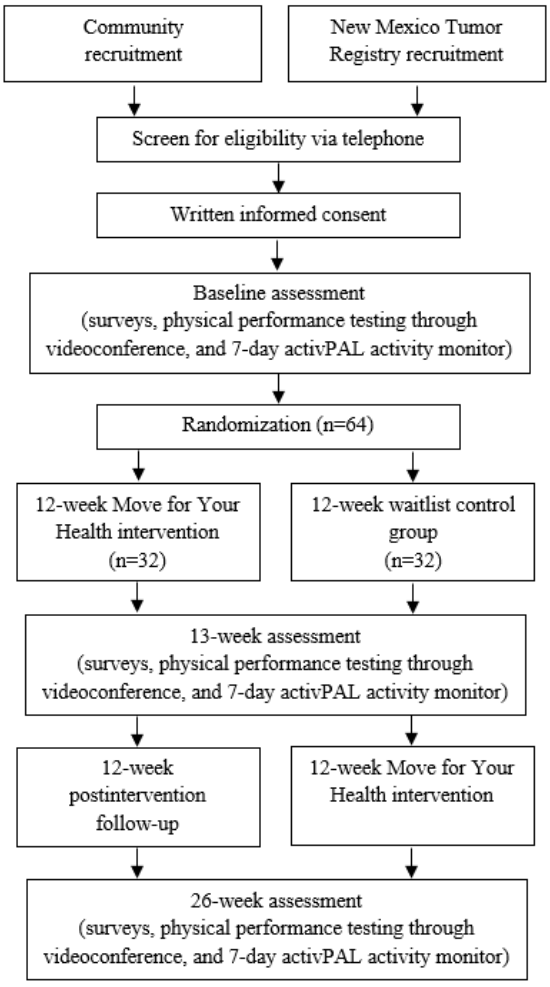

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Recruitment and Eligibility

A multipronged recruitment approach was used, including (1) identification of cancer survivors from the New Mexico Tumor Registry (NMTR), one of the founding registries of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program [62,63]; (2) clinician referrals; and (3) flyers distributed to cancer survivor support groups, community and senior centers, and health fairs and other community events with the assistance of a community engagement liaison specialist from the University of New Mexico Health Sciences Center. Random quota sampling based on ethnicity (Hispanic vs non-Hispanic) and geography (rural vs urban) was used to enhance balance across key subgroups. The sample frame included the entire state of New Mexico. Rural status was determined based on the population size (<50,000=rural; ≥50,000=urban) of the participant's place of residence. This definition incorporated the population size of the town or city from the Rural-Urban Commuting Area classification system [64] but ignored the commuting area codes to better reflect the participants' immediate environment, since this is a home-based study among older adults (ie, to support physical activity near one's home). Eligible individuals identified by the NMTR were mailed a letter that briefly introduced the study and provided recipients an opportunity to refuse to participate. Following a defined time period, contact information was provided to the study team. Individuals were then mailed a letter explaining the study and inviting their participation; 2 consent forms (one to keep and one to mail back) were included with the letter. Individuals (identified by the NMTR) not refusing contact, who were referred by their provider, or who self-referred to the study were contacted by phone to discuss the study, verify eligibility, and begin the consent process; a maximum of 4 calls were made. The total time to accrue the full sample, contact and cooperation rates, and reasons for nonparticipation were tracked as part of the feasibility assessment of recruitment.

Eligibility criteria included (1) age 65 years or older; (2) residing in New Mexico and not planning to move out of state during the next year; (3) previous cancer diagnosis and completed primary treatment (patients with metastatic cancer were eligible with physician approval); (4) mild-to-moderate physical function impairment (raw score between 15 and 29 on the 8-item Patient-Reported Outcomes Measurement Information System physical function survey; representing approximately 0.5 and 1.5 SD below the population mean, respectively); (5) able to speak, read, and understand English or Spanish; (6) participating in less than 120 minutes per week of MVPA (allows for self-report bias in overreporting physical activity or misclassification of light-intensity activity as moderate-intensity activity, determined using the Godin Leisure-Time Exercise Questionnaire—low respondent burden); (7) living independently and capable of walking 3 blocks (approximately 1300 steps or 0.25 mile) without an assistive device (eg, cane or walker) and without stopping to rest; (8) own a smartphone, or be willing to use a study-provided smartphone, capable of running the Fitbit app (Google) and accessing the internet; and (9) willingness to be randomized to either study arm and to wear an activity tracker.

Exclusion criteria included (1) severe impairments (in seeing or hearing) or preexisting medical limitations that would constrain engaging in daily LPA (eg, severe orthopedic conditions, pending hip or knee replacement, dementia, oxygen dependent, or chronic vertigo) or (2) currently participating in a program (eg, personal or structured program) to decrease sedentary time or increase physical activity.

Randomization

Upon completion of the baseline assessment, participants were block-randomized with equal allocation to 2 arms (intervention vs waitlist control) within 4 strata defined by self-reported ethnicity (Hispanic vs non-Hispanic) and geographic location (urban vs rural). A computer-generated allocation table (created by a statistician) was uploaded into the Research Electronic Data Capture (REDCap; Vanderbilt University) database, and allocation assignment was announced by the project manager upon completion of the baseline assessment. Given the trial design, it was not possible to blind the participants or the health coaches to the group allocation, though study statisticians were blinded.

MY Health Intervention

Conceptual Framework

The remotely delivered lifestyle activity intervention was guided by social cognitive theory and self-determination theory and used motivational interviewing (MI; Figure 2). Social cognitive theory emphasizes self-efficacy, behavioral capability (knowledge and skills to perform a behavior), self-monitoring, and outcome expectancies to promote behavior change [65,66]. Self-determination theory posits that intrinsic versus extrinsic motivation leads to a greater commitment to behavior change and maintenance of change [67]. Intrinsic motivation is more likely when 3 core psychological needs are met: autonomy, competence, and relatedness [67,68]. MI is a person-centered method of communication to help resolve ambivalence related to behavior change, enhance intrinsic motivation to change, and brainstorm ways to overcome barriers [69].

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Figure 2. The Move for Your Health (MY Health) study conceptual model.

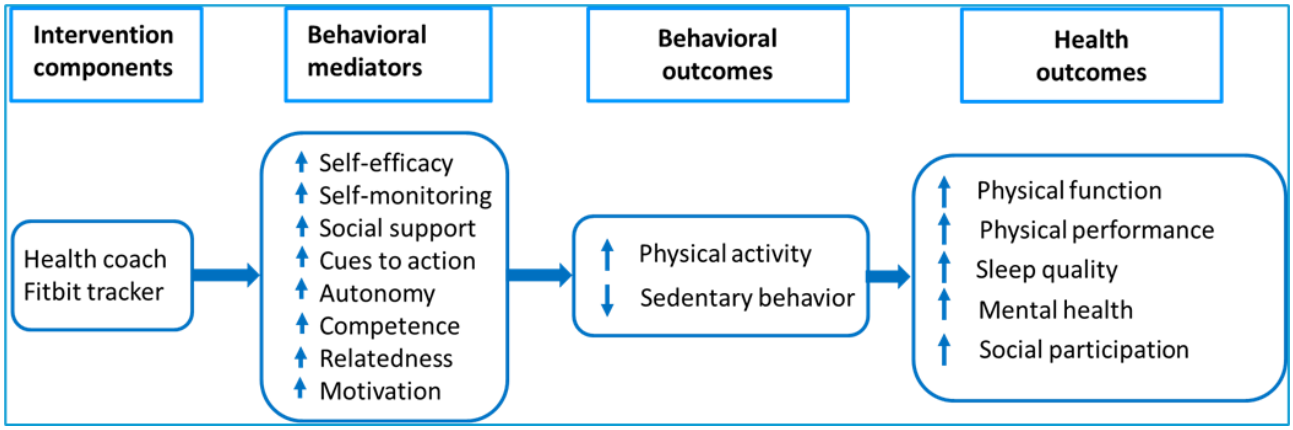

Overview and Goals

The goal was to encourage participants to be more active throughout the day—a whole-of-day approach—without regard for minimum intensity or duration of activity bouts. Walking, important for maintaining mobility and independence, served as the primary form of LPA. The primary behavioral target was to reach and maintain an extra 3000 steps per day above baseline (established during the second week post enrollment). This target represents approximately 30 extra minutes of LPA [70] and is associated with health benefits [29,71]. The secondary behavioral target was to increase the number of active h/d (defined as >250 steps/h in Fitbit) to at least 10 h/d to encourage activity throughout the day and to interrupt and replace sedentary time. Frequent interruption of sitting is associated with better physical function [36,72-74]. To promote gradual and sustained change, participants were asked to increase the number of steps per day during weeks 3-12 (Table 1). Participants were asked to "practice" achieving their new step goal on at least 3 days during the first week and then at least 5 days during the second week. This allowed participants to have one or more low-activity days and still be able to achieve their step goal. In accordance with self-determination theory and MI, participants chose their own strategies for becoming more active and achieving their weekly goals with guidance and (technology) support from their health coach.

Table 1. Intervention schedule.

Week	Study activity	Active hours per day[a], n	Targeted steps per day (above baseline), n	Minimum days meeting step goal, n
0-1	Baseline assessment, randomization, and Fitbit mailed to the participant	—[b]	—	—
2	Establish Fitbit baseline step data	—	—	—
3	Health coaching call	6	1000	3
4	—	6	1000	5
5	Health coaching call	7	1500	3
6	—	7	1500	5
7	Health coaching call	8	2000	3
8	—	8	2000	5
9	Health coaching call	9	2500	3
10	—	9	2500	5
11	Health coaching call	10	3000	3
12	—	10	3000	5
13	Postintervention assessment	—	—	—
14-25	Maintain goals (no study contact)	—	—	—
26	3-month postintervention assessment	—	—	—

[a]An active hour is defined by Fitbit as 250 or more steps during an hour (awake hours only).

[b]Not applicable.

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Fitbit Inspire 3 Wearable Activity Tracker and App

A Fitbit activity tracker and mobile app were used to promote awareness and enable self-monitoring of both activity (steps per day) and inactivity (activity tracker vibrates as a reminder to move each hour). During week 2, participants in the intervention group were mailed the Fitbit Inspire 3 (Google) activity tracker, with instructions for installing the app on their smartphone and for using the Fitbit app. The distinguishing feature of this tracker is an activity reminder, in which the tracker gently vibrates if fewer than 250 steps were taken in the previous 50 minutes and provides a suggestion to take more steps in the next 10 minutes (to achieve a goal of ≥250 steps/hour). Data from the tracker were wirelessly synced to the app. Participants were instructed to wear the tracker during waking hours and were encouraged to check their activity by their app at least once a day. The app includes a daily summary of the total steps and number of active hours (hours with ≥250 steps). The health coach assisted with the installation, reviewing instructions for using the tracker and app, setting goals (steps per day, number of active hours), and checking their progress. If needed, a family member or close friend was included in telephone calls to assist the participant.

Health Coaching Calls

Bilingual research assistants were trained in MI core processes (engaging, focusing, evoking, and planning) and microskills (open-ended questions, affirmations, reflections, and summaries) to promote behavior change and use in their role as health coaches. MI techniques and microskills were used to guide 5 sessions of telephone-based health coaching. While these calls were designed to occur during weeks 3, 5, 7, 9, and 11 (45 minutes for initial 1-2 calls, then 15-20 minutes each), participants were allowed to reschedule due to illness, etc. Key intervention topics and techniques included establishing rapport; eliciting knowledge about the health benefits of physical activity and interrupting sedentary time; assessing motivation, confidence, and perceived importance and barriers to becoming more active; eliciting change talk; and enhancing participants' self-efficacy (competence) and motivation to be more active (eg, small, achievable goals). The health coach also provided tech support to the participants for setting up their Fitbit and using their mobile app. The health coaches regularly checked Fitabase (Small Steps Labs LLC) and sent reminders (telephone, email, or text, depending on the participant's preference) if participants had not synced their Fitbit in 4 or more days or were not wearing their Fitbit (limited or no steps recorded).

Visual Aids for Health Coaching Calls

Participants were mailed visual aids to serve as a reference for discussions with the health coach. The health coaches followed a semistructured guide that corresponded to the visual aids. The initial call included a discussion about the number of daily steps associated with good health in older adults (7000-9000) [75-77] and the benefits of spreading out activity throughout the day (ie, breaking up sedentary time through at least minimal stepping each hour). Participants were asked to rate the importance of meeting the recommended level of daily steps and to provide reasons why it was important for them to be physically active; examples for participants to consider include reducing stress and anxiety, increasing energy levels, enhancing balance, improving sleep quality, etc. After reviewing the baseline Fitbit data, participants were provided with the suggested goals (daily steps and active hours) for the next 2 weeks (Table 1) and examples for adding 1000 steps per day (one 10-minute or two 5-minute brisk walk, one 15-minute leisurely walk, or adding at least an extra 150 steps for 6 hours). The participants identified strategies and created a plan for achieving these goals. Examples for participants to consider included playing music and dancing, walking the dog, parking further from an entrance, etc. While examples were provided, participants were encouraged to choose their own strategies. The calls ended with a review of how to set the step goal and the reminders to move in the Fitbit app. Subsequent calls reviewed the previous 2 weeks and created plans for meeting subsequent goals. For example, participants who achieved their step goal during the previous week might have chosen the study recommended goal (increase by 500 steps), whereas participants who did not meet the goal (eg, due to illness) might have chosen to maintain their previous step goal. Participants may have kept their same strategies or identified new strategies for achieving their goals and then created a plan for the next 2 weeks. Table 2 provides examples of the use of MI and visual aids by the health coaches in the theoretically-guided approach.

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Table 2. Examples of how behavioral theory and motivational interviewing (MI) were used to promote physical activity among older cancer survivors.

Theoretical construct	Health coaching with MI and visual aids
Autonomy support	Visual aids include examples of strategies to increase steps; however, participants select strategies that work best for them. During subsequent health coaching calls, participants decide whether to maintain their step goal or increase it and by how much. The health coach actively emphasizes the individual's own personal control and choice in decisions.
Motivation	MI is a person-centered method of communication for helping to resolve ambivalence around behavior change and enhance an individual's intrinsic motivation to change. Each health coaching call uses MI core processes (engaging, focusing, evoking, and planning) and micro skills (open-ended questions, affirmations, reflections, and summaries) to promote behavior change. For example, the health coaches may call attention to positive progress or evidence of strength and competence (affirmations). Reflections and summaries can be used to focus on the most important reasons for change and the plan of action, thereby facilitating a transition from talk about motivation to talk about action.
Outcome expectations	A visual aid slide during the first health coaching call includes an importance ruler: How important is it to you to be meeting the recommended level of physical activity (scale of 1 to 10; not important to very important)? The follow-up question encourages change talk (versus sustain talk): Why did you say that number and not a lower number?
Self-efficacy and competence	A visual aid slide during each health coaching call includes a confidence ruler: How confident are you that you can meet these goals during the next 2 weeks (scale of 1 to 10; not confident to very confident)? The follow-up question encourages change talk (versus sustain talk): Why did you say that number and not a lower number? The health coach encourages incremental and achievable goals.
Self-monitoring	Participants were taught how to use the Fitbit app to review their daily and weekly progress regarding their step goal and their number of active hours.
Social support and relatedness	Each health coach is assigned participants and provides support and encouragement to their participants throughout the study. The health coach will provide suggestions when asked. In addition, the visual aids include examples of strategies to include other people in physical activities.

Intervention Fidelity

We used evidence-based MI training procedures identified in previous studies [78,79]. The health coaches received an initial 1.5 days (12 hours) of in-person MI training by an experienced MI trainer (STW). Before interacting with participants, the coach completed 4 practice sessions and received feedback through 4 phone supervision sessions. These sessions were spread over 6-8 weeks to allow for further review of materials between feedback sessions. STW coded the sessions for MI fidelity by using the MI Treatment Integrity Coding System (version 4.1) [80] and used this information during supervision sessions. During the study period (15 months), each health coach submitted 1 audio recording and participated in 1 phone supervision per month (months 1-3), then every other month (months 4-15). Health coaches were provided with training on the intervention design, measures, and outcomes. Fidelity to the intervention delivery was ensured through the use of the operations manual, spreadsheet software for tracking day-to-day activities, and weekly team meetings.

Waitlist Control

A waitlist control was selected to help boost retention [81] and balance validity, cost, and time. Participants were asked to maintain their usual lifestyle during the initial 12 weeks. Upon completion of the 13-week assessment, waitlisted participants were mailed a Fitbit Inspire 3, instructions, and visual aids and received the full intervention (Table 1).

Retention

To compensate participants for their time, a US $50 merchandise card was provided for each outcome assessment (US $150 total). In addition, both groups were permitted to keep the Fitbit activity tracker after the study ended to maintain activity (at the time of the intervention, a US $100 value).

Data Collection

Data were collected by mailed packets (activity monitor and questionnaires) and videoconferencing (physical performance tests) at baseline, immediately after the intervention, and at longer-term follow-up (3 months after intervention). The assessment packet included an activity monitor (for objective measurement of steps, LPA, and sedentary behavior), questionnaires, and print instructions for attaching the activity monitor and for completing the remote assessment of physical function. In addition, participants were emailed links to the YouTube videos of the instructions. Participants were instructed to wear the activPAL (PAL Technologies Ltd; using 24-hour protocol) activity monitors [82] for 1 week, consistent with other studies [40,83,84]. At the end of the week, participants completed questionnaires on both sedentary behavior and physical activity to provide context to the objective data. Instructions were provided for returning (through self-addressed stamped mailer) the monitor and questionnaires to study staff. The health coach called to verify receipt of the assessment packet, review the instructions, if necessary, answer any questions, and schedule the remote assessment of physical performance. Participants were provided an option to complete the study surveys online through a REDCap database. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of New Mexico [85]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [85].

Fitabase (Small Steps Labs LLC) was used to collect data from participants' Fitbit trackers. The data collected by Fitabase

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included total daily steps, number of steps per minute, estimated energy expenditure, distance moved, minutes of vigorous, moderate, and light activity, minutes of sedentary time, sleep length and quality (if Fitbit worn overnight), heart rate, and manually entered and automatically detected physical activities such as walking or running. Fitabase also indicated the last day and time each study Fitbit tracker was synced. Each study participant was deidentified with a participant ID.

Based on our earlier work [58], physical performance tests were conducted in the home setting and remotely assessed using videoconferencing software. Participants used their smartphone, tablet, or camera-enabled computer for the remote assessment. If a participant did not have a suitable device, the study provided a smartphone to capture the physical performance tests. Both written and video instructions were provided that demonstrated the performance tests, safety measures, and how to prepare for the videoconference session with the study investigator. The investigator (TB) performed the assessment from a remote location using videoconferencing software (Zoom [Zoom Communications, Inc] [86] or Skype [Microsoft] [87]; participant's choice). During the videoconference, the investigator reviewed the instructions for the tests and timed the tests. A separate software (Snagit [TechSmith]) run on a study computer was used to record the assessments for later viewing for quality control purposes.

Feasibility and Acceptability Outcomes

Although primary enrollment and data capture activities have been completed, final analyses have not yet been completed. For this feasibility study, our goal was to meet the accrual target of 64 inactive, older cancer survivors within 18 months, retain 80% of the sample, and achieve 80% adherence and fidelity to the intervention while minimizing the number of adverse events. Retention will be calculated as the percentage of participants who completed the final assessment. Adherence to the intervention will be calculated as (1) the percentage of participants who complete all 5 health coaching calls and (2) the percentage of days that participants wore their Fitbit during the intervention. Fidelity to intervention delivery will be calculated as the average score on global ratings for MI (scale of 1 to 5; higher scores are better), which includes cultivating change talk, softening sustain talk, partnership, and empathy. The number of adverse events that were attributable, possibly attributable, or not attributable to the intervention were tracked and reported. Satisfaction with the intervention will be evaluated by a 13-item survey that we developed to assess the level of agreement or disagreement (5-point Likert scale, ranging from strongly disagree=1 to strongly agree=5) on questions about the Fitbit activity tracker, the Fitbit app, and the health coach. Example questions include "The Fitbit activity tracker made me more aware of my activity and inactivity during the week," "The Fitbit mobile phone app was easy to use," and "Talking to a Health Coach helped me to identify strategies to be more physically active (get more steps)." Satisfaction with the intervention will be calculated as the average score.

Primary and Secondary Outcomes

The measures and a brief description for each primary outcome, secondary outcome, safety assessments, covariates, and theoretical constructs are provided in Table 3.

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Table 3. Outcomes and measures (T0=week 0 (before randomization); T1=week 13; and T2=week 26).

Outcome, measure, and description		T0	T1	T2
Primary outcome				
Physical function	PROMIS[a] physical function short form (8a): 8 items to assess the ability to perform daily activities ranging from basic care to vigorous activities [88,89].	✓	✓	✓
Secondary outcomes				
Physical performance				
	A total of 2 standard gerontology assessment tests were used to measure physical performance. Both of these tests are included in the CDC[b] STEADI[c] toolkit for the assessment of falls [55].			
	A 30-second chair stand test: number of times a person comes to a full standing position from a chair in 30 seconds; a measure of lower extremity strength and dynamic balance.	✓	✓	✓
	A 4-stage balance test: includes standing in each of four positions for 10 seconds: (1) feet side-by-side, (2) semitandem stand (1 foot slightly behind but touching the other foot), (3) tandem stand (1 foot in front of the other, heal touching toe), and (4) stand on 1 foot.	✓	✓	✓
Physical activity and sedentary behavior				
	Objective measures: Daily LPA[d], MVPA[e], and sedentary behavior were objectively measured before and after the intervention using the activPAL monitor [90]. The activPAL, worn on the thigh, includes both a triaxial accelerometer and an inclinometer (to detect change in posture, ie, sitting vs upright posture) [91-94].	✓	✓	✓
	Operational definitions [91]: (1) Total LPA and MVPA: sum of stepping bouts with a step rate of <100 and ≥100 steps per minute, respectively; (2) total sedentary behavior: sum of all sitting or lying bouts; (3) total steps per day; and (4) total waking hours with ≥250 steps [70,95].			
	Subjective measures: (1) The Godin Leisure-Time Exercise Questionnaire [96,97] provided context for activities that changed in frequency, intensity, and duration during the intervention as objectively measured by activPAL, and (2) the Sedentary Behavior Questionnaire [98] was used to estimate self-reported sedentary activities during a typical weekday and a typical weekend. Response items range from none to 6 or more hours per day for 9 common activities (eg, watching television, using a computer, etc).	✓	✓	✓
Quality of life				
	PROMIS-57 Profile [88]: a combination of short forms designed to assess patient-reported outcomes across a variety of chronic diseases, including cancer [99-102]. It includes 8 items from 7 domains (anxiety, depression, pain interference, fatigue, sleep disturbance, satisfaction with participation in social roles, and physical function) using a 5-point Likert-type scale; 1 item for pain intensity (an 11-point rating scale). Scores are normed to a general population [103].	✓	✓	✓
Safety assessment	Measured by surveys, participants were encouraged to contact the study team immediately for events that occurred between time points.	✓	✓	✓
Fall history	Defined as “unintentionally coming to rest on the ground, floor, or other lower level” [104]. The number of falls, nature of falls, and resulting injuries during the past 6 months were recorded before the remote physical performance assessment to inform safety measures, for example, not safe to perform tests, 2 (instead of 1) people needed to supervise or provide support.	✓	✓	✓
Fall self-efficacy	FES-I[f]: self-reported level of concern about falling either inside or outside the home for various social and physical activities (16 questions) [105,106].	✓	✓	✓
Covariates	Used to characterize the study population or as predictors of adherence or moderators of intervention effects.			
Sociodemographics	Age, sex, race and ethnicity, education, income range, marital status (self-report)	✓		
Health-related behaviors	Smoking status; height and weight to calculate BMI (kg/m^2) (self-report)	✓		
Tech-savviness	A brief survey about the use of and comfort level of using their smartphone (developed for this study). Used to prepare study team members to support study participants through the technological aspects of the study (setting up and using Fitbit and app, videoconferencing).	✓		
Cancer data	Obtained from the New Mexico Tumor Registry (cancer site, stage, age, and year of diagnosis, and summary treatment) and self-report (treatment (yes/no): surgery, chemotherapy, radiation, hormone therapy; year primary therapy completed)	✓		

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Outcome, measure, and description		T0	T1	T2
Comorbidities	OARS[g] Comorbidity Index: assesses the number of chronic medical conditions (n=35) and symptoms (n=8) and whether each condition/symptom interferes with activities (not at all, a little, or a great deal) [107].	✓	✓	✓
Theoretical constructs				
Self-efficacy	Domain specific; we measured confidence for using a Fitbit tracker and app, and increasing the number of active hours and steps.	✓	✓	✓
Self-monitoring	Fitbit data will be used to evaluate self-monitoring, for example, the percentage of days the Fitbit tracker was worn and the percentage of days within 5% of reaching the daily step goal.	✓	✓	✓
Social support	Social Support for Exercise Survey: 10 items using a 5-point scale to measure support from family and friends while making changes to physical activity behavior [108].	✓	✓	✓
Outcome expectations	Multidimensional Outcome Expectations for Exercise Scale: 15 items to assess physical, social, and self-evaluative beliefs about the consequences of being physically active [109,110].	✓	✓	✓
Motivation	BREQ-2[h]: 19 items to assess autonomous motivation on a continuum from amotivation to intrinsic motivation. Was adapted using identical anchors for LPA [111,112].	✓	✓	✓
Autonomy	Perceived Autonomy Support—Sport Climate Questionnaire: 15 items to assess autonomy support of the health coach to characterize the quality of the social environment for influencing motivation [113].	✓	✓	✓

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]CDC: Centers for Disease Control and Prevention.

[c]STEADI: Stopping Elderly Accidents, Deaths, & Injuries.

[d]LPA: light-intensity physical activity.

[e]MVPA: moderate- to vigorous-intensity physical activity.

[f]FES-I: Falls Efficacy Scale-International.

[g]OARS: Older Americans Resources & Services.

[h]BREQ-2: Behavioral Regulations in Exercise Questionnaire.

Statistical Analysis

Power

Using a 2-sided, 2-sample *t* test, with a significance level of .05 and 25 people per arm, we estimated that we would have 80% power to detect a mean difference of 8.1 (SD 10) in physical function scores (a large effect size). To allow for 20% attrition, we planned to enroll 32 participants per arm. This feasibility trial will provide estimates of within-group SDs and between-group differences of physical function scores for the target population. These results will inform the design (sample size, effect size) of a larger trial powered to examine the efficacy of the intervention.

Analysis Overview

Outcome variables violating the normality assumption will be transformed before analyses. The pattern of missing data will be evaluated [114], and the appropriate procedures for multiple imputation will be used. Primary analyses will be performed according to the intent-to-treat principle; as this is a feasibility study, complete case analyses will also be explored. activPAL data will be downloaded using PAL technologies software (version 8) [115] and analyzed using SAS (version 9.4, SAS Institute) and R software (version 3.4.3; R Foundation for Statistical Computing). Raw and event data (start and stop time for sitting or lying, standing, and stepping) will be processed using standard methods, for example, determining valid wear time [116-118], threshold values for activity intensity [119,120], etc. A valid day is defined as 10 or more hours of wear during awake time. Consistent with the intention-to-treat principle and similar to other recent trials [53,54,121], participants with at least one valid day of activPAL data at baseline will be included in the analyses. If needed, a sensitivity analysis will be conducted that will exclude participants with fewer than four valid days of activPAL data. Quality controls (daily logs and visual examination of heat maps) will be used to check the classification of accelerometer data. Accelerometer methods will be published according to guidelines [122-124].

Preliminary Estimates of Effect Sizes

We hypothesize that physical function scores will improve in the intervention group compared with the control group. We will calculate means and precision estimates for between-arm differences in physical function scores at each time point. A linear mixed-effects model will be used with group, time, and group-by-time interaction, adjusted for ethnicity, rural or urban status, and baseline values as needed. The appropriate variance-covariance structure will be selected to account for the potential correlation among repeated measurements from the same participant. The primary test of interest is the group-by-time interaction, indicating whether there was a difference between groups in the primary outcome over time. Similar analyses will be conducted for secondary outcomes.

Process Evaluation

Acceptability and satisfaction related to the intervention will be evaluated by a mailed survey. Process data and other study-related outcomes will be reviewed to identify the next

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steps and strategies to ensure the most appropriate design and methods for the future, larger RCT, with a potential for broad dissemination and implementation.

Ethical Considerations

The study protocol and materials were approved by the University of New Mexico Health Sciences Center Institutional Review Board (17-335). Written informed consent was obtained from all study participants. The trial was registered on ClinicalTrials.gov (NCT05582889).

Results

Enrollment began in October of 2022 and ended in June of 2023. The study enrolled and randomized the targeted number of 64 participants: 40% rural and 33% Hispanic. Data collection was completed in March of 2024. Data analyses for the primary and secondary outcomes are expected to be completed by December 2024. The results of these analyses will be reported in a separate manuscript.

Discussion

Expected Findings

Despite decades of research on physical activity, there are few interventions that are effective and accessible to older cancer survivors with comorbidities and functional impairment. Most studies have focused on MVPA, which is difficult for some older survivors to adopt and especially to maintain [125]. Also, academic center– or clinic-based interventions have limited potential for dissemination. Evidence suggests that LPA also confers physical and psychosocial health benefits [29,33,35,126,127], while sedentary activity is associated with deleterious effects [21-24,28,128]. Thus, we proposed a remotely delivered intervention focused on increasing LPA and reducing sedentary behavior throughout the day—likely more obtainable goals—for maintaining and improving physical function in vulnerable populations. By reducing barriers to participation, a remote delivery and assessment approach can expand the reach to underserved cancer survivors who are older or from rural areas.

One of the limitations of this study is that it only included a 3-month follow-up of activity. A future study to examine efficacy in a fully powered trial will include a longer follow-up period. Although our goal was to enroll 50% Hispanic and 50% rural cancer survivors, our actual enrollment was 33% Hispanic and 40% rural. More time and resources would have been needed to achieve our original goal. While heterogeneity exists between cancer types, the common features targeted by this intervention are physical functional impairment and a physically inactive lifestyle, which are not cancer-type specific. This broad-based sample of older cancer survivors improves generalizability and potential for widespread dissemination. By design, this study is focused on promoting LPA, primarily through walking, as opposed to the currently recommended guidelines of 150 minutes per week of moderate-intensity physical activity (or 75 minutes per week of vigorous-intensity physical activity) plus 2 days of resistance training. However, even the guidelines mention “some activity is better than none.” Our proposed approach could lay the foundation for further increases in activity intensity or duration with the potential to achieve even greater health benefits.

Conclusion

The proposed intervention is responsive to the call for studies that include more diverse cancer survivor populations [11,43], rigorously designed trials to evaluate the benefits of increasing LPA and reducing sedentary behavior in older adults [129-131], and interventions with the potential for dissemination and implementation in a variety of settings [11]. The results of this trial will provide information on the feasibility of implementing this intervention in the target patient population, as well as data that will provide information about the potential impact of the intervention on the outcomes. Both of these outcomes will inform the design of a larger RCT to fully test a physical activity intervention in an older cancer survivor population. Rigorously designed trials such as this will help elucidate the amount of LPA and reduction in sedentary behavior needed to improve physical functioning and other health outcomes in older cancer survivors with comorbidities.

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Data Availability

Deidentified data will be made available from CKB upon reasonable request. Data to be provided will be group-level data unless participant-level data can be released without revealing an individual’s identity. Please contact CKB at CiBlair@salud.unm.edu. Data will not be available until the primary and secondary results have been published.

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Authors' Contributions

CKB, STW, CP, TB, AYK, WD-W, VSP, and SD conceived the study and participated in the design of the protocol and development of the intervention. CKB, CP, TB, LB, and EB participated in the acquisition of data. CKB drafted the manuscript. UB-G, SWT, CP, TB, LB, EB, BT, CK, AYK, WD-W, ALM, CLW, VSP, and SD provided critical review of the manuscript for important intellectual content. CKB obtained funding. UB-G, SWT, CP, TB, BT, CK, ALM, and CLW provided administrative, technical, or material support. CKB, STW, and CP performed supervision. All authors approved the final manuscript for submission.

Conflicts of Interest

None declared.

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Abbreviations

LPA: light-intensity physical activity
MI: motivational interviewing
MVPA: moderate- to vigorous-intensity physical activity
MY Health: Move for Your Health
NMTR: New Mexico Tumor Registry
RCT: randomized controlled trial
SEER: Surveillance Epidemiology and End Results

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Protocol

Examining Share plus—A Continuous Glucose Monitoring Plus Data-Sharing Intervention in Older Adults and Their Care Partners: Protocol for a Randomized Control Study

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Abstract

Background: Older adults with type 1 diabetes (T1D) are increasingly turning to care partners (CPs) as resources to support their diabetes management. With the rise in diabetes technologies, such as continuous glucose monitoring (CGM), there is great potential for CGM data sharing to increase CP involvement in a way that improves persons with diabetes' glucose management and reduces distress.

Objective: The specific aims of this paper are to (1) evaluate the feasibility, usability, and acceptability of the Share plus intervention compared to the CGM Follow app plus diabetes self-management education and support; (2) evaluate the effect of the Share plus intervention on time-in-range (TIR; primary outcome) and diabetes distress (secondary outcome); and (3) explore differences between groups in person with diabetes and CP dyadic appraisal and coping, quality of life, diabetes self-care, and CP burden at 12 and 24 weeks and associations of dyadic variables on outcomes.

Methods: This is a protocol for a feasibility, pilot randomized controlled trial. Older adults with T1D and their CP (N=80 dyads) will be randomized 1:1 to the Share plus intervention or Follow app plus diabetes self-management education. The trial will include a 12-week active intervention to determine the change in primary (TIR) and secondary (diabetes distress) outcomes, followed by a 12-week, observation-only phase to examine maintenance effects. The evaluation is guided by the Dyadic Coping Model. Patient-level effectiveness outcomes (TIR, hemoglobin A_{1c} [HbA_{1c}], diabetes distress, diabetes appraisal, coping, quality of life, diabetes self-care behaviors, and CP burden) will be assessed, using patient-reported outcomes measures and a home HbA_{1c} test kit. Patient- and CP-level acceptability and feasibility will be assessed using surveys and interviews. Quantitative feasibility, acceptability, and usability data will be described using frequencies and percentages. Acceptability will be summarized based on Likert questions and open-ended questions. Usability will be examined separately for the intervention and control groups based on the System Usability Scale, with a study benchmark of ≥68 indicating good usability. TIR will be computed based on 2 weeks' worth of data at baseline (prior to intervention) and 2 weeks each after the intervention (week 12) and at follow-up (week 24).

Results: Recruitment started in August 2023 and enrollment began in November 2023. To date, 24 participants have been enrolled in this study. We expect to conclude this study in March 2026 and expect to disseminate results in March 2026.

Conclusions: To our knowledge, this will be the first pilot randomized controlled trial to evaluate both feasibility and effectiveness outcomes for the web-based, platform-delivered Share plus intervention for older adults with T1D and their CP. This research has implications for CGM data sharing in other age groups with T1D and type 2 diabetes.

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Trial Registration: ClinicalTrials.gov NCT05937321; https://clinicaltrials.gov/study/NCT05937321
International Registered Report Identifier (IRRID): DERR1-10.2196/60004

(JMIR Res Protoc 2024;13:e60004) doi:10.2196/60004

KEYWORDS

type 1 diabetes; T1D; older adults; continuous glucose monitoring; data sharing; dyadic coping; diabetes management; diabetes self-care; glucose monitoring; quality of life; mobile phone

Introduction

Background

Type 1 diabetes (T1D) is a significant public health problem, with increasing numbers of adults now living into late adulthood [1]. T1D self-management requires a number of daily diabetes tasks including checking blood glucose (either through a blood glucose meter or a continuous glucose monitor [CGM]) and administering insulin to account for changes in food intake and exercise. Older adults with T1D are at increased risk for hypoglycemia, hyperglycemia, and glucose variability that may result in seizures, falls, and myocardial infarctions [2,3]. These risks are due to a number of factors including reduced awareness of hypoglycemic warning symptoms; reduced hormonal counterregulatory response; and changes in dexterity, visual acuity, cognitive function, depression, and anxiety that may prevent affected individuals from taking corrective actions [3,4].

Care partners (CPs; eg, spouse, adult child, romantic partner, and friend) can serve as important resources for older adults living with T1D in reducing these risks to self-management [5-9]. Over half of the adults with diabetes have an unpaid CP who regularly assists with diabetes management [8], and age-related changes often increase persons with diabetes' need for CP assistance. One tool that is available to persons with diabetes and their CPs to reduce harmful glucose levels is real-time CGM. A CGM transmits glucose trend data to the smartphone of persons with diabetes and provides predictive alarms before problematic and potentially dangerous hypoglycemia and hyperglycemia levels [10]. Recommendations for standards of care in diabetes [11] now include the use of CGM with older adults with T1D to address increased risks of hypoglycemia. Persons with diabetes are given glucose goals of 70-180 mg/dL, and the percentage of time spent within this range is called time-in-range (TIR), an important metric for evaluating glucose targets [12,13]. In older adults, CGM is effective at decreasing glucose variability, with older adults highly adherent to wearing CGMs [14,15]. The data provided by the CGM can now be shared with a CP's smartphone to facilitate diabetes support for the person with diabetes [16]. Yet, few older adults and CPs are sharing data with CGMs [17].

There is great potential for CGM data sharing to increase CP involvement in a way that improves glucose targets and reduces distress for persons with diabetes. For instance, the free data-sharing app, Dexcom Follow [18], allows CGM readings to be displayed on the smartphone or smartwatch of persons with diabetes and their selected CPs. Follow also allows the user to see CGM glucose levels and receive predictive hypoglycemia and hyperglycemia alerts. Additional apps such as the free Dexcom Clarity app [19] use the data from CGM to create glucose data reports to allow persons with diabetes and their selected CPs to identify glucose patterns and trends and has also been associated with a greater quality of life (QoL) when reports are viewed with a CP [14]. However, few older adults share their CGM data or review clarity reports with a CP. Data from the Wireless Innovation for Seniors with Diabetes Mellitus trial showed that only 9.2% of older adults with T1D used data sharing, and only 32% used their smartphones to monitor their CGM data [15]. In our preliminary studies, older adults with diabetes reported an increased perceived need to have others monitor their glucose levels for safety purposes [20], but few persons with diabetes are adopting this technology.

This intervention was designed to maximize the use of data sharing by persons with diabetes and their CPs. Our prior work identified several barriers to using data sharing involving dyadic communication that involved patients' and partners' different expectations regarding family involvement [20]. Persons with diabetes frequently regarded diabetes as "their own illness," whereas spouses viewed the illness as more shared [21,22]. Improving collaboration and communication among those with type 2 diabetes [23] was associated with lower distress in persons with diabetes and their partners, higher satisfaction, and improved glycemic levels (among those with moderately elevated hemoglobin A_{1c} [HbA_{1c}]).

The intervention is guided by the Dyadic Coping Model (Figure 1) [24,25], a widely used framework for how individuals with chronic illness and CPs can be involved in chronic illness management. As applied to diabetes, dyadic coping involves two components: appraisal of the illness and coping efforts. Appraisal refers to whether the persons with diabetes and their CPs perceive diabetes as "our" problem versus "my" or "your" problem. Shared appraisal can initiate and facilitate coping strategies that are more collaborative to address diabetes stressors that are also perceived as shared [26]. When a person with diabetes appraises diabetes as an illness that is shared with a CP, persons with diabetes report more collaborative involvement from their spouse, greater relationship satisfaction, and less regimen distress [22]. Challenges can arise when one person in a dyad (eg, the person with diabetes) appraises diabetes as their own issue to deal with and the CP engages in high levels of involvement (eg, wishes to be very involved in data sharing). That is, collaborative involvement of the CP may be detrimental when the person with diabetes views diabetes as only their illness to deal with and does not consider its effects on the CP. The Dyadic Coping Model supports the value of a CP's collaborative involvement in a person with diabetes' glucose monitoring via CGM.

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Figure 1. Dyadic coping process affected by Share plus intervention (reproduced from Bristol et al [27], which is published under the terms of Creative Commons Attribution 4.0 license [28]). CP: care partner.

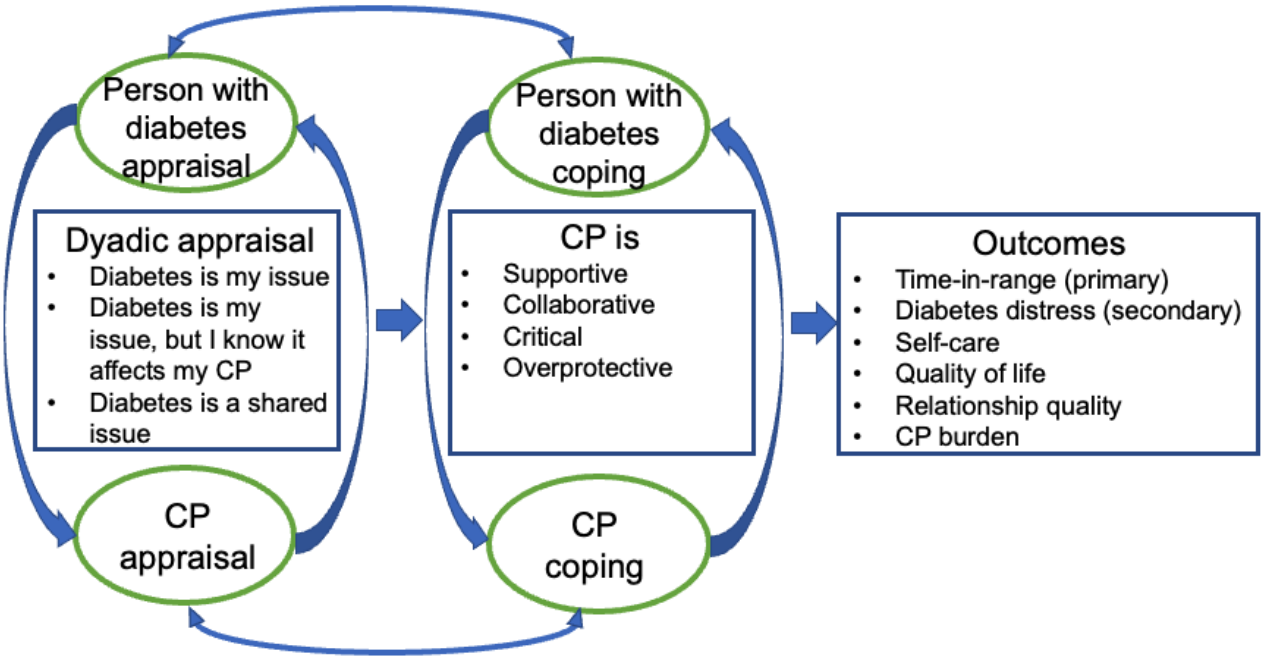

The Share plus intervention framed by the Dyadic Coping Model begins with a discussion of how persons with diabetes and CPs appraise diabetes (eg, patients alone or shared with CP) and the next communication regarding the preferred ways of involving the CP in data sharing (Figure 1). For instance, the person with diabetes is asked what words would be helpful and supportive from their CPs in response to a high or low glucose alarm and what might be viewed as critical or overprotective. Next, CPs are asked if this communication is acceptable to them and if they are willing to provide this requested support. In our preliminary studies, persons with diabetes who were initially hesitant to share their glucose data reported high satisfaction at 12 weeks [29,30]. These discussions facilitate an understanding of diabetes as a shared illness and the collaborative and supportive strategies that the CP can engage in. Moreover, these discussions match data-sharing strategies that fit with a person with diabetes' appraisal of diabetes and are viewed as supportive rather than unsupportive. Such discussions will facilitate an action plan that will best align with the appraisal process of the person with diabetes and their CP.

Study Objectives

This study aims to (1) evaluate the feasibility, usability, and acceptability of the Share plus intervention compared to Follow plus diabetes self-management education (DSME); (2) evaluate the effect of the Share plus intervention on TIR (primary outcome) and diabetes distress (secondary outcome); and (3) explore differences between groups in person with diabetes and CP dyadic appraisal and coping, QoL, diabetes self-care, and CP burden at 12 and 24 weeks and associations of dyadic variables on outcomes.

Methods

Study Design

This study will use a 1:1 randomized controlled trial to conduct a pilot test of 80 dyads to compare the Share plus intervention to the Follow plus DSME intervention. The trial will include a 12-week active intervention to determine the change in primary (TIR) and secondary (diabetes distress) outcomes, followed by a 12-week, observation-only phase to examine maintenance effects. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines were used in reporting this study [31].

Setting

This clinical trial will be conducted in Utah, and participants will be recruited at the state level and the national level using telehealth.

Sample and Recruitment

Persons with diabetes and CPs are actively being recruited from 3 major health care systems in Utah in which we have identified champions who have assisted with recruitment in our preliminary studies. The University of Utah Enterprise Data Warehouse will be used to identify eligible persons with diabetes. An opt-out strategy will be used using letters, postcards, emails, and SMS text messages. Additionally, the Electronic Data Warehouse will be used to build a recruitment dashboard allowing the research team to reach out to contact high-volume providers to inform them of the study and to recruit participants in person before or after clinic visits.

Recruitment inside and outside of Utah will include (1) digital marketing strategies and (2) diabetes clinician and provider networks. Digital marketing strategies include posting to T1D

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social media groups. Professional groups, such as the Association of Diabetes Care and Education Specialists (ADCES), will also be contacted to post information and digital flyers about the study. We are committed to reaching racial or ethnic minorities at rates at least equivalent to their proportion in our catchment area population [32] as required by National Institutes of Health policy [33] and by our own strong commitment to principles of equity and social justice.

Eligibility Criteria

Participants with diabetes will be eligible if they (1) are aged 60 years or older, (2) have a T1D diagnosis (may add more detail here), (3) are currently using CGM, (4) have HbA_{1c} ≥7.5 and ≤11%, (5) are able to read and write in either English or Spanish, (6) are able to manage diabetes with respect to insulin administration and glucose monitoring (which may include assistance from a CP), and (6) are naïve to using the Follow app and are willing to use the Follow app. Participants with or without an insulin pump are eligible. Participants will be excluded if they have (1) a life expectancy estimated at <1 year, (2) extreme visual or hearing impairment that would hinder the ability to use CGM, (3) stage 4 or 5 renal disease, (4) a history of psychiatric or psychosocial issues that could limit adherence to required study tasks, or (5) a Montreal Cognitive Assessment score <19 indicating moderate to severe dementia.

CP participants will be eligible if (1) the participant with diabetes identifies them, (2) they are aged 18 years or older, (3) they are able to read and write in either English or Spanish, and (4) they are willing to participate in a data-sharing telehealth intervention study with the participant with diabetes. CPs will be excluded if they have a self-reported diagnosis of moderate or severe dementia or other medical conditions that make it inappropriate or unsafe to fulfill the role of a CP. CPs will not be directly recruited.

Group Randomization

Persons with diabetes (n=40) and CPs (n=40) who meet the study criteria and agree to participate will be asked to sign an informed consent with a digital signature. The persons with diabetes will be randomly assigned to 1 of 2 groups (40 dyads in the Share plus intervention group and 40 dyads in the Follow plus DSME group) using a computer-generated schedule of randomly permuted blocks of sizes 2, 4, and 6 to minimize knowledge of the next participant's assignment. Group allocation will be executed in REDCap (Research Electronic Data Capture; Vanderbilt University).

Description of Intervention and Education Groups

Share plus Intervention

Overview

The Share plus intervention will be delivered by Certified Diabetes Care and Education Specialists (CDCESs) over three 60-minute sessions using a Health Insurance Portability and Accountability Act (HIPAA)–compliant Zoom (Zoom Video Communications) meeting platform with audio transcription, with 2 additional dyad phone calls to reinforce the counseling sessions (Table 1). The 3 Share plus intervention sessions introduce new and increasingly advanced educational material and are designed to overcome the persons with diabetes and CPs' reluctance in data sharing and to improve diabetes management. This includes training in dyadic CGM communication and problem-solving, leading to a data-sharing action plan.

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Table 1. Intervention and education group activities.

Week	Intervention group—over the web with Dyad Follow + Share plus	Control group—over the web with Dyad Follow + DSME[a]

0	• Baseline
	  • CGM[b] data collection for 14 days; no active intervention
	  • Survey and home HbA_{1c}[c] kit completion
	  • Set up Clarity to allow access to data
		• Baseline
		  • CGM data collection for 14 days; no active intervention
		  • Survey and home HbA_{1c} kit completion
		  • Set up Clarity to allow access to data

2	• Start Share plus intervention
	  • Set up the Follow app
	  • Start the Share plus intervention
	  • Communication and problem-solving strategies
	  • Detailed action plan including glucose targets
		• Start usual care
		  • Set up the Follow app
		  • Two education handouts provided covering ADCES7[d] self-care education topics: Monitoring and Taking Medication

3	• Dyadic phone call • Reinforce the Share plus intervention and provide technology support	__[e]

4	• Share plus intervention + glucose pattern management with focus on food choices and healthy eating
	  • Review communication and problems
	  • New communication content
	  • Revise action plan as needed for communication and problem-solving hypoglycemia and hyperglycemia
	  • Dyadic glucose pattern management training using Clarity, set automatic Clarity downloads
	  • Dyad set goals for regular times to discuss glucose trends and problem-solving,
		• Usual care intervention
		  • Review goals and progress
		  • Two education handouts provided on ADCES7 topics: Reducing Risks and Health Eating

6	• Dyadic phone call • Reinforce the Share plus intervention and provide technology support	—

8	• Share plus Intervention + glucose pattern management with lifestyle (exercise, stress, illness, etc)
	  • Review communication and problems
	  • Dyadic glucose pattern management using Clarity
	  • Dyadic review of glucose targets after an in-depth analysis of CGM data and dyadic treatment strategies to improve glucose TIR[f]
		• Usual care interventions
		  • Review goals and progress
		  • 3 education handouts ADCES7 handouts on Being Active, Problem Solving, Healthy Coping

12	• Data collection—end of active intervention
	  • Measures and home HbA_{1c} kit completion.
	  • Retrieve TIR data from Clarity
		• Data collection—end of active intervention
		  • Measures and home HbA_{1c} kit completion
		  • Retrieve TIR data from Clarity

24	• Data collection—end of observation phase
	  • Measures, home HbA_{1c} kit completion, Clarity download
		• Data collection—end of observation phase
		  • Measures, home HbA_{1c} kit completion, Clarity download

[a]DSME: diabetes self-management education.

[b]CGM: continuous glucose monitoring.

[c]HbA_{1c}: hemoglobin A_{1c}.

[d]ADCES: Association of Diabetes Care and Education Specialists.

[e]Not applicable.

[f]TIR: time-in-range.

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Step 1: Shared Appraisal Assessment

Dyads are asked how they appraise diabetes with the following question: "When you think about diabetes, is it: (1) my issue to deal with as an individual, (2) my issue but I know it affects my CP, or (3) a shared issue." The CPs are asked the same question, but "my" is substituted with "his or her." A follow-up question will be asked, "Help me to understand why you selected this response." If a person with diabetes or CP views diabetes as their own, they are asked to consider something that was shared. The CDCES explores why it is shared and if it is easier to work on the problem together than alone. Next, persons with diabetes and CPs are each asked about their confidence in sharing glucose data. Using scripted motivational interviewing questions, persons with diabetes and their CPs are asked to discuss their answers. The objective of this discussion is to determine the initial comfort level with CGM data sharing within the dyad.

Step 2: Communication

Dyads are asked how comfortable they feel about data sharing. Examples are provided about how other persons with diabetes have described the benefits of sharing their diabetes, such as an increased sense of teamwork, support, QoL, and decreased diabetes-related burden. The barriers to sharing glucose levels are also identified (eg, glucose levels are private and the person with diabetes does not want to be judged). The person with diabetes next identifies effective and ineffective communication strategies around sharing hyperglycemia and hypoglycemia. The person with diabetes is asked (1) how they feel about their partner seeing their glucose levels and any concerns they have about sharing their glucose data; (2) how they would like their CP to respond to their glucose numbers, and specifically what words or actions are viewed as supportive and helpful and what is unhelpful, nagging, or controlling behavior; and (3) if or how they want their CP to help them to figure out the cause of a low or high glucose level. Education is provided about steps for clear communication. Finally, the CP is asked how they feel about this type of communication and if it is acceptable. The objective of this discussion is to explore supportive and unsupportive conversation strategies and foster their commitment to data sharing.

Step 3: Problem-Solving

The dyad is asked to work together to set alarms on the smartphones of the persons with diabetes and CPs (they can be set differently), set the volume of alerts (eg, can cause frustration), or use vibrate mode. First, CPs are asked to confirm their willingness to be a safety net for emergencies and look at alarms. The persons with diabetes are asked to acknowledge their willingness to look at their alarms. Next, dyads are coached to identify the expectations and length of waiting time before the CP should contact the person with diabetes for a concerning glucose level and problem-solve an agreeable strategy for different alarms. For example, when a CP gets a low alarm with two arrows indicating a more rapidly decreasing glucose level, how long should they wait to contact the person with diabetes; how long should they wait for reply; and if there is no reply, what action should they take? This discussion also includes the preferred mode by which the CP will contact the person with diabetes (eg, phone call, text, and email). The dyad is also asked to discuss glucose trends once per week and then problem-solve if they will do this, when, and how. The objective of this third step is to guide the dyad in making and agreeing upon boundaries around data sharing.

Step 4: Action Planning

Dyads are asked to agree in writing how, when, and if they would like to be contacted for specific alarms as outlined in step 3. The type of communication that is identified as supportive responses to hyperglycemia and hypoglycemia are recorded in the action plan from step 2. The action plan is documented and given to the dyad to set clear expectations around data sharing.

Step 5: Re-evaluating, Practicing, and Advancing

At weeks 4 and 8, dyads will review their experience using data sharing and discuss their concerns regarding communication, dyadic problem-solving around hypoglycemia and hyperglycemia, and alarms, so that they can update their plan. Supplemental information is provided (as needed) on communication strategies (eg, listening, reframing, being positive, and providing appreciative feedback). Dyads are asked to practice problem-solving skills related to their biggest identified problem in the previous weeks with data sharing. The Clarity app produces several reports, including an ambulatory glucose profile that helps to determine glucose trends and patterns that can be downloaded on a computer or smartphone. The CDCES will have data-driven conversations from these reports at each session, and through shared decision-making, will develop a plan to help increase TIR to 70-180 mg/dL. In session 2, the CDCES will instruct the dyad on how to use the Clarity app to download reports of glucose trends, how to review glucose patterns, and strategies to address hypoglycemia or hyperglycemia patterns with a focus on food choices and healthy eating. Dyads will be instructed on setting up weekly automatic Clarity downloads and asked to set aside time to discuss these reports. In session 3, the CDCES will review the Clarity download with a new focus on glucose pattern management with lifestyle changes (exercise, stress, sleep, and illness). The action plan will be revised as needed at each session.

Handouts are provided at baseline to the dyads that support topics in each Share plus session. The format of the handouts includes education on topics such as hypoglycemia, CGM-specific actions to take to treat hypoglycemia, and tips for CPs on how to be supportive when the person with diabetes is experiencing hypoglycemia.

Overview of Education Group—Follow plus DSME Intervention

Dyads in the Follow plus DSME Intervention will receive 3 diabetes education sessions (Table 1). The CDCES will cover topics from the ADCES7 educational curriculum including healthy coping, healthy eating, being active, taking medication, reducing risks, and problem-solving in 3 sessions. ADCES handouts are provided at baseline on the ADCES7 educational topics.

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Outcomes and Measures

Feasibility, usability, and acceptability measures will be collected throughout the study, both quantitatively and qualitatively. Feasibility for this study is operationalized to include the ability to recruit the target population, retention of participants, participant adherence to the study protocol, CDCES fidelity in delivering the intervention, and the intervention dose provided. Our team will measure intervention fidelity as a continuous process to ensure that intervention components are delivered in a standardized way through in-depth training and standardized protocols. This will include a 10% review of Zoom intervention and control sessions conducted by 2 CDCESs. Data will be collected and reviewed in an ongoing basis for attendance, adherence to the intervention script, delivery of assigned topics, and self-report of intervention delivery and completion per study protocols. The research team will use an observation form to collect intervention fidelity data on a 4-point scale (from 0=none to 3=high level of intervention fidelity) to monitor the intervention sessions. This observation form will be used to counsel CDCESs and to monitor for any intervention delivery problems. Usability includes measures of processes to complete the intervention and a measure used to examine the reliability and validity of the telehealth and Share plus technology intervention. Process measures include appointment attendance, length of all sessions, number of unscheduled appointments for extra assistance, and number of telephone calls for support by the persons with diabetes or CPs. Engagement data include persons with diabetes and CPs' frequency of viewing glucose data and responding to alarms; intent to continue using Follow; and a tailored System Usability Scale, to assess reliability or validity of the telehealth and Share plus technology intervention and to determine usability between groups and against System Usability Scale benchmarks. Acceptability will include persons with diabetes and CPs' satisfaction with the Share plus intervention. Acceptability will be assessed using a 7-item Likert scale and 4 open-ended questions developed in our preliminary studies.

The 3 Share plus sessions will be conducted on HIPAA-compliant Zoom and recorded and transcribed using the meeting transcription feature. Dyadic data will be collected qualitatively in our intervention feasibility data and quantitatively. The qualitative feasibility intervention data includes collaborative involvement, cooperative actions, challenges, supportive or critical communication, problem-solving discussions regarding hyperglycemia and hypoglycemia, solutions discussed then implemented, unsuccessful and successful solutions, and barriers to protocol completion. Quantitative measures usability measures include process measures such as appointment attendance, length of all sessions, number of unscheduled appointments for extra assistance, and number of telephone calls for support by the persons with diabetes and CPs. Engagement data include persons with diabetes and CP's reported frequency of viewing glucose data, responding to alarms, and intent to continue using the Follow app. Other quantitative measures will be available at baseline and at 12 and 24 weeks, including interpersonal processes such as diabetes appraisal [22], social support [34], relationship quality [35], diabetes self-care [36], CP burden [37], QoL [38], and percentage of protocol completion. The primary outcomes are TIR and diabetes distress [39] and partner diabetes distress [40]. CGM data will be collected from the Clarity reports for 14 days at each time point (Clarity website stores data continuously). Other descriptive measures include glycemic metrics from CGM data [41].

Data Management

All data will be entered into the REDCap database, with data storage on a secure, dedicated research server. CGM data will be collected from the Clarity reports for 14 days each at baseline, 3 months, and 6 months. All individuals involved in screening and data entry will be trained to use the database. The research team and the principal investigator will review entered data for completeness and accuracy.

Ethical Considerations

The study procedures were approved by the University of Utah Institutional Review Board (NIDDK Share plus: Continuous Glucose Monitoring with Data Sharing in Older Adults with T1D and Their Care Partners, 00160673). Consistent with best practices in research, informed consent will be collected from the participants, and they have the ability to opt out at any time. All data will be deidentified to protect the privacy of participants. Participants will be compensated US $50 at baseline, 12 weeks, and 24 weeks.

Statistical Methods and Analysis

Study Aim 1 Analysis

Quantitative feasibility, acceptability, and usability data will be described using frequencies and percentages. Acceptability will be summarized based on Likert questions and open-ended questions. Usability will be examined separately for the intervention and control groups based on the System Usability Scale [42], with a study benchmark of 80% or more of participants having a score of ≥68 indicating good usability. The qualitative data from intervention transcripts will be checked for transcription accuracy. Next, feasibility data will be qualitatively coded, line-by-line, using principles of qualitative thematic analysis [43,44]. Codes from a codebook will be compared, contrasted, and collapsed to develop corresponding themes [45-47].

Study Aim 2 Analysis

Our primary research question asks if the percentage of TIR (70-180 mg/dL) will be significantly higher in the Share plus versus the control group. TIR will be computed based on 2 weeks' worth of data at baseline (prior to intervention) and 2 weeks each after the intervention (week 12) and at follow-up (week 24). Primary efficacy evaluation expectation would show no difference for percentage of TIR at baseline but improvement in the Share plus condition at 12 weeks in comparison to the control. Further, improvement at 24 weeks in comparison to control would be suggestive of a maintained benefit. We will assess the efficacy of our intervention for percentage of TIR using a multilevel model with a random intercept. Time will be captured through 2 dummy codes treating the baseline as the referent. The significance and direction of the first dummy code capture change from baseline to 12 weeks. The significance and

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direction of the second dummy code capture change from baseline to 24 weeks. Condition will then moderate these effects as a means to determine the efficacy. Follow-up analyses will compare 12 to 24 weeks if some efficacy is still found at 24 weeks in comparison with baseline. Exploratory analyses will include examining age, duration of T1D, education level, and number of complications as covariates. In all cases, mean differences along with 95% CIs will be reported. All tests will be evaluated using α=.05 (two-tailed).

Study Aim 3 Analysis

Our exploratory question asks what differences in person with diabetes and CP dyadic appraisal and coping, QoL, diabetes self-care, and CP burden will be found between the Share plus intervention versus the control group. We will explore differences between the groups on these measures, analogous to the multilevel models in study aim 2, separately for persons with diabetes and CPs. Exploratory evaluation will be performed through a between-by-within interaction with the expectation of there being no difference for measures at baseline but significant differences between the two conditions at 12 and 24 weeks. For the second half of the aim, we will explore questions like "Does improvement in self-care behaviors and dyadic relationship quality lead to improvements in persons with diabetes' TIR?" In this case, we will use regression models with persons with diabetes' TIR at 24 weeks regressed on baseline TIR and difference change score of self-care at 12 weeks minus baseline. Interaction terms with treatment will be included to look at the impact of the intervention on these associations. While we recognize that the study is underpowered for formal analysis, these preliminary trends can inform future fully powered dyadic and mediation analyses to determine the underlying processes that are influenced by the intervention.

Power and Sample Size

Power analyses were conducted in G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf) based on population-level values. It will parallel the results of a Monte Carlo study as long as there is minimal missing data and assumptions (eg, normality) are met. We deemed these acceptable assumptions for the proposed study. Power calculations were based on the *F* statistic from within-by-between, mixed design, repeated-measures ANOVA. We stipulated an n=80, power=0.80, and α=.05 with 3 repeated-measures time points and 2 between-level groups. This parallels aims 2 and 3, examining for an intervention by time interaction such that no difference is expected at baseline, but a difference should be detectable at 12 and 24 weeks. The sample size allows us to detect an *F* of 0.15, which corresponds to a *d*=0.3, which falls into the small to moderate effect size range following Cohen's suggested benchmarks. This would be sufficient given that we wished to detect a minimally important difference of ≥5% improvement in TIR, which with an SD of 20% corresponds to Cohen *d* of 0.25. Detecting a smaller effect size even with a larger sample size would not have as much clinical utility. Analyses and power calculations are similar for the diabetes distress scale. With a clinically meaningful change of 0.5 points and an SD of 1.5-2.0, this corresponds to *d*=0.25 to *d*=0.3. Therefore, the power to detect *d*=0.3 as described above for TIR will also be sufficient to detect a meaningful change in the distress scale. For both sample size calculations, there is minimal loss in effect size detection with losing as much as 20% of the expected sample size. This implies that we should be fairly robust to power loss due to attrition, technical issues, or other reasons for expecting incomplete data, though data loss should be fairly minimal for TIR, with the common occurrence being technical issues that might lead to 2-3 of the days lost for calculating % out of range. Of note, given that we will use *Best Linear IMPutation* to impute missing data, this, therefore, provides a conservative estimate of power and sample size.

Missing Data

The proposed analyses will be based on all available observations in combination with multiple imputations to avoid distorting variance or inducing bias [48]. We operationalize adherence as the mean hours that CGM is worn per day. The CGM r package *iglu* [49,50] uses linear interpolation for customizable small windows of missing data (eg, 20 min) within the hours specified. For longer periods of missing data beyond 20 minutes, the data will not be interpolated by iglu as this may bias results, based on current recommendations for CGM [51]. Instead, we will use the *Best Linear IMPutation* program, which can generate a fully conditional multiple imputation solution for multilevel data structures [51]. The missing-completely-at-random test will be used to identify necessary imputation predictors. This methodology should be efficient for both missing at random and missing completely at random circumstances. Missing data patterns will be examined and discussed by the team experts to consider if any may be suggestive of nonrandom missingness. Similar procedures will be applied to the validated behavioral measures.

Data Monitoring

Our team has developed a study operations manual and an intervention manual building on the manuals developed in our feasibility studies [29,30,52]. These manuals are used to ensure maximum compliance and protection with good clinical practices for research and include processes such as recruitment, informed consent, and protection of personal health information and video data. Participants complete electronic surveys using a web link to REDCap, a HIPAA-compliant, web-based application hosted at the University of Utah Center for Clinical and Translational Science Institute, which securely stores and protects data. No names appear on any surveys and will only be used by the study team. The qualitative data collected from the Zoom educational sessions will be entered into REDCap by trained research assistants. These data are backed up continuously and protected by the University of Utah computer security systems.

CGM data are collected from Clarity [19] reports for 14 days at each time point and are stored in REDCap. The CDCESs access Clarity reports at each Share plus intervention session to provide dyadic coaching.

HbA_{1c} data are being collected using HbA_{1c} test kits, which require one drop of blood (similar to checking a glucose level) [53]. Participants mail the HbA_{1c} kits directly to the laboratory,

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which is traced with a tracking number to ensure privacy. This process will allow the study team to link the data to the participant once the HbA_{1c} data have been processed.

The risk of harm to participants, persons with diabetes, and their CPs is minimal. However, we have protocols in place if a participant is harmed. These protocols include reporting events to the institutional review boards and our data safety monitoring board in accordance with institutional and federal policies.

Results

This study was funded in February 2023. We began enrolling participants on November 11, 2023. To date, 24 participants have been enrolled in this study. We expect to conclude this study in March 2026 and expect to disseminate results in March 2026.

Discussion

Expected Findings

The expected outcome is that the Share plus intervention will have a clinically significant intervention signal (increased TIR and lower diabetes distress) indicating readiness for a fully powered trial. The Share plus intervention examines dyadic support for using CGM with data sharing in older adults with T1D. The clinical promise of CP data sharing to improve diabetes management and glycemic levels, and thus, reduce complications, will be greatly enhanced through an intervention that removes barriers and strengthens dyadic communication and support for the growing number of older adults with diabetes.

Conclusions

In this randomized controlled trial, we will evaluate feasibility and acceptability. By leveraging the full potential of technology and CP interventions, we may optimize the support that CPs can provide for effective glucose management in older adults with T1D.

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Authors' Contributions

NAA, MLL, and CAB conceptualized the study. NAA, BRG, and EI are actively curating the data. NAA, EI, and JEB will conduct the formal analysis. EI and JEB will conduct the statistical analysis with NAA overseeing this analysis. NAA, MLL, EI, CAB, and JEB participated in submitting and securing funding. NAA, MLL, EI, CAB, and JEB designed the investigation. NAA, CAB, MLL, EI, and JEB designed the study methodology. NAA and BRG have conducted the administration of all aspects of this study with oversight from CAB, MLL, and JEB. NAA, BRG, and EI set up the resources for this study. NAA, EI, and JEB set up the software to run and analyze this study. NAA has supervised all aspects of this study. BRG assisted NAA in supervising the interventionist and study recruitment. Validation was done by NAA, EI, and JEB. Visualization was done by NAA, MLL, CAB, EI, JEB, and BRG. CAB wrote the manuscript introduction. NAA wrote the remaining sections of the manuscript. NAA, MLL, BRG, EI, JEB, and BRG participated in the review and editing of the final manuscript.

Conflicts of Interest

Dexcom Inc provided partial equipment funding to NAA for this study.

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Abbreviations

ADCES7: Association of Diabetes Care and Education Specialists Educational Curriculum
CDCES: Certified Diabetes Care and Education Specialist
CGM: continuous glucose monitor
CP: care partner
DSME: diabetes self-management education
HbA_{1c}: hemoglobin A1c
HIPAA: Health Insurance Portability and Accountability Act
QoL: quality of life
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1D: type 1 diabetes
TIR: time-in-range

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Protocol

Novel Strategy to Assess the Neurotoxicity of Organic Solvents Such as Glycol Ethers: Protocol for Combining In Vitro and In Silico Methods With Human-Controlled Exposure Experiments

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Abstract

Background: Chemicals are not required to be tested systematically for their neurotoxic potency, although they may contribute to the development of several neurological diseases. The absence of systematic testing may be partially explained by the current Organisation for Economic Co-operation and Development (OECD) Test Guidelines, which rely on animal experiments that are expensive, laborious, and ethically debatable. Therefore, it is important to understand the risks to exposed workers and the general population exposed to domestic products. In this study, we propose a strategy to test the neurotoxicity of solvents using the commonly used glycol ethers as a case study.

Objective: This study aims to provide a strategy that can be used by regulatory agencies and industries to rank solvents according to their neurotoxicity and demonstrate the use of toxicokinetic modeling to predict air concentrations of solvents that are below the no observed adverse effect concentrations (NOAECs) for human neurotoxicity determined in in vitro assays.

Methods: The proposed strategy focuses on a complex 3D in vitro brain model (BrainSpheres) derived from human-induced pluripotent stem cells (hiPSCs). This model is accompanied by in vivo, in vitro, and in silico models for the blood-brain barrier (BBB) and in vitro models for liver metabolism. The data are integrated into a toxicokinetic model. Internal concentrations predicted using this toxicokinetic model are compared with the results from in vivo human-controlled exposure experiments for model validation. The toxicokinetic model is then used in reverse dosimetry to predict air concentrations, leading to brain concentrations lower than the NOAECs determined in the hiPSC-derived 3D brain model. These predictions will contribute to the protection of exposed workers and the general population with domestic exposures.

Results: The Swiss Centre for Applied Human Toxicology funded the project, commencing in January 2021. The Human Ethics Committee approval was obtained on November 16, 2022. Zebrafish experiments and in vitro methods started in February 2021, whereas recruitment of human volunteers started in 2022 after the COVID-19 pandemic–related restrictions were lifted. We anticipate that we will be able to provide a neurotoxicity testing strategy by 2026 and predicted air concentrations for 6 commonly used propylene glycol ethers based on toxicokinetic models incorporating liver metabolism, BBB leakage parameters, and brain toxicity.

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Conclusions: This study will be of great interest to regulatory agencies and chemical industries needing and seeking novel solutions to develop human chemical risk assessments. It will contribute to protecting human health from the deleterious effects of environmental chemicals.

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KEYWORDS

organic solvent exposure; workers; general population; neurotoxicity; blood-brain barrier; liver toxicity; human cell cultures

Introduction

Environmental and occupational exposure to chemicals may contribute to the development of several neurological diseases [1,2]. In particular, organic solvents used in industries such as car repair, painting, furniture manufacturing, printing, and cleaning have been associated with several central nervous system (CNS) conditions. These include mild to severe toxic encephalopathy [3]; deficits in cognitive function [4-7]; and, in some cases, neurodegenerative diseases [8,9]. The diffuse neuropathological effects of acute solvent intoxication reflect neurophysiological abnormalities involving multiple brain regions. With increasingly intense or prolonged exposure, the severity of acute impairment may progress along the spectrum of delirium. Chronic high-level exposure may lead to global cognitive impairment including deficits in memory, attention, energy, and personality, which are well-described forms of dementia [10-13]. Much of the initial work on organic solvent toxicity originated in Scandinavia, where a neurobehavioral syndrome in painters leading to their early retirement was first described [14]. However, although the neurotoxicity of solvents such as toluene, trichloroethylene, and n-hexane has been recognized, the neurotoxicity of common solvents currently on the market has not been evaluated. Notably, neurotoxicity testing is only required if the chemical is deemed a pesticide; otherwise, all other chemicals are evaluated on a case-by-case basis. The only exception is if the compound structure is suspected to have nervous system targets and no data are available for read-across or when effects on the nervous system are found in single-dose (Organisation for Economic Co-operation and Development [OECD] Test Guidelines [TGs] 402, 403, 420, 423, or 425) or repeated-dose toxicity studies (TG 407 or 408). Because the nervous system effect endpoints considered as triggers (ie, modifications of wet brain weight or basic histopathology, or both) are quite insensitive, high amounts of potentially neurotoxic compounds are available on the market. The European Union Classification, Labelling, and Packaging Regulation does not include a classification for neurotoxicity. Exposure to organic solvents, especially among workers with higher exposure than the general population, can produce neurotoxic effects, depending on the internal dose. Therefore, to efficiently protect the population from possible solvent toxicity, it is important to determine the air concentrations at which neurotoxicity does not occur. To this end, we propose a strategy using a combination of in vivo (zebrafish embryo), in vitro, and in silico tools coupled with controlled in vivo human exposure experiments to assess the neurotoxicity of solvents (Figure 1).

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Figure 1. Overview of project rationale, organization, and outcomes. The project will develop a strategy based on various models to assess the neurotoxicity of solvents. Scientific and regulatory outcomes are foreseen. AOP: adverse outcome pathway; BBB: blood-brain barrier; DNT: developmental neurotoxicity; KE: key event; NT: neurotoxicity; OECD: Organisation for Economic Co-operation and Development; PBTK: physiologically based toxicokinetic; TG: Test Guideline; WP: work package.

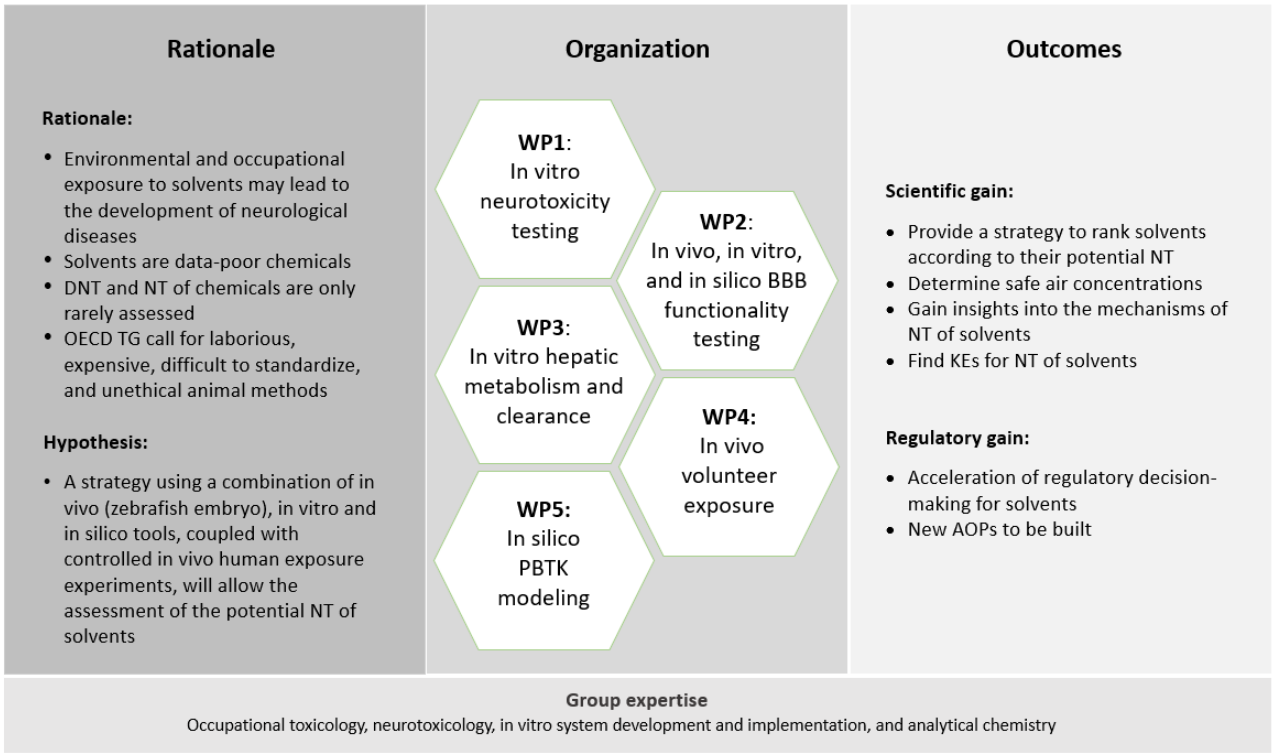

The recognized method for the evaluation of the neurotoxic potential of chemicals, the OECD TG 424 (neurotoxicity in rodents), uses complex in vivo tests in rodents, which are laborious, expensive, difficult to apply in a standardized manner, and ethically debatable. Regulators from different agencies worldwide as well as the scientific community are becoming increasingly aware of the limitations of the current toxicity testing paradigm. Animal-based high-dose testing in typically 1 stand-alone guideline test is not always relevant for human exposure scenarios [15]. One of the most challenging aspects of this animal-centric approach is the impossibility of coping with the thousands of chemicals for which data are still lacking. Conducting animal tests is time consuming and expensive. Therefore, they cannot be carried out routinely because of the sheer number of chemicals that are currently on the market and those anticipated to enter it in the coming years [16]. In addition, there are shortcomings regarding interspecies concordance between different mammalian or rodent species as well as with respect to extrapolation from experimental animals to humans. These ambiguities in results or poor reproducibility performance call into question the relevance of such test methods for human risk assessment [16-21]. All this prompts a move away from animal testing toward a combination of in vitro and in silico approaches that address functional mechanistic endpoints [15,16,22].

Numerous in vitro models have been proposed for the evaluation of neurotoxicity in the last decades. Monolayer cultures of a single brain cell type are far from representing the human brain in terms of architecture and functionality. Given the sophistication of brain cell-to-cell interactions, some complexity is required to recapitulate human-relevant cellular processes and functions in vitro. However, a good balance must be found between this complexity and the simplicity needed to have robust and reproducible systems that can be applied for chemical screening in a high-throughput manner [23]. The 3D hiPSC–derived brain test system (BrainSpheres) we previously developed [24] will be used in this study, as it fulfills these requirements.

The blood-brain barrier (BBB) protects the brain parenchymal cells from the deleterious effects of xenobiotics. However, some chemicals are able to cross or impair the BBB [25]. The transient or permanent opening of the BBB provides xenobiotics, plasma proteins, and immunoregulatory mediators access to the CNS, where they can induce toxic effects. Therefore, we will implement a predictive model to assess the impact of solvents on BBB based on in vivo (zebrafish embryo), in vitro (human brain microvascular endothelial cells [hCMEC/D3]), and in silico models [26] to assist in the interpretation of the results obtained in in vitro neurotoxicity testing.

Glycol ethers will be used as a case study to evaluate the feasibility of our protocol. Glycol ethers form a wide family of a few dozen solvents with different physicochemical properties making them versatile and usable in a variety of industrial applications ranging from pharmaceuticals and microelectronics to domestic cleaning, personal care, and printing. The 2 main groups of glycol ethers are the E series (ie, ethylene glycol ethers [EGEs]) and the P series (ie, propylene glycol ethers [PGEs]). EGEs and PGEs show differences in their toxicological properties regarding teratogenicity, hemolysis, and testicular atrophy [23], apparently resulting from their distinct production

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of metabolites [24,25]. EGEs have a primary alcohol group and are oxidized by alcohol dehydrogenase and aldehyde dehydrogenase to form the toxic alkoxyacetic acid. Therefore, PGEs are progressively introduced as a less toxic replacement of EGEs. PGEs are sold as a mixture of 2 isomers, with the bulk having a secondary alcohol (a) group and generally <5% of primary alcohol (b) groups [22]. The b-isomer is oxidized by alcohol dehydrogenase and aldehyde dehydrogenase to form the toxic alkoxypropionic acid in the body. However, the actual toxicity of PGEs is poorly characterized. Therefore, it is essential for our strategy to study not only the parent compound but also the metabolites. Metabolically competent liver cell models will be used to screen for liver toxicity of solvents and for the production of potential metabolites.

Exposure to solvents in human volunteers is fundamental when quantifying possible risks from chemicals because toxicological effects are related to internal exposure, that is, the concentration of a chemical inside the body and its biotransformation. Therefore, in vivo human volunteer studies are necessary to quantify absorption, distribution, metabolism, and excretion (ADME) kinetics in humans under controlled exposure conditions, which are necessary to understand the relationship between solvent concentrations in the air and biological samples, such as blood, urine, or exhaled air. These experiments provide important data on the total absorbed dose after inhaled solvent concentration, absorption rate (ie, from the site of absorption into the bloodstream), biotransformation rate (ie, metabolization of the parent chemical with production of metabolites), and elimination rate (ie, excretion of the parent chemical and metabolites from the body) [27]. These toxicokinetic parameters are representative of the target organ or of the tissue concentrations that may trigger an effect and are, therefore, relevant for understanding chemical risks in humans.

Toxicokinetic models quantitatively describe the body's ADME of a chemical or substance (different terms for this concept are preferred in different fields, including "toxicokinetics," "pharmacokinetics," and "biokinetics") [28]. Furthermore, using a toxicokinetic model in reverse dosimetry, we can predict the solvent air concentrations leading to brain concentrations below the levels found to produce neurotoxic effects in vitro in the BrainSpheres. The toxicokinetic model will incorporate metabolism parameters derived from the in vitro liver system and passage through or toxicity to BBB. Once calibrated, the toxicokinetic model can be used to simulate chronic exposure scenarios to predict cumulative brain concentrations and used in reverse dosimetry to predict air concentrations that will not likely result in brain concentrations associated with toxicity.

Methods

Ethical Considerations

Ethics committee approval was obtained from Swiss ethics (Commission cantonale d'éthique de la recherche sur l'être humain) in 2022 for this nonclinical human study (2022-01567). Healthy women and men were recruited as participants in our study. Each participant signed a written informed consent form before inclusion in the study. The participants will be reimbursed for their time and inconvenience according to the Swiss guidelines.

Global Strategy

The choice of solvents to be included in the study will be based on the amount annually placed on the European market and the number of products registered containing known glycol ethers. The selected organic solvents will be applied to various in vitro models to determine their neurotoxicity. They must be amphiphilic to be solubilized in the cell culture media. We established the following solvent selection criteria: (1) used or produced >1 metric ton per year, (2) incorporated in numerous industrial and commercial products, and (3) water solubility. This selection process involves consulting government databases and contacting different industry sectors. We will start the project concomitantly by testing 2 solvents of the P series, propylene glycol methyl ether (PGME), for which we have already developed a toxicokinetic model, and propylene glycol butyl ether. We will test 1 additional solvent from the E series with the in vitro test system, namely, ethylene glycol methyl ether (EGME), which has been banned for use in cosmetic products in Europe [29].

The study is organized into 5 work packages (WPs). The information workflow between the WPs is shown in Figure 2. All results collected from the abovementioned systems will contribute to refining the toxicokinetic model we previously developed for PGME [30]. The toxicokinetic parameters of the solvent and the metabolites will then be characterized in human volunteers after exposure to PGE vapors under controlled conditions. These results will be used to calibrate and expand our toxicokinetic model [30]. The toxicokinetic model will be constructed to predict brain concentrations of selected solvents and, consequently, will include a brain compartment to predict the target organ solvent and metabolite concentrations. BBB parameters such as barrier transport, transport of the solvent once in the brain, and solvent-brain binding will be incorporated. Solvent neurotoxicity may depend on the metabolic modifications of the substances; therefore, we will incorporate the parameters for the parent compound and the metabolites found in the in vitro liver system. The data necessary to build the model will be retrieved from peer-reviewed scientific literature for tissue:blood partition coefficients (PCs) [31] following the fit-for-purpose dose-response analysis approach. The toxicokinetic model should be able to predict human brain concentration for each of the tested solvents after inhalation exposure, given the air concentration of vapors and duration of exposure. The simulated human brain concentrations will then be compared with the no observed adverse effect concentrations (NOAECs) obtained from the neurotoxicity in vitro system (BrainSpheres). In addition, the toxicokinetic model will be used to predict solvent air concentrations that are unlikely to lead to brain concentration equal to or superior to the brain NOAECs using reverse dosimetry. The specific aims of each WP are summarized in Table 1.

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Figure 2. Information workflow between the work package (WP). BBB: blood-brain barrier; IVIVE: in vitro-in vivo extrapolation; NOAEC: no observed adverse effect concentration; PBTK: physiologically based toxicokinetic.

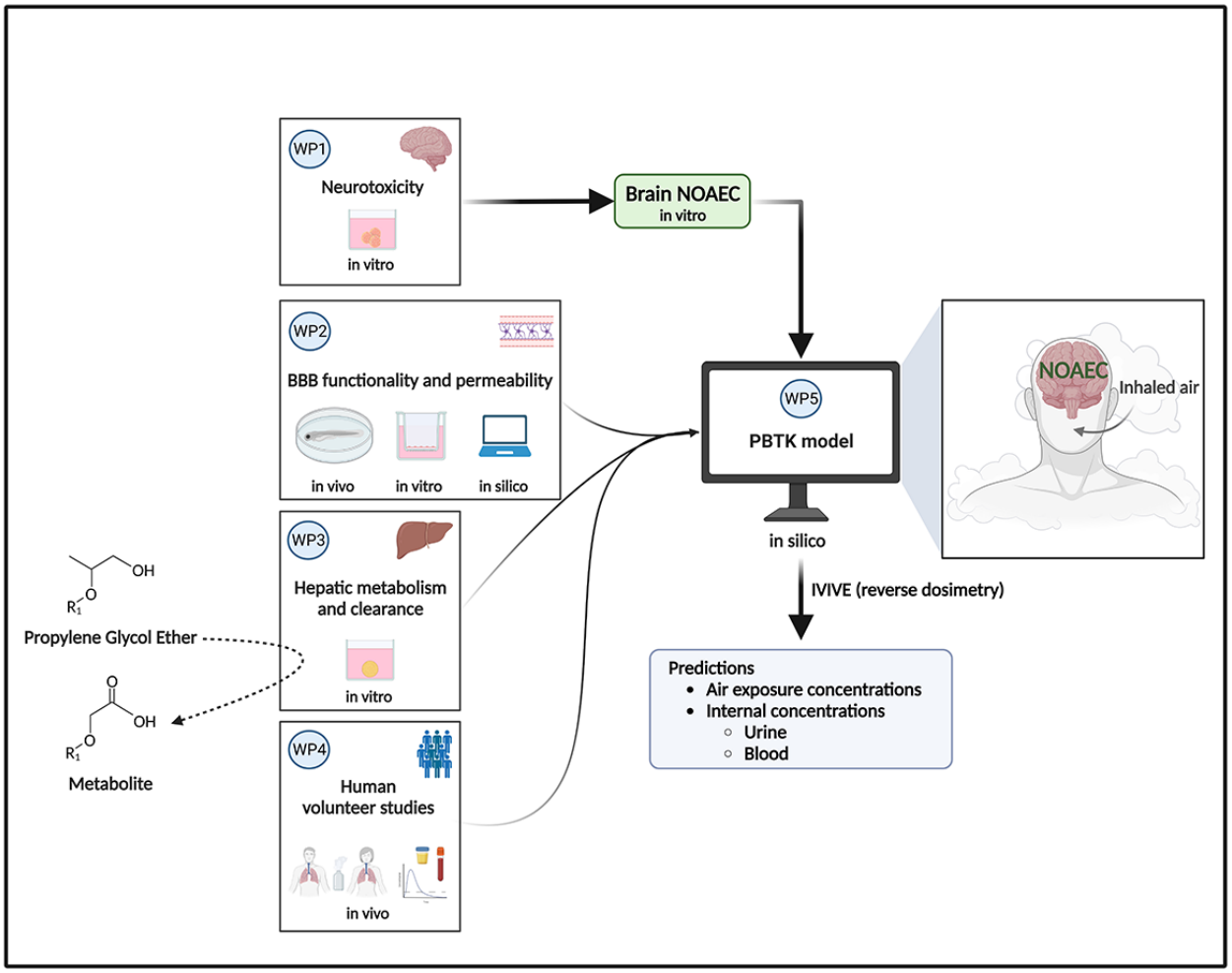

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Table 1. Specific aims of the work packages (WPs).

WP	Name	Specific aims
WP1	In vitro neurotoxicity testing	1. Determine NOAEC[a] for neurotoxicity of each solvent 2. Determine the in vitro distribution kinetics of solvents 3. Identify toxicity pathways and KEs[b] for solvent neurotoxicity
WP2	In vivo or in vitro or in silico BBB[c] functionality testing	1. Evaluate the suitability of the zebrafish embryo model to study BBB integrity and functionality 2. Determine the impact of solvents on BBB integrity and transport in zebrafish and hCMEC/D3[d] 3. Determine the solvents permeability coefficient (Pe) 4. Provide quantitative data on BBB permeability and tissue distribution of solvents based on computational modeling
WP3	In vitro hepatic metabolism and clearance	1. Elucidate hepatic metabolism 2. Calculate substrate-enzymatic parameters (Vmax[e] and Km[f]) 3. Detect and identify possible metabolites produced by the liver
WP4	In vivo volunteer exposure	1. Characterize human blood absorption and urinary elimination kinetics for parent glycol ether as well as the metabolites identified in WP3 2. Find neurotoxic and vascular injury effect biomarkers for solvent exposure
WP5	In silico PBTK[g] modeling	1. Establish and calibrate the PBTK model for various organic solvents 2. Use reverse dosimetry to determine air concentrations below human brain toxicity concentrations

[a]NOAEC: no observed adverse effect concentration.

[b]KE: key event.

[c]BBB: blood-brain barrier.

[d]hCMEC/D3: human brain microvascular endothelial cells.

[e]V_{max}: maximum velocity.

[f]Km: Michaelis constant.

[g]PBTK: physiologically based toxicokinetic.

WP1: In Vitro Neurotoxicity Testing

Testing strategies are needed to evaluate the neurotoxicity of chemicals in a more cost-effective, efficient, and ethical manner. Participating in an international effort, we developed a 3D human-induced pluripotent stem cells (hiPSC)–derived brain model containing several subtypes of neurons, astrocytes, and oligodendrocytes [24]. This system allows the cells to reach a high level of differentiation and cellular maturation, exemplified by the presence of functional synapses and compact myelin. The presence of myelin is important for this project because solvents more easily target lipid-rich structures [32]. This 3D human brain model has already proven its usefulness for neurotoxicity testing [33-36]. We hypothesized that glycol ethers are neurotoxic. Therefore, we propose to take advantage of our hiPSC-derived BrainSpheres model to study the neurotoxicity induced by uncharacterized glycol ethers present on the market, which will be compared with the neurotoxicity of well-characterized solvents known to induce human encephalopathy.

Solvents are data-poor substances. It was originally hypothesized that they exert their toxic effects largely through nonspecific physicochemical effects that modulate membrane fluidity and perturb the hydrophobic force regulating macromolecular interactions [37]. However, recent evidence supports the view that solvents interact with lipophilic areas on protein receptors [38,39]. They have also been shown to induce lipid peroxidation, leading to mitochondrial dysfunction, failure of electron transport, and energy production [40,41]. In this study, omics (eg, proteomics, metabolomics, and lipidomics) technology will be used to decipher the mechanisms of glycol ether neurotoxicity and to identify potential biomarkers of toxic effects.

Primary 3D hiPSC-derived brain cell cultures will be prepared and maintained as previously described [24]. This model contains neurons that form synapses, astrocytes, and oligodendrocytes myelinating the axons (Figure 3). Cytotoxicity will be determined by a resazurin assay after repeated exposure (7 d) to the selected glycol ethers (parent compounds and metabolites). Gene expression for cell type–specific genes, markers of synapses and myelin, and markers of cell stress will be quantified by quantitative reverse transcription polymerase chain reaction at concentrations of solvents under half-maximal effective concentration (EC50) for cytotoxicity. Immunostaining will be performed to assess the effects of solvents on synapses, myelin, and astrocyte reaction, and immunofluorescence will be quantified. NOAECs (Figure 2) will be determined for all tested endpoints, as previously shown for gene expression [42]. Brain cell cultures will also be exposed to the metabolites of PGME, propylene glycol butyl ether, and EGME and to the metabolites of the newly selected uncharacterized solvents, potentially produced by liver metabolism (WP3).

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Figure 3. Brain model used in work package (WP) 1. Immunostainings of human induced pluripotent stem cell–derived 3D BrainSpheres after 8 weeks of differentiation, showing the presence of proteins specific for neurons (neurofilament heavy polypeptide [NF200]), synapses (postsynaptic density-95 protein [PSD95] and synaptophysin [SYP]), astrocytes (glial fibrillary acidic protein [GFAP]) and oligodendrocyte (proteolipid protein 1 [PLP1]). Scale bars: 40 µm.

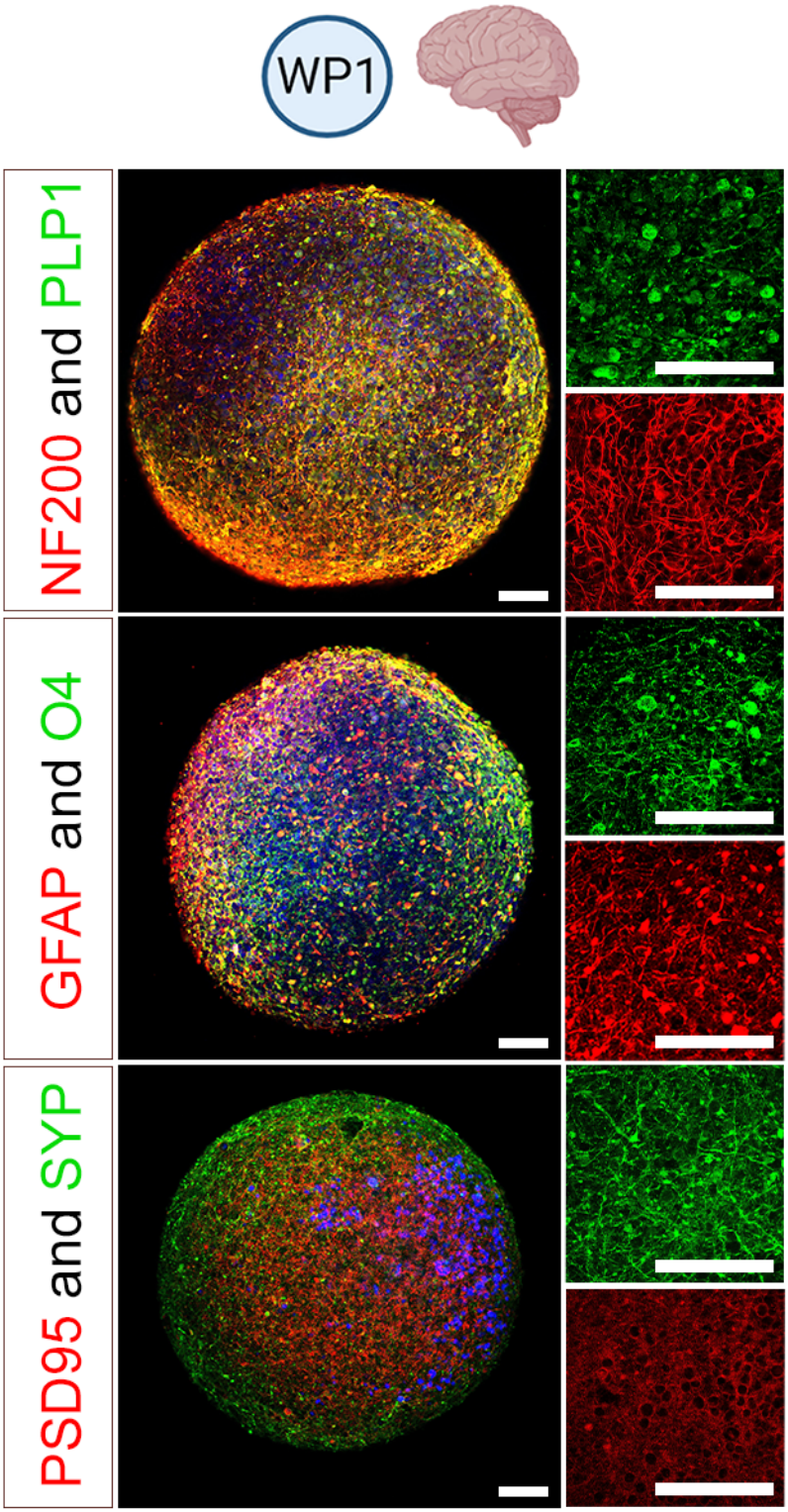

To establish the in vitro distribution kinetics of selected solvents necessary for toxicokinetic modeling, 3D brain cell cultures and medium will be collected 3, 6, 24, and 48 hours after the first exposure and after the last exposure of the repeated treatment. The solvent and its main metabolites (if relevant) will be quantified to establish a time course of disappearance from the medium and appearance in the cells as well as to assess the potential accumulation for the entire period of exposure. The fraction bound to culture plates' plastic will be quantified after desorption. In silico modeling of glycol ethers in vitro distribution kinetics will then be developed. This model will be able to predict the change in cell-associated concentrations of solvents in BrainSpheres with time, as previously shown for amiodarone [43].

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WP2: In Vivo, In Vitro, and In Silico BBB Functionality Testing

We previously established the zebrafish as a predictive vertebrate screening model to study the systemic circulation and tissue distribution of particulate drug carriers [44,45]. At 72 hours postfertilization, zebrafish embryos have a functional CNS and, presumably, a fully functional BBB. Anatomical structures such as the vascular endothelium can be visualized using transgenic fish lines expressing fluorescent proteins (Figure 4). Defined exposure of the zebrafish can be achieved by the simple addition of solvents to the fish incubation medium within a closed container. Other advantages of the model include the possibility of studying BBB functionality under physiological conditions in vivo and the high throughput. A well-known in vitro model for the human brain endothelium, hCMEC/D3 cell line (Figure 4) showing the formation of tight junctions and the expression of most transporters and receptors of the in vivo BBB [46], cultured in a transwell system, will also be used. Furthermore, extrapolation of in silico, in vitro, and zebrafish data to higher vertebrates seems feasible [47].

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Figure 4. Blood-brain barrier (BBB) models used in work package (WP) 2: zebrafish larvae (ZFL) and human brain microvasculatur endothelial cells (hCMEC/D3). ZFL (2 top panels): tracer permeability across BBB. Dorsal view of the midbrain region of the zebrafish lines Tg (kdrl:enhanced green fluorescent protein [eGFP]), which expresses eGFP (green signal) in the endothelial cell membranes. ZFL were injected with the tracer 1 kDa maleimide (red signal). Scale bars: 50 µm. hCMEC/D3 cells (lowest panel): actin filament stained with fluorescein isothiocyanate phalloidin. Scale bars: 100 µm.

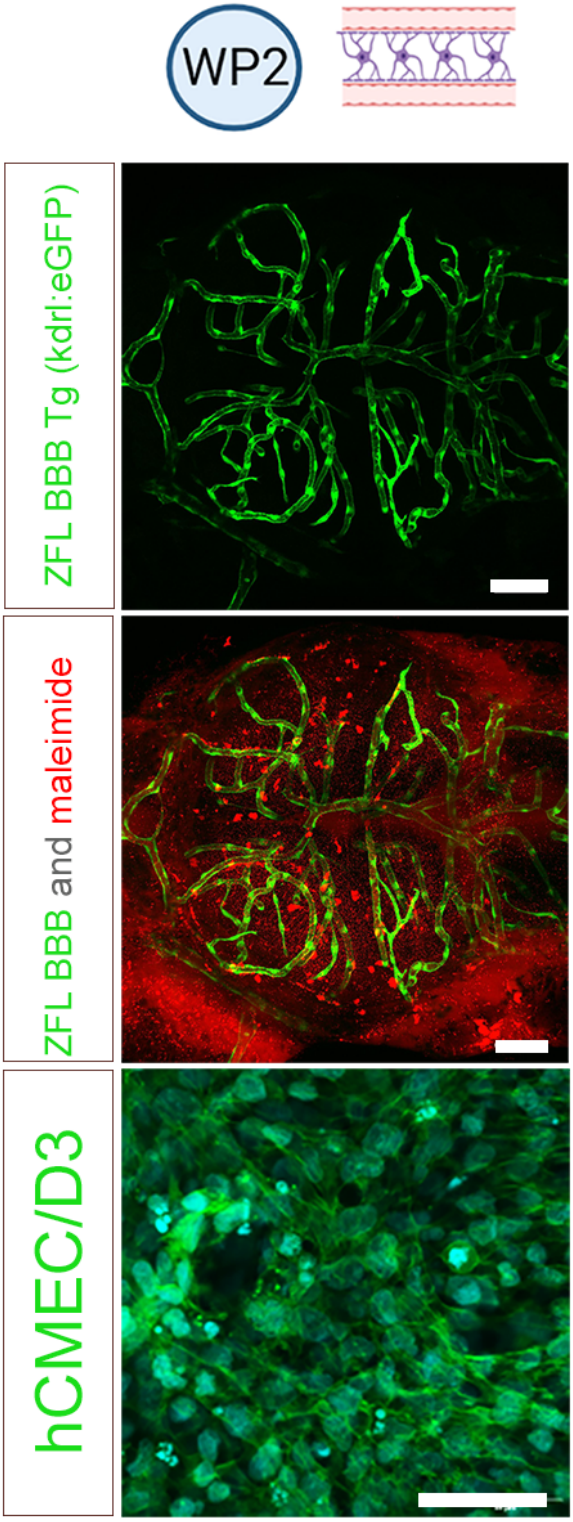

Zebrafish larvae are frequently used in developmental biology or toxicological studies. However, in this study, we will use zebrafish larvae exclusively to study BBB integrity and functionality [48]. Fluorescently labeled reference compounds (Figure 4) will be intravenously injected into the Duct of Cuvier, as markers of paracellular permeability (eg, fluorescein isothiocyanate dextran 70 or fluorescently labeled liposomes), substrates of drug export transporters (eg, rhodamine-123 as P-glycoprotein substrate), or nutrient transporters (eg, fluorescently labeled transferrin as a marker for receptor-mediated transcytosis). PGME will be the first reference compound to be tested because of its high water miscibility. To precisely assess exposure, analytical methods (gas chromatography-tandem mass spectrometry [GC-MS/MS])

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will be used to determine the concentrations of solvents and their metabolites in zebrafish medium, in the headspace of closed incubation vessels and tissue samples (ie, zebrafish homogenates). Circulation, tissue distribution, and brain uptake of the reference compounds will be monitored by confocal laser scanning microscopy (live imaging of anesthetized fish embryos for up to 24 hours). The concentration-dependent toxicity of solvents or their metabolites will be monitored based on the viability and malformations of embryos. The integrity of vasculature will be visualized in transgenic zebrafish kdrl: enhanced green fluorescent protein embryos. The metabolic capacity of the zebrafish will be determined by quantifying potential metabolites (determined in WP3; Figure 2) in zebrafish tissue homogenates. The concentration-dependent toxicity to BBB and the coefficient of permeation of solvents will additionally be evaluated in the hCMEC/D3 cell line cultured in a transwell system.

Finally, quantitative estimates of passive cellular uptake and BBB permeability of solvents and their metabolites will be provided based on computational modeling using physicochemical molecular descriptors according to the methods we previously established [26,49]. These methods provide very high throughput, allowing the screening of web-based chemical libraries.

WP3: In Vitro Hepatic Metabolism and Clearance

Because the liver is the main organ responsible for metabolism and a large contributor to compound clearance, we will implement a system suitable for predicting the hepatic metabolism of solvents. In recent years, 3D liver cell models have been proposed as an alternative to less physiological 2D cell monolayers, and their applications have progressed substantially [50]. They are widely used for the assessment of hepatotoxicity [51-55]. An advantage of spheroids is that they overcome the limitation of rapid decline of drug-metabolizing enzyme activities in primary human hepatocyte suspension culture and cell lysates [56], such as microsomes and liver S9 fractions. In this study, we will use 3D liver cultures of the well-characterized human HepaRG cell line (Figure 5), which represent a promising model to evaluate hepatotoxicity and hepatic metabolism [57].

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Figure 5. Liver model used in work package (WP) 3. Bright field and immunostainings of liver 3D HepaRG cultures showing the presence of albumin and cytochrome P450 3A4 (CYP3A4). Bars: 100 µm.

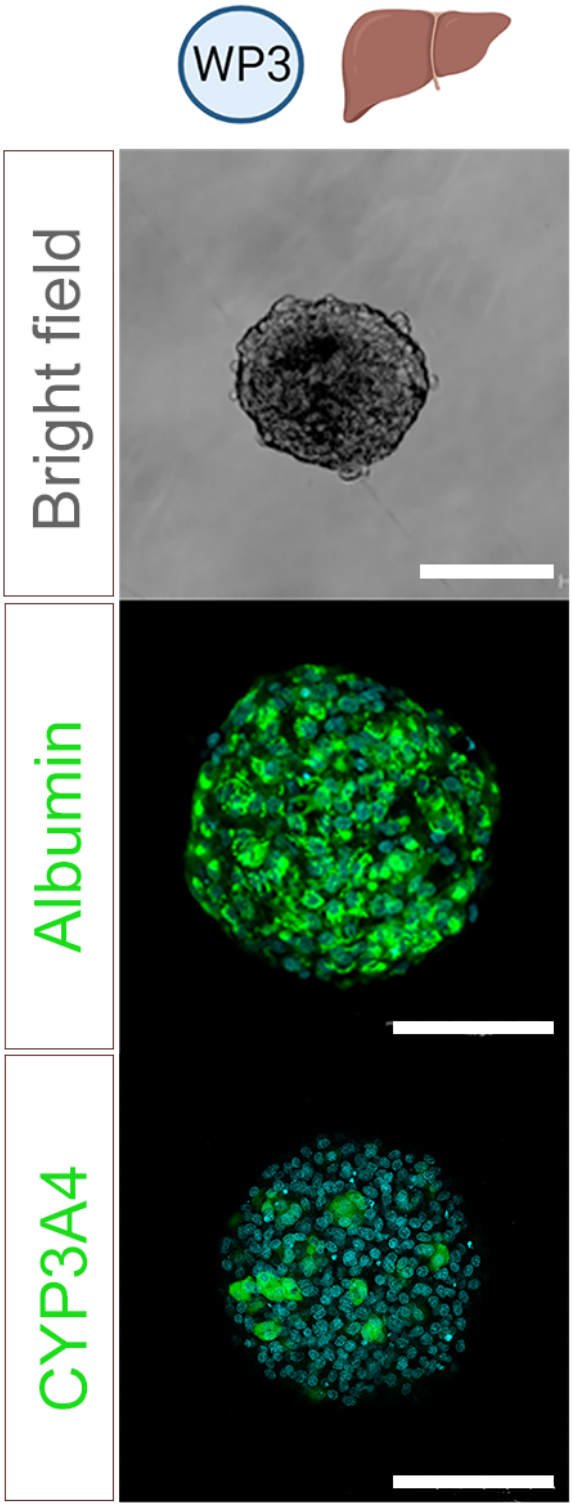

Determining the appropriate experimental test system (eg, cell plate, incubation time, and exposure concentration) will be an essential part of the development of the 3D model. Moreover, analytical methods (GC-MS/MS and liquid chromatography-tandem mass spectrometry) to detect and quantify the solvents and the metabolites formed must be developed to calculate hepatic metabolism and clearance. Then, proof of metabolic competence and maintenance of the 3D HepaRG cells will be carried out by assessing the metabolism of known P450 substrates. The presence and secretion of albumin as a specific hepatocyte marker will be assessed using immunostaining and enzyme-linked immunosorbent assay. Solvent- and metabolite-induced cytotoxicity will be assessed after 48 hours and 7 days (repeated) of exposure to determine the nontoxic concentration range for subsequent experiments. The metabolic abilities of the 3D HepaRG model and 3D

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primary human hepatocytes will be compared. Furthermore, the clearance data obtained from the 3D HepaRG model will be compared with the short-term clearance measured in the human liver cell lysate (S9 fractions). In addition, Michaelis-Menten-Kinetic parameters (V_{max} and Km) for the formation of the metabolites will be derived using the S9 fractions. These data will be used to build a physiologically based toxicokinetic (PBTK) model (Figure 2).

WP4: In Vivo Volunteer Exposure

Human biomonitoring refers to monitoring exposure-related health risks by analyzing biological samples, usually blood and urine samples [58]. The biomonitoring limit values (BMLVs) are set to protect human populations against the potential toxic effects of chemical substances. These limit values account for all routes through which a chemical can enter the body. These are most often the inhalation and skin routes in occupational and environmental settings. Kinetic studies that provide absorption, biotransformation, and elimination rates as well as the absorption and elimination half-lives of the parent compound and its metabolites are necessary to set BMLVs. The apparent urinary elimination half-lives of the parent compound and its metabolites will later be used to develop a biomonitoring method. Sample collection time is crucial and is determined by the apparent elimination half-life of the chemical. Blood concentrations will be used to calibrate the air:blood PC for the toxicokinetic models.

We will recruit 4 participants for 2 of the selected solvents. All participants must meet the following criteria: they should be healthy individuals who do not smoke or use contraceptive hormones, do not consume alcohol, be aged between 18 and 65 years, have normal red blood cells and hemoglobin concentrations, maintain a BMI between 18 and 25, and should not be working with glycol ethers. Pregnant and breastfeeding women will be excluded from this study. Participants will be recruited using flyers and announcements distributed at the teaching hospital, university websites, and bulletin boards. All participants will sign a written informed consent form before being included in the study.

The participants will be exposed to a single glycol ether for 4 hours under controlled conditions in an exposure chamber (12 m^3). PGE concentrations will be set at or below the Swiss occupational exposure level (OEL) if one exists. In the absence of an OEL, we will rely on existing OELs for other propylene glycols. The parent compound (free and conjugated) and the oxidative metabolites (free and conjugated) of the selected glycol ethers will be monitored in blood, urine, and exhaled air samples. These are noninvasive methods used for human participants, and the results will be used in WP5 to estimate brain concentrations. All compounds will be quantified using capillary gas (parent compound in blood, urine, and exhaled air) or liquid (metabolites in blood and urine) chromatograms with tandem mass spectroscopy detection.

WP5: In Silico PBTK Modeling

PBTK models can be used to estimate human brain concentrations. The risk of neurotoxic effects can be estimated by comparing the predicted solvent-brain concentrations with the NOAEC obtained from the in vitro models. Mathematical models such as PBTK models can be used to predict the ADME of a chemical and its metabolites. In these PBTK models, the body is represented by 1 or more compartments. Each compartment represents 1 or more tissues that are kinetically homogeneous, that is, that have similar perfusion rates and an assumed similar substance solubility. PBTK models are described by a set of parameters that define the compartments and a set of mass balance differential equations for each compartment.

A previously developed toxicokinetic model for PGME with metabolism that is assumed to follow Michaelis-Menten kinetics calibrated for different age groups serves as the basis for our development [30,31,59]. We aim to modify this previously developed toxicokinetic model to include a separate compartment for the brain using BBB flux rates obtained from in vivo, in vitro, and in silico models (WP2). In addition, we will implement PC obtained from empirical human experiments (WP4) and metabolic parameters assessed in a hepatocyte assay (WP3). The toxicokinetic models will be able to simulate not only acute but also chronic exposures; therefore, both short-term and long-term exposures can be explored in silico. We will develop the toxicokinetic model into a physiologically based pharmacokinetic model based on the existing inhalation-only toxicokinetic model originally developed for PGME [40] and build it in the Berkeley Madonna software or equivalent. We will model the brain as a single compartment with direct contact with the blood flow and where organic solvent uptake will be assumed to be diffusion limited, which is in line with other physiologically based pharmacokinetic models [60]. Values for physiological parameters (volume of vascular brain, as fraction of brain volume [FVvb], volume of extravascular brain, as fraction of brain volume [FVevb], volume fraction of brain tissue [FVB; as percent of body weight], BBB surface [Sh] in cm^2, fraction of cardiac output in brain at rest [BFbrainrest]/cardiac output in brain at light work [BFbrain]) required to build the TK model are from the scientific literature. Depending on the substance, values of chemical-specific parameters such as the pulmonary retention (Rpulm), central:air PC (Pca), blood:air PC (Pba), and brain tissue:vascular brain PC (Pevb_vb) are either taken from the literature or estimated in silico. Since the partitioning of organic compounds between human tissue homogenate and blood is a function of water and lipid content of tissues and the n-octanol:water PC (Kow), PCs are estimated in silico based on LogKow. Kinetic coefficients needed for each organic solvent included in this study will be found in WP3 for liver metabolism (Michaelis-Menten parameters [V_{max} and Km]), WP2 for BBB uptake (BBB permeability-surface area product [PS]). The fraction unbound in blood (Fu_blood) will be estimated based on the fraction unbound in plasma (Fu_plasma) and the blood-to-plasma ratio (Rb), and the fraction unbound in brain (Fu_brain) will be considered when modeling each solvent as only the free fraction is able to distribute to different tissues and is biologically active. The model will be calibrated by comparing the predicted and actual urinary organic solvent concentrations obtained from the controlled human experiments (WP4). Both the free and total

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organic solvent concentrations (free+conjugated) will be obtained for calibration.

Results

With this project, we expect to provide a strategy to rank uncharacterized solvents and their potential liver-formed metabolites, according to their potential neurotoxicity, and in comparison with the banned EGME. More importantly, a series of PBTK simulations will be conducted to predict occupational exposure, assuming 8 hours of exposure per day, 5 days per week, physical activity for 12 hours per day, and rest for the remaining 12 hours. We will use the PBTK model in reverse dosimetry to estimate air concentrations that do not produce brain concentrations determined as neurotoxic in the hiPSC-derived 3D brain model. We will recommend that authorities setting occupational exposure and public health limits consult these values. Keeping the exposure below the brain effect level should ultimately increase the protection of exposed workers and the general population with domestic exposures.

We also anticipate gaining insights into the mechanisms of action of solvents of the glycol ether family. We will elucidate the possible toxic endpoints in the brain, liver, and zebrafish models. Furthermore, we will be able to establish how toxicity is related to the compounds' lipophilicity and metabolites.

Discussion

Overall, our strategy combining multiple, fit-for-purpose 3D advanced cell culture systems; zebrafish larvae; biomarker analysis; human ADME experiments; and in silico prediction is expected to contribute to the improvement of human risk assessment. Although we identified some risks we could encounter during the project, we are confident that our already determined mitigation measures will be able to overcome potential pitfalls.

Determination of the passage of solvent through the BBB may be challenging; hence, we are applying 3 different complementary methods: in vivo zebrafish larvae, in vitro human cells (hCMEC/D3), and in silico models. We are also considering and assessing the effects of the hepatic metabolites of the solvents on human BBB cells. With this experimental strategy, issues regarding the potential direct effect of solvents on cell membranes, the relatively low miscibility of solvents with water, and the physiological differences between zebrafish and humans (eg, metabolism and route of expected) should be overcome.

We have extensive experience in recruiting human volunteers for controlled human exposure sessions in the exposure chamber. Sometimes, recruitment takes longer than anticipated, and if that is the case, we will extend the timeline to not compromise the size of the study. New analytical chemical methods will need to be determined, which is time consuming. However, we will use a laboratory with extensive experience in analyzing PGME in urine and blood samples. This will also have to be accommodated with a delay in the timeline.

Future developments, not included in this study, are a strategy extended to include developmental neurotoxicity by determining other endpoints, such as proliferation and neurite outgrowth, after exposure of BrainSpheres to solvents at earlier developmental stages and by adding an in vitro test system to take into account the passage of solvents through the placental barrier [61]. We might also consider combining zebrafish embryo behavioral assays (eg, spontaneous tail coiling) with the BrainSpheres model as readouts for developmental neurotoxicity. Finally, the PBTK model could be adapted to determine solvent air concentrations that are unlikely to cause neurotoxic effects in fetuses or pregnant women.

Acknowledgments

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Data Availability

Data will be available from the corresponding author on reasonable request.

Authors' Contributions

NBH, LSD, JH, and MGZ conceptualized the paper. NBH, LSD, JH, and MGZ wrote the original draft. All authors reviewed and edited the paper. LH, DP, HP, RDP, and SW visualized the paper. NBH, LSD, JH, and MGZ administered the project. NBH, LSD, JH, and MGZ acquired the funding.

Conflicts of Interest

None declared.

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Abbreviations

ADME: absorption, distribution, metabolism, and excretion
BBB: blood-brain barrier
BFbrain: cardiac output in brain at light work
BFbrainrest: cardiac output in brain at rest
BMLV: biomonitoring limit value
CNS: central nervous system
EGE: ethylene glycol ether
EGME: ethylene glycol methyl ether
Fu_blood: fraction unbound in blood
Fu_brain: fraction unbound in brain
Fu_plasma: fraction unbound in plasma
FVB: volume fraction of brain tissue
FVevb: volume of extravascular brain, as fraction of brain volume
FVvb: volume of vascular brain, as fraction of brain volume
GC-MS/MS: gas chromatography-tandem mass spectrometry
hCMEC/D3: human brain microvascular endothelial cells
hiPSC: human induced pluripotent stem cell
NOAEC: no observed adverse effect concentration

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OECD: Organisation for Economic Co-operation and Development
OEL: occupational exposure level
Pba: blood:air partition coefficient
PBTK: physiologically based toxicokinetic
PC: partition coefficient
Pca: central:air partition coefficient
Pevb_vb: brain tissue:vascular brain partition coefficient
PGE: propylene glycol ether
PGME: propylene glycol methyl ether
PS: blood-brain barrier permeability-surface area product
Rb: blood-to-plasma ratio
Rpulm: pulmonary retention
Sh: blood-brain barrier surface
TG: Test Guideline
Vmax: maximum velocity
WP: work package

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Protocol

Implementation of a Primary Prevention Program for Posttraumatic Stress Disorder in a Cohort of Professional Soldiers (PREPAR): Protocol for a Randomized Controlled Trial

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Abstract

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can manifest after a traumatic event where the individual perceives a threat to his or her life or that of others. Its estimated prevalence in the European population is 0.7% to 1.9%. According to the "dose-response" model, individuals who are most exposed to traumatic events are most at risk of developing PTSD. Hence, it is unsurprising that studies have observed a higher prevalence among the military population, ranging from 10% to 18%, or even up to 45%. This project's overall goal is to evaluate the primary prevention actions that can strengthen the resilience of at-risk professionals, notably military personnel, in the short term, with the medium- to long-term aim of preventing the occurrence of PTSD and improving the patient's prognosis.

Objective: This study's objectives are (1) to design a primary prevention program for PTSD, tailored to the studied military population and compatible with operational constraints; and (2) to implement and validate the Primary Prevention of Posttraumatic Stress Disorder in Military Professionals (PREPARE) program in the short term with operational personnel belonging to the French Mountain Infantry Brigade.

Methods: This is a single-center, prospective, randomized, parallel-group controlled cohort study. The cohort is divided into 2 groups: the nonintervention group receives no training, and the intervention group follows a dedicated prevention program (structured into 8 workshops and 2 debriefing and practice reinforcement workshops). Each participant is evaluated 4 times (at inclusion, +4 months, +6 months, and +12 months). During each visit, participants complete several psychosocial questionnaires (which take 15-80 minutes to complete). Samples (a 30-mL blood sample and three 5-mL saliva samples) are collected on 3 occasions: at inclusion, +4 months, and +12 months. Emotional reactivity (electrocardiogram and electrodermal activity) is measured before, during, and after the classic and the emotional Stroop task.

Results: The project is currently ongoing, and results are expected to be published by the end of 2024.

Conclusions: The study adopts an integrative approach to the processes that play a role in the risk of developing PTSD. Our biopsychosocial perspective makes it possible to target levers related to factors specific to the individual and socio-professional

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factors. The following dimensions are addressed: (1) biophysiology (by studying markers of the neurobiological stress response, wear and tear, and vulnerability phenomena and reinforcing the flexibility of the autonomic nervous system), (2) psychology (by facilitating and measuring the development of flexible coping strategies to deal with stress and evaluating the moderating role of the individual's sense of duty in the development of PTSD), and (3) social (by facilitating community strategies aimed at reducing stigmatization and supporting the use of care by professionals in difficulty, in the institutional context).

Trial Registration: ClinicalTrials.gov NCT05094531; https://clinicaltrials.gov/study/NCT05094531

International Registered Report Identifier (IRRID): DERR1-10.2196/47175

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KEYWORDS

posttraumatic stress disorder, military, primary prevention, biopsychosocial, resilience, coping, stigma, biophysiology; PTSD; implementation; soldier; veterans; prevention program

Introduction

Background and Rationale

Overview

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that manifests following the experience of a traumatic event (TE) where the individual has perceived a threat to his or her life or that of others [1]. In France, it is considered to be the third most widespread psychiatric disorder, after major depression and specific phobias. Its prevalence in the European population is estimated to be between 0.7% and 1.9% [2,3]. According to the "dose-response" model, individuals who are most exposed to TEs are most at risk of developing PTSD [3-5]. At-risk occupations, such as the military, law enforcement, and first responders, carry an inherent risk of experiencing trauma. Hence, it is unsurprising to observe a high prevalence of PTSD in military populations, ranging from 10% to 18% or reaching up to 45% [5-9], depending on the study. Although cumulative exposure seems to be an important determinant in the general population [10], the literature does not establish a clear link among at-risk professionals. Nevertheless, it is reasonable to think that cumulative exposure is detrimental, and may even lead to fragilization, which would be consistent with the intensity of PTSD symptoms [11,12]. Repeated exposure triggers a reaction that builds on the consequences of previous exposures, increasing the complexity of the link between cumulative exposure and PTSD development, via multiple pathways.

PTSD Prevention

New medical research has influenced public policy, and the promotion of good health has become a key priority where policies seek to encourage certain behaviors that protect, improve, or restore the health of individuals, groups, or the entire population, while a prevention framework is used when the goal is to limit or prevent the development of a specific disease.

In the 1980s, evidence-based medicine emerged. The approach is founded on the principle of structuring prevention and public health decisions based on scientific evidence (eg, epidemiological studies and systematic clinical studies). A given health problem can be addressed by preventive interventions at primary, secondary, or tertiary levels. The objective of primary prevention is to intervene before the problem occurs; actions target the determinants of the problem by reducing risk factors or by promoting or reinforcing protective factors. In the context of PTSD, primary prevention can intervene at the level of preventing the trauma or at the level of PTSD prevention after the TEs. For at-risk professions in particular, PTSD prevention is the primary target, as the risk of exposure to trauma is integral to the profession. Secondary prevention seeks to define interventions once the problem is identified; it consists of early detection and referral for treatment (ie, after exposure to a TE). Finally, tertiary prevention seeks to manage the problem and prevent relapse. If necessary, the goal is to treat or limit any aggravation of the problem, notably any psychosocial consequences or comorbidities associated with PTSD. At all 3 levels, prevention must respect individual freedom [13].

Primary Prevention of PTSD

Effective primary prevention relies upon a sound theoretical understanding of the processes and determinants of the problem, knowledge of actions that have been scientifically validated in other populations, and clinical expertise in the field, which reflects the characteristics (eg, sociocultural) of the target population. This "selective prevention" approach seeks to target exposed participants.

In the domain of PTSD, primary interventions are rare, as such actions aim to prevent the impact of TEs before they occur. Nevertheless, this literature [14] gives us an insight into the potential effects of cumulative exposure to TEs during the career of military professionals. In this context, primary prevention interventions target several determinants that contribute to developing resilience following the TE. The approach underlines the need to characterize the factors that support individual and collective resilience processes, tailored to the characteristics of the population of at-risk professionals. This initial step is a prerequisite to the definition of relevant targets and the development of an appropriate prevention intervention for the population.

The proposed program (which we call Primary Prevention of Posttraumatic Stress Disorder in Military Professionals [PREPAR]) is part of a comprehensive prevention approach that synergistically links physiological, psychological, and social determinants. The approach stems from the etiological model proposed by Jones and Barlow [15]. This model is a comprehensive framework used in clinical psychology to understand the development and maintenance of psychological

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disorders, particularly PTSD. It integrates various factors that contribute to the onset and perpetuation of these disorders. Several etiological factors, including biological, cognitive, and behavioral components, are implemented in this model. The model also takes into account predisposing factors and moderating variables. It emphasizes a holistic approach to understanding mental disorders, taking into account the complexity of the human experience.

The Physiological Dimension

PTSD is described as a failure of emotional extinction which develops following exposure to intense fear. Exposure to a stressful event leads to a neurobiological stress response, resulting in the activation of the sympatho-adrenergic neurovegetative system and the corticotropic neuroendocrine axis. Although this dual physiological response is effective in the short term, it comes with a biological cost; regulatory mechanisms aim to compensate for this loss by supporting poststress recovery. A repeated inability to recover and extinguish the stress response in the long term (repeated exposures over a short time period) creates a so-called "allostatic load" [16], which progressively limits the flexibility of the central and peripheral nervous system. The peripheral nervous system is of particular interest, due to its role as a mediator of the allostatic load. The parasympathetic branch plays a role in the emotional extinction and correction of the load, making it a key vulnerability factor for health when it is insufficiently effective [17]. Certain professions (frontline responders and military personnel) are at risk of developing a significant allostatic load, due to their repeated exposure to TEs (inherent in the nature of their work). On top of this, personnel must adapt, on a daily basis, to various environmental demands: physiological (sleep debt, altered sleeping patterns, etc), physical (hypoxia, etc), and cognitive and emotional (traumatic exposure, etc), among others. All of these factors test the flexibility of the individual's physiological systems, particularly the autonomic (ie, parasympathetic) nervous system, which, consequently, appears to be a key target for prevention measures.

The Psychological Dimension

Military personnel participate in multiple missions in conflict zones, and this is likely to alter the flexibility of their executive and emotional regulation functions. Although training programs aim to develop automated responses to well-known mission scenarios, they do not focus on developing the change in viewpoint that contributes to the resilience process. Moreover, preclinical data show that both acute and repeated stress are likely to reduce cognitive flexibility [18,19]. A slight reduction in cognitive flexibility likely reduces the flexibility of emotional regulation strategies following a TE, thus increasing the impact of exposure. This hypothesis draws upon the notion of "coping flexibility." The latter concept represents the individual's ability to evaluate the effectiveness of his or her strategies for coping with stress in a specific situation and then adopting alternative strategies, if necessary [20]. The evaluation of training in the diversification of emotional regulation strategies in military populations has found a reduced risk of PTSD after exposure to TEs. Furthermore, a relationship has been identified between cognitive flexibility and self-compassion [21]. The data also suggest that increasing self-compassion contributes to increasing cognitive flexibility [22].

Finally, a clear sense of duty has been found to counterbalance perceived constraints associated with the mission [23,24]. The literature reports that the meaning attributed to the work environment can, to a significant degree, compensate for the perception and impact of occupational stressors [25].

The Social Dimension

The social dimension targets normative pressure and stigmatization. These determinants are specific to the institutional context of military personnel and may represent risk factors. Thus, normative group pressure to follow codes that encourage the nonexpression of emotions [26] can be a risk factor, as military personnel can be reluctant to speak about their psychological and somatic symptoms, which delays treatment. A fear of stigmatization by the institution and peers is another potential barrier to care. Overall, these social factors are obstacles to both individual and collective positive health behaviors.

Research Hypotheses

Overview

The goal of this project is to evaluate a multidimensional biopsychosocial primary prevention intervention for PTSD aimed at strengthening the resilience of at-risk professionals, namely military personnel, in order to prevent the occurrence of PTSD or reduce its severity.

The objectives of the project are as follows: (1) to design a primary prevention program for PTSD specific to the studied military population and compatible with operational constraints; (2) to implement or validate the program with operational personnel belonging to the French Mountain Infantry Brigade (*Brigade d'Infanterie de Montagne*); and (3) to understand PTSD and its prevention from 3 perspectives: biophysiological (by studying key markers of the neurobiological stress response, strain and vulnerability and increasing the flexibility of the autonomic nervous system); psychological (by facilitating and measuring the development of flexible strategies to cope with stress and evaluating the moderating role of the meaning of the mission in the development of PTSD); and social (by facilitating community strategies aimed at reducing stigmatization and helping professionals in difficulty to access care in the institutional context).

Our biopsychosocial approach adopts an integrative understanding of the processes at play in the risk of developing PTSD. This perspective makes it possible to target levers related to factors specific to the individual (at physiological and psychological levels), and contextual and social factors (related to the working environment).

The Physiological Dimension

The change in parasympathetic vagal flexibility is an early and silent sign of physiological deterioration. It can be identified by noninvasive measurements (resting or tonic heart rate variability, and activation or phasic heart rate variability) and modulated by exercises that target vagal activity (cardiac

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coherence techniques), which can be easily integrated into a busy professional agenda. A preliminary feasibility study among a group of firefighters (SDIS 73) demonstrated very good acceptance of this technique by the selected professionals and good adoption in daily life [24].

The Psychological Dimension

Two factors are targeted in the psychological dimension: coping flexibility and the sense of duty. These 2 determinants have rarely been targeted in studies of the prevention of occupational PTSD. The focus on coping flexibility and self-compassion seeks to improve emotional regulation, and the focus on the sense of duty seeks to target the silent determinants of occupational PTSD, with the overall aim of identifying an effective primary prevention intervention.

The Social Dimension

The targeted determinants are the beliefs and socio-normative processes that play a role in PTSD in a military population (self-stigmatization, stigmatization by others, normative pressure, and group cohesion). The intervention aims to establish a dedicated space to normalize the discourse, with the overall aim of discussing PTSD and making it visible, along with the signs of emerging psychological and somatic injuries. Specific group facilitation techniques are used, notably social modeling, which aims to reinforce feelings of self-efficacy that support the public expression of signs of injury and to support the search for appropriate care, when necessary [27].

Objectives of the Research

The main objective is to determine the effectiveness of a biopsychosocial program targeting the resilience (developing stable resources to adapt to occupational demands, in order to cope with TEs) of military personnel in the context of PTSD prevention.

The secondary objective is to better understand interindividual variability regarding the program's impact. We will study levels of vulnerability at inclusion and their impact on the program's effectiveness. We will also track postprogram changes in resilience (at 6 and 12 months). In addition, we will evaluate (1) the impact of the program on activation and psychobiological deterioration biomarkers and (2) the psychosocial determinants at 4 months (the end of the program) and 12 months (to evaluate persistence). In addition, we will measure adherence to the intervention at group and individual levels, through an evaluation at the end of the program. Finally, we will examine user satisfaction with the URGOfeel sensor and its application during workshops.

Methods

Ethical Considerations

Prior to their participation in the study, all participants will receive 2 separate notifications: one detailing the primary study and the other focusing on the genetic part. It is essential to emphasize that participation in the genetic segment is entirely optional, allowing individuals to engage solely in the main study if they prefer. Both of these notifications provide comprehensive information about the study's objectives, limitations, and legal requirements, especially in terms of privacy and confidentiality. Additionally, they clearly outline the potential benefits and risks associated with participation.

All collected data will undergo rigorous anonymization and processing in strict accordance with the MR001 reference methodology, in compliance with the regulations of the French Data Protection Authority (CNIL).

Our study maintains a steadfast commitment to ethical standards, in alignment with the principles set forth in the 1964 Helsinki declaration and its subsequent amendments. Furthermore, the ethics committee of Ile de France 8 formally approved the research protocol on January 12, 2021 (reference 20.12.10.58611). It is important to note that participants will not receive any form of compensation for their participation in this research.

Recruitment

The study will be conducted with members of the 27th Mountain Infantry Brigade, located in the Auvergne-Rhône-Alpes region of France. Participants will be recruited from companies proposed by the Brigade's line manager, depending on the ability to operationalize and implement measurement sessions, and the intervention.

Randomization

Individual randomization is not feasible for two reasons: (1) the logistics involved in deploying the training program and the availability of participants; and (2) the need to avoid a contagion effect between members of the Brigade who benefit from the program and those who do not.

Eligibility Criteria

After obtaining informed, written consent, the following inclusion criteria will be verified: affiliated to a social security scheme; a male adult; a member of a combat unit with external operations (OPEX) capability; a soldier with a current contract with the Brigade, lasting a minimum of 12 months; a soldier who is able to attend all measurement sessions and workshops, according to the schedule defined upstream; a soldier who is not a member of the *Groupements Commando Montagne* (to ensure homogeneity); and, finally, nonparticipation in one of the studies included in phase 1 of the PREPAR project. The latter social psychology study aimed to understand the day-to-day experience of frontline professionals and was approved by the ethics committee of the University of Aix-Marseille (2019-12-12-001). Noninclusion criteria are as follows: being female; receiving treatment for a chronic disorder (daily medication for at least 1 month); participation in an external operation planned within 12 months; and being an adult ward of court.

Participant Timeline

Figure 1 presents the timeline for participants, and Table 1 presents a synopsis of how the study will unfold.

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Figure 1. Study timeline. *: 2 to 3 hours to take measurement; △: "debriefing and anchoring of the practice" workshop.

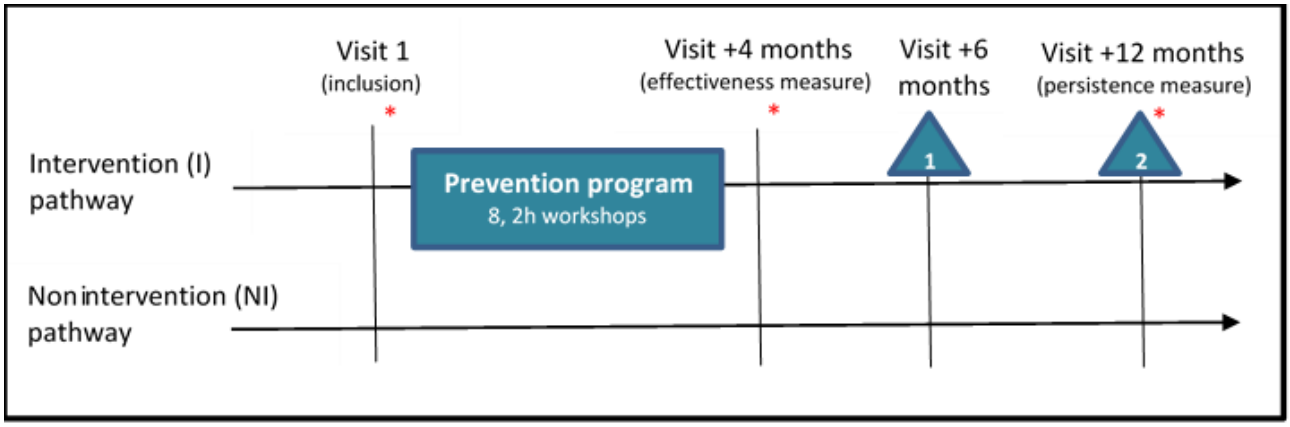

Table 1. Summary of the stages of the study.

	Visit 1 inclusion	+4 months	+6 months	+12 months
Information – consent	✓			
Sociodemographic data	✓			
Self-administered questionnaires	✓	✓	✓	✓
Blood and saliva collection (physio-biology and genetic)	✓	✓		✓
Emotional reactivity	✓	✓		✓
"Debriefing and anchoring of the practice" workshop			✓	✓

The first step is a briefing session with 2 of the Brigade's companies. Each individual will receive 2 information letters (1 regarding participation in this study, and 1 regarding participation in genetic studies), in order to allow time to reflect before the inclusion visit.

Visit 1: Inclusion

Inclusion will take place over a 3-week period. This time is needed to be able to disseminate information to the groups concerned and collect data. Once informed consent has been obtained, and eligibility criteria have been verified by one of the investigators, the following samples will be collected: (1) a 30-mL blood sample; (2) three 5-mL saliva samples (the participant will be asked to collect a sample on waking, getting up, and 30 minutes later [28]); (3) noninvasive measurements of cardiac variability and electrodermal conductance (using patches applied to the skin) during Stroop tasks, estimated to take 20 minutes; and (4) a psycho-cognitive evaluation (standardized and validated questionnaires). The latter will make it possible to evaluate the psychological and somatic symptoms (Patient Health Questionnaire [PHQ-15] [29]; psychosocial factors; Perceived Stress Scale [PSS] [30]; coping flexibility [20]; inner correspondence and peaceful harmony [ICPH] [31]; stigma and barriers to care [32]; Multidimensional Scale of Perceived Social Support [MSPSS] [33]; the Siebold vertical and horizontal cohesion questionnaire [34]; and the presence of any psychopathologies such as anxiety and depression: Hospital Anxiety and Depression Scale [HADS] [35,36], Posttraumatic Checklist-5 [PCL-5] [37], unsure, and Burnout Measure Short Version [BMS] [38,39]). The time required to fill out the questionnaires is estimated to be 45-60 minutes (184 items in total).

The Prevention Program: Workshops

Members of the intervention group will participate in 8 workshops. Each lasts 2 hours and is divided into three parts: (1) welcome participants with time allocated for inclusion (time approximately 20 minutes); (2) a presentation of the pedagogical objectives of the session, and its practical application; and (3) group wind-up (approximately 20 minutes). Please see Multimedia Appendix 1 for a description of the workshop program. At the end of the study, members of the nonintervention group, who wish to do so, will be able to benefit from the same prevention program during a later session, which will be scheduled as a function of operational constraints.

Visit +4 Months: Follow-up

A second round of data collection will take place at the end of the prevention program (approximately 4 months after inclusion). Each participant will be asked to allocate half a day to the collection of biopsychological measurements.

Visit +6 Months: Follow-up

Two months after the end of the program, during the first debriefing workshop, participants will be asked to complete a set of self-administered questionnaires (the same set as the one completed during the inclusion visit a part for the sociodemographic information).

Visit +12 Months: End of Study

Eight months after the end of the prevention program, each participant will take part in a final measurement session (lasting 2-3 hours). They will also be asked to allocate another half a day to the collection of biopsychological measurements.

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Measurements recorded at +4 and +12 months are identical to those performed at inclusion, except for sociodemographic data, and the sample needed to assess vulnerability (genetic polymorphism).

Thus, all participants are required to attend 4 measurement sessions: visit 1, inclusion; +4 months; +6 months; and +12 months. During each of these visits, they will be asked to complete a self-administered (using a tablet) questionnaire to collect psychosocial data. In addition, at inclusion, +4 months, and +12 months, (1) biological samples will be collected for each participant (blood and saliva) and (2) activation of the autonomic nervous system (heart rate variability and electrodermal activity) will be measured at rest, during emotional activation (the classic, then the emotional Stroop task), and at recovery.

Outcomes

Primary End Point

There is no consensus in the literature regarding the definition of resilience, and there are references to several dimensions. Consequently, measuring the effect of the intervention on resilience requires the use of several indicators. A simple approach would be to measure PTSD symptomatology reported by participants, with the expectation that the intervention will result in a decrease in symptoms. Although this approach would be relevant for long-term measures [40], using this criterion in a short-term study, such as ours, would be restrictive and fail to support the processes that are assumed to be activated during the intervention [41]. The latter consists, in part, of removing barriers to seeking care when necessary, in order to support the building of resilience as a process, and not simply as a state. Our short-term approach is also justified by the difficulty of conducting studies in a military environment over the long term (personnel are transferred every 3 years) and attrition among professional soldiers.

The proposed composite criterion groups indicators of resilience that are described as protective factors for PTSD and are recognized to be sensitive to interventions. The first is the participant's emotional state. It is known to be highly impacted in PTSD, where there is an increase in negative emotions. At the same time, it is a marker of resilience in cases where emotions become positive following trauma. We will therefore use the Positive and Negative Affect Scale (PANAS) score [42], which measures the intensity of positive and negative emotional states. Our second indicator measures self-compassion, which refers to a general tendency to be kind to oneself, despite knowing one's failures and successes. Self-compassion is very directly linked to the process of self-acceptance and is a predictive criterion for both the development of PTSD (when it is deficient), and increased resilience (when stimulated by a psychotherapeutic intervention). Self-compassion also contributes to cognitive flexibility. Finally, the third indicator is the hardiness score. This measure is classically used in the literature to study, from a psychological point of view, an individual's ability to remain in good health under stressful conditions. It should be noted that this measure should not, by itself, be considered a sufficient criterion for resilience in our protocol, given that any modification is observed over the long term, based on a quasi-dispositional approach.

Consequently, the hardiness score will be combined with mood and self-compassion criteria. The composite criterion will be evaluated at 4 months (Figure 1). A change in resilience will be defined as favorable if at least two of the following three criteria are met: (1) a 20% improvement in the PANAS score; (2) given the military context, and the nonspecific nature of our intervention, a 20% improvement in scores on the Self-Compassion Scale; or (3) a 5% change in hardiness, measured using the Dispositional Resilience Scale (DRS-15) [43]. If these criteria are not met, any change will be considered to be unfavorable. The choice of thresholds for variables making up the composite criterion is based on data from research conducted by the project's teams.

Emotional State

The data based on the STEP study, carried out in the framework of Delphine Traber's thesis [24], show a 33.68% long-term increase in the PANAS score among members of the *Bataillon de Chasseurs Alpins* who had undergone training (pretraining score=12.32, posttraining score=15.21, and 6-month posttraining score=16.47). Thus, in the PREPAR study, we consider a 20% improvement as significant (for questionnaire details, see Multimedia Appendix 2 [42-44]).

Self-Compassion

According to Kotsou and Leys [44], the mean score is 2.88 in the French population. A score between 3.5 and 5.0 indicates a high level. Thus, in the context of this study, an increase of 20% (0.62) will be considered relevant (for questionnaire details see Multimedia Appendix 2).

Hardiness, the Ability to Stay Healthy Under Stressful Conditions

In the literature, global hardiness scores (measured by the DRS-15 scale) in military populations are around 29 (scores can range from 0 to 45). To the best of our knowledge, there are no studies that have evaluated the effect of a prevention program on this variable. Thus, as this is a dispositional measure, we consider a 5% increase as relevant (for questionnaire details see Multimedia Appendix 2).

Secondary End Points

The evaluation criteria used to meet the secondary objectives are provided in the following sections.

Objective 2.1: Vulnerability

We will assess the following regarding vulnerability:

1. Innate: based on a study of the polymorphism of genes involved in stress regulation mechanisms (see Multimedia Appendix 3). These analyses will not be used in a diagnosis.
2. Acquired: based on miRNAs that target regulatory phenomena established in earlier work (see Multimedia Appendix 4.
3. General psychological and somatic symptomatology (the PHQ-15, HADS, and PCL-5).

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Objective 2.2: Change in Resilience

We will assess follow-up of the change in scores on composite end point questionnaires: PANAS, Self-Compassion Scale, and DRS-15 at 6 and 12 months after inclusion.

Objective 2.3: Change in Psychobiological Biomarkers of Activation and Deterioration

We will assess the following regarding change in physiobiological biomarkers of activation and deterioration:

1. Indirect markers of oxidative stress: lipoperoxidation markers thiobarbituric acid reactive substances and 8-iso-prostaglandin F2alpha [45,46].
2. Circulating markers of central nervous system activity: GABA, brain-derived neurotrophic factor, kynurenic acid, and dopamine [47-49].
3. Inflammation: proinflammatory cytokines (including C-reactive protein, TNF-alpha, IL23, and IL12), anti-inflammatories (IL10 and IL6), and chemokines [50,51].
4. Hypothalamic-pituitary-adrenal axis: cortisol (analysis of saliva on waking, getting up, and 30 minutes later), catecholamines, and neuropeptide Y [52].
5. Markers of physiological activation (autonomic nervous system): cardiac variability index (temporal, frequency, and nonlinear analysis of the electrocardiogram signal to measure indices of parasympathetic flexibility), and electrodermal conductance (level of tonic activity, and amplitude of phasic activity to assess activation of the sympathetic system and its persistence) [53,54].
6. Psychological: follow-up of perceived stress (Cohen questionnaire) and psychological symptomatology scores (the PCL-5, the HADS, and the BMS).

Objective 2.4: Change in Psychosocial Factors

We will assess the following regarding change in psychosocial factors:

1. Flexibility of coping strategies, Flex Cop [55].
2. Sense of duty, inner correspondence, and peaceful harmony (ICPH) questionnaire [31].
3. Emotional reactivity (scores on the emotional Stroop task are compared with the classic Stroop task before and after the intervention at 4 and 12 months) [56,57]. The aim of this task is to evaluate the flexibility of sympathetic and parasympathetic systems inherent in the emotional response to trauma. The classical Stroop task (baseline) will be followed by the emotional Stroop task (reactivity). No learning effect has been documented with using this experimental modality.
4. Self and public stigma scores of PTSD in the military.
5. Perceived social support (the multidimensional scale of perceived social support) [33], and institutional support (the Sieblod vertical and horizontal cohesion questionnaire).

Objective 2.5: Describe Changes in Adherence to the Intervention

Adherence will be assessed using quantitative criteria at 4, 6, and 12 months (the Treatment Motivation Questionnaire). This analysis will be based on (1) an analysis of the processes put in place to operationalize the intervention; (2) a focus group consisting of 8 participants, and 10 individual interviews carried out at 4 and 12 months after inclusion; and (3) a qualitative analysis of discussions that took place during workshops to anchor the practice held at 6 months and 1 year. The latter will also make it possible to identify both obstacles and drivers of adherence.

Objective 2.6: Describe User Satisfaction With the URGOfeel System

We will assess user satisfaction with the URGOfeel (Urgothech) application using visual analog scales, and short questionnaires that measure (1) the user experience and (2) its benefits.

Ancillary Study

We plan to run a qualitative analysis of the transferability of the intervention. The transferability assessment will be carried out at the very end of the research protocol (1 year after inclusion) and will use the transferability and support to the adaptation of health promotion interventions ASTAIRE tool. The aim is to facilitate the transfer of the intervention to other populations, both military and civilian. The intervention could then be tailored to other populations, based on this evaluation. The ancillary study will focus on qualitative details, notably the conditions, obstacles, and drivers facilitating the transferability of the intervention to other populations or other contexts. The criteria required by ASTAIRE will be supplemented by a qualitative evaluation based on interviews (n=20), and a focus group (n=8) at the end of the intervention. To limit bias, we will ensure that participants in the various segments of this ancillary study (ASTAIRE, focus groups, and interviews) are distinct from one another. A summary of the analysis of these criteria (qualitative, Astaire, and quantitative, in the long term) could be used as a guide for future deployments of the intervention.

Statistical Methods

Continuous variables will be presented as mean and SD, if the distribution is normal (the Shapiro-Wilk test will be used, if necessary). In case of a nonnormal distribution, data will be presented as median, quartiles, and extreme values. Scale variables will be treated as ordinal data and analyzed as above. Depending on the analysis, data may be classed as categorical variables. Categorical variables will be expressed as absolute values and percentages. To control for attrition, calculations will assume 20% of data are missing.

The primary analysis will examine the effectiveness of the prevention program. This will be evaluated by comparing the percentage of responses between intervention and nonintervention groups, using a χ^2 test. Secondary analyses will examine the abovementioned markers. Values for the intervention and the nonintervention group will be compared using a repeated measures ANOVA if the conditions for applying an ANOVA are met. Vulnerability will be initially identified using a cluster analysis of the measured biological variables (a *k*-means or Gaussian model mixture, depending on the distribution). The analysis will seek to identify the most biologically at-risk cluster (vulnerable compared with nonvulnerable). The effect of the intervention as a function of vulnerability status will be evaluated using repeated measures

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ANOVA, by comparing vulnerable and nonvulnerable groups. Psychosocial variables will be compared between intervention and nonintervention groups using repeated measures ANOVA, if the conditions for its application are met. A regression analysis will aim to test the mediating role of psychosocial determinants in the improvement of the composite score.

Sample Size

The number of participants to be included is not based on an a priori calculation. This is due to the absence of data in the literature regarding the effectiveness of a primary prevention program in the military context, measured using a composite criterion that encompasses affect, self-compassion, and hardiness. In order to determine the sample size needed to observe a significant between-group difference, we used the following parameters: a 2-tailed statistical test; a 55% response rate in the intervention group; a 30% response rate in the nonintervention group (significance P=.50; power =0.80). If we take into account potential dropouts (estimated at 20%), each group should consist of 58 individuals, making a total of 116 participants.

Results

The project is currently ongoing, and results are expected to be published by the end of 2024.

Discussion

This project aims to evaluate an interventional research program for the primary prevention of occupational health problems. The program is as comprehensive as possible and synergistically links physiological, psychological, and social factors. We hope that the integration of biopsychosocial factors, which are suited to the characteristics of the occupational environment, will reinforce the effectiveness of current strategies. The project respects the three pillars of evidence-based prevention: (1) it investigates what is the best evidence and contributes to research-based knowledge; (2) it considers experiential knowledge; and (3) it takes into account the values, preferences, and characteristics of populations and individuals. This type of primary prevention intervention could provide a framework for other interventions that can be modified and adapted to different professional contexts. Data regarding transfer and feasibility collected during our study with operational military personnel could be used in further work to optimize the program for other army corps. Finally, it is imperative to stress that this study adopts an ecological approach, that is, it strives to reflect as closely as possible the real-life experiences of French army soldiers. This approach is essential to obtain information directly applicable to their daily routines and challenges. However, it is essential to recognize that there are potential limitations inherent in this approach, particularly with regard to adherence to the research protocol. Operational constraints within the military environment can sometimes override the ideal execution of the research program. These constraints may require adjustments to the protocol to ensure practicality and feasibility. For example, modifications in the number and frequency of workshops may be necessary to meet service needs and requirements, without compromising operationality. However, the encouraging exploratory results and the interest shown by the military personnel observed by Traber [24] mean that we can be confident that this study will provide a better understanding of the field of PTSD prevention in the military.

The research team is committed to maintaining the integrity of the study while adapting flexibly to these challenges, in order to obtain meaningful and relevant results that will contribute to the well-being and effectiveness of our soldiers in the French army.

Acknowledgments

The authors warmly thank officers and operational staff of the Mountain Infantry Brigade and, more specifically, the 4th company of the 3rd *Batallion de Chasseurs Alpins* and the 3rd company of the 7th *Bataillon de Chasseurs Alpins*. This work is supported by the French *Direction Générale de l'Armement*. The opinions or assertions expressed herein are the private views of the authors and are not to be considered as o cial, or as reflecting the views of the French Military Health Service.

Data Availability

The data sets generated during or analyzed during this study are not publicly available due to French Army data policy but are available from the French Military Health Service at dcssa-paris@sante.defense.gouv.fr upon request.

Authors' Contributions

SP, ELB, ETC, MH, MT, DC, and AMD were involved in the conception and design of the trial, and they were also responsible for obtaining ethics committee approval. SP, ELB, MMB, MH, MT, DC, and AMD wrote the paper. All the authors contributed to the refinement of the study protocol and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Workshop schedule.

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[DOCX File , 18 KB - resprot_v13i1e47175_app1.docx]

Multimedia Appendix 2
Questionnaires used for the primary composite end point.
[DOCX File , 13 KB - resprot_v13i1e47175_app2.docx]

Multimedia Appendix 3
Genetic polymorphisms involved in stress regulation mechanisms studied in the project.
[DOCX File , 14 KB - resprot_v13i1e47175_app3.docx]

Multimedia Appendix 4
miRNAs targeting regulatory phenomena established by earlier work and studied in the project.
[DOCX File , 14 KB - resprot_v13i1e47175_app4.docx]

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Abbreviations

BMS: Burnout Measure Short Version
DRS-15: Dispositional Resilience Scale
HADS: Hospital Anxiety and Depression Scale
ICPH: inner correspondence and peaceful harmony
MSPSS: Multidimensional Scale of Perceived Social Support
OPEX: external operation
PANAS: Positive and Negative Affect Scale
PCL-5: Posttraumatic Checklist-5
PHQ-15: Patient Health Questionnaire
PREPAR: Primary Prevention of Posttraumatic Stress Disorder in Military Professionals
PSS: Perceived Stress Scale
PTSD: posttraumatic stress disorder
TE: traumatic event

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Protocol

Investigation of the Association Between e-Cigarette Smoking and Oral Mucosal Health Status Among Young People: Protocol for a Case-Control Trial

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Abstract

Background: Given the paucity of current safety studies related to e-cigarettes, there are no definitive studies on whether e-cigarettes cause oral mucosal lesions or even oral cancer. Although it is still undetermined whether e-cigarettes are harmless, an increasing number of teenagers choose to smoke e-cigarettes and believe that they are not harmful to the human body.

Objective: This aims to determine whether e-cigarettes cause damage to the oral mucosa. This study also aims to evaluate the association between e-cigarette smoking and oral mucous membrane lesions in young adults. The objectives are to (1) compare the oral mucosal conditions in participants with and without e-cigarette smoking habits, (2) assess the effect of the amount of e-cigarette smoking on oral mucosal conditions, and (3) assess the effect of the duration of e-cigarette smoking on oral mucosal conditions.

Methods: In this prospective study, 304 youths aged 15 to 24 years (n=152, 50% who smoke only e-cigarettes and n=152, 50% who do not smoke e-cigarettes or cigarettes) will be divided into 2 groups for a controlled study. Whether e-cigarettes cause oral mucosal lesions will be verified by comparing the odds of oral mucosal lesions in the 2 experimental groups. For this experiment, the predefined power is 80% (P=.04), and the predefined proportions of groups 1 and 2 are 11% and 2.5%, respectively.

Results: This experiment is at the conceptualization phase and has not yet been carried out. Experimenters have not been recruited and no data have been collected.

Conclusions: e-Cigarettes are still an unfamiliar topic to the public, and it is still unknown whether they can cause damage to the oral mucosa. This experiment aims to find out whether there is a link between the 2. There are still many limitations in this study, such as the lack of categorization of e-cigarettes and the lack of testing methods for oral mucosal status. These limitations are expected to be addressed in the future as the experiment is formally conducted and further optimized.

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KEYWORDS

oral mucosal lesions; e-cigarette; youth; oral; moth; lesion; lesions; cigarette; cigarettes; smoker; smoking; smokers; smoke; mucosa; mucosal; dental; dentist; dentistry

Introduction

Background

Oral cavity cancer is the most prevalent head and neck malignancy worldwide [1,2]. This malignant phenotype is often associated with habitual and lifestyle factors, such as tobacco smoking, excessive alcohol consumption, betel nut chewing, and low intake of fruits and vegetables [1]. Due to restrictive government policies and proven negative health effects in many parts of the world, the use of tobacco has declined in recent decades [3]. Electronic cigarettes (e-cigarettes) were invented by a Chinese pharmacist, Hon Lik, in 2003, who envisioned that they would replace conventional cigarettes due to their

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deleterious effects [4]. e-Cigarette companies claim that handheld devices can provide smokers with the same experience as conventional cigarettes while reducing their negative effects. e-Cigarettes were introduced with the hope that the smoking population would gradually stop using conventional cigarettes and switch to e-cigarettes. With the waning consumption of regular cigarettes, the use of e-cigarettes has surged worldwide, indicating that smokers now consider e-cigarettes viable replacements. Moreover, recent data have indicated that e-cigarette smoking practices are more common among teenagers and young adults [5,6]. However, most people do not take this soaring statistic seriously and allow young people to use e-cigarettes freely. Most people believe that the health hazards of smoking only manifest with increasing age and, thus, concern is unnecessary regarding the use of e-cigarettes by young people.

It is no surprise that young adults are the primary habitual e-cigarette users. The portability of the devices, different flavors with less nicotine, and convenient use of e-cigarettes make them appealing to young people. Data from the 2011-2018 National Youth Tobacco Survey in the United States demonstrated that e-cigarette use among high school students increased from 1.5% in 2011 to 20.8% in 2018 [3]. In 2022, the Centers for Disease Control and Prevention indicated that 2.55 million US middle and high school students reported current (past 30 days) e-cigarette use; nearly 85% of these young people used flavored e-cigarettes, and more than half used disposable e-cigarettes [7]. This increase has also become noticeable in community settings. Unfortunately, adults do not pay enough attention to the use of e-cigarettes, especially in schools.

Current research on e-cigarettes has solely focused on their ingredients and compared satisfaction levels of e-cigarettes with those of regular cigarettes [8,9]. The safety of e-cigarettes, especially regarding the etiology of oral and maxillofacial diseases or other possible intraoral side effects, is still unclear. Moreover, few studies have reported on the adverse effects of e-cigarette smoking [10]. Recent experiments have only indicated that the use of e-cigarettes could impact the balance in the oral microbiome while allowing for the rapid growth of foreign microorganisms [4]. Nevertheless, many studies recommend that individuals replace cigarettes with e-cigarettes irrespective of concerns about their safety.

Smoking causes damage to the oral mucosa as well as lesions that can lead to the progressive development of oral cancer [11]. According to research, smoking can cause “oral mucosal leukoplakia” and a variety of other oral mucosal diseases. Additionally, it has been shown that leukoplakia is the oral mucosal lesion that is most likely to lead to oral cancer [12]. Most of the white spots on the lips occur on the lower lip, in the junction of the middle, and on the outer third of the lip, which is where people usually hold cigarettes; this can explain the relationship between holding cigarettes and white spots on the lip. White spots are precancerous lesions, and approximately 4% to 7% can develop into oral cancer. According to statistics, 93.1% of patients with oral white spots are smokers [13]. The development of oral mucosal lesions is based on the principle that tobacco irritates the oral mucosa (through cigarette smoke and the chemicals in cigarettes), causing it to react adversely to prolonged irritation. e-Cigarettes operate in a similar way to tobacco, which also irritates the oral mucosa through atomization and chemicals.

The only difference between e-cigarettes and cigarettes is simply that e-cigarettes do not contain tar; both contain many chemicals as well as nicotine. e-Cigarettes tend to have more types of chemicals than cigarettes because of the wide variety of flavors.

Given that it is still unknown whether e-cigarettes influence the development of oral mucosal lesions, the possibility that e-cigarettes can cause damage to the oral mucosa and increase the risk of oral cancer similar to tobacco needs to be studied.

To date, no definite investigation of the association between e-cigarettes and oral cavity cancer has been conducted. When available, this study will be the first to determine whether e-cigarettes are mechanistically linked to the development of oral cancer to further educate young users and students on the potential for malignancy due to e-cigarette use. It is assumed that e-cigarettes cause damage to the oral mucosa and oral cancer, which is similar to cigarettes. The following experimental studies and designs will be conducted to test this hypothesis. Therefore, this study aims to investigate the association between e-cigarette smoking and oral mucosal health status among young adults and determine whether e-cigarettes cause damage to the oral mucosa and increase the risk of oral cancer. Compared to that of other similar studies, the methodology of this study is simpler, and the results will be clearly comparable. If the results show that e-cigarettes can cause damage to the oral mucosa similar to that caused by cigarettes, this study could provide strong support for subsequent experiments to determine whether e-cigarettes cause oral cancer.

Hypothesis

This study hypothesizes that e-cigarettes, in the speculated absence of tobacco, may still induce carcinogenesis. Alternatively, it is suggested that this habit may trigger an imbalance in the oral microbiome that predisposes the mucosal epithelium to oral cavity cancer with other etiological factors. This presupposed risk is likely proportional to the frequency and duration of e-cigarette smoking. The oral mucosal health of participants will be determined by determining the presence of white spots in the mouth (the main feature of the oral mucosa that is damaged by smoking behavior).

Primary Outcome

The primary outcome is the effect of e-cigarette smoking on oral mucosal conditions.

Research Significance

The results of this study will provide preliminary evidence of the malignant potential of e-cigarettes in the deterioration of oral mucosal conditions or exclude them as a cause of oral carcinogenesis. If a direct association is observed, the results of this study would be vital to inform e-cigarette users of the harmful and even carcinogenic nature of e-cigarette smoking, despite e-cigarettes being considered tobacco free. In addition, this would help guide the implementation of legislative policies to bring awareness to the additional risks associated with the use of e-cigarettes and vaporizers. Moreover, these findings, if

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positive, will pave the way for future research on chemical products that may be present in e-cigarettes that are directly involved in the malignant transformation of oral keratinocytes.

Methods

Trial Registration

Given that this study is at this stage of conceptualization and has received no support or sponsorship from any organization at this time, this experiment has not yet been applied for trial registration. The registration will be done in the future when support is received from the relevant organizations.

Ethical Considerations

This study has not yet been submitted to the ethical review board for assessment, mainly due to lack of financial support and lack of assistance from large organizations. We emphasize that this is an independent study and is still at the research protocol stage. As the project has not received sufficient financial support, we are unable to cover the costs of applying for evaluation by the ethics review committee at this time. At this stage, we are working to ensure that the study design meets ethical standards and will seek possible review and approval at a future stage. We understand and value participant rights and will take appropriate measures to ensure the ethical and legal nature of the study.

Study Design

The adoption of a case-control, prospective, observational study design is motivated by the relatively low incidence of oral mucosal lesions within the general population. This design allows for a focused exploration of the relationship between e-cigarette smoking and oral mucosal health.

Case-control design is particularly suitable for investigating rare outcomes such as oral mucosal lesions, as it efficiently compares individuals with the outcome of interest (cases) to those without (controls).

A prospective design involves following participants over time, allowing for the collection of data on exposures and outcomes as they occur. By prospectively tracking participants, the study can gather real-time information on e-cigarette smoking habits and observe the development of oral mucosal lesions, providing a temporal sequence crucial for establishing causation.

An observational design is chosen over an experimental one due to ethical considerations and the nature of the research question. Since randomly assigning participants to smoke e-cigarettes for an extended period is ethically challenging, an observational approach allows for the examination of naturally occurring exposure to e-cigarette smoking in real-world settings.

The low incidence of oral mucosal lesions in the general population necessitates a design that efficiently targets and investigates this specific outcome. By focusing on a population at risk (e-cigarette smokers) and carefully selecting controls, the study maximizes its ability to detect and understand the potential impact of e-cigarette smoking on oral mucosal health.

Study Population

According to the United Nation definition, people between the ages of 15 and 24 years are defined as young people [14]. This age group coincides with the rapidly growing population of e-cigarette smokers, which is not a concern to mainstream society. Therefore, the 15- to 24-year-old group has been selected as the study population. American participants between 15 and 24 years of age will be recruited irrespective of their sex, race, occupation type, and socioeconomic status and divided into “e-cigarette case” and “control” groups. The selection criteria for each group are as follows.

The exclusion criteria for the two groups (the following criteria will be applicable in both groups and do not need to be listed repeatedly) are (1) participants with histologically diagnosed recurrent oral cavity cancer whose primary tumors occurred outside the recruitment timeframe (2 years before the first diagnosis); (2) participants with synchronous solid or hematological malignancies in other regions at the time of oral cavity cancer diagnosis; (3) participants with a genetic predisposition to oral cavity cancer, including those with Fanconi anemia, systemic lupus erythematosus, and dyskeratosis congenita; (4) participants who meet the inclusion criteria but are unwilling to participate in the study after detailed information has been provided; and (5) participants with severely debilitating systemic conditions that preclude participation in the study.

Selection of the “e-Cigarette Case” Group

Inclusion Criteria

A prospective study among experimental participants who smoked e-cigarettes over the last 210 days or 7 months will be conducted. According to the article “Effects of Duration of Electronic Cigarette Use,” the average duration of use among e-cigarette smokers is 210 days or 6.8 months [15]. The same criteria will be used in this study to standardize the duration of use for both the conventional cigarette smoking population and the e-cigarette smoking population.

Exclusion Criterion

The exclusion criterion is participants who smoke tobacco.

Selection of Controls

Inclusion criteria are individuals without a history of smoking e-cigarettes, drinking alcohol, and smoking tobacco at the time of recruitment.

Exclusion criteria are participants who smoke e-cigarettes and tobacco.

Recruitment Strategy

Overview

The recruitment strategy, targeting customers at e-cigarette stores and pedestrians, is strategically aligned with the study’s focus on e-cigarette users. The inclusion of community selection for matching controls, if quotas are not met, demonstrates flexibility in the recruitment approach. The disclosure of convenience and nonprobability sampling methods ensures transparency, thereby acknowledging the limitations inherent

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in these methods. A nuanced understanding of participant selection challenges is crucial for the accurate interpretation of study findings.

Community Selection Details

If quotas for controls are not met through the initial recruitment strategy, a community selection approach will be considered. This involves identifying and recruiting controls from community settings, ensuring a diverse representation.

Clinical Recruitment Procedures

e-Cigarette Store Recruitment

The e-cigarette store recruitment consists of 3 stages, which are as follows:

1. Approach: e-cigarette stores will be approached to seek their cooperation in the recruitment process.
2. Informed consent: store owners and managers will be provided with detailed information about the study objectives, procedures, and ethical considerations. Upon agreement, consent forms may be obtained from the store owners to allow recruitment on their premises.
3. Participant identification: e-cigarette users within the specified age range will be approached, and the study will be explained to them. Interested individuals will be given detailed information about the study and their consent will be sought.

Pedestrian Recruitment

The pedestrian recruitment consists of 2 stages, which are as follows:

1. Approach: pedestrians in high-traffic areas will be approached with an invitation to participate in the study.
2. Informed consent: similar to the e-cigarette store recruitment, detailed information will be provided to potential participants, and consent will be obtained before proceeding with any study-related activities.

Community Selection (if Necessary)

If quotas for controls are not met through the initial recruitment strategy, community selection may be considered.

1. Approach: community settings such as local community centers or public spaces will be identified. Consent from relevant authorities and community leaders will be sought.
2. Participant identification: controls meeting the study criteria will be approached in these settings, and recruitment will follow the same informed consent procedures.

Sampling Methods

Convenience and nonprobability sampling methods will be used for the recruitment of cases and controls. The detailed sample size determination is shown in Multimedia Appendix 1 [16]. Briefly, the predefined power is 80% (P=.04), and the predefined proportions of the case and controlled groups are 11% and 2.5%, respectively. In all, 304 youths aged 15 to 24 years (n=152, 50% who smoke only e-cigarettes and n=152, 50% who do not smoke e-cigarettes or cigarettes) will be recruited.

Data Collection: Questionnaire

Interviewer-administered questionnaires will be used to collect data on demographic, lifestyle, and socioeconomic variables for the cases and controls. The questionnaire tool will comprise 2 parts: exposure information (part A) and sociodemographic information (part B). A life grid sheet will be used during interviews to efficiently collect retrospective information on lifestyle habits and other risk factors. To reduce observer bias, interviewers will not initially be informed about the aim of the research. Once cases are identified and interviewed, matching controls will be recruited and interviewed. Answers provided by participants will be converted to objective scores after data collection by the investigator (SC). The details on the parts of the questionnaire are as follows.

Exposure information (part A) will include (1) oral mucosal health status (whether white spots are present), (2) smoking habits, (3) type of products used, (4) e-cigarette smoking status (yes or no and current or previous), (5) age of onset, (6) duration of smoking, (7) pattern of smoking duration (continuous or intermittent), (8) frequency of smoking (daily, weekly, and occasionally), (9) number of cartridges (frequency), and (10) Tobacco consumption. Sociodemographic information (part B) will include (1) age, (2) sex, (3) occupation type, (4) education level, (5) income, and (6) ethnicity.

Questionnaire Validity and Reliability

Before the deployment of the questionnaire for field use, face validity and qualitative content validity will be determined by a panel of experts in oral and maxillofacial surgery, dental public health, biostatistics, and laypersons. The internal consistency of the scales used to measure e-cigarette smoking exposure will be determined using Cronbach α, with a minimum α value of .70 indicating good and acceptable reliability.

Data Analysis

Descriptive statistics will be used for all binary, categorical, and continuous variables and expressed as tables, texts, and figures. Bivariate analysis will then be performed for relevant variables. The Shapiro-Wilks test will be performed for continuous variables to determine whether they follow the Gaussian distribution. Afterward, the independent 1-tailed t test and 1-way ANOVA will be used; otherwise, the Mann-Whitney U test and Kruskal-Wallis test will be performed. For cross-tabulation of 2 categorical variables, the chi-square test will be used. Variables that do not fulfill the assumption of this test will be analyzed using Fisher exact test. Comparisons with P=20 will be used to implement multivariable analysis using multiple logistic regression. Odds ratios and 95% CIs will be determined for e-cigarette smoking and other individual factors. For all analyses, P<.05 will be used to denote statistical significance. Statistical analyses will be performed using the SPSS (version 27; IBM Corp).

The control and e-cigarette groups will be subjected to a t test (assuming the data meet the normality criteria and do not meet the criteria for the rank sum test) to verify whether e-cigarettes cause harm.

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Results

This experiment is at the conceptualization phase and has not yet been carried out. Experimenters have not been recruited and no data have been collected.

Discussion

In examining the potential negative impact of e-cigarettes on the oral mucosa, this study deliberately focused its investigation on this specific aspect, excluding other potential confounding factors that might influence the results. Notably, variables such as alcohol consumption, daily routines, and gender differences were not considered in the experimental design. While these factors were omitted from this study, they were duly documented in the questionnaire phase, laying the groundwork for future investigations to delve into these variables. This strategic choice aimed to isolate the primary relationship between e-cigarette use and oral mucosal health, with the intention to refine and expand the scope in subsequent research endeavors.

The findings of this study align with existing literature on e-cigarettes, which suggests a correlation between the chemicals present in e-cigarettes and cytotoxicity, leading to damage to the oral mucosa. This corroborates with prior research, providing further evidence of the potential harm associated with e-cigarette use [10,16,17]. The recognition of this association holds significant implications for public health, emphasizing the need for awareness campaigns and regulatory measures to mitigate the adverse effects on oral health. Moreover, the study acknowledges the diverse landscape of e-cigarettes in the United States, encompassing various brands and flavors, each containing distinct chemical compositions. Given this complexity, it is acknowledged that the study does not comprehensively analyze all individual chemicals present in different e-cigarettes. This limitation prompts a call for future experiments to undertake a more nuanced examination of the diverse chemical profiles within e-cigarettes to better understand their distinct impacts on oral mucosal tissues.

Despite the valuable insights provided by this study, certain limitations should be acknowledged. The decision to exclude factors such as alcohol consumption and daily routines may have implications for the generalizability of the findings. In addition, the complexity of e-cigarette compositions poses a challenge, as the study did not extensively investigate the myriad chemicals present in different e-cigarette products. Future research endeavors should consider a more comprehensive approach, encompassing a broader range of variables and a detailed analysis of the chemical constituents of various e-cigarettes.

In conclusion, this study contributes valuable evidence to the growing body of knowledge on the potential negative impact of e-cigarettes on oral mucosal health. By focusing on a specific aspect while recognizing its limitations, this research paves the way for future investigations to build upon these findings. The implications extend beyond the immediate scope of oral health, emphasizing the broader need for public health interventions and regulatory measures in response to the evolving landscape of e-cigarette use.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

SC was in charge of the study conceptualization, writing and reviewing the original draft, and editing the final draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample size determination.
[DOCX File , 15 KB - resprot_v13i1e53644_app1.docx]

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Protocol

An Individual Music Intervention for Adults With Intellectual Disabilities and Challenging Behavior: Protocol for a Randomized Controlled Trial

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Abstract

Background: Individuals with intellectual disabilities (ID) are more likely to have problems with executive functioning (EF) and challenging behavior (CB), which are negatively linked to well-being. Among clinical populations, music interventions have been shown to improve various outcome measures, such as CB and EF. Until now, no randomized controlled trials (RCTs) have been conducted to examine the effectiveness of an individual music intervention for adults with ID and CB.

Objective: The study aims to identify the effect and feasibility of an individual music intervention compared with care-as-usual for people with ID and CB.

Methods: In this study, a 2-group RCT with a pretest, posttest, and follow-up assessment after 8 weeks is presented. Participants of the music intervention condition will receive 16 individual music sessions within 8 to 10 weeks. The music intervention will be guided by a manual for music workers, in which every session will have a different focus (introduction, emotions, different EF, and end performance). Participants receiving care as usual will function as a control group. After the research is finished, they will be offered a budget, which they can spend on musical activities or musical instruments as they wish. Assessments will include caregiver rating scales and self-report questionnaires and tests, which will assess outcome measures of CB, well-being, depression, anxiety, self-esteem, and 4 domains of EF. A process evaluation will be conducted after the completion of the study, which entails the analysis of data on multiple aspects of the intervention and the study overall.

Results: Enrollment commenced in July 2021, and data collection ended in May 2023. A total of 97 participants were recruited, with 44 participants allocated to the intervention group and 53 allocated to the control group. Data will be analyzed after this protocol has been accepted for publication.

Conclusions: Because there are currently no published RCTs of an individual music intervention for adults with ID and CB, this study will provide insight into the effectiveness and experiences of an individual music intervention for this target group.

Trial Registration: International Clinical Trials Registry Platform NL8482; http://tinyurl.com/4565s5pd

International Registered Report Identifier (IRRID): DERR1-10.2196/52497

(JMIR Res Protoc 2024;13:e52497) doi:10.2196/52497

KEYWORDS

music intervention; intellectual disability; challenging behavior; executive functioning; self-esteem; anxiety; depression; randomized controlled trial; RCT; study protocol; well-being

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Introduction

Background

Intellectual disability (ID) is characterized by significant limitations in both intellectual functioning and adaptive abilities, such as conceptual, social, and practical skills. ID originates before the age of 18 years and can be categorized as mild, moderate, or profound [1]. Besides having a lower IQ and problems with adaptive functioning, people with ID are more likely to develop mental health problems, for example, affective and anxiety disorders and challenging behavior (CB) [2,3]. Mental health and CB are negatively linked to quality of life (QoL) [4].

People with ID not only have a higher chance of developing mental health problems and CB, but there is evidence that their executive functioning (EF) is also impacted [5]. EF refers to the set of abilities involved in planning, self-monitoring, and purposive action, which are "at the heart of all socially useful, personally enhancing, constructive, and creative activities" ([6], p. 281). There is broad consensus that there are 3 core EFs: inhibition, working memory, and cognitive flexibility [7,8]. Some studies in the ID field use a broader definition that includes attention [9,10], planning, and categorization [9]. A few studies suggest that regarding EF, people with ID perform at levels commensurate with their mental age [11,12]. Mental age can be calculated from raw scores on intelligence tests: mental age = (IQ score × chronological age) / 100 [13].

Poorer performance on EF tests is linked to more CB, especially externalizing behavior problems, among children, adolescents, and adults with ID. This holds for tests that measure inhibition [14], working memory [15], and cognitive flexibility [16]. Because CB has a major impact on the lives of people with ID and their caregivers, attempts to help diminish CB cover a wide range of different approaches, from environmental approaches [17] and support staff training [18-20], to pharmacological interventions [21]. In 2 meta-analyses, effects were found in reducing CB among people with ID for biological and nonpharmacological (such as psychotherapeutic and contextual) interventions [22,23]. Another example of such a nonpharmacological intervention is music therapy, which a recent review found to have a positive effect on CB, anxiety, self-esteem, management of emotions, cognitive measures, and QoL of people with ID [24]. However, this review concluded that most of these studies had several shortcomings, such as no control group, small sample sizes, lack of follow-up measurements, and no use of self-reports.

Several empirically valid studies have been carried out with participants who have other cognitive or communication disabilities, such as dementia, acquired brain injury, or autism spectrum disorder [25]. In these studies, beneficial effects of music interventions on various outcomes were found, such as self-esteem [26], anxiety [26-29], CB [27], mood [28,30,31], QoL [30,31], and EF (ie, working memory, attention, and EF in general) [30]. However, even in these well-researched fields, there seems to be a paucity of high-quality empirical studies [32,33], which emphasizes the need for more rigorous randomized controlled trials (RCTs) with sufficiently large sample sizes studying the different effects of music interventions.

Although music interventions seem effective on CB, anxiety, mood, self-esteem, management of emotions, cognitive measures, and QoL, it is worth noting that the type of music interventions used can vary widely, depending on the goal and the characteristics of the participant. Some interventions are group sessions, whereas others are individual music sessions that can be tailored more to a participant's individual needs and that show tangentially higher effects, for instance, on agitation in persons with dementia [34]. Some interventions include music therapy (which involves a trained professional using music to address specific therapeutic goals), music listening, or general music-based interventions [35]. It is not uncommon to follow a guideline, with specified principles and procedures of the music intervention, while still leaving enough flexibility to tailor the intervention to the characteristics and needs of the participant and the specific requirements of the situation [33]. Music interventions range from daily to weekly, lasting 10 to 60 minutes, and can have "passive" (listening) or "active" (making music or sounds together) components [33,36]. Active music interventions generally provide greater individual benefits than passive music engagement among older people [37,38], people with autism spectrum disorder [36], and in the general population [39].

Overall, evidence suggests that active music participation can enhance one's emotional, psychological, and social well-being and even increases EF (eg, working memory and attention) in specific clinical populations; however, to the best of our knowledge, no RCTs are available assessing the effectiveness of an individual music intervention for adults with ID, let alone for adults with ID and CB. In this protocol paper, the design and rationale of an RCT are described, in which a manual for an individual active music intervention for adults with ID and CB is presented, matched with persons with ID and CB who receive care as usual (CAU) functioning as a control group.

Objectives

Primary Objective

The primary objective of the proposed RCT is to evaluate the effect of receiving 16 individual active music sessions compared with CAU in adults with a mild or moderate ID with CB on various outcome measures such as CB, well-being, depression, anxiety, self-esteem, and 4 domains of EF.

Secondary Objective

A secondary goal of this study is to evaluate the implementation, impact, and context of the individual music intervention with input from participants, caregivers, and music workers.

Methods

Study Design

This study is an RCT with a pretest (T1), posttest (T2, 9 weeks after T1, unless the last intervention session was not yet completed; posttest was postponed by 1 or 2 weeks until the week after the final session), and follow-up assessment (T3, 8 weeks after T2), including 2 groups of individual participants

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(see Figure 1). Participants belonging to the music condition will receive 16 individual music sessions within 8 to 10 weeks, and participants belonging to the control condition will receive (individual) CAU. Randomization will be performed at a facility level for 3 reasons: first, to prevent possible interference between participants belonging to both groups in a facility; second, it is deemed unethical and difficult to explain to people with ID who are assessed to the control condition that they have to wait for the music sessions, whereas fellow residents already receive them; finally, it can also promote recruitment [17]. For randomization, a computerized random number generator will be used. There is no maximum number of participants per facility. Blinding is not possible because it is clear to the caregivers, participants, and research assistants which type of intervention a participant receives. The independent research assistants are also not blinded because the participants of the music intervention have to fill in an extra questionnaire at the second and third assessment.

Figure 1. Study flowchart.

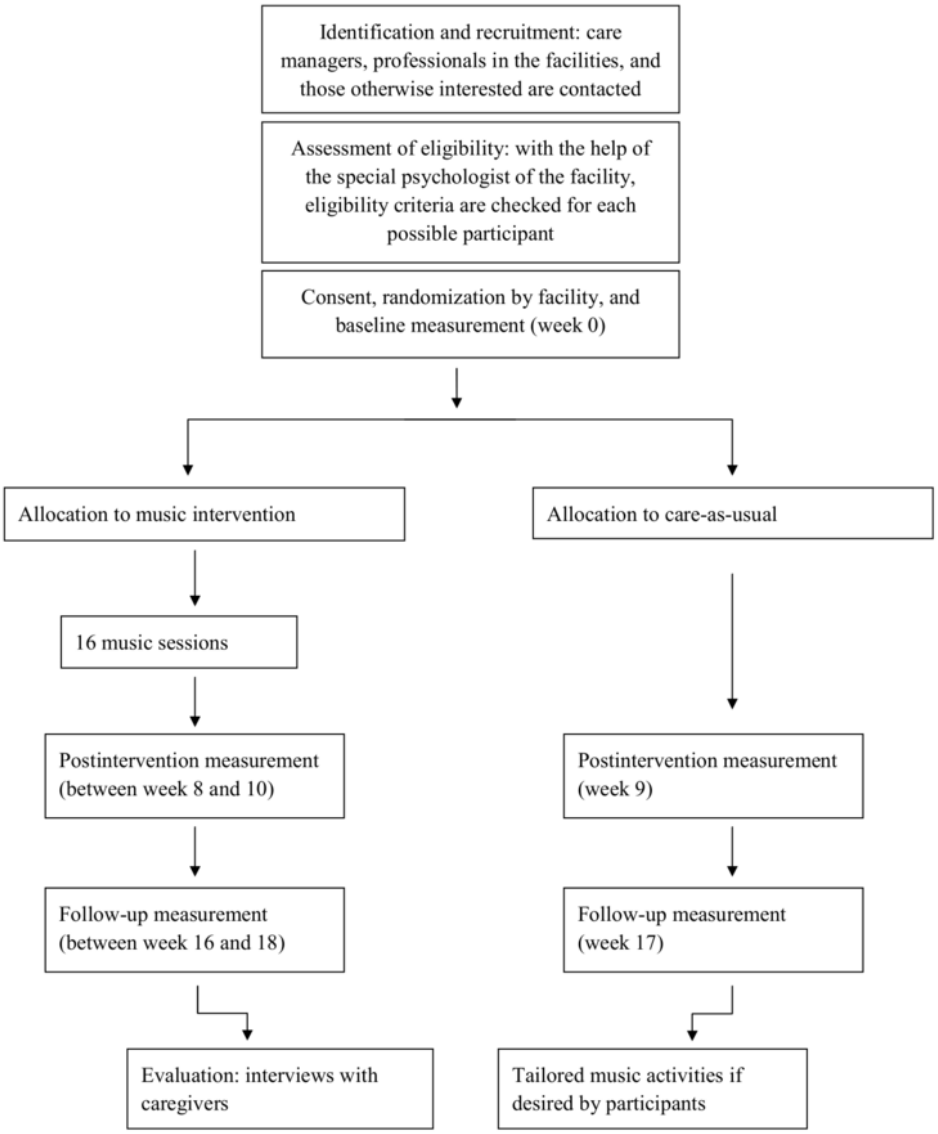

Study Population

Participants will be included based on 4 criteria and 3 exclusion criteria. The inclusion criteria are as follows: (1) participants must have a mild or moderate ID, (2) they are 18 years or older, (3) they show either internalizing or externalizing CB, and (4) they are mentally competent to give consent to participate in this research. The exclusion criteria are as follows: (1) inability to participate in an intervention for at least 1 hour; (2) a hearing impairment that cannot be corrected with a hearing aid; and (3) a serious medical condition that limits participation, such as dementia. Already being involved in prior musical activities is not an exclusion criterion.

Procedure

Participants will be recruited from residential facilities for people with ID of the Philadelphia Care Foundation throughout the Netherlands. Because participating in this study requires time and effort of their staff, care managers of facilities serving adult residents with mild to moderate ID are contacted about their willingness to participate in the study. Managers with interest will receive an information letter explaining the research aims and responsibilities of all parties involved. Next, the special

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psychologist of the facility will check which residents are eligible for inclusion, who then will receive an information letter and an informed consent form in a Dutch easy-to-read format [40]. Caregivers will be asked to read the letter together with potential participants and help them to fully understand the text, if needed. Legal representatives of the eligible residents will also receive an information letter and an informed consent form, whereas nonlegal representatives of the eligible residents will only receive an information letter. Residents will only become participants in the study if (both) informed consent forms are signed. Subsequently, the special psychologist of the facility will be asked for the participant characteristics, which are age, gender, level of ID, syndrome (when applicable), and comorbid psychiatric diagnoses.

After all assessments are completed, participants will receive a compliment postcard from the Philadelphia Care Foundation and a gift card of €15 (US $17.82 when enrollment commenced).

Intervention

In this RCT, 2 conditions are compared: a music intervention and CAU.

Music Intervention Group

The music intervention consists of 16 individual music sessions held twice a week within 8 to 10 weeks. Besides this individual music intervention, regular musical activities that participants already are involved in before the start of this study will continue, as music participation is a central theme of the Philadelphia Care Foundation. The 16 music sessions will be conducted by a music worker, who can be anyone who is able to play an instrument and is enthusiastic and capable to conduct musical sessions with a person with ID. Music workers are not music therapists because the focus is not on therapy but on a general active music intervention. Before the start of the music intervention, the facility in which it will take place will receive a box with an assortment of different kinds of musical instruments, including rhythm instruments (eg, cajon, djembe, and small percussion) and harmony and melody instruments (eg, keyboard and guitar). In general, during the sessions, the music worker adapts the genre or specific pieces of music to the wishes and preferences of the participant. The music intervention will be guided by a training manual for the music workers, in which the frequency, average time per (elements of the) session, and the content of every music session are outlined. The manual is designed based on the input of different advisory groups with professional music coaches, caregivers, and people with ID.

In the manual, intervention procedures are specified, such as the setting, general goals, contents of the music sessions, basic principles of the intervention, and exemplifications. An outline of the music session can be seen in Table 1. Every session will be centered around a different aspect (introduction, emotions, different EF, and end performance), and in the training manual, example exercises are described focusing on every aspect. These examples are provided by advisory groups of professional music coaches and stem from different other manuals [41-43]. Each session will start with a welcome song, after which a listening exercise will take place. Then, a warm-up of the voice and body is scheduled, and subsequently, participants actively engage in music activities by singing or playing an instrument, after which a cool-down and a farewell song are performed. The manual provides a fixed frame for the intervention, but it leaves enough flexibility to tailor the intervention to the characteristics and needs of every participant. Participants will receive a diploma at the final session.

To study for exploratory purposes the impact of the music sessions' frequency, some participants will receive extra music sessions, resulting in 24 to 27 sessions within the same time period, aiming at approximately 3 sessions a week.

Table 1. Outline music session.

Music intervention	Time (minutes)	Attendees
Preliminary meeting	30	Music worker, participant, and caregiver
Music session • 1: Welcoming or introduction • 2-6: Emotions • 7+10: EF[a] (Inhibition) • 8+11: EF (Cognitive flexibility) • 9+12: EF (Working memory) • 13-15: Working toward the end performance or song • 16: End performance or song	60	Music worker and participant
Final meeting	30	Music worker, participant, and caregiver

[a]EF: executive functioning.

CAU Group

Participants receiving CAU will function as a control group. CAU includes regular care such as assistance with acts of daily living and day care activities. CAU can include musical activities that participants already performed before the start of this study, as music is a central theme of the Philadelphia Care Foundation. However, new individual musical activities will be postponed for these participants until after the follow-up measurement. Participants receiving CAU will be offered a budget at the end of the study, which they can spend on musical activities or musical instruments to their own wishes, with the help of a musical specialist who works at the Philadelphia Care Foundation.

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Measures

All assessments (T1, T2, and T3) will take place by applying caregiver rating scales and self-report questionnaires and tests and all will be conducted in the same week. Students from several Dutch universities will work as research assistants assisting with the data collection. Research assistants receive theoretical and practical training in assessment through a training program in the test administration protocol. They will administer all irregularities and deviations from this protocol in a study log report. The research assistants will not be involved in the intervention itself. An overview of the outcome measures and the process evaluation can be seen in Table 2.

Table 2. Overview outcome measures and process evaluation.

Assessment	Proxy or self-report			Measurement moment				
	Caregiver	Music worker	Person with ID[a]	Each music session	Baseline (T1)	Postintervention (T2)	Follow-up (T3)	After follow-up
Outcome measures								
Self-reports and tests			✓		✓	✓	✓	
Proxy questionnaires	✓				✓	✓	✓	
Evaluation[b]								
Evaluation questionnaire music sessions		✓	✓			✓		
Follow-up evaluation	✓		✓				✓	
Self-report with emoticons			✓	✓				
Log reports music sessions		✓		✓				
Semistructured interview	✓							✓

[a]ID: intellectual disabilities.

[b]Only in the music intervention.

Outcome Measures

Challenging Behavior

The Dutch version of the Aberrant Behavior Checklist (ABC) will be used to assess CB, and the form will be filled out by a caregiver [44]. The ABC consists of 58 items, which are rated on a 4-point Likert scale, ranging from 0 (“not at all a problem”) to 3 (“the problem is severe in degree”). The sum of the questions provides a total score (range 0-174), with higher scores indicating more CB. In this study, the cluster structure as suggested by Kaat et al [45] will be used. The first cluster (28 items; α=.96, β=.57) represents behavior that is directed outward (ie, externalizing CB). The second cluster (26 items; α=.93, β=.76) represents behavior that is directed inward (ie, internalizing CB). For externalizing CB, the score ranges from 0 to 84, and for internalizing CB, the score ranges from 0 to 78. The total score on cluster 1 (ie, externalizing CB) will be used to assess externalizing CB, the total score on cluster 2 (ie, internalizing CB) will be used to assess internalizing CB, and the total score on all items of the ABC will be used to assess overall CB.

Well-Being

Subjective well-being will be assessed using the Dutch version of the 7-item Personal Well-being Index—Intellectual Disability (PWI-ID) [46]. An example of an item is as follows: “How happy do you feel about the things you have? Like the money you have and the things you own?” Each item is scored on a 3-point Likert scale (0=sad, 1=neither happy nor sad, and 2=happy). Three pictures of colored smileys are used to represent the 3 answers. The pretesting protocol, which screens for acquiescent responding, will not be applied, to diminish the data collection burden for participants. PWI-ID scores range from 7 to 24, with higher scores indicating a better subjective well-being. The PWI-ID seems to be an appropriate measure for people with a mild or upper moderate level of ID [47].

Depression and Anxiety

Symptoms of depression and anxiety will be assessed using the Depressed Mood and General Anxiety subscales from the Dutch version of the Anxiety, Depression and Mood Scale [48]. This questionnaire will be completed by the caregiver. The Depressed Mood subscale consists of 13 items, for example, “somber mood,” which are scored on a 4-point Likert scale (0=behavior has not occurred or is not a problem, 1=behavior sometimes occurs or is a slight problem, 2=behavior often occurs or is a relatively large/moderate problem, and 3=behavior occurs a lot or is a severe problem). Depression scores can range from 0 to 39. The General Anxiety subscale of 7 items, for example, “nervous or anxious,” are also scored on this 4-point Likert scale. Anxiety scores range from 0 to 21. For both subscales, a higher score indicates more symptoms. Its reliability and validity are satisfactory to good [49].

Self-Esteem

Self-esteem will be assessed using the 5-item Global Self-Worth subscale of the Self-Perception Profile for Adolescents [50]. In this study, the Dutch adaptation of the Self-Perception Profile for Adolescents [51] will be used, with a Cronbach α of >.70 and 1 statement per item [52]. An example of an item is “I am quite happy with myself.” Each item is scored on a 4-point Likert scale (1=completely untrue for me, 2=a little untrue for

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me, 3=a little true for me, and 4=completely true for me). The total score can range from 5 to 20, and a higher score indicates higher self-worth.

EF Tasks

Overview

EF will be assessed on a tablet using 3 computer-based games to assess cognitive flexibility, attention, inhibition, and working memory, which were custom-developed in earlier research and are adapted to the needs of individuals with ID, that is, fewer trials, shorter tasks, visual support during test instructions, and attractive stimuli [14,53]. After each game, the research assistant will complete 2 questions about how often the participant needed to be motivated and how often the participant was distracted during the games.

Cognitive Flexibility

The game to assess cognitive flexibility is based on the flanker task [54]. The principle of the flanker task is that participants have to respond to a target arrow, which is flanked by distracter arrows. In this study, this task will consist of 5 arrows per trial, with 32 random trials per condition, with 3 conditions. In the first condition, there are 5 green arrows pointing in different directions (left or right). Participants have to ignore the irrelevant stimuli and press the button in the same direction as the green arrow in the middle. In the second condition, the participants are presented with red arrows. Unlike the previous condition, participants have to press the button with the opposite direction as the arrow in the middle. In the third condition, participants are presented with alternating trials of red or green arrows and are requested to press the button with the opposite direction if the arrow in the middle is red and to press the button with the same direction if the arrow in the middle is green. All 3 conditions had a practice round before the official task. The score used to measure cognitive flexibility consists of the correct responses in the third condition (range 0-32). A higher score implies a higher degree of cognitive flexibility.

Attention

Attention will be assessed with the first condition of the already mentioned flanker task, where participants have to respond to the green arrow in the middle, regardless of the nature of the flanking distractor items, by pressing the right button for right-faced arrows and the left button for left-faced arrows. Both correct and incorrect (ie, missing or lack of on-time response) responses will be added, standardized as *z* scores, to create a composite total attention score. The incorrect responses will be reversed to create a variable in which a higher score represents better attention.

Inhibition

Inhibition will be assessed using two different tasks: (1) the second condition with red arrows of the already mentioned flanker task, which measures interference control [54] and (2) the go or no-go paradigm, which measures the inhibition of a prepotent motor response [55]. The *z* scores on both outcome variables will be added to create a composite total inhibition score for each participant. This new variable will be reversed, so a higher score represents better inhibition skills.

The outcome variable from the flanker task that will be used is the number of faults in the task with only red arrows, representing the inability to suppress an initial response. In this task, participants have to press the arrow corresponding with the opposite direction of the central arrow.

The go or no-go task consists of 2 parts. In the first part, the participant is requested to press the button as soon as a green apple, that is, a “go” stimulus, appears on the screen. In the second part, participants have to tap on the button when the green apple appears, but they have to inhibit their response when a red cross appears through the apple, that is, a “no-go” stimulus. An incorrect answer is given when the participant presses the button, and the green apple appears with a red cross. Both conditions had a practice round before the official task. The outcome measure for the go or no-go task is the total incorrect answers in part 2.

Working Memory

To assess the working memory construct, a visuospatial computerized task, based on the Klingberg principles for working memory, will be used [56,57]. In the Klingberg task, participants have to remember the order that a circle shifts over a 4-by-4 grid of open squares. The task consists of 2 conditions that both start with an instruction and a 4-trial practice session before the regular session. The regular session starts with a pattern of 2 circles on adjacent units and gradually increases in length and difficulty with each trial. Each trial consists of 2 patterns of the same length and difficulty. In the first condition, patterns with a green circle are presented to the participants who have to tap on the squares in the grid in the same order afterward (forward version). In the second condition, patterns of red dots are shown which participants have to tap in the reverse order afterward (backward version). When a participant taps a wrong pattern twice on a trial of the same length and difficulty, the task ends. In this study, the average number of total correct trials in the forward and backward task will be used as a measure of working memory [56,58]. A higher score represents better working memory. There is no absolute maximum score; in theory, the task can go on indefinitely.

Process Evaluation

Overview

Because conducting clinical trials in the field of adults with ID and CB seems to be challenging [25], it is also important to share the practical experiences when conducting trials using a process evaluation [59]. For conducting a process evaluation, different frameworks are developed, which all focus on several process evaluation components. For this study, the following frameworks are used: the Medical Research Council guidance [59], process evaluations for cluster-randomized trials of complex interventions as proposed by Grant et al [60], and the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [61,62]. The Medical Research Council guidance and the RE-AIM framework have recently been used in the ID-research field [19,63-65].

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Evaluation per Music Session

The music worker will ask the participant before and after each music session how he or she feels at that moment: happy, sad, scared, angry, or tired. Sheets representing 5 emoticons with associated feelings are shown to help the participant. If possible, the participant also indicates whether this feeling is little, normal, or intense. When it is too difficult for a participant to choose a specific emotion, the participant is asked whether he or she feels pleasant or nonpleasant.

Music workers will also complete a log report after each music session. The log report contains questions about that specific session: whether the session was performed according to the manual and how much time was spent on active music making.

Evaluation of Music Intervention

Participants in the music intervention and music workers will be asked to complete an evaluation questionnaire after the last music session. These questionnaires are designed to gain the participants' personal views about the music intervention and their satisfaction with specific elements of it (eg, musical instruments and frequency of the sessions). The music workers will share their observations regarding behavioral, cognitive, and emotional changes within a participant during sessions.

After the last music session, caregivers will be asked to participate in a semistructured interview. This interview will focus on observed changes in the participants' behavior and the experiences of caregivers with this music intervention study. Topics that will be covered are related to acceptability or satisfaction, reach, and context. The interviews will be recorded with the permission of the respondents and transcribed.

Follow-Up Evaluation

The participants in the music intervention and caregivers from participants in the music intervention will answer a few questions about the long-term use of musical activities after the last music session. For participants, this questionnaire will be conducted at T3, and for caregivers, it will be conducted 6 months after the last session.

Sample Size Calculation

The sample size is calculated using G*Power software (version 3.1.9.7) [66]. The sample size calculation is based on a small effect size of 0.2, a statistical power of 0.95, and a type I error probability of α=.05, which results in an unadjusted sample size of 67 participants. Because cluster randomization negatively affects the power, the sample size needs to be adjusted. With the average cluster size of 2 participants per residential facility and allowing an intraclass correlation of 0.2, the adjusted sample size is 80. To allow for a dropout rate of 20% over the course of the study, we will aim at recruiting a total of at least 96 participants.

Data Analysis

Participant characteristics will be compared between the group receiving the individual music intervention and the group receiving CAU. Further analyses will be adjusted for any potential significant differences. The primary analyses will be undertaken on an intention-to-treat basis, and 2-sided tests will be applied at a 5% α level. In addition, per-protocol analyses will be conducted based on the sample of participants who adequately adhered to the intervention protocol by completing at least 12 of the 16 music sessions (ie, 75%), which is similar to 67% and 80% of 2 other intervention studies among adults with mild to moderate ID [67,68]. In addition, by setting the threshold at 12 sessions, we know for sure that all intervention participants followed at least 1 or 2 sessions with a focus on emotions and EF.

To minimize the number of analyses on outcome domains, the 4 different EF measures will be converted into *z* scores and, according to factor analysis, summed up into an EF domain if possible. Subsequently, to test differences in changes from baseline to follow-up between the 2 conditions, a linear mixed model analysis for each treatment variable will be used. Within each analysis, only time and the interaction between the treatment variable and time will be used [69], making it possible to adjust for the dependence of the repeated observations within the subjects. The effect of the intervention on the 2 follow-up measurements will be assessed. This analysis allows for participants with only a baseline measurement but with missing data at follow-up to be included. The normality of the residuals from the linear mixed model analysis will be visually inspected.

Secondary analyses will be performed as well. The effect of extra music interventions will be tested applying a Mann-Whitney *U* test for the between-group comparisons. The self-reported feelings before and after each music session will be compared using a Wilcoxon signed rank test.

Descriptive statistics will be used to summarize the quantitative data of the log reports, evaluation questionnaires, and the follow-up evaluation.

Qualitative data of log reports, evaluation questionnaires, follow-up evaluation, recruitment log, trial log, and semistructured interviews will be analyzed using thematic context analysis on multiple aspects of the intervention and the overall study process, including recruitment, retention, acceptability or satisfaction, maintenance, dose, fidelity, reach, adaptation, and context.

Ethical Considerations

Participation in the study will be voluntary. Participants and their legal representatives can withdraw consent at any time during the intervention and have the right to demand the removal of the original data. Random allocation of participants to 1 of the 2 conditions is considered reasonable as no adverse effects are expected in any of the conditions. Inconveniences caused by the necessity to attend 2 or 3 music sessions per week are considered tolerable in view of the anticipated benefit for the participant receiving music sessions. Participants assigned to CAU will receive a considerable budget after the study has ended, which they can spend on musical activities or musical instruments to their own wishes. Ethical approval for this study was granted by the review board of the Faculty of Behavioral and Movement Sciences of the VU University Amsterdam (protocol VCWE-2021-081). The Medical Ethical Committee of the VU University Medical Center stated that the research was not subject to the Dutch Medical Research Involving Human

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Subjects Act. The trial has been registered in the International Clinical Trial Registry Platform (NL8482).

Data Management

To ensure the accuracy of the data, all entered data will be triple-checked by different research assistants. Every participant will be assigned an anonymous code after their informed consent form is received to store and identify their trial data. The coding key and person-related data will be saved in a password-protected file in a restricted folder, which will only be accessible by the study-related researchers. All paper files will be kept in locked cabinets in the researcher's office for the duration of the study, and digital files will be stored on a password-protected and secure system, which is also exclusively accessible by the study-related researchers.

Results

Enrollment commenced in July 2021, and data collection ended in May 2023. The aim to recruit at least 96 participants has been achieved with a total of 97 participants, of whom 44 were randomized in the intervention group. Data will be analyzed after this study protocol has been accepted for publication.

Discussion

In this paper, the design of an RCT is presented, which aims at exploring the effectiveness of and experiences with a music intervention for adults with ID and CB on various outcome measures, including CB, well-being, depression, anxiety, self-esteem, and EF. The first strength of this study is that it concerns a clustered RCT design with a sufficient sample size. The second strength is that the multisource data collection, including the use of self-report questionnaires and tests as well as proxy measures, improves the research quality. Third, because distal outcomes (measured over a longer period of time) and proximal outcomes (measured immediately after the intervention) will be used, immediate effects can be assessed too. Lastly, as qualitative data are collected alongside quantitative data, further insight into the process or mechanisms of change can be gained.

However, some limitations also have to be taken into consideration. First, blinding is not possible in the design because the nature of the intervention and the different questionnaires at the data collection points for both groups precludes blinding of the assignment for all parties involved. The absence of an active control condition might entail difficulties in ascribing possibly disclosed effects to power factors of the music intervention, such as level of attention [70]. Furthermore, there are several anticipated challenges, which are based on previous work conducting RCTs with adults with ID. These include challenges with recruiting adequate numbers, resistance to the use of control groups, assessing participants through gatekeepers (ie, the caregivers), and staff turnover that impacts the data collection [25]. The following steps to minimize attrition are considered in this study: (1) the research team follows a flexible participant-led approach to gathering all data—with contacts being at times suggested by participants and at the convenience of the facility of the participant; (2) the incentive to complete all questionnaires and tests is increased with the compliment card that participants receive after every data collection measurement; (3) caregivers will receive multiple reminders, either live, via mail, or telephone, to return the questionnaires on time; and (4) the combination of collecting data from both participants and caregivers reduces the burden for them and diminishes the impact of participant dropout or staff turnover.

In sum, more evidence-based interventions are needed to help improve the mental well-being of this population. It is important to not only fill this evidence-base gap with the outcomes of the ID RCTs but also share the practical experiences conducting trials through the reporting of process evaluations. Therefore, it is expected that this study will provide insight into the effectiveness and experiences of an individual music intervention for adults with ID and CB. If the intervention proves to be effective, broad-scale implementation in the care for people with ID can be considered and results can guide further music intervention guidelines and enrich the work environment of music workers engaging in supporting people with ID.

Conflicts of Interest

None declared.

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Abbreviations

ABC: Aberrant Behavior Checklist
CAU: care as usual
CB: challenging behavior
EF: executive functioning
ID: intellectual disabilities
PWI-ID: Personal Well-being Index—Intellectual Disability

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RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
QoL: quality of life

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Protocol

Survivorship Care for Women Living With Ovarian Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: Ovarian cancer ranks 12th in cancer incidence among women in the United States and 5th among causes of cancer-related death. The typical treatment of ovarian cancer focuses on disease management, with little attention given to the survivorship needs of the patient. Qualitative work alludes to a gap in survivorship care; yet, evidence is lacking to support the delivery of survivorship care for individuals living with ovarian cancer. We developed the POSTCare survivorship platform with input from survivors of ovarian cancer and care partners as a means of delivering patient-centered survivorship care. This process is framed by the chronic care model and relevant behavioral theory.

Objective: The overall goal of this study is to test processes of care that support quality of life (QOL) in survivorship. The specific aims are threefold: first, to test the efficacy of the POSTCare platform in supporting QOL, reducing depressive symptom burden, and reducing recurrence worry. In our second aim, we will examine factors that mediate the effect of the intervention. Our final aim focuses on understanding aspects of care platform design and delivery that may affect the potential for dissemination.

Methods: We will enroll 120 survivors of ovarian cancer in a randomized controlled trial and collect data at 12 and 24 weeks. Each participant will be randomized to either the POSTCare platform or the standard of care process for survivorship. Our population will be derived from 3 clinics in Texas; each participant will have received some combination of treatment modalities; continued maintenance therapy is not exclusionary.

Results: We will examine the impact of the POSTCare-O platform on QOL at 12 weeks after intervention as the primary end point. We will look at secondary outcomes, including depressive symptom burden, recurrence anxiety, and physical symptom burden. We will identify mediators important to the impact of the intervention to inform revisions of the intervention for subsequent studies. Data collection was initiated in November 2023 and will continue for approximately 2 years. We expect results from this study to be published in early 2026.

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Conclusions: This study will contribute to the body of survivorship science by testing a flexible platform for survivorship care delivery adapted for the specific survivorship needs of patients with ovarian cancer. The completion of this project will contribute to the growing body of science to guide survivorship care for persons living with cancer.

Trial Registration: ClinicalTrials.gov NCT05752448; https://clinicaltrials.gov/study/NCT05752448

International Registered Report Identifier (IRRID): PRR1-10.2196/48069

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KEYWORDS

chronic survivorship; metastatic survivor; metavivor; ovarian cancer; persons living with cancer; quality of life; survivor; survivorship care; survivorship transition

Introduction

Ovarian cancer ranks twelfth in cancer incidence among women in the United States but fifth among causes of cancer-related death [1,2]. Treatment of ovarian cancer has benefited from recent scientific advances; however, the impact of novel treatments, including maintenance therapies, on life expectancy remains unclear [3]. Women with ovarian cancer typically complete their initial round of treatment with no evidence of disease but have a high risk of recurrence, with a majority of patients experiencing recurrence 18-24 months after the completion of initial platinum-based chemotherapy [4,5]. The focus becomes disease management, with an emphasis on treatment of cancer, minimization of toxicities, and optimization of quality of life (QOL). Historically, little attention has been paid to the survivorship needs of persons living with controlled cancer, advanced disease, and cancers that have high recurrence rates [6]. Qualitative work describes the unmet need for survivorship in this space of uncertainty, but there is little evidence to guide the delivery of survivorship care for persons living with cancer as a chronic condition.

Cancer health services science incorporated cancer survivorship as a target for care improvement following the 2006 publication of the seminal work "*From Cancer Patient to Cancer Survivor: Lost in Transition*" [7]. This foundational work summarized the challenges associated with cancer survivorship care, including the absence of systematic strategies for care provision, coordination of care across settings, unmet symptom management and psychosocial needs, and an unclear locus of responsibility for care. Subsequent years have seen dramatic increases in cancer survivorship science publications and the development of interventions and programs to meet the needs of cancer survivors. Science, however, has disproportionately focused on breast cancer and other "curable" cancers, and gaps in science and care for persons living with serious or incurable cancer remain to be addressed.

Ovarian cancer is a model of those cancers not typically encompassed in survivorship science and care. Over 19,000 women in the United States will receive a new diagnosis of ovarian cancer this year. For most of them, the point of diagnosis is the beginning of several years of living with cancer, treatment, and uncertainty. Most of these women will be diagnosed with advanced disease; 4 out of 5 patients have regional or advanced disease at the time of diagnosis. This contributes to the unfortunate outcomes associated with ovarian cancer, and 5-year survival rates remain below 50% despite improvements over the past 10 years. Women with ovarian cancer typically undergo treatments including surgery, chemotherapy, sometimes radiation therapy, and increasingly maintenance therapy with targeted therapies [8]. Survivorship care needs for women with ovarian cancer are unique, and frequently, their gynecologic oncology treatment program will also serve as the site of much of their cancer-focused survivorship care [9,10]. Most patients experience residual physical and psychological symptoms posttreatment [11]. Recurrence anxiety, psychosocial needs, sexual functioning, depressive symptoms, and uncertainty related to the care plan moving forward are all reported as sources of impaired well-being among ovarian cancer survivors [12-16]. Women with ovarian cancer being treated in safety net systems are more likely to have poor QOL and less likely to comply with follow-up visits, etc, making it more imperative to develop systems and processes to facilitate their survivorship transition.

Few studies have examined the impact of survivorship care plans (SCPs) for survivors of ovarian cancer on their QOL. The Registration System Oncological Gynecology trial was a pragmatic cluster randomized trial in which 12 hospitals were randomized to deliver computer-generated SCPs or usual care. The SCP was based on a Dutch translation of the Institute of Medicine format [7]. A total of 174 patients with ovarian cancer enrolled in the trial, of whom 61 received care at an SCP hospital and 113 received care at a usual care hospital. The primary analysis outcomes included satisfaction with care, illness perception, and health care use. There were no overall effects of SCP delivery on any of the scales of satisfaction with care; at 12 months of intention to treat (ITT) analysis, patients in the SCP arm rated the interpersonal skills of nurses lower than patients in the usual care arm. Patients in the SCP arm experienced more symptoms, were more concerned about their illness, and were more emotionally affected than patients in the usual care arm [17]. Further analyses showed increases in health care use among women with anxiety symptoms and those who received radiotherapy [18,19]. Investigators found that patients with ovarian cancer who had lower trust that the treatment would cure their disease due to the SCP reported worse emotional functioning 6 months after treatment [20]. Taken in total, the Registration System Oncological Gynecology trial underscores that for women with ovarian cancer, a templated SCP that emphasizes the frightening long-term outcomes of this disease may impair outcomes. In response to this study and the concerns of our patients, we engaged patients with ovarian cancer and

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providers to provide input on the development of POSTCare-O. Their input resulted in a goal related to living well with a serious illness and the inclusion of specific strategies to cope with recurrence anxiety.

We developed the POSTCare survivorship transition platform to deliver a patient-centered and Institute of Medicine (now National Academy of Medicine)–adherent SCP in breast cancer. Women with ovarian cancer experience a significant symptom burden resulting from depression and anxiety [12]. This burden is substantially higher compared with that observed in healthy populations of women and is a phenomenon that persists years into survivorship [15]. The impact of the POSTCare survivorship transition platform on reducing depressive symptom burden has been observed among survivors of breast cancer [21]. However, it remains unknown what effect the adapted intervention may have on patients with ovarian cancer. For this population, the intervention has been modified to target coaching toward the concept of "living well with a serious illness" and symptom self-management. Participants identifying a goal related to recurrence anxiety will receive a brief cognitive intervention based on acceptance and commitment therapy [22]. Strategies to address these issues in survivors of ovarian cancer are currently lacking, and this study may identify potential pathways for improved psychosocial well-being.

The POSTCare survivorship care platform is framed by the chronic care model [23,24] and is also informed by the wealth of literature on care setting transition support [25-27] and patient informants (Figure 1) [28]. Designed to be delivered through telehealth or in-person, POSTCare is best understood as a health services delivery platform that coaches the survivor to engage as an activated agent in her own survivorship care. Recommendations are anchored in existing evidence-based approaches that have historically not found avenues for effective dissemination. The POSTCare platform explicitly maps onto the chronic care model essential elements, including self-management coaching and support directed at both symptoms and wellbeing for survivors. The engagement of community resources occurs with services such as exercise or mental health care to support patients' goals. Delivery system design includes the platform's "plug and play" approach to evidence-based behavioral change support that allows the nature of survivorship support to adjust to patients' needs and goals. Decision support for providers delivering care is built into the platform in a "tool kit" of evidence-based behavioral interventions to support patients' goals [29]. We hypothesize that POSTCare will increase the effective use of evidence-based care and improve outcomes for patients.

Figure 1. Alignment of POSTCare elements with the chronic care model. Developed by The ACT Center, formerly known as the MacColl Center for Health Care Innovation, reprinted with permission from ACP-ASIM Journals and Book.

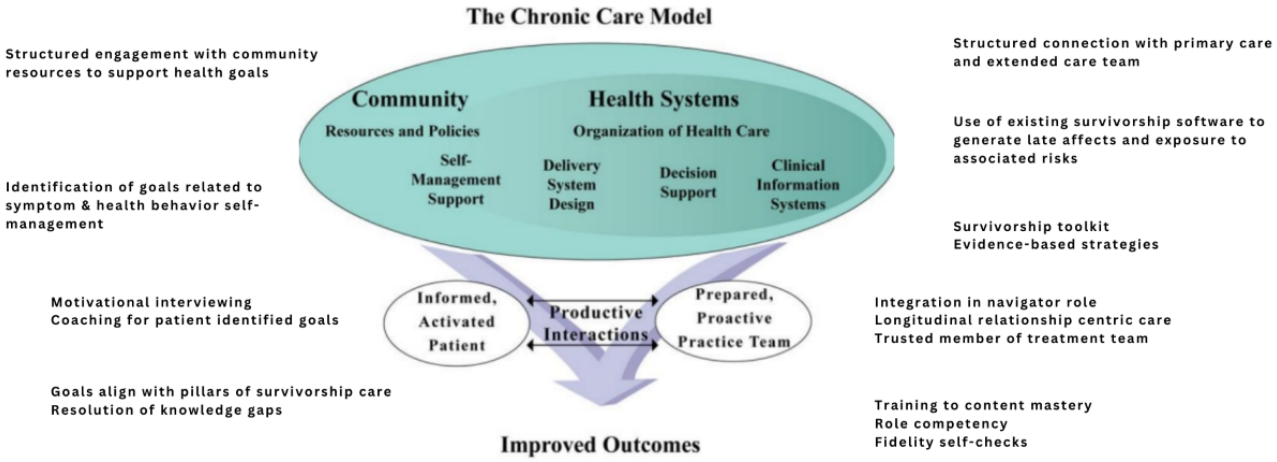

In POSTCare-O, the POSTCare platform is adapted to meet the needs of survivors of ovarian cancer. We worked with members of the CanSurvive GYN Cancer Support Group in Birmingham, Alabama, and gynecologic oncologists to identify survivorship priorities and needs. Patients with ovarian cancer and their caregivers were clear that they wanted to focus on living well during the survivorship transition, and clinicians felt that concerns that may be important for other cancer types, such as transition to primary care, might be of lesser priority in the context of ovarian cancer. They helped us understand that the essential "work" of cancer survivorship in ovarian cancer is the work of living well despite serious illness and the specter of mortality. Using the palliative dual framework, a technique used to assist patients in the task of living well despite serious illness [30,31], and a brief acceptance and commitment therapy intervention [22], we have incorporated a goal focused on living well with a serious illness that was not a component of the breast cancer POSTCare platform.

The overarching goal of this study is to test processes of care that support outcomes, including QOL, in survivorship. We will use QOL as a primary outcome, but we will also look at factors such as recurrence worry, depressive symptom burden, and survivorship efficacy that may also be influenced by improved care processes. The specific aims of this study are to conduct a randomized controlled trial (RCT) enrolling 120 women with advanced ovarian cancer. We will test the efficacy of the POSTCare platform in supporting QOL, reducing depressive symptom burden, and reducing recurrence worry. In our second aim, we will examine factors associated with the impact of the intervention. Our final aim focuses on understanding aspects of care platform design and delivery that are likely to affect the potential for dissemination. We will use both qualitative and

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quantitative methods to assess patient experience, provider experience, and pragmatic aspects of clinical implementation, with the goal of redesigning the implementation for greater dissemination potential.

Methods

Study Design

We will conduct a 2-arm RCT to evaluate the impact of a telehealth-delivered survivorship transition care platform. Survivors of ovarian cancer (N=120) will be randomly allocated to receive survivorship care either using the POSTCare Platform or standard of care. Study design and reporting will be in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist. We will use quantitative and qualitative methodologies in a concurrent triangulation mixed methods design using qualitative data to augment our interpretation of quantitative data. Outcomes will be collected at baseline, 12 weeks, and 24 weeks, with the primary outcome being a QOL assessment at 12 weeks after the survivorship transition (Figures 2 and 3).

Figure 2. POSTCare-O randomized clinical trial flow demonstrating enrollment, randomization, and data collection time points.

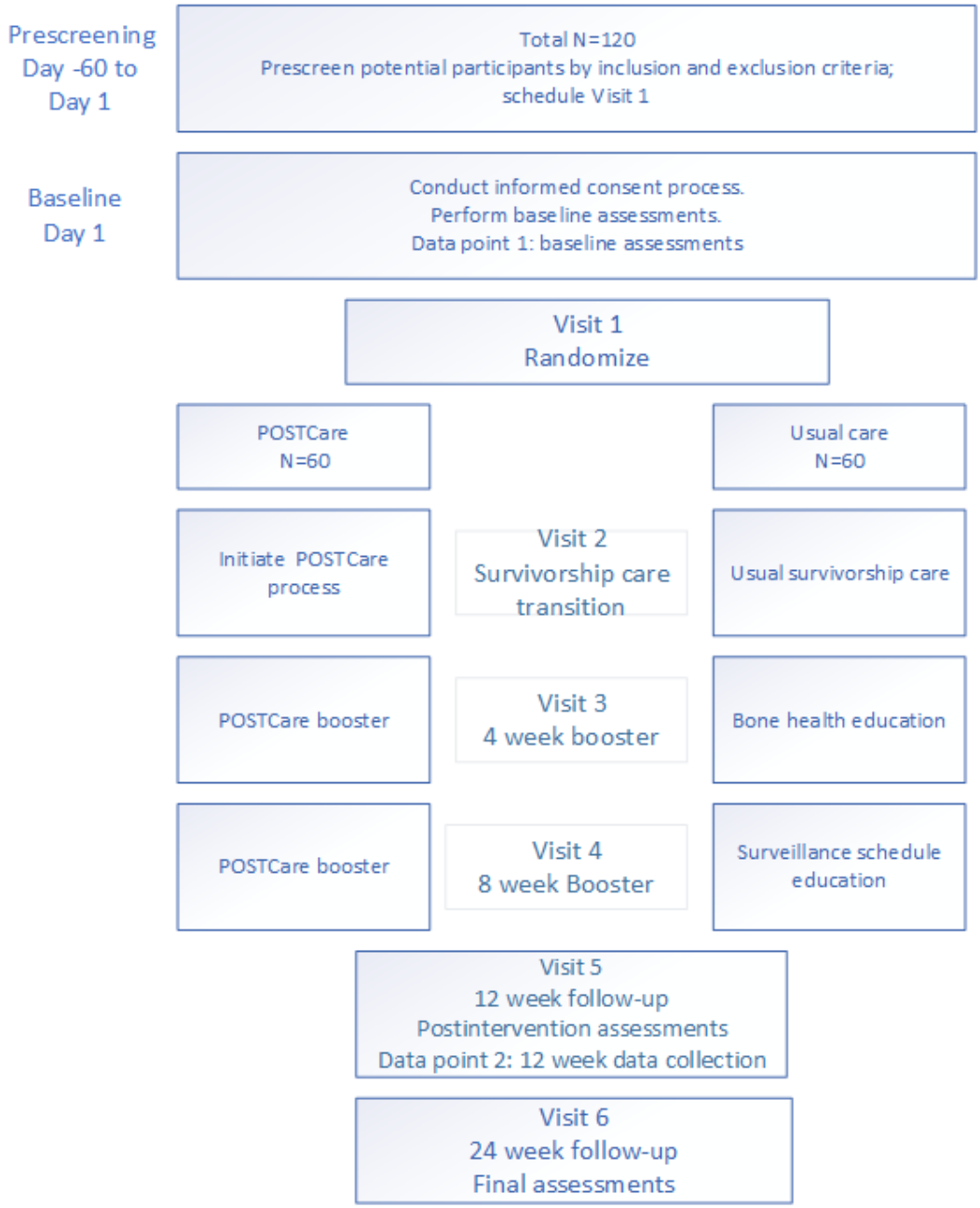

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Figure 3. Mixed methods framework demonstrating data sources and integration schema.

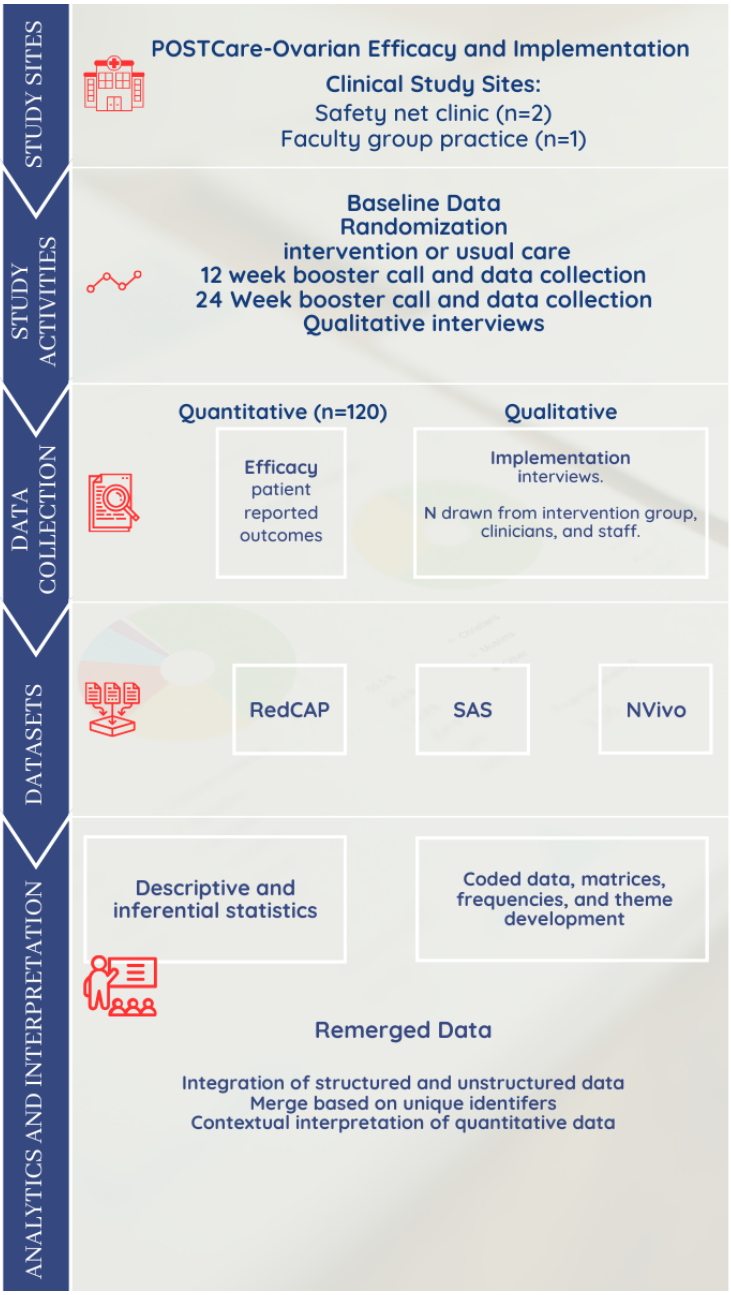

Sample Size

We will enroll 120 women completing primary treatment for stage 2-4 ovarian cancer from 3 urban gynecologic oncology clinics located in the US state of Texas. Participants will have received some combination of surgery, chemotherapy, radiation therapy, and biologics. Continued maintenance therapy is not an exclusion factor. The disease-stage sample frame was developed with input from our gynecologic oncology collaborators based on treatment exposures and the similarity of survivorship challenges. Aim 1 proposes to implement a RCT devised to compare QOL measures among patients with ovarian cancer randomized to receive usual care versus the POSTCare survivorship care transition program. The Functional Assessment of Cancer Therapy-Ovarian (FACT-O) QOL survey will be collected at baseline as well as 12 and 24 weeks after the initial course of adjuvant chemotherapy. The primary end point will be the 12-week survey. The sample size of 120 patients provides at least 80% power to detect a 7% increase in the mean FACT-O score for women randomized to the POSTCare survivorship care intervention. This is sufficient to ascertain a minimally important difference of 8 points [32].

Recruitment and Setting

We will recruit participants from gynecologic oncology practices at 3 clinic settings in Texas: 1 safety net practice located in Dallas, 1 safety net practice located in Houston, and 1 faculty group practice located in Houston. Cumulatively, the sites serve approximately 140 eligible patients per year and ensure a diverse population of 120 participants can be recruited during the 24-month recruitment period. A total of 60 participants will be randomly assigned to the intervention group and receive care using the POSTCare process, and another 60 will be randomly assigned to the control group. To be included, patients must (1)

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be diagnosed with ovarian cancer at the age of 18 years or older; (2) be within 3 months of completing initial treatment for stage 2-4 ovarian cancer. Treatment may include surgery, chemotherapy, radiation therapy, immunotherapy, or other biologics. Participants may be on maintenance therapy; and (3) be able to provide consent in English or Spanish. Patients who are enrolled in hospice care directly following the treatment conclusion will not be eligible for the study. It is anticipated that this study sample will reflect the ethnic and racial diversity of our clinical settings.

Recruitment Procedures

Study research coordinators will have access to the electronic medical record at each site. They will collaborate with clinical personnel to identify patients who will be completing initial therapy. Coordinators will work to identify patients in treatment at least 8 weeks before the completion of therapy. They will identify an upcoming clinical appointment, either in clinic or infusion, where the team will approach patients to provide information about the study, answer questions they may have, and obtain informed consent. Enrolled participants will be asked to complete a web-based, self-administered survey using a smart device to collect baseline measurements before randomization.

Randomization

After the baseline survey is administered, the biostatistician will use SAS (SAS Institute) to perform a permuted stratified blocked randomization [33]. The stratification variable used maintenance therapy versus no maintenance therapy. The rationale for this stratification is that those patients with ovarian cancer who receive maintenance therapy with a poly (ADP-ribose) polymerase (PARP) inhibitor may experience a different symptom burden or illness trajectory that impacts outcomes [3]. Survivors will be randomly allocated to either the control group or the POSTCare intervention group with a 1:1 ratio (N=120). Stratification will be based on disease stage and maintenance therapy (a PARP inhibitor vs Bevicizumab vs no maintenance). Each of these factors is associated with overall QOL and symptom burden. Participants, clinicians, data collectors, biostatisticians, and investigators will be blinded to allocation. The research nurse interventionist (described below) will not be blinded but will not conduct study activities related to measuring, collecting, or interpreting outcomes. Although this is a low-risk intervention, unblinding decisions will be made by the investigators in the context of serious adverse events attributable to the study. If a decision is made to unblind a participant, the study data coordinating center will undertake the unblinding and protect the confidentiality of treatment assignments for other participants. The treatment assignment will be communicated to the participant and the participant's treating physician. The unblinding event will be reported to the Baylor College of Medicine institutional review board, documented in trial records, and the analysis of study outcomes may be adjusted to account for the unblinded participant to ensure that the integrity of the overall trial results is maintained. Criteria for study dropout include withdrawal of consent, failure to adhere to protocol, loss to follow-up, health changes making further participation burdensome, and personal reasons or changes in life circumstances.

Control Group

The control group will receive standard survivorship care delivered through telehealth. All sites have a standard survivorship visit that includes the use of a software package to generate the delivery of a paper SCP based on American Society of Clinical Oncology guidelines. This comprises a treatment summary, an upcoming surveillance visit schedule, and guidance on late effects. This visit includes the delivery of information and specifically does not include goal setting, use of the dual framework technique (described in the "Intervention" section), acceptance and commitment intervention (described in the "Intervention" section), self-management coaching, or the use of motivational interviewing techniques. To ensure fidelity to control group standards, all visits will be audio-recorded and reviewed to evaluate for evidence of contamination of the control condition. Telephone-based booster contacts will serve as attention control with structured delivery of educational material on surveillance visits and bone health.

Intervention

POSTCare is a structured cancer survivorship navigation platform that seeks to improve cancer outcomes for survivors. Key elements of the platform include personalized self-management support and tailored SCP delivery. The platform is delivered through telehealth (a video platform) and comprises an initial survivorship care transition visit that includes the development and delivery of a personalized care plan. Within the platform framework, a trained nurse uses motivational interviewing and communication skills to engage patients in the development of a POSTCare plan that incorporates health goals and strategies related to surveillance, symptom management, and health behavior [34,35]. Survivor engagement with the POSTCare plan is supported by monthly navigator phone booster follow-up for 2 months, also delivered by the nurse survivorship navigator. Participants will be offered an additional nonstructured phone check-in before their first follow-up visit at 3 months.

Patient-Centered Design

The POSTCare session begins with the coach engaging the survivor in sharing her cancer treatment narrative, anchoring the activity to the patient's experience and needs. The identification of health goals is the central activity of POSTCare and distinguishes this approach to survivorship care from those that simply deliver information. The survivor is asked to think about identifying 1 or more goals in the following survivorship domains: social support, healthy habits, symptom management, and coping with uncertainty. Resource and activity support materials related to goals are maintained in the POSTCare-O web-based survivorship toolkit and used by coaches. As an adaptation for the needs of survivors of ovarian cancer, the dual framework [31] is introduced by coaches in goal-setting as a strategy for living with uncertainty. The dual framework is a strategy used in palliative encounters to help patients focus on what living well means to them while holding the possibility of advancing illness or death in the same cognitive frame. It provides a structure to anchor the focus on living well across the longitudinal trajectory of survivorship navigation. We will introduce a brief cognitive exercise derived from acceptance

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and commitment therapy to address recurrence worry if participants articulate this as a survivorship concern and goal [22,36-38]. Our informants indicated that using a focus on what it means to live well despite serious illness is an acceptable palliative intervention even at the initiation of the survivorship period when they wish to be focused on the positive aspects of treatment completion.

The coach and survivor strategize about potential barriers to goal accomplishment and explore ways to address barriers, with the coach using motivational interviewing techniques to explore survivor ambiguity about health goals and nurture self-efficacy in working toward goals. The components of the platform, drawn from an evidence-based approach to care setting transition [24,25,27,39-41], include an emphasis on survivor engagement and activation. The average length of the coaching session is 75 minutes, which includes the creation of the SCP [21].

Booster survivorship navigation telephone contacts occur at 4 weeks and 8 weeks after baseline. The survivorship coaches will review health goals, including living well, adjust goals as needed, discuss progress, identify barriers, and brainstorm about strategies to overcome barriers. The survivorship coaching intervention is delivered through telehealth by the nurse survivorship navigation coach. For participants who do not have a smart device, the intervention can be delivered through a smart device provided by the study in a clinic setting.

Qualitative Methods

Qualitative methods will be used to inform the adaptation and refinement of the intervention. Interviews will be undertaken with 3 groups of informants: women living with ovarian cancer; nurses who have been trained in the POSTCare model; and gynecologic oncologists, clinic staff, and administrators. Semistructured exit interviews will be conducted by specially trained research team members within 30 days of completing the intervention. Although the exit interview questions will be stated as broad questions, the researcher will be trained to probe for details, including asking for specifics and operational examples.

We will partner with women enrolled in this study to conduct semistructured interviews on the POSTCare survivorship care experience. Interview topics will include (1) timing of survivorship care—both initiation of survivorship transition and longitudinal care; (2) critique of proposed intervention content and existing materials; (3) understanding the meaning of this intervention for participants; (4) exploring individual differences between experiences and outcomes; and (5) evaluation of intervention length, intensity, frequency, and mode of delivery. Interviews will be conducted with gynecologic oncology nurses who have completed the POSTCare-O web-based training and used components of the POSTCare model to provide the intervention. Finally, we will explore the same interview topics with clinic staff at each study site to learn what elements of the POSTCare model work well in their clinical setting, which elements they are able to use routinely, which components seem to most meet the needs of their patients, and which elements of survivorship care they find most satisfying.

Outcome Measures

We will use the FACT-O instrument as the primary end point for the clinical trial. The FACT-O is a 38-item assessment that comprises a core QOL instrument (the FACT-General) and a 12-item ovarian module. The internal consistency for the complete instrument is Cronbach α=.92, and the test-retest reliability is r=0.81 [42]. The subscales demonstrate similar acceptable psychometrics. This instrument is widely used in trials and will allow us to meaningfully compare the results of this trial to those of other studies that examine QOL. The minimally important difference is the “smallest difference” in FACT-O scores that patients perceive as clinically important and is 3-8 points [43]. We have powered the study to identify this level of change.

The Patient Health Questionnaire-9 (PHQ-9) is a widely used screening tool for depression, consisting of 9 items [44]. It takes approximately 5 minutes to complete and has been found to be a valid and reliable measure of depressive symptoms in various populations, including patients with cancer. The total score on the PHQ-9 can range from 9 to 27, with higher scores indicating a higher level of depressive symptom burden. A study by Thekkumpurath et al [45] found that the PHQ-9 was a valid and reliable measure of depression in patients with cancer and recommended its use in clinical practice. Additionally, the PHQ-9 has been used as an outcome measure in various interventions for depression, including those targeting patients with cancer [46]. The PHQ-9 has demonstrated good internal consistency and test-retest reliability, with a coefficient α=.89 and an intraclass correlation coefficient of 0.84, respectively [44].

The Fear of Cancer Recurrence-7 (FCR-7) is a 7-item questionnaire designed to offer a psychometrically sound assessment of fear of cancer recurrence with a limited response burden. The instrument comprises 7 questions: 5 that use a 5-point Likert scale ranging from 1 (not at all) to 5 (all the time), and a single question that uses an 11-point Likert scale ranging from 0 (not at all) to 10 (a great deal). Total scores on the measure range from 6 to 45 [47]. A cutoff score of 17 or above reflects moderate fear of cancer recurrence, and a score of 27 or above indicates severe fear of cancer recurrence. The measure demonstrates good internal consistency (Cronbach α=.92) and validity as compared to measures of anxiety and depression [48].

Other measures used as secondary outcomes and potential predictors were selected with a priority on acceptable psychometric performance in similar populations and acceptable performance in one of our previous studies.

“Aim 1” proposes to implement a RCT devised to compare QOL measures among patients with ovarian cancer randomized to receive usual care versus the POSTCare survivorship care transition program. Outcome measures, including the FACT-O QOL survey, the FCR-7 survey, and the PHQ-9, will be collected at baseline as well as 12 and 24 weeks after the initial course of adjuvant chemotherapy. The primary end point will consist of the 12-week FACT-O survey. The sample size of 120 patients provides at least 80% power to detect a 7% increase in the mean FACT-O score for women randomized to the

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POSTCare survivorship care intervention. This is sufficient to ascertain a minimally important difference of 8 points. Secondary outcomes (Table 1) will also be assessed at 12 and 24 weeks. Baseline descriptive statistics will be presented by site. Longitudinal analysis of the FACT-O QOL scores will use a mixed effects linear model with a restricted maximum likelihood estimation method, and an unstructured covariance matrix will be used to estimate trends. An interaction between intervention and time will be estimated to explore the effectiveness of POSTCare for time-varying trends [49]. Though the mixed effect model can accommodate some degree of missing data under the ignorability assumption, we also plan to use multiple imputations using the random forest method [50,51] to accommodate missing data (if greater than 10% of survey items), which will be assumed to be missing at random. In the event of a sign of a violation of that assumption, a pattern mixture model will be used to mitigate the effect of informative missingness. Secondary analyses will evaluate relationships between baseline and 12-week FACT-O scores and clinical end points progression-free survival (PFS) and overall survival (OS). Cox proportional hazard models will be used to estimate the relative risk of PFS and death per increase in FACT-O [52]. Ties in failure times will be handled with the approximate likelihood of Efron. PFS and OS will be measured from the date of randomization. PFS is defined as the minimum amount of time until clinical progression, death, or the date of last contact. OS is the duration from randomization to death or to the date of last contact (right-censoring). As is customary, secondary analyses are not powered but may help generate additional evidence that needs to be tested in the future by a properly powered study.

Table 1. Summary of variables and outcomes.

Variables for outcome analysis	Measures	Reliability, *r*	Source
Primary outcomes			
Quality of Life	• Functional Assessment of Cancer Therapy-Ovarian [42]	• .92	Patient self-report
Depression	• Patient Health Questionnaire-9 [45]	• .94	Patient self-report
Recurrence anxiety	• Fear of Cancer Recurrence-7 [47]	• .93	Patient self-report
Secondary outcomes			
Patient self-efficacy	• Stanford Chronic Illness Self-Efficacy Scale [53] • Patient Activation Measure [54]	• .91 • .87-.91	Patient self-report
Satisfaction with communication	• Stanford communication with physicians [55]	• .89	Patient self-report
Health care use	• Stanford Health Care Utilization [53]	• .76-.97	Patient self-report
Satisfaction with care coordination	• Stanford Self Efficacy [55]	• .91	Patient self-report
Perception of Informational Support	• Patient-Reported Outcomes Measurement Information System: informational support measure [56]	• __[a]	Patient self-report
Symptom Burden	• MD Anderson Symptom Inventory for ovarian cancer • Stanford Social/Role Activities Limitations	• .89-.90 • .91	Patient self-report
Predictor variables			
Demographic or medical information	• Demographic questionnaire: will include gender, race, and treatment history	• N/A[b]	Electronic medical record
Cancer coping style	• Brief version of the Coping Orientation to Problems Experienced [57]	• .75	Patient self-report
Social support	• Social Provisions Scale [58]	• .92	Patient self-report
Education level	• Stanford Education [59]	• N/A	Patient self-report

[a]Not available.

[b]N/A: not applicable.

"Aim 2" applies mediation analysis to the data acquired from the RCT proposed in Aim 1. Aim 2 explores the potential for heterogeneity in the effectiveness of the POSTCare survivorship program. The primary end point for aim 2 is QOL at 6 months, as measured by the FACT-O. Combining both study arms, subgroup analysis will assess the distributions of potential prognostic factors for QOL at 6 months. Analyses will adjust for statistically significant prognostic factors. Mediation

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modeling will be applied to decompose the relationships among the care plans, intermediate surrogate markers of QOL acquired during the course of follow-up, and QOL at 6 months. Surrogate markers include patient activation, goal setting, self-efficacy, and care satisfaction, to be collected at 12 weeks and 24 weeks from surveys identified in Table 1. For each surrogate marker, an intermediate response will be defined. The direct and indirect impact of POSTCare will be estimated for each surrogate response using mediation analysis [60-62] to elucidate the causal mechanisms of QOL and assist with planning for larger confirmatory studies and studies in other disease types.

Qualitative data for intervention adaptation will be analyzed using a thematic analysis framework. At the outset of the process of analysis and interpretation, the qualitative team will read each transcript from interviews in its entirety to achieve a global sense of substance and context. Working independently of one another, we will engage in a line-by-line search for recurring ideas, coding each transcript for themes. After identifying dominant themes, we will evaluate the degree of consensus among participants. An initial codebook will be developed from the interview guide and adaptation framework. A master code book will be entered into NVivo (version 11; QSR International). The data will be merged with the quantitative data to inform interpretation and draw stronger inferences. As described by Farquhar et al [63], mixed methods are particularly beneficial where the interventions are complex and the platform for evaluation and identification of suitable outcomes is challenging. Insights gained from quantitative and qualitative approaches complement each other to provide a more in-depth understanding. This deeper understanding can inform the process of refining interventions and hypothesis generation and facilitate replication of the intervention through greater knowledge of the active components and potential barriers to implementation. Moreover, qualitative research can be used to examine and address key uncertainties before dissemination efforts [64]. Interviews will be conducted by experienced qualitative interviewers on our established research team. We anticipate conducting up to 30 interviews at the outset of the process of analysis and interpretation. We will use all data sources to inform the revision of the POSTCare-O platform before active dissemination [65-68].

Ethical Considerations

Ethical approval for this trial has been obtained through the Baylor College of Medicine Institutional Review Board (H52939). All participants in the trial will provide informed consent before the initiation of study activities. The primary risk in this study is a risk to confidentiality. All study data will be uploaded directly to the data coordinating center, REDCap (Research Electronic Data Capture; Vanderbilt University), which is implemented to be compliant with HIPAA (Health Insurance Portability and Accountability Act) standards. Participants will receive compensation for their participation in the trial in a longitudinal manner, with US $10 at baseline and 12 week data collection timepoints and US $30 at the 24 week time point. Total participant compensation is US $50.

Results

This study will be conducted over a period of 3 years. Data collection was initiated in November 2023 and will continue for approximately 2 years. Approval for the study protocol has been obtained from the institutional review board of Baylor College of Medicine, and a reliance agreement has been approved by the University of Texas Southwestern Medical Center and Parkland Health. We will report on the outcomes identified above as a primary study activity. We also plan to collaborate with patients and clinicians to identify adaptations to the POSTCare-O platform to optimize dissemination potential. Results from this study will inform preparation to study survivorship care for patients living with advanced cancer and other disease types. We expect results from this study to be published in early 2026.

Discussion

Overview

The overarching goal of this research program is to improve QOL and well-being for women living with ovarian cancer. This paper details the protocol for a randomized, controlled, dual-blinded study testing a survivorship care platform for women completing initial treatment for ovarian cancer. The gaps in science related to the care of patients with advanced or incurable cancer are thoughtfully articulated in a recent National Cancer Institute meeting report [6].

This study will address several of the gaps in science that exist relative to women living with ovarian cancer. Much of the science focused on the needs of survivors of cancer has been conducted in breast cancer populations; however, a solid body of work exists that characterizes the impact of ovarian cancer and treatment on QOL, sexual well-being, care preferences, and health care use. This study, with a collection of measures related to symptom burden and psychosocial well-being, will characterize unmet needs at baseline among survivors of ovarian cancer, and we will be able to place our work in the context of the existing science for interpretation. Further, our qualitative stream will provide additional context for interpretation of our quantitative data as we work to better understand the patients' experience.

Although overt efforts have been made to minimize limitations by design, this study will have several limitations. While we expect to meet our sample size target of recruiting 120 women with ovarian cancer, practical aspects of participant recruitment and budgetary constraints will constrain our ability to stratify the population and evaluate potential mediators. Furthermore, the highly structured nature of care delivery for this study, including consistent intervention delivery by a single research nurse, may not reflect the conditions encountered in a "real-world" implementation of this health services intervention that is intended to be optimized for dissemination. While we have put in place measures to address concerns related to intervention fidelity, including review of recordings of intervention sessions with fidelity checklists and ongoing education to ensure consistent delivery, inconsistent delivery remains a potential source of bias for this study. This study will

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take place at 2 US "safety net" clinics that serve economically disadvantaged patients primarily, as well as a university practice that serves individuals with private or federal insurance. While this design should give us a representative sample within our geographic region, the results may not be generalizable to other regions of the United States or health care systems outside the United States. Despite these limitations, this study will make a significant contribution to survivorship science in ovarian cancer by examining aspects of supportive care that may improve QOL for patients.

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Data Availability

The data sets generated during and/or analyzed during this study are available in the Palliative Care Research Collaborative De-Identified Data Repository [69].

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
FACT-O: Functional Assessment of Cancer Therapy-Ovarian
FCR-7: Fear of Cancer Recurrence-7
HIPAA: Health Insurance Portability and Accountability Act
ITT: intention to treat
OS: overall survival
PARP: poly (ADP-ribose) polymerase
PFS: progression-free survival
PHQ-9: Patient Health Questionnaire-9
QOL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCP: survivorship care plan

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Protocol

Cerebral Mechanism of Tuina on the Descending Pain Inhibitory System in Knee Osteoarthritis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis (KOA) is reputedly the most common musculoskeletal disease of the lower limbs and the main cause of pain and disability among older individuals. Pain is the most significant and widespread symptom of KOA. The descending pain inhibitory system has a cardinal role in normal pain consciousness, and its malfunction may be one of the pathophysiological mechanisms in KOA. Crucially, the rostral ventromedial medulla (RVM) and periaqueductal gray (PAG), as important components of the descending pain inhibitory system, directly modulate the activity of the spinal neurons involved in pain transmission. Tuina, a manual therapy, is effective and safe for reducing clinical symptoms of KOA; however, the mechanism that influences pain through the descending pain inhibitory system in KOA is unclear.

Objective: This study aims to investigate the modulatory implications of Tuina on the RVM and PAG, which have critical roles in the descending pain inhibitory system in patients with KOA.

Methods: This randomized controlled parallel trial will be conducted at the Tuina Clinic of the Third Affiliated Hospital of Henan University of Chinese Medicine (Zhengzhou, China). Patients with KOA will be randomly assigned (1:1) to 6 weeks of health education or Tuina. All patients in both groups will accept a resting-state functional magnetic resonance scan at the beginning and end of the experiment, and the resting-state functional connectivity and the voxel-based morphometry analysis will be performed to detect the RVM and PAG function and structure changes. The clinical outcome assessments will be (1) the pressure pain thresholds, (2) the Numerical Rating Scale, (3) the Hamilton Depression Scale (HAMD), and (4) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Considering that this trial is a study of resting-state functional magnetic resonance imaging technology, resting-state functional connectivity and voxel-based morphometry are the primary outcomes, and clinical outcome assessments are secondary outcomes. Adverse events will be documented and assessed throughout. All main analyses will be carried out on the basis of the intention-to-treat principle. The outcome evaluators and data statisticians will be masked to the treatment group assignment to reduce the risk of bias.

Results: This trial was approved by the ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine. Enrollment began in December 2023, and the results of this trial are expected to be submitted for publication in May 2025.

Conclusions: This trial will identify a possible relationship between function and structure changes of RVM and PAG and the improvement of clinical variables, elucidating the effect of Tuina on the descending pain inhibitory system of patients with KOA. This trial will provide much-needed knowledge for Tuina for patients with KOA.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300070289; https://www.chictr.org.cn/showproj.html?proj=182570

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KEYWORDS

brain; knee osteoarthritis; magnetic resonance imaging; pain; Tuina

Introduction

Knee osteoarthritis (KOA) is reputedly the most common musculoskeletal disease of the lower limbs and the main cause of pain and disability among older individuals. Approximately 80% of individuals aged 65 years or older show radiological symptoms of KOA [1]. Pain is the most significant and widespread symptom of KOA. International recommendations for KOA treatment consist of pain alleviation and physical interventions via a combination of pharmacological and nonpharmacological therapies, such as massages [2,3]. Tuina, a massage remedy built on Chinese Medicine meridian theories and Zang-Fu organs, consolidates contemporary scientific knowledge, including anatomy, biomechanical role, and physiology. Previous randomized controlled trials (RCTs) have supported the effectiveness of Tuina for the treatment of different health conditions, such as acute bronchitis [4] and musculoskeletal disorders [5,6]. In relation to KOA, 2 systematic reviews have identified positive clinical effects of Tuina in improving the outcomes of patients with KOA [7,8]. Furthermore, our recent RCT demonstrated the safety and effectiveness of Tuina for improving pain, increasing joint flexibility, and improving KOA-related disability [9].

The pathogenesis of KOA is complex and involves heterogeneous factors in the central and peripheral nervous systems. However, peripheral candidate mechanisms are insufficient to explain widespread pain and the range of concomitant symptoms; thus, centrally driven mechanisms are deemed pivotal in the etiology of KOA. Our recent research demonstrated that the brain also participates in the pathophysiological changes in KOA and that central nervous system remodeling and function modifications may be among the central mechanisms associated with KOA [10]. Patients who reported higher levels of arthritic pain had greater opioid receptor availability in the periaqueductal gray (PAG), a key region of the descending pain inhibitory system, suggesting the alteration of this system in KOA [11]. Additionally, a functional magnetic resonance imaging (fMRI) trial demonstrated that the degree of PAG activation provides a sensitive and objective assessment of patellofemoral pain pressure in patients with KOA [12]. The descending pain inhibitory system originates in the PAG of the midbrain conduction duct and exerts its analgesic function through the relay of the rostral ventromedial medulla (RVM), inferior projection neuron of the cephalic medulla, and spinal-thalamic projection neurons in the superficial dorsal horn of the spinal cord [13]. Moreover, the subcortical structures and multiple cortices of the brain, comprising the anterior cingulate cortex, amygdala, insula, and hypothalamus, are also involved in pain modulation via the descending pain inhibitory system. The function of the descending pain inhibitory system in pain modulation and the management of the same have been substantially referenced [14,15].

We have, therefore, designed a single-center, parallel RCT to investigate the implications of Tuina and health education on KOA pain, resting-state functional connectivity (rsFC) of the cardinal regions of the descending pain inhibitory system (RVM and PAG), modifications of the voxel-based morphometry (VBM) of RVM and PAG, and behavioral alterations and their connections. We hypothesized that all treatments would relieve knee pain and share common pathways and that pain relief would be associated with the descending pain inhibitory system.

Methods

Trial Design

Patients will be recruited through advertisement in the Tuina clinic of the Third Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, China. We will follow the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [16] to guide the reporting and development of our protocol. All eligible participants will be required to sign an informed consent form and will be notified that the trial will not contain any collection of human biological specimens.

Eligibility Criteria

The inclusion criteria are as follows: (1) met the classification and reporting of KOA, per the 1986 American College of Rheumatology criteria [17]; (2) age between 40 and 70 years; (3) experienced knee pain for ≥3 months; (4) knee pain score is ≥3 on the Numerical Rating Scale (NRS) [18]; and (5) radiologically confirmed KOA (Kellgren and Lawrence [K-L] score of 2 or 3) [19].

Exclusion Criteria

The exclusion criteria are as follows: (1) knee pain associated with other diseases, (2) the individual has undergone intra-articular injections within the last 6 months, (3) a history of knee surgery, (4) psychiatric disorders or chronic severe or acute organic diseases, (5) bleeding disorders, and (6) magnetic resonance imaging (MRI) contraindications, such as phobias or pacemakers.

Exit Criteria and Management

Exit criteria are as follows: (1) request by the participant and (2) intratreatment side effects.

Sample Size

The sample size of 64 patients was planned, based on our previous clinical research [9]. The formula is determined:

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wherein *N* refers to the sample size in each group, σ represents the SD, α represents type I error, β represents type II error, 1–β represents the test power, and δ represents the difference between mean groups.

The pressure pain threshold (PPT) values of the treatment and control groups were 9.53 (1.26) and 9.02 (2.62), respectively. We took α=0.05, β=0.10, 1–β=0.90, set the 2-sided test level α=0.05, and found out from the *t*-distribution boundary value table: u_{α}=1.96, u_{β}=1.282. In this study, δ=0.51, σ with the larger SD of 1.36, and an approximate *N* of 29 after substituting the formula. With an estimated drop-off rate of 10%, a total of 64 patients with KOA were needed.

Recruitment Strategies and Enrollment

The participants will be recruited between December 2023 and December 2024. Participants will also be recruited through a multi-modal strategy, including dissemination through WeChat and posters at community service centers. Figure 1 presents a flow diagram consisting of recruitment, screening, and randomization. Table 1 presents a schematic overview of our trial designs, conduct, review, and analysis.

Figure 1. Flowchart of the trial. fMRI: functional magnetic resonance imaging; HAMD: Hamilton Depression Scale; NRS: Numerical Rating Scale; PPT: pressure pain threshold; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

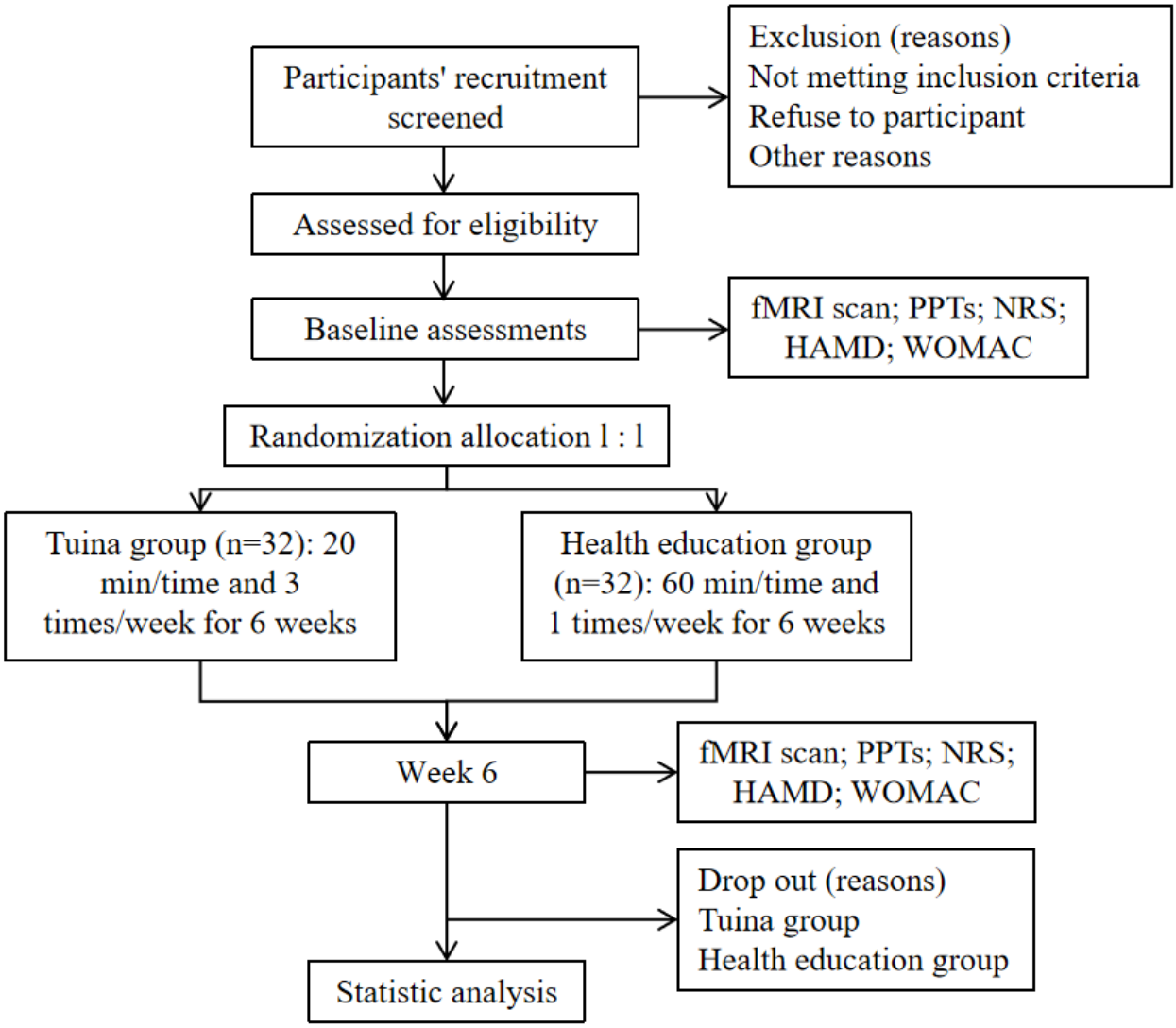

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Table 1. Chart of the trial's time points.

Research process	Enrollment	Allocation	Beginning	End of the experiment
Eligibility screen	✓			
Demographic variables	✓			
Medical variables	✓			
Allocation		✓		
Consent			✓	
fMRI[a] scan			✓	✓
PPTs[b]			✓	✓
NRS[c]			✓	✓
HAMD[d]			✓	✓
WOMAC[e]			✓	✓
Adverse events			✓	✓
Working practice record			✓	✓

[a]fMRI: functional magnetic resonance imaging.

[b]PPT: pressure pain threshold.

[c]NRS: Numerical Rating Scale.

[d]HAMD: Hamilton Depression Scale.

[e]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Randomization

Independent research staff will use SPSS 25.0 (IBM Corp) to generate a randomly numbered sequence for complete randomization. Participants will be randomly assigned into 1 of 2 groups (ie, health education or Tuina group) and applied in a 1:1 allocation ratio. The random sequence will be sealed by a self-governing research assistant via an opaque envelope that contains information regarding the participant's allocation.

Blinding

The outcome evaluators and data statisticians will all be masked to the group assignment to prevent bias.

Interventions

A panel of 2 clinical medical professionals with an academic background in Tuina and clinical medicine agreed to develop a standard protocol for Tuina and health education. The protocol's feasibility will be examined to determine whether it is practicable and acceptable and to identify any realistic issues caused by the procedures. Given the nature of the treatment, participants will be informed that the trial will be without harm, compensation, and posttrial care.

Clinical medical professionals with ≥3 years of experience with Tuina will conduct the health education for the participants. Before the trial, clinicians will be trained to ensure standard procedures and compliance with treatment protocol. All participants in the Tuina group will receive three 20-minute sessions a week over a 6-week treatment course. The participants in the health education group will participate in health education sessions lasting 1 hour each (administered once weekly for 6 weeks). The participants are to maintain their dietary habits and regular physical activity throughout the study period. Throughout the trial, they will be informed that they are not permitted to entertain other remedies. To guarantee compliance, all participants are required to register for therapy in a written log.

Tuina Group

The standard Tuina procedure will be performed based on Tuina Therapy, a textbook of the 13th Five-year Plan [20]. The specific administration procedure will first start with the hand disinfection of the Tuina clinical medical professional. Second, the specific application of Tuina will be performed according to the following methods [9]: (1) the participant will be placed supine on the treatment bed, and the Tuina therapist will press at the points Xuehai (SP10), Yinlingquan (SP9), Yanglingquan (GB34), Liangqiu (ST34), Xiyan (EX-LE5), and Zusanli (ST36; based on the standard of the World Health Organization [21]; Figure 2); (2) the participant will be asked to sit in a chair, the knee will be flexed to 90 degrees, and the Tuina therapist will revolve the foot of the participant to a neutral position and lightly press the patella's lower edge; the therapist's other fingers will then be wrapped around the knee's rear without force. The participant will be instructed to stand, and the therapist will push the patella. The participant will then be required to sit down. This process will be repeated 3 times.

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Figure 2. Location of the acupoints.

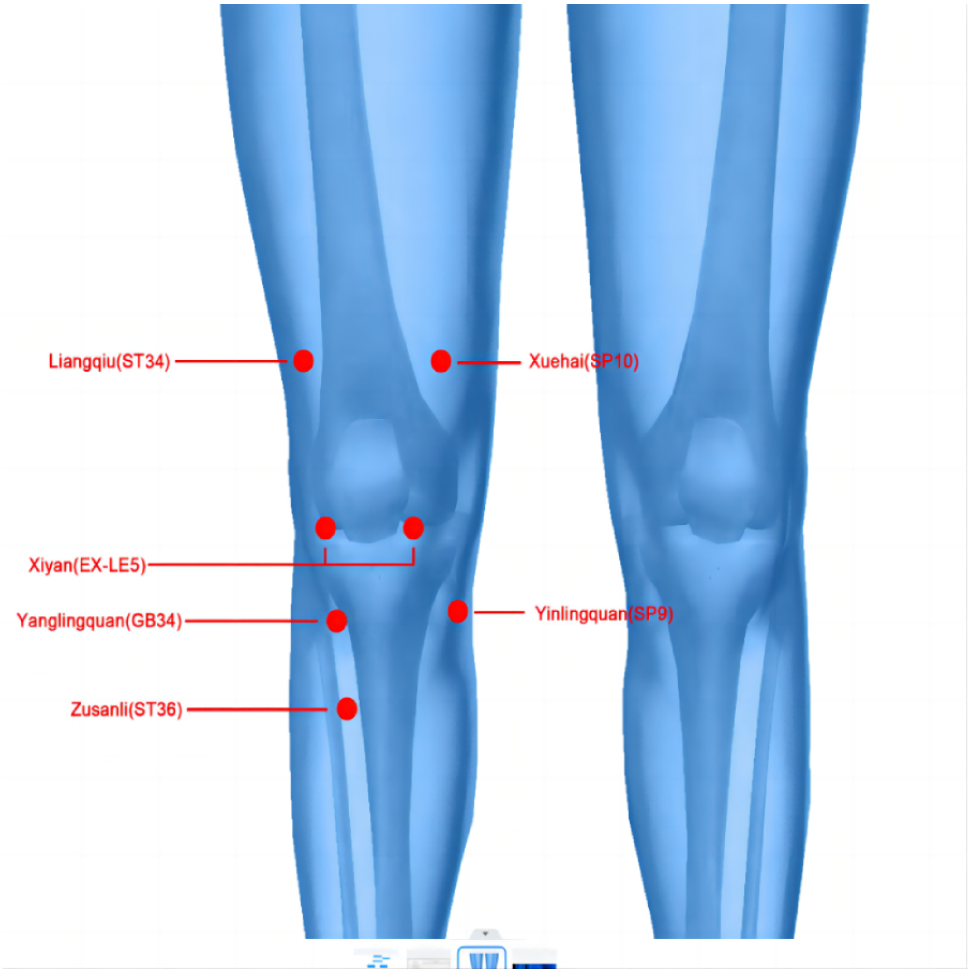

Health Education

We will introduce the basic concepts of KOA and the methods used to manage the associated risks to help participants protect their knees.

MRI Data Acquisition

MRI will be performed at the MRI Center of The Third Affiliated Hospital of Henan University of Chinese Medicine. Resting-state fMRI will be performed at the beginning and end of the experiment. MRI data will be acquired using a 3.0-T magnetic resonance scanner (General Electric) with a 32-channel phase-array head coil. During the full scanning period, the participants will be asked to remain awake and motionless with their eyes closed.

Blood oxygen level independent resting-state functional images will be acquired using the following parameters: TR=2000 ms, TE=30 ms, flip angle=90°, 33 axial slices, and field of view (FOV) = 220 mm × 220 mm. T1-weighted images will be collected using the following parameters: 160 axial slices, TE=2.93 ms, flip angle=9°, TR=1900 ms, TE=30 ms, and FOV = 256 mm × 256 mm. T2-weighted images will be collected with the following parameters: 25 axial slices, TE=2.93 ms, flip angle=150°, TR=6300 ms, TE=86.0 ms, and FOV = 240 mm × 240 mm.

Clinical Outcome Assessments

Validated pain detectors and questionnaires will be used to assess knee pain, psychological characteristics, and function at the beginning and end of the experiment. The clinical outcome assessments will be (1) the PPTs, (2) the NRS, (3) the Hamilton Depression Scale (HAMD), and (4) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Additional outcome indices included the adverse events of treatment.

Pressure Pain Thresholds

The PPT is a form of quantitative sensory testing that enhances the understanding of pain sensitivity and musculoskeletal pain [22-24]. Moreover, it has strong interrater reliability across multiple raters [25]. The PPT effectively depicts pain intensity and is widely applied in patients with KOA. PPTs will be measured using a portable machine (FDX50, Digital Force Gauge, Wagner Instruments) [26,27]. The patient will be placed in a supine position. The variable collector will select four points for measurement: (1) 3 cm medial to the midpoint of the medial patellar border, (2) the center of the patella, (3) 3 cm lateral to the midpoint of the lateral patellar border, and (4) the belly of the deltoid muscle of the affected upper limb (Figure 3) [28]. The pain test needle will be moved slowly at 0.1 kg/s until the participant feels pain. The measurement will be repeated 3 times at each site with an interval of 25 s, and the average will be calculated [29].

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Figure 3. Points used to measure the PPTs. PPT: pressure pain threshold.

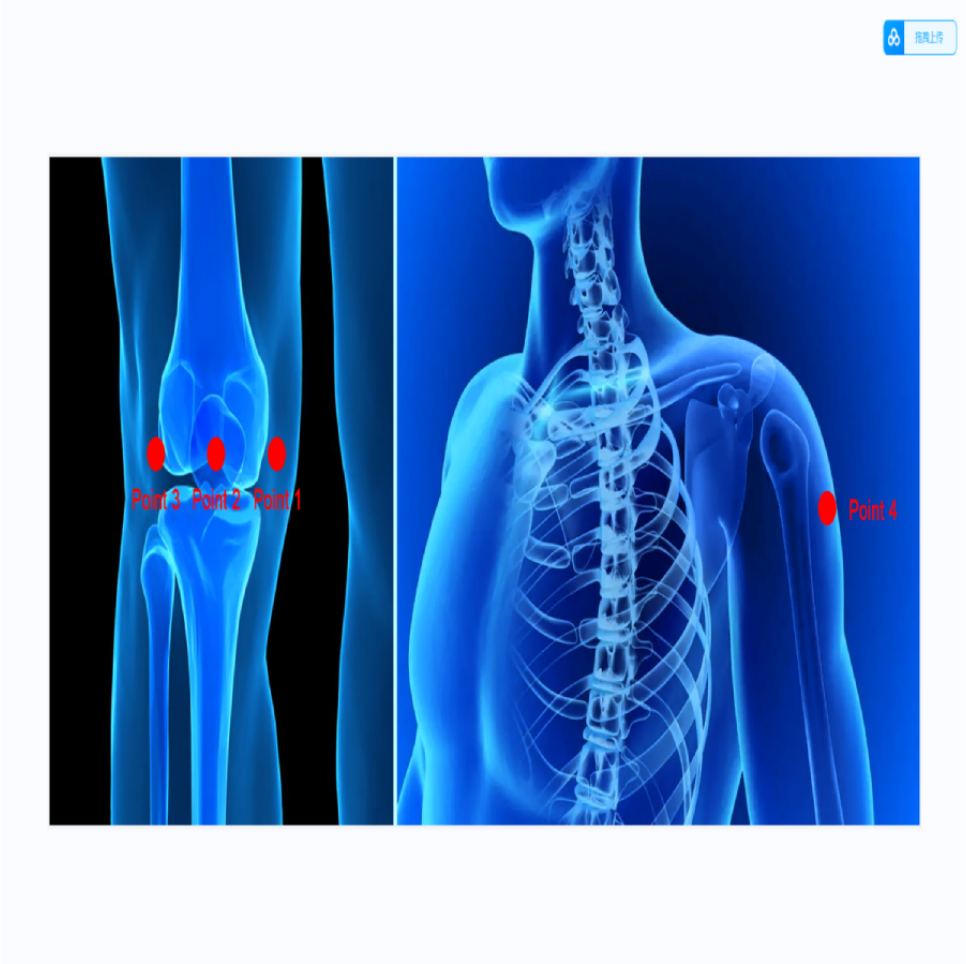

Numerical Rating Scale

The NRS is an elementary well-managed scale to assess pain intensity. Patients express the intensity of rest and movement pain using the numbers 0-10.

Hamilton Depression Scale

The HAMD comprises 24 items, most of which are evaluated on a 5-point scale (0-4 points): 0="none," 1="mild," 2="moderate," 3="serious," and 4="very serious." A few items are assessed on a 3-point scale (0-2 points): 0="none," 1="mild to moderate," and 2="serious."

Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC (0-10 cm) comprises 3 dimensions (ie, pain, stiffness, and joint function). The score ranges from 0 to 96, with higher scores indicating worse symptoms.

Adverse Events of Treatment

All adverse events that may occur throughout the trial will be documented, including the time of occurrence, symptoms of discomfort, particular indications, severity, remedy supplied, time course of the action of amelioration, time of determination, and date of remedy termination.

Demographic or Medical Variables

The following demographic and medical variables will be collected for analysis: sex, age, marital status, occupation, ethnicity, education level, blood pressure, temperature, respiration, pulse, height, weight, body mass index, combination of disease and medication, K-L score, course of KOA, and history of major surgeries.

Data Management

Clinical data will be carefully saved using printed and electronic case report forms (CRFs). Only outcome assessors will access the CRFs for data entry to guarantee data quality. CRFs will be verified for double entry and accuracy. During the trial, the Third Affiliated Hospital of the Henan University of Chinese Medicine will conduct regular visits (once a week) to review the conduct of the trial.

Data Monitoring

The ethics committee will monitor for trial breaches and guarantee no conflicts of interest exist. Statisticians can obtain the last trial data set, which will exclusively accommodate coded data. The safety, advancement, and research integrity will be supervised throughout the research team conferences.

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fMRI Preprocessing

rsFC Preprocessing

rsFC will be conducted by applying a seed-based approach using the CONN toolbox (Version 17.f) [30]. CONN is Matlab/statistical parametric mapping (SPM)–based software for the analysis of functional connectivity data. This analysis will use predefined regions of interest (ROIs) based on masks of the a priori specified brainstem nuclei (PAG and RVM) [31], as previously described [32].

Preprocessing of fMRI data will be performed using a pipeline in the CONN toolbox, including translation by centering to (0, 0, 0) coordinates, slice-timing correction, realignment, coregistration to participants' respective structural images, normalization, artifact detection, smoothing with an 8 mm Gaussian kernel, and segmentation into gray matter volume (GMV), white matter (WM), and cerebrospinal fluid volume (CSF). Linear detrending will be performed with a frequency window of 0.008-0.09 Hz. Linear detrending will be executed, and a frequency window of 0.008-0.09 Hz will be applied. Artifact detection will be run using the ART toolbox to eliminate correlations caused by head motion and artifacts. During the denoising processes, WM, CSF, and outliers will be detected using the ART toolbox and entered into the linear regression analysis as confounding effects.

Subsequently, a correlation map will be produced for each participant by extracting the blood oxygen level independent time course from the left/right PAG and left/right RVM seeds separately and computing the Pearson correlation coefficients between the time course in the PAG or RVM and every voxel of the whole brain. Correlation coefficients will be converted by applying Fisher transformation into *z* scores to raise their normality.

VBM Preprocessing

We will use the Diffeomorphic Anatomical Registration With Exponentiated Lie Algebra (DARTEL) SPM 12's segmentation algorithm for whole brain VBM analysis. All T1-weighted images will be analyzed using SPM 8 (Wellcome Institute) software, as implemented in Matlab (Matlab 2013a, Math Works). First, the new segmentation algorithm from SPM 8 will be applied to every T1-weighted image will be segmented into GMV, WM, and CSF. Second, all segmented tissue maps will be used to create a vervet population template using the DARTEL template-creation tool. We will use a set of standard Montreal Neurological Institute tissue maps and a multivariate tissue-affinity-registration and segmentation algorithm carried by SPM's VBM DARTEL for that process. Finally, each patient's GMV map will be warped using its corresponding smooth (Gaussian kernel of 8 mm full-width at half maximum), reversible martensitic parameters to transform it to the customized template space and then to the Montreal Neurological Institute template space.

Statistical Analysis

Prior to the analysis, a statistical program will be undertaken by a statistician. The program will embrace the processing approaches and the demanded data. Variables will be analyzed with IBM SPSS Statistics for Windows (version 25; IBM Corp).

rsFC Analysis

For the ROI analysis, the ROI-to-ROI connectivity connections will be placed to a threshold by the intensity at the false discovery rate-corrected $P<.05$ (2-sided).

For the analysis of rsFC, we will use ROIs derived from the rsFC results. For the ROIs, we will use a threshold of voxel-wise $P<.005$ uncorrected and $P<.05$ corrected using Monte Carlo simulations with the 3dFWHMx and 3dClustSim applied [33].

VBM Analysis

After completing these image analyses, we will obtain the GMV values of the key regions derived from rsFC for subsequent statistical analysis. The statistical significance between-group differences will be set at $P<.05$ with family-wise error correction.

Data Analysis of Clinical Outcomes

Measurement Data

The Shapiro-Wilk test will foremost be conducted to confirm the normality of the uninterrupted data distribution. Independent sample *t* tests will be conducted for normally distributed data to evaluate the baseline characteristics. The Mann-Whitney U test will evaluate between-group differences for nonnormally distributed data.

Ranked Data and Count Data

The body mass index categorization, K-L score, NRS score, and WOMAC score are the rank data. Therefore, the Mann-Whitney U test will be applied for the between-group comparisons, and the Wilcoxon symbolic test will be applied for the intragroup comparisons. Count data will involve the ratio of the sex variable and knee constituent ratio, compared between the 2 groups via χ^2 test of 4-fold table or Fisher test. Statistical significance will be set at $P<.05$ (2-sided).

Ethical Considerations

This trial was registered in the Chinese Clinical Trials Registry in 2023 (ChiCTR2300070289). The ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine has approved this study protocol (ethics approval number 2022HL-031).

This RCT will adhere to the ethical principles governing biomedical research on human participants and respect fundamental human rights in accordance with international recommendations included in the Declaration of Helsinki and its subsequent revisions.

Participants will be given both written and oral information about why the trial will be conducted, its objectives, the potential risks associated, and the guidelines set out during the monitoring period. If a patient fulfills the inclusion criteria and agrees to enroll in the trial, they will provide written informed consent. Patients are free to withdraw consent and discontinue the trial at any time and for any reason.

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Results

This trial was approved by the ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine. Enrollment began in December 2023, and the results of this trial are expected to be submitted for publication in May 2025.

Discussion

Overview

To the best of our knowledge, our trial will be the first to assess the modulatory effect of Tuina on the descending pain inhibitory system in patients with KOA. The results will improve the apprehension regarding Tuina's mechanisms in patients with KOA.

KOA can cause joint dysfunction, reduce physical fitness and capability to tackle activities of daily living, and cause depression and anxiety [3,34,35]. Previous researchers have indicated that peripheral factors such as synovial inflammation and articular cartilage devastation may have a cardinal role [36-38]. However, many studies found that the severity of radiographic KOA and the inflammatory response of the synovial membrane do not positively correlate with KOA [39-41]. Consequently, peripheral mechanisms cannot completely explain KOA. Patients with KOA have simultaneously raised pain sensitivity in affected and nonaffected areas. Therefore, some investigators suggest that an "abnormal central processing" of afferent pain messages may be a cardinal factor in KOA [26].

Based on the theory of traditional Chinese Tuina, all the acupoints can treat the disease of the adjacent area and local area. In our study, 6 local acupoints are selected in the Tuina group, including Xuehai (SP10), Yinlingquan (SP9), Yanglingquan (GB34), Liangqiu (ST34), Xiyan (EX-LE5), and Zusanli (ST36). Yanglingquan (GB34) and Yinlingquan (SP9) are also known as the converging point of the tendon footprint and are usually recommended to relieve knee pain. Xuehai (SP10) and Liangqiu (ST34) are the most commonly used acupoints for the treatment of dysfunction caused by KOA. Xiyan (EX-LE5) is supplemented to adjust the tension of soft tissue. Zusanli (ST36) is commonly used for the treatment of inflammation and pain. Our previous results showed that the above 6 acupoints used together can effectively improve the pain of patients with KOA [7].

Moreover, Tuina is safe and effective for pain, physical function, stiffness, and other clinical symptoms associated with KOA [42]. It likewise has been demonstrated to activate and modulate functional connectivity in the hippocampus to facilitate cognitive function in patients with poststroke depression [43]. The brain has a powerful control over nociceptive input in the spinal cord at the brain stem level. This top-down control occurs through the "descending modulation" of the pain transmission pathway mechanism [44-46]. The descending pain inhibitory system has a cardinal role in normal pain consciousness, and its malfunction may be one of the pathophysiological mechanisms in KOA. This factor possibly clarifies how other centrally mediated processes, such as sleep, mood, the placebo effect, and cognition, influence the pain experience [47]. Crucially, the PAG and RVM, as important components of the descending pain inhibitory system, directly modulate the activity of the spinal neurons involved in pain transmission [48]. Furthermore, animal experiments have demonstrated that the PAG is involved in opioid-mediated analgesia since the microinjection of morphine into this nucleus produces a reduction in sensory pain behaviors [49]. Similarly, the analgesic effects of stimulating the PAG directly have also been evidenced in humans [50]. Moreover, direct PAG stimulation is used to diminish chronic pain intensity in individuals [51]. The RVM is the pontomedullary area where opioid microinjection generates analgesia [48]. Making allowances for this, the PAG-RVM axis, as a significant component of the descending pain inhibitory system, can possess an inhibitory implication on harmful transmission. However, the mechanism of the descending pain inhibitory system in the analgesic effect of Tuina in the treatment of KOA is unclear, especially the relationships among PAG and RVM and clinical behavioral indicators, which limits its promotion and application. Therefore, fully exploring the central analgesic mechanism is necessary to alleviate the pain of KOA. As a main type of fMRI, resting-state fMRI has the advantage of providing more comprehensive information on the functional architecture of the brain. Resting-state fMRI is widely used to study the analgesic mechanism of Tuina in the treatment of KOA [52].

In summary, this clinical trial will aim to investigate the influence of Tuina on the descending pain inhibitory system in order to explain the potential central mechanism of Tuina treatment. We will use a combination of resting-state MRI and clinical behavior indicators such as rsFC and VBM to perform research and analysis of Tuina analgesia.

Limitations and Strengths

Although this study's potential strengths, it anticipates limitations. First, there is potential for methodological bias, as blinding is particularly difficult when delivering a physical intervention or health education. Second, the long-term implications of Tuina will not be investigated; thus, further research is warranted. Despite these several different limitations, this study's strengths lie in its focused investigation of the potential central mechanism of Tuina treatment, which contributes valuable insights into the modulatory effect of Tuina on the descending pain inhibitory system in patients with KOA.

Conclusions

This trial is designed to investigate the central mechanism of Tuina in the treatment of KOA, with the involvement of health education as a control intervention. We expect that Tuina would relieve pain symptoms in patients with KOA and that pain relief would be associated with the descending pain inhibitory system.

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Acknowledgments

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Data Availability

The data sets used and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

YZ will be the sponsor. HX will take responsibility for designing the trial. Zheng Wang will take responsibility for supervising the trial. Zhen Wang drafted and revised the manuscript. HX takes responsibility for ethics approval and clinical trial registration. HZ planned the statistical analysis protocol. WL will be the evaluator. JG will be responsible for all data collection. All bylined authors will follow the trials’ authorship guidelines and have consented to publication.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
CSF: cerebrospinal fluid volume
DARTEL: Diffeomorphic Anatomical Registration With Exponentiated Lie Algebra
fMRI: functional magnetic resonance imaging
FOV: field of view
GMV: gray matter volume
HAMD: Hamilton Depression Scale

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K-L: Kellgren and Lawrence
KOA: knee osteoarthritis
MRI: magnetic resonance imaging
NRS: Numerical Rating Scale
PAG: periaqueductal gray
PPT: pressure pain threshold
RCT: randomized controlled trial
ROI: regions of interest
rsFC: resting-state functional connectivity
RVM: rostral ventromedial medulla
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPM: statistical parametric mapping
VBM: voxel-based morphometry
WM: white matter
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

Comparing Repeated (Annual) Couples HIV Testing and Counseling to Individual HIV Testing and Counseling Among Male Couples at High Risk of HIV Infection: Protocol for a Randomized Control Trial

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Abstract

Background: Couples HIV testing and counseling (CHTC) is now a standard of care prevention strategy recommended by the Centers for Disease Control and Prevention for sexual minority men (SMM) in relationships. Despite standard recommendations that couples complete CHTC every 6-12 months, no study has empirically evaluated the effects associated with CHTC retesting.

Objective: This study aims to understand the benefits associated with continued dyadic engagement in the HIV prevention continuum through routine CHTC retesting, which is of particular importance for emerging-adult SMM in relationships who use drugs.

Methods: Eligible couples for this CHTC retesting trial must already be enrolled in the 4Us trial, where they completed a CHTC session after their baseline survey. The purpose of the original 4Us trial was to test the efficacy of 2 intervention components for CHTC: a communication skills training video and a substance use module. Couples were eligible for the original 4Us trial if they identified as cisgender male, were in a relationship for 3 months or longer, were aged 17 years or older, and communicated in English. At least 1 partner had to be aged 17-29 years, report HIV negative or unknown serostatus, report use of at least 1 drug (cannabis, cocaine or crack, crystal methamphetamine, ketamine, gamma-hydroxybuterate [GHB], psychedelics, ecstasy, prescription medication misuse, opiates, and nitrates) use, and engage in condomless anal sex (CAS) acts with a casual partner or have a main partner who is nonmonogamous or serodiscordant. Those who complete the 4Us 12-month follow-up and remain in a relationship with the partner they participated in 4Us with are offered the opportunity to participate in this CHTC retesting trial. Those consenting are randomized to either CHTC retesting or individual HIV testing. Follow-up assessments are conducted 3 and 6 months after randomization to evaluate the effects of repeat CHTC on 2 primary outcomes: (1) CAS with a casual partner in the absence of preexposure prophylaxis (PrEP), and (2) CAS with a serodiscordant main partner who is not virally suppressed or concurrent CAS between main and casual partners in the absence of PrEP.

Results: The CHTC retesting trial launched in January 2023, and enrollment is ongoing. As of February 2024, the study had enrolled 106 eligible participants (n=53 couples).

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Conclusions: Findings from this CHTC retesting study will contribute to knowledge about the benefits associated with regular (repeated) CHTC testing versus routine individual HIV testing for SMM in relationships. The results of this trial will inform CHTC retesting guidance.

Trial Registration: ClinicalTrials.gov NCT05833074; https://www.clinicaltrials.gov/study/NCT05833074

International Registered Report Identifier (IRRID): DERR1-10.2196/53023

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KEYWORDS

club drugs; counseling; dyadic interventions; emerging adults; gay and bisexual men; HIV; male couples; men who have sex with men; randomized controlled trial; RCT; relationships

Introduction

Background

Sexual minority men (SMM), a group that encompasses gay, bisexual, and other men who have sex with men, account for 69% of new HIV infections in the United States [1]. Despite the emergence of novel biomedical prevention options (eg, preexposure prophylaxis [PrEP], postexposure prophylaxis [PEP], and HIV undetectable=untransmittable, or treatment as prevention), this overall rate has changed little over the past decade [2]. The majority (68%) of these new infections occur among SMM under the age of 35 years [2]—a proportion that was largely unchanged in the decade between 2009 and 2019 [2].

Nearly 2 decades of research have indicated that HIV prevention interventions that address the needs of SMM in relationships are an essential component of any comprehensive US national HIV prevention plan. Findings first emerged in the early 2000s, indicating that primary partnerships were often a risk for HIV infection [3-5]. Subsequently, epidemiological modeling estimated that between 35% and 68% of HIV infections among SMM are among main partners [6-8]. Rates of primary partner transmission were particularly high (accounting for between 79% and 84% of new infections) among emerging adult SMM (aged 18-29 years) [6]. More recently, Starks et al [9] found that SMM in nonmonogamous relationships (where sex with outside partners is permitted in some way) engage in condomless anal sex (CAS) with casual partners at rates comparable to those who are single. Although men in monogamous relationships were less likely to engage in CAS with casual partners, those who do have CAS with casual partners report doing so more frequently than nonmonogamous men [9].

As evidence of the risk for HIV acquisition in couples has increased, couples HIV testing and counseling (CHTC) has emerged as a standard of care prevention strategy recommended by the World Health Organization and is now considered a proven and effective public health strategy by the US Centers for Disease Control and Prevention [10]. Protocols have been adapted for SMM in the United States [11] and demonstrated safety (with no evidence of increasing intimate partner violence [IPV] among those participating in CHTC) [12]. During CHTC, couples receive all elements of the counseling, testing, and results delivery together. In addition, the HIV tester facilitates a future-oriented dialogue between the partners about their HIV prevention practices, sexual agreement, and communication related to HIV risk. The goal is for the couple to leave with a shared vision—a set of agreed-upon actions—about HIV prevention and relevant sexual practices [13,14]. CHTC has shown marginally significant reductions in HIV-related sexual risk-taking in men who test HIV negative [15] as well as men who were newly diagnosed with HIV [12,15]. A recent trial showed that participation in CHTC also increased rates of viral suppression among serodiscordant male couples [16].

There are 3 rationales that indicate the potential importance of CHTC retesting. First, sexual health outcomes for relationship partners are interdependent. A coordinated effort maximizes prevention outcomes for both partners. Second, the potential for fluidity and change in behavior means that ongoing communication about sexual behavior and dyadic participation in HIV prevention is essential for partners to maintain effective coordination. Third, CHTC works by activating prevention communication among partners, conferring benefits for SMM in relationships that routine individual HIV testing cannot.

The Interdependence of Sexual Health Outcomes

Much of the research on couples HIV prevention has been organized by interdependence theory [17] and dyadic coping [18]. Within this framework, HIV prevention can be understood as a shared or joint goal, one that requires effort from both partners to be accomplished. The shared nature of this goal is evident in data on main partner HIV transmission risk behavior (TRB). If 1 partner in the relationship engages in sexual risk behavior leading to HIV infection, or if 1 partner in the relationship is not aware that he is living with HIV for whatever reason, the likelihood of transmission between main partners is high. In short, prevention outcomes for both partners in a relationship are maximized when they coordinate or contribute joint effort to accomplish HIV prevention goals.

Interdependence theory [19] suggests coordination is easier for couples with better relationship functioning and communication. Interdependence theory suggests that in relationships characterized by a high degree of satisfaction, commitment, and emotional investment, partners are more likely to consider the impact of their behavior on one another and their relationship overall. This transformation of motivation, away from a focus on personal priorities and toward a consideration of one's partner, enhances partners' motivation to reach consensus around shared sexual agreements and related HIV prevention plans. It also provides the impetus for partners to then support one another in adhering to these agreements or accomplishing the goals implied within them.

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The Importance of Ongoing Communication—Why One-Time Agreement on a Goal Is Not Enough

Research on the prevalence of sexual agreements in male couples suggests a substantial number disagree about the nature of their sexual agreement. For example, 1 partner believes that sex with outside partners is in some way permitted; meanwhile, the other believes they are monogamous. While estimates vary widely, Stephenson and colleagues [20] found that, even in a sample of couples where 84.7% of men reported having an agreement, partners had discrepant perceptions of what that agreement was in 58.7% of couples. Perhaps not surprisingly, couples with discrepant perceptions of their sexual agreement score lower on measures of adaptive communication compared to those whose perceptions are aligned. The completion of CHTC resolves discrepant perceptions by catalyzing direct, explicit communication about the couple's rules and understandings related to sex with outside partners.

Once formed, sexual agreements and HIV prevention plans are neither fixed nor static. They have the potential to change over time as the needs and priorities of the individual partners in the couple evolve. Stephenson and colleagues [21] recently found that just 6 months after completing CHTC, partners in 22.6% of couples had discrepant perceptions of their sexual agreements, and 12.7% had broken (or failed to fully adhere to) their agreement. Cross-sectional studies consistently indicate that couples who have been together longer are more likely to develop sexual agreements that permit sex with outside partners [9,22-24]. This trend has been observed even in samples of couples that are age-restricted to emerging adulthood [25]. Some findings also show that partners reporting discrepant perceptions of their sexual agreement and breaking their agreement increase with relationship length [24].

This potential for change over time necessitates ongoing communication about sexual agreements and HIV prevention practices to maintain partners' alignment and coordination and underscores the need for repeat CHTC. Unfortunately, several factors complicate HIV prevention communication for relationship partners. In general, partnered SMM perceive themselves to be at lower risk of HIV infection and test for HIV less often compared to single SMM [26,27]. For at least some couples, forfeiting HIV prevention, engaging in CAS together, or stopping PrEP is interpreted as an indicator of commitment or emotional closeness [28-31]. As a result, the introduction of condom use, PrEP, or PEP to prevent HIV infection is complicated by the potential that it might convey a lack of commitment to or trust in their partner [32-37] for these couples.

For SMM in Relationships, CHTC Retesting May Confer Specific Benefits Above and Beyond Those Associated With Routine Individual HIV Retesting

During CHTC, partners obtain updated information on their own and one another's HIV status. As part of routine CHTC retesting, the CHTC provider can reinforce the couple's relationship functioning. The CHTC provider also initiates a conversation among partners with the goal of updating their HIV prevention plan and clarifying any changes in behavior or perception that would impact the couple's sexual agreement. These provider-initiated interactions may be of critical importance in couples where 1 partner desires to discuss such changes but is concerned that raising the topic might harm the relationship or is uncertain about how to initiate conversation.

Understanding the benefits associated with continued dyadic engagement in the HIV prevention continuum through routine CHTC retesting is of particular importance for emerging adult SMM in relationships who use drugs. Rates of illicit drug use are generally higher among SMM (11.1% to 27.1%) compared to heterosexual men (5.7% to 16.2%) [38,39]. Rates of cannabis use are also higher among SMM (36%) compared to heterosexual men (20.4% to 24.7%).

High rates of drug use and associated sexual risk-taking extend to partnered SMM, particularly those in nonmonogamous agreements. SMM in nonmonogamous relationships consistently report rates of illicit drug use that are comparable to single SMM; meanwhile, men in monogamous relationships are significantly less likely to use illicit drugs [9,22,23,40]. Extensive research has shown that SMM who use cannabis and illicit drugs are more likely to have CAS [41-44] with casual partners. Associations between drug use and sexual risk-taking are comparable for partnered and single SMM. Our research suggests the association between illicit drug use (excluding cannabis) and the odds of CAS with casual partners is comparable for single SMM and those in nonmonogamous agreements [9]. Meanwhile, the association between cannabis use and the odds of CAS with casual partners is comparable for single SMM and those in monogamous agreements—for whom the behavior breaks their agreement. This converges with other evidence suggesting that drug use during sex is associated with breaking a sexual agreement [45] and decreased condom use among partnered SMM [40,46].

Objective

The purpose of this study is to evaluate the efficacy of annual CHTC retesting to reduce indicators of sexual risk relative to routine individual HIV testing and counseling among male couples.

Methods

Trial Design

This study uses a randomized controlled trial design integrated with the ongoing 4Us trial [47]. The purpose of the original 4Us trial is to test the efficacy of 2 intervention components for CHTC: a communication skills training video and a substance use module. Couples are eligible for the original 4Us trial if at least 1 partner reports HIV negative or unknown serostatus, reports at least 1 drug, and engages in HIV TRB. Participants in this ongoing trial (4Us) complete an individual baseline assessment, after which couples complete a CHTC session following the standard CHTC protocol. In a full-factorial design, half of the couples are randomly assigned to complete an adjunct module addressing drug use, and half are assigned to view an assertive communication training (ACT) video (later referred to respectively as the substance use calendar and ACT video). This results in 4 study conditions (CHTC as usual, CHTC plus the substance use calendar, CHTC plus the ACT video, and CHTC plus both adjunct components). Follow-up assessments

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occur 3, 6, 9, and 12 months post intervention using procedures analogous to the baseline. Participants who complete the 12-month follow-up of the 4Us trial and meet eligibility criteria for the CHTC retesting trial are consented individually to participate in this protocol. If both couples consent into this protocol during their 12-month assessment, they are randomly assigned to either couples retesting or individual HIV testing. Those randomized to couples retesting complete the same 4Us condition they were assigned at baseline. Follow-ups are then completed 3 and 6 months later (15 and 18 months post completion of the baseline in the original 4Us trial).

Rationale for Comparison Condition (Individual HIV Testing and Counseling)

Current Centers for Disease Control and Prevention (CDC) recommendations advise that all individuals between the ages of 13 and 64 years should be tested for HIV at least once. Individuals with additional risk factors, including men who have sex with men, are advised to test at least annually [48]. Recommendations for retesting every 3-6 months apply to the highest-risk groups. CDC has summarized the benefits of routine individual HIV testing [48]. Routine testing reduces the onward transmission of HIV infection. It is estimated that 40% of new HIV infections are transmitted by individuals who do not know they are HIV positive. HIV diagnosis is a prerequisite to the initiation of antiretroviral treatment (ART) for those who are living with HIV, and achieving viral suppression through ART nearly eliminates the likelihood of sexual HIV transmission. For those who learn they are HIV-negative, routine HIV testing presents an opportunity to discuss HIV prevention options and risk reduction practices.

Study Setting

All research staff are based at a university research center at Hunter College of the City, University of New York. All study assessments and intervention sessions are conducted remotely through Zoom (Zoom Video Communications, Inc), a Health Insurance Portability and Accountability Act (HIPAA)–compliant videoconferencing software.

Eligibility Criteria

All participants must be enrolled in the original 4Us trial [47] and complete their assigned intervention condition after baseline. Eligibility criteria for the original 4Us trial necessitate that partners in a couple identify one another as “main partners.” In addition, both partners in each couple must identify as cisgender male, be 17 years of age or older, and have a US residence. In addition, at least 1 participant in each couple must (1) be aged 17-29 years; (2) self-report HIV-negative or unknown serostatus; (3) report use of at least 1 illicit drug (cocaine or crack, opiates, misuse of prescription medication, stimulants, psychedelics, ecstasy, ketamine, and GHB) in the past 30 days; (4) have engaged in CAS with a casual partner or a main partner who is nonmonogamous or serodiscordant in the past 90 days; and (5) be able to speak and read in English. If a serodiscordant couple enrolls in the study, the partner living with HIV is not asked to submit viral load test results.

To be eligible for participation in this CHTC retesting study, participants must complete the 12-month follow-up assessment associated with the 4Us trial [47]. In addition, they must remain in a relationship with the same partner with whom they completed their intervention session after baseline in that trial, and that partner must also agree to enroll in this study.

Participants will be excluded from the study if they indicate that they are single or if they are in a relationship with a new main partner (different from the person with whom they completed their initial 4Us intervention session with the following baseline). Participants will also be excluded if they exhibit signs of serious mental illness or cognitive deficit that impair their functioning during routine research interactions; report IPV with their main partner accompanied by ongoing safety concerns in the current relationship; or indicate being coerced to participate.

Recruitment and Enrollment

Following completion of their 12-month follow-up in the 4Us trial, [47] eligible participants will be offered the opportunity to enroll in this study. Those who are interested will be given a separate consent form detailing the purpose and activities involved. Assessments are conducted separately with each partner in a couple. The first partner in a couple to complete their 12-month follow-up and consent to continue in this study will be told that the couple’s intervention session will be scheduled after their partner also completes the follow-up and pending their partner’s individual consent to participate.

Interventions

All participants will be randomly assigned to either CHTC retesting or individual rapid HIV testing session. Intervention sessions for both conditions are conducted remotely over Zoom. All sessions are audio-recorded for data collection, fidelity monitoring, and supervision.

CHTC Retesting

CHTC retesting involves the completion of the CDC standard CHTC protocol [49]. This includes (1) introducing the CHTC process and receiving testing consent from the couple, (2) explaining the HIV test and potential results and collecting the sample, (3) building rapport by exploring the couple’s relationship, (4) discussing HIV risk concerns and reasons for testing, (5) discussing the couple’s sexual agreement and how they handle sex outside of the relationship, (6) providing the results to each partner in the couple, (7) developing a care, treatment, and prevention plan based on results, and (8) providing referrals as needed. Each participant provides a saliva sample for an Oraquick Home testing kit. The test develops during the CHTC session while the counselor discusses steps 3 through 5.

Participants assigned in the original 4Us trial to a condition that includes viewing ACT videos before completing CHTC. The ACT video portrays 4 couples in scenes discussing HIV testing, drug use, sexual agreements, and drug use during sex. Each scene is depicted twice. The initial viewing shows the couple making one or more communication errors. The second viewing shows the couple using more effective communication skills, resolving the situations more adaptively.

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Participants assigned to a condition that includes the substance use calendar module complete this module just before the delivery of HIV testing results. The substance use calendar occurs in the CHTC session before the HIV test results are given. The couple is asked to collectively complete a 30-day calendar of daily drug and alcohol use. The counselor provides the calendar on a shared computer screen as a Microsoft Excel (Microsoft Corporation) document. After the completion of the calendar, the counselor engages the couple in a discussion about their use, establishes the couple's goals and limits for drug use, and makes plans to achieve these goals. Additional details about the content of these intervention components are available elsewhere [47]. The intervention session in the CHTC retesting study follows the same procedures as the original 4Us trial. The same counselor may or may not conduct the resting intervention, which mirrors how testing may occur in a community setting.

Individual Rapid HIV Testing Session

Individual rapid HIV testing session, also known as the individual HIV counseling, testing, and referral (CTR), is the current standard of care for individual testing and first involves preparing to conduct an HIV test (explaining the HIV test and possible results the participant could receive). After answering any participant questions and gaining consent to conduct the test, the HIV counselor walks the participant through the rapid, oral HIV test. While the HIV test is processing for 20 minutes, the counselor and participant discuss a prevention plan, avoiding the topic of their partner and steering the conversation to address only the individual. HIV-negative individuals are given a standard referral list for future HIV testing, sexually transmitted infection (STI) testing, and PrEP options. Those testing HIV positive are counseled about their test result and referred to confirmatory testing. When serodiscordant couples are randomized to individual rapid HIV testing control condition, individuals who are living with HIV do not receive HIV testing. Instead, they receive information about ART adherence, undetectable=untransmittable, and STI testing.

Intervention Training

As part of the ongoing 4Us trial [47], all interventionists complete Sullivan et al [11] CHTC training curriculum (adapted by the CDC) as well as training in motivational interviewing. Each counselor role played motivational interviewing–spirited CHTC at least 3 times with fellow project staff and at least once with principal investigators TJS and RS. All role-play practice sessions were audio-recorded for training purposes. Booster training was offered at least once per year for counselors by TJS. In addition to CHTC and motivational interviewing training, counselors were refreshed on individual HIV CTR during 2 half-day training sessions. During these trainings, counselors practiced through a plethora of role-play scenarios, and a standard protocol was developed. These trainings were followed by at least 3 audio-recorded, role-play practice sessions with fellow project staff. TJS conducted individual and group feedback and skills coaching sessions for the CTR counselors. Following training, the counselors maintained weekly supervision with TJS.

Fidelity Monitoring and Supervision

TJS provides weekly supervision to study counselors. These sessions involve a review of participant CHTC session audio recordings, discussion, and additional skills training as needed. In addition, 20% of CHTC session recordings are assessed using the CDC's CHTC fidelity checklist [11]. Separately, fidelity to motivational interviewing during delivery of the substance use calendar is assessed using the Motivational Interviewing Treatment Integrity system [50] with supplemental codes developed by Starks et al [51].

Primary Outcomes

Primary analyses focus on 2 (individual-level) behavioral indicators of HIV transmission risk: (1) the number of CAS acts with a casual partner in the absence of the respondent taking PrEP and (2) CAS with a serodiscordant main partner who is not virally suppressed or concurrent CAS between main and casual partners in the absence of the respondent taking PrEP. The availability of day-level data generated by the timeline followback (TLFB) assessment allows for an examination of event-driven PrEP dosing as well as overall day-level adherence. Self-reported sexual behavior will be corroborated with results from bacterial STI (gonorrhea and chlamydia) testing. In instances where these indicators of HIV TRB suggest CAS with a casual (or main) partner occurred but was not reported, we will use data from the objective indicator.

Secondary Outcomes

Secondary analyses focus on indicators of drug use and severity (primary outcomes in the parent study). Drug use is operationalized in 2 ways. First, using TLFB interview data, the quantity of drug use will be operationalized using the total number of instances reported during the assessment period. We will examine cannabis and other illicit drug use frequency separately. Urine assay will corroborate the self-report. In instances where urine results signal the use of drugs not reported, we will use data from the objective indicator. Second, drug use severity will be assessed using the Drug Abuse Screening Test [52] total score.

Participant Timeline

See Figure 1 for a timeline of participant flow through the study.

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Figure 1. Timeline of participation. ACT: assertive communication training; CHTC: couples HIV testing and counseling; STI: sexually transmitted infection; SUC: substance use calendar; TLFB: timeline followback.

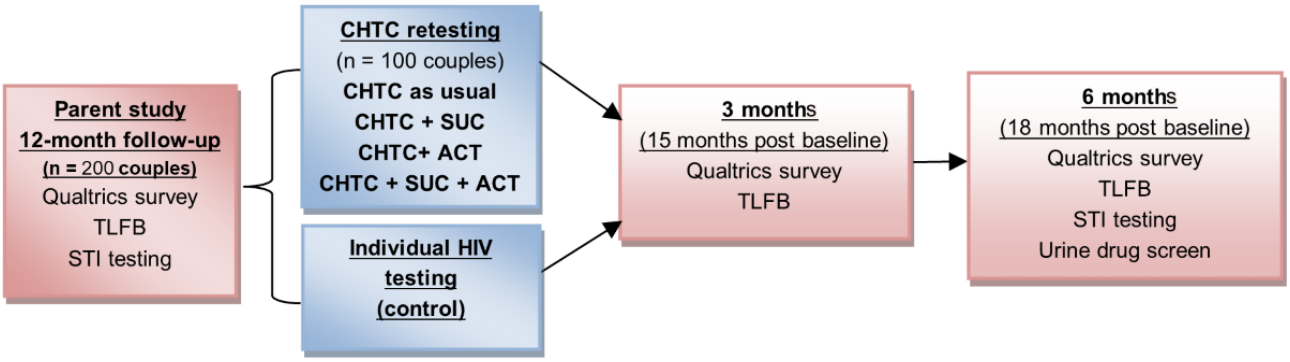

Sample Size

Power to detect significant between-group differences in primary outcomes was calculated using the PASS program (version 2022; NCSS, LLC). Analyses focused on power to detect a significant between-group difference at any 1 follow-up time point. Results from the tests for difference between 2 Poisson rates in a cluster randomized design module indicated the study had power of >0.80 to detect a 20% or greater reduction in the rate of CAS with casual partners. This estimate assumed a sample of 200 couples with equal allocation to condition, and models were tested with based rates of 2-4 instances of CAS with a casual partner among the control (individual HIV testing and counseling) condition. Results from the tests for 2 proportions in a cluster-randomized design suggested proposed study has power of >0.80 to detect a 22% reduction in the proportion of reporting main partner TRB, assuming a sample of 200 couples and a 70% base rate in the control condition.

Assignment of Interventions

Randomization

Couples will be randomly assigned to 1 of 2 conditions, CHTC retesting or individual rapid HIV testing. Randomization will be stratified for previous randomization in the 4Us trial (CHTC as usual, CHTC plus the substance use calendar, CHTC plus the ACT video, and CHTC plus both adjunct components). The random assignment will be performed by the project manager, who will enter the stratification criteria in Qualtrics to obtain the condition before intervention delivery.

Blinding

Intervention staff cannot be blinded to the condition they are delivering. Likewise, participants cannot be blinded to the condition. The 12-month follow-up in the 4Us trial (which serves as the preintervention data point for this study) is completed before participants are consented to this study. Assessment staff are blinded to condition at follow-up. Where blinding is possible, unblinding is not anticipated.

Data Collection, Management, and Analyses

Data Collection for Primary Outcomes

Self-Reported Sexual Behavior

Procedures are the same as those used in the ongoing 4Us protocol [47]. Research assistants gather self-reported sexual behavior data for the past 30 days using a structured TLFB interview (Sobell and Sobell [53]). A Microsoft Access (Microsoft Corporation) database is used to facilitate the capture of data, including “anchor dates” or significant events; missed PrEP doses (for those on PrEP); heavy drinking and drug use; and sexual events. Sexual event data further comprise partner type (main or casual), the sex act performed (eg, anal insertive and anal receptive), and whether a condom was used.

Biological Testing

The Molecular Testing Laboratory (MTL) coordinates at-home STI testing. Materials necessary for collection and return shipping are delivered before the scheduled assessment meeting with the research assistant. Specimen collection is completed at a time designated in the assessment. The research assistant is available to review collection procedures, confirm the accuracy of shipping information, and observe the packaging of specimens for shipment.

The presence of urethral STIs will be tested in urine specimens; meanwhile, the presence of rectal STIs will be tested in (self-administered) rectal swab. The Abbott RealTime CT/NG assay is used to evaluate the presence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. This is a Food and Drug Administration (FDA)–cleared real-time polymerase chain reaction assay for direct, qualitative detection of a region of the cryptic plasmid DNA of *C trachomatis* and the Opa gene of *N gonorrhoeae*.

HIV Testing

HIV testing, during CHTC and individual HIV testing sessions, will be performed using the Oraquick 4th generation testing kit. These kits are approved for at-home self-testing, and FDA-approved instructions are included. At follow-up (6 months), HIV testing will be conducted individually using self-administered dried bloodspot, giving participants the option of an Oraquick HIV to complete their HIV test if they prefer.

Retention Plan

Retention procedures continue those used in the ongoing 4Us trial [47], from which participants for this study are recruited. Assessments are conducted individually to retain participants who break up and whose relationship may have ended during the course of their participation in the study and to reduce the burden associated with coordinating a single assessment session with both partners. Study staff have at least quarterly contact with participants through email, SMS text messaging, and

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telephone (based on participant preference), which serves to maintain engagement and the accuracy of contact information over the study period.

Data Management

TLFB data are gathered by a trained interviewer using a data-entry system programmed in Microsoft Access. The institutional review board of Hunter College has reviewed all study procedures. In addition, procedures are reviewed by the Data Safety Monitoring Board (DSMB), which consists of experts in sexual health and substance use intervention research with SMM.

Data Analysis Plan

Data Screening Procedures and Analyses of Attrition

We will follow standard procedures for cleaning data and assess whether variables conform to the distributional assumptions of our analyses. The 12-month follow-up assessment in the parent study serves as prerandomization (ie, baseline) data for the purposes of these analyses. We will begin with a sensitivity analysis to examine whether couples enrolled into the randomized controlled trial proposed in this revision differ from those participants in the parent study (DA050508) who are not enrolled either due to relationship termination or lack of interest. This analysis will serve to identify behavioral factors (eg, drug use or sexual risk-taking) and relationship factors (eg, satisfaction, commitment, or communication skills) that are associated with relationship termination and uptake of CHTC retesting (among those couples who remain together). Subsequently, we will conduct an analysis of randomization success and attrition to determine if either is associated with (1) demographic variables or (2) drug use or TRB outcomes assessed at the 12-month 4Us follow-up. Factors that are observed to covary significantly with randomization or attrition will be incorporated in outcome analyses.

Primary Analyses of Intervention Effects

The primary hypothesis is that CHTC retesting will be associated with significant reductions in sexual HIV TRB (primary) outcomes compared to individual HIV testing. Using procedures similar to our previously published studies [54], outcome analyses will be conducted in a multilevel modeling framework. Analyses will use full-information maximum likelihood estimation and specify a negative binomial distribution consistent with the count nature of primary outcomes. The appropriateness of a Poisson distribution will be determined by inspection of the significance of the dispersion parameter in negative binomial models. This accounts for the nesting of individuals within couple. Because randomization occurs at the couple level, condition is a level 2 variable. The effect of the intervention will be evaluated by examining the regression coefficient (and associated *P* value). Separate models will be calculated to predict outcomes at 3- and 6-month follow-ups (with Bonferroni correction for repeated nonorthogonal tests). Mplus (Muthén and Muthén) accommodates count and dichotomous outcomes within the multilevel modeling context. Analysis of secondary outcomes will follow analogous analytic procedures.

Moderation or Mediation Analyses

Where possible, we will evaluate whether retesting using the adjunct (substance use calendar and ACT video) components is associated with specific reductions in primary (HIV TRB) outcomes. While the primary goal of this analysis is to test whether CHTC retesting, in general, is associated with benefits above and beyond individual HIV testing, the study design permits a preliminary examination of whether retesting that involves these adjunct components developed by our team is associated with additional benefits above and beyond retesting using the standard CHTC protocol. We will conduct a preliminary examination of this possibility using analytic procedures analogous to those used to evaluate effects on secondary drug use outcomes.

Data Monitoring

The DSMB, comprising 3 independent experts in the fields of HIV prevention, substance use intervention, and biostatistics, was convened in accordance with NIH policy to oversee the original 4Us trial (NCT05000866). The DSMB convenes at least annually in response to the occurrence of any serious adverse events.

Study staff will monitor the occurrence of 2 anticipated adverse events, including HIV incidence and IPV. Participants provide data on these at each follow-up, and responses are reported to the DSMB annually by the primary investigator. The primary investigator will report unanticipated events and those reported spontaneously by participants to the DSMB on an ongoing basis. These are also summarized in their annual meeting report.

Trial Modification and Discontinuation

There are no plans to conduct interim analyses, and no a priori stopping rule has been established for this trial. Randomization may be discontinued, and the trial stopped under the guidance of the DSMB in response to adverse event review. Sponsor and DSMB approval are required for substantive changes to trial design. Changes also require institutional review board approval before implementation, and the clinicaltrials.gov record would be updated to reflect modifications.

Confidentiality

Unique study ID numbers, assigned in the 4Us trial, are used to link participant data. Only essential study staff have access to the password-protected file that links contact information to study ID. All materials will be stored in databases that are HIPAA-compliant. Laboratory test results are ordered and received through a HIPAA-compliant platform maintained by the MTL. Participants consent to having the MTL conduct state-level, name-based reporting for positive HIV or STI results.

All study-affiliated staff complete mandatory training in good clinical practice and the responsible conduct of research. Standard operating procedures are created to minimize breaches in confidentiality. Participants indicate their preferred mode of communicating with staff (eg, telephone call, SMS text messaging, email) and may request that study staff use discretion when leaving messages. As a standard measure, NIH grants a federal certificate of confidentiality.

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Posttrial Care

The study team has compiled an index of national resources that are made available to participants. These include search engines that identify HIV prevention and care providers in the United States. Positive HIV or STI results are delivered by study staff, and linkage to care is discussed. The MTL also complies with state-level, name-based reporting procedures, and local or state department of health staff may follow up in some instances. Participants who exhibit signs of serious mental illness or clinically significant distress in interactions with study staff will be evaluated by a study team member with training in mental health counseling and crisis risk assessment.

Dissemination

The authorship team is committed to the dissemination of study results. This will be accomplished through several mechanisms. First, we convey information on study activities and progress to participants through a newsletter to participants. Second, the investigative team regularly attends local, national, and international conferences to share findings with other researchers, service providers, and policymakers. Finally, the investigative team will prepare manuscripts for publication in peer-reviewed journal articles. Authorship in publications will be based upon intellectual contribution and guided by American Psychological Association guidelines for authorship. There are no plans to make participant-level data available to the public. Data will be available to other researchers upon request from the study principal investigator.

Ethical Considerations

This study protocol was approved by the City University of New York's Human Research Protection Program (2022-0630) and is registered with ClinicalTrials.gov (NCT NCT05833074). All participants who complete their original 4Us 12-month appointment, meet study eligibility, and agree to be enrolled in this CHTC retesting trial provide consent individually over Zoom. After reading the consent form, the research assistant obtains verbal consent to participate. Given the remote nature of study activities and the geographic diversity of the sample, a waiver of documentation of consent was obtained. All data are deidentified to protect participants' privacy by assigning each participant a unique identifier. Data systems are established to only keep participants' name and their unique identifier in a secured database. Participants are compensated US $20 for attending the intervention session, US $40 for completing the 3-month assessment (US $30 for survey and TLFB and US $10 for urine drug testing), and US $60 for completing the 6-month assessment (US $30 for survey and TLFB and US $30 for urine drug testing, STI, HIV testing, and PrEP adherence, if applicable). Compensation for this trial's baseline is paid as the 12-month assessment for the original 4Us trial.

Results

This study began recruitment in January 2023, and all participant components are projected to end in May 2025. As of December 2023, 102 individuals (51 couples) have enrolled in the CHTC retesting trial.

Discussion

The results of this trial have the potential to inform a previously unstudied aspect of CHTC—the utility of repeated, annual completion. This trial will be the first experimental evaluation of CHTC retesting. Results therefore have the potential to substantively inform CHTC guidance.

At the same time, several limitations arise as a function of study design. Both partners in a couple must consent to participate in resting. We are therefore unable to compare CHTC to a condition in which 1 (but not both) partner receives an individual HIV test. In addition, this trial is subject to the limitations of the 4Us study from which participants are recruited. Briefly, the demands of dyadic participation may present barriers to study enrollment or engagement, particularly for couples with relatively lower relationship quality [55]. The sample will not include partnered SMM in relationships where one partner is unable or unwilling to participate. The 4Us sample is recruited through advertisements on social networking and dating applications. It, therefore, underrepresents SMM who do not engage in these digital spaces. Furthermore, all participants in the 4Us study are aged 17 years or older, and at least 1 partner must be aged 17-29 years. This limits the generalizability of findings to adolescents and older adults.

Despite these limitations, this study has the potential to enhance knowledge about the effects of CHTC on the sexual health of SMM couples. This may inform future efforts to disseminate the intervention in the United States and internationally, as well as to gender-diverse couples.

Conflicts of Interest

None declared.

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Abbreviations

ACT: assertive communication training
CAS: condomless anal sex
CDC: Centers for Disease Control and Prevention
CHTC: couples HIV testing and counseling
CTR: counseling, testing, and referral
DSMB: Data Safety and Monitoring Board
FDA: Food and Drug Administration
GHB: gamma-hydroxybuterate
HIPAA: Health Insurance Portability and Accountability Act
IPV: intimate partner violence
MTL: Molecular Testing Laboratory
NIH: National Institutes of Health
OR: odds ratio
PEP: postexposure prophylaxis
PrEP: preexposure prophylaxis
SMM: sexual minority men
STI: sexually transmitted infection
TLFB: timeline followback
TRB: transmission risk behavior

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Protocol

Pan-Indian Clinical Registry of Invasive Fungal Infections Among Patients in the Intensive Care Unit: Protocol for a Multicentric Prospective Study

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Abstract

Background: Fungal infections are now a great public health threat, especially in those with underlying risk factors such as neutropenia, diabetes, high-dose steroid treatment, cancer chemotherapy, prolonged intensive care unit stay, and so on, which can lead to mycoses with higher mortality rates. The rates of these infections have been steadily increasing over the past 2 decades due to the increasing population of patients who are immunocompromised. However, the data regarding the exact burden of such infection are still not available from India. Therefore, this registry was initiated to collate systematic data on invasive fungal infections (IFIs) across the country.

Objective: The primary aim of this study is to create a multicenter digital clinical registry and monitor trends of IFIs and emerging fungal diseases, as well as early signals of any potential fungal outbreak in any region. The registry will also capture information on the antifungal resistance patterns and the contribution of fungal infections on overall morbidity and inpatient mortality across various conditions.

Methods: This multicenter, prospective, noninterventional observational study will be conducted by the Indian Council of Medical Research through a web-based data collection method from 8 Advanced Mycology Diagnostic and Research Centers across the country. Data on age, gender, clinical signs and symptoms, date of admission, date of discharge or death, diagnostic tests performed, identified pathogen details, antifungal susceptibility testing, outcome, and so on will be obtained from hospital records. Descriptive and multivariate statistical methods will be applied to investigate clinical manifestations, risk variables, and treatment outcomes.

Results: These Advanced Mycology Diagnostic and Research Centers are expected to find the hidden cases of fungal infections in the intensive care unit setting. The study will facilitate the enhancement of the precision of fungal infection diagnosis and

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prompt treatment modalities in response to antifungal drug sensitivity tests. This registry will improve our understanding of IFIs, support evidence-based clinical decision-making ability, and encourage public health policies and actions.

Conclusions: Fungal diseases are a neglected public health problem. Fewer diagnostic facilities, scanty published data, and increased vulnerable patient groups make the situation worse. This is the first systematic clinical registry of IFIs in India. Data generated from this registry will increase our understanding related to the diagnosis, treatment, and prevention of fungal diseases in India by addressing pertinent gaps in mycology. This initiative will ensure a visible impact on public health in the country.

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KEYWORDS

mycology; invasive fungal infections; diagnosis; clinical registry; public health; fungal infections; fungal infection; ICU patients; ICU patient; in-patient; in-patients; long-term stay; mortality; mycoses; India; knowledge gaps; epidemiological; epidemiological factor; antifungal resistance; antifungal; descriptive method

Introduction

Background

Public health is seriously threatened by fungal infections, especially in people with immunosuppression and underlying illnesses such as uncontrolled diabetes, influenza, and COVID-19, where they can result in fatal mycoses and elevated death rates [1,2]. Fungal infections manifest in various clinical forms, each with a different severity range, including superficial, cutaneous, subcutaneous, mucosal, and systemic infections. Some fungi that are a part of the microbiota, such as *Candida* spp, can transform into opportunistic pathogens affecting people who are immunocompromised, including those with HIV, patients with cancer receiving chemotherapy, and people on immunosuppressive medications [2-6]. In 2022, the World Health Organization (WHO) aimed to draw attention to the significance of combating fungal infections. There were 3 categories on this list: critical, high, and medium priority. The WHO described it as “the first global effort to systematically prioritize fungal pathogens, considering their unmet research and development needs and perceived public health importance” [7]. Nevertheless, despite the enormous prevalence of fungal propagules in the environment, which makes exposure inevitable, fungal infections are very uncommon in healthy people and animals with strong immune systems compared to bacterial and viral illnesses [8,9]. However, over the past few decades, there has been an increasing trend of persistent and recurrent fungal infections affecting both humans and animals worldwide, which are driven by both true and opportunistic pathogens [8,10-14]. A small but gradually growing number of ubiquitous fungus species that usually pose little harm to humans have emerged as carriers of deadly illnesses, especially in those with compromised immune systems [12]. The natural warmth of a mammalian body has historically constrained fungi’s ability to cause disease [15]. However, many once harmless fungal species have evolved into infectious agents due to climatic changes brought out by human activity [16,17]. Additionally, the recognized geographic ranges of known fungal infections have grown due to the continually rising global temperatures and increased moisture in some areas [18].

To overcome these lacunae and strengthen the diagnosis and research on fungal diseases in India with a focus on high throughput nonculture antigen, antibody, and molecular testing, the Indian Council of Medical Research (ICMR) has established 8 state-of-the-art Advanced Mycology Diagnostic and Research Centers (AMDRCs) in the country under ICMR-MycoNet Task Force Program. This national network of laboratories aims to improve human resources training and enhance fungal diagnostics, clinical care, research, and public health policies. The primary focus of all these centers is to create awareness of different fungal infections among the general population, develop research, cater diagnostic facilities to its catchment areas, and assess the impact of mycology laboratories on patient care and fungal mapping in the country. As an additional component of this Task Force project, it is proposed to develop a Web-based Mycology Inpatient Clinical Registry to perform prospective surveillance of all fungal infections among patients hospitalized at the ICMR AMDRCs in India. It aims to improve the knowledge gaps related to different fungal infections and understand current approaches to the diagnosis and treatment of invasive fungal infections (IFIs).

Aim and Objectives

The primary aim of the proposed study is to establish a national clinical registry in mycology to overcome the lack of knowledge on epidemiology, clinical course, and pathological characteristics of IFIs for evidence-based decision-making in clinical practice, public health programs and policy in the Indian context. The objectives of this study are to (1) develop advanced diagnostic facilities (culture, serology, molecular, therapeutic drug monitoring [TDM], and antifungal drug sensitivity test [AFST]) for fungal infections and a comprehensive digital clinical registry of IFIs; (2) describe the overall trends of fungal diseases, emerging fungal infections, and antifungal resistance; (3) map the distribution of fungi in the country through regional surveillance; (4) investigate the clinical features, diagnostics, treatment and patient outcomes among intensive care unit (ICU) patients with IFIs; (5) study the contribution of IFIs in the morbidity and mortality caused by different diseases in ICUs; and (6) investigate the clinical features, diagnostics, treatment, and outcomes among patients with chronic subcutaneous infections, such as mycetoma and chromoblastomycosis (neglected tropical diseases) [19].

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Methods

Case Definition of IFIs

The proposed study will include proven and probable cases of IFIs as per the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG; proven cases) or Blot criteria and Modified EORTC/MSG (probable cases) [20-22] (Multimedia Appendix 1).

Study Design

A hospital-based multicenter, prospective, noninterventional, observational clinical registry with prospective data collection through ICMR AMDRCs was established under the ongoing MycoNet Task Force project. The project duration is 5 years, with staggered entry of clinical sites following a standardized training and onboarding process.

This multicentric, Pan-India study was initiated with 5 AMDRCs in 2019. With a scope of increasing the number of reference centers in the next sequential phases of the Task Force project by the expert committee, 3 more centers were introduced and initiated in the financial year 2022-2023. Currently, the network has 8 AMDRCs dispersed across various regions of India. These AMDRCs include (1) All India Institute of Medical Sciences (AIIMS), Bhopal; (2) Assam Medical College and Hospital, Dibrugarh; (3) AIIMS, Bhubaneswar; (4) King George's Medical University, Lucknow; (5) P.D. Hinduja Hospital, Mumbai; (6) AIIMS, New Delhi; (7) Nizam's Institute of Medical Sciences, Hyderabad; and (8) St. John's Medical College, Bengaluru. A timeline for the respective centers with a structural makeup is depicted in Figure 1. To develop a comprehensive network, apart from 8 data collection centers, Postgraduate Institute of Medical Education and Research, Chandigarh, for External Quality Assurance Scheme and laboratory training and ICMR-National Institute of Medical Statistics for data management have been included. ICMR is the overall coordinator of the project. The structural organization of ICMR-MycoNet is depicted in Figure 1. The network offers cutting-edge diagnostic tools for fungi, performs laboratory training to develop trained labor, investigates outbreaks, and conducts research on the epidemiology of fungi and antifungal resistance. The inclusion and exclusion criteria are given in Textbox 1.

Figure 1. Structural organization of Indian Council of Medical Research (ICMR) Advanced Mycology Diagnostic and Research Centers: 4-tier structure of MycoNet clinical registry. In 2020, 1 site was initiated (All India Institute of Medical Sciences [AIIMS], Bhopal). In 2021, 4 sites were initiated (Assam Medical College and Hospital [AMCH], Dibrugarh; AIIMS, Bhubneswar; P.D. Hinduja, Mumbai; and King George's Medical University [KGMU], Lucknow). In 2022, 3 centers were initiated (St. John's Medical College and Hospital [SJMC], Bangalore; Nizam's Institute of Medical Sciences [NIMS], Hyderabad; and AIIMS, New Delhi). ICMR-NIMS is the data monitoring center; Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, is the External Quality Assurance Scheme (EQAS) and Laboratory Training Center; and the ICMR headquarters is the overall coordinator.

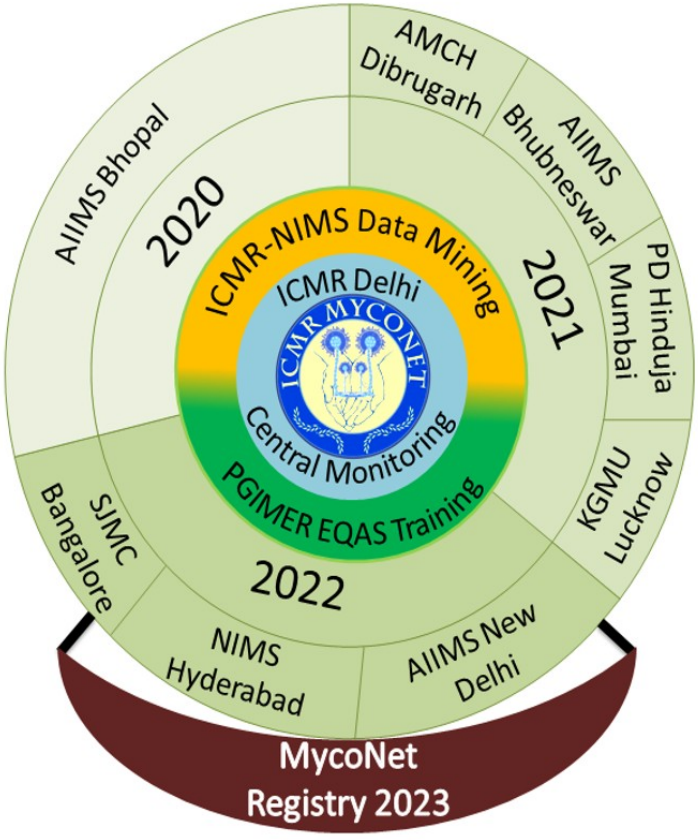

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Textbox 1. Inclusion and exclusion criteria for MycoNet clinical registry.

Inclusion criteria

- Intensive care unit or hospitalized patients with proven or probable invasive fungal infections confirmed by culture, histopathology, microscopy, or DNA evidence of any age and gender as per European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium guidelines.
- For individual cases where invasiveness remains unclear, data will be documented, but analysis will be limited to patients with proven and probable invasive fungal infections.
- All patients with a diagnosis of chromoblastomycosis or mycetoma.

Exclusion criteria

- Outpatient department or referral patients, patients who may be possible cases of invasive fungal infections, and patients without evidence of invasive disease or those with colonization only will not be included in the registry.
- Additionally, patients with superficial infections, infections limited to the skin, and allergic fungal diseases like allergic bronchopulmonary aspergillosis will be excluded.

Each team consists of a principal investigator from the mycology department and coprincipal investigators from different clinical divisions; including critical care; dermatology; ear, nose, and throat; hematology; infectious disease; internal medicine; and oncology to obtain patient samples. The AMDRCs also work closely with all ICUs, including hemato-oncology, trauma, respiratory, cardiac, and newborn care.

Data Collection and Management

A case report form (CRF) and standard operating procedures or data entry guidelines were developed. CRF field testing was done to identify the gaps in generated CRF through real-time data recording. Based on the finalized CRF, the electronic CRF was developed using the programming language by ICMR–National Institute of Medical Statistics. Data entry was facilitated through an interactive macrodesigned within the software that can be accessed from any web browser. A digital database will automatically store all the recorded data. The CRF is designed with a drop-down menu to minimize data entry errors. For additional security, a double data entry method will be followed.

The MycoNet Registry app will be maintained on a secure web server at ICMR New Delhi. The hospitals participating in the study will be able to register digitally to initiate the work.

Each AMDRC would receive log-in credentials with access control for data entry, data monitoring, and data download. Data validation will be done by the principal investigator. A dashboard for a snapshot of the data collected from all the AMDRCs (day wise, weekly, or time period) will also be developed for real-time monitoring.

The data on age, sex, signs, symptoms, date of admission, date of discharge or death, diagnostic tests, identified pathogen, treatment history, AFST report, TDM, any other disease or immunosuppression condition, medical history, outcome, and so on will be obtained from the hospital CRF record. A national fungal strain repository for clinically important and rare fungal strains (yeast and molds) will be developed for future research (Figure 2).

Descriptive analysis of the data will be performed by generating means and proportions. Univariate and multivariate analyses will be undertaken. Further, data analysis will be performed based on the expert committee's suggestions.

A descriptive analysis of the pattern of clinical presentations by age, sex, and association with risk factors and comorbid conditions across urban and rural regions and states in India will be accomplished. Predictive factors for hospital clinical courses and outcomes will be derived for different treatment settings. The burden of IFIs and associated manifestations will be assessed using standard case definitions and reporting frameworks. Additionally, developing treatment guidelines will be aided by the pattern of comorbidities or risk factors affecting clinical recovery among with patients IFIs.

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Figure 2. Overview of data variables in the general CRF. AFST: antifungal drug sensitivity test; CNS: central nervous system; CRF: case report form; GI: gastrointestinal; ICU: intensive care unit; TDM: therapeutic drug monitoring.

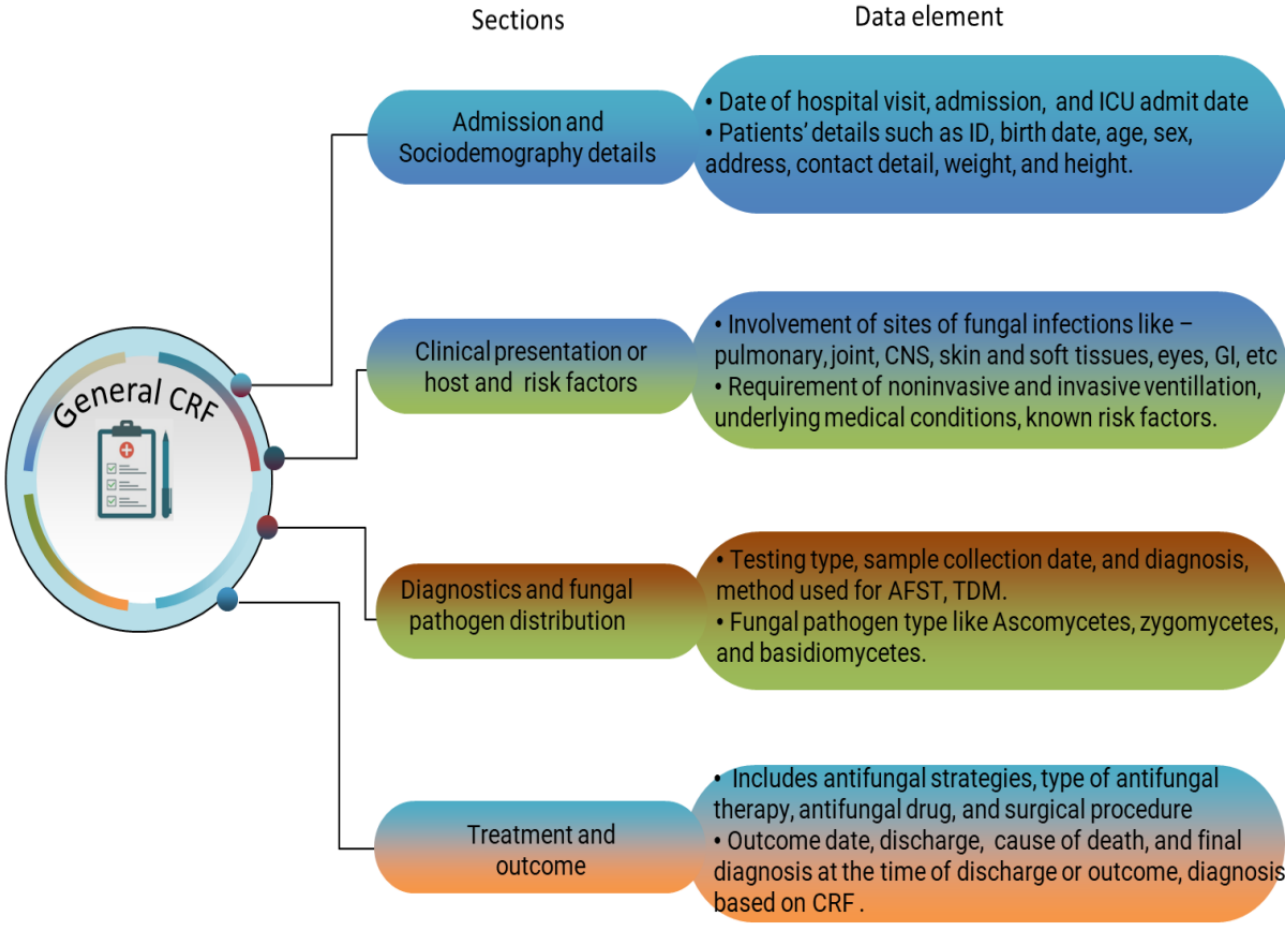

Ethical Considerations

There is no interventional aspect to this study. Therefore, there are neither associated risks nor benefits for the patient when participating in the study. The data will be extracted from medical records with no interaction with patients to undertake the secondary data analysis. The study was granted the "waiver of consent," and ethical approval of the study (CECHR 009/2022) was obtained from the ICMR–Central Ethics Committee on Human Research (reference NCDIR/BEU/ICMR-CECHR/75/2020) as well as the following ethical committees: AIIMS, Bhopal (IHEC-LOP/2021/EF0160); Assam Medical College & Hospital (AMCH), Dibrugarh (2022/AMC/EC/1937); AIIMS, Bhubneswar (T/EMF/Micro/22/38); PD Hinduja Hospital, Mumbai (IRB/1552/AL/22/41); King George's Medical University (KGMU), Lucknow (1515/Ethics/2022); AIIMS, New Delhi (IEC-695/02.09.2022); Nizam's Institute of Medical Sciences (NIMS), Hyderabad (EC/NIMS/3038/2022); St John's Medical College (SJMC), Bangalore (IEC/1/1061/2022) and ICMR–National Institute of Medical Statistics (ICRM-NIMS), New Delhi (11/2022). Memorandums of agreement were signed between the ICMR and all established AMDRCs for shared principles, objectives, and responsibilities. Data security and patient privacy were given the utmost importance throughout the entire process. All information and data extracted from the medical records of the patients for this registry will be considered confidential. The digital documentation of the clinical data will take place in an anonymized fashion. No identifiable data, for example, name or date of birth, will be entered into the database. There will also be no pseudonyms, which would make a retrospective reidentification of the patient possible. Clinical data collected refer to common conditions and treatment modalities in medical care, such that no reidentification of the individual case based on these data will be possible. Any data manipulation by users and administrators will be logged into an audit trail allowing complete data reconstruction. All data and results will be stored for at least 10 years after the publication of the results.

Administration of the electronic CRF will be limited to selected and named administrators at AMDRCs, who will receive comprehensive training in the system before access. Secure passwords are also enforced for administrators, and they must regularly change their passwords.

Results

This study has been funded by the ICMR. Data collection began in January 2023 in all 8 AMDRCs study sites, after approval from the central and local ethics committee in June 2022. The registry has also been registered with the Clinical Trial Registry–India (registration CTRI/2022/09/045489). To date, 531 cases of IFI, 29 cases of mycetoma, and 1 case of chromoblastomycosis were enrolled in the registry. First-year

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data analysis has been initiated to be published by the second quarter of 2024. Data from the study are expected to improve the knowledge gaps related to different fungal infections and understand current approaches to diagnosing and treating IFIs. The trends of IFIs, AFST patterns, and the contribution of IFIs to total ICU mortality will be the most valuable outcome of this project. Data on rare fungal diseases such as mycetoma and chromoblastomycosis will be obtained.

Discussion

Principal Findings

ICMR has set up a network of laboratories established to address the long need for modern facilities for fungal diagnostics, antifungal resistance mapping, and advanced fungal research in the different geographical regions of the country. Through the ICMR-MycoNet, the generation and systematic collection of robust comprehensive data on IFIs in ICU patients have the potential to fill in important knowledge gaps and guide evidence-based decision-making in clinical practice, public health efforts, and policy reforms in India.

The proposed study has great potential for filling critical knowledge gaps regarding invasive fungal diseases and their effects on public health. A national clinical registry in mycology is being established to lay a solid platform for evidence-based decision-making in clinical practice, public health efforts, and policy creation. The main goals include creating a multicenter digital clinical registry, a thorough examination of epidemiological variables, research into clinical issues, and monitoring of emerging fungal disease trends, which are essential steps toward gaining a thorough understanding of this significant health care issue. Additionally, achieving the secondary goals, which include analyzing the role of fungal infections in morbidity and inpatient mortality across a range of diseases and identifying emerging antifungal resistance patterns, will undoubtedly improve our capacity to control and treat these infections successfully. We can learn a lot more about IFIs from this work, which could greatly impact health care plans and policy.

Impact of AMDRCs

AMDRC is a new initiative of ICMR headquarters in Delhi to support the establishment of AMDRCs in different geographical regions of the country. Mycology has been one of the neglected areas of research in India. Therefore, advanced diagnostic services and research are required in addition to the cutting-edge research and training of health care professionals to combat IFIs. AMDRCs have considerably increased the diagnostic capacity for fungi illnesses, with a notable improvement in accuracy that has reached up to 95%. The increased diagnosis accuracy ensures that patients get the right care when needed. The AMDRCs have attained a remarkable 95% to 100% detection rate of fungal infections. This lowers the risk of poor management because the majority of cases that were previously undetected are now effectively diagnosed. One of the outstanding advantages of AMDRCs is the free diagnostic services they offer. As a result, patients no longer need to rely on expensive private laboratories for fungal testing, thereby improving access to and affordability of treatment. With AMDRCs' better diagnostic capabilities, referring patients for identification to higher tier medical centers is no longer necessary. This eliminates the workload on tertiary health care facilities, speeds up the diagnostic process, and decreases treatment delays. AMDRCs have significantly reduced the time it takes to diagnose fungal diseases. It now just takes a few weeks to complete what used to take many months. Clinicians can start prompt and accurate therapy because of the quick reporting, which eventually leads to better patient outcomes. Programs for antifungal stewardship have been made easier by the development of AMDRCs. Clinicians are now better equipped to make decisions about antifungal treatment, and ensuring judicious use of these drugs is a vital step in preventing antifungal resistance. The ability of AMDRCs to provide real-time diagnostic reports has reduced the need for empiric antifungal treatment. By adjusting therapies based on precise fungal identifications, clinicians can lower the likelihood of overmedicating. Drug toxicity is decreased, and therapeutic efficacy is increased due to AMDRCs' integration of TDM. With this personalized approach, patients are assured of receiving the best antifungal care with minimal side effects. Apart from helping diagnose fungal diseases, adding *Aspergillus* antigen or antibody testing to AMDRC services benefits the overall health care system. These tests demonstrate the adaptability and significance of AMDRCs beyond the control of fungal illness by supporting tuberculosis elimination programs. Thus, this study will be able to address a long-neglected public health issue. However, to get access to diagnostics and antifungal treatment, the study may face regional limitations due to the exclusion of some territories or countries with a hostile environment, poor communication, and fewer populations [23,24].

Future Plan

WHO on Global Antimicrobial Resistance Surveillance System Fungi Program (Global Collaborative Effort to Compile Available Data on IFIs)

The goal of this program is to compile a complete database of information on these diseases, including data concerning the various types of fungi causing the infections, the geographical areas where they tend to be more prevalent, the patterns of antifungal resistance, and other pertinent aspects. By gathering this information, the WHO and its collaborators expect to comprehend better and address the problems caused by IFIs and antifungal resistance.

Extended Multicenter Registry Development to Obtain More Validated Data

The purpose of expanding the registries is to include more centers to produce a more robust and extensive database. This is in the context of gathering information on invasive fungal diseases from a wider geographical area and multiple health care facilities for the study. Data gathered from multiple centers will enhance the validity and authenticity of the information.

Collaborative Approach

In collaboration with other data sharing registries, researchers can find patterns, trends, and potential treatments for fungal infections by pooling their data more efficiently. Similar to

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other registries, it encourages teamwork in problem-solving and may result in more efficient diagnosis, treatment, and prevention approaches [25,26]. For surveillance of neglected tropical diseases, a database of mycetoma and chromoblastomycosis will help to identify different nodal areas for future surveillance through active case searches.

One Health Approach

Fungi are ubiquitous. Their interaction with agriculture and animals is certain. As part of the "One Health" concept, keeping in view the data of drug-resistant fungi reported through the registry, we can further collaborate with the Indian Council of Agricultural Research and Indian Veterinary Research Institute (both under the Ministry of Agriculture and Farmer Welfare) to study the effect of use of different fungicides in agriculture and animals and study the transmission dynamics within these.

Conclusions

IFIs are hidden ICU killers. Unfortunately, in a tropical country such as India with a high potential population for fungal infections, mycology is still a neglected area. The present recommendations mostly rely on a compilation of case reports, studies from specific medical facilities, and professional judgments. Analyses must be performed on a large cohort of patients to make treatment recommendations based on sound evidence. It is imperative to explore the contribution of opportunistic fungal infections in the morbidity and mortality of immunocompromised patients and determine the frequency of occurrence of this condition in the country by establishing a registry. Therefore, the development of a Mycology Clinical Registry through the established ICMR-MycoNet centers is proposed to improve the lack of knowledge on epidemiology, clinical course-biology, pathology mechanisms of IFIs and their trends, and AFST and to aid in facilitating an evidence-based diagnostic therapeutic integrated approach to IFI. Antifungal stewardship through this unique initiative will help to reduce empirical antifungal therapy. Any emerging threats, such as the spread of resistant strains or outbreak signals, can be picked up quickly through this real-time database for quick action and policy decisions. These state-of-the-art facilities will be the game changers and able to find cryptic fungal cases successfully, which will visibly change the public health profile of the country.

Acknowledgments

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Data Availability

The data sets used or analyzed during the study will be made available from the corresponding author on reasonable request.

Authors' Contributions

AKO contributed to writing and revising the paper. VA, SS, VH, GS, UP, KJS, HK, and JS critically reviewed and revised the manuscript. TK, RN, IX, PG, and AS reviewed the manuscript. MD developed and conceptualized the study and contributed to review and revise the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Guidelines for invasive fungal infection (IFI) diagnosis for respective case definitions.
[DOCX File , 25 KB - resprot_v13i1e54672_app1.docx]

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Abbreviations

AFST: antifungal drug sensitivity test
AIIMS: All India Institute of Medical Sciences
AMDRC: Advanced Mycology Diagnostic and Research Center
CRF: case report form

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EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium
ICMR: Indian Council of Medical Research
ICU: intensive care unit
IFI: invasive fungal infection
TDM: therapeutic drug monitoring
WHO: World Health Organization

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Protocol

The Efficacy of Bepotastine Besilate Compared With Hydroxyzine Pamoate for Preventing Infusion Reactions to the First Dose of Rituximab in Patients With Non-Hodgkin Lymphoma: Protocol for a Phase II, Double-Blind, Multicenter Randomized Trial

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Abstract

Background: Rituximab, an anti-CD20 monoclonal antibody, can cause infusion reactions (IRs), especially during the initial rituximab infusion therapy. Generally, patients are administered a histamine H_1-receptor antagonist before the rituximab infusion, along with an antipyretic analgesic, to prevent or reduce IRs. Multiple retrospective case-control studies indicate that the second generation of histamine H_1-receptor antagonists might be more effective than the first generation in suppressing IRs caused by the rituximab infusion.

Objective: This study aimed to assess the efficacy of first- and second-generation histamine H_1-receptor antagonists for preventing IRs resulting from the initial infusion of rituximab in patients diagnosed with non-Hodgkin lymphoma.

Methods: This is a phase II, double-blind, active-controlled randomized trial. It will be a multicenter study conducted across 3 facilities that aims to enroll a total of 40 patients diagnosed with non-Hodgkin lymphoma who will receive their initial rituximab infusion. Participating patients will be administered hydroxyzine pamoate or bepotastine besilate, representing first- or second-generation histamine H_1-receptor antagonists, respectively. This will be combined with 400-mg acetaminophen tablets taken approximately 30 minutes before the first infusion of rituximab. The primary end point of this trial is to assess severe IRs, equivalent to grade 2 or higher as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, that occur within a 4-hour period after the initiation of rituximab infusion. The secondary end points include assessing the severity of the initial IR, the maximum severity of the IR, and the duration between rituximab infusion initiation and the onset of the first IR within a 4-hour period. Additionally, the trial will evaluate histamine H_1-receptor antagonist–induced drowsiness using the visual analogue scale, with each patient providing their individual response.

Results: This study began with patient recruitment in April 2023, with 17 participants enrolled as of November 12, 2023. The anticipated study completion is set for February 2026.

Conclusions: This study is the first randomized controlled trial comparing the effects of oral first- and second-generation histamine H_1-receptor antagonists in preventing IRs induced by the initial administration of rituximab. The findings from this study hold the potential to establish the rationale for a phase III study aimed at determining the standard premedication protocol for rituximab infusion.

Trial Registration: Japan Registry of Clinical Trials jRCTs051220169; https://jrct.niph.go.jp/latest-detail/jRCTs051220169

International Registered Report Identifier (IRRID): DERR1-10.2196/54882

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(JMIR Res Protoc 2024;13:e54882) doi:10.2196/54882

KEYWORDS

non-Hodgkin lymphoma; rituximab; infusion reactions; bepotastine besilate; histamine H1-receptor antagonist; hydroxyzine pamoate; drowsiness

Introduction

Background

Rituximab, an anti-CD20 monoclonal antibody, is one of the most common chemotherapy agents used for non-Hodgkin lymphoma (NHL) [1-3]. Specifically, treatment protocols involving rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), as well as polatuzumab combined with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola-R-CHP), have emerged as the established therapeutic standards for various NHL types, including diffuse large B-cell lymphoma [4,5]. In addition, a rituximab plus bendamustine (BR) regimen is a chemotherapy option for follicular lymphoma categorized as the NHL type [6].

Infusion reactions (IRs) commonly occur within the initial 24 hours of rituximab infusion and are a troublesome side effect associated with this treatment. Typically, the first rituximab infusion begins at a rate of 50 mg/h, increasing by 50 mg/h every 30 minutes, reaching a maximum of 400 mg/h [7]. Severe IRs tend to manifest 30 to 120 minutes after the initiation of rituximab infusion, especially during the escalation of the rituximab infusion rate [7]. The key symptoms include fever, pruritus, rash, and anaphylaxis-like symptoms, with reported instances of fatalities in severe cases [8,9]. While the precise mechanisms behind IRs remain unclear, the presence of tumor necrosis factor–α, interleukin-6, and other cytokines in the bloodstream at the time of administration might be responsible [10]. Moreover, immunoglobulin E–mediated type I reactions associated with histamine release have been identified as a potential mechanism for IR development in patients who previously experienced allergic reactions to rituximab [7,11]. Therefore, patients usually take an antipyretic analgesic and a histamine H_1-receptor antagonist 30 minutes before rituximab infusion to mitigate or prevent an IR. However, as there is no standard premedication, the combination of an antipyretic analgesic and a histamine H_1-receptor antagonist varies among medical facilities. Despite the frequent use of first-generation histamine H_1-receptor antagonists [12,13], patients frequently experience IRs, particularly during the first rituximab infusion, even with these premedications [8]. In addition, first-generation histamine H_1-receptor antagonists have potent central nervous system effects [14], causing drowsiness in patients both during and after rituximab infusion.

Nowadays, various retrospective case-control studies have indicated the potential superiority of the second generation of histamine H_1-receptor antagonists over the first generation in suppressing the occurrence of IRs due to rituximab infusion [15,16]. However, these retrospective studies had a significant limitation, as they subjectively evaluated IRs based on individual physicians' assessments. While a prospective study investigating the supplementary effects of second-generation drugs has been conducted, it specifically examined montelukast, a leukotriene receptor; rupatadine, a second-generation H_1-receptor antagonist; or their combination alongside a standard premedication consisting of the first-generation H_1-receptor antagonist diphenhydramine hydrochloride and acetaminophen [17]. Since the previous prospective study did not directly compare first-generation histamine H_1-receptor antagonists with second-generation ones, its immediate applicability in clinical settings might be limited. Consequently, there is a need to establish an effective and safe premedication regimen that significantly suppresses IRs while causing minimal drowsiness.

Hence, we designed a prospective study to compare the impact of 2 antihistamines during the initial rituximab dose for NHL patients: hydroxyzine pamoate, a first-generation H_1-receptor antagonist frequently used in clinical settings, and bepotastine besilate, a second-generation antihistamine identified in a retrospective case-control study as potentially superior in suppressing IRs triggered by rituximab infusion [15]. Hydroxyzine pamoate is superior to other first-generation H_1-receptor antagonists such as chlorpheniramine and diphenhydramine, since it has no contraindications for angle-closure glaucoma or prostatic hyperplasia patients. It will be combined with acetaminophen to assess its effect on IR occurrence. This is an exploratory study, laying the groundwork by providing basic evidence for subsequent confirmatory studies.

Study Objectives

The primary objective of this study is to estimate the incidence rate of IRs (grade 2 or higher) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [18], in each of the 2 study drug groups within the 4-hour period following the initiation of rituximab infusion. The secondary objectives include (1) estimating the severity of the first and the most severe IR within the same 4-hour time frame after rituximab infusion; (2) estimating the time of onset for the initial IR during this 4-hour period; and (3) estimating the rate of adverse events, including drowsiness attributed to histamine H_1-receptor antagonists, using the visual analog scale (VAS).

Methods

Study Design and Study Location

This study is an ongoing phase II, double-blind, active-controlled randomized trial (Figure 1). It is a multicenter study conducted across 3 facilities, including Kobe University Hospital.

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Figure 1. Flowchart illustrating the study design. CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; IR: infusion reaction; VAS: visual analogue scale.

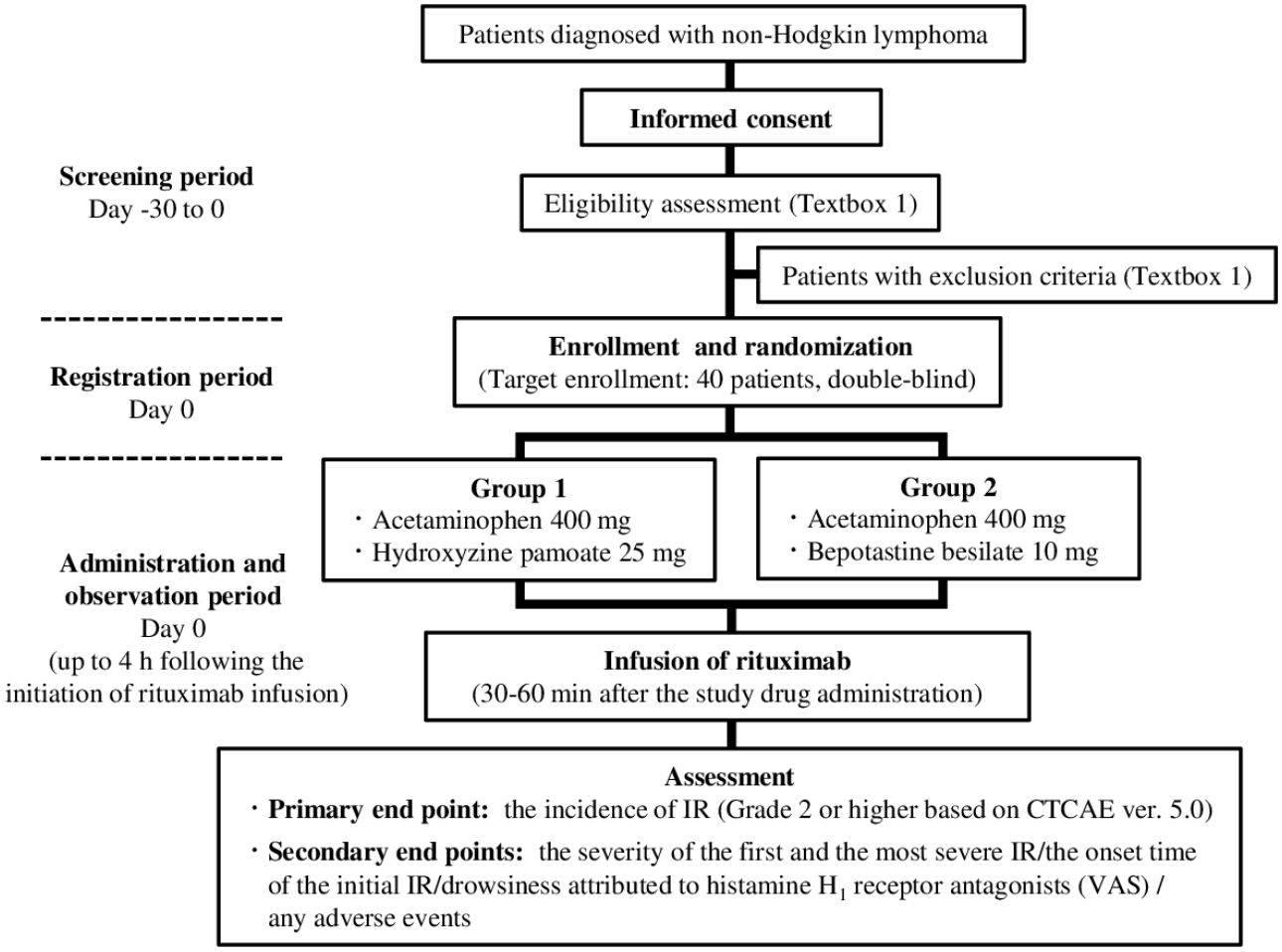

Ethical Considerations

This study was approved by the Kobe University Clinical Research Ethical Committee (C220009) on December 22, 2022. All participants will sign an informed consent form after receiving detailed explanations from the researchers. This study will adhere to the protocols and principles outlined in the Declaration of Helsinki. Any proposed changes to the protocol will require prior approval from the ethics committee before implementation.

Inclusion and Exclusion Criteria

Textbox 1 outlines the criteria for inclusion and exclusion in this study. In addition, Table 1 shows the periods of restricted use of concomitant medication, which are listed in the exclusion criteria (Textbox 1; exclusion criteria 1-3). The specific time frames are determined by the half-life of each medication.

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Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

1. Aged 18 years or older at the time of consent
2. Written informed consent and voluntary participation in this clinical study
3. Diagnosed with non-Hodgkin lymphoma
4. Receiving a first rituximab infusion, irrespective of regimen
5. Receiving rituximab as a standalone treatment before other anticancer agents in one of the following regimens: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); polatuzumab combined with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola-R-CHP); and rituximab plus bendamustine (BR)

Exclusion criteria

1. Administered or scheduled to receive the following medications orally or intravenously within 2 days of the study drug administration: a short half-life antipyretic analgesic (listed in Table 1) or corticosteroid
2. Administered or scheduled to receive histamine H_1-receptor antagonists orally or intravenously within 5 days of the study drug administration
3. Administered or scheduled to receive a long half-life antipyretic analgesic (listed in Table 1) orally or intravenously within 10 days of the study drug administration
4. Received obinutuzumab before the rituximab treatment
5. Presence of renal dysfunction, indicated by a creatinine clearance <50 mL/min
6. Presence of liver dysfunction, indicated by a Child-Pugh score of C
7. Severe interstitial pneumonia
8. Porphyria
9. Pregnancy or possible pregnancy
10. Known allergies or sensitivities to the drugs used in this clinical study
11. Determined to be unsuitable for inclusion by the investigator

Table 1. Prohibited period of concomitant use of medications as part of the exclusion criteria.

Prohibited period before study drug administration	Category and nonproprietary name
10 days	Antipyretic analgesics with a long half-life (oxaprozin, piroxicam, meloxicam, nabumetone, sulindac, and naproxen)
5 days	All histamine H_1-receptor antagonists
2 days	Antipyretic analgesics with a short half-life (acetaminophen, etodolac, celecoxib, flurbiprofen axetil, pranoprofen, flurbiprofen, lornoxicam, ibuprofen, tiaprofenic acid, ketoprofen, indometacin, loxoprofen sodium hydrate, diclofenac sodium, and acetylsalicylic acid), all corticosteroids

Study Drugs

The study drugs are prepared at the Department of Pharmacy, Kobe University Hospital. To maintain the blind nature of the study, the drug preparation involves placing either a 25-mg hydroxyzine pamoate capsule or a 10-mg bepotastine besilate tablet inside an opaque capsule (size 2).

Intervention

Patients are randomly allocated to receive either hydroxyzine pamoate or bepotastine besilate based on the presence or absence of bone marrow infiltration [19]. Approximately 30 minutes before the rituximab infusion, patients will take a combination of the assigned H_1-receptor antagonist with acetaminophen tablets (400 mg). To maintain the blind nature of the study, the block size used for randomization will remain undisclosed and concealed until the completion of all analyses. Throughout the study's duration, the randomization information will be kept confidential by the data management and statistical analysis team. The allocation manager, independent of the study, will retain the randomization details. The study schedule is outlined in Table 2. Rituximab administration follows the regimen specific to each facility and is delivered intravenously. In general, the first infusion starts at an initial rate of 50 mg/h, escalating every 30 minutes by increments of 50 mg/h to a maximum of 400 mg/h [17]. All rituximab products (original or biosimilar) are allowed in each facility and the information on the rituximab administration schedule will be recorded.

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Table 2. Summary of the study schedule.

	Screening period (day –30 to 0)	Registration period (day 0)	Administration and observation period (day 0)
Informed consent	✓		
Eligibility screening	✓		
Registration		✓	
Randomization		✓	
Patients' backgrounds[a]	✓	✓	
Ann Arbor classification	✓		
Eastern Cooperative Oncology Group Performance Status Scale	✓		
Child-Pugh score	✓		
Stratification factors (the presence or absence of bone marrow involvement)	✓		
Hematology[b] and biochemistry[c] tests	✓		
B symptoms (the presence or absence of fever, night sweat, or weight loss)	✓		
Administration of study drug			✓
Evaluation of infusion reaction			✓
Observation of adverse events			✓
Evaluation of drowsiness (visual analogue scale; performed 90, SD 15 minutes after study drug administration)			✓

[a]Including age, sex, weight, height, diagnosis, medical history, complications, and concomitant medications.

[b]Hematology tests encompass red blood cell counts, hemoglobin, hematocrit, differential leukocyte counts, and platelet counts.

[c]Biochemistry tests include aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total bilirubin, albumin, creatinine, blood urea nitrogen, lactate dehydrogenase, IL-2 receptor, and prothrombin activity.

Data Collection and Management

Upon receiving consent from prospective patients, the investigators assess their eligibility. Subsequently, either the research secretariat or the branch have access to the REDCap (Research Electronic Data Capture; an electronic data system for clinical research) system to confirm eligibility before inputting essential information for case registration and assigning a case number. The registration process concludes upon the display of a confirmation of the case registration.

Study Outcomes

Primary End Point

The primary end point of this study is the incidence of IR (grade 2 or higher) according to CTCAE within the time frame of up to 4 hours following the initiation of rituximab infusion.

Secondary End Points

The secondary end points of this study include assessing the severity of the initial IR, the maximum severity of the IR, the duration between rituximab infusion initiation and the onset of the first IR within a 4-hour period, evaluating drowsiness due to histamine H_1-receptor antagonists, and determining the incidence rate of any adverse events resulting from participation in clinical research.

Assessments

Evaluation of IR

Investigators assess the severity of the IR using the CTCAE (Table 3) as a reference. Furthermore, they evaluate IR severity based on the specific criteria outlined in this study, aligned with routine medical care. Grade 1 is a temporary interruption of rituximab infusion followed by a restart at the same rate. Grade 2 or higher necessitates a temporary halt in infusion along with interventions such as additional symptom treatment or resumption of infusion at a reduced rate. Grade 2 or higher also includes situations where the rituximab infusion rate remains unchanged due to concerns about the patient's condition. In the event of an IR, standard rescue care protocols specified by the medical facility are implemented. Procedures for rituximab dosing rates and rate adjustments are also implemented.

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Table 3. The Common Terminology Criteria for Adverse Events, version 5.0, defines infusion-related reaction. The items in the Criteria column are extracted directly from the source [18].

Grade	Criteria
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous injection fluids); prophylactic medications indicated for < = 24 h
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

Evaluation of Drowsiness Caused by Histamine H_1-Receptor Antagonists

Patients report the severity of drowsiness using a VAS ranging from 0 mm (awake) to 100 mm (falling asleep) approximately 90 (SD 15) minutes after taking the study medication.

Statistical Procedure

All analyses will be carried out using R (R Foundation for Statistical Computing). There will be no interim analyses conducted.

Sample Size Calculation

The target sample size for this study is 40 participants, evenly divided into groups receiving hydroxyzine pamoate and bepotastine besilate, with 20 patients in each group. The main objective is to compare the incidence of IR (grade 2 or higher) according to the CTCAE within 4 hours after initiating rituximab infusion in the 2 study drug groups. In our retrospective exploratory study at Kobe University Hospital, grade 2 or higher IR incidence was 8/30 (27%) in NHL patients who received hydroxyzine pamoate before their first rituximab dose. In contrast, a previous report indicated that the incidence was 3/33 (9%) in patients treated with bepotastine besilate [15]. Therefore, we conservatively estimated that the grade 2 or higher IR incidence would be 25% for hydroxyzine pamoate and 10% for bepotastine besilate. This assumption implies a 15% difference in the IR incidence rate between the 2 groups. Assuming 20 patients in each group, the calculated 90% and 95% CIs of the incidence difference between the 2 groups are –0.044 to 0.344 (width 38.8%) and –0.081 to 0.381(width 46.2%), respectively. If both widths for the 90% and 95% CIs of the incidence difference of observed data are narrower than the presumed interval widths, respectively, we consider the accuracy of the estimates suitable for planning a phase III trial.

Primary Analysis

In this study, a full analysis set (FAS) comprises patients randomly assigned to the study who completed the evaluation of IR within 4 hours after rituximab infusion initiation. We will analyze the difference in IR incidence between the 2 study drug groups within the FAS and determine their respective 90% and 95% CIs. The calculation of Clopper-Pearson CIs will be used for this analysis.

Secondary Analysis

A supplementary assessment will be conducted using the per-protocol set (PPS) for the primary outcome. In this study, the PPS consists of patients excluded from the FAS due to significant violations, such as incompatibility in meeting the selection or exclusion criteria and severe noncompliance with the research protocol. For each analysis, the null hypothesis will be that the IR incidence rate is equal between the 2 groups. Following this, we will calculate the *P* value using the Pearson chi-square test. The analysis of secondary outcomes aims to provide additional insights into the primary outcome. The severity of the initial and the maximum severity of IR will be indicated by the number and percentage within each grade. The null hypothesis for each analysis population will be that the IR incidence rate is equal to each grade within the 2 groups. The *P* value will be calculated using the Fisher exact test. The time to the onset of the initial IR and the VAS value indicate drowsiness caused by histamine H_1-receptor antagonists. These will be presented as the mean (SD) for each group, along with the 95% CI for the mean difference.

Data Monitoring and Pharmacovigilance

The study will undergo regular monitoring to safeguard human rights and welfare. The research will be conducted in strict adherence to the protocol and all relevant regulatory requirements, ensuring safety. The principal investigator has designated responsible individuals to oversee the outlined procedures for study monitoring. To ensure quality control, the monitor will assess adherence to the protocol and outlined procedures during the study.

In this research, an adverse event encompasses any illness, disability, infection, or death occurring during the study specifically related to the study drugs but excluding those related to rituximab and acetaminophen. Investigators will document these adverse events in the electronic case report form (eCRF). Affected patients will receive appropriate treatment and continued monitoring until symptoms resolve, as managed by the investigators. If there are cases in which the investigators identify unpredictable adverse events or deaths potentially linked to the study drug, these occurrences will be promptly reported to the review board. To address potential claims resulting from health issues related to the study's conduct, the principal investigator has secured clinical research insurance covering compensation for death, serious disability, medical expenses, and medical benefits.

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Privacy and Confidentiality

The eCRF will be protected by using a password. Additionally, privacy measures will involve using deidentified data instead of personal identifiers across all eCRF entries to further enhance security.

Results

This study is ongoing, and recruitment of participants began in April 2023, with 17 patients enrolled as of November 12, 2023. Anticipated study completion is scheduled for February 2026. The study protocol and statistical analysis plan will be made available on the Japan Registry of Clinical Trials. The study findings will be presented at medical conferences and published in scientific papers. Subsequent to publication, the corresponding author will make the collected data accessible in a non–personally identifiable form on reasonable request from other researchers within a prescribed period.

Discussion

Principal Findings

This phase II study is designed as a double-blind, prospective investigation, building upon insights from our retrospective exploratory study at Kobe University Hospital and a previous retrospective study [15]. While various reports have discussed IR prophylaxis during rituximab infusion, most have primarily assessed the efficacy of first-generation histamine H_1-receptor antagonists. Recent retrospective case-control studies have suggested the potential superiority of second-generation histamine H_1-receptor antagonists in suppressing IRs triggered by rituximab infusion. However, these studies often carried significant limitations, as IR assessments were subjective and varied among physicians [15,16]. This prospective study aims to address the research bias commonly found in retrospective studies and aims to provide more reliable results.

Severe IRs typically tend to manifest between 30 to 120 minutes after the commencement of rituximab infusion, as well as when the rituximab infusion rate is escalated [7]. Given that our study involves both inpatients and outpatients, assessing IRs over an entire day becomes challenging as outpatients leave the outpatient chemotherapy room after the rituximab infusion. To streamline the evaluation process without having the assessments focus only on inpatients, we considered a practical time frame for evaluation. Our retrospective exploratory study showed that the total rituximab infusion time was approximately 4 hours. Therefore, we have set the evaluation period for IR up to 4 hours following the initiation of rituximab infusion to align with actual practice.

It has been reported that the time to maximum concentration (T_{max}) of histamine H_1-receptor antagonists when used as premedication can impact prophylaxis against an IR [15]. In our retrospective exploratory study at Kobe University Hospital, we observed that the incidence time of IR was a median 90 (IQR 60-135) minutes after the onset of rituximab infusion in NHL patients who had received hydroxyzine pamoate before their initial rituximab dose. The reported mean T_{max} values for hydroxyzine pamoate and bepotastine besilate are 2.1 (SD 0.4) hours [20] and 1.2 (SD 0.2) hours [21], respectively. Notably, when patients take the H_1-receptor antagonist approximately 30 minutes before rituximab infusion, bepotastine besilate reaches T_{max} before the median IR incidence time. To maintain blinding in this study, the study drug is encapsulated in an opaque gelatin capsule. Considering that the mean disintegration time for these capsules in the fed state was reported to be 12 (SD 4) minutes [22], we do not anticipate that the use of capsules will influence the study results. However, it is unclear whether the T_{max} of histamine H_1-receptor antagonists only impacts prophylaxis against IRs. Among first-generation H_1-receptor antagonists used for rituximab premedication in a clinical setting, the T_{max} of hydroxyzine pamoate is closest to bepotastine. We assume that class effects other than T_{max} contribute to the prevention of IRs. Furthermore, it is essential to consider that drowsiness resulting from histamine H_1-receptor antagonists is influenced not only by their half-lives but also by their interaction with H_1 receptors in the central nervous system [23,24]. These factors will be taken into consideration during the final assessment.

Several studies have investigated the correlation between the development of an IR and various risk factors. Factors such as soluble interleukin-2 receptor, hemoglobin, bone marrow infiltration, and lactate dehydrogenase levels have been identified as potential risk factors for IRs [19,25,26]. In this study, bone marrow infiltration is being treated as a stratification factor. We will also explore the potential associations between IR occurrence and multiple factors in an exploratory manner. However, due to the inclusion of a small and limited number of patients, our study serves as a preliminary investigation to determine whether further confirmation studies are warranted.

If this study demonstrates increased effectiveness of bepotastine besilate, a second-generation histamine H_1-receptor antagonist, a confirmatory study will be designed to gather robust evidence supporting its effective use in routine practice.

Conclusions

This study is the first randomized controlled trial comparing the effects of oral first- and second-generation histamine H_1-receptor antagonists in preventing IRs induced by the initial administration of rituximab. The findings from this study have the potential to establish a rationale for a phase III study aimed at determining a standard premedication protocol for rituximab infusion.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

YK conceptualized the study, formulated the study protocol, and drafted the manuscript. K Yamamoto, TI, and MT provided support in drafting the study protocol. HM and K Yakushijin reviewed the study protocol. IY supervised the study protocol and reviewed the final manuscript. All authors have reviewed and approved the final manuscript. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

Conflicts of Interest

K Yakushijin declares receiving an honorarium from Pfizer. HM declares receiving honoraria from Pfizer and Nipro.

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Abbreviations

BR: bendamustine hydrochloride plus rituximab
CTCAE: Common Terminology Criteria for Adverse Events
eCRF: electronic case report form
FAS: full analysis set
IR: infusion reaction
NHL: non-Hodgkin lymphoma
Pola-R-CHP: polatuzumab plus rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone
PPS: per-protocol set
R-CHOP: rituximab plus cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone
REDCap: Research Electronic Data Capture
Tmax: time to maximum concentration
VAS: visual analogue scale

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Protocol

Changes in Oral Health and Dental Esthetic in Smokers Switching to Combustion-Free Nicotine Alternatives: Protocol for a Multicenter and Prospective Randomized Controlled Trial

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Abstract

Background: Although the detrimental effects of conventional combustible cigarettes on oral health and dental esthetics are well known, there is limited information about the long-term impact of combustion-free nicotine alternatives (C-F NA) such as e-cigarettes or heated tobacco products.

Objective: This multicenter, prospective, 3-parallel-arm randomized controlled trial will investigate whether switching from combustible cigarettes to C-F NA will lead to measurable improvements in oral health parameters and dental esthetics over 18 months in adult smokers with limited gum disease.

Methods: Regular smokers not intending to quit and without clinical signs of periodontitis will be randomly assigned (1:4 ratio) to either standard of care with brief cessation advice (control group; arm A) or C-F NA use (intervention group; arm B). The study will also include a reference group of never smokers (reference group; arm C). The primary end point is the change in the

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Modified Gingival Index (MGI) score from baseline between the control arm (arm A) and the intervention arm (arm B) at the 18-month follow-up. In addition, the study will analyze the within- and between-group (arms A, B, and C) changes in MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires measured at each study time point. All participants will attend a total of 7 clinic visits: screening, enrollment, and randomization (visit 0); baseline visit—day 14 (visit 1); day 90 (visit 2); day 180 (visit 3); day 360 (visit 4); and day 540 (visit 5). This multicenter study will be conducted in 4 dental clinics in 4 countries. The statistical analysis will involve descriptive statistics for continuous and categorical data. Primary end points will undergo tests for normality and, based on distribution, either a 2-sided *t* test or Mann-Whitney *U* test. Linear mixed model with random factors center and study arms by center will also be applied. Secondary end points, including MGI assessment and quality of life, will be subjected to similar tests and comparisons. Only if one value of the parameter MGI is missing after day 1, the last available observation will be carried forward. The analysis will be performed on the substituted data. Secondary parameters will not have missing value replacement.

Results: Participant recruitment began in October 2021, and enrollment was completed in June 2023. Results will be reported in 2025.

Conclusions: This will be the first study to provide key insights into oral health benefits or risks associated with using C-F NA in smokers who are seeking alternatives to cigarette smoking.

Trial Registration: ClinicalTrials.gov NCT04649645; https://clinicaltrials.gov/ct2/show/NCT04649645

International Registered Report Identifier (IRRID): DERR1-10.2196/53222

(JMIR Res Protoc 2024;13:e53222) doi:10.2196/53222

KEYWORDS

electronic cigarettes; heated tobacco products; tobacco harm reduction; smoking; oral health; gingivitis; periodontitis; Modified Gingival Index; MGI; dental plaque imaging; dental shade; smartphone; mobile phone

Introduction

Background

Periodontal diseases, commonly including gingivitis and periodontitis, arise in response to the accumulation of oral bacteria in the gingival sulcus and are characterized by tissue changes in the periodontium that occur as part of the inflammatory process [1]. Gingivitis is characterized by inflammation such as redness, swelling, or bleeding on gentle provocation of the gingival sulcus, whereas periodontitis exhibits increased probing depth, clinical attachment loss, and radiographic alveolar bone loss, reflecting the destructive aspects of the disease process [2,3].

Periodontal disease is a well-known independent risk factor for cardiovascular disease [4,5], and reducing gingivitis and periodontitis is likely to have an overall positive impact on human health in general.

There are multiple risk factors for periodontal disease, and cigarette smoking is considered among the key independent risk factors for the development and progression of periodontal disease [6-9]. Depending on the disease definition and extent of exposure to cigarette smoke, the risk of developing destructive periodontal disease is 5- to 20-fold higher in smokers than in nonsmokers [10]. Cigarette smokers appear to be prone to more severe periodontal manifestations even after adjusting for age, education level, history of diabetes, BMI, alcohol consumption, perceived mental stress, and oral hygiene levels [11]. In addition to periodontal diseases, cigarette smoking can cause visible dental manifestations, including dental discoloration and tobacco stains, the intensity of which mainly depends on smoking duration and frequency [12]. In a large cross-sectional study in the United Kingdom [13], smokers were more likely to report dental discoloration and being dissatisfied with their own tooth color compared with nonsmokers. Dissatisfaction with teeth appearance (because of enamel discoloration and tobacco stains) is often perceived as a significant social problem for smokers [14,15].

The importance of dental care and oral health for healthy longevity is emphasized in the 2022 declaration of the World Health Organization (WHO) for which greater advocacy is needed to increase the prominence of oral health on the global health agenda. Moreover, reducing oral health issues calls for stronger policies addressing the determinants of oral diseases and no communicable diseases and to tackle inequalities through inclusive universal health care access [16]. More recently, the WHO has provided policy recommendations for integrating brief tobacco interventions into oral health programs in primary care in accordance with the WHO Oral Health Program and as part of the WHO Global action plan on the prevention and control of noncommunicable diseases, particularly pertaining to the needs of low- and middle-income countries [17].

Although it is clear that abstaining from smoking will have beneficial effects on oral health and overall dental esthetic, most smokers are reluctant to seek formal treatment to stop smoking, with the vast majority making attempts to quit without assistance [18,19]. Consequently, novel and efficient approaches are required.

Although not authorized as medications for smoking cessation, combustion-free technologies for nicotine delivery, such as e-cigarettes (ECs) and heated tobacco products (HTPs), have become de facto harm reduction tools from cigarette smoke [20,21] and aid in quitting smoking [22,23].

Combustion-free technologies for nicotine delivery such as ECs and HTPs offer substantial reduction in exposure and harm to harmful constituents compared with tobacco cigarettes [24-27],

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but there is limited information about the long-term impact on oral health and dental esthetics in people who use combustion-free nicotine alternatives (C-F NA).

Objectives

This multicenter, prospective, randomized, controlled, 3–parallel arm trial will be the first to determine whether adult smokers who switch to C-F NA will experience measurable improvements in oral health parameters and dental esthetics. A group of never smokers will also be recruited for comparative measures of the study parameters.

Data from this study will provide valuable insights into the overall potential of C-F NA in reducing the risk of periodontal diseases and consequential cardiovascular risk. In addition, the findings may have important implications for reducing the smoking burden globally, especially for smokers for whom bad breath or poor dental esthetic is a significant concern. For these individuals, an oral-centric narrative (such as achieving a healthier and brighter smile) may serve as a more compelling reason to quit smoking than the fear of future lung cancer or cardiopulmonary diseases.

Methods

This is a multicenter, 3-parallel-arm, randomized controlled trial of 18 months duration designed to assess whether cigarette smokers switching to C-F NA will undergo measurable improvements in oral health parameters and dental esthetics as a consequence of avoiding exposure to cigarette smoke. This study aims to assess differences in study end points of oral health parameters and dental esthetics at multiple study time points between smokers switching to C-F NA and smokers who continue to smoke.

Study Population

Eligible participants will be healthy adult regular cigarette smokers (self-reported daily smoking of >10 cigarettes per day for at least 5 consecutive years) and never smokers without clinical signs of periodontitis.

Smokers will be offered access to free smoking cessation programs. Only those who refuse to participate in the smoking cessation program and express willingness to switch to C-F NA will be eligible for randomization.

Never smokers (those who have smoked <100 tobacco cigarettes in their lifetime) will also be included as a reference group.

Participants will be required to satisfy all the inclusion criteria as presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria for smokers (study arms A and B)

- Adults (aged 18-50 years)
- Cigarette smokers of ≥10 cigarettes per day
- Smoked for at least 5 consecutive years before screening
- Verified smoking status by exhaled breath carbon monoxide (CO) ≥7 ppm at screening
- Willingness to switch to a combustion-free nicotine alternatives, if required by the randomization
- Refusal to participate in smoking cessation programs
- Presence of at least 10 natural anterior teeth in total (cuspid to cuspid and lower and upper jaw)
- Healthy participants, not taking regular medications for chronic medical conditions
- Accepting to comply with the requirements of the study, including installing an app on their smartphone

Inclusion criteria for never smokers (study arm C)

- Adults (aged 18-50 years)
- Have not smoked >100 tobacco cigarettes in their lifetime
- Verified nonsmoking status by exhaled breath CO <7 ppm at screening
- Presence of at least 10 natural anterior teeth in total (cuspid to cuspid and lower and upper jaw)
- Healthy participants, not taking regular medications for chronic medical conditions
- Accepting to comply with the requirements of the study, including installing an app on their smartphone

Exclusion criteria for smokers (study arms A and B) and never smokers (study arm C)

- Significant oral soft tissue pathology or any type of gingival overgrowth other than plaque-induced gingivitis
- Periodontitis based on the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [28], which requires the following:
  - Detectable interdental clinical attachment loss ≥3 mm at ≥2 nonadjacent teeth
  - Buccal or oral clinical attachment loss ≥3 mm with pocketing ≥3 mm detectable at ≥2 teeth
  - Only participants with mild to moderate gingivitis will be recruited
- Fixed and removable orthodontic appliances or removable dentures
- Any other medical condition that, in the opinion of the principal investigator, would jeopardize the participant's safety or diminish the validity of the study results
- A course of treatment with any medications that
  - interfere with the cyclooxygenase pathway (eg, anti-inflammatory drugs including aspirin and ibuprofen) within 3 days before each visit
  - are known to have antibacterial activity (eg, antibiotics) within 7 days before each visit
- Significant history of alcohol or drug abuse within 24 months before screening, as determined by the investigator
- For smokers, planning to quit smoking within the next 6 months
- For smokers, regular use of nicotine (eg, e-cigarettes, nicotine replacement therapy, nicotine pouches) or tobacco products (eg, heated tobacco products, oral smokeless) other than their cigarettes within 14 days of screening
- Pregnant or breastfeeding or intention to become pregnant during the study
- Active participation in another clinical trial

Study Design

This is an 18-month, prospective, multicenter, open-label study with 3 parallel arms, using randomization and control to assess a range of oral health and dental esthetic metrics (Figure 1). The primary objective is to compare these metrics between cigarette smokers transitioning to C-F NA and those who continue smoking.

Eligible smokers will be allocated randomly to either the control group (arm A), which will receive standard care inclusive of cessation counseling (ie, very brief advice [VBA]) or the intervention group (arm B), which will be given a C-F NA of their choice and will also receive VBA. Individuals who have

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never smoked will form a reference group (arm C). Throughout the study, participants from all 3 groups will undergo regular assessments of their oral health and dental esthetic. The study will be conducted in 4 dental clinics across 4 different countries (Italy, Poland, Moldova, and Indonesia).

The study protocol adheres to the guidelines stipulated by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Figure 1. Study design. Smokers not intending to quit and without clinical signs of periodontitis were randomized to either standard care (arm A) or combustion-free nicotine alternatives (C-F NA; arm B). A reference group of never smokers will also be included but not randomized (arm C). Participants were prospectively reviewed at 4 dental clinics for cigarette consumption and C-F NA use, oral health and dental esthetic measurements, vital signs, and adverse events for up to 18 months.

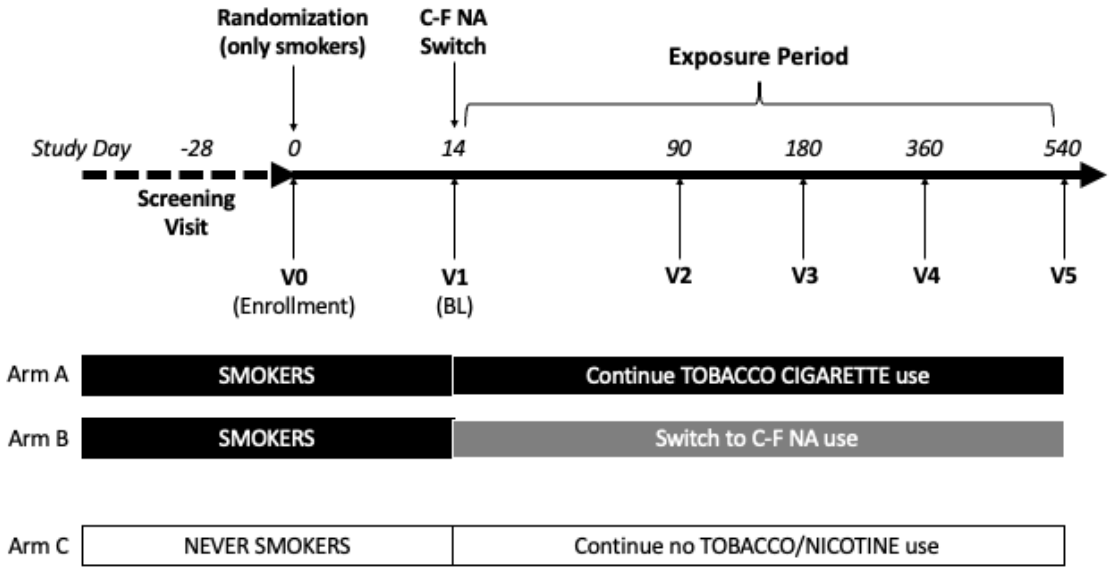

The study flow is illustrated in Figure 2.

All participants will attend a total of 7 clinic visits: day −28 to day −1—screening; day 0—enrollment and randomization (visit 0); day 14—baseline visit (visit 1); day 90—week 12 (visit 2); day 180—week 24 (visit 3); day 360—week 52 (visit 4); day 540—week 76 (visit 5).

Figure 2. Study flow diagram of study participants. C-F NA: combustion-free nicotine alternatives.

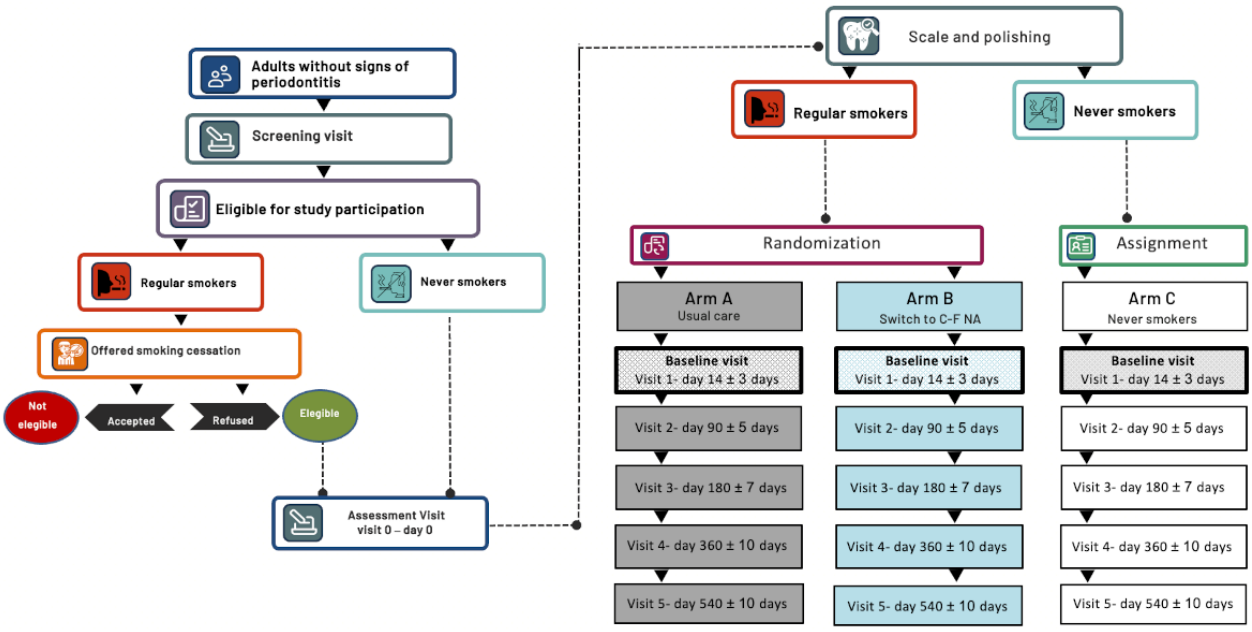

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Screening visits will be performed within 28 days before enrollment to verify the eligibility criteria (visit 0; Figure 2). During the screening visit, sociodemographic data, medical and oral health history, detailed information about nicotine and tobacco consumption, and interest in trying C-F NA will be recorded. Screening for periodontal disease will be performed to exclude periodontitis, as per the definition of the guidelines of the 2017 Classification of Periodontal and Peri-implant Diseases and Conditions [28]. Smokers will be offered a smoking cessation program as per local guidelines. Any smokers who express the intention of booking for the cessation program or to quit smoking in the next 6 months will be urged to do so and will not be recruited in the study. Participants taking part in the study will be informed that they are free to quit smoking and withdraw from the study at any time. Moreover, smokers will be encouraged to quit smoking at every contact throughout the study.

Within 28 days of the screening visit, eligible participants will be invited to attend an enrollment visit (visit 0). Inclusion and exclusion criteria will be verified again. Smokers will be reminded of the risks associated with smoking before enrollment in the study and that they are free to voluntarily quit smoking and nicotine or withdraw from the study at any time. All participants will undergo a series of measurements (Tables 1-3) followed by dental scaling and polishing procedures to remove calculus, plaque, and stain.

Smokers not intending to quit will then be randomly assigned to either the control (arm A) or the intervention (arm B) group. The randomization sequence will be generated by a computer, with an allocation ratio of 1:4 (arm A: arm B) to accommodate for the estimated 25% proportion of participants achieving a sustained reduction in cigarette consumption of at least 90% in arm B (as detailed in the Statistical Considerations section). Smokers in the control group (arm A) will receive standard care, inclusive of cessation counseling (ie, VBA) at each study visit. Smokers in the intervention group (arm B) will have the option to try and choose a preferred C-F NA (ECs and HTPs) from a given pool of popular options present in the respective markets and will also receive VBA.

Individuals who have never smoked will be allocated to the reference group (arm C). Never smokers in the reference group will serve as comparators for assessing any background changes in the primary study end point (ie, Modified Gingival Index [MGI]) that may occur over time. Although never smokers will not undergo randomization, efforts will be made to achieve a comparable distribution of sex and age across all study arms.

The trial is designed as an unblinded trial because of the nature of the intervention, where participants and trial staff cannot be blinded to the specific intervention being provided. However, data analyses will be conducted blind to study arms allocation. All other trial staff who have access to outcome data will remain blinded until prespecified data analyses will be completed.

Baseline measurements will be performed at visit 1 (baseline visit) and 14 days after scaling and polishing procedures at enrollment (visit 0). Study measurements will include MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires (Tables 1-3).

Smokers in arm B will be provided with a C-F NA of their choice. They will receive training and counseling on how to use the chosen C-F NA and will be provided with a full 2-week supply of the required consumables (cartridges or pods or e-liquid refill bottles for ECs and tobacco sticks for HTPs). Participants wishing to use an HTP will receive one kit and a supply of tobacco sticks of their choice. They will receive the number of tobacco sticks per day corresponding to the number of cigarettes smoked per day at baseline. Participants wishing to use a vaping product will receive one vaping kit and a supply of e-liquids of their choice. Products will be supplied at each subsequent visit throughout the study according to the study product supply schedule in Table 4.

After the baseline visit, participants will be invited to attend 4 more clinical visits (visits 2-5) to repeat study measurements (Tables 1-3).

Throughout the study, monitoring of cigarette consumption, daily C-F NA use, and oral hygiene routine will be carried out regularly using the tracker app and personal diaries. Monitoring of cigarette consumption and daily C-F NA use will also be achieved by asking participants in arm B to return all empty, partly used, and unused consumables (tobacco sticks, EC cartridges, and e-liquid refill bottles) at each study visit. The tracker app will also identify any protocol violations, collect adverse events (AEs), and send reminders (eg, next scheduled appointment, study restrictions, and instructions) throughout the study duration. The use of a dedicated tracker app adds an innovative element to continuously collect data and enhances adherence to the study protocol.

Before each study visit (visits 1-5), all participants will be required to refrain from scaling and polishing procedures, avoid modifying their habitual oral hygiene (eg, mouthwash, mouth rinse, and interdental floss), refrain from flossing for at least 72 hours before each study visit, refrain from mouth rinsing for at least 24 hours before each study visit, refrain from tooth brushing for at least 2 hours before each study visit, refrain from eating and drinking (except water) for at least 2 hours before each visit, and abstain from smoking for 2 hours before each visit. This is to minimize any potential interference with study outcomes and to maintain consistency in data collection. Throughout the study, any modifications in the oral hygiene routine of participants will be recorded using the tracker app.

A detailed description of the measurements that will be specifically performed at each trial visit is provided in Multimedia Appendix 1.

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Table 1. Study schedule of procedures (control group—arm A).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3), day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Intention to quit smoking	✓						
Smoking cessation advice	✓	✓	✓	✓	✓	✓	✓
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓	✓	✓	✓	✓	✓	✓
Interest to switch to C-F NA[c]	✓						
Informed consent		✓					
FTND[d]		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Randomization		✓					
Tracker app installation		✓					
BP[e], HR[f], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[g] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[h] questionnaires (OHQoL[i] and EQ VAS[j])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.

[b]CO: carbon monoxide.

[c]C-F NA: combustion-free nicotine alternatives.

[d]FTND: Fagerström Test for Nicotine Dependence.

[e]BP: blood pressure.

[f]HR: heart rate.

[g]MGI: Modified Gingival Index.

[h]QoL: Quality of Life.

[i]OHQoL: Oral Health Quality of Life.

[j]EQ VAS: EuroQoL Visual Analog Scale.

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Table 2. Study schedule of procedures (intervention group—arm B).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3); day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Intention to quit smoking	✓						
Smoking cessation advice	✓	✓	✓	✓	✓	✓	✓
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓	✓	✓	✓	✓	✓	✓
Interest to switch to C-F NA[c]	✓						
Informed consent		✓					
FTND[d]		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Randomization		✓					
Familiarization with C-F NA			✓				
C-F NA use				✓	✓	✓	✓
Tracker app installation		✓					
BP[e], HR[f], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[g] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[h] questionnaires (OHQoL[i] and EQ VAS[j])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.
[b]CO: carbon monoxide.
[c]C-F NA: combustion-free nicotine alternatives.
[d]FTND: Fagerström Test for Nicotine Dependence.
[e]BP: blood pressure.
[f]HR: heart rate.
[g]MGI: Modified Gingival Index.
[h]QoL: Quality of Life.
[i]OHQoL: Oral Health Quality of Life.
[j]EQ VAS: EuroQoL Visual Analog Scale.

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Table 3. Study schedule of procedures (reference group—arm C).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3); day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓						
Informed consent		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Assignment to arm C		✓					
Tracker app installation		✓					
BP[c], HR[d], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[e] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[f] questionnaires (OHQoL[g] and EQ VAS[h])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.
[b]CO: carbon monoxide.
[c]BP: blood pressure.
[d]HR: heart rate.
[e]MGI: Modified Gingival Index.
[f]QoL: Quality of Life.
[g]OHQoL: Oral Health Quality of Life.
[h]EQ VAS: EuroQoL Visual Analog Scale.

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Table 4. Study schedule of combustion-free nicotine alternatives (C-F NA) supply and use checks (only for arm B).

Procedure	Screening	Enrollment (V0)	Baseline (V1)	Week											
				4	8	12 (V2)	20	24 (V3)	32	40	48	52 (V4)	60	68	76 (V5)
C-F NA use			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide C-F NA device			✓												
Hand out 2 weeks supply of consumables[b]			✓												
Hand out 4 weeks supply of consumables[a]				✓	✓		✓				✓				
Hand out 2×4 weeks supply of consumables[b]						✓		✓	✓	✓		✓	✓	✓	✓
Product use checks (collect used and unused consumables[b])				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Participants wishing to use a heated tobacco product will receive one kit and supply of tobacco sticks of their choice; they will receive the number of tobacco sticks per day corresponding to the number of cigarettes smoked per day at baseline. Participants wishing to use a vaping product will receive one vaping kit and supply of e-liquids of their choice.

Study End Points

Primary End Points

The primary objective of the study is to compare changes in MGI by Lobene et al [29] between baseline and end of the study (ie, 18 months' time point) among participants who continue to smoke tobacco cigarettes (arm A) and participants who switch to C-F NA (arm B).

Secondary End Points

In addition, the study will analyze the number of secondary objectives, including within- and between-group variations at each study time point from baseline for MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires.

Study Measurements and Calibration

A detailed description of the study measurements that will be specifically carried out at the dental clinic is provided in Multimedia Appendix 2.

All assessors will be trained on MGI scoring, tooth stain assessment, and the correct use of technologies and software used to quantify dental plaque, tooth discoloration, exhaled carbon monoxide monitoring, and electronic case report form (eCRF) use. Assessors will be periodically calibrated on MGI scoring and tooth stain assessment. To ensure consistency in the measurements, the same assessor will collect all study end points in the same participant over the entire study period.

Data Monitoring and Study Safety

A trial monitoring plan will be developed based on the trial risk assessment and includes on-site monitoring. The clinical research organization will arrange an independent monitor, separate from the investigators and the sponsor, to ensure compliance with trial protocols and policies, participant protection, and accurate data collection.

AEs and serious AEs (SAEs; eg, those related to oral conditions, tobacco cigarette smoking, C-F NA use, nicotine withdrawal symptoms, or nicotine overdosing) will be recorded on the AE page of the eCRF throughout the study. Participants will be interviewed at each visit to investigate signs or symptoms. Signs or symptoms will be elicited at each visit by open questioning, such as "How have you been feeling since your last visit?" "How have you been feeling regarding your oral cavity?" Participants will also be encouraged to spontaneously report AEs occurring at any other time during the study via the dedicated mobile app or the communication channels provided for the study. The investigator must gather sufficient information to determine the outcome and causality of AEs and SAEs and promptly notify the competent authority, if necessary.

Study Withdrawal

Participants may be withdrawn from the study prematurely for the following reasons: (1) experience an SAE, (2) develop a

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concurrent disease which at the discretion of the investigator no longer justifies the participant's participation in this study, (3) sustain any uncorrectable protocol deviations during the study, (4) decide to stop their participation, (5) become pregnant, and (6) exhibit uncooperative behavior or nonattendance. After consultation with the clinical research organization, the investigator will notify participants' discontinuation from the study.

Data Collection and Protection

For data collection, each participant will be allocated an eCRF. Anonymized data from each study visit will be entered directly into the eCRF, which will then serve as a source document for the trial. This data entry process ensures that data are collected accurately and consistently at all study sites.

Each participant will be assigned a unique study identification number (participant ID). Participant's personal data will not be linked to the research results, and only a limited number of members of the research team will have access to the decoding list that links participant IDs to their personal information. All information obtained during the study procedures, including participant data and personal details, will be treated as private and confidential in accordance with ethical and privacy regulations.

The trial will reach its formal conclusion on the date of the final visit of the last participant in the last country involved in the study.

Ethical Considerations

The study will be conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. All 4 local ethics review boards reviewed and approved the study and, where appropriate, translated the relevant documentation (eg, informed consent form, participant's information sheet). The trial is registered with ClinicalTrials.gov (NCT04649645). The study was approved by the ethics review board of the coordinating center, the Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione "Garibaldi" (697/CE; dated November 11, 2020). Informed consent was obtained from all the participants.

The intention is to disseminate the study results through articles in peer-reviewed journals and conference presentations. A summary of the results will be available on the study website for public access. The anonymized data will be available to researchers upon reasonable request.

Statistical Considerations

Sample Size Calculation

For a valid sample size calculation, literature research was performed for the primary end point of the study (ie, MGI). Unfortunately, no data were available for such a study. However, data from studies with mouth rinse were available, and based on these studies [30,31], a mean MGI change of 0.08 with an SD of 0.18 of the MGI seemed relevant.

However, in these studies, higher mean MGI changes were observed because active treatment was administered, which was not the case in this study. Thus, several scenarios with different mean MGI changes and SDs will be applied.

The following hypotheses will be tested with a 1-sided independent *t* test:

H0: $\mu A \leq \mu B$ versus H1: $\mu A > \mu B$

where μA denotes the mean change MGI from baseline to after 18 months of regular smoking and μB denotes the mean MGI from baseline to after 18 months of C-F NA use.

For sample size calculation, SAS software (version 9.4; SAS Institute) was used and several scenarios were applied, assuming that the data are normally distributed. The results are summarized in Table 5, which presents the calculated sample sizes for the comparison of μA versus μB by a 1-sided independent *t* test, a significance level of 5%, and a power of 90%, depending on the expected MGI change and SD.

As no active treatment is given in this study, a lower effect than the observed values needs to be assumed. Therefore, a mean MGI change of 0.1 with an SD of 0.21 was chosen. Hence, a sample size of 77 patients per treatment group is required. Considering a dropout rate of 20% over 2 years' observation phase [32,33], a sample size of at least 92 per treatment group is required. In addition, it is estimated that approximately 25% of those switching to C-F NA use will abstain or substantially (≥90%) reduce smoking [34], and only these participants deliver valid results. Therefore, 4 times more participants should be recruited in the C-F NA group (4 × 92 = 368). This results in a total sample size of 460 (92 in arm A+368 in arm B).

In arm C, we have determined a sample size of 40, empirically with no formal statistical analysis, as this cohort's primary study end point (ie, MGI) is expected to be stable throughout the study.

Table 5. Summary table including the sample size for each arm of the study depending on the mean Modified Gingival Index (MGI) change and SD.

Nominal power	Mean MGI change	SD[a]				
		0.20	0.21	0.22	0.23	0.24
0.9	0.10	70	77	84	92	100
0.9	0.15	32	35	38	41	45
0.9	0.20	18	20	22	24	26

[a]Expected sample size is the same per each group and it is indicated by the rows (ie, 70-100, 32-45, and 18-26) according to the SD and MGI combinations.

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Statistical Analyses

Statistical methods used in the analysis of this study will include descriptive statistics with the descriptive presentation of the total sample value, mean, SD, median, minimum, maximum, and 95% CIs for (pseudo) continuous data and categorical data. Further evaluations will be summarized in tables by counts and percentage of scores.

Statistical methods for primary study end points will include the following: the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test) and a linear mixed model with the random factors "center" and "study arms by center."

Designated as study arm C, the never-smoker group will establish a baseline reference for the oral health parameters. This group is anticipated to provide insights into the underlying changes in the primary study end point (MGI) that may emerge over time in individuals who have never smoked.

Statistical methods for secondary study end points will include the following: for comparisons of each study arm for parameters such as MGI assessment, plaque imaging, dental shade quantitation, tooth stains scores, and oral health–related quality of life questionnaires, the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test); for comparisons of each assessment time for parameters such as MGI assessment, plaque imaging, dental shade quantitation, tooth stains scores, and oral health–related quality of life questionnaires, the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test); accounting for missing, unused, and spurious data.

If only one value of the parameter MGI is missing after day 1, the last available observation will be carried forward. The analysis will be performed on the substituted data. For secondary parameters, no replacement of missing values will be applied.

A generalized linear regression model will be used to adjust for all identified confounders. To identify possible predictors of primary and secondary study end points, a regression model will be estimated in which each study end point will be entered as the dependent variable. Possible predictors will be entered into the model as independent variables (including study group; age; gender; cigarette consumption; combustion-free nicotine delivery systems use; and frequency of personal oral hygiene, eg, tooth brushing, mouth washing, and dental flossing frequency) to assess the interactions. Following the results obtained from each regression model, comparisons between and within study groups will be performed using analysis of covariance adjusted for age, gender, and frequency of personal oral hygiene followed by the Tukey post hoc comparison test.

The goal of our study is to help smokers abstain from cigarette smoking to assess changes in oral health regardless of the product used. This study is not designed to compare the efficacy between HTPs and ECs in terms of smoking cessation. Nonetheless, we will consider a secondary analysis that takes into account the potential different impact of HTPs versus ECs in terms of oral health outcomes.

Results

Participant recruitment began in October 2021, and enrollment has been completed in June 2023. Results will be reported in 2025.

Discussion

Overview

Although the negative effects of cigarette smoking on oral health and tooth discoloration are well known [35,36], there are only limited data about the impact of C-F NA such as ECs and HTPs. In particular, there are no long-term studies assessing the impact on oral health and teeth appearance when substituting conventional cigarettes for these combustion-free alternatives. This study was specifically designed to address these research questions. In particular, this study tests the hypothesis that avoiding exposure to cigarette smoke toxicants may translate into measurable amelioration in gingival response, dental plaque build-up, enamel discoloration, and tooth staining in participants with mild to moderate gingivitis by comparing participants who smoke tobacco cigarette with those who switch to using C-F NA or participants who never smoked.

In addition to its obvious relevance to health and esthetic concerns, this study seeks to expand on regulatory science. Regulatory authorities (eg, the US Food and Drug Administration) recommend investigating the oral health effects of novel tobacco and nicotine products to better understand their impact at individual and population levels as well as exploring additional study end points for the assessment of their short- and long-term effects in oral health studies [37]. Our study is designed to provide improved design knowledge for oral health switching studies and, most importantly, to streamline new innovative cutting-edge technologies that can be used for future studies on existing and emerging tobacco and nicotine products (including oral smokeless products).

The study design incorporates several significant and groundbreaking characteristics. First, we aim to enhance adherence to C-F NA and optimize overall compliance with the study's instructions through the provision of a diverse range of products, encompassing the most popular options available in the market. This approach allows participants to tailor their own gratifying "nicotine experience" by selecting the C-F NA that aligns with their preferences. By doing so, we anticipate not only fostering a transition to the latest technology but also facilitating the reduction of cigarette smoking and bolstering long-term prevention of relapse [38-42]. It is worth highlighting that this aspect of personal choice is notably absent in studies of harm reduction. Furthermore, it is important to emphasize that the outcomes of this research will not be product specific, thereby minimizing constraints on generalizability.

Second, the study is being run in many different locations across the globe and so the challenge was to find a primary end point that could be measured by different operators in different sites, using a standardized measurement system that has been used

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previously and so has provenance. The index to be used had to be simple, reproducible, and relatively easy to compare between different sites and different operators. Ideally, the assessors should be able to calibrate the index to be used and compare the calibration results. The MGI is a widely used industry-standard index to determine changes in the gingival health of volunteers in clinical studies [29,43,44]. This index is simple, noninvasive, and reproducible, and it is hoped that it will be possible to train different examiners in different locations to align their assessments, thus making the results comparable. As the MGI is noninvasive, there is no gingival probing, and it is thought to be easier to calibrate examiners and compare kappa scores. Although subjective in nature, the lack of probing removes one of the variables present in using pressure to probe the gingivae. It is also thought to afford greater sensitivity in determining therapeutic efficacy [45]. This study will be the first to investigate the long-term impact of smoking or C-F NA intervention on MGI.

Third, the selection of secondary study end points is strategic because it considers what drives smokers to turn to cleaner nicotine and tobacco products. This is particularly persuasive for young adults, for whom a cardiovascular-cancer-respiratory risk–based narrative is either ineffective or even counterproductive, and for whom concern about bad breath and poor dental esthetic (because of enamel discoloration and “tar” stains) may be a much more significant reason to refrain from smoking. Although experimental work comparing the effects of C-F NA on tooth staining and discoloration has been published [46-48], this study is the first to consider this powerful narrative of oral health in a clinical trial; therefore, we have included innovative 21st century technologies for objective and consistent quantitation of dental shade discoloration (by calibrated spectrophotometry) and dental plaque changes (by digital imaging technology; quantitative light-induced fluorescence) among the study end points to investigate whether switching completely from cigarettes to C-F NA can improve gum health, reduce bad breath, and restore teeth appearance. Small-scale clinical trials have been recently conducted at the Center of Excellence for the Acceleration of Harm Reduction of the Catania University to confirm the validity and reproducibility of dental shade assessment by digital spectrophotometry and dental plaque quantitation by light-induced fluorescence technology in current, former, and never smokers [49,50].

Fourth, maximizing the magnitude of observable changes at the study end points is critically important. Given that several factors (including duration of smoking exposure, variations in oral hygiene practices, type of diet, and level of alcohol consumption) can significantly affect assessments of gum health and dental esthetics, we reduced baseline variability by using data obtained after the visit during which scaling and polishing was carried out. By removing dental plaque, calculus, and stains, we provide all study participants with the best possible oral health status (gum health and teeth appearance) at the beginning of the study. Considering that a 14-day interval is generally required to allow gingival restoration from tissue trauma caused by scaling and polishing [51], measurements that will be considered for this normalized baseline will be obtained 14 days after scaling and polishing. Any progressive change in gum health or tooth appearance will be compared with the reference data of this baseline. In addition to the inclusion of a full scale and polish at the beginning of the study in an attempt to maximize the magnitude of observable changes of study end points, it is also important to consider that the length of the study is adequate and that the study population will have to be one that allows the possibility of measuring such a change. Although the long-term impact of smoking and smoking cessation on gingival health and tooth appearance has never been investigated in a prospective trial, the planned 18 months duration of the study is deemed to be adequate for the detection of significant changes in study end points. Chronic periodontal disease is common in smokers and is an irreversible condition that may stabilize with active treatment [52]; however, it is unlikely to improve with the simple measure of smoking cessation alone. Therefore, participants with periodontitis will be excluded and only participants with mild to moderate gingivitis will be recruited, as they are more likely to show measurable changes in study end points with continuing to smoke, smoking cessation, or the use of C-F NA.

Fifth, personal oral hygiene and dietary patterns can significantly influence both primary and secondary study end points. To mitigate this impact, a standardized approach to oral hygiene will be implemented within the study parameters. Participants will be explicitly advised against altering their established oral hygiene practices for the duration of the study. Furthermore, adherence to specific restriction criteria before each scheduled study visit will be emphasized, aiming to prevent any confounding of the collected data. Recognizing the variable effects stemming from individual oral hygiene and dietary habits, we incorporated a cohort of never smokers as a reference group. This inclusion serves to establish a benchmark for comparison and analysis. To address the inherent challenge of ensuring consistent measurement of study end points, especially in cases involving diverse operators across multiple sites, we will provide comprehensive training and implement meticulous calibration procedures.

Finally, compliance with the research protocol is important because it would decrease or nullify the anticipated improvements in study end points if cigarettes were not fully or largely replaced with C-F NA. Participants will be reminded of the importance of adhering to their randomized product allocation and of abstaining from or substantially reducing the daily consumption of cigarettes (by at least 90% of their regular cigarette smoking at baseline) at every study visit. A significant feature of switching studies is close reporting of cigarette consumption and (or) C-F NA use; participants will record the consumption of cigarettes and use of C-F NA on each visit in their study diary. In addition, participants will be asked to return all empty, partly used, and unused consumables. Throughout the study, smoking and C-F NA use will be monitored via an app. The SMILE Tracker app is an integral component of the Smile study designed to monitor participants’ behaviors and lifestyle choices. Through daily prompts, the app assists in tracking cigarette consumption, use of combustion-free nicotine delivery systems, and regular oral hygiene practices such as brushing, flossing, and mouthwash use. In addition, it functions

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as a personal diary for participants to log any changes in their oral care routine. Moreover, the SMILE Tracker app features a system to monitor protocol adherence, identify deviations, and gather data on potential AEs and SAEs. It sends automated reminders to participants for their upcoming appointments and study restrictions and provides instructions to ensure adherence and accurate data collection during the study. Furthermore, it includes a step counter to encourage physical activity among users. Of note, noncompliance with the study items is an interesting outcome in itself (particularly in consideration of the wide selection of different products offered in the study). Although compliance with this study is not expected to be significantly different compared with other comparable studies, our power calculations are overestimated to account for a 75% noncompliance rate. The C-F NA population would therefore be overrepresented by recruiting4 times the number of participants in the C-F NA category (ie, for every participant randomized in the control population, 4 will be randomized in the C-F NA population).

The acknowledgment of the impact of COVID-19 pandemic restrictions on recruitment is duly noted. However, it is deemed unlikely that these restrictions will exert a significant impact. This assertion is based on the fact that recruitment proceedings were initiated in October 2021, a period during which well-defined guidelines had already been established at the dental clinic across all 4 participating sites.

Conclusions

This study represents a pioneering effort in assessing the long-term effects of smoking and smoking abstinence on oral health. Through a prospective approach, it aims to provide novel insights into the relationship between smoking habits and oral well-being. The data derived from this study will significantly enhance our existing understanding of the impact of smoking on oral health. Moreover, the study outcomes hold the potential to shed light on the role of C-F NA as a potentially cleaner nicotine alternative to tobacco smoking. This is particularly relevant for individuals who prioritize concerns such as bad breath and dental esthetics. This study's emphasis on oral health aligns with a broader objective of alleviating the burden of smoking. Several parameters measured in this study (including MGI and dental plaque build-up) are linked to the development of periodontal disease. It is noteworthy that the progression from chronic gingivitis to periodontitis raises the risk of cardiovascular disease [4,5], thereby underscoring the broader health implications of the study's results.

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Data Availability

The data sets used during or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

GC, DG, PC, RM, and RP conceived and designed the study. GC, DG, and RM formalized the statistical analysis plan. GC, DG, SU, and RP drafted the manuscript. SU designed the figures and tables. All authors have provided critical revisions to the working draft and have read and approved the submitted manuscript.

Conflicts of Interest

RP is a full-time professor of internal medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same university. He has received grants from U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) and AIRPROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling); Integral Rheumatology & Immunology Specialists Network; Foundation for a Smoke-Free World; Pfizer; GlaxoSmithKline; CV Therapeutics; NeuroSearch A/S; Sandoz; Merk Sharp & Dohme; Boehringer Ingelheim; Novartis; Arbi Group Srl; Duska Therapeutics; Forest Laboratories; Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union; and the ministerial grant PON REACT-EU 2021 GREEN-Bando 3411/2021 by MUR—PNRR EU Community. He is the founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and the GLG Group. He receives textbook royalties from Elsevier and is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo and the International Network of Nicotine Consumer Organizations), and he is chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of

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electronic cigarettes" (CEN/TC 437; WG4). SAP is a professional dentist and the chairman of the Board of Directors of ECLAT Srl, the spinoff of the University of Catania that sponsors this study through a grant from the Foundation for a Smoke-Free World Inc, a US nonprofit 501(c)(3) private foundation. PC has been affiliated with the Center of Excellence for the Acceleration of Harm Reduction since December 2019 in a pro bono role. He is the coauthor of a protocol paper supported by the Investigator-Initiated Study award program established by Philip Morris International in 2017.

Multimedia Appendix 1
Study activities—detailed description of the measurements that will be specifically performed at each trial visit.
[DOCX File , 45 KB - resprot_v13i1e53222_app1.docx]

Multimedia Appendix 2
Study procedures—detailed description of the study measurements that will be specifically carried out at the dental clinic.
[DOCX File , 87 KB - resprot_v13i1e53222_app2.docx]

Multimedia Appendix 3
CONSORT checklist.
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e53222_app3.pdf]

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Abbreviations

AE: adverse event
C-F NA: combustion-free nicotine alternatives
eCRF: electronic case report form
EC: e-cigarette
HTP: heated tobacco product
MGI: Modified Gingival Index
SAE: serious adverse event
VBA: very brief advice
WHO: World Health Organization

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Protocol

Matrix Metalloproteinase-9 Testing of Golden Rice Cookies With Piper Crocatum Active Extract for Preventing Foot Ulcers in Patients With Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetic foot ulcers (DFUs) present a formidable challenge to both patients and health care systems. DFUs significantly reduce the quality of life for patients, prolong hospital stays, and are the cause of approximately 70,000 lower limb amputations across the globe annually. Prevention of DFUs primarily involves the optimization of blood sugar levels and the effective management of complications, particularly peripheral neuropathy. Golden Rice has been proven to lower blood sugar levels due to its beta-carotene content, and Piper crocatum (*P. crocatum*) has been found to be effective in reducing the risk factors of DFUs through biomolecular regulation because of its polyphenol content.

Objective: The principal objective of this study is to identify the efficacy of *P. crocatum*–enriched cookies, with Golden Rice as their primary ingredient, in preventing DFUs. The evaluation will center on their impact on the expression of matrix metalloproteinase-9 (MMP-9), a pivotal factor in the development of DFUs.

Methods: This study is an experimental clinical research that follows the randomized controlled trial method and uses a single-blind design. The participants in the study are outpatients from primary health centers in Makassar, Indonesia, who have been diagnosed with diabetes mellitus. The sample for the study will be randomly selected and subsequently categorized into 2 groups: the intervention group and the control group. The intervention group consumes *P. crocatum*–enriched Golden Rice cookies, while the control group receives cookies without these additives. The participants from both groups will consume their respective cookies (packaged identically) twice a day for 14 days. The cookies will be prepared according to a modified recipe with an emphasis on low glucose content, resulting in 51 calories per cookie, comprising 1% carbohydrates, 6% fat, 4% cholesterol, and 4% fiber, excluding gluten, sugar, and salt. They will be baked at 158°C for 20 minutes. The process involves the addition of 20% Golden Rice and 10% *P. crocatum* ethanol extract, both prepared via maceration with 96% ethanol. The dependent

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variable in this study is the expression of gelatinases matrix metalloproteinase, to be assessed at 2 distinct time points—preintervention (pretest) and postintervention (posttest)—with the evaluation conducted through the western blotting method.

Results: The recruitment and testing phase started in January 2024. The study is scheduled to be completed by the end of March 2024. Data analysis will commence in April 2024, and the publication of the results is anticipated in the same year (2024). The study will report on the changes in primary data, encompassing gelatinases matrix metalloproteinase, as well as secondary data, including the ankle-brachial index, neuropathy score, and random blood glucose level.

Conclusions: The findings of this trial are expected to significantly impact the selection of strategies by health care practitioners to enhance diabetes self-management, particularly in the domain of therapeutic snacking, for patients diagnosed with diabetes mellitus.

Trial Registration: Thai Clinical Trials Registry TCTR20230502001; https://www.thaiclinicaltrials.org/show/TCTR20230502001

International Registered Report Identifier (IRRID): PRR1-10.2196/49940

(JMIR Res Protoc 2024;13:e49940) doi:10.2196/49940

KEYWORDS

diabetic foot ulcer; prevention; diabetic neuropathy; cookies; food supplement; study protocol

Introduction

Diabetic foot ulcer (DFU) is a major problem in patients with diabetes, affecting 15% of the diabetic population. DFUs significantly reduce the quality of life for patients, prolong hospital stays, and are the cause of approximately 70,000 lower limb amputations across the globe each year [1]. Diabetic foot disease is among the top 10 medical conditions in terms of burden, and it is estimated that up to 34% of individuals with diabetes will experience DFU at some point in their lives [2]. Preventing DFUs and amputations is of utmost importance to alleviate this significant burden on patients, health care systems, and society as a whole [3].

Peripheral neuropathy, the most prevalent type of diabetic neuropathy, primarily affects the nerves in the extremities, especially the feet. It accounts for 6.4% of all complications related to diabetes [4]. This condition predominantly disrupts sensory function, leading to gradual numbness, which increases the susceptibility to developing ulcers due to external injuries. It is crucial to identify these risk factors to enhance the effectiveness of preventive measures for DFUs [5]. Treating diabetic neuropathy presents a significant clinical hurdle. According to some studies, the gelatinase matrix metalloproteinase 9 (MMP-9) has been found to play a vital role in the demyelination of axons and the development of diabetic neuropathy in rodents [6,7]. As gelatinase MMP-9 plays a pivotal role in the initial onset of neuropathy, it is considered crucial in the progression of diabetic neuropathy and could potentially be targeted for treatment purposes [6,7].

Elevated levels of blood sugar and insulin resistance in patients with type 2 diabetes further contribute to the generation of reactive oxygen species (ROS), which intensifies the complications associated with this disease [8]. The activity of vascular MMP-9 is heightened in individuals with diabetes mellitus, partly due to increased production by vascular endothelial cells. Additionally, the activity of ROS plays a significant role in this process [9]. The high levels of ROS and MMP-9 have been found to be associated with glycemic index and diabetes complications [10].

Different types of diabetic-friendly cookies and breads are already in circulation, such as cassava bread, flax meal powder, and grape seed oil bread. However, their purpose is solely to limit glucose intake rather than directly affecting insulin levels. In contrast, noncookie products made with Golden Rice as the main ingredient contain beta-carotene, which can stimulate insulin production in the body by boosting the beta pancreas and decreasing the glycemic index [11]. However, the reduction in glycemic index needs to be supported by the biomolecular environment as an effort to prevent DFUs. The suitable herbal ingredient for combination in these cookies is *Piper crocatum (P. crocatum*). The oral consumption of *P. crocatum*, belonging to the Piperaceae family, has been proven safe among the population in Indonesia [12].

The use of *P. crocatum* has been documented to exhibit numerous therapeutic activities, such as anti-inflammatory effects. It has shown to reduce the expression of tumor necrosis factor alpha, nitric oxide, and interleukin-1β in a liver injury model using rats [13]. In addition, *P. crocatum* also exhibits wound healing activities by increasing the expression of superoxide dismutase 1, alpha-smooth muscle actin, and E-cadherin, and reducing p53 in hyperglycemic fibroblasts [14]. It has antibacterial properties when used topically [15]. *P. crocatum* acts as an antioxidant by reducing the expression of ROS and increasing glutathione peroxidase and cytochrome P450 2E1 [16]. It also demonstrates antihyperglycemic effects when administered orally [17].

Based on relevant studies on *P. crocatum* and its various mechanisms, *P. crocatum* can be used as a base ingredient for cookie-based therapies for the prevention of DFU. If the reduction of MMP-9 is recognized as a beneficial therapeutic target for DFU treatment [18], MMP-9 would also be a favorable target for DFU prevention. This is because the activity and expression of vascular MMP-9 in patients with diabetes mellitus are inherently elevated [19]. Furthermore, the gelatinase MMP-9 plays a crucial role in the pathogenesis of diabetic neuropathy through axonal demyelination, which is one of the risk factors for DFU [6]. Therefore, this study aims to identify the effectiveness of *P. crocatum* cookies with Golden Rice as the

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main ingredient for preventing DFUs through the regulation mechanism of MMP-9.

Methods

Study Design

This randomized controlled trial will be conducted at a public health center in Makassar, Indonesia, following a 2-arm, parallel-group, randomized, double-blind, placebo-controlled design. The study protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist (Multimedia Appendix 1). Figure 1 shows the flowchart detailing participant enrollment, allocation, intervention, and assessment, and Table 1 presents the participant timeline.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart for participant recruitment and progress through a randomized controlled trial investigating the efficacy of Golden Rice cookies with Piper crocatum (*P. crocatum*) active extract in preventing foot ulcers among patients with diabetes at a public health center in Makassar, Indonesia, from November to December 2023.

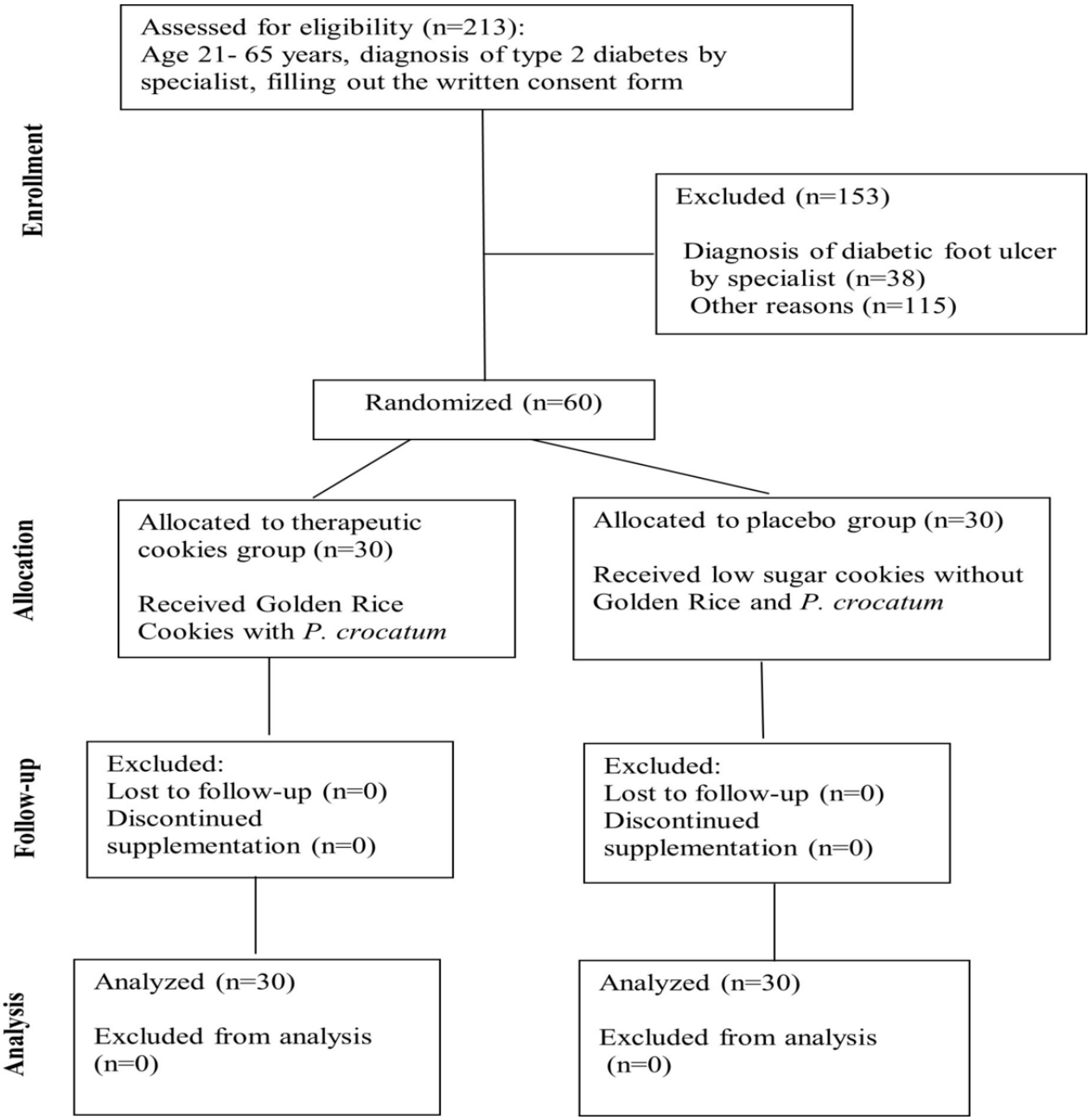

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Table 1. Participant timeline in a randomized controlled trial investigating the efficacy of Golden Rice cookies with Piper crocatum active extract in preventing foot ulcers among patients with diabetes at a public health center in Makassar, Indonesia, from November to December 2023.

Activities	Enrollment	Allocation	Postallocation		Close-out
	Week 1	Week 2	Week 3	Week 4	Week 5
Enrollment					
Eligibility screening	✓				
Informed consent	✓				
Randomization		✓			
Allocation		✓			
Patients training		✓			
Intervention					
Supplementation			✓	✓	
Compliance			✓	✓	
Adverse events			✓	✓	
Assessment					
Demographics		✓			✓
Clinical information		✓			✓
Neuropathy score		✓			✓
Ankle-brachial index		✓			✓
Random blood glucose		✓			✓
Supplement checklist					✓

Outcomes

The main focus of this study, or the primary outcome, is determining the level of MMP-9. The secondary outcomes include examining neuropathy scores and ankle-brachial index (ABI) as well as assessing random blood glucose.

Randomization and Blinding

After obtaining informed consent and discussing the research objectives, a total of 60 eligible participants will be divided into 2 equal groups. Block randomization with a 1:1 allocation ratio will be used. An assistant will conduct the block randomization, ensuring that both the investigators and participants remain blinded to the intervention allocation. The sequence of the blocks will be generated using a random numbers table. All participants will be randomly assigned to either the intervention group or the placebo group. The manufacturer responsible for preparing the supplements will be requested to label the cans containing either therapeutic cookies or placebos with a unique code.

Sample Size Calculation

With a significance level (type 1 error) of 5% and a statistical power of 90%, the sample size for each study group will be calculated to be 25, using a 2-sided *t* test, taking into account the changes in MMP-9 values as one of the primary outcomes [20]. We will clarify that the block lengths in our randomization process will be constant. To account for an estimated attrition rate of approximately 20% during the study, the final sample size will be increased to 30 participants in each group. The estimation of the sample size is calculated using the following formula:

In this formula, α=5%, 1-β=90%, SD1=2.7, SD2=2.7, *d*=2.5.

Cookies Production

Cookies will be created by following the formula provided by Olawoye et al [21], with some modifications. They will be made with a low glucose ingredient composition, resulting in each cookie containing 51 calories, with a composition of 1% carbohydrates, 6% fat, 4% cholesterol, and 4% fiber, free from gluten, sugar, and salt. Following the optimal conditions for producing gluten-free cookies for patients with diabetes, the cookies are baked at a temperature of 158°C for 20 minutes. The procedure is modified by incorporating 20% Golden Rice extract and 10% *P. crocatum* ethanol extract. Each extract will be prepared using the maceration method with 96% ethanol, and its yield will be calculated. The specific details of the *P. crocatum* extraction procedure are mentioned in a previous study [14].

Intervention

A total of 60 eligible participants diagnosed with type 2 diabetes will be assigned randomly to either the therapeutic cookies group (n=30) or the placebo group (n=30). Over 14 weeks, participants in the intervention group will take therapeutic cookies (20 g) twice daily, while participants in the control group will take identical placebo cookies. The therapeutic cookies will be provided by Evelyn Food Supplement company,

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chosen for their reputation for providing high-quality, standardized ingredients, which is essential for the integrity of the study. Both therapeutic and placebo cookies will be indistinguishable in terms of weight, size, shape, taste, color, and odor. The placebo cookies are also produced by Evelyn Food Supplement company. The choice of company was made to maintain the highest research standards and to ensure that there are no conflicts of interest, financial support, or other compensation for the researchers.

The trial will consist of 3 study visits: before the intervention, 1 week after the intervention, and at the end of the intervention period. Study participants will receive instructions on how to use their supplements and will be followed up with phone calls every 3 days throughout the study. Compliance will be assessed by evaluating the number of unused supplements returned by each individual, with the remaining cookies counted to determine total supplement intake. Additionally, participants will be asked to maintain a reporting diary to document any adverse events experienced following the consumption of therapeutic cookies. If any adverse events are attributed to the consumption of therapeutic cookies, participants will be instructed to discontinue taking the supplements and will be promptly referred to a specialist for appropriate treatment. The study participants will not receive any specific dietary recommendations or dietary regimens.

Blood Sample Collection

Blood samples for the identification of MMP-9 will be collected from each participant at a specific time point in the morning, following an overnight fast. The samples will be drawn at approximately 8 AM to ensure consistency and minimize potential variations in MMP-9 levels due to diurnal rhythms. This fasting state collection will aim to provide a baseline measurement of MMP-9 levels. Additionally, blood samples will be collected both before and after the intervention involving the administration of cookies to assess potential changes in MMP-9 levels in response to the intervention.

Measures and Measurements

Demographic Questions

Participants will be requested to provide information about their gender, age, marital status, the medication and herbs currently being consumed, profession, educational level, distance from the place of residence to the nearest health care service, residence in a city or rural area, duration of having diabetes, and any other diseases or illnesses experienced.

Primary Outcome

A blood sample of 5 mL will be collected, and the samples will be centrifuged at 3000 rpm for 5 minutes to separate the serum samples before and after the intervention. The levels of MMP-9 will be determined using western blotting in triplicate. Proteins will be extracted using M-PER Mammalian Protein Extraction Reagent (Thermo; catalog number 87785) according to the manufacturer's instructions. Protein quantification will be performed using Pierce 660 nm protein assay reagent (Thermo; catalog number 22660). The proteins will be separated on a 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a polyvinylidene fluoride membrane (Immun-Blot, Bio-Rad). Then, the membrane will be incubated with specific primary antibodies, including anti–MMP-9 (catalog number EP1254; anti-rabbit; 1:500 dilution) and anti–β-actin (catalog number ab8227; anti-rabbit; 1:1000 dilution). Blocking will be performed using 5% skim milk in Tris-Buffered Saline with Tween 20, followed by incubation with the appropriate secondary antibody. The protein bands will be visualized using enhanced chemiluminescence Prime Western Blotting Detection Reagents (GE Health Care; catalog number RPN2232), and the blots will be captured using a Gel Doc machine (Geldoc Syngene Gbox Seri Chemi xrq) [22].

Secondary Outcomes

The secondary outcomes include examining neuropathy score, ABI, and random blood glucose. The neuropathy score will be assessed following a previous study [23], using a 10-g Semmes-Weinstein Monofilament. During the monofilament testing, the participants will be instructed to lie flat on the examination table. To ensure that they could not see their feet, a standard monofilament (5.07/10-gram Semmes-Weinstein nylon monofilament) will be used to lightly apply pressure to three specific areas of the participants' feet: (1) the underside of the first metatarsal head, (2) the underside of the fifth metatarsal head, and (3) the top surface between the first and second metatarsals. The monofilament will be positioned on the foot's surface, forming a perpendicular angle with the skin. The pressure will be gradually intensified until the filament is bent, indicating the application of a predetermined level of pressure. The sites will be examined in a random order, rather than following a specific sequence. If the examinee provided the correct response at any site during the test, further testing at that site was not necessary. However, if the examinee could not correctly identify the interval in which the stimulus was applied, the test would be repeated at that site up to 2 times, aiming to obtain 2 similar correct responses. A site will be considered sensate if either the first response is correct or 2 out of 3 tests yield a correct response. On the other hand, a site will be classified as insensate if there are 2 incorrect responses and 2 "unable to determine" responses or 1 incorrect response and 1 "unable to determine" response. The presence of an insensate area at any of the 3 sites indicates a positive result for peripheral neuropathy in the monofilament test [24,25].

The ABI will be determined by measuring the systolic blood pressure in the arm and leg after a 10-minute rest in a supine position, with both arms and legs straight and relaxed [26]. Manual cuffs will be used for all blood pressure measurements, and the appropriate cuff size will be selected based on the arm circumference determined during screening. The same cuff size will be used for the lower leg, and a straight wrapping technique will be employed. The arm blood pressure will be measured using a sphygmomanometer along with an 8 MHz Doppler device to detect pulses. A single measurement will be taken at each of the 6 sites in the following sequence: left arm, left ankle (dorsalis pedis and posterior tibialis), right arm, and right ankle. The right ABI will be calculated by dividing the higher-pressure measurement from the right ankle (dorsalis pedis or posterior tibialis) by the higher brachial pressure (right or left side). The left ABI will be calculated using a similar method. The lower

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ratio from either side will be considered as the participant's ABI [27].

To evaluate the random blood glucose levels, blood samples will be obtained from the capillary of the index finger for each patient. Subsequently, the Accu-Chek Active glucometer, a device manufactured in Germany, will be used to measure the samples, and the recorded values will be documented [28].

Statistical Analyses

The demographic characteristics of all participants will be summarized using descriptive statistics, such as means (SDs), frequencies, and ranges, which will be presented in a tabular form. Statistical analysis of the data will be performed using the SPSS statistical software (version 2, SPSS Inc). $P<.05$ will be considered statistically significant. The normality of the data will be assessed using the Kolmogorov-Smirnov test. Numerical variables will be presented as mean (SD) or median (IQR) values, while categorical variables will be presented as frequency (percentages). To determine differences in numerical variables between the therapeutic cookies and placebo groups, independent sample *t* tests or Mann-Whitney *U* tests will be used. The same tests will also be used to compare alterations in outcome variables between the 2 groups. For within-group comparisons, paired-sample *t* tests or the nonparametric Wilcoxon test will be used. To account for the effects of confounding factors, a general linear model will be applied. In addition, analysis of covariance will be used to account for the effects of confounding factors when appropriate.

Ethical Considerations

Prior to the commencement of this study, ethical review and approval were obtained from the local ethical committee of the Public Health Faculty of Universitas Hasanuddin, Makassar, Indonesia (approval number 10973/UN4.14.1/TP.01.02/2023). This study adheres to all applicable ethical guidelines and regulations governing research involving human subjects.

Informed consent was obtained orally from all participants involved in the primary and data collection. In the case of secondary analyses of research data, the original informed consent, as approved by the institutional review board, explicitly allowed for secondary analyses without the need for additional consent. Participants were informed that their data would be used for research purposes beyond the initial study.

The privacy and confidentiality of participants in this research were rigorously protected. All data collected were anonymized or deidentified to ensure the confidentiality of participants. Any personal identifying information was removed, and data were stored securely to prevent unauthorized access.

Participants received compensation in the form of monetary compensation for their time and participation. The compensation amount was set at IDR 100,000/week (US $7-8/week) and was disclosed to participants during the informed consent process.

The study has been registered on the Thai Clinical Trials Registry website (TCTR20230502001). Any changes to the study protocol will be communicated to the Trials journal.

Results

The recruitment and testing phase started in January 2024. The study is scheduled to be completed by the end of March 2024. Data analysis will commence in April 2024, and the publication of the results is anticipated in the same year (2024).

Discussion

Expected Outcomes

This study focuses on the significant issue of DFUs in patients with diabetes and the importance of preventing DFUs and associated amputations. DFUs affect approximately 6.4% of the global diabetic population [29], reduce quality of life, prolong hospital stays, and lead to a considerable number of lower limb amputations globally each year [30]. Notably, peripheral neuropathy, the most prevalent type of diabetic neuropathy, plays a critical role in the development of DFUs due to its impact on sensory function and increased susceptibility to ulcers [31].

In the realm of diabetic neuropathy, MMP-9 is considered crucial in its progression and holds a potential target for treatment purposes [32]. Furthermore, it is important to acknowledge that elevated blood sugar levels and insulin resistance in diabetes contribute to the generation of ROS, intensifying the complications associated with the disease [33]. The activity of MMP-9 is heightened in individuals with diabetes, partially due to increased production by vascular endothelial cells and the influence of ROS [33].

MMP-9 plays a role in increasing tissue inflammation, which is one of the contributing factors to diabetic neuropathy [32]. By reducing MMP-9 activity, we can decrease inflammation that harms peripheral nerves. MMP-9 can damage blood vessel walls, leading to impaired blood circulation to nerves [34]. Reducing vascular damage can enhance blood flow to nerves, aiding in the prevention of neuropathy. Additionally, MMP-9 can harm the extracellular matrix surrounding nerve cells. If MMP-9 is reduced, the extracellular matrix may be better preserved, offering improved protection against nerve damage. Excessive MMP-9 activity has been linked to apoptosis or nerve cell death [35]. By reducing MMP-9 activity, we can help safeguard nerve cells from death, which contributes to neuropathy. Furthermore, MMP-9 can contribute to nerve degeneration and loss of nerve function. Lowering MMP-9 can assist in slowing down or halting this degenerative process [36].

The main interest of this study is the concept of diabetic-friendly cookies, which can stimulate insulin production in the body by boosting the beta pancreas and decreasing the glycemic index through the mechanism of MMP-9 reduction. To further support the reduction in glycemic index and prevent DFU, the suitable herbal ingredients for combination in these cookies are Golden Rice and *P. crocatum*. They are known for their safety and therapeutic activities, such as anti-inflammatory effects, wound healing activities, antibacterial properties, antioxidant effects, and antihyperglycemic effects. The oral consumption of *P. crocatum* and Golden Rice extracts has been proven to be safe in humans. A functional beverage containing *P. crocatum* was

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developed, demonstrating significant antioxidant and antidiabetic properties, and it was acceptable by consumers [37]. A recent study has also identified the use of *P. crocatum* as a healthy food and drink option for reducing blood sugar levels in patients with diabetes mellitus [38].

The reduction of MMP-9 as the study objective may not be sufficient to completely prevent diabetic neuropathy, as this disease is highly complex and involves numerous factors. However, reducing MMP-9 can be a potentially helpful step in mitigating the risk and impact of diabetic neuropathy, particularly when combined with other appropriate treatment approaches.

This study explores the biological mechanisms underlying diabetic neuropathy and the potential role of MMP-9, providing valuable insights into the pathophysiology of DFUs and potential therapeutic targets. The safety and acceptance of *P. crocatum* and Golden Rice extracts in humans, as demonstrated in previous studies, support the feasibility of incorporating these ingredients into dietary interventions to prevent DFUs.

Although this study delves into biological mechanisms and potential therapeutic interventions, the translation of these laboratory findings into clinical applications may require further research and clinical trials. The study may have limitations regarding the generalizability of its findings. It is essential to acknowledge that dietary interventions may have varying effects on individuals with different demographics, comorbidities, and genetic factors. The study duration is also considered a limitation, as it does not cover a long-term assessment of the effects of cookies and herbal ingredients.

Conclusions

In conclusion, the findings of this study hold the potential to significantly influence the strategies used by health care practitioners in enhancing diabetes self-management, particularly in the domain of therapeutic snacking, for patients diagnosed with diabetes mellitus. Considering the substantial burden of DFUs on patients, health care systems, and society, it is crucial to focus on preventing DFUs and amputations. Exploring potential therapeutic targets like MMP-9 and using natural ingredients like *P. crocatum* in combination with other diabetes-friendly products may provide promising avenues for preventing DFUs and improving the outcomes for patients with diabetes. Further research and clinical trials would be necessary to validate the efficacy and safety of such interventions. These insights can inform the selection of strategies for health care practitioners to enhance diabetes self-management, thereby benefiting patients with diabetes mellitus.

Acknowledgments

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The authors would like to express their gratitude to all participants for their valuable contributions.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to patient confidentiality concerns but are available from the corresponding author upon reasonable request. All requests will be subject to review and approval on a case-by-case basis. We are dedicated to making the data available, where possible, while ensuring the protection of participants' confidentiality and privacy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 115 KB - resprot_v13i1e49940_app1.pdf]

Multimedia Appendix 2
Consort checklist.
[PDF File (Adobe PDF File), 1194 KB - resprot_v13i1e49940_app2.pdf]

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Abbreviations

ABI: ankle-brachial index
DFU: diabetic foot ulcer
MMP-9: matrix metalloproteinase-9
***Piper crocatum*:** *P. crocatum*
ROS: reactive oxygen species
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Improving Health Professional Recognition and Response to Child Maltreatment and Intimate Partner Violence: Protocol for Two Mixed Methods Pilot Randomized Controlled Trials

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Abstract

Background: The optimal educational approach for preparing health professionals with the knowledge and skills to effectively recognize and respond to family violence, including child maltreatment and intimate partner violence, remains unclear. The Violence, Evidence, Guidance, and Action (VEGA) Family Violence Education Resources is a novel intervention that can be completed via self-directed learning or in a workshop format; both approaches focus on improving health professional preparedness to address family violence.

Objective: Our studies aim to determine the acceptability and feasibility of conducting a randomized controlled trial to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of VEGA, as an adjunct to standard education, to improve learner (*Researching the Impact of Service provider Education [RISE] with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters.

Methods: The *RISE with Residents* and *RISE with Veterans* research studies use embedded experimental mixed methods research designs. The quantitative strand for each study follows the principles of a pilot randomized controlled trial. For *RISE with Residents*, we aimed to recruit 80 postgraduate medical trainees; for *RISE with Veterans*, we intended to recruit 80 health professionals who work or have worked with Veterans (or their family members) of the Canadian military or the Royal Canadian Mounted Police in a direct service capacity. Participants complete quantitative assessments at baseline, after intervention, and at 3-month follow-up. A subset of participants from each arm also undergoes a qualitative semistructured interview with the aim of describing participants' perceptions of the value and impact of each VEGA modality, as well as research burden. Scores on potential outcome measures will be mapped to excerpts of qualitative data via a mixed methods joint display to aid in the interpretation of findings.

Results: We consented 71 individuals to participate in the *RISE with Residents* study. Data collection was completed on August 31, 2023, and data are currently being cleaned and prepared for analysis. As of January 15, 2024, we consented 34 individuals in the *RISE with Veterans* study; data collection will be completed in March 2024. For both studies, no data analysis had taken place at the time of manuscript submission. Results will be disseminated through peer-reviewed publications; academic conferences; and posting and sharing of study summaries and infographics on social media, the project website, and via professional network listserves.

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Conclusions: Reducing the impacts of family violence remains a pressing public health challenge. Both research studies will provide a valuable methodological contribution about the feasibility of trial methods in health professions education focused on family violence. They will also contribute to education science about the differences in the effectiveness of self-directed versus facilitator-led learning strategies.

Trial Registration: ClinicalTrials.gov NCT05490121, https://clinicaltrials.gov/study/NCT05490121; ClinicalTrials.gov NCT05490004, https://clinicaltrials.gov/study/NCT05490004

International Registered Report Identifier (IRRID): DERR1-10.2196/50864

(JMIR Res Protoc 2024;13:e50864) doi:10.2196/50864

KEYWORDS

medical education; health professions education; child maltreatment; intimate partner violence; mixed methods; pilot trial; qualitative description; family violence

Introduction

Background

The prevention of family violence, which includes intimate partner violence (IPV) and child maltreatment, remains a global public health priority. IPV encompasses a range of behaviors by a current or former romantic or sexual partner that causes or can cause physical, psychological, or sexual harm, including physical assault or violence, sexual coercion or assault, threats of harm, stalking or surveillance, and verbal degradation or humiliation [1]. Child maltreatment refers to adverse caregiver or parent behavior, including physical, sexual, or emotional abuse; physical or emotional neglect; coercive control; and exposure to IPV between adult caregivers, which result in actual or potential physical or emotional harm to the child. Globally, up to 1 in 3 children are exposed to at least 1 form of maltreatment before the age of 18 years [2-4]. Similarly, 27% of ever-partnered women between the ages of 15 and 29 years will experience IPV in their lifetime, with 24% of women aged 15-19 years and 26% of women aged 19-24 years having experienced IPV before the age of 15 years [5]. The literature details a significant and positive association between exposure to child maltreatment and increased vulnerability to IPV victimization over the life course [6,7]. In addition, a fulsome and consistent body of evidence demonstrates that exposure to child maltreatment or IPV is associated with a range of health-risk behaviors and negative health outcomes, including significantly elevated risk for early-onset smoking and alcohol use, teen pregnancy, underimmunization, obesity, heart disease, chronic pain conditions, substance abuse, suicide attempts, posttraumatic stress disorder, eating disorders, depression, anxiety, among others [1,8-10]. Importantly, the prevalence of child maltreatment and IPV in families of Active Duty and Veteran service members is even higher. For example, nearly 63% of Active Duty and Veteran members of the Canadian Armed Forces (CAF) report exposure to maltreatment in childhood [11], and upward of 25% of Active Duty or Veteran members of the CAF (or whose partner is a member or a Veteran of the CAF) self-report IPV victimization or perpetration in their lifetime [12-14]. Among this subgroup of the population, a history of child maltreatment or IPV exposure is also associated with a range of physical and mental health disorders, which can be exacerbated by deployment-related traumatic experiences, including military sexual trauma; receipt of incoming artillery, rocket, or mortar fire; or knowing someone seriously injured or killed while deployed [11,15].

Critically, a growing compilation of clinical guidance and guidelines indicates that the probability for negative health outcomes related to family violence exposure, including child maltreatment and IPV, can be attenuated via early interaction with a health care professional that is considerate and who prioritizes not only physical and emotional safety in the health care encounter but also the broader social, psychological, and physical health needs of an exposed patient [4,16-20]. For this reason, health professionals have been identified as having an essential role in family violence prevention via recognizing and responding to this exposure and its associated sequelae in their health care practice. Unfortunately, several studies detail uniform challenges to family violence recognition and response across the health professions, including limited formal curriculum during preservice training, discomfort and a lack of confidence related to asking about and responding to family violence disclosures, and the perception that there is insufficient time to adequately address family violence disclosures in health care practice [21]. Paralleling these barriers is a dearth of evidence regarding how to best prepare health professionals with the knowledge and skills to effectively recognize and respond to suspected or disclosed family violence exposures in health care contexts [21,22]. It is also unclear whether family violence education efforts should be optimally targeted to preservice versus in-service health professionals, nor is it clear the extent to which repeated exposure to family violence curriculum is necessary to achieve and maintain professional competencies in this area.

Broadly, educational interventions focusing on family violence, which have been evaluated in undergraduate, postgraduate, and continuing education contexts, vary in their instructional approaches and often fail to consider active controls in their research designs [22-27]. In addition, there has been limited emphasis on developing and evaluating interventions that address the complex overlap between IPV, children's exposure to IPV, and other forms of child maltreatment [28,29]. Given the prevalence, overlap, and health-related burdens of child maltreatment, IPV, and children's exposure to IPV, there is an urgent need to identify empirically supported educational interventions that adequately prepare the health professionals to care for individuals and families impacted by all forms of family violence. Additionally, the field of health professions

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education stands to benefit from research studies that provide evidence for the optimal educational approach (eg, self-directed learning vs facilitator-based approaches) to improve health professionals' knowledge and skills in complex areas, such as family violence. This methodological contribution can also offer guidance on whether the optimal educational approach varies according to the health professional's status as a learner or an independent practitioner.

Aims

The objective of our 2 complementary studies are to determine the acceptability and feasibility of conducting a randomized controlled trial (RCT) to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of the Violence, Evidence, Guidance, and Action (VEGA) Family Violence Education Resources [30], as an adjunct to standard education, to improve learner (*Researching the Impact of Service provider Education [RISE] with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters. Detailed information about the VEGA Family Violence Education Resources (hereafter referred to as "VEGA") is available on the web [31] and in the *Methods* section. Briefly, VEGA was developed based on systematic reviews and consultations with members of 22 national health care and social service organizations in Canada [30]. VEGA is a web-based suite of resources that uses a participatory, encounter-focused curriculum across 4 learning modules that focus on the following areas of family violence: (1) the epidemiology of child maltreatment, IPV, and children's exposure to IPV in Canada; (2) evidence-informed strategies for safely recognizing and responding to (a) child maltreatment and (b) IPV (including children's exposure to IPV) in health care encounters; and (3) principles for ensuring physical and emotionally safe health care encounters for family violence discussions [30]. VEGA can be completed as a self-directed educational activity (ie, self-directed VEGA) via completion of the web-based modules at the learner's own pace, or as a remote or face-to-face workshop (ie, workshop VEGA). VEGA workshops are delivered by trained facilitators who are also regulated and practicing health care professionals; both self-directed VEGA and workshop VEGA take approximately 3 hours to complete [21,30].

Methods

Study Design

The *RISE with Residents* and *RISE with Veterans* research studies use quantitatively dominant, embedded experimental mixed methods research design ("QUAN(qual)") [32]. The use of this design allows for the measurement of important acceptability and feasibility metrics related to enrollment, retention, attrition, and data completeness and the generation of exploratory estimates of the education effect for both VEGA modalities. This design also allows for the systematic collection of qualitative data to provide important contextual information regarding the tenability of a full RCT, as well as a description of how VEGA modalities influence any measured changes in health professional preparedness, knowledge, and skills related to recognizing and responding to family violence. Given the cost and complexity of implementing RCTs, as well as well-documented challenges related to recruiting and retaining health professionals in clinical and education research [33-35], pilot randomized studies that allow for responsive amendments to recruitment, retention, and data collection are an imperative proviso to reduce the possibility of failed or incomplete phase-3 RCTs [36-38].

Quantitative Strand of Data Collection

Quantitative Design and Participants

The quantitative research design for both studies follows the principles of a 2-armed pilot RCT [37,38]. Figures 1 and 2 detail the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow diagrams for *RISE with Residents* and *RISE with Veterans*, respectively [39,40]. For *RISE with Residents*, we aimed to recruit a voluntary sample of 80 participants from postgraduate medical residency programs in psychiatry or pediatrics in Ontario, Canada. Directors of each program were asked to circulate recruitment-related materials to their respective program residents, requesting that interested individuals contact the research team to determine eligibility and complete consenting procedures. For *RISE with Veterans*, we aimed to recruit a voluntary sample of 80 health professionals who currently work or have worked in a direct service capacity with Veterans of the Canadian military or the Royal Canadian Mounted Police (RCMP), or their family members, to participate. Directors of Veteran-serving programs, agencies, and organizations had the opportunity to meet with members of the research team to discuss the components of the study and were asked to distribute recruitment materials to potentially eligible staff. Recruitment materials requested that those who were interested in participating contact the research team.

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Figure 1. RISE with Residents SPIRIT flow diagram. RISE: Researching the Impact of Service provider Education; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; VEGA: Violence, Evidence, Guidance, and Action.

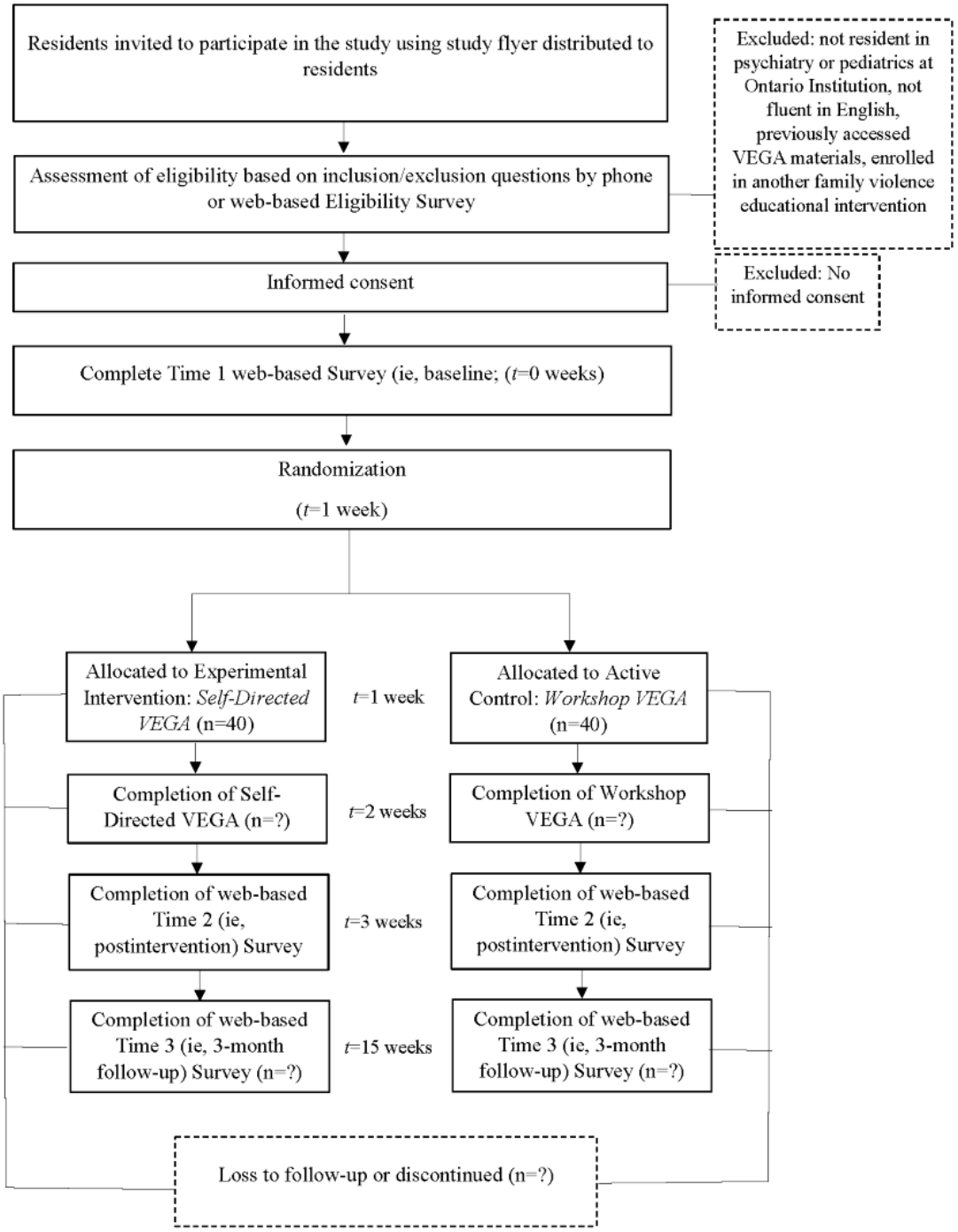

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Figure 2. RISE with Veterans SPIRIT flow diagram. RISE: Researching the Impact of Service provider Education; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; VEGA: Violence, Evidence, Guidance, Action.

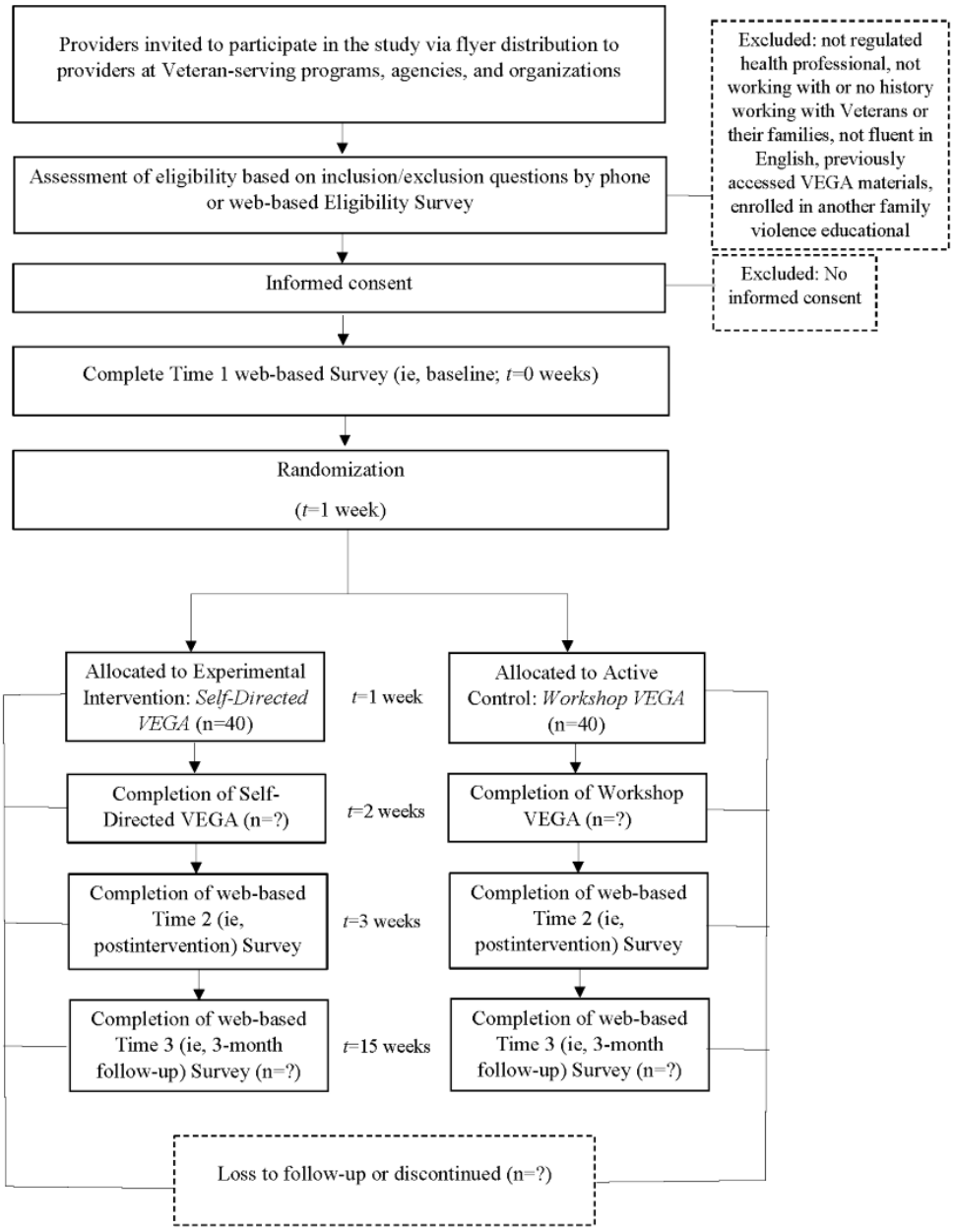

Eligibility Criteria

Eligibility screening was completed over the phone with the study research coordinator (RC) or electronically via REDCap (Research Electronic Data Capture; Vanderbilt University) using the eligibility criteria outlined in Textbox 1. At this time, we also collected sociodemographic characteristics of participants, including age, sex at birth, and self-identified gender. For *RISE with Residents*, we also included information about their residency program; *RISE with Veterans* additionally asked questions about the organization the participants work for, whether they work directly with Veterans of the military or the RCMP, or their family members, and if the latter, whether consent is required by the Veteran for the participant to provide services to the Veteran's family member. We obtained consent from potential participants to keep their responses to the screening measures in cases they were ineligible or did not end up participating in the study. This was for the purpose of comparing those who end up participating with those who do not end up participating to understand if our criteria are systematically excluding any groups. After completing screening, individuals were informed of their eligibility to participate and underwent an electronic informed consent process to participate in the remainder of research activities. Potential participants were provided the option to speak with a member of the research team to review any questions about the consent procedures and research process.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- *Researching the Impact of Service provider Education (RISE) with Residents*
  - Physician resident enrolled in a postgraduate medical residency program in psychiatry or pediatrics within Ontario, Canada
  - Willing and able to provide informed written consent and complete all project activities in English
- *RISE with Veterans*
  - 18 years of age or older
  - Regulated health care or social service professional
  - Working with military or Royal Canadian Mounted Police (RCMP) Veterans, or military or RCMP Veteran's family members in a direct service capacity at least 1 day per week

    OR

    Have 2 years of experience working with military or RCMP Veterans, or their family members, in a direct service capacity

    OR

    Have worked with 15 or more clients or patients who were either military or RCMP Veterans, or their family members, in a direct service capacity
  - Willing and able to provide informed written consent and complete all project activities in English

Exclusion criteria

- *RISE with Residents*
  - Have previously accessed the Violence, Evidence, Guidance, and Action (VEGA) web-based or workshop materials
  - Are currently enrolled in or expected to enroll in any other educational intervention focused on family violence (intimate partner violence [IPV], child maltreatment, childhood exposure to IPV) within the study time period
- *RISE with Veterans*
  - Have previously accessed the VEGA materials
  - Are currently enrolled in or expected to enroll in any other educational intervention focused on family violence (IPV, child maltreatment, or childhood exposure to IPV) within the study time period

Randomization and Concealment

Randomization occurred after consent has been obtained and the web-based baseline survey (ie, time 1 survey, see below) is complete. To reduce the possibility of "availability bias," we required the accumulation of 20 consenting participants who indicated their availability to attend a VEGA workshop before randomization, as each VEGA workshop requires a minimum of 10 participants. The cohort of 20 consenting participants were then randomly assigned to the experimental (ie, self-directed VEGA) or active control (ie, workshop VEGA) condition using stratified block randomization [41] with a block size of 4 (blocking factor of 2), using a third-party, internet-based randomization service, Randomize.net. For *RISE with Residents*, randomization was stratified based on two variables: (1) sex at birth (female, male, intersex, or prefer not to answer) and (2) discipline (pediatrics vs psychiatry). For *RISE with Veterans*, randomization was stratified based on sex at birth only. Sex at birth, as opposed to gender identity, was selected as the stratification variable because of a limited number of categories needed to achieve balance across trial arms. The analysis section outlines our proposed approach to disaggregate sex- and gender-based data after the conclusion of both studies.

Masking

Given the nature of experimental and control arms, it is impossible to conceal allocation status from participants, as well as the facilitators of the active control arm (ie, workshop VEGA). Participants were informed of their allocation status by the RC. The RC did not reveal participant allocation status to the study research assistant, the latter of whom was responsible for ensuring quantitative data collection. Participants were also encouraged not to inform the research assistant of their allocation status.

Intervention

VEGA Family Violence Education Resources

Time for completion of self-directed VEGA or workshop VEGA is approximately 3 hours, and pedagogical elements for both approaches have been informed by education scholarship (see Table 1) [42-51]. Participants had or have the option of completing self-directed VEGA in either English or French as the VEGA website offers the content in both languages. Workshop VEGA is delivered in English only in a remote or in-person workshop format by trained facilitators who are regulated health professionals. VEGA workshops are

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recommended to have a 10:1 participant-to-facilitator ratio and are standardized via the use of a flexibly structured facilitator guide [30].

Table 1. Pedagogical elements of self-directed VEGA (ie, experimental arm) and workshop VEGA (ie, active control arm) educational approaches.

Pedagogical elements	Self-directed VEGA[a] (experimental arm)	Workshop VEGA (active control arm)
Didactic material [48]	Asynchronous reading	Synchronous lecturing with 2 facilitators
Deliberate practice [49,50]	Case-based animated simulations	Case-based role play
Enabling learning tools [51]	Remote patients, clinical handbook, clinical scripts	Remote patients, clinical handbook, clinical scripts
Test-enhanced learning [46]	Individual multiple-choice questions with response feedback	Group-based polling (ie, multiple-choice) and feedback

[a]VEGA: Violence, Evidence, Guidance, and Action.

Experimental Arm (Self-Directed VEGA)

If a participant is randomized to the experimental arm, they will be or were asked to complete self-directed VEGA at their convenience, within 1 week of being informed of their allocation status. To complete the intervention, individuals are asked to register their access to the VEGA Resources and review and complete all module activities at their own pace during the weeklong intervention period [30].

Active Control Arm (Workshop VEGA)

If a participant is randomized to the active control arm, they will be or were informed that they need to attend a remote VEGA workshop. Because of COVID-19 restrictions in place at the outset of both studies, VEGA workshops take place via Zoom and are delivered by 2 trained facilitators. Workshops include 10 to 20 participants, keeping the recommended 10:1 participant-to-facilitator ratio, and last 3 hours [30].

Intervention Adherence

Intervention adherence is monitored by the RC. The RC has received or will receive attendance reports for participants allocated to VEGA workshops from the VEGA project team, who will also provide the research team confirmation of whether self-directed participants completed the “Self-Declaration of Module Completion Form” embedded within the self-directed VEGA website. Self-directed VEGA participants receive email reminders from the RC every 2 days to complete the modules within the intervention window [30].

Data Collection

The primary outcomes for the *RISE with Residents* and *RISE with Veterans* research studies are related to the acceptability and feasibility of RCT implementation. To this end, the RC tracked or is tracking the number of individuals for each study who (1) agreed to be screened, (2) are eligible for participation, and (3) enroll. We are also recording the number of (4) emails or phone calls needed to arrange all research assessments and the number of participants who (5) drop out, (6) could not be reached for follow-up, (7) complete the interventions, and (8) partially complete versus fully complete secondary outcome research assessments. As an indicator of feasibility, we are also recording the total time to complete all secondary outcome research assessments and track the number of protocol amendments (if any) and their rationale. Acceptability and feasibility metrics will be matrixed alongside sociodemographic characteristics (sex at birth, gender, age, etc) of screened and consented participants.

Table 2 details the list the measures that are being used to assess the secondary (ie, education-related) outcomes and their correlates in the *RISE with Residents* and *RISE with Veterans* research projects and their respective overlap. The research assistant is administering research assessments of family violence knowledge and skills via REDCap to participants in both studies at 3 time points: the week before they begin their VEGA intervention (time 1), posteducation (ie, postintervention; time 2), and 3 months after the time 1 survey is completed (time 3). Participants are being asked to complete the surveys within 1 week, from the date they are initially sent, on their own time. Each assessment takes approximately 30 minutes to complete.

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Table 2. Quantitative research assessments for *RISE with Residents* and *RISE with Veterans*.

Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Postedu-cation	3-month follow-up	Baseline	Postedu-cation	3-month follow-up
Adapted Brief Individual Readiness to Change Scale (BIRCS) [52]: The original BIRCS was developed by Goldman [52] to assess health professional readiness to learn and implement new evidence-based practices in the field of addictions; respondents were asked to indicate on a 5-point Likert scale the extent to which they disagreed (0=strongly disagree) or agreed (4=strongly agree) with 5 statements about their use of "direct service techniques that are based on research" (eg, I believe I have the skills to use them; I believe I have the flexibility to use them). For the purposes of our research, we adapted the items to be specific to child maltreatment, added 2 items (eg, "I believe I have the knowledge to recognize and respond to all forms of child maltreatment in my practice"; "I am motivated to learn about child maltreatment"), and replicated the set of items for intimate partner violence (IPV) (ie, BIRCS—Child Maltreatment; BIRCS—IPV). After reverse scoring 1 item, the mean score of the responses for each scale is used to interpret the results, with a higher mean score indicative of a greater readiness to make practice changes related to child maltreatment or IPV.	✓	—[b]	—	✓	—	—
Adapted Child Maltreatment Vignette Scale (CMVS) [53,54]: For the original CMVS, respondents are prompted to review 14 distinct analog vignettes that depict a range of signs and symptoms of child maltreatment exposure. On completing their review of each vignette, participants are asked to indicate their responses to four items: (1) "is this child being maltreated" (yes/no); (2) "please indicate how confident you are in your response (50%-100%, your answer must be between 50% and 100%)"; (3) "would you report this case to children's services?" (yes/no); and (4) "please indicate how confident you are in your response (50%-100%, your answer must be between 50% and 100%)." With permission from the original authors, the measure was adapted to the Canadian context via removing 1 scenario from the measure (due to concerns about multiple maltreated children), amending physician-focused language to "health professional" and changing (1) for each vignette to "for any child/youth in this scenario, do you have a reason to suspect child maltreatment?" (yes/no) and changing (3) for each vignette to "would you report this case to Child Welfare Services?" (yes/no). Adaptations were made in consultation with clinical experts in child maltreatment impact assessment at a tertiary care center in Ontario, Canada. Responses to (1) and (3) for each vignette will be scored as either correct ("1") or incorrect ("0") as predetermined, a priori; a mean "knowledge and skill accuracy" score is generated for analysis, with higher scores indicative of greater knowledge and skill accuracy related to child maltreatment.	✓	✓	✓	✓	✓	✓
Mandatory Reporting Self-Efficacy Scale (MRSES) [55]: The MRSES is a 7-item measure that asks respondents to indicate the extent to which they perceive their ability to implement a series of behaviors related to mandatory reporting of child maltreatment. Response options for each item are anchored on a scale from 0 to a 100, with statements at 0, 50, and 100 indicating "cannot do at all (0)," "moderately can do (50)," and "highly certain can do (100)." A total score is generated by summing items across the scale for each participant, with higher scores indicative of greater self-efficacy related to recognizing and reporting suspected child maltreatment.	✓	✓	✓	✓	✓	✓

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Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Postedu-cation	3-month follow-up	Baseline	Postedu-cation	3-month follow-up
Adapted Preparedness Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]: The PREMIS is a 67-item self-report tool that was developed to assess physician management of IPV across 10 subscales. The Preparedness Subscale asks respondents to indicate the extent to which they feel prepared to address various aspects of IPV recognition and response when working with their clients across 11 items; these aspects include the conduct of safety assessments, asking appropriate questions about IPV, responding to IPV disclosures, among others. Response options are on a 7-point Likert scale ranging from "not prepared" (1) to "quite well prepared" (7), and items are averaged to generate a mean score for practitioner preparedness, with higher scores indicative of generally greater preparedness to recognize and respond to IPV. Preparedness items were adapted to focus on child maltreatment, allowing our team to determine participant preparedness to recognize and respond to both IPV and child maltreatment in their practice encounters.	✓	—	✓	✓	✓	✓
Adapted Knowledge Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]: The knowledge subscale of the PREMIS assesses the accuracy of participants actual knowledge about IPV against a set of multiple-choice, matching, and true-or-false questions capturing information about IPV signs and symptoms and risk factors that are informed by the current literature. A total score of correct items is used to represent actual IPV knowledge, with higher scores indicative of greater knowledge.	—[b]	—	—	✓	✓	✓
Adapted Opinions and Self-Efficacy Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]. The opinions (24 items) and self-efficacy (3 items) subscale of the PREMIS assesses participants' agreement with statements capturing thoughts and beliefs related to recognizing and managing IPV in clinical practice. Response options are on a 7-point Likert scale ranging from "strongly disagree" (1) to "strongly agree" (7); items are averaged to generate a mean score for opinions and self-efficacy, with higher scores indicative of generally positive opinions and self-efficacy to recognize and manage IPV in practice. Developed in the United States, the original scale contained an item related to state-specific reporting of "IPV, elder abuse, and child abuse"; this item was removed for our studies to reduce redundancy with other measures and to reduce measurement burden. Self-efficacy items were asked at all time points in the study, with opinions items asked at baseline and 3-month follow-up.	—	—	—	✓	✓[c]	✓
Thoughts and Beliefs about Role Responsibility to Recognize and Respond to Family Violence (TBR-FV) [21]. The TBR-FV is a measure created by our research team that captures participants' perceived professional responsibility related to recognizing and responding to IPV and child maltreatment in their health professional encounters. The generation of this measure was informed by a mixed methods program of research evaluating health professions education in family violence [21].	✓	—	—	✓	—	—
Healthcare Provider Attitudes toward Child Maltreatment Reporting Scale (HPA-CMRS) [58,59]: The HPA-CMRS is a 26-item psychometrically validated scale that asks respondents to indicate the extent to which they agree with statements that capture attitudes and beliefs regarding the reporting of child maltreatment to child protective services. Items are rated on a 5-point Likert scale ranging from "0" (strongly disagree) to "4" (strongly agree) and summed to produce a total score, with higher total scores indicative of more positive attitudes and beliefs toward the reporting of child maltreatment.	✓	—	✓	—	—	—
Adapted Version of the Achievement Goals for Work Domain (AGWD) [60,61]: The AGWD is a 23-item, psychometrically validated measure of work-related achievement goals that map onto the 4 goal orientations described by Achievement Goal Theory. Respondents are asked to indicate their agreement with 22 statements that follow the stem of "In residency, my goal is..." Response options range from "1" (strongly disagree) to "7" (strongly agree), and responses are summed to generate a total score for each subscale corresponding to each type of goal orientation; higher scores are more indicative of the respondent's affinity to that goal orientation.	✓	—	—	—	—	—

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Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Posteducation	3-month follow-up	Baseline	Posteducation	3-month follow-up
Sociodemographics (current age, sex at birth, current gender identity, race, child maltreatment training history, IPV training history, etc)	✓	—	—	✓	—	—

[a]RISE: Researching the Impact of Service provider Education.

[b]Not applicable.

[c]Only the self-efficacy items will be administered at this time point.

Sample Size

A sample size of 80 participants (40 per arm) for each study was selected based on the recommendations of Whitehead et al [62] and Norman et al [63]. Based on these guidelines, a sample of 40 participants randomly allocated to each intervention arm would provide, at minimum, 80% power to detect a moderate (0.5 SD to 0.6 SD) effect size, which is indicative of a clinically significant change. In following this algorithm, our team will be able to consider the needed recruitment and retention rates to successfully implement a definitive education trial.

Qualitative Strand of Data Collection

Qualitative Design and Participants

The qualitative portion of both studies is guided by the principles of qualitative description, which is a flexible yet rigorous approach to conducting qualitative health research that has clinical and practical relevance [64]. Qualitative description is being used to expand and extend what we learn about acceptability and feasibility of implementing the experimental and active control interventions and associated research activities, as well as capture the perceived value and impact of VEGA's educational modalities, using the language of participants. Given that the qualitative data will complement the quantitative strand of data collection, we used purposive criterion sampling [65] to select a subsample of the participants from the active control and experimental arms of each study (n=60; 15 per arm, per study) to participate in a one-on-one semistructured interview with an unmasked member of the research team. For *RISE with Residents*, recruitment of qualitative participants is stratified by resident discipline and residency year, whereas for *RISE with Veterans*, qualitative recruitment is stratified by participants' sex at birth (male vs female).

Data Collection

Individual semistructured interviews take place after intervention completion. Interviews are up to 60 minutes in length and conducted via Zoom using the audio function only (or by phone, if the participant prefers). Interviews are being audio-recorded and transcribed verbatim to ensure data integrity. A semistructured interview guide of 5 to 7 key questions and probes is used to guide interview experiences. Field notes completed by the interviewer document interview observations that may be relevant to analysis.

Quantitative and Qualitative Data Analysis and Integration

On the completion of data cleaning, descriptive statistics (means, SDs, relevant quantiles, and proportions) will be used to compare VEGA modalities with respect to measures taken at baseline to ensure that groups do not significantly differ on sociodemographic characteristics [66]. The proportion of participants who met eligibility requirements, who enrolled, who were lost to follow-up, and who completed all quantitative secondary outcome assessments will be calculated. Assuming a normal distribution, standardized effect estimates for each of our educational outcomes in the form of Cohen *d* will be calculated for postintervention and 3-month follow-up time points. These data will be analyzed using intention-to-treat analysis. Depending on acceptability and feasibility outcomes, sample size calculations for a proposed RCT will be generated using the effect size and variance estimates from the posteducation change data for the selected outcome measures. Although forced-choice frameworks in REDCap reduce the proportion of missing data at the item level, missing follow-up data will be addressed using imputation procedures, where appropriate [67].

Transcripts of qualitative interviews, as well as associated field notes, are being exported into and managed in NVivo (Lumivero). On completion of both studies, transcripts will be analyzed using reflexive thematic analysis [68] and the constant comparison technique, which will allow for the identification codes, categories, and themes related to implementing and evaluating both VEGA modalities among health professionals in a postgraduate training (ie, learner) and independent practice setting. After conducting separate quantitative and qualitative analyses, quantitative and qualitative data will be integrated for interpretation via a mixed methods joint display [69]. Quantitative acceptability and feasibility metrics will be mapped to excerpts of qualitative data on perceived acceptability or educational burden; this joint display will support a comprehensive interpretation of the extent to which definitive trials examining VEGA in our sample populations are tenable. A separate joint display will cross-tabulate scores on secondary outcome measures with qualitative excerpts of VEGA's perceived value and impact for improving health professional knowledge and skills in family violence.

Ethical Considerations, Protocol Deviations and Amendments

Risks associated with the *RISE with Residents* and *RISE with Veterans* studies are minimal. All de-identified data are being stored on a secure server at McMaster University, as approved

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by the Hamilton Integrated Research Ethics Board (HiREB). Any identifying data will be destroyed on completion of both studies. Only the research team has access to study-related data; anyone outside of the research team who wishes to analyze the data can request to do so via formal secondary data analysis approval procedures administered via the HiREB. Anticipated adverse events that are relevant to this study include those related to participant safety and well-being and include (1) participants' own experiences with IPV or child maltreatment, which may raise or contribute to distress during the educational intervention or during research activities, and (2) participants' experiences with providing care to patients who have experienced IPV or child maltreatment, which may be distressing. Anticipated adverse events that are not serious are discussed, as needed by research staff, with the principal investigator if the nature of the adverse event is considered to signal unresolved risk to the participant. VEGA workshop facilitators are regulated health professionals with significant training and expertise in distress protocols. As per our protocols, emergency medical services are alerted as required if there is concern about imminent risk to life of an adult or safety of a child. The principal investigator, who is a registered social worker and psychotherapist, continues to follow regulated reporting requirements as necessary and determine whether other steps are needed to mitigate any risks to participants. Given that the purposes of both studies are to determine acceptability and feasibility of RCT implementation, a detailed accounting of any adverse events, research protocol deviations, and amendments continues to be tracked and documented by the RC, in collaboration with the principal investigator. Given the emphasis of both studies on the acceptability and feasibility of proposed RCT procedures, a data monitoring committee has not been established; however, findings from the present studies will inform the development of a data monitoring committee should results indicate that pursuit of a full RCT is acceptable and feasible.

Ethics Review

The *RISE with Residents* and *RISE with Veterans* research projects have been approved for human research by the HiREB, affiliated with McMaster University in Ontario, Canada. The associated project approvals are HiREB #14381 (*RISE with Residents*) and HiREB #14243 (*RISE with Veterans*), respectively. All research procedures will be performed in accordance with the relevant guidelines and regulations of the HiREB and Tri Council Policy Statement on the Ethical Conduct for Research Involving Humans. In both studies, informed consent for study participation is obtained from all participants.

Results

Study Timeline

The *RISE with Residents* and *RISE with Veterans* studies were registered and posted to ClinicalTrials.gov on August 5, 2022. As of January 15, 2024, we consented 71 individuals to participate in the *RISE with Residents* study and data are currently being cleaned and prepared for analysis. A total of 6 amendments were submitted to the HiREB throughout the duration of the *RISE with Residents* data collection period; no adverse events were reported by research participants. For the *RISE with Veterans* study, as of January 15, 2024, we have consented 34 individuals to participate in the study and data collection will be completed in March 2024. At the time of writing (January 2024), 7 amendments were submitted to the HiREB and no adverse events have been reported by research participants.

Dissemination Plan

In addition to the open-access publication of our research protocol, our team has identified several strategies that will accelerate the translation of our findings into education guidelines, practice, and scholarship. First, we will publish study findings for both the *RISE with Residents* and *RISE with Veterans* studies in open-access, peer-reviewed journals according to reporting guidelines for mixed methods [70], pilot trial [71], and education studies [72]. Second, end-of-grant knowledge translation will involve the preparation of 1-page infographics and curriculum recommendations for project funders at the Royal College of Physicians and Surgeons of Canada, the Atlas Institute for Veterans and their Families, and our network of health professions associations; representatives from each association generously disseminate our knowledge translation products via posts to their website, social media channels, and listserve platforms. Finally, we will present our findings at national and international conferences focused on health professions education and education scholarship.

Discussion

Key Findings

The *RISE with Residents* and *RISE with Veterans* research studies aim to determine the acceptability and feasibility of conducting an RCT to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of the VEGA Family Violence Education Resources [30], as an adjunct to standard education, to improve learner (*RISE with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters. We compare these 2 educational modalities for 2 key reasons. First, evidence indicates that self-directed education may be as effective as traditional education methods for improving knowledge and skills among health professionals, especially when self-directed methods incorporate active learning strategies [73,74]. Given that VEGA is a free, online, and brief intervention, determining the extent to which self-directed education yields improved preparedness, knowledge, and skills among learner and independently practicing health professionals, as an adjunct to formal curriculum, could (1) widely (and rapidly) shift the preparation of Canadian health professionals to effectively recognize and respond to family violence without requiring formal curricular changes and (2) meaningfully contribute to our understanding about effective postgraduate and continuing education strategies, which has education implications beyond family violence and the VEGA intervention.

Second, the comparison of educational modalities in our respective studies minimizes the variability that could not be

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accounted for if VEGA were compared with a non-VEGA control; this includes variability related to intervention content and emphasis, student enthusiasm, among others. RCTs in education scholarship have been controversial because they typically average too many variables to yield any real insights [75,76]. This is particularly true when an intervention is compared with a passive control or an active control that is focused on a separate subject. By keeping the content standard, varying only the educational modality, and placing emphasis on evaluating the acceptability and feasibility of an RCT, both studies address each of these important issues [77-79].

Strengths and Limitations

A particular strength of the *RISE with Residents* and *RISE with Veterans* research studies lies in their emphasis on postgraduate and continuing education contexts. It is possible that family violence education may be especially impactful in the postgraduate training period given the need to (1) understand that children, youths, and adults can present with signs and symptoms of all types of family violence in every health professional subspecialty and (2) demonstrate competencies related to the scope of one's professional responsibilities (eg, mandatory reporting) and the purview of one's clinical practice, including when and how to make appropriate treatment referrals to prevent or reduce mental or physical health impairment. To this end, the results of the *RISE with Residents* and *RISE with Veterans* studies provide a valuable methodological contribution about the feasibility and acceptability of trial methods in postgraduate and continuing education focused on family violence in the Canadian context; it will also contribute new knowledge to education science about the differences between the effectiveness of self-directed versus facilitator-led learning strategies at different stages of the learning trajectory, more broadly.

The limitations of the *RISE with Residents* and *RISE with Veterans* research studies are influenced by the scope of the available literature on effective interventions for preventing family violence and mitigating associated harms, more generally. For example, it is important to note that IPV occurs in all countries, cultures, religions, and socioeconomic groups in the world. However, generally speaking, IPV is a gendered phenomenon; cisgender and transgender women and girls are disproportionately affected by IPV. Yet, increasing evidence indicates that IPV may be perpetrated by men toward women and by women toward men and occur in same-sex, gender, and sexually diverse relationships [10]. IPV may materialize in marital relationships, common-law relationships, cohabitation, or any intimate relationship including dating and casual sexual relationships across the age spectrum [10]. Yet, most epidemiological and intervention data related to IPV and its prevention have been collected in the context of cisgender, heterosexual adult relationships; thus, the information contained in VEGA is largely informed by that lens. Similarly, information regarding evidence-based approaches, practices, and programs for individuals who use violence (ie, perpetrators of IPV or child maltreatment) is limited. This limitation is also reflected in the evidence reviews and available guidance for working with perpetrators contained within the VEGA education modalities [10,80-82]. Finally, and methodologically, our quantitative measures rely on learner and independent practitioner self-report, which can be prone to bias. However, our selected measures have undergone psychometric scrutiny and heavily rely on a behavioral intention framework, which is consistent with the concept of self-efficacy (ie, beliefs about capabilities)—a construct with moderate-to-strong associations with provider behavior change [83,84].

Conclusions

We expect that the *RISE with Residents* and *RISE with Veterans* research studies will provide critical evidence related to the acceptability and tenability of evaluating VEGA in postgraduate and continuing education settings. Both studies will also provide foundational estimates of intervention impact among 2 distinct populations. To this end, the findings have broader implications for the possibility of improving the preparation of health professionals to be able to recognize and respond to family violence in their care encounters safely and effectively. The generated effect estimates will serve as benchmarks for replication and, more specifically, the design of adequately powered and methodologically robust evaluations of the VEGA and other family-violence focused educational interventions over the long term.

Acknowledgments

For *RISE with Residents* and *RISE with Veterans*, a Letter of Permission from McMaster University was provided to evaluate the Violence, Evidence, Guidance, Action (VEGA) Family Violence Education Resources. We acknowledge the support of Dr Harriet MacMillan, who is the lead of the VEGA Project, to undertake this work and appreciate Dr MacMillan acting as the VEGA Advisor for the *RISE with Residents* and *RISE with Veterans* research projects. We would also like to acknowledge the input of Fardous Hosseiny, MaryAnn Notarianni, Ashlee Mulligan, and Catherine Virelli of the Atlas Institute for Veterans and Families on the *RISE with Veterans* recruitment procedures. *RISE with Residents* is funded by a 2021 Medical Education Research Grant from the Royal College of Physicians and Surgeons of Canada (award reference number: 21/MERG-05). *RISE with Veterans* is funded by the Atlas Institute for Veterans and Families (formerly the Centre for Excellence for PTSD and Related Mental Health Conditions; agreement number: 2021-0630). The views expressed in this paper do not necessarily represent the views of the Royal College of Physicians and Surgeons of Canada, nor the Atlas Institute for Veterans and Families. The Royal College of Physicians and Surgeons of Canada and the Atlas Institute for Veterans and Families were not involved in the design of these studies, nor were they involved in the writing of this manuscript.

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Data Availability

To protect human privacy, data are not publicly available. Should researchers wish to complete secondary analysis of the *RISE with Residents* and *RISE with Veterans* research data, they may formally apply with a request to do so via the Hamilton Integrated Research Ethics Board (HiREB).

Authors' Contributions

MK, EBS, DES, and MV were all involved in the development of this protocol. MK drafted this manuscript. All authors were involved in the critical revision of the paper for intellectual content and its final approval before submission. All authors read and approved the final manuscript. Generative AI was not used for writing any portion of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAF: Canadian Armed Forces
HiREB: Hamilton Integrated Research Ethics Board
IPV: intimate partner violence
RC: research coordinator
RCMP: Royal Canadian Mounted Police
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RISE: Researching the Impact of Service provider Education
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VEGA: Violence, Evidence, Guidance, and Action

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Protocol

Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee): Protocol for an Effectiveness-Implementation Hybrid Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis (KOA) is one of most prevalent and fastest-growing causes of pain, impaired mobility, and poor quality of life in the rapidly aging population worldwide. There is a lack of high-quality evidence on the efficacy of traditional Chinese medicine (TCM), particularly acupuncture, and a lack of KOA practice guidelines that are tailored to unique population demographics and tropical climates.

Objective: Our HARMOKnee (Heat and Acupuncture to Manage Osteoarthritis of the Knee) trial aims to address these gaps by evaluating the short- and medium-term clinical and cost-effectiveness of acupuncture with heat therapy in addition to standard care, compared to standard care alone. Through a robust process and economic evaluation, we aim to inform evidence-based practice for patients with KOA to facilitate the large-scale implementation of a comprehensive and holistic model of care that harmonizes elements of Western medicine and TCM. We hypothesize that acupuncture with heat therapy as an adjunct to standard care is clinically more effective than standard care alone.

Methods: A multicenter, pragmatic, parallel-arm, single-blinded, effectiveness-implementation hybrid randomized controlled trial will be conducted. We intend to recruit 100 patients with KOA randomized to either the control arm (standard care only) or intervention arm (acupuncture with heat therapy, in addition to standard care). The inclusion criteria are being a community ambulator and having primary KOA, excluding patients with secondary arthritis or previous knee replacements. The primary outcome measure is the Knee Osteoarthritis Outcome Score at 6 weeks. Secondary outcome measures include psychological, physical, quality of life, satisfaction, and global outcome measures at 6, 12, and 26 weeks. A mixed method approach through an embedded process evaluation will facilitate large-scale implementation. An economic evaluation will be performed to assess financial sustainability.

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Results: Patient enrollment has been ongoing since August 2022. The recruitment process is anticipated to conclude by July 2024, and the findings will be analyzed and publicized as they are obtained. As of November 6, 2023, our patient enrollment stands at 65 individuals.

Conclusions: The findings of our HARMOKnee study will contribute substantial evidence to the current body of literature regarding the effectiveness of acupuncture treatment for KOA. Additionally, we aim to facilitate the creation of standardized national guidelines for evidence-based practice that are specifically tailored to our unique population demographics. Furthermore, we seek to promote the adoption and integration of acupuncture and heat therapy into existing treatment models.

Trial Registration: ClinicalTrials.gov NCT05507619; https://clinicaltrials.gov/study/NCT05507619

International Registered Report Identifier (IRRID): DERR1-10.2196/54352

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KEYWORDS

knee osteoarthritis; acupuncture; heat therapy; effectiveness-implementation hybrid study; randomized controlled trial; RCT

Introduction

Knee osteoarthritis (KOA) is an age-related degeneration representing “wear and tear” of the knee joint, and it is one of the most prevalent and fast-growing causes of pain, impaired mobility, and poor quality of life (QOL) in the rapidly aging population worldwide [1]. The 2019 Global Burden of Disease Study reported that the knee is the joint most frequently affected by osteoarthritis, with a prevalence of approximately 365 million, followed by the hand and the hip [2].

Acupuncture is the most prevalent form of traditional medicine practice, with 183 of 202 (90.5%) surveyed countries recognizing its use, as reported by the World Federation of Acupuncture-Moxibustion Societies [3]. A bibliometric analysis reported that of 2189 positive recommendations for the use of acupuncture, about 68% were associated with 107 pain indications [4].

A review of 10 randomized controlled trials (RCTs) concluded that acupuncture is an effective treatment for KOA-related pain and physical dysfunction [5]. However, major updated clinical guidelines from the American Academy of Orthopaedic Surgeons, Joint Surgery Branch of the Chinese Orthopaedic Association, American College of Rheumatology/Arthritis Foundation, and others still consider acupuncture treatment to be insufficient, limited, conditional, or unrecommended for KOA [6]. A review highlighted the lack of evidence supporting the efficacy and cost-effectiveness of acupuncture in osteoarthritis due to poor methodological quality, significant heterogeneity, inadequate reporting of acupuncture treatment details, small sample sizes, and high placebo responses in studies [7].

The primary aim of our study is to evaluate the short- and medium-term clinical effectiveness of acupuncture, part of traditional Chinese medicine (TCM), with far-infrared heat therapy in addition to standard care, compared to standard care alone. The secondary aims include (1) performing a process evaluation to understand the context and identify mechanisms of impact that will inform large-scale implementation of the intervention and (2) performing an economic evaluation to assess the cost-effectiveness of the intervention. We hypothesize that acupuncture with heat therapy as an adjunct to standard care is clinically more effective than standard care alone.

Methods

Design

The study is an effectiveness-implementation hybrid trial, which combines effectiveness and implementation components [8,9]. This will be a type 1 hybrid trial where the emphasis and primary aim is to evaluate the effectiveness of acupuncture with far-infrared heat therapy as an adjunct to standard care through a pragmatic RCT under real-world conditions, and its secondary aim is to understand the context of implementation through a mixed-method, process-oriented approach. The pragmatic nature of the study was guided by the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool [10].

The study will be conducted as a multicenter, pragmatic, parallel-arm, single-blinded RCT using a mixed method approach comparing the clinical effectiveness of acupuncture with far-infrared heat therapy as an adjunct to standard care and standard care alone. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [11] and the Osteoarthritis Research Society International (OARSI) clinical trial recommendation on the design and conduct of clinical trials for KOA [12] guided the development of the trial protocol. To ensure clear reporting of acupuncture treatment details, Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) reporting guidelines [13] will also be followed. The findings of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 [14] guidelines for reporting parallel-group randomized trials. The study will use an explanatory sequential mixed method design where the qualitative data from interviews will be used to interpret and provide context for the quantitative results.

Participants

We will recruit patients based on the eligibility criteria outlined in Textbox 1.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- National Institute of Health and Care Excellence (NICE) clinical criteria for knee osteoarthritis (KOA) [5]:
  - Being aged 45 years or older
  - Having activity-related joint pain
  - Having either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes
- Being a community ambulator with or without walking aid

Exclusion criteria

- Alternative diagnosis to KOA, such as referred pain from the spine or hip
- Other forms of arthritis, such as inflammatory arthritis
- Inability to comply with study protocol (eg, due to dementia)
- Previous knee arthroplasty
- Being a wheelchair user
- Medical conditions that would medically interfere with study involvement, such as decompensated heart failure, stroke, and end-stage renal failure
- Allergies to metal (needles)

Components of the Study

The Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee) study will have three components: (1) an RCT, (2) an economic evaluation, and (3) a process evaluation.

Component 1: RCT

This RCT will be administered in accordance with the STRICTA guidelines, an extension of the CONSORT statement designed to enhance the quality of clinical trials of acupuncture [13].

Trial Procedure and Recruitment

By using the hospital's electronic medical records and appointment system, patients who are referred to the orthopedic surgery outpatient clinic at a tertiary hospital in Singapore will be screened based on the eligibility criteria prior to their actual consultation visit. During the clinic visit, potential patients will be invited to participate in the study if they meet all the inclusion and exclusion criteria. A research assistant will share details of the study with patients who are interested. Written informed consent will be obtained for those who subsequently agree to join the trial. The reasons for rejection to participate will be recorded. Each consenting participant will be asked to complete the baseline measures. Patients will then be randomized into the control arm or the intervention arm. Considering previous studies [15,16], patients who have received TCM treatment within 1 week prior to the trial will be subject to a 2-week washout period, counting from their last TCM treatment date. They will be requested to stop any form of acupuncture before beginning the trial. For this group of patients, randomization and baseline measures will be performed after the wash-out period. Participants are allowed to take any analgesics as needed throughout the study duration, and this will be recorded. All medications (prescription and over the counter), vitamin and mineral supplements, and herbs taken by the participant will be documented. Data collection will be done at baseline and weeks 6, 12, and 26. The research assistant will follow up with the participants regularly to ensure study completion. Figures 1 and 2 illustrate the study schedule of enrollment, interventions, and outcome measurements according to the SPIRIT guidelines and the CONSORT flowchart, respectively.

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Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of the study schedule. TCM: traditional Chinese medicine.

		Study period										
	Description	Enrollment/ baseline	Allocation	Postallocation (week)							Closeout	Remarks
Timepoint		$-t_1$	0	1	2	3	4	5	6	12	24	
Enrollment												
Eligibility screen		✓										
Informed consent		✓										
Allocation			✓									
Interventions												
Intervention arm	Standard care + acupuncture with heat therapy			←	—	—	—	—	→			2 sessions per week
Control arm	Standard care			←	—	—	—	—	→			
Assessments												
1. Baseline measures	Demographics	✓										
	Height and weight	✓								✓	✓	
2. Primary outcome	Knee Osteoarthritis Outcome Score	✓							✓	✓	✓	
3. Secondary outcomes	EQ-5D-5L	✓							✓	✓	✓	
	Patient Health Questionnaire-4	✓							✓	✓	✓	
	Pain, Enjoyment of Life and General Activity Scale	✓							✓	✓	✓	
	Global Perceived Effect								✓	✓	✓	
	Patient Acceptable Symptom State								✓	✓	✓	
	Medication use	✓							✓	✓	✓	
	Cost Questionnaire	✓								✓	✓	
	Functional assessment	✓								✓	✓	
	Knee Osteoarthritis TCM Evaluation			✓			✓		✓			Prior to first and seventh session and after twelfth session
	Knee Osteoarthritis Visual Analog Scale; Range of Motion Evaluation			✓	✓	✓	✓	✓	✓			Pre- and posttreatment

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Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study.

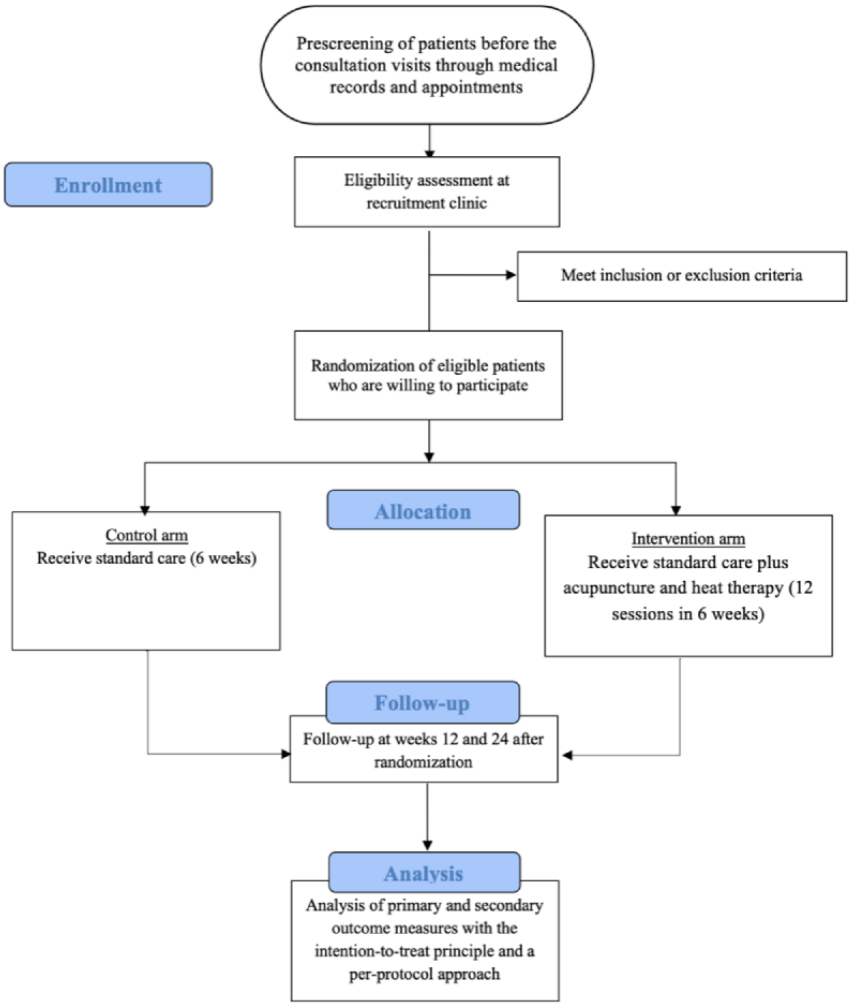

Randomization and Concealment of Allocation

Patients who consent to participate will be randomized in a 1:1 allocation ratio to intervention or standard care using a stratified, permuted, block randomization method (block sizes of 4, 6, and 8). Stratification is based on gender with a female to male ratio of 2:1. The unbalance ratio was based on the World Health Organization's estimate of the prevalence of symptomatic osteoarthritis for people aged 60 years or older, among whom the prevalence of women is almost double that of men (male vs female: 9.6% vs 18%) [17]. The allocation sequence is generated by an independent statistician a priori using Stata (version 16.1; StataCorp) and will be kept concealed from the study team. Randomization will be done using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module based on the allocation sequence; allocation will be locked once assigned. Randomization and intervention allocation will only be performed by the study team after the patient is counselled fully about the study and provides informed consent.

Intervention: Acupuncture Plus Heat Therapy and Standard Care

After reviewing international literature and engaging with local TCM experts, this clinical intervention was designed in accordance with local practice. The intervention involves acupuncture with far-infrared heat therapy in addition to standard care, which will be administered by qualified TCM practitioners from Tan Tock Seng Hospital's Complementary Integrative Medicine Clinic (CIMC) and Singapore Chung Hwa Medical Institution (SCHMI), who have full registration with the Traditional Chinese Medicine Practitioners' Board and a minimum of 3 years of acupuncture practice. Before the commencement of the trial, all the acupuncturists from the participating institutions will undergo training on acupoint locations and needling methods to ensure standardization of acupuncture techniques in accordance to the acupuncture protocol that was developed by consensus among all the senior acupuncturists participating in this trial. The treatment protocol and rationale are elaborated below.

Our study aims to evaluate the therapeutic effectiveness of acupuncture combined with far-infrared heat therapy in addition to standard care, compared to standard care alone. To achieve this purpose, we have not included sham acupuncture as an inactive control in our study design. There are controversies about the validity of sham acupuncture. A study found that sham acupuncture may produce comparable effects on biomarkers as *verum* acupuncture, which suggests that sham acupuncture, being an inactive intervention akin to a placebo, should be reevaluated [18]. Additionally, heat therapy will yield beneficial

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outcomes in the treatment, regardless of whether *verum* or sham acupuncture is used.

Acupuncture Intervention Rationale

Although the 2007 Singapore Ministry of Health clinical guidelines for KOA recommend electroacupuncture as an adjunct therapy, anecdotal input from our local subject matter experts suggests that some patients are afraid of electrical stimulation and that it is generally less well tolerated due to the pain of electrical stimulation. Studies have also shown that even though electroacupuncture has advantages compared to standard care, acupuncture with heat therapy, a more tolerable option, possesses similar efficacy as electroacupuncture when combined with the usual pharmacotherapies [19]. Therefore, we chose to evaluate acupuncture with heat therapy to establish its clinical effectiveness as an adjunctive therapy in the management of KOA, with long-term implementability a key consideration.

Upon careful review of the evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion for KOA [20] and the intervention protocols of several acupuncture RCTs that examined patients with KOA (Multimedia Appendix 1, Figure S1 [10, 21-29]), acupoints that were previously reported to be effective in pain relief and improving knee flexibility were identified.

Guided by international evidence in consultation with the local TCM collaborators, a consensus on a set of proximal and distal acupoints based on TCM meridian differentiation was reached (Multimedia Appendix 1, Figure S2 [30,31]).

Acupoint Selection

In total, 14 needle insertions will be made on a fixed set of proximal and distal acupoints for each patient per session (Figure 3).

Distal acupoints will be applied on the opposite elbow [32] to increase the analgesic efficacy according to contralateral collateral needling (缪刺) from *Huang Di Nei Jing* (*Yellow Emperor's Inner Classic* in English). It is a therapy where the right side is acupunctured if the left side is diseased and vice versa; the upper side is acupunctured if the below is diseased and vice versa. Studies have shown that contralateral collateral needling unblocks collaterals and is potentially more effective than conventional acupuncture for some conditions, including hemiplegia following acute ischemic stroke, cervical shoulder pain, insomnia, and KOA [33-35]. From a pragmatic perspective, patients with bilateral knee pain will only receive acupuncture on the most painful knee and the opposite elbow. This practice is supported with evidence that suggests unilateral acupuncture is equally as effective as bilateral acupuncture in increasing function and reducing the pain associated with KOA [36].

Figure 3. Proximal and distal acupoints.

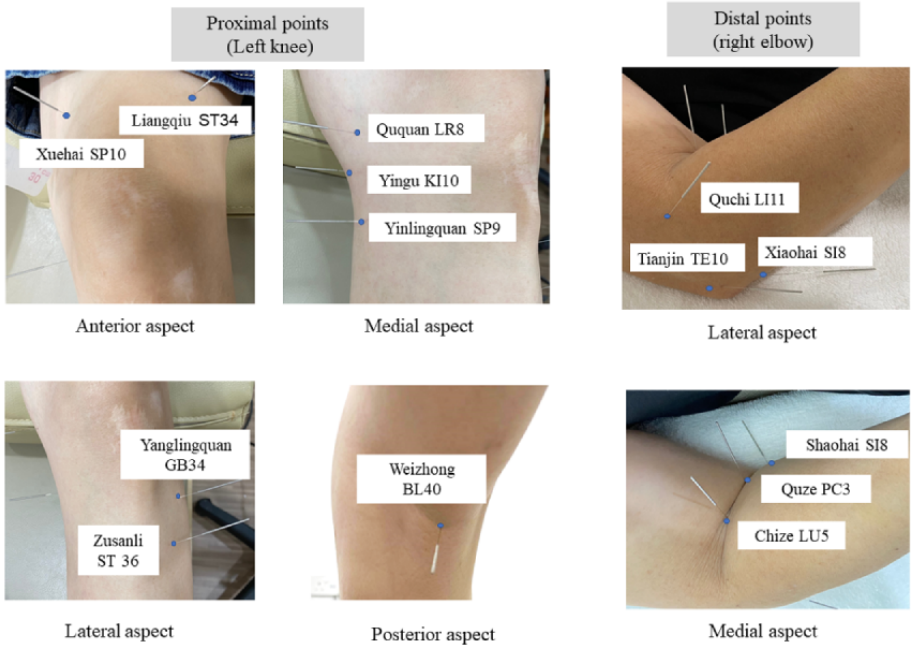

Treatment Regimen

The patient will be treated in a supine position with pillows under both knees. After a standard disinfection procedure, a 30 × 40–mm disposable stainless steel acupuncture needle (YangTzeKing Impex S Pte Ltd) will be inserted according to the location defined; the direction of insertion and the safe depth range are specified in Multimedia Appendix 1, Figure S2 [21, 30,31]. Basic manipulations such as lifting and thrusting, twirling, and rotating are applied until the needling sensation (*de-qi*) is obtained. After *de-qi* is obtained, uniform reinforcing-reducing (平补平泻) manipulations are applied. The needles will be retained for 30 minutes (except for weizhong [BL40], where the needle is removed immediately after the needling sensation is obtained), whereupon 2 manipulations will be applied at 10-minute intervals before needle removal. During needle retention, far-infrared heat therapy will be applied at the lateral, medial, and anterior sides of the knee for 10 minutes each for a total of 30 minutes while maintaining a 30-cm safety distance (Figure 4). The treated region will be observed

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and checked for redness at 10-minute intervals to prevent burn injury. A total of 12 acupuncture sessions will be administered twice a week for 6 weeks in addition to standard care. A minimum of 50% attendance (6 of 12 sessions) is required to qualify as completing the study treatment. There are no make-up sessions should the patient miss the scheduled appointment. Total numbers and dates of attended and missed sessions will be recorded for analysis purposes. The study intervention will be conducted at TTSH, CIMC, or SCHMI. The patients are allowed to indicate their preference for the treatment location at the start of the intervention and must attend at the selected location throughout the 6-week intervention. Each TCM session takes approximately 40 minutes, involving acupuncture and heat therapy. Safety precautions will also be exercised to ensure the safety of the patients. Generally, acupuncture is safe and has a low risk of adverse events [37]. However, since the most common adverse events are subcutaneous hematomas and hemorrhages at the site of needling [37], the TCM practitioner will take extra precaution if patients indicate during informed consent that they are taking antiplatelets or anticoagulants. All adverse events that occur during the treatment will be documented.

Figure 4. Heat therapy applied during acupuncture.

Standard Care

Standard care generally constitutes simple lifestyle advice, analgesia, and a referral to the outpatient physiotherapist. The physiotherapist conducts an assessment and recommends a variety of lifestyle modifications and exercise therapy. Any other treatment or the involvement of allied health professionals, such as dieticians, will take place at the discretion of the managing physician. The patients in the standard care group will be discouraged from seeking acupuncture treatment for 6 to 8 weeks after randomization. However, if they do so, it will be noted and accounted for in the analysis.

Withdrawal Criteria

The study intervention may be discontinued under the following circumstances: (1) a serious adverse event arises from the intervention, (2) a participant opts for total knee replacement, (3) a participant is unable to continue the study (eg, because of the sudden onset of any medical condition that prohibits continuing the study), and (4) a collaborator withdraws due to unforeseen circumstances. The participants may also withdraw voluntarily from the study intervention for any reason.

Outcome Measures

The choice of outcome measures is based on the OARSI guidelines for lifestyle diet and exercise clinical trials in osteoarthritis [38]. The recommended core outcomes include pain, physical function, and global patient assessment. Additional outcomes include health-related QOL and global physician assessment. Outcome measures will be collected at baseline (pretreatment), week 6, week 12, and week 26. The primary end point in this study is the Knee Osteoarthritis Outcome Score (KOOS-12) at week 6. KOOS-12 is a specialized tool designed to evaluate patients' knee condition, and it assesses the short- and long-term effects of knee injuries [39]. It reduces respondent burden by 70% from the original KOOS while providing scale scores for knee-specific pain, function, and QOL, along with a summary measure of overall knee impact [40]. The KOOS score has been validated in Singapore [39,41].

Baseline measures such as demographics, socioeconomic status, medical comorbidities, knee symptoms, radiographic severity, height, and weight will be collected.

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Additionally, after considering the progression and severity of KOA as defined in TCM clinical guidelines published in China (Multimedia Appendix 1, Figure S3), 2 evaluation forms have been designed. The Knee Osteoarthritis TCM Evaluation Form (Multimedia Appendix 1, Figure S4) was specifically created to integrate the KOOS-12 knee survey with questions based on TCM syndrome differentiation for KOA. This will enable the investigators to assess the efficacy of the treatment by analyzing syndrome differentiation. This form will be administered at week 1 (start of treatment, before the first acupuncture session), week 4 (midtreatment, before the seventh acupuncture session) and week 6 (end of treatment, after the 12th or last acupuncture session). The Knee Osteoarthritis Visual Analog Scale and Range of Motion Evaluation Form (Multimedia Appendix 1, Figure S5) will be administered before and after each of the 12 biweekly acupuncture sessions over 6 weeks.

Clinical data (glycated hemoglobin, blood pressure, and other chronic disease parameters) and operational and cost data (health care use) will also be obtained through the health care administrative databases for economic evaluation.

Outcome Assessment and Blinding

Except for the TCM evaluation forms (Multimedia Appendix 1, Figures S4 and S5), the remaining outcome measures will be measured by blinded outcome assessors. All outcome assessors will receive training prior to study initiation to ensure good inter- and intraobserver reliability, particularly for the functional performance testing. Patients will be instructed not to reveal their allocation to the outcome assessors. Outcome assessment will be conducted at the TTSH physiotherapy clinic. Unblinding will be carefully considered and justified in each case of medical emergency or clinical treatment decisions that require the intervention to be known, following the study protocol and ethical guidelines.

Sample Size Calculation

The sample size needed to find a 10-point difference for KOOS-12 (the primary outcome) between the intervention and control arms with a power of 90%, a *P* value of .05 (2-sided) and an SD of 14 is n=42. The 10-point difference is based on the minimal clinical important difference for KOOS [42]. The anticipated baseline and SD are based on studies done in similar populations. Accounting for a 20% drop-out rate, a total of 100 patients will be needed for the study.

Data Analysis Plan

Results will be analyzed by the intention-to-treat principle. However, data will also be analyzed by a per-protocol approach to account for protocol violations, such as patients who were deemed not compliant to treatment or patients who underwent a surgical procedure of the knee due to treatment failure during the study. Descriptive frequency analysis will be used for baseline characteristics. For continuous variables, the mean and SD will be reported and for categorical variables, the frequencies and percentages will be reported. Between-group comparisons of change from baseline to the 26-week follow-up in the primary and secondary continuous outcomes will be analyzed using a generalized linear mixed model (GLMM). Testing for normality of distributions of outcomes will be based both on the Shapiro-Wilks test and a visual analysis of the histogram plot. Categorical secondary outcomes will be analyzed using the ordinal logistic regression function under the GLMM. A 2-sided *P* value less than .05 will be considered statistically significant. An analysis will be done on the nature of the missing data to determine if the data are missing at random or a systemic bias is present resulting from the missing data.

Data Management

All data will be monitored by the principal investigator and the study team independently of the study sponsor. Data quality measures include queries to identify outliers and missing data. A unique identifier will be assigned to each patient after enrollment to ensure patient confidentiality. Data will be collected and stored on the REDCap system, which is a widely used and secure web application for clinical data management in research. REDCap is password protected, and access rights to the study database are only granted to authorized people. Physical study files will be stored under lock and key.

Safety Monitoring Plan

A safety monitoring review will be done quarterly. Data monitored include serious adverse events and research-related events such as pain, burn, or any other adverse events that may arise due to the conduct of study activities. Safety monitoring reviews will be done by the principal investigator and the co–principal investigator of the study team. The study may be stopped by the principal investigator if serious safety concerns emerge. In the event that a critical adverse event occurs and a decision must be made to terminate the study, interim analyses will be conducted by an independent statistician.

Adverse events and other unanticipated effects of the intervention will be spontaneously reported by the acupuncturists. All reporting will be collected and assessed by the study team. Unanticipated problems involving risk to participants or other events will be reported to the institutional review board.

Confidentiality of Data and Patient Records

Only authorized study personnel will have access to the secured cabinet(s) or room(s) where hard-copy data will be stored. The electronic data will be stored on a password-protected desktop computer, laptop, and external HDD. The databases will not include subject identifiers, and the data relating subject identifiers to subject identification codes will be stored separately.The research data will only be accessible to the study team (including principal investigators, co-investigators, research coordinators, and statisticians). The anonymized and password-protected sharing of research data will be allowed with external institutions.

Ancillary and Posttrial Care

Enrolled participants are covered by indemnity for unexpected negligent harm due to the trial procedure.

Dissemination Plan

We anticipate that it will take between 3 and 4 months to compile the final results for the appropriate journal. The study results will be made available to the participating physicians

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and the medical and TCM practitioner community via academic publication.

Component 2: Economic Evaluation

An economic evaluation will be conducted in tandem. The Panel on Cost-Effectiveness in Health and Medicine recommends the use of a societal perspective to ensure that potentially important indirect costs, such as productivity and caregiver cost, are not omitted [43]. The study will be conducted from a societal perspective to determine the cost-effectiveness of the intervention [43].

The cost data will be collected via hospital administrative databases and patient-reported questionnaires to estimate direct medical, direct nonmedical, and indirect costs based on the validated OA Cost and Consequences Questionnaire (OCC-Q), which has been adapted to the Singapore context. The OCC-Q will be administered at baseline, 12 weeks, and 26 weeks.

The primary measure of health benefit will be quality of life years measured using the EQ-5D [44]. The incremental cost-effectiveness ratio over the trial period of acupuncture with heat therapy in conjunction with standard care compared to standard care only will be determined.

Results from the economic evaluation will be reported based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [45].

Component 3: Process Evaluation

The process evaluation will be embedded within the trial. The process evaluation is crucial in understanding the functioning of an intervention by examining its implementation, mechanisms of impact and contextual factors, and use of evaluation to understand how interventions work in practice. This is vital in building an evidence base that informs policy and practice. The Medical Research Council guidelines for the conduct of process evaluations [45] will be used to design the process evaluation.

The focus will be on fidelity of actual delivery, context, and mechanisms of impact with the goal of eventual large-scale implementation. Context includes anything external to the intervention that may act as a barrier or facilitator to its implementation. The examination of mechanisms of impact seeks to identify the potential causal pathways that resulted in the changes seen.

Ethical Considerations

Ethics approvals were obtained from the National Healthcare Group Domain Specific Review Board (2021/01106) and Parkway Independent Ethics Committee (PIEC/2022/022), which oversee human research studies in the participating centers. This study will be conducted in accordance with the ethical principles in the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and it is consistent with the applicable regulatory requirements of the Human Biomedical Research Act in Singapore. Written informed consent will be obtained from all participants who agree to join the study after screening. A translator and an impartial witness will be present throughout the consent process if a participant is unable to understand English. All study documents were deidentified and research data will be anonymized and password-protected to ensure privacy and confidentiality. This trial is covered under the National Clinical Trials Insurance.

Results

Patient enrollment has been ongoing since August 2022. The recruitment process is anticipated to conclude by July 2024, and the findings will be analyzed and publicized as they are obtained. As of November 6, 2023, our patient enrollment stands at 65 individuals.

Discussion

Overview

TCM has been growing in popularity as a viable treatment option for KOA in recent times. Systematic reviews have suggested that TCM has potential effectiveness in terms of pain relief and functional improvement and leads to few adverse events [46]. However, there have been significant concerns raised about the quality of evidence, with significant methodological flaws in many of the studies and a high risk of bias. Acupuncture in particular has had a fairly large base of evidence, but an overview of the various systematic reviews on the effectiveness and safety of acupuncture in KOA suggested while it has advantages in KOA, there is a significant risk of bias and reporting deficiencies that needs to be addressed [47].

In addition, there is little evidence for TCM treatment of KOA that is tailored to the unique demographics of populations in tropical climates. Many local practitioners often refer to China's Clinical Guidelines of Acupuncture and Moxibustion for KOA, published in 2015 [20]. The guidelines include treatment options based on various TCM syndrome classifications, such as liver and kidney yin deficiency with blood stasis in tendons, spleen and kidney deficiency with dampness in the joint, and kidney yang deficiency with phlegm and blood stasis syndromes. Each syndrome delineates a distinct pattern of symptoms. A local study highlighted a significant difference in the syndrome differentiation for KOA (Multimedia Appendix 1, Figure S6 [48]), with a very high proportion (51%) of patients with KOA in Singapore experiencing the spleen and kidney deficiency with dampness in joint syndrome type, as compared to a mere 4.2% of patients with KOA in China [48,49]. The guidelines from China therefore may not be suited to Singapore's unique patient demographics.

Our HARMOKnee study aims to (1) add high-quality evidence for acupuncture treatment for KOA to the existing literature on a broader scale; (2) support the development of locally standardized national evidence-based practice guidelines tailored to our unique population demographics; (3) support the implementation and integration of acupuncture and heat therapy into current treatment models supported by process and economic evaluations; and (4) establish a foundation for the development of an integrated model of care that harmonizes both Western and Eastern care components.

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Strengths and Limitations

One of the major strengths of our HARMOKnee study is that it follows the gold standard for research design: an RCT. The RCT design guarantees that the research uses a rigorous methodology and controls for potential confounding variables. The likelihood of bias can be reduced through allowing more precise assessment of the intervention's efficacy. This study also adheres to the STRICTA guidelines, which provide a standardized framework for reporting acupuncture trials. All relevant data will be reported, thereby enhancing the study's transparency and reproducibility. Moreover, this effectiveness-implementation hybrid study has incorporated an implementation component with the clinical effectiveness assessment. Its benefits include allowing the researchers to maximize the efficiency of their research while collecting data on both effectiveness and implementation, thereby identifying gaps in implementation and increasing the likelihood that the interventions will be effectively implemented and disseminated in real-world settings.

Limitations include the use of a pragmatic study design to mimic real-world conditions as closely as possible. This has an impact in terms of what treatment the control arm receives and how the intervention is delivered. Considerations to ensure intervention delivery fidelity have been incorporated, including standardization and training among acupuncturists. In addition, the treatment that the control arm receives will be meticulously recorded as part of the cost questionnaire and will be included in the analysis. Second, due to logistical and funding limitations, we are only able to include a follow-up period of up to 26 weeks. This will not allow us to establish the long-term effectiveness of this intervention.

Conclusions

The findings of our HARMOKnee study will contribute substantial evidence to the current body of literature regarding the effectiveness of acupuncture treatment for KOA. Additionally, we aim to facilitate the creation of standardized national guidelines for evidence-based practice that are specifically tailored to our unique population demographics. Furthermore, we seek to promote the adoption and integration of acupuncture and heat therapy into existing treatment models.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions on information that could compromise the privacy of research participants.

Authors' Contributions

BYT was the principal investigator. TLT and HPN were the site investigators. All authors participated in the study methodology design and reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
HARMOKnee Study Protocol.
[PDF File (Adobe PDF File), 419 KB - resprot_v13i1e54352_app1.pdf]

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Abbreviations

CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CIMC: Complementary Integrative Medicine Clinic
CONSORT: Consolidated Standards of Reporting Trials
GLMM: generalized linear mixed model
HARMOKnee: Heat and Acupuncture to Manage Osteoarthritis of the Knee
KOA: knee osteoarthritis
KOOS-12: Knee Osteoarthritis Outcome Score
OARSI: Osteoarthritis Research Society International
OCC-Q: OA Cost and Consequences Questionnaire
PP: per-protocol
PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary
QOL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCHMI: Singapore Chung Hwa Medical Institution
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
TCM: traditional Chinese medicine

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Protocol

Assessing the Effectiveness of a Multicomponent Intervention on Hand Hygiene and Well-Being in Primary Health Care Centers and Schools Lacking Functional Water Supply in Protracted Conflict Settings: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Hand hygiene is crucial in health care centers and schools to avoid disease transmission. Currently, little is known about hand hygiene in such facilities in protracted conflict settings.

Objective: This protocol aims to assess the effectiveness of a multicomponent hand hygiene intervention on handwashing behavior, underlying behavioral factors, and the well-being of health care workers and students. Moreover, we report our methodology and statistical analysis plan transparently.

Methods: This is a cluster randomized controlled trial with 2 parallel arms taking place in 4 countries for 1 year. In Burkina Faso and Mali, we worked in 24 primary health care centers per country, whereas in Nigeria and Palestine, we focused on 26 primary schools per country. Facilities were eligible if they were not connected to a functioning water source but were deemed accessible to the implementation partners. Moreover, health care centers were eligible if they had a maternity ward and ≥5 employees, and schools if they had ≤7000 students studying in grades 5 to 7. We used covariate-constrained randomization to assign intervention facilities that received a hardware, management and monitoring support, and behavior change. Control facilities will receive the same or improved intervention after endline data collection. To evaluate the intervention, at baseline and endline, we used a self-reported survey, structured handwashing observations, and hand-rinse samples. At follow-up, hand-rinse samples were dropped. Starting from the intervention implementation, we collected longitudinal data on hygiene-related health conditions and absenteeism. We also collected qualitative data with focus group discussions and interviews. Data were analyzed descriptively and with random effect regression models with the random effect at a cluster level. The primary outcome for health centers is the handwashing rate, defined as the number of times health care workers performed good handwashing practice with soap or alcohol-based handrub at one of the World Health Organization 5 moments for hand hygiene, divided by the number of moments

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for hand hygiene that presented themselves during the patient interaction within an hour of observation. For schools, the primary outcome is the number of students who washed their hands before eating.

Results: The baseline data collection across all countries lasted from February to June 2023. We collected data from 135 and 174 health care workers in Burkina Faso and Mali, respectively. In Nigeria, we collected data from 1300 students and in Palestine from 1127 students. The endline data collection began in February 2024.

Conclusions: This is one of the first studies investigating hand hygiene in primary health care centers and schools in protracted conflict settings. With our strong study design, we expect to support local policy makers and humanitarian organizations in developing sustainable agendas for hygiene promotion.

Trial Registration: ClinicalTrials.gov NCT05946980 (Burkina Faso and Mali); https://www.clinicaltrials.gov/study/NCT05946980 and NCT05964478 (Nigeria and Palestine); https://www.clinicaltrials.gov/study/NCT05964478

International Registered Report Identifier (IRRID): DERR1-10.2196/52959

(JMIR Res Protoc 2024;13:e52959) doi:10.2196/52959

KEYWORDS

water, sanitation, and hygiene; WASH; hand hygiene; impact evaluation; conflict settings; behavior change; handwashing; students; handwashing stations; primary schools, primary health care facilities; humanitarian crisis; mobile phone

Introduction

Background

Globally, approximately 3% of deaths and 5% of disability-adjusted life years are attributable to the effects of a lack of safe water, sanitation, and hygiene (WASH) [1]. More than half of WASH-attributable deaths occur in sub-Saharan Africa [1].

Hand hygiene is crucial to sustaining individual and community health. Pathogens can easily be transmitted from contaminated hands to other people's hands, eyes, and mouths [2]. Inadequate hand hygiene can therefore increase the risk for transmission of diarrheal, respiratory, and skin diseases [3-5].

In 2022, a quarter of people worldwide [6] and three-quarters of people living in sub-Saharan Africa [7] lacked access to basic hygiene, defined as having a functioning handwashing station on the premises with water and soap. Hand hygiene is of particular importance in health care centers and schools (which we collectively refer to here as facilities) because populations considered vulnerable frequent them. In these facilities, pathogens can spread easily over health care workers' or students' hands [8,9]. In health care centers, basic hygiene means additionally that the handwashing station needs to be at the point of care and within 5 m of toilets, while it can be equipped with hand sanitizer instead of soap [10]. Access to basic hygiene in both facility types is low. Only three-fifths of schools worldwide [11] and two-fifths of health care centers at the point of care in low- and middle-income countries [10] are estimated to have access to basic hygiene services. Handwashing stations are half as common in primary health care centers compared to secondary and tertiary health care centers [12].

In fragile and conflict settings, sanitation infrastructure is often overburdened, water quality is poor, and water quantity is insufficient [13,14]. Water is thus primarily used for drinking and cooking, and hygiene and sanitation needs become secondary [15,16]. Basic hygiene access in health care centers and schools is therefore of even greater importance. There are little data on handwashing practices in these facilities, although the United Nations Children's Fund estimates that >50% of children without basic hygiene at school live in fragile or conflict contexts [17]. Such facilities are often excluded from hand hygiene investigations during crises, despite the increased risk of infections [18,19]. Furthermore, collecting baseline data and following monitoring and evaluation activities of hand hygiene usually have a low priority in these facilities [14,18,19].

Objectives

Our study is embedded in the hands4health (h4h) project as an effectiveness evaluation component. The project is funded by the Swiss Agency for Development and Cooperation and led by 10 partners from academia, nongovernmental organizations, and the private sector [20] in close collaboration with the ministries of health (MoHs), ministries of education (MoEs), and other key stakeholders of the project countries, Burkina Faso, Mali, Nigeria, and Palestine (refer to Multimedia Appendix 1 for the project consortium overview). The h4h project has the overarching objective of increasing hygiene in primary health care centers and schools without any functional water supply in the context of protracted conflict settings. The h4h consortium developed a systematic approach with a multicomponent hand hygiene intervention (MCHHI; refer to the Intervention and Control subsection) to improve the health of patients, health care providers, students, and teachers by improving their hand hygiene and water infrastructure. Our study aims to evaluate the effectiveness of the h4h MCHHI on the hand hygiene of health care workers and students by achieving objectives 1 to 4 (Textbox 1). All our objectives will be assessed using a cluster randomized controlled trial (cRCT) design because the MCHHI is implemented at cluster level (ie, health care center or school). By publishing this protocol, we aim to transparently report our study design, methods, and statistical analysis plan. Consequently, we intend to avoid duplicate studies, coordinate research efforts, and demonstrate our accountability to report the results in a timely manner.

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Textbox 1. The hands4health (h4h) study aim with the more specific objectives 1 to 4.

Evaluate the effectiveness of the h4h multicomponent hand hygiene intervention (MCHHI) on the hand hygiene of health care workers and students

- Objective 1: assess the effectiveness of the h4h MCHHI on the hygiene-related risks, attitudes, norms, abilities, and self-regulation (RANAS) behavioral factors; handwashing behavior; and well-being of health care workers and students.
- Objective 2: assess the hygiene-related RANAS behavioral factors, handwashing practices, and well-being of health care workers and students at baseline.
- Objective 3: assess the perceived effectiveness of the h4h MCHHI on the health and well-being of health care workers and students in the intervention facilities.
- Objective 4 (exploratory): assess the effectiveness of the h4h MCHHI on the predefined health conditions and absenteeism of health care workers and students (objective 4 is exploratory because we did not take it into account during the sample size calculation; therefore, the sample size might be too small to detect a difference in the incidence of hygiene-related health conditions between the 2 study arms; however, as patient information remains anonymous, and the data collection does not add a big burden to the implementation partners, we decided to include this objective).

Methods

Study Design

We are conducting a parallel cRCT in 4 countries (Burkina Faso, Mali, Nigeria, and Palestine) with 2 study arms per country (Figure 1). For the cRCT, we collected baseline data in 24 primary health care centers per country (March to May 2023 in Burkina Faso and Mali) and 26 schools per country (February to June 2023 in Nigeria and Palestine). The data collection included hand hygiene observations; a survey about hand hygiene-related risks, attitudes, norms, abilities, and self-regulation (RANAS) behavioral factors as well as practices and well-being; and microbiological analyses of hand-rinse samples. The project partners implemented the h4h MCHHI in 12 randomly assigned primary health care centers and 13 randomly assigned schools per country. One to 2 months after the implementation of the intervention, we conducted follow-up data collection in both study arms where we repeated the observations and the survey, plus additional qualitative data in the respective intervention arms (November to December 2023 in all 4 countries). One year after baseline, we collect endline data in both study arms, including the same types of quantitative data as in the baseline data collection period (February to April 2024 in Burkina Faso and Mali and May-June 2024 in Nigeria and Palestine).

Figure 1. Overview of the hands4health study design, including the data collection methods M1 to M6. M1: module 1 (risks, attitudes, norms, abilities, and self-regulation and well-being survey); M2: module 2 (structured observation); M3: module 3 (hand-rinse samples); M4: module 4 (diary approach); M5: module 5 (focus group discussions); and M6: module 6 (key informant interviews).

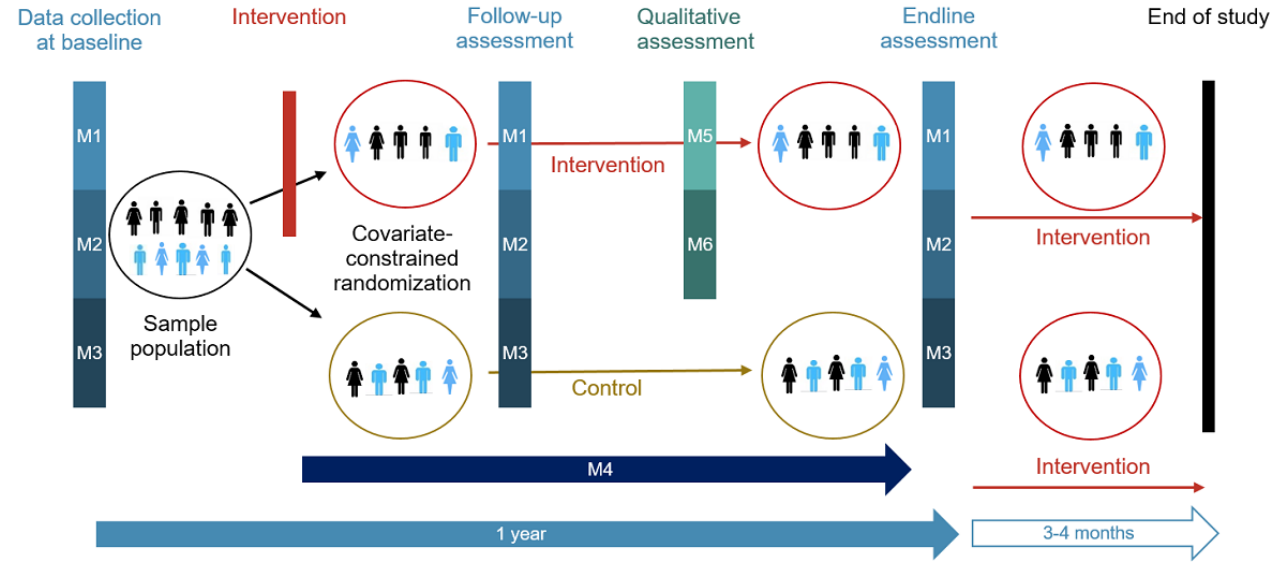

We use a mixed methods design [21,22]. By collecting qualitative data before the start of the cRCT and during the cRCT, we assess WASH-related needs and perceptions about the effectiveness of our intervention on the health and well-being of our study population. By collecting quantitative data about WASH-related health determinants such as the prevalence of handwashing and RANAS behavioral factors, we will assess the effectiveness of the h4h MCHHI on our study population's hand hygiene and well-being.

Our study design is based on previous h4h project activities. First, the project coordination partner commissioned 2 reviews on current tools used for WASH infrastructure in health care centers and schools [23]. Second, the main local implementation partners used a Facility Evaluation Tool for Water, Sanitation, and Hygiene in Institutions (FACET) to assess the WASH

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infrastructure of the facilities in the study regions [24]. Third, the project coordination partners led a theory of change approach [25]. The theory of change aims to understand the complexity of the WASH system in the study countries to identify key stakeholders, problems, and starting points for potential solutions. The partners conducted various workshops and interviews with stakeholders and project staff to support this process. Fourth and last, we collected qualitative data with focus group discussions (FGDs) to investigate the local perceptions and needs of hygiene in the pilot facilities. The project consortium then used all this information to develop the h4h MCHHI for each country (refer to Multimedia Appendix 2 [26-37]).

Setting

This study focuses on primary health care centers in rural areas of Burkina Faso and Mali and primary schools in Nigeria and Palestine from 2021 to 2024 (Table 1). All 4 countries involved in this study are subject to protracted conflicts. In the West African countries, jihadists and other radical groups have been terrorizing the population, leading to a rise in internally displaced persons, while Palestine has been under Israeli military occupation for 56 years [38-41]. All targeted facilities in our study regions suffer severe water shortages and a lack of WASH infrastructure and maintenance activities. Moreover, most facilities expect being overcrowded in the near future due to a rise in internally displaced persons. In Maiduguri, Borno State, Nigeria, the schools are already overcrowded, with an average of 101 students per elementary class [42].

Table 1. Description of the country settings of the hands4health project.

	Burkina Faso	Mali	Nigeria	Palestine
Cluster type	Primary health care centers	Primary health care centers	Primary schools	Primary schools
Clusters (n=100), n (%)	24 (24)	24 (24)	26 (26)	26 (26)
Geographic region	West Africa	West Africa	West Africa	Middle East
Country region	Boucle du Mouhon	Ségou and San	Borno State	West Bank
Districts	Dédougou and Boromo	Macina, Markala, San, and Tominian	Maiduguri	Hebron
Reasons for instability	Occupation by jihadist and other radical groups; 2 coups d'états and a political crisis	Occupation by jihadist and other radical groups; 2 coups d'états	Boko Haram insurgency	Israeli military occupation
Internally displaced people per country, n	2.06 million[a]	375,500[b]	2.2 million[c]	N/A[d]

[a]Burkina Faso: Aperçu des personnes déplacées internes (Overview of internally displaced persons; United Nations Office for the Coordination of Humanitarian Affairs [OCHA]; March 31, 2023) [43].

[b]Mali: Tableau de bord humanitaire (Humanitarian dashboard; OCHA; April 30, 2023) [44].

[c]Nigeria: Situation Report (OCHA; July 18, 2023) [45].

[d]N/A: not applicable.

Intervention and Control

The MCHHI varies by study country because it was adapted to each country's needs, local acceptability of intervention components, and tools available for health care centers or schools (refer to Multimedia Appendix 2 for a detailed description). The intervention components, covering hardware, management and monitoring, and behavior change are depicted in Figure 2. In terms of hardware, a handwashing station that recycles water, called Gravit'eau, was locally built and adapted in terms of height and size of basin to the type of institution (ie, health care center or school) in the African countries. Per health care center, 2 individual stations were installed and positioned according to the health care provider's wishes. In Nigeria, 2 stations were placed near 4 to 6 classrooms and toilet areas serving our selected sample of 50 students in each school. In Palestine, recycled water was not culturally accepted. Therefore, instead of receiving a station, we supported the schools with infrastructure rehabilitation work. Facilities in the control arm will receive the intervention once the cRCT is completed. Any viable potential improvements identified during the trial will be implemented.

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Figure 2. The hands4health multicomponent hand hygiene intervention components implemented in at least one of the study countries grouped according to hardware (yellow), management and monitoring (blue), and behavior change (green). The icons were sourced from Freepik. RANAS: risks, attitudes, norms, abilities, and self-regulation; WASH FIT: Water and Sanitation for Health Facility Improvement Tool.

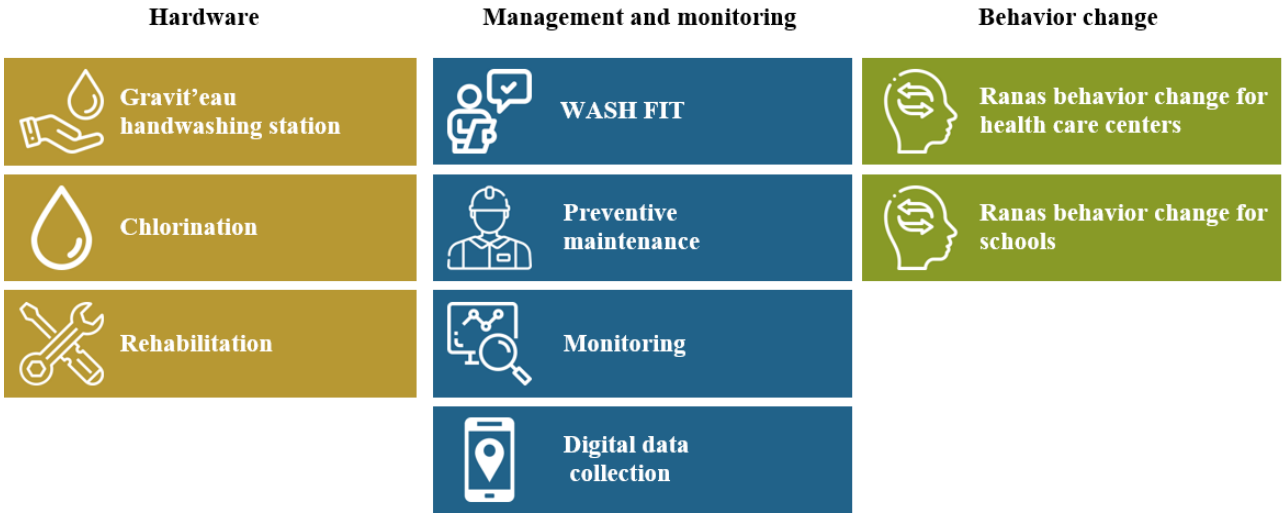

Recruitment and Eligibility

Primary Health Care Centers

We selected the primary health care centers with the support of the local implementation partners. They conducted a FACET survey in 179 centers in Burkina Faso and 60 centers in Mali. From these centers, we selected a subset based on the following inclusion criteria: at the time of the FACET survey, the facility (1) did not have any water source directly connected to the building, (2) had a maternity ward, (3) had at least 5 employees, and (4) was impacted by insecurity but was still deemed accessible to the implementation partners. Of the centers meeting these criteria, the implementation partners chose 48 (n=24, in each country) that were most likely to remain accessible for at least 1 year.

As study participants in the health care centers at baseline, we invited all health care workers who met the inclusion criteria and were present at the time of data collection for the quantitative data collection. The inclusion criteria for the quantitative data collection were as follows: health care workers (1) aged at least 18 years and (2) in direct physical contact with patients. The exclusion criteria were as follows: health care workers (1) whose primary occupation does not involve the health care center of the h4h project, (2) who have a skin condition that precludes the use of soap or alcohol-based handrub, and (3) who refuse to participate. All recruited participants received a unique ID. The same eligibility criteria will apply for the follow-up (1-2 months after the intervention) and endline (12 months from the baseline) data collection.

As part of the quantitative data collection in health care centers, we conducted structured observations during patient consultations. The patients needed to fulfill the following inclusion criteria: (1) aged at least 18 years or being accompanied by a legal guardian aged ≥18 years; and (2) visiting the facility for a physical examination, injections or vaccinations, or a blood test. We did not observe sensitive procedures such as giving birth.

Participants for the qualitative data collection at follow-up will be recruited from those who participated in the quantitative baseline data collection. In addition, we will seek to recruit others working in the intervention centers, such as hygiene technicians or people working in administrative positions, as well as stakeholders within the community, state, region, or country of the intervention whose position is related to WASH in health care centers.

Primary Schools

The MoE in Nigeria and Palestine identified 51 and 50 schools, respectively, as being greatly in need of WASH infrastructure. The implementation partners conducted a FACET survey in each of these schools before the start of this study. From these 101 schools, we selected 52 (51.5%; n=26, in each country) based on the following inclusion criteria: at the time of the FACET survey, the school (1) was deemed accessible to the implementation partners, (2) lacked a functional water source, and (3) had ≤7000 students studying in grades 5 to 7.

For the baseline data collection, we selected 50 eligible students aged 10 to 12 years from 1 or 2 classes from each school using random sampling. If a school had a single class consisting of ≥50 students within our target age group, we selected our sample from this class. However, if no class in our target age group had ≥50 students, we randomly selected 2 classes from within the target age group and selected our sample from these classes. For the different data collection modules, we randomly selected subsets from the 50 previously selected students (Figure 1). The inclusion criteria for both quantitative and qualitative data collection were as follows: (1) aged 10 to 12 years and (2) registered at the school for the duration of the study period (1 year). The exclusion criteria included (1) not providing signed consent (for the guardians) and assent form (for the students), (2) having a medical condition that prevents them from washing their hands, (3) having unexplained intermittent attendance in school (school teachers were consulted, and the school's absenteeism records were checked), and (4) not being in the same school for the course of the study (1 year). The same 50 students will be revisited for the follow-up (1-2 months after

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the intervention) and endline (12 months from the baseline) data collection.

In addition to the data collected from students, we will collect qualitative data from teachers and key stakeholders at follow-up. The eligibility criteria for teachers are as follows: (1) aged ≥18 years, (2) permanent employee in one of the intervention schools, and (3) teaching one of the classes included in the intervention. The exclusion criterion is refusal to participate. Key stakeholders will be identified through purposeful sampling, primarily through consultation with the local implementation partners. Key stakeholders will be eligible for inclusion in the study based on the following criteria: (1) they occupy a role within the community, state, or region of the study that is associated with WASH in schools (eg, teachers and school principals or people working in any of the organizations that are part of the WASH cluster, such as the MoE or MoH); and (2) they are aged ≥18 years. The exclusion criterion is refusal to participate.

Ethical Considerations

All our study protocols were approved by the Ethikkommission Nordwest- und Zentralschweiz (Ethics Committee for Northwestern and Central Switzerland; AO_2023-00004 and AO_2023-00047) and the ethics boards in each project country: (1) the Comité d'Ethique pour la Recherche en Santé (Ethics Committee for Health Research) in Burkina Faso (2023-02-020), (2) the National Institute of Public Health in Mali (05/2023/CE-INSP), (3) the National Health Research Ethics Committee in Nigeria (21/2023), and (4) the institutional review board of An-Najah National University in Palestine (H Sp. Feb. 2023/18). Study participants in the health care centers and legal guardians of schoolchildren gave written informed consent to participate in this study, whereas schoolchildren gave oral assent. For structured observations, the local implementation partners obtained consent in both facility types before the baseline observations. At the health care center level, consent was obtained from the director of the center for the duration of the study period. In addition, oral consent was obtained from the patients who visited the centers at the time of the observations. Similarly, at the school level, consent was secured from the school administration and from the parents of the participating students. All participants received a unique ID that was coded and will be completely anonymized by the end of this study. Our study protocols for health care centers and schools are registered in ClinicalTrials.gov (NCT05946980 and NCT05964478). We report our study in line with the CONSORT (Consolidated Standards of Reporting Trials) statement: extension to cluster randomized trials [46].

Randomization

We used covariate-constrained randomization to allocate facilities into the control and intervention arms. This methodology, also referred to as restricted randomization, was first suggested by Moulton [47] to minimize the risk of baseline imbalances. These issues are usually more prominent in cRCTs due to the relatively low number of randomized units.

A statistician who was not involved in any h4h field activities performed the covariate-constrained randomization after baseline data collection following these steps: (1) definition of a set of maximum imbalance criteria for several important baseline characteristics, (2) generation of a list of all potential allocation sequences that satisfy these criteria, (3) verification of the independence of units, and (4) random selection of one of the valid sequences as the final allocation.

For health care facilities in Mali and Burkina Faso, we defined the following four constraints: (1) proportions of health care facilities with shortages in water sources should be perfectly balanced, (2) a difference in the proportion of secure facilities of <10 percentage points, (3) a difference in the mean proportions of the population living within 5 km of <10 percentage points, and (4) a difference in the mean proportions of accurate handwashing in each facility of <3 percentage points. In Mali and Burkina Faso, 248,574 and 767,792 potential allocation sequences, respectively, satisfied all 4 criteria.

For schools in Palestine, we first stratified the clusters before applying the restricted randomization. This stratification was based on two key parameters: (1) the directorate in which the school is located; and (2) the school's geographic location, categorized as city, town, or village. After stratification, the allowed allocation sequences had to satisfy the following criteria: (1) balanced administrative areas for schools across both arms, (2) balanced sex, (3) a difference of ≤33% points in the proportions of schools connected to a water network across the arms, (4) a difference of ≤33% percentage points in the proportions of schools with consistent access to water, (5) a difference of <50 in the mean numbers of students across the arms, (6) a difference of <0.2 in the mean grades across the arms, and (7) a difference of <50 in the mean ratios of the number of handwashing stations to the total number of students across the arms. In total, 394 potential allocation sequences satisfied all criteria.

For Nigeria, we defined the following criteria: (1) similar proportions of schools with no currently available water source, (2) similar proportions of schools with <2 days of water availability, (3) similar proportions of schools located in a village as opposed to a city or town, and (4) similar proportions of primary schools in comparison to mixed primary and secondary schools. Other variables allowed a certain degree of imbalance but still required consideration to ensure appropriate balance. These included (1) a difference of ≤200 students in the average student numbers per school between the study arms, (2) a difference of ≤25 percentage points in the proportions of schools with water network connections across the arms, and (3) a difference of ≤25 percentage points in the proportions of schools with water availability for 3 to 5 days a week across the arms. Of all potential allocation sequences, 57,054 satisfied all criteria.

Blinding

To reduce selective counting of colony-forming units (CFUs) of bacteria in the hand-rinse samples collected at baseline, the laboratory workers assessing the number of CFUs were blinded. The data collectors delivered the coded samples to the laboratory workers. From the identification code of the samples, the laboratory workers could not derive whether the sample was collected in an intervention facility or a control facility. The

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laboratory workers will be blinded again at endline data collection.

Quantitative Methods

We collected quantitative data with four different modules: (1) module 1 (RANAS and well-being survey), (2) module 2 (structured handwashing observations), (3) module 3 (microbiological analysis of hand-rinse samples), and (4) module 4 (diary approach for predefined health conditions).

Module 1: RANAS and Well-Being Survey

We started the survey by asking participants about sociodemographic information, followed by knowledge questions about hand hygiene and self-reported hand hygiene practices (for detailed descriptions of the variables, refer to Multimedia Appendix 3). The survey proceeded with questions to measure the RANAS behavioral factors, such as perceptions of costs and benefits of consistent hand hygiene, social norms, and ability beliefs, on 5-point Likert scales to measure frequencies, magnitudes, and degrees [27]. Questions about the hygiene infrastructure in the facilities followed this section. In health care centers, there were additional survey items on the quality of care, and in schools, on student well-being. Well-being was assessed with the KINDL tool (Kinder Lebensqualität Fragebogen, Children's Quality of Life Questionnaire), which was developed specifically to measure health-related quality of life in children and adolescents by assessing different domains of well-being [48].

We conducted the survey with all participating primary health care workers and a randomly chosen subset of 25 students per school at baseline and will repeat at follow-up (1-2 months after the intervention) and endline (12 months from the baseline). The survey will be interviewer administered using Open Data Kit Central software (version 2022.3.1) on Android tablets or smartphones.

Module 2: Structured Handwashing Observations

Structured handwashing observations are considered the gold standard method to assess handwashing behavior [12,49]. We conducted the observations with primary health care workers and schoolchildren at baseline and will repeat these observations at follow-up and endline. Due to structural differences in health care centers and schools, we chose 2 different observation approaches for the 2 facility types.

In primary health care centers, staff members from the implementation partner or the regional MoH were trained by the first author (AG) as observers for the baseline data collection. Observers usually worked in the health care centers in a different role, and they visited the facility under the pretext of performing their usual role and did not declare that they were observing handwashing. Hence, the handwashing observations were conducted covertly. The observers were equipped with an observation tool programmed in Open Data Kit Central (version 2022.3.1) on their smartphone. During their visit, they spent 1 hour in each unit to record all hand hygiene actions taken by the health care providers, as well as their handwashing techniques [50]. The same observation process will be repeated at follow-up and endline.

In schools, student handwashing was observed by implementation partners who were trained by the second author (YA). To aid the identification of participating students, all children were given badges, with 1 color for those participating and another for those not participating. The students were told that the color assignment was random. The implementation partners observed each student's handwashing practices across a variety of occasions, including the 2 critical moments: before eating and after using the toilet (among others, eg, after eating and after playing). To observe handwashing before eating, we involved the students in an experiment. We engaged the children in a 30-minute painting activity, after which the children were rewarded with a popcorn snack and granted a 15-minute break to enjoy it together. This created an opportunity to observe whether the children washed their hands before eating the snack. Observers did not reveal their intention of observing handwashing throughout the time of the data collection. In Nigeria, we additionally observed the children for 3 hours. The observation started at 9 AM (60 minutes before the breakfast break) and ended at noon (90 minutes after the break). Four observers were stationed near all available water points and toilets. Using a paper-based observation tool, the observers recorded all participating students who washed their hands and whether they did so before eating, after using the toilet, or at another time point. In addition, any participating student observed using the toilet who did not wash their hands was also recorded.

Observers then cross-checked their results to eliminate instances of duplicate observations for the same students. They merged observations made at different critical times or water points for the same student and confirmed whether those who used the toilet also washed their hands, particularly in scenarios where toilets were situated at a considerable distance from the water points. After this cross-checking process, the data were transferred to Open Data Kit Central (version 2023.3.1) for analysis and storage. These observations yielded a dichotomous measure: whether handwashing occurred at each critical event. However, options such as "not visible" or "soap or water was not available" were included to account for potential complications. If feasible, we observed the handwashing steps of students who washed their hands. Observations will be repeated in schools at follow-up and endline.

Module 3: Microbiological Analysis of Hand-Rinse Samples

We collected hand-rinse samples of all participating health care workers and a randomly selected subset of 12 students at baseline with a modified glove juice method as described by Pickering et al [51]. We asked the participants to insert their hand into a Whirl-Pak bag (Nasco Sampling LLC; sizes 2041 mL and 7120 mL for adults and children, respectively), filled with 350 mL of bottled drinking water without chlorine. The participants were asked to shake their hand in the water and rub their thumb and fingers together for 15 seconds, and then the sample collector massaged the participant's hand through the bag for another 15 seconds [51]. Afterward, we repeated the procedure with the other hand.

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We kept the Whirl-Pak bags containing the samples on ice in an isolation box and processed them within 8 hours of sampling [51]. We used membrane filtration to detect CFUs of *Escherichia coli* and total coliforms. In a field laboratory, we passed 100 mL of the bag's content through the filter paper, which we then placed on Nissui Compact Dry EC plates (Shimadzu Diagnostics Europe) to incubate them at 35 °C −0.5 °C to +0.5 °C for a duration of 24 hours [51]. For quality control, we carried out a duplicate filtration of every 10th sample and a negative control, only containing the bottled water, each day.

We calculated the lower detection limit of CFUs by dividing 1 CFU per plate by the filtrate volume and then multiplying it by the total Whirl-Pak volume of 350 mL. We calculated the upper detection limit by dividing 301 CFUs per plate by the filtrate volume and then multiplying it by the Whirl-Pak volume. We normalized and $\log_{10}$-transformed the CFUs per hand for the statistical analysis [51]. We will repeat the same hand-rinse sampling procedure again at follow-up and endline.

Module 4: Diary Approach for Predefined Health Conditions

Using a diary approach, we will ask health care center directors to collect longitudinal data on the hygiene-related health conditions of patients. These conditions include maternal and neonatal mortality, stillbirths, postpartum endometritis, neonatal sepsis, umbilical cord infections, and infections of wounds after treatment. For each relevant health condition among patients, the director will be asked to report the date of diagnosis, and if known, the duration of the condition, the etiology, and ultimate outcome (eg, recovery or death). Detailed descriptions of the health conditions are presented in Multimedia Appendix 4 [52].

Similarly, hygiene-related absences of all participating health care workers and the 50 students will be reported during the period after the intervention until the endline data collection in both study arms. For absenteeism in health care centers or schools, the person responsible will record the event, the number of days absent, and the reason for the absence. We define absenteeism as hygiene related if the facility worker or student experienced diarrheal diseases (including cholera), respiratory tract infections (including tuberculosis, COVID-19, and influenza), bacterial infections of the skin and eyes (including trachoma), and newly diagnosed HIV and hepatitis B or C. The diary will consist of 1 table per month containing all different health conditions and subcategories. No personal information will be recorded in this module.

Outcomes

Primary Outcome

Due to the difference in settings, health care centers and schools have different primary outcomes. In health care centers, the primary outcome is the handwashing rate, defined as the number of times each health care worker performs good handwashing practice with soap or alcohol-based handrub at one of the World Health Organization (WHO) 5 moments for hand hygiene [53], divided by the number of moments for hand hygiene that presented themselves during the patient interaction. The handwashing rate was assessed by structured handwashing observations over 1 hour per unit in a health care center. The 5 moments for hand hygiene are defined by the WHO as follows:

1. Before touching a patient
2. Before clean or aseptic procedures
3. After risk or exposure to body fluids
4. After touching a patient
5. After touching a patient's surroundings

In schools, the primary outcome is the number of participating students who wash their hands before eating. This number was collected using structured handwashing observations after students were given a snack after their participation in a painting activity. We selected this outcome because it allows for an objective assessment across all participating students, given that all were presented with this handwashing opportunity during the course of the experiment.

Secondary Outcomes

The most important secondary outcomes in both settings are as follows:

1. Self-reported handwashing practice on a Likert scale ranging from *almost never* to *almost always* (in health care centers: for each of the 5 moments for hand hygiene; in schools: before eating and after using the toilet)
2. The $\log_{10}$-transformed number of total coliforms and *E. coli* CFUs per hand before handwashing
3. RANAS behavioral factors measured on a 5-point Likert scale
4. Hygiene-related absenteeism and health conditions, which are summarized in Multimedia Appendix 4; the sum of each outcome variable will be used separately per facility (cluster) as a measure for statistical analysis, and health conditions will be reassessed with local experts in the respective countries to ensure feasibility before the start of the intervention

Secondary outcomes only applying to the school setting are as follows:

1. Good handwashing practice defined as the number of students who wash their hands after using the toilet (assessed by structured handwashing observation)
2. Self-reported well-being of students assessed using the KINDL tool [48], with responses given on a Likert scale ranging from *almost never* to *almost always*

Statistical Analysis

Sample Size Calculation

We ran a series of simulations using R software (version 4.1.3; R Foundation for Statistical Computing) to determine the required sample size for health care centers. For the simulations, we assumed 6 staff members per health care center, a mean number of 5 (SD 5) times a person was supposed to wash their hands, and an intracluster correlation coefficient of 0.15; we needed to enroll 10 health care centers in each trial arm to detect a difference of 15 percentage points in the proportions of handwashing during the 5 critical moments for handwashing (30% control vs 45% intervention) with 81% power at a 2-tailed 5% significance level. To account for potential loss to follow-up,

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we enrolled 24 health care centers per country in Burkina Faso and Mali.

Within schools, we assessed the number of clusters (schools) and students per school with simulations using R. We aimed for a power of 80% at the 95% CI and anticipated an intraclass correlation coefficient of 0.2. In the simulation, we assumed a prevalence of handwashing before eating of 20% in control schools versus 45% in intervention schools after 1 year from the baseline. On the basis of this assumption, we needed 13 schools per trial arm with 50 students per school. However, the number of students assessed for different modules will differ throughout the study due to capacity limitations of assessing the 50 students included in each school.

Statistical Methods

We summarized baseline characteristics using descriptive statistics (Textbox 2). We will investigate the difference in the observed proportions of always handwashing at the 5 critical moments as defined by the WHO for primary health care centers and of the number of participants who wash their hands before eating for primary school students between the 2 study arms at follow-up using random effect logistic regression models. We will only include the intervention as a predictor in the primary analysis. For the primary analysis, we will use the available case population of health care workers and students, which will be analyzed according to the intent-to-treat principles.

Textbox 2. Statistical methods used for the analysis of the results of the different quantitative modules of the hands4health study.

Modules and statistical methods

- Risks, attitudes, norms, abilities, and self-regulation and well-being survey (module 1)
  - Descriptive statistics
  - Random effect linear regression modeling
  - Random effect logistic regression modeling
- Structured handwashing observations (module 2)
  - Random effect logistic regression modeling
- Microbiological analysis of hand-rinse samples (module 3)
  - Random effect negative binomial regression modeling
- Diary approach for predefined health conditions (module 4)
  - Descriptive analysis with the sum of each outcome variable calculated separately per facility
  - Random effect linear regression modeling

Qualitative Methods and Analysis

Before the baseline data collection and at follow-up, we supplement our quantitative methods with two modules of qualitative methods: (1) module 5 (FGDs) and (2) module 6 (key informant interviews [KIIs]).

Module 5: FGDs

FGDs offer a practical way to gather insights more efficiently than other qualitative methods [54,55]. Before the onset of the study, the local implementation partners with experience in qualitative data collection collected data through FGDs involving health care workers, students, and teachers. These FGDs helped us to gain insight into the hygiene-related needs as well as the acceptability of our intervention among health care workers and students. We let the groups vote for their most urgent hygiene-related needs as well as the potential positive and negative impacts of our intervention. After counting and discussing the votes during the FGD, the project consortium adapted the country-specific interventions, and we identified what we needed to include in the quantitative data collection.

We collect data with FGDs again since January 2024 and will continue this data collection until April 2024 with the same trained implementation partners for health care workers and students to assess the perceived effectiveness and potential improvements of the h4h intervention. In addition, we will conduct FGDs with teachers from the schools in the intervention arm. We will train the team containing at least 1 moderator and 1 observer or notetaker before data collection. If the security situation allows, AG or YA will join the team. We will use a field research journal throughout the study to take structured notes and observations of the FGDs. We will audio record and transcribe the discussions and then translate into French or English for further analysis.

All health care workers in the intervention centers will be invited to participate in FGDs.

In health care centers, we will take into account the structures of hierarchy and gender when building mini groups of 3 to 4 participants to allow participants the greatest possible freedom of speech. We chose to have mini groups because the health care workers who participate are expected to have a high expertise in hand hygiene. Usually, the higher the expertise of participants, the smaller the group can be [54]. Depending on the hierarchical levels, 1 to 4 FGDs will take place per facility. We expect to conduct a maximum of 20 FGDs per country (fewer if we reach saturation beforehand) [55].

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In schools, we will select students from each class in the intervention arm, in consultation with the school administration. We will conduct FGDs with 5 to 10 boys and girls separately until saturation is reached (or up to the maximum of 5 FGDs with each sex) and 5 FGDs with teachers [55]. KIIs may be conducted instead of FGDs if we do not have enough participants to form groups in both facility types.

Module 6: KIIs

Aiming to further explore issues arising from the FGDs and to understand perceptions of the intervention, we will conduct KIIs with other stakeholders who influence the project's intervention areas, such as representatives of the MoH and MoE as well as local majors. We have identified some of these key informants through the theory of change approach, while others will be suggested by local partners. Here, we chose individual interviews rather than FGDs so that the stakeholder's status does not influence other participants' freedom of speech [55].

If necessary and appropriate, we may carry out interviews on the web, in French or English. Local project partners with experience in interviewing will conduct stakeholder interviews until saturation is reached [55]. We will apply the same steps of audio recording, transcription, and translation for the KIIs as for the FGDs.

We will analyze FGD and KII transcripts as well as field and observation notes using the framework method [56] with MAXQDA software (VERBI GmbH) with at least 1 local partner per country with qualitative expertise.

Triangulation of Results

We triangulate our results throughout the study. Qualitative data from the pilot phase informed our quantitative data collection at baseline. Moreover, questions identified during the quantitative baseline and follow-up data collection will guide our qualitative FGDs and KIIs, which can then be used to better understand our results from the endline data collection By triangulating the results, we will be able to validate them, find discrepancies, and increase our understanding of why certain quantitative results emerged [21,22]. In addition, we might identify new research gaps and potential solutions to issues that we identified during the study period.

Results

The baseline data collection of this study started in February 2023 and ended in June 2023. In Burkina Faso, we conducted 95 RANAS surveys, observed 82 participants, and collected 99 hand-rinse samples in 24 primary health care centers. In Mali, we conducted 105 RANAS surveys, observed 111 participants, and collected 100 hand-rinse samples in 24 primary health care centers. As of March 2024, the analysis of the baseline results in health care centers is completed and a manuscript will be submitted within the same month for publication. In Nigeria, we conducted 640 RANAS surveys, observed 1300 participants, and collected 369 hand-rinse samples in 26 primary schools. In Palestine, we conducted 646 RANAS surveys and observed 1127 participants in 26 primary schools. We did not collect hand-rinse samples in Palestine because the method was deemed culturally inappropriate by the MoE. As of March 2024, data analysis for schools is ongoing. Follow-up data collection took place from November to December 2023 in 24 health care centers in Burkina Faso and Mali, respectively and in 26 schools in Nigeria. Due to the crisis in Palestine, follow-up activities were suspended. As of March 2024, data analysis remains ongoing. Qualitative data collection started in Burkina Faso in January 2024 and is planned to start in Mali and Nigeria in March 2024. Endline data collection started in Mali in February 2024 and will be completed in all countries by June 2024. We will publish more results investigating data collected during the follow-up, qualitative, and endline data collection in the year 2024. Project funding is guaranteed until December 2024.

Discussion

Summary

By implementing a mixed methods approach within a cRCT study design with multiple stakeholders from academia, the private sector, humanitarian organizations, and MoHs and MoEs, we aim to better understand the complex situations in our 4 project countries. We used mixed methods to generate much-needed quantitative data about the WASH infrastructure and behavior in primary health care centers and schools in regions where such data are usually very scarce. At the same time, the qualitative data help to better understand the reasons behind the effectiveness of our intervention and to capture intricacies missed with quantitative data collection. In our opinion, conducting research across disciplines is crucial in humanitarian crisis contexts to guarantee ethical and beneficial outcomes, which policy makers can then use locally.

Research in Conflict Settings

The demand for research in conflict settings is increasing to support evidence-based interventions and impact evaluations [49]. Unfortunately, this type of research is still rare and the quality of existing studies poor [57]. Apart from obvious challenges such as the researchers' and participants' security as well as political instability, additional difficulties might hinder research in these settings [58]. These difficulties include a lack of data, determining the study population, knowing the baseline health status of the study population, displacement of the study population, and issues with logistics [58]. We tried to respond to these difficulties by involving local actors from humanitarian and governmental organizations and the facilities from the project outset. However, the rapidly changing political and security situations in the project countries make it difficult to plan ahead.

Strengths and Limitations

Our study has some noteworthy strengths: first, with the cRCT, we use the study design with the highest level of evidence [59]. Second, by using mixed methods, we can further strengthen our results by triangulation. Third, the design of the MCHHI is data driven and hence well adapted to promoting sustainability in the contexts in which it was implemented. Fourth, one of the core strengths of this study lies within our inter- and transdisciplinary teams and consortium. By including the humanitarian sector, local authorities, health care personnel, teachers, and students early in the process through regular

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meetings, the theory of change workshops, and FGDs, we expect to address real needs with our research. Throughout the process of developing the study protocol, we kept consulting with our partners through regular remote meetings and several in-person workshops in the respective countries. This close exchange throughout the project enabled us to rigorously and continuously evaluate the situation in the unstable settings we worked in. Fifth, by conducting this project in 4 different countries, we can gain valuable insights into how the h4h MCHHI needs to be adapted to different contexts and how it can be made more readily available for future interventions in other regions. Finally, we address big data gaps with this study. In Burkina Faso and Mali, the current MoHs actively want to strengthen hygiene, water, and sanitation in health care. However, they lack data about hand hygiene and WASH infrastructure in primary health care to inform their campaigns. This study can inform them directly about current practices and how they can or cannot be influenced with our proposed MCHHI. In schools, the respective MoEs have expressed a keen interest in this study. The findings, which clarify student hand hygiene, are anticipated to be of considerable value. These insights will not only inform about the intervention's impact but will also guide the MoEs in scaling the intervention across a broader spectrum. By identifying the strengths and weaknesses of the intervention, they can further enhance and replicate the successful aspects while avoiding any identified shortcomings.

Despite the strengths, our study has some limitations. First, we could not choose facilities completely at random. They needed a high probability of remaining accessible to the local partners. Therefore, our results are not fully generalizable and might miss some of the people considered most vulnerable and inaccessible. Second, due to the nature of this study, we could not blind the participants, our implementation partners, or the people conducting the statistical analysis. Therefore, a nonblinding bias cannot be excluded. Third, to maintain a balance between achieving a sample size of institutions for a high enough statistical power and having a sufficient budget to implement hardware interventions in all these institutions, 2 Gravit'eau stations per institution were implemented. In health care centers, we expect an average of 3 health care workers using 1 station and, if accessible to patients, approximately 20 patients per day. In schools, the stations were designed to accommodate up to 100 individuals per hour. Judging from the station's strategic positioning, we estimate that 250 to 300 students will be using 1 station during a school day. Fourth, we expect a high social desirability bias in the self-reported handwashing and hygiene behavior data. We anticipate having a more realistic and objective view of handwashing and hygiene behavior by complementing the survey data with observation and hand-rinse data. Fifth, the structured observations might be subject to a Hawthorne effect [60]. We aim to counteract this effect by conducting the observations covertly before the official beginning of the study. In health care centers, we chose implementation partners and MoH staff who regularly visit the centers for other supervision activities unrelated to handwashing. This might still change the participants' behavior, but we expect they did not focus too much on handwashing. We had to inform the head of health care centers before the observations for ethical reasons. Therefore, the possibility that the participants knew why they were observed remains.

Conclusions

To our knowledge, this is one of the most innovative studies to investigate the effectiveness of an MCHHI on the health determinants of beneficiaries in primary health care centers and schools. With our sound inter- and transdisciplinary methodological approach, we expect to generate results and conclusions that can sustainably impact local policy makers and the humanitarian sector working in the project countries and beyond.

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Authors' Contributions

MSW is the principal investigator of all impact evaluation research activities of the hands4health study. AG and YMA are responsible for the study design, ethics approval, trial registration, fieldwork supervision, and data analysis. JH was the main statistical adviser, supported by BNO, and KG was the main adviser for the qualitative study design. AB is a focal point of the implementation partner and advised during the process of developing the study protocol, supported all implementation activities, and leads the Water and Sanitation for Health Facility Improvement Tool intervention. MH, MNDF, and AT developed the risks, attitudes, norms, abilities, and self-regulation survey and led the whole RANAS approach. CB and MP developed all infrastructure-related tools and were involved in the overall project management. AG, YMA, BNO, and MSW drafted the manuscript. CB, AB, MNDF, MH, JH, KG, MP, and AT revised the manuscript.

Conflicts of Interest

AT, MNDF, and MH are cofounders of Ranas Ltd. However, Ranas Ltd has no patents, products in development, or marketed products associated with this research. MP is a cofounder of Gravit'eau. However, Gravit'eau is a nonprofit organization that does not promote the handwashing stations with marketing. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
The hands4health consortium.
[PDF File (Adobe PDF File), 435 KB - resprot_v13i1e52959_app1.pdf]

Multimedia Appendix 2
The hands4health multicomponent hand hygiene intervention.
[PDF File (Adobe PDF File), 552 KB - resprot_v13i1e52959_app2.pdf]

Multimedia Appendix 3
Description of the variables of the risks, attitudes, norms, abilities, and self-regulation and well-being survey.
[PDF File (Adobe PDF File), 446 KB - resprot_v13i1e52959_app3.pdf]

Multimedia Appendix 4
Details of hygiene-related absenteeism and health conditions.
[PDF File (Adobe PDF File), 425 KB - resprot_v13i1e52959_app4.pdf]

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Abbreviations

CFU: colony-forming unit
CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
FACET: Facility Evaluation Tool for Water, Sanitation, and Hygiene in Institutions
FGD: focus group discussion
h4h: hands4health
KII: key informant interview
MCHHI: multicomponent hand hygiene intervention
MoE: ministry of education
MoH: ministry of health
RANAS: risks, attitudes, norms, abilities, and self-regulation
WASH: water, sanitation, and hygiene
WHO: World Health Organization

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Protocol

Effectiveness of Sensitization Campaigns in Reducing Leprosy-Related Stigma in Rural Togo: Protocol for a Mixed Methods Cluster Randomized Controlled Trial

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Abstract

Background: In the global strategy to eliminate leprosy, there remains a need for early case detection to successfully interrupt transmissions. Poor knowledge about leprosy and leprosy-related stigma are key drivers of delayed diagnosis and treatment. Sensitization campaigns to inform and increase awareness among the general population are an integral part of many national neglected tropical disease programs. Despite their importance, the effectiveness of such campaigns has not been rigorously studied in the West African context. A multilingual rural setting with low health literacy in this region presents challenges to the potential impact of sensitization campaigns.

Objective: The primary objective of this study is to assess the causal effect of common practice community sensitization campaigns on leprosy-related knowledge and stigma at the community level and among community health volunteers. Additionally, we will test the potential of novel educational audio tools in the 15 most prominent local languages to overcome literacy and language barriers and amplify sensitization campaigns.

Methods: We will conduct a cluster randomized controlled trial using a sequential mixed methods approach in 60 rural communities across all regions of Togo, West Africa. The study features 2 intervention arms and 1 control arm, with intervention and control assignments made at the community level through randomization. Communities in intervention arm 1 will receive a sensitization campaign in line with the current Togolese national neglected tropical disease program. Communities in intervention arm 2 will receive the same sensitization campaign along with educational audio tools distributed to community households. The control arm will receive no intervention before data collection. Quantitative outcome measures on knowledge and stigma will be collected from a random sample of 1200 individuals. Knowledge will be assessed using the 9-item standardized Knowledge, Attitudes, and Practices Questionnaire. Stigma will be measured using the 7-item Social Distance Scale and the 15-item Explanatory Model Interview Catalogue Community Stigma Scale. We will estimate intention-to-treat effects at the individual level, comparing

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the outcomes of the intervention and control arms. In an accompanying qualitative component, we will conduct in-depth interviews with community members, community health volunteers, and health care workers in both treatment arms and the control arm to explore intervention and stigma-related experiences.

Results: This paper describes and discusses the protocol for a mixed methods cluster randomized controlled trial. Data collection is planned to be completed in June 2024, with ongoing data analysis. The first results are expected to be submitted for publication by the end of 2024.

Conclusions: This trial will be among the first to test the causal effectiveness of community-based sensitization campaigns and audio tools to increase knowledge and reduce leprosy-related stigma. As such, the results will inform health policy makers, decision-makers, and public health practitioners designing sensitization campaigns in rural multilingual settings.

Trial Registration: German Clinical Trials Register DRKS00029355; https://drks.de/search/en/trial/DRKS00029355

International Registered Report Identifier (IRRID): DERR1-10.2196/52106

(JMIR Res Protoc 2024;13:e52106) doi:10.2196/52106

KEYWORDS

audio; community health worker; information campaign; knowledge, attitude, and practices; language; leprosy-related stigma; qualitative and quantitative research; stigma intervention; Togo; West Africa

Introduction

Overview

Leprosy is a communicable neglected tropical disease (NTD) caused by *Mycobacterium leprae*. In 2022, more than 140,000 cases were reported globally, mainly in Southeast Asia, Africa, and the Americas [1]. Across sub-Saharan African countries, leprosy is found in endemic pockets and is most common among the rural poor [2,3]. Despite effective antibiotic treatment being widely available, new cases of leprosy continue to occur in Togo [4]. In line with experiences in other countries, a significant number of hidden cases is expected [1,5,6]. In its global strategy to eliminate leprosy, the World Health Organization emphasizes the need for early case detection to successfully interrupt transmissions. Additionally, as an independent objective, the need to reduce stigma is emphasized to further alleviate the burden of the disease [7].

Leprosy is a highly stigmatized disease, mainly due to low understanding and knowledge about the disease itself, including misconceptions regarding transmission and treatment [8-10]. While knowledge and stigma are distinct constructs, they often interact. Consequently, a lack of knowledge about the disease can foster false beliefs that may contribute to the stigmatization of patients. However, even with increased understanding of the disease, stigmatizing attitudes can persist [8]. This stigma contributes to patients' hesitation to seek care [10], as well as delayed diagnosis and treatment [11,12]. As a consequence, a delayed or missed diagnosis of leprosy often results in irreversible disabilities causing permanent visible impairments [13], which in turn reinforce stigma and discrimination [14].

Existing sensitization campaigns aim to create awareness and improve understanding of leprosy among the general population and ultimately achieve early case detection and treatment [15]. Common practice leprosy sensitization campaigns include information on the disease itself, transmission, incubation, development, and potential treatment. Group discussions, leaflets, and positive testimonies of people successfully cured are used to overcome potential entrenched misconceptions among the population. Although there is a comprehensive body of literature on conceptualizing the drivers and consequences of health-related stigma [8,16-20], the effectiveness assessment of interventions targeting leprosy-related stigma are rare. A nonrandomized intervention study in India found health posters and focus group discussions to be associated with improved leprosy-related knowledge and reduced stigma [21]. A before-and-after study in Indonesia also showed leprosy sensitization campaigns to be associated with a reduction of stigma [22]. To the best of our knowledge, the effectiveness of leprosy-related stigma interventions has not been studied in the West African context.

Togo has a literacy rate of 67%, and aside from French being the official working language, 49 local languages are widely spoken [23]. Especially in rural communities, local languages are often the predominant mother tongue. Several scholars have shown the impact of language on education outcomes in the multilingual sub-Saharan African context [24-26]. As such, literacy and language barriers are challenging to the potential effectiveness of one-time sensitization campaigns to build comprehensive knowledge and reduce stigma.

In this study, we assess the effectiveness of community-based sensitization campaigns in increasing leprosy-related knowledge and reducing stigma among the target populations in rural Togo. The common practice sensitization campaigns are carried out by the Togolese National NTD program. The campaigns are building on the inclusion of local health care workers (HCWs) and community health volunteers (CHVs) to mobilize community members and convey knowledge. Furthermore, we will establish the effectiveness of novel audio-based tools that provide target populations with information in local languages to overcome language barriers and increase the effectiveness of sensitization campaigns.

We will conduct a mixed methods cluster randomized controlled trial (cRCT) study in 60 rural communities in Togo.

Study Objectives

The main objective of this study is to assess the effectiveness of community-based sensitization campaigns to increase leprosy-related knowledge and reduce stigma. Our results will

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inform national policy and decision makers, as well as stakeholders delivering health services and sensitization campaigns.

Specific research objectives are to (1) establish the effectiveness of community-level sensitization campaigns and local language audio tools to increase knowledge and decrease stigma related to leprosy among community members; (2) determine the effects of leprosy training for CHVs (knowledge on diagnosis, treatment, and prevention); and (3) elucidate the mechanisms and experiences of sensitization interventions among community members, HCWs, and CHVs.

Trial Design

We will use a cRCT using a sequential mixed methods design by collecting and analyzing quantitative and qualitative data. The trial will have 2 intervention arms that are randomly assigned across 60 study communities. Intervention arm 1 will receive the sensitization campaign (common practice by the national NTD program). Intervention arm 2 will receive the sensitization campaign (a common practice by the national NTD program) accompanied by audio tools. Control arm will receive no sensitization campaign exposure before endline data collection.

Communities assigned to the control arm will receive intervention arm 1 after data collection to ensure that all communities will receive common practice sensitization campaigns by the end of the study period.

Conceptual Framework

We use the universal health-related stigma and discrimination framework proposed by Stangl et al [27] to guide our understanding of leprosy-related stigma. Stigma is understood as an attribute discrediting the patient, enabling discrimination, and eventually limiting the opportunities of the affected persons [16,18]. The stigma and discrimination framework describes 4 different stages of health-related stigma: the first stage includes drivers and facilitators of stigma, followed by stigma marking to either health conditions or characteristics of affected groups in the second stage. Once stigma marking takes place, the third phase represents the manifestation of stigma, with experience and anticipation of stigma and stigmatizing behavior. Eventually, the manifestation of stigma affects several outcomes in the fourth stage at the individual level for affected persons and at the institutional level, manifesting as discriminating laws and guidelines. Following Stangl et al [27], the first 3 stages are key areas of applied research and interventions aiming at health-related stigma reduction.

In the context of leprosy, potential drivers of stigma are the fear of infection, social exclusion, and devaluation [8]. Misconceptions of leprosy, such as infection being a consequence of committed sins or social misconduct, can also drive stigma [28,29]. Facilitators of stigma are characteristics of affected groups such as low socioeconomic status or low educational background [8,30]. Leprosy-related stigma is commonly expressed by the loss of the social status, reputation, and self-esteem of affected persons. Patients are often socially isolated and face difficulties achieving socially desirable goals such as marriage [31]. Stigma manifestation also includes the anticipation and internalization of stigma [20]. As a consequence of stigma, early symptoms are often concealed, and delays in diagnosis lead to treatment being initiated at a disease stage where permanent, visible impairments and irreversible disabilities already occur.

While we acknowledge that education alone is never as effective as a combination of strategies for stigma reduction [8,32,33], the interventions in this study are designed to primarily target underlying causes and drivers of stigma by addressing knowledge and beliefs about leprosy at the community level. Additionally, the interventions also engage community members in activities aimed directly at reducing stigma. Through the inclusion of audio tools for information dissemination, we aim to acknowledge potential stigma facilitators, such as low literacy rates, in affected groups [30]. Offering learning content in local languages (rather than French), the audio tools could potentially improve campaign effectiveness by increasing self-efficacy through the ability to participate in the intervention as well as being able to understand the content [24-26]. Additionally, our trainings for CHVs and health facility staff in our intervention arms aim to reduce stigma at the organizational and institutional level (for example, avoiding segregation of patients) [15].

Methods

Study Setting and Implementation Partner

This study will be conducted in rural communities in Togo, West Africa. Study communities have been selected from the national NTD database. A community is considered eligible if it is located in a rural area and if at least one leprosy case has been reported in the national register between 2010 and 2020. A community has been classified as rural if its population (aged 18 years and older) did not exceed 1500 individuals based on remote censoring data [34]. Selected study sites span all 6 regions of Togo, yet districts bordering Burkina Faso were excluded due to security concerns. Between 2010 and 2014, 2630 new cases of leprosy were recorded by the Togolese National Leprosy/Buruli Ulcer Control Program. Nonetheless, a high number of undetected cases are expected [5,6]. To increase awareness, promote active case finding, and facilitate access to leprosy treatment, the Togolese National NTD program is working closely with the international nongovernment organization German Leprosy and Tuberculosis Relief Association (DAHW). The main activities of the collaboration include the implementation of skin screening campaigns in particularly vulnerable communities at risk of leprosy. During campaigns, individuals can receive professional skin screenings by dermatologists and appropriate treatment if needed. To increase help-seeking and prevent stigmatization of diagnosed patients, skin screening camps are preceded by a sensitization campaign on general skin diseases and leprosy in particular. Mobilization for sensitization campaigns and skin screenings is typically done by the respective HCWs and CHVs. Where HCWs are trained staff working from health facilities, CHVs received basic training and are voluntarily providing health services within their communities. The sensitization campaigns implemented by the National NTD program and the DAHW form the basis of the intervention to be evaluated in this study,

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and study team members include representatives of the Togolese National NTD program and the DAHW to facilitate data collection and implementation.

Intervention Description

The sensitization campaigns in intervention arms 1 and 2 will be carried out in three steps: (1) planning, (2) social mobilization, and (3) implementation. The planning of sensitization and skin screening activities will be done in collaboration with influential forces in the community (eg, traditional chiefs, religious leaders, school principals, CHVs). Choices regarding the date, time, and place of the activity will be made in collaboration with the local opinion leaders. The social mobilization will entail the mobilization of all influential forces in the community to encourage individuals and families to participate in the activity.

On the day of the implementation of the sensitization activities, community members will be invited to educational sessions. The CHVs will give key information on skin-related NTDs, including leprosy. HCWs will support the CHVs to ensure the accuracy of the information and message given out. Topics covered will be clinical signs, symptoms, treatment, environmental aspects conducive to the contraction of the disease, methods of prevention, management, and prevention of disabilities. The knowledge dissimilation will be done with the help of posters, images of leprosy, and the screening of a documentary film on skin-related NTDs, followed by community debates. In addition, community members are actively involved in activities aimed at reducing stigmatizing attitudes and behaviors toward individuals affected by leprosy. Community leaders play a pivotal role in developing strategies to transform community norms that contribute to the stigma surrounding leprosy patients.

After the sensitization stage, consultations will take place for the screening of cutaneous dermatoses. In a private area, health staff will individually assess people who presents with a lesions, sores, or stains on the body. First aid will be offered by health professionals to any person who presents with a skin disorder, and individuals diagnosed with leprosy will be referred to the health facility for treatment initiation and follow-up consultations.

In intervention arm 2, in addition to the activities described above, the CHVs will offer audio tools to households in the study communities. The solar powered tools will contain the learning content of the campaign in audio form [35]. The content will be translated into the 15 most prominent local languages of the communities in intervention arm 2. The tools will remain within the community until endline data collection (approximately 2 months) to allow repetitive learning for all household members.

Implementation

This study is a cRCT, with the randomization unit being the administrative communities. We stratified the random assignment by administrative regions in Togo (Maritime, Plateaux, Central, Kara, and Savanes) to ensure representation of all intervention and control arms across all regions. Since the sensitization campaigns are carried out at the community level and are targeted at the whole community population, cluster randomization was the natural choice of study design. Participation in the sensitization campaign is voluntary, open to all community members, and does not imply participation in the study as such. Survey participants will be recruited from the general community population, irrespective of their participation in the sensitization campaigns.

We used computer-generated random numbers for intervention arm assignment. We set a random seed to 585,506 in Stata (StataCorp) to execute a replicable and random intervention arm assignment. Misfits at the regional level have been balanced at the global level.

Quantitative data have been collected at baseline in all 60 communities and will be complemented with an endline survey 2 months after intervention implementation. Primary outcomes will be collected in all intervention arms before and after intervention.

Baseline data collection took place in March 2023, and endline survey data and qualitative data are planned to be collected in November 2023. Training of health volunteers and professionals and the implementation of campaigns will take place between August and September 2023.

Eligibility Criteria

As described above, intervention participation is voluntary, open to all community members, and does not imply participation in the survey as such. Eligibility criteria for survey participation vary by study component.

Quantitative Study Component

People aged 18 years and older who are resident of the respective community. All CHVs serving a study community and aged 18 years and older will be eligible to participate in the survey.

Qualitative Study Component

People aged 18 years and older and are residents of the respective community. We will also purposefully select some patients with leprosy. CHVs and HCWs serving a target study community and aged 18 years and older will be eligible to participate in the study.

Outcome Measures

Quantitative End Points

Our primary outcomes to assess leprosy-related knowledge among community members will be based on the standardized Knowledge, Attitudes, and Practices Questionnaire adapted to leprosy. We will assess different forms and perceptions of leprosy-related stigma using the Social Distance Scale, asking for individuals own stigmatizing attitudes. Further, we will ask about the perceived attitudes and behaviors in the community using the Explanatory Model Interview Catalogue (EMIC). Individuals not affected by leprosy will receive the Community Stigma Scale. Affected individuals will receive questions related to their experience with stigma. In addition, we will assess a number of secondary outcomes, such as the Participation Scale. The primary and secondary outcomes are shown in Textbox 1.

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Textbox 1. Primary and secondary outcomes.

Primary outcomes

- 15-item Knowledge, Attitudes and Practices Questionnaire [36].
- 7-item Social Distance Scale [36].
- 15-item Explanatory Model Interview Catalogue Community Stigma Scale for persons not affected and Explanatory Model Interview Catalogue for persons affected [37].

Secondary outcomes

- 18-item Participation Scale [38].
- 10-item Rosenberg Self-Esteem Scale [39].
- 3-item University of California, Los Angeles Loneliness Scale [40].
- 2-item Patient Health Questionnaire [41].
- 2-item Generalized Anxiety Disorder Scale [42].
- 3-item Alcohol Use Disorders Identification Test for Consumption [43].

Qualitative End Points

We will explore the needs, preferences, and understanding of HCWs and CHVs regarding training on leprosy treatment and care. With in-depth interviews (IDIs) and shared walks, we will build place-based data, examine the practices and perceptions of HCWs and CHVs relating to pathways to treatment and care, and analyze how stigma may mediate these pathways. Additionally, our IDIs with community members will explore cultural norms and beliefs around health seeking and treatment for leprosy and examine perceptions and experiences regarding the sensitization campaign.

Areas of particular interest are (1) understanding the perceptions of HCWs and CHVs regarding the use and appropriateness of the training received on leprosy treatment and care; (2) understanding the perceptions of HCWs and CHVs regarding stigma, diagnosis, treatment, and care of leprosy; and (3) understanding community perceptions regarding the sensitization campaign, the audio tool, and the diagnosis, treatment, and care of leprosy.

Sample Size

Quantitative Sample Size

We conducted a power calculation for our primary end points to determine the required sample size. The power calculation considers the study design of randomized intervention assignment across clusters (communities). To reach a power of 80% in detecting an effect size of 10 percentage points at a significance level of 5% (SD 30, intracluster correlation coefficient=0.05), a sample of a minimum of 15 individuals in each community is given a fixed number of 60 clusters. This leads to an overall required sample size of 900 individuals. To account for potential complications, we targeted a sample size of 1200 individuals. Baseline data collection took place in March 2023, with 1200 individuals successfully interviewed.

Qualitative Sample Size

To determine the qualitative sample size, we follow the principle of achieving data saturation, which ensures that reoccurring themes are exhausted [44]. With a study that uses IDIs and shared walks—with a relatively focused research question—saturation should occur at approximately 20 interviews or with 20 participants. Therefore, we aim to conduct 5-10 IDIs with HCWs in each of the intervention and control arms (15-30 in total) and 10-15 IDIs with community members in each of the intervention and control arms (30-45 in total).

Recruitment and Data Collection

Over the course of the study, we will integrate several rounds of quantitative and qualitative data collection with community members, CHVs, and HCWs. For an overview of all data collection instruments, see Table 1.

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Table 1. Data collection instruments of a mixed methods cluster randomized controlled trial to assess the effectiveness of leprosy sensitization campaigns in rural Togo. A summary of study instruments, respondents, and procedures. Data collection and intervention implementation will take place between March 2023 and June 2024.

Data collection type and instrument	Population and recruitment					Sample size	Estimated duration (minutes)	Timing of data collection
	Population	Observation unit	Sampling unit	Sampling method	Eligibility			
Quantitative								
Survey baseline	Community members of all 60 study communities	Individual	Households	Random selection	Adult men and women aged ≥18 years, preferably household head and spouse	1200	20	Before Intervention
Survey endline	Community members of all 60 study communities	Individual	Households	Random selection	Adult men and women aged ≥18 years, preferably household head and spouse	1200	30	After Intervention
Survey CHV[a]	CHVs of all intervention communities	Individual	Community	Census (intervention arm 1 and 2)	CHV of study community	40	20	After Intervention
Qualitative								
In-depth interview cover sheet	HCWs[b], CHVs and community	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	45-75	N/A[c]	During intervention
In-depth interview guide	HCWs and CHVs	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	15-30	45-60	During intervention
Shared walk guide	HCWs and CHVs	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	15-20	N/A	During intervention
In-depth interview guide	Community members	Individual	Community	Purposive	Adult men and women aged ≥18 years that identify as a community member in the respective communities and provide written informed consent	30-45	45-60	During intervention

[a]CHV: community health volunteer.

[b]HCW: health care worker.

[c]N/A: not applicable.

Quantitative Survey Participants

At baseline, before intervention implementation, community members were sampled through a random selection of households in all 60 study communities. In each community, 10 households were selected following a random walk procedure adjusted to the local context of widely spread farmsteads [45]. In each selected household, one female and one male household member were interviewed, preferably the household head and respective spouse or husband. For the endline survey, the same individuals will be interviewed. All CHVs will be selected for a quantitative survey during the endline data collection.

Qualitative Interview and Shared Walk Participants

We will conduct IDIs with 5-10 HCWs and CHVs in each of the intervention and control arms. In this phase, we will also invite selected 15-20 IDI respondents to participate in a “shared walk” to walk through their community and show research assistants (RAs) where their work takes place, what locational influences there are on their work, and how they feel anything influences their work in relation to leprosy. We will also conduct IDIs with community members in each of the intervention and control arms (30-45 members in total) to understand (depending on the intervention assignment) their perceptions of the services being offered, the sensitization campaign, and their feelings and experiences regarding leprosy.

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A total of 3 RAs will conduct the IDIs and shared walks using standardized instruments. These include a participant information sheet, a consent form, a cover sheet, and interview guides (Table 1). Cover sheets will capture sociodemographic data, including sex, age, employment status, children, partner status, and religion. Cover sheets also include a section for RAs to make reflexive and observational notes. Written informed consent will be obtained from all study participants before beginning interviews. Depending on the preference of the participants, IDIs will be conducted one-on-one in a local language or French and will be audio-recorded. Participants in the IDIs will be asked broad, open-ended questions regarding topics such as the training, the intervention and audio tool, stigma, and perceptions of leprosy. IDIs will be designed to elicit personal responses and then lead to more in-depth and specific narrative-building questions. RAs will probe themes that seem to be of relevance to the participant or that are identified as important recurring themes through the debriefing process.

The "shared walk" will follow the tenets of the docent method defined by Chang [46] to provide more place-based data. The participants decide the route and duration of the walk. The RA will ask the participant to show them locations on the walk that are of significance to them for any reason, but will also ask the participant to show locations that are of particular relevance for the work they do and where significant events (such as education or outreach) take place. Each participant is considered to be an expert guide. The participant is the educator, while the RA is the person who needs to learn from and follow the lead of the participant. These walks will be audio recorded and can be supported by photos if the participant wishes to take them. Any photographs submitted in which it is possible to identify individuals will be anonymized.

Data Analysis

Quantitative Analysis

Our primary analysis will be based on intention-to-treat at the individual level using linear regression comparing the outcomes of intervention and control arms. We will measure our primary outcomes in terms of absolute scores and as a percentage of the total possible score. We will use adjusted standard errors for clustering at the community level, our unit of randomization [47]. We will control for a number of baseline covariates, including gender, age, and education, among others.

Qualitative Analysis

Analysis will begin in the field with systematic debriefings. Debriefings are daily meetings with RAs and are designed to identify where interview questions are gaining in-depth responses and where questions need to be changed or refined [48]. Debriefings will also allow the research team to gain a superficial understanding of the main topics arising from the interviews and the shared walks, so that an initial codebook can be developed [48]. Once all data have been collected, IDIs will be translated, transcribed, and managed using NVivo (version pro 12; QSR International) [49]. We will follow a reflexive thematic analysis approach using the recursive 6 stages of analysis as defined by Braun and Clarke [50]. Data analysts will independently read and re-read transcripts for data familiarization. Transcripts will then be inductively analyzed in blocks of 5, and codes will be reviewed to identify similarities or divergence of ideas. This process will be followed until the coding is complete. The main codes will be presented to the study team to decide where reoccurring codes could build our core themes. After revising the codebook, we will develop a thematic scheme that will be presented to the study team, refined, named, and finalized for interpretation and writing.

Our mixed methods process will follow a sequential approach where we begin with quantitative data collection and analysis and, upon completion, start the qualitative component [51]. We assume that the quantitative data will allow us to develop more focused qualitative questions and that the qualitative data will help us to address any gaps in information that we cannot explain through the quantitative results. Further mixing of the 2 methods will occur during the data analysis of both data sets, when we will combine the qualitative and quantitative to present our findings to support the interpretation of the results. As such, we envision the shared walk data to allow us to identify potential intervention improvements with respect to the information provided, the dissemination of this information, and, in particular, participant understanding of the audio tool.

Ethical Considerations

This study was approved by the Togolese Bioethics Committee for Health Research (025/2022) and the Ethics Commission of the Medical Faculty Heidelberg (S-670/2022), Germany. Before consent, information about the study will be provided (verbal or written). All participants will give (verbal or written) informed consent to participate in the research. Participants will not receive compensation for their participation. The data will be deidentified before analysis and securely stored in a password-protected file and on a password-protected computer. Any photographs submitted during qualitative data collection, in which it is possible to identify individuals, will be anonymized. The trial is registered at the German Clinical Trials Register (DRKS-ID: DRKS00029355).

Results

Data collection started in March 2023 and is planned to be completed in June 2024, with ongoing data analysis. Analysis of the quantitative baseline data has been initiated, and results are planned to be submitted for peer-reviewed publication in the second quarter of 2024. The first quantitative endline and qualitative results are expected to be submitted for publication by the end of 2024.

Discussion

We will use the mixed methods cRCT to measure the causal effect of community sensitization campaigns and audio tools distributed to households on knowledge and stigma related to leprosy. The setting of this study is rural communities in Togo, West Africa. Our nested qualitative components, involving interviews and shared walks with community members and local stakeholders such as CHVs and HCWs, will explore the implementation of the intervention and contextualize the

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quantitative results of the trial, while also helping to further characterize the mechanisms through which sensitization campaigns and audio tools affect leprosy-related knowledge and stigma.

The contribution of this study to the literature will be 3-fold. First, we will provide causal evidence on the effectiveness of sensitization campaigns on community-level leprosy-related knowledge and stigma. The literature on this is limited, especially in the West African context. Second, we will test novel audio tools for information dissemination to amplify potential campaign effects. The tools are designed to overcome literacy and language barriers in a multilingual context. Third, our results will contribute to the general understanding of leprosy-related stigma in the West African context. The qualitative and quantitative findings will inform policy makers and public health agents to effectively tailor and implement sensitization campaigns, particularly in challenging rural settings.

A potential limitation of this study is the fact that quantitative stigma indicators are self-reported by community members; this outcome might be affected by social-desirability bias. We will test intervention effects on the respondent's knowledge of the disease, which is a key driver of stigma and not prone to social desirability bias. Further, qualitative IDIs with unaffected and affected community members will allow us to triangulate quantitative findings on stigma.

This cRCT serves to provide rigorous scientific evidence about the causal effectiveness of 2 particular interventions in the broader field of health-related stigma interventions and multilingual low-literacy settings. The results will be beneficial for policy makers and public health agents to guide sensitization campaigns and inform them about the potential of audio tools to complement common practice.

Acknowledgments

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Data Availability

The final data set used and analyzed for this study will be available from the corresponding author on reasonable request.

Authors' Contributions

DJ, AWB, KB, NMS, DAYG, CK, and TB were responsible for the overall conceptualization of the study design. DJ led the design of the quantitative study components. KB led the design and writing of the qualitative study components and edited the protocol paper. DJ led the writing of the protocol paper. DAYG and AWB oversaw the Togolese ethics approval process and set up the local study implementation systems. DJ oversaw the German ethics approval process. CK and MV are grant holders. JW advised on the qualitative study design and edited the protocol paper. TWM advised on the qualitative study design. SL advised on the quantitative study design. SP supported the quantitative data collection and survey design. DJ conducted the power calculations. AWB, PPB, BS, PG and DAYG provided technical input and contributed with local context expertise and implementation in Togo. TB advised on the quantitative study design and sample size calculation. All authors have read and approved of the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CHV: community health volunteer
cRCT: cluster randomized controlled trial
DAHW: German Leprosy and Tuberculosis Relief Association
EMIC: Explanatory Model Interview Catalogue
HCW: health care worker
IDI: in-depth interview
NTD: neglected tropical disease
RA: research assistant

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Protocol

Needs and Experiences With Health Care Providers of Adult Rare Disease Patients and Caregivers of People With Rare Diseases: Protocol for a Qualitative Study

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Abstract

Background: Rare diseases in Europe are defined as diseases with a prevalence of less than 5 per 10,000 people. Despite their individual rarity, the total number of rare diseases is considerable. Rare diseases are often chronic and complex, affecting physical, mental, and neurological health. People with rare diseases face challenges such as delayed diagnosis, limited medical support, and financial burden. Caregivers, usually family members, bear significant physical and emotional burdens. Understanding the experiences of patients with rare disease and their caregivers is critical to effective care, but this is still underresearched. Better support and understanding of the challenges faced by both patients and caregivers is clearly needed. Our study will explore the experiences and needs of people with rare diseases and caregivers of people with rare diseases in relation to accessing health services.

Objective: This study aims to explore the experiences of patients with rare disease and their caregivers with Slovenian health care providers and to create a theoretical model of needs and experiences.

Methods: This is a qualitative thematic analysis study, using the codebook approach. The study will conduct semi–open-ended interviews to understand the experiences and needs of people with rare diseases and caregivers of people with rare diseases in relation to accessing health services. The interview questions will be based on an extensive literature review. Data from the interviews will be analyzed using thematic analysis to identify patterns and build a thematic map. Data will be analyzed by at least 2 coders. To ensure reliability, respondent validation will be conducted and negative cases investigated. Any discrepancies will be resolved by consulting the entire research team until a consensus is reached.

Results: This study was not specifically funded. However, author TČ is supported by grant number P3-0339 from the Slovenian Agency for Research and Innovation. This study was approved by the Medical Ethics Committee of the Republic of Slovenia (0120-47/2022/3), and recruitment is expected to begin in May 2024, with data analysis results anticipated by the end of 2025.

Conclusions: This study will fill an important research gap in Slovenia by exploring the needs and experiences of people living with rare diseases and their caregivers. The results will contribute to the broader field of rare diseases and add knowledge that can inform future research processes and intervention strategies. It also aims to identify neglected areas that have a significant impact on the lives of people with rare diseases. This study is important not only because it addresses the immediate needs of the Slovenian rare disease community, but also because it contributes to a discussion on patient-centered care, health policy design, and the inclusion of psychosocial components in health care.

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KEYWORDS

rare diseases; patients; caregivers; needs; barriers; access to health care

Introduction

Rare Diseases in Europe and Slovenia

In Europe, rare diseases are defined as diseases with a prevalence of less than 5 per 10,000 people in the population [1]. While individual disease incidence is small, the collective number of all types of rare diseases is large [2]. The estimated number of rare diseases is currently between 6000 and 8000 [3]. They are usually chronic and complex and are associated with physical, mental, or neurological disorders. The psychosocial and emotional impact on affected individuals and families is significant and often exacerbated by a lack of adequate community support and services [4].

Health Care Needs of Patients With Rare Disease

Rare diseases, due to their multisystemic nature and associated cognitive and developmental challenges, manifest a wide range of symptoms, resulting in diverse health care needs. Managing these symptoms necessitates the involvement of various health care professionals, the use of medical devices, and "orphan drugs" [5]—specialized medicinal products developed to treat, diagnose, or prevent specific rare diseases [6].

Challenges Faced by Patients With Rare Disease and Caregivers

Rare diseases present numerous challenges, not only for those directly affected but also for their caregivers. These challenges include delayed diagnosis, difficulties accessing health care, and the financial burden of medical treatment [7]. Caregivers of individuals with rare diseases, who are often parents or spouses, shoulder a substantial physical and emotional burden without receiving financial compensation [8]. Their responsibilities encompass providing transportation, running errands, offering emotional support, monitoring symptoms, and performing additional household tasks [9,10]. Many caregivers are forced to reduce or quit their jobs due to these caregiving responsibilities, leading to additional financial strain [11]. The caregivers' physical and mental well-being directly impacts the level of care they can provide to patients with rare diseases [2].

Research Gap in Slovenia

In Slovenia, rare diseases pose a significant public health concern and represent a considerable challenge for the health care system [12]. It is roughly estimated that around 150,000 patients are affected by rare diseases in Slovenia [13], which emphasizes the importance of addressing this issue [14]. Recently, a register of rare, nonmalignant diseases was established in the Republic of Slovenia, which should provide valuable insights into this topic. While some studies have been conducted, such as the one by Halec et al [15] on the impact of rare diseases on an individual's quality of life, and others by Stanimirović et al [12-14] focusing on systems development and strategies to improve care for patients with rare disease, there remains a notable absence of research centered on the experiences and needs of patients with rare disease and their caregivers in Slovenia.

Addressing Research Gap by This Qualitative Study

In Slovenia, there is little research on the experiences of caregivers of people with rare diseases, especially compared with the studies on caregivers worldwide. While studies often focus on specific diseases and their pathophysiology [8], a comprehensive exploration of the experiences of both patients and caregivers is crucial for health care providers. Such insights can aid in developing treatments and support services that align with the unique challenges faced by this population [16].

Preliminary findings of a scoping review [17] and discussions with representatives of various rare disease associations highlight the pressing need for better support and understanding of such issues and that there is a lack of knowledge in the field about the challenges experienced by caregivers and people with rare diseases. The Ministry of Health states in the work plan in the field of rare diseases in the Republic of Slovenia for the period 2021-2030 that it would be useful to research the needs of patients with rare diseases in Slovenia, with special attention to social aspects, palliative care, psychological support, and economic aspects [18]. There is, therefore, a need to identify clear areas for change to help researchers, health care providers, and health policy makers develop, plan, and facilitate better services. The establishment of the rare non-malignant diseases registry of the Republic of Slovenia [19] and the development of a more comprehensive rare disease ecosystem [14] are important steps, but qualitative research focusing on the experiences of people living with rare diseases will complement these efforts and provide valuable insights.

Potential Contributions of This Study

This research study holds the potential to contribute significantly to science and the rare disease community in Slovenia by providing a better understanding of the human dimension, which is essential for developing patient-centered policies that consider the psychosocial, emotional, and practical challenges faced by people with rare diseases and their caregivers; identifying gaps in access to health services and psychosocial support; offering insights into priority areas for action that can guide policy makers; and filling a critical research gap in Slovenia by adding valuable knowledge to the rare disease field.

By addressing these aspects, this study has the potential to make a substantial and unique contribution to both the scientific community and the rare disease community in Slovenia.

Objectives

The primary aim of the study is to explore the needs and experiences of adults with rare diseases and caregivers of people with rare diseases with health care service providers in Slovenia. The secondary aim is to identify gaps in access to health care services and psychosocial support.

The objectives of the research are as follows: (1) to gain insights into the needs and experiences of adults with rare diseases with health care providers in Slovenia; (2) to gain insight into the needs and experiences of caregivers of people with rare diseases

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with health care service providers in Slovenia; and (3) based on the obtained data, develop a thematic map of experiences and needs.

Research Questions

Our research questions are as follows: (1) What are the needs and experiences of adults with rare diseases in relation to health care providers in Slovenia? (2) What are the needs and experiences of caregivers of people with rare diseases in relation to health care providers in Slovenia?

Methods

The reporting of this study follows the guidelines of the Consolidated Criteria for Reporting Qualitative Studies in the areas that can be applied to a protocol [20].

Research Team and Reflexivity

In this qualitative research study, the interviews will be conducted by TČ, who has a master degree in psychology and is currently working as a researcher. TČ has previous experience with interviews and has spent over a year researching rare diseases and access to health care. Informal discussions were held with representatives of rare disease associations in Slovenia before the study began. These discussions served to develop an initial understanding of the challenges faced by the rare disease community. The main goal was to create a basic knowledge base and gain deeper insights into the problems faced by people living with rare diseases and their caregivers. Participants were informed that the study was part of a doctoral degree pursuit. Disclosure of this information provided transparency regarding the academic aims of the researcher and the context in which the study was conducted. The motivation for the research is rooted in the identified lack of comprehensive studies in this area and emphasizes a commitment to contribute meaningful knowledge to better support people living with rare diseases.

Study Design—Theoretical Framework

The study uses a conceptual framework based on the biopsychosocial model of health [21], which recognizes the interconnectedness of biological, psychological, and social factors associated with rare diseases [22,23]. The biopsychosocial model requires a multidisciplinary approach [24] and emphasizes the importance of a dynamic and empathetic dyadic relationship between clinicians and patients [25]. This approach includes examining various health-related factors, such as access to psychological support, impact on mental health, social support (family support, self-help groups or networks, and help from caregivers), availability of health care services, and financial resources for health-related needs. By applying the biopsychosocial model, this study aims to provide a comprehensive understanding of the unique experiences of people living with rare diseases and, based on this, make recommendations to improve health care services for people living with rare diseases.

The study follows the approach of qualitative thematic analysis [20]. Given the larger scope of our study and the expected high number of participants, we deliberately chose a “codebook” thematic analysis approach [26]. This structured approach aligns with the pragmatic demands of applied research offering a systematic and organized framework for handling a large volume of qualitative data [26]. We will use a structured coding framework to develop and document the analysis [27]. The codebook developed inductively after (some) data familiarization and coding will serve as a tool to guide data coding and a way of mapping or charting the coded data [26]. Themes that will be developed at an early stage after familiarization, will later be refined or new themes developed based on the subsequent inductive data engagement and analytical process [27].

In the final phase of the analysis, the identified themes generated from the coded data will be used to create a thematic map, and the results will be compared with the existing and new data to assess their relevance and reliability [26].

Participant Selection

Participants will be selected through purposive and snowball sampling. Participants will be invited by the research team by email or telephone. Email invitations will be sent by the research team using contact details from a public database of the National Contact Point for Rare Diseases, to which individuals have previously given consent to be contacted. We will also ask participants to invite other people with rare diseases and caregivers of people with rare diseases to participate in the study by using snowball sampling.

We will use snowball sampling, as it is difficult to identify and reach people with rare diseases and their caregivers. We will start with an initial group of participants contacted through the National Contact Point for Rare Disease, conduct interviews, and collect data, followed by an explanation of the snowball sampling process. We will ask the initial participants to provide us with their contact details or to facilitate communication with those who are eligible and willing to participate in the study.

In addition, the research team will contact the pediatric clinic and collaborate with the doctors in the Department of Family Medicine by email. The email will include a presentation of the study explaining the purpose, methodology, potential benefits, and the importance of participation in identifying suitable participants, as well as relevant study documents such as an information leaflet, consent forms, and contact details of the research team. These documents will serve as a reference for the pediatric clinic to inform eligible participants about the study. Approval and cooperation from the relevant authorities at the pediatric clinic will be obtained before contact is made. The aim of contacting the pediatric clinic is to invite eligible caregivers of people with rare diseases to participate in the study, and the aim of contacting the Department of Family Medicine is to invite adult patients with rare diseases.

To avoid overrepresentation of a particular rare disease in the sample, we will follow the guideline that for each rare disease included, a maximum of 2 participants (either the adult patient or the caregiver) will be included.

Sample Size

Braun and Clarke [28] suggest that studies of experiences and needs collected through interviews require a sample size of 15

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to 30 people in order to effectively uncover patterns while maintaining a focus on individual experiences.

Considering the concept of information power, which suggests that a broader study aim, a less specific combination of participants for the research question, and the inclusion of cross-case analysis may require a larger sample size, we decided on a target sample size of at least 40 participants [29]. This includes 20 adults with rare diseases and 20 caregivers of people with rare diseases. As Malterud et al [29] suggest, the appraisal of information power will be repeated during the process, supported by an initial analysis. After the first 3 interviews, an initial review of the data will be done and first suggestions of relevant theory will be made [29].

We will also try to identify and document the reasons for nonparticipation, which will contribute to the transparency and reliability of the study.

Setting

This study is being conducted in Slovenia. It includes health care providers at all 3 levels of health care (primary, secondary, and tertiary care). Data will be collected either in our research offices or participants will have the option of a home visit or digital interview. As caregivers of people with rare diseases may have ongoing care needs [30], we decided to offer them the option of a home visit or digital interview. This gives participants the opportunity to take part at a time and place that is convenient or safe for them [31]. The individual interviews with adults diagnosed with a rare disease will be conducted independently. Caregivers will have the option to participate in the interviews either separately or, if they prefer, together with the person they care for. This flexibility aims to accommodate the preferences and comfort levels of both participants and caregivers.

Description of Sample

We will include adult patients with rare diseases and caregivers of people with rare diseases in our study. It is important to emphasize that our research will focus on rare, nonmalignant diseases. To determine the rarity of the disease, we will use the European definition of rare diseases, according to which rare diseases are categorized as those that affect less than 5 in 10,000 people in the population. To ensure a comprehensive representation of experiences, we aim to include people with different rare diseases. In addition, our sample will indirectly include people with impaired decision-making capacity, such as those with developmental or cognitive impairments, by involving their caregivers. This decision is in line with ethical considerations, as we recognize that it is difficult for people with developmental disabilities to give fully informed consent due to the nature of their condition. Involving caregivers is seen as an ethical strategy to ensure a full understanding of the research topic while upholding the principles of respect and protection of vulnerable populations. Caregivers can be family members, spouses, unmarried partners, close friends, or other people with direct caring responsibilities. To account for possible regional differences in access to health care and support services, our study will include participants from all 9 health regions of Slovenia. The inclusion criteria extend to people who are directly responsible for people diagnosed with a rare disease.

Data Collection

Separate interview guides will be used to explore the perspectives of adult patients with rare disease and their caregivers. The interview questions were formulated based on a literature review and will be pilot-tested to ensure clarity and effectiveness in data collection. The questions formulated for the interviews are also based on the biopsychosocial model of health [21]. In line with the biopsychosocial model, our interview questions refer not only to biological factors but also to psychological and social dimensions (how the rare disease affects the participants' social life and how these conditions influence psychological well-being and social interactions). If subsequent interviews reveal significant topics not covered previously, already interviewed participants may be contacted for additional exploration of those specific areas. Audio recording will be used to capture interviews, ensuring accurate and complete data representation. Participants will be informed about the recording, and explicit consent will be obtained. Field notes will be taken during or after interviews to document contextual information and observations that may enhance the understanding of participants' experiences. The duration of interviews will be based on the natural flow of the conversation, allowing participants to express themselves fully. Specific timeframes will be tailored to individual preferences and needs. As part of the respondent validation process, we plan to present the results of the study to participants and ask for their feedback and comments. While we will not necessarily provide full transcripts, this approach will ensure that participants have the opportunity to validate the results of the study and contribute to their interpretation.

The sociodemographic questionnaire will collect the following data: age, gender, marital status, education level, employment status, relationship to caregiver (caregiver questionnaire), monthly income, housing situation, rare disease diagnosis, year of diagnosis, duration of symptoms, impact of the disease on daily life, nature of costs associated with the rare disease, frequency of medical visits and difficulties in accessing health care services, and the participants' support networks.

Data Analysis

Two researchers will code and compare the data. The coding process will be a collaborative effort to ensure reliability and validity. Themes will be derived through a process. First, a series of initial themes will be developed based on the interview guide and existing literature. Coding will be conducted to provide evidence for these initial themes and to identify additional themes derived from the data. The themes and codes will be refined after the initial coding phase through the development and refinement of a coding template. The final phase of coding will be guided by the final template for theme development. We will use the NVivo program (Lumivero), for coding, editing, and structuring the data. We will also carry out respondent validation, that is, we will present results to the participants and ask them for comments [32]. We will also enrich the data obtained by examining so-called negative cases that deviate from the patterns that otherwise emerge through

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data saturation [33]. By examining these cases, we will increase the reliability of the research and gain better insight into the strengths and weaknesses of the research [33].

Eligibility Criteria

The eligibility criteria for this study are listed in Textbox 1.

Textbox 1. The eligibility criteria for this study.

Inclusion criteria for adults with a rare disease

- Aged 18 years or older with a confirmed diagnosis of a rare disease
- Written consent to participate in the study of a person with a rare disease
- Persons who use health services in Slovenia
- Willingness to comply with the study protocol

Exclusion criteria for adults with a rare disease

- Inability to meet the requirements of the study (Participants with severe cognitive impairment or intellectual disabilities will be included in the study indirectly through their caregivers. As qualitative research relies on participants' ability to articulate their experiences, cognitive impairment may limit meaningful participation).
- Unwillingness to meet the demands of the study
- Refusal to fulfill the requirements of the study (refusal to actively participate in the in-depth interviews, to complete a sociodemographic questionnaire, and to consent to data collection)
- Persons who are unable to communicate in Slovene or who are not able to sufficiently understand and express themselves in Slovene will be excluded from the study

Inclusion criteria for caregivers of people with a rare disease

- Family caregivers who directly care for a person with a confirmed diagnosis of a rare disease. Family caregivers are usually relatives (often the patient's parents or spouse) who take on most of the physical and emotional burden of caring for the patient without receiving financial compensation (with the exception of family caregivers who receive payment in the form of social benefits) [34]. They carry out the tasks of monitoring, interpreting, making decisions, taking action, making adjustments, providing care, accessing resources, working with the sick person, and negotiating with the health system [35]
- Written consent to participate in a study of the caregiver of a person with a rare disease

Exclusion criteria for caregivers of people with a rare disease

- Unwillingness to comply with the requirements of the study (refusal to actively participate in in-depth interviews, to complete a sociodemographic questionnaire, and to consent to data collection)
- Inability to meet the study requirements (lack of cognitive ability to participate in the study, such as severe cognitive impairment, Alzheimer disease, or intellectual disability)
- Persons who have not reached the legal age of adulthood in Slovenia (younger than 18 years) will be excluded from the study
- Persons with whom it is not possible to communicate in the Slovene language or who are not able to understand and express themselves sufficiently in the Slovene language will be excluded from the survey
- Persons who provide care in the context of an employment relationship and who are not close persons to the person they are caring for (eg, paid home caregivers or home help, persons employed in social care institutions) will be excluded

Ethical Considerations

The medical ethics committee of the Republic of Slovenia considers the research to be ethically justifiable. The commission notes that all necessary documentation has been included, the statement is written in a way that is understandable for the participants, the security of data storage is guaranteed, and the anonymization of responses is ensured. The document bears the number 0120-47/2022/3. Explicit informed consent will be obtained from all participants. This comprehensive process will ensure participant understanding, adherence to ethical principles, and compliance with the statement approved by the medical ethics committee. The data collected as part of this study will be stored securely in both physical and electronic form, with access to the data restricted to those directly involved in the research. The electronic data will be anonymized by assigning identification codes and stored in a special database located on the premises of the Department of Family Medicine at the Faculty of Medicine in Ljubljana. Before the data are stored in the database, an anonymized version of the research data is created in order to preserve its usefulness while ensuring the confidentiality of the participants. Data protection is ensured by secure passwords, and passwords are stored separately. Participants will not receive any financial or nonmonetary compensation for their participation in this study.

Results

This study was not specifically funded. However, the author TČ is funded by the Slovenian Agency for Research and Innovation under grant number P3-0339. Data collection through

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semistructured interviews for the study is scheduled to begin in May 2024 and is expected to be completed on 30 December 2024.

Discussion

Principal Results

This study aims to gain a deeper understanding of the needs and experiences of people living with rare diseases and their caregivers when interacting with health care providers in Slovenia and to shed light on the gap between them. The results of the research will be presented in a thematic map of the needs and experiences of people living with rare diseases and their caregivers. The thematic map will serve as a visual representation that will provide an overview of the interconnected themes identified in the analysis and improve our understanding of the complex relationships between the needs and experiences of the target groups. As identified in the exploratory phase of our research, we spoke informally with representatives of rare disease associations in Slovenia to understand the challenges faced by this community. They highlighted key issues, including the need for psychological support, gaps in palliative care for children, concerns about the attitudes of health care providers, and gaps in respite care. In addition, they highlighted issues around delays in diagnosis, poor communication with health care professionals, stigmatization, lack of information, and poorly coordinated care. Ongoing research will shed further light on these issues and contribute to a comprehensive understanding of the gap between needs and available services. We expect to gain a deeper understanding of the barriers to accessing health services, the impact of these barriers on disease progression, and their psychosocial consequences. We expect participants to express their needs in terms of support services and to give examples of good practices that can later be used for better planning of health services. We hope that the results will also point to previously overlooked areas that have a significant impact on the lives of people significantly affected by rare diseases. Based on the results, we will make recommendations to improve health services for people with rare diseases.

Limitations

A potential challenge of this study arises from the diversity of rare diseases included. Given the uniqueness of each rare disease, it might be difficult to identify commonalities in experiences and needs. While a national register for rare diseases has recently been established in Slovenia, our main resource remains a web-based website that serves as a national contact point for rare diseases. This website lists various associations. Our approach to recruiting participants is a purposive sampling combined with a snowball approach. However, a potential limitation is that individuals who are more involved in supportive communities may be overrepresented in our sample. Consequently, those who are less proactive in seeking the support they need might be underrepresented. To mitigate this bias, we try to use the snowball principle to recruit people who do not belong to these associations and contact participants through doctors. However, it is important to be aware that using the snowball principle may also have a disadvantage. This method could lead to limited diversity among our informants, which could limit the range of perspectives and experiences we can capture [36].

Another challenge is that the study focuses primarily on experiences and needs related to access to health services. However, patients with rare diseases and caregivers of people with rare diseases may face challenges and needs beyond health care, such as education and employment. These aspects may not be fully explored in the study.

Comparison With Prior Work

Previous research has shown that participants have a significant need for information, particularly in relation to psychological and health care aspects [22,37]. In particular, the Depping study highlights the importance of personalized information and the desire for better access to experts and treatments within the health care system [22].

In line with the aims of our study, we found that caregivers and patients often encountered health care professionals whom they perceived as lacking the necessary knowledge and understanding of them or (in the case of caregivers) the person they were caring for [22,37-40]. Consequently, they saw a noticeable gap in their access to vital and necessary care, emphasizing the urgency of better training for health care providers [22,37-40].

Our study protocol represents a step forward in capturing the specific needs and experiences of people living with rare diseases and their caregivers in Slovenia and differs from previous large-scale surveys, such as the comprehensive study conducted in the United States [40]. In contrast to these large-scale initiatives, our focus is tailored to the Slovenian health care landscape and provides a local understanding of the challenges faced by this population. By focusing on the specific context of Slovenia, our study aims to fill existing gaps and contribute valuable insights to the current state of knowledge in rare disease research.

Conclusions

This study will fill an important research gap in Slovenia by exploring the needs and experiences of people living with rare diseases and their caregivers. The results will contribute to the broader field of rare diseases and add knowledge that can inform future research processes and intervention strategies. It also aims to identify neglected areas that have a significant impact on the lives of people with rare diseases. This study is important not only because it addresses the immediate needs of the Slovenian rare disease community, but also because it contributes to a discussion on patient-centered care, health policy design, and the inclusion of psychosocial components in health care.

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Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available due to confidentiality and ethical considerations but are available from the corresponding author on reasonable request.

Authors' Contributions

TČ contributed to the conceptualization and methodology of the project. DRP, ET, and ŠM provided supervision.

Conflicts of Interest

None declared.

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Protocol

Marital Self-Disclosure Intervention for the Fear of Cancer Recurrence in Chinese Patients With Gastric Cancer: Protocol for a Quasiexperimental Study

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Abstract

Background: Patients with gastric cancer experience different degrees of fear of cancer recurrence. The fear of cancer recurrence can cause and worsen many physical and psychological problems. We considered the “intimacy and relationship processes in couples’ psychosocial adaptation” model.

Objective: The study aims to examine the effectiveness of a marital self-disclosure intervention for improving the level of fear of cancer recurrence and the dyadic coping ability among gastric cancer survivors and their spouses.

Methods: This is a quasiexperimental study with a nonequivalent (pretest-posttest) control group design. The study will be conducted at 2 tertiary hospitals in Taizhou City, Jiangsu Province, China. A total of 42 patients with gastric cancer undergoing chemotherapy and their spouses will be recruited from each hospital. Participants from Jingjiang People’s Hospital will be assigned to an experimental group, while participants from Taizhou People’s Hospital will be assigned to a control group. The participants in the experimental group will be involved in 4 phases of the marital self-disclosure (different topics, face-to-face) intervention. Patients will be evaluated at baseline after a diagnosis of gastric cancer and reassessed 2 to 4 months after baseline. The primary outcome is the score of the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) for patients. The secondary outcomes are the scores of the FoP-Q-SF for partners and the Dyadic Coping Inventory.

Results: Research activities began in October 2022. Participant enrollment and data collection began in February 2023 and are expected to be completed in 12 months. The primary results of this study are anticipated to be announced in June 2024.

Conclusions: This study aims to assess a marital self-disclosure intervention for improving the fear of cancer recurrence in Chinese patients with gastric cancer and their spouses. The study is likely to yield desirable positive outcomes as marital self-disclosure is formulated based on evidence and inputs obtained through stakeholder interviews and expert consultation. The study process will be carried out by nurses who have received psychological training, and the quality of the intervention will be strictly controlled.

Trial Registration: ClinicalTrials.gov NCT05606549; https://clinicaltrials.gov/study/NCT05606549

International Registered Report Identifier (IRRID): DERR1-10.2196/55102

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KEYWORDS

fear of cancer recurrence; dyadic coping ability; gastric cancer; intervention; nursing; protocol; psychological; marital self-disclosure

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Introduction

In 2020, there were 1,089,103 new cases of gastric cancer and 768,793 deaths worldwide, accounting for 5.6% and 7.7% of the total incidences and deaths, respectively [1]. The standardized morbidity and mortality rates were 11.1/100,000 and 7.7/100,000, respectively, and the cumulative morbidity and mortality risks of those aged 0 to 74 years were 1.31% and 0.90%, respectively. Gastric cancer ranks second in terms of cancer incidence and mortality in China, with 679,000 cases and 498,000 deaths, followed by lung cancer (733,000 deaths) [2]. The disability-adjusted life years associated with gastric cancer in China is 9.825 million person-years, accounting for 44.21% of the gastric cancer cases globally [3].

Advancements in postoperative chemotherapy for gastric cancer have led to an increase in the 5-year survival rate of patients to 68% [4]. Although surgery and combined chemotherapy have improved the survival of patients to a certain extent, the high postoperative recurrence rate and metastatic rate, as adverse psychological events, have a tremendous psychological burden on patients [4]. The fear of cancer recurrence, which first appeared in the subject of oncologic psychology, has particular specificity and independence, which is different from other mental and psychological diseases [5]. Studies reported that about 72% of patients experienced various degrees of fear of cancer recurrence during cancer, of which about 46% were mild or moderate and about 7% were severe [6]. To our knowledge, to date, there have been no psychological intervention studies explicitly targeting the fear of cancer recurrence in Chinese patients with gastric cancer, and only 1 study has conducted a cross-sectional survey of cancer recurrence fear in patients with gastric cancer, which ignored the effect on spouses [7]. However, a spouse's high fear of cancer recurrence can affect the spouse's physical and mental health and further jeopardize the patient's health [8]. Therefore, designing a brief, practical, and feasible intervention to alleviate the fear of cancer recurrence in Chinese patients with gastric cancer and their spouses is critical.

Researchers, patients with cancer, representatives of patient rights, policymakers, and oncology psychologists from many countries reached an expert consensus, which defined the fear of cancer recurrence as "fears and concerns of patients with cancer regarding possible future cancer recurrence and/or metastasis and/or progression" [9]. The primary manifestations of high-level fear of cancer recurrence have been explained as follows: "highly focused, highly concerned, persistent, hypervigilant of physical symptoms and present for at least 3 months" [10].

The treatment cycle of advanced gastric cancer is long, and the recurrence rate is high. Although the progress of medical technology and the resection rate of advanced gastric cancer have increased, the high postoperative recurrence rate and metastatic rate, as adverse life events, have a tremendous psychological impact on patients [11]. Adverse reactions, such as nausea, vomiting, dry mouth, constipation, and bone marrow suppression, aggravate the psychological burden of patients, making them more fearful of the recurrence and progression of the disease [12].

Several studies [12-14] showed that the level of fear of cancer recurrence (as measured by the Fear of Progression Questionnaire-Short Form [FoP-Q-SF]) among patients with gastric cancer (120-170 cases) was middle to high (score of 35.43-42.3 points), the physical health dimension score was 18.09 (SD 4.52), and the social family dimension score was 17.34 (SD 6.34). The scores of the fear of cancer recurrence were higher in patients with gastric cancer than in patients with breast cancer [15] and early-stage prostate cancer [16]. A previous study [17] found that Chinese patients with gastric cancer have less knowledge of the fear of cancer recurrence. High levels of fear of cancer recurrence seriously affect the health of patients with gastric cancer, resulting in a series of dysfunctional behaviors, including avoidance behavior, hypervigilance of symptoms, and inability to plan for the future, which can reduce quality of life, and at the same time, the unmet supportive needs of cancer patients can lead to lower treatment compliance. These effects can persist for months or even years after treatment, and in severe cases, they can lead to anxiety disorders, posttraumatic stress symptoms, and depression [18].

In the relationship intimacy model of couples' adaptation to cancer by Manne et al [19], the authors emphasized that self-disclosure in relationship-enhancing behaviors is the primary factor affecting the psychological adjustment of cancer patients and their spouses and plays a positive role in the face of cancer. Marriage psychoeducation can help couples understand the value of communicating with each other, provide emotional and problem-focused support, help in the takeover of a spouse's responsibilities and tasks when one spouse is stressed, and help couples work together to cope when both partners are stressed [20]. In the long run, improvements in dyadic coping are more likely to increase relationship satisfaction than improvements in communication skills [21]. In short, dyadic coping is strongly associated with relationship satisfaction. Therefore, incorporating dyadic coping into a relationship enhancement program may benefit couples' relationships [22].

Emotional disclosure is a core component of marital emotional support, and it involves expressing feelings, ideas, and opinions to each other [23]. Couple discussion of cancer-related distress may help spouses understand the needs of patients and provide more effective support. Married patients with cancer tend to rate their spouses as their most important confidant. However, patients with cancer often feel constrained in talking about their concerns with their spouses, and partners often withdraw or distance themselves from the emotional distress of patients [24]. These avoidance patterns are present even in couples with satisfying relationships. The inability of patients to talk openly with their spouses about their cancer-related concerns may reduce the ability of couples to cope with stress and compromise the quality of the patient-partner relationship and the patient's psychological adjustment.

Multiple linear regression analysis results showed that the self-disclosure and intimacy of patients influenced their fear of cancer recurrence [8]. To date, most intervention studies focused

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on the impact of self-disclosure on the psychological aspect of patients, and they ignored the role of their spouses regarding the psychological state [25-27] and failed to treat patients and their spouses as a whole [12]. Given the vast differences between Western countries and China in terms of race; cultural background; religious beliefs; economic development; and the adaptability and accuracy of the related theory, evaluation scale, and influencing factor analysis, the study results based on Western cultural background cannot be directly applied to the Chinese population. Research on spousal disease communication has primarily focused on patients recovering from breast cancer, lung cancer, and even prostate cancer [28,29]. The treatment cycle for advanced gastric cancer is extended, and the recurrence rate is high, which can intensify the psychological burden on patients [12]. During chemotherapy, patients with gastric cancer encounter numerous dietary restrictions and potential complications, such as nausea and vomiting, heartburn, and acid reflux, resulting in a loss of appetite for food [30]. In Chinese culture, it is believed that food is of utmost importance to people. Being unable to eat or having no appetite is a sign of worsening disease, which further exacerbates both the psychological and physical burdens of patients. No research has been performed on the spousal communication of patients with gastric cancer. Additionally, the research findings of other types of cancers cannot be generalized to patients with gastric cancer, and it is necessary to implement targeted psychological intervention measures for Chinese patients with gastric cancer.

The main objective of this study is to assess a marital self-disclosure intervention that is suitable and feasible based on Chinese culture and clinical practice, focuses on the fear of cancer recurrence, guides patients to adjust to a positive attitude through couple self-disclosure, and improves cancer recurrence fear and the marital relationship with their spouses. If the intervention is proven to be effective, the intervention can be adopted as a practical strategy of psychological care for patients with gastric cancer in China.

Methods

Aim

This study aims to develop a marital self-disclosure intervention and evaluate the effectiveness of this intervention for improving the fear of cancer recurrence and the dyadic coping ability in Chinese patients with gastric cancer and their spouses. The trial was registered in November 2022 at ClinicalTrials.gov (NCT05606549).

Hypotheses

The main hypothesis is as follows: Compared with the control group, participants (patients with gastric cancer and their spouses) in the experimental group show lower scores on the FoP-Q-SF after the intervention.

The secondary hypothesis is as follows: Compared with the control group, participants (patients with gastric cancer and their spouses) in the experimental group show improvements in the dyadic coping ability measured by the Dyadic Coping Inventory (DCI) after the intervention.

Theoretical Framework

Manne and Badr [31] believed that it is necessary to not only evaluate the psychological adaptation process of patients in the face of cancer, but also evaluate their spouses. On the basis of summarizing multiple theories, such as the resource theory and social cognition theory, Manne proposed the relationship intimacy model of couple adaptation to cancer [32]. This model divides the factors that affect psychological adaptation into 2 parts: relationship-enhancing behaviors and relationship-compromising behaviors. Relationship-enhancing behaviors, including reciprocal self-disclosure, partner responsiveness, and relationship engagement, have a positive effect on intimacy and psychological adaptation, and intimacy also has a positive effect on psychological adaptation. Relationship-compromising behaviors, including avoidance, criticism, and pressure withdrawal, have a negative effect on intimacy and psychological adaptation. In this model, Manne et al [19] emphasized that reciprocal self-disclosure in relationship-enhancing behaviors is the primary factor affecting the psychological adaptation of patients with cancer and their spouses, and plays a positive role in the face of cancer stressors. This model provides a theory basis for this study to analyze the effect of marital self-disclosure on the fear of cancer recurrence and dyadic coping ability from a binary perspective.

Methodology and Design

A quasiexperimental study with a nonequivalent (pretest-posttest) control group design will be used to examine the effect of marital self-disclosure on the fear of cancer recurrence and dyadic coping ability among patients with gastric cancer and their spouses. The study will be conducted at 2 tertiary hospitals in Taizhou City, Jiangsu Province, China. Considering the time constraints, sample availability, and prevention of contamination, the research will be conducted in the oncology departments (digestive system) of 2 hospitals. The 2 hospitals will be assigned randomly. A total of 42 patients with gastric cancer undergoing chemotherapy and their spouses will be recruited from each hospital. Eligible patients with gastric cancer undergoing chemotherapy who agree to participate and sign the informed consent form will be included in this research. Participants from Jingjiang People's Hospital will be assigned to the experimental group, while participants from Taizhou People's Hospital will be assigned to the control group. Patients with gastric cancer share similar characteristics, such as demographics, treatment, and nursing care plans. The treatment methods refer to the "Guidelines for Diagnosis and Treatment of Gastric Cancer" [32]. The chemotherapy scheme is selected according to the patient's actual situation, which is predicted for 4 to 6 cycles. The study includes 4 stages of face-to-face interventions. The researchers will take measurements at 3 time points: baseline and 2 and 4 months postintervention.

Study Setting and Recruitment

The study will recruit patients and their spouses who are interested in the study. The nurse practitioners will inform the researchers of the patients' interest, and the researchers will explain the research methods and requirements, and the ethical information in detail to the patients. Nurse practitioners from

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the Oncology Department of the 2 hospitals will screen the eligible patients based on the inclusion criteria and will inform the patients and their spouses about the study. The patients who agree to participate will sign a written informed consent form.

Participants

Inclusion Criteria

Patients

The inclusion criteria for patients are as follows: (1) the disease meets the diagnostic criteria of the "Guidelines for Diagnosis and Treatment of Gastric Cancer" [32], the preoperative gastroscopy and pathological diagnosis indicate advanced gastric cancer, and the postoperative pathological classification is type II, III, or IV; (2) age ≥18 years and ability to write and communicate effectively; (3) the main caregiver is their spouse; (4) clear consciousness and no understanding barriers; and (5) written informed consent to participate in this study.

Spouses

The inclusion criteria for spouses are as follows: (1) age ≥18 years and ability to write and communicate effectively; (2) the main caregiver is the spouse; (3) clear consciousness and no understanding barriers; and (4) informed consent to participate in this study.

Exclusion Criteria

Patients

The exclusion criteria for patients are as follows: (1) another diagnosis of gastric cancer or another type of cancer, with severe complications, such as gastrointestinal obstruction and perforation; (2) received or is currently receiving psychotherapy from a psychiatrist or psychologist; (3) cognitive impairment or mental impairment; and (4) severe visual, hearing, and speech impairments.

Spouses

The exclusion criteria for spouses are as follows: (1) presence of serious physical diseases or acute diseases, such as cancer, stroke, and cardiovascular or cerebrovascular diseases; (2) received or is currently receiving psychotherapy from a psychiatrist or psychologist; (3) cognitive impairment or mental impairment; and (4) severe visual, hearing, and speech impairments.

Sample Size

The sample size will be calculated using the following formula for sample size based on the study by Charan and Biswas [33]: sample size = 2 (SD) 2 × (Zα/2 + Zβ)2 / D2. It is based on the FoP-Q-SF (primary outcome) from a previously published study [15]. It showed a 95% power to detect a mean difference of 2.88 points between the control and experimental intervention groups in 61 Chinese patients with breast cancer. Statistical significance will be calculated to achieve a statistical power of 0.9 at a 5% significance level for 70 participants in each group. A 2-tailed test will be used to test the hypothesis. The sample size of each dependent variable is 35. To address dropout, an additional 20% is added to the calculation. As a result, the sample size for the experimental and control groups is 42. Consecutive sampling will be used in this study.

Study Interventions

Control Intervention

Participants in the control group will only receive routine nursing care [34]. When patients are admitted to the hospital, apart from routine nursing related to patient treatment, nurses will provide a booklet to patients about gastric cancer and treatment introduction, adverse reactions of chemotherapy, nutrition management, exercise guidance, psychological support (eg, relaxation and music), and life guidance during chemotherapy. In addition, the researchers will contact patients by phone or WeChat every week and send relevant health education messages to reduce the dropout rate. The nurses will not provide patients with any training in communication skills and will not actively encourage couples to discuss cancer-related thoughts and feelings.

Experimental Intervention

The marital self-disclosure intervention is divided into 4 stages. Each stage will be divided into the chemotherapy and hospitalization phase and the interval and home phase. Both phases include verbal and written disclosures, and the intervention will be conducted in 16 weeks. The flowchart of the trial is shown in Figure 1.

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Figure 1. Flowchart of the trial. The primary outcome is the score of the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) for patients. The secondary outcomes are the scores of the FoP-Q-SF for partners and the Dyadic Coping Inventory.

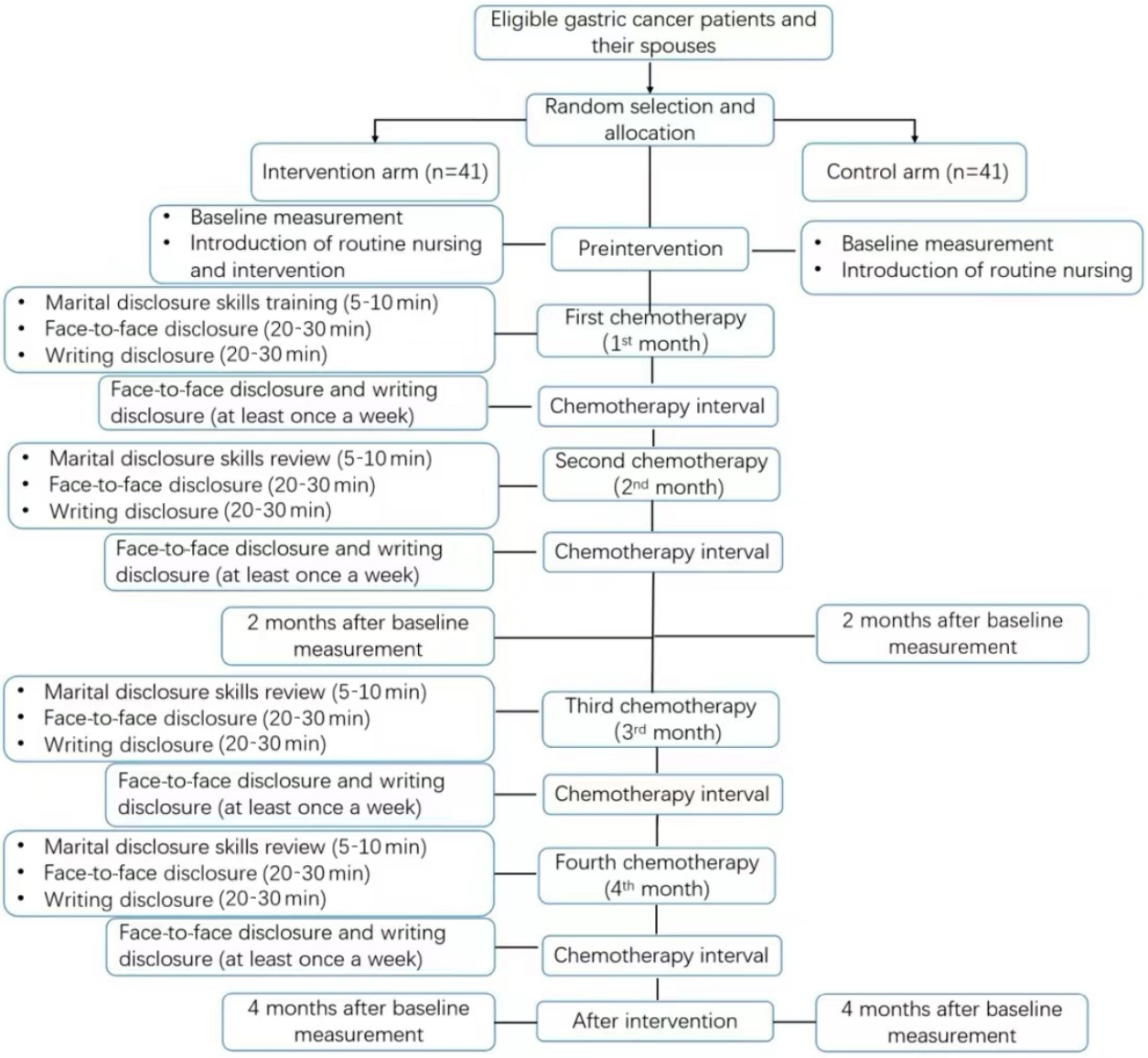

Phase 1: Development of the Marital Self-Disclosure Intervention

A previous systematic study [35] by our team found that the most common methods of couple communication are one-on-one and face-to-face communication. They should accept training in marital communication methods before marital self-disclosure, such as how to incorporate the materials from the course into their daily lives through the communication skills learned [36], the strategies for expressing their thoughts and feelings about cancer, and the strategies for accepting and affirming each other's feelings and opinions [23]. Psychological evaluation indicators are stable, and no significant changes are observed in frequent evaluations [15]. Therefore, 3 to 5 weeks per session can obtain a trend change in the index and will not lead to patient evaluation fatigue, which involves better evaluation frequency. Patients with cancer become unwell due to chemotherapy, and short-term interventions (3-6 stages, 40-60 minutes each step) increase memory and application of what couples have learned and increase patient confidence and motivation to manage their disease [37]. In situations where disclosure to a partner becomes challenging or problematic, individuals may gain some benefit from writing a disclosure diary [15,38,39]. The researchers have developed and designed the intervention. The literature mentions the disclosure needs of cancer couples and the changes in cancer patients' fear of recurrence during chemotherapy, and provides information on the interview framework, objectives, benefits, mechanisms, and strategies to implement marital self-disclosure. To further improve the marital self-disclosure intervention, the researchers will conduct in-depth interviews with 3 patients with gastric cancer and their spouses to explore the experiences and needs of marital communication. Furthermore, 6 nurses from the oncology ward will be interviewed to explore the intervention preference and obtain their suggestions for the content of marital self-disclosure. The findings of in-depth interviews will be used to improve the frame, stage, time, and disclosure process of marital self-disclosure.

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Phase 2: Panel Evaluation by Experts

An expert panel will be invited to provide expert inputs for developing the marital self-disclosure intervention. The expert selection criteria are as follows: (1) medical staff specializing in oncology, the gastrointestinal system, and psychology; (2) educational background of a bachelor's degree or above; (3) deputy senior title in a medical or nursing position or above; (4) rich experience in the above fields and ability to provide professional advice and guidance for this research; (5) working experience of more than 10 years; and (6) willingness to participate in this study. A total of 12 experts will be selected. Before the consultation, the research background and methods will be explained to the experts to obtain support and cooperation.

The contents and methods of marital self-disclosure are derived from the 2 phases mentioned above.

Chemotherapy and Hospitalization

The intervention time during hospitalization is the first day after chemotherapy, and the intervention is used once per chemotherapy for a total of 4 times for 45 to 70 minutes each time. The intervention includes verbal and written disclosures. The researcher will preside over the marital self-disclosure process and introduce it to patients with gastric cancer and their spouses (definitions of dyadic coping ability, marital self-disclosure, benefits, stages, process, techniques, and time). Both the patient and their spouse will take turns as speakers and listeners, and receive training or undergo review on marital self-disclosure skills for 5 to 10 minutes each time. The training or review details are shown in Table 1. The training will focus on emphasizing the strengths of dyadic coping and distinguishing between problem-solving and supportive communication. Couples will be encouraged to spend more time understanding each other through supportive communication rather than directly addressing communication issues. Couples will practice marital self-disclosure skills through 4 revealing themes. Couples will be encouraged to express their fear of cancer recurrence. When partners disclose information, supporters should allow the speakers to fully express their feelings and should respond positively to the messages of the speakers, showing empathy for them and acknowledging their points of view.

Each stage has different revealing goals, and the disclosure outline set according to the goals differs. The goals of the personal emotional expression stage are to reveal the person's thoughts and feelings after the illness, reveal the person's concerns about the progression of the disease, and express other emotions. The goals of the social cognition expression stage are to disclose the impact of cancer on family or social functioning after the illness, reveal the couple's specific concerns about the progression of the disease, and express other emotions. The goals of the benefit discovery stage are to disclose the benefits of couples from the experience of illness, reveal positive emotions after the illness, and reveal positive changes that have occurred in their life during treatment. The outlook to the future stage aims to disclose the couple's plans, reveal the couple's needs, formulate a cancer recurrence prevention plan, and express other emotions. The patient with gastric cancer and their spouse will disclose information to each other according to the disclosure outline (20-30 minutes) at each stage. When one party is disclosing information, the other party is required to listen actively. After the verbal disclosure, the patient will participate in a written disclosure based on the given topics for 20 to 30 minutes each time. During the written disclosure, the researcher and the patient's spouse are required to maintain silence and respond to the patient timely if there are any questions. After writing, the researcher will take back the notebook. The disclosure topics of the 4 stages are described in detail in Table 2.

Table 1. Disclosure training of the speaker and listener.

Disclosure request	Description
Disclosure request of the speaker	• Share a topic-related experience that evokes strong emotions • Follow your heart and express your thoughts sincerely • Tell your partner about the experience in as much detail as possible, including the event itself and psychological feelings • Do not talk too much at one time; pause occasionally to give your partner a chance to show understanding and support
Disclosure request of the listener	• Try to stand in your partner's role and understand their experience • Avoid immediately solving the problem or giving advice, focus the conversation on how your partner feels, reveal your thoughts when necessary, and facilitate the expression of your partner • Listen reflectively, summarize what your partner has said, pay attention to your tone of voice, maintain eye contact, and nod your head to show understanding

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Table 2. Marital self-disclosure topics.

Theme and aspects	Description
First chemotherapy: personal emotional expression	
Verbal disclosure goals (couple)	• Reveal the person's thoughts and feelings after the illness • Reveal the person's concerns about the progression of the disease • Express other emotions
Disclosure outline	• How have you felt since (your partner) became ill? • Are you worried about the progression of the disease? What are the specific aspects? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please write down your inner thoughts and feelings during the illness and how they affect you
Second chemotherapy: social cognition expression	
Verbal disclosure goals (couple)	• Disclose the impact of cancer on family or social functioning after the illness • Reveal the couple's specific concerns about the progression of the disease • Express other emotions
Disclosure outline	• What impact does the illness (of your partner) have on your family, work, and social interactions? • Are you worried about the progression of the disease? What are the specific aspects? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please write down the couple's specific concerns during the illness and how they affect you
Third chemotherapy: benefit discovery	
Verbal disclosure goals (couple)	• Disclose the benefits for couples from the experience of the illness • Reveal the positive emotions after the illness • Reveal the positive changes that have occurred in your life during treatment
Disclosure outline	• Did you benefit from the experience of being sick? What are the specific aspects? What are the good influences on you? • What positive emotions did you experience after (your partner) got sick? • What positive changes have you made during the (partner) treatment?
Written disclosure (patient)	• Please write down the positive changes and emotions that you have experienced from the illness
Fourth chemotherapy: outlook to the future	
Verbal disclosure goals (couple)	• Disclose the future plans of the couple • Reveal the needs of the couple and formulate a cancer recurrence prevention plan • Express other emotions
Disclosure outline	• What are your plans for the future? • What other needs do you have for preventing disease recurrence and what are your plans to prevent the recurrence of the disease? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please summarize and write about your cancer recurrence prevention plan and hopes for the future

Chemotherapy Interval and Homework

With regard to homework requirements, couples will determine the time of disclosure according to the actual situation. The verbal and written disclosures will be conducted at least once a week for 20 to 30 minutes each time. The disclosure outline during the chemotherapy interval is the same as that during the chemotherapy. At the end of every stage, a notebook will be provided to the patient, and the patient will be required to complete homework after chemotherapy.

Phase 3: Marital Self-Disclosure Intervention Workshop for Facilitators

First, 2 oncology nurses with strong nursing and communication skills will gain the trust of patients, screen patients who met the inclusion and exclusion criteria, ask them whether they are willing to participate in this study, and assist the consenting patients in signing the informed consent form. Second, participants in the experimental group will receive the marital self-disclosure intervention delivered by 2 communication-led nurses who have master's degrees in nursing and who are

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certified psychological counselors. The communication-led nurse will (1) prevent negative interactions; (2) use the checklist to facilitate the disclosures of patients and their spouses; (3) ensure that the communication does not deviate from the outline; and (4) guide the disclosure content to focus on the speaker's experience. Furthermore, the research nurse will (1) add the WeChat ID of the patient or spouse; (2) provide weekly WeChat reminders; and (3) require the patient or spouse to take photos, upload data, and check in regarding the disclosure execution status and disclosure diary through WeChat. If patients have any nursing or treatment questions, they can consult the research nurse through WeChat. For patients who do not have WeChat, the nurse will follow-up on the implementation status through telephone contact. Moreover, the nurse will record the reasons for patient dropout.

Instruments and Measures

Sociodemographic and Clinical Variables

Variables include the demographic information of patients with gastric cancer and their spouses, including age, gender, education level, employment status, family per capita monthly income, duration of the marriage, and fertility status (couple). In addition, information on clinical variables, including pathological classification, tumor stage, treatment type, and time since cancer diagnosis (patient), will be collected.

Fear of Cancer Recurrence for Patients

The FoP-Q-SF is a 1-dimensional scale based on the Fear of Progression Questionnaire (FoP-Q). The FoP-Q-SF for patients includes 12 items, which are rated on a 5-point Likert scale (1 point indicating "never" and 5 points indicating "always"), with a total score ranging from 12 to 60 and with higher scores indicating higher fear of disease progression [40]. Wu et al [41] translated the scale into Chinese and tested its reliability and validity. The authors found that the Cronbach α coefficient of the total scale was 0.886 and the Guttman split-half coefficient was 0.855. Moreover, the Cronbach α coefficients of the 2 extracted common factors were 0.836 and 0.804, respectively, and the Guttman split-half coefficients were 0.806 and 0.828, respectively, which indicated good content consistency and met the requirements of psychometrics.

Fear of Cancer Recurrence for Partners

The FoP-Q-SF for partners was developed by Zimmermann et al [42] based on the structure of the FoP-Q-SF scale to assess the degree of partners' fear of disease progression in patients. The FoP-Q-SF for partners includes 12 items, which are rated on a 5-point Likert scale (1 point indicating "never" and 5 points indicating "always"), with a total score ranging from 12 to 60 and with higher scores indicating higher fear of their spouses' disease progression. The Cronbach α coefficient of the scale was 0.88. Wu et al [41] translated the scale into Chinese and tested its reliability and validity. The authors found that the Cronbach α coefficient of the total scale was 0.834 and the Guttman split-half coefficient was 0.818. The Cronbach α coefficients of the 2 extracted common factors were 0.835 and 0.699, respectively, and the Guttman split-half coefficients were 0.774 and 0.721, respectively, which indicated good content consistency and met the requirements of psychometrics.

Dyadic Coping Ability

The DCI based on the system interaction model was initially developed by Bodenmann [43], which included 6 dimensions (55 items) and used a 5-point Likert scale. After further improvement, the DCI [44] was revised to 37 items and was measured on a 5-point Likert scale ranging from 1 (not at all/very rarely) to 5 (very often). To assess the stress and coping behaviors of couples, the DCI includes 5 subscales for the patient and a corresponding subscale for the partner: (1) stress communication by self; (2) emotion-focused supportive dyadic coping by self; (3) problem-focused supportive dyadic coping by self; (4) delegated dyadic coping by self; and (5) negative dyadic coping by self. The DCI also assesses 2 common dyadic coping behaviors: emotion-focused common dyadic coping and problem-focused common dyadic coping. Xu et al [45] translated this questionnaire into Chinese. The Cronbach α coefficient was 0.73.

Outcome Assessment

Permission to adopt the 3 questionnaires has been obtained from the original researchers. A trained researcher will assess the outcomes, including sociodemographic variables and psychosocial variables. The sociodemographic variables include demographic and clinical characteristics. The psychosocial variables include fear of cancer recurrence for patients, fear of cancer recurrence for partners, and dyadic coping ability. The psychosocial variables will be repeatedly collected at 3 time points: baseline, after the second session of the intervention (nearly 2 months after baseline), and after the last intervention (almost 4 months after baseline). The control group will be reassessed at the same intervals. Furthermore, participants in the experimental group will be assessed to determine their experiences with the intervention after the last intervention session (Table 3). The conceptual framework is shown in Figure 2.

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Table 3. Study measures.

Variable	Outcome (measure)	Time point		
		Baseline	2 months after baseline (after the second intervention)	4 months after baseline (after the fourth intervention)
Inclusion criteria	Sociodemographic and clinical information	Yes	No	No
Primary outcome	FoP-Q-SF[a] for patients	Yes	Yes	Yes
Secondary outcome	FoP-Q-SF for partners and Dyadic Coping Inventory	Yes	Yes	Yes
Intervention experience	In-depth interview	No	No	Yes

[a]FoP-Q-SF: Fear of Progression Questionnaire-Short Form.

Figure 2. Conceptual framework.

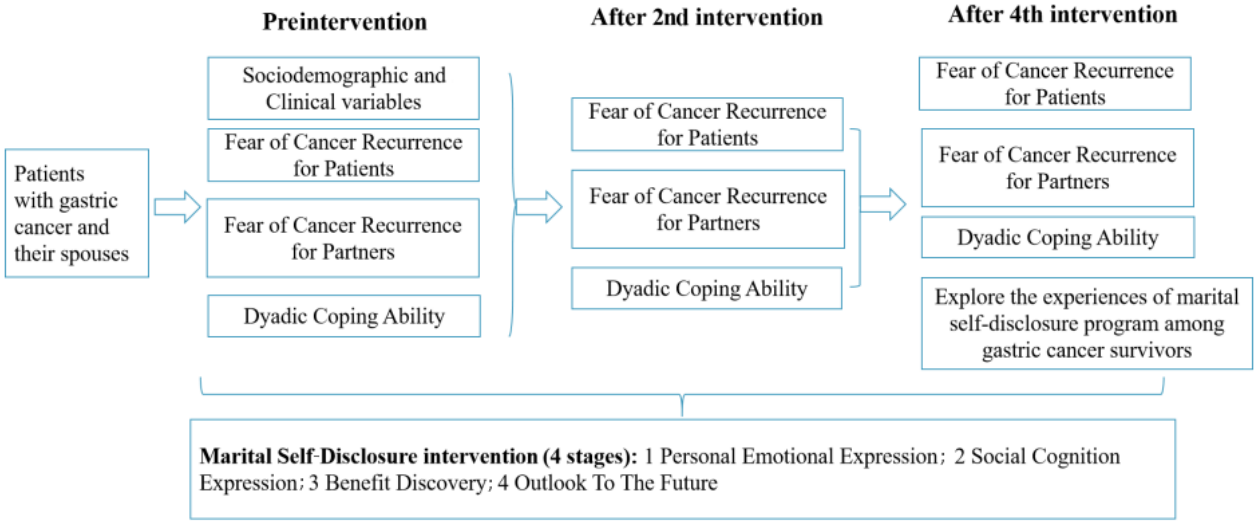

Data Collection and Compensation

Upon agreeing to participate in the study, participants will be required to complete a paper-based baseline survey questionnaire. Participants in the intervention group will have the option to receive the marital self-disclosure intervention directly after completing the survey, while participants in the control group will only receive routine care. Both groups of participants will be tracked for a duration of 16 weeks after recruitment, and data will be collected at 3 time points: baseline and 2 and 4 months postintervention.

To ensure participant confidentiality, information collection will be restricted to face-to-face communication and a paper-based questionnaire. Birth dates or participant addresses will not be collected. All data will be stored on secure internal platforms of Hospitals A and B. At the end of the study period, only researchers will have access to the data set.

At each time point, the research team will contact participants via phone or WeChat, according to their preferences. Participants will be notified of upcoming follow-up studies and will be assisted in completing subsequent survey questionnaires. Upon completing each survey, they will receive small gifts, such as a hand sanitizer. Recruitment is expected to last for 12 months, with an additional 16 weeks needed for follow-up with all recruited participants to complete data collection. Data analysis will commence at the end of recruitment.

Allocation and Blinding

This study will recruit an equal number of patients with gastric cancer and their spouses. Participants from Jingjiang People's Hospital will be assigned to the experimental group, while participants from Taizhou People's Hospital will be assigned to the control group. As the study involves a face-to-face psychological intervention, participants and personnel will be unblinded, but the outcome assessment will be blinded. Participant data will be anonymized using individual participant codes, and the database will not contain participant identifiers (eg, birth dates and case numbers).

Data Analysis

Statistical analysis will be conducted using IBM SPSS 21.0 (IBM Corp). The level of statistical significance will be set as α=.05. Descriptive statistics will be used to describe the sociodemographic and psychosocial variables, including percentages, means, and standard deviations. For comparing the baseline characteristics of the 2 groups, the Student *t* test or Mann-Whitney *U* test will be used for quantitative variables and the chi-square test will be used for categorical variables. Two-way repeated-measures ANOVA will be performed to determine the presence of a significant change in the fear of cancer recurrence and DCI in the intervention and control groups in order to analyze the effects of the intervention and compare the control group with the experimental group at baseline and 2 and 4 months postintervention. This analysis will be performed

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on an intention-to-treat basis. A *P*-value of <.05 will be considered statistically significant for differences between the 2 groups.

Ethical Considerations

The study protocol has been approved by the ethics committees of Jingjiang People's Hospital and Taizhou People's Hospital (TZRY-LL-AF/SQ-018-3.0 and KY 2022-167-01). A cover letter will be provided to guarantee human rights and ethical transparency, and inform the participants about the aims and benefits of this study. Participants will be informed that they can voluntarily participate and withdraw from the study without any impact on their treatment or nursing care. If they agree to participate, they will be required to sign an informed consent form with detailed information concerning the goals and procedures of the intervention. The data of this research will be kept confidential and anonymous. The trial was registered in November 2022 at ClinicalTrials.gov (NCT05606549).

Results

The research activities for this study commenced in October 2022. Participant recruitment and data collection began in February 2023, with the expectation of completion within 12 months (by December 2024). As of October 30, 2023, a total of 97 gastric cancer patients and their spouses have been recruited, and all baseline data have been collected. Once sufficient participants are recruited, subsequent measures will be performed and data analysis will commence. The primary results of this study are anticipated to be announced in June 2024.

Discussion

Marital Self-Disclosure Intervention and Protocol Design

Improvement of the fear of cancer recurrence and dyadic coping ability in patients with gastric cancer is necessary. To date, few psychological interventions effectively manage the fear of cancer recurrence in patients with gastric cancer. This is the first and only intervention with the explicit aim of improving the fear of cancer recurrence in Chinese patients with gastric cancer. The intervention focuses on personal emotional expression, social cognition expression, benefit discovery, and outlook to the future, with a further focus on the fear of cancer recurrence. This study will provide evidence of the effectiveness of the marital self-disclosure protocol for improving the fear of cancer recurrence compared with routine nursing care.

There are several advantages of the marital self-disclosure intervention. First, the study involves a long-term intervention that spans from the participant's diagnosis of gastric cancer until the end of chemotherapy. In a preview study, among patients with gastric cancer in the first, third, and sixth chemotherapy stages, greater family support was associated with a lower fear of cancer recurrence [7]. Therefore, early and lasting intervention is essential.

Second, the study considers the marital factors related to the fear of cancer recurrence and has developed relevant communication topics in each phase. The husband and wife will be trained in marital self-disclosure, and formal disclosure will be made after both husband and wife have mastered the method of disclosure. Moreover, before each phase, the couple will review the method of disclosure again so that the couple can fully grasp the method of disclosure and return it as a homework exercise, making the research results more credible. Finally, this study combines written and verbal representations to facilitate better participant expression of concerns regarding the fear of cancer recurrence.

Third, the study is based on not only a literature review but also Chinese cultural background, clinical practice, and stakeholder input to design a feasible intervention for Chinese patients with gastric cancer.

Fourth, the marital self-disclosure intervention will be designed for implementation by nurses, and it may appeal to nurses who seek flexibility and dynamism in their work. The intervention will train nurses to teach patients and their spouses to use the theory of respect, empathy, and positive attention in emotional communication and marital interaction. Stable, friendly, and trusting relationships will be built between nurses and patients.

Limitations

This study has some minor limitations. First, this study involves a long-term intervention, and some participants may not complete the study owing to loss of follow-up or physical deterioration during treatment. Second, missing data may influence the results and must be addressed statistically. To overcome this bias, a 20% attrition rate will be included in the sample size calculation, and an intention-to-treat analysis will be performed during the data analysis. Finally, this study will only include patients during chemotherapy.

Conclusion

This is the first attempt to develop a brief and feasible intervention to manage the fear of cancer recurrence in Chinese patients with gastric cancer. If the marital self-disclosure intervention is effective, it will be implemented at the hospital. This brief and focused intervention will be integrated to enhance clinical practice. Even with null results, participants with gastric cancer and their spouses will obtain more comprehensive self-care nursing knowledge. Furthermore, investigators will obtain a large amount of data to analyze the fear problems of patients with gastric cancer.

Acknowledgments

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Authors' Contributions

HZ, Y Zhou, Y Zheng, YH, CC, and Y Zhu substantially contributed to conception and design, acquisition of data, and analysis and interpretation of data. HZ, Y Zhou, CCC, and MCC were involved in drafting the manuscript or revising it critically for important intellectual content. Y Zhou, CCC, and MCC provided final approval to the manuscript. Y Zhou agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

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Abbreviations

DCI: Dyadic Coping Inventory
FoP-Q-SF: Fear of Progression Questionnaire-Short Form

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Protocol

Motor Effects of Intervention With Transcranial Direct Current Stimulation for Physiotherapy Treatment in Children With Cerebral Palsy: Protocol for a Randomized Clinical Trial

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Abstract

Background: Children diagnosed with cerebral palsy (CP) often experience various limitations, particularly in gross motor function and activities of daily living. Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that has been used to improve movement, gross motor function, and activities of daily living.

Objective: This study aims to evaluate the potential additional effects of physiotherapy combined with tDCS in children with CP in comparison with physiotherapy only.

Methods: This is a 2-arm randomized controlled trial that will compare the effects of tDCS as an adjunctive treatment during rehabilitation sessions to rehabilitation without tDCS. Children with CP classified by the Gross Motor Function Classification System as levels I and II will be randomly assigned to either the sham + rehabilitation group or the tDCS + rehabilitation group. The primary outcome will be the motor skills assessed using the Gross Motor Function Measure domain E scores, and the secondary outcome will be the measurement scores of the children's quality of life. The intervention will consist of a 10-day stimulation protocol with tDCS spread over 2 weeks, with stimulation or sham tDCS administered for 20 minutes at a frequency of 1 Hz, in combination with physiotherapy. Physical therapy exercises will be conducted in a circuit based on each child's baseline Gross Motor Function Measure results. The participants' changes will be evaluated and compared in both groups. Intervenient features will be tested.

Results: Data collection is ongoing and is expected to be completed by January 2025. A homogeneous sample and clear outcomes may be a highlight of this protocol, which may allow us to understand the potential use of tDCS and for whom it should or should not be used.

Conclusions: A study with good evidence and clear outcomes in children with CP might open an avenue for the potential best use of neurostimulation.

Trial Registration: Brazilian Registry of Clinical Trials RBR-104h4s4y; https://tinyurl.com/47r3x2e4

International Registered Report Identifier (IRRID): PRR1-10.2196/52922

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(JMIR Res Protoc 2024;13:e52922) doi:10.2196/52922

KEYWORDS

cerebral palsy; tDCS; motor; development; randomized clinical trial; RCT; clinical trial; randomized; transcranial direct current stimulation; stimulation; children; child; brain stimulation; physical therapy; quality of life; researchers; researcher; neurological injuries; injury; injuries; gait; patient; patients

Introduction

Cerebral palsy (CP) is a prevalent cause of physical disability among children, with reported incidence rates ranging from 2.0 to 2.5 per 1000 live births in developed countries, and even higher in low and middle-income countries, reaching up to 7 per 1000 live births [1]. The treatment goals for CP primarily focus on improving motor function and promoting independence in activities of daily living, as well as enhancing quality of life (QoL) [2]. Despite the efforts made in this area, the heterogeneous clinical presentations and responses to interventions pose a challenge in generalizing information about the effectiveness of specific treatment methods [2]. Guidance from the Cochrane Collaboration in 2019 suggests there is a need to standardize the outcomes studied in interventions, to provide functional and informative results and guide the selection of the most effective interventions and an effective individualized treatment [3].

Children with CP have difficulties in balance, motor function, and movement coordination. Physical therapy is used to improve these disabilities. Transcranial direct current stimulation (tDCS) is a complementary intervention that has been shown to enhance balance and improve movement coordination and gross motor function in children with CP [2,4,5]. There is a difference in oscillation speed when associating tDCS with virtual reality [5]. De Almeida Carvalho Duarte et al [2] have shown that children with CP subjected to 5 sessions of treadmill training stimulated with tDCS for 2 weeks with stimulation in M1 for 20 minutes exhibited improvements in temporal functional mobility, such as gait. The results were still maintained 1 month after the intervention. Balance and functional performance seem improved in children with CP after 5 sessions of tDCS anodal stimulation of the motor cortex plus treadmill training for 2 consecutive weeks.

Just 1 session of tDCS realized in the M1 region for 20 minutes in a group of children with CP showed a momentary increase in cortex activation with a direct influence on motor control and an improvement in gait and balanced outcomes [6]. Permanent effects in the population submitted to tDCS with clinical effects were observed in promoting functional improvement in children with CP [2,4].

According to the previous results, we hypothesized that tDCS use might improve specific motor skills and positively impact QoL in a more homogeneous population with CP. This study was designed to examine the impact of the combination of tDCS and conventional rehabilitation exercises on the improvement of gross motor function in children with CP classified as level I and II in the Gross Motor Function Classification System (GMFCS). The primary outcome measure will be assessed using the scores of the Gross Motor Function Measure (GMFM) dimension E and the secondary outcome is the children's QoL.

According to Castelli and Fazzi [7], rehabilitation is a complex process that aims to promote the best possible participation and QoL for the child and the family. Rehabilitation for children with CP must be timely, intensive, and family-centered [7]. Despite the importance of understanding the effects on children's QoL, QoL is not commonly measured.

Castelli and Fazzi [7] recommend intensive rehabilitation with trained professionals and a multidisciplinary team focused on the child's functional improvement. Rehabilitation is one of the main parts as it involves performing functional assessments, establishing a functional prognosis, constructing a rehabilitation plan, and promoting a multidisciplinary approach [7].

Methods

This study is a single-blind randomized controlled trial (RCT). The participants will be blinded to the treatment allocation during the trial, but the researchers conducting this study will be aware of the treatment allocation. This study will conform to the CONSORT (Consolidated Standards of Reporting Trial) guidelines for nonpharmacological interventions. This study has been approved by the ethics committee in research.

Recruitment

All patients with CP who meet the previously described criteria for inclusion will be invited to participate in this study which will be realized in the Molecular Medicine Center of the Universidad Federal de Minas Gerais in Brazil.

Sample Size

The sample size was calculated using G* Power software (version 3.1; Universität Düsseldorf) [8]. Considering an effect size of 0.5, power of 0.95, and probability of type I error (α) of 5%, the total sample size should be 176 volunteers, with 2 groups of 88 volunteers. The impact of the intervention will be evaluated in the pilot phase to determine a more accurate estimate of the population sample size. The participants will be included from July 2023 to July 2024. After the end of the intervention, the data collected will be separated into groups, these being the intervention group (IG) and the control group (CG). We will carry out the analysis of the pre- and postintervention GMFM variables and the Pediatric Quality of Life Inventory (PedsQL). We will carry out the analysis between groups (CG and IG) and between individuals in the same group, and will compare participants with themselves, to quantify and describe the results. Analysis of covariance will be chosen to observe preexisting differences between groups, allowing for comparison of postintervention scores while controlling for baseline scores.

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Participants and Eligibility Criteria

The participants in this study will be recruited through advertisements at clinics and the intervention will take place at the Molecular Medicine Center of the Universidade Federal de Minas Gerais in Brazil. To be eligible, participants must have a medical diagnosis of CP, be classified as GMFCS I or II, be aged between 8 and 12 years, be able to walk independently, and be able to understand commands. Exclusion criteria include other neurological conditions, recent history of surgery, uncontrolled epilepsy, a cranial metallic implant, and the use of a hearing aid. The waiting list group will have access granted afterwards based on the evidence.

Ethical Considerations

This study was evaluated and approved by the local ethical board at Universidade Federal de Minas Gerais (50504021.0.0000.5149). All participants and their guardians will be informed about the research protocols and will be required to sign the free and informed consent form and the free and clarified assent form. Participation will only be allowed when both the child and parent have agreed to participate. All data will be handled as anonymous. Following the national law, participation in the intervention must be voluntary and reimbursement will be available only for research-related transportation.

Measures

Overview

Both instruments will be used with all participants before and after the interventions to assess whether there was a significant improvement in gross motor movement according to the E domain of the GMFM or in QoL.

About GMFCS

This is a scale used to classify the level of impairments of the gross motor function of the CP population [9]. GMFCS allows us to classify functionality about walking, sitting, and standing [8]. It classifies gross motor function into 5 levels, as follows: level I: no access; level II: walks with limitation; level III: walks using a manual mobility device (such as a Canadian crutch, walker, or cane); level IV: self-mobility with a limitation (such as using a regular or automatic wheelchair); level V: patient transported via manual wheelchair by a responsible person. Initially, the entire sample will be evaluated using this instrument [10].

About GMFM

This instrument evaluates quantitatively the change in gross motor function in children with CP. The evaluation has five dimensions: dimension A, bed and roll; dimension B, sitting; dimension C, crawling and kneeling; dimension D, standing; and dimension E), walking, running, and jumping [11]. The scoring system is as follows: a score of zero is assigned if the individual is unable to start the activity, a score of 1 is assigned if the individual starts the activity, a score of 2 is assigned if the individual starts the activity but only completes half of it, and a score of 3 is assigned if the activity is completed. The scores for each dimension should be calculated separately by summing the scores for that dimension and dividing by the total score for that dimension [11].

In the end, the scores for each dimension should be multiplied by 100 to find the percentage that the child achieved in each dimension. Finally, the percentages for all dimensions should be added and divided by 5 (the number of dimensions evaluated), yielding the percentage that the child scored in the GMFM (dimension E). This method is based on the techniques of Luciana Ventura De Pina, PhD and Ana Paula Cunha Loureiro, PhD [12]. Both scales, the GMFM and the GMFCS, have been validated for use with children with CP. The GMFM assesses gross motor function and the GMFCS stratifies the functional level of children with CP. The Gross Motor Ability Estimator (GMAE) program will be used to analyze the GMFM results.

About PedsQL

The PedsQL is a multidimensional tool to measure health-related QoL in children and adolescents. It is a practical scale on the dimensions of health outlined by the World Health Organization, with questions related to the frequency of problems faced in the last month. The 23 item-PedsQL has 8 items for physical functioning; 5 for social functioning; 5 for emotional functioning; and 5 for school functioning, with 15 on patients' psychosocial health.

tDCS Intervention

Overview

The IG will receive 10 sessions of tDCS with a frequency of 5 daily sessions per week, over a period of 2 weeks. The stimulation will be administered during rehabilitation sessions. The electrodes will be 35-cm^2 sponges moistened with normal saline (0.9% NaCl solution). The stimulation will consist of anodal stimulation in the primary motor cortex (M1) and cathodal stimulation in the supraorbital region on the contralateral side, at an intensity of 1 mA and a duration of 20 minutes at a steady-state level, with a ramp-up and ramp-down of 4 seconds. The stimulation will be combined with specific exercises in a circuit format to target dimensions D and E of the GMFM [13]. CG will undergo 10 sessions of sham tDCS associated with rehabilitation activities 5 times per week, for a total of 2 weeks. Activities that target dimension E of the GMFM will be organized as a circuit including running, walking, and jumping. Any change to the trial will be informed along with the reason for the change.

Safety

The device used, tDCS Soterix Medical (Soterix Medical Inc), model number 1300-A and serial number 13ITC0619005, is approved by the Food and Drug Administration for use as an experimental device and some for clinical purposes (ANVISA-80969860041). Further, 3.5-cm^2 electrodes will be used. Bikson et al [13], prove if the purpose is to modulate neurophysiological measures for resting motor cortex stimulation in healthy young people (1 mA intensity), tDCS for 4 seconds induces acute excitability alterations.

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Krishnan et al [14] demonstrated adequate safety of tDCS in children and adolescents. Well-accepted threshold of tDCS current density is <142.9 A/m^2 or 14.29 mA/cm^2. Each patient will undergo a thorough health assessment and medications in use will be registered as well as all health conditions. Cardiac frequency, blood pressure, temperature, respiration, clinical assessment of mental and functional status, and physical examination will be measured [15]. Any apparent side effects will be registered, and all changes to the study will be described so that individuals have the option to interrupt the trial; the trial may also be suspended.

Adverse Effects

Adverse effects will be assessed using the tDCS adverse effects questionnaire [16]. The dropout rate will be reported, and dropout reasons will be stated [15]. tDCS is generally well-tolerated with no serious adverse events [14]. The effects reported are rare, mild, and transient, with "redness," "slight tingling," "itching," and "burning sensation" as the most reported events. The intensity of current, density, and electrode size will be optimized to modulate the tingling and itch perception during transcranial stimulation. Furthermore, we will not pass the well-accepted threshold of tDCS current density (<142.9 A/m^2 or 14.29 mA/cm^2) [14].

Allocation

Participants will be randomly assigned to tDCS groups with a 1:1 allocation as per a computer-generated randomization schedule stratified by the patient's age using 5 permuted blocks of 6 participants.

Implementation

All participants will be randomized, and the randomization will be performed by the researcher who will carry out an intervention; the others will not know which group the participant is in. This member will upload the randomization results to the institution's REDCap (Research Electronic Data Capture) database [17]. The researcher who will perform a physiotherapeutic intervention and the researcher who will apply the assessments and questionnaires will not have information about group allocation.

Blinding

This will be a double-blinded study; during this study, the participants will be seen by three different teams: (1) the researcher who performs the assessment and questionnaires, (2) the neuromodulation team who apply the tDCS, and (3) the physiotherapist who performs the physiotherapy exercises. There will be no members working simultaneously on both teams. The results of randomization will only be available to the neuromodulation member responsible for the intervention, and the scales' results will only be available to the researcher who performed the assessment and questionnaires. The results will be held in a different project in REDCap and will be available only to the researcher who makes the assessment and questionnaires.

Emergency Unblinding

Emergency unblinding will be available under the determination of this study staff, in case of safety concerns related to the intervention.

Interventions: Participants

Initially, we will explain to the child how the intervention process will be carried out. The electrodes will be moistened in saline solution and will be placed on the participant's head, which may cause slight discomfort as it will wet the child's head, and, to minimize this discomfort, we will frequently dry their face. Associated with this, the child will perform physical therapy exercises.

CGs for tDCS will receive placebo stimulation for 30 seconds, for 10 sessions to give the child an initial feeling of stimulation. Associated with the placebo, the child will perform physical therapy exercises, focusing on the demands of the GMFM dimension E. The tDCS intervention will receive a current of 1 mA, for 20 minutes, for 10 sessions also associated with physical therapy exercises, focusing on the demands of the GMFM dimension E.

The intervention lasts from 25 to 35 minutes with each participant and will have a researcher exclusively dedicated to it during the intervention period for data collection. There will be 5 sessions with each participant per week over 2 consecutive weeks, with sessions taking place on weekdays and not weekends. All included participants will complete 10 sections of physiotherapy with or without tDCS stimulation. The tDCS device contains 2 electrodes, an anode, and a cathode, in the form of 2 nonmetallic sponges measuring 5×5 cm^2, moistened with saline solution. The anode will be positioned on the M1 of the participant's dominant hemisphere, according to the 10-20 System EEG, while the cathode will be placed on the supraorbital region of the region contralateral to the anode. In the case of the experimental group, a current will be applied to M1 for 20 minutes for neurorehabilitation.

After 10 sessions, the GMFM test will be repeated with each patient along with the PedsQL. Further, 1 researcher will carry out the intervention or the placebo with tDCS and the other researcher will evaluate the results blindly, without knowing which group is the intervention and which is the control. The use of the equipment and the evaluation will be carried out in different rooms to guarantee the researchers' blindness. Only the researcher in charge of using the tDCS will be aware of the allocation of children between experimental and CGs.

It is worth noting that the patients in the CGs learned, at the end of this study, the intervention that had the best effect on their motor function, respecting this study's ethical perspective that all children should receive the best treatment.

Results

There is a compelling need to tailor medical approaches more precisely, catering to individual differences. Achieving successful outcomes requires studies that use informative measures, robust evidence, and are applicable across diverse demographics.

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In this proposal, we emphasize the importance of incorporating targeted and universally recognized outcomes, specifically focusing on motor skills impacted by the disorder. These skills are universally acknowledged and play a fundamental role in an individual's daily life. Additionally, we are examining how these interventions influence the overall QoL for affected individuals. Data collection is ongoing and is expected to be completed by January 2025.

Moreover, our study aims to optimize treatment efficacy by exposing participants to multiple sessions. This strategy is designed to fine-tune the intervention's impact, building upon a baseline established using the most credible rehabilitation practices available for this condition.

RCTs are not commonly conducted in pediatric populations, leading to a lack of dedicated information specific to this demographic's unique needs and responses. Addressing this gap is crucial to better understand how interventions impact children with this condition.

Discussion

A randomized controlled protocol using an additional tDCS was designed to improve specific motor skills and positively impact QoL in a homogeneous population with CP. This study aims to examine the impact of the combination of conventional rehabilitation exercises on the improvement of gross motor function in children with CP classified as level I and II in the GMFCS. The primary outcome was assessed using the scores of the GMFM dimension E and children's QoL as the secondary outcome. tDCS seems to improve balance, gross motor function, and gait in children with CP [2,4-7]. Mixed and heterogeneous outcomes of varied motor skills made it difficult to understand who and in what conditions individuals may benefit from tDCS complementary use.

To address this issue, the specific protocol proposed focuses on a homogeneous population of children with CP who have preserved walking skills and will evaluate them for motor features and QoL. By using the GMFCS and GMFM to classify and map the skills and their changes, we aim to improve the evidence, since there is a clear outcome that can be measured, and optimize treatment for a personalized medicine approach in the heterogeneity of CP. Our goal is to gather evidence for a stratified population of children with lower locomotion restrictions, as suggested by de Almeida Carvalho Duarte et al [2], who highlighted the importance of studying more homogeneous populations in the field of CP to better understand gains in the functional independence of these children. This will allow us to know the treatment effect size and for whom it should be a good choice.

The costs and presence of adverse effects will be features considered to reveal the individual cost-effect balance [16], and dropout rates will indicate any potential reason for dropping out [15].

Stimulation has been done on the M1 motor area in children with GMFCS I, II, and III [18]. Children with GMFCS III compared with children classified as I and II present an important difference in the use of aid devices. Children with GMFCS levels I and II are very functional, running and walking independently and having fewer limitations, while children with GMFCS III need an assistive device, such as walker assistance. In places with ramps, they may not be able to go up and down, due to the difficulty in controlling their movements independently. In De Moura et al's [4] meta-analysis, the difference in results was attributed to a high level of heterogeneity, potentially compromising the generalization of results and the understanding of who and in what conditions children would benefit from the use of tDCS. This protocol evaluated TDCS stimulation on the motor standardized measure and QoL outcomes.

Besides the efforts on RCT protocols, there are always the limits related to the artificial scenario observed in RCTs; many things are controlled and compared that differ from natural scenarios. However, the limitation in heterogeneity considering the differences in functional classification in motor skills may be an interesting strategy to decrease heterogeneity and truly understand the role of TDCS in the improvement of motor skills. Reporting quality, including sample size, control characteristics, important outcomes, and the methodology of intervention training and delivery may help in building a body of literature with better evidence [19,20].

QoL and health-related QoL are increasingly being considered therapeutic goals [19]. In the past decades, QoL has been defined as well-being across various domains and has become an important treatment goal, especially in diseases like CP [19]. Many studies have observed that parents report lower QoL for their children with CP than the children themselves report [19]. The emotional and social domains were evaluated equally for children and parents [19]. Furthermore, parents of children with severe impairment often report better QoL in the psychosocial domain [19]. Consistent findings suggest that children with CP can adapt well to their activity limitations and may have a satisfactory QoL despite deficits [19]. Improving QoL represents a crucial treatment objective for children with CP, necessitating precise measurement and targeted interventions aimed at achieving this outcome [19]. In conclusion, CONSORT-based report protocols based on homogeneous sampling and using relevant outcomes seem necessary to improve the evidence for personalized medicine, especially for the pediatric population.

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Conflicts of Interest

None declared.

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Abbreviations

CG: control group

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CP: cerebral palsy
GMFCS: Gross Motor Function Classification System
GMFM: Gross Motor Function Measure
IG: intervention group
PedsQL: Pediatric Quality of Life Inventory
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
tDCS: transcranial direct current stimulation

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Protocol

Effect of Rural Trauma Team Development on the Outcomes of Motorcycle Accident–Related Injuries (Motor Registry Project): Protocol for a Multicenter Cluster Randomized Controlled Trial

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Abstract

Background: Injury is a global health concern, and injury-related mortality disproportionately impacts low- and middle-income countries (LMICs). Compelling evidence from observational studies in high-income countries shows that trauma education programs, such as the Rural Trauma Team Development Course (RTTDC), increase clinician knowledge of injury care. There is a dearth of such evidence from controlled clinical trials to demonstrate the effect of the RTTDC on process and patient outcomes in LMICs.

Objective: This multicenter cluster randomized controlled clinical trial aims to examine the impact of the RTTDC on process and patient outcomes associated with motorcycle accident–related injuries in an African low-resource setting.

Methods: This is a 2-arm, parallel, multi-period, cluster randomized, controlled, clinical trial in Uganda, where rural trauma team development training is not routinely conducted. We will recruit regional referral hospitals and include patients with motorcycle accident–related injuries, interns, medical trainees, and road traffic law enforcement professionals. The intervention group (RTTDC) and control group (standard care) will include 3 hospitals each. The primary outcomes will be the interval from the accident to hospital admission and the interval from the referral decision to hospital discharge. The secondary outcomes will be all-cause mortality and morbidity associated with neurological and orthopedic injuries at 90 days after injury. All outcomes will be measured as final values. We will compare baseline characteristics and outcomes at both individual and cluster levels between the intervention and control groups. We will use mixed effects regression models to report any absolute or relative differences along with 95% CIs. We will perform subgroup analyses to evaluate and control confounding due to injury mechanisms and injury severity. We will establish a motorcycle trauma outcome (MOTOR) registry in consultation with community traffic police.

Results: The trial was approved on August 27, 2019. The actual recruitment of the first patient participant began on September 01, 2019. The last follow-up was on August 27, 2023. Posttrial care, including linkage to clinical, social support, and referral services, is to be completed by November 27, 2023. Data analyses will be performed in Spring 2024, and the results are expected to be published in Autumn 2024.

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Conclusions: This trial will unveil how a locally contextualized rural trauma team development program impacts organizational efficiency in a continent challenged with limited infrastructure and human resources. Moreover, this trial will uncover how rural trauma team coordination impacts clinical outcomes, such as mortality and morbidity associated with neurological and orthopedic injuries, which are the key targets for strengthening trauma systems in LMICs where prehospital care is in the early stage. Our results could inform the design, implementation, and scalability of future rural trauma teams and trauma education programs in LMICs.

Trial Registration: Pan African Clinical Trials Registry (PACTR202308851460352); https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=25763

International Registered Report Identifier (IRRID): DERR1-10.2196/55297

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KEYWORDS

randomized controlled trial; medical education; trauma team; trauma registry; rural health; global health; team development; Africa; rural; trauma; motorcycle injury; multicenter cluster randomized controlled clinical trial; injury; accident; low- and middle-income countries; patient outcomes; education program

Introduction

Background

Transport-related injuries are a global public health threat and are anticipated to rank fifth in the global burden of disease by 2030 [1]. Evidence suggests that 90% of the transport-related crash mortality burden disproportionately occurs in low- and middle-income countries (LMICs), such as those in Africa [1], despite concerns of underreporting [2]. The main causes of injury-related mortality in Africa are road traffic accidents [3], which have serious economic consequences. According to Ryan-Coker et al [4], despite high poverty levels and minimal access to insurance and social protection schemes in Africa, which imply out of pocket expenditure, road traffic accidents cost US $119-$178 per injury and US $486-$12,845 per hospitalization, resulting in a gross domestic product (GDP) loss of 0.8%-9%.

Uganda is one of the LMICs in Africa with a high road traffic injury burden [5]. Our recent studies showed that most fatal injuries in Uganda result from motorized 2-wheeler and car collisions, contributing to 52.6%-64.7% of orthopedic and traumatic brain injuries [6-8]. Further, the majority (74%) of Uganda's population lives in rural areas [9], which could partly explain the high injury-related mortality rates. Research has shown that the risk of trauma-related deaths in rural areas increases with remoteness owing to health care disparities, such as large commute distances, scarce resources, delays in referral, and lack of skilled trauma care providers, as well as population-specific and contextual challenges, such as poverty and impassable road networks [10].

Uganda lacks universal access to trauma care and injury surveillance systems owing to limited health care funding. Thus, Uganda has made sluggish progress toward attaining the sustainable development goal (SDG3) for universal health care coverage [11]. As such, in terms of the level of specialty care, the ratio of surgeons to patients is 0.7:25,000 as interns and medical trainees represent the largest proportion of Uganda's health workforce [12,13].

Research has shown than more than half of the trauma patients in Uganda do not receive first aid prior to hospital arrival [6,7]. Moreover, most of these patients arrive at dedicated trauma centers much later than the recommended limit of 1 hour, and they are transported by either public vehicles, such as motorcycles [8], or police vans, without any focus on key factors, such as changes in blood pressure and oxygen circulation, which could lead to death, during transit [7,14]. These aspects have 3 important implications. First, strengthening the capacity for injury care among lay frontline workers. Second, stabilizing patients at rural regional trauma centers prior to transfer. Third, ensuring closed-loop communication between primary (level 3) and tertiary (level 1) trauma centers to enable safely coordinated referrals and adequate preparation at the receiving hospitals prior to patient transfer.

The key challenge that needs to be addressed in Ugandan rural settings is the lack of a formal prehospital care system as evidenced by emergency evacuation and transfer of trauma patients by untrained police staff [14]. Further, there is an immense need to redress the weak immediate care response after an accident as medical trainees are the first point of contact after an accident as opposed to specialists [12]. We will attempt to fix these challenges at the community level and at level 3 rural trauma centers by creating and providing training capacity for rural trauma networks between traffic police and medical interns or trainees at regional referral hospitals.

Rationale

Evidence from 2 systematic reviews has shown that trauma education programs have the potential to improve skill acquisition and knowledge retention among health professionals; however, with regard to LMICs, most of these programs have not been locally contextualized and have been largely assessed based on their theoretical merit rather than their clinical impact on patients [15,16]. A recent observational study in Portugal showed that the European trauma course (ETC) improved self-efficacy and organization skills in individual routine practice, but the authors mentioned that future investigations should be conducted to examine the effect of the training on trauma outcomes [17]. This European study and systematic reviews in LMICs have recommended high-caliber epidemiological studies to evaluate the effects of such educational programs on process outcomes, such as

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organizational efficiency, and on patient outcomes, such as morbidity and mortality [15,16,18].

Except for an ongoing pilot trial comparing a primary trauma course (PTC) to advanced life support (ATLS) and routine care in India [19], trauma education programs in LMICs have mostly been evaluated based on nonrandomized studies, limiting their clinical uptake [15]. Moreover, most programs limit the course participants to qualified hospital-based medical providers [18], although interns, medical and allied health trainees, and road traffic law enforcement professionals are the most readily available frontline workers for managing injured patients in LMICs [14]. Inclusive planning while leveraging services that have no trauma designation, such as police services, is critical for expanding and strengthening complex rural trauma systems to improve injury reporting [2].

Locally contextualized trauma training has been identified as one of the most crucial steps for operationalizing nonfunctional rural trauma networks [10]. However, in a scoping review by Brown et al [18], only 12 out of 34 trauma courses in LMICs had been contextualized to suite low-income settings. Moreover, a cautiously executed integrative literature review on the challenges faced by trauma systems recommended that the next step for future research should be an examination of how trauma training impacts the outcomes of patients in remote environments [10]. This multicenter cluster randomized controlled trial will address this gap by examining the effect of the locally contextualized Rural Trauma Team Development Course (RTTDC) of the American College of Surgeons [20] on process and patient outcome measures in Ugandan trauma centers. The trial will focus on musculoskeletal and neurological injuries, which have been recently identified as the most important targets for strengthening health systems in rural Uganda [8], and it has been developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting outcomes in trial protocols [21].

Objectives

Broad Objective

The main objective of this trial is to determine the effect of RTTDC training on the time efficiency of the clinical process and the patient-centered outcomes of motorcycle accident–related injuries.

Specific Objectives

The specific objectives are to (1) determine the effect of RTTDC training on the time interval from the accident to hospital admission and the time interval from the referral decision to hospital discharge (primary outcomes) and (2) determine the effect of RTTDC training on the outcomes of neurological and musculoskeletal injuries (secondary outcomes).

Null Hypothesis

The null hypothesis of this trial is that RTTDC training has no effect on the time efficiency of the clinical process and the outcomes of orthopedic and neurological injuries.

Methods

Trial Design

This will be a pragmatic, 2-arm, parallel, multi-period, cluster randomized, controlled, clinical trial with 1 intervention (RTTDC) arm and 1 control (standard care) arm. The trial was set to start in 2019 but was delayed owing to the COVID-19 pandemic, and the subsequent prioritization of COVID-19–related studies by trial registers and target journals led to the delayed publication of this protocol.

This trial will embrace simultaneous cluster randomization, which is an ideal method for evaluating community-level interventions and overcoming ethical constraints that make randomization at the individual level impractical while avoiding probable contamination between the control and treatment groups [22]. Moreover, simultaneous randomization will enable timely operationalization and concurrent participant enrollment as all the outcomes will be measured as final values and there are no foreseen plans for study modifications in accordance with Esserman et al [23]. This arrangement is based on the fact that our previous studies have already provided insights on the likely rates of loss to follow-up and baseline mortality in our target trauma population and have informed the feasibility and relevance of collecting the intended primary and secondary outcomes [6,7].

Study Setting

This study will be conducted in 6 specialized teaching and regional referral hospitals in Uganda, including Kiryandongo, Jinja, Hoima, Fort Portal, Mubende, and Kampala International University Hospital. These facilities have similar characteristics and serve as teaching, residency, and internship sites for undergraduate and graduate medical doctors and nurses. The hospitals offer 24/7 emergency surgical services for trauma patients through multidisciplinary teams of orthopedic, general, and visiting neurosurgeons, as well as imaging, rehabilitation, and physiotherapy. Each surgical department in these facilities is typically composed of about 1-4 faculty members, 2-4 specialty residents often referred to as senior house officers, 4-6 interns, and 10-30 undergraduate medical trainees.

These facilities are suited for this study as they serve both rural populations and populations in newly created populous cities that are still struggling with urban planning. Uganda is the 8th most populous country in Africa and the 30th most populous country in the world [9], and its trauma surveillance systems are in the infancy stage with weak preaccident and postaccident responses [6,12]. Despite efforts made in the past decade by the Ugandan government to address the unmet need for trauma care through infrastructure development, such as equipping operating theaters and intensive care units (ICUs) in public hospitals, limited standardized preservice and in-service trauma training, prehospital delays, and human resource constraints still contribute to preventable trauma mortalities [14]. To guarantee the quality of data for this project, a prospective motorcycle trauma outcome registry (MOTOR) will be piloted at the participating 6 regional referral hospitals in parallel with this trial.

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Eligibility Criteria

Inclusion Criteria

Study Sites

We will include level 3 trauma centers that are teaching hospitals; are staffed with medical trainees, interns, surgery residents, and consultants; and offer 24/7 emergency surgical care with access to blood banks, ultrasound scans, X-ray scans, and computed tomography (CT) scans as locally available or outsourced services.

Trainee Participants

We will include third-year or fifth-year medical or allied health students, interns, or specialty residents in surgery and traumatology clinical rotations who stay at the hospital of attachment for at least 2 months. Medical students may only rotate to a different hospital without crossing the study arm. In addition, we will include road traffic law enforcement professionals concerned with the evacuation of trauma patients from accident scenes.

Patient Participants

We will include patients who sustain motorcycle accident–related injuries and present to the study sites within 24 hours following the accident, as defined in a previous study [6]. These will include passengers on motorcycles, motorcycle riders, pedestrians or cyclists hit by motorcycles, and patients experiencing motorcycle-motorcycle collisions, motorcycle-static object collisions, or motorcycle-car collisions.

Exclusion Criteria

Study Sites

We will exclude trauma centers that do not offer placements and teaching facilities for students, interns, and residents.

Trainee Participants

We will exclude medical students who have not commenced their surgery clinical rotation and those not directly involved with the care of trauma patients at the time of the training, as trainee medical participants are expected to have already been introduced to surgery, emergency trauma resuscitation concepts, and trauma clinical scenarios through clerkships onto which we will be building the rural trauma team concept.

Patient Participants

We will exclude pregnant women, neonates, and infants aged 0-23 months owing to the known teratogenic effects of radiation in this population, as trauma evaluation in this study will involve obtaining radiographs for orthopedic injuries and CT scans for neurological injuries. Patients with documented stroke will also be excluded, as the study outcomes involve assessment for functional, physical, and neurological disabilities directly attributable to trauma. Moreover, mentally incapacitated patients who have no legally authorized representatives to sign an informed consent form and patients who die before hospital arrival or before imaging results are obtained will be excluded. Patients who are passengers in a car or drivers in a car at the time of the accident will be excluded, as the protective casing of the car body would make these patients less vulnerable to direct impacts compared with pedestrians, cyclists, or passengers on motorcycles. In addition, elderly patients older than 80 years will be excluded owing to their increased risk of fragility fractures that could misrepresent the severity of trauma. This cutoff age was used based on a systematic review by Tsuda et al [24], which documented a mean age of 80 years for long bone fragility fractures owing to increased muscle weakness, balance disorders, visual impairment, and dementia that predispose elderly people to falls. The number of ineligible participants and the reasons for their exclusion will be recorded in both arms in the consolidated standards of reporting trials flow diagram.

Ethical Considerations

Research Approval

Prior to recruitment, this study has been approved and registered by the research and ethics committees of the Uganda National Council for Science and Technology (reference number: SS 5082) and Mbarara University of Science and Technology (reference number: MUREC 1/7; 05/5-19).

Consent to Participate

Written informed consent will be obtained from all study participants or their legally authorized representatives prior to participation. The official informed consent form documents for Mbarara University of Science and Technology will be adopted for this purpose. Both trainee and patient participant informed consent documents are provided in Multimedia Appendix 1 and Multimedia Appendix 2, respectively. The ethical committees ruled that trainees involved in the data collection process at control centers do not need to provide any consent as this study will neither directly affect their practices nor collect their personal data.

Collection of Informed Consent

All participants or their legally authorized representatives (for minors and unconscious patients) will endorse a predesignated consent form document with their signatures in the presence of the principal investigator or research assistants (surgery specialty residents).

Additional Consent Provisions for the Collection and Use of Participant Data and Biological Specimens

There will be no biological specimens retained for this study. The informed consent form documents will have provisions for consenting to follow-up and the use of data for approved ancillary studies, and for permission to archive the anonymized data in a public data repository.

Consent for Publication

This manuscript does not contain any identifying individual participant information or images; thus, consent for publication is not applicable.

Privacy and Confidentiality Protection

To protect participants' confidentiality before, during, and after the trial, all hard copy data collection items will be kept under lock and key and will bear unique nonidentifying codes. Soft copies will be kept in password-protected computers, with a second-layer protection login password required for REDCap,

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which will be only accessible to the study team. The final data sets will be anonymized prior to archiving and publication. Hard copies of the data will be destroyed 6 months after completion of the trial.

Compensation Type and Amount for Participants

Participation in this trial will be voluntary. However, transport reimbursement of 20,000 Ugandan shillings (US $5.0) will be provided to participants turning up for research follow-up appointments outside of their routine hospital visits. Moreover, time compensation of 10,000 Ugandan shillings (US $2.5) will be provided.

Interventions

Explanation for the Choice of Comparators

The intervention for this trial is based on the fourth edition of the RTTDC of the American College of Surgeons [20], which will be delivered to medical trainees, interns, and traffic law enforcement professionals at the 3 intervention study centers (intervention group). Specialty surgical residents will be trained as faculty who will later serve as trainers since they directly supervise interns and undergraduate medical students in Ugandan settings. The research and ethics committees approved training residents as opposed to specialists to avoid constraining the scarce specialized human resource as this is a trainee-capacity building trauma education program. Moreover, consultants rarely attend to trauma patients for immediate resuscitation as the first point of contact in Ugandan settings. The patient participants at intervention sites will be those with motorcycle accident–related injuries at any of the study sites. The comparator in this trial is a control group of hospitals that will offer standard care to eligible patients, without their care providers receiving the RTTDC training intervention.

Intervention Description

The 2-day RTTDC interventional training will be conducted in designated spacious multimedia surgical simulation conference rooms at the study sites randomized to the intervention arm and will be delivered in the described standard format [20]. This training model is the most appropriate for Uganda, with its health worker to patient ratio of 1:25,000 and its large population of 48 million [12]. The model dwells on team concepts to improve coordination and efficiency of the existing “skeletal” health structure in the rural environment. We hope to train a total of 66 road traffic police officers, 12 specialty residents, 30 intern doctors, 140 fifth-year medical students, and 264 third-year medical students. These figures have been determined based on the average annual number of traffic police officers and trainees at the respective regional police headquarters and hospitals [25].

Our target is to train at least 80% of each cohort of eligible trainees identified every 1-5 months within the surgery department during the 4-year study period until the required trainee and patient participant sample sizes are attained. If trainees drop out prior to completion of data collection, compensations will be made to maintain the criterion during the next cohort of surgical rotation trainee intake. The details of how the training will be conducted have been provided elsewhere [25]. The research core team has agreed that trainee participants who score more than 60% in posttraining trauma-based multiple-choice questions (MCQs) at the intervention sites will be retained to form a rural trauma team network, which will constitute multiple local 6-member trauma committees of first responders with defined roles (ie, each team having 5 medical trainees and 1 contact road traffic officer).

To enable an active “alarm” activation criterion for the trauma committees, closed-loop communication, and a smooth “handover” process from police officers to medical trainees prior to patient transfer, the trained traffic officers on highways will serve as focal contact persons for the rural trauma teams from the parish (subcounty) level. In the event of a road traffic accident, teammates will freely contact each other both within and across teams to coordinate evacuation, consultation, referral, and arrival at recipient centers, with the support of trained interns and surgery residents as team leaders. Weekly audit meetings will be conducted remotely via Zoom (Zoom Video Communications) to discuss team challenges, otherwise a trained surgery resident will be available 24/7 to advise on referrals, transfers, and treatments in liaison with consultants who may be physically or remotely available. The control hospitals in this trial will be allowed to provide routine standard care without the RTTDC intervention as summarized in Figure 1.

Figure 1. Conceptual framework summarizing the intervention and the interaction of variables. RTTDC: Rural Trauma Team Development Course.

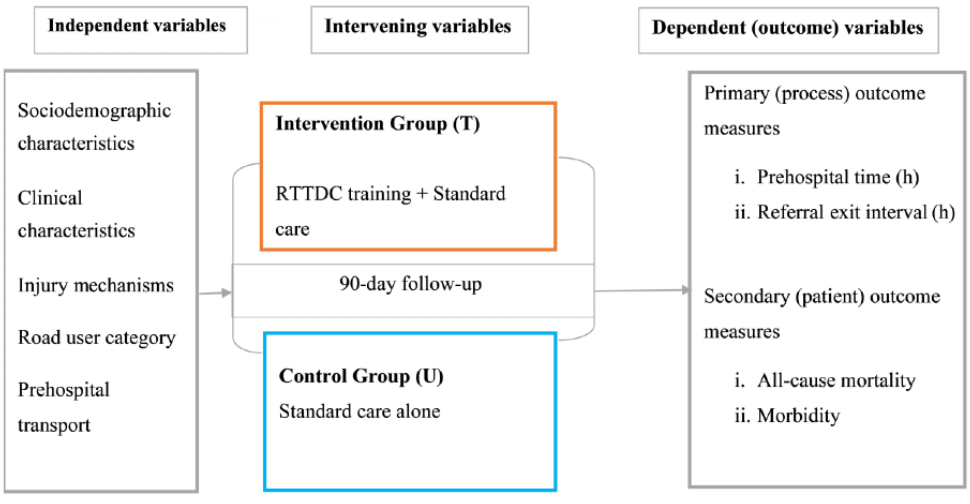

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Criteria for Discontinuing or Modifying the Allocated Intervention

The fourth edition of the RTTDC will be delivered in its standardized form [20] without any modifications.

Strategies to Improve Adherence to the Intervention

The RTTDC is the intervention; thus, participants who do not attend all the modules and complete the posttraining MCQs will be excluded. Adherence to teachings in the RTTDC among care providers during clinical practice, such as the time taken from referral decision to execution and improper closed-loop communication leading to loss to follow-up, will be assessed as process measure outcomes.

Relevant Concomitant Care Permitted or Prohibited During the Trial

The baseline quality of care given to trauma patients at each of the participating 6 hospitals is based on the regulations of the Uganda Medical and Dental Practitioners Council (UMDPC), which regulates medical practice, and the National Council for Higher Education (NCHE), which regulates both undergraduate and graduate surgical curricula [26]. The councils require that graduating doctors undergo clinical rotations in surgery and traumatology, perform clerking activities, and present and document trauma scenarios in patient case files.

In addition, medical graduates should demonstrate the ability to initiate emergency resuscitation in accordance with advanced trauma life support protocols [27], such as execution of primary and secondary surveys; carefully discern, request, and comprehend the necessary imaging and laboratory investigations in trauma; acknowledge self-knowledge and resource limitations; and consult or refer patients whose surgical care demands exceed their own skills or the local trauma capacity. Further, upon graduation, Ugandan doctors are required to obtain a minimum of 48 hours of continuous professional development points annually to maintain their licensure.

In terms of the standards of care, both intervention and control facilities have medical trainees, interns, specialty residents, and specialists who provide care for injured patients. The care typically involves receiving trauma patients who may be brought by staffed ambulances, police officers, or public means to accident and emergency units, and these patients may be received by trainees, interns, or surgical residents. These cadres open case files; initiate immediate care through horizontal consultation; request X-ray scans, CT scans, and laboratory workup; and plan definitive care or referral in liaison with a senior surgical resident and in consultation with a multidisciplinary team of specialists on call. As such, procedures, such as surgical suturing and toileting, limb fracture casting and immobilization, and chest tube insertion, are often performed by interns. More demanding procedures, such as splenectomy, external fixation of fractures, and burr holes, are usually performed by specialty residents after notification of the consultant on duty, whereas major cases of polytrauma warrant the decision of the consultant specialist on call before the patient is taken to the operating room.

Imaging and blood transfusion services are often freely available at emergence units as government services but may be outsourced from private hospitals at a cost owing to long waiting times or service maintenance for CT scanners and X-ray machines. Finally, in terms of patient disposition, patients with minor injuries requiring surgery under local anesthesia are discharged on the same day. Moreover, patients with major trauma requiring conservative treatment, such as closed fractures, are treated in surgical wards, whereas those who are deeply unconscious or require critical care after major operations are admitted to the ICU until they are fit for care in general surgical wards prior to discharge. Alternatively due to overcrowding, often with higher bed occupancy rates exceeding the predetermined bed capacity, patients with major trauma may be referred to other centers, and the common reasons for referral include further neurosurgical evaluation with magnetic resonance imaging or further evaluation by a neurosurgeon, need for multiple specialty care and rehabilitation, and need for ICU admission elsewhere when local ICU beds are limited.

Provisions for Posttrial Care

Any participants requiring further care beyond the 90-day follow-up will be linked to their attending clinicians during an additional 3-month period after completion of the trial. There will be no compensation other than transport reimbursement for participants visiting solely for study follow-up outside routine clinical visits as this study was considered minimal risk by the approving research ethics committees. The principal investigator will refund the cost of imaging when the request is approved by attending surgeons and radiologists in cases where the services are unavailable free of charge.

Outcomes

This trial will examine both process measures and patient outcomes. The primary (process) outcomes of this trial will involve comparisons of (1) the time interval from the accident to hospital admission and (2) the time interval from the referral decision to hospital discharge between patients with motorcycle accident–related injuries presenting to the intervention centers and those presenting to the control centers.

The secondary (patient) outcomes of this trial will involve comparisons of (1) all-cause mortality at 90 days from the time of injury and (2) morbidity of motorcycle accident–related orthopedic and neurological injuries between patients presenting to the intervention centers and those presenting to the control centers. The morbidity of orthopedic injuries will be measured based on the Trauma Expectation Factor Score (TEFS) at admission and the Trauma Outcome Measure Score (TOMS) at 90 days as reported to outcome assessors [28]. On the other hand, for neurological injuries, the Glasgow Coma Scale (GCS) at admission and Glasgow Outcome Scale (GOS) at 90 days will be used as documented by the attending clinicians [29].

The tertiary outcomes will involve the effects of the training on provider knowledge based on pretraining and posttraining trauma-related MCQ scores and the barriers to injury care faced by providers during execution of definitive treatment. These will be determined in 2 ancillary studies that have been approved as part of this trial, and the protocols have been detailed

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elsewhere [25]. A summary of all outcomes and their case definitions, specific measurement variables, analysis metrics, methods of aggregation, and time points has been provided in Multimedia Appendix 3.

The patient outcomes were selected based on their validity and relevance in previous studies [7,30]. Further, level III evidence suggests that prolonged prehospital times may be associated with increased mortality among trauma patients [31]. However, it is unclear how these results relate to time-sensitive orthopedic and neurological injuries in LMICs that lack formal coordinated prehospital systems [32]. Thus, our process outcome measure variables were selected within the context of evidence-based practice. This practice stipulates that in accordance with the golden hour rule, a major trauma patient should be in the right place within 60 minutes following injury, otherwise there is a risk of mortality or morbidity [33].

These variables align well with the proposed global surgery framework to improve national surgical, obstetric, and anesthesia care provider plans [34]. In addition, the variables expand on outcomes for trauma-informed interventions [35]. All outcomes will be measured as final values but will be discussed in relation to the baseline established in our prior feasibility studies [7,30]. The comparisons of outcomes will be made at both individual and cluster levels, using mixed effects regression models.

Participant Timeline

Initially, cluster randomization of the trauma centers will be performed 3 weeks prior to commencement of the training to determine which centers will receive the training. Potential participants for the training will be screened for eligibility by the hospital and study administrators 2 weeks prior to the training, and eligible trainee participants will be consented and assigned to “rural trauma teams” of 6 members on the first day of the training, during which they will complete a pretraining questionnaire involving trauma-based MCQs. Subsequently, trainee participants will be followed up at 90 days (3 months) to complete posttraining MCQs. The first eligible patient participants at both control and intervention sites will be enrolled concurrently through a motorcycle trauma outcome registry (MOTOR) that will run parallel to the trial.

Informed consent, baseline sociodemographic and clinical characteristics, and prehospital intervals will be obtained at admission, and the GCS score will be determined. The TEFS will be obtained during the first week of admission or prior to discharge on the assumption that patients would have received their definitive surgical intervention or would have been referred for further care during this period. Further, the GOS score, all-cause mortality rate, and TOMS will be obtained at the 90-day follow-up. The GCS will be used to assess the level of traumatic brain injury in the acute phase, whereas the GOS will be used to determine neurological outcomes within the context of the level of independence at a later phase of traumatic brain injury [29]. On the other hand, the TOMS will be used to assess patient-reported trauma outcomes with reference to their expectations (TEFS) at the time of the trauma intervention in relation to the levels of pain, physical function, disability, injury treatment satisfaction, and overall satisfaction [28,30]. Throughout the study period, any individual patient barriers encountered during the pathway to execution of definitive injury care will be documented as summarized in the timeline presented in Multimedia Appendix 4.

Sample Size

To estimate the sample size, we used the open-source R Shiny application for cluster randomized controlled trials with a parallel design and discrete time decay correlation structures for multiple periods [36] available at [37]. Further, we assumed *t*-distribution due to plans for small sample corrections at the analysis stage in accordance with the report by Rutterford et al [38]. The study was approved for 4 years, but the core research team foresaw it feasible to actively collect data for a period of 3 years considering university semester breaks, public holidays, and unexpected events, such as COVID-19–related interruptions, which led to suspension of the trial for 12 months from March 2020 to March 2021. The 3 years (36 months) would yield 12 study periods given the planned training of cohorts of medical students on a 3-monthly basis in accordance with the average duration of internship deployment by the Ugandan Ministry of Health (1-5 months) and the average duration of surgery clinical rotation for university medical students (2 months).

Fixing the study power at 80% for a parallel cluster randomized trial with different cross-sections, considering a discrete time decay period of every 3 months for a total of 12 periods, and assuming correlations to decay with each period, we explored the minimum number of patient participants (cluster size) required per period using the R Shiny application [36]. Assuming a significance level of .05, a within-period intraclass correlation coefficient (ICC) of 0.02 (lower extreme: 0.01, upper extreme: 0.05), and a cluster autocorrelation coefficient (CAC) (ratio of between-period ICC to within-period ICC) of 0.8; allowing for varying cluster sizes with a coefficient of variation of 0.5; and considering a mean difference of 1.02 hours in prehospital transfer time and a pooled standard deviation of 1.64 hours as continuous outcomes reported in a previous observational study from the United States [39], the upper ICC and base CAC plateaued between 5 and 10 participants (Figure 2).

Considering a maximum of 10 participants per cluster period, an 80% power could be attained (Figure 3) and could be met with a total of 3 clusters per arm (Figure 4). This indicates a total of 6 study centers (clusters) drawn from a pool of 17, which reasonably represents 35.3% of Uganda’s regional referral hospitals.

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Figure 2. Reduction in the number of clusters required with an increase in the cluster-period size at a fixed power of 0.8. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.

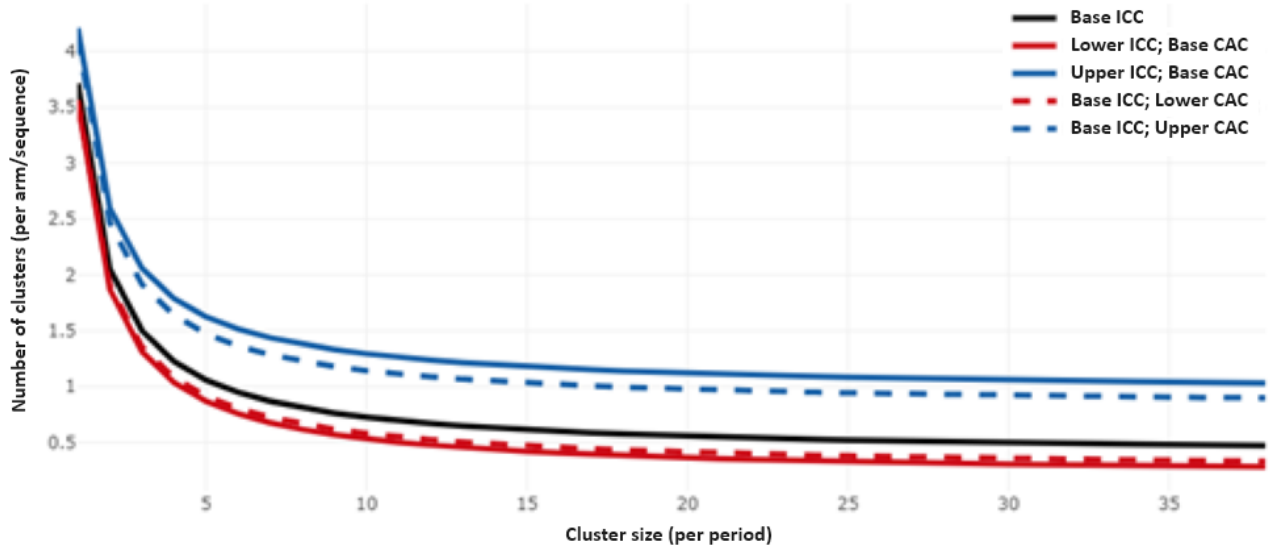

Figure 3. Cluster-period size of 10 meeting the required power of 0.8 for 12 periods. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.

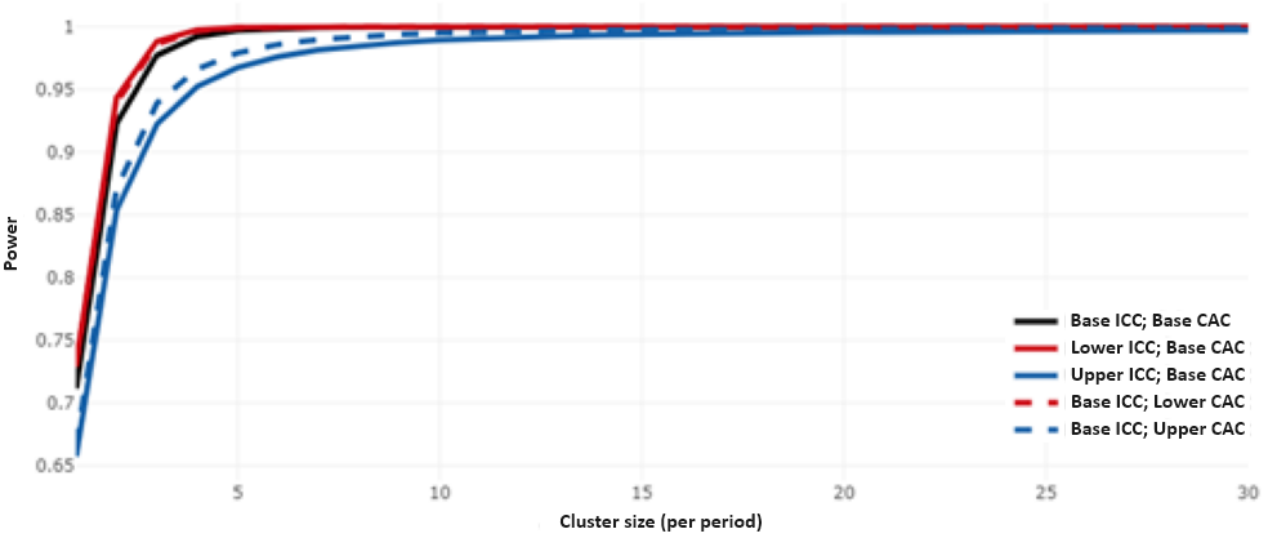

Figure 4. Three clusters per arm meeting the minimum required power of 0.8 for 12 periods. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.

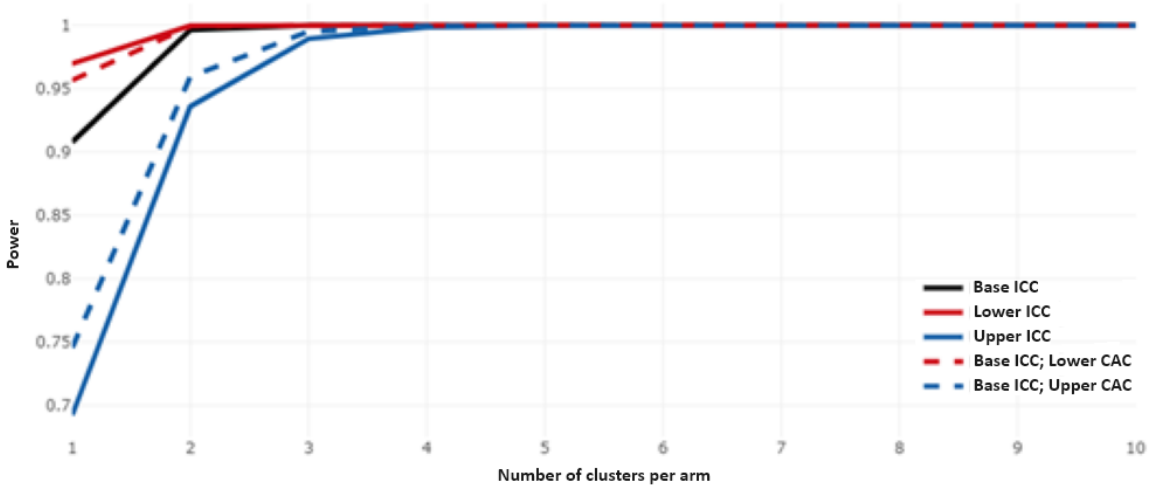

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The sample required per arm is calculated as follows: 10 participants per cluster period multiplied by 12 cluster periods multiplied by 3 clusters, yielding a total of 360 participants. The total sample required for 2 arms would be 720. However, we inflated the sample and variance to cater to the clustering design effect based on the assumption that this increases the statistical power in accordance with the repost by Hemming et al [36]. Thus, the derived sample size (s) is calculated using the following formula:

$$s = n(1 + [m - 1]\rho) \quad \textbf{(1)}$$

where s is the required sample size, m is the cluster size per period (ie, 10), and ρ is the within-period ICC (0.02).

This formula yields a total of 850 participants.

We will add a rate of loss to follow-up of 18% assuming the worst scenario based on our previous dropout rate of 9% in a feasibility study [7]. Therefore, the final sample will include approximately 1003 participants. Assuming an equal allocation ratio of 1:1, there will be 502 participants per arm and about 168 individuals per cluster. This sample is deemed feasible considering the high trauma burden in Uganda. According to a study at one of the Ugandan rural regional referral hospitals, a total of 900 motorcycle accident–related injuries were recorded during a 3-year period, of which 30.9% (278/900) and 15.8% (142/900) of patients sustained musculoskeletal and neurological injuries, respectively [8]. We will not compute sample sizes for each individual secondary outcome as previous studies have not reported any difference in mortality [40].

Recruitment

The training will be advertised by hospital administrators, class representatives, and regional traffic law enforcement leaders, and course participants will be recruited by the principal investigator and the respective hospital administrators. The patient participants will be recruited by dedicated project officers at the accident and emergency departments.

Assignment of Interventions: Allocation

Sequence Generation

We will perform cluster randomization for a permuted block size of 6 hospitals (clusters) using an open-source simulation software [41], with seed numbers that will be kept confidential to the offsite study administrator. A list of 6 random codes will be generated to assign hospitals to the intervention or control group. As we plan to perform analyses at both the individual level and treatment arm level, we will not add any stratification factors in the simulation model.

Concealment Mechanism

The allocation sequence and assignment codes will be generated by and kept secret by an offsite study administrator. Both outcome assessors and patient participants will be blinded to the treatment allocation.

Implementation

Trainee participants will be enrolled by the respective university hospital administrators, whereas patient participants will be enrolled by project medical officers at the respective study sites, who will serve as outcome assessors.

Assignment of the Intervention: Blinding

Who Will Be Blinded

Trial patient participants and outcome assessors will be blinded using blocked allocation sequence codes.

Procedure for Unblinding if Needed

Unblinding will only be permissible in the likely occurrence of adverse events among the study participants, which can be directly attributed to the study intervention. Such events will be discussed with the attending physicians. Otherwise, the allocation codes will only be revealed to the biostatistician at the time of interim analysis when half of the sample size is recruited. At this point, unblinding the biostatistician is considered more beneficial to inform termination or continuation of the trial, which outweighs the perceived fear of unknown bias [42].

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Data collection will start simultaneously at all the study sites. Medical officers (blinded outcome assessors) with a minimum qualification of Bachelor of Medicine and Bachelor of Surgery (MBChB) and at least 2 years of clinical experience will prospectively collect data through clinical observations, interviews, home visits, and extraction from hospital and police records. All outcome assessors must be willing to undertake a 1-day budgeted training in the use of data collection tools for this trial and the World Health Organization (WHO) ICD-10 online coding module. The data will be collected daily as medical trainees and interns will attend clinical rotations every day. Upon obtaining informed consent, the venue for data collection, including follow-up information, will be at accident and emergence departments during admission, surgical wards, and outpatient clinics, as well as through home visits and phone calls to patients, care takers, or recipient hospital physicians in the case of referrals.

The study variables will include sociodemographic and clinical variables, such as sex, age, injury mechanisms, including nature of collision and road user category, time of injury, prehospital transit time, prehospital care, mode of arrival, vital signs, nature of physical injuries, radiological findings, and injury severity based on the GCS score and Kampala Trauma Score (KTS) [43]. In addition, data on the nature of the treatment administered; need for referral; referral-exit interval; and outcomes, including the TOMS, GOS score, mortality, and time from injury to death, will be obtained. The data collection tools that will be used in this trial, such as the GCS, GOS, TEFS, TOMS, and KTS, have been shown to demonstrate excellent criterion internal validity, consistence, and reproducibility in previous studies [28,29,43,44].

Further, the tools are recognized for their high interrater reliability, sensitivity to change, and ability to be used as continuous or categorical variables in validation studies [28,29,43,44]. The baseline TEFS, GCS score, and KTS will

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be added as covariates whose interaction and confounding will be assessed and controlled since the inclusion of baseline values of outcomes as covariates is arguably one of the strongest factors to reduce ICC estimates [45]. The difference in distribution of baseline characteristics will be compared using means (SDs), medians (IQRs), and ranges for quantitative data; otherwise, frequencies and percentages will be used for categorical variables. All data collection forms for this trial and detailed definitions of assessment tools for patient and trainee participants are available in Multimedia Appendix 5 and Multimedia Appendix 6, respectively.

Plans to Promote Participant Retention and Complete Follow-Up

Coffee breaks will be facilitated during training to optimize participation. Phone and email contacts will be obtained from all medical trainees and law enforcement professionals. In addition, 2 phone contacts will be obtained for each patient participant at the time of enrollment at accident and emergency departments (ie, the patient and their next of kin or legally authorized representative who will in turn be provided with the phone contact of the study nurse coordinators for the purpose of follow-up). Automated reminders will be sent to data collection assistants through mobile phones and the research electronic data capture (REDCap) platform.

Where applicable, home visits will be conducted for participants who are unable to turn up for appointments because of their disability. Transport costs will be reimbursed for traffic law enforcement professionals and patient participants turning up for appointments outside of the routine hospital visits. Participants will be considered as lost to follow-up if they are untraceable by phone, clinic appointment, or home visit. Data on the baseline sociodemographic and clinical characteristics of those lost to follow-up or those who discontinue because of a breach of the intervention protocol will be retained for comparisons between groups, but the data of those who withdraw their consent will be deleted.

Patient and Public Involvement

Using semistructured questionnaires and semistructured interviews, a 1-day consultative meeting will be conducted at each study site with chief residents, heads of interns, patient caregivers, student representatives, and regional traffic police commanders in the month preceding study commencement to discuss their perceived barriers to injury care in order to uncover themes for potential sources of delays ranging from accident scene discovery, evacuation, and prehospital transportation to emergency care, which shaped the final data collection tools.

During this engagement, trainee and caregiver representatives will provide insights on the feasibility of the outcome assessment tools and the time commitment required to respond to the questionnaire, which will inform the data collection time points of day 1, the first week, and day 90. This strategy will strike a balance regarding the feasibility of maximizing response rates and obtaining data while not overloading the already scarce human resources of traffic law enforcement, and trainees and clinicians at accident and emergency departments. Further engagements will be made during RTTDC training sessions and audit meetings, during which bidirectional feedback will be provided on team performance, challenges with individual team dynamics, and proposed areas of improvement to help shape future training. The results of patient and public engagement will be reported in an ancillary study on the barriers to injury care.

Data Management

Due to expected network breakdowns in rural centers, data will be collected in hard copies, coded, and entered into the REDCap secure virtual network hosted by the University of Turku. Data entry will be performed by outcome assessors who will be issued with a confidential login password for REDCap. Later, the data will be exported to Stata version 15.0 (StataCorp) for analysis. The REDCap software was preferred owing to its presumed secure web-based intuitive interface for validated data capture, offering an additional advantage to prohibit dual entry, restrict values, calibrate data ranges, and retrieve audit trails for tracking data manipulation [46]. Further, the software permits seamless data export and download procedures that are compatible with Stata, while allowing for data integration and interoperability with external sources [47]. Any data errors will be resolved during weekly audit meetings in reference to the online codebook with a visible description of variables accessible to the principal investigator and all outcome assessors.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis

There are no plans to collect any biological laboratory specimens for storage or for genetic or molecular analysis in this trial.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

Primary (Process) Outcomes

The primary (process) outcomes of (1) the time interval from the accident to hospital admission and (2) the time interval from the referral decision to hospital discharge will be compared between the intervention and control groups using a 2-sample *t* test if the data are normally distributed or a 2-sample Wilcoxon rank sum test if the data are not normally distributed. The normality of distribution will be assessed using the Shapiro-Wilks test, whereas the equality of variance will be determined using the Levene test. A difference in means of 60 minutes (1 hour) will be considered clinically meaningful in accordance with the golden hour principle [33].

Secondary (Patient) Outcomes

For assessing the morbidity of musculoskeletal injuries, the validated 10-item TEFS will be used at baseline and the 10-item TOMS will be used at 90 days [30]. The mean difference in the TEFS and TOMS will be compared between the intervention and control groups using the 2-sample *t* test. Further, the TOMS will be dichotomized into favorable (TOMS ≥ TEFS) and unfavorable (TOMS < TEFS) outcomes in accordance with previous studies [30]. The difference in these proportions between the intervention and control groups will be compared

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using the adjusted chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise.

Further, subgroup analyses will be performed to determine and control for factors that could be associated with an unfavorable TOMS, using individual-level between-within mixed effects regression models, which inherently overcome the effect of smaller clusters and permit adjustment for covariates in a single stage, assuming equal allocation. The fixed effect variables will be the treatment arms (intervention vs control) as the unit of analysis, with the odds ratios (ORs) and their corresponding 95% CIs as direct estimates of the effect size. The covariates will include age, sex, education level, occupation, employment status, marital status, commute distance, road user category, injury severity score based on the KTS, presence or absence of fracture, nature of fracture if present, number of serious injuries, and treatment (surgical vs conservative).

For assessing the morbidity of neurological injuries, the validated GOS will be used at 90 days after injury. The mean difference in the GOS score will be compared between the intervention and control groups using the 2-sample *t* test. Further, the GOS score will be dichotomized into favorable (GOS score of 4 or 5) and unfavorable (GOS score of 3, 2, or 1) outcomes in accordance with previous studies [7]. The difference in proportions between the intervention and control groups will be compared using the adjusted chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise.

For all-cause mortality, the difference in proportions of all deaths at 90 days after injury will be compared between the intervention and control groups using the chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise. Lastly, we will conduct subgroup analyses to determine and control for factors associated with all-cause mortality using individual- and cluster-level between-within mixed effects regression models. The covariates will include age, sex, injury mechanism (including helmet use), mode of arrival, prehospital interval, referral decision to hospital discharge interval (dichotomized as ≤1 hour or >1 hour), prehospital first aid status, comorbidities, injury severity score based on the GCS at baseline, multiplicity of injuries, head and brain CT-based diagnosis, and neurosurgical intervention.

These variables have been found to influence outcomes following neurological trauma in previous studies [7]. All variables will be analyzed for confounding and effect modification using Mantel-Haenszel statistics to probe necessary interaction terms. Variables with *P* values of ≤0.2 in the bivariate analysis will be included in the multivariate analysis. The median (IQR) of the time to the event, that is, from the accident to death (in days), will be stratified by treatment arm, and the difference will be compared using the Wilcoxon 2-sample test. All analyses will be performed using Stata 15.0, and where appropriate, graphics, such as box plots, will be used to visualize the data.

Interim Analyses

The Uganda National Council for Science and Technology accessed a preliminary report of the interim analysis, which was performed on August 28, 2022, when half of the sample size (n=500) was attained, and at its discretion, it recommended continuation of the study. The requisite characteristics for early termination set by the ethics committee included the occurrence of an index patient-reported adverse outcome definitely attributable to the study in accordance with the framework described by Okoniewska et al [48].

Methods for Additional Analyses

Subgroup analyses will be performed for (1) varying road user categories (pedestrian, passenger, and motorcyclist); (2) injury mechanisms (motorcycle-motorcycle accident, motorcycle-pedestrian accident, motorcycle-static object accident, and motorcycle-car accident); (3) varying injury severities (mild, moderate, or severe based on the KTS and GCS); and (4) multiplicity of serious injuries (one or multiple). To determine the training-effect heterogeneity across time periods, we will use an extension of Hussey and Hughes fixed effects model [49] for determining whether the intervention effect differs for each training period as summarized in the schematic representation of the study design (Multimedia Appendix 7).

For the ancillary study on provider outcomes, the difference in pretraining and posttraining mean scores will be computed with 95% CIs if the data are normally distributed; otherwise, the difference in median and IQR will be reported. For the qualitative ancillary study on the perceived barriers to injury care, directed content analysis of themes of transcribed data will be collated manually and presented as percentages.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

We will impute values for participants with missing end points, such as those lost to follow-up, those who withdraw consent, and those who crossover. The baseline sociodemographic and clinical characteristics of such participants will be compared between the intervention and control groups. For individual participants, crossover from the intervention group to the control group or vice versa for any reason will result in ultimate discontinuation from the trial.

Plans to Provide Access to the Full Protocol, Participant-Level Data, and Statistical Code

The full protocol will be published open access, and anonymized participant-level data sets and statistical codes will be shared publicly through a permanent weblink that will be provided by the publishing journal. Since the primary country of recruitment, which approved and registered the study prior to recruitment, lacks a publicly available electronic research register, this protocol has been retrospectively registered with the WHO-approved Pan African Clinical Trials Registry (PACTR202308851460352).

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The principal investigator and a central study administrator will form a steering committee that will run the day-to-day activities

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of the trial. The trial will have 2 onsite overseers and 2 off-site supervisors. In addition, the principal investigator will provide organizational support to rural trauma teams at the intervention study centers through weekly audit meetings. Each of the rural trauma teams is composed of a road traffic law enforcement professional, a third-year medical student, a fifth-year medical student, an intern doctor or nurse, and a specialty surgery resident.

Composition of the Data Monitoring Committee, and Its Role and Reporting Structure

The research and ethics committee of Mbarara University of Science and Technology is the designated independent data monitoring committee that will oversee this trial (reference number: MUREC 1/7; 05/5-19). The committee reports directly to the Uganda National Council for Science and Technology. The council, at its discretion, can recommend continuation, amendments, or termination of the trial at any time.

Adverse Event Reporting and Harms

Immediate medical concerns from participants will be reported to their attending clinicians. Any reported adverse events and other unintended effects of trial interventions or trial conduct will be reported to the trial monitoring committee. Patient-reported adverse outcomes resulting from the intervention (study) rather than biological injury progression will be captured during the follow-up interviews and evaluated on a 5-point Likert scale in accordance with the framework described by Okoniewska et al [48] as follows: (1) no evidence that the event is due to the intervention, (2) little evidence that the event is due to the intervention, (3) the event is possibly due to the intervention but most likely due to injury, (4) the event is more likely due to the intervention than injury, and (5) the event is definitely due to the intervention. Case files with 4 to 5 points will be forwarded for external auditing in surgery departmental meetings to ascertain if the adverse event was preventable, ameliorable, or neither.

Frequency and Plans for Auditing Trial Conduct

The trial monitoring committees will independently conduct annual and impromptu audits and may choose to extend or terminate the trial at any time. Such situations that could warranty termination include adverse events directly attributable to the intervention. The investigators will submit annual progress reports to the committees each year as part of continuing review.

Plans for Communicating Important Protocol Amendments to Relevant Parties

Any protocol amendments will be submitted to the data monitoring committee. Any approved amendments will be communicated to the Uganda National Council for Science and Technology and trial participants, and will be updated in the registries within 5 working days following approval.

Ancillary Studies

This trial has been approved with 2 ancillary studies. The first is a study to assess the effect of the RTTDC on provider knowledge, and the second is a qualitative study to assess the barriers to injury care as perceived by traffic police, medical trainee frontline workers, and individuals encountered in the real-time management of patient participants. The data collection team for the qualitative study will be surgery residents at the 6 regional referral hospitals who will be blinded to the cluster or treatment allocation. The results of the ancillary studies will be collected and analyzed separately and will be concealed from the trial team until the analysis of the main clinical trial findings is nearly complete. We hope that the findings of the ancillary studies will complement and inform the interpretation of the trial findings.

Dissemination Plans

Participants of the RTTDC training will receive feedback after the posttest questionnaire evaluation. Patient participants will be advised on the next plans of management during follow-up calls or through outpatient consultations. Before presentation of the study findings at scientific conferences and publication in peer-reviewed journals, copies of the findings in final bound reports will be submitted to the main libraries of the participating hospitals, the departments of surgery, and the internal review boards of Mbarara University of Science and Technology, Kampala International University, and Uganda National Council for Science and Technology.

The implications of the findings will be shared with authorities, including intern and medical student associations, district health officers, hospital directors, regional traffic police commanders, and chairpersons of the motorcycle riders' associations in the respective regions, as well as with the rural trauma networks of first responders. Priority will be made to present the preliminary findings at an international conference hosted in Uganda and at the annual world safety conference. Anonymized participant data sets from this trial will be archived on a publicly accessible permanent weblink that will be provided by the publishing journal within 12 months from the actual date of completion of the trial.

Results

The trial was approved on August 27, 2019. The actual recruitment of the first patient participant began on September 01, 2019. The last follow-up was on August 27, 2023. Posttrial care, including linkage to clinical, social support, and referral services, is to be completed by November 27, 2023. Data analyses will be performed in Spring 2024, and the results are expected to be published in Autumn 2024.

Discussion

Study Implications and Future Directions

This trial is meant to compare (1) the time interval from the accident to hospital admission, (2) the time interval from the referral decision to hospital discharge, (3) the all-cause mortality, and (4) the morbidity of patients with motorcycle accident–related orthopedic and neurological injuries between RTTDC (intervention) and standard care (control) study centers in Uganda, Africa.

This study is anticipated to reveal the overall impact of the rural trauma team development and training on the clinical process time efficiency and patient-centered outcomes of

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musculoskeletal and neurological injuries in controlled clinical settings, using validated injury severity scores [43] and trauma outcome and process measures [29,30]. The findings will add value to the emerging evidence from previous nonrandomized studies in high-income countries, which have evaluated the RTTDC. The available evidence suggests that the RTTDC potentially reduces the prehospital interval [50] and referral decision time [50], and enhances trauma team role identity, but has no perceived impact on mortality reduction [51]. It remains unclear how these findings relate to LMICs whose trauma care systems are still in the infancy stage.

Study Limitations

Despite the strengths of this trial, we anticipate some limitations. First, while the authors are ambitious to assume that the study centers are homogeneous, the heterogeneity among the 6 participating regional referral hospitals could cause bias and affect study estimates. Further, the relatively smaller number of clusters could affect the power of the study. However, randomization of 6 out of the 17 trauma centers is within the ethical constraints as this sample already represents 35.3% of Uganda's regional referral hospitals. To overcome the statistical power bias limitation, the sample size is inflated for individual randomization to cater to the design effects in accordance with the report by Hooper et al [45]. Moreover, we plan to use mixed effects regression models, which permit adjustments for covariates at both the cluster and individual levels in a single-stage approach, and plan to use the *t* test, which is robust in terms of normality deviations. According to Borhan et al [52], mixed effects models are deemed suitable for smaller clusters in situations where the primary outcomes are continuous, which is the case in this trial. Further, we hope that the ancillary studies with mixed methods will add value to the overall interpretation of the trial results by providing data from individuals outside the health sector, such as traffic law enforcement professionals.

Conclusion

Existing systematic reviews on trauma education programs in LMICs have identified a critical gap with regard to a lack of robust epidemiological studies that assess the effect of such interventions on patient outcomes within the low-resource context [16]. By relying on the strength of local needs contextualization to extend the training to nontrauma specialists, such as traffic law enforcement professionals, the results of this trial could inform the design, implementation, and scalability of rural trauma team development in similar low-resource settings. To the best of our knowledge, this is the first cluster randomized controlled trial using prospectively collected data to compare the effects of RTTDC training and standard care on patient outcomes and process measures in LMICs.

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Data Availability

The anonymized data sets arising from this study will be archived and made publicly available through a permanent weblink to a repository that will be provided by the publishing peer-reviewed journal.

Authors' Contributions

HL is the principal investigator and has contributed to conceptualization, data curation, investigation, methodology, project administration, resources, and writing of the original draft. HL and MM have contributed to formal analysis, software, and visualization. RS, PK, TB, JPP, and MLW have contributed to validation, writing–review, and editing. TB, JPP, and MLW have contributed to supervision and funding acquisition. All authors have read and approved the final manuscript. We plan to include a blinded external biostatistician to validate the final data analyses, and this person will be included as a co-author for the resulting manuscripts.

Conflicts of Interest

JPP has received funding from the Academy of Finland (grant 17379). The authors have no further interests to declare.

Multimedia Appendix 1
Informed consent form for rural trauma team development course participants.
[DOCX File , 37 KB - resprot_v13i1e55297_app1.docx]

Multimedia Appendix 2
Informed consent form for patient participants.

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[DOCX File , 37 KB - resprot_v13i1e55297_app2.docx]

Multimedia Appendix 3
Outcome measurement variables and their analysis metrics.
[DOCX File , 19 KB - resprot_v13i1e55297_app3.docx]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table showing the study timelines.
[DOCX File , 18 KB - resprot_v13i1e55297_app4.docx]

Multimedia Appendix 5
Patient participant data collection tool for the motorcycle trauma registry.
[PDF File (Adobe PDF File), 63 KB - resprot_v13i1e55297_app5.pdf]

Multimedia Appendix 6
Trauma care frontline worker and public engagement trainee data collection tool.
[DOCX File , 52 KB - resprot_v13i1e55297_app6.docx]

Multimedia Appendix 7
Schematic representation of the study design.
[DOCX File , 16 KB - resprot_v13i1e55297_app7.docx]

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Abbreviations

CAC: cluster autocorrelation coefficient
CT: computed tomography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
ICC: intraclass correlation coefficient
ICU: intensive care unit
KTS: Kampala Trauma Score
LMIC: low- and middle-income country
MCQs: multiple-choice questions
RTTDC: Rural Trauma Team Development Course
TEFS: Trauma Expectation Factor Score

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TOMS: Trauma Outcome Measure Score
WHO: World Health Organization

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Protocol

Effectiveness of Gerontechnology Empowerment Program on Awareness and Use of Mobile Apps Among Older Adults for Instrumental Activities of Daily Living: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Instrumental activities of daily living (iADLs) are crucial for older adults to live independently. Health care and technological advancements will increase the older adult population and life expectancy globally. Difficulties with iADLs impact older adults' quality of life. Mobile apps can assist older adults, but many require help due to limited awareness. Lack of awareness is a barrier to app use. Existing literature mainly covers health care and app design, needing more focus on iADL apps for older adults.

Objective: The study objectives encompass 2 main aspects: first, to evaluate the awareness, use, and factors influencing the use of apps among older adults for iADLs; and second, to create and assess the effectiveness of a gerontechnology empowerment program (GEP) for older adults on the awareness and use of apps for iADLs.

Methods: This research uses a quantitative approach divided into 2 distinct phases. In phase 1, we conduct a descriptive survey to assess the level of awareness and use of mobile apps for iADLs and identify the factors that influence the use of such apps among older adults. To ensure clarity and comprehension among participants, we provide them with a subject information sheet in both Kannada and English. The data collected during this phase enable us to gain insights into awareness levels, use patterns, and factors that shape older adults' use of apps for iADLs. The results serve as the foundation for designing the GEP. In phase 2, a cluster randomization method will be used to select older adults aged 60 to 75 years in Udupi district, Karnataka, India, who are active smartphone users. These participants will be divided into 2 groups: the experimental and the control groups. The experimental group will join the GEP. The sample size for phase 1 is 554, and phase 2 is 50. To assess the effectiveness of this program, we will measure the outcomes before and after its implementation using the same assessment tools used in phase 1.

Results: This study is funded by the Indian Council of Medical Research (Adhoc/193/2022/SBHSR on November 18, 2022). Phase 1 data collection is expected to be completed by November 2023, and phase 2 is scheduled to commence in the upcoming months. Phase 1 and 2 findings will be analyzed and discussed in the main paper, which we intend to submit to a high-quality peer-reviewed journal for publication. The research protocol, informed consent forms, and associated documentation received approval from institutional ethics committees (214/2020).

Conclusions: Upon the successful testing of the GEP, it can be recommended that welfare departments encourage older adults to use mobile apps for iADLs and establish training programs to provide support to older adults in using these apps.

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Trial Registration: Clinical Trials Registry - India CTRI/2020/09/027977; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=NDUxMzM=&Enc=&userName=027977

International Registered Report Identifier (IRRID): DERR1-10.2196/53587

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KEYWORDS

gerontechnology; older adults; awareness; older people; instrumental activities of daily living; iADLs; mobile apps; mobile phone; empowerment

Introduction

Background

Advancements in health care, lifestyle improvements, and technological progress are poised to elevate the global average life expectancy from 72.6 to 77.1 years by 2050, with India also experiencing a similar upward trajectory. In 1960, India had an overall life expectancy of merely 40 years, but today, it stands at approximately 69 years [1]. Forecasts indicate a continued increase in life expectancy in the coming decades [2]. According to a United Nations report, India's older adult population is expected to grow substantially, reaching 19% by 2050 in contrast to the global average of 22%. Consequently, the aging demographic will encounter significant challenges in both activities of daily living (ADLs) and instrumental activities of daily living (iADLs), including tasks like communication, shopping, medication management, financial handling, travel, meal preparation, cleaning, and laundry [3]. This, in turn, will considerably impact older adults' overall quality of life (QOL). Given these evolving trends, it becomes increasingly crucial for researchers and practitioners to identify cost-effective, feasible, and practical strategies to mitigate or prevent any decline in ADL and iADL abilities among older adults [4].

Experts consider the judicious use of technology as a facilitator and a potential solution for enhancing the QOL among the older population [5]. Specifically, mobile technologies and smartphones have proven highly effective in assisting older adults in self-management and prosperous living by providing them with increased access to relevant, valuable, and timely information for efficient self-governance, addressing ADLs and iADLs [6]. However, despite a growing inclination among older adults in India toward adopting mobile-related technologies, it is evident that they need help with mobile technology adoption [7]. Nevertheless, these challenges tend to diminish with the continuous use of mobile and related technologies, eventually becoming an integral part of their lives, aiding them in ADLs and iADLs [8]. Recognizing that smartphone technology use tends to be more prevalent among younger individuals, experts emphasize the importance of research that explores the motivations and barriers influencing smartphone and related technology use among older adults. This research is crucial because older adults stand to benefit as much, if not more, from technology compared to younger adults [9].

Considering the abovementioned observations, this research addresses these gaps by focusing on older adults. It aims to assess their awareness and use of mobile apps for iADLs, pinpoint the factors that drive or inhibit their use, and ultimately establish a sustainable gerontechnology empowerment program (GEP) based on the empirical findings [10]. This program aims to enhance and empower older adults' propensity, interest, adoption, and use of the latest mobile apps designed for iADLs. This study is rooted in several interconnected areas, including the anticipated rise in the older adult population, the potential advantages of mobile apps in aiding iADLs, the factors influencing their adoption among older adults, and the empowerment of older adults in using mobile apps for iADLs. The demographic landscape of our world is undergoing a significant transformation, with older adults playing an increasingly substantial role. Older adults account for approximately 11.5% of the global population, projected to surge to 22% by 2050 [3]. The importance of iADLs in the lives of older adults cannot be overstated. These activities are notably more intricate than the basic ADLs and are pivotal for older adults to maintain their independence [11].

Significance of the Study

In the context of ADLs, it is noteworthy that, as of 2011, around 7.6% of older adults in India faced difficulties in performing them. However, the distinction between ADLs and iADLs becomes more evident when we consider that iADLs demand heightened expertise, decision-making abilities, skills, and individual discretion compared to the tasks associated with ADLs [1]. The challenges older adults encounter in managing iADLs are well-documented by research, consistently affirming the previously mentioned perspective [11]. Studies have shown that older individuals experience escalating difficulties in food preparation, shopping, handling telephones and related devices, and basic laundry [12]. These challenges underscore the pressing need for research and intervention to facilitate the adoption of technology, particularly mobile apps, to empower and support older adults in their pursuit of independent living [7]. Older adults' use of technology, including computers and the internet, is influenced by various factors, including age, education, and attitudes toward technology [13]. Previous research has consistently shown that age is a strong negative predictor of technology use, suggesting that older individuals tend to be less inclined to embrace technological advancements [14].

In the context of developing countries, mobile phones, mobile apps, and related technologies have emerged as crucial components of information and communication technology (ICT) systems designed to assist individuals of all ages [15]. These technologies have found significant use, particularly in the health care sector. Mobile apps, as integral components of mobile health (mHealth) interventions, offer a wide range of benefits, such as assessing fall risks in home settings for older adults [14]. Mobile phones also play a vital role in supporting

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telemedicine and providing remote health care services in developing nations [16].

The advent of net banking has brought about advantages for older adults, including 24-hour access, flexibility, independence, and the ability to overcome physical barriers associated with age in accessing financial services. Similarly, mobile apps related to food preparation, such as recipes and diet apps, as well as service-oriented apps for housekeeping, laundry, and cleaning, have the potential to enhance various aspects of older adults' lives. However, despite the widespread adoption of mobile phones and related technologies and their proven potential to improve services like health care, banking, and travel, these technologies' adoption, acceptance, and use among older adults remain notably low [17].

Mobile phones and related technologies and apps have demonstrated their capacity to significantly enhance the QOL for older adults in areas such as health care, commerce, independent living, reduced isolation, strengthened connections with family and friends, and more [9,18].

Connecting with loved ones through technology contributes to higher mental and physical well-being. Notably, technology use for nonsocial purposes is linked to enhance the overall physical well-being, while its social use mitigates the negative impact of loneliness on overall life satisfaction [19]. Consequently, mobile phones and related technologies and apps extend beyond mere communication devices; they have a profound societal impact by liberating us from geographical constraints.

Despite older adults demonstrating a generally positive attitude toward technology, they often encounter complexities. Additionally, demographic characteristics such as age, gender, and education level play crucial roles in predicting their adoption of mobile technology [20]. Understanding the motivations and obstacles behind older adults' behavior regarding the use of mobile apps is essential [9].

In the context of mHealth adoption among older adults in a developing country, a study applied parameters from the well-established unified theory of acceptance and use of technology framework along with 2 additional variables: technology anxiety and resistance to change. The study revealed that factors such as performance expectancy, social influence, technology anxiety, effort expectancy, and resistance to change significantly influenced older adults' behavioral intentions to use mHealth. Interestingly, facilitating conditions did not substantially affect behavioral purposes [17]. This underscores the importance of considering the perceived benefits and ease of use and factors like anxiety and resistance to change when designing interventions to promote technology adoption among older adults.

A randomized controlled trial was implemented on smartphone use training programs among older adults and found a positive effect on smartphone use skills and overall QOL. This underscores the importance of providing detailed instructions and guidance to older adults by technology and service providers to cultivate favorable perceptions and confidence in using new technology [10]. Furthermore, any training program designed for older adults to promote the practical use of mobile apps is expected to result in significantly lower depressive symptom scores than baseline measurements. Additionally, it is anticipated that such programs will facilitate the use of mobile apps for various purposes, including health management, entertainment, transportation, and social media interaction, thereby contributing to the overall well-being of older adults [21]. While the impact of ICT on ADLs has been acknowledged, more research needs to examine the influence of ICT on iADLs [22]. Given the increasing older adult population, there is a pressing need for a comprehensive understanding of effective empowerment and training interventions tailored to their unique needs [23]. This will be instrumental in improving their QOL and enabling them to lead more independent and fulfilling lives. With this study, we would like to contribute to achieving the Sustainable Development Goal (4.3.2) by educating the general public and encouraging lifelong learning.

Novelty

This study intends to fill the following gaps in the literature: (1) While there is substantial literature on mobile technology and apps for older adults in the context of their iADLs, existing studies predominantly emphasize health care, app features, design considerations, and overall effectiveness. (2) This study uniquely focuses on using mobile apps by older adults to facilitate their performance of iADLs. (3) The GEP represents a pivotal aspect of this research, aiming to foster awareness and encourage the use of mobile apps among older adults. (4) This program empowers older adults to effectively perform their iADLs through technology.

Objectives

The objectives of the study are to assess the awareness and factors influencing the use of mobile apps among older adults for iADLs and to develop and determine the effectiveness of a GEP for older adults on awareness and use of mobile apps for iADLs.

Methods

Research Design

The research design for phase 1 is cross-sectional descriptive research, and phase 2 is a cluster randomized control trial. The Indian Council of Medical Research Guidelines for Extramural Research was adopted to prepare the funding proposal [24].

Participants

The participants in this phase exclusively consist of older adults aged between 60 and 75 years who use smartphones and are affiliated with welfare organizations associated with the District Disabled Welfare Office in Udupi district, Karnataka state, India. Additionally, participants must be able to read and write in English and express a willingness to participate in the study. Nonsmartphone users will be excluded from this research study.

Sample Size

Sample size calculations were performed separately for phase 1 and phase 2 of the study. For phase 1, a sample size of 369 participants was estimated based on proportion values. This

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sample size was then adjusted by a design effect of 1.5 to account for potential clustering or stratification, resulting in a required sample size of 554 participants. In phase 2, the focus was on comparing 2 proportions. To ensure the study's robustness in the face of potential dropouts (estimated at 20%), an initial sample size of 31 participants was calculated for each group. This initial size was adjusted by a design effect of 1.5 to consider the study's specific design characteristics, yielding a total required sample size of 46 participants per group, rounded up to 50 participants per group.

Ethical Considerations

The research protocol, informed consent forms, and associated documentation received approval from the institutional ethics committee (214/2020) of Kasturba Medical College and Kasturba Hospital Institutional (Registration no.: ECR/146/Inst/KA/2013/RR-19). This study is also registered under the Clinical Trials Registry - India (CTRI/2020/09/027977). In this study, participants will receive a subject information sheet in both Kannada and English to help them understand the study. The data will be collected only after informed consent is obtained. The confidentiality and anonymity of the participants will be maintained.

Recruitment

This study is structured around a 2-phase research design (Figure 1). The sample was selected purposively from welfare associations of the Udupi district. Phase 1 was initiated after the ethics and Clinical Trials Registry - India approval. For the study's second phase, the sample will be randomly allocated to experimental and control groups from various welfare organizations of the Udupi district. We have planned to use the clustered randomization process to select participants based on the study's eligibility criteria.

Figure 1. Research framework. GEP: gerontechnology empowerment program.

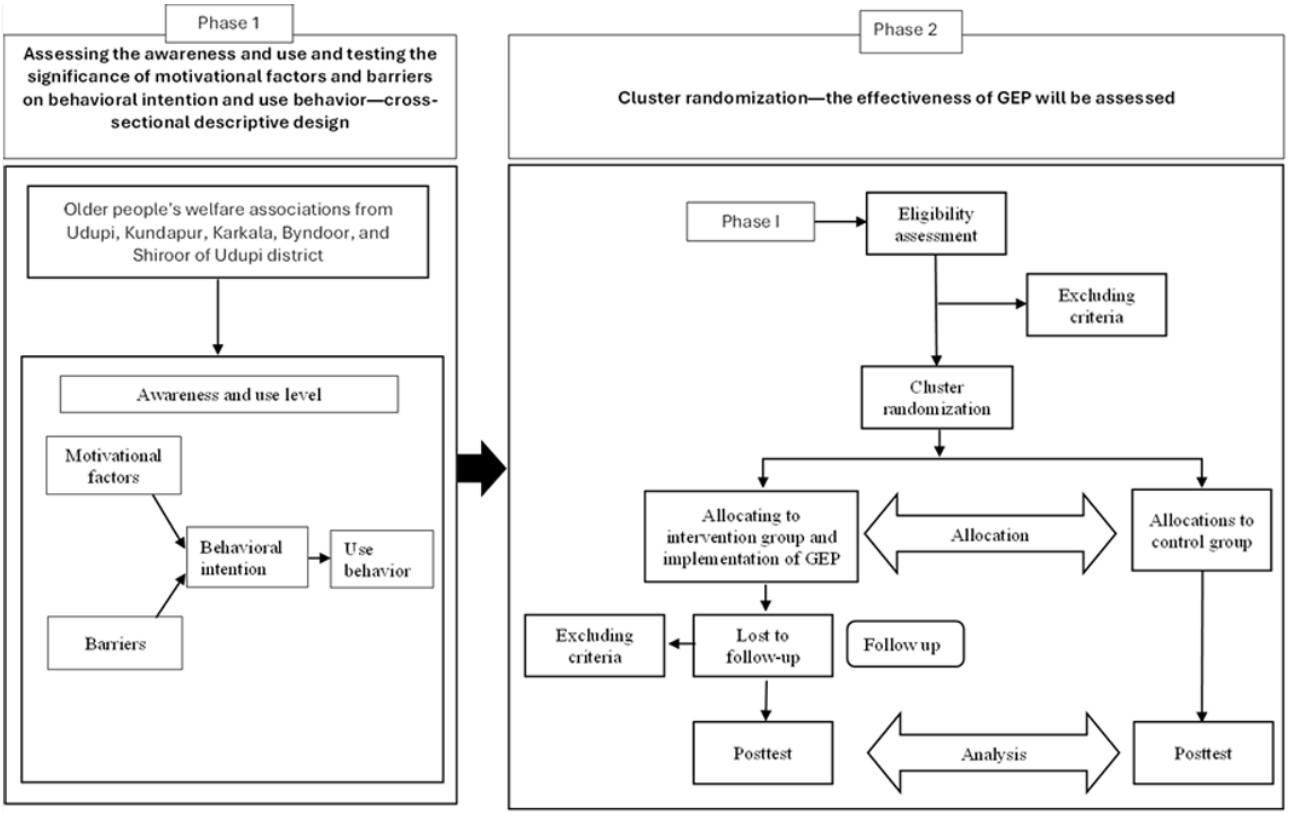

Research Instrument

The data collection process for this study will involve the use of structured questionnaires in both English and Kannada. The questionnaire will cover the following key areas: demographic information—participants will provide essential demographic details, including age, gender, educational qualifications, income range, the presence of chronic diseases, and the type of smartphone they use; awareness and use level of mobile apps for iADLs—this section will measure older adults' awareness and usage level regarding various mobile apps designed to address the 8 components of iADL; and motivational factors and barriers—this portion of the questionnaire will explore the motivational factors and barriers influencing older adults' adoption and use of mobile apps. It will encompass dimensions such as performance expectancy, social influence, facilitating condition, effort expectancy, technology anxiety, awareness factors, and resistance to change.

Collecting data in both English and Kannada ensures that participants can comfortably respond in their preferred language, facilitating accurate and comprehensive data collection from a diverse group of older adults.

Instrument Validity and Reliability

The instruments used in this study underwent a rigorous validation process. Experts from various fields, including health care, social studies, information technology, and the older adults' welfare department, were engaged in the validation process. These experts were presented with a clear understanding of the

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study's objectives and its blueprint. The reliability was established among 20 participants and evaluated through the test-retest method, ensuring consistent responses. Additionally, Cronbach α, a statistical measure of internal consistency, was used to assess the reliability of awareness and usage level on mobile apps for iADLs (r=88) and motivational factors and barriers (r=73) instruments. Furthermore, a pilot study was conducted among 10 participants to assess the study's feasibility and accuracy in January 2023.

Data Collection Plan

The study is in progress by visiting older adults' welfare organizations after obtaining prior approval. In phase 1, participants will receive a subject information sheet in both Kannada and English to explain the study details. Data will be collected using a structured questionnaire, with participants' consent, to assess their awareness and the factors influencing the use of mobile apps for iADLs. In phase 2, cluster randomization will be used to select older adults for the experimental or control groups. The GEP will be administered to the experimental group. The effectiveness of the GEP will be assessed through measurements taken before and after its implementation.

Statistical Analysis

Plan for Data Analysis

To evaluate the awareness and use of mobile apps among older adults, frequency and percentage distribution will be used as a statistical method. A combination of statistical techniques will be used to analyze the influencing factors, including descriptive statistics to provide a summary of the data and logistic regression to model the relationship between the influencing factors and mobile app use. A sequence of statistical tests will be applied to measure the effectiveness of the GEP. These tests include repeated measures ANOVA, 2-tailed t test, Mann-Whitney U test, Wilcoxon signed rank test, and χ^2 test. These tests will help assess the impact and changes brought about by the GEP on various outcome measures.

Develop and Determine the Effectiveness of a GEP

The GEP will be a comprehensive intervention designed to facilitate the use of smartphone apps for iADLs. The development of GEP will be based on the findings from the study's first phase, incorporating insights from experts in health care, mobile technology, and older adults' welfare departments or organizations. The structure of the GEP program will encompass the following components: information and features—detailed information about smartphone apps relevant to iADLs, including their features and functionalities; installation procedures—step-by-step guidance on installing and setting up these smartphone apps; general awareness—fundamentals of smartphone use and general awareness regarding its capabilities; security awareness—guidelines on ensuring smartphone security and safe use; dos and don'ts—best practices and precautions for effective and responsible smartphone use; operation manuals—manuals provide instructions on operating specific smartphone apps for iADLs. The training program will be conducted through 8 sessions, each lasting 3 hours. These sessions will incorporate hands-on training using audiovisual facilities to enhance participants' understanding and practical skills in using smartphone apps effectively for iADLs.

Results

Overview

This study is funded by the Indian Council of Medical Research (Adhoc/193/2022/SBHSR on November 18, 2022). Phase 1 data collection is expected to be completed by November 2023, and phase 2 is scheduled to commence in the upcoming months. Phase 1 and 2 findings will be analyzed and discussed in the main paper, which we intend to submit to a high-quality peer-reviewed journal for publication. The research protocol, informed consent forms, and associated documentation received approval from institutional ethics committees (214/2020).

Expected Outcomes

The expected outcomes are as follows: The data collected from this study will provide valuable insights into the actual awareness levels and the influencing factors affecting the use of mobile apps for iADLs among older adults. The design and testing of the GEP have the potential to significantly enhance the ability of older adults to manage iADLs, leading to improved self-management and overall well-being, which in turn has a positive societal impact. To further extend the benefits of this research, collaboration with nongovernmental organizations and self-help groups can be explored to implement the GEP on a larger scale. This would allow for a broader reach and greater empowerment of older adults. Additionally, the results of this study can serve as a valuable reference for other researchers seeking to empower older adults in using mobile technologies. As part of the GEP, developing the iADLs Guide, a mobile app providing regular updates on technology, will be an ongoing service for older adults. This tool will ensure older adults have access to the latest information and updates in the ever-evolving field of mobile technology, further enhancing their ability to perform iADLs effectively. This initiative contributes to achieving sustainable development goal 4.3.2 to provide education to the general public and encourage lifelong learning [25].

Discussion

Principal Findings

The primary objective of the GEP is to enhance awareness and use of mobile apps among older adults for iADLs. The study findings can improve older adults' participation in the GEP, significantly increasing awareness and usage levels. This aligns with previous research, such as the study by Xie and Kalun Or [26], which demonstrated that targeted interventions like mHealth can effectively improve technology adoption and use among older adults. In our research, the GEP provided structured guidance, hands-on training, and resources to bridge the gap in awareness and facilitate the use of mobile apps for iADLs. One of the noteworthy outcomes of the GEP was its positive impact on the QOL among older adults. The program can empower older adults to perform iADLs more independently and efficiently, enhancing well-being. This finding resonates with

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existing literature. For instance, a study by Sen et al [27] emphasized through a systematic review that using technology, including mobile apps, can reduce social isolation, increase engagement in daily activities, and improve mental and physical well-being among older adults. The GEP's focus on addressing the specific needs of older adults in iADLs aligns with the principles of person-centered care and empowerment.

The success of the GEP can be attributed to its tailored approach. The program was developed based on older adults' specific needs and preferences, considering technological anxiety and resistance to change. This personalized approach aligns with the recommendations of Charness and Boot [28], who emphasized the importance of designing technology interventions that consider individual differences and provide ongoing support. The GEP's combination of information, hands-on training, and ongoing assistance through the iADLs Guide mobile app ensured that older adults received the necessary support at every stage of their technology adoption journey. Collaboration with older adults' welfare organizations, nongovernmental organizations, and self-help groups is pivotal in successfully implementing the GEP. This collaborative approach resonates with Baker et al [29] findings, highlighting the importance of involving community organizations in technology interventions for older adults. The positive outcomes observed in this study suggest that the GEP model can be scaled up and replicated in other regions and populations, further extending its benefits to a larger demographic of older adults.

This protocol addresses a pressing issue—the growing digital divide among older adults. Older adults may face challenges in keeping pace with technological advancements as the world becomes increasingly digital. This protocol aligns with the findings of the Pew Research Center, which reported that while technology adoption among older adults is rising, a substantial digital divide persists. The GEP represents an effort to bridge this divide and empower older adults to leverage technology for iADLs. This protocol builds on prior research, highlighting the potential benefits of technological interventions for older adults. For example, a systematic review by Wildenbos et al [30] emphasized that technology interventions can enhance older adults' independence, well-being, and social connectivity. This protocol seeks to contribute to the existing body of knowledge by assessing the effectiveness of a structured empowerment program tailored to older adults' unique needs and challenges in adopting mobile apps for iADLs.

The study plan and methodology emphasize on assessing the real-world impact of the GEP. While many studies have explored the potential benefits of technology for older adults in controlled settings, this protocol seeks to evaluate the program's effectiveness in the context of participants' daily lives. This aligns with the recommendations of Mitzner et al [31], who stressed the importance of studying technology use in ecologically valid environments to capture its true impact. Therefore, this protocol for the effectiveness of GEP represents a significant endeavor to empower older adults with the necessary skills and knowledge to use mobile apps for iADLs. Drawing from supportive studies and available evidence, the protocol underscores the importance of addressing the digital divide, tailoring interventions to individual needs, and collaborating with stakeholders to enhance the well-being and independence of older adults in the digital age.

Limitations

Acknowledging the study protocol's limitations and ethical considerations is crucial. The sample size may be restricted to a specific geographic area, and participants will need a baseline level of English literacy. Researchers must ensure informed consent and safeguard participants' privacy and data security, following established ethical guidelines.

Conclusions

Following the successful testing of the GEP, there will be an opportunity to recommend its implementation to welfare departments. This proposal encourages older adults to embrace mobile apps for performing iADLs. Additionally, establishing a mobile app training initiative can provide training and support to older adults in using these apps effectively.

Acknowledgments

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Authors' Contributions

The study was prepared by YNS, GR, and PPK. Furthermore, the reporting of the study protocol and the oversight of the study's progress to date were jointly contributed to by YNS, GR, PPK, and VB.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activity of daily living
GEP: gerontechnology empowerment program
iADL: instrumental activity of daily living
ICT: information and communication technology
mHealth: mobile health
QOL: quality of life

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Protocol

Effects of Empagliflozin in Type 2 Diabetes With and Without Chronic Kidney Disease and Nondiabetic Chronic Kidney Disease: Protocol for 3 Crossover Randomized Controlled Trials (SiRENA Project)

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Abstract

Background: Sodium-glucose-cotransporter 2 inhibitors (SGLT2is) have revolutionized the treatment of type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD), reducing the risk of cardiovascular and renal end points by up to 40%. The underlying mechanisms are not fully understood.

Objective: The study aims to examine the effects of empagliflozin versus placebo on renal hemodynamics, sodium balance, vascular function, and markers of the innate immune system in patients with DM2, DM2 and CKD, and nondiabetic CKD.

Methods: We conducted 3 double-blind, crossover, randomized controlled trials, each with identical study protocols but different study populations. We included patients with DM2 and preserved kidney function (estimated glomerular filtration rate >60 mL/min/1.73 m^2), DM2 and CKD, and nondiabetic CKD (both with estimated glomerular filtration rate 20-60 mL/min/1.73 m^2). Each participant was randomly assigned to 4 weeks of treatment with either 10 mg of empagliflozin once daily or a matching placebo. After a wash-out period of at least 2 weeks, participants were crossed over to the opposite treatment. End points were measured at the end of each treatment period. The primary end point was renal blood flow measured with ^{82}Rubidium positron emission tomography–computed tomography (^{82}Rb-PET/CT). Secondary end points include glomerular filtration rate measured with ^{99m}Technetium-diethylene-triamine-pentaacetate (^{99m}Tc-DTPA) clearance, vascular function assessed by forearm venous occlusion strain gauge plethysmography, measurements of the nitric oxide (NO) system, water and sodium excretion, body composition measurements, and markers of the complement immune system.

Results: Recruitment began in April 2021 and was completed in September 2022. Examinations were completed by December 2022. In total, 49 participants completed the project: 16 participants in the DM2 and preserved kidney function study, 17 participants in the DM2 and CKD study, and 16 participants in the nondiabetic CKD study. Data analysis is ongoing. Results are yet to be published.

Conclusions: This paper describes the rationale, design, and methods used in a project consisting of 3 double-blind, crossover, randomized controlled trials examining the effects of empagliflozin versus placebo in patients with DM2 with and without CKD and patients with nondiabetic CKD, respectively.

Trial Registration: EU Clinical Trials Register 2019-004303-12; https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-004303-12, EU Clinical Trials Register 2019-004447-80;

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https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-004447-80, EU Clinical Trials Register 2019-004467-50; https://www.clinicaltrialsregister.eu/ctr-search/search?query=and+2019-004467-50

International Registered Report Identifier (IRRID): DERR1-10.2196/56067

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KEYWORDS

SGLT2i; empagliflozin; renal function; blood flow; DM2; diabetes mellitus type 2; CKD; chronic kidney disease; vascular function; sodium-glucose cotransporter 2 inhibitors; T2DM; type 2 diabetes mellitus; randomized controlled trial; RCT; CVD; placebo; renal; recruitment; Denmark; cardiovascular disease

Introduction

Overview

The World Health Organization has recently named diabetes the ninth leading cause of death globally [1]. Worldwide, more than 500 million people are living with diabetes. By 2045, this number is expected to rise to more than 780 million [2]. The disease burden is immense and complications are common. One of the most common and serious complications is cardiovascular disease (CVD), which affects more than 30% of all patients with diabetes [3]. Other complications include retinopathy, neuropathy, and nephropathy.

Chronic kidney disease (CKD) affects up to 50% of all patients with type 2 diabetes mellitus (DM2) [4,5] and is common in patients without diabetes as well. It ranks just below diabetes as the 10th leading global cause of death, resulting in an estimated 1.3 million deaths annually. The most common cause of death in both patients with diabetes and patients with CKD is CVD [3,6].

Recently, sodium-glucose-cotransporter 2 (SGLT) inhibitors (SGLT2is) have revolutionized the treatment of both DM2 and CKD. Originally developed as an antidiabetic medication, SGLT2is block the SGLT2 channels in the proximal kidney tubule, inhibiting the reabsorption of sodium and glucose from the preurine, leading to glycosuria and a modest decrease in plasma glucose [7].

Several recent large randomized controlled clinical trials (RCTs) have shown that SGLT2is exert remarkable effects in patients with diabetes, both with and without CKD, reducing the risk of death by CVD, hospitalization for heart failure, and progression of CKD [8-10]. The effects are similar in patients with nondiabetic CKD, reducing the risk of CKD progression and death by renal or cardiovascular causes by 30% to 40% [11,12]. As a consequence, current guidelines recommend treatment with SLGT2i for patients with DM2 both with and without concomitant CKD, as well as for patients with nondiabetic CKD [13,14].

The mechanisms underlying these remarkable effects are, however, not yet fully understood. There are several possible pathways [15]. In this study, we examine 4 pathways.

SLGT2i and Renal Hemodynamics

Increased renal reabsorption of sodium and glucose mediated by the SGLT2 channels is thought to be an important pathophysiological feature of diabetic nephropathy, instigating an increase in renal blood flow (RBF) via tubule-glomerular feedback mechanisms [16]. This, in turn, causes renal hyperfiltration; intraglomerular hypertension; and in time, kidney damage.

Intraglomerular hypertension is not unique to diabetic nephropathy but is thought to play a key role in the pathophysiology of nondiabetic CKD as well. A decline in functioning nephrons leads to a cascade of maladaptive hemodynamic changes, including increased intraglomerular pressure and hyperfiltration in the remaining nephrons [17,18].

Conversely, by blocking the SLGT2 channels, SGLT2is are hypothesized to alleviate the changes by reducing RBF and hyperfiltration, which could be a possible explanation of the observed beneficial effects. The acute drop in estimated glomerular filtration rate (eGFR) seen after initiation of SGLT2is could be a part of this mechanism as well [19]. While the effects of eGFR are well known, the reduction in RBF has only been demonstrated in a single study in patients with type 1 diabetes as well as in animal models [20,21]. None of the studies examining hemodynamic effects of SGLT2is in DM2 have found decreases in RBF [22,23], and it has, to our knowledge, never been examined in patients with CKD.

SGLT2i and Sodium Balance

In addition to blocking glucose reuptake, SGLT2is inhibit sodium reuptake in the proximal tubule, which leads to a transient increase in urinary sodium excretion [24]. Furthermore, a modest reduction in body weight, plasma volume, and a decrease in sodium skin content is seen and may point to a decrease in volume status and total body sodium [25,26]. This might help explain the rapid improvement in cardiac function seen after SGLT2i initiation [27]. However, the natriuretic effects of SGLT2is seem to dissipate quickly, possibly due to renal compensatory mechanisms [28]. These mechanisms are not yet fully understood and have been sparsely studied.

SGLT2i and Vascular Function

SGLT2is are also thought to exert an effect on the endothelial cells lining the inner walls of the blood vessels. DM2, CKD, and especially the combination of the 2 are associated with endothelial dysfunction and the subtle signs of endothelial dysfunction are often evident long before the clinical signs of vascular damage [29,30]. One of the most important reasons for endothelial dysfunction is the decreased synthesis and bioavailability of nitric oxide (NO), which leads to a decrease in systemic vasodilation, dysfunctional cell adhesion, smooth muscle cell proliferation, and hypercoagulability [31,32].

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SGLT2is improve endothelial function in animal studies and seems to be able to improve vascular function and arterial stiffness in patients with DM2 [33-36]. So far, no studies have examined the effects in patients with CKD.

SGLT2i and the Immune System

Inflammatory changes are common in the kidneys of patients with CKD and could be an important component in the development of glomerular injury, albuminuria, and CKD progression [37]. The innate immune system is involved in CKD progression and could be a target for SGLT2is. Both pattern recognition molecules (eg, collectin and mannan-binding lectin [MBL]) and complement activation pathways, notably the lectin pathway, could be involved in the progression of CKD, particularly in diabetes. Therefore, it is of interest to examine this system in diabetic and nondiabetic CKD and determine sensitivity to SGLT2is. Complement system components such as collectins, split products such as anaphylatoxins C3a and C5a, and terminal complexes (membrane attack complex) can be measured in plasma and urine along with other markers of the immune system [38,39]. SGLT2is can reduce the expression of inflammatory molecules such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) [40]. Whether SGLT2is also affect markers of the immune system in the kidney remains to be examined. Since the complement system is associated with cell surfaces, we plan to use urine microvesicles (exosomes) and use them as imprints or "wet biopsies" for apical membrane deposition of complement activation products along with quantitation of soluble components in plasma and urine.

Aims and Hypotheses

We aim to examine the effects of the SGLT2i empagliflozin versus placebo on renal hemodynamics, vascular function, sodium balance, and markers of the immune system in patients with DM2 with and without CKD, as well as in patients with nondiabetic CKD, hereby reflecting patient populations who would be offered SGLT2is in a clinical setting. In this paper, we describe and discuss our research hypothesis and the methods we used.

We hypothesize that the SGLT2i results in the following changes: (1) SLGT2i reduces RBF and glomerular filtration rate (GFR); (2) SGLT2i increases NO activity and improves endothelial function; (3) SGLT2i increases fractional sodium excretion, which is modified by more distally localized compensatory mechanisms; (4) SGLT2i increases renin angiotensin aldosterone system activity and decreases 24-hour ambulatory blood pressure and arterial stiffness; and (5) SLGT2i decreases renal innate immune activity.

Methods

Design

We conducted 3 double-blind, crossover RCTs, each with identical study protocols but different study populations. We included patients with (1) DM2 and preserved kidney function, (2) DM2 and CKD, and (3) nondiabetic CKD.

Each participant started with a run-in period of at least 2 weeks, wherein ongoing SGLT2i or nonsteroidal anti-inflammatory drug (NSAID) treatment, which is known to affect both renal hemodynamics and fluid homeostasis [41], was paused. If patients were not treated with SGLT2i or NSAID prior to inclusion, they could proceed directly to randomization. If deemed necessary, the SLGT2i could be substituted with a different class of antidiabetic treatment. The substitution was done in accordance with national treatment guidelines at the time [42]. After run-in, participants were randomly assigned to 4 weeks of treatment with either 10 mg of empagliflozin or a matching placebo, both taken once daily. After a wash-out period of at least 2 weeks, participants were crossed over to 4 weeks of the opposite treatment. Each 4-week treatment period was finalized with 2 examination days: 1 day at The University Clinic in Nephrology and Hypertension, Gødstrup Hospital, Denmark, and 1 day at The Department of Renal Medicine, Aarhus University Hospital, Denmark.

We aimed to keep examination days adjacent, but due to logistic considerations, we allowed for an interval of up to 1 week between examination days in each treatment period. If there was an interval between the examination days, the treatment period was extended concomitantly, ensuring that the last dose of study medication was taken on the morning of the last examination day (Figure 1).

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Figure 1. Study design.

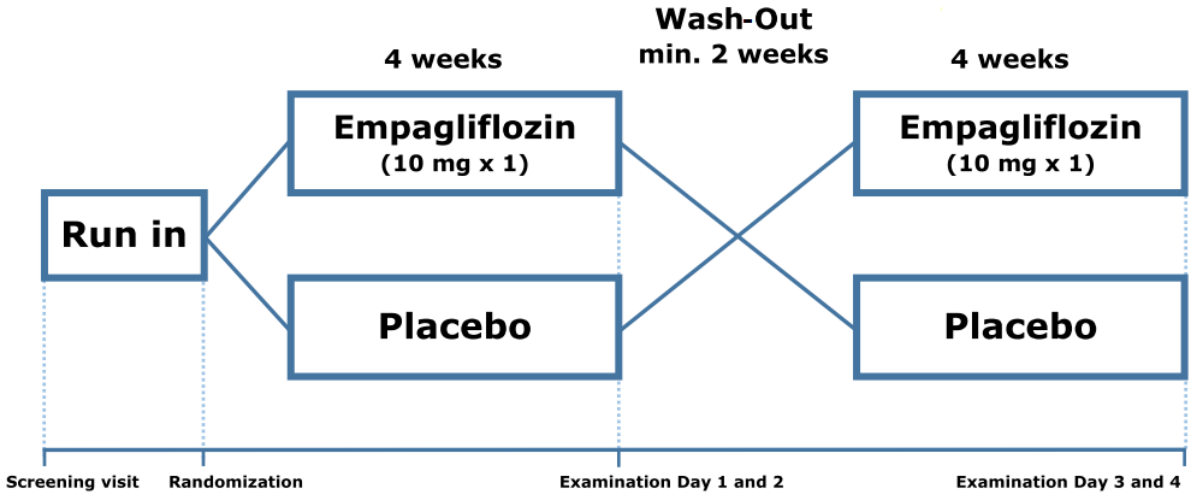

Recruitment and Screening

Participants were recruited through announcements at general practitioners, through newspaper advertisements, and through email or letters to participants from previous trials, who have consented to being contacted about new trials. Furthermore, participants could be recruited from the outpatient clinics at The Department of Internal Medicine, Nephrology and The Department of Internal Medicine, Endocrinology, Gødstrup Hospital, Denmark.

Participants were screened prior to inclusion to ensure they fulfilled all inclusion criteria and none of the exclusion criteria. Screening involved physical examination; medical history; office blood pressure; electrocardiogram; urine test strip measurement; urinary albumin and albumin-to-creatinine ratio; and the following blood samples: p-glucose, p-alanine transaminase, b-glycated hemoglobin A_{1c} (HbA_{1c}), p-potassium, p-sodium, p-albumin, p-creatinine, eGFR, B-leukocytes, B-hemoglobin, B-erythrocytes, and B-thrombocytes. Office blood pressure was measured 3 times and calculated as an average of the last 2 measurements. It was measured in both arms, and in case of difference between arms, the arm with the highest values was chosen for further measurements. If identical, the left arm was chosen. Inclusion, exclusion, and withdrawal criteria can be seen in Textbox 1.

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Textbox 1. Inclusion, exclusion, and withdrawal criteria.

Inclusion criteria

Study 1: Type 2 diabetes mellitus (DM2) and preserved kidney function

- Aged 18 years or older
- Estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2
- DM2 was diagnosed at least 1 year before inclusion and in stable medical antidiabetic treatment for at least 3 months
- Hemoglobin A_{1c} (HbA1c) 48-70 mmol/mol (Diabetes Control and Complications Trial [DCCT] values 6.5%-8.6%)
- Fertile women were to use safe contraception

Study 2: DM2 and chronic kidney disease (CKD)

- Aged 18 years or older
- eGFR 20-60 mL/min/1.73 m^2
- DM2 was diagnosed at least 1 year before inclusion, and in stable medical antidiabetic treatment for at least 3 months
- HbA_{1c} 48-70 mmol/mol. (DCCT values 6.5%-8.6%)
- Fertile women were to use safe contraception

Study 3: Nondiabetic CKD

- Aged 18 years or older
- eGFR 20-60 mL/min/1.73 m^2
- Fertile women were to use safe contraception

Exclusion criteria

Study 1 and 2: DM2 and preserved kidney function and DM2 and CKD

- Type 1 diabetes
- Alcohol or substance abuse
- Pregnancy or breastfeeding
- Anamnestic or clinical signs of heart or liver failure
- Active cancers, aside from skin cancers (spinocellular or basocellular carcinomas)
- BMI > 35 kg/m^2
- Allergies or unacceptable side effects to the experimental treatment or background treatment
- If the investigator found the participant unfit to complete the trial.
- Previous kidney transplant
- Autosomal dominant polycystic kidney disease (ADPKD).

Study 3: Nondiabetic CKD

- Same as in study 1 and study 2
- DM2

Withdrawal criteria

- For all 3 studies, participants were withdrawn if they developed an exclusion criterion, withdrew consent, were noncompliant, or experienced serious or unacceptable adverse events.

Participants

Our power calculation was based on the primary end point, RBF. In total, 15 patients were needed in each study to detect a minimal relevant difference in RBF of 0.167 mL/min/g, with an SD of 0.180 mL/min/g, a 2-sided α-level of 5%, and a power of 90%.

Randomization and Study End Points

Randomization numbers were provided by the manufacturer, Boehringer-Ingelheim. Randomization was performed by the

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Hospital Pharmacy, Central Denmark Region, Department Gødstrup. Participants were randomized in blocks of 4. Treatment assignment and allocation were concealed from clinicians, participants, and research staff until the trials were completed and as long as they were involved in data analysis. A copy of the randomization list and sealed envelopes with individual randomization numbers were kept in a locked safe at The University Clinic of Nephrology and Hypertension, in case unblinding was required. A single participant could be unblinded without it affecting the rest of the trial. At the end of the project, the envelopes will be returned to the Hospital Pharmacy where a receipt will be drawn up. The primary and secondary study end points can be viewed in Textbox 2.

Textbox 2. Primary and secondary study end points.

Primary end point

- Renal blood flow

Secondary end points

- Glomerular filtration rate
- Renal vascular resistance (RVR), filtration fraction, afferent and efferent arteriolar resistance (Ra and Re)
- Vascular function
- The nitric oxide–system, measured as plasma and urinary levels of nitrite, nitrate, and cyclic guanosine monophosphate (cGMP)
- The complement system, measured as plasma and urine levels of mannan-binding lectin (MBL), collectin kidney 1 (CL-K1), collectin liver 1 (CL-L1), mannan-binding lectin serine protease (MASP) 1-3, C4c, C3c, C3dg, sC5b-9, and urinary exosomes.
- Systemic hemodynamics, measured as 24-hour ambulatory brachial blood pressure, heart rate, pulse wave velocity, and peripheral resistance
- Plasma levels of renin, angiotensin II, aldosterone, vasopressin, and brain natriuretic peptide
- Water and sodium excretion: urinary sodium, free water clearance, urinary glucose, urinary albumin, fractional sodium excretion, urinary excretion of tubular transporter proteins (aquaporin 2 [AQP2], endothelial sodium channel [ENaC], sodium chloride symporter channel [NCC], and sodium-potassium-chloride cotransporter [NKCC]), extracellular body water (EBW), total body water, intracellular body water (IBW), adipose tissue mass, and erythrocyte salt sensitivity
- Hemoglobin A_{1c} (HbA_{1c}) and p-glucose
- β-hydroxy butyrate and urate
- Urinary excretion of adenosine, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin 6 (IL-6)
- Plasma concentrations of parathyroid hormone, phosphate, calcium, alkali phosphatase and fibroblast growth factor (FGF23), and urinary excretion of phosphate and calcium

Study Medication

The active treatment, 10 mg of empagliflozin, and a matching placebo were produced and distributed by the manufacturer, Boehringer-Ingelheim. The placebo tablet was identical to empagliflozin in every way, except for the lack of active substance. The study medication was delivered from The Hospital Pharmacy in identical pill bottles and was allocated corresponding to the randomization number.

Compliance was checked with a phone call midway through each examination period and by pill count when the study medication was returned on the last examination day.

Study Methods

^{82}Rubidium Positron Emission Tomography–Computed Tomography

RBF was measured with ^{82}Rubidium positron emission tomography–computed tomography (^{82}Rb-PET/CT) scans. All scans were performed on a Siemens Biograph mCT; 64 slice-4R (Siemens Healthcare GmbH). The method has been previously described by Langaa et al [43,44].

Participants rested in a sitting position for at least 30 minutes prior to the scan. During the scan, participants were placed in a supine position with arms resting over their heads. After positioning, a low-dose CT scan (25 mAs, 100 kV) was performed for attenuation control. This was immediately followed by a bolus injection of 555 megabecquerel (MBq) ^{82}Rb through a peripheral venous catheter (PVC), whereafter an 8-minute dynamic PET scan was performed. Through iterative reconstruction, 3D images of the activity changes in the abdominal aorta and the parenchyma of both kidneys were generated.

A 1-tissue compartment model was used for flow estimation, and RBF was calculated as a K1-value based on activity uptake in the abdominal aorta and both kidneys. Values were calculated using PMOD (PMOD Technologies Ltd).

^{82}Rb was obtained using an ^{82}Rb-generator (Cardiogen-82; Bracco Diagnostics Inc). Scans were done in cooperation with The Department of Nuclear Medicine, Regional Hospital Gødstrup.

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Venous Occlusion Strain Gauge Plethysmography

Vasodilatory function was measured using classic forearm venous occlusion plethysmography (Hokanson EC6) as previously described by Fredslund et al [45], although we did not perform measurements in the contralateral arm. An indium-gallium strain gauge placed around the forearm senses changes in forearm volume. Changes in forearm volume during brief, very fast, occlusions (using the Hokanson E20 inflator) of venous outflow by a cuff on the upper arm will then reflect the arterial inflow. The plethysmography method, therefore, allows direct assessment of the effects of vasoactive drugs infused into the brachial artery. In this project, we used the infusion of acetylcholine (ACh) and sodium nitroprusside (SNP) for the evaluation of endothelium-dependent and independent vasodilatation, respectively.

GFR

GFR was determined through clearance of ^{99m}Technetium-diethylene-triamine-pentaacetate (^{99m}Tc-DTPA). Through a PVC, 25 MBq of ^{99m}Tc-DTPA was injected intravenously. Before injection, a zero sample was drawn. Blood samples were drawn after 3, 4, and 5 hours, measuring residual plasma ^{99m}Tc-DTPA activity, whereby GFR was calculated. Measurements were done in cooperation with The Department of Nuclear Medicine, Regional Hospital Gødstrup.

Blood Pressure Measurement and Arterial Stiffness

24-Hour ambulatory brachial blood pressure, heart rate, pulse wave velocity, and arterial stiffness were measured with Mobil-O-Graph (IEM GmbH).

Biochemical Analyses

Plasma and serum levels of sodium, HbA_{1c}, glucose, brain natriuretic peptide, potassium, albumin, creatinine, phosphate, parathyroid hormone, alkali phosphatase, urate, total protein, hemoglobin, erythrocyte volume fraction, thrombocytes, and calcium were routinely analyzed by The Department of Biochemistry, Gødstrup Hospital, Denmark. β-hydroxy butyrate was measured with a FreeStyle Precision Neo point of care devise (Abbott Laboratories).

Plasma levels of renin, angiotensin II, aldosterone, and vasopressin were measured by radioimmunoassay. Plasma levels of cyclic guanosine monophosphate (cGMP) and fibroblast growth factor 23 (FGF23) were measured by enzyme-linked immunosorbent assay (ELISA).

Plasma and urine levels of nitrite and nitrate were measured by spectrophotometry.

Erythrocyte salt sensitivity was measured with a salt blood test (CARE Diagnostica Laborreagenzien GmbH). Plasma and urinary osmolality were measured by freeze point depression with an A2O osmometer (Advanced Instruments).

Plasma and urinary levels of MBL, collectin kidney 1 (CL-K1), collectin liver 1 (CL-L1), mannan-binding lectin serine protease (MASP) 1-3, C4c, C3c, C3dg, sC5b-9, and urinary exosomes were measured at The Department of Cardiovascular and Renal Research, University of Southern Denmark.

Urine volume and urinary levels of sodium, creatinine, albumin, calcium, and phosphate were measured routinely by The Department of Biochemistry, Gødstrup Hospital, Denmark.

Urinary levels of glucose, aquaporin 2 (AQP2), epithelial sodium channel (ENaC), sodium chloride symporter channel (NCC), and sodium-potassium-chloride cotransporter (NKCC) were measured by radioimmunoassay; cGMP, IL6, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and adenosine were measured by ELISA.

Bioimpedance Measurement

EBW, total body water, intracellular body water, and Adipose Tissue Mass were measured with bioimpedance spectroscopy using a body composition monitor (Fresenius Medical Care AG & Co KGaA).

Renal Hemodynamics

Renal vascular resistance was calculated as mean arterial pressure/RBF. Filtration fraction was calculated as GFR/renal plasma flow. Afferent and efferent arteriolar resistance were calculated using the Gomez equations [46].

Statistics

Data following a normal distribution was calculated with parametric statistics. Paired data were compared with either paired 2-tailed *t* test or ANOVA. Nonparametric statistics were applied if variables were not normally disrupted. Paired comparisons were compared with Wilcoxon Signed Rank test or Friedman test. Statistics were performed using STATA (version 18.0; StataCorp LLC).

Experimental Procedure

Prior to Examination

Fluid intake was standardized from 4 days prior to the first examination day till the last examination day in each treatment period. Each participant was encouraged to drink at least 2 L of water per day, and 2 cups of coffee or tea daily was allowed, except for 8 hours prior to the examinations. Alcohol or soft drinks were prohibited in this period. The use of mouthwash products was prohibited throughout the study period. Furthermore, in each treatment period, participants were encouraged to adhere to their usual diets from 4 days prior to the first examination and till the last examination. Participants were not required to fast prior to the examination but did not eat throughout the examinations.

Examination Day: University Clinic in Nephrology and Hypertension, Gødstrup Hospital

Participants were set to meet at 8 AM, having ingested their usual medication and the study medication. First, participants emptied their bladder, body weight was measured, and they rested in a chair for 30 minutes. A pregnancy test was performed on fertile women. Then, a PVC was inserted and the Mobil-O-Graph was placed on the upper arm, opposite the PVC. At time point 0 blood samples were drawn and a bolus injection of ^{99m}Tc-DTPA was given (Figure 2). After this, the ^{82}Rb-PET/CT scan was performed. Two successive body

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composition monitor measurements were done within the first 2 hours of the examination day.

Figure 2. Schematic illustration of the examination day at Gødstrup Hospital. 82Rb-PET/CT: ^{82}Rubidium positron emission tomography/ computed tomography; ^{99m}Technetium-diethylene-triamine-pentaacetate (^{99m}Tc-DTPA); BCM: body composition monitor.

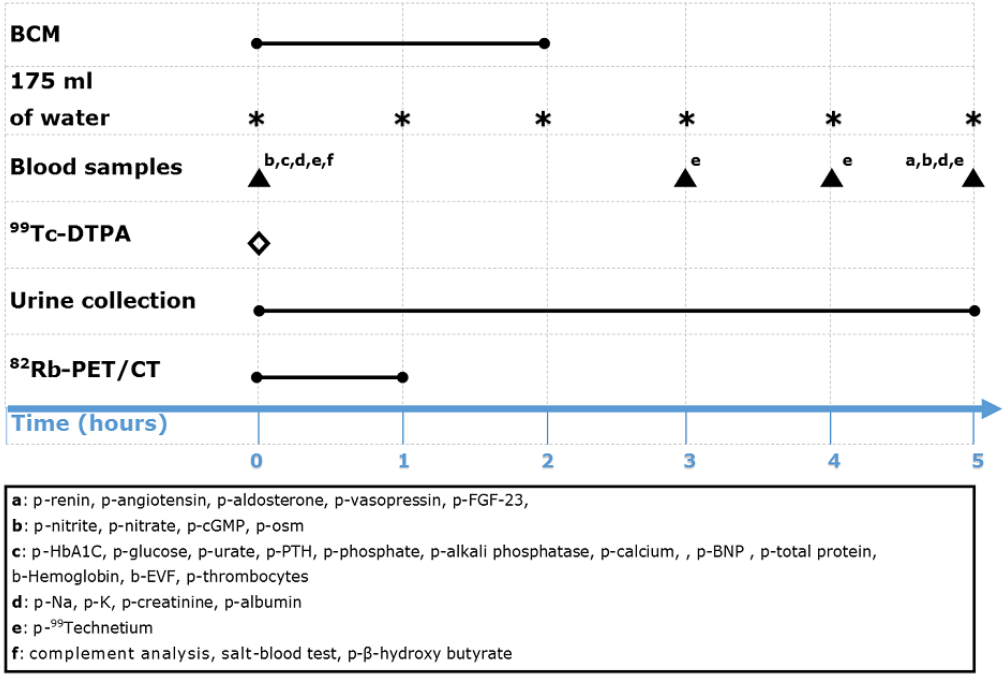

Urine was collected at 2 and 5 hours and if additional voiding was necessary. All urine, except the first void, was pooled and analyzed. From the first void, 50 mL of fresh spot urine was collected, a protease inhibitor was added, and the sample was frozen for later exosome analyses. Two mL of spot urine, also from the first void, was frozen for analysis of complement factors. Blood samples were drawn at 3, 4, and 5 hours. At the end of the examination day, body weight was measured again. The Mobil-O-Graph was removed by the participant 24 hours after mounting. During the entire examination day, participants were to rest in a bed or on a chair. Voiding was done standing or sitting. Participants were given 175 mL of water each hour from time point 0 till the end of the examination day.

Examination Day: Department of Renal Medicine, Aarhus University Hospital

The strain gauge plethysmography was performed at the Department of Renal Medicine, Aarhus University Hospital (Figures 3 and 4). Participants had taken their usual medication and the study medication on the morning prior to the examination. Participants were placed in a supine position in a room where the temperature was kept fixed at 25 °C. The brachial artery was then cannulated with a 27-gauge needle and kept from clotting by a slow infusion of isotonic saline. The strain gauge was placed on the broadest part of the forearm, a venous occlusion cuff was placed on the upper arm, and an arterial occlusion cuff was placed at the wrist. After 30 minutes of saline infusion, baseline measurements were recorded (8 readings were performed per measurement). ACh was infused in increasing concentrations at 5-minute intervals. Measurements were recorded at each concentration. After the last measurement, saline was infused for another 30 minutes. Afterward, isotonic glucose was infused for 5 minutes, and new baseline measurements were recorded. SNP was now infused in increasing concentrations again at 5-minute intervals, with measurements done at each concentration. Arterial circulation to the hand was interrupted during infusion. When the last measurement had been performed, the infusion was stopped, the needle was removed, and the examination day ended.

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Figure 3. Schematic timetable of the strain gauge plethysmography experimental protocol using ACh. ACh: acetylcholine; SNP: sodium nitroprusside.

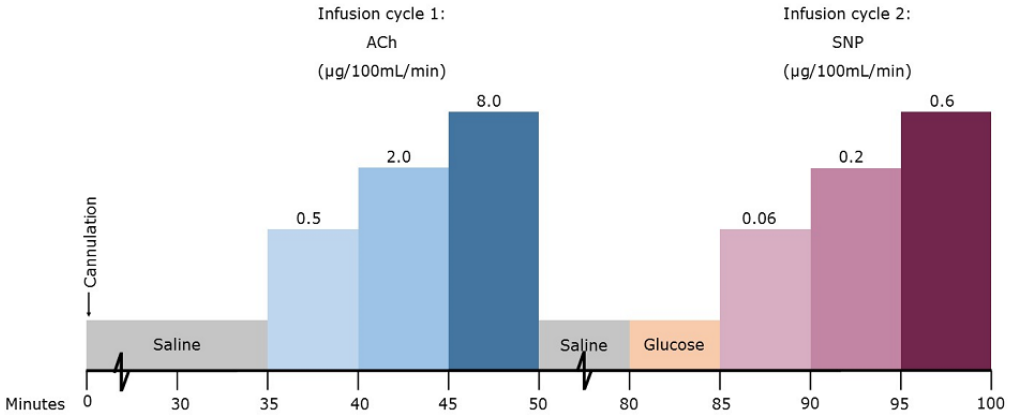

Figure 4. Schematic timetable of the strain gauge plethysmography experimental protocol using CCh. CCh: carbachol; SNP: sodium nitroprusside.

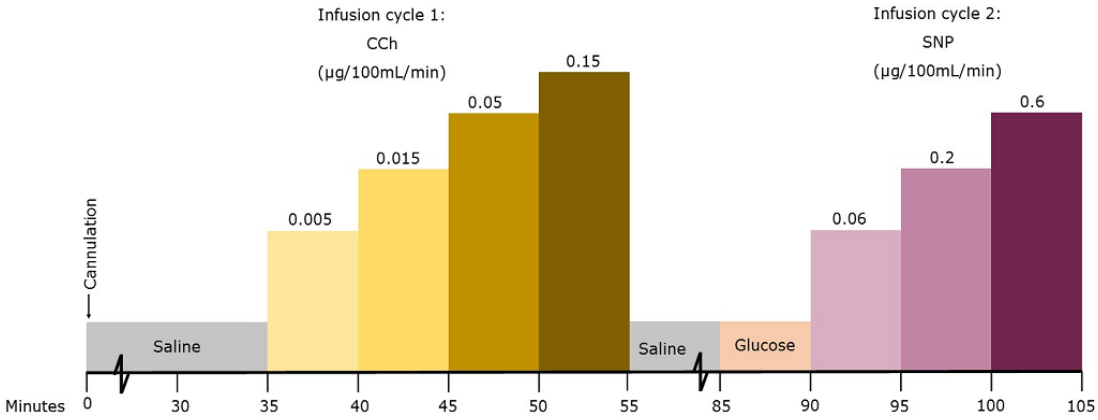

Due to delivery issues, ACh was replaced with carbachol (CCh) after the first 23 participants had been examined. Two participants, both in the DM2 and CKD group, had their first examination done with ACh and the second with CCh. The remaining examinations were done entirely with CCh.

Ethical Considerations

All 3 studies were approved by The Central Denmark Region Committees on Health Research Ethics (cases: 1-10-72-214-20, 1-10-72-339-20, and 1-10-72-340-20, respectively) and The Danish Medicines Agency (EU Clinical Trials Register: 2019-004303-12, 2019-004447-80, and 2019-004467-50) and were conducted in accordance with the Declaration of Helsinki 2013. Informed and signed consent was obtained from all participants. The study was monitored by the Good Clinical Practice (GCP) Unit of Aarhus and Aalborg University Hospitals. All the data have been deidentified. Participants could be compensated for travel expenses related to the studies.

Results

Approval from the regulatory agencies was obtained for the first study (DM2 and preserved kidney function) by October 2020. Recruitment began in April 2021. Approval for the remaining studies was obtained by May 2021 and recruitment began in March 2022. The inclusion of participants for all studies was completed by September 2022. Examinations started in August 2021 and were completed (last patient, last visit) by December 2022. In total, 49 participants completed the project: 16 in the DM2 and preserved kidney function study, 17 in the DM2 and CKD study, and 16 in the nondiabetic CKD study. Data analysis is currently ongoing. So far, no results from the project have been published.

Discussion

Future Perspectives

In this paper, we present the background, hypothesis, design, and methodology of a project consisting of 3 RCTs examining the effects of the SGLT2i empagliflozin versus placebo on a wide range of parameters in different patient populations. This will hopefully provide important information on the mechanisms underlying the beneficial effects of SGLT2is and is the first project to examine both patients with and without diabetes and with and without CKD using the same experimental setup. To our knowledge, very few mechanistic studies have examined SGLT2is in a CKD population.

We use a novel method for estimating RBF by using ^{82}Rb-PET/CT. Compared with measuring effective renal plasma flow (ERPF) with para-aminohippuric acid (PAH) clearance, a method often used in other studies examining hemodynamic effects of SGLT2is [20,23,47], flow estimation with ^{82}Rb-PET/CT can be performed much quicker (in less than half an hour) without the need for blood or urine samples and allows for estimation of single kidney RBF. Furthermore, the effective

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radiation dose of a single scan is limited (≈1 milliSievert [mSv]). There is an ongoing discussion around whether our method in fact reflects RBF or rather RPF. This should be taken into account when calculating intrarenal hemodynamics since the calculations rely on which parameter is used. However, the method has proven both precise and reliable when evaluating relative changes in kidney perfusion, which is what we assess in this project [43,44].

Vascular function and SGLT2is have been studied widely, as specified in the introduction, though mainly by flow-mediated dilation [34,35]. The venous occlusion strain-gauge plethysmography gives a more in-depth examination of the potential mechanisms at play by measuring both endothelial-dependent and independent vasodilation.

A clear strength of our project is the robust, randomized, placebo-controlled, crossover design. We examine different patient populations using the exact same design, allowing for comparison of effect between groups. Furthermore, we investigate a number of different variables, allowing for different mechanisms to be examined. With the current updated guidelines, all 3 examined groups represent patient populations who would be offered SGLT2is in a clinical setting, which adds to the generalizability of our results. It is important to note that inclusion in the DM2 and CKD group did not require a diagnosis of diabetic nephropathy, so participants could potentially have kidney disease or other etiologies. We used 10 mg of empagliflozin and not the 25-mg dose, since this was the dose used in the EMPA-KIDNEY study and since both doses have equivalent effects on both renal outcomes and eGFR decline [8].

Limitations

Our project has several limitations: one being the small study sample sizes, increasing the risk of the studies being underpowered for detecting changes in secondary end points. In addition to being a strength, examining multiple mechanisms of action can be a limitation, since it increases the risk of type 1 errors; thus, most of our secondary end points should be interpreted as exploratory. Our inclusion criteria are broad by design, mainly to reflect a real-world patient population that could potentially be prescribed SGLT2is, but the broad criteria make for a more heterogeneous study population and increase the risk of heterogeneity of the outcome effects. Despite being a well-known risk factor for disease progression in both DM2 and CKD [48], we did not make albuminuria an inclusion criterion. We chose this approach because albuminuria was not an inclusion criterion for all patients in either the EMPA-REG OUTCOME, DECLARE-TIMI 58, or EMPA-KIDNEY trial [49-51], although it was in the CREDENCE and DAPA-CKD trials [9,12]. By allowing the inclusion of patients without albuminuria, we risk including patients at low risk where treatment benefits could be less pronounced. Furthermore, patients were not fasting before examinations, nor did we take steps to ensure stable blood glucose levels throughout the examination days. This was considered, but discarded for feasibility reasons, but it does increase the risk of our outcomes being affected by confounders. Adding to this was the fact that we allowed for the substitution of antidiabetic treatment in the run-in period if SGLT2is were paused. This was done to ensure glycemic control during the trial period but may have introduced further confounding. This methods paper was written after data collection was completed. While it would have been optimal to publish it prior to inclusion, we judge this to be a precise description of the methods used and it will provide a valuable framework for future articles, detailing exactly how our results were obtained and what considerations lay behind them.

Conclusions

This paper describes the rationale, design, and method used in a project consisting of 3 double-blind, crossover RCTs, examining the effects of empagliflozin versus placebo in patients with DM2 with and without CKD and patients with nondiabetic CKD, respectively.

Acknowledgments

This project is supported by The Augustinus Foundation, The Research Foundation of the Central Denmark Region, The Medicine Fund of the Danish Regions, The Research Fund of the Hospital of Western Jutland, and Boehringer-Ingelheim, who delivered the study medication, including placebo.

Boehringer-Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to Boehringer-Ingelheim substances, as well as intellectual property considerations. Boehringer-Ingelheim had no role in the design of the study nor will they have a role in the analysis and interpretation of results.

Authors' Contributions

All authors contributed to the manuscript. SFN, JNB, NHB, and FHM designed the project. SFN drafted the manuscript. SFN, CLD, JNB, NHB, and FHM edited the manuscript. All authors approved the final manuscript. Generative artificial intelligence was not used in any portion of the manuscript.

Conflicts of Interest

FHM disclosed advisory board participation and speaker honoraria from Boehringer-Ingelheim and AstraZeneca. JNB disclosed advisory board participation for AstraZeneca, Boehringer, and Bayer. SFN, CLD, and NHB have no conflicts of interest to declare.

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Abbreviations

^{82}Rb: ^{82}Rubidium
^{99m}Tc: ^{99m}Technetium
ACh: acetylcholine
AQP2: aquaporin 2
CCh: carbachol
cGMP: cyclic guanosine monophosphate
CKD: chronic kidney disease
CL-K1: collectin kidney 1
CL-L1: collectin liver 1
CT: computer tomography
CVD: cardiovascular disease
DM2: type 2 diabetes mellitus
DTPA: diethylene-triamine-pentaacetate
EBW: extracellular body water
eGFR: estimated glomerular filtration rate
ELISA: enzyme-linked immunosorbent assay
ENaC: epithelial sodium channel
ERPF: effective renal plasma flow
FGF23: fibroblast growth factor 23
GFR: glomerular filtration rate
HbA_{1c}: hemoglobin A_{1c}
IL-6: interleukin 6
KIM-1: kidney injury molecule-1
MASP: mannan-binding lectin serine protease
MBL: mannan-binding lectin
MBq: megabecquerel
mSv: milliSievert
NCC: sodium chloride symporter channel
NGAL: neutrophil gelatinase-associated lipocalin
NKCC: sodium-potassium-chloride cotransporter
NO: nitric oxide
NSAID: nonsteroidal anti-inflammatory drugs
PAH: para-aminohippuric acid
PET: positron emission tomography
PVC: peripheral venous catheter
PWV: pulse wave velocity

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RBF: renal blood flow
RCT: randomized controlled trial
RVR: renal vascular resistance
SGLT2: sodium-glucose-cotransporter 2
SGLT2i: sodium-glucose-cotransporter 2 inhibitor
SNP: sodium nitroprusside
TNF-α: tumor necrosis factor-α

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Protocol

The Effects of a Dietary Supplement (PediaFlù) Plus Standard of Care in Children With Acute Tonsillopharyngitis/Rhinopharyngitis: Protocol for a Randomized Controlled Trial

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Abstract

Background: A dietary supplement containing *Pelargonium sidoides* extract, propolis, zinc, and honey has been recently developed and proven to be an effective adjuvant in clinical practice for seasonal diseases and the treatment of respiratory tract disorders.

Objective: This trial aims to verify the efficacy of the tested dietary supplement in a pediatric population with acute tonsillopharyngitis/rhinopharyngitis (ATR).

Methods: The trial includes children aged between 3 and 10 years with ATR ≤48 h, a negative rapid test for beta-hemolytic streptococcus or culture identification of nasal and/or pharyngeal exudates, and SARS-CoV-2 infection. The dietary supplement tested is an oral solution already on the market based on Pelagon P-70 (equivalent to *Pelargonium sidoides* d.e. 133.3 mg/100 ml), propolis, zinc, and honey. The product is administered at 5 ml 3 times a day for 6 days for children younger than 6 years and 10 ml 3 times a day for 6 days for children older than 6 years. The study design is open label, randomized, and controlled, with the tested dietary supplement plus standard of care (SoC) versus SoC alone. Patients are enrolled from 3 sites in Romania. The change in Tonsillitis Severity Score and number of treatment failures (using ibuprofen or high-dose paracetamol as rescue medication) are the primary end points. Based on the Tonsillitis Severity Score and the 2-sample comparison of the means formula with a 5% significance level, 80% power, and a minimally clinically important difference of 2 (SD 3.85) points, 120 patients are required. To account for potential screening failures and dropouts, we need to screen a population of approximately 150 children.

Results: Patient enrollment began on June 3, 2021 (first patient's first visit), and ended on August 12, 2021 (last patient's last visit). The data collection period was from June 3, 2021, to September 16, 2021. The study was funded in February 2023. Data analysis is currently ongoing (April 2024). We expect the results to be published in a peer-reviewed clinical journal in the third quarter of 2024 and presented at scientific meetings in the last quarter of 2024.

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Conclusions: The data from this trial may help identify new adjuvant treatments for children with ATR when streptococcal infection is excluded by a negative rapid test, thereby avoiding unnecessary antibiotic administration.

Trial Registration: ClinicalTrials.gov NCT04899401 https://clinicaltrials.gov/study/NCT04899401

International Registered Report Identifier (IRRID): DERR1-10.2196/53703

(JMIR Res Protoc 2024;13:e53703) doi:10.2196/53703

KEYWORDS

dietary supplements; tonsillitis; pharyngitis; nasopharyngitis; Pelargonium; propolis; zinc; severity score

Introduction

Background

Acute tonsillopharyngitis/rhinopharyngitis (ATR) is a leading cause of pediatric consultations among children and adolescents [1]. Viruses are the primary causative agents of ATR [2], whereas bacterial infection is the cause in only a small percentage (approximately 30%) of cases [2,3]. ATR diagnosis primarily relies on clinical evaluation and is confirmed using cell culture or rapid antigen tests. The predominant symptoms of virus-induced ATR include sore throat, dysphagia, cervical lymphadenopathy, and fever. Antibiotic treatment is exclusively recommended for bacterial tonsillopharyngitis as it encourages antibiotic resistance and can cause adverse reactions [4,5]. Therefore, the focus is on symptom control and acceleration of recovery through analgesia, hydration, and rest [6], with the necessity for new treatment approaches coming to light.

Pelargonium sidoides has proven efficacy in managing respiratory tract disorders [7-13]. A long tradition of use and literature also supports the use of zinc, propolis, and honey to prevent seasonal diseases and as adjuvants during the acute phase of the common cold [14,15]. These findings underscore the potential of these natural remedies for treating colds. Therapeutic zinc therapy may be effective in inhibiting viral replication and reducing the duration of symptoms associated with the common cold [16]. The flavonoid content of propolis contributes to its antibacterial, antiviral, and anti-inflammatory properties [17]. A systematic review and meta-analysis demonstrated that honey is more effective than usual care in improving symptoms of upper respiratory tract infections (URTI) [18].

Rationale

A recent review of the medical literature indicates that the median incidence of streptococcal pharyngitis is 1764 per 100,000 children [19]. Considering the small subset of patients who experience streptococcal infections and that these cases rarely develop late complications, such as rheumatic fever, the widespread prescription of antibiotics for sore throats has become increasingly criticized. These opinions are supported by the Committee on Infectious Diseases of the American Academy of Pediatrics [20], which recommends antibiotic therapy only for children with pharyngitis clearly caused by group A streptococcus. Therefore, new therapeutic strategies are needed for the first-line treatment of acute respiratory tract infections beyond the strict indication for antibiotic treatment, in addition to the purely symptomatic treatment recommended in various guidelines.

Recently, Pediatrica Srl (Livorno, Italy) developed PediaFlù, a dietary supplement for the pediatric population (DSPP) specifically designed for the well-being of the respiratory tract, containing an extract of *Pelargonium sidoides*, propolis, zinc, and honey. Its efficacy has been proven on a bibliographic basis as required for dietary supplements.

Its efficacy has been proven on a bibliographic basis, as is required for dietary supplements. The product is currently marketed as an adjuvant for seasonal illnesses and could now be evaluated as a potential add-on to the standard of care (SoC) for children with ATR.

Objectives

This clinical trial aims to verify and confirm the positive results observed in pediatric clinical practice. The study is designed to evaluate the effectiveness and safety of this DSPP in combination with SoC for 6 days compared to SoC alone in children with ATR. The visual abstract is presented in Multimedia Appendix 1.

Methods

Overview

The project team is composed of the scientific supervisor of the study, who prepared the outline of the study protocol, and 3 investigators in Timi oara (Romania), coordinated by the Academic Research Organization Department of Clinical Trials of the University of Medicine and Pharmacy Victor Babes.

The team outlined the following points: (1) ATR is diagnosed through a clinical evaluation of symptoms, including sore throat and catarrhal angina, and complaints lasting ≤48 h; (2) a negative result from a rapid test for group A beta-hemolytic streptococcus (GABHS) or culture, and the identification of nasal and/or pharyngeal exudates, along with a negative SARS-CoV-2 test are mandatory; (3) the Tonsillitis Symptom Score (TSS) should be greater than or equal to 8 points; and (4) patients should undergo follow-up for 6 days after the onset of ATR.

The study team submitted the study protocol to Pediatrica Srl. The company provided the study team with dietary supplements and a partial grant to conduct a study on ATR among children. The agreement between the parties specified that the sponsor would have no role in the study design and planning or the collection, analysis, and interpretation of data in a future manuscript reporting the results.

Finally, the team selected Opera CRO, a Tigermed company (Timisoara, Romania) as the contract research organization

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(CRO) responsible for the logistics and management of the study (protocol submission, project management, site monitoring, data management, and statistical analysis).

Ethical Considerations

A total of 3 centers in Romania are participating in this study. Following approval by the National Agency for Medicines and Medical Devices (Agentia Nationala a Medicamentului si a Dispozitivelor Medicale), the protocol was approved by the local ethics committee (EC) Cabinet Medical Dr Cristian Radu Matei in O elu Ro u (Romania) on April 23, 2021. The remaining 2 Romanian ECs in Timisoara approved this study a few days later. Cabinet Medical Medicina de Familie Dr. Morariu Bordea EC granted approval on April 27, 2021, whereas the Cabinet Medical Dr. Herteg Dorina EC provided approval on the same day. The EC approvals are reported in Multimedia Appendix 2.

Informed consent from parents of each potentially eligible child followed the International Council for Harmonization-Good Clinical Practice (ICH-GCP) and Declaration of Helsinki guidelines. A patient information sheet, approved by the local EC and written in plain Romanian, is provided that outlines the study purpose, procedures, and the food supplement's nature and safety profile. It also outlines visit frequency, procedures, and potential outcomes. This document ensures that the parents understand the risks, benefits, and discomforts. The sheet is regularly updated with product and study information that could be available in the future. Parents are informed about the voluntary nature of their child's participation in the study, emphasizing their right to withdraw at any time during medical care without repercussions. They are notified that no compensation is offered for participation and that insurance coverage is provided by the sponsor in case of trial-related injuries. Additionally, parents are made aware that their children's medical records may be accessed by the sponsor, CRO personnel, and regulatory authorities as per relevant laws and regulations, with personal information maintained in a confidential database.

Informed consent is obtained after allowing participants sufficient time to review the information and ask questions. The written consent process entails both the parent and investigator manually writing and signing their names on 2 copies of the consent form. One copy of the signed consent form and 1 copy of the signed informed consent form (ICF) are provided to the parents, while the second copy of the original signed forms is retained in the on-site study file. The study adheres to current General Data Protection Regulations (GDPR). Specific procedures for data collection, anonymization, and the possibility of data sharing with other researchers in aggregated and anonymous form are outlined in a dedicated document (GDPR form) written in the local language. This document is provided to parents for approval and signature before the study commences. The physician in charge of each center bears responsibility for managing patient data at the clinical site in compliance with the GDPR.

The study is registered at Clinical Trials.gov (NCT04899401).

Study Design

This study is a multicenter, controlled, open-label, randomized parallel-group superiority trial. The study formulates a superiority hypothesis to assess whether symptoms in patients with ATR can be improved by a 6-day course of DSPP plus SoC compared with SoC alone.

Screened patients who meet all eligibility criteria for the study are randomly assigned to either study arm, SoC plus DSPP or SoC alone, receive sufficient products to complete the study, and are instructed on how to adhere to the assigned treatment.

Randomization is conducted using an internet-based platform provided by the CRO, which is available 24 hours a day.

Patients are allocated in a 1:1 ratio to the control group receiving SoC or the interventional group receiving DSPP plus SoC.

The allocation is carried out by a noninvolved staff member and the patients. The patients' parents are not blinded to the process.

Study Setting and Patient Recruitment

The 3 study centers were selected for their extensive experience in ATR treatment in children and their wide catchment area for patients with this condition. The coordinating center, Cabinet Medical Medicina de Familie Dr Maria Morariu Bordea, is situated in Timi oara (Romania), while the other 2 centers are satellite sites: Cabinet Medical Dr Dorina Herteg in Timi oara and Cabinet Medical Dr Cristian Radu Matei in Otelu Rosu (Table 1). At each center, a principal investigator is responsible for the identification, recruitment, data collection, and completion of case report forms (CRFs), as well as for checking patients' compliance with the protocol during the study period.

Only children who were accompanied by their parents or caregivers to the participating clinical sites during the study period were enrolled in the study. No flyers, social media, or other advertising methods were used to invite patients to participate in the study.

The time required to define the study protocol and prepare relevant documents for study submission (informed consent, patient information sheet, and CRF) was longer than originally planned. As a result, EC approval was received in April, and the first patient enrollment at the 3 sites occurred between June 3 and June 21, 2021, during the summer period. Even if viral infections are less prevalent during this period, the investigators were able to complete enrollment in only 3 months, with the last patient visit occurring on September 16, 2021

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Table 1. Centers involved in the study.

Center type	Investigators[a] (study coauthors)	Hospital	Town	FPFV[b] and LPLV[c]
Coordinator center	MMB	Cabinet Medical Medicina de Familie Dr Maria Morariu Bordea	Timisoara	June 21, 2021, and September 16, 2021
Satellite center	DH	Cabinet Medical Dr Dorina Herteg	Timisoara	June 3, 2021, and September 16, 2021
Satellite center	CRM	Cabinet Medical Dr Cristian Radu Matei	Otelu Rosu	June 7, 2021, and September 16, 2021

[a]The scientific supervisor of the study is author FC.

[b]FPFV: first patient's first visit.

[c]LPLV: last patient's last visit.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this study are outlined in Textbox 1.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Male and female children aged 3 to 10 years
- Acute tonsillopharyngitis/rhinopharyngitis (ATR; sore throat, catarrhal angina), duration of symptoms ≤48 h
- Negative with rapid test for group A beta-hemolytic streptococcus (GABHS) or culture and identification of nasal and/or pharyngeal exudates; negative for SARS-CoV-2 infection
- Tonsillitis Symptom Score (TSS) ≥8 points
- Both parents are willing to provide written informed consent prior to participation in the clinical trial.
- Children older than 6 years are able the ability and willingness to provide written informed consent.

Exclusion criteria

- Evidence of lacunar or follicular angina
- More than 2 past episodes of tonsillitis in the previous 12 months
- Mandatory indication for antibiotic therapy (eg, abscess, septic tonsillitis, status postrheumatic fever, poststreptococcal glomerulonephritis, and minor Sydenham chorea)
- Treatment with antibiotics within 4 months prior to study enrollment
- Hemorrhagic diathesis increases and chronic illnesses (eg, severe heart, kidney, or liver disease, and primary or secondary immunodeficiencies)
- Close contact history with individuals infected with SARS-CoV-2 within 10 days before showing symptoms
- Known or suspected allergic reactions to any study medication
- Concomitant therapy that may affect study results or have known interactions with study medications (such as coumarin derivatives)
- Participation in another clinical trial within 3 months before enrollment

Intervention

Tested Product

The DSPP tested is a dietary supplement already on the market; its composition is based on Pelagon P-7 (equivalent to *Pelargonium sidoides* d.e. 133.3 mg/100 ml), PropolNext Plus (equivalent to propolis d.e. 7.7 mg/100 ml), zinc (13.3 mg/100 ml), and honey (5.5 g/100 ml). DSPP is supplied as an oral solution, and the instructions for use provide detailed information on its dosage, at 5 ml 3 times a day for children under 6 years for 6 days and 10 ml 3 times a day for children over 6 years of age for 6 days (oral administration for both age groups).

Pelargonium sidoides [11] has demonstrated its efficacy in standard clinical practice and medical literature. A double-blind, placebo-controlled clinical trial was conducted in 124 pediatric patients (60 in the active ingredient group and 64 in the placebo group) with acute nonstreptococcal tonsillopharyngitis, wherein an extract from the roots of *Pelargonium sidoides* was administered for 6 days in comparison with a placebo. The primary efficacy variable was the change in the total TSS from baseline on day 4. Treatment with the product was shown to reduce the severity of symptoms and shorten the duration of

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illness compared with placebo (*P*<.001) [12]. In addition, *Pelargonium sidoides* extract is effective and well-tolerated in the treatment of acute bronchitis in children and adolescents outside strict antibiotic indications [10].

For safety reasons, the investigator was able to stop the administration of DSPP at any time and prescribe other therapies necessary for patient health.

Outlining the SoC

In this study, all patients are treated according to the SoC: both children assigned to the control group (SoC only) and those assigned to an intervention group (DSPP plus SoC) for ATR. The products and treatments administered are outlined in Textbox 2.

Textbox 2. The products and treatments administered as part of the standard of care (SoC).

- Nasopharyngeal lavage by hydration with drinking fluids to support the excretion of body fluids, aspiration of secretions, NaCl solution for nasal irrigation, nasal sprays with seawater, and nasal spray with active ingredients (to be used only when indicated by the physician)
- Throat sprays with benzydamine hydrochloride (Tantum Verde, CSC Pharmaceuticals, 0.15%), pediatric use according to the package insert (each spray corresponds to 0.17 ml of solution), for 6 days:
- Children (under 6 years of age): 1 spray per 4 kg of body weight, up to a maximum of 4 sprays at one time, 2 to 6 times daily
- Children (6 to 12 years): 4 sprays 2 to 6 times daily
- Paracetamol (acetaminophen) (Panadol, GlaxoSmithKline, 120 mg/5 ml): as antipyretic (fever is defined as body temperature >38.5 °C), as needed, 10 mg/kg/dose, every 6 to 8 hours, according to the leaflet; maximum dosage 30 mg/kg/day

Rescue Medicine and Interventions Not Permitted

Ibuprofen and paracetamol are the only treatments allowed in cases of need as rescue medicines to relieve disabling symptoms of ATR, when needed, as follows: (1) ibuprofen (Algin Baby, 100 mg/5 ml) per os; (2) high dose (>30 mg/kg/day) paracetamol (Panadol, 120 mg/5 ml) per os. Treatment failure was defined as the use of rescue medication.

Coumarin-based products and antibiotics are not permitted during the study period.

Potential Risks

The potential risks to children involved in the study are related to the administration of oral DSPP and rescue medicine (paracetamol). In this section, we do not evaluate the potential risks of SoC because this treatment should be administered only for the benefit of the patient and independently of this interventional clinical trial.

In addition to its decades-long presence on the international market, the efficacy and safety of *Pelargonium sidoides* extract in children's respiratory pathologies have been widely demonstrated in several placebo-controlled clinical trials and open clinical studies. A recent systematic review [21] evaluated the safety profile of *Pelargonium sidoides* extract based on 29 clinical trials and postmarketing surveillance studies completed by February 2010. Among all the studies, 11 enrolled only children, 14 enrolled only adults, and 4 enrolled both children and adults. Across all studies, a total of 10,026 patients and 31 healthy participants were included. Of these, 8005 individuals were exposed to EPs 7630, 1883 to placebo, 139 to the comparator acetylcysteine (bronchitis), and 30 to symptomatic therapy not otherwise specified. In total, 3939/10,026 (39.3%) patients were infants, children, or adolescents up to the age of 18 years, among whom 3243 were exposed to *Pelargonium sidoides* extract and 527 to placebo. No serious adverse drug reaction was reported in this large patient population, confirming the *Pelargonium sidoides* extract's optimal safety profile.

Given the limitations of the use of paracetamol (occasional use only, with restrictions on dosage and duration, and exclusion of individuals with renal or hepatic impairment), the associated risk is expected to be minimal. However, the potential risks include hypersensitivity reactions (paresthesia or pruritus transient rash), thrombocytopenia (generally asymptomatic, rarely bleeding or bruising, blood in urine and feces, and black and soft stools), dermatitis, agranulocytosis, oligoanuria, renal colic, and hepatic impairment.

The allowed dosage of ibuprofen as rescue medication in this trial is very low. In addition, prolonged treatments are not permitted, and preexisting cardiovascular, renal, and hepatic impairments are in the exclusion criteria. The remaining possible risks of nonsteroidal anti-inflammatory drugs (NSAIDs) are typical gastrointestinal side effects like bleeding, ulceration, abdominal pain, diarrhea, vomiting urinary tract side effects (cloudy urine, oliguria), hypersensitivity reactions (pruritus, itching skin), unusual bleeding, and weight gain.

Statistical Methods Analysis

Trial Hypothesis or Pass/Fail Criteria

The primary hypothesis is that the minimal clinical difference between the test group (DSPP plus SoC) and the control group (SoC only) will result in a 2-point decrease in mean TSS after 6 days of treatment.

The null hypothesis of this study is that treatment with DSPP plus SoC will not significantly improve the symptoms of the treated patients compared to the control group (treated with SoC alone).

A greater improvement in TSS in the DSPP-treated group from baseline to day 6 of treatment supports the alternative hypothesis and demonstrates the efficacy of the supplement. The overall type I error rate remains at 5%.

Sample Size Calculation

The sample size is calculated based on the primary outcome of the TSS and the results of a similar study [12].

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Based on the sample size formula for comparing 2 means (2-sample) at a 5% significance level, 80% power, and a minimum clinically important difference of 2 (SD 3.85 points), 120 patients are required. To obtain 120 evaluable participants, approximately 150 will be screened (including potential screening failures and estimated dropout patients). Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) 2010 flow diagram. DSPP: dietary supplement; SoC: standard of care.

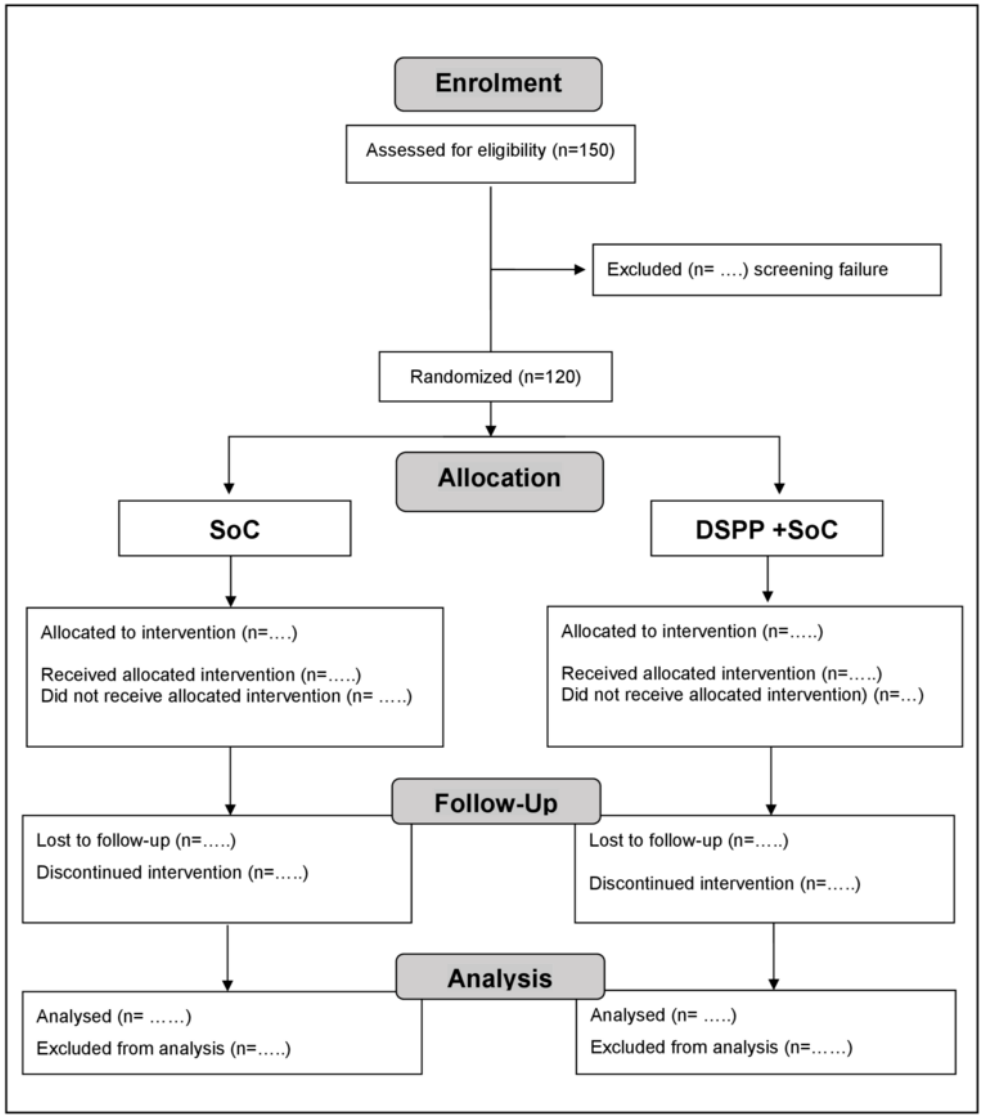

Statistical Analyses

All statistical analyses are performed using R statistical software (version 4.1.0; R Foundation for Statistical Computing). The final analysis will be performed after all patients have completed the study, all queries have been resolved, and the database has been locked.

The overall type I error rate is maintained at 5%. All tests are 2-sided. Data from unscheduled visits are excluded from the analyses.

Statistical analyses are performed for all patients who completed the study without protocol deviation, which is considered to affect the assessment of key variables. The quality and completeness of the collected data are assessed before data analysis. If a patient has missing information for 1 or more variables, the missing data are not replaced, even after the queries are resolved. If a patient violates the inclusion/exclusion criteria, the corresponding data are excluded from analysis.

Quantitative (ie, demographic) variables, if normally distributed, are described by mean and SD; nonnormally distributed variables are described by median and IQR. The Student *t* test and Mann-Whitney U test are used to perform comparative analyses according to the distribution of these variables. Factorial analysis of variance can also be used to evaluate any interactions between quantitative variables and linear progression models to relate possible confounding biases to the independent variables.

Categorical variables are described using frequencies and percentages, and comparative analyses are performed using the chi-square test.

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Evaluation Outcomes

Primary Outcomes

The primary efficacy outcomes investigated are the change in TSS and the number of treatment failures.

The TSS is composed of 5 subscores that reflect the nature of acute non-GABHS tonsillopharyngitis as a viral-induced inflammatory URTI: difficulty swallowing, sore throat, increased salivation, pharyngeal erythema, and fever. At the visits, each of the symptoms of difficulty swallowing, sore throat, increased salivation, and pharyngeal erythema is rated by the investigator as severe (3), moderate (2), mild (1), or absent (0). Finally, a fever score is added with the categories <37.5 °C=0, 37.5 °C to <38.5 °C=1, 38.5 °C to <39.5 °C=2, and ≥39.5 °C=3, resulting in a possible TSS range of 0 to 15. The results are compared in terms of absolute change in score from baseline to the final visit, between groups, and within groups. The TSS (total score and subscores) is assessed and scored at each visit.

The number of treatment failures is calculated by comparing the administration of rescue medication (paracetamol >30 mg/kg/dose or ibuprofen 100 mg/5 ml) between the 2 groups.

The primary safety outcome is the incidence of adverse events (AEs) and serious adverse events (SAEs) during the study.

Secondary Outcomes

The following outcomes are collected:

First, the Investigator Global Assessment of Efficacy (IGAE). It uses a 4-point scale ranging from 1 (excellent to 4 (poor), and the comparison is between groups at the end of the study.

Second, the Patient Global Assessment of Efficacy (PGAE). The outcome is rated by patients on a 5-point scale, ranging from 1 (very satisfied) to 5 (very unsatisfied). A comparison is made between groups at the end of the trial.

Third, the Investigator Global Assessment of Safety (IGAS). This assessment is made by the investigators using a 4-point scale ranging from 1 (very good safety) to 4 (poor safety). A comparison is made between groups at the end of the trial.

Compliance is also assessed between the groups at the end of the study.

Study Procedures and Visits

Prior to each study procedure, each patient and their parent or legal guardian are informed of the purpose and nature of the study, as well as the potential risks and benefits. They are also asked to give their consent by signing an ICF.

The study timeline is presented in Table 2.

A total of 4 visits are planned for the study (Figure 2). At each visit, an eligibility assessment (or confirmation) and physical examination (including disease assessment and TSS score evaluation) are performed, and concomitant medications and AE/SAE are assessed and recorded.

In addition, at the screening visit (visit 1; day –2 to day –1), GABHS and SAR-CoV-2 screening is performed, medical history and demographics are recorded, and parents or legal guardians of the eligible children are asked to sign the ICF. At the baseline visit (visit 2; day 0), each participant's baseline characteristics are recorded, and study products and patient diaries are supplied. The diary is reviewed at the interim visit (visit 3; day 4 of enrollment). At the end-of-study visit (visit 4; day 6 of enrollment), final assessments, symptom and compliance assessments are performed, and the study products and diaries are collected.

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Table 2. Timeline of the study

Time point	Visit 1 (day –2 to –1)	Visit 2 (day 0)	Visit 3 (day 4)	Visit 4 (day 6)
Informed consent	✓			
Inclusion criteria	✓			
Exclusion criteria	✓	✓	✓	✓
Demographics and medical history	✓			
Physical examination	✓	✓	✓	✓
Disease assessment	✓	✓	✓	✓
Rapid test for GABHS[a] or nasal and/or pharyngeal exudate culture plus SARS-CoV-2	✓			
Concomitant treatments	✓	✓	✓	✓
TSS[b]	✓	✓	✓	✓
Product delivery		✓		
Product return				✓
Patient diary delivery		✓		
Patient diary verification			✓	
Patient diary return				✓
Product accountability				✓
IGAE[c]				✓
PGAE[d]				✓
IGAS[e]				✓
Adverse events	✓	✓	✓	✓

[a]GABHS: group A beta-hemolytic streptococcus.

[b]TSS: Tonsillitis Symptom Score.

[c]IGAE: Investigator Global Assessment of Efficacy.

[d]PGAE: Patient Global Assessment of Efficacy.

[e]IGAS: Investigator Global Assessment of Safety.

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Figure 2. Flow chart of the study.

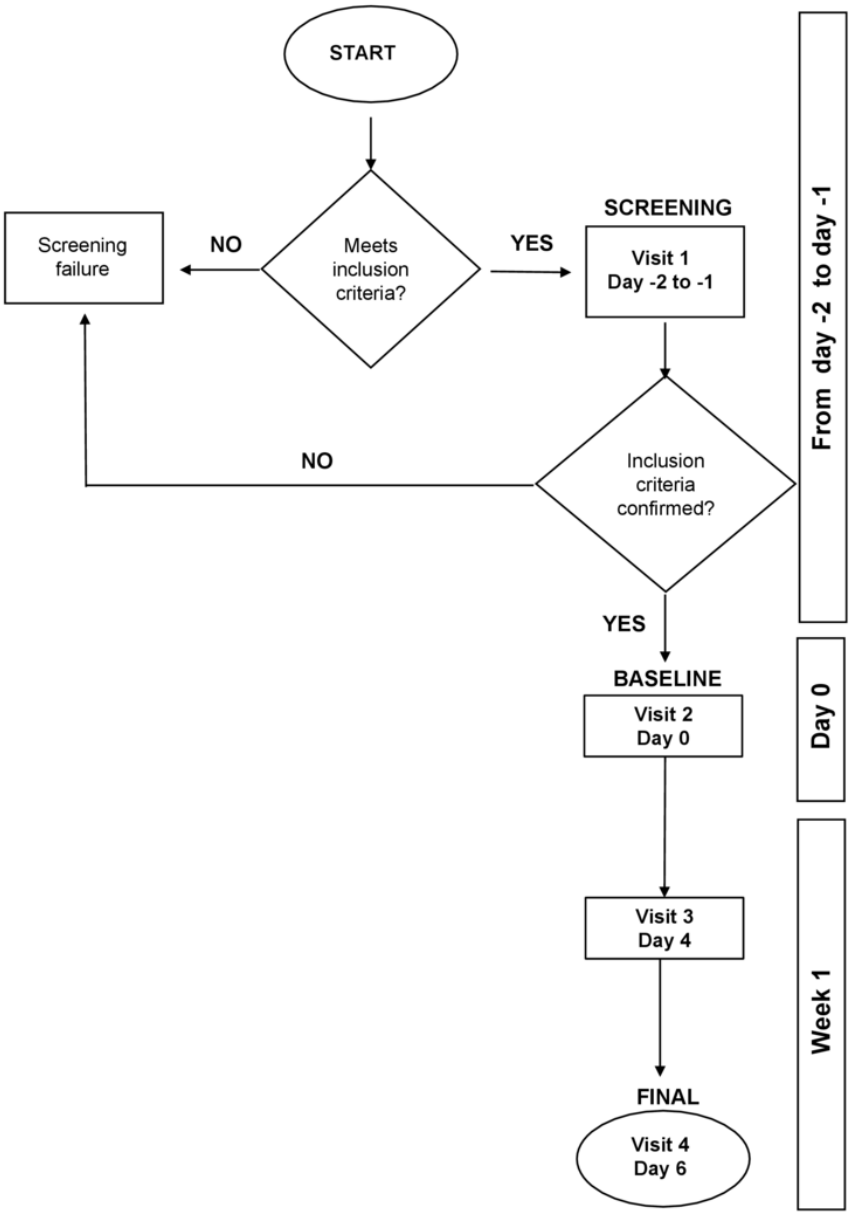

Results

Patient recruitment started on June 3, 2021 (first patient's first visit), and ended on August 12, 2021 (last patient's last visit). The data collection period was from June 3, 2021, to September 16, 2021. The study was funded in February 2023. Data analysis is currently ongoing (April 2024). We expect the results to be published in a peer-reviewed clinical journal in the third quarter of 2024. The results will be also presented at scientific meetings in the last quarter of 2024.

Discussion

Comparison With Prior Works

Physicians and pediatricians recognize that the use of antibiotics for viral pharyngitis may be inappropriate, expensive, and contribute to antimicrobial resistance, in addition to causing adverse reactions (ie, rash, abdominal pain, diarrhea, and vomiting) without medical benefit. As noted by several authors, the balance between modest symptom reduction and potential risks of antimicrobial resistance must be recognized [4]. Thus, new strategies are needed, at least when streptococcal infection is excluded by a negative rapid test, as in this study, where only children with ATR for no more than 48 hours and a negative rapid test for GABHS and SARS-CoV-2 infection were included. In addition, to avoid the inclusion of any participants with bacterial diseases, a negative culture of the nasal/pharyngeal exudate was required.

Limitations of the Study

The main limitation of this study is its open-label and controlled rather than double-blind design. This choice is motivated by logistical and economic reasons.

Conclusions

When developing this study, we paid particular attention to the selection of the primary outcome. This choice was difficult and laborious; however, in our opinion, it is the most qualified point

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of our work. The ideal characteristics of the primary outcome had to: (1) be scientifically robust and already used in clinical trials published in the pediatric literature; (2) be proven to be a sensitive tool capable of highlighting the effectiveness of one treatment over another in trials; (3) have a direct relationship with pediatric clinical practice, represented by clinical objectivity and the detection of patients' signs and symptoms; and (4) be aligned with the objective of confirming the positive results observed by many pediatricians administering DSPP with SoC in their clinical practice for children with viral ATR. A reduction in the total TSS score as the main outcome met these needs.

The TSS is a widely used test in the medical literature [22,23]. Recently, the TSS has also been shown to be a sensitive and reliable tool for measuring the overall clinical effectiveness of treatment. It was shown that in 236 children with ATR [24], the marked reduction in TSS scores after antimicrobial treatment in severe and moderate cases indicated the high efficacy of these treatments for diseases with higher severity. In the same study, mild cases showed a decrease in scores regardless of antimicrobial treatment. Thus, using the outcome results in terms of reduction of the total TSS score will reflect the severity of the disease well and be useful for assessing the clinical course and monitoring and evaluating the effectiveness of treatment during the 6 study days. In addition, the TSS subscores are a direct expression of the symptoms that the pediatrician verifies and measures in the child and, therefore, represent the outcome closest to their sensitivity and daily practice. Finally, to avoid compartmentalizing judgment by reducing it to individual clinical symptoms or signs, we considered the global subjective evaluation by the investigator and parents as secondary outcomes.

It must be emphasized that our goal is not only to demonstrate that DSPP associated with SoC will produce a clinical benefit but also that this administration is accompanied by good DSPP compliance and optimal safety, both of which represent the fundamental requirements for a product to be administered in such young children. In this case, our research hypothesis of associating the use of DSPP with SoC may represent a potential therapeutic alternative in the first-line treatment of acute respiratory tract infections beyond the strict indication for antibiotic treatment, in addition to the purely symptomatic treatment recommended by various guidelines. This research hypothesis should also validate the therapeutic approach of thousands of pediatricians who use this product, marketed as an adjuvant for seasonal illnesses, in daily clinical practice. In fact, initial treatment with DSPP may also be helpful between the patient's presentation and the final decision to administer an appropriate antibiotic, providing the benefit of rapid symptomatic improvement regardless of the bacterial or viral etiology of the respiratory illness.

Because we believe that the confirmation of our research hypothesis may be relevant to the therapeutic practice of many pediatricians, we will make a special effort to disseminate the results of our study. Therefore, as soon as we have completed the process of signing the clinical study report, we will upload the results to ClinicalTrials.gov and prepare an article in accordance with the CONSORT statement and in a format that will allow it to be included in a potential systematic review. This manuscript will be submitted for publication in a peer-reviewed journal and presented as a poster at the scientific meeting. It will also be submitted in parallel to a preprint journal.

Acknowledgments

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Data Availability

The full protocol of the study has been deposited at Protocols.io. The data sets analyzed for this study are available from the corresponding author upon request.

Authors' Contributions

FC, DFB, and SR conceptualized the study. FC, MMB, DH, CRM, SR, and DFB were involved in the methodology. FC, DFB, and SR were responsible for the formal analysis. The investigation during the study was performed by MMB, DH, and CRM. FC, SR, DFB, FS, and CRM wrote the original draft, and DFB, CRM, FS, and GG performed the review and editing of the manuscript. The visualization was created by GG and AC. The project was supervised by FC. DFB, AC, and GG were involved in the project administration. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

DFB and FS are employed at Opera CRO, the contract research organization that managed the study. GG and AC are employed at Pediatrica Srl. FC, SR, MMB, DH, and CRM declare no conflicts of interest.

Multimedia Appendix 1
Visual abstract.

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[PDF File (Adobe PDF File), 677 KB - resprot_v13i1e53703_app1.pdf]

Multimedia Appendix 2
Ethics committees' approvals.
[PDF File (Adobe PDF File), 617 KB - resprot_v13i1e53703_app2.pdf]

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Abbreviations

AE: adverse event
ATR: acute tonsillopharyngitis/rhinopharyngitis
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
CRO: contract research organization
DSPP: dietary supplement for the pediatric population
EC: ethics committee
GABHS: group a beta-hemolytic streptococcus
GDPR: General Data Protection Regulations
ICF: informed consent form
ICH-GCP: International Council for Harmonization Good Clinical Practice
IGAE: Investigator Global Assessment of Efficacy
IGAS: Investigator Global Assessment of Safety
NSAID: nonsteroidal anti-inflammatory drug
PGAE: Patient Global Assessment of Efficacy
SAE: serious adverse event
SoC: standard of care
TSS: Tonsillitis Severity Score
URTI: upper respiratory tract infection

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Protocol

Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e63678

Abstract

Background: Clinical trials examining lifestyle interventions for weight loss in cancer survivors have been demonstrated to be safe, feasible, and effective. However, scalable weight loss programs are needed to support their widespread implementation. The ASPIRE trial was designed to evaluate real-world, lifestyle-based, weight loss programs for cancer survivors throughout Maryland.

Objective: The objectives of this protocol paper are to describe the design of a nonrandomized pragmatic trial, study recruitment, and baseline characteristics of participants.

Methods: Participants were aged ≥18 years, residing in Maryland, with a BMI ≥25 kg/m^2, who reported a diagnosis of a malignant solid tumor, completed curative treatment, and had no ongoing or planned cancer treatment. Enrollment criteria were minimized to increase generalizability. The primary recruitment source was the Johns Hopkins Health System electronic health records (EHRs). Participants selected 1 of 3 remotely delivered weight loss programs: self-directed, app-supported, or coach-supported program.

Results: Participants were recruited across all 5 geographic regions of Maryland. Targeted invitations using EHRs accounted for 287 (84.4%) of the 340 participants enrolled. Of the 5644 patients invited through EHR, 5.1% (287/5644) enrolled. Participants had a mean age of 60.7 (SD 10.8) years, 74.7% (254/340) were female, 55.9% (190/340) identified as non-Hispanic Black, 58.5% (199/340) had a bachelor's degree, and the average BMI was 34.1 kg/m^2 (SD 5.9 kg/m^2). The most common types of cancers were breast (168/340, 49.4%), prostate (72/340, 21.2%), and thyroid (39/340, 8.5%). The self-directed weight loss program (n=91) included 25 participants who agreed to provide weights through a study scale; the app-supported program (n=142) included 108

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individuals who agreed to provide their weight measurements; and the coach-supported weight loss program included 107 participants. We anticipate final analysis will take place in the fall of 2024.

Conclusions: Using EHR-based recruitment efforts, this study took a pragmatic approach to reach and enroll cancer survivors into remotely delivered weight loss programs.

Trial Registration: ClinicalTrials.gov NCT04534309; https://clinicaltrials.gov/study/NCT04534309

International Registered Report Identifier (IRRID): DERR1-10.2196/54126

(JMIR Res Protoc 2024;13:e54126) doi:10.2196/54126

KEYWORDS

cancer; obesity; weight loss; pragmatic trial; oncology; weight; overweight; obese; USA; United States; survivor; survivors; remote; self-directed; self-guided; coach; coaching; mHealth; mobile health; app; apps; application; applications; EHR; health record; health records; mobile phone

Introduction

Obesity is a major public health concern that adversely affects cardiometabolic health [1-3]. Less well appreciated is that obesity increases the risks of some cancers [4]. In addition, obesity is associated with cancer recurrence. A meta-analysis showed obesity was associated with increased risks of recurrence in breast, colorectal, prostate, and esophageal cancers [5]. Furthermore, certain cancer treatments lead to weight gain [6]. Hence, for many cancer survivors, obesity poses a dual risk of decreased cardiometabolic health and increased cancer recurrence.

In the United States, there were an estimated 18 million cancer survivors in 2022 [7], and this number is expected to increase to 22.5 million by 2032 due to advancements in treatment and early detection [8]. It is estimated that 32.5% of cancer survivors are overweight or obese [7]. Scalable weight loss interventions are needed to help cancer survivors reduce their cardiometabolic risk, lower their risk of cancer recurrence, and improve their long-term health profile.

The International Agency for Research on Cancer and the American Cancer Society recommend a lifestyle approach that includes diet and physical activity to avoid weight gain and maintain a healthy body weight, which can reduce the risk of cancer recurrence [9,10]. Over the past decade, trials examining lifestyle interventions for weight loss in cancer survivors have been demonstrated to be safe, feasible, and effective [11]. However, there is a need to implement effective programs at scale and to enroll a diverse population [11]. With these long-term goals in mind, we intended to implement scalable approaches to providing lifestyle-based weight loss programs for cancer survivors throughout Maryland, including its rural communities.

Many trials, including several by our team, have demonstrated the effectiveness and feasibility of remotely delivered weight loss programs. For example, the POWER trial at Johns Hopkins, a comparative effectiveness trial, was one of the first large-scale, long-term weight loss trials to demonstrate that a remote weight loss program could be as effective as an in-person weight loss program [12]. Specifically, individuals who received in-person support and remote support achieved a 5.2% and 5% decrease in weight at 24 months, respectively. Subsequently, we tailored the remote weight loss program for cancer survivors and found it to be effective [13,14]. This study takes an important next step in translating clinical trial results into more scalable programs that could be used to disseminate and implement these programs.

The ASPIRE trial was designed to evaluate real-world, lifestyle-based, weight loss programs for cancer survivors throughout Maryland. In this protocol paper, we describe the design of this nonrandomized pragmatic trial, recruitment and enrollment, and baseline characteristics of participants.

Methods

Study Overview

The objective of the ASPIRE study was to design, implement, and evaluate lifestyle-based weight loss programs to support cancer survivors with overweight or obesity throughout Maryland. This protocol paper describes the design of the ASPIRE study, the feasibility of recruiting a diverse sample using electronic health records (EHRs), and the sample characteristics, to demonstrate the diversity of this study's population. The ASPIRE study offered three programs: (1) self-directed weight loss (SDWL), (2) app-supported weight loss (ASWL), and (3) coach-supported weight loss (CSWL). Participants self-selected a program. Eligibility and interest were determined via self-report on surveys and screening phone calls. Those who opted for weight tracking were mailed a scale with the cellular capability to transmit their weights. The primary outcome is the 6-month weight change in the CSWL program. Secondary outcomes include examining weight change among those with scales in the ASWL and SDWL programs.

We designed this study to maximize generalizability through several approaches. First, this study was not restricted to patients with a specific solid tumor. Rather, we designed the interventions to be suitable for cancer survivors with overweight or obesity who can benefit from behavioral weight loss. Second, we minimized the inclusion and exclusion criteria to reduce barriers to participating in a clinical trial. Third, the entire study was conducted remotely, which allowed for recruitment throughout the state, including both urban and rural areas; it also allowed for study assessments during COVID-19 restrictions. Our previous weight loss trials generally required in-person weight assessments, thereby limiting recruitment efforts to the greater Baltimore area [12-14]. By leveraging

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technology such as email, web-based surveys, study scales that use cellular technology for data transmission, and a commercially available weight loss app, the current study design could be implemented across the state and included weight loss programs that had low marginal costs and were readily scalable.

Ethical Considerations

The Institutional Review Board at Johns Hopkins School of Medicine reviewed and approved the protocol (IRB00229163). All participants provided informed consent. This study was conducted per the tenets of the Declaration of Helsinki. The background, procedures, and aims of this study were provided to prospective participants before the consent process. Confidentiality was protected by assigning participants unique study identification. To acknowledge the time and effort they dedicated to participating in this study, participants who tracked their weight with study scales were offered a US $25 gift card for completing each follow-up data collection (months 3, 6, and 12) that consisted of a set of study weights and web-based surveys.

Study Population

This study included cancer survivors aged 18 years or older, residing in Maryland, with a BMI of ≥25 kg/m^2 (≥23 kg/m^2 for Asians), who self-reported a previous diagnosis of malignant solid tumor, had completed curative intent treatment, and had no ongoing or planned active treatment (surgery, radiation therapy, or chemotherapy other than chemoprophylaxis). Major inclusion criteria also included: completion of all required surgical, chemotherapy, or radiation curative intent therapy at least 3 months before enrollment; anticipated treatment-free life span of 12 months or longer (study physician assessment based on self-reported cancer type and stage at diagnosis, treatments, and comorbidities); weight ≤400 lb (limitation due to maximum weight obtainable from study scales); and had an email address for regular personal use. Chemoprophylaxis with tamoxifen or aromatase inhibitors for breast cancer in women was permitted, as was anti-luteinizing hormone-releasing therapy for prostate cancer in men. Major exclusion criteria included receiving any chemotherapy (unless antihormonal therapy) or radiation 3 months or less before the proposed program date, and women who were breastfeeding, pregnant, or planning pregnancy within the next year. These were the inclusion or exclusion criteria to qualify for the SDWL program.

Additional Criteria for the ASWL Program

To qualify for the ASWL program, patients must also meet the following criteria: have a smartphone for personal use; sufficient data plan or internet to support daily use of a weight loss app; and a willingness to track weight, diet, and physical activity through a commercial app (Lose it!).

Additional Criteria for the CSWL Program

In addition to the above criteria to qualify for the CSWL program, participants must also have a willingness to lose weight by changing diet and physical activity habits; a willingness to complete coaching calls (12 weekly calls and 3 monthly calls); and a sufficient call plan to support coaching calls. All participants in the CSWL program and a self-selected subgroup of SDWL and ASWL participants who elected to receive a study scale were required to meet an additional set of study criteria. The additional eligibility criteria for participants using a study scale included the willingness to record or transmit quarterly weights for 12 months. Exclusion criteria included self-identification of uncontrolled concurrent medical condition (eg, chronic kidney disease receiving dialysis) likely to limit compliance with the program as determined by investigators, current involvement in another organized weight loss program, current use of steroids or other medication known to affect body weight, bariatric surgery scheduled within the next 6 months, and plans to move outside the continental United States in the next 12 months.

Recruitment

Recruitment strategies and materials were aligned with previous trials that ensured recruitment efforts were appropriate to engage a diverse target population related to biological sex, race, and ethnicity [12-14]. Strategies included flyer distribution to in-state cancer groups, invitations to cancer survivors enrolled in previous studies, prior study participants, and email invitations through MyChart, the Johns Hopkins Medicine EHR patient portal. The use of EHR allowed us to identify potential study participants based on zip code, BMI, race-ethnicity, and previous cancer diagnosis. Specifically, we used EHR to target recruitment in Maryland's 5 geographic regions: Western Region, Capital Region, Central Region, Southern Region, and Eastern Shore Region [15]. The Western, Southern, and Eastern Shore regions were comprised of rural counties [16]. Using the EHR-based recruitment, we sent email invitations through the MyChart portal to patients in all 5 regions. The MyChart invitation referred interested individuals to a study-specific website that provided participants with general study information, assessed basic eligibility, and served as an entry point for participants to express interest in this study.

Self-Selection of Weight Loss Program

During screening, participants would indicate which program they were interested in joining. The 3 weight loss programs offered different types of support, required different commitments from the participants, and had different screening criteria. Study staff guided participants toward the program that was best aligned with the participants' interests and eligibility. For example, those interested in but not eligible for the ASWL program (eg, they did not want to friend study staff on the app) were enrolled in the SDWL program. In this manner, this study provided program options to meet the varying needs and interests of cancer survivors throughout Maryland. Based on study resources, we set the enrollment limit for the CSWL program at approximately 100 participants. Once we reached this target, we deemed enrollment to be complete. The SDWL and the ASWL programs were readily scalable and had no enrollment limits during this study's enrollment period.

Weight Loss Programs—Theoretical Framework

All 3 weight loss programs used lifestyle approaches based on social cognitive theory and incorporated behavioral self-management approaches designed to help participants with safe and effective weight loss. These programs were based on

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previously successful coach-supported weight loss programs [12-14]. The programs had a social cognitive theoretical framework for teaching participants strategies to increase their self-efficacy in making behavior changes [17,18]. This included setting realistic weight loss goals and establishing early success with both process goals (changing behaviors) and outcome goals (losing weight). Specific daily strategies that were encouraged among the participants included self-monitoring, goal-setting, and problem-solving. Problem-solving recommendations took a solution-focused approach [19,20]. The programs were designed to build the participant's skills and confidence with weight reduction strategies including self-weighing, caloric restrictions, increased physical activity, and self-monitoring. Motivational interviewing was the style of communication used to interact with the participants in the CSWL program [21]. This patient-centered approach was also integrated into the written materials for all 3 programs. In addition, the programs were based on previous programs that ensured materials were appropriate to engage a diverse target population related to biological sex, race, and ethnicity [12-14]. Weight loss recommendations in these programs correspond with weight management guidelines for cancer prevention and cancer survivors [9,22].

Weight Loss Programs—Descriptions

Participants in the SDWL program received written weight loss group materials by email and no further weight loss program-related contact. These materials included recommendations for a weight loss goal of 5% in 6 months (see Table 1). The materials also included weight loss strategies of caloric restriction, following a Dietary Approaches to Stop Hypertension–aligned diet [23], self-monitoring weight at least weekly, and suggestions to gradually increase to at least 150 minutes per week of moderate-intensity aerobic exercise. All 3 weight loss programs used the same fundamental weight loss materials. Since smoking is a major risk factor for cancer [24], all participants who identified as current smokers received information on the free Maryland Tobacco Quitline [25]. This support was congruent with this study's overall objective of reducing cardiometabolic risk and risk of cancer reoccurrence.

Table 1. Weight loss program summaries.

Program component	Self-directed	App-supported	Coach-supported
Behavioral weight loss information			
Information on general behavioral weight loss strategies for cancer survivors	✓	✓	✓
Weight goal			
5% weight loss in 6 months	✓	✓	✓
Exercise goal			
Build up to 150 minutes per week of aerobic physical activity	✓	✓	✓
Calorie recommendations			
1200 kcal/day if ≤170 lb; 1500 kcal/day if >170 lb and <220 lb; 1800 kcal/day if >220 lb and <270 lb; 2200 kcal/day if >270 lb	✓	✓	✓
Diet recommendation			
Dietary Approaches to Stop Hypertension–like diet	✓	✓	✓
Weight tracking			
Tracking weight at least weekly	✓	✓	✓
Smoking cessation			
Referral to *Maryland Tobacco Quitline* for current smokers	✓	✓	✓
Weekly support emails			
Weekly support emails reinforcing study strategies	None	✓	✓
Expected app use			
Insider's guide to using the app including tracking weight, physical activity, food, and drink	None	✓	✓
Study scale	Optional	Optional	Provided
Additional weight loss information			
Monthly weight loss strategy modules, months 4-6	None	None	✓
Coaching calls			
Weekly calls for months 1-3 (total 12 calls expected); monthly calls for months 4-6 (total 3 calls expected)	None	None	✓

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The ASWL program received additional suggestions tailored to the use of a specific free commercially available app, Lose it! (FitNow, Inc). Using a commercially available app supports the participants in the continued use of the app at the end of this study. The ASWL program received directions for signing up for the app and for verifying their app account by friending this study's profile on the app. They received recommendations on which app features should be used to stay consistent with the evidence-based weight loss recommendation of this study. They also received 25 weekly emails reinforcing the suggested behavioral weight loss strategies.

The CSWL program received the same program features as the ASWL program plus 3 additional monthly weight loss program modules: taking the exercise challenge, eating away from home, and mindful eating. The CSWL program was offered telephonic coaching calls weekly for the first 3 months and monthly for months 4 to 6. Participants in the CSWL program were asked to use this study's scales for their self-monitoring throughout this study. The coaches had access to this scale data, as well as detailed food tracking data, providing increased accountability.

Measures

All participants self-reported their type of cancer, basic demographic information, height, and weight. Participants could report more than one type of cancer. Among those receiving study scales, the scales served two purposes: (1) to assess weight as an outcome measure and (2) for regular self-weighing during the weight loss program. The scales (BodyTrace) transmitted weight data to the researchers using cellular technology, did not require the use of the participant's internet or a mobile phone data plan, and had been used in previous weight loss trials [24,26].

Power and Sample Size

Given the available coaching resources, we set the enrollment target of the CSWL program at 100 participants. By assuming the correlation between the baseline and the 6-month weight measurements as 0.9, and the SD of baseline weight as 17 kg (conservative assumption based on a previous trial in cancer survivors [14]), we estimated that with 80% power, we could detect a mean weight change of 2.15 kg over a 6-month follow-up within each program using a 2-sided test with type I error of 0.05.

Data Management

A study database manager maintained this study's database and merged data collected from the wireless scales with the REDCap (Research Electronic Data Capture; Vanderbilt University) database. Using REDCap, study staff entered data, reviewed participant study status, and regularly monitored data for completeness and accuracy. For example, before enrollment, staff checked the database to ensure that all screening activities had occurred, that the participant met all eligibility criteria, and that all required baseline data had been collected.

Analytic Plan

We defined the enrollment rate of EHR-based study invitations as the percentage of invitations that resulted in participant enrollment. We described the distribution of baseline characteristics of the participants by the weight loss programs using means and SDs for the continuous variables, and percentages and frequencies for the categorical variables. The primary outcome is weight change from baseline to 6 months by program. Additional analysis will use mixed models including weights from 3, 6, and 12 months of data collection. We anticipate final analysis will take place in the fall of 2024.

Results

Figure 1 shows the flow of recruitment and enrollment. This study screened 422 individuals between September 2020 and December 2021, of whom 378 were eligible, and 340 enrolled. Targeted invitations using EHR accounted for 84.4% (287/340) of the participants. Of the 5644 invited through the EHR portal, 287 (5.1%) enrolled. Among the 97 previous study participants who were invited, 16 (16.5%) enrolled. We did not have a known denominator from our other recruitment channels and were not able to report on yield for the remaining 37 participants.

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Figure 1. Flow of study participants.

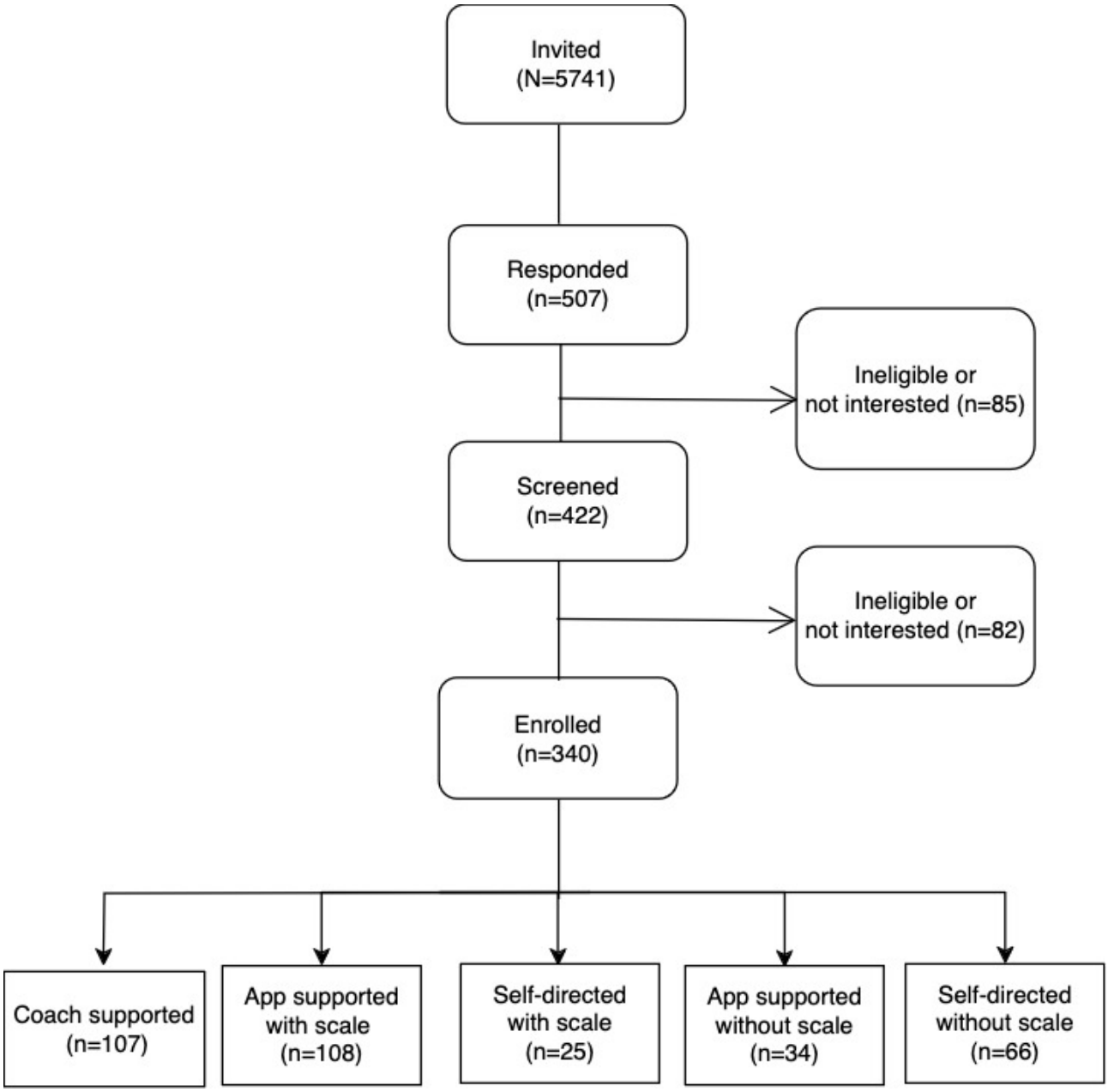

As shown in Table 2, the reach ranged from 6.4% (87/1363) in the Capital Region to 4.1% (26/631) in the Western Region. Participants had an average age of 60.7 (SD 10.8) years, were predominantly female (254/340, 74.7%), had an average BMI of 34.1 kg/m^2 (SD 5.9 kg/m^2) based on self-reported height and weight, and over half (199/340, 58.5%) had a bachelor's degree (Table 3). Participants could report more than one type of cancer and the most frequently reported types of cancer were breast cancer (168/340, 49.4%), prostate cancer (72/340, 21.2%), and thyroid cancer (29/340, 8.5%). In terms of race-ethnicity, 55.9% (190/340) of participants were identified as non-Hispanic Black adults and 38.8% (132/340) were identified as non-Hispanic White adults.

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Table 2. Reach of electronic health record recruitment in Maryland by region[a].

	Recruitment invitations sent, n	Participants enrolled, n (%)
Total	5644	287 (5.1)
Region		
Capital	1363	87 (6.4)
Central	1806	95 (5.3)
Eastern Shore	1027	47 (4.6)
Southern	739	32 (4.3)
Western	631	26 (4.1)

[a]Study invitations were sent to those aged 18 years and older, with BMI ≥25 kg/m^2, a record of a malignant tumor on file, and living within the designated target areas.

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Table 3. Participant characteristics at baseline.

Characteristics	Total (N=340)	Received a study scale			No study scale	
		Coach supported (n=107)	App-supported (n=108)	Self-directed (n=25)	App-supported (n=34)	Self-directed (n=66)
Age (years), mean (SD)	60.7 (10.8)	59.2 (10.0)	60.7 (10.2)	68.2 (6.4)	56.5 (10.7)	62.5 (12.5)
Female, n (%)	254 (74.7)	87 (81.3)	77 (71.3)	14 (56)	27 (79.4)	49 (74.2)
BMI (kg/m^2), mean (SD)[a]	34.1 (5.9)	35.1 (6.1)	33.6 (5.2)	31.6 (3.5)	34.5 (6.9)	33.9 (6.3)
Race or ethnicity, n (%)						
Non-Hispanic Black or Latina	190 (55.9)	57 (53.3)	56 (51.9)	13 (52)	25 (73.5)	39 (59.1)
Hispanic or Latina, not Black	6 (1.8)	1 (0.9)	4 (3.7)	0 (0)	0 (0)	1 (1.6)
Non-Hispanic or Latina White	132 (38.8)	46 (43)	43 (39.8)	11 (44)	9 (26.5)	23 (34.9)
Other or unknown	12 (3.5)	3 (2.8)	5 (4.6)	1 (4)	0 (0)	3 (4.5)
Education, n (%)						
Up to some college	99 (29.1)	33 (30.8)	38 (35.2)	3 (12)	13 (38.2)	12 (18.2)
Bachelor's degree or higher	199 (58.5)	70 (65.4)	70 (64.8)	22 (88)	17 (50)	20 (30.3)
Missing or did not answer	42 (12.4)	4 (3.7)	0 (0)	0 (0)	4 (11.8)	34 (51.5)
Type of cancer[b], n (%)						
Breast	168 (49.4)	63 (58.9)	47 (43.5)	11 (44)	17 (50)	30 (45.5)
Prostate	72 (21.2)	19 (17.8)	25 (23.2)	10 (40)	6 (17.7)	12 (18.2)
Thyroid	29 (8.5)	9 (8.4)	11 (10.2)	1 (4)	3 (8.8)	5 (7.6)
Current smoker	14 (4.1)	5 (4.7)	4 (3.7)	1 (4)	1 (2.9)	3 (4.6)
Region, n (%)						
Capital	94 (27.6)	26 (24.3)	32 (29.6)	9 (36)	9 (26.5)	18 (27.3)
Central	129 (37.9)	45 (42.1)	36 (33.3)	8 (32)	16 (47.1)	24 (36.4)
Eastern Shore	55 (16.2)	17 (15.9)	15 (13.9)	4 (16)	4 (11.8)	15 (22.7)
Southern	34 (10)	7 (6.5)	17 (15.7)	3 (12)	2 (5.9)	5 (7.6)
Western	28 (8.2)	12 (11.2)	8 (7.4)	1 (4)	3 (8.8)	4 (6.1)

[a]BMI based on self-reported height and weight from prescreening.

[b]Categories are not mutually exclusive.

A direct comparison of the persons enrolled through MyChart to the 5644 who received invitations is not possible, because the list of 5644 was not retained by the data warehouse. However, to overcome this limitation, a repeat search using the same enrollment criteria was carried out, resulting in a contemporary comparison group of 8024 patients who would have met the criteria for potential enrollment; this group was used as an approximate comparison group. Our study participants were younger (mean age 60.7, SD 10.8, vs 70.0, SD 12.9 years, in EHR sample), more likely to be women (74.7% vs 56.3% female in EHR), less likely to be non-Hispanic White (38.8% vs 66% in EHR), had higher BMI (mean BMI 34.1, SD 5.9, vs 31.3, SD 5.4 kg/m^2, in EHR), and had a lower prevalence of current smokers (4.1% vs 6.7% in EHR).

Among those who enrolled in this study (N=340), 107 individuals selected the CSWL program, 142 selected the ASWL program (of whom 108 were willing to use a study scale to track weight), and 91 selected the SDWL program (of whom 25 were willing to use a study scale). There were differences in participants' characteristics among programs: participants in the ASWL-nonscale program had an average age of 56.5 (SD 10.7) years and participants in the SDWL-scale program had an average age of 68.2 (SD 6.4) years. The CSWL program had the highest proportion of females (87/107, 81.3%) and the highest average BMI mean, 35.1 kg/m^2 (SD 6.1 kg/m^2), while the SDWL with scale had the lowest proportion of females (14/25, 56%) and lowest average BMI mean 31.6 kg/m^2 (SD 3.5 kg/m^2). The ASWL-no scale program had the highest

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proportion of non-Hispanic Black participants (25/34, 73.5%). There were no apparent differences in region by weight loss program. The sample sizes in some programs were modest; hence group comparisons should be interpreted with caution.

Discussion

In this pragmatic trial, participants self-selected which program they were interested in joining. The 3 weight loss programs offered varying types of support and required different commitments from the participants. Participants who selected the CSWL program tended to be female and with an average BMI of 35.1 (SD 6.1) kg/m^2. This study demonstrated the ability to recruit a racially diverse sample of cancer survivors who were overweight and with obesity, primarily through an EHR. Among the participants, 56.9% identified as non-Hispanic Black and 38.8% identified as non-Hispanic White. These findings correspond with this study's objective to recruit a diverse sample and reflect the racial diversity of Maryland where 32% of the population identify as non-Hispanic Black and 48% identify as non-Hispanic White [27].

Recruitment for this pragmatic trial was consistent with our prior success in recruiting racially diverse samples for weight loss studies. Our prior studies have included in-person requirements for study enrollment in urban areas such as Baltimore City, Baltimore County, and Howard County (Central Region) [12-14]. The current study used an all-remote study design and had similar success recruiting in these urban areas. The all-remote design also enabled us to recruit cancer survivors from rural counties in the Western, Southern, and Eastern Shore regions, thereby addressing the need for weight loss programs to support cancer survivors in rural areas [11].

Using EHR-based invitations we were able to target geographic regions throughout Maryland and adjust our recruitment based on program capacity. Although other, more traditional recruitment methods were also used (eg, providing flyers to cancer support groups), EHR-based recruitment accounted for 84% of the participants. In a previous weight loss study for cancer survivors, approximately 54,000 brochures were mailed to targeted zip codes, resulting in 65 enrolled participants or a 0.1% yield [28]. Using Facebook advertisements, 3 million advertisement impressions resulted in 4 enrolled participants, resulting in an extremely low yield [28]. The yield in the current study, namely 5.1% (287/5644) of the MyChart invitations, was substantially higher than the yields from mass mailing and social media advertising used in our prior study targeting cancer survivors [28]. The success of EHR-based recruitment is aligned with supporting physicians who have an ongoing need for multicomponent weight loss programs to which they can refer patients [29]. As such, the ASPIRE programs hold the potential to support health behavior change in the context of a health care system.

The recruitment approach had some limitations. Although we recruited across the 5 geographic regions in Maryland, we primarily used a single EHR system for recruitment creating a potential for selection bias. For example, the prevalence of smoking in the current sample (4.1%) is lower than that in Maryland (10.1%) and for cancer survivors (12.2%) [30,31]. Alternative recruitment approaches, such as provider referrals may be needed to better engage smokers and thus support this high-risk group. Although the EHR recruitment provided a strong yield in this study, relying on EHR from a single organization would not reach all cancer survivors in Maryland. A comprehensive approach to supporting cancer survivors in Maryland would require multiple recruitment channels. This study's materials were developed using a theoretical framework, however, those in the ASWL program may have relied on the app rather than this study's materials for guidance. A review of the theory-based content of weight loss apps indicated the theory-based for Lose it! was low. However, compared to other reviewed apps, Lose it! had the most robust theoretical background and incorporated an essential theory-based element of self-tracking [32].

Our study design also had several strengths. The weight loss programs were adapted from programs previously demonstrated as effective in the general population and among cancer survivors [12-14]. The all-remote design ensured study continuation during COVID-19 restrictions and is aligned with the concept of large-scale dissemination. The ASWL and SDWL programs are readily scalable. Unlike a clinical trial where only those who qualify for the trial receive support, the pragmatic approach in the current study offered weight loss options for individuals with varying interests. Had this study only implemented intensive interventions, for example, the CSWL program, as accomplished in our prior trials, the 233 individuals in the SDWL and ASWL programs would not have received weight loss support. By providing a range of programs and working with participants to find an approach they preferred, the current pragmatic design doubled the reach compared to a more traditional randomized control trial. This collection of programs has the potential to be offered on a larger scale and serve cancer survivors throughout Maryland. In conclusion, these results support EHR-based recruitment efforts as a pragmatic approach to reach and enroll cancer survivors into remotely delivered, weight loss programs.

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Data Availability

The data sets generated or analyzed during this project are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the concept and design of the paper. GJJ, LJA, LB, ATD, ND, JBC, MAC, NYW, and HCY contributed to the acquisition, analysis, or interpretation of data. GJJ and HCY drafted this paper. ND and NYW conducted the statistical analysis. All authors contributed to the critical revision of this paper for important intellectual content.

Conflicts of Interest

NFK is Executive Director of the Maryland Cigarette Restitution Fund Research Grant at Johns Hopkins and is partially supported by the Regional Oncology Research Center (5*t* P30 CA006973 60).

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Abbreviations

ASWL: app-supported weight loss
CSWL: coach-supported weight loss
EHR: electronic health record
REDCap: Research Electronic Data Capture
SDWL: self-directed weight loss

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Protocol

Testing a Biobehavioral Model of Chronic Stress and Weight Gain in Young Children (Family Stress Study): Protocol and Baseline Demographics for a Prospective Observational Study

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Abstract

Background: Chronic stress is an important risk factor in the development of obesity. While research suggests chronic stress is linked to excess weight gain in children, the biological or behavioral mechanisms are poorly understood.

Objective: The objectives of the Family Stress Study are to examine behavioral and biological pathways through which chronic stress exposure (including stress from COVID-19) may be associated with adiposity in young children, and to determine if factors such as child sex, caregiver-child relationship quality, caregiver education, and caregiver self-regulation moderate the association between chronic stress and child adiposity.

Methods: The Family Stress Study is a prospective cohort study of families recruited from 2 Canadian sites: the University of Guelph in Guelph, Ontario, and McMaster University in Hamilton, Ontario. Participants will be observed for 2 years and were eligible to participate if they had at least one child (aged 2-6 years) and no plans to move from the area within the next 3 years. Study questionnaires and measures were completed remotely at baseline and will be assessed using the same methods at 1- and 2-year follow-ups. At each time point, caregivers measure and report their child's height, weight, and waist circumference, collect a hair sample for cortisol analysis, and fit their child with an activity monitor to assess the child's physical activity and sleep. Caregivers also complete a web-based health and behaviors survey with questions about family demographics, family stress, their own weight-related behaviors, and their child's mental health, as well as a 1-day dietary assessment for their child.

Results: Enrollment for this study was completed in December 2021. The final second-year follow-up was completed in April 2024. This study's sample includes 359 families (359 children, 359 female caregivers, and 179 male caregivers). The children's mean (SD) age is 3.9 years (1.2 years) and 51% (n=182) are female. Approximately 74% (n=263) of children and 80% (n=431) of caregivers identify as White. Approximately 34% (n=184) of caregivers have a college diploma or less and nearly 93% (n=499) are married or cohabiting with a partner. Nearly half (n=172, 47%) of the families have an annual household income ≥CAD $100,000 (an average exchange rate of 1 CAD=0.737626 USD applies). Data cleaning and analysis are ongoing as of manuscript publication.

Conclusions: Despite public health restrictions from COVID-19, the Family Stress Study was successful in recruiting and using remote data collection to successfully engage families in this study. The results from this study will help identify the direction

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and relative contributions of the biological and behavioral pathways linking chronic stress and adiposity. These findings will aid in the development of effective interventions designed to modify these pathways and reduce obesity risk in children.

Trial Registration: ClinicalTrials.gov NCT05534711; https://clinicaltrials.gov/study/NCT05534711

International Registered Report Identifier (IRRID): DERR1-10.2196/48549

(JMIR Res Protoc 2024;13:e48549) doi:10.2196/48549

KEYWORDS

stress; child, preschool; adiposity; household chaos; cortisol; COVID-19; behavioral mechanisms; caregiver-child relationship quality

Introduction

Chronic stress is increasingly recognized as an important risk factor in the development of obesity [1]. Among children aged as young as 2-6 years, exposure to chronic stress, including parental divorce, parental depression, and household chaos has been associated with higher weight status and excess weight gain over time [2-4]. The COVID-19 pandemic fundamentally disrupted life for families and has been a key source of chronic stress for young children [5,6] and their parents [7].

While research suggests chronic stress is linked to excess weight gain in children, the biological or behavioral mechanisms are poorly understood [8]. Biologically, a central aspect of the stress response is the activation of the hypothalamic-pituitary-adrenal axis, leading to increased circulating cortisol levels [9]. Prolonged elevation of cortisol, a glucocorticoid, leads to increased adiposity, particularly abdominal adiposity, as well as increased appetite and preferences for high-fat and high-sugar foods [9]. Few studies have examined the association between cortisol and obesity among young children and most of this research has been cross-sectional [10-12]. Biological stress could be implicated in weight gain through complex pathways that develop over time; thus, longitudinal research is needed to elucidate the direction of these pathways [8]. Putative behavioral mechanisms linking stress with excess weight gain include consumption of energy-dense foods [13], eating for comfort [14], low physical activity [15], high screen time [16], and poor sleep [17]. However, research examining these mechanisms over time is sparse, particularly among young children [8]. Understanding these behavioral mechanisms, including the relative contributions of weight-related behaviors linking family stress and excess weight gain in children, can help inform behavioral targets for obesity interventions for young children who experience stress in the home.

In previous studies, researchers concluded that the damaging impact of stress can be buffered when children have supportive relationships with their caregivers [18-20]. The ability of parents to manage their own emotions during times of stress, that is, parental self-regulation, also influences their child's stress response [21]. Epidemiologic [3] and laboratory [22] research suggests that, when exposed to similar stressors, females have stronger biological reactivity to stress compared to males. Further, low-income households and households with less educated parents are associated with higher-stress environments [23,24] and children from these families bear a disproportionate share of the burden of obesity [25]. These findings underscore the need to examine how child sex, caregiver-child relationship quality, and caregiver self-regulation and education may moderate the pathways linking stress and excess weight gain in children.

Building on this existing research, the primary objective of the Family Stress Study is to test the conceptual model (Figure 1), using longitudinal structural equation modeling (SEM), that exposure to chronic stressors is directly associated with higher adiposity among children and partly mediated through alterations in children's cortisol production and weight-related behaviors. It is hypothesized that (1) chronic stress at baseline will be positively associated with children's BMI *z* score and waist circumference (WC) at 1- and 2-year follow-up, (2) the association between chronic stress and children's adiposity outcomes will be partially mediated by children's cortisol levels and children's weight-related behaviors, and (3) associations between children's cortisol levels and weight-related behaviors will be bidirectional (modeled as a cross-lagged structure within the longitudinal design). The secondary objective of this study is to examine the extent to which child sex, caregiver-child relationship quality, caregiver education, and caregiver self-regulation, moderate the associations examined in objective 1. Based on previous research, it is hypothesized that associations between chronic stress, cortisol levels, weight-related behaviors, and adiposity will be stronger among (1) children with less supportive caregiver relationships as compared to those with more supportive relationships [18,19], (2) female children as compared to male children [3,22], (3) children whose caregivers have lower education as compared to children whose caregivers have higher education [23,24], and (4) children whose caregivers have lower self-regulation as compared to children whose parents have higher self-regulation [21].

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Figure 1. Conceptual model for the Family Stress Study: a prospective observational study of biological and behavioral pathways linking stress and child adiposity in young children.

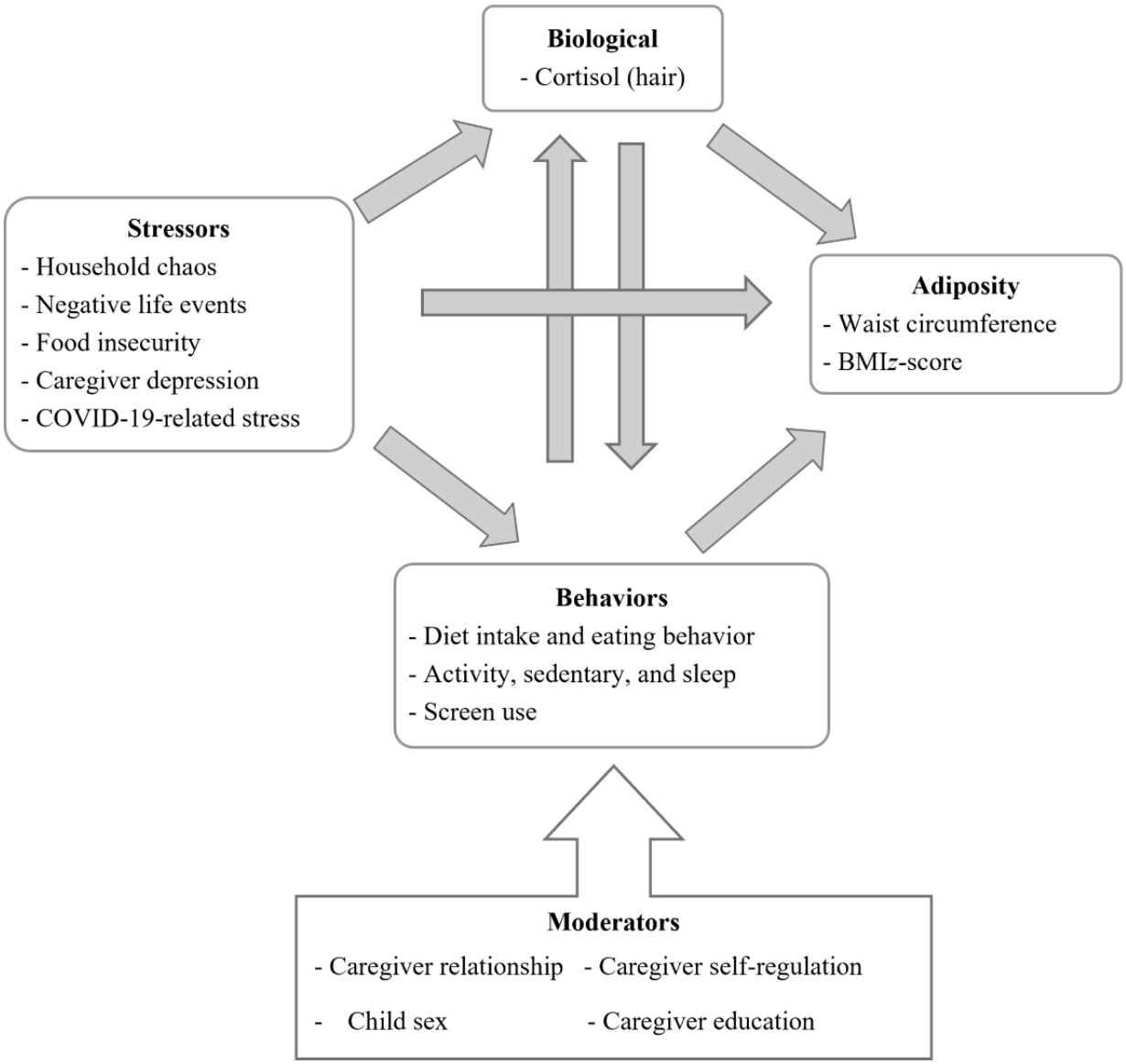

The variables depicted in Figure 1 will be assessed across 3 time points, measured 1 year apart, which will allow the elucidation of the direction and the relative contributions of the complex biological and behavioral pathways linking chronic stress and adiposity. Study results will help inform interventions to modify these pathways and reduce obesity risk among young children in the post–COVID-19 context. This paper describes the approach, protocol methods, and baseline demographics of the participants enrolled in the Family Stress Study.

Methods

Study Design

The Family Stress Study is a prospective cohort study of children aged 2-6 years recruited from 2 Canadian sites: the University of Guelph in Guelph, Ontario, and McMaster University in Hamilton, Ontario. Ethics approval was obtained before the restrictions due to the COVID-19 pandemic were enacted in Ontario in March 2020, but recruitment had not begun. The original protocol, which included an in-person health assessment of adiposity using air displacement (bod pod) and researcher-led measures of child and caregiver height, weight, and child WC, was revised to a caregiver-led at-home health assessment of child and caregiver weight, height, and child WC to adhere to the COVID-19 safety protocols. Measures of COVID-19–related stress were added to the web-based health and behaviors survey. The revised protocol was approved by both research ethics boards. Figure 2 provides an overview of this study's design.

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Figure 2. Design of the Family Stress Study for remote recruitment and data collection to test a biobehavioral model of chronic stress and weight gain in young children.

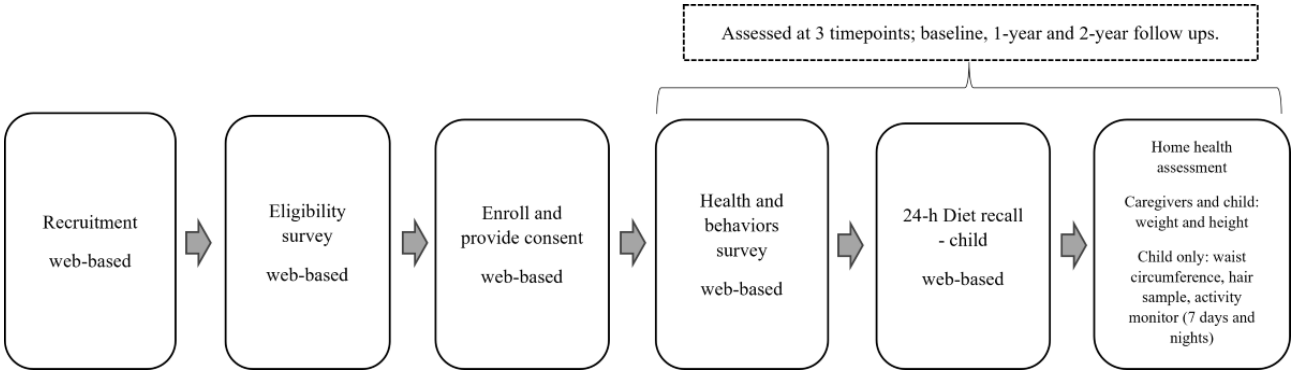

Study Participants and Recruitment

Between July 2020 and December 2021, participants were recruited from the city of Guelph, the city of Hamilton, and surrounding areas. Recruitment was conducted primarily via the web using paid advertisements on Facebook (Meta) and Instagram (Instagram from Meta), and social media posts, including posts by community organizations that serve families, and through posters in community locations, including libraries and toy stores. All methods of recruitment provided caregivers with study contact information and directed them to this study's website, where caregivers obtained additional details regarding this study's process and interested caregivers completed an eligibility screener.

To be eligible to participate, families had to have at least one child aged 2-6 years and have no plans to move from the area within the next 3 years. Participants were excluded if they were (1) enrolled in the Guelph Family Health Study (a longitudinal study led by the investigative team) at the University of Guelph to allow data to be merged across the 2 studies; (2) children born preterm (before 34 weeks gestation); (3) children with any health condition expected to affect cortisol production, obesity, or growth or body composition (eg, Prader Willi syndrome and Cushing disease); and (4) children taking steroid medications, including oral or inhaled corticosteroids, medications for attention-deficit/hyperactivity disorder, or antidepressants or antipsychotic medications.

To participate, caregivers had to live with the child at least 50% of the time and could include parents (biological, related, adoptive, or foster), grandparents, aunts, and uncles. The primary caregiver was the caregiver who first signed up for this study and served as the main contact for the family. Eligible primary caregivers completed a web-based consent to enroll themselves and their oldest eligible child in the target age range (2-6 years). Primary caregivers provided contact information for themselves and, if applicable, an email address for a second caregiver. The secondary caregiver was contacted separately to enroll and complete web-based consent. Study coordinators also connected regularly with families via email, text, or phone to provide them with support throughout the data collection process.

Ethical Considerations

This study was approved on March 11, 2020, and the amended protocol for remote data collection was approved by the University of Guelph Research Ethics Board (11-19-047) on June 12, 2020. The Hamilton Integrated Research Ethics Board approved this study on July 7, 2020, along with approval for the amended protocol on July 20, 2020 (10763). Recruitment and data collection began in July 2020 (Guelph) and August 2020 (Hamilton); primary caregivers enrolled in this study provided informed consent for themselves and their oldest eligible child and secondary caregivers provided informed consent for themselves. All participant data will be deidentified and only group data will be presented in all reports of this study's results. At each data collection time point, participating families receive a CAD $25 grocery gift card per caregiver for completing a health and behaviors survey (also includes the diet recall for the child), and a CAD $30 grocery gift card per family for completing the at-home health assessment as a thank you for their time.

Data Collection

Chronic stress and children's weight-related behaviors including diet and physical activity or sleep, cortisol levels, and adiposity are assessed at baseline, 1- and 2-year follow-ups. Further, 1-year intervals for assessment are based on Canadian health practice guidelines that recommend measuring height and weight once per year for children aged 2 years and older [26]. At each time point, primary caregivers complete a web-based health and behaviors survey with questions about family demographics, family stress, child weight-related behaviors, mental health, and their own weight-related behaviors. Secondary caregivers complete an abbreviated version of the health and behaviors survey focused on measures of stress and their own weight-related behaviors. Primary caregivers complete a web-based 1-day dietary assessment for their child. Caregivers complete anthropometric measures, collect a hair sample for cortisol analysis, and fit their child with an activity monitor for the at-home health assessment.

Measures

Child Adiposity

Families are provided with the necessary materials (a nonelastic flexible tape measure and Seca 803 digital scale [Seca]) and detailed, illustrated instructions [27-29] to complete the at-home health assessment, including the child's WC [30], height [31], and weight. Caregivers report the measurements using a web-based survey. This process has been validated among preschool-aged children in previous studies [27-29]. BMI *z*

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scores are calculated in R[22] using the "zscorer" package, based on the World Health Organization child growth standards [32]. WCs are measured by a caregiver to the nearest 0.1 cm using a soft retractable tape measure at the top of the iliac crest as per the protocol in the Canadian Health Measures Survey [30].

Child Hair Cortisol

Hair samples are used to assess children's chronic cortisol concentrations as an indicator of chronic biological stress. Primary caregivers are instructed to cut a lock of hair approximately 1 cm in width from the posterior vertex [33], as close as possible to the scalp, and secure it to a collection card with the scalp end identified. Using hair to assess cortisol is more reproducible than other physiological measures, for example, saliva, because it aggregates day-to-day variations in hypothalamic-pituitary-adrenal axis activity, thereby reflecting chronic rather than acute stressful exposures [34,35]. Hair samples are sent for cortisol analysis at the Centre for Studies on Human Stress, Montreal, Quebec, a laboratory focused on analyzing stress hormones.

The Centre for Studies on Human Stress analyzes 3 cm of hair, representing approximately 3 months of stress exposure [36]. In brief, a 25 mg sample of hair is placed in a vial to which 2.5 mL of isopropanol is added and mixed for 3 minutes on a plate rotator. This wash procedure is repeated once, and hair samples dry overnight. Then, the washed hair is transferred to a new vial to which 1.5 mL of pure methanol is added and vials are rotated for 24 hours. Samples are spun in a centrifuge for 2 minutes at 10,000 rpm and 1 ml of the clear supernatant is transferred into a new vial. Methanol is then evaporated under a constant stream of nitrogen at 60°C for 20 minutes or until dry. When dried, 0.4 mL of phosphate buffer (CAL A, IBL-Hamburg) is added to the tube, and then vortexed for 15 seconds [37]. A commercially available immunoassay with chemiluminescence detection from IBL-International is used to determine cortisol concentrations. The ranges of assays at 0.015-3.20 µg/dL are converted to picograms or milligrams for reporting.

Chronic Stress

Chronic stress is assessed using 5 different measures of stress: household stress, food insecurity, caregiver depression, children's negative life events, and COVID-19–related stress. Household stress is quantified using the 15-item Confusion, Hubbub, and Order Scale (CHAOS) [38]. Primary caregivers respond to items including "you can't hear yourself think in our home" or "there is very little commotion in our home" on a 4-point Likert scale from 1 (very much like your own home) to 4 (not at all like your own home). After reverse scoring relevant items, a total score will be calculated by summing the responses. The full CHAOS score [39-41], as well as the Emotional CHAOS subscale [4], created using 8 of the full-scale items, have been associated with obesity risk and obesogenic eating behaviors among young children. Standardized Cronbach α for the CHAOS survey was found to be 0.78 in the Guelph Family Health Study [42], which is a longitudinal study of families with toddlers and preschoolers [43].

Food security is examined using the Household Food Security Survey Module, an 18-item measure that includes 10 items that assess uncertain, insufficient, or inadequate food access related to adults in the household and 8 items focused on children over the previous 12 months [44]. Households will be categorized based on the total number of positive responses: food secure households (0 responses), marginally food insecure households (1 responses), moderately food insecure households (2 to 5 responses), or severely food insecure households (≥6 responses). While evidence for an association between food insecurity and obesity risk in children has been mixed [45], food insecurity is a prevalent source of stress among families, affecting 1 in 6 Canadian children [46], and has been shown to be associated with poorer diets in children [47].

Caregiver depressive symptoms are assessed using the 20-item short-form Centre for Epidemiologic Studies Depression Scale (CES-D) [48-50]. Both the primary and second caregivers respond to statements about the previous week including "everything I did was an effort" and "I felt lonely." Responses are to be scored as 0 (less than 1 day), 1 (1-2 days), 2 (3-4 days), or 3 (5-7 days) and, after reverse scoring relevant items, a total score out of 30 will be calculated by summing the responses. The standardized Cronbach α for the CES-D was found to be 0.88 for mothers and 0.80 for fathers of young children in the Guelph Family Health Study [51]. Parental depression assessed using CES-D has been found to be associated with obesity risk and obesity-related behaviors in children [51,52].

Children's negative life events are reported using an abbreviated List of Threatening Experiences [53], an 8-item measure of negative life events, for example, divorce. Primary caregivers report negative events for their child across their lifetime (or for the past year on the follow-up surveys) by answering "yes" or "no" to whether or not their child has encountered various events, such as "divorce or separation of parents" or "severe disease or accidents." The total score will be determined by summing the number of negative events. This measure has been found to be associated with obesity risk in children [54].

COVID-19–related stress is assessed by asking both the primary and secondary caregiver about quarantine or illness due to COVID-19, change in employment status due to COVID-19 (eg, loss of job and change in work hours per location), and employment in essential services (eg, first responder, health care worker, critical infrastructure worker, food production and supply, production, supply of medicine, hydro, and gas, and corrections). Given that COVID-19 disrupted home and work life among families with young children, measures assessing work conflict [55], financial insecurity [56], and parenting stress [57] are also included in the caregiver's web-based survey. Work-to-family conflict is assessed using a 5-item scale adapted from Carlson et al [55]. Caregivers are asked questions including "my work keeps me from family activities more than I would like" and "when I am home from work, I am often too frazzled to participate in family activities or responsibilities." Responses are on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree) [55]. A total score will be calculated by summing the responses.

Financial insecurity is evaluated using 2 items adapted from the measures by Gundersen and Boushey [56]: "during the past month, was there a time when you were worried you would not

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be able to pay the mortgage, rent or other bills on time?" and "are you worried about not being able to pay the mortgage, rent or other bills on time over the next 6 months?" to which caregivers respond "yes" or "no." Families will be coded as financially insecure if they respond positively to either item.

Parenting stress is assessed by asking caregivers 12 items from the parenting distress domain of the short-form parenting index [58]. Items include "I feel trapped by my responsibilities as a parent/caregiver," "there are quite a few things that bother me about my life," and "having a child has caused more problems than I expected in my relationship with my spouse/partner (or male/female friend)." Responses are on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse scoring relevant items, a total score will be calculated by summing the responses. The standardized Cronbach α in a similar sample was 0.86 among mothers and 0.78 among fathers [59].

Child Weight-Related Behaviors

Dietary Intake and Diet Quality

Primary caregivers report their child's dietary intake for 1 day using the web-based Automated Self-Administered 24-hour Dietary Assessment Tool (ASA24)-Canada. ASA24 includes multiple prompts for participants to facilitate accurate data entry. A validity study that compared parent reports to children's true diet intake among 40 parent-child dyads found that parents could accurately report what young children ate and drank [60]. ASA24-Canada analyzes the dietary data using the Canadian Nutrient File and a Health Canada recipe database along with the United States Food and Nutrient Database for Dietary Studies and the Food Patterns Equivalents Database. These databases enable ASA24-Canada to output a summary of the food descriptions, energy and nutrient intakes, and United States Department of Agriculture Food Pattern components. This information will be used to examine children's intake based on evidence that stress is associated with a higher intake of fast food [61,62], high-fat and high-sugar foods [13], and lower intake of fruit and vegetables [13].

Eating Behavior

Further, 4 eating behaviors that are most consistently associated with increased obesity risk in children (enjoyment of food [4 items], food responsiveness [5 items], emotional overeating [4 items], and satiety responsiveness [5 items]) [3,63,64] are assessed using the Children's Eating Behavior Questionnaire [65]. Parents report their children's eating behavior for each of these behaviors, for example, "my child eats more when anxious." Response options for each item include "never" (1), "rarely" (2), "sometimes" (3), "often" (4), and "always" (5). After reverse coding relevant items, a mean score will be calculated for eating behavior with higher scores reflecting higher endorsement of these behaviors. The Children's Eating Behavior Questionnaire subscales have been shown to have good internal consistency (Cronbach α ranging from 0.72 to 0.91) when tested among a sample of families with young children [65].

Physical Activity, Sedentary Behavior, Sleep, and Screen Time

A lightweight activity monitor (wGT3x-BT; Actigraph; 100 Hz) with idle sleep mode enabled to preserve battery life, is fixed to a soft strap and placed on the child's right hip for 7 consecutive days, 24 hours/day, and the monitors are returned via prepaid mail or picked up from participant's homes. To aid with compliance, caregivers are provided with a link to an animated video to share with their child about the activity monitor and why they are being asked to wear it. Caregivers complete a log sheet to track monitor wear-time, including times that the device is removed (ie, bathing) in addition to their child's sleep and wake times. Using validated age-appropriate cut-point values [66], data collected from the monitors will then be used to quantify physical activity, that is, total physical activity and moderate to vigorous physical activity, total sedentary time [67], and total sleep [68,69].

Primary caregivers report child screen time defined as "any time that is spent on screens such as televisions, cell phones, iPads or tablets and video games" on a typical weekday and weekend day over the past week [70]. Weekday and weekend day values will be summed and averaged to calculate the average daily screen time.

Potential Moderating Variables

Primary caregivers report their child's sex. Both the primary and secondary caregiver report their education level. Quality of caregiver relationship is assessed for both primary and secondary caregivers using the warmth or affection subscale of the Parenting Acceptance and Rejection Questionnaire [58,71] which measures parents' feelings of warmth and acceptance (vs rejection) toward their child, a central aspect of relationship quality [72,73] that has been associated with multiple child outcomes [74,75]. Caregivers respond to items including "I say nice things about my children" on a 4-point Likert scale from 1 (almost always true) to 4 (almost never true). After reverse coding relevant items, a total score will be calculated by summing the responses. Both the primary and secondary caregivers completed an abbreviated 30-item version of the Behavior Rating Inventory of Executive Function [76] to assess caregiver self-regulation. A total score will be calculated by summing the responses across the 30 items. Time-varying moderators will be assessed at all 3 time points, whereas time-invariant moderators will only be assessed at baseline.

Covariates

Primary caregivers report their child's birth weight, gestational age, duration of breastfeeding, annual and sources of household income, child and caregiver race or ethnicity, and caregiver employment status (full- or part-time). Secondary caregivers report their race or ethnicity and their employment status.

Retention

The research team has extensive experience in strategies for retention in longitudinal family studies [77-79]. To maximize retention in the Family Stress Study, many of these same strategies are used including (1) regular emails to maintain connection with participants, (2) mailings with tracking to obtain

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forwarding address information, and (3) financial incentives for assessments.

Data Analyses

To summarize baseline caregiver and child characteristics for this paper, descriptive statistics were used. Percentages are presented for categorical data. Means and SDs are used for continuous data.

This study's objectives will be tested using an SEM approach for longitudinal models that combines latent growth models (LGMs) with auto-regressive and cross-lagged paths using a special parameterization that separates the time-invariant (between-individuals) and time-varying (within-individuals) components [80,81]. Before constructing the SEM models, distributions of all the variables, their skewness and kurtosis levels, and their presence of extreme or outlier responses above or below 3 times the IQR will be explored and outliers will either be removed or Winsorized.

An incremental model-building approach similar to the recommended approach by Curran et al [80] will be used to test this study's objectives. The first component in the model-building approach is the LGM of the trajectories across time for the variables' chronic stressors (explanatory variable), child cortisol and child behavior (mediator variables), and child adiposity (outcome variable). Each variable has its own trajectory and includes an intercept (I), which refers to a baseline value, and a slope (S), which refers to change over time. Of particular importance is that individual child variation in these I and S parameters will be modeled. If any of these components are found to be not statistically significant, they are removed from the model. Typically, the I means and variances are significantly different from 0, but the S means may or may not depict significant linear change. The second component consists of the auto-regressive associations (ie, T2 regressed on T1, and T3 on T2) capturing the rank-order stability of the variables across the 3 time points (eg, the relationship between cortisol at T1 and T2). The third component typically consists of cross-lagged paths or other hypothesized paths between the variables, accounting for growth factors, and stability factors. In this study, this component will consist of the longitudinal mediation paths (ie, from explanatory variable at T1 to mediator at T2, to outcome at T3). The hypothesized model includes 2 partial mediators of the relation between stressors and child adiposity: child cortisol and behaviors. To test mediation, a direct path from stressors at T1 and child adiposity at T3 is also included. A correlational path between the residualized mediators is also included to model any leftover covariance between them. The fourth component will assess the moderation of the mediated paths. For example, to test the hypothesis that the cortisol mediation may differ across the sex of the children, we can use a multiple groups SEM approach that compares the effect size of mediation across male and female children.

As with any longitudinal study, attrition is expected. Patterns of missing data and potential bias at time 2 and time 3 will be investigated by comparing demographics and variable scores of participants who are missing to those who are not missing at each time point. In addition to noting and acknowledging any bias due to missingness, the SEM modelling procedure uses a maximum likelihood estimator which also provides one of the best ways to estimate the model parameter estimates in the presence of missing data. While there is no guarantee that the data are missing completely at random, in longitudinal designs, data from earlier time points compensates for the missingness at later time points in the estimation procedure.

Sample Size Estimation

To estimate the power of specific paths in the model, an empirical simulation approach was used [82,83]. To run power analysis for LGM models, Muthén and Muthén [83] proposed a general framework using Monte Carlo simulation. Further, 2 separate a priori power analyses were conducted to determine whether a sample size of 300 is sufficient to detect the cross-lagged effects of interest. The first model assumed data were normally distributed and the second model assumed nonnormality in 10% (n=30) of the cases. For each simulation, a sample size of 300 was specified with 10,000 replications successfully completed. For both the normally distributed and nonnormally distributed data scenarios, all estimated parameters had between 82% and 86% coverage, and the parameter estimate and SE bias were below 5%, suggesting sufficient power.

Results

As illustrated in Figure 3, a total of 571 primary caregivers completed eligibility surveys (Guelph n=298; Hamilton n=273). Of those, 129 did not enroll in this study: 119 did not meet inclusion criteria, 8 declined to participate, and 2 were excluded for incomplete registrations. Of the 442 eligible families enrolled (ie, provided consent), 79 did not complete any baseline measures (ie, did not start this study) and 4 withdrew. Baseline health and behavior surveys were completed for 359 families including 359 primary caregivers (96% women [n=346]), 179 secondary caregivers (92% men [n=166]), and 359 children. Diet recalls were completed for 313 children and 226 children had valid activity monitor wear time (minimum of 360 min for a minimum of 3 days). A total of 301 families completed an at-home health assessment which included anthropometric measures for 301 primary caregivers, 168 secondary caregivers, and 301 children along with the collection of 268 hair samples from the children. Of the 359 families who completed baseline health and behavior surveys, 79% (n=284) identified that they heard about this study through social media, including posts by community organizations that served families and through paid Facebook advertisements.

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Figure 3. Diagram of participant flow from recruitment to collection of baseline data of the Family Stress Study (July 2020 and May 2022).

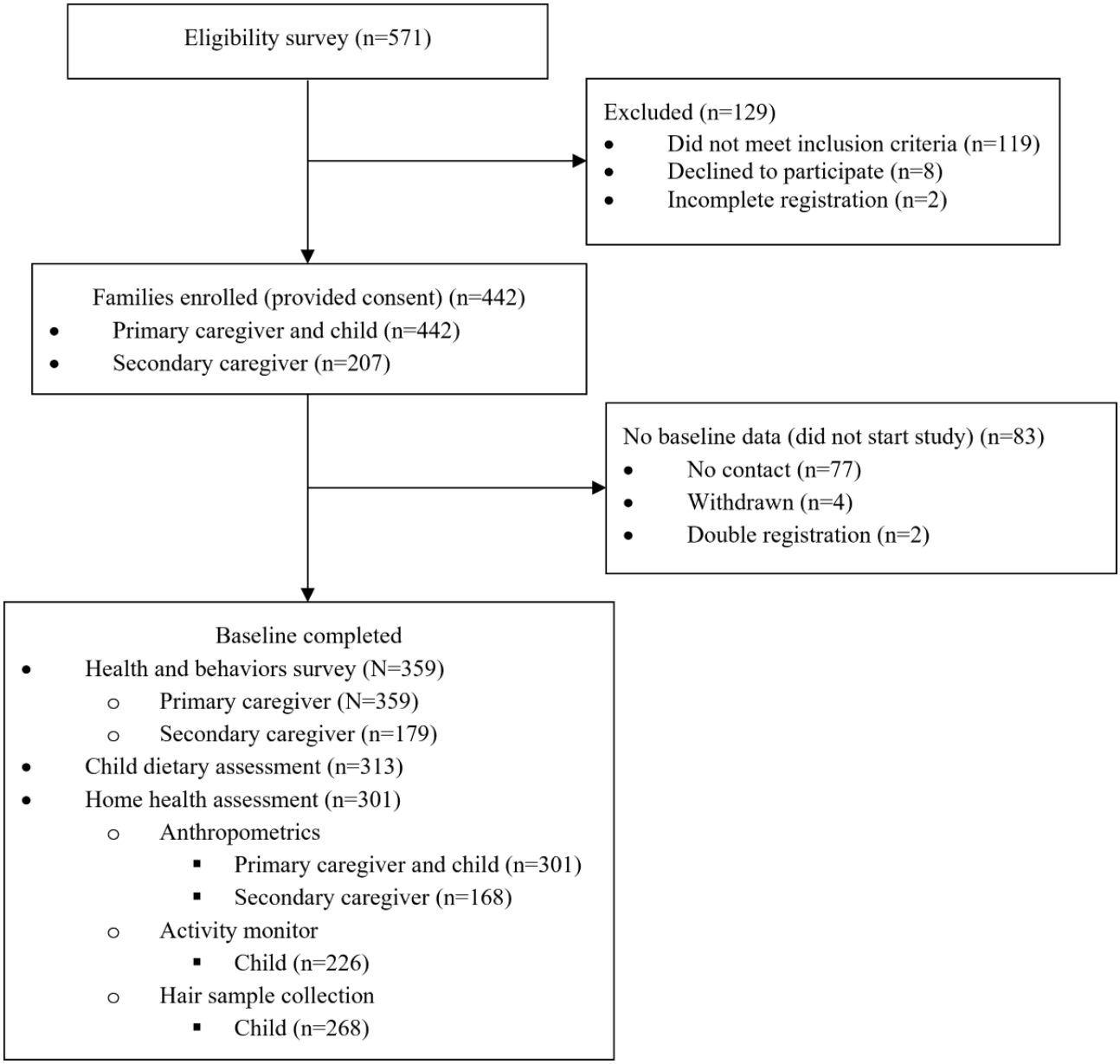

Participant baseline characteristics are shown in Table 1 for the children and Table 2 for the caregivers. There were 182 female (50.7%) and 176 male (49%) children, with a mean (SD) age of 3.9 (1.2) years. There were 359 female and 179 male caregivers, with a mean (SD) age of 36.3 (4.8) years. Approximately 74% (n=263) of children and 80% (n=431) of caregivers identified as White. Approximately 34% (n=184) of caregivers had a college diploma or less and nearly 93% (n=499) were married or cohabiting with a partner. Nearly half (n=172, 47%) of the families had an annual household income of CAD $100,000 or more.

Enrollment for this study completed in December 2021. The final second-year follow-up was completed in April 2024. Data cleaning and analysis are ongoing.

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Table 1. Baseline characteristics of data collected from July 2020 to May 2022 from Guelph and Hamilton, Ontario, for children (n=359) enrolled in the Family Stress Study.

Characteristics	Values (n=359)
Age (years), mean (SD)	3.9 (1.2)
Gender, n (%)	
Male	179 (33.2)
Female	359 (66.6)
Race or ethnicity, n (%)	
Aboriginal or First Nations	9 (2.5)
Black	10 (2.8)
Chinese	8 (2.2)
Latin American	7 (1.9)
South Asian	11 (3.1)
Southeast Asian	8 (2.2)
West Asian	4 (1.1)
White	263 (73.5)
Not stated	5 (1.4)
Other races or ethnicities (including mixed)	34 (9.5)

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Table 2. Baseline characteristics of data collected from July 2020 to May 2022 from Guelph and Hamilton, Ontario, for caregivers (n=538) enrolled in the Family Stress Study.

Characteristics	Values (n=538)
Age (years), mean (SD)	3.9 (1.2)
Sex, n (%)	
Male	176 (49)
Female	182 (50.7)
Race or ethnicity, n (%)	
Aboriginal or First Nations	9 (1.7)
Black	10 (1.9)
Chinese	12 (2.2)
Latin American	13 (2.4)
South Asian	20 (3.7)
Southeast Asian	9 (1.7)
West Asian	7 (1.3)
White	431 (80.3)
Not stated	6 (1.1)
Other races or ethnicities (including mixed)	17 (3.2)
Household income, n (%), CAD $[a]	
≤49,999	34 (9.5)
50,000 to 99,999	128 (35.8)
100,000 to 149,999	101 (27.9)
>150,000	71 (19.8)
Not stated	25 (7)
Household income, median $ (IQR)	102,800 (50,000)
Married or cohabiting, n (%)	
Married or cohabiting	499 (92.8)
Not married	37 (6.9)
Not stated	2 (0.3)
Education, n (%)	
College diploma or less	184 (34.3)
Some university or degree	161 (30.3)
Postgraduate training	189 (35.2)
Not stated	3 (0.6)

[a]An average exchange rate of 1 CAD=0.737626 USD applies.

Discussion

Principal Results

Despite public health restrictions due to COVID-19, which prevented in-person recruitment, the Family Stress Study was successful in recruiting 359 families into the Family Stress Study cohort, and 301 of those families completed all baseline measures for their child. Web-based recruitment, in particular partnering with various community organizations that serve families with young children, was critical to the recruitment success during this time when in-person engagement was limited. Identifying creative ways to connect and share information with families was also needed to ensure effective data collection. This included having research staff connect regularly with families via email, text, or phone to provide them with support throughout the data collection process and by providing information about using accelerometers to measure physical activity in a family-friendly video that could be shared remotely. These approaches were well received by families and could help inform future family-based research using remote recruitment and data collection.

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Limitations

Although successful in engaging the required sample size, the use of remote recruitment strategies may have impacted the socioeconomic diversity of the sample. While a previous family-based intervention study found that web-based recruitment of families with young children resulted in equivalent participant demographics to traditional recruitment strategies (eg, in-person or via practitioners) [84], other intervention [85] and noninterventional [86] family-based obesity studies have found that in-person recruitment was critical to engaging families, particularly low-income families. Thus, it is possible that had in-person recruitment been possible, more low-income families could have been recruited. Nearly half of the families in the sample reported an annual household income greater than CAD $100,000, which may limit the generalizability of the findings to more socioeconomically disadvantaged families. However, the median income of the sample was CAD $102,800, which is similar to the 2020 median household income (before taxes) for families in Guelph and Hamilton, which was CAD $114,000 and CAD $107,000, respectively [87]. Similarly, in our sample 73.1% (n=263) of the children identified as White, which is similar to the 2021 census data for Guelph and Hamilton which was 73.1% and 72.6%, respectively [87], suggesting that the annual household incomes and race or ethnicity of the children in our sample may be representative of the overall population within these cities.

The need to use remote data collection for the primary outcome, child adiposity, is also a limitation of the Family Stress Study. While the protocols are based on validated methods, the use of caregiver assessments may result in greater error in child adiposity measures than if using researcher-led assessments and this could lead to misclassification for some children. However, the use of caregiver-led assessments allowed the researchers to feasibly implement this study during the COVID-19 pandemic, which represented an unprecedented disruption to family life and associated increase in family stress.

Conclusions

To design effective obesity prevention interventions, there needs to be a clear understanding of key factors influencing excess weight gain in children. By identifying both the direction and the relative contributions of the biological and behavioral pathways linking chronic stress and adiposity, results from the Family Stress Study will help inform interventions to modify these pathways and reduce obesity risk among young children. Specifically, this research will identify the key behavioral drivers linking stress and obesity to inform which weight-related behaviors should be targeted with interventions in families experiencing high stress. This research will also identify whether the quality of caregiver relationships, child sex, and caregiver education and self-regulation moderate the pathways linking stress and obesity; this information is needed to inform what types of families may be best targeted in obesity prevention interventions. Thus, the results of this research will provide a much-needed basis to inform future childhood obesity prevention interventions.

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Data Availability

Due to privacy concerns, the data generated and analyzed during the Family Stress Study are not publicly available as related to the research ethics board requirements.

Authors' Contributions

JH designed this study, obtained funding, and provided supervision of the overall study. SMP and EG collected the data. JH, SMP, and EG drafted this paper. DWLM, AMD, ALM, PFT, ACB, and KMM provided critical revision of this paper.

Conflicts of Interest

None declared.

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Abbreviations

ASA24-Canada: Automated Self-Administered 24-hour Dietary Assessment Tool
CES-D: Centre for Epidemiologic Studies Depression Scale
CHAOS: Confusion, Hubbub and Order Scale
I: intercept
LGM: latent growth model
S: slope
SEM: structural equation modeling
WC: waist circumference

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Protocol

Combination of Curcuminoids and Acupressure for Inflammation and Pain in Older People with Osteoarthritis Genu: Protocol for a Randomized Controlled Trial

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Abstract

Background: Curcuminoids and acupressure have beneficial effects in reducing pain and inflammation in patients with osteoarthritis. However, only a few clinical trials are investigating biomarkers to prove this objectively.

Objective: This study aims to investigate the effect of acupressure and curcuminoids on inflammatory markers and pain in older people with osteoarthritis genu.

Methods: A randomized controlled trial (RCT) was conducted among older people with osteoarthritis. All participants were randomized to a group that received 30 mg of curcuminoids in turmeric extract capsules and acupressure (group 1) or a group that received a placebo and sham acupressure (group 2) for 3 weeks.

Results: The study was approved by the research ethics board; ClinicalTrials.gov reviewed this protocol. The extracts were manufactured from May 2023 to June 2023. Participant recruitment was conducted in September and October 2023; a total of 72 participants aged 60 years or older participated, of whom 75% (n=54) were female. Data were analyzed in April 2024, and dissemination of results is expected by the end of 2024.

Conclusions: Primary outcomes were assessed at baseline and after the intervention. Relationships were assessed with inflammatory markers, endorphin hormones, and blood level of cycloxygenase-2 hormone. Additionally, secondary outcomes included pain, ability to perform activities of daily living, and quality of life. The beneficial effects that may be found in this trial may be exceptionally relevant in clinical practice, justifying this scientific inquiry. The benefits of herbs and acupressure can be helpful as additional options in treating inflammation and pain in patients with osteoarthritis.

Trial Registration: ClinicalTrials.gov NCT06105840; https://clinicaltrials.gov/study/NCT06105840

International Registered Report Identifier (IRRID): DERR1-10.2196/54970

(JMIR Res Protoc 2024;13:e54970) doi:10.2196/54970

KEYWORDS

osteoarthritis; acupressure; curcuminoids; endorphins; biomarkers; genu; older people; randomized controlled trial

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Introduction

Background

One of the degenerative processes that occurs in older people involves the musculoskeletal system. Deterioration includes bone loss and decreased joint fluid volume, which are exacerbated by the body bearing its own weight and can cause older people to experience pain [1]. The experience of prolonged pain in patients with osteoarthritis is considered unendurable and reflected in the common cliché, "reaching the breaking point," which describes the experience and process of living with unremitting pain; limitations in mobility, leisure, and social activities; and the resulting negative consequences for a patient's physical and psychological well-being [2]. Patients with osteoarthritis often seek some turning point for positive changes in their quality of life and relief from the incessant pain. The development of complementary nursing knowledge continues to be carried out, including in the energy and biofield therapies and biologically based therapies groups, which are types of complementary alternative medicine (CAM). People aged 50 years and older are likely to be using CAM. Common use of CAM as a complement to conventional medicine—and the high use of multiple prescription drugs—further underscores the need for health care providers and clients, patients, and families to have an open dialogue to ensure safe and appropriate integrated health care [3]. One common therapy practiced in many Asian communities, especially the Javanese, is acupressure, a traditional development of massage. Historically, massage is an action that people often do independently that can act psychologically to make patients feel relief and comfort, but research needs to be conducted empirically to ensure its effectiveness.

The pain experienced by patients with osteoarthritis affects many areas of their quality of life, including physical function, emotional behavior, and mental health. Osteoarthritis-related pain is a significant factor in poor quality of life. The most common pharmacological treatment to control pain is nonsteroidal anti-inflammatory drugs, but these drugs have a considerable risk of causing side effects [4]. Limitations associated with pharmacological treatment result in patients choosing commonly available alternative therapies for pain management. Popular alternative therapies include herbal therapy, therapeutic touch, relaxation techniques, music therapy, acupuncture, and acupressure. Unlike the use of drugs, these alternative therapies do not have dangerous side effects [5].

Research concerning the effectiveness of herbal therapy in patients with inflammatory osteoarthritis was conducted in Indonesia by Kertia [6] among 80 patients. The results showed that administration of curcuminoids extracted from turmeric rhizomes significantly suppressed the activity of synovial fluid monocytes to secrete cyclooxygenase-2 (COX-2) and reactive oxygen intermediates; it also reduced leukocyte numbers and fluid malondialdehyde levels. Synovia reduces osteoarthritis-related joint pain, with an ability that is not significantly different from that of diclofenac sodium therapy at 3×25 mg per day. Recently, Bertorio [7] conducted research on the development of herbal therapy for osteoarthritis and demonstrated that the combination of ginger, soybean, and shrimp shell extracts provided significant results in reducing joint pain, stiffness, and physical disability. The findings were evaluated based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and did not show a significant difference when compared with meloxicam.

Recently, research was conducted in several countries to evaluate the effectiveness of acupressure therapy for the pain of patients with osteoarthritis. The study by Alinaghizadeh et al [8] involved 40 patients with osteoarthritis who were divided into 2 groups (intervention and control). In the intervention group, 30 minutes of acupressure therapy was given for 5 days. The results showed that the average pain score in the intervention group decreased significantly, from 5.89 at the beginning to 4.11 at the end of the study, while the pain score did not change substantially in the control group. These findings remained consistent after adjusting for age, weight, and pretreatment covariates. This study supports the evidence that acupressure therapy provides an effective option for short-term knee pain relief in patients with knee osteoarthritis. In line with the results of this research, Akbarznezhad et al [9] conducted research on 51 older persons with osteoarthritis. The participants were divided into 3 groups (acupressure intervention, placebo, and controls). The findings of this study revealed that those who received acupressure therapy for 3-4 weeks, for 10-15 minutes each time, showed a significant reduction in the total WOMAC score, pain, and physical dysfunction.

Osteoarthritis with joint disfigurement causes continuous pain that results in increased medicine consumption, leading to a need to consider alternative complementary therapies for reducing pain [10]. Management of osteoarthritis still needs improvement. To date, no research has combined standardized curcuminoid turmeric extract therapy with acupressure for inflammation and pain in patients with osteoarthritis. More clinical trials with an appropriate methodology are needed to confirm the effectiveness of standardized turmeric extract, curcuminoids, and acupressure in treating physical problems in patients with osteoarthritis.

Purpose

This study aims to investigate the efficacy of acupressure and standardized curcuminoids from turmeric extract to reduce inflammatory markers and pain, as well as endorphin hormones in the blood, while increasing quality of life in older patients with osteoarthritis genu.

Methods

Study Objectives

Primary Objective

This study aimed to determine the effectiveness of a combination of 2 regimens (acupressure and curcuminoid) as measured by changes from baseline in leukocytes, neutrophil leukocyte ratio, blood sedimentation rate, pain, secretion of COX-2, and endorphin hormones in the blood compared to placebo after 3 weeks of treatment in older patients with osteoarthritis.

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Secondary Objectives

The secondary outcomes included pain, ability to perform activities of daily living, and quality of life. Pain was assessed with a visual analog scale. The ability to perform activities of daily living was assessed with the Barthel index and WOMAC. Quality of life was measured by respondents' satisfaction in daily activities based on indicators in the Knee injury and Osteoarthritis Outcome Score (KOOS) instrument.

Study Design

We conducted a 2-arm, double-blind (patient and investigational blinded) randomized controlled trial (RCT) to assess the efficacy, tolerability, and safety of the combination of acupressure and curcuminoid versus placebo.

Prescreening

Patients were prescreened for specific X-ray and laboratory parameters. Following a screening visit, eligible participants started a washout period. After the washout period, eligible participants were randomized and treated for 3 weeks. The total duration of the study was 5 weeks.

Study Setting and Source Population

Eligible participants were individuals recruited from communities covered by government-owned primary care hospitals who consulted a rheumatology subspecialist physician with symptoms of pain and discomfort around the knee.

Participants were recruited from August to October 2023. An informed consent form was provided to participants in their local language to gain credibility. To maintain the secrecy of data gathering, participant codes were provided, restricting access to only the lead researcher. After obtaining agreement from the participants, a thorough screening process was conducted to determine their eligibility.

Population

The study population consisted of male and female patients (aged ≥65 years) with osteoarthritis (osteoarthritis with knee joint pain, knee joint stiffness in the morning for less than 30 minutes, crepitus, deformity, joint swelling [asymmetrically on the right and left], and other signs of inflammation [eg, a feeling of even warmth and reddish color]). The objective was to achieve a random allocation of about 70 patients. Given an anticipated screening failure rate of 25% and a washout failure rate of 20%, a total of about 100 patients underwent the screening procedures.

Inclusion Criteria

In order to be considered for participation in this study, patients had to satisfy all of the following requirements: a clinical diagnosis of osteoarthritis that was confirmed by physical examination and X-rays; experience of pain with a numeric rating scale of 1-7; ability to swallow capsules; and mobility without assistance or with minimal assistance.

Exclusion Criteria

Patients fulfilling the following criteria were not eligible for inclusion in this study (the investigator applied no additional exclusion criteria to ensure the study population represented all eligible patients): the presence of Parkinson disease, dementia, psychosis, new bone fractures, joint dislocations, cancer, rheumatic diseases other than osteoarthritis (eg, rheumatoid arthritis), and analgesic-dependent disease. Patients were also excluded if they were undergoing joint replacement therapy.

Eligibility Test Procedure

Radiographs were used to assess participants for osteoarthritis using the Kellgren and Lawrence criteria, which categorize osteoarthritis from mild to severe. It should be noted that at the beginning of the disease, the radiographic appearance of the joint is still normal. According to Kellgren and Lawrence, radiologically, osteoarthritis is classified into 5 grades: grade 0 (normal), no signs of osteoarthritis; grade 1 (doubtful), without osteophytes, doubtful joint narrowing; grade 2 (minimal), few osteophytes on the tibia and patella and asymmetrical narrowing of the joint surface; grade 3 (moderate), moderate osteophytes present in several places, narrowing of the joint surface, and presence of subchondral sclerosis; and grade 4 (severe), presence of large osteophytes, complete narrowing of the joint surface, severe subchondral sclerosis, and joint surface damage.

The Mini Mental State Examination (MMSE) was used to assess the patient's cognitive abilities, which is essential to ensure that a patient can understand the treatment and outcome measurement process instructions.

Randomization, Allocation, and Blinding

Seventy eligible participants were randomized to the group with curcuminoid capsules and acupressure (C+A; group 1) or the group with placebo and sham acupressure (P+S; group 2) via lottery randomization. Following this, the individuals were assigned randomly to either the C+A or P+S groups. Figure 1 displays the schematic CONSORT (Consolidated Standards of Reporting Trials) [11] flow diagram for the study procedure, as reported in the study.

The baseline characteristics for each participant were determined by the therapist using a standardized assessment form. During the measurement of baseline characteristics, various data were documented, including sex, age, body mass, pain characteristics, history of sickness, and medication use. The timetable of participant participation was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [12] (Table 1). The primary and secondary outcome indicators were assessed prior to administering the intervention.

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Figure 1. Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

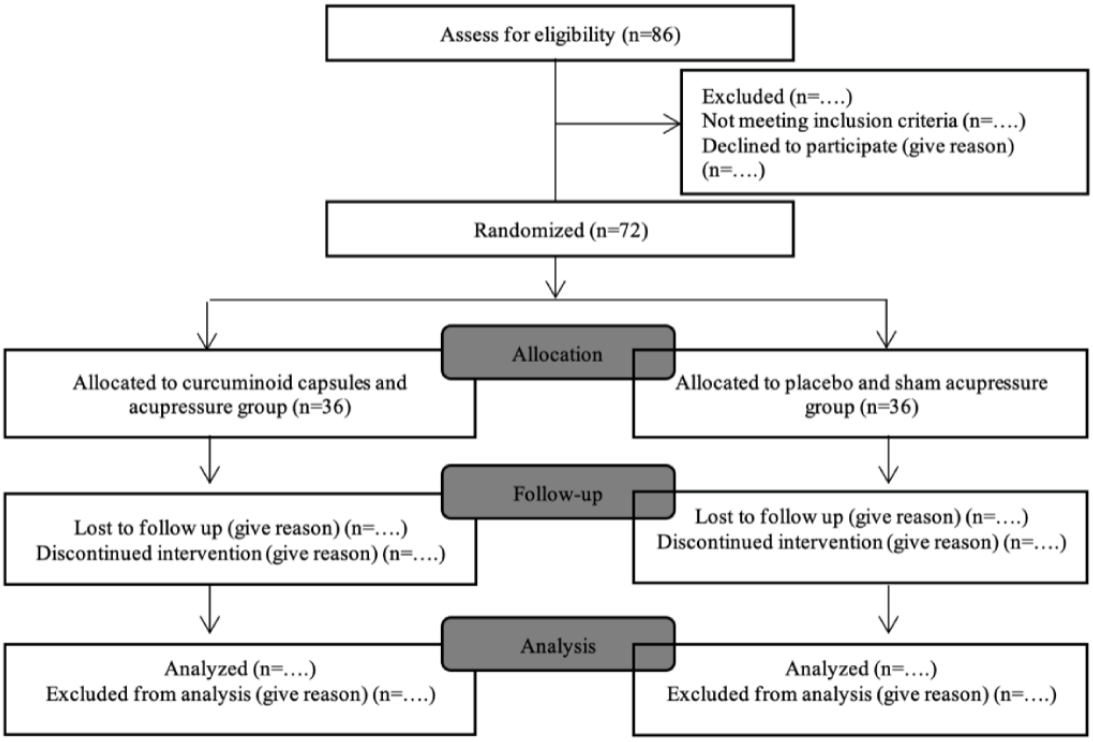

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommended schedule for participation.

Timepoint	Enrollment	Allocation	Postallocation			Close-out			
		Week 0	Week 1	Week 2	Week 3	Day 1	Week 1	Week 1	After week 3
Enrollment									
Eligibility screening	✓								
Informed consent	✓								
Radiography and MMSE[a] test	✓								
Allocation		✓							
Interventions									
C+A[b] therapy			✓	✓	✓				
P+S[c] therapy			✓	✓	✓				
Assessments									
Demographic details	✓								
Inflammatory markers						✓			✓
Endorphins						✓			✓
Quality of life						✓	✓	✓	✓

[a]MMSE: Mini Mental State Examination.

[b]C+A: curcuminoid capsules and acupressure.

[c]P+S: placebo and sham acupressure.

Intervention

Following the administration of standardized evaluations and baseline measurements, the intervention was implemented. The participants were grouped randomly to either the C+A group or the P+S therapy group in a random manner. In the study, both the acupressure therapy and sham acupressure groups underwent a total of 2 sessions each week, each lasting 20 minutes, for a period of 3 consecutive weeks. During this period, participants were prohibited from regularly using any medications, with the exception of antihypertensive agents, thyroid medications, and antidiabetic therapies. The participants

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were provided with electronic message reminders in order to facilitate their adherence to the intervention. Preintervention session reminder texts were dispatched prior to each session. Each participant consumed curcuminoid capsules or placebo 3 times daily for a duration of 21 days.

To perform acupressure in the C+A therapy group, the patient was put in the supine position with legs straight (Figure 2). The tools and materials were prepared, such as a seat (or bed), warm water, olive oil, wet and dry tissues, and towels. The therapist washed their hands, and the participant sat in a comfortable position. The patient was taught breathing relaxation techniques to use during therapy. The patient was allowed to pray according to their beliefs. To ensure the participant was relaxed and comfortable, some of the client's clothing or accessories were removed if they might hinder the acupressure action being performed, if necessary. A client pain assessment was performed. The parts to be massaged were wiped with warm water treated with a disinfectant solution using a small towel, then dried with a clean towel. Using cream or oil, a warming massage was done with basic massage techniques, according to the client's condition (using rubbing, squeezing, or pressing) and the patient's feet were stretched. Acupressure massage was performed at the following points: ST34, ST36, *tai xi* acupoint, GB34, SP 9, and SP 8.

Sham acupressure was performed at 6 points in the P+S therapy group, all in the foot area, avoiding the therapeutic points used in the C+A therapy group.

The patient was asked to report any abnormal sensations or discomfort during the intervention. The researchers provided the study medications to the curcuminoid and placebo groups in a double-blind fashion. A standardized curcuminoid turmeric extract was prepared. Samples were first made from extracted turmeric and then optimized. The capsule formulation was made from turmeric rhizome extract, which contains 30 mg of curcuminoids per capsule. In the study, standardized curcuminoid turmeric extract was given in capsules 3 times a day for 3 weeks.

The researchers confirmed that the participants did not use any other intervention by performing a routine anamnesis that included visiting the participants at home 1 by 1 twice in a week, which was assisted by a village health worker (*kader*) and therapist.

Figure 2. Acupressure massage points.

Study Outcomes

All outcome measures were assessed at baseline and after 3 weeks of intervention.

Primary Outcomes

Inflammatory Markers

Leukocyte numbers, the neutrophil lymphocyte ratio (NLR), and blood sediment rate were measured as inflammation markers. The examination used a complete blood test using a hematology analyzer, a laboratory tool used to measure and count the number of blood cells. The blood samples were mixed using a mixture of reagents to create a hemolyzing process. This process was divided into several parts for each purpose, that is, to measure leukocytes, neutrophils, platelets, and erythrocytes.

Secretion of the COX-2 Enzyme

The COX-2 enzyme is an essential mediator in increasing the inflammatory response. In the blood plasma of patients with osteoarthritis, the COX-2 enzyme can be detected. The COX-2 enzyme examination was conducted using the enzyme-linked immunosorbent assay (ELISA) method with blood plasma.

Secretion of Endorphin Hormones

Endorphins, in this case β endorphins, are hormones released by the pituitary gland in response to stress or pain, which are also secreted in blood plasma. Endorphin hormone levels in the blood were measured before starting therapy and after 3 weeks of therapy.

Endorphin hormone examination was done using the ELISA method on blood plasma that had been incubated at room

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temperature for 10-20 minutes, after which the tube was centrifuged for 20 minutes at a speed of 2000-3000 rpm.

Secondary Outcomes

The effectiveness of therapy is its ability to suppress other expected output indicators. Other output indicators were measured before starting therapy and after 3 weeks of therapy: (1) knee pain, as measured by the VAS score; (2) the WOMAC score, which assesses joint stiffness and joint functional ability; (3), the Barthel index; and (4) the KOOS.

WOMAC is a questionnaire developed by Bellamy et al [13] that continues to be developed to measure the functional abilities of patients with knee osteoarthritis. The WOMAC instrument has been translated into Indonesian. It has been tested for validity by Karsten et al [14] and has a Cronbach α coefficient of 0.966, indicating relatively high internal consistency. It is highly correlated, meaning that the WOMAC questionnaire in Indonesian is correct, validated, and can be used in Indonesian. This questionnaire evaluates 3 subscales by scoring on a 5-point ordinal scale: pain (5 items), stiffness (2 items), and physical function (17 items). The details of the scores are as follows: for pain, score 0 (no pain), score 1 (mild pain), score 2 (moderate pain), score 3 (severe pain), and score 4 (very severe pain); for stiffness, score 0 (not stiff), score 1 (mildly stiff), score 2 (medium stiffness), score 3 (extremely stiff), and score 4 (stiff to the point of locking); and for physical function, score 0 (not difficult), score 1 (somewhat difficult), score 2 (quite difficult), score 3 (very difficult), and score 4 (very difficult). The subscale score ranges are 0-20 for pain, 0-8 for stiffness, and 0-68 for physical function. The total score is obtained by adding up the scores of the 3 subscales, with a maximum score of 96. A higher WOMAC score indicates pain, stiffness, and worse physical function. The total WOMAC score can be categorized into 3 groups, namely low risk (score ≤60), moderate risk (score 60-80) and high risk (score ≥81).

The ability to perform activities of daily living in older people was assessed with the Barthel index questionnaire, which was first developed in 1965 by Mahoney and Barthel [15]. The Maryland State Medical Society holds the inventory of this instrument. In 2020, Pongantung et al [16] translated it into Indonesian and conducted a validity test, finding that interrater reliability was satisfactory. Regarding content validity, the Indonesian version of the Barthel index is acceptable. The construct validity test reveals 2 main factors: functional performance and physiological function.

Quality of life was assessed with the KOOS, an instrument to assess patient opinions about the condition of the knee and problems related to the knee. The KOOS has been translated into Indonesian and tested for validity by Phatama et al [17] with Cronbach α results of 0.84 to 0.97 for all subscales, indicating adequate internal consistency. The test-retest reliability demonstrates a high level of accuracy, as indicated by the intraclass correlation coefficients ranging from 0.91 to 0.99 across all subscales. There were no statistically significant variations observed in the replies of the KOOS subscales between the initial administration of the questionnaire and the subsequent administration within a span of 21 days. The validity and reliability of the Indonesian adaptation of the KOOS have been established, indicating that it serves as an objective tool for assessing knee ligament injuries and knee osteoarthritis in the Indonesian community. The KOOS can be used as a measurement of quality of life because it includes measurements of 5 subscales, namely, symptoms, rigidity, pain, daily activities, sports and recreation activities, and knee-related quality of life. The week prior to the test is the period considered when answering the questions. Answer options are standard (Likert scale), and each question is scored from 0 to 4. Scores are normalized (a score of 100 indicates no symptoms and 0 indicates extreme symptoms).

Sample Size

The following formula was used to estimate the sample size:

where *N* is the sample size required in both groups, and *s* is the SD of the primary outcome. This research has a confidence level (1–α) of 95%, so the value obtained is α=5%. Accordingly, the research hypothesis is unidirectional, so the magnitude of Z1–α=1.96. The research's power (1–β) was also set at 80%, so if the value of β=20%, then the amount of Z1–β=0.842. Previous research [18] that analyzed changes in leukocytes in participants treated with curcuminoid therapy based on 30 mg turmeric extract taken 3 times a day for 14 days, amounting to 30.00±5.10 mg and meloxicam 1×15 mg per day, obtained a mean Δ value of leukocytes in the control group of 164.1 µL+50.91, and in the treatment group, 174.27 µL+78.93. The total number of participants required in the 2 groups was 60. Considering a dropout rate of 20%, the sample size was increased to 36 in each group.

Ethical Considerations

The Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University – Dr Sardjito General Hospital approved the study protocol, which was registered with the Forum for Ethical Review Committees in Asia and the Western Pacific (project number KE-FK-0674-EC-2023). The study was conducted according to Indonesia's 2021 National Health Research and Development Ethical Guidelines and Standards by the Health Research and Development Ethics Committee and the Declaration of Helsinki, as revised in 2013. ClinicalTrials.gov has reviewed this protocol (NCT06105840).

Participation in this research was voluntary, without any coercion. All participants received comprehensive information about the research, especially about the intervention that would be given and the possible benefits and risks. Participants were allowed to withdraw at any time without penalty.

Participants were screened and provided a unique ID number to protect their personal information. The unique ID number was used to differentiate participants in an anonymous manner across measures and follow-up questionnaires. Participants who met the eligibility requirements of the initial screening form were prompted to fill out a contact form with their full name and address. Participants obtained benefits including an x-ray examination to determine the knee joint condition and therapy

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according to the research group they were assigned to. Participants were given tools for massage therapy (a towel and massage oil) that were theirs to keep. After the research activities were completed, participants in the control group received the same herbal therapy and acupressure as the treatment group. All information related to the identity of the research participants was kept secret and known only by the researchers, research staff, and auditor. Research results are published without the identity of the research participants.

Adverse Events

We conducted an investigation of potential adverse events that could arise with the administration of the combined curcuminoid and acupressure therapy, encompassing symptoms such as heightened soreness, pain, numbness, and tingling. All instances of adverse events that pose a threat to life or were associated with a substantial impairment were duly reported to the ethics research committee of the institution. During the research, the researchers provided necessary protection in case of adverse events. This protection comprised examination by a physician and treatment in hospital.

Data Analysis

The baseline characteristics of the participants will be assessed using descriptive statistics. The Shapiro-Wilk test will be used to determine the normality of the data gathered. Descriptive statistics will be presented using either the mean (SD) or the median (IQR), depending on the normality of the data. The Wilcoxon signed-rank test or a paired *t* test (2-tailed) will be used for within-group comparisons. In a similar vein, the Mann-Whitney *U* test or an independent *t* test (2-tailed) will be used to conduct comparisons between groups. The chosen level of significance for this study will be established at .05.

Data Management

The collected data will be maintained in a secret manner for the duration of the study and disposed of after a period of 5 years. The process of collecting the initial data will involve the use of printed data-collection forms. These forms will afterward be organized and transcribed into an electronic format. The electronic data will be saved on a desktop computer that is not connected to the internet, as a precautionary measure to mitigate the risk of illegal access. This stored data will be used for further analysis. The individual appointed as the chair of the student project committee at the institute will be responsible for supervising data management.

Results

In June 2023, the capsule formulation was prepared from turmeric rhizome extract, which had been tested and found to contain 30 mg of curcuminoids per capsule. The acupressure technique was formulated based on the therapeutic points recorded in the Acupressure Therapy Procedure Module to Improve Comfort in Knee Osteoarthritis, which has received a copyright from the Ministry of Law and Human Rights of the Republic of Indonesia with ID 000564960. The sham acupressure technique used points that had the potential to provide benefits and a relaxing effect in the feet but not at the main location of therapy. Therapeutic procedures and dosage were checked and approved by all authors.

In September 2023, a total of 84 older people who experienced joint pain declared themselves willing to be recruited. Physical examination and radiographs were used to assess the participants for osteoarthritis; 72 older people met the inclusion criteria. This allowed data analysis to take place in April 2024, and results should be submitted for publication in an international peer-reviewed journal by the end of 2024.

Discussion

Principal Findings

The benefits of herbs and acupressure can be helpful as additional options in treating inflammation and pain in patients with osteoarthritis. Curcuminoid is an active compound in turmeric that has natural anti-inflammatory properties. A meta-analysis conducted by Kou et al [19] showed that curcuminoid supplementation was effective in reducing clinical symptoms in the treatment of arthritis. The use of curcuminoid supplementation in patients with arthritis could reduce the possibility of unpleasant consequences. The results of systematic review showed that acupressure as a single or complementary intervention provides significant benefits in the management of osteoarthritis [10].

These studies showed that curcuminoid supplements may help reduce pain and inflammation in osteoarthritis. Acupressure points can stimulate the release of natural endorphins, which can help reduce pain and increase feelings of relaxation. Acupressure also works to help restore uninterrupted energy flow in the body, which can help reduce inflammation and improve joint function. Therefore, we deliberately chose an RCT design as it is often regarded as the preferred strategy for assessing and comparing the efficacy of therapies.

The strength of this study lies in its ability to prove the efficacy of a combination therapy for osteoarthritis with curcuminoids and acupressure. This is achieved through the use of an RCT design, which has never been used by other studies. This study uses an RCT because it can demonstrate the superiority of a new treatment over an existing standard treatment or a placebo. RCTs are the gold standard for ascertaining the efficacy and safety of a treatment. After conducting a systematic review [20], the researchers will continue their research using an RCT in the hope of obtaining the highest level of empirical evidence with control of the risk of systematic error (bias). Another advantage of this study is that the participants came from identical communities, so they are likely to have homogeneous demographics and characteristics, which is needed in RCTs.

Limitations

The limitation of this study is that it does not consider the severity of osteoarthritis or the duration of osteoarthritis.

The main expected findings of the research are to determine biomarker changes, such as a decline in inflammatory markers as shown by leukocyte numbers and the NLR, a decline in the secretion of the COX-2 enzyme, and an increase in the secretion of endorphin hormones after conducting the intervention for 3

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weeks. The secondary outcomes are the decline in knee pain, the increase in joint functional ability, and the increase in activities of daily living and quality of life.

Leukocyte count and the NLR are thought to increase linearly with the severity of osteoarthritis. The research of Taşoğlu et al [21] showed that a severe knee osteoarthritis group had a higher blood NLR than a mild to moderate group. A blood NLR of ≥2.1 was taken as the cutoff based upon the receiver operating characteristics (ROC). In the ROC curve analysis, a blood NLR ≥ 2.1 had 50% sensitivity and 77% specificity in predicting severe knee osteoarthritis. The results of this study suggest that blood NLR may be a novel and promising inflammatory marker indicating the severity of knee osteoarthritis. Blood NLR is a recent indicator of systemic inflammation. A blood NLR ≥2.1 is an independent risk factor for severe knee osteoarthritis.

This study seeks empirical evidence that COX-2 is expressed in peripheral blood as a result of the inflammatory process in patients with osteoarthritis. The anti-inflammatory action of curcuminoid-standardized turmeric extract is achieved by inhibiting the activity of cyclooxygenase and lipoxygenase, and also by acting as an antioxidant. In vitro curcuminoid can inhibit the activity of phospholipase, lipoxygenase, COX-2, leukotriene, prostaglandin, thromboxane, nitric oxide, collagenase, elastase, hyaluronidase, interferon, tumor necrosis factor α, and interleukin-12 [22].

In addition to COX-2 and NLR, the endorphin hormone was measured as a biomarker in this study. Pain changes experienced by people with osteoarthritis genu can be associated with secretions into the blood. The more endorphin enzymes are secreted by monocytes into the blood, the less pain will occur and the more comfort.

Knee pain in osteoarthritis is an unpleasant sensory and emotional experience due to potential or actual tissue damage. Pain is caused by the stimulation of chemical mediators such as histamine, bradykinin, acetylcholine, and prostaglandins. In addition to these substances that can stimulate pain sensitivity, the body also has substances that can inhibit pain. Endorphins and encephalin can relieve pain. Osteoarthritis pain is associated with severe inflammation and joint disfigurement. The more severe the inflammation and the joint changes, the more painful the joint becomes.

Joint stiffness and joint functional ability are related to pain and inflammation in osteoarthritis patients. The more severe the inflammation and pain, the more joint stiffness increases and joint functional ability declines. Pain is a significant factor in determining an individual's perceived breakpoint, which in turn affects other aspects of life. The most prevalent symptom combinations are joint locking, knee swelling, and stiffness. Mobility limitation and the need for assistance increase as a result of pain and limited mobility. Another functional activity affected by limited functional mobility is the ability to perform self-care [23].

Quality of life is related to pain and the ability to be active. The more severe the pain and the greater the inability to perform daily activities, the lower the quality of life. The prolonged experience of pain in patients with osteoarthritis represents a breakpoint, a pivotal point in the experience of living with unrelenting pain, mobility limitations, and the subsequent consequences for physical and psychological well-being. These breakpoints experienced by patients with osteoarthritis are turning points for changes in quality of life. They are turning points that are precipitated by an increase in pain, the emergence of a combination of other symptoms, an increased limitation or loss of mobility, and changes in other functional activities [10].

Conclusions

This document outlines a randomized clinical experiment that aims to examine and compare the impacts of curcuminoid and acupressure interventions on the amelioration of inflammation and pain and the enhancement of quality of life among older people diagnosed with osteoarthritis.

Acknowledgments

This study would not be possible without the support of the Universitas Gadjah Mada and Stikes RS Baptis Kediri. The authors of this protocol would like to thank all village health workers (*kader*) for effectively coordinating the participants. In addition to personal funds, this research was conducted with support from other parties through partial funding, among them Universitas Gadjah Mada (Final Project Recognition Grant Universitas Gadjah Mada 5075/UNI.P.II/Dit-Lit/PT.01.01/2023) and also the Doctor of Medicine, Public Health, and Medicine Study Program of the Faculty of Medicine, Public Health and Medicine, Universitas Gadjah Mada, through the Damas Grant Program 2023 (2342/UN1/FKKMK.1.3/PPKE/PT/2023).

Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SM contributed to data curation, formal analysis, investigation, writing the original draft, review, and editing. NK contributed to conceptualization, project administration, resources, supervision, methodology, review, and editing. EM contributed to conceptualization, data curation, formal analysis, investigation, review, and editing.

Conflicts of Interest

None declared.

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Abbreviations

CAM: complementary alternative medicine
COX-2: cyclooxygenase-2
ELISA: enzyme-linked immunosorbent assay
KOOS: Knee injury and Osteoarthritis Outcome Score
NLR: neutrophil lymphocyte ratio
RCT: randomized controlled trial
ROC: receiver operating characteristic
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

Evaluation of Staining Propensity of Silver Diamine Fluoride With and Without Potassium Iodide in Children (Project Healthy Smiles): Protocol for a Randomized Controlled Trial

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Abstract

Background: Silver diamine fluoride (SDF) is becoming more widely recognized as a simple, cost-effective approach to minimize sensitivity and arrest caries. However, SDF results in caries that are stained black. Potassium iodide (KI) treatment with SDF may minimize or lessen the staining. However, the effectiveness of KI on staining has not been investigated. Studies demonstrating that potassium iodide reduces the black staining are still insufficient. This paper presents the study protocol for Healthy Smiles, a randomized controlled trial implemented to compare the staining propensity of SDF and SDF+KI.

Objective: This study, Healthy Smiles, aims to evaluate the staining propensity of SDF and SDF+KI using a Nix Mini color sensor among children aged 4 to 6 years. Another objective of the study is to evaluate the caries-arresting effect of SDF and SDF+KI in the treatment of carious primary teeth.

Methods: This study is a randomized controlled trial. A total of 60 children with caries that meet the criteria of the International Caries Detection and Assessment System (code 1 or above) will be randomly assigned to treatment groups, where group 1 will be treated with SDF and group 2 will be treated with SDF+KI. Discoloration of treated lesions will be assessed digitally using a Nix Mini color sensor. Participants will be followed up at 1, 3, and 6 months after treatment to digitally record the ΔL and ΔE values using the Nix Mini color sensor. Data will be analyzed using SPSS (version 28; IBM Corp). Independent sample *t* tests and the Mann-Whitney *U* test will be used to compare the 2 groups.

Results: Enrollment started in October 2023. It is estimated that the enrollment period will be 12 months. Data collection is planned to be completed in 2024.

Conclusions: The presented paper describes Happy Smiles, a project that provides an opportunity to address the aesthetic inconvenience of patients without compromising the effectiveness of the SDF treatment. The trial findings will contribute to the limited evidence base related to discoloration after SDF intervention to improve aesthetic appearances in child oral health. If the results from the trial are promising, it will lead to the development of a model for child oral health and pave the way for further research in child oral health.

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KEYWORDS

silver diamine fluoride; SDF; potassium iodide; KI; tooth discoloration; dental caries; dental esthetics; dental; teeth; healthy smile; staining; treatment; oral health; child

Introduction

Developments in our understanding of the pathophysiological processes underlying dental caries led to the development of minimal intervention dentistry, which emphasizes the critical importance of maintaining the integrity of the natural tooth structure and adopts a biological approach in the management of caries lesions [1,2]. Nishino et al [3] described the caries-arresting properties of silver diamine fluoride (SDF) in 1969. SDF is a colorless liquid substance with a pH of 10 that contains 5% to 5.9% fluoride and 24.4% to 28.8% (weight by volume) of silver [4]. The primary reason for SDF's efficacy in preventing caries is its microbicidal impact on cariogenic biofilm [5,6]. SDF treatment results in a decrease in size and an increase in mineral density and hardness in carious lesions [7].

Children, hospitalized patients, people with mental disorders, people who have received radiation and chemotherapy, and patients with xerostomia, as well as all those with high rates of tooth decay, can benefit from SDF [8]. This is a therapy option in dental clinics and community dental health initiatives due to its low cost and the simplicity of its application. A significant service that dental auxiliaries can be trained to provide is stopping active caries [9]. SDF should be applied every 6 months and no more than 3 weeks apart [10].

Despite the strong evidence for SDF's antibacterial effectiveness in arresting tooth caries, its clinical application has been relatively limited until now [11]. Location and tooth type have a major impact on parental acceptance of SDF therapy. Parental acceptability of SDF treatment is considerably greater for primary teeth than permanent teeth, and for posterior teeth than anterior teeth in both dentitions [12]. Regardless of the type and location of the teeth, parents of children who had previously exhibited resistant behavior during dental treatment were significantly more receptive of SDF treatment than parents of cooperative children [12].

Contrary to anterior teeth, posterior tooth staining is more widely accepted. Even though anterior tooth discoloration is undesirable, parents prefer SDF treatment to any other complex behavioral approaches like sedation or general anesthesia, which are not appreciated by most parents [13]. The precipitation of silver phosphate is what causes the discoloration that occurs after applying SDF (which has the formula Ag_3PO_4) [14].

In order to overcome this problem and increase the clinical use of SDF, a new method of application has been suggested [15]. This includes treating the initial layer of SDF with a layer of potassium iodide (KI), which combines with the free silver ions in SDF and inhibits the precipitation of silver phosphate. Since then, numerous investigations have shown that using KI after SDF creates a yellow silver iodide precipitate and prevents tooth stains from turning dark [10,16]. Following the application of KI in a dose-dependent manner, Detsomboonrat et al [17] noticed a considerable and immediate reduction in staining caused by SDF.

Studies demonstrating that KI reduces black staining are still insufficient. This paper presents the study protocol for Healthy Smiles, a randomized controlled trial implemented to compare the staining propensity of SDF+KI.

The aim of the study is to evaluate the staining propensity of SDF+KI among children aged 4 to 6 years by incorporating artificial intelligence in dentistry as a tool for precise interpretation of the findings, which will add to the evidence pool. The objectives of the study include (1) to evaluate the staining propensity of SDF+KI using a Nix Mini color sensor (Nix Sensor Ltd) among children aged 4 to 6 years, (2) to evaluate the caries-arresting effect of SDF+KI in the treatment of carious primary teeth, and (3) to assess parental satisfaction with dental appearance and color following treatment with SDF versus SDF+KI using a detailed questionnaire (Table 1). We hypothesized that there would be no difference in the staining propensity of SDF+KI among the children.

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Table 1. Objectives and measures.

Objectives	Measures	Description
1. To evaluate the staining propensity of SDF[a] and SDF plus KI[b] using the Nix Mini color sensor among children aged 4 to 6 years.	Child dental examination	• At the end of 1, 3, and 6 months after treatment each tooth will be photographed and each tooth's color change will be measured using the Nix Mini color sensor.
2. To evaluate the caries-arresting effect of SDF and SDF+KI in the treatment of carious primary teeth.	Arrest of carious lesions (6 and 12 months after treatment)	• The progression in the size of the carious lesions will be evaluated using the ICDAS[c] index as stable or progressing. • The consistency of the lesions will be evaluated upon gentle probing using a ball-ended World Health Organization probe as soft or hard carious lesions.
3. To assess parental satisfaction with dental appearance and color following treatment with SDF and SDF+KI.	Parental questionnaire using prevalidated 5 point-Likert scale (immediately after treatment)	• "You are satisfied with your child's aesthetics after SDF/SDF+KI treatment." • "SDF/SDF+KI application is an easy process." • "SDF/SDF+KI application is pain free for your child." • "SDFSDF+KI taste is acceptable to your child."

[a]SDF: silver diamine fluoride.

[b]KI: potassium iodide.

[c]ICDAS: International Caries Detection and Assessment System,

Methods

Study Design

Healthy Smiles will be carried out for a period of 1 year. The study is an active-controlled, parallel-group randomized controlled trial. A detailed schedule of enrollment, interventions, and assessments is given as a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule (Figure 1).

Baseline data will be collected and the children will receive the intervention. The examination will be done by a single examiner with the help of recorders from government-run nonformal preschools and primary schools in Mangaluru, India. This schedule is designed with slight flexibility in order to accommodate any unforeseen lapses or inconveniences. This trial has 3 phases, including data collection, intervention, and follow-up (Figure 2).

Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments. ICDAS: International Caries Detection and Assessment System; KI: potassium iodide; SDF: silver diamine fluoride; t0: baseline; t1-t4: 1-, 3-, 6-, and 12-month follow-ups.

	STUDY PERIOD						
	Enrollment	Allocation	Follow-up				Close-out
TIMEPOINT	t_0 (baseline)	t_0 (baseline)	t_1	t_2	t_3	t_4	
ENROLLMENT:							
Eligibility screen	✓						
Informed consent	✓						
Randomization	✓						
Allocation		✓					
INTERVENTIONS:							
SDF			←	—	—	—	→
SDF+KI			←	—	—	—	→
ASSESSMENTS:							
ICDAS criteria	✓						
Staining propensity		✓	✓	✓	✓		
Arrest of carious lesion					✓	✓	✓
Level of satisfaction					✓		

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Figure 2. Phases of Healthy Smiles. CPI: Community Periodontal Index; ICDAS: International Caries Detection and Assessment System.

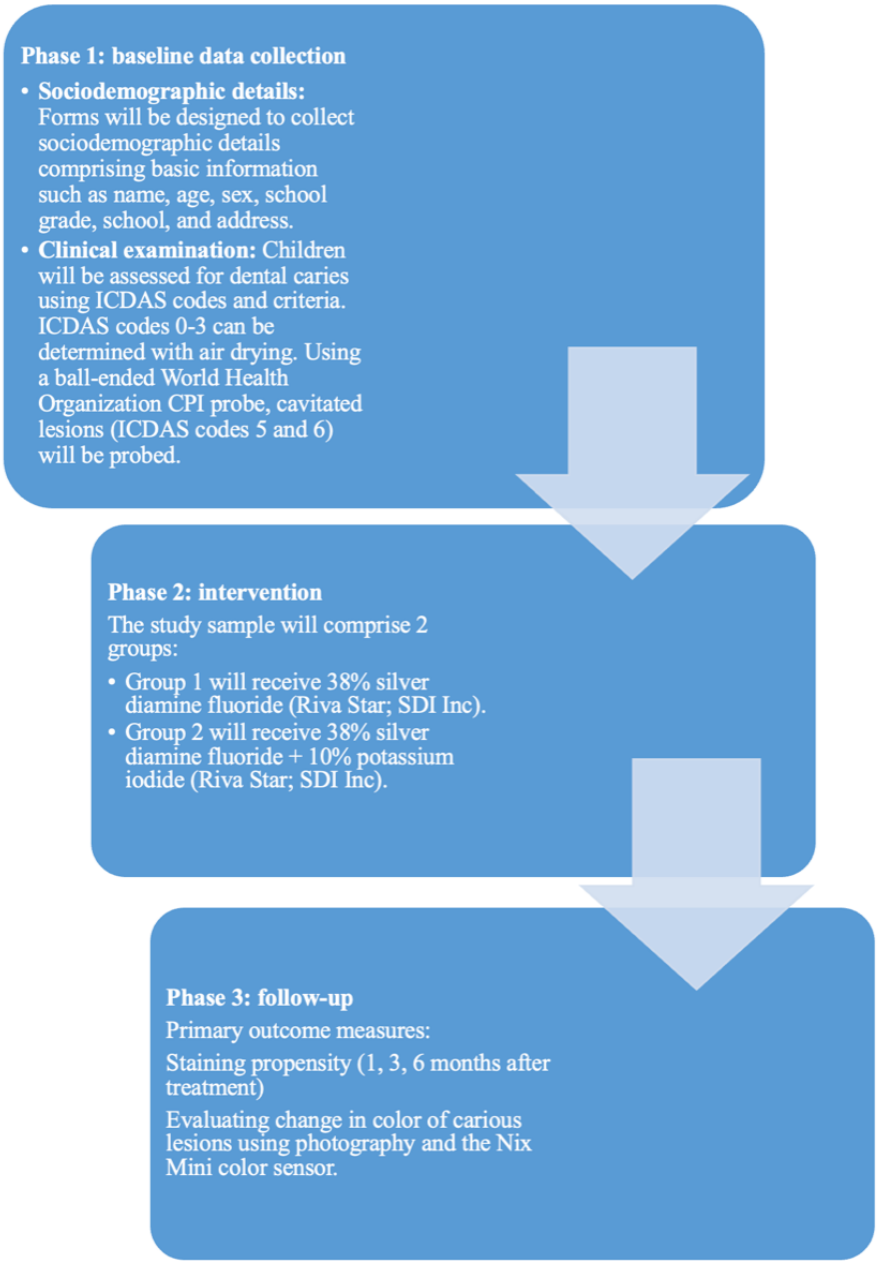

Study Location

The study will be conducted in primary schools and government-run nonformal preschools in Mangaluru, India. Inclusion and exclusion criteria are shown in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Children aged from 4 to 6 years
- Children who meet the criteria for International Caries Detection and Assessment System (ICDAS) code 1 or greater
- Children who have one or more active carious lesions in primary teeth not involving the pulp
- Parents who give consent for participation in the study

Exclusion criteria

- Children with preshedding tooth mobility
- Children with signs of pulpal or periapical infection
- Children with gingival or perioral ulceration or stomatitis
- Children who have any history of allergies

Recruitment: Trial Participants

A total of 120 children will be examined in the government-run nonformal preschools and primary schools by the supervising staff (guide) and the primary investigator. The sample size will be 60 children.

Randomization

The names of 60 children will be selected randomly with a computer-generated table of random numbers by an independent assistant using the Stat Trek (StatTrek.com) random number generator. The names will be randomly distributed into 2 groups (SDF and SDF+KI) with a lottery method for the next phase. For the trial, 2 groups will be assigned: group 1 and group 2. The assistant, who is independent of the trial, will be responsible for giving each child a serial number indicating his or her allocation. Blinding of the examiner or the children will be impossible during the intervention and follow-up due to the different natures of the materials. However, the assistant, who will be responsible for giving and collecting the questionnaires from the parents or guardians, as well as the statistician, will not know the group to which the child belonged.

Standardization and Calibration

Clinical examinations using the ICDAS codes and criteria will be performed among children with active dental caries by the primary investigator and the supervising staff (guide). Standardization and calibration for the ICDAS index will be done before commencing the study. Calibration will be done at the Department of Public Health Dentistry. For this, 10 participants will be chosen in the 4- to 6-year age group with dental caries with an ICDAS code of 1 or greater, for whom the examiners will record the index. For determination of intra-examiner variability, these participants will be recalled on different days and the same examiner will repeat the examination. Interexaminer reliability will be assessed and compared with the gold standard examiner (guide). The κ coefficient value will be calculated, and a κ coefficient of 0.80 and above will be accepted as a reliable level of agreement.

Statistical Power

The sample size was calculated with G*Power (version 3; Universität Düsseldorf). Based on the results of Aly and Yousry [18], at a 5% level of significance and 95% power with an effect size of 1.594, (calculated by considering that the mean lightness value of one group was 71.3, SD 14.2 and the other group was 53.6, SD 6.7), and the primary end point being an evaluation of the staining propensity of SDF+KI at the end of 1, 3, and 6 months after treatment, with a 95% chance of detecting an increase in the mean lightness value from 53.6 in the control group to 71.3 in the experimental group, the minimum sample size in each group is 16. The expected dropout rate is 10%, so after considering the dropout rate, the sample size in each group is 30. Thus, the total sample required for the intervention will be 60 children (N=60).

For the secondary objective, with a significance level of 5%, a power of 80%, and an estimated critical *Z* value of 3.193, the study required 48 teeth, or 24 teeth per group. Finally, assuming 40% loss to follow-up, a sample size of 34 teeth was gathered in each group [19] to evaluate the caries-arresting effect of SDF+KI in the treatment of carious primary teeth at 6 and 12 months after treatment.

Data Collection

Data were collected with research data management software, including REDCap (Research Electronic Data Capture), a web-based application designed specifically for clinical research for consent tracking and data validation. A detailed schedule of data collection and a CONSORT (Consolidated Standards of Reporting Trials) flowchart of the study protocol, including baseline data collection, intervention, and follow-up, is shown in Figure 3.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart of Healthy Smiles. ICDAS: International Caries Detection and Assessment System; KI: potassium iodide; SDF: silver diamine fluoride.

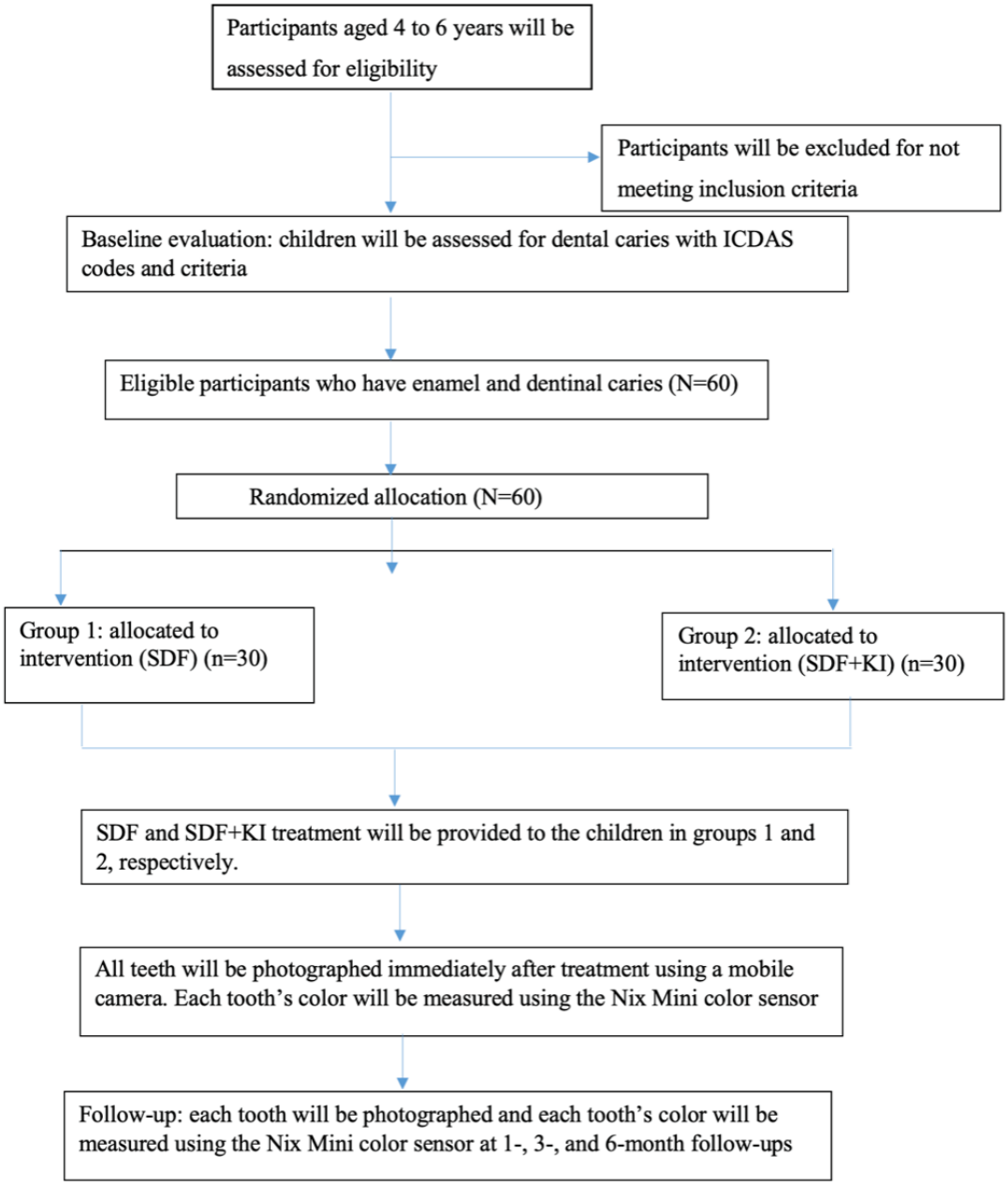

Phase 1: Baseline Data Collection

Sociodemographic Details

The details about the Healthy Smiles will be clearly explained at a parent-teacher association meeting. Parents who give consent for participation will be considered. A standard form will be designed on Google Forms to collect sociodemographic details, comprising basic information such as name, age, sex, school grade, school, and address. Data will be protected and kept confidential.

Clinical Examinations

Clinical examinations will be performed by visual inspection under visible light, with the children in an upright position. The children will be assessed for dental caries using ICDAS codes and criteria. ICDAS codes 0-3 can be determined with air drying. Using a ball-ended World Health Organization (WHO) Community Periodontal Index probe, cavitated lesions (ICDAS codes 5 and 6) will be probed.

Phase 2: Intervention

The Healthy Smiles study sample will comprise 2 groups: group 1 will receive 38% SDF (Riva Star; SDI Inc); group 2 will receive 38% SDF with 10% KI (Riva Star; SDI Inc).

Method of Application

In group 1, we will use cotton gauze to carefully clean and dry the affected tooth surface. The gingival tissue of the tooth will be protected with petroleum jelly. An applicator will be dipped into the SDF and 2-3 mg will be applied to the lesion with a microbrush, which will be used to paint the solution over the carious lesion; then, we will wait for 1 minute for absorption.

In group 2, we will apply SDF with the same technique. After the SDF application, KI will be applied using a separate

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microbrush, which will be saturated with the solution and will be used to paint the solution over the carious lesion. No rinse will be performed and special instructions will be given following application.

After treatment, an individual report on the child's oral health will be provided, and after-treatment instructions will be given to the parents. If there is any adverse drug reaction associated with the SDF treatment, the parents will be asked to contact the principal investigator immediately by telephone.

All teeth will be photographed immediately after treatment. A high resolution mobile camera will be used to capture all of the images throughout the study. The high-resolution mobile camera features a 64-megapixel primary camera with an 8-megapixel secondary depth camera and an 8× optical zoom to provide images at a 2340×1080-pixel resolution.

Each tooth's color will be measured using a Nix Mini color sensor. The Nix Mini color sensor is a wireless colorimeter that uses artificial intelligence to measure the exact color of surfaces and transmits the digital color values to a smartphone or tablet using Bluetooth.

Measurements will be calibrated in accordance with the manufacturer's instructions to determine the first shade of the carious lesion. The ΔL and ΔE values will be measured 3 times by a single operator, and the average values will be noted. Despite the fact that SDF treatment had no adverse effects in other studies, if any adverse events occur, the primary investigator will duly report them to the institutional ethics committee.

Phase 3: Follow-Up

Primary Outcome Measures

Staining propensity will be measured 1, 3, and 6 months after treatment. Evaluation of the change in color of the carious lesions will use photographs and the Nix Mini color sensor.

Secondary Outcome Measures

The arrest of carious lesions will be measured 6 and 12 months after treatment. The size of the carious lesions will be evaluated using the ICDAS index as stable or progressing. The consistency of the lesions will be evaluated with gentle probing using a ball-ended WHO probe as soft or hard. The level of satisfaction will be measured immediately after intervention. Parental satisfaction with dental appearance and color following treatment with SDF and SDF+KI will be assessed using a prevalidated 4 item, 5-point Likert-scale questionnaire in English developed by Clemens et al [20] in 2018.

Data Analysis

Data will be analyzed using SPSS (version 28; IBM Corp). Descriptive statistics will include the mean and SD for continuous data and frequency and percentage for categorical data. An independent-sample 1-tailed *t* test or the Mann-Whitney *U* test will be used for comparing the 2 groups. *P* values will be considered statistically significant at ≤.05.

Ethical Considerations

Ethical approval of this trial was obtained from the institutional ethics committee (REF/2022/06/05559) of the Yenepoya (Deemed To Be University). Parent or guardians will be asked to provide a written informed consent form, which also covers the secondary analysis. All procedures will be conducted in accordance with the ethical standards of the Declaration of Helsinki and in accordance with relevant guidelines and regulations.

A participant information sheet describing the purpose of the study; details of the research, including the secondary analysis; procedures; and benefits and adverse effects, specifically tooth discoloration, will be given to the parents or legal guardians of the children. Their concerns about the adverse effects will be answered. Informed consent will be sought before the trial's start. The study's participants, including the children and their legal guardians, are free to discontinue at any moment during the study. Additionally, they are free to seek out extra dental treatment in accordance with their own preferences.

The drugs will be obtained by the primary investigator and are not sponsored. Drugs are stored at room temperature according to the manufacturer's instructions. The manufacturer played no role in this study. The data safety sheet from the manufacturer for the SDF is provided in Multimedia Appendix 1. The drug controller general of India does not prohibit SDF use. Furthermore, no dental professional organizations or research associations have yet issued any SDF recommendations.

The privacy of the children will be respected. The data collected from the children will be kept confidential and will be shared only among the members of the research team, ethics committee, and regulatory authorities. No one else shall be privy to the children's details. The photographs will be masked.

There will be a clinical evaluation for dental caries, during which the principal investigator will administer the necessary treatment if any pulpal involvement or abscess is found. The right to refuse or right to withdraw at any point of time will be given to the children. No monetary compensation will be provided in case of withdrawal. Participants who stay in the study will receive no monetary compensation, but will receive referral cards for further dental treatments at our institution free of cost.

Risks and Discomforts

There are no major known risks to the study. There are minor risks, such as black stains on the carious tooth surface or temporary stains on the skin. Temporary stains on the skin will disappear within 48 hours without treatment. Participants who are allergic to the products will be excluded from the study.

Results

Enrollment started in October 2023. It is estimated that the enrollment period will be 12 months. Data collection is planned to be completed in 2024.

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Discussion

Principal Findings

Riva Star is a commercially available product that contains 38% SDF, so it will be used in the control group. Riva Star is the only commercially available product with 38% SDF+KI. As a result, it will be used in the case group. With oral administration, the average lethal dose (LD50) is 520 mg/kg. One drop (25 µL) contains 9.5 mg SDF, which is sufficient to treat 5 teeth. Considering that the smallest child with caries weighs around 10 kg, the dose would be 0.95 mg/kg. Hence, the relative safety margin for administering a complete drop to a 10-kg child is 380 mg/kg, so for an LD50 of 0.95 mg/kg the dosage is 400 times the safety margin. The actual dose is likely to be significantly lower. The recommended limit is 1 drop (25 µL) for 10 kg of body weight at every treatment visit. The maximum applied dose for 3 teeth is 2.37 mg, which would allow for over 400 applications [21].

Silver ions in the SDF solution have the potential to darken the tooth structure. It has been proposed that the KI solution can react with SDF to generate a bright yellow solid product (silver iodide), which could reduce the excess free silver ions that cause the black staining. Despite the presence of brilliant yellow precipitates following KI application, staining of tooth surfaces was still observed in an SDF+KI treatment group in a previous investigation. While KI is anticipated to eliminate SDF staining, its effect has not previously been quantified [22].

Patients are concerned about the aesthetic appearance of a restoration. Rather than analyzing color variations with the naked eye, which is typically subjective, we will quantify color changes using smart device measurements incorporating artificial intelligence, as these are more precise and repeatable [23].The Nix Mini color sensor is a wireless colorimeter that uses artificial intelligence to measure the exact color of surfaces and communicates the digital color values through Bluetooth to a smartphone or tablet. The color sensor blocks out ambient light and provides its own calibrated light source using the industry-standard 45/0° measurement. The device provides color readouts in International Commission on Illumination L*a*b* (CIELAB) format and calculates color differences in ΔE2000 [10]. The Nix Mini color sensor will be used immediately following treatment. From the Nix Mini color data, ΔL and ΔE values will be recorded and compared among the groups.

This is the first randomized controlled trial in which artificial intelligence–based sensing equipment and qualitative opinions of both the dentist (investigator) and parents will be ascertained. This study will help dentists and parents make the important clinical decision to choose a 2-step, noninvasive, low-cost treatment that is more acceptable and practicable in places lacking complete dental facilities, for hospital patients, and for low-income children with restricted access to comprehensive dental care.

Strengths and Limitations of the Study

First, this is a randomized controlled trial that quantifies the color change after SDF and SDF+KI treatment to help maximize the acceptability of the preventive treatment program.

Second, the use of ICDAS codes as a measurement of the stability of the lesion size as a standard for arrested caries is another feature of the study design. Prior studies only considered hardness and color, which are challenging to calibrate. The calibrated examiners in this investigation were able to provide an accurate evaluation of lesion size stability.

Finally, this study will use the Nix Mini color sensor, which senses colors and readouts in CIELAB; ΔL and ΔE values will be quantitatively recorded.

A limitation of the study is that it is a short-term trial; longitudinal studies will have to be done to report the long-term effect on discoloration of SDF.

Conclusions

Healthy Smiles provides an opportunity to address the aesthetic inconvenience of patients without compromising the effectiveness of SDF treatment. This trial's findings will contribute to the limited evidence base on discoloration after SDF intervention to improve aesthetic appearance in child oral health. If the results from the trial are promising, it will lead to the development of a model for child oral health and pave the way for further research in child oral health.

Acknowledgments

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Authors' Contributions

PN is the principal investigator of the study and obtained the necessary funds. PN and IPM designed the study and wrote the study protocol. Together with RPS, JJ and SA prepared the tables and wrote the manuscript. All authors reviewed, read, and approved the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Certificate of analysis for quality control of silver diamine fluoride.
[PDF File (Adobe PDF File), 307 KB - resprot_v13i1e51087_app1.pdf]

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Abbreviations

CIELAB: International Commission on Illumination L*a*b*
CONSORT: Consolidated Standards of Reporting Trials
ICDAS: International Caries Detection and Assessment System
KI: potassium iodide
REDCap: Research Electronic Data Capture
SDF: silver diamine fluoride
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

Deprescribing as a Way to Reduce Inappropriate Use of Drugs for Overactive Bladder in Primary Care (DROP): Protocol for a Cluster Randomized Controlled Trial With an Embedded Explanatory Sequential Mixed Methods Study

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Abstract

Background: Potentially inappropriate medication remains a significant concern in general practices, particularly in the context of overactive bladder (OAB) treatment for individuals aged 65 years and older. This study focuses on the exploration of alternative options for treating OAB and the deprescribing of anticholinergic drugs commonly used in OAB. The research aims to comprehensively evaluate the efficiency of deprescribing through a mixed methods approach, combining quantitative assessment and qualitative exploration of perceptions, experiences, and potential barriers among patients and health care personnel.

Objective: This study aims to evaluate the efficiency and safety of the intervention in which health care staff in primary care encourage patients to participate in deprescribing their drugs for OAB. In addition, we aim to identify factors contributing to or obstructing the deprescribing process that will drive more informed decisions in the field of deprescribing and support effective and safe treatment of patients.

Methods: The drugs for overactive bladder in primary care (DROP) study uses a rigorous research design, using a randomized controlled trial (RCT) with an embedded sequential explanatory mixed methods approach. All general practices within the North Denmark Region will be paired based on the number of general practitioners (GPs) and urban or rural locations. The matched pairs will be randomized into intervention and control groups. The intervention group will receive an algorithm designed to guide the deprescribing of drugs for OAB, promoting appropriate medication use. Quantitative data will be collected from the RCT including data from Danish registries for prescription analysis. Qualitative data will be obtained through interviews and focus groups with GPs, staff members, and patients. Finally, the quantitative and qualitative findings are merged to understand deprescribing for OAB comprehensively. This integrated approach enhances insights and supports future intervention improvement.

Results: The DROP study is currently in progress, with randomization of general practices underway. While they have not been invited to participate yet, they will be. The inclusion of GP practices is scheduled from December 2023 to April 2024. The follow-up period for each patient is 6 months. Results will be analyzed through an intention-to-treat analysis for the RCT and a thematic analysis for the qualitative component. Quantitative outcomes will focus on changes in prescriptions and symptoms, while the qualitative analysis will explore experiences and perceptions.

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Conclusions: The DROP study aims to provide an evidence-based intervention in primary care that ensures the deprescription of drugs for OAB when there is an unfavorable risk-benefit profile. The DROP study's contribution lies in generating evidence for deprescribing practices and influencing best practices in health care.

Trial Registration: ClinicalTrials.gov NCT06110975; https://clinicaltrials.gov/study/NCT06110975

International Registered Report Identifier (IRRID): DERR1-10.2196/56277

(JMIR Res Protoc 2024;13:e56277) doi:10.2196/56277

KEYWORDS

deprescribing; overactive bladder; general practice; patient safety; potentially inappropriate medication; geriatric; elderly; medication safety; geriatrics; anticholinergic drugs; safety; prescription; Denmark; general practitioner; evidence-based intervention; evidence-based; intervention; health care; medication; efficacy; DROP study; DROP

Introduction

Background

Potentially inappropriate medication (PIM) is a significant issue in general practices. PIMs are defined as medications that may have an unfavorable risk-benefit profile, and alternative options may be better, safer, or more cost-effective [1-3]. Anticholinergic drugs for overactive bladder (OAB) are a common example of a PIM in older adults and are frequently used in general practice [4]. OAB is a chronic condition characterized by a frequent urge to urinate and nocturia, with or without urgency urinary incontinence [5]. Although available treatment options may improve symptoms, they do not cure them. Therefore, informing patients on therapeutic options is critical in general practice [6].

There are 2 main classes of drugs used to treat OAB: anticholinergic medications and selective beta-3 adrenergic agonist medications. The initial step in treatment involves nondrug methods, followed by the consideration of anticholinergic drugs. In cases where these drugs cannot be used due to medical reasons or prove ineffective, the option of using a selective beta-3 adrenergic agonist comes into play [7]. However, there is no consistent evidence to show the superiority of drug therapy over conservative therapy [8]. This lack of evidence emphasizes the need for general practice to consider the risks and benefits of treatment options carefully.

It is known that approximately 20% of patients treated with anticholinergic drugs experience adverse drug effects consisting of dry mouth and constipation. Older people can also experience impaired attention, delayed memory, visual disturbances, dizziness, and somnolence [9]. In addition to the potential adverse effects of anticholinergic drugs, general practitioners (GPs) must also be mindful of the risks associated with polypharmacy in older patients. Many older patients are already taking various medications for other conditions, and interaction with other drugs (eg, antidepressants, antihistaminic agents, and medication for Parkinson disease) leads to an increased risk of anticholinergic side effects [9,10]. Additionally, drugs with anticholinergic effects may be associated with a higher risk of falls [11] and an increased mortality rate among older adults [12,13].

International guidelines and the Danish Health Services recommend an early review of the efficacy and tolerability of drugs for OAB and a review and deprescribing once a year to assess continued needs [7,14,15]. In this study, "deprescribing" refers to the planned and supervised process of reducing or stopping medications [16]. Primary care, as the central stakeholder in the patient's medication management, is typically the optimal setting for conducting medication reviews and deprescribing interventions.

In Denmark, when patients present with OAB symptoms, GPs play a pivotal role. They conduct medical histories, physical examinations, and basic tests to confirm the diagnosis. Specialists, such as urologists and urogynecologists, provide in-depth evaluations based on individual needs, and specialist consultations are required for advanced diagnostics and specialized treatment in complex cases with underlying pathologies. Both GPs and specialists can initiate pharmacological treatment for OAB. However, after initiating and ending treatment in specialist care, patients often return to their GP for follow-up.

However, several challenges at the patient level, the health care professional level, and the surrounding health care system may impact the success of deprescribing interventions [17]. Health care professionals report time constraints, limited data on the deprescribing process, and the need for feasible and effective medication management models to implement in routine care [17-19]. Ideally, the individual GP and the staff members should attain a sense of influence and ownership [18].

Deprescribing is an established management strategy to minimize polypharmacy and PIMs. It is, in general, a safe process, with a minor risk of causing withdrawal symptoms or return of the condition that was being treated [18,20]. Deprescribing is proven effective, leading to less treatment burden, reduced side effects, and lower medication expenses. However, there is less evidence on the impact of deprescribing on clinical and patient-centered outcomes [21]. Deprescribing is thus a multifaceted topic and requires a comprehensive understanding of both quantitative and qualitative aspects to deliver robust knowledge on the subject.

While several studies have investigated deprescribing by reviewing the entire medication list, focusing on a specific class of medicine can also effectively reduce adverse drug effects and improve quality of life. To our knowledge, no studies have investigated deprescribing interventions in primary care focusing on anticholinergic drugs for OAB. However, a recent quasi-experimental study conducted in a primary care setting investigated the efficacy of medication revision specifically for

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mirabegron. The study found that deprescribing optimized the use of mirabegron in 56.8% of cases [22], highlighting the potential benefits of a targeted deprescribing approach. By focusing on specific drug classes, GPs may be able to identify and address inappropriate prescriptions, leading to improved patient outcomes more effectively. Moreover, there is sparse knowledge on how health care staff and patients engage in the process of deprescribing drugs. Therefore, we aim to evaluate the efficiency and safety of the intervention in which health care staff in primary care encourage patients aged 65 years or older to participate in deprescribing their drugs for OAB. In addition, we aim to identify factors contributing to or obstructing the deprescribing process, which will drive more informed decisions in the field of deprescribing and support effective and safe treatment of patients.

Objectives

The aim is divided into four objectives: (1) to evaluate the difference in the proportion of prescriptions picked up between the control and intervention groups; this metric will indicate the extent to which medication reduction has been achieved within the intervention group; (2) to evaluate the efficiency of the intervention regarding the proportion of patients in whom medication for OAB is deprescribed within the intervention group and the impact on symptoms; (3) to gain insight into the perceptions of patients and health care personnel regarding the deprescribing intervention by exploring their experiences and attitudes and identifying any potential barriers or contextual factors that may hinder future implementation; and (4) to comprehensively explore the complex phenomena of reducing the risk of potentially inappropriate drugs in general practice in patients aged 65 years and older with a specific focus on drugs for OAB.

Methods

Study Design

The drugs for overactive bladder in primary care (DROP) study is a randomized controlled trial (RCT) with an embedded sequential explanatory mixed methods approach targeting the RCT's intervention group. In the embedded mixed methods study, which will be carried out at the immediate conclusion of the RCT, quantitative data from the intervention group in the RCT and qualitative data from interviews and focus groups will be used to explore the nuances of how, when, and under which circumstances these individuals actively participate in the deprescribing process. Figure 1 provides an overview of the phases of the DROP study. Overall, this research design combines quantitative and qualitative data collection and analysis techniques to better understand the contextual factors influencing engagement in the deprescribing process among GPs, staff members, and patients.

The RCT will commence by pairing all general practices within the North Denmark Region, encompassing an estimated population of 0.58 million individuals. The pairing will be determined based on the number of GPs in each practice and their respective urban or rural locations. The matched pairs will be randomized to either intervention or control groups.

The randomization for selecting these specific practices will be generated using the web-based tool "Research Randomizer" [23]. Figure 2 provides an overview of the matching and randomization process.

The intervention group will be provided with an algorithm designed to guide the deprescribing of drugs for OAB, aiming to promote the appropriate use of these medications.

Figure 1. Overview of the drugs for overactive bladder in primary care (DROP) study. The intervention group, depicted by the red boxes, will provide data for the sequential explanatory mixed methods study.

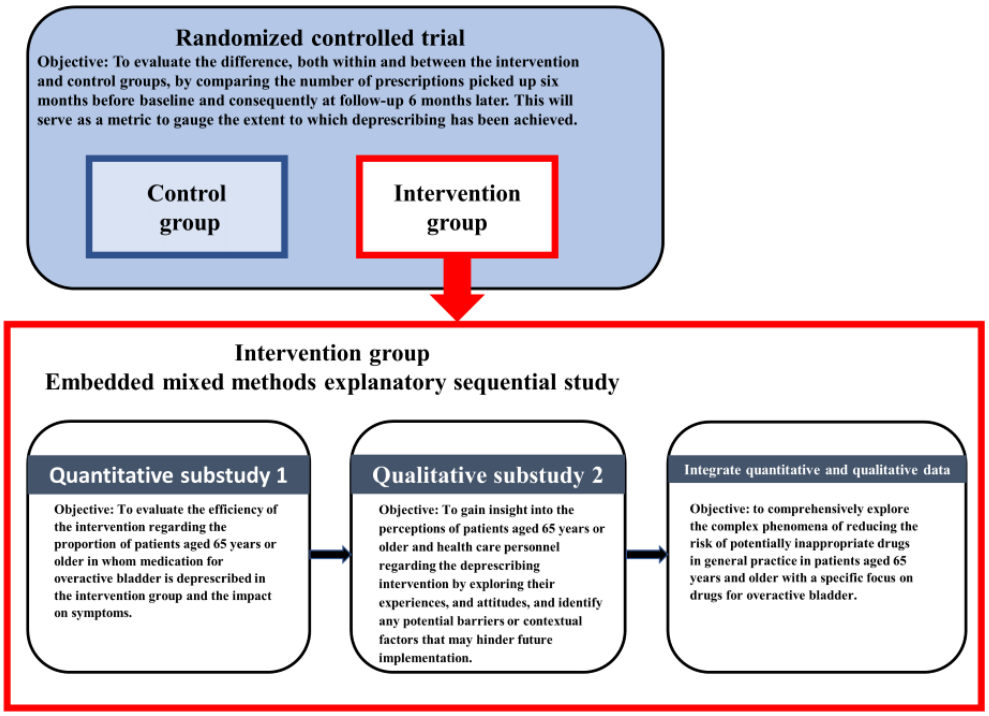

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Figure 2. Flowchart illustrating the randomization process. GP: general practitioner.

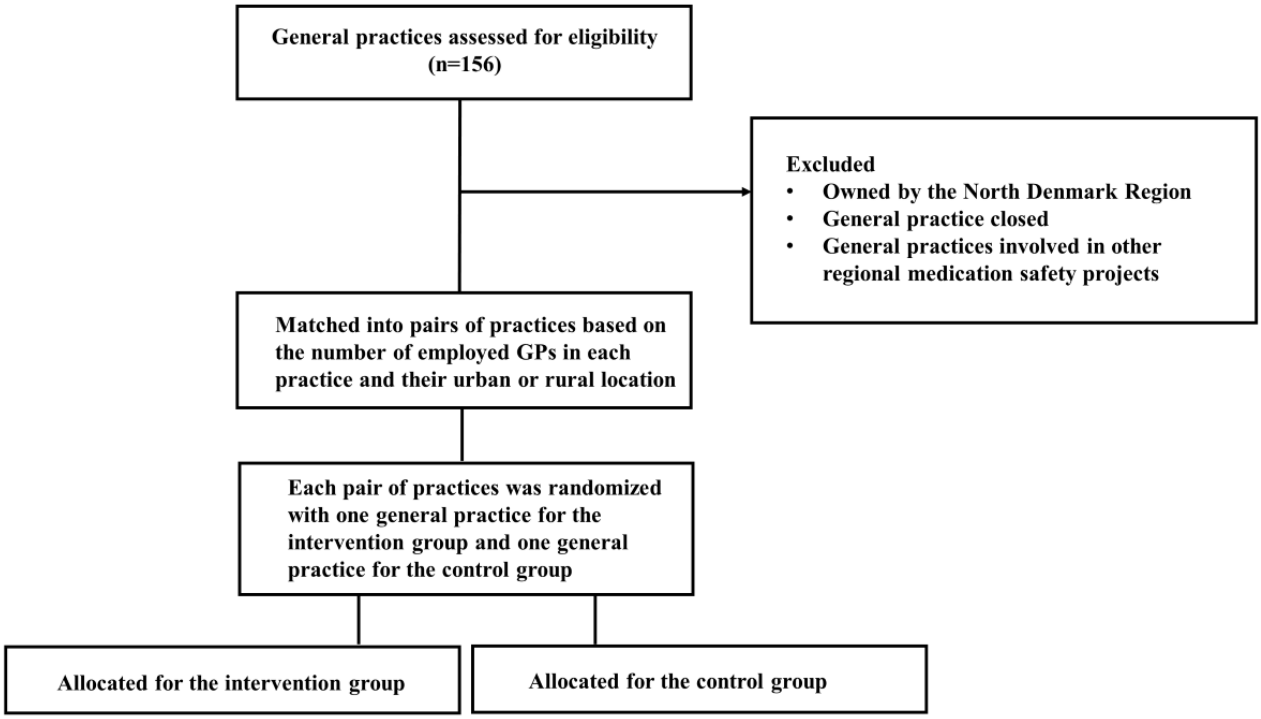

Randomized Controlled Trial

Overview

Using data from Danish registries, the RCT will evaluate the difference, both within and between the intervention and control groups, by comparing the number of prescriptions picked up 6 months before baseline and consequently at follow-up at 6 months. The 6-month follow-up period was chosen to balance practical considerations and the need for adequate evaluation time. The comparison to a randomized control group will allow for an assessment of whether other external factors have impacted the results using safety measures. The proportion of prescriptions picked up between the control and intervention groups does not directly measure deprescribing as defined by discontinuing and reducing dosage. Instead, it serves as an indicator of potential changes in medication use.

Primary Outcome

The primary outcome will be the difference in prescriptions picked up 6 months before the baseline and 6 months after the baseline.

Secondary Outcomes

The secondary outcomes will be the descriptive characteristics of the study population and the difference in hospital admissions, health care contacts, and mortality between the intervention and control groups.

Embedded Sequential Explanatory Mixed Methods Study

This part of the DROP study will support a deeper understanding and explanation of the results of the RCT.

Quantitative Substudy 1: Follow-Up in the Intervention Group

Overview

Substudy 1 will estimate the proportion of patients who discontinue drugs for OAB or reduce the dosage of OAB with a 6-month follow-up. Staff members will fill out a baseline questionnaire and provide descriptive data about the cohort. A total of 2 questionnaires about symptoms at 4 weeks and 6 months will be filled out using self-reported data. The descriptive data will encompass significant variables like family status and other concurrent illnesses.

Primary Outcome

The primary outcome will be the proportion of patients who were deprescribed OAB before and after a 6-month follow-up period.

Secondary Outcomes

The secondary outcomes will be as follows: changes in bladder symptoms, descriptive characteristics of the proportion of patients in the intervention group who had deprescribing initiated and sustained over a 6-month follow-up period, descriptive characteristics of the proportion of patients in the intervention group who had deprescribing initiated but not sustained, and descriptive characteristics of the proportion of patients in the intervention group where deprescribing was not initiated.

Qualitative Substudy 2: Interviews and Focus Groups

Substudy 2 will use qualitative interviews and focus groups to explore how GPs, staff members, and patients experienced the intervention and which strategies have been used to successfully deprescribe OAB to understand when and how the algorithm is applicable. Participants will possess a variety of criteria

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informed by the quantitative data to ensure maximum variation and will be selected based on purposeful sampling. Interview guides will be developed based on the existing literature.

Integration and Interpretation

Subsequently, the quantitative and qualitative results will be integrated, describing congruence and complementarity or the lack thereof. Finally, an interpretation of the integrated data will form inference as part of the answer to the overall aim.

Integration of the 2 types of data sets occurs at multiple stages in this study. First, integration takes place during the qualitative interview sampling process. Second, integration is evident in developing semistructured interview guides informed by the quantitative results. Finally, integration is vital to the analysis phase, where joint display methods will be used.

Through a merging process, we combine the quantitative results from the follow-up study on deprescribing OAB and the qualitative data gathered from interviews with GPs, staff members, and patients. We aim to interpret these integrated data collaboratively. Specifically, we focus on how health professionals and patients articulate their experiences with deprescribing treatment for OAB, their interactions with the algorithm, and any advantages or shortcomings they have identified during its extended use. Additionally, we seek to ascertain if circumstances or life events critically influence patients' ability to complete the deprescribing process.

Study Setting

The study will take place in The North Denmark Region, Denmark. In Denmark, GPs contract with and are reimbursed by the National Health Service. Traditionally, GPs practice singly, but there is a tendency to join groups of practitioners. All Danish residents are entitled to register with a GP of their own choice, and >99% of the population are registered with a GP, and on average, each GP serves 1600 patients. Though no clear guidelines exist for when and how to treat the individual patient, the GP is advised to evaluate the pharmacological treatment for OAB yearly by suggesting the patient discontinue the drug for approximately 4 weeks [24].

Participants

GP Practices

All GP practices in The North Denmark Region, Denmark, will be eligible for randomization. It is important to note that GP practices already participating in interventions focusing on medication reviews will be excluded from the study before the randomization, as this could potentially interfere with the outcomes in both the intervention and control groups. There are currently 156 practices in the North Denmark region, of which half will be invited to participate. GP practices randomized to the intervention group will receive an initial invitation via email, followed by subsequent telephone contact. Those GP practices that accept the invitation and agree to participate will be enrolled in the study. As a token of appreciation for their involvement, these practices will receive a small reimbursement for their participation in the study.

Patient Recruitment

A list of patients (65 years or older), who, within the last 14 months, have been prescribed a drug for OAB by a GP will be generated and presented to the included GP practices. Table 1 provides a list of the relevant drugs. Staff members will then identify the patients in the GP practice's electronic system. Patients receiving outpatient care for OAB (eg, in urological or neurological clinics) or are cognitively impaired to a degree incompatible with participation will be excluded.

Table 1. Overview of drugs included in this study.

Anatomical Therapeutic Chemical code	Name
G04BD04	Oxybutynin
G04BD07	Tolterodine
G04BD08	Solifenacine
G04BD09	Trospium
G04BD10	Darifenacin
G04BD11	Fesoterodine
G04BD12	Mirabegron

Sample Size

According to an unpublished pilot project, approximately 26% of patients in current treatment may be candidates for deprescribing drugs for OAB. With a 5% margin of error, 95% CI, and a population of 500 patients (for the GP practices randomized to the intervention), it was calculated that 187 patients should participate in the study. Therefore, 250 patients will participate to give room for "dropouts" and "missing data." Control patients will consist of a similar number of patients in the control group who are currently treated. The mixed methods study does not report a desired sample size as emphasis is placed on the richness and depth of collected data by integrating qualitative and quantitative data. Instead, we aim to ensure an adequate range of patients and staff to capture diverse perspectives and experiences. The focus is on the data's quality, relevance, and credibility rather than a predetermined numerical sample size [25].

Deprescribing Intervention

The clinical guideline on "Deprescribing drugs for OAB" in The North Denmark Region serves as the basis for the intervention. The guideline, originally published in Danish, provides recommended procedures for the deprescribing process.

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The guideline offers procedures for the deprescribing process and includes a deprescribing algorithm and a symptom questionnaire designed to evaluate the impact of medications used in treating OAB [26]. The questionnaire consists of inquiries about the patient's bladder symptoms such as how they affect their daily life and whether there are any medication-related side effects. The intervention encompasses a systematic approach to support GPs, staff members, and patients in evaluating the feasibility of discontinuing medication. This systematic approach, bolstered by support from the research group, goes beyond merely presenting the guideline; it aims to facilitate its systematic implementation within clinical practice. The research group's involvement is geared toward evaluating the guideline's efficacy and identifying optimal implementation strategies, all while ensuring patient safety and minimizing practitioner effort. It is important to note that clinics already using similar routines are still eligible for participation in this study. Practically, staff members will contact each patient for whom deprescribing may be relevant and gather baseline characteristics over the phone. Patients who agree to participate in the deprescribing intervention can provide their data web-based or via phone call with the GP practice. Whether the questionnaire is filled out by the patients themselves or the staff members, all the data will be securely stored in REDCap (Research Electronic Data Capture; Vanderbilt University) [27]. REDCap is a secure web application that builds and manages web-based surveys and questionnaires. The patient's treatment is then deprescribed, and 4 weeks later, the patient evaluates the effect either web-based or by receiving a phone call from the GP practice, using a symptom questionnaire, and following the algorithm described in clinical guidelines. The final follow-up, using the symptom questionnaire, will take place 6 months after deprescribing.

Timeline

The study, in which GP practices are invited to participate, launches on December 1, 2023.

Methods of Data Collection

Randomized Controlled Trial

In the RCT, we will apply solely registry data to evaluate the efficiency of the intervention. The intervention and the control group will be compared using registry data including prescription records, sociodemographic information, and health-related outcomes such as hospitalizations and mortality rates. The data will be extracted from the appropriate Danish registries. It will be essential to know whether the algorithm is effective and identify potential safety issues, such as higher hospitalization or mortality rates.

Embedded Sequential Explanatory Mixed Methods Study

The mixed methods part of the study consists of quantitative data from substudy 1, which is the follow-up in the intervention group, and qualitative data from substudy 2, which is generated from interviews and focus groups.

Substudy 1: Follow-Up in the Intervention Group

Substudy 1 will estimate the proportion of patients who can discontinue OAB or reduce the dosage of OAB with a 6-month follow-up considering bladder symptoms and patient characteristics. See the description for the deprescribing intervention.

Substudy 2: Qualitative Interviews and Focus Groups

Once substudy 1 is completed, we will conduct qualitative in-depth interviews at 4 weeks and 6 months to explore the experiences of GPs, staff members, and patients regarding deprescribing drugs used to treat OAB. Individual qualitative interviews and focus groups were deemed suitable and valuable for capturing the perceptions and experiences of the intervention and deprescribing medication [28]. By using individual qualitative interviews, it is possible to explore and clarify experiences and opinions with as much information as possible and with the participant's own words and voice [28]. Interviewee selection will be based on purposeful sampling, an iterative process that aims to achieve richness and depth in data [28]. Participants will be sampled based on variation in role (GPs, staff, or patients), clinic size, gender, age, and location, divided into urban and rural. If possible, we will sample one GP, one of the staff, and one patient from 8 different clinics as we believe this to meet the aim of this study, sample specificity, theory, anticipated quality of the dialogue, and the applied analysis strategy [29]. However, this will be applied should elements of information power [29] call for a change in strategy. Information power feeds into data saturation, which will be achieved by using the model of Guest et al [30] model, incorporating elements such as Base Size, Run Length, and New Information Threshold to determine saturation points in the data collection. The interviews will be planned and carried out based on the Theoretical Domains Framework "determinants of behavior" [31] and the 7 stages proposed by Brinkmann and Kvale [32].

Methods of Data Analysis

Randomized Controlled Trial

Using an intention-to-treat analysis, an evaluation of the deprescribing intervention will be done by comparing primary and secondary outcomes between the intervention and control groups. Additionally, comparing variables at baseline will provide a basis for assessing the impact of the deprescribing intervention over time. Access to register data for both the intervention and the control group facilitates a sensitivity analysis by systematically analyzing participation and adjusting for potential confounding factors, thus providing a robust assessment of selection bias and enhancing the reliability of the study results. The distribution of variables will be evaluated using histograms and the Shapiro-Wilk test. Nonnormal data will be analyzed using boot-strapping resampling methods, and differences between groups will be examined using regression analysis. Binary outcomes will be compared using the chi-square test and reported as the number and percentage of cases. A P value less than .05 will be considered statistically significant.

Embedded Sequential Explanatory Mixed Methods Study

Substudy 1: Follow-Up Study

We will assess the efficacy of the deprescribing intervention in the intervention group by comparing primary and secondary outcomes at baseline and follow-up. Additionally, we will

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compare variables to evaluate the evolving impact of the deprescribing intervention over time. To understand the distribution of variables, we will use histograms. Differences between groups will be examined using regression analysis. Binary outcomes will be compared using the chi-square test, with results reported as the number and percentage of cases. We will consider a *P* value less than .05 as statistically significant.

Substudy 2: Qualitative Interviews and Focus Groups

The data will be analyzed using thematic analysis [33] to identify and explore key themes and patterns within the interview data. This will involve carefully reviewing and coding the data, followed by categorizing these codes to derive overarching themes. This approach will assist us in comprehending the perspectives and behaviors associated with deprescribing medication. We recognize that this field of study is novel and complex, requiring careful analysis and interpretation.

Integration and Interpretation

The design will include data sets from the quantitative analysis and evaluation of the study to establish the effect of the intervention longitudinally and a qualitative analysis of interviews with stakeholders (GPs, staff members, and patients) to understand the experiences and opinions that might influence the process of GPs. The 2 types of data sets will be analyzed separately before merging in final integration using a "joint display" [34]. The joint display will assist in understanding how the qualitative data supports the understanding of quantitative data and draw inferences [35], which may help in best practices when discontinuing relevant categories of drugs.

Ethical Considerations

The study has received approval from the Institutional Management at Aalborg University Hospital. Under Danish legislation, no formal permission from the national or regional Committee on Health Research Ethics is needed for this type of study, as it does not involve treatments inferior to standard care or the collection of biological material. Thus, the North Denmark Region Committee on Health Research Ethics has reviewed the DROP study and deemed it exempt based on its design, which involves only surveys and interviews (2021-000438). This study will be carried out as a quality improvement project, thus specific data collection does not require informed consent. Nevertheless, informed consent will be obtained for all qualitative data. Participation in GP practices will be voluntary, and informed consent will be obtained from them. Patients' participation is voluntary. Both GP practices and patients can withdraw from the study at any time. Danish legislation prohibits patient compensation for participating in research, but the participating general practices will be compensated for their time. The study complies with the General Data Protection Regulation and is part of the North Denmark Region's record of processing activities (K2023-012). It is also registered on ClinicalTrials.gov (NCT06110975). No identifying information will be published. The DROP study will adhere to the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October, 2013.

Results

The DROP study is ongoing. GP practices are randomized but not yet invited for participation. GP practices will be included from December 2023 to April 2024. The follow-up period for each patient is 6 months. Thus, the expected follow-up for the last patient is scheduled for November 2024.

Discussion

Principal Findings

The DROP study will generate a GP-led intervention, which is expected to lead to a reduction in the use of potentially inappropriate drugs. The overall quality of the intervention experienced by the patient will likely remain unchanged or improved. At the same time, doctors and support staff are anticipated to be satisfied with the process and the intervention. It is also expected that the methods used for the intervention are transferable to other drug classes. The study design combining several methods could improve research outcomes with the increasing complexity of the area under investigation, allowing for a deeper understanding of complex phenomena [35,36]. Thus, the RCT with an embedded integrative mixed methods analysis is expected to provide evidence for efficacy and a more comprehensive understanding of the deprescribing process, minimizing the risk of generating misleading results and guiding future clinical practice.

Limitations

Systems- and organizational-related factors, such as political changes and resources, could be limitations in all stages of the DROP study. Moreover, GP engagement may fluctuate and diverge due to various factors. It is essential that GPs take ownership of the intervention, and the intervention must be simple and feasible in practice. Acknowledging the potential limitations of a 6-month follow-up period for data collection, our mixed methods approach will consider it valuable information for future studies of deprescribing in general practices. Although a possible limitation, the study will contribute to a broader understanding of the most appropriate follow-up duration in this context, enriching our insights for future research endeavors.

Conclusions

The DROP study will generate evidence on interventions in primary care, ensuring that drugs for OAB are deprescribed when an unfavorable risk-benefit profile exists. This could lead to lower medicine costs for the patient and society, as there may be better, safer, or more cost-effective alternatives when the risk-benefit ratio favors deprescribing in people aged 65 years or older. Information drawn from the 2 approaches will support a generic model for deprescribing individual drug classes. Results from an RCT combined with insights from mixed methods research will prove instrumental in understanding why these results are achieved. This dual approach enhances the validity of our findings and offers a comprehensive view of the underlying mechanisms and contextual factors driving the observed outcomes. This comprehensive perspective is vital for

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generating robust results of deprescribing specific drug classes, thereby fortifying best practices in health care.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization of the protocol. ALS, MHJ, MG, JKK, and AEO designed the research methodology. ALS drafted the initial manuscript and all authors participated in reviewing and editing the manuscript. ALS and AEO created figures.

Conflicts of Interest

None declared.

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Abbreviations

DROP: drugs for overactive bladder in primary care
GP: general practitioner
OAB: overactive bladder
PIM: potentially inappropriate medication

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RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Efficacy and Mechanism of Acupoint Catgut Embedding in the Treatment of Chronic Spontaneous Urticaria: Protocol for a Randomized Double-Blind Placebo-Controlled Trial

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Abstract

Background: Chronic spontaneous urticaria (CSU) is a common chronic inflammatory skin disease that manifests as itching and wheals, seriously affecting quality of life. Clinical observations and previous research trials have shown that acupuncture is safe and effective for the treatment of CSU. However, there are problems, such as a short duration of action and frequent treatment. Compared with traditional acupuncture, acupoint catgut embedding (ACE) has the advantages of a longer effect and higher compliance. Clinical trials are needed to prove its efficacy and mechanism of action.

Objective: This trial aims to provide definitive evidence for the treatment of CSU with ACE and explore the mechanism of ACE.

Methods: This is a randomized, double-blind, placebo-controlled trial. In this trial, 108 participants aged 18-60 years with a diagnosis of CSU and no history of ACE will be randomly assigned to 2 groups (1:1 ratio) using the Statistical Analysis System: treatment (ACE) and control (sham ACE). The participants and efficacy evaluators will be blinded to the grouping. Both the ACE and sham ACE groups will undergo acupuncture, but the sham ACE group will not receive catgut sutures. Treatment will be performed twice weekly for 8 weeks, with a 1-week run-in period and a 16-week follow-up period. Twenty patients will be randomly selected to undergo functional magnetic resonance imaging before and after the treatment period. The primary outcome will be the urticaria activity score over 7 days (UAS7). We will use R (version 4.0.1; R Project for Statistical Computing) to perform ANOVA and independent samples *t* tests to compare the differences within and between groups before and after treatment by judging the rejection range based on a significance level of .05.

Results: The study protocol has been approved by the Ethics Committee of Guang'anmen Hospital on September 7, 2022, and has been registered on November 30, 2022. Recruitment began on March 1, 2023. A total of 4-6 participants are expected to be recruited each month. The recruitment is planned to be completed on March 1, 2025, and we expect to publish our results by the winter of 2025. As of November 1, 2023, we have enrolled 25 participants with CSU.

Conclusions: This randomized, double-blind, placebo-controlled trial aims to provide definitive evidence for the treatment of CSU with ACE and explore the mechanism of ACE. We hypothesize that wheals and itching will show greater improvement in participants receiving active therapy than in those receiving sham treatment. The limitations of this study include its single-center trial design, small sample size, and short treatment duration, which may have certain impacts on the research results.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2200066274; https://www.chictr.org.cn/showprojEN.html?proj=179056

International Registered Report Identifier (IRRID): DERR1-10.2196/54376

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KEYWORDS

chronic spontaneous urticaria; acupoint catgut embedding; functional magnetic resonance imaging; randomized controlled trial; mechanism of action

Introduction

Chronic spontaneous urticaria (CSU) is a common chronic inflammatory skin disease that accounts for 90% of all chronic urticaria cases. It manifests as itching and wheals with continuous or intermittent attacks for more than 6 weeks. Angioedema accompanies 40% of cases of CSU, with 10% primarily presenting with angioedema [1,2]. CSU has no clear inducing factors, and a single episode usually disappears within 24 hours. The majority of individuals with this condition experience a disease duration of 2 to 5 years, often with self-limiting tendencies. However, in 20% of cases, the disease persists for more than 5 years, and 1.4% endure it throughout their life [3,4].

The pathogenesis of CSU is complex, and currently, it is mainly thought to be related to 2 types of autoimmune reactions: type I autoimmune reaction, which is caused by immunoglobulin E, and type IIb autoimmune reaction, which is caused by immunoglobulin G autoantibodies [5]. Recent studies have shown that factors, such as skin mast cell degranulation [6,7], basophil activation [8], and other serological factors, can also induce vasodilation, increase vascular permeability, stimulate sensory nerve endings, and lead to skin swelling, redness, and pruritus. However, the specific pathogenesis of CSU remains unclear. When considering patients who develop the disease without the influence of external triggers, it becomes evident that the primary factor at play is the disruption of internal regulatory mechanisms within the human body. Clinical observations have found that the psychological factors of patients, such as anxiety and depression, have an impact on the onset of urticaria [9]. CSU is characterized by repeated attacks that are prolonged and difficult to cure, which seriously affect the quality of life of patients [10], bring mental and psychological pressure to patients, and further aggravate the occurrence of CSU [11], forming a vicious circle.

Currently, there are no effective radical treatments for CSU. First-line treatment revolves around standard doses of second-generation H1 antihistamines. Second-line treatment involves combinations of medications, often in high doses. Third-line treatment primarily consists of cyclosporine and biologic agents [3], which have problems such as long drug cycles, easy recurrence of drug withdrawal, and obvious side effects. Traditional Chinese medicine (TCM) is widely used as a complementary and alternative therapy to treat CSU [12].

Research has confirmed that the skin is both an immediate stress perceiver and a target of stress responses [13]. The psychological stress resulting from depression, anxiety, and other illnesses can ultimately lead to the development of CSU by exerting its effects on the skin through intricate neural systems. These systems include the activation of neuropeptides and neurokinins, the mediation of inflammatory mediators and cells, and the regulation of hypothalamic-pituitary-adrenal (HPA) axis hormones [14]. Neural metabolites or neurotransmitters released by the brain cause changes in skin function through the HPA axis. Abnormalities in the HPA axis can stimulate mast cells, which are the main effector cells of CSU, to release histamine. In addition, brain-derived neural metabolites can mediate or enhance skin inflammation.

In the TCM theory, all painful and itching sores are ascribed to the heart, which stores the spirit. This is consistent with the modern medical theory of urticaria and its associated psychological factors. The TCM theory can be integrated with modern medical research. TCM frequently uses treatments like herbal medicine and acupuncture in the clinical management of CSU. These treatments aim to nourish the heart, soothe the spirit, purge heart fire, and alleviate feelings of anxiety and depression. However, some patients may experience adverse reactions to herbal medicine, and the bitter taste of the medicine may intensify these reactions. These reactions can lead to resistance and increased psychological stress, potentially exacerbating their condition. Consequently, it is recommended to explore alternative therapies, such as acupuncture, as soon as possible.

In 2018, we selected acupoints related to the heart channel and conducted a randomized, double-blind, placebo-controlled clinical observational study titled “Treatment of CSU by acupuncture from the heart.” We enrolled 60 subjects and divided them randomly into 2 groups (a “treatment group” that received acupuncture and a “control group” that received oral loratadine only) for a 6-week study of acupuncture treatment performed 3 times weekly. As the treatment duration progressed, both groups exhibited improvements, with a significant reduction in the urticaria activity score over 7 days (UAS7). In addition, we used functional magnetic resonance imaging (fMRI) to reveal the brain mechanisms of CSU, and acupuncture was found to alleviate itch through a cerebellar reward-somatosensory circuit for the first time [15,16]. However, traditional acupuncture therapy has a short action time, a long treatment cycle, and many operations, which means that patients require frequent medical attention. This reduces patient compliance. Compared with traditional acupuncture, acupoint catgut embedding (ACE) has the advantages of a longer effect and higher compliance; however, there is a lack of high-quality clinical studies.

The main purpose of this research is to verify the efficacy and safety of ACE in the treatment of CSU based on the theoretical principle that “all pain and itchy sores belong to the heart.” Additionally, fMRI is used to reveal the central mechanism of ACE during CSU treatment.

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Methods

Study Design

This study is designed as a 2-arm, randomized, placebo-controlled trial with both patients and evaluators blinded to group allocation. The study is divided into 3 phases: a 1-week run-in period, an 8-week intervention period, and a 16-week follow-up period. A total of 108 patients will be randomized into 2 groups (ACE and sham ACE groups), with 54 patients in each group. In each group, 20 patients will be selected to participate in fMRI before and after the treatment period. Additionally, we will recruit an age- and sex-matched control group of 20 healthy participants, who will undergo fMRI only before and after the treatment period. A flowchart of the trial is shown in Figure 1.

Figure 1. Flowchart illustrating the randomized, placebo-controlled, double-blinded trial of acupoint catgut embedding for CSU. ALFF: amplitude of low-frequency fluctuation; CSU: chronic spontaneous urticaria; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; DLQI: Dermatology Life Quality Index; FC: functional connectivity; fMRI: functional magnetic resonance imaging; ICA: independent component analysis; ISI: Insomnia Severity Index; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; UAS7: urticaria activity score over 7 days; UCT: urticaria control test.

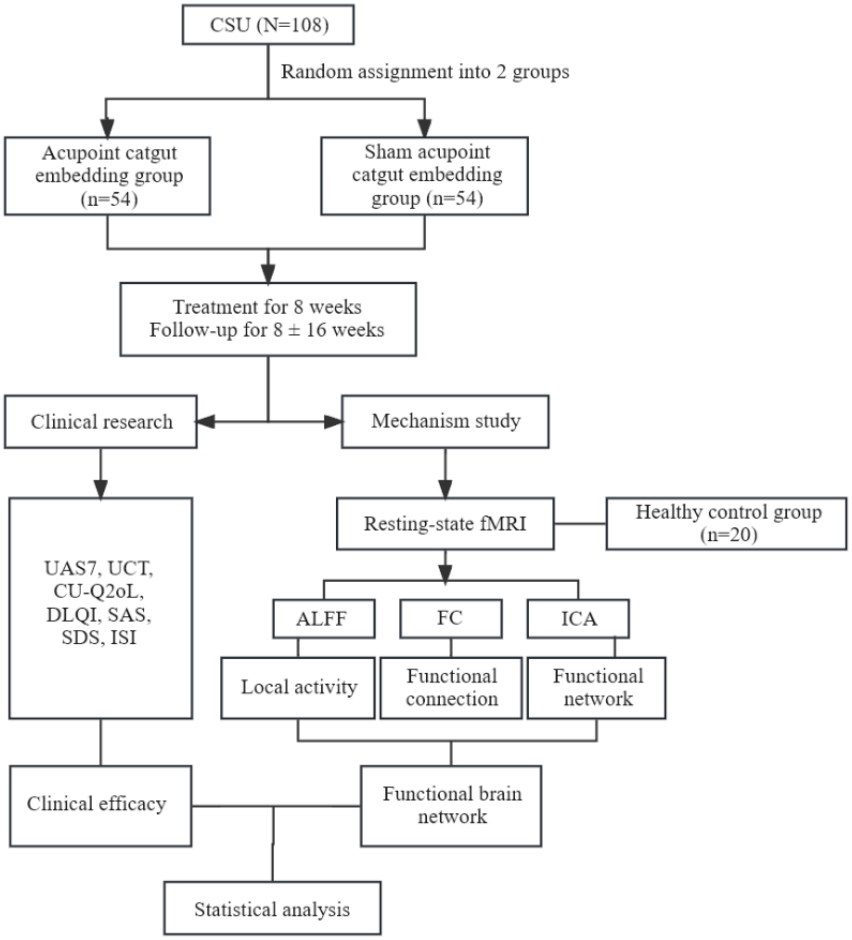

Eligibility Criteria

Inclusion Criteria

The inclusion criteria are as follows: (1) age between 18 and 60 years, regardless of sex; (2) meeting the diagnostic criteria for CSU; (3) wheals and itching occurring continuously for at least 6 weeks before enrollment (despite using H1 antihistamines; occurring at least once daily) and wheals and itching being the main symptoms (without severe systemic symptoms); (4) a UAS7 of ≥16 and a weekly pruritus score of ≥8; (5) no history of ACE; and (6) signing of informed consent and volunteering to participate in the study.

Exclusion Criteria

The exclusion criteria are as follows: (1) clear identification of the cause of chronic urticaria (eg, physical urticaria); (2) use of glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulins for any indication (daily or more than 3 consecutive days) within the first 30 days of enrollment; (3) use of H2 antihistamines, leukotriene receptor antagonists, omalizumab, or other biological agents in the 7 days preceding screening or 14 days before randomization; (4) exceeding the recommended dosage of H1 antihistamines within 3 days before screening; (5) presence of serious cardiovascular and cerebrovascular diseases, diabetes, abnormal bone metabolism, liver and kidney diseases, hematopoietic system diseases, systemic lupus erythematosus, other serious autoimmune diseases, other diseases, and other serious primary diseases; (6) diseases other than chronic urticaria with symptoms of urticaria or angioedema, such as urticaria vasculitis, erythema multiform, cutaneous mastocytosis (pigmentary urticaria), and hereditary or acquired angioedema (eg, due to deficiency of C1 inhibitors);

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(7) skin diseases related to chronic pruritus (eg, atopic dermatitis, bullous pemphigus, herpetic dermatitis, and pruritus in old age), which may affect the evaluation and treatment in the study; (8) allergy to the buried wire material; (9) fertility needs, pregnancy, or lactation during the study period; (10) contraindicating magnetic resonance imaging (MRI) findings; (11) participation in other clinical trials within the last 3 months; and (12) use of psychotropic drugs within the previous month.

Inclusion Criteria for Healthy People

The inclusion criteria are as follows: (1) good health; (2) no serious physical illness and no family history of mental illness; (3) no history of alcohol or drug addiction; and (4) no contraindications for MRI scanning and no structural abnormalities in the brain.

Withdrawal Criteria and Management

Participants may be permitted or required to withdraw from the study for the following reasons: (1) experiencing serious adverse events or adverse events during the study period; (2) demonstrating poor compliance and showing a lack of cooperation with treatment and efficacy follow-up; (3) unauthorized use of nonclinical emergency drugs without information; (4) voluntarily requesting to withdraw from the trial; and (5) withdrawal from the trial before the end of the treatment course, loss to follow-up, or death for various reasons.

Recruitment

The primary recruitment for this study will target outpatients from Guang'anmen Hospital in Beijing, China. In addition, recruitment efforts will include posters and online advertisements providing a concise overview of the trial along with the contact information of researchers. Before enrollment, all participants will receive a comprehensive briefing on the test procedures, study's objectives, potential adverse events, and expected benefits. During the screening phase, each participant's eligibility for inclusion will be assessed, and they will be explicitly informed of their right to withdraw from the trial at any point. Those who choose to participate in the trial will be required to sign 2 informed consent forms: one for their records and another to be retained by the researcher.

Randomization, Concealment, and Blinding

Random numbers will be generated using the Statistical Analysis System PROC PLAN process statement to determine the number of seeds and the segment length. Treatment assignments corresponding to running numbers 001-108 will be listed. To ensure allocation concealment, the randomization process will be managed by an independent statistician who is not involved in the study. Eligible participants will be randomly assigned to the treatment or control group in a 1:1 ratio.

Random numbers will be sealed in an opaque envelope, which will be stored in the study center. To ensure the objectivity of the research, operators and efficacy evaluators will be strictly distinguished, and efficacy evaluators and statisticians will be blinded. Only operators will have access to random numbers before treatment, and they will not be involved in the evaluation process. The selected acupoints are mainly on the lower limbs and back. The control group will also undergo acupuncture, which will ensure patient blinding. Two-stage unblinding will occur only at the end of the case collection.

Sample Size

Referring to relevant literature [17], a formula for the superiority test is used to calculate the sample size:

where c=1, n_2=n_1; if α=.05, u_1-T=1.64 and u_1-u=1.28.

According to previous research [15] based on the UAS7 as the main therapeutic evaluation index, e is set at 9.12, W is set at 6, and the data are substituted into the formula to calculate n_1=n_2≈40. Considering a 25% dropout rate, we establish a sample size of 54 cases in each group, with a total of 108 cases.

However, it is worth noting that when conducting MRI research on the human body, the calculation of sample size does not strictly adhere to the methods used in clinical trials. Currently, there are no clear guidelines for determining sample size in fMRI studies. After an extensive review of the literature spanning the past decade, we did not find a standardized sample size calculation method for experimental studies involving brain fMRI. The previous results of the research group showed that 20 cases in each group met the statistical and practical requirements [13,14]. In this study, 40 subjects are selected for fMRI examination based on the results of previous studies and the scale of the subjects.

Interventions

ACE Approach

Both the ACE and sham ACE groups will undergo acupuncture at identical acupoints in the acupuncture treatment room at Guang'anmen Hospital. To investigate the potential for ACE to extend the therapeutic duration, the control group will not receive catgut sutures. The procedure involves the insertion of a 1.0-cm catgut suture into a hypodermic needle, which is then introduced into the acupoints through the skin [18]. The angle of the hypodermic needle will be selected according to the thickness of the muscle. The hypodermic needle will be withdrawn from the skin once the patient obtains qi.

The treatment will be administered once every 2 weeks for a total of 8 weeks at the same 12 acupoints biweekly, including 4 acupoints on the dorsum, 6 acupoints on the lower limbs, 1 acupoint on the head, and 1 acupoint on the abdomen. The acupoints on the dorsum will be prone and others will be supine. These acupoints include Baihui (DU20), bilateral Xinshu (BL15), bilateral Geshu (BL17), Guanyuan (CV4), bilateral Xuehai (SP10), bilateral Zusanli (ST36), and bilateral Fengshi (GB31). The specific distribution of acupoints is provided in Table 1 and Figure 2. The precise locations of these acupoints and their Chinese pinyin names are according to acupuncture nomenclature established by the World Health Organization (WHO) [19]. The selection of these acupoints is based on a review of classical and modern literature, the neuroanatomical theory, and a consensus of acupuncture experts in Guang'anmen

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Hospital [20-22]. Twenty patients will be randomly selected from the ACE and sham ACE groups to undergo fMRI before and after the treatment period. For comparison, 20 healthy participants will be recruited to participate in fMRI before and after the treatment period without treatment.

The study will use sterile hypodermic needles produced by Jiangsu Zhenjiang Gaoguan Medical Equipment Co, Ltd, and 4-0’ catgut sutures produced by Jiangxi Longteng Biological Technology Co, Ltd.

Table 1. Locations and manipulation of acupuncture points.

Acupuncture point	Location	Suggested technique
Baihui (DU20)	On the head 5 cun (traditional Chinese unit of length) superior to the anterior hairline and on the anterior median line	Subcutaneous insertion (angle of 10°-15° and depth of 10-16 mm)
Xinshu (BL15)	In the lumbar region at the same level as the inferior border of the spinous process of the fifth thoracic vertebra (T5) and 1.5 cun lateral to the posterior median line	Perpendicular insertion (depth of 20-35 mm)
Geshu (BL17)	In the lumbar region at the same level as the inferior border of the spinous process of the seventh thoracic vertebra (T7) and 1.5 cun lateral to the posterior median line	Perpendicular insertion (depth of 20-35 mm)
Guanyuan (CV4)	On the lower abdomen 3 cun inferior to the center of the umbilicus and on the anterior median line	Perpendicular insertion (angle of 90° and depth of 20-35 mm)
Xuehai (SP10)	On the lower limbs 2 cun above the medial end of the patellar base	Perpendicular insertion (angle of 90° and depth of 20-35 mm)
Zusanli (ST36)	On the lower limbs 3 cun inferior to the outer knee and on the tibial edge	Perpendicular insertion (depth of 10-15 mm)
Fengshi (GB31)	On the lower limbs 7 cun superior to the popliteal transverse line	Perpendicular insertion (depth of 10-15 mm)

Figure 2. The locations of acupoints. DU: Du meridian; BL: bladder; SP: spleen; ST: stomach, GB: gall bladder; CV: conception vessel.

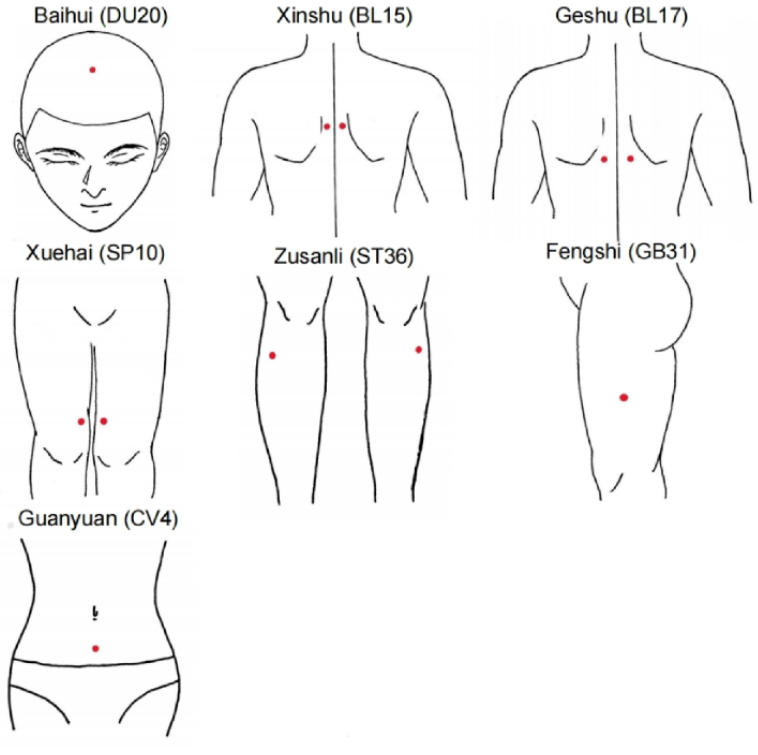

Concomitant Therapy

During the trial, only 1 H1 antihistamine can be taken. Other medicines or TCM with similar clinical efficacy, such as biological agents, H2 antihistamines, and hormones, must not be taken. If other therapies are combined, they will be recorded in the “Case Report Form (CRF).” If subjects require other treatments or concomitant care, they will need to contact the doctor in advance.

fMRI Examination

Pretest Preparation

The fMRI test will be conducted using a 3.0T Skyra (Siemens) MRI machine located at Guang’anmen Hospital, Chinese

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Academy of Medical Sciences. Following the completion of informed consent forms and subject checklists by the participants, the experimenter will explain the testing procedure and precautions. Prior to entering the scanning room, a thorough check will be conducted to ensure that there are no magnetic foreign objects on the participants' bodies. Subsequently, the participants will be positioned in the supine posture on a scanning bed, and fMRI scans will be conducted under the conditions of quietude, closed eyes, and no specific cognitive activities. In the event of a rash attack, the scan will be postponed until the rash subsides for at least 12 hours.

Scanning Program and Parameters

A whole-brain transverse scan will be conducted in parallel with the anterior commissure-posterior commissure line and will include the cerebellum and brainstem. Resting-state functional magnetic resonance parameters will be as follows: time to repetition (TR), 2000 ms; time to echo (TE), 30 ms; flip angle (FA), 90°; layer thickness, 3.5 mm; layer spacing, 0.6 mm; 32 layers; field of view (FOV), 224×224 mm; interlayer resolution, 64×64; and scan time, 6 minutes and 46 seconds. A whole-brain 3D T1-weighted structural image will be captured through a 200-layer sagittal scan with the following parameters: layer thickness, 1.0 mm; no layer spacing; intralaminar resolution, 256×192; TR, 25300 ms; TE, 2.98 ms; FA, 7°; FOV, 256×256 mm; and scan time, 6 minutes and 3 seconds.

Adherence

To promote participant retention and ensure complete follow-up, the research team will initially emphasize the importance of subject compliance at the outset. The team will be in regular contact with the participants, checking on their progress once a week, providing reminders to remain engaged in treatment, and offering support throughout the treatment period. Following the completion of the full treatment regimen, participants will receive a subsidy as a token of appreciation. Participant adherence will be assessed by counting the number of treatments received, with the criterion of 80% or more of the prescribed treatments as the threshold for good adherence. The formula for calculating treatment adherence is as follows: treatment adherence = (number of treatments received by the subject / total number of treatments to be received by the subject) × 100.

Outcomes

The study schedule is presented in Figure 3. All outcome measures explained below will be recorded from baseline until the end of follow-up.

Figure 3. Schedule of trial enrollment, intervention, assessment, and follow-up. CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; DLQI: Dermatology Life Quality Index; ISI: Insomnia Severity Index; MRI: magnetic resonance imaging; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; UAS7: urticaria activity score over 7 days; UCT: urticaria control test.

	Study period									
	Enrollment	Allocation	Treatment (weeks)				Follow-up period (weeks)			
Time point	−1	0	2	4	6	8	8+4	8+8	8+12	8+16
Enrollment										
Eligibility screen	X									
Informed consent	X									
Baseline assessment	X									
Assessment										
UAS7	←					→	X	X	X	X
CU-Q2oL		X	X	X	X	X	X	X	X	X
UCT		X		X		X	X	X	X	X
DLQI		X	X	X	X	X				
SAS		X		X		X				
SDS		X		X		X				
ISI		X		X		X				
MRI		X				X				
Medication use	←						→			
Treatment safety			X	X	X	X				
Adverse reaction			←				→			
Adverse events			←				→			

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Primary Outcome

The primary outcome measure for this clinical trial will be the UAS7. The UAS7 is the gold standard for CSU, evaluating 2 skin symptoms: wheals and itching. Participants will self-assess and record the severity of their symptoms on a 4-point scale. For itchiness, the scoring will be as follows: 0, no symptoms; 1, mild symptoms (occasional itching, no scratching, and no effect on life and sleep); 2, moderate symptoms (occasional itching, scratching, and life and sleep slightly disturbed, but tolerable); 3, severe symptoms (frequent itching, scratching, life and sleep disturbed, and intolerable). For wheals, the scoring will be as follows: 0, no symptoms; 1, mild symptoms (<20 in 24 h); 2, moderate symptoms (21-50 in 24 h); 3, severe symptoms (>50 in 24 h or large confluent masses). The UAS7 ranges from 0 to 42, with lower scores indicating milder skin symptoms [23].

Secondary Outcomes

Quality of Life

The quality of life measures in this clinical trial will include the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) [24] and the Dermatology Life Quality Index (DLQI) [25]. The CU-Q2oL comprises [25] questions that assess the physical, psychosocial, and everyday impact of CSU over the past 2 weeks. Meanwhile, the DLQI comprises 10 questions that evaluate how skin problems have affected the quality of life over the past week.

Urticaria Control Test

The urticaria control test (UCT) measures the level of disease control among patients with CSU over the past 4 weeks. It evaluates the level of distress caused by the physical symptoms of urticaria, the impact on QoL, the effectiveness of treatment in controlling urticaria symptoms, and the overall perceived level of urticaria control. Higher scores indicate better disease control.

Emotion

The emotion measures in this clinical trial will include the Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Insomnia Severity Index (ISI). After conversion, higher scores indicate severe emotional problems, such as depression, anxiety, and stress.

Oversight and Monitoring

Data Collection and Management

The investigator will prepare original documents for each participant upon their random entry into the study. All pertinent information will be documented in the CRFs weekly and saved in a Microsoft Excel spreadsheet. The fMRI results will be archived on a CD-ROM. To ensure data integrity and quality, an internal data supervision team of researchers, led by the principal investigator, will oversee and audit clinical data. They will regularly or sporadically review the CRFs and promptly provide feedback to researchers in case of any identified issues to prevent the recurrence of similar errors or omissions. It is important to note that all participant data will be strictly confidential and not accessible to the public.

Quality Control

Prior to the trial's commencement, all involved team members will undergo investigator training to acquaint themselves with the administration processes, clarify the procedures for embedding, and become familiar with fMRI [26]. Throughout the trial, each participant will be treated by the same surgeon. The head movement test involving blood oxygenation level–dependent (BOLD) images will be promptly conducted during the scanning process to ensure that head movement remains ≤1.2. If head movement exceeds 1.2, a new BOLD scan will be carried out. Following the scanning, data backup will be performed using both a removable hard disk and CD burning. There will be no changes in assignments, and the migration of individuals between groups will not be allowed. If participants discontinue treatment, the reasons for leaving the study will be recorded.

Safety Assessment

Adverse events that occur during treatment and follow-up, such as needle fainting, infection, subcutaneous hematoma, and subcutaneous nodules, will be recorded on the subject's adverse event record sheet at any time. If a participant develops these adverse reactions, they will be asked to report in detail the symptoms, time of occurrence, duration, and time of abatement. Participants will be closely monitored until all indicators return to a state of complete normalcy. Serious adverse events and unintended events will be reported to the Ethics Committee of Guang'anmen Hospital and relevant authorities promptly in accordance with the regulations. The principal investigator will conduct a cumulative review of all adverse events regularly and may convene meetings with the investigators to assess the study's risks and benefits if deemed necessary.

Modifications

The specific stopping criteria are as follows: (1) adverse reactions or serious complications occurring in patients during clinical treatment; (2) significant errors in the established clinical trial protocols, making it difficult to evaluate the efficacy of the treatment; and (3) significant deviations in the implementation of a well-designed protocol, making it difficult to evaluate the therapeutic effect.

Confidentiality

Each participant's privacy will be maintained to the extent permitted by law. Ombudsmen, inspectors, ethics committees, and regulatory authorities will be granted direct access to participants' original medical records to verify clinical trial procedures and data to the extent permitted by applicable laws and regulations and without infringing on participants' privacy. The personal data of the participants will be kept confidential.

Amendments

All amendments and adjustments to this protocol must be agreed upon and signed by all study investigators. The amendments will be submitted to the Ethics Committee for approval and updated in the clinical trial registry.

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Statistical Methods

Primary and Secondary Outcomes

Continuous variable data following a normal distribution will be expressed using means (SDs), while those not following a normal distribution will be expressed using medians and quartiles. Categorical data will be depicted as component ratios or percentages. Group comparisons for continuous variables will be conducted using independent samples *t* tests and repeated-measures ANOVA (multiple time-point comparisons). Nonparametric data comparisons will be carried out using rank-sum tests. Categorical variables will be compared using chi-square tests or Fisher exact tests. All data analyses and graph representations will be processed using R 4.0.l software (R Project for Statistical Computing). Statistical significance will be defined as $P<.05$.

fMRI Examination

Resting-state fMRI data processing and analysis will be conducted using DPABI (Chao-Gan Yan) and SPM12 (Functional Imaging Laboratory) software with the MATLAB platform.

Preprocessing

The initial 10 time points will be removed, and corrections will be made for both time and head movements. Data with head movements exceeding translations of >2 mm or rotational shifts of >2° will be excluded. Linear drift will be removed, and regression will be applied to remove interference from white matter, cerebrospinal fluid, and the whole brain signal. Functional images will be registered to T1 gray matter structural images, followed by spatial smoothing with a Gaussian kernel (4-mm half-width height), delinearization, drift correction, and filtering within the range of 0.01-0.1 Hz. All data from participants will be assessed for quality.

Methods for Brain Functional Network Connectivity Analysis

The amplitude of low-frequency fluctuation (ALFF) method will be employed to calculate changes in brain-wide low-frequency amplitudes before and after treatment. Brain regions identified in the ALFF results, related to the study hypothesis, will serve as seed points. The average time series of these seed regions and their domain signals will be extracted, and correlations with the remainder of the whole brain will be calculated.

Ethical Considerations

The study protocol complies with the ethical standards of the Declaration of Helsinki. The Ethics Committee of Guang'anmen Hospital has approved the study protocol (approval number: 2022-114-KY; September 7, 2022), which has been registered in the Chinese Clinical Trial Registry (trial registration number: ChiCTR2200066274; registered on November 30, 2022). The investigators have the responsibility to fully and comprehensively introduce the purpose, procedures, possible risks, and subsidy of this study to the participants and get signatures on 2 informed consent forms, one kept by the participant and the other kept by the researcher, which should be retained as a clinical research document for reference. The participants will receive a subsidy of 300 CNY (US $41.27) through bank transfer after completing treatment and follow-up. All participants will be free to participate in this study and can decide to withdraw at any time. During the study process, the privacy and confidentiality of the participants will be protected. Each participant's name will be replaced by a serial number and initials. Their personal information will not be disclosed when the paper is published, and the results will be published regardless of whether the research is positive or negative.

Results

Recruitment began on March 1, 2023. A total of 4-6 participants are expected to be enrolled per month. The recruitment is planned to be completed on March 1, 2025, and we expect to publish our results by the winter of 2025. As of November 1, 2023, we have enrolled 25 participants with CSU.

To compare all the results, including both primary and secondary outcomes, and evaluate the treatment effect, we will use R (version 4.0.1) for the analyses. ANOVA and independent samples *t* tests will be repeatedly performed for determining differences in variables between baseline and posttest in the treatment and control groups and for comparing the effects of the program between the groups. Moreover, we will determine whether there is a significant difference between the groups by judging the rejection range based on a significance level of .05. Drawing upon the outcomes of prior research, we anticipate that when comparing the primary and secondary efficacy indicators across the intervention and baseline periods, both the treatment and control groups will exhibit a downward trend in scores. However, it is expected that the decrease will be more pronounced and significant in the treatment group.

Discussion

We hypothesize that wheals and itching will show greater improvement in participants receiving active therapy than in those receiving sham treatment. The results of this study will provide new insights into the effects and mechanisms of acupoint stimulation in the treatment of CSU, aiming to reduce the disease burden and economic cost and to contribute to both academia and public health.

ACE, a variant of acupuncture therapy, is based on the theory of acupuncture in TCM and employs absorbable surgical sutures to produce long-lasting acupoint stimulation in the human body [27]. While the specific mechanism of action remains under investigation, it is believed to be associated with improved local circulation, inhibition of the release of inflammatory factors, reduction in apoptosis, and regulation of cellular factors [28]. Currently, ACE is not widely used to treat skin diseases. However, research and evidence-based medicine [29] have demonstrated that ACE is more effective compared to acupuncture and medicine for the treatment of chronic diseases related to the immune system, such as psoriasis [30], allergic rhinitis [31], and ulcerative colitis [32]. Referring to some research studies [33-35] and previous experience, we designed a randomized, double-blind, placebo-controlled trial to observe the therapeutic effect of ACE on CSU by comparing the

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outcomes before and after treatment. To the best of our knowledge, this is the first study to use ACE for CSU and to observe its clinical efficacy.

This study will employ ACE—an evolved form of acupuncture—as the primary intervention owing to its swift onset, prolonged effects, and improved compliance. We will enroll 108 CSU patients and conduct a randomized, double-blind, sham-controlled study to corroborate the therapeutic benefits of ACE. Additionally, we will use fMRI to delve into the central mechanism of this therapy and validate the hypothesis of modulating the "cerebellum-limbic lobe-reward-somatosensory circuit," thereby providing robust clinical evidence for the acupuncture treatment of CSU. Compared with previous studies, this study has a larger sample size, less frequency of treatment, and a higher patient compliance rate.

However, this study has certain limitations. On the one hand, this trial is a single-site randomized controlled trial involving a relatively limited number of CSU patients. In our subsequent phase, we aim to embark on a multicenter clinical study to expand the participant pool and thereby enhance the generalizability of our findings. On the other hand, this study requires the enrollment of patients aged 18-60 years with a UAS7 of ≥16. However, this selection criterion may exclude some patients with mild symptoms, patients who can effectively control their condition with medication, and younger or older patients, thereby preventing them from receiving ACE treatment. Furthermore, this study only involves an 8-week intervention for patients, and there may be patients who require a longer period of treatment to achieve significant effects.

If ACE is proven to be effective, it could lead to comparisons with acupuncture or pharmaceutical treatments, offering evidence to support ACE as a novel nonpharmacological approach for CSU management. Furthermore, we can endeavor to integrate modern and traditional techniques to develop a medicinal thread as a potential material for ACE. After the research results are released, we will promote the acupuncture treatment plan for CSU through academic conferences, training courses, standardized training, and other forms of promotion. Moreover, we will promote this project at corresponding community health service centers and support institutions. Through academic exchange, guidance, and article publication, we will promote the academic achievements of this project nationwide, which will facilitate the transformation, promotion, and application of the research results.

Acknowledgments

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Authors' Contributions

JB, LL, ZF, and BC chose the topic. SQ, CX, and JY collected the data. JB and LL wrote the first draft of the paper. All authors were involved in the design of the study and have contributed to and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACE: acupoint catgut embedding
ALFF: amplitude of low-frequency fluctuation
BOLD: blood oxygenation level–dependent
CRF: Case Report Form
CSU: chronic spontaneous urticaria
CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire
DLQI: Dermatology Life Quality Index
FA: flip angle
fMRI: functional magnetic resonance imaging
FOV: field of view
HPA: hypothalamic-pituitary-adrenal
MRI: magnetic resonance imaging
TCM: traditional Chinese medicine
TE: time to echo
TR: time to repetition
UAS7: urticaria activity score over 7 days

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Protocol

Efficacy and Safety of Shi Cervical Rotational Manipulation in Patients With Atlantoaxial Joint Subluxation: Protocol for a Randomized Controlled Trial

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Abstract

Background: The clinical diagnosis of atlantoaxial joint subluxation (AJS) in traditional Chinese medicine (TCM) is characterized by an unequal distance between the lateral mass of the atlas and the odontoid process on imaging, resulting in neck pain accompanied by symptoms such as dizziness, headache, and limited cervical mobility. In Shanghai, Shi cervical rotational manipulation (SCRM) is a commonly employed TCM manual therapy for treating this condition. Nevertheless, there is a lack of evidence-based medical information regarding the clinical efficacy and safety of this technique.

Objective: The principal aim of this study is to evaluate the efficacy and safety of SCRM in patients diagnosed with AJS.

Methods: This study is a prospective randomized controlled clinical trial that will be conducted at a single center and that has a follow-up period of 24 weeks. A total of 96 patients diagnosed with AJS will be recruited from outpatient and inpatient clinics at Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine. These patients will be randomly assigned to either the experimental group (SCRM) or the comparison group (basic cervical manipulation [BCM]). Treatment sessions consisting of SCRM or BCM will be administered twice a week for a duration of 4 weeks. Clinical monitoring indicators include the presence or absence of clinical symptoms as recorded on a symptom recording form, cervical imaging examination findings using cervical computed tomography, degree of neck pain measured by a visual analog scale (VAS), cervical range of motion assessed through cervical mobility measurement, degree of vertigo evaluated using the Vertigo Symptoms Scale-Chinese Version (VSS-C), and adverse events that may occur during the follow-up period. The time points for data collection and follow-up are baseline and postintervention (weeks 4, 8, 12, 16, 20, and 24).

Results: This paper presents an overview of the reasoning and structure of a prospective randomized controlled trial with the objective of investigating the clinical efficacy and safety of SCRM in patients with AJS by assessing improvements in clinical symptoms, neck pain severity, and vertigo severity and evaluating changes in cervical imaging findings. Recruitment was started in March 2023. By the end of May 2024, 76 patients were included in this project. The last follow-up data are predicted to be collected by the end of February 2025.

Conclusions: This investigation will yield dependable evidence regarding the efficacy and safety of SCRM in patients with AJS.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300068510; https://www.chictr.org.cn/showprojEN.html?proj=186883

International Registered Report Identifier (IRRID): DERR1-10.2196/57865

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(JMIR Res Protoc 2024;13:e57865) doi:10.2196/57865

KEYWORDS

atlantoaxial joint subluxation; Shi cervical rotational manipulation; efficacy; safety; randomized controlled trial

Introduction

Joint subluxation is a distinct medical diagnosis within the realm of traditional Chinese medicine (TCM) [1]. In November 2020, the National Health Commission of China and the China Administration of Traditional Chinese Medicine officially incorporated the term “joint subluxation” into the updated edition of the “International Classification of Diseases 11th Revision, ICD-11” instead of “Gu Cuo Feng,” which was previously widely used in TCM clinical diagnosis, thereby establishing its recognition as a universally accepted diagnostic term [2]. While joint subluxation can manifest in various articulations throughout the body, the spinal region, particularly the cervical spine, frequently serves as a prevalent site of occurrence [3]. Hence, in TCM diagnosis, the specific location of manifestation is referred to as joint subluxation of the site, with atlantoaxial joint subluxation (AJS) being a prevalent clinical condition. Meanwhile, AJS is also considered a type of cervical spondylosis. The primary visual indication of AJS is an asymmetrical gap observed between the lateral mass of the atlantoaxial joint and the odontoid process on cervical spine X-ray or computed tomography (CT) scans, along with misalignment of the axis of the spinous process relative to the midline of the spinous process [4].

The atlantoaxial joint, situated in the human cervical spine, functions as a relatively autonomous unit. Within this joint, the atlas assumes the role of the central axis for neck motion, contributing to over 40% of the rotational movement of the cervical spine. Conversely, the axis serves as the focal point for stress in the upper cervical spine and functions as a primary attachment site for the neck’s short muscles and ligaments [5]. In instances where the atlantoaxial joint experiences a pathological state known as “joint subluxation,” it can lead to the entrapment of the synovial membrane and joint capsule, resulting in localized swelling and pain in the cervical spine, impaired joint movement, and stimulation of the corresponding regions of the nerves, blood vessels, and receptors, which can cause symptoms such as vertigo and pain [6]. For a long time, AJS has been commonly referred to as atlantoaxial joint instability, atlantoaxial joint disorder, etc [7,8]. The clinical manifestations are mainly neck pain accompanied by dizziness, headache, and cervical limited mobility, and thus, clinicians previously used to diagnose patients as having cervical vertigo [9,10].

Cervical manipulation is a frequently employed approach in the management of cervical spondylosis, with cervical rotation manipulation or small joint mobilization being the most prominent technique [11,12]. This method involves the rotation of the subject’s head along the longitudinal axis of the cervical spine, resulting in an audible “clicking” sound from the cervical vertebra joint. The clinical use of this technique has garnered significant attention and has been supported by empirical evidence demonstrating its efficacy and safety through various studies. Studies have demonstrated that this technique has the potential to ameliorate the pathological condition of joint subluxation, restore bones and joints to their typical physiological and anatomical alignments, and re-establish dynamic and static mechanical equilibrium in the cervical vertebra joint, thereby accomplishing therapeutic objectives [13-15]. Nevertheless, variations in clinical effectiveness arise due to divergent approaches to manipulation and the focus of the manipulation on the atlantoaxial joint, a crucial anatomical region within the cervical spine, and the safety of manual therapy has always been a concern of clinicians [16,17].

Shi cervical rotational manipulation (SCRM) is a technique for treating AJS created by Shi’s Traumatology TCM Academic School, which is the largest traumatology school of TCM in Shanghai. The technical attributes of SCRM encompass the swift application of stress, which belongs to the high velocity and low amplitude (HVLA) technique. In our prior investigation, we formulated a standard operating procedure (SOP) for SCRM, which will be explained subsequently [18]. Our research team quantified objective metrics and kinematic and kinetic parameters pertaining to the technique, considering the viewpoints of both recipients and practitioners [19]. Furthermore, we assessed the safety of the technique through finite element analysis and provided preliminary insights into its biomechanical mechanism of action [20]. Regarding the clinical assessment of the immediate efficacy of SCRM, a 50% reduction in visual analog scale (VAS) scores was observed immediately following the procedure. Additionally, approximately 70% to 80% of participants reported subjective improvements such as a sensation of a lighter head, a relaxed neck, and brighter eyes [18]. These findings suggest the significant immediate efficacy of the SCRM technique. In our subsequent short-term and medium-term clinical follow-up study in which we applied SCRM to treat patients with cervical spondylotic radiculopathy, the intervention had an efficacy rate of 94.74%. Furthermore, the overall efficacy rate at 3 months was 89.47%, with no notable discomfort or adverse events reported [18]. Nonetheless, there is still a lack of standard randomized controlled studies on SCRM, and there is limited evidence-based medical information on the efficacy and safety of SCRM. Consequently, the aim of this randomized controlled trial is to assess the efficacy and safety of SCRM in patients with AJS.

Methods

Study Design

This study will be a single-center, prospective, randomized controlled clinical trial to evaluate the effectiveness and safety of SCRM in patients with AJS. We have used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines to introduce this protocol [21]. A total of 93 participants with AJS from outpatient and inpatient clinics will be recruited and randomly allocated to either the

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SCRM group or the basic cervical manipulation (BCM) group. Screening (visit 0) will be performed within 3 days prior to enrollment to assess eligibility and collect baseline data and imaging data. Those participants who meet the inclusion criteria will be randomly assigned to the SCRM group or BCM group and receive the corresponding treatment of each group twice a week for 4 weeks. After the end of treatment (visit 1), all patients will undergo evaluations, including assessment of symptoms and signs, cervical mobility examination and measurement, assessment of VAS scores and Vertigo Symptoms Scale-Chinese Version (VSS-C) scores, imaging, efficacy evaluation, and assessment of adverse events. Then, all patients will be followed up every 4 weeks until the end of the study at 24 weeks. Additionally, imaging and efficacy evaluations will be conducted at week 4 (visit 1) and week 24 (visit 6), and assessment of the VSS-C score will be conducted at week 4 (visit 1), week 16 (visit 4), and week 24 (visit 6). The flowchart schedule is shown in Table 1, and the flow diagram of participants is shown in Figure 1.

Table 1. Flowchart schedule.

Assessment	Time window						
	Visit 0 (screening stage; –3 to 0 days)	Visit 1 (week 4)	Visit 2 (week 8)	Visit 3 (week 12)	Visit 4 (week 16)	Visit 5 (week 20)	Visit 6 (week 24)
Baseline information	Yes	No	No	No	No	No	No
Basic medical history and drug combination	Yes	No	No	No	No	No	No
Inclusion and exclusion criteria	Yes	No	No	No	No	No	No
Informed consent	Yes	No	No	No	No	No	No
Randomization allocation	Yes	No	No	No	No	No	No
Symptoms and signs	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cervical mobility examination and measurement	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VAS[a] score	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VSS-C[b] score	Yes	Yes	No	No	Yes	No	Yes
Imaging (CT[c] or X-ray)	Yes	Yes	No	No	No	No	Yes
Efficacy evaluation	No	Yes	No	No	No	No	Yes
Adverse events	No	Yes	Yes	Yes	Yes	Yes	Yes

[a]VAS: visual analog scale.

[b]VSS-C: Vertigo Symptoms Scale-Chinese Version.

[c]CT: computed tomography.

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Figure 1. Flow diagram of participants. AJS: atlantoaxial joint subluxation; BCM: basic cervical manipulation; CT: computed tomography; SCRM: Shi cervical rotational manipulation; VAS: visual analog scale; VSS-C: Vertigo Symptoms Scale-Chinese version.

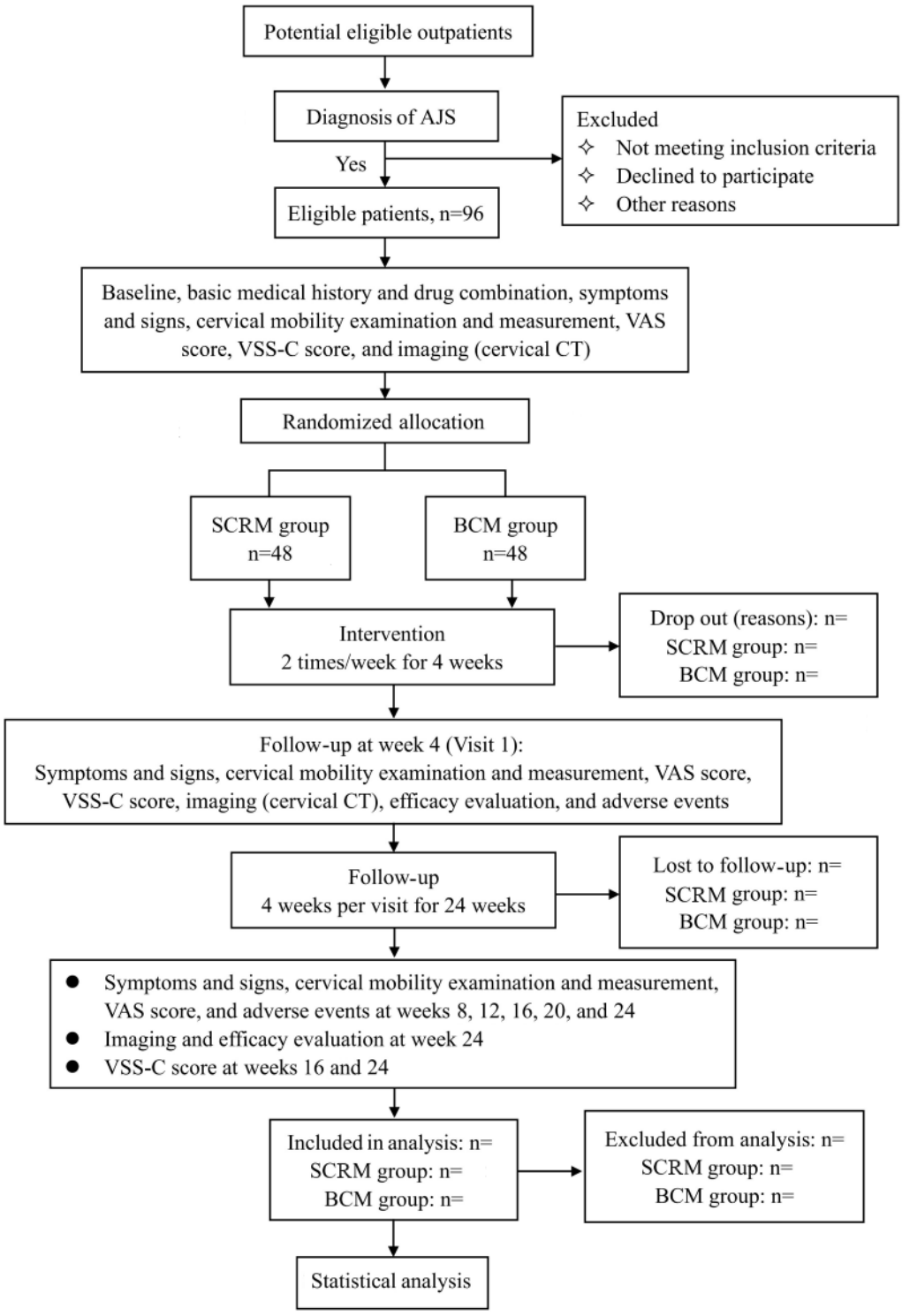

The Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine will be responsible for the recruitment, screening, and intervention of all participants and the assessment of all outcomes. Management of the randomization sequence and data analyses will be carried out by the Institute of Traumatology, Shi's Center of Orthopedics and Traumatology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

Participants

Patients who are aged between 18 and 70 years with AJS will be included in the study. The screening, inclusion, and exclusion procedures for all patients; the notification and signing of informed consent; and the documentation of each follow-up visit will be meticulously recorded on an individual basis.

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Diagnostic Criteria

The diagnosis of AJS is based on the Diagnostic Criteria for Traditional Chinese Medicine and the International Classification of Diseases 11th Revision (ICD-11), and several aspects are considered. First, the patient has a history of neck strain or injury and has a long-term habit of working or living with a low head. Second, the clinical manifestations are mainly vertigo, dizziness, headache, and soreness in the neck. Third, the cervical movement is mainly limited to the left-right rotation of the atlantoaxial joint. When performing palpation, the muscle tension around the atlantoaxial joint increases or small blocky or strip-shaped muscle nodules are felt, which may induce or exacerbate dizziness or vertigo. Fourth, cervical X-ray or CT shows an asymmetrical gap between the lateral mass of the atlantoaxial joint and the odontoid process, with a difference of more than 2 mm, along with the misalignment of the axis of the spinous process relative to the midline of the spinous process.

Inclusion Criteria

The inclusion criteria are as follows: (1) meeting the diagnostic criteria of AJS; (2) male or female sex and age of 18 to 70 years; (3) recurrent clinical symptoms, such as neck pain, vertigo, dizziness, and headache, for less than 4 weeks, which cannot be relieved; and (4) voluntary participation in this trial and signing of the informed consent document.

Exclusion Criteria

The exclusion criteria are as follows: (1) cervical spondylosis of the nerve root type or spinal cord type and severe spinal stenosis; (2) a history of spinal surgery or severe spinal trauma; (3) a history of congenital variation or malformation of an unstable cervical vertebral structure; (4) dizziness or vertigo caused by other diseases diagnosed by specialized examinations such as those performed by cardiovascular, otolaryngology, and neurology departments; (5) imaging findings, including spinal infection, fracture, tumor, tuberculosis, severe spinal deformity, severe osteoporosis, ankylosing spondylitis, and osteitis deformans; (6) severe primary diseases of the endocrine system, cardiovascular system, and autoimmune system, and tumor or mental illness; (7) pregnancy and breastfeeding; and (8) no acceptance of cervical manipulation therapy.

Withdrawal Criteria

The withdrawal criteria are as follows: (1) severe or intolerable adverse reactions during the observation process; (2) persistent or progressive symptoms and no suitability for participation in the trial; (3) risk of health damage (such as sudden serious complications); and (4) voluntary withdrawal or interview miss for other reasons.

Sample Size

The sample size calculation is based on our previous clinical research in patients with cervical spondylosis of the nerve root type, using the same primary outcome instrument. The efficiency of SCRM is 89.5%, while that of BCM is 54.6%. The sample size calculation formula is as follows:

The α is .05 and $1-\beta$ is .90. According to estimations, 48 participants per group are needed considering that this is a long-term follow-up that is expected to have a dropout rate of no greater than 20%.

Randomization and Allocation

The randomization schedule will be prepared by the Institute of Traumatology, Shi's Center of Orthopedics and Traumatology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. The specific randomization number lists will be computer-generated using IBM SPSS 22.0 (IBM Corp) and concealed from the screeners, assessors, and patients by a specialized staff member who is not involved in the study. Within a set of randomly generated numbers, odd numbers will be attributed to the SCRM group, while even numbers will be attributed to the BCM group. Subsequently, all numbers and their respective group assignments will be documented on a card and securely sealed within opaque envelopes. These envelopes will be labeled with sequential numbers corresponding to the patients and entrusted to the screeners who bear the responsibility of participant screening. Once a patient is successfully enrolled, provides written informed consent, completes the baseline measurements, and is confirmed as an eligible participant, the sealed envelope will be transferred to the manual therapist. The manual therapist will unseal the envelope and administer the intervention (SCRM or BCM) based on the instructions provided on the card. The allocation list containing sensitive information will be kept confidential by specialized personnel who are not involved in participant recruitment or outcome assessment. This information will not be disclosed to the data analysts or outcome assessors.

Blinding

Participants will be unaware of their group assignment and will remain unaware of receiving SCRM or BCM treatment. The outcome assessors will also be unaware of the randomization allocation and will not be involved in the intervention process. The manual therapists will not be able to be blinded owing to their involvement in performing the interventional protocols. However, they will not participate in the outcome measurements or statistical analyses and will be instructed to refrain from disclosing treatment details to the outcome assessors or participants. The statistician will remain blinded to the group allocation until the completion of the statistical analyses.

Interventions

The techniques used in this study are SCRM in the experimental group and BCM in the control group. The two techniques are commonly used in clinical treatment and have established SOPs in Shanghai. All patients will receive treatment twice a week, with a 2-day interval between sessions, for a duration of 4 weeks. In addition, there will be a relaxation therapy step before the 2 techniques, after which the SCRM or BCM technique will be performed. The relaxation therapy will be performed as follows:

1. The patient assumes a seated position, while the manipulation therapist positions themselves behind one side of the patient's body.

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2. One hand of the therapist provides support to the patient's forehead, while the other hand employs pressing, pulling, and kneading techniques on both sides of the patient's cervical spine, as well as the trapezius, sternocleidomastoid, and levator scapulae muscles, repeating these actions 3 times.
3. Subsequently, the therapist applies pushing techniques along the line extending from the 7th cervical spine to the acromion, repeating this action 3 times.

The entire relaxation therapy session lasts approximately 10 minutes.

SCRM Technique

The primary technological approach in SCRM involves applying pressure with the thumb on the spinous process, transverse process, or pedicle of the patient's axis while simultaneously rotating the cervical spine in an effort to restore it to its original alignment. AJS is categorized into 8 distinct techniques, which are determined by the specific imaging characteristics of the atlantoaxial joint. Figure 2 shows the comprehensive classification of AJS according to X-ray findings. Each technique within these categories employs different SCRM methods. When there is a simple asymmetrical gap between the lateral mass of the atlantoaxial joint and the odontoid process, the spinous process of the axis remains aligned with the midline of the spinous process, yet the discrepancy in distance between the lateral mass of the left and right atlas and the dentate process is evident. If the left block displays a 2-mm greater distance compared with the right block, it falls under type A (left oblique type). Conversely, if the right block displays a 2-mm greater distance compared with the left block, it is classified as type B (right oblique type). When there is a simple misalignment of the axis spinous process relative to the midline of the spinous process, the distance between the lateral masses of the left and right atlas and the dentate process is either equal or exhibits a difference within a 2-mm range. However, the spinous process of the axis deviates from the midline of the spinal axis. If the spinous process of the axis is located at the left of the midline, it is classified as type C (left rotation type). Conversely, if the spinous process of the axis is located at the right of the midline, it is categorized as type D (right rotation type). The types can mix as follows: when type A merges with type C, it is referred to as type AC; when type A merges with type D, it is referred to as type AD; when type B merges with type C, it is referred to as type BC; and when type B merges with type D, it is referred to as type BD. The SOPs of SCRM according to the different types are presented below [18].

Figure 2. Comprehensive classification of atlantoaxial joint subluxation using X-ray. The green line indicates the distance between the lateral mass of the atlantoaxial joint and the odontoid process. The blue line indicates the axis line of the C2 spinous process. The yellow line indicates the midline of the spinous process. (A) Normal atlantoaxial joint; (B) Type A; (C) Type B; (D) Type C; (E) Type D; (F) Type AC; (G) Type AD; (H) Type BC; (I) Type BD.

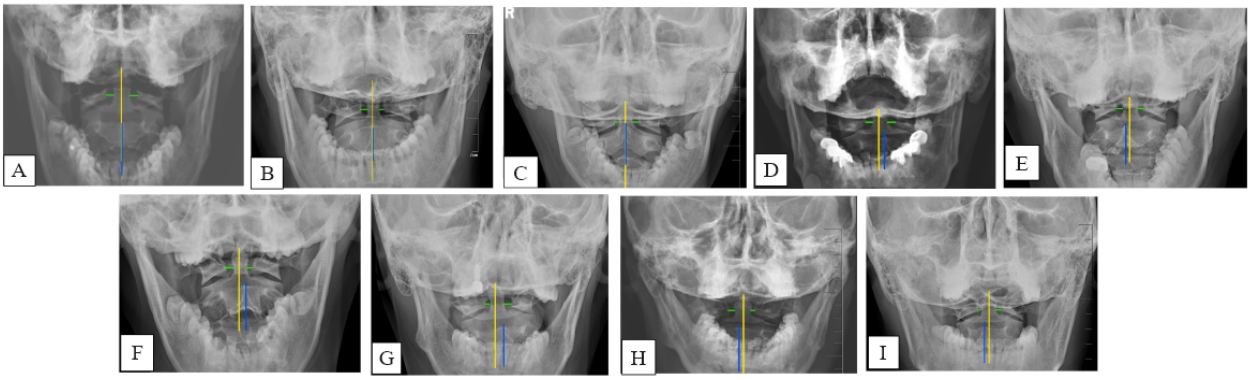

For type A, the steps are as follows. First, the patient assumes a seated position, while the medical therapist stands behind the patient on the left side. The therapist's left hand supports the patient's forehead, specifically positioning the right thumb at the left transverse process of the patient's axis. The remaining 4 fingers of the therapist's right hand rest gently on the right side of the patient's neck, resulting in a forward flexion of the patient's neck by approximately 10°. Second, the therapist subsequently alters the position of their left hand, placing it on the patient's right chin nodule, while maintaining the unchanged posture of the right hand. This adjustment allows the therapist to rotate the patient's neck to its maximum range of active movement. Third, the therapist's left hand persists in applying force to achieve the maximum range of passive movement in rotating the patient's neck, while the right thumb maintains a fixed position. The patient is instructed to relax their neck. Subsequently, the left hand momentarily intensifies the force of left rotation, while the right thumb applies pressure to the transverse process in a rightward direction. This maneuver often elicits an audible "click" sound emanating from the neck, accompanied by a subtle sliding sensation beneath the therapist's right thumb, and the procedure is considered concluded.

For type B, the therapist stands behind the patient's right side, and the therapist's right hand supports the patient's forehead, specifically positioning the left thumb at the right transverse process of the patient's axis. The remaining steps are the same as those for type A, except that they are all performed in the opposite direction.

For type C, the operation steps are the same as those for type A, while the right thumb of the therapist is fixed at the left spinous process of the patient's axis.

For type D, the operation steps are the same as those for type B, while the left thumb of the therapist is fixed at the right spinous process of the patient's axis.

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For type AC, the operation steps are the same as those for type A, while the right thumb of the therapist is fixed at the left pedicle of the patient's axis.

For type AD, the first operation steps are the same as those for type A, and the second operation steps are the same as those for type D.

For type BC, the operation steps are the same as those for type B, while the left thumb of the therapist is fixed at the right pedicle of the patient's axis.

For type BD, the first operation steps are the same as those for type B, and the second operation steps are the same as those for type D.

BCM Technique

The BCM technique does not differ depending on the type of AJS. The SOP of BCM for patients with AJS (all types) is as follows [18]. First, the patient assumes a seated position, and the manipulation therapist stands behind the patient's left side. Second, the therapist manipulates the patient's jaw by flexing their left elbow and applies pressure to the occipital area with their right hand, which is supporting the occipital bone with the right palm and supporting the other 4 fingers. Third, the therapist gradually rotates the patient's head to the left until reaching the active limit position and then instructs the patient to relax their neck while continuing to rotate the head to the passive limit position using both hands. During this process, a momentary force is exerted to further facilitate the left rotation of the patient's head, resulting in audible clicking sounds emanating from the neck. Fourth, the therapist performs the 3 steps on the right side of the patient. It is important to note that the therapist can freely select one side (left or right) of the patient for the procedure.

Follow-Up Period

Follow-up assessments with questionnaires will be conducted. During the 24-week unsupervised follow-up period, no participants will undergo special therapy, with the exception of routine cervical care.

It is important to acknowledge that every subsequent patient will schedule an appointment in advance via telephone and visit the outpatient department. Subsequently, the outcome assessors will aid patients in completing the questionnaire, will conduct and document physical examinations, and will administer cervical CT scans.

The outcome assessors will establish an electronic information group, inviting all participants to join. Throughout the follow-up period, any adverse events or physical discomfort experienced in any circumstance will be promptly reported within the information group.

Outcome Measurement

The following baseline descriptive data will be obtained using questionnaires: age, gender, marital status, education level, occupation, basic medical history, and drug combination. A summary of all measures and follow-up time points in this trial is shown in Table 1.

Primary Outcome

Efficacy Rate

The clinical symptoms of all subjects will be recorded and evaluated using the numerical rating scale (NRS), which is composed of a horizontal line having a length from 0 to 10 cm, with "0" indicating "normal" and "10" indicating "unbearable." We will refer to the efficacy evaluation standards in the "Diagnostic and Therapeutic Efficacy Standards for Traditional Chinese Medicine Diseases" issued by the China Administration of Traditional Chinese Medicine in 1994.

We define clinical cure as a decrease of more than 80% in the NRS score for clinical symptoms and the ability to live and work normally. We define clinical improvement as a decrease of 20% to 80% in the NRS score for clinical symptoms. We define clinical cureless as a decrease of less than 20% in the NRS score for clinical symptoms. We define clinical recurrence as the reappearance of the original symptoms after treatment, with the degree being equivalent to or greater than that before treatment.

All patients will be followed up, and the efficacy rate will be calculated at visit 1 after the intervention. The efficacy rate and clinical recurrence rate will be calculated at visit 6. The calculation formulas are as follows:

Efficacy rate = ([number of clinical cure cases + number of clinical improvement cases – number of clinical cureless cases] / total number of patients) 100

Clinical recurrence rate = (number of clinical cureless cases / [number of clinical cure cases + number of clinical improvement cases]) 100

Secondary Outcomes

Severity of Neck Pain (VAS)

The VAS score will be used to evaluate the severity of neck pain in all participants [22]. The VAS score sheet consists of a horizontal 100-mm line with "painless" and "extremely painful" end points. Patients select a point on the line segment based on their own pain perception and draw a vertical line through that point to express the intensity of pain.

Severity of Vertigo (VSS-C)

The VSS-C scale has been used in many studies to evaluate the severity of vertigo and has shown high reliability and validity [23]. The VSS-C is a self-assessment scale consisting of 22 questions, with a score of 0-4 for each question. A total score of 0-33 points indicates mild vertigo, 34-67 points indicates moderate vertigo, 68-101 points indicates severe vertigo, and 102-136 points indicates extremely severe vertigo.

Imaging Changes of Cervical CT

All participants will undergo cervical CT examination at visits 0, 1, and 6. Two radiologists will measure the distance from the lateral mass of the atlantoaxial joint to the dentate process and the distance from the axis to the midline of the spinous process. Each radiologist will measure each image 3 times, and the average of the 6 outcomes will be taken as the final result. The

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improvement rate will then be calculated based on the results. The calculation formula is as follows:

Improvement rate = ([distance at pretreatment – distance after treatment] / distance at pretreatment) 100

Cervical Mobility

A cervical inclinometer will be used to measure cervical mobility. The outcome assessor will measure and record the cervical angles of the patient in 6 directions: flexion, extension, left rotation, right rotation, left lateral bending, and right lateral bending [24]. The outcome assessor will take 3 measurements in each direction, and the average of the 3 values will be used as the final result.

Adverse Events

Any adverse events, including symptoms, signs, and physical or laboratory examination abnormalities, will be carefully evaluated and recorded. Researchers will analyze the causes of these adverse events, make judgments, and track and record them in a timely manner. Once an adverse event occurs, doctors will provide the corresponding treatment to the patient for free. All adverse events will be judged for their characteristics, severity, and potential relationship to the study treatment. The correlation between adverse events and the study treatment is divided into 5 levels: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated. Based on the judgment and severity of adverse events, the primary investigator and ethics committee will be informed immediately to decide whether to discontinue observation, retain the medical records of participants who withdraw from the experiment, conduct a full data set analysis of the efficacy and adverse reactions, and fill in the experiment conclusion and the reason for case withdrawal.

Data Collection and Management

An electronic information data collection system for our research has been created by the Institute of Traumatology, Shi's Center of Orthopedics and Traumatology. All data will be electronic, double-checked, and backed up by 2 research assistants and entered into the system for mutual verification and correction of errors. Once all electronic data are verified against the original data, the data will be locked, and any modifications and their reasons will leave a trace in the data backend.

Statistical Analysis

The main objective of this study is to evaluate the clinical effectiveness of SCRM therapy in patients with AJS. Additionally, secondary analyses will be conducted to assess changes in VAS scores, VSS-C scores, imaging findings, and cervical mobility before and after treatment in patients with AJS. Analyses will be performed using IBM SPSS 22.0. The measurement data will be expressed using mean differences (mean and standard deviation). The repeated measurement data will be analyzed using within-group variance analysis. Enumeration data will be presented as rates. The sample size needed for the Pearson chi-square test to compare rates between the 2 groups before and after treatment will be determined using the normal approximation algorithm and a 1-sided test. This study employs the superiority test that uses a 1-sided test level of α=.05. A *P* value of ≤.05 signifies the rejection of H0, thereby establishing the superiority of the SCRM group over the BCM group. Conversely, a *P* value >.05 indicates that a definitive conclusion regarding superiority cannot be drawn at this stage. The safety analysis will employ the chi-square test to compare the incidence of adverse reactions between the 2 groups. In instances where the data fail to meet the requirements of the chi-square test, the Fisher exact probability method will be employed.

Ethical Considerations

The study procedures have been reviewed and approved by the Institutional Review Board of Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (approval number: 202218), and protocol version 1.0/20221201 is currently active. The full trial has been registered through the Chinese Clinical Trial Registry (identifier: ChiCTR2300068510). Written informed consent will be obtained from all participants before enrolment in the study. Any modifications to the protocol related to deviation of the study aim, study design, patient population, or study procedures will not be implemented until the formal amendment to the protocol is approved by the Institutional Review Board.

Results

This paper presents an overview of the reasoning and structure of a prospective randomized controlled trial with the objective of investigating the clinical efficacy and safety of SCRM in patients with AJS by assessing improvements in clinical symptoms, neck pain severity, and vertigo severity and evaluating changes in cervical imaging findings. Recruitment was started in March 2023. By the end of May 2024, 76 patients were included in this project. The last follow-up data are predicted to be collected by the end of February 2025. The findings of this study are expected to be submitted for publication in late 2025.

Discussion

Findings and Strengths

Globally, manual therapy is considered one of the most crucial clinical therapies for the treatment of cervical spondylosis, and approaches, such as spinal manipulation, chiropractic adjustment, the Mulligan technique, small joint adjustment, and the HVLA technique, are widely used [25-27]. In the context of China, doctors employ diverse techniques in various regions and schools, each possessing distinct technical attributes. In Shanghai, China, the most prevalent technique employed is SCRM, which has demonstrated satisfactory therapeutic outcomes [28]. However, there exists a dearth of evidence-based medical information regarding its efficacy and safety. Consequently, this study aims to examine the effectiveness and safety of SCRM in treating patients with AJS through a prospective randomized controlled trial.

The optimal sample size has been accurately determined based on the findings of our prior research to guarantee sufficient test performance [18]. Subsequently, randomization and blinding procedures will be fully implemented to ensure the study's

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classification as a randomized controlled trial. Additionally, a statistical analysis employing a superiority test will be conducted to ascertain that all patients with AJS can receive authentic clinical treatment. As Shi's Orthopedics and Traumatology Academic School is well known throughout China, with a history of 160 years, it is officially recognized by China's Health Care Administration, and Shanghai Baoshan Hospital is a branch of Shi's Orthopedics and Traumatology Academic School. We ensure that the interventions (SCRM and BCM) will be performed by a fixed chief physician with more than 10 years of clinical experience. Moreover, proficient research assistants will be assigned to carry out screening, selection, and follow-up, possessing a comprehensive understanding of the research process for all participants. These measures will greatly contribute to enhancing patient adherence and mitigating the likelihood of attrition in this study. In terms of evaluation metrics, we will employ appropriate standards and develop meticulous professional scales as the primary outcome evaluation indicators to prevent subjective and ambiguous classification assessments, thereby minimizing data distortion and bias. Lastly, we have developed a dedicated electronic information data collection system for this study, guaranteeing the precision, novelty, and security of the data. This study aims to examine the clinical effectiveness and safety of SCRM in patients with AJS by assessing improvements in clinical symptoms, neck pain severity, and vertigo severity and evaluating changes in cervical imaging findings. If successful, this investigation will yield dependable evidence on the efficacy and safety of SCRM in individuals with AJS.

Limitations

For classification, AJS has been divided into 8 types. For the different types, the SCRM techniques are different, while the BCM techniques are the same. As the incidence rate of AJS is not high, it may be difficult to recruit patients with each type of AJS, who meet the statistical requirements, in a limited time. Therefore, we will not separate the different AJS types, but instead combine them to observe the difference in efficacy between SCRM and BCM. In the future, we will further extend our project timeline and recruit as many subjects as possible for each type of AJS, so that efficacy analysis can be conducted for different types of AJS.

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Authors' Contributions

DZ is the principal investigator and sponsor, who has initiated the current trial. DZ, DR, and SZ conceived and designed the study. SH, AY, YW, and WH executed the statistical methods and obtained ethics approval. DZ, SZ, ZH, and LG drafted the article or revised it critically for important intellectual content. DZ, DR, and SZ reviewed and edited the manuscript. Final approval of the version to be published was provided by all authors.

Conflicts of Interest

None declared.

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Abbreviations

AJS: atlantoaxial joint subluxation
BCM: basic cervical manipulation
CT: computed tomography
HVLA: high velocity and low amplitude

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NRS: numerical rating scale
SCRM: Shi cervical rotational manipulation
SOP: standard operating procedure
TCM: traditional Chinese medicine
VAS: visual analog scale
VSS-C: Vertigo Symptoms Scale-Chinese Version

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Protocol

Effects of Defatted Rice Bran–Fortified Bread on the Gut Microbiota Composition of Healthy Adults With Low Dietary Fiber Intake: Protocol for a Crossover Randomized Controlled Trial

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Abstract

Background: Inadequate dietary fiber (DF) intake is associated with several human diseases. Bread is commonly consumed, and its DF content can be increased by incorporating defatted rice bran (DRB).

Objective: This first human study on DRB-fortified bread primarily aims to assess the effect of DRB-fortified bread on the relative abundance of a composite of key microbial genera and species in fecal samples. Secondary outcomes include clinical (cardiovascular risk profile), patient-reported (daily bread consumption and bowel movement, gut comfort, general well-being, and total DF intake), biological (fecal microbiota gene abundances, and fecal and plasma metabolites), and physiome (whole-gut and regional transit time and gas fermentation profiles) outcomes in healthy adults with low DF intake.

Methods: This is a 2-armed, placebo-controlled, double-blinded, crossover randomized controlled trial. The study duration is 14 weeks: 2 weeks of lead-in, 4 weeks of intervention per phase, 2 weeks of washout, and 2 weeks of follow-up. Overall, 60 healthy adults with low DF intake (<18 g [female individuals] or <22 g [male individuals] per day) were recruited in Christchurch, New Zealand, between June and December 2022. Randomly assigned participants consumed 3 (female individuals) or 4 (male individuals) slices of DRB-fortified bread per day and then placebo bread, and vice versa. The DRB-fortified bread provided 8 g (female individuals) or 10.6 g (male individuals) of total DF, whereas the placebo (a matched commercial white toast bread) provided 2.7 g (female individuals) or 3.6 g (male individuals) of total DF. Before and after each intervention phase, participants provided fecal and blood samples to assess biological responses; completed a 3-day food diary to assess usual intakes and web-based questionnaires to assess gut comfort, general and mental well-being, daily bread intake, and bowel movement via an app; underwent anthropometry and blood pressure measurements; and drank blue food dye to assess whole-gut transit time.

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Additionally, 25% (15/60) of the participants ingested Atmo gas-sensing capsules to assess colonic gas fermentation profile and whole-gut and regional transit time. Mean differences from baseline will be compared between the DRB and placebo groups, as well as within groups (after the intervention vs baseline). For metabolome analyses, comparisons will be made within and between groups using postintervention values.

Results: Preliminary analysis included 56 participants (n=33, 59% female; n=23, 41% male). Due to the large dataset, data analysis was planned to be fully completed by the last quarter of 2024, with full results expected to be published in peer-reviewed journals by the end of 2024.

Conclusions: This first human study offers insights into the prospect of consuming DRB-fortified bread to effectively modulate health-promoting gut microbes, their metabolism, and DF intake in healthy adults with low DF intake.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622000884707; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383814

International Registered Report Identifier (IRRID): DERR1-10.2196/59227

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KEYWORDS

dietary fiber; defatted rice bran; bread; healthy adults; gut microbiota; metabolites; gut physiome; randomized controlled trial; mobile phone

Introduction

Background

Diet strongly influences the gut microbiota composition [1-3]. Diets low in dietary fibers (DFs) may contribute to gut dysbiosis, where specific bacterial taxa and microbial diversity are diminished [1,2]. This phenomenon mostly occurs in industrialized populations consuming a low-DF, high–fat and protein diet [3]. However, alteration of the gut microbiota profile may be reversible by improving DF intake [2].

DFs are carbohydrates that are neither digestible nor absorbable in the small intestine. Some DFs are fermented by gut microbes in the large intestine, which produces metabolites such as organic acids [4]. These metabolites, in particular the short-chain fatty acids acetate, butyrate, and propionate, play major beneficial physiological and immunological roles for the human host [4]. They modulate the luminal pH and immune system, lower pathogenic bacteria load, act as a catalyst for calcium and magnesium absorption, and provide energy sources for colonic cells [4]. Therefore, increasing DF intake may provide the required substrates for microbial growth and energy, ultimately benefiting the human host's health [2].

DFs are found in a wide range of plant foods, yet inadequate DF intake is still a ubiquitous issue in the adult population worldwide [5-12]. Fortification of commonly consumed foods with synthesized or extracted DF may improve the DF intake of adult populations [2]. Bread is the main source of DF worldwide [6,10,12,13] and is one of the oldest foods that offer health benefits to humans [13]. Bread is commonly consumed by all cultures and ethnicities and is a staple food for many individuals. Furthermore, bread is ideal for incorporating ingredients such as cereal brans to increase DF content [14,15], which may modulate the gut microbiota.

Rice bran is a cheap cereal by-product of rice milling [14]. Rice bran has a purported hypo-allergenicity and has a unique nutrient profile rich in DF, protein, antioxidants, and minerals as well as phytochemicals [13,16-18]. Only a few human studies have been undertaken on rice bran [19-36]. These studies have focused on the use of modified arabinoxylan (a phytochemical) rice bran on subjective global assessments in participants with predominant-diarrhea or mixed-type irritable bowel syndrome [19], heat-stabilized rice bran on modulation of the gut microbiota composition [20,22] and metabolites (short-chain fatty acids and bile acids) [20,22] or rice bran fermented using *Lentinus edodes* on natural killer cell activity and cytokine production [30] in healthy adults, rice bran intervention in colorectal cancer survivors [21] or individuals with a high risk of colorectal cancer [23] or cardiovascular diseases [24,26-28,31-36], or hydrolyzed rice bran in patients with cervical cancer [29].

Among these published rice bran studies, only 4 adult human studies have reported the impact of rice bran on the gut microbiota. When compared with baseline values, a daily consumption of 30 g of heat-stabilized rice bran over 2 weeks increased the relative abundance of the genera *Methanobrevibacter*, *Paraprevotella*, *Ruminococcus*, *Dialister*, *Barnesiella*, and *Anaerostipes* and, at 4 weeks, increased the genera *Bifidobacterium* and *Clostridium* [20], whereas 40 g over 24 weeks increased the taxa from the family *Veillonellaceae* in healthy adults [22]. Similarly, in a population at high risk of colorectal cancer, a 24-week intervention of 30 g of rice bran increased the relative abundance of the *Firmicutes* phylum, *Lactobacillus* genus, *Bifidobacterium* genus, and *Prevotella_9* species [23] compared with baseline levels. However, other measures of the microbial community based on the *Firmicutes*-to-*Bacteroidetes* ratio and α-diversity showed mixed effects. Heat-stabilized rice bran reduced the *Firmicutes*-to-*Bacteroidetes* ratio at 2 weeks, with no difference at 4 weeks compared with baseline [21], yet the ratio increased following a 24-week rice bran intervention [23]. While other studies did not report α-diversity [19,20,22], one study found an increased diversity at 4 weeks but not at 2 weeks [21] or at 24 weeks compared with baseline values [23].

The interventions of these studies were either modified arabinoxylan rice bran or heat-stabilized or normal rice bran.

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They were administered to participants of varied health status and in various forms (powder, rice bran–enriched meals and snacks, and oil) [19-32,34-37]. However, to the best of our knowledge, no human studies have used defatted rice bran (DRB) in bread as an intervention. The process of defatting increases the insoluble fiber content, thereby increasing its proportion of DF [14]. Therefore, several studies have suggested using DRB as a value-added food ingredient [17,38-41]. Taken together, bread, which is commonly eaten by adults, fortified with DRB may help promote beneficial gut microbes and DF intake and, ultimately, provide beneficial health effects to the adult population.

Hypotheses and Objectives

This study was based on the hypothesis that the consumption of 3 (for female individuals) or 4 (for male individuals) slices of DRB-fortified bread per day for 4 weeks will increase the relative abundance of a composite of key genera and species in fecal samples (proxy of lower gut microbiota) known to be involved in plant glycan metabolism or known to be modulated by the DRB-fortified bread.

Secondary hypotheses were that consumption of DRB-fortified bread would lead to improvements in clinical, patient-reported outcomes; biological measurements; whole-gut and regional transit time; and gas fermentation profiles.

DFs are compounds that require a network of microbes to degrade their complex structures [42,43]. Furthermore, due to the inconsistent findings on the relative abundance of microbial taxa reported by existing rice bran studies, a microbiome composite index is a useful primary outcome for this study.

The primary aim of this study is to determine the influence of the consumption of 3 (for female individuals) or 4 (for male individuals) slices of DRB-fortified bread on the composition of selected genera and species of microbiota that are known to be involved in plant glycan metabolism or known to be modulated by DRB-fortified bread using shotgun metagenomics sequencing of fecal samples.

The secondary aims were to investigate the influence of the consumption of 3 (for female individuals) or 4 (for male individuals) slices of DRB-fortified bread in comparison with placebo white bread on (1) upper- and lower-gut comfort using validated gut-specific questionnaires; (2) mental health and general well-being parameters using validated questionnaires; (3) DF intake using 3-day food diaries; (4) relative abundance of individual taxa, predictive function (gene abundances), and diversity indexes of the fecal gut microbiota using shotgun metagenomic sequencing and of fecal and plasma metabolites using liquid chromatography mass spectrometry (LCMS); (5) cardiovascular risk profile based on anthropometry, blood pressure, and blood lipid concentrations; (6) whole-gut transit time using blue food dye in all participants; and (7) regional and whole-gut transit time and gas fermentation profiles using Atmo gas capsules (Atmo Biosciences) in a subset of participants.

Methods

Study Design

This protocol was put together in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trial protocols [44].

Study Overview

The Bread Related Effect on Microbial Distribution study was a double-blinded, placebo-controlled, crossover randomized controlled trial of healthy adults with low DF intake. The design and management of the clinical study adhered to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [45]. This design accounts for the recognized variability in individuals and enables each participant to be their own control for their assigned interventions [46,47]. The study duration was a nominal total of 14 weeks, consisting of a 2-week lead-in phase, two 4-week intervention phases separated by a 2-week washout phase, and a final 2-week follow-up phase (Figure 1). During the first intervention period, one group of participants consumed 3 slices (for female individuals) or 4 slices (for male individuals) of DRB-fortified bread daily for 4 weeks, whereas the other group consumed placebo bread. Following a 2-week washout period, participants who consumed the fortified bread in the first period crossed over to consume placebo bread in the second period, and vice versa (Figure 2). Participants were instructed not to alter their diet during the 2-week washout period. The washout period was selected based on gut microbiota studies reporting a return of microbiota abundances to baseline level within 2 weeks after the intervention [48].

Before study commencement, a mutually agreed schedule was discussed and set with each participant to ensure that they understood all expected clinic or visit times and the study timeline. However, when a participant could not come to the clinic on the day a phase was ending, the participant's needs were accommodated by allowing for earlier visits to the clinic for up to 3 days before the end of the intervention phase (minimum of 25 days of the 28-day intervention). This approach reduced the risk of participants exhausting intervention supplies before the visit and noncompliance or dropout due to scheduling issues.

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Figure 1. Overview of the schedule of screening, enrollment, interventions, and assessments. DRB: defatted rice bran.

	Screening	Study period							
		Enrollment	Baseline 1	Allocation 1	Washout 1	Baseline 2	Allocation 2	Washout 2	Follow-up
Time point		Day 14 or week 2	Day 0 or week 1	Days 7-28 or weeks 2-5	Days 29-41 or weeks 6-7	Day 42 or week 8	Days 49-77 or weeks 9-12	Days 78-90 or weeks 13-14	Day 91 or week 15
Screening									
Eligibility screening	✓								
Informed consent	✓								
Biochemical blood panel	✓								✓
Enrollment									
General health and living standard		✓							
Allocations			✓			✓			
Interventions									
DRB, then placebo				←	—	—	→		
Placebo, then DRB				←	—	—	→		
Assessments									
Fecal samples			✓	✓		✓	✓		✓
Blood samples			✓	✓		✓	✓		✓
Anthropometry	✓		✓	✓		✓	✓		✓
Blood pressure	✓		✓	✓		✓	✓		✓
Atmo capsules			✓	✓		✓	✓		
Blue dye			✓	✓		✓	✓		
Digestive comfort			✓	✓		✓	✓		✓
Anxiety and depression symptoms			✓	✓		✓	✓		✓
Well-being and vitality			✓	✓		✓	✓		✓
Fatigue symptoms			✓	✓		✓	✓		✓
3-day food diary			✓	✓		✓	✓		✓
Daily bowel movement and bread diaries		✓	✓	✓	✓	✓	✓	✓	✓

Figure 2. Study flowchart. DRB: defatted rice bran; F: female; M: male.

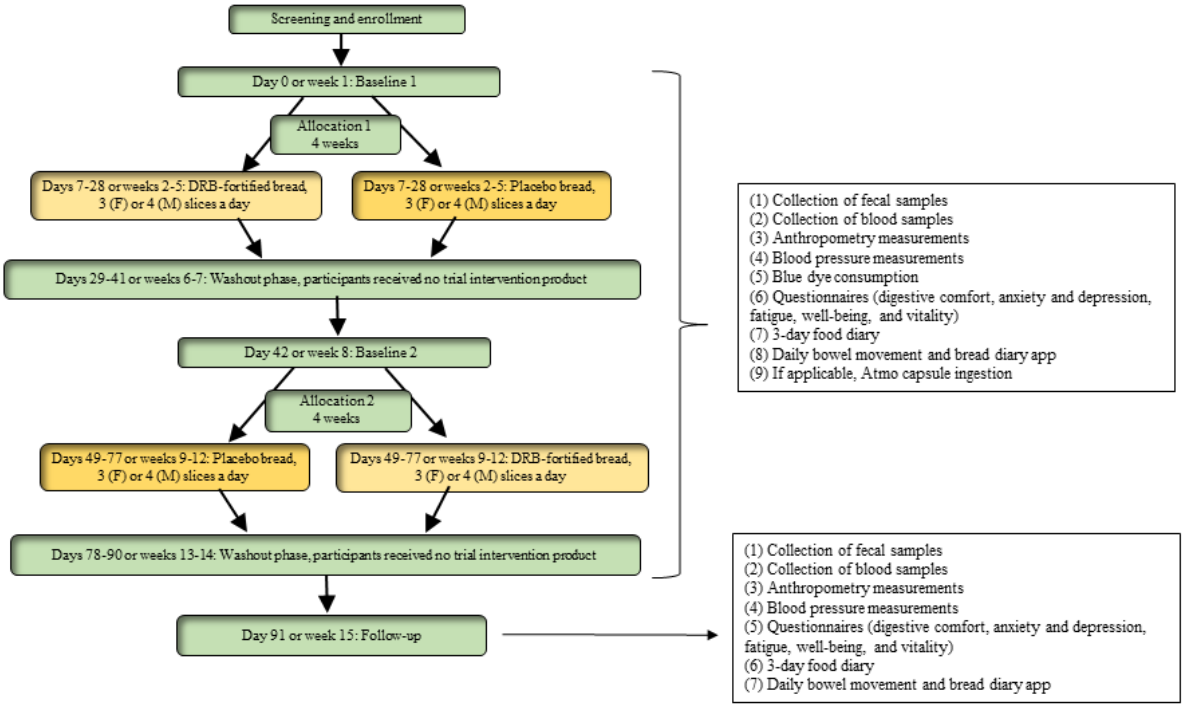

Ethical Considerations

The study was carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, national and local requirements, and the Declaration of Helsinki. All participants gave written, informed consent before taking part in the study. Ethics approval was sought from the University of Otago Human Ethics Committee for Health (H22/061), and consultation took place with the University of Otago, Christchurch, Māori Research Advisor. Before commencement, the study was registered at the Australian New Zealand Clinical Trials Registry (registration ACTRN12622000884707). Recruitment and interventions were conducted at the University of Otago, Christchurch, New Zealand.

The researchers collecting data were experienced in data collection, maintaining security and health-related confidentiality. No identifying or identifiable information about participants was reported in this study, including names, dates

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of birth, images, or aspects of their circumstances that could identify them. Identifying information of participants was gathered at enrollment, entered by the researchers collecting data, and accessed via REDCap (Research Electronic Data Capture; Vanderbilt University) only by these researchers.

To encourage compliance, enrolled participants were provided with supermarket vouchers worth NZD $300 (US $185; NZD $60, US $37 per visit) upon completing the study. The selected participants for the substudy were also given an additional NZD $100 (US $62) to compensate for their time and inconvenience.

Protocol Amendments

Any modifications to the protocol that may impact the conduct of the study, the potential benefit to the patients, or patient safety, including changes in study objectives, study design, patient population, sample sizes, study procedures, or substantial administrative aspects, required a formal amendment to the protocol. Any amendments to the study protocol were required to be reported to the University of Otago Human Ethics Committee for Health and all other local approval committees. Changes pertaining to Māori (eg, recruitment processes and analyses) were required to be reported to the Māori Research Advisor. However, the study had no amendments or changes to the protocol.

Recruitment

Volunteers from the public were recruited through study posters, advertisements translated into Te Reo Māori, social media (web-based presence and Facebook), and word-of-mouth advertisements through Māori health nurses and general practitioners. Interested individuals contacted the research team via email or phone call. They were then sent a patient information sheet, including a consent form, via email, and individuals were provided with sufficient time to consider participating in the study. Once the individual agreed to participate, a web-based screening questionnaire was sent to ascertain their eligibility, DF intake, approximate self-reported BMI, and health conditions.

Eligibility Criteria

All interested volunteers were assessed for eligibility based on the inclusion and exclusion criteria.

Inclusion Criteria

Participants were deemed eligible according to the following criteria: (1) good general health; (2) age between 18 and 65 years; (3) BMI between 18 and 35 kg/m^2; (4) low DF intake, defined as <22 g per day for male individuals and <18 g per day for female individuals, estimated using a validated habitual DF intake short food frequency questionnaire (see the following sections for further details); (5) no history of bowel disease; (6) nonsmokers; (7) no fiber supplement consumption during the month before screening; and (8) willingness to consume 3 slices (for female individuals) and 4 slices (for male individuals) of bread provided during the intervention periods.

Exclusion Criteria

The exclusion criteria were as follows: (1) indication of inability to comply with the study procedures; (2) antibiotic use within the last month; (3) allergies or intolerance to wheat, rice, or gluten; (4) pregnancy, breastfeeding, or plans for a pregnancy in the 3 months after screening or during the study period; (5) alarm features associated with bowel habits, such as recent changes in bowel habits (onset of <3 months), rectal bleeding, sudden weight loss, occult blood in fecal matter, anemia, anal fissures, bleeding hemorrhoids, and family history of gut cancer at an early age; (6) known significant gut disorders and diseases, such as chronic constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease, diverticulitis, celiac disease, or previous bowel resection; (7) chronic diseases, including cardiovascular disease, cancer, renal failure, previous upper- or lower-gut surgery other than cholecystectomy or appendectomy, and neurological conditions (such as multiple sclerosis, spinal cord injury, or stroke); (8) known systemic conditions, such as heart disease, kidney disease, diabetes, metabolic syndrome, and psychological disorder that could influence the gut directly or through medication use, such as prokinetic, opioid, and opiate or nonsteroidal anti-inflammatory drug use; (9) fasting blood glucose of ≥6.0 mmol/L; and (10) laxative or pre- and probiotic supplement use and indicated inability or unwillingness to stop using 7 days before sample collections.

Assessment of Low DF

Low DF intake was assessed during the preliminary screening process using a DF intake short food frequency questionnaire [49]. This questionnaire assesses the frequency of fruit, vegetable, bread and cereal, nut and seed, and legume consumption over the previous year. The author of this questionnaire (Dr Genelle Healey) provided a DF calculation spreadsheet to the specified research team members. The raw food group frequency data were entered into the spreadsheet to calculate total DF intake (grams per day).

Participants were grouped as either low, moderate, or high DF intake based on New Zealand gender–specific DF intake cutoffs. The cutoff points were low (<18 g per day for female individuals and <22 g per day for male individuals), moderate (18-24.9 g per day for female individuals and 22-29.9 g per day for male individuals), and high (>25 g per day for female individuals and >30 g per day for male individuals). Only participants meeting the low DF intake cutoffs were included in the study.

Nonexclusion Criteria

Participants were included in the study if they were diagnosed and had stable health conditions (systemic conditions and diabetes) for >3 months. Selective serotonin reuptake inhibitors, tricyclics, or nonsteroidal anti-inflammatory drugs were permitted if the medication had been continually used and the condition was stable for >3 months.

Screening

Individuals who fulfilled the inclusion criteria were invited to an on-site full screening visit at research clinics in Christchurch, New Zealand. The screening visit involved a full explanation of the study, health history and dietary habit interviews, collection of written informed consent, standard blood tests (9-hour fast before visit), and blood pressure measurement. Height and weight were used to calculate BMI as body weight (kilograms)/height (meters squared).

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Participants who specified being unable to swallow capsules were not considered for the Atmo substudy but were still eligible for the main study.

Enrollment

Questionnaires

Upon being informed of their enrollment into the study, participants were emailed an individualized link to complete 2 web-based enrollment questionnaires. These questionnaires, which were administered via REDCap, took approximately 10 minutes to complete. The Modified Hunter New England Health Survey includes the validated 12-item Short-Form Health Survey version 2 (SF-12v2) and selected question domains from the New South Wales Population Health Survey for diabetes, smoking, alcohol consumption, and physical activity. The SF-12v2 assesses 8 health domains (physical functioning, role—physical, bodily pain, general health, vitality, social functioning, role—emotional, and mental health). This questionnaire was used to assess the general well-being of each participant and raise any important issues. Only the SF-12v2 was scored.

Participants also completed the Economic Living Standard Index Short Form developed and validated by the New Zealand Ministry of Social Development assessing the standard of living and socioeconomic background.

Daily Bowel Movement and Daily Bread Diary App

Participants were instructed to download an app titled "BREAD STUDY." The app consists of both the daily bowel movement and bread diary questions. The questions in the app were captured electronically via the REDCap system using the unique identifier allocated to the participants at the point of consent to the study. The app was designed to be more user-friendly as compared with receiving daily SMS text messages or email links to questionnaires. These daily diaries aimed to obtain a comprehensive record of bowel habits, intervention compliance, and other bread consumption during washout periods. More information pertaining to these questionnaires will be provided later in the *Measurements and Outcomes* section.

Removal and Withdrawal Criteria

Participation in this study was voluntary, and participants could withdraw at any time without explanation, as stated on the participant information sheet.

In case of the following occurrences, participants were withdrawn:

- The participant requested withdrawal from the study. Participants could decide to end their involvement in the study for any reason and at any time during the study.
- The investigator decided to withdraw a participant from the study when considered necessary. Examples include (1) nonrespect of at least one of the selection criteria after inclusion, (2) noncompliance with the study protocol, and (3) gastroenteritis or antibiotic use.
- The participant reported allergic reactions or adverse effects from either intervention.

Regardless of eligibility or continuing participation, an electronic case report form (eCRF) record was generated for each participant. The eCRF was designed specifically for the needs of this study and was the data collection instrument for the study. Therefore, all data requested on the eCRF were recorded, and all missing data were explained. Each eCRF had a unique 5-digit identifier to link the participant who had completed the screening questionnaire to their own data in a deidentified manner. Collected deidentified data, such as laboratory information, demographic information, and obtained questionnaire data, were stored in a password-protected customized database.

Termination Criteria for the Whole Study

In case of serious safety concerns, the principal investigators could terminate or interrupt the study. If new information on the risk-to-benefit ratio of the intervention (including treatment or investigational processes) used in the study was obtained in the meantime, the principal investigators reserved the right to interrupt or terminate the project. In addition, premature termination of the study was possible if the principal investigators noticed that participant recruitment was insufficient and could not be accelerated through appropriate measures.

Study Intervention

The main intervention was bread fortified with DRB. It is a commonly eaten grain and is safe for human consumption [14,50-54]. On the basis of measured composition, the main intervention had 18% of the flour (cereal weight) replaced with 18% of the flour (cereal) weight used in the placebo bread and provided 8 g (for female individuals) and 10.6 g (for male individuals) of total DF. Of the 8 to 10.6 g of DF in 3 to 4 slices of fortified bread, 2.2 g (for female individuals) and 2.9 g (for male individuals) were fiber from wheat, and 5.8 g (for female individuals) and 7.7 g (for male individuals) were from the DRB. The placebo was a matched commercial white toast bread without DRB, providing 2.7 g of DF for female individuals (3 slices) and 3.6 g of DF for male individuals (4 slices). Toast slices were chosen for this study to ensure that the production of DRB-fortified bread had a texture similar to that of the placebo white toast bread while providing the required DF content.

Blinding and Allocation Concealment

Participants were not informed of the bread ingredients until the completion of the study data collection to maintain blinding. Analysts and researchers were blinded to the order of treatment that the participants received and to which group the participants were assigned during data collection and remained blinded until the statistical analysis of the primary outcome data was completed. The manufacturer of the bread was responsible for labeling both breads to maintain blinding of research team members. To further increase blinding, the manufacturer added colored malt to the placebo bread to make both breads visibly indistinguishable. Specified research team members were responsible for the randomization, enrollment, and data collection of participants; the handout of the intervention and placebo bread; and the management of the stock. Unblinding

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was only permissible once statistical analysis of the primary outcome data was completed.

Randomization

One week before the first baseline visit, participants were randomly assigned in a 1:1 allocation using randomized permuted blocks (block size 4) to either DRB-fortified or placebo bread. Randomization was performed by drawing a folded note from a sealed opaque box.

Measurements and Outcomes

Timing of Assessments

Upon enrollment, there were 5 clinic visits in total. Study assessments were conducted at baseline 1 (day 0 or week 1), postintervention assessment 1 (day 29 or week 5), baseline 2 (day 42 or week 8), postintervention assessment 2 (day 78 or week 12), and follow-up (day 91 or week 15). A total of 15 participants who were part of the Atmo substudy ingested capsules at 4 time points: baseline 1 (day 0 or week 1), postintervention assessment 1 (day 29 or week 5), baseline 2 (day 42 or week 8), and postintervention assessment 2 (day 78 or week 12).

Biological Measurements

Fecal Samples

Overview

The primary outcome was the differences in the relative abundance of a composite of selected key genera and species of the gut microbiota known to be involved in plant glycan metabolism or known to be modulated by the DRB-fortified bread (see the *Sample Size* section for more details) as compared with the placebo bread.

Once enrolled, participants received a posted cooler bag containing a fecal collection kit and ice pack. Participants collected a fecal sample into the provided fecal container 24 hours before their clinic visits at baseline, the postintervention time point of each phase, and follow-up. Participants were instructed to label the fecal container with the time and date collected and record it again on the bowel movement diary app. Participants had to refrigerate the collected fecal sample and transport it within 24 hours of sample collection in the provided cooler bag for each clinic visit. If participants could not provide a fecal sample 24 hours before, they were encouraged to collect and bring the sample in the cooler bag as soon as possible following their clinic visits.

In total, 5 aliquots (1 g each) of a fecal sample were frozen for microbial composition, gene abundance, and metabolite analyses. The samples were kept chilled until aliquoted in the laboratory. All aliquots were snap frozen in liquid nitrogen before storage at –80 °C until analysis.

Microbial Composition and Gene Abundances

Taxonomic composition and gene abundance of the fecal microbiome were assessed through shotgun metagenomics. Libraries for metagenomics sequencing of the extracted DNA were performed by Auckland Genomics at the University of Auckland, New Zealand. Microbial metagenomic libraries were then generated using the seqWell purePlex DNA library preparation approach. Briefly, genomic DNA was diluted to 5 ng/µL and then sheared and bar-coded with unique dual indexes using transposases to produce a library with fragment sizes of 300 to 1500 base pairs (bp). Libraries were pooled in batches of 24 samples and subjected to a paramagnetic bead-based cleanup. The DNA samples underwent quality control checks for purity and concentration using a bioanalyzer. The samples were shotgun sequenced using the Illumina NovaSeq 6000 platform using 2 × 150 bp paired-end sequencing at Novogene in Singapore.

The quality of the raw data was checked using FastQC (version 0.11.9; Babraham Bioinformatics) [55]. The Trimmomatic software (version 0.36; USADEL LAB) [56] was used for the removal of adapters and low-quality (Phred scores of <30) and short (<36 bp) sequencing reads. Read pairs were aligned to the human reference genome (RefSeq: GCF_000001405) using the "mem" algorithm of BWA (version 0.7.17-r1188) [57], and FASTQ files were generated from the unmapped sequencing reads using the "fastq" function of SAMtools (version 1.8) [58]. Read pairs were joined using PEAR (version 0.9.6) [59] with default settings. Read pairs that did not join were pasted together with a string of Ns using the "fuse" function from the BBMap package (version 38.22-0; Department of Energy Joint Genome Institute) [60]. Joined and fused reads from different lanes from the same sample were compiled into a final "clean" read sample file. Metagenomics functions were obtained through the "blastx" function of DIAMOND (version 0.9.22) [61], mapping the reads against the "nonredundant" National Center for Biotechnology Information database [62]. MEGAN (version 6; ultimate edition) [63] was used to assign putative functions to the alignment files produced by Diamond. This alignment was performed by Paul Maclean (statistician; AgResearch).

Differential relative abundance was performed using *DESeq2* in R (version 1.40.2; R Foundation for Statistical Computing). This package analyzes differential expressed taxa based on a negative binomial distribution. The effect of group was assessed by comparing between groups. The top 10 differentially abundant taxa were extracted based on adjusted *P* values for both baseline and postintervention assessments for each group. Taxa that changed within each group were identified by finding the set difference between the top taxa between baseline and the postintervention assessment. Log2FoldChange values were extracted for the identified changed taxa in each group [64]. Enrichment of functional gene attributes arranged hierarchically as level 1 (broadest level of function, eg, metabolism and cellular processes), level 2 (specific functions, eg, carbohydrate metabolism and amino acid metabolism), and level 3 (detailed pathways, eg, glycolysis and glycan degradation) were analyzed using the R package *Microbiome Multivariable Associations with Linear Models*, which uses general linear models that accommodate crossover designs [65]. Fixed effects included in the model were groups (DRB-fortified vs placebo bread).

Metabolome

The relative intensity of fecal metabolites was assessed in the polar, semipolar, and nonpolar fractions of fecal samples using untargeted metabolite profiling (metabolomics).

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Fecal samples were freeze-dried under vacuum and extracted using a previously described method [66] with minor modifications. Briefly, 50 mg of lyophilized fecal samples were homogenized with a ceramic bead for 1 minute, and then 400 µL of 75% methanol/Milli-Q water were added. The tubes were vortexed for 30 seconds, sonicated for 2 minutes, and transferred into ice for 10 minutes. Afterward, 1 mL of methyl tert-butyl ether was added, and the mixture was incubated for 1 hour at 450 revolutions per minute. Then, 550 µL of Milli-Q water were added, and after 10 minutes of incubation, the mixture was centrifugated at 14,000 × g for 25 minutes to separate the aqueous (lower) and organic (upper) phases. The polar and lipid extracts were evaporated under a stream of nitrogen at room temperature. The dried samples were stored at –80 °C until LCMS analysis. The metabolite profiling analyses were carried out using high-resolution LCMS on a Shimadzu 9030 quadrupole time-of-flight mass spectrometer equipped with electrospray [67]. An aliquot of the polar extract was taken and analyzed using hydrophilic interaction liquid chromatography [67], and semipolar metabolites were resolved using reverse-phase chromatography [68]. The organic phase was analyzed using the lipidomic methodology [69].

Targeted Metabolites

Aliquots of 1 g of fecal samples were sent to Plant & Food Research, New Zealand, for organic acid (including short-chain fatty acids) measurement using an LCMS method. In total, 14 linear and branched organic acids (carbon-1 to carbon-6) were derivatized with a probe using mass spectrometry (MS) probe and stable isotope techniques as previously described [70] with modifications (J Cooney, unpublished data, September 2017) and measured using targeted LCMS on a SCIEX LCMS/MS QTRAP 5500 instrument equipped with a Turbo V ion source and atmospheric pressure chemical ionization probe coupled to an ExionLC ultra–high-pressure liquid chromatography (HPLC) system (Shimadzu). Labeled internal standards for each organic acid were used to ensure accurate quantification [71]. Textbox 1 provides the names and corresponding acronyms of the organic acids analyzed.

Textbox 1. Plasma and fecal organic acids analyzed using liquid chromatography mass spectrometry with the corresponding acronym.

Full name and acronym

- Formic acid: FA
- Lactic acid: LA
- Acetic acid: AA
- Propanoic acid: PA
- Isobutyric acid (2-methylpropanoic acid): IBA
- Butyric acid (butanoic acid): BA
- Succinic acid: SucA
- 2-methylbutyric acid (2-methylbutanoic acid): 2MBA
- Isovaleric acid (3-methylbutanoic acid): IVA
- Valeric acid (pentanoic acid): VA
- 3-methylvaleric acid: 3MVA
- 4-methylvaleric acid (isocaproic acid): 4MVA
- Caproic acid: CA
- Hexanoic acid: HA

Extraction methods for bile acid analysis followed those outlined elsewhere [72]. Briefly, 50 mg of wet fecal samples were extracted with 100 µL ice-cold methanol containing internal standards (10,000 nM of deuterium labelled cholic acid and deuterium labelled chenodeoxycholic acid). The mixture was homogenized for 30 seconds, incubated at –4 °C for 30 minutes, and centrifuged at 18,000 × g for 20 minutes. Then, 20 µL of the supernatant were dissolved in 80 µL of 0.1% aqueous formic acid solution, vortexed, and proceeded to HPLC for analysis. This analysis was carried out using high-resolution LCMS on a SCIEX LCMS/MS QTRAP 6500+ system coupled to an ExionLC system [73]. Textbox 2 provides the names and corresponding acronyms of the bile acids analyzed.

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Textbox 2. Fecal bile acids analyzed using liquid chromatography mass spectrometry with the corresponding acronym.

Full name and acronym

- β-muricholic acid: βMCA
- Cholic acid: CA
- Chenodeoxycholic acid: CDCA
- Deoxycholic acid: DCA
- Glycocholic acid: GCA
- Glycohyodeoxycholic acid: GHDCA
- Glycoursodeoxycholic acid: GUDCA
- Glycolithocholic acid: GLCA
- Hyocholic acid: HCA
- Hyodeoxycholic acid: HDCA
- Isolithocholic acid: ILA
- Lithocholic acid: LCA
- Taurine: Taurine
- Tauro-β-muricholic acid: TβMCA
- Tauro-α-muricholic acid: TαMCA
- Taurocholic acid: TCA
- Taurochenodeoxycholic acid: TCDCA
- Taurodeoxycholic acid: TDCA
- Tauroursodeoxycholic acid: TUDCA
- Ursodeoxycholic acid: UDCA

Blood Samples

Overview

In total, 2 research team members trained in phlebotomy collected peripheral blood at each clinic visit. At both screening and follow-up clinic visits, 1 aliquot (6 mL) of a blood sample was taken into a lithium-heparin vacutainer tube to measure fasting blood glucose, lipid panel (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), C-reactive protein, and liver function, enzymes, or general health markers, and 1 aliquot (4 mL) of blood was taken into an ethylenediaminetetraacetic acid tube (Becton, Dickinson and Company) for a complete blood count. Before and following each intervention phase, 1 aliquot (6 mL) of a blood sample was taken into a lithium-heparin vacutainer tube (Becton, Dickinson and Company) to analyze the complete lipid profile. The collected blood samples were kept at room temperature and delivered to Canterbury Health Laboratories (Christchurch, New Zealand) for analysis within 1 hour of collection.

At all time points except for the screening clinic visits, an additional 6 mL of blood were collected into 1 × 6-mL lithium-heparin vacutainer tubes to assess plasma metabolome and known metabolites (bile acids and organic acids). The 6-mL vacutainer was kept on ice and processed within 1 hour. The tubes were centrifuged at 4 °C for 5 minutes at 2000 × g, with high acceleration and slowest deceleration to separate plasma from cells. Plasma samples were distributed into 500-µL aliquots and stored at –80 °C until further analysis.

Metabolome

Polar metabolites were extracted using a single-phase extraction [68]. Briefly, 50 µL of plasma were extracted using 450 µL of prechilled acetonitrile:water (9:1 v/v). The mixture was shaken for 60 seconds and then centrifuged at 14,000 × g and 4 °C for 10 minutes, and then the extract was placed into an HPLC vial for analysis. Plasma semipolar metabolite extraction was conducted as described previously [74]. Plasma semipolar metabolite extraction was performed by adding 400 µL of ice chloroform to methanol in a 1 to 1 part volume to volume ratio to 50-µL plasma samples, vortexing it for 30 seconds, and incubating it for 1 hour at –20 °C. Then, 200 µL of Milli-Q water were added to the mixture, vortexed, and centrifuged at 14,000 × g and 4 °C for 10 minutes. The supernatants were evaporated to dryness under a stream of nitrogen and stored at –80 °C until analysis. On the day of the analysis, the semipolar extracts were thawed at room temperature (18 °C, –2 °C to +2 °C) and redissolved in redissolved in acetonitrile to water in a 1 to 9 part volume to volume ratio. The mixture was vortexed for 1 minute and then centrifuged (14,000 × g at 4 °C for 10 minutes). The extract was then transferred into an HPLC vial for analysis. Lipid extraction was performed by placing 10 µL of plasma into an Eppendorf tube, adding 95 µL of butanol to methanol in a 1 to 1 part volume to volume ratio, and then spiking it with 5 µL of internal standard SPLASH mix (Avanti

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Polar Lipids, Merck KGaA) [69]. The mixture was then vortexed for 1 minute, sonicated at room temperature for 60 minutes, and centrifuged at 14,000 × g for 10 minutes at 20 °C. The extract was then transferred to an HPLC vial and stored at –80 °C until LCMS analysis. The plasma polar, semipolar, and nonpolar extracts were analyzed using the LCMS methods for the plasma samples [69].

Targeted Metabolites

Textbox 1 shows the names and corresponding acronyms of the organic acids analyzed. Aliquots of 200 µL of heparin plasma were sent to Plant & Food Research, New Zealand, for analysis of organic acids via LCMS. A total of 14 linear and branched organic acids (carbon-1 to carbon-6) were derivatized with a probe using MS probe and stable isotope techniques as previously described [70] with modifications (J Cooney, unpublished data, September 2017) and measured using targeted LCMS on a SCIEX LCMS/MS QTRAP 7500 instrument equipped with a Turbo V ion source and atmospheric pressure chemical ionization probe coupled to a Nexera ultra-HPLC system (Shimadzu). Labeled internal standards for each organic acid were used to ensure accurate quantitation [71].

Clinical Measurements

Anthropometry

Height, weight, BMI, and waist circumference were measured at each visit (ie, screening, baseline, postintervention assessment, and follow-up) according to the procedures established by the New Zealand Ministry of Health protocols for collecting height, weight, and waist measurements [75].

Standing height was measured to the nearest 0.1 cm using a calibrated stadiometer. Body weight was measured to the nearest 0.1 kg using calibrated body weight scales. Both measurements were taken with participants removing heavy outer clothing and shoes. Waist circumference was taken over clothing, and hence, the level of the measurement was determined by the participant to identify their waist. This measurement was taken to the nearest 0.1 cm using a calibrated measuring tape. All measurements were conducted twice, with a third reading when the 2 readings varied by >0.5 units. BMI was calculated as weight (in kilograms) divided by height (in meters squared).

Blood Pressure

Blood pressure was also measured at each morning clinic visit (ie, during screening, at each phase of baseline, at the postintervention assessment, and at follow-up) according to the recommendations established by the Australian expert consensus [76]. The measurement was taken using a validated, automated blood pressure monitor with a fitted-sized upper arm cuff. Participants were seated at rest for 5 minutes with feet flat on the floor, legs uncrossed, back and arm supported in a relaxed position, and the cuff at heart level. Measurements were taken on their nondominant arm. The blood pressure readings were then recorded immediately and compared with those recorded in previous clinic visits. When a high blood pressure value reading was noted, participants were asked about any unusual incidents that may affect the readings. These were then recorded on the eCRF of the participant.

Lipid Profile

As mentioned previously, the full lipid profile was measured at each morning clinic visit (ie, during screening, at each phase of baseline, at the postintervention assessment, and at follow-up) according to the recommendations of the Canterbury Health Laboratories (Christchurch, New Zealand). The lipid profile consisted of 5 components: total cholesterol, LDL, HDL, triglycerides, and TC/HDL ratio. Total cholesterol measures overall cholesterol level; LDL is a fat that circulates in the blood, moving cholesterol around the body where it is needed for cell repair and depositing it inside artery walls. HDL, also known as “good cholesterol,” helps remove cholesterol from the bloodstream. Triglycerides represents the main lipid component of dietary fat. The TC/HDL ratio, a sensitive predictor of heart disease [77], was also calculated.

Patient-Reported Outcomes

Daily Bowel Movement and Daily Bread Diary

Upon enrollment and throughout the study, participants were asked to complete a daily bowel movement and bread diary via an app. This app was developed by one of our research team members (Hilary Dewhurst from AgResearch, New Zealand) using a REDCap application programming interface token. The token is a unique code that is associated with a single user on a specific REDCap project, which allows the user to programmatically access data within the project. Upon installing the app by the participants, the app downloaded the diary questions from REDCap, linking the app (on that phone) to the corresponding participant’s allocated unique identifier at the point of consent to the study. All submissions were then recorded under the corresponding participant identifier. The submissions were stored on the app and submitted to REDCap with each entry. To ensure data integrity, the app “talks to” REDCap to retrieve the most recent record for the participant and increment accordingly, preventing any answers from being overwritten.

Each diary took approximately 2 minutes to complete each time. The bowel movement diary provided a comprehensive record of the bowel habits of the participants and assessed the following variables: (1) frequency of bowel motions, which included questions on spontaneity and completeness of bowel movement; (2) ease of defecation or level of straining; (3) fecal form based on the Bristol stool scale; (4) menstruation (if applicable); and (5) presence of blue dye (if applicable, see the following sections for further details).

The daily bread diary assessed compliance with the consumption of intervention bread and general bread consumption preferences. Consumption of bread slices and days consumed for each participant were determined through the following equations:

Compliance regarding bread slices consumed = ([number of bread slices consumed / number of bread slices expected to be consumed] × 100%)

Compliance regarding days consumed = ([number of days consumed / number of days expected to be consumed] × 100%)

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Compliance with the intervention (bread slices and days consumed) was determined by calculating the mean percentage compliance for each bread and the proportion of participants meeting >50% compliance.

This bread diary also determined (1) whether the DRB-fortified and placebo breads were toasted; (2) minutes of toasting (if applicable); (3) additional commercial sliced bread consumed (if applicable, during the washout period); and (4) the type, brand, and amount of additional bread consumed (if applicable).

Web-Based Questionnaires

Overview

One day before each phase of baseline, postintervention, and follow-up clinic visits, participants received an individualized email with a link to 6 web-based questionnaires. These web-based questionnaires, which were emailed to participants, were similarly administered via the REDCap system. All these questionnaires took approximately 15 minutes to complete each time.

Gastrointestinal Symptom Rating Scale

The Gastrointestinal Symptom Rating Scale, a validated instrument that assesses gut comfort, was administered before and during the intake of intervention and placebo bread. The Gastrointestinal Symptom Rating Scale has a 1-week recall that assesses symptom severity using a 7-point Likert scale ranging from "no discomfort at all" to "very severe discomfort." The complete instrument consists of 15 primary items clustered into 5 domains: diarrhea, constipation, reflux, abdominal pain, and indigestion [78-80].

Patient-Reported Outcome Measurement Information System: Anxiety and Depression

This consists of a validated system with multiple domains, where specific domains can be chosen to be integrated into diverse data collection tools. This chosen questionnaire evaluates anxiety and depression in the last 7 days in detail as well as mental symptoms rated by severity from "not at all" to "very much" and from "never" to "always" [81,82].

World Health Organization 5-Question Well-Being Index

This is a short self-reported rating scale of current well-being. It consists of 5 statements concerning the previous 2 weeks adjusted to 1 week (*all of the time*=5; *most of the time*=4; *more than half of the time*=3; *less than half of the time*=2; *some of the time*=1; *at no time*=0) [83].

Warwick-Edinburgh Mental Wellbeing Scale

A 14-item scale adjusted to 1 week was used to explore mental health and well-being over the previous 2 weeks. The Warwick-Edinburgh Mental Wellbeing Scale has 5 response categories summed to provide a single score. The items are all worded positively and cover both feeling and functioning aspects of mental well-being. This questionnaire covers key aspects of psychological functioning—optimism, autonomy, agency, curiosity, clarity of thought, and positive relationships—and positive affect (feelings)—confidence, feeling relaxed and cheerful, and having energy to spare (*none of the time*, *rarely*, *some of the time*, *often*, and *all of the time*) [84].

Multidimensional Fatigue Symptom Inventory–Short Form

This is a 20-item self-report instrument with a 7-point scale that indicates to what extent each statement applies to the participant, ranging from "yes, that is true" to "no, that is not true," designed to measure fatigue. It covers the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity [85].

Subjective Vitality Scale

A 6-statement instrument assesses the state of feeling alive and alert (ie, having energy available to oneself). The statements explore the current feeling on a scale of 1 to 7 (1=*not at all true*, 4=*somewhat true*, and 7=*very true*) [86].

Dietary Intake

Paper copies of a nonconsecutive 3-day food diary were posted to all enrolled participants to complete before each of the 5 study visits (ie, at baseline, postintervention assessment, and follow-up). All enrolled participants were provided with verbal and written instructions by the study dietitian on completing a food diary. The written information included instructions on how to describe food using household measures. The food diary included written prompts for detailed information about when and where the food was consumed and who they were with when the food was consumed; the type of food or drink; brand details; preparation or cooking methods; and quantity, as well as a section for recipe details. Participants were also asked to record any reasons why their intake may have differed from their normal eating routines. Before each subsequent appointment, participants received reminder emails to start the food diary and the same written information on completing the food diary. Participants could contact the study dietitian if they required further guidance on completing the food diary. At each clinic visit, the study dietitian reviewed each food diary to ensure that adequate detail was provided and check whether additional foods and beverages were consumed but not recorded. In total, 2 nutrition graduates trained in dietary assessment entered the food diaries into a dietary analysis software, Foodworks Online Professional (version 1.0; Xyris Software) [87]. The New Zealand Food Composition Database (FOODfiles 2018; version 1.0) was used to estimate energy and nutrient intakes. After the primary outcome was analyzed and the study was unblinded to the intervention, the macro- and micronutrients from the 2 types of study bread were manually added to the dataset based on the type of bread and actual reported bread consumption. This final dataset was then exported into SPSS (version 29; IBM Corp) and was treated as continuous data.

Physiome Measurements

Blue Food Dye

At each baseline and postintervention clinic visit, participants ingested 1 teaspoon of Royal Blue Liqua-Gel (Chefmaster) food coloring (12 drops per 1.5 grams) in water. The intake time and date were recorded. The dye was poorly absorbed or fermented, which allowed for analysis of whole-gut transit time upon passing through visual confirmation [88,89]. Visual confirmation was recorded by the participant on the daily bowel movement diary app.

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Atmo Gas-Sensing Capsule

A subset of participants (n=15) completed an assessment of colonic gas profiling and whole-gut and regional transit time through the Atmo gas-sensing capsule. The capsule measures temperature; a range of gaseous fermentation by-products, including carbon dioxide and hydrogen; and an indication of oxygen level, capsule tumble, and antenna reflectometry [90,91]. The selected participants received a separate participant information sheet and completed a specific consent form before the transit assessment. The capsule was ingested at each phase of baseline and at the end of the postintervention clinic visits. These participants consumed a standardized cereal bar and an Atmo gas-sensing capsule (Atmo Biosciences).

The selected participants were fitted with a sling bag containing a transponder. It consists of a receiver and smartphone with a custom app that "listens" to the capsule ingested. These participants wore or kept the Atmo transponder close to them (approximately 1 m) until the exit of the capsule or for up to 5 days. They were also asked to enter additional daily bowel movement diary information into the Atmo transponder. The data were collected in real time on the smartphone app and transmitted to an Atmo cloud during the passage to allow for remote monitoring and troubleshooting. Once the participant confirmed the exit of the capsule, they returned the transponder to the research team. The diary data from the Atmo app were then synchronized to the Atmo cloud for review and analysis. Blinded and deidentified data synchronized to the Atmo cloud were assessed using specialized Atmo software by trained Atmo team members. The analysis included colonic gas profiling (hydrogen and carbon dioxide) and the determination of whole-gut and regional transit times.

Adverse Events

Although the study is considered low risk, all participants were provided with information about managing possible side effects. Participants were encouraged to contact their health care provider, followed by our research team, in the event of side effects. Participants were encouraged to record any symptoms and may withdraw if they experienced any side effects. Any participants experiencing harm directly due to their involvement in the study were withdrawn from the study immediately.

Sample Size

Sample size calculations were based on the GutFeelingKB cohort [92]. The percentage of relative abundance of a composite microbiome index (incorporating 15 operational taxonomic units as outlined in this section) was estimated to be 28.3% with an SD of 14%. The sample size needed was 60 participants in this crossover study to account for a 15% dropout rate. The crossover study had >80% power to detect a difference in the absolute increase in the relative abundance of approximately 6% as statistically significant (2-tailed α=.05). An increase of 6% compared with the baseline level of 28% equates to a relative increase of approximately 22%. The consumption of 3 (for female individuals) or 4 (for male individuals) slices of DRB-fortified bread per day for 28 days is thought to affect individual and combined groups of the microbial taxa making up the composite.

The composite microbiome index included genera from 5 phyla found in the gut microbiota of healthy human adults. This index included the *Prevotella* and *Barnesiella* genera and *Bacteroides ovatus* and *Bacteroides xylanisolvens* from the *Bacteriodetes* phylum; the *Roseburia*, *Anaerostipes*, *Blautia*, *Eubacterium*, *Ruminococcus*, *Faecalibacterium*, and *Lactobacillus* genera from the *Firmicutes* (*Bacillota*) phylum; the *Bifidobacterium* and *Eggerthella* genera from the *Actinobacteria* (*Actinomycetota*) phylum; the *Akkermansia* genera from the *Verrucomicrobiota* phylum; and the *Methanobrevibacter* genera from the *Euryarcheaota* phylum.

Statistical Analysis Plan

This study was conducted as a superiority trial. The guidelines of the Committee for Proprietary Medicinal Products (now termed Committee for Medicinal Products for Human Use) require intention-to-treat analysis [93]. For a crossover design, the intention-to-treat analysis means that every enrolled participant who has consumed both the intervention and placebo bread is included despite dropout or noncompliance. All data from randomized participants who received at least one intervention dose and had at least one postintervention measurement will be analyzed.

The mean differences from the baseline of most outcomes will be compared between groups and referred to as a between-group comparison. For most outcomes, within-group analysis (after the intervention compared with baseline) will also be performed. For metabolome analyses, postintervention values (not the mean differences) will be compared within and between groups.

All statistical analyses will be performed using SPSS statistics (version 29; IBM Corp) or R (version 4.3.1) by blinded researchers under the guidance of an independent biostatistician.

Baseline characteristics will be presented using descriptive statistics. The mean and SD, or median and range, will be used to describe continuous variables. Frequencies or percentages will be used to describe categorical variables. The group effects (ie, the mean change from baseline between groups) will be assessed using (parametric) 2-tailed *t* tests and (nonparametric) Mann-Whitney or Kruskal-Wallis tests for symmetrically and asymmetrically distributed data. Categorical variables will be assessed using chi-square tests (or Fisher exact tests for small samples). A 2-tailed $P<.05$ is determined as statistically significant. A value of $P\leq.10$ will be considered a trend for most variables except for the microbiome data.

For the primary outcome, to determine the microbiome composite, the selected genera and species will be summed to give a composite relative abundance for each participant. Changes in the composite of the microbial taxa within and between groups will be assessed using the nonparametric Wilcoxon signed rank test. The statistical significance level is determined at $P<.05$, with a false discovery rate (FDR) of $P<.10$. A probable biological significance level (trend) is assumed at an unadjusted $P\leq.10$. For other fecal microbiome measures, univariate and multivariate statistical analyses will be used to assess α- and β-diversity variations, individual relative abundance differences in taxa, and gene abundance differences between groups. Differences in α-diversity between

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baseline and the postintervention assessment and between groups after the intervention will be assessed using the nonparametric Wilcoxon signed rank test with continuity correction. The Benjamini-Hochberg method will be applied to control the FDR inherent in multiple-hypothesis testing for variables in the microbiome and metabolome analyses. The resulting adjusted *P* values will be computed to address the inflated type-I error rates associated with numerous comparisons. $P<.05$ and an FDR of $P<.10$ will be deemed significant, with a probable biological significant difference (trend) assumed at an unadjusted $P\leq.10$.

Box plots will be created using *ggplot2* to compare groups for each Chao1 and Shannon Indexes. The permutational multivariate ANOVA and the analysis of dissimilarity functions will then be used to assess the statistical significance of microbial community composition between individuals. Analysis of dissimilarity uses permutation testing and provides statistical assessments and their significance using *F* tests based on the sequential sums of squares from the permutations to determine whether the observed differences in β-diversity are statistically meaningful. Microbial differential gene expression will be performed using quasi-likelihood *F* tests. This test provides stricter error rate control by accounting for the uncertainty in dispersion estimation. Genes with an absolute log fold change of >1.1 will be considered as differentially expressed.

As mentioned previously, the comparisons will be between each group and baseline and between groups after the intervention for plasma or fecal metabolome measures. The partial least squares projection discriminant analysis (PLS-DA) model will be performed to identify metabolites using SIMCA (version 17; Umetrics). The PLS-DA models will be subject to 100-fold permutations to evaluate performance; the models will be validated using the predictive ability of the model (Q2) and the ANOVA testing of cross-validated predictive residuals (ANOVA testing of cross-validated predictive residuals) [94]. The most discriminating features will be selected for building PLS-DA models. These models will be again subjected to prediction accuracy and overfitting assessment by the corresponding tests (ANOVA testing of cross-validated predictive residuals) and comparison of the Q2 afterward. Features will be selected based on their variable importance in the projection score. Univariate statistical analysis and heat maps will be performed using MetaboAnalyst (version 5.0) [95]. The metabolite and lipid relative intensity differences between groups will be tested through *t* tests or Wilcoxon rank sum tests. The multiple testing corrections will be controlled using FDR correction [96].

Data Quality and Assurance

The researchers collecting data were trained accordingly in data collection, maintaining security and health-related confidentiality.

Due to the large amount of data to be collected, there may be an inherent risk of errors during the data entry into the data bank. All paper-based data were handled by blinded study personnel, and participants were strongly encouraged to enter survey data directly into the database via email links to the surveys and via the app to minimize this risk.

The nutrition graduates who entered the raw food and beverage diary data maintained a data entry assumption spreadsheet to ensure consistency of data entry. The study dietitian will independently audit 20% of the food diaries entered into the dietary analysis program (Foodworks Online; version 1.0) by the nutrition graduates. Diaries were checked for accuracy, consistency, and completeness. Extreme values or outliers for specific nutrients were identified and clarified by reviewing the assumption spreadsheet and raw food and beverage diary data.

A formal data monitoring committee was not required as the intervention and placebo breads in this study are considered as sufficiently low risk that no harm is anticipated to occur beyond the risks of standard care and everyday life.

Data monitoring occurred through weekly meetings of the research team. The unblinded research team maintained concealment.

Data Collection and Storage by Researchers

Data collection for questionnaires occurred electronically via the REDCap system using the unique identifier allocated to the participants at the point of consent to the study. Participants who preferred paper data collection were accommodated. Paper-based and telephone-collected data were entered directly into electronic data collection systems (using REDCap) as soon as they were received.

Biological and physiome data were analyzed as per the aforementioned measures. The data files were stored in Microsoft Excel (Microsoft Corp) for raw data and as data analysis files (SPSS statistics version 29.0 or R statistical software version 4.3.1). These data were only identified by the unique code of each participant. Participants were identifiable to researchers only by their study code. Biological samples were stored in secure facilities with restricted access until publication of the results but not longer than 10 years, after which they will be destroyed hygienically in accordance with New Zealand Standard 4304:2002 (management of health care waste) or with the appropriate *karakia* (for Māori participants).

Raw data collected in hard copy were stored after electronic data entry as part of the case report form in a locked filing cabinet. All electronic data files generated in the study were stored on a password-secured University of Otago server or Otago OneDrive cloud storage and were accessed (and downloaded as needed) via the password-protected computers of named investigators and stored on locked premises. A master file containing participants' personal identifying information was only accessible to the researchers involved in data collection. The blinded researchers had only access to deidentified raw data files and were responsible for the final data analysis.

Results

Recruitment of participants began on June 1, 2022, and was completed on December 15, 2022. The study was approved by the University of Otago Human Ethics Committee (Health) on May 23, 2022. Of the 66 individuals who completed the web-based preliminary screening questionnaire and attended

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an on-site screening, 6% (n=4) were excluded as they did not meet the inclusion criteria. Therefore, 62 participants were randomized. During the first intervention phase, 10% (6/62) of the participants dropped out, resulting in a total of 56 participants (n=33, 59% female; n=23, 41% male; n=41, 73% New Zealand European; n=1, 2% Māori) included in the analysis.

The mean age for the entire cohort is 40.4 (SD 13.4) years, and the mean BMI is 21.9 (SD 10.3) kg/m^2. Due to the large dataset, data analysis for all outcomes was planned to be completed by the last quarter of 2024, with full results expected to be published in peer-reviewed journals by the end of 2024.

Discussion

Anticipated Findings

The primary aim of this study is to determine the influence of DRB-fortified bread on the relative abundances of a composite of selected key genera and species of the gut microbiota that are relevant in DF degradation and metabolism in healthy adults with low DF intake as compared with placebo white toast bread. In addition, relative abundance or concentration of fecal or plasma biological markers of host and microbial interactions (microbial taxa, bile acids, and organic acid concentrations) alongside cardiovascular health, patient-reported outcomes, and physiome outcomes of the recruited healthy participants will be described. The findings of this study are anticipated to provide a better understanding of the habitual impact of DRB-fortified bread on the gut microbiome and all other assessed parameters in healthy individuals with low DF intake.

Preliminary analysis showed that, during the first intervention phase, 10% (6/62) of the participants dropped out, resulting in a total of 56 participants (n=41, 73% New Zealand European and n=1, 2% Māori) included in the intention-to-treat analysis. Due to the large dataset, data analysis and publication of full results are expected to be completed by the end of 2024.

This is the first human study to explore DRB-fortified bread as a dietary intervention. Therefore, it was decided to recruit a generally healthy population of male and female individuals with low DF intake before the commencement of the study. In addition, participants were given a daily dose of 3 to 4 slices of DRB-fortified or white toast bread, which could easily be added to the diet. The bread slices were provided in separate doses tailored to the nutrient requirements for female (3 slices) and male (4 slices) individuals. Consequently, these strategies to improve DF intake among low DF consumers were practical and could be implemented in real-life settings. Furthermore, participants were specifically asked about their regular bread consumption. Therefore, only individuals who consumed bread were included in the study, which may reduce the generalizability of the study results. Nonetheless, these risk management measures aimed to minimize dropout and enhance the cost-effectiveness of the study.

Fecal samples were collected to determine the gut microbiota composition, gene abundances, bile acid concentrations, organic acid concentrations, and moisture content. Immediate analysis of fresh fecal samples is often unrealistic, raising concerns about storage methods by participants, which may cause microbial DNA degradation, overgrowth, and species death in fecal samples [97]. However, there are room-temperature microbial stabilization methods with high technical reproducibility and compositional stability [98], which should be considered for future studies. From a cultural perspective, these advanced methods offer an alternative for future studies in which refrigerating fecal samples is not feasible, particularly in cases in which it may be culturally insensitive, such as for Māori and Pasifika participants. Nonetheless, all participants were given clear written instructions, ice packs, and a cooler bag for returning their samples during clinic visits, minimizing potential confounding effects.

Strengths of the Bread Related Effect on Microbial Distribution study include using shotgun metagenomics to analyze extracted fecal microbial DNA. This approach allowed for the exploration of the composition and predictive functional aspects of the gut microbiota. These analyses provided insights into the community structure and diversity as well as the identification of changes in taxa and genes associated with the study interventions [99]. In addition, this study included other multiomic approaches (metabolomics), validated subjective questionnaires, and dietary records collected before and after each intervention. Integrating these data will allow for a better understanding of the complex interactions among diet, gut microbiota, and other health outcomes in healthy adults with low DF intake. Furthermore, this study is a blinded crossover study, allowing participants to be their own controls [47]. A crossover design was chosen due to the recognized inter- and intraindividual variabilities among populations, allowing for a reduced sample size while achieving the required statistical power. In addition, sequence effects were accounted for in the analysis [100].

Future studies may consider recruiting individuals with gut abnormalities, such as individuals with constipation, or conduct further subgroup analysis on the same dataset to separate individuals with different BMI statuses and gut microbiota compositions and of different ethnicities at baseline. These considerations may provide a better understanding of the effects of DRB-fortified bread on all the assessed study outcomes.

In addition, there is also a possibility that participants felt obligated to consume the interventions provided considering the perceived notion of being part of research. Future studies should consider supplementing the study with qualitative interviews or surveys. Including consumer insights as part of the study would allow for a better understanding of participants' perspectives and experiences. Subsequently, this may allow for further generalization to the general population should DRB-fortified bread be introduced to the market.

Conclusions

In this double-blinded, crossover randomized controlled trial, the collection of diet, clinical, biological (microbiota, metabolites, and lipids), and physiome (transit time and gas profile) data will provide crucial information on the benefits of fortifying DRB in commonly consumed foods. This knowledge may help support the public health system and food industry in developing targeted interventions aimed at modulating health-promoting gut microbes, general and mental well-being,

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DF intake, whole-gut and regional transit time, and fermentation gas profiles in healthy adults with low DF intake.

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Authors' Contributions

CLW, CF, and MF were responsible for the formal analysis, supervision, and writing review and editing. CSG was responsible for the formal analysis, investigation, supervision, and writing review and editing. DLC, JAM, JC, and KF were responsible for the formal analysis, investigation, methodology, supervision, and writing review and editing. HMN and JM were responsible for the data curation, formal analysis, investigation, project administration, writing original draft, and writing review and editing. NCR was responsible for conceptualization, funding acquisition, investigation, methodology, supervision, and writing review and editing. RBG was responsible for conceptualization, investigation, methodology, supervision, and writing review and editing. SBB was responsible for investigation, supervision, validation, and writing review and editing. TT was responsible for investigation, methodology, and writing review and editing. WCM was responsible for formal analysis, investigation, methodology, supervision, and writing review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Outcomes 2022 Checklist.
[PDF File (Adobe PDF File), 393 KB - resprot_v13i1e59227_app1.pdf]

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Abbreviations

bp: base pairs
CONSORT: Consolidated Standards of Reporting Trials
DF: dietary fiber
DRB: defatted rice bran
eCRF: electronic case report form
FDR: false discovery rate
HDL: high-density lipoprotein
HPLC: high-pressure liquid chromatography
LCMS: liquid chromatography mass spectrometry
LDL: low-density lipoprotein
MS: mass spectrometry
PLS-DA: partial least squares projection discriminant analysis
REDCap: Research Electronic Data Capture
SF-12v2: 12-item Short-Form Health Survey version 2
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Nourishing the Infant Gut Microbiome to Support Immune Health: Protocol of SUN (Seeding Through Feeding) Randomized Controlled Trial

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Abstract

Background: The introduction of complementary foods during the first year of life influences the diversity of the gut microbiome. How this diversity affects immune development and health is unclear.

Objective: This study evaluates the effect of consuming kūmara or kūmara with added banana powder (resistant starch) compared to a reference control at 4 months post randomization on the prevalence of respiratory tract infections and the development of the gut microbiome.

Methods: This study is a double-blind, randomized controlled trial of mothers and their 6-month-old infants (up to n=300) who have not yet started solids. Infants are randomized into one of 3 groups: control arm (C), standard kūmara intervention (K), and a kūmara intervention with added banana powder product (K+) to be consumed daily for 4 months until the infant is approximately 10 months old. Infants are matched for sex using stratified randomization. Data are collected at baseline (prior to commencing solid food) and at 2 and 4 months after commencing solid food (at around 8 and 10 months of age). Data and samples collected at each timepoint include weight and length, intervention adherence (months 2 and 4), illness and medication history, dietary intake (months 2 and 4), sleep (diary and actigraphy), maternal dietary intake, breast milk, feces (baseline and 4 months), and blood samples (baseline and 4 months).

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Results: The trial was approved by the Health and Disability Ethics Committee of the Ministry of Health, New Zealand (reference 20/NTA/9). Recruitment and data collection did not commence until January 2022 due to the COVID-19 pandemic. Data collection and analyses are expected to conclude in January 2024 and early 2025, respectively. Results are to be published in 2024 and 2025.

Conclusions: The results of this study will help us understand how the introduction of a specific prebiotic complementary food affects the microbiota and relative abundances of the microbial species, the modulation of immune development, and infant health. It will contribute to the expanding body of research that aims to deepen our understanding of the connections between nutrition, gut microbiota, and early-life postnatal health.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000026921; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378654

International Registered Report Identifier (IRRID): DERR1-10.2196/56772

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KEYWORDS

infant; complementary feeding; gut microbiota; immune; complementary food; feeding; gut microbiome; microbiome; immune system; kūmara; infancy; immune development; infant health; prevalence; respiratory tract infections; RTI

Introduction

Background

The early stages of gut microbiome development are marked by unique temporal microbe uptake, colonization, and selection, all of which have variable functional characteristics throughout time. This carefully managed microbial sequence begins at birth and continues until the microbiome acquires an adult-like makeup and function around 3 years of age [1]. These many stages of microbiome development are increasingly becoming recognized as critical periods for immune and metabolic development, which can impact long-term health [2].

Early-life postnatal nutrition has been shown to be the most important modulator of the gut microbiome, with breast milk seeding and modulating the microbiome with beneficial bacteria [3]. The gut microbiota of breastfed infants is dominated by *Bifidobacterium* species, which proliferate due to the high levels of human milk oligosaccharides in breast milk [4]. The introduction of solid foods, which are largely influenced by physiological development, culture, and tradition, has a significant impact on the composition and functional capacity of the gut microbiome [5-7]. If an infant continues to be breastfed during the complementary feeding (CF) phase, this can also influence changes in microbial patterns [3]. An increase in dietary intake of complex polysaccharides and proteins increases the abundance of microbes capable of their degradation, including those taxa from the Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae families [1]. The change in the diversity of species increases the production of the short-chain fatty acids (SCFAs) butyrate and propionate [8]. SCFAs are probable mediators of microbiota-host interactions that affect infant health due to their physiological effects, including influence on the intestinal barrier function, host metabolism, and immune system [1].

There is a growing body of research on early-life postnatal nutrition and the effects on the development of the microbiome and subsequent immunological outcomes [9,10]. The infant's immune system and microbiota coevolve throughout the first few months of life, starting a 2-way interaction that eventually leads to competence and maturity [6]. Breast milk and vertical maternal transmission of microorganisms are factors that influence colonization patterns and the immune system's development [1]. Understanding how the microbiota and immune system interact with the introduction of complementary foods opens possibilities to enable us to provide suitable dietary recommendations in order to maintain an age-appropriate microbiome for short- and long-term health.

Randomized controlled trials conducted in this age group tend to be predominated by infant formula and isolated probiotic interventions [11-14]. Although these studies have been useful to characterize differences in microbiota according to formula or probiotic type, there are a limited number of controlled trials that have evaluated the effects of complementary foods, their effect on the gut microbiota, and their efficacy in immune health and development in infancy [15]. One of the reasons for this lack of research is probably because of the complexities of designing robust trials using weaning foods and the difficulties of measuring the dynamic changes in breast milk and food intake in this age group [16].

Respiratory tract infections (RTIs) are a common cause of morbidity and mortality in children under the age of 2 years [17,18]. Observational studies of infants have demonstrated associations between the gut microbiome and RTI, and in particular, the positive effect of breastfeeding on reducing the number and severity of infections [10]. However, none of these studies have examined the effects of food and nutrient intake during the CF phase on the gut microbiome and the risk of RTI.

The aim of the SUN (seeding through feeding) randomized controlled trial is to evaluate the effect of consuming kūmara (sweet potato) (K) or kūmara with added banana powder containing resistant starch (RS; K+) compared to the C at 4 months post randomization on the prevalence of RTI and the development of the gut microbiome. We will also explore how changes in the gut microbiome influence immune development. Kūmara (sweet potato) is commonly used in CF and is a source of starch and nondigestible carbohydrates. RS is a carbohydrate that resists digestion and acts as a prebiotic food for beneficial gut bacteria.

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Primary Outcomes

Primary outcomes include the following: (1) a between-group difference in general practitioner (GP)–confirmed RTI at 4 months post randomization; and (2) parent self-report of respiratory infections validated by GP records collected via a daily health record.

Secondary Outcomes

Secondary outcomes include the following: (1) between-group differences in other measures, including infant health, assessed using daily records of illness (reporting frequency, illness type, medication prescribed, use of antibiotics, and antibiotic course length). Differences in infant fecal microbiome relative abundance and diversity; (2) differences in infant fecal concentrations of SCFAs and intermediate metabolites; (3) differences in immune cell development, as determined by high-dimensional flow cytometry, as well as the magnitude of antibody responses to the oral rotavirus vaccine in infants paired with rotavirus-specific secretory immunoglobulin A (IgA) quantification in breast milk (breastfeeding mothers only); and (4) differences in nighttime sleep, daytime sleep, and activity of infants assessed using actigraphy and sleep dairy.

Methods

Study Design

The SUN study is a parallel 3-arm, randomized controlled trial conducted in Auckland, New Zealand. A total of 300 infants who have not yet started CF are randomized using computer-generated randomization sequences in a 1:1:1 ratio to receive 1 of 2 daily prebiotic food interventions (double-blind standard kūmara powder or kūmara powder with banana powder containing RS) or be in the control arm (C) of the study.

Participants and Recruitment

Infants are being recruited from the general population in urban central and greater areas of Auckland, New Zealand, from January 2022 to January 2024. Recruitment strategies include electronic and print advertising targeted toward postnatal and community groups, media releases, and appropriate social media platforms such as Facebook. All families that show interest in the study receive an email explaining the study in detail and are provided with the study participant information sheet and consent form.

Ethical Considerations

The study was approved by the Health and Disability Ethics Committee of the Ministry of Health, New Zealand (reference 20/NTA/9). Parents or legal guardians are provided with an information sheet explaining the purpose of the trial; details of the research; specific procedures; benefits and risks; the voluntary nature of enrolment and the ability to opt out of the research at any time. A written informed consent form from the infant's parents or legal guardian is an inclusion criterion, without which the infant cannot be included in the study.

Participants' data are stored in a password-protected secure study database and are anonymized for analyses. The University of Auckland standards for data handling will be adhered to for data storage and management. No monetary compensation is provided for being in the trial, but on completion, parents are provided with a gift voucher as a thank you for taking part.

Inclusion and Exclusion Criteria

Infants are eligible for participation in the study if they are healthy; are between 3 and 6 months of age; were at least 32 weeks gestation at birth; will be introduced to their first complimentary foods at around 6 months of age, and not before 4 months of age, as per the New Zealand Ministry of Health Food and Nutrition Guidelines for Infants [19]; and have parents or legal guardians that can provide written informed consent to participate in the study.

Infants are not eligible for participation if they were born <32 weeks gestation; were small for gestational age (as they may have special dietary requirements); have a developmental disability (ie, autism and intellectual disability); have an illness likely to influence their nutritional status (eg, a chronic illness known to cause malabsorption and any digestive or metabolic disorders); have health conditions that affect feeding; are undergoing treatment with antibiotics; have had any complementary foods at recruitment; are receiving a supplement with a prebiotic or probiotic; are not immunized according to the New Zealand Immunization Schedule; and have parents or legal guardians who have written or spoken English comprehension that is likely to make participation difficult for them.

Infants already taking a probiotic or prebiotic as a supplement are still eligible to participate if parents are willing to stop giving these to their infants.

Randomization

The trial outline is shown in Figure 1. A "participant randomization form" was designed for the study on REDCap (Research Electronic Data Capture) tools hosted at the University of Auckland, which allows the independent administrator to randomly allocate the participant into the K, K+, or C group. Randomization is stratified by gender (female or male) using block randomization with variable block sizes of 3 or 6. The randomization list was prepared by the trial statistician (YJ) and is maintained by an independent database administrator. The lists are concealed until the point of randomization, and the 2 groups with kūmara intervention will remain double-blinded throughout the trial.

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Figure 1. Trial outline.

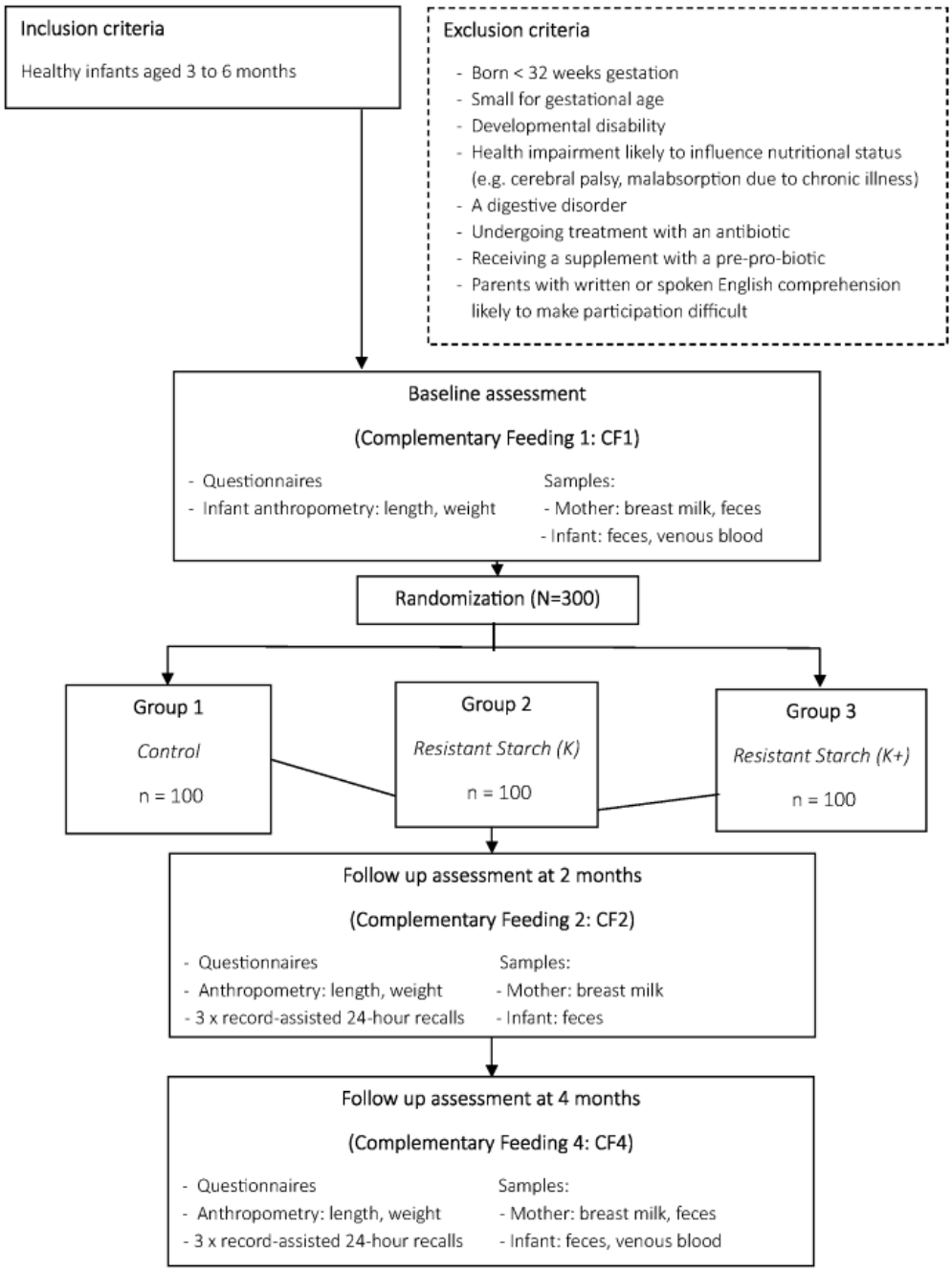

Intervention

All participants randomized to either the K or K+ intervention groups are supplied with the kūmara powder at no cost to the participant. The kūmara powder is intended to be introduced alongside the first complementary food offered to participating infants and is to be consumed daily for a period of 4 months until the child is approximately 10 months of age. The kūmara powder is packaged in identical 5 g freeze-dried powder sachets and provided as a 2-month supply of study product at each of their clinic visits (baseline and midway through the study). A random number is assigned to each participant kit, using computer-generated sequences. For those randomized to receive one of the kūmara powders (K or K+), both study participants and the researchers will remain blinded throughout the trial.

Any kūmara powder not consumed within the 2-month interval is returned to the research team and recorded at the participant's next clinic visit. Adherence is measured using a daily consumption record completed by parents prospectively and information from a monthly questionnaire on the average amount of the kūmara powder consumed per day in the previous month. Participants randomized into the C group follow general feeding guidelines as per the New Zealand Ministry of Health [19] and receive gift vouchers at their clinic visits to the value of the kūmara powder as a token of appreciation for their continued participation.

Compliance

Adherence to the kūmara powder is determined using a prospective daily record. Adherence will be defined as the consumption of 5 g of kūmara powder per day (approximately

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1 tsp reconstituted with water) on 80% of the days within the monitored interval (ie, the previous month).

Sample Size

A sample size of 80 participants per group will have 80% power at the 5% significance level (2-sided) to detect an absolute difference of 20% between the K+ and C groups on the primary outcome. This is equivalent to a 25% relative reduction, assuming a retention rate of 80%. To allow for a 20% loss to follow-up, we aim to recruit 300 participants in total (n=100 per group; Figure 1).

Data Collection

Data collection takes place at baseline, when the child is 4-6 months of age, prior to commencing CF (CF1), and then around 8 months of age (CF2) and around 10 months of age (CF4) post randomization. Prior to the baseline clinic visit, written informed consent is obtained, and parents are given verbal and written information about participation. Questionnaires collecting information on sociodemographic characteristics and participating infant health are completed digitally using REDCap electronic data capture tools hosted by the University of Auckland [20]. At baseline, participants are assessed according to the schedule presented in Table 1 and either provided with a 2-month supply of kūmara powder or the equivalent value in gift vouchers (if randomized to the C group).

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Table 1. SUN[a] trial schedule of enrolment, interventions, and assessments.

Timepoint	Study period					
	Enrollment	Allocation	Post allocation			Closeout
			Baseline	CF2	CF4	
Infant age	<4 mo	4-6 mo	≥4-6 mo	≤8 mo	≤10 mo	>10 mo
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Allocation		✓				
Intervention						
Intervention A						
Intervention B						
Control						
Assessments						
Measurements						
Weight (kg)			✓	✓	✓	
Length (cm)			✓	✓	✓	
Questionnaires						
Demographics	✓					
Child health and nutrition	✓		✓	✓	✓	
Maternal health and household	✓		✓		✓	
Three×record-assisted 24-hour recalls				✓	✓	
Daily health record			✓	✓	✓	
Daily intervention adherence			✓	✓	✓	
FFQ—maternal			✓	✓	✓	
Sleep questionnaire—mother			✓	✓	✓	
Biological sample collection						
Infant						
Feces			✓	✓	✓	
Blood			✓		✓	
5-Day sleep diary (using actigraphy)[b]			✓	✓	✓	
Mother						
Feces			✓	✓	✓	
Breast milk			✓	✓	✓	
Completion and review of electronic trial documentation			✓	✓	✓	
Unblinding and data analyses						✓

[a]SUN: seeding through feeding.

[b]An actigraph is a noninvasive method of recording infant sleep patterns through movement. The small sensor is fitted around the lower leg using a neoprene strap.

Demographic Data

At baseline, information on family size (household structure, number of siblings, and presence of pets), parental education, parental occupation, parental ethnicity, living conditions, smoking habits, and family history of disease (eg, common allergens, including pets and pests, respiratory conditions, atopic disease, and chronic disease) is obtained. Information about the participating child includes birth weight and length, mode of delivery, initiation of breastfeeding, feeding patterns since birth, and health records, including hospital admissions and allergy history.

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Illness

Participating infants' recent health history is captured prospectively via daily records of illness and use of medicines. The incidence and duration of illness or infections, including airway-related illness and gastrointestinal symptoms, are documented. Specific consent is obtained to contact the nominated family GPs to verify records of infection-related visits, medication prescription and use, and hospitalization events throughout the trial [16].

Measuring Fecal Microbiota, Microbiome, SCFAs, and Rotavirus Vaccine–Specific Antibody Titer

Infant fecal samples are collected at 4-6 months of age (baseline), 8 (CF2), and 10 months of age (CF4) to assess the extent to which the kūmara interventions (K/K+ groups) and CF (all groups) have modulated the infant gut microbiota and to quantify rotavirus vaccine–specific antibody responses. Fecal samples are also analyzed for SCFAs by liquid chromatography-mass spectrometry using modifications to the method reported by Han et al [21]. to investigate the differences in fecal SCFAs and intermediate metabolites in infants in the different feeding interventions. Maternal fecal samples from consenting mothers are collected at baseline, CF2, and CF4 to assess the relationship between maternal and infant gut microbiota composition. The fecal microbial function is assessed using shotgun sequencing of metagenenomic DNA [22] using the Illumina HiSeq platform in conjunction with microbial profiling by pyrotag sequencing of 16S sRNA gene amplicons. Sequencing data will be analyzed using bioinformatics tools such as quantitative insights into microbial ecology [23], Rapid Annotation using Subsystems Technology for metagenomes [24], and Integrated Microbial Genomes [25]. The infant fecal metabolome is measured using high-resolution liquid chromatography–mass spectrometry using the method reported by Abshirini et al [26] to investigate differences in fecal metabolite profiles from the different feeding interventions over time.

Measuring Rotavirus Vaccine–Specific Antibody Response and Immune Development in Blood

Venipuncture blood samples (this is an optional activity, so only infants whose caregivers will give specific consent) are collected by a trained pediatric phlebotomist at baseline (4-6 months of age) and CF4 (10 months of age). The total collected blood volume is approximately 5 mL (~0.7 mL/kg per 24 hours). Available blood samples will be used to assess the protective antibody response in plasma following oral rotavirus vaccination (administered at 6 weeks and 3 months of age), as well as the frequency of innate and adaptive immune cell subsets by spectral flow cytometry [27].

Sleep

Quantitative infant sleep data are recorded using a standard ActiGraph (GT3X; Pensacola) worn at each timepoint continuously over 5 days. The actigraph is a watch-sized device fitted around the infant's lower limb using a neoprene strap and is commonly used to measure sleep via sensing movement (acceleration), where the absence of movement infers sleep and movement infers wake [28,29]. The data will be processed for standard actigraphy sleep variables, inclusive of naps, using the count-scaled algorithm developed in MATLAB (MathWorks) [30]. Parents also record infant sleep in a sleep diary, which captures sleep-wake timing data across a 24-hour period for 5 consecutive days, and the Brief Infant Sleep Questionnaire, which is used to assess sleep patterns, parent perception, and sleep-related behaviors in young children (0-36 months) [31]. Validated parent-completed questionnaires on sleep-related impairment and sleep disturbance are used as a symptom assessment tool. These questionnaires measure 8 items on 5-point scales to rate the frequency of problems related to insufficient sleep and sleep disturbance in the past 7 days [32,33].

Dietary Intake and Feeding Behaviors

Infant dietary intake is assessed using a 3-day food record at CF2 (infant approximately 8 months of age) and CF4 (infant approximately 10 months of age). Parents are asked to record the participating infant's food and drink intake over 3 consecutive days, with even distribution across weekdays and weekends at a group level. Parents are instructed on how to complete the 3-day food records and use household measures to describe their infant's dietary intake. Diet records will be analyzed with FoodWorks (version 10; Xyris Software) using the New Zealand Food Composition database FOODfiles 2018 (version 01).

At baseline (CF1), infant feeding practices such as method (breastfeeding, formula, or mixed feeding) and frequency or amount are recorded. A questionnaire at baseline and diet records at CF2 and CF4 captures the volume of milk intake (expressed breast milk or formula). Breast milk remains an important component of the diet and has important impacts on both the gut microbiota and immune function. Breast milk volume will be estimated using the previously validated methodology, whereby breastfeeding is recorded as time (minutes) and quantity estimated using a conversion factor of 10 mL/min, with a maximum of 10 minutes of breastfeeding or 100 mL of breast milk [34,35].

Habitual maternal food and nutrient intake will be assessed using a semiquantitative food frequency questionnaire, which has previously been validated in the New Zealand setting [36].

Anthropometry

Anthropometric measurements are taken at baseline when the participating child is around 4-6 months of age (CF1), around 8 months of age (CF2), and around 10 months of age (CF4), using standardized protocols. Measurements include weight, length, and weight for length Z-scores [37].

Measuring Breast Milk for Rotavirus Vaccine–Specific Antibody Titer and Secretory IgA

Breast milk samples are collected (where possible) from breastfeeding mothers at baseline, CF2, and CF4. Samples will be analyzed for rotavirus vaccine–specific titer quantification and the role of secretory IgA factors in shaping the gut microbiota during infancy and to examine the change in breast milk metabolome with prolonged breastfeeding (ie, beyond 6 months of age) and its continued modulating effect on infant

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gut microbiota diversity during CF. Sample collection is completed according to a predefined protocol, and breastfeeding mothers will have access to instructional videos on standardized sample collection (by hand expressing or pumping). To account for diurnal variation [38] and compositional differences between fore- and hindmilk [39], breast milk mothers are asked to express by emptying the full breast from the right side between 7 AM and 10 AM and at least 2-3 hours after a previous breastfeed. Wiping the breast with antiseptic (benzalkonium chloride) wipes to limit skin microbial contamination. After mixing the full sample by swirling or gently inverting, 15 mL of breast milk is decanted into a 15-mL falcon tube. Samples are kept in the fridge at home for up to 24 hours before the next clinic appointment. Samples are stored at –80 °C until analysis.

Statistical Analysis

Participants' data are stored in a secure study database and imported to SAS software (version 9.4; SAS Institute Inc) for data analysis at the end of the trial. The demographic and baseline characteristics of all randomized participants will be summarized for each group using descriptive statistics. Categorical variables will be described as frequencies and percentages. Continuous variables will be described as mean and SD or median and IQR as appropriate. Descriptive data on important subgroups (gender and ethnicity) will also be presented if a sufficient number of participants are recruited. No formal statistical tests will be conducted to compare the 3 groups at baseline, as recommended by the CONSORT guidelines [40].

There are 3 randomized groups (K+, K, and C) in the trial; however, the primary comparison will be based on the statistical test between K+ and C groups only. Additional comparisons between the other randomized groups will be conducted in secondary analysis using similar statistical models. This is to control the overall type 1 error rate, with the assumption that the proposed sample size will have sufficient power to detect the difference in primary outcome between the K+ and C groups. Primary outcome analysis will be conducted by intention-to-treat (where participants are analyzed according to their allocated treatment arm). The impact of missing data on the primary outcome will be explored in sensitivity analysis using different imputation strategies to test the robustness of the main results.

A secondary analysis of the primary outcomes will be conducted using a per-protocol population, including those participants in the intention-to-treat population who have no major protocol deviations. Inclusion in the per-protocol population and analysis will be based on the degree of intervention compliance, defined as the total number of days where less than the predefined amount of intervention food was consumed per day within the last study month. This information will be determined using a monthly intervention adherence record completed by parents or caregivers. Adherence will be defined as the consumption of 5 g of the intervention food per day on 80% of the days within the monitored interval.

Logistic regression models will be used to test the difference in the proportion of participants with at least 1 episode of RTI at a 4-month follow-up between the K+ and C groups (primary comparison), adjusted for gender (stratification factor). The effect of the intervention will be estimated between the 2 groups using a model-adjusted odds ratio with a 95% CI. Statistical tests will be 2-sided at a 5% significance level.

Generalized linear regression models will be used on other secondary outcomes to test the group differences at 2- and 4-month follow-ups separately, using a link function appropriate to the distribution of the outcome measure. All regression analyses will be adjusted for baseline outcome value (if available) and gender. The effect of the intervention will be estimated and tested using a model-adjusted point estimate on the group difference with a 95% CI and a 2-sided *P* value. Multiple testing on secondary outcomes will not be adjusted as they are considered exploratory and provide supporting information on the primary outcome. A random-effects mixed model will be used on the outcomes collected repeatedly over time to account for correlated data collected from the same participants and take into account any missing data in maximum likelihood estimates. The consistency of the short- and long-term effects of the dietary intervention will be assessed using the interaction term between the treatment group and visit. The effects of the intervention on predefined subgroups will also be assessed, and separate subgroup analyses will be considered if a sufficient number of participants are recruited.

Quality Control and Quality Assurance

The SUN study researchers are trained and monitored by an independent academic research organization based in Auckland, New Zealand. The Green Lane Coordinating Centre conducts training and monitoring in accordance with the International Council on Harmonization—Guideline for Good Clinical Practice within the setting of a nutrition intervention trial. The Green Lane Coordinating Centre performs a centralized review of SUN study data (blinded to intervention allocation) and other documents to assess protocol adherence, data accuracy and completeness, source data verification, and review investigator files.

Data Management and Governance

Each participant is given a unique study identification number, which serves as identification on all forms, questionnaires, and measurements and as a participant identification number on the study database. Only 1 document exists that links participant numbers to personal data. All study data are regarded as confidential and stored electronically using REDCap, hosted by the University of Auckland [20]. All files (electronic and hard copy) will only be available to the key researchers at the University of Auckland performing data collection. After completion of the study, the University of Auckland will retain all data for 10 years after the youngest participant has turned 16 years of age. Access to deidentified data will be available to lead scientists within the wider SUN team for inclusion in analyses.

Results

Recruitment and data collection did not commence until January 2022 due to the COVID-19 pandemic. Data collection and analyses are expected to conclude in January 2024 and early 2025, respectively.

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Discussion

At 4 months after randomization, our study aims to assess the impact of consuming kūmara (sweet potato) (K) or kūmara with added banana powder containing RS (K+) on the development of the gut microbiome and the prevalence of RTI in comparison to the C. We will also investigate the impact of gut microbiome modifications on immunological development. To our knowledge, this is the first intervention study to examine the effects of a dietary intervention in the CF phase on RTI and the gut microbiome. The study has many advantages over previous designs, including strict inclusion and exclusion criteria, 2 intervention arms and a C (reference group), and a wide range of biological specimen collections.

The completion of a pilot feasibility study prior to the development of the RCT has also enabled the development of robust operational processes that will ensure the successful completion of the trial [16]. The study has been powered to enable the examination of the effect of K and K+ on RTI as this is a tangible clinical outcome; however, the study design also allows us to explore how the intervention impacts the development of the gut microbiome and if the gut microbiome is a mediator between dietary intake and immune development.

There are also several novel exploratory aspects of the study. The first is the collection of breast milk samples, fecal samples, and dietary intake from the infants to examine the role of breast milk and its interaction with food intake on the seeding of the infant's gut microbiota. The second is the analysis of the infant blood samples to assess the antibody response following oral rotavirus vaccination, which will be complemented by a high-dimensional profiling of the infant's peripheral immune system; these analyses will enable us to examine the relationship between dietary intake, the gut microbiome, and immune development and function. The third is the collection of objective measurements of several sleep variables important for sleep health [41].

Clinical trials in infants are challenging, and compliance with a dietary intervention and the collection of biological and dietary intake data place a significant burden on caregivers. Previous experience in RCTs in this age group and the completion of the pilot feasibility study provide us with some significant insights into how to support families through the study to ensure retention and completion. There are limited risks to the infants from being involved in the study. The intervention (kūmara) is a common and acceptable complementary food with no known allergenicity. The benefits of using kūmara as a candidate prebiotic food were identified through an in silico reverse genomic approach [42]. This integrated pipeline, based on literature searching, text mining, reverse metabolic analysis, and food database exploration, identified exogenous metabolites required by gut microorganisms potentially capable of enhancing the immune system against infant infections and localized those metabolites in foods and food components.

This study will provide some understanding of the effects of the introduction of a prebiotic complementary food on the development of the gut microbiota, the modulation of immune development, and health in infancy. It will add to the body of growing literature that seeks to expand our understanding of the interactions between diet, gut microbiota, and health in early postnatal life. This knowledge will assist in providing evidence for suitable CF recommendations to maintain an age-appropriate gut microbiome for short- and long-term health.

Data Management Committee

The principal investigator is responsible for project coordination and oversight of the operational aspects of the trial. A data monitoring committee monitors the adverse events of the study.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request through the university Figshare platform [43].

Conflicts of Interest

None declared.

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Abbreviations

C: control
CF: complementary feeding
GP: general practitioner
IgA: immunoglobulin A
K: kūmara
K+: kūmara with added banana powder containing resistant starch
REDCap: Research Electronic Data Capture
RS: resistant starch
RTI: respiratory tract infection
SCFA: short-chain fatty acid
SUN: seeding through feeding

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Protocol

Adapting and Evaluating a Brief Advice Tobacco Cessation Intervention in High-reach, Low-resource Settings in India: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: About 1.35 million deaths annually are attributed to tobacco use in India. The main challenge, given the magnitude of tobacco use and limited resources, is delivering cessation support at scale, low cost, and through a coordinated cross-system effort; one such example being brief advice interventions. However, highly credentialed staff to identify and counsel tobacco users are scarce. Task-shifting is an important opportunity for scaling these interventions.

Objective: The LifeFirst SWASTH (Supporting Wellbeing among Adults by Stopping Tobacco Habit) program—adapted from the LifeFirst program (developed by the Narotam Sekhsaria Foundation, Mumbai, India)—is a tobacco cessation program focusing on lower-socioeconomic status patients in Mumbai receiving private health care. This parallel-arm, cluster randomized controlled trial investigates whether the LifeFirst SWASTH program increases tobacco cessation rates in low-resource, high-reach health care settings in Mumbai.

Methods: This study will target tuberculosis-specific nongovernmental organizations (NGOs), dental clinics, and NGOs implementing general health programs serving lower-socioeconomic status patients. Intervention arm patients will receive a pamphlet explaining tobacco's harmful effects. Practitioners will be trained to deliver brief cessation advice, and interested patients will be referred to a Narotam Sekhsaria Foundation counselor for free telephone counseling for 6 months. Control arm patients will receive the same pamphlet but not brief advice or counseling. Practitioners will have a customized mobile app to facilitate intervention delivery. Practitioners will also have access to a peer network through WhatsApp. The primary outcome is a 30-day point prevalence abstinence from tobacco. Secondary outcomes for patients and practitioners relate to intervention implementation.

Results: The study was funded in June 2020. Due to the COVID-19 pandemic, the study experienced some delays, and practitioner recruitment commenced in November 2023. As of July 2024, all practitioners have been recruited, and practitioner recruitment and training are complete. Furthermore, 36% (1687/4688) of patients have been recruited.

Conclusions: It is hypothesized that those patients who participated in the LifeFirst SWASTH program will be more likely to have been abstinent from tobacco for 30 consecutive days by the end of 6 months or at least decreased their tobacco use. LifeFirst SWASTH, if found to be effective in terms of cessation outcomes and implementation, has the potential to be scaled to other settings in India and other low- and middle-income countries. The study will be conducted in low-resource settings and will reach

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many patients, which will increase the impact if scaled. It will use task-shifting and an app that can be tailored to different settings, also enabling scalability. Findings will build the literature for translating evidence-based interventions from high-income countries to low- and middle-income countries and from high- to low-resource settings.

Trial Registration: ClinicalTrials.gov NCT05234983; https://clinicaltrials.gov/study/NCT05234983

International Registered Report Identifier (IRRID): DERR1-10.2196/57236

(JMIR Res Protoc 2024;13:e57236) doi:10.2196/57236

KEYWORDS

tobacco use Cessation; India; resource-limited settings; task-shifting; counseling; nonprofit organizations; dental health services; tuberculosis; social media; mobile app

Introduction

Tobacco Burden and Control in India

About 1.35 million deaths are attributed to tobacco use in India each year [1]. In 2017 [2], there were roughly 267 million tobacco users including 199 million smokeless tobacco users, 100 million smokers, and 32 million dual users. Per the nationally representative 2016-2017 Global Adult Tobacco Survey (GATS-2), tobacco use is higher among men than women (42.4% or 32,436/76,500 men vs 14.2% or 10,863/76,500 women). Cessation is of interest to tobacco users in India; 38.5% (29,453/76,500) of smokers and 33.2% (about 25,398/76,500) of smokeless tobacco users reported a quit attempt in the year preceding the survey [2]. Although India is a signatory to the World Health Organization (WHO) Framework Convention on Tobacco Control and launched the National Tobacco Control Program in 2007 [3], the program was hampered by limited resources and inconsistent enforcement across states and regions [4]. The main challenge in India, given the magnitude of tobacco use and limited resources, is in delivering cessation supports at scale, at low cost, and through a coordinated effort among those engaged in tobacco cessation: nongovernmental organizations (NGOs) and clinics [5].

Barriers to Scaling Up Evidence-Based Tobacco Cessation in India

Low-resource settings require tobacco cessation evidence-based interventions (EBIs) that can be delivered, sustained, and scaled up at low cost [6-8]. However, tobacco cessation EBIs typically include pharmacotherapy, a resource still beyond the reach of most tobacco users and many health care systems in India [9], even though a limited number of pharmacotherapeutic treatments were recently added to the Indian Ministry of Health and Family Welfare's List of Essential Medicines [10]. Also, most tobacco cessation EBIs focus solely on cigarette smoking, which is a mismatch for India given the high rates of smokeless and dual tobacco use [11], and the fact that the smokeless tobacco market in India is the largest in the world [12]. Additionally, EBIs are more likely to be scaled up in low- and middle-income countries (LMICs) if they are simple and inexpensive and can be delivered via alternative channels, such as NGOs or small private practices, rather than relying entirely on government infrastructure and highly skilled personnel [13]. Finally, there is an overall lack of effective interventions to support health care practitioners in implementing evidence-based practices across various health topics in LMICs [14].

Brief Advice Interventions

One type of low-cost, scalable cessation support is brief advice interventions, or short engagement by health care providers to screen for tobacco use, offer brief cessation advice, and refer users to treatment resources [15]. Brief advice interventions are effective for both smoked and smokeless tobacco [16,17]. However, according to the GATS-2 in India, only 49.6% (37,332/76,500), of smokers and 31.7% (24,251/76,500) of smokeless tobacco users were advised to quit by a health care provider [2], highlighting a potential role for brief advice interventions [18].

Task-Shifting: Benefits and Training Requirements

The use of diverse health professionals (rather than only highly credentialed individuals) is an important opportunity for brief advice interventions [9]. India meets only 25% of the WHO benchmark for health care staffing, and the available educational facilities are insufficient to grow the workforce to needed levels [19]. To reach the needed staffing levels, the number of physicians would need to increase by 151%, but the current annual growth rate is 10%-14% [20]. Task-shifting is a strategy that emphasizes moving tasks from highly credentialed workers to less credentialed (but more readily available) workers and can promote access to preventive services and health. The task-shifting model has been effectively used to deliver mental health EBIs in LMICs, showing that health care providers with little or no prior mental health training, and often little formal education, can deliver EBIs effectively with positive clinical outcomes [21]. An important consideration for task-shifting models is the changes needed to adapt practitioner training to meet the needs of practitioners who have fewer formal credentials. For example, an EBI for autism spectrum disorder was adapted from the United Kingdom to sites in India and Pakistan. The use of nonspecialists to deliver the program necessitated a change from a 2-day training for therapists to a 4-week training for nonspecialists and new referral patterns and measures for nonspecialist competencies [22]. Another study trained community health workers (CHWs) in Tamil Nadu, India, to screen, examine, refer to further care, and follow up with patients with diabetes with the support of a tablet-based app. The CHWs were successful in their efforts compared to usual care, further indicating the use of task-shifting [23] The specific question addressed by this study is whether brief advice interventions can be delivered by a diverse range of health professionals instead of highly trained counselors.

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Delivering Sufficient Training Dose Using Technology

Practitioner training is a critical driver of program success [24,25] and can increase practitioners' knowledge, skills, motivation, and ability to implement EBIs [25-30]. Successful training requires spending enough time (achieving sufficient dose) and offering supports (such as ongoing technical assistance), connections, and resources, a challenge in low-resource settings [29]. Communication technologies, such as mobile phones, offer a tremendous opportunity and have been used with frontline health workers to increase knowledge and skills, deliver learning materials and reminders, improve guideline adherence, increase patient follow-up rates, increase worker credibility in the community, and support knowledge generation [31-34]

The Current Intervention

Narotam Sekhsaria Foundation (NSF) is an organization that has been working on tobacco cessation programs at various sites in the Mumbai Metropolitan Region (MMR) in India for more than 10 years. The NSF team developed and implemented LifeFirst, an evidence-informed tobacco cessation program involving cessation service provision in multiple settings including hospitals, workplaces, and schools, and conducting training for health care providers. It is based on EBIs developed in North America and Europe using the 5A's framework [35-38]. The 5A's framework (Ask, Advise, Assess, Assist, and Arrange) is a tool to help practitioners identify tobacco users, advise quitting, assess their readiness to quit, help them develop a plan, and arrange a follow-up visit or consultation [39]. The training builds skills and motivation to offer brief advice routinely and has two tiers: (1) a sensitizing version that orients practitioners to the need for tobacco control and builds skills for brief advice (Level 1) and (2) an intensive version to support practitioners in tobacco cessation counseling (Level 2).

The NSF team recently delivered the Level 1 training to 2000 practitioners. Before this, most participants had not received training to screen clients for tobacco use (83% or 1660/2000) or to provide cessation counseling (86% or 1720/2000). After receiving the training, participants reported increased knowledge to support patients and improved self-efficacy for counseling. Additionally, the team recently delivered the Level 2 training to 600 diverse health care providers from private and public hospitals, private practices, public health departments, and NGOs in Mumbai. Recently, NSF identified the potential for NGOs working on tuberculosis (TB) and treatment to deliver tobacco cessation, along with a need for less intensive interventions, setting the stage to test a brief intervention that requires few resources to implement [40].

The LifeFirst program has been adapted to develop LifeFirst Supporting Wellbeing among Adults by Stopping Tobacco Habit (SWASTH), which focuses on lower-socioeconomic status (SES) communities in Mumbai who receive health care through private dental practices and NGOs, including those working with TB patients (ClinicalTrials.gov NCT05234983). ("Swasth" means "healthy" in Hindi.) It is an EBI that involves training health care practitioners who serve lower-SES communities to ask their patients about tobacco use during health-related encounters, advise users to quit, and refer users willing to receive cessation support to LifeFirst SWASTH for 6 months' cessation counseling. Counseling will be conducted by trained NSF staff counselors. The practitioners and counselors will use a customized mobile app to facilitate intervention delivery. Practitioners will also have access to a peer network through the social media platform WhatsApp, which will enable them to problem-solve together and enhance their capacity to implement EBIs in their clinics or practices.

Objectives

Our objectives are as follows:

- Aim 1: adapt the LifeFirst program and pilot-test LifeFirst SWASTH in 3 low-resource, high-reach settings: NGOs implementing general health programs, TB-specific NGOs, and dental clinics.
- Aim 2: conduct a cluster randomized controlled trial (RCT) to assess whether the adapted brief advice program results in increased cessation rates among tobacco users (compared to receiving a pamphlet explaining the health effects of tobacco use) in the aforementioned 3 types of low-resource, high-reach health care settings in Mumbai.
- Aim 3: evaluate the use of communication technologies, such as social media and an app, to support ongoing training and networking among practitioners in the intervention arm.

Our main focus in this paper is on effectiveness outcomes and will report more robustly on our exploratory implementation findings in the future.

Theoretical Framework

The objective of this study is to test the effect of an adapted EBI, LifeFirst SWASTH, compared to receiving a pamphlet about the health effects of tobacco use, on improving cessation rates among tobacco users in 3 types of low-resource, high-reach health care settings in Mumbai: NGOs implementing general health programs, TB-specific NGOs, and dental clinics. This Hybrid Randomized Control Trial Type 1 study [41] will evaluate program effectiveness and explore the implementation of LifeFirst SWASTH, drawing on the US Public Health Service 5A's model of tobacco control [42] and the Exploration, Preparation, Implementation Sustainment framework [24]. Figure 1 details the study's theoretical framework. We hypothesize that 30-day point prevalence abstinence (PPA) will increase, and tobacco use will decrease at 6-month follow-up among patients in the adapted EBI, LifeFirst SWASTH, arm compared to the patients in the control arm.

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Figure 1. Theoretical framework supporting a hybrid effectiveness and implementation study. EBI: evidence-based intervention; NSF: Narotam Sekhsaria Foundation.

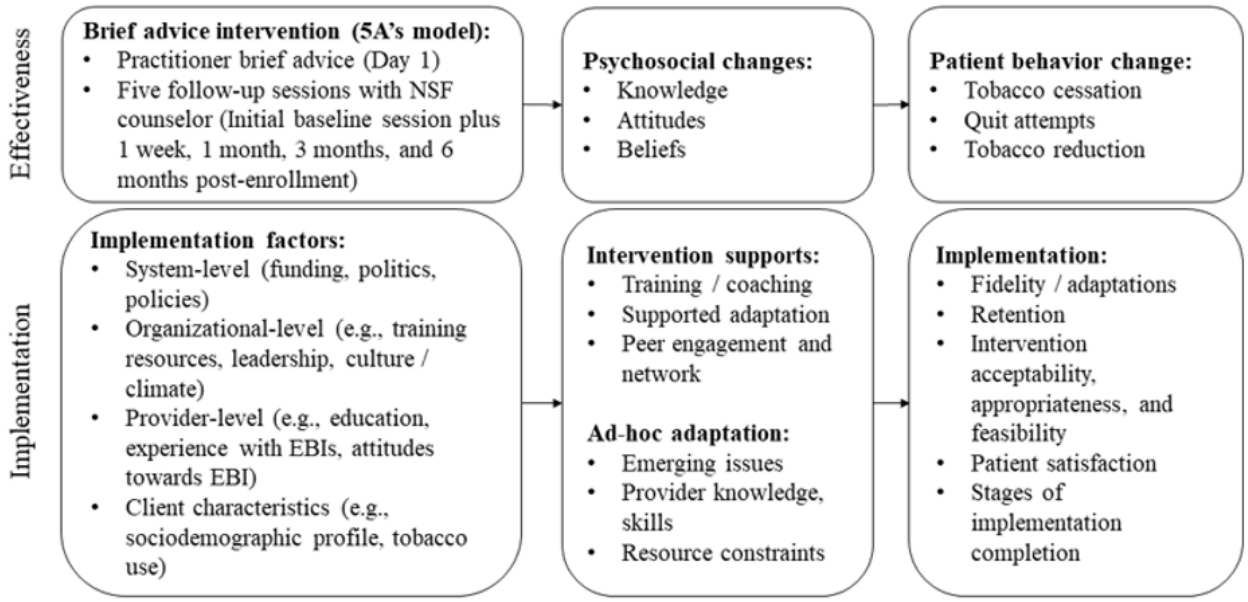

Methods

Design Overview

This study is a parallel-arm cluster RCT. Textbox 1 outlines the eligibility criteria for study sites. Textbox 2 details the participant eligibility criteria for practitioners and patients. Figure 2 provides an overview of the intervention design and flow.

Textbox 1. Site eligibility criteria.

- Private (separate from the public or government-run health care system) nongovernmental organizations implementing general health programs, tuberculosis nongovernmental organizations, or dental practice
- Serves lower-socioeconomic status patients
- Located in the Mumbai Metropolitan Region
- Has not previously received LifeFirst counseling training (Level 2)
- Is not currently running a tobacco cessation program

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Textbox 2. Participant eligibility criteria.

Practitioner eligibility (n=132)

- Is aged 18 years and older
- Is a targeted worker from a targeted setting (an outreach worker in a nongovernmental organization implementing general health programs, a community health worker in a tuberculosis-specific nongovernmental organization, or a dentist in private practice)
- Sees lower-socioeconomic status patients
- Has sufficient language proficiency in English and/or Hindi to attend the training and take surveys, and have sufficient language proficiency in Hindi and/or Marathi to interface with patients
- Has not received prior training in tobacco cessation counseling
- Can recruit 10-60 tobacco users in a 6-month period
- Works in a setting in which brief advice can be added to the workflow
- Delivers care in the Mumbai Metropolitan Region and expects to continue doing so for 1 year after completing the Supporting Wellbeing among Adults by Stopping Tobacco Habit practitioner training
- Can secure institutional signoff to participate and use the program in practice
- Has an Android smartphone

Patient eligibility (n=4688)

- Has used smokeless or smoked tobacco even once in the past 30 days
- Is aged 18 years and over
- Speaks Hindi or Marathi
- Attends the practice of an enrolled practitioner
- Has a mobile phone (required for data collection)
- Does not have another member of their household participating in the study
- Is not currently participating in any tobacco cessation program (such as through the National Quitline)

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. LifeFirst SWASTH: LifeFirst Supporting Wellbeing among Adults by Stopping Tobacco Habit.

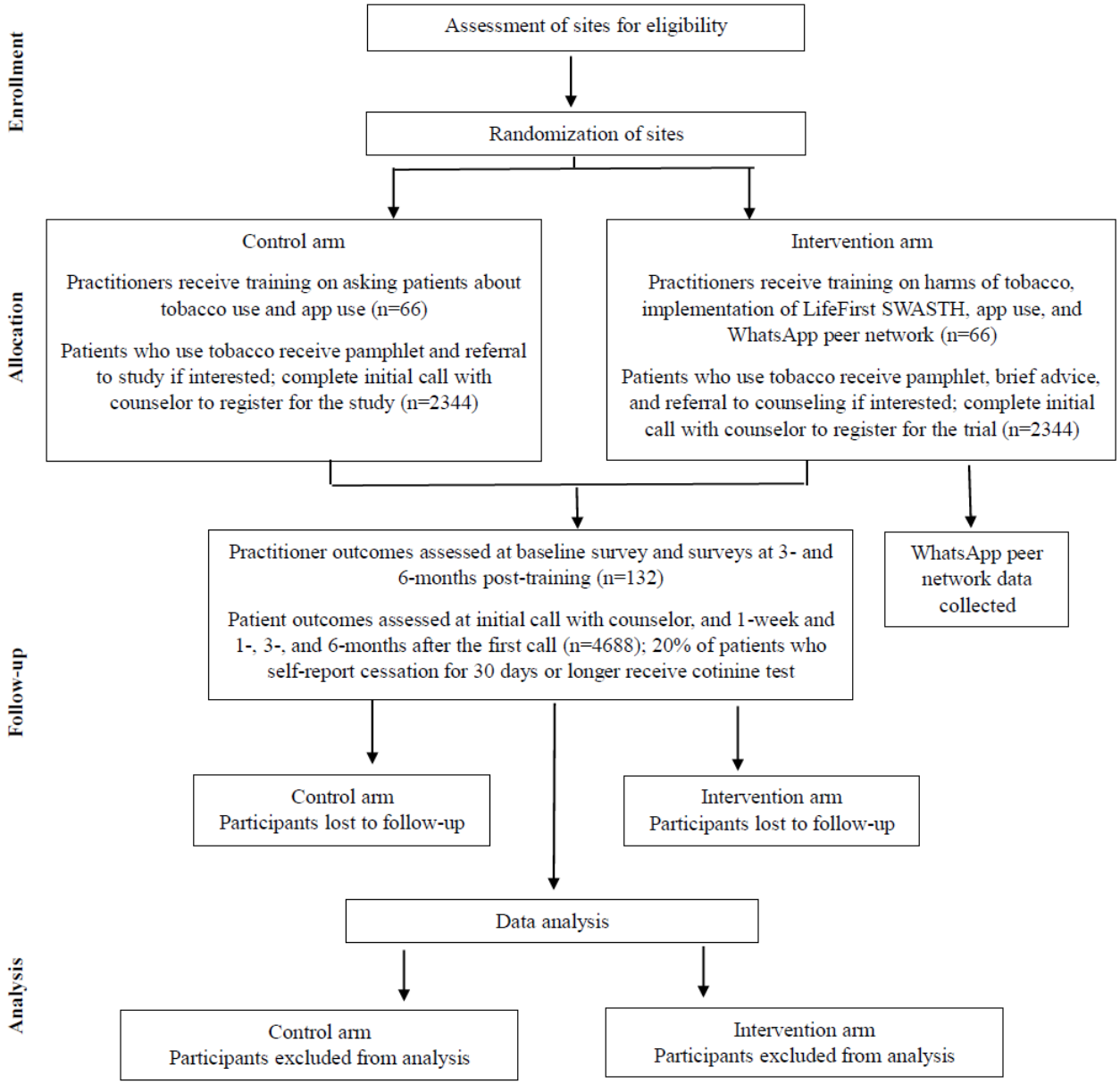

Recruitment and Retention

The NSF team has rich experience in recruiting practitioners who meet these criteria and is already working with practitioners and leaders in each of the 3 practice settings in Mumbai. The team will leverage these connections to recruit a diverse pool of sites and practitioners. Additionally, all practitioners and patients in both the intervention and control arms will receive nominal monetary incentives for their time and effort. Participating NGOs will also receive nominal monetary incentives at the site level. As private dental practices are run by dentists (who are, in this case, practitioners), they will not receive an additional site-level incentive.

Randomization

Sites will be randomized to conditions using random number generators in the SAS (version 9.4; SAS Institute). To ensure equivalence across treatment conditions, we will stratify random assignment based on two factors: (1) clinic types (eg, TB-specific NGOs, dental clinics, and NGOs implementing general health programs); (2) size of clinics with respect to the numbers of health care providers and patients. Randomization will be conducted within clinic types and matched by clinics with similar sizes. We will check the balance of treatment assignment on these 2 factors to assess the result of the random assignment. The health care providers and patients will not be blinded to their intervention condition.

A parallel study design will be used [43]. This design is considered the gold standard in assessing unbiased treatment effects given that randomization helps mitigate bias from known and unknown confounders. After randomization, individuals in each arm will stay in their assigned condition for the duration of the study. A cluster parallel RCT has the advantage of preventing inadvertent exposure to intervention or cross-over, thus reducing the risk of contamination [43].

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Intervention Arm

In LifeFirst SWASTH, patients who use tobacco will receive a pamphlet in Hindi about the harmful effects of tobacco. Practitioners will be trained to deliver the brief advice intervention. They will use an app to facilitate ongoing engagement and learning related to the adapted brief advice intervention. The app offers:

(1) a system to document patients' tobacco use and refer them to LifeFirst SWASTH for counseling; (2) a dashboard allowing them to follow the progress of the patients they have referred; and (3) a repository of training materials and additional resources, for example, support material for promoting cessation, and quiz questions to test their knowledge.

An NSF-moderated group chat in the popular social media channel, WhatsApp, will also be used as a forum to share practitioners' innovations and successes.

Within 15 days of referral, patients will be contacted by a trained NSF counselor over the telephone, given more details about the study, and asked whether they would like to provide informed consent and participate. The counselors will follow up with the patients for a total period of 6 months, with 4 specific follow-up intervals at 1 week, 1 month, 3 months, and 6 months after the initial detailed counseling call to ask about tobacco use and provide continued support.

Control Arm

Patients in the control arm will be asked about tobacco use and will receive the same pamphlet as the intervention arm about the harmful effects of tobacco. Patients interested in participating in the study will be referred by practitioners to LifeFirst SWASTH. They will be contacted by NSF data collectors (who are not trained in counseling) over the telephone at the same 4 follow-up intervals as the intervention arm patients but will only be asked about their tobacco use status (this will be presented as NSF assessing the tobacco cessation landscape in MMR). During the RCT, if control patients request counseling, they will be referred to the NSF's regular programmatic counselors and withdrawn from the study. They will subsequently be assigned to the lost-to-follow-up group (due to requesting counseling). After their final follow-up, those control arm patients who have not quit will be offered LifeFirst counseling by NSF staff through the regular counseling program, separate from the study.

Like intervention arm practitioners, practitioners in the control arm will use an app to document patients' tobacco use and register patients to be followed up by NSF. However, they will not be trained on the harms of tobacco use or advising tobacco-using patients on quitting and referring them to counseling. They will also not be part of a WhatsApp peer network. The training for control arm practitioners will emphasize that all patients will be given the option to access the intervention, including counseling, after their final follow-up with NSF. The control arm practitioners will also be offered the opportunity to receive the training after data collection is complete.

Primary Outcome: Intervention Effectiveness

The primary outcome is a 30-day PPA from tobacco. Twenty percent of those who self-report tobacco cessation 6 months post recruitment will receive a cotinine test (using a urine sample) to biochemically verify abstinence.

Secondary Outcomes

Patients

The secondary outcomes for patients are quit attempts, reduction in tobacco use, and psychosocial antecedents of behavior change such as knowledge, attitudes, and perceptions regarding the use of smoked or smokeless tobacco. These questions are primarily drawn from the GATS-2 survey, which was standardized, pretested in the field, and validated before being executed throughout India [2]. For the intervention arm patients, the survey includes questions regarding plans to quit and whether they have accessed other supports to do so, which will be tracked over time to assess the patient's progress and readiness to quit.

Practitioners

The secondary outcomes for practitioners are knowledge, appropriateness, feasibility, acceptability, motivation to implement the intervention, and intervention delivery skills. The appropriateness, feasibility, and acceptability questions were adapted from the Intervention Appropriateness Measure, Feasibility of Intervention Measure, and Acceptability of Intervention Measure [44]. The original measures were validated thoroughly by Weiner and colleagues and demonstrated substantive and discriminant content validity [44]. We recognize that the populations with which the original validation studies were conducted are dissimilar from our practitioner groups, and thus will conduct cognitive testing of the items. Some questions, such as those measuring knowledge, are standard questions the NSF team uses for their LifeFirst training.

Counselors

The secondary outcomes for counselors will be the appropriateness, feasibility, and acceptability of the intervention. This information will be documented by the NSF team, as the counselors are NSF staff members.

Data Collection and Analysis or Statistical Considerations

We will first examine the demographic characteristics of the intervention and control arms to verify that randomization has resulted in arms with similar baseline characteristics. Analyses will be based on intent-to-treat. To control for potential confounders identified in bivariate analyses, as well as variables of a priori clinical significance (SES, gender, age), we will regress the 6-month follow-up outcomes on the intervention status with the adjustment of baseline measures. We will use a regression model with a logit link function for binary outcomes (eg, tobacco cessation as our primary outcome), an identity link function for continuous outcomes (eg, number of cigarettes), and a Poisson link function for count outcomes (eg, number of attempts to quit). We will use robust standard error estimates (Generalized Estimating Equations method), adjusting for the clustering of patients among practitioners. We will conduct stratified analyses by clinic types to assess potential effect

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modification by settings. Independent variables with strong high correlations may result in collinearity. To assess the extent of collinearity, we will assess variance inflation factors and the standard error estimates for the adjusted model.

We will also measure the receipt of intervention using process data from the NSF team and conduct a dose-response analysis of the program impact. We will categorize patients in the intervention arm into 6 subgroups (brief advice, brief advice + intake, brief advice + intake + 1 follow-up, brief advice + intake + 2 follow-ups, etc). The mobile app will capture this information. While the study is not powered to detect differences between the subgroups definitively, we expect to be able to detect trends in response to the level of receipt of intervention, contingent on the distribution of exposure across subgroups.

Power Analysis and Sample Size

Our sample size estimates were calculated conservatively. Based on the estimates of a risk ratio of 1.75 and the proportion (3.72%) of the control arm who quit smoking (216/5811) in a recent meta-analysis of brief advice interventions [45], we calculated an estimated proportion (6.50%) of the intervention arm who received the brief tobacco intervention and quit tobacco use. We are conducting a cluster RCT with practice settings as the unit of random assignment. Assuming an intraclass correlation of 0.01 and the potential pool of practitioners to be 131, we will need about 36 tobacco-using patients for each practitioner to have a total sample size of 2344 tobacco users per arm, based on a type I error rate of 0.05 and 80% statistical power. Thus, our proposed final sample size is 4688, accounting for 20% attrition among practitioners and 30% among patients. Our effect size estimate is conservative in light of a recent study suggesting a 12.5% quit rate at 6 weeks among smokers receiving behavioral counseling in a pre-post comparison without a control arm receiving standard care in India [9]. Although the 6-month quit rate tends to be lower than the 6-week quit rate after brief advice, we expect our conservative sample size estimate should provide adequate statistical power.

Informed Consent

During their initial in-person training, study staff will review the consent form with practitioners and obtain written consent. Practitioners will take preliminary verbal consent from patients who are interested and eligible and document it in the app. The counselors and data collectors will be able to view patients who have provided preliminary consent. During the first phone call with the patient, the NSF counselor or data collector will review the participation consent form with the referred patients over the phone and answer any questions. The institutional review board (IRB) has granted us a waiver of written consent for the patients, given that they will be interacting with the counselors and data collectors over the phone. After the 6-month follow-up call, if a patient has been randomly selected for cotinine testing, the counselor or data collector will double-check that they still consent to the test. The NSF team will use data from the app to document who has provided consent. It will be made clear during the consent process that all participants (practitioners and patients) may decide not to participate at any time with no consequences.

Privacy and Confidentiality

All identifiable data will be securely stored with the NSF team. They will remove the data of any identifiable information and save the deidentified data in password-protected Cloud-based files. Only deidentified data will be used for analysis. Urine specimens collected for the cotinine tests will be stored securely by the lab conducting the tests in Mumbai, India, for 48 hours after collection.

Compensation Details

All study participants will receive small monetary incentives to express our appreciation for their participation. Practitioners will receive INR 500 (about US $6) for completing each of the following activities: attending training, registering each patient, completing a 3-month posttraining follow-up survey, and completing a 6-month posttraining follow-up survey. Patients will receive INR 500 (about US $6) when they register for the study, INR 200 (a little over US $2) for completing each of the 1-week, 1-month, and 3-month follow-ups, and INR 500 (about US $6) for completing the 6-month follow-up. The patients who undergo cotinine testing will also receive INR 500 (about US $6) for completing the test. Each of the health and TB NGO sites will receive a one-time payment of INR 10,000 (about US $120) per practitioner participating to account for overhead costs. Given that the dentist practitioners operate their own practices, they will not receive a site-level incentive. These amounts were selected based on the NSF team's past experiences delivering similar programs to ensure that the amounts are enough to be meaningful to the study populations but not coercive.

Additional Considerations

All patients in both intervention and control arms will be provided with a pamphlet on the ill effects of tobacco use. Although this is not a "standard of care" in India at this time, it is a common intervention and also accounts for ethical requirements given the degree to which the patients are marginalized and underserved.

No generative language models have been used in this project or this paper.

Ethical Considerations

This study was approved by the Harvard Longwood Campus IRB in Boston (IRB19-0562) on April 25, 2019, and the Joint Ethics Committee for Narotam Sekhsaria Foundation and Salaam Bombay Foundation in Mumbai (JEC/NSF-SBF nAl9lOS) on August 5, 2019. It is registered in ClinicalTrials.gov of the US National Institutes of Health and in the Clinical Trials Registry of India.

Results

Recruitment for the RCT commenced in November 2023. As of July 2024, 102% (135/132) have been recruited and trained, including both the intervention and control arms of all 3 setting types. The 3 extra practitioners trained will provide additional help to address attrition; recruitment and training of practitioners are complete. Approximately 36% of patients (1687/4688) have been registered. The first follow-up has been completed for 93%

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(1460/1574) of the eligible patients; the second follow-up has been completed for 90% (1089/1204) of the eligible patients; the third follow-up has been completed for 87% (583/667) of the eligible patients; and the fourth follow-up has been completed for 76% (188/248) of the eligible patients.

Discussion

Principal Findings

In terms of effectiveness outcomes, it is hypothesized that those patients who participate in the adapted LifeFirst SWASTH program will be more likely to have been abstinent from tobacco for 30 consecutive days at the final (6-month) follow-up compared to those patients in the control arm. Furthermore, the patients assigned to the intervention arm will have decreased their tobacco use, even if they did not quit entirely, compared to those in the control arm at the 6-month follow-up.

There are several limitations to be noted. Although 20% of the subsample will provide biomarker-verified cessation outcomes, the majority of patient-level cessation outcomes will be based on self-report. This allows for the possibility of social desirability bias, as tobacco users may under-report their use. Loss to follow-up, especially in low-resource community settings, remains a limitation that may result in potential bias in missing data for engaging patients for follow-ups and outcome measures. While randomization at the cluster level is an effective approach to mitigate potential contamination, it is possible that even a large cluster RCT may not result in a balance of patient-level characteristics between the 2 arms. Selection bias at both patient- and health care provider or practice levels could affect the causal rigor in ascertaining the trial effect. This trial aims to recruit a large sample of current tobacco users across multiple low-resource clinical settings. The large samples of both health care providers and patients yield important information about the delivery and receipt of the intervention, which will eventually affect tobacco cessation. The longitudinal design involving both short- and long-term follow-ups and repeated measures of tobacco cessation outcomes including biomarker verification on a subset of patients will advance our understanding of both proximal and distal effects of this trial. Longitudinal analysis of these repeated-measures outcomes will elucidate the impact of this pragmatic cessation trial on the behavioral trajectories of tobacco use severity and cessation outcomes.

Conclusions

Given the low-resource and high-reach nature of the intervention, LifeFirst SWASTH could move the needle on tobacco cessation among marginalized groups. Simple brief advice programs have been shown to have an impact of 1%-3% increased cessation rates over no advice, which could translate to 7.8-23.4 million fewer tobacco users in India [45,46]. Programs such as LifeFirst SWASTH that incorporate further counseling are expected to be even more impactful.

In 2022, for the first time, nicotine replacement medications were added to the Indian Ministry of Health and Family Welfare's List of Essential Medicines, marking an important step in the effort to address tobacco use in India. Ultimately, this will allow insurance to cover the medications, and generally, access will increase [10,47]. However, some medications, such as additional pharmacotherapies (bupropion, varenicline, and others) that would benefit smokeless tobacco users, were not included in the list [10]. Brief advice and counseling interventions such as LifeFirst SWASTH do address smokeless tobacco use and will pave the way for interventions to include both behavioral and pharmacotherapeutic components by preparing the system to support both in tandem.

Furthermore, this study has the potential to promote health equity. It is a free intervention that is primarily delivered over the phone, minimizing the burden for lower-SES patients. It will advance the implementation science literature by focusing exclusively on lower-SES populations and identifying ways to tailor implementation strategies to meet their unique needs [48].

LifeFirst SWASTH, if found to be effective in terms of cessation outcomes and implementation processes, has the potential to be scaled to other settings in India and other LMICs. The study will be conducted in low-resource settings that will reach many patients, which will increase the impact if demonstrated to be effective and then scaled. It will use task-shifting and a mobile app that can be tailored to different settings, also enabling scalability. Additionally, its findings will build the literature for translating EBIs from high-income countries to LMICs and from high- to low-resource settings.

Acknowledgments

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Authors' Contributions

This study was conceptualized and the funding was acquired by SR, KV, and HG. SLM conceptualized the paper and wrote the first draft with SR. ZX wrote the first draft of the methodology section. All authors contributed to reviewing and editing the draft and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

5A's framework: ask, advise, assess, assist, and arrange framework
CHW: community health worker
EBI: evidence-based intervention
GATS-2: 2016-2017 Global Adult Tobacco Survey
IRB: institutional review board
LifeFirst SWASTH: LifeFirst Supporting Wellbeing among Adults by Stopping Tobacco Habit
LMIC: low- and middle-income country
MMR: Mumbai Metropolitan Region
NGO: nongovernmental organization
NSF: Narotam Sekhsaria Foundation
PPA: point prevalence abstinence
RCT: randomized controlled trial
SES: socioeconomic status
TB: tuberculosis
WHO: World Health Organization

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Protocol

Dexmedetomidine Versus Midazolam for End-of-Life Sedation and Agitation: Protocol for a Randomized Controlled Trial (The DREAMS Trial)

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Abstract

Background: Sedation at the end of life is used to relieve distressing symptoms including agitation and delirium. Standard care may include infused benzodiazepines or antipsychotics. These agents often result in deep sedation with loss of interaction with loved ones, which may be distressing.

Objective: The DREAMS (Dexmedetomidine for the Reduction of End-of-life Agitation and for optiMised Sedation) trial aimed to compare the sedative and antidelirium effects of the alpha-2 agonist dexmedetomidine, a novel palliative care sedative, compared with midazolam, a benzodiazepine when administered by subcutaneous infusion at the end of life, with doses of both agents targeting lighter, or potentially interactive sedation.

Methods: Participants were recruited from adult inpatients admitted for end-of-life care under a palliative care team in regional New South Wales, Australia. Inclusion criteria included patients older than 18 years, with a preference for lighter sedation at the end of life. Exclusion criteria included severe cardiac dysfunction (contraindication to dexmedetomidine). Participants consented and were placed on a treatment-pending list. Upon experiencing terminal deterioration, patients were randomized to either arm 1 (dexmedetomidine) or arm 2 (midazolam) as their treatment arm. These treatments were administered by continuous subcutaneous infusion. The level of consciousness and agitation of the patients were measured by the Richmond Agitation-Sedation Scale–Palliative version and the Memorial Delirium Assessment Score. Richmond Agitation-Sedation Scale–Palliative version assessments were performed by both nursing and medical staff, while Memorial Delirium Assessment Score assessments were carried out by medical staff only. Families and patients were asked to complete, as able, a patient comfort assessment form, to gauge perceptions of distress. Data were collected and matched with the breakthrough medication doses administered, along with qualitative comments in the medical record. In addition, the study tracked symptoms and patient functional status that were recorded as part of the Palliative Care Outcomes Collaborative, a national tracking project for monitoring symptom outcomes in palliative care.

Results: The DREAMS trial was funded in May 2020, approved by the ethics committee in November 2020, and started recruiting participants in May 2021. Data collection commenced in May 2021 and is anticipated to continue until December 2024. Publication of results is anticipated from 2024 to 2026.

Conclusions: The evidence base for sedative dosing in palliative care for distress and agitation is not robust, with standard care based primarily on clinical experience and not robust scientific evidence. This study is important because it will compare a standard and a novel sedative used in end-of-life treatment. By assessing the potential efficacy and benefits of both, it seeks to optimize the quality of dying by providing targeted sedation that can improve the communication between dying patients and their loved ones.

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Trial Registration: Australia New Zealand Clinical Trials Register ACTRN12621000052831; https://uat.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380889

International Registered Report Identifier (IRRID): DERR1-10.2196/55129

(JMIR Res Protoc 2024;13:e55129) doi:10.2196/55129

KEYWORDS

palliative; sedation; delirium; dexmedetomidine; midazolam; antipsychotics; deep sedation; palliative care; sedative; adult; inpatient; Australia; quality of life; end of life; protocol; dexmedetomidine for the reduction of end-of-life agitation and for optiMised sedation; DREAMS trial; DREAMS; deep sedation

Introduction

Background

Palliative care includes the holistic, person-, and family-centered care provided for patients with a life-limiting diagnosis where the primary goal is to optimize quality of life. At the end of life, patients may experience hardship from an array of distressing symptoms including pain, nausea, agitation, and distress, with up to 88% of patients admitted to a palliative care unit enduring terminal delirium [1]. When targeted symptom management is unsuccessful and patients are distressed, the most appropriate therapy offered may be sedation to relieve these symptoms [2-4] The current standard of care for distress at the end of life includes infused benzodiazepines and antipsychotics, or infused barbiturates in refractory cases [5,6]. In Australia, the injectable benzodiazepine, midazolam, is the typical first-line sedative used, which is in line with the position statement of the Australian and New Zealand Society of Palliative Medicine (ANZSPM) [5] and is consistent with recommendations from the European Association for Palliative Care (EAPC) framework for sedation at the end of life [6].

What constitutes comfort at the end of life is variable, but freedom from pain and severe symptoms along with clear communication is valued by patients and families [7,8]. Patients requiring end-of-life sedation to control their symptoms may appear externally comfortable to their treating clinicians. However, the loss of their biographical life and interactivity is often difficult and distressing to their families and loved ones, as well as to the patients themselves [9]. The use of alternative sedatives to relieve end-of-life distress or delirium that may allow meaningful interaction may be considered desirable if symptoms remain controlled.

There is currently poor-quality evidence for the use of midazolam at the end of life. Doses are based on the outcomes from a total of 319 patients, reported across a series of small case series [10-14], 1 multicenter study [15], and 1 prospective study [16]. There is no evidence base presented for the doses chosen, with usage predominantly predicated on professional consensus and guidelines [5,6]. Despite this, the use of midazolam is recommended as the first-line therapy by palliative care specialist society consensus [5].

Dexmedetomidine is an imidazole alpha-2 receptor agonist commonly used in intensive care and anesthetic settings [17,18]. It exhibits activity in the central nervous system, which includes decreasing sympathetic activation at the locus coeruleus [19]. Patients sedated with dexmedetomidine may achieve a state resembling non–rapid eye movement sleep, may be easily woken, and may interact with often minimal stimulation, as well as a experience a decrease in delirium [18]. Dexmedetomidine was investigated in a pilot clinical trial at the Port Kembla palliative care unit (PKPCU) for agitated delirium at the end of life, with results showing a trend toward interactive sedation and decreased delirium [20].

Dexmedetomidine, outside of the recent pilot trial, has been used in the palliative care setting for intractable pain [21,22], refractory nausea and vomiting [23], and sedation [24,25]. In addition, there is an ongoing clinical trial in palliative medicine investigating dexmedetomidine for delirium (ClinicalTrials.gov NCT04824144). It is currently approved in Australia and the United States for administration at doses of up to 0.7 µg/kg/h by infusion [26]. In intensive care unit settings, its usage has often exceeded this dosage level without significant side effects [16,17]. Traditionally given as an infusion, dexmedetomidine has also been shown to be safely tolerated as a rapid intravenous bolus without significant hemodynamic compromise [27,28].

Dexmedetomidine is also well-tolerated subcutaneously with attenuated side effects [29] and a very low incidence of injection-site reactions [20]

Comparative literature on dexmedetomidine and midazolam is limited, with only a single entry in clinical trial registries (ClinicalTrials.gov NCT01687751). The trial, registered in 2012, focused on using rapidly titrating continuous subcutaneous infusion (CSCI) and was withdrawn before recruitment due to feasibility issues.

Overall, there is limited robust evidence to guide the use of dexmedetomidine or midazolam as end-of-life sedatives in the palliative care population.

Objectives

Given the knowledge gap, the investigators proposed a randomized controlled trial, “Dexmedetomidine for the Reduction of End-of-life Agitation and for optiMised Sedation” (DREAMS). This trial aimed to investigate the use of dexmedetomidine versus midazolam by CSCI in patients for sedation at the end of life. The subcutaneous route was chosen for the DREAMS trial as the preferred route of delivery as this conforms to the current standard of care for medication infusions given to patients under palliative care in Australia [4].

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Hypothesis

Dexmedetomidine provides more interactive sedation at the end of life while maintaining comfort when compared with midazolam.

Primary Objective

The primary objective of this study was to determine if dexmedetomidine is superior to midazolam arousability without agitation as measured by the Richmond Agitation-Sedation Scale–Palliative version (RASS-PAL) [30] in the terminal phase of life.

Secondary Objectives

The key secondary objectives are to determine if dexmedetomidine, for terminal patients, is superior compared with midazolam for (1) reduction in delirium as measured by the Memorial Delirium Assessment Scale (MDAS) [31], (2) reduction in the use of breakthrough medications for symptom burden, and (3) improving perceptions of comfort by families and loved ones as measured by patient comfort assessment (PCA) form [32].

The DREAMS trial is designed as a randomized, controlled, nonblinded multicenter superiority trial with 2 parallel groups and a primary end point of average daily RASS-PAL score during the terminal phase. Randomization will be performed as block randomization, with a 1:1 allocation.

Methods

Trial Setting

The trial was conducted with patients under the care of the palliative care service in the Illawarra Shoalhaven Local Health District in New South Wales, Australia. It was conducted within the palliative care units located across multiple sites, including Port Kembla Hospital, The Wollongong Hospital, and Shoalhaven Memorial District Hospital. Each of the 3 sites was chosen pragmatically with the allocation made of numbers based on their historical referral base. The trial was sponsored by the Illawarra Shoalhaven Local Health District Research Office.

Ethical Considerations

Human Participant Ethics Review Approvals

The DREAMS trial received ethical approval from the joint University of Wollongong (UOW) and Illawarra Shoalhaven Local Health District Human Research Ethics Committee in November 2020 (approval 2020/ETH01943). Research was conducted in line with the National Statement on Ethical Conduct in Human Research, Australia.

Informed Consent

All participants approached in the DREAMS trial provided informed consent. This process included the provision of the participant information sheet, opportunities for discussion with investigators and families, and the assurance that participants could withdraw at any point from the trial. Consent directly from the participant was preferred. However, consent provided by a responsible person (proxy), as permitted under NSW Law [33], was deemed acceptable but not preferred.

Privacy and Confidentiality

All data collected were deidentified before analysis. Preanalysis data are stored in encrypted cloud storage within the NSW Health and UOW networks, with hard copies of data retained within secure health storage.

Compensation

No compensation was provided for participation in the DREAMS trial.

Eligibility Criteria

Participants were considered for recruitment if they met the inclusion and exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Admitted to hospital under a palliative care physician, for end-of-life care.
- English speaking or able to converse through a medical interpreter.
- Adults aged 18 years or older.
- Preference or acceptance of lighter sedation at the end of life expressed by the participant during consent discussions and questions around the trial.

Exclusion criteria

- Known severe left ventricular dysfunction (defined as an ejection fraction of <20% on known echocardiography), in patients with a previous history of heart failure, as available within the past 12 months either by inpatient or outpatient scans.

Participants who consented to take part in the DREAMS trial remained enrolled until death or until choosing to withdraw from participation. If participants did not meet the initiation criteria and therefore could not be randomized, they were automatically withdrawn from the study.

Randomization and Initiation

Participants were randomly assigned to either dexmedetomidine or midazolam through blocks of 6 in a 1:1 allocation as per a computer-generated randomization schedule. Randomization was based on total patient recruitment and was not site-specific. Assignment occurred when participants were determined to be appropriate for treatment by a senior clinician. Appropriateness

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was determined on 2 criteria—a clinician's prediction of survival of 7 days or less and the presence of symptoms of distress requiring treatment with sedative medications at the end of life.

Interventions

Eligible patients were randomized in equal proportions to receive either dexmedetomidine or midazolam. Both drugs, in generic formulations, were purchased through the contract supplier for NSW Health. The doses were targeted based on weight and administered by CSCI using a NIKI T34 syringe pump (CME Biomedical Services) [34]. *Pro re nata* (PRN) subcutaneous bolus injection doses were also available and calibrated by weight with reference to literature as well as previous practice [26,35-37] and the previous trial at the PKPCU [20]. Doses were calculated as per Table 1.

Table 1. Doses of dexmedetomidine and midazolam given per trial. All dexmedetomidine doses were rounded up to the nearest 10 µg, and midazolam infusion doses were rounded up to the nearest 1 mg.

Administration	Dexmedetomidine	Midazolam
Infusion	0.5 µg/kg/h	0.25 mg/kg/d
Breakthrough	0.5 µg/kg every 2 hours	2.5-5 mg every 2 hours

Infusion doses were rounded to the nearest 10 µg (dexmedetomidine) or 1 mg (midazolam) due to the practicalities of ward-based administration, as were dexmedetomidine breakthrough doses. Midazolam breakthrough doses were not rounded up or down. Requirements for breakthrough medications were clinically determined by staff members caring for individual patients in response to symptoms of agitation and distress that did not spontaneously resolve and were distressing to patients or family members. Breakthrough doses were limited to a maximum of 5 doses daily to ensure expedited clinical review if needs exceeded availability. For patients who were not benzodiazepine-naïve, an equivalent use of their previous benzodiazepine [37], converted to midazolam, was added to their calculated dose.

Both midazolam and dexmedetomidine were administered using separate infusion devices to other medications (although in practice both are compatible in admixture) to eliminate potential reactions. Daily intervention delivery and assessments were performed as per Figure 1.

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Figure 1. Trial daily run. MDAS: Memorial Delirium Assessment Scale; RASS-PAL: Richmond Agitation-Sedation Scale–Palliative version; CSCI: continuous subcutaneous infusion.

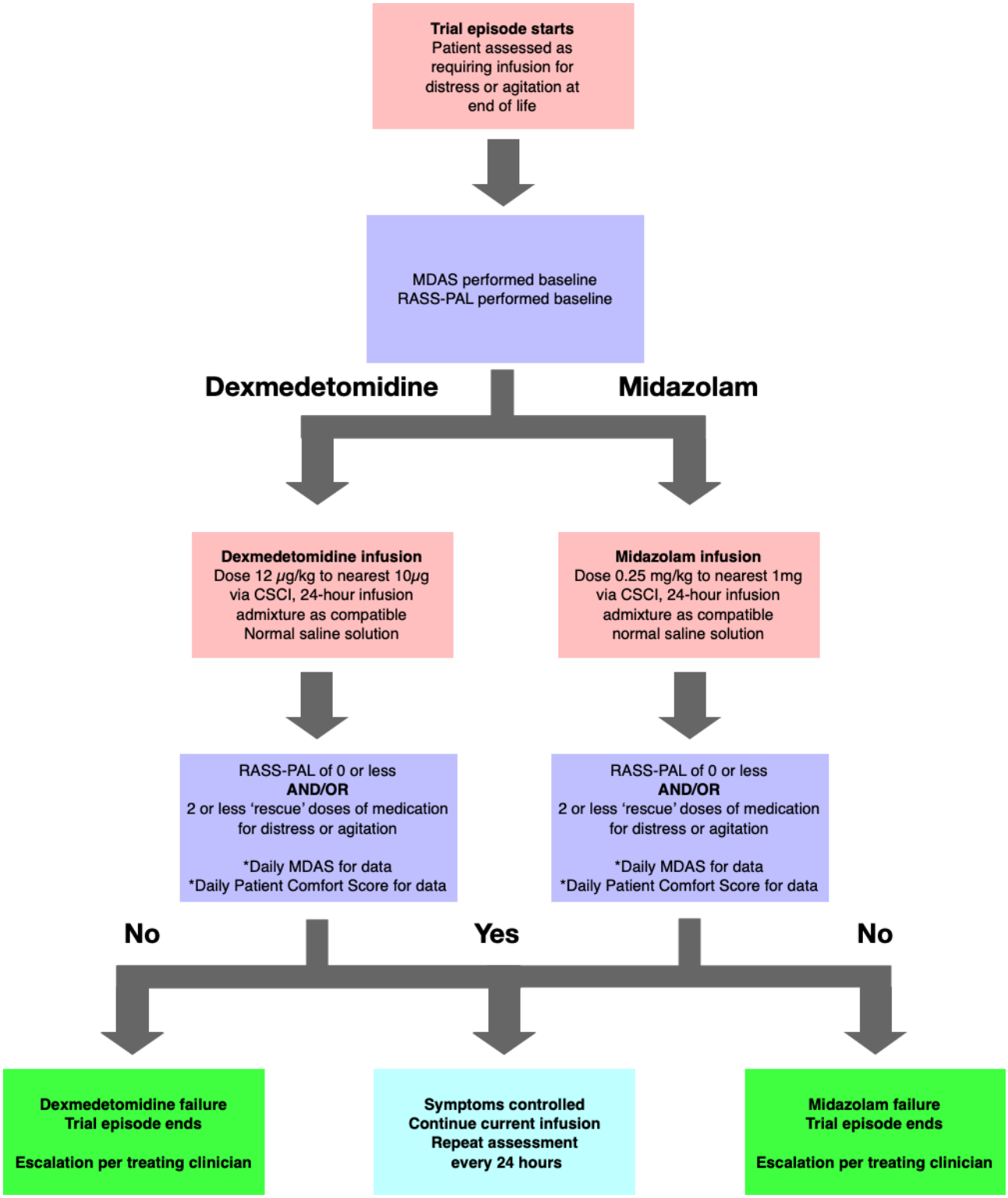

Patients were administered a RASS-PAL and an MDAS on initiation by the treating medical staff, and then a RASS-PAL once per shift by nursing staff. The daily average RASS-PAL score was collated, with a target of 0 or below. If patients remained comfortable and the RASS-PAL score was in the appropriate range, or there had not been a high use of rescue PRN medication for distress (defined as 3+ doses of either dexmedetomidine or midazolam, without other rationale), infusions continued with daily MDAS and regular RASS-PAL assessments. For patients who were uncomfortable, or who had an inappropriate range of RASS-PAL scores or PRN use, trial episodes were ceased, and treatment was continued as per the admitting specialist's clinical discretion, in line with the ANZSPM and EAPC frameworks [5,6].

Regular training sessions were held with staff members involved in the trial. The chief investigator provided group and one-to-one education with nursing and medical staff, which were repeated

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during the trial run at all involved sites. Regular education was scheduled for the primary site at Port Kembla Hospital, with opportunistic education around recruitment performed for the smaller sites. Training included discussion of tools, medications, dosing, side effects, and adverse reaction reporting.

Sample Size

The sample size was calculated based on the primary outcome. Based on an expected between-group difference of 1 unit on the RASS-PAL (10% difference) with an SD of 1.26, it was estimated that each study arm would require 26 patients (52 in total) to achieve statistical significance. This calculation, targeting an α of .05 and 80% power, was performed by the Statistical Consulting Centre, UOW based on an independent sample 2-tailed *t* test for between-group differences.

Recruitment

Each site screened participants according to the inclusion and exclusion criteria (Textbox 1), with varying recruitment targets based on referral rates (40 patients in Port Kembla Hospital, 8 patients in Wollongong Hospital, and 4 patients in Shoalhaven Hospital). The enrollment period initially planned to take place over 18 months, was impacted significantly by the COVID-19 pandemic, leading to an extension of 32-month duration as well as a heavier focus on recruitment at Port Kembla Hospital due to recruitment difficulties at the other sites.

Baseline characteristics of consented patients were collected, including sex, primary diagnosis, background diagnoses, weight, and liver and kidney function. Liver function was assessed by the model of end-stage liver disease-sodium (MELD-Na). Kidney function was assessed by estimated glomerular filtration rate (eGFR). MELD-Na and eGFR were calculated based on the most recent blood tests taken within the past 3 months upon entry into the trial. If no recent blood test was performed, a biochemical profile including serum sodium, bilirubin, creatinine, and international normalized ratio was obtained to perform dose calculations of MELD-Na and eGFR. Weight was used to calculate doses of both dexmedetomidine and midazolam in the event of randomization.

Data Collection and Management

Primary Outcome

Agitation and sedation were measured using the RASS-PAL on all patients on initiation of trial phase, and regularly by nursing and medical staff during their treatment episodes. The RASS-PAL is a 10-point scale, ranging from –5 (completely sedated) to +4 (significant agitation), with a score of 0 indicating alert and calm. The Richmond Agitation-Sedation Scale (RASS) has excellent interrater reliability and has been used in previous studies in palliative care and consciousness [38]. The palliative adapted version of the Richmond Agitation-Sedation Scale (ie, RASS-PAL) was used due to its appropriateness in the palliative care setting, and previous use in palliative care [20,30]. The RASS-PAL was performed every shift by nursing staff, and daily by medical staff.

Secondary Outcomes

Delirium was monitored using the MDAS, which has been validated in cancer delirium and the palliative care population, as well as delirium treated with dexmedetomidine [1,20,31,39]. The MDAS is a 10-item, 4-point clinician-rated scale that is designed to quantify the severity of delirium in medically ill patients [34]. Some patients required pro-rata scoring of the MDAS due to the inability to complete the full item list; this scoring was done in line with the instruction per instrument [31]. Comfort was assessed by patients and carers using the validated PCA [32], which assesses comfort on a 1-10 scale with family comments, as well as recording ratings for specific symptoms including grimacing, groaning, shouting, movements, and labored breathing [32]. Data regarding symptom severity, associated distress, and breakthrough medications administered as well as potential effectiveness are routinely collected and documented in the patient's electronic health record (EHR). These data are also used for reporting and analysis by the Palliative Care Outcomes Collaboration (PCOC), an Australian partnership providing longitudinal data on palliative care outcomes across various sites and services [40]. Palliative Care Outcomes Collaborative data will be matched with the PCA tools collected, facilitating a comparison of family, patient, and staff perceptions of comfort. These will also be correlated to breakthrough and background medication doses as documented in the EHR to assess potential effects.

Data Management

The RASS-PAL, MDAS, and PCA were collected as hardcopy printouts and scanned and stored in secure cloud storage in the NSW Health and UOW networks. EHR data will be extracted and stored in encrypted spreadsheets and within secure cloud storage. Data will be retained for a minimum of 15 years after publication of study results, as per the NSW State Archives and Records Guidance GDA17.

Statistical Methods

The dexmedetomidine arm and the midazolam arm will be compared against one another for all primary analyses. The authors will also perform intra-arm analysis for day-to-day differences in each treatment arm for the MDAS analysis and the RASS-PAL analysis. Binary outcomes will be assessed by chi-square and continuous outcomes by the 2-tailed *t* test. *P* values will be reported to four decimal places, with values less than .001 reported as <.001. We will use 2-tailed *P* values with an $\alpha<.05$ level of significance.

Descriptive statistics will be used where data are not amenable to the above analysis.

Monitoring

A formal data monitoring committee was not established due to the relatively low-risk nature of the study and population. Oversight was provided by 2 senior clinicians associated with the PKPCU, who reviewed interim analysis of the data after the first 10 patients were recruited and were appraised of adverse effects as the trial progressed.

The DREAMS trial used reporting as per Common Terminology Criteria for Adverse Events for adverse event reporting [41]. Minor adverse events deemed secondary to either study drug were recorded by medical staff and will be collated for the therapeutic regulator. Major adverse events requiring immediate

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notification were planned to result in immediate trial episode infusion for affected patients, reversal of adverse effects if clinically appropriate, and reporting to the oversight team and the regulator.

During the clinical phase of the trial, there was only 1 adverse outcome reportable to the oversight team, consisting of an accidental excess breakthrough dose administration of 1 of the trial medications, which resulted in no harm and no adverse outcome to the participant in question.

Results

The study was funded by an Early Career Research Grant from the Illawarra Shoalhaven Local Health District Research Office in May 2020, with ethics approval granted in November 2020. Participant enrollment began in May 2021 and completed in November of 2023. Consent was obtained from 58 patients in total, with only 1 patient declining consent when the trial was discussed. Of the 58 consented patients, 52 in total were treated, 26 per arm, with 6 patients not requiring treatment with a trial medication due to not developing symptoms of agitation or distress in their dying phase.

Data collection is expected to continue until December of 2024. Data analysis is anticipated to begin in mid-2024, with initial results anticipated to be reported on and published after the completion of data collection. Ongoing publications based on ongoing analysis and collection are anticipated to continue in 2025 and 2026.

Discussion

Principal Findings

The DREAMS trial investigators aim to test the efficacy of a novel sedative versus a standard care sedative at the end of life with targeted dose protocols, with the goals of maintaining comfort while improving interactivity and ability for dying patients to interact with their loved ones and thus maximize the quality of dying. It is hypothesized that there will be an observed difference in both sedation and delirium. The protocol for the DREAMS trial has been designed to balance the need for rigorous scientific investigation with the flexibility and pragmatism involved in the provision of end-of-life care to a vulnerable population [42,43]. The trial aims to compare the effects of dexmedetomidine against midazolam through subcutaneous infusion with doses targeting lighter sedation to assess the acceptability and efficacy of both, with a hypothesis to the superiority of dexmedetomidine in maintaining arousability as measured by RASS-PAL. The alleviation of symptoms of pain, agitation, and distress at the end of life will remain paramount, with pragmatic titration of other medications for symptoms provided as per best practice [37,44], to ensure that individual patient needs remain fulfilled.

Strengths and Limitations

This study is notable in being the first randomized controlled trial of midazolam in the palliative care setting, as well as the first to compare novel and traditional sedatives. Significant potential exists to impact the standard of care based on this study's findings, given the lack of robust previous data. The study's methods are limited by a lack of blinding, which was due to a lack of funding for research staff as well as unpredictable time frames and admission numbers that were exacerbated by the COVID-19 pandemic. Randomization by computer-generated allocation was intended to help alleviate bias in treatment provision. Logistical barriers to ongoing education for nursing and medical staff completing trial assessments were identified, with staggered shifts necessitating recurring education to capture the whole cohort of assessors, as well as rotational and casual staff members requiring frequent refresher training. The lack of validated midazolam dosing in palliative care resulted in extrapolation and calculation from the anesthetic literature as well as standard practice [14,36,37].

If the dexmedetomidine intervention proves superior to midazolam, it may result in an increase in the provision of and use of that agent at end-of-life care. Conversely, if midazolam proves noninferior, assuming both agents provide comfort and symptom relief, this could validate both the standard care arm and the novel arm as potentially useful tools for the treatment of symptoms. Analysis of the patient-centered data including the PCA forms and qualitative comments would be of paramount importance then to help discriminate between options, and to aid in improving and optimizing the quality of dying for patients at the end of life.

Acknowledgments

The authors are grateful to Dr Zivai Nangati and Dr Camilla Chan, who assisted in the initial planning phase for the protocol. The study was funded by the Illawarra Shoalhaven Local Health District, with a grant awarded to BT for the purpose of this trial. There was no usage of generative artificial intelligence or other assistance tools in any phase of this manuscript writing or design.

Data Availability

The data sets generated during and/or analyzed during this study will be available from the corresponding author on reasonable request, with appropriate consent from the ethics committee for potential sensitive data release if required.

Authors' Contributions

BT designed the initial trial protocol for clinical use, with GB and W-SAL. BT drafted the manuscript for dissemination and publication, with assistance from JM and KM. All authors critically revised the manuscript and agreed on the final version.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT Checklist.
[PDF File (Adobe PDF File), 83 KB - resprot_v13i1e55129_app1.pdf]

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Abbreviations

ANZSPM: Australian and New Zealand Society of Palliative Medicine
CSCI: continuous subcutaneous infusion
DREAMS: dexmedetomidine for the reduction of end-of-life agitation and for optiMised sedation
EAPC: European Association for Palliative Care
eGFR: estimated glomerular filtration rate
EHR: electronic health record
MDAS: Memorial Delirium Assessment Scale
MELD-Na: model of end-stage liver disease-sodium
RASS: Richmond Agitation-Sedation Scale
PCA: patient comfort assessment
PCOC: Palliative Care Outcomes Collaboration
PKPCU: Port Kembla palliative care unit
PRN: pro re nata
RASS-PAL: Richmond Agitation-Sedation Scale–Palliative version
UOW: University of Wollongong

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Protocol

Evaluation of Comparative Efficacy of Levothyroxine Versus Kshar Basti and Kanchanar Guggul in the Treatment of Hypothyroidism: Protocol for a Randomized Controlled Trial

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Abstract

Background: The thyroid gland is an endocrine gland that has an impact on the body's general metabolism. Thus, the secretions of the thyroid gland can modify the overall metabolism of the entire body. The prevalence of hypothyroidism is increasing quickly, with rates of 2%-5% in affluent countries and 11% in India. Individuals diagnosed with hypothyroidism need to take medication for the rest of their lives, resulting in significant stress. Therefore, conducting a study in this area is imperative.

Objective: This study aims to assess the effectiveness of the therapeutic enema (Kshar Basti) and oral Kanchanar Guggul in the treatment of hypothyroidism.

Methods: The trial group (n=45) will receive a therapeutic enema (Kshar Basti) followed by oral Ayurvedic drugs for 180 days. The control group (n=45) will be given levothyroxine tablets at a dosage of 1.6 µg/kg/day for the same duration. The objective is to examine the alterations in thyroid stimulating hormone (TSH) levels before and after the treatment.

Results: Any deviation of the serum TSH by more than 20% from the initial values, while keeping triiodothyronine (T_3), and thyroxine (T_4) levels within the normal range, will be deemed statistically significant. Consequently, we anticipate a statistically significant variation in serum TSH levels between the therapeutic enema and Kanchanar Guggul treatments. Presently, the drug preparation operations are in progress. We expect to start enrolling patients in June 2024, do data analysis in December 2025, and acquire results by early 2026, marking the end of this trial.

Conclusions: This study will evaluate the efficacy of the therapeutic enema, specifically Kshar Basti, in treating hypothyroidism. Furthermore, more research can determine the efficacy of a therapeutic enema (Kshar Basti) in treating overt hypothyroidism and hypothyroidism during pregnancy.

Trial Registration: Clinical Trials Registry India CTRI/2023/05/052389; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=Nzk1NjY=&Enc=&userName=052389

International Registered Report Identifier (IRRID): PRR1-10.2196/57287

(JMIR Res Protoc 2024;13:e57287) doi:10.2196/57287

KEYWORDS

ayurveda; complementary and alternative medicine; hypothyroidism; levothyroxine; rectal enema; massage therapy; sudation

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Introduction

Overview

Thyroid hormones have various impacts on different biological systems. They play a crucial role in regulating many physiological processes, such as the vascular system, heart function, brain function (including cognition and mood), skeletal muscle, and bone health. Hypothyroidism refers to the inadequate production of thyroid gland secretions.

Hypothyroidism is primarily characterized by subclinical hypothyroidism (SCH), where levels of thyroid stimulating hormone (TSH) are elevated, but both free thyroxine (T_4) and triiodothyronine (T_3) levels remain within the normal range [1]. Overt hypothyroidism (OH) is the second kind of hypothyroidism, characterized by an increase in TSH, a drop in T_4 and T_3 levels, and the presence of clinical symptoms indicating hypothyroidism.

As per recommendations from endocrine societies, SCH is frequently managed with levothyroxine (L-thyroxine). This approach perhaps led to L-thyroxine becoming the most often prescribed medication in the United States starting in 2014, with over 15% of Americans aged 61 years and older using it. A recent extensive study conducted on older adults, known as the TRUST (Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial), along with a subsequent thorough analysis of randomized controlled trials (RCTs), found no evidence of any advantages of L-thyroxine in terms of symptom relief or improvement in quality of life for patients with SCH [2]. Nevertheless, L-thyroxine is typically recommended indefinitely for SCH, which can be stressful for patients [3].

SCH is a burgeoning lifestyle-related ailment in India. In prosperous countries, the prevalence rate of hypothyroidism ranges from 2% to 5%. However, in India, the prevalence rate is 11% [4].

The prevalence rate of hypothyroidism increases with advanced age [5]. The American Thyroid Association guidelines advise the use of L-thyroxine in individuals with SCH and a TSH level of 10 mIU/L or higher. The supposition of SCH leading to OH is the basis of this statement [6].

There are 2 primary issues associated with L-thyroxine therapy, one of which is the uncertainty around the role of L-thyroxine in SCH. There are conflicting observations regarding it, and the patient must take L-thyroxine for the rest of their lives, which is distressing. Hence, there is an urgent requirement for Ayurvedic therapies in SCH.

Ayurveda is practiced in India, Nepal, and Sri Lanka, and is increasingly being adopted in Western countries. Modern medicine has demonstrated efficacy in managing acute medical emergencies, while Ayurveda may effectively handle chronic conditions that pose challenges for Western medical treatment. Individuals diagnosed with hypothyroidism frequently pursue Ayurvedic remedies [7].

Ayurveda recognizes a limited number of disorders that might be associated with hypothyroidism, and by applying Ayurvedic principles, it is possible to effectively manage this illness. Previous research [8] has examined the effectiveness of Ayurvedic treatment for hypothyroidism in multiple studies [9-11]. Nevertheless, these studies are subject to notable constraints, such as the lack of randomization, the absence of consistent therapy in the control group, a poor sample size, and insufficient follow-up time. We have chosen the following research to revise our protocol to overcome their limitations.

A recent study [10] demonstrated that administering Basti for a duration of 30 days, together with oral intake of 1 gram of Kanchanar Guggul twice a day with tepid water, and Vardhaman Pippali for 12 weeks, yielded better results compared to using only Kanchanar Guggul and Vardhaman Pippali in the same dosage for 12 weeks. However, the study conducted for only 12 weeks is inadequate to induce alterations in TSH concentration. Thus, we selected Kanchanar Guggul as the designated medication.

A study [12] indicated that a therapeutic decoction enema (Kshar Basti) was effective in treating hypothyroidism. A 10-day therapy regimen consisting of oral medications and therapeutic enemas using a decoction called Kshar Basti resulted in significant improvement in the symptoms of hypothyroidism. After 2 months of follow-up, the level of serum TSH decreased to 5.76 mIU/L, while T_3 and T_4 remained within the normal range. However, it is important to note that this study is limited to a single example.

Objectives

Research Question

Can Ayurvedic treatments involving Kshar Basti (a therapeutic enema with herbal decoction) and oral administration of Kanchanar Guggul tablet effectively treat SCH?

Hypothesis

In SCH, the administration of Ayurvedic interventions, specifically Kshar Basti (decoction enema) followed by oral Kanchanar Guggul, has the potential to decrease elevated TSH levels while maintaining normal T_3 and T_4 levels.

Primary Objective

The main goal is to ascertain whether Ayurvedic therapy involves the administration of Kshar Basti, which is an herbal decoction enema, followed by an oral tablet. Kanchanar Guggul is efficacious in treating SCH.

Secondary Objective

Our secondary goal is to evaluate the appropriateness of Basti Karma (rectal enema therapy) and determine the dropout rate of the Basti course.

Methods

Overview

To assess and compare the effectiveness of the therapeutic decoction enema (Kshar Basti) and Kanchanar Guggul with L-thyroxine in the treatment of hypothyroidism, we will

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administer the therapeutic enema (Kshar Basti) for 24 days, followed by oral intake of Kanchanar Guggul for 153 days (a total of 180 days) in the study group. In the control group, L-thyroxine tablets will be taken for 180 days. The results will then be evaluated.

Ethical Considerations

This study plan was presented to the Institutional Ethical Committee (IEC) of Mahatma Gandhi Ayurved College, Hospital, and Research Centre, and approval from the IEC has been obtained (Ref. MGACHRC/IEC/May-2022/479, dated May 23, 2022).

The participants of SCH will be informed regarding the ayurvedic procedures and the medications, and their written consent will be obtained on an informed consent form that is prepared in English and Marathi.

Periodically, participants will be required to provide their consent for panchakarma treatments and the collection of blood samples.

Study Setting

This is a single-blind, RCT that aims to determine the superiority of one treatment over another (Figure 1). The study consists of 2 arms and follows a prospective design. Participants will be randomly assigned to either arm in a 1:1 ratio.

The study will be carried out in the Panchakarma department of the hospital affiliated with Mahatma Gandhi Ayurvedic College, hospital, and Research Center (Salod, Wardha district, Maharashtra, India). This study will be conducted following SPIRIT standards for RCTs (Figure 2).

Figure 1. Study design. DM: diabetes mellitus; HTN: hypertension; TSH: thyroid stimulating hormone.

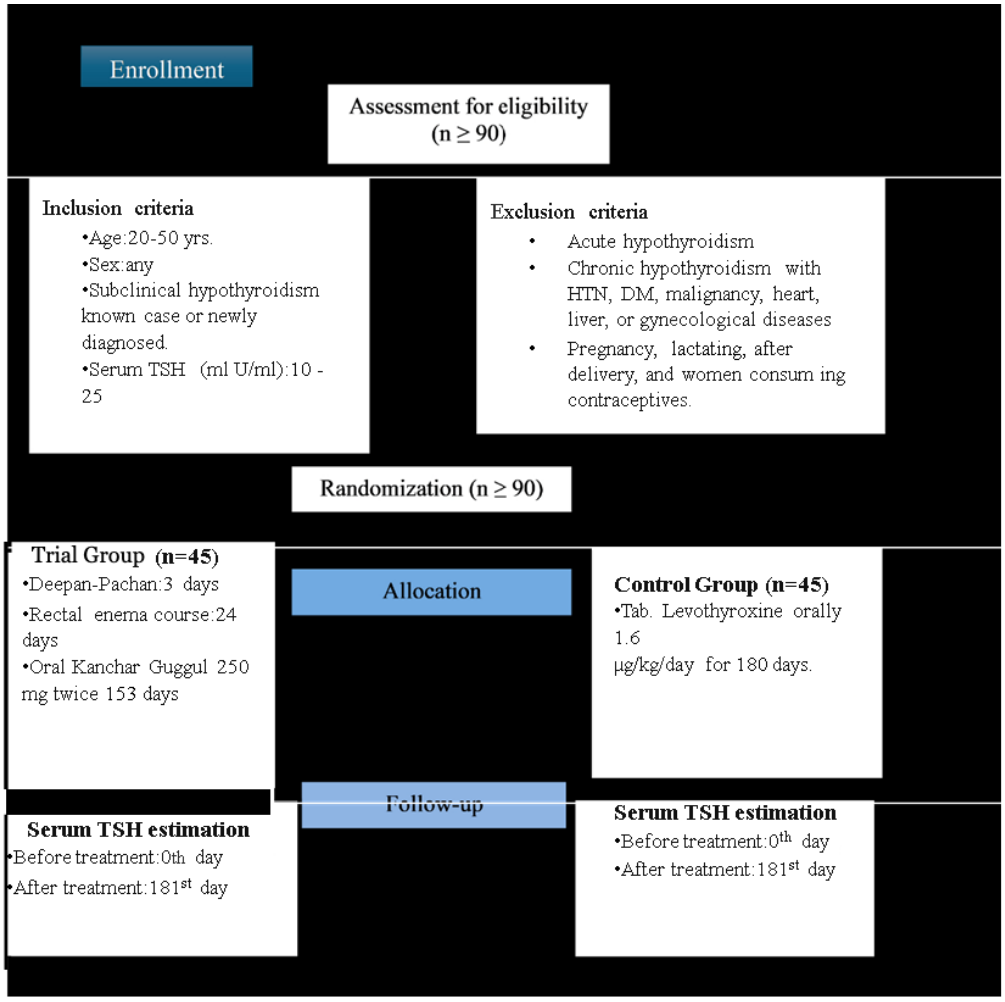

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flowchart.

	Enrollment	Allocation	Post allocation				Closeout
TIMEPOINT			0th day	3rd day	24th day	180th day	181st day
ENROLLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTION							
Deepan-Pachan				←			
Ksharbasti					←		
Tab.Kanchnar Guggul						←	
Levothyroxine Tablets				←		→	
ASSESSMENT							
Baseline			x				
postintervention							X

Diagnostic Criteria

The diagnosis of SCH will be made per the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) criteria (SCH) as follows: TSH>4.50 µIU/mL, fT4=0.8-1.8 ng/dL, fT3=1.4-4.4 Pg/mL [13] (Textbox 1).

Textbox 1. Eligibility, exclusion, withdrawal, and adverse drug reaction criteria.

Eligibility criteria:

1. Age: 20-60 years
2. Sex: Any
3. Known case, or newly diagnosed case of subclinical hypothyroidism

Exclusion criteria:

1. Overt hypothyroidism
2. Subclinical hypothyroidism with Diabetic Mellitus, hypertension, pregnancy, and gynecological disorders
3. Hashimoto thyroiditis
4. Kshar Basti contra-indications

Withdrawal criteria:

The participant may be withdrawn from the trial if there is one of the following:

1. Any adverse event and adverse drug reaction (ADR) occurrence
2. Voluntary withdrawal by the participant
3. Violation of inclusion and exclusion criteria
4. There is noncompliance with the treatment regimen (a minimum of 80% compliance is essential to continue in the study)

ADR

If an ADR occurs during the trial, the participant will be treated at the institute-attached hospital, and the investigators will cover the costs.

Criteria for discontinuing from the trial

If the participant breaks the sequence of panchakarma therapy and misses the oral therapy for ≥7 days, he/she will not be considered in the trial.

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Grouping

The grouping of participants is done in a parallel design where Group A (the trial group) consists of 45 participants and Group B (the control group) consists of 45 participants.

Interventions

In this randomized clinical trial, Group A, referred to as the trial group, will be administered conventional treatment, while Group B, referred to as the control group, will be administered Ayurvedic treatment (Textbox 2 and Figure 1).

Textbox 2. Interventions.

- For Group A (the trial group), the therapeutic decoction enema (Kshar Basti) with oil massage to the whole body, followed by hot fomentation before the enema, will be administered for 8 days. We will use the Course of Eight Therapeutic Enemas (Yoga Basti) method. We will use plain sesame oil for the therapeutic unctuous enema (Anuvasan Basti).
- For Group B (the control group), levothyroxine tablets at a dose of 1.6 µg/kg/day will be administered for 180 days.

Randomization

We will apply random allocation to recruit the participants in the study. Computer-generated random numbers will be used.

Blinding

The allocation will be researcher blind. A third person, such as a nurse or panchakarma therapist, will help to allocate the participant using computer-generated random numbers. Since this study is researcher-blind, a PhD guide will allocate and assign the participants.

Screening Investigations

Serum TSH will be measured before and after the study. On the 181st day, serum TSH, T_3, and T_4 will be measured. The above findings will be compared to the baseline findings.

Criteria of the Assessment or Outcome Variable

A variation of more than 20% of the baseline value of serum TSH with normal values of T_3 and T_4 will be considered to determine the efficacy of the intervention. Therefore, decreasing serum TSH with no change in T_3 and T_4 means, Kshar Basti with Kanchanar Guggul is efficacious in SCH.

Interventions for the Study Group

Deepan-Pachan

Shivakshar Pachak Churna is an Ayurvedic medication that should be taken orally, with a dosage of 1 gram, twice a day, for 3 days (Table 1). Before commencing Basti therapy, it will enhance the appetite, a crucial factor. The preparation will be conducted in the pharmacy that is connected to our institute.

Table 1. Contents of Shivakshar Pachak Churna.

Ayurvedic name	Latin name/English name
Sunthi	*Zingiber officinale*
Marich	*Piper nigrum*
Pippali	*Piper longum*
Ajmoda	*Trachyspermun roxburghianum*
Jeeraka	*Cuminum cyminum*
Krishnajeerak	*Nigella sativa*
Hingu	*Ferula asafoetida*
Haritaki	*Terminalia chebula*
Saindhav	Rock salt
Sajjikshar	Carbonate of soda

Kanchanar Guggul [10]

It will be prepared in the pharmacy attached to our hospital. It will be designed per the standard operating procedure (SOP) mentioned in the pharmacy attached to the hospital. The contents are provided in the table (Table 2).

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Table 2. Contents of Kanchnar Guggul.

Ayurvedic name	Latin name
Kanchanar	*Bauhinia variegata linn*
Amalaki	*Embelica officinalis*
Haritaki	*Terminalia chebula*
Bhibtak	*Terminalia bellirica*
Pippali	*Piper longum*
Varuna	*Crateva religiosa*
Dalchini	*Cinnamomum cassia*
Ela	*Elettaria cardamomum*
Tejpatra	*Cinnamomum tamala*
Guggul	*Commiphora wightii*

Kshar Basti and Its Procedure

Preoperative

Kshar Basti [12] is a therapeutic decoction enema [14]. Therefore, we will follow the same operative procedures that apply to Niruha Basti. The Yoga Basti method (Figure 3) will administer Niruh Basti and Anuvasan Basti (therapeutic unctuous enemas) on alternate days, except the last day. For 3 days, we will administer Deepan-Pachan, which enhances metabolic fire. Kshar Basti's decoction will be prepared per the SOPs followed in the hospital. Table 3 lists Kshar Basti's contents. For the Anuvasan Basti, we will use plain sesame oil. We will call the participants to the hospital early for the Kshar Basti during the day (before 3 PM). Sesame oil massage and hot fomentation will be performed on the whole body. The fomentation will be conducted as per the SOPs of the hospital as mentioned by the National Accreditation Board for Hospitals.

Figure 3. Intervention details. KB: Kshar Basti; OE: oil enema; SCH: subclinical hypothyroidism.

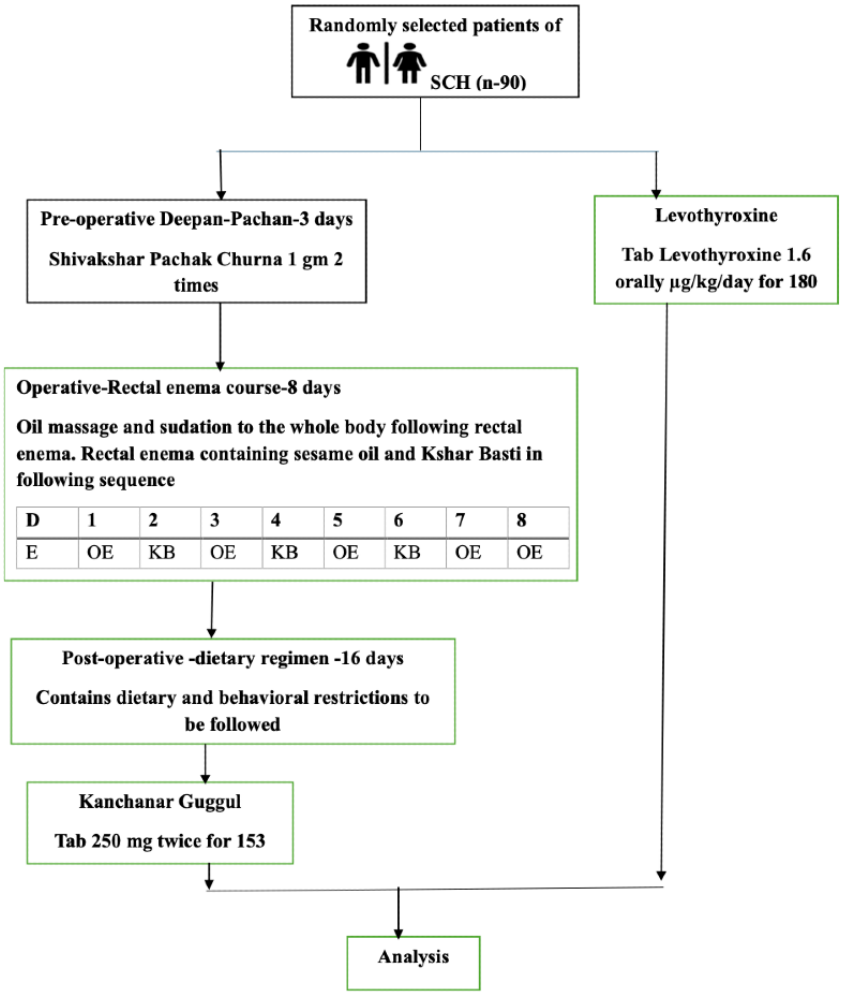

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Table 3. Contents of Kshar Basti.

Content	Quantity
Jaggery (Guda)	100 g
Tamarind pulp (Amlika)	100 g
Rock salt (Saindhav)	10 g
Cow's urine (Gomutra)	400 mL
Paste of Anthem Sova (Shatavha Kalka)	10 g
Total	500 mL

Operative

The raw medicines will be collected, prepared, and made lukewarm by indirect heating. Materials will be taken into an enema can. The participant will be asked to lie over the table in the left lateral position. The nozzle of the enema can be slowly inserted into the anal canal after applying oil to it. It will be slowly inserted till it reaches the rectum, and now the decoctions will enter the rectum. Soon after the administration of Kshar Basti, the participant will be allowed to defecate.

Postoperative Period

The participant will be asked to follow a dietary regimen like Yusha (a soup of vegetables or pulses) and rice and drink hot water during the Kshar Basti course.

Course Duration

Basti will be administered daily for 8 days; after that, the participant must follow the regimen for 16 days. The total duration of the course will be 27 days (including Deepan-Pachan for 3 days), and after this course, Kanchanar Guggul will be administered for 153 days. The duration of the therapy will be 180 days, and the follow-up period will be 180 days.

Both groups of patients are restricted from taking or consuming any medications, devices, or nonpharmacological treatments that have an impact on hypothyroidism.

Sample Size Calculations

We used the following formula for the determination of sample size (N=40) [15]:

Thus, there will be 45 participants in each group (5 added to minimize the error), and our study's sample size will be 90 (n=90).

We also noted the sample size utilized in past studies conducted on hypothyroidism at this institute. Thus, a sample size of 90 would be both practical and adequate.

(N=size per group; $z_{1-\alpha}$= the standard normal deviate for one group; $z_{1-\beta}$= the standard normal deviate for the other group, δ_0= a clinically acceptable margin.)

Data Collection Methods

The researcher will gather and archive the data. The data will be collected using appropriate software, such as Epi-Info. We will examine the data after the trial concludes. Replicates will be discarded. We will choose a conventional laboratory to quantify serum TSH.

Data Confidentiality

Only the PhD guide will have access to the acquired data, which includes biological samples from the individuals. However, upon completion of the study, any researcher may request access to the data for a systematic review and meta-analysis.

Audit

We will conduct the audit 6 months after the trial begins, under the supervision of a PhD mentor. Furthermore, we will closely observe and track any negative reactions caused by the drugs or treatments used in our operations, as well as ensure strict adherence to the established protocol.

We will educate the participants about the favorable attributes of Kshar Basti (the therapeutic enema), to ensure their compliance with the treatment regimen and adherence to the established procedures. We will closely observe the reduction in participants from this experiment and the factors contributing to this reduction.

Statistical Analysis

After summarizing the data, we will use the Kolmogorov-Smirnov test to decide if the data are following a normal distribution. If normally distributed, the student *t* test will be used; otherwise, the z-test will be applied. We will use IBM SPSS (version 26) for statistical analysis. We will set the *P* value to less than .05 for statistical significance.

Results

Overview

We will examine the following factors in the demographics: age, gender, location, smoking behavior, alcohol consumption, and the type of salt used to achieve the secondary purpose of this study. We will examine the rate at which participants drop out of the Kshar Basti course, as well as any occurrences of difficulties associated with the Kshar Basti course.

We will only recruit participants for this study once. We will finish the drug preparation and acquisition by June 2024. The projected timeline for the recruitment process is June 2024 to December 2025. We will evaluate the information right away and conclude at the start of 2026.

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Evaluation Outcomes

The primary assessment result of our study is the disparity in the TSH, T3, and T4 levels compared to the initial values. We will deem any deviation of 20% or more from the baseline as statistically significant.

Discussion

Principal Findings

The 45 participants in the control group will receive oral L-thyroxine. On the other hand, the trial group, also consisting of 45 participants, will get a treatment involving Kshar Basti and oral Kanchnar Guggul tablets. Both groups will undergo treatment for 180 days, and on day 181, we will assess the levels of TSH, T3, and T4 in the blood. We will compare the changes before and after therapy. We expect that the Ayurvedic intervention, specifically the combination of Kshar Basti and Kanchnar Guggul, will demonstrate statistically significant outcomes compared to the standard treatment. This would establish Ayurvedic intervention as a viable treatment option for SCH, eliminating the need for lifelong consumption of L-thyroxine tablets by the patient.

Hashimoto thyroiditis typically correlates with hypothyroidism. The thyroid gland produces numerous growth and vasoactive substances. The epithelial cells of the thyroid gland contain the glycoprotein known as vascular endothelial growth factor. It plays a critical role in the elevated levels of TSH in SCH.

A study compared the administration of Nigella sativa powder at a dosage of 2 grams per day for 8 weeks with the administration of placebos consisting of starches at the same dosage and duration. This RCT involved 47 human participants diagnosed with Hashimoto thyroiditis. Nigella sativa treated 23 of them, while starches served as a placebo for the remaining 24. The study determined that Nigella sativa seeds were useful in alleviating Hashimoto thyroiditis. It also successfully reduced vascular endothelial growth factor levels and body weight.

In Ayurveda, Nigella sativa is referred to as “Krishnajeeraka.” In our study, we will be administering Shivakshar Pachak Churna as “Deepan-Pachan” for the first 3 days. Nigella sativa is a constituent of Shivakshar Pachak Churna [16].

In a separate trial [17], the authors randomly assigned 53 individuals with hypothyroidism to either the treatment group or the control group, administering a placebo to the latter. The ginger group, consisting of 27 participants, was given a 500 mg capsule containing ginger twice a day, whereas the placebo group, consisting of 26 participants, was given starch. This treatment lasted for 30 days. Both groups were administered L-thyroxine. The thyroid symptoms rating questionnaire was used to evaluate the results. The initial findings of this trial showed that individuals with primary hypothyroidism who consumed ginger powder daily while receiving appropriate hormone replacement therapy (achieving biochemical euthyroid) experienced a notable decrease in symptoms associated with hypothyroidism. Our study incorporates Zanzibar as a component of the “Shivaksharpachak Churna.”

Basti therapy is recommended for the treatment of numerous physical and psychological conditions [18]. Immunomodulation was observed following Basti, according to a study that evaluated the metabolic and immunologic response to Basti therapy. One potential mechanism by which it operates is by modulating T cells, immunoglobins, and proinflammatory mediators.

A study [17] found that over 50% of people with hypothyroidism have small intestinal bacterial overgrowth (SIBO). The study found that 54% of hypothyroidism patients tested positive for SIBO using the glucose breath test, compared to 5% in the control group. Diarrhea is a common symptom among hypothyroidism patients, with a positive hydrogen breath test and antibiotic response indicating SIBO. Hypothyroidism can cause less movement in the gastrointestinal tract, leading to long-lasting gastrointestinal problems.

An additional investigation [18] demonstrated that 300 mg of Ashwagandha root extract twice daily for 8 weeks produced statistically significant outcomes. The impact of Ashwagandha root extract on the hypothalamic-pituitary-thyroid axis was hypothesized by the authors. Ashwagandha has antidopaminergic and anti-inflammatory properties. These characteristics may contribute to the thyroid-modulating effect.

Kshar Basti is a therapeutic mixture containing Tamarindus pulp, which acts as a laxative and helps alleviate gastrointestinal troubles [19]. Jaggery is beneficial for the gut microbiota [20]. It is believed that Shatavha (Anthem sowa) possesses estrogenic characteristics [21]. It affects the blood, bones, and central nervous system. The rock salt contains sodium, potassium, and chloride ions [22]. It causes the solution to become hypertonic. Guggul is derived from the latex of the Guggul plant. Recently, an article revealed the antihypothyroidism properties of the Guggul herb [23]. Therefore, the Ayurvedic treatment involving Kshar Basti and Kanchnar Guggul is believed to enhance the immune system and alleviate SCH.

The efficacy of Kshar Basti and Kanchanar Guggul in the treatment of hypothyroidism can be substantiated with dependable evidence in this study, owing to its RCT design and moderate sample size of 90. In addition, the duration of the study will be 180 days, which is sufficient to detect fluctuations in TSH and thyroid hormone levels.

Principal Results

The primary findings will establish that the Ayurvedic therapy including Kshar Basti (administration of herbal decoction through enema) followed by oral administration of Tab Kanchanar Guggul is effective in treating hypothyroidism.

Publication Plan

We intend to disseminate the results of our study by publishing it as either an original research article or a short communication in a journal that is indexed.

Limitations

Our investigation has some limitations. To begin with, 90 samples is still a moderate amount. To account for this prevalence rate, a minimum of 300 samples would be adequate.

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The duration of treatment is extended. Consequently, a large dropout rate is possible. Hence, a practical sample size of 90 was selected.

The preventive effect of these Ayurvedic interventions on SCH cannot be determined through our research. To accomplish this, an additional observational study with a minimum 1-year follow-up period is required.

Conclusions

Our proposed study will evaluate the effectiveness of Ayurvedic intervention, specifically Kshar Basti and oral Kanchanar Guggul tablets, in managing SCH. Additionally, we will assess the appropriateness of the Kshar Basti course. The findings of this study will provide evidence for the use of Ayurvedic treatment as an option for SCH.

We suggest doing a further investigation to assess the independent effectiveness of Kshar Basti and Kanchanar Guggul in alleviating OH. There is a need for a study to assess the effectiveness of these Ayurvedic therapies in treating hypothyroidism during pregnancy.

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Authors' Contributions

SPK reviewed the literature, conceptualized the study, presented it to the Institutional Ethical Committee (IEC), obtained the IEC approval, and prepared the manuscript and its revision. SP reviewed the literature, conceptualized the study, guided the presentation to IEC, and helped to prepare the manuscript and revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 151 KB - resprot_v13i1e57287_app1.pdf]

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Abbreviations

***ICD-10*:** *International Statistical Classification of Diseases, Tenth Revision*
IEC: Institutional Ethical Committee
L-thyroxine: levothyroxine
OH: overt hypothyroidism
RCT: randomized controlled trial
SCH: subclinical hypothyroidism
SIBO: small intestinal bacterial overgrowth
SOP: standard operating procedure
T3: triiodothyronine
T4: thyroxine
TRUST: Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial
TSH: thyroid stimulating hormone

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Protocol

Examining the Acceptability of Helminth Education Packages "Magic Glasses Lower Mekong" and "Magic Glasses Opisthorchiasis" and Their Impact on Knowledge, Attitudes, and Practices Among Schoolchildren in the Lower Mekong Basin: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Helminths are a major global health issue, impacting health, educational, and socioeconomic outcomes. Infections, often starting in childhood, are linked to anemia, malnutrition, cognitive deficit, and in chronic cases of *Opisthorchis viverrini* (OV), cholangiocarcinoma. The main control strategy for helminth infection is mass drug administration; however, this does not prevent reinfection. As such, prevention strategies are needed. The "Magic Glasses" is a school-based cartoon health education package that has demonstrated success in improving knowledge, attitudes, and practices (KAP) surrounding soil-transmitted helminths (STH) in China and the Philippines. This study is designed to assess the acceptability and impact of the 2 new versions of the Magic Glasses targeting STH and OV designed for the Lower Mekong audience in Cambodia, Lao People's Democratic Republic (PDR), and Thailand.

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Objective: The objective of this study is to evaluate the acceptability of the "Magic Glasses Lower Mekong" and "Magic Glasses Opisthorchiasis" education packages among schoolchildren in the Lower Mekong Basin, and the impact of these education packages on students' KAP surrounding STH and OV, respectively.

Methods: Schoolchildren will be recruited into a cluster randomized controlled trial with intervention and control arms in rural schools in Cambodia, Lao PDR, and Thailand. Schoolchildren's initial acceptability of the intervention will be evaluated using an adapted questionnaire. Sustained acceptability will be assessed at 9-month follow-up through focus group discussions with students and interviews with teachers. Impact will be evaluated by KAP questionnaires on STH and OV. KAP questionnaires will be administered to children at baseline and at follow-up. Indirect impact on parents' KAP of OV and STH will be assessed through focus group discussions at follow-up.

Results: The trial is in progress in Lao PDR and Thailand and is expected to commence in Cambodia in January 2024. The results of the study are expected to be available 18 months from the start of recruitment. We hypothesize that participants enrolled in the intervention arm of the study will have higher KAP scores for STH and OV, compared with the participants in the control arm at follow-up. We expect that students will have initial and sustained acceptability of these intervention packages.

Conclusions: This trial will examine the acceptability of the "Magic Glasses Opisthorchiasis" and "Magic Glasses Lower Mekong" interventions and provide evidence on the effectiveness of the "Magic Glasses" on KAP related to OV and STH among schoolchildren in the Lower Mekong Basin. Study results will provide insight on acceptability and impact indicators and inform a scaling up protocol for the "Magic Glasses" education packages in Cambodia, Lao PDR, and Thailand.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12623000271606; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=385315&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/55290

(JMIR Res Protoc 2024;13:e55290) doi:10.2196/55290

KEYWORDS

attitude; child; health education; helminths; knowledge; practices; Opisthorchis viverrini; randomized controlled trial; schools; Ascaris lumbricoides; Trichuris trichiura; hookworm; Magic Glasses

Introduction

Background

Helminthiases, or infections caused by parasitic worms, are a major global health concern [1]. Communities impacted by poverty and located in tropical regions, such as the Lower Mekong Basin (LMB; a region including Cambodia, Lao People's Democratic Republic [Lao PDR], and northeast Thailand) are particularly vulnerable to such infections. The most common helminthiases in the LMB are soil-transmitted helminths (STH)—including *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma* spp. and *Necator americanus)*—and *Opisthorchis viverrini* (OV), commonly known as the Southeast Asian liver fluke [2]. Reported prevalence of STH infections have reached 74% (227/308) [3], 83% (134/162) [4], and 28% (24/85) [5], in Cambodia, Lao PDR, and Thailand, respectively. OV is estimated to affect 10 million people in the LMB, the highest reported burden globally [6,7]. Several studies have reported high incidence of helminthiases among preschool- and school-aged children (SAC), often with high infection intensity [2,8-11]. Kaewpitoon et al [2] reported overall STH prevalence of 11.88% (233/1957) among SAC in the LMB in 2015; however, in some areas, prevalence reached 16.08% (152/945). Given the low sensitivity of the Kato-Katz thick smear technique used (particularly for low intensity infections), it is also possible that infection prevalence in the region was underestimated [12]. While there is limited research on OV burden in children, Yoshida et al [13] reported an OV infection rate of 39% (64/164) among children in secondary school in Vientiane, Lao PDR. Helminthiases are associated with stunting, malnutrition, anemia, chronic pain, fatigue, and cognitive deficit [14-17]. In addition, chronic OV infections are causally linked to cholangiocarcinoma, a cancer of the bile duct [18]. Transmission route varies by helminth type: STH is typically transmitted via contact with egg-infected soil, such as consumption of contaminated fruit or vegetables, or playing in contaminated outdoor spaces [19]. OV is transmitted via ingestion of raw or undercooked infected freshwater cyprinid fish [20]. The primary control strategy for STH and OV infection is mass drug administration (MDA); STH infection is typically treated with benzimidazole anthelmintics [19]. Treatment efficacy varies against species: cure rates exceed 90% for *Ascaris*, 50% for hookworm species [21], and 25% for *Trichuris* [22]. The recommended treatment for OV is praziquantel [23]. Several studies have found praziquantel to be highly efficacious against OV infection, with cure rates exceeding 90% [24,25]. However, while MDA is effective in treating helminthiases, it does not prevent reinfection. As such, further measures such as education on helminth control and prevention are needed.

Children are an important group for targeted behavioral and educational interventions. Between the ages of 5 and 12 years, children undergo major cognitive growth, including the formation of beliefs and attitudes [26,27]. Health education during this period can inform long-term habits and behaviors [26-28]. SAC are also a well-placed group for intervention delivery, as schools are institutions trusted by children and their families, and can facilitate delivery to a large population, as recognized in World Health Organization's (WHO) Global School Health Initiative [29].

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The "Magic Glasses" is a school-based cartoon health education package that has demonstrated success in improving STH knowledge and attitudes, improving water, sanitation, and hygiene (WASH) practices and reducing disease burden in affected communities [30,31]. The intervention is designed to be relatable and engaging for children, with the cartoon set in the local context, and the protagonists being schoolchildren who learn about STH transmission, symptoms, treatment, and prevention as they explore their community [30,31]. The original "Magic Glasses" in China achieved major improvements in self-reported STH knowledge, attitudes and behaviors, as measured by a knowledge, attitudes, and practices (KAP) questionnaire: the intervention group scored 24.9 percentage points higher than the control after adjusting for baseline scoring (95% CI 23.4-26.4; $P<.001$) [31]. Overall KAP scores were inversely correlated with STH infection, with uninfected students scoring 9.9 percentage points higher than infected students (95% CI 5.8-14.0; $P<.001$) [31]. With respect to infection burden, the intervention led to a 50% decrease in STH incidence among intervention schools (odds ratio 0.5, 95% CI 0.35-0.70; $P<.001$) [31]. From 2016 to 2017, the "Magic Glasses" educational package was adapted for the Philippines, a country with estimated 33% STH prevalence [30]. "Magic Glasses Philippines" led to significant improvements in knowledge and behavior among intervention schools scoring 5.5 percentage points higher than control schools in the knowledge component of the KAP questionnaire (56.8, 95% CI 55.7-57.9 vs 51.5, 95% CI 50.3-53.7; $P<.001$) and 1.1 percentage points higher in the behavioral component (87.2, 95% CI 86.6-87.9 vs 86.1, 95% CI 85.4-86.8; $P=.002$) [30]. With respect to disease burden, the intervention achieved a 60% reduction in the odds of any STH infection in intervention schools with a baseline prevalence <15% (adjusted odds ratio 0.4, 95% CI 0.20-0.70; $P<.001$), although it is important to note that the intervention did not significantly reduce odds of infection when higher prevalence schools were included [30]. Following the success of the "Magic Glasses Philippines" trial, the intervention is now being recommended for roll-out across the Philippines as part of the school curriculum.

The present study is designed to assess the acceptability of 2 new "Magic Glasses" cartoons, developed for the LMB, and their impact on schoolchildren's self-reported KAP of STH and OV. Several studies have identified acceptability as a key indicator for initial and sustained intervention success [32-36]. However, there remains a lack of consistency among acceptability measures and definitions in public health research. Sekhon et al [37] developed the Theoretical Framework of Acceptability (TFA), and defined acceptability as "a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" [37]. The TFA outlined 7 domains of acceptability, "affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy" [37]. In order to conduct a robust assessment of all the domains of acceptability, the acceptability of the intervention will be assessed using mixed methods. Quantitatively using an adapted version of the TFA questionnaire [38] and qualitatively using focus group discussions (FGDs) with schoolchildren and key informant interviews (KIIs) with teachers. The KAP questionnaire will be administered at baseline and follow-up to assess the impact of the intervention, and the intervention coherence domain of acceptability.

Aims

While previous Magic Glasses studies have demonstrated the impact of the cartoon in improving KAP surrounding helminths, a more detailed assessment of acceptability is required. Firstly, this study aims to determine whether the "Magic Glasses" OV and STH video education packages will be acceptable to schoolchildren and their teachers in LMB. Secondly, this study will be the first "Magic Glasses" to target OV, in addition to STH. Finally, this study aims to determine the impact of the "Magic Glasses" cartoons on students' KAP on OV and STH infection.

Methods

Trial Design

The trial is a cluster randomized controlled trial (cRCT) with 2 arms, intervention and control. As the intervention will be delivered through schools, a cRCT design was chosen for practical reasons and to minimize contamination. Each school participating in the trial is a "cluster." Schools will be randomly allocated to intervention and control. Schools in the intervention arm will receive the "Magic Glasses" education package developed for LMB, consisting of "Magic Glasses Opisthorchiasis" (MGO) and "Magic Glasses Lower Mekong" (MGLM), in addition to the standard health education activities in accordance with local government guidelines. Schools in the control arm of the study will receive the standard health education activities only in accordance with local government guidelines.

Ethical Considerations

The study will be conducted in accordance with the ethical principles of the Australian National Statement on Ethical Conduct in Human Research [39]. Prior to data collection, an information sheet detailing the purpose of the study, potential risks, research contact information, and informed consent form in the local language will be distributed to parents and caregivers. Only schoolchildren who have provided informed assent and parental consent will be included in the study. Participants will not receive compensation for their involvement in the study but will be able to withdraw at any time. In the case that a participant does withdraw from the study, their responses will not be used in analyses. All quantitative data will be collected on paper questionnaires. Qualitative data (KIIs, FGDs) will be recorded using audiotapes and transcribed. To protect participant privacy, all responses will be deidentified prior to data analyses.

The study protocol was submitted to and received ethical approval from the Australian National University Human Ethics Committee (approval number 2022/507), the Cambodia Ministry of Health National Ethics Committee for Health Research (N197NECHR dated June 27, 2023), the Lao PDR Ministry of Health National Ethics Committee for Health Research, and

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Khon Kaen University Ethics Committee for Human Research (HE651147, record number 4.2.03:16/2565). The study is registered at Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12623000271606.

Setting

The trial will be conducted in rural primary schools in Preah Vihear Province, Cambodia; Savannakhet Province, Lao PDR, and Khon Kaen Province, Thailand. To maximize homogeneity within each country, schools will be recruited from the same district where possible. To minimize the risk of contamination, all control and intervention schools will be at least 3 km apart.

Participants

A total of 684 schoolchildren in Grades 3-6 from randomly selected schools in Cambodia, Lao PDR, and Thailand will be recruited into the study cohort and followed up approximately 9 months after baseline. During the follow-up period, 1 teacher and 3-5 parents will be recruited from each intervention school.

Eligibility Criteria

Among the recruited schools, children across Grades 3-6 who provided consent and assent will be eligible for this study.

Consent and Recruitment

Based on local expertise on school student numbers in each country, approximately 6 schools will be selected in each country to achieve a total sample size of 228 per country. Prospective schools will be selected in consultation with the local departments of education. Once schools are identified, permission to conduct the study will be sought from the principal of each selected school. Teachers and parents or legal guardians of prospective participants will then receive an information sheet outlining the procedure and purpose of the study and contact information, and a consent form. On receiving the written parental or guardian consent, the aims, process, and outcome of study will be explained to prospective student participants and their written assent will be sought. Only schoolchildren who have provided informed assent and parental consent will be included in the study. Teachers and parents will be recruited a month before follow-up. As part of the recruitment process, an information sheet will be provided and informed consent will be sought. Once written consent is obtained, teachers and parents will be recruited into the study.

Randomization

Schools within each country will be randomly allocated to control or intervention arm using Microsoft excel (Microsoft 365) RAND function. Allocation will remain for the duration of the project.

Blinding

Blinding will not be possible in this cRCT. Due to the nature of the intervention, participants will be aware of whether they are in the intervention or control arm.

Intervention

The “Magic Glasses” education package will be comprised of two animated cartoon packages developed specifically for the Lower Mekong setting: (1) MGO, an educational cartoon addressing OV infection, including transmission, symptoms, treatment, and prevention, and (2) MGLM, an educational cartoon addressing STH infection, including transmission, symptoms, treatment, and prevention. Each package includes an educational cartoon, an accompanying comic pamphlet with key messages and images from the cartoon, and engaging reinforcement activities for students (drawing competition and essay competition).

Cartoon Production

The MGO and MGLM interventions were adapted from previous Magic Glasses interventions [30,31], informed by literature reviews on risk factors and KAP regarding STH and OV in LMB. In line with previous “Magic Glasses” cartoons, the health messages of the cartoon were informed by developmental psychology theories including the Theory of Planned Behavior [40] and Social Cognitive Theory [41] to promote engagement and effectiveness with schoolchildren. In order to ensure that the cartoon style and backgrounds are relevant to SEA audiences, the cartoons were produced by 2D animation company, a Thai animation company based in Khon Kaen. Once the Thai versions of MGO and MGLM were finalized, Cambodian and Lao versions of each cartoon were adapted to include culturally appropriate attire and local languages (see Figure 1). The dialogues for each country’s cartoons were then recorded by voice actors in Thai, Khmer, and Lao. In total, 6 cartoons were developed.

Figure 1. Cambodia, Lao, and Thai versions (left to right) of the Doctor character in the “Magic Glasses Opisthorchiasis” and “Magic Glasses Lower Mekong” educational cartoons.

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Comic Pamphlet

A comic pamphlet was developed for OV and STH summarizing the key health messages for each cartoon. The images included in the OV and STH comic pamphlet were taken from the health message summary at the end of the MGO and MGLM cartoon, respectively.

Study Procedures

Study commencement will be staggered across Thailand, Cambodia, and Lao PDR, based on the school periods in each country. Prior to study commencement and intervention delivery, all study materials will be translated into the local language by the local research team in each country. For anticipated study dates in each country, see Multimedia Appendix 1.

Baseline KAP Assessment

Prior to intervention delivery, all consenting participants in Grades 3-6 in control and intervention schools will complete 2 questionnaires on KAP surrounding OV and STH. The first questionnaire will include questions on demographic information and students' knowledge of OV, including general knowledge, transmission, symptoms, and treatment; attitudes and health education, and behavior. The second questionnaire will follow the same format to assess students' knowledge of STH. The STH KAP questionnaire is a validated questionnaire used in previous "Magic Glasses" projects [30,31]. The OV KAP questionnaire was adapted from the STH KAP and reviewed by disease experts on the project prior to finalization (see Multimedia Appendices 2 and 3 for questionnaires). Paper questionnaires will be administered in classrooms by research staff and completed by students individually. To minimize confusion between OV and STH, baseline questionnaires for the respective infections will be administered on separate days.

"Magic Glasses Opisthorchiasis" Delivery and Acceptability Assessment

In intervention schools, the OV-baseline KAP assessment and OV intervention will be administered on the same day. Once OV-baseline KAP assessment has been completed, the MGO intervention package will be administered. MGO will be presented to schoolchildren and teachers in their classroom twice. Once the cartoon has been shown, schoolchildren will receive a comic pamphlet with the key messages of the cartoon. A classroom discussion will then be held to go over the messages and clarify any confusion among the students. Following the classroom discussion, an acceptability questionnaire will be administered to assess students' initial acceptability of the cartoon. As with the KAP assessment, paper questionnaires will be administered in classrooms by research staff and completed by students individually. The acceptability questionnaire will contain multiple-choice and open-ended questions (see Multimedia Appendices 4 and 5). The questionnaire was adapted from the TFA [38] to include age-appropriate language for the schoolchildren, and specific questions on OV. Once the acceptability assessment is completed, the homework drawing competition will be explained: students will be asked to draw warning signs of OV infection, using the messages from the cartoon and comic pamphlet as a guide.

A reinforcement session will be held 6-8 weeks after the first presentation of MGO. The cartoon will be replayed twice to the student cohort, followed by a classroom discussion and explanation of the homework essay competition. Students will be asked to identify people who are at risk of liver fluke infection and write down why they are at risk, and how they can avoid liver flukes.

"Magic Glasses Lower Mekong" and Acceptability Assessment

In intervention schools, delivery of the MGLM intervention package will take place on the same day as the STH KAP questionnaire, once baseline data collection is complete. The MGLM package will follow the same delivery procedures used for the MGO intervention package.

Follow-Up

All participants in control and intervention schools will be recruited for follow-up approximately 9 months after baseline. Participants will complete the same questionnaires for OV and STH to assess the impact of the interventions on KAP for the respective diseases. KAP scores will also provide insight on acceptability domains of intervention coherence and perceived effectiveness. In intervention schools, impact and acceptability will also be assessed using qualitative measures. FGDs will be conducted with a subset of schoolchildren in the original cohort to discuss the sustained acceptability and effectiveness of each cartoon. FGDs will also be conducted with parents of participants to investigate the indirect impact of the MGO and MGLM intervention packages on parents' knowledge of OV and STH, respectively. KIIs will be held with teachers to discuss the acceptability and impact of the cartoons on health-related attitudes and behavior.

Follow-up assessments will employ the same delivery timing as used at baseline and intervention delivery to ensure consistency and minimize confusion between OV and STH.

The trial study design is shown in Figure 2. See Multimedia Appendices for anticipated delivery times for each country.

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Figure 2. Trial Profile: Expected study enrollment and timeline diagram for the "Magic Glasses Opisthorchiasis" and "Magic Glasses Lower Mekong" acceptability and impact cluster randomized controlled trial. FGD: focus group discussion; KAP: knowledge, attitudes, and practices; KII: key informant interviews; MGLM: Magic Glasses Lower Mekong; MGO: Magic Glasses Opisthorchiasis.

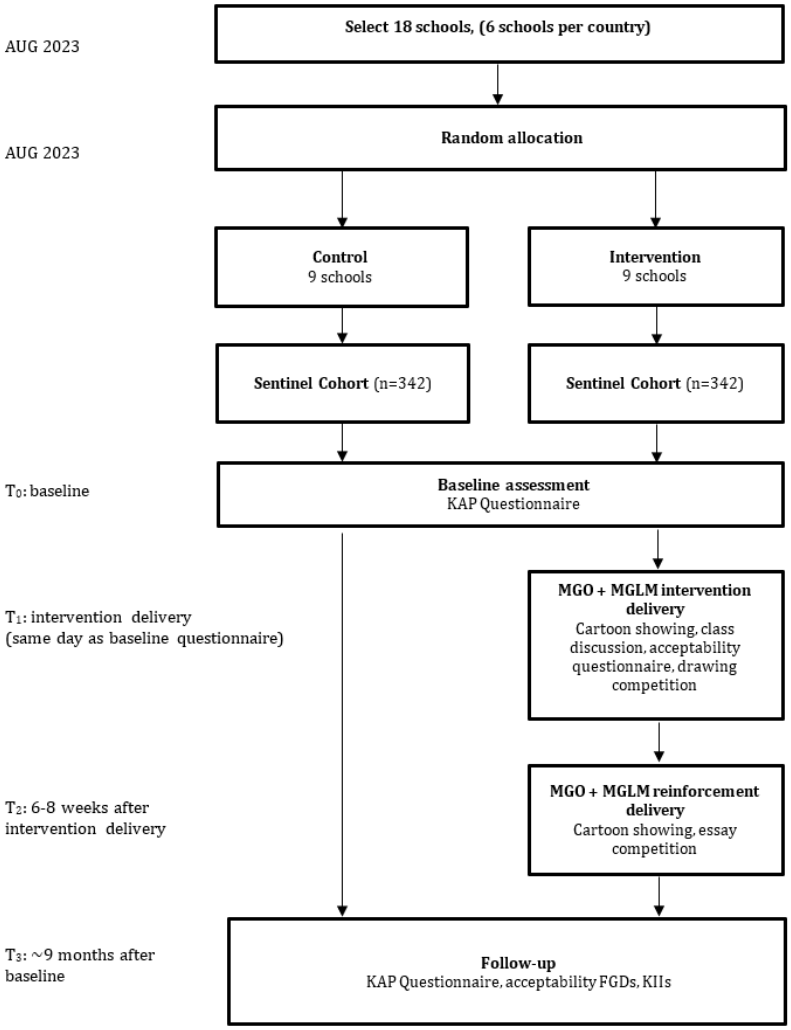

Data Analysis

Quantitative

Descriptive statistics will be computed to ascertain variable distributions.

Normality of distribution will be checked using the Shapiro-Wilk test, with significance set to $P<.05$ (2-sided). In acceptability analyses, negatively worded statements will be reverse scored to align the direction of the scale. Spearman correlation coefficient will be used to assess criterion validity among different questionnaire items. Exploratory factor analysis with oblique rotation will then be performed to assess construct validity. The primary outcome of the study is KAP scores for OV and STH.

OV and STH KAP scores will be analyzed separately. KAP scores for each questionnaire will be developed by calculating the total points for knowledge, attitude, and behavior for each student and expressed as a percentage score. Changes in self-reported KAP scores will be analyzed using linear regression. To assess the differences in KAP between control and intervention schools at baseline and follow-up, generalized-estimating equation models will be used to account for clustering within schools and repeated KAP assessment for participants. Potential confounders including age and sex will be incorporated in the model. Spearman correlation coefficient will be used to estimate correlations among acceptability, knowledge, attitudes, and self-reported behavior. Chi-square tests will also be used to measure associations between KAP and acceptability.

Qualitative

Content analysis [42] and thematic analysis [43] will be undertaken to determine the major categories in the qualitative data (acceptability FGDs and KIIs). Recordings will be translated verbatim to English and transcribed. An inductive approach will then be employed to analyze the recordings of FGDs and KIIs. Codes will be generated as part of the initial review process and entered into a standardized extraction table. Coded data will then be examined for key themes. Themes will be categorized using thematic maps to identify key and shared concepts across themes. Once organized, themes will be reviewed and defined, and key extracts identified. Acceptability and KAP qualitative data will first be examined separately, and then reviewed together to identify shared themes.

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All statistical analyses will be performed using IBM SPSS (IBM SPSS Inc), Stata (StataCorp) or SAS software (SAS Institute Inc). Microsoft Excel, and NVivo (QSR International) will be used for qualitative analyses.

Power

The sample size was calculated to achieve 80% power, assuming baseline knowledge of 30 percentage points (as reported in the original "Magic Glasses" intervention by Bieri et al [31]) and a design effect of 2 to account for cluster sampling. Accounting for 10% attrition, it was estimated that a total of 227 participants would be needed to detect a difference of 5 percentage points in knowledge between intervention and control groups. As such, we will aim to enroll a total of 228 schoolchildren in years 3-5 (114 in intervention arm, 114 in control arm) in each country.

Results

The trial is in progress in Lao PDR and Thailand and is expected to commence in Cambodia in January 2024. Study results are expected to be available 18 months from the start of recruitment and will be submitted for publication thereafter.

Discussion

This study was designed to assess the acceptability of the MGO and MGLM cartoon packages, and to evaluate the impact of these packages on schoolchildren's KAP on OV and STH infection, respectively, in Cambodia, Thailand and Lao PDR. The expected outcomes are initial and sustained acceptability of the MGO and MGLM cartoon packages and improved KAP on OV and STH infection among intervention students. Several studies have outlined the importance of child-targeted health education interventions to improve health knowledge and behavior and prevent disease [26-28]. This is particularly important for populations at-risk of diseases such as OV and STH, which can have long-term health and developmental impacts [14-18]. Previous "Magic Glasses" studies have demonstrated the effectiveness of a school-based educational cartoon in improving KAP among schoolchildren in China and Philippines, and reducing the STH burden [30,31]. The "Magic Glasses Philippines" demonstrated the generalizability of "Magic Glasses" to other regions with endemic infectious diseases [30]. This trial will provide insight on the translatability of "Magic Glasses" to other infectious diseases with different methods of transmission and prevention. In addition, this will be the first study to formally assess the acceptability of "Magic Glasses" intervention.

This study does have some limitations. First, this study relies on self-reported data from children, which could lead to measurement error. Schoolchildren's self-reported OV and STH behavior in particular, may be misrepresented due to social desirability bias. However, several studies have supported child self-reporting as a valid and reliable measure in health research [44-46]. Second, while children receiving the intervention will learn how to prevent OV transmission by adequately cooking freshwater cyprinid fish, it is possible that they will not be able to do this, due to parental control over household food preparation. For this reason, we will also investigate the indirect impact of the intervention on parents' KAP relating to OV and STH infection. Second, due to the nature of the study, it was not possible to blind participants or research staff. Therefore, it is possible that nonblinding bias could occur.

It is expected that the acceptability and KAP findings will provide evidence for the scalability of the "Magic Glasses: Lower Mekong" and "Magic Glasses: Opisthorchiasis" interventions for Cambodia, Lao PDR, and Thailand and more broadly, provide further support for the "Magic Glasses" intervention. These findings have implications for the expansion of the "Magic Glasses" to other infectious diseases and countries, as a novel, engaging and cost-effective tool in school-based health education.

Acknowledgments

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Data Availability

Data will be archived in an encrypted server at the QIMR Berghofer Medical Research Institute. The deidentified data sets generated over the course of this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

DJG, DPM, and GMW conceived and designed the "Magic Glasses" intervention. SYO, MLM, MJK, KW, and DJ designed the research. SYO drafted the first version of the manuscript with input from all authors. DJG, MLM, MJK, and GMW provided guidance on the design as well as data analysis planning. SYO, MLM, MJK, GMW, ACAC, BS, SS, BK, KW, DES, ST, ATS, VS, Virak K, PO, CAG, SW, and DJG reviewed the manuscript. All authors approved the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Anticipated delivery dates for baseline, intervention delivery, reinforcement and follow-up for the “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” cluster randomized controlled trial in Cambodia, Lao PDR, and Thailand.
[DOCX File , 23 KB - resprot_v13i1e55290_app1.docx]

Multimedia Appendix 2
Opisthorchis viverrini knowledge, attitudes, and practices questionnaire for the “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” cluster randomized controlled trial.
[DOCX File , 29 KB - resprot_v13i1e55290_app2.docx]

Multimedia Appendix 3
Soil-transmitted helminths knowledge, attitudes, and practices questionnaire for the “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” cluster randomized controlled trial.
[DOCX File , 35 KB - resprot_v13i1e55290_app3.docx]

Multimedia Appendix 4
Magic Glasses Opisthorchiasis acceptability questionnaire for the “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” cluster randomized controlled trial.
[DOCX File , 27 KB - resprot_v13i1e55290_app4.docx]

Multimedia Appendix 5
Magic Glasses Lower Mekong acceptability questionnaire for the “Magic Glasses Lower Mekong” and “Magic Glasses Opisthorchiasis” cluster randomized controlled trial.
[DOCX File , 28 KB - resprot_v13i1e55290_app5.docx]

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Abbreviations

cRCT: cluster randomized controlled trial
FGD: focus group discussion
KAP: knowledge, attitudes, and practices
KII: key informant interviews
LMB: Lower Mekong Basin
MDA: mass drug administration
MGLM: Magic Glasses Lower Mekong
MGO: Magic Glasses Opisthorchiasis
OV: Opisthorchis viverrini
PDR: People's Democratic Republic
SAC: school-aged children
STH: soil-transmitted helminths
TFA: Theoretical Framework of Acceptability
WASH: water, sanitation, and hygiene
WHO: World Health Organization

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Protocol

Peer Intervention to Link Overdose Survivors to Treatment (PILOT): Protocol for a Multisite, Randomized Controlled Trial Conducted Within the National Institute on Drug Abuse Clinical Trials Network

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Abstract

Background: The increase in opioid-related overdoses has caused a decrease in average life expectancy, highlighting the need for effective interventions to reduce overdose risk and prevent subsequent overdoses. Peer support specialists (PSSs) offer an appealing strategy to engage overdose survivors and reduce overdose risk, but randomized controlled trials are needed to formalize peer-led interventions and evaluate their effectiveness.

Objective: This National Institute on Drug Abuse Clinical Trials Network (CTN) study is a multisite, prospective, pilot randomized (1:1) controlled trial (CTN protocol 0107) that aims to evaluate the effectiveness of an emergency department (ED)–initiated, peer-delivered intervention tailored for opioid overdose survivors (Peer Intervention to Link Overdose survivors to Treatment [PILOT]), compared with treatment as usual (TAU).

Methods: This study evaluates the effectiveness of the 6-month, PSS-led PILOT intervention compared with TAU on the primary outcome of reducing overdose risk behavior 6 months after enrollment. Adults (aged ≥18 years; N=150) with a recent opioid-related overdose were identified and approached in the ED. Participants were screened and enrolled, either in the ED or within 7 days of ED discharge at research offices or in the community and then asked to complete study visits at months 1, 3, 6 (end of intervention), and 7 (follow-up). Participants were enrolled at 3 study sites in the United States: Greenville, South Carolina; Youngstown, Ohio; and Everett, Washington. Participants randomized to the PILOT intervention received a 6-month, PSS-led intervention tailored to each participant's goals to reduce their overdose risk behavior (eg, overdose harm reduction, housing, medical, and substance use treatment or recovery goals). Participants randomized to TAU received standard-of-care overdose materials, education, and services provided through the participating EDs. This paper describes the study protocol and procedures, explains the design and inclusion and exclusion decisions, and provides details of the peer-led PILOT intervention and supervision of PILOT PSSs.

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Results: Study enrollment opened in December 2021 and was closed in July 2023. A total of 150 participants across 3 sites were enrolled in the study, meeting the proposed sample size for the trial. Primary and secondary analyses are underway and expected to be published in early 2025.

Conclusions: There is an urgent need to better understand the characteristics of overdose survivors presenting to the ED and for rigorous trials evaluating the effectiveness of PSS-led interventions on engaging overdose survivors and reducing overdose risk. Results from this pilot randomized controlled trial will provide a description of the characteristics of overdose survivors presenting to the ED; outline the implementation of PSS services research in ED settings, including PSS implementation of PSS supervision and activity tracking; and inform ED-initiated PSS-led overdose risk reduction interventions and future research to better understand the implementation and efficacy of these interventions.

Trial Registration: ClinicalTrials.gov NCT05123027; https://clinicaltrials.gov/study/NCT05123027

International Registered Report Identifier (IRRID): DERR1-10.2196/60277

(JMIR Res Protoc 2024;13:e60277) doi:10.2196/60277

KEYWORDS

opioids; overdose; nonfatal overdose involving opioids; peer support specialist; harm reduction; emergency department

Introduction

Background

An increase in overdose deaths globally [1] and in the United States have caused a decrease in average life expectancy [2]. One of the greatest risk factors for a fatal overdose is experiencing a nonfatal overdose involving opioids (NFOO) in the previous year. Indeed, 6% to 10% of individuals who experience an NFOO die in the following year [3-5]. Survivors of NFOOs most commonly die of another overdose (67%) [3], with the highest risk period being the month following NFOO [5]. Interventions that reduce the risk of a subsequent overdose among NFOO survivors would substantially impact premature mortality.

US emergency departments (EDs) treat nearly 140,000 nonfatal overdoses per year [4], providing a point of contact to engage at-risk patients [6,7]. Although EDs have had some success in implementing certain treatment strategies to reduce overdoses, such as initiating medications for opioid use disorder (MOUDs) [8], which decrease mortality among those with opioid use disorder (OUD) [9,10], NFOO survivors have generally low rates of treatment engagement [3,11,12] and low readiness for treatment [13]. Furthermore, substance use disorder (SUD) diagnoses extracted from the medical record show that only 47% of those experiencing an NFOO meet the diagnostic criteria for an SUD and only 27% meet the criteria for OUD [14]. Taken together, traditional SUD treatment approaches initiated or referred in the ED may have limited success and uptake among an appreciable proportion of patients with NFOO who remain at high risk for a subsequent overdose. Strategies are needed to intervene with NFOO survivors in the ED to reduce the risk of subsequent overdoses, regardless of SUD diagnosis or interest and readiness for treatment or recovery.

Acknowledging that the population with NFOO may be more difficult to engage through traditional medical approaches, work has been focused on developing and evaluating ED interventions that are led by peer support specialists (PSSs) with lived experience with substance use that aim to increase treatment engagement. Preliminary results and recent randomized controlled trials characterizing PSS interventions have been promising [15-22], although few programs to date have been rigorously evaluated with a generalizable, multisite sample and with a focus on harm reduction, rather than SUD treatment initiation. One overdose prevention program developed through Faces and Voices of Recovery in Greenville, South Carolina (Faces and Voices of Recovery Overdose Recovery Coaching Evaluation [FORCE]) has shown preliminary success. FORCE is a recovery program led by PSSs that trains peers in overdose risk reduction and initiates connection in the ED when an overdose survivor is identified. A recent study evaluated the FORCE model among individuals who were hospitalized [23] and found impressive rates of treatment engagement 6 months after discharge (84% vs 34% in the control condition). While that study showed promise for PSS-led recovery coaching, the FORCE intervention has not yet been evaluated among those presenting the ED with an NFOO.

This Study

This paper describes a study protocol to evaluate a PSS-led intervention initiated in the ED among NFOO survivors conducted within the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN). This study adapted the PSS-led FORCE model into the Peer Intervention to Link Overdose Survivors to Treatment (PILOT), with the goal of testing this intervention through a multisite, pilot randomized controlled trial conducted in 3 EDs across the United States. This paper details study procedures, design, the PILOT intervention, and implementation of the CTN-0107 PILOT clinical trial, using Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines [24]. Enrollment of study participants commenced in December 2021 and concluded in June 2023, with a final sample of 150 participants being enrolled and randomized.

Methods

Study Design Overview

This 2-arm, multisite, pilot randomized controlled trial will evaluate the effectiveness of the 6-month, PSS-led PILOT intervention compared with treatment as usual (TAU) initiated in the ED on the frequency of self-reported overdose risk

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behaviors at 6 months (end of intervention). This trial (also referred to as PILOT) aimed to enroll 150 patients (aged >18 years) who experienced a recent NFOO from 3 ED sites in the United States. In addition to routine ED care at the time of admission, all ED sites had peer recovery support systems in place in their ED that served as part of TAU (refer to *Study Setting* subheading mentioned subsequently).

Participants were approached during their ED admission or shortly after admission (Figure 1). If interested, eligible, and enrolled in the study, participants completed research study visits and data collection at months 1, 3, 6, and 7. Participants randomized to the PSS-led PILOT intervention engaged in the PILOT intervention for 6 months (refer to the description in the subsequent sections of the peer-led intervention). The primary outcome of this trial is a reduction in overdose risk behavior compared between participants in PILOT and TAU. Secondary outcomes include engagement in the study and intervention, as well as engagement in recovery and treatment, using a modified SUD Cascade of Care model (detailed description provided in the *Outcomes* section).

Figure 1. Overview of the CTN-0107 study design. CTN: Clinical Trials Network; ED: emergency department; PILOT: Peer Intervention to Link Overdose survivors to Treatment; TAU: treatment as usual.

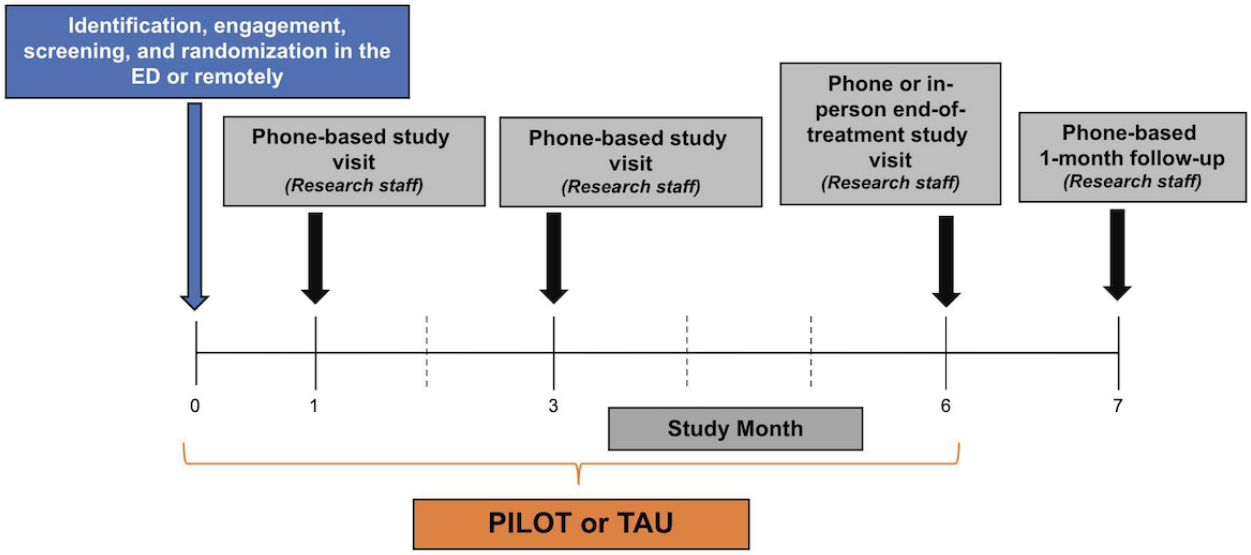

Study Setting

CTN-0107 study sites were selected through a 3-phase process (Figure S1 in Multimedia Appendix 1) to determine the appropriateness for inclusion in this trial and the ability to recruit NFOO survivors in the ED. Sites with already functional ED–based peer recovery services in place were used, because the successful operationalization of a peer recovery team in an ED setting is a separate research question outside the scope and timing of this pilot study. Therefore, the TAU arm did include the possibility of interacting with a TAU ED–based PSS, and such interaction was documented. In addition, because MOUD receipt strongly predicts treatment retention, all sites were required to offer MOUD in the ED setting and to have a community system in place to provide MOUD for individuals without insurance. All sites were also required to be able to prescribe or dispense naloxone for overdose reversal.

The 3 sites selected for the study were Prisma Health—Upstate (Greenville, South Carolina), Mercy Health St Elizabeth Youngstown Hospital (Youngstown, Ohio), and Providence Regional Medical Center Everett (Everett, Washington). To optimize the fidelity of the intervention, all PSSs attended weekly group supervision with members of the PILOT intervention team (refer to the *Effective Supervision* section) and adhered to the PILOT manual if there were divergent peer recovery approaches.

Ethical Considerations

The Medical University of South Carolina (MUSC) institutional review board (IRB) was the IRB of record for this study and reviewed and approved all study procedures, documentation, and safety events, etc. The study was approved by the IRB in February 2021 (Pro00103441). All study sites participating in this trial operated under the MUSC policies through a SmartIRB master reliance agreement. This trial is registered with ClinicalTrials.gov (NCT05123027).

Approach, Screening, and Eligibility in the ED

After stabilization as part of routine TAU in the ED, research team members identified and approached patients who may have qualified for the study, in person or remotely (over the phone after ED discharge or if the patient leaves against medical advice but only if verbal permission to contact had been obtained). Routine TAU in the ED included medical care consistent with treating an overdose, including possible interaction with a TAU PSS, who offered Screening, Brief Intervention, and Referral to Treatment (SBIRT)–like services in the ED. If the participant was interested in the study and eligible (inclusion and exclusion criteria presented in Table 1), informed consent and screening procedures were performed either in the ED or up to 1 week following ED discharge. Participants were informed of the study components in greater detail, the required and optional assessments, potential risks and benefits of study participation, and the breakdown of study

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compensation (up to US $520). Patients could be admitted to the ED for any health issue, substance-related issue, or an NFOO. To be included, patients had to meet the criterion for an NFOO, including (1) being admitted to the ED for any reason and endorsed experiencing an NFOO within the past 72 hours or (2) being admitted to the ED with any substance-related condition and endorsed experiencing an NFOO in the past 30 days. These time frames and reasons for ED admission were meant to be inclusive to allow for non-NFOO reasons for ED admission while still capturing those with recent NFOO and who were at high risk of subsequent overdoses. This allowed for a more generalizable sample of patients in the ED with recent NFOOs but not necessarily presenting to the ED for an NFOO. Participants did not have to be computer or internet literate to be included in study procedures. Study sites were also able to provide study cell phones if a participant did not have their own device for contact and completing mobile phone study assessments.

Table 1. Study inclusion and exclusion criteria and rationale.

Criteria and description	Rationale
Inclusion	
Aged ≥18 years	Study focused on adult population
Meet 1 of the following *NFOO*[a] criteria: (1) presented to ED[b] for *any* reason in the past 48 hours and self-report having a known or suspected opioid-involved overdose in the past 72 hours and (2) presented in the ED in the past 48 hours for any SUD[c]-related issue and self-report having a known or suspected opioid-involved overdose in past 30 days	Definition of study sample
Identify at least 2 additional contacts on the study locator information Form	Reduce loss to follow-up and to help ensure participant will provide useful data over the 7-month study
English-speaking and able to provide written informed consent	Good clinical practice requirement to ensure informed consent
Willing and able to confirm future SUD treatment receipt as evidenced by 2 out of 3 of the following: (1) signing appropriate releases for study staff to confirm treatment with follow-up provider, (2) having technology necessary to visualize medication bottles and transmit to study team using HIPAA[d]-compliant platform, and (3) able and willing to undergo toxicology tests	To help ensure participant will provide useful data and confirmation of treatment status
Exclusion	
Identified as having had an intentional overdose as the index NFOO	Safety and outside of the scope of standard peer support
Actively suicidal at the time of screening	Safety and outside of the scope of standard peer support
Unable to complete study baseline procedures due to medical or psychiatric condition	Safety
Meets the Office for Human Research Protection definition for prisoner status	Promote participant confidentiality and to help ensure participant will provide useful data
Previously randomized as a participant in this study	To avoid confounding results
Unwilling to follow study procedures	Safety and to help ensure participant will provide useful data

[a]NFOO: nonfatal overdose involving opioids.

[b]ED: emergency department.

[c]SUD: substance use disorder.

[d]HIPAA: Health Insurance Portability and Accountability Act.

Given the potentially short time that NFOO survivors were available to the research staff in the ED (given short ED patient disposition times), with verbal consent obtained during the ED visit, screening, consent, and baseline procedures were allowed to be completed within 1 week after ED discharge. All assessments and procedures conducted during screening, baseline, and during the study are shown in Table S1 in Multimedia Appendix 1. If patients were not interested in participating in the study or were not eligible, they were offered a brief survey assessing demographics, substance use, and overdose history and reasons for not being interested or eligible for the study.

Randomization

Eligible participants were randomized 1:1 to the PILOT intervention condition or TAU. Explanation was provided to the participants that if they were randomized to the PILOT intervention, they would engage with a PILOT PSS with specialized training in overdose prevention (different than the TAU PSS in the ED unaffiliated with the study), and the PILOT PSS would coordinate with the TAU PSS during the ED visit to ensure no duplication of services and would engage with them for 6 months in the community. Participants randomized to TAU received all standard treatment services provided in the ED, and TAU PSSs conducted standard procedures as they would for any NFOO or patient with substance use admitted to

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the ED, with all sites offering an SBIRT-like model. The resources that TAU PSSs offered within the SBIRT-like model in their ED varied (and were reported through regular surveys completed by the site principal investigator and research staff), but all sites had the ability to offer naloxone as part of TAU, as required in site selection. PSS TAU interactions were generally contained within 1 meeting in the ED to provide treatment and harm reduction resources.

For participants randomized to the PILOT intervention, there was an on-call system for the PILOT PSSs such that they were available to come to the ED in person or remotely (over the phone or through research staff–facilitated video chat) to connect with participants. If possible, intervention participants began the PILOT intervention in the ED, immediately following randomization. If a connection was not made in the ED, the PILOT peer made attempts to contact the participant as soon as possible after randomization.

Randomization was stratified by study site and unstable housing status (yes or no). A permuted block randomization procedure with random block sizes was used to balance per site and housing status. The randomization schedule used balanced blocks of varying sizes within strata to ensure the lack of predictability along with relative equality of assignment across treatment groups. The randomization procedure was conducted centrally through the CTN Data and Statistics Center.

Study Visits and Retention

During the 7-month study, participants were asked to complete study visits with the research staff at months 1, 3, 6, and 7. All research data were collected by the research staff at the study site and de-identified. PILOT PSSs did not collect research data or outcome data to ensure consistency and standardization across groups. PILOT intervention participants engaged with their assigned peers during the 6-month intervention. PILOT PSSs did not collect any data for research or outcome purposes, which is the responsibility of research coordinators for both PILOT and TAU groups. Assessments completed at study visits are shown in Table S1 in Multimedia Appendix 1, and all participants received weekly mobile diaries to complete during the study. To improve retention, study phones were provided to participants, as needed. Retention efforts were pursued throughout the study by research coordinators (for both PILOT and TAU participants) and PILOT PSSs (for PILOT-assigned participants only) followed up with their assigned PILOT participants throughout the 6-month intervention phase. If participants were unable to be reached by phone or could not attend study visits at research offices, assertive outreach was used by the research staff, which included mailed letters, text messages, visits in the community, and in rare circumstances, home visits with appropriate safety precautions in place, etc. Participants provided detailed locator information for at least 2 additional contacts if they could not be directly reached.

PILOT Intervention Development, Peer Training, and Supervision

Involvement of People With Lived Experience in Protocol Development and Study Conduct

The value of inclusion of people with lived experience in SUD and recovery in developing and delivering this trial is recognized throughout study design, implementation, and dissemination of findings. Two PSSs (RJ and TL) have been integral members of the lead research team and intervention team since the inception of the study concept. These individuals bring years of lived experience in SUD recovery as well as supervision of PSSs within recovery-based organizations and have contributed meaningfully to the study design, implementation, and dissemination.

PILOT Intervention Development and Components

The PILOT intervention was adapted from the FORCE program, which used certified PSSs trained in engaging overdose survivors presenting to the ED. The CTN-0107 lead intervention team, including FORCE PSSs (RJ and TL), adapted the FORCE intervention (developed and implemented by RJ) and developed the PILOT intervention manual for this trial. The process of manual development included a literature search to complement what was learned from the FORCE implementation and an iterative process involving all members of the intervention team to identify the key principles of the intervention. The underlying philosophy of the intervention was grounded in a combination of motivational interviewing (MI), case management, health coaching, and assertive community engagement. The PILOT intervention manual was reviewed by an independent PSS, and feedback was incorporated before study enrollment began. The PILOT intervention manual was considered a living document to be further molded and adapted by the PSSs trained in the study.

The PILOT intervention manual describes three key principles as follows: (1) *assertive engagement*, (2) *participant-directed* care, and (3) *effective supervision*. *Assertive engagement* refers to the relationship between the PILOT PSS and the participant, as well as the expectation of active engagement with community partners. Characteristics of *assertive engagement* include (1) connection with and support of the participant informed by the PSSs' lived experience, (2) the PSS taking responsibility for maintaining connection, (3) comprehensive knowledge of community resources, (4) linkage to services, (5) integration of family and other social supports, and (6) effective use of overdose harm reduction techniques.

The principle of *participant-directed* care in the PILOT intervention refers to the inclusion of participant-defined goals. Training on this approach, grounded in MI [25], was provided to PSSs during peer national training (described in subsequent sections) and is reinforced during regular supervision sessions. The PSS assumes responsibility for follow-up after ED discharge and continued engagement and contact throughout the intervention. By keeping in contact with the participants over time and using MI approaches, PSSs were available to individuals regardless of their level of interest in or readiness for treatment. Engagement with the individual was based on

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their needs, which evolved during the intervention and PSSs were encouraged to adapt their strategies, content, and services based on the individual participant.

Effective supervision was initiated from the time of PSS hire and continued throughout the study. At the study site level, supervision was conducted by a lead PSS, who was the on-site PILOT peer supervisor and provided at least weekly supervision. At the national level, a weekly, virtual supervision call for all PSSs was led by the intervention team, which included a PhD-level psychologist, a master's level social worker, and 2 experienced PSSs. All PSS supervision sessions included informal discussions of participant cases, facilitated sharing of work-related experiences with feedback and support, and formal case presentations. National supervision also included a brief didactic, formal case presentations, and experiential review of key principles, including real-time practice of MI, promotion of self-care, awareness of safety in the field, and implementation of practical, participant-directed, and strengths-based case management.

PSS Training

All PILOT PSSs were required to hold a nationally recognized certified PSS certificate (or equivalent based on the state). PILOT PSSs participated in the virtual all-study national training led by the national intervention team and were required to complete all Human Subjects Protections and Good Clinical Practice training. The PSS training provided didactic and experiential (role-play) training using the PILOT intervention manual, including a discussion of PILOT PSS roles, responsibilities, and boundaries; detailed overviews of each treatment group; appropriate MI-based techniques and role-plays; and the importance of active supervision. During the national training, training on the MI approach was provided, and role-plays were conducted in groups of 2 PSSs with feedback provided by the intervention team. Postnational training was delivered via conference calls, webinars, and written materials. Competence in basic MI was reinforced through a taped recording of a mock participant session or a real-time role-play over videoconferencing, which was reviewed by the intervention team.

Peer Documentation and Fidelity

Given the interactions between a PSS and an individual are fluid, responsive to changing needs, and often spontaneous, the intervention team worked with the lead team PSSs to develop a checklist of the most common activities used (eg, outreach, engagement, discussion of lived experience, connection to resources, naloxone distribution, and identification of participant-directed goals). These activities were captured in the Peer Intervention Log that the PILOT PSSs filled out daily, describing the activities they used with a participant. The Peer Intervention Log was completed daily, even if no contact or intervention had been delivered on that day.

On the basis of feedback from the lead team PSSs, direct fidelity measurement (eg, recorded PSS-participant interactions) was found to be infeasible as this could inhibit spontaneity and rapport-building. Instead, metrics of PSS activity, content, frequency, etc, were collected during the 6-month intervention through the Peer Intervention Log. In addition, local and national supervisors performed fidelity assessments via case presentations during weekly supervision at the local level and during formal case presentations delivered by each PSS during national supervision.

Measures and Assessments

Primary Outcome

The primary outcome measure for this study is a modified and expanded version of the Overdose Risk Behavior Checklist (ORBC), adapted from the study by Bohnert et al [26]. The modified ORBC (Figure S2 in Multimedia Appendix 1) was adapted from similar questionnaires to capture overdose risk behaviors in this or similar populations [17,26,27] (RELAY RCT; ClinicalTrials.gov identifier NCT04317053) and developed based on known factors associated with risk for overdose [26,28-33]. The PILOT ORBC is a 13-item scale, with 11 of the items used to generate a total risk score (ranging from 0-44); higher scores indicate greater frequency and number of overdose risk behaviors. The frequency of nonfatal and fatal overdoses will also be measured but given the relative infrequency of these events, the ORBC was a more proximal potential marker for change that could be measured within a 6-month pilot intervention.

Secondary Outcomes

The secondary outcomes of the study are (1) the number of steps achieved on a modified SUD Cascade of Care at 6 months after ED admission (Table 2); and (2) engagement with the study and PILOT intervention, measured by the number of potentially eligible patients *approached* in the ED compared with the number willing to be enrolled in study procedures and the length of enrollment in the trial among those randomized to PILOT (defined as the time from baseline to last meeting with the PILOT PSS). The SUD Cascade of Care was developed by the CTN-0107 lead team, informed by published work documenting an OUD Cascade of Care [34], to capture improvements that may otherwise be missed through existing assessments meant for those with SUDs or greater severity of substance use. The Cascade of Care outlines 10 steps representing different stages of SUD treatment or recovery engagement ranging from harm reduction to engagement in formal SUD treatment or MOUD. Participants do not need to meet the criteria for an SUD or OUD to be included in the steps achieved, which also includes steps toward overdose harm reduction and recovery capital. To assess steps achieved on the SUD Cascade of Care, participants are asked to complete an assessment battery, which includes a study-developed Harm Reduction Checklist, a Steps Achieved Assessment Form, MOUD Confirmation Assessment, a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition Checklist for SUDs [35], a urine drug test, and the Assessment of Recovery Capital Scale [36] (refer to Table S2 in Multimedia Appendix 1 for the scoring rubric and Figure S2 in Multimedia Appendix 1 for locally developed assessments). All enrolled participants are considered to have 0 steps achieved at the time of the baseline visit, even if they are engaging in treatment or recovery services at the time of enrollment or baseline, with a maximum of 10 steps possible to be achieved by the end of treatment visit (month 6).

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Table 2. Modified substance use disorder (SUD) Cascade of Care showing the cascade category, the steps achieved on the continuum of care, and the measure used to determine meeting that step.

Cascade and steps	Measure
Overdose identification and harm reduction	
1. ↑ Harm reduction	Harm Reduction Checklist
Engagement in care	
2. Any care	SAF 2-7[a]
3. Regular care	SAF 2-7
MOUD[b] initiation	
4. Any MOUD	SAF 2-7
MOUD retention	
5. MOUD × 1 month	SAF 2-7 and MOUD Confirmation Form
6. MOUD × 3 months	SAF 2-7 and MOUD Confirmation Form
7. MOUD × 6 months	SAF 2-7 and MOUD Confirmation Form
Treatment response and remission	
8. ↓ SUD severity	*DSM-5*[c] Checklist toxicology screen
9. Early remission	*DSM-5* Checklist toxicology screen
10. ↑ Recovery score	Assessment of Recovery Capital Scale

[a]SAF 2-7: Steps 2-7 Achieved Form.

[b]MOUD: medication for opioid use disorder.

[c]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Safety Assessment

The population with NFOO is at high risk of adverse events and subsequent overdoses, and this study conducted targeted safety monitoring. Targeted safety monitoring events included participant deaths, overdoses, ED visits, and hospitalizations. Assessment for suicidality was screened for and handled according to approved safety procedures at all study visits. In addition, study staff and PSS safety protocols for community visits were developed when conducting in-person visits in the community. Safety and data oversight is provided by the NIDA CTN and Emmes Clinical Coordinating Center, site-level IRBs, and the MUSC IRB, as well as a Data Safety Monitoring Board that meets annually.

Statistical Analysis Plan

Primary Outcome Analyses

The primary outcome is the effectiveness of PILOT (compared with TAU) as measured by the past month's total score of the self-report ORBC assessment at month 6 (end of intervention). The study hypothesis is that PILOT intervention participants will have a lower ORBC total score at month 6 (ie, lower frequency of self-reported overdose risk behaviors) compared with TAU participants. The primary outcome of ORBC total score at month 6 will be analyzed with a longitudinal mixed effect Poisson regression model incorporating total score at earlier time points. Fixed effect covariates include baseline ORBC total score, treatment assignment, days in the study (time since randomization), site, stratum, and an interaction between treatment and days. Days will be treated as a categorical variable. A random effect will be included to account for repeated measures per participant. The treatment effect will be given as a rate ratio (RR; as the exponential of group and days interaction at month 6 plus the main effect of randomized group) along 2-sided *P* values and 95% CIs. This can be interpreted, conditionally, as a ratio of the mean risk behaviors for those assigned to PILOT divided by the mean risk behaviors for those assigned to TAU at month 6, while all other variables are the same.

Secondary Outcome Analyses

For the number of steps achieved along a modified SUD Cascade of Care, analysis will be similar to that for the primary outcome, with an overdispersed Poisson regression model with fixed effect covariates for treatment, site, and stratum. It is noteworthy that no baseline score covariate is included as all participants will be considered to have achieved 0 steps at baseline. An RR with 95% CI and *P* value will be reported. Participants entering the trial may not have a primary diagnosis of OUD or any SUD. Because of this, some steps may not be eligible at baseline. If, during the study, the participant endorses OUD or other SUD, they will become eligible for these steps. Alternatively, with the increasing co-use and contamination of methamphetamine with fentanyl, people with primary methamphetamine use disorder (and no diagnosis of OUD) may be placed on MOUD, and this study will measure that within this population.

Other secondary outcomes (ie, the number of participants approached, the number of participants who were willing to engage with PILOT peers, and the percentage of those

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approached who were willing to engage) will be reported by summary statistics with 95% CIs. The length of engagement with PILOT will be similarly summarized.

Power Analysis and Sample Size Estimation

Power analyses and sample size calculation were based on the primary outcome of comparing ORBC total score differences at month 6 between PILOT and TAU participants. The self-reported overdose risk behaviors to be used for this trial are modified and expanded from a version used by Bohnert et al [26], in which the maximum score was 32, with average baseline scores of 3.3 and 3.8 in their control and intervention groups, respectively. They used a Poisson regression model to estimate the intervention effect, reported to be a 0.72 RR. For the power simulations conducted for this study, a baseline mean score of 3.55 was used, with a treatment effect of 0.72. With a mean of 3.55 at baseline and an RR of 0.72, there is over 90% power to detect the expected treatment effect with a total sample size of 150.

Missing Data

The prespecified primary outcome analysis method considers all available data so that special provisions are not needed for missing data. However, missing data handling methods, such as multiple imputation, may be considered as possible sensitivity analyses. By definition, the secondary outcome of the number of steps achieved on the modified SUD cascade of care will have no missing data. Either evidence was previously obtained that a step was achieved, or evidence was never collected that the step was achieved (and thus was not achieved).

Results

The overall goal of this pilot trial is to provide data on the potential effectiveness of a 6-month, specialized, PSS-led intervention for NFOO survivors presenting to ED settings in reducing overdose risk behavior at 6 months following ED admission. This study will also provide important information characterizing NFOO survivors presenting to the ED as well as the rate of engagement with and content of PSS-delivered services over the 6 months of intervention.

The PILOT study was effectively implemented at 3 geographically diverse sites in the United States, with enrollment of study participants commencing in December 2021 and concluding in June 2023, meeting the enrollment goal of 150 study participants. Final follow-up visits occurred through February 2024. As of July 2024, the PILOT study has developed and delivered an ED–based, PSS-led intervention within a research model and completed enrollment, demonstrating the feasibility of both completing a multisite trial in this area and recruiting the target population. Final primary and secondary outcome analyses within the final study report are expected in August 2024, with dissemination expected in October 2024.

Discussion

Overview

Outcomes of this trial will contribute important information to the field, including (1) a detailed description of the characteristics of and 6-month course of NFOO survivors presenting to 3 geographically different ED settings between December 2021 and June 2023; (2) a description of the nature, content, and dosing of a research-delivered PSS intervention; and (3) lessons learned in the research implementation of an ED-initiated PSS intervention. Study results will also contribute much-needed, rigorous, randomized, controlled data to the growing field of research and interventions to address overdoses and reduce the risk for subsequent overdoses among a generalizable sample of NFOO survivors.

Design Decisions

Several key design decisions were made regarding the most appropriate sample for this study and outcome measurements. As a randomized pilot study, this protocol was designed to inform a larger, multisite randomized trial. Therefore, all procedures used in the trial attempt to test those procedures intended for the implementation in the subsequent larger trial [10].

The study enrolled patients in ED who had experienced a recent NFOO, though a diagnosis for OUD or SUD was not required for inclusion. Even among NFOO survivors who acknowledge SUD, treatment engagement is low and decreases with each additional month after overdose [14]. Moreover, given that less than half of the population with NFOO identifies as having SUD, this low level of treatment entry and decline in treatment use over time raises the critical question of what treatment or risk reduction measures are appropriate for NFOO survivors who do not identify as having an SUD and how to improve the retention of those with SUD who enter treatment after an overdose [21,22]. PILOT was designed to assess and address overdose risk factors for those who survive an NFOO, regardless of whether the individual identifies as having an SUD or is interested or ready for treatment entry. As it has also been shown that NFOO survivors without SUD or OUD are less likely to engage with outreach efforts [11], the primary outcome measure, screening, and PILOT intervention were tailored to include risk reduction for individuals in any SUD category. Specifically, the modified SUD Cascade of Care was developed to ensure several steps could be achieved by those without SUD or for those for whom MOUD is not indicated or desired. Although the traditional SUD Cascade of Care is used at a population level and not an individual level, for the purposes of this pilot study, the Cascade of Care logic was felt to be the most inclusive to identify where, outside of formal treatment engagement, PSS services might improve outcomes for NFOO survivors.

For overdose characteristics, the PILOT study included individuals in the ED who experienced an overdose in the past 30 days and considered an individual to have experienced an NFOO if they self-reported affirmatively that they believed they experienced an overdose and that the overdose *may have* involved opioids. These broader characteristics of overdose were chosen for several reasons. First, this approximates ED clinical practice of self-reported overdose. Second, urine toxicology cannot always identify very recent drug exposure, and some individuals admitted to the ED after an NFOO may not be confident which drugs were involved with the NFOO. Third, not all individuals who experience NFOOs receive

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naloxone or seek medical attention, even after naloxone is administered (therefore, naloxone administration or post-NFOO medical attention was not required and a 30-day window for overdose was allowed for those who presented to the ED with an SUD-related condition). If an individual denied having an overdose, even if they were given a reversal agent or it was medically assessed to be an NFOO, they were not eligible for inclusion, given the PILOT intervention specifically focuses on overdose risk behaviors. Design decisions regarding the PILOT study population aimed to maximize inclusivity, generalizability, and representation of the heterogeneity of the population with NFOO during the period of the opioid crisis this study was delivered.

Finally, our primary outcome was based on self-reported overdose risk behavior (via the ORBC) rather than subsequent overdoses between groups. Although the frequency of self-reported nonfatal overdoses and National Death Index-reported fatal overdoses Index will be measured, given the relative infrequency of overdose events, the ORBC was considered a more proximal potential marker for change that could be measured within a 6-month pilot intervention. The ORBC was developed based on factors associated with overdose, and the relationship between ORBC scores and overdose events will be an exploratory analysis in this study.

Limitations

This study protocol and design include several limitations. The recruitment and enrollment of study participants in the ED following an overdose is a logistically challenging time to engage potential participants, especially when asking individuals in the ED for an acute medical event to complete extensive screening and baseline procedures. Similarly, informed consent during the ED visit presents a challenge for the research staff to ensure that participants are truly informed regarding study procedures. Through extensive staff training and oversight, we ensured that participants consenting to the study understood study procedures, risks, potential benefits, etc and were able to provide informed consent. These measures may have favored those with a higher level of functioning and cognitive ability required to understand informed consent and excluded those who experienced a very recent overdose who may not have been cognitively, physically, or emotionally well enough to complete informed consent. To mitigate this limitation, the study design incorporated the option to obtain verbal consent to follow up with a potential participant after they were home and feeling better. We also acknowledge the potentially important variables that we did not collect in this study to keep the assessment battery as minimal as possible. For example, the study did not evaluate the cost-effectiveness and other key variables that may affect substance use and craving, such as hormonal changes due to the menstrual cycle in biological women. However, analyses will evaluate outcomes by gender, age, and race and ongoing studies are evaluating the cost-effectiveness of PSS services. Finally, although this study measured nonfatal and fatal overdoses as exploratory measures, we acknowledge the choice of a self-report measure (eg, ORBC) as the primary outcome measure for PILOT is a limitation. Data from this pilot study will inform and power future studies to more rigorously determine the efficacy of the peer-led PILOT intervention on overdoses in this population at high risk.

Conclusions

This PILOT study will evaluate the preliminary effectiveness of a 6-month, PSS-delivered intervention on reducing self-reported overdose risk behaviors among 150 individuals in the ED who experienced a recent NFOO. PILOT will contribute much-needed, rigorous, randomized, controlled data to a growing field of research on interventions aimed at preventing overdoses and reducing overdose risk among a generalizable sample of NFOO survivors. In addition to describing and providing preliminary effectiveness data for a PSS-led intervention targeting overdose risk behaviors, this study will also describe the characteristics of the NFOO population from December 2021 to June 2023, at the height of the overdose crisis, which will inform intervention targets for this population at high risk. PSS services are already being incorporated into medical settings to advocate for and address the needs of populations with SUD at high risk, and PILOT results will aid in implementing the most effective PSS practices for and inform a larger study powered to measure overdose events (fatal and nonfatal). Future work in this area is needed for the implementation of PSS services in EDs and other medical settings, as well as economic analyses to demonstrate the potential cost savings of implementing PSS services.

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The study sponsor was not involved with the design, collection, management, analysis, or interpretation of data, nor in writing the report or decision to submit the report for publication.

Data Availability

Data sets that will be generated during and analyzed during this study will be made available on the NIDA Clinical Trials Network data share website. Any questions regarding data or availability can be sent to the lead investigator KB.

Authors' Contributions

CP, EAM, and KSB drafted the manuscript. RJ, TL, EAM, KSB, LH, TM, JM, CP, LJ, RW, and KB reviewed and edited the manuscript and provided substantial content revision. RJ and TL conceptualized the original peer intervention and RJ, TL, EAM, KSB, LH, TM, JM, CP, LJ, RW, and KB modified the intervention for research and developed the study methodology and protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary tables and figures.
[PDF File (Adobe PDF File), 444 KB - resprot_v13i1e60277_app1.pdf]

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Abbreviations

CTN: Clinical Trials Network
ED: emergency department
FORCE: Faces and Voices of Recovery Overdose Recovery Coaching Evaluation
IRB: institutional review board
MI: motivational interviewing
MOUD: medication for opioid use disorder
MUSC: Medical University of South Carolina
NFOO: nonfatal overdose involving opioids
NIDA: National Institute on Drug Abuse
ORBC: Overdose Risk Behavior Checklist
OUD: opioid use disorder
PILOT: Peer Intervention to Link Overdose survivors to Treatment
PSS: peer support specialist
RR: rate ratio
SBIRT: Screening, Brief Intervention, and Referral to Treatment
SUD: substance use disorder
TAU: treatment as usual

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Protocol

Ayurveda Management of Allergic Rhinitis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Allergic rhinitis (AR) is the inflammation of the membranes lining the nose due to allergen exposure and is characterized by sneezing, nasal congestion, itching of the nose, or postnasal discharge. The prevalence varies worldwide, perhaps due to the geographic and aeroallergen differences, with 10% to 30% of the world's population experiencing AR. In this study, Anu Taila Nasya, Naradiya Laxmivilas Rasa, and Shirishadi Kwath will be compared to a fluticasone nasal spray.

Objective: The primary aim is to assess the efficacy of Ayurvedic management for AR (or vataja pratishyaya) by comparing it to a conventional control group. The secondary aims are to determine the mean change in the nasal endoscopy index and the mean change in the laboratory tests.

Methods: This ongoing study is an open-label randomized controlled interventional trial, with a sample size of 90 both in the trial and standard control group (including dropouts, 20%), and will be carried out for 24 months. Participants in the trial group will receive Ayurvedic treatment, that is, Anu Taila Nasya (6 drops in each nostril for 7 days for 3 consecutive weeks), Naradiya Laxmivilas Rasa (250 mg twice per day), and Shirishadi Kwath (40 ml twice per day for 45 days). The participants in the control group will receive a fluticasone propionate nasal spray (2 sprays once per day for 45 days). The primary outcome will include the mean change in the Control of Allergic Rhinitis and Asthma Test score, and the secondary outcomes will include the mean change in the nasal endoscopy index (assessment of nasal membrane color, pale or hyperemia; rhinorrhea, watery or yellow; and inferior turbinate swelling, hypertrophy) and the mean change in the laboratory tests.

Results: As of May 2024, 72 patients have been enrolled in both groups. Data analysis should be completed by February 2025. The study will be reported following standard guidelines for reporting randomized controlled trials. Clinical results will be disseminated through conferences and peer-reviewed publication in a relevant journal.

Conclusions: The Ayurvedic approach could be an evidence-based therapeutic tactic for the management of AR.

Trial Registration: Clinical Trials Registry India CTRI/2023/06/053395; https://tinyurl.com/564d2zz8

International Registered Report Identifier (IRRID): DERR1-10.2196/56063

(JMIR Res Protoc 2024;13:e56063) doi:10.2196/56063

KEYWORDS

allergic rhinitis; AR; Anu Taila Nasya; fluticasone propionate nasal spray; Naradiya Laxmivilas Rasa; randomized controlled trial; Shrishadi Kwath

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Introduction

Allergic rhinitis (AR), a heterogeneous disorder, often remains undiagnosed despite its high prevalence. It is characterized by one or more of the following symptoms: sneezing, itching, nasal congestion, and rhinorrhea [1]. The nose is exposed to a variety of microorganisms, allergens, and environmental pollutants present in the atmosphere because of its direct contact with the external environment. If the early stage of AR is not adequately treated, it causes mucosal changes in nostrils and results in turbinate hypertrophy, nasal polyps, allergic bronchitis, etc. AR is the inflammation of the membranes lining the nose due to an allergen exposure [2].

AR affects 26% of the population in India [3]. The prevalence of AR has increased significantly in some countries, but national trends are inconsistent [4]. AR is the most common atopic condition, affecting about 10%-30% of adults and up to 40% of children worldwide [5]. In India, its prevalence has gradually risen in the last 2 decades [6]. The diagnosis is based on clinical manifestations and supported by positive results from a skin prick test or demonstration of serum-specific immunoglobulin E antibodies to aeroallergens or direct nasal endoscopy.

In this study, the diagnosis of AR and its classification into mild and moderate-severe groups were made according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification [7]. The cardinal symptoms, according to ARIA guidelines, are paroxysmal sneezing; itching in the nose; itching of the eyes, palate, or pharynx; watery nasal discharge; nasal obstruction; and history of urticaria, while the clinical signs include pale boggy nasal mucosa; hypertrophied turbinates; thin, watery, or mucoid discharge; allergic shiner; and transverse nasal crease (allergic salute) [8]. The control group was selected as per ARIA guidelines.

The lack of curative treatment necessitates other systems of health providing remedial treatment, such as Ayurvedic science. As treatments with standard medications have their own limitations, there is scope for using Ayurveda, which emphasizes a holistic approach to every disease based on the Doshas (psychobiological rhythm: vata, pitta, and kapha), Dhatus (body tissues and their nourishing elements), and malas (excreta). In Ayurveda, AR is similar to vataja pratishyaya [9], and as per the Ayurvedic literature, it is a curable disease [10]. There are few published preclinical and clinical studies proving the efficacy of Ayurveda interventions, such as Rajanyadi Churna and Guduchi Kwath [11], Ayurvedic herbo-mineral formulation IMMBO [12], Triphala [13], Haridra Khanda and Manjisthadi Kwath (brihat) [14], Tamalakyadi decoction [15], and Haridra Khanda and Pippalyadi Taila [16].

One study was carried out at the Institute of Post Graduate Teaching and Research in Ayurveda, Jamnagar [17], and one pilot study was also conducted at the Central Council for Research in Ayurvedic Sciences (CCRAS) studying an Ashwagandhadi compound, Shirishadi Kwath, and Anu Taila Nasya (intranasal drug administration), which found significant results [18]. Naradiya Laxmivilas Rasa's (NLR) use for respiratory disorders has previously been discussed in Ayurvedic literature [19]. No randomized controlled trial studies have been published comparing NLR, Shirishadi Kwath, and Anu Taila Nasya to a fluticasone nasal spray used in an allopathic system as per standard treatment for patients with AR. Considering these facts, a randomized controlled trial has been proposed here.

Methods

Study Objectives

The primary objective is to assess the efficacy of Ayurvedic management for AR (vataja pratishyaya) by comparing it with a conventional control group. The secondary objectives are to determine the mean change in the nasal endoscopy index (assessment of nasal membrane color, pale or hyperemia; rhinorrhea, watery or yellow; and inferior turbinate swelling, hypertrophy) [20] and mean change in the laboratory tests.

Study Setting

This study will be conducted at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

Eligibility Criteria

Inclusion Criteria

Patients of either sex between the ages of 18 and 65 years with intermittent or persistent AR (as per the internationally recognized ARIA diagnostic standard) who were diagnosed based on their medical history and who were willing to participate and provide informed consent were eligible for the study.

Exclusion Criteria

The following exclusion criteria were used: patients who had a history of chronic nasal or upper respiratory tract symptoms or disorders other than AR, non-AR chronic sinusitis, or serve bronchial asthma with nasal anatomical defects (grossly deviated nasal septum), nasal polyposis, tonsillitis, or airway obstructions (adenoids); patients with a nasal condition likely to affect the outcome of the study; patients receiving any treatment of H1 antihistamine medication or nonsteroidal analgesics; patients using corticosteroids nasal drops, leukotriene antagonists, or nasal vasoconstrictors; patients who have received a surgical procedure on the nose like septoplasty/submucous resection, inferior turbinate reduction, or endoscopic sinus surgery; women who are pregnant and lactating mothers; patients with any debilitating chronic disease (eg, tuberculosis or uncontrolled diabetes mellitus), any unstable cardiovascular diseases, evidence of malignancy, concurrent hepatic disorder (defined as aspartate amino transferase or alanine amino transferase >2 times the upper normal limit) or renal disorders (defined as *S creatinine* greater than the upper limit of laboratory value), pulmonary dysfunction (bronchial asthma or chronic obstructive pulmonary disease), or acute mental disorder; and patients who are currently participating in any other clinical trial.

Study Interventions (Investigational Products)

Participants in the treatment group will undergo Nasya therapy for 7 days for 3 consecutive cycles. Along with the Nasya therapy, the participants will receive a 250 mg dose of NLR twice daily after meals with lukewarm water and 40 ml of

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Shirishadi Kwath twice daily on an empty stomach for 45 days. In the standard control group, participants will receive a 200 mcg dose of fluticasone propionate nasal spray (50 mcg/spray) per day (2 puffs once daily) for 45 days. The treatment group medicine (investigational products) will be procured from good manufacturing practice–certified pharmacies through the Indian Medicines Pharmaceutical Corporation Limited (Mohaan) and the Central Ayurveda Research Institute (Jhansi), along with a certificate of analysis to ensure the investigational products' quality standards and safety. The control group's medicine will be procured from a good manufacturing practice–certified government agency. The study drugs will be kept in a secure place and will only be supplied to the participants under the guidance of the investigator. A record will be maintained for the drug dispensed. Any discrepancies between the amounts dispensed and returned will be explained.

Strategies to Improve Adherence to the Study Protocol

Medication adherence will be assessed at each follow-up visit (days 16, 31, 45, 75, 105, and 135) by assessing the approximate quantity consumed. The participant will be asked to return the empty medicine container at each follow-up visit. Repeated phone reminders to regularly take the medicine from project staff will be given to the participants or their family members.

Outcome Measures

Primary Outcome Measure

The primary outcome measure is the mean change in the Control of Allergic Rhinitis and Asthma Test (CARAT) score [21] at baseline and days 16, 31, 45, 75, 105, and 135. The CARAT questionnaire comprises 10 questions about upper and lower airway symptoms, sleep interference, activity limitation, and the need to increase medication over a 4-week period (Multimedia Appendix 1, also available on the web [22]). The total possible score ranges from 0 (minimum control) to 30 (maximum control) [21].

Secondary Outcome Measures

The secondary outcome measures are the mean change in the nasal endoscopy index (assessment of nasal membrane color, pale or hyperemia; rhinorrhea, watery or yellow; and inferior turbinate swelling, hypertrophy) and the mean change in laboratory tests at baseline and on day 45.

The nasal endoscopy index will be evaluated using the assessment method by Kim et al [20]. The doctor assesses the nasal membrane and inferior turbinate of the patient via nasal endoscopy. When evaluating the nasal membrane color, either the score for paleness or hyperemia must be 0 (eg, if the pale score is 2, the hyperemia score should be 0; if the nasal membrane color is normal, both pale and hyperemia scores are 0). The same rule is applied in the case of the rhinorrhea score. If there is no rhinorrhea, the scores for wateriness and yellowness are 0, and the yellow score is measured by evaluating the rhinorrhea parameter. An inferior turbinate swelling score is used to evaluate the nasal obstruction (Multimedia Appendix 2).

Timelines With Deliverables

The total study period is 24 months and divided into 3 cycles (ie, 1-3.5 months for the treatment and standard trial drugs) along with the procurement of the certificate of analysis and finalization of the laboratory tests. Staff recruitment, purchases of equipment and other logistics, finalization of case report forms (CRFs), etc, were also done during this period. The timeline for participant recruitment will be 15 months, the treatment period will be 1.5 months, and the follow-up period will be 3 months. Data compilation, analysis, report preparation, and publication will be done during the last month.

Sample Size

In a previous pilot study on this Ayurvedic intervention, a change of 14 points in the CARAT score was observed. For this study, it was assumed that a change of 10 points would be seen in the placebo group. With an SD of 6 points based on the results of the previous pilot study, a sample size of 35 participants per group was calculated to provide 80% power, with a 95% CI.

Assuming a dropout rate of 20%, a total of 90 participants, 45 per group, will be included in this trial.

$$n_1 = n_2 = 2\,\sigma^2\,[(Z_{1-\alpha/2}) + (Z_{\beta})]^2 \div \Delta^2$$

$$n_1 = n_2 = 2 * (6)^2\,[(1.96 + 0.84)]^2 \div (4)^2$$

$$n_1 = n_2 = 35$$

where Δ is $|\mu_2 - \mu_1|$ (the absolute difference between two means), σ is the variance of two means, n_1 is the sample size for group 1, n_2 is the sample size for group 2, α is the probability of type 1 error (usually .05), β is the probability of type 2 error (usually .2), and z is the critical *Z* value for a given α or β.

Randomization and Allocation

A randomization chart has been generated with the help of computer-generated random numbers. Participants will be randomized in a ratio of 1:1 to either the study group or the control group. The randomization schedule will be strictly controlled and remain with the biostatistician/data analyst. Sequentially numbered, sealed, opaque envelopes will be used to conceal the allocation.

Study Procedure

The participant will be screened for AR as per the inclusion criteria. Prior to any trial-related activity, the investigator will give the participants or their parents or guardians information about the trial verbally and in printed form. The investigator will ensure that the participant is fully informed about the aims, procedures, discomforts, and expected benefits of the trial. It must be emphasized that participation is voluntary, and participants have the right to discontinue the trial at any time without any prejudice.

After the screening, suitable participants will be enrolled in the study after signing the consent form. The required tests will be carried out. Within 1 week or as soon as the laboratory results are received and found to be within the eligibility limits, the participant will be enrolled in the study, with this day being recorded as visit 1 or the baseline visit. The treatment will be

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given to her after fulfilling all the formalities as per the protocol. The subsequent follow-up will be on day 16 (visit 2), day 31 (visit 3), day 45 (visit 4), day 75 (visit 5), day 105 (visit 6), day 135 (visit 7), and completion of the active treatment (visit 8). Participants will visit the study site 8 times during the trial. The activity details during each visit are presented in Table 1 and Figure 1.

Table 1. Study schedule.

Component	Screening	Baseline	Days 16 and 31	Day 45	Days 75 and 105	Day 135
Informed consent	✓					
Demographics and medical history		✓				
Assessment of Prakriti		✓				
Laboratory tests	✓			✓		
Clinical examination		✓	✓	✓	✓	✓
Assessment of Ayurvedic parameters		✓		✓	✓	✓
Concomitant medication		✓	✓	✓		
Rescue medication			✓	✓		
Assessment of adverse drug reactions			✓	✓		
Assessment of drug compliance			✓	✓		
Issue of trial drugs		✓	✓			
Control of Allergic Rhinitis and Asthma Test score	✓			✓		
Diagnostic nasal endoscopy		✓		✓		✓

Figure 1. Study procedure. NLR: Naradiya Laxmivilas Rasa.

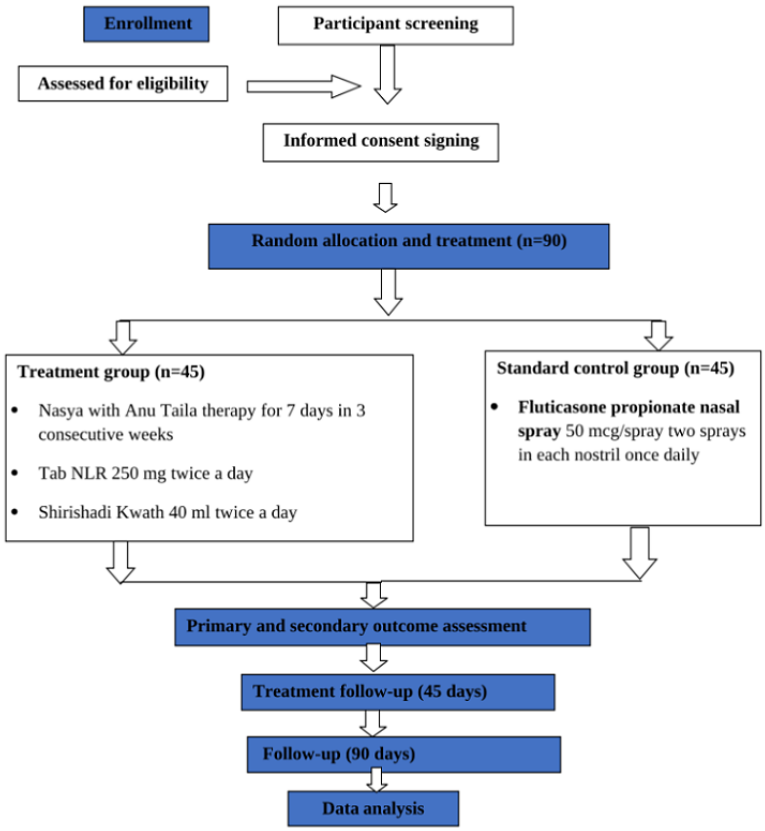

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Laboratory Tests

The laboratory tests (hematological/biochemical/ultrasound sonography) will be conducted at identified reputed laboratories or National Accreditation Board for Testing and Calibration Laboratories–accredited facilities. The laboratory tests and hematological examination carried out at baseline and the end of treatment (day 45) will collect the following values: hemoglobin (%), total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, absolute eosinophil count, fasting blood sugar, blood urea, serum creatinine, serum uric acid, total bilirubin, direct bilirubin, indirect bilirubin, serum alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and total serum immunoglobulin E.

Data Collection, Management, and Analysis

The data collection will include all information in the CRFs. All participants will be assigned an enrollment number, which will be used for CRFs and electronic databases. Consent forms and CRFs will be stored in locked cupboards, and electronic databases will be password protected. The data will be entered using the double-entry method for accuracy. All data will be accessible to the principal investigator and coinvestigators during and after the study, and will be available to sponsors and monitors as required. Data will be stored for 5 years and then destroyed. In case of dropout, 10% of the data will be inserted through the imputation technique. Proper documentation will be done to ensure accurate interpretation and verification related to the study. The analysis will be done by the CCRAS statistical unit. If any participants withdraw from the study prematurely, an attempt will be made to collect data for at least 1 month after enrollment, which includes the objective clinical and laboratory results. Data are important to the integrity of the final study analysis since early withdrawal could be related to the study drug's safety profile.

Statistical Methods

Continuous variables will be presented as means, SDs, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. When inferential analyses are conducted for continuous variables, they will be tested for normality. Nonparametric methods will be used for comparison of nonnormal data. Within-group comparisons will be done by using paired *t* tests, while between-group comparisons will be done using independent sample *t* tests for the data with normal distribution. Nonnormal data within the group will be compared using the Wilcoxon sign rank test, while between-group comparisons will be done by using the Mann-Whitney *U* test. Categorical data between groups will be compared using the χ^2 or Fisher exact test. A 2-sided *P* value <.05 will be considered statistically significant. Per-protocol and intention-to-treat analyses will be carried out at the end of the study. All data will be analyzed using STATA 16.1 (StataCorp).

Ethical Considerations

This research protocol has been reviewed and approved by the Institutional Ethics Committee of Vardhman Mahavir Medical College, Safdarjung Hospital, New Delhi (IEC/VMMC/SJH/Project/2023-02/cc-320 dated 28.03.2023). Participants will receive an information sheet with the research details given in two languages (Hindi and English). Voluntary signed informed consent will be obtained from the participants before any clinical trial–related procedure. The participants will be informed by the investigator that all trial data recorded will be treated in strict confidence. During documentation and analysis of the trial, the individual participant will only be identified by their enrollment number.

Participant confidentiality will be guaranteed, and only researchers will have access to the data. Participants are nominally compensated for their loss of wages and conveyance charges by paying an amount of 100 (US $1.19) for every visit to the hospital during the study period. The safety of the trial intervention will be evaluated by recording the incidence of adverse events on every scheduled follow-up visit. All adverse events during the study timeline will be recorded and monitored per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Guideline for Good Clinical Practice guidelines. The investigator will report the same to the institutional ethics committee and the sponsors as soon as possible.

For facilitating appropriate reference standards for scientific, ethical, and safety issues before the trial begins, this protocol has been developed according to the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) statements.

Data Safety and Monitoring

After 25% of the participants complete the study, the data will be analyzed for the trial drugs' safety. The project monitoring committee will monitor the trial's progress through review meetings and site visits as per the requirement for ensuring strict adherence to the trial protocol and accurate completion of the CRFs.

Drug Compliance

The compliance of taking trial drugs will be assessed at each visit during the follow-up visits (days 16, 31, 45, and 75) by assessing the approximate quantity consumed. The participants with ≥80% compliance will continue the study.

Prior and Concomitant Medication

The participants will be instructed to not take medications other than the trial drugs for any disease without consulting the investigators. The investigator will instruct the participants to consult them for any other signs and symptoms or if anything unusual occurred. The investigator will record any other medications the participants took.

Rescue Medication

Rescue medication will be used to alleviate any emergency condition at the investigator's discretion and will be documented in detail in the CRF.

Results

The project was funded by the CCRAS in February 2023. Participant recruitment was initiated on September 22, 2023. As of May 2024, we enrolled 72 participants in both groups.

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Data analysis will be completed by February 2025, and the results will be published afterward.

Discussion

Conclusions

Ayurveda scholars correlate AR with types of diseases (pratishyaya/pinasa; National Ayurveda Morbidity Code: I-1) based on the similarities in causes, clinical features, and treatment. This paper describes the protocol for the Ayurvedic management of AR. We undertook a randomized controlled trial to objectively assess the efficacy of Ayurvedic treatments for the management of AR and compared it with the gold standard intranasal corticosteroids for mild to moderate AR. We assessed the changes objectively by using the CARAT score and nasal endoscopy index as the outcomes for participants with AR.

The literature suggests that, based on the severity of the disease and condition of the patient, Ayurveda has multiple treatment modalities for this ailment, including Shodhana Karma (biocleansing therapy; Standard Ayurveda Terminology [SAT]: I.76) and Samshamana (palliative procedure; SAT: I.37) [23]. The primary treatment modality for managing diseases of the head and neck is Nasya (medication through the nasal route; SAT I.156). Most Ayurveda drugs and preparations used for the treatment of AR have been proven to have immunomodulatory, antiallergic, and anti-inflammatory properties [24]. Studies have demonstrated promising results of some Ayurveda interventions for managing AR. With this study, we aim to observe the effectiveness and safety of Ayurvedic management using the formulations of NLR, Shirishadi Kwath, and Anu Taila Nasya in reducing symptoms associated with AR, such as rhinorrhea, nasal itching, paroxysmal sneezing, nasal congestion, and obstruction. If beneficial, this study could contribute significantly to integrative approaches for managing AR.

Strengths and Limitations

The strengths of this study include its randomized design and inclusion of enough participants to allow for adequate statistical power for subgroup analyses. This study uses the CARAT score and nasal endoscopy index, which are well-validated instruments to assess AR.

One potential limitation of this study is that the investigators were aware of the participants' group assignment, and therefore, bias in favor of any particular group cannot be excluded. However, every effort was made to ensure blinding of the participants during the group allocation. An independent evaluator blind to study conditions was responsible for administering all study measures. A second limitation is the short intervention of the trial (ie, 45 days). However, the study follow-up was longer (ie, 90 days) to assess the recurrence of the symptoms/disease.

The results are expected to show better relief for AR for the treatment group. The protocol may also serve as a reference for the planning of similar clinical trials.

Acknowledgments

The authors are thankful to the institutional ethics committee for approving the protocol and to the Vardhman Mahavir Medical College, Safdarjung Hospital, and Central Ayurveda Research Institute, New Delhi, India, for allowing the study to be conducted at their facilities.

The study was funded by the Central Council for Research in Ayurvedic Sciences, New Delhi, India.

Data Availability

The findings will be disseminated to the public through conference presentations and published in open-access peer-reviewed journals. Analyzed data will be made available for interested researchers with a reasonable request after the publication of the results.

Authors' Contributions

SM, IPT, SR, PM, BG, NS, and RA developed the protocol. SM registered the protocol and generated the first draft of the manuscript. SM and IPT revised the manuscript according to suggestions. The manuscript was reviewed and approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Control of Allergic Rhinitis and Asthma Test.
[DOCX File , 15 KB - resprot_v13i1e56063_app1.docx]

Multimedia Appendix 2
Nasal endoscopy index for patients with allergic rhinitis.

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[DOCX File , 125 KB - resprot_v13i1e56063_app2.docx]

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Abbreviations

AR: allergic rhinitis
ARIA: Allergic Rhinitis and Its Impact on Asthma
CARAT: Control of Allergic Rhinitis and Asthma Test
CCRAS: Central Council for Research in Ayurvedic Sciences
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
NLR: Naradiya Laxmivilas Rasa
SAT: Standard Ayurveda Terminology
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Graded Intensity Aerobic Exercise to Improve Cerebrovascular Function and Performance in Older Veterans: Protocol for a Randomized Controlled Trial

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Abstract

Background: Growing health care challenges resulting from a rapidly expanding aging population necessitate examining effective rehabilitation techniques that mitigate age-related comorbidity and improve quality of life. To date, exercise is one of a few proven interventions known to attenuate age-related declines in cognitive and sensorimotor functions critical to sustained independence.

Objective: This work aims to implement a multimodal imaging approach to better understand the mechanistic underpinnings of the beneficial exercise-induced adaptations to sedentary older adults' brains and behaviors. Due to the complex cerebral and vascular dynamics that encompass neuroplastic change with aging and exercise, we propose an imaging protocol that will model exercise-induced changes to cerebral perfusion, cerebral vascular reactivity (CVR), and cognitive and sensorimotor task-dependent functional magnetic resonance imaging (fMRI) after prescribed exercise.

Methods: Sedentary older adults (aged 65-80 years) were randomly assigned to either a 12-week aerobic-based interval-based cycling intervention or a 12-week balance and stretching intervention. Assessments of cardiovascular fitness used the YMCA submaximal VO_2 test, basal cerebral perfusion using arterial spin labeling (ASL), CVR using hypercapnic fMRI, and cortical activation using fMRI during verbal fluency and motor tapping tasks. A battery of cognitive-executive and motor function tasks outside the scanning environment will be performed before and after the interventions.

Results: Our studies and others show that improved cardiovascular fitness in older adults results in improved outcomes related to physical and cognitive health as well as quality of life. A consistent but unexplained finding in many of these studies is a change in cortical activation patterns during task-based fMRI, which corresponds with improved task performance (cognitive-executive and motor). We hypothesize that the 12-week aerobic exercise intervention will increase basal perfusion and improve CVR through a greater magnitude of reactivity in brain areas susceptible to neural and vascular decline (inferior frontal and motor cortices) in previously sedentary older adults. To differentiate between neural and vascular adaptations in these regions, we will map changes in basal perfusion and CVR over the inferior frontal and the motor cortices—regions we have previously shown to be beneficially altered during fMRI BOLD (blood oxygen level dependent), such as verbal fluency and motor tapping, through improved cardiovascular fitness.

Conclusions: Exercise is one of the most impactful interventions for improving physical and cognitive health in aging. This study aims to better understand the mechanistic underpinnings of improved health and function of the cerebrovascular system.

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If our hypothesis of improved perfusion and cerebrovascular reactivity following a 12-week aerobic exercise intervention is supported, it would add critically important insights into the potential of exercise to improve brain health in aging and could inform exercise prescription for older adults at risk for neurodegenerative disease brought on by cerebrovascular dysfunction.

Trial Registration: ClinicalTrials.gov NCT05932069; https://clinicaltrials.gov/study/NCT05932069

International Registered Report Identifier (IRRID): DERR1-10.2196/58316

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KEYWORDS

aerobic exercise; exercise; functional magnetic resonance imaging; fMRI; veterans; quality of life; sedentary lifestyle; elderly; geriatrics; geriatric; older adults; cardiovascular disease; health promotion; aging; cognitive; cognitive health; physical health

Introduction

The rapid growth of the aging global population introduces significant health care and fiscal challenges due to an increased prevalence of age-related neurodegenerative disease and disability. For example, of the 60 million Americans over 65 years of age, it is estimated that 1 in 3 will be diagnosed with Alzheimer disease (AD) or a related dementia in their lifetime. Intertwined with aging-related pathologies are physiological changes in cerebrovascular function [1]. In fact, recent epidemiological and clinicopathological data indicate considerable overlap between cerebrovascular dysfunction in aging and AD [2,3]. While AD is an overt pathology, its "subclinical" progression appears to take decades before crossing a diagnostic threshold [4]. This subclinical stage spans a significant time frame for targeted interventions aimed at limiting vascular dysfunction in high-risk older adults.

It has been demonstrated that of all modifiable risk factors for dementing illness, decreasing sedentary behavior is the most statistically significant and effective measure to counter disease progression and associated cognitive decline in older adults [5]. For example, nearly a quarter million cases of AD could be prevented in the United States alone by improving the cardiovascular fitness profile in older adults. This staggering number is an exciting target not only for prevention during aging but also to better understand aging processes and their underlying mechanisms that are malleable to exercise. Equally significant, this number probably underestimates the total impact of increasing cardiovascular fitness due to its effects on other risk factors in aging, including hypertension and obesity [6].

This study will explore the impact of aerobic exercise on cerebrovascular health in older adults. Research over the last few decades has driven the continual promotion of exercise as one of the most impactful interventions for central nervous system health and function [7-9]. We know that older adults who are physically active have improved peripheral vascular health, but the impact of an exercise intervention on cerebrovascular health is less known. We will fill this gap by examining changes in basal cerebral perfusion and cerebral vascular reactivity (CVR) in older adults following a proven cardiovascular fitness intervention [10-12]. If our hypotheses of improved perfusion and CVR are supported, it would inform intervention strategies and add important new information about the potential of exercise to improve brain health in aging. This would have immediate implications for older adults at risk for neurodegenerative disease brought on by cerebrovascular dysfunction.

Methods

Overview

This study design followed a parallel group design where participants engaged in exercise for 12 weeks.

Participants

Older adult participants were pseudorandomized to 1 of two 12-week interventions: interval-based aerobic "spin" cycling exercise or nonaerobic balance and stretching exercise to serve as an active control condition. Each intervention was group-based and in-person, with trained personnel leading each class. Before beginning any portion of this study, we had to receive written approval from a qualified physician for participation in the fitness assessment and exercise intervention.

The key inclusion criteria and final participant pool will consist of right-handed, English-speaking individuals aged 65 to 80 years. Participants must also self-report a sedentary lifestyle defined as not participating in at least 30 minutes of moderate-intensity physical activity on at least 3 days/week for at least 3 months. Additionally, participants will not have dementia or any deficits in cognitive-executive function, as indicated by a Montreal Cognitive Assessment score (MoCA) score ≥26. Those with severe diabetes requiring insulin will also be excluded. However, individuals with controlled diabetes who meet our inclusion criteria for sedentariness and cognitive function will be allowed to participate. Individuals with any conditions contraindicated by magnetic resonance imaging (MRI) acquisition (including but not limited to ferrous metal implants, cardiac pacemakers or similar devices, claustrophobia, and morbid obesity) and those with any history of major psychiatric disorder (including but not limited to psychosis, major depression, and bipolar disorder) will also be excluded.

Measures

Overview

Pre- and posttests of cardiovascular fitness, cognitive and motor function, and brain imaging will be conducted over 2 days (<3 hours per day) within a 2-week time frame.

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Day 1: Cognitive/Motor and Physical Function Assessments

Table 1 highlights each of the physical, cognitive, and motor assessments performed in the study. Each of the indicated outcomes will be assessed before and after the 12-week interventions. This pre/post repeated measures design will be conducted on all randomized sedentary, older adult participants aged 65 to 80 years.

Table 1. Physical, cognitive, and motor assessments performed in the study.

Systems and assessment	Description	Outcomes	Component function	Relevant cortices
Cardiovascular-motor				
Modified Balke VO_2 test	Treadmill test where participants walk at a constant 3 mph and treadmill grade is increased by 2.5% every 2 minutes until 90% of estimated heart rate max ((220-age)*0.90) is achieved.	Estimated VO_2 max, peak VO_2	Cardiovascular fitness, gross movement economy	Whole brain (gray matter)
Cognitive-executive				
MoCA[a]	This brief instrument asks a series of questions to screen for cognitive impairment.	Scaled score (0-30). A score <26 indicates cognitive impairment and is a study disqualifier.	Visual/executive, naming, memory, attention, abstraction, orientation	Frontal, temporal, parietal
Digit span forward/backward	Participants are provided a sequence of digits and prompted to immediately repeat the sequence as heard (forward) or in reverse order (backward). If repeated correctly, the next trial is presented with a longer sequence. The task ends with 3 incorrect response attempts at a given digit span.	Longest digit span repeated correctly	Working memory	Frontal, temporal, parietal
D-KEFS[b]: verbal fluency	Letter fluency: participants recall words beginning with a specified letter as quickly as possible. Category fluency: participants recall words belonging to the designated semantic category.	Number of words within 60 seconds	Letter fluency, semantic fluency	Frontal (IFG[c])
D-KEFS: Color word interference (Stroop)	Inhibition: participants are presented with the words “red,” ”green,“ and ”blue“ printed incongruently in red, green, or blue font. They are instructed to state the font color as quickly as possible while minimizing mistakes. Switching: the same words with incongruent font colors are presented to participants; however, some words will be presented with a box outlining them. Participants are instructed to state the font color in nonoutlined text conditions and instead read each word aloud (as opposed to font color) when the word is outlined by a box.	Total time + (total time/100) x number of uncorrected errors	Response Inhibition, response switching	Frontal, temporal, parietal
Cognitive-motor				
D-KEFS: trail-making test	Participants are timed as they connect numbers and letters in ordered sequences	Time to completion (seconds)	Cognitive flexibility, visual sequence tracking	Visual, primary motor, frontal
Computerized N-back	Participants are provided a target letter before this task. They are then presented with a series of individual letters on a computer screen. They are instructed to denote, via keyboard response (1: “No”; 2: “Yes”), whether a presented letter corresponds with the target letter. The 0-back condition requires a response based on the letter immediately presented to them, and the 2-back condition requires a response based on the letter presented 2 steps behind the immediate letter presented.	Response accuracy (% correct), reaction Time (ms)	Working memory, processing speed, manual dexterity	Visual, primary motor, frontal

[a]MoCA: Montreal Cognitive Assessment.

[b]D-KEFS: Delis-Kaplan Executive Function System.

[c]IFG: inferior frontal gyrus.

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Day 2: MRI Environment

MRI Acquisition

MRI data will be collected on a 3T Siemens Prisma fit (Erlangen). This will consist of an anatomical T1-weighted MP-RAGE (magnetization-prepared rapid gradient-echo) scan (echo time = 3 ms, repetition time = 2500 ms, flip angle = 7^o) and 7 fMRI scans for each participant: 1 fMRI scan collected during dual-echo pCASL (pseudocontinuous arterial spin labeling) (TE1/TE2 = 10/25 ms, TR = 4000 ms, 1 fMRI scan collected during CVR (TE = 21 ms, TR = 1000 ms, voxel size = 3mm x 3mm x 3mm, flip angle = 50^o, number of volumes = 420), 3 runs of a language based task (TE = 25 ms, TR = 5800 ms, voxel size = 3 mm x 3 mm x 3 mm, flip angle = 70^o, number of volumes = 71), and 2 runs of a motor based task (TE = 25 ms, TR = 2000 ms, voxel size = 3 mm x 3 mm x 3 mm, flip angle = 70^o, number of volumes = 154).

Preprocessing

The preprocessing of anatomical T1w and fMRI data will be conducted using fMRI Prep 22.0.22 (RRID: SCR_016216), which is based on Nipype 1.8.5 (RRID: SCR_002502). The pipeline included brain extraction, tissue segmentation, and spatial normalization to the Montreal Neurological Institute (MNI) template space for the T1w. Regarding the fMRI data, preprocessing involved an estimation of the BOLD (blood oxygen level dependent) image and head-motion, slice timing correction, registration to the T1w image, and resampling to MNI space. Multimedia Appendix 1 contains the full preprocessing pipeline details.

Semantic Fluency

During the MRI session, participants will perform 3 blocks of a verbal fluency task programmed using via E-Prime software (version 3.0, Psychology Software Tools) [13] (Figure 1). At the start of each block, the phrase “please wait” is projected to participants via a 20-inch HP computer display for 20 seconds. The task is initiated when this phrase is replaced by a word corresponding to a specific semantic category. This category disappears and reappears 8 separate times, and participants are instructed to verbalize a single response corresponding to this category each time it reappears on the screen. Participants are also instructed to avoid repeating any responses from the same category. A single task block consists of 6 separate categories (requiring 8 individuated/nonrepeating responses per category). Interleaved between each semantic category is a “reading” condition. Here, participants are presented with the word “rest” 4 separate times and instructed to verbally respond with the word “rest” each time it appears. During these scans, the verbal responses will be manually recorded by an investigator and subsequently scored based on the total number of correct (and nonrepeating) responses divided by the number of response windows provided. The block score will be calculated as the number of correct responses/48 response windows × 100, and the session score as the number of correct responses/144 response windows × 100.

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Figure 1. Visual representation of a single block of the semantic fluency task performed during task-dependent functional magnetic resonance imaging (fMRI). Each participant will perform the sematic fluency fMRI before and after the 12-week interventions. This pre/post repeated measures design will be conducted on all randomized sedentary, older adult participants (65-80 years).

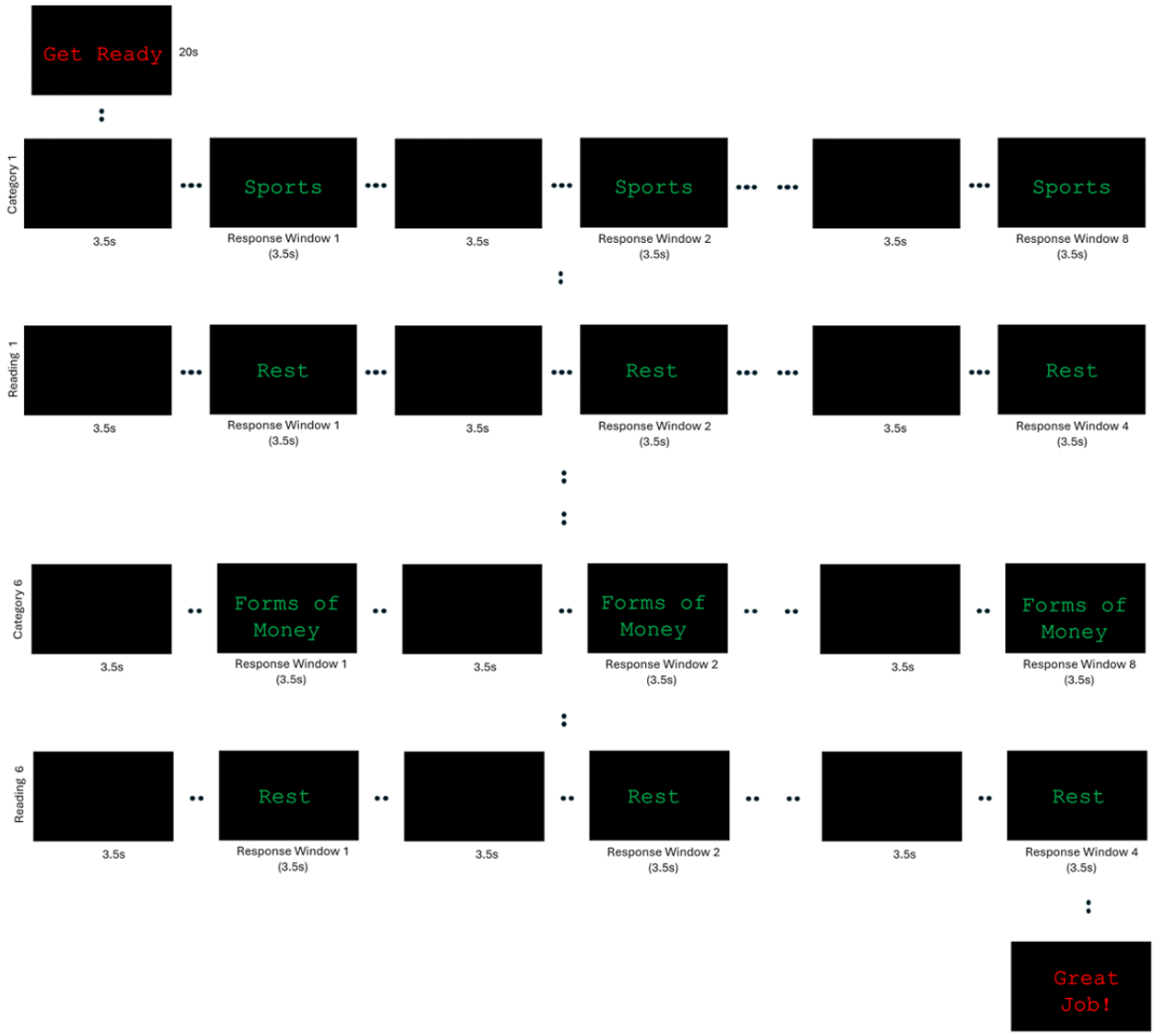

Motor Tapping

Participants will also perform 2 blocks of a motor tapping task programmed using PsychoPy [14] and using an MR-compatible 4-button box (MagConcept response unit) (Figure 2). Briefly, individuals are presented with a red dot in the center of the projected screen for 15 seconds. The task will commence when this dot turns green and subsequently alternates between red and green at a frequency of 1 Hz. Participants are instructed to press the button oriented to their index finger at the pace of the flashing green dot. Each block consists of five 28-second tapping intervals separated by six 28-second rest intervals. During these rest intervals, a solid red dot is projected, and participants are instructed to do nothing until they are presented with the next sequence of green dots.

The arterial spin labeling (ASL) sequence acquisition first magnetically labels blood water at the region of interest by applying a 180-degree radiofrequency inversion pulse. The labeled water exchanges with tissue water, which alters the tissue's magnetization and the image intensity, creating a "tag" image. This process is repeated without labeling blood to create a "control" image. Subtracting the control and tag images produces perfusion imaging that reflects the amount of arterial blood delivered to voxels within a given region of interest. This difference signal is directly proportional to cerebral blood flow and can be mapped on a voxel-wise basis to obtain regional blood flow information. To convert the difference signal (=control-label) into physiological units, a single-compartment model is utilized to obtain units of mL/100g/min. The ASL scan lasts approximately 7 minutes.

The aforementioned sequence parameters to be used for ASL acquisition are standard for assessing blood flow maps of the whole brain, including our regions of interest (inferior frontal and the motor cortices). The Harvard-Oxford cortical atlas developed in the MNI 152 atlas space will be the starting point for the frontal region of interest. The resulting ASL with corresponding T1-weighted images will be registered into the MNI 152 atlas space using nonlinear algorithms from the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL). The images will be imported into Analysis of

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Functional NeuroImages (AFNI) software (Scientific and Statistical Computing Core) for analysis.

CVR will be assessed using a block-design hypercapnic response paradigm where participants alternate between breathing room air and a 5% carbon dioxide (CO_2) gas mixture during fMRI (see the detailed description in [15]). Participants will be fitted with a nose clip and mouthpiece attached to a 2-way breathing valve that affords inhalation of normal room air or a CO_2 mixture filled in a 100 L Douglas bag. Additional physiological parameters, including end-tidal (Et) CO_2 and breathing rate, will be continuously monitored and recorded using a Philips NM3 capnograph. At the onset of this scan, participants will inhale normal room air for 50 seconds. A research staff member will then manually switch the valve to CO_2 air for 50 seconds and subsequently alternate between breathing conditions until three 50-second blocks of CO_2 breathing and four 50-second blocks of room air breathing have been collected (total scan duration ~7 minutes).

Provided that Et-CO_2 is essentially the input function to the brain vasculature, it is critical to measure this trace as it is a quantitative metric for the degree of stimulation the blood vessels receive. As such, the primary outcome from this measure is BOLD changes per mmHg of inhaled CO_2 in our regions of interest.

Figure 2. Visual representation of a single block of the motor tapping task performed during the functional magnetic resonance imaging (fMRI). Each participant will perform the sematic fluency fMRI before and after the 12-week interventions. This pre/post repeated measures design will be conducted on all randomized sedentary, older adult participants (65-80 years).

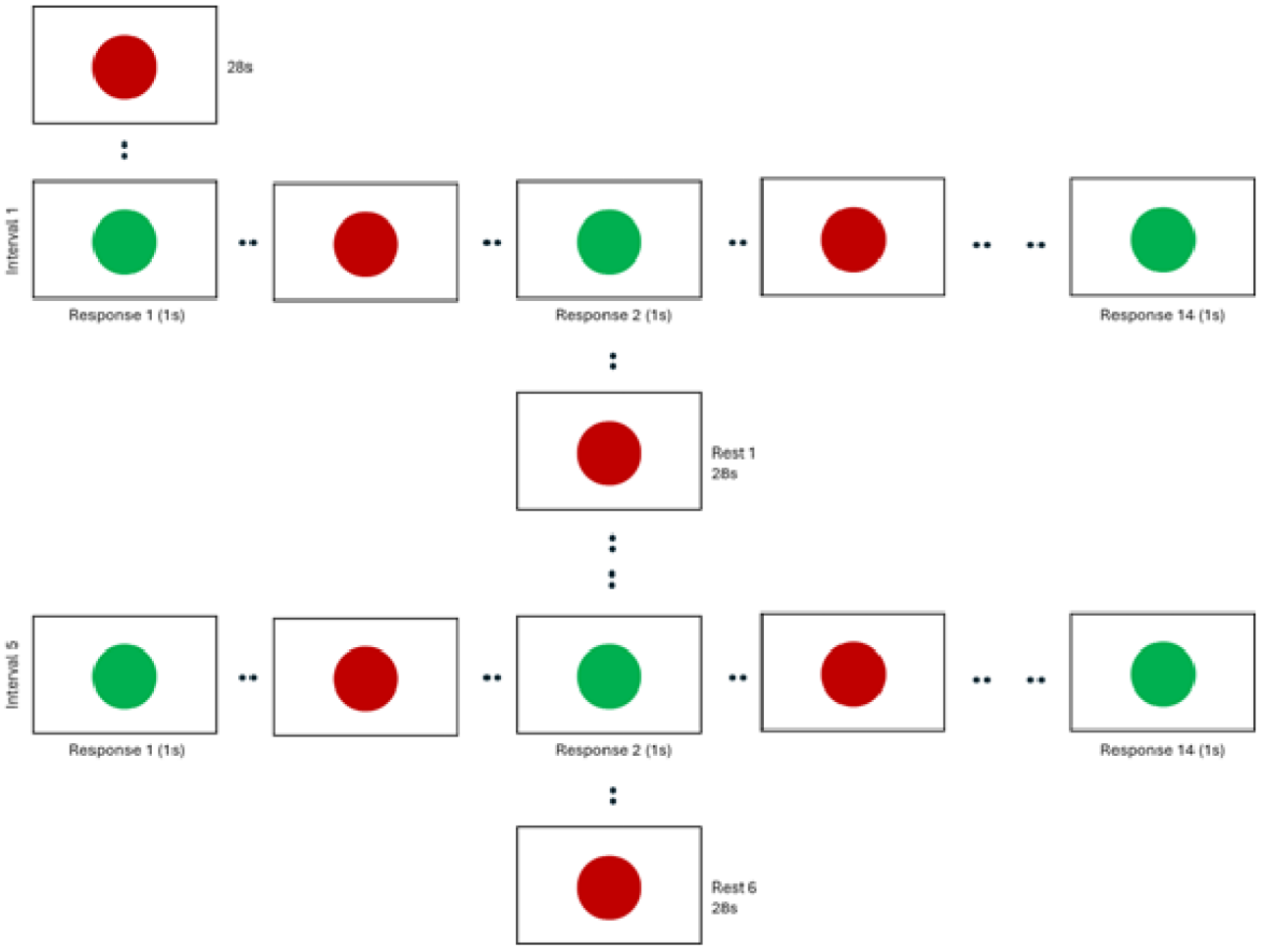

Ethical Considerations

All participants will provide informed consent before any testing commences. All study protocols will follow the Declaration of Helsinki and have been approved by the Emory University Internal Review Board and Atlanta Veteran Affairs (VA) Research and Development Office (RX002825-01). All interventions and assessments will take place at Emory University and Atlanta VA. Participants will be compensated US $150 for completing all pre/post assessments and the intervention. To ensure that all personal information collected during this study is kept strictly confidential, identifiable data will be stored securely and accessible only to authorized personnel involved in the research. Any published results will be presented in aggregate form, ensuring that individual participants cannot be identified. Participants' identities and sensitive information will be protected throughout and beyond the duration of this study, in accordance with ethical guidelines and legal requirements.

Data Analyses

For data analyses, we aim to determine whether the 2 groups (spin and control) have different responses to cerebral perfusion in the regions of interest following the intervention. Our a priori

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hypothesis is that individuals in the aerobic group will show increased perfusion in both the right and left inferior frontal gyri and motor cortices when compared to those in the control group. The primary outcome is cerebral blood flow in units of mL/100 g/min within each region of interest. We will test each mL/100 g/min region of interest value jointly using a mixed effects linear model to determine whether the mean change of the groups is significantly different across the time points (pre and post). The fixed effect will be group (spin vs control), and the random effect will be time (pre vs post). We expect that modeling the outcomes jointly will allow for some gains in power. This model will enable us to estimate the overall effects of time and the interventions, and most importantly, how the effects of the interventions differ with time. Additional analyses will use multiple regressions to describe the effect of participant demographics (gender, race, age, and hypertensive status) or by preintervention cognitive status (MoCA). A false discovery rate (FDR) of q=0.05 will be calculated and used to correct for multiple tests, and effect sizes will be computed.

Next, we aim to determine the impact of an aerobic intervention on CVR. Our a priori hypothesis is that individuals in the aerobic group will show increased CVR in both the right and left inferior frontal gyri and motor cortices when compared to those in the control condition. Similar to our analyses for perfusion, we will test each region of interest BOLD change value jointly using a mixed effects linear model to determine whether the mean change of the groups is significantly different across the time points (pre and post). The fixed effect will be group (spin vs control) and the random effect will be time (pre vs post). Additional analyses will use multiple regressions to describe the effect of participant demographics (gender, race, age, and hypertensive status) or by preintervention cognitive function (MoCA). An FDR of q=0.05 will be calculated and used to correct for multiple tests, and effect sizes will be computed.

After the aforementioned preprocessing steps are performed on ASL and CVR, the images will be scaled to accurately determine the relative percent signal change in BOLD induced by the task. Finally, task-induced BOLD changes (ΔBOLD) from pre- to postaerobic intervention and corresponding hemodynamic response functions will be quantified using the deconvolution technique.

Since the goal of this aim is to quantify the impact of baseline physiologic measures (ie, resting blood flow and CVR on task-induced BOLD changes), we plan to accomplish this task by modeling the contributions of CBF and CVR to ΔBOLD responses. The following equations describe our simple modeling approach using linear regression:

Where $_i$=pre or post session, *ROI* refers to the regions of interest, and coefficients *A* is the modeled intercept, *B* and *C* are modeled slopes for perfusion and CVR contributions, and *D* is the modeled slope for the interaction between perfusion and CVR respectively.

We will compare the slopes obtained for pre- and postexercise periods to explore how each of the baseline measures (ie, CBF and CVR) changes (1) in response to exercise and (2) within each condition (pre or post). We also aim to disentangle the perfusion and vascular influences on task-induced BOLD changes.

Additionally, modeling for the interaction will account for the coupling effect, which can provide insights into exercise-induced perfusion-CVR coupled effects. We plan to carry out the processing and modeling at the ROI level as it renders more detection power and is computationally less intensive. From a statistics standpoint, we will compute the F score to test the significance of the overall fitting of the model, and we will also obtain the *t* test score for each predictor (perfusion and CVR) to test the significance of their association with changes in the measured variable (ΔBOLD).

The average area under the curve (AUC) will be taken from the right and left inferior frontal gyri ROIs during semantic fluency for both pre- and postsessions. The AUC will be averaged from the right and left inferior frontal gyri and treated as a single ROI for this analysis. The base analyses for this aim will be 2 analyses of variance (ANOVAs), 2 groups X 2 times (before vs after aerobic exercise).

The analysis plan for behavioral performance will include the following dependent variables: VO_2, in-scanner verbal fluency performance, the motor task, as described previously, and our cognitive battery. Paired *t* tests will be performed to test for a pre-to-post effect. Spearman correlations (*r*) will be used to correlate behavioral performance to primary outcomes, and a mixed regression will be used to assess the influence of session (pre and post) on outcomes.

Potential Outcomes

Decreased vascular health due to aging, particularly sedentary aging, fosters both cognitive and motor dysfunction [16], which has implications for neurodegenerative disease. Task-based fMRI and the resultant BOLD map are dominant methods of neurocognitive investigation, particularly related to documenting the beneficial changes demonstrated with rehabilitation. At the forefront of much of this research is the use of task-based fMRI BOLD to quantify beneficial changes in cortical function following aerobic exercise [11,17,18]. While transformative, the true impact of this research is limited in scope until we can define the influence of cerebrovascular function on the well-documented beneficial change in BOLD response. Because the BOLD signal reflects the health and function of the cerebrovasculature [19,20], we believe the changes brought on by exercise are at least partially mediated by improved perfusion and CVR. No single imaging technique can resolve the complexities of imaging neural plasticity in brain systems; therefore, we propose a solution of combining imaging techniques and modeling the impact of perfusion and CVR on the BOLD response. We will model the hypothesized change in perfusion and CVR to the BOLD response following the intervention to quantify the percentage of variance both perfusion and CVR account for in the task-induced BOLD signal. This will allow us to understand the degree to which change in perfusion and CVR impacts the well-documented beneficial change in task-induced BOLD following exercise.

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Results

This study was funded on December 3, 2018, by the Department of Veteran Affairs (grant RX004563-01A1). Final data was obtained by mid-2024, and the preliminary results of this study are expected to be published by early 2025. We expect the research to offer a clearer understanding of how aerobic exercise improves health and cerebrovascular function in older adults. We believe this will guide exercise prescriptions for older adults at risk of neurodegenerative diseases and provide stronger justification for large-scale implementation and expanded access to this low-cost intervention

Discussion

Aim and Previous Findings

This study aimed to explore the impact of aerobic exercise on cerebrovascular health in older adults. We know that older adults who are physically active have improved peripheral vascular health, but the impact of an exercise intervention on cerebrovascular health is less known. Therefore, we will fill this gap by examining changes in basal cerebral perfusion and CVR in older adults following a proven exercise intervention. If the hypotheses of improved perfusion and CVR are supported, it would inform intervention strategies and have implications for age-related disease brought on by cerebrovascular dysfunction.

The brain uses ~20% of available oxygen for normal function, making tight blood flow regulation and oxygen delivery critical for survival [21]. This high demand, coupled with a lack of energy stores within the cortex, necessitates that cerebral blood flow be constantly and consistently maintained. In a normal physiological state, total blood flow to the brain is remarkably constant; however, with advancing age, basal cerebral blood flow declines by roughly 4 mL min per year [22]. It is presumed reactive oxygen species in the cerebral vasculature decreases nitric oxide (NO) bioavailability leading to the gradual decline in endothelial function and subsequently perforating arteries, arterioles, and capillaries [18]. Ultimately, extracellular matrix components lose elasticity, causing decreased vessel function and decreased blood flow [23].

Morphological studies have demonstrated age-related degradation throughout the intracranial vessels. However, these studies have demonstrated that age-related decreases in perfusion are notably amplified in the frontal cortex [15]. It has been highlighted that age-related decline in cerebral perfusion is not great enough to cause major ischemic injury but leads to hypoperfusion that prevents sufficient nutrients from reaching highly metabolically demanding areas (eg, frontal cortex) [24]. Of note, the decreased blood supply and inadequate delivery of nutrients is noted as a key physiologic process in age-related cognitive decline and specifically cognitive-executive processes partially mediated by the frontal cortex [25].

Impact of Exercise on Cerebral Blood Flow

Studies have focused on the beneficial effects of exercise on age-related changes in blood flow in the periphery, but less is known about aging and exercise on cerebral perfusion. In the periphery, exercise with an aerobic component is associated with improved perfusion in older adults compared to their sedentary peers [18]. Specific to the cerebral cortex, a cross-sectional study showed blood flow velocity in the middle cerebral artery, probed using Doppler, was significantly higher in adults with high levels of cardiovascular fitness [26]. Of note, the decrease in basal cerebral blood flow is tapered in people who report higher levels of physical activity [27]. Although these data give us an indication that aerobic exercise can enhance cerebral perfusion, it is currently unknown whether a proven aerobic intervention in previously sedentary older adults can benefit basal cerebral perfusion.

Decreased Cerebrovascular Reactivity in Aging

In addition to the static parameter of blood flow, the dynamic parameter of CVR has a critical role in cerebrovascular health and function. The cerebral vasculature must maintain blood flow within precise limits during rest, activity, disease, or injury. In healthy individuals, the cerebral blood flow is tightly regulated to meet the metabolic demands of the brain via vasoconstriction or vasodilation. Thus, the ability of cerebrovasculature to dilate in the face of increased demand is vital for cerebral function. However, the vasoproperties and vascular response to demand have repeatedly been demonstrated to degrade with age and neuropathology [6,18]. Most often, to quantify the efficiency of cerebrovascular response, the degree of vasodilation in response to a vasoactive agent (CO_2) is measured. Decreased responsiveness to CO_2 is a proven marker of CVR dysfunction and has been demonstrated to be sensitive to changes brought on by aging and neural disease [15,27].

While the mechanisms are difficult to directly probe in human cerebrovasculature, extensive work in the periphery demonstrates that age-related arterial stiffening and endothelial dysfunction play critical roles in the development of CVR dysfunction [18]. Impairment of the oxidative stress response and dysfunctional inflammatory pathways feed a cascade of age-related CVR malfunction. Dysfunction in the stress response and inflammatory pathways causes increased reactive oxygen species and reduced NO. Together, the increase in reactive oxygen species and decrease NO suppresses the response of the immune cells, causing systemic vascular endothelial dysfunction [28-30]. Behaviorally, decreased CVR has been observed in cognitive decline demonstrated in aging as well as dementia [31].

Impact of Exercise on Cerebral Blood Flow

Aerobic exercise has consistently been associated with enhanced flow-mediated dilatation in the brachial artery of older adults [32]. In the cortex, vasodilation of the cerebrovascular in response to a CO_2 challenge is associated with maximal aerobic capacity in both young and old adults [5,6,33]. Thus, in both the periphery and the cortex, those with higher levels of cardiovascular fitness have improved CVR to stimulus. CVR was also shown to increase among stroke survivors after 6 months of aerobic training [26]. Our own pilot data, described in greater detail in the subsequent paragraphs, demonstrate a marked decline in CVR with age. However, the degree of CVR decay is lessened in older adults who have high levels of

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self-reported aerobic activity. Thus, the purpose of this study is a key next step toward quantifying CVR change following a proven aerobic intervention in previously sedentary older adults.

Link Between Cerebral Perfusion, CVR, and Task-Based fMRI BOLD Response

Seminal studies have continually demonstrated that previously sedentary individuals who undergo exercise intervention show BOLD activity that coincides with improvements in an array of tasks in both motor and cognitive domains [7,11,34]. While the accessibility and ease of implementation have made BOLD a valuable tool, its interpretation is not straightforward [20]. BOLD is a convoluted neurovascular signal that arises due to the interplay between changes in blood flow and metabolism in response to inhibitory/excitatory stimuli (Figure 2). Task-induced BOLD change (ΔBOLD) is measured relative to the baseline BOLD signal, which means that baseline physiology (blood flow and perfusion; red box in Figure 2) affects the task-induced ΔBOLD (especially magnitude). We believe improvements in these baseline physiological factors are at least partially responsible for the well-documented, exercise-induced BOLD change. As noted, precise levels of blood flow depend on the health of the blood vessels that carry them. Blood carries important nutrients such as glucose and oxygen to support cellular energy demands; thus, the amount of baseline cerebral blood flow is an indirect measure of tissue baseline metabolic demand. It should be noted that perfusion is a proxy for baseline neural activity, as increased neural activity results in increased demand for blood flow [35]. Further, the blood vessels must dilate in response to an increased demand for blood flow. CVR is an index of baseline vascular health that is necessary to support efficient cerebral perfusion. Thus, to tease out the issue of vascular "plumbing" versus lower baseline neural activity, we need to quantify both perfusion and CVR. Taken together, for a better interpretation of task-induced ΔBOLD, it is important to understand the relationship between baseline cerebral physiology (perfusion and CVR) and task-induced ΔBOLD. To better understand the literature highlighting BOLD alterations following exercise, it is critical to quantify the impact of baseline physiologic measures, including perfusion and CVR on task-induced BOLD changes. We plan to accomplish this task by modeling the contributions of perfusion and CVR to ΔBOLD response both before and after the intervention.

Limitations

We have considered the following potential weaknesses. First, the length of the intervention (12 weeks) is not sufficient to induce change in cerebrovascular function. Of note, we encourage all our research participants to maintain a lifelong commitment to physical activity and hope that our 12-week intervention is the beginning of behavioral change. We do believe, however, that the 12-week timeline is sufficient to significantly change both perfusion and reactivity based on (1) the significant change demonstrated in cardiovascular fitness and BOLD response in 12 weeks utilizing the proposed spin intervention, and (2) numerous studies demonstrating changes in perfusion and reactivity in the periphery with 12-week interventions. Further, it is known that acute bouts of moderate-intensity aerobic exercise reduce both central and peripheral femoral artery stiffness [36], while increasing endothelial function [37,38] has anti-inflammatory benefits.

An additional potential weakness is that older adults will not be compliant and adherent to the intervention. Compliance in our studies generally has been at or above 90% with retention consistently being above 85%; however, the long-term success of interventions will depend on accessibility and sustainability. Community exercise programs that increase accessibility are yielding positive results [39], but sustainability is still an issue. Dealing with these issues in later-stage clinical trials is in our long-term goals once we know the full extent of the intervention and it is consistent with our long-term goals.

Conclusion

We believe this study will impact older adults and the state of science by defining and quantifying the positive impact of aerobic exercise on cerebrovascular health. Decreased vascular health because of aging, and particularly sedentary aging, lays the groundwork for both cognitive and motor dysfunction and is linked to neurodegenerative disease. Cross-sectional works and our preliminary data suggest that our aerobic exercise intervention will improve cerebrovascular health. If our hypotheses are supported, it would inform current intervention strategies and would add important new information on the implications of the cerebrovasculature on the BOLD signal. These findings would advance the current literature regarding the beneficial impact of exercise on brain health and function.

In terms of future direction, our lab has repeatedly shown that neurologic changes brought on by aging and disease may not be inevitable or immutable. We have new evidence that indicates increased levels of physical fitness through aerobic activity may mitigate losses in interhemispheric inhibition. We anticipate that cerebrovascular health in aging is intertwined with levels of interhemispheric inhibition, and both will improve throughout our exercise intervention. The next steps for our lab would be to further develop a continuum of research investigating the relationship between neurodegenerative disease, cerebrovascular reactivity, and physical activity, providing a cornerstone to build on our understanding of cerebrovascular disease processes and opportunities to prevent, intervene, or reverse.

Acknowledgments

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Data Availability

Data will be shared in accordance with the Department of Veteran Affairs Rehabilitation Research policy.

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Authors' Contributions

JRN, LCK, VK, and KMM conceived and designed the presented study. MOB, JRN, KMM, MAV, DGW, CAD, and TSN planned and carried out logistical and regulatory aspects of the study. MOB and TSN wrote the manuscript with consultation and input from all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preprocessing pipeline details.
[DOCX File , 338 KB - resprot_v13i1e58316_app1.docx]

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Abbreviations

AD: Alzheimer disease
AFNI: Analysis of Functional Neuroimages
ANOVA: analyses of variance
AUC: area under the curve
BOLD: blood oxygen level dependent
CO_2: carbon dioxide

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CVR: cerebral vascular reactivity
Et: end tidal
FDR: false discovery rate
fMRI: functional magnetic resonance imaging
FSL: Functional Magnetic Resonance Imaging of the Brain Software Library
MNI: Montreal Neurological Institute
MoCA: Montreal Cognitive Assessment Score
MP-RAGE: magnetization-prepared rapid gradient-echo
MRI: magnetic resonance imaging
NO: nitric oxide
pCASL: pseudocontinuous arterial spin labeling
VA: Veteran Affairs

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Protocol

Acupuncture as Adjuvant Therapy for Glaucoma: Protocol for a Randomized Controlled Trial

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Abstract

Background: Glaucoma is a chronic progressive optic neuropathy that necessitates lifelong treatment to reduce the decline of the optic nerve. Due to the extended and continuous treatments required for patients, complementary therapies are often considered alongside conventional treatments to enhance the effectiveness of the treatment. Acupuncture has demonstrated the potential to lower intraocular pressure in previous clinical trials, making it a promising glaucoma intervention.

Objective: The primary objective of this study is to conduct a single-center randomized control trial involving patients with glaucoma. Acupuncture will be evaluated as an adjunctive therapy. The trial aims to explore its effectiveness for glaucoma.

Methods: In this single-center randomized controlled trial, participants (N=50) with primary open-angle glaucoma will be randomly assigned to the treatment group, receiving ophthalmic acupuncture with “De Qi” sensation, or the control group, receiving minimum acupuncture stimulation on nonophthalmic acupoints. The intervention will consist of weekly acupuncture treatments for a total of 6 sessions. Participants will be assessed at 8 time points, which are baseline, during the intervention (6 times), and at a 3-month follow-up. The primary outcome measure is a change in the intraocular pressure before and after each acupuncture treatment. Secondary outcomes will include measurements of heart rate and blood pressure before and after acupuncture, best-corrected visual acuity, visual field, optical coherence tomography, optical coherence tomography angiography, the Glaucoma Symptom Scale, and the Glaucoma Quality of Life-15 questionnaire.

Results: Recruitment of participants for the trial commenced on June 28, 2023. A total of 10 participants have been enrolled to test the feasibility of the experiment. We anticipate that the preliminary data from this trial will be completed by December 2025.

Conclusions: This trial uses rigorous methodology and comprehensive outcome measurements to assess the clinical efficacy of acupuncture as an adjunctive therapy for glaucoma, providing valuable insights for future clinical treatment guidelines.

Trial Registration: ClinicalTrials.gov NCT05753137; https://clinicaltrials.gov/study/NCT05753137

International Registered Report Identifier (IRRID): DERR1-10.2196/57888

(JMIR Res Protoc 2024;13:e57888) doi:10.2196/57888

KEYWORDS

acupuncture; open-angle glaucoma; optical coherence tomography; intraocular pressure; glaucoma; adjuvant therapy; optic neuropathy; disease progression; ophthalmic disorders; optic; conventional treatment; efficacy; adjunctive therapy

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Introduction

Glaucoma is a chronic optic nerve disease involving progressive loss of retinal ganglion cells, necessitating long-term treatment with minimal side effects. Some patients may choose to supplement their conventional medical interventions with complementary or alternative medicine [1-3].

In complementary and alternative therapies, there is literature on treating glaucoma with acupuncture, auricular acupressure [4], herbal medicine [5,6], nutritional supplements [7], and Ayurvedic medicine [8]. Possible mechanisms for acupuncture treatment have been proposed, including the release of neurochemical substances through acupuncture stimulation; the influence of acupuncture on ocular blood flow parameters [9,10]; and the upregulation of neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor expression in the retina [11]. In an observation study on acupuncture treatment for glaucoma, Law et al [12] conducted a prospective study including 11 patients with glaucoma and observed a short-term increase in intraocular pressure (IOP) after acupuncture [12]. However, another study presented a different perspective, suggesting that acupuncture at the acupoints Jingming (BL1) and Qiuhou (EX-HN7) was beneficial in reducing IOP [13]. Systematic literature reviews have also supported the potential of acupuncture in lowering IOP and improving visual fields [14].

The objective of this single-center randomized control trial is to evaluate the clinical efficacy of acupuncture in the context of glaucoma and provide a reference for future clinical treatment guidelines.

Methods

Design and Setting

The study is designed as a single-center, parallel-arm, randomized controlled trial. It will take place in the clinic of China Medical University Hospital. The trial will be conducted from June 2023 until 50 patients finish acupuncture treatment and follow-up assessment. This protocol is reported following the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) 2013 statement, which defines standard protocol items for clinical trials [15].

The main purpose of the trial is to investigate the effectiveness of acupuncture in the treatment of glaucoma, including its potential to decrease IOP and reduce optic nerve damage. All participants will be randomly assigned to 2 groups: the treatment group and the control group. Participants in the treatment group will receive acupuncture treatment targeting acupuncture points related to ophthalmology, while participants in the control group will receive minimum acupuncture targeting nonophthalmic acupuncture points.

In addition, all participants will undergo ophthalmic examinations and follow-up. Figure 1 illustrates the enrollment process of the trial. The assessments will include measurements of IOP, heart rate (HR), blood pressure (BP), best-corrected visual acuity (BCVA), central corneal thickness, visual field (VF), optical coherence tomography (OCT) imaging, optical coherence tomography angiography (OCTA), and visual function questionnaire.

Figure 1. The enrollment process of the trial.

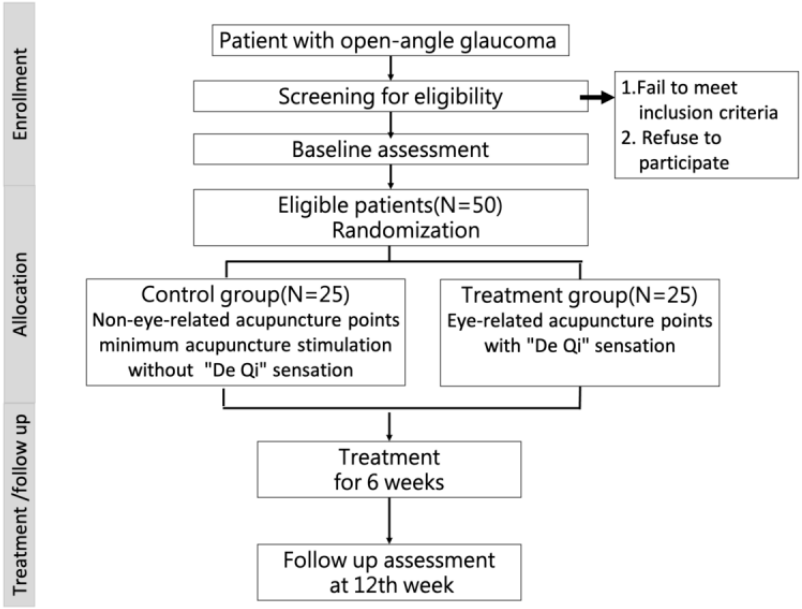

Sample Size Calculation and Power

Assuming an effect size of 0.40 and a type I error (α) of .05, a sample size of 40 people (20 in each group) is required to achieve a statistical power of 95% CI. Assuming a dropout rate of 25%, a total of 50 people (25 in each group) is needed (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Primary open-angle glaucoma was diagnosed at least 3 months ago
- Diagnosed with mild or moderate open-angle glaucoma
- Use 1 or 2 kinds of glaucoma drugs
- Age ≥20 years old
- All participants will be required to sign an informed consent form and cooperate with the experimental procedures

Exclusion criteria

- Accept any ophthalmic laser or surgery within 1 year
- High myopia (≤6.0D)
- Use of any drugs that affect intraocular pressure
- Visual acuity with correction lower than 0.2
- Previous or existing uveitis or retinopathy
- Unable to receive acupuncture treatment continuously or allergic to acupuncture needles
- Pregnancy or breastfeeding
- Refusal to sign the informed consent form

Ethical Considerations

Ethics approval was obtained from the institutional review board of China Medical University Hospital (CMUH111-REC3-210), and the trial was registered on ClinicalTrials.gov (NCT05753137). The informed consent discussion will take place before the trial. The informed consent form will be explained in clear and understandable language by a hospital doctor, and it will cover the intervention, risks, benefits, and patient rights in the trial. The informed consent form will be signed by the patients. If a patient wishes to withdraw from the trial, we will use the available data for the final analysis and accommodate their wishes accordingly. Confidentiality of information will be assured to the participants. All data will be anonymized or deidentified. As indicated on the recruitment poster, participants received NT $1000 (US $31) as compensation.

Randomization and Allocation Concealment

The participants will be randomly assigned to 2 groups with a 1:1 ratio using random number generation in Microsoft Excel. A computer-based simple random sampling method without stratification with a 1:1 ratio will be used. After the random allocation is completed, the researchers will assign sequential numbers (1-50) to the participants and prepare 50 folders. The appearance of the folders will be identical for both groups, and the section containing the participant's group and the intervention measures will be sealed. When participants complete the informed consent process, the acupuncturist will unseal the section and begin the acupuncture treatment.

Blinding

Upon revealing the treatment allocation, the acupuncturist will proceed to administer acupuncture based on the patient's assigned group. Throughout the entire experiment, all sterile needles will have the same appearance, thickness, and size. Only the acupuncturist will be aware of the patient's group allocation.

Participants will be informed that there are 2 different acupuncture groups, but they will only receive 1 of them. In addition, they will undergo treatment in separate rooms to prevent any communication between them. At the end of the trial, participants will be orally questioned about whether they are aware of the treatment strategy they received, confirming the effectiveness of the blinding implementation. Throughout the entire study, there will be no communication between the acupuncturist and the participants, as well as between the acupuncturist and the assessors. This is to maintain the blinding of the participants, researchers, assessors, and statisticians to the group allocation.

Interventions

Patients who meet the inclusion criteria at the Ophthalmology Clinic of China Medical University Hospital in Taiwan will be enrolled in a trial and randomly assigned to different groups. Both groups of patients will receive ophthalmic prescriptions and care. Acupuncture treatment will be performed using sterile acupuncture needles manufactured by "Jia Shun" (FDA 000470).

The acupuncturist will disinfect the acupoints using alcohol pads containing 70% alcohol. Then, they will apply acupuncture treatment by inserting the needles perpendicularly into the muscle layer, followed by up and down manipulation to induce the "De Qi" sensation in the treatment group. However, the control group will not experience the "De Qi" sensation; the needles will penetrate the skin, but the needling process will be halted as soon as the patients start feeling stimulation. During the 20-minute acupuncture session, the patients will maintain either a supine position or a sitting position. The acupuncturist is not allowed to communicate with the patients during the trial, except to inquire about the sensation of "De Qi." In addition, after patients are enrolled in the trial, if no serious adverse events

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occur, the ophthalmologist evaluator will remain blinded and isolated until the completion of the trial at the 12th week to maintain the integrity of blinding in the trial.

Treatment Group

In addition to routine ophthalmic prescription treatments, patients in the treatment group will receive traditional Chinese medicine–style acupuncture at the following bilateral acupoints once a week for 6 weeks: Fengchi (GB20), Cuanzhu (BL2), Sibai (ST2), Taiyang (EX-HN5), Hegu (LI4), and Taichong (LR3), for a total of 6 acupoints. The acupoint selection in this group is specific to treat symptoms of glaucoma. Figure 2 shows acupoints used in the treatment group.

Figure 2. Acupoints used in the treatment group: Fengchi (GB20), Cuanzhu (BL2), Sibai (ST2), Taiyang (EX-HN5), Hegu (LI4), and Taichong (LR3).

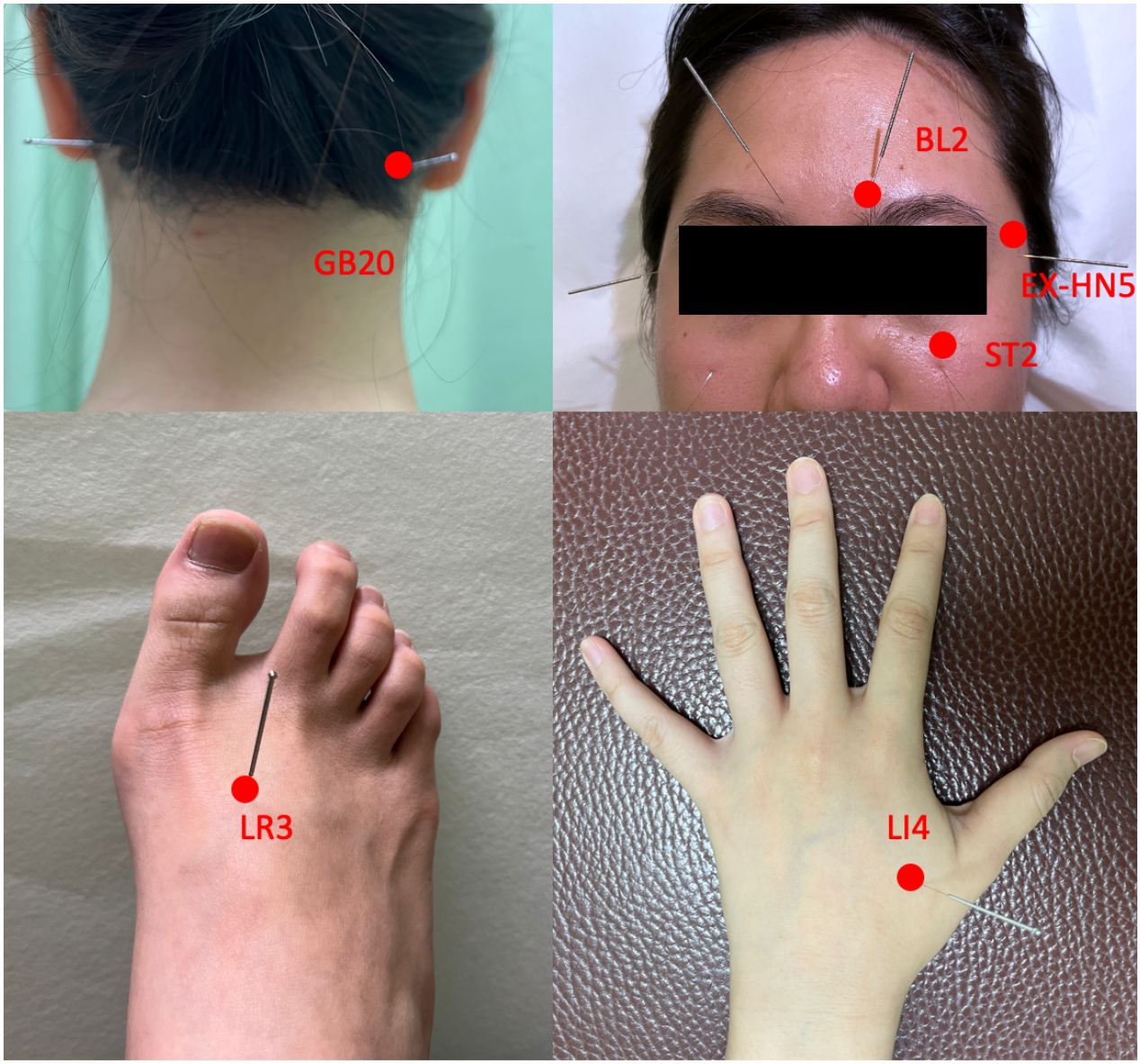

Control Group

In addition to routine ophthalmic prescription treatments, patients in the control group will receive minimum acupuncture stimulation at the following bilateral acupoints once a week for 6 weeks: Yinlingquan (SP9), Liangqiu (ST34), Xiajuxu (ST39), Yanglingquan (GB34), Shousanli (LI10), Sanyangluo (TE8), for a total of 6 acupoints. Figure 3 shows acupoints used in the control group. The nonophthalmological acupoints are not indicated for the treatment of ophthalmological pathologies and are not reported to improve ophthalmological function [16].

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Figure 3. Acupoints used in the control group: Yinlingquan (SP9), Liangqiu (ST34), Xiajuxu (ST39), Yanglingquan (GB34), Shousanli (LI10), and Sanyangluo (TE8).

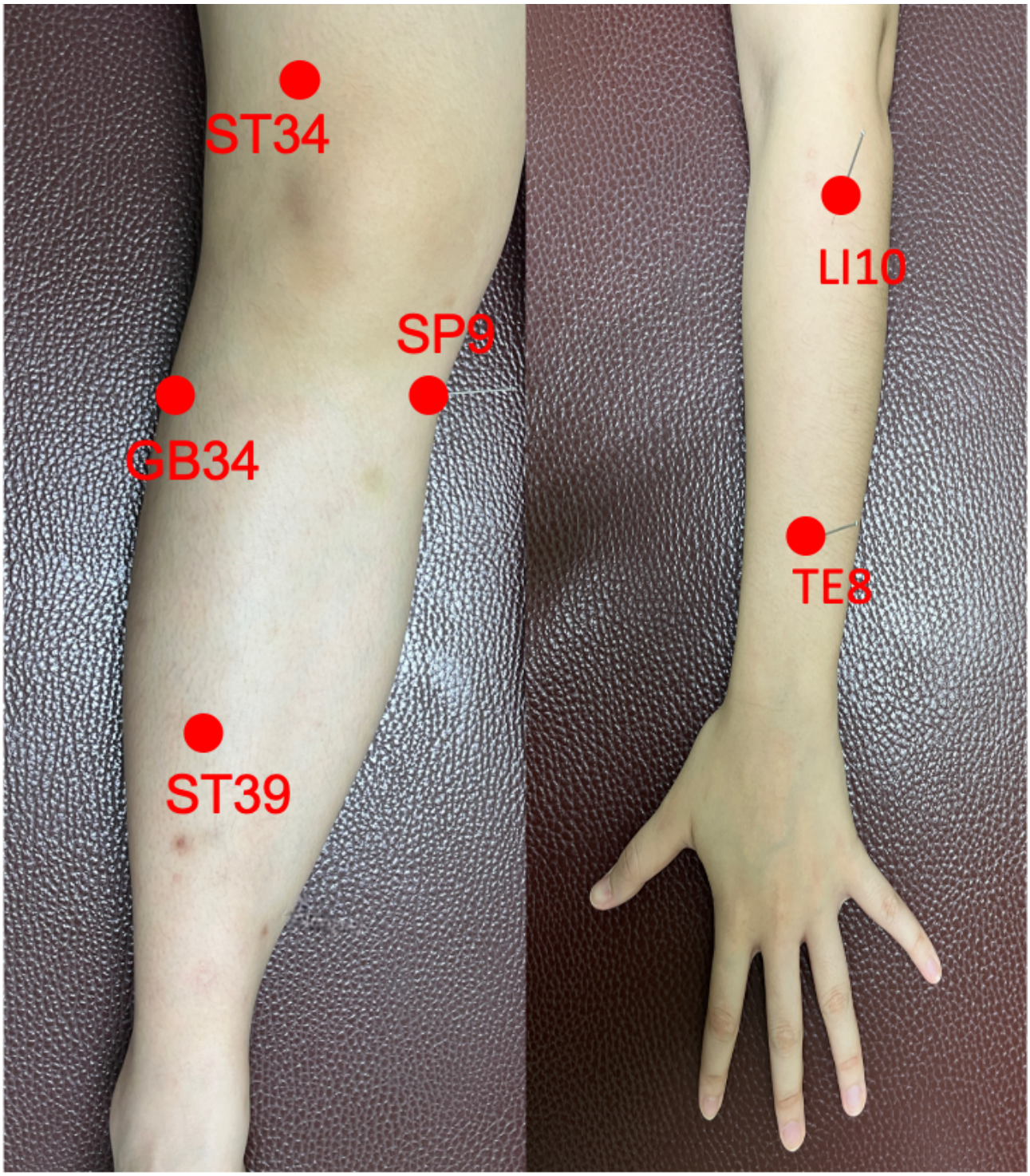

Outcome Measures

The primary outcome is the change in IOP as measured using the CT-80 Computerized Tonometer (TOPCON). Before the start of the trial, the participants' baseline IOP will be measured. Subsequently, IOP data will be collected before each acupuncture treatment and 15 minutes after the treatment. By comparing these measurements, the effect of acupuncture treatment on IOP can be assessed.

The secondary outcomes include the long-term effects of acupuncture on the eyes. Baseline measurements and measurements after the completion of the sixth acupuncture session will be taken using OCTA (AngioVue, QuickVue version, Optovue Inc) to assess the vessel density of the radial peripapillary capillary and macula. In addition, VF, OCT, BCVA, central corneal thickness, and 2 questionnaires will be recorded at baseline and during follow-up at week 12. VF measurements will be conducted using the Humphrey Field Analyzer 3 (ZEISS) to measure the mean deviation, pattern SD, and VF index values. OCT imaging will be performed using

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the ZEISS HD-OCT model 5000, and measurements of the retinal nerve fiber layer, ganglion cell complex and symmetry, and the cup-to-disc ratio will be recorded. The 2 questionnaires used in the trial are the Glaucoma Symptom Scale (GSS; score range 0-100) and the Glaucoma Quality of Life-15 (GQL-15; score range 0-75) [17,18]. These questionnaires are used to quantify the extent of functional impairment or inconvenience in patients with glaucoma. In addition, to ensure the safety of participants during the trial and to address other relevant considerations related to the pathophysiology of glaucoma, BP and HR measurements will be taken at baseline, before and after acupuncture sessions, and during follow-up assessments. Table 1 depicts the trial schedule, illustrating the journey of patients from initiation to the completion of the trial.

Table 1. Trial schedule, showing the journey of patients from initiation to the completion of the trial.

Time point	Enrollment	Treatment		Follow-up
	Visit day 1	Week 1-6	Week 6 (after acupuncture)	Week 12
Eligibility screen	✓			
Informed consent	✓			
Allocation	✓			
Acupuncture				
Treatment group		✓		
Control group		✓		
Data collection				
Intraocular pressure	✓	✓	✓	✓
Blood pressure	✓	✓	✓	
Heart rate	✓	✓	✓	
OCTA[a]	✓		✓	
OCT[b]	✓			✓
BCVA[c]	✓			✓
Visual field	✓			✓
Central corneal thickness	✓			✓
GSS[d]	✓			✓
GQL-15[e]	✓			✓

[a]OCTA: optical coherence tomography angiography.

[b]OCT: optical coherence tomography.

[c]BCVA: best-corrected visual acuity.

[d]GSS: Glaucoma Symptom Scale.

[e]GQL-15: Glaucoma Quality of Life-15.

Adverse Events

The study will document adverse reactions including the location of adverse reactions, the acupuncture site, the time of occurrence, the duration of symptoms, and the recovery status. In addition, appropriate medical resources and financial assistance, such as arranging emergency or outpatient care, will be provided to participants as needed.

Statistical Analysis

The statistical analysis will be performed by a statistician from the YCL's laboratory who is completely blind to patient allocation, using SPSS software (version 29.0; IBM Corp). The demographic data between the 2 groups, including sex, age, initial IOP, HR and BP, and BCVA will be compared using the 1-tailed Student *t* test. For the data from the 2 glaucoma questionnaires, a 1-way ANOVA will be used. In addition, a repeated measures analysis will be conducted in the trial. The data will be presented as mean (SD), and a *P* value of less than .05 will be considered statistically significant. Subgroup analysis will be conducted based on factors, such as age; gender; changes in IOP before and after treatment; VF, OCT, and OCTA data; and central corneal thickness, among others. In cases of small sample size, the Mann-Whitney *U* test and the Wilcoxon signed-rank test will be used if data do not follow normal distribution. Missing data will be analyzed using pairwise deletion.

Results

Recruitment of participants for the trial commenced on June 28, 2023. A total of 10 participants have been enrolled to test the feasibility of the experiment. We anticipate that the preliminary data from this trial will be completed by 2025.

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Discussion

Expected Findings

Glaucoma, the second leading cause of blindness globally, has an alternative medicine usage rate of approximately 5% to 14% [3,19]. Our study delves into the potential of acupuncture as an adjunctive therapy for glaucoma, drawing inspiration from compelling evidence from previous research. The selection of acupuncture points was based on the following arguments. Takayama et al [20] conducted acupuncture on 11 patients with open-angle glaucoma, targeting the acupoints BL2, M-HN9, ST2, ST36, SP6, KI3, LR3, GB20, BL18, and BL23. This treatment showed a significant reduction in IOP, had effects on the short posterior ciliary artery, and improved retrobulbar circulation [9]. The ophthalmic artery is responsible for the main blood supply to the eyes, while the anterior cerebral artery, middle cerebral artery, and ophthalmic artery are downstream branches of the internal carotid artery. In a series of studies, it has been observed that the acupoints GV20, GB20, and GB34 are associated with increased blood flow velocity in the anterior cerebral artery and middle cerebral artery, as well as increased cerebral blood flow [21-23]. In a mouse model of traumatic optic neuropathy, the acupoint GB20 significantly altered the expression of posttraumatic retinal genes. This suggests that acupuncture may target specific genes involved in the treatment of glaucoma, such as MT3 (associated with ocular neovascularization) and FBN1 (related to macular degeneration) [24].

LR3 is an acupoint located on the liver meridian. It is known for its functions related to “soothing the liver,” “regulating blood,” and “affecting the eyes.” According to traditional Chinese medicine theory, LI4 and LR3 are considered intermediate stations for the gathering and transformation of energy within the body. The combination of acupuncture stimulation at these 2 acupoints is referred to as “the 4 gates.” It is commonly used to promote the circulation of Qi and blood throughout the body and can influence brain areas involved in BP regulation, thus having a regulatory effect on BP [25,26]. LR3 activation leads to the activation of the visual cortex BA 19 and the inhibition of the ipsilateral BA 17 and 18 [27,28]. In addition, LR3 also results in a significant reduction in vascular resistance in the central retinal artery and short posterior ciliary artery [20].

Patients with migraine have an increased risk of developing open-angle glaucoma, and the most commonly used acupoints in acupuncture for this condition are EX-HN5 and GB20 [29-31]. LI4 is also believed to be associated with pain relief, particularly in the treatment of muscle or nerve pain or paralysis in the head and face, and has shown significant benefits [32]. Based on these beneficial effects, we chose the acupoint combination of EX-HN5, GB20, BL2, ST2, LI4, and LR3 for treatment.

The effectiveness of glaucoma treatment extends beyond clinical measures and should consider the holistic well-being of individuals. Therefore, this study assessed the influence of acupuncture on the daily life convenience and functionality of individuals with glaucoma, using the GSS and GQL-15 questionnaires. This includes evaluating the psychological, social, and functional dimensions that contribute to their overall well-being. By extending the focus to these elements, we gain a better understanding of the treatment’s effects on the individuals’ day-to-day experiences and functionality. In this trial, the impact of acupuncture on the daily life convenience and functionality of patients with glaucoma was quantified using the GSS and GQL-15 questionnaires. The GSS is a simple questionnaire used to measure symptoms and functional loss in daily life. In the 1998 version of the GSS by Lee et al [17], the questionnaire consists of 10 items, and each eye is rated on a 5-point scale ranging from 0 (very bothersome) to 4 (not bothersome). The scores are then converted to a scale of 0 to 100 for statistical analysis, where 0 represents the presence of significant problems and 100 indicates the absence of problems [18]. In addition, the GQL-15 by Nelson et al[18] assesses the impact of glaucoma on the quality of life of patients. It consists of 15 items related to various aspects of daily life, such as reading newspapers and walking after dark. Each question is rated on a scale of 0-5. The total score ranges from 0 to 75, with a higher score indicating a poorer quality of life.

Conclusions

This study strengthens our understanding of acupuncture as a potential adjunctive therapy for glaucoma, The methodological rigor, including a randomized controlled trial, enhances the credibility of findings. The comprehensive evaluation, incorporating diverse outcome measures such as IOP, cardiovascular parameters, and various ophthalmic assessments, provides valuable insights into acupuncture’s impact on glaucoma management. The 12-week observation period contributes valuable information on both short-term and potential long-term effects.

However, limitations include the single-center design, affecting generalizability, and a modest sample size that may compromise statistical power. The study’s duration may not fully capture long-term effects.

Acknowledgments

We appreciate the personnel at the Ophthalmology Department of China Medical University Medical Center for their knowledge and professional technical support. The investigators would like to express their sincere appreciation for the valuable contributions of the participants. This research is funded by China Medical University (CMU111-IP-02) and the Ministry of Science and Technology of Taiwan (MOST 113-2320-B-039-047-).

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Data Availability

Data sharing does not apply to this article as no datasets were generated or analyzed during this study. For any additional inquiries, please contact the corresponding author directly.

Authors' Contributions

YFL and YCS conducted data analysis and interpretation. YFL conceptualized the study. YFL performed a formal analysis. Funding acquisition was managed by YCL. Both YFL and YCS were involved in the investigation, and YFL, YCS, YCL, and HJL contributed to the methodology. Project administration was handled by YCL and HJL, and they were responsible for the allocation of resources. YCL also oversaw the supervision. YFL took charge of data curation, formal analysis, and software usage. Validation was conducted by YCS and YCL.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH (V 1.6.1).
[PDF File (Adobe PDF File), 1618 KB - resprot_v13i1e57888_app1.pdf]

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Abbreviations

BCVA: best-corrected visual acuity
BP: blood pressure
GQL-15: Glaucoma Quality of Life-15
GSS: Glaucoma Symptom Scale
HR: heart rate
IOP: intraocular pressure
OCT: optical coherence tomography
OCTA: optical coherence tomography angiography
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
VF: visual field

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Protocol

Over-the-Counter Hearing Aids Versus Traditional Hearing Aids in Patients With Mild-to-Moderate Hearing Loss: Protocol for a Noninferiority Randomized Controlled Trial

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Abstract

Background: With the aging of society, the prevalence of hearing loss (HL) is increasing. Currently, approximately 5% of the global population has HL, and this number is projected to reach 7 million by 2050. Although hearing aids (HAs) are the primary treatment for HL, their use is limited by barriers such as high costs and social stigma. To address these limitations, over-the-counter (OTC) HAs have been introduced, but their effectiveness and drawbacks require further investigation.

Objective: This study aims to conduct a noninferiority randomized controlled trial comparing OTC HAs with traditional HAs to assess the clinical effectiveness of OTC HAs.

Methods: We designed a noninferiority randomized controlled trial comparing OTC HAs and traditional HAs in adults with mild-to-moderate HL. A total of 64 participants (32 per group) will be recruited. Randomization will be performed using block randomization (block sizes of 2 or 4) with an equal allocation ratio. The study will include 2 types of HAs: an OTC HA (Jabra Enhance Pro) and a traditional HA (LiNX Quattro LE561-DRW) by GN ReSound A/S. OTC HAs will be self-fitted using a smartphone app, while traditional HAs will be fitted by a licensed audiologist using the National Acoustics Laboratories–Non-Linear Prescription, second generation. Assessments, including functional gain, real-ear measurement, speech audiometry, and questionnaires, will be conducted at 6-month intervals over the course of 3 visits. Statistical analysis will compare the 2 outcomes, focusing on functional gain, to determine noninferiority.

Results: This study is scheduled to begin in August 2024 and has not yet recruited any participants. The study will be conducted over 2 years, from August 2024 to July 2026. Each participant will have 2 follow-up visits at 6-month intervals, making the total follow-up period 1 year.

Conclusions: Since 2022, the introduction of OTC HAs has revolutionized access to these devices. Researchers, clinicians, and the general public are keen to evaluate the clinical effectiveness of OTC HAs, as more individuals will likely use them for HL. This increased usage will provide valuable real-world data to understand the benefits and limitations of OTC HAs. Monitoring the outcomes and user feedback will provide insights into their effectiveness and impact on hearing rehabilitation.

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KEYWORDS

hearing aids; over-the-counter hearing aids; correction of hearing impairment; randomized controlled trial; evidence-based medicine; hearing loss; aging; hearing sensitivity; mobile phone

Introduction

Background

As society undergoes a rapid transition toward an aging population, the prevalence of hearing loss (HL) is significantly increasing. According to the World Health Organization, approximately 5% of the global population (4.3 million individuals) currently has HL, and this number is projected to reach 7 million by 2050 [1]. One of the reasons HL has attracted attention recently is due to its association as the most modifiable risk factor for dementia [2]. Therefore, proactive hearing rehabilitation is crucial.

Hearing aids (HAs) serve as the first-line management for patients with HL. However, several barriers can prevent people from using HAs. These barriers include economic limitations such as high costs (ranging from US $3000 to US $6000 a pair), limited insurance coverage, and social stigma [3-6]. As evidence of these barriers, one study demonstrated that the rate of purchasing HAs among individuals with HL was 17.4%, whereas the use rate was merely 12.6% [7].

In an effort to increase accessibility to HAs, the US Food and Drug Administration (FDA) has recently created a regulatory category for over-the-counter (OTC) HAs. These are classified as a type of medical device that can be purchased without requiring a prescription or consultation with licensed hearing health care professionals (HHPs) [8]. Unlike traditional HAs, OTC HAs are specifically designed for adult patients with mild-to-moderate HL. The introduction of OTC HAs is anticipated to broaden access to affordable hearing care for millions of patients who currently have HL but are not adequately served by the traditional HA market.

The market for OTC HAs has been expanding rapidly. However, due to the recent FDA approval, empirical research is not available regarding their clinical effectiveness. Furthermore, OTC HAs come with multiple disadvantages that require thorough validation. One prominent drawback is that patients are responsible for fitting the HAs themselves, potentially leading to reduced accuracy in amplification [9]. In addition, the predominant older adult population, who may lack technical proficiency, may encounter difficulties in operating OTC HAs. Consequently, there is a need for studies aimed at demonstrating that OTC HAs are not inferior to traditional HAs.

To address this, we aim to conduct a noninferiority randomized controlled trial (RCT) comparing OTC HAs with traditional HAs. We hypothesize that OTC HAs will demonstrate noninferiority when compared with traditional HAs.

Objectives

The primary objective of this study is to compare the effects of OTC HAs and traditional HAs on patients with HL. The primary outcome of interest is functional gain at the conclusion of a 1-year intervention period. Secondary objectives include assessing the impact of OTC HAs and traditional HAs on speech audiometry in both quiet and noisy environments, conducting real-ear measurement (REM), and administering questionnaires to gather additional information.

Methods

Study Design and Setting

In this noninferiority RCT, patients will be randomly assigned to 2 groups. The study will take place at a tertiary hospital in South Korea, serving as a single center for the research. The protocol for this study follows the guidelines outlined in the Standard Protocol Items Recommendations for Interventional Trials statement [10] (Figure 1).

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Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. HA: hearing aid; OTC: over-the-counter; PTA: pure-tone audiometry; REM: real-ear measurement; WRS: word recognition score.

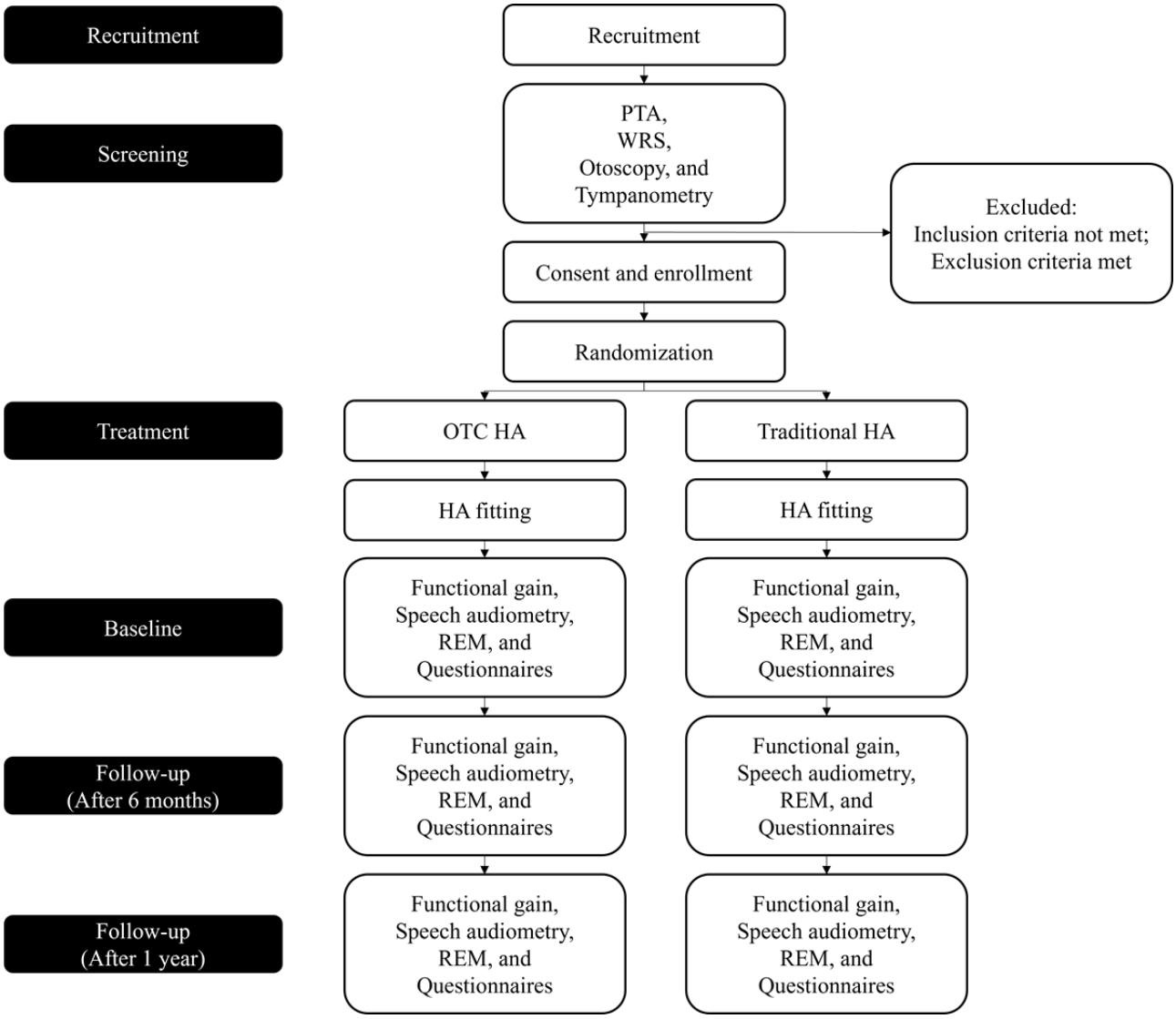

Study Population

To be eligible for this study, participants must meet specific inclusion and exclusion criteria (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Voluntary willingness and ability to participate
- Aged 18 years or older
- Proficiency in the Korean language
- Hearing threshold ranging from 26 dB to 55 dB (indicating mild-to-moderate hearing loss) based on the average of 4 frequencies (0.5, 1, 2, and 4 kHz) in both ears
- Absence of significant abnormalities in the outer ear and middle ear as determined by otoscopy
- Type A tympanogram
- No previous history of sudden hearing loss

Exclusion criteria

- Mental incapacity to participate in this study
- Previous use of hearing aids
- Absence of outer or middle ear diseases

Sample Size

The number of participants for this study was determined using G*Power (version 3.1.9.4) software (Institute for Experimental Psychology). The estimated sample size was based on the findings of a previous study [11]. The calculated total sample size was 56 participants, considering an effect size (Cohen *d*) of 0.9, an error probability of .05, and a power (1– error probability) of .95. Therefore, considering an attrition rate of 15%, a total of 64 participants will be recruited, with 32 participants allocated to each group.

Recruitment

Announcements regarding the study will be disseminated through hearing-related support groups, audiology organizations, newsletters (daily newspapers, magazines, etc), hearing clinics of primary and secondary hospitals, otorhinolaryngology outpatient clinics of a tertiary hospital, and social media platforms (Facebook [Meta], Instagram [Meta], X [formerly known as Twitter], etc). Individuals who express interest will receive information and undergo a screening test. If they meet the inclusion criteria, they will be enrolled in this study.

Assignment to Intervention Groups

After inclusion, the patients will be randomly assigned to 1 of 2 intervention groups: OTC HAs or traditional HAs. Randomization will be performed electronically using R software (R Core Team) with block randomization and an equal allocation ratio of 1:1. The block sizes will be 2 and 4. The researchers will remain blinded to the randomization sequence. However, due to the nature of the intervention, it is not possible to blind the participants and care providers to their assigned group.

Data Collection Methods

The results will be recorded on paper and then transferred to a Microsoft Excel document for data entry. These files will be stored as electronic records for archiving purposes.

Data Management

The data will be securely stored on a designated server and access will be strictly controlled and limited to authorized personnel authorized by the institutional review board (IRB). Only individuals with explicit permission will have the authority to manage and access the recorded data.

Statistical Analysis

In the descriptive analysis, continuous data will be presented using means or medians, depending on their normality. Categorical data will be quantitatively presented, including the number and percentage for each variable. For primary and secondary outcome variables, if the normality assumption is met, repeated measurements of analysis of variance will be conducted. If the normality assumption is not met, the Friedman test will be used. Independent variables will be types of HAs and time, while the dependent variables will be outcome variables. Post hoc analysis using Bonferroni correction will be conducted for significant variables. If there is no significant difference in the primary outcome of functional gain between the 2 HAs, it will be considered noninferior.

Interventions

The study involves 2 types of HAs: (1) an OTC HA (Jabra Enhance Pro; GN ReSound A/S) and (2) a traditional HA (LiNX Quattro LE561-DRW; GN ReSound A/S). Both HAs used in the study are receiver-in-canal type devices and are manufactured by the same company. The OTC HAs will be fitted by the patients themselves following the manufacturer's guidelines through a dedicated smartphone app. On the other hand, the traditional HAs will be fitted by a licensed audiologist using the National Acoustics Laboratories–Non-Linear prescription, second generation (NAL-NL2). All HA settings, such as noise reduction, directionality, and feedback cancellation, will be set to their default values.

Outcome Measurements

The participants will be screened using otoscopy, tympanometry, PTA, and WRS at the first visit (baseline). The participants who

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pass the screening tests will undergo main tests, including functional gain, REM, speech audiometry, and questionnaires at every visit.

Screening Tests

PTA Assessment

PTA will be conducted to determine participants' hearing sensitivity. PTA will be conducted using an audiometer (GSI Audio Star audiometer; Grason-Stadler Inc) with TDH-39 headphones in a double-walled soundproof booth. PTA measurements will be performed in each ear at 0.25 kHz and 8 kHz frequencies following standard procedures [12]. The participants will respond by pressing a button each time they hear the tone. A total of 4 frequency averages (0.5, 1, 2, and 4 kHz) will be calculated.

WRS Assessment

WRS provides insight into the participants' ability to discriminate speech sounds. In this study, WRS will be measured using the same audiometer used for PTA with the TDH-39 headphone in a double-walled soundproof booth. A compact disc player (Yamaha TSX-B232; Yamaha Corporation) will be connected to the audiometer. A total of 25 monosyllabic words [13] at the most comfortable level will be presented. The participants will be asked to repeat the word back to the tester. Percentage-correct scores will be calculated for scoring.

Otoscopy

Otoscopy (mini 3000 F.O.; HEINE Optotechnik GMbH and Co) will be used to visually examine structures of the external ear canal, tympanic membrane, and middle ear. The audiologists will insert the cone of the otoscope into the participants' ear canal.

Tympanometry

Tympanometry is an objective, physiological measurement of acoustic admittance of the middle ear as a function of air pressure in a sealed ear canal. A tympanometry will be conducted with a tympanometer (Titan; Interacoustics A/S). The audiologist will insert the probe tip into the participants' ear canal to measure the air pressure produced by the tympanometer. The tympanogram will illustrate positive and negative variations in air pressure.

Main Tests

Functional gain

Functional gain will be measured by comparing the hearing thresholds at predetermined frequencies before and after wearing the HAs in a double-walled soundproof booth. The functional gain is theoretically equivalent to the real-ear insertion gain measured through REM. By comparing the functional gain at each frequency with the fitting formula for HA, we can determine the appropriateness of the HA fitting.

Speech Audiometry

In quiet conditions, a different list from the Korean standard monosyllabic word lists for adults [13] used in WRS will be used. The testing will be conducted in a free field sound, where 25 target monosyllabic words will be presented at a level of 50 dB HL. The participants will be instructed to repeat the words. The presentation of the target sounds will be positioned 1 meter away from the participant, facing them directly (0°). The percentage of correct responses will be compared before and after wearing HAs. In noisy conditions, the Korean version of the Hearing In Noise Test (K-HINT) will be used [14]. The K-HINT presents speech spectrum noise from front and lateral speakers. For each condition, the noise level is set to 65 dBA, while the speech level is adjusted to measure the reception threshold for speech (RTS). The RTS is determined by measuring the signal-to-noise ratio at which target sentences are perceived correctly 50% of the time. RTS will be compared before and after wearing HAs.

REM Assessment

We will use the Aurical Free Fit device (Natus) for REM. After fitting the HAs on the patient, a probe tube will be inserted near the tympanic membrane within a proximity of 6 mm. The REM process involves entering the PTA results into the REM software, selecting the fitting formula (NAL-NL2), and comparing the target gain derived from the fitting formula with the real-ear insertion gain obtained from the REM. During the measurements, participants will hear the stimulus sound from a speaker placed 1 meter away at 0° azimuth. The stimulus sound used will be an Inter Speech Test Signal presented at an intensity of 65 dB SPL, which is comparable with the average level of conversational speech.

Questionnaires

The Korean version of the Abbreviated Profile of Hearing Aid Benefit (K-APHAB) consists of a total of 24 items divided into 4 subscales of ease of communication, reverberation, background noise, and aversiveness to measure HL in everyday situations. For each item, a 7-point Likert scale is used (always=1 [99%]; never=7 [1%]). The benefit of the HA will be calculated as unaided scores minus aided scores [15]. The Korean version of the international outcome inventory for hearing aids (K-IOI-HA) is composed of 7 questions designed to subjectively evaluate the performance of HAs solely based on daily use, benefit, residual activity, satisfaction, residual participation restrictions, impact on others, and quality of life. Each item is rated on a 5-point scale, with higher scores indicating greater benefit. The total score ranges from 0 to 35 points [16].

Participant Timeline

All participants will undergo in-person assessments over the course of 3 visits conducted at 6-month intervals. During the first visit, the participants will be screened and randomly assigned to 1 of 2 groups: OTC HAs and traditional HAs. Each HA will be fitted according to the guidelines described in the "Interventions" section before conducting the main tests. Subsequently, the participants will undergo main tests and be instructed to use the HA for at least 6 hours daily throughout the intervention period. After 6 months, the participants will return to the clinic for assessments using the same tests from the first visit as an intermediate evaluation. During the final visit (after 6 months), the participants will undergo the same evaluations as during the second visit and return the HAs. If participants experience any discomfort or issues with HA usage

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during the study period, they will be encouraged to visit the clinic at any time for adjustments (Table 1).

Table 1. Timeline for this study.

Outcomes	Screening and baseline	After 6 months	After 1 year
Study consent	✓	—[a]	—
Screening tests			
PTA[b]	✓	—	—
WRS[c]	✓	—	—
Otoscopy	✓	—	—
Tympanometry	✓	—	—
HA[d] provision and fitting	✓	✓	—
Main tests			
Functional gain	✓	✓	✓
Speech audiometry			
Quiet	✓	✓	✓
Noisy (K-HINT[e])	✓	✓	✓
REM[f]	✓	✓	✓
Questionnaires			
K-APHAB[g]	✓	✓	✓
K-IOI-HA[h]	✓	✓	✓
HA return	—	—	✓

[a]Not applicable.

[b]PTA: pure-tone audiometry.

[c]WRS: word recognition score.

[d]HA: hearing aid.

[e]K-HINT: Korean version of the Hearing In Noise Test.

[f]REM: real-ear measurement.

[g]K-APHAB: Korean version of the Abbreviated Profile of Hearing Aid Benefit.

[h]K-IOI-HA: Korean version of the International Outcome Inventory for Hearing Aids.

Ethical Considerations

The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki. Furthermore, it has received approval from the Institutional Review Board (IRB) of Samsung Medical Center (IRB 2023-04-149). Informed consent must be obtained prior to any clinical trial-related activities. Before participants join the clinical trial, the researcher will explain the trial process to them, obtain a signed consent form, and provide a copy of the consent form to the participants. Participation in the trial is voluntary, and consent can be withdrawn at any time.

To ensure privacy and confidentiality, no personally identifiable information will be recorded in any documents where trial results are documented, and participant identification will be coded. Screening numbers will be assigned sequentially as OTC_01, _02, etc, and documents linking the code to participant identities will be attached to the researcher's file and stored in a locked cabinet. All clinical trial data collected and stored at the research institution may be kept for up to three years after the trial concludes.

If participants agree to take part in the study, they will not incur any costs for the tests conducted as part of the trial; however, they will be responsible for hospital admission fees, any tests unrelated to the trial, and consultation fees. The trial involves three visits in total, and participants will receive $50 for transportation costs at each visit. However, if a participant does not meet the inclusion criteria, drops out, or withdraws from the trial, transportation costs will not be provided.

Results

This study is scheduled to begin in August 2024. The trial is currently in the recruitment phase after receiving IRB approval; however, no patients have been enrolled yet. The study will be conducted over 2 years, from August 2024 to July 2026. Each participant will have 2 follow-up visits at 6-month intervals, making the total follow-up period 1 year.

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Discussion

Expected Findings

The purpose of this study is to conduct a noninferiority RCT comparing OTC HAs with traditional HAs to assess the clinical effectiveness of OTC HAs. The expected findings of the study are that OTC HAs will demonstrate noninferiority to traditional HAs in terms of functional gain. This means that OTC HAs will provide similar performance to traditional HAs. Recent research has focused on the clinical effectiveness of personal sound amplification products; however, there is still a lack of studies on the clinical effectiveness of OTC HAs, as they have only recently been introduced. To the best of our knowledge, this study is the first to investigate and potentially confirm the noninferiority of OTC HAs compared with traditional HAs. These findings could have significant implications for the accessibility and affordability of HAs, providing more options for individuals with HL.

Strength and Limitations

The strengths of this study include its innovative approach, being the first to conduct a noninferiority RCT comparing OTC HAs with traditional HAs, thus addressing a significant gap in the existing literature. The clinical relevance is noteworthy, as assessing the clinical effectiveness of OTC HAs provides valuable insights that could influence clinical practice and policymaking. Furthermore, the findings from this study could have substantial implications for the accessibility and affordability of HAs, potentially offering more affordable options for individuals with HL. The study uses rigorous RCT methodology to ensure reliable and valid results, enhancing the credibility of the findings. Finally, the study's timeliness is significant, as OTC HAs have only recently been introduced, and this research addresses a current need for evidence on their clinical effectiveness.

The limitations of this study include a short-term focus, as it may primarily address short-term outcomes, potentially overlooking longer-term effectiveness and user satisfaction with OTC HAs. In addition, the generalizability of results may be limited to specific populations and settings and may not extend to all individuals with HL or different health care systems. There is also a risk of potential bias, as with any RCT, where selection bias or other unforeseen biases could affect the results. Furthermore, technological variability in the OTC HAs available on the market could influence the outcomes, making it challenging to generalize findings across all OTC HAs. Finally, the study's scope may be limited, as it may not address all potential factors influencing the effectiveness of HAs, such as user preferences, ease of use, or long-term adherence to using the devices.

Conclusions

Since 2022, the introduction of OTC HAs has brought significant developments in the field. The availability of OTC HAs has resulted in a notable shift in how patients with HL can access and obtain these devices. With OTC HAs now being sold directly to consumers without the need for a prescription from HHPs, there is growing anticipation and curiosity surrounding their clinical effectiveness. Researchers, clinicians, and the general public are keen to explore the extent to which these devices can provide meaningful improvements in hearing ability and overall quality of life. As a result, there is a previous demand for studies to evaluate the clinical effectiveness of OTC HAs. With the wider availability and accessibility of OTC HAs, it is anticipated that more individuals will be inclined to try these devices as a potential solution for their HL. The increased usage will likely contribute to a wealth of real-world data and experiences that can be analyzed to further understand the benefits and limitations of OTC HAs. Researchers and HHPs will closely monitor the outcomes and feedback from users to gain insights into the effectiveness, user satisfaction, and overall impact of OTC HAs on hearing rehabilitation.

Acknowledgments

This research was supported by a grant from the Patient-Centered Clinical Research Co-ordinating Centre funded by the Ministry of Health and Welfare, Republic of Korea (grants HI19C0481 and HC19C0128).

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

GYK, MJ, YSC, and IJM managed the conceptualization of the study, methodology, and writing–original draft, review and editing. IJM performed funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

HA: hearing aid
HHP: hearing health care professional
HL: hearing loss
IRB: Institutional Review Board
K-APHAB: Korean version of the Abbreviated Profile of Hearing Aid Benefit
K-HINT: Korean version of the Hearing In Noise Test
K-IOI-HA: Korean version of the International Outcome Inventory for Hearing Aids
NAL-NL2: National Acoustics Laboratories–Non-Linear Prescription, second generation
OTC: over-the-counter
PTA: pure-tone audiometry
RCT: randomized controlled trial
REM: real-ear measurement
RTS: reception threshold for speech
WRS: word recognition score

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Protocol

High Potassium Diet Rich in Spices and Herbs-Salt Substitution (HPSH-SS) for Blood Pressure Reduction in Older Adults: Protocol for Diet Concept and Randomized Controlled Trial

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Abstract

Background: Hypertension increases with age, often due to high sodium (Na) and low potassium (K) intake. Reducing salt and increasing K intake is challenging, especially for older adults due to taste preferences. Culinary herbs and spices, rich in K, offer a potential solution. The High Potassium Diet Rich in Spices and Herbs-Salt Substitution (HPSH-SS) diet has not yet been studied for its effectiveness in lowering blood pressure.

Objective: This study aims to create an HPSH-SS diet, analyze its effects on blood pressure in older adults, and study the molecular mechanism occurring in the kidneys and blood vessels influenced by this diet.

Methods: This study consists of 2 phases. The first phase involved formulating and assessing the HPSH-SS diet tailored for older adults. The intervention group (IG) received a diet of 1800 kcal/day, with 3500 mg K and 1500 mg Na, while the control group (CG) received 1500 mg K and 2000 mg Na. The diet was administered for 14 days and standardized using the NutriSurvey program and biochemistry analysis by atomic absorbance spectrophotometry (AAS). The second phase was a 14-day parallel randomized controlled trial (RCT) with the older adult participants divided into IG and CG. Primary outcomes included blood pressure; serum potassium; aldosterone; F2 isoprostane; nitric oxide plasma levels; and urine analysis of Na, K, and the Na/K ratio. Confounding variables were controlled through randomization and stratified analysis.

Results: The menu formulation and organoleptic assessment of the HPSH-SS diet began in mid-2022 and was approved by the Ethics Committee of the Faculty of Public Health at Universitas Airlangga (78/EA/KEPK/2022) on May 11, 2022. The diet was standardized to achieve daily nutritional values of 1800 kcal energy, 3500 mg K, and 1500 mg Na. K and Na contents were analyzed using AAS from several participants' spice diet menus. Recruitment for the RCT started in March 2023, with approval from the Health Research Ethics Committee Universitas Airlangga School of Medicine, Surabaya (35/EC/KEPK/FKUA/2023). The study was registered from February 9, 2023, to February 9, 2024. Between March and June 2023, 64 participants were recruited, with 32 participants in the IG and CG. The intervention and data collection will take place over 1 year. Data management is in progress, and data analysis is yet to be performed.

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Conclusions: This RCT protocol hypothesizes that the diet will increase serum K, plasma aldosterone, and nitric oxide levels; decrease plasma F2 isoprostane; increase urinary Na and K levels; lower the urinary Na/K ratio; and reduce systolic and diastolic blood pressure. If effective, it will offer valuable insights into dietary strategies for blood pressure regulation in older adults.

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KEYWORDS

sodium; potassium; spices and herbs; blood pressure; hypertension; elderly; vascular; kidney; gerontology; aging; protocol study; dietary; phytochemical; anti-hypertensive; Indonesia; molecular mechanism; control group; oxidative stress

Introduction

Hypertension is a major public health problem worldwide, and its prevalence continues to rise with age. The prevalence of hypertension is predicted to increase around 60% by 2025 with nearly 1.5 million deaths, accounting for 9.4% of total deaths annually [1,2]. Both modifiable and nonmodifiable risk factors for developing hypertension are considered, with a focus on diet modifications as a modifiable risk factor. The risk factors for hypertension are closely related to dietary habits, particularly excess dietary salt and potassium (K) deficiency [3]. Population studies reported that most populations around the world consume less than the recommended intake of K, while unfavorably high sodium (Na) intake remains prevalent globally [4-6]. It is widely known that excessive Na consumption and insufficient K intake play important roles in the pathogenesis of hypertension and are more strongly associated with blood pressure than either Na or K alone [7,8].

Nonpharmacological therapy is the primary approach for managing hypertension, consisting of lifestyle changes and dietary patterns aimed at lowering blood pressure and controlling risk factors and comorbidities. Salt reduction strategies have become a cornerstone program in various countries, including Indonesia, to reduce the incidence of hypertension and cardiovascular diseases. Various salt reduction programs have been proven to be low-cost and effective, and some countries have successfully reduced salt consumption in their populations. However, Na or salt consumption among the global population still exceeds the World Health Organization (WHO) recommendation of 5 g per day [5,9-14]. A low-cost strategy for managing hypertension is to reduce salt in food. However, this is not always easy due to issues with taste and food acceptance, especially since older adults often have a high salty taste threshold [15-17]. This can lead to decreased appetite, potentially resulting in long-term malnutrition and deteriorating health status [15,18]. Another strategy is salt substitution. Recent studies have found a way to replace salt with spices and yielded good results regarding taste acceptance [19]. Some practices involve replacing sodium chloride (NaCl) with alternatives like potassium chloride (KCl) or calcium chloride (CaCl); however, these substitutes can have drawbacks, including a bitter taste and potential toxicity risks [16,20]. Substitution with monosodium glutamate (MSG) has also been reported. While MSG can replace the function of salt without compromising taste acceptance, its use in large quantities has been associated with various side effects [21,22]. Recent studies have investigated substituting salt with herbs and spices, yielding promising results in taste acceptance; however, adding spices may alter the taste and aroma of food, which may not be universally accepted. Studies on salt substitution with spice blends remain limited and are generally conducted on a single type of food [17,23].

Programs for increasing K intake at the population level are still rare and not progressive. K is a nutrient closely related to diet quality, although the cost of the diet may inhibit its intake [24,25]. It is recommended that K be consumed through food due to its safety and lack of an upper intake limit. Therefore, presenting food sources of K that are affordable and commonly used is an important requirement [5,24,26]. Herbs and spices with their phytochemical components have been widely studied as antihypertensives [27,28]. However, the relation to K content in spices, which acts as an antihypertensive agent, has not been widely studied. A high K and low Na diet, which includes 4 to 5 servings of fruits and vegetables and is low in fat, is known as the Dietary Approaches to Stop Hypertension (DASH) diet [29,30]. The benefits of the DASH diet have been recognized by general dietary guidelines from the US National Heart, Lung, and Blood Institute (NHLBI); the US Department of Agriculture (USDA); the International Diabetes Federation (IDF); and the European Association for the Study of Diabetes (EASD) [31-33]. However, the DASH diet has not yet been fully applied and studied in Indonesia. Indonesia is the largest producer of herbs and spices in the world, which can easily be found in traditional markets, supermarkets, and even in peoples' homes [27].

The kidney is the main regulator of Na and K in the blood. High K intake stimulates gastrointestinal signaling, specifically enteric K sensors, which increases plasma K levels and aldosterone directly. Aldosterone stimulates the aldosterone-sensitive distal nephron (ASDN) and the renal outer medullary potassium channel (ROMK), which triggers a decrease in salt and water absorption, causing diuresis and natriuresis. High K intake stimulates kaliuresis, natriuresis, and diuresis by increasing plasma K from both aldosterone and nonaldosterone pathways. This occurs via the inactivation of phosphorylation of the natrium-chloride cotransporter (NCC) and increased ASDN and ROMK [34]. Increased K intake inhibits free radical formation from endothelial dysfunction and vascular smooth muscle cell proliferation. Increased K also inhibits platelet aggregation and arterial thrombosis, conditions often associated with platelet oxidative stress in older adults. Consequently, elevated K levels decrease urine and plasma isoprostane F2 levels [35]. Additionally, increased K plasma levels improve endothelial cell stiffness and increase nitric oxide (NO) release through the

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mechanism of cortical actin depolarization by cytochalasin [36,37].

Indonesia is the largest producer of herbs and spices in the world, and their consumption among older adults is common. Spices and herbs are proven to have high K content and can be applied to salt substitution methods. However, a healthy diet specifically designed with these components, known as the High Potassium Diet Rich in Spices and Herbs-Salt Substitution (HPSH-SS), has not yet been established. Since population-level programs to increase K intake, particularly among older adults, are still rare and widely implemented, this study aims to develop and evaluate the HPSH-SS diet. This study will analyze the effect of this diet on blood pressure in older adults and investigate the molecular mechanisms occurring in the kidneys and blood vessels influenced by the diet. The data generated will provide valuable information in developing new approaches to managing blood pressure in older adults.

Methods

Study Overview

Data collection was carried out at a government institutional setting in Surabaya, Indonesia, namely Griya Wreda Surabaya nursing home. This study enrolled older adult residents at the nursing home in 2023 as participants. The research implementation was divided into 3 periods: the pretreatment period (day –10 to day 0), the treatment period (day 1 to day 14), and the posttreatment period (day 15). A parallel randomized controlled trial (RCT) intervention study compared the intervention group (IG), who received a low-salt, high-K spice-enriched diet (3500 mg K and 1500 mg Na per day), with the control group (CG), who received a control diet (1700 mg K and 2000 mg Na per day) for 14 consecutive days.

This study involved almost all workers or staff members at the nursing home, including cooks, nurses, and nutrition experts during data collection. Due to institutional regulations, we were not permitted to alter the daily intake provided by the care facility. As a result, we had to adjust the diet concept for this study. The initial step involved observing all menus and food compositions of the older adults' daily intake. We then arranged and adjusted the diet to fit our study design: the IG received a diet with 3500 mg of K and 1500 mg of Na per day, while the CG received a diet with 1500 mg of potassium and 2000 mg of sodium per day. We specifically recorded the composition of spices and herbs in their menus and found that commercial seasoning packets were commonly used in main courses, such as side dishes and vegetables.

Cooks in the institutional setting, as meal providers, played a crucial role in facilitating the older adults' daily food intake. They cooked daily menus as usual, the same for both groups. They received guidance and information about their involvement in this study. During the 14-day intervention period, cooks were instructed to use only commercial spices provided by the institution without adding any additional seasonings. They were also asked to reduce the salt content for the older adults' meals, particularly those in the IG. Nurses were responsible for accompanying the older adults in their daily activities to ensure their health conditions remained optimal. In this study, nurses were involved in measuring blood pressure, collecting blood samples, collecting 24-hour urine samples, and recording any health complaints from the participants during the study period. Involving dietitians as part of the research team in this study was crucial, as there were no dietitians in the nursing home. The dietitians monitored and evaluated the older adults' dietary intake. They observed the entire food preparation process, especially cooking, and recorded all ingredients used, including seasonings and added salt. Providing the intervention and control menus and evaluating the overall food leftovers, including main meals and intervention menus from the participants for 14 consecutive days, were the dietitians' main tasks during the intervention period.

Study Design

Description

This study consisted of 2 phases. The first step involved trials of menu formulation and organoleptic assessment of the HPSH-SS diet concept, which began in mid-2022. The next phase is the RCT, with recruitment starting in March 2023. The intervention and data collection will take place over 1 year.

Phase 1: Trials of Menu Formulation and Organoleptic Assessment

Developing the HPSH-SS diet involved trials of menu formulation and organoleptic assessment, which began in mid-2022. We did not provide the daily intake entirely because the nursing home did not allow changes to its usual menu. Instead, we adjusted the existing menu to align with the HPSH-SS diet concept by arranging a low-salt, high-K spice-enriched diet (3500 mg K and 1500 mg Na per day) and a control diet (1500 mg K and 2000 mg Na per day). The initial step was to observe the older adults' daily menus. The nutritional composition of the foods was calculated using the NutriSurvey software (EBISpro).

Based on the nutritional values of the older adults' menu, the next step was to design intervention and control menus to achieve nutritional values that aligned with this study's diet concept. Both the IG and CG were provided with the same energy intake of approximately 1800 kcal. However, Na and K were the main variables in this spice-enriched diet, and their roles were specifically examined. The IG received 3500 mg of K and 1500 mg of Na, while the CG received 1500 mg of K and 2000 mg of Na. Therefore, adjustments were made to the daily dietary menus of the older adults in the nursing home to meet the designed intervention's nutritional targets.

For each intervention menu recipe, a detailed report on food ingredient specifications and standard operational procedures (SOPs) for the production process was prepared beforehand. The next step involved conducting trials and organoleptic taste evaluations for taste acceptance by a limited panel of testers and participants, followed by biochemical laboratory examinations for K and Na nutritional values. The entire process sequence is described in Figure 1.

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Figure 1. Flowchart of the High Potassium Diet Rich in Spices and Herbs-Salt Substitution (HPSH-SS) intervention and monitoring evaluation.

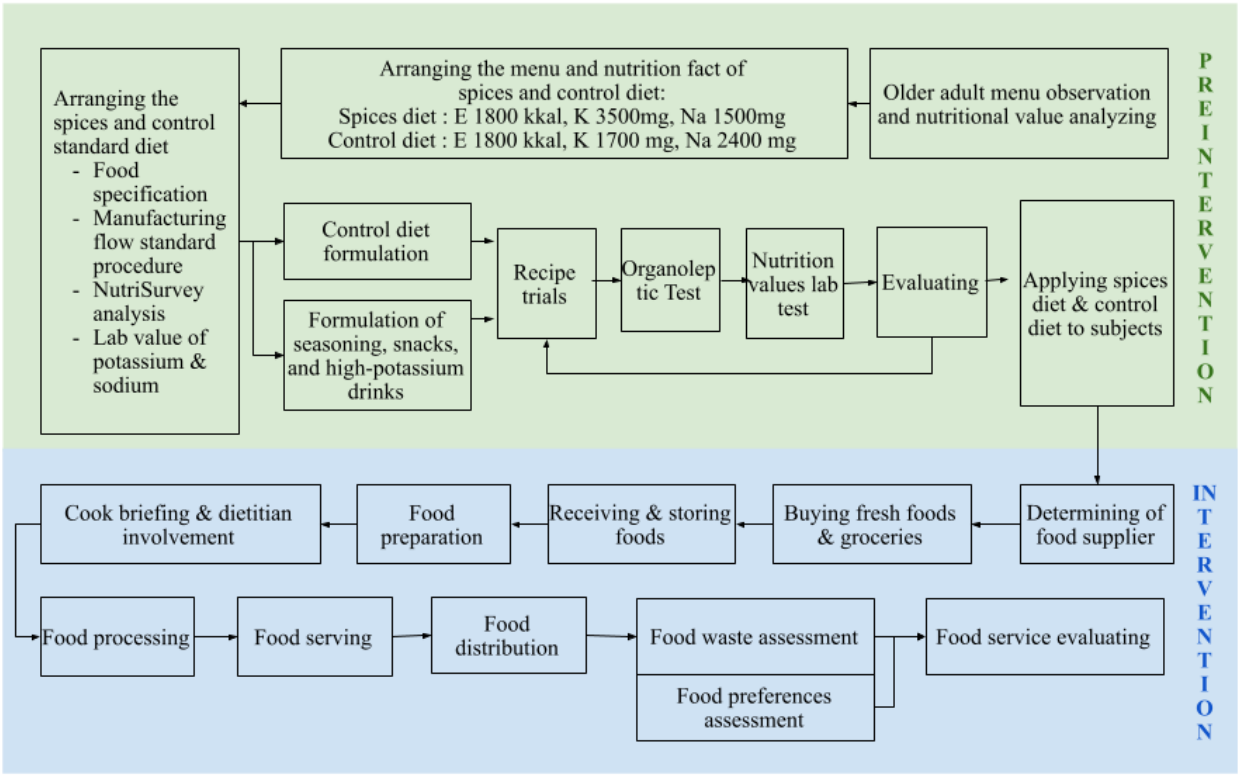

Phase 2: RCT Study

The RCT study was implemented with recruitment commencing in March 2023 until the end of 2023. This study is a parallel randomized controlled feeding trial testing the effect of 2 dietary patterns on blood pressure by analyzing serum K levels, plasma aldosterone, plasma isoprostane F2, plasma NO, urinary Na, urinary K, and urinary Na/K ratio changes in the older adults with hypertension for 14 consecutive days. Both IG and CG were provided with the same energy intake of approximately 1800 kcal. The IG received 3500 mg of K and 1500 mg of Na, while the CG received 1700 mg of K and 2000 mg of Na.

Study Population and Participants

The study population consisted of older adults registered as residents in an institutional nursing home in Surabaya, Indonesia. The sample size for each group was set at a minimum of 28 participants. The sample size was calculated following the formula by Lachenbruch et al [38]. Based on SD calculations by Geleijnse et al [39], the sample size yielded a minimum of 25 participants for each group. When accounting for a 10% dropout rate, the minimal sample size for each group was 28 individuals, resulting in a total sample size of 56 participants for this study. The inclusion criteria were older adults aged ≥60 years residing in the nursing who were active and not bedridden and those without infectious disease, taste disorders, or dementia. Additionally, participants were required to have blood pressure measurements indicating a systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg. The exclusion criteria involved individuals with impaired kidney function (creatinine serum levels >1.2 mmol/L), uncontrolled diabetes mellitus (fasting blood sugar >126 mg/dL), obesity (BMI ≥30 kg/m^2), active smokers, and those with memory impairment and depressive conditions. Additionally, participants declining continued participation, requiring intensive hospital care, or experiencing persistent vomiting and diarrhea were excluded from the intervention.

Study Variables

This study included independent, dependent, mediating, controlling, and confounding variables. Independent variables were the HPSH-SS diet and the control diet. Dependent variables included SBP and DBP. Mediating variables were serum K level, plasma aldosterone, urine Na, urine K, plasma F2 isoprostane, and plasma NO. Controlling variables included the duration of the intervention, the treatment timing and method, the evaluation timing and method, participant criteria, laboratory examination of outcome results, equal energy content of both diets, and sources of the food ingredients and commercial seasonings containing spices and herbs used for both groups, as well as cooks involved in both the food preparation and presentation. Finally, the confounding variables consisted of age, gender, consumption of antihypertensive medications, amount of diet consumed during the intervention period, occurrence of mild nausea and vomiting during the intervention period, and other metabolic diseases such as dyslipidemia and hyperuricemia. The randomization process was used to control the confounding variables (age, gender, and consumption of antihypertensive drugs) between the 2 groups to ensure that the participant characteristics were evenly distributed between both groups.

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Operational Framework

The research implementation was divided into three periods as shown in the operational framework in Figure 2: (1) the pretreatment period, (2) the treatment period, and (3) the posttreatment period. The pretreatment period (day –10 to day 0) consisted of giving information to the participants and explaining the study's purpose and benefits. Then, interviews were conducted to obtain baseline data (age, medical history, and medication consumption), anthropometric measurements (including body weight and height), and blood pressure measurements. Moreover, screening for kidney function and serum K levels was performed. Participants who met the research criteria were divided into 2 groups, namely IG and CG, through randomization. Starting from day 7, the participants entered a 7-day run-in period to standardize food intake and physical activity. The older adults were educated not to change their usual eating patterns or activities. Both groups consumed meals provided only by the institution. On day –1, participants were informed and briefed on the treatment they would receive, including receiving a new menu to be consumed for 14 consecutive days and the evaluation and various examinations that would be conducted. Finally, on day 0, SBP and DBP measurements were taken, and serum K levels, plasma aldosterone, urine Na and K levels, plasma F2 isoprostane levels, and plasma NO were examined.

Figure 2. Operational framework. CG: control group; IG: intervention group.

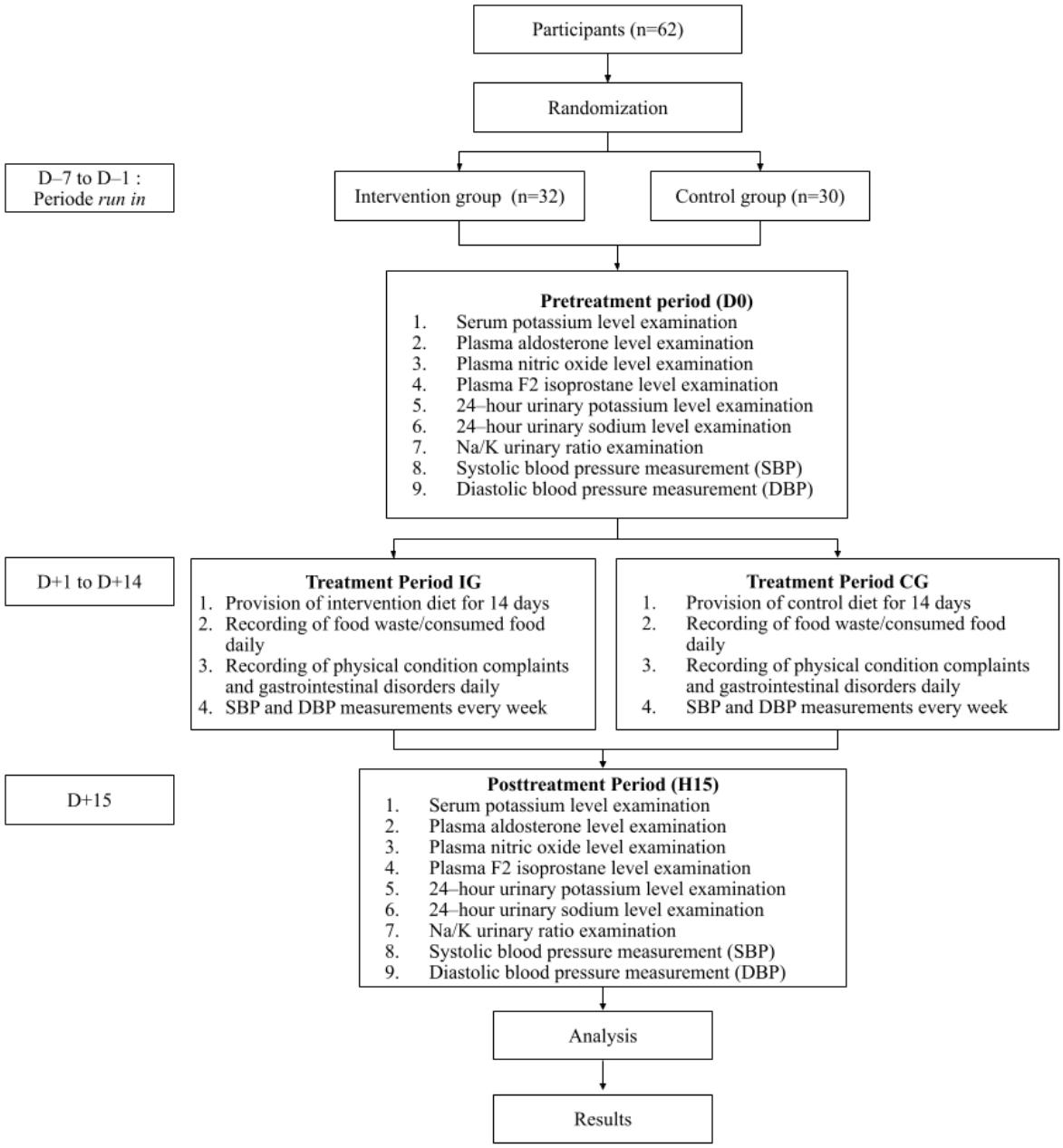

The treatment period (day +1 to day +14) consisted of the participants consuming the diet every day for 14 days consecutively. Every mealtime, participants were asked and assessed about taste acceptance and food waste for the food served. The older adults were informed that uneaten food should not be discarded and should be kept on the plate for recording by the research team. On the morning of day +8, SBP and DBP measurements were conducted by trained nurses following

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standardized measurement procedures. During the intervention, any complaints of health disturbances experienced by the participants, especially those related to digestive problems such as nausea, vomiting, or diarrhea, were noted and addressed by providing medication to reduce and treat the issues. Finally, on the posttreatment period (day +15), SBP and DBP measurements were taken again, and serum K levels, plasma aldosterone, urine Na and K levels, plasma F2 isoprostane levels, and plasma NO were examined.

This study sought to determine whether a high potassium spice diet and salt substitution in older adults with a history of hypertension can increase serum potassium levels, increase plasma aldosterone levels, increase plasma nitric NO levels, decrease plasma F2 isoprostane levels, increase urinary Na and K levels, decrease the urinary Na/K ratio, and decrease SBP and DBP.

Statistical Analysis

All statistical calculations were conducted with SPSS software (version 21.0; IBM Corp), and $P<.05$ was considered significant. The Shapiro-Wilk test was used to check normality data. In normal distributions for continuous variables, mean and SD were applied, while in abnormal distributions, the median and minimum to maximum were used. Data classified as categorical variables were summarized as numbers and percentages. Bivariate analysis was carried out to analyze the different outcomes between the 2 groups (IG and CG) using the *t* test or the Mann-Whitney *U* test. To compare ratio data between the pre- and posttest, a paired *t* test or Wilcoxon test was used.

Ethical Considerations

In mid-2022, trials began on menu formulation and organoleptic assessments for the HPSH-SS diet concept. Ethics approval was granted by the Ethics Committee of the Faculty of Public Health, Universitas Airlangga (78/EA/KEPK/ 2022) on May 11, 2022. The application of the RCT study started in March 2023. Ethical approval was obtained from the Health Research Ethics Committee at Universitas Airlangga School of Medicine, Surabaya, Indonesia (35/EC/KEPK/FKUA/2023) for the study titled “The Mechanism of Lowering Blood Pressure in Older adults with Diet of Spice and Herb High Potassium and Salt Substitution,” registered on February 9, 2023. All procedures performed in this study involving human participants were conducted in accordance with the ethical standards outlined by the committee. The data collection procedure was initiated by seeking approval from the head of the institutional nursing home and the participants. The research commenced with a preliminary socialization process. The participants sign an informed consent after receiving a detailed and clear explanation about the study, including the research title, the benefits of participation, and the research procedures. This study was submitted for registration in clinicaltrials.gov at the end data collection and analysis.

Results

The HPSH-SS Diet Concept

The initial step before arranging diet menus was observing the older adults’ daily menu in the home and analyzing its nutritional value. Table 1 shows the nutritional values of the master menu providing approximately 1321 kcal of energy, which met around 73% of the energy requirement, 1661 mg of Na, and 130 mg of K, accounting for only about 30% of the recommended intake.

Table 1. Nutritional values of the master menu at the Griya Werdha Surabaya nursing home.

Nutritional values	Energy (kcal)	Protein (g)	Fat (g)	Carb (g)	Fiber (g)	Na[a] (mg)	K[b] (mg)	Calcium (mg)
Daily average, mean (SD)	1321 (109.59)	47 (5.79)	53 (10.18)	168 (18.94)	7 (1.82)	1661 (363.9)	1305 (211.39)	289 (100.67)
RDA[c] and fulfillment, n (%)	1800 (73)	65 (73)	50 (106)	275 (61)	25 (28)	1500 (111)	4700 (28)	1200 (24)

[a]Na: sodium.

[b]K: potassium.

[c]RDA: recommended dietary allowance.

Considering the nutritional values of the older adults’ menu, the next step was to design intervention and control menus to achieve nutritional values according to this study’s diet concept. The energy content was arranged to meet the nutritional needs of the older adults, consisting of 1800 kcal/day, so both groups (IG and CG) were provided with the same energy intake. The IG received 3500 mg of K and 1500 mg of Na, while the CG received 1500 mg of K and 2000 mg of Na daily. Therefore, adjustments were needed in the daily dietary menu of the older adults at the nursing home to align with the nutritional values of the designed intervention.

Since we were not permitted to change the usual menus provided by the nursing home, the main breakfast, lunch, and dinner menus were the same as usual; however, we added a combination of fried onion and garlic and reduced salt in the main meals. Furthermore, to fulfill the K and Na nutritional requirements of both diets, we added snacks and a beverage. Additional food menus for both groups were created with different nutritional contents (Table 2).

K and Na were examined using atomic absorbance spectrophotometry (AAS) from the additional foods in both groups. Tables 3 and 4 show the nutrient compositions of the HPSH-SS menus and the control menus, respectively.

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Table 2. Additional foods in the intervention and control menus.

Mealtime	HPSH-SS[a] menus	Control menus
7 AM (breakfast)	Herbal tea	Teabag
10 AM (morning snack)	Cinnamon spinach pudding	Sweet milk pudding
2 PM (afternoon snack)	Mung bean Kampferia galanga	Coconut milk dawet
7 PM (evening snack)	Spices potato schotel	Tofu noodle schotel
Additional treatments	Onions (10 g) and garlic (5 g) in every main meal and salt amount reduced when cooking	N/A[b]

[a]HPSH-SS: High Potassium Diet Rich in Spices and Herbs-Salt Substitution.

[b]N/A: not applicable.

Table 3. Nutrient composition of the HPSH-SS[a] menus.

Menu	Energy (kcal) (N=548.4)	K[b] (mg) (N=2193.8)	Na[c] (mg) (N=152.5)
Ginger tea	79	402.8	3.4
Cinnamon spinach pudding	64.4	336	15.7
Mung bean kaempferia galanga	182.1	600	21.3
Spiced potato schotel	147.9	780	62.2
Fried onion and garlic	7	75	50
Master menu of the older adults	1321	1661	1305
Total intake	1869	3555	1563

[a]HPSH-SS: High Potassium Diet Rich in Spices and Herbs-Salt Substitution.

[b]Na: sodium.

[c]K: potassium.

Table 4. Nutrient composition of the control menus.

Menu	Energy (kcal) (N=601.2)	K[a] (mg) (N=188.8)	Na[b] (mg) (N=433.3)
Tea (400 ml)	109	0.6	12
Milk pudding	66.2	11.4	2.7
Dawet coconut milk (400 ml)	286.5	87.2	24.1
Tofu schotel (80 g)	139.5	89.6	394.5
Total intake	1922	1494	2094

[a]Na: sodium.

[b]K: potassium.

Equal energy content was maintained in both diets. Food ingredient sources, commercial seasonings containing spices and herbs used in both groups, and food preparation and presentation were the controlled variables. All menu recipes followed SOPs for the production process, including the evaluation of taste acceptance and food taste. Figure 3 shows the composition of one of the menu items, spinach pudding, which was a morning snack in the HPSH-SS diet consumed by the IG every day during the intervention period. It contained the following ingredients and specifications: 125 g agar-agar, 25 g Nutrijell, 30 g spinach, 35 g cinnamon, 75 g milk, 14 g sugar, and 75 ml water. We applied spinach and cinnamon as K-source foods. Moreover, cinnamon was chosen as a spice with a high K content.

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Figure 3. Cinnamon spinach pudding.

RCT Study

The recruitment of randomized controlled trials started in March 2023. The study was approved by the Health Research Ethics Committee Universitas Airlangga School of Medicine, Surabaya (35/EC/KEPK/FKUA/2023), and all participants provided written consent. The study was registered for the period between February 9, 2023, and February 9, 2024. Intervention and data collection will take place for 1 year. During the beginning of the research period (March-June 2023), 64 participants had already been recruited for the study, with 32 assigned to the IG and CG. Data management and analysis are still in progress, so data analysis has not yet been performed. This study was funded by the Indonesian Directorate of Research, Technology, and Community Service and the Universitas Airlangga for Doctoral Dissertation Research Grant 2023.

Discussion

A high prevalence of hypertension in older adults persists as a major public health issue worldwide. Excessive Na or salt consumption and low intake of K play a vital role in the pathogenesis of hypertension and cardiovascular disease [7,40]. Comprehensive strategies are needed to simultaneously reduce salt and increase K intake, as both are essential nutrients that work complementarily at the cellular and are more strongly associated with blood pressure than either Na or K alone [41]. This study aims to create a diet containing high K and low Na intake and analyze the effects of this diet on blood pressure in older adults. This parallel RCT intervention study compares an IG receiving a high-K spice diet (3500 mg K and 1500 mg Na per day) with a CG receiving a control diet (1500 mg K and 2000 mg Na per day) for 14 consecutive days. This adhered to SOPs for the production process of the diet, including the evaluation process of taste acceptance and food waste for every food menu eaten by the older adults. This RCT will test the hypothesis that the HPSH-SS diet is effective in lowering blood pressure by examining some markers of vascular and kidney in older adults.

Na or salt consumption reduction has become a major health program in various countries worldwide to reduce the incidence of hypertension and cardiovascular diseases [42]. Epidemiological studies highlight excessively high dietary intake of sodium at the community level in most parts of the world [42]. Several countries have implemented salt-reduction strategy programs and have successfully limited dietary salt in their populations [10,43]. However, in older adults, this can be challenging due to issues related to high salt taste threshold and taste preference, which can lead to overall reduced intake [44]. According to WHO recommendations, total Na intake should not exceed 2 g/day, and extremely low Na consumption is not recommended, as both too low and too high intakes potentially increase the risk of mortality, especially for older adults [45,46]. Therefore, this study provided Na intervention at 1500 mg for the IG and 2000 mg for the CG. Our analysis of Na intake from the menus of the older adults in the nursing home indicated that their Na intake was not too high, averaging 1661 mg and meeting 111% of the recommended dietary allowance (RDA). Therefore, we reduced salt in the cooking process to 1500 mg for the IG. In contrast, the control menus allowed for an additional Na intake, increasing to 2000 mg from other food sources. We did not lower Na intake below 1500 mg because reducing salt intake too much can affect taste and lead to deficiencies and undernutrition in older adults over time [47,48]. Moreover, providing Na intake of more than 2000 mg could have harmful effects on older adults and is inappropriate for individuals with high blood pressure [49,50].

Most populations consume less than the requirement of K and still fail to reach the recommended levels, emphasizing the urgent need for dietary interventions. Unlike salt-reduction strategy programs that are low cost and effective [6], increasing K intake and achieving the recommended daily K intake of 4700 mg is challenging, particularly for low socioeconomic groups, as K-rich foods such as fruits, vegetables, legumes, and dairy products are associated with higher food costs [19,24]. Low K intake generally occurs due to low fruit and vegetable intake. A systematic review study showed almost all Indonesian people consume inadequate amounts of fruits and vegetables [51]. Additionally, previous studies have shown that K intake is associated with nutritional quality, so increasing it will improve diet quality and reduce blood pressure [24]. Specifically, for K intake, we did not adhere to the Indonesian RDA of 4700 mg

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per day because the K intake among older adults in the nursing home was only 1300 mg, or 28% of the daily requirement [51]. Instead, we administered 3500 mg of K in this study, which is in line with the WHO recommendation for a minimum daily K intake of 3500 mg, preferably from food sources rather than supplements [6].

This study provided Na intervention at 1500 mg for the IG and 2000 mg for the CG. An Na/K ratio of 1 is considered beneficial for health; in this study, the Na/K ratio was much above the recommended level. Finding effective ways to lower this ratio in the population by reducing Na consumption while promoting dietary K consumption is important [4,7]. Our study showed that the Na/K ratio in the HPSH-SS diet was 1500/3500 mg (less than 1), while in the control diet, it was 2000/1500 mg (more than 1). Interventions involving K intake and Na restriction have been carried out both through supplementation and food or dietary intake. High-K and low-Na diets, including 4 to 5 servings of vegetables and fruits per day, and low-fat DASH diets, have been proven effective in reducing blood pressure [29]. DASH diets with varying K contents and Na-restricted diets have been studied. However, the development of a DASH diet with the main addition of spices has not been reported. Since spices as a source of K have also been less studied, a 2023 study by Singh [52] examined the K, Na, and their ratio in 45 commercial cultivars of onions in India. The results of this study demonstrated that onions are a potential source of K and low Na. Strategies involving salt reduction face challenges, particularly regarding taste acceptance, especially among older adults. Replacing salt with spices has shown potential in addressing taste acceptance issues while benefiting blood pressure management.

A recent study by Farapti et al [53] demonstrated using herbs and spices is an effective method for salt substitution in food and is acceptable in terms of taste preference and taste acceptance by older adults. However, an implementation study of a spice diet in daily food menus for reducing blood pressure has not been reported, and it is the novel aspect of our study. Nevertheless, the detailed mechanism of reducing blood pressure in older participants is complicated. This study only evaluated the effectiveness of HPSH-SS diet on lowering blood pressure by vascular and kidney mechanisms, not including sympathetic nerves that might explain the comprehensive mechanism of reducing blood pressure. The result of this study might not be applicable to the general population, particularly older adults with impaired kidney function and other diseases.

Indonesia is the world’s largest producer of spices and herbs with a contribution of around 21.06% of the total world market [54]. Given the high consumption of spices among older adults in Indonesia, the HPSH-SS diet is expected to be well accepted. This study introduced K-rich food sources that are nutritionally high quality, affordably priced, readily available, and easy to process daily. Thus, this diet can be applied to fulfill the daily K intake. Additionally, this study presents innovative functional foods containing spices and herbs that are high in K for lowering BP. If proven effective, our findings could provide valuable insights into dietary strategies for blood pressure regulation, particularly for older populations, and can contribute to improving their overall health status.

Acknowledgments

We would like to express our sincere appreciation to the Surabaya Social Service, the head of the Griya Werdha Surabaya nursing home, and all residents who participated in this study including the older adults, cooks, nurses, and dieticians. We also thank all investigators who collected and analyzed this data. Finally, we are grateful to Universitas Airlangga for funding this publication. This study was supported by the Doctoral Research Schema from the Ministry of Research, Technology, and Higher Education of Indonesia (2023-2024).

Data Availability

All data that will be used or analyzed in the study will be supplied upon reasonable request. Data supporting the findings of this study are included in the manuscript. Personal data are not publicly accessible due to ethical considerations, but they can be obtained from the corresponding author upon request.

Authors' Contributions

FF contributed to the conceptualization, methodology, formal analysis, investigation, writing of the original draft, and review and editing of the manuscript. SAP and AWF were responsible for data collection, formal analysis, table preparation, and writing parts of the manuscript. PSR and MM contributed to the investigation and supervision of the study. All authors participated in the writing and revision of the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

AAS: atomic absorption spectrometry
ASDN: aldosterone-sensitive distal nephron
CaCl: calcium chloride
CG: control group
DASH: Dietary Approaches to Stop Hypertension
DPB: diastolic blood pressure
EASD: European Association for the Study of Diabetes
HPSH-SS: High Potassium Diet Rich in Spices and Herbs-Salt Substitution
IDF: International Diabetes Federation
IG: intervention group
K: kalium (potassium)
KCl: potassium chloride
MSG: monosodium glutamate
Na: natrium (sodium)
NaCl: sodium chloride
NCC: natrium-chloride cotransporter
NHLBI: National Heart, Lung, and Blood Institute
NO: nitric oxide
ROMK: renal outer medullary potassium channel
SBP: systolic blood pressure
SOP: standard operational procedure
USDA: United States Department of Agriculture
WHO: World Health Organization

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Protocol

Impact of Dance or Music and Meditation on the Progression of Parkinson Disease With Mild or Moderate Severity: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by motor dysfunctions and nonmotor symptoms. Current treatments do not alter disease progression, highlighting the need for alternative therapies. Music, dance, and mindfulness meditation have shown the potential to improve symptoms and quality of life in patients with PD.

Objective: This study aims to evaluate the effectiveness of dance or music and meditation on PD progression, cognitive functions, mood, behavior, and caregiver burden.

Methods: This study is a single-blinded, longitudinal, parallel, randomized controlled trial. The participants consist of 30 patients with mild to moderate PD residing in Mumbai, India, who can physically participate in the activities. The exclusion criteria include advanced PD, severe balance issues, age >80 years, and other movement disorders. Participants in the intervention group will engage in dance or music sessions and guided meditation thrice weekly for 6 months. The control group will continue their usual activities and medication. The primary outcome is the progression of PD symptoms, measured using the Unified Parkinson's Disease Rating Scale I-III, and quality of life, measured using the Parkinson's Disease Questionnaire-39. The secondary outcomes include cognitive functions (Mini-Mental State Examination), mood (Beck Depression Inventory and Parkinson Anxiety Scale), mobility (timed up and go and Berg Balance Test), behavioral disorders (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale), and caregiver burden (Zarit Burden Interview and Parkinson's Disease Questionnaire-Carer).

Results: Data collection was completed in February 2024, with 28 participants finishing the study (intervention group: n=15, 54% and control group: n=13, 46%). Data analysis is underway, with results expected to be published in December 2024.

Conclusions: This study aims to provide significant insights into the effectiveness of dance or music and meditation in improving the quality of life and slowing the progression of PD. The findings are anticipated to support using these nonpharmaceutical therapies as complementary approaches to managing PD.

Trial Registration: CTRI/2023/03/051064; https://tinyurl.com/2xdus53j

International Registered Report Identifier (IRRID): DERR1-10.2196/59018

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KEYWORDS

music therapy; dance therapy; neurodegenerative disorders; meditation; quality of life; music; pilot study; Parkinson disease; well-being

Introduction

Background

Parkinson disease (PD) is the second most common neurodegenerative disease, with over 10 million people worldwide having PD [1]. PD is highly prevalent in Asia, with a frequency of 70 patients with PD per 100,000 people in India [2,3]. PD is a progressive, multidimensional disorder characterized by the degeneration of dopaminergic neurons, resulting primarily in motor dysfunctions including bradykinesia, rigidity, tremors, and postural instability [4]. PD can also result in concurrent nonmotor manifestations including psychiatric and mood-related alterations such as apathy, depression, and anxiety [5,6]. Cognitive involvement is prevalent as well, with a high occurrence of slow processing speed and deficits in learning and attention in patients with PD [7,8]. They are also seen to experience behavior disturbances [9].

Previous research suggests that medical or surgical treatments do not change the progression of PD [10]. It is seen that alternative therapies such as music, dance, and mindfulness might help delay the progression of PD symptomatology while improving the quality of life (QoL) [11,12]. In addition, therapies such as exercise and aerobic dance can have neuroprotective effects led by neuroplasticity [13]. Exercise is further seen to modulate dopamine neurotransmission [14].

Music Therapy

It has been observed that music modulates the brain regions related to movement, behavior, and cognitive processes [15]. Musical rhythm offers time-based groupings of sounds that provide auditory cueing and signaling strategies. This can help in restoring internal synchronization mechanisms and enable easier control of motor rhythmicity [15]. Evidence suggests that music exposure can enhance balance and functional mobility in patients with PD [13]. Listening to different musical genres has also been shown to induce spatiotemporal sense and trunk oscillations in the gait of patients with PD [16]. The music further activates the amygdala-related pathways and is seen to reduce depression and elevate mood in patients with PD [17]. Abell et al [18] conducted a study demonstrating that choral singing for a minimum of 6 months led to improvement in both motor and non-motor symptoms in patients with PD.

Dance Therapy

Dance therapy uses sensory-motor methods such as visual and spatial focus to facilitate improvement in one’s physical and mental health [11]. Dancing entails the practice of movements, postures, and body control, which might address bradykinesia, postural instability, and rigidity associated with PD [19]. McNeely et al [20] conducted a 2-year longitudinal study, wherein significant improvements in motor measures were observed in weekly tango dance sessions, reflected through the assessments of the outcome measures at 12 and 24 months. Dance is also seen to enhance mood, socialization, self-esteem, and QoL in patients with PD [21]. Additionally, high levels of commitment are observed in training programs offering American tango versus traditional exercise [22]. Dance programs among patients with PD can further improve the QoL of caretakers [22].

Certain dance forms and particular cultural dances are seen to have varied influences on PD symptoms [23,24]. For instance, a study claims that ball dancing might be more effective than tango [23]. Furthermore, there is evidence that Amazonian dances have distinct cultural peculiarities such as knee flexion and accentuated hip movements that can improve PD motor symptoms [24]. However, there is limited research on the effect of Indian art forms on PD symptomology and progression.

Meditation

Meditation is a mental state of quiescence that affects the body's functioning and helps patients gain attentional control and maintain focus on their intentions rather than being controlled by external environmental factors [25,26]. Mindfulness meditation stimulates the parasympathetic nervous system of the body through deep breathing exercises and positively impacts concentration and emotion regulation [27]. A mindfulness meditation research study conducted in South Korea, among patients with depression, anxiety disorders, and drug abuse, showed that meditation has positive effects on emotional and psychological stability, depression, anxiety, and memory loss [28].

Most of the studies to date have either been conducted over a short duration of time or on a small group of patients or have evaluated limited parameters. There has been no comprehensive review exploring the effect of dance or music and meditation on QoL, and limited studies take the QoL of caretakers into consideration. Additionally, there is limited research on the effectiveness of alternative therapies on the Indian population. This study aims to evaluate the effectiveness of music or dance and meditation on QoL and the progression of symptoms in patients with PD.

Methods

Study Design

The study is a single-blinded, longitudinal, randomized controlled trial (RCT) that will take place over a 6-month time period at Jaslok Hospital and Research Center, Mumbai, India. Participants will be randomly allocated into 2 groups: the control and intervention groups, having 15 participants in each arm. The intervention group will be further divided into dance or music as per the participant’s choice. The CONSORT (Consolidated Standards of Reporting Trial) flowchart summarizes the enrollment and allocation of the participants (Figure 1).

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Figure 1. CONSORT (Consolidated Standards of Reporting Trial) flowchart summarizing the format of the study. PD: Parkinson disease.

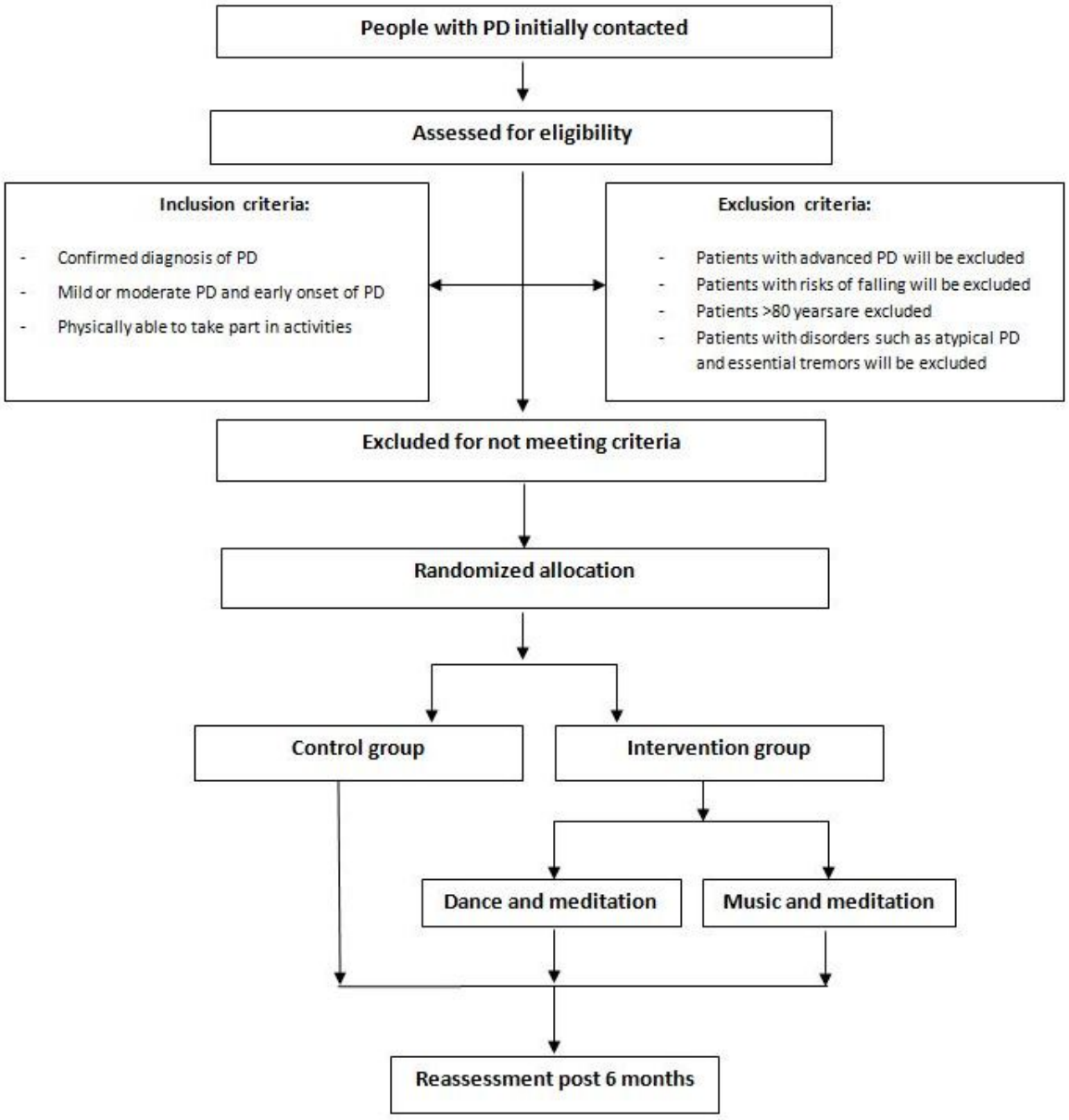

Aims

Primary End Point

The primary end point is to examine the effect of dance or music and meditation on the progression of mild and moderate PD using the Unified Parkinson's Disease Rating Scale (UPDRS) I-III and Parkinson's Disease Questionnaire-39 (PDQ-39) scores in patients with PD.

Secondary End Point

The secondary end points include the following.

- Detecting the impact of these therapies on cognition, mood, and behavior through neuropsychological batteries.
- Assessing the impact on the QoL of the caregivers of patients with PD.

Participants

Inclusion Criteria

The inclusion criteria are as follows:

- Patients with a confirmed diagnosis of mild to moderate PD (motor UPDRS III score of 43 or below)
- Patients should be residents of Mumbai (the city where the research is conducted)
- All patients should be physically able to take part in the activities

Exclusion Criteria

The exclusion criteria are as follows:

- Patients with advanced PD
- Participants with extreme balance-related problems or the inability to move

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- Age >80 years
- Patients with other movement-related disorders such as atypical Parkinsonism and essential tremors
- Patients who underwent deep brain stimulation
- All patients with secondary Parkinsonism
- Patients with a history of falls

Randomization

Eligible participants will be randomized into the intervention and control groups through a randomized allocation sequence devised by an independent statistician.

Blinding

This is a single-blinded study, as the assessors measuring the outcomes will be blinded to the allocation of groups.

Assessments

All assessments will be conducted during the "on phase," that is, during the phase when the PD medication is in effect. The outcomes will be assessed by a specialist nurse, a neuro-consultant, and a consultant psychologist. The neuro-consultant is a functional neurosurgeon with pioneering work in this field and more than 30 years of experience in movement disorder surgeries. The specialist nurse has been involved in the treatment of movement disorder patients for more than 26 years and is a certified UPDRS assessor. For the reassessments, the marker who conducted the initial assessment will conduct subsequent assessments.

Attrition and Missing Data

Due to the long duration of the study, it is expected that there will be a moderate attrition rate. To reduce the attrition rate and maintain commitment to the project, the importance of complete participation and consistency during the sessions will be conveyed to the team members and participants. The reassessments will be arranged at the participants' convenience to minimize the possibility of missing data.

Intervention Group

The patients will be given the option to choose from dance and music modalities. Meditation will be provided in every session. Active engagement for therapy is required for up to 6 months. All the activities will be improvised as per the abilities of the patients. The duration of each class will be around 1 hour. Both music and dance modalities follow a similar structure. All the classes will be followed by a 3-part format.

- Part 1: Classes will begin with 10 minutes of warm-up activities that will cover a wide range of stretching and hand-leg-eye coordination exercises.
- Part 2: The 45-minute dance or music sessions will follow a different format during this stage.
- Part 3: The sessions will conclude with 15 minutes of guided meditation.

The dance sessions will begin with warm-up activities with a focus on Indian classical dance steps. The classical dance focuses on gait and balance-related tasks, intending to reduce bradykinesia, shuffling gait, and the tendency to freeze in PD [29]. Classical dances emphasize greatly on hand-motor coordination and eye movement [29,30]. The eye-movement exercises might further improve lower gaze palsy in patients with PD. Alongside this, the patients will be engaged in the dance form of their choice. They will be offered various options of dance forms such as Bollywood dance, group dance, and garba. Patients can follow the choreography of the dance invigilator or perform freestyle. Following this provided that every session has at least 2 couples, the patients will practice waltz for 10 minutes.

Meanwhile, in the music sessions, the patients will engage in vocal exercises and will be given the choice of playing a musical instrument; singing the karaoke; or auditory stimulation, that is, listening to the karaoke. They will be encouraged to actively participate in the sessions.

The meditation will be administered by a professional trained in conducting meditation classes for the general population. Participants will be asked to close their eyes and sit in a relaxed posture either cross-legged or on a chair. Hands will be on knees with palms open. The mindfulness meditation will include guided instructions for deep breathing followed by a body scan and then guided instructions to pay attention to their thoughts and feelings.

All participants will be instructed to follow their daily routine and normal medication schedule. They will be instructed to keep the program coordinator informed if they make any significant changes to their treatment or their medication dosage or schedule. The participants in the intervention group will be asked to commit to the program and to take part in music or dance and meditation sessions thrice, weekly, for 6 months. On a weekly basis, patients should attend at least 1 session in physical presence, while the other sessions will be monitored through videoconferencing and home-based logs.

The patients will also be provided with the recordings of videos with instructions and a breakdown of each activity taught during the face-to-face sessions, making it easier for the participants to practice at home. A complete audio of the guided meditation schedule will be shared with the patients as well. The patients will be instructed to maintain an activity logbook documenting their adherence to home-based practice. Class attendance will be monitored and documented.

Control Group

Participants in the control group will be instructed to continue their regular activities and medication during the study period. They will be offered the chance to enroll in the dance or music sessions after the completion of the study. During the study, the patients from the control group will not interact with participants in the intervention group.

Reassessments

Reassessments for all participants will take place within 6 months of allocation (this is a deviation from the originally submitted protocol, which had assessments at 2 time points: 3 and 6 months. The deviation was incorporated considering the fact that major changes were likely to be noted in only at 6 months).

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Outcomes Measures

Primary Measures

Progression of PD Symptoms

The UPDRS I-III consists of 31 items assessing the severity of nonmotor and motor aspects of daily living and motor examination [31]. The responses will be scored from 0=no impairment to 4=severe impairment. Higher scores indicate higher severity (maximum score=124). This measure has demonstrated a strong internal consistency with α=0.96 and high concurrent validity against other similar constructs [31].

Quality of Life

The PDQ-39 is a 39-item self-report measure that measures the functional impairments in the following modalities: Parkinsonism symptoms, systemic symptoms, and emotional and social functioning [32]. Each item will be scored on a categorical scale from 0=never to 4=often. A summary index is further calculated ranging from 0 to 100. Higher scores indicate worse QoL. The PDQ-39 is widely used with good internal consistency of α=0.72-0.93 [33] and good concurrent validity against the Hoehn and Yahr Index and other similar constructs (0>0.60) [34].

Secondary Measures

Mood

The Beck Depression Inventory is a 21-item measure that is used worldwide to assess the severity of depression [35]. The items can be grouped into distinct symptoms of depression: cognitive, somatic, affective, and vegetative symptoms. This scale has a strong internal consistency of 0.88 and strong concurrent reliability with the depression subscale of the Symptom Checklist-90-R [36].

Additionally, the Parkinson Anxiety Scale is a 12-item measure that assesses 3 categories of anxiety: persistent anxiety, episodic anxiety, and avoidance behavior [37]. Each item will be scored on a categorical scale from 0=never to 5=often. Higher scores indicate worse anxiety (maximum score=63). This measure has a strong internal consistency of α=0.87-0.89 and good known-group and convergent validity [37].

Balance and Mobility

The timed up and go (TUG) and Berg Balance Test (BBT) assess mobility and risk of falls. The TUG is an observational test testing the gait, style, and time taken for the participant to get up from a chair, move for 3 meters, turn around, and return to the seat [38]. The TUG is seen to have good retest and interrater reliability in patients with PD [39]. Additionally, the BBT is an assessor-rated scale that records mobility through 14 tasks, with their performance being rated on a 5-point scale ranging from 0=poor performance to 4=good performance [40]. The BBT has a good internal consistency of α=0.93 and strong concurrent validity as strongly correlated with the Mini Balance Evaluation Systems Test [41].

Caregiver Scale

The Zarit Burden Interview is a 29-item self-report measure assessing the burden of the caregiver, measuring the psychological well-being, financial, and overall burden [42]. Each item is to be scored from 0=never to 4=always. The Zarit Burden Interview has good reliability with α=0.89-0.95 and good external validity with PD-related carer scales [42]. The Parkinson's Disease Questionnaire-Carer is a 29-item measure further assessing the mood, social life, and relationships of the caregiver with a good test-retest reliability [43]. This scale will be rated from 0=never and 4=always. Higher scores indicate worse QoL (maximum score=100).

Cognition Scale

The Mini-Mental State Examination evaluates performance at various cognitive components including orientation, attention, and recall [44]. A higher score signifies better cognitive abilities (maximum score=30). This measure has good test-retest reliability (0.80-0.95) and satisfactory construct validity against various gold standards used to diagnose cognitive impairment [44].

Behavioral Disorders

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale is a 28-item scale that records impulsions, compulsions, and compulsive medication usage [45]. Responses will be recorded on a 5-point Likert scale with 0=Never and 4=Often. This measure demonstrated high sensitivity and specificity across all subscales [45].

Data Analysis

IBM SPSS software will be used for the statistical analysis. Descriptive statistics will summarize the demographics, health conditions, and clinical outcomes at all 3 time points. Categorical variables including the Likert rating scales will be expressed in percentages and frequencies. The median and mode will also be ascertained for these data. Additionally, chi-square tests will be conducted, and *P* values will be ascertained to decipher the difference between the 2 groups against each outcome variable throughout the 3 time points.

Ethical Considerations

The study was approved by the scientific committee of the Jaslok Hospital and Research Centre (vide letter dated February 18, 2023; reference: -EC/1156/2023; Amendment 1). It was further approved by the ethics committee of Jaslok Hospital (vide letter dated February 18, 2023). It was also registered with Clinical Trials Registry India (dated March 27, 2023; CTRI/2023/03/051064). All participants provided informed consent (Multimedia Appendix 1). All data will be anonymized. The participants were provided travel compensation ($200 US per participant).

Expected Outcomes

Participants in the intervention group are anticipated to show significant improvements in both motor and nonmotor aspects of PD. Improvements in gait and balance are expected, alongside positive changes in QoL, mood, cognition, and behavior. Caregivers of participants in the intervention group are also likely to report an enhanced QoL due to the improved condition and mood of the patients they care for.

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Results

The data collection for this paper commenced in February 2023 and was completed in February 2024. A total of 30 participants were recruited, of which 28 completed the study (intervention group: n=15, 54% and control group: n=13, 46%). The data are currently being analyzed, and the final results are anticipated to be published in December 2024.

Discussion

Expected Findings

This RCT explores the effects of dance, music, and meditation on functional mobility, balance, QoL, cognition, mood, anxiety, behavior, and caregiver burden in individuals with PD. To date, there has been no research comprehensively investigating the benefit of dance or music and meditation on the QoL of patients with PD or the caretakers in Asian populations (including Indians). This will be the first study of its kind to be conducted in an Indian setup. It is also to be noted that none of the earlier studies offered the participants the choice to choose a modality of their preference. This will be the first paper that allows the participant to choose from music and dance.

The RCT, including 10 patients with PD, by Duncan et al [13] aimed to examine the effects of a 2-year, community-based dance class on disease severity and functional mobility in patients with PD. Assessments at baseline, 12 months, and 24 months showed that the intervention group had lower scores on the Movement Disorder Society-UPDRS III, Mini Balance Evaluation Systems Test, and other measures than the control group. The study concluded that participating in community-based dance classes over 2 years improved motor and nonmotor symptom severity, activities of daily living, and balance in individuals with PD [13].

The recent study by Hashimoto et al [46] involved 46 patients with mild to moderate PD who participated in a 12-week intervention. The patients were divided into a dance group, a PD exercise group, and a nonintervention group. The primary outcome measures included the TUG and BBT for motor assessment, the Frontal Assessment Battery at the bedside and Mental Rotation Task to assess cognitive function, the Apathy Scale and Self-rating Depression Scale to assess mental symptoms, and the UPDRS for general assessment. The results showed that the dance group exhibited significant improvements in all the outcome measures, highlighting dance's positive impact on the mental well-being, self-esteem, and social engagement of those with PD [46]. The guided meditation component may further contribute to stress reduction and relaxation.

The study by Katlen da Silva et al [12] aimed to evaluate the effects of music-based physical therapy on individuals with PD in terms of muscle strength (Medical Research Council Test and Sitting-Rising Test), cognition (Trail Making Test), muscle strength, balance (BBT), and functional mobility (TUG). It was a controlled, nonrandomized clinical trial with an A-B-A design involving 13 individuals with PD. The results showed that music-based physical therapy helped improve balance and functional mobility in individuals with PD. However, these improvements were not maintained after the therapy was discontinued.

The study by Lihala et al [47] in India examined the impact of dance therapy on cognition, QoL, and motor symptoms in 10 patients with mild-to-moderate PD. The results showed improved cognitive function and QoL, as indicated by increased Montreal Cognitive Assessment scores and decreased PDQ-39 scores [47].

Lee et al [48] examined the effects of virtual reality dance exercises on patients with PD. They found that after 6 weeks of treatment, the experimental group showed significant improvements in BBT (from mean 46.0, SD 1.3 to mean 48.1, SD 3.0); activities of daily living (from mean 87.9, SD 1.4 to mean 91.1, SD 3.0); and Beck Depression Inventory (from mean 20.4, SD 0.9 to mean 18.2, SD 2.0) compared to the control group, highlighting a positive impact on these aspects for patients with PD [48].

The studies mentioned above highlight that dance, music, and mindfulness have improved motor and nonmotor symptoms, activities of daily living, balance, cognitive function, and QoL in patients with PD.

Limitations and Future Implications

However, the study might be subject to some limitations. The 2 limitations to consider are the small sample size and the short duration of the study. A 6-month timeframe may not be sufficient to observe changes in nonmotor symptoms. Future larger, longitudinal RCTs are warranted to verify results. Motor and nonmotor symptoms of PD such as motor disability, gait and balance difficulties, speech disability, and pain are likely to hinder participation in activities such as dance and music. To compensate for this, each session will be customized according to the participants' needs and abilities. Additionally, the results might be confounded by factors such as changes in medication or differences in baseline medication taken by the patient. Therefore, any changes made to lifestyle and medication over the course of the study will be constantly monitored. This paper will build upon previous research and delve into the effectiveness of non-pharmaceutical therapies in possibly delaying the progression of PD.

Conclusions

This study aims to provide significant insights into the effectiveness of dance or music and education in improving the QoL and slowing the progression of PD. The findings are expected to support the use of nonpharmaceutical therapies as a complementary approach to managing PD, offering potential benefits to both patients and their caregivers.

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Data Availability

The datasets generated during or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

The conceptualization and methodology were developed by PD. All authors were involved in the investigation. Data curation, formal analysis, software development, and visualization were carried out by RVA and PD. PD also secured the funding for the project. The project administration and resources were managed by BM, NR, AB, RMR, RA, MT, SP, RVA, and PD. All authors contributed to the supervision and verification of the work. The original draft of the manuscript was written by RVA, BM, and PD, while all authors participated in the reviewing and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
A consent form.
[PDF File (Adobe PDF File), 2428 KB - resprot_v13i1e59018_app1.pdf]

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Abbreviations

BBT: Berg Balance Test
CONSORT: Consolidated Standards of Reporting Trial
PD: Parkinson disease
PDQ-39: Parkinson’s Disease Questionnaire-39
QoL: quality of life
RCT: randomized controlled trial
TUG: timed up and go
UPDRS: Unified Parkinson’s Disease Rating Scale

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Protocol

Influence of Distraction Factors on Performance in Laparoscopic Surgery in Immersive Virtual Reality: Study Protocol of a Cross-Over Trial in Medical Students and Residents—DisLapVR

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Abstract

Background: Working in an operating room (OR) is physically and mentally challenging: the operation itself demands the surgeon's full attention, while time and cost efficiency constraints, daily planning, and emergency care interfere with the procedure. Thus, multitasking becomes an integral surgical competence. This study aims to examine the effect of disruptions during surgery in a highly immersive virtual reality (IVR) operation environment combined with a virtual reality (VR) laparoscopy simulator.

Objective: This study aims to identify distractions in the OR and their importance in the clinical setting.

Methods: An IVR environment was created using a high-resolution, stereoscopic 360° video of the OR. Different distractions were identified, classified as auditory, visual, or audio-visual, and recorded accordingly. The surrounding was combined with a VR laparoscopic simulator. Participants—medical students and surgical residents—received proficiency-based training in basic laparoscopic skills and were blinded to the aim of the experiment. Following a cross-over design, each participant received a unique order of virtual distraction factors while performing tasks on the laparoscopic simulator. During the experiment, subjective passing of time, stress, heart rate, and visually induced motion sickness are recorded. After the experiment, validated questionnaires for usability, immersion, and stress were completed, as well as subjective evaluation of the distractions. The questionnaires used included the system usability scale, Self-Assessment Manikin score, National Aeronautics and Space Administration Task Load Index, and the immersion rating scale as described by Nichols. Performance in the laparoscopic tasks in relation to distractions will be evaluated by the Wilcoxon test and ANOVA for continuous variables. Subgroup analyses in regard to age, gender, and expertise (medical students vs surgical residents) are planned.

Results: The described trial started in August 2022 and is ongoing. By July 2024, a total of 30 medical students and 9 surgeons have completed the study.

Conclusions: We present a study protocol aiming to identify the impact of different disruptions in OR during laparoscopic training in IVR. Hence, it may lead to an improved awareness of distractions and facilitate accommodations toward an improved work environment. Prior research leads to the hypothesis that the performance of a more experienced surgeon is less impacted by distractions than the performance of inexperienced surgeons and medical students. Furthermore, we investigate which type of distraction has the largest impact on performance. With this knowledge, specific multitasking training can be devised, which may be particularly useful in medical education, for which VR might play a leading role. Additionally, workplace surroundings in the OR can be optimized with this knowledge.

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KEYWORDS

immersive virtual reality; distractions in surgery; ; laparoscopy; medical training; medical students; surgical education; surgical training; VR; cognitive load; multitasking; stress resilience

Introduction

Laparoscopic simulation has been shown to be beneficial in the training of surgical residents [1-3] and has been a mandatory part of surgical education in different countries. Following this example, an obligatory laparoscopic simulation curriculum consisting of 6 tasks was implemented in the Department of General, Visceral and Transplant Surgery, University Medical Center Mainz, Germany.

Surgery requires different professions to cooperate closely and efficiently to facilitate a smooth workflow while maintaining high levels of concentration on the procedure itself. Patient safety and cost efficiency demand swift procedures, which are regularly impaired or interrupted by various factors: emergency care, organizational tasks, and management of complications cannot be postponed in many cases; thus, multitasking becomes a surgical key competence. Moreover, teaching residents and medical students remains an integral part of working in an operating room (OR). In combination, these circumstances turn the OR into a bustling workplace with high physical and mental demands, rendering the ability to multitask a key surgical competence. Prior studies have identified and quantified distractions in the OR and examined their influence on surgeons [4-6]. Experienced surgeons were found to be more adept at handling distractions and were less impaired by them [7], suggesting this to be an ability that can be trained.

Laparoscopic simulation training usually takes place away from the hustle of everyday clinical work, yet structured training for multitasking or stress resilience has not been developed so far.

To test laparoscopic simulation in more realistic conditions, the institute designed a highly immersive virtual reality (IVR) application using high-resolution, stereoscopic 360° videos of the OR and displaying them on a head-mounted display (HMD; Vive Pro, HTC Corp) [8,9]. This application includes the surgery-unrelated background work in the OR including typical background noises and movements. In a prior study of our group, an IVR setting using 360° videos was deemed more realistic and was preferred by participants over an artificial virtual reality (VR) setting [10]. Furthermore, it has been previously shown that 360° video-based VR experiences enhanced memory recall, compared to conventional 2D videos [11], suggesting facilitated learning.

Prior studies could show that training in immersive laparoscopy induces a higher cognitive load, making this method already more demanding than conventional laparoscopy training [12]. Sankaranarayanan et al [13] have presented a simulated IVR program with similar goals and were able to show a significant difference in performance with or without distraction. As mentioned, our group was able to show in the past that IVR using real video material is preferred by users over simulated environments [10,14]. We aimed to create a realistic environment with realistic distractions, that is, phone calls or presentations of the next case, in contrast, other studies in the past have used unrelated distractions like music or other noises [13]. To achieve a realistic environment, different distractions were identified and classified as auditory (ie, a phone call), visual (ie, somebody walking through the field of vision), and audio-visual (ie, somebody presenting an emergency case including a computed tomography scan). These distractions were recorded and can be inserted into the simulation at any time. Participants can immerse themselves into this realistic environment and perform tasks on a laparoscopic simulator including haptic feedback (LapSim, Surgical Science, software version LapSim 2020.2). The simulator detects numerous parameters such as task completion time, tissue handling, amount of bimanual work, and instrument path length to calculate a performance score. Laparoscopy tasks are designed to train numerous abilities and competencies.

We present a protocol for a study aiming to identify the impact of different distractions during laparoscopic simulation in IVR. This study aims to identify distractions in the OR and their importance in the clinical setting.

Methods

Aims

This study aims to examine the influence of distractions on laparoscopic surgery in IVR. Therefore, a unique presentation sequence was created for each participant repeating the 6 tasks combined with 5 different distractions and without distractions. Each task will be performed with each distraction once and without distraction twice following a cross-over design. Figure 1 depicts one of the distractions in VR.

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Figure 1. Part of the participant's view in immersive virtual reality is shown. The scrub nurse is standing beside the participant. On the left edge of the picture, the laparoscopy monitor with an exercise is shown. In the background, a colleague is demonstrating a CT scan of the next emergency patient with a bowel obstruction (audio-visual distraction). CT: computed tomography.

After completing the proficiency-based curriculum and passing the final tests, all surgical residents as well as residents in gynecology are eligible to participate in the study. As a second group, medical students, who complete the same curriculum with lower thresholds, are eligible to participate in the study. These thresholds were introduced to eliminate the influence of the learning curve during the experiment.

Participants are blinded toward the aim of the study. They are instructed to test the familiar curriculum in an IVR environment but are unaware of possible distractions. Prior research has shown simulation to be a useful tool not only for training practical skills, but also regarding communication, stress, and handling of difficult situations [15].

The results may suggest how to improve the work environment in the OR by identifying distractions, and classifying and reducing them, wherever possible. As mentioned earlier, however, complete elimination is nearly impossible, but reduction should be attempted especially during critical steps of the operation. Different surgeons react differently to stress and distractions [16] and experienced surgeons appear to be less impaired by them [7]. This suggests that the individual reaction to stress may be a subject to training, which could be conducted in VR.

Objectives

The primary objective of this study is to examine the influence of simulated distractions in IVR on performance in laparoscopic surgery. The LapSim with haptic feedback is able to evaluate laparoscopic performance using the time required for an exercise, tissue handling, amount of bimanual work, and instrument path length. Secondary objectives are to collect participant-specific data, such as grade of immersion, subjective perception of the passing of time, subjective perception of stress in the form of the National Aeronautics and Space Administration Task Load Index (NASA TLX) questionnaire, system usability scale, visually induced motion sickness (VIMS), eye strain, heart rate, and eye tracking behavior.

Trial Design

The trial is designed as a cross-over trial. Each participant trains in 6 exercises on the simulator until a proficiency cutoff level is reached. After the training phase, participants enroll in the experiment. They complete the exercises wearing an HMD in IVR in a 360° video of the OR while 5 different auditory, visual, and audio-visual distractions are played. Each exercise is completed once combined with all 5 distractions and twice without distractions, amounting to 42 exercises in total. The order of exercises and distractions is determined by a Latin squares design, which minimizes potential order effects as each

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participant has an individual order of exercises and distractions [17]. The sequences are prepared with control for neighboring exercises and distractions, ensuring that there is no clustering of the same exercises or distractions.

Study Setting

The study will be conducted as a single-center study in the University Medical Center Mainz, Germany. The Department of General Visceral and Transplant Surgery is a high-volume center for minimally invasive surgery and has implemented mandatory laparoscopy training for all residents. Facilities for training are available. The department conducts mandatory laparoscopy training for all medical students and offers an elective about minimally invasive surgery.

Eligibility

Overview

Eligible are volunteer medical students of the University Medical Center Mainz, who have completed the training of the 6 laparoscopic exercises to a predetermined proficiency level as well as residents in visceral surgery and gynecology after completion of the department-specific laparoscopy training.

Inclusion and Exclusion Criteria

Since the presented program is a novelty design there is no effect size known. Due to prior experience, a sample size of 30 medical students and 20 residents in visceral surgery and gynecology was chosen. Medical students are recruited through announcements via posters and flyers in the University Medical Center Mainz, as well as during classes in visceral surgery. Surgical and gynecological residents are informed about the study on a personal basis and recruited if interested. To improve adherence to the experiment, breaks are offered after each exercise and can be taken at the liberty of the participants. The experiment can be paused or discontinued at any time if the participant wishes to, the number and duration of additional pauses will be recorded.

Exclusion criteria are impacted sight or hearing, which are tested before inclusion using standardized tests. All participants must be able to stand for 120 minutes upright to work on the laparoscopy simulator and are excluded if this is not possible. Furthermore, all participants have to complete a laparoscopy curriculum and reach a threshold to rule out the learning curve as an effect on the study. Not passing the threshold is an exclusion criterion.

Data Collection and Management

Data are collected immediately after the experiment using LimeSurvey (LimeSurvey GmbH, licensed by the Johannes Gutenberg-University Mainz) and later transferred to SPSS (version 27; IBM Corp).

Data are checked manually for correct transfer. Data are going to be stored in anonymized fashion on password-protected computers of the study group in locked rooms, to which only members of the study group have access to.

Ethical Considerations

The trial including all information, and the consent form has been reviewed and approved by the local ethics committee (Ethik-Kommission der Landesärztekammer Rheinland-Pfalz, application: 2022-16528-andere Forschung erstvotierend). Each eligible participant will be informed concisely about the study's potential and risks. If participation is desired, written consent is obtained by a member of the study group before inclusion in the trial. All participants have the option to withdraw their consent or quit the study at any time. All data is handled confidentially and in an anonymized fashion. There is no compensation for participants.

Interventions

Performance in laparoscopic exercises will be evaluated with and without different distractions. A cross-over design was chosen to allow within-subject control for each participant. Primary comparators are performance in laparoscopic surgery during different distractions. This will be assessed by the parameters of the laparoscopic simulator. Prior studies have shown more experienced surgeons to be less impacted by distractions [7], deeming the 2 eligible groups—medical students and surgical residents—an interesting contrast. Further comparators are subjective passing of time, subjective stress levels, and heart rate [18-20], as well as usability, VIMS, eye strain, and immersion, which are key comparators in newly developed VR programming [21-23]. Furthermore, the Self-Assessment Manikin score is assessed to employ a measurement for psychological stress and emotion [24]. Most of the aforementioned parameters are assessed by validated questionnaires, which have been used in similar experiments for years. Eye tracking is performed using HMD, to examine whether participants look at distractions without consciously perceiving them.

Each participant is going to complete each of the 6 laparoscopic exercises with all 5 distractions and twice without distraction. This amounts to 42 exercises, breaks will be taken after exercises 14 and 28. Mandatory breaks are 10 minutes long but can be extended as needed. Additional breaks will be offered after each exercise and can be taken at the freedom of the participant. The order of exercises and distractions is determined by a Latin squares design. After each exercise, participants are asked for their subjective stress levels using the NASA TLX score, subjective passage of time, VIMS (measured by the Fast Motion Sickness Scale [17]), and eye strain. After the experiment, participants are questioned about usability and immersion and are asked if they have noticed any distractions and, if yes, of which kind and how disruptive they were perceived to be. The trial design is depicted schematically in Figure 2 with all data collected at different time points.

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Figure 2. The course of the study with its different phases and the data collected at different time points. Before enrolling in the study, participants complete a mandatory laparoscopy curriculum. Right before the experiment, a warm-up phase is conducted. During the experiment, data about performance on the laparoscopy simulator as well as heart rate and the items of multiple questionnaires are collected. After completion of the experiment participants evaluate the distractions as well as usability of the system. *NASA TLX: National Aeronautics and Space Administration Task Load Index. **FMS: Fast Motion Sickness Scale. ***SAM: Self-Assessment Manikin. ****SUS: system usability scale.

	Study period				
	Enrollment	Postallocation			Close-out
Time point	–1 day to 0	+ 1-2 weeks	Warm-up	Experiment	After experiment
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Interventions					
Training		⟷			
Experiment				✓	
Assessments					
Participants' characteristics	✓				
NASA TLX*			✓	✓	✓
FMS**		✓		✓	
Eye strain			✓	✓	
SAM*** score				✓	
Heart rate			✓	✓	
Eye tracking				✓	
SUS****					✓
Subjective passing of time				✓	
Noticed distractions					✓

Statistical Methods

Statistical analysis of the primary outcome, perceived passage of time, and perceived stress will be conducted using the Wilcoxon test since it consists of a connected sample. Participant-related data, usability, immersion, and visually induced motion sickness are analyzed using repeated-measures ANOVA and 1-tailed *t* tests. Eye tracking is analyzed qualitatively (ie, the participant looked away from the laparoscopy monitor: yes or no). The students' and residents' performance, subjective passing of time, and NASA TLX variance over different time points and exercises will be analyzed using ANOVA.

Results

The trial started recruitment on August 31, 2022 and is still ongoing. By July 2024, the trial had recruited 30 medical students and 9 surgeons and is still recruiting. Recruitment of surgeons has been progressing slowly because of high demand and workload in the department, thus inclusion has been prolonged.

Discussion

This study aims to explore the effect of different distractions during laparoscopic surgery using laparoscopic simulation in high IVR. The OR can be a demanding and at times stressful workplace. Distractions during surgery are often triggered by necessary communication and urgent incoming demands [4],

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which cannot be eliminated even with utmost consideration and thoughtfulness. Furthermore, teaching, organizational tasks, and care for emergencies and complications disrupt the workflow, without the option for delay.

This trial is the first evaluation of distractions in the OR using highly immersive VR and may be able to assist in the possible improvement of working conditions and environments as well as the development of specific training. A group of 50 participants is sufficient for the exploratory aim of the study and according to experience attainable. Novel technologies like VR using HMDs usually spark the interest of possible participants and others alike but have not found extensive everyday application, yet. Simulation has been known to be a useful resource for years not only in laparoscopy [1,15]. If a laparoscopic curriculum extended by highly VR can be tested successfully, implementation as a set curriculum for the improvement of more than only manual skills could be possible.

Limitations of this trial include the usability of VR HMDs, which can be distracting and exhausting to wear to some participants while performing complex tasks. This might reduce immersion during training. However, we have not experienced any difficulties with this yet.

Prior research suggests, that more experienced surgeons are able to handle demanding situations more easily and are able to multitask [7]. This knowledge offers an opportunity for targeted training of stress resistance and multitasking. The future use of this program could include standardized training of medical students and surgical residents. Furthermore, a future extension of the program could facilitate an even more high-stress environment simulating an unstable patient and including different distractions that are common in an emergency situation. This would make the program interesting for more advanced surgeons as well.

Acknowledgments

All researchers participating are listed as authors.

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The used laparoscopic simulator was funded by the Alexander Karl Foundation Mainz.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request in a condensed and thus not trackable manner. The data acquired during the trial will be kept strictly confidential and only be accessible to members of the research group. The personal information of participants will not be released, and their privacy will be protected.

Authors' Contributions

LH and TH are the chief investigators. The study protocol was developed by TH, LH, CB, and FH under the consultation of HH, CC, and MW (conceptualization). LH and RS are conducting the study, preparing the questionnaires, and managing and analyzing data (investigation). The crossover sequence was prepared by MW, CC, and HH (resources). The programming of the VR application was performed by PS and VC under the supervision of CH (resources, software). HL as head of the department oversaw the development and will oversee the conduction of the trial (supervision). The manuscript was prepared by LH (writing); all authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HMD: head-mounted display
IVR: immersive virtual reality
NASA TLX: National Aeronautics and Space Administration Task Load Index
OR: operating room
VR: virtual reality
VIMS: visually induced motion sickness

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Protocol

Remotely Delivered Video Interaction Guidance for Families of Children With an Intellectual Disability Referred to Specialist Mental Health Services: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Children with an intellectual disability (ID) are 3-4 times more likely to present with behaviors that challenge and mental health problems than typically developing children. Parenting and the quality of parent-child relationships are risk factors for these families. The COVID-19 pandemic further exacerbated difficulties, leading to an increase in child mental health problems and behaviors that challenge, a deterioration in parental mental health, and further strain on family relationships. Remote family interventions could be an effective solution for both families and specialist mental health services. Video interaction guidance (VIG) has shown promise for improving child mental health. However, it is unclear whether it is widely acceptable to families and feasible to implement across specialist child mental health services.

Objective: This randomized controlled trial aims to evaluate the feasibility of delivering VIG as a remote intervention for parents of children aged 6-12 years with ID who have been referred to specialist mental health services.

Methods: The study will be undertaken across 5-7 National Health Service specialist mental health services in England, involving 50 participants randomly allocated on a 1:1 basis to either the intervention group (receiving remote VIG) or the treatment-as-usual (TAU) group. The intervention group will engage in 3-5 cycles of VIG delivered remotely over 12 weeks. The primary feasibility outcomes include the recruitment rate, retention at 6-month follow-up, and VIG cycle completion rate. The secondary outcomes will assess the acceptability of VIG and the feasibility of remote implementation, including fidelity to the intervention protocol. Data will be gathered through online surveys and telephone interviews at baseline, 3 months, and 6 months. Feasibility outcomes will be summarized using descriptive statistics, while thematic analysis will be applied to qualitative data from semistructured interviews with participants, VIG practitioners, and service managers. An embedded process evaluation will explore barriers and facilitators to engagement with VIG, and a parallel health economics evaluation will assess the feasibility of capturing service use data and intervention costs.

Results: The trial was open to recruitment between December 2022 and March 2024. The first results should be available in 2025.

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Conclusions: The study is the first randomized evaluation of VIG as offered to parents of children with ID who have been referred to specialist mental health settings. The outcomes from this feasibility trial will inform the decision to proceed with a definitive trial, using a traffic light system to evaluate recruitment, retention, and VIG completion rates alongside qualitative insights and economic evaluations.

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International Registered Report Identifier (IRRID): DERR1-10.2196/54619

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KEYWORDS

learning disability; intellectual disability; ID; child mental health; challenging behavior; family therapy; parent-child relations; parenting

Introduction

Background

Around 300,000 children in England have an intellectual disability (ID) [1]. ID often co-occurs with other neurodevelopmental conditions, such as autism. Children with IDs are 3-4 times more likely to exhibit challenging behaviors and mental health problems compared with typically developing children. By the age of 5 years, up to 88% of these children show clinical levels of hyperactivity, conduct problems, and emotional issues [2-5]. By mid-childhood (ages 11-12 years), challenging behaviors and mental health problems remain significantly higher in children with IDs compared with typically developing children [4,6].

The term “behaviors that challenge” is specifically used in relation to individuals with IDs or other groups who may have difficulty communicating. It refers to behaviors that, due to their frequency or intensity, place the individual or those around them at risk of harm or exclusion [7,8]. The term emphasizes that these behaviors pose a challenge to services, rather than being inherent problems within individuals with IDs. The term encompasses a diverse range of phenotypically different behaviors (eg, self-injury, aggression), defined by their impact on the environment. In ID, there is evidence of a close association between these behaviors and mental health problems [9].

Parenting and the quality of the parent-child relationship are risk factors for challenging behaviors and mental health problems in these families [10-13]. Children with IDs are at higher risk of experiencing negative parenting and poorer parent-child relationships [12]. The COVID-19 pandemic has further exacerbated these difficulties, leading to an increase in child mental health problems and challenging behaviors, a decline in parental mental health, and additional strain on family relationships due to service disruptions and restrictions [14].

Children with IDs who are suspected of having mental health problems or who exhibit challenging behaviors are typically referred to specialist mental health services. These services are increasingly under strain, often resulting in long wait times for families seeking therapy and support. Remotely delivered family interventions could offer an effective solution for both families and specialist mental health services [15]. In the United Kingdom, there is a growing impetus to adopt digital interventions to alleviate pressure on child mental health services, especially in the postpandemic context [16].

Specialist Child and Adolescent Mental Health Services (CAMHS) often provide either group- or individual-based programs. However, evidence shows very low access rates [17] and high dropout rates, often due to a perceived poor fit with family needs [18]. Parents tend to prefer personalized support that is flexibly delivered in their own environment and tailored to their family’s specific needs [19,20].

A comprehensive review of the literature on the effectiveness and acceptability of online-delivered family or parenting interventions highlights a growing body of research showing promising outcomes and generally positive user perceptions [21-23]. Numerous studies have demonstrated the effectiveness of these interventions in improving various aspects of family functioning, parent-child relationships, and child behavior [21,22]. Meta-analyses and systematic reviews consistently demonstrate significant improvements in parenting skills, parent-child interactions, and child behavior problems through online interventions [23]. Furthermore, online interventions targeting specific issues such as parental stress, child developmental delays, or behavioral disorders have shown promising results [24,25].

Overall, users tend to find online family or parenting interventions highly acceptable due to their accessibility, convenience, and flexibility. Parents value the ability to access support and resources from the comfort of their homes, eliminating the need for travel or scheduled appointments [22,26]. Online platforms often provide a variety of multimedia resources, interactive tools, and peer support networks, which enhance user engagement and satisfaction [23,25]. However, challenges such as limited internet access, low technological literacy, and concerns about privacy and confidentiality can affect the acceptability of online interventions for some families, particularly those from disadvantaged backgrounds [21,23,26]. Tailoring interventions to meet the needs and preferences of diverse families, offering clear instructions and technical support, and addressing privacy and security concerns are crucial for improving the acceptability and effectiveness of online family interventions [22,24].

In addition to positive service user feedback, staff who developed expertise with remote interventions during the pandemic are eager to integrate them into regular service

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offerings. This could improve access, reduce waiting times, and lower nonattendance rates [27].

Video Interaction Guidance

Video feedback interventions have shown promise in improving child mental health [28]. These interventions typically involve using videotaped parent-child interactions as a therapeutic tool [29]. Video interaction guidance (VIG) is a widely used video feedback intervention in services across the United Kingdom. VIG is a brief, personalized, strengths-based intervention that focuses on successful moments of parent-child interaction as a key therapeutic tool [29,30]. The theoretical foundation of VIG is rooted in Colwyn Trevarthen's [29-32] theory of intersubjectivity, which describes the development of shared understanding between a parent and an infant through the parent's responses to the infant's communicative cues. A key proposition of this theory is that positive communicative interactions are fostered when the parent is attentive and responds to the child's communicative attempts in an attuned manner [31,32]. Consistently doing this allows the dyad to progress from attuned communication to "mediated learning" [31,32]. This concept, derived from Vygotsky's [33] work, suggests that during parent-child interactions, the parent must provide the right amount of "scaffolding" to help the child progress independently. Too little support may cause the child to fail, while too much support can prevent learning. The Principles of Attuned Interaction and Guidance (Textbox 1; [34]) that underpin VIG propose that children who feel listened to by their parents are more likely to follow parental instructions. When parents provide a consistent "foundation of love, play, and work," they are more likely to find it easier to manage problematic behavior [29]. Furthermore, the clinician's role and the recording of sessions enable parents to gain an objective perspective on their interactions with their child, offering an opportunity to more clearly observe their communication patterns, emotional responses, and parenting strategies [30]. As the clinician and parent engage in a shared review of the parent-child interaction, focusing on strengths and areas of competence, the parent gains deeper insights into their parenting practices and develops self-reflection skills [30]. By offering personalized guidance and support, the clinician mirrors the experience of an attuned and collaborative relationship for the parent [30]. Therefore, VIG is an intervention that primarily aims to enhance attuned interactions between the 2 communication partners, which may lead to improvements in child behavior problems through more positive interactions and relationships.

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Textbox 1. AVIGuk (Association of Video Interaction Guidance UK) principles of attuned interaction and guidance.

1. Being attentive

- Looking interested with a friendly posture
- Giving time and *space* to other
- Turning toward
- Wondering about what they are doing, thinking, or feeling
- Enjoying watching the other

2. Encouraging initiatives

- *Waiting*
- Listening actively
- Showing emotional warmth through interaction
- Using friendly or playful interaction as appropriate
- *Naming* what the child is doing, might be thinking or feeling
- Naming what you are doing, thinking, or feeling
- *Looking for initiatives*

3. Receiving initiatives

- Showing you have heard, noticed the other's initiative
- Receiving with body language
- Being friendly or playful as appropriate
- Returning eye contact, smiling, and nodding in response
- Receiving what the other is saying or doing with words
- Repeating/using the other's words or phrases

4. Developing attuned interactions

- *Receiving and then responding*
- Checking the other is understanding you
- Waiting attentively for your turn
- Having fun
- Giving a second (and further) turn on the same topic
- Giving and taking short turns
- Contributing to interaction/activity equally
- Co-operating—helping each other

5. Guiding

- Scaffolding
- Saying "no" in the "yes" cycle (attuned limit setting)
- Extending, building on the other's response
- Judging the amount of support required and adjusting
- Giving information when needed
- Providing help when needed
- Offering choices that the other can understand
- Making suggestions that the other can follow

6. Deepening discussion

- Supporting goal setting

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- Sharing viewpoints
- Collaborative discussion and problem-solving
- Naming differences of opinion
- Investigating the intentions behind the words
- Naming contradictions/conflicts (real or potential)
- Reaching new shared understandings
- Managing conflict (back to being attentive and receiving initiatives with the aim of restoring attuned interactions)

Note: Principles taken from [34].

Systematic reviews have identified significant improvements in the quality of parent-child interactions and enhancements in child attachment following video feedback interventions [28,35,36]. Despite being recommended by the National Institute for Health and Care Excellence (NICE), empirical evidence regarding the effectiveness of video feedback interventions, particularly VIG, remains notably sparse. NICE guidelines advocate for the use of video feedback interventions for preschoolers exhibiting social-emotional problems [37] and for children experiencing attachment difficulties [38]. However, the existing evidence does not specifically pertain to VIG, and to date, no efficacy trials focusing solely on VIG have been conducted. Furthermore, the available evidence lacks specificity regarding child behavioral and mental health concerns. Nevertheless, insights from research into risk mechanisms suggest that video feedback interventions may provide direct benefits by enhancing parent-child relationships and indirect benefits by addressing child mental health issues and challenging behaviors [10-13]. Additionally, preliminary findings suggest that video feedback interventions have the potential to alter adults' perceptions of their relationship with a child who has an ID and presents challenging behaviors [39]. It is noteworthy that while NICE guidelines advocate for video feedback interventions in certain contexts, such as for children and young adults with autism [40], VIG is not specifically mentioned as a potential intervention for parents or caregivers of older children with IDs. This population may require tailored interventions that specifically address their unique needs. In the context of ID, there is a focus on interventions that directly reduce challenging behaviors (eg, parenting courses) [41]. It is important to highlight NICE's recommendation for further research involving children with IDs, specifically calling for studies that examine community-based interventions aimed at reducing the frequency and severity of challenging behaviors [41]. Interventions designed to support communication and interaction between young people with IDs and their families are crucial. Interpersonal interventions, such as VIG, could be highly beneficial due to their focus on enhancing communication between parents and children, as well as their potential to indirectly impact other child outcomes, such as challenging behaviors [42].

Specialist mental health services are beginning to offer VIG to families of children with IDs and comorbid conditions aged 6 years and older. Although VIG shows promise and is utilized in some services, it remains unclear whether it is widely acceptable to families and feasible to implement across specialist services. VIG has never been evaluated in specialist mental health services, and only 2 small studies have been conducted to date: a pilot trial (N=31) involving preterm neonates [43] and an uncontrolled feasibility study (N=19) with infants [44]. Although neither of these studies included families of children with IDs, Barlow et al's [43] pilot randomized controlled trial (RCT) investigated the application of VIG with preterm infants, finding improvements in parent-baby interaction and parental sensitivity. Improvements can be attributed to the key therapeutic components of VIG, such as attuned communication, reflective dialog, positive reinforcement, and the promotion of sensitive and responsive caregiving behaviors. Similarly, the feasibility study by Chakkalackal et al [44] in infant mental health supports these findings, indicating improvements in parental insight and sensitivity; however, the primary outcome of that study was participant engagement and recruitment. Although neither study directly assessed the efficacy or effectiveness of VIG, they do provide preliminary evidence for the types of outcomes that could be observed when VIG is used within a health setting. Furthermore, both studies included only immediate follow-up assessments [43,44], whereas VIG outcomes should be measurable beyond this initial phase [28,36]. In particular, any changes should be demonstrated in the medium term (eg, at a 6-month follow-up), as longer-term impacts on child outcomes in this population are unlikely to be sustained [45].

A recent study indicated that the key therapeutic mechanisms of VIG are present at similar levels when offered remotely compared with face-to-face [46]. Specifically, the study compared face-to-face and online interactions between VIG practitioners and parents, finding no significant differences in the levels of warmth, responsiveness from both clients and clinicians, or the balance in their interactions [46]. Therapists who used VIG remotely during the COVID-19 lockdown offered insights into how to enhance remote delivery, with 82% expressing a desire to continue providing VIG remotely after the pandemic [46]. While the "Zoom or Room" study provided encouraging evidence of the efficacy of online VIG, it is important to acknowledge the limited literature on the impact of delivering VIG remotely compared with face-to-face interactions. While online interventions offer advantages in terms of accessibility and flexibility, general concerns persist regarding the depth of connection, quality of communication, and therapeutic alliance developed within online therapeutic interventions compared with traditional face-to-face interactions [47,48]. Furthermore, the "Zoom or Room" study was conducted

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during the COVID-19 pandemic, a time when online therapies were in high demand and served as a primary means of social interaction. This context may have influenced participant attitudes and engagement, potentially biasing the findings. Given the limited evidence regarding the effectiveness of VIG delivered remotely outside of a pandemic context, further investigation is warranted to assess the feasibility of online VIG in a postpandemic environment, where the demand for and reliance on online interventions may vary.

A study is therefore needed to determine the feasibility of an RCT evaluating remotely delivered VIG for parents of children with IDs referred to specialist child mental health services. The study will focus on assessing the acceptability of remote VIG in this population, as indicated by both recruitment rates and engagement with the intervention. It will also investigate whether parents referred to specialist services for child mental health problems or challenging behaviors prefer support focused solely on the child. Additionally, the study will assess whether an appropriate primary outcome for a definitive evaluation can be identified, based on stakeholder perspectives regarding perceived impacts and the adequacy of child outcome measures.

Objective

This study aims to determine the feasibility of an RCT evaluating remotely delivered VIG to parents of children aged 6-12 years with IDs who have been referred to specialist child mental health services. The primary feasibility objectives of the study are to assess (1) the participant recruitment rate, (2) study retention at the 6-month follow-up, and (3) the rate of VIG completion (defined as completing 3 out of a maximum of 5 VIG cycles). The study's secondary objectives are as follows: (1) to assess the completeness of outcome measures; (2) to investigate the acceptability of VIG among parents and practitioners, including identifying barriers and facilitators to the remote offering and uptake of VIG; (3) to evaluate the feasibility of remote implementation, which includes measuring VIG fidelity, perceived effectiveness, necessary adaptations, and any unintended implementation failures; and (4) to provide preliminary evidence regarding service use assessments and the costs associated with the remote delivery of VIG in specialist mental health services. Additionally, the study will use a traffic light system [49] to evaluate the feasibility of progressing to a definitive trial.

Methods

Study Design

This feasibility RCT will involve 50 parents, who will be allocated on a 1:1 basis to either the intervention or treatment as usual (TAU), along with an embedded process evaluation. Additionally, service use data will be collected for cost comparison as part of a parallel feasibility economic evaluation (Figure 1).

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Figure 1. Flowchart of participants through the VIG-LD feasibility trial with 2 randomized groups. LD: learning disability; VIG: video interaction guidance.

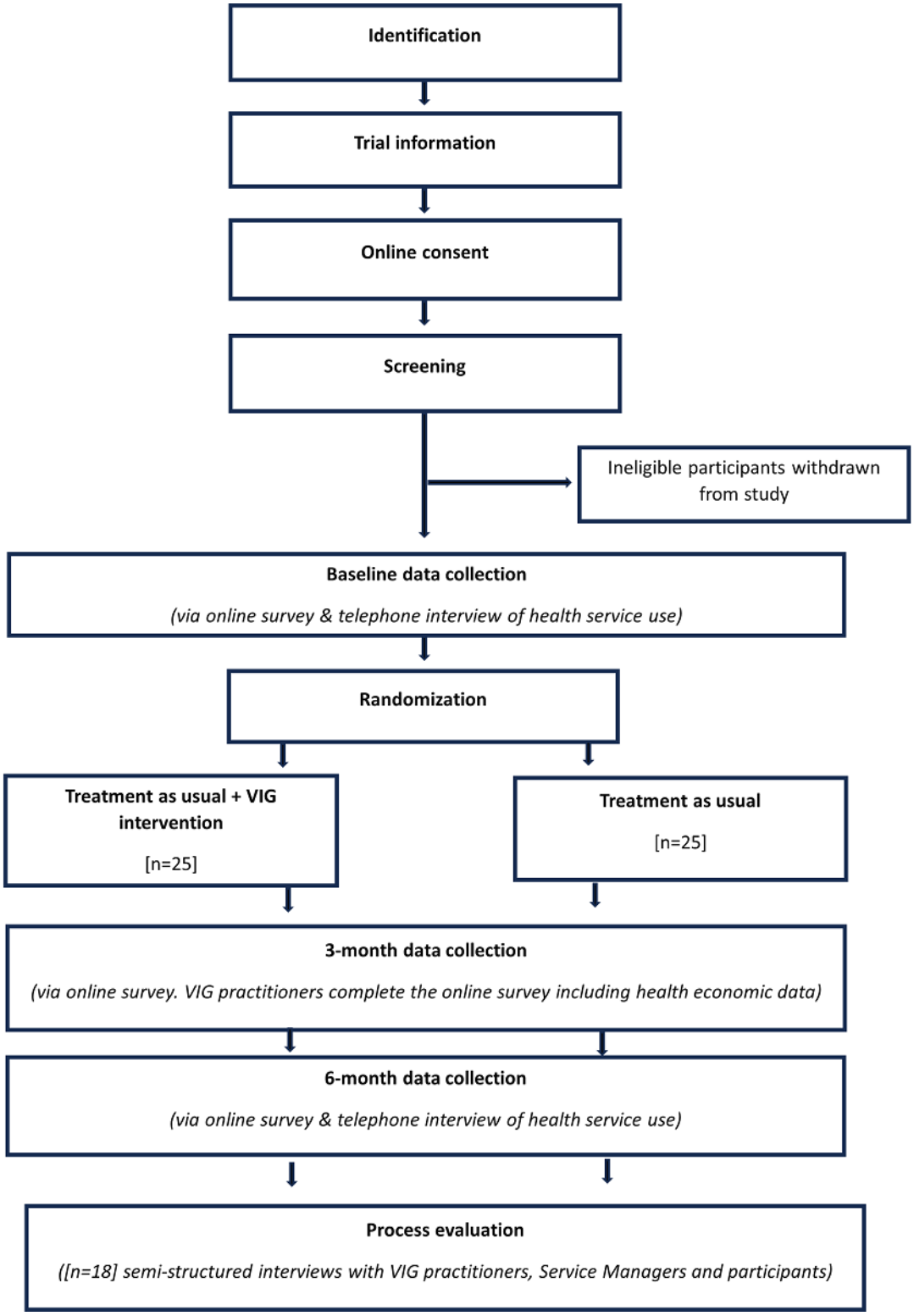

Study Setting

The study will be conducted in National Health Service (NHS) specialist mental health services. Children with an ID are referred to these services due to high levels of challenging behaviors or if they are suspected of having mental health problems. There are generally 2 types of specialist mental health services. The first type includes CAMHS that specifically caters to children with IDs, known in the United Kingdom as CAMHS Learning Disability (LD), or those that have a neurodevelopmental pathway. The second type consists of specialist pediatric neurodevelopmental services that include a pathway for addressing a child's behavioral and mental health problems. If the service includes a diagnostic pathway, children may be referred for an assessment of suspected neurodevelopmental disabilities. In these cases, diagnostic

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assessments may lead to a referral to the service's mental health pathway if mental health problems or challenging behaviors are identified during the referral process or the initial assessment. Specialist CAMHS services typically accept children from the age of 6 years, whereas specialist pediatric neurodevelopmental services accommodate a broader age range.

The study will be a multicenter investigation, with 5-7 sites anticipated to participate in England. Each site will carry out the same activities, including recruitment for the study, providing VIG to the intervention group, and offering treatment as usual (TAU) to both the intervention and comparison groups. Some sites may already have 1 or more trained VIG therapists who incorporate VIG into their therapeutic pathways, while others may not have any trained VIG therapists and may not include VIG in their standard offerings.

Ethics Approval

The study received approval from independent reviewers of the London South East Ethics Committee (22/LO/0819).

Participants and Eligibility Criteria

The study population comprises parents of children aged 6-12 years with IDs who have been referred to specialist mental health services. The lower age limit was chosen to align with the typical age at which children are referred to these services (as outlined in the study settings above), while the upper age limit reflects the age at which the UK NICE recommends that parenting support be provided [50]. Eligible participants will be identified from the waiting lists of specialist mental health services, including both new and existing referrals. They will be screened according to the inclusion and exclusion criteria outlined in Textbox 2.

Textbox 2. Participant inclusion and exclusion criteria.

1. **Inclusion criteria**
   - The parent is at least 18 years of age.
   - The parent has a child who is aged between 6 and 12 years (up to 1 day before the 13th birthday on screening day).
   - The parent is the child's biological, foster, adoptive or stepparent, or any other caregiver who lives with the child.
   - The child has an administratively defined intellectual disability: that is, an administrative label within the education, health, or social care system identifying intellectual disability; or as eligible for neurodevelopmental services; or a diagnosis (learning/intellectual disability or [global] developmental delay for younger children). The child may be diagnosed with additional conditions (eg, Down syndrome) or co-occurring neurodevelopmental conditions (autism). Children with co-occurring conditions are eligible.
   - The child has a composite score of <80 on the Vineland Adaptive Behavior Scales (Vineland-3 30), indicating significant developmental delay.
   - The child has been referred to a specialist child mental health service (new or existing referral).
2. **Exclusion criteria**
   - Another sibling participates in the trial.
   - The parent is receiving another video feedback intervention (Video-Feedback Intervention to Promote Positive Parenting (VIPP), Video-Feedback Intervention to Promote Positive Parenting and Sensitive Discipline (VIPP-SD), Marte Meo, Video Parent-Child Interaction, Paediatric Autism Communication Therapy) either remotely or in person.
   - The child lives with the parent <50% of the time or is in a 24-hour residential placement (inpatient unit or residential school).
   - The family is under active family court proceedings.

Recruitment

Identification of Potential Participants for the RCT

During the recruitment stage, potential study participants will be identified through 2 methods: either directly by clinicians during routine clinical contact or via site mail-outs that utilize the service's referral or waiting or active caseload lists. In both cases, eligible participants will receive a summary of the study. For cases referred by a participant identification center, clinicians will receive guidance information. Additionally, participant identification centers will be provided with supporting information about the study in case they wish to refer a parent of a suitable child.

Interested parents who receive the study information will contact the researcher directly. The researcher will respond to all expressions of interest via email or SMS text message, offering to discuss the study in more detail. If the potential participant does not respond after 3 attempts, no further contact will be made. For those who do respond, a time will be scheduled to discuss the study and review the participant information sheet (PIS).

Identification of Process Evaluation Interview Participants

The study will use random sampling to identify potential interview participants from among the parents who consented and were deemed eligible for the trial. We will ensure a balanced sample across variables such as group allocation and site. Clinical service staff who have provided VIG to at least one family will be approached for an interview, with a minimum of 1 practitioner recruited per site. Additionally, all service managers will be invited to participate in an interview.

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Consent

Before any data collection, including screening, written informed consent will be obtained from all study participants through an online form via Qualtrics (Qualtrics International Inc.). Participants will first receive the PIS when they express interest in the study. They will then discuss the PIS with a researcher to ensure full understanding. The PIS includes information about the intervention, the research tasks required, the randomization process, details of ethical approval, and how any data will be managed and stored. All personal information will be stored securely within the study host organization, and anonymized data will be transferred from clinical staff involved in VIG delivery or collaborating organizations. At the end of the meeting, participants will receive a personalized link to the informed consent form via email. The consent form was designed in accordance with the joint statement on e-consent from the Health Research Authority and the Medicines and Healthcare Regulatory Agency [51]. If participants are unable to complete the consent process in Qualtrics, an editable offline version of the consent form will be provided, which they can sign by hand and return to the research team.

Consenting and eligible participants will receive a child notification letter that explains the purpose and process of the study to the children. This letter will include information on how children can contact the trial manager if they wish to do so.

For participants in the process evaluation interviews, which include both clinical service staff and parents, a separate consent form will be obtained alongside a PIS.

Screening of Potential Participants for RCT Eligibility

The screening assessment will be conducted over the phone or via videoconference by a researcher using a standardized form. The Vineland Adaptive Behavior Scales (Vineland-3; 52) will be completed during the same meeting or in a subsequent appointment if necessary. Once screening is complete and eligibility is confirmed, participants will receive a personalized link to the first data collection questionnaire (baseline).

Randomization

Randomization will occur after participants have provided consent, had their eligibility confirmed through the screening process, and completed baseline data collection. Participants will be randomly assigned on a 1:1 basis to 1 of the 2 study arms (VIG + TAU vs TAU). Random block allocation stratification techniques will be used to ensure a balanced sample across variables such as group allocation and site.

Sample Size and Power

As this study is a feasibility RCT, a power calculation was not used to estimate the target sample size. Instead, we examined similar studies [44,52] to determine an appropriate recruitment rate for the study. Based on this analysis, we expect to recruit at least 50 participants from approximately 100 families invited to participate. The feasibility of recruitment will be assessed using a hypothesis-testing approach [53]. This assessment is 1 of the 3 primary research objectives, with a green signal indicating a recruitment rate of 50% of eligible families, amber indicating a rate of 35%-50%, and red indicating less than 35%. To achieve 90% power and a 5% 1-sided α, 97 families will need to be approached.

Intervention

Video Interaction Guidance

The VIG intervention involves the practitioner capturing a short video of the parent interacting with their child during the first meeting, which lasts approximately 20 minutes. In the subsequent meeting, known as the shared review, the practitioner and parent watch selected moments from the video where the interaction between parent and child is particularly positive, based on the parent's successful communication [30]. The practitioner guides the parent in identifying these moments and highlights their contributions to successful, attuned interactions.

The VIG practitioner facilitates the video recording of a parent-child interaction during an initial meeting with the parent before the recording date. In this meeting, the parent identifies their goals for the VIG intervention. The practitioner assists the parent in recognizing when these goals are being met, even if only briefly, and they discuss activities where such moments might occur. The parent is encouraged to engage in 1 of these activities during the recorded interaction with their child. This approach ensures that the video captures a particularly positive interaction, rather than just typical free play. The chosen activity should be enjoyable and comfortable for both the parent and child. Typically, VIG practitioners film for 5-10 minutes.

For this study, remote meetings are conducted via familiar video calling platforms such as Microsoft Teams (Microsoft Corporation) or Zoom (Zoom Video Communications, Inc.); however, the initial meeting may occur face-to-face if both the practitioner and parent agree. The practitioner helps the parent and child set up the activity, ensuring good visibility and audio. Afterward, they start the recording and turn off their own camera and microphone. They monitor the recording, intervening if the child or parent becomes upset, with the goal of maintaining a positive interaction. Afterward, the practitioner analyzes the recording using principles of attuned interaction, identifying short clips of the most attuned moments for review with the parent. Shared review meetings typically last between 30 minutes and 1 hour. Each recording and review session constitutes 1 cycle of VIG intervention, with 3-5 cycles making up a full intervention. Typically, 3 cycles are offered, with the option to request 2 additional cycles. For the purposes of this study, the maximum intervention duration is 12 weeks, which includes an introductory meeting and a review session. Parents in the VIG group may also receive additional support, either face-to-face or remotely, as provided by their service.

Treatment as Usual

Participants allocated to TAU will serve as the comparison group and receive the standard clinical care provided by the specialist mental health service. In parallel with the feasibility RCT, a survey of specialist mental health services across the United Kingdom will be conducted to provide an in-depth description of how widely these services offer video feedback and other interventions, at either the referral/waiting list stage or the active caseload phase.

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Data Collection and Analysis

Overview

The primary aim of the study is to assess the feasibility of conducting a full trial of VIG-LD using the current design, with potential modifications (and, if so, which ones), or to determine whether a full trial should not be pursued. Below, we describe the analysis approach for each outcome and outline the traffic light criteria to be used where applicable. Table 1 presents the primary outcomes and the associated progression criteria.

Table 1. Primary outcomes and traffic light progression criteria.

Outcome	Definition
Recruitment rate	• The number of participants eligible to participate among those undergoing formal screening and the number of those screened who are randomized. • The desired (green light) criterion to be met is that at least 50% of eligible parents participate, that is, 50 of the 97 eligible. The traffic light system is set to red if fewer than 35% agree to randomization.
Study retention rate (participants at 6 months)	• The number/proportion of randomized participants who have at least one parent questionnaire completed at the 6-month follow-up among all participants who consented to participate. The number of participants who at the 6-month follow-up provide useable data on Developmental Behaviour Checklist-2 among those randomized. • The desired (green light) criterion to be met is that at least 70% of recruited participants are retained at the 6-month follow-up. The traffic light system is set to red if fewer than 60% are retained.
VIG[a] completion/adherence	• The number/proportion of participants who complete the recommended amount of the VIG-LD[b] intervention (3 cycles) among all participants randomized in the VIG intervention group. • The desired (green light) criterion to be met is that at least 80% of participants receive 3 VIG cycles. VIG cycle completion is defined as 1 meeting to take a video and 1 meeting to go through the shared review. A traffic light system is set to red if fewer than 65% receive 3 VIG cycles.

[a]VIG: video interaction guidance.

[b]LD: learning disability.

Primary Outcomes

Summary

The primary outcomes being assessed include the feasibility of delivering and evaluating remote VIG, the participant recruitment rate, study retention at the 6-month follow-up, and the VIG completion rate. The primary outcomes that will be analyzed are described in the subsequent sections.

Recruitment

The study will record the number of referrals directly from clinicians, the number of individuals on mailing lists who were emailed study information, the number of interested parents undergoing screening, the number deemed eligible or ineligible (with reasons for ineligibility), the number who provide consent, the number randomized, and the reasons for refusing randomization. The recruitment rate will be estimated based on the number of parents found eligible for the trial after formal screening and the number of those eligible who are randomized. The desired criterion is that at least 50% of eligible parents are randomized. However, the traffic light system sets 35% as the threshold for the amber zone, meaning 34 out of 97 eligible parents would need to be randomized. If recruitment falls within the amber zone but exceeds the critical value of 42 (54%), minor adjustments will be needed to improve recruitment. If recruitment falls below 42, major changes will be necessary.

Study Retention

This will be measured as the percentage of participants who have completed at least one questionnaire at the 6-month follow-up among all those who consented to participate. The criterion to be met is that at least 70% of randomized participants are retained at the 6-month follow-up (60%-69% falls within the amber zone and <60% within the red zone). See Table 2 for a full list of questionnaire measures.

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Table 2. Full list of data collection measures completed within the trial.

Measure	Screening	Baseline	3-Month follow-up	6-Month follow-up
VABS-3[a] (socialization and communication subsections only at the 6-month follow-up)	✓			✓
PHQ-4[b]		✓	✓	✓
PSOC[c]		✓	✓	✓
CPRS[d]		✓	✓	✓
APQ[e]		✓	✓	✓
DBC-2[f]		✓		✓
CA-SUS[g]		✓		✓
ESQ[h]			✓	
GBO[i] (VIG[j] therapist only)			✓	
Process evaluation semistructured interview				✓

[a]VABS-3: Vineland Adaptive Behaviour Scale (Vineland–3) [54].

[b]PHQ-4: Patient Health Questionnaire-4 [55].

[c]PSOC: Parenting Sence of Competence Scale [56].

[d]CPRS: Child-Parent Relationship Scale [57].

[e]APQ: Alabama Parenting Questionnaire [58].

[f]DBC-2: Developmental Behaviour Checklist-2 [59]

[g]CA-SUS: Child and Adolescent Service Use Survey [60].

[h]ESQ: Experience of Service Questionnaire [61].

[i]GBO: Goal Based Outcomes [62].

[j]VIG: video interaction guidance.

VIG Completion

This will be measured by the number of participants in the intervention group who complete at least three VIG cycles. The criterion to be met is that at least 80% of participants receive 3 VIG cycles (65%-79% fall within the amber zone and <65% within the red zone). A VIG cycle is defined as 1 meeting to record a parent-child interaction and 1 meeting to view and discuss edited clips of the most attuned moments during the shared review.

Secondary Outcomes

Overview of Secondary Outcomes and Health Economic Evaluation

Secondary outcomes will include the completeness of outcome measures (ie, usable items), acceptability, barriers and facilitators to engaging with remote VIG for both parents and VIG practitioners, and the feasibility of remote implementation (both VIG and study processes). This will encompass aspects such as VIG fidelity, perceived effectiveness, potential adaptations, and any unintended implementation failures. The health economic evaluation will assess the feasibility of measuring health and social care services utilized by children with IDs whose parents participate in either the treatment as usual or VIG groups. This evaluation will include information on medications used by both the study participants and their children with IDs. Additionally, the health economics evaluation will aim to estimate the total cost of delivering remote VIG and assess how these costs compare with those of providing treatment as usual.

Qualitative data will be collected from semistructured interviews with participants, VIG practitioners, and service managers. These interviews will focus on discussions about participants' experiences engaging with the research tasks, including what they found favorable or unfavorable about the research process and the intervention itself. Additionally, participants will be invited to share suggestions for potential improvements in both the research methodology and the delivery of the intervention.

Health economics data will be collected through telephone-based interviews with participants, conducted at baseline and at the 6-month follow-up, as well as through an online survey completed by clinical staff at the 3-month follow-up. Health and social care utilization will be captured via the telephone interview by adapting the Child and Adolescent Service Use Schedule (CA-SUS) for this study. This questionnaire has been previously adapted for this population [14] and includes items related to primary and secondary care services, as well as medications used over the past 6 months. Service use will be costed using unit costs from the Personal Social Services Research Unit, while medication costs will be determined using the British National Formulary. The CA-SUS will aim to collect all relevant health and social care utilization data, including any service use components that may overlap between VIG and TAU interventions. Costs associated with the delivery of VIG will be gathered through an online survey completed by staff.

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This survey will collect data on staff salary banding and the number of hours spent on delivery-related tasks.

The economic evaluation will be conducted from a health and social care perspective; therefore, recruitment costs will be excluded.

The secondary outcomes will be analyzed as described in the following sections.

Completeness of Outcome Measures

This will refer to the number of participants who provide usable data for each study measure, estimated separately at each time point. The definition of "usable" data will be based on having enough items to allow for the calculation of a total or subscale score. The percentage of participants who provided data on the DBC-2 [59] at the 6-month follow-up will be estimated among those recruited (likely the primary outcome in the final trial). A green signal for completeness will be defined as having 80%-100% usable data for DBC-2 scores. Any measure with less than 70% usable data will be reevaluated.

Acceptability of VIG

Qualitative data from interviews with parents, VIG practitioners, and service managers will be analyzed using framework analysis to assess the acceptability of VIG [63]. This analysis will also identify key barriers and facilitators to engaging with remote VIG.

Feasibility of VIG Remote Implementation—Intervention Fidelity

Fidelity will be measured using the VIG-Skills Development Scale (SDS) [64]. This tool provides a structured assessment of VIG skills and is typically used in training and reflective practice to ensure practitioners' fidelity to the therapeutic model, which emphasizes a strengths-based and balanced approach. The VIG-SDS will be used to measure the fidelity of VIG implementation by reviewing practitioners' selection of video clip moments during the shared review, which is the meeting between the VIG practitioner and the parent (see the "Intervention" section). A total of 25 VIG cycles will be selected from the 75-125 cycles likely generated during the study. Fidelity will be assessed based on the percentage of reviewed cycles achieving a VIG-SDS score that corresponds to the expected level for the practitioner's training.

Feasibility of Remote Implementation—Intervention and Study Processes

Guided by the Medical Research Council framework for process evaluation [65], the analysis will integrate both bottom-up and top-down approaches to identify key themes emerging from the data across the process evaluation domains of context, implementation, and mechanisms of impact. Satisfaction with specialist mental health service input will be measured by summing the 9 items from the Experience of Service Questionnaire (ESQ) and comparing the results between the 2 groups [61].

Health Economics Data Analysis

The health economic analysis will adopt a health and social care perspective. Costs associated with VIG practitioners and other health and social care service usage will be calculated using unit costs from health and social care sources [66]. Health and social service utilization, as well as medication use, will be captured using the CA-SUS [60]. The total cost of remote VIG delivery will be estimated based on the amount of time VIG practitioners spend on delivery and the number of completed VIG sessions or cycles.

Participant Compensation

A small monetary compensation, in the form of a gift voucher, will be provided to participants after each instance of data collection (screening, baseline, 3-month follow-up, 6-month follow-up, and qualitative interview).

Patient and Public Involvement

During the development of the study protocol, interviews were conducted with parents and VIG practitioners who had experience with remote VIG. Two parents who had received VIG remotely through their Educational Psychology service were interviewed, and 1 family had experience with an LD CAMHS referral while also receiving remote VIG from Educational Psychology. Parents shared their experiences and reflected on the process and perceived impacts, which contributed to the draft logic model and helped researchers identify additional outcomes for measurement, such as parenting efficacy. Parents questioned whether the effects of VIG were sustained in the medium term and expressed a desire for support that focused more on the child. This raised concerns about the acceptability of a parent-focused therapy such as VIG within a specialist CAMHS setting. Consequently, acceptability was considered the primary outcome of the feasibility study.

Consultations were also conducted with several VIG practitioners experienced in delivering VIG remotely, some of whom had worked with families of children with IDs. They emphasized that VIG is highly feasible for these families, even in a remote setting, and expressed support for its adoption by more services to improve accessibility.

During the conduct of the study, a Parent Carer Advisory Group (PCAG) consisting of 10 parents of children with IDs will be established to provide guidance on study materials and develop a participant recruitment video explaining the study. The PCAG will advise on recruitment materials, processes, data analysis, and dissemination of content and strategy. Additionally, 2 parents from the group will contribute directly to the academic paper during the dissemination phase. The study's approach to patient and public involvement is informed by Staniszewska et al [67].

Data Management and Storage

Investigators and research staff will adhere to the Data Protection Act 2018 and General Data Protection Regulation (GDPR) guidelines for handling personal information throughout the study. Qualtrics, a secure and GDPR-compliant platform, will be utilized for online data collection. Personal information will be kept separate from other data, with participant IDs linked to pseudonyms stored in a separate location. Transcripts and verbatim quotes will be pseudonymized, and audio recordings will be deleted after transcription. All data will be stored

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securely with password protection on study host servers. Access to participant-identifying information will be restricted to designated research staff. Pseudonymized data will be transferred securely between NHS and collaborating organizations for analysis. Personal identifying information will be retained until the study's completion, while pseudonymized data will be stored for at least 20 years. Participants will be informed of these procedures in the PIS.

Safety Reporting

In the event that any adverse events or serious adverse events related to the intervention or research procedures occur, the chief investigator and study coordinator will be informed through the completion of an adverse event/serious adverse event form. All events will be reported immediately, and within 24 hours of becoming aware of the event, to the sponsor by the study team. All events will be assessed at each follow-up time point, and intervention delivery staff will be trained to report these directly to the study team at any time during the study.

Results

The study recruitment period was planned from December 2022 to March 2024. Recruitment has now been completed and analyses are planned to be completed by November 2024. The first results are expected to be available in 2025.

Discussion

Expected Findings

The findings from this feasibility trial are expected to provide valuable information about the acceptability and feasibility of VIG for parents of children with IDs within specialist mental health services. As the first randomized evaluation of VIG in these settings and for this population, no hypotheses can be made regarding the level of acceptability of the intervention or the feasibility of its remote delivery and evaluation. Previous research has emphasized the value of video feedback interventions, such as VIG, in improving parent-child interactions, which are crucial for supporting the mental health and behavioral development of children with IDs [29,30]. However, a previous single-group feasibility study of VIG with a different population (parents of infants) faced difficulties with recruitment and retention, despite high levels of acceptability for VIG (which was delivered face-to-face) [44]. Therefore, conducting a feasibility RCT is a necessary step in determining feasibility, acceptability, and other parameters required before a definitive trial.

Conclusions

This study represents the first randomized evaluation of VIG offered remotely to parents of children with IDs referred to specialist mental health settings. The findings regarding acceptability and feasibility will inform the design of a definitive randomized trial, should the progression criteria be met.

Dissemination Plan

The results of this feasibility trial will be disseminated as noted in Textbox 3.

Textbox 3. Dissemination of the trial results.

1. Parent Carer Advisory Group Involvement

The Parent Carer Advisory Group (PCAG) will play an integral role in the dissemination process. Members of the PCAG will coauthor academic papers to ensure that the findings are communicated in a manner that is accessible and relevant to families of children with intellectual disabilities.

2. Academic Publications and Conference Presentations

The study's findings will be submitted for publication in peer-reviewed journals that focus on child mental health, intellectual disability, and digital health interventions. Additionally, efforts will be made to present the results at national and international conferences to engage with the broader academic and clinical communities.

3. Funder's Website and Public Engagement

The trial outcomes will be published on the funder's website to ensure accessibility for the public, including families, health care professionals, and other interested parties.

4. Collaborations With Specialist Services

The findings will be shared with the National Health Service specialist mental health services that participated in the trial. These services will receive tailored reports highlighting the practical implications of the study, which may guide the wider adoption of remote video interaction guidance within these settings.

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Data Availability

The final data sets from the trial will be available upon request, and any third-party requests for access will be reviewed by the chief investigator.

Conflicts of Interest

SL was a co-opted board member of the Association of Video Interaction Guidance UK (unpaid voluntary role without voting rights) from January 2016 to January 2019.

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Abbreviations

CAMHS LD: Child and Adolescent Mental Health Services Learning Disability
CA-SUS: Child and Adolescent Service Use Schedule
DBC-2: Developmental Behaviour Checklist 2 Scale
ESQ: Experience of Service Questionnaire
GDPR: General Data Protection Regulation
ID: intellectual disability
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PCAG: Parent Carer Advisory Group
PIS: participant information sheet
RCT: randomized controlled trial
SDS: Skills Development Scale
VIG: video interaction guidance

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Protocol

Improving Oral Health in Prisons (PriOH): Protocol for a Randomized Controlled Trial

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Abstract

Background: People living in prisons often experience poor oral health, which could be attributed to their limited access to (dental) care, financial constraints, and a general lack of awareness and prioritization toward their oral hygiene. A pilot study involving motivational interviewing (MI) has shown promising results for improving the oral health outcomes of people living in prisons.

Objective: The protocol for this study aims to assess the efficacy of integrated MI and oral hygiene packages in improving oral health among people living in prisons, compared to controls without added MI.

Methods: This oral health in prisons study is a multicenter, randomized, double-blinded controlled trial that recruited inmates from 4 prisons in Rogaland County. The trial aimed to recruit 320 participants before randomly allocating them to either a control or intervention group. The intervention group received MI, consisting of a 30-minute session encouraging inmates to discuss their current and desired oral health behaviors and attitudes, highlighting discrepancies to motivate change. Assessments were conducted at 4 and 12 weeks after initiation. The primary outcome measurement is the mucosal-plaque scores to assess oral health behaviors, attitudes, and oral hygiene. Secondary outcome measurements are oral hygiene routines, sugary food and drink intake, oral health perception, and oral health-related questions.

Results: Data collection started in November 2021 and ended in June 2023. A total of 327 participants were recruited, of which 126 received the intervention.

Conclusions: Integrating MI in oral health programs at prisons can significantly improve the oral health of incarcerated individuals. Should the results from this study demonstrate efficacy, it could be valuable insight for policy makers, oral health practitioners, and correctional services in addressing the needs of a traditionally underserved group before being scaled up to enhance dental care practices in prisons.

Trial Registration: ClinicalTrials.gov NCT05695443; https://clinicaltrials.gov/study/NCT05695443

International Registered Report Identifier (IRRID): DERR1-10.2196/60817

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KEYWORDS

intervention; motivational interviewing; oral care; marginalized groups; correctional services; implementation; oral hygiene; oral health; randomized controlled trial; RCT; prison; dental care; pilot study; people living in prison

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Introduction

Background

Poor oral health tends to affect people living in prisons disproportionately [1,2], which may be attributed to the lack of accessible oral health services within correctional facilities, financial barriers, a lack of awareness and priority, and limited use of oral health hygiene products and tools [3]. Scholars argue that ensuring good oral health for people who have been incarcerated and are in the process of reintegrating into society is particularly important because it can lead to a more successful outcome [4]. Assuring good oral health for people living in prisons is described as an international challenge. It is often related to the lack of staffing and logistical issues during transfer to and from dental clinics [3,5,6]. These barriers may also explain why, in Norwegian prisons, emergency dental treatment tends to be the most sought reason for dental care [6].

Another critical factor as to why people living in prisons tend to have poorer oral health is that they are more likely to have disadvantaged backgrounds, experienced social exclusion, and often have lifestyles increasing the risk of developing oral diseases [7-10]. With the prison parameters directly limiting one's ability to engage in risk behaviors leading to poor health, one could argue for exploiting these contextual parameters and providing people living in prisons with oral health improvement measures.

Promoting and assuring good oral health for people in prisons has been advocated at structural levels by The World Health Organization's Prison Programmes, calling for health promotion to be equal outside as within prisons [11], and at the dental practitioners' level [6]. Assuring and promoting good oral health is different worldwide. In Norway, along with France and the United Kingdom, the health care for people living in prisons falls under the responsibility of the national public health department [8]. Moreover, Norwegian legislation states that public dental services should work preventatively toward those incarcerated. Currently, people living in prisons receive free dental care for acute matters from their first day of incarceration [12,13]. After that, regular dental examinations, with means to prevent and treat oral decay, are made accessible and free of cost when incarceration exceeds 3 months [13]

Nonetheless, a recent Norwegian regional report highlighted the need to strengthen the preventative and health-promotive measures [12]. In light of this recent report and the international literature revealing a lack of interventions despite this population scoring disproportionally poorer on oral health measures [14], the Oral Health Centre of Expertise Rogaland developed an intervention that included motivational interviewing (MI), with means to promote good oral health behaviors and thereby prevent oral diseases for people living in prisons, and results from a pilot study on this reveals promising findings [15].

MI is a collaborative, person-centered technique that strives to achieve change through conversational techniques [16]. The driving conversation aims to last around 30 minutes, exploring the participant's current and desired (oral) health behaviors and attitudes. An MI-led conversation assumes that asking questions illuminating the discrepancy between the desired and current state and behavior motivates the person to change [16]. Although MI leading to behavior changes has been well studied [17], more evidence is needed to uncover whether this technique effectively leads to oral health-related changes within prison parameters. This protocol outlines a randomized control trial, assessing whether an MI-led conversation can enhance people living in prisons' oral health, cleaning routine behaviors, and oral health attitudes.

From here on, this protocol refers to the MI-led conversation as the intervention. More details on the specific techniques of the MI-led conversation used in this study are outlined in the Methods section.

Aims and Objective

Previous research and a pilot study conducted by the Oral Health Centre of Expertise Rogaland have shown that MI techniques can promote oral health and prevent oral health challenges by altering unhealthy habits and behaviors [15,16,18,19]. Our study is a randomized controlled trial that builds on the pilot study [15], to assess whether a conversation following MI techniques (the intervention) can enhance people living in prisons' oral health, cleaning routine behaviors, and oral health attitudes. To answer this study's aim, five hypotheses have been outlined:

H1: The intervention will reduce observed plaque and gingival inflammation for prisoners (mucosal-plaque score [MPS]).

H2: The intervention will lead to improved reported oral hygiene routines, particularly the brushing of teeth.

H3: The intervention will lead to a reduced intake of food and drinks that contain sugar, specifically in between meals.

H4: The intervention will lead to improved perceptions about their oral health. It improves how they view their oral health, they consider their oral health as more important, and they report an increased wish to improve it and have increased efforts to improve it.

H5: The intervention will lead to more questions asked during the clinical examination, suggesting increased curiosity concerning their oral health.

Methods

Design

A multicenter randomized controlled trial with a parallel group design and superiority framework will be used to assess the effectiveness of the intervention in improving oral health behaviors, attitudes, and hygiene for people living in prisons. From November 2021 to June 2023, all people convicted of serving time in any of the 4 correctional facilities (prisons) in Rogaland County and who passed a security and language assessment were recruited.

After giving oral consent, this study's participants were randomly assigned to an intervention or augmented control group that was blocked at the prison level. This means, although study participants were randomized, there was an equal number of participants in both the intervention and augmented control groups within each of the 4 participating prisons (striving for

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1:1 allocation). The randomization was computer-generated [20].

To prevent selection bias, this study's concealment methods were computer-generated randomization at the back office by the research team. This, in practice, meant the research team received unidentifiable participant numbers that were added to the randomization pool. Prison staff were then notified which participant number should receive the intervention. They generated a list of participants, grouping them according to criteria, before giving this list to the dental practitioners who performed the intervention. This study did not use a data monitoring committee as the intervention was assessed as minimally invasive, alluding to a low risk of harming the participants.

A 2-fold survey, consisting first of a clinical examination before a questionnaire, was administered at 3 data collection points that aimed at a 4- and 8-week interval (T0, T1, and T2 in Figure 1). At the end of each survey, all participants were given an oral hygiene package (OHP) consisting of mouthwash, toothpaste, a toothbrush, and interdental cleaners (plackers and soft gum picks). Providing all participants with the same material to enhance their oral health also ensured that all participants had equal equipment and opportunity at baseline to enhance their oral health. Moreover, ethical considerations also played a role in giving the control group an OHP, which is detailed in the Ethical Considerations section. Given the prophylactic effect the OHP could have and the presumably increased focus on oral health related to the assessment, the control group is an augmented control group (hereon defined as the control group), as it does not reflect a regular prison context.

Figure 1. Study timeline and process. Surveys 1, 2, and 3 included a clinical examination and questions related to their incarceration and oral hygiene routines, sugary food and drink intake, oral health perception, and mental health (MHI-5). Still, they varied in the length of their additional questions. *Dental practitioners performing the MI were blinded until they had finished the survey (consisting of a clinical examination and questionnaires). Thus, although the research team had already randomized participants into intervention or control groups, dental practitioners did not know the effects of the randomization until measurement scores were taken, to avoid bias. MHI-5: Mental Health Inventory-5; MI: motivational interviewing; OHP: oral hygiene package.

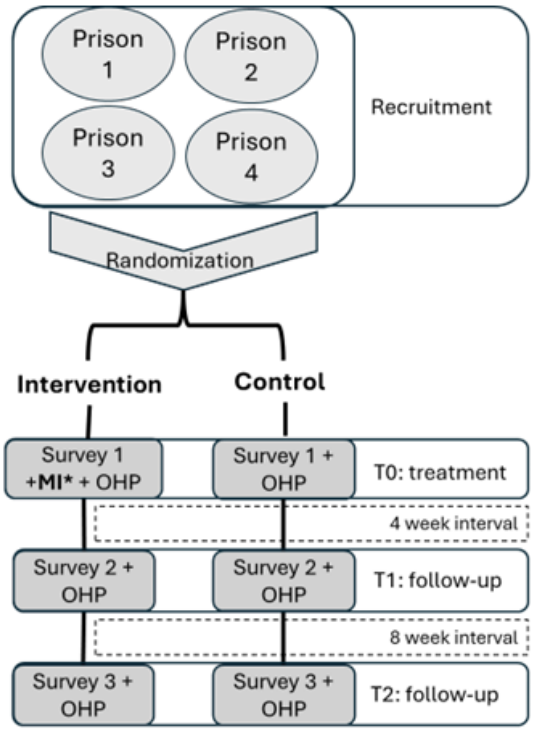

Study Setting, Participants, and Procedures

This study has already collected data. Thus, procedures related to recruitment are written in the past tense. Participants were recruited from 4 prisons in Rogaland, 3 being high-security and 1 being low-security.

Study recruitment was a process that varied due to logistics in the prisons and constant enrollment. Recruiting participants who were already serving time in prison was done by a dental staff or prison officer approaching eligible inmates (Table 1) and informing them about this study. For new inmates arriving at the prisons, recruitment became embedded on their first day of entry, because they were informed about study participation by prison staff while learning about the prison's procedures and drills. Participants gave their preliminary consent to participate within a few days after being informed about this study by notifying prison staff. To ensure voluntary motivation for study participants, recruiting staff were sensitive in their approach and study participants were reminded throughout that participation was voluntary and that they could withdraw at any point without repercussions.

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Table 1. Inclusion and exclusion criteria for study participation.

	Inclusion	Exclusion	Rationale	Procedure
Language	Norwegian speakers	English[a] speakers and non-Norwegian speakers	This study lacked trained and calibrated staff to conduct the motivational interview in languages other than Norwegian	Prison staff assessed this either at face value or by asking a standard question from an official Norwegian language test that detects a person's ability to engage in a simple conversation
Security	Those who were not at risk of harming themselves or others	Inmates whose incarceration was in isolation	This study did not seek to compromise any of the staff or inmates' security	Prison staff assessed this throughout this study's period
Age	≥18 years	—[b]	The prison facilities in Norway are split for adults and adolescents. This study recruited from adult prisons	By recruiting at the given prisons, all prisoners aged older than 18 years were included
Gender	All genders: male, female, and other	None	—	By recruiting at the given prisons, a female division at one prison was a natural part of the participation pool

[a]Considering the potential number of English speakers, the survey and consent form was outlined and administered in English to capture more baseline data. These will not be included in analyses assessing the effects of motivational interviewing.

[b]Not applicable.

Study participants were then randomized to either the intervention or control group. Formal written consent was given to the dental practitioners after they had been randomized (T0, Figure 1), and prison staff was not present, minimizing the superiority of the observer, which could be linked to the prison staff. Information about study participation was similar across all 4 prisons; they received verbal and written information, which was repeated by the dental staff before the written consent was obtained. At the recruitment stage, individuals were screened for language and study eligibility criteria, including inmates who could speak English or Norwegian and who passed a security assessment (Table 1). Only Norwegian-speaking participants were allocated to either the control or intervention group based on the assumption that dental practitioners would struggle with MI in a different language. Table 1 outlines this study's inclusion and exclusion criteria.

As outlined in Figure 1, this study has 3 data collection points: baseline (T0) and follow-up (T1 and T2). At T0, the participants were administered survey 1, which was 2-fold and consisted of a clinical examination and questionnaires. The clinical examination assessed the mean number of Decayed, Missing, and Filled Permanent Teeth [20] and the MPS [21]. The questionnaire in survey 1 consisted of 83 questions on their incarceration, oral hygiene routines, sugary food and drink intake, oral health perception, and oral health-related questions on dental anxiety (Modified Dental Anxiety Scale) [22,23] and quality of life (Oral Health Impact Profile-14) [24,25], sociodemographic and socioeconomic factors, use of dental and health services, general health and mental health (Mental Health Inventory-5 [MHI-5]) [26] and alcohol and drug use (Alcohol Use Disorders Identification Test–Consumption and Drug Use Disorders Identification Test–Consumption) [27,28]. Survey 1 was expected to take around 60 minutes. Data collection with participants receiving MI was expected to last around 90 minutes, where an additional 30 minutes were allocated to the intervention.

The follow-up phases, T1 and T2, each lasted around 30 minutes. At T1, survey 2 was administered, which contained the MPS oral examination and questions related to their incarceration, oral hygiene routines, sugary food and drinks intake, oral health perception, the MHI-5, and a short screening for learning disabilities (Hayes Ability Screening Index) [29,30]. At T2, survey 3 was administered, which contained the MPS oral examination and questions related to their incarceration, oral hygiene routines, sugary food and drink intake, oral health perception, and the MHI-5.

MI and Training

The dental practitioners who led the MI conversation were employed by public dental services (Rogaland, Norway) and consisted of 6 dental hygienists, 1 dentist, and 3 dental assistants. After reading about this study in an email sent to all public dental practitioners in Rogaland County, these dental practitioners applied for positions as research participants. Following the application was a short interview between the research group and dental practitioner that assessed their motivation and outlined the details of participation.

Within prison parameters, these dental practitioners performed the MI-led conversation with incarcerated people (Figure 1), closely following techniques described by Miller and Rollnick [16]. The MI-led conversation involved engaging, focusing, evoking, and planning by asking open-ended questions, and conversing affirmative, reflective, and summarizing with this study's participants. In practice, the typical MI-led conversation would start with the dental practitioner asking openly, "What cleaning routines do you have for your teeth?" or "What benefits could you get from brushing your teeth twice daily?" Following the respondent's answer to that open question would often lead to an affirmation by the dental practitioner, "You are truly trying hard to take good care of your teeth" or "You have managed to have good cleaning routines multiple times in the past." By using the reflection technique, during the MI-led conversation,

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the dental practitioners would typically repeat or use synonyms, extracting the underlying opinion or gut feeling, or dually highlighting the participant's pros and cons. The MI-led conversation closes with summarizing the participants' words.

By using open-ended questions and techniques such as affirmation, reflection, and summarizing, the conversation is steered from first concentrating on the task of being engaged with the interviewee, toward becoming more focused on illuminating and clarifying the goal and desired behavior changes, to then evoking the individuals' strength and motivation. The MI-led conversation ends with planning how this change is to come about and does so by incorporating a SMART (small, measurable, attainable, realistic, and time-specific) plan embedded in the action plan. The dental practitioner and participant jointly outline this action plan that summarizes what and how the change would come about. The action plan was a handout that this study's participants could keep, hang in their room, and serve as a reminder of the participants' goals and steps in their change process, and help them overcome obstacles. The action plan and aid dental practitioners had in the MI-led conversation are uploaded as Multimedia Appendix 1.

Before conducting the MI-led conversation, the dental practitioners underwent a comprehensive three-day training seminar led by an MI-certified specialist from the Regional Alcohol and Drug Competence Center in Rogaland County (KORUS). This training, which included group work, discussions, and a practice session was designed to equip them with the necessary skills and knowledge. The dental practitioner's conversations were also recorded, transcribed, and graded by KORUS in Bergen, with direct feedback provided. The MI specialist at the Center for Alcohol and Drug Research at Stavanger University Hospital was also available for continuous guidance if needed, ensuring that the dental practitioners were well-prepared for their role.

Measurements

Primary Outcome

The primary outcome measurement to assess the interventions' effectiveness in improving oral health behaviors, attitudes, and oral hygiene for people living in prisons is the MPS. This score is a composite measure that includes assessments of mucosal inflammation (MS) and plaque, which are indicators of changes in dental hygiene routines and attitudes [21]. The MPS was assessed at three time points: baseline (T0), midpoint (T1), and at the completion of the study (T2). The assessment procedure is simple and minimally invasive, ensuring minimal participant discomfort. Both the MS and plaque scores range from 1 to 4.

During scoring, dental practitioners undertaking the clinical MPS assessment were advised to score lower (a score of 1) in cases where there is doubt between the score of 1 and 2, and higher (a score of 4) for cases where there is doubt between the score of 3 or 4—combined the MS and plaque give an MPS score that has a total score of 8 and a minimum score of 2. Assessment guidelines define a score of 2-4 as good or acceptable, 5-6 as not acceptable, and 7-8 as in no way acceptable [21].

Secondary Outcome

The secondary outcome measurements this study is interested in are oral hygiene routines, sugary food and drink intake, oral health perception, and oral health-related questions, which were assessed in the survey at T0, T1, and T2.

For oral hygiene routines, participants were asked about their use of dental hygiene products such as toothbrushes, toothpaste, mouthwash, floss, and toothpicks over the last 4 weeks.

Participants were asked about their consumption within the last 4 weeks for sugary food and drink intake.

For oral health perception, participants were asked about their view of their health, the importance of good oral health, and their willingness to improve and take better care of their oral health. Dental practitioners noted how often study participants asked about their oral health during the clinical examination.

Participants were also asked about using the action plan (handed out after the MI-led conversation, Multimedia Appendix 1), which also serves as a secondary outcome measure.

Lastly, the survey collected descriptive data from participants that will be used to describe the population based on sociodemographic and socioeconomic factors, the use of dental health services and health services, and indicators of general and mental health (MHI-5). Additionally, the burden of oral decay (Decayed, Missing, and Filled Permanent Teeth), substance use patterns (assessed by Alcohol Use Disorders Identification Test–Consumption for alcohol and Drug Use Disorders Identification Test–Consumption for drug use), the presence of learning disabilities (Hayes Ability Screening Index), levels of dental anxiety (Modified Dental Anxiety Scale), and the impact of oral health-related quality of life (Oral Health Impact Profile-14) were also collected and will be used as descriptive data for the population. These data will also serve as covariates in the statistical analysis evaluating variables associated with oral health.

Sample Size and Justifications

Determining the needed sample size and power was assumed before data collection (ClinicalTrials.gov NCT05695443). Setting the α at .05, power of 0.80, for a nonparametric Wilcoxon-Mann-Whitney *U*-test. Data from previous studies using MI to improve oral health deviates from this study's population and in scoring plaque. Studies with a plaque index score as the primary variable to explain the effect reported a plaque range from 0.286 to 1.213 [31,32]. A conservative calculation through the computation tool G*Power (Heinrich-Heine-Universität Düsseldorf), determined a sample size of 320 people living in prisons to meet an observable effect size of 0.80, which was strived for. Given data has already been collected, we have performed a sensitivity power analysis through the computation tool G*Power, to compute the required effect size with our sample size of 126 in the intervention group and 157 in the control group. Setting the same parameters as prior (α at .05 and power at 0.8) gives us an effect size of 0.305.

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Data Analysis

Analysis will be performed using the statistical software package SPSS (IBM Corp). The unit of analysis is at the individual level. As this study is interested in uncovering the group differences between the intervention and control groups, a nonparametric Wilcoxon-Mann-Whitney *U*-test will be run, and group means will be compared at T0, T1, and T2 (Figure 1). The outcome of interest (primary outcome variable) is whether the participants' MPS scores have changed since baseline.

The main covariate is the preintervention (T0) MPS index score.

Double Blinding

Study participants and dental practitioners were blinded to group assignments during the initial oral examinations and questionnaires (survey 1) at baseline (T0). This double blinding was maintained until the dental practitioners completed the initial survey, after which they conferred with a list to check if participants were in the intervention or control group. At the follow-up data collection points (T1 and T2), dental practitioners might have recalled the participants' group assignments, potentially introducing bias. To mitigate this, our study incorporated MPS assessments from 2 independent dental practitioners at these stages, and scores were confidentially maintained to prevent bias.

As a final measure to ensure objectivity, data analysis will be conducted by a researcher who was not involved in any previous stages of this study, effectively establishing a third level of blinding during the analytical stage.

Missing Values

Missingness is presumed to be unrelated to the observed and unobserved data, thus, as missing completely at random. For analytical purposes, variables missing in the primary outcome will be handled with an intention-to-treat (ITT) analysis approach, allowing this study to use baseline data.

Ethical Considerations

The Norwegian Regional Committee for Medical and Health Research Ethics (282231), Criminal Services, and the Norwegian Agency for Shared Services in Education and Research (300281) have approved this study.

This study relies on informed written consent. To ensure prison inmates have been fully informed about study participation, recruitment processes have relied on help from both dental practitioners and prison staff. The written consent form was read out loud as well as handed out to ensure those with reading deficiencies understood what study participation entailed. As English speakers were included for baseline data, a consent form in English was also presented. Participants' ability to opt-out was stated at the recruitment phase as well as reminded of during data collection. All collected data has been deidentified.

Ethical deliberations led this study to administer the questionnaire part of the surveys verbally to ensure participants fully comprehended the questions asked. Verbally performing the questionnaires also gave latitude for the participant to ask questions in return and the dental practitioners to remind participants that they could withdraw or refrain from answering at any point without any form of consequence.

All participants (intervention and control group and English speakers) received an OHP because of the assumption that not all prison inmates had equal and sufficient tools to perform and potentially enhance their oral hygiene routines. Considering participants were randomly allocated into the control or intervention group, it was considered unethical to only give a hygiene package to those enrolled in the intervention group. The OHP passed prison security clearance.

All study participants (intervention and control group and English speakers) also received a clinical examination, which allowed dental practitioners to refer participants who needed dental treatment. This referral line was established due to ethical concerns, deeming it unethical for dental practitioners to detect oral diseases needing treatment without attending to them.

This study chose not to ask and collect data on what offenses were committed due to ethical and safety concerns. It was believed that knowing the crime offended could affect the dental practitioner's approach and conduct toward this study's participants.

Although this study was assessed as minimally invasive for its participants, all studies can impose a risk of impairment resulting from participation. To ensure this study limited its adverse events, dental practitioners who conducted the intervention and survey had direct contact with prison staff and were on alert, reacting to any signs of harm following the survey or intervention.

Results

Data collection started in November 2021 and finished in June 2023. Out of the total 327 participants, 283 were given the questionnaire in Norwegian, while 44 received it in English. A total of 126 of these received the intervention. This study is still plotting all data and will refrain from analysis until this protocol has been reviewed. All results from the data collection phases are expected to be ready by 2026.

Discussion

Principal Considerations

The global prison population has grown by 27% since 2000, and currently, over 11 million people are living in prisons [33]. Being incarcerated directly limits the ability to access health care services. This might be attributed to the lower outcome measurements of oral health for inmates in prisons. Moreover, routine interventions in prison contexts are scarce [14], and there is a lack of focus on oral health promotion in prison research [34].

This calls for a change in how oral health is promoted for people living in prisons. The opportunities the MI techniques provide could lead to more health promotion, less need for acute treatment, saving resources for the prison, and reducing the number of prison inmates who need transport to the dental clinic. This study was developed to improve the oral health of people living in prisons. Thus, the findings from this study will allow

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us to understand if the currently underserved population could benefit from an alternative approach.

Moreover, providing MI to the prison population can serve as a low-cost, effective procedure for increasing prison inmates' motivation to routinely care for their oral health by engaging a dental hygienist to conduct the conversation. Cost-effective studies could investigate whether MI with people living in prisons could be a more cost-effective way to build a dental clinic at the prison site.

Strengths and Limitations

A strength of this study is ensuring that dental practitioners who were undertaking the clinical examination were calibrated and received the same MI training. Dental practitioners were calibrated through a one-day workshop where they met physically to discuss clinical oral examinations, questionnaires, and procedures. Fifteen clinical photos were scored for MPS: First, the photos were individually scored before being jointly discussed and agreed upon. As the dental practitioners varied in background, the 3 participating dental assistants received an additional hour of calibration, compensating for their lack of clinical experience. This supplementary calibration hour for the dental assistants involved reviewing and MPS scoring 50 clinical photos. Lastly, 2 independent MPS scores on the participants were retained to avoid biases during data collection by having 2 dental practitioners scoring the same person individually. Data obtained from the calibration, describing the interrater variability between the 2 independent MPS scorers, will be analyzed and published along with the main study.

Although dental practitioners who led the intervention were trained, they could also lack confidence in the therapeutic role due to the novelty of using MI in prisons, which could affect the intervention delivery and outcome.

A notable limitation of this study is that both groups received an OHP comprising oral hygiene products that could act as a preventative for oral decay. Moreover, survey 1 included 83 questions, which were asked before the MI-led conversation. These questions might have caused fatigue in participants, deterring the effects of the MI.

Lastly, this study deviates from the pilot study by including the MI communication element of *reflection* [15,16].

Conclusion and Directions for Dissemination

This study aims to test and measure the effects of an MI-led conversation on improving people living in prisons' oral hygiene, cleaning routines, and attitudes. Granted that the intervention has an effect, the results can aid in how public dental health services can promote oral health for an underserved population, thereby increasing their objective of acting health promotive.

Results from this study will be published in national and international academic journals. This study's findings will also be shared through conferences for academics and practitioners and various forms of public media. A report of the project will also be written and shared with the collaborating partners and will also be open to the public.

This protocol has followed SPIRIT (Standard Protocol Items for Randomized Trials) guidelines.

Acknowledgments

We want to thank our collaborative partners, the KORUS, who contributed to the design of the MI intervention and training of dental practitioners; the Center for Alcohol and Drug Research, Stavanger University Hospital who contributed to developing the questionnaires and in supervising dental practitioners in MI; and the Directorate of Norwegian Correctional Service, Rogaland, and the 4 prisons for recruiting study participants and facilitating this study. We extend our utmost gratitude to this study's participants and dental practitioners for their time, encouragement, and motivation. We also want to thank the Regional and Public Oral Health clinic leaders for managing logistics. A major thanks to Kjersti Berge Evensen, PhD, for aiding the study's conceptualization and development and setting the necessary grounds for continuing this study. Lastly, Else Bjørheim, MSc, thank you for helping with the ongoing data plotting. Artificial intelligence has been used as a spell-check assistant during manuscript drafting. This oral health in prisons study is funded by Oral Health Centre of Expertise Rogaland and public dental services in Rogaland, providing this study with material support for OHPs and financial support for using dental practitioners.

Data Availability

Data collected from this study are sensitive, and participants have not consented to freely distributing it, limiting its availability.

Authors' Contributions

WGG has led this study's conceptualization, formal analysis, and development of its methodology. KHB contributed with resources. KHB and WGG contributed to this study's data collection procedures. KHB and EB contributed to data curation. EB contributed with visualization. EB is the project administrator, contributing with supervision and writing of the original draft. EB, KHB, and WGG reviewed and edited this paper. All authors have read and approved the final paper for publication.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
The action plan and aid dental practitioners had in the MI-led conversation. MI: motivational interviewing.
[PDF File (Adobe PDF File), 127 KB - resprot_v13i1e60817_app1.pdf]

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Abbreviations

ITT: intention-to-treat
KORUS: Regional Alcohol and Drug Competence Center in Rogaland County
MHI-5: Mental Health Inventory-5
MI: motivational interview
MPS: mucosal-plaque score
MS: mucosal inflammation
OHP: oral hygiene package
SMART: small, measurable, attainable, realistic, and time-specific
SPIRIT: Standard Protocol Items for Randomized Trials

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Protocol

Leveraging Community Health Workers and a Responsive Digital Health System to Improve Vaccination Coverage and Timeliness in Resource-Limited Settings: Protocol for a Cluster Randomized Type 1 Effectiveness-Implementation Hybrid Study

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Abstract

Background: Tanzania is 1 of 20 countries where the majority of unvaccinated and undervaccinated children reside. Prior research identified substantial rural-urban disparities in the coverage and timeliness of childhood vaccinations in Tanzania, with children in rural settings being more likely to receive delayed or no vaccinations. Further research is necessary to identify effective and scalable interventions that can bridge rural-urban gaps in childhood vaccination while accounting for multifaceted barriers to vaccination.

Objective: This protocol describes a type 1 effectiveness-implementation hybrid study to evaluate Chanjo Kwa Wakati (*timely vaccination* in Kiswahili), a community-based digital health intervention to improve vaccination timeliness. The intervention combines human resources (community health workers), low-cost digital strategies (electronic communication, digital case management, and task automation), a vaccination knowledge intervention, and insights from behavioral economics (reminders and incentives) to promote timely childhood vaccinations.

Methods: The study will be conducted in 2 predominantly rural regions in Tanzania with large numbers of unvaccinated or undervaccinated children: Shinyanga and Mwanza. Forty rural health facilities and their catchment areas (*clusters*) will be randomized to an early or delayed onset study arm. From each cluster, 3 cohorts of mother-child dyads (1 retrospective cohort and 2 prospective cohorts) will be enrolled in the study. The timeliness and coverage of all vaccinations recommended during the first year of life will be observed for 1200 children (n=600, 50% intervention group children and n=600, 50% nonintervention group children). The primary effectiveness outcome will be the timeliness of the third dose of the pentavalent vaccine (Penta3). Quantitative surveys, vaccination records, study logs, fidelity checklists, and qualitative interviews with mothers and key informants will inform the 5 constructs of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework. The results will be used to develop an implementation blueprint to guide future adaptations and scale-up of Chanjo Kwa Wakati.

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Results: The study was funded in August 2022. Data collection is expected to last from February 2024 to July 2027.

Conclusions: This study will address the lack of rigorous evidence on the effectiveness of community-based digital health interventions for promoting vaccination coverage and timeliness among children from sub-Saharan Africa and identify potential implementation strategies to facilitate the deployment of vaccination promotion interventions in low- and middle-income countries.

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International Registered Report Identifier (IRRID): PRR1-10.2196/52523

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KEYWORDS

childhood vaccinations; timeliness; vaccine hesitancy; digital health; community health workers; Tanzania; low- and middle-income countries; SMS; reminder; conditional incentive

Introduction

Background

Globally, the number of children missing their first dose of the diphtheria-pertussis-tetanus (DPT) vaccine rose from 19 million in 2019 to 25 million in 2021 [1,2]. The vast majority (14.2 million, 78%) of such *zero-dose* children reside in 20 countries, including Tanzania [3]. As in other low- and middle-income countries (LMICs), substantial rural-urban disparities in routine childhood vaccination exist in Tanzania, with vaccination rates being lower in rural areas than in urban areas [4]. Using data from the 2015-2016 Tanzanian Demographic and Health Survey, we demonstrated gaps in vaccination coverage (receipt of each recommended vaccine dose by age 1 y) and timeliness (receipt of each vaccine dose within 28 d of the recommended age) for Tanzanian children [4]. The coverage of the first dose of the pentavalent vaccine (Penta1, which includes antigens of DPT, *Hemophilus influenzae*, and hepatitis B) was 79.4% nationally in this analysis, with the remaining 21% of children classified as zero dose [4]. We documented receipt of the third dose of the pentavalent vaccine (Penta3) in even fewer children (72.7%), suggesting dropouts in the multidose vaccine series. Finally, rural children had lower timeliness of vaccination (47.8% delayed for Penta3) than urban children (24.2% delayed for Penta3). New interventions are needed to reduce the number of children who are zero dose, receive delayed vaccines, or drop out and to close the rural-urban gap in vaccination [4,5]. Such interventions must consider multifaceted barriers to vaccination and variations in the availability of human resources and infrastructure in rural areas.

In prior research in southern Tanzania, we identified challenges with the availability of, and access to, vaccination services, including challenges with distance and transportation to health facilities, temporary nonavailability of vaccines owing to a lack of reliable refrigeration at health facilities, and vaccine wastage policies that prevented the use of multidose vials when clinics had low volumes of children to be vaccinated [6]. Service unreliability and lack of communication about service interruptions were noted as causes of frustration among mothers of vaccine-eligible children [6]. Our research also identified vaccine hesitancy owing to vaccine-related knowledge gaps and concerns. In general, rural mothers reported more vaccine-related knowledge gaps and concerns than urban mothers [6]. Despite challenges, vaccination intention was high among mothers, and conditional incentives were identified as a potential *nudge* to increase vaccination timeliness [7,8]. In addition, a community health worker (CHW)–delivered knowledge intervention was piloted and determined to be feasible to implement in rural areas. On the basis of the findings of this formative research and other published reports [9], we designed Chanjo Kwa Wakati (*timely vaccination* in Kiswahili, the most commonly spoken language in Tanzania), a community-based digital health intervention to improve childhood vaccination coverage and timeliness. The intervention seeks to combine human resources (CHWs), low-cost digital strategies (electronic communication, digital case management, and process automation), a vaccination knowledge intervention (counseling scripts addressing specific knowledge gaps), and insights from behavioral economics (reminders and incentives) to promote timely childhood vaccination.

Objectives

This protocol describes our planned evaluation of the implementation and impact of Chanjo Kwa Wakati. The study seeks to contribute evidence to the literature in 3 key ways. First, although many studies have evaluated mobile phone–based reminders for promoting childhood vaccinations [10], evidence is lacking [9] for more complex community-based digital health interventions that target multifaceted barriers to vaccinations, such as those identified in our prior research [4,6,7]. Second, few community-based digital health interventions for promoting childhood vaccination have been evaluated using rigorous randomized controlled study designs, especially in sub-Saharan African countries and in rural areas [11-15]. Third, evidence on implementation strategies associated with deploying community-based digital health interventions in LMICs is limited but critically important for supporting scale-up in the context of highly resource-constrained national health systems. To bridge these gaps in the literature, we will use a type 1 effectiveness-implementation hybrid study [16,17] to evaluate the effectiveness of Chanjo Kwa Wakati in improving the timeliness of childhood vaccinations in rural areas in Tanzania and identify strategies that support its implementation. The detailed protocol of the study is presented in the following sections.

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Methods

Study Overview and Aims

This type 1 effectiveness-implementation hybrid study [16,17] uses a cluster randomized trial to evaluate intervention effectiveness and mixed methods to describe implementation outcomes. A cluster randomized design was chosen because the delivery of the intervention is organized at the cluster level. In addition, there are ethical concerns with the randomization of intervention activities, including incentives, at the individual level in rural communities in Tanzania. The evaluation of the Chanjo Kwa Wakati intervention will be guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework. The methods used in this study are described in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist for cluster randomized studies (Multimedia Appendix 1). The study aims and hypotheses are described in the following subsections.

Aim 1

The first aim is to evaluate the effectiveness of Chanjo Kwa Wakati for increasing the timeliness of childhood vaccinations due by age 1 year compared with the standard of care. The effectiveness of Chanjo Kwa Wakati will be evaluated in a cluster randomized trial with 1200 mother-child dyads enrolled from the catchment areas of 40 rural health facilities (*clusters*) in 2 regions in Tanzania. Clusters will be randomized into an early or delayed onset study arm. The intervention will target the mother-child dyad; outcomes will be assessed at the child level. Our hypothesis is that Chanjo Kwa Wakati is effective for increasing the timeliness of childhood vaccinations due by age 1 year compared with the standard of care. The primary outcome measure used to evaluate intervention effectiveness will be a continuous measure of the timeliness of the third dose of the pentavalent vaccine (Penta3), due at age 14 weeks, and determined using the birth and vaccination dates abstracted from official vaccination cards issued for the child. A secondary outcome will be a binary measure of timeliness, defined as receipt of Penta3 within 28 days of the due date. Other outcomes measures include the timeliness and coverage of all other vaccine doses due by age 1 year.

Aim 2

The second aim is to evaluate the implementation factors associated with variation in intervention effectiveness and develop an implementation blueprint for intervention scale-up to other settings. Study logs, fidelity checklists, quantitative surveys, and qualitative interviews with mothers and key informants will be used to inform other constructs of the RE-AIM framework, specifically reach, adoption, implementation, and maintenance. Two key implementation outcomes of interest are participants' reports of the receipt of intervention components (intervention fidelity) and their reports of intervention acceptability. Analyses of variation in intervention implementation at the cluster level and systematic variation in the effectiveness for aim 1 outcomes across children will guide the future optimization of Chanjo Kwa Wakati. The results will be used to develop an implementation blueprint to guide future adaptations and scale-up of Chanjo Kwa Wakati.

Study Setting

The study will be conducted in 4 rural districts in Mwanza and Shinyanga regions in Tanzania. Both regions have large numbers of unvaccinated or undervaccinated children. The populations of Mwanza and Shinyanga region were estimated to be 3,699,872 and 2,241,299, respectively [18]. In 2022, only 56% of children aged 12 to 23 months in Mwanza region and 32.2% of children in Shinyanga region were estimated to have received all basic vaccinations, including one dose of Bacillus Calmette-Guerin vaccine, 3 doses of polio vaccine, 3 doses of DPT-containing vaccine, and one dose of measles-containing vaccine [19]. Fewer children aged 12-23 month were considered fully vaccinated according to the national vaccination schedule shown in Table 1 (32.8% in Mwanza and 2.5% in Shinyanga) [19]. Notably, 3.3% of children aged 12-23 months in Mwanza and 14.5% in Shinyanga were reported to have received no vaccinations. [19].

Table 1. Routine childhood immunizations recommended in Tanzania before age 1 year.

Antigen	Age at vax due date
Bacillus Calmette-Guerin (BCG) and oral polio vaccine (OPV) 0	At birth or first contact
OPV1; pentavalent vaccine comprising antigens of diphtheria, pertussis, tetanus, *Hemophilus influenza* B, and hepatitis B (Penta) 1; pneumococcal vaccine (PCV) 1; and rotavirus vaccine (Rota) 1	6 weeks
OPV2, Penta2, PCV2, and Rota2	10 weeks
OPV3, Penta3, PCV3, and injectable polio vaccine (IPV)	14 weeks
Measles and rubella 1	9 months

Intervention Components

Chanjo Kwa Wakati focuses on individual-level barriers to timely vaccination to complement the Tanzanian government's efforts to strengthen vaccination systems and reduce structural barriers [20]. Chanjo Kwa Wakati comprises the following individual-level intervention components: a vaccination knowledge intervention, reminders about upcoming vaccination due dates, service notifications, and conditional incentives for timely vaccination (Table 2). The intervention's target population is the mother-child dyad from the time of pregnancy (third trimester) until the child is aged 1 year. Intervention activities are targeted toward the mother, whereas the timeliness of Penta3 (primary outcome) and other vaccinations recommended before age 1 year (secondary outcomes; Table 1) is assessed for the child.

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Table 2. The Chanjo Kwa Wakati intervention.

Timing	Activities	Detailed description of activities
Last trimester of pregnancy	• Enrollment • Registration in digital health system • Knowledge intervention • Baseline assessment[a]	• Informed consent[a] • Register pregnancy and phone numbers in the digital health system • Identify knowledge gaps for an individualized knowledge intervention based on a study by Vasudevan et al [6] • Assess postintervention change in vaccination knowledge and attitudes as well as potential correlates of coverage and timeliness[a]
≤4 wk after the date of delivery	• CHW[b] phone call or home visit	• Ascertain date and place of birth as well as the receipt of vaccinations due at birth • Register the birth, record the 6-wk vaccination due date, and update phone numbers in the digital health system
Before each vaccination due date (6, 10, and 14 wk, and 9 mo)	• SMS text message reminders with incentive offers • Backup: CHW phone calls or home visits • Knowledge intervention	• Messages are sent to the mother and vaccine advocates 7 d and 1 d before each vaccination • Messages are individualized and account for information on service interruptions • Messages include conditional incentive offers • Individualized knowledge intervention focused on vaccinations due at an upcoming visit
≤1 wk after each vaccination due date	• CHW phone call or home visit	• Verify vaccination status and date against vaccination card and issue incentive as appropriate • Update vaccination due dates (and thus reminders) as necessary
12-15 mo after birth	• Follow-up assessment[a]	• Validate vaccination coverage and dates using vaccination cards[a] • Issue incentive as appropriate

[a]Research activity. All other activities are intervention activities.

[b]CHW: community health worker.

Individualized Knowledge Intervention

The knowledge intervention consists of 9 true or false statements that assess key knowledge gaps about childhood vaccinations. A brief counseling script is provided with each statement that will be read out by the CHW after an incorrect response. Statements are based on prior research in Tanzania [6]. Statements and counseling scripts were tested extensively for content, comprehension, and cultural appropriateness with national key informants from Tanzania's Immunization and Vaccines Development program, regional and district health officials, CHWs, and pregnant women from rural Tanzania. In addition to the in-person individualized vaccination education provided by CHWs, SMS text message–based vaccination promotion messages, sent via the Chanjo Kwa Wakati digital health system, will be individualized to each participant's knowledge gaps and aligned with the child's vaccination schedule.

Vaccination Reminder Messages

CHWs will verify the due date for the next vaccination using the child's vaccination card and update the child's information in the Chanjo Kwa Wakati digital health system. The system will automatically schedule SMS text message reminders to be sent 7 days and 1 day before each vaccination due date. The SMS text messages will include the name of the intended recipient, the child's name, the vaccination due date, and other relevant information.

Service Notifications

In the event of stockouts or service nonavailability, SMS text messages with relevant information will be sent to mothers whose children are due for vaccination.

Incentive Offers

Conditional incentive offers will be specific to each child's vaccination schedule. In our prior work [7,8], we identified a set of incentives (eg, pharmacy vouchers and birth certificates) that are likely to be acceptable to mothers. The specific incentives, their value, conditionality, and the timing of disbursement will be determined in discussion with local key informants.

Implementation Strategies

Relevant implementation strategies will be identified in collaboration with local key informants, and a detailed logic model will be developed to guide study activities.

Intervention Activities

Figure 1 describes the sequence of intervention activities. Pregnant women, enrolled in their third trimester, will receive a home visit from a CHW before the birth of their child, be registered with the Chanjo Kwa Wakati digital health system, and receive an individualized knowledge intervention to screen and counsel for common knowledge gaps and concerns about routine childhood vaccinations. After the birth of the child, the

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mother will receive individualized SMS text message reminders for upcoming vaccinations, messages aimed at mitigating persistent vaccination knowledge gaps, service notifications (eg, related to stockouts or service nonavailability), and conditional economic incentive offers aimed at encouraging timely vaccinations. CHWs will use the digital health system for work planning, recording vaccination dates and due dates, and following up on missed vaccination appointments and backstop the digital health system with phone calls and in-person visits as needed for vaccination reminders and assessing and addressing mothers' knowledge gaps.

Figure 1. Sequence of intervention activities. CHW: community health worker.

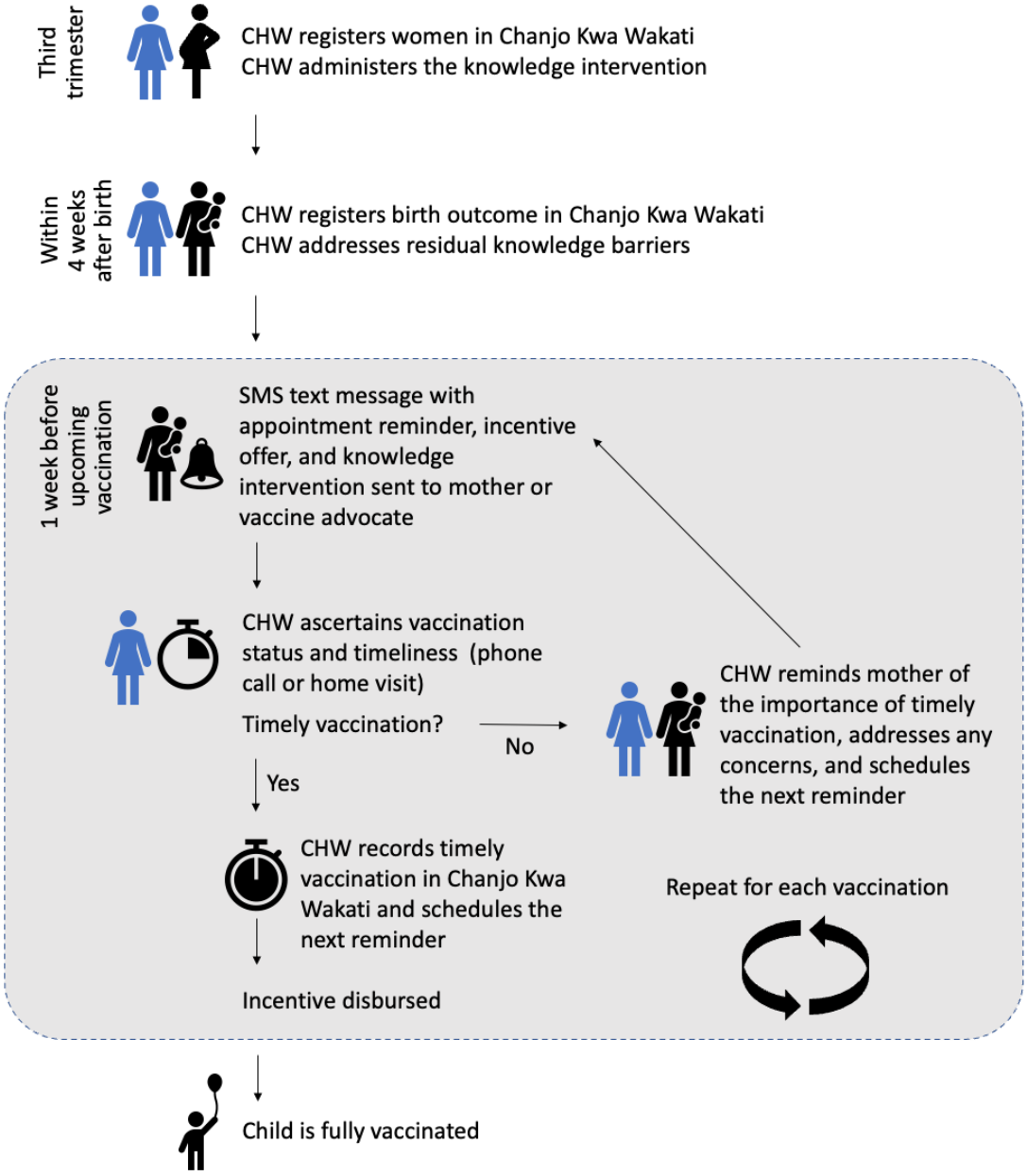

Study Population

Sampling Area

The sampling area comprises 2 rural districts in Mwanza region and 2 rural districts in Shinyanga region, selected based on district-level information about vaccination rates, logistical considerations, and input from key informants.

Cluster Eligibility

Twenty clusters will be selected in each region for a total of 40 clusters. Clusters are defined as the catchment area of eligible health facilities in the sampling area. Eligible health facilities include public and public-designated (private not-for-profit facilities that serve the functions of public health facilities) hospitals, health centers, and dispensaries. Facilities must be operational, offer routine prenatal care and childhood vaccination services, have at least 2 active CHWs operating in the catchment area, and have reported at least 100 pregnancies or births in the year before study implementation. Eligibility will be determined initially using administrative data obtained from district offices and verified using surveys with health facilities.

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Study Participants, Eligibility, and Recruitment

The study population will include 3 groups of participants.

Cross-Sectional Retrospective Cohort

This cohort (n=400) will be used for retrospective assessments of children's vaccination records during their first year of life. Eligible participants will be mothers or legal guardians (henceforth referred to as *mothers*) of children aged 12 to 23 months, aged ≥15 years, and residing in the sampling area since the birth of the child.

Before recruiting this cohort, CHWs, with help from local key informants (eg, village leaders, health care providers, and traditional birth attendants), will compile a list of children aged 12 to 23 months residing in each cluster. The lists will be randomized, and mothers will be approached by the research team for eligibility determination, informed consent, and enrollment until 10 mother-child dyads from each cluster are enrolled into the study. Up to 40 additional women, who are not necessarily living in the study area but meet the other eligibility criteria, may be enrolled to pilot-test the study instruments.

Longitudinal Prospective Cohort

This cohort (n=800) will be used for prospective assessments of children's vaccination records during their first year of life. Eligible participants will be pregnant women in their last trimester of pregnancy, aged ≥15 years, residing in the sampling area, and expected to reside in the sampling area until the child reaches age 1 year.

Before recruiting this cohort, CHWs, with help from local key informants (eg, village leaders, health care providers, and traditional birth attendants) will compile a list of pregnant women residing in each cluster. The lists will be randomized, and pregnant women will be approached by the research team for eligibility determination, informed consent, and enrollment until 10 pregnant women from each cluster are enrolled into the study. One additional eligible woman will be enrolled from each cluster during each prospective enrollment round to account for loss to follow-up (refer to the *Retention* subsection).

Participants in Qualitative Feedback

This group will be used to obtain feedback on the RE-AIM constructs. Eligible participants will be key informants at the national, regional, or local levels (target: n=12), health providers from participating facilities who are responsible for childhood vaccinations (target: n=40, approximately 1/cluster), CHWs in study clusters (target: n=80, approximately 2/cluster), and women enrolled in the prospective cohort (target: n=60).

To recruit these participants in qualitative work, a combination of purposive and snowball sampling strategies will be used. The numbers of participants represent target numbers; additional participants will be enrolled if saturation is not reached. Key informants, including policy makers, decision makers, and implementers at the national, regional, or local levels (eg, officials from Tanzania's Immunization and Vaccines Development program as well as regional, district, and local health officials) will be asked to participate in qualitative interviews on implementation factors and to recommend other individuals who can provide relevant information. Health providers who are responsible for childhood vaccinations will be enrolled from participating health facilities. CHWs will be enrolled from participating clusters. Women will be purposively selected from the prospective cohort based on data collected during enrollment or follow-up surveys, study logs, or the digital health system during study implementation.

Study Design

Cluster Randomized Trial Design

Forty rural health facilities and their catchment areas (*clusters*), 20 per region, will be randomized to an (A) early or (B) delayed onset study arm (Figure 2). From each cluster, 3 cohorts of 10 mother-child dyads (1 retrospective cohort and 2 prospective cohorts) will be enrolled into the study. For the retrospective cohort, 400 mothers of children aged 12 to 23 months (10/cluster) will be enrolled as a cross-sectional sample for retrospective assessments of children's vaccination records during the first year of life. These cohorts, denoted by A1 and B1, will be part of the care-as-usual control group. For the longitudinal prospective cohort, 800 pregnant women in their last trimester of pregnancy will be enrolled during 2 rounds of enrollment (10 women/enrollment round/cluster) for prospective assessments of their children's vaccination records during the first year of life. These cohorts are denoted by A2, A3, B2, and B3. In the first round of enrollment, 200 (50%) of the 400 prospective participants (those enrolled from early onset clusters; A2) will receive the intervention, and the other 200 (50%) participants (B2) will be part of the care-as-usual control group. In the second round of enrollment, all 400 participants (A3 and B3) will receive the intervention. In total, vaccination uptake and timeliness will be observed for 1200 children (n=600, 50% intervention group children and n=600, 50% nonintervention group children) during their first year of life. The nonintervention group children represent the *care-as-usual* control group in the trial.

The trial design, which analytically resembles a difference-in-difference design, allows for an analysis of the effectiveness of the intervention even in the context of contemporaneous changes in the rate and timeliness of vaccinations at the national level (eg, through national vaccination campaigns or changes in the vaccination schedule).

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Figure 2. Design of the 2-arm cluster randomized trial (n=1200).

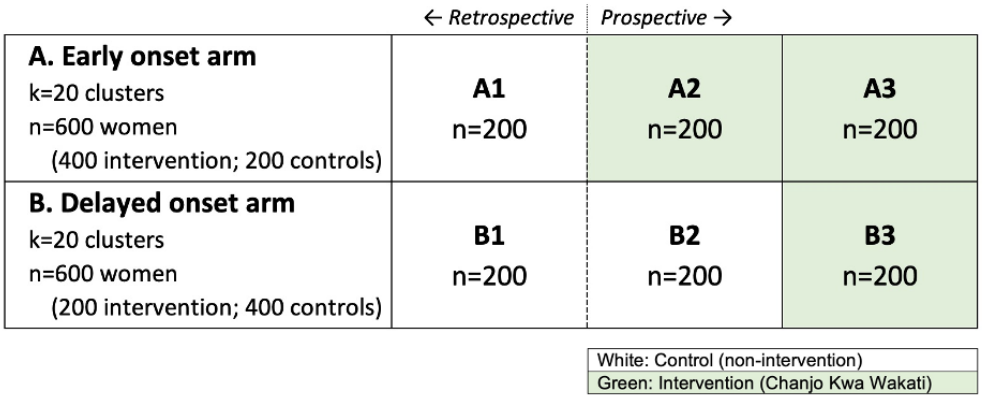

Evaluation Framework

The evaluation of the Chanjo Kwa Wakati intervention will be guided by the RE-AIM framework. Quantitative survey data will be the primary source of information for the analysis of the effectiveness of the intervention. These data will be complemented by study logs, fidelity checklists, and qualitative interviews with Tanzanian key informants, facility-based health workers, CHWs, and mothers to assess the acceptability, reach, and fidelity of Chanjo Kwa Wakati, as well as factors that may inform sustainability and scalability in the future.

Outcomes Assessments

Vaccination outcomes are described in Table 3. Vaccination coverage and dates will be ascertained for each study child using government-issued vaccination cards, which will be photographed, scanned, or copied and entered by research staff. For the retrospective cohort, the enrollment survey will assess vaccination outcomes for the child; their participation will end after the enrollment survey. Outcome data for the prospective cohort will be collected during an endline survey 12 to 15 months after the birth of the child. All vaccination doses of all vaccination series will be tracked. For women who cannot provide vaccination cards at the time of the survey, consent will be sought to access their children's paper-based or electronic vaccination records at their local health facility.

Table 3. Outcome measures for the cluster randomized controlled trial.

Outcome measure	Type	Source
Timeliness of the third dose of the pentavalent vaccine, Penta3 (number of days delayed)	Primary	Vaccination cards
Timeliness of Penta3 (≤28 days delayed)	Secondary	Vaccination cards
Timeliness of all other vaccine doses recommended by age 1 y (number of days delayed)	Other	Vaccination cards
Coverage of all vaccine doses recommended by age 1 y	Other	Vaccination cards

Study Procedures

Cluster Randomization

In each district, all eligible health facilities will be assigned random IDs. Random IDs will be generated using a random number generator in Stata (version ≥16; StataCorp LLC) with a fixed seed to ensure reproducibility. In each district, the 10 clusters with the smallest random IDs will be allocated to either the early onset arm (odd ranks) or delayed onset arm (even ranks). Facilities that are not willing to participate or are deemed ineligible will be replaced with the next odd- or even-ranked facility, respectively. If the distributions of key characteristics of clusters (eg, the number of pregnant women/y, the number of births/y, the percentage of home births, vaccination coverage, and the number of days vaccinations are offered each wk) differ significantly between study arms, a covariate-constrained randomization [21,22] approach will be used to maximize the balance of these characteristics across study arms.

Blinding

Owing to the nature of the intervention, there will be no blinding of investigators, implementers (CHWs), data collectors, or participants.

Enrollment

Participants may be enrolled at their homes, health facilities, or other mutually agreed-upon locations. The potential risks and benefits of research participation will be carefully explained during the informed consent process (refer to the *Ethical Considerations* subsection). To maximize the reach of the intervention, participants without mobile phones will be able to designate a vaccine advocate of their choice to receive mobile phone–based messages.

Retention

Retention only applies to the prospective cohort. To ensure the retention of study participants, extensive contact information, including the names and mobile phone numbers of both parents, vaccine advocates, and other contacts, as well as expectations for the place of delivery, travel plans after birth, and GPS

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coordinates of homes will be documented at enrollment. In the event of child death, maternal death, or participant withdrawal, intervention activities related to the mother-child dyad will be suspended, and the dyad will be withdrawn from the study. In the event of child relocation or family travel during study activities, efforts will be made to collect outcomes data for the child using a combination of mobile phone–based surveys; a review of the child's records at the local health facility; and proxy reports from the father, other legal guardians, or other informants. As the intervention involves local CHWs, for participants relocating outside their cluster for the remainder of the study period, intervention activities will stop after relocation.

Data Collection

Overview

Trained research assistants will conduct enrollment and data collection in Kiswahili. Survey instruments will be developed in English, translated into Kiswahili, and back-translated into English. The development of the surveys will be informed by prior surveys [6,8].

Enrollment Survey

All participants will complete an enrollment survey. The survey will last approximately 45 minutes and assess knowledge and attitudes, sociodemographic characteristics of participants and their households, access barriers, digital literacy, residual knowledge gaps, and other correlates of vaccine uptake and timeliness. The mother's engagement in prenatal care will be assessed via self-report and scanned prenatal care cards. For retrospective participants, the enrollment survey will also assess vaccination uptake and timeliness (Table 3), whereas for prospective participants, extensive contact information will be collected (refer to the *Retention* subsection).

Follow-Up Survey

Prospective participants will complete a follow-up survey 12 to 15 months after their child's birth. The survey will last approximately 30 minutes. The primary purpose of the follow-up survey is to collect data on vaccination outcomes (Table 3). The follow-up survey will include the knowledge intervention that addresses each woman's vaccination-specific knowledge gaps and assess vaccination attitudes and experiences with vaccine uptake and timeliness during the study period. The follow-up survey will also be used to update information on mothers' engagement in prenatal care via self-report and scanned prenatal care cards. For intervention group women, the follow-up survey will also assess implementation measures, experiences with the intervention, and the acceptability and perceived efficacy of Chanjo Kwa Wakati.

Facility Survey

During the enrollment and follow-up work, we will conduct a survey of the health facility in each cluster. The purpose of the facility survey is to assess the implementation context. The survey will collect service information (eg, information on vaccine stockouts and facility closures), procedural knowledge (eg, vaccination dates, scheduling, and rescheduling), and contact information.

Qualitative Data

In-depth interviews (IDIs) will elucidate wide-ranging feedback on all constructs of the RE-AIM framework. IDIs will be conducted by local trained study staff in English or Kiswahili. Study staff will follow a semistructured interview guide. IDIs will be recorded to facilitate transcription and data analysis. Depending on the availability of the participants, IDIs may be conducted by phone or in person. IDIs are expected to last 45 to 60 minutes.

Statistical Power

The aim 1 cluster randomized trial will include 1200 women, enrolled from 40 different clusters, across 3 distinct enrollment phases, with 10 women enrolled from each cluster in each phase. This equates to k=120 statistical clusters with n=10 women per cluster. Half of these clusters (k=60/120, 50%; n=600/1200, 50%) will be allocated to the intervention arm and half to the control arm. Assuming that the primary outcome—the timeliness of the Penta3 vaccine—has an SD of 28 days, the power of the trial to detect an intervention-related difference of 7 days is 0.95 with an intracluster correlation coefficient of 0.05; the power is 0.88 with an intracluster correlation coefficient of 0.10.

The aim 2 qualitative formative work will yield data from IDIs with key informants (n=12), facility-based health workers (up to n=40), CHWs (up to n=80), and mothers (up to n=60). Prior research suggests that thematic saturation can be achieved with 12 interviews, with metathemes presenting as early as 6 interviews [23-25]. Thus, these proposed sample sizes should be sufficient to achieve thematic saturation of implementation barriers and residual barriers to timely and equitable vaccinations, as well as to identify any regional variation in reasons for delayed vaccinations.

Data Analysis

Quantitative Analysis of Intervention Effectiveness

The primary outcome measure of interest will be a continuous measure of vaccination timeliness, expressed as the delay, in days, between the vaccination due date and the date on which the vaccination was received for the third dose of the pentavalent vaccine, Penta3, due at age 14 weeks (Table 1). The secondary and other outcome measures include the timeliness and coverage of all vaccine doses recommended by age 1 year. Owing to the randomization, a comparison of mean outcomes between participants in the intervention group and those in the nonintervention group yields an unbiased estimate of the effect of the intervention.

To control for variation in sociodemographic characteristics across participants, seasonal effects, and other potential correlates of vaccination timeliness, outcomes will also be analyzed in a multivariable regression framework using accelerated failure time models with the completed vaccination dose as the failure event, age in days describing time to failure, and membership in the intervention versus control groups as the primary covariate of interest.

Robust SEs will be estimated to account for the clustering of observations across mother-child dyads enrolled from the same geographic clusters at the same time.

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Analysis of Implementation Outcomes

We will generate summary measures (eg, means) for continuous data and use proportions to summarize categorical data. For outcomes assessed using validated measures (eg, the Acceptability of Intervention Measure [26]), we will present composite scale scores. Qualitative implementation outcomes will be analyzed as described below.

Analysis of Qualitative Data and Integration With Quantitative Data

Thematic analyses will be facilitated by qualitative software (eg, NVivo [Lumivero]) and a codebook made up of a priori and emergent structural codes based on the interview guide and 4 interrelated steps: reading, coding, data display, and data reduction [27]. The data will be used to fully map the Chanjo Kwa Wakati process from the perspectives of the mother and the CHW and characterize the opportunities and limitations of using digital and in-person resources to support vaccination timeliness. Using convergent mixed methods, we will use joint displays and narrative integration to connect the quantitative and qualitative data [28-30].

Analysis of Systematic Variation in Effectiveness

Extensive sensitivity analysis for the aim 1 primary and secondary outcomes analyses will characterize variation in intervention effectiveness with population, setting, and implementation factors. Variation in intervention effectiveness will be evaluated using interactions between geographic, maternal, or child characteristics and the intervention variable. Statistically significant parameters on interaction terms are indicative of differential intervention effects for different subgroups. To account for variation in implementation, sensitivity analysis will include per-protocol (as-treated) and intention-to-treat analyses in which a vector of variables describing the fidelity of the different intervention components will be used in place of the binary intervention variable.

Missing Data

The *Study Limitations and Adaptations* subsection in the *Discussion* section discusses considerations regarding missing data on outcomes and covariates and their handling in the analyses.

Ethical Considerations

The study protocol, informed consent forms, and procedures have been reviewed and approved by the Health Sciences South Carolina Institutional Review Board (the reviewing institutional review board [IRB]; Pro00120675) and the ethics review committee of the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol.IX/4242), as well as the relying IRBs at Duke University (Pro00111772), Emory University (STUDY00005518), and the University of North Carolina at Chapel Hill. Informed consent will be sought from all study participants.

To maintain confidentiality, interviewers will conduct the consent process in a private space or in a mutually agreed-upon location where other people are not present. The interviewers will read out the consent form to potential participants and answer any questions. The potential risks and benefits of participation as well as the details of data confidentiality and use will be carefully explained in culturally appropriate and understandable language. Participants can refuse to participate and will only be consented after the research staff is satisfied that they understand all substantive provisions of the informed consent document. Persons with obvious psychological or psychiatric disorders that preclude informed consent will be excluded. Participants will be asked to provide written consent. They will be provided with a copy of the consent form. Informed consent documents will be developed in English, translated into Kiswahili, and back-translated into English.

Participants in the trial will be aged ≥15 years and either pregnant in their last trimester of pregnancy or mothers or legal guardians of children aged 12 to 23 months. For adolescents aged 15 to 17 years who are pregnant or mothers of children aged 12 to 23 months and are otherwise eligible to participate in the study, we obtained a waiver of parental consent. Tanzanian national policy indicates that adolescents aged <18 years who are sexually active and pregnant have the right to access reproductive health services (eg, HIV testing, care, and treatment [31], as well as family planning [32]) without parental or spousal consent, and they can make associated medical decisions on their own behalf. Given that these adolescents have this *adult* right to medical decision-making, we posit that they are also able to consent to research participation for themselves without parental or spousal consent. Risks from participation in this study are considered commensurate with ordinary daily life.

Protocol amendments will be submitted to the relevant IRBs for approval before implementation. Adverse events will be reported to the ethics review committee of the National Institute for Medical Research in Tanzania and the US-based IRBs.

Participants will be compensated for the time they spend participating in study activities. Ethically and culturally appropriate compensation will be established in collaboration with community advisers and other key informants. Subject to IRB approval and discussions with key informants, incentive amounts may be adjusted during the study period to account for exchange rate fluctuations and cost-of-living increases.

Results

Results are pending. The study was funded in August 2022. Data collection is expected to last from February 2024 to July 2027.

Discussion

Relevance

The Chanjo Kwa Wakati intervention and proposed evaluation are aligned with the strategic priorities of the Immunization Agenda 2030 and Tanzanian priorities for digital health and community health workforce development [33,34]. Specifically, our study builds on a Tanzanian digital health investment road map [35] to digitize health care data and is in line with Tanzania's 2020 National Operational Guideline for Community-Based Health Care Services, which seeks to build a strong community health workforce for health promotion,

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including for child health [36]. The relevance of our study extends beyond rural Tanzania. The low-cost strategies developed and evaluated in this study are applicable to other rural contexts where some populations are less likely to be vaccinated, experience poor vaccine access, or express low confidence in vaccinations, and our study may inform the development and implementation of multipronged programs to promote timely vaccinations in such settings.

Contributions to the Literature

Our study is expected to make several important contributions to the scientific literature on digital health and vaccination interventions. First, numerous studies have documented low timeliness of vaccinations for children from LMICs, with a disproportionate burden for rural children [4,6,37-41]. Our study is significant because it seeks to evaluate an intervention for promoting vaccination timeliness for rural children. Second, lay health care workers such as CHWs play a critical role in delivering health services in LMICs. Our study will use a hybrid digital and in-person approach and contribute evidence on effective and scalable strategies for supporting lay health workers with digital health tools to promote childhood vaccination equity. Third, although many studies have evaluated mobile phone–based reminders for promoting childhood vaccinations [10], evidence is lacking for community-based systems that target multifaceted barriers to vaccinations. Our study will contribute data on the effectiveness of a community-based digital health intervention to promote equitable and timely vaccination in LMICs. Fourth, research studies support the use of screening tools to identify vaccination knowledge gaps and deliver targeted interventions to combat vaccine hesitancy. Our study will integrate CHW outreach and mobile phone–based vaccination education to bridge gaps in vaccination knowledge, respond to parental concerns, and reduce hesitancy. Finally, our study will contribute evidence on strategies to bridge the *digital divide* in rural areas and the *gender gap* in mobile phone access by using a combined digital and in-person approach.

Study Limitations and Adaptations

Unknown Number of Eligible Women per Cluster

Although we estimate that 20 clusters per region are required to reach our enrollment targets for the cross-sectional and longitudinal samples, neither the number of eligible women per cluster nor the number of refusals are known a priori. If the sample size across clusters is too small, sampling may be extended to additional clusters until sample size targets have been reached in each region and study arm.

Randomization

If the distributions of key characteristics of clusters vary greatly between the initially specified study arms (based on randomized IDs), a covariate-constrained randomization approach may be used that maximizes the balance across study arms in the distribution of key characteristics of clusters.

Spillover and Contamination

Cluster randomization is expected to minimize spillover effects; however, contamination may exist for participants living at the boundaries between intervention and nonintervention clusters. Sensitivity analyses will evaluate potential spillover effects by including geographic proximity to an intervention cluster as a covariate for the nonintervention group women in our models.

External Events

A potential threat to validity stems from the possibility of a local vaccination campaign or selective stockouts among subsets of clusters during follow-up. Given our collaboration with regional and national stakeholders, enrollment from multiple clusters, multiple vaccination time points for each participant, and the robust design, the likelihood and potential impact of such external events on our findings is low. The effects of stockouts on timeliness will be assessed in the *per-protocol* sensitivity analysis.

Missing Data

If vaccination cards are missing for >10% of the cross-sectional sample, and their vaccination information cannot readily be ascertained from records at the local health facility, enrollment into the cross-sectional cohort will continue until key outcome measures can be ascertained for the target number of 400 mothers. This may include the expansion of enrollment to additional clusters. Enrollment into the longitudinal cohort will be increased proportionately. Missing data on other characteristics will be addressed using full information maximum likelihood estimation or sensitivity analyses [42-45].

Mobile Phone Access and Use

In the target population, mobile phone access and use is not universal, and mobile phones may be shared within households. Chanjo Kwa Wakati is specifically designed to compensate for gaps in mobile phone ownership and coverage, including through the designation of vaccine advocates who will receive reminders and in-person outreach by CHWs to those who are not reached by mobile phone.

Sustainability of Reminders and Incentives

Reminder messages and incentive offers, which were informed by our prior work, will be carefully reviewed by investigators and key informants to ensure their ethical implementation and sustainability for a scaled-up intervention.

Generalizability

To assess the generalizability of the study's context and findings, study data and the relationships among key variables of interest will be compared with information in publicly available survey data and administrative data sources.

Interpretation and Dissemination

If successful, this study will contribute data on the effectiveness and implementation of the Chanjo Kwa Wakati intervention that engages recent mothers to increase the timeliness and coverage of routine childhood vaccinations in rural Tanzania. Key findings will be presented in peer-reviewed manuscripts, presentations at national and international conferences, and media outlets. Policy and programmatic recommendations will be developed in collaboration with key informants and decision makers at the national, regional, and district levels.

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Data Availability

The data from this study will be available from the National Institute for Medical Research, Muhimbili Research Centre, Dar es Salaam, Tanzania, but restrictions apply that are governed by consent forms and data transfer agreements. Data may be made available by the authors upon reasonable request and with the permission of the National Medical Research Review Committee of the National Institute for Medical Research, Tanzania. The open-source digital health system will be made available to interested researchers and practitioners.

Authors' Contributions

LV, JO, and EN designed the study with critical input from JNB, NT, DS, MvZ, and AH. LV and JO wrote the first draft, and EN, JNB, NT, DS, MvZ, and AH contributed to revisions. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist of information to include when reporting a cluster randomized trial.
[DOCX File , 36 KB - resprot_v13i1e52523_app1.docx]

Multimedia Appendix 2
Peer-review report: Clinical Informatics and Digital Health Study Section, Healthcare Delivery and Methodologies Integrated Review Group, Center for Scientific Review, National Institutes of Health.
[PDF File (Adobe PDF File), 155 KB - resprot_v13i1e52523_app2.pdf]

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Abbreviations

CHW: community health worker
CONSORT: Consolidated Standards of Reporting Trials
DPT: diphtheria-pertussis-tetanus
IDI: in-depth interview
IRB: institutional review board
LMICs: low- and middle-income countries
OPV: oral polio vaccine
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

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Protocol

Testing an Evidence-Based Self-Help Program for Infertility-Related Distress: Protocol for a Randomized Controlled Trial

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Abstract

Background: Infertility—the inability to achieve pregnancy despite ≥12 months of focused attempts to conceive—is experienced by 1 in 6 couples. Women typically carry a disproportionate share of the psychological burden associated with infertility, experiencing poor quality of life, and 30%-40% experiencing depressive mood or anxiety. Unfortunately, currently available psychological interventions targeting infertility-related distress are associated with modest effects.

Objective: Our team, in collaboration with patient advisors, has designed a self-help intervention for infertility-related distress involving 7 weekly 10-minute videos addressing the cognitive, behavioral, and interpersonal challenges associated with infertility, delivered through a mobile app. A feasibility study suggests that it is well accepted and highly effective in reducing symptoms of anxiety and depressed mood among distressed individuals dealing with infertility. This study represents the next step in this line of research: a fully powered randomized controlled trial comparing the intervention to a waitlist control group.

Methods: We will recruit 170 individuals struggling to become pregnant in Canada or the United States to be randomized to our 7-week self-help program or a treatment-as-usual condition. The primary outcome will be fertility quality of life, while secondary outcomes will include depressive symptoms, anxious symptoms, and relationship quality, assessed before and after the program as well as biweekly for 16 weeks following completion of the program. Self-reported health care use and the presence of diagnosed mood and anxiety disorders, assessed through a structured psychiatric interview, will also be assessed immediately following the intervention and at the 16-week follow-up assessment. Treatment adherence and retention will also be recorded throughout the intervention. Multilevel modeling will compare the intervention arm to the treatment-as-usual condition in terms of all continuous outcomes across the 9 measurement points. Logistic regression will be used to assess the occurrence of mood and anxiety disorders in the 2 treatment arms at the posttreatment assessment as well as at the 16-week follow-up. Sensitivity analyses will examine potential treatment moderators: membership in the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) communities, baseline fertility quality of life, cultural background, disability status, and pursuit of conception through medical intervention.

Results: We expect our intervention to be more effective than treatment-as-usual in improving all mental health parameters assessed and decreasing health care use related to both mental and reproductive health. Effects are expected to be larger with decreasing baseline quality of life and equally effective regardless of membership in the LGBTQIA+ communities, cultural background, or disability status.

Conclusions: If our intervention is successful, this would suggest that it should be scaled up and made publicly available. The availability of this program would fill an important gap in light of the high rates of psychopathology among those experiencing infertility and considering the current lack of effective psychotherapy approaches for infertility.

Trial Registration: Clinicaltrials.gov NCT06006936; https://classic.clinicaltrials.gov/ct2/show/NCT06006936

International Registered Report Identifier (IRRID): PRR1-10.2196/52662

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KEYWORDS

anxiety; cognitive-behavior therapy; depression; infertility; infertility-related distress; mHealth

Introduction

Overview

The Canadian Community Health Survey reveals that 16% of Canadian reproductive-aged couples are currently infertile [1], defined as being unable to achieve pregnancy despite ≥12 months of focused attempts to conceive. Although male- and female-factor infertility are equally prevalent, women bear the brunt of the infertility-related burden as treatments require that women monitor their menstrual cycles, attend near-daily ultrasounds, self-inject gonadotropins, and undergo invasive and painful procedures. Women who travel for fertility treatments face additional psychosocial burdens, including schedule disruptions, time off work, and coordination of care among multiple health care providers. It is therefore not surprising that women carry a disproportionate share of the psychological burden associated with infertility, with infertile women consistently reporting lower self-esteem, more instances of depressed mood and anxiety, and lower life satisfaction than their male partners [2]. Lesbian couples pursuing sperm donation experience similar distress, with the intended pregnant individual being at higher risk for depression and anxiety relative to their partner [3].

Around 30%-40% of women presenting for the evaluation of infertility report clinical symptoms of depressed mood and/or anxiety [4-7]. In addition, research from our team [8] suggests that the COVID-19 pandemic has exacerbated distress amid fertility treatment suspensions and delays. Untreated symptoms of depressed mood and anxiety among women with infertility may, in turn, reduce the likelihood of achieving pregnancy, given that psychological burden is the most commonly cited reason for prematurely discontinuing fertility treatments [9]. In a study of 450 couples who were offered 3 government-funded in vitro fertilization (IVF) cycles, 54% did not complete all 3 cycles despite not achieving pregnancy, with “psychological burden” being the primary reason for discontinuing IVF [10]. It is critical that women with infertility who are distressed receive effective mental health treatment to reduce distress and improve conception rates.

Despite high rates of distress among women with infertility, currently available psychological interventions are often ineffective or associated with relatively small benefits. In our recent systematic review of psychological interventions for infertility-related distress [11], we observed that typical interventions are associated with a small beneficial effect on anxiety but a nonsignificant effect on depressive mood, marital quality, or quality of life. Our conclusions confirm findings from a previous meta-analysis [12] and those of a recent review [13] concluding that “a new intervention (targeting infertility-related distress) should be developed.”

Intervention Development

This trial seeks to test the efficacy of a novel infertility-specific intervention. In developing a treatment that is designed to improve upon the limitations of current approaches, we have used a methodical and evidence-based framework in designing and refining our intervention, using the Medical Research Council [14] and National Institute of Health’s ORBIT Model [15] for trial design interventions as guides. Specifically, we have completed the following milestones to date: (1) completed a systematic review of available interventions, (2) conducted a needs-based assessment using qualitative research methods, (3) carried out an evaluation of potential intervention components, and (4) performed a preliminary test of the acceptability and effect of our newly developed intervention. These steps are described in greater detail below.

Systematic Review and Meta-Analysis

As a starting point, we conducted a systematic review and meta-analysis of psychological interventions for infertility [11,16], which included an examination of treatment moderators such as psychotherapeutic approach (eg, mindfulness-based approaches vs cognitive behavioral therapy) and therapy format (eg, self-administered vs group). This process not only confirmed that currently available interventions were largely ineffective but also revealed that neither therapeutic approach nor format significantly impact treatment benefits.

Qualitative Needs Assessment

Our team then used semistructured interviews with women with infertility and mental health professionals specializing in infertility to identify the unique aspects of infertility-related distress [17]. Table 1 depicts the themes and subthemes identified. Unique features include the avoidance of infertility reminders (eg, pregnant women and children), excessive cognitive and behavioral focus on one’s infertility to the exclusion of previously enjoyed activities, and negative interactions with loved ones perceived as insensitive.

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Table 1. Themes and subthemes of infertility-related distress identified through a qualitative research project by our team [17].

Theme 1: anxiety	Theme 2: mood disturbance	Theme 3: threat to self	Theme 4: threat to couple	Theme 5: weakened social support
Anxious rumination	Emotional lability	Unmet expectations for self and one's future	Differences in coping	Strained romantic relationship
Avoidance of infertility reminders	Helplessness	Shame	Sexual dysfunction	Social stigma
Narrowed focus on infertility-related activities	Emotional exhaustion	Self-blame	Financial stress	Social isolation
Excessive information seeking	N/A[a]	N/A	Disagreement on next steps	Dismissal by health care providers

[a]N/A: not applicable.

In addition to identifying clear psychological targets for our intervention, this study also aimed to clarify which interventions were currently being used by practicing clinicians. Our findings indicated a near-universal use of an eclectic and unstructured approach associated with the widely held opinion that no existing therapeutic approach sufficiently addresses all of the biopsychosocial factors contributing to infertility-related distress.

Evaluation of Potential Intervention Components

The next step in our intervention development was to identify and consider all candidate techniques that might effectively target the psychological challenges identified as being common in infertility. To do so, we identified all of the psychotherapeutic approaches endorsed by the American Psychological Association's Clinical Section as being evidence-based for the treatment of anxiety, mood disorders, relationship difficulties, and chronic illness. The 5 identified approaches were then further broken down into their component procedures, resulting in a total of 14 different psychological techniques. In collaboration with a panel of patient advisors and using lay language, we described how each of these techniques would look when applied to infertility-related distress and what their purpose would be. We then surveyed a total of 644 women from online infertility-specific support groups [18], asking them to rate the perceived usefulness of each of the 14 techniques while asking them to identify up to 5 that were "most liked" and "most hated." Participants were also given the opportunity to provide written feedback on each of the techniques, such as how they might be better tailored to infertility. We then presented the results of this survey to our panel of patient advisors and collaboratively decided on the content of our intervention. We decided on 6 core modules plus a bonus module, the content of which is described in Textbox 1 [18].

Textbox 1. Chosen modules based on a survey of 644 women with infertility [18] and collaboration with patient advisors. Mean helpfulness ratings for each module, as assessed in a feasibility study of 21 women, are shown.

Modules and focus

- Cognitive restructuring: identifying and challenging the extreme negative thoughts that contribute to a depressive and anxious mood (eg, "In vitro fertilisation will never work").
- Challenging core beliefs: identifying and challenging unhelpful deep-seated beliefs about themselves, other people, and the world that are perhaps not based on reality (eg, "nothing ever works out for me"). It involves looking for patterns in one's thinking from the first module.
- Behavioral activation: identifying activities that have been dropped or engaged in less because of an increased focus on infertility. Aim to reintegrate these previously enjoyed activities into their day-to-day lives.
- Sharing your grief: learning about different styles of coping and how clashes in coping styles can lead to conflict within a couple. The individual is instructed on how to engage their partner in a structured conversation about how each can help the other in times of grief, such as following a negative pregnancy test.
- Strengthening your relationship (bonus module): provides evidence-based information about how to better connect with one's partner in general. Was offered along with Module 4 for those experiencing relationship distress.
- Living your values (ie, stopping avoidance): reflecting on one's overarching life values and considering how one's daily actions align with those values. Indirectly addresses avoidance that is common among individuals with infertility (eg, withdrawing from friends and family and avoiding children and pregnant women). Encourages the individual to consider ways in which they can reduce avoidance without worsening their distress.
- Summary or wrap up: providing an overview of the program's content and encouraging the individual to reflect on what's been accomplished as well as areas for further development.

When it came time to decide on the format of our intervention, a self-help internet-delivered intervention was chosen for several reasons. First, the findings from our systematic review indicate that self-administered interventions are as effective in improving mental health as other, more costly formats. Second, when asked what format a new intervention should take, 71% (15/21) of women from our needs assessment qualitative study responded that it should be self-delivered through the internet. Third, we reasoned that this format could be most effectively scaled up and made accessible to diverse populations of women and in

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regions with limited access to psychological services. Thus, in close collaboration with our patient advisors, each module was translated into a 10-minute PowerPoint (Microsoft Corp) slideshow with professional voiceover. A mobile app was then developed to increase accessibility to the modules.

Preliminary Testing of Our New Infertility-Specific Intervention

With a new program developed and fully vetted in consultation with our patient advisory panel, we conducted a pilot study of 21 women recruited through local support groups, assessing intervention acceptability [19]. All participants exhibited clinically significant levels of infertility-related distress, as indicated by a Fertility Quality of Life Scale (FertiQoL) score ≤52 [20]. Enrolled through a Zoom (Zoom Video Communications)-administered enrollment session, participants received 1 module per week through email and were asked to view the 10-minute slideshow within 24 hours of receipt. Midweek, they received an email reminder of the homework assignment, encouraging them to apply their homework assignment throughout the week. At the end of each week, participants were asked to rate the extent to which the module and homework were perceived as helpful in lowering their distress (0-10). At baseline and each week, participants completed the Generalized Anxiety Disorder-7 (GAD-7) and 9-item Patient Health Questionnaire (PHQ-9); the FertiQoL was completed at baseline and after the intervention. Each week and in an interview at the end of the study, participants provided written and verbal feedback, respectively, on the intervention.

Of the 21 women enrolled in the study, 2 became pregnant and were removed from the program prematurely (all outcomes assessed until the point of pregnancy were analyzed). Of the remaining 19 women, 15 completed all 6 modules, and 4 completed a portion of the program. Data from all 19 women were included in the analysis. The average helpfulness rating of each module was found to be 7.4 or above out of 10. Fertility quality of life increased by an average of 12 points out of 100, translating to a Cohen *d*=0.9. Large reductions in both mean symptoms of anxiety and depressed mood were observed (pre-to-post Cohen *d*=–1.2 and –1.3, respectively, where effects above 0.8 are considered large), corresponding with clinically meaningful improvements. In addition, 85% of participants experienced a clinically significant decline in either anxious or depressive symptoms (defined as a change of 4 points on the GAD-7 [21] and 5 points on the PHQ-9 [22]).

While the intervention was successful, areas for improvement were identified. For example, homework assignments were modified to include examples of completed homework. Participants reported that our “bonus” relationship module deserved to be a core part of the program, extending it to a total of 7 weeks.

The Current Trial

Over the last 3 years, our team has carefully designed a self-help intervention for infertility-related distress that is patient-informed and developed using best practices in intervention design. Results from this feasibility study suggest that it is well accepted and effective in increasing quality of life and reducing symptoms of depressed mood and anxiety among women with infertility-related distress. The proposed project, a sufficiently powered randomized controlled trial comparing the intervention to a treatment-as-usual control group, is the next step in this line of inquiry. It is hypothesized that the intervention will result in greater increases in fertility quality of life and relationship quality as well as decreases in symptoms of depressed mood and anxiety relative to a treatment-as-usual condition, and that these improvements will be maintained over a 16-week follow-up assessment period.

If the proposed trial confirms that the intervention is effective in improving quality of life and mental health symptoms among those with infertility, our next step will be to make this program widely available to women, including making the intervention available through YouTube and engaging our collaborating knowledge users and partner organizations to promote it widely. We will also aim to tailor the program for diverse and marginalized underserved groups.

Methods

Trial Design

The proposed research is a single-blind randomized controlled trial comparing the above-described self-help program to a waitlist control condition. As the project requires no in-person contact, we will recruit women living throughout Canada and the United States. Fertility quality of life, infertility-related distress, symptoms of depressed mood and anxiety, and relationship quality will be assessed before and after the program, as well as every other week for 16 weeks.

Treatment Conditions

Intervention Condition

Participants will be given access to a 10-minute module video per week through a mobile app created for this trial. Midweek, participants will receive an automated email reminder of the homework assignment for that week, encouraging them to incorporate the homework into their daily lives. Participants will be permitted to engage in any other psychological interventions they wish but will be asked to report other psychological interventions accessed at the end of their participation.

Treatment-As-Usual Control Condition

Participants assigned to the control condition will be instructed to continue their pursuits to conceive without accessing the self-help program. They will be permitted to access other psychological resources that are available to them, though, like the intervention condition, they will be asked to report any treatments accessed in the postintervention survey. They will complete the outcome measures at the same time as participants in the treatment condition. Following completion of the study, the control group will be offered the program in the same manner as the treatment group.

In the original funded grant protocol, we had proposed a waitlist control condition in which participants were not permitted to access other mental health services; however, we have since changed the control condition to treatment-as-usual in order to

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more accurately estimate the real-world effectiveness of the treatment. This change also allows us to open the trial to individuals reporting suicidal ideation because these participants will likely require additional mental health services while participating in the current trial.

Randomization Scheme

The Clinical Research Support Unit at the University of Saskatchewan will create the randomization scheme and provide the principal investigator with opaque envelopes containing treatment assignments, ensuring that the research team has no control over the assignments. Randomization will take place at the end of each enrollment session, after the baseline surveys have been completed, and will be stratified based on whether a woman is undergoing fertility treatments or attempting to conceive without medical intervention, as this will be a potential moderating variable.

Protecting Against Sources of Bias

A number of strategies will be used to protect against bias. First, the trial will be registered with clinicaltrials.org before any data collection commences. Second, as described above, the randomization scheme will be created by a third party, and the study research assistants will be instructed to strictly adhere to the randomization protocol without exception. Third, though it is not possible to maintain full blinding of either the participant or research team given the nature of the intervention, all outcomes will be collected by a research assistant who is blind to the participant's treatment allocation. Fourth, an intent-to-treat approach will be taken in analyzing the results—every effort will be made to continue to collect outcome data on all participants, regardless of whether participants dropped out of the intervention early or not. Final, we will follow the CONSORT-SPI (Consolidated Standards of Reporting Trials for Social and Psychological Intervention Trials) reporting guidelines [23] in reporting the results of the trial, strictly adhering to the original trial protocol. Any deviations will be clearly described and justified.

Participants

Inclusion and Exclusion Criteria

Based on our sample size calculations, we will recruit 170 women, recruited through the web. The inclusion criteria will include the following: is infertile as defined as either actively attempting to conceive for ≥12 months without success or is currently undergoing fertility treatments (eg, ovulation induction medication, IVF, and intrauterine insemination). This definition ensures that this study is inclusive of both individuals who cannot afford fertility treatments and women who are in same-sex couples and cannot conceive naturally. Though the original funded protocol excluded individuals reporting active suicidal ideation, those already receiving psychotherapy, and those with high levels of fertility-related quality of life (FertiQoL above 70), we have since decided to remove these exclusion criteria in order to closely estimate the program's anticipated real-world effectiveness. Rather than exclude individuals based on baseline quality of life, we will perform secondary analyses, considering baseline quality of life as a treatment moderator.

Sex and Gender Considerations

In light of research finding that the intended pregnant individual experiences the most distress in the context of infertility, we will only recruit individuals who have a uterus. However, we will ensure that this study is welcoming to individuals of all gender identities and sexual orientations, as this study will aim to contribute to current knowledge surrounding the psychological experiences of individuals from minority genders, and sexual groups experiencing infertility. This study materials including advertisements, will use inclusive language. Advertisements will not use the word "woman" but instead "individuals attempting to get pregnant but experiencing infertility." The intervention itself has also been designed with inclusive language, a gender-neutral design, and pictures of individuals from diverse backgrounds and sexual orientations. To ensure adequate diversity among our participants, we will advertise on subreddits specifically targeting members of the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) community.

Participant Screening and Enrollment

Prospective participants will be emailed the link to a web-based eligibility survey. If found to be eligible, they will be asked to provide their contact information, and a research assistant will contact them to schedule an enrollment session through videoconference.

During the Zoom-facilitated remote enrollment session, eligibility will be confirmed, a brief introductory video explaining the study and intervention will be presented, and consent will be obtained. An enrollment session in which visual contact is made will ensure that our recruited participants are not simply "bots" posing as eligible participants. During the session, participants will complete the baseline questionnaires through a link emailed to them by the research assistant. Upon completion of the questionnaires, the research assistant will open an opaque envelope, revealing the participant's random assignment to either the treatment or control condition. The research assistant will then ask the participant which day of the week they would like to receive their weekly module video (if assigned to the treatment condition) or weekly outcomes survey (if assigned to the control condition).

Participant Safety

Participants endorsing suicidal ideation on question 9 of the PHQ-9 at baseline will be permitted to participate in the study but will be informed that their level of risk will be reassessed weekly. Specifically, each week, they will receive a survey question, "Please pick out the one statement that best described how you have been feeling during the past week, including today: (A) I don't have any thoughts of killing myself. (B) I have thoughts of killing myself, but I would not carry them out. (C) I would like to kill myself, or (D) I would kill myself if I had the chance." If participants choose either C or D, a message including contact information for 2 suicide hotlines will appear. As well, an automatic notification will be sent to the study therapist, flagging the response. They will then follow up with the participant immediately by phone, at most within 24 hours.

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If participants endorse A or B, they will simply be allowed to continue with the program.

In addition, the presence of active suicidal ideation (presence of a plan or intent) will be assessed by the researcher during the Zoom-facilitated enrollment session. Those endorsing active suicidal ideation will be referred to additional in-person mental health resources available in their geographic area. They will be given access to the program for their own benefit but will not be enrolled in the study.

Primary and Secondary Outcomes

Overview

Self-reported psychological outcomes will be assessed immediately postintervention (ie, at the end of the 7th week) and every 2 weeks for 16 weeks. Mood and anxiety disorders will be assessed immediately postintervention as well as 16 weeks postintervention. Finally, health care use will be assessed at postintervention week 16. The control group will follow an identical outcome assessment schedule.

Demographic and Medical Information

Age, ethnicity, gender identity, sexual orientation, marital and parental status, years of education, income, occupation, reproductive health history, and medications will be assessed using a survey created for this study.

Primary Outcome

Fertility-related quality of life was assessed using the 24-item Core FertiQoL [24], yields 4 subscales: mind-body, relational, social, and emotional. High scores on the FertiQoL scale indicate a better quality of life. It is the most widely used infertility-specific measure of quality of life [25] and has been well validated in multiple studies [20]. This primary outcome was chosen in collaboration with our patient advisors as it provides an integrated measure of the emotional, physical, and interpersonal impacts of infertility.

Secondary Outcomes

Secondary outcomes will include depressive and anxious symptoms, instances of mood and anxiety disorders, relationship quality, and health care use. Treatment adherence and acceptability will also be assessed.

Depressive Symptoms

Self-reported symptoms will be assessed using the PHQ-9 [26], a 9-item measure assessing symptoms in the last 2 weeks that closely parallels the criteria for major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [27]. Internal consistency coefficient (ICC) has been estimated at α=.89 and test-retest reliability at r=0.84. The PHQ-9 has been shown to be superior to other questionnaires in detecting changes in depressive mood following treatment [28]. Participants endorsing suicidal ideation on item 9 of the PHQ-9 will be required to answer a weekly question.

Anxious Symptoms

Self-reported symptoms will be assessed using the GAD-7 [29], a 7-item measure that asks about symptoms in the last 2 weeks and closely parallels the DSM-5 criteria for generalized anxiety disorder. ICC is α=.92. The GAD-7 has been shown to be superior to other questionnaires in detecting change in anxious mood following treatment [30].

Mood and Anxiety Disorders

These will be assessed using NetSCID (TeleSage), the computerized version of the Structured Clinical Interview for the DSM-5 (SCID). Though the originally funded protocol proposed to use the Primary Care Evaluation of Mental Disorders (PRIME-MD), we decided to switch to the SCID because of the availability of the computerized version of this interview. The SCID is also the gold standard assessment for psychiatric diagnoses.

Relationship Quality

Relationship quality will be measured through the 7-item Relationship Assessment Scale. Internal consistency among individuals with infertility has been found to be high, with α=.83 [31].

Health Care Use

The questionnaire on health care consumption and productivity losses for patients with a psychiatric disorder will be administered 16 weeks following the intervention, asking participants to report on health care use in the last 4 months. This survey has shown good agreement with hospital- and employer-confirmed data. An additional section has been added to specifically ask about the receipt of fertility treatments.

Treatment Adherence

The total number of minutes spent accessing each moule video will be tracked through the mobile app. Homework completion between the weekly module videos will be tracked using Qualtrics, a web-based survey platform that facilitates scheduled survey distribution, notifications, and reminders. Homework compliance will be further measured at the end of each week through the 12 items contained within the Homework Rating Scale, which assesses comprehension of homework assignments as well as effort spent on assignments [32].

Treatment Acceptability

The Credibility Expectancy Questionnaire [33] will be administered at baseline to assess participants' initial expectations about the intervention. Postintervention, the Treatment Acceptability and Adherence Scale [34] will be used to assess treatment acceptance. The Negative Effects Questionnaire [35] will assess any potential adverse events perceived to be related to the intervention. Final, participants will be invited to provide written feedback about any of the modules or the program as a whole, including suggestions for further improvement and refinement.

Outcomes Assessment

A research assistant who is blinded to the participant's treatment condition will email the participant a link to a web-based survey containing the outcome measures. If a participant fails to complete the survey within 48 hours of receipt, they will receive up to 3 reminders through email, voicemail, and SMS text messaging. Though participants will not be compensated for

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completing the intervention, they will be compensated US/CAD $10 (or its equivalent depending on their location) for each postintervention survey completed (postintervention +8 biweekly follow-up surveys) and an additional US/CAD $20 for each of the 2 postintervention interviews, for a maximum total of US/CAD $130, to maximize the chances that even those participants who abandoned the intervention prematurely will complete the outcome surveys.

Statistical Analyses

Descriptive statistics will examine treatment acceptability outcomes as well as the trial recruitment rate. A 2-tailed *t* test will be used to compare the treatment arms in terms of baseline characteristics, assessing randomization success. A mixed model design using the MIXED procedure in SAS (version 9.4; SAS Institute) applying an intent-to-treat approach will compare the intervention arm to the waitlist control group in terms of FertiQoL, PHQ-9, GAD-7, Copenhagen Multi-Center Psychosocial Infertility Fertility Problem Stress Scale, and Relationship Assessment Scale (RAS) score across the 9 outcome measurement points (ie, at the end of intervention week 7 and biweekly for 16 weeks). Each outcome will be examined in a separate model; subject will be treated as a random effect, and the treatment assignment will be treated as a fixed effect. A repeated statement will identify assessment week as a repeated measure factor. Baseline levels of the outcome will be included as a covariate. This method has been shown to provide optimal statistical power relative to measuring pre- and postintervention outcome change [36]. In using all available data, a mixed model design has also been shown to outperform ad hoc approaches, such as the last-outcome-carried-forward approach [37].

In addition to examining the main effect of treatment assignment on outcomes, the interaction between assignment and assessment week will be examined to determine whether outcomes are maintained across the 9 postintervention measurements. Sensitivity analyses will use a similar approach to examine potential treatment moderators: membership in the LGBTQIA+ communities, baseline FertiQoL score, cultural background, disability status, and pursuit of conception through medical intervention.

The LOGISTIC procedure will assess the occurrence of mood (major or minor depressive episode or persistent depressive disorder) and/or anxiety disorders (generalized anxiety disorder, social anxiety disorder, or panic disorder) in the 2 treatment arms at the posttreatment assessment as well as at the 16-week follow-up.

To limit the family-wise error rate, the Benjamin and Hochberg [38] false discovery rate correction will be applied to all analyses.

Power Calculations

Power calculations were performed using G*Power (Axel Buchner) and are focused on the primary outcome, infertility-related quality of life. Based on SDs observed in the population of distressed women with infertility [18], setting α at .05 and power at 80%, a total of 128 participants would be needed to detect a moderate effect size (Cohen f=0.25), equivalent to a 6-point difference on the FertiQoL (out of 100) between 2 arms. To allow for a 25% (42/170) dropout rate, we will recruit 170 participants (85 per arm), in line with average completion rate of 82% observed in our meta-analysis of psychological interventions for infertility-related distress and allowing for additional drop-out given considering the 16-week follow-up.

Planned Recruitment Rate

We propose to complete the trial within 2 years. The timeline relies on a recruitment rate of 3 participants per week, which we consider to be a highly conservative estimate of what is possible based on our previous experience successfully recruiting participants from this population.

Through our experience in our preliminary work, we have determined that the most successful strategy for recruiting the target population is to advertise through online infertility support or special interest groups—this will therefore be the primary method used to recruit for this study. We have found these groups to be very willing to share our research, and their members are extremely receptive as well as highly likely to be eligible to participate. We have also had great success in recruiting individuals from LGBTQIA+ communities attempting to conceive through IVF. In an ongoing study specifically targeting this population, we approached a pair of social media influencers (a lesbian couple who regularly share their experiences of undergoing IVF) who enthusiastically shared our project with their followers. Within 2 days, we had received over 400 entries in our eligibility survey.

In addition to providing large pools of highly engaged, eligible participants, one important advantage of web-based recruitment is that samples tend to be much more diverse in terms of race, education, and income relative to studies that recruit through fertility clinics, the patients for which are disproportionately high-income. While web-based recruitment can increase the risk of recruiting noneligible individuals posing as eligible participants, the use of a face-to-face Zoom enrollment session greatly reduces this risk. Our research team is also experienced in identifying suspicious survey responses.

Ethical Considerations

This study has been reviewed and approved by the University of Regina Ethics Board (REB #2023-210) as well as registered on ClinicalTrials.gov (NCT06006936). All prospective participants will provide informed written consent before enrolling in the trial.

To protect participant confidentiality, all participant data, including both interview data and questionnaire data, will be saved under ID numbers only, with no identifying information attached. Only the research team will have access to the collected survey data. The team will maintain a document associating participant names with their anonymous subject numbers. This document will be password-protected, opened only on encrypted devices, and stored separately from the rest of the data.

Participants will receive US $10 for each postintervention and follow-up survey completed and US $20 for each of the 2 postintervention interviews, for a maximum total of US $130.

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Results

Recruitment will begin in January 2024 and continue for approximately 1.5 years. All data are expected to be collected by January 2026. Results will be uploaded on the ClinicalTrials.gov website shortly thereafter.

Discussion

Significance of the Study

It is expected that participants assigned to the Coping with Infertility program will exhibit improved fertility quality of life as well as depressive and anxious symptoms, with moderate to large effect sizes. We also expect rates of clinical mood and anxiety disorders as well as self-reported health care use to be lower among participants randomized to the treatment arm. Baseline fertility quality of life is furthermore expected to moderate the effect of treatment such that effect sizes will increase with decreasing baseline fertility quality of life. Based on the pilot study results, we expect adherence and retention to be favorable. If our hypotheses are confirmed, these findings would suggest that the Coping with Infertility program is more effective than currently available psychological interventions for infertility. Indeed, a recent meta-analysis by our team identified 58 randomized controlled trials testing psychological interventions for infertility and found that, with the exception of trials conducted in the Middle East, interventions were associated with only small psychological benefits, highlighting the need for more effective interventions [16]. The self-help nature of the Coping with Infertility program also likely makes it more cost-effective than individual psychotherapy, which typically costs US $100-$200 per session.

If our intervention proves effective, we will aim to make our mobile app publicly available through the Apple Store and Google Play Store. Decreased health care use in the treatment arm relative to the treatment-as-usual arm would provide a strong rationale for seeking government funding to upkeep the Coping with Infertility mobile app, which would allow us to make the program available free of charge. We would provide flyers and posters to fertility clinics across North America, to be posted in clinic waiting rooms and physician offices. We will reach out to relevant professional societies and nonprofit organizations, asking them to include the app as a mental health resource listed on their website. Online forums relevant to infertility will also be contacted and asked to share information related to the app. A YouTube channel will be created to house all of the weekly module videos along with a professionally produced animated explainer video introducing the intervention and describing the results from the trial supporting its efficacy. Final, we will publish our findings in open-access journal articles in respected scientific journals.

In addition to disseminating the Coping with Infertility program as a stand-alone intervention, it may also be worthwhile to pair it with other traditional mental health resources. For example, future research pairing the Coping with Infertility program with infertility support groups, or with individual psychotherapy may help target a broader audience of individuals experiencing infertility-related distress who wish to benefit from peer or therapist support. Translating the content of the program into a workbook format may also appeal to a subset of the target population.

Limitations

First, access to the Coping with Infertility program is contingent upon internet access; research participants may therefore not include individuals who do not have such access, such as those who cannot afford internet access or those living in remote communities. Second, due to the nature of the intervention, it is impossible to conduct this trial as a double-blind, randomized trial. Third, health care use will be self-reported and therefore may not capture use as accurately as hospital and clinic records.

Conclusions

This study will test a self-help program for infertility-related distress through a mobile app. If the intervention proves effective, it will provide a highly cost-effective and accessible mental health resource for those struggling with the mental health impacts of infertility. This will fill an important gap in light of high rates of psychopathology among those experiencing infertility and considering the current lack of effective psychotherapy approaches for infertility.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 80 KB - resprot_v13i1e52662_app1.pdf]

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Abbreviations

CONSORT-SPI: Consolidated Standards of Reporting Trials for Social and Psychological Intervention Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FertiQoL: Fertility Quality of Life Scale
GAD-7: Generalized Anxiety Disorder-7
ICC: internal consistency coefficient
IVF: in vitro fertilization
LGBTQIA+: lesbian, gay, bisexual, transgender, queer, intersex, and asexual
PHQ-9: 9-item Patient Health Questionnaire
PRIME-MD: Primary Care Evaluation of Mental Disorders
SCID: Structured Clinical Interview for the DSM-5

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Protocol

Effects of a Powered Ankle-Foot Prosthesis and Physical Therapy on Function for Individuals With Transfemoral Limb Loss: Rationale, Design, and Protocol for a Multisite Clinical Trial

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Abstract

Background: Powered ankle-foot prosthetic devices can generate net positive mechanical work during gait, which mimics the physiological ankle. However, gait deviations can persist in individuals with transfemoral limb loss because of habit or lack of rehabilitation. Prosthetic research efforts favor the design or evaluation of prosthetic componentry and rarely incorporate any type of rehabilitation, despite evidence suggesting that it is critical for minimizing gait imbalances. Given the accelerated rate of innovation in prosthetics, there is a fundamental knowledge gap concerning how individuals with transfemoral limb loss should learn to correctly use powered ankle-foot devices for maximum functional benefit. Because of the recent advances in prosthetic technology, there is also a critical unmet need to develop guidelines for the prescription of advanced prosthetic devices that incorporate both physical and psychological components to identify appropriate candidates for advanced technology.

Objective: The primary goal of this investigation is to examine the roles of advanced prosthetic technology and a device-specific rehabilitative intervention on gait biomechanics, functional efficacy, and pain in individuals with transfemoral limb loss. The secondary goal is to develop preliminary rehabilitation guidelines for advanced lower limb prosthetic devices to minimize gait imbalances and maximize function and to establish preliminary guidelines for powered ankle-foot prosthetic prescription.

Methods: This prospective, multisite study will enroll 30 individuals with unilateral transfemoral limb loss. At baseline, participants will undergo a full gait analysis and assessment of function, neurocognition, cognitive load, subjective preferences, and pain using their current passive prosthesis. The participants will then be fitted with a powered ankle-foot device and randomized into 2 equal groups: a powered device with a device-specific rehabilitation intervention (group A) or a powered device with the current standard of practice (group B). Group A will undergo 4 weeks of device-specific rehabilitation. Group B will receive the current standard of practice, which includes basic device education but no further device-specific rehabilitation. Data collection procedures will then be repeated after 4 weeks and 8 weeks of powered ankle use.

Results: This study was funded in September 2017. Enrollment began in September 2018. Data collection will conclude by March 2024. The initial dissemination of results is expected in August 2024.

Conclusions: The projected trends indicate that the number of individuals with limb loss will dramatically increase in the United States. The absence of effective, evidence-based interventions may make individuals with transfemoral limb loss more susceptible

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to increased secondary physical conditions and degenerative changes. With this expected growth, considerable resources will be required for prosthetic and rehabilitation services. Identifying potential mechanisms for correcting gait asymmetries, either through advanced prosthetic technology or rehabilitative interventions, can provide a benchmark for understanding the optimal treatment strategies for individuals with transfemoral limb loss.

Trial Registration: ClinicalTrials.gov NCT03625921; https://clinicaltrials.gov/study/NCT03625921

International Registered Report Identifier (IRRID): DERR1-10.2196/53412

(JMIR Res Protoc 2024;13:e53412) doi:10.2196/53412

KEYWORDS

amputation; limb loss; physical therapy; powered prosthetic ankle-foot device; lower extremity

Introduction

Background

There are approximately 1.9 million Americans with limb loss today, with an estimated 185,000 people who undergo an amputation procedure each year [1]. Over the last 2 decades, the Department of Veterans Affairs (VA) and the Department of Defense (DoD) have experienced an increase in the number of veterans and service members with lower limb loss [2]. Since the start of the most recent conflicts, more than 1700 service members have experienced combat-related limb loss, with the vast majority of these traumatic amputations of the lower limb [2-4]. VA, the largest integrated health care network in the United States, serves this unique population after their separation from active duty and provides care for an additional 41,000 veterans with lower limb loss [5]. Transfemoral limb loss, the second most common level of lower limb loss, accounts for one-fifth of the total limb loss population in the United States [6]. With this already large population expected to grow, effective outcomes-based clinical practice will be necessary to improve mobility, decrease long-term disability, and provide a higher quality of life.

Abnormal Gait Mechanics for Individuals With Transfemoral Limb Loss

Individuals with transfemoral limb loss have unique functional challenges owing to the loss of the knee and ankle joints [7-9]. Gait mechanics of individuals with transfemoral limb loss have been extensively investigated, with abnormalities typically characterized by asymmetries in stance phase biomechanics [10-13]. Individuals with transfemoral limb loss exhibit increased ipsilateral hip extensor activity and hip power, which is thought to be compensation for the lack of ankle power normally provided by the gastroc-soleus complex [14]. Consequently, compensatory mechanisms at joints proximal to the level of limb loss are often used to replace the function normally delivered by the muscles surrounding the ankle joint [12]. Individuals with unilateral transfemoral limb loss also tend to walk with longer stance times on the intact versus prosthetic limb [10], which can lead to a corresponding asymmetrical load distribution [15]. These asymmetrical joint forces place greater demands on the intact limb, which may explain the higher prevalence of musculoskeletal injuries, pain, and joint degeneration of the intact limb compared with uninjured individuals [16,17]. Significant among these secondary conditions is pain, specifically in the intact knee and lower back. In a study of experienced prosthesis users, knee pain in the intact limb was the primary complaint of 75% of individuals with transfemoral limb loss [18]. In a sample of 63 male veterans with traumatic lower limb loss, individuals with transfemoral limb loss were 5 times more likely to have intact knee pain compared with neurotypical participants [16]. Among individuals with lower limb loss (both transtibial and transfemoral), 71% reported back pain within the previous month, but individuals with transfemoral versus transtibial limb loss were significantly more likely to have greater pain intensity [19]. Chronic, persistent pain can lead to limitations in function. There is a significant need to explore the effects of advanced prosthetic technologies and rehabilitative interventions on pain reduction, function, and biomechanics.

Biomimetic Prosthetic Technology

New technologies in lower limb prostheses have attempted to combat gait pathologies by generating biomimetic ankle power through spring-clutch mechanisms or advanced sensor and actuator technology [20]. Recent advances in microelectronics, battery technologies, and the development of several new types of actuators [21,22] have ushered in the development of powered lower limb prostheses that can better replicate the positive work phases of the ankle through the use of actuators, motors, or pneumatic muscles [23-27].

The Empower (Ottobock Inc), which uses a series-elastic actuator and a carbon-composite footplate, is currently the only commercially available powered ankle-foot device [28,29]. The Empower has been investigated in the population of individuals with transtibial limb loss, but it has yet to be fully investigated in individuals with transfemoral limb loss [30-33]. In a study of individuals with transtibial limb loss, the use of a powered versus passive ankle-foot device reduced the peak resultant force and knee adduction moment on the unaffected leg during level ground walking, potentially limiting the risk of secondary musculoskeletal comorbidities [31]. Individuals with transtibial limb loss using the same powered ankle-foot device had improved ankle power, greater net trailing limb step-to-step transition work, and a lower metabolic rate compared with a passive energy storing and returning ankle-foot prosthesis during level ground ambulation [32].

Although biomimetic prosthetic devices can better approximate biological ankle biomechanics, residual gait deviations can persist, either because of habit or a lack of proper rehabilitative training. For example, despite greater ankle power generation with powered ankle-foot device use, individuals with transtibial

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limb loss can still walk with compensatory strategies at the proximal joints, which can be attributed to the introduction of new interlimb asymmetries from the uniarticular function of the device [30]. Therefore, device-specific rehabilitation may be needed to minimize or correct the reported deficiencies. Similarly, in the absence of an evidence-based rehabilitation program to correct or minimize preexisting gait asymmetries, instrumented gait analyses that assess the biomechanical function of prosthetic devices may be more likely to quantify the physical gait deviations developed through habit or lack of training rather than device-specific attributes [34]. Therefore, it may be more accurate to postulate that powered ankle-foot devices, through the generation of normative ankle power during push off, offer an opportunity to minimize gait deviations and normalize prosthetic function but not without the incorporation of a rehabilitation program to train prosthesis users to reduce existing gait deviations.

Prosthetic Rehabilitation Programs

The current state of prosthetic research efforts appears to favor the design and evaluation of prosthetic componentry, particularly with respect to gait mechanics, and rarely incorporates or reports any type of physical therapy (PT) program or device-specific training [34]. Given the accelerated rate of technological innovation in prosthetic devices, there is a fundamental knowledge gap concerning how individuals with lower limb loss should learn to correctly use this advanced, powered technology for maximum benefit. However, previous investigations have examined the effectiveness of rehabilitation protocols on the outcomes of individuals with transfemoral limb loss who used passive prosthetic devices. Prosthetic gait training based on proprioceptive feedback for individuals with transfemoral limb loss was more effective for improved weight-bearing and temporal-spatial parameters than traditional gait training [35]. Sjodahl et al [36] used instrumented gait analysis to measure the gait parameters of individuals with unilateral transfemoral limb loss before and after a training program and reported improved walking speed and sagittal plane hip kinematic symmetry after training. However, the authors also reported increases in compensatory strategies for the intact limb, including an increase in the intact knee extension moment. Virtual reality–based gait training with real-time biomechanical feedback improved frontal plane hip, pelvis, and trunk motion during level ground walking [37]. Currently, there have been no published studies detailing the effects of a device-specific rehabilitation program on the biomechanical or functional outcomes of individuals with transfemoral limb loss who use a powered ankle-foot prosthesis. In this investigation, this knowledge gap will be addressed, and a benchmark to understand optimal treatment strategies will be provided for individuals with transfemoral limb loss to minimize gait impairments.

Summary

The development of evidence-based health care practices is critical to maximizing prosthetic and health outcomes in the growing population of individuals with transfemoral limb loss. Identifying potential mechanisms for correcting gait asymmetries, through advanced prosthetic technology, rehabilitative interventions, or both, can provide a benchmark to better understand the optimal treatment strategies for individuals with transfemoral limb loss. Despite research suggesting that an evidence-based rehabilitation program that incorporates prosthetic gait training is a critical factor in minimizing compensatory mechanisms [38-40], most prosthetic device protocols fail to incorporate any type of significant rehabilitation or device-specific training. Therefore, this investigation will be the first to elucidate the effects of an advanced powered prosthesis and the role of rehabilitative interventions on gait biomechanics, performance, and pain in individuals with transfemoral limb loss.

Study Objectives

The overarching goal of this investigation is to examine the roles of advanced prosthetic technology and a device-specific rehabilitative intervention in individuals with transfemoral limb loss. The central hypothesis is that powered plantarflexion, coupled with an evidence-based, device-specific PT intervention, will improve biomechanical outcomes, which will correlate with decreased pain and improved functional performance. The objectives of this investigation are as follows:

1. To examine the biomechanical and functional efficacy of a powered prosthesis compared with a passive prosthesis for individuals with transfemoral limb loss
2. To determine the effects of a powered prosthetic ankle-foot device and a PT intervention on lower extremity kinematic and kinetic patterns, functional efficacy, and pain in individuals with transfemoral limb loss
3. To develop preliminary rehabilitation guidelines for a powered ankle-foot device to minimize gait imbalances and maximize function, as well as to establish preliminary guidelines for powered ankle-foot prosthetic prescription

Methods

Study Overview

This investigation will be a prospective, multisite study including VA New York Harbor Healthcare System (VANYHHS), James A. Haley Veterans' Hospital (JAHVH), and Walter Reed National Military Medical Center (WRNMMC). Enrollment began in September 2018, and data collection is expected to conclude in 2024. Briefly, 30 individuals with transfemoral limb loss are expected to be enrolled equally across the 3 sites. For all participants, a full biomechanical gait analysis, functional measures, surveys, neurocognitive assessment, cognitive load assessment, and pain assessment will be captured at baseline with their clinically prescribed passive energy storing and returning ankle-foot prosthesis. The participants will be fitted with a powered ankle-foot device (Empower) and then be evaluated for safe use. The participants will then be randomly assigned into 2 groups: a powered ankle-foot device with a 4-week, 8-session device-specific PT intervention (group A) or a powered ankle-foot device with the current standard of practice (group B), which includes basic device education and training provided by the study prosthetist (outlined in the Powered Ankle-Foot Device Standard of Practice section), but no device-specific PT intervention. Group A will then undergo 4 weeks of

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device-specific rehabilitation, while group B will not receive any further PT. All participants will then undergo a full gait analysis as well as assessments of function, subjective preferences, neurocognition, cognitive load, and pain after 4 weeks and 8 weeks of powered ankle-foot device use (Figure 1). A comparison between the 2 groups will help evaluate the efficacy of a powered versus passive prosthesis, as well as elucidate the contribution of device-specific effects to rehabilitation-specific effects for individuals with transfemoral limb loss.

Figure 1. Participant timeline of activities.

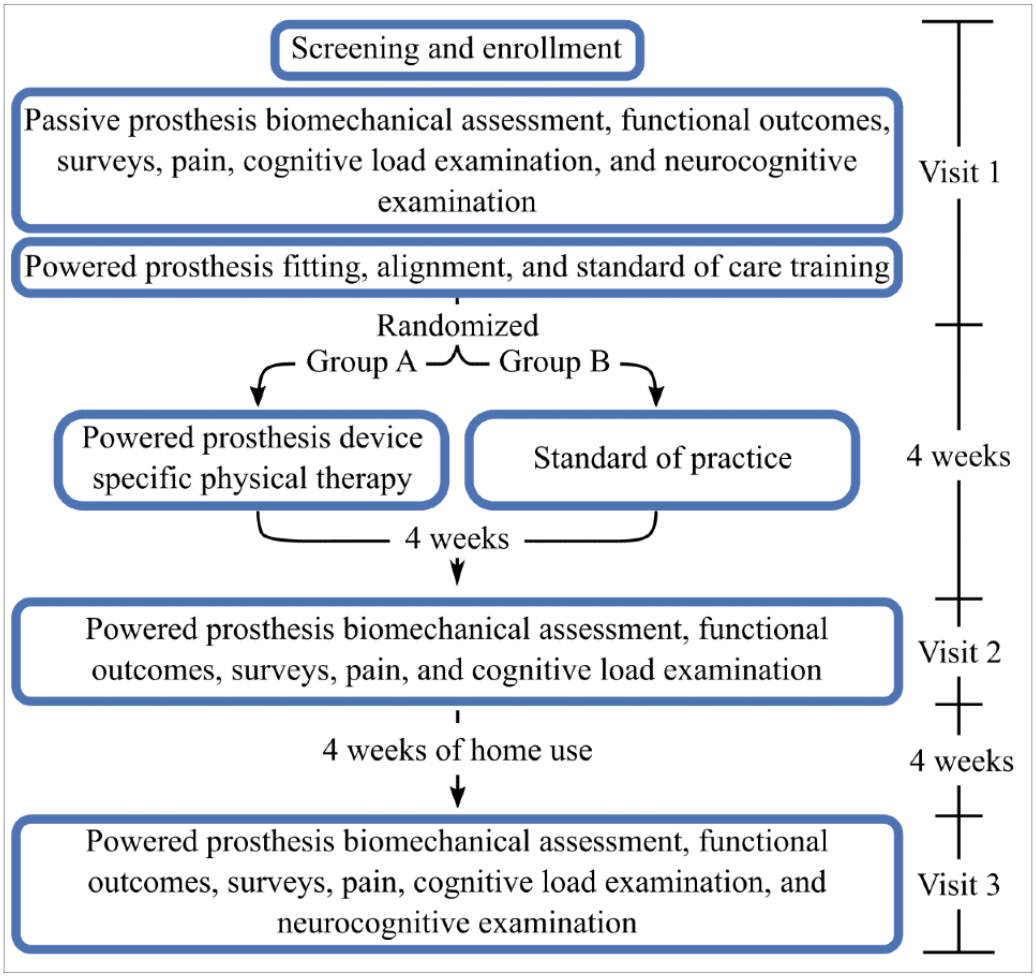

Participants

A convenience sample of 30 individuals with unilateral transfemoral limb loss will be recruited for this study (Textbox 1 shows the inclusion and exclusion criteria). All participants will consent to participate before participating in any study activities. The participants will be randomly stratified into 2 study arms: group A, a powered ankle-foot device with device-specific PT (15/30, 50%), and group B, a powered ankle-foot device with standard of practice (15/30, 50%), which includes basic device education and training but no device-specific PT intervention. Recruitment of participants will be on a first-come, first-serve basis among the patients of VANYHHS, JAHVH, and WRNMMC. The participants will be recruited through the VANYHHS, JAHVH, and WRNMMC rehabilitation and prosthetic clinics. All participants will have experience using a microprocessor knee and will currently use a passive-elastic ankle-foot prosthesis.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Unilateral transfemoral limb loss because of any etiology
- Use of a microprocessor knee with >6 months of experience
- ≤8 limb loss–related physical therapy sessions in the previous 6 months
- Aged at least 18 years
- Score of ≥33 on the Amputee Mobility Predictor, corresponding to a high K2 or above ambulator
- Able to walk a minimum of 30 meters without an assistive device
- Able to walk on a treadmill for 5 minutes at self-selected speed with or without the use of handrails

Exclusion criteria

- Inability to tolerate the wearing of a socket or a poorly fitting socket
- Conditions of the intact limb prohibit prosthesis use (eg, ulcers, sores, skin breakdown, burns, poor skin coverage, contractures, and severe heterotopic ossification)
- The length of the residual limb prohibits socket or prosthesis fitting
- Cognitive deficits or a mental health pathology limiting the ability to participate fully in the study or any deficit deemed by the principal investigator to be detrimental to the completion of the study
- Significant comorbidity, which would interfere with the study (eg, neuropathy, uncontrolled diabetes, receiving dialysis, insensate feet, severe phantom pain, or a history of skin ulcers)
- Severe circulatory problems, including peripheral vascular disease and pitting edema
- Pregnant women in the second trimester or beyond or women who will be in the second trimester within the enrollment period
- Weigh >130 kg at screening
- Use of nonprescribed opioids or overuse of any prescription drugs
- Major upper limb loss
- Currently uses a powered ankle-foot prosthesis as a primary prosthesis or used a powered ankle-foot device as a primary prosthesis in the previous 6 months
- Any cardiopulmonary, metabolic, or integumentary diagnosis where walking for 15 minutes is contraindicated

Ethical Considerations

This study was approved by the following institutional review boards (IRBs): VANYHHS IRB (1643), WRNMMC IRB (WRNMMC-2018-0167), and the University of South Florida IRB, which is the IRB of record for JAHVH (IRB STUDY000870). The oversight and protection of human participants was also approved by the US Army Medical Research and Development Command Office of Human Research Oversight (E04081). All participants will provide informed consent before participating in any study activities.

Baseline Visit

Informed Consent, Enrollment, and Randomization

Informed consent for each potential participant will be conducted in person in a private room. The site-principal investigator or qualified designee will explain the study protocol in detail. The participants will be asked to consent to randomization of the treatment group, either to be fit with the powered ankle-foot device and receive device-specific PT (group A) or to be fit with the powered ankle-foot device and receive the current standard of practice that does not include device-specific PT (group B). The participants will be asked to make a commitment to be available for all study-related activities. The individuals will be given adequate time to review and comprehend all information about the study before agreeing to participate, minimizing the possibility of coercion and undue influence. After the study has been explained and consent has been given, the participants will be randomized into the 2 groups using a computer-generated algorithm that block randomizes participants into each group at each site.

Baseline Data Capture

Regardless of the group assignment, all participants will undergo baseline data capture using their current passive energy storing and returning prosthesis. The study prosthetist will ensure proper fit and alignment of the prosthesis before any data collection. Once fit and alignment are confirmed, the participants will complete 3 surveys: an assessment of quality of life, the Prosthesis Evaluation Questionnaire (PEQ), and the PEQ Addendum. Then, pain, cognitive load, neurocognition, biomechanical gait analysis, and functional outcomes will be captured at baseline for all participants on their current passive energy storing and returning prosthesis.

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Quality-of-Life Assessment

A single-item assessment will ask the participants to rate their quality of life over the past 4 weeks on a 100-mm visual analog scale.

Assessment With PEQ

The PEQ is a self-reported visual analog–style questionnaire for people with lower limb loss who use a prosthesis to evaluate the prosthesis and life with the prosthesis. The PEQ is organized into 9 domains that may be used independently to measure a specific domain of interest. Domains of utility, appearance, sounds, residual limb health, and ambulation will be used in this investigation. In addition, the PEQ contains items beyond the domains that can be evaluated individually, including questions on satisfaction, pain, and transfers that will be used in this study [41].

Assessment With PEQ Addendum

The PEQ Addendum asks 2 open-ended questions assessing any falls or stumbles that the participant may have experienced over the previous 4 weeks [42].

Pain Assessment

Participants will complete the Patient-Reported Outcomes Measurement Information System Pain Interference Scale 8a, which is a self-report survey that assesses the extent to which pain interferes with physical, psychosocial, cognitive, emotional, and recreational activities [43].

Neurocognitive and Cognitive Load for Prosthesis Use

Prosthesis use requires physical capabilities and the cognitive capacity to learn new techniques across different situations and environments. These skills include spatial organization, memory, attention, and visuospatial function [44]. Powered ankle-foot devices can be more complex than passive devices and may require certain levels of neurocognition and cognitive load for ambulation, especially for higher-level functional tasks. Diabetes and peripheral vascular disease, the most prevalent causes of lower limb loss, are linked to declining neurocognition [45,46]. Importantly, diminished neurocognitive function is not often observed until late in the rehabilitation process (well after prosthetic prescription) [47], which can result in the mismanaged use of staff and patient time and prosthetic resources. If certain levels of neurocognitive abilities correlate with successful prosthetic outcomes with the powered prosthesis, neurocognitive assessment (before prosthetic prescription) can potentially aid in the selection of appropriate candidates for advanced technology.

Cognitive Load Assessment

Cognitive load assessments will be performed at baseline using the passive energy storing and returning ankle-foot prosthesis. Before any cognitive load testing, a self-selected walking speed will be established via treadmill walking. The participants will be encouraged to walk unsupported on the treadmill, if possible. The treadmill console will be covered to prevent number distractions, and the participants will be reminded to hold their gaze straight ahead. To determine the self-selected speed, the participants will begin walking on the treadmill at a comfortable speed in the absence of any additional cognitive load. The treadmill will then be increased by 0.09 m/s every 10 seconds until the participant verbalizes their preferred speed. To avoid quick trigger responses, the speed will be increased by 0.18 m/s and then subsequently lowered by 0.04 m/s every 5 seconds until the participant verbalizes their preferred speed. If the final speed does not match the initial speed, this procedure will be repeated until the participant matches the preferred walking speed.

Cognitive load testing consists of five 1-minute standardized cognitive tasks: 1 serial subtraction task, 3 controlled oral word association tasks, and 1 category task. These tasks consist of auditory and verbal cognitive measures to simulate real-world conditions. Visual tasks will not be used to avoid measures that require reading while walking. The participants will complete each cognitive task while walking on a treadmill at the previously noted self-selected speed. The directions will be read to each participant to ensure protocol consistency. The number of correct answers will be determined for each 1-minute test using a digital voice recorder and paper recordings to ensure accurate documentation of the participants' answers. The participants will complete a practice trial before each task initiation to ensure complete comprehension. The participants will also be allowed to rest between cognitive tests as needed. The cognitive tasks are as follows:

- Serial subtraction: Serial subtraction is a mental arithmetic task [48]. The participants are given a random 3-digit number and asked to continually subtract 3 while they walk for 1 minute. The number of errors will be calculated. The participants are not penalized for multiple errors if 1 error was made; however, they continued sequentially thereafter.
- Controlled Oral Word Association Test: This measure consists of 3 tests that measure verbal phonemic fluency and other neuropsychologic domains [49]. The participants will be asked to list words beginning with a certain letter while walking for 1 minute. The test is then repeated for 2 other letters. The total number of unique words for each letter will be documented.
- Category Test: The participants are asked to list words belonging to a certain category within 1 minute (eg, fruits or parts of a car). Category naming has shown validity and reliability [50]. The total number of unique words for each category will be documented.

After each cognitive load test, the participants will be asked to rate on a 0 to 10 scale (with 0 being "none" and 10 being "a great deal") their focus on walking, their focus on thinking of words or subtracting numbers, and their focus on distractions. This will provide information on the subjective experience of cognitive load.

Neurocognitive Assessment

Following the cognitive load assessment, the participants will take an electronic neurocognitive battery (CNS Vital Signs) [51]. The computerized neurocognitive assessment measures 5 domains (memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility), is designed to be administered serially, and has demonstrated good test-retest

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reliability. The neurocognitive assessment consists of the following 7 tests:

- Verbal memory: the participants are instructed to remember 15 words that are displayed 1 at a time every 2 seconds. The target words are then randomly mixed with 15 new words. The participants are instructed to press the space bar when a target word is displayed. This test is repeated at the end of the assessment with the same 15 target words randomly mixed with 15 new nontarget words.
- Visual memory: the participants are instructed to remember 15 geometric shapes that are shown 1 at a time every 2 seconds. The shapes are then randomly mixed with 15 new nontarget shapes. The participants are instructed to press the space bar when they identify a target shape. This test is repeated at the end of the neurocognitive assessment period.
- Finger tapping: the participants are instructed to tap the space bar with their right index finger as quickly as possible during the 10-second test. The test is then repeated with the left index finger.
- Symbol Digit Coding: this test consists of 8 digit-symbol pairs, followed by a list of digits. The participants are instructed to serially type numbers that correspond to the symbols during the 120-second test.
- Stroop test: in part 1 of the Stroop test, the participants are randomly shown the words "GREEN," "YELLOW," "RED," and "BLUE." These words are printed in black. The participants are instructed to press the space bar when they see one of these words. In part 2, the same words appear on the screen but are printed in different colors. The participant is instructed to press the space bar when the color presented matches the word (eg, the word "RED" is printed in red). In part 3, the same words are presented on the screen in different colors. The participants are then instructed to press the space bar when the color presented does not match the word (eg, the word "RED" is printed in green).
- Shifting Attention: in this test, 3 figures appear on the screen. There is a single figure at the top of the screen (either a circle or a square). At the bottom of the screen, 2 figures are presented (both a square and a circle). The figures are randomly mixed to be either red or blue. The participant is then instructed to match one of the corresponding bottom figures with the top figure by shape or color. However, the rules for matching by shape or color change at random. This test occurs for 90 seconds.
- Continuous performance test: during a 5-minute period, the participants are asked to press the spacebar when the letter *B* appears on the screen. The participants are further instructed not to respond to any other letters. The letters are presented at random.

Biomechanical Gait Analysis

Gait analyses will be performed at the biomechanics laboratories at VANYHHS, WRNMMC, and JAHVH. The VANYHHS laboratory is a 133-m^2 space comprising an 11-camera motion capture system (Qualisys, Inc) with 4 multiaxis force platforms (AMTI, Inc). At WRNMMC, the biomechanics laboratory is an 167-m^2 space comprising an 18-camera motion capture system (Qualisys, Inc) and 6 multiaxis force platforms (AMTI Inc). At JAHVH, the motion capture laboratory is a 74-m^2 space equipped with a 12-camera motion capture system (Vicon Inc) and 4 multiaxis force platforms (AMTI Inc). All 3 systems track the positions of passive reflective markers at a rate of 120 Hz, and force platforms sample ground reaction forces at a rate of 1200 Hz. Visual3D software (C-Motion Inc) will be used for the analysis of 3D motion capture data.

All laboratories in this investigation will follow recommendations provided by an interlab reliability study that was conducted between gait laboratories at the 3 military treatment facilities [52]. Specifically, all sites will use identical marker sets, identical anatomical segment definitions, and a single examiner at each site to conduct postprocessing of the respective data to reduce potential variability between the laboratories.

For all participants, biomechanical gait analysis will be performed at baseline using their prescribed energy storing and returning prostheses. All kinematic and kinetic biomechanical measures will be captured using an identical 6-degrees-of-freedom marker set. A custom, full-body passive reflective marker set will be placed on each participant, which tracks each segment independently, allowing for the accurate measurement of movements. As previously described [53], 78 markers will be placed or digitized on the head, trunk, pelvis, and extremities. Marker placements for the prosthetic limb will be matched to those of the intact leg or placed on the centers of rotation of the prosthetic ankle-foot and knee devices. The cluster technique will be used to minimize the surface-to-bone displacements for the thigh, shank, and upper arm–mounted markers [54]. Tracking clusters will be placed bilaterally on the thigh, the tibial crest, and the upper arm. Functional joints, adapted from Schwartz and Rozumalski [55], will also be calculated for the intact ankle and knee as well as bilaterally for the hips.

During each experimental session, the participants will separately walk at 3 speeds across an instrumented walkway until 5 acceptable trials for each foot at each speed are completed. Trials will be considered acceptable when a foot makes full contact with a force platform. Because kinetic outcome measures are speed-dependent, the participants will ambulate at 3 controlled speeds: 0.7, 1.0, and 1.3 m/s. These speeds were selected to represent a slow, moderate, and fast walking speed, respectively, for individuals with transfemoral limb loss. The order of speeds will be randomized for each data collection visit. Auditory feedback will be provided to the participant by the study team to ensure that all participants walk at the targeted speed (−5% to +5%). The main purpose of this session is to collect joint motion, force, torque, and power data at each walking speed. The ranges of motion; speeds and accelerations; and hip, knee, and ankle joint moments of force and generated and absorbed powers will be computed using inverse dynamics methods. Temporal-spatial parameters will also be recorded.

The reflective marker positions will be digitized using motion tracking software. A 15-segment rigid body model (head, trunk,

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pelvis, bilateral upper and lower arms, hands, thighs, shanks, and feet) will be created based on the skin-mounted markers and functional joints. Local coordinate systems for each segment will be defined using the International Society of Biomechanics recommendations [56,57]. The data of 5 acceptable walking trials at each speed will be processed using Visual3D. Marker data will be filtered with a 6 Hz Butterworth low-pass filter. Raw analog data will be filtered using a second-order low-pass Butterworth filter with a 25-Hz cutoff frequency. Visual3D will be used to calculate temporal-spatial values, walking speed, and lower extremity kinematics and kinetics. Inverse dynamic analysis will be applied to the kinematics of the biomechanical model and to the location, magnitude, and direction of ground reaction forces acting on the foot to calculate lower extremity joint torques and powers, including ankle, knee, and hip power of the biological and prosthetic limb over the stance phase, as well as the frontal plane knee moments for the unaffected leg.

Functional Outcome Measures

The effects of the prosthetic devices and the rehabilitative intervention on physical performance will be evaluated using agility and mobility tests, including the 6-minute walk test (6MWT) [58], the Amputee Mobility Predictor with prosthesis (AMPpro) [59], and the Comprehensive High-Level Activity Mobility Predictor (CHAMP) [60]. By capturing the functional measures in each group, the effects of the ankle-foot device can be isolated from the rehabilitation effects on physical performance. These measures are as follows:

- 6MWT: the 6MWT measures the distance an individual can walk in 6 minutes without help or encouragement. It is a valid and reliable measure that correlates with physical function and has good interrater and intrarater reliability in individuals with lower limb loss [58].
- AMPpro: the AMPpro is a 21-item instrument designed to measure prosthetic mobility in individuals with lower limb loss [59].
- CHAMP: participants who attain a score of 37 or higher on the AMPpro will undergo the CHAMP, which consists of the following tasks:
    - Single limb stance: participants fold their arms across their chest and then lift their foot above a 15-cm cone or box. The test ends when the foot touches the ground again (or until 30 s) or if the arms uncross. This procedure is performed on both feet.
    - Edgren Sidestep Test: participants sidestep left and then right along a 5-meter line of cones (1 meter apart). The sidestep test lasts for 10 seconds.
    - T-Test: the T-Test measures forward, lateral, and backward walking (or running) and sidestepping in a T pattern.
    - Illinois Agility Test: this advanced agility test requires the participant to run or walk and change direction around multiple cones. Over 60 meters, participants perform 90° and 180° turns 11 times around multiple cones.

Powered Ankle-Foot Prosthesis Fitting

Following all baseline data collection procedures, all participants will then be fit with the Empower. Study prosthetists at VANYHHS, WRNMMC, and JAHVH are highly experienced in fitting all commercial microprocessor knees and the Empower. The study prosthetists will bench align the powered ankle-foot device onto the participant's existing microprocessor prosthetic knee and socket. Once the powered ankle-foot device is fitted and bench-aligned to the prosthetic knee and socket, dynamic alignment of the prosthetic knee and ankle will occur. Initially, the study prosthetist will ensure proper alignment of the microprocessor prosthetic knee with the Empower turned off. The Empower will still function (ie, articulate) with the power off but will not provide net positive plantarflexion torque. The microprocessor prosthetic knee software and prosthesis alignment will be adjusted during standing and walking tasks, as necessary, until the prosthetist and the participant are satisfied with the knee alignment. Once the microprocessor knee setup is completed, the Empower will be powered on and adjusted according to the manufacturer's specifications. Briefly, the participants will sequentially walk at 3 different speeds (slow, self-selected, and fast) while the stiffness and power delivery of the powered ankle-foot device is tuned [33]. If further dynamic adjustments to prosthetic knee alignment are necessary, these adjustments will be made at this point.

Powered Ankle-Foot Device Standard of Practice

Once a stable and comfortable alignment has been established, all participants will be educated by the study prosthetist on the proper use of the Empower, which includes battery handling and charging, understanding low battery indicators, considerations while driving with the Empower (if applicable), and avoidance of exposure to rain and water. Next, the participants will ascend and descend an Americans with Disabilities Act–compliant ramp under the supervision of the study physical therapist or prosthetist. The intent of ramp walking is to trigger the power for ascent but not during descent. Each participant will be given the opportunity to practice the ramp as often as necessary to ensure safe and comfortable use. The participants will then negotiate a standard staircase with handrails under the supervision of the study physical therapist or prosthetist to ensure that they can safely negotiate stairs using the Empower. Proper technique will consist of demonstrating the correct foot placement on each step to activate powered push off during ascent. Participants unable to ascend stairs in a step-over-step pattern will be shown the correct foot placement using a step-to gait pattern. For proper stair descent, participants will be shown the correct foot placement to initiate rollover and not trigger the power. Participants will be given time to practice stair ascent and descent. After stair and ramp ambulation, participants will be asked to demonstrate safe use of the Empower in different situations, including turning, varying speeds, sudden stops, obstacle avoidance, stepping over obstacles, and different surfaces. Once the physical therapist is satisfied that the participant has demonstrated safe use and all questions have been answered, the participant will be released home with the Empower. If the physical therapist feels that the progress is unsatisfactory, the participant will not take the Empower home and will be asked to return for continued

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supervised use until the participant demonstrates safe use. The standard of practice to use the powered prosthesis is approximately 30 to 45 minutes after fitting and tuning.

Following the baseline visit, group A will undergo the device-specific PT program, whereas group B will not undergo any further training.

PT Program: Group A

Overview

Participants in group A will complete, on average, 8 PT sessions lasting 30 to 45 minutes each. The exact PT protocol and criteria for advancement are outlined by level in the subsequent section. In brief, level 1 of the PT plan will focus on education, strengthening through therapeutic exercises, and early neuromuscular reeducation. A home exercise program (HEP) will be initiated during the initial sessions and will progress along with the program. Level 2 will include gait training on level surfaces, sit-to-stand transitions, and ramp negotiation. Level 3 will include multidirectional training for both neuromuscular reeducation and gait and the introduction of stair ascent and descent. Training will conclude with level 4 where the previous skills will be further challenged and advanced gait skills, including ambulation on ramps and uneven surfaces, will be introduced. Participants must meet the outlined criteria before progressing through each level. Participants who do not meet the specified criteria will be offered additional PT sessions. The number of additional sessions will be recorded and used to refine the PT program for future use.

Level 1 (Sessions 1 and 2)

Level 1 (Table 1) includes initial evaluation, patient education, gait assessment, training to ensure safe use in the community, therapeutic exercises (including introduction of the HEP), and the initiation of early neuromuscular reeducation training.

Table 1. Level 1 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement to level 2
Level 1 (sessions 1 and 2)		
Evaluation	Assessment of prosthesis fit and gait to determine deficits	N/A[a]
Strengthening	Strengthening of transversus abdominis and multifidus, gluteus maximus, gluteus medius, and general trunk strengthening	Able to perform HEP[b] independently
Stretching	Address deficits from evaluation, including iliopsoas	Within normal limits for range of motion
Education	Explanation of function of powered ankle-foot device	Verbalizes understanding of function of powered ankle-foot device
Gait training	Safely negotiate level surface without increased falls or stumbles	Able to ambulate 46 meters without an assistive device independently on a flat, level surface; self-reported occurrence of stumbles or falls is no greater than baseline
Mobility training	Side stepping, backward stepping, and turns	Able to ambulate outdoors without increased falls or stumbles with or without an assistive device
Neuromuscular reeducation	Weight shifting and control over prosthesis, intact limb mobility (toes in and toes out, heel in and heel out) to promote weight shifting, static single limb balance training on prosthesis side with upper limb support, and anterior and posterior stepping exercises with the intact limb	Independent in HEP
HEP	Initiated with all therapeutic exercises outlined in level 1	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 2 (Sessions 3 and 4)

Level 2 (Table 2) will include the progression of therapeutic exercises through increased frequency, duration, and resistance.

All strengthening and stretching will be shifted to the HEP by the completion of level 2. Lumbar, abdominal, and closed kinetic chain lower extremity strengthening exercises will progress to more dynamic positions. Single limb stance progressions (neuromuscular reeducation) will include decreased upper limb support for stepping exercises and progressing to step touches with the intact limb. Upper limb support will progress from bilateral support to support provided only on the side of the prosthesis. Anterior and posterior stepping exercises will begin with the support of parallel bars while maintaining weight on the prosthesis.

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Table 2. Level 2 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement to level 3
Level 2 (sessions 3 and 4)		
Evaluation	Reassessment as needed	N/A[a]
Strengthening	Progression to sitting, quadruped, planks, standing, and transitions	Independent in HEP[b]
Stretching	Primarily used for cooldown at completion of each session	Independent in HEP
Education	Description of HEP and purpose of each exercise	Verbalizes understanding of each exercise
Gait training	Improving step length symmetry (eg, verbal cueing to increase step length on nonprosthesis side) and improving rollover on prosthesis side (eg, resistive gait training with TheraBand)	Ability to trigger power in prosthetic foot during gait >50% of steps and increased gait symmetry with verbal cueing for step length as determined through observational gait analysis
Mobility training	Transfers (eg, stand-to-sit), and ramp negotiation	Able to maintain midline center of mass with stand-to-sit transfer
Neuromuscular reeducation	Intact limb mobility (eg, rolling ball under intact limb) to promote weight shifting, static single limb balance training on prosthesis side with minimally necessary upper limb support and stepping exercises (eg, step touches 15-20 cm step in parallel bars and step touches to a cone in the parallel bars)	Independent in HEP
HEP	Includes therapeutic exercises outlined in level 2	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 3 (Sessions 5 and 6)

At level 3 (Table 3), all strengthening will be performed exclusively in the HEP. PT will include neuromuscular reeducation progression, including multidirectional movements.

Stepping exercises will be performed with decreasing upper extremity support at a tolerance demonstrated by the participant maintaining an appropriate body position. Single limb stance activities will include perturbations, such as resistance with movements of a non–weight-bearing intact limb or standing on a foam pad or balance disc. Gait training will include multidirectional stepping with upper extremity support in the parallel bars. Resistive gait training will be introduced to promote proper mechanics for loading the prosthesis in stance and achieving maximal energy return at push off. In addition, manual proprioceptive neuromuscular facilitation will be performed to promote proper anterior pelvic rotation. Multidirectional ambulation will be progressed to outside of parallel bars.

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Table 3. Level 3 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement
Level 3 (sessions 5 and 6)		
Evaluation	Reassessment as needed	N/A[a]
Strengthening	Review as needed	Independent in HEP[b]
Stretching	To be used for cooldown at session completion	Independent in HEP
Education	Gait training and purpose for improving symmetry	Verbalizes understanding of gait training
Gait training	Promoting gait initiation on prosthesis side with anterior pelvic rotation (ie, manual techniques to facilitate or initiate anterior pelvic rotation while in parallel bars with progression to anterior stepping on prosthesis side), relaxed upright posture with ambulation (ie, verbal cueing to keep chest upright), and resistive gait training with TheraBand and verbal cues for increased step length with intact limb	Demonstrates ability to trigger power with at least 80% accuracy during level ground ambulation and increased gait symmetry, including upright posture, step length, and toe break as determined through observational gait analysis
Mobility training	Ramp and stair negotiation	Hill Assessment Index score ≥6 (ie, step past more than half foot length, with assistive device)
Neuromuscular reeducation	Four-directional resistance exercise on intact side while maintaining single limb stance on prosthesis side, static single limb balance training on prosthesis side to be progressed to noncompliant surface (eg, foam), and progression of stepping exercises to increase time in single limb stand on the prosthesis	Able to maintain single limb stance on prosthesis side with or without an assistive device for 15 seconds
HEP	Includes therapeutic exercises in level 3	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 4 (Sessions 7 and 8)

At level 4 (Table 4), PT will include advanced neuromuscular reeducation and gait training, followed by a final PT evaluation.

Neuromuscular reeducation will include single limb squats in the parallel bars with upper extremity support, as needed. Gait training will continue resistive training on even surfaces, proprioceptive neuromuscular facilitation for pelvic rotation, verbal and tactile cueing for symmetrical and appropriate trunk rotation, and negotiation of uneven surfaces.

Individuals who do not meet the criteria to complete the PT program will be offered an additional 8 PT sessions after completion of the study.

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Table 4. Level 4 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement
Level 4 (sessions 7 and 8)		
Evaluation	Re-evaluation at final session	N/A[a]
Strengthening	N/A	N/A
Stretching	To be used for cooldown at session completion	Independent in HEP[b]
Education	Importance of continuation of HEP	Verbalizes understanding
Gait training	Promoting gait initiation on prosthesis side with anterior pelvic rotation, manual techniques and verbal cues to promote increased trunk rotation and trunk rotation symmetry, verbal cueing for symmetrical arm swing and trunk rotation (eg, "relax your shoulders"), and resistive gait training with TheraBand and verbal cues for increased step length with the intact limb and relaxed upright posture	Demonstrates ability to trigger power with at least 90% accuracy for powered prosthetic foot and increased gait symmetry for trunk rotation and arm swing, as determined through observational gait analysis
Mobility training	Ascending and descending ramps and stairs	Stair Assessment Index score of at least 4 (with assistive device, step-to pattern) for ascending and descending stairs, and ambulates in the community without increased participant-reported stumbles or falls compared with baseline
Neuromuscular reeducation	Applied during HEP	Demonstrates increased gait symmetry for step length, push off, anterior pelvic rotation, upright posture, trunk rotation, and arm swing
HEP	Review HEP	Demonstrates independence in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Data Collection Visit 2

After completion of the device-specific PT program, all participants will undergo data collection on the powered ankle-foot prosthesis. The participants will repeat the quality-of-life assessment, subjective surveys, pain assessment, cognitive load assessment, biomechanical gait analysis, and functional measures using the powered ankle-foot prosthesis, as described in the baseline visit. Following visit 2, participants will keep the powered ankle-foot prosthesis for an additional 4 weeks of home use and community use but will not undergo any further device-specific training.

Data Collection Visit 3

After the final 4 weeks of powered ankle-foot prosthesis use, participants will undergo final data collection. Participants will repeat the quality-of-life assessment, subjective surveys, pain assessment, cognitive load measurements, neurocognitive assessment, biomechanical gait analysis, and functional measures, as described in the baseline visit. Following data collection, all participants will be refitted with their energy storing and returning ankle-foot devices, and the powered ankle-foot devices will be returned to the study staff.

Statistical Analysis

Across the study population, outcomes will be assessed with descriptive statistics and compared between each ankle-foot device category as well as by PT intervention (ie, device-specific PT and standard of care). Inferential statistics for ordinal data will be conducted with a repeated-measures Friedman test (α=.05) and a Dunn post hoc test at a 95% CI. To address which measures are the most sensitive to intervention type, a linear mixed-effects model will be used. Separate models will be used for each type of measure (pain, subjective, cognitive, neurocognitive, functional, and biomechanical), and measures that have a significant association with the intervention type in the presence of adjusting (control) variables will be determined. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable. The following sections outline the specific analyses that will be performed for each study objective.

Planned Statistical Analysis for Biomechanical and Functional Outcomes

Although there are numerous biomechanical and physiological parameters that can be evaluated following gait analysis [61], this investigation will focus on the biomechanical parameters that are most relevant, commonly used, able to discriminate, and have specific clinical relevance for individuals with transfemoral limb loss. The primary biomechanical outcome measures will include measures of rollover shape, individual characteristics of the 3D ground reaction force, and ankle, knee, and hip joint angles, moments, and powers (on both the intact and affected limbs). To evaluate the load distribution of the medial and lateral knee compartments, the peak resultant ground reaction force, ground reaction force rate, peak knee external adduction moments, and knee external adduction moment rate will be compared between the baseline (passive energy storing and returning condition) and the powered condition at each follow-up visit.

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Linear mixed-effects models will be used to identify statistically significant differences in gait temporal-spatial and biomechanical variables for all walking speeds. The fixed effects will be the average differences in gait biomechanical and temporal-spatial variables by prosthetic ankle type (powered vs passive). These models also estimate random effects because of differences in mean biomechanical variables across participants, as well as the random effects associated with minimized variability, as the participants will be tested with both prostheses. For example, a linear mixed-effects regression will be used to examine the relationship between the intact knee peak external adduction moment and the prosthetic ankle-foot condition. Peak intact knee external adduction moment will be the dependent variable, whereas ankle-foot condition will be the independent variable, and participant-by-ankle-foot condition will be modeled as random effects. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable. In addition, linear mixed-effects regression will be used to determine the association between prosthetic peak ankle power and foot condition.

Planned Statistical Analysis for Pain Outcomes

The following parameters will be measured and statistically compared between baseline (energy storing and returning condition) and each follow-up visit with the powered ankle-foot prosthesis (weeks 4 and 8):

- Joint reaction forces on the lower back (L5 and S1) and contralateral (intact) knees
- PEQ pain scores
- Functional outcome measures (6MWT, AMPpro, and CHAMP)

Spearman correlations will be calculated to correlate data between pain and lower extremity kinematic and kinetic parameters of interest and pain and functional outcome values across the groups. Linear mixed-effects models will be used to identify statistically significant differences in pain scores and biomechanical variables listed in the previous section for all walking speeds. For example, a linear mixed-effects regression will be used to examine the relationship between peak reaction moments at L5 and S1 and pain for each prosthetic ankle-foot condition. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable.

Multiple linear regression will be performed with PEQ pain as the dependent variable. Because of the large number of predictor variables in relation to the number of participants, penalized methods (eg, ridge regression or lasso) will be used to identify variables that contribute the most to the prediction model. Penalized methods add a tuning parameter to the regression model that shrinks the less important coefficients toward 0. Cross-validation will be used to select the best tuning parameter value [62]. The independent variables will be comprised of functional parameters (eg, peak joint reaction forces) and the condition (ankle-foot type and intervention).

Planned Statistical Analysis for Cognitive Load and Neurocognitive Outcomes

Linear mixed-effects models will be performed to examine the differences between the ankle-foot devices on cognitive performance, walking speed, and subjective responses to attention. The parameters in the linear effects model will include prosthetic ankle-foot type, PT intervention, and participants. Ankle-foot type, PT intervention, and cognitive performance will be treated as fixed effects, whereas participants will be treated as random. The total number of errors and the error rates for the cognitive task will be calculated, and the mean error rate will be determined for each cognitive task performed by each participant. Repeated-measures ANOVA will be used to compare the error rates for the 3 cognitive tasks. Fisher least significant difference test will be used to make post hoc comparisons.

For the neurocognitive battery, Pearson correlation coefficients (pair-wise 2-tailed) will be calculated for all variables of interest. Stepwise multiple regression will be performed with the neurocognitive scores (Neurocognitive Index, composite memory, cognitive flexibility, and complex attention scores) as the dependent variable. The independent variables will comprise functional outcomes, pain, and gait biomechanics, including asymmetry index.

Power Analysis and Sample Size Estimation

The sample size was based on a power analysis of 3 biomechanical measures (leading limb work, ground reaction force rate, and knee adduction moment rate) and 1 functional outcome (6MWT distance), and 1 subjective outcome (PEQ—utility) obtained from preliminary analyses, with all measurements obtained at baseline and 2 additional measurements over an 8-week period. The sample size was calculated for the group-by-time interaction, which tests the differences in change over time between the study groups. Assuming an α error rate of 5%, Table 5 presents the power achieved for each measurement for 30 participants, 15 (50%) in each group.

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Table 5. Power analysis and sample size estimation.

Measure	Difference, mean (SD)	Power (N=30)
Leading limb work (J/kg)	0.03 (0.04)	85
Ground reaction force rate (N/kg/s)	15 (26.9)	82
Knee adduction moment rate (N m/kg/s)	1.1 (1.2)	98
6MWT[a] distance (m)	60 (61)	96
PEQ[b]—utility	8.4 (8.8)	96

[a]6MWT: 6-minute walk test.

[b]PEQ: Prosthesis Evaluation Questionnaire.

Results

This study was funded in September 2017, with enrollment beginning in September 2018. Data collection is expected to conclude by March 2024. Data analysis of the completed data set is expected to begin after final data collection. The initial dissemination of results is expected in August 2024, with subsequent publication of secondary analyses in December 2024.

Discussion

Expected Outcomes and Anticipated Principal Findings

After the completion of this research project, this investigation will have quantified the dependence of symmetrical lower limb gait biomechanics, physical function, and pain reduction on advanced prosthetic technology and device-specific rehabilitation. Furthermore, a device-specific treatment strategy designed to minimize impairments and maximize function will be evaluated. Finally, an objective measure of cognitive load and neurocognition to guide the prosthetic prescription of powered ankle-foot prostheses will be assessed. As such, the evidence-based outcomes obtained from this research investigation can be appropriately translated into clinical practice as well as drive the future of clinical care in this population.

VA provides care for veterans with limb loss of all generations, including the influx of service members with limb loss from the most recent conflicts [5]. Projected trends indicate that the overall number of individuals with limb loss will continue to increase dramatically, largely attributable to the aging population and the growing number of people with dysvascular disease and diabetes [1]. With this large population expected to grow, considerable resources will be required for rehabilitation and prosthetic services, driving limb loss care to become a high priority for VA. Effective outcomes-based clinical practice will be necessary to decrease long-term disabilities associated with prosthetic use and improve the quality of life. Therefore, it is the goal of this study to examine the effectiveness of a powered ankle-foot prosthesis and device-specific rehabilitation on gait biomechanics, performance, and pain in individuals with transfemoral limb loss. Results from this investigation will provide evidence-based outcomes that can be translated into successful strategies to minimize impairments and maximize function and may drive the evaluation of future advancements in prosthetic technology.

Dissemination Plan

The results of this investigation can help form evidence-based guidelines for individuals with transfemoral limb loss that can serve as a source for lower limb loss clinical practice guidelines. Dissemination of the results of this study within the DoD, VA, and the civilian health care systems will be performed in 3 ways. First, the results will be disseminated to the scientific and clinical community through traditional means, such as peer-reviewed submissions to professional conferences (eg, the Gait and Clinical Movement Analysis Society Annual Conference, the American Congress of Rehabilitation Medicine Annual Conference, and the Military Health System Research Symposium), targeted limb loss and rehabilitation publications (eg, *Archives of Physical Medicine and Rehabilitation*, *Gait & Posture*, and *Frontiers in Bioengineering and Biotechnology*), as well as sharing the data through large data repositories. Second, both VA and the DoD have national, interdisciplinary groups and committees that enable the national dissemination and adoption of best practices among different disciplines. For the VA and DoD limb loss care teams, the Extremity Trauma and Amputation Center of Excellence and the VA Amputation System of Care hold a bimonthly webinar series for clinicians, scientists, and researchers that is available across the entire DoD and VA health care network. This series allows research results to be presented to a large, diverse audience of researchers and health care professionals in limb loss care, which can directly influence the care provided to veterans and service members with limb loss. Finally, the outcomes will be disseminated directly to leaders in the prosthetics industry to provide real-world feedback on their products. The results provided to industry leaders can help in the evolution of lower extremity prosthetic components, which can then lead to improved devices for individuals with transfemoral limb loss.

Limitations

This investigation will not address the varied dosing, timing, frequency, and duration of the device-specific rehabilitation protocol. However, the frequency of PT visits and protocol timing will be evaluated for each participant, which can provide preliminary data for a future study to optimize the rehabilitation strategy. The heterogeneity of the sample population may also limit the generalizability of the outcomes to a more diverse population. In addition, the statistical analysis models will also adjust for specific parameters (eg, age, time since limb loss, and etiology of limb loss), which may limit the sample size and interpretability of the results. The type of microprocessor knee

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used by each participant will not be prescribed and may be a confounding factor. This influence of the microprocessor knee type will be evaluated in the statistical models. Finally, a 4-week assessment following completion of the device-specific protocol may not be sufficient to evaluate any PT rebound effects or long-term changes in gait, specifically regarding the effectiveness of the acute PT intervention on gait biomechanics.

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Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the official policy of the departments of the Air Force, Army, Navy, Defense, Veterans Affairs, or the United States government. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, the Department of Veterans Affairs, the Department of Defense, or any component agency.

Data Availability

All data for this manuscript are included in this published paper. Final results will be available via a publicly available data repository.

Authors' Contributions

JTM, ALP, and LMN participated in conceptualization of the study. JTM, ALP, BDH, and CLD participated in methodology development. JTM, ALP, BDH, DVH, JMC, MJH, SLP, and ANS participated in data collection. JTM, ALP, BDH, DVH, JMC, MJH, SLP, ANS, CLD, and LMN participated in writing, editing, and review of the manuscript. JTM, BDH, MJH, and SLP participated in project administration. JTM, BDH, and SLP participated in supervision of the project and staff. JTM, ALP, CLD, and LMN participated in funding acquisition. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review summary statement.
[PDF File (Adobe PDF File), 121 KB - resprot_v13i1e53412_app1.pdf]

Multimedia Appendix 2
Peer-review response from the investigators.
[PDF File (Adobe PDF File), 126 KB - resprot_v13i1e53412_app2.pdf]

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Abbreviations

6MWT: 6-minute walk test
AMPpro: Amputee Mobility Predictor with prosthesis
CHAMP: Comprehensive High-Level Activity Mobility Predictor
DoD: Department of Defense
HEP: home exercise program
IRB: institutional review board
JAHVH: James A. Haley Veterans' Hospital
PEQ: Prosthesis Evaluation Questionnaire
PT: physical therapy
VA: Veterans Affairs
VANYHHS: Veterans Affairs New York Harbor Healthcare System
WRNMMC: Walter Reed National Military Medical Center

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Protocol

Physical Activity Intervention for Urban Black Women With Asthma: Protocol for a Randomized Controlled Efficacy Study

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Abstract

Background: Black women experience a higher prevalence of poor asthma outcomes and physical inactivity than their White counterparts. Black women comprise a particularly vulnerable group of patients with asthma, with some of the highest rates of asthma in adults, high health care use (emergency department visits and hospitalizations), and the highest crude asthma mortality rate of all race or ethnicity groups. Despite recommendations to engage in regular physical activity, fewer than 15% of Black women meet the 2008 National Physical Activity Guidelines, the lowest of all racial subgroups of adults. Given the connection between physical inactivity and poor asthma outcomes, addressing physical activity among Black women with asthma is imperative.

Objective: This 2-arm randomized controlled trial aims to (1) determine the efficacy of a lifestyle walking intervention on asthma control compared to an education (control) group over 24 weeks, (2) examine the maintenance effects of the lifestyle walking intervention on asthma control at 48 weeks, (3) explore the behavioral mediators (eg, self-efficacy, social support, self-regulation, and daily physical activity levels) and contextual moderators (eg, baseline asthma severity, neighborhood environment, comorbid conditions, and social determinants of health) that contribute to treatment responsiveness, and (4) assess the reach and implementation potential of the intervention.

Methods: The proposed study (ACTION [A Lifestyle Physical Activity Intervention for Minority Women with Asthma]) delivers a 24-week lifestyle walking intervention designed for and by urban Black women with asthma. Participants (n=224) will be recruited through 2 urban health care systems that care for a diverse Black population. Patients will be randomized to one of two groups: (1) ACTION intervention (group sessions, physical activity self-monitoring—Fitbit, and text-based support for step goal setting) or (2) education control (an individual asthma education session and SMS text messages related to asthma education). Outcome assessments will take place at baseline, 12, 24, and 48 weeks. The primary outcome is a change in asthma control from baseline to week 24 as assessed by the asthma control questionnaire-6 (ACQ-6). Secondary outcomes include asthma-related quality of life, health care use, and asthma exacerbations and behavioral outcomes such as self-efficacy, self-regulation, social support, and physical activity.

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Results: This study was funded by the National Institute of Minority Health Disparities in August 2022. We pilot-tested our recruitment and intervention procedures and began recruitment in April 2023, with the enrollment of our first participant in May 2023. The anticipated completion of the study is April 2027.

Conclusions: This study will deliver a new approach to physical activity interventions in Black women with asthma and help to provide guidance for addressing physical activity within this subgroup. This study will also provide a potential framework for future studies in minoritized populations with other disease conditions associated with low levels of physical activity.

Trial Registration: ClinicalTrials.gov NCT05726487; https://clinicaltrials.gov/study/NCT05726487

International Registered Report Identifier (IRRID): DERR1-10.2196/55700

(JMIR Res Protoc 2024;13:e55700) doi:10.2196/55700

KEYWORDS

asthma; physical activity; lifestyle; Black women

Introduction

Background

Asthma is a serious global health problem affecting about 358 million people worldwide [1]. Black women comprise a particularly vulnerable group of patients with asthma, with the highest rates of asthma among adults (11.4%), high health care use (emergency department visits and hospitalizations), and the highest crude asthma mortality rate of all racial or ethnic groups [2,3]. There are multiple factors that contribute to this increased morbidity and mortality including, high rates of exposure to environmental pollution, and limited access to quality health care [4]. Low levels of physical activity (PA) are associated with worse asthma outcomes including higher health care use, poorer lung function, lower asthma control, and decreased exercise capacity [2]. Despite recommendations to engage in regular PA, fewer than 15% of Black women meet the 2008 National Physical Activity Guidelines, the lowest of all adult subgroups [5,6]. Given the connection between physical inactivity and poor asthma outcomes, there is a critical need for interventions to address low rates of PA among Black women with asthma.

Lifestyle PA interventions, such as walking, have been shown to be an effective and sustainable way to engage in regular PA. Research shows that people living with asthma prefer low-intensity activities such as walking, which has a low propensity to cause asthma symptoms [7-9]. Yet, only 2 randomized controlled trials (RCTs) of lifestyle PA (walking) interventions have focused on adults with asthma [10,11]. One occurs in a supervised research or academic setting and the other in the community setting. While both studies found improvements in asthma outcomes (asthma quality of life or asthma control), they were conducted predominantly in White women, and neither assessed the maintenance of effects on asthma control.

Research testing strategies to encourage Black women with asthma to increase their PA is a nascent area of study. While asthma is a known barrier to PA participation due to exercise-induced bronchoconstriction, contextual factors influencing PA engagement among people with asthma have also been identified. This includes previous negative experiences with the disease such as frequent asthma exacerbations; marked limitations in daily living due to asthma; and the effect of extreme weather, pollen, or pollution on asthma [10,12-14]. This is in addition to the many PA barriers urban Black women face, such as social and culturally based preferences for hair and body type, neighborhood characteristics (safety and walkability), family or caregiver responsibilities, and lack of role models or social support [5,15,16].

A Lifestyle Physical Activity Intervention for Minority Women With Asthma

Culturally tailored lifestyle PA interventions among Black women without asthma are more effective and sustainable than more generalized interventions [17]. However, similar interventions have not been applied to PA interventions in asthma. Using a theory-informed approach, A Lifestyle Physical Activity Intervention for Minority Women With Asthma (ACTION), was developed as one of the first culturally tailored lifestyle PA interventions for Black women with asthma. Pilot work demonstrated the feasibility and acceptability of the intervention and yielded preliminary findings of improvement in asthma outcomes and moderate PA [18]. This study takes the next step to examine the efficacy of a lifestyle walking program designed for Black women with asthma.

Conceptual Model

The conceptual model that guided this project is shown in Figure 1. Within the conceptual framework, explanatory relationships among various determinants of PA or factors that influence behavior, intervention strategies, and subsequent participant outcomes have been examined. Important contextual factors include individual demographics (age, income, and education), disease severity, comorbid conditions, and neighborhood environment. To explain motivation to become more physically active, the intrapersonal characteristics of self-efficacy (belief in one's ability to perform a behavior), social support, and self-regulation (the process of guiding one's own thoughts, behaviors, and feelings to reach goals) are used [19].

These intrapersonal characteristics can influence an intervention and thereby influence behavior change. The intervention is targeted to the characteristics of Black women with asthma, such as environmental safety factors, current health, and intrapersonal characteristics. The participant outcomes are those elements that are improved by exposure to the intervention, including PA and health outcomes. The framework specifies that participant outcomes are dynamically related; the greater

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the tailoring of the intervention to the determinants of the behavior, the greater the likelihood of positive outcomes. Theoretical support for the core elements of the ACTION intervention is derived from social cognitive theory and augmented by self-regulation theory, which stems from social cognitive theory [19,20].

Figure 1. Conceptual framework. ACTION: A Lifestyle Physical Activity Intervention for Minority Women With Asthma.

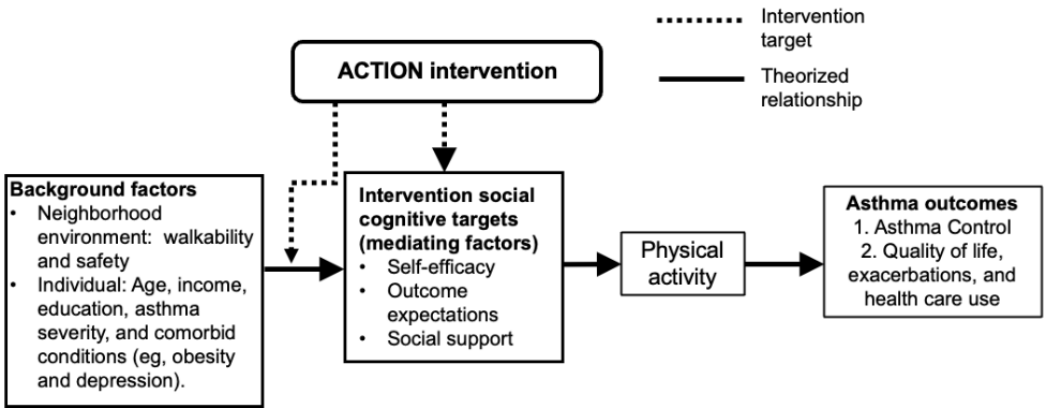

Objectives and Aims

The proposed study has 3 aims involving a total of 224 sedentary urban Black women with asthma.

- Aim 1A is to determine the efficacy of ACTION intervention on asthma control. We will test the hypothesis that at 24 weeks, Black women with asthma who receive the intervention will have a greater improvement in asthma control (asthma control questionnaire [ACQ]) compared to women in the education control group (efficacy end point).
- Aim 1B is to examine the maintenance effects of the ACTION intervention on asthma control at 48 weeks. We will examine the long-term impact of the intervention on asthma control (eg, control and quality of life). We hypothesize the effects of ACTION on asthma outcomes will be maintained at 48 weeks.
- Aim 2 is to explore the behavioral mediators (eg, self-efficacy, social support, self-regulation, and daily PA levels) and contextual moderators (eg, baseline asthma severity, neighborhood environment, comorbid conditions, and social determinants of health) that contribute to treatment responsiveness. Mediation and moderation analyses will be performed with behavioral mediators and contextual moderators.
- Aim 3 is to assess the reach and implementation potential of ACTION. Reach will be measured by the number of potential participants (based on the recruitment pool) who are randomized into the study. Implementation potential will be measured using a mixed methods approach to identify important explanatory factors underlying the performance of the intervention components.

Methods

Project Overview

This study uses a theory-driven intervention (ACTION) to deliver a 24-week lifestyle PA intervention designed for and by urban Black women with asthma. Participants are recruited through 2 urban health care systems that care for a diverse urban Black population. Patients are randomized to one of two groups: (1) ACTION intervention (group sessions, PA self-monitoring, and text-based support for goal setting) or (2) education control (an individual asthma education session and text messages related to asthma education). Participants are followed for an additional 24 weeks after the intervention to assess for the maintenance of intervention effects on asthma health outcomes.

This efficacy study focuses on asthma outcomes, explores behavioral mechanisms of the intervention, and assesses factors that influence its reach and implementation potential.

Ethical Considerations

This study is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and approved by the relevant institutional review boards at the University of Chicago (22-0911). The University of Illinois Chicago and the University of Texas at Austin have ceded institutional review board reliance to the University of Chicago institutional review board. This study has been registered at ClinicalTrials.gov (NCT05726487).

Study Design

This is a 2-arm RCT enrolling participants at the University of Chicago and the University of Illinois at Chicago in which 224 Black women with asthma will be randomly assigned to an education control group or receive ACTION intervention for 24 weeks (Figure 2). The remaining 24 weeks is the maintenance phase, and participants in the intervention group will receive 1 booster group session at ~36 weeks. Assessments will occur at 0, 12, 24, and 48 weeks.

The primary efficacy end point is a change from baseline to week 24 asthma control as assessed by asthma control questionnaire-6. We hypothesize that ACTION will be superior to education control for improving asthma control by week 24. The 48-week time point is important for examining behavioral mediators, contextual moderators, and maintenance of intervention effects.

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Figure 2. Study design. ACTION: A Lifestyle Physical Activity Intervention for Minority Women With Asthma. *Participant must return accelerometer and have adequate data (10 hours of data for 3 days or more) prior to randomization **Individual/Group sessions are in-person except group session 3 and 5 which are remote.

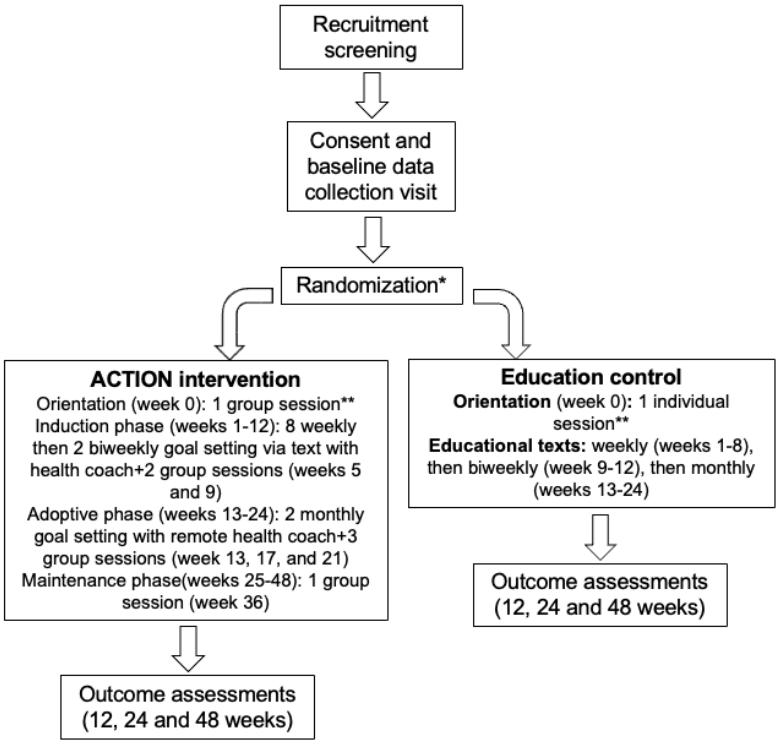

Participants and Eligibility

Recruitment

The primary recruitment strategy uses electronic health records to identify patients who meet the basic inclusion criteria: age≥18 years old, female, Black or African American, International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis of asthma, and no ICD-10 diagnosis of chronic obstructive pulmonary disease (Textbox 1). An electronic health record data of patients meeting these criteria is obtained for each respective institution. Patient registries, in-clinic referrals, and flyers are also used as recruitment methods. Emails, SMS text messages, and postcards containing information about the study and a link to the eligibility screening survey are sent to randomly selected batches of potential participants.

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Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Self-identify as female and Black or African American
- Age≥18 years
- Physician diagnosed asthma that is suboptimally controlled based on Asthma Control Test (<20) or history in the past year of an asthma exacerbation (a need for systemic corticosteroids or hospital admission or emergency treatment for worsening asthma)
- Willing to enroll and provide written informed consent
- Willing to be randomized to 1 of the 2 study arms
- Has a smartphone or tablet with unlimited texting capabilities and uses text messaging at least daily

Exclusion criteria

- Plans to move from the Chicagoland area during the study period
- Unable to ambulate without the use of a wheelchair or scooter
- Currently pregnant, less than 3 months postpartum, or pregnancy anticipated during the study
- Significant medical (eg, unstable heart disease, uncontrolled high blood pressure, active cancer treatment in the past 1 year, and end-stage organ failure) or psychiatric (eg, active bipolar disorder and psychosis) comorbidities
- Diagnosis of chronic obstructive pulmonary disease (emphysema or chronic bronchitis) suggested by patient report of doctor diagnosis or smoking history (≥20 pack year history)
- A contraindication to exercise as indicated by the exercise assessment and screening tool unless written permission by a health care provider
- Participation in another structured physical activity program
- Asthma exacerbation, defined by an urgent care visit for asthma in the last 4 weeks, or the need for an acute course of systemic corticosteroids for asthma in the last 4 weeks
- Family or household member of another participant or staff member
- Inability to speak, read, or understand English
- Investigator discretion for safety or protocol adherence reasons

Eligibility Screening

Potential participants can self-screen using a REDCap (Research Electronic Data Capture; Vanderbilt University) eligibility screening form. This screener is accessed by scanning a QR code on this study's flyers and postcards or through a link that may be emailed or texted to potential participants. This survey is also verbally administered by the study staff over the phone.

If potential participants are immediately eligible, they are asked to schedule their baseline visit. Those who do not immediately meet the eligibility criteria or need medical clearance will be contacted by the study staff.

Baseline Assessment, Randomization, and Blinding

The baseline visit begins with the informed consent process facilitated by study staff. Participants are asked to complete study surveys (patient demographics, asthma demographics, Asthma Control Questionnaire, Asthma-related Quality of Life Questionnaire, Asthma Safety Measures, Adult Asthma Adherence Questionnaire, Patient Health Questionnaire Depression Scale Scored, PROMIS SF v 1.0-Sleep Disturb, SDQ-SA, PWMAQ, Exercise Self-Regulation, Self-efficacy for Walking Scale, Social Support for Walking Scale, Social Support and Exercise Survey, Active Where); baseline spirometry [21] and anthropometrics are obtained by trained study staff. Participants at 1 site are also asked to wear an accelerometer for 7 days.

Eligible participants will be randomized following recruitment and of all baseline measures, using stratified randomization in REDCap at each site after baseline data collection is complete. Stratification will be based on age (18-45 and 46+ years) and current BMI (≤25 and >25 kg/m^2). Blinding of participants is not feasible for this study. Participant's health care providers are blinded to group allocation.

Intervention

Overview

ACTION is a behavioral lifestyle intervention that promotes lifestyle PA in accordance with the current PA guidelines in the United States [17]. This intervention is a 24-week group lifestyle PA intervention consisting of 7 group sessions, PA self-monitoring, and text-based support for goal setting. The active period of the intervention is 24 weeks. Trained interventionists and remote health coaches deliver the intervention via a combination of in-person group walking sessions and text-based goal setting. Trained research staff provide a Fitbit for the participant and deliver the text messaging component of the intervention.

Group Sessions

Session 1

Participants attend an in-person or Health Insurance Portability and Accountability Act (HIPAA)–compliant audio or video

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platform (eg, Zoom) group session on "Becoming Physically Active with Asthma." The group session includes a 45-minute asthma education session, based on the American Lung Association's Asthma Basics course, led by a Black, female asthma educator. Participants in the intervention group are given a manual with educational materials, which include information on increasing PA with asthma. Following the education content, each intervention group participant receives a Fitbit Charge 5 for self-monitoring of steps and heart rate. Specific step-by-step instructions on setup and use of the Fitbit monitor are provided with individual support as needed in the group setting. The study team reviews Specific Measurable Attainable Relevant and Time bound (SMART) goal setting [22], assesses text preferences, and sets individualized step goals based on their baseline PA levels.

Sessions 2-7

Women attend a 2-hour, in-person, or video remote group meeting at a convenient time during the induction or adoptive phases (weeks 0-24) and once during the maintenance phase (weeks 25-48). Participants from the individual sites are kept separate and do not attend group sessions together. Group session content is described in Textbox 2.

After 24 weeks of active intervention, participants randomized to ACTION no longer receive remote health coach text messages and attend monthly group sessions. A booster group session at 36 weeks will occur for the intervention group only.

Textbox 2. Content of ACTION (A Lifestyle Physical Activity Intervention for Minority Women With Asthma) group sessions.

Session 1 (week 0)

- Safely exercising with asthma: "Becoming Physically Active with Asthma"
- Receive Fitbit and discuss setting step goals

Sessions 2-7 (weeks 5,9,13, 17, 21, and 36)

- Video (10 minutes) on physical activity topics (eg, identifying realistic expectations for PA outcomes with asthma, handling personal and environmental problems that interfere with physical activity, and handling relapses)
- Group discussion and problem-solving (45 minutes)
- Group stretching and walking (20 minutes)

PA Tracking as an Intervention Component

Each intervention participant is given a Fitbit Charge 5 that counts steps per day, distance, active minutes (time spent in moderate to vigorous activity), sedentary time, and heart rate. Participants work with health coaches (as above) to set their step goals and monitor their PA on the Fitbit App. Participants are required to download the Fitbit app on their phone or tablet. The Fitbit mobile app and device require the creation of individual digital accounts with Google for all study participants. During the study, participants will use their study-created Google account to interact with the features of the Fitbit mobile app. Upon completion of the program, participants will be able to transfer their Fitbit device to an account using their personal Google login for continued use of the device.

Fitbit data are managed through iCardia. The iCardia platform [23] is used to remotely collect real-time PA data from study participants' Fitbit app and to send personalized SMS text messages to participants' cell phones (Figure 3). iCardia (University of Illinois at Chicago) is a secure password-protected system that comprises user-friendly visualization and data exportation tools, allowing key research personnel to view participants' Fitbit data in the form of graphs every time participants sync their wearable tracker with the Fitbit mobile app. Study participants do not have access to iCardia; they will only interact with the Fitbit mobile app and activity tracker. The SMS text messaging feature is integrated with the iCardia clinical dashboard and uses Twilio's application programming interface to send messages via the SMS protocol.

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Figure 3. Screenshot of the iCardia platform.

Remote Health Coach and Individualized Step Goal Setting and Tracking

Study participants will work with the health coach through texts to set a SMART goal [22]. This will begin within 1 week of the completion of session 1. The process includes contingency planning (what if…). Goals will be set once a week for 8 weeks, every 2 weeks for weeks 9-12 sessions, and monthly through 24 weeks. We have set a realistic PA goal for intervention participants of 3000 steps per day of moderate intensity above each participant's baseline (based on Fitbit-based step counts per day), recognizing that baseline levels of activity will vary across individuals. Thirty minutes of walking at moderate intensity produces an estimated average of 3000 steps in most free-living adults [24]. Health coach texting will be managed through iCardia (described above). Health coaches can monitor Fitbit steps to evaluate goal attainment and send texts to support self-regulation via the text messaging protocol. The Fitbit data collected in iCardia will be used to generate process indicators but not as the primary measure to assess changes in health-enhancing PA (moderate to vigorous intensity physical activity [MVPA]). Health coaches will be sensitive to health status that may impact the ability to escalate steps. Weekly meetings will be conducted with health coaches to ensure texts are following the SMART goal framework and discuss any safety issues or questions.

Education Control Group

The education control group will receive (1) 1 group asthma education session similar to session 1 described above and (2) text messages with asthma facts and tips (see Table S1 in Multimedia Appendix 1). The asthma education session consists of a 45-minute video on basic asthma education based on American Lung Association's asthma basics content followed by a live Q&A with an asthma educator. The video was culturally tailored using feedback from stakeholders and includes a Black female asthma educator and other Black women with asthma. The SMS text messages with asthma facts and tips were also developed using feedback from stakeholders and will be delivered twice weekly (weeks 1-8), biweekly (weeks 9-12), and monthly (weeks 13-24). At the completion of the study, participants in the education control group will receive the study manual, a pedometer, and access to the videos presented in the ACTION intervention group sessions.

Measures

Asthma Measures

Asthma control will be measured using the validated ACQ [25]. Asthma quality of life will be measured using the mini-asthma quality of life measure, a well-validated survey [26]. Asthma exacerbation will be defined as the need for systemic corticosteroids, hospital admission, or emergency treatment for worsening asthma. This will be self-reported, and the time frame will be captured at 3- and 6-month time frames (Table S2 in Multimedia Appendix 2). Health care use is defined as the number of urgent care or emergency room or hospitalization visits. This will be self-reported, and the time frame will be in 3- and 6-month time frames (Table S2 in Multimedia Appendix 2). Spirometry will be performed using standard procedures at baseline, 24, and 48 weeks. Asthma severity will be assessed per the National Heart Lung and Blood Institute National Guidelines for Asthma management based on current asthma treatment [27].

PA Measures

Given that the intervention centers on increasing PA levels through walking, it is important to accurately assess the changes in health-enhancing PA among intervention and control participants throughout the study period. Health-enhancing PA

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is defined as having MVPA and can occur in the domains of discretionary time, travel, home, or work [17]. Our intervention focuses on increasing overall MVPA levels by adding time spent in moderate-intensity PA during discretionary time, through walking. We will measure domain-specific PA through self-reported data for the full sample. We will also measure PA objectively in half of the sample, as this is a more cost-prohibitive assessment instrument.

Accelerometry

MVPA (minutes per day) at baseline (before randomization), 12, 24, and 48 weeks will be assessed objectively using accelerometry. During each assessment period, accelerometer data will be collected over 7 consecutive days using the ActiGraph wGT3X-BT activity monitor (ActiGraph, LLC), a small, triaxial piezoelectric accelerometer (4.6 cm×3.3 cm×1.5 cm; 19 g) that will be worn around the waist on an elastic belt. Accelerometry data will be collected using a standardized protocol. ActiGraph monitors have been extensively validated in laboratory and free-living conditions [28]. At the first data collection appointment, study staff will introduce the accelerometer and provide participants with verbal instructions and a package that includes (1) an initialized accelerometer, (2) detailed written wear instructions, (3) tracking log, (4) contact information, and (5) a padded prepaid trackable envelope to return the devices after concluding the 7-day wear period.

In the tracking log, participants will enter the (1) time they put the monitor on in the morning, (2) time removed it in the evening, and (3) time that the monitor was removed and replaced for ≥30 minutes throughout the day (eg, bathing or swimming activities). Raw triaxial data will be sampled at 40 Hz for 7 consecutive days. Once the accelerometer and tracking log are returned by the participant, data will be downloaded by the study staff and prepared for processing and analysis. Data will be processed using ActiLife software (ActiGraph) through a digitally matched filter, reintegrated up to a 60-s epoch, and screened for wear time using the Choi algorithm [29]. Weekly summary accelerometer estimates will be averaged (across days) for all participants with ≥4 valid days of ≥10 hours per day of wear time (minimum wear time to consider the data valid for analysis). If insufficient wear time is detected, the participant will be contacted and asked to rewear the device to provide valid data. Average accelerometer counts (per minute per day) will be calculated using summed daily counts detected over wear periods, and vector magnitude will be calculated as the square root of the sum of the squares obtained from each axis (ie, 3) of data. Time (ie, minutes per day) spent sedentary and in light-, moderate-, and vigorous-intensity physical will be estimated using Freedson cut points (for adults) based on triaxial data [30]. Data checks, including a descriptive analysis of the accelerometer estimates, will be performed quarterly.

Self-Reported Discretionary Time and Travel-Based PA

Self-report data adds rich context that accelerometers lack [31]. Our self-report measures will provide information on the domain (eg, recreational and transportation) of PA. These data will be important to quantify the effect of the intervention in increasing leisure-time walking (its main intention), as well as any potential unintended consequence in increasing or decreasing time spent on other types of activities. Participants will self-report PA using the Past Week Modifiable Activity Questionnaire (PWMAQ). The Modifiable Activity Questionnaire is a self-report instrument that assesses leisure PAs over the past 7 days [32,33]. The structure of the PWMAQ is similar to the Modifiable Activity Questionnaire and includes questions that quantify occupational activity (eg, sedentary, low, and high active occupations), active transport, and common sedentary behaviors. The PWMAQ includes information on 38 leisure-time PAs common among diverse adults. The PWMAQ has been shown to be a reliable and valid measure of PA compared to accelerometry and physical fitness [34,35].

Additional PA-Related Measures

Self-efficacy for walking, social support for exercise, and self-regulation will also be assessed as they constitute behavioral mediators for attaining increased PA levels, and the physiologic response to increases in PA, respectively. Details on these measures can be found in Table S3 in Multimedia Appendix 3.

Contextual Moderators

Contextual moderators will be collected at the in-person baseline data collection visit. The neighborhood environment will be assessed using a validated survey about neighborhood safety, crime, and areas to engage in PA [36]. Social determinants of health, including age, income, education level, marital status, and economic hardship will be assessed using validated questions that the principal investigator has used in prior studies. These have been chosen as they can impact PA levels [37,38]. The comorbid conditions of interest are obesity and depression as they are known to moderate PA levels and asthma outcomes [39,40]. Obesity is defined as a BMI ≥30 kg/m^2, and depression will be assessed by a validated depression questionnaire, Patient Health Questionnaire Depression Scale-8 [41].

Implementation Measures

We propose an explanatory sequential mixed methods design in which quantitative analyses are followed by qualitative analyses to maximize our understanding of the implementation of ACTION [42,43]. The quantitative data will include detailed process metrics and surveys, and qualitative data will include brief interviews with participants. Process metrics will be collected based on the number of participants screened and randomized. Surveys to assess the acceptability of the intervention components will be collected at the end of each group session and at the end of the intervention (after group session 6). Evaluations of the intervention will be conducted using open-ended questions with intervention participants at 24- and 48-week data collection visits. Questions will focus on aspects of the intervention they found helpful, barriers to engagement in each component of the intervention (eg, groups, remote health coach, and Fitbit), and suggestions for improvement. General prompts will be used to orient qualitative data descriptively on the core intervention components. The qualitative portion of the intervention will be conducted by trained and experienced data collectors at the end of the brief quantitative data collection, audio-recorded, and professionally transcribed.

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Data Analysis Plan

Data will be analyzed based on the intent-to-treat principle in this multisite RCT. We will use descriptive statistics to describe the sample by intervention group, and any assumption behind each statistical method will be examined during the analysis. Missing data will be handled by each model's assumption or by using multiple imputation with a fully conditional specification approach, as appropriate [44]. A 2-sided *P* value less than .05 would be considered statistically significant, and the exact *P* value will be reported. All quantitative analyses will be conducted by using SAS (version 9.4; SAS Institute Inc) and R (version 4.0.2; R Core Team).

The primary research outcome for aim 1A is the differences in ACQ score between baseline and 24 weeks for aim 1A and between baseline and 48 weeks for aim 1B. This will be compared between education control and ACTION intervention groups first using 2 sample *t* test to examine the efficacy and the maintenance effect of the proposed intervention, respectively. Two-tailed statistical tests will be conducted throughout the entire analysis unless specified otherwise. A linear mixed model with a subject-level random intercept then will be built on the same outcome in its original scale having time (12 weeks vs baseline; 24 weeks vs baseline; 48 weeks vs baseline), group (ACTION vs education control), and their interaction as the main factors while adjusting for site, recruitment wave, and any imbalanced confounder [45]. This model will allow us to estimate the efficacy of the intervention through the interaction terms after controlling for confounders and subject dependence. Moreover, any missing data can be handled by this model under the missing at random assumption. The estimated coefficients on the mean scale of the outcome will be reported, along with their SEs, 95% CIs, and *P* values. The similar modeling approach mentioned above using generalized linear mixed models instead will be applied to secondary outcomes (asthma quality of life, health care use, and asthma exacerbations) as secondary analyses.

For aim 2, we will explore the potential mediation effects of multiple variables on the relationship between the intervention and clinical outcomes. That is, a portion of the intervention effect on an outcome may be going through the path via a mediator indirectly. Through mediation analysis, the direct effect, the indirect effect also known as the mediated effect, and their total effect will be measured using the approach by Yu et al [46,47] along with their CIs via bootstrapping. The multiple mediators of interest here include social support, self-regulation, self-efficacy, and PA, while the clinical outcomes of interest are the ACQ score and mini-AQLQ score. To avoid the problem of mediation analysis with cross-sectional data, we define the mediation relationship generally noted as *X-M-Y*, using X_{BL} as the exposure at baseline, $M_{j,24w}$ as the *j*th mediator at 12 weeks (j=1,…, 6), and $Y_{k,48w}$ as the *k*th outcome at 48 weeks (k=1,2) [48]. As a secondary analysis, multilevel mediation analysis using the method by Yu and Li [49] will also be considered. For moderation analysis, we will examine moderators including comorbid conditions (depression and obesity), social determinants of health (age, income, and education level), asthma severity (mild, moderate, and severe), and neighborhood environment (walkability and safety) by separately adding their interaction terms with the treatment group to the models mentioned for aim 1A to estimate their moderating effects on treatment responsiveness. We will focus on several plausible behavioral mechanisms. We anticipate improved PA will lead to improved asthma outcomes (control and quality of life) and a reduction in self-reported exacerbations and emergency health care use.

For aim 3, we will report process metrics, such as recruitment rate, monthly to assess reach overall, within key patient subgroups, and each site. Simple descriptive statistics and 95% CIs will be used to summarize measurement for reach and implementation potential at the end of the study. To identify participant characteristics (eg, age, income, and education level) or site-level factors that may be associated with reach, we will examine those associations using the chi-square test or Fisher exact test for categorical variables and the Kruskall-Wallis test for continuous variables. For analysis of qualitative data, the deidentified interview transcripts will be uploaded to the qualitative data software (eg, NVivo [OSR International] or Dedoose [University of California, Los Angeles]). Qualitative assistants will work with qualitative experts to code the data. All coders will initially read all 112 transcripts to become familiar with the data. Thematic interpretation will focus on individual, social, and structural factors associated with acceptability and reasons for variability in uptake and effectiveness of the intervention components. Ten transcripts will be independently coded by all coders. The codes will be reviewed and discussed collectively to develop a shared understanding of how the codes should be applied to the transcripts. This process of independent coding will be repeated ≥2 times until a consistent agreement is reached. Coded transcripts will be sorted to identify thematic groupings. The thematic groupings will be reviewed to identify emergent themes within each domain of the coding framework and quotes that best represent each domain.

Results

This project received funding in August 2022 and received institutional review board approval in July 2022. The first year of this project was focused on hiring and training staff, regulatory approvals, setting up data collection processes, and recruitment. We pilot-tested our recruitment and intervention procedures and began recruitment in April 2023. At the time of manuscript submission, 76 participants have been recruited. We anticipate study completion in 2027.

Discussion

Principal Findings

As one of the first lifestyle PA interventions in asthma to explore behavioral mechanisms, and the only focusing on a group most in need—Black women, this study is expected to contribute importantly to this very limited body of literature and offer useful insights for PA interventions in asthma. Our intervention focuses on walking as a lifestyle approach in urban Black women with asthma, which has been shown to be the preferred method of PA among Black women and people living with

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asthma. Walking is affordable, accessible, and sustainable even for Black women residing in urban neighborhoods with high levels of crime or low-resourced neighborhoods. This approach to PA also considers activities done in leisure, household, transportation, and occupational roles. We also use a patient-centered perspective, which has yet to be used in developing PA interventions in adults with asthma. Modifications to the intervention leverage the high levels of technology use in this population while reducing the participant burden associated with in-person sessions [50]. Moreover, from a public health standpoint, interventions using technology-based platforms can provide researchers the ability to reach a large number of people at a relatively low cost, which ultimately leads to a greater public health impact.

Anticipated Challenges and Limitations

As this study will take place in the Midwest, there is a concern that the weather may have an impact on the ability to engage in walking during the winter and even summer months. The intervention addresses this through providing free or low-cost resources on where to exercise indoors during challenging weather. Furthermore, the study team tailors the text messages to local weather and air quality alerts. For example, during the Canadian wildfires in July 2023 when Chicago was experiencing the poorest air quality in the world, we cautioned participants to monitor the air quality index before going outdoors but also provided alternatives to walking outdoors. During our pilot, the participants requested more flexibility with the in-person sessions and have the option to remote in with a secure video platform, which we incorporated into this study. There may still be challenges in having participants attend all the in-person group sessions, but we will work with the participants to find an optimal time to attend, and if needed, allow for a hybrid group session model with some participants in-person and others virtual. Although not an issue in pilot work, it is possible that differential dropout across study groups may occur. To mitigate this concern, participants in the control arm will receive asthma education session text messages at a similar frequency as the intervention participants. In the pilot study, the asthma education session was valued by participants in the control arm. Nonetheless, should problems arise, coinvestigators and a recruitment or retention core will be engaged for input on changes to improve retention. Finally, the information gained from our implementation measures will be critical for revising the conceptual model and rethinking the choice of intervention components to be tested in future studies and will also inform theory development in implementation science.

Conclusions

The findings from this study will provide insight into the next steps for addressing PA in Black women with asthma. It will deliver a new approach to PA interventions in chronic lung diseases such as asthma and a better understanding of the underlying behavioral mechanisms among a high-risk underresearched population. This field is in its infancy and showing the short- and long-term efficacy of a culturally tailored lifestyle PA intervention in a vulnerable patient population, as well as identifying the behavioral mechanisms, are important and will be critical. This study will also set a standard for future studies in minority populations with other disease conditions associated with low levels of PA.

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Authors' Contributions

ED and ET drafted and edited the manuscript. AC, YFC, DEH, SK, WK, IM, EO, KP, VGP, TR, DS, and BW reviewed and edited the manuscript. LKS assisted with study conceptualization and reviewed and edited the manuscript. SMN conceptualized the study and assisted with drafting and editing the manuscript. YFC drafted the statistical analysis plan.

Conflicts of Interest

SMN reports funding from National Institutes of Health (NIH), Asthma and Allergy Foundation of America, and receives consulting or royalty fees from GlaxoSmithKline, PRIME education, Wolters Kluwer, and Springer. VGP reports funding from the NIH and Agency for Healthcare Research and Quality and receives consulting fees from Humana regarding patient education programming.

Multimedia Appendix 1
Sample asthma education text messages.
[DOCX File , 16 KB - resprot_v13i1e55700_app1.docx]

Multimedia Appendix 2

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Study procedures occurring at each time point.
[DOCX File , 16 KB - resprot_v13i1e55700_app2.docx]

Multimedia Appendix 3
Outcome measures and variables for A Lifestyle Physical Activity Intervention for Minority Women With Asthma (ACTION).
[DOCX File , 20 KB - resprot_v13i1e55700_app3.docx]

Multimedia Appendix 4
Peer-review report by the National Institute of Minority Health and Disparities.
[PDF File (Adobe PDF File), 145 KB - resprot_v13i1e55700_app4.pdf]

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Abbreviations

ACQ: asthma control questionnaire
ACTION: A lifestyle Physical Activity Intervention for Minority Women With Asthma
HIPPA: Health Insurance Portability and Accountability Act
ICD-10: International Statistical Classification of Diseases, 10th Revision
MVPA: moderate-to-vigorous intensity physical activity
PA: physical activity
PWMAQ: Past Week Modifiable Activity Questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMART: Specific Measurable Attainable Relevant and Time bound

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Protocol

Telehealth Behavioral Intervention for Chronic Disease Self-Management in Adults With Physical Disabilities (My Health, My Life, My Way): Protocol for Intervention Fidelity and Dashboard Design for a Randomized Controlled Trial

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Abstract

Background: Individuals with physical disabilities experience higher rates of chronic health conditions than individuals without physical disabilities. Self-management programs that use health coaching are effective at eliciting health behavior change in health outcomes such as goal setting, adherence, and health care use. Additionally, web-based resources such as telehealth-based technologies, including SMSS text messaging, web-based applications, and educational multimedia content, can complement health coaching to improve health-related behaviors and the use of health services. The complexity of studies using these resources requires a fidelity protocol to ensure that health behavior studies are administered properly.

Objective: The My Health, My Life, My Way fidelity protocol provides methods, strategies, and procedures of a multifaceted telehealth program for individuals with permanent physical disabilities and chronic health conditions. This health behavior study is a randomized controlled trial with four study arms: (1) scheduled coaching calls with gamified rewards, (2) no scheduled coaching calls with gamified rewards, (3) scheduled coaching calls with fixed rewards, and (4) no scheduled coaching calls with fixed rewards. To guide the fidelity protocol developed, we used the National Institutes of Health Behavior Change Consortium framework (NIH BCC).

Methods: The fidelity intervention protocol was developed by using the 5 primary domains provided by the NIH BCC: study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills. Following the NIH BCC guidelines and implementing social cognitive theory, this study is designed to ensure that all study arms receive equal treatment across conditions and groups. Health coaches and providers will be trained to deliver consistent health coaching, and thus participants will receive appropriate attention. Educational content will be developed to account for health literacy and comprehension of the material. Multiple fidelity intervention steps such as coaching call logs, regular content review, and

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participant progress monitoring will translate to participants using the skills learned in their daily lives. Different monitoring steps will be implemented to minimize differences among the 4 treatment groups.

Results: My Health, My Life, My Way has been approved by the institutional review board and will begin enrollment in January 2024 and end in December 2024, with results reported in early 2025.

Conclusions: Intervention fidelity protocols are necessary to ensure that health behavior change studies can be implemented in larger real-world settings. The My Health, My Life, My Way fidelity protocol has used the guidelines by the NIH BCC to administer a telehealth intervention combined with health coaching for individuals with physical disabilities and chronic health conditions. This fidelity protocol can be used as a complementary resource for other researchers who conduct similar research using telehealth technologies and health coaching in real-world settings.

Trial Registration: ClinicalTrials NCT05481593; https://clinicaltrials.gov/study/NCT05481593

International Registered Report Identifier (IRRID): PRR1-10.2196/53410

(JMIR Res Protoc 2024;13:e53410) doi:10.2196/53410

KEYWORDS

chronic health conditions; telehealth; health coaching; self-management; intervention fidelity protocol

Introduction

Background

According to the US Centers for Disease Control and Prevention, nearly 60% of Americans currently live with a chronic health condition, such as diabetes, heart disease, or hypertension [1]. The prevalence of individual conditions varies and affects activities of daily living differently for each subpopulation. For example, nearly 10% of Americans live with a version of diabetes, including type 1, type 2, and prediabetes [2]. For heart disease, the most common form is coronary artery disease, which is prevalent in the United States in approximately 7% of the population [3]. For example, individuals with physical disabilities experience higher rates of chronic conditions than individuals without physical disabilities [4,5]. Different approaches have been used to manage chronic health conditions and their related symptoms. Prior research has shown that self-management programs, which refer to one's ability to care for their health, are able to promote positive self-care, increase physical activity, and monitor dietary behavior for individuals with chronic health conditions [6].

Different approaches have been used to provide mechanisms for individuals with chronic health conditions to successfully manage their health. Telehealth interventions have been used as effective strategies for self-management across a variety of chronic health conditions [7-10]. A primary benefit of using telehealth technologies for self-management is the convenience of engaging in programs at flexible times and locations, such as home settings [11,12]. Telehealth programs also provide benefits for clinicians and health care providers, that is, the ability to engage with patients remotely to provide adequate care and promote healthy behaviors. However, there are no accessible and inclusive telehealth programs for individuals with physical disabilities. The lack of inclusive programming for individuals with physical disabilities highlights barriers that this population experiences, including transportation and inadequate time to participate in telehealth interventions [13].

The lack of programming for individuals with physical disabilities demands an immediate remedy. Therefore, we are developing a telehealth program that includes a website with inclusive multimedia educational content combined with access to trained health coaches to provide optimal self-management programming to individuals with physical disabilities. As part of this intervention, we will use an artificial intelligence (AI)–assisted, customized lifestyle program to increase the overall fidelity of the intervention and optimize health coaching resources for telecoaching.

Reporting Fidelity

To ensure that a health behavior intervention is delivered as intended, it is necessary to develop fidelity protocols to minimize issues with protocol implementation. The complexity of telehealth interventions, the research designs used, and the multiple development teams (health coaches, technical staff, etc) introduce several challenges to maintaining overall study fidelity. Because variations exist in health behavior studies, guidelines have been developed to provide recommendations and strategies for using fidelity concepts in future projects. The National Institutes of Health Behavior Change Consortium (NIH BCC) published recommendations for implementing fidelity concepts for health behavior interventions. The specific areas covered by the NIH BCC include recommendations for study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills [14]. Therefore, we aim to use the guidelines set forth by the NIH BCC to describe and report the fidelity protocol for the My Health, My Life, My Way study. This intervention will use mobile health technology in conjunction with health coaching to create a comprehensive web-based self-management program for individuals with physical disabilities who experience chronic health conditions. Furthermore, the development of this protocol addresses the 5 domains of fidelity monitoring set forth by the NIH BCC and will provide valuable insight into reproducing future telehealth interventions.

Methods

Overview of the Study and Fidelity Protocol

The My Health, My Life, My Way study aims to optimize an AI, telehealth-based self-management program for individuals with physical disabilities and chronic conditions. This program

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includes a telecoaching website where participants can communicate with health coaches through different communication mediums (ie, texting and phone calls), access customized, educational material related to their specific health conditions, and track health-related behaviors such as physical activity and nutrition. Additionally, the program aims to actively encourage positive lifestyle changes by incorporating features that promote healthy behaviors. These features encompass aiding users in creating well-balanced meal plans and encouraging regular physical activity. By integrating these elements, the program provides a comprehensive toolset for both fostering healthier habits and receiving expert guidance, ultimately contributing to participants' overall well-being.

Within the website system, AI-embedded technology will be implemented that will have access to an ingredient and recipe database system which will offer personalized dietary suggestions based on the participant's dietary preferences or restrictions, cooking resources, financial status, and cooking skills. Similarly, the system will be able to provide physical activity recommendations based on health status, preferred activities, and climate. Health coaches will have access to participants' web-based website to monitor and approve health behavior changes and goals set by the participants. Individuals will be able to communicate with the health coaches through multiple communication mediums, including smartphone apps, SMS text messaging, phone calls, and conversation agents (ie, Amazon Echo). Educational content provided on the website will be created and tailored to individuals with physical disabilities. The combination of these technologies, with a focus placed on the participant, will minimize the time, effort, and costs of using health coaching staff; promote adherence and regular use of the system; and ultimately promote health self-management.

The purpose of this study is to use the Multiphase Optimization Strategy to pilot-test and identify the optimal combination of intervention components that are effective in improving health-related quality of life in adults with physical disabilities and chronic health conditions. We will be using a pilot randomized controlled trial study design, in which 200 adults with physical disabilities and chronic health conditions will be randomized into 1 of 4 groups with 50 participants in each group: (1) scheduled coaching calls with gamified rewards, (2) scheduled coaching calls with independent rewards, (3) no scheduled coaching calls with gamified rewards, and (4) no scheduled coaching calls with independent rewards. Those not receiving scheduled coaching will be able to communicate with health coaches as needed to discuss health-related behaviors and goal setting. Participants will be able to communicate with the health coaches through communication methods such as SMS text messages, phone calls, and the telehealth website. Recruitment will be conducted nationally through web-based advertisements and social media accounts associated with the National Center on Health, Physical Activity and Disability, and ResearchMatch platform. Inclusion criteria include (1) 18 years of age or older; (2) diagnosis of heart disease, chronic lung disease, or type 2 diabetes; (3) living with a permanent physical disability such as spinal cord injury, spina bifida, multiple sclerosis, or stroke; (4) ability to converse and read English; and (5) smartphone or computer access.

Within the intervention, participants will be randomly assigned to 1 of 4 groups (Table 1). The total duration of the program is 24 weeks (6 months). Those receiving scheduling coaching calls will have weekly coaching calls with trained health coaches who will provide customized recommendations and education based on participant needs, including physical activity, nutrition, and other health-related topics. Those not receiving scheduled coaching calls will have the capability to contact health coaches through the telecoaching website, SMS text messages, or phone call to discuss similar health-related objectives. Participants will also receive a physical activity tracker (FitBit) to track activity during the program.

We incorporated the NIH BCC Treatment Fidelity recommendations to develop our fidelity protocol to monitor fidelity and ensure the external and internal validity of the intervention.

Table 1. Research design.

Gamification rewards	Coaching calls	
	Scheduled coaching calls	No scheduled coaching calls
Gamification-based rewards	Scheduled coaching calls with gamified rewards	No scheduled coaching calls with gamified rewards
Rewards independent of gamification	Scheduled coaching calls with rewards independent of gamification	No scheduled coaching calls with rewards independent of gamification

Ethical Considerations

The protocol for the My Health, My Life, My Way study was approved by the University of Alabama at Birmingham's institutional review board (300009485). Enrollment is expected to begin in January 2024 and study completion is expected to end in December 2024.

Study Design

Overview

The principles of the NIH BCC state that fidelity interventions must make certain that (1) appropriate theory and clinical practice are aligned with procedures and implementation, (2) treatment and dose across participants are equal, and (3) possible setbacks in intervention implementation are addressed. Textbox 1 provides the study design and monitoring plan for My Health, My Life, My Way.

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Textbox 1. Fidelity of the study design and monitoring plan.

Goal

- Intervention will be congruent with the presented theory and practice
- Ensure equal treatment and dose are provided across and within all conditions
- Implementation setbacks are addressed

Description from National Institutes of Health Behavior Change Consortium

- Operationalize treatment to optimally reflect theoretical roots and precisely define variables most relevant to the "active ingredients" of the intervention
- Setbacks in implementation are addressed

Fidelity plan for My Health, My Life, My Way

- Monthly review of coaching call checklist
- Monthly review of coaching call logs
- Quarterly assessment of random coaching call audio recordings
- Quarterly assessment of education content provided to participants
- Weekly review of participant journals
- Monthly review of the telecoaching platform and events log
- Quarterly assessment of participant log-ins and time spent on the platform
- Weekly team meetings to discuss participant progress and protocol adherence

Presented Theory and Clinical Practices Are Congruent With Procedures and Implementation

My Health, My Life, My Way is grounded in Social Cognitive Theory and is designed to serve as a support system and communication platform among health coaches, participants with disabilities and their caregivers, and health care providers. The website will allow joint efforts for all parties to promote support among friends and family, regular physical activity and healthy dietary behaviors, and goal settings.

Equal Dose of Treatments Across Participants

As this study is a 2×2 factorial design, half of the participants will not receive scheduled coaching calls, while the other half will receive scheduled coaching calls. The duration and frequency of coaching calls for the scheduled group will be consistent to ensure an equal dose of calls. Those not receiving scheduled coaching calls will be able to contact the health coaches as needed during the study. For gamification elements, half of the participants will receive incremental rewards for engaging with the study. Such engagement includes but is not limited to (1) engaging with the telehealth website, (2) logging health behavior data, and (3) engaging with educational content. Half will receive independent rewards by performing similar tasks, thereby making the requirements for rewards equal across all participants. Additionally, all groups will be subject to the same data collection methods and study protocols.

Protocols for Setbacks in Implementation

All adverse events, emergencies, and issues with participant engagement and intervention will be collected and reported. We will track participant feedback and issues in adherence through the coaching logs and notes collected on the telehealth website, call logs, and staff logs.

Provider Training

All team members in the study have appropriate backgrounds and experiences in conducting every study activity. The multidisciplinary team includes technical, academic, and programmatic personnel who are able to perform all relevant tasks to ensure the successful completion of the My Health, My Life, My Way study. Academic staff include researchers who are charged with the overall administration of the program and trained health coaches who will engage with participants and provide relevant health-related content such as physical activity and nutrition. Technical staff are trained in developing the website that participants will use and will maintain the technological infrastructure through feedback from academic personnel and participants. Textbox 2 shows the strategies that we will use to monitor provider training based on the NIH BCC.

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Textbox 2. Fidelity of provider training.

Goal

- Standardized training
- Ensure provider skill acquisition
- Minimize “drift” in provider skills
- Accommodate provider differences

Description from National Institutes of Health Behavior Change Consortium

- Similar training conducted by providers
- Providers trained using predetermined and defined criteria
- Reduce provider skill decay over time
- Ensure adequate training of providers with different levels of skills, experience, and background

Strategy used in My Health, My Life, My Way

- Health coaches will receive equal training through specified a curriculum
- Review and monitor coaching calls and call logs
- Evaluate audio recordings of coaching calls
- Collect audio recordings of coaching calls
- Regular team meetings to monitor participant progress and provider protocol adherence

Treatment Delivery

Overview

The NIH BCC provides guidance on how to ensure that interventions are delivered as intended. By using their guidance, we will address four concerns cited by the NIH BCC for treatment delivery: (1) controlling provider differences, (2) reducing differences within study groups, (3) ensuring adherence to study protocols, and (4) reducing contamination between study groups. Textbox 3 shows the strategies used in My Health, My Life, My Way.

Textbox 3. Fidelity strategy for treatment delivery.

Goal

- Control for provider differences
- Reduce differences within study groups
- Ensure adherence to the study protocol
- Reduce contamination between study groups

Description from National Institutes of Health Behavior Change Consortium

- Monitor and control for subject perceptions of nonspecific treatment effects (eg, warmth and credibility) across conditions
- Ensure that providers in the same condition are delivering the same intervention
- Ensure that the treatments are being delivered in the way in which they were conceived with regard to content and treatment dose
- Minimize contamination across treatment or control conditions, especially when implemented by the same provider

Strategies used in My Health, My Life, My Way

- Coaching call checklist
- Coaching call logs
- Audio recording of coaching calls
- Review of the telecoaching platform and its event log
- Team meetings to discuss participant progress and protocol adherence

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Controlling Provider Differences

We have developed several strategies to monitor treatment delivery in the study. First, we have developed several coaching guides and scripts that will inform health coaches on what content to cover during coaching calls. We also plan to track the frequency of coaching calls through call logs. This will allow us to evaluate whether participants are receiving an equal number of coaching calls throughout the program. Next, we will collect audio recordings of coaching calls and randomly select calls to evaluate content delivery. The study team will conduct weekly team meetings to evaluate the progress of participants, health coaching curriculum, and protocol adherence.

Reducing Differences Within Treatment Groups

This study uses AI to enhance the fidelity of coaching sessions and minimize the effort required by health coaches to provide customized telecoaching. The program will use a telehealth website that will be an assistive tool for health coaches to deliver appropriate content to each participant during coaching call sessions. Health coaches will be provided standardized protocols and guidelines regardless of intervention group assignment. All educational content will be developed by experts to be inclusive of individuals with physical disabilities.

Regardless of group assignment, all procedures will be standardized to reduce differences within treatment groups. Coaches will focus on domains of health, including but not limited to physical activity, mindfulness, and nutrition. In these areas of health, the health coach will follow a progressive routine. For example, if a participant has a goal to increase physical activity participation, the health coach will start with lower activity goals with the ultimate aim of meeting physical activity guidelines of 150 minutes of aerobic activity per week. Similar approaches to nutrition and other health-related behaviors will be used. Although half of the participants will not receive scheduled coaching calls, those participants will be able to communicate with the health coaches through on-demand services through different communication methods regarding health behaviors they seek to improve. Health coaches will follow the same standardized protocols and guidelines for these participants as well.

Finally, the My Health, My Life, My Way telehealth website will include multimedia educational content (ie, videos, infographics, and SMS text messages) to deliver the intervention. All participants will have access to the material and can view them at their discretion.

Ensuring Adherence to Treatment Protocols

Health coaches will be given standardized checklists and protocols to ensure adherence to intervention treatment and delivery. The collection of call logs, monthly evaluation of audio recordings, and weekly team meetings will be conducted to further ensure that all protocols are regularly followed. All documents provided to the health coaches will serve as reminders to prepare for any coaching call and discuss relevant content with each participant.

Minimizing Contamination Between Conditions

All enrolled participants will be randomized into 1 of 4 groups (Table 1). Each group will have a developed protocol that will be given to the health coaches to use during the study duration. The coaches will use the same educational material that will be adapted for individuals with physical disabilities.

Receipt of Treatment

A primary element of the success of an intervention is its simplicity and applicability. The NIH BCC emphasizes treatment receipt, which involves assessing the degree to which participants understand the material provided to them and are able to perform health behavior–related skills during the intervention. My Health, My Life, My Way fidelity protocol seeks to achieve goals suggested by the NIH BCC (Textbox 4).

Textbox 4. Fidelity strategy for receipt of treatment.

Goal

- Ensure participant comprehension
- Ensure participant's ability to use cognitive skills
- Ensure participant's ability to perform behavioral skills

Description from National Institutes of Health Behavior Change Consortium

- Ensure that participants understand the information provided by the intervention
- Make sure that participants are able to use the cognitive skills taught in the intervention
- Make sure that participants are able to use behavioral skills taught in the intervention

Strategies used in My Health, My Life, My Way

- Use plain language for content with a target reading at fifth-grade reading level
- Review audio recordings of coaching calls
- Review participant website journals for physical activity, medication, and nutrition behaviors
- Review duration spent on the website by participants
- Conduct study team meetings to review participant progress in the intervention

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It is estimated that 80 million US adults have low health literacy, which refers to the inability to listen effectively, read, understand, and interpret text and numerals related to health management, such as food labels, blood glucose measurements, and clinical instructions. Using plain language is important to increase health literacy for individuals with physical disabilities who experience chronic health conditions. As My Health, My Life, My Way is designed for populations with disability, we plan to use language at a fifth-grade reading level for all written content. Such modification to education material is necessary to increase participants' capacity to perform self-management skills.

My Health, My Life, My Way will incorporate principles of cognitive behavioral therapy to counsel participants on diet, exercise, and positive psychological behaviors like motivation and managing stress. Health coaches will use similar techniques derived from cognitive behavioral therapy to provide proper motivational interviewing that will assist participants in creating and following through on creating goals and implement strategies to meet those goals.

Enactment of Treatment Skills

The enactment of treatment skills refers to the ability to monitor and increase the capacity of participants to act on behavioral and cognitive skills in real-world settings that they learned during the study intervention [14]. Because we aim to promote long-term adherence to skills beyond the study duration, this program will use adapted and engaging content designed for individuals with physical disabilities in mind. Such content will include multimedia, textual, and graphical material and access through a telehealth website that will provide access to all content (Textbox 5).

Textbox 5. Fidelity strategy for the enactment of treatment skills.

Goal

- Ensure participant's use of cognitive skills
- Ensure participant's use of behavioral skills

Description from National Institutes of Health Behavior Change Consortium

- Ensure that participants use the cognitive skills provided at the intervention in appropriate life settings
- Ensure that participants actually use the behavioral skills provided in the intervention in appropriate life settings

Strategies used in My Health, My Life, My Way

- Review participant logs for physical activity, food, medication, etc
- Review the number of log-ins and time spent on the telehealth website
- Regular team meetings to assess participant progress and overall protocol adherence
- Review and monitor coaching notes collected during the intervention

My Health, My Life, My Way Telehealth Coaching Dashboard

This program provides a comprehensive telehealth coaching dashboard, a multifaceted solution designed to elevate participant engagement, communication, and monitoring within the realm of health and wellness. This dynamic platform seamlessly integrates 3 essential components. The telehealth coaching dashboard will serve as the pivotal interface enabling participants to establish effective and real-time communication with their designated health coaches. Through a variety of mediums such as SMS text message–based messaging and phone calls, participants can engage in meaningful conversations, seek guidance, and receive personalized support. For participant monitoring and tracking, the platform will offer robust capabilities for monitoring and tracking health-related behaviors, including physical activity, time spent on reading health-related contents, and watching minutes of exercise videos and nutritional choices. This helps health coaches to provide guidance to participants during health coaching sessions. Finally, the user interface for participants will receive an intuitive user interface tailored to their needs. This interface provides them with convenient access to an array of features, such as customized educational materials catering to their specific health conditions, exercise videos, and on-demand health coaching. Moreover, the interface empowers participants to log and manage their activities for promoting positive behavior changes, ranging from effective meal planning to encouraging regular physical activity through goal settings. Overall, through seamless communication channels, comprehensive monitoring tools, and a user-friendly interface, the telehealth coaching dashboard will empower participants to take charge of their health journey while receiving expert guidance and support. Figures 1-3 provide the samples of the telehealth coaching monitoring dashboard.

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Figure 1. Sample fidelity monitoring dashboard screenshot—participant monitoring dashboard.

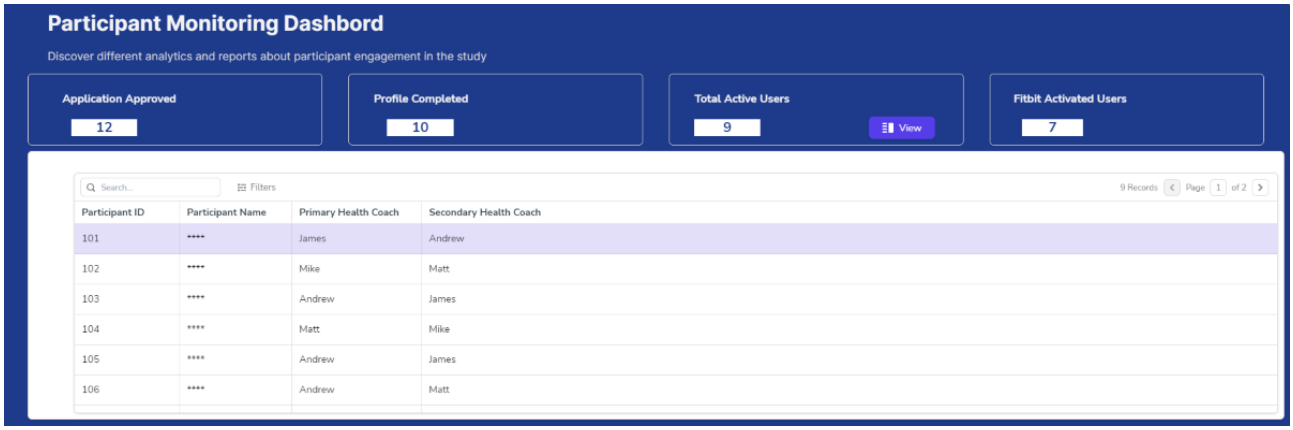

Figure 2. Sample fidelity monitoring dashboard screenshot—log-in analytics.

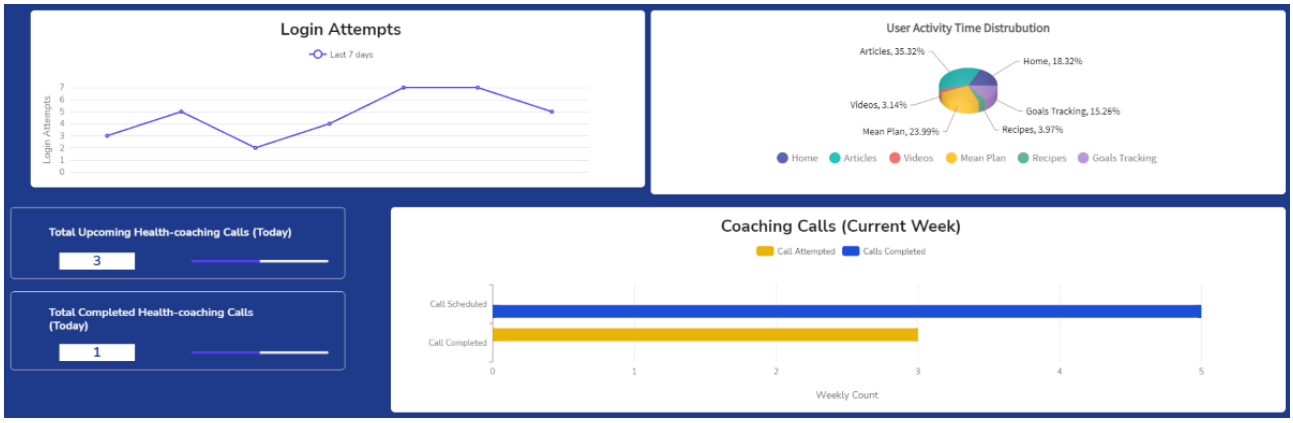

Figure 3. Sample fidelity monitoring dashboard screenshots —summary dashboard.

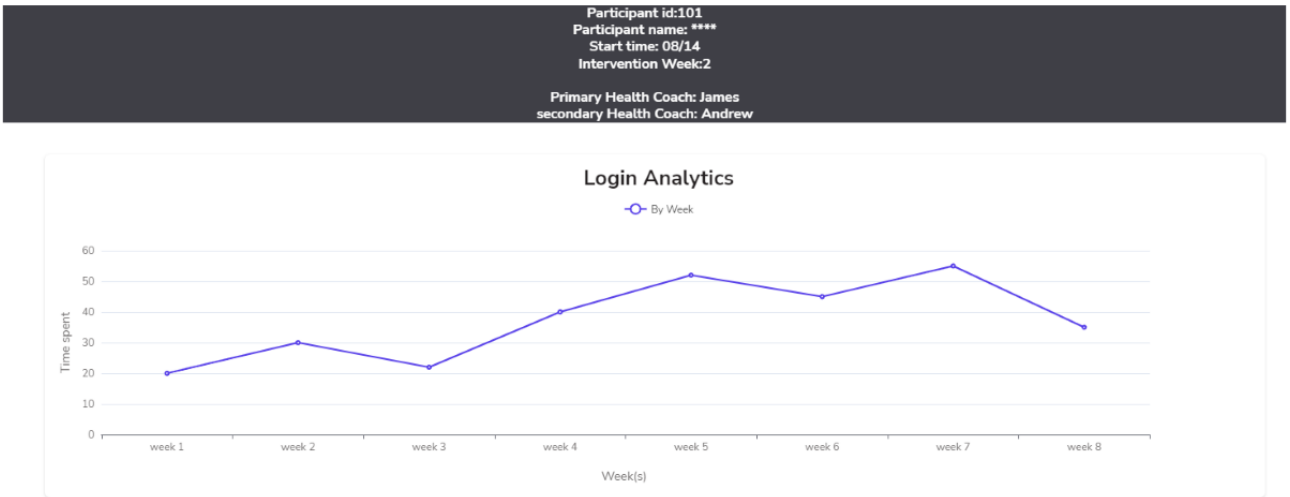

Results

Enrollment for the My Health, My Life, My Way program will begin in January 2024 and will end in December 2024. The results of this study will be reported in early 2025.

Discussion

The purpose of this paper was to outline and describe the intervention fidelity protocol for the My Health, My Life, My Way study. This randomized controlled trial aims to develop and evaluate a telehealth platform, which is paired with inclusive education content for individuals with physical disabilities who experience chronic health conditions. Intervention fidelity refers to mechanisms of monitoring the planned delivery of study interventions [14]. Maintaining strict fidelity throughout study interventions will minimize external influence on both participants and research team members. It will also ensure that results from the intervention are reflective of the participants' behaviors in real-world settings.

By using strategies provided by the NIH BCC, we developed an intensive fidelity intervention protocol addressing the 5 main

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domains to monitor, assess, and enhance overall study fidelity. The NIH BCC has provided relevant guidelines and strategies for health behavior interventions to maintain both internal and external validity. Telehealth studies can positively impact self-management skills for individuals with chronic health conditions. The My Health, My Life, My Way program will be the first self-management program for individuals with physical disabilities and chronic health conditions. Because this program is conducted through the web, it has the capability to become accessible, inclusive, scalable, and sustainable. Therefore, by reporting the fidelity intervention protocol for My Health, My Life, My Way, this paper will inform future studies using telehealth technology and health coaching.

The 5 domains to maintain fidelity provided by the NIH BCC addressed in this paper include study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills. The fidelity monitoring protocol described here was developed in conjunction with a similar telehealth study using similar technology and health coaching for individuals with physical disabilities and diabetes [15,16]. Similar to that fidelity intervention protocol, a challenge of ensuring high fidelity is that My Health, My Life, My Way will use different technological platforms for different fidelity purposes. Examples include using the telehealth website, REDCap (Research Electronic Data Capture; Vanderbilt University) for data collection, and communication platforms for health coaches to engage with participants. Possible implementation setbacks will be addressed, and ongoing collaboration with the multidisciplinary team (ie, research staff, health coaches, and technical support) will reduce variations in fidelity monitoring.

Several steps in program implementation have been conducted prior to fidelity development and standardized protocols have been developed for future steps. In the context of health coaching, strict coaching session guidelines have been developed to reduce variation in conducting health coaching calls, which is a significant concern in telehealth interventions [17,18]. The development of AI that is embedded in our telecoaching website provides convergent communication capabilities that will reduce health coaching workload and need to aid in the personalization of self-management skills for participants. Other monitoring procedures have been created to evaluate the consistency of health coaching sessions, including audio recordings, call logs, and a review of the training used by the coaching team. Such procedures will enhance the internal validity of the protocol and contribute to the creation of effective, evidence-based telecoaching programs.

Acknowledgments

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Conflicts of Interest

TM received consulting fees from Novo Nordisk, Heart Rythm ClinicalResearch Solutions, New Balance Foundation Obesity Prevention Center, and fees as an editor by The Obesity Society and PLOS One.

Multimedia Appendix 1
Peer review report from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR).
[PDF File (Adobe PDF File), 374 KB - resprot_v13i1e53410_app1.pdf]

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Abbreviations

AI: artificial intelligence
NIH BCC: National Institutes of Health Behavior Change Consortium framework
REDCap: Research Electronic Data Capture

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Protocol

A Digital Intervention to Improve Skin Self-Examination Among Survivors of Melanoma: Protocol for a Type-1 Hybrid Effectiveness-Implementation Randomized Trial

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Abstract

Background: Although melanoma survival rates have improved in recent years, survivors remain at risk of recurrence, second primary cancers, and keratinocyte carcinomas. The National Comprehensive Cancer Network recommends skin examinations by a physician every 3 to 12 months. Regular thorough skin self-examinations (SSEs) are recommended for survivors of melanoma to promote the detection of earlier-stage, thinner melanomas, which are associated with improved survival and lower treatment costs. Despite their importance, less than a quarter of survivors of melanoma engage in SSEs.

Objective: Previously, our team developed and evaluated a web-based, fully automated intervention called mySmartSkin (MSS) that successfully improved SSE among survivors of melanoma. Enhancements were proposed to improve engagement with and outcomes of MSS. The purpose of this paper is to describe the rationale and methodology for a type-1 hybrid effectiveness-implementation randomized trial evaluating the enhanced MSS versus control and exploring implementation outcomes and contextual factors.

Methods: This study will recruit from state cancer registries and social media 300 individuals diagnosed with cutaneous malignant melanoma between 3 months and 5 years after surgery who are currently cancer free. Participants will be randomly assigned to either enhanced MSS or a noninteractive educational web page. Surveys will be collected from both arms at baseline and at 3, 6, 12, and 18 months to assess measures of intervention engagement, barriers, self-efficacy, habit, and SSE. The primary outcome is thorough SSE. The secondary outcomes are the diagnosis of new or recurrent melanomas and sun protection practices.

Results: Multilevel modeling will be used to examine whether there are significant differences in survivor outcomes between MSS and the noninteractive web page over time. Mixed methods will evaluate reach, adoption, implementation (including costs), and potential for maintenance of MSS, as well as contextual factors relevant to those outcomes and future scale-up.

Conclusions: This trial has the potential to improve outcomes in survivors of melanoma. If MSS is effective, the results could guide its implementation in oncology care and nonprofit organizations focused on skin cancers.

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KEYWORDS

melanoma; cancer survivorship; skin self-examinations; digital interventions

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Introduction

Background

More than 97,610 cases of cutaneous malignant melanomas will be diagnosed in the United States in 2023, making it the fifth most commonly diagnosed cancer. With incidence rates more than tripling from 1975 to 2020, the population of survivors of melanoma is estimated at >1 million. Among persons diagnosed with localized, regional, or distant-stage melanoma, the 5-year survival rates have improved in the last decade, with 99%, 65%, and 25% survival rates, respectively [1]. Improved survival and increased incidence have translated to an estimated annual treatment cost for melanoma of approximately US $2.5 billion [2].

Survivors of melanoma remain at risk of recurrence, second primary cancers, and keratinocyte carcinomas. Recurrence rates depend on tumor thickness and nodal involvement and range from 3% to 24% among persons with thinner lesions to 51% among persons with thicker lesions or lymph node involvement [3-5]. Recurrent or new primary melanomas occur most commonly during the first 5 years after diagnosis but can arise many years later [6,7]. Recurrent melanoma typically occurs at local or regional sites, and approximately half of distant recurrences present within the skin or lymph nodes [8,9]. Psychosocial morbidity is an issue for patients and survivors, with studies reporting higher anxiety and depressive symptoms than in the general population [10] and elevated anxiety about recurrence.

For survivors of melanoma, National Comprehensive Cancer Network guidelines recommend several actions, including skin examinations by a physician every 3 to 12 months and regular thorough skin self-examination (SSE) [11-13], which entails a deliberate, systematic inspection of all areas of the body using a mirror or the assistance of another person to examine hard-to-view areas [14]. Patient education about SSE by a health care professional is also recommended. Engagement in regular sun protection behavior is also recommended to reduce the risk of subsequent skin cancers as UV radiation from the sun is a contributing factor for melanoma and other skin cancers [2].

Limited data suggest that performance of SSE is associated with differential survival rates among patients with melanoma, and professional recommendations for regular SSE are supported by 3 research findings. First, more than half of recurrences and new primary melanomas are detected by survivors themselves [11,15,16]. Second, individuals who perform SSE are diagnosed with significantly earlier-stage melanomas than those who do not. Detection and treatment of recurrent disease and new primary cancers at earlier stages leads to improved survival, which is not accounted for by lead-time bias [17]. Third, melanomas identified through SSE are thinner than those found incidentally [16,18,19]. Retrospective studies suggest that individuals who perform SSE have lower tumor thickness. Thinner melanomas are associated with better survival [19-23]. Thus, promoting regular SSE will likely enhance the early detection of easier-to-treat recurrences and new primary cancers among survivors. For example, Robinson et al [24] found that 13.4% of patients in their SSE randomized controlled trial (RCT) developed a new melanoma over the 2-year follow-up. Patients in the SSE intervention condition detected 81% of these melanomas, approximately 34% of which were invasive, with only a 1% increase in physician visits. The costs of treating earlier- versus later-stage melanomas are significantly lower [25,26]. In summary, regular thorough SSE is recommended for survivors of melanoma and results in the detection of earlier-stage, thinner melanomas, which is associated with improved survival and lower treatment costs.

Despite its importance, engagement in regular, thorough SSE is low. Compliance rates with thorough SSE range between 7% and 17% among survivors of melanoma [14,20,22,27,28]. Studies document wide variation in SSE performance, with figures dependent upon the way that SSE is measured and the time frame for assessment. When patients are asked whether they have performed any form of SSE in the past 2 months, high rates of performance are observed (71.5%) [29]. SSE rates are higher when specifying any performance in the past year (84.3%) [30]. However, significantly lower rates are found if SSE is defined by its thoroughness. We reported that 13.7% of survivors checked 4 key areas and had someone assist them or used a mirror for hard-to-see areas [30]. Loescher et al [31] found that 16% of women and 7% of men examined each of the 7 designated body parts in the previous 2 months. Mujumdar et al [32] reported that 17% of survivors examined a minimum number of areas of the body (8 out of 9 areas) in the previous 2 months. In our recent work, 65% reported having conducted an SSE in the previous 2 months, but only 7.5% of the sample checked all 15 body parts. Hard-to-see areas were missed, including the scalp (37.9%), buttocks (40.4%), soles of the feet (41.6%), and genitals (44.4%). Less than half (46.2%) [33] reported using a mirror to view hard-to-see places, and only 39% reported asking for assistance. In total, 2% reported using a mole map to guide their most recent SSE.

A limited number of interventions have been evaluated to improve SSE among survivors of melanoma [24,34-37]. Existing interventions have used in-person, print, or web-based delivery modes. Several have demonstrated improvements in SSE [34,35]. Limitations of previous studies include lack of a comparison group [35]; being an in-person or partner-assisted intervention, which compromises the ability to disseminate it [24]; lack of inclusion of long-term outcomes [24]; lack of inclusion of SSE performance [36] as an outcome; and low intervention use and high dropout [35]. No existing intervention is fully automated and, thus, potentially cost-effective and highly scalable. To this end, our team developed and evaluated mySmartSkin (MSS), a web-based, fully automated intervention to improve SSE among survivors of melanoma. MSS is a behaviorally based program that is delivered via the internet, tailored to the user, and fully automated with no human clinical support. MSS was compared with usual care (UC) in an RCT of 430 survivors of melanoma from New Jersey [38,39]. The results indicated a beneficial impact of MSS versus UC on the performance of thorough SSE at all follow-ups up to 1 year [24,34-37]. Effect sizes were in the small to medium magnitude range for SSE, but these effects were not sufficiently strong to scale up for implementation in the existing form.

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In addition to SSE, professional agencies recommend engagement in regular sun protection behaviors, such as staying in the shade, applying sunscreen with a sun protection factor of at least 30, and wearing protective clothing (eg, hats and long sleeves). Survivors of melanoma report engaging in higher levels of sun protection behaviors than the general population [40], but their sun protection behaviors do not meet the recommended guidelines [30,32,41]. To date, only 2 intervention studies have targeted improved sun protection behaviors among survivors of melanoma [34,38]. Bowen et al [34] reported significant improvements in some sun protection behaviors (eg, wearing sunglasses and staying in the shade). In our prior work [38], we evaluated the effects of MSS on sun protection behaviors, which was included as a component of the original intervention. The effects of MSS compared with UC on sun protection behaviors were only statistically significant at the 24-week follow-up in analyses that did not control for baseline sun protection behaviors or other potential covariates. Stronger and more consistent improvements in sun protection would be an important goal for future work.

Theoretical Frameworks

Previous empirical findings regarding factors associated with SSE [29,30,32,42,43] and sun protection, as well as the preventive health model (PHM) [44,45], inform the content of MSS. The PHM posits that the performance of preventive behaviors is influenced by background, affective, cognitive, and social factors. Background factors include sociodemographic characteristics, risk factors for skin cancer, medical history, and knowledge about melanoma. Affective factors include concerns about melanoma recurrence and distress about the diagnosis. Cognitive factors include perceived controllability of melanoma, self-efficacy, and benefits and barriers. Social normative factors include family and friend support and physician recommendations. In addition to our previous research on skin cancer risk reduction practices among family members of patients with melanoma [46,47], the PHM has been used successfully to understand and promote screening for colorectal and prostate cancer [44,48]. The original MSS focused on improving the perceived controllability of melanoma through the performance of comprehensive SSE; increasing the perceived benefits of SSE and sun protection; reducing barriers to SSE and sun protection; enhancing self-efficacy for SSE and sun protection; and enhancing family, friend, and physician support for sun protection.

A major challenge for intervention research is that most interventions that demonstrate a beneficial impact are not tested in effectiveness or dissemination trials and are not conducive to “real world” delivery or use. As a result, they do not penetrate the general population and, unfortunately, are not received by those who most need them [49]. Our work is guided by the Practical, Robust Implementation and Sustainability Model (PRISM), which extends the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) [50] framework to consider not only implementation outcomes but also multilevel contextual factors influencing implementation. *Reach* refers to the percentage and representativeness of persons exposed to a program. *Effectiveness* refers to the impact on key survivor-level outcomes. As MSS is a free-standing, recipient-facing intervention, *adoption* is defined as the proportion and representativeness of recipients (in this case, survivors) who adopt (ie, at least log into) the program. *Implementation* refers to the degree to which a program is delivered and received as intended. This is measured through costs, engagement, acceptability, feasibility, and appropriateness. *Maintenance* is the extent to which a program and its survivor-level effects are sustained over time. The integration of these models with the study’s aims is shown in Figure 1 [51-55]. In the proposed study, in aim 1, the goal of the iterative process of enhancing the MSS intervention using stakeholder feedback and usability testing is to improve RE-AIM outcomes, which will be assessed in aims 2 and 3. In aim 2, we focus on the effectiveness of the enhanced MSS, testing its effects on survivor-level outcomes, including clinical outcomes (eg, melanomas found). In aim 3, we address the remaining RE-AIM dimensions. In addition, to proactively identify barriers to and facilitators of future scale-up and widespread dissemination and implementation of MSS, we explore multilevel contextual factors identified by key stakeholders drawn from the PRISM domains of recipients, external environment, intervention design, and implementation and sustainability infrastructure. We anticipate that incorporating PRISM and RE-AIM throughout the study aims will ensure that the enhanced intervention is responsive to key stakeholder preferences and that we “design for dissemination” [56], recognizing potential barriers to and facilitators of future scale-up and informing our next stage of developing dissemination and implementation strategies to maximize the public health impact of MSS.

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Figure 1. Integration of preventive health model and implementation frameworks with the study aims. RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

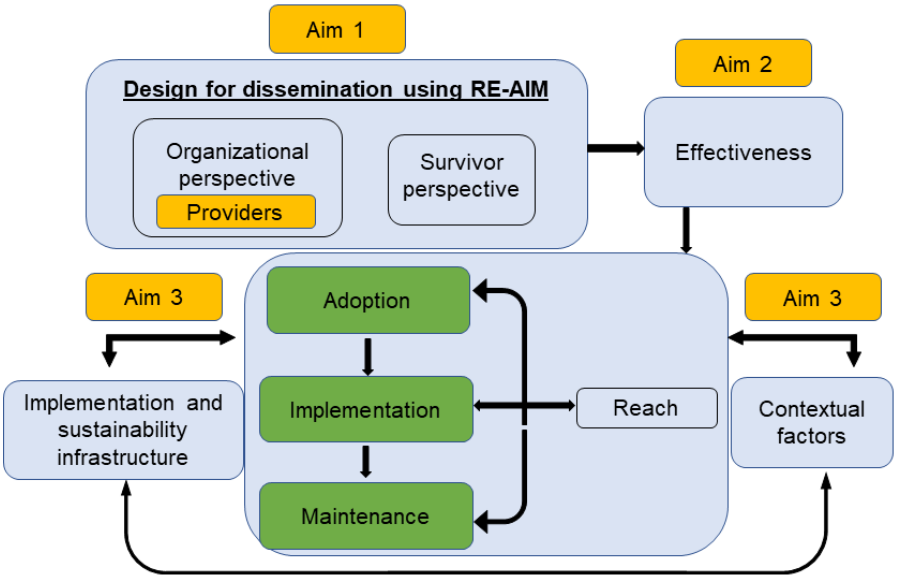

Study Objectives

Overview

The purpose of this type-1 hybrid effectiveness-implementation study is to evaluate the effectiveness of a web-based intervention, MSS, and explore its implementation and relevant contextual factors. A type-1 hybrid effectiveness-implementation approach requires the engagement of multilevel stakeholders throughout the research process, focus on evaluating the effectiveness of the enhanced MSS, and identification of critical factors that could promote or prevent wide-scale implementation. The study's 3 aims are guided by implementation frameworks and behavior change theories.

Aim 1

The first aim is to enhance MSS by collaborating with multilevel stakeholders. We will collaborate with stakeholders to enhance MSS through qualitative interviews and usability testing of potential intervention enhancements. Enhancements are based on empirically validated behavior change techniques (BCTs) and lessons learned from survivors' feedback in our previous study. We will use an iterative process that includes (1) key informant interviews with survivors, providers, and professional organization representatives regarding proposed enhancements; (2) conversion to an enhanced mobile-based delivery platform; (3) usability testing; and (4) iterative program refinements.

Aim 2

The second aim is to evaluate the effects of the enhanced MSS on thorough SSE (primary outcome) and examine its impact on the diagnosis of new or recurrent melanomas (secondary outcome) and sun protection practices (secondary outcome). We will conduct an RCT comparing MSS and a noninteractive educational web page with 300 survivors to test the intervention effects on these outcomes.

Aim 2 Hypothesis

We propose that MSS participants will be more likely to perform thorough SSE over the 18-month follow-up period. We will explore the impact of MSS on new or recurrent melanomas and sun protection behaviors. We anticipate diagnosing a greater number of earlier-stage melanomas and observing higher sun protection behaviors among those in MSS compared with those in UC.

Aim 3

The third aim is to assess selected implementation outcomes and identify factors relevant to future scale-up for widespread dissemination, implementation, and maintenance of MSS. We will use mixed methods to assess implementation outcomes and explore perspectives from survivors, care providers, and professional organizations to inform the selection of strategies to best disseminate and implement MSS on a broad scale. The subaims are as follows:

1. Aim 3a is to estimate program costs and assess the cost-effectiveness of MSS relative to control. We hypothesize that MSS costs will be higher than UC costs. We expect that MSS will be a more cost-effective strategy given its previous positive effects on SSE and the identification of new or recurrent melanoma. If our findings support this as expected, exploratory cost-effectiveness analyses from the health care and societal perspectives will be conducted using simulation models of melanoma-related costs, disease progression, and survival over 5- and 10-year analysis horizons.
2. Aim 3b is to examine the reach, adoption, implementation (ie, engagement, acceptability, appropriateness, and feasibility), and maintenance of MSS. For reach, we predict that the demographic characteristics of those exposed to MSS will not differ from those of the general population of survivors of melanoma. For adoption, we propose that the proportion of contacted and eligible survivors randomized to MSS who consent, complete the baseline questionnaire, and log into MSS will be equal to or greater

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than the proportion in our previous efficacy trial. For engagement, we propose that 80% of MSS participants will log into the intervention at least once. For acceptability, we predict that MSS will be rated as highly acceptable. We do not have hypotheses regarding appropriateness, feasibility, and maintenance as these data will be evaluated in terms of future implementation of MSS should it have an impact on SSE and sun protection outcomes. For each of these implementation outcomes, we will assess the demographic characteristics of MSS participants to determine whether outcomes differ among survivors in specific subgroups (eg, by age, sex, race, ethnicity, and socioeconomic status).

3. Aim 3c is to identify and describe contextual factors experienced by multilevel stakeholders as key to scale-up and widespread implementation of MSS, including consideration of potential delivery settings, timing of delivery, and resources needed to promote its implementation.

Methods

Ethics Approval

Study procedures were approved by the Rutgers University institutional review board (IRB; protocol Pro2022000948).

Aim 1: Enhancements to the Existing Version of MSS Using Multilevel Stakeholders

Overview

This phase engages multilevel stakeholders in optimizing MSS by targeting multiple RE-AIM outcomes: effectiveness, adoption, implementation, and maintenance. Iterative enhancements will be made to MSS intended to increase the effects on SSE by increasing adoption, acceptability, appropriateness, feasibility, and maintenance. This process will include key informant interviews with survivors, health care delivery stakeholders, and professional organizations to inform the selection of enhancements from the potential theory-based strategies we identified based on the findings and survivor feedback from our previous RCT. This user-centered process will involve assessment of preferences regarding content (eg, "What are your thoughts on the option of uploading pictures of your moles?"), use (eg, "How useful would it be to log in to MSS three months after you complete it and what would you use it for?"), and preferred ways to motivate targeted behaviors (eg, "What are your thoughts about incentives such as free products?"). This phase of our design for dissemination approach will use an iterative process that includes (1) key informant interviews with survivors of melanoma and care providers to inform the selection of proposed theory-based enhancements, (2) conversion to a mobile-based intervention delivery platform incorporating selected enhancements, (3) usability testing with survivors who use the program for 1 month, and (4) program refinement.

Proposed Enhancements

The existing MSS content was guided by PHM and evidence-based BCTs. The original MSS included two categories of BCTs: (1) prompts (participants could set an email reminder to perform SSE on specific dates for the duration of study participation) and (2) planning (participants could set a goal related to SSE and select up to 2 action steps to address barriers). The other material primarily targeted SSE knowledge (eg, how to recognize a suspicious growth) and self-efficacy (building confidence in identifying suspicious growths), which were the mediators of MSS effects on SSE.

Our selection of proposed enhancements was guided by two goals: (1) to optimize engagement with MSS and (2) to increase sustained performance of SSE. A summary of enhancements is shown in Textbox 1. We focused on optimizing engagement as participants who used MSS more were more likely to perform SSE across the follow-up period, which we are now extending. Thus, increasing engagement with MSS should enhance its impact over time.

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Textbox 1. Proposed enhancements to mySmartSkin (MSS).

Self-monitoring and performance feedback

- Upload pictures of moles each month on mole map
- Illustrate body parts checked each month
- Bar graph of completed skin self-examinations (SSEs) over time from baseline to 1 year on the MSS home page
- Monthly feedback on progress with SSE

Incentives for success

- Incentives for self-reported SSE, core completion, and SSE and sun protection goal setting: rulers, reminder stickers, sun hats, sunscreen, sun protection factor ChapStick, sun safety checklist magnet, calendars, hanging door signs with the ABCDEFs (asymmetry, border irregularity, color variation, diameter of >6 mm, evolving, and funny looking) of melanoma, sun umbrella, among others (up to 6 incentives)

Prompts

- Personalized text reminder delivered the day before SSE is due each month to perform it, with a link to the self-check program
- Tailored reminder of body parts to remember to check

Goals and planning

- Identification of personal barriers to SSE and sun protection behaviors
- Continued troubleshooting of ways to address SSE barriers and sun protection behaviors
- Regular personalized feedback and ability to track progress on SSE and sun protection goals

Social support

- Discuss the importance of support for change
- Identify someone to support SSE (eg, spouse) and how the patient would like to talk to and involve them
- Provide SSE information via email to authorized support person

To optimize initial engagement, we are implementing four enhancements: (1) enhancing participant-facing recruitment materials (eg, advertisements, emails, and study home page) by including narratives from survivors and oncologists about MSS and the importance of thorough SSE, (2) streamlining enrollment materials and processes (eg, screening and baseline surveys and instructions), (3) reaching out to participants who do not log into MSS by day 3 to provide a brief orientation session fostering ease of access (ie, review modules and topics and the importance of completing modules, show the participant how to log in, and discuss SSE benefits for finding recurrence early), and (4) informing participants about incentives for completion of each core and other tasks within the program.

To improve sustained SSE, we identified 6 categories of BCTs for the proposed enhancements [57]; we included (1) self-monitoring and performance feedback to improve self-efficacy (eg, uploading photos of moles and saving them to compare with the next SSE); (2) behavioral incentives (eg, provided for completing SSE); (3) additional prompts for SSE (eg, programmed reminders about missed areas of the body); (4) adding a more comprehensive approach to setting goals and planning, including continued troubleshooting of barriers; (5) including more content on receiving assistance and support from others in performing SSE (including the option to email an authorized support person about assisting with the participant's SSE); and (6) adding a goal-setting component that fosters habit formation and maintenance of behavior change. We created an in-depth goal-setting section that allows users to track their progress and make updates to their goals and progress over time. The goal-setting component is tailored based on the user's current SSE and sun protection behaviors, and the purpose of this component is to assist in the creation of a plan to improve both behaviors.

In terms of sun protection behaviors, we included a sun safety core with content categorized into chapters addressing (1) learning more about sun safety with topics such as risks of UV rays, risks of unprotected sun exposure, sunscreen education, how to avoid sunburns, and other sun protection behaviors; (2) assessing current sun protection behaviors; (3) increasing confidence in and motivation for sun protection; and (4) setting sun protection goals. A more detailed summary of the content of each core is provided in Table 1.

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Table 1. Enhanced mySmartSkin intervention content.

Section	Key content	Interactive features
Tutorial	• Overview of navigation, sections, and features	• N/A[a]
Core 1: learn about spots	• Personal melanoma history • Skin cancer facts and figures • Melanoma risk factors • Risk of recurrence • Purpose of SSE[b] • How to conduct an SSE • The ABCDEFs[c] of melanoma • Your experience doing SSE • What to do when you find a suspicious spot • Importance of SSE and physician skin examinations • Confidence in checking spots	• Mole facts and fiction • ABCDEF-identifying challenge quiz • Suspicious or not mole challenge • Vignette and physician video and audio clips • SSE goal setting
Core 2: sun-safe behaviors	• Sun-safe behaviors • Risks of sun exposure • UV index • Types of sunscreen • Avoiding sunburns during outdoor activities • Risk assessment for outdoor activities • Sun-safe clothing • Limiting sun exposure • Increasing confidence and motivation for sun safety • Prioritizing sun-safe behaviors • SSE goal setting	• Sunscreen FAQs[d] • Sunscreen facts and fiction • Tanning facts and fiction • Assessing current tanning beliefs • Vignette and physician video or audio clips • Sun-safe behavior importance rating • Sun safety goal setting
MyStuff	• Goal summary • SSE progress tracker • Badges and prizes	• Goal progress tracker

[a]N/A: not applicable.

[b]SSE: skin self-examination.

[c]ABCDEF: asymmetry, border irregularity, color variation, diameter of >6 mm, evolving, and funny looking.

[d]FAQ: frequently asked question.

Key Informant Interviews to Gather Input on Enhancements

This phase of aim 1 has been completed. The procedures are described in the following sections, and the results are described later in the paper (see the *Results* section).

Sample

We planned to recruit 10 survivors of melanoma who had completed treatment within up to 3 years since diagnosis from the Rutgers Cancer Institute of New Jersey (CINJ) through new case ascertainment by research staff using electronic medical records. On the basis of our past experience in qualitative assessments, this sample was expected to provide thematic saturation of the data, although additional interviews could be conducted if needed.

Questionnaire

Following informed consent procedures, participants completed a brief demographic questionnaire before their interview began. Participants self-reported their age, sex or gender, race, ethnicity, education, current insurance coverage, school enrollment, employment, and marital status. Patients also reported current SSE practices.

Procedures

The project coordinator (AS) conducted the interviews, which were audio recorded with participant permission and approximately 45 minutes in duration. During the interviews, participants were shown prototypes and wireframe illustrations of the proposed enhancements. To ensure that feedback was gathered on all aspects of the MSS platform, interviewers highlighted different sections, including the goal-setting activity sequence and skin self-check body map. The semistructured interviews elicited feedback on the proposed enhancements. We included probes about enhancements based on stakeholders' positive, neutral, or negative reactions (eg, "What parts of the site did you think were most interesting and helpful?" and "What parts were less helpful or seemed less relevant to you?"). Phase 1 participants received US $50 for the interviews. These interviews were conducted in person at the CINJ or using videoconferencing software. The interviewer took field notes, and the interviews were transcribed verbatim.

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Refining Enhancements

The study team reviewed the field notes and verbatim transcriptions of key informant interviews. The responses to each proposed enhancement were coded as positive, neutral, negative, or mixed. Although potential enhancements were based on findings from the previous RCT, suggestions from participants, BCTs, and proven ways to optimize engagement, if particular enhancements were perceived negatively by multiple stakeholders, we used these interviews to explore alternatives that would be more acceptable. For those enhancements with multiple negative or mixed comments, the team decided whether the issue could be addressed feasibly and crafted changes to the content and approach that were congruent with stakeholder feedback. The stakeholders in later interviews reviewed the changes made in response to feedback given in earlier interviews to provide confirmation on whether the issue was adequately addressed. The study team provided feedback to the web developer, Radiant (Radiant Creative Group LLC), throughout the interview process for changes to be incorporated in a timely manner.

Conversion to a Mobile-Based MSS Platform, Usability Testing, and Refinements With Multilevel Stakeholders

Stakeholder-informed enhancements to content and program features will be incorporated with the existing content and migrated to the mobile-based delivery platform in collaboration with Radiant. Testing will be conducted throughout the preproduction and production stages to ensure the suitability of the content for the intended audience. Weekly meetings with Radiant will be conducted to review uploaded content.

Usability Testing, Feedback, and Refinements

Testing will be accomplished by conducting focused interviews with up to 10 survivors of melanoma, 5 health care providers, and 5 organization representatives who will each receive US $100. Testing is modeled after a National Cancer Institute website design project [58]. The process will involve checking the content with participants for attractiveness, comprehension, acceptability, and persuasion. In addition, participants will be able to use MSS for approximately 1 week before the interview so that we can gather input on features that are planned over time, such as self-monitoring and performance feedback, incentives, and prompts. A series of questions and structured guides will be prepared in advance related to the elements to be evaluated.

In the set of interviews, all enhancements and engagement tools, including reminder prompts, will be activated, providing an opportunity to evaluate all components of the enhanced MSS. After that, we will set up a virtual meeting in which the participant will provide feedback about acceptability, ease of use or intuitiveness, and satisfaction. During this session, we will discuss the topic areas and review MSS using a shared screen to allow participants to react to each screen. Participants will be asked to provide feedback on features. These sessions will be digitally video recorded and transcribed, and AS will take notes. The data will be summarized and reviewed to determine further modifications to be made. These efforts will yield a set of understandable, acceptable, and appealing enhancements to MSS that are customized to the needs, capabilities, and preferences of patients with melanoma, providers, and organizational stakeholders. We will conduct weekly meetings that include Radiant and the study team to review and produce content. Once the final beta website has been agreed upon by the full research team, it will undergo extensive testing by Radiant to ensure that the programming is functioning correctly.

Aim 2: Evaluate Effects of MSS Versus a Noninteractive Educational Web Page on SSE

Overview

Phase 2 is a randomized effectiveness trial in which MSS will be tested in an RCT comprising 2 groups (MSS vs a noninteractive educational web page) and 5 assessments (baseline, 3 months, 6 months, 1 year, and 18 months) with 300 survivors of melanoma. The main goal is to evaluate the effects of MSS on thorough SSE and examine the impact on clinical outcomes (eg, diagnosed early-stage skin cancers).

Recruitment

Overview

We will recruit participants from 2 sources: state cancer registries and Facebook. This approach was adopted to prepare for dissemination by assisting the team in comparing the reach of the 2 methods of recruitment. This will foster our ability to determine future settings. The registries include all patients with melanoma in each state, which facilitates eventual generalizability. We chose NJ and CA registries because the 2 states are geographically disparate and sociodemographically diverse, and we have worked successfully with both registries on current projects (CA2219854 and CA221854). We chose Facebook as a second approach as the vast majority of Americans (84% in 2021) [59] use social media, with use steadily increasing each year. This strategy will reach a broad audience of survivors. In addition, many melanoma and skin cancer advocacy groups are active on social media, which will inform the potential for working with them on future dissemination.

Registries

We will recruit from the New Jersey State Cancer Registry (NJSCR) and the Cancer Registry of Greater California (CRGC). Owing to state laws, allowable recruitment procedures differ. NJSCR procedures entail case ascertainment, a letter to the physician, an address check, a letter mailed to the patient, up to 12 calls to verify that they received the letter, and the provision of verbal consent to send contact information to the CINJ. The CINJ reaches out to the patient to describe the study and send a link to the MSS website. We have enhanced the CRGC procedures to be as similar as possible to those of the NJSCR. The CRGC queries their database, confirms that the patient is alive, and checks this information with the provider. Case information is sent to the CINJ, a letter is sent explaining the study followed by up to 12 calls to the patient to obtain their email address, and a link to the study web page is emailed. The process takes approximately 2 months.

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Facebook

We will use paid Facebook advertisements. We will work with a social media marketing company to develop keywords and advertisements targeting individuals with characteristics similar to those of survivors of melanoma (eg, older age). As noted previously, this approach has been successfully used in 2 previous and one current skin cancer–related intervention project [60-62]. This approach will also recruit a broader population of survivors of melanoma than the previous efficacy trial.

Eligibility

The eligibility for this trial is as follows:

1. Diagnosis of primary pathological stage-0 to stage-III cutaneous malignant melanoma
2. Being 3 months to 5 years after surgery
3. No current evidence of cancer
4. No adherence to thorough SSE [14] (ie, did not check the entire body at least once during the past 3 months)
5. Age of ≥18 years
6. Internet access
7. Ability to speak and read English
8. Ability to provide informed consent

The incidence is most common among non-Hispanic White individuals, who have an annual rate of 28 cases per 100,000 compared with 7 in American Indian or Alaska Native individuals; 5 in Hispanic individuals; and 1 in non-Hispanic Black, Asian, and Pacific Islander individuals (92.4% among non-Hispanic White individuals). Consistent with population rates, we will oversample minority groups from cancer registries to ensure a minimum of 7.6% racial and ethnic minority group survivor enrollment.

Sample

The projected sample size is 300. Participants will be recruited using 2 methods. Half of the sample will be recruited from 2 state cancer registries. We expect >10,000 eligible patients with melanoma from the 2 registries during our recruitment period. We will select a random sample from each diagnosis year to balance the year of diagnosis. The acceptance rate for the previous MSS study was 40.9%, but we anticipate a lower recruitment from the registry participants in this study based on our recent work with both CRGC and NJSCR patients (CA221854) [63]. Both cancer registries have a large number of survivors annually. Thus, we will randomly select a subset of cases from each of the retrospective 5-year time frames. The other half of the sample will be recruited via Facebook. We will use paid Facebook advertisements targeted at persons who follow skin cancer–related causes and organizations**.** We will end recruitment from each source when the required sample size is reached.

Enrollment, Randomization, Intervention Delivery, and Follow-Up Surveys

Potential participants recruited via registries will be asked for their email when they verbally consent to participate in the study. Staff will then email these potential participants the link to the study's web page. Participants recruited via social media advertisements will be automatically linked to the study web page when they click on the "learn more" part of the advertisement. Once on the web page, the following automated, completely web-based procedures will be used for enrollment. On the study's web page, there is a screening survey to determine eligibility. Potential participants will complete the eligibility screener. If eligible, the program automatically moves to the electronic consent. Once consent is obtained, the program automatically moves to the baseline survey. After survey completion, the program randomizes the participant to MSS or the comparison condition and automatically moves to either the MSS landing page or the comparison condition landing page. Randomization will be stratified according to disease stage and time since diagnosis (3 months-3 years and 4-5 years) and, then, within strata, block randomized using blocks of 20 participants overseen by the study statistician following standard operating procedures of the CINJ Biostatistics Shared Resource.

Participants who do not log into the MSS program by day 3 will be contacted by a study coordinator via SMS text message, email, or phone 3 times between days 3 and 10 to remind them about logging into MSS. Participants who log in but do not review core 1 by day 5 will be contacted 3 times via email, SMS text message, or calls to invite them to review core 1. These interactions will also serve as an orientation for the participants allowing them to ask any questions about the study or the intervention.

Survey Procedures

Participants will be prompted (via automated email, as well as via SMS text message, telephone, and mail, as necessary) to complete the following web-based surveys: follow-up 1 at 3 months after the baseline, follow-up 2 at 6 months after the baseline, follow-up 3 at 1 year after the baseline, and follow-up 4 at 18 months after the baseline. Participants who do not complete the surveys will be reminded as follows: (1) reminder email and SMS text message with a link to the survey if it is not returned after 1 week, (2) call with a voicemail if no contact is made and email with a link to the survey if it is not returned after 2 weeks, and (3) the same procedure as at 2 weeks if the survey is not returned after 3 weeks. Participants who do not return the survey after a month will be considered lost to follow-up at that time point. Our primary effectiveness analyses will focus on individuals' performance of thorough SSE at 18 months, which will ensure that all participants' SSE practices are assessed over a long time frame and increase the likelihood of detecting new or recurrent melanomas. Participants will receive incremental gift card amounts for each survey (maximum total of US $120).

Intervention Procedures

Participants will have a unique identifying user code and create a password to access the interventions. If users forget their password, they will provide a unique answer to a personal question and the database will return the forgotten password. If users forget both their user ID and password, they can contact the technical assistance hotline. In the previous study, navigation issues were rare. We anticipate that it will take participants approximately 1 hour to complete the entire MSS intervention once and approximately 15 minutes to complete the comparison

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condition. Participants will have access to the interventions for 18 months.

Comparison Group

We chose a noninteractive educational web page comparison group for the following reasons: (1) the information incorporated is widely available to the public and used in dermatology and primary care, (2) the digital delivery method is similar to that of MSS, (3) it allows for a comparison of MSS effects with a minimal knowledge-based educational intervention, (4) it permits a comparison of MSS effects with the results of previous studies that used minimal comparison interventions, (5) it presents a standardized intervention rather than a variable treatment-as-usual intervention, (6) a no-intervention control would be unethical for this high-risk population, and (7) we considered using an intervention for another health issue (eg, nutrition) but anticipated that survivors of melanoma would be less likely to participate. We will create a static educational web page whose content will be based on freely available, accurate information relevant to melanoma, melanoma risk, and SSE. Possible topics include the warning signs of melanoma [64], the risk of recurrence among survivors of melanoma, and how to perform an SSE [65].

Aim 2 Measures

Covariates

Demographics

The demographic information collected will include age, sex, race, ethnicity, education, marital status, state of residence, employment, income, and insurance.

Clinical Characteristics

The clinical characteristics collected will be date of diagnosis, stage, and treatment received.

Melanoma Risk

The melanoma risk information collected will be eye color, natural hair and skin color, skin reactivity to the sun, freckling, moles, sunburn history, indoor UV tanning, and family history.

Environmental Factors

The environmental factors collected will be month of assessment, residential location, and average UV index at solar noon over the 3 months before each time point.

Primary Outcome Measure: Skin Self-Check Comprehensiveness

A full list of outcome measures and covariates is shown in Table 2. The primary outcome consists of the following items: (1) “Have you, or anyone else, not including a doctor or other healthcare professional, ever checked any part of your body for signs of skin cancer?” (yes or no), (2) “If yes, in the last three months, did you check your body for early signs of skin cancer?” (yes or no), and (3) “Doing a thorough skin check or skin self-examination means spending time looking at the skin systematically and deliberately. Please indicate whether you thoroughly checked each of the following areas of your body the last time you checked your body for early signs of skin cancer: Scalp, face, neck, shoulders, front of arms, back of arms, chest, stomach, upper back, lower back, front of legs, back of legs, bottom of feet, buttocks, and genitals” (yes or no for each). For all time points, comprehensiveness will be based on the total number of body parts checked among participants who conducted an SSE in the last 3 months. Participants who did not conduct an SSE in the last 3 months will be coded as 0 for this outcome.

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Table 2. Aim 2 measures.

Measure	Baseline	Time 2	Time 3	Time 4	Time 5
Covariates					
Date of birth	✓				
Sex	✓				
Marital status	✓				
Race and ethnicity	✓				
Education	✓				
Insurance status	✓				
Employment status	✓				
Time since diagnosis	✓				
Month of assessment	✓	✓	✓	✓	✓
Residential location					
Average UV index at solar noon	✓	✓	✓	✓	✓
Outcomes					
Skin self-examination	✓	✓	✓	✓	✓
Sun protection behaviors	✓	✓	✓	✓	✓
Melanoma diagnosis, stage, thickness, and date		✓	✓	✓	✓
Clinician confirmation of cancer		✓	✓	✓	✓

Secondary Outcomes

Sun Protection Behaviors

Participants report how often they engage in 4 behaviors when outside on a sunny day: wearing sunscreen with a sun protection factor of ≥30, wearing a long-sleeved shirt, wearing a wide-brimmed hat, and staying in the shade [66]. Items are rated on a 5-point Likert scale (1=*never*; 5=*always*).

Clinical Outcomes

Participants report whether a new melanoma or other skin cancer was diagnosed and the stage, thickness, and date. Physician confirmation of this information will be collected.

Analyses of the Impact of MSS on SSE, Sun Protection, and Clinical Outcomes

Analyses of Thorough SSE and Sun Protection

Demographics and baseline variables will be compared between the 2 conditions using chi-square tests and ANOVAs for categorical and continuous variables, respectively. These variables, including outcomes, will also be compared by recruitment source. Missing data will be handled using multiple imputation with 50 imputed samples [67]. Tests of intervention effects on thorough SSE and sun protection will be conducted separately for each wave of postintervention data collection using logistic regression models that treat baseline SSE or sun protection, respectively, as a covariate. Given the large number of potential additional demographic and medical covariates, additional analyses will include the covariates that are significant predictors of the outcome.

Sample Size and Power

On the basis of our previous study, we expect follow-up survey completion rates between 80% and 93% at the 1-year time point and 80% to 85% at the 18-month time point, which will result in an expected final sample size of N=255. In the previous trial, thorough SSE occurred at a rate of approximately 30% in MSS at each time point, and effect sizes for conducting a thorough SSE ranged from w=0.29 (8 weeks) to w=0.21 (6 months). Given that the MSS intervention will be enhanced, we expect that the SSE rate will be higher (45%), which will result in approximately w=0.36. A sensitivity power analysis using G*Power indicated that a sample of N=255 will be able to detect an even smaller effect of w=0.22 with a 2-tailed test, Cronbach α of .05, and power of 0.95. Thus, the expected effect of w=0.36 with a sample size of N=255 will be detectable with a power of 0.99. Given that sun protection behavior is a secondary outcome, we are not powering the trial for this variable.

Analyses of the Impact of MSS on the Diagnosis of New or Recurrent Melanoma

The impact of MSS would be strengthened with data suggesting that survivors who use MSS detect suspicious growths and bring them to physicians for appropriate workup and diagnosis. Given the likely low recurrence rate over the 18 months that participants are followed for in this trial, the study is not powered for testing hypotheses on this end point. Rather, we will conduct an exploratory analysis to examine whether diagnoses differ between MSS and UC. Specifically, the number of diagnoses of earlier-stage new and recurrent melanoma at 18 months will be compared for the 2 conditions using either negative binomial regression models or binary logistic models depending on the distribution of new diagnoses (ie, if there are patients with more than one new diagnosis during the period).

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If our findings show that more melanomas are detected in MSS, we will conduct exploratory cost-effectiveness analyses from the health care and societal perspectives by creating simulation models of melanoma-related costs, disease progression, and survival over 5- and 10-year analysis horizons from the start of the trial (aim 3a).

Aim 3: Implementation Outcomes and Contextual Factors Relevant to Future Scale-Up

Overview

The type-1 hybrid effectiveness-implementation approach allows us to obtain vital data to inform future scale-up, dissemination, and implementation. This aim has 3 parts. In aim 3a, we will assess the costs of delivery of MSS and the control condition website; if indicated by the results of aim 2, we will conduct cost-effectiveness analyses. In aim 3b, guided by RE-AIM, we will evaluate the implementation outcomes of MSS from the aim 2 effectiveness trial. In aim 3c, we will elicit actionable feedback on contextual factors relevant to future scale-up, dissemination, implementation, and maintenance from multilevel stakeholders, including survivors, providers, and representatives of organizations invested in melanoma survivorship care. Quantitative and qualitative data from aims 3a, 3b, and 3c will be analyzed and interpreted together to provide valuable insights and directions regarding implementation strategies needed to inform the scale-up and widespread implementation, focusing particularly on reach, adoption, implementation, and maintenance. The results of aim 3 as a whole will answer the following key questions: how can we increase the number of MSS users to maximize adoption? What dissemination channels are preferred to increase our reach to survivors? How can MSS be maintained to provide a sustainable intervention for survivors? What resources or adaptations are needed for organizations and practices to integrate MSS into their survivorship care offerings?

Aim 3a: Costs and Cost-Effectiveness

Assessment of Program Costs

The research team will track the costs of delivering both MSS and the noninteractive educational web page. Costs will first be estimated from a program perspective, capturing the explicit resources required to deliver and maintain the program after all start-up costs (eg, development and programming costs) have been incurred. Costs that are needed to deliver the intervention will be collected to inform the cost of scale-up, but any research-related costs that would not be required for standard program implementation will also be tracked. Sunk costs, which are one-time upfront costs, will be reported separately from ongoing program implementation costs. Program cost data will be collected using a modified version of previous cost surveys developed by the research team and adapted for several interventions [68-73]. The cost surveys capture all relevant labor- and non–labor-related inputs necessary to quantify costs. Labor costs for program staff time (via questionnaires) will be valued using actual or estimated wages. Nonlabor costs will be obtained from program billing records; these include materials and supplies used to support program and intervention activities and costs of facilities and contracted services. The feasibility of including the value of participant time spent on the intervention will also be explored, where participants' time will be valued using age- and sex-specific wage rates. In addition, if the results of the analysis in aim 2 indicate that more melanomas are found among MSS participants than among the educational web page arm participants, costs to the health care sector will be estimated. These include the costs of diagnosing and treating recurrent melanoma. Published estimates of stage-specific medical costs of melanoma will be used to calculate the treatment costs of melanoma by stage at detection [74-79]. To estimate costs from a societal perspective, the costs to each stakeholder group will be summed, including program implementation costs, costs to the health care sector, and the value of participants' time.

Cost Analysis

Total and incremental program costs will be estimated for each arm. Program development costs, a one-time capital investment, will be calculated separately from ongoing implementation costs, or the costs to maintain program delivery for the duration of the intervention. Analyses will distinguish between fixed costs, those that do not vary with enrollment rates (eg, server maintenance), and variable costs, which increase for each participant added. As most costs for MSS are expected to be fixed, the mean cost per participant will be driven largely by the number of enrolled participants. To explore the costs of scale-up, sensitivity analyses will be conducted regarding additional program dissemination efforts and variations in uptake rates. The primary cost-effectiveness analysis will evaluate the additional costs per thorough SSE completed for MSS versus educational web page participants over the 18-month trial. This analysis will be conducted from the program, health care sector (including program costs and costs of health care use for lesions detected), and societal (ie, health care sector plus participant costs) perspectives. The incremental cost-effectiveness of MSS relative to the educational web page will be determined as the difference in mean costs between the 2 arms divided by the difference in mean outcome changes [80,81].

Simulation Models of Melanoma-Related Costs, Disease Progression, and Survival

If the findings show that more melanomas are detected in early stages for the MSS arm relative to the educational web page arm as expected, secondary or exploratory cost-effectiveness analyses will be conducted from the health care sector and societal perspectives by creating statistical simulation models of melanoma-related costs and disease progression over 5- and 10-year analysis horizons from the start of the trial. Assuming the equivalent likelihood of a melanoma recurrence for MSS and educational web page participants, trial data on stage at diagnosis for melanomas detected during the trial (from aim 2) and published estimates of average stage at diagnosis for survivor recurrences in the general population will be used. Melanoma treatment costs beyond the trial period will be simulated for both arms, where the hypothesis is that MSS participants will have lower treatment costs than those in the educational web page arm as earlier detection requires less aggressive treatment. Mortality will also be simulated for both arms to create an effectiveness measure of simulated life years gained (LYGs) for MSS versus the educational web page

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comparison group. To estimate LYGs, reductions in melanoma mortality for MSS versus the comparison group will be combined with life expectancy data [82]. As health-related quality of life among survivors of melanoma is similar to health-related quality of life in the general population, there will be no quality adjustment of LYGs as any differences across arms in quality-adjusted life years would be driven by differences in mortality [83-88]. The cost-effectiveness analysis will examine the total incremental costs of MSS compared with the educational web page arm. Incremental costs include program implementation costs (excluding sunk and research costs), health care use costs incurred during the trial and any melanoma treatment costs simulated to occur beyond the trial, and the value of patients' time to participate in the intervention. Incremental effectiveness will be calculated as LYGs for MSS compared with the educational web page arm. Base analyses will discount future costs and life years and use bootstrapping methods to generate 95% CIs for the incremental cost-effectiveness ratio. Sensitivity analyses will explore factors such as rates of detection of thin lesions through SSE, which may make MSS more cost-effective than the educational web page comparator.

Aims 3b and 3c: Exploration of Implementation Outcomes and Contextual Factors Relevant for Future Scale-Up

Sample

MSS Participants

All participants in the intervention trial assigned to MSS will complete surveys assessing specific implementation outcomes. A subset of MSS participants (n=30) will be purposively selected to participate in key informant interviews to reflect a diversity of MSS outcomes, MSS use, ratings of acceptability, and sociodemographic and clinical characteristics.

Additional Stakeholders

To ensure that we obtain a breadth of perspectives on the potential for scale-up, dissemination, widespread implementation, and maintenance of MSS, we will also identify and invite 20 individuals from multiple groups involved in melanoma treatment and survivorship to participate in key informant interviews. These stakeholders will include additional health care providers and representatives from the same organizations participating in aim 1. Participants in aim 3 key informant interviews will receive US $50 for completing the interviews, which will be conducted in person or via videoconferencing software.

Procedures, Measures, and Analyses

Overview

Aim 2 addresses the effectiveness of MSS. Aim 3a addresses the costs associated with delivering MSS, an important factor in the future potential scale-up of the intervention. In aims 3b and 3c, we use mixed methods to focus on the remaining RE-AIM outcomes and PRISM domains using data from the aim 2 RCT combined with surveys and stakeholder interviews.

Quantitative Implementation Outcomes and Analyses

As this is a type-1 hybrid effectiveness-implementation study, our analyses of implementation outcomes are primarily descriptive and meant to inform future planning for scale-up, dissemination, and implementation. Analyses of *Reach* will describe the proportion of contacted individuals who express interest by completing an eligibility survey. The clinical and sociodemographic characteristics of potential participants will be described and compared with those of the population of survivors of melanoma. Analysis of *Adoption* will describe the proportion of eligible participants who enter the intervention website (Table 3). Analyses of *Implementation* will describe the indicators listed in Table 3 and examine their variability by participant clinical characteristics, sociodemographic characteristics, and melanoma risk factors assessed in aim 2. We will also examine the variability in indicators of implementation by recruitment source (registry vs social media advertisements). The Acceptability of Intervention Measure (AIM) is a brief, quantitative measure of intervention acceptability that has demonstrated content and structural validity and test-retest reliability [89] as well as face validity [90]. Participants respond to 4 statements using 5-point Likert-type scales, with higher scores indicating higher acceptability. The AIM will be completed by MSS arm participants at the first follow-up. Acceptability ratings will be summarized using descriptive statistics and compared across clinical, sociodemographic, and risk factor groups.

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Table 3. Aim 3 implementation measures.

Outcome	Definition	Measurement	Data source
Reach	• Proportion and representativeness of individuals who express interest in MSS[a]	• Proportion of contacted participants who complete an eligibility survey • Sociodemographic and medical characteristics of individuals who screen vs the population of survivors	• Recruitment and enrollment data • National survivor data set (eg, NHIS[b] and HINTS[c])
Adoption	• Proportion of individuals who begin an intervention	• Proportion of contacted participants who consent, complete baseline survey, and enter the intervention website	• MSS automated data
Engagement	• How much individuals use MSS	• Number of core modules completed • SSEs[d] performed with self-check program • Number of views of MSS • Use of each enhancement (incentives)	• MSS automated data
Program costs and cost-effectiveness	• Total and incremental costs of MSS vs comparison arm; cost-effectiveness of MSS	• Surveys and billing and invoicing documents	• Staff, service provider, and participant surveys; billing and invoicing, including payments; and published literature
Feasibility	• Perception that MSS is feasible for use, dissemination, and delivery	• Qualitative key informant interviews	• Health care providers and professional organizations
Acceptability	• Perception that MSS is satisfactory	• Acceptability of Intervention Measure • Qualitative key informant interviews	• Participant surveys • Survivors, providers, and organizations
Appropriateness	• Perception that MSS is an appropriate fit for intended use	• Qualitative key informant interviews	• Survivors, health care providers, and organizations
Maintenance	• Perceptions of the likelihood, needs, and resources for maintaining MSS delivery	• Qualitative key informant interviews	• Health care providers and organizations
PRISM[e] contextual factors	• Perceived contextual factors related to scale-up and D&I[f]	• Qualitative key informant interviews	• Survivors, health care providers, and organizations

[a]MSS: mySmartSkin.

[b]NHIS: National Health Interview Survey.

[c]HINTS: Health Information National Trends Survey.

[d]SSE: skin self-examination.

[e]PRISM: Practical, Robust Implementation and Sustainability Model.

[f]D&I: dissemination and implementation.

Qualitative Key Informant Interviews

Interviews will be conducted with stakeholders from each group (ie, participants, providers, and organizations) to assess the perceptions of potential barriers and facilitators to consider for future scale-up, widespread implementation, and maintenance. MSS participant interviews will be conducted within the month following their final follow-up during the aim 2 trial. Interviews with other stakeholders will be conducted following completion of the effectiveness trial during the final study year. Semistructured interview guides will include open-ended questions and probes regarding [91] implementation outcomes of feasibility, acceptability, and appropriateness of widespread implementation of MSS for survivors of melanoma. The potential for MSS maintenance will also be explored using open-ended questions and probes, including resources available and needed for the sustainability of the intervention from multiple stakeholder perspectives. In addition, we plan to focus on three PRISM domains: (1) organizational, provider, and patient perspectives on the intervention; (2) characteristics of the recipients of the intervention (survivors); and (3) implementation and sustainability infrastructure (if MSS were to be disseminated and supported by specific organizations outside the research context). To elicit perspectives on the 3 PRISM domains of interest to scale-up, dissemination, implementation, and maintenance, interview questions (as appropriate for each stakeholder group) will focus on (1) current approaches and practices relevant to the promotion of SSE; (2)

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the benefits and shortcomings of the MSS intervention; (3) barriers to MSS use (for survivors and those who may suggest it as a resource); (4) possible strategies to disseminate MSS to survivors; (5) pros and cons of suggested dissemination channels and strategies; (6) the "fit" of MSS with the missions and objectives of providers, practices, and organizations; and (7) resources, infrastructure, and other factors needed to sustain MSS.

Qualitative Analyses of Implementation Outcomes

We will follow the guidelines established by the COREQ (Consolidated Criteria for Reporting Qualitative Research) for data collection, analysis, and reporting. The audio recordings of the interviews and focus groups will be transcribed verbatim, deidentified, and imported into the ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH) for analysis. Directed content analysis will be used. This structured method allows researchers to specify constructs of interest a priori (eg, acceptability, feasibility, appropriateness, and PRISM domains) and obtain detailed descriptions or elaborations of them, classifying and coding themes within and across constructs [92]. The study investigators will develop a preliminary codebook for each stakeholder group. A primary and secondary coder will independently code and discuss an initial subset of interviews to explore thematic content and then merge and explore them for concordant and discordant coding. After refining the codebooks, they will recode the first set of transcripts and determine the interrater reliability. After achieving consistency, the coding process will continue. In total, 4 randomly selected transcripts will be identified for double coding and evaluation of discordant coding, followed by any needed modifications and recoding to achieve consensus. Once the initial coding has been completed, 10% of the sample (ie, 1-2 participants from each stakeholder group) will be randomly selected and invited to participate in a member-checking process to determine whether additional data collection is necessary and ensure that valid inferences are made through coding procedures [93]. Following any further corrections, the team will develop a summative grid of emergent themes across and within stakeholder groups.

Synthesis of Quantitative and Qualitative Data to Inform Scale-Up

Mixed methods data will be analyzed and integrated using a concurrent parallel design [94]. As described previously, each type of data (quantitative and qualitative) will initially be collected and analyzed separately. A mapping and matrix approach will facilitate the integration and interpretation of the results, and joint displays will present the integrated results, connecting qualitative themes with quantitative outcomes. The results will be summarized within and across stakeholder groups to allow for consideration of multilevel dissemination and implementation strategies needed for future scale-up, dissemination, implementation, and maintenance.

Data Safety and Monitoring

Before initiating this study, the Rutgers Scientific Review Board will review the study procedures to ensure their scientific merit, safety, legality, and technical feasibility per the established policy. The proposed procedures will then be reviewed for protection against risks by the Rutgers health sciences IRB. Adverse events will be reported through the Rutgers CINJ for processing as per the established policy. This policy includes specific timelines for reporting events that are stipulated by the IRB. In addition to the IRB, the Rutgers CINJ Protocol Monitoring Committee reviews all adverse events for investigator-initiated trials as they occur. The project coordinator, under the direct supervision of the principal investigator, will be responsible for reporting any adverse events that are documented on the safety or adverse events form or reported by the study interventionist. The Rutgers CINJ Protocol Monitoring Committee will oversee the validity and integrity of the data by conducting periodic audits of the study records. The committee is empowered to suspend or close studies with major deficiencies and provides direction to investigators in the development of corrective action plans to rectify and meet identified deficiencies. As part of the Protocol Monitoring Committee function, accrual is monitored for clinical trials. All clinical trials undergo a semiannual review by the Protocol Monitoring Committee, at which time accrual figures are reviewed. Specific accrual rates for each trial are required under protocol monitoring policy. The Rutgers CINJ uses an internal audit program to address retention of participants, adherence to protocol, and data completeness. This audit program is reviewed and governed by the Protocol Monitoring Committee. In addition, there is a Data Safety and Monitoring Advisory Board. This team will consist of a dermatologist, a psychologist, and a survivor of melanoma from the community. The board, along with the study principal investigators, will convene for an in-person or virtual meeting annually. The agenda of the annual meeting will be to review risk procedures, adverse event reporting, and quality assurance. The Data Safety and Monitoring Advisory Board will review any serious adverse events reported as well as investigator adherence to eligibility rules.

Results

To date, we have completed the first phase of aim 1; the remaining phases of this aim are currently in progress. The prototype and content for the MSS intervention were developed in collaboration with Radiant Inc. Following the procedures described in the *Methods* section, one set of stakeholder interviews was conducted with 5 survivors of melanoma who were shown the SSE body map component. A second set of stakeholder interviews was conducted with another sample of 5 survivors of melanoma who were shown the goal-setting module. Participants were shown the prototypes and wireframe. The responses were summarized in field notes, and we reviewed the notes and verbatim transcriptions of key informant interviews. Each proposed enhancement was coded as supportive, neutral, negative, or mixed. For those enhancements that had multiple negative or mixed comments, the team decided whether the issue could be addressed and crafted changes to the content and approach that were congruent with stakeholder feedback.

For the 2 sets of interviews, 19 patients were approached. Of these 19 patients, 10 (53%) were enrolled and 9 (47%) refused. The sample consisted of 50% (5/10) women and 50% (5/10)

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men, ranging in age from 32 to 75 (mean 57, SD 14.55) years. They were primarily non-Hispanic White (9/10, 90%) individuals, with 10% (1/10) of the participants identifying as non-Hispanic Black. Most (9/10, 90%) were employed, and 50% (5/10) had a college degree or higher education. In total, 40% (4/10) had conducted a partial SSE in the last year, another 30% (3/10) had conducted a comprehensive SSE in the last year, and 30% (3/10) had not conducted an SSE in the last year.

A summary of the comments regarding design and navigation suggestions is provided in Multimedia Appendix 1. A summary of comments about content is shown in Table 4.

The team provided the recommended changes based on the feedback to the web developer. The interviewees in later interviews reviewed the changes made in response to feedback given in earlier interviews to provide confirmation on whether the issue was adequately addressed.

Table 4. Feedback regarding mySmartSkin (MSS) content and coding for phase 1.

Feedback	Coding	Team decision
Mixed reviews on the incentive options	Mixed	Changed incentive options based on feedback
MSS would be very helpful for survivorship care	Positive	—[a]
Wish MSS was available for public use	Positive	—
Content is thorough but quick to get through, which will motivate patients to use the app	Positive	—
Helps user feel in control of their health	Positive	—
Content seems overwhelming	Mixed	As some users felt that the content was manageable whereas others felt that it was overwhelming, we added a time estimate for each chapter so users will know how long it will take to complete so they can break the content into manageable sessions based on their own schedule.
Make the app more fun	Negative	Included gamification aspects such as badges and prizes that users can win
The importance of SSE[b] and MSS comes through in the content	Positive	—
Content is straightforward, direct, and concise	Positive	—
The app is visually pleasing	Positive	—
User likes the ability to make the text bigger	Positive	—
User likes the use of statistics to reinforce the importance of SSE	Positive	—
Want to share app with family and friends	Positive	—

[a]No decision made as feedback as positive.

[b]SSE: skin self-examination.

Discussion

Principal Findings

Once the analyses are completed, we anticipate that MSS participants will be more likely to perform thorough SSE and sun safety behaviors over the 18-month follow-up period and propose that there will be more earlier-stage melanomas diagnosed in MSS than in UC. In terms of the cost analysis, we expect that MSS will be a more cost-effective strategy given its greater effectiveness in increasing SSE and identifying new or recurrent melanoma. For the reach outcome, we predict that the demographic variables of survivors exposed to MSS will not differ from those of the general population of survivors of melanoma. For adoption, we propose that the proportion of contacted or eligible survivors randomized to MSS who consent, complete the baseline survey, and log into MSS will be equal to or greater than the proportion who adopted the intervention in our previous efficacy trial. For engagement, we propose that 80% of MSS participants will log into the intervention site at least once. For acceptability, we predict that MSS will be rated as highly acceptable, with mean acceptability ratings of ≥4 (out of 5) on the AIM.

Strengths, Limitations, and Unanticipated Problems

The study's strengths are the focus on both effectiveness and implementation through the type-1 hybrid approach; multilevel stakeholder engagement throughout the trial; a novel integration of RE-AIM, PRISM, and health behavior frameworks; the enhancement of a promising fully automated intervention; the scalability of this mobile or web-based intervention; the cost analysis; the longitudinal study design; and the inclusion of clinical outcomes. There are few interventions that have been evaluated to improve SSE among survivors of melanoma. No published intervention is fully automated, which represents a potentially cost-effective and scalable intervention delivery

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method. This study will advance the science of cancer survivorship by optimizing a promising intervention for an underserved group of survivors and preparing for widespread dissemination and implementation. Few studies have focused on implementation science aspects of consumer-facing digital interventions. Our use of a type-1 hybrid effectiveness-implementation trial will inform not only our understanding of the effects and implementation of MSS but also our understanding of future large-scale dissemination of self-administered web-based interventions. By evaluating and modeling the clinical outcomes, cost, and cost-effectiveness of MSS, our work will provide information about the costs associated with possible implementation and value.

There are at least 2 limitations. First, some individuals will not use MSS despite its high dissemination. Second, SSE outcomes are measured through self-report. However, this weakness is mitigated by the fact that self-report measures have excellent reliability and validity [14,66,95-100] and self-report has been recommended as the most appropriate assessment approach for wide-scale skin cancer risk reduction research [101].

Future Directions

If effective, MSS could be disseminated and delivered via dermatologist practices, public health organizations such as the American Cancer Society, and nonprofit organizations focused on melanoma or in partnership with existing social media channels. Future research should evaluate potential dissemination and implementation strategies to reach survivors building upon what we will learn in this study about the contextual factors that may impede or promote the future reach, adoption, implementation, and maintenance of MSS.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Science of Implementation in Health and Healthcare Study Section Healthcare Delivery and Methodologies Integrated Review Group Center For Scientific Review (SIHH, USA).
[DOCX File , 17 KB - resprot_v13i1e52689_app1.docx]

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Abbreviations

AIM: Acceptability of Intervention Measure
BCT: behavior change technique
CINJ: Cancer Institute of New Jersey
COREQ: Consolidated Criteria for Reporting Qualitative Research
CRGC: Cancer Registry of Greater California
IRB: institutional review board
LYG: life year gained
MSS: mySmartSkin
NJSCR: New Jersey State Cancer Registry
PHM: preventive health model
PRISM: Practical, Robust Implementation and Sustainability Model
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SSE: skin self-examination
UC: usual care

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Protocol

Telehealth Movement-to-Music With Arm-Based Sprint-Intensity Interval Training to Improve Cardiometabolic Health and Cardiorespiratory Fitness in Children With Cerebral Palsy: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Children with mobility disabilities, including those with cerebral palsy, have limited options and limited time to exercise to manage their cardiometabolic health and cardiorespiratory fitness. Regular cardiovascular exercise during childhood is a critical health behavior for preventing health decline in adulthood. Thus, there is an urgent need for accessible, age-appropriate, convenient exercise modalities in this group. Sprint-intensity interval training (SIT), combined with telehealth procedures, may be ideal for children with disabilities. SIT includes repetitive bouts of maximal exercise effort combined with rest periods, which can be effective in eliciting comparable results to moderate-exercise training with very short training durations.

Objective: This phase 1 pilot feasibility randomized controlled trial aims to investigate the potential effects of a 12-week SIT program on indicators of cardiorespiratory fitness and cardiometabolic health among children with cerebral palsy. An ancillary aim is to evaluate the feasibility of the program through several process feasibility metrics.

Methods: This study uses a 2-armed parallel group design. A total of 50 physically inactive children with cerebral palsy (aged 6-17 years) will be randomly allocated into 1 of 2 groups: a 12-week SIT or a waitlist control group that continues habitual activity for 12 weeks. The SIT prescription includes 3 tele-supervised sessions per week with 30 repeated sequences of 4 seconds of maximal arm exercise, with active recovery, warm-up, and cooldown periods (for an approximately 20-minute total session). SIT includes guided videos with child-themed arm routines and music. The exercise sessions will be remotely supervised through a web-based videoconference application and include safety monitoring equipment. Outcomes are measured at pre- and postintervention (weeks 0 and 13, respectively). Health outcome measures include peak oxygen consumption (VO_2 peak), measured by a graded exercise test; high-sensitivity C-reactive protein and blood insulin, hemoglobin A_{1c}, triglycerides, and cholesterol using a finger stick dried blood spot test; blood pressure, using a sphygmomanometer; and body composition (total mass, total lean mass, tissue % lean, and tissue % fat) using dual x-ray absorptiometry. Feasibility will be evaluated by the following metrics: adverse events or problems experienced throughout the intervention related to participant safety; perceived enjoyment; and recruitment, enrollment, and attrition rates.

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Results: Recruitment procedures started in November 2023. All data are anticipated to be collected by February 2025. Full trial results are anticipated to be analyzed and submitted for publication by March 2025. Secondary analyses of data will be subsequently published.

Conclusions: This trial tests an accessible and low-cost exercise program that leverages principles of high-intensity exercise to provide a convenient program for children with physical disabilities. Knowledge obtained from this study will inform the development of a larger trial for improving the cardiometabolic health, cardiorespiratory fitness, and well-being of children with physical disabilities.

Trial Registration: ClinicalTrials.gov NCT05619211; https://clinicaltrials.gov/study/NCT05619211

International Registered Report Identifier (IRRID): DERR1-10.2196/56499

(JMIR Res Protoc 2024;13:e56499) doi:10.2196/56499

KEYWORDS

disability; high-intensity; interval training; pediatrics; physical activity; telehealth

Introduction

Overview of Cerebral Palsy

Cerebral palsy (CP) is a clinical syndrome that results from a developmental brain injury and is prevalent in approximately 1 million people in the United States and 23 million people worldwide [1]. CP is characterized by disorders of movement and posture due to nonprogressive disturbances of the fetal or developing brain, which is often accompanied by disturbances of sensation, perception, cognition, communication, and behavior [2]. Secondary neurological conditions such as epilepsy, along with other musculoskeletal issues, are also found among people who are diagnosed with CP [2]. Recent innovations in treatments and technology have increased the survival rates of people with CP, resulting in a steadily growing population of adults with CP [3]. Health professionals can now focus on how to help empower young people with CP to live well with a disability, amid a variety of health conditions and socioecological challenges they face with community engagement in adulthood [4,5].

Adulthood and Cardiometabolic Risk

The transitory age between childhood and adulthood is a critical stage for health prevention interventions. As children with CP age into their 20s, they have a substantially increased risk of cardiovascular disease (CVD), related conditions, metabolic syndrome [6], and a 3-fold increased risk of CVD mortality compared to the general population [7-12]. The risk for these cardiometabolic diseases can be lowered by participation in regular moderate-intensity exercise [13-15]. However, recent studies demonstrate that children with CP do not engage in sufficient levels of exercise to obtain health-enhancing benefits, and these levels of exercise participation are far lower than those observed among children without CP [16-18]. Children with CP who exercise regularly are twice as likely to exercise as adults [16]. Consequently, there is a need to identify interventions that promote the early adoption of exercise as a behavior for preventing disease onset, particularly among children with CP who have a mobility disability and have the greatest risk of cardiometabolic disease [19].

Limited Aerobic Exercise Options for Mobility Disability

Conventional exercises that are known to improve cardiorespiratory fitness (eg, walking, running, and cycling) generally require long durations of training that [20] are unsuitable for a large majority of children with CP. As children transition into adulthood, approximately 27% will be unable to walk, 35% will experience decreased walking ability, and 9% will lose their ability to walk [21,22]. Children and adults with CP often experience secondary conditions, such as hemiparesis, fatigue, impaired balance, and joint pain, and these factors impede their mobility to walk or perform types of exercise (eg, cycle) for prolonged periods [22-25]. A recent scoping review demonstrated that a top research priority in the field of disability and exercise is to develop aerobic exercises that are inclusive of wheelchair users [26]. The standard options for exercise training methods require leg work or full body involvement. Aside from arm-ergometry or wheelchair propulsion, there are limited aerobic exercise modalities that are efficacious or effective for people who require seated training, particularly modalities that accommodate hemiparesis [26]. Of note, no randomized controlled trial of exercise has demonstrated a clinically meaningful improvement in cardiorespiratory risk factors in children with CP, likely due to a lack of a sufficient exercise dose [26].

Limited Generalizability of Research Interventions

A second notable limitation of published exercise interventions for CP is low rates of both recruitment and participation [26,27]. Despite over 30 years of research, including 49 published randomized controlled trials, the average sample size for a study was 30 [26]. Most participants were ambulatory, and wheelchair users were typically excluded from participation. These issues hinder the generalizability and transferability of study findings [26-30]. Moreover, low levels of participation in exercise trials were speculated to be due to the following barriers: (1) in-person supervision by a rehabilitation professional or exercise specialist, (2) on-site training at a laboratory or fitness facility, and (3) costly, specialized equipment [26,27]. The identification of an effective evidence-based modality that is inclusive of wheelchair users will require a protocol that can be replicated in a large trial that can provide confirmatory study findings.

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Rationale for Sprint-Intensity Arm Exercise

High-intensity interval training (HIIT) has been studied as an effective dose of exercise that has a moderate to large effect on cardiorespiratory fitness and cardiometabolic health while requiring a lower duration of training compared with continuous moderate-intensity exercise [31,32]. Sprint-intensity interval training (SIT) is a form of HIIT that also emphasizes short bouts of exercise with maximum effort at or above a power output associated with a peak oxygen consumption (VO_2 peak) [33]. A meta-analysis [34] found that SIT has a moderate-to-large effect on VO_2 peak that is similar to both moderate-intensity [35,36] and HIIT exercise [33]. Regarding the mechanism, SIT is believed to use anaerobic energy pathways of type IIB muscle fibers, the fast-twitch glycolytic pathways, which are replenished through oxidative metabolism [37], primarily from the kidneys [38]. In other words, extremely short bouts of exercise at maximal intensity can be sustained through the use of lower-intensity aerobic energy pathways. Specifically, higher exercise intensities result in increased renal hypoxemia and, thus, greater production of the hormone erythropoietin. Erythropoietin initiates the production of red blood cells that enhance oxygen use of performing muscles [39] and, thus, VO_2 peak. SIT may further increase VO_2 peak through mitochondrial biogenesis and capillary density [37]. A higher VO_2 peak is linked with reduced risk for cardiometabolic disease [36,40], which is relevant among children with CP who generally have low levels of cardiorespiratory fitness [41]. HIIT with a treadmill has been found to be safe and effective in improving VO_2 peak among ambulatory children with CP [42]. To the best of our knowledge, no randomized controlled efficacy or effectiveness trial has examined a wheelchair-accessible SIT program among children with CP [26,27]. SIT with arm-cycling results in greater gains in VO_2 peak versus leg-cycling (eg, 52% vs 6% increase in VO_2 peak, respectively) [43], likely due to a higher proportion of fast muscle fibers in the arms [43], and this information holds great value for nonambulatory children who can use their arms for exercise.

Telehealth Interventions Foster Enrollment and Attendance

To address low participation, telehealth interventions are especially promising because they remove many of the geographic, environmental, and financial burdens associated with traveling and paying for community programs and classes [44]. Telehealth interventions are especially helpful in delivering health services to children because of reduced burden on the caregiver, who would otherwise have to miss work or other commitments to travel or allocate transportation for the child's appointment [44]. Transportation and time are substantial barriers to exercise participation among people with disabilities [5]. Studies have shown that overall ratings of caregivers toward telehealth appointments are highly positive, and most view telemedicine consultations as at least as effective as those on-site; caregivers had modest reductions in out-of-pocket costs and less missed work costs [45]. In addition, telehealth programs are believed to enhance adherence by providing a sense of accountability, which is created by performance monitoring and social bonds with trusted professionals, as explained by the Supportive Accountability Theory [46]. Home-based exercise programs that incorporate telecommunications and monitoring have achieved the largest sample sizes of people with disabilities [26,27,47]. It is important to note that telehealth interventions that aim to promote strong attendance to an exercise regimen will require remote behavioral coaching strategies to maintain participant engagement. One meta-analysis found that exercise interventions that include behavioral techniques have stronger effects on exercise behavior than those that do not have such techniques [48].

Study Rationale and Purposes

In consideration of exercise barriers (lack of time and transportation) and facilitators of engagement among children (enjoyable exercises and music), this study aims to test a program among children with CP that incorporates (1) age-appropriate prerecorded videos with movement-to-music exercises that are based on child-appropriate themes (eg, superheroes, sports, and pop music), (2) replicable cloud-based telemonitoring procedures, (3) behavioral tele-physical education supervision during exercise, and (4) SIT adapted for varying arm abilities.

Aims

This study has 3 aims, described in following sections.

Aim 1: Examine the Effects of a 12-Week Home-Based SIT Program on Cardiorespiratory Fitness (VO_2 Peak) Compared to a Waitlist Control Among 50 Children With CP

This study will compare pre-post changes in cardiorespiratory fitness between 2 study groups. One group will receive 12 weeks of home-based SIT (n=25), and the second group, waitlist control (WC; n=25), will resume their normal daily activities for 12 weeks. VO_2 peak is the cardiorespiratory outcome of interest, which will be assessed by a graded exercise test using an arm ergometer. We hypothesized that the immediate start group would achieve greater improvements in VO_2 peak versus WC.

Aim 2: Explore the Effect Estimates of SIT on Cardiometabolic Risk Indicators Versus WC

Cardiometabolic outcomes will include high-sensitivity C-reactive protein (hsCRP) and blood insulin, hemoglobin A_{1c} (HbA_{1c}), triglycerides, and cholesterol using a finger stick dried blood spot test, and blood pressure using a sphygmomanometer. Additionally, body composition (total mass, total lean mass, tissue % lean, and tissue % fat) will be measured using dual x-ray absorptiometry (DXA). We hypothesized that arm-based SIT would demonstrate greater improvements in outcomes versus WC.

Aim 3: Evaluate the Feasibility of Arm-SIT Among Children With CP

Feasibility will be measured by process feasibility metrics [49] to inform a larger efficacy or effectiveness trial. Variables will include (1) intervention adherence (class attendance and video minutes through cloud-based analytics), (2) safety (adverse events or problems experienced throughout the intervention

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related to participant safety), (3) perceived enjoyment, and (4) engagement (recruitment, enrollment, and attrition rates).

Methods

Study Design and Overview

This phase 1, pilot feasibility randomized controlled trial will include a 2-armed parallel group design to examine the preliminary effects of 12 weeks of arm-based SIT on cardiorespiratory fitness compared to a WC that undergoes habitual activities for 12 weeks. The project will include 50 children with CP (n=25 per arm) and caregivers (n=50 parent-child dyads). One caregiver is required to participate by supporting their child's safety through the intervention and managing the child's exercise schedule. Participants will come to the laboratory for 2 total visits (baseline and week 13) to complete the data collection procedures. Participants will perform the intervention at home, with supervision by a research staff member through telecommunications.

Participants

Textbox 1 contains eligibility criteria for child participants.

Contraindications were informed by guidelines that were established by the American College of Sports Medicine [50] and the Pediatric Physical Medicine and Rehabilitation physician of the study team (DD).

Eligible caregivers will include parents or legal guardians of the child, who can commit sufficient time to support the child in their roles for the study and communicate in English. Caregivers who have complete blindness or deafness will be excluded from participation.

Textbox 1. Eligibility criteria for child participants.

Inclusion criteria

- medical diagnosis of cerebral palsy, as determined by the International Classification of Diseases–Tenth Revision codes
- age 6-17 years
- Gross Motor Function Classification System level 1 to 3 (as determined through participant screening, explained in the Screening and Recruitment section)
- medical clearance from a physician to participate in high-intensity exercise (using the attached medical screening form and explained in the intervention safety, monitoring, and response plan)
- access to a Wi-Fi internet connection in the home through a mobile phone or tablet computer
- a *z* score of ≤–3, indicative of high risk for fracture that could occur from torsion of spine

Exclusion criteria

- physically active (defined as >150 minutes per week of self-reported moderate to vigorous intensity exercise in a typical week)
- cannot use their arms for exercise
- Gross Motor Function Classification level of 4 to 5
- complete blindness or deafness
- pregnant
- uses a pacemaker
- has not been seen by a physician within the previous 12 months of their baseline visit
- uses a g-tube
- any past history of a contraindication to exercise testing: ischemia; myocardial infarction or other acute cardiac event; unstable angina; uncontrolled cardiac dysrhythmias; aortic stenosis; heart failure; pulmonary embolus or pulmonary infarction; myocarditis or pericarditis; aneurysm; low bone-mineral density of the spine (a *z* score of ≤–3, indicative of high risk for fracture that could occur from torsion of spine, determined at baseline data collection through the dual x-ray absorptiometry scan)

Participant Roles

Both the child and caregiver are considered participants in the study, and both will sign the informed consent or assent document.

The child's role in the study is to exercise, following along with exercise videos, 3 times per week for 12 weeks while being supervised through a videoconference web platform by a telecoach.

The caregiver's roles in the study are to (1) attend each videoconference exercise session with the child, (2) schedule and manage the child's exercise schedule, (3) support the safety of the child, and (4) achieve cardiopulmonary resuscitation (CPR) and automated external defibrillator (AED) certification through the Red Cross (certified by the principal investigator, BL, who is certified as a Red Cross CPR/AED instructor).

Screening and Recruitment

Screening for this study will occur in 3 phases. First, contact lists are screened for a medical diagnosis of CP based on the International Classification of Diseases, Tenth Revision (ICD-10) codes. Second, during the initial recruitment contact with a caregiver, research staff will screen participants based

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on the study eligibility criteria. As noted previously, to enhance intervention safety, this study aims to enroll children with CP who have only mild to moderate mobility disability and have a low risk of adverse events from exercise. Therefore, the initial recruitment contact through telephone will include the Gross Motor Function Classification System (GMFCS) level [51], using the GMFCS Family Report Questionnaire [52-54]. This assessment will be asked over the phone to avoid wasting participants' time arriving at the laboratory and learning that they do not qualify for the study. Third, a physician (study physician or participants' physicians) will review the patient's medical record and screen the participant for contraindications to exercise testing and risks for participation in high-intensity exercise (based on the Medical Clearance Form, Multimedia Appendix 1). In summary, if an absolute contraindication is identified, the participant will be excluded or withdrawn from the study. If no absolute contraindication is identified, the physician will identify major and minor risks based on the latest information within the patient's medical record and then decide based on major and minor risks to clear the participant for high-intensity exercise training at home. To ensure that record review information is relevant, if the patient has not been seen in the past year, they will have to be seen before obtaining medical clearance and participating in the study.

Candidates will be prescreened and recruited primarily from medical and billing records from the Children's Hospital of Alabama. Medical and billing record databases will be prescreened for potentially eligible patients by patient diagnoses codes (ICD-10, Clinical Modification) related to CP. Contact lists will be generated from the databases. Specific methods of recruitment will include word of mouth and flyers, physician, and staff referrals, mailouts, and phone calls.

Randomization and Clinical Trial Considerations

Parent-child dyads will be randomized into 1 of 2 groups: arm-based SIT or WC (n=25 per group) with a 1:1 allocation ratio using a permuted block randomization approach. The randomization sequence was generated by the project statistician (RAO) using a computer-generated randomized permuted block design (SAS software, version 9.4; SAS Institute). The project statistician sent the randomization sequence to the database manager (RY) during the study preparation phase. The database manager will unfold the randomization sequence for successfully enrolled participants into 1 of the 2 groups. Study outcomes will be assessed by a research assistant, who will be blinded to group allocation (single-blinded trial design). Recruitment will occur primarily through the Children's Hospital of Alabama. All other activities will be conducted at the Human Performance Laboratory in the Wellness Health and Research Facility at the University of Alabama at Birmingham.

Equipment and Telehealth Monitoring Platform

The study will use a web-based platform with physiologic devices to support remote telehealth supervision of the intervention. The platform, referred to as TeleRehab, includes an Android app that is installed on a computer tablet with Bluetooth capability, which sends data and allows 2-way communications to a secure web server. This setup allows a user on an Android computer tablet to communicate in real time with a member of the research team on a desktop computer. Communication features include videoconference and SMS text messaging. Heart rate data are recorded and transmitted for real-time view by both the user and research staff using a heart rate device (Polar Sense). The heart rate device was placed on a headband and worn on the head to avoid disruption caused by the rapid and vigorous arm movements required for the exercise intervention. Based on internal testing among research staff (nonpublished findings), placement on the head may result in more accurate readings during intervention exercise than when the device was worn on the forearm or upper arm. The device instructions from the manufacturer state that the Polar Sense can be worn on the head, forearm, or upper arm. The TeleRehab app system was an upgraded version of one used previously in a telemonitored feasibility exercise study among people with spinal cord injury [55]. A demonstration of an exercise session in the TeleRehab web portal, as viewed by a telecoach, is displayed in Figure 1. Additional equipment to support the safety of the intervention exercise sessions will include: (1) a blood pressure monitor (Omron HEM-7200/BP7200, 5 Series); (2) a medical alert device (Monitored Medical Alert System), a necklace-worn device that allows 2-way communication between the user and the American District Telegraph (ADT) emergency response team, who is available at all hours of the day to provide remote support for obtaining local emergency response to the user; and (3) a defibrillator (Philips HeartStart OnSite AED Home). Participants will be trained to use all devices at baseline data collection.

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Figure 1. Telecoach view of an exercise session with a participant through the TeleRehab app.

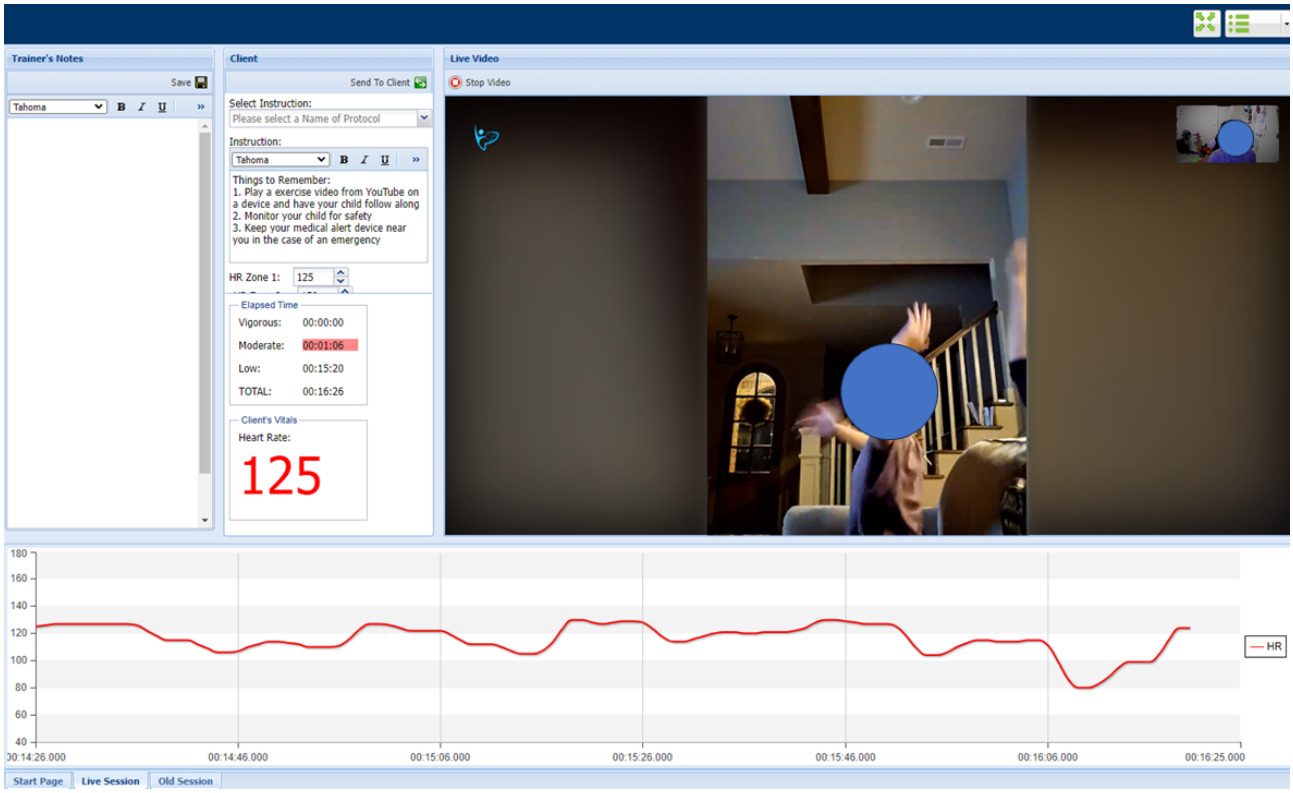

Procedures

Participants in the immediate start group will complete a 12-week exercise intervention with 2 data collection visits to the laboratory (pre- and postintervention; weeks 0 and 13, respectively). Participants in the control group will wait 12 weeks before starting the intervention, and they will also complete week 0 and week 13 data collection. Before arrival on a data collection visit, participants will be asked to fast for 10 to 12 hours overnight.

The first data collection visit (week 0) will include the following: (1) study briefing (purpose, procedures, roles, risks, and benefits), (2) informed consent and assent documentation, (3) study questionnaires, (4) cardiorespiratory fitness and cardiometabolic outcome measures, (5) Red Cross CPR and AED training for the caregiver, (6) ADT subscriber agreement form (to receive a medical alert device, shipped to the home from ADT), and (7) intervention or wait briefing (12-week prescription and equipment instructions).

The second data collection visit (week 13) will include (1) study questionnaires, (2) cardiorespiratory fitness and cardiometabolic outcome measures, and (3) debriefing (reviewing pre-post changes in outcomes) for the intervention group or intervention briefing for the control group.

Measures

Questionnaires

The study will include a demographic questionnaire of participant characteristics (eg, age, sex, and BMI) and the Godin Leisure-Time Exercise Questionnaire (GLTEQ). The GLTEQ [56] is a 3-item self-report questionnaire that is used to measure physical activity participation. The GLTEQ asks participants to report the number of times that low, moderate, and vigorous intensity of physical activity was performed for longer than 15 minutes in a typical week. The numbers reported for moderate and vigorous exercise intensity are then multiplied by 7 and 9, respectively, and summed for a score, which is referred to as the health contribution score. A health contribution score of <24 is classified as physically inactive, whereas a score of ≥24 is considered physically active [57]. There is evidence to support the GLTEQ as a valid and reliable measure of physical activity among adults with multiple sclerosis [58] and adolescents [59].

Cardiometabolic Outcomes

Aim 1 Primary Outcome: Peak Oxygen Consumption (VO_2 Peak)

The $V0_2$ peak will be measured during a graded exercise test on an arm ergometer using open-circuit spirometry with a metabolic cart (TruOne, ParvoMedics). Arm ergometers are considered the gold-standard modality for exercise testing among people with disabilities who use wheelchairs or cannot run or cycle for prolonged periods [60,61]. Arm ergometry has been suggested as a valid and reliable method for measuring VO_2 peak among children with CP with mild to moderate disability [62]. Before starting the test, participants rest for 3 minutes. They will then be instructed to maintain a pedaling cadence of 60 revolutions per minute. Resistance is increased every minute by 10 watts until the participant reaches volitional fatigue or achieves 3 of 5 criteria: age-predicted heart rate max of more than 85%; 17 or higher on the Borg rating of perceived exertion (RPE) 6-20 scale; respiratory exchange ratio of 1:1 or higher; plateau in oxygen consumption; volitional fatigue [63]; and subjective signs of exhaustion [64]. Heart rate and oxygen consumption will be measured continuously.

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Aim 2 Outcomes: Indicators of Cardiometabolic Health

Cardiometabolic health will be measured through a dried blood spot test, a blood pressure cuff, and a DXA scan.

DXA Scan

DXA scan variables will include total mass, total lean mass, tissue % lean, and tissue % fat. Scans will be analyzed using CoreScan software (GE HealthCare).

Blood Pressure (mm Hg)

Blood pressure will be measured by a sphygmomanometer. Elevated blood pressure during childhood is associated with intermediate markers and hard outcomes of CVD in adulthood [65]. Small changes in blood pressure (–6.4 mm Hg systolic and –4 mm Hg diastolic pressure) can occur from endurance training interventions with durations of up to 12 weeks [66].

Dried Blood Spot Fingerstick Test

A dried blood spot fingerstick test (ZRT Laboratory) will be used to assess blood-related cardiometabolic profiles and include hsCRP, HbA_{1C}, fasting insulin, triglycerides, and cholesterol (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]). Dried blood spot tests will be shipped for analysis to the ZRT Laboratory [67]. The ZRT Laboratory blood spot test has been conducted with children [68,69] and has demonstrated excellent validity with venous serum samples (eg, hsCRP, r=0.99; fasting insulin, r=0.93; fasting triglycerides, r=0.95) [67,70].

hsCRP (mg/L): C-reactive protein is a critical marker of inflammation that contributes to proinflammatory and prothrombotic elements of CVD risk. A single hsCRP measure is a strong predictor of myocardial infarction or coronary heart disease mortality, and several other diseases of the circulatory system in people without a history of such conditions [71]. Changes in hsCRP may occur from as early as 8-weeks of exercise [72].

HbA_{1c} (mmol/mol): HbA_{1c} is a measure of red blood cell mean hemoglobin glycation over the previous 3 months. A 1-month exercise intervention without a dietary component can expect a small to moderate effect [73].

Fasting Insulin (µIU/mL): High fasting insulin indicates the presence of insulin resistance, whether an individual shows glucose intolerance. Exercise interventions without a dietary component can expect a small beneficial change in fasting insulin levels after 1 month of training [73].

Fasting Triglycerides (mg/dL): A triglyceride level >150 mg/dL, is supported as an indicator of CVD risk [74,75]. Exercise interventions without a dietary component can expect a small beneficial change in triglyceride levels following 1 month of training [73], even among people with normal triglyceride levels [76].

Fasting Cholesterol (mg/dL): Abnormalities in the lipid profile, including high total cholesterol (TC), high LDL cholesterol, and low HDL cholesterol, are predictors of future CVD among young and middle-aged people [77,78]. Exercise interventions without a dietary component can expect a small effect after 1 month [73].

Aim 3 Intervention Feasibility

Feasibility will be measured using process metrics that will inform a larger trial [49]. Metrics will include adherence to the exercise prescription (measured through an attendance log managed by the telecoaches and TeleRehab cloud-analytics); technological issues; perceived enjoyment after completing the program will be assessed using the Physical Activity Enjoyment Scale (PACES) [79]; recruitment, enrollment, and attrition rates; and adverse events or problems experienced throughout the intervention.

Home-Based Intervention

The SIT intervention will be performed by participants at home and include 3 sessions of exercise per week for a total of 12 weeks. Each SIT session will include 30 repeated sequences of 4 seconds of maximal arm exercise [38], supplemented with active recovery periods of low-intensity posterior shoulder movements to prevent overuse of anterior muscles. Recovery will be gradually reduced from 30 seconds in week 1, 24 seconds in weeks 2-4, to 15 seconds in weeks 5-12 [38]. The total session duration changes from 24 minutes in week 1 to 16.5 minutes in weeks 6-12. Included in the total session duration are a 5-minute warmup and a 2-minute cooldown. A similar leg exercise protocol was found to be effective for raising VO_2 peak [38], and this dose may be optimal for achieving a high training volume while preventing fatigue due to muscle acidosis [38,80]. To achieve maximum intensity, participants are encouraged by the guidance in the videos to perform the 4-second bouts at their maximal effort. Regarding progression, resistance bands (low, medium, and heavy) will be gradually introduced into the exercises so that a participant will report a near maximum intensity (≥7 on the Borg RPE 0-10 scale; explained in detail in the next section) [81,82]. Children with CP from a home-based movement-to-music pilot intervention, from which this study protocol was based, reported that 20-minute videos would be ideal for their attention spans and busy school and care schedules [83]. Sessions will be guided by prerecorded videos that include an adapted exercise instructor (principal investigator BL) and a young adult actor with CP (LB; Figure 2).

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Figure 2. Exercise video themes guided by a disability exercise specialist and a young adult with cerebral palsy.

Videos will include 5 themes that were requested by children with CP from our pilot: 3 themes related to superheroes, 1 theme for pop music, and 1 theme for sports. Each theme will include 3 sequential videos that coincide with the rest periods (1 video for week 1, 1 video for weeks 2-4, and 1 video for weeks 5-12), totaling 15 videos. Children with CP can choose to exercise with any themed video that corresponds to their exercise week. Videos include songs that relate to the video themes. Music tempo and volume coincide with sprint and recovery periods. Sprint training incorporates repetitive arm movements that relate to video themes (eg, Spiderman videos include web shooting, football, and arm running or passing). Participants are instructed by the 2 actors in the videos, who demonstrate and guide participants through the exercises. Videos include CP-specific adaptations to enhance engagement [83]: verbal cues, visualized movement adaptations for hemiparesis, slow and repetitive instructions, positive reinforcement, judgment-free atmosphere, and imagery. Videos will be archived within a YouTube playlist. The benefits of archiving videos within YouTube (as opposed to a custom-designed mobile or web application) are that videos are easily accessible on any device, many people are already familiar with YouTube, and this process can easily be replicated. Videos will include themes that are based on copyrighted material, which will only be used for research purposes to adhere to “fair use” for “education” and “research purposes” of the Fair Use Act Copyright Disclaimer, Section 107 of the Copyright Act 1976.

WC participants will be asked to maintain their habitual activity behavior for 12 weeks and then receive the SIT intervention. All participants will be asked to maintain their habitual diet and eating patterns.

Intervention Development

The SIT intervention was adapted from a clinical adult exercise program, referred to as movement-to-music [84]. The program originated from a clinical efficacy trial that demonstrated improvements in lower extremity function and fatigue among adults with mobility disabilities [84]. The success of movement-to-music led to its implementation in larger confirmatory trials among adults with disabilities [85-87]. In contrast, a pilot feasibility trial found that several aspects of movement-to-music required modification to enhance participant engagement among children with CP who had mobility disabilities [69]. Findings from that study informed the development of the present SIT program.

Telecoach and Fidelity

This study will test a high volume of supervised training to ensure children with CP achieve the desired intensity before testing a more scalable self-regulated protocol in a larger randomized controlled trial. All 3 of the weekly prescribed SIT sessions will be supervised through a Zoom (Zoom Video Communications) videoconference by a telecoach. The telecoach will support participants in maintaining maximal effort intensity by monitoring RPE and providing motivational support. Motivational strategies will include positive verbal encouragement to bolster exercise confidence (ie, self-efficacy) and performing the exercises with the participant to enhance learning through observation (ie, vicarious learning). These strategies are informed by social cognitive theory [88], and the research team has used these strategies in other trials [55,83,86,89]. To monitor exercise intensity, the telecoach will ask participants how hard they are working after every change in song (~5 minutes) throughout the session. If participants report <7 RPE, coaches or caregivers will provide positive

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verbal encouragement to enhance motivation. Post session, participants will report an overall RPE for the entire bout to determine the need to add resistance bands. RPE has been found to be effective in controlling vigorous exercise intensity in people with spinal cord injury [90]. Since caregiver knowledge and attitude are determinants of participation [91-93], they will be asked to help manage the child's exercise schedule. The telecoach procedure was framed on supportive accountability theory: building a social relationship and bond with a trusted and knowledgeable health professional, with the inclusion of motivation strategies, can enhance intervention adherence [46].

Analyses

Statistical Power

The chosen sample size of 50 participants permits at least 20 in each of the 2 study groups at 12-week follow-up after allowing for up to 20% dropout (in each arm). Power calculations were performed using nQuery (version 8.7) for aims 1 and 2, and SAS (version 9.4) for aim 3.

For aims 1 and 2, baseline measurements will be compared with those obtained in week 13. We obtained estimates of the SD for VO_2 peak of 7.11 mL/kg/min [64], percent body fat (BF) of 8.5% [94], TC of 27.3 mg/dL [95], systolic blood pressure (SBP) of 14.0 mmHg [95], and diastolic blood pressure (DBP) of 11.7 mmHg [95]. With these assumptions and those of a 2-sided 2-group *t* test, an α of .05, and 20 participants per group, the study will have at least 80% power to detect between-group differences of at least 6.47 mL/kg/min in VO_2 peak, 7.7% BF, 24.9 mg/dL in TC, 12.8 mmHg in SBP, and 10.7 mmHg in DBP as being statistically significant (at any time point); with the previous assumptions and those of a 2-sided paired *t* test, an α of .05, and 20 participants, we will have at least 80% power to detect within-group changes of at least 4.70 mL/kg/min in VO_2 peak, 5.6% BF, 18.1 mg/dL in TC, 9.3 mmHg in SBP, and 7.8 mmHg in DBP as being statistically significant (between any 2 time points).

For aim 3, we anticipate adherence to the supervised exercise sessions of this study will be 75%, based on the 70% adherence found from our pilot, which had unsupervised sessions and videos that were not designed for adolescents. For an adherence rate of 75%, and assuming 40 participants in total, with 20 per study arm, complete the study, the corresponding exact binomial 95% CIs are 0.588-0.873) and 0.509-0.913.

Analyses

For all aims, data analyses will follow intent-to-treat principles. Descriptive statistics will be obtained and reported for study variables. The normality of data distribution of the continuous outcomes will first be confirmed using graphical techniques and tests of normality; continuous outcomes that deviate greatly from a normal distribution will be adjusted (eg, transformed) so that the data distribution approximates a normal distribution. All statistical tests will be 2-sided. Differences will be considered significant at $P<.05$. Statistical analysis will be performed using SAS software (version 9.4). Missing data that are not rectified through ongoing review of source documents may be managed with multiple imputations, and the influence of the missing data will be assessed with sensitivity analyses.

For aims 1 and 2, our primary method of analysis will be general linear mixed model techniques, such as mixed model repeated measures analyses, as there will be 2 study groups (SIT and WC) and 3 time points (baseline, 6 weeks, and 12 weeks). Post hoc analyses will be performed using the Tukey-Kramer multiple comparisons test. These models will allow us to assess the between-group effect, the within-group effect, and the group-by-time interaction. Covariates to be included in some models include age, sex, and GMFCS level. Analysis of categorical variables between groups will be performed using the chi-square test (or Fisher exact test, if needed). Pairwise correlations between study parameters will be assessed using Pearson (or Spearman, if needed) correlation analysis.

For aim 3, we will calculate adherence rates, adverse event rates, and other rates of interest and corresponding exact binomial 95% CIs. These rates will be calculated overall and stratified by the study group. Exploratory comparisons of rates between groups will be performed using the chi-square test (or Fisher exact test, if needed).

Ethical Considerations

The protocol and informed consent and assent forms were approved by the University of Alabama at Birmingham Institutional Review Board for Human Use (IRB-300008913) on January 12, 2023. Prospective participants provide written informed consent or assent documentation before participation in the study. Consent and assent forms are completed on the baseline data collection visit.

Before the enrollment of participants, this study was approved by the institutional review board of the university. Written informed consent documentation will be obtained from all participants before their engagement in the study. Participants will receive an electronic gift card that will be loaded for US $500 for each of the data collections completed, for a total of up to US $1000. The rationale for this value is to account for the commitment and time required of both the child and caregiver to complete the study. No artificial intelligence software or program was used in the writing of this manuscript.

Results

This study was approved by the university's institutional review board on January 12, 2023. The study was funded and initiated in May 2023, and the first participant was enrolled in October 2023. As of this manuscript submission on February 7, 2024, a total of 11 people have been enrolled in the study. The study's end date is April 30, 2025. The anticipated publication of the study findings will be in March 2025.

Discussion

Overview

This study will investigate the preliminary efficacy of a home-based, low-cost program for improving cardiorespiratory fitness and metabolic health that is child-appropriate for CP. A program that is short in duration, accessible for various physical

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abilities, and can be accessed anywhere through the internet could benefit this population. CP is a low-prevalence disability group that is often geographically isolated from suitable clinics, specialists, and adapted exercise services. Moreover, children with CP have limited options for exercise that are evidenced to improve their health [26,27] and have experienced lower participation in exercise since the outbreak of the COVID-19 pandemic [96].

Strengths and Limitations

Considering that this program can be delivered entirely through an internet video cloud server, YouTube, it has the potential to be carried forward in a scale-up randomized controlled trial of exercise for children with CP. This is important, considering that the average sample size for a randomized controlled trial for children and youths with disabilities has been found to be 27 people, and one of the largest trials included 159 people [27], numbers that are certainly not representative of the diverse needs of children with CP [97]. Another strength of this study is the incorporation of child-appropriate themes and music. Music-based therapy has been found to have an effect on functional ability and goal attainment among children with CP [98]. Child-appropriate themes were requested by this age group and could enhance engagement in therapeutic exercise [83].

This is a preliminary study with a high focus on examining the safety of the intervention and its efficacy under carefully controlled conditions (supervised exercise sessions). Supervised training through telehealth communication provides a sense of accountability that enhances adherence to the intervention prescription [46]. Thus, this study assumes that participants will adhere strongly to the intervention exercise, and the research question is not whether they will perform the exercise; instead, the question focuses on how well they will enhance their health with strong attendance. Should this trial be successful, there will be a need to compare the effects of supervised exercise training versus self-regulated, asynchronous training, which will be the primary format in which prerecorded videos will be used in real-world settings. Supervised training is burdensome for both the research staff and participants.

An additional limitation of this study is the requirement for on-site data collection procedures, which warrants investigation. On-site visitations are difficult for children with CP and their caregivers due to difficulties with transportation and lack of time with busy school schedules, therapies, and daily activities [5,99]. There is a need to develop home-based data collection procedures that provide comparable results to those obtained from in-person testing. The blood spot test can be performed remotely by shipping blood spot test kits to the homes of children with CP. However, to the best of our knowledge, there is no home-based alternative method for measuring cardiorespiratory fitness or body composition imaging, particularly among people with mobility disabilities [20].

Conclusions

Should the findings of this study suggest that the program can improve cardiorespiratory fitness or cardiometabolic health, the study may discover an innovative and, most importantly, scalable method of exercise intervention among children with physical disabilities.

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Data Availability

The data sets generated and analyzed during this study will be made publicly available at the completion of the study and can be obtained from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the final draft of the manuscript and project design. BL and TS created the initial manuscript draft. All authors contributed to either the study design, the creation of the study videos, or procedures.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medical clearance screening form.
[DOCX File , 17 KB - resprot_v13i1e56499_app1.docx]

Multimedia Appendix 2

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CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 90 KB - resprot_v13i1e56499_app2.pdf]

Multimedia Appendix 3
Peer-review report from the National Institutes of Health (NIH).
[PDF File (Adobe PDF File), 1098 KB - resprot_v13i1e56499_app3.pdf]

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Abbreviations

ADT: American District Telegraph
AED: automated external defibrillator
BF: body fat
CP: cerebral palsy
CPR: cardiopulmonary resuscitation
CVD: cardiovascular disease
DBP: diastolic blood pressure
DXA: dual x-ray absorptiometry
GLTEQ: Godin Leisure-Time Exercise Questionnaire
GMFCS: Gross Motor Function Classification System
HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
HIIT: high-intensity interval training
hsCRP: high-sensitivity C-reactive protein
ICD-10: International Classification of Diseases–Tenth Revision
LDL: low-density lipoprotein
PACES: Physical Activity Enjoyment Scale
RPE: rating of perceived exertion
SBP: systolic blood pressure
SIT: sprint-intensity interval training

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TC: total cholesterol
VO_2 peak: peak oxygen consumption
WC: waitlist control

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Protocol

An mHealth Intervention to Address Depression and Improve Antiretroviral Therapy Adherence Among Youths Living With HIV in Uganda: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: People living with HIV often struggle with mental health comorbidities that lower their antiretroviral therapy (ART) adherence. There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes. Given that mental health services are severely underequipped in low-resource settings, including in Uganda, new solutions to increase access to mental health care and close the treatment gap are urgently needed. This protocol paper presents the Suubi-Mhealth study, which proposed to develop a mobile health (mHealth) intervention for use among Ugandan youths (14-17 years) with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs.

Objective: The proposed study is guided by the following objectives: (1) to develop and iteratively refine an intervention protocol for Suubi-Mhealth based on formative work to understand the needs of youths living with HIV; (2) to explore the feasibility and acceptability of Suubi-Mhealth on a small scale to inform subsequent refinement; (3) to test the preliminary impact of Suubi-Mhealth versus a waitlist control group on youths' outcomes, including depression and treatment adherence; and (4) to examine barriers and facilitators for integrating Suubi-Mhealth into health care settings.

Methods: Youths will be eligible to participate in the study if they are (1) 14-17 years of age, (2) HIV-positive and aware of their status, (3) receiving care and ART from one of the participating clinics, and (4) living within a family. The study will be conducted in 2 phases. In phase 1, we will conduct focus group discussions with youths and health care providers, for feedback on the proposed intervention content and methods, and explore the feasibility and acceptability of the intervention. In phase II, we will pilot-test the preliminary impact of the intervention on reducing depression and improving ART adherence. Assessments will be conducted at baseline, 1-, 2-, and 6-months post intervention completion.

Results: Participant recruitment for phase 1 is completed. Youths and health care providers participated in focus group discussions to share their feedback on the proposed Suubi-Mhealth intervention content, methods, design, and format. Transcription and

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translation of focus group discussions have been completed. The team is currently developing Suubi-Mhealth content based on participants' feedback.

Conclusions: This study will lay important groundwork for several initiatives at the intersection of digital therapeutics, HIV treatment, and mental health, especially among sub-Saharan African youths, as they transition through adolescence and into adult HIV care settings.

Trial Registration: ClinicalTrials.gov NCT05965245; https://clinicaltrials.gov/study/NCT05965245

International Registered Report Identifier (IRRID): DERR1-10.2196/54635

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KEYWORDS

depression; adherence; mHealth; cognitive behavioral therapy; antiretroviral therapy; youth living with HIV; Uganda

Introduction

Overview

Globally, an estimated 39 million people were living with HIV in 2022; of these, 1.5 million were children <15 years [1]. Approximately 84% of new HIV infections among children <15 years occurred in sub-Saharan Africa (SSA) [1]. HIV disproportionately impacts children from poor and disadvantaged backgrounds, and the prevalence of HIV–related complications and mortality are highest among those struggling with poverty and deprivation [2,3]. Poor children living with HIV are more likely to experience compromised health, inconsistent antiretroviral therapy (ART) adherence, and elevated mental health difficulties, including depression, which increases the risk of HIV transmission [2,3]. In Uganda, the focus of this study and one of the SSA countries hardest hit by HIV, over 80,000 children (0-14 years) are living with HIV [4]. Improvements in access and use of HIV services, including testing, care, and availability of free ART have reduced child mortality [5] and resulted in an increased number of children now growing up with a highly stigmatizing and transmittable infection.

Depression is the most common psychiatric disorder among people living with HIV [6,7]. The prevalence of depression among people living with HIV is estimated to be as high as 63% in SSA [8]. Among young people, the prevalence of major depression is estimated between 16% and 40.8% [9]. Depression is associated with compounding and exacerbating negative HIV outcomes [10,11]. While high levels of ART adherence are necessary for young people to benefit individually from ART, as well as for reducing the risk of HIV transmission, depression has been found to significantly impede ART adherence [10,11]. Previous studies have found that patients with depression are nearly 3 times more likely to be nonadherent to medication regimens than patients without depression [12,13]. Depression can impact ART adherence through isolation from social support, impaired adaptive coping skills, apathy, forgetfulness, and hopelessness [14]. In addition, depression-related fatigue, low energy, inconsistent or lack of sleep, and loss of appetite may make it hard to take ART and attend medical appointments [15]. Indeed, due to limited ART adherence and associated medical complications, patients with depression have a higher risk of increased HIV viral load [16], rapid disease progression, and mortality relative to patients who are not depressed [17,18], making this a crucial population with which to intervene. Thus, failure to address the mental health needs of youths living with HIV, including depression, may lead to costly long-term consequences.

There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes [19,20]. Studies have shown that treating depression was associated with up to 83% higher odds of adhering to HIV treatment [19,21]. Among adults, improvements in cognitive processes have been shown to increase confidence and motivation to engage in HIV management behaviors [22,23]. However, few studies targeting the treatment of depression and evaluating the subsequent improvement in ART adherence have been conducted with adolescents [24], and even fewer studies have been conducted with populations from SSA [25]. Therefore, it is crucial to develop interventions for depression that are tailored to the needs of this specific population, given the prevalence of HIV in the region and the elevated risk factors and myriad barriers to care.

Youths are the lowest ART adherent age group and are at the highest risk of dropping out of ART care programs [26-28]. Poor ART adherence among youths is due, in part, to their transition from youth-focused care into adult-focused care that is less accommodating to the needs of this age group who are at the cusp of taking on new roles and responsibilities including their own disease management [29-31]. Moreover, insufficient staff training to support youths living with HIV during this period, lack of pediatric ART formulations in adult clinics, insufficient clinical monitoring, rigid scheduling that interferes with schooling, as well as loss of pediatric clinic relations with peers and clinical support staff all contribute to poor engagement in care during this transition period [27,28]. Indeed, studies indicate that this period in the life course is associated with a significant drop in ART adherence with up to 50% of youths discontinuing their HIV care entirely during this shift [32]. Thus, targeted interventions to improve retention and treatment outcomes during this period are critical.

Cognitive behavioral therapy (CBT) is a promising approach to reduce depression and improve ART adherence [33-35]. CBT is a form of psychotherapy that is focused on changing patterns of thinking and the associated behaviors [36]. CBT has a growing evidence base as an efficacious approach to reducing depressive symptoms and improving ART adherence among people living with HIV [24,33,37-39]. Moreover, evidence

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supports the efficacy and effectiveness of CBT in reducing self-stigma for people with mental illness—one of the major barriers to treatment adherence [40,41]. Some key principles of CBT that specifically target ART adherence and depression include instruction for behavioral activation, cognitive restructuring that addresses negative automatic thoughts, problem-solving, and relaxation training [39,42,43]. Despite the promise of CBT, youths with depression living with HIV, particularly those in resource-constrained settings such as Uganda, are challenged by numerous barriers to treatment including lack of access to health care and a severe shortage of trained providers [43-45]. As such, there is a need for interventions developed to take into account these numerous treatment barriers and to structure intervention components and delivery methods to fill the gaps in the current system of traditional assessment and treatment access.

A mobile health (mHealth) intervention is a feasible approach for the delivery of interventions to youths with depression living with HIV in Uganda. Upwards of 85% of countries in SSA have accomplished a high level of mobile phone penetration [46]. According to the 2021 Uganda Communications Commission Report, over 70% of Ugandans own a mobile phone [47]. Indeed, several studies in Uganda have used mobile technology to deliver health interventions, including the promotion of correct HIV or AIDS knowledge and testing [48], improving patient-provider communication [49], increasing clinic attendance among individuals on ART [50], and improving HIV care [51].

However, none have focused on addressing depression among youths living with HIV. Moreover, in our own work in Uganda, 80% of youth indicate access to a mobile phone [52]. In neighboring Kenya, a mobile app tested to deliver individual counseling services and facilitate peer support among youth living with HIV documented positive experiences, peer network development, as well as benefits related to treatment adherence, stigma reduction, and mental and behavioral health [53]. Thus, given the many barriers to care experienced by Ugandan youths living with HIV, as well as the lack of access to trained providers [54,55], the proposed Suubi-Mhealth intervention is a viable and sustainable approach for treating depression treatment in this priority population.

This Suubi-Mhealth study will develop a mHealth intervention for use among Ugandan youth with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. This mobile app will apply user-centered design methodologies we have used to develop and evaluate similar evidence-based digital therapies [56]. The study will be conducted in 2 phases and will be guided by the following specific aims:

1. Phase 1, aim 1: develop and iteratively refine an intervention protocol for Suubi-Mhealth based on formative work to understand the needs of youths with depression living with HIV (14-17 years).
2. Phase 1, aim 2: based on the results of aim 1, we will explore the feasibility and acceptability of Suubi-Mhealth for use with youths with depression living with HIV on a small scale to inform subsequent refinement for the larger phase of this project.
3. Phase 2, aim 1: pilot-test the preliminary impact of Suubi-Mhealth versus a waitlist control group, on reducing depression (primary outcome) and improving ART adherence, mental health functioning, quality of life, and lowering HIV stigma (secondary outcomes).
4. Phase 2, aim 2: qualitatively examine barriers and facilitators for integrating Suubi-Mhealth into health care settings.

Theoretical Frameworks Guiding the Study

The Suubi-Mhealth study is guided by two complementary frameworks: (1) the mHealth development and evaluation framework [57], and (2) PRISM (Practical, Robust Implementation, and Sustainability Model) [58]. The mHealth development and evaluation framework involves an iterative process for refining a mHealth intervention through integrating various information sources including published evidence, theory, and formative research with the target group [57]. Specifically, this process involves the following steps: (1) formative research to inform the development of the intervention content and regimen; (2) pretesting to determine the acceptability of the proposed intervention, improve and refine the intervention based on feedback; (3) pilot study to test intervention content and regimen as well as the process, including recruitment and data collection; (4) randomized control trial to test the effect of the intervention in comparison with a control group; (5) qualitative research to improve the intervention and implementation issues and methods; and (6) evaluation and implementation to determine the effect of the intervention once scaled up [57].

Similarly, PRISM is a comprehensive intervention development and implementation framework [58]. It emphasizes the following: (1) organizational perspectives on an intervention (eg, feasibility, adaptability, and barriers); (2) external environment (eg, community resources); (3) recipients' characteristics (youths, provider, and parent response); and (4) implementation and sustainability infrastructure (training and supervision supports). PRISM provides a framework to study the interaction of interventions with the characteristics of multilevel contexts or factors that may influence uptake, implementation, integration, and youths' outcomes (youths' responses, provider preparedness, motivation and fidelity, and community-level support).

Methods

Study Overview

The overall goal of this study is to develop a mHealth intervention (Suubi-Mhealth) for use among Ugandan youths with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. In phase 1 of the study, we will conduct 4 focus group discussions, each with 6-8 youths and 2 focus group discussions with health care providers, for feedback on the proposed intervention content and methods. Based on the results from focus group discussions, we will recruit 30 youths to engage with the Suubi-Mhealth app to explore its feasibility and acceptability so as to inform

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subsequent refinement for the larger phase of this project. In phase 2, a total of 200 youth from 10 health clinics will be recruited, and randomly assigned to either the Suubi-Mhealth condition or waitlist control condition (5 clinics with 100 youths per condition), to pilot-test the preliminary impact of the intervention on reducing depression and improving ART adherence, mental health functioning, quality of life, and lowering HIV stigma. Upon intervention condition, we will qualitatively examine participants' intervention experiences, as well as barriers and facilitators for integrating Suubi-Mhealth into health care settings. The hypothesized relationships are provided in Figure 1 below.

Figure 1. Suubi-Mhealth conceptual model. ART: antiretroviral therapy.

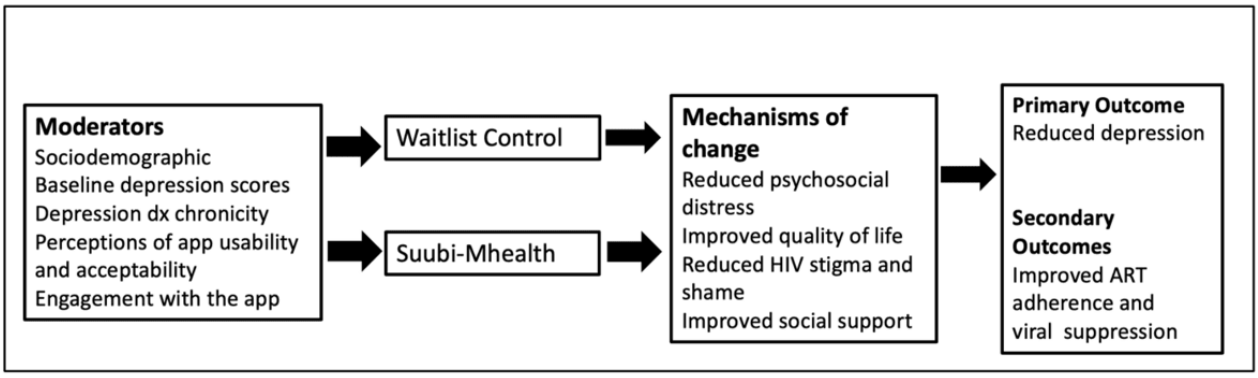

Research Setting

The Suubi-Mhealth study will be implemented in the greater Masaka region located in Southern Uganda, with one of the highest HIV prevalence in the country [4]. Youths will be recruited from health clinics where the International Center for Child Health and Development (ICHAD), which will house the study, and our collaborating institution, Reach the Youth Uganda, operate. For phase 1, youths will be selected from 2 clinics within 1 district. These clinics will be excluded from phase 2. For phase 2, we will select 10 clinics based on size (total number of youth served) and health facility level (levels II, III, IV, or hospital) in each district. For a health clinic to be included in the study, it will have to be credited by the Uganda Ministry of Health to provide ART and have adolescent-friendly services, for example, adolescent clinic days. The procedures have been used in our other studies implemented in the study region [52,59,60].

Inclusion Criteria

Youths will be eligible to participate if they meet the following criteria: (1) 14-17 years of age with the cognitive ability to understand and comprehend the assenting process; (2) HIV-positive and aware of their status, that is, disclosed to; (3) receiving ART and care from one of the participating clinics; and (4) living within a family, including with extended family members (not in institutions). We will identify youths with depressive symptoms by administering the Patient Health Questionnaire-9 (PHQ-9) [61], which has been validated in rural settings in Uganda [62,63]. Youth scoring ≥10 on the PHQ-9 will be considered for enrollment. Youths will be excluded if they do not meet the inclusion criteria above or are unable to understand the informed consent process, or inability or unwillingness to commit to study completion. Health care providers will be recruited if they are working directly with youths living with HIV at their clinics and agree to participate in the study.

Participant Recruitment and Consent

Procedures tested in our previous and ongoing studies in the study region will be used [59,60,64,65]. Specifically, participants will be identified and recruited from health clinics that are currently collaborating with ICHAD and Reach the Youth in the study region. A list of eligible participants will be created from medical records. Health care providers will present the study to adult caregivers of eligible youth during adolescent clinic days. These are scheduled days when youths visit clinics for ART refills, counseling, and treatment check-ins. If caregivers are interested, verbal consent to be contacted by a research staff (who will be onsite) will be requested. Next, the adult caregiver and the youth will separately provide consent or assent for the youth to be screened. Youths who meet the inclusion criteria and their caregivers (separately) will undergo an informed consent process to participate in the study. The consent and assent forms will clearly state that the youth can withdraw from the study at any time, for any reason, with no explanation, and will not be penalized. Caregivers will sign the consent form consenting for their children to participate. Youths will sign an assent form. If either the youth or the caregiver refuses to participate, the youth will not be enrolled. Health care providers will go through the same process and sign a standard consent form.

Sample Tacking and Retention

The project will take place in a highly stable region of Uganda, where geographical moves are rare. In addition to recommendations garnered by focus group discussion participants in aim 1, we will use several practices to increase retention. During our interviews, youths will be asked to provide details of contacts, including telephone number, and names, addresses, and contact information for 3 people who will always know how to reach them. Participants will be reminded that if the research team were to contact the people listed, the team would never discuss any details about the participant's involvement in the study. A phone call reminder will be made prior to each assessment. Our team has effectively used these

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methods in all our research projects, resulting in very low attrition [66-69]. We will keep careful records for those who drop out of the study and test for attrition bias based on data collected prior to study dropout. To the extent that such bias is present, we will limit generalizations accordingly, or, where possible, introduce statistical adjustments to address bias. Retention efforts will be periodically reassessed, reviewing best practices to reduce attrition.

Ethics Approval

We obtained approval for all study procedures from the Uganda Virus Research Institute Research Ethics Committee (Ref: GC/127/919) on August 29, 2022, Washington University in St. Louis Institutional Review Board (IRB; 202209115) on October 06, 2022, and from the Uganda National Council for Science and Technology (Ref: SS1442ES) on November 15, 2022. The study is registered in the Clinical trials.gov database (Identifier: NCT05965245).

Description of the Study Conditions

In phase 2 of the study, participants will be randomized to 2 conditions (100 youths per condition): a waitlist control condition or the Suubi-Mhealth condition, as detailed below.

Waitlist Control Condition

A waitlist control condition method will be used [70]. Participants will be randomly assigned to a waitlist and will receive the Suubi-Mhealth intervention after the active treatment group. In addition, participants will receive a smartphone without the Suubi-Mhealth app at the same time as the intervention group.

Suubi-Mhealth Treatment Condition

Overview

Participants in this condition will receive the Suubi-Mhealth intervention, with the specific components described below. All modules will be available in text, video, and audio format. All app content will be available in Luganda local language.

Evidence-Based Multimedia Psychoeducational Content to Reinforce Treatment Plans

Educational content will be provided within Suubi-Mhealth and broken into 20 modules. Users will be provided access for 2 months and will be instructed to review ≥2 modules per week. The research team has aligned Suubi-Mhealth content with state-of-the-science recommendations for CBT for ART adherence and depression as applied to HIV medication adherence [33]. In addition, the research team has implemented a group- CBT intervention to address depression and HIV-related stigma among adolescents [59,71]. This manualized intervention, developed with close consultations with mental health experts in the region, will be adapted into Suubi-Mhealth content. Core instruction will include psychoeducation on the interplay between HIV and depression; minimizing cognitive distortions related to ART adherence, stigma, and depression; challenging negative automatic thoughts; analysis and development of behavioral skills; reducing environmental stressors; creating support and helping communicate concerns adaptively and clearly; and problem-solving [37,38].

Safety Plan

To ensure safety while using the app, participants will be informed that the social networking center is informational only and not equipped for managing crises. Messages from users will be reviewed by a trained member of the research team within 24 hours. If signs of an imminent crisis are detected, a supervisor will send a crisis referral, make a report, and notify the parent so that no user waits longer than 24 hours to receive support. Emergency contact information will be shown in the corner of the survey page for all assessments.

Goal Setting and Self-Monitoring Features to Enable Self-Management

Our previous mHealth participants have indicated their desire for a goal-setting feature within an app, and studies of mobile apps have demonstrated that goal-setting, self-tracking, and monitoring features are essential to facilitate self-management skills and sustain user engagement [72,73]. With this in mind, there will be an ability to set goals and monitor symptoms of depression over time within Suubi-Mhealth. Rewards within an app have been shown to motivate and sustain healthy behaviors [74]. Our rewards feature will be used to inspire completing psychoeducation content and attaining goals by awarding digital “trophies” for participants who successfully meet a goal or reach a milestone (eg, complete a module on how to challenge negative automatic thoughts).

Clinical Dashboard to Monitor Participants’ Use of Suubi-Mhealth

A clinical management dashboard will make it efficient for the research team to input participant data and monitor participant use of the app and assessment responses.

Data Collection

Data will be obtained through an eligibility screening checklist, computer-assisted, interviewer-administered structured questionnaires, focus group discussions, and semistructured in-depth interviews. All assessments will take place at the clinic, participant’s home, or ICHAD’s field offices in Masaka. Assessments will be conducted by trained Ugandan Research Assistants.

Qualitative Assessments

Focus group discussions and semistructured interviews will be conducted. In phase 1, we will conduct 4 separate 60-minute in-person focus group discussions (6-8 youths each) and 2 focus group discussions for health care providers. Participants will be asked about impressions of expert-suggested content and design and their own suggested components for Suubi-Mhealth that could be of greatest utility for unique needs. They will also be asked for input regarding methods to increase participation and retention for follow-up assessments. All focus groups will be conducted in Luganda, will last approximately 1-hour and will be held in a private location at each clinic. In addition, we will conduct a 30-minute semistructured qualitative interview with each participant to further explore their experiences with Suubi-Mhealth, including perceived benefits and challenges of participation, and suggested modifications to improve specific components of the intervention. Complications or technical glitches with the app, and how it fared in regard to its ease of

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understanding, helpfulness, intuitive flow, presentation, and pacing will also be assessed. We will also conduct in-depth interviews with research staff who will be moderating the app.

In phase 2, we will conduct semistructured in-depth interviews with 30 participants upon completion of the intervention to explore their experiences with the intervention as well as barriers and facilitators to implementation and participation. Participants will be purposefully sampled [75], using a combination of high- and low-app users, that is, those in the upper and lower quartiles of engagement with the app (15 participants per group), to take part in a 30-minute semistructured qualitative interview. Interviews will focus on participants' experience with Suubi-Mhealth and how it fared in regard to its ease of understanding, helpfulness for supporting ART adherence and depression, intuitive flow, presentation, pacing, and the likelihood that they would recommend this intervention to a peer. Reactions to specific content and suggestions for improvement will also be assessed. We will additionally perform in vivo observations in which participants actively use the tool during the interviews to more directly observe challenges to use and implementation.

Quantitative Assessments

Quantitative assessments will be administered as follows. In phase 1, interviewer-administered quantitative assessments will be collected at 2 months post intervention to examine the usability characteristics and engagement with Suubi-Mhealth. To assess usability characteristics, we will administer a modified version of the 19-item USE (Usefulness, Satisfaction, and Ease of Use) questionnaire to measure usability characteristics of Suubi-Mhealth [76,77]. The USE will ask participants to rate the ease of use and learning (ie, efficiency), usefulness (ie, technical effectiveness), and likability (ie, satisfaction) of Suubi-Mhealth on a 7-point Likert scale (with 1= strongly disagree and 7= strongly agree).

To assess engagement with Suubi-Mhealth, automatically captured data within the app platform will be used to measure app engagement for each participant, including (1) the number of modules completed, (2) the number of messages sent, (3) the number of times self-monitoring and goal-setting features used, (4) the number of times logged into the app, (5) the time spent in the app once logged in, and (6) the time difference between app log-ins.

In phase 2, assessments will be completed at baseline and at 1, 2, and 6 months post intervention to evaluate whether participants' ART adherence and self-reports on symptoms of depression, mental health functioning and physical health, and quality of life and stigma improve with access to Suubi-Mhealth and whether improvements remain consistent over time. The measures to be used are provided in Table 1 below.

Table 1. Phase 2 assessment measures.

Variable	Measures
Demographics	Sociodemographic questionnaire
Depressive symptoms	Patient Health Questionnaire-9 (PHQ-9) [61] and Brief Symptom Index (BSI) [78]
Physical health	The Medical Outcomes Study HIV Health Survey (MOS-HIV) [79]
Quality of life	Pediatric Quality of Life Inventory (PedsQL 4.0) [80,81]
HIV shame	Shame questionnaire [82,83]
HIV stigma	Berger HIV Stigma Scale [84]
Social support	The Multidimensional Scale of Perceived Social Support [85] and Social Support Behavior Scale (SS-B) [86]
ART[a] adherence	Viral load; self-reports [87]
Intervention feedback	In-depth interviews

[a]ART: antiretroviral therapy.

Data Analysis Procedures and Milestones

Phase 1, Aim 1: to Develop and Iteratively Refine an Intervention Protocol for Suubi-Mhealth Based on Formative Work

Overview

We will conduct 4 focus group discussions, each with 6-8 youths (N=32), and 2 groups with health providers (n=16) for feedback on proposed intervention content and methods to increase participation and retention. Focus groups will be audio-recorded and transcribed verbatim. Transcripts will be translated into English and imported into Dedoose to assist with qualitative data management and coding. Inductive thematic analysis of focus group transcripts will be conducted by 2 research team members using the 6 steps described by Braun and Clarke [88] (getting familiar with the data, creating initial codes, looking for themes, reviewing and refining themes, defining and naming themes, and producing the report).

Milestone for Aim 1

We will have garnered input from youths and health care providers about the proposed Suubi-Mhealth content, features, and design. Participants will provide feedback on additional suggested components for Suubi-Mhealth that could be of the greatest utility for their unique needs. Suubi-Mhealth will be refined accordingly including its technical aspects, features to add or edit, and content updates or revisions. Participants will also be asked for input regarding methods to increase participation and retention for follow-up assessments. The study design and methods will incorporate feedback received from

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participants. Specifically, the research team will incorporate relevant suggested content and features into the Suubi-Mhealth intervention protocol before testing.

Phase 1, Aim 2: to Explore the Usability, Feasibility, and Acceptability of Suubi-Mhealth in a Small Sample to Inform Subsequent Refinement for the Larger Phase

Overview

Following the integration of input and feedback from focus groups to update and refine Suubi-Mhealth (phase 1, aim 1), we will β test Suubi-Mhealth among 30 youths. This is within the range of sample sizes for other pilot tests of digital therapeutics [77,89], and the suggested number of participants for pilot studies [90]. This sample size should be sufficient to explore the usability of and engagement with Suubi-Mhealth and for data saturation for qualitative interviews [91]. Participants will be instructed to use all features of Suubi-Mhealth for 2 months for the purpose of this β test. Two months for β testing is similar in length to other pilot tests for mental health apps [92,93], and will allow sufficient time for participants to engage with as many of the modules and features as they would like. Upon completion, we will garner feedback from each participant via mixed methods exploratory design in order to inform further enhancements of Suubi-Mhealth prior to the RCT (phase 2). We will conduct both quantitative assessments to examine the utility and usability of the Suubi-Mhealth and qualitative interviews to explore participants' experiences with the app.

Analysis Procedures

Quantitative assessments will be recorded using Qualtrics, an electronic data capture system. The data will be exported into the Statistical Analysis System for analysis. App usability will be examined using descriptive measures (mean, SD, median, and range) on the efficiency, technical effectiveness, and satisfaction components of the USE questionnaire. Descriptive statistics will also be used to describe engagement with the app (eg, the median number of logins and time spent in the app). Qualitative data will be analyzed in Dedoose following the same procedures provided in aim 1 above.

Adaptation and Feedback Integration Process

We will use procedures similar to those in our other studies for adapting mental health interventions based on target user feedback [94]. Specifically, participants' feedback gathered from content and usability testing, as well as from experiences obtained during in-depth interviews, will be incorporated into the app based on the level of importance and feasibility including cost. The research team, including the research staff overseeing the app and selected youth, will go over each module to make sure that relevant revisions have been incorporated. Together, the research team will review and approve the adapted content and design before launching phase 2.

Milestone for Aim 2

Participants will have, on average, engaged with 75% or more of the mobile app modules and will express enthusiasm over its potential to be a supportive tool. Participants will score Suubi-Mhealth as having high ease of use and learning (ie, efficiency), usefulness (ie, technical effectiveness), and likability (ie, satisfaction). Participants' provided feedback will be integrated into the app design.

Phase 2, Aim 1: to Pilot-Test the Preliminary Impact of Suubi-Mhealth

Overview

During phase 2, participants will be randomized to the intervention condition to engage with the Suubi-Mhealth app or the control condition (waitlist control group) to receive the app after the active intervention period. Assessments will be completed at baseline and at 1 month, 2 months, and 6 months post intervention to evaluate whether participants' self-reports on symptoms of depression, ART adherence, mental health functioning, quality of life, and stigma improve with access to Suubi-Mhealth and whether improvements remain consistent over time.

Participants will also complete the USE measure to assess acceptability and usability, as well as in-depth interviews to explore their experiences with the intervention.

Analysis Procedures

Following guidelines for clinical trial analysis, all primary analyses will be intention-to-treat analyses and missing data will be handled using multiple imputations.

Mixed-Effect Models

The principal strategy to examine primary and secondary outcomes over time between the Suubi-Mhealth group and the control group will be the use of linear mixed models and generalized linear mixed models, including a random intercept to allow for the correlation of within-participant measurements over time. Models will include the fixed effects of the intervention group (Suubi-Mhealth vs control), time, and group-by-time interaction. Effect sizes and 95% CIs will be reported.

Moderation Analysis

First, we will provide descriptive statistics on engagement (session duration, number of modules viewed) and usability scores. We will then use moderation analysis to examine whether Suubi-Mhealth engagement and usability scores moderate the effect of the interventions on our primary and secondary outcomes of interest (ie, depression, ART adherence, psychological distress, overall quality of life, shame, and HIV stigma).

Structural Equation Models

We will use mediation analysis to examine whether depression symptoms mediate ART adherence. We will test for mediation using structural equation models with CIs derived from bootstrapping of indirect and total effects. By applying mediation analyses, we will be simultaneously testing whether the intervention engages the targets and whether intervention-induced changes in targets are associated with clinical benefit. Models will account for baseline scores. For sensitivity analyses, we will use a per-protocol approach to address noncompliance by only including participants who completed the study according to the protocol.

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App Engagement and Usability

Basic descriptive statistics will be reported for Suubi-Mhealth engagement (session duration and number of modules viewed), as well as app usability scores (USE scores and subscales of efficiency, technical effectiveness, and likability). To determine the relationships between app usability and engagement, we will use linear regression models with an index of engagement (derived from principal components analysis using the above raw metrics of engagement) as the dependent variable and overall usability score as the primary predictor of interest. Demographics associated with both the usability scores and the index of engagement will be included as covariates in the model. In a separate model, we will include each usability subscale (efficiency, technical effectiveness, and satisfaction) rather than the overall usability score in order to explore which subscale might be most predictive of engagement with the mobile app-based tool. In addition, linear mixed models will be used to investigate the association between the intervention engagement index with the primary outcomes over time. Covariance structures for the models will be selected as described above. Effect sizes and 95% CIs will be reported.

Sample Size and Power

The primary outcome in aim 1 is whether depression decreases between baseline and postintervention initiation. This is calculated from the depression score change between these 2 time points and categorized as yes versus no. The intracluster correlation for clinics is assumed to be 0.093 and the rate of depression decrease in the control group is 5% [95]. Given our total sample (N=200, 100 youths per condition, 5 clinics per condition), we expect to achieve at least 80% power to detect a rate difference of depression decrease when the rate of depression decrease in the intervention group is 40% and the 2-sided significance level of the test is .05.

Milestone for Phase 2, Aim 1

Successful completion of a parallel-group RCT to test the feasibility, acceptability, and preliminary efficacy of Suubi-Mhealth. Participants will not experience any adverse events. Participants will have engaged with Suubi-Mhealth daily for 2 months and engaged with at least 75% or more of the modules.

Phase 2, Aim 2: to Examine the Barriers and Facilitators for Integrating Suubi-Mhealth Into Real-World Contexts

Overview

Upon completion of the intervention, we will conduct semistructured in-depth interviews with 30 participants upon completion of the intervention to explore their experiences with the intervention as well as barriers and facilitators to implementation and participation. Based on prior research [79], we anticipate that barrier themes may include (1) lack of knowledge and self-efficacy in using mHealth tools; (2) participants' inability to receive mobile service due to lack of service coverage and connectivity issues; (3) participants' inability to understand, maintain, or properly use the mHealth tool due to technology literacy issues; and (4) financial sustainability concerns related to the inability to charge a fee for service, bill, or otherwise be reimbursed for services provided via technology. We anticipate that facilitators may include working collaboratively with the app development team to address technical barriers and adapt the app to meet participants' needs and consistently reviewing app use data to inform progress [80]. The perceived relative advantage of the app over usual care, the ease of use and ability to adapt the app to improve participants' use, and awareness of participants' needs and resources will also likely serve as facilitators.

Milestone for Phase 2, Aim 2

Completion of an implementation evaluation in which barriers and facilitators are successfully identified as actionable inputs to inform the integration of Suubi-Mhealth into real-world contexts for youths with depression living with HIV. To ensure that this assessment is constructive in facilitating future implementation, we will map each key barrier and facilitator to a relevant implementation strategy identified in the literature to address a similar barrier or leverage a similar facilitator for maximal benefit [96,97]. For example, if the barriers related to service coverage and connectivity issues are mentioned, then the actionable solution will include working with a different service or network provider. This process will yield a concise yet informative implementation toolkit to support future implementation efforts that may face similar patient, provider, and organization-level challenges.

Data Integration and Triangulation

Findings from qualitative and quantitative data analyses will be integrated during the interpretation and discussion stages [98]. Conclusions and inferences will be synthesized for a more contextualized and thorough understanding of the preliminary impact of the intervention. The mixed methods design will serve two purposes: (1) complementarity and (2) expansion [99,100]. Qualitative findings will be connected to quantitative findings where the former will provide explanations and context for findings produced by the latter. Moreover, qualitative findings will complement our understanding of attendance and participant satisfaction with the intervention.

Results

The team completed the recruitment of phase 1 study participants (phase 1, aim 1) in January 2023. A total of 32 youths and 16 health care providers from 2 health clinics were recruited. Youths and health care providers participated in focus group discussions (4 groups for youths and 2 groups for health care providers). During the discussions, participants shared their feedback on the proposed Suubi-Mhealth intervention content, methods, design, and format, to inform the development of the app. All focus group discussions were audio-recorded to ensure accuracy of participants' responses. Transcription and translation of focus group discussions have been completed. The team is currently conducting data analysis of participants' responses, to inform the development of the Suubi-Mhealth app content. Concurrently, the development of Suubi-Mhealth content is ongoing. Specifically, the team is developing short videos to be incorporated into the app, including those related to depression and its symptoms, strategies to reduce negative thoughts, skill building, daily activities, and goal monitoring, to be incorporated into the app. Upon completion, the app will

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be tested among 30 youths to garner feedback on usability (phase 1, aim 2).

Discussion

Overview

People living with HIV, including adolescents, often struggle with mental health comorbidities that lower their adherence to ART treatment [7,9]. There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes [19,20]. This Suubi-Mhealth study will develop a mHealth intervention for use among Ugandan youths with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. We expect Suubi-Mhealth to be an acceptable and feasible mHealth tool to reduce depression and improve ART adherence and overall mental health functioning among youths.

The study innovates in the following ways. First, while mHealth interventions have been tested and implemented to improve adherence to ART among youths [50,51,53], digital intervention strategies addressing depression plus ART adherence among youths living with HIV in SSA are very limited [101]. This study will generate data-driven knowledge to address depression and ART adherence and will ultimately improve HIV-related health outcomes for youths, including adherence to medication. Second, delivering CBT—a theoretically driven intervention, delivered via a mobile app—has the potential to facilitate timely linkage and access to mental health services for youths, one of the major challenges to addressing mental health in impoverished communities. Previous studies have documented the potential of CBT to improve ART treatment outcomes [102]. Third, the study makes use of existing local institutions—both research and community-based institutions and locally recruited and trained research staff—to deliver its intervention, building research capacity and ensuring eventual scale-up and sustainability. Fourth, partnering with local institutions, including health clinics and community organizations, as well as the youths, grounds the project with a practical understanding of the needs of youths in the greater Masaka region—an area of Uganda hardest hit by HIV or AIDS [4]. Finally, the study takes advantage of the increasing penetration of cellphones and mobile phone ownership in Uganda [46], to test and deliver an innovative, culturally-tailored intervention with significant public health outcomes. Taken together, this study will lay important groundwork for several initiatives at the intersection of digital therapeutics, HIV treatment, and mental illness, especially among SSA youths, as they transition through adolescence and into adult HIV care settings.

Dissemination

The research team will facilitate learning across stakeholders and maximize the use of the evidence generated through dissemination meetings. Uganda's HIV prevention and treatment guidelines and policies recognize the burden and impact of mental health and HIV stigma on HIV treatment outcomes among youths, their families, and communities. If findings warrant, we will leverage these policy guidelines to maximize dissemination of study findings.

Data Sharing

The research team is committed to open, timely, and widespread sharing and dissemination of study findings. The team adheres to the National Institutes of Health's Public Access Policy that requires final, peer-reviewed papers to be submitted to the National Library of Medicine's PubMed Central upon acceptance for publication. We will also make study results available via papers written for professional and layperson publications, presentations at scientific and professional conferences, special lectures or talks in academic and professional settings, websites, and newsletters. Once all data have been deidentified, cleaned, and validated, and the main findings have been published, the investigators expect to share data with the scientific community. The research team will make data sets available to any individual who makes a direct request to the principal investigators and indicates the data will be used for the purposes of research. In sharing participant data, the team will follow Office of Sponsored Projects' data sharing agreements at Washington University in St. Louis, which are similar in their specification of the following conditions to be met before data are shared: (1) a formal research question is specified a priori; (2) names, affiliations, and roles of any other individuals who will access the shared data; (3) the deliverables—for example, paper, conference presentation—are specified a priori; (4) proper credit and attribution—for example, authorship, coauthorship, and order—for each deliverable are specified a priori; (5) a statement indicating an understanding that the data cannot be further shared with any additional individuals or parties without the Principal Investigators' permission; and (6) IRB approval for use of the data (or documentation that IRB has determined the research is exempt).

The research team will strip data of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual participants. We will share data in electronic format native to the software used by the research team; requestors are expected to handle converting electronic formats. Upon completion of the deliverables, the MPIs will instruct the requestor to destroy all copies of the data. If deliverables have not been produced yet, the agreement to share data will be revisited annually by the MPIs and the research team to decide whether to continue sharing or terminate the sharing agreement.

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clinics, and expert clients, for agreeing to participate in the study. The study outlined in this protocol is supported by the National Institute of Mental Health (NIMH; Grant R21MH131044; MPIs: PN; PC-R, and JM). NIMH has no role in the study design, data collection, analysis, interpretation of findings, and manuscript preparation. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIMH.

Conflicts of Interest

PC-R is a consultant for Rissana, LLC, PredictView, and Woebot. The other authors declare no conflicts of interest.

Multimedia Appendix 1
Peer-review reports from the National Institute of Mental Health (NIMH) | National Institutes of Health (NIH).
[PDF File (Adobe PDF File), 149 KB - resprot_v13i1e54635_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
CBT: cognitive behavioral therapy
ICHAD: International Center for Child Health and Development
IRB: institutional review board
mHealth: mobile health
PHQ-9: Patient Health Questionnaire-9
PRISM: Practical, Robust Implementation, and Sustainability Model
SSA: Sub-Saharan Africa
USE: Usefulness, Satisfaction, and Ease of Use

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Protocol

Improving Quality of ICD-10 (International Statistical Classification of Diseases, Tenth Revision) Coding Using AI: Protocol for a Crossover Randomized Controlled Trial

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Abstract

Background: Computer-assisted clinical coding (CAC) tools are designed to help clinical coders assign standardized codes, such as the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*), to clinical texts, such as discharge summaries. Maintaining the integrity of these standardized codes is important both for the functioning of health systems and for ensuring data used for secondary purposes are of high quality. Clinical coding is an error-prone cumbersome task, and the complexity of modern classification systems such as the *ICD-11* (*International Classification of Diseases, Eleventh Revision*) presents significant barriers to implementation. To date, there have only been a few user studies; therefore, our understanding is still limited regarding the role CAC systems can play in reducing the burden of coding and improving the overall quality of coding.

Objective: The objective of the user study is to generate both qualitative and quantitative data for measuring the usefulness of a CAC system, Easy-ICD, that was developed for recommending *ICD-10* codes. Specifically, our goal is to assess whether our tool can reduce the burden on clinical coders and also improve coding quality.

Methods: The user study is based on a crossover randomized controlled trial study design, where we measure the performance of clinical coders when they use our CAC tool versus when they do not. Performance is measured by the time it takes them to assign codes to both simple and complex clinical texts as well as the coding quality, that is, the accuracy of code assignment.

Results: We expect the study to provide us with a measurement of the effectiveness of the CAC system compared to manual coding processes, both in terms of time use and coding quality. Positive outcomes from this study will imply that CAC tools hold the potential to reduce the burden on health care staff and will have major implications for the adoption of artificial intelligence–based CAC innovations to improve coding practice. Expected results to be published summer 2024.

Conclusions: The planned user study promises a greater understanding of the impact CAC systems might have on clinical coding in real-life settings, especially with regard to coding time and quality. Further, the study may add new insights on how to meaningfully exploit current clinical text mining capabilities, with a view to reducing the burden on clinical coders, thus lowering the barriers and paving a more sustainable path to the adoption of modern coding systems, such as the new *ICD-11*.

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KEYWORDS

International Classification of Diseases, Tenth Revision; ICD-10; International Classification of Diseases, Eleventh Revision; ICD-11; Easy-ICD; clinical coding; artificial intelligence; machine learning; deep learning

Introduction

Background

Artificial intelligence shows a lot of promise for many health care applications, but its implementation in clinical settings is still limited [1]. One promising implementation area is clinical coding, which involves clinical staff or trained personnel going through large amounts of clinical text, such as discharge summaries, and assigning clinical codes to the texts. Clinical staff can thus summarize the patient's stay at the hospital using a system of codes such as the International Statistical Classification of Diseases and Related Health Problems (version 10; *ICD-10*[*International Statistical Classification of Diseases, Tenth Revision*]) [2].

A systematic way of summarizing patient care at hospitals is important for multiple reasons. The primary use of such data is to judge both the quality and volume of care. The data also serve as a consideration point for resource allocation. In addition, good coding practice is important for improving the quality of data available for secondary purposes such as research and knowledge generation.

An analysis of the literature reveals at least 2 major uses for computer-assisted clinical coding (CAC) systems [3]. The first type of use is to assist clinical coders in their work in real time, while the other type of use is in auditing the quality of existing coding. Audits are a principal element of quality control, especially since there have been reports of significant coding errors in electronic health record (EHR) systems. For instance, in a Swedish study, Jacobsson and Serdén [4] reported that 20% of the main diagnosis codes were wrong. For this user study, we focus on the former type of use, that is, assisting clinical coders in real time.

Available Knowledge

In terms of the informatics methods that CAC systems use, there is wide variation. Depending on specific use cases, rule-based methods have been successfully used to extract clinical concepts from texts [5-7] or to classify clinical texts into standard terminology such as Systematized Nomenclature of Medicine—Clinical Terms or International Classification of Diseases [8,9]. Rule-based methods appear to work well, but generally, texts have to be tokenized into short phrases or n-grams. Words within each sentence are usually treated independently of each other. Unless considered separately, clinical language peculiarities such as negation [10], uncertainty and speculations, and acronyms and abbreviations [11] can obscure the meaning of words in sentences.

With the advances in deep learning, in particular, transformer architectures, longer text sequences can be processed using contextual embeddings, where the representation of each word is based on its context. This contextual understanding of words makes deep learning an appropriate tool for CAC systems that process long and complex clinical texts. Santos et al's [12] systematic review on the topic shows a clear timeline transition toward deep learning methods, and this finding is echoed in a recent review by Kaur et al [13]. However, occasioned by multiple limiting factors related to the nature of clinical coding, current state-of-the-art (SOTA) performance is still unsatisfactory and lags other application areas of deep learning.

One of the major limiting factors is that assigning clinical codes to large sequences of text is a hard problem, compounded by a very large number of codes that represent the label space (eg, more than 20,000 *ICD-10* codes for Norwegian). In addition to the large number of codes, the level of class imbalance is rather extreme in this use case. Another limiting factor is that many close codes have semantically similar descriptions. An example of 2 semantically similar codes is "Other diseases of tongue (K14.8)" and "Disease of tongue, unspecified (K14.9)." It is challenging for a model to discriminate the two, since they both appear to describe some unnamed condition of the tongue [14]. Combined with other limiting factors such as poor data quality and availability, these factors make the design of automatic *ICD-10* coding systems nearly unattainable, especially for minor languages such as Norwegian and Swedish.

To get around this automatic coding problem, 2 popular approaches have emerged. In the first approach, researchers experiment with just a small portion of the codes, for instance, top-10 [15] or top-50 codes [16]. In many instances, these few top-N codes represent the majority of the data, but such systems perform poorly on rare codes. In the second approach, rather than automatically assigning *ICD-10* codes, multiple possible codes are provided as suggestions, much like recommender systems, with top-N suggestions. It is conceivable that this second work-around approach is useful to clinical coders because it provides potentially meaningful cues and pointers to the correct codes. This is the approach taken by the current user study.

It is important to note that a number of inconsistent findings have emerged from the little that has been published. In a recent study, Chen et al [17] concluded that, while their system improved the accuracy of *ICD-10* assignment, the system did not reduce the time required to assign the codes. In complete contrast to these findings, an earlier study by Wang et al [18] found significant time efficiencies when the CAC system was used, as did Fung et al [19]. We hypothesize that text complexity partially explains the conflict. Since text complexity is a factor that has not been fully explored in existing studies, we base our analysis of accuracy and time on the complexity of the clinical text.

Specific Aims

The aim of the project is to investigate artificial intelligence tools, natural language processing specifically, to improve the

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quality of *ICD-10* coding. The goal of the user study is to test whether our Easy-ICD system can reduce the burden of coding and also improve the quality of *ICD-10* coding. The main end points to measure are (1) the individual's coding accuracy averaged across all instances and F_1-score (harmonic mean of recall and precision, each of which is averaged over all instances), (2) time use for assigning codes, and (3) usability based on the system usability scale [20].

Methods

Study Population and Location

The user study will recruit clinical coders (physicians, health care staff, professional coders, etc) from Norway and Sweden on a rolling basis. Even though clinical notes are in Swedish, most of the target population understands both the Scandinavian languages.

Inclusion and Exclusion Criteria

In terms of participants, the main inclusion criterion is that the participant has coded clinical texts before, preferably *ICD-10* coding. Participants could be clinicians, nurses, professional coders, or other health care staff who understand Swedish with any amount of coding experience. We shall exclude participants outside Sweden or Norway.

Study Time Frame

Recruitment of participants commenced toward the end of 2023, and we will continue recruitment on a rolling basis until the target number of participants is reached.

Ethical Considerations

The data curated for this study is available through Permission Dnr 2022-02386-02 from the Swedish Ethical Review Authority. This user study is part of the ClinCode Project approved by The Regional Committee for Medical and Health Research Ethics, Norway (260972). Participation is based on informed consent. A web page with information based on the template from the Norwegian Centre for Research Data is used to provide information about (1) purpose of the project; (2) institution responsible for the project; (3) why the user is being asked to participate; (4) what the user is expected to do as a participant; (5) participation as voluntary; (6) user personal privacy, when and what happens with their data; (7) information about user rights (under the General Data Protection Regulation); (8) who to contact for more information or concerns; and (9) the final section where the user clicks on "Consent" or "Decline." If the user consents to participate, the consent is logged, and the user can proceed to the study. Thus, we have a written record of consent. If the user declines, they are redirected away from the study. It is important to note that no personal or identifying information is collected, and browser cookies are only used to track progress. Thus, all the data we store will be completely anonymous.

Intervention

The CAC system, Easy-ICD, is based on deep learning transformer models, also called language models. The system uses a language model trained in 3 main cycles, based on a typical natural language processing pipeline involving unsupervised or semisupervised training (pretraining) and supervised training (fine-tuning). First, the base model, Kungliga Biblioteket—Bidirectional Encoder Representations From Transformers (KB-BERT), was obtained from the transformers library [21]. KB-BERT is a Swedish general language model that was pretrained by the National Library of Sweden [22] and is publicly available. This pretraining represents the first training cycle. In the second cycle, KB-BERT was further pretrained on 17.8 GB of pseudonymized Swedish clinical text from the Health Bank infrastructure at Stockholm University [11], resulting in the current clinical language model named SweDeClinBERT [23]. In the final training cycle, also called fine-tuning, the model was fine-tuned on a pseudonymized data set, the Stockholm EPR GastroICD-10 Pseudo Corpus II, encompassing 120,000 patients. Using pseudonymized data for training improves security by decreasing the likelihood of private information leakage.

This model achieves SOTA results on this clinical coding task, comparable to results reported for English health data sets like the Medical Information Mart for Intensive Care [24]. This clinical coding task is framed as a multilabel problem, where participants can select and assign more than one *ICD-10* code to the clinical text. Actual performance results of the model are reported in a paper under consideration, and these results will be released in the final reporting of the user study.

Considering the Easy-ICD user interface, instead of displaying only the top label or labels as predicted by the model, we display the top-N predictions, where N is between 5 and 10. Through experimentation, we determined that an ensemble output from the deep learning model and fuzzy logic had the best results. Fuzzy logic is based on word-level and sentence-level minimum edit distance, using Levenshtein distance [25], comparing between *ICD-10* descriptions and the clinical text.

Easy-ICD is implemented as a web application for this user study, but in the future, the functionality will be incorporated into an EHR system. We used the classical model-view-controller pattern involving the deep learning model module, HTML 5 web interface, and a Python back-end controller, respectively. The web interface has the following sections: (1) the clinical note, (2) color-coded visualization to explain the suggestions, (3) the top-N suggestions from where the participant selects relevant *ICD-10* codes to assign, (4) qualitative feedback with star-rating and text feedback, and (5) a lookup feature for *ICD-10* codes.

Disease and Data

We use Swedish clinical notes in the gastrointestinal (gastro) domain in our study. The data used are from the gastrointestinal department of the Health Bank infrastructure at Stockholm University [11]. The data contain both in- and outpatient records of patients receiving treatment at the department, both surgery and other medical interventions. The data originate from a hospital, and no effort was made to include only similar cases; therefore, the cases vary.

The data are pseudonymized and have been curated by 2 professional clinical coders, so as to double-check the coding

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and create a gold standard. The 2 coders reviewed the data independently and reconciled their differences through discussion. This curation process also ensures that it will be possible to assign a code based on the clinical text alone, without the need for further information about the patient. This is important since the user study will not have access to further EHR data such as laboratory results or drug lists.

Study Design

This study is designed as a 2×2 crossover study as illustrated in Figure 1. This design, AB|BA (2 different sequences and 2 periods), is chosen for its uniform and balanced properties, aiming to control the carryover effect between periods. The design is suitable not only for comparing treatments but also for assessing pre-post effect of an intervention [26]. In addition, the crossover design requires a comparatively smaller number of participants than what a randomized controlled trial would ordinarily require.

Figure 1. Crossover randomized controlled trial where study participants are randomized into 2 groups. The first group first uses a control interface and then switches to our Easy-ICD tool, while the second group starts with our tool and switches to a control interface.

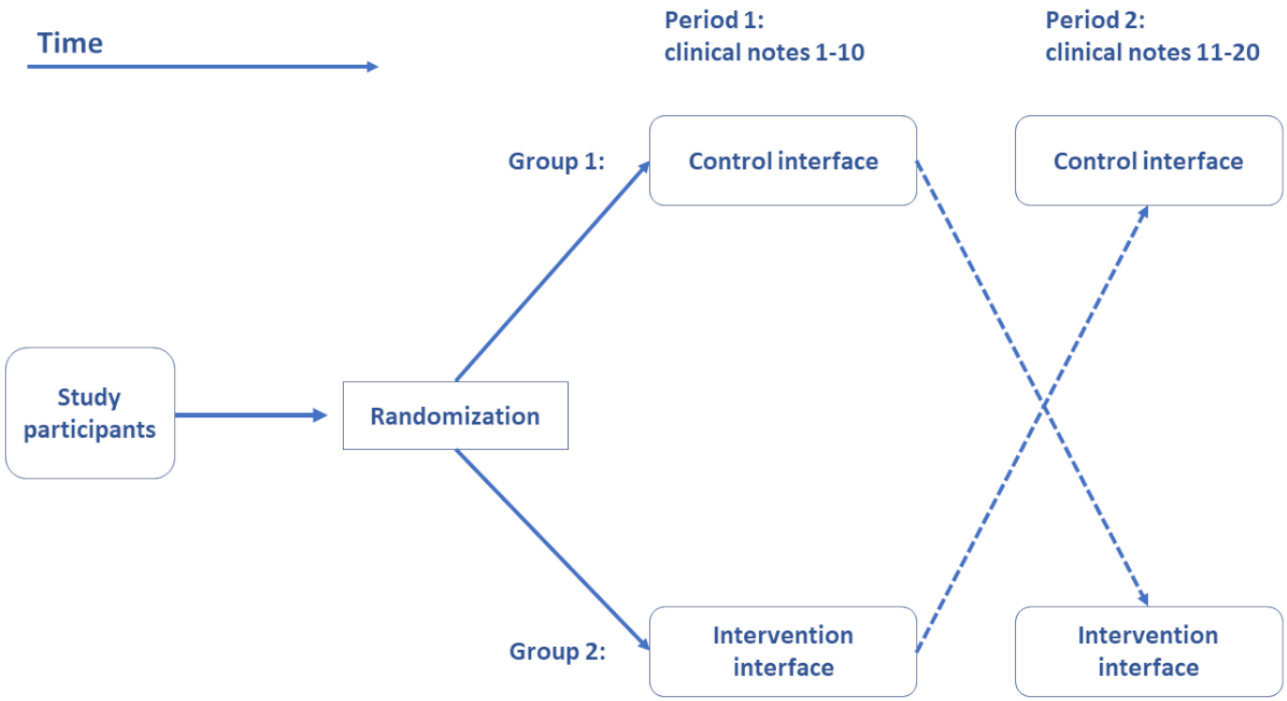

We will not incorporate a washout period partly because the learning element in the tasks measured is limited and partly because we do not want to risk losing participants in a long break between periods. The data sets in the 2 periods are different, and this limits any carryover effect in the sense that coders cannot memorize the text or the correct codes.

Once participants are recruited, they are randomly allocated to the 2 groups without allocation concealment. Allocation concealment will not be relevant for coders since it is known whether a participant is assisted or not, and we will not develop a placebo coding assistant. We will, however, conceal the allocation of subjects for the analyses.

In total, participants will code 20 clinical notes, where each note belongs to a single patient. The participants are asked to complete the experiment in 1 sitting without interruptions, and they cannot revisit or go back to previous notes. In the event that participants are interrupted, they are asked to exit the experiment, and any incomplete experiments are discarded as invalid.

In terms of the coding process, both the control and intervention user interfaces have a search utility for looking up *ICD-10* codes. Participants will be free to access any other additional search tools they wish to use without restriction. Since we measure time using a before and after design, the effect of additional tools is not expected to be a significant factor. The time is logged based on the browser button presses such as “Start,” “Next,” and “Complete.”

The user study process can be summarized in the following steps:

1. Study participants are randomly allocated to group 1 and group 2.
2. To prepare participants for the experiment, a short video tutorial is played after the consent form is signed and right before the clinical coding task commences.
3. In period 1 with 10 clinical notes, group 1 uses the control interface, while group 2 uses the intervention interface.
4. Data are logged in the background using button presses—time, assigned codes, and comments.
5. Then, there is an immediate crossover to period 2 for the last 10 clinical notes.
6. Data continue to be logged in the background using button presses.

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7. At the end, participants in both groups will complete the system usability scale.

Sample Size Calculation

This experiment is novel, and we have not succeeded in finding many similar studies from which to estimate test parameters. Therefore, our experiment is important in that it provides baselines that may be useful for similar experiments in the future. We do expect a correlation between periods; the same coders are measured twice on mean performance in time, making a matched 2-tailed *t* test suitable for the task [26]. This matched 2-tailed *t* test (period) is done in 2 sequences, and the sample size calculation must therefore be doubled [27]. Further, each sequence will consist of approximately 10 coding instances, giving extra power to the estimation of the sequence mean. Due to the unknown nature of the expected effect size, the sample calculation in Figure 2 is made with 3 different effect estimates ranging in the upper level of medium to high effect. A pilot study is necessary to establish a probable effect size and adjust sample size estimation if needed.

Figure 2. Statistical power of a 2-tailed t test at the level of 5% depending on sample size per sequence (2-tailed t test with equal SD in both study sequences to compare means).

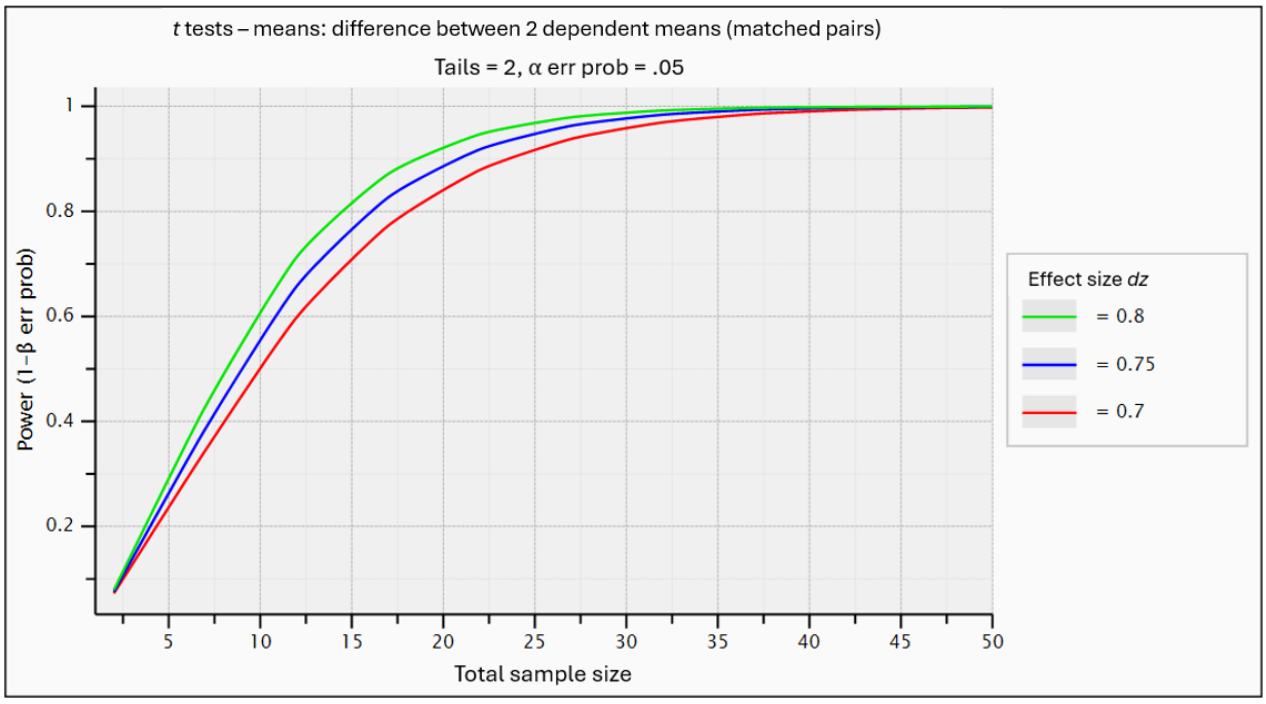

Based on the plot in Figure 2 derived from power analysis in G*Power [28], we aim to recruit up to 30 participants in total. Multiple methods are used to recruit participants, including contacting hospitals and health authorities directly, announcing at coding seminars and conferences, publishing news in popular science media, and advertising on social media groups and other electronic media.

Measurements and Analyses

The focus of our measurements is on how clinical coders perform with and without our system:

1. Compared with the performance of the unaided user, statistical tests of significance are used to check whether there are significant differences in the quality of coding when Easy-ICD is used, as measured by accuracy and F_1-score.
2. Time spent is the time it takes for a clinical coder to assign a code.
3. System usability survey will be given to all participants to measure usability of the web interfaces, both with and without our Easy-ICD system.

Main analyses are based on hypothesis testing using the paired *t* test and Wilcoxon test to compare the before and after means at a significance level of .05. Table 1 summarizes these hypotheses based on a test of equivalence.

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Table 1. Time use and coding quality hypotheses testing to compare the before and after means.

Time use	Coding quality (accuracy and F_1-score)
Null hypothesis: (H_0: $\mu_1=\mu_2$)	
There is no time difference between using CAC[a] and not using CAC for coding Swedish clinical notes	CAC does not affect a clinical coder's coding quality
Alternative hypothesis: (H_1: $\mu_1\neq\mu_2$)	
There is a significant time difference between using CAC and not using CAC for coding Swedish clinical notes	CAC affects a clinical coder's coding quality by a significant margin

[a]CAC: computer-assisted clinical coding.

In additional exploratory analyses, we will examine the effect wrong suggestions have on the coder's performance, and how often coders adopt these wrong suggestions. In addition, the distribution of the different professions between the groups as well as the coding experience will be explored.

To enable us to analyze the main outcomes in relation to text complexity, we distinguish between two categories of clinical texts: (1) short and simple texts (<512 tokens) and (2) long and complex texts (>512 tokens). However, we only consider the length of the text as the complexity dimension, as opposed to the complexity of the case or provided care, for example.

Results

Overview

Our results will be based on the statistical significance of the 2 tests related to time use and coding quality, which will allow us to conclude whether or not our CAC tool, the Easy-ICD, has the potential to impact clinical coding practice in a meaningful way. The expected results to be published summer 2024.

Evaluation Outcomes

The evaluation outcomes are as follows: (1) clinical coders aided by our Easy-ICD system are expected to yield better performance, that is, the accuracy and F_1-score. (2) We expect that the Easy-ICD system will result in time savings during coding tasks. Looking at the 2 categories of clinical notes, it can be expected that the most time savings could be gained with large and complex texts. Such cases take more resources than shorter and simpler texts. (3) We expect the usability of the system to have a system usability score over the generally accepted normal score of 68 [29]. Further, we do not expect any significant differences between the usability of the user interfaces with and without our CAC system.

Discussion

Principal Findings

There are 2 primary areas of interpretation with which our study is concerned. The first relates to the quality or accuracy of clinical coding. If it shows that coders aided by our system perform better than unaided coders, we can conclude that our system is a useful tool to improve the quality of clinical coding. If, on the other hand, no significant improvement in accuracy is noted, we have to look to the other measurement point for complete interpretation. Time efficiency is the other interpretation point, where we would like to see significant time improvement between the intervention and control.

If the accuracy is not better, then the time savings must be significant. If there are no time savings, then the improvement in accuracy must be significant. It can also be argued that the CAC system is still useful even if the timing is slightly worse, while the performance is better by a significant margin.

If neither time nor accuracy improves, then we have to think about improving the system for future studies. Regardless, we plan to publish our findings in an international (or Nordic) peer-reviewed journal or conference and note all the facilitating factors and barriers.

In terms of usability, if there are no significant differences in usability scores, then usability issues can be ruled out. If the CAC system has significantly better usability scores, we expect the usability scores of the standard interface to be no worse than what is considered normal.

Limitations

Perhaps one limitation of this study is that we curate the clinical texts used in the study so that the participants should be able to assign a code simply by assessing the text. In practice, some clinical texts need supporting information from other information sources such as pathology or radiology systems [9]. This supporting information would normally be available in patient record systems.

Another limitation is that we only considered data from the gastrointestinal department (K-codes), and this *ICD-10* chapter has a comparatively smaller number of codes. There were 415 unique codes in the training data, and just over 480 K-codes exist in the Norwegian version of *ICD-10*. In contrast, the whole *ICD-10* system has a total of over 20,000 codes in Norwegian. Therefore, the generalizability of our system is an important factor to consider for future studies when expanding to other clinical domains.

Comparison to Prior Work

Even though there are many papers on experimental work dealing with assigning *ICD-10* codes to clinical text, only a few studies with health care staff exist. The planned user study holds the potential to yield new insights about the usefulness of CAC systems in terms of reducing coding time and improving coding quality, both of which are important impact indicators for reducing the burden on clinical coders.

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Conclusions

In terms of impact, positive outcomes from this study contribute to the evidence that supports the adoption of CAC tools to reduce barriers to the implementation of modern coding systems such as the *ICD-11* (*International Classification of Diseases, Eleventh Revision*).

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

TC conceptualized the study. TC, AL, AB, TOS, PDN, KØM, and HD participated in methodology deliberations. TC, AL, and AB developed the software. TC prepared the original draft, and AL, AB, TOS, PDN, KØM, and HD contributed to the review and writing process. TOS and LIH worked on data curation, and LIH provided advice as a domain expert in clinical coding. TOS led the statistical analysis. HD acquired the funding and supervised the study. All authors reviewed the final paper.

Conflicts of Interest

None declared.

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Abbreviations

CAC: computer-assisted clinical coding
EHR: electronic health record
ICD-10: International Classification of Diseases, Tenth Revision
ICD-11: International Classification of Diseases, Eleventh Revision
KB-BERT: Kungliga Biblioteket—Bidirectional Encoder Representations From Transformers
SOTA: state-of-the-art

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Protocol

Integration of an Electronic Screening, Brief Intervention, and Referral to Treatment Program Into an HIV Testing Program to Reduce Substance Use and HIV Risk Behavior Among Men Who Have Sex With Men: Protocol for Intervention Development and a Pilot Randomized Controlled Trial

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Abstract

Background: Men who have sex with men (MSM) are disproportionally affected by HIV and drug and alcohol use; however, few effective HIV prevention interventions for MSM who use substances exist. Screening, Brief Intervention, and Referral to Treatment is an early intervention for non–treatment-seeking individuals with problematic substance use and for timely referral to treatment for those with substance use disorders. Electronic screening and brief interventions (e-SBIs) reduce implementation challenges. An e-SBI tailored for MSM at the time of HIV testing might be particularly opportune to strengthen their motivation to reduce substance use and HIV risk behavior.

Objective: This study aims to develop a tailored e-SBI program to reduce substance use and HIV risk behavior among MSM seeking HIV testing at Nexo Asociación Civil, our community partners in Argentina (primary); assess the feasibility and acceptability of integrating the e-SBI into the Nexo HIV testing program (primary); assess the feasibility and acceptability of implementing an adapted Men's Health Project (MHP) at Nexo (secondary); and finally, explore preliminary findings on substance use and sexual risk reduction outcomes (exploratory).

Methods: This mixed methods study has 2 stages. During stage 1 (development), we will use the User Centered Rapid App Design process consisting of focus groups (n=16), individual interviews (n=24), and a pilot deployment of the e-SBI (n=50) to iteratively develop the e-SBI. Quantitative and qualitative assessments at each step will inform the revision of the e-SBI. Furthermore, we will use the assessment, decision, administration, production, topic experts, integration, training, testing framework to adapt MHP. During stage 2 (pilot randomized controlled trial [RCT]), we will randomize 200 MSM coming to Nexo for HIV testing. They will complete a baseline assessment and then their assigned intervention (e-SBI vs screening only) and will be followed-up for 6 months. We will also conduct in-depth interviews with up to 45 participants: 15 participants from either study condition who entered or completed MHP or other substance abuse treatment and 15 from each arm who met the criteria for MHP but did not request it.

Results: The study began recruitment in October 2022, and the stage-1 pilot study is near completion. Preliminary findings from stage 1 show high e-SBI acceptability. Data analysis of the stage-1 pilot is now beginning. The stage-2 pilot RCT will be launched in March 2024, with all data collection completed by May 2025.

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Conclusions: This study will allow us to assess the acceptability and feasibility of e-SBI implementation during HIV testing encounters. We will also build the necessary research infrastructure for a subsequent RCT to assess the efficacy of e-SBIs in reducing substance use and HIV sexual risk behavior among MSM in this setting.

Trial Registration: ClinicalTrials.gov NCT05542914; https://tinyurl.com/yyjj64dm.

International Registered Report Identifier (IRRID): DERR1-10.2196/56683

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KEYWORDS

HIV; substance use; community health; implementation science; eHealth

Introduction

Background

Men who have sex with men (MSM) are disproportionally affected by HIV and drug and alcohol use [1-11]. Given the association between substance use and HIV risk behavior among MSM [12-25], the dearth of effective HIV prevention interventions for MSM who use substances is striking. However, as in the general population, identifying and engaging MSM with problematic substance use (PSU) in treatment is a significant challenge [26-28] that results in most MSM with PSU never receiving treatment [29].

The Substance Abuse and Mental Health Services Administration recommends Screening, Brief Intervention, and Referral to Treatment (SBIRT) as an early intervention for nontreatment-seeking individuals with risky alcohol and drug use and for timely referral to more intensive treatment for those with substance use disorders [30]. However, implementing SBIRT is a challenge; brief intervention (BI) is often missed and not evidence based, which can diminish its effectiveness. For example, when SBIRT was implemented in sexually transmitted disease clinics in New York City, out of 66,989 positive screens, only 17,474 received BI [31]. In medical settings, factors such as limited staff time, commitment to implementation, training requirements, difficulty in learning evidence-based BIs, skepticism about the effectiveness of SBIRT, and poor fidelity to recommended BI guidelines are all obstacles to the successful implementation of SBIRT [32-39]. These factors limit the BI in a particular setting. BIs can range from providing normative feedback to the individual on their level of severity (at times just a written report), brief advice (10-15 min), or a single 30- to 45-minute session. However, studies have shown that interventions that go beyond normative feedback and provide an empathic [33] or motivational component [34], or consist of multisession interventions for high-risk users, have better outcomes but can be difficult to implement. As a result, sizeable percentages of patients in a setting go unscreened, those who meet the criteria for a BI may not receive it, the BI may be delivered inconsistently, and the BI may not be of sufficient intensity to reduce substance use among those with low or moderate risk use or to improve entry into substance abuse treatment among those with high-risk use or dependence [35].

Electronic screening and brief interventions (e-SBIs) reduce implementation challenges such as extensive training, demands on staff time, and inconsistency in the delivery of BI [32,36-42], while remaining as effective as in-person SBIs [43-46]. Because an e-SBI demands only that a staff member provide an individual with a tablet or computer space to complete both the screening and BI, more individuals can be screened and receive the BI. For example, in an implementation pilot study that used e-SBI in rural clinics, approximately 92% of patients were screened, with over 95% of screen-positive women receiving the tablet-based BI, which far exceeds the rates in trials of person-delivered SBIRT (SJ Ondersma, personal communication). Furthermore, e-SBIs are consistently rated highly for acceptability among users and may facilitate greater disclosure of PSU than in-person SBIs because of concerns of being judged by providers. As such, an e-SBI tailored for PSU and sexual risk behavior among MSM at the time of HIV testing, when a contemplative client is already concerned about his risk behavior and cares enough about his health to seek an HIV test, might be particularly opportune to strengthen his motivation to reduce substance use and HIV risk behavior.

The need for such interventions is particularly acute in Argentina and Latin America, where there is little implementation of evidence-based interventions for MSM with PSU. In *Proyecto LINKS*, our study of 500 MSM in Buenos Aires [47], 61% of the men reported drug use and over 40% reported polydrug use during the previous 2 months. Marijuana, tranquilizers, cocaine, and *pasta base* (cocaine sulfate) were particularly prevalent. Furthermore, over 20% of users of these substances used them daily [9]. Most participants in the study consumed alcohol during the past 2 months: 32% of them reported drinking at least weekly and drinking enough to “feel it a lot,” “get drunk,” or “feel like you might pass out.” Substance use was higher among participants who were younger, unemployed, had greater mood variability, and did not identify as gay [9]. HIV prevalence, at 17% (31% among gay-identified men), and incidence, at 4.53 per 100 person-years (5.60 per 100 person-years in gay-identified men), were also alarming [48]. These findings highlight the critical need for effective, evidence-based HIV prevention interventions for substances using MSM in Argentina.

The proposed study seeks to address this glaring gap by using a user-centered process to develop and pilot a tablet-based e-SBI program tailored to MSM awaiting their HIV test at Nexo Asociación Civil, our community partners in Buenos Aires, who conduct over 1500 HIV tests per year with MSM. The e-SBI will integrate substance use and sexual risk behavior screeners and individually tailored motivational interviewing (MI) as the BI. Furthermore, we will adapt and pilot the implementation of the Young Men’s Health Project (YMHP)

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[49], a 4-session MI-based intervention that effectively reduced substance use and condomless anal intercourse among MSM who use substances, as a brief treatment provided at Nexo for participants with moderate-risk substance use or to build motivation to enter specialized substance abuse treatment among those with high risk or dependence.

Study Objectives

As a National Institutes of Health R34 (Clinical Trial Planning Grant) study, the main goal of the study is to develop and pilot all the study components and build the necessary research infrastructure for a subsequent randomized controlled trial (RCT) to assess the efficacy of the e-SBI to reduce substance use and sexual risk behavior. The specific aims of this R34 study are as follows:

1. Develop a tailored e-SBI program to reduce substance use and HIV risk behavior among MSM seeking HIV testing
2. Conduct a pilot RCT of e-SBI versus screening only (3:1 ratio) to assess the acceptability and feasibility of integrating e-SBI into the Nexo HIV testing program and the feasibility of a future large-scale efficacy trial of e-SBI, as measured by the following:
    - Percent of MSM testing clients at Nexo who accept entry into the study (recruitment rate)
    - Percent of participants who complete the e-SBI (retention rate)
    - Retrospective acceptability ratings of the 2 RCT conditions (primary)
3. Assess the feasibility and acceptability of implementing the Men's Health Project (MHP) at Nexo, as measured by the following:
    - The percentage of MSM with moderate or high-risk substance use who enter MHP from either RCT condition (recruitment rate)
    - The percentage of MHP participants who complete all 4 sessions
    - Prospective acceptability of MHP among participants in either RCT condition
    - Retrospective acceptability of MHP among those who received it
    - Percentage of sessions conducted by each MHP counselor that meet the criteria for MI proficiency on the Motivational Interviewing Treatment Integrity (MITI.4) ratings

Methods

Study Design

This 3-year study began on August 1, 2022, and comprises 2 stages. The first stage, *Development*, will consist of developing the e-SBI, adapting the YMHP into MHP, training counselors to deliver MHP, and piloting the e-SBI with 50 MSM coming to Nexo for HIV testing. During the second stage, *the Pilot RCT*, we will randomize 200 MSM coming to Nexo for HIV testing at a 3:1 ratio (e-SBI to screening assessments only) to assess the feasibility and acceptability of the e-SBI among MSM coming to Nexo for HIV testing and establish and pilot the RCT process for a future trial. As a secondary aim, we will assess the uptake, acceptability, and feasibility of delivering MHP to participants with moderate-risk substance use and subsequent referrals to substance abuse treatment among participants with high-risk substance use or dependence. Finally, we will explore the preliminary findings on substance use and sexual risk reduction outcomes.

At the outset of the study, we will convene a Community Advisory Board (CAB) composed of 6 members, including representatives from a local community-based organization focused on policy, training, and social marketing regarding substance abuse; a representative from the Department of Sexual Health, AIDS, and STIs at the Ministry of Health of the City of Buenos Aires; and 4 MSM who report using drugs and alcohol recreationally (these criteria will not be known to others). The CAB will meet study investigators (in person or via videoconferencing) quarterly throughout the study. The CAB will be responsible for reviewing and providing feedback on the e-SBI, MHP, and assessment instruments that will be used in the study before they are used with the study participants.

This study was registered at ClinicalTrials.gov on September 16, 2022. The identifier number was NCT05542914.

Ethical Considerations

Ethics Committee Approvals

The study was reviewed and approved by the Florida State University Institutional Review Board (IRB ID: STUDY00002530) and the Ethics Committee of Nexo Asociación Civil (protocol 26082022).

All participants were provided with a written informed consent form to read before participating in the study. The consent form included an overview of the study, study procedures, risks of participation, procedures implanted to minimize risks of participation, a statement of voluntary participation, and contact information for the principal investigators in Argentina and the United States, along with contact information for the respective institutional review boards. Consent was documented with the signature of the participants and research staff.

The results of the study may be published or presented, but no information that can identify individual participants will ever be provided or released in publications or presentations. To protect the privacy and confidentiality of participants, the study staff will keep any records containing identifying information in a locked cabinet accessible only to the research staff. The computer programs used in tablet-based interventions are compliant with US regulations on personal health information, as are the servers on which the data are stored. All data captured on the tablet, although it does not include identifying information, are encrypted in transit to maintain confidentiality. Any other study data will be stored on a secure computer that is protected by passwords. All records will be kept confidential. This is consistent with the guidelines of the US National Institutes of Health. After removing all identifying information, the remaining deidentified information collected during the study could be used for future research studies or distributed to another investigator for future research studies without additional consent.

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All participant incentives will be paid in cash in Argentine pesos. In stage 1, focus group (FG) participants will receive US $25; individual interview participants will receive US $20; and e-SBI pilot participants will receive US $10 and an additional US $10 for those who complete a qualitative interview. In stage 2, RCT participants will receive US $15 for completing the baseline assessment and e-SBI screeners, US $15 for the month 3 follow-up assessment, and US $20 for the month 6 follow-up assessment. Participants who complete the 6-month in-depth interview (IDI) will receive an additional US $20.

Components of the Intervention

MI Intervention

MI is the basis for both the e-SBI and MHP. MI is "a collaborative, goal-oriented method of communication aimed at strengthening an individual's motivation for and movement toward a specific goal by eliciting and exploring the person's own arguments for change." [50] In an MI session, a clinician guides rather than pushes a client toward change, sidestepping resistance, and actively works with the patient's strengths to build self-efficacy toward the desired outcome. MI uses standard tools of counseling and psychotherapy (ie, open-ended questions, affirmations, reflections, and summaries) strategically to elicit and reinforce change talk (patient statements that argue against the status quo, such as "I have been doing crazy things when I use drugs," or for behavior change, such as "I want to have sex sober so I don't want to worry the next day about whether I got HIV") and to inhibit sustain talk (patient statements that argue against change, such as "Sex a little high is fun"). Process research on the mechanisms of action in MI shows that more change talk [51,52] and less sustained talk during a session are related to better outcomes [51,53]. In addition, counselor behaviors such as advising, confronting, directing, and warning clients are associated with greater sustained talk [54,55], whereas affirming a client's strengths or effort, emphasizing client control, and supporting clients are associated with increased change talk [55,56]. Thus, to facilitate behavior change, the goal of an MI counselor is to interact with the client in a way that fosters change talk and inhibits sustain talk [51]. These key aspects of MI will inform the programming of the narrator in the e-SBI (described below), the revision of MHP, and the training of MHP counselors. The e-SBI will be created using the Computerized Intervention Authoring System (CIAS) V.3, which is an authoring tool that allows the creation and editing of electronic screening and intervention packages without the need for a programmer. Interventions built using CIAS feature a synthetic text-to-speech engine that reads all questions and speaks aloud to the participant (via headphones); synchronous interactivity; natural language reflections; branching logic; a clean user interface; and the ability to easily incorporate images, text graphs, figures, or videos. CIAS is consistent with human-computer interaction literature, suggesting that interactive, lifelike software can engage users and promote behavior change [57-61]. Thus, CIAS uses an optional interactive cartoon character capable of over 50 specific animated actions (smile, wave, read a message, express concern, etc) that talk for the entire program. The character acts as a narrator and guide throughout the process and provides occasional comic relief. Everything the character does is specifically programmed during the development phase, including interacting with participants in an MI-consistent manner and reflecting participants' change talk derived from their responses to the assessments. For example, using the participants' responses, the narrator might be programmed to say "You don't drink very often, but when you do, you drink a lot (from Alcohol Use Disorders Identification Test [AUDIT] responses) and you are noticing that it is impacting your physical health and your relationship with others (from responses to the Short Inventory of Problems)." CIAS has been used with thousands of participants (primarily those with low socioeconomic status) and has consistently received high satisfaction ratings [62-66].

YMHP Intervention

YMHP is a 4-session MI-based intervention that was the first intervention to demonstrate reductions in substance use and sexual risk behavior among non–treatment-seeking MSM who use substances [49]. Compared with the time- and content-matched control group, YMHP recipients were 18% less likely to use drugs and 24% less likely to engage in unprotected anal intercourse. On days when drug use and sex co-occurred, drug use reductions led to a decrease in unprotected anal intercourse. Secondary analyses showed that drug use among partnered participants was stable but declined significantly at all follow-up time points among single men [67]. We will adapt and implement YMHP as an in-house brief treatment for participants with PSU, either as a stand-alone treatment (for those with moderate-risk use) or as an intervention to link those with high-risk use or dependence on substance abuse treatment.

Stage 1: Development

Overview

The development of the e-SBI app will be guided by the User Centered Rapid Application Development (UCRAD) process [68-72]. UCRAD merges the streamlined and iterative Rapid Application Development approach with a user-centered design approach, which engages intended users throughout the app development process. This integrated approach aims to develop successful apps with good functionality, simple features, and usable interfaces [69]. As such, the intended users are given access to prototypes of the app, allowing them to provide feedback before the next iteration of the app. The process is relatively brief, approximately 6 to 9 months. UCRAD uses a 3-phase process as follows:

1. Predesign and interface prototyping: Data are gathered from key stakeholders to understand the requirements of the app in terms of content and interface. While continuing to assess user needs, developers offer potential solutions for the design. At the end of this stage, an initial prototype is developed based on the initial requirements.
2. System architecture and coding: The prototype is shared with the intended end users to obtain feedback. The developers update the prototype according to the feedback provided and begin system coding to develop a more complete version of the app. This version is returned to users for another round of feedback and development. The

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result of this stage is an advanced but often incomplete product with basic system architecture and system specifications.

3. Deployment: The app is implemented in the field to obtain further feedback from potential end users, and further development of the application is conducted to reach a final product.

Predesign and Interface Prototyping

To accomplish this phase, we will obtain feedback from the CAB regarding the study screening instruments and preliminary plans for the e-SBI content. After incorporating their feedback, we will conduct 2 FGs with MSM (n=16) recruited from Nexo testing clients who were 18+ years of age and self-identified as male. They will complete a substance use screener consisting of an illicit drug use question on the National Institute on Drug Abuse–modified Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) brief screen and the AUDIT-C (a 3-item alcohol use screen). Those who indicate using illicit drugs at least monthly or receive a score of ≥4 on the AUDIT-C will be eligible to participate. After obtaining informed consent, they will complete paper and pencil versions of the screening instruments planned for inclusion in the e-SBI, including:

- The *National Institute on Drug Abuse–modified ASSIST* [73,74] substance use assessment, which has high consistency in detecting moderate and high substance use, and high concordance (90%-98%) and correlation (intraclass correlation coefficient 0.90-0.97) for tobacco, alcohol, and drug risk scores [75]. A self-administered computer ASSIST was found to have a 0.93 interclass correlation with the interviewer-administered version [76].
- *AUDIT* [77,78] is a widely used tool developed by the World Health Organization to identify individuals whose alcohol consumption has become hazardous or harmful to their health. AUDIT is a 10-item screening questionnaire with 3 questions on the amount and frequency of drinking, 3 questions on alcohol dependence, and 4 on problems caused by alcohol.
- *Short Inventory of Problems-Alcohol and Drug Use (SIP-AD) for MSM* [79] is a 10-item version of the SIP-AD [80] (α=.95) derived through Item Response Theory, which was found to be highly valid and reliable among non–treatment-seeking MSM. The SIP-AD assesses the frequency (0=never; 3=daily or almost daily) of commonly experienced consequences of alcohol or drug use across the physical, intrapersonal, interpersonal, social responsibility, and impulse dimensions.
- *Sexual Practices Assessment Schedule* [81] asks about the number of partners and occasions of oral, anal, and vaginal sex with male, female, and transgender sexual partners in the past 2 months; use of condoms during sexual intercourse; and assumed HIV status of the partner.
- *Readiness to Change Rulers* for alcohol use, risky sexual behavior, and drug use: although they vary in their specific wording, single-item readiness to change rulers that ask respondents to place themselves on a scale of change from 1-7 or 1-10 have shown concurrent and predictive validity for alcohol use [82-85], drug use [82,86-88], and sexual risk behavior [84,89]. These scales are also often used in MI interventions to strategically evoke change talk and increase motivation to change problem behaviors.

The 90-minute audio-recorded FGs will (1) explore participants' reactions to the screeners and their impact on risk perception and motivation to reduce PSU and risk behavior and (2) evoke content for the BI component to develop options for reasons to change and potential approaches to reduce PSU and sexual risk behavior from which e-SBI users can choose. Within 48 hours of completing the FG, we will initiate a rapid analysis of these data [90,91] using a qualitative matrix [92,93] onto which participants' responses and recommendations will be entered to quickly organize and summarize FG findings. These findings will be used to build a prototype of the e-SBI.

System Architecture and Coding

This iterative app development process will be conducted with waves of 6 MSM recruited from Nexo testing clients, with the same inclusion criteria as in the FGs. They will be recruited during 2-week intervals to maintain a steady pace of feedback and revisions. The participants completed the intervention on the tablet. They then complete a 7-item self-report instrument used by CIAS developers [64] that assesses how much participants (1) liked the e-SBI and fount it to be (2) interesting, (3) easy to use, (4) made up of understandable questions, (5) respectful, (6) annoying, and (7) humorous; each item is rated from 1=not at all to 5=very much. Afterward, participants will be debriefed during an audio-recorded interview to explore (1) their responses to the acceptability assessment; (2) overall reactions to e-SBI; (3) emotional reactions as e-SBI progressed, including heightened risk awareness, concern, or motivation to reduce substance use and sexual risk behavior; and (4) recommendations for improving the ability of the e-SBI to engage MSM with high-risk drug and alcohol use in treatment. The interview data will undergo the same matrix-based, rapid analysis process used for the FG to quickly inform the next revision of the e-SBI. This process will be repeated with waves of 6 participants until mean scores on each acceptability question are ≥4.0 (≤2.0 on annoying), which we expect within 3 to 4 cycles. Figure 1 depicts our current conceptualization of the e-SBI, with specific content informed by the stage-1 findings. The development of the e-SBI will be guided by Choice Theory [94], which has been used extensively to inform goal choice interventions [95-100], including MI interventions to reduce substance use among MSM [97,98]. Rather than preset outcome expectations (ie, abstinence), goal choice interventions highlight personal choice and goal setting to engage individuals in reducing drug and alcohol use. Goal choice interventions are equally effective as abstinence-based interventions, allowing individuals to set their own treatment goals, which appears to increase success rates [99,100].

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Figure 1. Conceptualization of the electronic screening and brief intervention (e-SBI) intervention to reduce substance use and HIV sexual risk behavior among men who have sex with men in Argentina; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT: Alcohol Use Disorders Identification Test; MI: motivational interviewing; MHP: Men's Health Project.

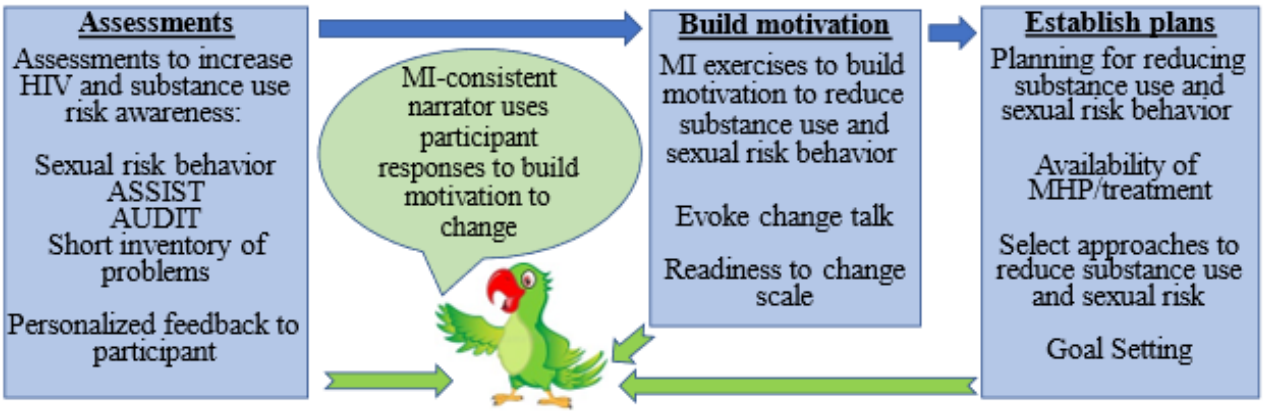

Deployment

The initial version of the e-SBI will be deployed with 50 MSM coming to Nexo for HIV testing to be used while awaiting their HIV test. On the basis of the findings from LINKS and Nexo screening data, we estimated that at least 50% will report using drugs and 80% will report using alcohol, and that 20% to 25% will report PSU. As such, a sample of 50 will allow us to explore reactions to the e-SBI from MSM with no, low-risk, and moderate to high-risk substance use. After obtaining informed consent, these individuals will complete the e-SBI and a brief quantitative acceptability assessment and then proceed to undergo their HIV test (to minimize participant distress). Subsequently, up to 25 of these participants will be randomly selected (5 with low-risk substance use and 20 with moderate or high-risk substance use) to undergo an audio-recorded IDI that will be guided by the theoretical framework of acceptability (TFA; see components in Textbox 1) [101], which has been used to guide qualitative and mixed methods research on the acceptability of health care interventions [102-105]. Data from these interviews will also undergo a rapid qualitative analysis as previously described for the FGs.

Textbox 1. Components of the theoretical framework of acceptability.

- *Affective Attitude:* how the individual feels about the intervention
- *Burden:* perceived amount of effort that is required to participate in the intervention
- *Ethicality:* extent to which the intervention has a good fit with an individual's value system
- *Intervention Coherence:* extent to which the participant understands the intervention and how it works
- *Opportunity Costs:* extent to which benefits, profits, or values are given up to engage in the intervention
- *Perceived Effectiveness:* extent to which the intervention is perceived as likely to achieve its purpose
- *Self-efficacy:* the participant's confidence that they can perform the behaviors required to participate in the intervention

Adaptation of YMHP to MHP

In consultation with our CAB, the research team will adapt YMPH while guided by the modified ADAPT-ITT (assessment, decision, administration, production, topic experts, integration, training, testing) framework (Textbox 2) [106]. The adaptation will focus on three main areas: (1) tailoring YMHP to Argentine MSM (including translation and cultural relevance for MSM aged over 29 y); (2) adapting YMPH from a stand-alone intervention to an intervention within an SBIRT program by minimizing duplication with e-SBI content and incorporating content to improve linkage to specialized substance abuse treatment for participants with high-risk substance use or dependence; and (3) adding content to address its poorer efficacy among partnered MSM.

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Textbox 2. Overview of the ADAPT-ITT (assessment, decision, administration, production, topic experts, integration, training, testing) framework.

- Assessment phase: completed as part of our earlier studies and discussions with stakeholders
- Decision phase: completed as part of our earlier studies and discussions with stakeholders
- Administration phase: perform theater test to obtain feedback
- Production phase: produce revised intervention, maintain fidelity to core elements and underlying theory. Develop quality assurance and process measures
- Topic experts phase: involve topic experts in adapting the intervention
- Integration phase: integrate content from topical experts; integrate new assessments based on revised content
- Training phase: train staff to deliver the intervention
- Testing phase: test revised intervention in pilot study

Administration

To obtain feedback from members of the target population and key stakeholders, we video recorded a mock YMHP session (conducted in Spanish) that will be shown to the CAB, Nexo counselors (most of whom identify as gay men), and study coinvestigators. As they watch the videos, audience members will be asked to complete a feedback form, divided by portions in the session, so that they can provide feedback on issues they felt needed to adapt from the original. Next, we will discuss recommendations for addressing the issues raised.

Production

Feedback obtained during the administration phase will inform draft 1 of MHP. The revised intervention will be translated into Spanish and manualized to standardize counseling sessions and provide support and guidance for counselors.

Topic Experts and Integration

Draft 1 of MHP will be reviewed by substance abuse experts on the CAB, Nexo counselors, and coinvestigators to identify any other components of the intervention that need revision. Feedback from this review will be integrated into the intervention to create draft 2, which will be pilot-tested during the stage-2 RCT.

Training of MHP Counselors

The training of MHP counselors will be consistent with research on learning MI, which recommends a 2-day workshop with follow-up feedback and coaching [107,108]. As such, we will conduct a 4-day training with MHP providers; the first 2 days will focus on general MI principals and skills and the last 2 days will focus on specifics of MHP. Counselors will then conduct at least 2 mock cycles of MHP, which will be audio recorded and uploaded to a secure internet site for the MI trainer to rate using the MITI.4 scale [109], which captures the counselor's level of fidelity to MI and establishes specific criteria for *Proficiency* in MI. These ratings will be used to assess MI skills that require further development, which will guide videoconference coaching sessions.

Testing

Although the primary aim of this study was to focus on the e-SBI component, as a secondary aim, we will assess the potential uptake and acceptability of MHP during the stage-2 pilot RCT.

Stage 2: Pilot RCT

Overview

With the e-SBI finalized, MHP adapted, and MHP counselors trained, the study will proceed to the stage-2 RCT comparing e-SBI to screening assessment only (see the CONSORT [Consolidated Standards of Reporting Trials] diagram for an overview; Figure 2). We will assess the feasibility and acceptability of e-SBIs and conduct a preliminary exploration of substance use and sexual risk reduction outcomes. On the basis of the findings from LINKS and Nexo data, we estimated that 50% of participants will report using drugs and 80% will report using alcohol, and that 20% to 25% will report moderate- or high-risk use based on the ASSIST and AUDIT criteria, respectively. As a secondary aim, we will assess the uptake, acceptability, and feasibility of delivering MHP at Nexo and the subsequent linkage to substance abuse treatment among those with high-risk substance use or dependence. The RCT process is described below.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for the proposed phase-2 pilot randomized controlled trial of electronic screening and brief intervention (Reflexiones). MHP: Men's Health Project; TLFB: Timeline Followback.

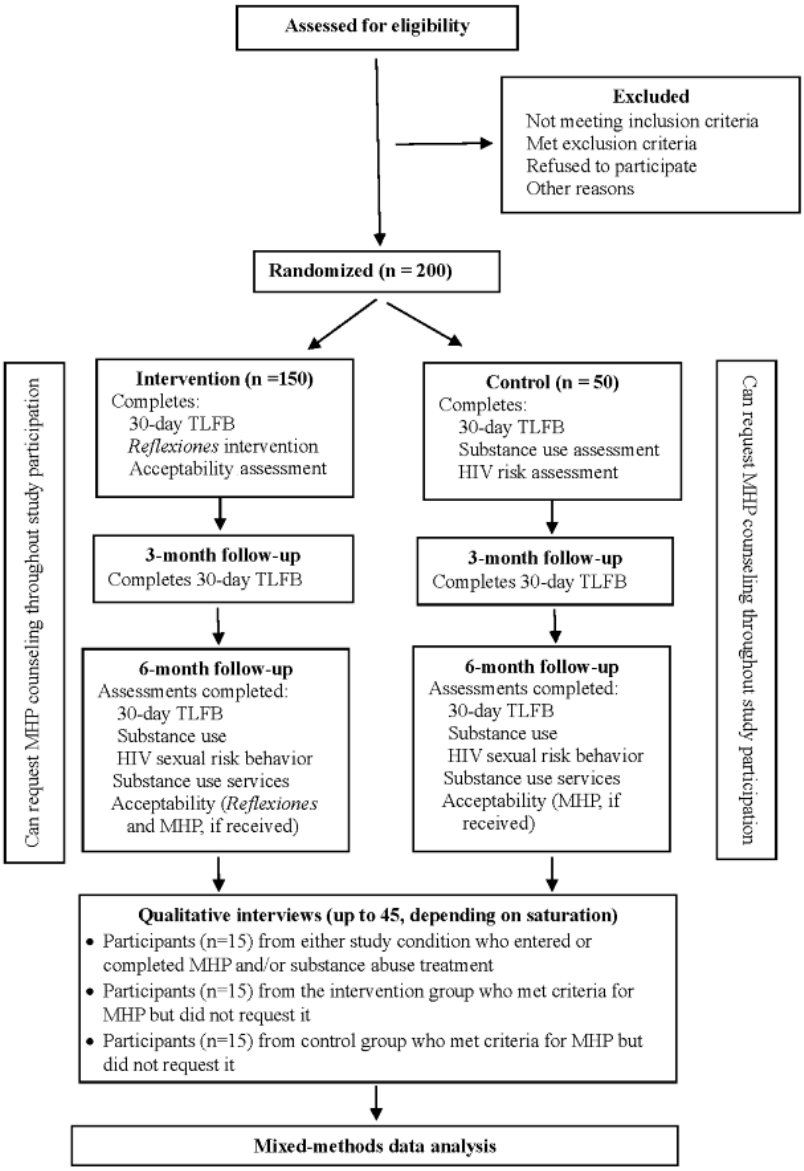

Recruitment

To ensure that the flow of participants is manageable during the study in the context of an HIV testing program, we will recruit up to 4 participants per day, 3 days per week, adjusting as necessary based on recruitment patterns to ensure the recruitment of all 200 participants. MSM who come to Nexo for HIV testing and are 18 years of age or older will be offered participation in the study. These clients will be given a flyer that, consistent with goal-choice interventions, will create a low threshold for study participation by stressing personal choice, goal selection, and an intervention tailored specifically for MSM to determine how to best reduce behavior that puts them at risk of HIV infection. Clients who wish to participate will complete informed consent, be randomized immediately, and be given a tablet logged on to their respective study arm (and disposable headphones) to complete their study procedures. Clients who declined participation will undergo the standard HIV testing process at Nexo. The research staff will record the number of clients who refused to participate.

Baseline Assessment

Participants in both conditions will complete a demographics questionnaire and then a self-administered, tablet-based 30-day *Timeline Followback (TLFB)* [110] to track days of drug use; number of alcoholic drinks; and HIV risk behavior, defined as anal sex with (1) an HIV-positive partner who they were not sure had an undetectable viral load or (2) a partner who had not tested HIV negative within the past 3 months. The TLFB has demonstrated good test-retest reliability, convergent validity, and agreement with collateral reports for daily drinking [111] and sexual behavior [112]. The TLFB will be used to assess primary substance use and sexual risk behavioral outcomes (which are exploratory outcomes in this study). After completing the e-SBI, participants in the intervention condition also completed a brief quantitative assessment of acceptability (8 items) based on the TFA [113].

RCT Study Conditions

Participants will be randomly assigned into 1 of 2 study arms.

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Intervention Group Participants

After completing the baseline assessment, the tablet will immediately lead these participants to the e-SBI, as finalized in stage 1. The CIAS branching logic allows the e-SBI to tailor the BI based on factors such as participants' substance use risk level (based on ASSIST and AUDIT scores), risk perception, and readiness to change. Thus, BI may range from affirming and sustaining motivation among those with low-risk substance use to actively motivating and encouraging (in an MI-consistent manner) those with moderate or high-risk use to speak with a research assistant to obtain an appointment for MHP. The e-SBI will also target the participant's sexual risk behavior and help them develop a risk-reduction plan, regardless of their substance use. Then, they proceed to the usual HIV testing process at Nexo.

Control Group Participants

After completing the baseline assessment, the tablet will lead these participants to the same screening instruments as in the e-SBI, but with no MI-based BI. Due to ethical considerations, control group participants with moderate- or high-risk substance use based on the ASSIST or AUDIT scores will receive brief feedback on the tablet stating their level of risk, availability of MHP at Nexo, and instructions to see the receptionist for an appointment, if desired. Then, they proceed to the usual HIV testing process at Nexo.

Referral for MHP

All individuals with moderate- or high-risk substance use will be recommended for MHP (either *actively motivated* to enter MHP through the MI component of the e-SBI for those in the intervention condition or recommended to enter treatment and made aware of the availability of treatment at Nexo for those in the control condition). MHP sessions will be conducted in-person at Nexo (later sessions can occur remotely, based on the participant's preference) and will follow the intervention manual as finalized at the end of stage 1, with sessions expected to be 60 minutes in duration. As in the YMHP efficacy study, the 4 MHP sessions can be conducted over a period of up to 2 months. To maximize retention, participants will be offered reminder calls or text before each scheduled visit. For participants with moderate-risk substance use, MHP focuses on reducing substance use and sexual risk behavior. For participants with high-risk use or dependence, MHP sessions focus on building motivation to enter substance abuse treatment. After accepting the referral, the participant and Nexo staff contact the treatment provider to obtain an appointment at the clinic of the participant's choice (ie, closer to home). Nexo staff will offer to accompany the participant to the appointment to provide a *warm handoff* to facilitate linkage to care. To ensure intervention fidelity, all MHP sessions will be audio recorded, uploaded to a secure website, and rated using the MITI.4. MITI.4 ratings will be conducted throughout the study and used to inform weekly videoconferencing coaching sessions for MHP counselors to improve and sustain MI skills.

Follow-Up Assessments

All participants, including those who enter MHP or substance abuse treatment, will repeat the self-administered 30-day TLFB at 3 and 6 months after enrollment to assess drug use, alcohol use, and sexual risk behavior. At 6 months, they will also complete the screener instruments in the e-SBI and TFA-based quantitative retrospective acceptability assessments of e-SBI and MHP (if they enter MHP), all of which will be self-administered. We will also conduct IDIs with up to 45 participants (or less if saturation is reached): 15 participants from either study condition who entered or completed MHP and substance abuse treatment and 15 from each arm who met the criteria for MHP but did not request it. Also guided by the TFA, we expect these IDIs to be similar to those conducted in the stage-1 e-SBI pilot; however, revisions will be made to the IDI guide based on how well the questions elicited the desired material from the stage-1 participants. The use of one framework to guide all of these IDIs and the qualitative data analysis will allow us to more rigorously compare participants with PSU who entered MHP and substance abuse treatment with those who did not to identify factors that might impact their decision to enter MHP. IDIs will be conducted at Nexo, audio recorded, and transcribed.

Data Analysis

Qualitative Data Analysis for Stage-2 IDIs

For the stage-2 pilot RCT, transcripts from the audio recordings will be reviewed for accuracy and uploaded onto Dedoose for management and analysis. Codebook development will begin when 10 transcripts are available. First-level codes will be guided by TFA components, whereas second- and third-level codes emerge from themes identified in the narratives. An initial set of codes will be generated independently by 2 research staff members, compared, and then synthesized to compile shared coding categories and subcategories, all with definitions, inclusion and exclusion criteria, and examples. As transcripts become available, coding will continue, refining codebook definitions that will be used to process the remainder of the manuscript. The coders discussed discrepancies until they achieved 80% intercoder convergence. As per Patton [114], we will identify indigenous (ie, participant-generated) and analyst-constructed typologies. Once data are coded, analysis of coding reports will include categorization, abstraction, comparison (especially between groups in stage-2 RCT), integration, iteration, and refutation of themes.

Integration of Quantitative and Qualitative Data

We seek to exploit the richness of our mixed methods approach, with quantitative and qualitative findings enriching each other. Quantitative assessments allowed us to systematically explore variables of interest across all participants. Qualitative data will add nuances and new insights to quantitative findings. During data analysis, the interpretation of quantitative results will be enriched by the summary of codes for specific components of the e-SBI. In Dedoose, participants will be categorized based on their responses in the quantitative assessment (eg, severity of drug or alcohol use; ratings on readiness to change rulers) and use these categories to compare themes and concepts that emerge from the qualitative data.

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Quantitative Data Analysis

Primary Aims

The primary aim of this study is to assess the feasibility and acceptability of integrating e-SBI into the HIV testing process at Nexo by estimating and comparing (1) the percentage of MSM testing clients at Nexo who accept entry into the study among those who are asked (recruitment rate); (2) the percentage of participants who complete e-SBI (retention rate); and (3) the mean score of 7-item e-SBI acceptability ratings between MSM participating in the e-SBI and those in the screening-only group. The secondary aim is to assess the feasibility and acceptability of implementing MHP at Nexo by estimating and examining the group difference with respect to (1) the percentage of MSM with moderate or high-risk substance use who enter or complete MHP; (2) percentage of high-risk enrollees in MHP who proceeded to substance abuse treatment; (3) mean acceptability of MHP and substance abuse treatment among those who received it (based on quantitative assessment to be developed); and (4) percentage of sessions conducted by each MHP counselor that meet the criteria for MI proficiency MITI.4 ratings. The estimation is accomplished by generating a point estimate with its corresponding 95% CI. We will use a 2-tailed *t* test for continuous outcomes and Fisher exact test for binary outcomes for the above comparisons. Adjustment for covariates, if necessary, with control baseline values, will be accomplished using multiple linear (continuous outcomes) or logistic (dichotomous outcomes) regression.

Exploratory Aims

Although this study did not recruit a sufficiently large sample to provide adequate power for assessing the efficacy of e-SBI, we will use data from the 30-day TLFB to explore changes in days of drug use, days of alcohol use, days of heavy alcohol use (5 or more drinks), and occasions of anal intercourse with a risky partner. To examine the efficacy of the above outcomes, a generalized linear model with a log link function was constructed, and generalized estimating equation methods were used to estimate model parameters and their SEs to account for correlation introduced by accessing the participants at multiple time points. Accompanying each of these tests will be point and interval estimates for the parameters of interest (ie, the ratio of the 2 group rate ratios). Although the hypotheses consider several simultaneous measures of effect, for the routine reporting of these results, there will be no adjustment for multiple comparisons.

Power Considerations

The primary goal of this pilot study was to collect preliminary data on the feasibility, acceptability, and target outcomes of the proposed intervention. We will use these pilot data to rule out unusually large or small true effects using standard 95% CI procedures. We confirm that the extrinsic effect sizes are contained within our CIs from the pilot. We examine the distribution of each variable and calculate the summary statistics by intervention condition. We will estimate key intervention parameters with sample means and proportions together with 2-sided 95% CIs and test the primary null hypotheses at the traditional 2-sided level α=.05 (simulation of the subsequent RCT). To plan the RCT, we will also consider 1-sided 90% confidence limits for mission-critical design parameters such as SDs and reference group end-point rates and proportions in the conservative direction. This is because we intend to plan sample size for the RCT so that power will be *excellent* (at least 80% power) for the clinically relevant effect size to be specified. This strategy will make proper allowance for the limited sample size of the pilot study with its consequent uncertainties and still yields appropriate sample sizes for the RCT. *Mission-critical* parameters include proportions for dichotomous variables (eg, recruitment rate and retention rate) and means and SDs for continuous outcomes (eg, days of drug use, days of alcohol use, acceptability of MHP and Substance abuse treatment). Large sample sizes are not required to locate these parameters approximately, but adequately, to plan the subsequent trial, whereas testing the study hypothesis in the pilot will generally not have sufficient statistical power. The estimation of mission-critical design parameters with point and CI estimates will be considered highly important; continuous outcome measures make it feasible to detect promising effect effects even in small samples. Means and SDs were estimated for continuous measures. For approximately normally distributed variables, an upper 1-sided 90% confidence limit for the SD, *sU*, was constructed from $sU = s \times c2n,.10 \times 1/2$, where *s* is the sample SD and *c2n,.10* is the upper 10th percentile of the chi-square distribution with *n* degrees of freedom. For approximately log-normally distributed variables, logarithmic transformation was applied to achieve approximate symmetry and normality. For dichotomous variables (such as the primary and secondary outcomes or the PDR performance criteria), exact binomial methods will be used for the CIs for proportions. As an example, the width of the 95% CI around a point estimate of 50% (eg, MSM with moderate- or high-risk substance use who complete e-SBI and then enter MHP) would be 43% to 57% with 200 participants.

Results

The study began with recruitment for stage 1 in October 2022. Currently, we are nearing the completion of stage 1. As part of the stage-1 development process, we conducted 2 FGs (n=16) and 2 waves of individual interviews (n=12). Consistent with the protocol, we ended the individual interviews after 2 of the 4 possible waves because acceptability scores were consistently high (mean score was >4 out of 5 for all participants). At present, we have almost completed the stage-1 pilot. At the conclusion of stage 1, we will conduct a rapid qualitative data analysis [90,91] to assess any additional changes that need to be made to the e-SBI before the stage-2 RCT, which we expect to launch in March 2024. At that time, we will also begin a deeper analysis of the stage-1 data from FGs, individual interviews, and the stage-1 pilot and include that in a future mixed methods manuscript to describe the intervention and its acceptability among the intended audience. We expect all data collection to be completed by February 2025 and the study results to be available by June 2025.

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Discussion

Overview

This study addresses the critical need for interventions that reduce both PSU and HIV risk behavior among MSM in Latin America by adapting 2 evidence-based interventions, e-SBI and YMHP, for MSM in Argentina seeking HIV testing. Given that many MSM seek HIV testing in lesbian, gay, bisexual, and transgender (LGBT) community agencies, these interventions have the potential to reach large numbers of MSM, help them reflect on their use of drugs and alcohol, and help link those with PSU to evidence-based intervention (MHP). The provision of substance abuse treatment within an LGBT community agency can help facilitate entry and retention in treatment, as sexual minority men will not be concerned about the discrimination and microaggressions they might face at agencies serving the public. If proven efficacious in a future RCT, the implementation of these interventions in such agencies will help address a key contributor to HIV risk behavior and infection as well as reduce drug and alcohol use among MSM, who are disproportionately affected by HIV and substance use.

Strengths

A key strength of this study is the iterative development of the intervention based on end user feedback to ensure its high acceptability among intended users. Feedback from end users is essential to create an intervention that achieves its aim of heightening risk awareness of PSU to motivate reductions in use in a respectful, nonjudgmental manner without creating resentment or defensiveness.

An additional strength is that the study and the intervention were developed in close collaboration with a community HIV testing center, where the intervention was designed to be delivered. Development within a community HIV testing program provides an early assessment of the implementation challenges that need to be overcome to maximize access to the intervention and minimize the burden on organizational processes and resources.

Finally, the e-SBI was developed using CIAS. As this system was designed for use by nonprogrammers, the CIAS minimizes costs for developing, revising, and maintaining electronic interventions. In addition, it was designed for long-term sustainability. For example, contrary to a custom-designed platform for a specific task, CIAS is a broad platform for use by many people; supporting only this single platform will automatically support the availability of everyone is work. Its ongoing development is still funded by the US National Institutes of Health for 2 years, and additional funding will be obtained to continue support. In addition, a yearly fee for funded projects provides income to support CIAS in the long term, especially given the high interest in its use. Finally, the source code will soon be made publicly available at no cost; therefore, it can be installed on a local server. This sustainability plan addresses a key challenge to other e-interventions that support falters once study funding has concluded, impeding the use of interventions in community settings.

Limitations

This study and the intervention were designed in close collaboration with our community partners in Argentina. As such, there may be specific characteristics of our community partners and their client populations that may limit the generalizability of the findings to other community HIV testing programs. As a voluntary research study, HIV-testing clients with PSU may decide not to participate in the study, limiting the potential utility of this approach to identifying and engaging MSM with PSU to reduce their substance use. Finally, acceptability data (both quantitative and qualitative) are subject to social desirability. To minimize this risk, we will highlight for participants the importance of openly sharing their experiences and opinions, whether positive or negative.

Conclusions

Completion of this Clinical Trial Planning Grant (NIH R34) will allow us to develop and pilot all the study components and build the necessary research infrastructure for a subsequent RCT to assess the efficacy of e-SBI in reducing substance use and HIV sexual risk behavior among MSM coming to a community agency for HIV testing.

Acknowledgments

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Data Availability

Once the study is completed, the data sets generated and analyzed during the study will be available from the corresponding author upon reasonable request. We will compile structured deidentified data sets and make them available for additional and secondary data analyses. For data sharing, the research team will follow the “standards for privacy of individually identifiable health information.” The principal investigator and research team will develop a process to review and approve data release based on concept sheets submitted by interested investigators and whether the data request is for new lines of analysis. Formal data-sharing agreements will be developed to guide and encourage further data mining of the proposed datasets for various purposes.

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Authors' Contributions

ICB was the principal investigator of the study, led the design of the study and the development of the interventions, and led the writing of this manuscript. ROM is a coinvestigator of the study and the site principal investigator in Argentina. He significantly contributed to the study design and led the implementation of the study. He critically reviewed the manuscript, provided feedback, and approved the final version. VB collaborated with the implementation of the study and led the qualitative component of the research assessing the acceptability of the interventions. She critically reviewed the manuscript, provided feedback, and approved the final version. SN is a coinvestigator who collaborated on the study design, as it pertains to the adaptation and implementation of the Young Men's Health Project (YMPH). She critically reviewed the manuscript, provided feedback, and approved the final version. YW was the data manager of this study. She collaborated in the design of the various data capture components of the study and will provide data management and statistical support for the study. She critically reviewed the manuscript, provided feedback, and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 147 KB - resprot_v13i1e56683_app1.pdf]

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Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topic experts, integration, training, testing
ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AUDIT: Alcohol Use Disorders Identification Test
BI: brief intervention
CAB: community advisory board
CIAS: Computerized Intervention Authoring System
CONSORT: Consolidated Standards of Reporting Trials
e-SBI: electronic screening and brief intervention
FG: focus group
IDI: in-depth interview
LGBT: lesbian, gay, bisexual, and transgender
MHP: Men’s Health Project
MI: motivational interviewing
MITI.4: Motivational Interviewing Treatment Integrity
MSM: men who have sex with men
PSU: problematic substance use
RCT: randomized controlled trial
SBIRT: Screening, Brief Intervention, and Referral to Treatment
SIP-AD: Short Inventory of Problems-Alcohol and Drug Use

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TFA: theoretical framework of acceptability
TLFB: Timeline Followback
UCRAD: User Centered Rapid Application Development
YMHP: Young Men's Health Project

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Protocol

Providing Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer Adolescents With Nurturance, Trustworthiness, and Safety: Protocol for Pilot Cluster Randomized Controlled Trial Design

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Abstract

Background: Sexual and gender minority youths (lesbian, gay, bisexual, transgender, nonbinary, and queer individuals) face elevated risks of substance use (eg, alcohol and tobacco) and mental health issues (eg, depressive symptoms and suicidality) compared to their cisgender heterosexual peers. These inequities are hypothesized to be reduced by building supportive high school environments via the training of school staff. An intervention that trains school staff to better understand and support sexual and gender minority youths and engage in positive bystander behaviors that protect them from bullying exposure may reduce disparities in drug and alcohol use among them. Experts, school staff, and sexual and gender minority youths developed Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety (PLANTS), a web-based intervention to train school staff on how to support, affirm, and protect sexual and gender minority youths.

Objective: This paper describes the design of the PLANTS pilot trial primarily aimed at assessing its acceptability, usability, appropriateness, and feasibility. We hypothesize PLANTS will have high acceptability, usability, appropriateness, and feasibility as rated by the school staff. Secondary objectives focus on implementation, safety, and pre-post changes in high school staff outcomes, including self-efficacy and skills (eg, active-empathic listening and bullying intervention). Exploratory objectives focus on the impact of PLANTS on student health outcomes.

Methods: In a 2-arm cluster randomized controlled trial, high schools in Massachusetts are allocated to PLANTS or an active comparator group (publicly available sexual and gender minority youths resources or training). High school staff complete pretest and posttest surveys containing validated scales. Primary outcomes are validated measures of acceptability, usability, appropriateness, and feasibility of the intervention completed by staff during posttest surveys. To test our primary hypotheses for each outcome, we will calculate means and 95% CIs and *P* values using 1-sample 2-sided *t* tests against a priori thresholds or benchmarks of success. Secondary outcomes include staff's active-empathetic listening skills, self-efficacy for working with sexual and gender minority youths, bystander intervention behaviors for bullying and cyberbullying, and self-efficacy for PLANTS' change objectives completed during pretest and posttest staff surveys. Staff can also complete a posttest interview guided by the Information-Motivation-Behavior model and Consolidated Framework for Implementation Research. Exploratory outcomes include student-level data collected via the 2021 and 2023 MetroWest Adolescent Health Surveys, a health behavior surveillance system in 30 Massachusetts schools.

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Results: School enrollment began in May 2023 and participant enrollment began in June 2023. Data collection is expected to be completed by February 2024.

Conclusions: This pilot trial will yield important information about the PLANTS intervention and provide necessary information to conduct a fully powered trial of the efficacy of PLANTS for reducing the deleterious health inequities experienced by sexual and gender minority youths.

Trial Registration: ClinicalTrials.gov NCT05897827; https://clinicaltrials.gov/study/NCT05897827

International Registered Report Identifier (IRRID): DERR1-10.2196/55210

(JMIR Res Protoc 2024;13:e55210) doi:10.2196/55210

KEYWORDS

sexual minority youths; gender minority youths; cluster randomized controlled trial; web-based behavior change intervention; high school staff

Introduction

Background

Sexual and gender minority youths (ie, adolescents who are lesbian, gay, bisexual, transgender, nonbinary, or queer [LGBTQ+]) are at significantly higher risk than their heterosexual peers for mental health problems and substance use [1-22]. For example, alcohol use is 123%-155% higher among sexual minority youths than among heterosexual youths and up to 250% higher among gender minority youths than among cisgender youths [2,5-7,22]. These substantial persistent health inequities make sexual and gender minority youths a priority population for interventions and were deemed so by national health agencies [3,23,24]. However, there are few efficacious substance use and mental health interventions for sexual and gender minority youths [3].

One way to reduce substance use and improve mental health for sexual and gender minority youths is to foster more supportive and inclusive high school environments by training school staff (eg, teachers, principals, nurses, and counselors) to effectively support and protect them. Sexual and gender minority youths who have support from adults at school, greater school connectedness, and lower bullying exposure also have reduced depressive symptoms, suicidality, and drug and alcohol use [5,25-30].

Unfortunately, sexual and gender minority youths are more likely than their heterosexual peers to lack supportive adults at school, have lower school connectedness, and be exposed to bullying [5,6,25,26,31-39]. An intervention that trains school staff to better understand and support sexual and gender minority youths and engage in positive bystander behaviors that protect them from bullying exposure may reduce health disparities among them. Despite many school staff having a strong desire to support sexual and gender minority youths [40], their primary barrier to supporting this population is a lack of training [40,41]. In 2014, 13% of teachers across the United States and 29% in Massachusetts received training on issues related to sexual and gender minority youths [41], highlighting the need for professional development training related to this population in schools. An intervention for training school staff is further warranted because the presence of gender-sexuality alliances and sexual and gender minority youth–inclusive school policies fail to eliminate health disparities among them [4,42-44].

Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety (PLANTS) is a new web-based training program for high school staff. This intervention was informed by the Information-Motivation-Behavior theory to target the skills, self-efficacy, knowledge, and outcome expectations of the high school staff. School staff and other collaborators invested in the well-being of sexual and gender minority youths assisted in developing PLANTS. PLANTS aims to train school staff to support, affirm, and protect sexual and gender minority youths, which is hypothesized to reduce bullying exposure, increase school support and connectedness, and mitigate health disparities among them [45].

Prior to testing efficacy, it is critical to ensure that PLANTS is acceptable to high school staff. This paper describes the design of the PLANTS pilot trial, which primarily tests the PLANTS intervention acceptability (perceptions that PLANTS is tolerable), usability (perceived extent to which PLANTS can be used effectively, efficiently, and satisfactorily), appropriateness (perceived fit and relevance of PLANTS), and feasibility (the extent to which the PLANTS intervention is successfully used and executed) as reported by high school staff. Using a cluster randomized design, this study will secondarily examine the implementation, safety, and pre-post changes in high school staff outcomes within the PLANTS arm and then compare them to an active comparator condition composed of publicly available resources. This study will also explore intervention effects on student-level behavioral health outcomes. The results from the PLANTS pilot trial will inform the development of a fully powered trial of the efficacy of PLANTS for improving health outcomes among sexual and gender minority youths.

Objectives and Hypotheses

The primary objective of the PLANTS pilot trial is to assess the acceptability, usability, appropriateness, and feasibility of the intervention. Investigators expect that high school staff will rate the PLANTS intervention as having high acceptability, usability, appropriateness, and feasibility. Investigators' benchmarks of success are averages of >3.75 out of 5 for acceptability, appropriateness, and feasibility and scores >75 out of 100 for usability.

The secondary objectives are to examine trial implementation, intervention demand, intervention safety, and pre-post changes in school staff outcomes within the PLANTS arm and then

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compare them to an active comparator condition. Investigators hypothesize the following results: school staff will have high participation rates in the study (≥50% consent); school staff will have a high retention rate for the follow-up survey (≥75%); high school staff in the PLANTS arm will have high intervention demand (≥75% adhere to PLANTS); high school staff in the PLANTS arm will have low adverse event prevalence (≤20% of PLANTS participants will report adverse events); high school staff participants in the PLANTS arm will report pre-post improvements in active-empathic listening, self-efficacy for supporting, affirming, and protecting sexual and gender minority youths; positive bystander intervention behaviors for bullying; and pre-post differences will be greater in the PLANTS arm than in the active comparator arm.

The exploratory objectives concern student-level health outcomes, including substance use, mental health, violence, and school experiences. Investigators hypothesize that sexual and gender minority youths will have greater increases in adult support at school and school connectedness and greater reductions in bullying exposure, depressive symptoms, suicidality, drug use, and alcohol use in PLANTS intervention schools versus active comparator schools, and the differences between sexual and gender minority youths and cisgender heterosexual youths in alcohol use, drug use, depressive symptoms, and suicidality will be more reduced in PLANTS intervention schools versus the active comparator schools.

Methods

Design

The PLANTS pilot trial is a cluster randomized controlled trial with 2 parallel groups and primary end points of PLANTS acceptability, usability, appropriateness, and feasibility among school staff. Such outcomes are aligned with pilot study best practices [46-49]. This unblinded study will randomly assign 4 schools in a 1:1 ratio to the intervention or comparator conditions. Importantly, investigators will analyze both student- and staff-level outcomes before and after the intervention. Figure 1 shows the study flow.

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Figure 1. Study flow of the PLANTS pilot trial. PLANTS: Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety.

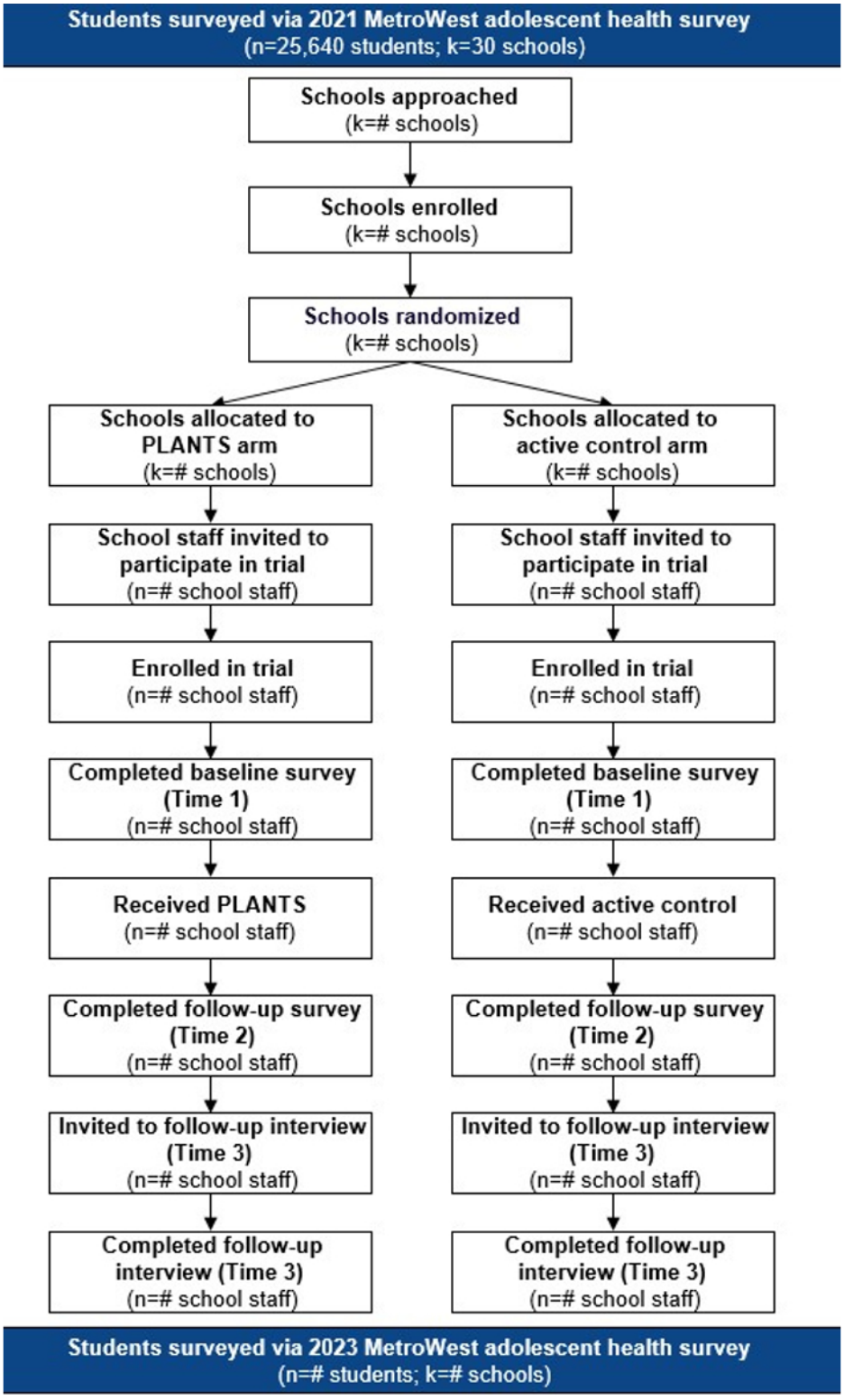

Setting

This study will enroll high schools (grades 9-12) from the 30 schools participating in the MetroWest Adolescent Health Survey (MWAHS) located in and near the MetroWest Region outside Boston, Massachusetts. The PLANTS pilot trial leverages the strengths of the MWAHS research infrastructure, which has biennially collected health surveillance data from a census of students since 2006. To be eligible for the PLANTS pilot trial, a school must have participated in the 2021 MWAHS, plan to participate in the 2023 MWAHS, grant investigators permission to access their MWAHS data, be willing and able to provide email addresses of all school staff, and provide a site permission letter.

Randomization

School-level randomization occurs after schools enroll in the study but before staff are enrolled. The investigators will use

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block randomization in a 1:1 ratio, stratified by larger schools (≥1000 students) versus smaller schools (<1000 students). The primary investigator will create the randomization files using the "ralloc" package in Stata (StataCorp). Trained study staff will allocate schools using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module. Allocation will be concealed from school personnel.

Study Populations, Sampling, Recruitment, and Data Collection

Students

To be eligible to participate in the MWAHS, students must be enrolled in grades 9-12 at a study school and be literate in English, Spanish, or Portuguese. Students are excluded if they provide an implausible pattern of responses via an evidence-informed algorithm that removes students with extreme responses.

Biennially, MWAHS collects student-level health surveillance data, similar to the Youth Risk Behavior Survey [50] except MWAHS data are collected from a census of students in each high school. The census-like sampling is a major strength of this study, providing a substantial sample of sexual and gender minority youths. Administered via the internet, the MWAHS is voluntary, anonymous, and data are linked at the school level across years (but cannot be linked at the student level). The baseline for intervention efficacy for students will be the fall 2021 MWAHS data, when 30 high schools participated, and 25,640 students completed surveys (83% of all students). The follow-up occurred in fall 2023.

Staff

To be eligible to participate in the PLANTS pilot trial, staff must be currently employed by an enrolled school, be 18 years or older, and consent to participate. Staff are excluded from participation if they do not interact directly with high school students at work.

At enrolled schools, all school staff will be invited to participate via email and advertisements sent by research staff and school administrators. Using REDCap, a personalized link to the screening survey will be provided to staff. If eligible, individuals will be given a digital informed consent form followed by a 30- to 45-minute baseline survey. Intervention and comparator conditions will be delivered to participants over 6 weeks. At the program's conclusion, participants will be sent a follow-up survey. A subset of participants (n=20-30 in PLANTS and n=10-20 in e-Learning to Maximize Academic Inclusion of LGBTQ+ Students [EMAILS] arms) will then be invited for a follow-up interview to explore the implementation outcomes more deeply.

Ethical Considerations

Staff

The Human Research Protection Office at the University of Pittsburgh approved the trial (STUDY23040142). Informed consent is obtained from staff participants. Consent forms describe in detail the study intervention, study procedures, foreseeable risks and discomforts, benefits to the participant, and contact information for the principal investigator. We requested and received a waiver for written consent for all staff participants because consent procedures are happening digitally, the study presents no more than minimal risk to participants, and written consent is not usually obtained for participation in a web-based program or interview outside of a research context.

Privacy and confidentiality protections are in place. For all identifiable data collected, we will remove identifiers and assign a unique study ID to protect the identity of the participant. Coded deidentified data and identifiable data will be stored in separate REDCap surveys and separate folders within a secure password-protected database and will be only accessible to select members of the research team.

To incentivize school staff to complete the baseline survey, we will provide US $20 to each participant and will conduct a drawing of an extra US $30 to 1 in 5 participants who take the survey within each school. To incentivize school staff to complete the follow-up survey, we will provide US $30 to each participant who completes the survey, and we will conduct a drawing of an extra US $40 to 1 in 5 participants who take the survey within each school. For staff who complete the follow-up interview, we will provide a US $50 incentive as a thank you for their time.

Students

The Education Development Center's institutional review board–approved the MWAHS. Parents or guardians are provided the opportunity to opt their child out of the survey (ie, passive consent), and students provide assent to participate. Assent forms describe in detail the study procedures, foreseeable risks and discomforts, benefits to the participant, and contact information for the principal investigator. Data are collected anonymously, preserving student privacy and confidentiality. No incentives are provided to students for participation.

PLANTS Intervention

The PLANTS intervention is a web-based training program for high school staff. Figure 2 illustrates the PLANTS Behavior Change Model. Staff behavior change outcomes target evidence-based intermediary outcomes rooted in theories of minority health and general adolescent psychosocial health models. In turn, these intermediary outcomes are associated with reduced substance use and mental health issues. The behavior change outcomes are that PLANTS uses asynchronous and synchronous web-based activities to achieve the behavioral change outcomes via targeting the skills, self-efficacy, knowledge, and outcome expectations of the school staff based on Information-Motivation-Behavior theory. PLANTS has 3 primary modules: trustworthiness, safety, and nurturance. Asynchronous activities include voiceover presentations, podcasts with student and staff stories based on research [51], activities, and downloadable resources for future reference. Synchronous activities include three 1.5-hour live Zoom events; each moderated by a trained interventionist and tailored to the needs of participants. The modules were developed by the research team, including undergraduate and graduate students with a variety of academic backgrounds, in partnership with high school staff and other professionals who specialize in

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LGBTQ+ youth or education. PLANTS is delivered using Canvas Learning management software (Instructure).

Figure 2. Behavior change model with high school staff behavior outcomes and student health outcomes. SGM: sexual and gender minority; SGMY: sexual and gender minority youths.

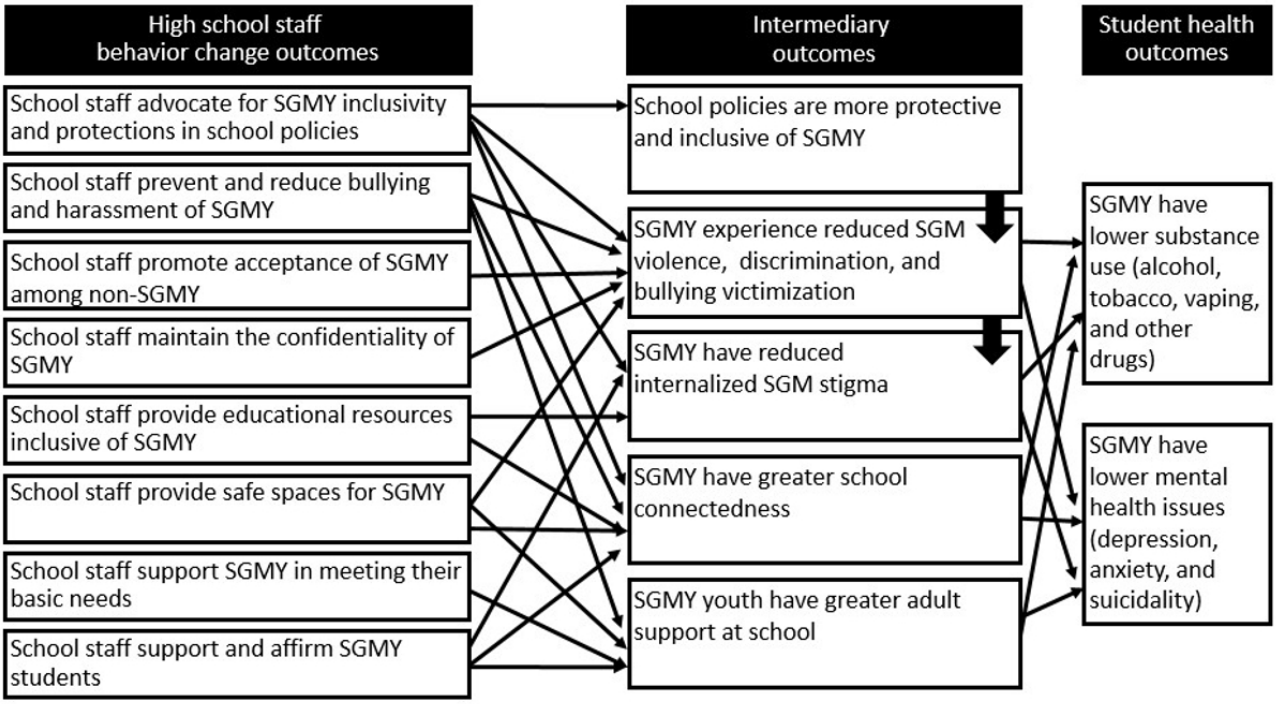

Active Comparator: EMAILS

Given the urgent need to support sexual and gender minority youths coupled with the dearth of evidence-based interventions for reducing alcohol and drug use in this population [3], choosing a comparator was difficult. Pragmatically, staff may search the internet to identify training opportunities. Thus, the active comparator, EMAILS, is an email-based intervention comprised of free existing web-based resources for supporting, affirming, and protecting sexual and gender minority youths. Informed by the Information-Motivation-Behavior theory, EMAILS has materials from Adagio Health, the Gay, Lesbian, & Straight Education Network, the American Psychological Association, and the Human Rights Campaign, which include self-paced training modules, YouTube videos, and PowerPoints. There is no direct human interaction in this intervention other than email. EMAILS is 3 hours long and is delivered in 3 modules as in PLANTS. Investigators will monitor active comparator compliance and fidelity by disseminating materials in Qualtrics, which allows for personalized link tracking and short end-of-module questionnaires about uptake or completion.

Outcomes

Primary Outcomes

The primary outcomes are intervention acceptability, usability, appropriateness, and feasibility as reported by school staff. At the follow-up survey, these are measured via scales with strong psychometric properties such as the acceptability of intervention measure (AIM), System Usability Scale (SUS), intervention appropriateness measure (IAM), and feasibility of intervention measure (FIM) [52,53]. AIM, IAM, and FIM each have 4 items with 5-point Likert scale response options. This instrument can be found in Table S1 in Multimedia Appendix 1. Investigators will calculate mean scores (range: 1-5). The SUS has 10 items with 5-point Likert scale response options. Investigators will calculate scores as recommended for the total scale (range: 0-100) [54]. The same outcomes are assessed about EMAILS among comparator participants, but these are not primary outcomes.

Secondary Outcomes

Trial Implementation

To assess the success of the pilot trial in reaching an adequate number of school staff, investigators assess the overall trial participation rate (number of people enrolled divided by the number of people invited to participate) and the follow-up survey retention rate (the number of people who take the follow-up survey divided by the number of people enrolled).

PLANTS Intervention Demand

To assess the school staff's demand for PLANTS, investigators assess PLANTS adherence, which is a composite variable ranging from 0% to 100%, comprised of 55% for module completion (based on the number of completed items divided by the total number of items offered) and 45% for Live Zoom Event attendance (where each event is 15%). These proportions are based on approximate time allocations.

Safety

Investigators assess a myriad of safety outcomes in follow-up surveys, including contact from parents or guardians because there was too much LGBTQ+ inclusivity in the school, contact from people who were upset, the school being attacked, the

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school board getting upset or concerned, and LGBTQ+ censorship at the school. Response options include the frequency of each event occurrence. Investigators also assess participants' emotional discomfort with the courses using a 4-point Likert scale. For affirmative responses, open-ended textboxes are provided to describe the safety-related events. Investigators also track the presence or severity of adverse events and unanticipated problems.

Self-Efficacy for Working With Sexual and Gender Minority Youths

Investigators assess participants' perceived abilities for working with LGBTQ high school students using 9 items adapted from the Gay Affirmative Practice Scale [55]. Originally for social work practitioners, investigators replaced therapy-oriented words with school-oriented words (eg, "students" instead of "clients").

Example items include "I am able to help LGBTQ+ students develop positive identities as LGBTQ+ individuals" and "I am able to challenge misinformation about LGBTQ+ individuals in the classroom." Response options include a 5-point Likert scale. Investigators will calculate the mean score. In a prior study, the Cronbach α is 0.90 [56].

Active-Empathic Listening

Investigators measure the valid and reliable Active-Empathic Listening Scale containing 11 items [57]. This scale has 3 domains: sensing (4 items), processing (3 items), and responding (4 items). Response options include a 7-point Likert scale. Investigators will calculate the mean score for the total scale. Prior research showed a Cronbach score of α=0.88-0.90 [56].

Bystander Intervention Behaviors for Bullying and Cyberbullying

Two multidimensional scales (Teacher Bystander Intervention Model in Traditional Bullying and Teacher Bystander Intervention Model in Cyberbullying [58,59]) measure 5 subscales of bystander behaviors for bullying and cyberbullying: noticing the event (3 items), interpreting the event as an emergency (3 items), accepting responsibility to help (3 items), knowing how to help (3 items), and implementing intervention decision (4 items). The psychometric properties of these subscales are acceptable (Cronbach α=0.57-0.88). Investigators will calculate average subscale scores.

Self-Efficacy of PLANTS' Change Objectives

Given the limited research on validated scales of behavior change pertaining to LGBTQ+ inclusive practices in schools, investigators developed items pertaining directly to the self-efficacy change objectives in PLANTS. There are 50 total items across the following domains: provide interpersonal support and affirmation to sexual and gender minority youths; provide educational resources that are inclusive of this population; provide safe spaces for them; promote the acceptance of this population among cisgender heterosexual youths; prevent and reduce bullying, cyberbullying, and harassment of this population; evaluate and advocate for their inclusivity and protections in school policies; and maintain the confidentiality of sexual and gender minority youths.

Exploratory Outcomes

Student-level outcomes will be explored using the MWAHS data. Measures are described in Table S2 in Multimedia Appendix 1, and most have strong test-retest reliability and internal consistency.

Follow-Up Interview Questions

The purpose of the follow-up interview is to better understand trial and intervention implementation. Interviews are guided by the CFIR (Consolidated Framework for Intervention Research) [60]. Question domains include intervention characteristics (relative advantage, adaptability, and design quality), outer setting (external policies and incentives), inner setting (structural characteristics, networks, communication, culture, implementation climate, compatibility, relative priority, and leadership engagement), characteristics of individuals (beliefs about the intervention and self-efficacy), and process (opinion leaders). Interview questions are based on the publicly provided CFIR interview questions [60].

Demographics and Potential Confounders

Staff and student surveys assess many potential confounders. Table S3 in Multimedia Appendix 1 contains measurement details. School-level data will be collected from the Massachusetts Department of Elementary and Secondary Education public website.

Analyses

General Approach

Investigators will calculate baseline descriptive statistics for each study arm and test for differences in potential confounders between intervention and comparator arms using baseline student-, staff-, and school-level data with Rao-Scott chi-square tests and linear mixed models accounting for school clustering. Secondary analyses will adjust for imbalances between arms.

For validated scales, investigators will report internal consistency via Cronbach α. For newly created items, investigators will conduct exploratory factor analyses to examine the dimensions of outcomes using baseline surveys. Investigators will use the most recent version of Stata, 2-tailed tests, and α=.05.

Investigators will also conduct bias assessments. Selection bias assessment will compare participants' demographics to publicly available school-level data. The attrition bias assessment will compare staff respondents who completed follow-up surveys versus those who did not by baseline demographics and outcomes. Investigators will report significant differences as potential validity threats.

Primary Outcome Analyses

To answer the primary research questions, investigators will use best practices for pilot or feasibility studies [46-49]. Investigators will analyze the primary outcomes using descriptive statistics [46-49] and will not correct for multiple tests [46-49]. Among people in the PLANTS arm, investigators will calculate means and 95% CIs for participants' responses to the FIM, AIM, IAM, and SUS [53] and *P* values using 1 sample two-sided *t* tests against a priori thresholds.

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Secondary Outcome Analyses

For trial implementation outcomes, investigators will calculate the participation and retention rates with a percentage and 95% CIs in the overall study sample. For PLANTS intervention demand, investigators will calculate average adherence with a percentage and a 95% CI among participants in the PLANTS study arm.

For safety outcomes, investigators will estimate the prevalence of adverse events reported by school staff at any time after intervention or comparator deployment. Investigators will report by study arm: the overall frequency of adverse events; the frequency of each type; and the frequency and percentage of school staff reporting adverse events.

To examine the pre-post changes in high school staff outcomes, investigators will first use descriptive statistics, such as means and percentages at each timepoint within arms. To test for within-arm statistical significance, investigators will use linear mixed models for continuous outcomes and generalized linear mixed models for binary outcomes, which account for within-school and within-person clustering using random effects. Investigators will estimate the intraclass correlations for within-school and within-person effects. These models will adjust for school size (a priori design variable).

Subsequently, investigators will compare pre-post changes between arms using regression models that include a fixed term for school size (a priori design variable), intervention group (intervention or comparator), time (baseline or follow-up), and the interaction of the intervention group×time (variable of interest for between-arm differences in pre-post changes). The intervention effects on secondary outcomes will be primarily based on intent-to-treat (ITT) estimates. Investigators will estimate as-treated and per-protocol effects in secondary models. If there are differences in potential confounders by intervention group, investigators will adjust for them in secondary multivariable analyses.

Exploratory Outcome Analyses

To explore the intervention effects among sexual and gender minority youths (within-group analyses), investigators will conduct ITT analyses using linear mixed models or generalized linear models accounting for within-school clustering effects using random effects. Investigators will restrict the sample to participants who reported a sexual minority identity or gender minority identity. Regression models will include a fixed term for school size (a priori design variable), intervention group (intervention or comparator), time (baseline or follow-up), and the interaction of intervention group×time (variable of interest). First, investigators will estimate ITT effects. Second, because subsetting a randomized sample may lead to naturally imbalanced arms, investigators will adjust for any imbalanced confounders.

To explore the intervention effects on inequities among sexual and gender minority youths (between-group analyses), investigators will use mixed models like previously described, except investigators who will include all student data in these analyses, including cisgender heterosexual youths, to assess reductions in inequities. Regression models will include fixed terms for the intervention group (PLANTS or EMAILS), time (baseline or follow-up), all 2-way interactions between the intervention group, time, and sexual and gender minority youths, and the 3-way interaction of the intervention group×time×sexual and gender minority youths (exploratory variable of interest for this hypothesis). Investigators will primarily explore the ITT effects.

Qualitative Analyses

Investigators will transcribe, deidentify, and check the quality of all data [61-64]. Investigators will perform use CFIR as a guiding framework. Two trained qualitative coders from our research team will independently read interviews and compare coding until they agree. Once the coders agree all major codes have been identified, they will create a final codebook with definitions, rules, and examples for each code [63,64]. Two coders will then recode all data using the final codes. Investigators will calculate inter-rater reliability (Kappa statistic) to examine code application between coders [65]. Coders will discuss any discrepancies until they reach an agreement; the principal investigator (RWSC) will resolve disagreements [63,64]. Investigators will use either a qualitative descriptive coding approach [66] (describing and counting code applications) or axial coding [67] (combining inductive codes into broader categories to define emerging patterns or themes). Investigators will identify and interpret patterns using thematic analysis [68].

Sample Size

Investigators calculated statistical power based on the primary outcomes, a 5% error rate, and best practices for feasibility studies. The median number of teachers at each MetroWest region high school is 86. With 4 schools, investigators anticipate inviting a total of ≥344 school staff (including teachers and other school staff with direct contact with students) to participate in the pilot study. Assuming 50% agree to participate, 50% of participants are in the PLANTS study arm, and 75% of PLANTS participants complete the follow-up survey (reduced n=65), investigators can estimate 95% CI widths ≤0.33 for AIM and IAM, and ≤10.1 for SUS. Such precision levels are sufficient. For qualitative interviews, investigators aim to interview people with a diversity of intervention fidelity, acceptability, usability, feasibility, and appropriateness. This is an exploratory interview study in nature, so idea generation and exploration are the goal, not thematic saturation. Investigators aim to interview PLANTS (n=20-30) and EMAILS (n=10-20) participants, and these sample sizes will provide ample information about the CFIR domains.

Results

School enrollment began in May 2023 and participant enrollment began in June 2023. Data collection is expected to be completed by January 2024. As of December 4, 2023, a total of 99 school staff enrolled in the study. Data collection is expected to be completed in January 2024.

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Discussion

Principal Findings

This pilot trial rigorously evaluates the acceptability, usability, appropriateness, and feasibility of PLANTS, a web-delivered intervention aimed at improving school staff's skills, self-efficacy, knowledge, and outcome expectations for working with sexual and gender minority youths. Schools provide an ideal setting for interventions specific to sexual and gender minority youths for health disparities. High school students spend ~1195 hours per year in school [69], and sexual and gender minority youths regularly interact with adults who are professionally bound by certifying bodies to support the needs of students, including this population [70-73]. Implementing interventions in schools is challenging because of schools' limited resources, increasing demands placed on teachers, and difficulty in acquiring school buy-in. By using an economical and easily implementable web-based intervention, and by developing interventions and implementation strategies in collaboration with school personnel, these barriers may be overcome. PLANTS meets each of these criteria. A strength of this study is how it is embedded within the existing surveillance infrastructure. MWAHS conducts a census of students and has high student participation rates, minimizing biases common in convenience samples of sexual and gender minority youths.

Limitations

The primary limitation is generalizability because the study is solely in Massachusetts, a predominantly liberal US state. Selection bias could be present, for example, if school staff with the greatest stigmatizing attitudes toward sexual and gender minority youths do not participate. Investigators will examine if attitudes toward sexual and gender minority youths are associated with retention or attrition. Despite using numerous validated measures, the reliance on self-reported measures for both staff and students can be seen as a limitation. Because there is concern that school staff may be dishonest, investigators include a measure of social desirability bias [74]. Investigators will control for social desirability in analyses if it is high or if it is unevenly distributed among intervention versus comparator schools. For the exploratory student-level outcomes, another limitation is the lack of assessing individual-level change in student outcomes, since MWAHS data are collected biennially and anonymously. Investigators minimize historical and maturation biases by comparing youths in intervention schools to their same-aged peers in comparator schools across the same time periods while also assessing school-level policy and programmatic changes via surveys.

Conclusions

This study will rigorously test the hypothesis that PLANTS will be rated highly acceptable, usable, appropriate, and feasible by high school staff. PLANTS is hypothesized to be more efficacious for improving staff's support of sexual and gender minority youths and therefore reducing health inequities in this population than the active comparator. The results from this pilot trial will inform a fully powered trial of the efficacy of PLANTS for fostering health equity in sexual and gender minority youths.

Acknowledgments

The research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under award number (K01AA027564 to Coulter). MetroWest Adolescent Health Survey is funded by the MetroWest Health Foundation in 26 school districts, with 3 additional school districts providing direct funding to Education Development Center, Inc. Funders had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the MetroWest Health Foundation.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RWSC conceived of the PLANTS pilot trial. RWSC and SKS secured funding. RWSC, SKS, EM, and KZA designed the study. IKM, CAL, SKS, ASM, and KB helped with the study implementation and acquisition of data. KZA provided statistical expertise in clinical trial design. RWSC and IKM are conducting statistical analyses. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

EM receives royalties for writing content for UpToDate, Wolters Kluwer. The other authors received no external funding.

Multimedia Appendix 1
Survey items for primary outcomes, secondary outcomes, exploratory outcomes, demographics, and confounders.
[PDF File (Adobe PDF File), 156 KB - resprot_v13i1e55210_app1.pdf]

Multimedia Appendix 2

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Peer-reviewer report from the National Institute on Alcohol Abuse and Alcoholism.
[PDF File (Adobe PDF File), 162 KB - resprot_v13i1e55210_app2.pdf]

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Abbreviations

AIM: Acceptability of Intervention Measure
CFIR: Consolidated Framework for Intervention Research
EMAILS: e-Learning to Maximize Academic Inclusion of LGBTQ+ Students
FIM: feasibility of intervention measure
IAM: intervention appropriateness measure
ITT: intent-to-treat
LGBTQ: Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer
MWAHS: MetroWest Adolescent Health Survey
REDCap: Research Electronic Data Capture
PLANTS: Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety
SUS: System Usability Scale

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Protocol

A Social Media–Delivered Melanoma Prevention Program for Young Women Engaged in Frequent UV Tanning: Protocol for a Randomized Controlled Trial

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Abstract

Background: Rates of melanoma have increased dramatically in the United States over the past 25 years, and it has become among the most prevalent cancers for young adult women. Intentional skin tanning leads to a pattern of intense and intermittent UV radiation exposure that is associated with increased risk of melanoma. Frequent tanning is most common among young women and is linked to a variety of sociocultural pressures that negatively impact body image and drive appearance control behaviors. Unfortunately, there are no established interventions designed for frequent tanners. This intervention addresses this gap with unique content informed by body image and acceptance-based interventions. The intervention is delivered using Facebook secret groups, an approach designed to support behavior change and ensure scalability.

Objective: This study aims to describe the rationale and methodology of a randomized controlled trial of a melanoma prevention program targeting young women engaged in frequent indoor or outdoor UV tanning.

Methods: Participants are women aged 18-25 years who report high-risk tanning (ie, at least 10 indoor tanning sessions in the past 12 months or 10 outdoor sessions in the previous summer). After recruitment and screening, participants completed a baseline survey and were randomly assigned to receive the intervention or an attention-matched control condition. Both conditions were 8-week-long Facebook groups (approximately 25 members each) with daily posting of content. Follow-up surveys are administered at 3, 8, and 18 months after baseline. The primary trial outcome is the combined number of indoor and outdoor tanning sessions reported at the 8-month follow-up. Hypothesized intervention mediators are assessed at the 3-month follow-up.

Results: This project was funded by a National Cancer Institute award (R01 CA218068), and the trial procedures were approved by the University of Kentucky Institutional Review Board in February 2020. Trial recruitment and enrollment occurred in 6 waves of data collection, which started in February 2022 and closed in May 2023. The study is closed to enrollment but remains open for follow-ups, and this protocol report was prepared before data analyses. As of February 2024, all participants have completed the 8-month follow-up assessment, and data collection is scheduled to close by the end of 2024 after the collection of the 18-month follow-up.

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Conclusions: This trial will contribute unique knowledge to the field of skin cancer prevention, as no fully powered trials have examined the efficacy of an intervention designed for frequent indoor or outdoor tanning. The trial may also contribute evidence of the value in translating principles of body image and acceptance-based interventions into the field of skin cancer prevention and beyond. If successful, the use of the Facebook platform is intended to aid in dissemination as it provides a way to embed the intervention into individuals' everyday routines.

Trial Registration: ClinicalTrials.gov NCT03441321; https://clinicaltrials.gov/study/NCT03441321

International Registered Report Identifier (IRRID): DERR1-10.2196/56562

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KEYWORDS

acceptance and commitment therapy; body image; dissonance-based intervention; eHealth; Facebook; indoor tanning bed; melanoma; randomized controlled trial; skin cancer; social media; sunbathing

Introduction

Tanning and Skin Cancer Risk

Prolonged exposure to UV radiation induces a skin tanning process in response to cellular skin DNA damage that can lead to skin cancer [1]. Excessive UV exposure through the use of artificial UV-emitting tanning beds or intense, intermittent sun exposures, like outdoor tanning (eg, sunbathing), has been linked to increased risk for all skin cancer types, including melanoma [2-6]. Excessive UV exposure is most common among young adult women and is likely driving concerning melanoma trends in the United States, including a decades-long climb in overall and site-specific melanoma incidence (eg, melanoma of the trunk) [7]. Melanoma has become among the most common cancers among women aged between 20 and 29 years [8].

Public health and policy efforts have produced an increasing number of federal regulations and state-level restrictions on access to tanning beds among minors in the past 2 decades. These efforts have helped to produce a continuing decline in the overall prevalence of tanning bed use in the United States from a peak in 2009 [9-11]. However, recent studies suggest nearly 7% of adolescents and 13% of adults still use indoor tanning in the United States each year [12], and rates of frequent, higher-risk indoor tanning remain concerning, with 24% of recent tanners reporting tanning 25 or more times in the past year in 2018 compared to 13% in 2007 [13]. Internet search results have revealed that public interest in outdoor tanning may have increased during the widespread shutdowns of tanning salons during the height of COVID-19–related restrictions [14]. National prevalence estimates of outdoor tanning are lacking because the behavior is not routinely assessed in surveillance surveys, but recent studies of young adults have found between 32% and 64% report outdoor tanning [15,16]. A recent analysis of protanning videos on the popular social media platform TikTok showed that outdoor tanning was nearly twice as likely to be portrayed as indoor tanning [17]. Overall, while indoor tanning rates have declined, intentional outdoor UV exposure or sunbathing may have increased in popularity.

Public health efforts and existing behavioral interventions have primarily focused on preventing the uptake of indoor tanning and lack attention to frequent tanning behaviors that increase the risk for melanoma development [18]. Indeed, the *Surgeon General's Call to Action to Prevent Skin Cancer* identified a critical research gap related to an absence of interventions that target high-risk tanners and address underlying motives for tanning, including "the desire to look attractive and healthy and to conform to societal beauty standards" [19]. Further, recent trends support the need for interventions targeting frequent indoor and outdoor tanners. The proposed study addresses a gap in the melanoma prevention field by testing a skin cancer risk reduction intervention targeted to frequent indoor or outdoor tanners.

Behavioral Determinants of Tanning Behaviors

Our intervention is designed to address key factors from our conceptual dual-process model of tanning, which is supported by a body of behavioral research that demonstrates tanning is both an intentional, planned behavior to maintain appearance and a reactionary behavior used to avoid negative thoughts and feelings (Figure 1).

The intentional pathway is supported by studies demonstrating the role of tanning expectancies (ie, the anticipated positive and negative aspects of tanning) on tanning intentions and behavior. Tanners endorse positive aspects of tanning, including perceiving a tanned appearance as attractive, rating others with tans as more attractive than their pale counterparts, viewing indoor tanning as a convenient way to enhance appearance, and believing their peers approve of and engage in tanning [20-24]. Many young women experiment with indoor tanning in preparation for a special event, such as getting a tan before a high school prom or a wedding [25-27]. Those experimenting with tanning may begin viewing it as a regular part of their beauty routine and transition to frequent use [27]. Relaxation expectancies are also a primary motive for tanning [28], which have been reinforced by a marketing approach emphasizing a spa-like experience or fitness or health amenities for tanning [29]. This marketing may contribute to tanners' beliefs that tanning has positive health benefits by contributing to mental wellness or self-care [28,30].

Sociocultural body image theories posit that societal influences and perceived expectations regarding appearance negatively influence body image, including how women think and feel about their bodies, and, as a result, drive them to engage in reactive behaviors they know are physically harmful for the sake of appearance enhancement and relief of body image concerns [31,32]. Research from our team and others has demonstrated that constructs from body image theories relate

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to indoor tanning and thus form important skin cancer risk factors among female tanners [33-38]. Tanners are likely to experience perceived pressure to look tan, which is produced in Western cultures that associate being tan as a central aspect of feminine beauty ideals and is reinforced through interactions with peers and family members. Through her buy-in and internalization to the tan ideal, a tanner views being tan as central to feeling attractive and begins actively monitoring her tan. Perceived discrepancies between her current and ideal tan will lead to dissatisfaction and negative appearance-related thoughts or feelings. In this reactive pathway, tanning represents a behavior driven by a desire to avoid such unwanted thoughts and feelings driven by routine thinking that is often flawed, negatively biased, or self-critical.

Figure 1. The dual process model of tanning behavioral determinants is a summary of key tanning motives identified in behavioral studies. The corresponding intervention objectives show how the intervention content is designed to target these key determinants to produce behavior change.

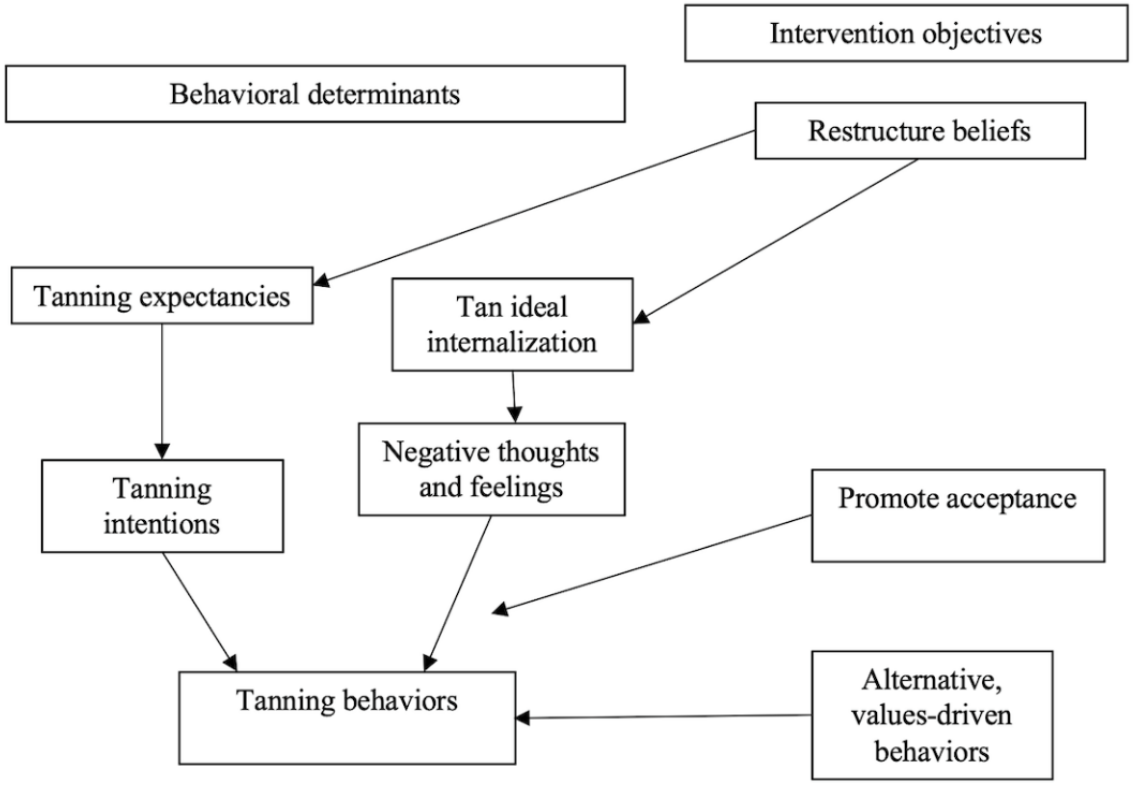

Intervention Content

This intervention incorporates behavior change techniques and content that have been tested in our pilot tanning interventions [39-41] (see Methods section) and are designed to address both intentional and reactionary aspects of tanning (Figure 1). First, our intervention is designed to restructure key psychosocial drivers of tanning, specifically tanning-related expectancies, and body image–related beliefs underlying the internalization of a tan ideal. Participants engaged in risky behaviors may not be highly motivated to change their behavior but are likely to hold views about why they should and should not continue their risky behavior, called behavioral ambivalence [42]. Indeed, most tanners hold positive expectancies about the appearance and relaxation benefits of tanning while also reporting concerns about the appearance-damaging effects of UV exposure and perceiving advantages to reducing their tanning [43-46]. Our intervention is designed to restructure tanning expectancies by encouraging participants to reflect on underlying reasons for tanning and undesirable aspects. Such reflection has been shown to shift the balance of perceived benefits and costs of behaviors, promoting openness to behavioral change [41,42,47,48]. Drawn from body image theory–informed interventions, we also seek to restructure tanners' body image beliefs that underlie tan internalization with content that encourages participants to critique image ideals (in this intervention, through comments in response to intervention content prompts) [49-54]. Body image interventions, including those for tanning [39,40,55], have consistently found that asking participants to consider perspectives that are critical of body image ideals and advocate for counterperspectives can change these underlying beliefs (eg, reduce perceived pressure to tan), which can ultimately reduce buy-in to these beliefs (ie, reduce internalization) and associated body image dissatisfaction. These approaches can be particularly powerful when this process occurs in a group-based setting [53,56]. Accordingly, we use Facebook groups to deliver intervention content to frequent tanners.

Although body image beliefs can be changed in brief interventions, it can be challenging because of the pervasiveness of societal messages focused on women's appearance. Thus, the intervention is also designed to raise awareness of the impact of self-critical thoughts and negative feelings on behaviors such as tanning. The intervention messaging is consistent with the acceptance and commitment therapy (ACT) perspective that uncomfortable thoughts and feelings that accompany some deeply held beliefs cannot be controlled and attempts to do so often perpetuate self-critical thinking and maladaptive coping behaviors [57-59]. Our acceptance-based content encourages

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participants to embrace an acceptance mindset, defined as an increased tolerance for experiencing negative thoughts and feelings that can drive unhealthy behaviors, rather than attempting to control them through such behaviors. The intervention also includes mindfulness skill–building exercises, which are critical for enacting acceptance through increasing the ability to identify and sit with negative thoughts and feelings as they occur [57,59].

Finally, our final intervention encourages participants to focus on healthier self-care behaviors as a substitute for tanning. Consistent with ACT principles, the intervention encourages participants to consider the importance of making daily choices guided by higher-order values to ensure they spend time on the things that are truly important to them (eg, healthy lifestyle, helpful self-care, self-compassion, acceptance, and personal growth) [57,60,61]. Participants identify their core values and contrast them with the values underlying societal messages about appearance that often drive critical self-talk. Participants are then asked to consider whether their ongoing behaviors, including tanning, are consistent with their core values (eg, healthy lifestyle) and, if not, consider approaches for enacting alternative behaviors better aligned with these core values.

Trial Objectives and Design

This randomized controlled trial (RCT) aims to examine the intervention's efficacy versus an attention-matched control group on reducing tanning behaviors among high-risk tanners. Both interventions are delivered through the secret groups feature of Facebook, with a target group size of 25 members each. Participants were frequent tanners (indoor or outdoor) recruited from across the United States. After completing an eligibility screening and a baseline survey, participants were randomized with a 1:1 allocation ratio to each condition after finishing the baseline survey. The 8-week intervention and control groups began 1-3 weeks after baseline completion. Self-reported surveys captured tanning-related beliefs and behaviors at baseline, with follow-ups at 3, 8, and 18 months after baseline. Our primary outcome analysis will compare the tanning rates of intervention and control participants at the 8-month follow-up study. Our study is also designed to explore the impact of hypothesized mediators of intervention efficacy collected on the 3-month postbaseline survey. We hypothesize that intervention participants will report lower tanning rates at the 8-month follow-up, and these effects will be mediated by psychosocial constructs, including increasing tanning expectancies, tanning-related body image factors, and openness to changing indoor tanning. Exploratory outcomes include tanning intentions and an 18-month long-term follow-up assessment to test whether any observed intervention effects extend to the following year.

Intervention Delivery

Intervention content is delivered within secret groups on the social media site Facebook. Participants are invited to join a Facebook group and receive twice-daily intervention content posts from a study moderator. Participants are asked to read and react to posts through the "like" feature or by commenting on them. Facebook groups provide a remotely delivered opportunity to facilitate group-based interactions within the intervention, which can facilitate stronger attitude and behavior change in disordered eating dissonance–based interventions (typically delivered within small groups) [54,56,62,63]. Further, participants in group-based social media interventions often share information and receive and provide motivation to others [64,65], which may facilitate intervention goals related to boosting positive body image and adopting healthy behaviors. Facebook remains the most popular social media site among all adults and is used by 70% of individuals on the internet who are aged between 18 and 29 years [66]. Our preliminary research found that 72% of high-risk tanners used Facebook at least once a day [67] and that Facebook-delivered tanning interventions are feasible and acceptable to our target audience.

Choice of Control

The control condition is administered using the same procedures as the intervention, including delivery through secret Facebook groups. However, the post content differs, with posts related to nontanning health topics of interest identified in our pilot research (eg, physical activity, healthy eating, alcohol misuse prevention, stress reduction, and sleep). An attention-matched control ensures that the conditions are matched on total social media exposure, amount and type of content delivered, and intervention engagement. The design also avoids threats from demoralization among control users who expect but do not receive health content in a no-treatment control.

Methods

Participants

Study Setting

Study participants were young adult women recruited with web-based methods with reach throughout the United States. Recruitment and screening procedures were conducted primarily in partnership with Qualtrics and using Facebook advertisements. A few participants were recruited through additional methods, including posting on social media pages and recruitment flyers posted on a US college campus. Participants completed all study procedures electronically (ie, surveys and participating in Facebook groups) from their chosen location. All study enrollment, tracking, and participant engagement were conducted at the University of Kentucky. Moderating and monitoring of the Facebook groups was performed by research personnel at both the University of Kentucky and the University of Connecticut.

Eligibility

Eligible participants were women aged between 18 and 25 years who reported high-risk tanning (defined as using an indoor tanning bed or intentionally tanning outdoors at least 10 times in the previous 12 months) [68-70]. The study population was limited to young women due to the intervention's emphasis on body image theory and the use of content targeted to this group. We also required that participants report regular use of Facebook (defined as self-reported use of Facebook at least 4-6 times per week in the past 4 weeks). Social media use requirements are standard in trials to ensure that participants have incorporated the chosen platform into their daily media activities and are likely to engage in the intervention [71-74].

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Procedures

Recruitment and Screening

Participants were primarily recruited by the internet research recruitment company Qualtrics Sample Providers using their participant panels that comply with or exceed all applicable industry standards [75]. Qualtrics emailed a randomly selected sample frame of panel participants with a study invitation, which contained a brief description of the study procedures and a brief screening eligibility assessment. Qualtrics also supplemented recruitment with web advertisements posted on various websites and platforms of their partner organizations. Additional recruitment approaches included Facebook advertisement posts with study information and links to access the screening assessment and printed flyers with QR codes to access the screener on a US college campus.

Study announcements and advertisements included a link to a 7-item brief screening assessment. Screener items assessed the eligibility criteria of gender, age, Facebook use, and past 12 months of indoor and outdoor tanning. The 2 additional health behavior questions related to the frequency of physical activity and fruit and vegetable intake were included to mask the purpose of the study. The screening survey was programmed with skip logic to identify eligible participants based on their responses. Eligible participants were provided a brief description of the study procedures immediately following the screening assessment and asked if they were interested in getting additional detailed information about the study. If they clicked yes, participants provided their contact information, which was recorded with their screening results. Screening data were reviewed for quality control to identify potentially fraudulent responses or bots. Specifically, we reviewed the pattern of responses, the total completion time, and IP addresses to identify responses that were likely from duplicate or fake respondents (including bots). Suspicious responses were removed from consideration for the study at the time of screening.

Study Procedures

Following screening, eligible participants who indicated their interest were emailed by study staff a link to a web-based baseline survey that also included the implied consent form. The baseline survey (and all follow-up surveys) were programmed using Research Electronic Data Capture (REDCap) survey software (Vanderbilt University) with encrypted responses collected on the University of Kentucky's secure servers.

After completing the baseline survey, participants were randomized with a 1:1 allocation ratio to either condition. We used a permuted block randomization design to create 2 randomly shuffled assignment lists (ie, intervention or control) in each of 2 strata (ie, indoor tanning: n=500 and outdoor tanning: n=500). These lists were used to assign participants sequentially based on tanning status (within the 2 strata) following their completion of the web-based baseline survey. Following randomization, participants were invited to their assigned group using the group email feature on Facebook. As secondary options, we emailed participants to remind them to join the Facebook groups and asked participants to "friend" the moderator's Facebook account to add them to the appropriate group manually [72].

At 3 months after baseline, each participant was invited by email to complete the first web-based follow-up survey (follow-up 1). Additional follow-ups occur at 8 months (follow-up 2) and 18 months after baseline (follow-up 3). All surveys were designed to be completed in 30 minutes. Incentives were US $30 gift cards for completing each baseline and 3- and 8-month follow-ups and US $40 for the 18-month follow-up based on similar incentive structures that have produced high retention rates in our previous indoor tanning intervention studies [76,77]. High-risk tanners often use indoor tanning throughout the year, with a peak in use in spring (ie, March-May) and outdoor tanning peaks during the summer [25,77,78]. Accordingly, our intervention was designed to be delivered during peak indoor tanning season, with the 8-month follow-up distributed near the end of the year to capture indoor tanning and cover outdoor tanning during the North American summer season. The 18-month follow-up survey will determine if intervention effects extend to tanning behaviors in the subsequent year.

Intervention

Preliminary Data

Our first pilot intervention trial was designed to test the feasibility, acceptability, and preliminary efficacy of the content and messaging strategy that form the foundation of the current intervention [39]. The text-based intervention was delivered through a self-paced, single-session website. Participants were provided psychoeducation content, encouraged to reflect on their tanning behavior, and prompted to type responses to counterattitudinal perspectives to the tan ideal. We conducted an RCT in 2014 with 186 young women who reported indoor tanning at least once in the previous year assigned to receive the website or a waitlist-control condition. We found preliminary evidence of efficacy as intervention participants reported 2.29 times higher odds of abstaining from indoor tanning over a 6-week follow-up period than participants in the waitlist control ($P<.05$). Intervention participants also reported significantly lower intentions to tan. Participants also provided positive overall acceptability and favorability ratings of the website and content focused on body image and behavioral reflection.

Our subsequent pilot trial was to adapt this website intervention content for delivery across 8 weeks through posts to a secret Facebook group [40]. Website content was divided and delivered using 2 daily posts in the group, and participants responded to the reflection posts using the comments feature. We conducted a small, single-arm feasibility trial of the adapted intervention in a study of 17 young women who used indoor tanning beds. On average, participants viewed 92% (26/28) of all posts, reacted to (eg, "liked") 32% (9/28), and commented on 27% (2/28) during the 8-week intervention group period. Further, 82% (14/17) of participants indicated they would recommend the intervention to a friend, and all agreed that they would continue to check the group if it were to continue. Responses to evaluation questions indicated that participants felt connected to and identified with the group, both of which are important for sustaining interest in Facebook groups [79]. Importantly, participants reported a lower number of average past-month

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indoor tanning sessions at the postintervention assessment (mean 0.69, SD 2.3) compared to the baseline (mean 2.31, SD 4.4; Cohen *d*=0.47).

Intervention Refinement

Together, our pilot work demonstrated that our intervention content and delivery platform were feasible and acceptable and had the potential to reduce tanning intentions and behavior. Before this RCT, we conducted 2 formative studies with tanners to refine our content and messaging approach further. The first was a 2018 focus group study of indoor tanners (4 focus groups [total n=20]) designed to (1) refine our planned advertising, recruitment, and enrollment strategies; (2) receive feedback on our general Facebook strategy as well as our examples of planned intervention posts; and (3) receive recommendations for how to best integrate indoor tanning as a discussion topic within the intervention. Although most participants shared that Facebook was not their most frequently used social media platform, most were active users, and they felt the Facebook group feature was uniquely valuable in connecting them with larger groups of friends or others with shared interests. Participants in all 4 groups suggested broadening the intervention purpose and post topics beyond a tanning-specific focus to promoting physical and mental wellness as part of a healthy lifestyle. Messaging related to body acceptance and female empowerment was also suggested as key desirable topics associated with a healthy lifestyle. Participants also expressed interest in content design to help them establish healthy routines and habits (eg, eating, going to the gym, and sleeping). Most participants viewed tanning as a bad habit but not necessarily as inconsistent with a healthy lifestyle. For example, tanners did not often equate tanning with other behaviors considered to be "unhealthy," such as smoking or poor diet. However, when asked to reflect on the harms of tanning, members acknowledged that it is indeed a risky behavior and consistent with other unhealthy lifestyle choices. Finally, most participants felt they commonly encountered body image messaging and recommended we expand the discussion of body image to more broadly reflect pressures that young women experience beyond physical appearance, such as the pressure to live a "perfect" life that may cause mental stress and be inconsistent with their personal preferences.

We made several changes to the planned intervention based on this feedback. First, we refined the intervention framing, messaging, and post content to focus on promoting healthy self-care and empowerment to embrace a physical and mental wellness lifestyle. We named the intervention "empowerfulme" to reflect this focus. We also incorporated the concept of helpful self-care behaviors (ie, those with health benefits) as a contrast to unhelpful self-care behaviors, which were defined as "things we do that feel like self-care but often cause problems." We crafted new intervention content that encouraged participants to reflect on the short- and long-term consequences of unhelpful self-care, using tanning as an example of how unhelpful self-care may be perpetuated by idealistic thinking and societal messaging. Our incorporation of messaging and exercises based on ACT approaches was also in response to the described interest in learning more about self-acceptance and living by internal values over externally imposed values.

After content refinement, we conducted a usability trial in a sample of 29 frequent tanners using the same procedures as the fully powered RCT (except for multiple follow-up assessments). We experienced a slower-than-expected rate of recruitment and enrollment that delayed enrolling a sufficient number of tanners into Facebook groups to start groups with a targeted size of 25 participants. This led to an expansion of our recruitment strategy and study description. We also examined participants' interactions with our posts in this version and modified those that received low levels of engagement.

Intervention Engagement and Posting Strategy

Our intervention is administered within a study-specific "secret" Facebook group with membership and content limited to invited group members. Facebook groups ran for 8 weeks and contained 25 members each. Given that ideal intervention length and group size have not been empirically established and differ based on intervention content and objectives [74], we modeled our intervention on our pilot Facebook study. Our intervention included strategies found to boost participant involvement and group engagement in Facebook group–delivered health interventions for young adults [40,71,72,80,81]. We provided clear expectations, including checking the group study account at least once a day and "icebreaker" activities to increase comfort with commenting. We also used a young woman as the intervention moderator; all posts came from this account. Under the research team's guidance, the moderator commented or reacted to various posts (ie, liking them) to reinforce participant activity and encourage engagement.

Intervention content was delivered through posts made by the group moderator twice daily for 8 weeks, for a total of 112 posts. Each week addressed a thematic topic introduced in the first weekly post (Monday morning), with corresponding goal-setting and monitoring activities throughout the week (Table 1). Other posts were designed with activities and prompts to address change objectives, reinforce intervention messaging, or promote group engagement [40]. We also structured the content and timing of our posts to maximize engagement. Posts were written in a conversational tone and designed to take less than 3 minutes to read and comment on. A graphic designer enhanced the visual appeal of our posts and included relevant photos and videos [82]. We included polls and prompts in our posts for participants to share tips and successes with others [74,83].

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Table 1. A description of the types, frequency, purpose, and content of the posts used for intervention and control group content.

Post type	Weekly frequency	Purpose and content
Goals	3	Participants set a goal related to the weekly topic (Monday evening), completed monitoring or check-in related to progress (Thursday morning), and reported back about goal progress (Sunday).
Reflection and discussions	5	To restructure key expectancies and beliefs with content that is discussion-based and designed to encourage reflection on one's ongoing behavior or speaking out against idealistic perspectives.
Reinforcement messages	2-3	Posts drawn from popular sources and designed to reinforce intervention messaging. Unlike other "active ingredient" posts, content may change between waves to accommodate ongoing events or provide recent and relevant articles.
Sharing content	2-3	Memes, inspirational quotes, and humorous posts intended to promote engagement and provide positive messaging.

Intervention Content

Our intervention strategy and content were developed through a mapping process [84] that included (1) identifying specific behavioral determinants (ie, factors that lead to tanning behavior) to target for change (described previously); (2) developing specific performance objectives (POs) to specify the changes in these targets that must occur to produce the overall behavioral outcome of reducing tanning; and (3) applying behavior change theory and techniques to produce intervention content to meet the POs.

POs 1-3 (Table 2) are designed to restructure tanning expectancies and body image beliefs that drive tanning intentions and idealistic thinking. Initial intervention content is framed within the context of considering that "self-care" behaviors can be either helpful (eg, exercise) or unhelpful (ie, they may provide some immediate benefit but have costs in the short- or long-run). Participants are asked to reflect on their self-care and reflect on their view of whether tanning is helpful or unhelpful self-care (POs 1 and 2). Participants are asked to consider the balance of benefits and problems with various forms of self-care and consider plans to increase helpful and reduce unhelpful self-care. Tanning-specific content encourages participants to reflect on underlying reasons and undesirable aspects of tanning to restructure beliefs by shifting the balance of pros and cons and thus promoting openness to behavioral change [41,42,47,48].

PO 3 also seeks to restructure beliefs by incorporating counterattitudinal advocacy techniques that effectively alter risky body image beliefs [49-54]. This approach has the person speak out against and question commonly held idealistic thoughts. If done effectively, the alternative perspectives considered during these exercises will conflict with idealistic thinking, producing psychological discomfort (ie, cognitive dissonance) [63]. The person is then motivated to seek psychological relief by altering their original unhealthy beliefs to be more consistent with the healthier perspective being advocated. Creating dissonance is optimized when participants share counter perspectives in group-based settings, which leads to more robust attitude and behavior change [53,56]. Accordingly, the intervention approach is to solicit counterattitudinal comments as responses to our Facebook group posts.

POs 4 and 5 are guided by the ACT concept of promoting acceptance. It can be difficult to completely change and mitigate the impact of strongly ingrained beliefs, such as those underlying idealistic thinking. ACT defines fused beliefs as routine thinking that can be self-critical and may lead to unwanted thoughts and feelings that drive habitual behaviors that are often unhealthy in an attempt to control these difficult experiences [57-59]. The intervention provides psychoeducational content and messaging that thoughts and feelings cannot be controlled and attempts to control them can create additional problems and perpetuate self-critical thinking. The intervention messages emphasize the value of willingness to experience negative thoughts and feelings by using mindfulness skills [57-59].

Finally, PO 6 encourages participants to consider the importance of making daily choices guided by higher-order values [57,60,61]. The intervention content encourages participants to consider the importance of broad values (eg, healthy lifestyle, helpful self-care, self-compassion, acceptance, and personal growth) and consider their alignment with societal messages and expectations promoting tanning. Participants identify their core values and contrast them with the values underlying societal messages about "perfection" in appearance and other aspects that often drive self-critical thinking. They are also asked to consider whether their ongoing behaviors are consistent with their core values and engage in goal-setting for enacting behaviors aligned with them [57,60,61].

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Table 2. The intervention performance objectives (POs) that guided the content of corresponding intervention posts.

POs	Intervention content
PO 1: engage in helpful self-care behaviors	1a. Describe helpful self-care behaviors
	1b. Identify benefits of helpful self-care behaviors
	1c. Identify and enact plans for increasing helpful self-care behaviors
PO 2: reduce unhelpful self-care behaviors (with tanning as an example)	2a. Identify unhealthy forms of self-care, including tanning
	2b. Describe how tanning is not aligned with helpful self-care. Describe problems with tanning.
	2c. Identify and enact plans to reduce unhelpful self-care
PO 3: reduce buy-in to appearance messages about ideal women	3a. Critique societal expectations for women that lead to negative affect and unhealthy behaviors like tanning
	3b. Describe the messages underlying these expectations and their sources
	3c. Speak out against the problems caused by self-critical appearance values
PO 4: increase acceptance and willingness to experience uncomfortable feelings	4a. Identify problems with trying to control thoughts and feelings through behaviors like tanning
	4b. Understand the concept of acceptance
	4c. Express a commitment to adopting an acceptance mindset
PO 5: practice mindful acceptance	5a. Enact general skills for self-observation (ie, mindfulness skills)
	5b. Practice identifying self-critical beliefs and related feelings and sitting with them
PO 6: engage in behaviors that are consistent with personal growth values	6a. Describe the most important personal growth values
	6b. Evaluate alignment of current behaviors with growth values
	6c. Identify and enact plans to ensure values-consistent behavior

Measures

Self-Report Survey Items

Our primary outcomes are self-reports of indoor and outdoor tanning at the 8-month follow-up (Table 3). We chose items that are expert-recommended [85] and commonly used in tanning intervention trials [39,41,77]. Outcomes have open-ended response options to increase reporting accuracy and have been shown to be reliable compared to daily diary reports of behavior assessed over the same period [77,86]. Mediators and other measures are also listed in Table 3 and include measures adapted for tanning and validated in our previous research [38].

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Table 3. The trial measures captured with self-report surveys.

Construct	Description of measures
Primary outcomes (measured at 8-month follow-up)	
Indoor tanning	• Open-ended reporting of the number of times participants used a tanning bed or booth in the past 8 months [85]
Outdoor tanning	• Open-ended reporting of the number of times spent outdoor tanning in the most recent summer (eg, between June 1, 2023, and August 31, 2023) [86]
Secondary outcomes	
Tanning intentions	• Intentions to use indoor tanning or spend time outdoor tanning (2 separate questions) in the next 12 months [39,41,77]
Long-term tanning	• Indoor and outdoor tanning outcomes assessed at the 18-month follow-up
Primary mediators (measured at 3-month follow-up)	
Tanning expectancies	• Beliefs related to tanning benefits (eg, tanning is attractive and relaxing) and risks (eg, appearance damage and skin cancer risk), tanning attitudes, and temptations to tan [87,88]
Tanning-specific body-image factors	• Items adapted from the Objectified Body Consciousness Scale to assess actively monitoring and comparing one's tans with others [38,89] • Internalization of the thin and tan ideal [21,35,38,88] • Appearance conversations with friends [90] • Items adapted from the Multidimensional Body Self-Relations Questionnaire to reflect tan dissatisfaction [38,91]
Openness to changing tanning	• Perceived difficulty in stopping indoor or outdoor tanning (2 separate questions) [92] • The Readiness to Change Questionnaire adapted to tanning behavior [93]
Exploratory mediators	
Values and values-consistent living	• Valued Living Questionnaire [94] • Valuing Questionnaire [95]
General body image acceptance	• The Acceptance and Action Questionnaire II [96] • Beliefs About Appearance Scale [97]
Perceptions and use of tanning alternatives	• For both sunless tanning products and spray-tanning, past 12 use, intention, attitudes, and self-efficacy [77,85]
Mindfulness	• Mindful Attention Awareness Scale [98]
Covariates	
Demographics	• Age, education, race, ethnicity, urban, rural, and SESa
Sun protection habits	• Typical use of sun protection (eg, shade and sunscreen) [99]
Use of social media	• Frequency of use of popular social media sites and integration of Facebook within social behaviors and daily routines [67,100]
Melanoma risk factors	• Natural hair color, eye color, skin type, skin reactivity to the sun, and history of sunburns [101]
Depression, anxiety, and stress	• The Depression Anxiety Stress Scale-10 [102]
Other health behaviors	• Alcohol use [103] • Cigarette use [104] • Physical activity [105] • Sedentary behavior [106] • Sleep [107] • Diet [108]

[a]SES: socio-economic status.

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Facebook Engagement

The 3-month follow-up survey contained several Facebook-specific evaluation items, including perceived connectedness with a group, identification with posts and other group members, enjoyment, and ease of participation [79,109,110]. Items from the Audience Engagement Scale were used to measure key aspects of engagement with intervention content, including personal involvement (ie, was information judged to be personally relevant) and personal reflection (ie, was the knowledge acquired used to reevaluate personal conduct) [111]. Software (GRYTICS [112]) was also used to capture objective measures of participants' engagement, including comments and reactions to our posts or comments from others within our posts.

Statistical Analysis

Power

The primary outcome will be a sum of the 8-month indoor tanning outcome and the number of outdoor tanning sessions in the summer. One of the only intervention trials to focus on high-risk tanners was an in-person counseling intervention that produced significantly lower tanning rates among intervention participants at a 3-month follow-up [113]. This analysis suggested means for indoor tanning sessions of 4.40 (SD 7.74) for the intervention group and 11.78 (SD 13.03) for controls for a between-group difference of 7.38, which corresponded to a moderate to large size effect (0.69). Because our intervention is less intensive than a counseling intervention, we powered our study based on the scenario that the treatment effect will be at least 60% of the counseling study (corresponding to an effect size of 0.41). In our usability trial baseline data, the mean number of previous 3-month measures of indoor tanning and past summer outdoor tanning was 22.5 (SD 22.9; our means will likely be higher in the trial since the past 8-month indoor tanning will be used). Assuming similar means in our trial control group, an intervention effect of 0.41 would produce a mean of 13.1 (SD 22.9) tanning sessions in the intervention group, a difference of 9.4 total tanning sessions. Assuming these estimates from our follow-up means (ie, tanning control: mean 22.5, SD 22.9; tanning intervention, mean 9.4, SD 22.9), we will achieve 80% power with at least 186 participants (93 in each group). We anticipated a 70% follow-up rate at the primary 8-month outcome, which led us to target the enrollment of 266 participants to test the effects adequately.

Primary Outcome Analyses

Using intention-to-treat analyses, 2-sided tests for the effect of treatment will be conducted at the 0.05 level. If less than 10% (26/266) of outcomes are missing, we will consider data to be missing at random and apply multiple imputations. If missing data are more than 10% (27/266), we will examine patterns of missing data, including comparing demographics for those with and without missing outcomes. If missing data are not random, we will consider alternative missing data approaches. We will also conduct sensitivity analyses by first comparing baseline characteristics by condition and modifying the analyses to adjust for differences.

Multilevel models (eg, random coefficient) will test the primary study hypothesis that participants who received the intervention will report less total tanning behavior at 8-month follow-up compared to those who received the control. The level 1 model represents individuals nested within Facebook groups (the level 2 model). In particular, the effect of the intervention will be considered a random effect that may vary by block (ie, Facebook group). Thus, the model for analysis will use the following form as a starting point: $Y_{ij} = \beta_{0j} + \beta_{1j}T + \varepsilon_{ij}$, where Y_{ij} represents the number of tanning sessions used for the *i*th individual within the *j*th block, T is an indicator for whether the individual was randomized to the treatment or control. As such, the analysis accounts for (by including the random intercept β_{0j}) random differences between blocks (eg, previous tanning behavior) and allows the effect of the intervention to vary by block (with β_{1j}). If necessary, sensitivity analyses may control for individual-level covariates and appropriate transformations (ie, square root), or additional analysis methods will be considered if the normality assumption is strongly violated.

Mediation Analyses

Mediator analysis will be used to assess whether participant attitudinal factors (level 1 variables), including tanning expectancies, tanning-related body image factors and change perceptions, mediate the effect of the intervention. In particular, for each potential mediator, the 4 component steps [114] will be examined through regression models similar to those described above. The contribution of the mediated effect will be assessed directly using the approach recommended by Kenny and colleagues [115]. For multilevel models, we will calculate the product of the 2 pieces of the mediating path (from intervention group assignment to the mediating variable and from the mediating variable to the outcome). Bootstrap procedures will be used to formally test for the significance of the mediating pathway.

Ethical Considerations

The University of Kentucky Institutional Review Board reviewed and approved all study procedures before data collection (review number 56153 2019). A web-based informed consent form was included as the first page of the baseline survey, and it described the study procedures, privacy, confidentiality, risks, benefits, and data protection. Participants provided implied consent by agreeing to the consent form and starting the survey. All survey data were collected with a deidentified approach, using a unique participant identifier in place of a name or other personal information. The engagement data downloaded from Facebook were deidentified before storage or analysis by replacing participant names with their unique identifier. Our consent form also provided a description of the certificate of confidentiality provided by the National Institutes of Health as part of their funding support. Participants were emailed Amazon gift card incentives in the amount of US $30 for completing each of the baseline, 3-month, and 8-month surveys and US $40 for the 18-month follow-up.

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Results

This trial was funded by the National Cancer Institute (R01 CA218068) in July 2017 and approved by the University of Kentucky Institutional Review Board in February 2020. Trial recruitment and enrollment occurred in 6 waves of data collection, starting in February 2022 and closing in May 2023. The study is closed to enrollment but remains open for follow-up. This protocol report was prepared before data analyses. As of February 2024, all participants have completed the 8-month follow-up assessment, and data collection is scheduled to close by the end of 2024 after the collection of the 18-month follow-up.

Discussion

Frequent tanning has been linked to an exponential increase in melanoma risk, but there are no established interventions targeting this group. This is the first study to test an intervention for frequent tanners in a fully powered trial. The prevailing approach to tanning interventions has been to raise awareness about the health risks as well as the appearance-damaging effects of tanning (eg, premature skin aging and wrinkling) [77,116-120]. These interventions have been delivered as educational-based interventions in various formats, with some incorporating UV facial photographs showing existing skin damage in combination with health risk information. Several trials have demonstrated the efficacy of these appearance-focused interventions when tested among typical tanners (eg, participants who have tanned at least once). However, the efficacy of this approach is likely to be limited among more frequent tanners [121] who generally report knowledge of and perceived susceptibility to the appearance risks of tanning but believe the immediate benefits outweigh the longer-term risks [20,122,123].

Beyond their primary focus on occasional tanners, appearance-focused interventions do not address key motives that are likely driving frequent tanning, including sociocultural influences, body image, and tanning dissatisfaction. This intervention approach represents an extension of the previous intervention literature by attempting to change core motives and influences that make tanning "worth the risks" among frequent tanners as well as incorporating key elements of an acceptance-based intervention. A small number of studies have demonstrated the potential value of using dissonance-based, body image–focused intervention strategies in melanoma prevention efforts [39,40,55,124]. This trial extends this work by (1) testing a fully powered skin cancer prevention program delivered entirely through social media; (2) delivering the intervention to both frequent indoor tanners and sunbathers; (3) broadening the intervention content focus beyond body image ideals to also challenging general expectations of how young women should look, think, and act; and (4) translating concepts from ACT principles to create acceptance-based content that encourage participants to accept that negative thoughts and feelings will happen and consider the importance of making daily choices that are guided by higher-order values.

Existing indoor tanning interventions have not been widely disseminated. The use of social media to deliver intervention content embeds the intervention into a platform that has become ingrained in the lives of our target young adult population and is a preferred method for exchanging information and communicating with peers [125]. A Facebook-delivered intervention can be integrated into individuals' existing, routine social media habits and avoids the burden of requiring users to find and use a stand-alone, unfamiliar website. The impact of this work lies in the potential for dissemination in a variety of contexts, given the use of a familiar and freely available intervention platform. This study will produce an intervention guide and content library of posts that could be implemented with minimal costs and staffing. Further, the intervention allows for social connection and self-expression among participants, which are key reasons people use social media [109]. These intervention features, along with the focus on positive body image, may increase the interest of potential intervention participants and thus lead to a more impactful intervention.

Limitations

Potential limitations to using Facebook include the fact that the nascent social media literature lacks firmly established, empirically based guidelines for effective practice. Thus, several of our choices (eg, content, length, and group size) are based on our experiences in pilot studies and available best practice guidelines. An alternative to the proposed Facebook approach would be retaining the previously tested website intervention. Websites have advantages, including increased control over content, easier user tracking, and the ability to deliver more in-depth content. However, website interventions have restrictive barriers for the target population, including the need to direct them to an unfamiliar website and a possible lack of interest in engaging on the website for any substantive period of time (as noted in our focus group research). The group discussions critical to the success of dissonance-based intervention are more easily implemented on the freely available Facebook setting but are more difficult to achieve with a website. There are also limitations in using Facebook to deliver content across several weeks. Developers of Facebook group support interventions for smoking cessation have raised concerns about the "empty room phenomenon," which describes the hesitancy of some social media users to engage with strangers [64]. We have engaged in several formative user-centered studies to inform the messaging and content of our intervention, but low engagement can occur in social media–delivered interventions. It is possible that users could alter the topic of discussion in ways not conducive to indoor tanning prevention or make unfavorable comments. We attempt to prevent this behavior by providing general guidelines for posting, daily monitoring, and following an established intervention manual for moderators.

Conclusions

This trial will contribute unique knowledge to the field of skin cancer prevention, as no fully powered trials have examined the efficacy of an intervention designed for frequent indoor or outdoor tanning. Our intervention builds from and meaningfully extends existing skin cancer interventions and incorporates innovative elements from body image and acceptance-based

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interventions in its content and delivery. If efficacious, findings can inform best practices in skin cancer prevention and provide evidence of the value of translating principles from body image and acceptance-based interventions to target other behavioral contexts. The use of Facebook groups allows group-based interactions among participants, which can facilitate stronger changes in attitudes and behaviors and provide a platform to embed the intervention into individuals' everyday routines.

Acknowledgments

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Data Availability

The data sets generated during this study are not publicly available due to the data sharing plan that was approved as part of our funded application and the certificate of confidentiality provided by the National Institutes of Health. Deidentified data sets are available from the corresponding author on reasonable request following the issuance of our final project funding report.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Cancer Institute (National Institutes of Health).
[PDF File (Adobe PDF File), 134 KB - resprot_v13i1e56562_app1.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
PO: performance objective
RCT: randomized controlled trial

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Protocol

Efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) in Individuals With Chronic Pain and Opioid Use Disorder: Protocol for a Randomized Clinical Trial of a Digital Cognitive Behavioral Treatment

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Abstract

Background: Chronic pain is common among individuals with opioid use disorder (OUD) who are maintained on medications for OUD (MOUD; eg, buprenorphine or methadone). Chronic pain is associated with worse retention and higher levels of substance use. Treatment of individuals with chronic pain receiving MOUD can be challenging due to their increased clinical complexity. Given the acute and growing nature of the opioid crisis, MOUD is increasingly offered in a wide range of settings, where high-quality, clinician-delivered, empirically validated behavioral treatment for chronic pain may not be available. Therefore, digital treatments that support patient self-management of chronic pain and OUD have the potential for wider implementation to fill this gap.

Objective: This study aims to evaluate the efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT), an interactive digital treatment program with asynchronous coach feedback, compared to treatment as usual (TAU) in individuals with chronic pain and OUD receiving MOUD.

Methods: Adult participants (n=160) receiving MOUD and reporting bothersome or high-impact chronic pain will be recruited from outpatient opioid treatment programs in Connecticut (United States) and randomized 1:1 to either IMPACT+TAU or TAU only. Participants randomized to IMPACT+TAU will complete an interactive digital treatment that includes 9 modules promoting training in pain and addiction coping skills and a progressive walking program. The program is augmented with a weekly personalized voice message from a trained coach based on daily participant-reported pain intensity and interference, craving to use opioids, sleep quality, daily steps, pain self-efficacy, MOUD adherence, and engagement with IMPACT collected through digital surveys. Outcomes will be assessed at 3, 6, and 9 months post randomization. The primary outcome is MOUD retention at 3 months post randomization (ie, post treatment). Secondary outcomes include pain interference, physical functioning, MOUD adherence, substance use, craving, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy. Semistructured qualitative interviews with study participants (n=34) randomized to IMPACT (completers and noncompleters) will be conducted to evaluate the usability and quality of the program and its outcomes.

Results: The study has received institutional review board approval and began recruitment at 1 site in July 2022. Recruitment at a second site started in January 2023, with a third and final site anticipated to begin recruitment in January 2024. Data collection is expected to continue through June 2025.

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Conclusions: Establishing efficacy for a digital treatment for addiction and chronic pain that can be integrated into MOUD clinics will provide options for individuals with OUD, which reduce barriers to behavioral treatment. Participant feedback on the intervention will inform updates or modifications to improve engagement and efficacy.

Trial Registration: ClinicalTrials.gov NCT05204576; https://clinicaltrials.gov/ct2/show/NCT05204576

International Registered Report Identifier (IRRID): DERR1-10.2196/54342

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KEYWORDS

chronic pain; digital treatment; medications for opioid use disorder; methadone; opioid use disorder

Introduction

Background

Despite increased attention from the media, policy makers, researchers, and clinicians, the opioid epidemic in the United States remains a significant public health crisis. Approximately 107,000 US adults died by drug overdose in 2021, with increases in every age group and an overall age-adjusted 14% increase from the previous year [1]. An estimated two-thirds of overdose deaths involved synthetic opioids other than methadone (eg, illicitly manufactured fentanyl) [2]. Medications for opioid use disorder (MOUD), including buprenorphine and methadone, are protective against mortality in individuals with opioid use disorder (OUD) [3,4], reducing overdose death and all-cause death by 8 and 2.5 times, respectively [5]. Furthermore, longer retention in MOUD is associated with a continued reduction in mortality [5]. Retention of at least 6 months, and often longer, is needed to obtain full benefits, including a return to work and improvements in fulfilling family and social responsibilities [6,7]. Despite these benefits, only 36% of individuals who initiate are retained in MOUD for 6 months, with retention rates falling to 22% at 1 year [8]. Therefore, developing interventions that support MOUD retention and address co-occurring conditions that interfere with retention is essential to enabling people with OUD to obtain the full benefits of MOUD treatment.

Role of Pain in the Development of OUD

One condition that commonly co-occurs with OUD is chronic pain, frequently defined as pain that persists for 3 months or more. Chronic pain is a widespread affliction in the United States, affecting approximately 1 in 5 adults [9], and is more common among people with OUD. A large study of electronic health records revealed that 64.4% of individuals with OUD also had a chronic pain condition [10]. Chronic pain can be a pathway to OUD, with 4 out of 5 individuals who use heroin reporting their initial exposure to opioids was through a prescription for pain treatment [11,12]. It is a common misconception, even among addiction providers, that methadone and buprenorphine provide adequate pain treatment for individuals with OUD [13]. Unsurprisingly, chronic pain typically persists when MOUD is the sole treatment modality. Among individuals enrolled in methadone or buprenorphine treatment, estimates of chronic pain range from 40% to 80% [14-17].

Chronic Pain Negatively Affects MOUD Outcomes

The presence of chronic pain may undermine the effectiveness of MOUD. A large randomized, controlled multisite trial of buprenorphine in individuals with OUD found greater pain severity significantly increased the odds of opioid use in the following week [18]. Follow-up analyses revealed that variability or volatility in pain intensity was associated with craving, relapse to opioid use, and poorer outcomes [18,19]. Furthermore, the experience of pain has been cited as the most common reason for returning to use while engaged in MOUD [20]. Finally, few people receiving MOUD receive adequate evidence-based pain care; this has been recognized as an important gap in the treatment of comorbid OUD and chronic pain [15,21-24].

Individuals with chronic pain receiving MOUD, compared to those without chronic pain, have higher rates of psychiatric and medical comorbidities, including sleep disturbances, and higher rates of health service use and levels of functional impairment [21,25-27]. Comprehensive treatment for individuals with concurrent chronic pain and OUD may require interventions that address mood, anxiety, sleep, and functional difficulties to maximize OUD treatment outcomes, such as MOUD retention. That is, chronic pain with OUD does not necessarily indicate more severe OUD; rather, it represents a concurrent disorder that may have a different clinical course and treatment response than OUD alone [22,28]. Accordingly, treatments should consider the relationship between chronic pain and opioid use while addressing barriers to engagement in resource-limited MOUD clinics.

Cognitive Behavioral Therapy Is an Evidence-Based Treatment for Both Chronic Pain and Substance Use, but it has Limited Accessibility

Cognitive behavioral therapy (CBT) has a strong evidence base for the treatment of chronic pain [29] and substance use disorders [30-33]. CBT for chronic pain has been recommended by the Centers for Disease Control and Prevention and the National Institutes of Health (NIH) as a first-line treatment to reduce pain and improve function [34,35]. Although MOUD clinicians report interest in nonpharmacologic pain treatment, very few report confidence in their own ability to address chronic pain [36]. Similar to chronic pain, CBT for substance use disorders has been shown to have moderate effects on reducing substance use, promoting abstinence from substances, increasing the use of coping skills, and promoting other positive psychosocial outcomes in individuals with addiction [37]. Engagement in CBT for substance use disorder is a mainstay

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in outpatient and inpatient treatment, but, akin to CBT for chronic pain, implementing CBT with high fidelity is challenging due to the lack of trained clinicians in the setting [38,39]. For these reasons, offering adjunctive CBT in MOUD clinics has resulted in mixed findings [40-42]. Taken together, there is a critical gap in treatment where individuals with OUD receiving MOUD have few options for addiction or pain treatment. Accordingly, there has been a recent call to develop rigorous, evidence-based digital treatments for individuals with OUD, which can be integrated into MOUD clinical settings [43].

Development of Integrating the Management of Pain and Addiction via Collaborative Treatment

Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) combines 2 evidence-based digital CBT treatments: Computer-Based Treatment for Cognitive Behavioral Therapy (CBT4CBT) and Cooperative Pain Education and Self-Management (COPES) treatment programs (Figure 1). CBT4CBT is a web-based program designed to improve behavioral and cognitive coping skills that have been evaluated in a range of substance use disorders [44-47], including 2 trials indicating its effectiveness and durability for individuals with OUD on methadone maintenance [48,49] and office-based buprenorphine maintenance [50]. COPES is an interactive voice response–based treatment for chronic pain that is delivered asynchronously through telephone [51] and has been shown to be similarly effective in reducing pain intensity and improving physical functioning, sleep quality, and quality of life as real-time CBT with a therapist [52]. IMPACT was designed to provide an easily accessible, standardized evidence-based intervention for those with OUD and chronic pain that could ultimately be easily integrated into MOUD clinic settings.

Figure 1. Core program features of the Computer-Based Treatment for Cognitive Behavioral Therapy (CBT4CBT) and Cooperative Pain Education and Self-Management (COPES) programs.

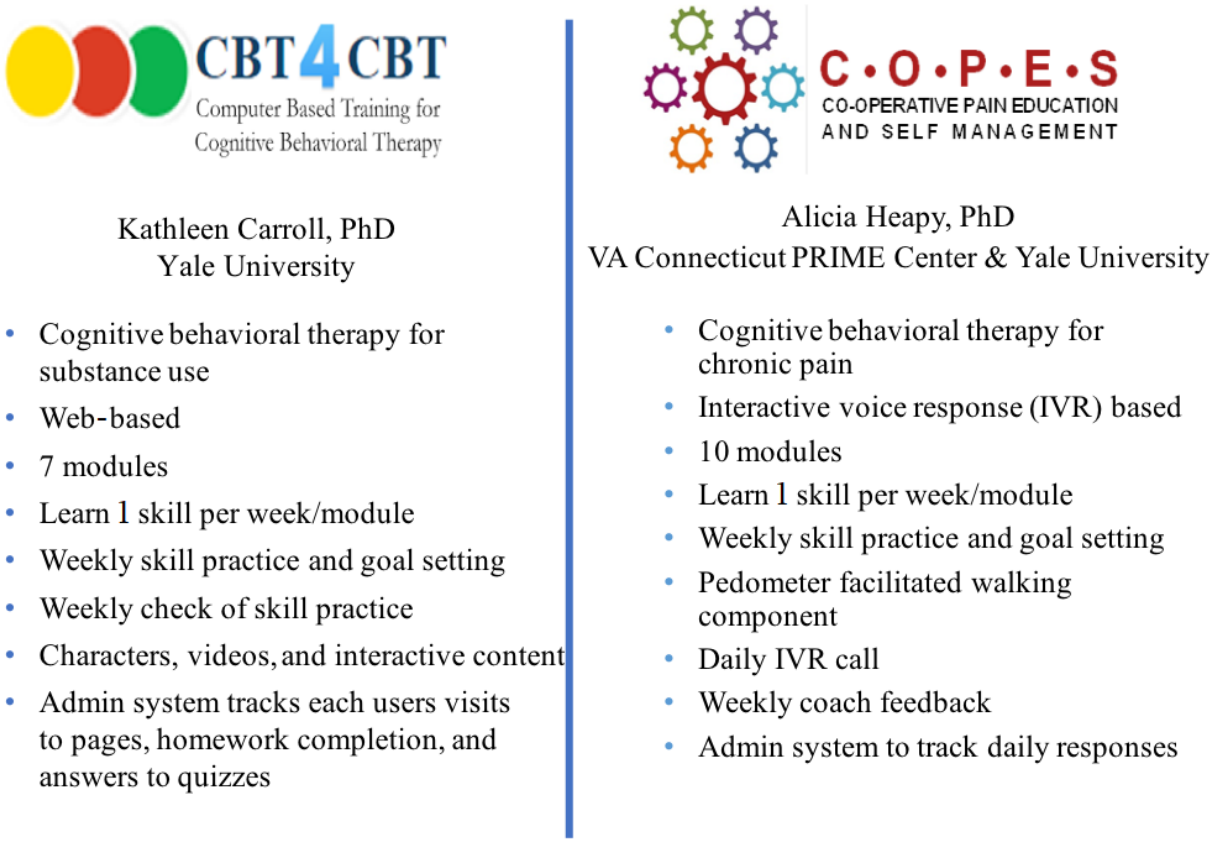

This study was funded by the National Center for Complementary and Integrative Health's Behavioral Research to Improve Medication-Based Treatment (BRIM) program. The goal of BRIM, funded by NIH's Helping to End Addiction Long-Term (HEAL) initiative, is to examine the role of behavioral interventions in improving the outcomes of MOUD, particularly MOUD access and retention. The R61/R33 award described here consists of 2 phases: a preparatory R61 phase used to develop the intervention and identify recruiting sites and the R33 clinical trial that is the focus of this protocol.

Study Objectives

The study is designed to evaluate the efficacy of IMPACT along with treatment as usual (IMPACT+TAU) versus TAU only at 3 months post randomization (primary end point). The primary OUD outcome is verified retention in MOUD treatment, defined as enrollment in MOUD (ie, yes or no), with evidence of MOUD use in the week before the 3-month time point. Secondary treatment outcomes will include pain interference, physical functioning, MOUD adherence, substance use, craving, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy at 3 months post randomization. The secondary aim is to evaluate the durability of effects for MOUD retention

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at 6 and 9 months post randomization. The tertiary aim is to examine treatment usability and quality through qualitative interviews with individuals randomized to IMPACT.

Methods

Study Design

This is a randomized clinical trial comparing the efficacy of IMPACT+TAU relative to TAU among individuals enrolled in MOUD treatment who have chronic pain. Outcomes will be assessed at baseline, 3, 6, and 9 months post randomization (Figure 2).

Figure 2. Study protocol for Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT). MOUD: medications for opioid use disorder; TAU: treatment as usual.

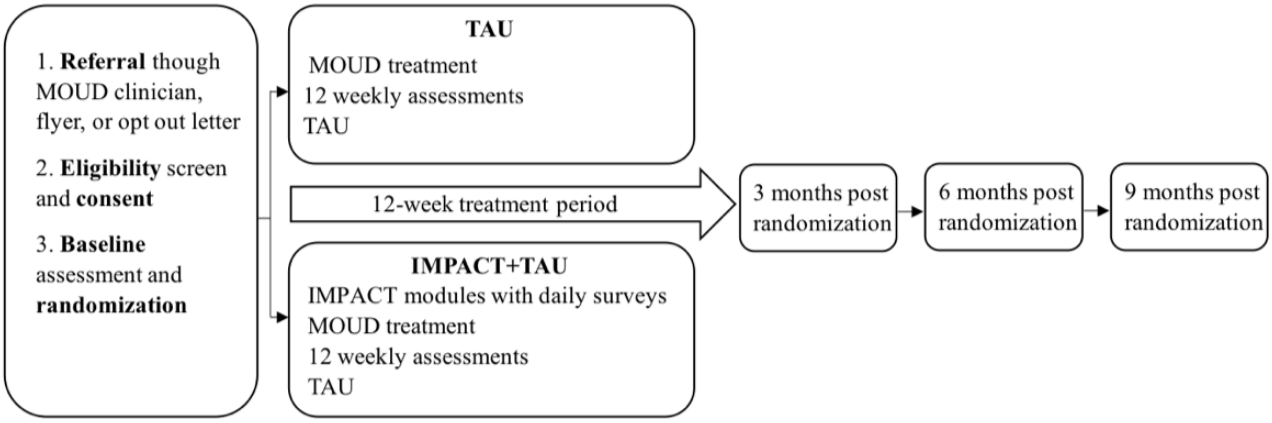

Study Population and Setting

Participants will be 160 individuals with chronic pain receiving MOUD (methadone or buprenorphine) at participating outpatient opioid treatment program (OTP) sites located in Bridgeport, Danbury, and Waterbury (Connecticut).

Ethical Considerations

The study was approved by the Yale University Institutional Review Board on September 4, 2019 (2000026276). Subsequent modifications were implemented to add posttreatment qualitative interviews to assess treatment satisfaction and usability, as well as to refine recruitment materials and add recruitment sites. The study was subsequently approved by the Veterans Affairs Connecticut Human Subjects Subcommittee because, although not enrolling Veteran Affairs patients, several study staff are employees of the Department of Veterans Affairs.

Study Population

Textbox 1 contains inclusion and exclusion criteria for patients.

Textbox 1. Eligibility criteria for patients.

Inclusion criteria

- Be 18 years of age or older
- Meet the

  Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for opioid use disorder and be enrolled in methadone or buprenorphine treatment at the participating medications for opioid use disorder (MOUD) clinic
- Receiving a stable (ie, unchanged in 2 weeks) dose of MOUD as judged by the prescribing clinician
- Report bothersome or high-impact chronic pain defined by the Graded Chronic Pain Scale–Revised
- Have a self-reported ability to walk at least 1 block

Exclusion criteria

- Inability to read, write, and speak English at a third-grade level
- Untreated or inadequately treated bipolar or psychotic disorder or current suicide risk for the previous 2 weeks before screening (identified using baseline measures)
- Life-threatening health conditions that would impede participation (eg, end-stage renal failure, malignant cancer requiring chemotherapy)
- Planned surgical treatment related to pain
- Pending legal action or planned relocation that would interfere with participation

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Justification for Criteria

Participants will be adults receiving a stable dose of MOUD because, until the dose is stable, pain ratings may fluctuate and obscure the intervention's effect. We require bothersome or high-impact chronic pain (ie, moderate to severe pain that limits life and work activities on most days or every day in the past 3 months) because, compared to individuals with mild chronic pain, it is more commonly associated with negative health indicators addressed in cognitive behavioral treatment for chronic pain (eg, negative pain coping beliefs, pain interference, and psychological distress) [53]. IMPACT contains a progressive walking program; therefore, to ensure participant safety, participants must be able to walk at least 1 block. Individuals with low literacy (ie, <third grade) or medical or psychiatric diagnoses that would interfere with their ability to meaningfully participate in the IMPACT treatment, such as severe mental health conditions (eg, unmedicated or untreated bipolar or psychotic disorder, current suicide risk, or diagnoses requiring palliative or end-of-life care), are excluded. Individuals with circumstances that may predictably interfere with participation (eg, legal actions with imminent incarceration) or produce large changes in pain (pain-related surgeries) will be excluded. Women of childbearing age will be included, as there is no contraindication for CBT for pain or substance use disorder for pregnant women. Participants who do not have a digital device (eg, smartphone or tablet) for participating in IMPACT will be supplied with one for the duration of the study.

Recruitment, Screening, and Consent Procedures

Study recruitment occurs through clinician referral of interested patients and patient self-referral in response to informational study materials posted in patient care areas at the recruiting sites. Site clinicians receive information about the study and eligibility criteria through research staff presentations and study informational material provided at clinical staff meetings. Self- and clinician-referred individuals are screened by a study research assistant and, if eligible, invited to consent and complete a baseline assessment. Procedures are conducted in a quiet and private office space provided by the OTP clinic to the research team. The research assistant and the participant discuss the consent document, and potential participants are provided an opportunity to ask questions and time to consider their decision to participate. A comprehension quiz is given to ensure the participant has an adequate understanding of the study, and a copy of the consent form is given to the participant. After consent, the research assistant assigns a unique study ID code and administers baseline measures on a study laptop using the REDCap (Research Electronic Data Capture) software platform.

Randomization and Masking

Following the baseline assessment, participants are randomized 1:1 to IMPACT+TAU or TAU (control) using urn randomization [54] balanced by demographic variables (self-reported gender identification and race or ethnicity [combination of ethnicity and racial identity]), as well as likely prognostic variables (severity of OUD as mild, moderate, or severe based on the DSM-5 [*Diagnostic and Statistical Manual of Mental Disorders* {Fifth Edition} OUD symptom count), buprenorphine versus methadone treatment, and length of MOUD treatment (<6 months, 6-12 months, and >12 months). Allocation is masked using a Microsoft Access (Microsoft Corp) program that our group has developed and implemented successfully in multiple previous trials [55-58]. Participants randomized to IMPACT+TAU are provided with a unique username and password to access the IMPACT website. To facilitate their participation in the walking portion of the treatment, participants are given a pedometer and a brief demonstration of its use. Study staff measure each participant's stride length and calibrate the pedometer accordingly. The research assistant then guides the participants through the first IMPACT module to ensure they are comfortable using the program and answer any questions they might have.

Interventions

IMPACT

Participants allocated to IMPACT+TAU receive standard MOUD treatment (ie, TAU) along with access to IMPACT for 12 weeks. IMPACT is a self-directed, 9-module digital treatment program with weekly personalized feedback messages from a trained masters- or doctoral-level coach under the supervision of a clinical psychologist. Participants are asked to complete 1 module per week using a study laptop that is available in the MOUD clinic or outside of the clinic using their own web-enabled device (eg, at home). We hope to maximize treatment adherence and engagement by providing multiple ways of accessing the IMPACT program [50]. The IMPACT program passively tracks individual behaviors to capture engagement (ie, number of logins, access to each module and component, time spent using the program, and digital survey completion). Module topics are shown in Figure 3. For each module, participants are asked to practice a specific skill that corresponds with the topic for that week. After indicating a baseline average number of steps during their first week of completing the daily survey, participants are provided with a daily step goal by their coach during the weekly feedback message. The goal is to increase their daily steps by 10% of the average daily step count reported in the previous week. All modules include a narrated introduction of the skill, video vignettes of characters in challenging situations and using skills, interactive practice exercises and weekly skill practice goals, and a quiz to evaluate the understanding of the module content. The IMPACT dashboard landing page displays personalized information for each participant, including a badge for each completed module, stars for completion of practice exercises, weekly averages of daily steps and step goals in graphical form, and a link to weekly coach messages.

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Figure 3. Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) module topics and descriptions. MOUD: medications for opioid use disorder; SMART: specific, measurable, achievable, relevant, and time-bound.

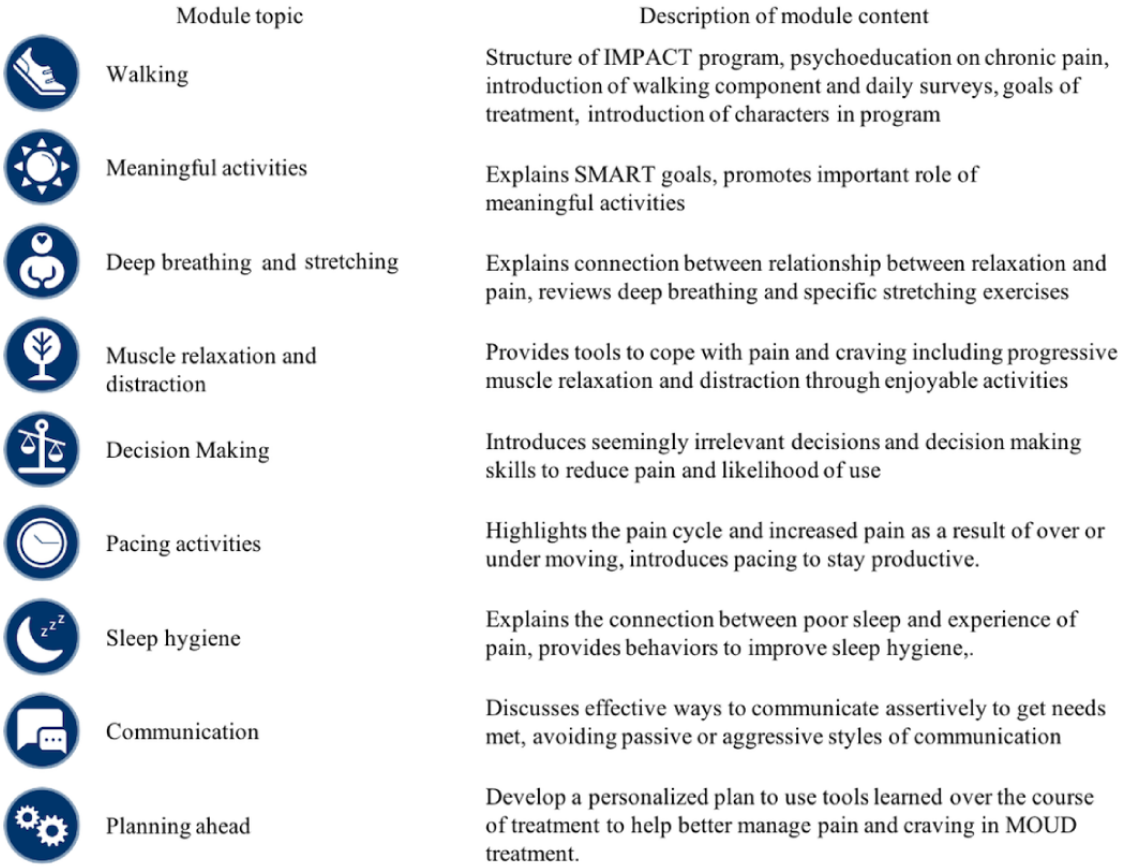

Participants receive links to daily digital surveys through MMS text messages on their mobile phone at a participant-selected time for the duration of treatment. Surveys assess pain intensity, pain interference, pedometer-measured step counts, sleep quality, sleep duration, craving to use opioids, self-efficacy, MOUD adherence, and questions regarding the practice of the treatment skills. Based on our previous work, digital surveys are estimated to take no longer than 2 minutes to complete. Coaches review summaries of the daily survey data through a web portal that displays survey responses from the past week (as weekly averages or individual days). The coach records an audio message based on the participant-provided responses to the current week's surveys, as well as previous weeks, that is uploaded to the participant's IMPACT dashboard. The coach's message provides reinforcement of skill practice and goal attainment and highlights associations between participants' daily responses and trends in weekly averages over the course of treatment. Coaches receive training in message preparation and attend weekly supervision with a clinical psychologist. Participants are not able to directly respond to the coach's feedback through the program but are able to indirectly communicate with the coach by leaving a message with the research assistant during their weekly clinic visit, who can relay the message to the coaches.

TAU (Control)

Participants in both conditions receive TAU for the buprenorphine and methadone programs at participating MOUD clinics, which includes regular medication management by the clinic physician and regular individual and group counseling sessions delivered on-site by counselors employed at participating MOUD clinics. Participants randomized to IMPACT+TAU and TAU will receive MOUD dosing as indicated by their OTP clinician in conjunction with regular meetings as dictated by their treatment plan. Both groups are free to access any OTP clinic resources, including prescriptive services for mental health issues, group treatment, and individual counseling as offered at each recruitment site.

Assessment Visits

The study includes a baseline visit followed by brief weekly visits during treatment (up to 12 weeks) and a 3-, 6-, and 9-month postrandomization assessment visit. Neither participants nor research assistants are blinded to group assignments. However, outcome measures are obtained through self-report using REDCap digital assessments, and MOUD retention will be verified with MOUD clinic records, limiting the potential for bias. Participants complete the baseline, weekly visit, posttreatment, and follow-up measures at their outpatient MOUD clinic to facilitate the collection of a urine sample for urine toxicology analysis (Table 1). After baseline, if in-person attendance is not possible, study measures may be completed remotely. Remote participation is facilitated by the use of digital data collection, videoconferencing, or the telephone.

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Table 1. Study measures.

Measure	Items	Baseline	Weekly	3 months	6 and 9 months
Baseline measures					
Demographic information, MOUD[a] information, and clinical characteristics of chronic pain		✓			
MINI[b] International Neuropsychological Interview [59]	Interview	✓			
Graded Chronic Pain Scale–Revised (frequency, severity, and impact of pain) [53]	6	✓			
Addiction Severity Index [60]	Interview	✓		✓	✓
Primary outcome (in 3 months)					
Buprenorphine retention	none	✓		✓	✓
Secondary outcome measures					
PROMIS[c] Pain Interference 6a [61]	6	✓		✓	✓
MOUD Adherence[d]	None	✓	✓	✓	✓
The Craving Scale [62]	3	✓		✓	✓
Timeline Follow-Back Substance Use Calendar [63]	Interview	✓	✓	✓	✓
Urine toxicology	None	✓	✓	✓	✓
NRS[e] Pain Intensity Rating [64]	1	✓		✓	✓
PROMIS Physical Function 6b [65]	7	✓		✓	✓
Pain Catastrophizing Scale [66]	14	✓		✓	✓
Pain Self-Efficacy Questionnaire [67]	11	✓		✓	✓
PROMIS Sleep Disturbance 6a and Duration [68]	9	✓		✓	✓
Other measures					
Brief Symptom Inventory [69]	18	✓		✓	✓
Cold pressor task	None	✓		✓	✓
PHQ-4[f] (brief screen for anxiety and depression) [70]	4	✓		✓	✓
Program and Client Cost-Substance Abuse Treatment (treatment use) [71]	Interview	✓		✓	✓
IMPACT[g] engagement data (IMPACT+TAU[h] only)	None		✓		

[a]MOUD: medications for opioid use disorder.

[b]MINI: Mini-International Neuropsychiatric Interview.

[c]PROMIS: Patient Reported Outcomes Measurement Information System.

[d]Adherence will be assessed with the Timeline Followback for daily MOUD use for the previous week, clinic dispensing records, and urine toxicology screen for buprenorphine or methadone collected at each weekly assessment visit.

[e]NRS: Numerical Rating Scale.

[f]PHQ-4: Patient Health Questionnaire-4.

[g]IMPACT: Integrating the Management of Pain and Addiction via Collaborative Treatment.

[h]TAU: treatment as usual.

Primary Outcome Measure (Retention in MOUD)

Retention is defined as dichotomous enrollment in MOUD (ie, yes or no), with evidence of MOUD uptake in the week before the 3- (primary), 6-, and 9-month time points. Using data from the 7 days before the 3-month time point, dichotomous enrollment in MOUD services will be verified by clinic records and evidence of MOUD compliance will be assessed using clinic records and self-report. When these sources disagree, clinic records will be used to determine compliance. Retention will be a binary outcome, with 1=retained (conditions met) and 0=not retained.

Secondary Treatment Outcome Measures

We will also collect OUD (ie, MOUD adherence, craving, and substance use) and pain (ie, pain interference, physical functioning, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy) secondary outcome measures. These outcomes evaluate other important treatment effects that have an evidence base in OUD and chronic pain

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treatment studies and will provide a more detailed assessment of possible treatment outcomes. Outcome measures are detailed in Table 1.

Other Measures

To better characterize other treatment effects, we will also evaluate general psychological symptoms, depression symptoms, anxiety symptoms, OTP treatment use and cost, cold pressor task (pain threshold), and digital treatment engagement (only participants randomized to IMPACT+TAU).

Data Sharing

Data collected during baseline, post treatment, and follow-up visits will be made available in compliance with the HEAL Public Access and Data Sharing policy. The study is registered in ClinicalTrials.gov and is in the process of being registered in the HEAL Data Platform. Once data collection is complete, 1 master data file will be created that includes all variables necessary to address the primary study aims and hypotheses. All analyses will be performed using the master data file. The final master data set will then be submitted to the appropriate HEAL-approved repository. All data will be deidentified before submission using procedures that are in compliance with the HIPAA (Health Insurance Portability and Accountability Act), the Yale Human Investigation Committee, and NIH standards.

Qualitative Interviews

Among those randomized to IMPACT+TAU, individual interviews (N=34) will be conducted at 3-month follow-up with a sample of completers (n=17) and noncompleters (n=17). This sample size should be sufficient to achieve saturation on interview themes; however, if saturation is not reached, additional participants will be interviewed until saturation is attained [72]. Completers will be defined as any participant that engages in 7-9 IMPACT modules. Noncompleters will be defined as any participant who completed between 1 and 4 IMPACT modules. Interviews will take place on the internet or in person, be digitally recorded, and be transcribed. All respondents will be asked a series of open-ended questions to probe participant experiences with IMPACT, including barriers or facilitators to engagement and how IMPACT influenced their ability to manage pain and OUD. Semistructured questions will elicit feedback on various features of the intervention, including the various module topics (Figure 3), the walking component, impressions of the weekly personalized feedback, the IMPACT platform, study outcomes, daily surveys, and combined emphasis on pain or OUD.

Data Analyses

Quantitative Data Analysis

Data will be reported for each treatment arm and overall at all time points in the study. Summary descriptions of recruitment rates, attrition, daily survey completion, and treatment outcomes will be calculated. The baseline demographic characteristics of both groups will be summarized.

We will perform a true intent-to-treat analysis of the primary MOUD retention outcome that will include all randomized participants and use logistic regression models to assess differences in MOUD retention by treatment condition at the 3-month time point. MOUD type (ie, buprenorphine or methadone) will be specified as a covariate. Similarly, the logistic regression model will be used to assess differences in MOUD retention by treatment condition at each follow-up time point (ie, 6 and 9 months post randomization).

In addition to retention, we will run secondary analyses to evaluate differences in several OUD (ie, MOUD adherence, craving, and substance use) and pain (ie, pain interference, physical functioning, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy) measures by treatment condition and by time using multilevel longitudinal models with MOUD type (ie, buprenorphine or methadone) specified as a between-person covariate.

Qualitative Data Analysis

Analysis of qualitative data will be conducted using Atlas.ti, a qualitative software program allowing fluid interaction of data across types or sources [73]. A qualitative-descriptive approach is suitable when information is needed to develop, summarize, or refine an intervention [74]. A constant comparative approach with sequential analysis will be used to reach a thematic consensus. Memos, field notes, and debriefing notes after each interview will also be incorporated into the analysis [75]. Each transcript will first be read in its entirety and then coded, proceeding from line-by-line in vivo codes to more broad codes and themes, comparing data across participants [75]. Coding will be completed independently by 2 researchers and compared, and final themes will be arrived at through consensus. Findings will be summarized and presented in tables. It is expected that the collected data will reflect mechanisms underlying engagement and participant perspectives of IMPACT.

Results

The funding for the clinical trial component of the study (phase 2) was obtained in June 2022, and the trial study protocol that included changes from phase 1 was approved by the institutional review board in January 2022. Enrollment began on July 15, 2022, at a single outpatient clinic; a second outpatient clinic was added on March 6, 2023; and a third site is expected in January 2024. Enrollment is expected to continue until June 2024. Final data are expected to be collected in March to May 2025, and the primary results of the study are expected to be published in March to May 2026.

Discussion

Summary of Study Significance

Given the prevalence of OUD and the increased mortality by overdose, the provision of MOUD and support for retention in MOUD are critical. Only a third of individuals receiving MOUD are retained in treatment after 6 months. Clearly, many people receiving MOUD require additional support to remain in treatment and attain its full benefit. Chronic pain, a common co-occurring condition among those receiving MOUD, interferes with MOUD retention and diminishes functioning and quality of life. An asynchronous digital integrated treatment for addiction and chronic pain, such as IMPACT, holds promise to increase access to evidence-based behavioral treatment in

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MOUD clinical care. IMPACT is designed to be accessible, low-burden, and easily integrated into MOUD clinics despite their limited resources.

Benefits of Daily Surveys

Importantly, IMPACT collects individual responses through daily surveys that are used to generate weekly personalized feedback for participants. These data are the foundation of personalized coach feedback that may enhance engagement with treatment, which has been suggested in previous reviews [76] and yield relatively fine-grained data on patient reports of pain and pain interference, craving to use opioids, sleep problems, and physical activity for a comparatively large sample of individuals enrolled in MOUD. Daily ratings of pain and pain fluctuations in this population are unique, and the data generated will be critical in addressing key gaps in the literature, including understanding fluctuations in relationships between pain and pain interference, drug craving, treatment retention, sleep, and functioning in this population. These data may provide actionable information for further treatment refinement.

Benefit of Digital Interventions in the MOUD Setting

An integrated, digital intervention offers 2 particularly attractive benefits in the MOUD setting: a means to both (1) obtain treatment in a less stigmatizing manner and (2) provide treatment with high fidelity to evidence-based protocols without adding staff. Individuals receiving MOUD report high levels of stigma that can significantly impact the course of treatment [77-79]. Increased stigma is a primary barrier to engaging in MOUD treatment and is present even among addiction providers. In a recent qualitative study of MOUD providers, the perception of psychosocial interventions is mixed, with some providers suggesting that MOUD undermines the effectiveness of behavioral treatment while others argue that any provision of behavioral treatment is not a necessary component of MOUD treatment [80]. Furthermore, integrating evidence-based psychotherapies, such as CBT, into MOUD clinical care has been met with mixed results [81-83]. Some researchers have posited that the inconsistent findings are likely related to methodological flaws in previous research, including low fidelity and an inadequate control group [42]. IMPACT treatment materials can be delivered with a high degree of fidelity and consistency, effectively removing a lack of fidelity as a potential driver of outcomes in this study. The patient demands of MOUD clinical care often preclude trained providers from delivering behavioral treatment [84]. Technology-based and digital interventions, such as IMPACT, can address these barriers by offering treatment with high fidelity that can be completed outside the clinic, further reducing the possible stigma of discussing problems related to addiction and pain in MOUD settings.

Limitations

There are several limitations to the current protocol. First, as is common in behavioral intervention trials, participants will be unblinded to the condition once randomized. However, all participants and researchers will be blind to the condition when completing baseline structured interview measures. The primary outcome is based on objective measures and clinic attendance and, therefore, is less vulnerable to biases associated with being unblinded. Other treatment outcomes are collected through self-reported responses in REDCap, which also limits the potential for bias. There is also no attention control for IMPACT. We chose to use TAU as the control condition to maximize our ability to determine the efficacy of adding a digital treatment to the existing gold standard treatment (ie, MOUD). Next, participants randomized to IMPACT may not complete all daily surveys, resulting in missing data. While we expect that participants will miss surveys, completing the surveys benefits participants because they provide personalized feedback; and even 1-2 surveys per week can provide insight for weekly coach feedback. Additionally, previous research on COPES has shown high survey completion [85], which is consistent with findings from other asynchronous chronic pain interventions using daily surveys [86]. Finally, participants in both groups may receive other pain and addiction treatments both within and outside their MOUD clinic. We will inquire about additional treatment at weekly visits during treatment to account for any effects that could be attributed to other interventions.

Conclusions

Access to behavioral treatment for individuals with OUD and chronic pain is a critical gap in MOUD care. Offering access to a combined pain and addiction treatment may help retain individuals in MOUD while improving clinical outcomes for people who otherwise may not receive treatment. Digital treatments are especially well-suited to MOUD treatment settings because they reduce stigma and provide access to high fidelity, evidence-based behavioral treatment.

Acknowledgments

We would like to respectfully acknowledge the late Kathy M Carroll, PhD, for her contributions to the design of this study before her untimely passing in late 2020. Dr Carroll's brilliance was only surpassed by her unwavering commitment to increasing the accessibility of evidence-based treatment to improve the lives of individuals with substance use disorders. With this project, we continue her legacy with the same compassion and empathy that defined her professional and personal life. This research is supported by R61/33AT010619 (Heapy). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the National Center for Complementary and Integrative Health, or the Department of Veterans Affairs.

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Data Availability

Deidentified data sets generated during the course of this study will be made available on the Helping to End Addiction Long-Term (HEAL) Data Platform through a HEAL-approved repository.

Authors' Contributions

AAH, MAG, TLF, CN, WCB, SM, and MS contributed to the conceptualization of the study. AAH, RRM, BA, MAG, TLF, CN, SNE, WCB, SM, and MS contributed to the study design, development of the Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) program during the R61 phase, and clinical trial during the R33 phase. RRM wrote the initial draft, and AAH, SKS, JML, LB, MIPR, MAG, and MAD provided critical edits. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-viewer report from the National Centre for National Center for Complementary and Integrative Health (NCCIH).
[PDF File (Adobe PDF File), 200 KB - resprot_v13i1e54342_app1.pdf]

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Abbreviations

BRIM: Behavioral Research to Improve Medication-Based Treatment
CBT: cognitive behavioral therapy
CBT4CBT: Computer-Based Treatment for Cognitive Behavioral Therapy
COPES: Cooperative Pain Education and Self-Management
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
HEAL: Helping to End Addiction Long-Term
HIPAA: Health Insurance Portability and Accountability Act
IMPACT: Integrating the Management of Pain and Addiction via Collaborative Treatment
MOUD: medications for opioid use disorder
NIH: National Institutes of Health
OTP: opioid treatment program
OUD: opioid use disorder
REDCap: Research Electronic Data Capture
TAU: treatment as usual

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Proposal

Personalized AI-Driven Real-Time Models to Predict Stress-Induced Blood Pressure Spikes Using Wearable Devices: Proposal for a Prospective Cohort Study

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Abstract

Background: Referred to as the "silent killer," elevated blood pressure (BP) often goes unnoticed due to the absence of apparent symptoms, resulting in cumulative harm over time. Chronic stress has been consistently linked to increased BP. Prior studies have found that elevated BP often arises due to a stressful lifestyle, although the effect of exact stressors varies drastically between individuals. The heterogeneous nature of both the stress and BP response to a multitude of lifestyle decisions can make it difficult if not impossible to pinpoint the most deleterious behaviors using the traditional mechanism of clinical interviews.

Objective: The aim of this study is to leverage machine learning (ML) algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices such as Fitbit, providing actionable insights to both patients and clinicians to improve diagnostics and enable proactive health monitoring. This study also seeks to address the significant challenges in identifying specific deleterious behaviors associated with stress-induced hypertension through the development of personalized artificial intelligence models for individual patients, departing from the conventional approach of using generalized models.

Methods: The study proposes the development of ML algorithms to analyze biosignals obtained from these wearable devices, aiming to make real-time predictions about BP spikes. Given the longitudinal nature of the data set comprising time-series data from wearables (eg, Fitbit) and corresponding time-stamped labels representing stress levels from Ecological Momentary Assessment reports, the adoption of self-supervised learning for pretraining the network and using transformer models for fine-tuning the model on a personalized prediction task is proposed. Transformer models, with their self-attention mechanisms, dynamically weigh the importance of different time steps, enabling the model to focus on relevant temporal features and dependencies, facilitating accurate prediction.

Results: Supported as a pilot project from the Robert C Perry Fund of the Hawaii Community Foundation, the study team has developed the core study app, CardioMate. CardioMate not only reminds participants to initiate BP readings using an Omron HeartGuide wearable monitor but also prompts them multiple times a day to report stress levels. Additionally, it collects other useful information including medications, environmental conditions, and daily interactions. Through the app's messaging system, efficient contact and interaction between users and study admins ensure smooth progress.

Conclusions: Personalized ML when applied to biosignals offers the potential for real-time digital health interventions for chronic stress and its symptoms. The project's clinical use for Hawaiians with stress-induced high BP combined with its methodological innovation of personalized artificial intelligence models highlights its significance in advancing health care interventions. Through iterative refinement and optimization, the aim is to develop a personalized deep-learning framework capable of accurately predicting stress-induced BP spikes, thereby promoting individual well-being and health outcomes.

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KEYWORDS

stress; hypertension; precision health; personalized artificial intelligence; wearables; ecological momentary assessments; passive sensing; mobile phone

Introduction

How This Research Benefits the People of Hawaii

According to the Department of Health Chronic Disease Prevention and Health Promotion Division, 1 in every 3 adults in Hawaii has been diagnosed with hypertension [1]. Mortality rates associated with heart disease are particularly high for Native Hawaiian and Other Pacific Islander populations, leading to 628 deaths per 100,000 residents as opposed to 154 deaths per 100,000 residents among Asian residents and 167 deaths per 100,000 among White residents in Hawaii [1].

A recent study conducted by researchers at the John A Burns School of Medicine found that Native Hawaiian and Other Pacific Islander individuals under a physician's care for hypertension experienced an 18.3 point drop in systolic blood pressure (BP) on average when participating in a 12-week hula program [2,3]. This study provides strong evidence that stress-reducing interventions can reduce hypertension in Native Hawaiian individuals. We hope to build upon this foundational research by leveraging consumer devices (ie, Fitbit) to detect moments of high stress and to provide just-in-time interventions that are culturally grounded. The first step of this long-term research plan is to develop the artificial intelligence (AI) that will power the digital intervention, and that first step is the focus of this grant proposal.

Clinical and Unmet Needs

Hypertension is an indirect cause of hundreds of thousands of annual deaths in the United States alone [4]. Known as the "silent killer"[5], elevated BP often remains unnoticed by affected individuals due to a lack of perceptible symptoms, resulting in accumulated harm over the years. While several causes of hypertension are related to an underlying health condition such as kidney disease, diabetes, sleep apnea, or hormone problems [6]; health condition; and medications combined only account for roughly 1 in 20 cases [7]. Chronic stress has been repeatedly documented to increase BP [8-10].

Prior studies have found that elevated BP often arises due to a stressful lifestyle, although the effect of exact stressors varies drastically between individuals. Due to the heterogeneous nature of both the stress and BP response to a multitude of lifestyle decisions, it can be difficult if not impossible to pinpoint the most deleterious behaviors in a personalized manner using the traditional mechanism of clinical interviews. Passive sensing technologies deployed on consumer devices have the potential to disrupt this status quo in a positive manner. By continuously monitoring a patient's lifestyle in naturalistic settings, digital technologies can provide clinicians and patients alike with actionable insights into their health trends with fine-grained precision.

We are interested in the use of wearable technologies to sense cardiovascular signals, as they are noninvasive and are already widely adopted. We will develop machine learning (ML) algorithms that analyze these biosignals to make real-time predictions about BP spikes. The resulting predictions could be used to alert, in real time, patients about unintentionally adverse behaviors as well as clinicians about the frequency of such behaviors. There is a critical opportunity and need to improve diagnostics for repeat health events to enable clinicians to monitor their patients and forecast future issues.

Innovation

There are countless situations in health care and biomedicine where vast amounts of unlabeled data are collected from a single patient [11]. Annotations for the event of interest are frequently sparsely dispersed. The development of predictive supervised ML models is infeasible in such circumstances, as classical approaches cannot handle the complexity of the data and modern deep learning approaches require vast amounts of data [12]. For example, continuous readings from continuously worn glucose monitors can provide enough input data to train a model to make a prediction about patient energy based on glucose, but it is impracticable to require users to log their perceived energy at the same sampling frequency as a wearable device. Similar situations arise from data collected by consumer wearable health devices (eg, smart watches), smartphones, and other devices that measure biological signals.

To support AI development in these situations where vast longitudinal data are collected with minimal human-provided annotations, we propose the development of personalized ML models that are trained solely on an individual's unlabeled data to learn feature representations that are specific to their baseline temporal dynamics. We will train these models with a novel data set of Fitbit biosignals and corresponding BP readings (Figure 1). We are creating a novel method and framework, which has never been explored in health care, consisting of pretraining neural networks to learn the temporal dynamics of a patient's biosignals. This method will enable powerful, deep networks to be trained using relatively small data sets, which would not be possible without the self-supervised approach proposed here. From a usability standpoint, patients will only be required to provide tens of annotations tens of times to get a personalized predictive model.

While we propose to apply this new technological innovation toward the prediction of cardiac signals, multimodal time-series personalization can be applied to a variety of other biology and health problems where (1) multiple signals are emitted, (2) the baseline signal patterns are specific to each individual or organism, and (3) it is infeasible to acquire the vast amounts of labels required to train a supervised deep learning model from scratch. Examples of future apps of the proposed methodology include predictions stemming from nanopore signal data or multielectrode neuronal recordings. This method has the potential to dramatically advance the field of precision health care by enabling reliable ML predictions from massive but mostly unlabeled data sets which are trained in a self-supervised manner on data from a single user.

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While this novel methodology could be applied to myriad domains within health and biology, a natural application is the prediction of cardiac events from wearable biosignals data. We will focus on high BP.

Figure 1. We will collect wearable biosignals from a Fitbit and use them to predict BP as measured by an Omron HeartGuide wearable BP monitor. We will use personalized self-supervised learning to enable the prediction of BP using minimal samples from the end user. BP: blood pressure; HR: heart rate.

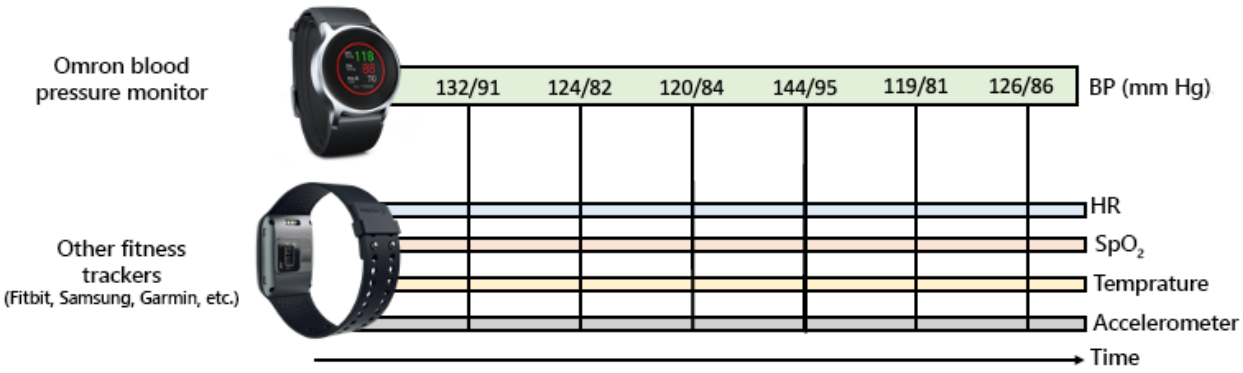

Dissemination Plan

We plan to disseminate our research findings through a combination of (1) research publications in journals, (2) presentations at conferences, (3) as preliminary data for an National Institutes of Health (NIH) R01 application, and (4) as the basis of community-based participatory design sessions where we iteratively develop a culturally informed digital intervention using the AI created in this project. Target journals for submission include Nature Digital Medicine, Science Translational Medicine, Institute of Electrical and Electronics Engineers (IEEE) Transactions on Affective Computing, PLoS Digital Medicine, and Cell patterns. Target conferences include the American Medical Informatics Association (AMIA) Annual Symposium, the Pacific Symposium on Biocomputing (PSB), and the Conference for Computer-Human Interaction (CHI). There are several notices of special interest posted by the NIH that would support a large R01 grant application using the preliminary data from this work.

Specific Aims

We propose the following specific aims: (1) aim 1: create a novel data set of wearable sensor data and corresponding BP measurements, (2) aim 2: develop a personalized self-supervised pretraining procedure for time-series data using both contrastive learning and masked predictions, and (3) aim 3: develop a novel personalized pretraining procedure which exploits the multimodal nature of wearable time series-data.

Methods

Recruitment

We will recruit 40 carefully selected participants with diagnosed hypertension and self-reported stressful lifestyles to each participate in a 4-week remote data collection period. Each participant will wear an Omron HeartGuide BP wearable device and a Fitbit Sense 2 wearable watch during all waking hours for at least 15 hours each day. Apart from wearing the devices and periodically syncing the data to the cloud, participants will be asked to follow their normal routine for the duration of the study.

We will recruit adults aged 30 to 70 years in the state of Hawaii who have been diagnosed with hypertension and self-identify as living a high-stress lifestyle. Given the diversity of the population of Hawaii [13], we aim for the following demographic composition of our participants: 23% White, 37% Asian, 11% Native Hawaiian or Pacific Islander, 7% Black or African American, and 22% of 2 or more races. Approximately 9.5% of the recruited population will have Hispanic or Latino ethnicity.

PW has a network of clinical collaborators at the John A Burns School of Medicine at the University of Hawaii at Mānoa who also practice at local medical centers such as Queen's Medical Center and Kaiser Permanente's branch in Hawaii. We will recruit using the following sources: (1) direct recruitment from the Hawaii Pacific Health Center, which the collaborators at the Department of Psychiatry at the University of Hawaii are affiliated with and where they practice clinically; (2) via flyers and emails at the clinics which the Department of Psychiatry at the University of Hawaii regularly provides inpatient and outpatient psychiatric services and consultation at, including The Queen's Medical Center, Kapi olani Medical Center for Women and Children, and Hawaii State Hospital Community mental health centers on Hawaii Island, Moloka i, Maui, Kaua i, and Lāna i; (3) advertisements posted on the University of Hawaii campus and in public settings in Honolulu; and (4) targeted advertisements posted to social media websites. We will work with Anthony Guerrero, the chair of the Department of Psychiatry at the University of Hawaii, to ensure that the recruitment strategies and advertisement of the research program translate across cultures and to ensure effective recruitment as well as diverse and representative data.

We will exclude participants younger than 30 years and older than 70 years. We will require all potential participants to remotely complete the Perceived Stress Scale (PSS), a 10-item scale that is the most widely used psychological instrument for measuring the perception of stress [14]. We will exclude participants whose PSS score does not exceed 1 SD above the mean for at least one of their demographic brackets (age, gender, or race) as reported by Cohen et al [14]. We will also ask participants to self-report their BP. We will also exclude

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participants who do not own a smartphone with continuous network connectivity. During the in-person study intake, we will measure the BP of potential study participants 3 times. We will exclude participants whose BP does not exceed 130/80 mm Hg for at least one of the measurements, as 130/80 mm Hg is the minimum cutoff for stage 1 hypertension.

Data Collection and Storage

We will leverage the existing application programming interface (API) provided by both Omron and Fitbit to record the user's wearable sensor readings and upload the data to the cloud. Omron's health care API offers access to time-stamped BP readings as well as activity and sleep approximations. The Fitbit API provides access to sensor readings of heart rate (HR), gyroscope, accelerometer, breathing rate, blood oxygen levels (SpO_2), and skin temperature sensor readings. The data will be managed on each participant's smartphone devices through a mobile app, implemented for both iOS (Apple Inc) and Android, that we will develop. The study team will install the app on the user's smartphone and configure the Omron and Fitbit devices during study onboarding. The smartphone app will periodically trigger a notification reminding the participant to (1) measure their BP with the Omron wearable, (2) sync the Omron and Fitbit data to the app, and (3) connect to a network while the study app is open to allow the data to be uploaded to a centralized server.

We will store the curated data from each participant on a centralized server hosted on Amazon Web Services (AWS). Because Fitbit is owned by Google, participants' Fitbit data will be uploaded directly to Google's cloud servers, which use the same level of security as other Google products such as Gmail. Access to each participant's Fitbit data on Google's cloud servers is implemented through OAuth, which provides clients with secure delegated access to server resources on behalf of a resource owner (ie, the participants of this study). This mechanism is used by companies such as Amazon (Amazon.com, Inc), Google (Alphabet Inc), Facebook (Meta Platforms, Inc), Microsoft Corporation, and X (X Corp) to permit users to share information about their accounts with third-party applications or websites. In this case, the "third party" is the study team. The Fitbit data and BP readings will be preprocessed on an Elastic Cloud Compute instance on AWS, which is HIPAA (Health Insurance Portability and Accountability Act)-compliant. The Elastic Cloud Compute instance will store the data onto respective database tables using DynamoDB (Amazon.com). Each table will have columns for the child ID and the time-stamp. We will encrypt all server-side data and require secret access keys for data access. DynamoDB tables are automatically encrypted on the server side. To add an additional layer of security, we will implement client-side encryption on the mobile app, ensuring encrypted data transmission over HTTPS connection to move BP data between the devices and AWS. Data access will require a secret access key provided by the AWS administrators to any data analysis team. The data will not be accessible without this key. For further security, we will anonymize all user data on the server side by removing all protected health information from the DynamoDB tables.

We intend to release the curated data (Figure 2) as a publicly available data set for use in the evaluation of multimodal time-series ML models. Such data sets exist for activity and emotion recognition from wearable data, but the prediction of BP from these measurements will be a challenging task that other researchers can attempt with the release of our data set. This will be the first publicly available data set that includes at-home BP measurements alongside wearable sensors such as HR, SpO_2, and accelerometer readings. This fully anonymized data set will only be released to researchers who sign a Data Use Agreement, which will be approved by the University of Hawaii Data Governance Office.

The app comprises 2 primary screens, account and home. The account screen features user details, a star reward system for active participation in the study, and options to link 2 wearable devices (Fitbit and Omron Heartguide) for data synchronization with our secure and encrypted database. The home screen is divided into 6 sections, including questionnaires, messages, feedback, records, BP readings, and app instructions. Additionally, the CardioMate app includes an administrative area for study managers to view participant statistics and initiate personalized chats, complete with alarm and notification functions.

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Figure 2. Workflow of the CardioMate app, comprising account and home screens with user details, study rewards, wearable device integration, and an administrative section for study managers.

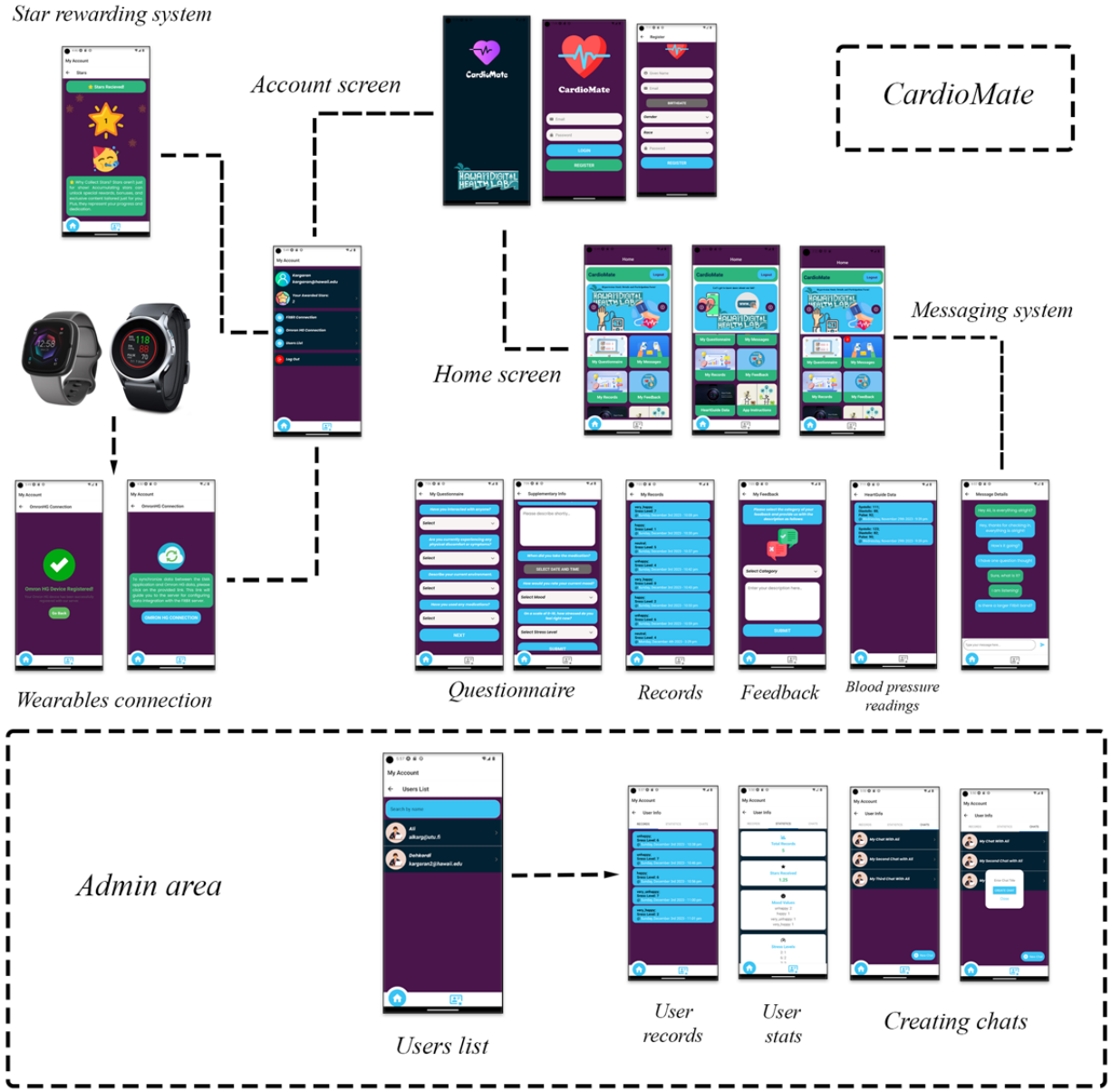

Feasibility

The most difficult aspect of this aim will be maintaining participant engagement throughout the 4-week study period. The graduate research assistant funded by this project will dedicate some time each day toward running the study and interfacing with participants. We expect participants to open the smartphone app to sync and upload their data on a daily basis, which is a 1-minute time commitment per day.

While we expect no trouble recruiting 40 subjects for participants, we expect some participants to drop off during the study. Since we will have enough devices for 5 concurrent subjects, it will take 8 months to collect all data if no participants drop off. Our study timeline allocates 6 additional months of make-up time to collect data from new participants, accounting for >50% drop-off rate. Given the remote nature of the data collection procedures, we expect some participants to drop off from the study prematurely or to not comply with the study processes. We will therefore remotely monitor the upload progress and send an automated text and email notification to the participant if the data are not uploaded in a timely manner. If 3 consecutive days of participant noncompliance are detected, we will contact the participant for a device return.

Ethical Considerations

Under an expedited review procedure, this research project was approved on April 26, 2023, by the University of Hawaii Institutional Review Board (UHMUIF_2023-00130). The application qualified for expedited review under CFR 46.110 and 21 CFR 56.110, categories 1b, 4a, 4d, and 6. The informed consent process for this human subject research study involves participants completing an interview session where they receive comprehensive information about the research, including its purpose, procedures, and potential risks and benefits. Participants are assured of the voluntary nature of their participation and their right to refuse or withdraw at any time without penalty. For secondary analyses of research data, it is

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clarified that the original informed consent allows for such analyses without additional consent, as approved by the institutional review board. Privacy and confidentiality protections are emphasized, with participant data anonymized and stored securely on HIPAA-compliant servers. Compensation for participation includes US $135 upon completion along with an additional US $15 for certain eligibility interview tasks, reflecting the time and effort required from participants while respecting the ethical standards. The consent form ensures that no identification of individual participants or users is possible in any images or supplementary materials without explicit consent, with researchers providing relevant consent forms or written communications to uphold participant privacy and consent.

AI Model Training

Self-supervised learning (SSL) is usually used to pretrain an entire data set with no explicit labeling by humans to guide the supervision task. We propose to redesign the SSL paradigm toward the task of model personalization. By pretraining a model only on the vast amounts of data curated from a single individual, the weights of the neural network will learn to make predictions using the inherent structure of each participant's biosignals. This is essential because the baseline HR, SpO_2, skin temperature, and movement patterns, regardless of stress, will vary drastically across individuals, limiting the performance of general-purpose ML models.

To train ML models that predict BP based on a user's wearable biometrics, we will develop and evaluate a series of both long short-term memory and transformer neural networks. The inputs to the models will consist of a separate 1D convolutional backbone for each biometric modality. The convolutional features will be fused upstream into a shared joint dense representation space and finally a dense prediction layer with linear activation for regression prediction. We will implement all models using Tensorflow (Google Brain) [15].

We will perform a series of self-supervised pretraining tasks to allow the networks to learn the baseline temporal dynamics of each individual's biosignals. As a pretraining task, we will develop contrastive learning methods to automatically learn embeddings that encode the structure of the signal. For each wearable sensor modality, we will run a sliding window to isolate short-time segments. We will apply signal-based data augmentation techniques to derive a new signal. We will perform contrastive learning to learn neural network embeddings that maximize the similarity between each original segment and its modified version while minimizing the similarity across segments.

We will develop a modified version of the SimCLR (simple framework for contrastive learning of visual representations) algorithm, which will be tuned for the task of personalization to a user's wearable signal readings. It is often the case that biosignals look highly similar, either due to temporal locality or relative homogeneity of the individual's activity. To account for this possibility of recurring signal patterns, we will weigh the attract and repel strength of SimCLR based on the temporal distance between two segments of a particular signal. We will run a grid search to tune this repel strength.

The data augmentation techniques that we apply to the signals will be domain-specific, keeping in mind the inherent nature of each sensor. For example, for accelerometer data, rotations simulate different sensor placements and cropping is used to diminish the dependency of event locations [16]. Across several modalities, sensor noise can be simulated through scaling, magnitude-warping, and jittering [16]. We will be careful to not apply augmentation strategies that might change the meaning of the underlying signal.

As another pretraining task, we will perform generative pretraining by masking the input signal and predicting the missing portion of the signal using a deep autoencoder architecture. Pretraining in this manner will teach the model to understand the dynamics of each time series signal independent of BP or any other labels.

We will train the model on the first 60% of data (by time), tune hyperparameters on the next 20% of data, and calculate the mean absolute error and mean squared error on the final 20%. This evaluation pattern mimics real-world use, where a model will be calibrated by a user prior to real-world deployment. It is important to emphasize that we will train and test a separate personalized ML model for each individual.

We will evaluate the models by comparing the performance with respect to the number of labeled examples used for supervised fine-tuning. A plot of this comparison will elucidate the number of BP measurements required for model calibration to a single individual. We will plot the mean squared error at 10, 20, 30, 40, 50, 75, 100, 125, and 150 BP annotations, as these are feasible amounts of labels that might be provided by a user in real-world use. To ensure a robust evaluation, we will bootstrap at least 20 random samples of BP annotation subsets for each point on the x-axis and will report the mean and 90% CI. Just as in the plain supervised learning condition, we will create a separate plot for each study participant, as the ML portion of this proposal is testing the personalization of ML models rather than a general-purpose one-size-fits-all ML model which is more typical in ML evaluations.

We will perform a similar style of analysis for other clinical outcomes using publicly available data sets such as the Wearable Stress and Affect Detection (WESAD) [17] data set, a multimodal sensor data set for stress detection of nurses in a hospital [18], and K-EmoCon, a multimodal sensor data set for continuous emotion recognition in naturalistic conversations [19]. Each of these data sets, as well as several other publicly available data sets, contains several hours of multimodal biosignal data that overlap with the signals that we propose to collect, such as skin temperature, accelerometer streams, and HR. These data sets also include time-stamped annotations of end points that are likely to be correlated with BP, including self-perceived stress.

In prior work by other researchers, SSL pretraining approaches have repeatedly demonstrated improved performance over pure supervised learning in a variety of contexts [20-23]. Our preliminary data (see Results section) support that self-supervised pretraining on data solely from each individual results in improved models over purely supervised learning. While unlikely given our preliminary data and prior SSL

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publications, it is possible that minimal performance gains will be observed when applying the SSL strategies in a personalized manner. In such cases, the negative result would be a noteworthy finding due to prior successes of SSL.

Results

We have developed a smartphone app, CardioMate, that will prompt participants to measure their BP and log their stress (Figure 2). The app comprises 2 primary screens, account and home. The account screen features user details, a star reward system for active participation in the study, and options to link 2 wearable devices (Fitbit and Omron Heartguide) for data synchronization with our secure, encrypted database. The home screen is divided into 6 sections, including questionnaires, messages, feedback, records, BP readings, and app instructions. Additionally, the CardioMate app includes an administrative area for study managers to view participant statistics and initiate personalized chats, complete with alarm and notification functions.

Data collection commenced on February 15, 2024. As of the manuscript submission date of February 24, 2024, a total of 2 participants have been recruited. The data collection period for each participant spans 28 days. Upon completion of the data collection period for each participant, we will proceed with the personalized machine learning model development to predict stress-induced BP spikes in real time. We aim to recruit a total of at least 45 participants and complete the relevant data collection, data analysis, and personalized ML development for each participant by the end of December 2024.

Our initial sets of published experiments have demonstrated promise for personalized SSL of stress but with some caveats. Our experiments on the WESAD data set demonstrated that deep learning model performance improves drastically when using self-supervised personalization when compared to personalization without SSL when there are a small number of labeled data points for supervision [24]. This effect diminishes with increasing amounts of labeled data [25,26], aligning with prior work that demonstrates that SSL is only beneficial under low-label settings. We have also tried these methods on a particularly challenging data set, a multimodal sensor data set for stress detection of nurses in a hospital [18]. This data set consists of wearable biosignals measured from nurses who wore Empatica E4 wristbands while conducting their normal shifts. This data set is difficult because (1) the data were collected in the wild rather than in controlled laboratory settings and (2) individual nurses were not consistent about their labeling practices, leading to sparse, irregular, noisy, and otherwise messy labels. Consequently, we found that the difference in area under curve and the receiver operating characteristic curve scores for self-supervised models was only about 2.5% higher on average compared against an equivalent baseline model [27], and this increase is within the margin of error due to the limited sample size. This lack of improvement in noisy annotation settings highlights the need for HCI innovations to improve data labeling quality for personalized AI within naturalistic settings.

We have also observed improved performance when personalizing affect-related prediction tasks without personalization both using classical ML [28] and deep learning [29], as well as when only applying SSL without personalization [30]. When disentangling and comparing the effects of SSL and personalization separately, we find that SSL yields more benefit than individualization on nonaffective medical data with large time intervals between data points, suggesting that the sampling frequency and other data considerations must be considered [30]. Collectively, these preliminary results demonstrate promise for the core ML approach that we propose.

Discussion

The primary objective of this study is to leverage ML algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices such as Fitbit, providing actionable insights to both patients and clinicians to improve diagnostics and enable proactive health monitoring. Our study is motivated by recent research conducted at the John A Burns School of Medicine, which found that Native Hawaiian and other Pacific Islander individuals under a physician's care for hypertension experienced an average drop of 18.3 points in systolic BP after participating in a 12-week hula program [2,3]. This study provides strong evidence that stress-reducing interventions can reduce hypertension in Native Hawaiian individuals. We hope to build upon this foundational research by leveraging consumer devices, such as Fitbit, to detect moments of high stress and provide just-in-time interventions that are culturally grounded. The first phase of this long-term research plan involves developing the AI necessary to power the digital intervention, which is the primary focus of this proposal.

The successful development of ML algorithms tailored to individual participants signifies a significant advancement in personalized health care interventions. By using longitudinal data from Fitbit devices and corresponding stress level labels from Ecological Momentary Assessment reports, the study will be able to capture individual-specific patterns effectively, enabling accurate predictions of stress-induced BP spikes. This approach not only enhances the understanding of stress-related hypertension but also provides opportunities for targeted interventions and improved patient outcomes.

Furthermore, the findings of this study contribute to the growing body of literature on the use of wearable devices and ML in health care. The adoption of transformer models for personalized prediction tasks, coupled with SSL techniques for pretraining, represents a novel approach to leveraging advanced computational techniques for real-time health monitoring. By dynamically weighing the importance of different time steps and focusing on relevant temporal features and dependencies, transformer models offer a powerful tool for predicting complex physiological responses such as stress-induced BP spikes. These findings will add to the existing literature by highlighting the potential of ML in improving the accuracy and efficiency of health monitoring systems, particularly in the context of personalized interventions for stress-related hypertension.

It is essential to acknowledge the limitations of this study design. One limitation is the relatively small sample size, which may

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limit the generalizability of the findings. Additionally, the study focuses primarily on predicting stress-induced BP spikes using wearable device data streams and may not capture other factors contributing to hypertension. Future research should aim to address these limitations by including larger and more diverse samples and exploring additional predictors of hypertension.

The findings of this study will demonstrate the feasibility and potential benefits of leveraging ML algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices. By developing personalized AI models based on individual biosignals, the study will provide valuable insights into the monitoring and management of stress-related hypertension. These findings will have broader implications for personalized health care interventions and underscore the importance of integrating advanced computational techniques into health care systems to improve patient outcomes. Through iterative refinement and optimization, we aim to develop a personalized deep-learning framework capable of accurately predicting stress-induced BP spikes, thereby promoting individual well-being and health outcomes.

Acknowledgments

This project received a grant (#MedRes_2023_00002689) from the Robert C Perry Fund of the Hawaii Community Foundation.

Data Availability

Upon the completion of the data collection phase, the data sets generated and analyzed during this study will be available in a public repository. The data citation should include a persistent identifier (eg, web URL or DOI) cited per journal style in the reference list. The amassed data will be fully anonymized and made accessible to the academic community. Subsequently, comprehensive guidelines, together with a designated link facilitating data retrieval and use, will be provided.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Medical Research Advisory Committee of the Hawaii Community Foundation (HCF).
[PDF File (Adobe PDF File), 949 KB - resprot_v13i1e55615_app1.pdf]

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Abbreviations

AI: artificial intelligence
AMIA: American Medical Informatics Association
API: application programming interface
AWS: Amazon Web Services
BP: blood pressure
CHI: Computer-Human Interaction
HIPAA: Health Insurance Portability and Accountability Act
HR: heart rate
IEEE: Institute of Electrical and Electronics Engineers

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ML: machine learning
NIH: National Institutes of Health
PSB: Pacific Symposium on Biocomputing
PSS: Perceived Stress Scale
SimCLR: simple framework for contrastive learning of visual representations
SpO_2: blood oxygen level
SSL: self-supervised learning
WESAD: Wearable Stress and Affect Detection

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Protocol

Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e59383

Abstract

Background: Alcohol and other substance use disorders usually begin with substance use in adolescence. Pediatric primary care offices, where most adolescents receive health care, are a promising venue for early identification of substance use and for brief intervention to prevent associated problems and the development of substance use disorder.

Objective: This study tests the effects of a computer-facilitated screening and brief intervention (cSBI) system (the *CRAFFT [Car, Relax, Alone, Forget, Family/Friends, Trouble] Interactive System* [CRAFFT-IS]) on heavy episodic drinking, riding with a driver who is substance impaired, or driving while substance impaired among adolescents aged 14 to 17 years presenting for a well visit at pediatric primary care practices.

Methods: We are conducting a cluster randomized controlled trial of the CRAFFT-IS versus usual care and recruiting up to 40 primary care clinicians at up to 20 pediatric primary care practices within the American Academy of Pediatrics (AAP) Pediatric Research in Office Settings network. Clinicians are randomized 1:1 within each practice to implement the CRAFFT-IS or usual care with a target sample size of 1300 adolescent patients aged 14 to 17 years. At study start, intervention clinicians complete web-based modules, trainer-led live sessions, and mock sessions to establish baseline competency with intervention counseling. Adolescents receive mailed recruitment materials that invite adolescents to complete an eligibility survey. Eligible and interested adolescents provide informed assent (parental permission requirement has been waived). Before their visit, enrolled adolescents seeing intervention clinicians complete a self-administered web-based CRAFFT screening questionnaire and view brief

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psychoeducational content illustrating substance use–associated health risks. During the visit, intervention clinicians access a computerized summary of the patient's screening results and a tailored counseling script to deliver a motivational interviewing–based brief intervention. All participants complete previsit, postvisit, and 12-month follow-up study assessments. Primary outcomes include past 90-day heavy episodic drinking and riding with a driver who is substance impaired at 3-, 6-, 9-, and 12-month follow-ups. Multiple logistic regression modeling with generalized estimating equations and mixed effects modeling will be used in outcomes analyses. Exploratory aims include examining other substance use outcomes (eg, cannabis and nicotine vaping), potential mediators of intervention effect (eg, self-efficacy not to drink), and effect moderation by baseline risk level and sociodemographic characteristics.

Results: The AAP Institutional Review Board approved this study. The first practice and clinicians were enrolled in August 2022; as of July 2023, a total of 6 practices (23 clinicians) had enrolled. Recruitment is expected to continue until late 2024 or early 2025. Data collection will be completed in 2025 or 2026.

Conclusions: Findings from this study will inform the promotion of high-quality screening and brief intervention efforts in pediatric primary care with the aim of reducing alcohol-related morbidity and mortality during adolescence and beyond.

Trial Registration: ClinicalTrials.gov NCT04450966; https://www.clinicaltrials.gov/study/NCT04450966

International Registered Report Identifier (IRRID): DERR1-10.2196/55039

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KEYWORDS

alcohol; substance use; adolescent; primary care; prevention; intervention; screening; brief intervention; computer-facilitated screening and brief intervention; cSBI; mobile phone

Introduction

Background and Rationale

Alcohol and other drugs are a major contributor to morbidity and mortality each year [1]. Most substance use disorders (SUDs) have a pediatric origin, and substance use remains among the most prevalent of adolescent risk behaviors [2-4]. In addition, motor vehicle crashes remain a leading cause of death among adolescents, and alcohol- or drug-impaired driving and riding with a driver who is substance impaired play a major role [5].

Pediatric primary care offices, where the majority of adolescents receive health care [6], are a promising venue for early identification of problematic substance use among adolescents and for brief intervention to prevent further problems. A substantial and increasing proportion of adolescents see a primary care clinician yearly [7] and have trusting, longitudinal relationships with their clinicians [8]. Primary care visits are opportunities for private conversations that support adolescents' autonomy and confidentiality while placing topics such as substance use in a nonpejorative health risk context.

The American Academy of Pediatrics (AAP) recommends alcohol, tobacco, and other drug use annual screening as part of routine care starting at age 11 years [9,10]. However, a national survey found that only approximately half of adolescents who had a past-year visit with a physician reported being asked about alcohol use [11,12]. Even when substance use screenings are performed, they can be of low quality if clinicians do not use a structured, validated screening tool or if they ask questions while caregivers are present [13,14]. Screenings also seldom include questions about substance-impaired driving or riding with a driver who is substance impaired [15]. Pediatric primary care clinicians also face barriers to brief intervention based on screen responses, including insufficient time during the appointment, a lack of familiarity with validated screening tools, and a lack of experience with managing care for patients who screen positive [16-18].

To overcome these barriers, digital technology can be applied to support consistent, effective screening and tailored intervention for adolescent substance use using evidence-based tools and approaches [19,20]. Clinicians may prefer to use technological tools such as tablet computers for previsit screening and electronic medical record–embedded decision support to enable brief intervention delivery [21]. Accordingly, we designed the CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble) Interactive System (CRAFFT-IS) to increase the frequency and quality of screenings in pediatric primary care, support a personalized response to results, and efficiently address alcohol and drug use and associated riding risks [22]. The CRAFFT-IS comprises a computer self-administered screening for patients (using the well-validated and widely used CRAFFT screening tool [23-25]), followed by psychoeducational content on the health risks of substance use, which adolescents complete before the clinician encounter. Clinicians access a computerized dashboard to view their patient's screening results and prompts for brief motivational interviewing (MI)–based counseling tailored to their patient's screening responses (clinician report).

CRAFFT-IS development was informed by the information-motivation-behavioral skills model [26], the health belief model [27,28], and social cognitive theory [29,30]. These models posit that individuals' health risk behaviors are predicted by their *attention* to the behavior, *knowledge* about its health impacts, perceived *severity* of the harms that could result, perceived *benefits* of avoiding the behavior, and perceived *self-efficacy* to avoid the behavior. The CRAFFT-IS uses an MI-based approach to alert patients' attention to the topic of alcohol use within a health context, enhance their awareness

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and perceived severity of the potential health harms of alcohol use, and boost their motivation and self-efficacy to avoid use.

We tested an initial version of the CRAFFT-IS among adolescent primary care patients at 9 practices in 3 New England states (Connecticut, Massachusetts, and Vermont) using a quasi-experimental design in which each office served as its own historical control (usual care [UC] phase followed by intervention phase; details reported elsewhere) [31-34]. Compared to UC patients, intervention patients reported double the rate of receiving clinician advice about alcohol and, among those with prior drinking at baseline, had one-third lower drinking risk in the 3-month follow-up [31]. We also found a 22% lower risk for heavy episodic drinking (HED) among those with prior HED at baseline and a 30% lower risk for riding with a driver who is substance impaired [33].

We then enhanced the clinician advice to include brief MI strategies (eg, eliciting a patient's own reasons for avoiding use) while keeping the counseling brief enough for delivery by busy primary care clinicians. We pilot-tested this enhanced system compared to UC among adolescent patients seen for well visits at 5 Boston-area pediatric practices in a patient-randomized controlled trial. Intervention patients reported a 21% higher rate of receiving counseling about alcohol. Those reporting prior drinking at baseline (n=192) had a 34% lower risk for reporting HED during the 12-month follow-up [22]. Furthermore, those with riding risk at baseline (n=99) had a 42% lower risk of reporting riding with a driver who is substance impaired at the 12-month follow-up [35]. The CRAFFT-IS was also highly acceptable to the clinicians in the study, with 90% of the 49 clinicians agreeing that the system was useful, and 82% reporting that it increased their confidence in providing brief counseling [36].

To evaluate the replicability of these findings in a larger, more geographically diverse sample, we are now conducting a multisite effectiveness trial of the CRAFFT-IS among adolescent patients aged 14 to 17 years presenting for a well visit at practices within the national AAP Pediatric Research in Office Settings (PROS) network. This trial uses a clinician-randomized design, plans an adequately powered sample, and tests the intervention more broadly beyond New England. The CRAFFT-IS being tested in this study includes an updated version of the CRAFFT screen that includes nicotine vaping, now a leading form of substance use among adolescents [37]. It also includes updated psychoeducation material to reflect more current scientific knowledge and a revised brief counseling protocol to enhance alignment with MI-based counseling approaches.

Objectives

The primary objective of the Adolescent Substance Use Prevention and Intervention Research (ASPIRE) study is to test the effect of the CRAFFT-IS on past 90-day HED over 12 months' follow-up among adolescents who report past 12-month drinking at baseline. Our secondary objective is to test the effect of the CRAFFT-IS on riding with a driver who is substance impaired or driving while substance impaired (*riding or driving risk*) over 12 months' follow-up. Additional exploratory study objectives include evaluating (1) hypothesized effect mediators (eg, perceived risk of harm and refusal self-efficacy) and moderators (eg, baseline risk level and gender), (2) efficacy for reducing the use of other commonly used substances among adolescents (ie, nicotine and cannabis), and (3) efficacy for reducing the negative consequences of substance use.

Methods

Study Team

This study is being performed in the national AAP PROS network of pediatric primary care practices.The AAP PROS network consists of pediatrician members whose guiding mission is to improve the health of children and enhance primary care practice by conducting and fostering national collaborative practice-based research. Boston Children's Hospital (BCH) investigators are conducting the study in collaboration with the AAP PROS team. BCH conducts patient recruitment; participant retention; and data collection, management, and analysis activities. BCH also provides training and fidelity monitoring for clinicians delivering the intervention and convenes the data safety and monitoring board (DSMB). The AAP PROS team leads practice and clinician recruitment and data collection activities and hosts 2 PROS-member pediatrician advisors who provide input on study decisions from the perspective of community-based pediatric primary care clinicians.

Ethical Considerations

The AAP Institutional Review Board (IRB) is the single IRB for the study. The AAP IRB initially approved this study on May 27, 2022, after full board review (#22 HA 01). Approval included a waiver of parental permission and a partial waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization. We sought a partial waiver of HIPAA authorization because patient recruitment activities involve the exchange of patient health information from practices to the BCH study team. Furthermore, we sought a waiver of parental permission due to the minimal risk nature of the study, the developmental maturity of the target sample (adolescents aged 14-17 years), and the sensitivity of the substance-related topic. Our previous study on consent in adolescent substance use research showed that requiring parental permission resulted in a substantially higher study refusal rate (60% vs 20%) and a sample biased toward lower levels of substance use and substance-related problems [38]. Importantly, recruitment and assent materials state the voluntary nature of the study, emphasize that eligible adolescents *do not* have to have used alcohol or other substances to join the study, and encourage—but do not require—adolescents to discuss the study with their caregivers. The combination of these conditions supports parental involvement, preserves the privacy and confidentiality of adolescents who *do* use alcohol or other substances, and acknowledges adolescent autonomy to make an informed decision about participating.

The protocol version described in this paper was approved on June 21, 2023. Should there be modifications to the approved protocol or study materials, we will submit an amendment to the AAP IRB, and if applicable, the relying IRB at BCH. In addition, we will report scientific changes to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as needed

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or in the yearly progress report, at which point we will also update the trial registry on ClinicalTrials.gov.

In this trial, patient privacy and confidentiality protection is supported by executing a data transfer agreement between participating practices and BCH, assigning patients a numeric study identifier and by storing identifiable data in secure and restricted-access network locations separate from survey data. This study operates under a National Institutes of Health certificate of confidentiality. Assent materials state that only deidentified data will be shared outside of the study team (refer to the Data Access and Dissemination subsection).

Participating clinicians and practice staff members are required to provide informed consent. AAP PROS staff will send study recruitment materials to the designated contact clinician at each potentially eligible practice. Practices that are interested in participating will have a designated lead clinician submit a practice intake survey to confirm study eligibility of the practice and its clinicians. If practices are eligible, the AAP PROS staff will obtain written informed consent from all participating clinicians (Multimedia Appendix 1) as well as designated practice staff members who will handle and exchange patient data, answer patient or family questions, and otherwise support study activities at their site. Each participating practice will be offered a US $1000 honorarium after concluding patient recruitment at their practice and be able to keep all intervention-related materials, including the tablet computers provided for CRAFFT-IS implementation. Clinicians will be offered lunch accommodations (up to US $25 per person) for attending study orientation training and debriefing focus groups. In addition, clinicians in both trial arms can receive up to 12 continuing medical education credits for completing study training activities (UC clinicians will be offered CRAFFT-IS training at study completion at their practice). Board-certified pediatricians in the intervention arm may also receive optional maintenance of Certification Part 4 (up to 25 points) for a quality improvement activity spanning at least 3 quarterly feedback cycles. To complete this certification, intervention clinicians receive their participating patients' aggregated postvisit data reporting receipt of counseling and compare their performance with a standardized benchmark. Intervention clinicians receive a US $5 electronic merchandise gift card for attending an optional *office hour* with the trainers by videoconference every 1 to 2 months and US $10 for completing a debriefing survey about their experience of, and views about, the CRAFFT-IS at study completion.

Adolescents must provide verbal informed assent to participate (Multimedia Appendix 2). On a regular schedule (eg, every 2 weeks), each practice will send a BCH research assistant (RA) a list of age-eligible adolescent patients with upcoming well visits in the next 2 to 6 weeks. The BCH RA will then mail a study invitation coaddressed to adolescents and their caregivers, which includes an informational letter on the practice's letterhead and a study flyer with a QR code that leads to the brief study eligibility survey. Recruitment materials emphasize that adolescents do not need to have used substances to join the study, just as those with riding risk do not need to have used a substance themselves. Within 2 weeks of an adolescent's scheduled visit, the RA will attempt to contact the adolescent by telephone to invite them to complete the eligibility survey, which the RA, based on the adolescent's preference, can administer verbally or send for self-completion using an electronic link by SMS text message or email. At any point, a caregiver or adolescent can opt out of being contacted further. Eligible patients will be directed to an electronic information sheet and a 5-minute video brochure developed in collaboration with youth advisors. During a telephone call before the adolescent patients' visit, a BCH RA will summarize key information using a standard assent script. If willing to join the study and able to answer 6 questions assessing study understanding correctly, adolescents will have the option to discuss the study with a parent or guardian and may then provide their verbal assent to participate. Adolescents who turn 18 during the study period will be asked to consent as an adult on or near their 18th birthday.

In addition to obtaining study assent, we will ask adolescents whether they assent or decline to have their deidentified study data shared with the NIAAA Data Archive ($NIAAA_{DA}$), a national data repository to which NIAAA-funded investigators conducting human subjects research are expected to submit deidentified individual-level data [39]. This data sharing is not a condition of study participation and does not require parental permission. Adolescents can receive up to US $100 in small-value merchandise electronic gift cards for completion of study surveys (US $5, US $10, or US $15 for a survey, depending on its length).

Study Design and Randomization

The study is a cluster randomized controlled trial involving 2 arms, intervention (CRAFFT-IS) and control (UC), with prospective follow-up for 12 months. Clinician randomization occurs within practice and on a rolling basis as practices enroll into the study. Participating pediatric primary care clinicians (doctor of medicine [MD], doctor of osteopathic medicine [DO], nurse practitioner [NP], and physician assistant [PA]) are randomly assigned to 1 of the study arms in a 1:1 ratio. Randomization is performed using a computerized, adaptive biased coin minimization scheme, which minimizes imbalance on the following factors, ranked by priority: clinician type (MD or DO vs NP or PA) and years in practice (≥10 vs <10) [40,41]. Compared to permuted blocks, adaptive biased coin minimization randomization has superior efficiency for achieving balance across multiple factors in studies with small units of randomization.

Clinicians are assigned a unique numeric code for temporary blinding while being randomized. After randomization, clinician study arm assignments are unblinded and shared with the study team. Study arm assignments cannot be blinded because the study team needs to train clinicians according to group assignment.

Study Population, Sample Size, and Statistical Power

Practices and Clinicians

We will recruit up to 20 practices within the AAP PROS network, with up to 40 clinicians enrolled across these practices. To be eligible to participate, practices must (1) have at least 2 interested and eligible clinicians (clinician eligibility criteria

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are presented later in this subsection), (2) have a high-speed wireless internet connection available to ensure connectivity of study tablet computers, and (3) have an adolescent patient population that is primarily English speaking (the CRAFFT-IS has, to date, been tested only in English). Practices must not (1) be a practice or continuity clinic where residents or medical students routinely provide adolescent care (because trainees may not be available for training, implementation, and data collection for the duration of the practice's participation in the study) or (2) have recently participated or be participating in other initiatives to improve adolescent substance use screening and brief intervention in their practice. Eligible clinicians (1) must be a clinician (MD, DO, NP, or PA) who sees patients for well visits and (2) must see ≥6 adolescents aged 14 to 17 years per week, on average, or approximately 300 adolescents per year, for well visits.

Adolescents

We aim to enroll a minimum of 1300 adolescent participants. Eligible adolescents must (1) present for an annual well visit with a participating clinician in either study arm, (2) be aged 14 to 17 years at the time of their well visit, (3) report past 12-month alcohol use or past 12-month riding risk, and (4) have a smartphone and be willing to share their mobile phone number with the study team. We chose the minimum age of 14 years because there is low prevalence of prior alcohol use among younger adolescents (<5% of adolescents aged 12-13 years in our prior studies reported past 12-month drinking [Harris SK, unpublished data, 2019]). In addition, to be considered fully enrolled, all adolescents must complete the previsit survey before seeing their clinician, as well as the CRAFFT screen for those scheduled to see a clinician in the intervention arm. Adolescents must be willing and able to complete monthly surveys for 12 months after their well visit.

Adolescent patients must not be (1) in foster care, (2) in college or trade school at the time of their well visit, (3) currently receiving counseling or treatment for a substance use concern from a specialty clinician, or (4) perceived by their clinician to be inappropriate for the study (eg, due to neurodevelopmental delays or another medical priority at the time of visit).

We calculated the adolescent patient sample size by applying recruitment and retention rates, alcohol use and riding risk prevalence rates, intervention effect sizes, a within-clinician clustering design effect (0.90), and the clinician intraclass correlation coefficient for HED (0.008) seen in our pilot study [22]. We estimated a 37% past 12-month drinking prevalence rate, 28% riding risk prevalence rate among adolescents with past 12-month drinking, and a 5.8% riding risk rate among those with no past 12-month drinking. The 37% past 12-month drinking prevalence rate is similar to the 36.1% prevalence rate found on the 2018 Monitoring the Future Survey [42]. We applied slightly more conservative rates of participation (80% vs 82%) and retention (70% vs 75%) than those found in our pilot study to ensure that we achieve a sample size with sufficient power. With α set at ≤.05 and β at ≥.80, our power calculation indicated that a minimum analysis sample size of 888 participants with 12-month follow-up data would provide 86% power to detect an effect size of ≥20% in our primary outcome measure of HED. Applying the conservative estimate of 70% retention at 12 months, we need to recruit a minimum of 1268 participants. Thus, we estimate needing approximately 4200 adolescents to complete the eligibility survey, with 1600 (40% of those screened) meeting eligibility criteria, and 1300 (80% of those eligible) enrolling. To enroll this sample, we anticipate enrolling an average of 40 patients per clinician among up to 40 clinicians completing the study.

Intervention

Overview

The CRAFFT-IS was developed to leverage the power of digital technology to provide a time-efficient and feasible way for busy pediatric practices to improve both the frequency and quality of adolescent substance use screening and counseling in primary care. To this end, the CRAFFT-IS consists of the following components: (1) previsit self-administered screen (CRAFFT version with extra questions that are related to nicotine vaping and tobacco use [CRAFFT 2.1+N]), immediately followed by (2) brief interactive psychoeducational content on substance use–related health risks, and (3) clinician delivery of brief MI-based counseling during the confidential portion of the well visit, guided by a computerized point-of-care decision support tool called the clinician report. In addition, as an intervention to reduce riding and driving risk, intervention clinicians provide all participating patients and their caregivers with the *Contract for Life* document [34,43]. These components are described in greater detail in the following subsections.

Previsit Screening

To complete the previsit self-administered substance use screening, adolescents will log in to a secure website via their smartphone (before or at visit) or a tablet computer (at visit only) and complete the CRAFFT 2.1+N, which assesses past 12-month substance use frequency, substance-related riding and driving, and signs of problematic use (eg, uses when alone) [44]. At a cut point of ≥2 *yes* answers, the CRAFFT is highly sensitive (91%) and specific (90%) for detecting SUD in adolescents [23]. The CRAFFT 2.1+N includes an item on past 12-month days of nicotine vaping and tobacco use and, if yes, an item on past 30-day use. Endorsement of past 30-day nicotine vaping or tobacco use is followed by the Hooked on Nicotine Checklist (HONC), a well-validated 10-item screen for detecting loss of autonomy over nicotine use in adolescents [45]. This study will use a modified HONC that incorporates nicotine vaping.

After completing the substance use screen, adolescents will be asked to choose up to 3 personal values from a prespecified list of 14 values (eg, creativity, family, honesty, and wealth), with the option to write in their own. The selected values are presented in the clinician report to support clinician-patient rapport building and patient-centered MI-based counseling.

Previsit Psychoeducation

Next, adolescents view brief interactive psychoeducational web pages on the health risks of substance use. These web pages illustrate the unique vulnerability of adolescents to the health harms of substance use through the presentation of scientific

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evidence and true-life stories of adolescents. We developed this content based on input from focus groups of youth who reported that this type of information was compelling [31]. For this study, the content was updated to include information about the health risks of nocotine vaping.

Clinician Report and Brief Counseling Protocol

The clinician report is a web-based dashboard designed to help clinicians efficiently view their adolescent patients' responses to the substance use screening and values items and deliver brief counseling tailored to the responses. On the basis of the screening responses, counseling guidance is tailored to 1 of three substance use profiles: (1) *recent use* (use of alcohol, cannabis, or another drug in the past 3 months or use of tobacco or nicotine in the past 30 days), (2) *distant use* (use of any substance in the past 12 months but not in the past 3 months or past 30 days for nicotine vaping and tobacco), and (3) *riding risk* (no past 12-month substance use but past 12-month riding in a vehicle with a driver who was substance impaired).

The brief counseling protocol is a modified form of the brief negotiated interview, a structured MI-based counseling intervention originally developed for use in emergency departments and found to be efficacious in reducing substance use in adolescents [46]. The counseling protocol is designed for delivery in 5 to 10 minutes, depending on the severity of risk. Counseling steps are summarized in Table 1.

Table 1. Overview of the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized controlled trial's brief counseling protocol, which is delivered by intervention clinicians to participating adolescent patients who present for a well visit and report past 12-month alcohol use, past 12-month riding risk, or both.

Counseling protocol steps	Recent use[a]	Distant use[b]	Riding risk[c]
1. Engage and build rapport	✓	✓	✓
2. Review screening results and assess further	✓	✓	✓
3. Consider pros and cons of substance use (decisional balance)	✓		
4. Discuss health risks of substance use and riding risk	✓	✓	✓
5. Evaluate readiness to change substance use (readiness ruler [47]) and reasons for change	✓		
6. Elicit next steps toward behavior change and anticipate challenges	✓	✓	✓[d]
7. Wrap up by summarizing discussion and affirming autonomy and self-efficacy	✓[d]	✓[d]	✓

[a]Patient reports past 3-month substance use. Patient may or may not report past 12-month riding with a driver who was substance impaired.

[b]Patient reports past 12-month substance use but no past 3-month use. Patient may or may not report past 12-month riding with a driver who was substance impaired.

[c]Patient reports past 12-month riding with a driver who was substance impaired and no past 12-month substance use.

[d]Clinician provides patient with the *Contract for Life* [43].

Recent use counseling uses the MI style of communication to elicit the adolescent's reasons for and problems with substance use. The clinician discusses the adolescent's values, shares health information, explores the adolescent's reasons for and readiness to change their substance use behavior using a readiness ruler [47], and guides the adolescent through planning behavior change. The counseling concludes by summarizing the discussion and affirming the adolescent's autonomy and self-efficacy. *Distant use* counseling involves affirming and supporting the adolescent's continued nonuse, discussing health risks associated with past substance use, and anticipating and planning for challenges with maintaining abstinence. *Riding risk* counseling also includes affirmation and support of the adolescent's continued nonuse, discussion of health risks associated with riding with a driver who is substance impaired, and counseling to identify and plan safe transportation at all times. Both the *distant use* and *riding risk* counseling protocols are guided in a structured step-by-step manner similar to *recent use* counseling.

Near the end of the brief tailored counseling, intervention clinicians provide *all* participating patients with a paper or electronic version of the *Contract for Life*. Developed by Students Against Destructive Decisions, the *Contract for Life* asks youth and their caregivers to develop and commit to a plan to ensure that adolescents always have a safe ride home with a sober driver [43].

Intervention Training and Fidelity Monitoring

Two clinicians with expertise in MI train intervention clinicians to deliver the intervention counseling. Training was initially structured as 5 self-study modules on a web-based learning platform and 5 live sessions with expert trainers (approximately 7 total training hours). As scheduling the 5 live sessions was found to be challenging with the first practice, the study team restructured the training to include longer self-paced asynchronous modules to reduce scheduling challenges without changing the total number of training hours. The updated training schedule consists of 5 self-study modules with recorded lectures, 2 live counseling practice sessions, and 1 live technical training session to orient clinicians to the clinician report and tablet computers.

The self-study modules include video-recorded presentations on MI-based counseling principles, the counseling steps for each of the 3 risk categories, video-recorded mock counseling demonstrations with accompanying annotated transcripts, and self-assessment questions. In the 2 live sessions, the expert trainers guide clinicians through case-based practice of the counseling steps and provide feedback.

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To establish baseline competency, each clinician completes the counseling steps with a standardized patient for each of the 3 risk categories in a single recorded videoconference session. The trainers and 2 research staff members review these recordings using a standardized rating form. The trainers then meet with each clinician for individualized feedback and coaching. For fidelity monitoring, clinicians complete mock counseling sessions and receive feedback quarterly. In addition, the intervention trainers host optional live videoconference sessions (*office hours*) every 1 to 2 months for extra coaching.

Intervention Modification or Discontinuation

No concomitant care and interventions are prohibited during the trial beyond those defined in the practice inclusion criteria. We will withdraw a participant from the study if there is evidence to suggest that continuing in the study may be inappropriate (ie, there are intervening medical, mental health, or social circumstances that preclude or disrupt participation). Data collected from withdrawn participants will still be used in the analysis.

Outcomes and Measures

Study Activities and Assessment Timeline

Figure 1 illustrates the chronology of participating clinician and adolescent study activities.

Figure 1. Chronological overview of clinician and adolescent milestones during the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized trial. CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble.

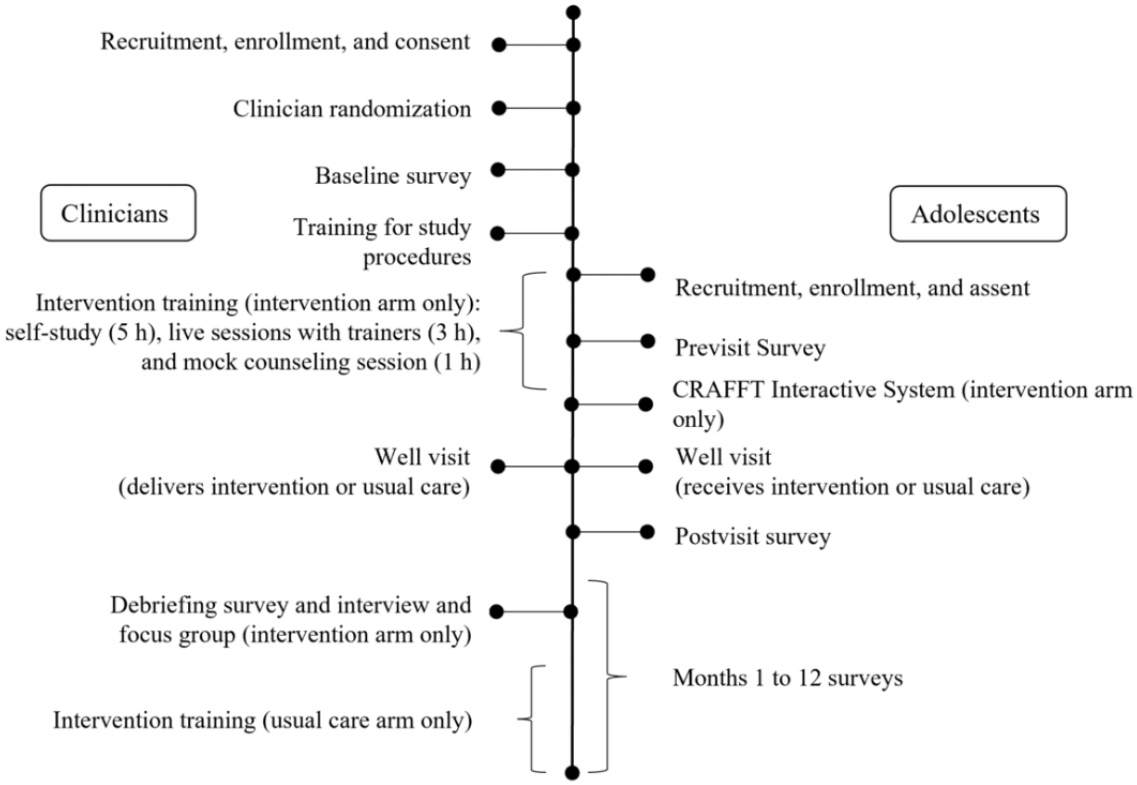

Outcome Measures

A detailed listing of study outcome measures, their reference sources where applicable, and time points of data collection is presented in Table 2, and thus they are only briefly described here. These measures are also reported in the ClinicalTrials.gov registry.

Our primary outcome measure is past 90-day HED, as reported by adolescents during the 12-month follow-up period, among adolescents who report past 12-month drinking at baseline. HED is defined using the age- and sex-specific cut points recommended by the NIAAA: ≥3 drinks on a single occasion for youth assigned female at birth who are aged 14 to 17 years, ≥4 drinks for youth assigned male at birth who are aged 14 to 15 years, and ≥5 drinks for youth assigned male at birth who are aged 16 to 17 years [68]. Our secondary outcome measure is any past 90-day riding with a driver who was substance impaired (who used alcohol, cannabis, or another drug) or driving while substance impaired. The exploratory outcomes of interest include past 90-day days of use of other commonly used substances among adolescents (ie, nicotine and cannabis) and experience of negative consequences associated with alcohol use (eg, missing school or work and getting into trouble at school, home, or work). In addition, we will explore the following intermediate outcome measures as hypothesized effect mediators: (1) report of readiness to reduce or stop alcohol use using a readiness ruler [47], (2) perceived risk of harm from use, and (3) self-efficacy to refuse alcohol.

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Table 2. Adolescent participant study assessment measures by data collection time point across 12 months in the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized controlled trial.

Measure	Data collection time point								
	Eligibility survey	Previsit survey	CRAFFT-IS[a]	Postvisit survey	Monthly[b]	3 mo	6 mo	9 mo	12 mo
Primary outcomes									
Heavy episodic drinking[c]									
TLFB[d,e] [48,49]		✓			✓	✓	✓	✓	✓
AUDIT-C[f,e] [50]		✓			✓	✓	✓	✓	✓
Substance use[g] (CRAFFT[h] [24,44] on eligibility and TLFB all other times)	✓	✓			✓	✓	✓	✓	✓
Negative consequences									
Negative consequences of alcohol and cannabis use scales[e] [51]		✓				✓	✓	✓	✓
PEI[i] Personal Consequences Scale[e] [52,53]		✓				✓	✓	✓	✓
NCANDA[j] study[e] [54]		✓				✓	✓	✓	✓
Secondary outcome									
Riding and driving risk frequency									
National College Alcohol Study[e] [55]		✓				✓	✓	✓	✓
Young Adult Driving Questionnaire[e] [56]		✓				✓	✓	✓	✓
Adapted from previous cSBI[k] studies [22,54]		✓				✓	✓	✓	✓
Other measures									
Hypothesized mediators									
Readiness to reduce or stop use (readiness ruler [47] used in previous cSBI study [22])		✓		✓					
Perceived risk of harm (National Monitoring the Future Survey[e] [37])		✓		✓		✓	✓	✓	✓
Refusal self-efficacy (DRSEQ-SRA[l,e] [57])		✓		✓		✓	✓	✓	✓
Receipt of health services for substance use (adapted from previous cSBI study [22])						✓	✓	✓	✓
Control variables									
Substance use severity profile									
CRAFFT	✓		✓						
TLFB		✓			✓	✓	✓	✓	✓
ASSIST[m,e] [58]		✓				✓	✓	✓	✓
Peer substance use (PEI)		✓				✓	✓	✓	✓
Family substance use (PEI)		✓					✓		✓
Patient-clinician relationship									
Number of previous visits with clinician				✓					

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Measure	Data collection time point								
	Eligibility survey	Previsit survey	CRAFFT-IS[a]	Postvisit survey	Monthly[b]	3 mo	6 mo	9 mo	12 mo
Youth Connectedness to Provider Scale [8,31]				✓					
Process measures									
Intervention duration (new)			✓						
Visit format (new)				✓					
Protocol adherence and visit quality (adapted from previous cSBI studies [8,31])				✓					
Contract for Life [43] discussion with caregivers (adapted from previous cSBI study [35])						✓			
Validation of modified HONC[n]									
Nicotine use disorder risk									
HONC[e] [45,59]			✓						
PROMIS-E[o,e] [60]		✓							
Other exploratory variables									
Quality of life and overall health									
CHU9D[p] [61]		✓				✓	✓	✓	✓
PATH[q] Study [62]		✓				✓	✓	✓	✓
YRBS[r,e] [63]		✓				✓	✓	✓	✓
Sexual and gender minority status (YRBS and others [64-66])	✓					✓	✓	✓	✓
Social determinants of health									
MSPSS[s] [67]		✓				✓	✓	✓	✓
YRBS		✓				✓	✓	✓	✓

[a]CRAFFT-IS: CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble) Interactive System (collected before the well visit among intervention arm patients only).

[b]Monthly surveys 1, 2, 4, 5, 7, 8, 10, and 11 are brief in length; monthly surveys 3, 6, 9, and 12 are extended in length.

[c]Defined by the National Institute on Alcohol Abuse and Alcoholism Alcohol Screening and Brief Intervention for Youth Guide [68].

[d]TLFB: timeline followback.

[e]Modified or adapted for purposes of this study.

[f]AUDIT-C: Alcohol Use Disorders Identification Test–Concise.

[g]Includes alcohol, nicotine, tobacco, marijuana, inhalants, misused prescription medication, and other drugs (synthetic marijuana, stimulants, opioids, and hallucinogens).

[h]CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble.

[i]PEI: Personal Experience Inventory.

[j]NCANDA: National Consortium on Alcohol and Neurodevelopment in Adolescence.

[k]cSBI: computer-facilitated screening and brief intervention.

[l]DRSEQ-SRA: Drinking Refusal Self-Efficacy Questionnaire–Shortened Revised Adolescent version.

[m]ASSIST: Alcohol, Smoking and Substance Involvement Screening Test.

[n]HONC: Hooked on Nicotine Checklist.

[o]PROMIS-E: Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes.

[p]CHU9D: Child Health Utility–9 Dimensions.

[q]PATH: Population Assessment of Tobacco and Health.

[r]YRBS: Youth Risk Behavior Survey.

[s]MSPSS: Multidimensional Scale of Perceived Social Support.

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Other Measures

We will explore potential intervention effect moderation by age group, sexual and gender identity and social determinants of health that enhance substance use risk for sexual and gender minority youth, baseline severity of substance use involvement, peer and family substance use, and patient-clinician relationship (number of prior visits the patient had with this clinician and perceived connectedness to their clinician).

We will also examine intervention implementation measures, including the time required to deliver the various CRAFFT-IS components and patient-reported receipt and quality of substance use counseling during their visit. Time information will be collected through computerized capture of patient clickstream times and clinician counseling start and stop times, as well as clinician report of average substance use–related counseling time and overall visit length on the clinician debriefing questionnaire completed at the end of patient recruitment at a practice. Adolescents complete an immediate postvisit questionnaire that includes items on the health topics discussed during the visit, ratings of counseling quality and the degree to which it reflected an MI-based counseling style, and whether they received the *Contract for Life*.

To assess the validity of the modified HONC for identifying risk for nicotine use disorder in adolescents, we will compare it to the 4-item Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes (PROMIS-E) [60] administered in the previsit assessment. While the CRAFFT screening items are well validated [24], the modified HONC, which now includes nicotine vaping and is included in the CRAFFT-IS previsit screening for adolescents seeing intervention clinicians, needs validation.

Data Collection

Clinicians

Enrolled clinicians are assigned a unique numeric identifier for use in data collection throughout the study. A baseline survey assesses previous experience and training and UC practices around screening, brief intervention, and referral to treatment (10 min), as well as training on study procedures and human subjects protections (up to 90 min; all clinicians). Clinicians assigned to the intervention arm additionally complete brief (5 min each) postsession evaluation surveys after each live training session and a final summative evaluation after all training components have concluded. Clinician surveys and evaluations are completed on paper or by email or SMS text message link to an online survey per clinician preference. After adolescent recruitment and intervention delivery have concluded at a practice, intervention clinicians complete a 10-minute debriefing survey assessing experience using the CRAFFT-IS and seeking suggestions for improving the system, as well as participate in a 30- to 60-minute interview or focus group (along with participating staff) to offer feedback on their study experience.

Adolescents

All adolescent participants are assigned a unique numeric identifier at the time of recruitment for use in data collection, storage, and linkage throughout their study participation. Once assented, participants indicate their contact preferences. Adolescents who agree to have their data shared with the $NIAAA_{DA}$ are assigned a Global Unique Identifier using their first, middle, and last names; sex assigned at birth; and date and city of birth. Global Unique Identifiers are numeric codes that allow participant data to be submitted to the $NIAAA_{DA}$ without any personally identifiable information. All participants self-administer the confidential electronic previsit survey (approximately 20 min; refer to Table 2 for details on all surveys), and participants seeing an intervention clinician complete the screening and psychoeducational components of the CRAFFT-IS (5 min) before seeing their clinician. After their visit, all participants complete the immediate postvisit survey (approximately 10 min), and then, through the 12-month follow-up period, brief monthly surveys about their past 30-day substance use and longer surveys at 3, 6, 9, and 12 months (approximately 15 min each). Participants may choose to skip questions or entire surveys and still remain in the study.

All surveys can be completed electronically on smartphones and desktop or tablet computers through a link sent by SMS text message or email to participants' personal mobile phone numbers or email addresses, as preferred. Electronic surveys are protected by a password set by the adolescent. Adolescents can also complete a survey by mobile phone with a study RA. If the adolescent does not complete a survey after electronic reminders, a study RA will call the adolescent to encourage survey completion.

Data Management

Study data, including survey responses and internal study tracking data, will be collected and stored in Research Electronic Data Capture (REDCap), a HIPAA-compliant web-based data management and survey distribution tool hosted at BCH [69,70]. Data transmission among BCH, AAP PROS staff, and practices will occur securely via password-protected email or fax. Paper-based data (eg, faxes and verbally administered surveys) will be stored securely for 7 years and identifiable electronic data for 3 years. Deidentified data will be kept indefinitely.

Data Analysis Plan

Analysts will be blinded to treatment arm. We will evaluate randomization success and level of attrition bias by comparing baseline characteristics of adolescents by treatment arm and by those retained versus those lost to follow-up (ie, adolescent participants who stop completing study surveys during the 12 months after their well visit). Baseline variables meeting a P value of <.20 in randomized group comparisons will be entered as control variables in multivariable modeling of the intervention effect to yield adjusted estimates of effect. We will compare rates of counseling receipt and patient ratings of their visit between groups. We will also generate variables related to intervention *dose* (eg, receipt of clinician counseling and receipt of *Contract for Life*) for use in sensitivity analyses.

To assess intervention effects on our primary and secondary outcome measures (past 90-day HED and any past 90-day riding or driving risk) at each of the 3-, 6-, 9-, and 12-month follow-up time points, we will use multiple logistic regression modeling with generalized estimating equations to compute adjusted

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relative risk ratios (CRAFFT-IS vs UC). Generalized estimating equations account for clustering of participants within practice and clinician. Furthermore, we will explore intervention effects on the number of days of drinking and of HED and on the number of times participants experienced alcohol-related negative consequences from baseline to each follow-up time point. As these variables are likely to have distributions that are highly skewed and overdispersed, we will specify a negative binomial distribution and log link in these regression models. We will also conduct longitudinal data analysis using mixed effects modeling to compare group outcomes trajectories through the entire 12-month follow-up period. We plan to explore intervention effect mediation by applying the product of coefficients test for mediation [71,72] and potential effect moderation by future-determined variables by testing the significance of interaction terms in regression models.

All intervention effect analyses will use intent-to-treat groups. We will transform continuous variables with skewed data and collapse categories as needed to preserve adequate cell sizes. To handle missing data, we will use multiple imputation based on regression modeling and compare the results of analyses using the imputed data set versus the original data set [73].

Safety and Monitoring

We define the following as nonemergency safety risks: drinking twice the NIAAA-defined HED amount for the adolescent's age and sex [68], daily use of alcohol or cannabis, use of other drugs on >6 days during the past 3 months, driving after use of substances >1 time in the past 3 months, and riding with a driver who is substance impaired >1 time in the past 3 months. When an adolescent's survey responses indicate any of these nonemergency risks, a BCH RA will notify the patient's clinician within 1 business day. If an adolescent spontaneously discloses an emergency safety risk (eg, abuse, suicide risk, or intentions to harm others), a BCH RA will immediately notify their clinician or appropriate contact person according to site-specific preferences.

This study has an independent DSMB that consists of 3 members: a child psychiatrist with expertise in adolescent SUD screening and treatment research (chair), a biostatistician with experience in clinical trial research, and an adolescent medicine primary care clinician. The DSMB will (1) review study procedures and progress, including recruitment, retention, and dropout; and (2) assess adverse events and unanticipated problems, if any, and their relationship to study participation. The full DSMB will meet annually to review overall study progress and will also convene as needed to review and address any adverse events or other study-related problems, should they arise. The DSMB is responsible for recommending whether to stop the study; no interim analyses are planned.

Given that this is a minimal risk study, we do not anticipate that participants will experience harm from study participation. However, we have planned for situations in which participants spontaneously report harms. Harms may consist of nonserious adverse events (eg, participant complaints or upset related to study activities and inadvertent disclosure of confidential information) or serious adverse events (eg, motor vehicle crashes and hospital visits). If we learn of an adverse event, we will consult with the DSMB chair and notify the AAP IRB and the patient's practice. The DSMB will determine whether a serious adverse event is related to study participation and recommend the appropriate response, including possible study withdrawal. Study data are protected by a certificate of confidentiality from the National Institutes of Health.

Results

Recruitment and Enrollment

The first practice enrolled in August 2022. As of July 2023, a total of 6 practices (23 clinicians) had enrolled in the study.

Adolescent recruitment began in December 2022 and is expected to continue until late 2024 or early 2025. Data collection is expected to conclude in 2025 or 2026, and data analysis will follow.

Data Access and Dissemination

The final trial deidentified data set will be provided to the study's biostatistician, the AAP PROS team, and any other interested investigators upon request. We will report results on ClinicalTrials.gov, and select deidentified data will be available to researchers worldwide via the $NIAAA_{DA}$.

In addition to this paper, we aim to publish at least 2 papers that disseminate study findings: 1 focused on our primary alcohol use–related outcomes and 1 focused on other substance use outcomes. We also anticipate submitting at least 2 abstracts to present at national conferences. Members of the study team will develop and write all publications resulting from this study. Authorship will be designated according to those who offer intellectual contribution to the design or preparation of a given publication and claim responsibility for its contents.

Discussion

The ASPIRE study aims to test the effectiveness of the CRAFFT-IS, compared to UC, in reducing alcohol use and substance use–related riding risk among adolescents aged 14 to 17 years presenting for well visits. Despite the AAP's recommendation for universal substance use screening in primary care beginning at age 11 years, the US Preventive Services Task Force gave primary care–based adolescent alcohol screening and brief behavioral counseling an "I" rating in its most recent review, indicating insufficient evidence for or against its recommendation [74]. The ASPIRE study builds on prior research supporting the promise of CRAFFT-IS as a feasible, acceptable, and efficacious approach to increasing high-quality screening and counseling.

Our study protocol has limitations. Although our virtual recruitment and enrollment approach allows the study team to contact a larger volume of individuals over an expanded time frame (eg, in comparison to in-person recruitment restricted to clinic operating hours), practices may not have up-to-date contact information for adolescent patients. Likewise, it is not guaranteed that adolescents will see or read the mailed recruitment invitation before their visit. Our approach also reduces burden on practice staff to conduct recruitment activities, but it may underuse pre-established connections

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between practice staff and adolescent patients. Furthermore, the addition of the CRAFFT-IS to well visits may delay clinic flow. Further limitations to our study may emerge during the trial and will be reported in future outcomes manuscripts.

If the CRAFFT-IS is shown to be effective, we intend to scale, promote, and widely disseminate the instrument for use in pediatric practice, either as a tablet application or as a confidential add-on to existing electronic health record systems. We also envision this study informing future investigators interested in studying computer-facilitated screening and brief intervention for youth substance use, whether in primary care settings or elsewhere, with the aim of reducing alcohol-related morbidity and mortality during adolescence and beyond.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed.

Authors' Contributions

LAS and SKH conceptualized, designed, and obtained funding for the study. MMO and AT obtained ethics approval for the study, with oversight from LPS and AGF and assistance from JAP, JLM, NHM, and DH. LAS and PJB developed the intervention counseling. TF and MLM served as pediatrician advisors to the study. LS codeveloped and programmed the computer-facilitated screening and brief intervention. All authors contributed to the development of the protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinician consent form.
[PDF File (Adobe PDF File), 318 KB - resprot_v13i1e55039_app1.pdf]

Multimedia Appendix 2
Verbal assent script delivered to eligible adolescents.
[PDF File (Adobe PDF File), 349 KB - resprot_v13i1e55039_app2.pdf]

Multimedia Appendix 3
Peer-review reports from the Clinical, Treatment and Health Services Research Review Subcommittee, National Institute on Alcohol Abuse and Alcoholism Initial Review Group (National Institutes of Health).
[PDF File (Adobe PDF File), 190 KB - resprot_v13i1e55039_app3.pdf]

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Abbreviations

AAP: American Academy of Pediatrics
ASPIRE: Adolescent Substance Use Prevention Intervention Research
BCH: Boston Children's Hospital
CRAFFT 2.1+N: CRAFFT version with extra questions that are related to nicotine vaping and tobacco use
CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble
CRAFFT-IS: CRAFFT Interactive System
cSBI: computer-facilitated screening and brief intervention
DO: Doctor of Osteopathic Medicine
DSMB: data safety and monitoring board
HED: heavy episodic drinking
HIPAA: Health Insurance Portability and Accountability Act
HONC: Hooked on Nicotine Checklist
IRB: institutional review board
MD: Doctor of Medicine
MI: motivational interviewing
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAAADA: National Institute on Alcohol Abuse and Alcoholism Data Archive
NP: nurse practitioner
PA: physician assistant
PROMIS-E: Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes
PROS: Pediatric Research in Office Settings
RA: research assistant
REDCap: Research Electronic Data Capture
SUD: substance use disorder
UC: usual care

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Protocol

eHealth-Enhanced Peer Navigation for Substance Use Treatment and HIV Prevention Service Linkage for Young Adults Surveilled by the Criminal Legal System: Protocol for a Pilot Randomized Trial Study

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Abstract

Background: In the United States, the proportion of criminal legal–involved (CLI) adults with a substance use disorder reaches 72%, and ~150,000 persons with HIV pass through a carceral setting annually, which represents 16% of the HIV-infected population nationally. Despite the high need for substance use treatment and HIV prevention services, few carceral settings successfully link CLI individuals to treatment upon release. Young adults represent 41.9% of the adults incarcerated in the United States and have the highest HIV incidence rates nationally. Peer patient navigation has successfully increased community-based care linkage for people living with HIV leaving jail; yet, peer-led navigation for HIV prevention among HIV-negative CLI populations is undeveloped and untested. eHealth approaches to substance use and HIV prevention services hold promise because they improve access to effective intervention services, particularly for younger people.

Objective: This paper describes a protocol for a pilot randomized controlled trial that aims to improve linkage to substance use treatment and HIV prevention services using peer navigation and a codeveloped eHealth technology adjunct.

Methods: The three aims of this study are to (1) adapt an existing evidence-based navigator model and incorporate codeveloped eHealth technology to refer and link young adults (18 to 29 years) surveilled by the criminal legal system to substance use and pre-exposure prophylaxis (PrEP) services; (2) refine and test the intervention with criminal legal–involved young adults (CLI-YAs); and (3) assess the feasibility, acceptability, and impact of the intervention. Data to inform the intervention will be collected via system partner interviews (n=4) and focus groups with CLI-YAs (n=24). Next, an open trial (n=10) will be conducted. The intervention will be refined via interviews with participants and facilitators, and a randomized pilot trial (n=75) will be conducted to assess the feasibility, acceptability, and preliminary impact of the eHealth-enhanced navigation on substance use and PrEP services linkage. Exit interviews conducted with a subsample of intervention participants (n=10), the navigator (n=1), and system partners (n=4) will assess intervention acceptability and suggestions for improvement. A community of practice, a group of system partners with an interest in working toward solutions to common problems, will inform each phase of the study.

Results: The project is currently ongoing. The project was funded in September 2022. Internal review board approval was received on March 21, 2022. The first results from early study aims are expected to be published in 2025.

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Conclusions: This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a systemically marginalized group: young CLI-YAs. The results will contribute to the development and testing of a future multilevel randomized controlled trial.

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KEYWORDS

substance use; HIV prevention; carceral system; intervention development; young adult

Introduction

In the United States, annually, individuals involved in the criminal legal (CL) system are at an increased risk of substance use disorders (SUDs) and HIV acquisition [1-4]. HIV rates among CL-involved (CLI) adults range from 3 to 15 times the rate among individuals not involved in the CL system [2]. Individuals involved in the CL system have high rates of lifetime and recent substance use: between 81% and 84% report lifetime substance use and between 63% and 83% test positive for substance use at the time of their arrest [3]. The proportion of CLI individuals with an SUD reaches 72% [3]. Despite the high need for treatment services, few correctional settings link CLI individuals to community-based substance use treatment upon release.

Young adults (YAs; ages 18-34 years) represent 41.9% of the adults impacted by the carceral system [5] and have the highest HIV incidence rates nationally; YAs aged 20 to 24 years and 25 to 29 years have the highest rates of HIV infections (27.9 and 32.6 per 100,000, respectively) [6]. YAs also disproportionately experience SUD, with 25.6% of those aged 18 to 25 years estimated to meet the Diagnostic and Statistical Manual of Mental Disorders criteria for SUD in the last year (as of 2021) compared to 16.1% of those over the age of 26 years [6]. Factors that increase the likelihood of substance misuse and SUD among YAs include an imbalance of brain maturity through the second decade of life as well as psychosocial factors like increased peer influence and substance use as part of identity exploration [7]. Notably, the criminalization of substance use can also shape vulnerability to HIV as periods of detention can disrupt health care access, employment, caregiving, and social networks [8].

Significant racial disparities exist among new HIV acquisitions for YAs; African American populations accounted for 45.7% of all new HIV infections among YAs, and Hispanic populations accounted for 28.8% [9]. Given the disproportionate number of racial and ethnic minoritized CLI-YAs [10], prioritizing interventions that reduce racial and ethnic disparities in HIV and SUD treatment engagement for CLI-YAs is essential [11,12]. Multiple negative outcomes are known to be associated with involvement with the carceral system itself, including increased prevalence of SUD and infectious diseases like hepatitis C and HIV, increased indicators of poor mental health, and high prevalence of traumatic experiences (physical, sexual, and emotional) that linked directly to carceral policies (eg, solitary confinement) [13,14]. In light of the fact that ~5 million adults pass through CL settings annually and one-third are YAs [10], it is critical to link CLI-YAs who misuse substances and are at risk for HIV with innovative prevention strategies (ie, pre-exposure prophylaxis [PrEP]) and substance use treatment.

PrEP, in the form of a fixed-dose combination of 2 antiretroviral drugs, has emerged as a powerful HIV prevention tool [15]. In addition to 2 oral PrEP medications available (ie, Truvada and Descovy), the US Food and Drug Administration recently approved long-acting injectable PrEP (ie, Apretude) as another PrEP administration tool [15]. Significant disparities exist both between PrEP eligibility and uptake. For example, there are significant racial disparities with low PrEP uptake for Black individuals compared to people with other racial identities [16]. Hispanic and Latinx populations face similar disparities in PrEP use; people assigned female at birth, transgender populations, and bisexual and heterosexual populations also experience lower odds of PrEP use compared to their counterparts despite their not insignificant HIV incidence rates [16]. A variety of factors impede efforts to increase PrEP and substance use treatment access among CLI populations including discrimination based on one's racial or ethnic identity, misinformation about HIV transmission and treatment, stigma related to an individual's intersecting identities (eg, CLI status, substance use, race, and ethnicity), distrust of the CL and medical systems, psychiatric symptoms, inability to pay for transportation, lack of familial and social support, and inconsistent access to health care [17-20]. Although PrEP has been found to be efficacious, its maximal impact depends on uptake among those at high risk, including CLI-YAs.

Peer navigation holds strong potential to address multifactorial and complex barriers to PrEP and substance use treatment linkage and uptake for CLI-YAs. Navigation uses a one-on-one relationship to promote the timely movement of an individual through a health care continuum by eliminating barriers [18]. One such intervention, The Navigator Project (NAV), found that navigation-enhanced case management supported linkage to care (<30 days) and consistent retention in care (<1 year) for persons with HIV leaving jail as compared to persons with HIV living in the community and not exposed to jail detention. Using a harm reduction framework, peer navigators use motivational interviewing and prevention care management to navigate reentry back into the community, including referrals for mental health treatment, substance use treatment and harm reduction support, housing, employment, legal aid, and social services [20]. While peer navigation has been successful in increasing connections to care for persons with HIV leaving jail settings [20,21], peer-led navigation for HIV prevention among HIV-negative CLI populations is nascent [22].

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In tandem with patient navigation, eHealth has the potential to improve health care engagement for CLI-YAs [23,24]. eHealth-enhanced peer navigation for HIV-infected individuals released from jail has been shown to be effective in maintaining virologic suppression [21]. The private nature of eHealth makes it an appealing modality to deliver components of a navigation intervention and link individuals with stigmatized services (eg, HIV prevention and SUD treatment) [25-27]. Of YAs aged 18-29 years, nearly 100% own a mobile phone and 92% possess a smartphone, making eHealth health intervention approaches feasible [23]. eHealth interventions can improve attendance at health care appointments [28,29], medication adherence [30,31], and behavior changes [32], and can provide support in real time [33]. To our knowledge, however, eHealth-enhanced navigation is untested for integrated substance use treatment and HIV prevention service linkage for CLI-YAs who have returned to the community after incarceration or who are subject to community surveillance. This study aims to address this gap in the literature by examining the feasibility, acceptability, and impact of an eHealth-enhanced peer navigator-led SUD and HIV prevention referral and linkage intervention for CLI-YAs supervised in the community. This paper is intended to provide a thorough summary of this study protocol.

The objectives of this study are to (1) adapt an existing evidence-based navigator mode (NAV) and incorporate codeveloped eHealth technology to refer and link CLI-YAs (ages 18-29 years) to substance use treatment and HIV prevention (PrEP) services; (2) refine the adapted eHealth-enhanced navigator-led substance use treatment and HIV prevention (PrEP) linkage intervention for CLI-YAs and test for fidelity, appropriateness, and satisfaction; and (3) assess the feasibility, acceptability, and impact of the adapted eHealth-enhanced navigator program to refer and link CLI-YAs to substance use treatment and HIV prevention (PrEP) services.

Methods

Study Setting

Surveillance data from Allegheny County, Pennsylvania, the study location, indicate that YAs (aged 20-29 years) account for 43% of all new HIV infections [34]. Notably, most adults newly diagnosed with HIV in Allegheny County are from racial and ethnic minority groups (65.8% in 2020) [34], making research in this geographic area generalizable to other high HIV incidence US locales. As of 2020, 30% of individuals who died from drug overdoses in Allegheny County were involved with adult probation and 19% had been booked in a county jail in the prior year. Additionally, Black residents in Allegheny County were disproportionately represented in overdose deaths, with a rate more than 2 times that of White residents [35].

eHealth Enhancement

The proposed technology is a non-native web-based app that will facilitate resource linkage and communication between the navigator and participants. Expected functions of the eHealth technology include appointment scheduling and reminders, the provision of tailored resources (eg, substance use treatment information), motivational messages, and linkage to support persons. The partner for developing this technology is Chorus Innovations, Inc, which uses a participatory informatics approach that combines best practices from community-based participatory research (eg, equity and power sharing) [36] and user-centered design (eg, active user participation in design) to build technology products [37]. These practices ensure that the user participates in the design process [38], and there is a collaborative and equitable partnership in the research and design process, the process is iterative, and knowledge and action are mutually beneficial to all partners.

Implementation Research Logic Model

This study uses the CFIR (Consolidated Framework for Implementation Research) to identify key determinants [39], the “Expert Recommendations for Implementing Change” [40,41] to describe implementation strategies, and the Proctor Framework [42] to define implementation, service, and participant outcomes (Figure 1). The CFIR is organized into 5 domains based on context (intervention, outer setting, inner setting, individual, and process). We will use three implementation strategies from Expert Recommendations for Implementing Change [41] to (1) adapt and tailor to context for the eHealth enhancement protocol; (2) education to train navigators; and (3) engage consumers, develop stakeholder interrelationships, and use evaluative and iterative strategies achieved via the community of practice (CoP). This study focuses on feasibility, acceptability, fidelity (implementation outcomes), effectiveness, appropriateness (service outcomes), and satisfaction (clinical outcomes).

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Figure 1. Intervention logic model for a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA, based on the CFIR (Consolidated Framework for Implementation Research), Expert Recommendations for Implementing Change (ERIC), and the Proctor Framework. +/- in the determinants column indicates directionality of impact. CLI-YA: criminal legal–involved young adult; PrEP: pre-exposure prophylaxis.

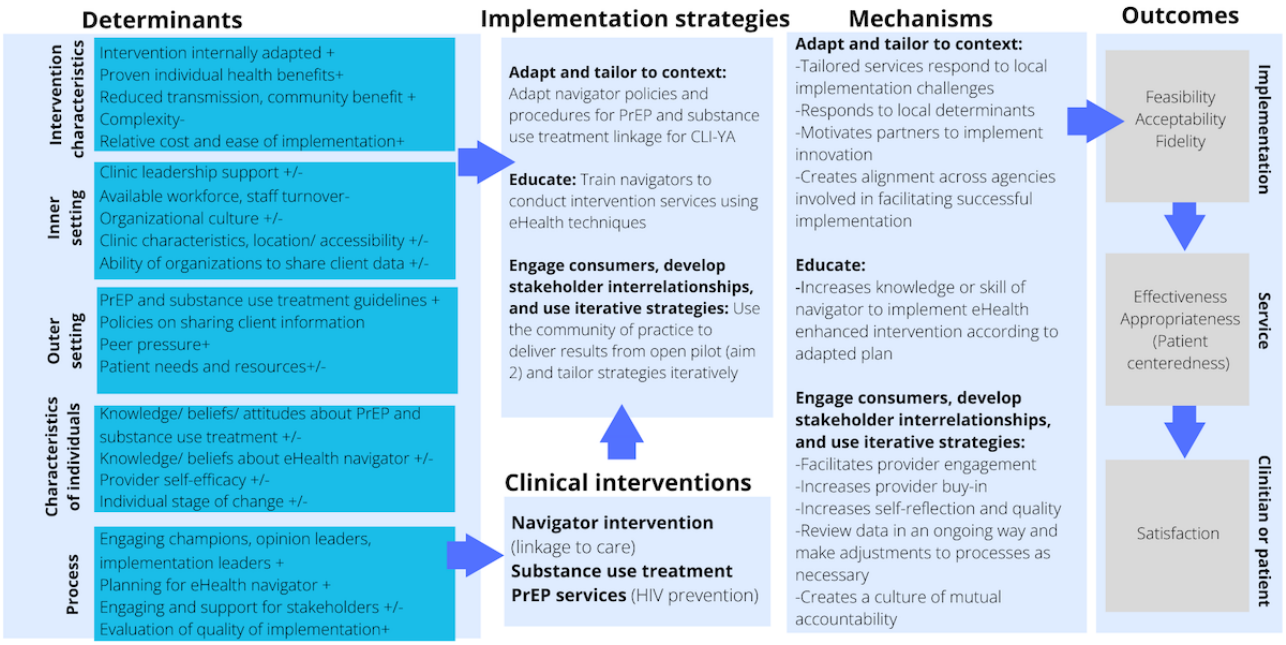

CoP

A CoP, originally conceptualized by anthropologists Lave and Wenger [43], is a community with a shared domain of interest or knowledge that provides support, resources, strategies, and best practices related to the shared domain. Our CoP will meet regularly throughout the intervention and be comprised of individuals from the public health and social service sectors with knowledge of substance use treatment and HIV prevention in CL settings, navigators with previous experience working with CLI-YAs, and YAs with a history of CLI. The CoP will be community experts who will participate in and support all 3 aims of the study including reviewing data collection tools and sampling frames, examining results from each aim, providing guidance on navigation structure and content, codeveloping the adaptation of the Chorus-supported navigation intervention in real time, and guiding research dissemination.

Aim 1: Development Phase

Participants

We present eligibility criteria by separate participant population. CLI-YAs (ages 18-29 years; n=24) will be eligible if they self-report recent CLI (past year); self-identify as HIV negative; endorse behaviors in the past 6 months indicating consideration of PrEP per the Center for Disease Control and Prevention's risk indices [44]; meet the Tobacco, Alcohol, Prescription medication, and other Substance use Tools' criteria for identifying the Diagnostic and Statistical Manual of Mental Disorders SUD (ie, ≥2 for tobacco, alcohol, and marijuana, and ≥1 for other substances) [45]; and are conversant in English. Exclusion criteria include being on PrEP, cognitive delays that would interfere with consent or participation, or inability to provide contact information for ≥2 locator individuals. CL system partners (n=2) will be in probation administration or frontline staff (eg, probation officers). Medical or public health system partners (n=2) will be involved in substance use treatment delivery and PrEP participant care in a setting where CLI participants are referred and will include individuals who have had experience navigating CLI to health services.

Recruitment

CLI-YAs will be recruited for participation in focus groups. To recruit focus groups, study staff are partnering with community-based carceral settings and community-based organizations serving CLI-YAs. Study staff will approach YAs for participation when they (1) come to meetings with their probation officers or (2) access services at community-based agencies serving CLI-YAs.

System partners will be recruited for individual interviews. Recruitment will be conducted using purposive sampling of community partners via email and phone outreach. We will identify initial contacts who work in CL and public health or health care spaces relevant to the study and use snowball sampling to include additional unknown system partners.

Data Collection

Overview

Focus groups and interviews will be held at times and locations convenient for participants (eg, for CLI-YAs, around probation visits, work schedules, or on weekends; for system partners, during lunch, or after work). Focus groups will be held via Zoom (Zoom Technologies Inc) or in a private room depending on participant preference and availability, while individual

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interviews will be conducted by phone; both will be audio-recorded. A semistructured focus group and individual interview format will allow participants to respond freely and in an open-ended way [46].

Focus Groups

The research team will conduct 3 separate (75-90 minutes) focus groups with CLI-YAs (n=24). Focus groups will be informed by 2 domains of the CFIR relevant to CLI-YAs: characteristics of the intervention and individuals involved in the intervention. Sample content areas will assess the (1) knowledge about navigation as an effective approach to substance use treatment and HIV prevention service linkage, (2) perceptions of relevance of *NAV* content and gap areas, (3) strategies to support the likelihood of engaging with a navigator throughout the intervention period, and (4) attitudes toward and capabilities of using eHealth intervention enhancements of the CLI-YAs.

Interviews

As with the focus groups, individual interviews will be guided by several domains from the CFIR (eg, inner setting, intervention characteristics, and implementation process). Sample interview topics include (1) how a navigation intervention could be adopted, delivered, and sustained within the probation system; (2) perceptions of what YAs do or do not like to hear from them and what they might or might not like to have the navigator do on the topics of substance use, HIV risk, PrEP eligibility, and linkage; (3) identify intervention practices that might facilitate information sharing within and across probation and medical system while respecting participant privacy and confidentiality; and (4) areas of training relevant for navigators. At the end of the focus groups and individual interviews, study staff will administer a brief questionnaire to assess the sociodemographic characteristics of the sample.

Data Management and Analysis

We will conduct a content analysis, guided by CFIR domains, of notes collected as part of the CoP meetings occurring during this aim, focus groups, and individual interviews. Executive summaries, which provide data quickly, and evidence of whether theme redundancy is achieved, will be written within 48 hours of data collection. Digital recordings of all qualitative data will be transcribed verbatim. Following transcription and the completion of the executive summaries, data will be analyzed according to Inductive Thematic Analysis [47]. Inductive Thematic Analysis is often used to find solutions to real-world problems and provide program recommendations [48]. An initial codebook will be developed based on the focus group and individual interview guides and transcripts. To improve reliability and ensure adequate intercoder agreement, members of the research team will compare coding patterns, and the codebook will be refined until consensus is reached. Study team staff will generate memos to highlight connections between codes and subcodes. The team will meet weekly to discuss data as they are being collected and to come to a consensus on themes. To identify unique developmental, gender, and cultural perspectives, we will also examine data by race, ethnicity, sexual orientation, gender identity, and age or development (18-25 vs 26-29 years). NVivo (QSR International) will be used to facilitate analyses.

Outcomes

The primary outcome of aim 1's formative work is the adaptation of the existing navigator model (NAV) and the codevelopment of the proposed technology for eHealth enhancement. Both will be informed by the CoP and findings from focus groups with CLI-YAs and individual interviews with system partners. Both adaptation of the existing model and navigator training will be completed prior to the open pilot in aim 2.

Aim 2: Open Pilot Phase

Participants

To refine and test the adapted eHealth-enhanced intervention for CLI-YA, we will pilot the intervention with CLI-YAs (n=10). Final eligibility criteria for aims 2 and 3 will be determined from insights gained through the implementation and data collection of aim 1.

Recruitment

To recruit participants, study staff will be stationed in probation offices and community-based organizations working with individuals involved in the carceral system and will approach individuals to ask if they are interested in participating in the study screening. After consent, the study staff will refer participants to the navigator who will make contact within 24 hours.

Pilot Intervention Navigation Protocol

The navigation process will be informed by evidence-based practices from NAV, including harm reduction, peer navigation, motivational interviewing, and prevention care management to navigate reentry back into the community (eg, referrals for mental health treatment, substance use treatment, and social services) [20]. Navigation processes will be informed by 2 cascade frameworks: the *PrEP Continuum of Care* model [49] and the *JuvenileJusticeBehavioralHealth ServicesCascade* [50]. The PrEP continuum emphasizes identifying individuals at risk for HIV acquisition, increasing awareness of and willingness to take PrEP, ensuring linkage and access to PrEP, and adherence to PrEP medications. The *Juvenile Justice Behavioral Health Services Cascade* [50] was developed to move CLI youth from substance use screening and identification in CL settings to community-based treatment initiation and engagement; this cascade will be adapted to reflect processes specific to YAs.

Navigators will act as role models who can steer participants through the upstream steps of these cascades from screening to linkage with an exploratory look at engagement or initiation, adherence (PrEP specific), and continuing care (substance use treatment) or persistence (PrEP specific). We will test a 30-day intervention period (Textbox 1 for sample navigator visits, adapted from *NAV*). The first session (~75 minutes) will occur within 5 days of referral. In line with the *NAV* protocol, the navigator will initiate contact with the participant ≥3 times per week after the first session (the number of contacts may be higher, depending on the participant's needs and desires) [20]. Additional contacts could be made throughout the 30-day period in-person or with support via Chorus (eg, SMS text messages). Visits can occur via Zoom, telephonically, or in person based

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on the participant's preferences. To maximize program retention, each navigation session will begin by updating the participant's contact information. If detention interrupts intervention delivery, we will "reset," where the participant left off to complete 30 days of exposure. Intervention "graduation" will be acknowledged and included in each participant's action plan (eg, certificate of completion).

Textbox 1. Sample navigator session content for a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA.

Session 1: Program orientation, relationship building, and needs assessment (~75 minutes)

- The navigator will build rapport by introducing themselves, their role, and the program. The navigator will identify significant contacts, and complete study documentation (eg, release of information forms). Finally, the navigator will conduct a comprehensive needs assessment of sexual health and substance use to develop an individual risk reduction plan. Relevant community resources will be presented to the participant.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 2: Substance use education and treatment cascade (~60 minutes)

- Provide psychosocial education on substance use (tailored to the client's behaviors and needs identified in session 1), provide participants with information on how patterns of substance use can affect their health, social, and legal outcomes and the Juvenile Justice Behavioral Health Services Cascade. The navigator will revisit the risk reduction plan (session l) and tailor it to any changes in the participant's life. Participants will be referred to local substance use treatment.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 3: HIV and Pre-exposure Prophylaxis knowledge and care cascade (~60 minutes)

- Provide psychosocial education on sexual health (tailored to the client's behaviors and needs identified in session 1) and can shape an individual's risk of sexually transmitted infections and HIV. Provide basic HIV (eg, transmission) and pre-exposure prophylaxis information, and outline the pre-exposure prophylaxis Care Continuum. The navigator will revisit the risk reduction plan (session 1) and tailor to any changes in the participant's life. Participants will be referred to local pre-exposure prophylaxis–related services.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 4. Substance use and Pre-exposure Prophylaxis care appointment scheduling and goal setting (~60 minutes)

- Provide follow-up information on where and how to access substance use and pre-exposure prophylaxis–related services. Develop a plan for substance use and pre-exposure prophylaxis linkage and maintenance to include planning for transportation to health care services, keeping appointment dates, obtaining medication (pre-exposure prophylaxis), formulating a medication schedule, and identifying motivation for appointment attendance and pre-exposure prophylaxis adherence.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Follow-up contacts (~30 minutes)

- Maintain regular contact between the navigator and the participant, provide guidance and support for goal setting, and ongoing emotional and psychosocial support.
- eHealth approaches identified in aim 1 (eg, SMS text messages and telehealth) will be incorporated to support follow-up contacts.

Navigator Training

The Navigator will receive a minimum of 7 days of training focused on relational service provisions (ie, emotional and psychosocial support), logistical service provisions (ie, assistance to overcome task-oriented barriers like scheduling and finding transportation to appointments), technology training, and population-specific training (eg, carceral system processes and harms perpetuated by the carceral system) [51]. Aim 1 system partner interviews will inform additional areas of training relevant to implementing a peer-led model, as well as preferred navigator characteristics (ie, peer navigators will share an age range and at least 1 intersecting identity or experience such as CLI, PrEP use, or substance use treatment with participants).

Intervention Fidelity

During the open pilot, navigators will audio record and complete a checklist documenting the delivery of session material [52]. Navigators will engage in weekly supervision with the principal investigator, and the principal investigator will periodically audit records and conduct field visits to observe sessions (required activities will be rated for completeness using a 4-point scale ranging from 0 "not at all" to 3 "completely").

Exit Interviews

The research team will collect qualitative feedback on the open pilot regarding intervention content, structure, and delivery (type of contact, ie, in-person or over the phone, eHealth [Chorus] enhancement acceptability, and a number of contacts) via individual interviews with CLI-YAs. We will also obtain

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feedback from system partners regarding intervention recruitment, referral, delivery, and implementation. The navigator will be actively involved in the intervention pilot testing as well as in making further intervention manual revisions according to their lived experience of navigation delivery. Exit interview data will be analyzed using rapid qualitative analysis methods to reduce the time completing analysis to ensure timely results for use in aim 3; rapid analysis has been shown to have considerable overlapping findings with traditional qualitative analytic approaches [53,54].

Open Pilot Outcomes

In addition to completing a 7-day minimum navigator training, the open pilot's primary outcome is qualitative feedback to assess appropriateness and satisfaction. The results will be used to refine the intervention for pilot testing in aim 3.

Aim 3: Pilot Randomized Controlled Trial Phase

Participants

To assess the feasibility, acceptability, and impact of the adapted eHealth-enhanced intervention for CLI-YAs, we will test the intervention in a randomized pilot trial with CLI-YAs (n=75).

Recruitment and Randomization

Recruitment procedures will be informed by aim 2 results. Participants will be randomized either to the intervention group (n=50) or the standard of care (n=25) using a 2:1 randomization allocation scheme (Figure 2). Figure 3 provides a schematic of our study processes. Each participant will complete a baseline assessment immediately following the consent process. At the end of the baseline assessment, participants will be randomized to the intervention or control condition using a computerized algorithm programmed into REDCap (Research Electronic Data Capture; Vanderbilt University). Randomization will be blocked to avoid "runs" of assignment to the same.

Figure 2. Randomization protocol for aim 3, a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA. PrEP: pre-exposure prophylaxis.

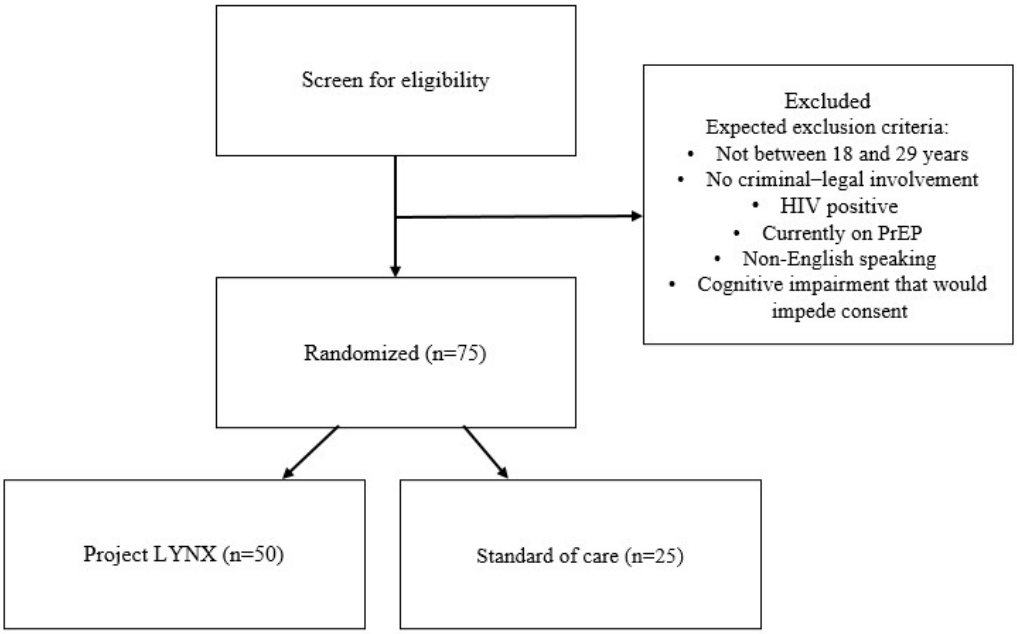

Standard of Care

The standard of care is a referral to substance use treatment and HIV prevention services from an individual's case worker.

Data Collection

The baseline assessment will occur immediately following participant consent, prior to randomization, and follow-up assessments will occur at 1 month and 3 months (Figure 3). Data will be collected via face-to-face one-on-one interviews in private locations to ensure confidentiality. If face-to-face interviews are not possible, a participant will be given the option of completing the assessment via a secure web-based survey link. Regardless of the method of interview administration, REDCap will be used to collect data (ie, in person on tablets or via a secure REDCap survey sent via email). If completing the assessment via a secure link, specific instructions will be provided to the participant to inform them about how to keep their data private.

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Figure 3. Recruitment, randomization, and intervention practices for aim 3, a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA. PrEP: pre-exposure prophylaxis.

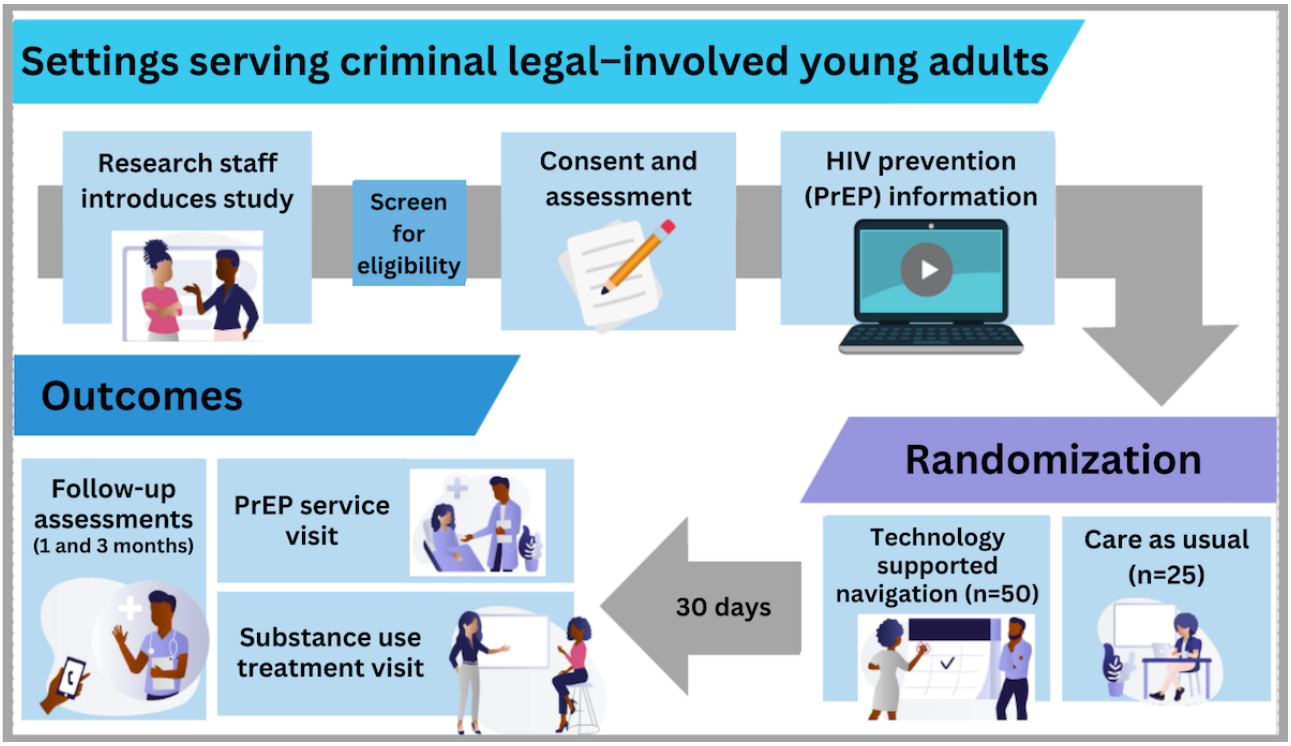

Pilot Trial Outcomes

Primary outcomes are linkage to substance use treatment and PrEP services. Because PrEP and substance use treatment health service linkage are a process and not a 1-time event, we will also explore prelinkage (eg, navigator satisfaction) and downstream outcomes (eg, PrEP initiation, adherence, and substance use treatment continuing of care) in an exploratory fashion [55]. The navigator will track these outcomes, but the primary outcomes of (1) PrEP linkage will be attendance at a PrEP services appointment, verified by medical records and (2) substance use treatment linkage will be attendance at a substance use treatment appointment, verified by the navigator and medical provider collateral (if the participant agrees). Other exploratory outcomes include time to health service linkage (substance use and PrEP) and data on HIV testing at the PrEP linkage appointment (uptake, result). Participants will be asked whether and for how long they have experienced hospitalization, residential treatment, and detention since the intervention to account for any system barriers to linkage. We will also assess preferred methods for communicating with the navigator as well as participant satisfaction with the intervention and navigator services. Table 1 provides additional detail on outcomes and correlates.

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Table 1. Description and schedule of outcomes from a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA.

Primary outcomes	Baseline	30 days	90 days
PrEP[a] linkage: medical record		✓	✓
Substance use treatment linkage: self-report, medical provider collateral if the participant agrees		✓	✓
Secondary outcomes			
Navigator satisfaction: NAVSAT Pt 1		✓	
Client intervention satisfaction: Study Participant Feedback Questionnaire	✓	✓	✓
PrEP care continuum (accepted, initiated, and adhered): navigator report, medical record, and self-report		✓	✓
Substance use treatment continuum (accepted, initiated, and adhered): navigator report, medical record, and self-report		✓	✓
Linkage to other services: self-report and Navigator report		✓	✓
Sociodemographic, psychosocial, and behavioral correlates			
Demographic information (age in years, race or ethnicity, legal history, etc)	✓		✓
Health care use	✓		✓
Medical mistrust: Health Care System Distrust Scale	✓		✓
HIV knowledge or attitudes or risk: HIV-related knowledge scale, HIV-related attitudes scale, HIV stigma scale	✓		✓
PrEP knowledge or attitudes: willingness, intentions to use, barriers, stigma or conspiracy beliefs	✓		✓
Substance use: Alcohol use Disorders Identification Test, Texas Christian University Drug Screen V, Internalized Stigma of Substance Abuse	✓		✓
Psychiatric symptoms: Global Appraisal of Individual Needs-Short Screener	✓		✓

[a]PrEP: pre-exposure prophylaxis.

Data Management and Analysis

REDCap will facilitate routine data checking and exportation of data for analysis. Analyses will be conducted using SAS (version 9.4; SAS Institute). Preliminary analyses will include the examination of descriptive statistics, distributions, and internal consistency reliability of scaled measures. Logistic regression will be used to examine the relationship between the condition and the primary outcomes (services linkage, ie, PrEP, substance use treatment), and all other dichotomous outcomes (eg, acceptance of PrEP and substance use treatment referral). Dependent variables in initial analyses will be summary dichotomous indicators based on both month 1 and 3 assessments, reflecting whether the outcome ever occurred. Subsequent analyses will separately examine whether outcomes occurred by month 1 and by month 3. Generalized linear models will be used to examine variously distributed continuous outcomes (navigator contacts, time-to-service linkage, and satisfaction). Exploratory analyses will build on these models to preliminarily examine the impact of potential moderating variables including sociodemographic characteristics, HIV risk behaviors and perceptions, PrEP-related knowledge and attitudes, substance use treatment behaviors, psychiatric symptoms, social support, and substance use on primary and secondary outcomes.

Exit Interviews

We will conduct exit interviews with a subsample of intervention arm participants (n=10), the navigator (n=1), and partners from participating systems (n=4). Interviews will assess intervention acceptability and suggestions for improvement. To recruit for qualitative exit interviews, a member of the study team will contact intervention participants to invite them to a phone interview (~30 minutes). To ensure a range of responses, we will sample for (1) participants who connect or did not connect to the navigator and who linked or did not link to PrEP and substance use treatment services and (2) variation in characteristics that may impact the intervention (eg, psychiatric symptoms). We will seek to understand reasons why the intervention was or was not successful for a particular participant (via participant and navigator report). To analyze exit interview data, we will mirror aim 2's rapid qualitative analysis processes.

Ethical Considerations

Overview

This study was approved by the University of Pittsburgh internal review board (reference 22020053). As the intervention is refined, changes to the protocol will be submitted to the internal review board for further approval. Additional protections for participants are provided via a Certificate of Confidentiality through the National Institute of Health. This certificate allows the researchers to legally refuse to disclose information that may identify participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. To ensure confidentiality, all data will be deidentified and participants will be assigned a unique participant ID. Participant contact information will be stored

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separately from any data that have been collected (eg, screening surveys, transcripts, and assessments).

Aim 1: Development Phase

CLI-YA

To determine eligibility, participants will undergo a confidential screening survey with study personnel. Following screening, participants will be compensated US $10 regardless of eligibility status. Eligible participants will undergo a verbal consent process with study personnel prior to participating in focus groups. The consent process will include (1) a review of the information sheet in detail, (2) an explanation of all study procedures in full detail, and (3) an opportunity for the participant to ask questions and have them answered. Potential participants will be asked to paraphrase the information sheet and will be asked basic questions to determine their understanding of key elements of the informed consent. Participants will be compensated US $40 following focus group participation.

System Partners

Prior to participating in interviews, system partners will undergo a verbal consent process that follows the same protocol as the focus group consent process outlined above. Participants will be compensated US $50 following completion of an individual interview.

Aim 2: Pilot Trial Phase

Prior to participation in the pilot trial, CLI-YAs will undergo a 2-step consent process. Potential participants will be given an information sheet and provide verbal informed consent for screening. Next, should individuals be interested in participating and eligible based on their HIV risk assessment and SUD screening, they will provide written informed consent to allow participation in the open pilot navigation intervention and exit interview. Participants will be compensated US $40 for participating in exit interviews.

Aim 3: Assessment Phase

The consent process for aim 3 follows the same 2-step process as outlined above for aim 2. Participants will be compensated US $40 for the baseline assessment, US $20 for the 1-month assessment, US $40 for the 3-month assessment, and US $30 for participating in exit interviews.

Results

The project was funded in September 2022. Internal review board approval was received on March 21, 2022. Data collection for aim 1 began on April 19, 2023, and is ongoing. At the time of publication, 5 system stakeholders and 16 CLI-YAs have been enrolled in aim 1 data collection activities. The first results from early study aims are expected to be published in 2025.

Discussion

Principal Findings

This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a systemically marginalized group of YAs. This emerging area of research has been rapidly amplified in the context of the ongoing coronavirus pandemic, for which empirical study of effective adjunctive technology tools to promote increased substance use and HIV prevention services access is greatly needed. The results will contribute to the development and testing of a future multilevel randomized controlled trial targeting CLI-YAs, CL system partners, and treatment providers.

Gaps in Literature and Comparisons With Prior Work

Previous studies leveraging peer navigation as a mechanism to link CLI individuals to HIV care have proved efficacious [19,20]. Patient navigation interventions led by individuals who share key personal characteristics, circumstances, or qualities with their participants (eg, ethnic background, culture, and membership in a subpopulation [formerly engaged in transactional sex or IDU]) or “peers” are ideal because they have demonstrated efficacy in building trust and reducing stigma and discrimination-related barriers to health care engagement, particularly among vulnerable populations [24,56]. The inclusion of eHealth technology in patient navigation is appealing because it provides a discrete platform for individuals to engage with potentially stigmatizing services (eg, substance use treatment and HIV prevention services). It also has the potential to facilitate frequent, meaningful communication between individuals and their peer navigators. Previous studies have found eHealth-enhanced peer navigation effective in maintaining viral suppression among people living with HIV [21]. However, there has been little research using this framework to link CLI-YAs to HIV prevention and substance use treatment services. This study will fill an important gap in the literature and provide insights that will inform future efforts to improve service linkage for CLI-YAs, a vulnerable and structurally precarious population [57].

Strengths and Limitations

A core tenet of this study is the codevelopment of the eHealth technology and navigation protocol. Including the perspectives of individuals who are a part of the population of focus, in addition to system partners, ensures the intervention will be reflective of the wants and needs of the community it will be serving. The inclusion of system partners and people with lived experience in the CoP is important but comes with challenges due to encounter challenges related to power dynamics between these groups. For example, individuals with lived experience may be hesitant to share their thoughts and opinions when they are in a room of service providers and system partners with whom they might already be familiar. The study team will begin each meeting with an overview of agreements and expectations and moderate the discussion to mitigate issues as they arise; however, we acknowledge the challenge that navigating these relationships might pose.

Additionally, the technology being developed will not be a native app. The benefit of this is that it will be accessible from a mobile device or a computer, which ensures that participants will be able to access the technology whether they have regular access to a mobile device. However, data will not be stored directly on a participant’s personal device, so it will not be accessible without an internet connection. This could be a

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limiting factor for participants who have a phone but do not have regular internet access.

The inclusion of the eHealth portion of the study has the potential to expand access to linkage services for CLI-YAs. This is especially important because CLI-YAs experience structural and institutional obstacles that can hinder their ability to regularly engage in services [57]. However, there is no funding to distribute phones to participants if they do not have them. This may limit the eHealth functionalities available to participants who do not have phones (eg, SMS text messaging) and may make it difficult for them to engage in the intervention in the same way as participants with their personal devices. We will measure where and how participants are engaging with the technology to better examine the impact of technology access.

Conclusions

This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a vulnerable, underserved group of young adults (CLI-YAs) by adapting an evidence-based navigation intervention and incorporating eHealth technology. The need to further this line of research has been rapidly amplified in the context of the COVID-19 pandemic, for which empirical study of effective adjunctive technology tools that can promote access to substance use and HIV prevention services is greatly needed. The results will contribute to the development and testing of a future multilevel randomized controlled trial targeting CLI-YAs, CL system partners, and substance use treatment and PrEP providers.

Acknowledgments

With gratitude, the authors acknowledge the participants in previous studies whose pilot data contributed to this grant being funded. The funding for this study was provided by the National Institute on Drug Abuse (grant R34DA054853; EFD principal investigator).

Data Availability

The data sets generated in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SLC wrote the original draft and contributed to manuscript review and editing, and is assisting with project administration. SS and NM supported the writing of the original draft and contributed to manuscript review and editing, and is assisting with project administration including conducting data collection activities and supporting data analysis, and contributing to intervention refinement JJM, MS, and MTS contributed to project conceptualization and manuscript review and editing. EFD led the conceptualization of the project and the development of the proposed methodology, acquired project funding, supported the writing of the original draft and contributed to manuscript review and editing, and is leading the overall project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review grant documentation from the National Institute on Drug Abuse.
[PDF File (Adobe PDF File), 99 KB - resprot_v13i1e54815_app1.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CL: criminal legal
CLI: criminal legal involved
CLI-YA: criminal legal–involved young adult
CoP: community of practice
NAV: The Navigator Project
PrEP: pre-exposure prophylaxis
SUD: substance use disorder
YA: young adult

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Protocol

The Feasibility of Using the National PulsePoint Cardiopulmonary Resuscitation Responder Network to Facilitate Overdose Education and Naloxone Distribution: Protocol for a Randomized Controlled Trial

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Abstract

Background: The use of naloxone, an opioid antagonist, is a critical component of the US response to fatal opioid-involved overdoses. The importance and utility of naloxone in preventing fatal overdoses have been widely declaimed by medical associations and government officials and are supported by strong research evidence. Still, there are gaps in the current US national strategy because many opioid-involved overdose fatalities have no evidence of naloxone administration. Improving the likelihood that naloxone will be used to prevent fatal overdoses is predicated on facilitating an environment wherein naloxone is available near each overdose and can be accessed by someone who is willing and able to use it. How to accomplish this on a national scale has been unclear. However, there exists a national network of >1 million cardiopulmonary resuscitation (CPR) layperson responders and 4800 emergency responder agencies linked through a mobile phone app called *PulsePoint Respond*. *PulsePoint* responders certify that they are trained to administer CPR and are willing to respond to possible cardiac events in public. When such an event occurs near their mobile phone's location, they receive an alert to respond. These motivated citizens are ideally positioned to carry naloxone and reverse overdoses that occur in public.

Objective: This randomized controlled trial will examine the feasibility of recruiting first responder agencies and layperson CPR responders who already use *PulsePoint* to obtain overdose education and carry naloxone.

Methods: This will be a 3-arm parallel-group randomized controlled trial. We will randomly select 180 first responder agencies from the population of agencies contracting with the PulsePoint Foundation. The 3 study arms will include a standard recruitment arm, a misperception-correction recruitment arm, and a control arm (1:1:1 allocation, with random allocation stratified by zip code designation [rural or nonrural]). We will study agency recruitment and, among the agencies we successfully recruit, responder certification of receiving overdose and naloxone education, carrying naloxone, or both. Hypothesis 1 contrasts agency recruitment success between arms 1 and 2, and hypothesis 2 contrasts the ratios of layperson certification across all 3 arms. The primary analyses will be a logistic regression comparing the recruitment rates among the arms, adjusting for rural or nonrural zip code designation.

Results: This study was reviewed by the Indiana University Institutional Review Board (20218 and 20219). This project was funded beginning September 14, 2023, by the National Institute on Drug Abuse.

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Conclusions: The hypotheses in this study will test whether a specific type of messaging is particularly effective in recruiting agencies and layperson responders. Although we hypothesize that arm 2 will outperform the other arms, our intention is to use the best-performing approach in the next phase of this study if any of our approaches demonstrates feasibility.

Trial Registration: OSF Registries osf.io/egn3z; https://osf.io/egn3z

International Registered Report Identifier (IRRID): PRR1-10.2196/57280

(JMIR Res Protoc 2024;13:e57280) doi:10.2196/57280

KEYWORDS

naloxone; PulsePoint; randomized controlled trial; RCT; first responder; overdose; community engagement; citizen mobilization; opioids; Narcan; mobile phone

Introduction

Background

In 2017, the US Acting Secretary of Health and Human Services formally declared that the opioid overdose crisis in the United States is a public health emergency [1]. Since that time, the prevalence of morbidity and mortality related to opioid overdoses has gotten substantively worse [2]. Beyond the prima facie impact of tens of thousands of overdose-involved deaths annually, the secondary impacts of the crisis strain the health care system across numerous axes; for example, even in 2013, when annual fatal prescription overdose incidence was "only" 16,235 persons, scientists at the Centers for Disease Control and Prevention found that these fatal cases accrued US $21.5 billion in costs [3]. The magnitude of the emergency is such that even in the midst of major global news on multiple fronts, news stories about fatal opioid overdoses are ubiquitous, often with calls from family members to build awareness and seek solutions [4]. Overdose and harm reduction strategies (including naloxone administration) have also received direct attention from the federal government, including as part of the 2023 State of the Union address [5].

Naloxone Is a Critical Part of the US Overdose Emergency Response

Naloxone (including Narcan, Kloxxado, Evzio, Zimhi, and other formulations) is an opioid antagonist that can be used to reverse an opioid overdose and restore breathing, converting a potentially fatal overdose into a nonfatal overdose [6,7]. Even before the formal declaration of a public health emergency around opioids, the Department of Health and Human Services included expanded use and distribution of naloxone in its 3 priority areas to address the overdose epidemic [8]. The importance and utility of naloxone have been widely declaimed, including by the American Medical Association ("should be available almost everywhere") [9], the American Society of Addiction Medicine ("remarkably effective, inexpensive and safe") [10], and the US Surgeon General ("Be Prepared. Get Naloxone. Save a Life.") [11]. Such statements are predicated on strong evidence of, and arguments for, naloxone's effectiveness and utility in reducing fatal opioid-involved overdoses [12-16].

Barriers Exist That Inhibit Proliferation of Expedient and Effective Overdose Responses

Data from 2019 indicate that in the majority of fatal opioid-involved overdoses, there is no evidence of naloxone administration [17]. Given the current evidence for the effectiveness of overdose education and naloxone distribution (OEND) programs [12-16], the national expansion of such programs [18,19], and simultaneous high rates of fatal opioid-involved overdoses without naloxone administration [17], we might reasonably conclude that there are one or more gaps in the current US national approach to opioid-involved overdose reversal.

For many years, the lack of availability of naloxone has been seen as a primary barrier. Most states have passed legislation intended to increase layperson access to naloxone and provide limited legal immunity to those who administer naloxone to persons experiencing an opioid-related overdose [10]. By 2021, a total of 47 states and Washington, District of Columbia, had enacted both Good Samaritan and naloxone access laws [20], and programs to facilitate distribution of naloxone to laypersons have steadily become more common [18], especially since 2010 [19]. Unfortunately, a 2018 study in Indiana and Arizona found that such policies did not always sufficiently facilitate layperson access [21]. The availability of naloxone *at cost* will likely increase in the United States in the next several years given a recent 19-0 US Food and Drug Administration advisory committee vote in favor of granting some naloxone products over-the-counter (OTC) status [22]. However, national data from a similar OTC change in Australia suggest that people may not automatically begin purchasing naloxone in response [23] (eg, other factors such as willingness may be salient).

More ubiquity in carrying and being willing to use naloxone is critical because, as described by Kim et al [24], the efficacy of naloxone is fundamentally time dependent. Brain injury from hypoxia is more likely the longer oxygen deprivation occurs [25]. In some cases, overdose death from heroin can be extremely rapid [26], and death typically occurs within 1 to 3 hours [27]. Overdoses from fentanyl and fentanyl analogs often present differently than other opioid overdoses and may be even more likely to rapidly result in fatality [28]. Thus, it is important that naloxone is *present at or near the scene* and *used as quickly as possible.* Unfortunately, despite a surge in OEND programs in the United States, relatively few people carry and are willing to use naloxone [29].

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Misperceptions About Naloxone and Overdose May Inhibit OEND Programs

Evidence suggests that misperceptions about overdose and naloxone, as well as stigmatizing beliefs about people who use drugs, may affect both layperson and first responder willingness and interest in carrying and using naloxone [29-33]; for example, first responders may be ambivalent about "providing naloxone to those they deem undeserving" [34], and a review found that stigmatizing attitudes among first responders may reduce the likelihood of bystander response [35]. Some first responders have noted that laypersons in their communities may fear "real and perceived cultural opposition" to harm reduction strategies [36]. Such reticence and stigma may even persist after OEND training [29,37] and have been described as fundamentally hindering the US response to the opioid overdose crisis [38].

To the best of our knowledge, the prevalence of specific belief statements about naloxone and overdose that do not align with current scientific evidence had not been explored in depth until 2022 [39]. We conducted a study (using the Prolific platform) consisting of 702 respondents who were representative of the US adult population across race, ethnicity, gender, and age. Several misperceptions around naloxone and overdose were fairly common in our sample, and there was a surprisingly large minority of participants (approximately one-seventh of the sample) who believed that users could "get high on naloxone" [39]. We also observed potential evidence of cognitive dissonance about OEND; specifically, large latent profiles simultaneously believed, in the framed context of naloxone reversing an opioid overdose, that "if trained and provided with naloxone, bystanders can effectively prevent overdoses in the community" and "opioid users will use more opioids if they know they have access to naloxone" [39].

Our Proposed Study to Mitigate Barriers to Effective Overdose Response

Improving the likelihood that naloxone will be used to prevent fatal overdose is logically predicated on facilitating an environment wherein naloxone is available near each overdose and can be accessed by someone who is willing and able to use it. Conceptually, in a given community, the likelihood of an opioid overdose in the given community being reversed with naloxone is proportional to the likelihood that a trained person with access to naloxone is nearby, willing to administer it, and aware of the need. As noted, current approaches to OEND have not succeeded in reaching the threshold of sufficient coverage. With too few trained persons and sparse coverage, overdose survivability can be subject to the whims of chance, something implicitly recognized even in how lay news sometimes covers overdose reversals ("finds herself in the right place at the right time" [40]).

Recent, innovative pilot work demonstrated that a smartphone app (*UnityPhilly*) could support overdose reversal in a small group of volunteers [41]. Other innovative projects include multifaceted technology-based efforts by Brave Technology Co-Op [42]. In these cases, building to scale will take substantial time and investment. However, it may also be possible to integrate OEND within widespread but existing systems that perform other but similar services. Our particular interest is in a large, highly engaged system for cardiopulmonary resuscitation (CPR) that already exists nationally (*PulsePoint*), with >1,085,000 active monthly layperson users across approximately 4800 communities overseen by >755 agencies [43]. These individuals respond to unconscious and unresponsive persons within a prespecified radius of their smartphone based on alerts generated by local first responder agencies. While *PulsePoint* does not specifically generate alerts for an opioid overdose, the designation *unconscious and unresponsive* can refer to individuals possibly in need of CPR or those who may need overdose reversal; therefore, these laypersons are likely already responding to possible overdoses. However, they are neither systematically being encouraged to receive training around overdose and naloxone nor being reminded to carry naloxone.

We believe that the *PulsePoint* network may be an effective means of achieving widespread OEND coverage in the United States. With this preliminary study, our goal is to better understand whether and how it is feasible to recruit first responder organizations and *PulsePoint*-connected laypersons to broaden the scope of their voluntary service to include opioid overdose reversal.

Objectives

Overview

We will conduct a feasibility trial to assess whether, in a random sample of 180 agencies where *PulsePoint* is already active, revised procedures (hereinafter *PulsePoint-OD*) to facilitate OEND can successfully recruit first responder agencies and layperson responders. For this study, *agency* refers to a single implementation site where *PulsePoint* is active and that is bound by the service area or jurisdiction of the first responder agency collaborating with *PulsePoint* (we provide more detailed information about agencies in the *Methods* section).

Using a parallel-group randomized controlled trial design, we will randomize 180 agencies using a 1:1:1 allocation ratio within strata to 1 of 3 arms: arm 1 (*PulsePoint-OD*, which will include the recruitment of coordinating community first responder agencies; targeted recruitment, eg, push messages, aimed toward 100% of the active *PulsePoint* users in these communities; ongoing solicitation for training of these users; and naloxone facilitation), arm 2 (same as arm 1 but with stigma-focused misinformation-debunking messages embedded), or arm 3 (a control condition).

Hypotheses

We will test the following hypotheses:

- H1: more first responder agencies will be successfully recruited by arm 2 than by arm 1.
- H2: more layperson responders will report engaging with OEND programming in arm 2 than in arms 1 or 3 and in arm 1 than in arm 3.

As an exploratory follow-up, we will conduct incentivized qualitative follow-up interviews with agencies to better understand barriers to participation and how to improve uptake feasibility.

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Methods

As the participant types for H1 and H2 are different, we provide separate methodologies for each hypothesis. A conceptual diagram of the study and hypotheses is provided in Figure 1.

Figure 1. Conceptual diagram of the study and hypotheses. OEND: overdose education and naloxone distribution.

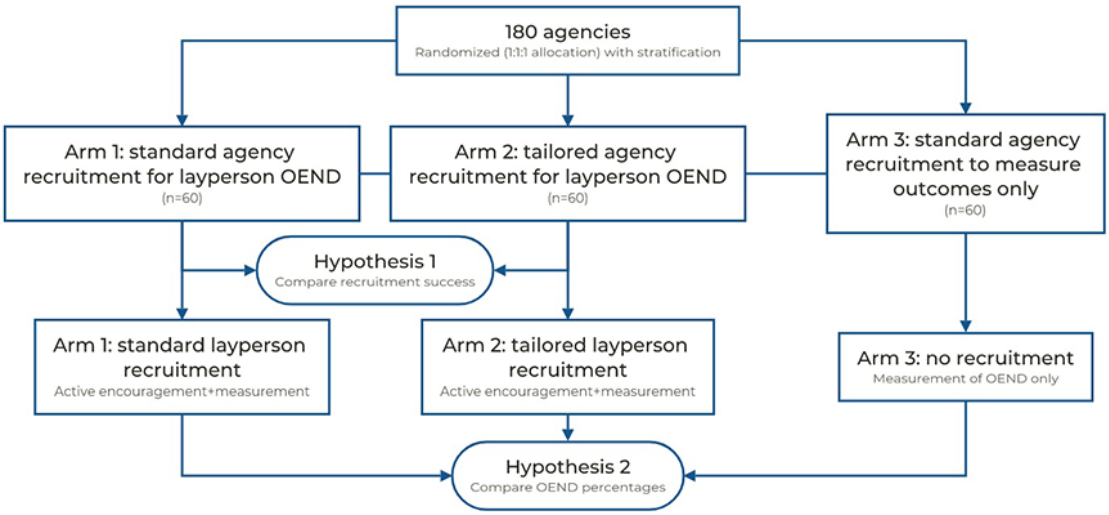

H1: First Responder Agencies

Parameters

The following parameters describe the interrelationships between communities and agencies for this study:

- The PulsePoint Foundation reports that approximately 4800 communities currently use the *PulsePoint* app.
- Community participation and the use of the *PulsePoint* app are supported by agency contract holders; there are >755 such contracts in place.
- A contract-holding agency can serve multiple communities (eg, a county 911 office can offer *PulsePoint* to 9 different communities in the county, such as townships). An agency can also serve a single community (eg, a city fire department can offer *PulsePoint* to that city only).
- Any number of *additional* first responder agencies (eg, fire or police departments, emergency medical services, 911 call centers, or related entities) can contribute to a community or cluster of communities covered by a single *PulsePoint* contract, but these agencies are not contract holders.

When *PulsePoint* is introduced to a community for layperson use, the PulsePoint Foundation neither directly recruits nor interfaces with individual lay responders. Instead, the contracted first responder agencies conduct local recruitment and have the ability to send *push messages* (app-driven notices and messages) to users. Therefore, to integrate OEND into the *PulsePoint* network (eg, *PulsePoint-OD*) and for our study team to directly contact the subset of active users within each study community, it is necessary that the contract-holding first responder agencies in each community agree to participate. This first phase of the overall study (and the first hypothesis) pertains to agency-level recruitment.

Participants, Eligibility, and Assignment

We will use the complete list of *PulsePoint* contracting agencies as constituted approximately 3 months before the study start date (to ensure sufficient experience with the *PulsePoint* program) as the population from which to draw a random sample. At present, this list includes >755 agencies, but the actual number will vary depending on the final start date and changes in *PulsePoint* membership.

All active agencies on the final list will be eligible for sampling and randomization, with 2 exceptions. First, an agency will be excluded (and a replacement resampled and assigned to the same study arm) if further communication identifies that it is not actually a *PulsePoint* subscriber. Second, we will exclude agencies a priori or a posteriori if we learn of a similar project being conducted, or having been conducted, with *PulsePoint* with the agency. Random sampling of communities will be accomplished by having a study statistician generate a random sequence of numbers, including all values between *1* and *X*, where *X* is the total number of eligible agencies. These numbers will be directly overlaid on the list of agencies, and agencies with the lowest 180 numbers will be selected. These numbers will also be carried forward to indicate the random arm assignment.

Agencies will be randomly assigned to a study arm using stratified allocation, with a 1:1:1 allocation ratio. Specifically, one-third of the rural agencies will be randomly assigned to each study arm, and separately, one-third of the nonrural agencies will be randomly assigned to each study arm. We will determine rural status using the definition from the US Office of Management and Budget (zip codes within metropolitan areas with an urban core of ≥50,000 people are not rural, and all other areas are rural [44]). In cases where agencies hold *PulsePoint* contracts that cover both rural and nonrural areas, we will assign a status based on the location of the numeric

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majority of the population in the area. Arm assignment will be according to sequential numbers (from the simple random sample; therefore, this allocation approach is also by definition random) within each stratum (eg, if there are 60 rural agencies, the 20 rural agencies with the lowest random numbers will be assigned to arm 1). This procedure will ensure allocation concealment from the rest of the investigative team until the moment of assignment. Agencies will not be informed that they have been assigned to a specific trial arm; they will simply be contacted using the procedures developed for that arm. Thus, this can be considered a blinded trial.

Establishing Correspondence With Local PulsePoint Decision Makers

Although the PulsePoint Foundation will provide us with a list of participating agencies, its database does not include raw contact details (eg, telephone number and email address), and even these details may not link our study team with the people within the agency who manage the *PulsePoint* system. On the basis of discussions with the PulsePoint Foundation, the following examples describe cases that have occurred in the past:

- The point of contact on the agency list may be the accounting or billing representative for the agency, not the person who manages the program, especially among long-term subscribers.
- The decision makers for the agency may be different now than when the subscription to *PulsePoint* was purchased.

We will need to locate contact information for agencies and verify that the contact details link us with the person who manages the *PulsePoint* subscription, and if not, identify who in the agency does so and how to contact them. In other words, while our trial is intended to study recruitment strategies, we must first ensure that we can access the appropriate individuals at an agency. Once we have identified these points of contact, we can begin recruitment at the agency.

Intervention (Recruitment) Arm 1

Overview

The minimum goal of agency recruitment is to reach a memorandum of understanding (MOU) with agencies in which they agree to encourage their layperson *PulsePoint* responders to attend OEND programming and to carry naloxone (arms 1 and 2) and to indicate whether they have done so (arms 1, 2, and 3; Figure 2). The agencies will be asked to accomplish this using push messages prepared by our team and sent out by the agencies; the specific nature of these agency activities is outlined in the *H2: Layperson Responders* section.

Figure 2. Differing agency recruitment procedures for the PulsePoint-OD study by study arm.

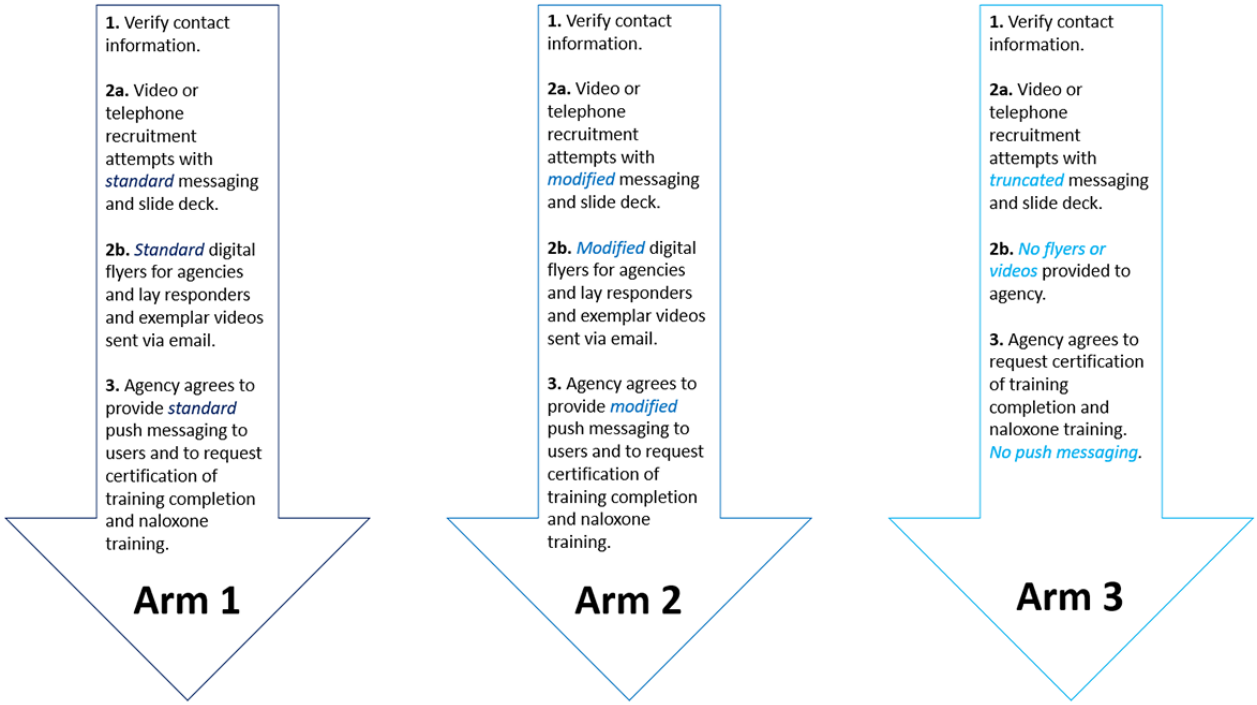

Development

Our agency recruitment materials will be developed during the first phase of the study and provided in full when the study results are published. Oversight and review of marketing development will be provided by members of the study team and marketing consultants external to the study team. Review of all marketing materials will be granted to the PulsePoint Foundation (a not-for-profit 501[c][3] organization) to ensure consistency with the organization's branding. As a result of the development timeline, the exact phrases and examples used to illustrate components of the recruitment processes may change between the submission of this paper and the launch of the study.

Approaches

To be replicable at scale, recruitment will be conducted using a combination of video or telephone correspondence (preferably Zoom [Zoom Video Communications, Inc], but telephone where necessary), web links, and emails containing tangible materials. A full recruitment attempt with fidelity to our model will consist

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of providing emailed materials and web links and attempting between 6 and 10 telephone contacts over approximately 6 months, based on best practice telephone recommendations from the American Association for Public Opinion Research [45]. Recruitment efforts will stop in the event that (1) an agency agrees to participate in the project, (2) an agency asks not to be contacted about the project again, (3) the aforementioned recruitment approaches clearly seem unlikely to yield a change in disposition, or (4) the recruitment timeline ends without the agency making a decision.

Materials

Members of our project staff will develop a short visual presentation to be used as a guideline for videoconference recruitment, along with a parallel set of core written or verbal statements reflecting the content of the presentation in cases where only telephone calls are possible. Drawing lessons from our previous successful agency and organization recruitment experiences [46-49], both the presentation and written statements will cover a limited list of important concepts that need to be imparted (eg, "Participating in this project will require very little time from your agency – we are only asking you to send out one push message each month."). While moving through these concepts, we will allow conversation to flow freely (eg, semistructured messaging) and also use live documentation of key concepts to ensure message fidelity.

The tangible documentation will consist of digital flyers based on the open-source marketing tools developed by the PulsePoint Foundation for general community agency recruitment, including the use of similar graphical assets and fonts. However, flyers will be differentiated sufficiently from the default *PulsePoint* flyers to make it clear that the organization itself is not conducting this project (eg, we will not use the *PulsePoint* logo). For reference, *PulsePoint*-branded recruitment flyers can be viewed by clicking on the hyperlink provided in the associated reference [50]. As community agencies have already committed to offering standard *PulsePoint* services, we expect that distributing these modified documents to agencies will be a high-leverage recruitment approach. Key messaging will be drawn from local demonstration projects by the study team (eg, "Be a Lifesaver" and "Citizen Opioid Responders") [51] as well as general marketing and recruitment principles.

As supplemental recruitment content, exemplar videos will be drawn from work produced by the Dearborn County Health Department in Lawrenceburg, Indiana, in collaboration with the study authors to create awareness of this type of initiative and will be included as web links to YouTube versions of the videos [51].

After Recruitment

When communities agree to participate, they will be asked to sign an MOU regarding their participation and to respond to a small set of readiness and implementation items, such as whether the organization is already involved in naloxone distribution and whether there are local laws pertaining to opioid overdose reversal. This information will be used to locally tailor piped text into messages used for H2 (layperson recruitment).

Intervention (Recruitment) Arm 2

The recruitment procedures for arm 2 will be similar to those outlined for arm 1. The primary difference will be that the messaging in arm 2 will proactively address several misperceptions or stigmatizing ideas about overdose and naloxone that our recent research has suggested may be prevalent [39]. In particular, content in the fact sheets and scripts for recruitment used in arm 2 will address and preempt the following scientifically unsupported ideas (potentially among others):

- "Naloxone causes risk compensation or presents a moral hazard": it is fairly well established that OEND is not associated with increased opioid use [52-55], nor is it associated with reduced risk perceptions for heroin use [56].
- "Repeated overdoses are inevitable and people who experience nonfatal overdoses will die of an overdose in the near future": while individuals who nonfatally overdose are at meaningfully increased risk, especially if they do not matriculate into a cascade of care, the substantive majority will not overdose again in the near future, and even fewer will die of a fatal overdose in the near future [57-60].
- "Individuals can get high from naloxone": while this is not possible [6], our study found that 14.2% of our nationally-representative sample still believed this claim [39] to some extent.

Though brief, our debunking content will follow specific procedures that recent research (particularly around COVID-19 misinformation and vaccine hesitancy) has found to improve the efficacy of debunking messaging. These include ensuring the credibility of the source of the factual correction [61] and including a sufficient level of detail and explanation for *why* the facts are correct and the misperceptions are not [62]. This level of detail will vary in extensiveness depending on the format of a given piece of communication. The use of such short-format corrections does not seem to result in a backfire effect [63]; for example, a statement made in the arm 1 recruitment flyer (standard) might be, "Overdoses involving opioids are a public health emergency in the United States (US). The US Surgeon General recommends: 'Be Prepared. Get Naloxone. Save a Life.'" The permutation for the arm 2 recruitment fact sheet (modified), in parallel, would be, "Rapid use of naloxone (Narcan) nasal spray is often an overdose victim's best chance for survival. Studies show that opioid use in a community does not increase when naloxone is widely available."

Inert Arm for H1 (Arm 3)

Arm 3 recruitment will mirror recruitment for arm 1, except that the stated goal for the agencies will be only to ask layperson respondents to indicate at 3 different time points whether they have attended OEND programming or carry naloxone (eg, no encouragement or messaging campaign will occur in this arm). This arm will not be actively analyzed when we test H1.

Outcome Variables and Measurement

In H1, we hypothesize that more community first responder agencies will agree to participate in the *PulsePoint-OD* program when contacted using procedures in arm 2 (tailored messaging)

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compared to procedures in arm 1 (standard messaging) within 6 and 12 months of initial contact. Our primary outcome to test this hypothesis will be the number of agencies that agree to participate in the project as a percentage of the number of agencies with which we have been able to identify appropriate points of contact for recruitment. This metric *M* will be computed as follows:

- Each agency from the initial PulsePoint Foundation list that is randomized to participate in the study will be given a value *A* that is set at *0*, which indicates that we have not yet identified the appropriate point of contact at the agency.
- When we have identified a point of contact who can discuss *PulsePoint*, we will set the value for *A* at *1*.
- To define when a community first responder agency has agreed to participate, each agency will be assigned an ordinal value *R* ranging from *0* to *2*, where *0* will indicate nonparticipation or refusal, *1* will indicate that there is an agreement in principle to participate but that no formal MOU has been established, and *2* will indicate that a formal MOU has been put into place between the agency and the study team. For the purposes of hypothesis testing, we will aggregate values of *1* and *2*, but the data will be documented in ordinal form so that we can identify whether there is a concern with agencies failing to enter the MOU stage after agreeing in principle to participate.
- Next, the agency recruitment metric *M* for each arm will be the ratio of recruited agencies to total agencies with which active communication has been established: $M=(R_{R>0}/A_{A>0})$.

In addition to computation of the primary outcome metric, recruitment activities will be documented in a shared internal database, which will track, at a minimum, the nature, date, and outcome of each instance of correspondence with each community to inform our understanding of the uptake of *PulsePoint-OD* among *PulsePoint* communities and support ongoing mitigation of any issues with recruitment. Using this documentation, we will be able to estimate several secondary descriptive outcomes:

- An estimate of the dose-response uptake of the intervention (eg, mean number and types of correspondence associated with agreement to participate and completion of an MOU)
- An estimate of the average length of time between initial contact and agreement to participate

H1: Sample Size, Power, and Analysis

Although we plan for 180 agencies to compose the total sample size, only 120 (66.7%) will be allocated to arms 1 (n=60) and 2 (n=60), meaning that the sample size for this hypothesis is 120. With 60 agencies in each arm, we will have 80% power to detect significant differences (2-tailed α=.05) between arms 1 and 2 in the proportions of agencies that are successfully recruited if the difference in proportions is at least 0.25 (eg, 18/60, 30% recruited in arm 1 vs 33/60, 55% recruited in arm 2). The primary analysis will be conducted using logistic regression, comparing the recruitment rate between the arms. We will report exact P values and commit to a cautious interpretation of the findings, avoiding overreliance on P values as the single arbiter of meaning [64]. We do not expect any missing data in the outcome variable because the nature of its computation is such that missing data mean that either *A=0* or *R=0* and are therefore built into outcome variable *M*.

The primary study outcome (*M*) will be tested separately for the periods 6 and 12 months after initial recruitment correspondence. Analysis covariates are planned to include, but may not be limited to, community rurality and the community's percentage vote share for the Republican candidate in the 2020 presidential election (available for 2523 US counties and separable by zip code [65]), given that political orientation was 1 of 2 strongly predictive variables in our regression model examining misperceptions of OEND [39].

H2: Layperson Responders

Overview

Layperson responders who are part of the *PulsePoint* system register with a local first responder agency using their smartphone. Most layperson responders (eg, those who are not also off-duty first responders themselves) are only alerted to incidents in public spaces. No identifying information is collected from these users except the unique ID of the device.

The first responder agency in each community that manages the *PulsePoint* subscription can only determine the number of active users and, broadly, the type of smartphone being used (eg, Android smartphone or iPhone). Each time a first responder agency sends out a push notification, it is provided with an exact count of the number of unique devices, separated by type, that were active in the system and reached by the message.

It is important to note that we will have a count of unique active devices but not necessarily a count of unique active users (eg, it is unlikely but possible that someone will install the app on 2 different mobile phones at the same time). In correspondence with the PulsePoint Foundation, it is likely that the count of unique active devices serves as a very close approximation of unique active users. Furthermore, by virtue of randomization, the distribution of any unmeasured anomalies related to user-device mismatches should be evenly distributed across the arms.

Conceptualizing Recruitment for Layperson Responders

Currently, for a *PulsePoint* user to be officially recruited as a CPR responder and to be sent notifications regarding unconscious and unresponsive persons in public places, they need to affirmatively indicate that they are trained in CPR *and* are "willing to assist in case of an emergency." Individuals who so verify are sent push alerts and auditory alert tones, regardless of whether the app is open, whenever there is an unresponsive and unconscious person within a specific radius of their mobile phone (the radius is specified by the first responder agency for that community) [66].

For the purposes of this study, a layperson responder will be considered to have been recruited for *PulsePoint-OD* if they certify that they have received training on overdose and naloxone and that they currently carry naloxone on their person (both outcomes are of interest, which we describe later in the *Outcome Variables and Measurement* section). Once an MOU is in place with a first responder agency, it will send out a

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customized baseline push message to all active users containing a link to a landing page. This page will contain brief introductory text explaining the importance of recognizing an overdose when responding to unconscious persons and the efficacy of naloxone, as well as 2 questions asking them to indicate, by pressing radio buttons, whether they have received training on recognizing an overdose and administering naloxone and whether they currently carry naloxone on their person. Additional push messages encouraging users to respond to the certification questions will be sent twice within the month to maximize the number of participants providing baseline data. A user's responses to these questions will not change their status within the app or the behavior of the app because all users are already alerted to unresponsive or unconscious persons who may have experienced an overdose. This certification procedure will be repeated twice (6 months and 12 months after the baseline certification requests are sent). These messages will emphasize that even users who have previously provided such information should do so again.

The *PulsePoint* app is structured in such a way that push notification hyperlinks can open an external web page in a web browser window inside the app. Using the style guides and templates from the PulsePoint Foundation, the certification web pages will be designed to be similar to the appearance of the app to avoid disrupting the user experience while avoiding cross-contamination of messaging between the study arms. Each web page will be accessible only via the hyperlink in its associated push notification, and users will not be able to navigate among web pages or access the web pages for other study arms.

As multiple data collection reminders will be sent each time (baseline, 6 months, and 12 months), we want to minimize the likelihood of an individual repeatedly certifying their involvement. This risk exists because of the completely anonymous way that individual *PulsePoint* users are managed by the system. Thus, the landing page will be configured to store a cookie [67] on the mobile device. Although cookies are typically perceived as tracking devices, this cookie will not *record anything except whether the user has previously responded to either question on the landing page* during the data collection cycle, and it will be programmed to delete itself after each data collection period (eg, 3 weeks). When users who have already completed the questions return to the landing page, the cookie will prevent the questions from being displayed, although we anticipate that some of the users may clear their smartphone browser cache or actively prevent the use of cookies.

Layperson Intervention (Recruitment) Arm 1

Users randomized to arm 1 will receive standard monthly recruitment push messages. These push messages will differ from the certification messages because they will contain language intended to foster engagement with OEND services (eg, to get trained and carry naloxone) alongside the link to a landing page (eg, "Are you trained to recognize an overdose? Be a community hero! Click here for more information!"). The messages will be developed based on best practice recruitment principles in cooperation with an external marketing team and then reviewed and finalized by the study team. Messages will be different each month. The monthly time frame was selected based on our need to balance contact with responders and research or expert opinions on push messaging saturation. In a hypothesis-driven objective measure study, increased push messaging frequency was associated with additional app uninstalls *and* lower push message opening rates [68]. This information is generally consistent with the much larger volume of layperson marketing gray literature on push notification optimization (eg, *how-to* blogs [69]). Figure 3 displays the planned timing of the recruitment and data collection messages.

Figure 3. Push notification types and timing relative to agency recruitment. B: baseline.

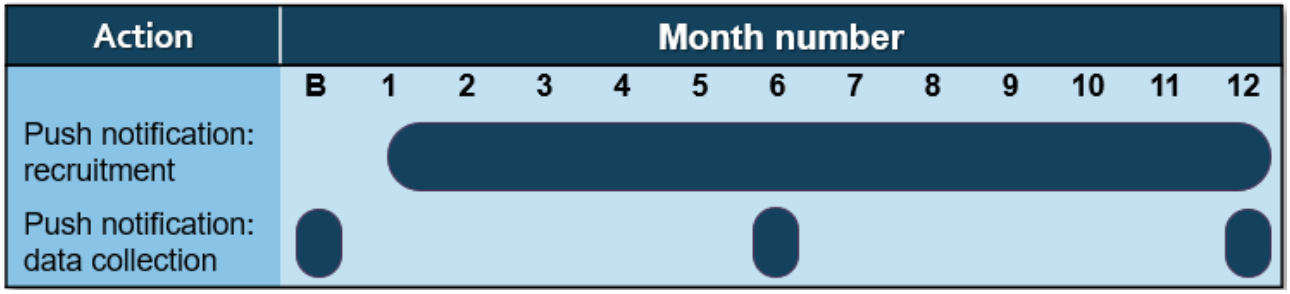

The landing page for recruitment will be updated to include a link to the Community Overdose Responder naloxone training [70], which has been designed specifically for laypersons and integrates elements of OEND programming and *PulsePoint*. Where provided by community first responder agencies, we will also include a list of ways to obtain free or reduced-cost naloxone locally as well as information about upcoming local OEND events. Separately, we note that accessing at-cost naloxone (ie, not free or subsidized) will be relatively easy, in principle, given its transition to OTC status [22].

Layperson Intervention (Recruitment) Arm 2

As in the case of the differentiation between agency recruitment in arm 1 and arm 2, the recruitment of layperson responders for arm 2 will follow the same procedures that are described for arm 1 but will use separate messaging. Specifically, the push messages and landing page will contain additional, brief messages that specifically provide factual information that counteracts misperceptions about overdose and naloxone [39]; for example, whereas an example message for arm 1 might be "Are you trained to recognize an overdose? Be a community hero! Click here for more information!" the permutation for arm 2 might be "Are you trained to recognize an overdose? Studies show that most people revived with naloxone will not overdose again within the next year! Click here for more information!"

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Layperson Intervention (Control) Arm 3

Arm 3 functions as the control arm and will not receive any monthly recruitment messaging or encouragement, but laypersons will still be asked, using push notifications, to provide information at baseline and 6 and 12 months later to document whether they have been trained to recognize an overdose and administer naloxone and whether they currently carry naloxone on their person (eg, "Please let us know whether you have ever been trained to recognize an overdose or if you carry naloxone by clicking here."). The landing page will likewise contain the questions with radio button responses but will not link to training opportunities or contain additional information.

Outcome Variables and Measurement

In H2, we hypothesize that more layperson responders will indicate that they have received OEND programming and carry naloxone on their person within 6 and 12 months of initial contact using procedures in arm 2 (tailored messaging) compared to procedures in arm 1 (standard messaging) and using procedures in either arms 1 or 2 versus arm 3 (control). We will use several different data points to assess our hypothesis.

All push notifications sent out by first responder agencies already return information through the *PulsePoint* app indicating the total number of active devices, by type, that were messaged. As we explained previously, this is a strong proxy measure for the total number of active users messaged because most people use a single smartphone.

For purposes of computation, this total number of recipients of any push notification will be designated as *T*. Next, the total number of individuals who click on the pushed link will be represented by *O*, which will be a number between *0* and *T*. Importantly, the link will also be coded using HTML and CSS so that it sends additional data when clicked, indicating the originating community (cluster identity) and the data collection point (*D*, a value ranging from *0*, which is the initial push message cluster, to *2*, which is the final data collection message set at 12 months after baseline). Subsequently, the number of instances of an individual (ie, unique device) indicating that they have been trained on recognizing an overdose and administering naloxone (represented by *N*, a binary value of *0* or *1*) and whether they currently carry naloxone (represented by *C*, also a binary value of *0* or *1*) will be captured from the landing page itself.

This information will allow us to determine the following, separately by community:

- At baseline, we will calculate the ratio of persons certifying that they are trained (numeric count of *N*) compared to the total number of push message recipients (*T*), the ratio of persons certifying that they carry naloxone (numeric count of *C*) compared to the total number of push message recipients (*T*), and the ratio of individuals who clicked on the link (*O*) compared to the total number of push message recipients (*T*).
- Separately at 6- and 12-month follow-ups, the numbers of certifications of training and carrying naloxone (*N* and *C*, respectively) that were submitted compared to the numbers of push recipients (*T*) in each period (tracked by *D*) and the ratio of individuals who clicked on the link (*O*) each month compared to the number of total push message recipients (*T*).
- Our outcome variables are ratios: $X = (N / T)$ for each value of *D* (0, 1, or 2) and $Y = (C / T)$ for each value of *D*. The ratio $Z = (O / T)$ is a covariate representing engagement with push messages at each value of *D*.

Sample Size, Power, and Analysis

Our power analysis for H2 depends on the number of communities that agree to participate during the agency recruitment conducted as part of testing H1. To compare the average proportions of users who certify that they have received overdose education and personally carry naloxone, we sought 80% power to detect significant differences (2-tailed α=.05) among the 3 arms across 3 time points. Assuming a correlation of 0.5 in responses over time, we expect that we will be able to detect a medium effect size ranging from f=0.21 (if 50, 83% of the 60 communities participate in each arm on average) to f=0.34 (if 20, 33% of the 60 communities participate in each arm on average).

Our primary analyses will be metrics *X* and *Y* (as described previously), which will be analyzed separately. The primary analyses will be conducted using generalized linear mixed models, adjusting the *df* for the number of agencies. As with H1, we will report exact P values and commit to a cautious interpretation of the findings, avoiding overreliance on P values as the single arbiter of meaning [64]. In addition, as in the case of H1, we do not expect any missing data in the outcome variable because the nature of its computation is such that missing data mean that either *N=0* or *C=0* and are therefore built into outcome variables *X* and *Y*. Study covariates will include but may not be limited to variable *Z* to control for the conversion of push messages to clicks.

Exploratory Agency Follow-Up

We will conduct a set of intensive follow-up agency interviews with community first responder organizations with whom we have established active communication. We will prioritize qualitative recruitment of organizations and agencies that did not agree to be recruited after establishing correspondence because the elicitation of barriers to participation in the *PulsePoint-OD* program may be most informative when carried out with those who did not participate. This procedure will be similar in principle to, but more extensive than, our brief study of clinical providers who dropped out from a continuing medical education program [71]. However, we will not exclude participating agencies from the qualitative component of the project; instead, we will continue data collection until we have reached a point of theoretical inductive saturation, when new conversations and data no longer seem to add to our understanding of the topic [72]. Interviews will be guided by a semistructured interview guide to be developed during the agency recruitment process and will be coded using the general inductive approach to qualitative analysis [73], which does not make a priori assumptions about the data and allows themes to emerge organically based on repeated readings of the data.

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Ethical Considerations

Ethics approval for the proposed work was determined to fall into 2 separate categories. Agency-level recruitment and interaction were determined not to constitute human participant research (Indiana University Institutional Review Board: 20218). The collection of information from layperson responders was approved under an expedited procedure (Indiana University Institutional Review Board: 20219). Data from layperson responders will be anonymous (no identifiers will be collected). Participation in the intensive follow-up agency interviews will be incentivized with an honorarium (US $500) to the organization to encourage participation.

Results

At the time of protocol submission, we had not engaged in any data collection or participant recruitment. This research was funded beginning September 14, 2023, by the National Institute on Drug Abuse of the National Institutes of Health (R34DA058162).

Discussion

Summary

The primary goal of this study is to understand the feasibility of recruiting current *PulsePoint* communities and layperson responders to complete overdose and naloxone training and to carry naloxone. Our hypotheses are intended to determine whether a specific type of correspondence targeting anticipated misunderstandings around opioid overdose and naloxone performs better when recruiting agencies and laypersons than standard messaging and whether active recruitment of laypersons using either message type performs better than the control.

At the same time, a separate consideration—regardless of the results of null hypothesis significance testing—is an overall sense of recruitment feasibility (eg, data on agency and responder uptake). Successful completion of this study is anticipated to improve the level of naloxone coverage in the United States, which remains insufficient [29]. We are also interested in examining elements that did and did not work and how we would ideally structure a similar recruitment process for a larger, outcomes-focused study (eg, comparing fatal overdose ratios in communities). Our exploratory discussions with agencies will be important to facilitate a better understanding of the mechanisms through which the proposed recruitment procedures did (or did not) work as intended.

Where possible, we have tried to control for anticipated limitations at the stage of study design. Owing to the nature of this real-world study, we still anticipate some limitations in the interpretation of the results. In particular, the degree to which agencies will agree to participate in arm 3 is uncertain because participation does not directly benefit those communities (unlike arms 1 and 2). This would not affect H1 (which only includes arms 1 and 2) but might affect the statistical power of H2. We expect that additional limitations may be uncovered in the process of conducting the study, and we plan to transparently note, and where possible mitigate, all such limitations, providing a comprehensive description of this information in subsequent documentation of the study.

Conclusions

If we successfully recruit agencies and laypersons and thereby facilitate training around overdose and naloxone and increase the numbers of layperson responders carrying naloxone, the next step will be to conduct a larger study examining opioid-involved overdose reversals using these procedures. This is predicated on current evidence for OEND, which allows us to hypothesize that our successful mobilization of layperson responders might reduce the prevalence of opioid-involved overdose [12-16], a theory that we will then prospectively test.

Acknowledgments

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Portions of this paper, including some verbatim text, will be presented as a 5-minute “lightning talk” and abstract at the 2024 American Academy of Health Behavior conference in Savannah, Georgia.

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Data Availability

Data sharing is not applicable to this paper because no data have been obtained or analyzed at this stage of the study.

Authors' Contributions

JA, CH, and DCS contributed to conceptualization. DT contributed to software development. JA contributed to visualization, supervision, and project administration. All authors contributed to methodology, resources, funding acquisition, and writing the original draft as well as reviewing and editing it.

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Conflicts of Interest

JA, CH, MP, and DCS have received funding through their employer (Indiana University) to conduct various research projects pertaining to opioids, harm reduction, and naloxone from federal, state, and local government entities and nonprofit foundations. CH was co–principal investigator of a National Institute on Drug Abuse Small Business Innovation Research grant that facilitated the development of a web-based naloxone training (Community Overdose Responders) being provided as an option for layperson responders in this study, but their participation was as an Indiana University employee; therefore, they do not have any mechanisms in place (eg, trademarks, patents, and access agreements) that would result in any personal profit or financial benefits accruing from the use of the training. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer-review report by the National Institute on Drug Abuse of the National Institutes of Health.
[PDF File (Adobe PDF File), 81 KB - resprot_v13i1e57280_app1.pdf]

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Abbreviations

CPR: cardiopulmonary resuscitation
MOU: memorandum of understanding
OEND: overdose education and naloxone distribution
OTC: over-the-counter

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Protocol

The Effects of an Educational Intervention About Front-of-Package Labeling on Food and Beverage Selection Among Children and Their Caregivers: Protocol for a Randomized Controlled Trial

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Abstract

Background: Overweight and obesity pose a global public health challenge and have a multifactorial origin. One of these factors includes obesogenic environments, which promote ultraprocessed foods characterized by being high in calories, saturated fats, added sugars, and sodium. In Mexico, it has been estimated that 30% of the total energy consumed comes from processed foods. The Modification to the Official Mexican Standards introduces nutritional information through black octagonal seals that alert consumers about products with excessive amounts of some components for a better food selection in the population. However, the effects of warning labels on processed food selection and purchases among children remain unknown.

Objective: We aimed to evaluate the impact of a digital educational intervention focusing on front-of-package warning labels on the food selection and purchasing behavior of elementary schoolchildren and their caregivers.

Methods: Children from 4 elementary schools in Mexico City, 2 public and 2 private schools, will participate in a randomized controlled trial. The schools will be chosen by simple random sampling. Schools will be randomized into 2 groups: intervention and control. In the control group, the dyads (caregiver-schoolchildren) will receive general nutritional education, and in the intervention group, they will receive guidance on reading labels and raising awareness about the impact of consuming ultraprocessed products on health. The educational intervention will be conducted via a website. Baseline measurements will be taken for both groups at 3 and 6 months. All participants will have access to an online store through the website, allowing them to engage in exercises for selecting and purchasing food and beverages. In addition, other measures will include a brief 5-question exam to evaluate theoretical understanding, a 24-hour reminder, a survey on food habits and consumption, application of a food preference scale, anthropometric measurements, and recording of school lunch choices.

Results: Registration and funding were authorized in 2022, and we will begin data collection in September 2024. Recruitment has not yet taken place, but the status of data analysis and expected results will be published in April 2025.

Conclusions: The study is expected to contribute to evaluating whether reinforcing front-of-package warning labels with education enhances its effects and makes them more sustainable. Conducting this study will allow us to propose whether or not it is necessary to develop new intervention strategies related to front-of-package labeling for a better understanding of the population, improved food choices, and better health outcomes.

Trial Registration: ClinicalTrials.gov NCT06102473; https://clinicaltrials.gov/study/NCT06102473

International Registered Report Identifier (IRRID): PRR1-10.2196/54783

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KEYWORDS

e-Health nutrition education; ultraprocessed foods; malnutrition; children; Mexico; intervention; obesity; food; food selection; labeling; package labeling

Introduction

Overweight and obesity pose a global public health challenge. In Mexico, data from the National Health and Nutrition Surveys from 2012, 2018, and 2020 show that the combined prevalence of overweight and obesity in children between the ages of 5 and 10 years has remained high (33.2%, 35.6%, and 38.2%, respectively) [1].

Obesity has a multifactorial etiology, involving genetic, environmental, and behavioral aspects. Obesogenic environments promote ultraprocessed foods, which are high in calories, saturated fats, added sugars, and sodium [2,3].

Therefore, public policies aimed at reducing the incidence and prevalence of childhood obesity must consider actions that modify the environment to improve nutrition. Labeling of ultraprocessed products has been a common strategy that governments worldwide use to improve people's diets [4].

In Mexico, it has been estimated that more than 30% of the total energy consumed comes from ultraprocessed foods, favoring the prevalence of overweight and obesity. The daily dietary guidelines by the Ministry of Economy and the Ministry of Health in Mexico were an effort for people to improve their food selection and purchasing; however, they did not show good results due to the complexity of interpreting them [5].

The Modification to the Official Mexican Standard (NOM-051-SCFI/SSA1-2010 [NOM 051]) was approved in 2020. This proposed a front labeling system for foods and beverages that consisted of nutritional information through black octagonal seals, with legends like "excess calories," "excess sodium," "excess saturated fat," "excess trans fat," "excess sugars," and other explanations, such as "contains caffeine, avoid for children" and "contains sweeteners, not recommended for children," to provide information to the consumers to help them make food selections [5,6].

Ultraprocessed products targeted at children are offered in all supermarkets and represent an important commercial income for the food industry [7,8]. At home, parents are primarily responsible for purchasing food and have a significant influence on their children's eating behaviors [7-10].

On the other hand, children also influence parents' purchasing decisions, especially when they want to choose unhealthy foods, which is why the influence of front labeling must be studied from both perspectives (ie, children's and parents') [11]. To reduce the purchase and consumption of ultraprocessed foods, various marketing strategies have been implemented, especially for products aimed at school children; however, the results have been varied and limited [12,13].

It is known that food packaging has an impact on how children perceive these products. For instance, the use of drawings and bright colors can make them associate the product with something suitable to eat, which is why changes have been made to packaging designs to discourage consumption, mainly by removing cartoon slogans or legends that promote their consumption [14].

Some types of front-of-package labeling guide the daily intake by indicating the proportion (%) of nutrients found in a serving according to the recommended daily intake for adults. This includes the traffic light system, which uses colors (green, yellow, and red) to indicate the amount of nutrients in a product, as well as warning labels, which are black octagonal symbols, which indicate the excess of nutrients, energy, and substances present in the product and are intended to discourage purchase and consumption [15].

Having identified the relationship between packaging and food consumption, it is expected that front-of-package nutritional labels will reduce the consumption of unhealthy foods [16].

Furthermore, it has been documented that another effective strategy to improve food selection is to enhance nutritional education to develop skills to distinguish healthy products from those that are not considered healthy [17].

Mobile nutritional interventions have been observed to reach a broader range of social and demographic groups and can facilitate the selection of healthy foods at the point of purchase, optimizing decision-making times [18].

In Mexico, it is estimated that 78.6% of the Mexican population aged 6 years and older has access to the internet, with 97% connecting through mobile devices. This is why various health institutions have implemented web portals, social networks, and the use of cell phone messages, telephone, and mobile apps for managing, preventing, and treating health-related activities [19-21].

The objective of this clinical trial is to evaluate the impact of a digital educational intervention focusing on front-of-package warning labels on the food selection and purchasing behavior of elementary school children and their caregivers [22].

Methods

Recruitment and Study Design

Third-, fourth-, and fifth-grade elementary school students and their caregivers from 4 primary schools—2 public and 2 private schools—in Mexico City will participate in the study. The schools will be chosen by simple random sampling. Schools will be randomized into 2 groups: intervention and control.

After approval from the directors of the primary schools, meetings will be held with parents to invite them to participate; they will be explained the intervention's objectives, activities, and duration. Parents and schoolchildren will be invited to sign a consent and informed assent, respectively, clarifying that their participation is voluntary, and they may choose to discontinue at any time without affecting their activities at school.

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The main question this study aims to answer is the following: What is the effect of a digital educational intervention about front-of-package warning labels on food selection among children attending primary schools in Mexico City, compared to a control group?

Schools will be randomized into 2 groups. In the control group, the dyads (caregiver-schoolchildren), will receive general nutritional education, and in the intervention group, they will also receive guidance on reading labels, which raises awareness about the impact of consuming processed or ultraprocessed foods on health.

The intervention will be carried out via a website [23] (Figure 1) with audiovisual material, and all participants will also be asked to complete a multiple-choice evaluation (5 questions) to ensure a theoretical understanding of the topics. Other measures will include a lunch register, 24-hour dietary recall, a survey of food habits and consumption, a validated food preference questionnaire, anthropometric measurements (eg, weight, height, and waist circumference), a socioeconomic survey, as well as participation in a simulated web-based food and beverage selection and shopping activity. These measures will help assess if the digital educational intervention on front-of-package warning labeling for children and caregivers improves the selection and purchase of foods.

Figure 1. Website “Applicate por tu salud” (www.viviendo-saludable.org).

Inclusion Criteria

Inclusion criteria for children are as follows: students in third, fourth, and fifth grades (aged 8 to 12 years), of both sexes, enrolled in the selected primary schools, with normal weight, overweight, and obesity, who sign the written informed consent.

Inclusion criteria for caregivers are as follows: primary caregivers of any sex of children in the third, fourth, and fifth grades with normal weight, overweight and obesity, who sign the written informed consent.

Exclusion Criteria

Caregivers and children without internet access, computers, or mobile devices, as well as those participating in a weight reduction program with pharmacological treatment, will be excluded.

Nutritional Education Interventions

The control group and the intervention group in dyads (caregiver-schoolchildren) will receive general nutritional education, and only the intervention group will receive guidance on reading warning labels, which raises awareness about the impact of consuming processed and ultraprocessed foods on health.

On the website, there will be 4 sections. Participants will receive an account and password to access the educational content corresponding to the group they belong, intervention or control group.

The intervention and control groups will have access to the first section, which contains general nutritional education topics. The second section will contain nutritional education topics related to warning labeling, and only the intervention group will have access to it.

Each topic will be presented through videos, released every 15 days, as well as weekly infographics and tips to the caregivers and children via the website. This material will also be sent to the participants’ mobile devices.

The third section will have the “Online shop,” which will be used as part of the food selection evaluation. The fourth section will evaluate theoretical understanding with 5 multiple-choice questions per topic (Figure 2).

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Figure 2. Nutritional intervention topics by groups.

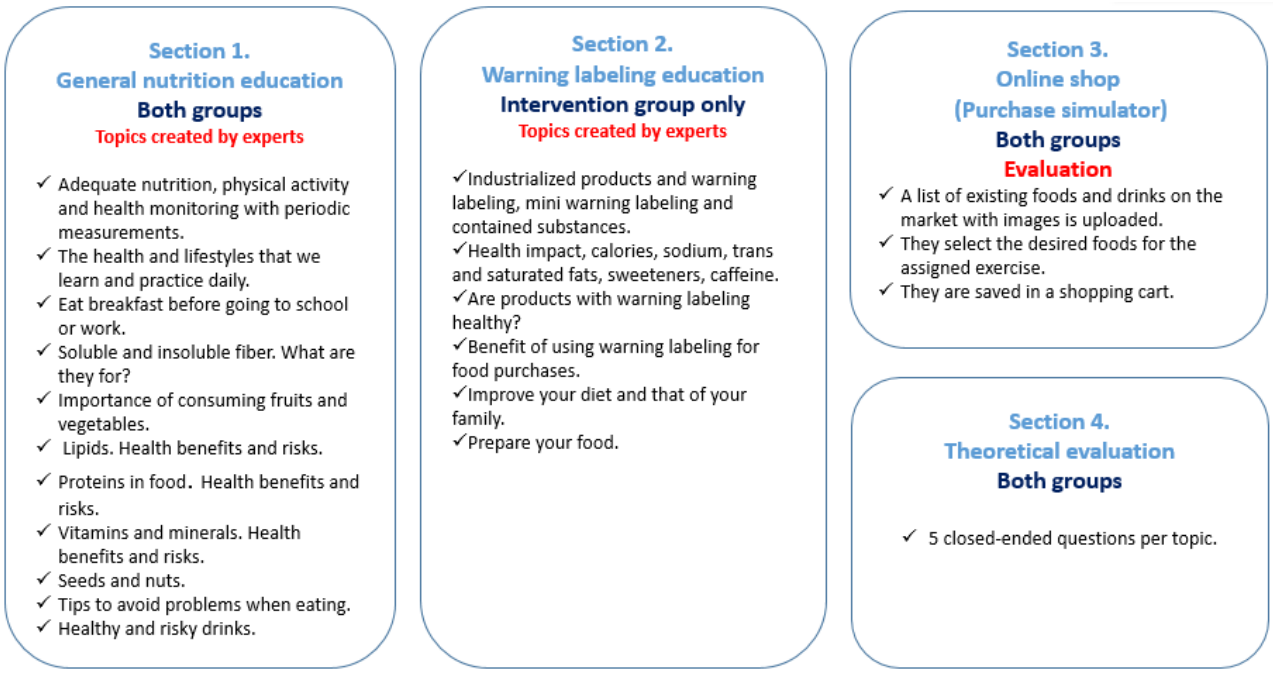

Primary Outcomes

Time Frame

The measurements will be carried out in 2 scenarios (in schools and through the website) at baseline (1 week before starting the educational interventions), at 3 months, and at 6 months after the intervention ends.

A socioeconomic survey will be used in the baseline measurement.

The following assessments will be conducted at 3 frame times (baseline, 3 months, and 6 months): a food preference questionnaire, a 24-hour dietary recall, lunch register, and a survey of food habits and consumption. Anthropometric measurements (eg, weight, height, and waist circumference) will only be performed at baseline and the end of the 6-month intervention.

Through the website, dyads will engage in food and beverage purchasing exercises in the online shop simulator at the 3 measurement points (baseline, 3 months, and 6 months), along with multiple-choice evaluation (5 questions).

Food and Drink Selection

The percentage of products purchased by each participant in the online store, whose content indicates “high in calories, sugar, fat, and sodium” and the average content of these nutrients in 100 g of each product will be measured.

Energy and Macronutrient Intake

The amount of kilocalories consumed as well as saturated fat, trans fat, sodium, and added sugar will be measured.

Statistical Analysis

Descriptive statistics will be used to characterize variables, and tables will be made with summary measures. Independent *t* tests and chi-square tests for categorical data will be used to compare baseline characteristics between the intervention and control groups. The Mann-Whitney *U* test will be used to evaluate differences between groups in case of nonnormal distribution.

Repeated measures ANOVA will be used to evaluate the change in the number of warning labels in nutrient consumption between groups and throughout the intervention. We will use a mixed-effects model to evaluate the effect of the intervention on changes in food and beverage selection, adjusting for confounding variables. Intention-to-treat analysis will be performed.

Ethical Considerations

The protocol has obtained ethics approval by the bioethics committees of the Hospital Infantil de México Federico Gómez (HIM/2022/054). This protocol has also been registered with ClinicalTrials.gov (NCT06102473).

The objectives and activities of the study will be explained to the caregivers and children. To participate, they must sign the informed consent and informed assent forms to give their authorization to participate, with confidentiality guaranteed.

The website will contain health education material and an online shop to simulate the selection and shopping of food and beverages. No personal or medical information will be uploaded to the website. The results will only be used for the study and will be stored by the research team on password-protected computers. In case of any changes to the protocol, the ethics committee will be informed.

Results

The protocol was registered in 2022 and was approved by the committees of the Federico Gómez Children's Hospital of Mexico, and they also obtained federal resources for the project. We expect to begin the study in schools in September 2024.

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We are not recruiting yet. The results will be analyzed and published in April and May 2025.

Discussion

Expected Outcomes

This protocol aims to study a public health policy in Mexico, which seeks to contribute to improving the health of the Mexican population by facilitating the understanding of nutritional information about ultraprocessed foods and beverages using front-of-package warning labeling. Studying the effects of this intervention on the population is essential for continuing with the initiative, improving it, or considering other measures to achieve the expected health outcomes.

Some studies have been conducted around the world on different types of front labeling, exploring their effectiveness in selecting and purchasing healthier foods.

A study on adults [24] explored the effectiveness of different types of frontal labeling. Participants were given a brief educational session through a smartphone app before being exposed to 2 experimental shopping tasks. The study found that all types of front labeling, after the educational intervention, resulted in better food selection. In Mexico, a study [25] provided guidance on front labeling via video before participants engaged in online food selection, showing positive effects on food selection.

Another study [26] demonstrated that nutritional warning labels with stamps significantly reduced the percentage of participants who selected products with excessive content of at least one nutrient, compared to the control group (62% vs 85%), and a statistically significant difference was observed for participants who selected products with an excess of certain nutrients, such as sugar (P<.001), saturated fats (P<.001), and sodium (P=.01).

A study in the United States [27] targeting parents concluded that warning labels on sugary beverages reduced the purchase of these products for their children. Although the evidence indicates that front-of-package warning labels can improve the selection of foods and beverages, the effects of these labels on the pediatric population and how children influence the selection and purchase of foods in their homes are still unknown.

On the other hand, the guidance received by participants in the aforementioned studies is limited to ensuring understanding of reading the label.

One limitation of the study is that the exercise of food and beverage selection will be made in a simulated shopping scenario, which may differ from real-life situations of food and beverage purchasing and consumption; however, this study is important to determine whether a structured educational intervention on key nutrients and raising awareness about their implication in health enhances the effects of front-of-package warning labeling to reduce overweight and obesity as well as other chronic diseases, such as diabetes and hypertension.

Conclusions

It is expected that the study will contribute to evaluating whether reinforcing front-of-package warning labeling with education enhances its effects and makes them more sustainable. Carrying out this study will allow us to propose whether or not it is necessary to develop new intervention strategies related to front-of-package labeling for a better understanding of the population, improved food choices, and better health outcomes.

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Data Availability

The data sets generated and analyzed during this study are not publicly available to comply with the ethical requirements and participants' confidentiality protection but are available from the corresponding author upon reasonable request.

Authors' Contributions

DAM, JVG, and MKK conceptualized the study and drafted the manuscript. ALML and LVL conceptualized the study and reviewed the manuscript.

Conflicts of Interest

None declared.

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Protocol

Investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI): Protocol for a Randomized Controlled Trial

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Abstract

Background: Patients after kidney transplantation eventually face the risk of graft loss with the concomitant need for dialysis or retransplantation. Choosing the right kidney replacement therapy after graft loss is an important preference-sensitive decision for kidney transplant recipients. However, the rate of conversations about treatment options after kidney graft loss has been shown to be as low as 13% in previous studies. It is unknown whether the implementation of artificial intelligence (AI)–based risk prediction models can increase the number of conversations about treatment options after graft loss and how this might influence the associated shared decision-making (SDM).

Objective: This study aims to explore the impact of AI-based risk prediction for the risk of graft loss on the frequency of conversations about the treatment options after graft loss, as well as the associated SDM process.

Methods: This is a 2-year, prospective, randomized, 2-armed, parallel-group, single-center trial in a German kidney transplant center. All patients will receive the same routine post–kidney transplant care that usually includes follow-up visits every 3 months at the kidney transplant center. For patients in the intervention arm, physicians will be assisted by a validated and previously published AI-based risk prediction system that estimates the risk for graft loss in the next year, starting from 3 months after randomization until 24 months after randomization. The study population will consist of 122 kidney transplant recipients >12 months after transplantation, who are at least 18 years of age, are able to communicate in German, and have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. Patients with multi-organ transplantation, or who are not able to communicate in German, as well as underage patients, cannot participate. For the primary end point, the proportion of patients who have had a conversation about their treatment options after graft loss is compared at 12 months after randomization. Additionally, 2 different assessment tools for SDM, the CollaboRATE mean score and the Control Preference Scale, are compared between the 2 groups at 12 months and 24 months after randomization. Furthermore, recordings of patient-physician conversations, as well as semistructured interviews with patients, support persons, and physicians, are performed to support the quantitative results.

Results: The enrollment for the study is ongoing. The first results are expected to be submitted for publication in 2025.

Conclusions: This is the first study to examine the influence of AI-based risk prediction on physician-patient interaction in the context of kidney transplantation. We use a mixed methods approach by combining a randomized design with a simple quantitative end point (frequency of conversations), different quantitative measurements for SDM, and several qualitative research methods

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(eg, records of physician-patient conversations and semistructured interviews) to examine the implementation of AI-based risk prediction in the clinic.

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International Registered Report Identifier (IRRID): PRR1-10.2196/54857

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KEYWORDS

shared decision-making; SDM; kidney transplantation; artificial intelligence; AI; decision-support system; DSS; qualitative research

Introduction

Shared decision-making (SDM) is increasingly important in health policy and clinical practice. Over the past decades, researchers, patient advocates, and policymakers all over the world have increased efforts to shift health care from a paternalistic to a patient-centered approach, focusing on the patient as a person [1,2]. Kidney transplantation is the most frequently performed solid organ transplantation and although the application of SDM prior to kidney transplantation has been discussed, little is known about how to improve SDM after transplantation [3]. This is surprising as there are numerous potentially preference-sensitive decisions that patients, support persons, and physicians have to make in this setting, for instance relating to the management of comorbidities, effects of treatment on fertility, use of immunosuppressant drugs, and resulting second cancers [4,5].

In patients with chronic kidney disease, choosing the right kidney replacement therapy and the optimal timing for kidney replacement therapy is an important preference-sensitive decision. Implementing SDM has been shown to leave more patients satisfied with their choice of dialysis modality [6]. Not only the modality itself but also details like the vascular access and the specific dialysis regimen are preference-sensitive and should be part of an SDM process that also considers age-dependent needs [7-9].

Since most patients after kidney transplantation eventually face the risk of graft loss with the concomitant need for dialysis or retransplantation, comparable considerations should be applied to kidney transplant recipients at risk for graft loss. However, the rate of conversations about treatment options after kidney graft loss is as low as 13% in conventional physician-centered care settings [10]. This leaves room for optimization with respect to the frequency of conversations as well as the associated SDM process. While care-based interventions have shown to be effective in increasing the frequency of conversations about treatment options after graft loss, it is unknown whether the implementation of artificial intelligence (AI)–based risk prediction models can have such influence on physician-patient interactions [10].

Different risk prediction models for graft loss using methods of statistics or AI have been introduced and show good predictive performance [11,12]. More importantly, they are more accurate than experienced physicians in predicting risks for graft loss [11,13]. Implementing such models into routine care could indicate patients at risk for graft loss and thereby increase the frequency of conversations about treatment options after graft loss. However, little is known about the impact of AI-based interventions on the interaction between patients, support persons, and physicians [14].

While there are several studies discussing the potential of AI to support SDM in the bioethical literature [15], there is a lack of empirical studies to systematically investigate the impact of AI on SDM [16].

In this study, we aim to evaluate the influence of an AI-based risk prediction model for 1-year risk of graft loss on the frequency of conversations about treatment options after graft loss, as well as the associated SDM process, in patients who had kidney transplants with low estimated glomerular filtration rate (eGFR).

Methods

Study Design and Setting

The Prospectively investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI) trial is a 2-year, prospective, randomized, 2-armed, parallel-group, single-center trial in a German kidney transplant center (KTC). Patients more than 12 months after kidney transplantation with eGFR <30 mL/min/1.73 m^2 and support persons will be randomized to routine care or to AI-supported care in a 1:1 ratio. During the study, 5 study visits are planned at the KTC—at randomization, and 3, 6, 12, and 24 months after randomization (Figure 1). In both groups, routine care visits will be scheduled as needed, depending on the patient's medical condition and time posttransplant, which is usually every 3 months.

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Figure 1. Study flowchart summarizing inclusion criteria, interventions, and end points. An estimated number of 122 KTRs will be recruited in the outpatient clinic of a tertiary care center and randomized 1:1 into routine care or AI-supported care and followed up over 24 months. AI: artificial intelligence; eGFR: estimated glomerular filtration rate; KTR: kidney transplant recipient; KTx: kidney transplantation; PROMIS-29: Patient Reported Outcomes Measurement Information System 29; SDM: shared decision-making; Tx: transplantation.

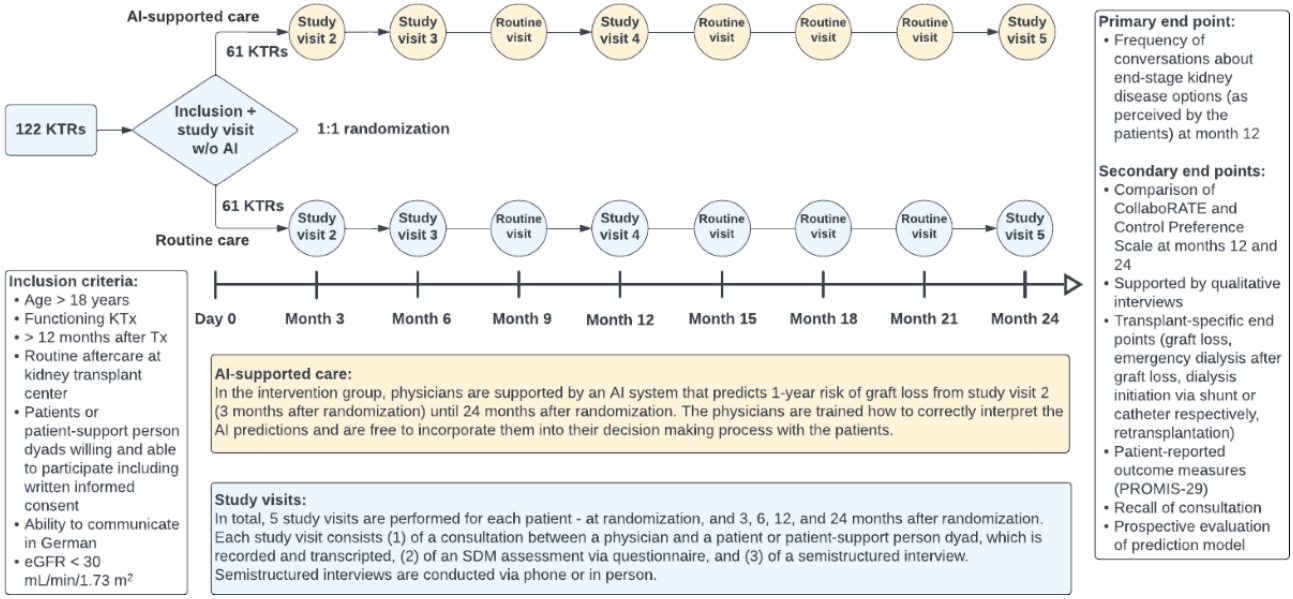

Recruitment Process

Patients after kidney transplantation regularly undergo routine follow-up at the KTC in an outpatient clinic. Patient data are available in a proprietary electronic health record that allows data extraction for research purposes [17]. Patients who are potentially eligible for the study based on their previous medical data will be contacted via telephone 1 week before their next scheduled appointment and will be asked if they are interested in study participation. If patients are potentially interested, they are provided detailed information about the study by trained study physicians and provide written informed consent after checking inclusion and exclusion criteria at the time of their next outpatient visit at the KTC. Recruitment will occur in the regular outpatient treatment at the KTC by designated study physicians who are not the treating physicians. After recruitment and randomization, the first study visit is performed. No study investigations are performed before written informed consent is obtained from the patients. The KTC is a tertiary care center specializing in kidney transplantation, where approximately 200 kidney transplantations per year are performed.

Participants

Participants may enter the trial if all the following apply: (1) they provide written informed consent, (2) they are patients with a functioning kidney allograft, (3) it has been at least 12 months after kidney transplantation, (4) they have an eGFR <30 mL/min/1.73 m^2 according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 formula, (5) they are aged at least 18 years, (6) they can communicate in German, and (7) they attend regular follow-ups at KTC. Participants may not enter the trial if any of the following apply: (1) they have undergone multi-organ transplantation, (2) it has been less than 12 months after kidney transplantation, (3) they have an eGFR >30 mL/min/1.73 m^2 according to CKD-EPI 2021 formula, (4) they are aged less than 18 years, (5) they cannot communicate in German, (6) they do not attend regular follow-ups at KTC, and (7) they enrolled in another interventional study less than 1 month before participation in this study. Additionally, support persons will be eligible if they are nominated by the patient as someone helping them cope with the consequences of their kidney transplant through support, encouragement, and communication. Support persons will be aged 18 years or older, German-speaking, and able to provide informed consent. Treating physicians who work at the participating clinics and use the AI-based decision-support system (DSS) will be eligible to participate in the study. Clinic staff will record the age and gender of nonconsenters who provided permission, which allows for the examination of consent bias.

Sample Size

The primary analysis will be performed based on the frequency of conversations about treatment options after graft loss as perceived by the patient, which is assessed in a questionnaire after the respective consultation. Based on the data from Bissonnette et al [10], we estimate that in the control group, 10%-15% of patients will have a conversation about therapy options at the end of graft function. Regarding the intervention studied herein, we estimate that this frequency can be increased to 40%-45%, which is half of the effect size achieved by Bissonnette et al [10]. Using a 2-sided χ^2 test, an α error of .05, and a power of 80%, 25-49 patients per group are needed. Estimating a dropout rate of 10% per year, this increases to 31-61 patients per group. Therefore, 61 patients per group were regarded as sufficient. In order to identify 122 participating patients, local study personnel will have to screen approximately 150 potentially eligible kidney transplant recipients over a period of 6 months.

Randomization

Randomization will be performed using a predefined variable block randomization scheme using a web-based randomization

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service [18]. After screening for eligibility and assignment of the individual patient identifier, each patient-support person dyad can only be assigned once to 1 of the treatment arms. The sites will record the time of randomization.

Blinding

Blinding of participants and study staff is not possible given the nature of the intervention.

Intervention

Control Group: Routine Care

Routine care will be scheduled according to the current standard of care [19], which depends on the time after transplantation, medical condition, and other individual factors. Standard immunosuppression will be applied according to the international recommendations [20]. The prophylaxis and treatment of infections will follow the current standard of care as outlined in recent guidelines [21-26], for example, *Pneumocystis jirovecii* pneumonia prophylaxis for 4 to 6 months, cytomegalovirus prophylaxis according to the guidelines, and regular posttransplant BK virus monitoring according to guidelines [19]. Screenings for the antibodies against human leukocyte antigen once within the first 3 months, after 1 year, and every year thereafter, as well as in case of suspected rejection [27]. The overall medical treatment of kidney transplant recipients will be performed according to the Kidney Disease Improving Global Outcomes guidelines [19] and in patients with suspected rejection, a kidney biopsy should be performed and classified according to the most recent Banff criteria [28]. An integral part of the current routine aftercare is regular visits to the home nephrologist and KTC, where data are captured in an electronic health record [17]. Table 1 highlights the proposed schedule for posttransplant aftercare. The proposed schedule is adapted to the individual patient's needs.

Table 1. Frequency of routine visits in the outpatient clinic of the kidney transplant center (KTC) depending on time after transplantation.

Time after transplantation	Frequency of routine visits
Month 1	Once per week after discharge at the KTC
Month 2	Once per week
Month 3	Once per 2 weeks
Months 4 to 6	Once per 3 weeks
Months 6 to 12	Once per month
After 12 months	Once every 3 months

Intervention Group: AI-Supported Care

The kidney transplant recipients, who are randomized to the interventional arm, will receive identical routine posttransplant care as patients in the control group (see Table 1). In addition, the physicians in the KTC will be provided an AI-based decision support system making predictions for the risk of graft loss based on the patient's most recent clinical, laboratory, and histopathology data, beginning from the second visit. A previous version of the AI-based decision support system has been studied in silico and in a reader study [11]. The physicians are provided a recommendation on how to proceed in case of a high-risk score. Briefly, physicians are recommended to inform the patients about this risk and discuss the potential necessity of return to dialysis or retransplantation, as well as planning, which mode of renal replacement therapy is preferred by the patient (hemodialysis, peritoneal dialysis, or listing for retransplantation by living donation). Depending on the patient's preference, preparation for a smooth transition to dialysis or retransplantation should be performed.

Outcomes

Primary End Points

For the primary end point, the frequency of conversations about treatment options after graft loss as perceived by the patient will be compared between the 2 groups at 12 months after randomization.

Secondary End Points

As the main secondary end points, the 2 different assessment tools for SDM, the CollaboRATE mean score and the Control Preference Scale (CPS; adapted version as used in previous studies [29]), are compared between the 2 groups at 12 months after randomization. The CPS is widely used as a validated tool to assess involvement in SDM [29,30]. However, it has been suggested that CPS may be misleading in some contexts of medical decision-making since it does refer explicitly to a "decision," whereas, CollaboRATE is a brief process-orientated measure that recognizes that study participants may not always realize that a decision has been made or have difficulties focusing on 1 decision in the context of a complex care experience [31,32]. CollaboRATE has shown discriminative validity and interrater reliability. To supplement the quantitative outcome measures, qualitative data collection in the form of interviews will be performed and analyzed. All questionnaires and interview guides will be developed with the help of a multidisciplinary research group and pilot tested with patients and support persons to optimize acceptability and feasibility. Other secondary end points are summarized in Textbox 1.

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Textbox 1. Secondary end points and time frame after which they are assessed

End points

- CollaboRATE mean score of all study visits from study inclusion until month 12 (values 0-9, higher values indicating better outcome)
- CollaboRATE mean score of all study visits from study inclusion until month 24 (values 0-9, higher values indicating better outcome)
- Mean Control Preferences Scale of all study visits from study inclusion until month 12 (values 1-5, higher values indicating better outcome)
- Mean Control Preferences Scale of all study visits from study inclusion until month 24 (values 1-5, higher values indicating better outcome)
- Frequency of kidney replacement therapy after graft loss at 12 months
- Frequency of kidney replacement therapy after graft loss at 24 months
- Frequency of emergency dialysis after graft loss at 12 months
- Frequency of emergency dialysis after graft loss at 24 months
- Frequency of dialysis initiation via arteriovenous-shunt after graft loss at 12 months
- Frequency of dialysis initiation via arteriovenous-shunt after graft loss at 24 months
- Frequency of dialysis initiation via permanent catheter after graft loss at 12 months
- Frequency of dialysis initiation via permanent catheter after graft loss at 24 months
- Frequency of retransplantation after graft loss at 12 months
- Frequency of retransplantation after graft loss at 24 months
- Qualitative analysis of semistructured interviews after at 24 months
- Qualitative analysis of physician-patient conversations after at 24 months
- Frequency of conversations about treatment options after graft loss as perceived by the patient will be compared between the 2 groups at 24 months

Procedures

Overview

The study plan is summarized in Table 2.

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Table 2. Study plan including the data and time points at which these are assessed.

Data	Day 0 (visit 1)	Month 3 (visit 2)	Month 6 (visit 3)	Month 12 (visit 4)	Month 24 (visit 5)
Consent	✓				
Inclusion or exclusion criteria	✓				
Randomization	✓				
AI[a] system (intervention group)		✓	✓	✓	✓
Demography, transplant data, medical history, and height	✓	✓	✓	✓	✓
CollaboRATE score	✓	✓	✓	✓	✓
Control preferences scale	✓	✓	✓	✓	✓
Qualitative interviews	✓	✓	✓	✓	✓
Recall	✓	✓	✓	✓	✓
Vital signs (BP[b], HR[c], and weight)	✓	✓	✓	✓	✓
Safety lab	✓			✓	✓
Serum creatinine and eGFR[d]	✓	✓	✓	✓	✓
Proteinuria or albuminuria	✓	✓	✓	✓	✓
HLA[e] antibodies	✓			✓	
Tacrolimus trough level	✓	✓	✓	✓	✓
Quality of life (PROMIS-29[f])	✓	✓	✓	✓	✓
Clinical assessment	✓	✓	✓	✓	✓
AEs[g] or SAEs[h], AEs of interest, graft loss, and death	✓	✓	✓	✓	✓
Hospitalizations (reason, length, and type)	✓	✓	✓	✓	✓
Physician visits and contacts	✓	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓	✓
Prior or concomitant medications	✓	✓	✓	✓	✓

[a]AI: artificial intelligence.

[b]BP: blood pressure.

[c]HR: heart rate.

[d]eGFR: estimated glomerular filtration rate.

[e]HLA: human leukocyte antigen.

[f]PROMIS-29: Patient Reported Outcomes Measurement Information System 29.

[g]AE: adverse event.

[h]SAE: serious adverse event.

Details of the AI-Based DSS and Recommended Procedures

An AI-based prediction model will be implemented to provide real-time predictions of the 1-year risk for graft loss based on the patient's clinical, laboratory, immunological, and histopathological data. A previous version of the prediction model has been described in detail before, and all substantial changes will be made publically available. The predictions are provided as regression scores from 0 to 100 with higher scores indicating higher risk. For ease of interpretability, each score is classified into low-, medium-, or high-risk categories, which are color-coded as green, yellow, and red. Along with the risk score and risk category over time, relevant risk factors are provided to increase interpretability for the latest risk assessment.

Physicians will undergo training, in which technical details of the underlying model (training cohort, inclusion and exclusion criteria, end point definition, and performance), and results of preclinical studies are presented [11]. Hereby, the physicians can gain familiarity with the AI-DSS and also discuss potential limitations with the developers and study physicians. These training sessions will be recorded and analyzed as part of the qualitative subproject.

During the study, the physicians are advised to use the AI-DSS as an additional source of information and be especially cautious in case of high risks detected by the AI-DSS. In any case, it will

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be left to the physician's choice on how to include the system's information in the conversation with patients and support persons.

However, if the AI-DSS shows a high risk for graft loss, the physicians are free to discuss this with the patient and offer 1 procedure depending on their own assessment. First, physician—high risk for graft loss: if the physician agrees that there is a high risk of graft loss in a patient during the next year, the physician is advised to discuss this risk with the patient, when the situation is appropriate (enough time, no other major problems to be discussed, etc) or to discuss it during the next appointment. The physician should assess, whether the preferred renal replacement modality (hemodialysis, peritoneal dialysis, and retransplantation) of the patient is known and take measures to ensure a smooth transition without the need for emergency hospitalization (shunt planning, peritoneal dialysis catheter implantation, appointment for living donation, etc). Second, physician—low risk for graft loss: if the physician disagrees with the AI system and estimates a low risk for graft loss in a particular patient, the physician is advised to reconsider potential risk factors. The physician is free to incorporate or ignore the AI-DSS assessment into the SDM with patients and support persons.

Details on Qualitative Research Methodology

Overview

The physician-patient conversation will be recorded if physicians, patients, and support persons do not withdraw consent at randomization, as well as 3, 6, 12, and 24 months after randomization. Additionally, patients will be interviewed at randomization, as well as 3, 6, 12, and 24 months after randomization. Data collection at randomization, as well as 12 and 24 months after randomization will be conducted face-to-face, if possible and preferred by study participants. Data collection at 3 and 6 months after randomization will be conducted via telephone. This is to reduce the research-related burden on the participants. It has been suggested that telephone interviews produce similar quality data as face-to-face interviews [33-35]. Also, patients may appreciate being interviewed via telephone as they may feel more relaxed when being interviewed on the telephone and may find it easier to rearrange a telephone interview, rather than having to rearrange a face-to-face interview [36-39]. Participants will be encouraged to tell their views on how the AI-based DSS impacted physician-patient-support person communication and how treatment decisions were made, in the way they prefer, with as little interruption as possible from the interviewer. This narrative approach will help elicit the variety and interplay of potential factors related to treatment discussions [40]. The initial narrative will be followed by semistructured questions which will be developed based on a literature review and discussions among the research team which involves experts in the areas of medicine, communication and behavioral science, health services research, ethics, and medical informatics.

Influence of AI-Based Decision Support on the Normative Foundations of the Use of AI in SDM

Participants will be asked questions on their perceptions of concepts such as trust, agency, or transparency, for instance about how they evaluate the outputs of the tool and how these outputs relate to their physicians' judgments. Participants may also be asked to report on their views on the system's validity, effectiveness, and the perceived likelihood of errors, as well as on who is morally and legally liable for single treatment decisions.

Use of AI-Based Decision Support and Barriers and Enablers to its Implementation

Participants will be asked about their perceptions of acceptability, ease of use, agreement with specific components of the system's outputs, and self-efficacy (ie, the belief that one can understand and use the system's output). Participants will also be asked about further potential barriers to the use of AI in routine care, such as environmental factors like time pressure. These questions will be informed by the literature and discussions among the research team [41,42].

Sociodemographic and Disease Variables

Sociodemographic and disease variables obtained from patients and support persons will include gender, marital status, country of birth, postcode, highest level of education completed, income, and perceived health status. The support persons will also be asked to self-report their relationship to the patient and whether they are living with the patient. All sociodemographic and disease variables will be assessed at baseline and follow-ups to account for changes in participants' circumstances which may affect their views and experiences [43]. With patients' permission, information regarding diagnosis, disease stage, and treatments received will be obtained from patients' medical records to decrease the research-related burden on patients. At the end of the interview, participants will be given the option to provide additional comments.

Statistical Analysis

Preliminary analysis will involve computing descriptive statistics for all quantitative variables. For continuous variables, means, SDs, and quartiles will be estimated, while categorical variables will be summarized with counts and percentages in each category. Summaries will be performed by group and by assessment, as well as for the entire study group. Primary data analysis of the primary end point will involve comparing the frequencies of conversations about treatment options after graft loss between both groups using a 2-sided χ^2 test. Secondary data analysis will include a comparison in secondary outcomes between both groups using a χ^2 test. In general, test results will be described as significant if their P values are less than .05 without adjustments for multiple inferences. Multiple imputations will be used to deal with missing data.

Qualitative Research Analysis

Interviews will be transcribed verbatim. The interviews will be recorded for the purpose of transcription on provided devices and will be deleted after the end of the research process. Transcripts will be checked for accuracy by 1 researcher and

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analyzed using framework analysis. This approach belongs to a broad family of qualitative data analysis methods often related to as "thematic analysis" or "qualitative content analysis" [44]. As suggested by these approaches, both manifest and latent content will be analyzed and descriptive and explanatory conclusions will be drawn from the data [45]. Each interview will serve as a unit of analysis. A journal of reasoning and additional ideas regarding data analysis will help ensure transparency in the coding process. This strategy has been extensively used to facilitate the reconstruction of the analysis and provide justification for the analytical steps undertaken [46,47]. Codes will frequently be compared with each other and parts of the material will be recoded, if necessary, as an intercoder agreement test and additional measure for reliability [48]. This method of qualitative data analysis will provide a systematic model for mapping and interpreting the data and is thus considered appropriate to develop a profound in-depth understanding of participants' communication experiences and preferences [46,49].

Data Management

Designated investigator staff must enter the information required by the protocol into the assigned database. Individual interviews, telephone interviews, and patient-physician conversations will be audio recorded, transcribed verbatim by a professional transcriptionist or a research team member, deidentified, and filed for data management and analysis. All qualitative data will be collected by a research team member with extensive experience in qualitative research.

Safety

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious AEs, the regular monitoring of blood chemistry and urine, and regular monitoring of vital signs, physical condition, and body weight. Appropriate sponsor personnel and investigators will monitor the safety of the participants throughout the conduct of the study. AEs mean "any untoward occurrence in a trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment" [50]. In the PRIMA-AI trial, subjects will not receive any investigational medicinal product, but physicians will be assisted by an AI-based decision support system. Thus, in this study, an AE can be any unfavorable and unintended sign, symptom, or disease (including concomitant illness), deterioration of a preexisting illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values whether or not considered to be related to the AI-based intervention. Adverse reactions (ARs) mean "all untoward and unintended responses to an investigational medicinal product unrelated to the dose administered" [50]. In PRIMA-AI, subjects will not receive any investigational medicinal product. Therefore, the definition of AR implies in this trial a reasonable possibility of a causal relationship between the event and the investigational AI-based intervention.

The period of observation for AEs extends from the baseline visit (month 0, visit 1) after informed consent was given until and including month 24 (visit 5). AEs have to be followed up until resolution or stabilization or until the subject's end-of-study visit (month 24, visit 5), whichever comes first. Preexisting conditions that do not worsen during the course of the study are not reportable as AE. To determine whether a condition has worsened, it is compared to the condition of the subject at baseline visit (month 0, visit 1). All AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means will be assessed and recorded in detail in the subject's file and on the case report form, the AE report form. All AEs will be coded appropriately at the end of the clinical study using MeDRA or, in addition, on request by the study coordinator.

The following information must be recorded: (1) AE diagnosis (if possible) or main symptom; (2) date (and time, if relevant) of onset; (3) severity (maximum observed); (4) causal relationship (reasonable possibility or no reasonable possibility); (5) seriousness (yes or no); (6) outcome; (7) action taken with the study intervention; (8) AE leading to discontinuation of the study subject (yes or no); (9) treatment of AE; and (10) stop date (and time, if relevant). For the assessment of severity, the investigator should use grades from 1 to 5 as outlined in Textbox 2.

Textbox 2. Grades of assessments of severity for adverse events.

Grade 1

Mild or asymptomatic symptoms, clinical or diagnostic observations only, and intervention not indicated.

Grade 2

Moderate, minimal, local, or noninvasive intervention indicated, and limiting age-appropriate instrumental activities of daily living. Instrumental activities of daily living are activities such as preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Grade 3

Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, and limiting self-care activities of daily living. Self-care activities of daily living are activities such as bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

Grade 4

Life-threatening consequences and urgent intervention indicated.

Grade 5

Death related to adverse event.

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Ethical Considerations

Written informed consent will be collected from all study participants before performing any research activity by a research team member. To ensure the eligibility of a participate in the trial, the researcher will review the inclusion and exclusion criteria with potential participants prior to beginning the informed consent process. Prospective participants will be asked to personally sign and date the latest approved version of the informed consent forms before any trial procedure is performed. During the informed consent process, study participants will be informed of their right to withdraw from the study at any time without any impact on their treatment at the KTC. This study will be conducted in accordance with the tenets of the Declaration of Helsinki (1996). The ethics committee of Charité—Universitätsmedizin Berlin approved this study (EA1/177/23; August 08, 2023).

The trial results will be disseminated through a variety of strategies, including academic publications, research reports, infographics, media releases, and community events. Trial participants' anonymity and confidentiality will be protected during these activities by removing all identifiable information from the knowledge dissemination products.

Results

As of March 10, 2024, we enrolled 19 participants. The first results are expected to be submitted for publication in 2025.

Discussion

Principal Findings

This study is designed to investigate the influence of AI-based risk prediction on the frequency of conversations about treatment options after graft loss and the associated SDM process with a randomized design using a mixed methods approach. It is the first study in the context of kidney transplantation to analyze the potential effects of AI-based interventions on physician-patient interaction.

Despite tremendous enthusiasm surrounding the potential for AI to improve medical prognosis, diagnosis, and decision-making, only limited empirical data are available to help understand patients' and physicians' perspectives on how AI impacts their interactions, specifically SDM [16]. In the context of kidney transplantation, AI research has mostly focused on technical and medical challenges relating to robustness and implementation, excluding the sociotechnical environment into which such systems are embedded [12-14]. In the treatment of patients with cancer, an intervention that delivered machine learning mortality predictions with behavioral nudges to oncology clinicians significantly increased the rate of serious illness conversations [51,52]. While serious illness conversations are only in part comparable to conversations about graft loss, returning to dialysis after transplantation is also a life-changing event with serious effects on quality of life. We argue that increasing the frequency of conversation about treatment options after graft loss and improving SDM may improve patient satisfaction comparable to patients with chronic kidney disease without transplantation [6].

Strengths and Limitations

The main strength of this study is the mixed methods approach that will support the analysis of the primary end point with validated assessment tools for SDM and qualitative data from semistructured interviews. It is the first study in the context of kidney transplantation that investigates the impact of AI-based risk prediction on physician-patient interaction. While performed in a tertiary care setting, transplant nephrologists often serve as primary caregivers to kidney transplant recipients. Therefore, the results may generalize to a broader range of care settings as well. The randomized design enables to detect potential effects of the AI-based risk prediction on the conversation frequency about graft loss, which can improve patient information and patient care. It also provides us with a control group, in which SDM about treatment options after graft loss in kidney transplantation can be studied without any intervention, which has not been done so far. Another strength is the long observation time of 24 months, which enables to detect potential adaptations of physicians, patients, and support persons to the novel AI system and the emergence of a sociotechnical system in the recordings of patient-physician interactions as well as the semistructured interviews.

The main limitation is that potential effects of the AI intervention on SDM are indirect since no specific SDM intervention has been implemented and the AI system is not designed to improve SDM in particular, for example, by providing different scenarios or enabling input of patient preferences. Another potential limitation is that participation in the trial may influence physicians to talk about treatment options after graft loss, which may reduce the potential effect size of the AI intervention. Furthermore, the open-label design, which is unavoidable, introduces the possibility of bias, especially since the primary end point is not a medical end point.

Conclusions

In conclusion, this study will generate novel and important data about the impact of AI on physician-patient interaction and SDM in the context of kidney transplantation, which may be applicable to other disease contexts as well.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the German Federal Ministry of Education and Research.
[PDF File (Adobe PDF File), 367 KB - resprot_v13i1e54857_app1.pdf]

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Abbreviations

AE: adverse event
AI: artificial intelligence
AR: adverse reaction
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CPS: Control Preference Scale
DSS: decision-support system
eGFR: estimated glomerular filtration rate
KTC: kidney transplant center
PRIMA-AI: Prospectively investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care
SDM: shared decision-making

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Protocol

Combined Motivational Interviewing and Ecological Momentary Intervention to Reduce Hazardous Alcohol Use Among Sexual Minority Cisgender Men and Transgender Individuals: Protocol for a Randomized Controlled Trial

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Abstract

Background: Sexual minority cisgender men and transgender (SMMT) individuals, particularly emerging adults (aged 18-34 years), often report hazardous drinking. Given that alcohol use increases the likelihood of HIV risk behaviors, and HIV disproportionately affects SMMT individuals, there is a need to test interventions that reduce hazardous alcohol use and subsequent HIV risk behaviors among this population. Ecological momentary interventions (EMIs), which use mobile phones to deliver risk reduction messages based on current location and behaviors, can help to address triggers that lead to drinking in real time.

Objective: This study will test an EMI that uses motivational interviewing (MI), smartphone surveys, mobile breathalyzers, and location tracking to provide real-time messaging that addresses triggers for drinking when SMMT individuals visit locations associated with hazardous alcohol use. In addition, the intervention will deliver harm reduction messaging if individuals report engaging in alcohol use.

Methods: We will conduct a 3-arm randomized controlled trial (N=405 HIV-negative SMMT individuals; n=135, 33% per arm) comparing the following conditions: (1) Tracking and Reducing Alcohol Consumption (a smartphone-delivered 4-session MI intervention), (2) Tracking and Reducing Alcohol Consumption and Environmental Risk (an EMI combining MI with real-time messaging based on geographic locations that are triggers to drinking), and (3) a smartphone-based alcohol monitoring–only control group. Breathalyzer results and daily self-reports will be used to assess the primary and secondary outcomes of drinking days, drinks per drinking day, binge drinking episodes, and HIV risk behaviors. Additional assessments at baseline, 3 months, 6 months, and 9 months will evaluate exploratory long-term outcomes.

Results: The study is part of a 5-year research project funded in August 2022 by the National Institute on Alcohol Abuse and Alcoholism. The first 1.5 years of the study will be dedicated to planning and development activities, including formative research, app design and testing, and message design and testing. The subsequent 3.5 years will see the study complete participant recruitment,

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data collection, analyses, report writing, and dissemination. We expect to complete all study data collection in or before January 2027.

Conclusions: This study will provide novel evidence about the relative efficacy of using a smartphone-delivered MI intervention and real-time messaging to address triggers for hazardous alcohol use and sexual risk behaviors. The EMI approach, which incorporates location-based preventive messaging and behavior surveys, may help to better understand the complexity of daily stressors among SMMT individuals and their impact on hazardous alcohol use and HIV risk behaviors. The tailoring of this intervention toward SMMT individuals helps to address their underrepresentation in existing alcohol use research and will be promising for informing where structural alcohol use prevention and treatment interventions are needed to support SMMT individuals.

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KEYWORDS

alcohol use; sexual minority; transgender; young adults; mobile health; mHealth; HIV risk behaviors; sexual risk behaviors; motivational interviewing; ecological momentary interventions; mobile phone

Introduction

Background

Those who identify as sexual and gender minority individuals (eg, gay, bisexual, transgender, or queer individuals) are more likely to report hazardous drinking, defined as "drinking behavior (such as per episode, daily, or weekly) that reflects meaningful increases in risk of negative alcohol-related outcomes" [1] and to have alcohol use disorders (AUDs) than their cisgender and heterosexual peers [2-5]. Similarly, emerging adult (aged 18-34 years) sexual and gender minority individuals are at increased odds of being diagnosed with AUDs compared to older adults, with up to 44% meeting AUD criteria [3,6]. An extensive body of research suggests that the increased use of alcohol among young sexual and gender minority populations is attributable to interlocking structural underpinnings of stigma, homophobia, transphobia, and other manifestations of violence against queer people [5,7-9]. These trends are concerning because multiple studies have found that alcohol use increases the likelihood of acquiring HIV through various behaviors [10-13] and that HIV disproportionately affects emerging adult sexual minority cisgender men and transgender (SMMT) individuals [14]. Consequently, individuals who have reported unhealthy levels of alcohol use also were likely to experience interference with their decision-making with regard to adhering to pre-exposure prophylaxis (PrEP) [15], which can prevent HIV. Thus, it is essential to test interventions for reducing alcohol use among SMMT individuals as a means of preventing HIV among these populations considered to be at high risk.

A recent systematic review found that motivational interviewing (MI) is a frequently used method for reducing alcohol use [16]. MI is a goal-oriented and patient-centered approach to motivating behavior change and increasing self-efficacy. While it has been effective for reducing alcohol use among gay and bisexual men [17-19], this review found only 1 alcohol-related MI intervention for transgender people [20], suggesting the need for more research with this population. Prior studies also suggest the effectiveness of MI being delivered through technology to support the reduction of alcohol use behaviors [21]. The Tracking and Reducing Alcohol Consumption (TRAC) intervention, recently tested among people with HIV and currently being tested (since July 2023) among young adult survivors of cancer, uses smartphones to deliver 4 to 8 weekly sessions of MI for reducing risky drinking. The sessions focus on identifying triggers for drinking and strategies for addressing these triggers. TRAC also incorporates daily smartphone-based alcohol monitoring (SAM) using mobile breathalyzers and surveys. While preliminary results are promising in terms of TRAC's effectiveness and acceptability [22], there is potential for enhancing it by reinforcing content in real-time situations where people are more likely to experience triggers to use alcohol.

Ecological momentary interventions (EMIs), which use smartphones to deliver messages to reduce alcohol use and related risk behaviors during or before drinking events, can help to address triggers in real time. GPS tracking can determine when individuals visit places where they have previously reported drinking or triggers to drink, and then EMI messages can be delivered upon arrival to *prevent* hazardous alcohol use. However, this GPS-based approach has rarely been studied to date and has generally targeted individuals with AUDs (as opposed to those who engage in hazardous drinking but do not have an AUD) [23,24]. We have developed a mobile app for a previous observational study that uses GPS tracking to determine when emerging adult SMMT individuals visit *riskylocations* and then delivers a survey asking about aspects of the location's social and geographic context that may relate to drinking and other risk behavior.

Objectives

The goal of the proposed study is to use this app to enhance TRAC by delivering messages that encourage participants to use strategies discussed during TRAC sessions when arriving at risky locations. When they leave these locations, they will complete a survey and a breathalyzer reading to collect event-level self-report and biological data on alcohol use and HIV risk. If their breathalyzer result indicates alcohol use, they will receive harm reduction messaging. It is expected that combining TRAC with EMI (Tracking and Reducing Alcohol

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Consumption and Environmental Risk [TRAC-ER]) will increase effectiveness by reinforcing topics discussed during sessions, providing in-the-moment messaging to address triggers, and collecting real-time alcohol use data.

We will conduct a randomized controlled trial (RCT) of the TRAC and TRAC-ER interventions, examining their effects on alcohol use and HIV risk behaviors among SMMT individuals compared with a SAM-only control group. We will examine 2 aims.

- Aim 1: assess the effects of intervention conditions on drinking days (primary end point), drinks per drinking day, and binge drinking episodes (secondary end points).
  Hypothesis:
  TRAC and TRAC-ER will lead to significantly fewer drinking days compared with a SAM-only control group, with TRAC-ER having the strongest effects.
- Aim 2: assess the effects of intervention conditions on HIV risk behaviors (unprotected sex, number of partners, concurrent sex and substance use, and PrEP nonadherence).
  Hypothesis:
  TRAC and TRAC-ER will lead to significantly fewer HIV risk behaviors compared with a SAM-only control group, with TRAC-ER having the strongest effects.

Methods

Study Design

We will conduct a 3-arm RCT of TRAC and TRAC-ER (n=405 HIV-negative SMMT individuals; n=135, 33% per arm), with the following conditions: (1) SAM-only comparison group, (2) SAM+TRAC (no EMI messaging), and (3) SAM+TRAC-ER (participants receive EMI messaging when visiting risky locations).

Breathalyzer results and daily self-reports will be used to assess the primary and secondary outcomes of drinking days, drinks per drinking day, binge drinking episodes, and HIV risk behaviors. Additional assessments at baseline (T1), 3 months (T2), 6 months (T3), and 9 months (T4) will evaluate exploratory long-term outcomes, including diagnoses of HIV or other sexually transmitted infections (STIs).

Participants and Recruitment

Overview

Participants will be recruited using web-based and community-based recruitment, as well as through health clinics that serve SMMT individuals. A combination of venue-based and purposive sampling approaches appropriate for accessing populations considered to be hard to reach and at risk will be used to recruit participants [25-27]. Previous intervention studies with young adult SMMT populations have found 6-month dropout rates of 15% to 25% [28-30]. To reach our target final sample (n=324; refer to the Sample Size Justification subsection), we will recruit 405 individuals, accounting for an estimated 20% dropout rate based on prior literature.

Health Clinics

All patients presenting for appointments at participating clinics will be screened using a preprogrammed tablet computer to determine eligibility. The principal investigators will provide instruction to clinic staff regarding screening patients and distribute quick-reference study information sheets to keep in offices. The study coordinator will be available during business hours to help clinic staff as needed.

Web-Based and Community-Based Recruitment

Our previous studies have successfully used a variety of recruitment methods to reach SMMT individuals, which we will also leverage in the proposed study: flyer outreach (in locations frequented by SMMT individuals), social media recruitment (including paid and free posts on Instagram, Facebook, Reddit, and dating apps), a study website, and institutional collaborations. All advertisements will direct participants to the web-based screener. We will use a community advisory board, comprising members representing different subsets of the SMMT population, to obtain further guidance regarding ideal participant recruitment methods.

Inclusion and Exclusion Criteria

Participants will be eligible to participate if they meet the following inclusion criteria: (1) self-identify as a gender minority individual (eg, transgender man, transgender woman, nonbinary individual, agender individual, or gender fluid individual) or a sexual minority cisgender man (ie, assigned male sex at birth and identifies as a man with a sexual orientation other than heterosexual), (2) is aged between 18 and 35 years at the start of the study, (3) owns a smartphone, (4) is HIV-negative (confirmed through a test at baseline), (5) meets Centers for Disease Control and Prevention PrEP eligibility criteria (individuals will be eligible if they have had anal or vaginal sex in the past 6 months and have at least one of the following characteristics: a sexual partner with HIV, inconsistent condom and PrEP use, or a sexually transmitted disease diagnosis in the past 6 months; or if they inject drugs and have an injection partner with HIV or share needles, syringes, or other equipment to inject drugs) [31], and (6) screens positively for hazardous alcohol use. As most alcohol screening instruments rely on biological sex, we will use a combination of the Alcohol Use Disorders Identification Test–Concise (AUDIT-C), a validated 3-item screener for hazardous alcohol use [32], and a 1-item yes or no screening question to determine whether they engage in hazardous alcohol use (“Have you had 5 or more drinks on one occasion in the past year?”). This question was found to be a valid measure of hazardous alcohol use among gender-diverse individuals; despite it being a single item, this screening method performed better than the AUDIT-C for lower drink thresholds (eg, ≥4 drinks) in predicting hazardous alcohol use [33]. However, because this is still a new approach to assessing hazardous drinking and because we will also be enrolling cisgender individuals, we will consider AUDIT-C scores too; participants must also score ≥4 on the AUDIT-C to qualify [32].

Exclusion criteria include (1) not speaking English; (2) active psychosis or severe mental illness; (3) actively detoxifying from

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substances and needing medical supervision; or (4) a score of ≥20 on the Alcohol Use Disorders Identification Test [32], which indicates that participants exhibit increased or higher risk drinking behaviors.

Regardless of the recruitment method used, all participants will complete a web-based screener. If participants are determined to be eligible according to the screener, they will be informed of their eligibility and invited to provide their contact information if they wish to learn more about the study.

Sample Size Justification

Sample size determination was based on the primary outcome variable: number of drinking days in the past month across the repeated visits corresponding to T1, T2, T3, and T4 for the 3 groups (SAM only, SAM+TRAC, and SAM+TRAC-ER). Data on effect sizes from previous alcohol use interventions [34,35] and our preliminary data (within-participant correlation of 0.69) were used to derive the mean number of days of alcohol use and their SDs. With a final sample size of n=324 (after accounting for a 20% dropout rate with a total n=405), 108 (33%) participants in each group will give us at least 90% power at 5% type I error rate to detect a significant difference among the groups for an effect size of 0.071 when comparing the groups over the study period. This effect size is smaller than a *small* effect as defined by Cohen et al [36].

We expect our sample to have the following characteristics: 48.1% (195/405) cisgender men, 24.9% (101/405) transgender men, 20% (81/405) transgender women, and 6.9% (28/405) nonbinary individuals. Our sample will likely have a higher proportion of transgender participants compared to the general population due to recruitment within health clinics that provide care for transgender patients; we view this as a strength of our study, given the underrepresentation of gender minority individuals in previous alcohol intervention and HIV prevention research.

Enrollment

If participants are determined to be eligible according to their responses to the web-based screener, they will be informed of their eligibility and invited to provide their contact information if they wish to learn more about the study. If participants are ineligible, they will be informed of this upon completion of the screener. A member of the study team will contact eligible participants via their preferred contact method to complete an interview confirming eligibility. This interview is conducted via Zoom (Zoom Video Communications, Inc) and is included as protection against spam or false screener responses.

Study Interventions and Procedures

Description of TRAC-ER Study App

The app developed for this study has been designed to track participants' physical location through continuous GPS monitoring and to deliver assessments and messages at specific times of the day and in response to participants' physical location. At baseline, all participants will be asked to list the locations where they most frequently engage, or are triggered to engage, in alcohol use, unprotected sex, or other HIV risk behaviors as part of an activity space assessment. For each listed location, they will provide information regarding the types of alcohol triggers they experience (eg, social, situational, or emotional). These locations will then be programmed into the app and given a geofence (a distance around the location such that when participants break the geofence, intervention-specific actions such as surveys or messages are delivered). Before each follow-up monitoring period, participants will complete a short questionnaire that lists the locations they identified in the activity space assessment, as well as locations where they reported drinking via the random breathalyzer reading requests during prior monitoring periods. They will have the opportunity to revise the list of locations, which will ensure that the triggered surveys are being delivered for locations most relevant to the participants.

Every morning during the SAM periods, participants will receive a push notification asking them to report the number of drinks consumed in the previous day (if applicable), time spent drinking, alcohol withdrawal symptoms, and sexual risk behaviors. The app will also send requests for breathalyzer readings at least 2 times per day in response to visits to risky locations and through random requests. At the time of providing the breathalyzer reading, participants will also complete a brief mobile survey using the study app that includes questions related to their alcohol use. Participants can view a log of their breathalyzer readings in the app. Participants will have the option to report a trigger in the app and provide details about the trigger, including the location where the trigger was generated. Participants who are randomized to the TRAC-ER intervention will receive a harm reduction message based on the type of trigger (social, emotional, or other) they report. A guided breathing exercise and urge surfing exercise are included in the app for those in the TRAC and TRAC-ER conditions. Figure 1 presents a screenshot of the app. If, at any point during the monitoring periods, the app stops collecting GPS data, the study team will reach out to determine whether the participant accidentally turned off location tracking, lost their mobile phone, or is experiencing other technical difficulties.

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Figure 1. Tracking and Reducing Alcohol Consumption and Environmental Risk (TRAC-ER) app screenshots (app developed by Vista IT Solutions, LLC).

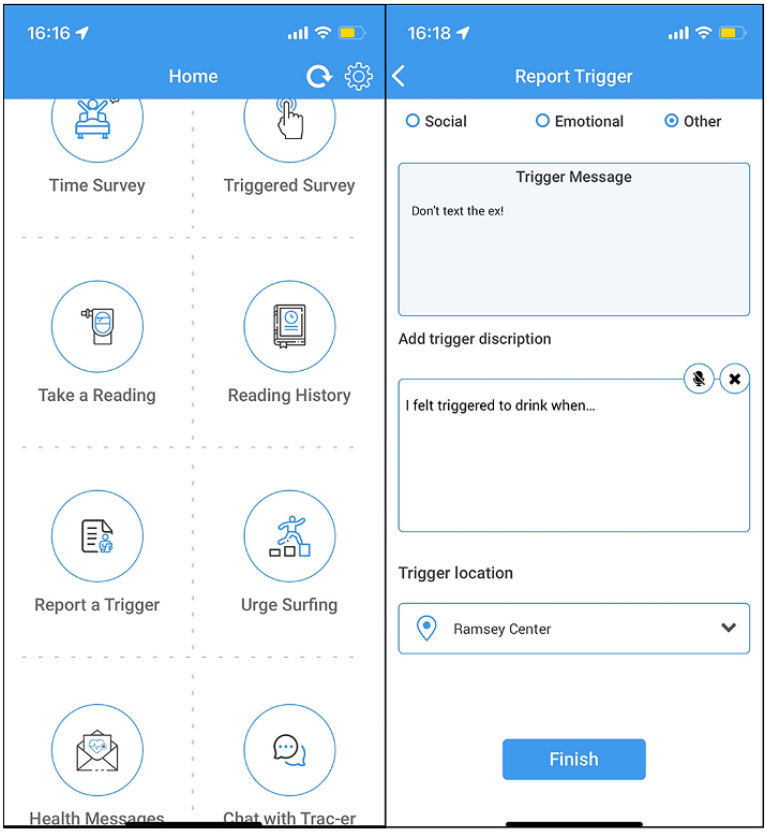

Description of Study Arms

Overview

Participants will be enrolled in the study for 9 months, including the 2-month intervention period and multiple follow-up monitoring periods to assess long-term effects. All participants will begin with a 30-day monitoring period, which will establish baseline alcohol use through daily breathalyzer reading requests and surveys. After this 30-day period, they will complete additional baseline measures (T1) and then begin their assigned intervention, if applicable. After the interventions are delivered, participants will complete an additional self-report (T2). Subsequently, there will be 2 additional monitoring periods and assessments spread across the 9-month study period to assess long-term intervention effects, with some months involving no study activities. A depiction of the participation timeline is included in Figure 2, and details of study activities completed across the study timeline and RCT arms are provided in Table 1.

Figure 2. Participation timeline. STI: sexually transmitted infection; TRAC: Tracking and Reducing Alcohol Consumption; TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk.

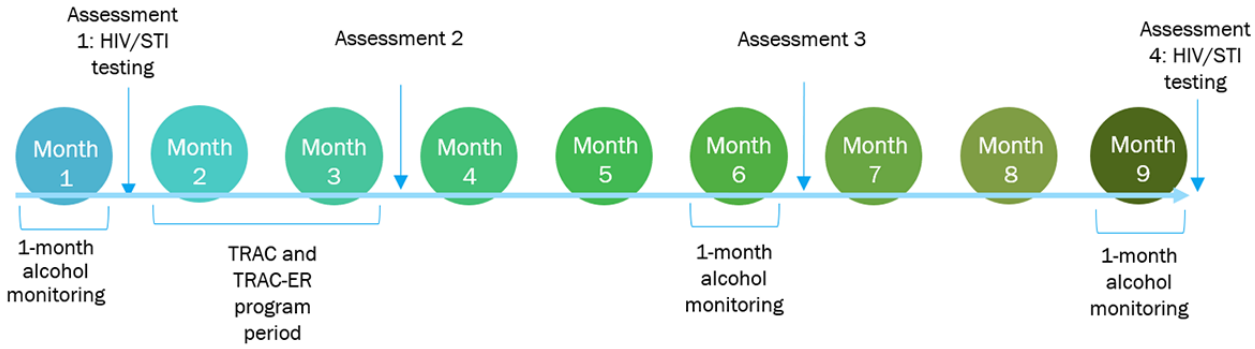

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Table 1. Summary of research activities across the randomized controlled trial conditions.

Days and research activities	Control	TRAC[a]	TRAC-ER[b]
1-30			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
31-90			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
TRAC intervention			
Participant completes 4 TRAC sessions via video or telephone call on a weekly basis		✓	✓
TRAC-ER in-app messages			
Deliver prevention message upon arrival at risky location			✓
Deliver harm reduction message if, upon leaving a risky location, participants have a positive			✓
Deliver a self-help message if participant taps *report a trigger* in the app			✓
91-150			
No research activities			
151-180			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
181-240			
No research activities			
241-270			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Two random breathalyzer readings and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓

[a]TRAC: Tracking and Reducing Alcohol Consumption.

[b]TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk.

SAM-Only Participants

Participants will complete alcohol self-monitoring tasks using the study app (daily surveys and breathalyzer readings) during months 1 to 3, month 6, and month 9. During these designated months, participants will receive prompts to complete morning surveys, random breathalyzer requests, and location surveys, as described in Table 1.

SAM-only participants will also complete the T1 to T4 assessments on the schedule illustrated in Figure 1.

TRAC Participants

TRAC participants will complete alcohol self-monitoring tasks and assessments following the schedule described for SAM-only participants. In addition, participants will receive the 4-session TRAC intervention. Individuals will meet for 30 minutes with an interventionist on a weekly basis via telephone or video chat, although the 6-week intervention period allows for some cancellations or rescheduling. Textbox 1 presents an overview of the 4-session TRAC intervention. Participants will be mailed a paper workbook to complete during the sessions. The SAM app will provide supplementary materials, including a triggers

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diary, a guided breathing exercise, and a record of the participants' goals for reducing their drinking. After participants complete all intervention sessions, they will continue daily monitoring for the remainder of the 2-month intervention period. Participants will complete the T1 to T4 assessments following the schedule described for SAM-only participants.

Textbox 1. Session overview of the Tracking and Reducing Alcohol Consumption (TRAC) intervention.

Session 1

- Introduction (5-8 minutes)
- Alcohol and health factsheet (10 minutes)
- Review current alcohol use (15 minutes)
- Complete change plan (10 minutes)
- Diaphragmatic breathing (8 minutes)
- Wrap up and schedule next session (5 minutes)

Session 2

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (10 minutes)
- Review strategies for managing triggers (20 minutes)
- Urge surfing skill (10 minutes)
- Wrap up and schedule next session (5 minutes)

Session 3

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (10 minutes)
- Strategies for reducing alcohol-related harm (20 minutes)
  - Before known drinking occasions
  - While drinking alcohol
  - After drinking alcohol
- Wrap up and schedule next session (5 minutes)

Session 4

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (5-8 minutes)
- Review overall progress (5-8 minutes)
- Set goals and plan for going forward (10-15 minutes)
- Wrap up and give reminder of remaining study tasks (5 minutes)

TRAC-ER Participants

Overview

Participants will complete all aspects of the TRAC intervention condition. In addition to receiving triggered surveys when they leave a risky location, participants will also receive prevention messaging when they first arrive at a risky location. This messaging will be tailored based on the data collected regarding participants' risky locations and the strategies to address triggers discussed during the MI intervention sessions. In addition, if participants return a breathalyzer reading >0.00%, they will receive harm reduction messaging encouraging them to engage in protective behaviors. These messages will continue throughout the 2-month intervention period, including after the 4 TRAC sessions have been completed. Participants will complete the T1 to T4 assessments following the schedule described for SAM-only participants.

MI Interventionist Training and Fidelity Assessment

The full-time study interventionist, an individual with a master's degree in counseling, will receive refresher training from a supervisor who is a licensed clinical social worker regarding the principles of MI as they relate to substance use and the key components of the TRAC intervention through 12 hours of instruction and mock interviews. This supervisor will review the interventionist's first TRAC case (or additional cases, if needed). Fidelity ratings will be conducted using a combination of the Motivational Interviewing Treatment Integrity (MITI)

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4.2.1 coding system and adherence checklists to be developed by the study team to code for the presence of specific skills and exercises included in the TRAC protocol. MITI is an established structured behavioral coding system that serves as a treatment fidelity measure for clinical trials of MI [37,38]. It provides a global impression of empathy and MI spirit, a reflection-to-question ratio, and summary scores for MI components based on behavior count ratios of complex reflections, open questions, and MI-adherent utterances. The interventionist will be *certified* as able to deliver the protocol with fidelity. Certification will involve meeting adherence of at least 80% of TRAC-specific skills and exercises and the recommended MI competency threshold on at least 80% of sessions for a given case. Until the interventionist is certified, the supervisor will review entire session recordings weekly to code TRAC adherence, and a randomly selected 20-minute segment will be coded with MITI. Individual feedback and training will be provided weekly. Overall trial fidelity ratings (adherence to TRAC skills and exercises and MI competency) will be determined via review of an additional randomly selected 20% of interviews (10% from each site), in line with recommendations for RCTs of MI [39], including double coding by the supervisor and a research assistant, both of whom will be certified in MITI coding.

Data Collection Procedures

Overview

As this study is examining both short- and long-term effects and comparing them among the groups, the primary end point of the number of past-month drinking days will be assessed based on SAM results collected before T1, throughout the intervention, and before T3 and T4. Secondary end points include drinks per drinking day and binge drinking episodes. All other variables measured, including those related to HIV risk behaviors, will be used to conduct exploratory analyses. The sources of data for this RCT include SAM data (including surveys and breathalyzer results, discussed in detail previously), baseline and follow-up self-report measures (T1-T4), HIV and STI testing, app-based process measures, and qualitative interviews.

Baseline and Follow-Up Measures

An assessment battery will be administered to all participants at T1, T2, T3, and T4. This will include several measures of alcohol use as well as more exploratory variables, including alcohol cravings, alcohol consequences, the use of alcohol treatment services, HIV risk behaviors, and experiences of discrimination related to participants' identity as sexual and gender minority individuals. Table 2 presents a description of the key study measures.

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Table 2. Description of key study measures.

Construct and time	Measure	End point	Description
Drinking days, 2× daily	Breath alcohol content	Primary	BACtrack Mobile breathalyzer result sent via mobile app; measured 2× daily for 8 weeks during the intervention and for 1 month before T1[a], T3[b], and T4[c]; 2 negative readings per day=nondrinking day
Drinks per drinking day, daily	Self-reported alcohol use through app	Secondary	3 items: alcohol consumed (yes or no), number of drinks, and time spent drinking; measured daily during the intervention and for 1 month before T1, T3, and T4
Binge drinking episodes, daily	Self-reported alcohol use through app	Secondary	Occasions when participants had ≥5 drinks based on self-reported number of drinks; measured daily during the intervention and for 1 month before T1, T3, and T4
Alcohol withdrawal symptoms, daily	Single-item AWSC[d] [40]	Exploratory	1 item: alcohol withdrawal symptom severity on a scale of 0 to 9; those scoring ≥2 are asked to complete the 17-item AWSC, which assesses the severity of symptoms; measured daily during intervention and for 1 month before T1, T3, and T4
Sexual activity, daily	Self-reported through app	Exploratory	6 items: past-day sexual activity, number of partners, partner type, partner HIV status, type of sexual activity, condomless sex, and PrEP[e] use
Location characteristics, up to 2× daily	Self-reported through app	Exploratory	12 items assessing alcohol and substance use, sexual behaviors, peer use of alcohol or substances, and harassment or discrimination experienced
Alcohol use, T1, T2[f], T3, and T4	PROMIS[g] Short Form–Alcohol Use 7a [41]	Exploratory	7 items that assess general alcohol use and problem drinking in the past 30 days (eg, drank too much and drank heavily)
Alcohol consequences			
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Negative Consequences 7a [41]	Exploratory	7 items that assess the negative consequences of using alcohol in the previous 30 days (eg, unreliability, social problems, and judgment)
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Positive Consequences 7a [41]	Exploratory	7 items that assess the positive consequences of using alcohol in the previous 30 days (eg, self-esteem, confidence, and enjoyment)
Alcohol expectancies			
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Negative Expectancies 7a [41]	Exploratory	7 items that assess the negative expectancies of alcohol use (eg, making bad decisions and behaving rudely)
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Positive Expectancies 7a [41]	Exploratory	7 items that assess the positive expectancies of alcohol use (eg, improves mood and sociability)
Readiness to change drinking, T1, T2, T3, and T4	Readiness to Change Questionnaire [42]	Exploratory	12 items that assess the stage of change toward reducing alcohol use (precontemplation, contemplation, and action)
Drinking refusal self-efficacy, T1, T2, T3, and T4	Drinking Refusal Self-Efficacy Questionnaire–Revised [43]	Exploratory	19 items that assess individuals' belief in their ability to resist alcohol, with 3 subscales: social pressure drinking, emotional relief drinking, and opportunistic drinking
Sexual risk behaviors, T1, T2, T3, and T4	National HIV Behavioral Surveillance System [44]	Exploratory	≥6 items: number of partners in previous 12 (T1) or 3 (T2-T4) months; partner type (main vs casual); partner HIV status; frequency of condomless sex (anal, vaginal, or oral), transactional sex, and concurrent sex and drug or alcohol use; and PrEP use
Condom attitudes, T1, T2, T3, and T4	Multidimensional Condom Attitudes Scale [45]	Exploratory	16 items that measure attitudes toward condoms across 7 factors: reliability, effectiveness, pleasure, identity stigma, embarrassment about purchase, negotiation, and action maintenance
Perceived HIV risk, T1, T2, T3, and T4	Perceived Risk of HIV Scale [46]	Exploratory	8 items that assess likelihood estimates, intuitive judgments, and salience of HIV risk based on previous behaviors
Discrimination due to sexual or gender identity, T1, T2, T3, and T4	Heterosexist Harassment, Rejection, and Discrimination Scale [47]	Exploratory	12 items that assess harassment, rejection, and family discrimination related to LGBTQ[h] identities
Alcohol cravings, T1, T2, T3, and T4	Penn Alcohol Craving Scale [48]	Exploratory	5 items that assess alcohol-related cravings; higher scores indicate higher rates of alcohol cravings

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Construct and time	Measure	End point	Description
Alcohol Use, T1, T2, T3, and T4	Alcohol Quantity Measures	Exploratory	7 items that assess alcohol use over the past 30 days

[a]T1: baseline assessment.

[b]T3: 6-month assessment.

[c]T4: 9-month assessment.

[d]AWSC: alcohol withdrawal symptom checklist.

[e]PrEP: pre-exposure prophylaxis.

[f]T2: 3-month assessment.

[g]PROMIS: Patient-Reported Outcomes Measurement Information System.

[h]LGBTQ: lesbian, gay, bisexual, transgender, and queer.

HIV and STI Testing

At T1 and T4, participants will receive HIV and 3-site gonorrhea and chlamydia testing. We will use myLAB Box, with whom we have worked successfully in prior research, to deliver home testing kits to participants. myLAB Box is a fully laboratory-certified company using College of American Pathologists– and Clinical Laboratory Improvement Amendments–certified testing organizations and a HIPAA (Health Insurance Portability and Accountability Act)–compliant web interface [49]. The home testing kits include written instructions for how to collect the samples; participants will complete a finger prick blood sample for the HIV test and collect swab and urine samples for the gonorrhea and chlamydia testing. The test kits will be mailed by the participants to myLAB Box using prepaid shipping boxes. Before completing testing, participants will complete a HIPAA release form giving permission for their results to be shared with the study team. In the case of a positive test, the participant will have the opportunity to complete a telehealth visit (free of charge) with one of myLAB Box's providers to discuss medications and linkage to care. The research team will also follow up with the participant to ensure that they have been connected to care and, in the case of a positive HIV test at T1, to communicate that they are no longer eligible to participate in the study.

Process Measures

We will assess several process measures related to the study app, including the number of opened and completed daily surveys, the number of messages opened, the length of time messages stayed open, the number of completed breathalyzer readings and location-based surveys, the frequency of missing GPS data, and the number of reported app issues. For each participant completing monitoring, we will generate a weekly report of these metrics to address any ongoing technical issues in a timely manner and to encourage the completion of surveys and breathalyzer readings if they are nonadherent. For the TRAC intervention, the interventionist will complete fidelity checklists after each session. We will also assess session attendance, dropout rates, and time spent in sessions. At the end of the intervention, we will conduct an overall fidelity assessment to aid in the interpretation of the intervention results. Overall, these process measures will inform future dissemination and implementation efforts.

Qualitative Intervention Assessment

At the T2 assessment, we will conduct a semistructured qualitative interview to obtain feedback on the SAM-only, and SAM+ TRAC, and SAM + TRAC-ER conditions. As applicable according to their intervention group, the interview will address the effects of the monitoring of alcohol use, attitudes toward MI intervention content, the impact of the EMI messages on drinking and HIV risk behavior, the impressions of intervention relevance and effects, challenges encountered during the intervention, and suggestions for improvement.

Participant Training

Participants in each condition will be trained to navigate the app and complete tasks, including completing location-based and daily assessments, reading messages, and providing breathalyzer readings. They will also be instructed on data safety and confidentiality procedures and how to remotely wipe their mobile phone data if it is lost or stolen. Wallet-size cards with information from the training and text reminders to carry the mobile phone and breathalyzers will be provided. A lack of response will be followed up with texts and telephone calls to ascertain the reason for noncompliance. If participants report problems, we will complete video calls to troubleshoot and further train participants, if needed.

Methods to Decrease Attrition and Missing Data

During the first 3 months of the study, participants will receive daily reminders to complete SAM, which will include information about potential incentives. Individuals in the SAM+TRAC and SAM+TRAC-ER arms will have weekly contact with research staff during the TRAC sessions and will receive reminders about upcoming appointments. We will contact participants 1 month before their follow-up monitoring periods to remind them about upcoming tasks and to ensure that contact information is up to date. The use of a novel smartphone app and a mobile breathalyzer, which has been highly rated by participants in past studies, will also help to ensure continued engagement with, and enthusiasm for, the study.

Ethical Considerations

All procedures were approved by the University of Kentucky Institutional Review Board (79109), with Yale University relying on the University of Kentucky for human participant oversight. All responses of participants will be held in confidence and kept secure. Only the researchers involved in this study and those responsible for the research oversight will have access to the information that may identify the participants.

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All participants will complete informed consent before beginning research activities. All consenting procedures will be completed remotely and electronically using the REDCap (Research Electronic Data Capture; Vanderbilt University) *eConsent* framework. First, participants will be given basic information about the study. If they indicate interest in learning more and meet eligibility criteria after completing a brief screening survey, a member of the research team will contact them via their preferred contact method to confirm eligibility, provide more details about the research procedures, and obtain informed consent.

The research team will review all aspects of the study, including specific research procedures, the length of time participants will be enrolled in the study, and the associated risks and benefits of participation (eg, benefiting from free alcohol reduction counseling, which may impact overall health, and the risks of emotional distress from completing sessions and assessments and of a loss of confidentiality). Contact information for study staff, the principal investigators, the University of Kentucky's Office of Research Integrity, and Yale University's Human Research Protection Program will be provided, and the participant will be encouraged to contact any of the relevant individuals if they have questions or concerns regarding this research or to discuss their rights as a research participant.

If a participant chooses to sign up for the study after this conversation with the research team, they will complete consent by providing an electronic signature in REDCap. A copy of the consent form will be provided to the participant electronically and retained in REDCap's file repository for study records. By signing this form, participants agree to allow for future use, and sharing of, their deidentified study data with other researchers, without additional informed consent. No participant will begin research procedures without first providing signed informed consent.

To protect confidentiality, participants will be assigned a unique study ID number. Any identifying information will not be stored alongside survey responses and will be permanently deleted after the completion of data collection in accordance with the University of Kentucky Institutional Review Board policies.

The research team will take all precautions to prevent a loss of confidentiality, one of the primary risks of this study. Data collected and stored on mobile phones are inherently less secure than other storage methods; however, participants will be advised on how to protect data stored on mobile phones, and study staff will be trained on best practices for securing information on mobile phones.

Electronic data will be stored and managed in REDCap and will be accessible only to authorized study personnel. All data collected through the mobile app will be hosted on a secure private server at Yale University. myLAB Box uses a HIPAA-compliant web portal that encrypts all medical information, and all communications sent by the company will minimize personal details. Due to the sensitive nature of HIV and STI results, we will give the test results a unique ID in addition to the study ID and maintain them in a separate REDCap database without other identifying information. Access to these, and all other study data, will be permitted only to authorized personnel, who will be trained in the areas of ethics, clinical trials, confidentiality protection, and human participant protection.

Participants can earn up to US $825 (US $685 for monitoring tasks and US $140 for assessments). All participants will receive a US $1 compliance payment for each breathalyzer sample submitted within a 90-minute period. They will also receive a US $1 payment for submitting their daily morning surveys. Thus, those who complete all monitoring tasks (all breathalyzer readings and daily self-reports) during the whole study (4 weeks before T1, 8 weeks during the intervention, and 4 weeks before T3 and T4) will receive US $685. Participants will also receive US $35 for completing the T1 assessment (US $20 for the questionnaire and US $15 for HIV and STI testing), US $25 for T2, US $30 for T3, and US $50 for T4. Escalating payments will be used to discourage study attrition.

While the compensation amount is relatively high, it is for activities completed across a full 9 months of participation. Total time spent on study activities ranges from 45 hours (SAM-only participants) to 50 hours (SAM+TRAC and SAM+TRAC-ER participants) when considering daily monitoring, assessments, time spent on screening and enrollment, and time spent in MI sessions. This results in an average compensation of US $16-$18 per hour in exchange for participation in study activities.

We will pay participants with reloadable debit cards, administered using OnCore clinical trial software (Advarra). Funds will be added to these cards as payments are earned, which then become immediately available. This system will allow for frequent payments without the burden of office visits or the delays from mailing checks.

Data Analysis Plan

Analysis of Alcohol Use Outcomes

Descriptive statistics for breathalyzer reading data will be summarized overall, by group (SAM only, SAM+TRAC, and SAM+TRAC-ER) and across time periods (T1-T4). The primary outcome is the number of drinking days in the past month, which is defined as the days on which individuals did not report 2 negative breathalyzer results. The rate of drinking (incidence of drinking) is the number of drinking days observed within the past month. The secondary outcomes include the number of drinks per drinking day, the number of days with binge drinking episodes, and the number of days for which HIV risk behaviors occur. All these outcomes are count data. The goal of this analysis is 2-fold: first, short-term analysis at the end of the 2-month intervention period, and, second, long-term analysis at the end of 9 months. We will fit a generalized linear model [50], with a general formulation for count data as follows:

$$g(E(y_i)) = g(\mu_i) = x'_i\beta \quad (1)$$

where y_i is the outcome variable for (i=1,2,3,...,n), n is the total number of observations, μ_i=$E(y_i)$ is the expected count, g is the link function (a mathematical function connecting the counts with the explanatory variables), β is a vector of regression parameters to be estimated, and x_i is a vector of independent covariates to be included in the model. These covariates include

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group, time, age (or age group), gender identity, sexual orientation, and site.

Short-Term Outcome Analyses

After 3 months, we will fit the aforementioned model to the data and compare the groups at T1 and T2 while adjusting for the covariates. The PROC GENMOD procedure in SAS (SAS Institute Inc) will be implemented to estimate the parameters of the model, where we specify a log-link function, Poisson distribution for the count data, an offset (which is a function of the total exposure), and the covariates. We will address overdispersion using negative binomial distribution. Overdispersion occurs when the expected count for the outcome variable is not the same as its variance. The generalized estimating equation procedure will be used to account for correlation induced by the repeated observations at T2.

Long-Term Outcome Analyses

At 9 months, the time variable will include observations at T1 to T4, and the procedure implemented for the short-term analysis will be repeated with the inclusion of additional covariates in the form of interaction terms among the groups and follow-up times (T1-T4). The interaction effect is central to the comparison of the groups over the study period. Generalized estimating equation fit criteria and quasi-likelihood under the independence model criterion value will be used to determine the adequacy of model fit. This modeling framework facilitates the easy computation of hypothesis tests and CIs for effects, which will form the basis of our inferential strategy in this project. Specifically, contrast statements will be used to test specific subgroup comparisons. Multiple imputation procedure will be implemented whenever necessary for missing data points. SAS (version 9.4 or higher) will be used for all analyses, and a standard 5% significance level will be used for all statistical tests.

Addressing Biological Variables

As this project is focused on SMMT individuals, rather than assessing the effects of biological sex, we will screen for the effects of gender identity and sexual orientation in the aforementioned modeling framework. This is accomplished by introducing indicator variables for these subgroups into the analyses and assessing statistical and practical significance. The stratified randomization procedure should prevent systematic differences at baseline among the groups. We will check for statistically significant differences after randomization and adjust for such differences in the analysis in the rare event that they manifest.

Qualitative Data Analysis

Audio files of postintervention interviews will be transcribed and imported into NVivo software (Lumivero). Each transcript will be examined and coded using a grounded thematic approach [51], drawing on observed themes regarding intervention attitudes, experiences, and effects. The research team will develop the coding scheme based on an initial review of the transcripts; next, 2 coders will independently code a random sample of 10% of the transcripts. Interrater reliability will be assessed, and the coding scheme will be refined if reliability is not acceptable (acceptable interrater agreement: >90%). Once interrater agreement is achieved, the coders will code the remaining transcripts and collect representative quotations.

Gender-Inclusive and Gender-Specific Approach to Analysis

As an analytic framing to examine inequities in alcohol behaviors within SMMT populations, we will use gender-inclusive and gender-specific approaches throughout the study's quantitative and qualitative analyses, following guidelines from Restar et al [52]. Given that there is epidemiological evidence that transgender and cisgender populations' health outcomes and behaviors, such as alcohol use, are dissimilar to each other and that the drivers of these inequities are contextually uniquely different [6,53-55], applying this approach to our analysis is appropriate. This approach allows our analytical modeling to examine and discern any potential shared versus differential intervention experiences and outcomes across gender groups (ie, between cisgender and transgender participants and within gender subgroups of transgender participants). On the basis of the findings, it will also allow us to provide future intervention recommendations for either the entire sample (ie, gender inclusive) or specific to each gender group (ie, gender specific).

Scientific Rigor

The proposed study uses a rigorous randomized comparative effectiveness trial design to assess intervention effects on alcohol use outcomes. The following characteristics add to the rigor of the study: (1) the use of a SAM-only control group so that all groups can be compared using daily-level alcohol use data, (2) the incorporation of breathalyzers to enhance the validity of self-reported alcohol use, (3) the inclusion of follow-up self-report and SAM data to assess long-term outcomes, (4) recruitment strategies that use in-person and web-based methods to enhance the diversity of the sample, (5) the inclusion of a dedicated biostatistician to provide rigorous outcome analyses, (6) support from app programmers to customize the app and address technical issues, and (7) the inclusion of a licensed social worker to ensure high-quality MI training and fidelity.

Results

The study is part of a 5-year National Institutes of Health research project that was funded in August 2022 by the National Institute on Alcohol Abuse and Alcoholism. The first 1.5 years of the study will be dedicated to planning and development activities, including formative research, app design and testing, and message design and testing. The subsequent 3.5 years will see the study complete participant recruitment, data collection, analyses, report writing, and dissemination. We expect to complete all study data collection in or before January 2027.

As of February 2024, we have published 1 manuscript, a systematic review exploring interventions for addressing alcohol use and sexual HIV risk–related behaviors [16]. We have also completed 2 rounds of focus groups to refine the intervention content and harm reduction messages delivered in TRAC-ER. Overall, 34 participants were enrolled in the first round of focus groups; however, 5 were excluded after further review showed they did not meet the eligibility criteria. This resulted in a final sample of 29 individuals for the first round of focus groups. We

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enrolled 22 participants for the second round of focus groups. First, we conducted separate focus groups with participants of different gender identities (sexual minority cisgender men, nonbinary and gender nonconforming participants, transgender men, and transgender women) to obtain feedback on harm reduction content added to the intervention manual and to help us generate initial harm reduction messaging. Next, we conducted an additional blended focus group to help us further refine the messages and develop our final *library* of messages that will be programmed into the app. A manuscript describing this process and the results is forthcoming.

Discussion

Summary

This manuscript describes the protocol for a 3-arm RCT evaluating the efficacy of a mobile-based EMI for reducing alcohol use and HIV risk behaviors among emerging adult SMMT individuals (N=405). We will compare a monitoring-only control to TRAC, a mobile-based MI intervention, and to TRAC-ER, an intervention combining TRAC with in-the-moment messaging to prevent hazardous alcohol use and reduce harm when participants visit risky locations. Mobile breathalyzers and surveys will be used to collect frequent data on alcohol and HIV risk behaviors. We will assess outcomes immediately before and after the intervention, as well as at 6-month and 9-month follow-ups. The primary outcome is the number of drinking days. Formative development work for this RCT has been completed, with the trial to begin recruiting soon (as of February 2024).

This study will make significant contributions to the literature on alcohol use interventions for SMMT populations. It uses an innovative precision health approach that draws upon the frequent use of smartphone technologies by emerging adult populations and the high acceptability of mobile breathalyzers. Despite the proliferation of mobile devices in society, the field of EMIs remains understudied, with very few RCTs being conducted related to alcohol use. In addition, EMIs have shown initial promise in being paired with MI approaches [56-58]; therefore, the proposed study would help to add to the fledgling evidence base regarding the effectiveness of this approach. The use of mobile technology and remote delivery of the tested interventions means that once the ideal approach is identified in terms of efficacy, the intervention will be easily scalable to individuals across wide geographic areas.

Our study has promising strengths, but it must be considered in light of several limitations. While the use of ecological momentary assessment (EMA) provides advantageous opportunities for real-time trigger location data and convenience reporting through smartphones, prior EMA studies highlight the potential exhaustion that participants may experience, which may reduce the level of participation. This study may further explore convenient assessment windows to diminish the intensity of EMA sampling. In addition, as previously mentioned, SMMT communities experience unique sociostructural challenges, such as unemployment, homelessness, forced displacement, and community violence [59]. These systems of power may operate dynamically and render difficulties in participating fully and equitably in hazardous alcohol use prevention programs [60]. Finally, the real-time tracking of alcohol use behaviors of participants may give rise to reporting bias. In the context of alcohol-related stigma, social desirability biases may subject participants to aligning their responses to the expectations of societal norms around alcohol consumption; however, the use of breathalyzers will help to protect against self-report bias.

Prior studies have also reported concerns for temporal bias, where participants were reluctant to complete location- and time-based–triggered EMA surveys due to the inconvenient times at which the surveys were sent. Similarly, EMA studies related to substance use have mentioned challenges with the time frame for EMA sampling [61]. In this study, EMA assessments will occur between 11 AM and 11 PM to avoid disturbing participants. However, participants in prior studies have discussed that these hours may not be representative of the time frames when drinking occurs because alcohol use may occur later at night, along with variations in mood and social activities. Thus, we may explore the potential options for personalized hours of EMA sampling for participants. Breathalyzer device loss may also pose a challenge. However, unlike prior EMA studies that distributed mobile phones and experienced challenges with device loss [62], our study enables participants to use their existing smartphones to use the app, which will reduce instances of device loss or misplacement.

We plan to follow this study with dissemination and implementation research that takes the most effective approach identified here and distributes it to a wider population of SMMT individuals. Overall, by reducing hazardous alcohol use among emerging adult SMMT individuals, we hope to reduce the rates of alcohol-associated HIV transmission among this population considered to be at high risk.

Conclusions

This protocol describes an RCT of an innovative intervention for reducing alcohol use and HIV risk among SMMT individuals. This study will provide evidence about the relative efficacy of using a smartphone-delivered MI intervention and real-time messaging to address triggers for hazardous alcohol use and sexual risk behaviors. The study has potential implications for advancing science and improving public health for a subpopulation that is disproportionately stigmatized and disconnected from prevention research and services.

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Solutions, LLC, as well as IntelliTransit Solutions, Inc, who developed the Tracking and Reducing Alcohol Consumption and Environmental Risk (TRAC-ER) app.

Data Availability

The data sets generated and analyzed during this study are available in the National Institute of Mental Health Data Archive repository (ID C4476) [63].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institutes of Health.
[PDF File (Adobe PDF File), 257 KB - resprot_v13i1e55166_app1.pdf]

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Abbreviations

AUD: alcohol use disorder
AUDIT-C: Alcohol Use Disorders Identification Test–Concise
EMA: ecological momentary assessment
EMI: ecological momentary intervention
HIPAA: Health Insurance Portability and Accountability Act
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SAM: smartphone-based alcohol monitoring
SMMT: sexual minority cisgender men and transgender
STI: sexually transmitted infection
TRAC: Tracking and Reducing Alcohol Consumption
TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk

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Protocol

Smartphone App–Delivered Mindfulness-Based Intervention for Mild Traumatic Brain Injury in Adolescents: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Concussion in children and adolescents is a significant public health concern, with 30% to 35% of patients at risk for prolonged emotional, cognitive, sleep, or physical symptoms. These symptoms negatively impact a child's quality of life while interfering with their participation in important neurodevelopmental activities such as schoolwork, socializing, and sports. Early psychological intervention following a concussion may improve the ability to regulate emotions and adapt to postinjury symptoms, resulting in the greater acceptance of change; reduced stress; and recovery of somatic, emotional, and cognitive symptoms.

Objective: The primary objective of this study is to assess the feasibility of conducting a parallel-group (1:1) randomized controlled trial (RCT) to evaluate a digital therapeutics (DTx) mindfulness-based intervention (MBI) in adolescents aged 12 to <18 years. The attention-matched comparator intervention (a math game also used in previous RCTs) will be delivered on the same DTx platform. Both groups will be provided with the standard of care guidelines. The secondary objective is to examine intervention trends for quality of life; resilience; self-efficacy; cognition such as attention, working memory, and executive functioning; symptom burden; and anxiety and depression scores at 4 weeks after concussion, which will inform a more definitive RCT. A subsample will be used to examine whether those randomized to the experimental intervention group have different brain-based imaging patterns compared with those randomized to the control group.

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Methods: This study is a double-blind Health Canada–regulated trial. A total of 70 participants will be enrolled within 7 days of concussion and randomly assigned to receive the 4-week DTx MBI (experimental group) or comparator intervention. Feasibility will be assessed based on the recruitment rate, treatment adherence to both interventions, and retention. All outcome measures will be evaluated before the intervention (within 7 days after injury) and at 1, 2, and 4 weeks after the injury. A subset of 60 participants will undergo magnetic resonance imaging within 72 hours and at 4 weeks after recruitment to identify the neurophysiological mechanisms underlying the potential benefits from MBI training in adolescents following a concussion.

Results: The recruitment began in October 2022, and the data collection is expected to be completed by September 2024. Data collection and management is still in progress; therefore, data analysis is yet to be conducted.

Conclusions: This trial will confirm the feasibility and resolve uncertainties to inform a future definitive multicenter efficacy RCT. If proven effective, a smartphone-based MBI has the potential to be an accessible and low-risk preventive treatment for youth at risk of experiencing prolonged postconcussion symptoms and complications.

Trial Registration: ClinicalTrials.gov NCT05105802; https://classic.clinicaltrials.gov/ct2/show/NCT05105802

International Registered Report Identifier (IRRID): DERR1-10.2196/57226

(JMIR Res Protoc 2024;13:e57226) doi:10.2196/57226

KEYWORDS

pediatric; concussion; persisting symptoms after concussion; mindfulness; randomized controlled trial; feasibility RCT; psychological intervention; youth; digital therapeutics; eHealth; mobile health; mHealth; mobile phone

Introduction

Background and Rationale

Approximately 30% to 35% of the children and adolescents who experience a concussion are considered to have persisting symptoms after concussion (PSAC) [1,2], defined as the persistence of somatic (eg, headache, dizziness, and fatigue); cognitive (eg, memory, concentration, and confusion); and other physical, psychological, and behavioral changes lasting beyond 1 month [3]. PSAC may impair daily activities including schoolwork, socializing, and sports and thereby reduce the quality of life (QoL) [4]. Studies have demonstrated that both noninjury and injury factors predict PSAC following a concussion [2,5,6], with the contribution of injury factors to PSAC decreasing over time. However, premorbid conditions such as preinjury somatic symptoms [7], migraine [2], preinjury cognitive ability [8], preexisting attention and mood concerns [9], anxiety [10], and coping strategies [11] remain important predictors of symptom persistence over time [8,12]. Preventive, early rehabilitation programs such as interventions focusing on building psychological resiliency, emotional regulation, and self-efficacy might be key to managing concussions, reducing PSAC risk, and promoting neural recovery.

Mindfulness-based interventions (MBIs) are *present-centered* interventions that encourage acceptance of thoughts and emotions as they occur in the moment without judgment. MBIs have been demonstrated to improve attentional focus, cognitive flexibility, depression and anxiety symptoms, self-concept, resiliency, and academic achievements as well as reduce affective reactivity and fear in clinical youth samples [13]. In addition, in-person MBIs seem effective at treating preinjury predictors of PSAC, such as mood disorders [14-17], somatization-related illness [14,18,19], headache disorders [20], and chronic pain [21]. However, in-person interventions may not be suitable for adolescents with acute concussion owing to high cost and low accessibility [22,23] and require commitment from parents and children for in-person weekly meetings for periods varying from 8 to 16 weeks. Brief (as short as 3 days to 4 weeks) web-based MBIs with guided meditation have been shown to have positive effects on anxiety, negative mood, perceived stress, and attention in different clinical populations [24-27]. MBIs may foster adaptive coping, increase resiliency, and reduce the risk of PSAC following pediatric concussion. Smartphone, or mobile, apps may present a versatile and personalized platform for the delivery of a dedicated MBI for populations experiencing a concussion [28].

Health care digital therapeutics (DTx; smartphone app) have gained popularity in the past decade as a means of screening patients, monitoring symptoms, and delivering psychoeducation and interventions [28,29]. The efficacy of mobile apps in delivering psychological interventions has been demonstrated in mental health samples, particularly in the treatment of depression and anxiety. Randomized controlled trials (RCTs) have shown that app-based interventions can effectively improve depressive and anxiety symptoms compared with waiting list, alternative care, or control conditions [29-34]. Similarly, a recent meta-analysis of RCTs on app-based MBIs has demonstrated significant small-to-medium effects in improving perceived stress, symptoms of depression and anxiety, QoL, psychological well-being, and positive affects, compared with control conditions, waitlist, and alternative interventions [35]. However, the application of an app-based MBI in pediatric concussion has not yet been studied.

We partnered with Mobio Interactive Inc (Toronto, Ontario, Canada), the creator of a clinically validated platform called *AmDTx*, to create an app-based dedicated DTx MBI for pediatric concussion. We assessed the acceptability and usability of the DTx with a small open-label single-arm study (N=10) [36]. The participants reported high satisfaction and found the app easy to use and the treatment to be credible. They also developed a strong alliance with their MBI guides (ie, those who are leading the meditation and psychoeducation sessions) [37]. The primary aim of this study is to assess the feasibility of the 4-week planned RCT methods to determine whether we can advance

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to an efficacy trial and, thereby, elevate our understanding of the optimal time points for collecting outcome measures. At 4 weeks, those randomized to the DTx MBI will have the opportunity to continue for another 4 weeks, that is, completing a total of 8 weeks of MBI. The goal of this additional 4-week intervention is to explore feasibility outcomes in an 8-week intervention. Finally, those who are part of the DTx control group (attention-matched comparator intervention) will have the opportunity to cross over to the DTx MBI group.

Primary Research Objective

The primary research objectives are to assess the feasibility of conducting a larger RCT by evaluating recruitment efficiency, adherence to treatment, credibility, and retention.

Secondary Research Objectives

The secondary research objectives were as follows:

1. Establish the participants' expectancy toward both interventions.
2. Examine the participants' satisfaction with the interventions.
3. Generate estimates to inform sample size calculations for a future multicenter RCT.
4. Assess whether there is preliminary evidence of an efficacy signal for QoL, fatigue, symptoms, resiliency, self-efficacy, cognition, anxiety, depression, and mindfulness.
5. Examine the experimental group's baseline characteristics, adherence, and attrition rates in those who chose to continue for an additional 4 weeks compared with those who chose to complete the study at 4 weeks compared with those who were lost to follow-up.
6. Examine the control group's baseline characteristics, adherence, and attrition rates in those who chose to cross over to the experimental interventions at 4 weeks versus those who chose to complete the study at 4 week versus those who were lost to follow-up.
7. Examine whether the experimental intervention is associated with differential brain-based imaging patterns of functional connectivity, cerebral blood flow, and spectroscopy.
8. Examine safety by examining whether the experimental intervention has increased adverse events (ie, total number) relative to the control intervention.

Methods

Trial Design

The proposed study is a Health Canada–regulated parallel-group (1:1) RCT, where patients within 7 days of a concussion will be randomly assigned to one of the two groups: (1) experimental group (n=35), early introduction of the DTx MBI program and (2) control group (n=35), sham DTx attention-matched comparator intervention. The participants will start the intervention the next day after being enrolled in the study. After 4 weeks, those in the experimental group will be offered the MBI program with 4-week additional education modules. Those who are part of the control group will be offered to cross over to start the DTx MBI. Of the 70 participants enrolled, 60 (86%) consenting participants (n=30, 50% from the experimental group and n=30, 50% from the control group) will be enrolled in neuroimaging, which requires participation in a brain scanning session within 72 hours of enrollment and during week 4 of the study. For a schematic diagram of the trial design, procedures, and stages, refer to the study flow diagram in Figure 1.

Figure 1. Flowchart of the study procedures. 360cc: 360 Concussion Care; ED: emergency department; MRI: magnetic resonance imaging; PQ: patient questionnaire.

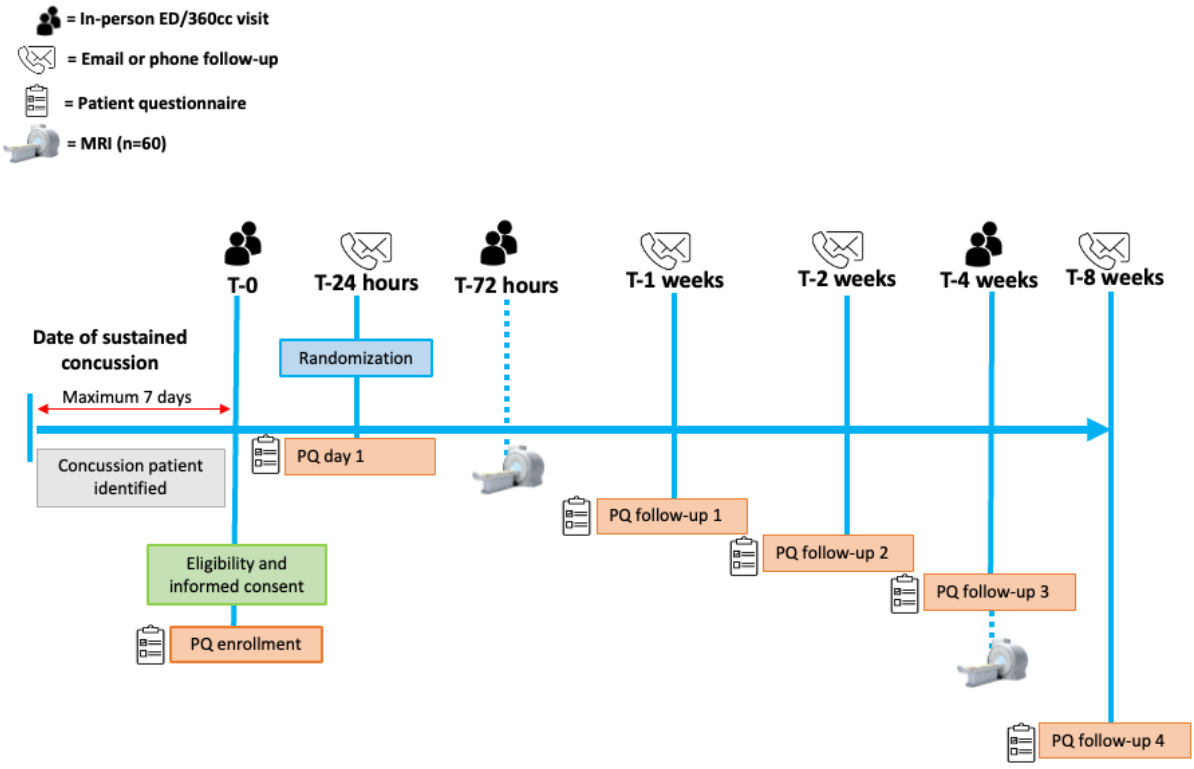

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Study Setting

The study will be conducted at the Children's Hospital of Eastern Ontario (CHEO) and the 360 Concussion Care (360cc) clinic, a tertiary health care concussion clinic. The neuroimaging component of the study will be completed at the Royal Ottawa Mental Health Centre's Brain Imaging Centre on a 3-Tesla Siemens magnetic resonance-positron emission tomography system with a 32-channel head coil (Siemens Biograph mMR, Siemens).

Eligibility Criteria

Inclusion Criteria

Adolescents presenting to either CHEO's emergency department (ED) or 360cc after sustaining a direct or indirect mild traumatic brain injury (TBI) will be eligible to participate in this study if they (1) are aged 12 to <18 years; (2) have a diagnosed concussion (by a physician), (3) presented to the ED or 360cc within 7 days of TBI; (4) have a score >4 on the Predicting and Preventing Post-Concussive Problems in Pediatrics (5P) clinical risk score, a prediction rule to identify those at risk of poorer outcomes at 4 weeks postinjury [2]; and (5) are proficient in English [38]. To increase the probability of including adolescents with a true concussion, the adapted version of the American Congress of Rehabilitation Medicine [39] framework will be used [40]. Those with either 1 *highest level of certainty* symptom (dazed, confused, or trouble thinking within minutes after injury, difficulty remembering what happened just before or minutes after injury, and loss of consciousness) or 2 *higher level of certainty* symptoms (nausea or vomiting, headache, dizziness, clumsy or balance problems, blurred or double or change in vision, difficulty concentrating, and sensitivity to light or noise) immediately or within 1 hour of injury will be included.

Exclusion Criteria

Patients will be excluded if they present with TBIs with any of the following: (1) a Glasgow Coma Scale score of ≤13; (2) abnormality on standard neuroimaging studies [41], including positive head computed tomography findings (neuroimaging is not required, but may be performed if clinically indicated); (3) neurosurgical operative intervention, intubation, or intensive care required; (4) multisystem injuries with the treatment requiring hospital admission, operating room, or procedural sedation in ED (hospital admission for observation or management of ongoing concussion symptoms is not an exclusion criteria); (5) severe chronic neurological developmental delay resulting in communication difficulties; (6) intoxication to alcohol or drugs at the time of ED presentation as per clinician judgment; (7) no clear history of trauma as primary event to the concussion (eg, seizure, syncope, and migraine); (8) prior psychiatric hospitalization; (9) inability to obtain written informed consent or assent (eg, language barrier); (10) legal guardian not present (certain forms need to be completed by parents or legal guardians); (11) no internet and mobile or tablet access; and (12) currently in therapy.

In addition, patients will not be included in the magnetic resonance imaging (MRI) component if they present with the following: (1) previous neurological or neurodevelopmental disorder such as epilepsy, intellectual disability, or autism (history of attention-deficit or hyperactivity disorder or learning disability is not exclusionary); (2) previous stroke or transient ischemic attacks; (3) sedation medication (eg, propofol, ketamine, nitrous oxide, midazolam, benzodiazepines, and fentanyl) administered before or during ED visit; (4) inability to be present at the 72-hour (+48 or –48 hours) and 4-week (+5 or –5 days) MRI follow-up visits; and (5) medical contraindications to MRI (eg, claustrophobia, pregnancy, or presence of braces or spacers or other metal implants).

Randomization, Blinding, and Allocation

Sequence Generation

The CHEO Clinical Research Unit will provide data management services for this study and retain randomization codes. The randomization sequence will be created using R software (version 3.1.1; R Foundation for Statistical Computing) [42] and will be stratified by sex, with a 1:1 allocation using random blocks.

Allocation Concealment

A statistician at the CHEO CRU (not involved in the study) will maintain the master list.

Implementation

The day after enrollment and once all questionnaire data are complete, research assistants (RAs) will call participants over the phone, and RAs will log into REDCap (Research Electronic Data Capture; Vanderbilt University) to obtain the patient's group allocation. Only the RAs who randomized participants will be unblinded. The research team will be blinded to data acquisition. In case of a serious adverse event, the principal investigator and appropriate research staff will be unblinded to the participant's group.

Methods for Protecting Against Bias

The investigators, coaches, other research staff, data management staff, and biostatisticians will be blinded to the group assignment. Patients and families will be blinded to the purpose and expected results of the interventions and to the other treatment arm.

Intervention Description

Experimental Group Description: MBI Training

To be delivered via the *AmDTx* platform (Figure 2), the targeted DTx MBI training consists of a 4- to 8-week custom-made program (containing 8-modules) for adolescents with concussion, including setting intentions and check-ins on mood and stress, audio-recorded lectures, guided meditations such as focused attention exercises, and journaling events (Table 1). Each standardized psychoeducation or meditation practice will be unlocked as the participant progresses through the MBI program. Participants will be encouraged to participate in the DTx MBI activities for approximately 10 minutes every day, for a minimum of 4 days a week, over the 4- to-8-week period. Those who choose to end their therapy on the fourth week will be immediately directed to module 8 *Reviewing the program and how to maintain practice*. Those who choose to continue for an additional 4 weeks will move on to modules 5 through

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8. The curriculum is based on previously validated *AmDTx* MBI app protocols [27,43] and team expertise in youth MBI (Sonia Roth, Craig Mackie, MC, and AAL) and was peer reviewed by experts in the field and parent engagement leaders (Ana Maria Vranceanu, Jonathan Greenberg, and Erin McCarthy). The intervention was piloted on 10 pediatric participants with concussion, and their feedback was integrated into the MBI and protocol [36]. We will track *meaningful* in-app use time, defined as the time spent engaging in meditation, psychoeducation, self-monitoring, and self-reflection, with a minimum threshold of 3 minutes per day. Any use time <3 minutes will not be counted toward the total weekly minutes spent using the *DTx*.

Figure 2. Adolescent concussion dedicated experimental and control interventions delivered through the AmDTx platform. (A) Initial loading screen of AmDTx; (B) main menu or home screen of AmDTx as seen by the participants randomized to the experimental intervention; (C) journey selection screen. Concussion Journey is shown; (D) main or menu page of the concussion MBI. Slices of the badge are awarded upon the completion of each module; (E) main or menu page of module 1; (F) stage 1 of module 1 play screen; (G) to complete the stage, the participant taps on the arrows at the top right; (H) main or menu page of module 3, with participant progression up to stage 5. (I, J and L) Before and after each the participant is prompted to complete the wellbeing measurements “Snapshot”; (K) stage 4 of module 2, “Body Scan” preplay screen with 2 meditation guide options; (L) snapshot ecological momentary assessment for stress and the open field box features; (M) journaling feature menu; (N) journaling feature input page relating to goal setting; (O) main menu or home screen of AmDTx as seen by the participants randomized to the control intervention. The feature “Concussion Recovery” is where the control math game is found; (P) main screen of the control task; (Q) to ensure as much similarity in the experience as possible and to collect valuable insights into the well-being of participants, the control is also book-ended with snapshots. Shown here is the mood circumplex feature; (R) control task midway through completion; (S) timer message prompting the participant to end their cognitive training for the day; (T) snapshot selfie scan feature after video has been captured; (U) the My Insights page where the participants randomized to either group can view how individual intervention stages or the control task impacted their well-being.

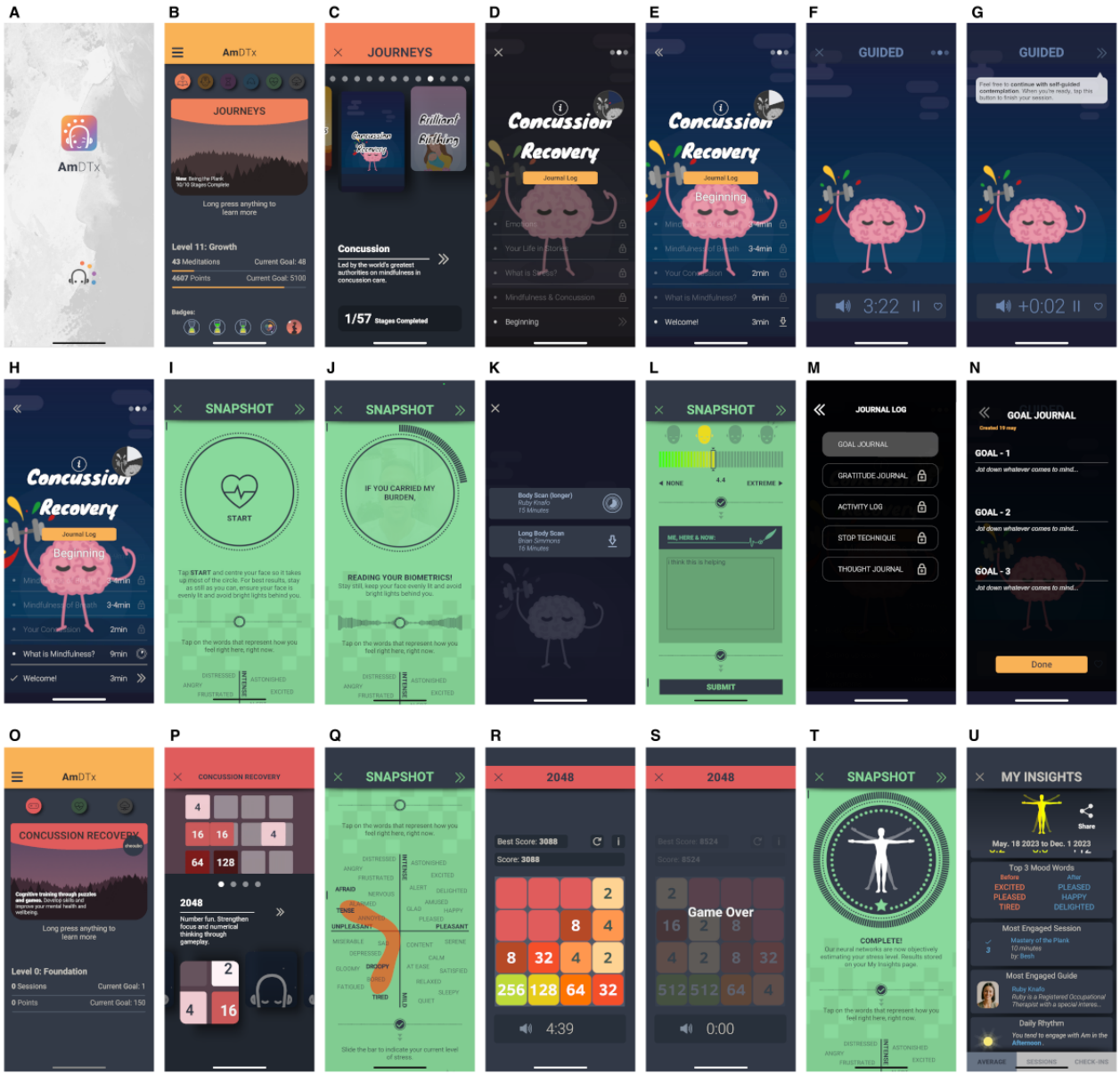

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Table 1. Four- or 8-week experimental intervention consisting of a targeted digital therapeutics mindfulness-based intervention for adolescents with concussion that includes setting intentions and check-ins on mood and stress, audio-recorded lectures, guided meditations such as focused attention exercises, and journaling events.

Module	Course or focus	Meditation practices	Exercise
1	• What is mindfulness • Setting intentions • Belly breathing exercise • Introduction to body scan	• Body scan (short): 7 minutes × 2 • Belly breathing: 3 minutes × 2	• N/A[a]
2	• Mindful attitudes (nonjudgment and acceptance) • How to skillfully meet concussion symptoms	• Mindfulness of breath: 5 minutes × 2 • Body scan: 15 minutes × 2	• Setting goals • Positive event journal • Doing 1 daily routine mindfully
3	• Stress response • The biology of stress • Inner narrative and chronic stress • STOP technique	• Mindful of breath: 10 minutes × 2 • STOP technique • Mindful movement: 7 minutes × 2	• Symptoms of stress checklist and mapping stress on the body • Journal when you used the STOP technique
4	• Thoughts: the stories we tell ourselves • Reframing symptoms with thoughts and attitudes • Moving mindfully through your life	• Mindfulness of sound transitioning to thoughts: 10 minutes × 2 • Mindfulness movement: 10 minutes × 2	• Thought journal
5	• Pain and emotions • How to mindfully manage pain • Being mindful of your emotion • The Breathe-Calm-Okay-Observe-Love technique	• Body scan: 12 minutes × 2 • Practice sitting meditation with emphasis on emotion: 10 minutes × 2	• N/A
6	• How to return to activities • Gratitude—who or what has helped you in your recovery	• Mindful movement practice: 10 minutes × 2 • Loving-kindness and gratitude practice: 10 minutes × 2	• Thought journal
7	• Integrating mindfulness more fully into daily life • Barriers to practice	• Open awareness practice: 10 minutes × 2 • Users choice practice: 5-15 minutes × 2	• Thought journal
4 or 8	• Review of program, strategies for maintaining practice, and reflection on how mindfulness has helped cope with your concussion or otherwise	• Users choice practice: 5-15 minutes × 4	• Review treatment goals • Goal setting for the future

[a]N/A: not applicable.

Control Group Description: Sham App

To control for daily access to the *AmDTx* platform, expectation, and clinical attention bias, we created a sham DTx for the control group. The sham DTx will be delivered on the same main interface, within *AmDTx*; however, these participants will not have access to any of the MBI training or psychoeducational content. Their sham DTx will consist of playing an open-source math game called 2048 developed by Gabriele Cirulli [44]; this will be communicated to the control participants as *cognitive training*. The game requires participants to slide number tiles on a grid and combine them to create a tile with the number 2048. In a previous study, *AmDTx* was compared with 2048, revealing that 2048 did not reduce stress or improve psychological well-being in university students with anxiety [27]. Furthermore, 2048 was previously tested in a pediatric population with concussion, and the study found no evidence of harm or symptom improvement at 4 weeks [45]. It is expected that the control intervention will not bother individuals with sensitivity to light or high velocity motion because it lacks fast visuals or movement. The game is programmed to only be accessible for 10 minutes per day.

Coaching

All participants will be followed weekly by a coach through SMS text messaging. The coaches' role will be to ensure that the participants adhere to the intervention. All the participants will receive weekly text messages from a coach. These messages will be sent on the same day and time every week and will be limited to 160 characters. The coaches will use a standardized question and answer protocol developed by the team. Coaches will also remind the participants to complete their follow-up surveys.

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Furthermore, both interventions are equipped with automated reminders (triggered by inactivity).

Standard of Care

All the participants will receive standard of care [46] instructions pamphlet provided by RAs in the ED or at 360cc. The standard of care indicates that the patient refrains from physical and cognitive activities for 24 to 48 hours after injury. After the rest period, it is recommended that low-to-moderate levels of physical and cognitive activity be gradually started, including screen time. The activities should be performed at a level that does not result in the recurrence or exacerbation of symptoms. Adolescents must refrain from any activities that increase the risk of reinjury (eg, contact sports or anything with risk of falls) until fully asymptomatic and cleared by their primary care or other medical providers.

Measures and Outcomes

Primary Outcomes

The prespecified thresholds (criteria for success), as outlined in Table 2 for the feasibility, are based on established benchmarks of previous feasibility trials [47,48] and our previous experience in recruiting pediatric patients with concussion from an ED [49]. We will use the *traffic light* system to determine whether proceeding to a full-scale trial is appropriate [50]. Progression can take place without any changes (green zone), with correctable adjustments (amber zone), or not occur because of issues that cannot be readily addressed (red zone). The decision to progress to a full-scale trial will be contingent on the criterion with the least favorable performance [50].

Table 3 provides an overview of all outcome measures collected and their specific end points.

Table 2. The criteria for success for progression to a full-scale efficacy trial.

Feasibility outcomes	Green zone (go)	Amber zone (amend)	Red zone (stop)
Eligibility	>40% of participants screened are eligible	20%-40% of participants screened are eligible	<20% of participants screened are eligible
Recruitment	>50% of eligible participants will be randomized [49]	30%-50% of eligible participants will be randomized	<30% of eligible participants will be randomized
Adherence	>70% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week	>50% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week	<50% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week
Credibility[a]	>70% of participants have score above the scale midpoint	>50% of participant have a score above the scale midpoint	<50% of participants have a score above the scale midpoint
Retention	>75% participants complete the follow-up assessment [49]	50%-75% participants complete the follow-up assessment	<50% participants complete the follow-up assessment

[a]Treatment credibility and expectancy will be assessed using the Credibility and Expectancy Questionnaire [51]. It is a 6-item questionnaire, scored using a Likert scale ranging from 1 to 9. The treatment will be considered credible (questions 1-3) if the participants scored above the midpoint. Furthermore, credibility and expectancy will be assessed to rule out the possibility of differential credibility as an explanation for the differences in therapy outcomes between the experimental and control groups. The credibility and expectancy of the intervention will be assessed at 1 week after enrollment.

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Table 3. Measures organized by domain, source of data, and assessment occasion.

Measures	Source or reporter	Time to complete (minutes)	CHEO ED[a]	360cc[b]	Daily[c]	Day 1 (CHEO)	Day 1 (360cc)	72-hours	Day 7	Day 14	Week 3	Week 4	Week 8
ED visit													
Screening form	RA[d]	N/A[e]	✓	✓									
Case report (acute signs and symptoms)	RA and MD[f]	5 RA and 5 MD	✓	✓									
Balance (balance error scoring system)	CP[g]	5-10	✓	✓									
Outcomes													
Psychological													
Self-Efficacy Questionnaire for Children	C	2-5				✓	✓					✓	✓
Connor-Davidson Resilience Scale	C	2-5				✓	✓					✓	✓
Generalized Anxiety Disorder 7-item scale	C	2-5	✓				✓					✓	✓
Center for Epidemiologic Studies Depression Scale for Children	C	2-5	✓				✓					✓	✓
Child and Adolescent Mindfulness Scale	C	2-5	✓				✓					✓	✓
Credibility Expectancy Questionnaire	C	5							✓				
Client Satisfaction Questionnaire	CP	5										✓	
Postconcussive symptoms (secondary)													
Health and Behavior Inventory	C	5-10	✓	✓						✓		✓	✓
Post-Concussion Symptom Inventory	C	5	✓	✓						✓		✓	✓
Functional impairments (secondary)													
Quality of Life (PedsQL[h,i]) scale	C	5-10	✓				✓					✓	✓
PedsQL Fatigue scale	N/A	N/A										✓	✓
Neurophysiological measures (subset of 60 participants)		45											
Arterial spin labeling	C							✓				✓	

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Measures	Source or reporter	Time to complete (minutes)	CHEO ED[a]	360cc[b]	Daily[c]	Day 1 (CHEO)	Day 1 (360cc)	72-hours	Day 7	Day 14	Week 3	Week 4	Week 8
Resting-state fMRI[j]	C							✓				✓	
MRS[k]	C							✓				✓	
Cognitive measures													
NIH[l] Toolbox	C	25										✓	
App Measurements	N/A	N/A			✓								
Godin-Shephard Leisure-Time Physical Activity Questionnaires	C	5				✓	✓			✓		✓	✓
Puberty Questionnaire	C	5	✓				✓						

[a]CHEO ED: Children's Hospital of Eastern Ontario emergency department.

[b]360cc: 360 Concussion Care.

[c]When accessing the app.

[d]RA: research assistant.

[e]N/A: not applicable.

[f]MD: treated ED physician.

[g]CP: concussed child and parent or guardian.

[h]PedsQL: Pediatric Quality of Life Inventory.

[i]Outcome measure.

[j]fMRI: functional magnetic resonance imaging.

[k]MRS: magnetic resonance spectroscopy.

[l]NIH: National Institutes of Health.

Secondary Outcomes

Treatment Expectancy

Treatment expectancy will be assessed with the Credibility and Expectancy Questionnaire (questions 4 to 6) [51]. Expectancy will be considered good if the participants score above the midpoint on questions 4 to 6. Expectancy will be assessed at 1 week after the enrollment.

Intervention Satisfaction

Intervention satisfaction will be assessed with the modified version of the Client Satisfaction Questionnaire [52]. This is a validated, reliable, 8-item questionnaire used to measure client satisfaction with a particular program or service. In this case, the questionnaire has been modified to assess participant satisfaction with the digital intervention. The intervention will be deemed satisfactory if >70% of the participants score above the midpoint on the questionnaire [52]. Intervention satisfaction will be assessed at 4 weeks after the enrollment (end of the intervention).

Quality of Life

QoL will be measured using the Pediatric Quality of Life Inventory (PedsQL; version 4.0) [53,54]. The PedsQL is a reliable and valid measure of QoL in healthy children and adolescents and in those with acute or chronic health conditions [55]. It is a 23-item, 5-point Likert scale questionnaire yielding a total score (0-92) and 4 domain scores: physical, emotional, social, and school. QoL will be collected in the ED (for CHEO participants) or on day 1 (for 360cc participants) and at the 4- and 8-week follow-ups.

Fatigue

Fatigue will be measured using the Multidimensional Fatigue Scale PedsQL. This 18-item, 5-point Likert scale assessment comprises 3 scales: the General Fatigue Scale (6 items), Sleep-Rest Fatigue Scale (6 items), and Cognitive Fatigue Scale (6 items). The PedsQL Multidimensional Fatigue Scale has demonstrated excellent internal consistency, reliability, and validity [56-58]. The assessment will be collected in the ED (for CHEO participants) or on day 1 (for 360cc participants) and at the 4- and 8-week follow-ups.

Symptom Burden

Symptom burden will be measured in the ED or at 360cc (both retrospective and postinjury acute symptoms) and at 1, 2, 4, and 8 weeks after enrollment using the Health and Behavior Inventory (HBI) [3]. The HBI is a 20-item self-report questionnaire that uses a 4-point Likert scale, with a total range

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0-60. It provides scores for cognitive and somatic symptom scales. Emotional symptoms and sleep disturbances will be assessed using the Post-Concussion Symptom Inventory (PCSI) [59-61]. The PCSI [59,60] is a validated, reliable, comprehensive, and self-administered instrument [59-61]. For the purpose of this study, the emotional and sleep domains of the PCSI adolescent scale version (20-item, 7-point Likert scale) will be used. The domains will be assessed in the ED or at 360cc and at 2, 4, and 8 weeks after enrollment.

Self-Efficacy

Self-efficacy will be measured using the Self-Efficacy Questionnaire for Children (SEQ-C). Self-efficacy is the individual's perceived and personal competence in their abilities to handle a situation. Self-efficacy reflects one's confidence in the ability to exert control over one's motivation, behavior, and social environment. Previous studies have demonstrated that at 12 weeks after the injury, children with a concussion lack confidence during physical activities at 12 weeks after a concussion as compared with that before the injury [62]. The SEQ-C is a valid and reliable assessment tool. It is a 24-item, 5-point Likert scale yielding a sum score (0-120) and emotional, social, and academic self-efficacy subscores [63]. The SEQ-C will be administered on day 1 and at 4 and 8 weeks after enrollment.

Attention, Working Memory, and Executive Function

Attention, working memory, and executive function will be assessed using the National Institutes of Health (NIH) Toolbox Cognitive Battery [64]. The NIH Toolbox is a validated and reliable computerized battery designed to measure executive function, attention, episodic memory, language, processing speed, working memory, and fluid cognition. Previous studies have demonstrated lower working memory, attention, and executive functioning scores after injury in pediatric samples with concussion [65-68]. Moreover, mindfulness has been shown to improve attention, working memory, and executive functioning [26,69,70]. The NIH Toolbox will be administered at the 4-week follow-up.

Resiliency

Resiliency will be measured using the Connor-Davidson Resilience Scale-10 (CD-RISC-10) [71]. The CD-RISC-10 is a 10-item questionnaire, scored on a 5-point Likert scale, that assesses an individual's perception of hardiness or perceived stress. Resiliency is defined as the ability to harbor interpersonal qualities, such as positive acceptance, to adapt or thrive in the face of adversity [71]. Previous research has shown that MBI increases resiliency in youth [13]. The CD-RISC-10 has been validated in an adolescent population with a concussion [72] and will be administered on day 1 and at 4 and 8 weeks after enrollment.

Anxiety and Depression

Anxiety and *depression* (mood) are frequently reported symptoms in pediatric concussion [73-75]. *Anxiety* will be measured using the Generalized Anxiety Disorder 7-item scale [73]. The Generalized Anxiety Disorder-7 is a validated, reliable, and sensitive to treatment-related changes tool that assesses anxiety symptoms in youth [76]. It is a 7-item, 3-point Likert scale that provides a sum score (0 to 21) of general anxiety symptoms. It will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preinjury anxiety, and at 4- and 8-week intervals after enrollment to assess postenrollment anxiety.

Depression symptoms will be measured using the validated and reliable Center for Epidemiologic Studies Depression Scale for Children [74,75]. It is a 10-item, 4-point Likert scale that provides a total score (0-30). The Center for Epidemiologic Studies Depression Scale for Children will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preinjury mood, and at 4- and 8-week intervals after enrollment to assess postenrollment mood.

Mindfulness

Mindfulness will be assessed using the validated Child and Adolescent Mindfulness Measure [77,78]. It is a 10-item, 5-point Likert scale. It will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preintervention mindfulness, and at 4- and 8-week intervals after enrollment to assess postenrollment mindfulness.

Safety

Safety of the MBI will be determined by capturing and monitoring the worsening of symptoms and adverse events. Adverse events will be defined as an unscheduled visit to the ED or primary medical provider because of exacerbation of symptoms during or within 30 minutes after using the app. The participant will be asked about any possible adverse events at the 1-, 2-, 4-, and 8-week follow-ups.

Longitudinal Mental Well-Being

AmDTx contains 4 easy-to-use measurement features that together provide a longitudinal readout of patient well-being. First, psychological stress is objectively quantified via a 30-second *selfie* video that uses photoplethysmography to extract heart rate and 2 power bands of heart rate variability from biosignals inherent to the human face [79]. The amount of psychological stress is determined via a deep neural network trained on tens of thousands of selfie scans captured in parallel with a validated ecological momentary assessment of stress. The artificial intelligence output has reported 86% accuracy for determining an individual's stress as *very low*, *medium low*, *medium high*, or *very high* [80]. Second, emotional affect and arousal levels are obtained via a digital 4-quadrant emotion mapping board (circumplex) that lists feelings such as *afraid*, *droopy*, and at ease ranging on one axis from unpleasant to pleasant (valence axis) and along another axis from mild to intense (arousal axis). Each emotion listed is associated with a score that is not disclosed to the user and is used to calculate an implicit measure of mood. Third, subjective stress is obtained via a slider ranging from *none* to *extreme*. Fourth, personal notes are imputed using an open field text box. The outputs of the mood and stress slider ecological momentary assessments have been benchmarked to standard psychological surveys [27]. If a participant chooses to use the selfie camera to observe their biological stress levels, there will be no recording or storage of the generated video in the app or elsewhere. The AmDTx uses secure web authentication, data logging, and encryption that

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ensure security and confidentiality of any personal identifiable information and in-app data. Personally identifiable information remains with the customer (ie, it is not downloaded by Mobio).

Imaging Measurements

Imaging measurements will be acquired within 72 hours of injury and during week 4 of the study on a subset of 60 participants. Each brain scanning session lasts 45 to 60 minutes and includes the following sequences: 3D T1-weighted anatomical scan to measure regional volumes and cortical thickness, resting-state functional MRI (rs-fMRI) to assess functional connectivity features or neural networks, arterial spin labeling to assess perfusion or cerebral blood flow, and magnetic proton spectroscopy in a single voxel in the anterior cingulate cortex to assess metabolite concentrations (ie, glutamate and gamma-aminobutyric acid). Table 3 lists the key imaging parameters.

Covariate Measurements

Information about injuries will be collected from medical records and medical personnel using a standardized case report form. Details regarding the injury and acute signs and symptoms of concussion (ie, loss of consciousness, Glasgow Coma Scale scores, mechanism of injury, neurological status, and other clinical features) will be collected by RAs, with clarification by physicians when necessary. The data will be verified by the site investigator. To calculate the 5P clinical risk score [2], balance will be evaluated by the RA using the balance error scoring system [81], a widely used instrument in the field of sports concussion [82] for objective assessment of postural stability. Pubertal status will be measured using a puberty questionnaire [83]. The questionnaire is a 5-item, self-administered rating scale for pubertal development without pictorial representations or interviews. Demographic data (ie, household annual income and parental education level) will be used as a proxy of socioeconomic status (SES). SES will be collected to assess whether randomization is equally distributed in both groups. If SES is not equally represented in the sample, it will be controlled for in our analysis.

Studies have shown that physical activity can reduce anxiety, improve mood, and help alleviate postconcussive symptoms [84]. We will evaluate physical activity to ensure balance between groups; physical activity levels will be assessed using the Godin-Shepard Leisure-Time Physical Activity Questionnaire [85] on day 1 and then at 2, 4, and 8 weeks after injury.

Procedures

Data Collection Methods

Recruitment will be conducted similar to the successful Pediatric Concussion Assessment of Rest and Exertion multicenter concussion study [86]. When an adolescent with a mechanism of injury and symptoms consistent with concussion presents to the ED, the nurse will triage the child as per the existing protocols. Once in the ED, a member of the ED clinical team (ie, an ED volunteer) will introduce the study to families of potentially eligible children to inquire whether they are interested in learning more about the study. If so, the electronic charts of potentially eligible participants will be flagged, and the research team will be notified. At 360cc, a health information custodian who is a part of the circle of care will mention to the family that there is a study on children who have head injuries and ask if they are interested in learning more about the study. In both the ED and 360cc, the RA will then approach the family to discuss the research study, and if they are interested, the RA will complete the screening form on an iPad.

During the screening procedure, we will evaluate the likelihood that the patients had a *definitive* or *probable* concussion based on the aforementioned inclusion criteria. Their 5P clinical risk score [2] will also be calculated with the following variables: age, sex, prior concussion and length of recovery, history of migraine, slow answers to questions, balance, headache, sensitivity to noise, and feeling fatigued. Only patients with a 5P score >4 will be eligible for the study. Patients who are ineligible based on the initial screening will be thanked for their time. Eligible and willing parents along with adolescents capable of consenting on their own behalf will be asked for written informed consent, and the adolescents who are unable to provide consent on their own behalf will be asked for assent.

Once enrolled in the study, the families will complete a series of questionnaires in an electronic survey format using a portable tablet computer on REDCap [87]. The survey includes questions regarding patient demographics, preinjury and injury characteristics, a symptoms checklist, and diagnostic history.

The day following the ED or 360cc visit, participants will receive a phone call from an RA to randomize the participants to either the experimental or the control group and give instructions to register an account on a study-dedicated landing page using a unique link for each participant. Following registration, participants will install *AmDTx* on the mobile device of their choice. After creating an account and logging in to *AmDTx*, each participant will be automatically directed to their assigned intervention (MBI or control).

During this phone call, an MRI appointment will be scheduled for the participants who have agreed to participate in that component of the study. Participants will complete the surveys or questionnaires for day 1 and MRI screener. They will have the option of completing the survey via phone or REDCap.

Follow-Up Procedures

The proposed duration of the app-based MBI is 4 to 8 weeks. After 4 weeks, all participants in the experimental group will be given the opportunity to pursue the MBI for an additional 4 weeks. At that time, participants in the control group will be offered to cross over and start the MBI intervention.

Participants will complete electronic follow-up questionnaires on REDCap at 1, 2, 4, and 8 weeks after enrollment and will have an in-person follow-up at 4 weeks for the cognitive assessment (and the MRI scan for a subset of participants). Cognitive testing will be conducted before brain scanning.

Neuroimaging Procedures

A subset of 60 participants (30 from each group) will undergo a 45-minute MRI scan at <72 hours and 4 weeks after injury. During the day 1 phone call, participants who have consented

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to the MRI component of the study will complete the MRI screener and schedule their MRI appointment.

Each scanning session will be approximately 1 hour and will include a high-resolution structural scan, arterial spin labeling, rs-fMRI, and magnetic proton spectroscopy (Table 4).

Table 4. Magnetic resonance imaging acquisition.

Image type	Sequence name	Total time (minutes:seconds)	Resolution (mm×mm×mm)	Slices, n	FOV[a] (mm)	TR[b] (milliseconds)	TE[c] (milliseconds)	Other
High-resolution anatomical	MEMPRAGE	5:48	1.0×1.0×1.0	192	256	2500	1.69, 3.55, 5.41, and 7.27	Flip angle=7; inversion time=1050 milliseconds; phase FOV=100%
rs-fMRI[d]	—[e]	12:08	3.0×3.0×3.0	40	204	2160	25	Flip angle=70; acceleration factor=2; 334 volumes
ASL[f]	3D ASL (GRACE)	5:37	1.8×1.8×5.0	34	230	4600	15.56	Perfusion mode=Flow-sensitive Alternating Inversion Recovery-QII; bolus duration=700 milliseconds; inversion time=860 milliseconds, 1060 milliseconds, 1260 milliseconds, 1460 milliseconds, 1660 milliseconds, 1860 milliseconds, 2060 milliseconds, 2260 milliseconds, 2460 milliseconds, 2660 milliseconds, 2860 milliseconds, 3060 milliseconds; average=1
ASL	Calibration image (M0)	0:54	1.8×1.8×5.0	34	230	7500	15.92	Perfusion mode=Flow-sensitive Alternating Inversion Recovery-QII; bolus duration=700; inversion time=7000 milliseconds; average=1
MRS[g]	PRESS	4:38	40×20×15	—	—	2000	30	Average=128
MRS	MEGAPRESS	4:36 (×2)	40×20×15	—	—	2000	68	Average=64

[a]FOV: field of view.

[b]TR: repetition time.

[c]TE: echo time.

[d]rs-fMRI: resting-state functional magnetic resonance imaging.

[e]Not available.

[f]ASL: arterial spin labeling.

[g]MRS: magnetic resonance spectroscopy.

Data Management

The CHEO Clinical Research Unit Data Coordinating Centre will be used as a central location for data processing and management. Data will be kept private and secured to industry standards for both clinical and patient-sensitive data in Canada. Data for the study will be collected and managed using REDCap [88] tools hosted and supported by the CHEO Research Institute. REDCap is a secure, web-based application designed to support data capture for research studies. Only members of the research team will be granted access to the database. Users will be assigned to *Data Access Groups* that will restrict their rights to viewing and entering data. For monitoring purposes, the study coordinator will be able to view the data. Within the Data Access

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Group, user privileges will be designated by the study coordinator to ensure that the research team members have only the minimum required rights to perform their duties. All identifying information that is collected will be flagged in the database and removed from data export unless the identifying information is required for statistical analysis (eg, date of birth).

Statistical Analysis

Primary Outcomes

Descriptive statistics will be used to summarize patient baseline characteristics and clinical information. The primary objective of this study is to assess the feasibility outcomes of the trial. This will be done by computing the observed points estimates for each criterion (eligibility, recruitment, adherence, credibility, and retention) and comparing them with our predefined red zone upper limits and green zone lower limits. The 3-tiered progression criteria will be used for each criterion (Textbox 1).

Textbox 1. Three-tiered progression criteria where E denotes the observed point estimate (ranging from 0 to 1 for proportions or percentages 0%-100%) [50].

Progression criteria

- Red (unacceptable): E≤red zone upper limit (*P* value nonsignificant, *P* value≥α)
- Amber (amend): red zone upper limit<E<green lower limit
- Green (acceptable): E≥G lower limit (*P* value significant, *P* value<α)

Secondary Outcomes

Mean and SDs will be computed for each collected measure. Pre-post correlations will be generated to assess preliminary evidence of *efficacy signal* for QoL, fatigue, symptoms, resiliency, self-efficacy, cognition, anxiety, depression, and mindfulness.

Neuroimaging Component: Nested Study

To acquire preliminary data on the association between the interventions and MRI metrics, per-protocol analyses will be conducted. A multivariable linear regression will be performed for each neuroimaging outcome, with age, sex, and handedness (for rs-fMRI) as covariates. If the groups differ at baseline on potentially confounding variables, such as attention-deficit or hyperactivity disorder, anxiety, medication, prior concussion, physical activity, and puberty, these variables will also be entered as covariates in the models. Per-protocol analyses will include only those participants who have adhered to the intervention.

Statistical Power

Feasibility Objective

The sample size calculations were informed on recommendations for feasibility trials using the *traffic light* system [50,89]. The significance cutoff points for each criterion, with green lower and red upper limits, were determined. Using Table 1 from the study by Lewis et al [50], to meet the individual >90% power requirements for each of the five criteria we would need the following: (1) for eligibility, the number of participants to be screened is 46; (2) for recruitment, the number of participants to be randomized is 54; (3) for adherence, the required number of participants to evaluate adherence is 55; (4) for credibility, the required number of participants is 55; and (5) for retention, the required number of participants is 34. To determine the overall sample size for the whole study, we based our decision on the criterion that requires the largest numbers (ie, adherence, n=55). Considering an approximately 20% rate of loss to follow-up and withdrawals, the required sample size for the adherence criteria is 70. We expect that 40% of the participants screened will be eligible and there will be a 50% recruitment uptake. Given these numbers, 350 children are expected to be screened: 350=[(1/0.4)×(1/0.5×70)]. Assuming that 70 of the 350 screened participants are randomized, criteria 1, 2, 3, 4, and 5 will have statistical powers of 100%, 99.9%, 95.8%, 95.8%, and 98.7%, respectively. This means that the null hypotheses can be rejected with a collective power of 90.5% if the alternative hypotheses (for acceptable feasibility outcomes) are true in each case.

Sample Size for the Nested Neuroimaging Component

As per Desmond and Glover [90], a liberal threshold of α=.05 requires 24 participants (12 per group) to achieve an 80% power for the single-voxel level for typical activations. To control the error rate when conducting multiple comparisons, it is suggested that the number of participants should be doubled to maintain this level of power. On the basis of our Pediatric Concussion Assessment of Rest and Exertion and MRI study, of the 89 participants with concussion who provided consent, 13 were lost to follow-up, 3 had incidental findings, and 5 had excessive motion [91]. Considering a 20% attrition, a total sample size of 60 participants (30 per group) will be recruited.

Data Safety and Monitoring

Data Safety Monitoring Board

The independent data safety monitoring board (DSMB) will consist of 1 independent pediatric ED physician, 1 neuropsychologist who specializes in pediatric concussion, and 1 statistician who is not involved in the research study. In keeping with the StaRChild Health guidelines [92], the DSMB will, in collaboration with the trial steering committee, establish safety outcomes and termination rules before the start of the study. The DSMB will be immediately advised of severe adverse events, and they will meet in case a serious adverse event occurs. The DSMB will meet annually to review enrollment, study procedures, form completion, data quality, loss to follow-up, and interim safety results. Given the low-risk intervention and

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no intention to stop the trial for benefit or futility, only an annual meeting will be required. On the basis of negative data trends (increased symptoms) and adverse events, the DSMB may decide to meet earlier than planned and may request unblinding if deemed necessary.

Potential Harms

The safety outcomes include (1) severe worsening of symptoms identified on HBI reliable changes or (2) any symptoms requiring an unscheduled visit to the ED or primary care provider. If concussion symptoms worsen during the treatment to the degree that the participant requires an unscheduled visit to the ED or primary care provider, then symptoms will be considered as a possible adverse event. Symptoms could develop into an adverse event if they become unbearable and the patient needs immediate medical attention. Patients will report possible adverse events through REDCap reports, and their responses will be monitored by RAs. In the case of a possible adverse event, defined as the *worsening of symptoms requiring an unscheduled visit to the ED or primary care provider*, site investigators will be notified to determine if the event is linked to the treatment. If linked, the event will be monitored and the CHEO Research Ethics Board and DSMB will be notified.

Ethical Considerations

This study was approved by the Research Ethics Board (protocol number 20/72X) of the CHEO Research Institute in August 2020. Authorization from Health Canada was granted in July 2022. The study will be carried out according to the principles outlined in the Declaration of Helsinki [93] and Good Clinical Practices, within the laws and regulations of the Tri-Council Policy Statement, and the institutional policies of the CHEO REB.

Before consent is sought, the study will be introduced, and its purpose will be explained verbally. The consent form will also present the purpose of the research, the procedures, potential risks and benefits, and the use and security of the data. Informed written consent will be obtained from the parents and participants deemed capable of consenting. Informed assent will be obtained from the participants deemed by the RA to be cognitively unable to provide informed consent.

The participants will be remunerated with a CAD $20 (US $15) gift certificate (eg, Tango) for completing surveys. Participants will receive an additional CAD $20 (US $15) gift certificate for completing the MRIs. The gift certificate will be sent electronically to their email address. They will also receive a parking voucher or vouchers for in-person meeting or meetings and a letter attesting that they have completed 20 hours of volunteer work (5 hours per week completing the intervention).

Participant information will be coded using study identification numbers. Research personnel will take all appropriate and customary steps to ensure that data remain secure and that patient privacy and confidentiality are maintained.

Results

Project Initiation

This trial is funded by the Children's Hospital Academic Medical Organization Innovation Fund and the multidisciplinary team grant from the University of Ottawa Brain and Mind Research Institute. Recruitment began in October 2022, and data collection is expected to be completed by September 2024. Data collection and management is still in progress; therefore, data analysis is yet to be conducted.

Dissemination

The results will be disseminated at international conferences and in scientific manuscripts to peer-reviewed journals. The main manuscript presenting the results of the primary objective will be published in a high-impact peer-reviewed journal. Furthermore, separate manuscripts will be written on the secondary objectives of the protocol, and these will also be submitted for publication in peer-reviewed journals. We plan to engage key stakeholder groups (eg, families, Parachute, Canadian Concussion Network, and Mobio Interactive) to ensure mobilization and uptake of the findings to end users to progress to the next step, that is, the efficacy trial.

Discussion

First, we will use this study to examine the feasibility of our RCT methods, including delivering a DTx-containing MBI to participants who are acutely or subacutely concussed, and whether we can move to the efficacy trial. Second, to better inform our larger RCT, this study will allow us to estimate the effect sizes of QoL and the symptoms at 4 and 8 weeks after enrollment compared with those randomized to the control group (sham intervention). Third, we will use this study to assess whether MBI induces measurable brain-based effects, that is, examine whether the intervention modulates neuroimaging indicators such as functional connectivity. This trial will offer insight into a cost-effective way to manage pediatric concussion in the acute and subacute phases of injury. This study will help support the development of a future full-efficacy trial to assess the effectiveness of the intervention in increasing QoL and decreasing the concussion symptom burden.

The development of an intervention to increase adaptive interpersonal qualities in acute settings is important for reducing the risk of PSAC. Formal in-person MBIs such as mindfulness-based stress reduction have been shown to increase perceived self-efficacy and teach positive acceptance of change [13]. However, these interventions may not be suitable for a youth population with acute concussion as they are costly and not easily accessible. A brief web-based MBI with guided meditation had positive effects on anxiety, negative mood, perceived stress, and attention in different clinical populations [24-27]. Furthermore, a 3-week RCT using the DTx MBI within *AmDTx* increased stress resilience and attentional control in university students self-described as experiencing mild anxiety [27]. The customization of a novel MBI, designed in collaboration with MBI therapists, patients, and Mobio Interactive, will bring a required concussion treatment into the

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homes of all patients, with the goal of increasing adaptive skills and cognitive performance, promoting neural recovery, and reducing the risk of PSAC. If found to be effective, DTx MBI holds promise as an accessible and low-risk preventative treatment for youth at risk for prolonged postconcussion symptoms and sequelae.

Acknowledgments

This study is funded by CHAMO Innovation grant, University of Ottawa Brain and Mind Research Institute, Martin Osmond Research Grant Award CHEORI and the Ontario Brain Institute NERD program.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

AAL is one of the authors of the Mindfulness-Based Intervention for Concussion protocol used in this study, but she did not receive any financial benefit. AAL received funding from the Ontario Brain Institute Neurotech Early Research & Development Program for a separate component of the study. AAL has no other conflict of interest to disclose. RZ received financial support through competitively funded research grants from the Canadian Institutes of Health Research, Ontario Neurotrauma Foundation, Physician Services Incorporated Foundation, Children's Hospital of Eastern Ontario Foundation, University of Ottawa Brain and Mind Research Institute, Ontario Brain Institute, National Football League, Ontario Ministry of Health, Public Health Agency of Canada, Health Canada, Parachute Canada, and Ontario SPOR Support Unit. RZ was supported by a Tier 1 Clinical Research Chair in Pediatric Concussion from the University of Ottawa. All grant funding goes directly to the institution. RZ sits on the board of directors for the North American Brain Injury Society, which is a volunteer (unpaid) role. RZ is a founding partner and a minority shareholder of 360 Concussion Care (a learning health system and network of interdisciplinary concussion clinics in Ontario); no proceeds have been transferred to RZ. MC is one of the authors of the Mindfulness-Based Intervention for Concussion protocol used in this study, but she did not receive any financial benefit. ADH holds a Canada Research Chair in Magnetic Resonance Spectroscopy in Brain Injury and received funding from the Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; the New Frontiers in Research Fund; the Alberta Workers Compensation Board; The Arthritis Society; and both the Hotchkiss Brain Institute and the Alberta Children's Hospital Research Institute, University of Calgary. LW received an honorarium for a speaking engagement. BJS is a cofounder of Mobio Interactive Ptd Ltd, and at the time of submitting the manuscript, owned approximately 23% of the company's shares. NR holds a Canada Research Chair (Tier 2) in Pediatric Concussion and has received research funding from the Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Council (SSHRC), Ontario Neurotrauma Foundation (ONF), Public Health Agency of Canada (PHAC), Parachute Canada, Special Olympics Canada, Greater Toronto Hockey League, Dr. Tom Pashby Sport Safety Fund, Holland Bloorview Kids Rehabilitation Hospital and Scotiabank. NR is an Executive Board Member for the International Pediatric Brain Injury Society (IPIBS) which is an unpaid and volunteer role. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer review comments from the Children's Hospital Academic Medical Organization (CHAMO), Innovation Fund.
[PDF File (Adobe PDF File), 67 KB - resprot_v13i1e57226_app1.pdf]

Multimedia Appendix 2
Peer review comments from the University of Ottawa Brain and Mind Research Institute Team Grant.
[PDF File (Adobe PDF File), 1067 KB - resprot_v13i1e57226_app2.pdf]

Multimedia Appendix 3
Peer review comments from the Children's Hospital of Eastern Ontario Research Insitute Research Growth Award.
[PDF File (Adobe PDF File), 329 KB - resprot_v13i1e57226_app3.pdf]

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Abbreviations

360cc: 360 Concussion Care
5P: Predicting and Preventing Post-Concussive Problems in Pediatrics
CD-RISC-10: Connor-Davidson Resilience Scale-10
CHEO: Children's Hospital of Eastern Ontario
DSMB: data safety monitoring board
DTx: digital therapeutics
ED: emergency department
HBI: Health and Behavior Inventory
MBI: mindfulness-based intervention
MRI: magnetic resonance imaging
NIH: National Institutes of Health
PCSI: Post-Concussion Symptom Inventory
PedsQL: Pediatric Quality of Life Inventory
PSAC: persisting symptoms after concussion
QoL: quality of life
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
rs-fMRI: resting-state functional magnetic resonance imaging
SEQ-C: Self-Efficacy Questionnaire for Children
SES: socioeconomic status
TBI: traumatic brain injury

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Protocol

Optimizing Outcomes in Psychotherapy for Anxiety Disorders Using Smartphone-Based and Passive Sensing Features: Protocol for a Randomized Controlled Trial

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Abstract

Background: Psychotherapies, such as cognitive behavioral therapy (CBT), currently have the strongest evidence of durable symptom changes for most psychological disorders, such as anxiety disorders. Nevertheless, only about half of individuals treated with CBT benefit from it. Predictive algorithms, including digital assessments and passive sensing features, could better identify patients who would benefit from CBT, and thus, improve treatment choices.

Objective: This study aims to establish predictive features that forecast responses to transdiagnostic CBT in anxiety disorders and to investigate key mechanisms underlying treatment responses.

Methods: This study is a 2-armed randomized controlled clinical trial. We include patients with anxiety disorders who are randomized to either a transdiagnostic CBT group or a waitlist (referred to as WAIT). We index key features to predict responses prior to starting treatment using subjective self-report questionnaires, experimental tasks, biological samples, ecological momentary assessments, activity tracking, and smartphone-based passive sensing to derive a multimodal feature set for predictive modeling. Additional assessments take place weekly at mid- and posttreatment and at 6- and 12-month follow-ups to index anxiety and depression symptom severity. We aim to include 150 patients, randomized to CBT versus WAIT at a 3:1 ratio. The data set will be subject to full feature and important features selected by minimal redundancy and maximal relevance feature selection and then fed into machine leaning models, including eXtreme gradient boosting, pattern recognition network, and k-nearest neighbors to forecast treatment response. The performance of the developed models will be evaluated. In addition to predictive modeling, we will test specific mechanistic hypotheses (eg, association between self-efficacy, daily symptoms obtained using ecological momentary assessments, and treatment response) to elucidate mechanisms underlying treatment response.

Results: The trial is now completed. It was approved by the Cantonal Ethics Committee, Zurich. The results will be disseminated through publications in scientific peer-reviewed journals and conference presentations.

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Conclusions: The aim of this trial is to improve current CBT treatment by precise forecasting of treatment response and by understanding and potentially augmenting underpinning mechanisms and personalizing treatment.

Trial Registration: ClinicalTrials.gov NCT03945617; https://clinicaltrials.gov/ct2/show/results/NCT03945617

International Registered Report Identifier (IRRID): DERR1-10.2196/42547

(JMIR Res Protoc 2024;13:e42547) doi:10.2196/42547

KEYWORDS

cognitive behavioral therapy; CBT; transdiagnostic; anxiety; digital; ecological momentary assessment; EMA; passive sensing

Introduction

Anxiety disorders, such as phobia, generalized anxiety disorder, or social anxiety disorder, represent the most common class of mental disorders present in the general population [1]. They are characterized by excessive fear in response to a specific object or situation and in the absence of actual danger and subsequent avoidance. Anxiety disorders are disruptive; they place psychological distress and role impairments on individuals and their families and create a serious economic burden for society [2]. Psychotherapies, such as cognitive behavioral therapy (CBT), are among the most effective treatments for anxiety disorders. CBT is typically delivered as a short-term treatment lasting about 14-20 (mostly weekly) sessions [3,4]. Notably, CBT treatment protocols for anxiety disorders with proven effectiveness span from disorder-specific to transdiagnostic treatment protocols (eg, Dalgleish et al [5]). Despite their evidence base and recommendations by current treatment guidelines (eg, National Institute for Heath and Care Excellence treatment guidelines), there remains significant room for improvement. Only about half of the individuals treated with CBT experience full remission or clinically meaningful symptom reduction [6,7].

One way to improve current psychotherapeutic treatments lies in precise forecasting of treatment response to adapt treatment choices accordingly. Personalized, augmented solutions or other treatment choices could be offered to likely nonresponders. Current evidence for such forecasting is often limited by a lack of validation studies and a focus on single biomarkers as a basis for treatment choice and patient allocation. Machine learning (ML) approaches have recently been applied to predictive modeling in clinical psychology and psychiatry [8,9]. With respect to CBT, such models have not yet produced consistent and comprehensive solutions, and it remains unclear which mechanisms drive symptom changes during CBT [10]. ML provides a robust statistical approach for dealing with high-dimensional, potentially nonlinear data [11] and has been successfully employed when more traditional statistical approaches have been insufficient (eg, due to high-dimensionality or nonlinearity of comprehensive data).

This study assesses the key psychological and neurobiological variables previously associated with treatment response [12,13] and enriched by smartphone-based and passive sensing predictors (ie, features indexed in the daily lives of patients using digital diaries) as well as passive mobile sensing [14,15]. We measure these variables using self-report questionnaires, clinical interviews, experimental tasks, electroencephalography (EEG) recordings, biological specimens, ecological momentary assessments, passive sensing, and activity tracking. All features capture clinically relevant factors or processes (Multimedia Appendix 1). Questionnaires capture key information processing, memory, and emotion regulation variables; experimental tasks capture clinically relevant processes (ie, processes related to the development of psychopathology) and CBT-relevant processes (ie, processes related to the recuperation of mental health through CBT), such as adaptation to emotional conflict, emotional reactivity, and reward learning; and ecological momentary assessments (EMAs) and passive sensing capture symptom expression and behavioral patterns in patients' daily lives. This study aims to develop a comprehensive statistical model that forecasts treatment responses based on these predictors. The efficacy of the unified protocol (UP) has been demonstrated for anxiety disorders, major depression, substance abuse, and borderline personality disorder, making it one of the transdiagnostic protocols with the strongest empirical support and broad applicability [16,17]. In this study, we aim to replicate these results in an independent European sample of patients with anxiety disorders, where few studies currently exist. Our key focus lies on predicting CBT responses based on a comprehensive multimodal feature set and understanding key mechanisms.

This study aims to (1) identify key features that predict CBT outcomes and (2) investigate the mechanisms of treatment response. The results have the potential to improve the clinical prediction of patients' responses to CBT treatment to develop tailored treatment choices.

Methods

Study Design

The study comprises a 2-arm randomized controlled clinical trial (NCT03945617). The study design and assessments are depicted in Figure 1.

Participants are randomly assigned to either a CBT group [18] following the UP or a waitlist control condition (WAIT) at a ratio of 3:1. In the CBT condition, participants receive an average of 16 weekly treatment sessions, and in the WAIT condition, participants undergo a waiting period of 16 weeks before receiving the same treatment. The WAIT condition is implemented to further test the specificity of predictive models.

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Figure 1. Study design.

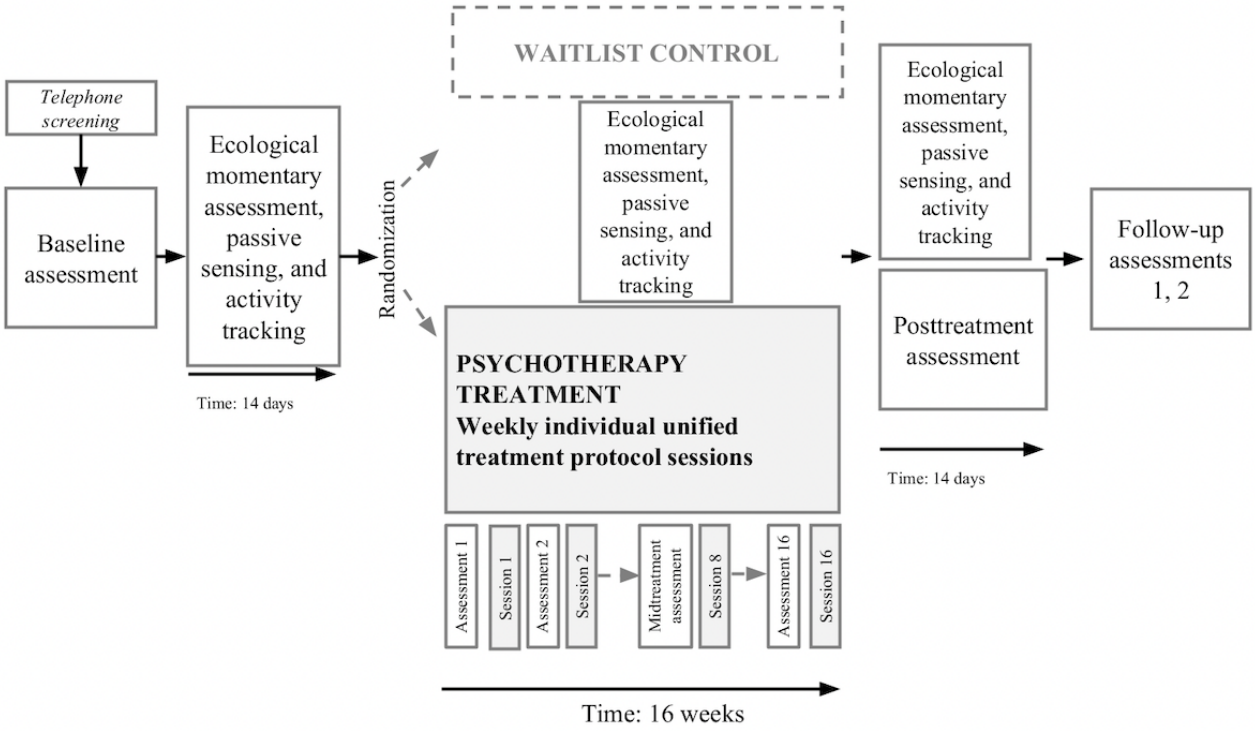

In total, 3 main assessments are implemented at baseline, midtreatment (week 8), and posttreatment (week 16). For the CBT group, follow-up assessments at 6 and 12 months (follow-up 1 and 2) are conducted to index anxiety and depression symptom severity. The predictive features indexed at baseline are psychological, behavioral, and neurobiological features, as well as digital variables reflecting core transdiagnostic factors, such as emotion regulation, self-efficacy, learning abilities and biases, physical activity, and sleep.

Participants

Study participants are recruited via social media, mailing lists, newspaper articles, a study website, and through general practitioners' offices and self-help groups located in Zurich. Participants are reimbursed for their time and expenses with 120 Swiss francs (US $134.62).

Inclusion and Exclusion Criteria

Participants with a primary anxiety diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, as assessed by the Mini International Neuropsychiatric Interview (MINI), German version 5.0 [19], are eligible to participate. Other inclusion criteria are as follows: (1) current diagnosis of an anxiety disorder as the primary diagnosis (eg, panic disorder with or without agoraphobia, social anxiety disorder, generalized anxiety disorder, anxiety disorder not otherwise specified, adjustment disorder with anxiety or adjustment disorder with mixed anxiety, and depressed mood); (2) aged between 18 and 65 years; (3) fluent in German; (4) currently not receiving psychotherapy; (5) provision of written informed consent; and (6) if on medication, stable dose(s) with no changes 3 months prior to treatment. Exclusion criteria are as follows: (1) medical contraindications and conditions that impede exposure (ie, cardiovascular diseases and autoimmune diseases); (2) current or past schizophrenia, psychosis, or bipolar disorder and current substance dependence or abuse (except for nicotine); (3) cluster A or B personality disorder; and (4) current suicidal ideation.

Sample Size and Power Analysis

For the planned analyses using ML algorithms, no established methods are available to determine the required sample size. Although sensitivity is less of a concern in ML, overfitting represents a significant risk. In this study, this risk will be addressed by assessing the generalizability of the estimated models using k-fold cross-validation and by implementing a loss function to penalize complex models [20,21]. It is planned to include 112 participants in the CBT group and 38 participants in the WAIT group. Data from the CBT group will be split into a training data set and a test data set at a ratio of 3:2 [22].

Unified Treatment Protocol

We used a transdiagnostic protocol to treat anxiety [18], which comprised 16 weekly individual CBT sessions. The first 2 sessions were scheduled to last 60-90 minutes, while the following sessions were scheduled for around 60 minutes. To ensure protocol fidelity, psychotherapists received a UP training course as well as ongoing supervision by a clinical expert. The UP comprised 8 different modules, as follows: (1) introduction and motivation enhancement, (2) identifying and understanding emotions, (3) emotional awareness training, (4) cognitive flexibility training, (5) emotional avoidance and emotion-driven behaviors, (6) awareness and tolerance of bodily sensations, (7) interoceptive and situation-based exposures, and (8) relapse prevention. The UP is relatively standardized, and patients will work through their individual workbooks along with the modules. We also used an additional form to assess basic anamnestic information (eg, family of origin, marital status,

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and hobbies) using a standard protocol. An individualized case conceptualization is implemented according to a template after the first session. UP workbooks are handed to patients at the first session and primarily comprise psychoeducational content and instructions for exercises (eg, symptom monitoring protocols and exposure exercises), which are given as homework, and the content of each homework will be briefly discussed with the patients in the following session.

Therapists and Treatment Fidelity

The study therapists (AS, MMB, DR, and CP) are trained clinical psychologists with several years of clinical experience who treat CBT and WAIT participants in approximately equal proportions. All therapists receive UP-specific training through workshops from the Center for Anxiety and Related Disorders at Boston University. Supervision is provided to study therapists by an experienced expert clinician (BS) to further enhance treatment fidelity and general quality. To estimate treatment fidelity, a random sample of 10% of all videotaped sessions will be rated for treatment fidelity based on standardized adherence ratings by an expert rater who is not involved in the study.

Measures

Multimedia Appendix 1 provides an overview of all measurements and their assessment time points.

Treatment Outcome Assessments

Primary Outcomes: Diagnostic Status and Anxiety Severity

Diagnostic status is assessed using the MINI [19] for indexing anxiety disorder diagnoses.

Anxiety severity is assessed using 3 different anxiety scales: the Hamilton Anxiety Scale [23], the Overall Anxiety Severity and Impairment Scale [24], and the Beck Anxiety Inventory [25]. The Hamilton Anxiety Scale is one of the most frequently used clinician-based rating instruments in research and clinical practice. It comprises 14 items reflecting psychological and somatic aspects of anxiety, which are rated on a 5-point Likert scale.

Secondary Outcomes: Depression Severity, Social Functioning, and Well-being

Secondary outcomes are depression severity, as indexed by the Hamilton Depression Scale [26] and the Beck Depression Inventory-II [27]. The Hamilton Depression Scale, which is the most widely used scale for clinician-rated assessments of depressive symptoms, exhibits strong psychometric properties [27]. The Beck Depression Inventory-II is widely used as a self-report measure of depression and comprises 21 items rated on a 5-point Likert scale. Social functioning is assessed using the Interpersonal Support Evaluation List [28] and the Social Adjustment Scale short version [29]. Well-being is assessed with the World Health Organization-5 Quality of Life Inventory [30].

Predictive Features

Core clinical, behavioral, psychological, and neural characteristics are assessed as predictive features; an overview of these assessments is available in Multimedia Appendix 1. Variable selection is based on empirical and conceptual evidence.

EMA, Activity Tracking, and Passive Sensing

The smartphone app “MAX—your therapy coach” (or MAX) measures the extent of anxiety-related symptoms (eg, intensity of anxiety, avoidance, and bodily symptoms) and the occurrence of different emotional states (eg, hope, anger, and low energy) within the last 30 minutes in everyday life for 14 days (Figure 2). MAX was developed for this trial based on MobileCoach [31], an open-source software platform for behavioral health interventions and data collection purposes [31,32]. It aims to assess dynamic symptom changes in a naturalistic, ecologically valid manner. The app prompts participants 5 times per day at block-randomized intervals and administers self-reports on anxiety-related symptoms and emotional states experienced within the last 30 minutes. Each self-report comprises 22 items and is rated on a visual analogue scale ranging from 0 to 100 [33]. Smartphone-based passive sensing of, for example, location data, Bluetooth connections, or app usage is sampled using the Aware framework [34]. A commercial fitness tracker (Fitbit Charge 2) is used for tracking physical activity, heart rate, and sleep behavior within 10 days, overlapping EMAs and passive sensing.

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Figure 2. MAX app screenshots: menu (left), assessments of anxiety-related symptoms (middle), and emotion assessments (right).

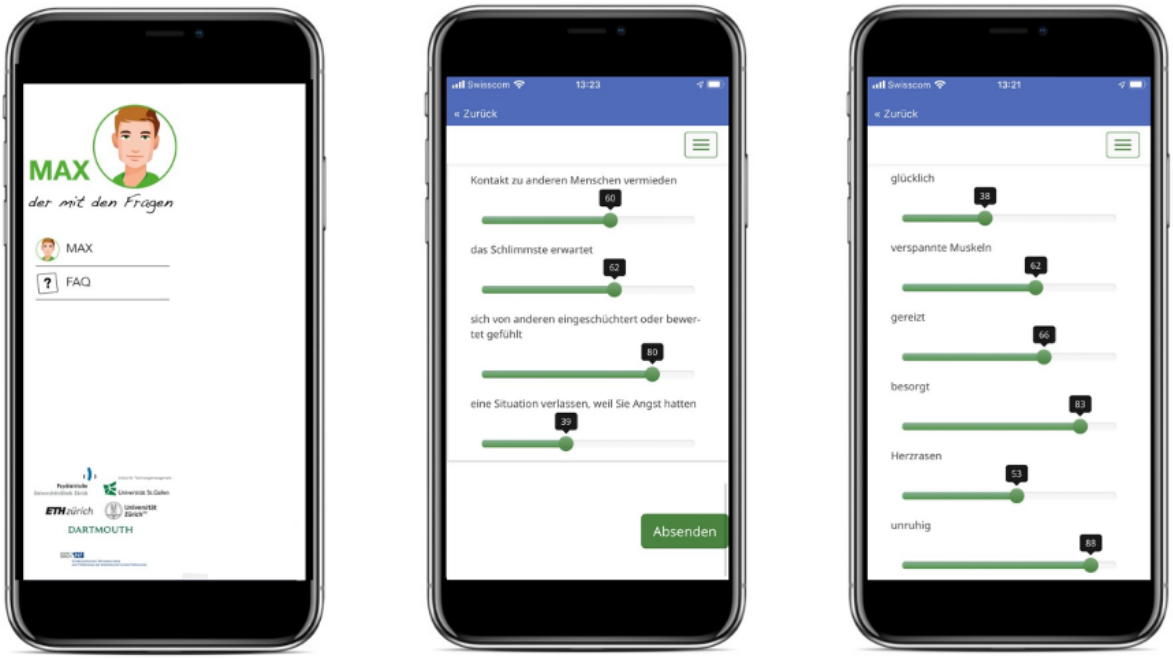

Biological Samples

Biological samples are collected via buccal swabs and saliva sampling tubes. Buccal swabs are taken for DNA extraction to derive gene-related predictors and to examine potential epigenetic changes, from baseline to postassessment, due to CBT treatment. Participants are asked to brush the inside of their cheek and the inner portion of their lips for 30 seconds using disposable cytological brushes. In total, 3 samples are taken at each assessment. Time of day and assessment time points are documented. Samples are stored at −20 ºC.

EEG-based Neural Indices

Task-based predictors are derived from 2 experimental tasks: an emotional conflict task [35,36] and a probabilistic learning task (adapted from a study by Etkin et al [37]). The former requires participants to recognize facial expressions (eg, fearful versus happy expressions) while ignoring emotion words overlaid over the facial expression. For incompatible emotional content, participants needed to resolve conflict and flexibly employ cognitive resources. The probabilistic learning task indexes the ability to learn from positive and negative feedback and thus rewards sensitivity and negative biases in information processing. Prior to the experimental tasks, a resting-state EEG is obtained with 10 minutes of the eyes open and 10 minutes of the eyes closed. Participants are instructed to remain still and let their minds wander without falling asleep. In the eyes-open condition, participants are asked to focus on a fixation cross. From the 2 tasks, different event-related potential indices are derived—emotional conflict (eg, N2 and N450) and probabilistic learning (eg, feedback-related negativity)—as well as bandwidth spectral power indices from the resting-state EEG. Data are recorded with NetStation (version 4.5.4) using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics).

Procedure

Prior to participation, participants receive information on procedures and study goals and undergo a telephone screening for the presence of inclusion and exclusion criteria. Those eligible for the study are invited to a baseline assessment, which comprises several assessment days conducted at the outpatient center, where therapy sessions will also take place. After obtaining written informed consent, participants undergo a clinical interview and complete clinical questionnaires. Assessors are trained graduate-level clinical psychologists supervised by trained clinicians. On assessment days 2 and 3, biological specimens (eg, salvia and buccal swabs) are taken, and an additional questionnaire as well as task-based EEG recordings are administered. At the end of this baseline assessment, the smartphone-based study coach MAX is installed on the participants' mobile devices to assess symptoms and emotions (using EMA and passive sensing), and the fitness trackers (activity tracking) are handed to the participants. Participants are instructed to use the MAX app consecutively on the following 14 days and to wear the fitness tracker day and night during the following 10 days.

All participants who meet the criteria are randomly assigned to an experimental group and cannot be excluded from then onward. Randomization is performed using DatInf Randlist (version 1.2) by an independent employee not associated in any further aspect of this study. Neither the study therapists nor the study team have access to the randomization list. Participants assigned to the CBT group receive treatment immediately after the baseline assessment, while WAIT group participants are required to undergo a waiting period of 16 weeks before treatment begins. The treatment comprises an average of 16 sessions of CBT according to the UP. After 8 weeks, participants complete a midassessment and a postassessment after treatment completion or after the waiting time.

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To monitor adherence and therapy content, therapists complete standardized documentation forms for every session (eg, implemented modules, percent of time spent outside the UP due to current problems, and other notable events). Sessions are videotaped or alternatively audiotaped if participants do not agree to be videotaped. The WAIT group receives the same assessments as the CBT group, except for the weekly post-CBT session assessments. To ensure objective evaluation of diagnostic status, assessors are blind to condition assignment at mid- and postassessments, and participants are advised not to disclose information about their treatment assignment. The midassessment comprises clinical interviews and questionnaires. In addition, the smartphone app and the fitness tracker are applied in the 14 following consecutive days. The postassessment comprises the same instruments as the midassessment but includes additional measures that correspond with the measures taken at baseline (eg, EEG and biological specimens). Six and 12 months after treatment completion, the CBT group participants undergo follow-up assessments comprised of clinical and psychological questionnaires administered on the web.

Treatment is considered completed per the protocol when participants have attended 16 sessions and worked through each module or prior to that in case of a complete remission. Participants can withdraw from participation at any time. Data on all subjects randomized into the CBT or the WAIT group will be analyzed (intention-to-treat analysis), but we will also investigate potential differences in results based on completer analyses.

Statistical Analysis

This study aims to develop a predictive ML model that forecasts primary therapy outcomes. Prior to ML modeling, data from different sources will be preprocessed, and relevant features will be extracted. With respect to EEG data (eg, event-related potentials related to emotion regulation and indices of bandwidth), spectral power will be extracted using software packages such as Brain Vision Analyzer II (Brain Products GmbH) and MATLAB, R2021b (The MathWorks, Inc). When the final set, including all predictive features, is established, the data will be forwarded as input to ML algorithms to build and test predictive models. Regarding ML, the data will be divided into a training data set and a test data set. The training data set will be used to derive the most promising model using parameter tuning and k-fold cross-validation, while the test data set will be used for an unbiased evaluation of the final model. Techniques to prevent overly complex models will be applied (eg, pruning of irrelevant features). Different algorithms will be used to optimize prediction accuracy and compare performance across algorithms. Applied algorithms include support vector machines, random forest, and gradient boosting [38-41], implemented using R (R Foundation for Statistical Computing). The final model tests will also include a test performed on the data from the WAIT group. This second test will serve as a test of the specificity of the final model (prediction accuracy for the WAIT group data is supposed to be lower than that of the CBT group).

We also aim to investigate prespecified and individually preregistered hypotheses regarding mechanistical associations between selected variables of interest and treatment outcomes to investigate active CBT mechanisms. Hierarchical models will be implemented as repeated measurements nested within the participants. For these analyses, we estimate both fixed and random intercepts and slopes. R will be used for the data analysis, and an intention-to-treat analysis will be used.

Ethics Approval

The study protocol and the documents for the informed consent were approved by the Cantonal Ethics Committee, Zurich (BASEC-No. 2017-01443). Written informed consent was obtained prior to participation. Participants have the option to opt out at any time. The study is carried out in accordance with the Good Clinical Practice and the Declaration of Helsinki.

Results

The trial is now completed. We will present study results in scientific peer-reviewed journals and conference presentations, hence stimulating collaboration and securing dissemination of the findings.

Discussion

The current trial aims to identify key clinical, digital, behavioral, and neurobiological features based on ML models to forecast treatment outcomes in transdiagnostic psychotherapy for anxiety disorders. Such treatments can be resource-intensive for therapists, patients, and the health care system. There is significant room to improve current psychotherapy for anxiety and related disorders. This trial may help identify patients who are likely to benefit from CBT and those who will not. Such knowledge can be used to personalize treatment.

We will also examine treatment-relevant mechanisms in detail and examine them using questionnaires in assessments (eg, emotion regulation, reward learning, and self-efficacy). By repeating selected measures and tasks after treatment completion, we also aim to investigate the effects of psychotherapy on these parameters. A better understanding of predictive values and changes following treatment in such underlying mechanisms of anxiety disorders will help refine and personalize current CBT treatments.

Results will be made available to clinical researchers, practitioners, and the general public, hence pushing forward clinical innovation and treatment optimization for patients with anxiety disorder and beyond.

Acknowledgments

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Data Availability

The protocol has been preregistered on the national clinical trial database (NCT03945617). Data and statistical codes will be published on GitHub as they become available. Data will be accessible after publication, as we will choose publishing houses that support an open data policy. Furthermore, we will inform clinical scientists about data availability and invite colleagues to collaborate when we present our study and data at conferences or other public science events (eg, state repositories in publications and publishing in journals that use badges for open data).

Authors' Contributions

BK is the principal investigator of this study. She designed the study together with AF, TK, and IGL and supervised the proposal and protocol development. AS and MMB wrote the first draft of the proposal and are thus joint first authors. All authors read and approved the final manuscript.

Conflicts of Interest

TK is affiliated with the Centre for Digital Health Interventions, a joint initiative of the Institute for Implementation Science in Health Care at the University of Zurich; the Department of Management, Technology and Economics at ETH Zurich; the Future Health Technologies Programme at the Singapore-ETH Centre; and the School of Medicine and Institute of Technology Management at the University of St. Gallen. The Centre for Digital Health Interventions is partly funded by CSS, a Swiss health insurer. TK is also a co-founder of Pathmate Technologies, a university spin-off company that creates and delivers digital clinical pathways. However, neither CSS nor Pathmate Technologies were involved in this study. IGL owns shares in Brooklyn Health and Google LLC, which work in digital sensor measurement.

Multimedia Appendix 1
Assessment overview and respective timepoints.
[PDF File (Adobe PDF File), 131 KB - resprot_v13i1e42547_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
EEG: electroencephalography
EMA: ecological momentary assessment
MINI: Mini International Neuropsychiatric Interview
ML: machine learning
UP: unified protocol

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Protocol

Mobile Phone–Based Confidential Social Network Referrals for HIV Testing (CONSORT): Protocol for a Randomized Controlled Trial

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Abstract

Background: Critical to efforts to end the HIV epidemic is the identification of persons living with HIV who have yet to be diagnosed and engaged in care. Expanded HIV testing outreach efforts need to be both efficient and ambitious, targeting the social networks of persons living with HIV and those at above-average risk of undiagnosed HIV infection. The ubiquity of mobile phones across many high HIV prevalence settings has created opportunities to leverage mobile health (mHealth) technologies to engage social networks for HIV testing outreach, prevention, and treatment.

Objective: The purpose of this study is to evaluate the acceptability and efficacy of a novel mHealth intervention, "Confidential Social Network Referrals for HIV Testing (CONSORT)," to nudge at-risk individuals to test for HIV using SMS text messages.

Methods: We will conduct the CONSORT study in Moshi, Tanzania, the commercial center and administrative capital of the Kilimanjaro Region in northern Tanzania. After qualitative formative work and pilot testing, we will enroll 400 clients presenting for HIV counseling and testing and 200 persons living with HIV and receiving care at HIV care and treatment centers as "inviters" into a randomized controlled trial. Eligible participants will be aged 18 years or older and live, work, or regularly receive care in Moshi. We will randomize inviters into 1 of 2 study arms. All inviters will be asked to complete a survey of their HIV testing and risk behaviors and to think of social network contacts who would benefit from HIV testing. They will then be asked to whom they would prefer to extend an HIV testing invitation in the form of a physical invitation card. Arm 1 participants will also be given the opportunity to extend CONSORT invitations in the form of automated confidential SMS text messages to any of their social network contacts or "invitees." Arm 2 participants will be offered physical invitation cards alone. The primary outcome will be counselor-documented uptake of HIV testing by invitees within 30 days of inviter enrollment. Secondary outcomes will include the acceptability of CONSORT among inviters, the number of new HIV diagnoses, and the HIV risk of invitees who present for testing.

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Results: Enrollment in the randomized controlled trial is expected to start in September 2024. The findings will be disseminated to stakeholders and published in peer-reviewed journals.

Conclusions: If CONSORT is acceptable and effective for increasing the uptake of HIV testing, given the minimal costs of SMS text reminders and the potential for exponential but targeted growth using chain referrals, it may shift current practices for HIV testing programs in the area.

Trial Registration: ClincalTrials.gov NCT05967208; https://clinicaltrials.gov/study/NCT05967208

International Registered Report Identifier (IRRID): PRR1-10.2196/55068

(JMIR Res Protoc 2024;13:e55068) doi:10.2196/55068

KEYWORDS

confidential referrals; HIV counseling and testing; mHealth; mobile health; social networks; stigma; sub-Saharan Africa; Tanzania

Introduction

Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) set for 2030 the ambitious 95-95-95 target: diagnosing 95% of all persons living with HIV, initiating antiretroviral therapy for 95% of those diagnosed, and achieving viral suppression for 95% of those treated. Traditional testing approaches have linked countless persons living with HIV to treatment; however, the cost-effectiveness of these approaches for reaching incrementally harder-to-reach persons living with HIV is declining. The 2022 Tanzania Demographic and Health Survey and Malaria Indicator Survey (TDHS-MIS) found that only 79.6% of Tanzanian women and 64% of Tanzanian men had tested for HIV during their lifetime [1]. Furthermore, despite the recommendation that those in the general population who test negative retest annually, only 36.5% of women and 30.6% of men reported testing for HIV in the previous 12 months. Thus, novel approaches that efficiently reach at-risk individuals are urgently needed.

Social and sexual networks play a critical role in HIV transmission [2], testing decisions [3,4], linkage to care [5], and adherence [6]. However, numerous barriers, including HIV-related stigma, legal concerns, and the risk of unwanted serostatus disclosure, can impede HIV-related communication within social and sexual networks [7,8]. The ubiquity of mobile phones across many high HIV prevalence settings, including those in low- and middle-income countries (LMICs), has created opportunities to leverage mobile health (mHealth) technologies to engage social networks along the HIV care continuum for contact tracing, partner notification, clinic engagement, adherence reminders, and support for persons living with HIV [9-11]. The privacy and confidentiality afforded by novel applications of mHealth technologies can help address stigma and legal concerns, and broadly improve the uptake of HIV testing.

This study describes the protocol for a randomized controlled trial (RCT) to evaluate the acceptability and efficacy of mobile phone–based "nudges" in the form of "Confidential Social Network Referrals for HIV Testing" (CONSORT) to reach high-risk individuals and encourage them to test for HIV. The study will adapt and use an existing, highly versatile mobile phone–based appointment reminder and incentive system (mParis) [12-14]. mParis resides in Tanzania and can autonomously send large numbers of SMS text messages according to prespecified algorithms, making it a low-cost tool that can easily be adapted and scaled. In previous work, we explored the hypothetical acceptability and efficacy of CONSORT [15]. The survey results from this work suggested high feasibility and moderate acceptability of CONSORT. This study will explore the actual acceptability and efficacy of the intervention.

This study aligns with Tanzania's 2017-22 "Health Sector HIV and AIDS Strategic Plan (HSHSP-IV)," which listed as its first challenge that HIV testing services need to be more efficient and ambitious [16]. Acknowledging the unfinished business from HSHSP-IV, the "Health Sector Strategic Plan July 2021–June 2026" highlights persistently low rates of HIV testing for some groups, particularly men and young people [17]. If CONSORT is shown to be acceptable and effective, confidential, digital, chain-referral methods could greatly improve the reach and cost-effectiveness of HIV testing efforts. While the CONSORT system will be developed and tested using SMS text messaging in a low-resource setting, the confidential chain-referral approach and the system's open-source architecture may be extended to promote other health behaviors across varied social networks, app-based technologies, health conditions, and geographic settings.

Study Aims and Hypothesis

This study aims to evaluate the acceptability and efficacy of automated confidential SMS text messaging–based HIV testing invitations as a means of "nudging" individuals to test for HIV. The overall study hypothesis is that an automated confidential referral system, developed and deployed in the Kilimanjaro Region of Tanzania, will be acceptable to both index participants (inviters) and their referrals (invitees), and it will be effective for increasing uptake of HIV testing.

The CONSORT Intervention

The CONSORT process is shown in Figure 1. A consented inviter completes an HIV risk assessment and a survey of their social and sexual network contacts. Next, the inviter selects invitation messages from a menu of options to send to any of their network contacts who they think could benefit from HIV testing. Invitee phone numbers and SMS text messages are transferred securely to mParis. mParis autonomously sends the invitation SMS text message with a unique referral code to each invitee phone number. Invitees presenting for HIV testing with

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a referral code (invitee testers) will be offered the opportunity to become inviters (Figure 1).

Figure 1. The Confidential Social Network Referrals for HIV Testing (CONSORT) process. (A) A consented "inviter" volunteers the phone numbers of social network contacts and (B) selects the invitation SMS text message. (C) A secure autonomous digital health system sends the selected SMS text messages to each "invitee" phone number. (D) An invitee responding to the invitation presents for HIV testing ("invitee tester") and is offered the opportunity to become an inviter. mParis: mobile phone–based appointment reminder and incentive system.

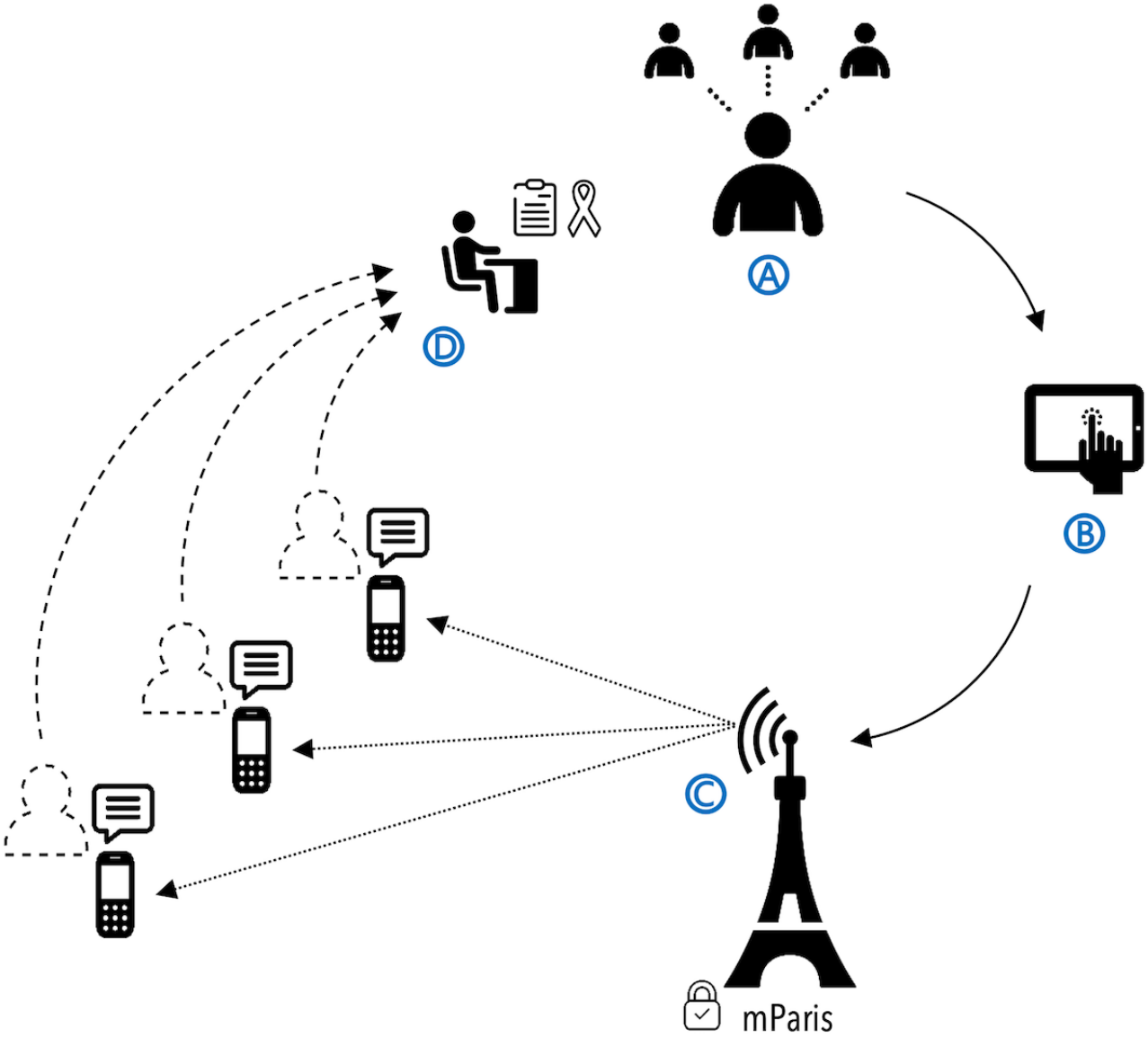

Methods

Study Setting

The study will be conducted in Moshi, Tanzania. Moshi is the commercial center and administrative capital of the Kilimanjaro Region in northern Tanzania and has an estimated population of about 535,000 [18]. Moshi has 25 HIV counseling and testing (HCT) facilities that offer free HIV testing; many of these function as HIV care and treatment centers (CTCs), providing free HIV care to persons living with HIV [19]. HCT and CTC facilities with adequate volume to support the proposed study activities will be eligible to participate in the recruitment of inviters for the RCT. The uptake of HIV testing among invitees will be assessed across all HCT facilities in the study area.

Study Sample

The RCT will include gender-balanced samples of 600 inviters, including 400 adult HCT clients and 200 adult persons living with HIV receiving care at participating CTCs.

Inclusion and Exclusion Criteria

Eligible participants will be aged 18 or older and live, work, or regularly receive care in Moshi. Minors (<18 years) will be excluded, as it will not practically be possible to obtain assent to minors' participation in a research study from a legal guardian.

Recruitment

Clients presenting for HIV testing and persons living with HIV and receiving care at participating facilities will be approached consecutively for eligibility determination and informed consent

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and offered enrollment in the RCT. Recruitment will continue until the target sample sizes have been reached.

Study Design

The study will evaluate the acceptability and efficacy of CONSORT. Because CONSORT may be a substitute for other referral options (eg, word-of-mouth referrals), full attribution of testing uptake to CONSORT would likely overstate the system's effectiveness. To derive valid estimates of the effect of CONSORT, we will evaluate CONSORT in the context of a traceable substitute referral option: physical invitation cards.

Design of the RCT

The design of the 2-arm RCT is shown in Figure 2. Arm 1 participants will be offered to extend CONSORT invitations or physical invitation cards to any of their network contacts. Arm 2 participants will be offered physical invitation cards alone. Arm 1 represents the intervention arm; Arm 2 represents the active control arm.

Figure 2. The design of the 2-arm randomized controlled trial (RCT). This RCT with 600 adult inviters will be conducted in Moshi, Tanzania. The primary outcome of interest is the uptake of HIV testing among invitees, defined as the number of invitees testing for HIV within 30 days of enrollment of the inviter per 100 inviters. While not all process elements can be observed, the RCT results yield an unbiased estimate of the efficacy of the Confidential Social Network Referrals for HIV Testing (CONSORT) for the primary outcome: inducing additional persons to test for HIV relative to physical invitation cards alone.

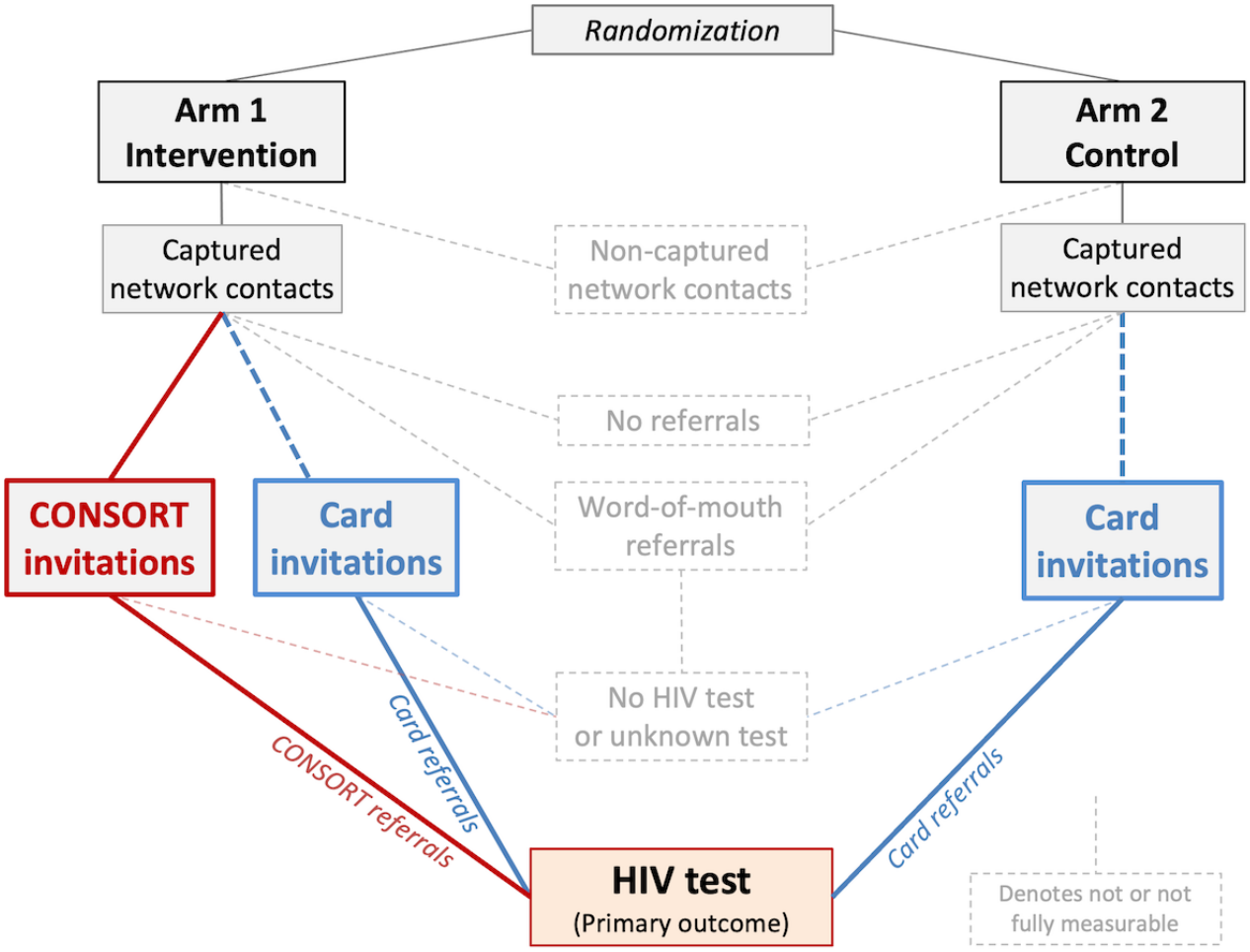

Assignment to Study Arms

Participant IDs will be randomly assigned to either arm 1 or arm 2 using a random number generator. The random assignment is expected to result in approximately equal numbers of participants in each study arm.

Blinding

Neither participants nor research staff will be blinded with respect to inviters' study arm assignments.

Primary Outcome

The primary outcome is counselor-documented uptake of HIV testing among invitees within 30 days of the enrollment of the inviter. For invitees who present for HIV testing (invitee testers) after a CONSORT invitation, referral codes, alphanumerical codes that are unique to the phone number of the invitee, will be documented by counselors in logbooks; for invitees presenting with physical invitation cards, counselors will collect the invitation cards.

Secondary Outcomes

Secondary outcomes include the acceptability of CONSORT among inviters, the number of new HIV diagnoses, and the HIV risk among invitee testers. The assessments of secondary outcomes are detailed later on in their own section.

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Study Activities

Enrollment Survey

Participants will complete an interviewer-administered enrollment survey to assess their HIV serostatus, HIV-related behaviors (eg, HIV prevention behaviors, HIV testing history, number of partners, and concurrency) [20], and stigma [21-23], as well as key demographic, socioeconomic, and household characteristics that may correlate with the acceptability and efficacy of CONSORT [24,25]. Surveys will be conducted in Kiswahili. The data will be captured electronically using tablet devices.

Social Network–Based HIV Testing Invitations

The enrollment survey will include a survey of inviters' preferences for extending HIV testing invitations within their social networks. Participants will be asked to think of social network contacts across multiple network dimensions, including partners, family members, friends, coworkers, and other people who are aged 18 years or older and who would benefit from HIV testing. Participants will be asked to whom they would prefer to extend an HIV testing invitation through a physical invitation card; arm 1 participants will also be able to select CONSORT invitations. At the end of the survey, inviters will be given the respective number of coded invitation cards, and arm 1 inviters will be able to send CONSORT invitations to their network contacts (Figure 1).

Phone-Based Follow-Up Survey

The extent to which physical invitation cards were distributed to invitees will be ascertained through self-reports from inviters during a phone-based follow-up survey after 30 days.

Assessment of Primary Outcome

The primary outcome measure is counselor-documented uptake of HIV testing by invitees within 30 days of the enrollment of the inviter. All clients presenting for HIV testing will be asked if they received an HIV testing invitation by SMS text message or a physical invitation card. Counselors will document referral codes from SMS text messages and collect invitation cards. Referral codes will be validated against a database of referral codes issued. A match is interpreted as an invitee presenting for HIV testing.

Assessment of Secondary Outcomes

The acceptability of CONSORT among inviters will be described by the percentage of inviters extending at least 1 CONSORT invitation and the average number of CONSORT invitees per inviter. This outcome is assessed only for arm 1 participants.

For invitee testers, basic sociodemographic and risk characteristics (age, gender, marital status, pregnancy status, and previous testing), as well as their HIV test result, will be abstracted in aggregate form from administrative data collected for reports to Tanzania's National AIDS Control Programme (NACP). Clients testing positive for HIV will be linked to care at a local CTC, following NACP guidelines [16]. Invitee testers consenting to become inviters will complete the same enrollment survey as their inviters, which includes a comprehensive HIV risk assessment.

Participant Retention

Inviters who choose to extend physical invitation cards to their network contacts will be recontacted by phone after 30 days and asked whether they distributed these cards to their contacts. For all other inviters, study activities will end after the initial visit.

Study Timeline

Details of the intervention will be finalized after formative qualitative work, including focus group discussions and in-depth interviews with HCT clients, CTC patients, and providers. Focus group discussions and in-depth interviews will explore ethical considerations and elucidate key client-side characteristics of CONSORT, including refining appropriate SMS text message content for invitees, defining parameters for the timing of invitation messages, and exploring the feasibility of incentives for inviters and invitees. Before the implementation of the RCT, the intervention will be pilot-tested with 50 adult HCT clients and 50 adult CTC patients. Formative work and pilot testing are expected to last 2 years.

Following formative work and a successful pilot test, the RCT is planned to commence in year 3 of this study. Enrollment in the RCT will continue until the target numbers of 400 HCT inviters and 200 CTC inviters have been reached. Assessments of invitation card distribution and HIV testing uptake will continue until 30 days after the last CONSORT invitation was sent through mParis and the last invitation card was issued.

Statistical Analysis

Analysis of the Primary Outcome

Efficacy will be analyzed descriptively by comparing, between the 2 study arms, the number of invitees testing for HIV within 1 month per 100 inviters (Figure 3). Analytically, efficacy will be modeled at the level of the inviter, using a zero-inflated negative binomial model, with the number of invitees returning for testing as the dependent variable. The primary explanatory variable will be a binary indicator variable for the study arm. Covariates will characterize variation in invitees' testing uptake with inviters' sociodemographic and network characteristics, HIV risk, and stigma.

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Figure 3. Visual representation of the estimated effect of Confidential Social Network Referrals for HIV Testing (CONSORT) on the primary outcome: number of invitees testing for HIV within 30 days per 100 inviters (hypothetical). The 2-arm randomized controlled trial with 600 adult inviters will be conducted in Moshi, Tanzania.

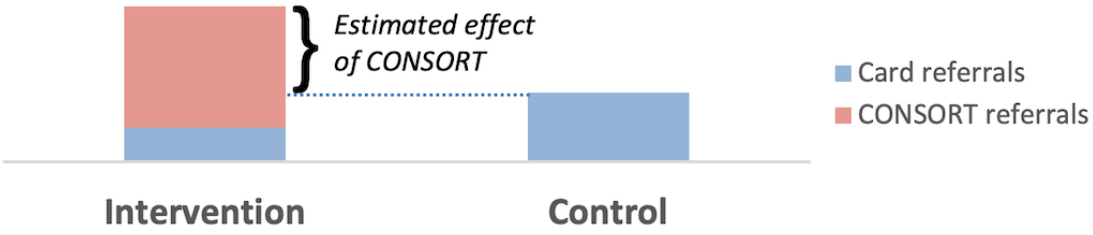

Analyses of Secondary Outcomes

Acceptability Among Inviters

Logistic regression will be used to model inviters' decisions to send at least 1 CONSORT invitation. Zero-inflated negative binomial models will model the number of invitations sent as a function of the covariates described above.

New HIV Diagnoses

Differences between study arms in the number of new HIV diagnoses among invitees, per 100 inviters, will be analyzed descriptively using a Fisher exact test.

HIV Risk Among Invitees

Differences in invitees' sociodemographic and risk characteristics between study arms will be assessed descriptively using 2-tailed Student *t* tests and chi-square statistics.

Analytic Considerations

The analysis of the primary outcome will be stratified by cohort (HCT inviters: n=400; CTC inviters: n=200); generalized Hausman tests will evaluate whether the data can be pooled.

Sensitivity Analyses

Sensitivity analyses will assess the potential impact of missing data on estimates and describe variation in the acceptability and efficacy of CONSORT by cohort (HCT vs CTC inviters) and gender (male vs female inviters).

Statistical Power

The primary outcome analysis will compare rates of HIV testing among invitees across study arms (Figure 3). As a priori estimates of invitees' testing rates in the control arm are not known, power calculations for differences in rates between study arms would be speculative. Instead, the power calculations refer to changes in the number of invitees presenting for testing, N_T, which can be assumed to follow a Poisson distribution with a SE of sqrt (N_T). Assuming that 20 (alternatively 40, 60, 80, or 100) invitees of arm 2 inviters present for testing, the study has 90% power to detect CONSORT-related differences of 7 (10, 13, 15, or 16) testers between study arms and 80% power to detect differences of 6 (8, 10, 11, or 13) testers between study arms. These calculations apply to cohort- or gender-specific as well as aggregate analyses.

Reporting

This manuscript was prepared in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for clinical trial protocols. The completed checklist and Figure S1 can be found in Multimedia Appendices 1 and 2.

Monitoring and Quality Assurance

Adherence to intervention protocols and the completeness and quality of study data will be monitored by the principal investigators or a designated study monitor. Electronic data capture on tablet devices and daily uploads to secure servers allow for the continuous monitoring of study activities in near real-time. All paper documents will be scanned. Rigorous quality assurance and quality control procedures will be established, including interviewer observation, validation and range checks during data entry, verification of entered data, and the monitoring of time stamps for electronic surveys.

Patient and Public Involvement

Formative, qualitative work with HCT clients, CTC patients, and providers will elucidate key characteristics of CONSORT, including the selection of relevant social network contacts, appropriate message content for invitees, and defining parameters for the timing of invitation SMS text messages. Discussions will also focus on ethical considerations and the potential role of economic incentives as a means of motivating inviters to invite additional network contacts to test for HIV. Findings will be used to identify features of the CONSORT system that will maximize its acceptability among inviters and invitees.

Ethical Considerations

This protocol was registered at ClinicalTrials.gov (NCT05967208) on July 25, 2023. The protocol was approved by the University of South Carolina Institutional Review Board (Pro00120208) in the United States; the Ethics Review Committee at Kilimanjaro Christian Medical University College (Protocol #1404); and the Tanzania National Institute for Medical Research (NIMR/HQ/R.8a/Vol.IX/4373). The project will consistently apply relevant ethical principles when working with individuals at risk for or affected by HIV. Protocol amendments will be submitted to these entities as required.

Informed consent documents will be developed in English and translated into Kiswahili. Trained research assistants will inform eligible individuals about the study's purpose, procedures, risks, and benefits before obtaining informed consent for participation. The potential risks and benefits of research participation will be carefully explained in culturally appropriate and understandable language during the consent process. Consenting

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individuals will be enrolled in the study, with the study ID dictating their assignment to 1 of the 2 RCT study arms.

The data will be kept in compliance with relevant privacy regulations in Tanzania and the United States. Access to identifying information will be strictly limited. Study personnel will be instructed to keep the identities of all research participants confidential and will sign confidentiality agreements. The CONSORT system will be designed with a focus on confidentiality. Only encrypted versions of the invitee phone numbers will be stored in mParis, and information about the invitee will be stored separately from information about the inviter. Encrypted invitee phone numbers will be decrypted only as necessary for SMS scheduling and when "in flight" to the SMS text message center.

Inviters and their invitee testers who agree to participate in the research will receive between TSH 5000-10,000 (approximately US $2.20-US $4.40) as compensation for their time.

Results

After qualitative formative work and pilot testing, enrollment in the RCT is expected to start in September 2024.

Research results from the CONSORT study will be disseminated through peer-reviewed publications, at national and international conferences, and through media outlets. To comply with the publication policies of the National Institute for Medical Research (NIMR) in Tanzania, approval for publications will be obtained from NIMR.

As many stakeholders and policy makers interested in this research reside in Tanzania, efforts will be made to translate the research abstracts into Kiswahili to make them more widely accessible. All system components and expertise needed to sustain and scale up CONSORT will be in place locally at the end of this project.

Discussion

Overview

This study will evaluate the acceptability and efficacy of automated, confidential SMS text message–based HIV testing invitations as a means of nudging individuals to test for HIV. If testing rates are higher in arm 1 invitees than arm 2 invitees, the results will support our hypothesis that an automated, confidential referral system is acceptable to both index participants (inviters) and referrals (invitees) and is effective for increasing uptake of HIV testing. If CONSORT is shown to be acceptable and effective, then confidential, digital, chain-referral methods could be used to improve the reach and cost-effectiveness of HIV testing efforts.

CONSORT's potential is based on 3 key premises.

The first premise is that testing network contacts of persons living with HIV and those testing for HIV is an effective means for HIV case-finding. Identifying, tracing, and testing sexual contacts of persons with a sexually transmitted infection has been an essential component of public health sexually transmitted infection management for decades. Assisted HIV partner notification, by which health care workers elicit information about an index case's sexual partners and contact partners to request HIV testing, has been shown to be effective for increasing testing uptake and identifying new HIV infections [26-36]. A meta-analysis of 3 individual randomized trials [33-35] found that assisted partner notification, compared with passive referral, resulted in a 1.5-fold increase in HIV testing uptake. Moreover, the proportion of HIV-positive partners identified was 1.5 times higher with this approach [37]. Previous research also suggests that persons presenting for HIV testing have higher rates of HIV infection and higher rates of HIV risk behaviors than the general population [38,39]. Owing to similarities between members of social networks, a property known as homophily, referrals of HCT and CTC clients are, thus, also more likely to be infected with HIV than the general population. CONSORT, therefore, is well positioned to reach populations with an above-average risk of HIV infection and nudge them to test for HIV.

The second premise is that an assurance of confidentiality promotes referrals for HIV testing within social networks. CONSORT is conceptually related to confidential partner notification strategies [40,41], which are known to be highly acceptable to participants [42,43]. The evidence for technology-based notification systems for testing for sexually transmitted diseases, mainly derived from internet-based applications in high-income settings, is mixed: some show success [44-51], while others do not [41,52,53]. The efficacy of an impersonal, confidential approach to accessing network contacts in LMICs has yet to be evaluated. On the one hand, this approach may reduce the cost of contacting partners [54] and circumvent barriers such as nonreciprocal relationships [55], stigma [56], disclosure, and legal risks [57]. On the other hand, a confidential SMS text message is likely to be less motivating than personal communication. This study will compare the acceptability and efficacy of CONSORT versus other means of inviting social network contacts to test for HIV.

The third premise is that SMS text message–based nudges are inexpensive, effective tools for influencing health behaviors. Apart from incentives, reminders are among the simplest available nudging tools [58]. SMS text message–based nudges in the context of HIV testing remain rare, despite their low cost and nearly universal reach. While there is evidence that SMS text message–based interventions are feasible and acceptable in LMICs [59-63], and that nudging can influence health-related behaviors [64-66], relatively few studies have evaluated the use of SMS text messaging to encourage HIV testing [9,67-75]. We identified only 5 protocols that evaluated SMS text messaging for increasing uptake of facility-based HIV testing among at-risk adults in sub-Saharan Africa [9,70-72,75]. Although these studies demonstrated the strong potential of SMS text message–based messages to influence testing uptake, each has significant limitations, including using self-reports of HIV testing [67,70-72,75], using a combined intervention that included SMS text messaging with phone calls and in-person reminders [9], and limiting the intervention to young adults [9,72,74], women [72], or specific high-risk populations [71,75-82]. The design of this study is more rigorous in that (1) we will isolate the effect of SMS text messaging alone, and (2)

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actual testing uptake will be assessed in real time (rather than by self-report). Finally, results from CONSORT will be more broadly applicable, as the index (inviter) population will include participants from both sexes and across a greater range of ages, and it will extend beyond specific high-risk populations. With low costs of SMS text messages in the study area and an open-source and largely autonomous implementation, CONSORT may overcome the limits to growth encountered in traditional chain referral approaches [56] and support continuous, sustainable growth.

Limitations and Considerations

This study is subject to several limitations and considerations.

First, feasibility considerations limit the study area to include only HCT facilities in Moshi municipality. Invitees may test outside the study area and may thus not be captured by our study. Furthermore, while referral codes and coded invitation cards collected from participating HCT providers offer definitive evidence of a completed HIV test, participants may test without disclosing receipt of CONSORT messages or invitation cards.

Second, the estimated effect sizes are not generalizable to other index populations, other areas in Tanzania, or other parts of Africa. While high mobile phone use rates and stable cellular network coverage suggest good technical feasibility of CONSORT, illiteracy, lack of trust in confidentiality assurances, and stigma remain potential challenges. In the formative work and the pilot study, we will explore options such as computer-assisted self-interviewing for capturing referral information, incentives, and system-level adjustments to maximize acceptability and efficacy.

Third, SMS text messages must be short and concise, can only contain text, and are not encrypted in transit. As implemented in this study, messages are presented as 1-way communication (although a phone number is provided if the invitee has questions). If successful, future work will explore the use of alternative communication options that allow for the secure transfer of audiovisual information and a more interactive experience (eg, through chatbots).

Finally, we note that this study is subject to 2 important ethical considerations: (1) inviters provide the phone numbers of their network contacts without the contacts' consent, and (2) CONSORT invitees need to be informed that the SMS text messages they receive are part of a research project. Regarding the first consideration, Tanzania's 2019 "National Comprehensive Guidelines on HIV Testing Services" sets a precedent in its section on Index Client Testing and Partner Notification [83]. The guidance outlines several assisted voluntary approaches to disclosing HIV status to the partners of index clients. One of the suggested approaches allows an HIV testing provider to contact the index client's partners directly and confidentially for testing. Providers need the index client's consent but not their partners' consent. While this approach is primarily focused on index clients who are diagnosed with HIV, the guidelines emphasize "enhanced use of this approach throughout the country as among the new innovations to rapidly increase the number of PLHIV diagnosed." Regarding the second consideration, SMS text messages to invitee phone numbers will include a statement indicating that the message is part of a research study. Throughout the study, we will continue discussions with the ethicists on our team to ensure that all procedures minimize potential risk of harm to both inviters and invitees, preserve strict confidentiality, and avoid potential stigmatization.

Conclusion

In conclusion, the CONSORT approach, which combines the ubiquity of mobile phones with an assurance of confidentiality, holds promise for efficiently engaging higher-risk populations by nudging their network contacts to test [84-86]. If CONSORT is acceptable and effective for increasing uptake of HIV testing, it can be readily sustained and scaled, and it has the potential to shift current practices in HIV testing programs in the study area. Given the minimal costs of sending SMS text message reminders and the potential for exponential, but targeted, growth using chain referrals, this system could prove to be a cost-effective tool for accelerating Tanzania's goal to reach HIV epidemic control by 2030. Leveraging social networks and technologies for nudging is readily extensible to other areas of public health, particularly where health concerns overlap and cluster within stigmatized or hard-to-reach social networks.

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All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

JO, NT, and BN conceptualized the study. AH, BN, JO, NT, and TY were involved in the development and submission of the funding application. All authors contributed to the development of the study protocol. JO, BN, and NT co-led the development of this manuscript, wrote the first draft of the manuscript, and led subsequent revisions. MVZ developed the mParis software. All authors read the manuscript, provided critical input, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) figure depicting schedule of enrollment, interventions, and assessments.
[PNG File , 45 KB - resprot_v13i1e55068_app1.png]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v13i1e55068_app2.pdf]

Multimedia Appendix 3
Peer review report from the National Institute of Health.
[PDF File (Adobe PDF File), 117 KB - resprot_v13i1e55068_app3.pdf]

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Abbreviations

CONSORT: Confidential Social Network Referrals for HIV Testing
CTC: HIV care and treatment center
HCT: HIV counseling and testing
HSHSP-IV: Health Sector HIV and AIDS Strategic Plan
LMIC: low- and middle-income country
mHealth: mobile health
mParis: mobile phone–based appointment reminder and incentive system
NACP: National AIDS Control Programme
NIMR: National Institute for Medical Research
RCT: randomized controlled trial
TDHS-MIS: Tanzania Demographic and Health Survey and Malaria Indicator Survey
UNAIDS: Joint United Nations Programme on HIV/AIDS

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Protocol

Standard Versus Family-Based Screening, Brief Intervention, and Referral to Treatment for Adolescent Substance Use in Primary Care: Protocol for a Multisite Randomized Effectiveness Trial

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Abstract

Background: Screening, brief intervention, and referral to treatment for adolescents (SBIRT-A) is widely recommended to promote detection and early intervention for alcohol and other drug (AOD) use in pediatric primary care. Existing SBIRT-A procedures rely almost exclusively on adolescents alone, despite the recognition of caregivers as critical protective factors in adolescent development and AOD use. Moreover, controlled SBIRT-A studies conducted in primary care have yielded inconsistent findings about implementation feasibility and effects on AOD outcomes and overall developmental functioning. There is urgent need to investigate the value of systematically incorporating caregivers in SBIRT-A procedures.

Objective: This randomized effectiveness trial will advance research and scope on SBIRT-A in primary care by conducting a head-to-head test of 2 conceptually grounded, evidence-informed approaches: a standard adolescent-only approach (SBIRT-A-Standard) versus a more expansive family-based approach (SBIRT-A-Family). The SBIRT-A-Family approach enhances the procedures of the SBIRT-A-Standard approach by screening for AOD risk with both adolescents and caregivers; leveraging multidomain, multireporter AOD risk and protection data to inform case identification and risk categorization; and directly involving caregivers in brief intervention and referral to treatment activities.

Methods: The study will include 2300 adolescents (aged 12-17 y) and their caregivers attending 1 of 3 hospital-affiliated pediatric settings serving diverse patient populations in major urban areas. Study recruitment, screening, randomization, and all SBIRT-A activities will occur during a single pediatric visit. SBIRT-A procedures will be delivered digitally on handheld tablets using patient-facing and provider-facing programming. Primary outcomes (AOD use, co-occurring behavior problems, and parent-adolescent communication about AOD use) and secondary outcomes (adolescent quality of life, adolescent risk factors,

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and therapy attendance) will be assessed at screening and initial assessment and 3-, 6-, 9-, and 12-month follow-ups. The study is well powered to conduct all planned main and moderator (age, sex, race, ethnicity, and youth AOD risk status) analyses.

Results: This study will be conducted over a 5-year period. Provider training was initiated in year 1 (December 2023). Participant recruitment and follow-up data collection began in year 2 (March 2024). We expect the results from this study to be published in early 2027.

Conclusions: SBIRT-A is widely endorsed but currently underused in pediatric primary care settings, and questions remain about optimal approaches and overall effectiveness. In particular, referral to treatment procedures in primary care remains virtually untested among youth. In addition, whereas research strongly supports involving families in interventions for adolescent AOD, SBIRT-A effectiveness trial testing approaches that actively engage family members in primary care are absent. This trial is designed to help fill these research gaps to inform the critical health decision of whether and how to include caregivers in SBIRT-A activities conducted in pediatric primary care.

Trial Registration: ClinicalTrials.gov NCT05964010; https://www.clinicaltrials.gov/study/NCT05964010

International Registered Report Identifier (IRRID): PRR1-10.2196/54486

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KEYWORDS

adolescent substance use; pediatric primary care; screening; brief intervention; referral to treatment; family-based

Introduction

Alcohol and Other Drug Use Problems Exert Enormous Negative Impacts on Adolescents

The level of unmet intervention need among adolescents with risky alcohol and other drug (AOD) use is a persistent public health problem. Recent data from the 2023 Monitoring the Future national survey indicate that, among 12th graders, 46% reported using alcohol (more than just a few sips); 39% marijuana; 39% nicotine via vaping; and 43% illicit drugs, including inhalants [1]. According to the 2023 National Survey on Drug Use and Health (NSDUH), among adolescents aged 12 to 17 years in 2022, 8.7% (or 2,228,000 adolescents) reported a substance use disorder in the past year [2]. Troublingly, the rates of treatment enrollment among this high-need age group are considerably low, with only 4.6% of the adolescents who meet the criteria for substance use disorders receiving specialty care [2]. When left unaddressed or ineffectively treated, AOD use during adolescence often continues into adulthood, precipitating long-term substance use and mental health disorders and being associated with a cascade of other health consequences, as well as imparting enormous economic costs to society [3].

Preventing youth AOD use and intervening early with those who use are key to reducing the many consequences of risky use. As shown in neurodevelopment research on risky behavior in youth, adolescence is the critical period both for starting AOD use and experiencing harmful consequences as a result [4]. Adolescence is a developmental stage characterized by risk behaviors, including AOD experimentation; adolescents are also vulnerable to negative impacts of addictive substances, which can further impair judgment, interfere with brain development, and increase addiction risk [5]. Moreover, AOD use is associated with the 3 leading causes of death among teenagers: motor vehicle crashes, homicides, and suicides [6]. Prevention and early intervention can also prevent progression to more severe AOD use that carries the risk of overdose and death.

Screening, Brief Intervention, and Referral to Treatment for Adolescents Is Widely Recommended for Addressing AOD Use in Primary Care

Given that the majority of teenagers in the United States visit primary care (PC) clinics at least once per year [7], PC settings provide rich opportunities to detect and intervene with adolescents at risk for AOD problems. The most recent guidelines issued by the American Academy of Pediatrics prescribe universal AOD screening for teenagers during both routine preventive appointments and nonpreventive PC visits [8]. Recognizing the unique role that PC providers can play in meeting the challenge of adolescent AOD use, the American Academy of Pediatrics further recommends that providers learn procedures for screening, brief intervention, and referral to treatment (SBIRT) and how to integrate SBIRT into medical care for adolescents [9]. SBIRT for adolescents (SBIRT-A) entails a set of clinical procedures for detecting youth at risk of AOD problems and delivering appropriate prevention or early intervention, including universal screening for AOD risk level and formulaic guidelines for providing brief motivational interventions and appropriate treatment referral to patients identified as at risk [8,10]. Notably, when delivered using standard procedures, SBIRT-A amounts to an adolescent-focused approach in which most or all activities involve only the given youth [11,12].

SBIRT-A is widely recommended to promote detection and early intervention for AOD use in PC [9,13]. In practice, although 50% to 86% of pediatricians report screening for AOD use, the use of standardized screening assessments and systematic brief interventions (BIs) is low [14]. In research trials, approximately 25% to 35% of adolescents screen positive for substance use when systematic screening is implemented [15,16]. Research reviews and meta-analyses show that BI procedures can be effective in reducing adolescent drinking [17,18] and, when delivered in PC settings, have demonstrable impacts and cost-effectiveness for quality-of-life indicators [18-20]. Recent studies, including 2 multisite effectiveness trials that collectively examined thousands of adolescent visits in PC

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clinics [15,21], further suggest that SBIRT-A is scalable in PC [16,22].

Despite these promising developments, there remain significant limitations in SBIRT-A research and practice in PC. Prior controlled SBIRT-A studies conducted in PC have yielded inconsistent findings with regard to implementation feasibility [23], in large part due to significant practice barriers to delivering SBIRT-A in pediatric care. PC providers are generally reluctant to implement SBIRT-A, citing insufficient time, limited training in substance use, unfamiliarity with the procedures, a lack of readiness to address a positive AOD screen result, limited resources for referrals to specialty care, and concerns about confidentiality [24-28]. Moreover, despite data from systematic reviews supporting BIs in PC [18], the US Preventive Services Task Force recently determined that evidence is insufficient to assess the balance of benefits versus harms of screening adolescents for unhealthy AOD use due to variability in study methods and quality [29]; consequently, it withheld a recommendation for widespread SBIRT-A delivery in pediatric settings [10,30]. Given existing gaps in the SBIRT-A research base on the effectiveness of SBI and the effect of involving caregivers in SBI procedures as well as the impact of BIs on outcomes beyond AOD use and the corresponding uncertainties in the policy and practice status of SBIRT-A in pediatric settings, there is urgent need to advance the scope of SBIRT-A effectiveness studies in PC [28].

Tablet-Guided SBIRT-A Procedures Have the Potential to Reduce Implementation Barriers

Tablet-guided SBIRT-A approaches have the potential to reduce documented implementation barriers through offering a standardized road map for addressing AOD use. Tablet-guided SBIRT-A procedures eliminate the need for the memorization of complicated adjunctive SBIRT-A procedures. Instead, tablet-guided SBIRT-A approaches provide a new and systematic way to address positive AOD screening that is more efficient than the existing eclectic practices that providers currently rely on. Providers are guided through step-by-step interventions designed with their time constraints in mind, leveraging automated tools and well-vetted workflow integration [16,31,32]. Procedures include recommendations for providers on addressing positive AOD screens with youth and their caregivers without jeopardizing youth autonomy or violating confidentiality.

Incorporating Caregivers in SBIRT-A Procedures Has the Potential to Enhance Effectiveness

Overview

The standard SBIRT-A approach focuses almost exclusively on the adolescent patient by including only the given youth in screening and intervention procedures [11]. Nevertheless, the SBIRT-A evidence base indicates a need for improvements in effectiveness and feasibility in PC [33,34]. Incorporating caregivers in SBIRT-A activities could enhance the effectiveness of the approach in several ways, as outlined in the following subsections.

Broaden the Screening Search

The “no missed opportunities” paradigm [35] recognizes caregivers as vital sources of information about adolescent AOD risk. Using multiple sources of information to assess youth AOD use is more accurate than relying on any single source [36]. Studies suggest that caregiver reports are fair to good proxy measures of youth AOD behavior [37], although they typically underestimate consumption [38]. Caregiver report may be particularly useful when youth have minimized self-report of AOD use or impairment. Involving caregivers in screening has the potential to boost the accuracy of problem identification and also set the stage for their involvement in BI and referral to treatment (RT) procedures [39].

Widen the Screening Net

In addition to assessing AOD use, screening procedures can collect supplemental data to generate a multidomain profile of AOD risk. The screening net can be widened in at least 2 ways. First, caregivers can complete screening tools for youth co-occurring behavior problems that both signal and exacerbate AOD risk: anxiety and depression, impulsivity and sensation seeking, and aggression and conduct problems [4,40]. Second, caregivers as well as youth can provide valuable data on family strengths, including key protective factors such as parent-adolescent communication about AOD use [41,42]. Data on these supplemental risk and protective factors can be converted into “risk algorithms” that more accurately codify AOD risk profiles, boosting both the acuity of risk screening and the attunement of subsequent SBIRT-A activities [43].

Deepen BI Impact

Developmental science asserts that supportive familial networks are potent protections against individual-level developmental processes that predispose adolescents to AOD and other risky behavior. BIs for adolescent AOD use that incorporate caregivers have shown their mettle [44] and are likely to have considerable added value over adolescent-only BIs in PC settings [45], especially given that caregivers who harbor AOD and related behavioral concerns for their children often seek anticipatory guidance from PC providers [27].

Strengthen RT Linkages

Influencing teenagers seeking medical care to enroll in AOD services typically requires caregiver involvement [39]. Nevertheless, there are numerous challenges to engaging caregivers in treatment referral, including caregiver skepticism about the value of AOD services, the stigma and fear of being judged for the youth’s problems, and hopelessness about the possibility of change [46]. PC providers are well positioned to shape caregiver attitudes and behaviors concerning treatment referral, given their authority on health care issues. Providers can explain AOD risks and ramifications, acknowledge past efforts to address AOD and related behaviors, and reinforce the importance of caregiver influence on adolescent well-being along with the possibility of behavior change—techniques common to family-focused treatment engagement models [47]. Providers can also join caregivers in talking directly with their teenagers about AOD risk, using evidence-based strategies [48]

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to mobilize caregiver capacity to facilitate youth enrolling in AOD services.

Specific Aims of the Randomized Effectiveness Trial

This randomized effectiveness trial will advance research on SBIRT-A in PC by conducting a head-to-head test of 2 conceptually grounded, evidence-informed approaches: a standard adolescent-only approach (SBIRT-A-Standard) versus a more expansive family-based approach (SBIRT-A-Family). The SBIRT-A-Family approach enhances the procedures of the SBIRT-A-Standard approach by screening for AOD risk with both adolescents and caregivers; leveraging multidomain, multireporter AOD risk and protection data to inform case identification and risk categorization; and directly involving caregivers in BI and RT activities [43]. The trial will test the effectiveness of SBIRT-A-Standard versus SBIRT-A-Family for preventing the escalation of AOD use (aim 1); reducing AOD use risk factors and consequences, decreasing co-occurring behavior problems, enhancing parent-adolescent communication about AOD use, and increasing quality-of-life indicators (aim 2); linking youth and families to behavior counseling services (aim 3); and investigating the extent to which the effects of SBIRT-A-Family vary based on youth characteristics (age, sex, and race or ethnicity) and youth AOD risk status (aim 4).

Methods

Trial Design

This trial uses a 2-arm parallel-group multisite randomized effectiveness design. The 2 SBIRT-A approaches (SBIRT-A-Standard and SBIRT-A-Family) both use digitally supported BIs [16,49] that are a substantial upgrade over routine practice and consistent with the recommendations of the American Academy of Pediatrics to leverage digital tools. Individual youth and their caregivers are randomized as a family unit to the study condition. Adolescent and family outcomes for 2300 youth (n=2000, 86.96% identified as at risk of AOD use and n=300, 13.04% as a developmental comparison identified as low risk) are assessed over 1-year follow-up.

The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement (Multimedia Appendix 1).

Study Participants

Study Sites and Providers

The study occurs in 3 hospital-affiliated pediatric settings: Mass General for Children, Boston Medical Center, and Columbia University Irving Medical Center. All 3 settings are in major urban areas that serve a diverse range of patients. In aggregate, these 3 settings receive approximately 20,000 visits annually from youth in the targeted age range (12-17 y); the sites reported that 10% to 15% of age-targeted youth routinely identify as positive for AOD use via existing site screening methods. All sites currently screen youth routinely for AOD risk via digital screening methods and expressed intention to adopt BIs. All site staff (eg, physicians, nurse practitioners, and behavioral specialists) who provide BI and RT services to adolescents are eligible to provide SBIRT-A services as part of this trial. Physicians in leadership roles at each site (eg, the medical director) will serve as site champions to pioneer the implementation of site-based study procedures and promote acceptance and buy-in among all site staff [50]. Each site will receive performance feedback (eg, the uptake of SBIRT procedures and progress toward patient enrollment goals) and participate in cross-site monthly learning collaboratives to discuss and problem-solve implementation barriers and facilitators. The study team will partner with participating providers to revise implementation procedures as needed to enhance the uptake of SBIRT procedures.

Study Patients and Inclusion Criteria

The study enrolls adolescents and their caregivers attending a PC visit at 1 of the 3 study sites. The study inclusion criteria are as follows: youth aged 12 to 17 years; a primary caregiver (ie, parental figure) also in attendance; youth is fluent in English, and caregiver is fluent in English or Spanish; both are capable of using audio-assisted informed consent procedures and independently operating a handheld tablet; and both complete routine site AOD risk screening questions prompted during PC visit intake. On the basis of existing patient flow at each site, we have projected aggregate self-reported demographic characteristics of enrolled youth (Table 1).

This profile supports planned moderator analyses for sex, race, ethnicity, and age subgroups. The randomization procedures will (1) block and stratify by clinic site and (2) use imbalance minimization procedures for adolescent age (12-14 y vs 15-17 y) and study clinician.

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Table 1. Projected aggregate self-reported demographic characteristics of enrolled youth (N=2000).

Demographic characteristics	Participants, n (%)
Sex	
Male	1000 (50)
Female	1000 (50)
Race and ethnicity	
Black	620 (31)
Latinx	580 (29)
White	680 (34)
Other	120 (6)
Age	
12 to 14 years	1100 (55)
15 to 17 years	900 (45)

Recruitment, Randomization, Intervention Flow, and Outcome Assessment Procedures

Study recruitment and randomization as well as all SBIRT-A activities occur on the day of the visit in PC offices. Figure 1 depicts the flow of patient recruitment, patient randomization, and SBIRT-A delivery for various risk categories. Recruitment efforts will be multimethod, consisting of (1) informational flyers in wait areas, (2) outreach to families by site research staff, and (3) warm handoff by site administrators and providers when needed. Interested caregivers are prompted to contact on-site research staff, who then give the designated caregiver a tablet to (1) complete an electronic research consent form, (2) provide family demographic and brief assessment information, and (3) complete a screening tool assessing their concerns about the adolescent's AOD use and related behavior problems as well as family communication about AOD issues. Simultaneously, research staff give a tablet to the youth, who completes an electronic research assent form, and if their caregiver gives consent, an AOD screening tool and brief assessment information.

For families in which both caregiver and youth give informed consent and assent and complete screening, the tablet automatically (1) randomizes the family to study condition, using urn randomization to achieve balanced allocation of participants based on sex, race, ethnicity, and age group; and (2) computes a risk category. In SBIRT-A-Standard, the risk category (*low risk*, *riding risk only*, *distant use*, or *recent use*) is assigned using youth screening data only, while SBIRT-A-Family uses youth plus caregiver screening data to assign the risk category (*low risk*, *hidden substance use risk*, *named mental health risk*, or *named substance use risk*). For youth and families assigned to the *low risk* category (ie, no positive screen result), youth are invited to view tablet-delivered psychoeducation slides, and caregivers are invited to view a video tour and enrollment link to web-based educational and support resources for adolescent AOD. For youth and families assigned to an *at risk* category, youth and caregivers each view tablet-delivered psychoeducation videos and (for some risk categories) complete provider-facing BI and RT activities that are differentiated based on condition assignment and tailored to the respective risk categories. Multimedia Appendix 2 summarizes study activities for each condition; full descriptions are provided in the Study Conditions subsection. All study providers are trained to deliver both SBIRT-A approaches (ie, provider crossover design).

Every adolescent or family assigned to an *at risk* category in either condition is enrolled until study capacity is reached (n=2000). In addition, a randomly selected subsample of adolescents (n=300; balanced across conditions) screened as *low risk* are followed for outcome assessments; the selection of the group categorized as *low risk* uses quota sampling based on sex, race, ethnicity, and age. Outcome data are collected via remote digital assessment methods at initial assessment (as soon as possible after the PC visit) and at 3, 6, 9, and 12 months after the PC visit using REDCap Cloud software (Research Electronic Data Capture developed at Vanderbilt University and licensed to cloud-based technology company nPhase, Inc), a widely used secure, Health Insurance Portability and Accountability Act (HIPAA)–compliant, web-based data collection platform. Figure 2 shows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist depicting the schedule of trial enrollment, interventions, and assessments. All youth and caregivers separately receive both email and SMS text prompts when assessments are due, using contact information provided during the consenting process. When either youth or caregiver fails to complete a follow-up assessment, research staff members blinded to condition assignment reach out to arrange a live assessment via telephone or videoconference. Each assessment requires approximately 20 minutes to complete.

Clinicians and families enrolled in the study retain the right to withdraw consent at any time. The protocol will be discontinued at any site where procedures become burdensome or otherwise impinge on the routine performance of participating staff. Analysis of intervention impacts and potential harm will be continuous throughout the trial. In cooperation with the administration of the partnering sites, investigators will provide full study debriefing and offer counseling referrals to any participant aggrieved or injured due to trial participation.

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Figure 1. Patient flow diagram of the screening, brief intervention, and referral to treatment for adolescents: standard adolescent-only approach (SBIRT-A-Standard) versus SBIRT-A: family-based approach (SBIRT-A-Family) for adolescent substance use (SU) in the primary care multisite randomized effectiveness trial: recruitment, screening, randomization, and intervention recommendations. BNI: brief negotiated interview; FC: facilitated conversation; MH: mental health; RT: referral to treatment.

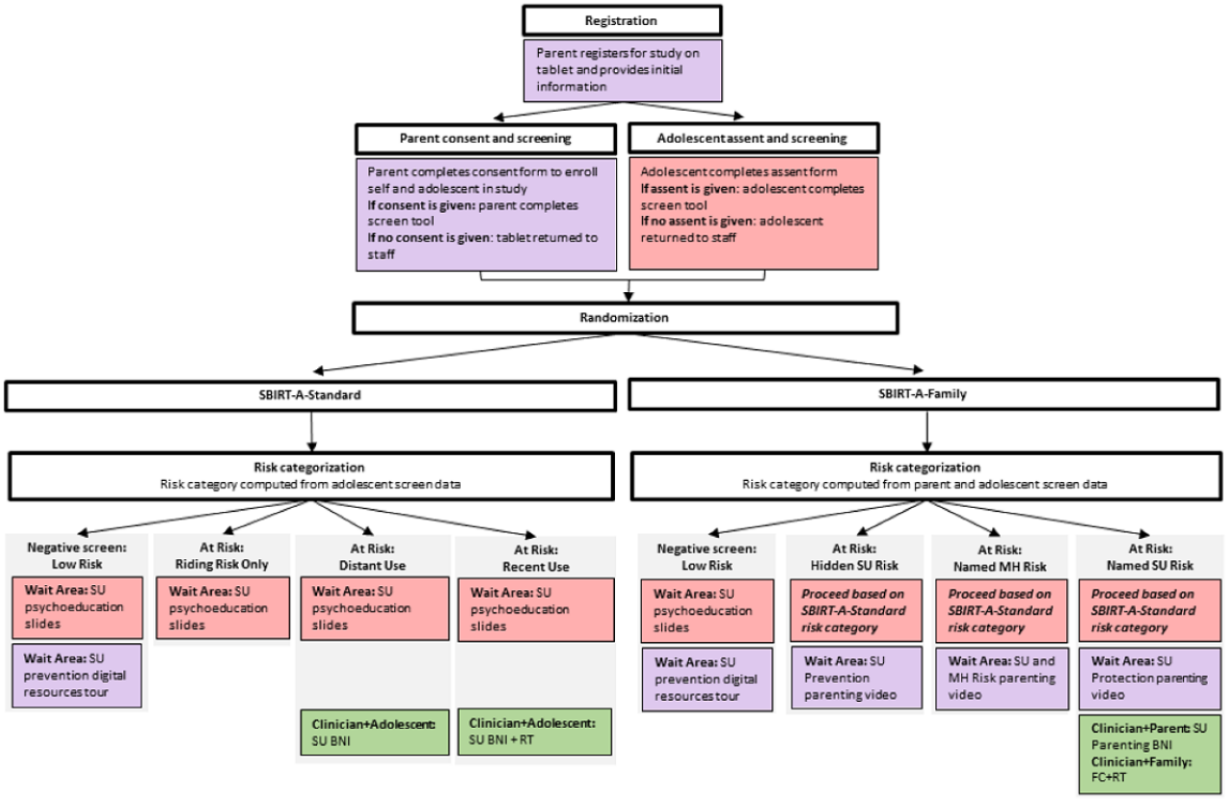

Figure 2. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for the screening, brief intervention, and referral to treatment for adolescents: standard adolescent-only approach (SBIRT-A-Standard) versus SBIRT-A: family-based approach (SBIRT-A-Family) for adolescent substance use (SU) in the primary care (PC) multisite randomized effectiveness trial: schedule of trial enrollment, interventions, and assessments. AD: adolescent participant; AOD: alcohol and other drug; CG: caregiver participant; CL: clinician participant.

		STUDY PERIOD						
		Enroll.	PC Appt.	Baseline	Follow-up			Close-out
TIMEPOINT		**0**	**0**	**Week 1**	***Mo. 3***	***Mo. 6***	***Mo. 9***	***Month 12***
ENROLLMENT:								
Informed Consent/Assent		X						
Allocation		X						
INTERVENTIONS:								
SBIRT-A-Standard			X					
SBIRT-A-Family			X					
OUTCOME INSTRUMENTS:	Reporter							
CRAFFT	AD	X		◆—	—	—	—	—◆
Hooked on Nicotine Checklist	AD	X						
Beliefs & Worries about Youth AOD Use	CG	X		◆—	—	—	—	—◆
Brief Problem Monitor	CG	X			◆—	—	—	—◆
Brief Problem Monitor	AD			◆—	—	—	—	—◆
Parent-Teen AOD Comm. Frequency	CG, AD	X			◆—	—	—	—◆
Parent-Teen AOD Comm. Quality	CG, AD	X			◆—	—	—	—◆
Timeline Followback	AD			◆—	—	—	—	—◆
Perceived Harm	AD			◆—	—	—	—	—◆
Peer Deviance	AD			◆—	—	—	—	—◆
Parent Rules on SU	CG, AD			◆—	—	—	—	—◆
KIDSCREEN-27	CG, AD			◆—	—	—	—	—◆
Family Assessment Device	CG, AD			◆—	—	—	—	—◆
Comprehensive Adolescent Severity Inventory	AD			◆—	—	—	—	—◆
Services Assessment for Children and Adolescents	CG			◆				◆
Youth-Provider Connectedness	AD			◆—	—	—	—	—◆
FIDELITY INSTRUMENTS:								
SBIRT Intervention Components	CG			X				
SBIRT Intervention Components	AD			X				
SBIRT Intervention Components	CL		X					

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Study Conditions

Both study conditions follow a similar set of procedures anchored in the use of handheld tablets. As depicted in Figure 1, tablets are used to collect screening data from youth and caregivers, calculate youth and family risk levels, and offer digitally supported BI and RT activities to users. Point-of-care digital SBIRT procedures can improve patient outcomes by facilitating more rapid and standardized services, data-informed clinical decision-making, and improved practice efficiency [16,51]. Both conditions feature 2 types of digital BIs: *patient facing* (ie, self-administered: patients navigate the BI alone on the tablet) and *provider facing* (ie, provider administered: providers and patients jointly navigate the BI on the tablet). The total time needed to deliver each approach matches the typical wait time for preventive visits plus time devoted to delivering comparable SBIRT-A procedures for youth identified as at risk in routine PC. Both conditions allow all youth and caregivers to speak with providers about AOD issues at any point they choose, in keeping with best practices honored at partner sites. When study interventions are not delivered during the main visit, providers can opt to complete interventions in a follow-up visit scheduled within 1 week or complete immediate handoff to an on-site behavioral health specialist (trained in all study procedures) to complete the intervention [21,52]. In addition, caregivers in both conditions are digitally prompted to enroll in a web-based suite of caregiver-focused resources (helpline, parent coaching, parent groups and electronic resources, and SMS text messaging) specifically designed to support youth AOD risk reduction and caregiver self-care [53].

SBIRT-A-Standard Procedures

Screening (Approximately 2 Min)

All consented youth aged 12 to 17 years complete the CRAFFT (car, relax, alone, forget, friends, trouble) screening tool [54,55], which assesses the number of days during the past year and then the past 3 months during which various formulations of AOD were used, as well as whether they have ridden in a car whose driver was intoxicated; youth who respond negatively to all questions are categorized as *low risk*. If youth report >0 days of AOD use, the tool asks 5 additional questions assessing use risk and consequences; in addition, youth who report nicotine use in the past 30 days complete a nicotine dependence measure, the Hooked on Nicotine Checklist [56], modified to include nicotine vaping. Screening data are then used to sort youth into 3 risk categories: *riding risk only* (no reported AOD use but indicated rode in car driven by intoxicated person), *distant use* (reported AOD use in past year but not past 3 months), or *recent use* (reported AOD use in past 3 months). All screening data are summarized in a tablet-delivered clinician report to guide provider-facing intervention activities.

AOD Psychoeducation: All Risk Categories (Approximately 5 Min)

In the wait area, youth receive a tablet-delivered brief digital AOD education tutorial that includes advice to abstain from, or reduce, AOD use. The tutorial focuses on adolescent AOD prevalence rates and related behavioral symptoms, AOD use neurobiology and its relation to adolescent health, and common AOD impacts on developmental milestones [57]. Psychoeducation for AOD has shown positive effects as both a universal and selective prevention strategy [58,59].

Brief Negotiated Interview: Distant Use (Approximately 5 Min) and Recent Use (Approximately 8 Min)

In PC offices, youth and providers together complete a tablet-supported brief negotiated interview (BNI) [60]. The BNI is informed by AOD use data gathered during youth screening [61]. The BNI focuses on (1) education about AOD disorders, including youth and family factors that impact AOD use; (2) user-tailored feedback comparing the given youth's AOD use and related problems to national norms, along with information on the neurobiological effects and developmental impacts of frequent use [32]; (3) motivational tools (eg, reduction readiness rulers) and decisional balance exercises (weighing positive vs negative personal impacts of AOD use) tailored to the youth's use levels [62,63]; and (4) AOD reduction goal-setting interventions tailored to the youth's readiness to change AOD use [64]. BNIs of this kind have demonstrated effectiveness in reducing AOD use and related problems [14,32,65].

RT: Recent Use (Approximately 5 Min)

In PC offices, providers and youth discuss the value of attending counseling services to address AOD-related problems [66] and counseling referral links that the PC site curates with local services, as well as the value of youth talking directly with caregivers about their AOD involvement as a first step toward support seeking and behavior change [45]. Providers directly recommend AOD counseling and facilitate a first appointment for youth who agree. The study team will continue to monitor and update curated referral lists with availability and wait-list times throughout the duration of the study.

SBIRT-A-Family Procedures

Screening (Approximately 2 Min Apiece)

Screening procedures incorporate CRAFFT procedures for youth described for the SBIRT-A-Standard condition. They also incorporate two sources of caregiver-report data: (1) an assessment of caregiver beliefs about their child's AOD use and worries about the impact of AOD use, and (2) a well-validated checklist of youth mental health problems [67] that yields clinical cut scores for 4 domains. If both youth and caregiver report no AOD use or clinically elevated mental health problem, the family is categorized as *low risk*. Otherwise, screening data are combined to sort families into 3 risk categories: *hidden substance use risk* (youth reports AOD use in past year; caregiver reports no youth AOD use in past year), *named mental health risk* (caregiver reports no youth AOD use in past year; caregiver reports clinical-level score for at least 1 youth mental health domain), and *named substance use risk* (caregiver reports youth AOD use in past year with or without reporting a clinically elevated mental health score). Adolescent and caregiver screening data are both summarized in the clinician report to guide provider-facing intervention activities.

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AOD Psychoeducation: All Risk Categories (Approximately 5 Min Apiece)

Youth proceed as indicated in the SBIRT-A-Standard condition based on youth screening data. In the wait area, caregivers receive a tablet-delivered parenting tutorial that covers two AOD risk domains: (1) education about adolescent AOD use, including prevalence rates, related behavior problems, neurobiological and health effects, and impacts on developmental milestones; and (2) education and video modeling about parenting strategies that reduce or moderate AOD use risk, including positive communication, fair and consistent discipline, and nonjudgmental conversations about AOD use [68]. Positive parenting education has been shown effective as a universal and selective prevention strategy in parent-focused AOD prevention trials [69-71]. The tutorials are tailored for each risk category.

BNI: Named Substance Use Risk (Approximately 5 Min Apiece)

Youth proceed as indicated in the SBIRT-A-Standard condition based on youth screening data. In PC offices, caregivers and providers together complete a tablet-supported parenting BNI informed by data from the caregiver screening only that parallels the youth BNI (eg, AOD education and developmental risks) and also includes motivation, modeling, and goal setting on positive parenting (eg, nonjudgmental conversations) and effective parent-youth communication about AOD use (Multimedia Appendix 3) [41].

Facilitated Conversation: Named Substance Use Risk (Approximately 5 Min)

In PC offices, providers meet with youth and caregivers together to discuss the value of talking directly with the other family member about AOD risk. Providers convene a brief facilitated conversation coaching youth and then caregivers to speak directly to one another about AOD risk using positive communication skills presented to caregivers via wait area psychoeducation. In this conversation providers (1) emphasize that a positive youth-caregiver relationship is the strongest protective factor for youth development and (2) follow guidelines for brief triadic risk reduction interventions focused on positive family communication about AOD risk (Multimedia Appendix 4) [72]. This facilitated conversation is meant to follow the caregiver BNI. Providers may conduct the youth BNI (when indicated) before the caregiver BNI or after the facilitated conversation depending on preference and workflow.

RT: Named Substance Use Risk (Approximately 5 Min)

When indicated, providers directly recommend AOD counseling and facilitate a first appointment for families who agree (Multimedia Appendix 5).

Intervention Training and Fidelity Monitoring

Site PC clinic staff who provide SBIRT-A to clinic patients are trained by experts in all intervention procedures for both conditions. We expect to train 10 providers per clinic. Providers attend a 1-hour site orientation followed by 3 hours of live training. First, providers complete a 1-hour introduction to motivational interviewing for adolescents, caregivers, and families. Next, providers attend two 1-hour live training sessions to apply motivational interviewing principles to support adolescent, caregiver, and family behavior change. The self-study training will include video-recorded presentations on motivational interviewing principles. Live training will include a review of counseling steps for each intervention, video-recorded counseling demonstrations, and opportunities to practice counseling steps. These training procedures have been successfully implemented in similar PC SBIRT studies [16,31]. Baseline fidelity is established via a 1-hour individual counseling practice with research staff. Thereafter, providers attend a monthly 1-hour clinical consultation meeting held by authors MB and NPP to maintain and enhance intervention skills, review notable clinical encounters, and troubleshoot procedural and technology challenges. In addition, providers will complete practice interventions using standardized case vignettes on a 6-month cadence. Vignette scenarios will be informed by implementation experiences shared by providers during the course of the consultation period; these serve as training refreshers and will also provide fidelity feedback data to be incorporated in consultation meetings, as will data summarized from the provider self-report fidelity checklist described in the next subsection [73].

Fidelity Measures

A provider self-report fidelity checklist is collected after every encounter with every family. The checklist assesses information on which the provider-facing intervention components were delivered: adolescent BNI, caregiver BNI, facilitated conversation, or RT. Checklist items feature 3-point Likert-type rating scales to indicate how clinically helpful the given component was for the encounter: *not at all*, *somewhat*, or *very*. The checklist also logs (1) which implementation scenario was selected for intervention delivery: pediatrician intervention during visit, pediatrician follow-up visit, or behavioral specialist intervention on the visit day; (2) whether the intervention occurred in person or via video call; and (3) the number of minutes spent delivering the intervention or interventions. Research indicates that clinicians can reliably self-report on the delivery of behavioral interventions with families using brief postencounter fidelity checklists [74-76]. In addition, during initial follow-up assessment, adolescents and caregivers report on which components they experienced during the encounter: psychoeducation, BNI, facilitated conversation, or RT.

Outcome Measures: Screening Interview

CRAFFT [54,55] is a widely used and well-validated youth report tool that measures patient use of alcohol, cannabis, nicotine, illegal drugs, prescription medication, or anything else to get high in the past year and the past 3 months. It also asks about riding in a car driven by someone (including self) who was intoxicated (described in the SBIRT-A-Standard Procedures subsection). If AOD use is reported, the tool asks 5 additional questions: “Do you ever use alcohol or drugs to relax, feel better about yourself, or fit in?” “Do you ever use alcohol or drugs while you are by yourself [alone]?” “Do you ever forget things you did while using alcohol or drugs?” “Do your family or friends ever tell you that you should cut down on your drinking or drug use?” “Have you ever got into trouble while you were

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using alcohol or drugs?" The Hooked on Nicotine Checklist [56] is a 10-item youth report of nicotine dependence completed by patients who report any days of using a vaping device containing nicotine, or any tobacco products, during the past 30 days. Parent-Adolescent AOD Communication Frequency [77] is a 6-item youth and caregiver report of how often parents and teens talk to one another about key AOD issues (eg, the health risks of use and discipline regarding use) scored on a 5-point scale ranging from *never* to *very often* [78-80]. Parent-Adolescent AOD Communication Quality [81] is a 6-item youth and caregiver report of the quality of communication between parent and teen about AOD issues (eg, "My caregiver/teen and I are interested in each other's opinions about AOD" and "If my caregiver/teen and I talk about drugs, I feel understood") scored on a 5-point scale ranging from *not at all* to *very much* [41,77]. Beliefs and Worries about Youth AOD Use is an 8-item measure that asks caregivers what they believe about their teen's use of AOD in the past year and in the past 3 months (response options: "I am sure or pretty sure my teen has not used," "I suspect but I am not sure my teen has used," and "I am sure or pretty sure my teen has used"). Follow-up questions ask which substances they believe their teen has or may have used and their worries about the impact of their teen's use of AOD across contexts (ie, home, school, peers, and safety). This measure was created for this study, inspired by the Screening to Brief Intervention tool [8] and the CRAFFT tool [55] and vetted by SBIRT experts. The Brief Problem Monitor is a 19-item caregiver report component of the well-validated Achenbach youth behavior problem assessment system [67] that yields normed scores with clinical cut levels for 4 problem domains: internalizing (anxiety, depression, and somatic complaints), externalizing (aggression and conduct problems), inattention or impulsivity, and total problems [82].

Outcome Measures: Follow-Up Interviews

The timeline followback (TLFB) method [83] is the gold standard method for collecting youth report retrospective estimates of AOD use using a calendar visual aid to facilitate recall. This study used a computer-administered and calendar-assisted instrument created for REDCap-compatible remote asynchronous follow-up assessment modeled after the TLFB [31]. This version assesses the number of days that youth used alcohol, tobacco, marijuana, non–medical prescription drugs, inhalants or vapes, and herbs or synthetic drugs over the past 90 days. If alcohol was used, follow-up questions assess binge drinking episodes. The KIDSCREEN-27 questionnaire (youth and caregiver report) [84] measures youth functioning in social and school domains. Items assess the degree to which youth have experienced problems with a specific task or activity during the past month. It is internationally used and has excellent psychometric properties with strong construct validity and test-retest reliability [84,85]. The Services Assessment for Children and Adolescents (caregiver report) [86] assesses the youth's past and current use of inpatient, outpatient, and school-based behavioral health services. It has shown strong validity and test-retest reliability [87] as well as interrater reliability between parent and child reports [88]. Items were added to assess caregiver enrollment and the use of web-based educational and support resources for adolescent AOD. Perceived Risk (youth report) [89] asks youth to rate the degree to which people risk harming themselves if they use various categories of substances on a 4-point scale ranging from *no risk* to *great risk*. Peer Deviance (youth report) [89] assesses the number of peers who use various substances on a 5-point scale ranging from *none* to *all*. Parent Rules about Substance Use (youth and caregiver report) [90] assesses parent rules about using various substances on a 6-point scale ranging from *not allowed to use AOD* to *no rules about using AOD*. The Family Assessment Device (youth and caregiver report) [91] assesses family relationships, communication, and problem-solving on a 4-point scale ranging from *strongly agree* to *strongly disagree*. The Comprehensive Adolescent Severity Inventory (youth report) [92] assesses academic achievement, school connection, and disciplinary record. Youth-Provider Connectedness (youth report) [93] assesses the level of trust and connection adolescents feel toward their health care providers on a 5-point scale ranging from *not at all* to *very much*. Psychoeducation Knowledge (caregiver report; created for this study) assesses caregiver knowledge of the tablet-delivered AOD psychoeducation. The Parent-Adolescent AOD Communication Frequency measure, Parent-Adolescent AOD Communication Quality measure, and Brief Problem Monitor (all described in the previous subsection) are also administered at follow-up to youth and caregivers.

Plan of Analyses

Aim 1 Analyses

Aim 1 evaluates the effectiveness of SBIRT-A-Family compared to SBIRT-A-Standard in preventing the escalation of AOD use. AOD use is measured using the TLFB, which computes the percentage of the days of use over the past 90 days across a range of substances. Given that we expect the percentage of the days of AOD use to be highly skewed within this population identified as predominantly low risk, we will collapse outcomes on this measure onto a 4-point ordinal scale indicating the levels of AOD use as follows: *none* (0% days of use), *once per monthor less* (1%-3% days of use), *between once per month and once per week* (4%-14% days of use), and *once per week or more* (≥15% days of use). Aim 1 hypotheses are tested using a mixed effects logistic regression model for ordinal longitudinal outcomes [94]:

(1)

(2)

wherein (1) and (2) are jointly estimated submodels for the SBIRT-A-Standard and SBIRT-A-Family conditions, respectively. The dependent variable in each equation is the log odds (*logit*) that AOD use response Y for person i at time point j (j=1 to 5) is in category c (c=1 to C−1) or lower where c is one of the ordinal response categories created from the AOD measure. The b_{0i} parameters in (1) and (2) are random intercepts estimating the log odds of $Y_{ij} \leq c$ at initial assessment in each condition; the b_1 parameters estimate the linear rate of change (ie, slope) in the log odds of $Y_{ij} \leq c$ across measurement points,

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which are indexed by the variable $TIME_j$. The γ_c parameter estimates thresholds between adjacent categories on the given AOD variable. The intercept in each submodel is specified as a random effect to account for the nesting of repeated measurements within individuals. Slope parameters are specified as fixed effects. The model is specified as jointly estimated simultaneous equations for each study condition, rather than a single model containing an intervention main effect and interaction term, to allow for greater flexibility in modeling group-specific effects as well as for comparing each condition to the normative comparison (NC) group of youth (in which the given youth, standard condition or youth and family, family condition, screened negative). Changes in the levels of AOD use are captured by the b_1 parameters in each submodel, where positive values of b_1 indicate an increase in the log odds of being in a lower AOD use category on each logit over time compared to the initial assessment. The causal effect of assignment to SBIRT-A-Standard versus SBIRT-A-Family on AOD use (ie, the intent-to-treat effect) is estimated as the difference between $b_{1,sbi-fam}$ and $b_{1,sbi}$. Separate models are fitted for each AOD use outcome variable. To account for nonindependence due to the clustering of individuals within clinic sites, indicator variables controlling for the fixed effect of each clinic will be included as covariates in submodels (1) and (2) [95].

Evaluating Clinical Significance

The clinical significance of intervention effects on youth AOD use at 1-year follow-up is evaluated by gauging the degree to which youth identified as at risk resemble youth in the NC group, which provides a normative benchmark against which to compare changes in AOD use in the 2 study conditions. Analyses are performed by adding a third submodel to those shown in (1) and (2) that estimates change in AOD use levels between initial assessment and 1-year follow-up among NC youth. By definition, 100% of NC youth are in the *none* AOD use category at initial assessment. On the basis of preliminary analyses using data from the NSDUH, this percentage is expected to decline to approximately 90% at 1-year follow-up, whereas increases are expected in both study conditions. The difference in the likelihood (ie, log odds) of reporting AOD use in the *none* category at 1-year follow-up in each study condition compared to the NC group is quantified in the following equations:

NC versus SBIRT-A-Standard: $[(b_{0i,no-risk} + b_{1,no-risk} \times 4 + \gamma_1) - (b_{0i,sbi} + b_{1,sbi} \times 4 + \gamma_1)]$ **(3)**

NC versus SBIRT-A-Family: $[(b_{0i,no-risk} + b_{1,no-risk} \times 4 + \gamma_1) - (b_{0i,sbi-fam} + b_{1,sbi-fam} \times 4 + \gamma_1)]$ **(4)**

where $b_{0i,no-risk}$ and $b_{1,no-risk}$ are the intercept and slope parameters in the mixed effects longitudinal logistic regression submodel for the group, *4* is the coded value for $TIME_j$ at 1-year follow-up, and γ_1 is the threshold for the *none* category on AOD use variable *Y*. A log odds value of 0 resulting from the aforementioned differences indicates equivalence between the groups, whereas positive log odds values indicate a higher likelihood of reporting *none* at 1-year follow-up in the NC group. These differences are converted into odds ratios and then into Cohen *d* values using an "odds ratio to *d*" conversion formula [96]. The Cohen *d* value between the NC and SBIRT-A-Family groups is expected to be in the *small* range (0.10-0.30), and the Cohen *d* value for the NC versus SBIRT-A-Standard comparison is expected to be in the *moderate* range (0.40-0.60). Small effect size values would indicate high concordance in AOD use between the NC group and the at-risk study categories, thereby supporting the clinical significance of intervention effects at 1-year follow-up.

Aim 2 and Aim 3 Analyses

Aim 2 evaluates the comparative effectiveness of study conditions on AOD risk factors (eg, peer conduct problems, susceptibility to peer pressure, school problems, and family functioning), co-occurring problems (internalizing, externalizing, and impulsivity), quality of life, and parent-adolescent AOD communication. A similar modeling approach to aim 1 is used, the primary difference being that all outcome variables are continuous rather than ordinal; as such, standard mixed effects growth models [97] are used to compare intervention effectiveness. Aim 3 compares the rates of behavioral counseling service use between the conditions. Differences are tested at 1-year follow-up using a simple logistic regression model with a binary *yes/no* outcome variable indicating whether the youth received any counseling during the study period. Higher rates of counseling use are expected in the SBIRT-A-Family condition.

Aim 4 Analyses

Aim 4 examines comparative effectiveness on AOD use outcomes within the subgroups of interest: age, sex, race, ethnicity, and youth AOD risk category (*recent use*, *distant use*, *ride risk only*, and *low risk*). To examine differential intervention effectiveness based on youth age, sex, and race or ethnicity, these demographic predictors are added to the submodels for aim 1 as exploratory analyses; there are no hypotheses for interactive effects. To examine differential intervention effectiveness based on risk category, analyses will be conducted separately for SBIRT-A-Standard and SBIRT-A-Family; the respective risk categories are added to the submodels for aim 1 as exploratory analyses for each condition, again with no specific hypotheses for interactive effects.

Missing Data and Multiple Significance Tests

Missing data are addressed using multiple imputation, a Bayesian procedure that simulates missing values in a data set based on the nonmissing data values and a prior distribution of the missing values, given the nonmissing data [98]. Multiple imputation yields valid results under the assumption that data are missing completely at random or missing at random, given a set of measured covariates. Potential violations of random data missingness due to study protocol dropout can be mitigated by incorporating baseline variables predicting dropout status into multiple imputation models [99]. A set of baseline variables is identified to predict dropout status in each condition. Baseline predictors of dropout are included as covariates in the models to control for potential nonrandomly missing data; the imputation procedure is run separately in each condition.

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To control type I error inflation due to multiple tests of statistical significance while also conserving power [100], the false discovery rate procedures developed by Benjamini and Hochberg [101] are used. False discovery rate correction adjusts *P* values based on the number of *P* values <.05 across all tests; as such, it provides a more tolerable balance between type I and type II error rates.

Study Power

Projecting 2000 youth identified as at risk enrolled in the study and allowing for a 20% attrition rate, a final 1-year follow-up sample size of 1600 youth identified as at risk is anticipated. Statistical power to detect small intervention effects on alcohol use (aim 1) was estimated; to be conservative, multiply imputed data for attritted cases were not included in the power analyses. An a priori power analysis was conducted using a Monte Carlo simulation [102]. Specifically, 1000 simulated data sets of 1600 youth randomly assigned to condition were generated. Each youth in each simulated data set had 5 follow-up outcome measurements (initial assessment and at 3, 6, 9, and 12 months), and youth were nested in 3 sites in proportions equal to those reported by PC partner sites. The intervention effect size was simulated as an increase in the proportion of youth reporting alcohol use in the *none* category at each assessment. On the basis of the preliminary analyses of data from the 2023 Monitoring the Future national survey [1], it was projected that 62.3% of the youth identified as at risk would report alcohol use in the *never* category at initial assessment, increasing to 78.4% in the SBIRT-A-Family condition and 67.9% in the SBIRT-A-Standard condition at 1-year follow-up. These increases represent a small effect size difference compared to the NC group at 1-year follow-up for SBIRT-A-Family, a moderate effect size difference compared to the NC group at 1-year follow-up for SBIRT-A-Standard, and a small effect size difference at 1-year follow-up between the 2 at-risk categories. The simulation program assumed a correlation of 0.90 between repeated measures within individuals. In addition, on the basis of power calculations in a similar randomized trial by Sterling et al [15], an interclass correlation of 0.02 was assumed to reflect the within-site clustering effect. To estimate power to detect an intervention effect on alcohol use, the submodels in (1) and (2) were fit to all 1000 simulated data sets. In each simulated analysis, the significance of the difference in the slope parameters between the submodels ($b_{1,sbi-fam}-b_{1,sbi}$) was tested. Power was computed as the proportion of *P* values <.05 across the 1000 sets of results, which was 0.99. Thus, the trial is well powered to detect small intervention effects on alcohol use. A similar level of power to detect effects on other substances is assumed, given that these outcomes are measured using the same scale. Power on aim 2 and aim 3 outcomes is expected to be >0.95, given that these outcomes are measured on continuous scales. The study is also powered for analyses aimed at examining moderator effects for demographic subgroups [21] and risk categories (aim 4); for example, to estimate power to detect effects within youth AOD risk categories, power analyses were repeated within the subsample of simulated youth classified as *recent use*, projected to comprise approximately 36% of the full sample based on the preliminary analyses of data from the 2020 NSDUH [103]. A power of 0.95 to detect a small effect on the change in the proportion of youth reporting alcohol use in the *never* category among youth categorized as *recent use* was obtained. These results extend to any subsample that comprises at least 35% (560/1600) of the projected sample; subsamples of at least this size are projected for male and female participants; Black, Hispanic, and White non-Hispanic youth; and younger and older youth.

Ethical Considerations

Central ethics approval for all study activities has been obtained from Solutions IRB (2023/01/3) and local ethics approval from research sites has been obtained. Caregivers and youth will independently provide informed consent or assent before the initiation of study activities (Multimedia Appendix 6). All study data will be collected on encrypted and password-protected tablets and stored on REDCap Cloud, a HIPAA-compliant data platform. All study activities will be subject to monitoring by the data safety and monitoring board of the same institution (Multimedia Appendix 7). Any modifications to the protocol that might impact the conduct of the study or its specified objectives and procedures will require a formal amendment to the protocol and approval by the institutional review board and the data safety and monitoring board before implementation. Families will receive a US $10 Amazon gift card for the completion of the screening, and each participant will receive US $170 in gift card vouchers of their choice during the follow-up period delivered via Tango Card (US $30 each for the initial assessment and 3- and 6-month follow-ups and US $40 each for the 9- and 12-month follow-ups).

Results

This study will be conducted over a 5-year period. Provider training was initiated in year 1 (December 2023). Participant recruitment and follow-up data collection began in year 2 (March 2024). We expect the results from this study to be published in early 2027.

Discussion

Summary

SBIRT-A is widely endorsed but currently underused in pediatric PC settings, and urgent questions remain about optimal approaches and overall effectiveness [21,104]. In particular, RT procedures in PC remain virtually untested among youth [66]. In addition, whereas research strongly supports involving families in various kinds of interventions for adolescent AOD [17], SBIRT-A effectiveness trials testing approaches that actively engage family members in PC are absent. This trial is designed to help fill these research gaps. Figure 3 presents a framework that depicts key conceptual and methodological factors across intervention components for the adolescent-only SBIRT-A-Standard approach, specifies the rationale for involving caregivers in all SBIRT-A components, and identifies key additions to the SBIRT-A-Standard approach that are introduced by the innovative SBIRT-A-Family approach. This framework aligns closely with kindred conceptual models for family-based AOD prevention in general [69,71] and for family-focused AOD prevention approaches specifically

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designed for PC [27,105,106], as well as for family-based SBIRT-A models in PC [43,107].

Although our study is not designed to evaluate implementation feasibility, both approaches tested in this trial feature procedures designed to surmount common barriers to SBIRT-A implementation in PC settings: the use of digital resources to enhance provider knowledge and intervention delivery, the embedding of interventions into routine workflow with minor disruption, ongoing technical assistance that incorporates site-specific data performance indicators, and the like [24,25]. Thus, we will gain important information about potential implementation strategies that we will test in future implementation trials once the most effective SBIRT intervention model is identified [49]. Ultimately, the trial results will inform the critical health decision of whether and how to include caregivers in SBIRT-A activities conducted in pediatric care. Guidelines for delivering SBIRT-A procedures based on the trial results will directly inform PC clinical practice and directly benefit the general pediatric population of adolescents at risk for AOD problems and their caregivers.

Importantly, this trial also emphasizes patient-centered outcomes research methods in several ways. It is recruiting participants representative of the full spectrum of adolescents and caregivers attending PC visits. Both SBIRT-A approaches rigorously protect the privacy and confidentiality of both youth and caregivers; neither learn directly or indirectly about the confidential information collected from the other person on surveys or during provider interviews without expressed permission to share such data. All SBIRT-A procedures can be delivered by trained staff across the PC provider spectrum: nurse practitioners, physicians, physician assistants, behavioral counselors, and so forth [108]. These patient-centered design features enhance the consistency and effectiveness of SBIRT-A delivery in PC.

Figure 3. Conceptual framework for the screening, brief intervention, and referral to treatment for adolescents: standard adolescent-only approach (SBIRT-A-Standard) versus SBIRT-A: family-based approach (SBIRT-A-Family) for adolescent substance use (SU) in the primary care multisite randomized effectiveness trial (family-based additions to SBIRT-A for adolescent alcohol and drug use in primary care). AOD: alcohol and other drug; BNI: brief negotiated interview; CRAFFT: car, relax, alone, forget, friends, trouble; MH: mental health.

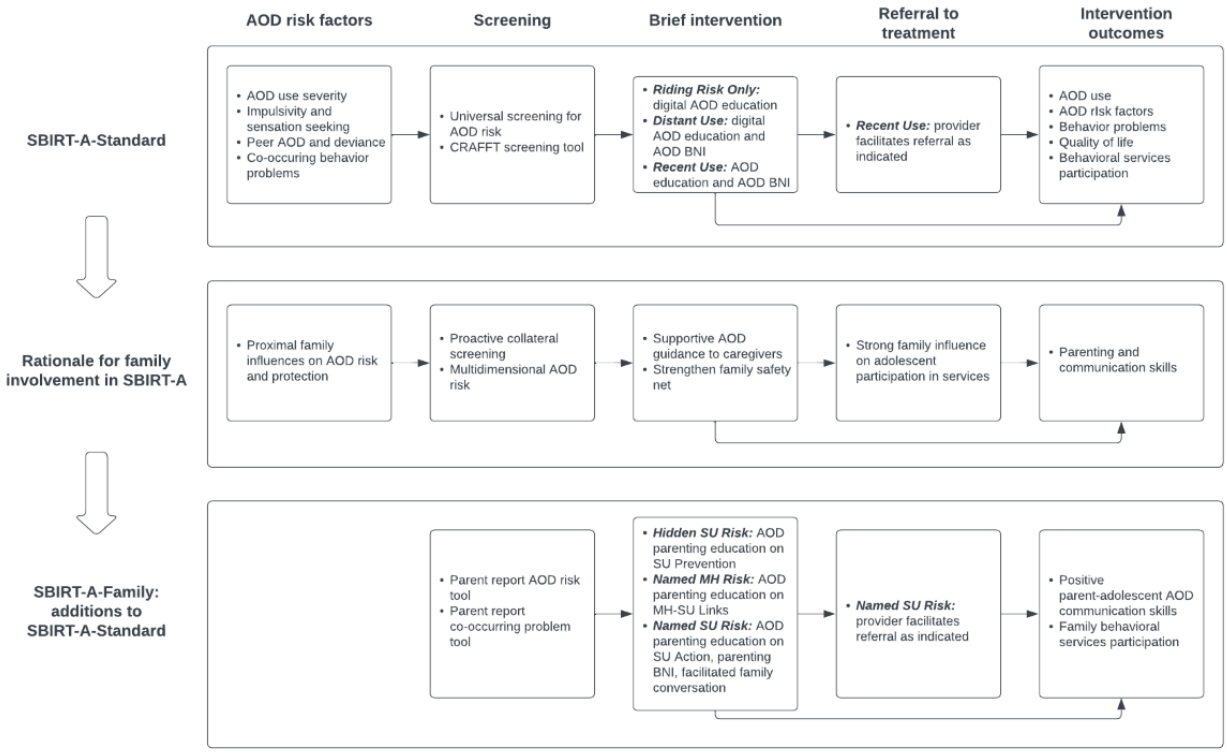

Study Limitations

As all partner sites are hospital affiliated and located in major urban centers, the study results may not be fully generalizable to pediatric PC practices that operate in distinctly different geographic regions (eg, rural settings), under different health care organizational structures, or without on-site internet support. Due to study inclusion criteria, the results will not be fully generalizable to the population of youth who attend PC visits without caregivers (such youth tend to skew as older) or to youth and caregivers who are not fluent in English or Spanish. The RT procedures embedded in both study conditions are limited to the degree that a given PC site has limited or no options for referring patients to behavioral care providers who serve teenagers with AOD problems. It is beyond the scope of SBIRT-A to intervene directly in cases of multigenerational AOD use, including when the caregiver is experiencing AOD problems; pediatric clinics routinely contend with this matter. Regarding condition allocation, a primary advantage of individual-level over site-level randomization is higher statistical power [109]. The primary drawback of individual-level randomization is the potential for cross-contamination between study conditions, which could dampen intervention effect sizes

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and reduce statistical power [110]. Cross-contamination is not expected to be substantial in this trial, given that both conditions feature large subgroups of patients who will receive SBIRT-A content in strictly digital format (ie, no research interaction with providers).

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Data Availability

The data sets generated and analyzed during this study will be archived on the web via the National Institute of Mental Health Data Archive.

Authors' Contributions

All authors contributed meaningfully to the study's initial conception and final design, and all authors vetted the full manuscript before original submission. In addition, each author made a focused contribution to the following sections: conceptualization of the research gaps and background information (SJB, SKH, AH, TJO, NPP, and LAS); development of the SBI intervention protocols (KA, SMB, MB, MC, HC, SEH, AH, AM, MAO, and NPP); development of the SBI training and fidelity procedures (KA, MB, SKH, AH, MO, MAO, and LAS); design of procedures for engaging sites in research activities (SMB, MB, HC, SEH, AH, and NPP); design of assessment procedures and measurement battery (MB, MC, AH, AM, NPP, and LS); plan of analyses and study power (SJB, AH, TJO, and NPP).

Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist: recommended items to address in a clinical trial protocol and related documents.
[DOC File , 123 KB - resprot_v13i1e54486_app1.doc]

Multimedia Appendix 2
Study conditions of the screening, brief intervention, and referral to treatment for adolescents: standard adolescent-only approach (SBIRT-A-Standard) versus SBIRT-A: family-based approach (SBIRT-A-Family) for adolescent substance use in the primary care multisite randomized effectiveness trial.
[PDF File (Adobe PDF File), 86 KB - resprot_v13i1e54486_app2.pdf]

Multimedia Appendix 3
Caregiver brief negotiated interview.
[PDF File (Adobe PDF File), 176 KB - resprot_v13i1e54486_app3.pdf]

Multimedia Appendix 4
Family-facilitated conversation.
[PDF File (Adobe PDF File), 156 KB - resprot_v13i1e54486_app4.pdf]

Multimedia Appendix 5
Family referral to treatment.
[PDF File (Adobe PDF File), 76 KB - resprot_v13i1e54486_app5.pdf]

Multimedia Appendix 6
Screening, brief intervention, and referral to treatment for adolescents adult consent form.

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[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e54486_app6.pdf]

Multimedia Appendix 7
Study committees and teams.
[DOCX File , 17 KB - resprot_v13i1e54486_app7.docx]

Multimedia Appendix 8
Peer-review report by the Patient-Centered Outcomes Research Institute.
[DOCX File , 49 KB - resprot_v13i1e54486_app8.docx]

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Abbreviations

AOD: alcohol and other drug
BI: brief intervention
BNI: brief negotiated interview
CRAFFT: car, relax, alone, forget, friends, trouble
HIPAA: Health Insurance Portability and Accountability Act
NC: normative comparison
NSDUH: National Survey on Drug Use and Health
PC: primary care
RT: referral to treatment
SBIRT: screening, brief intervention, and referral to treatment
SBIRT-A: screening, brief intervention, and referral to treatment for adolescents
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TLFB: timeline followback

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Protocol

Assessing the Efficacy of the ARMOR Tool–Based Deprescribing Intervention for Fall Risk Reduction in Older Patients Taking Fall Risk–Increasing Drugs (DeFRID Trial): Protocol for a Randomized Controlled Trial

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Abstract

Background: Falls in older patients can lead to serious health complications and increased health care costs. Fall risk–increasing drugs (FRIDs) are a group of drugs that may induce falls or increase the tendency to fall (ie, fall risk). Deprescribing is the process of withdrawal from an inappropriate medication, supervised by a health care professional, with the goal of managing polypharmacy and improving outcomes.

Objective: This study aims to assess the effectiveness of a deprescribing intervention based on the Assess, Review, Minimize, Optimize, and Reassess (ARMOR) tool in reducing the risk of falls in older patients and evaluate the cost-effectiveness of deprescribing FRIDs.

Methods: This is an open-label, parallel-group randomized controlled academic trial. Individuals aged 60-80 years who are currently taking 5 or more prescribed drugs, including at least 1 FRID, will be recruited. Demographic data, medical conditions, medication lists, orthostatic hypotension, and fall history details will be collected. Fall concern will be assessed using the Fall Efficacy Scale, and fall risk will be assessed by the Timed Up and Go test and Tinetti Performance-Oriented Mobility Assessment tool. In this study, all treating physicians will be randomized using a stratified randomization method based on seniority. Randomized physicians will do deprescribing with the ARMOR tool for patients on FRIDs. Participants will maintain diaries, and monthly phone follow-ups will be undertaken to monitor falls and adverse events. Physical assessments will be performed to evaluate fall risk every 3 months for a year. The rationality of prescription drugs will be evaluated using the World Health Organization's core indicators.

Results: The study received a grant from the Indian Council of Medical Research–Safe and Rational Use of Medicine in October 2023. The study is scheduled to commence in April 2024 and conclude by 2026. Efficacy will be measured by fall frequency and changes in fall risk scores. Cost-effectiveness analysis will also include the incremental cost-effectiveness ratio calculation. Adverse events related to deprescription will be recorded.

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Conclusions: This trial will provide essential insights into the efficacy of the ARMOR tool in reducing falls among the geriatric population who are taking FRIDs. Additionally, it will provide valuable information on the cost-effectiveness of deprescribing practices, offering significant implications for improving the well-being of older patients and optimizing health care resource allocation. The findings from this study will be pertinent for health care professionals, policy makers, and researchers focused on geriatric care and fall prevention strategies.

Trial Registration: Clinical Trials Registry – India CTRI/2023/12/060516; https://ctri.nic.in/Clinicaltrials/pubview2.php

International Registered Report Identifier (IRRID): PRR1-10.2196/55638

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KEYWORDS

deprescribing; geriatric; fall risk–increasing drugs; FRIDs; ARMOR tool; Assess, Review, Minimize, Optimize, and Reassess; falls; older patients; fall risk

Introduction

With the growing burden of multimorbidity among the older population, the concurrent use of multiple medications, known as polypharmacy, has become increasingly common. Unfortunately, polypharmacy is often associated with a high treatment burden and a diminished quality of life; more alarmingly, it can lead to the use of potentially inappropriate medications, increasing the risk of falls. Fall risk–increasing drugs (FRIDs) encompass a group of medications known to induce falls or elevate the risk of falling. These FRIDs include psychotropic drugs (eg, antipsychotics, antidepressants, benzodiazepines, and sedative-hypnotics), cardiovascular agents (eg, loop diuretics, digoxin, antihypertensives, and antiarrhythmics), and other agents (eg, hypoglycemic drugs, nonsteroidal anti-inflammatory drugs, opioids, anticholinergics, and antihistamines) [1-3]. Notably, falls are the leading cause of hospital admissions in the older population, with a reported prevalence of falls due to FRIDs reaching 41% [4].

In response to these challenges, deprescribing has emerged as a crucial strategy. Deprescribing is defined as “the process of identifying and discontinuing medications in which existing or potential harms outweigh potential benefits within the context of an individual patient’s care goals, function, values, and preferences” [5]. Various deprescribing strategies have been explored to reduce adverse events, including the STOPP/START criteria, Beer’s criteria, the Medication Appropriateness Index, and the ARMOR (Assess, Review, Minimize, Optimize, Reassess) tool [6,7].

This study is designed to evaluate the effectiveness of the ARMOR tool in reducing the fall risk in the geriatric population with FRID prescriptions as well as the cost-effectiveness of this intervention.

Methods

Study Design and Setting

This is a multicenter, open-label, parallel-group randomized controlled study. This non–drug intervention academic trial will be conducted at selected sites after obtaining approval from all the respective Institutional Ethics Committees (IECs). The trial application has been submitted for registration with the Clinical Trial Registry – India, prospectively. The study duration is approximately 2 years, and the patient participation duration in the study is approximately 1 year**.**

Participants

Participants will be enrolled in the study over a period of 1 year (approximately) based on the study’s eligibility criteria. Participants aged between 60 and 80 years; currently prescribed 5 or more medications, including at least one FRID; with a Montreal Cognitive Assessment (MoCA) score above 26; capable of walking 10 meters either independently or with the assistance of a walking aid (eg, walking stick, canes, or calipers); and voluntarily willing to participate and provide informed consent will be enrolled into the study.

Critically ill patients, patients with known neurological disorders (eg, cognitive impairment, dementia, Parkinsonism, or a history of stroke), older individuals receiving home care or specialized care, and older adults relying on a walker or wheelchair for mobility will be excluded from the study**.**

Sampling Technique

This study will follow a proportionate-to-size sampling technique. Initially, the participants will be recruited from 4 major departments where FRIDs are most commonly prescribed. The departments will be sequentially numbered as 1, 2, 3, and 4 based on the proportion of older patients attending the department. The proportion of recruitment will be 50%, 20%, 15%, and 15% from departments 1, 2, 3, and 4, respectively. In the first round, the first department will be visited first for participant recruitment, and in the second round, the second department will be visited first, and so on for further rounds. Once the required number of participants is recruited from that outpatient department, that department will be removed from the sequential list. On the day of the visit to the respective department, eligible participants who are willing to participate in the study will be included, with 1 patient recruited per day.

Randomization

Prescriber or Clinician randomization

After obtaining written informed consent, all treating physicians will be randomized using a stratified randomization method based on seniority in our study design. The clinicians will be divided into strata based on their seniority levels, for example, junior resident, senior residents, mid-level doctors (eg, assistant and associate professor levels), and senior doctors (eg, additional

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professor and professor cadre level). They will then randomly assign participants within each stratum to the intervention or control group. This stratified randomization ensures an equal distribution of doctors across the study groups, minimizing the potential for bias and contamination. Additionally, it accounts for any potential variations in expertise, experience, or treatment preferences among doctors of different seniority levels. The random allocation sequence will be generated using computer-generated random numbers. Enrolled participants will then be treated by the clinician randomized to the respective group.

Blinding (Masking)

Considering the nature of the intervention proposed, this study is designed as an open-label study; the participants and the intervention implementing team will not be blinded to the intervention. However, the statistician performing data analyses will be blinded to group assignments.

Baseline Assessment

Demographic details, such as age, gender, occupation, education, BMI, disease conditions details, and list of drugs used (including FRIDs with their costs and orthostatic hypotension details) will be collected from all the participants. Drug details, such as the name of the drug, indication, frequency, route of administration, and duration of use will also be collected. The rationality of the prescriptions will be assessed by the World health Organization prescription indicators.

Participants will then be asked about their previous fall history using the fall history questionnaire of McCrum 2020 [8] and their concern for falls assessed by the Fall Efficacy Scale [9,10]. Quality of life will be assessed by administering the EQ-5D-5 L questionnaire. Once the baseline data collection is completed, they will be assessed for fall risk. The fall risk assessment will be conducted by a staff nurse using the Timed Up and Go test and the Tinetti Performance-Oriented Mobility Assessment Tool.

Intervention Details

Clinical pharmacologists will do steps 1 and 2 of the ARMOR tool for the recruited participants' prescriptions and prepare a summary report of all the recruited participants' prescriptions.

Test Group

Participants randomized to this group will be managed using the ARMOR tool–based deprescribing intervention, which contains 5 steps—Assess, Review, Minimize, Optimize, and Reassess. A clinical pharmacologist provides a summary report of steps 1 and 2 of the ARMOR tool to the treating physician. The treating physician will complete steps 3 to 5.

The ARMOR tool

The ARMOR tool [11] is designed to guide health care professionals in a structured approach to medication management, emphasizing the importance of regular assessment, review, modification, optimization, and reassessment. It promotes patient-centered care and aims to enhance medication safety and effectiveness.

Step 1: Assessment

A comprehensive assessment of the patient's medication regimen will be done during this step.

Step 2: Review

In this step, the pharmacologist along with the treating physician will review the assessment findings (ie, the overall effectiveness and necessity of each medication) and will identify any potential risks or harms associated with continued use.

Step 3: Modify

Based on the review submitted, the clinician may consider a deprescribing intervention for medications that are no longer necessary, ineffective, or potentially harmful. If required clinicians will consider adjusting dosages, changing formulations, or switching to alternative medications.

Step 4: Optimize

In this step, clinicians will focus on enhancing the patient's medication regimen to achieve the best possible outcomes. They may initiate new medications when necessary, optimizing dosages for maximum efficacy, and addressing any identified gaps in therapy.

Step 5: Reassess

After modifications and optimization, the clinician will continue to monitor the patient's response to the medication changes. They reassess the patient's symptoms, side effects, and overall treatment outcomes.

Control Group

Participants randomized to the usual care group will receive treatment as per the standard practice or protocol. As there are no established gold standards for effective, deprescribing interventions, usual care is chosen as a comparator.

The Follow-Up Phase

Each participant will be followed for a period of 1 year after their enrollment into the study. Both groups will be followed up for 1 year. Each participant will be given a diary to record the falls and other adverse events. They will be followed up monthly over the phone for falls and for occurrence of other adverse events and for improving adherence to the intervention protocols of the study. Every 3 months, they will be followed up physically to assess fall risk, inquire about any fall history, and note any adverse events during that period.

Unscheduled Visits

In case of any adverse events and serious adverse events during the study period, there may be an unscheduled visit planned for the concerned participant. The details of any such event will be recorded and appropriate treatment will be provided. When trial participants experience an injury, adverse event, or serious adverse events, they will be noted, and appropriate treatment will be given.

End of Study

At the end of the study (after 1 year of follow-up), the complete information, such as the number of drugs with their details, fall history, fall concern, fall risk, and quality-adjusted life-year

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will be assessed. The rationality of the prescriptions will be assessed by the World Health Organization prescription indicators. Figure 1 provides an overview of the study methodology.

Figure 1. Flowchart of the overall study methodology. ARMOR: Assess, Review, Minimize, Optimize, and Reassess; FRID: fall risk–increasing drug; TUG: Timed Up and Go; POMA: Tinetti Performance-Oriented Mobility Assessment.

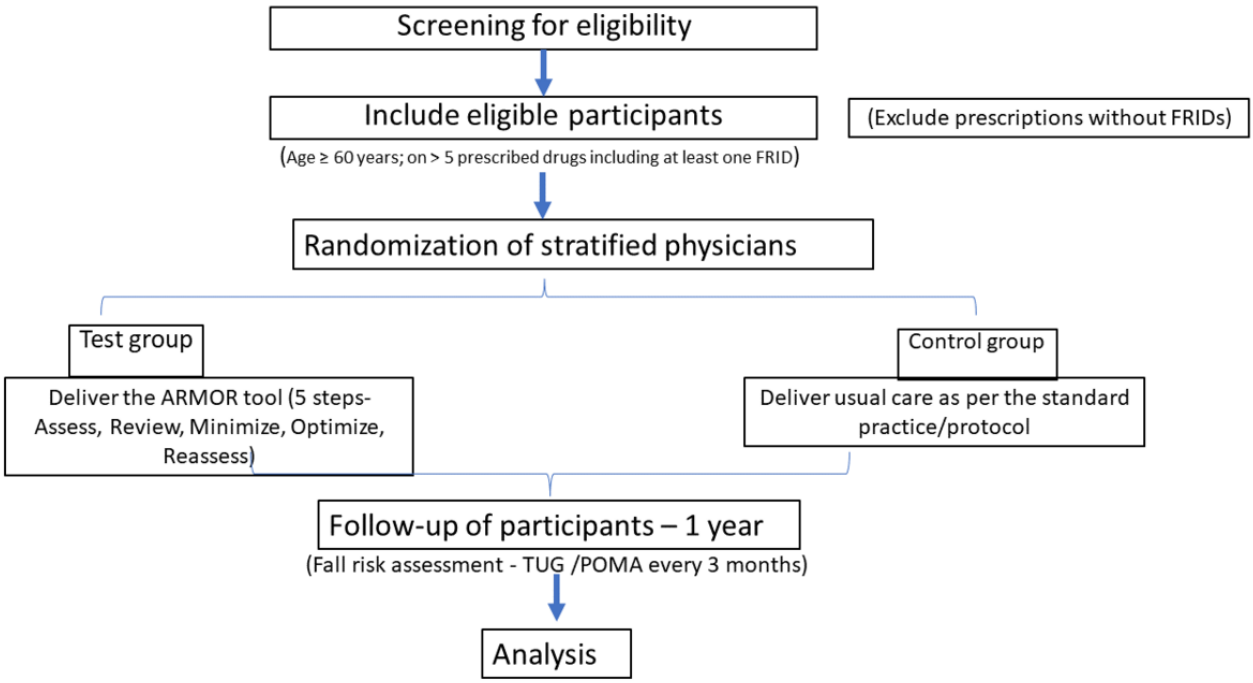

Adverse Events or SAE

Adverse events will be recorded in the adverse event form. The details will be collected in the adverse drug reaction reporting form and causality assessment will be done to find the adverse event's association with FRIDs. In the case of SAE, we will be recording and reporting the serious adverse events to regulatory authorities.

Statistical Methods and Analysis

Sample Size

The sample size is estimated using the sample size formula for estimating proportion between two groups**.** Considering the reported fall incidence with FRIDs as 73% [12], the sample size is estimated to be 478 (each arm: 239), with 90% power (as the outcomes measures are only falls and do not include any mortality, we have set the power to 90%) and 5% level of significance to detect a minimum of 20% reduction in falls in the intervention group relative to the control group (relative risk reduction of 20%). Considering the dropout of 10%, the final sample size will be 526 (263 in each arm). A total of135 participants are expected to be recruited from each center.

Data Analysis

The data will be entered in Research Electronic Data Capture (REDCap) and will be analyzed using Stata (version 16; StataCorp) software. Data will be stored in a secure server or cloud-based platform. A principal investigator and a co–principal investigator will have access to the REDcap data. The statistician will be given access to the blinded REDcap data. The occurrence of falls and fall risk during the study period will be summarized as frequency and percentages. The number of falls at these time points will be reported using the median (IQR) values. The fall risk score will be reported as mean (SD) or median (IQR) based on the normality of the data. The Mann-Whitney *U* test and Friedman test (chi-square test) will be used to analyze the change in the frequency of falls (%) at each time point between the groups and within the groups, respectively. The chi-square test will be used to analyze the fall risk score category at each time point between the groups. Additionally, repeated measures ANOVA (or Friedman test) and unpaired *t* test (or Mann-Whitney *U* test) will be used to assess the within-group fall risk score at different time points and at each time point within the group, respectively. Poisson regression analysis (both bivariate and multivariate) will be conducted to explore the association between the dependent variable (ie, the number of falls and fall risks assessed using Timed Up and Go and the Performance-Oriented Mobility Assessment) and independent factors (eg, age, gender, education, chronic illness, and intervention category). Adjusted risk ratios with 95% CIs will be reported for the factors included in the multivariate Poisson regression model. The rationality of prescriptions will be summarized using frequencies and percentages. Subgroup analysis will be performed for participants with recurrent fall history and different age categories.

Incremental Cost-Effectiveness Ratio (ICER)

Incremental Cost-Effectiveness Ratio (ICER) will be calculated by dividing the difference in costs between the interventions by the difference in outcomes. The ICER represents the

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additional cost per unit of outcome achieved by one intervention compared to another.

We will be following the intention-to-treat strategy to analyze the data. Therefore, even participants who discontinue but have at least 1 follow-up will be included in the study to achieve the required sample size, taking into account their age and health status.

Study Monitoring

This study will be monitored by the ICMR monitoring team. The investigator will allocate adequate time for such monitoring activities and ensure access to all the above-noted study-related documents and study-related facilities.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be constituted for this study independent of the study team members. The team will look into the safety of the intervention proposed with an interim analysis report.

Interim Analyses

Two interim analyses will be conducted during the study period: the first after the completion of the first follow-up of 200 participants and the second after reaching 400 participants.

Ethical Considerations

The study will be conducted as per the ICMR National Bioethical Guidelines 2017 [13] and New Drugs and Clinical Trial Rules 2019 [14]. The study received approval from All India Institute of Medical Sciences Bibinagar, Institutional Ethics Committee (AIIMS/BBN/IEC/JUNE/2023/294) on June 16, 2023.

Eligible participants who are willing to participate in the study will be enrolled after obtaining written informed consent.

Confidentiality of participation will be maintained, and personal identity will not be revealed during data collection, analysis, presentations, and publications. Study records will be preserved for 3 years and will be made available only to authorized persons conducting the study and to the funding agencies without revealing participant identities.

Reimbursement of Rs 500 (about US $6) per visit will be provided for participation in the study, as participants will be asked to visit the hospital every 3 months after their enrollment into the study.

For any foreseeable and unforeseeable complication, adequate compensation will be provided depending on the nature of the injury or illness. In addition, trial insurance coverage will be provided for any unforeseeable risks related to the study.

Results

The study received a grant from the Indian Council of Medical Research–Safe and Rational Use of Medicines (ICMR–SRUM) in October 2023. The study is scheduled to start in June 2024 and conclude by 2026. The study protocol is registered with the Clinical Trial Registry – India (registration number CTRI/2023/12/060516). Data collection and follow-ups are expected to be completed by the third quarter of 2026. The results are expected to be submitted for publication in 2026. Based on the results of this study, modules will be prepared and workshops will be organized for the prescribers on deprescribing interventions. The research findings will be presented at the national/international conference for large-scale public dissemination. The results of this study will be published in indexed peer-reviewed scientific journals. The full protocol, participant-level data set, and statistical code will be made publicly available after the completion of the study.

Discussion

Expected Outcomes

Polypharmacy has become a major concern in the geriatric population considering their multimorbid conditions. The number of prescribed drugs tends to increase with age, especially among individuals with multiple comorbidities. Although these drugs are prescribed to treat various conditions, some of them, known as FRIDs, contribute to falls in older people. FRIDS include psychotropic drugs (eg, antipsychotics, antidepressants, benzodiazepines, and sedative-hypnotics), cardiovascular agents (eg, loop diuretics, digoxin, antihypertensives, and antiarrhythmics), and other agents (eg, hypoglycemic drugs, nonsteroidal anti-inflammatory drugs, opioids, anticholinergics, and antihistamines). Reports indicate that falls among the older population are significant causes of morbidity, with FRIDs identified as one of the contributing factors for falls.

Deprescription is defined as systematically removing the drug, reducing the dose, or changing the medication without affecting the patient's health condition. There are various deprescribing tools available for controlling polypharmacy, but none has been considered as a standard with proven effectiveness, as they are often complicated, tedious, and not user friendly for implementation in the real-world settings.

The ARMOR tool-based deprescribing intervention, which contains 5 steps (Assess, Review, Minimize, Optimize, and Reassess) is very convenient and easy to use by physicians and will help in reducing the falls and fall risk in older people who use FRIDs. It is an effort to approach polypharmacy and inappropriate medications in a systematic and organized fashion. It is a functional and interactive evidence-based tool that considers a patient's clinical profile and functional status with the primary goal of improving functional status and mobility. This tool also emphasizes quality of life as a key factor for making decisions on changing or discontinuing medications.

A study was conducted to evaluate the implementation of the ARMOR tool to address polypharmacy in a rural nursing care facility. This nonrandomized, single-arm, pre- and postbaseline intervention study design was conducted with 600 residents using the ARMOR tool with an interdisciplinary team as an intervention in 7 centers. The residents were on psychotropic medications, experiencing recent or frequent behavioral disturbances causing distress to themselves or others, and exhibiting significant changes in their medical condition [15]. The results showed a negative trend in pain, falls, and anti-anxiety medication use, along with positive results in terms

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of reduction in the use of psychotropic medications. The average rate of reduction or improvement in antipsychotic risk with the intervention was 13.9% [15].

In India, there are no randomized controlled studies available on the use of this functional and interactive evidence-based tool. This trial will provide essential insights into the efficacy of the ARMOR tool in reducing falls among the geriatric population taking FRIDs. Additionally, it will provide valuable information on the cost-effectiveness of deprescribing practices, offering significant implications for improving the well-being of older patients and optimizing health care resource allocation. The findings from this study will be pertinent for health care professionals, policy makers, and researchers specializing in geriatric care and fall prevention strategies.

Conclusions

This randomized controlled trial will provide valuable insights into the potential of the ARMOR tool–based intervention to reduce the risk of falls in older patients and its cost-effectiveness in deprescribing FRIDs. The positive outcomes observed in this study would underscore the importance of medication review and optimization as part of comprehensive fall prevention strategies for the older population. Further, this research will guide the implementation of evidence-based interventions in clinical practice. This study marks the first of its kind to be conducted in India on deprescribing intervention using the ARMOR tool with a randomized control led design.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from ICMR.
[PDF File (Adobe PDF File), 353 KB - resprot_v13i1e55638_app1.pdf]

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Abbreviations

ARMOR: Assess, Review, Minimize, Optimize, Reassess
FRID: Fall Risk Increasing Drugs
ICMR: Indian Council of Medical Research
REDCap: Research Electronic Data Capture

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Protocol

Effects of a Patient Portal Intervention to Address Diabetes Care Gaps: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Despite the potential to significantly reduce complications, many patients do not consistently receive diabetes preventive care. Our research team recently applied user-centered design sprint methodology to develop a patient portal intervention empowering patients to address selected diabetes care gaps (eg, no diabetes eye examination in last 12 months).

Objective: This study aims to evaluate the effect of our novel diabetes care gap intervention on completion of selected evidence-based diabetes preventive care services and secondary outcomes.

Methods: We are conducting a pragmatic randomized controlled trial of the effect of the intervention on diabetes care gaps. Adult patients with diabetes mellitus (DM) are recruited from primary care clinics affiliated with Vanderbilt University Medical Center. Participants are eligible if they have type 1 or 2 DM, can read in English, are aged 18-75 years, have a current patient portal account, and have reliable access to a mobile device with internet access. We exclude patients with medical conditions that prevent them from using a mobile device, severe difficulty seeing, pregnant women or women who plan to become pregnant during the study period, and patients on dialysis. Participants will be randomly assigned to the intervention or usual care. The primary outcome measure will be the number of diabetes care gaps among 4 DM preventive care services (diabetes eye examination, pneumococcal vaccination, hemoglobin A_{1c}, and urine microalbumin) at 12 months after randomization. Secondary outcomes will include diabetes self-efficacy, confidence managing diabetes in general, understanding of diabetes preventive care, diabetes distress, patient portal satisfaction, and patient-initiated orders at baseline, 3 months, 6 months, and 12 months after randomization. An ordinal logistic regression model will be used to quantify the effect of the intervention on the number of diabetes care gaps at the 12-month follow-up. For dichotomous secondary outcomes, a logistic regression model will be used with random effects for the clinic and provider variables as needed. For continuous secondary outcomes, a regression model will be used.

Results: This study is ongoing. Recruitment was closed in February 2022; a total of 433 patients were randomized. Of those randomized, most (n=288, 66.5%) were non-Hispanic White, 33.5% (n=145) were racial or ethnic minorities, 33.9% (n=147) were aged 65 years or older, and 30.7% (n=133) indicated limited health literacy.

Conclusions: The study directly tests the hypothesis that a patient portal intervention—alerting patients about selected diabetes care gaps, fostering understanding of their significance, and allowing patients to initiate care—will reduce diabetes care gaps compared with usual care. The insights gained from this study may have broad implications for developing future interventions to address various care gaps, such as gaps in cancer screening, and contribute to the development of effective, scalable, and sustainable approaches to engage patients in chronic disease management and prevention.

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Trial Registration: ClinicalTrials.gov NCT04894903; https://classic.clinicaltrials.gov/ct2/show/NCT04894903
International Registered Report Identifier (IRRID): DERR1-10.2196/56123

(JMIR Res Protoc 2024;13:e56123) doi:10.2196/56123

KEYWORDS

patient portals; self-management; self-efficacy; diabetes mellitus; health literacy; attitudes

Introduction

Background

Diabetes is a prevalent chronic condition requiring effective monitoring and preventive services to avoid costly and potentially severe complications such as cardiovascular and kidney diseases [1]. Unfortunately, many patients do not consistently receive evidence-based diabetes monitoring and preventive services [2,3]. For instance, despite the potential to significantly reduce severe vision loss, approximately 40% of Americans with diabetes fail to undergo a recommended annual eye examination [2,3].

Previous studies have identified several barriers to accessing evidence-based diabetes monitoring and preventive services. These barriers encompass patient-related factors, such as limited health literacy and lack of awareness, as well as clinician- and system-related factors, such as time constraints and insufficient patient support between visits [4-8]. Previous attempts to improve the uptake of these services have yielded only modest results [9-11]. To achieve optimal rates of these services, there is an urgent need for an intervention that improves clinical efficiency, caters to patients with varying health literacy levels, and can be scaled and sustained effectively [4].

Patient portals present a promising platform to enhance access to services and support self-management by offering convenient health data tracking, educational resources, notifications, and improved patient-clinician communication, with the potential to address the limitations of costly and less scalable face-to-face interventions [12-16]. Recent advancements in patient portal technology have provided the infrastructure necessary for patients to self-schedule appointments and request health services, offering new opportunities to engage patients in their care [17-19]. Unfortunately, the varying design and usability of patient portals have resulted in inconsistent levels of patient engagement and impacts on diabetes care [12,20].

Recent research has demonstrated that patient-facing technology, enabling patients to self-order tests, can increase the uptake of colon cancer screening, enhance patient activation, and improve clinical efficiency by reducing the workload on clinicians [18,19]. In our previous work [21], our research team used the user-centered design sprint methodology to develop a patient portal intervention to address diabetes care gaps by notifying patients when any of the following four selected, evidence-based diabetes monitoring and preventive services [22] are due: (1) diabetes eye examination, (2) hemoglobin A_{1c}, (3) urine microalbumin, and (4) pneumococcal vaccination; fostering understanding of the importance of these services through literacy-level appropriate content (eg, educational content that may be more easily understood by patients with limited health literacy); and allowing patients to initiate an order for the corresponding care.

In a pilot study of this diabetes care gap intervention (DCGI), patients highly rated the overall system usability, and more than 80% of patients indicated that they would continue to use the system in the future [23].

Objective

This study aims to evaluate the effect of our novel DCGI on the completion of selected evidence-based, diabetes monitoring and preventive services and secondary outcomes (eg, diabetes self-efficacy).

Methods

Setting

For this study, we enrolled patients from 14 adult primary care clinics affiliated with Vanderbilt University Medical Center (VUMC) located throughout the Nashville, Tennessee, metropolitan area. The clinical data of these patients are stored in an electronic health record (EHR) system provided by Epic Systems Corp. To facilitate patient access to their clinical information, VUMC has implemented a widely adopted patient portal called My Health at Vanderbilt (MHAV) using Epic's MyChart platform [24]. This patient portal is accessible both via a web-based app and dedicated mobile app compatible with iOS and Android operating systems.

Study Design

This study is a 12-month pragmatic randomized controlled trial (RCT) with a 2-arm, parallel design. Participants assigned to arm 1 (usual care) have access to the standard version of MHAV, the patient portal. Participants in arm 2 have access to a modified version of MHAV that incorporates the DCGI described in detail below. Both groups of participants were informed that the study aims to assess satisfaction with 2 versions of MHAV among individuals with diabetes. Throughout the trial, the participants are requested to complete study questionnaires at 4 designated time points: T0 (baseline), T1 (3 months), T2 (6 months), and T3 (12 months).

The study protocol is guided by the principles outlined in the CONSORT Statement: Extension to Pragmatic Trials [25]. Consistent with pragmatic trial design, this study is designed to evaluate the real-world effectiveness of the DCGI in routine practice settings [26]. Due to the nature of the study and intervention, participants are aware of the intervention they are receiving, and the research team is not blinded to participant randomization.

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Eligibility and Recruitment

Participants were eligible if they received care at a participating VUMC clinic site and had type 1 or type 2 diabetes mellitus (patient reported and EHR verified), could read in English, were aged 18-75 years, had a current MHAV account, and had reliable access to a mobile device with the iOS or Android operating system with internet access. We excluded patients with a medical condition that prevents them from using a mobile device, severe difficulty seeing, pregnant women or women who plan to become pregnant during the study period, and patients on dialysis.

On a rolling basis, potentially eligible patients were selected from a randomly ordered list of established adult patients with diabetes from participating clinic sites and sent a recruitment letter describing the study. To facilitate a diverse study population representative of the population of patients with diabetes, we oversampled patients from minoritized groups. In addition, we sent secure messages via the patient portal to potentially eligible patients. To increase the diversity of study participants, we made follow-up phone calls to patients from minoritized groups who did not respond to the recruitment letter. Interested patients could contact a research assistant to learn more about the study. To enroll, participants reviewed a web-based study eligibility prescreener listing the study's inclusion and exclusion criteria and completed a web-based electronic consent form via REDCap (Research Electronic Data Capture; version 5.0.8; Vanderbilt University).

Procedures and Randomization

Study staff contacted all patients who completed a web-based electronic consent form to review study procedures, answer remaining questions, and confirm eligibility criteria. Enrolled participants were sent a baseline questionnaire via REDCap. After receiving the completed baseline questionnaire, the study coordinator (KJH) randomly assigned the participant to one of two groups: (1) intervention or (2) usual care, using REDCap's randomization module. The randomization sequence was generated by the research team biostatistician (AJH) using a stratified, permuted, block randomization with block sizes of 4. To obtain balance across treatment groups on key variables, the randomization scheme was stratified by (1) 6 clinic groups (clinic sites with similar patient demographics were grouped together), (2) adequate versus limited health literacy, (3) whether or not the participant was from a minoritized racial or ethnic group, and (4) whether or not the participant currently had a diabetes care gap (ie, whether or not the patient had at least 1 relevant diabetes-related "health maintenance" topic within Epic's EHR noted as overdue). Once the randomization assignment was finalized, participants in either arm received an email with their treatment assignment and an explanation of how to navigate to features of MHAV specific to their treatment group. A participant could withdraw from the study at any time by notifying the study team. In addition, participants were administratively withdrawn from the study by the investigators if they did not complete the baseline questionnaire needed for randomization.

Intervention and Control

Participants randomized to the intervention arm were provided access to a version of MHAV embedded with the DCGI. This included patient portal notifications to patients with reminders for timely completion when any of the following four diabetes care gaps existed: (1) no diabetes eye examination in the last 12 months; (2) no prior pneumococcal vaccination (ie, never received PPSV-23, PCV-13, PCV-15, or PCV-20); (3) no hemoglobin A_{1c} in the last 6 months; and (4) no urine microalbumin in the last 12 months. Also included were associated literacy-level appropriate content to foster understanding of the importance of these services and accompanying functionality allowing patients to initiate an order for the corresponding care via the patient portal and then receive a confirmation message with instructions for obtaining the care and next steps.

Since a considerable proportion of VUMC patients receive eye care outside of the Vanderbilt health system, the intervention also allows participants to indicate whether they received a diabetes eye examination in the last 12 months at a non-Vanderbilt clinic. In response to a diabetes care gap notification, patients can also indicate their preference to decline to self-initiate an order for the corresponding care (eg, patients with upcoming clinic appointments at which they expect to receive the care). A detailed description of the development of the intervention is available [21]. Figure 1 shows example screenshots of intervention components.

The DCGI uses Epic's "health maintenance" topics to identify diabetes care gaps and trigger corresponding to-do list items within MHAV and associated push notifications (Figure 1A). Patients who have unresponded items on their To-Do list receive a reminder message via patient portal secure messaging approximately every 2 weeks. To allow patients to self-initiate orders for care, the to-do list items repurpose Epic's questionnaire functionality to inform patients of diabetes care gaps and communicate their importance using language at or below a sixth grade reading level (Figure 1B). On the subsequent response screen, the to-do list item provides an "order" button that patients can click to initiate an order for the corresponding care (Figure 1C). Using Epic's Reporting Workbench, care coordination nurses identify all patients requesting care via the intervention and generate bulk orders for the corresponding care. Patients are promptly notified with a confirmation message containing detailed instructions on the subsequent steps (Figure 1D). Associated orders are routed to the primary care physicians' cosign basket for single-click cosignature within Epic's EHR (Epic Systems Corporation), and associated results and eye examination findings are transmitted to the primary care physician via the EHR as usual. Regardless of the presence of any diabetes care gaps, patients in the intervention group receive a monthly study-related to-do list item to acknowledge in order to create familiarity with the feature and ensure that their to-do list is functioning properly.

Participants assigned to the usual care group have access to the existing version of MHAV, enabling them to access and review relevant health data, medical information related to their conditions, and engage in communication with their health care

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team. Randomized participants who do not show evidence of accessing the patient portal (control group) or accessing the study intervention within the patient portal (intervention group) are contacted within the first 6 months of study participation to ensure that they are not experiencing any technical issues and confirm treatment fidelity for both groups.

Figure 1. Example screenshots (from a smartphone) of the diabetes care gap intervention. (A) Initial push notification directing patient to their to-do list. (B) To-do item alerting patient about the care gap and its significance. (C) Patient-facing options for addressing the care gap. (D) Confirmation message to patients to initiate care, outlining next steps.

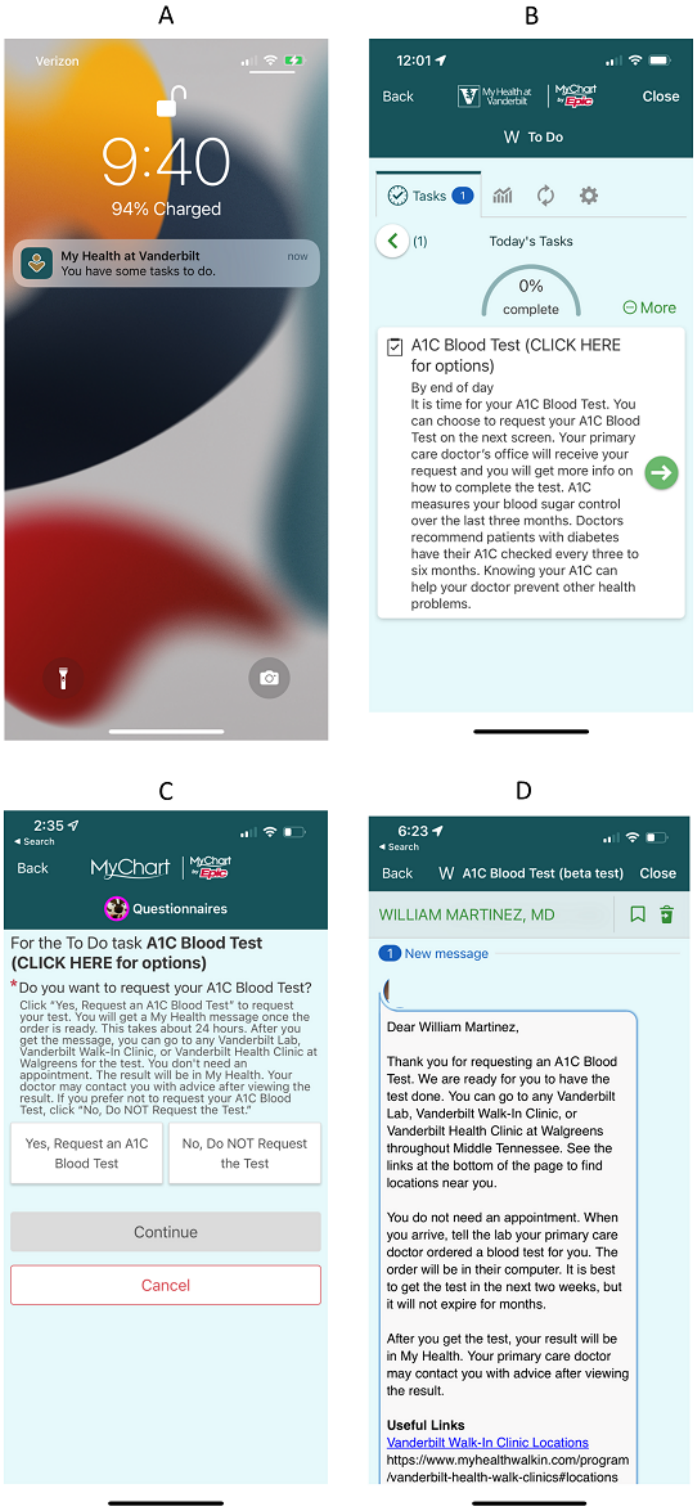

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Data Collection and Measures

Overview

Study participants complete questionnaires electronically via email using REDCap at 4 time points: baseline (T0), 3-month follow-up (T1), 6-month follow-up (T2), and 12-month follow-up (T3). The baseline questionnaire (T0) includes basic demographic questions and validated measures of health literacy [27], numeracy [28], and eHealth literacy [29]. Health literacy is assessed with a 1-item screener asking participants to rate their confidence independently completing medical forms. Consistent with prior research, participants noting any lack of confidence are classified as having limited health literacy [27,30,31]. Numeracy is assessed using the 8-item subjective numeracy scale with scale scores ranging from 1 (worst) to 6 (best) [28,32]. eHealth literacy is assessed by the 8-item eHealth Literacy Scale with scale scores ranging from 8 (worst) to 40 (best) [29]. We estimated the time to completion for each questionnaire to be about 20 minutes.

The primary outcome measure is the number of diabetes care gaps among 4 selected diabetes mellitus monitoring and preventive services at 12 months. Thus, the number of diabetes care gaps per patient can range from 0 to 4. Secondary intermediate outcomes include diabetes self-efficacy, attitudes toward managing diabetes in general, understanding of diabetes monitoring and preventive care, diabetes distress, satisfaction with MHAV, patient-initiated orders, and reported completion of diabetes eye examinations outside the VUMC system. Additional secondary outcomes, blood glucose control and treatment intensification, are assessed by EHR abstraction.

Primacy Outcome

Number of Diabetes Care Gaps at 12 Months

The number of diabetes care gaps per patient will be assessed via data abstraction from structured fields within the VUMC EHR. These data may include care received outside of the VUMC system and entered into the VUMC EHR by clinicians or patients. Consistent with diabetes evidence-based guidelines [22], the following diabetes care gaps will be assessed and defined as follows: (1) the diabetes eye examination gap, when there has been more than 12 months since the most recent diabetes eye examination date recorded in the EHR; (2) the pneumococcal vaccination gap, when there no record of any pneumococcal vaccination (ie, PPSV-23, PCV-13, PCV-15, or PCV-20) in the EHR; (3) the hemoglobin A_{1c} gap, it has been more than 6 months since the most recent hemoglobin A_{1c} result date in the EHR; and (4) the urine microalbumin gap, when it has been more than 12 months since the most recent urine microalbumin result date in the EHR.

Therefore, this outcome is ordinal, and participants can have between 0 (best) and 4 (worst) diabetes care gaps.

Secondary Outcomes

Number of Diabetes Care Gaps at 6 Months

The number of diabetes care gaps per patient at 6 months will be assessed and defined as above for the 12-month time point.

Diabetes Self-Efficacy

The Perceived Diabetes Self-Management Scale will be used to assess diabetes-specific self-efficacy [33]. The unidimensional, 8-item, validated scale is scored on a 5-point Likert scale. The total Perceived Diabetes Self-Management Scale score can range from 8 to 40, with higher scores indicating greater diabetes self-efficacy.

Confidence in Managing Diabetes in General

The Manage Disease in General Scale of the Chronic Disease Self-Efficacy Scales will be used to assess confidence toward managing diabetes in general [34]. The 5-item scale is a validated measure of the confidence a person has in managing his or her own health and health care. The items were adapted to be specific to diabetes rather than a generic chronic health condition or illness. Each item uses a 10-point Likert-type scale of response options ranging from 1 (not at all confident) to 10 (totally confident). The score for the scale is the mean of the items with scale scores ranging from 1 to 10. Higher scores indicate greater confidence toward managing diabetes in general.

Understanding of Diabetes Monitoring and Preventive Care

Unique study-specific items (4 items) that assess participants' understanding of the recommended frequency of selected diabetes monitoring and preventive services (eg, diabetes eye examinations) will be administered to all study participants. Each multiple-choice item has only 1 correct answer and item responses are scored as "correct" or "incorrect."

Diabetes Distress

The Problem Areas in Diabetes Scale (PAID-5) will be used to assess diabetes-related distress [35]. The 5-item, unidimensional scale is scored on a 5-point Likert scale ranging from 0="not a problem" to 4="serious problem." Scale scores range from 0 to 20, with higher scores indicating greater diabetes-related emotional distress.

Satisfaction With MHAV

Satisfaction with MHAV will be assessed using the 10-item System Usability Scale, which queries users' perceptions of ease of use, the likability of the interface, and overall satisfaction. The System Usability Scale uses a 5-point Likert scale from strongly disagree to strongly agree [36]. Participants' responses to each item are scored 0-4, added together and then multiplied by 2.5 to generate a total score for the scale from 0 (worst) to 100 (best). In addition, unique study-specific items will assess acceptability (ie, likelihood of recommending to other patients and continuing to use) and open-ended items to describe elements participants liked best as well as challenges or problems they encountered and suggested improvements.

Patient-Initiated Orders

Among patients in the intervention group, the number of patient-initiated orders for each evidence-based diabetes monitoring and preventive service will be assessed by querying the EHR (eg, patient-initiated A_{1c} orders).

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Reported Completion of Diabetes Eye Examinations Outside VUMC System

Among patients in the intervention group, the number of patient-reported diabetes eye examinations completed outside the VUMC system will be assessed by querying the EHR (ie, number of reports of diabetes eye examinations completed outside the VUMC system that are submitted in response to the To-Do item received via the DCGI). For each patient-reported diabetes eye examination outside the VUMC system, study staff will seek permission from participants to obtain the associated medical records. To assess the accuracy of patients' self-report, the number of outside diabetes eye examination records that include screening for diabetic eye disease will be assessed by medical record review by trained ophthalmology staff and overseen by an ophthalmologist (SG).

Glycemic Control

The change in glycemic control will be assessed by abstracting, from the VUMC EHR, the closest hemoglobin A_{1c} measurement to the study time points: T0, T1, T2, and T3. For the baseline time point (T0), the date and value closest to the study time point in the window of 90 days prior to the study point will be selected. For all subsequent study time points (T1, T2, and T3), the date and value closest to the study time point in the window of 28 days prior to the study time point up until 28 days after the study time point will be selected.

Treatment Intensification

Treatment intensification for antihyperglycemic and antihypertensive medications will be assessed by abstracting medication history from the EHR. Treatment intensification will be defined as the addition or increase in dose of (1) antihyperglycemic and (2) antihypertensive medications, respectively.

Data Analysis

Statistical Analysis Plan

The pragmatic, parallel design, RCT is designed to evaluate the effect of the intervention on diabetes care gaps as well as secondary intermediate outcomes (eg, diabetes self-efficacy). An ordinal logistic regression model will be used to quantify the effect of the patient portal intervention on the primary outcome of the number of diabetes care gaps at 12-month follow-up. For dichotomous secondary outcomes (eg, treatment intensification), a logistic regression model will be used with random effects for the clinic and provider variables as needed. For continuous secondary outcomes (eg, diabetes self-efficacy), a generalized linear regression model will be used. If there is imbalance, we will control for baseline patient-level covariates. We will allow for nonlinear associations by modeling continuous covariates with restricted cubic splines as needed. The characteristics of participants who do not complete the study will be compared for both study groups.

Primary Analysis

We will examine the impact of the DCGI on the number of selected diabetes care gaps at 12-month follow-up compared with the control condition (Table 1). We hypothesize that the patient portal intervention will facilitate the completion of selected evidence-based, diabetes monitoring and preventive services resulting in fewer diabetes care gaps. Analyses will be conducted using R statistical software (version 4.1.0 or higher; R Development Core Team).

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Table 1. Outcomes and measures.

	Measures	Variable type	How collected	Time points[a]
Primary outcome				
Number of diabetes care gaps at 12 months	Number of diabetes care gaps per patient out of 4 possible: no diabetes eye examination in the last 12 months; No prior pneumonia vaccinations (ie, never received PPSV-23, PCV-13, PCV-15, or PCV-20); No hemoglobin A_{1C} blood test in the last 6 months; No urine microalbumin in the last 12 months	Ordinal	EHR[b] abstraction	T0-T3
Secondary outcomes				
Number of diabetes care gaps at 6 months	Number of diabetes care gaps per patient out of 4 possible: no diabetes eye examination in the last 12 months; no prior pneumonia vaccinations (ie, never received PPSV-23, PCV-13, PCV-15, or PCV-20); no hemoglobin A_{1C} blood test in the last 6 months; no urine microalbumin in the last 12 months	Ordinal	EHR abstraction	T0-T2
Diabetes self-efficacy	Perceived Diabetes Self-Management Scale [33]	Continuous	Questionnaire	T0-T3
Confidence toward managing diabetes in general	Items adapted from the Manage Disease in General Scale of the Chronic Disease Self-Efficacy Scales [34]	Continuous	Questionnaire	T0-T3
Understanding of diabetes monitoring and preventive care	Unique study-specific items to assess participants' understanding of recommended diabetes monitoring and preventive care	Dichotomous	Questionnaire	T0-T3
Diabetes distress	Problem Areas in Diabetes Scale (PAID-5) [35]	Continuous	Questionnaire	T0-T3
Satisfaction with MHAV[c]	System Usability Scale [36] and user experience questions	Continuous	Questionnaire	T0-T3
Patient-initiated orders	Number of patient-initiated orders for evidence-based diabetes monitoring and preventive services (eg, hemoglobin A_{1C})	Continuous	EHR abstraction, tableau and clarity servers	T3
Reported completion of diabetes eye examination outside VUMC[d] system	Number of reports of diabetes eye examinations completed outside the VUMC system in response to the to-do item received via the intervention	Continuous	EHR abstraction, tableau and clarity servers	T3
Change in glycemic control	Hemoglobin A_{1C}	Continuous	EHR abstraction	T0-T3
Treatment intensification	Addition or increase in dose of: antihyperglycemic medications and antihypertensive medications	Dichotomous	EHR abstraction	T0-T3

[a]T0: baseline, T1: 3-month follow-up, T2: 6-month follow-up, and T3: 12-month follow-up.

[b]EHR: electronic health record.

[c]MHAV: My Health at Vanderbilt.

[d]VUMC: Vanderbilt University Medical Center.

Secondary Analysis

In addition, we will quantify the effects of the DCGI on secondary intermediate outcomes including diabetes self-efficacy, confidence toward managing diabetes in general, understanding of diabetes monitoring and preventive services, diabetes distress, and satisfaction with MHAV (Table 1). Additional secondary outcomes including the number of patient-initiated orders, reported completion of diabetes eye examinations outside VUMC system, blood glucose control, and treatment intensification will also be assessed by EHR abstraction.

Sample Size and Power

The targeted enrollment for the study is 250 patients per treatment arm to obtain sufficient effective sample size to detect an odds ratio of 1.66 at 12-month follow-up using a proportional odds regression model. The odds ratio gives the ratio of the odds that the patient portal intervention group has no diabetes care gaps over the odds that the usual care group has no gaps. Power estimates are based on an attrition rate of 20% at the time of study completion. The power analysis assumes that the distribution of diabetes care gaps is that 26% of the population had no gaps, 32% had 1 gap, 23% had 2 gaps, 14% had 3 gaps, and 5% had 4 gaps. This assumption was based on preliminary data obtained from VUMC during November 2021. The desired power is assumed to be 80% with a significance level of .05.

Ethical Considerations

This study was approved by the Vanderbilt University institutional review board (IRB# 212257). Patient participation was voluntary, and patients provided informed consent prior to their participation. REDCap electronic data capture tools hosted at Vanderbilt University were used to collect and manage study data [37,38]. REDCap is a secure, HIPAA-compliant, web-based software platform developed to support data capture and

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management for research studies. REDCap access was limited to the minimum number of study team members needed to conduct the trial. Participants are compensated US $40 for completing each study questionnaire (US $160 total if they complete all 4).

Results

Figure 2 shows a flow chart of recruitment. Recruitment began in April 2022 and ended in January 2023. Throughout the recruitment period, 5999 unique letters were sent to patients identified as potentially eligible. Separately, 1614 patient portal messages were sent to patients who use MHAV. Because it was not possible for the study team to cross-reference the list of those who were sent letters against the list of those who were sent patient portal messages, some overlap between the 2 is possible. The letters and emails generated 777 visits to the web-based REDCap eligibility prescreener and resulted in 496 completed informed consent documents. Among those who completed the informed consent document, 2.4% (n=12) were ineligible, 7.3% (n=36) were unreachable, and 90.3% (n=448) were confirmed eligible. Eight eligible patients declined to participate. All remaining eligible patients (n=440) were sent the baseline questionnaire. A total of 433 participants completed the baseline questionnaire and were randomized.

Of those randomized (n=433), the majority 66.5% (n=288) of participants were non-Hispanic White, and 33.5% (n=145) were from minoritized racial or ethnic groups. In addition, 33.9% (n=147) were aged 65 years or older. Furthermore, 8.8% (n=38) reported educational attainment of a high school degree or less, 30.7% (n=133) indicated limited health literacy, and 26.8% (116/433) had only a US governmental health plan (eg, military, Civilian Health and Medical Program of the Uniformed Services, Veterans Affairs, Medicaid, and Medicare).

Figure 2. Recruitment and enrollment flow chart. TN: Tennessee.

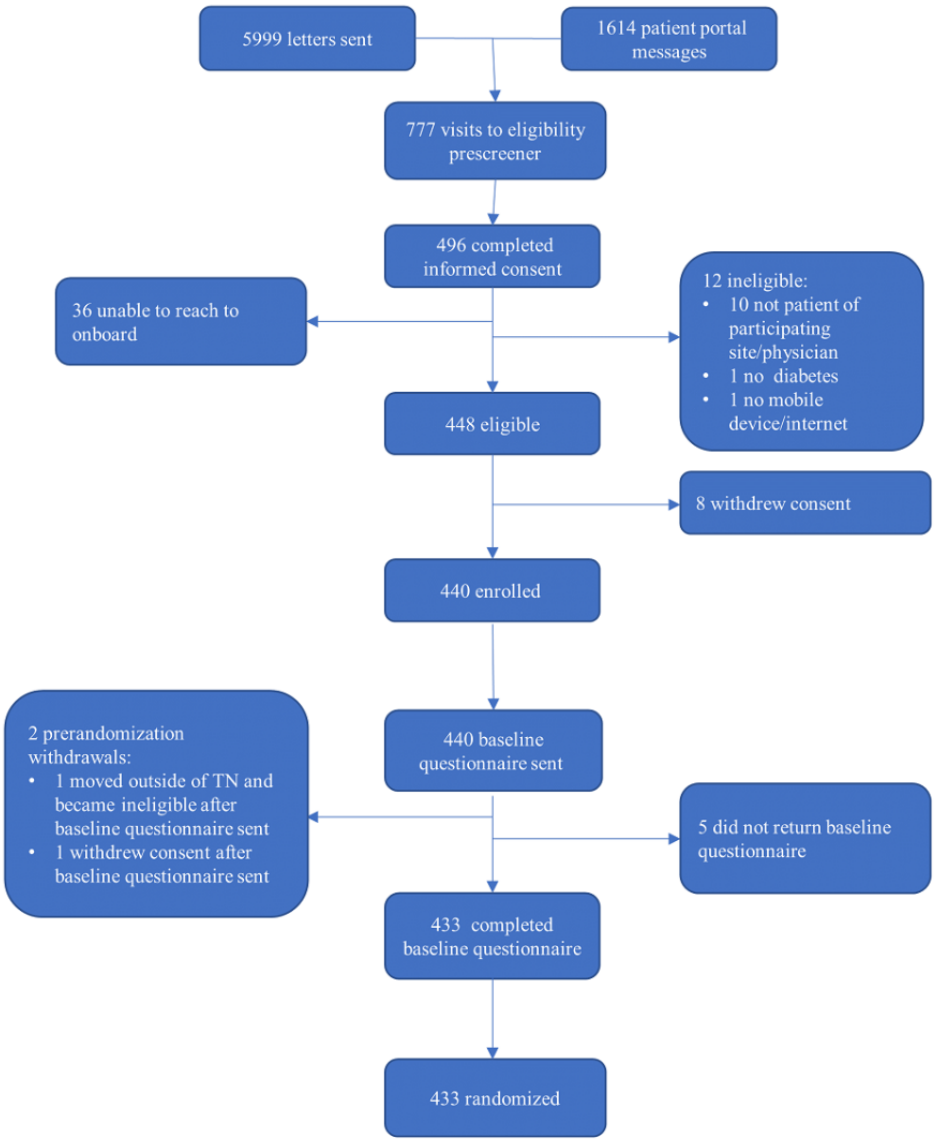

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Discussion

Principal Findings

This paper presents the protocol for a randomized trial evaluating the impact of a patient portal intervention empowering patients to address diabetes care gaps on the completion of selected evidence-based diabetes monitoring and preventive services. We aim to directly test the hypothesis that a patient portal intervention—alerting patients about selected diabetes care gaps, fostering understanding of their significance, and allowing patients to initiate orders for the corresponding care—will reduce diabetes care gaps compared with usual care. The study addresses an important need to find easily scalable and sustainable solutions to improve the rates of diabetes monitoring and preventive services that can reduce the incidence and severity of diabetes complications. By measuring attitudes toward managing diabetes and diabetes self-efficacy, we will also assess whether empowering patients to address their own care gaps has the secondary benefit of increasing their confidence to manage their disease. The study will also collect data on various demographic variables, including age, health literacy, education, and eHealth literacy. These variables will be analyzed to explore their potential predictive value in relation to intervention outcomes. Because the intervention, if successful, could be extended to address other important care gaps (eg, cancer screening), the study has broad implications for chronic disease management and disease prevention.

Comparison to Prior Work

Patient portal functionality, which allows patients to self-schedule appointments and initiate clinical services, is an emerging concept in health care. A recent review focused on the barriers and facilitators of patient self-scheduling in health care [39]. While most studies in the review focused on self-scheduling general health services, the DCGI aims to enhance the understanding and completion of disease-specific health services. In a recent retrospective observational study, Hahn et al [19] evaluated a patient portal reminder for colorectal cancer screening with an embedded order button allowing patients to self-order fecal immunochemical test kits. Participants who used the order button received their kits promptly, while those who did not were sent kits by mail at a later date. The authors found that patients who used the order button were nearly 4 times more likely to complete the kit suggesting that self-ordering may act as a commitment device. Our study builds on this work and is the first RCT to our knowledge to evaluate the effect of a patient portal “self-order” system on diabetes care gaps.

Limitations

The study has important limitations. Our study is limited to diabetes monitoring and preventive services data available in the VUMC EHR and may not be a complete record of all diabetes care received by patients. In addition, our study relies on self-reported measures of several secondary outcomes that are subject to recall and social desirability bias. However, these validated, widely accepted measures offer the advantage of being less costly and burdensome than more objective measures. Our study is powered to examine the effects of the intervention on the number of diabetes care gaps per patient. Analyses examining the effects of the DCGI on other secondary outcomes (eg, glycemic control) and comparing its effects among subgroups (eg, patients with limited health literacy) may be informative but underpowered. We hope that this study will provide a rigorous level of evidence for the effect of empowering patients to address diabetes care gaps via a patient portal. The current availability of the intervention is limited to English. This decision was made to ensure the feasibility of designing and successfully conducting the initial trial. However, it is important to note that Spanish-speaking groups are disproportionately affected by diabetes [3]. Thus, a crucial goal is to translate the DCGI into Spanish and other languages. While patient portal interventions offer a variety of advantages, they may be affected by inequities in patient portal adoption, potentially resulting in fewer patients from minoritized groups benefiting from them [40]. Encouragingly, recent data indicate that patient portal adoption is on the rise among diverse patient groups, and with appropriate design, patient portals may reduce health disparities [41,42]. A notable strength of our study is the diversity of our sample, which includes 33.5% (n=145) of patients from minoritized racial or ethnic groups.

Conclusions

The study aims to investigate the impact of a patient portal intervention empowering patients to address diabetes care gaps. We seek to understand not only whether the intervention reduces the number of care gaps per patient but also whether it increases patients’ confidence to manage their diabetes. The study will provide important insights that can be applied to design and implementation of interventions to address a broad range of care gaps, including cancer screening and vaccinations. These research findings, along with evolving patient portal functionality, will inform effective, scalable, and sustainable ways to engage patients in chronic disease management and disease prevention.

Acknowledgments

This research was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (R18DK123373) and the National Center for Advancing Translational Sciences (UL1 TR000445).

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

WM, the principal investigator, led development of the research protocol and oversaw the execution of the research plan. WM, AJH, and TAE conceived the study. WM and AJH drafted the manuscript. KJH coordinates participant recruitment, follow-up, and data collection. All coauthors contributed to the development of the study protocol and read and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel.
[PDF File (Adobe PDF File), 228 KB - resprot_v13i1e56123_app1.pdf]

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Abbreviations

DCGI: diabetes care gap intervention
DM: diabetes mellitus
EHR: electronic health record
MHAV: My Health at Vanderbilt
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
VUMC: Vanderbilt University Medical Center

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Protocol

Sustainable Lifestyle Among Office Workers (the SOFIA Study): Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Society is facing multiple challenges, including lifestyle- and age-related diseases of major public health relevance, and this is of particular importance when the general population, as well as the workforce, is getting older. In addition, we are facing global climate change due to extensive emissions of greenhouse gases and negative environmental effects. A lifestyle that promotes healthy life choices as well as climate and environmentally friendly decisions is considered a sustainable lifestyle.

Objective: This study aims to evaluate if providing information about a sustainable lifestyle encourages individuals to adopt more nutritious dietary habits and increase physical activity, as compared to receiving information solely centered around health-related recommendations for dietary intake and physical activity by the Nordic Nutrition Recommendations and the World Health Organization. Novel features of this study include the use of the workplace as an arena for health promotion, particularly among office workers—a group known to be often sedentary at work and making up 60% of all employees in Sweden.

Methods: The Sustainable Office Intervention (SOFIA) study is a 2-arm, participant-blinded, cluster randomized controlled trial that includes a multilevel sustainable lifestyle arm (intervention arm, n=19) and a healthy lifestyle arm (control arm, n=14). The eligibility criteria were being aged 18-65 years and doing office work ≥20 hours per week. Both intervention arms are embedded in the theoretically based behavioral change wheel method. The intervention study runs for approximately 8 weeks and contains 6 workshops. The study focuses on individual behavior change as well as environmental and policy features at an organizational level to facilitate or hinder a sustainable lifestyle at work. Through implementing a citizen science methodology within the trial, the participants (citizen scientists) collect data using the Stanford Our Voice Discovery Tool app and are involved in analyzing the data, formulating a list of potential actions to bring about feasible changes in the workplace.

Results: Participant recruitment and data collection began in August 2022. As of June 2024, a total of 37 participants have been recruited. The results of the pilot phase are expected to be published in 2024 or 2025.

Conclusions: Given the ongoing climate change, negative environmental effects, and the global epidemic of metabolic diseases, a sustainable lifestyle among office workers holds important potential to help in counteracting this trend. Thus, there is an urgent unmet need to test the impact of a sustainable lifestyle on food intake, physical activity, and environmental and climate impacts in a worksite-based randomized controlled trial. This study protocol responds to a societal need by addressing multilevel aspects, including individual behavior changes as well as environmental and organizational changes of importance for the successful implementation of sustainable lifestyle habits in an office setting.

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KEYWORDS

diet; physical activity; work life; health promotion; climate change; sustainable lifestyle; citizen science; Our Voice

Introduction

Background

Nations around the world, including Sweden, are facing multiple challenges driven by lifestyle- and age-related diseases of major public health relevance, such as diabetes type 2, cardiovascular disease, and cancer [1,2]. It is estimated that physical inactivity in the European population costs each country between €1 and €2 billion (US $1.09 and US $2.18 billion) in health care spending [3]. Moreover, improved adherence to healthy dietary patterns by 20% in the American population has the potential to save more than US $20 billion in costs associated with noncommunicable diseases (NCDs) [4]. This is of particular importance when the general population, including the global workforce, is getting older. Moreover, we are facing global climate change due to extensive emissions of greenhouse gases and substantial negative environmental effects [5]. A lifestyle that promotes both healthy life choices, as well as climate- and environmental-friendly behaviors, is considered a sustainable lifestyle [6,7]. It is important that individuals believe that they can take responsibility for their own lifestyle, but it is also essential that a sustainable lifestyle be encouraged and facilitated at work and through society at large.

Although many Swedish workplaces offer their employees tax-deductible preventive health care services (wellness allowance), such incentives have been used mostly to promote exercise outside of the workplace and have been used predominantly by employees who are already physically active [8,9]. In order to achieve a paradigm shift in the way we think about lifestyle factors and health in relation to work, a sustainable lifestyle in areas such as physical activity and healthful food access needs to be considered when new offices are built and designed in order to encourage and facilitate an active and healthy lifestyle during working hours. Such changes need to be feasible, user-friendly, and attractive, but at the same time, avoid creating undue pressure or feelings of guilt among employees [10,11]. A previous study by our team with 5364 well-educated adults aged 18-45 years showed that participants consumed, on average, 1 meal with meat per day for lunch or dinner, and the carbon footprint from their food consumption was, on average, 4.7 kg greenhouse gas emissions per person per day (CO_2 equivalents [CO_2e]), which corresponds to 1.7 tons of greenhouse gas emissions per person per year [12]. As different food sources generate different amounts of carbon emissions, with plant foods generally having lower emissions than animal products [13], there would be substantial climate benefits if more people reduced their intake of beef and increased their intake of plant-based foods. Moreover, epidemiological studies have consistently found that high consumption of plant-based foods, such as fruits, vegetables, legumes, and whole-grain products, reduces the incidence of NCDs, such as obesity, diabetes type 2, cardiovascular diseases, and certain types of cancer [14-16]. Health-enhancing behaviors such as regular physical activity are also linked to reduced risk of NCDs [17]. One form of physical activity is active commuting, such as walking or biking to work, which also has positive climate and environmental dimensions as it does not contribute to greenhouse gas emissions, traffic congestion, air pollution, or noise [18,19]. The above types of behavior changes would result in more nutritious and climate-friendly food habits and increased physical activity, which would impact public health substantially.

Current Guidelines

To promote good health and prevent major NCDs in the population, the Nordic countries have common dietary recommendations, the Nordic Nutritional Recommendations (NNR) [20,21], and Sweden has adopted the recommendation about physical activity from the World Health Organization (WHO) [22]. However, such preventive actions have consistently had a poor impact on the public's lifestyle choices, and few community members are aware of these recommendations. Therefore, new ways of impacting people's lifestyles are needed. Since 60% of all employees in Sweden work in an office setting [23], we suggest that a shift to healthy plant-based food should be encouraged at workplaces in the form of food served at events, catering, coffee breaks, and lunch, and physical activity should be encouraged by facilitating active commuting, walk-and-talk meetings, and other forms of everyday movement during office hours.

Objective

The overall aim of the Sustainable Office Intervention (SOFIA) study is to promote and facilitate the adoption of a sustainable lifestyle within an office environment, with the dual goals of enhancing public health and mitigating the adverse effects of climate change and negative environmental impact. Specifically, the research aims to assess the effectiveness of promoting sustainable lifestyle choices in the workplace compared to promoting a conventional healthy lifestyle.

Methods

Study Design and Sample Size

The SOFIA study is part of a larger mixed-method effort titled *Concepts for the Sustainable Office of the Future* (SOFCO) [24], which is studying how sustainable lifestyles and health may be supported among office workers in Sweden. Here, we describe the SOFIA substudy, which is a 2-arm, single-blind (participants), cluster randomized controlled trial comparing a sustainable lifestyle intervention arm with a healthy lifestyle control arm (Figure 1). The intervention study, which will occur in office sites in the Mälardalen region, Sweden, runs over 8 weeks, with each intervention consisting of 6 workshops occurring every week for the first 4 weeks and then every second week for the last 4 weeks (Figure 2). The data collection will occur at baseline and after 4 and 8 weeks, with the target number

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of randomly assigned participants per intervention arm being 47 participants each.

Figure 1. A SPIRIT flow chart of the SOFIA study. Based on power calculations from the study CLEAR 2018 (unpublished data), 94 participants will be recruited, accounting for an assumed dropout rate of 10% to 15% after the baseline assessment. SOFIA: Sustainable Office Intervention; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

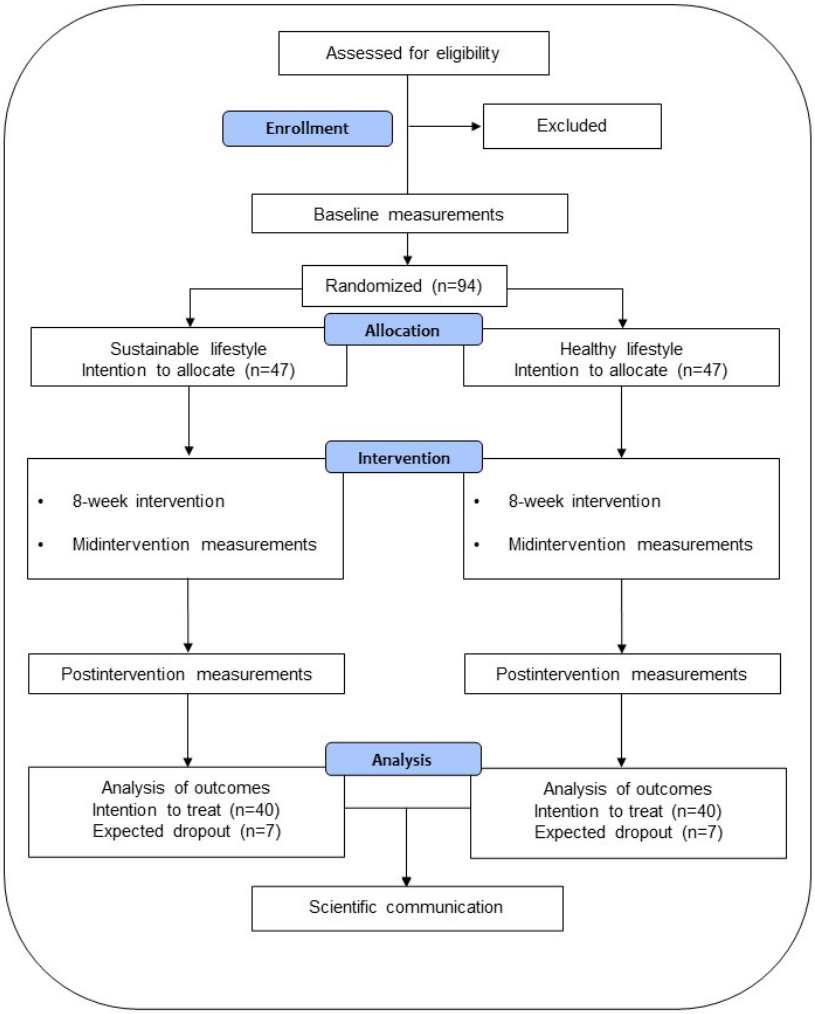

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Figure 2. Timeline for the SOFIA 8-week intervention study, which includes 6 workshops plus a follow-up meeting occurring 2-3 months after week 8. WS: workshops. SOFIA: Sustainable Office Intervention.

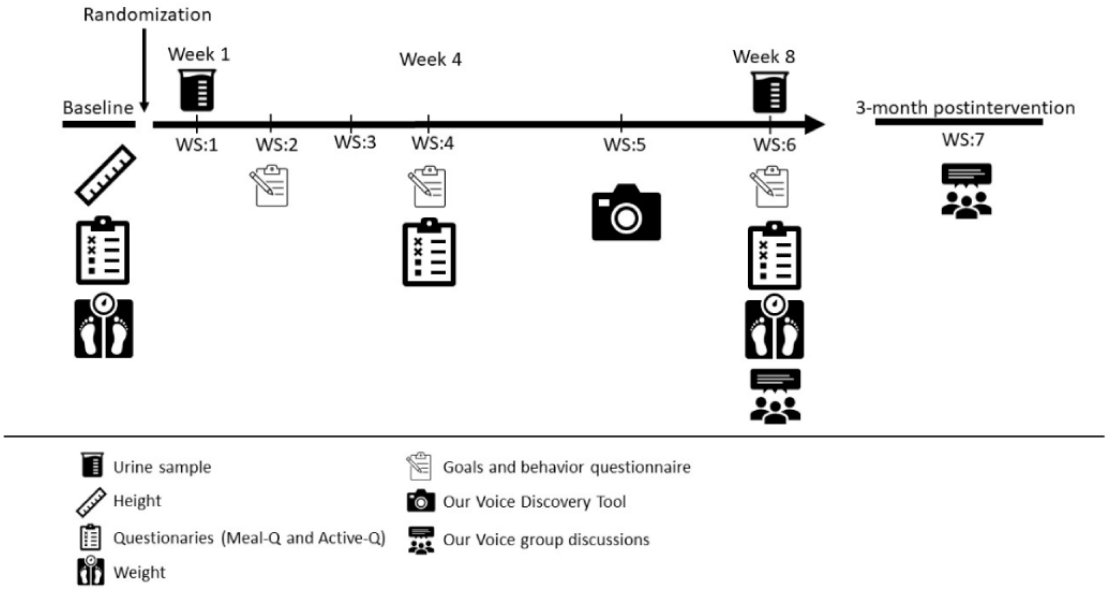

Ethical Considerations

The SOFIA study was approved by the Swedish Ethical Review Authority (2021-02309) concerning biological samples and research on human subjects. The study was registered at ClinicalTrials.gov as protocol ID 1-2020/0244. The research activities are conducted according to ethics principles set by the Declaration of Helsinki [25], and the study protocol strictly follows regulations by the Swedish Research Council concerning informed consent and confidentiality [26]. Trained personnel from the research team are responsible for data entry and cleaning. A senior statistician (AT) and data managers (OHU and KB) will ensure accurate and efficient data collection and analysis and guarantee confidentiality for the study participants. All personal data collected will be stored within the framework of European Data Protection Agreements [27] and on a 2-step authorized, password-protected server only accessed by authorized members of the research team. In addition, the Stanford Discovery Tool data are retained in a secure data repository that is reviewed annually by the Stanford University Institutional Review Board for Human Subjects Protections, as well as the Stanford Office of the General Counsel and the University Privacy Office, to ensure that it remains compliant with all European General Data Protection Regulations [27]. Prior to data collection, all participants will be provided with written and oral information about the study design and sign the informed consent form regarding all aspects of the study including primary and secondary objectives. Collected data will be deidentified using study-specific ID numbers. When the participants use the Discovery Tool to take photos, they will be instructed to avoid taking photos of persons or objects that may be linked to a specific person. The research team will review all photos, and if needed, blur humans or company logos to protect the confidentiality of participants. The participants will not be compensated, as participation takes place during working hours and participants are insured by their employer.

Study Population

The project is being conducted in collaboration with companies in the office sector in Sweden. Company A owns and develops office buildings, is located in a medium-sized city, and houses approximately 35 office workers. Company B coordinates and develops facility management, is located in a large city, and has approximately 400 office workers. Through advertisement at these offices, we will invite office workers to sign up via a short web-based screening questionnaire to confirm eligibility for the study, the number of hours working in their office per week, the office location, and active commuting and food habits, along with their contact information. The questionnaire takes approximately 2-5 minutes to complete and will be administrated using links and QR codes. Eligible study participants are aged 18-65 years and perform office work ≥20 hours per week. Exclusion criteria comprise not having access to a smartphone compatible with the Discovery Tool (such as iPhone 5 or Android 2, 3, or later versions), being blue-collar workers who perform ≥20 hours per week of strength or physical work rather than office work, having mental disabilities, and not speaking Swedish.

Procedure

Invitations to prospective participants working at the targeted companies will be sent through email, and upon their confirmation of interest, individuals will be subsequently invited to attend a baseline meeting. The primary objective of this meeting will be to provide individuals with comprehensive details about the study, have interested individuals sign the approved human subjects consent form, administer the baseline questionnaire, conduct anthropometrical assessments, and provide participants with a urinary sample test kit. A web-based questionnaire including questions about demographic factors, work environment, food habits, physical activity, workplace-related factors, as well as opinions and actions related to environmental and climate impact from one's lifestyle, will be administered at baseline. The baseline questionnaire takes

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between 20 to 30 minutes to complete and will be delivered to the participants' work email. A shorter version of the questionnaire, with a focus on food habits and physical activity, will be repeated at 4 and 8 weeks (Figure 2). The questions about food intake, diet-related CO_2e, and physical activity have been evaluated with regard to validity and reliability [28-31]. Urinary samples will be collected at baseline and 8 weeks. Thereafter, participants will be cluster-randomized based on their office's geographic location.

The interventions will start the following week and contain web-based educational sessions (Multimedia Appendix 1) and discussions about how to change behavior on an individual level to achieve a more sustainable and healthier lifestyle. Around 2-3 months after the final workshop, a follow-up meeting (workshop 7) will be held to discuss changes on an organizational level where participants will be encouraged to invite their workplace managers. All workshops will be in person at or near the participant's workplace. The leaders of each workshop were trained staff from the researcher team at Mälardalen University with a background in nutrition and physiotherapy, and the same staff attended all workshops, except for the first baseline assessment where extra staff will help out with the logistics of data collection.

A Framework for Behavior Change

The behavioral change wheel [32] serves as a framework for the novel multilevel (personal plus organizational) intervention, which is based on the framework of the COM-B model, including capability (C), opportunity (O), as well as motivation (M), which together have the capacity to support a change in behavior (B). Capability refers to the resources and skills necessary for the individual to adopt a healthy and sustainable lifestyle, for example, knowledge and culinary skills. Opportunity refers to organizational factors, policies, availability, and accessibility of resources supporting a healthy and sustainable lifestyle, for example, areas for physical activity and food options at work. Motivation refers to internal or personal factors that influence decision-making for adopting a healthy and sustainable lifestyle, such as a desire to improve one's health, contribute to reducing local food waste, reduce one's global footprint from food and transportation, and increase work productivity.

Supportive Structures

The research team will facilitate behavior change among participants using the following behavior techniques: goal setting, self-monitoring, social support, framing and reframing, prompts and cues, action planning, information on behaviors and outcomes of behaviors, information about social and environmental consequences, and lastly, review of behavior goals and outcomes (Multimedia Appendix 2) [33]. The 5 web-based educational workshops will be grounded in the principles of the behavioral change techniques framing and reframing, prompts and cues, as well as information regarding social and environmental consequences. These sessions will actively engage participants in discussions and problem-solving, aimed at fostering action planning, and the study personnel will offer constructive feedback on behaviors and outcomes aligned with the individual goals set by the participants (for a description of the intervention functions, see Multimedia Appendix 3 [32,33]).

Participants will complete short, printed questionnaires at workshops 2, 4, and 6 to establish and assess individual dietary goals; monitor behavioral changes; evaluate goal fulfillment, self-efficacy, and outcome expectations; assess social support types and levels; and identify potential barriers and facilitators related to their dietary goals. Throughout the study, participants will complete these questionnaires for the purpose of self-monitoring and reviewing their progress toward achieving their behavioral goals and process evaluation [34]. The questionnaires take between 1 and 3 minutes to complete and will be administrated in paper format at the workshops; the questions are based on the behavior change wheel and social cognitive theory [32,35]. The collected data will be analyzed and summarized using quantitative methods to determine common perceptions of social factors that support behavioral change, identify facilitators, highlight individual experiences, and pinpoint perceived obstacles to implementing behavior changes.

A digital behavioral support package (guidelines, recipes, culinary skills tips, and food choices) will be provided to support adherence to the recommended advice about sustainable and healthy lifestyles, respectively. Recipes will be provided based on guidelines set by the Swedish Food Agency [36] for the control arm, and recipes contributing to a maximum of 0.5-1.5 kg of CO_2e per portion developed by the Swedish World Wildlife Fund [37] and the Swedish consumer Agency [38] will be provided to the intervention arm. During the workshops, participants will be served lunch in line with the nutritional recommendations of the NNR [20], which is rich in plant-based food such as vegetables, legumes, seafood, and lacto-ovo-vegetarian options.

In addition, the individual-level education, instruction, and motivational factors for behavior change will be put in the context of environmental and organizational prerequisites for behavior change during workshops 1-4. This will be followed up during the fifth workshop in the intervention study when both arms will also be asked to use the research-supported Stanford Healthy Neighborhood Discovery Tool smartphone app (Discovery Tool) [39,40] to document contextual facilitators, barriers, or missing components in their work-related environments with regard to sustainable and healthy lifestyle. Barriers or problems in the workplaces' physical, social, and organizational environment will be identified and solutions for change will be discussed and implemented during the final workshops for the intervention and control arm, respectively.

The Intervention Arm: Sustainable Lifestyle

The participants in the sustainable lifestyle arm will be instructed to follow the current dietary and physical activity recommendations of the Food and Agriculture Organization of the United Nations, WHO, and NNR [6,20,22], as well as to adopt proenvironmental behaviors, defined as actions that minimize harm to the environment and combat climate change [41]. They will also be encouraged to increase active transportation to and from work, such as walking or biking [22]; use active transportation (walking) in and around the office;

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and break up prolonged sitting. The participants will be instructed to consume organically produced food to the highest possible degree and select food items that generate low amounts of greenhouse gas emissions by reducing their intake of red and processed meats.

The Control Arm: Healthy Lifestyle

The participants in the healthy lifestyle arm will be instructed to follow the dietary recommendations by NNR [20]. In brief, they will be instructed to increase the intake of fruit and vegetable to at least 500 g per day and follow the recommended distribution of energy from macronutrients, that is, energy coming from fat, protein, and carbohydrates, as well as general recommendations about the "plate model," the combination of food on the plate, to adhere to the recommended intake. Additionally, participants will be instructed to engage in physical activity corresponding to at least 150 to 300 minutes per week of moderate to vigorous intensity, according to the WHO and NNR [20,22]. Moderate-intensity activities include brisk walking, raking the yard, or biking to work, whereas vigorous activities comprise climbing stairs, jogging, or running [22,42].

Questionnaire Data

We will use self-administrated web-based questionnaires (Multimedia Appendix 4) to assess quantitative data about study participants and lifestyle factors. The questionnaires are implemented in the online system Survey Generator by Alstra, and a unique and personal link to the questionnaire will be sent to each participant by email. The questionnaires are the same for both the intervention and control arm.

Dietary intake will be assessed using the food frequency questionnaire Meal-Q, developed and validated by us [28,29]. Meal-Q covers five domains of food consumption: (1) habitual intake of food items, dishes, and beverages including alcoholic beverages; (2) portion sizes; (3) eating behaviors; (4) meal patterns; and (5) supplements. Photos of (1) rice, potatoes, and pasta; (2) meat, chicken, fish, and vegetarian substitutes; and (3) vegetables are used to estimate portion sizes. For all other food items, a standard portion size will be used. Data from Meal-Q will be converted to a daily intake of approximately 50 nutrients by linkage to the National Food Composition Table [43] to generate the average intake of nutrients per person and day.

Also, life cycle assessment will be used to assess the carbon footprint of food consumption, covering the entire "cradle-to-grave" impact of products, and expressed as kilogram CO_2e per kilogram of food products (kg CO_2e/kg) [44]. In brief, we have collected data from life cycle assessment studies aiming at representing the average consumption pattern in Sweden, and each food item in the dietary questionnaire Meal-Q has been assigned a specific CO_2e value and generates an average daily value of kg CO_2e per person [45]. The dietary questionnaire also includes questions about the consumption of organic products, both with the type of food groups or products that are consumed as organic versions and the proportion of organic versions within each food group or product.

Physical activity will be assessed using Active-Q, developed and validated by us [30,31]. Active-Q covers five domains of activity: (1) daily occupational activity; (2) transportation to and from daily occupation; (3) leisure-time activity; (4) exercise; and (5) sleep. Participants report the type, duration, and frequency of various activities in each domain. Data from Active-Q are used to calculate the time spent at different activity levels, daily total metabolic equivalent tasks, and energy expenditure [30,46]. Also, Active-Q includes questions about active transportation, such as walking and biking, to and from daily occupations.

Urinary Pesticide Residuals

To get an objective measure of the consumption of organic food, we will collect urine samples at baseline and at the end of the study to assess the excretion of pesticide residues. Participants will be asked to collect the first urine in the morning (between 6:00 and 8:00 AM) in 50 mL FALCON polypropylene containers and store it cold until the workshop later the same day (between 11.30 AM and 12:30 PM). Thereafter, all samples will be transported on ice to the Swedish Environmental Research Institute, where samples are to be stored at –80 ˚C until further analysis according to gold standard methods. The results will be calculated as µg pesticide/g creatinine to adjust for differences in urinary concentration.

Anthropometrical Assessments

For participant characteristics and calculation of BMI, standardized procedures and equipment will be used to measure participant height (cm) by stadiometer Seca 213 (seca) and body weight (kg) by a bioelectrical impedance (BIA) Tanita BC-418 MA Multi-Frequency segmental body composition analyzer (Tanita) [47]. Data on body composition will be given to the participants as an incentive to join the study but will not be included in future data analysis.

Photo and Narrative Documentation of Organizational Factors

The Stanford Healthy Neighborhood Discovery Tool smartphone app (Discovery Tool), based on the Our Voice citizen science framework [39], will be used during the fifth workshop of the sustainable and healthy intervention to document elements in the physical and organizational environment that either help or hinder employees' attempts to be active and eat in healthy ways at work. Participants in the intervention arm will be instructed to take photos of barriers and facilitators for a sustainable lifestyle at or near the office, whereas the control arm will document barriers and facilitators for a healthy lifestyle, for 1 week. The app prompts the participants to add a text narrative explaining each photo. This makes it possible to highlight positive and negative aspects of the work environment, as well as suggest improvements and things that are missing. The participants can also leave a reaction to the photo in the form of positive or negative smiley faces. After taking photos, the participants upload the photos and accompanying Discovery Tool data to a secure server at Stanford University in anonymized form. From there, study personnel will access the data and download it to a local server at Mälardalen University. The participants in both intervention arms will discuss the photos

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at the sixth workshop of the intervention and create a list of 3-4 prioritized actions to be made until the follow-up workshop 7, which is 2-3 months after the intervention. This way, the participants can impact their everyday environment on an organizational level to facilitate a sustainable and healthy lifestyle, respectively. Discussions and comments during the workshops will be noted and transferred to electronic format. The analysis of photographs, audio narratives (voice-to-text), and additional comments are to be analyzed through the "By the People" Our Voice citizen science method [48-50], followed by a content analysis [51] to quantify and analyze the presence, meanings, relationships of certain words, themes, or concepts. One of the research team members will take the lead in coding, which will be reviewed and discussed by the remaining team members. Thus, the "Our Voice" method amplifies the voices and perspectives of participants throughout the scientific process [52], which ensures the trustworthiness and credibility of the results.

Statistical Analyses

Data analysis will be performed according to the intention-to-treat principle [53], and all quantitative data will be analyzed using R statistics (R Foundation for Statistical Computing). Linear mixed-effects models [54] are planned for the analysis of intervention effects for numerical variables with a Gaussian distribution. These models are particularly suitable for repeated measures and can adeptly handle unbalanced groups. Linear mixed-effects incorporate both fixed and random effects, providing a robust method for accurately representing nonindependent data structures. For numerical variables with non-Gaussian distributions, the analysis will be conducted using generalized linear mixed-effects models. Generalized linear mixed-effects models are an extension of the generalized linear model in which the linear predictor contains random effects in addition to the usual fixed effects [54,55].

Power Calculations and Randomization

Participants working in the targeted offices will be cluster-randomized based on the office's geographic location by using a computer-generated random number generator in the statistical software R version 4.3.2 or later (Multimedia Appendix 5) [56]. Based on simulations derived from the pilot study CLEAR 2018 (unpublished data) using diet-related CO_2e expressed as kg/day/person derived from Meal-Q, where we have an effect size of η^2=0.11 for the interaction, a sample size of 40 observations in each arm at each assessment is indicated for 80% power. The estimated sample size was based on the interaction effect between control and intervention arms on CO_2e in a linear mixed model maintaining a significance level of 5% from the CLEAR 2018 study. We assume a dropout rate of 10% to 15% after baseline assessment, and therefore, we will recruit 47 people to each arm, in order to have at least 40 at the end of the study. If the dropout rate in this study is less than 10%, no particular method will be used to account for attrition.

Research Hypothesis

The study hypothesis is to investigate whether providing information about sustainable living encourages individuals to adopt more nutritious dietary habits and increase their levels of physical activity, as compared to receiving information solely centered around health-related recommendations for dietary intake and physical activity. The hypothesis will be tested among office workers to explore the workplace as an arena for health promotion.

Primary Objective

The primary objectives are to examine the amount of change in the consumption of nutrients (fat, protein, carbohydrates, and fibers), more climate-friendly foods (increased intake of plant-based food and less dairy, red and processed meat, diet-related CO_2e), more organic food, and increased practice of active transportation and related environmentally friendly behaviors. This will be evaluated by studying 1 variable at a time plus creating aggregated variables (the sums of all servings of fruits and vegetables expressed as servings per day), as well as creating a Sustainable Lifestyle Index, where each variable will be scored and summed to derive an overall score for each person [57], where higher scores indicate a more sustainable lifestyle. Finally, we will study the excretion of pesticide residues in urine as a validation of the consumption of organic food and explore if the excretion differs between the arms after the 8-week intervention.

Secondary Objectives

Secondary objectives cover the evaluation of the participants' workshop attendance rate; own goal setting; monitoring of behavior change (goal importance, self-efficacy, outcome expectations, and goal fulfillment); and supporting factors and obstacles regarding manager, colleagues, facilitating researchers, and family to study if there are any differences between the intervention and control arms (Multimedia Appendix 6). Also, data from the Discovery Tool app will be used to study if participants in the 2 arms identified different facilitators and barriers in the built, social, and organizational environment. Moreover, we aim to study if the intervention group reported a greater level of change in opinions and behaviors when it comes to environmental and climate aspects of their lifestyle, as compared to the control arm.

Results

Funding for this study was granted by the Knowledge foundation (KKS) in October 2020 and approved by the Swedish Ethical Review Authority in June 2021, with an amendment approved in September 2022. The start of the study and recruitment of research team members were delayed due to the ongoing COVID-19 pandemic in 2021. However, we started informing potential study participants about the study during the spring of 2022 and were able to start the recruitment of participants and data collection in August 2022 (iteration 1), and the second round of data collection (iteration 2) started in March 2023. Iterations 1 and 2 will be referred to as the pilot phase of the SOFIA study.

Groups of 5 to 15 participants were included in the intervention and control arms, respectively, during each iteration of the data collection, and the data collection will continue in the coming years. As of June 2024, a total of 37 participants have been recruited, of which 21 were included in the intervention arm

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and 16 in the control arm. The dropout after randomization was 2 in the intervention arm and 2 in the control arm, resulting in data from 19 participants in the intervention arm and 14 in the control arm, and a dropout rate of less than 10%. A majority of the participants are female (24/33, 73%) and are working in company B (22/33, 67%). The results of the pilot phase are expected to be published in 2024 or 2025.

Discussion

Principal Findings

This study aims to increase the understanding of the effectiveness of promoting a sustainable lifestyle to motivate behavioral change toward more nutritious food habits and increased physical activity, as compared to providing information based exclusively on health-related arguments in line with recommendations for food habits and physical activity. By targeting motivation, capabilities, and opportunities based on the behavioral change wheel model [58], we intend to increase the effect of the intervention in this specific context; moreover, it improves the understanding of behaviors in relation to the workplace environment [32]. A potential primary finding of this study would be that the intervention arm that received information about a sustainable lifestyle improved their food habits and physical activity level equally, or more, as compared to the control arm receiving information about health-related recommendations. Additionally, it is anticipated that the study will show that a shift to a sustainable lifestyle will lower diet-related CO_2e emissions and reduce the excretion of urinary residuals of pesticides to a larger degree in the intervention arm than in the control arm.

A novel feature of this study is the use of the workplace as an arena for health promotion, and in particular office workers, a group known to be sedentary at work [59]. A substantial proportion of the adult population spends a significant amount of time at work each day, and the advantage of an office-based intervention is that many individuals can participate simultaneously at work [23,60]. Moreover, from the employee's perspective, these types of interventions are convenient and easily accessible and allow employees to interact and support each other in their efforts to undertake behavior changes [61]. Full-time employees spend up to 60% of their waking hours at work [62] and typically return repeatedly to the same location, providing a significant opportunity to deliver health interventions. Recent review articles show that multicomponent workplace dietary interventions are effective but also an unutilized area to positively influence dietary intake and health outcomes among office workers [63]. However, the intervention needs to be tailored to the workplace and use behavioral and cognitive strategies to be successful [64,65]

In addition, we focus on the individual's behavior change as well as features on an organizational level to facilitate or hinder a sustainable or healthy lifestyle at work. By implementing a citizen science methodology within the trial, the participants (citizen scientists) collect data using the app, the Discovery Tool; are involved in analyzing the data and formulating a list of actions; and contacts managers to bring about changes in their workplace.

Comparison to Prior Work

We are not aware of any similar work, but a recent randomized controlled trial was conducted to assess the effects of an app-based intervention to improve the dietary intake of people with type 2 diabetes [66]. The intervention lasted for 12 weeks, with each week covering a new diet-related topic, with emphasis on the recommended intake of fruits, vegetables, legumes, and whole-grain products and reduction of red and processed meat. Although the primary aim was not to reduce diet-related greenhouse gas emissions, nor did the intervention study include information about carbon footprint, it was hypothesized that behavior changes toward more healthy food choices, would also result in lower emissions of CO_2e expressed as kg/day/person. However, ad hoc analyses of CO_2e did not show any differences between the intervention and the control arm.

Strengths and Limitations

A strength of the study is the low dropout rate, indicating that the participants found the study engaging and motivating. However, the pilot phase of the intervention study is relatively small and targets office workers at progressive companies, of which most are well educated and interested in healthy behaviors. Thus, it potentially leaves limited room for improvement over the 8-week intervention. Also, we will collect data related to a large number of exposures that may introduce the risk of chance findings.

Future Directions

As of the summer of 2024, the data collection of the pilot phase of the SOFIA study has ended, and the analysis of data is ongoing. A continuation of the recruitment process is planned for the coming years until the target number of participants is met. For now, this study protocol may serve as a framework to guide both scholarly research and the implementation of lifestyle interventions in office contexts. We anticipate that the company partners, where the SOFIA intervention was conducted, may implement aspects of the study to bring about change in their organizations. Additionally, future studies should include more diverse groups of employees, for example, from the public sector as well as blue-collar workers

Conclusions

In conclusion, given the ongoing climate change, negative environmental effects, and the global epidemic of metabolic diseases, a sustainable lifestyle among office workers holds an important potential to counteract this trend. There is an urgent unmet need to test the impact of a sustainable lifestyle intervention on food intake, physical activity, and environmental and climate-friendly behaviors. Thus, this study protocol responds to a societal need, by covering behavior changes of importance for successful implementation of sustainable lifestyle habits in an office setting.

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Acknowledgments

All authors contributed to the work. KB and OHU designed the study, created the educational material, collected data, and drafted the manuscript. OHU developed the program theory and intervention functions and provided figures for the manuscript. AT provided power calculations and R-syntax for randomization. JF and OHU designed and created the questionnaire for goal setting and monitoring of behavior change based on the theoretical perspective. ACK contributed with access to the Discovery Tool and input regarding citizen science. All authors contributed to the revision of the manuscript and have read the final version. The authors are grateful for careful language editing by Susan Stetson Clarke.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Themes for workshops 1-5 for the experimental and control arms.
[DOCX File , 17 KB - resprot_v13i1e57777_app1.docx]

Multimedia Appendix 2
Program theory.
[PDF File (Adobe PDF File), 110 KB - resprot_v13i1e57777_app2.pdf]

Multimedia Appendix 3
Intervention functions.
[DOCX File , 22 KB - resprot_v13i1e57777_app3.docx]

Multimedia Appendix 4
Screenshot showing portion sizes of food in the web-based dietary questionnaire.
[DOCX File , 544 KB - resprot_v13i1e57777_app4.docx]

Multimedia Appendix 5
R-syntax for randomization.
[DOCX File , 19 KB - resprot_v13i1e57777_app5.docx]

Multimedia Appendix 6
Questionnaire for goal setting and monitoring of behavior change translated to English.
[DOCX File , 33 KB - resprot_v13i1e57777_app6.docx]

Multimedia Appendix 7
Approved grant proposal.
[PDF File (Adobe PDF File), 198 KB - resprot_v13i1e57777_app7.pdf]

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Abbreviations

CO2e: CO2 equivalents
NCD: noncommunicable disease
NNR: Nordic Nutritional Recommendations
SOFCO: Concepts for the Sustainable Office of the Future
SOFIA: Sustainable Office Intervention
WHO: World Health Organization

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Protocol

Efficacy and Implementation Planning Across the Veterans Affairs Polytrauma System of Care: Protocol for the REACH Intervention for Caregivers of Veterans and Service Members With Traumatic Brain Injury

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Abstract

Background: The responsibility of care for Veterans and Service Members (V/SMs) with traumatic brain injury (TBI) often defaults to informal family caregivers. Caregiving demands considerable knowledge, skill, and support to facilitate the health and well-being of V/SMs and themselves. Persistent and common TBI caregiver issues include strain, depression, and anxiety. While evidence-based, brief interventions have been developed and implemented for family caregivers in Veteran neurodegenerative populations, few interventions have been developed, adapted, or tested to support the unique needs of caregivers of V/SMs with TBI.

Objective: This study will adapt and test an evidence-based, personalized, 6-session telehealth caregiver intervention, “Resources for Enhancing All Caregivers’ Health” (REACH), to meet the unique needs of caregivers of V/SMs with TBI. If successful, a community-based participatory research team will develop an implementation plan to roll out REACH TBI across the national Veterans Affairs Polytrauma System of Care.

Methods: This mixed methods, crossover waitlist control clinical trial will use a Type 1 Hybrid Effectiveness-Implementation approach to adapt and then test the effects of REACH TBI on key TBI caregiver outcomes.

Results: This study was funded by the Department of Defense in September 2023. Participant enrollment and data collection will begin in 2024.

Conclusions: If effective, REACH TBI will be the first evidence-based intervention for caregivers of V/SMs with TBI that can be scaled to implement across the Veterans Affairs Polytrauma System of Care and fill a notable gap in clinical services.

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KEYWORDS

traumatic brain injury; telehealth; caregiver; methodology; veterans; service members

Introduction

Between 2000 and 2021, a total of 444,328 US military Service Members were diagnosed with traumatic brain injury (TBI) [1], leading to TBI's designation as the "signature injury" of Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn [2,3]. Between 7% and 23% of OEF/OIF/Operation New Dawn-era Veterans and Service Members (V/SMs) have experienced a TBI [2-5]. In 2009, the annual health care costs for OEF/OIF Veterans with TBI were almost 4 times higher than those without TBI (US $5831 vs US $1547), and the highest costs (US $7974) were shown in those with TBI, pain, and posttraumatic stress disorder (Taylor et al [5]). V/SMs receiving services in the Veterans Affairs (VA) have over 93,000 documented TBIs [6]. TBI can result in a constellation of long-term physical, cognitive, and neurobehavioral impairments [7-10]. Recovery time is variable, and many symptoms remain years or decades after injury, especially with more severe injuries [11]. As a result of these long-term consequences and care needs, rehabilitation medicine now unequivocally considers TBI a chronic health condition requiring long-term management and support [12].

Informal family TBI caregivers experience a myriad of unmet emotional, instrumental, and professional support needs regarding symptom management [13], and research has shown these high rates of unmet needs are closely associated with mental health problems in caregivers [14]. Caregivers often receive little formalized training or support in caregiving and symptom management, and physical symptoms in individuals with TBI are associated with greater family household needs, and emotional symptoms with greater family informational needs [15]. Among caregivers of V/SMs with TBI, over 40% of their needs go unmet with caregiver peer support, respite from caregiving, and help with caregiver negative emotions being the least often met needs; greater environmental barriers keeping the V/SM from participating in activities and the presence of V/SM mental health issues translate into more unmet emotional, community, and professional support needs [16]. Despite some parallels to civilian populations with TBI, V/SMs can have unique features of TBI (eg, polytraumatic and blast-related) and high rates of particular comorbid conditions (eg, posttraumatic stress and pain) that impact V/SMs' health and needs [17-19] and may require additional and unique caregiving skills. Few military family members expect to provide the sort of long-term care that may be required by these complex injuries [20], and lack of training or formal support can compound caregiver strain and emotional distress [21]. Over time, military TBI caregivers experience declines in physical and mental health [22], reporting worse health than the general population [23]. Higher levels of TBI symptoms experienced by V/SMs are associated with greater caregiver strain and distress [24], which are in turn associated with caregiver grief and depression [24,25].

At present, there is no standardized, evidence-based, and widely implemented intervention for caregivers of V/SMs with TBI. Thus, there is a significant need for an evidence-based, portable caregiver telehealth intervention that is (1) adapted to TBI-specific needs, (2) relevant to caregivers of younger V/SMs with a range of neurobehavioral symptoms and strong potential for a positive recovery trajectory, and (3) readily accessible in rural and resource-limited communities. Resources for Enhancing All Caregivers' Health (REACH) VA [26] is a successful evidence-based, 4- or 6-session telehealth behavioral intervention for caregivers and a VA national program for dementia [27], spinal cord injuries and disorders [28], multiple sclerosis [29], and posttraumatic stress disorder caregivers [30]. REACH has never been tailored specifically for or tested in caregivers of V/SMs with TBI. This study protocol describes the adaptation, evaluation, and implementation of a telehealth intervention, REACH TBI, for caregivers of V/SMs with TBI during the chronic phase of recovery.

Methods

Study Design

This study is a prospective mixed methods (greater emphasis on quantitative over qualitative data), type 1 Hybrid Effectiveness-Implementation study [31,32], with a crossover waitlist control clinical trial [33]. This is a multi-aim, multi-phase, VA-wide clinical trial that will include (1) engagement with caregivers of V/SMs with TBI and Polytrauma System of Care (PSC) clinicians to inform REACH adaptation for TBI, (2) a national waitlist control clinical trial, (3) development of an ambitious PSC implementation plan, and (4) a foundational community-based participatory research (CBPR) approach with stakeholders throughout every phase. Human-centered design (HCD) is a 5-step guiding framework integrating the study's 3 aims and overall methodology and is fundamentally about identifying and responding to human needs [34]. As applied to implementation science in health care, studies based upon it often attempt to (1) develop an understanding of people and their needs, (2) engage stakeholders from early on and throughout the design process, and (3) adopt a systems approach to address systematical interactions among the micro, meso, and macro levels of health care [34]. During the initial HCD Discover and Define phases, interviews will be conducted with intended users and stakeholders (eg, TBI caregivers and PSC clinicians). These interviews will construct a narrative of TBI caregiver needs, engage intended users in meaningful discussion about REACH TBI appropriateness, and identify likely implementation facilitators and barriers. Ideas, emerging themes, and recommendations generated will help transition to the Design phase. The Design phase will inform REACH TBI

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optimization to meet the unique needs of caregivers of V/SMs with TBI. The Validate phase will test the effectiveness of REACH TBI nationally and support the Implementation phase when we develop an implementation plan to roll out REACH TBI across the PSC in a successive grant. As is consistent with the HCD, evaluation, progress, and milestone assessments will ensure process and outcome measures are met. The study is expected to recruit over 18 months.

Setting

There are 4 research cores in this multicenter study. The University of Virginia (UVA; Charlottesville, Virginia) is the administrative core responsible for overseeing and directing the clinical trial in collaboration with multiple principal investigators leading the other 3 study cores. The James A. Haley Veterans' Hospital (Tampa, Florida) is the data core where recruitment and data collection will be conducted. Virginia Commonwealth University (Richmond, Virginia) is the intervention core where the REACH TBI intervention will be delivered via telehealth. The University of Utah (Salt Lake City, Utah) is the implementation core where evidence-based strategies will be developed to implement REACH TBI throughout the VA PCS. Additionally, the University of Tennessee Health Science Center Caregiver Center (Memphis, Tennessee) will inform intervention protocol development and train REACH TBI interventionists.

Intervention Development

Central to our team is the VA National Caregiver Center to leverage the foundational REACH [35] intervention—including its associated tools (eg, Caregiver Notebook and Risk Assessment), trainings, and delivery resources (Coach Manual [36] with scripts and checklists)—to accelerate a deployable REACH TBI protocol for clinical trial testing within 6 months of grant commencement. During the first 6 months of the grant timeline, adapting REACH for TBI will include extensive qualitative assessment involving CBPR engagement with subject matter experts (SMEs) and research team members throughout the PSC including caregivers of V/SMs with TBI, clinicians, clinical researchers, and administrators.

Participants, Recruitment, and Sample Size

The eligibility criteria for V/SMs with TBI and caregivers are the following: (1) age of 18 years and older; (2) English-speaking; (3) primary caregiver for a V/SM who sustained a TBI at least 6 months prior; (4) primary caregiver who has provided care for a V/SM with TBI for at least 6 months; (5) provide some level of daily supervision or assistance with either a physical, cognitive, or behavioral issue they think is likely related to TBI; (6) believe that at least half of their caregiving responsibilities are likely related to TBI rather than another health condition or conditions; and (7) endorse a score of at least high burden (a score of 8 or higher) on the Zarit Burden Inventory-4 [37]. The exclusion criteria are (1) no access to the telephone or internet-accessible device, (2) auditory impairment that would make telephone use difficult, and (3) have completed a previous version of the REACH intervention. Participants had to report some level of burden associated with caregiving [35] based on prior research showing that burdened caregivers were more likely to benefit from the REACH intervention [38]. These criteria have been used successfully in caregiver studies to identify a stressed population.

A power analysis was completed to determine the number of participants necessary to achieve 80% power on the primary outcome assuming 10% attrition [39]. Baseline scores will be used as a covariate in the model as this increases statistical power, given that baseline and follow-up scores are usually highly correlated, resulting in a reduction in the error term of the model [40]. Assumptions used in computations included equal sample sizes in each contrast group, equal variances and attrition, probability of type I error of .05, and 2-sided testing of the null hypotheses [41]. Accordingly, 55 participants will be randomized to each group (N=110). With this sample size, we will have 80% power to detect a Cohen *d* of 0.50 assuming a correlation of pre- and postintervention scores of 0.50.

Ethical Considerations

The UVA institutional review board (IRB) will be overseeing research activities carried out at all civilian research universities (UVA IRB-SBS Protocol # 6237). The University of South Florida (USF) is the reliance-agreement IRB of the James A. Haley Veterans' Hospital and will be responsible for the oversight of the work occurring at this VA Medical Center (USF IRB Study # 006569). Using the VA's corporate data warehouse, Veterans will be identified with a TBI diagnosis. Recruitment of their caregivers will be conducted remotely by research coordinators, who will screen potential participants for eligibility. Participants must give permission to be screened after hearing a study description that includes the components of informed consent including information about the study and the screening process itself. Study components will include a statement of the research (purpose, procedures), reasonably expected benefits to participants, and costs. The screening process components will include the duration of screening, alternatives, extent of confidentiality, and authorization for the release of protected health information for research purposes.

After the screening, consent forms, signed by the consenting research coordinator, will be emailed via secure Docusign (Docusign, Inc) or mailed with a postpaid return envelope, depending on the preferences of the caregiver. Informed consent will follow procedures of the UVA IRB (UVA IRB-SBS Protocol # 6237), USF IRB (USF IRB Study # 006569), and Research and Development Committee of the Tampa VA. Participants must give written or electronic informed consent before enrolling. During the informed consent call, the potential participant will be asked to read the informed consent and be given the opportunity to ask questions. A research coordinator will review all key aspects of the study with the potential participant and question to ascertain whether the potential participant has understood the information.

After consent is obtained and baseline data collected, participants will be randomly assigned to the immediate intervention group or waitlist control group. Each caregiver will be offered US $25 for each completed data collection and the exit interview for a total of US $100 (immediate intervention group) or US $125 (waitlist control group).

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Randomization

A block randomization schedule [42] (with 6 participants per block) will be created with a web-based computerized random number generator. The UVA research coordinator will maintain allocation concealment and eliminate possible selection or recruitment biases by keeping the randomization schedule concealed from the on-site research coordinator engaged in recruiting. The randomization schedule will be generated by the UVA research coordinator who will not have any contact with participants, and sequentially numbered sealed envelopes will be prepared prior to the recruitment of any participants. After the recruiting research coordinator determines eligibility for a prospective dyad and obtains informed consent, the UVA research coordinator will be notified and then open the next sealed envelope in the assignment sequence; the group assignment for that participant to one of the two groups will be revealed at that point. In this fashion, only the postdoctoral fellow interventionist assigned to provide REACH TBI will know the group assignment of a specific TBI caregiver. Because the intervention will be delivered by trained personnel who will have minimal contact with the waitlist control group (other than during the randomization call when the caregiver is informed of their study arm), we anticipate minimal overlap or "contamination" between these interventions and waitlist control group participants. Although participants and interventionists cannot be blinded during the study, all research staff involved in data collection and biostatistics staff involved in formal statistical analyses will be blinded to reduce bias and preconceptions in collecting and analyzing data.

Intervention Implementation

The REACH TBI intervention will be carried out by a postdoctoral fellow interventionist who will be trained with didactic and hands-on content, knowledge assessment, skills practice, and role-playing for certification. Interventionist training includes strategies for overcoming problems associated with telephone interactions such as decreased cues and technological difficulties. The interventionist will use a mock caregiver to complete a role play of 2 key areas of the intervention: Target Concern Plan and Cognitive Reframing [43]. The Certification Role Play Observation Checklist for Individual Sessions used by the caregiver center will be used for the role play. The checklist includes behaviorally anchored ratings of specific procedural techniques (eg, correct use of forms) and clinical skills (eg, active listening). Performances will be observed for content and process. Feedback will be individually provided for each of the items listed on the checklist. The structure of the feedback will include positive behavior demonstrated; what behaviors should have occurred or occurred and were not in keeping with the protocol; and the rationale for the behavior that was expected. To assess intervention benefits accurately, early sessions for each interventionist will be monitored by study investigators, with caregiver permission. The investigators will provide feedback to the interventionist immediately after each session, focusing on fidelity, interventionist delivery, and evidence of caregiver receipt and enactment.

Intervention

REACH TBI will be delivered by telephone in 6 individual hour-long sessions over 3 months, about every 2 weeks by a trained and certified interventionist. The REACH TBI sessions incorporate evidence-based components that have been shown to be crucial to successful caregiving interventions including problem-solving, cognitive reframing, and stress management [35]. The interventionist and caregiver negotiate the concerns to be addressed using those identified by the risk assessment [26,36]. Using problem-solving techniques, the interventionist and caregiver attempt to find effective and workable solutions to a specific target concern that is causing strain and stress for the caregiver, using the Caregiver Notebook. The target concern could be something related to the caregiver, such as asking family members for help, or to the care recipient such as bathing or driving. In this way, the intervention accommodates whatever concern the caregiver is experiencing—from activities of daily living or instrumental activities of daily living challenges to caregiver stress, guilt, or grief.

Each session is structured to build on the previous session using the protocol. Although tasks are structured and predetermined (eg, problem-solving), the focus of the task is a risk area (eg, safety), concern (eg, lack of support), or patient problem (eg, angry outbursts) that the caregiver has identified as troubling. One of the main foci of REACH is problem-solving. The interventionist teaches the ABC (Antecedent, Behavior, Consequences) method of problem-solving, and the caregiver and interventionist identify action-oriented behavioral strategies to address caregiving problems or V/SM behaviors using topics from the Caregiver Workbook in a Targeted Concern Plan. An outline of the intervention can be seen in Table 1.

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Table 1. Outline of the REACH[a] TBI[b] intervention.

REACH TBI session or topic	Overview of content and structure
Assessment and session 1: stress management	• Caregiver assessment • Introduce intervention and review Caregiver Notebook • Discuss stress • Introduce stress management technique, signal breath
Session 2: problem-solving	• Introduce session • Review or modify the last session commitment, signal breath • Provide general information about the Veteran or Service Member's health condition • Present safety material • Introduce health care issues and health guide • Problem-solve—target concern #1
Session 3: cognitive reframing	• Review the health guide and safety • Review or modify problem-solving plan #1 • Make commitment for problem-solving plan #1 • Introduce cognitive reframing
Session 4: problem-solving or cognitive reframing or stress management	• Review the health guide and safety • Determine caregiver goal attainment for cognitive reframing and review or modify, if needed • Review or modify problem-solving plan #1 • Determine caregiver goal attainment for problem-solving plans and review or modify, if needed • If appropriate, identify target concern #2 • Introduce problem-solving plan #2 or • Work on cognitive reframing thought record
Session 5: problem-solving, cognitive reframing, stress management	• Review the health guide and safety • Determine caregiver goal attainment for any problem-solving plans and review or modify • Review or modify cognitive reframing • Offer stress management technique
Session 6 and Closure: problem-solving, stress management, and cognitive reframing review	• Review Caregiver Notebook • Review safety recommendations • Review health and use of health guide • Review caregiver well-being • Review stress management techniques and strategies that worked • Review cognitive reframing techniques • Review problem-solving plans covered and strategies that worked

[a]REACH: Resources for Enhancing All Caregivers' Health.

[b]TBI: traumatic brain injury.

Data Collections

Quantitative Data Collection

Demographic and baseline data will be collected either by telephone or Qualtrics (Qualtrics International Inc) after enrollment and before randomization. Baseline data collection includes validated measures of key TBI caregiver outcomes such as strain, depression, anxiety, self-efficacy, and health care frustration. Follow-up data will be collected at 3 and 6 months from all participants and at 9 months from waitlist control participants using the same validated measures as during the baseline data collection. The study timeline is illustrated in Figure 1.

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Figure 1. Waitlist control clinical trial timeline. REACH: Resources for Enhancing All Caregivers' Health; TBI: traumatic brain injury.

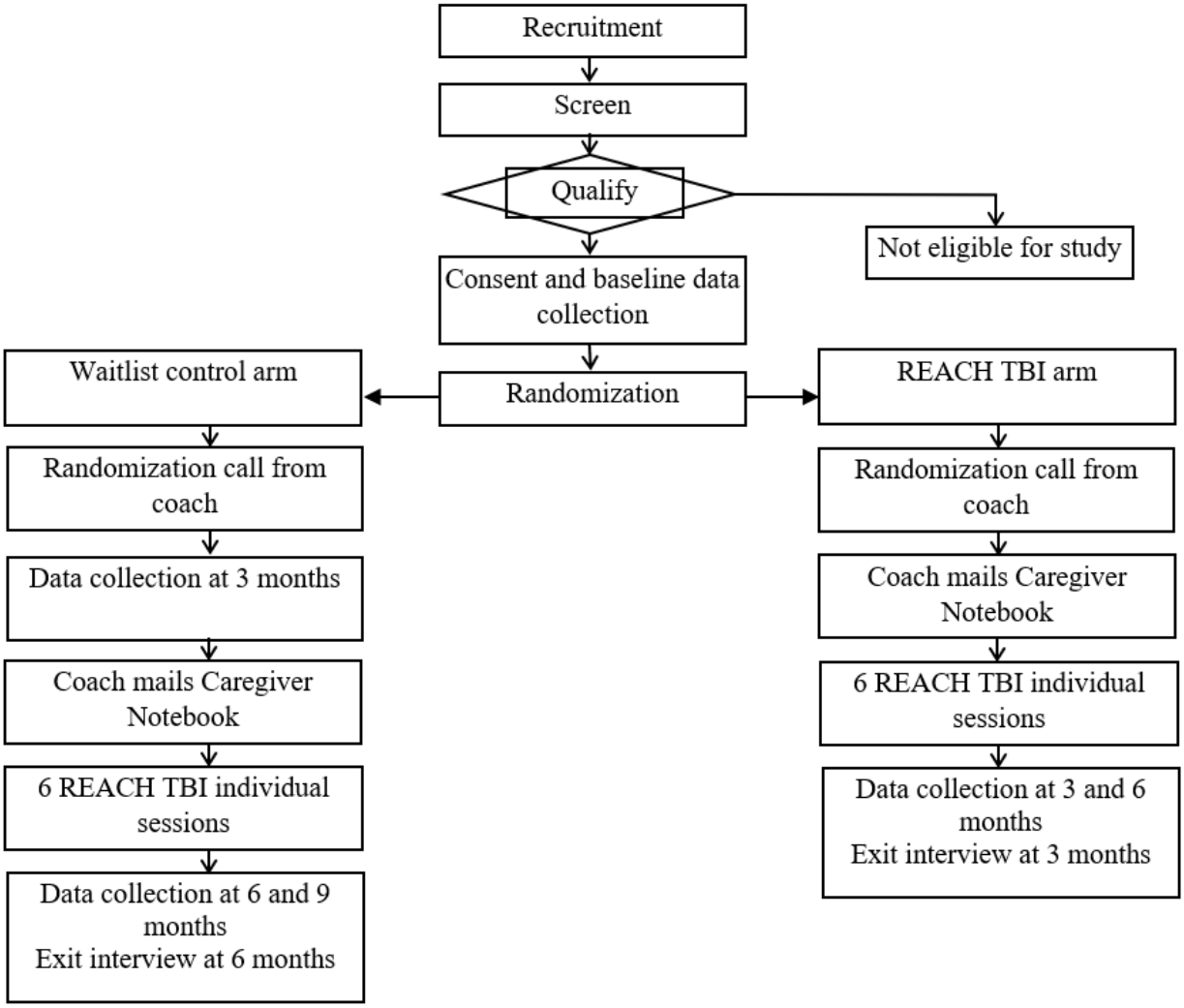

Qualitative Data Collection

A qualitative telephone exit interview will be conducted with all participants at the 3-month follow-up, after their last session, to evaluate their experiences using REACH TBI with a focus on caregiver satisfaction, usefulness, benefits, challenges, and implementation.

Data Management

ID numbers will be used for all participants rather than participant names. Once analytic files are cleaned, all identifiable private information associated with an individual will be deleted from the analytic files, and analysis will be limited to data that are identified by an ID. Authorized project staff members will be assigned an active, unique user identification code and password to the server or network containing the data. The outcome measures will be compiled into a single survey format in Qualtrics and collected at baseline, 3, and 6 months from all participants and at 9 months from waitlist control participants.

Outcome Measures

TBI Caregiver Quality of Life Caregiver Strain-short form 6a assesses caregiver strain [44]. A total of 6 items are scored from 1 (never) to 5 (always), with higher scores indicating greater strain. Among caregivers of V/SMs with TBI, internal consistency is α=.88, test-retest reliability is r=0.80, and convergent validity with mental health is r=–0.54 [45].

PROMIS (Patient-Reported Outcomes Measurement Information System) Emotional Distress—Depression—short form 8a assesses caregiver depression [46]. A total of 8 items are scored from 1 (never) to 5 (always). Scores range from 8 to 40 with higher scores indicating greater depression. Among caregivers of V/SMs with TBI, internal consistency is α=.94, test-retest reliability is r=0.70, and convergent validity with mental health is r=–0.73 [45].

PROMIS Emotional Distress—Anxiety—short form 8a assesses caregiver anxiety [46]. A total of 8 items are scored from 1 (never) to 5 (always). Scores range from 8 to 40 with higher scores indicating greater anxiety. Among caregivers of V/SMs with TBI, internal consistency is α=.89, test-retest reliability is

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r=0.65, and convergent validity with mental health is *r*=–0.66 [45].

PROMIS General Self-Efficacy assesses caregiver self-efficacy [47]. A total of 10 items are scored from 1 (I am not at all confident) to 5 (I am very confident), with higher scores indicating greater self-efficacy. Internal consistency is α=.94, and convergent validity with optimism is *r*=0.58 [47].

TBI-Caregiver Quality of Life Health Care Frustration—Self—short form 6a assesses frustrations a TBI caregiver has had with health care services [48]. A total of 6 items are scored from 1 (not at all) to 5 (very much), with higher scores indicating greater frustration with services received. Among caregivers of V/SMs with TBI, internal consistency is α=.96, test-retest reliability is *r*=0.89, and convergent validity with caregiver strain is *r*=0.60 [48].

Data Analysis

Preliminary Analyses

Descriptive statistics will be computed for the total sample and stratified by treatment group for baseline participant characteristics. Means and SD (or medians and IQR) or counts and proportions will be calculated for continuous and categorical variables, respectively. In addition, an analysis of missing data will be conducted to examine factors that may be associated with the likelihood of missing data. Any factor found to be associated with the likelihood of missing data will be included in the final model.

Once assigned to a study arm, participants will be considered in the study, and we will follow an intention-to-treat approach (see below for details). Primary outcomes are measured for all participants at baseline, at 3 months, and after 6 months (or 9 months for the waitlist control group). We estimate the necessary sample size based on comparing groups at 3 months post randomization using baseline scores as a covariate.

Primary Quantitative Analyses

The intention-to-treat principle will be applied to all analyses. Once a participant is assigned to a treatment group, they will be included in the group in all analyses even if they end treatment or are lost to follow-up. Parallel analyses will be completed for each outcome. A linear mixed effects model [41] will be used to test the effectiveness of the REACH TBI intervention compared to a waitlist control initially for the primary outcome of caregiver strain. Contrasts will be coded to allow for tests of the mean difference between groups at 6 months postintervention and 3 months postintervention with 3-month measurements as the primary outcome. Each participant's baseline score on the outcome will be included in the model in addition to a random intercept and fixed effects of treatment, time, and the treatment-by-time interaction. To account for multiple testing, Hochberg's step-up procedure will be used to control the false discovery rate to .05. All analyses will be completed using the lme4 package [49] in the R statistical software (version 4.4.0; R Core Team).

Secondary Quantitative Analyses

Parallel analyses to those described in the primary analysis section will be completed for all secondary outcomes (eg, depression, anxiety, self-efficacy, and military health care frustration). In addition, group means will be compared at 6 months post randomization. Given that both groups will have been exposed to the intervention at this point, no difference between groups is expected. Finally, pairwise change within each group (eg, baseline vs 3 months and baseline vs 6 months within the control group) will be tested [41]. We expect that the treatment group will show improvement from baseline to 3 and 6 months post randomization but not between 3 and 6 months. For the control group, it is anticipated there will be no improvement or worsening between baseline and 3 months post randomization but will show improvement for comparisons of baseline and 3 months with 6 months post randomization.

Exploratory Quantitative Analyses

A moderation analysis [50] will be completed to examine how disability level and V/SM health conditions impact the effect of the intervention. Each variable and its interaction with treatment will be added separately to the linear mixed effects models described in the primary analyses section. If statistically significant interactions are found, results will be reported with the mean treatment effect, and ±1 SD on the moderator to improve results interpretability.

Qualitative Analyses

We will engage in content analysis [51] and use interview transcripts to sort descriptions, concepts, and central ideas into potential themes and concerns that occur repeatedly using the scrutiny techniques of repetitions and similarities and differences [52] and link themes to verbatim quotes [53]. Qualitative transcript data will be analyzed using descriptive content methods to identify domains or taxonomies about REACH TBI experiences. Content analysis will allow a priori coding framework derived from previous research literature and interview data to develop the coding scheme [51]. To adequately capture access determinants among participants, a qualitative codebook will be developed using deductive codes generated by construct relevance and inductively from interview data [54], as well as input from SME stakeholders (eg, TBI caregivers and PSC clinicians). Interview transcripts will be coded by the qualitative team using the codebook augmented by our SMEs to assess intervention satisfaction and implementation issues. Additional codes will emerge inductively from the interview data. The coding team will read 1 interview transcript separately and discuss the addition of new codes with examples. This process will continue with subsequent transcripts until no new codes are generated (code saturation) [55]. Intercoder reliability will be established when the coding team reaches at least 80% coding agreement [56]. Intercoder reliability will be routinely monitored to ensure consistency and limit potential drift in coding. Any discrepancies will be discussed and resolved among study staff during weekly meetings to ensure coding and analysis are completed on schedule or earlier. ATLAS.ti (version 22; ATLAS.ti Scientific Software Development GmbH), a qualitative analysis software program, will be used to manage and code interview text using a constant comparative approach.

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Coded text will be displayed in Excel (Microsoft Corp) spreadsheets to conduct a matrix analysis, a rapid assessment approach, which will be used to develop themes for the overall sample. Comparative matrices enable the identification of the most relevant, shared, and perhaps representative components, thereby enhancing the potential representation of the findings and allowing discernment of the most salient and representative experiences with REACH TBI identified by participants.

Human Participants Protections and Adverse Events

We do not anticipate any severe adverse events or major psychological, legal, social, or economic risks from study participation. However, we anticipate the following (uncommon) minor risks: (1) participants may experience discomfort or fatigue in answering questions; (2) in the intervention, some of the discussion topics may be upsetting, and (3) if using a landline telephone, there will be no charges for calls from the REACH interventionist, but if using a cellular phone, calls by the REACH interventionist may use cellular minutes, and the participant may incur charges, depending on the user plan.

We will have multiple checks against adverse events. Alerts may be recognized during data collection, outside scheduled contacts, and during intervention sessions. Alerts or adverse event standardized procedures will address suicidal ideation, clinical depression levels, and safety risks. The procedure ensures that any alert is discussed immediately with a supervisor and appropriate action is taken. Alerts identified during data collection will be placed in the participant's secure shared folder and an email sent to the interventionists and principal investigator (PI). Alerts will be discussed by the interventionist either during the randomization call for waitlist control participants or during the randomization call and session 1 for treatment-arm participants. The procedure ensures that any alert is discussed immediately, and appropriate action taken. For example, for clinical depression levels, we will follow up with the participant who will also be advised to contact their physician or other resource. All alert events will be recorded on the project alert form that includes the event date, whether the event is treatment-related, and the date the event was addressed. Interventionists will address alerts with the caregivers, complete the alert form, upload it to the participant's secure shared folder, and email the PI that the alert was addressed. If appropriate, the PI will report the event to the IRB. Alerts, adverse events, and referrals will not cause a participant to be dropped from the study. Any contact outside data collection will be documented (time, reason, actions taken, and initiator) on an additional contact tracking form.

To ensure prompt reporting of research-related events, we will follow IRB guidelines. As soon as possible but in all cases within 1 to 5 working days, the PI will report to the IRB any changes to the protocol that were taken to eliminate hazards to a research participant, deviations to protect the physical well-being of a participant in an emergency, and any serious adverse event, related or possibly related to the research regardless of whether the event occurred during the study. Participants will have access to call study personnel and the PI during normal business hours to report concerning effects. A more thorough investigation of adverse effects will be performed as needed. While we do not anticipate serious adverse events that call for emergency care, if emergency care is required during a study visit, study staff will contact emergency services, and study staff will work with the participant to obtain such care. It will be emphasized to participants that they can take a break or discontinue either data collection or the REACH sessions at any time. An individual's participation in the study will be terminated if the participant wishes to stop their participation in the study or in response to any significant adverse event determined by staff to warrant stopping study treatments. If the V/SM objects to their caregiver participating, this can also be a reason for discontinuation.

Results

This study was funded by the Department of Defense in September 2023. Participant recruitment and data collection are expected to begin in 2024. Once REACH TBI effectiveness is demonstrated, the intervention will need to be spread throughout the VA PSC. Rigorous and systematic implementation planning will start in 2026 to broaden the impact of this clinical trial by rolling out REACH TBI among TBI clinicians across the PSC and sustaining intervention delivery.

Discussion

Principal Findings

Presently, there is no formalized or structured intervention for caregivers of V/SMs with TBI at a national level, and the existing services provided to caregivers for this population tend to be spread unevenly throughout the VA PSC. These gaps in services will be bridged by adapting the flagship program of the VA Caregiver Support Program's National Caregiver Center—the evidence-based REACH intervention—to be responsive and relevant to the needs of caregivers of V/SMs with TBI. This intervention has the potential to serve the caregivers currently supporting the needs of nearly half a million V/SMs with TBI, remediating the adverse strain and mental health effects of caregiving, as well as improving self-efficacy and health care frustration. Supporting caregivers directly impacts V/SMs with TBI: higher caregiver health-related quality of life is associated with better functioning in V/SMs with TBI [57], and better caregiver outcomes directly impact the quality of informal care they can provide [58]. The REACH TBI intervention represents a substantial improvement over the current complete lack of a TBI-tailored, standardized but flexible, and evidence-based telehealth intervention available for caregivers of V/SMs with TBI. Further, the telehealth delivery format of the intervention makes it highly suitable for caregivers in rural or other resource-limited environments. This intervention has the potential to increase resilience within caregiving families [59], sustain gains made in functional recovery through the PSC, and ameliorate the negative impacts of TBI-related disability for caregivers.

We foresee several potential limitations and have proactively developed strategies and alternatives to address these. To ensure fidelity of treatment delivery across multiple interventions, the multiple principal investigators will be highly involved in training and supervision of the interventionists on an ongoing

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basis including regular meetings among these study team members and multiple checks on the reliability and fidelity of the treatment delivery. To support caregivers' maximal engagement and retention in the trial, we will design the intervention to be responsive to new or ongoing emotional challenges among the participating caregivers, reasonably flexible to accommodate caregiver schedules and other life stressors or demands, and proactive in developing a structured retention plan. Finally, our team will be highly attuned to the complex needs of the V/SMs with TBI that might arise during the study, including detailed standard operating procedures to address behavioral health crises and referrals to appropriate services to address acute concerns within the VA Health Care System.

The near-term impact of this clinical trial will include multiple knowledge products advancing our options to prevent and treat complications resulting from TBI for V/SMs and their caregivers. The immediate outcome will include a manualized, highly portable intervention that can be delivered broadly by TBI clinicians. The intervention will include a resource companion, the REACH TBI Caregiver Notebook, which is being developed in consultation with subject matter experts in the areas of TBI, Military and Veteran health, and caregiving, as well as people with lived experience as TBI caregivers. This product will contain a wealth of information that will be relevant to caregivers of V/SMs regarding practical aspects of managing TBI, problem-solving, and reducing negative mood or affect. The long-term impact of this study is a standardized, evidence-based approach to supporting caregiving families for V/SMs with TBI throughout the entire PSC. This study will also catalyze a subsequent program of research focused on REACH TBI implementation (via subsequent grant proposals or formal PSC and Caregiver Support Program financial support to the caregiver center), to allow future evaluation of REACH TBI service utilization, cost, outcomes, and implementation. This study will provide a model for working from a CBPR framework to integrate perspectives of caregivers of V/SMs with TBI, clinicians who provide care to V/SMs with TBI, TBI clinical researchers, and PSC administrators in all phases of TBI intervention development and implementation.

Beyond its potential impact on the recovery and rehabilitation of V/SMs with a TBI and the well-being of caregiving military families, REACH TBI could be readily adapted and implemented in civilian health care systems. The modular nature of the training materials, the modifiability of the resource guide, and the digital platform to train a broad range of patient-facing staff throughout health care systems well positions REACH TBI to be used in a dual capacity among civilian populations.

Conclusions

This protocol will use a CBPR methodology to fill a critical gap in meeting the complex needs of V/SMs with TBI and their caregivers. This protocol will target upstream factors affecting adjustment to TBI as a chronic condition, provide solutions to families and communities to mitigate the negative impacts of TBI on V/SM psychological health and functional outcomes, reach V/SMs and caregivers in resource-limited environments via a telehealth modality, and support the uptake of evidence-based interventions at enterprise scale. By engaging key stakeholders throughout the development, testing, and planning to implement REACH TBI, we expect that the resulting intervention will be highly relevant to the target population, usable to a range of providers in multiple settings, and scalable to disseminate broadly.

Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review summary statement from the US Department of Defense.
[PDF File (Adobe PDF File), 133 KB - resprot_v13i1e57692_app1.pdf]

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Abbreviations

CBPR: community-based participatory research
HCD: human-centered design
IRB: Institutional Review Board
OEF: Operation Enduring Freedom
OIF: Operation Iraqi Freedom
PI: principal investigator
PROMIS: Patient-Reported Outcomes Measurement Information System
PSC: Polytrauma System of Care
REACH: Resources for Enhancing All Caregivers' Health
SME: subject matter expert
TBI: traumatic brain injury
USF: University of South Florida
UVA: University of Virginia
V/SM: Veterans and Service Members
VA: Veterans Affairs

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Protocol

Rationale, Design, and Intervention Development of a Mobile Health–Led Primary Care Program for Management of Type 2 Diabetes in Rural Thailand: Protocol for a SMARThealth Diabetes Study

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Abstract

Background: Noncommunicable diseases (NCDs), particularly diabetes and chronic kidney diseases, pose a significant health burden in Thailand, especially among socioeconomically disadvantaged populations. The existing primary health care system faces challenges in providing optimal care for NCDs due to inadequate primary care workforce. The SMARThealth program offers a technology-based solution to enhance NCD management through task-sharing among nonphysician health care workers.

Objective: This study aims to adapt and implement the SMARThealth Diabetes program in rural Thailand to improve diabetes management. The main objectives are to (1) adapt, validate, and integrate the SMARThealth Diabetes program for improving the management of type 2 diabetes mellitus at the primary health care level; and (2) to determine the feasibility and acceptability of the SMARThealth Diabetes program in rural communities of Thailand.

Methods: A pragmatic, type 2 hybrid effectiveness or implementation, parallel-group cluster randomized controlled trial of 12 months duration and involving 51 subdistrict health offices in rural communities of Kamphaeng Phet province, Thailand, will be conducted. The intervention arm will receive the SMARThealth Diabetes program, including workforce restructuring, clinical decision support system, and continuous performance monitoring, while the control arm will continue with usual practice. Data will be collected using the SMARThealth platform and will be stored on a server in Thailand. The primary outcome measure will be the change in mean hemoglobin A_{1c} (HbA_{1c}) measured at randomization and 12 months from randomization between the intervention and control clusters. Secondary outcomes will include the difference in change in albuminuria status, estimated glomerular filtration rate, systolic blood pressure, and low-density lipoprotein cholesterol level. The analysis for change in HbA_{1c} between baseline and end of study will be performed using linear mixed models. Any imbalances between the 2 arms will be addressed by sensitivity analyses. Additionally, a mixed methods process evaluation will be conducted to assess the implementation process, that will include in-depth interviews and focus group discussions, in addition to the quantitative data collected during the implementation process. The qualitative data will be thematically analyzed to explore factors that promote or inhibit the implementation and maintenance of the program.

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Results: The data collection commenced in November 2022, and the results will be ready for publication by the first quarter of 2025. Effectiveness of the intervention package will be assessed by change in mean HbA_{1c} measures, and detailed feasibility, barriers, and enablers for the implementation of the intervention will be documented through a detailed process evaluation.

Conclusions: The study protocol outlines a novel approach to enhancing diabetes management in rural Thailand through digital technology–based interventions that will facilitate task-sharing among health care workers. This can help inform future strategies for improving NCD care in low-resource settings globally.

Trial Registration: Thai Clinical Trials Registry TCTR20200322006; https://www.thaiclinicaltrials.org/show/TCTR20200322006

International Registered Report Identifier (IRRID): DERR1-10.2196/59266

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KEYWORDS

health workforce; primary health care; diabetes; digital technology; Thailand; capacity building.

Introduction

Background

South-East Asian countries (including Thailand) have been experiencing a steady rise in the burden of noncommunicable diseases (NCDs). The Global Burden of Disease Study 2015 reported diabetes and chronic kidney diseases (CKD) as Thailand's third and fifth leading causes of death [1]. According to the 5th Thai National Health Examination survey conducted in 2014 [2], Thailand has 4.63 million adults with diabetes (9.9% of the adult population), which is expected to grow to 5.2 million by 2035. In addition, 7 million adults in Thailand have prediabetes due to increasing childhood and adolescent obesity and is estimated that 25%-48% of people with diabetes will develop CKD [3]. According to the Microalbuminuria Prevalence Study survey in 2002 [4] across 10 Asian countries, it was found that 45% of the population in Thailand with diabetes had microalbuminaria and 15% had macroalbuminaria. Both conditions increase the risk for the development and progression of CKD, which will eventually lead to the need for dialysis or a kidney transplant. According to data from the Thai Renal Registry, diabetes was responsible for 34.6% cases of kidney failure in 2007 [5], increasing to 41.5% in 2020 [6]. Suboptimal treatment of diabetes leads to other macro- and microvascular complication such as cardiovascular disease, neuropathy, and retinopathy, all of which are associated with the use of more resources [7] and have grave economic and health impact.

The risk of suboptimal care and poor outcomes is worse among the socioeconomically disadvantaged. According to the World Bank reports, about 4.9 million people in Thailand live below poverty lines, with catastrophic health care cost being one of the factors contributing to relapse into poverty [8]. However, the launch of the universal health coverage program in Thailand that provided a comprehensive benefits package and zero copayment for health services was followed by a progressive decrease in the number of households (6% in 1996 to 2% in 2015) that experienced financial catastrophic events (defined as out-of-pocket payment for health exceeding 10% of household total consumption expenditure) due to health care [9].

Fortunately, the adverse outcomes, including the development of microvascular complications and progression to kidney failure can be prevented by optimal glycemic and blood pressure (BP) control and institution of effective interventions for CKD prevention. Healthy lifestyle (maintaining ideal body weight, physical activity, healthy diet, and smoking cessation), and pharmaceutical interventions including glycaemia management, BP control, use of renin-angiotensin system blockers, sodium-glucose cotransporter inhibitors, mineralocorticoid antagonists, and statins can substantially prevent the development of cardiovascular diseases and progression of kidney disease [10-12].

The key to early detection and prevention of renal and other complications in diabetes is the provision of effective and affordable primary care. However, major challenges undermine these efforts, especially among developing countries. For example, the size of the primary care workforce in developing countries is generally inadequate to meet the rising needs of giving care to those with diabetes and its complications. Maldistribution of health care workforce occurs in Thailand, similar to other developing countries. Due to the disproportionate doctor-population ratio, especially in the rural areas, there are not enough medical doctors to provide regular and optimum out-patient care to all patients with diabetes. The doctor-to-population ratio in Bangkok metropolitan area is as high as 1:515, whereas such ratio in the rural area is as low as 1:1723 to 1:2761 in the central and north-eastern regions, respectively [13]. In rural areas, it is commonly observed that those without serious complications could see a doctor in person only once or twice a year.

Health System in Thailand

Under the government's universal health coverage policy implemented in 2002, all Thai citizens are eligible to receive essential health care services with support from public health funding [14]. The Ministry of Public Health (MOPH) is the country’s largest public-sector agency, controlling over two-thirds of all hospitals and beds. The MOPH divides the country into 12 health administrative regions exclusive of Bangkok metropolitan area. Altogether, there are 165 tertiary, quaternary, or specialty hospitals (300-1000 beds) at the regional and provincial levels, 743 secondary and tertiary care hospitals (10 to 250 beds) at a district level, and about 9800 subdistrict health offices (SDHOs) [15]. The SDHOs provide basic clinical care, as well as health promotion and primary disease prevention, to more than 44 million (80%) Thais living in rural

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areas [15]. Each SDHO employs 1-2 community nurses, 1-2 public health officers, and 1 dental therapist to care for 3000-6000 residents' households. Though there is a well-connected system of patient referral from SDHO to its respective district hospital, most primary care services at SDHO are provided by its community nurses and public health officers.

In response to the growing burden of NCDs among the rural Thai population, the Thai MOPH launched the Thailand healthy lifestyle strategy 2018-2037 with the goal of improving care of diabetes and hypertension in public sector hospitals [16]. Each public hospital and SDHO must report the percentage of population screened for and found to have diabetes or hypertension and those having CKD. Though clinical practice guidelines have been developed, guideline-based clinical care is still far from reaching the targets. Only a minority of individuals with diabetes receiving continuous care could achieve recommended treatment targets for BP control (29.8%) and glycemic control (35%) [17].

Successful prevention initiatives after diabetes screening have been reported recently [14]. A cluster randomized study examining the effectiveness of integrated care on delaying the progression of stage 3-4 CKD in rural Thailand (ESCORT study) [18], evaluated integrated CKD care involving group counseling from a multidisciplinary team of district hospital staff and quarterly home visits by the community CKD care network (consisting of subdistrict health care officers and village health volunteers). The intervention was able to slow the decline in estimated glomerular filtration rate (eGFR) over a 2- to 3-year period (difference 2.74, 95% CI 0.60-4.50 mL/min/1.73 m²; P=.009), showing the feasibility of using nonphysician workforce to augment primary care delivery and underscoring the need to develop effective strategies to deliver low-cost, evidence-based treatments for the prevention of diabetes and diabetic kidney disease that can be implemented in the primary health care systems [18]. In the subsequent prospective follow-up study, ESCORT II study [19], the integrated care model was extended to 5 district hospitals without a parallel control group. This expanded approach, which encompassed hospital multidisciplinary care and community home visits, resulted in a consistent mean eGFR decline of –0.92 mL/min/1.73 m²/year over the 36-month duration [19]. These findings further underscore the effectiveness of the integrated care model at the community level in effectively delaying the progression of CKD.

SMARThealth

The SMARThealth program, based on a technology platform developed by the George Institute for Global Health, enables communities and health care providers to prevent and manage NCDs using guideline-based care, and continuous quality control [20]. This initiative is based on principles of "task-sharing," in which routine clinical procedures are conducted by nonphysician health care workers, including village health volunteers, community nurses, and public health officers to increase access to quality health care and reduce costs. SMARThealth for cardiovascular diseases was integrated with primary health care services and evaluated in 8 villages in Malang district, East Java, Indonesia (2016-2018). It was associated with an 8.3 (95% CI –10.1 to –6.6) mmHg reduction in BP [21]. The strategy has been adopted by the Malang district government for scale-up and integration with existing electronic medical record system (e-Puskesmas) in over 390 villages (2020-2023) and is being evaluated as part of the Global Alliance for Chronic Diseases scale-up funding round. Digital technologies, including affordable and innovative solutions, allow patients and health care providers to make evidence-based decisions.

The SMARThealth program [20] has been adapted for optimal management of patients with diabetes and kidney disease in the context of Thailand's health system and comprises the following elements. First, a platform for community nurses to assess the disease risk using a clinical decision support system (CDSS) app on an Android tablet device. The app allows community nurses to collect essential health-related information from patients, inform them of their risk status, provide lifestyle advice relating to physical activity, diet and tobacco and alcohol, and refer high-risk patients to the specialist doctor at the district hospital. In addition, the app provides decision support to community nurses for providing guideline-based recommendations and adjusting medication prescriptions during follow-up. Second, a 2-day training induction and ongoing support from the research team for community nurses. Third, data collected by the community nurses are asynchronously uploaded to a shared electronic medical record (OpenMRS) via the Sana Mobile Dispatch Server and stored on a centralized server in Thailand. Finally, availability of a central support team to visit the community nurses periodically and provide support such as re-training, co-ordinating, and solving IT issues. The quality of intervention is ensured by supervisor field visits.

Hypothesis

The primary study hypothesis is that compared with usual care, adapting, and implementing a multifactorial intervention (SMARThealth) that strengthens the existing primary health care system and addresses known constraints for diabetes management in rural Thailand will improve blood glucose levels and thereby reduce renal complications among adults with type 2 diabetes.

Main Study Objectives

The study objectives are to (1) adapt, validate, and integrate the SMARThealth Diabetes program for improving the management of type 2 diabetes mellitus at the primary health care level; and (2) determine if the SMARThealth Diabetes program is feasible for implementation and acceptable in the rural communities of Thailand.

Methods

Study Design

The overall study design is presented in Figure 1.

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Figure 1. SMARThealth Diabetes—study design and objectives.

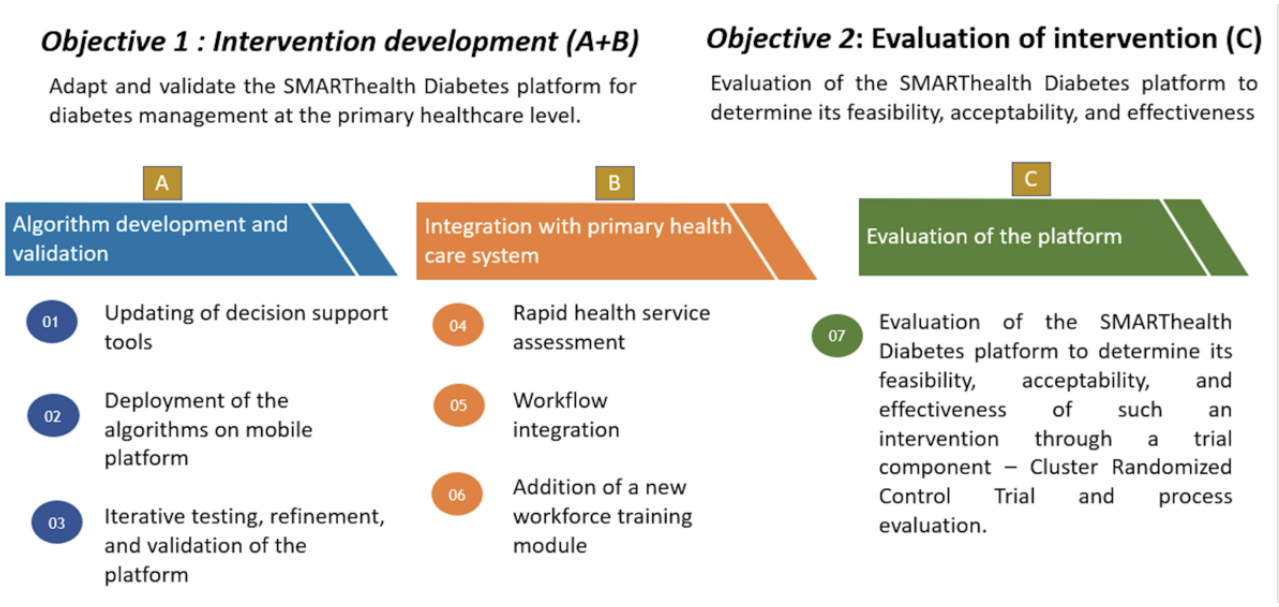

Objective 1: Intervention Development

Algorithm Development and Validation

Updating of Decision Support Tools

The existing global guideline-based algorithms [22] for the screening and management of diabetes were updated with recommendations consistent with Thai guidelines [23]. These included evidence-based guidance on monitoring BP and blood glucose, lifestyle changes (smoking cessation, weight loss, improved diet, exercise, alcohol, and sodium restriction), and adherence to medical treatments, including renin angiotensin aldosterone system blockade. The draft algorithm underwent expert review by leading diabetes and kidney disease specialists to assess consistency with global and local guidelines. Drugs for diabetes, hypertension, and hyperlipidemia were identified according to their availability at the SDHOs. The recommendations were converted into "pseudo-code" rules and developed into detailed software specifications. After programming, the algorithms underwent independent clinical and statistical validation using established methods [20].

Deployment of the Algorithms on the Mobile Platform

The algorithms were integrated and deployed using the existing Java-based SMARThealth platform, which can be accessed directly on low-cost Android devices. The existing platform was modified to accommodate additional inputs and outputs based on the updated algorithm. The recorded input information was ensured to be securely transferred (synchronous or asynchronous) to a shared electronic record located on a central server in Thailand. Output providing referral and monitoring recommendations for the nurses are generated based on the parameters entered. Nurses can adjust medications through the platform, and if a referral to a higher center is needed, referral advice with details of the referral center is also provided.

Iterative Testing, Refinement, and Validation of the Platform

The platform was rigorously validated in 2 steps. The first is to ensure that the local guidelines are correctly interpreted by the algorithm, and the second is to ensure that it is accurately deployed in the Java-based mobile platform. The outputs from the SMARThealth platform of about 100 patients were run through 2 clinicians to estimate the accuracy of the recommendations. Minor changes, as suggested by clinicians were considered, and the algorithms were modified till both clinicians were satisfied with the final recommendations.

Integration of the SMARThealth Platform With the Primary Health Care System in Thailand

Rapid Health Service Assessment

An audit of health service capacity was conducted using qualitative methods, including in-depth interviews and focus group discussions (FGDs) with community members, health care providers and district administrators in five primary catchments at all levels of health care. The interviews were conducted in local language (Thai) and led by a moderator trained in interview and group facilitation techniques. A total of 20 in-depth interviews and 2 FGDs were conducted with a total sample of 36 participants in 5 primary health care catchment areas, till no new information was obtained from the interviews. This assessment identified barriers and facilitators for the multifaceted system intervention implementation and identified modifications that will be required to maximize the likelihood of successful integration and implementation. Findings of the rapid health service assessment will be published separately.

Workflow Integration

Through the inputs from the health service assessment and ongoing discussions with nurses from SDHOs and doctors at health facilities, the SMARThealth platform was adapted to suit the existing workflow of the health offices. For example, the paper registration forms were digitized and integrated with the platform, the existing printers at the SDHOs are used to print treatment advice and referral cards, available laboratory records at SDHO are used for input into the platform, and mobile

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communication of doctors and nurses are retained through use of this platform.

Addition of a New Workforce Training Module

A SMARThealth Diabetes training program was developed. Inputs from the rapid health system assessment helped in the planning of the training program in terms of location of training, content, and timings. The training package is delivered in an initial workshop format and continuously reinforced through the program's digital platform. The training program delivery is supported by training manuals to nurses and doctors to ensure local relevance.

Objective 2: Evaluation of the Platform

Study Design

The intervention will be evaluated using a pragmatic, type 2 hybrid effectiveness or implementation, parallel-group cluster randomized controlled trial of 12 months duration. A total of 51 SDHOs will be randomized 1:1 into intervention and control arms. As the intervention is directed at the health system involving the nurses, doctors, and other staff working as teams, effectiveness is best evaluated through cluster randomized controlled trial with clustering at the SDHO level.

Study Setting

The study is conducted in rural communities in Kamphaeng Phet province in Thailand through the involvement of SDHOs selected in consultancy with the ministry. To be eligible, the SDHO personnel must be willing to participate in the study, have interest in using digital technology, and not participating in any competing research study.

Eligibility Criteria

Inclusion Criteria

Aligning with the Thai public health screening policies, and in discussion with MOPH, patients attending SDHOs will be eligible to participate if they are (1) aged 30 to 70 years; (2) known cases of type 2 diabetes currently on oral hypoglycemic medications or identified to have diabetes in the initial screening by the community nurses; (3) have CKD-EPI eGFR of > 60 mL/min/1.73 m^2 [24]; and (4) undergoing treatment at the SDHOs by a community nurse.

Exclusion Criteria

Participants with the following characteristics will not be eligible: (1) individuals who decline participation; (2) patients with a diagnosis of nondiabetic kidney disease (for example, ADPKD, lupus nephritis, obstructive uropathy, renal stone, nephrotic syndrome, or primary glomerular disease); (3) patients with expected life expectancy of less than 2 years; (4) patients with AIDS; (5) patients with known pregnancy; and (6) patients having communication problems, for example, migrant workers and people with dementia.

Informed Consent

Consent will be obtained based on a professional-cluster design approach proposed by Hemming and Eldridge [25]. Consent will be collected at three levels: (1) at the cluster level —verbal approval from each SDHO to participate in the trial; (2) from the health workers—verbal approval from nurses and doctors to participate in the study and provide information during and after the study; and (3) from individual participants—consent from patients with diabetes interested in participating in the study for data collection during the study.

Intervention Group

SDHOs randomized to the intervention group will receive the SMARThealth Diabetes program described earlier.

First, a workforce restructuring and training program to increase the involvement of community nurses in routine aspects of diabetes and kidney disease care. Using the module developed in objective 1, training will be provided to community nurses to promote awareness of lifestyle determinants, use of the CDSS to record risk factor information from the laboratory records available at the health center, guidance in the interpretation of the CDSS output, and processes to refer high-risk individuals to the district hospitals and training to monitor and promote adherence to prescribed medications. The training will be imparted for 2 days. After training and certification, community nurses will each be provided with a 7-inch tablet preloaded with the SMARThealth software. Second, the Thai CDSS will incorporate components related to referral, follow-up, and personalized recommendations about blood glucose control, BP lowering, pharmacotherapy including ACE inhibition, statin, and eye and foot care. Third, continuous performance monitoring. The performance of community health nurses will be monitored using standard, automated reports generated in real time and based on certain key performance indicators (eg, the proportion of individuals with diabetes on recommended combination treatment). These reports will be provided to health administrators in each district.

Criteria for Discontinuing or Modifying Allocated Interventions

There will be no predefined criteria for stopping the allocated intervention. In case new national clinical guidelines are published during the trial, this may justify modification of the content of the intervention without changing the form of the intervention. The decision for modification will be made by the steering committee.

Participants may withdraw from the trial at any time. Withdrawal will not negatively affect their ability to access usual care from the SDHO.

Control Group

SDHOs randomized to the control group will continue with usual practice, without access to the training and support package, the CDSS and associated tools.

Outcomes

Primary Outcome

The primary outcome will be the difference in change in mean hemoglobin A_{1c} (HbA_{1c}) measured at the SDHO between randomization and 12 months from randomization, between the intervention and control clusters. HbA_{1c} has been chosen as the primary outcome as it is recommended by local clinical guidelines as a treatment target.

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Secondary Outcomes

Secondary outcomes will include the difference in change in albuminuria status; change in eGFR, systolic blood pressure, and low-density lipoprotein cholesterol level; change in the proportion of patients with HbA_{1c}<7%, and patients with systolic blood pressure<140 mm Hg; measured at randomization and 12 months from randomization, between the intervention and control clusters.

Timeline

SDHOs will be recruited and randomized before individual participant recruitment commences. After randomization, community nurses in the intervention clusters will receive the training program (as described earlier). Eligible patients with diabetes registered within the SDHOs will be invited by the community nurses to participate in this study. After obtaining written informed consent, demographic and additional data, baseline parameters will be collected using previously validated, structured questionnaires. At the end of the study (12 months), data and biological samples will again be collected at the laboratory in SDHOs by trained laboratory technicians, along with completing the endline questionnaires by community nurses to allow analyses for all outcomes.

Statistical Considerations

Randomization of 51 SDHOs with an average cluster size of 40 individuals with diabetes at baseline will provide 90% power (2α=0.05) to detect an absolute mean HbA_{1c} difference of 0.5%. A change of 0.5% in HbA_{1c} is considered clinically meaningful [26]. Intracluster correlation coefficients of 0.05 for HbA_{1c} are assumed. By assuming a 10% dropout rate in our study, the sample size calculation indicated that a total of 1540 participants will be required to be recruited in both arms, with 770 in each group (Figure 2).

The analysis of change in HbA_{1c} between baseline and the end of study (primary end point) will be performed using a linear mixed model including treatment arm and baseline HbA_{1c} as fixed effects as well as SDHO as a random effect to account for clustering of individuals by village. In case of baseline imbalances between the 2 arms at the cluster or individual level, unbalanced characteristics will be added to the models as a sensitivity analysis. The same approach will be applied for continuous secondary end points.

Figure 2. Randomization and sampling based on the SDHOs. SDHO: subdistrict health office.

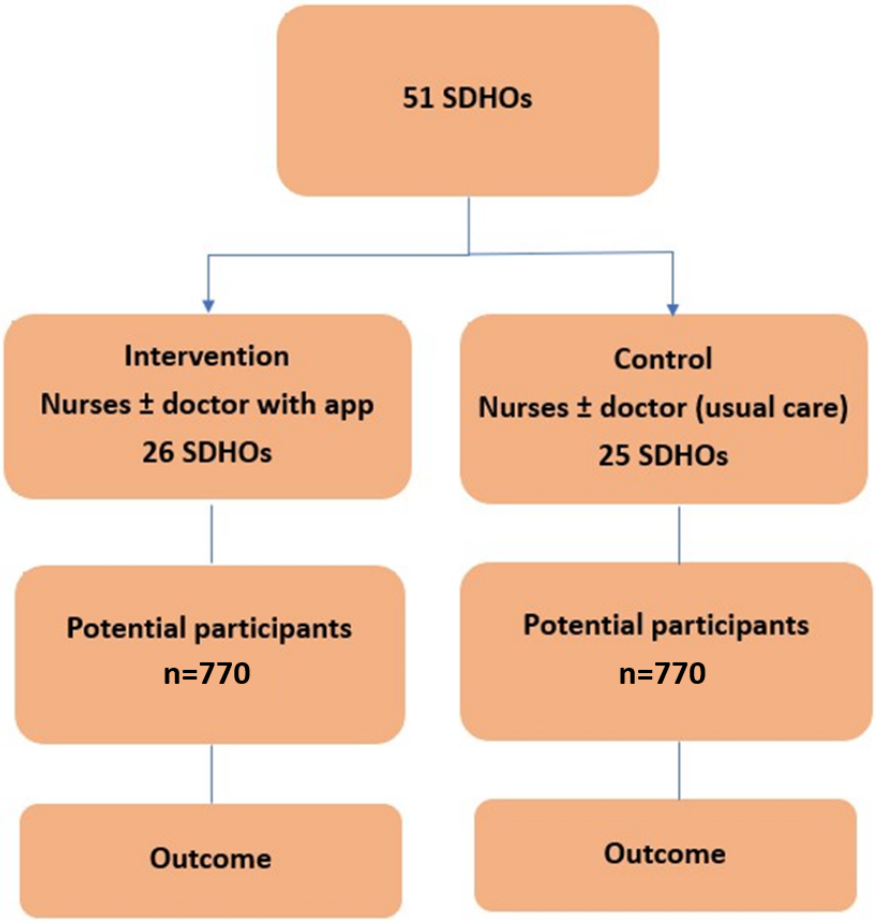

Data Collection and Management

Data collection will commence at baseline (0 months; randomization) and will be conducted quarterly at 3, 6, 9, and 12 months after randomization by community nurses. All data will be captured on tablet devices using the SMARThealth app adapted for the clinical research forms (CRFs). The CRFs collect information on anthropometric measurements, medical history, and current medication for hypertension, diabetes, and hyperlipidemia, in addition to laboratory test results. These

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CRFs will be completed at months 0, 3, 6, 9, and 12. The primary outcome variable (HbA_{1c}) and other laboratory tests will only be recorded at months 0, 6, and 12. Data will be deidentified, saved, and stored in a secure server located in Bangkok, Thailand. Published, validated questionnaires are used in the CRFs and tested using the SMARThealth platform before data collection. About 10% of all CRFs will be checked for accuracy against source data by the project team.

SMARThealth platform will be used for digitally collecting all baseline and outcome data. Data access will be restricted to delegated study staff and will require multifactor identification with a digital log kept of all logins. The project manager and data managers will be responsible for data quality. The project manager will ensure quality by interacting periodically with community nurses and checking for completeness of data, and data validation.

Confidentiality

Participant confidentiality will be maintained throughout the study. Each participant in the study will be assigned a 10-digit unique alphanumeric patient ID. The first 2 digits are the district code, the following 5 digits are the SDHO code, and the last 3 digits indicate the individual patient ID. This unique ID ensures that their personal identifiers remain anonymized throughout the research process.

Our data management system employs 3 robust security layers to safeguard patient data. First, password protection is implemented to regulate access, preventing unauthorized usage by individuals. Second, local data protection measures, including encrypted data communication and role-based access, are implemented to ensure the security of the locally stored data at the device level. Finally, at the server level, additional measures such as firewall protection, reliable maintenance, monitoring, and support services are implemented to safeguard the database.

Process Evaluation

A detailed awareness of local contextual factors will be undertaken to understand the impact of SMARThealth and barriers to its implementation and scale-up. The process evaluation will be designed in line with recommendations by the UK Medical Research Council in its “guidelines for developing and evaluating complex interventions” [27,28]. Evaluation data, data collected during intervention delivery, and data collected through qualitative methods will be used to investigate the process evaluation framework that includes identifying factors that promote or inhibit the implementation and maintenance of the program [29]. A maximum variation sampling technique will ensure diverse opinions are captured from participants and health care workers. The process evaluation will be informed by normalization process theory (NPT) [30] to assess the extent to which the new system fits within the normal processes of the current service provision in the villages and SDHOs. The 4 main concepts of NPT namely, coherence, cognitive participation, collective action, and reflective monitoring will be identified in the process of implementation of the SMARThealth diabetes program in the intervention SDHOs.

Key evaluation areas that the study will explore are: (1) how the health workers use the intervention, (2) what effects the intervention might have on doctor practices, and (3) participant experiences of receiving the intervention.

Qualitative data will be collected using semistructured, in-depth interviews and focused group discussions [31]. NPT will inform the semistructured interview guides and will also be used as a framework for analyzing the data. All interviews and group discussions will be audio-recorded, and then transcribed verbatim. The qualitative data will be thematically analyzed (from codes to categories and finally themes) to identify and interpret patterns and themes within the data. Data will be analyzed contemporaneously, and data collection will be stopped when thematic saturation is reached. Two researchers who are trained in qualitative methodology will be involved in coding the interview and FGD transcripts. In the event of a disagreement, a consensus meeting will be held with the principal investigator to reach an agreement on interpretation of the data. Intercoder reliability will be reported using qualitative assessments of agreement and consistency among the coders using processes described by O’Connor and Joffe [32]. Process evaluation data will be analyzed independently of the outcome evaluation data and then the 2 sets of data will be combined and triangulated to increase the reliability of the results.

Ethical Considerations

This program will be conducted, evaluated, and reported in compliance with all local regulatory requirements in Thailand. Ethical approval has been obtained from the Ethical Review Committee for Research in Human Subjects at MOPH in Thailand (25/2562) and the Oxford Tropical Ethics Research Committee (21/19).

All potential participants for both the qualitative and quantitative component of the study will be provided with a participant information sheet prior to their recruitment into this study.

Participation in the study is voluntary, and no financial compensation will be provided to the participants. Data collected using the SMARThealth Diabetes platform will be stored securely in a central server located in Bangkok, Thailand. Personal identifiable information will be stored securely; electronic data will be deidentified and analyzed. Findings will be written up as means and published without identifying information. Electronic audio files from interviews will be stored electronically on a local network server at the researcher’s organization, under both firewall and password protection. Access will be limited to study investigators. All the data collected in the study will be managed by the central research team. The data collection will be routinely monitored for completeness and quality control checks will be introduced. The physical documents will be stored securely and only accessible by the study researcher.

Results

The study was funded by the Medical Research Council, United Kingdom in April 2018 with additional funding received from Medical Research Council and Imperial College London in

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September 2022. We had to delay the recruitment of the participants into the trial between the period 2020-2021 due to the unprecedented COVID-19 pandemic. As of May 2024, we have enrolled 1599 patients with type 2 diabetes, who are managed and followed up by community nurses at 51 SDHOs. Final data analysis and results are expected to be published in the first quarter of 2025.

Discussion

Expected Findings

This study will address the growing epidemic of diabetes leading to CKD and kidney failure in Thailand. To our knowledge, the SMARThealth Diabetes study is the first randomized trial to use technology as a health system intervention to support the delivery of optimal management of diabetes at a primary health care level in Thailand. This intervention is designed to address several gaps in the treatment of diabetes and kidney disease, including inadequate workforce, disproportionate focus on physician-centric care models not aligned with the values and preferences of communities in which they are implemented, variation in the quality of care, and its high cost.

The SMARThealth Diabetes intervention relies on primary health care workforce reengineering and an electronic decision support with an emphasis on minimizing variations on quality of care. These components are embedded in the public health care system, enhancing the adaptation and sustainability of the intervention. Similar primary health care interventions have already been successfully implemented in primary health care settings in Indonesia and India for detection, prevention, and management of cardiovascular diseases [21,33]. Hence, there is a need to extend the platform to similar primary health care settings in other low- and middle-income countries. The evidence generated through this study will have substantial potential to inform policymakers and system planners to include high-quality primary health care for common NCD conditions.

Strengths and Limitations of the Study

There are many strengths in this study, including the use of a novel multifaceted mobile health strategy to engage communities, physicians as well as nonphysician health care providers in learning how to cope with diabetes and, as a result, strengthen the overall health system. Additionally, a comprehensive process evaluation will allow the assessment of the feasibility, scalability, and sustainability of such a strategy in the local health care system.

The main limitation is that it is conducted in selected rural areas, which might not represent the wider population in other districts and provinces in Thailand. However, integrating the intervention into the health system, which is similar throughout the country will help to learn from this project and support future scale-up if successful. Further, although this project will be deployed in rural Thailand, the components of the intervention are generic, and this study will generate important evidence that will inform the adaptation of similar interventions in other health care settings. Aligning to the study design, the study will need to collect information on HbA_{1c} and other laboratory tests from participants in both arms leading to better than usual care in the control arm. We have streamlined the timing of the data collection to the routine follow-up visit of patients in the control arm. Still, we need to acknowledge there could be additional communication with these patients to ensure follow-up visits are happening as per the need of the study.

Conclusions

In conclusion, we present a study protocol for a pragmatic, parallel group cluster randomized hybrid effectiveness or implementation trial to test the SMARThealth Diabetes platform in rural Thailand. The study aligns with guidelines developed by the Medical Research Council for developing and evaluating complex interventions. The platform will support the delivery of optimal management of diabetes at a primary health care level and we hope this trial will demonstrate the effectiveness of the platform in addressing the gaps in the treatment of diabetes and kidney diseases.

Acknowledgments

The authors acknowledge the support of the study team, health workers, nurses, patients, subdistrict health office staff, district medical officers, and other district officials in the study districts, and Dr Pittala Vara Prasad and Dr Priyakanta Nayak for managing various aspects of the study. The publication fees were paid by the Imperial College Open Access policy.

Data Availability

The data sets generated or analyzed during this study will not be publicly available in accordance with the data management plan but will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
CDSS: clinical decision support system
CKD: chronic kidney disease
CRF: clinical research form
eGFR: estimated glomerular filtration rate
FGD: focus group discussion
HbA1c: hemoglobin A1c
MOPH: Ministry of Public Health
NCD: noncommunicable disease
NPT: normalization process theory
SDHO: subdistrict health office

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Protocol

Efficacy of Real-Time Feedback Exercise Therapy in Patients Following Total Hip Arthroplasty: Protocol for a Pilot Cluster-Randomized Controlled Trial

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Abstract

Background: Osteoarthritis of the hip joint is an increasing functional and health-related problem. The most common surgical treatment is hip replacement to reduce pain and improve function. Rehabilitation after total hip arthroplasty (THA) is not regulated in Austria and mostly depends on the patient's own initiative and possibilities. Functional deficits, such as valgus thrust of the leg, functional Trendelenburg gait, or Duchenne limp, are characteristic symptoms before and, due to the performance learning effect prior to surgery, also after the operation. Addressing these deficits is possible through neuromuscular-focused exercise therapy. The efficacy of such therapy relies significantly on the quality of performance, the frequency of exercise, and the duration of engagement. Enhancing sustainability is achievable through increased motivation and real-time feedback (RTF) on exercise execution facilitated by digital feedback systems.

Objective: This study will be performed to quantify the medium-term effectiveness of digital home exercise feedback systems on functional performance following THA.

Methods: A clinical trial with a cluster-randomized, 2-arm, parallel-group design with an 8-week intervention phase and subsequent follow-ups at 3 and 6 months postsurgery will be conducted. Feedback during exercising will be provided through a blended-care program, combining a supervised group exercise program with a self-developed digital feedback system for home exercise. In total, 70 patients will be recruited for baseline. The primary outcome parameters will be the frontal knee range of motion, pelvic obliquity, and lateral trunk lean. Secondary outcomes will be the sum scores of patient-reported outcomes and relevant kinematic, kinetic, and spatiotemporal parameters.

Results: The trial started in January 2024, and the first results are anticipated to be published by June 2025. RTF-supported home exercise is expected to improve exercise execution quality and therapeutic adherence compared to using paper instructions for excise guidance.

Conclusions: The anticipated findings of this study aim to offer new insights into the effect of a blended-care program incorporating digital RTF on exercise therapy after unilateral THA, in addition to knowledge on the functional status 3 and 6 months postsurgery, for further improvement in the development of rehabilitation guidelines following THA.

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KEYWORDS

hip replacement; exercise therapy; real-time feedback; movement analysis

Introduction

Background

Osteoarthritis (OA) of the hip has become an increasing burden for patients, with a high impact on the socioeconomic system [1]. The prevalence of hip OA in the population aged over 45 years is 19 % in women and 27 % in men [2]. The main factors contributing to the development and progression of hip OA, such as obesity, nutrition, sociodemographic setting, injuries, or joint shape, have been extensively studied [3,4]. Further biomechanical aspects related to overload of the cartilage [2] induced by a sum of loads have been identified. Deciding to undergo conservative exercise treatment or surgical total hip arthroplasty (THA) and identifying the best time point for THA can be difficult due to low-level evidence [5]. In Austria, a total of 18,052 primary THAs and 1290 reimplantation surgeries were performed in 2015 [6]. Despite the significant number of THAs, there is a notable deficiency in guidelines and recommendations for both pre- and postoperative management, particularly in the context of functional restoration [7,8]. Notably, Austria lacks a nationally implemented postsurgery patient pathway. However, to some extent, there is existing knowledge on the effectiveness of exercise therapy in reducing functional deficits after THA, as evidenced by previous studies [9-11]. In particular, following motor re-education approaches [12-14] and enhancing the sustainability of exercising by means of real-time feedback (RTF) have been proposed in several studies [15-17]. Regarding motor re-education, the quality of performance, compliance, and adherence to exercising are essential. However, there is no system available focusing on the relevant functional deficits for RTF-supported home exercise. These deficits are valgus thrust, which is defined as the bowing in of the knee or abrupt worsening of the dynamic valgus [18], and pelvic drop, which is increased lowering of the contralateral pelvis side during dynamic single-leg stance (SLS) phases [19]. Additionally, lateral trunk lean is also addressed in the context of such functional deficits. In contrast to the neurologically induced Duchenne limp, this dynamic functional deficit can, among other factors, be induced by pain [20]. Furthermore, there is a lack of kinematic and especially kinetic 3D data addressing functional deficits during recovery after THA [9,10,21,22]. Therefore, the aim of this trial is to investigate the effect of RTF-supported home exercise compared to written home exercise instructions on the recovery of functional performance after THA. Specifically, we want to analyze the improvement of functional deficits at 3 and 6 months postsurgery using quantifiable three-dimensional movement analysis (3DMA) of activity-of-daily-living (ADL) tasks.

Study Goals

This pilot cluster-randomized, 2-arm, parallel-group controlled trial aims at enhancing the understanding of the effects of RTF on functional deficits such as knee valgus thrust, pelvic drop, and lateral trunk lean after THA. Biomechanical and patient-reported outcomes will be assessed prior to the intervention, as well as at 3- and 6-month follow-ups postsurgery.

The primary research question is whether blended-care digital RTF-supported home exercise (intervention group [IG]) leads to significant higher improvements in the control of the frontal knee range of motion (RoM), pelvic obliquity, and lateral trunk lean compared to blended-care exercise supported by written instructions (control group [CG]) as a comparator. The secondary aspect will focus on potential differences between groups concerning aspects of the quality of life, function, and physical activity. Tertiary functional outcomes between groups will be compared to quantify movement quality. Consequently, the underlying primary null hypotheses were prespecified as follows:

- Improvements in the frontal knee RoM are equal between the IG and the CG.
- Improvements in pelvic obliquity are equal between the IG and the CG.
- Improvements in lateral trunk lean are equal between the IG and the CG.

In addition, the primary alternative hypotheses are as follows:

- Improvements in the frontal knee RoM are not equal between the IG and the CG.
- Improvements in pelvic obliquity are not equal between the IG and the CG.
- Improvements in lateral trunk lean are not equal between the IG and the CG.

The 3 primary outcomes (frontal knee RoM, pelvic obliquity, and lateral trunk lean) will be tested in 3 independent hypotheses (each parameter will be tested independently of the others in 2 follow-ups).

Secondary hypotheses will be tested independently for differences between the IG and the CG in a series of metric patient-reported outcomes measures (PROMs): (1) the Harris Hip Score (HHS), (2) the Hip Osteoarthritis Outcome Score (HOOS), (3) the 12-item Short Form Health Survey (SF-12), (4) the International Physical Activity Questionnaire – Short Form (IPAQ-SF), and, if applicable, (5) the Knee Injury and Osteoarthritis Outcome Score (KOOS).

Tertiary hypotheses will be tested independently for differences between the IG and the CG in a series of metric movement analysis outcomes, including (1) kinematics, (2) kinetics, and (3) spatiotemporal results.

Methods

Trial Design

The study is set up as a pilot cluster-randomized controlled trial with 2 parallel groups. Patients will be recruited prior to surgery. At the time of recruitment, the HHS will be assessed routinely in the participating hospital. Additionally, all included patients will be equipped with an activity monitor (wGT3X-BT;

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ActiGraph LLC) for 2 days prior to surgery in order to assess their mobility level before THA. Baseline assessment will be conducted 4-6 weeks after surgery, and randomization will follow thereafter. During the active phase of 8 weeks, supervised group exercise therapy will take place in both groups. In addition, the IG will perform a home exercise program with the support of an RTF device. The CG will perform a comparable home exercise program without the support of an RTF device (home exercise program following written instructions). Follow-up assessments will take place as close as possible to 8 weeks after baseline and 6 months postsurgery. The schedule of the study is presented in Table 1.

Table 1. Schedule of the study.

Schedule	Study period						
	Enrollment (t_{-1})[a]	Surgery	t_0[b]	Allocation[c]	Intervention phase[d]	t_1[e]	t_2[f]
Eligibility screening	✓	—[g]	—	—	—	—	—
Informed consent	✓	—	—	—	—	—	—
2-day activity monitoring	✓	—	—	—	—	—	—
HHS[h]	✓	—	—	—	—	—	—
Allocation	—	—	—	✓	—	—	—
Intervention							
RTF[i] group	—	—	—	—	✓	—	—
CG[j]	—	—	—	—	✓	—	—
Assessments							
3D movement analysis	—	—	✓	—	—	✓	✓
Clinical status	—	—	✓	—	—	✓	✓
Body composition analysis	—	—	✓	—	—	✓	✓
7-day activity monitoring	—	—	✓	—	—	✓	✓
PROMs[k]	—	—	✓	—	—	✓	✓

[a]Enrollment will be 4-10 days prior surgery.

[b]Baseline t_0 is 4-6 weeks postsurgery.

[c]Randomized allocation will be conducted at the end of baseline assessment.

[d]8 weeks.

[e]3 months postsurgery.

[f]6 months postsurgery.

[g]Not applicable.

[h]HHS: Harris Hip Score.

[i]RTF: real-time feedback.

[j]CG: control group.

[k]PROM: patient-reported outcomes measure.

The number of participants assessed for eligibility, allocated to study arms, and analyzed will be recorded using the CONSORT (Consolidated Standards of Reporting Trials) extension flowchart on cluster randomized trials [23]. Figure 1 illustrates the trial design and participant flow through the trial. The protocol is according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [24].

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Figure 1. Flow diagram of the progress through the phases of the trial. CG: control group; IG: intervention group; PHO: paper handout; RTF: real-time feedback. *Eligibility based on clinical data.

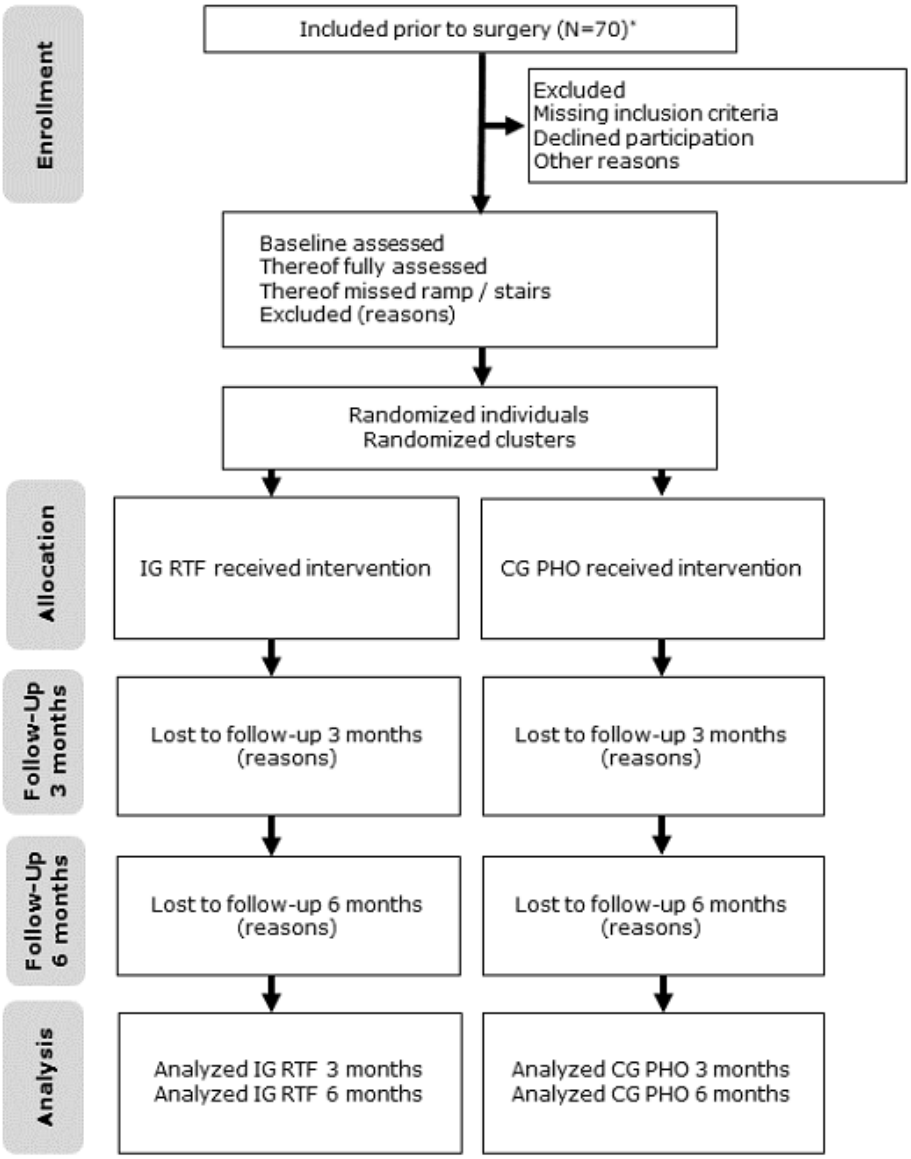

Sample Size Estimation and Study Population

As knowledge and studies concerning the effect of RTF on exercise following unilateral THA are missing, the sample size cannot be calculated based on given effect sizes. Therefore, the sample size for comparing 2 independent means was calculated using an estimated effect size (d) of 0.8. Assuming the planned 16 clusters with a cluster size of 3 participants each and an intracluster correlation of 0.05, a nominal sample size of 24 participants per group would give a power of 0.75 (α=.05). The effect size (d) of 0.8 and the intracluster correlation of 0.05 were estimated, and hence, the achieved power in this pilot cluster-randomized trial will be reported. The number of participants included in topic-specific studies range from 14 to 111 [5,11,14,25,26]. Considering a dropout of 30%, we will recruit 70 participants from the Orthopedic Hospital Speising, Vienna, Austria.

Inclusion Criteria

Participants will be included according to the following inclusion criteria: (1) age from 50-75 years, (2) BMI from 18.5 to 32.49 kg/m², (3) ability to walk without walking aids at baseline assessment, (4) scheduled for elective unilateral THA, (5) willingness to comply with all study-related procedures, and (6) providing informed consent.

Exclusion Criteria

Participants will be excluded in the case of (1) symptoms of delayed healing concerning the implant, (2) cardiorespiratory symptoms limiting exercise therapy (eg, severe heart disease), (3) symptoms of musculoskeletal or cardiorespiratory overload, (4) neuromotor diseases (eg, previous stroke, multiple sclerosis, Morbus Parkinson disease), (5) other reasons that would lead to obvious limitations concerning participation in the intervention (eg, severe contralateral OA, lower extremity fractures within the past 12 months, other elective lower extremity surgery within 6 months, inadequacy in German

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concerning questionnaires and exercise instructions, mentally unable to participate), and (6) nonadherence (see the definition in the *Therapeutic Adherence* section).

Recruitment

Patients scheduled for elective unilateral THA at the Orthopedic Hospital Speising will be informed by their orthopedic surgeon of an opportunity to participate in the study. If interested, they will be checked for eligibility by physicians. One of the enrolling physicians is also acting as the principal investigator according to Austrian medicinal product law. In the case of willingness and eligibility of the potential participant, written informed consent will be obtained by the informing and enrolling physician from the participant prior to surgery. On the day of discharge, participants will be finally checked by a physician concerning their status of recovery with regard to the exclusion criteria.

Clusters for the intervention phase have been defined as groups of 2-5 patients starting their collective training program at the same time. Due to logistics, only 1 clustered group will be considered at a time. The group exercise program will be the same for both the IG and the CG and will only differ in the home exercise program, which for the IG will be supported by a digital real-time exercise feedback prototype for digitally guided training. Patients who belong to the same cluster will be randomized to receive the same treatment. Clusters after baseline assessment will be randomized in blocks (block size blinded) by means of an online random sequence generator [27] to achieve equal allocation of clusters to both arms. Due to the small number of clusters (about 20), no stratified randomization approach will be applied. Patients will be arbitrarily clustered based on the surgery date. Due to the nature of the studied conditions, it will not be possible to blind researchers.

Patients' active participation will take 6 hours for assessments performed at baseline, 3-month, and 6-month follow-up. They will be offered a maximum of possible supervised exercise sessions of 24 hours and will be required to practice their home exercise program for 20 hours over the intervention period of 8 weeks. Shopping vouchers of €220 (US $239) will be offered as an incentive for participation.

Safety Considerations

Adverse events are unlikely. Participants will be clinically assessed prior to the baseline measurement and the intervention. Exercise therapy will be guided and supervised by a physiotherapist. Information about patients' settings at home regarding exercising space, safety, and possible risks will be retrieved, and if necessary, on-site visits to ensure safe home exercising will be performed. All participants will be insured through clinical trial insurance.

Medical and technical quality of the baseline assessment, intervention, and follow-up assessment will be guaranteed through written documentation of monitoring visits by the principal investigator and the designated clinical investigation monitor. This documented supervision will be carried out for the first 2 patients and the first group exercise session.

Examination Procedures

In the examination, initial status interviews including questions on personal data, such as age, gender, and insurance, and on health in terms of a health check will be conducted at t_0 (baseline 4-6 weeks postsurgery), t_1 (3 months postsurgery), and t_2 (6 months postsurgery). In particular, current pain in the surgical area, its occurrence and severity, and previous injuries and any other general medical interventions or complaints in the leg, pelvis, and spine during the past 6 months will be reviewed. Finally, participants will be asked about medications and known systemic diseases. The status interviews at t_1 will also incorporate questions on usability of the feedback prototype (IG) and on exercise adherence and subjective feelings concerning exercise execution, while status interviews at t_2 will include questions on exercise behavior and whether patients can incorporate exercising into their daily routine. All details concerning status interviews can be found in Multimedia Appendix 1. Within the status interviews, patient reported outcome measures (PROMs) will be gathered. The individual pain level on the 10-item Numeric Rating Scale (NRS-10), with focus on the surgery region, will be noted. In addition, the standardized PROM HHS (prior to surgery, t_0, t_1, and t_2) and the HOOS [28], SF-12 [29,30], and the IPAQ-SF [31] at t_0, t_1, and t_2 will be explained to the participants, and they will be asked to fill them out as part of the status interviews. If a participant reports additional problems with the knee joint, they will be asked to fill out the KOOS [32] at t_0, t_1, and t_2. At t_1, participants in the IG will also be asked to fill in their system usability score (SUS) for quantitative assessment of the usability of the real-time exercise feedback prototype.

Clinical Assessment

Following the status interviews, a clinical assessment will be conducted. During this, each patient's height will be measured to the nearest 0.5 cm with a stadiometer (SECA 213; Seca Vogel&Halke). Their weight will be derived from the body composition analysis (SECA mBCA 525). Participants will be instructed on how to wear a waist-worn activity-monitoring device (wGT3X-BT), which records habitual physical activity behavior over 7 consecutive days. A daily activity diary will provide information about ADLs. The current RoM of the hip, knee, and ankle joint will be assessed, respecting constraints to hip adduction and rotation given by the surgeon. The isometric strength of knee extension and flexion will be measured with a Microfet II handheld dynamometer (Hoggan Scientific). In a short functional assessment, participants will be checked for whether they can perform the following exercises at t_0: bipedal squat (maximum hip flexion≤90°), SLS, pelvic hinge, and mini single limb squat. The clinical assessment will be conducted by author KW.

For a detailed analysis of gait and task performance, all participants will be equipped with 43 retroreflective markers on bony landmarks, 16 markers on 4 rigid clusters on thighs and shanks, and 1 cluster with 3 markers on the sacrum [33]. After a calibration measurement to process the biomechanical model, 7 level walking (LW) trials with valid strikes for both feet each on a walkway equipped with 3 force plates

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(BMS464508 & OR6-7; AMTI) will be captured by a 28 infrared camera system with the software Nexus version 2.9.3 (Vicon Motion Systems Limited). The timed-up-and-go (TuG) test will be performed 3 times. Five repetitions of sit-to-stand (STS), sit-to-stand-reverse (STSr), and squat-lifting (SQL) tests will be captured. Thereafter, participants will walk on a 5 m ramp with a 10° inclination, which will be equipped with 2 force plates (9260AA3; Kistler). After 5 left and 5 right foot strikes on the force plates for ramp-up walking (UP) and ramp-down walking (DOWN) each, participants will perform 5 trials of stair-up climbing (SUP) and stair-down climbing (SDOWN) on a 4-array force plate (9260AA3) instrumented stair. All tasks will be performed in a self-paced manner.

The overall duration of the assessment is estimated at 120 minutes. Single task durations and requirements of the assessments are presented in Table 2.

Table 2. Tasks performed during assessments and estimated duration in minutes.

Task	Repetitions/valid strikes	Estimated duration (minutes)
Interview status	1	10
Questionnaires	1	15
Height/body composition	1	5
Instruction activity monitor	1	5
RoM[a]/muscles	1	10
Applying markers/distances	1	10
Calibration	1	7
LW[b] right/left	5	8
STS[c]/STSr[d]	5	5
TuG[e]	3	5
SQL[f]	5	5
UP[g]/DOWN[h] right/left	5	20
SUP[i]/SDOWN[j]	5	7
Demounting markers/check	1	8

[a]RoM: range of motion.
[b]LW: level walking.
[c]STS: sit to stand.
[d]STSs: sit to stand reverse.
[e]TuG: timed up and go.
[f]SQL: squat lifting.
[g]UP: ramp-up walking.
[h]DOWN: ramp-down walking.
[i]SUP: stair-up climbing.
[j]SDOWN: stair-down climbing.

Level Walking

Participants will be instructed to walk self-paced at a comfortable speed between start and end marks. Familiarization trials will be carried out in the preparatory phase.

Timed-Up-and-Go Test

Participants will be instructed to start on a "go" signal with rising from a chair, walking 3 m, turning beyond the 3 m line, returning to the chair, and sitting down again. Considering the performance learning effect in performing the test, 2 familiarization trials will be carried out in the preparatory phase.

Sit-to-Stand and Sit-to-Stand-Reverse Tests

Participants will be instructed to stand up from a lower leg–normalized chair with self-paced speed, keep standing still, and, on the instructor's signal, sit down again. Considering the performance learning effect in relation to the shank length–normalized seat height, 3 familiarization trials will be carried out in the preparatory phase.

Squat Lifting

Participants will be instructed to lift a box with a 5 kg weight inside with both arms and keep standing still for a moment. Considering the performance learning effect in relation to the height of the box, 3 familiarization trials will be carried out in the preparatory phase.

Ramp Walking

Participants will be instructed to walk up and down the ramp at a self-selected comfortable speed between start and end marks

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without using the handrail. Familiarization trials will be carried out in the preparatory phase with a 10° inclination.

Stair Climbing

Participants will be instructed to walk up and down the stairs at a self-selected comfortable speed with the whole foot placed on the single arrays without using the handrail. Familiarization trials will be carried out in the preparatory phase.

The examination procedure described before will be performed at baseline (t_0) prior to the randomization and at 3 months (t_1) and 6 months (t_2) postsurgery. Follow-up assessments (t_1 and t_2) will be accompanied by a structured interview on exercise behavior and well-being. In addition, the IG will be interviewed concerning the acceptance of the RTF device and possible suggestions for improvements.

Agreement Between the Real-Time Feedback System

The RTF prototype that will be provided to the IG for home exercise is a combination (Figure 2) of the Intel® RealSense Depth Camera D435i (Intel Corporation), the mini-PC Radxa Rock 5 Model B 8GB (Radxa Ltd), and a Raspberry Pi USB-C Power Supply. Using the Intel RealSense SDK 2.0, the red-green-blue (RGB) data are streamed to the mini personal computer (PC) for extraction of a 17-point kinematic model by the machine learning tool for pose estimation, MoveNet.SinglePose V4 (Google Inc). Via a self-programmed user interface operated using an infrared remote controller, the prior developed feedback modes can be selected and started.

Figure 2. System components of the prototype.

The recorded image data, which may potentially identify a person, will be solely used for key point recognition purposes and will not be stored in any form. The RTF prototype has no wireless local area network (LAN), and the existing LAN

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connection is covered by the housing. Therefore, an internet connection is excluded and access from outside is not possible. The complete data processing will be carried out locally on the prototype. The following data will be stored on the SD card of the prototype: test person ID, body height, training time, achieved exercise scores, number of repetitions of the exercises, and coordinates of the key points. The SD card is located inside the housing, making it difficult to access or remove. The data from the SD card will be analyzed only by the project team and will not be passed on to third parties.

The prototype is not certified as a medical device and was therefore submitted to the Austrian Federal Office for Safety in Health Care for a safety review after a successful ethics vote. Relevant individual parts have a Conformité Européene (CE) mark of conformity.

To compare the RTF prototype with the optoelectronic reference system Vicon Nexus, both systems will be synchronized both temporally and spatially. Temporal synchronization will be achieved through a time-to-live (TTL) signal sent from the prototype to the reference system. Spatial synchronization will be ensured by calibrating the prototype's coordinate system to match the reference coordinate system. For assessing this agreement, testing participants from the IG will perform a single set of their home exercise program at t1 after performing the set of ADL tasks.

Group Exercise Program

Group exercise therapy will be guided by experienced physiotherapists in groups (as defined per cluster) of 2-5 patients. Patients will participate in 2 group exercise therapy sessions of 90 minutes each per week, with at least 48 hours of rest in between sessions during 8 consecutive weeks. Both the IG and the CG will be instructed and supervised in an equal program, which will only be individualized regarding intensity and repetitions, depending on each patient's capacity. Group exercise therapy will take place in a suitable room at FH Campus Wien, which will be equipped with the necessary therapeutical/exercise therapy equipment and supplementary aids. At the beginning of each session, the well-being of participants will be assessed and documented.

To ensure self-paced intensity and number of repetitions for participants during the group exercise therapy sessions, time-based sets of 60 seconds will be used. Within those sets, fixed breaks of 60 seconds for recovery will be implemented. For each exercise used in the protocol, variants with decreased and increased intensity will be offered to the participants to ensure appropriate stimulus. Both group exercise therapy interventions and the home exercise program for the IG and the CG will follow the frequency, intensity, time, and type of training (FITT) principle for exercise prescription and will be reported following the Consensus on Exercise Reporting Template (CERT) [34]. The group exercise therapy intervention will consist of a 15-mintue warm-up, 60-minute exercise, and a 15-minute cool-down phase. During the group -exercise phase, patients will be instructed to complete exercises, with focus on movement quality, and if applicable, for specific exercises, they will be instructed to perform the concentric phase of each repetition fast, shortly maintain the individual end-of-range tension, and slowly perform the eccentric phase to reach an approximate time under tension of 5-6 seconds per repetition. The physiotherapists will provide verbal guidance, encouragement, and motivation during the group exercise therapy intervention. With this self-paced protocol, participants will reach approximately 8-12 repetitions per set. The intensity of each exercise will be increased or decreased following participants' self-reported perceived rate of exertion with the help of the Borg CR10 scale [35]. Intensity will be increased if participants rate an exercise below 4 and decreased if they rate an exercise higher than 7. For all participants, the absolute exercise therapy load will be recorded. Patient-reported hip pain before and after exercise sessions will be assessed during warm-up and cool-down using the NRS-10, graded from 0 (no pain) to 10 (worst pain imaginable). Pain levels from 0 to 2 will be considered safe, from 3 to 5 acceptable, and >5 as not acceptable. On the following day after the exercise therapy intervention, pain should be reduced to the participants' usual level, or the load will be decreased in the next session. Table 3 presents an overview of the intervention, and a detailed list concerning the planned exercise therapy intervention program, including exercise variants and steps of progression, can be found in Multimedia Appendix 2 following the CERT checklist [34].

Table 3. Structure and content of exercise sessions.

Phase	Description	Duration (minutes)
Warm-up	• Each session will begin with a warm-up for general activation, starting with assessing the individual well-being/pain level of participants and continuing with simple and self-paced exercises in the sitting and standing positions.	15
Exercise	• Sitting exercises: forefoot eversion with loop, activation exercises for lower limbs. • Floor exercises in supine and side positions + exercise mat): bridging, clam-shell, abduction/adduction exercises. • Standing exercises: pelvic hinge, squat, mini-SLS[a], flexion/extension/abduction/adduction exercises. • Gait training: gait phases, step up, lunge, calf raise.	60
Cool-down	• Each session will end with a 15-minute cool-down for reflexion, starting with simple and self-paced stretching/mobilization in sitting and standing positions, assessing the individual well-being/pain level of participants postexercise, and reporting the total exercise load of the session.	15

[a]SLS: single-leg stance.

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Home Exercise Program

In addition to semiweekly exercise therapy sessions, a daily 30-minute home exercise program, excluding days with the group exercise program, will be performed by participants. The home exercise program will be self-documented by the participants in an exercise diary, including the day, the exercises performed, number of repetitions, pain on the NRS-10, and perceived exertion on the Borg CR10 scale [35].

Both groups will receive printed handouts describing each exercise, as well as the full home exercise program in detail. Both groups will also receive standard care treatment, including the same group exercise and home exercise programs. The IG group will perform the home exercise program supported by the digital real-time exercise feedback prototype for digitally guided training (Figure 3).

Figure 3. Example of the feedback presented for a single exercise.

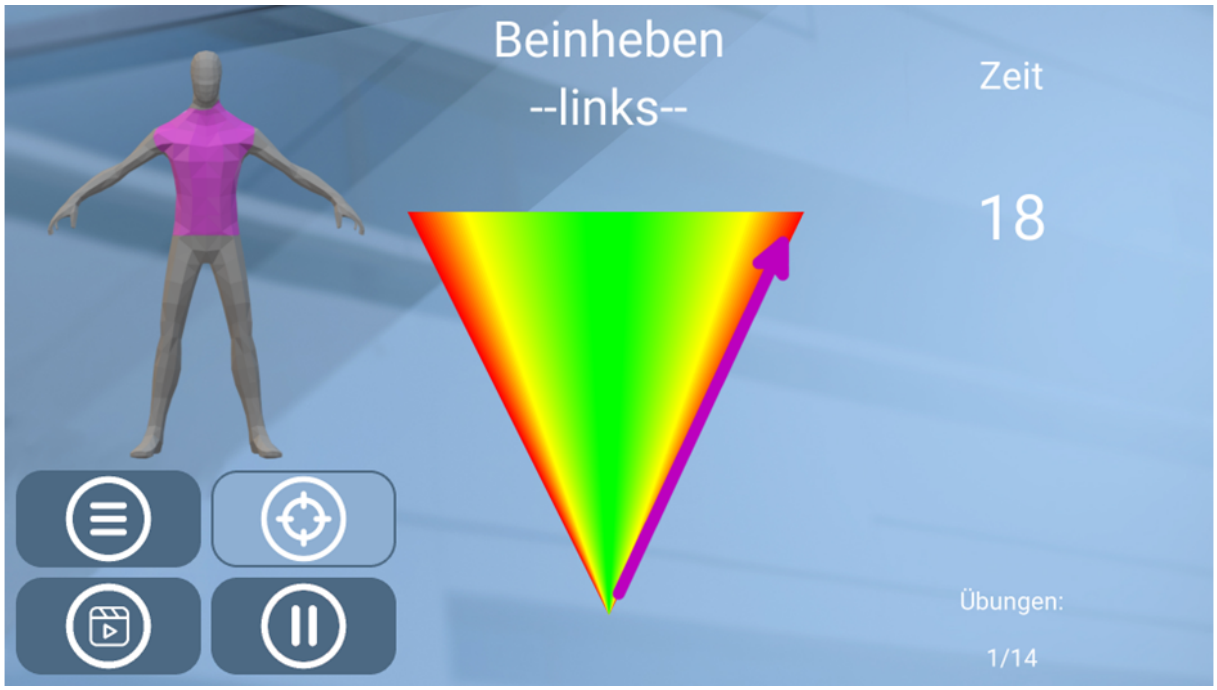

Therapeutic Adherence

Adherence to the therapeutic control and intervention will be recorded based on (1) participation in 16 group exercise sessions and (2) self-reported adherence to 40 home exercise sessions. Participants will be classified as nonadherent (and consequently excluded from the analysis) if participation is below 25% of the group exercise sessions (ie, less than 4 sessions) or below 25% of the home exercise sessions (ie, less than 10 sessions). Based on further 50% and 75% cutoffs, therapeutic adherence will be classified into (1) nonadherent, low, medium, or high.

Outcome Parameters

An overview of the outcome parameters related to the primary, secondary, and tertiary hypotheses is presented in Table 4. The raw data, processed data, and task parameters are described in detail next.

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Table 4. List of outcome parameters according to primary, secondary, and tertiary hypotheses.

Hypotheses	Outcome measures
Primary	Frontal knee angle RoM[a] (°)
	Pelvic obliquity angle RoM (°)
	Frontal trunk angle RoM (°)
Secondary	HHS[b] (sum)
	HOOS[c] (sum)
	SF-12[d] (sum)
	IPAQ-SF[e] (sum)
	KOOS[f] (sum)
Tertiary	3DMA[g] kinematic parameters
	3DMA kinetic parameters
	3DMA spatiotemporal parameters

[a]RoM: range of motion.

[b]HHS: Harris Hip Score.

[c]HOOS: Hip Osteoarthritis Outcome Score.

[d]SF-12: 12-item Short Form Health Survey.

[e]IPAQ-SF: International Physical Activity Questionnaire –Short Form.

[f]KOOS: Knee Injury and Osteoarthritis Outcome Score.

[g]3DMA: three-dimensional movement analysis.

Raw Data

Raw data are defined as directly measured data before they have been processed. The raw 3D data file is a binary file that will contain the recorded marker positions of the individual cameras, and another binary file exists that will contain the analog input signals of the force plates.

Processed Data

Processed data are data that are constructed from raw data. The data from the individual cameras will be merged and the trajectories of the markers reconstructed. Next, the trajectories will be filtered and a label assigned to them. A biomechanical model will be constructed using the data from the marker trajectories and the force plates. This biomechanical model will provide the trajectories of joint angles, joint moments, joint powers, and ground reaction force. These trajectories, as well as the anthropometric data collected and the time points of gait events, will be stored in binary form in so-called c3d-files

Analyzed Data

The parameters related to locomotion tasks will be normalized to gait and stance phases. The stance phase will be defined between the heel-strike and toe-off of the observed leg. Cyclic tasks will be normalized to start, turn, and end events. The circuit task TuG will be split into sit-to-walk, straight walking, turn, and walk-to-sit. STS and STSr will be analyzed according to the literature using the lift-off event. The ADL task SQL will be spatially defined by start, turn, and end events. During the exploration of the database, new variables will be calculated and reported.

Kinematic data will be time-normalized from heel strike to heel strike, and kinetic data will be time-normalized from heel strike to toe-off. Individual participant data will be expressed as an average per condition. Time normalization, data processing, and parameter calculations will be conducted using self-developed scripts in MATLAB 2018a (Mathworks). The analyzed data will be stored as single cycles, averaged cycles, and single data at certain time points in a .mat file. With the help of a self-written MATLAB tool, these .mat files will be made searchable with arbitrary filter settings. All data can also be used in future analyses according to the latest scientific knowledge.

Activity-Monitoring Data

Activity-monitoring data collected for 2 days prior to surgery and at t_0, t_1, and t_2 for 7 days will be stored as acceleration raw data and analyzed using the latest version of ActiLife software (ActiGraph LLC). Prior to parameter calculation, cutoffs of a minimum of 10 hours wear time a day, 3 valid weekdays, and 1 valid weekend day will be applied. Physical activity intensity will be categorized and daily step counts extracted [36].

Body Composition Data

Raw data of body composition measurements will be processed for the parameters body muscle mass, left and right leg muscle mass, and body fat rate.

Patient Characteristics

In addition to age, gender, and biometric characteristics, each patient's additional information, such as therapy adherence and physical activity, will be obtained for a possible confounding effect on the results (Table 5).

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Table 5. List of patient characteristic parameters.

Characteristic	Measure
Biometric	• Body height (m) • Body mass (kg) • Body fat mass (% body weight [BW]) • Muscle mass (% BW) • Left/right muscle mass (kg)
Personal	• Age • Gender • Private health insurance • Surgeon • Therapy adherence (by category) • Physical activity (by activity category and step counts)

Statistical Analysis

Data will be inspected for outliers using boxplots. Shapiro-Wilk tests and additional graphical inspections of q-q plots will be applied to test for the normality assumption. Metric baseline characteristics will be indicated as means (SDs) and categorical baseline characteristics as frequencies (n, %). Unadjusted outcome scores will be reported as means (95% CIs). People from the same cluster tend to be more similar than those from different clusters, and the analysis must allow for this. A common enhancement is to apply a linear mixed effects model with the cluster specified as a random intercept. To model changes between baseline and follow-up, we will include baseline measurements as covariates. Following suggestions by Klar and Darlington [37], we will adjust for each participant's baseline assessment and for the baseline cluster mean. Otherwise, no adjustments for covariates are foreseen. Treatment effects will be reported independently for follow-up t_1 and follow-up t_2, including unstandardized and standardized regression coefficients as effect estimates, standard errors, *t* statistics, and appropriate *P* values via the Satterthwaite degrees-of-freedom method. Between-cluster and residual variances will be reported for all outcomes. In the case of severe outliers or major violations of the normality assumption, logarithmic data transformation approaches will be explored. Outcome parameters on the ordinal scale will be analyzed descriptively and reported as medians with ranges. All descriptive statistics and corresponding numbers of subjects (n, %) will be reported, along with losses to follow-ups. Effect sizes will be calculated and reported accordingly (per protocol). In addition, the hypotheses will be analyzed according to the intention-to-treat principle (last value carried forward), providing a more conservative effect estimate [38] when missing observations introduce bias. The α value will be set to .05, and exact 2-sided *P* values will be reported. Hypotheses will be tested independently of each other. The 2-armed study design does not require post hoc tests, so no adjustment for familywise α error accumulation is needed.

Additionally, the agreement between the RTF prototype and the optoelectronic reference system will be analyzed. The spatial deviation of anatomical body key points from the reference system's key points will be determined using the root mean square error (RMSE). The measured RoM for the angle between the trunk and the thigh, as well as the angle between the thigh and the shank, will be displayed and interpreted using the Bland-Altmann plot.

Ethical Considerations

This study was approved by the Ethics Committee of the City of Vienna (EK-23-103-0623). Further authorization for medical device investigation was obtained from the Austrian Federal Office for Safety in Health and Care (BASG; 10239778, 2023-27-10). The trial was registered at ClinicalTrials (NCT06161194, December 7, 2023). The final protocol approved by the Ethics Committee refers to version 3.3 from December 7, 2023. Recruitment was planned to begin on December 19, 2023, and will approximately be closed by November 6, 2024.

Participants will be assigned a continuous study code (THA01-THA70) to protect identifiable data. The assignment key will be locked in the study manager's office, separate from identifiable study data.

Results

The trial started in January 2024, and the first results are anticipated to be published by June 2025. Based on the knowledge from comparable (to some extent) studies on RTF effectiveness in motor re-education conditions, we expect that RTF-supported home exercise will tend to be more effective compared to using paper instructions for exercise guidance. This effect might be reported for all 3 hypotheses (functional deficits, quality of life, and activity questionnaires), as well as biomechanical parameters.

Discussion

Principal Findings

RTF-supported home exercise is expected to improve exercise execution quality and therapeutic adherence compared to using paper instructions for exercise guidance. As a consequence thereof, we anticipate superior results for the selected outcome measures in the IG.

Limitations and Problems Anticipated

Participants might not be able to perform ramp walking or stair climbing without the use of handrails at baseline assessment. Dropouts are likely to occur, and thus, they may introduce a

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risk of attrition bias and, in the worst case, demand the premature termination of the study.

Concerning the use of the HHS and HOOS, subitems of these questionnaires will be interpreted cautiously in view of the limitation that they have been developed for patients with hip OA who did not undergo THA.

Conclusion

To the best of our knowledge, this is the first study to investigate the effect of RTF-supported home exercise following THA. Hypotheses will be tested not only using PROM data but also by means of objectively measured kinematic and kinetic data. Based on the results, the knowledge of more effective rehabilitation pathways after THA and the functional performance of patients 6 months postsurgery will be improved.

Acknowledgments

KW, LM, and SLB conceptualized the study. KW designed the study protocol. KW and LM designed the interventions. SD, LM, and KW developed the feedback application. PP and KW designed the statistical workflow. HK and PA supervised during study conceptualization. All authors provided feedback on the drafts of this paper and approved the final version of the manuscript.

This trial is set up as a 2-center study. The principal investigator (SLB) is responsible at the recruitment site, Orthopaedic Hospital Speising and also monitors the assessments and interventions at FH Campus Wien, where KW is responsible for the trial. The sponsor is located at FH Campus Wien.

Data Availability

Study data will be made available upon reasonable request and for noncommercial purposes.

Conflicts of Interest

None declared. This work is produced within the research project SETT (Smart Real-Time Feedback-Assisted Training Therapy) [39], funded within the 30th University of Applied Sciences Call for Proposals (Research at the Viennese Universities of Applied Sciences") by Municipal Department 23 of the City of Vienna.

Multimedia Appendix 1
Translated health check and interview protocols.
[ZIP File (Zip Archive), 528 KB - resprot_v13i1e59755_app1.zip]

Multimedia Appendix 2
Translated home exercise instructions and exercise overview.
[ZIP File (Zip Archive), 1510 KB - resprot_v13i1e59755_app2.zip]

Multimedia Appendix 3
Funding approval and peer review comments (translated version).
[ZIP File (Zip Archive), 223 KB - resprot_v13i1e59755_app3.zip]

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Abbreviations

3DMA: three-dimensional movement analysis
ADL: activity of daily living
CERT: Consensus on Exercise Reporting Template
CG: control group
DOWN: ramp-down walking
HHS: Harris Hip Score
HOOS: Hip Osteoarthritis Outcome Score
IG: intervention group
IPAQ-SF: International Physical Activity Questionnaire –Short Form
KOOS: Knee Injury and Osteoarthritis Outcome Score
LAN: local area network
LW: level walking
NRS-10: 10-item Numeric Rating Scale
OA: osteoarthritis
PROM: patient-reported outcome measure
RoM: range of motion
RTF: real-time feedback
SDOWN: stair-down climbing
SF-12: 12-item Short Form Health Survey
SLS: single-leg stance
SQL: squat lifting
STS: sit to stand
STSr: sit to stand reverse

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SUP: stair-up climbing
THA: total hip arthroplasty
TuG: timed up and go
UP: ramp-up walking

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Protocol

Effects of a Parent-Child Single-Session Growth Mindset Intervention on Adolescent Depression and Anxiety Symptoms: Protocol of a 3-Arm Waitlist Randomized Controlled Trial

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Abstract

Background: Depression and anxiety are common mental health problems among adolescents worldwide. Extant research has found that intelligence, emotion, and failure-is-debilitating beliefs (fixed mindsets) are closely related to more depression and anxiety symptoms, hopelessness, and suicidality. Recent research also points to the importance of parental mindset, which can strongly influence children's affect, behavior, and mental health. However, the effects of parent-child mindset interventions on a child's internalizing problems have not yet been empirically examined. As recent evidence has shown the promise of single-session interventions in reducing and preventing youth internalizing problems, this study develops and examines a parent and child single-session intervention on mindsets of intelligence, failure, and emotion (PC-SMILE) to tackle depression and anxiety in young people.

Objective: Using a 3-arm randomized controlled trial, this study will examine the effectiveness of PC-SMILE in reducing depression and anxiety symptoms among children. We hypothesize that compared to the waitlist control group, the PC-SMILE group and child single-session intervention on mindsets of intelligence, failure, and emotion (C-SMILE) group will significantly improve child depression and anxiety (primary outcome) and significantly improve secondary outcomes, including children's academic self-efficacy, hopelessness, psychological well-being, and parent-child interactions and relationships, and the PC-SMILE is more effective than the C-SMILE.

Methods: A total of 549 parent-child dyads will be recruited from 8 secondary schools and randomly assigned to either the PC-SMILE intervention group, the C-SMILE intervention group, or the no-intervention waitlist control group. The 45-minute interventions include parent-version and child-version. Both parents and students in the PC-SMILE group receive the intervention. Students in C-SMILE group receive intervention and their parents will receive intervention after all follow-up ends. Students in 3 groups will be assessed at 3 time points, baseline before intervention, 2 weeks post intervention, and 3 months post intervention, and parents will be assessed in baseline and 3-month follow-up. The intention-to-treat principle and linear-regression-based maximum likelihood multilevel models will be used for data analysis.

Results: Recruitment started in September 2023. The first cohort of data collection is expected to begin in May 2024 and the second cohort will begin in September 2024. The final wave of data is expected to be collected by the end of the first quarter of 2025. The results are expected to demonstrate improved anxiety and depression among students assigned to the intervention condition, as well as the secondary outcomes compared to those in the control group. The efficacy and effectiveness of the intervention will be discussed.

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Conclusions: This study is the first attempt to develop a web-based single-session intervention for students and their parents to enhance their well-being in Hong Kong and beyond, which potentially contributes to providing evidence-based recommendations for the implementation of brief digital parent-child interventions.

International Registered Report Identifier (IRRID): PRR1-10.2196/63220

(JMIR Res Protoc 2024;13:e63220) doi:10.2196/63220

KEYWORDS

implicit theory; fixed mindset; mental health; secondary school students; belief in change

Introduction

Background

Depression and anxiety are the leading causes of disability among adolescents worldwide [1]. In Hong Kong, 1 in 4 secondary school students report moderate to severe depression or anxiety symptoms [2]. Around 1 in 12 have been diagnosed with severe depression or anxiety disorders [3]. It is estimated that about 43,500 to 87,000 secondary students need support or intervention to manage their symptoms [4], but 65% of these students fail to access mental health services due to lengthy waitlists, costly clinic-based treatments, or concerns of stigmatization or discrimination [5]. Developing these disorders early in life can increase young people's suicidal risk and lead to a wide range of psychological and vocational impairments that result in harmful long-term effects [6], especially if left untreated or given insufficient support. Thus, there is a need for integrated and effective interventions that are acceptable to families, cost-effective, and nonstigmatizing to tackle these disorders by providing early intervention and preventing deterioration.

There is substantial, robust evidence on risk and protective parenting factors for adolescent anxiety and depression [7,8]. Beyond structural elements such as academic stress [7], increasing evidence highlights the importance of parent and child belief systems, which are potentially modifiable. Mindset studies have identified that a fixed mindset (ie, believing one's attributes are unchangeable) is a key predictor of youth mental health symptoms [9-12], while interventions promoting a growth mindset (ie, believing one's attributes are changeable) effectively reduce adolescent depression and anxiety symptoms [13,14]. Research has also revealed that parents' fixed mindset regarding intelligence and emotions can lead to more internalizing problems such as depression and anxiety among children and lower perceived control over mental health symptoms [15-18]. Children in fixed-mindset households might question their abilities, use ineffective coping strategies, and experience greater helplessness [9].

Research on implicit theory has found that people who believe that personal attributes can be developed (also referred to as growth mindset) are more likely to thrive in the face of difficulty and continue to improve. In contrast, those who hold a more fixed mindset may shy away from challenges or fail to meet their potential [19,20]. A growth mindset intervention's core content teaches that people's attributes, such as intelligence, personality, or emotions, can change and that people can improve through the actions they take (eg, making an effort, changing strategies, learning from failures, and asking for help) [19,21,22]. Emphasizing the potential to change in mindset interventions of 30 minutes to 1 hour resulted in different change effect sizes, from d=0.1 in changing school performance in a large-scale national study among heterogenous participants [23] to d=0.59 in randomized controlled trials (RCTs) on reducing anxiety [14]. Considering the brevity of the interventions and the effect sizes in relation to heterogeneity and contextual factors, low-intensity interventions on mindset have demonstrated high potential scalability for mental health prevention and early intervention measures.

Well-crafted growth mindset interventions promoting a core growth mindset are crucial to securing the effects of the intervention [19]. Existing interventions have focused on growth mindsets for intelligence [19,23], personality [14,24], and emotion [22] to promote school performance and resilience and to reduce mental health symptoms. Although these domain-specific growth mindset interventions have achieved positive improvements, there has never been an integrated intervention addressing multiple core growth mindsets. The factors for youth depression and anxiety are multifaceted, such as academic stress, failures and uncertainty in life, and the emotional struggles of puberty. Teaching multiple relevant growth mindsets in 1 intervention may address several key risk factors and strengthen the potency of growth mindset interventions to better reduce youth depression and anxiety symptoms. The proposed study will address this research gap by developing and examining an integrated intervention targeting growth mindsets for youth internalizing symptoms.

Parental mindsets matter for adolescents' mindsets and internalizing problems such as depression and anxiety [16,17]. Parents are the most direct social support for adolescents, but parents can also be a source of stress if they hold a fixed mindset and think failure is debilitating. For example, parental fixed mindsets about intelligence predict depression symptoms and social anxiety as children have more performance worries and are afraid of negative evaluation [17]. Parents' failure mindset also influences parenting practices in the face of setbacks [16]. A fixed emotion mindset and failure-is-debilitating beliefs in parents were associated with passive help-seeking preferences for children's mental health symptoms [18]. In contrast, building belief-in-change about intelligence and emotion may relieve family concerns about failure, mental health symptoms, and stigmatization, increase perceived control and active help-seeking, and build better parent-child relationships. As parents play a crucial role in preventing children's internalizing problems [25], joint parent-child growth mindset intervention

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is warranted and promising for promoting both parental and child well-being.

Although there is evidence of the importance of parents and children's mindsets in internalizing symptoms, we have identified 3 important research gaps which will be tackled in the present study. First, current interventions usually focus on fixed mindsets of a single domain—such as intelligence, personality, or emotion [14,22]—but have rarely used a few relevant mindset domains in one intervention, which are closely related to youth mental health. An integrated mindset intervention is very likely to strengthen intervention efficacy, especially for brief interventions. Second, although there is an ongoing parent-child mindset intervention to promote treatment access in the United States [26], there is no such intervention in the Chinese context. In Chinese culture, parents are very anxious about their children's education [27], and parental mindset is more likely to influence children's mental health [28]. Third, although evidence highlights the remarkable promise of preventive parenting interventions, parenting programs are often not used even when available because of barriers such as scheduling difficulties and privacy concerns [6]. Thus, it is important to develop brief, accessible, and nonstigmatizing interventions for parents and children.

The current study will therefore develop and examine a web-based parent and child single-session intervention on mindset of intelligence, failure, and emotion (PC-SMILE). The research question is if the PC-SMILE effectively reduce depression and anxiety symptoms among secondary school students and how does it impact academic self-efficacy, psychological well-being, hopelessness, and parent-child interactions and relationships.

Objectives

The primary objective of this study is to evaluate the effectiveness of the PC-SMILE in reducing depression and anxiety symptoms in secondary school students (primary outcome). The secondary objective is to examine the effectiveness of the PC-SMILE in (1) enhancing academic self-efficacy, enhancing psychological well-being, and reducing hopelessness; and (2) enhancing parent-child interactions and relationships (secondary outcomes).

Hypotheses

This study will examine the effectiveness of the PC-SMILE for adolescents and their parents by comparing it to a child single-session intervention on mindset of intelligence, failure, and emotion (C-SMILE) intervention group that provides the child-version intervention to children only and a no-intervention waitlist control group.

Our hypotheses are the following:

H1: The PC-SMILE and C-SMILE groups have better improved primary outcome compared to the waitlist control group, including reducing anxiety and depression symptoms in student participants, while PC-SMILE is more effective than C-SMILE.

H2: The PC-SMILE and C-SMILE are more effective in the secondary outcomes of (1) reducing hopelessness, (2) enhancing academic self-efficacy, (3) enhancing psychological well-being, and (4) enhancing parent-child interactions and relationships than waitlist control, and PC-SMILE is more effective than C-SMILE.

Methods

PC-SMILE Intervention

Although single-session interventions (SSIs) are a relatively new intervention approach for youth mental health, rich empirical evidence has suggested the promise of SSIs for youth mental health promotion in matters such as increasing hope and happiness [29]; adaptive coping with peer stressors [30]; and improving perceived control, stress recovery, and anxiety and depression symptoms [14]. According to the literature on promoting SSI effectiveness [19,31,32] and our experience in developing SSIs in the Chinese culture [22], the PC-SMILE was designed with 5 important features to ensure efficacy.

First, the PC-SMILE addresses core beliefs related to youth depression and anxiety. The selection of intelligence, emotion, and failure mindset is based on the extant literature [17,33-36] and our fieldwork in schools based on parent and public involvement. By instilling the belief that "intelligence and negative emotions are changeable" and "failure is necessary for personal growth," this innovative integrated intervention has a high potential to relieve parents and children's stress and to promote well-being.

Second, the PC-SMILE was designed based on concepts and findings based on neuroscience to normalize the concepts of a growth mindset; for example, the concept of neuroplasticity is introduced to explain how and why personal traits are malleable. The core message is conveyed to participants through scientific videos and memorable metaphors. The PC-SMILE uses the muscle metaphor (ie, the brain is like a muscle, it becomes stronger and smarter when you exercise it) [19] for both students and parents, and it uses the planting metaphor for parents to emphasize the importance of patience, respect for individual differences and support for children. Illustrating ideas with metaphors is more likely to motivate sustained behavioral change [19].

Third, PC-SMILE empowers both students and their parents to act as "helpers" or "experts" by framing the participants as active contributors to the improvement of the intervention and by asking them to provide support to peers [14,32]. This design aligns with adolescents' desire for respect [31].

Fourth, as in previous interventions [14,32], storytelling is a powerful feature of the PC-SMILE. Participants learn the stories from valued others, such as older peers and experts, which is helpful in conveying the core messages of the growth mindset. We also use the "saying-is-believing" exercise to invite the participants to share their learnings from the intervention with future intervention users. This exercise helps participants to internalize the growth mindset through cognitive dissonance processes [19,37].

Fifth, as the effects of SSIs may wane over time, booster messages will be adopted in the PC-SMILE. Weekly booster reminders [38] of core growth mindset quotations will be sent

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to both parent and child participants via email or text messages to sustain the mindset and behavioral changes.

Research Design

This study will be a 3-arm cluster-RCT with a waitlist control group design. A conceptual model is provided in Figure 1. The intervention protocol will strictly follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines [39,40] and has been preregistered before data collection in Open Science Framework and ClinicalTrials.gov. Classes in each eligible school will be randomized (using computer-generated random numbers) into the PC-SMILE intervention, C-SMILE, or waitlist group. The waitlist group will undergo intervention after the 3-month postintervention survey. All student participants will receive regular educational activities and interventions in school. A total of 3 repeated assessments of the measures will be conducted simultaneously for the children in three groups at (1) baseline, (2) 2-weeks post intervention, and (3) 3-months post intervention (Multimedia Appendix 1). The CONSORT flow diagram is provided in Figure 2. Cluster randomization will be conducted at the class level.

Figure 1. Design of the 3-arm waitlist randomized controlled trial. C-SMILE: child single-session intervention on mindset of intelligence, failure, and emotion; PC-SMILE: parent and child single-session intervention on mindset of intelligence, failure, and emotion.

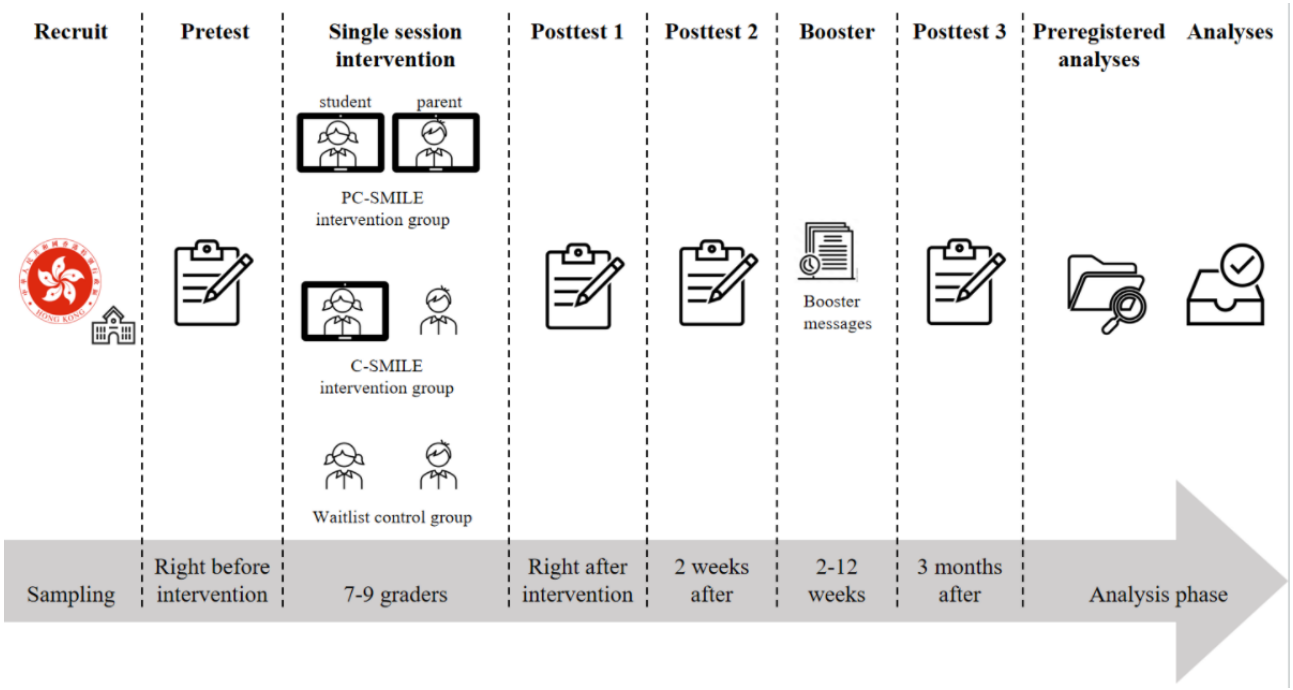

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Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. C-SMILE: child single-session intervention on mindset of intelligence, failure, and emotion; PC-SMILE: parent and child single-session intervention on mindset of intelligence, failure, and emotion.

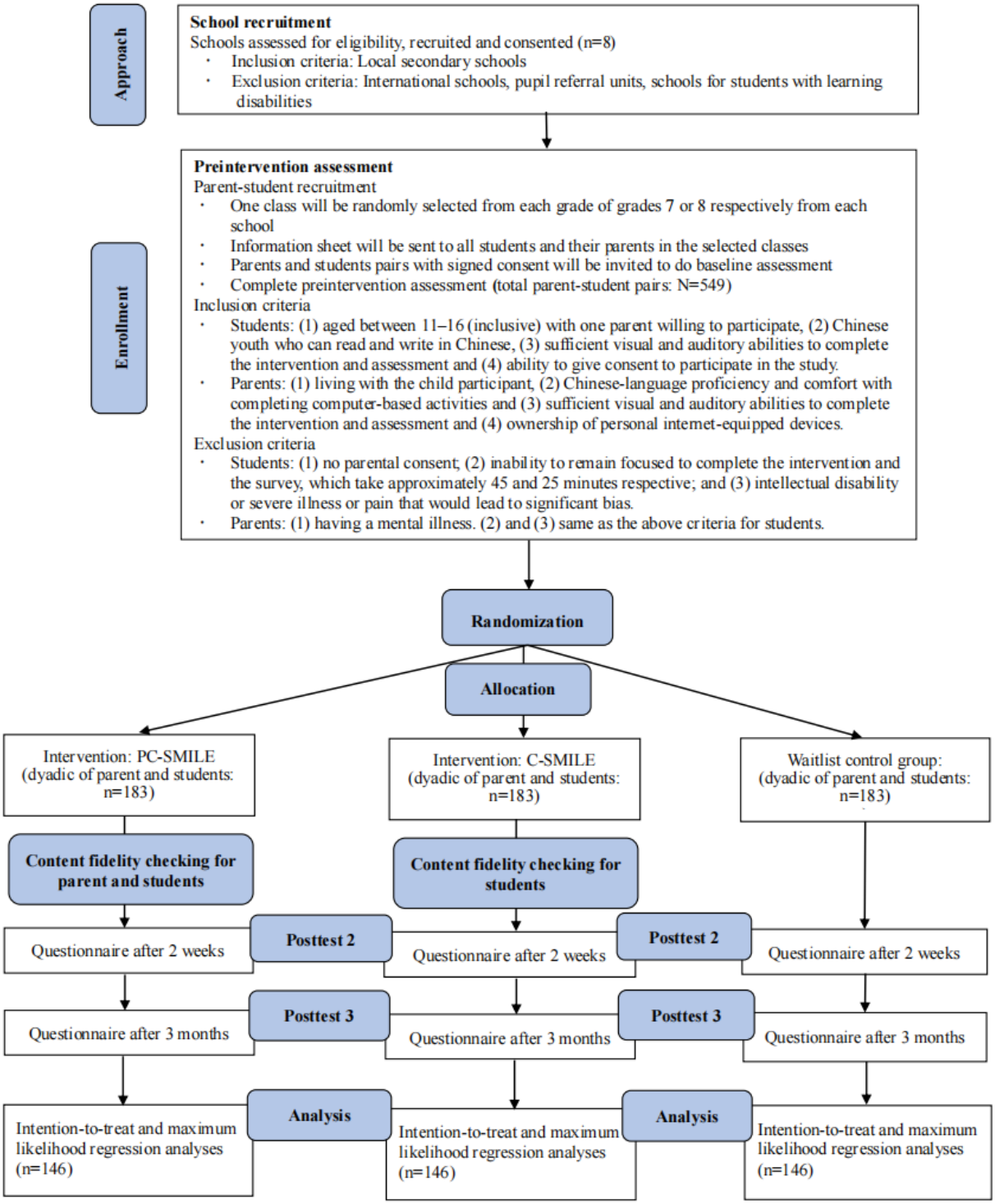

Sample Size Determination

Overview

We assume a small to medium effect size (Cohen *d*=0.33) of the current intervention according to a meta-analysis of SSIs addressing youth psychiatric problems [13], a power of 0.80 and an α of .05. A sample size of 438 (146 per arm) is required to detect statistical significance. With reference to the approximately 20% attrition rate of our previous studies in the school setting, 549 pairs of parent-student participants will be recruited at the baseline (183 per arm). Our existing research suggests that this is feasible within the timeframe.

Participants and the Randomized Control Process

Eligible adolescents in grades 7-8 and their parents will be recruited from 8 secondary schools through cluster-randomized

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sampling. The inclusion criteria for adolescent participants will include (1) aged between 11-16 years (inclusive) with 1 parent willing to participate; (2) Chinese youths who can read and write in Chinese language; (3) sufficient visual and auditory abilities to complete the intervention and assessment; and (4) ability to give consent to participate in the study. Exclusion criteria for adolescent participants will include (1) no parental consent; (2) inability to remain focused to complete the intervention and the survey, which take approximately 45 and 25 minutes respectively; and (3) intellectual disability or severe illness or pain that would lead to significant bias in students' health and mental health situation.

Inclusion criteria for parent participants are (1) living with the child participant; (2) Chinese-language proficiency and comfort with completing computer-based activities; (3) sufficient visual and auditory abilities to complete the intervention and assessment; and (4) ownership of personal internet-equipped devices. Exclusion criteria for parent participants include (1) having a mental illness as well as exclusion criteria (2) and (3) from the aforementioned criteria for adolescent participants.

The school and student recruitment process will include the following steps. First, we will send research invitations to schools chosen randomly from the secondary school list covering 3 areas of Hong Kong (ie, Hong Kong Island, Kowloon, and the New Territory). Invitations will not stop until 8 schools agree to participate. Then, 3 classes from grades 7 or 8 will be selected by a random number, and all students in the selected class will be invited to join the study. There are generally 35 students in 1 class. We estimate that approximately 25 pairs of parents and students will join the study. If too few participants join the study, the random class selection process will be repeated until 70 pairs of eligible parent-child participants in each school are recruited. Using random numbers, the selected 3 classes will be assigned to the PC-SMILE intervention group, the C-SMILE intervention group, and the waitlist control group. If the targeted sample size is met, the school invitation and recruitment will stop.

Students and parents will complete all study procedures via personal internet-equipped devices. Parent-student pairs will be assigned to the same condition (the PC-SMILE or C-SMILE or waitlist). They will receive the link of research material and complete Qualtrics-based baseline survey, intervention, and follow-up surveys independently. For student participants, the interventions will be conducted in school classrooms or activity rooms that offer sufficient computers or tablets, and headphones. All intervention activities will be self-administered by youths and delivered in a web-based format. The research team and trained research assistants will remain in the intervention rooms to provide help if needed. Parent participants will receive a study link with the baseline Qualtrics survey and the intervention. The interventions for parents and students are different in terms of narrative and content. Between the 2-week posttest and the 3-month follow-up survey, a total of 5 weekly booster messages with core intervention content will be sent to the intervention groups every 2 weeks. After completion of the 3-month follow-up, parents in the C-SMILE or the control group who do not initially receive the intervention will be granted the intervention access.

Intervention Groups

PC-SMILE Group

The PC-SMILE integrates the growth mindsets of intelligence, failure, and negative emotions and introduces these growth mindsets to students and parents. The interventions for both students and parents consist of five components: (1) an introduction to brain functions regarding the potential of neuroplasticity and the possibility of changes in intelligence and emotions, (2) stories and testimonials from school-aged youths who describe their belief-in-change, (3) short videos with stories of improving intelligence and emotions and of failure-is-enhancing, (4) common questions and misconceptions about growth mindset, and (5) self-persuasion writing exercises in which the participants write notes to young students or others about the growth mindsets. The interventions for parents and students are different in terms of narrative and content. Between the 2-week posttest and the 3-month follow-up survey, a total of 5 weekly booster messages with core intervention content will be sent to the intervention groups every 2 weeks. The interventions for children and parents last 45 minutes.

C-SMILE Group

In the C-SMILE group, only students receive the child-version intervention, but their parents do not receive parent-version intervention until the 3-month follow-up is finished. Parents are invited to do the preintervention survey and the 3-month follow-up survey.

Waitlist Control Group

The waitlist control group will continue with normal education activities and do the preintervention and follow-up surveys at the same timeframe as the intervention groups. Participants and their parents in the waitlist group will be invited to complete the PC-SMILE after the 3-month follow-up survey.

Measurements

Participants will be invited to read the instructions of the survey and complete self-rated scales. All the measures have been pilot-tested, and the questionnaires take approximately 25 minutes to complete.

Mindset about intelligence will be measured using the 3-item Implicit Theory of Intelligence Scale, which measures beliefs about the malleability of intelligence (eg, "You have a certain amount of intelligence and there is really not much you can do to change it") [41,42]. Each item is rated on a 6-point scale (1=strongly disagree to 6=strongly agree). A higher score represents a more fixed mindset. The Cronbach α in the previous study was 0.87 with good validity [42,43].

Mindset about failure will be measured by the 6-item Implicit Theory of Failure Scale [16], which measures views of failure as enhancing versus debilitating on a 6-point Likert scale (1=strongly disagree to 6=strongly agree). A sample item of an enhancing belief is "The effects of failure are positive and should be used," and a sample item of a debilitating belief is "The effects of failure are negative and should be avoided." Enhancing belief items will be reverse scored. A higher score reflects more debilitating beliefs. The Cronbach α of the parent survey in the previous study was 0.88 [16].

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Mindset about emotion will be assessed using the validated Chinese version of the 12-item Mindset of Depression, Anxiety, and Stress Scale [35] to measure children's belief in the change of negative emotion states. Sample items include "When you have a certain level of depression/anxiety/stress, you really cannot do much to change it." Parents' mindset about emotion will be measured by a 4-item version of Mindset of Depression, Anxiety, and Stress Scale, which includes sample item "If they want to, people can change the emotions they have." Each item is scored on a 6-point Likert scale (1=strongly disagree to 6=strongly agree), and a higher score means a more fixed mindset (Cronbach α=0.94) [35].

Primary Outcome

Children's depression and anxiety symptoms will be measured using the validated 25-item Revised Children's Anxiety and Depression Scale for both children and parents [44,45]. Sample items measuring anxiety and depression include "I/My child worry when I/My child think I/My child have done poorly at something" and "'I/My child feel sad or empty." The frequency of each item is rated on a 4-point Likert scale with reference to the past 2 weeks (0=never to 3=always). The child survey has an overall score, total anxiety score from the anxiety subscale (Cronbach α=0.94), and total depression score from the depression subscale (Cronbach α=0.79) [44].

Secondary Outcomes

The 4-item Hopelessness Scale [46,47] will be used to measure children and parents' faith in the future. Each item is scored on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree, and the mean of all 4 items is taken to measure hopelessness, with a higher score corresponding to a higher level of hopelessness. An example item is "My future seems dark to me." The Cronbach α was 0.834 with good validity [48].

The validated Chinese version of Short Warwick-Edinburgh Mental Well-Being Scale [49,50] will be used to measure children's and parents' general experience of well-being. The Short Warwick-Edinburgh Mental Well-Being Scale includes 7 items scored on a 5-point Likert scale from 1=none of the time to 5=all the time, and the average of all 7 items indicates participants' well-being. A higher averaged score represents a higher level of well-being. A sample item is "I have been feeling optimistic about the future." The Cronbach α was 0.93 [50].

Parent-child interactions will be assessed by 3 self-developed questions about how many days the children spend more than 15 minutes per day doing activities with their parents in a week. Children will answer the frequency by the number of days from 0=none to 7=seven days. Parenting activities include chatting, handing out, and watching television or movies or videos. Student participants who rate higher frequency of the parenting activities have better interactions with parents. Parent-child relationships will be measured using 3 self-developed items. Questions are "I am very satisfied with the relationship between me and my parents," "I proactively tell my family what had happened to me," and "I proactively share my feelings with my family" for adolescents. The adapted items "My children are very satisfied with the relationship between them and their parents," "My children proactively tell me what had happened to them," and "My children proactively share their feelings with me" are for parents. Each item is rated on a 4-point Likert scale (1=strongly disagree to 4=strongly agree). A higher score indicates a better parent-child relationship.

Perceived parent learning versus performance orientation will be assessed from both children and parents' perspectives. Child-version has 8 items and parent-version has 12 items, with half of the items measuring performance-orientation and half measuring learning orientation mindset, respectively [16]. The scale asks participants about the parents' responses to a scenario when their child gets a poor grade on a quiz. Sample items of performance-orientation are "My parents don't like it when I make mistakes in school" (child-version) and "I might worry (at least for a moment) that my child isn't good at this subject" (parent-version). Sample items of learning-orientation are "My parents want me to understand school concepts, not just do the work" (child-version) and "I'd discuss with my child whether it would be useful to ask the teacher for help" (parent-version). Participants rate the items on a 6-point Likert scale (1=strongly disagree to 6=strongly agree), and higher scores on performance- or learning-orientation items indicate their preferred orientations. The Cronbach α in previous study were 0.79 and 0.78 for performance-orientation and learning-orientation, respectively [16].

Academic self-efficacy will be measured by a 5-item scale that was adapted from the part of Patterns of Adaptive Learning Survey [51]. Children will rate the extent to which the skills taught in class could be mastered and the work could be done on a 6-point Likert scale (1=strongly disagree to 6=strongly agree). The sample question is "I'm certain I can master the skills taught in class." A higher score means a higher level of academic self-efficacy.

The motivation for applying the contents learned from the intervention will be assessed right after the intervention. We will ask participants the extent to which they would like to apply the intervention contents in life, and the extent to which they would like to improve their ability to cope with challenges on a 6-point Likert scale from 1=not very likely to 6=very likely.

The intervention feedback scale will be used to assess the acceptability of parent and child interventions. The scale will ask parents and children to indicate how much they enjoyed, understood, and felt helped by the program; whether they would recommend the program to a friend; whether they found the program interesting and fun; whether they agree with the program's message; whether the program is a burden; and the overall acceptability regarding this program [26]. Participants rate the items on s 5-point Likert scale (1=strongly disagree to 5=strongly agree). The items will be analyzed collectively as a single item.

Covariates

Sociodemographic information will be collected from parents and will cover a range of participant characteristics (gender, age, grade, and socioeconomic status) at baseline to examine variability between the groups.

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Data Analysis

An intention-to-treat approach will be adopted. A 2-level analysis will be used to account for the cluster randomization [52]. To examine the effects of the interventions, multilevel regression will be used to test the group effect, time effect, and interaction effect on outcome measures. Additionally, we will calculate effect sizes using estimated marginal means; these effect sizes compare mean change scores (Cohen *d*), reflecting the standardized levels of change in each outcome from baseline to 2 follow-ups for youths receiving the mindset versus active control interventions. A 95% CI will be provided for each effect size. SPSS (version 26; IBM Corp) will be used for all statistical analysis.

Ethical Considerations

Research ethical approval has been obtained from the Hong Kong Polytechnic University institutional review board for Ethical Review (HSEARS20211009001). Participation will be voluntary. Informed written consent will be obtained from participating parents and students. Participants will be reminded that they have the right to terminate the intervention or abstain from responding to any question on the questionnaire without providing a reason, and they will be assured of confidentiality. Additional information for referral services will be provided to participants with clinical-level mental health needs. All identifiable information will be removed, and codes will replace names to ensure privacy. All personally identifiable data will be stored on a secure server and destroyed 3 years after the study ends. Participants' data will not be identifiable in any publication or reporting. Each participating family in the study will receive a HK $100 (≈US $12) supermarket voucher after the intervention and another one after the 3-month follow-up, making the total compensation for each family HK $200 (≈US $40).

Results

We have started school invitation and participation recruitment in September 2023. The first school joined the study in May 2024. 75 students from 3 classes were randomly assigned into 3 groups. Students completed baseline surveys and intervention at school, while parents completed baseline assessment and intervention at home. Those have done the baseline receive reminders to complete the baseline assessment or intervention within 1 week after the baseline. Follow-up assessments will be finished by September. Meanwhile, we will send invitations to other schools until we have a sufficient sample size. The effect size will be calculated based on the data of the first school, and the sample size may be adjusted. We will conduct data collection from September 2024 to April 2025 and complete all follow-up surveys by April 2025.

Discussion

Expected Findings

This study develops the first a parent-child single-session integrated mindset intervention for Chinese adolescents which simultaneously targets to promote the growth mindset of intelligence, failure, and emotion among adolescents and their parents. This RCT will provide empirical evidence on the effectiveness of the intervention. The hypothesized main finding would be that PC-SMILE intervention has better intervention outcomes, including decreased anxiety and depression symptoms, reduced hopelessness, enhanced academic self-efficacy, psychological well-being, and parent-child interactions and relationships, than child intervention only or a waitlist control group.

As one of the first few attempts on parental mindsets, we will compare the effectiveness of parent-child intervention and child intervention only. This will be the unique evidence to show if intervention targeting parental mindset helps improve children's mental health outcome.

The challenge of SSIs is that it may be difficult to have sustainable and long-term effects. Thus, we measure the 2-week and 3-month follow-up with the latter as the primary outcome. This evidence-based program is novel, feasible and scalable to meet the needs of a large number of young people across the country. The digital delivery of PC-SMILE ensures that it has the potential to be scalable to provide consistent, evidence-based, and prevention-focused psychoeducation. However, given the scale of the study, a key limitation includes the reliance on self-report measures and lack of objective measurement. Although we measure parent-reported depression and anxiety symptoms and parent-child interaction time, the general mode of measure is self-report. Future directions would be incorporating objective measurements alongside self-report measures, such as behavioral observations in schools.

This study has several potential implications. For theoretical implications, the proposed study will elucidate the effectiveness of changing parents and children's mindsets on adolescent internalizing problems. In addition, this study will provide evidence of the effectiveness of integrated mindset intervention for both parents and children. From a practical or clinical perspective, by instilling both parents and children with a growth mindset, PC-SMILE can potentially help parents better support children with emotional distress. The PC-SMILE can serve as an add-on component of multisession psychosocial treatment. Finally, this study has social implications that PC-SMILE can potentially facilitate better family support and care, thereby reducing the social burden of mental health care needs. As the first attempt to develop and implement a web-based, single-session, parent-child intervention to promote youth and parental well-being in Hong Kong, this study will provide evidence-based service recommendations on brief interventions for young people and their parents in Hong Kong and beyond.

Conclusions

The current study uses a 3-arm RCT to examine the effectiveness of PC-SMILE in reducing depression and anxiety symptoms among children in Hong Kong. As an integrated intervention, PC-SMILE is highly likely to be a potent mindset intervention. If proven to be effective, PC-SMILE would be a low-cost, easily accessible self-help tool for thousands of families that could significantly promote youth and parental well-being.

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Acknowledgments

The authors would like to recognize the contributions of the principals, school counsellors, and social workers who share their insights in students' mental health care needs. Generative AI was not used in any portion of the manuscript generation.

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Data Availability

The data sets produced and analyzed in this study are not publicly accessible because of the confidentiality. However, the deidentified data can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

SZ designed the intervention and the randomized controlled trial study. YH and RW assisted to the intervention content design and visual design. SZ, YH, and DQ drafted the first draft of the report. PL contributed to the data analysis plan. SWN, QC, and PWCW were co-investigators of the grant proposal. SZ developed all aspects of the proposal and manuscript related to the implementation of intervention and data collection. All authors edited and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table of assessment elements.
[DOC File , 81 KB - resprot_v13i1e63220_app1.doc]

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Abbreviations

C-SMILE: child single-session intervention on mindsets of intelligence, failure, and emotion
CONSORT: Consolidated Standards of Reporting Trials
PC-SMILE: parent and child single-session intervention on mindsets of intelligence, failure, and emotion
RCT: randomized controlled trial

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SSI: single-session intervention

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Protocol

Effectiveness of a Mobile App (Meds@HOME) to Improve Medication Safety for Children With Medical Complexity: Protocol for a Randomized Controlled Trial

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Abstract

Background: This study will pilot-test the mobile app, Medication Safety @HOME—Meds@HOME intervention to improve medication administration accuracy, reduce preventable adverse drug events, and ultimately improve chronic care management for children with medical complexity (CMC). The Meds@HOME app was co-designed with CMC families, secondary caregivers (SCGs), and health professionals to support medication management for primary caregivers (PCGs) and SCGs of CMC. We hypothesize that Meds@HOME will improve caregivers' medication administration accuracy, reduce preventable adverse drug events, and ultimately improve chronic care management.

Objective: This study aims to evaluate the effectiveness of Meds@HOME on medication administration accuracy for PCGs and SCGs.

Methods: This study will recruit up to 152 PCGs and 304 SCGs of CMC who are prescribed at least 1 scheduled high-risk medication and receive care at the University of Wisconsin American Family Children's Hospital. PCGs will be randomly assigned, for the 6-month trial, to either the control group (not trialing Meds@HOME) or the intervention group (trialing Meds@HOME) using 1:1 ratio. The Meds@HOME app allows caregivers to create a child profile, store medication and care instructions, and receive reminders for upcoming and overdue care routines and medication refills. Surveys completed both at the start and end of the trial measure demographics, medication delivery knowledge, confidence in the CMC's caregiving network, and comfort with medical information. Univariate and multivariate generalized estimation equations will be used for primary statistical analysis. The primary outcome is the PCG's rate of medication administration accuracy measured as correct identification of each of the following for a randomly selected high-risk medication: indication, formulation, dose, frequency, and route at baseline and after 6 months. Secondary outcomes include SCG medication administration accuracy (indication, formulation, dose, frequency, and route), count of University of Wisconsin hospital and emergency department encounters, PCG-reported medication adherence, count of deaths, and PCG medication confidence and understanding.

Results: Recruitment for this study began on November 29, 2023. As of May 15, 2024, we have enrolled 94/152 (62%) PCGs. We expect recruitment to end by August 1, 2024, and the final participant will complete the study by January 28, 2025, at which point we will start analyzing the complete responses. We expect publication of results at the end of 2025.

Conclusions: The Meds@HOME mobile app provides a promising strategy for improving PCG medication safety for CMC who take high-risk medications. In addition, this protocol highlights novel procedures for recruiting SCGs of CMC. In the future,

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this app could be used more broadly across diverse caregiving networks to navigate complex medication routines and promote medication safety.

Trial Registration: ClinicalTrials.gov NCT05816590; https://clinicaltrials.gov/study/NCT05816590

International Registered Report Identifier (IRRID): DERR1-10.2196/60621

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KEYWORDS

medication safety; children with medical complexity; caregiving; polypharmacy; medication management

Introduction

Background

Medication errors during routine care at home are common among US children, occurring every 8 minutes [1]. Children with medical complexity (CMC), who have multiple chronic conditions, functional limitations, high health services use, and substantial family-identified needs [2], are uniquely vulnerable to medication errors and adverse drug events. Their treatment plans often include high-risk medications having serious potential consequences if doses are missed and toxicity if doses are in excess. In many cases, they have extreme polypharmacy, medical fragility, and reliance on complicated medication schedules and administration routes all typically managed by undersupported family caregivers [3,4]. A national sample found that CMC in the United States have nearly 5 times higher odds of an adverse drug event leading to an emergency department (ED) visit than other children, and more than 1 of 50 CMC ED visits are due to adverse drug events [5]. Administration discrepancies, which have been defined as inconsistencies in medication indication, dose, formulation, frequency, and route between caregivers and prescriptions, presumably lead to adverse drug events [6]. Such errors have been linked directly to preventable adverse drug events in children, including hospitalizations, ED visits, and morbidity [5-7].

Families who care for CMC experience at least 2 unmet needs that influence medication safety outcomes such as administration discrepancies [8]. First, there are no reliable and tested tools that support medication administration accuracy for families of CMC, despite the high risk and complex nature of CMC medication management [9]. Second, no tools exist to support families to ensure safe medication management across the network of all people involved in the 24-hour daily care that most CMC require. This network of secondary caregivers (SCGs) includes other family, in-home professionals, school aides, respite workers, and so forth. CMC networks are unstudied despite the impact caregiving network performance has on caregiver, patient, and health care system outcomes in other populations [10,11].

To address these gaps, we co-designed the mobile app, Medication Safety @HOME—Meds@HOME with CMC families, SCGs, and health professionals. Meds@HOME was designed specifically to meet challenges related to medication administration for CMC in the home and the community [12]: giving the right medication at the right time; communicating with others about medications; and accommodating complex medical routines. The app allows the primary caregiver (PCG), that is, the parent or the guardian primarily responsible for overseeing a child's care, to enter a child's medications and care needs into the app and then mark when activities have been completed. The app also allows users to (1) create a child profile (listing likes and dislikes, allergies, caregiver contact information, etc), (2) store care instructions (how to prepare medication, when to use a sick day plan, or what to do in certain health emergencies, etc), (3) receive reminders for upcoming and overdue care routines and medication refills, and (4) post alerts for other caregivers on the child's care team. The PCG invites as many SCGs as they would like, for example, extended family or a school or home nurse, to also use the account. SCG can then also view the child's profile and care instructions, receive reminders for upcoming and overdue care routines, and check off tasks as they are completed.

Although Meds@HOME was created using user-centered design methods [13], its impact on medication administration accuracy is unknown. This trial will evaluate the effectiveness of the Meds@HOME platform to improve medication accuracy for PCGs and SCGs. The research question is, "For children with medical complexity who receive at least one high-risk medication, does use of the Meds@HOME digital intervention improve medication administration accuracy for primary caregivers as compared to usual care over 6 months?" We hypothesize that Meds@HOME will improve caregivers' medication administration accuracy by creating standardized medication management across the group of individuals caring for a child.

Objectives

This study aims to evaluate the effectiveness of Meds@HOME on medication administration accuracy for PCGs and for SCGs.

Methods

Study Design

This randomized controlled trial will test the hypothesis that medication administration accuracy is improved for caregivers who use the Meds@HOME mobile app within the caregiving networks of CMC aged between 0 and 16 years who use high-risk medications. Participant accrual will occur over 12 months at 1 site, with participant's enrollment duration lasting 6 months.

Participants and Setting

The study will be conducted at 1 site: the University of Wisconsin (UW) Health Kids American Family Children's Hospital affiliated with the UW School of Medicine and Public

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Health, United States. We will recruit 152 PCGs, 152 children, and up to 304 SCGs over 12 months. If there is more than 1 PCG for a child, the other PCG may be invited to participate in the study as a PCG as well. If this occurs, the total number of PCGs will exceed 152 participants. The duration of the study for each participant will be 6 months.

The study population will consist of (1) CMC prescribed at least 1 scheduled high-risk medication and receive care at UW Health, and (2) their caregivers. The study distinguishes between 2 types of caregivers: (1) PCGs (child's parent or legal guardian), and (2) SCGs (others who regularly care for the child, defined in the section Inclusion Criteria). Potentially eligible children will be identified by an analyst, who is not a part of the research team, by querying the electronic health record (EHR) data warehouse using diagnostic codes and the eligibility criteria.

Inclusion Criteria

Participants are caregivers of CMC who take 1 or more high risk medications. Children, PCGs, and SCGs must meet all inclusion criteria to be eligible to participate in the study.

Child eligibility criteria include (1) providing assent, if appropriate; (2) being aged between 0 and 16 years at the start of study; (3) having 2 or more different complex chronic conditions [14]; (4) having had at least 2 or more encounters in the American Family Children's Hospital system; and (5) having at least 1 active outpatient prescription for a scheduled high-risk medication. High-risk medications are defined from prior literature [6,9,15-17] and include the following: antiepileptics, opioids, tone or spasticity medications, psychotropics, stimulants, anticoagulants, sleep aids, antiarrhythmics, pulmonary hypertension medications, and immunosuppressants. Medications must be *active* (currently being taken) and chronic, defined as a 90-day script or a 30-day fill plus 2 refills. As needed or PRN medications are not included.

PCG eligibility criteria include (1) written informed consent, (2) willingness to comply with study procedures and availability for the duration of the study, (3) age of 18 years or older, (4) comfort speaking and reading in English, (5) self-identifies as a PCG of the study eligible CMC, (6) providing care on an ongoing basis to the study eligible CMC in the home, and (7) having an iOS or android mobile device (smartphone or tablet) with a phone plan that includes daily Wi-Fi service and data.

SCG eligibility criteria include (1) identification by the PCG as a "secondary caregiver," (2) written informed consent, (3) willingness to comply with study procedures and available for the duration of study, (4) 18 years of age or more, (5) comfort speaking and reading in English, (6) providing care on an ongoing basis to the study eligible CMC, (7) administering medications to the study eligible CMC, and (8) having an iOS or android mobile device (smartphone or tablet) with a phone plan that includes daily Wi-Fi service and data.

Exclusion criteria for PCGs are having another child from the household who is already enrolled in the study in order to avoid the clustering effects of potentially having both multiple PCGs and multiple children within the same household. Otherwise, to maintain broad inclusivity in the study, the exclusion criteria for PCGs and SCGs are limited only to failing to meet each inclusion criterion.

High-Risk Medication Determination

Data on medication use are abstracted from the outpatient prescribing records in the EHR data warehouse by an analyst who is not a part of the research team. Data abstracted for all high-risk medications for all potentially eligible children include study ID, medication name (generic and brand), indication, dose, formulation, frequency, route, and high-risk medication category indicators (ie, antiepileptic, opioid, tone or spasticity, etc), and a randomly generated number. The medication database is updated monthly, so that study staff have access to current prescription orders throughout the recruitment period.

To avoid introducing sampling bias into the process of selecting a patient-specific high-risk medication for outcome assessment, a systematic, hierarchical procedure was designed for implementation prior to randomization. First, the research team rank-ordered high-risk medication categories from those perceived to be most to least prevalent and at highest risk for adverse events if incorrectly administered. The order is as follows (Textbox 1).

For children who receive multiple high-risk medications, study outcome assessments focus on 1 randomly selected medication from the highest category. Within each category, high-risk medications are arranged in random sequence using the random number assigned by the analyst. For example, if a child takes 3 antiepileptics, the study staff identifies the first high-risk medication in random order and confirms with the PCG that the child still takes this medication. If the child no longer takes the medication, the staff moves sequentially down the randomly ordered list until a medication the child is taking is identified. If no high-risk medications are confirmed by the PCG, then the child is deemed ineligible.

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Textbox 1. Medication determination order from highest to lowest risk.

High-risk medication determination order:

1. Antiepileptics
2. Opioids
3. Tone or spasticity medications
4. Psychotropics
5. Stimulants
6. Anticoagulants
7. Sleep aids
8. Antiarrhythmics
9. Pulmonary hypertension medications
10. Immunosuppressants

Enrollment

Potentially eligible PCGs will be mailed an opt-out letter describing the study and then contacted 1 week later by telephone to screen for eligibility and interest. Eligible and interested PCGs will be scheduled for a formal enrollment visit. Enrollment visits will be conducted via a web-based teleconference in a quiet, private area offering confidentiality. The enrollment visit will be considered T_0, and study enrollment will continue for 6 months from that date. First, PCG consent (and child assent) will be obtained. Staff will also conduct the following tasks.

Baseline Primary Outcome Assessment

Study staff will use a primary outcome assessment case report form and scripted interview to elicit and record PCGs' account of their child's high-risk medication prescription information. After the PCG is presented the name (generic or trade) of the high-risk medication as described in Textbox 1, PCGs will be asked via a standard script to describe the medication's indication, formulation, dose, frequency, and route. All answers are recorded verbatim, and families are asked not to refer to medication bottles or written materials.

Identification of SCGs

The PCG will identify SCGs and rank them from most to least involved with medication delivery. SCGs will be approached in that order until up to 2 have been enrolled per child. They will first be invited to the study via an opt-out letter that can come from either the PCG or the study staff, based on PCG preference. Once they receive an invitation, SCGs can indicate interest in participation through one of the following ways: (1) completing an web-based interest form using a hyperlink provided in the opt-out letter, (2) waiting for study staff to follow up by phone to discuss the study 1 week after the opt-out letter is sent, or (3) contacting study staff by phone or email to discuss the study.

Randomization Into a Study Group

Participants will be randomized into either the control group or the intervention group. The study will use a 1:1 allocation with random block sizes of 2 and 4 [18]. Block randomization will be achieved with a computer-generated random number list prepared by the study biostatistician with no clinical involvement in the trial. Only the biostatistician will have access to the table listing the randomly allocated block sizes and sequence of group assignments; study staff will not. This ensures balanced allocation to the intervention and control groups while maintaining allocation concealment for study staff [19]. Randomization will be stratified by enrollment status in the UW Pediatric Complex Care Program (ie, enrolled or not) because the additional health care support and education this population receives could influence outcomes and intervention use. SCGs will be assigned to the same group as the PCGs.

If assigned to the intervention group, staff will help the PCG download the app, create an account, invite a caregiver, and set up an initial routine.

After the enrollment visit, both PCGs and identified SCGs will be asked to complete a self-administered questionnaire (SAQ) using REDCap (Research Electronic Data Capture; version 14.2.2). The questionnaire will be emailed to both PCGs and SCGs following the PCG enrollment and expressed SCG interest (through either completion of the SCG interest survey or phone discussion with study staff). For PCGs, the questionnaire includes questions about general caregiving as well as medication delivery knowledge, attitudes, and practices, and the PCGs' confidence in their caregiving network, that is, all SGCs. For SCGs, the questionnaire includes questions about demographics, comfort with medical information, and for the identified high-risk medication, its indication, formulation, dose, frequency, and route. A similar questionnaire will be emailed at the study exit.

Description of the Intervention (App Use)

Participants randomized to the intervention group will be assigned to use the Meds@HOME app for 6 months. Meds@HOME is a software application designed for use on a personal mobile device (such as phone or tablet). It is available on iOS and Android operating systems (Multimedia Appendix 1).

The app has the following core functionalities, which are managed by the child's PCG.

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Caregiver Profile

To establish an account, specific profile fields are required, including name, email, phone number, relationship to child, caregiver photograph, and preferred method of communication. PCGs can invite as many other caregivers (eg, extended family, home nurse, and school aide) to use the app as they wish. They can also deactivate any caregivers. Based on co-design priorities set by caregiver stakeholders, the system was not designed for use by the child's hospital, primary, or specialty clinical team members.

Child Profile

At a minimum, the child's profile must include their name. Other optional fields include photograph, gender, date of birth, address, and "important things to know about me" (allergies, I'm calmed by, I'm upset by, I need assistance with, best way to communicate with me, comfort measures I prefer, and my technology).

Caregiving Routines and Routine Tracking

The app allows PCGs to create custom daily routines, for example, "Afternoon Meds," "Lunch," or "Prep for next day," and so forth. Routines can include general caregiving tasks, medication details, meal instructions, and so forth. PCGs can detail how to perform the routine, start dates and times, and recurrence frequency, such as daily, weekly, and monthly. Customizable push notifications can alert caregivers to upcoming routines in the manner they wish. Only PCGs can create, edit, and delete routines. All caregivers can mark routines as complete and receive notifications.

Inventory Reminders

For medications, caregiving supplies, and foods, PCGs can set notification intervals for refill reminders.

Most functionalities are optional or voluntary and can be left blank. A child's PCG determines the type and level of detail to input and who is invited to use the app.

Description of the Control Group (No App Use)

PCGs randomized to the control group will be asked to complete the SAQ at the beginning and end of the 6-month trial, similar to the intervention group. SCGs in the control group will not use the Meds@HOME app. During the 6-month time frame, PCGs and SCGs will continue their normal caregiving routines.

Conclusion of the Study

At the conclusion of the study, PCGs and SCG will be emailed via REDCap a follow-up SAQ that is identical to the one received at the beginning of the trial. Study staff will follow up with PCGs via phone to conduct an exit primary outcome assessment. The high-risk medication random selection and assessment procedures are the same at study entry and exit. The same medication can, but does not have to, be used for both outcome assessments. A PCG is considered to have completed the study if baseline and exit POA and SAQs are completed, while a SCG must complete the baseline and exit SAQs (Figure 1 and Table 1).

Figure 1. Meds@HOME study randomized controlled trial design. EHR: electronic health record.

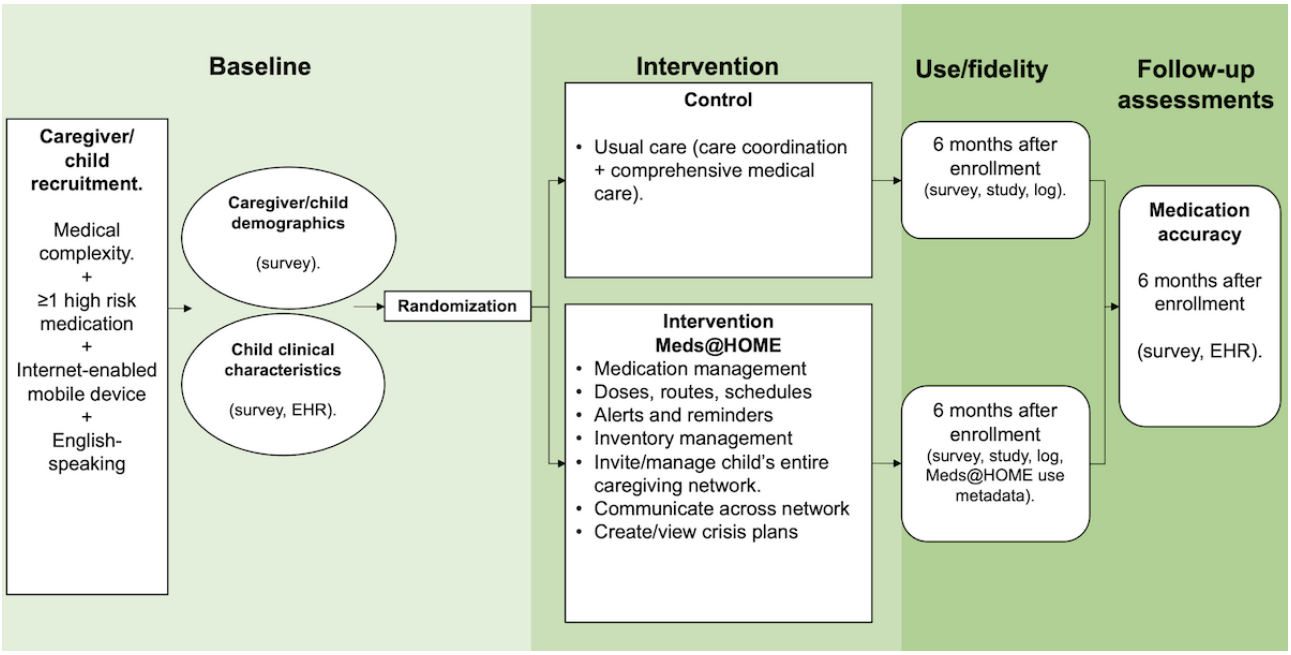

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Table 1. Schedule of activities of the Meds@HOME Trial-Plan for assessment of intervention at the beginning and end of the study period, with the depiction of staff involved.

	Study period, *T*=X months (staff involved)			
	Prior to enrollment visit (research coordinator)	Enrollment visit, *T*=0 months (research coordinator)	Exit visit, *T*=6 months (research coordinator)	Assessment, *T*>6 months (blinded assessor)
PCG[a] activities				
Phone screen and eligibility	✓			
Completion of SCG[b] worksheet	✓			
Confirm eligibility		✓		
Informed consent		✓		
Child assent (if applicable)		✓		
SCG individual identification		✓		
Randomization		✓		
Baseline SAQ[c]		✓		
Primary outcome assessment		✓	✓	✓
Exit SAQ			✓	
Participant payment		✓	✓	
SCG activities				
Baseline and outcome SAQ		✓		
Exit and outcome SAQ			✓	
Primary outcome assessment				✓
Participant payment		✓	✓	

[a]PCG: primary caregivers.

[b]SCG: secondary caregivers.

[c]SAQ: self-administered questionnaire.

Ethical Considerations

This study received approval from the UW institutional review board on January 19, 2022 (2021-1532). All participants will provide informed consent before taking part in the study. Informed consent materials will be provided in private spaces in both written and verbal formats and the study design will be reviewed in detail. Review of study design will include random assignment to the intervention and control groups, potential risks of participation, protections against risk, and the rights of human research participants. Parents or children can revoke their consent or assent at any point. Any identifying information kept for the purpose of contacting participants or linking data over time will be kept secure, in REDCap, a locked filing cabinet, or in a password-protected electronic file, and will be destroyed when the study is complete. Data will be de-identified at study conclusion. The study's data and safety are monitored every 6-12 months by the data-monitoring committee at the UW Institute for Clinical and Translational Research. All PCGs will receive an incentive of US $200, divided in 2 parts: US $100 at enrollment and US $100 after the exit survey, in the form of a gift card, check, or cash. SCGs will receive an incentive of US $150, divided into 2 parts: US $75 at both enrollment and after exit survey completion.

Outcomes

Primary End Point

The primary outcome is medication administration accuracy, defined dichotomously as correct identification of all the following for a selected patient-specific high-risk medication: indication, formulation, dose, frequency, and route of administration (Table 2).

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Table 2. Primary and secondary objectives of the study with corresponding end points being used for measurement.

Objectives	End points	Number of items and estimated time to complete
Primary		
To evaluate the effectiveness of Meds@HOME on PCG[a] medication administration accuracy [6].	Rate of medication administration accuracy measured dichotomously as correct identification of each of the following for a randomly selected high-risk medication: indication, formulation, dose, frequency, and route at baseline and after 6 months.	5 items, approximately 5 minutes.
Secondary		
To evaluate the effectiveness of Meds@HOME on SCG[b] medication administration accuracy [6].	Rate of medication administration accuracy, measured as in the primary outcome, among SCGs at baseline and after 6 months.	5 items, approximately 5 minutes.
To evaluate Meds@HOME's effect on ADE[c] hospital use [5].	Count of UW[d] hospital encounters during study period with ADE codes.	1 item, extracted from electronic health record diagnostic and procedure codes.
To evaluate Meds@HOME's effect on ADE UW ED[e] visits [5].	Count of UW ED encounters during study period with ADE codes.	1 item, extracted from electronic health record diagnostic and procedure codes.
To evaluate Meds@HOME's effect on parent-reported medication adherence [20,21].	Mean PCG-reported medication adherence using the Adherence to Refills and Medications Scale (ARMS) after 6 months.	12 items, approximately 5 minutes.
To evaluate Meds@HOME's effect on medication activation [22].	Mean Family Caregiver Activation in Transition (FCAT) 5 medication-specific items—composite and individual items after 6 months.	5 items, approximately 2 minutes.
To evaluate Meds@HOME's effect on parent-reported medication confidence [6].	Mean composite score after 6 months.	6 items, approximately 3 minutes.
To evaluate Meds@HOME's effect on parent-reported medication understanding [6].	Mean composite score after 6-months.	5 items, approximately 2 minutes.
To evaluate Meds@HOME's effect on all-cause hospital use.	Count of hospital encounters and hospital days during study period.	1 item, extracted from electronic health record encounters.
To evaluate Meds@HOME's effect on all-cause ED use.	Count of ED encounters during study period.	1 item, extracted from electronic health record encounters.
To evaluate Meds@HOME's effect on mortality.	Count of deaths during the study period.	1 item, 1 item, extracted from electronic health record encounters or study records.
To evaluate Meds@HOME's effect on the primary outcome measured as 5 individual components.	Rate of individual components each measured dichotomously (indication, formulation, dose, frequency, and route); mean of individual components after 6 months.	No new items, this disaggregates the primary end point.

[a]PCG: primary caregivers.

[b]SCG: secondary caregivers.

[c]ADE: Adverse drug event.

[d]UW: University of Wisconsin.

[e]ED: emergency department.

Assessment Procedures

The medication administration accuracy measure and many of the caregiving measures have been documented as reliable in prior literature; however, few validation studies have been conducted with these measures [22-27]. We will ensure reliability in data collection through direct observation, data auditing, establishing clear data dictionaries and definitions, using uniform variable definitions, and a central data repository coordinated and maintained at UW. The primary and secondary end points are measured following completion of the PCG enrollment and exit primary outcome assessment case report forms and SCG SAQs. The most recently abstracted EHR prescription data for the selected high-risk medication is considered the gold standard. Following data collection, a clinician with expertise in care for CMC and high-risk medication management who is blinded to treatment assignment (*blinded outcome assessor*) compares caregiver responses with the gold standard data. The blinded outcome assessor scores participant responses for each component of medication administration accuracy (ie, indication, dose, formulation, frequency, and route) as correct, incorrect, or missing. Each component must be correct to meet the study end point.

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To establish the reliability of the primary end point assessments, the first 25 cases are independently, dually coded by 2 blinded outcome assessors. The study biostatistician calculates interrater reliability using kappa for the primary end point (ie, the dichotomous composite measure of medication administration accuracy). If k value is ≥0.85, the coders have strong, almost perfect agreement [28,29] and the remaining data are single coded. If k value is <0.85, discrepant items are recoded, the outcome assessors are retrained, and the next 25 cases are again independently, dual-coded. Kappa is recalculated for the next 25, and the same procedures are completed until either k value is ≥0.85 or data collection is complete.

Data Collection, Storage, and Protection

All data will be collected via phone scripts, EHR abstraction, standardized SAQs, and case report forms completed by trained study staff. All data for this study will be housed in REDCap, managed by UW's Institute for Clinical and Translational Research as a 21 Code of Federal Regulation Part 11-compliant data capture system [30]. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify inconsistent, incomplete, or inaccurate data. Clinical data will be entered directly from the source documents or entered directly through secure SAQs emailed via REDCap surveys to participants.

Data from the Meds@HOME app will be stored in databases on the UW School of Medicine and Public Health Department of Pediatrics secure servers. The UW Department of Pediatric servers follow all UW campus and UW Health privacy and compliance requirements. Access to study folders will be limited to study staff with appropriate training and permissions.

Sample Size Considerations

We will enroll 152 PCG participants. The study is powered to detect an anticipated clinically important difference in the primary end point (medication administration accuracy rate). Based on preliminary data on medication administration accuracy, the observed rate was 41% in PCGs [31]. Hence, the anticipated medication administration accuracy rate for the control arm of this study is 41%. We estimate that Meds@HOME use will increase the outcome rate from 41% (control arm) to at least 70% (intervention arm). This increase is considered a clinically important improvement. The sample size (n=152) will detect this difference in the medication administration accuracy rates between arms, calculated for 90% power at the 2-sided .05 significance level based on a *z* test with continuity correction [32]. Recruitment needs are feasible based on a projected eligible population (n=1100), an estimated 20% enrollment rate, and a 10% loss to follow-up rate. Furthermore, we estimate that 2 caregivers may provide independent responses for up to 5%-10% of the households. With a proposed sample size of 152 households, the expected number of PCGs is between 160 and 167. With this sample size, the anticipated difference of 41% versus 70% in the medication accuracy rates will be detected with at least 94% power at the 2-sided .05 significance level, based on generalized estimating equation analyses, assuming an intraclass correlation coefficient (for up to 2 PCGs within the same household) of 0.05-0.50 [33].

With respect to secondary outcomes, the proposed sample size will also provide 82%-99% power to detect moderate (Cohen *d*=0.5) to large (Cohen *d*=0.8) effect sizes at the 2-sided .05 significance level in secondary outcomes between arms [28,29]. Because we assume that PCG will perform better than SCG, the anticipated medication administration accuracy rate is assumed to be <41% in the SCG cohort. If the SCG sample's control group performance was only 30%, we would have 90% power to detect an increase to 60% with only 136 enrollees. Therefore, with our planned enrollment of 152 (ie, 1 SCG for every PCG), we will have adequate power to conduct the SCG analysis even with poorer enrollment or smaller effect sizes than expected (Table 3).

Table 3. Sample size requirements for detecting differences in the medication administration accuracy rates between arms with 90% power at the 2-sided .05 significance level.

Sample sizes	Intervention group outcome, n				
	Medication administration accuracy = 60%	Medication administration accuracy = 65%	Medication administration accuracy = 70%	Medication administration accuracy = 75%	Medication administration accuracy = 80%
Final total sample needed	300	194	136	96	74
Final sample per treatment arm	150	97	68	48	37
Eligible subjects to achieve sample	370	240	168	120	91
Enrolled subjects to achieve sample	334	216	**152**	108	82

Statistical Analysis Plan

Given that the intervention being tested requires caregiver use to achieve success, we will use an intention-to-treat analysis approach [18]. We plan to use the primary outcome data to assess Meds@HOME's impact on medication administration accuracy of PCGs of CMC measured at study baseline and exit 6 months later. This binary measure is derived from prior studies involving CMC PCGs [6] and includes demonstrating parent recall of complete medication instructions for 1 patient-specific high-risk medication, compared with prescription details. Medication administration accuracy is defined dichotomously as correctly identifying all the following for a selected patient-specific high-risk medication: indication, formulation,

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dose, frequency, and route of administration. The outcome will be evaluated as the change in percentage of intervention participants compared with control participants demonstrating medication administration accuracy at 6 months compared with baseline. Primary analysis will test differences between treatment (intervention or control) groups in the primary and secondary outcomes. For the primary analysis, univariate generalized estimation equation analysis [33] with exchangeable correlation structure to account for potentially 2 PCGs responding from the same household will be conducted to compare the medication administration accuracy rates between study arms. The effect size of the difference in medication administration accuracy rates will be quantified by calculating the odds ratio, which will be reported along with the corresponding 95% CI. Furthermore, multivariate generalized estimation equation analysis [33] will be performed to compare the medication administration accuracy rates between study arms. In this analysis, clinical and demographic characteristics will be included as covariates in an initial nonparsimonious model. Collinearity will be evaluated and the least absolute shrinkage and selection operator and elastic net penalty methods for logistic regression models will be used to identify a parsimonious model with independent covariates.

The secondary outcome count variables include the numbers of adverse drug event ED visits and hospitalizations and total numbers of all-cause hospital days, hospitalizations, and ED visits. This will be analyzed using univariate and multivariate mixed-effects negative binomial regression models with household-specific random effects to account for overdispersion in the count data and responders from the same household. The cumulative number of these outcomes over the 6-month follow-up period will also be analyzed using a univariate linear mixed-effects model with household-specific random effects. In a secondary analysis, a multivariate linear mixed-effects model will be used where clinical and demographic baseline characteristics will be included as covariates and the least absolute shrinkage and selection operator method will be used to identify a parsimonious model. Secondary outcome binary variables, that is, individual components of the primary outcome, items from the medication activation, understanding and confidence measures answering, *strongly agree*, parent-reported medication adherence, and death rates, will be modeled in the same manner as the primary analysis. Each of these binary outcomes will be documented at final assessment and changes within and between study arms will be analyzed using univariate and multivariate generalized linear mixed-effects modeling with household-specific random effects.

Baseline comparisons of demographic variables and clinical characteristics will be conducted using a chi-square test (categorical variables) or a 2-sample test and nonparametric Wilcoxon rank sum test (continuous or quantitative variables) [34,35].

Because some participants may not use the Meds@HOME intervention, we will conduct a secondary analysis repeating all primary and secondary end point assessments using a per-protocol population analysis approach to complement the intention-to-treat approach [18]. The per-protocol population will be eligible participants who were randomized and achieved a level of compliance, defined as creation of at least 1 routine and 6+ log ins, 3 of which occurred in last 3 months of the enrollment period. The login number was chosen to reflect at least 1 login per month, with use throughout the intervention period.

To evaluate the impact of missing values (eg, due to loss of follow-up, incomplete data collection) we will conduct a sensitivity analysis by comparing the results obtained from the complete case analysis with the results obtained by imputation-based analyses. Specifically, multiple imputation will be used to impute the missing values of the primary and secondary clinical outcomes. For monotonic missing values data structures, we will use regression-based multiple imputation techniques. By contrast, we will use Markov Chain Monte Carlo–based imputation techniques for nonmonotonic missing value data structure.

Results

This study was funded in May 2022. Initial institutional review board approval for this study occurred on March 9, 2023. Recruitment began on November 29, 2023. Data collection began on December 11, 2023. As of May 15, 2024, we have enrolled 62% (94/152) of PCGs (Figure 2). We expect recruitment to end by September 1, 2024, and the final participant will complete the study by January 28, 2025, at which point we will start analyzing the complete responses. We expect publication of results in the winter of 2025.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for Meds@HOME. CG: caregiver; PCG: primary caregiver; PRN: pro re nata (as needed); SCG: secondary caregivers.

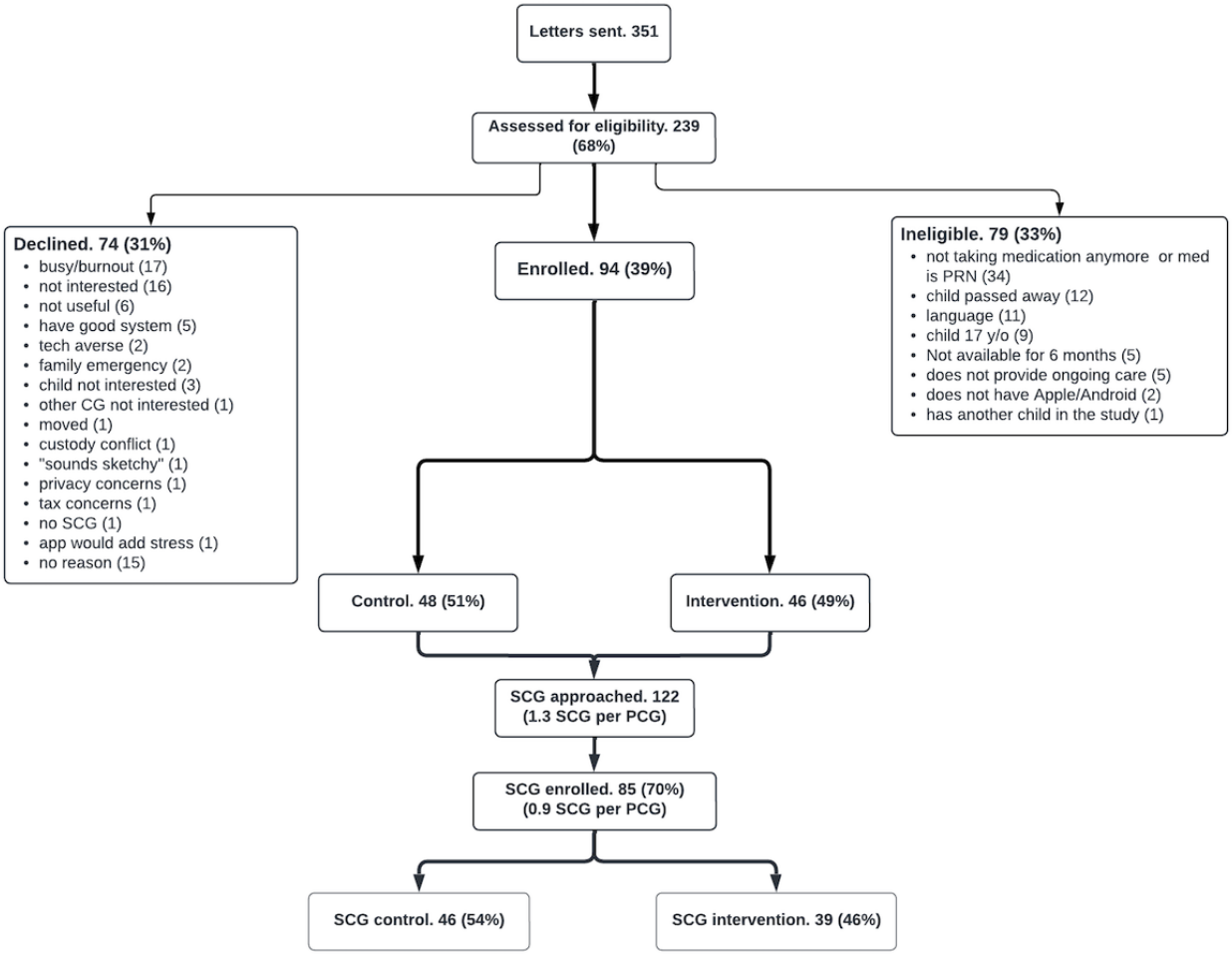

Discussion

Summary

The Meds@HOME mobile app is hypothesized to improve caregivers' medication administration, reduce preventable adverse drug events, and ultimately improve chronic care management [36]. Previous research indicates that caregivers for CMC experience multiple challenges related to medication administration, including giving the right medication at the right time, communicating with others about medications, and accommodating complex and sophisticated caregiving routines [12]. The Meds@HOME mobile app offers a solution to each of these challenges. As a result, we anticipate that compared with baseline medication administration accuracy, both PCGs and SCGs using Meds@HOME will have statistically significant increases in this measure compared with the control group.

Compared with other interventions, Meds@HOME was developed from the expert perspectives of PCGs and SCGs for CMC, as well as clinicians [12]. There is currently substantial interest in using mobile health technologies to improve CMC care [37-39]. Meds@HOME is also unique compared with other interventions because of its focus on medication safety in the home and on coordinating care among multiple caregivers in addition to parents. Meds@HOME has the potential to decrease medication errors for CMC and promote confidence and connection within a caregiving network. Such outcomes will be evaluated through the study's planned secondary outcome analyses. Importantly, Meds@HOME is a potentially scalable intervention that could be rapidly disseminated beyond the single site if efficacious. In this or future studies, Meds@HOME may also demonstrate broader improvements in CMC health, such as ED and hospital use. Following this randomized controlled trial, we intend to conduct real-world effectiveness and implementation research across multiple sites, with the goal of creating a tool that is widely available and promotes the health and safety of CMC.

Limitations

Although we anticipate having adequate power to assess for intervention efficacy, this study still has limitations. First, while assessors are trained and blinded, the evaluation of medication administration accuracy has some subjectivity that could influence reliability and validity. This risk will be minimized by the dual-coding procedures described in the section "Assessment Procedures." Although this study design introduces the possibility of interview bias, this risk is minimized by providing standard scripts embedded into for study staff to use when interacting with participants. Participants cannot be blinded to the intervention, and caregivers in the control and intervention groups will be aware of which they have been assigned to. We will attempt to minimize the risk of participant reactivity by not sharing the randomly selected high-risk

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medication ahead of time and by requesting participants not to refer to written materials or pill bottles during assessments. Finally, the limited ability to develop Meds@HOME in multiple languages requires participants to be comfortable reading and speaking English, limiting external validity. Future research will include software iterations in multiple languages to reach families with more geographic and culturally diverse backgrounds.

Conclusions

Despite the limitations, this detailed study protocol provides a real-world, promising strategy for improving PCG medication safety for children who are taking high-risk medications and novel procedures for recruiting SCGs of CMC. This intervention may have extended positive impact by improving SCG medication accuracy, improving caregiver medication understanding and confidence, and influencing hospital and ED use as well as other health outcomes. In the future, this app could be used more extensively by caregivers and youth who are navigating complex medication routines, promoting medication safety among diverse caregiving networks.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request and completion of a data use agreement and institutional review board–approved protocol. Due to risk to identifiability intrinsic to the study's data collection plans, the data set will not be deposited in a publicly available repository.

Authors' Contributions

RC and NEW, the principal investigators of this study, obtained grant funding and conceived the study. SK, MM, GW, JF, MC, BK, BS, and KS participated in the design of the study. NEW, RC, GW, MM, SK, and AJ drafted the manuscript. SK, GW, and MM were responsible for recruitment and major study activities. All authors contributed to the intellectual content of the manuscript and the development of the trial protocol, and all authors have read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example of application screens.
[DOCX File , 347 KB - resprot_v13i1e60621_app1.docx]

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Abbreviations

CMC: Children with medical complexity
ED: emergency department
EHR: electronic health record
PCG: primary caregiver
REDCap: Research Electronic Data Capture
SAQ: Self-administered questionnaire
SCG: secondary caregiver
UW: University of Wisconsin

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Protocol

Improving the Care of Severe, Open Fractures and Postoperative Infections of the Lower Extremities: Protocol for an Interdisciplinary Treatment Approach

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Abstract

Background: Patients with open fractures often experience complications during their injury. The treatments incur high costs. Interdisciplinary cooperation between different medical disciplines may improve treatment outcomes. Such cooperation has not yet been envisaged in the German health care system.

Objective: The aim of the study is to improve the treatment of fractures with open soft tissue damage or postoperative complications in terms of duration and sustainability in a region in northwest Germany. Largely standardized diagnostics and therapy are intended to optimize processes in hospitals. In addition, a reduction in the duration of treatment and treatment costs is to be achieved.

Methods: Using a digital platform, physicians from 31 hospitals present patient cases to an interdisciplinary group of experts from the fields of plastic surgery, infectiology, hygiene, and others. The group of experts from the environment of the University Hospital Münster promptly makes a joint treatment recommendation for the individual case. The plan is to examine 3300 patients with open fractures or surgical complications. As consortium partners, there are also 3 statutory health insurance companies. The extent to which the therapy recommendations are effective and contribute to cost reduction in the health care system will be empirically investigated in a stepped-wedge cluster-randomized design. In addition, medical and nonmedical professional groups involved in the project will be asked about their work in the project (in total, 248 clinic employees). The primary outcome is the complication rate of open fractures or the occurrence of postoperative complications. As secondary outcomes, the number of antibiotics administered, limb function, and quality of life will be assessed. The health economic evaluation refers to the costs of health services and absenteeism. For the work-related evaluation, workload, work engagement, work-related resources, readiness for technology, and ergonomic aspects of the new telemedical technology will be collected. In addition, clinic employees will give their assessments of the success of the project in a structured telephone interview based on scaled and open-ended questions.

Results: The project started in June 2022; data collection started in April 2023. As of mid-June 2024, data from 425 patients had been included. In total, 146 members of staff had taken part in the questionnaire survey and 15 had taken part in the interviews.

Conclusions: Standardized treatment pathways in the standard care of patients with open fractures and postoperative infections will be established to reduce complications, improve chances of recovery, and reduce costs. Unnecessary and redundant treatment steps will be avoided through standardized diagnostics and therapy. The interdisciplinary treatment perspective allows for a more

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individualized therapy. In the medium term, outpatient or inpatient treatment centers specialized in the patient group could be set up where the new diagnostic and therapeutic pathways could be competently applied.

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KEYWORDS

open fracture; open soft tissue damage; telemedicine; plastic surgery; infectiology; limb function; health-related quality of life; workload; work engagement; health economic evaluation

Introduction

Background

Open fractures of the lower extremities are common, occurring with an incidence of approximately 11.5 per 100,000 [1]. Patients with open fractures often experience complications in the course of the disease, such as soft tissue infections, bone inflammation, defective bone fuse, and increased tissue pressure around the injury, with negative effects on blood supply and the nervous system [2,3]. Even for highly experienced service providers, it is often not possible to provide a sufficient quality of care for disciplines such as trauma, vascular and plastic surgery, infectiology, microbiology, and hygiene [4]. However, such interdisciplinary treatment has not yet been established in German primary and standard care. Currently, many patients with complicated or incorrectly healed fractures, infections, or chronically open wounds see several physicians in different hospitals, combined with inpatient transfers, redundant diagnostics, and long sick leave [5-7]. In many cases, the healing process is significantly impaired, and it is not uncommon for serious restrictions to remain.

In addition to the physical and psychological consequences for those affected, there are also the considerable costs of the health care system [1,8,9]. Patients with open lower-leg fractures incur almost twice as much cost (€11,000 [US $12,000]) as patients with closed fractures (€6600 [US $7100]) [5]. Open fractures with soft tissue infections lead to increased antibiotic use, additional surgeries, and longer hospital stays, which can increase costs 6-fold [5,10,11]. Against the backdrop of demographic change [12,13] as well as the increasing incidence of fractures due to comorbidities (eg, osteoporosis, gait uncertainty, and neurological diseases) and complications in the healing process from the age of 65 years onward, improving treatment options for complicated fractures and reducing the complication rate are of extreme importance [14]. Main complications that are encountered in this context are pseudarthrosis and chronic osteomyelitis. Pseudarthrosis is defined as a problem in fracture healing with missing consolidation of >6 months after trauma. Chronic osteomyelitis is a state in which destructive changes within the bone occur due to an infectious process. Both conditions prolong the healing process and usually make several surgical procedures necessary. In some cases, even an amputation must be considered.

In the United Kingdom, treatment structures have already been put in place to provide adequate and timely care to patients with these kinds of injuries. The British Orthopaedic Association and the British Association of Plastic, Reconstructive, and Aesthetic Surgeons introduced evidence-based standards of care for the treatment of severe, open lower-leg fractures (British Orthopaedic Association Standards for Trauma and Orthopaedics) [15]. It has been demonstrated that an early transfer of patients to specialized trauma centers and cooperation between surgical and nonsurgical disciplines significantly improve the course of treatment. Studies show a significant reduction in the infection rate, fewer additional surgeries, more successful limb reconstructions, and a reduction in treatment time [16-20].

Thus, concrete guidelines for the treatment of complicated fractures with soft tissue damage help not only improve the chances of treatment and healing but also reduce the costs of medical care. In particular, the involvement of an interdisciplinary team is essential for high-quality and cost-effective care [21]. In a joint interdisciplinary case conference, information and expertise can be exchanged, and treatment recommendations can be made based on broad expertise. This saves time and reduces redundant examinations and collisions of different treatment recommendations.

To consolidate treatment competence and ensure treatment quality, the standardization of specifications as well as diagnostic and treatment-related processes is essential. In the field of cancer therapy, interdisciplinary therapy recommendations have been established for decades within the framework of tumor boards. After intensive, interdisciplinary expert discussions, such a board makes a binding, patient-specific treatment recommendation considering all disease-relevant aspects [22].

So far, there is nothing comparable in Germany for the treatment of trauma to the extremities. In some large centers, there are interdisciplinary structures that deal with complex treatment situations. However, there is still no established process for the regular implementation of therapy steps. To date, there is also no way to standardize postoperative complications and treat them using stringent treatment pathways. Currently, people who have an open fracture or, in this context, a postoperative complication are admitted to the primary care clinic and treated on a monodisciplinary basis. The healing process of complicated fractures is further complicated by the fact that there are no contact points that take over the management of further treatment when the treatment options of a clinic for primary and standard care have been exhausted.

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Objectives

The aim of the EXPERT (Extremity Boards for process optimization, evaluation, risk minimization, and therapy optimization for fractures with soft tissue damage or postoperative infection of the lower extremities in the trauma network) project is to improve the treatment of fractures with open soft tissue damage or postoperative complications in northwest Germany rapidly and sustainably. Reductions in the duration and costs of treatment are further aims.

To achieve this, an interdisciplinary group of medical experts with a wide range of university expertise (eg, plastic surgery, infectiology, and hygiene) will make joint treatment recommendations within the framework of video case presentations. Consortium partners are 3 German statutory health insurance companies (BARMER, Techniker Krankenkasse, and AOK NordWest; see also Multimedia Appendix 1).

Physicians in standard care hospitals present their cases to the expert group (the Extremity Board) via telemedicine software and receive treatment recommendations tailored to the respective patients in a timely manner. In this way, the treatment result can be improved by adapting the individual therapy at an early stage.

On the basis of the knowledge gained in the Extremity Board, the interdisciplinary specialist group will define guidelines during the project to objectify decision-making paths, streamline processes, and define therapy algorithms. Through the close cooperation of the expert group with hospitals of primary and standard care, a joint agreement can be reached on treatment and documentation standards that relate to both the care of acute symptoms and postoperative complication management. The introduction of a web-based software platform enables both a secure exchange of medical information across the boundaries of different professional groups and the provision of interdisciplinary expertise in rural, structurally weak regions and regions affected by a shortage of specialists.

The effects of the new form of care based on the interdisciplinary approach and the associated standardization of diagnostics and therapy will be scientifically evaluated. Patient-related clinical success criteria as well as economic outcomes will be collected. As the new form of care has both content-related and organizational effects on the work in the clinics, work-related aspects will also be examined.

Research Questions and Hypotheses

Clinical and Health Economic Hypotheses

It is assumed that efficient telemedical access to an interdisciplinary expert forum (the Extremity Board) with simultaneous therapy decisions in the treatment of fractures with open soft tissue damage and postoperative complications will achieve significant reductions in the length of inpatient stay, the total duration of treatment, and the complication and reoperation rate [23]. The measures optimize therapy pathways, standardize them, and make them more cost-effective. The establishment of the Extremity Board leads to higher guideline adherence, standardization, and documentation quality and, consequently, to reduced antibiotic consumption and a reduction in unnecessary diagnostics.

Work-Related Hypotheses

For the ergonomic evaluation of the EXPERT project, the job demands–resources (JD-R) model [24-26] on the influence of work resources and work requirements on work behavior will be used. In this theoretical model, which is backed up by a wide range of findings [27-29], work resources and work requirements are considered to be independent factors influencing work engagement and perceived stress from work. High cognitive, emotional, and physical demands such as time pressure, workload, complexity of tasks, and emotional stress lead to high demands, which has long-term negative consequences for employees and the company (eg, employee burnout, low job satisfaction, and low productivity [30]).

On the other hand, work resources such as social support, feedback, autonomy, and meaningfulness have a motivating effect because they satisfy basic needs for self-efficacy, attachment, security, and control [31,32]. Therefore, diverse work resources lead to more work engagement, which has positive consequences for employees and the company (eg, high job satisfaction and high productivity [30]).

The JD-R model also postulates that work requirements and work resources interact with each other, which affects the perception of stress and motivation. Thus, the availability of resources can mitigate the negative impact of the requirements. Resources seem to have a positive effect on motivation and work engagement, especially when work demands are high [33]. When work demands are high, employees increasingly perceive existing resources as helpful and useful, which helps them cope with the demands. This results in a subjectively lower burden (coping hypothesis [34,35]).

On the basis of the theoretical assumptions and empirical findings, the following hypotheses can be derived for the EXPERT project (Figure 1): (1) work requirements and workload increase in the intervention phase of the EXPERT project (hypothesis 1a); (2) work-related resources such as knowledge, competencies, and team support increase during the intervention phase (hypothesis 1b); and (3) the technical competence of employees increases during the intervention phase (hypothesis 1c).

Above- or below-average resources are recorded with the median of differences (pretest-posttest estimates of resources), leading to other hypotheses: (1) above-average resources are associated with lower workload, and below-average resources are associated with higher workload (hypothesis 2); (2) above-average resources are associated with higher work engagement (hypothesis 3a); (3) when resources increase, work engagement increases (hypothesis 3b); (4) if resources increase (exclusion of technical competence as a resource), then readiness for technology increases while the burden decreases (hypothesis 4a); (5) as technical competence (resource) increases, the burden decreases (hypothesis 5a); (6) when technical competence (resource) decreases, the burden increases (hypothesis 5b); and (7) above-average work engagement leads to higher readiness

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for technology, and below-average work engagement leads to lower readiness.

Figure 1. Overview of work-related hypotheses concerning the relationship among work resources, workload, work engagement, and readiness for technology.

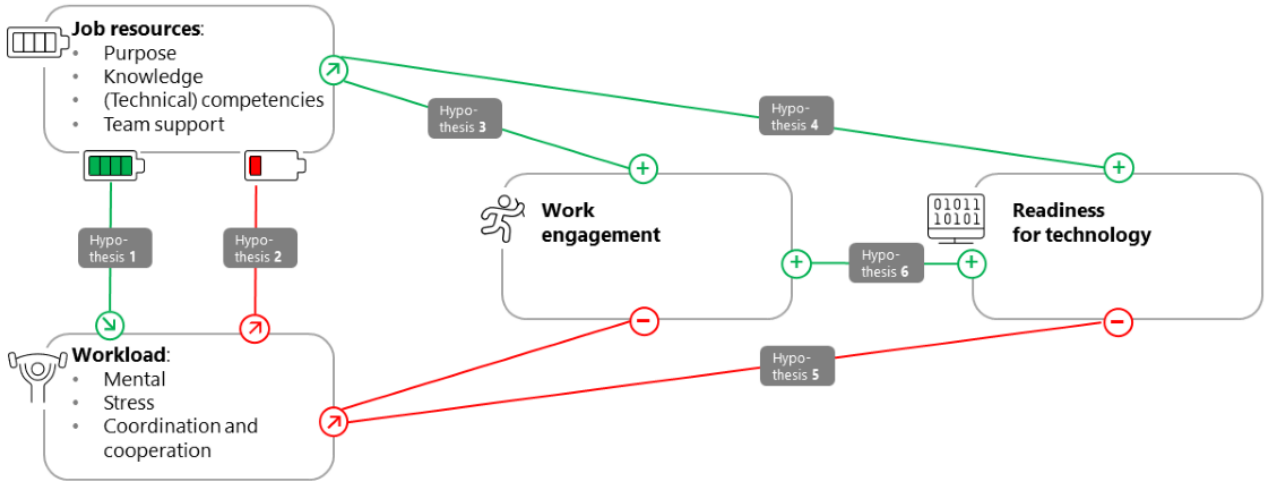

Methods

Study Design

Clinical and Health Economic Evaluation

For the organization and evaluation of the new form of care, a stepped-wedge design was chosen [36,37]. In a stepped-wedge design, there are different clusters that start recruitment at the same time in the control phase. The individual clusters then move gradually into the intervention phase in randomized cohorts. In the EXPERT project, there is a transition phase between the control and intervention periods, which serves to implement and test the new form of care in the individual clinics as well as train the staff.

Randomization in the EXPERT project will take place at the hospital level. There are 31 hospitals participating in the study. Each clinic forms a cluster that belongs to 1 of 4 cohorts. The clusters within a cohort always enter the next study phase (transition or intervention phase) at the same time. The study will be conducted over a period of 24 months (18-month recruitment period+6-month follow-up of the last enrolled person). Data collection regarding the individual course of treatment takes place from the time of enrollment in the patient sample until 6 months later. Figure 2 shows the planned course of the study in the stepped-wedge design.

Figure 2. Representation of the stepped-wedge design in the EXPERT (Extremity Boards for process optimization, evaluation, risk minimization, and therapy optimization for fractures with soft tissue damage or postoperative infection of the lower extremities in the trauma network) project.

18 months recruitment period						
Months	1-3	4-6	7-9	10-12	13-15	16-18
Cohort 1: 8 clusters	Control phase	Transition phase	Intervention phase			
Cohort 2: 8 clusters	Control phase		Transition phase	Intervention phase		
Cohort 3: 7 clusters	Control phase			Transition phase	Intervention phase	
Cohort 4: 8 clusters	Control phase				Transition phase	Intervention phase

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Work-Related Evaluation

For the ergonomic evaluation, the "difference-in-difference" method will be used within the stepped-wedge design [38]. This methodological approach includes a treatment group and a control group, each of which is examined at 2 measurement points (t0 and t1). In the treatment group, but not in the control group, an intervention takes place between the measurement points. The first difference that is measured refers to a possible change from measurement time t0 to measurement time t1. This is calculated for both the treatment and control groups. The second difference is the difference between these 2 differences (ie, the difference within the control group is subtracted from the difference within the treatment group). The result can be interpreted as a causal effect of an intervention [38,39].

In the EXPERT project, the clinics that have not yet implemented the project measures serve as a control group, which will be evaluated at the same time as the clinics that are already implementing the new measures. Cohorts 1 and 2 are the treatment group, whereas cohorts 3 and 4 act as the control group.

Data Sampling

Clinical and Health Economic Evaluation

Studies show that, in approximately 40% of cases, complications occur during the treatment in open fractures [40]. The new form of care is realistically intended to reduce the complication rate to 30%. A type-1 error (α) of 5%, a type-2 error (β) of 20% (80% power), and an intraclass correlation coefficient of ρ=0.05 are assumed [36]. Considering the transition phase and a dropout rate of 20%, the total number of cases required to demonstrate a treatment effect is 3366 patients (of whom n=1377, 40.91% would be in the control phase; n=1428, 42.42% would be in the intervention phase; and n=561, 16.67% would be in the transition phase). This equates to 17 patients per hospital per 3-month interval.

Only patients who can give consent and who have statutory health insurance will be included in the project and will give their written consent to participate and share their data in the use of telemedicine. The study will include patients with fractures of the extremities with open soft tissue damage (according to Gustilo et al [41]) or with postoperative complications (according to the criteria of the Association of the Study of Internal Fixation Anti-Infection Task Force) or people with unplanned resurgery within 6 months of initial surgery. Specifically, these are *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*), diagnoses [42] related to open soft tissue damage in fractures or dislocations, amputations of the lower extremity, infections of joints or joint endoprostheses of the lower extremities [43], and pseudarthrosis and delayed fracture healing of the lower extremity (see the list in Textbox 1).

Patients who are not capable of giving consent, who do not give their consent to participate or to data transfer, or who do not have statutory health insurance will be excluded from the study. Also excluded will be persons to whom the aforementioned *ICD-10* diagnoses do not apply (ie, who do not have a fracture of the extremities or extremities or have a closed fracture of the extremities without open soft tissue damage and who do not experience a postoperative complication within 6 months of initial surgery). The inclusion and exclusion criteria are summarized in Textbox 2.

Textbox 1. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), diagnoses to be included in the EXPERT (Extremity boards for process optimization, evaluation, risk minimization, and therapy optimization for fractures with soft tissue damage or postoperative infection of the lower extremities in the trauma network) study.

***ICD-10* code and description of diagnosis**

- S71.87: grade-I soft tissue damage due to open fracture or dislocation of hip and thigh
- S71.88: grade-II soft tissue damage due to open fracture or dislocation of hip and thigh
- S71.89: grade-III soft tissue damage due to open fracture or dislocation of hip and thigh
- S81.87: grade-I soft tissue damage due to open fracture or dislocation of lower leg
- S81.88: grade-II soft tissue damage due to open fracture or dislocation of lower leg
- S91.88: grade-II soft tissue injury due to open fracture or dislocation of foot
- S78: traumatic amputation of hip and thigh
- S88: traumatic amputation of lower leg
- S98: traumatic amputation of upper ankle and foot
- T84.6: infection and inflammatory reaction due to internal osteosynthesis device (any location)
- T84.7: infection and inflammatory reaction from other orthopedic endoprostheses, implants, or grafts

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Textbox 2. Inclusion and exclusion criteria.

Formal criteria

- Inclusion criteria
  - Consent to study participation and data transfer
  - Legal capacity to consent to study participation
  - Statutory health insurance
- Exclusion criteria
  - Lack of consent to study participation and data transfer
  - Unclear legal capacity or capacity to consent
  - Not covered by statutory health insurance

Clinical criteria

- Inclusion criteria
  - Patients who meet at least one of the following 2 criteria: fractures of the extremities with open soft tissue damage (according to Gustilo et al [41]) OR postoperative complications (according to the criteria of the Association of the Study of Internal Fixation Anti-Infection Task Force) or unplanned reoperation within 6 months of initial surgery; these criteria are operationalized via the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, codes for the following: open soft tissue damage in fractures or dislocations as well as amputations of the lower extremities; infections of the lower extremities (excluding joints and joint arthroplasty); infections of joints or joint endoprostheses of the lower extremities; pseudarthrosis and delayed fracture healing of the lower extremities
- Exclusion criteria
  - Patients who meet both of the following criteria: no fracture of the extremities or closed fracture of the extremities without open soft tissue damage AND no postoperative complication or unplanned reoperation within 6 months of initial surgery

Work-Related Evaluation

Physicians and nurses who are or will be involved with the project take part in the work-related evaluation. With medium to small effect sizes (η^2>0.05 and <0.15), a type-1 error (α) of 5%, and a type-2 error (β) of 20% (80% power), a minimum number of 120 people per measurement point is required for the work- and project-related evaluation (60 people each in the control and treatment groups). A total of 4 employees per clinic at measurement time t0 and 4 employees at measurement time t1 are included in the sample. This results in 31 × 8 = 248 elevations. Care is taken to interview physicians and nurses in equal parts, all of whom are or will be involved in the project measures.

Regarding the interviews for the assessment of the objectives and project implementation, 2 persons from the nursing service and 2 persons from the medical profession are to be interviewed at time t1 in the clinics that are already implementing the new form of care. Approximately 72 people from at least 18 clinics will take part in the interviews.

Ethical Considerations

Ethics approval has been granted by the ethics committee of the Medical Association of Westphalia-Lippe under the number 2023-067-f-S. This study is conducted per the tenets of the Declaration of Helsinki. All data have been collected, anonymized, analyzed, and stored in accordance with German General Data Protection Regulation legislation based on the European General Data Protection Regulation. The accordance to these data protection standards is approved and enforced by OFFIS-Institute for Information Technology, an institute related to the University of Oldenburg specializing on research services and data protection.

Participation is voluntary, and participants are required to provide oral and written consent to take part before entering the study. All participants received oral and written information before signing a consent form upon enrollment in the trial, and no financial compensation was made to participants in the study. The protocol was registered with the German Clinical Trials Register database (DRKS00031308).

Outcomes and Measures

Clinical and Health Economic Evaluation

The primary outcome and various secondary clinical outcomes are recorded based on data from the clinical case file as well as routine data from the health insurance companies.

The primary clinical outcome is the complication rate of open fractures or the occurrence of postoperative complications, which is collectively defined as a dichotomous outcome. Either the occurrence or nonoccurrence of complications is observed. The following events are complications if they occur within 6 months of enrollment in the sample: (1) occurrence of pseudarthrosis (incomplete fracture healing; *ICD-10* code M96.0); (2) occurrence of chronic osteomyelitis (*ICD-10* code M86.69); (3) unplanned follow-up procedures, such as wound revisions and Negative Pressure Wound Therapy (*ICD-10* code S81.801); (4) deviation from standardized antibiotic therapy

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(extension of the duration of therapy or change or expansion of the active substance; *ICD-10* code T36.95); (5) occurrence of antibiotic-associated complications (eg, clostridia infection or allergy; *ICD-10* code B96.7); (6) infection with resistant germs (eg, methicillin-resistant *Staphylococcus aureus*) that occurred during inpatient treatment and did not exist at the time of trauma (*ICD-10* code A49.02); (7) need for unplanned inpatient treatment; and (8) death of the patient related to the trauma (not due to other causes).

Secondary clinical outcomes include the number of antibiotics administered, limb function, and health-related quality of life (HRQoL) [44,45].

Health economic outcomes are mapped through claims data from health insurance companies. These will be recorded for each patient included in the project up to 6 months after enrollment in the sample. Specifically, the following features will be recorded: (1) use of health services (eg, contact with physicians and therapists, operations, and inpatient stays), (2) cost of health care services (inpatient hospital costs, outpatient costs, rehabilitation costs, medical and medical aid costs, drug costs, and total costs), (3) number of days on which there is incapacity for work, and (4) number of days on which sickness benefits are received.

Table 1 provides an overview of the clinical and health economic outcomes used in this study.

Patients' HRQoL is assessed at the time of enrollment and 6 months later using two internationally used measuring instruments: (1) the German-language version of the royalty-free Veterans RAND 36-item Health Survey [44] and (2) the German-language version of the EQ-5D of the EuroQol Group [45,46].

The Veterans RAND 36-item Health Survey is a generic profile questionnaire and measures HRQoL regarding the dimensions "Physical Functioning," "Role-Physical," "Role-Emotional," "General Health," "Social Functioning," "Vitality," "Bodily Pain," and "Mental Health."

The EQ-5D as a generic index instrument contains the 5 dimensions "Mobility," "Self-care," "Usual activities," "Pain/Discomfort," and "Anxiety/depression" as well as a visual analog scale. The results of the EQ-5D can be used to create a health profile as well as calculate an index value [46]. As an instrument validated in Germany, the index for HRQoL recorded using the EQ-5D is particularly well suited as a health economic outcome measure [46].

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Table 1. Clinical and health economic outcomes.

Outcome	Data source	Measurement time
Primary outcome		
Complication rate, defined as the occurrence of at least 1 of the following events within 6 months of trauma [42]:	Clinical and claims data	6 months
Occurrence of pseudarthrosis (incomplete fracture healing)	Clinical data	6 months
Occurrence of chronic osteomyelitis	Clinical data	6 months
Unplanned follow-up procedures, such as wound revisions and NPWT[a]	Clinical and claims data	6 months
Deviation from standardized antibiotic therapy (extension of the duration of therapy or change or expansion of the active substance)	Clinical and claims data	6 months
Occurrence of antibiotic-associated complications (eg, clostridia infection or allergy)	Clinical and claims data	6 months
Infection with resistant germs (eg, MRSA[b]) that occurred during inpatient treatment and did not exist at the time of trauma [43]	Clinical data	6 months
Need for unplanned inpatient treatment	Clinical and claims data	6 months
Death of the patient related to the trauma (not due to other causes)	Clinical and claims data	6 months
Secondary clinical outcomes		
Number of antibiotics administered	Clinical and claims data	6 months
Limb function	Clinical data	6 months
HRQoL[c], measured using the VR-36[d] [44] and EQ-5D [45,46]	Clinical data	0 and 6 months
Health economic outcomes		
Use of health care services	Claims data	6 months
Cost of health care services	Claims data	6 months
Days of incapacity for work	Claims data	6 months
Sickness benefit days	Claims data	6 months

[a]NPWT: negative pressure wound therapy.

[b]MRSA: methicillin-resistant *Staphylococcus aureus*.

[c]HRQoL: health-related quality of life.

[d]VR-36: Veterans RAND 36-item Health Survey.

Work-Related Evaluation

Questionnaires

Building on experiences and results from previous ergonomics studies in the fields of medical care and outpatient and inpatient care [47-49] and using the JD-R model as a theoretical frame of reference, the work-related evaluation uses validated measurement tools that measure workload, work engagement, work-related resources, and technological readiness. As the new form of care in the EXPERT project requires a competent application of telemedical technology, ergonomic aspects of the new telemedicine application are also recorded. The 7 items for the usability of the telemedicine application are only administered to the treatment group at the second measurement time. Therefore, the EXPERT questionnaire comprises 4 instruments with 31 items without ergonomic aspects and 5 instruments with 38 items with ergonomic aspects. Empirical comparative values are available for all measuring instruments used.

Workload is measured using the National Aeronautics and Space Administration Task Load Index [50] in a version for teamwork [51,52]. For this study, an abridged version of this questionnaire with 8 items in the German translation is used. On a scale of 1 to 10 (1=*very low*; 10=*very high*), employees estimate the mental, time, and performance-related work requirements as well as the effort regarding exchange, organization of work, team effectiveness, and mutual support for the past 3 months and give an assessment of their satisfaction with the cooperation. For example, a formulation is “How much effort was required to organize the work (e.g., coordination of who takes on which task, when which task is completed)?”

Work engagement is measured using the ultra–short form of the Utrecht Work Engagement Scale, which contains 3 items [53]. The German translations of “At work I am full of energy,”

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"I am enthusiastic about my work," and "I am completely absorbed in my work" are used, which are rated on a scale from 0 to 6 (0=*never*; 6=*always*).

Work resources are measured using the German-language questionnaire on resources and requirements in the world of work [54]. For the EXPERT project, 11 items are used, which relate to the resources "Leadership Support," "Feedback," "Peer-Support," "Transparency," "Diversity," "Meaningfulness," "Role Clarity," "Learning Opportunity," "Knowledge Management," "Team Atmosphere," and "Qualification." All items are formulated as statements (eg, "I will be informed about all important content when implementing the new measures" ["transparency" resource]), which are rated on a scale from 1 to 6 (1=*not at all true*; 6=*completely true*).

Affinity for technology is measured using the German-language short scale for measuring readiness for technology [55]. It is a questionnaire with 12 items in the 3 scales "TB acceptance," "TB control belief," and "TB competence," of which 9 items are used in this study. The item formulations have been adapted to the EXPERT project (eg, "I am very interested in the new telemedicine application" [acceptance scale], "It essentially depends on me whether I am successful in using the new telemedicine application" [control conviction scale], and "For me, dealing with technical innovations is usually too much to handle" [competence scale]).

The software ergonomics of the new telemedicine application are assessed using the German-language questionnaire Norm of the International Standard Organization 9241/10 [56,57]. On the basis of this instrument, software is evaluated regarding "adaptivity to requirements," "comprehensibility," "task appropriateness," "ability to describe itself," "fault tolerance," "individualizable," and "learning conduciveness." The assessment of the 7 items is made on a bipolar scale based on symbols (from "– – –" to "+++").

Finally, employees provide information about their profession (physician or nurse), whether they hold a management position (yes or no), and whether they already had experience in the use of telemedicine before the EXPERT project (yes or no).

Interviews

The structured telephone interview on the implementation of the project comprises both predetermined and open-ended questions, the content of which is based on the planned course of the EXPERT project. For each of the 4 project phases—"Preparation," "Development of new standards," "Cooperation with the Extremity Board," and "Implementation of therapy recommendations"—3 to 5 items were designed in the form of statements, which are assessed by the interviewees based on a 10-point scale. For example, one item regarding the project phase "Preparation" is as follows: "All employees involved in the project were able to obtain sufficient information about the new work steps and tasks, e.g., through training. (1=not true at all, 10=completely true)." An example for the project phase "Collaboration with the Extremity Board" is as follows: "The case presentations in the Extremity Board are helpful for the planning of treatments."

The open questions of the interview relate to aspects that the interviewees consider to be particularly important for the transfer of the project measures into standard care. The questioning technique used in this study is a simplified modification of the repertory grid technique [58,59]. In total, 2 open-ended questions refer to sequencing of steps within the project: (1) preparation phase, (2) development of new standards, (3) cooperation with the Extremity Board, and (4) implementation of the therapy recommendations. The participants are asked to describe what they like or dislike within the project steps. Regarding the most likeable and the most undesirable aspects, the participants are asked how important these aspects are for the future implementation of an Extremity Board (1=*not important at all*; 10=*very important*). This results in 8 aspects per interview that are relevant for the long-term implementation of the Extremity Board from the point of view of the hospital staff.

Data Analysis

Clinical and Health Economic Evaluation

The eligible patients are enrolled in the project by trained staff. Patients are informed about the objectives and course of the project and give their written consent to participate. Each case is summarized with all relevant information (eg, anamnesis, findings, and imaging) in a clinical case file using data-secure web-based software. The case files are checked for completeness and, after approval, transmitted digitally to the interdisciplinary expert group, the Extremity Board. This group of experts is recruited from the following disciplines: trauma surgery, plastic surgery, vascular surgery, radiology, angiology, and antibiotic stewardship (microbiology, hygiene, infectiology, and pharmacy) [43]. The experts meet at least weekly via web conference and, depending on the urgency, discuss the cases together. Agreed interdisciplinary therapy recommendations are written and transmitted back to the presenting clinic via the web-based software platform. In addition, guidelines will be defined in the course of the project on the basis of the findings gained by the Board to objectify decision-making paths, streamline processes, define therapy algorithms, and enable the supraregional applicability of these standards.

The clinical case files of all patients included in the EXPERT project will be merged with the respective patient-related health insurance data in an anonymized data file for each case while maintaining data protection. Claims data from health insurance companies provide information about the use of health services and the costs that arise in doing so. To obtain information about the individual course of treatment after the introduction of the new form of care, claims data for the following 6 months are included in the evaluation for each patient from the time of enrollment in the sample. Thus, the clinical case file and the associated health insurance data depict the course of treatment of a patient, which is included in the evaluation.

To be able to evaluate the extent to which the new care measures improve the chances of recovery and reduce costs, various clinical and economic outcomes are collected.

First, the primary outcome of the complication rate as well as the secondary and health economic outcomes are evaluated descriptively using absolute and relative frequency distributions

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as well as position and scattering measures (eg, median, variances, SD, and representation by means of box plots or histograms). The differences between patients in the control and intervention phases are checked using appropriate statistical methods (eg, Mann-Whitney *U* test [60,61], chi-square test, or odds ratio [62]). In addition, individual subgroups (eg, by sex and age) are analyzed to check the data for possible biases.

This descriptive analysis is followed by interference statistical analyses. By means of suitable regression analyses (eg, using generalized linear regression models), it can be examined which regressors have an influence on the primary and secondary outcomes. In addition to the consideration of temporal and intervention-related effects, the influence of potential confounders is also controlled for. This is because various patient- and trauma-associated factors are relevant risk factors for the development of a complication in the treatment of open fractures. For example, male sex, age of >60 years, BMI of >40 kg/m^2, use of nonsteroidal anti-inflammatory drugs, diabetes mellitus, and nicotine consumption are positively correlated with the development of an infection or fracture healing disorder [63]. This also applies to fractures in the context of multiple injuries (polytrauma) or in the context of agricultural accidents [64,65]. The quality of the statistical models is tested with the help of a residual analysis. Sensitivity analyses are carried out to check the stability of the evaluation and the assumptions made, for instance, the effects of changed influencing variables on the result.

As part of the health economic evaluation, the use as well as the costs of health services and absences from work are considered. For this purpose, a cost-effectiveness analysis is carried out whereby the incremental cost-effectiveness ratio will be calculated. The evaluation of routine statutory health insurance data is carried out according to the principles of good secondary data analysis [66], the recommendations of the "Methods for Health Services Research" memorandum [67], and the standards of the German Evaluation Society [68]. The data basis for the evaluation comprises the statutory health insurance routine data, the data from the case file, and the collected data on the health economic quality of life.

Work-Related Evaluation

The original item scaling of all 4 or 5 surveys respectively was retained, and all items were compiled into 1 questionnaire. In total, 4 versions of this questionnaire were created, which are identical in content but have been—with relation to the instructions—slightly adapted to the group (treatment group vs control group) and the time of measurement (before vs after the implementation of the new measures). For example, the instruction before treatment reads "Dear participant,...the clinic where you work...will soon start implementing the new measures" (treatment group) and "...will start implementing the new measures in the foreseeable future" (control group), whereas the instruction in the treatment group after implementing the new measures is "Dear participant,...the clinic where you work...is already implementing the new measures." The questionnaire was implemented, and postcards with a brief explanation and a QR code with a link to each specific questionnaire version were prepared. Interview guidelines and protocol sheets for the semistructured interview were created, and several fact sheets were written to inform the employees about the interview and data protection aspects.

In the practical implementation of ergonomic data collection, the project staff at Steinbeis University are supported by project staff from University Hospital Münster (Universitätsklinikum Münster [UKM]). Project staff from UKM have contact with the clinics and recruit people there to take part in the questionnaire surveys and interviews.

Before the clinics of cohort 1 start implementing the new form of care in project month 7 (Figure 2), both the clinic staff of cohort 1 (treatment group) and the clinic staff of cohort 3 (control group) will be examined with the EXPERT questionnaire in project months 4 and 5 (measurement time Pre). In project months 12 and 13, clinic staff from both cohorts will repeat the questionnaire (measurement time Post). The same procedure will be followed for cohort 2 and cohort 4, 3 and 9 months later, respectively. Project staff from UKM will recruit enough people in the individual clinics for the surveys. Interested employees in the clinics who are or will be involved in the project can find out more about the survey in advance by means of an information text. The UKM project staff receive a questionnaire link as a QR code from the Steinbeis project staff for the corresponding measurement time tailored to the corresponding group and cohort and send this QR code to a contact person in the clinics. The contact persons pass on the QR code to the participants, who scan it on their mobile phones and answer the questions. Participants are requested to do so as soon as possible after receiving the link. The completed questionnaires are automatically stored anonymously on the Steinbeis University server and later evaluated in summary form.

The UKM staff draw attention to the project-related interviews in the clinics that are already implementing the measures. Interested employees can find out more about the interviews by means of an information text and can contact the Steinbeis project staff to make an appointment for the telephone interview. They then receive an email from Steinbeis with the confirmation of the appointment, the interview questions, and the (renewed) promise that their email address and telephone number will be deleted after completion of the project. The transcripts of the telephone interviews are anonymized using a code. The content collected in the interviews will be evaluated in summary form, quantitatively, and qualitatively.

Regarding the topics of workload, work engagement, work-related resources, and readiness for technology, the main effects and interactions between measurement time (before vs after start of the Extremity Board) and group of measures (treatment vs control) are examined via variance analysis; the result is a 2 × 2 design with the factors time (before vs after) and group (treatment vs control group).

Ergonomic aspects of the telemedicine technology are collected and descriptively evaluated at the second measurement point in approximately half of the clinics.

As staff turnover in hospitals is high, it can be assumed that the groups of employees will be composed differently at each time

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of measurement. Therefore, no repeated-measure design can be applied. The analyses will be performed as balanced grouping factors with the same number of participants in all conditions (before vs after and treatment vs control). The measurements are considered as a grouping factor of a multiple ANOVA.

The evaluation of the repertory grids yields 2D representations of the negative and positive constructs mentioned by the interviewees during the interviews with respect to the different implementation steps, namely, preparation, development of new standards, interdisciplinary collaboration, and therapy implementation.

The combination of a questionnaire that can be used quickly and easily on a mobile phone and a telephone interview with both predetermined, scaled questions and open-ended evaluations according to the repertory grid technique results in a comprehensive picture of changes in pretest-posttest working conditions and of the success factors accompanying the process both in quantitative and qualitative terms. On the one hand, the web-based questionnaire before and after the introduction of the new form of care quantitatively captures influences on workload, work engagement, work-related resources, and readiness for technology and backs them up through the "difference-in-difference" design. On the other hand, central success factors regarding project implementation will be collected both quantitatively and qualitatively and made visible by means of the repertory grid technology as "mental maps" of the employees in the 31 participating clinics.

Results

The EXPERT project started in June 2022 with the necessary preparations and agreements among all partners involved. Patient data collection started in April 2023. As of June 13, 2024, data from 425 patients have been included. The web-based survey of clinic employees began in July 2023, and the interviews started in February 2024. So far, 146 people have taken part in the questionnaire survey, and 15 people have taken part in the interviews.

Discussion

Principal Findings

The aim of the EXPERT project is to improve the treatment of fractures with open soft tissue damage or postoperative complications rapidly and sustainably. To perform optimized multifaceted treatment, we consider the following disciplines an essential part of the interdisciplinary team: trauma surgeons, vascular surgeons, plastic surgeons, specialists for infectious diseases, radiologists, pharmacologists, hygienists, and microbiologists. We think that an interdisciplinary board needs several disciplines to not only enable a complete interdisciplinary treatment approach but also develop interdisciplinary treatment algorithms for infections or provide interdisciplinary prophylaxis in musculoskeletal surgery.

In addition to the evaluation of the clinical outcome, the cost reduction and cost-effectiveness of the new intervention will be evaluated based on claims data provided by 3 major statutory health insurance companies. The focus will be on use of health services and their cost as well as the duration of incapacity for work and HRQoL.

Furthermore, a process evaluation will explore the impact on workload, job satisfaction, and technology acceptance throughout the implementation phase and individual onboarding processes of the caretakers.

Comparison to Prior Work

The establishment of standardized treatment pathways in the standard care of patients with open fractures and postoperative infections may increase the chances of recovery for those affected and reduce costs. The previous heterogeneity of treatment methods, which is not expedient, can be reduced. Through largely standardized diagnostics and therapy, processes in the clinics can be optimized, and service processes can be standardized. Unnecessary and redundant diagnostics and treatment steps may be avoided. At the same time, the interdisciplinary treatment perspective allows for a more individualized therapy. This study aims to show that this results in a reduction in direct treatment costs and length of stay in hospital as well as a reduction in secondary costs (eg, due to long sick leave after discharge and revisiting practitioners). This is also in line with previous research findings.

Fractures impact function, quality of life, and psychological well-being. An multidisciplinary approach and early diagnosis are crucial for treatment success. Interdisciplinary support and patient-tailored treatment shortens hospital stays and reduces treatment costs, and standardized treatment pathways optimize clinic processes and reduce unnecessary steps [69-71]. In particular, hospital stays and costs induced by fracture-related infections are reduced [72]. The importance of multidisciplinary collaboration is especially effective for patients with hip fractures [73].

Strengths and Limitations

When measuring the quality of treatment in trauma surgery, several influencing factors must be considered. The type of injury, the extent of anatomical reconstruction during surgery, soft tissue management, perioperative management, and rehabilitation protocols as well as patient compliance have a major influence on the outcome and make evaluation difficult. For our study, we chose 4 outcome measures: the complication rate after initial surgery (nonunion, infection, unplanned surgical revision, and need for prolonged antibiotic therapy), the number of applied antibiotics, the functionality of the injured limb, and HRQoL.

The clinical outcome is examined using a stepped-wedge design, which allows for the statistical consideration of time effects. The design also has practical advantages, such as the easy implementation of a staggered rollout. Among the weaknesses of a stepped-wedge design are time-sensitive recruitment efforts, complex randomization requirements when assigning hospitals to different cohorts or wedges, the assumption of high treatment schedule fidelity, and effects of the observation (the so-called Hawthorne effect) [74].

We choose a difference-in-difference design, a widely used quasi-experimental design in clinical research, to evaluate

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work-related outcomes. This design eliminates confounding by comparing outcomes before and after treatment. However, the design relies on a parallel-slopes assumption, which is hard to manage and may not always apply [75].

Conclusions

The interdisciplinary, cross-disciplinary, and cross-departmental coordination of service providers enables comprehensive interface management in the clinics. The perspective of service providers can increasingly focus on holistic, patient-oriented coordination of management processes, which provides patients with the best possible access to individualized therapy in a timely manner. In addition to health economic advantages, the multidisciplinary treatment is expected to improve the quality of the therapy, which is to be proven through clinical follow-up. In addition, it is conceivable to establish specialized outpatient or inpatient treatment centers for patients with open fractures and postoperative infections in which the new diagnostic and therapeutic pathways are competently applied.

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Authors' Contributions

S Rosslenbroich contributed to funding acquisition, concept development, article writing, data interpretation, and article review. ML contributed to project management, data curation, data interpretation, and article review. JH contributed to funding acquisition, concept development, article writing, data analysis, data interpretation, and article review. S Rodde contributed to concept development, article writing, data analysis, data interpretation, and article review JG contributed to funding acquisition, project management, concept development, article writing, data analysis, data interpretation, and article review. WG contributed to funding acquisition, concept development, and article review. TH contributed to concept development, data interpretation, and article review. SW contributed to concept development, data interpretation, and article review. MJR contributed to funding acquisition, concept development, and article review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Deutsches Zentrum für Luft- und Raumfahrt e. V. (DLR) - DLR Projektträger - Bereich Gesundheit (Bonn, Germany).
[PDF File (Adobe PDF File), 185 KB - resprot_v13i1e57820_app1.pdf]

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Abbreviations

EXPERT: Extremity Boards for process optimization, evaluation, risk minimization, and therapy optimization for fractures with soft tissue damage or postoperative infection of the lower extremities in the trauma network
HRQoL: health-related quality of life
***ICD-10*:** *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
JD-R: job demands–resources
UKM: University Hospital Münster

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Protocol

Implementing and Evaluating a Mobile Phone–Supported and Family-Centered Rehabilitation Program for People With Stroke in Uganda (F@ce 2.0): Protocol for a Randomized Controlled Trial

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Abstract

Background: Stroke is a global societal challenge. Annually, 13 million people experience stroke, and the prevalence of stroke is increasing in low-income countries; hence, accessible rehabilitation needs to be developed. Information and communication technology can help by providing access to rehabilitation support through information, self-evaluation, and self-management of rehabilitation. The F@ce 2.0 rehabilitation program provides support in goal-setting and problem-solving strategies through phone calls from the interventionist twice a week and daily SMS text message reminders over 8 weeks to improve performance in valued activities in everyday life. Our hypothesis is that F@ce 2.0 will increase functioning in daily activities and participation in everyday life as well as improve performance and satisfaction in valued daily activities and self-efficacy (ie, confidence in own ability to perform activities) among people living with the consequences of stroke.

Objective: This study aims to implement F@ce 2.0, a mobile phone–supported and family-centered rehabilitation program, and evaluate its effects on performance in daily activities and participation in everyday life in comparison to ordinary rehabilitation among persons with stroke and their family members in Uganda. An additional aim is to explore experiences of participating in F@ce 2.0 and plausible mechanisms of impact that might explain the potential effects of F@ce 2.0.

Methods: A randomized controlled trial will be conducted to compare the outcomes of the F@ce 2.0 group and a control group receiving ordinary rehabilitation. Health care professionals will recruit 90 clients from both urban and rural areas. The primary outcomes for persons with stroke are perceived performance in daily activities assessed using the Canadian Occupational Performance Measure and self-efficacy assessed using the Self-Efficacy Scale; for family members, the primary outcome is caregiver burden evaluated using the Caregiver Burden Scale. Descriptive statistics will be used to present characteristics and outcomes at 3 and 6 months. All statistical analyses comparing the outcomes at the different time points between the F@ce 2.0 and control groups will be performed using intention-to-treat analysis. Qualitative interviews will be used to explore the experiences of persons with stroke and their family members participating in F@ce 2.0, using a grounded theory approach to data collection and analysis. A process evaluation will be conducted using a single-case study design with mixed methods to explore the implementation process.

Results: Recruitment and data collection in the randomized controlled trial were initiated in January 2022 and have been completed. The intervention has been provided to 51 participants in the intervention group. Interviews of persons with stroke, family members, and health care professionals have been conducted. Data analysis will be performed during autumn 2024 and spring 2025.

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Conclusions: This study will provide evidence of the plausible effects of F@ce 2.0 and the process of implementing the program in low-income countries.

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KEYWORDS

information and communication technology; ICT; mobile health; mHealth; telehealth; telemedicine; remote rehabilitation; activity of daily living; ADL; East Africa; sub-Saharan Africa; intervention; occupational therapy; physiotherapy

Introduction

Background

The point of departure for this study is that all people living with a disability and their families have needs and the right to participate and engage in everyday life. Social participation [1] and engagement in daily activities [2] are strongly associated with health and well-being [3]. Everyday life changes often occur for people with stroke and their families [4], and there is a need for rehabilitation and support to enable functioning in daily activities and social participation in the community.

Stroke is a noncommunicable disease and a global societal challenge according to the World Health Organization [5]. Annually, >13 million people experience stroke, which means that worldwide 1 in 4 people aged >25 years will have stroke in their lifetime, and one-third will subsequently live with remaining disabilities [6]. The burden of stroke is increasing substantially in Africa [7,8], which has some of the highest incidence rates in the world [9]. Stroke currently ranks as the sixth leading cause of mortality in Uganda [10].

Empirical studies on the effectiveness of rehabilitation after stroke have shown positive effects of activities of daily living (ADLs) interventions [11]. However, most research and evidence for beneficial rehabilitation interventions after stroke originates from high-income countries, and evidence is lacking that such interventions can be implemented with similar outcomes in the context of sub-Saharan Africa [8]. In 2021 in Uganda, 41% of the population was living below the poverty line, subsisting on the equivalent of US $1.90 per day [12]. Furthermore, the majority of the Ugandan population (74%) lived in rural areas, where medical rehabilitation was almost nonexistent [13]. In addition to the poor socioeconomic conditions in Uganda, access to rehabilitation services can be limited due to poor infrastructure, inadequate numbers of rehabilitation professionals, and poor health support systems.

To increase accessibility to rehabilitation services, the development and implementation of contextually appropriate rehabilitation programs is urgently needed. One way to increase accessibility to rehabilitation could be to use the knowledge of health care professionals (HCPs) to train village health workers, who in turn can provide rehabilitation support in agreement with the model for community-based rehabilitation (CBR) [14]. The CBR model respects diversity and aims to empower people with disabilities and reduce stigma against them; it is also in line with a client- and family-centered approach.

In addition to causing disabilities, stroke can lead to a stressful situation for family members, with risk for depression, perceived caregiver burden [15], social isolation, physical problems, and decreased life satisfaction [16]. In Uganda, families are commonly involved after stroke and take responsibility for care not only in the acute hospital setting but also in community living [17]. Rehabilitation programs after stroke should therefore involve family members to attain common goals for rehabilitation, such as participation in ADLs [18].

In our previous research [19], our findings stressed that it was important that people with stroke had “significant experiences that contributed to change” by performing activities they wanted and appreciated during their rehabilitation process. Therefore, activities that are relevant and valued for people in everyday life can be used as goals to improve ADL functioning [20]. Furthermore, if the people succeed in performing activities of their choice, their confidence in their capability to perform activities will be strengthened (ie, increased sense of self-efficacy) [21,22]. In our previous qualitative studies, the importance of including the client’s perspective as the point of departure for interventions has been expressed by persons with stroke as well as by HCPs [23,24]. Moreover, family support and engaging activities were described as increasing participation and functioning in everyday life [19]. The rehabilitation program F@ce 2.0 is therefore family-centered, that is, it includes both the person with stroke and his or her family members, which is in line with client-centered practice [25,26].

Mobile phones are part of information and communication technology (ICT), that is, according to the United Nations Educational, Scientific and Cultural Organization, they are “forms of technology that are used to transmit, process, store, create, display, share or exchange information by electronic means” [27]. Mobile phones have rapidly become an integral part of everyday living for people in sub-Saharan Africa and are often the sole means of communication with those living outside urban areas. According to The Mobile Economy Sub-Saharan Africa 2020 report, mobile services are predicted to continue growing in the region at an annual rate of 4.3% until 2025 [28]. Mobile phones have the potential to extend the reach of health care and rehabilitation [29] with an impact on the United Nations’ Sustainable Development Goal 3 [30], which seeks to ensure healthy lives and promote well-being for all at all ages. It has been shown that despite having physical and cognitive impairments, people with stroke could benefit from using mobile phone technology in their daily lives [31]. In addition, our previous studies [32,33] in Uganda have shown that mobile phone technology can be used to support the

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rehabilitation process after stroke via follow-up calls, SMS text message reminders, and feedback on the performance of activities. However, in our feasibility study of the mobile phone–supported rehabilitation program F@ce 1.0 [33], participants were recruited from an urban area, and the sample size was not powered to draw conclusions about the effects. Furthermore, F@ce 1.0 has been developed into an interdisciplinary intervention, F@ce 2.0 [34]. Hence, F@ce 2.0, which includes (1) educational workshops for the assigned HCPs, (2) a goal-directed and mobile phone–supported intervention, and (3) a web-based platform providing daily SMS text message reminders to patients, will be evaluated in a larger trial.

Objectives

The overall aim of this project is to implement F@ce 2.0, a mobile phone–supported and family-centered rehabilitation program, and evaluate its effects on performance in daily activities and participation in everyday life in comparison to ordinary rehabilitation among persons with stroke and their family members. An additional aim is to explore the experiences of participating in F@ce 2.0 and plausible mechanisms of impact that might explain the potential effects of using F@ce 2.0 by studying the implementation process in both urban (Kampala, the capital city) and rural (Greater Masaka) areas.

Our hypothesis is that persons with stroke who participate in the F@ce 2.0 intervention will increase their functioning in daily activities and participation in everyday life as well as perceive their performance and satisfaction in daily activities and their self-efficacy to be higher than those receiving ordinary rehabilitation.

Research Questions

We developed the following research questions (RQs):

- RQ 1: Are there any differences in effects after the 8-week intervention and at follow-up at 6 months between people with stroke who participated in F@ce 2.0 and those who received ordinary rehabilitation with regard to perceived performance in daily activities, self-efficacy, participation in everyday life, and independence in ADLs?
- RQ 2: Are there any differences after the 8-week intervention and at follow-up at 6 months between the family members of those receiving the F@ce 2.0 intervention in comparison to the family members of those receiving ordinary rehabilitation regarding caregiver burden and life satisfaction?
- RQ 3: How do the persons with stroke and their family members experience their participation in F@ce 2.0?
- RQ 4: How can the outcomes of F@ce 2.0 be understood and explained when considering the implementation process and the plausible potential mechanisms of impact?

Methods

Study Design

A randomized controlled trial with a pretest-posttest parallel design with an intervention group (IG) and a control group (CG) has been chosen to compare outcomes between participants receiving F@ce 2.0 (IG) and those receiving ordinary rehabilitation (CG). The study follows the Medical Research Council's guidance [35] for evaluating complex interventions; hence, the study uses both quantitative and qualitative methodologies and a process evaluation. The trial will be monitored according to the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement for nonpharmacological trials [36] and the CONSORT 2010 extension for pragmatic trials in health care [37]. Furthermore, this protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [38,39]. The study has been registered at ClincialTrials.gov (NCT04337034).

Study Setting

The F@ce 2.0 program will be implemented in 2 designated geographic areas in Uganda: Kampala (representing an urban area) and Greater Masaka (a rural area). Rehabilitation professionals or HCPs working at health care centers and CBR centers in these 2 geographic areas will be recruited to provide the F@ce 2.0 intervention or the ordinary rehabilitation intervention. These centers are funded either publicly or privately [40]. Staff numbers vary at these centers, and the recruitment of HCPs will differ depending on which types of professionals are employed. Preference will be given to occupational therapists, physiotherapists, and nurses, but other professionals might also be approached. HCPs assigned to deliver the F@ce 2.0 intervention will participate in educational workshops provided by the research group to prepare for delivering the intervention to the IG participants.

Eligibility Criteria

Persons with stroke, family members of the persons with stroke, and HCPs working at the participating centers will be eligible to participate.

Persons with stroke will be included if the following criteria are fulfilled: (1) stroke diagnosis confirmed by computer tomography scan or by clinical symptoms; (2) enrolled at 1 of the 3 participating centers; (3) aged >18 years; (4) having no psychiatric diagnosis; (5) able to understand and formulate activity goals in English or Luganda; (6) access to, and self-reported ability to use, a mobile phone; and (7) a modified Rankin Scale level ranging from 2 to 4, indicating a slight to moderately severe disability [41].

A family member, identified as close to the person with stroke (ie, wife, husband, friend, daughter, neighbor, etc) and chosen by the person with stroke, will also be invited to participate.

The F@ce 2.0 Program in the Ugandan Context

Workshops for Intervention Providers

The HCPs (ie, occupational therapists, physiotherapists, and nurses; n=4) assigned to deliver the intervention in the Kampala and Greater Masaka areas will participate in preparatory training workshops. The workshops will be organized on 2 days in 1 week as face-to-face seminars led by the research team. During the workshop sessions, the empirical and theoretical underpinnings of F@ce 2.0 will be presented and discussed. Further relevant issues regarding rehabilitation after stroke will be reflected on and discussed between the HCPs and the

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researchers. Furthermore, the use of ICT as a tool within rehabilitation will be initiated, discussed, and practiced during the workshop [33]. Finally, ways to integrate the F@ce 2.0 intervention into ordinary rehabilitation will be considered with the HCPs, and client cases will be used and elaborated on to facilitate their reflective learning process.

The F@ce 2.0 Intervention

The 8-week mobile phone–supported and family-centered intervention aims to increase functioning in daily activities for persons living with the consequences of stroke and participation in everyday life for persons with stroke and their family members. Using the Canadian Occupational Performance Measure (COPM) [42], the person with stroke formulates 3 *targets* (goals) in daily activities that they want and need to perform in the home environment. The participant, together with an identified family member, will be introduced to a problem-solving strategy framed as *target-plan-perform-prove*, intended to facilitate the learning and problem-solving process. Each activity will be practiced together with the family member, and the performance will be discussed together with the HCP to identify and formulate a *plan* for overcoming the difficulties in performing the activities chosen as targets. Different strategies will be developed and formulated together with the HCP, such as finding new ways to perform the target activities and to modify the environmental demands. To enable the family member to support the person with stroke to *perform* and practice if needed, they will be informed about the participant's target activities and the planned strategies.

The Web Platform and Use of the Mobile Phone in F@ce 2.0

The participants will practice the target activities in their home environment, supported via mobile phone calls and SMS text messages. The SMS text messages will be sent from a web platform (developed using Node.js/PostgreSQL for the backend and HTML/CSS/JavaScript for the front-end) [43] where the HCPs will register the participants' target activities and strategies for the training that they have agreed on. The participants or the family members will receive individual SMS text messages containing the 3 targets twice daily, morning and evening. The morning message will remind the participants to perform the activities during the day. In the evening, the participants, with or without support from a family member, will be asked to rate (on a scale ranging from 0 to 5) their performance of the 3 target activities, where 0=*has not performed the activity* and 5=*carried out the activity well*. If participants rate their performance as 0 or do not reply to the SMS text message reminder, a red flag alert will automatically be generated on the HCP's mobile phone. The HCP will contact the participant the following morning to find out what happened and come to an agreement regarding the next strategy. The participants receiving F@ce 2.0 will also receive mobile phone calls as a follow-up strategy from their HCP twice a week.

Additional Intervention for Study Participants

All participants in the study (IG+CG) will be given oral and written information about stroke during the initial assessments. Self-reported use of health services will be collected, with assistance from family members if needed. The participants in the CG will receive the health care intervention and rehabilitation provided by their center, but they will not receive any rehabilitation supported via SMS text messages.

Outcome Data

The primary outcomes for persons with stroke are perceived performance in daily activities evaluated with the COPM [42] and self-efficacy in performing daily activities (ie, the persons' confidence in their ability) measured using the Self-Efficacy Scale (SES) [44,45]. The secondary outcomes will be the perceived impact of stroke evaluated with the Stroke Impact Scale 3.0 (SIS 3.0; Ugandan version) [46] and independence and dependence in ADLs measured using the Barthel Index (BI) [47]. The outcomes for family members will be caregiver burden assessed with the Caregiver Burden Scale (CBS) [48] and life satisfaction assessed with the Life Satisfaction Questionnaire-11 (LiSat-11) [49].

Participant Timeline

Participant enrollment was initiated in 2022, and the last qualitative interview was performed during spring 2023. During this period, 90 persons with stroke and their family members were enrolled in the study. HCPs from the rehabilitation teams were enrolled as participants during the F@ce 2.0 intervention and will be followed until the study is completed.

For each participant, demographic data and baseline assessments were conducted during the first week after enrollment and postintervention assessments approximately 9 weeks after enrollment (ie, within 1 week after finalizing the program).

The study timeline is presented in Table 1.

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Table 1. Participant timeline and data collection.

	Study period					
	Enrollment	Allocation	After allocation			
	Wk 0	Baseline	Intervention (wk 1-8)	Wk 9	6 mo	After last participant completes intervention
Enrollment						
Eligibility screening	✓					
Informed consent	✓					
Interventions						
F@ce 2.0			✓			
Control: rehabilitation as usual			✓			
Assessments: persons with stroke						
Demographics		✓				
SSS[a]		✓				
Barthel Index		✓				
Self-Efficacy Scale		✓		✓	✓	
COPM[b]		✓		✓	✓	
SIS 3.0[c] (Ugandan version)		✓		✓	✓	
Use of health care and risk factors		✓			✓	
Qualitative interviews				✓	✓	
Survey regarding intervention (Multimedia Appendix 1)				✓		
Assessments: family members						
Demographics		✓				
LiSat-11[d]		✓		✓	✓	
Caregiver Burden Scale		✓		✓	✓	
Qualitative interviews				✓	✓	
Survey regarding intervention (Multimedia Appendix 1)				✓		
Assessments: team members and HCPs[e]						
Demographics		✓				
Team members' and HCPs' reflections after workshop and coaching	✓	✓				
Team members' and HCPs' logbooks on follow-up calls and additional services supplied			✓			
Qualitative interviews of HCPs on intervention process (Multimedia Appendix 2)						✓
Registrations on the web platform			✓			
Fidelity check[f]			✓	✓		

[a]SSS: Scandinavian Stroke Scale.

[b]COPM: Canadian Occupational Performance Measure.

[c]SIS 3.0: Stroke Impact Scale 3.0.

[d]LiSat-11: Life Satisfaction Questionnaire-11.

[e]HCP: health care professional.

[f]Conducted monthly with the whole team throughout the study.

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Sample Size and Power Considerations

A power calculation based on the results from our pilot study in Uganda [33] regarding the primary outcome—a clinically important difference of 2 points according to the COPM (ie, perceived performance and satisfaction in daily activities)—showed that 36 participants in each group are needed. Considering an attrition rate of 25%, a total of 90 participants will be required (α set at .05 and β at .80).

Recruitment and Informed Consent

HCPs assigned as data collectors will identify potential study participants who meet the inclusion criteria from hospital wards, community health care units, rehabilitation centers, or physiotherapy clinics and inform them verbally about the study. The HCPs will also inform them that participation is voluntary and that they have the right to withdraw from the study at any time. In addition, the HCPs will provide participants with written information and an informed consent form in English or, when appropriate, in Luganda. Each participant will sign a consent form for voluntary participation, which emphasizes their right to withdraw from the study at any time, in accordance with the Helsinki Declaration [50]. Before patients are included, a randomization sequence will be created by the second and last authors using a random number table developed by a researcher at Karolinska Institutet in Solna, Stockholm County, Sweden. After completion of the baseline assessment, the researcher in Uganda (JK) will contact the researchers at Karolinska Institutet to obtain information on group allocation. If a participant is allocated to the IG, the researcher in Uganda (JK) will contact the HCP and inform them to provide the intervention.

The participants who consent to take part in the study will be asked to identify a family member to enroll in the study. Potential participating family members will receive verbal and written information, and written informed consent will be obtained from those who agree to participate.

Data Collection

After informed consent is obtained, demographic data collection and baseline assessments will be performed by data collectors (HCPs at the 3 participating centers). The data collectors are not involved in delivering the intervention and are blinded to the allocation of the intervention. All data collectors will receive training before data collection to standardize data collection procedures. All information will be collected face-to-face. Demographic data (Multimedia Appendix 3) and baseline assessments will be conducted after enrollment, and follow-up assessments will be conducted within 1 week after the intervention ends and at 6 months after inclusion, preferably by the same assessors.

Primary Outcomes

Persons With Stroke

The COPM assesses an individual's perceptions of performance and satisfaction in valued daily activities within the areas of self-care, productivity, and leisure [38]. For the initial evaluation, the COPM starts with a semistructured interview lasting 30 to 40 minutes during which the persons with stroke identify activities in everyday life that they consider to be important but difficult to perform. Each activity is documented, and the participants rate the importance of each activity on a 10-point scale. They are then asked to choose 3 relevant activities and rate their performance and satisfaction with performance in each activity on separate scales, where a higher score indicates greater importance, better performance, and greater satisfaction. For the re-evaluation at the end of the intervention period, the participants are again asked to rate their performance and satisfaction in each activity. A difference of ≥2 points between the 2 evaluations indicates a clinically significant change [42]. The internal consistency of the COPM is within a reasonable range, and test-retest reliability is well above acceptable levels. Furthermore, the validity of the COPM as a measure of occupational performance has been supported by a large number of studies [51].

The SES assesses self-efficacy (ie, individuals' confidence in their ability). The social cognitive theory formulated by Bandura [44] is the base for self-efficacy and reflects an individual's belief in their capability to perform activities to attain a desired result. The theory of self-efficacy proposes that the stronger a person's efficacy expectations are, the more likely the person will start and continue performing these given activities. The persons with stroke will be instructed during the interview to rate how confident they are about performing each of 16 everyday activities on a 10-point rating scale ranging from 1=*not confident at all in my ability* to 10=*very confident in my ability*. The rating process takes approximately 10 minutes, and the responses are summarized into a total score. The SES (Multimedia Appendix 4) has been adapted from a similar scale for people with pain [52] and has been used in our previous feasibility study [33].

Family Members

The CBS will be used to describe the perceptions and characteristics of caregiver burden among the family members assisting the person with stroke [48].

The CBS assesses 22 items, reflecting factors that include the family members' health, general strain, isolation, disappointment, emotional involvement, and environmental aspects. The measure is administered as a self-report questionnaire and takes 20 to 30 minutes to complete. Each item is rated on a 4-point scale (1=*not at all*, 2=*seldom*, 3=*sometimes*, and 4=*often*), with a higher score indicating a greater burden. The ratings on the items are summarized into a total score. No cutoff score is used. The measure has good construct validity and test-retest reliability [48].

Secondary Outcomes

Persons With Stroke

The SIS 3.0 (Ugandan version) [46] will assess the self-perceived impact of stroke in 8 domains: strength, memory and thinking, emotions, communication, ADLs and instrumental ADLs, mobility, hand function, and participation. The SIS 3.0 (Ugandan version) includes 59 items within these 8 domains, and it is administered as a structured interview that takes approximately 30 minutes to complete. Aggregated scores for each domain are generated ranging from 0 to 100; the higher

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the score, the lower the perceived impact of stroke (ie, fewer problems in everyday life).

Most domains of the SIS 3.0 (Ugandan version) satisfy important criteria for rating scale functioning. The internal consistency and discriminant validity are satisfactory for use among people with stroke in Uganda [46].

The Scandinavian Stroke Scale will be used to describe clinical characteristics, assess neurological impairment, and define stroke severity. This scale is administered face-to-face and takes approximately 10 minutes to complete. It provides a score for stroke severity between 2 and 5 grades of deficit ranked in decreasing order based on the level of consciousness, eye movement, orientation, speech, hand and leg movement, gait, and facial paralysis; the lower the score, the worse the deficit. The interobserver reliability for the different components is very good, as is the agreement between the domains [53].

The BI will be used to assess independence or dependence in ADLs across 10 self-care and mobility activities [47]. The values assigned to each item (0, 5, 10, or 15) are based on the time and amount of physical assistance required if the person cannot perform the activity independently. Scores range from 0 to 100, with a lower score indicating greater dependency. The BI is administered through an interview that takes approximately 10 minutes to complete and is reliable and valid for people with stroke [54].

Family Members

The LiSat-11 will be used to measure global life satisfaction as well as satisfaction across 10 domains using a 6-point scale [49]. The LiSat-11 is completed through self-report, which takes approximately 10 minutes. The score on each domain is dichotomized and presented without summarizing the overall scores. The questionnaire has demonstrated acceptable test-retest reliability, specificity, and sensitivity [49].

Health care use will be collected through a structured interview with the person with stroke, together with the family member.

Experiences of Taking Part in F@ce 2.0 Among Persons With Stroke and Their Family Members

Semistructured qualitative interviews (Multimedia Appendix 2) will be conducted face-to-face with persons with stroke and their family members. Interviews with the person with stroke (n=6-10) and family members (n=6-10) from both rural and urban areas will be conducted in their home setting after they complete the F@ce 2.0 intervention. Their experiences of participating in F@ce 2.0 will be explored, and the data from the interviews will be analyzed using a grounded theory approach [55]. The participant group will be selected to represent a range of experiences (eg, varied characteristics regarding sex, level of disability, and living conditions) to ensure the collection of rich qualitative data. An interview guide with open-ended questions focusing on participants' everyday life experiences when participating in the F@ce 2.0 intervention will be used. Field notes will be taken during the interviews, and all interviews will be digitally recorded and transcribed verbatim and translated into English if conducted in Luganda. The transcripts from these interviews will also be used in the process evaluation described in the next subsection.

Process Evaluation of F@ce 2.0 in the Ugandan Context

A process evaluation is essential for designing and evaluating complex interventions, such as F@ce 2.0, and refers to activities related to the implementation, acceptance, and reach of an intervention. A process evaluation aims to answer questions about how the intervention interacts with its context, how different perspectives from stakeholders can be integrated, or how the intervention can be refined [56]. This study will use a single-case study design with mixed methods, combining qualitative and quantitative data to explore the implementation process and mechanisms of impact of the F@ce 2.0 program. Quantitative process data will include metrics such as the mean number of minutes per session with clients, the number of telephone contacts between HCPs and clients, and data from the web platform. The HCPs' logbooks will also be collected. In addition, semistructured interviews (Multimedia Appendix 2) will be conducted with persons with stroke, their family members, and the HCPs providing the intervention. The interviews with the persons with stroke and family members will focus on exploring their perceptions of the value, benefits, and detrimental or unintended consequences of the intervention, as well as their perspectives of the intervention's acceptability, fidelity, reach, and dose. The interviews with HCPs will cover their reflections and reasoning in relation to preparations for delivering the intervention at the workshops, as well as the intervention delivery process, aiming to explore the implementation of the intervention. The logbooks maintained by the HCPs will include their field notes and reflections after the workshop and coaching sessions. These field notes will describe conditions that facilitated or hindered session delivery, as well as potential positive or negative side effects. The HCPs' acceptability of the intervention will also be documented. From the web platform, information on response rates to SMS text messages as well as target achievement will be derived.

Data Analyses

Anonymized data will be entered into SPSS for Windows (IBM Corp) [57]. The number of participants (persons with stroke and family members) being recruited will be presented in a flowchart according to the CONSORT statement [36,37]. The retention rate and adherence to the intervention (eg, responses to SMS text messages, HCPs' follow-up meetings with the participants, and all other services related to the intervention, as well as the number of participants seen by each HCP or team) will be presented based on frequencies and percentages. Descriptive statistics will be used to present the characteristics of the participants, health care use, and the outcomes after the intervention and at 6 months.

All statistical analyses comparing the primary and secondary outcomes between the IG and the CG will be performed using intention-to-treat analysis [58]. For missing values, the imputation method of last value carried forward will be used. To assess differences in changes in primary outcomes between the IG and CG at the different data collection points, multivariate statistical methods will be used. Covariates will include sex,

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age, stroke severity, and independence and dependence in ADLs before stroke, as measured by the BI. The statistician will be blinded to the group allocation for the intervention.

The interviews with persons with stroke and their family members will explore their experiences of participating in F@ce 2.0, and we will analyze the interview data using a grounded theory approach [55]. The interviews will be transcribed verbatim. The interview material will be analyzed through constant comparison of the content in the transcripts. The material will be read several times to get to know the data profoundly. Next, the initial coding will be performed by coding the material line by line, followed by focused coding where the initial codes from each interview will be compared. In the next step, the codes will be compiled into categories and subcategories. The findings will present a meaning structure comprising a core category and subcategories of the studied phenomenon, that is, the meaning of participating in a mobile phone–supported and family-centered intervention and the implications for everyday life after stroke [55]. The qualitative data used in the process evaluation will be analyzed using content analysis [59]. In this analysis, meaning-bearing units will be identified, condensed, and abstracted to codes from each interview. The codes will be compared for similarities and differences and organized into categories and subcategories that will describe an abstract level of the content of all interviews [59].

All personal information (eg, names) will be removed during transcription. Copies of the digital recordings will be destroyed once transcription is complete. Interview transcriptions and all other data will be coded and stored in a secure electronic database.

Evaluation of Outcomes

The changes in performance and satisfaction in the 3 stated valued activities as perceived by the person with stroke will be assessed using the COPM scores. The 2 summative COPM scores—one for performance and one for satisfaction—will be divided by the number of chosen and rated activities to generate scores for comparisons across time and between groups [42].

The confidence in performance of daily activities as perceived by the person with stroke will be presented based on the SES scores [33].

All data regarding the BI and SIS 3.0 (Ugandan version) for the persons with stroke and the data for the family members will be analyzed and reported according to the norms of the measures [46,54].

Experiences of Daily Life of the Participants When Taking Part in F@ce 2.0

A grounded theory approach will be applied [55] for analyzing the qualitative interviews and discerning core categories and subcategories constituting the findings regarding the participants' experiences of daily life when taking part in F@ce 2.0.

Process Evaluation: Process Data and Qualitative Interviews

Both quantitative and qualitative data will be integrated in a mixed methods analysis to explain the outcomes of the F@ce 2.0 intervention, the implementation process, and the potential mechanisms of impact. Constant comparison [59] will be used to analyze the semistructured interviews from the persons with stroke, their family members, and the HCPs describing (1) the perceived value, benefits, and detrimental or unintended consequences of the intervention (ie, perceived harm); (2) the acceptability of the intervention in practice; and (3) the fidelity, reach, and dose of the intervention. All quantitative data will be analyzed using descriptive statistics. Data sources used to capture the process of implementation, contexts, and mechanisms of impact in different ways will be analyzed separately at first and integrated in a joint analysis thereafter to explore the relationships between the findings. The analysis of the data on context will be guided by the Promoting Action on Research Implementation in Health Services framework (the context component) [60].

Patient and Public Involvement

The feasibility study for F@ce 1.0 [33] and the experiences of family members participating in the intervention conducted in Uganda [61] provided important information for the continued modeling of the intervention. Furthermore, the process evaluation of F@ce 1.0 in the Ugandan context [62] included the experiences of health care staff, managers in health care, family members, persons with stroke, and technicians, which added to the knowledge base and informed the choice of RQs, design, and delivery of the studies that made up the research project. The modeling of F@ce 2.0 and its contextual adaptation, together with the results of this study, will be presented to, and discussed with, various stakeholders at regional and national levels as well as private rehabilitation clinics and CBR providers.

Ethical Considerations

The study will be performed in accordance with the Declaration of Helsinki, which outlines ethical principles for medical research [50], and has been approved by the Mulago Hospital Research and Ethics Committee for the intervention in urban Kampala (00941; February 26, 2021) and by the Masaka Regional Referral Hospital Research Committee for the intervention in rural Masaka (ADM. 170106; April 13, 2021). The Uganda National Council for Science and Technology has approved the entire project (HS1528ES; January 19, 2022).

All participants will sign an informed consent form of voluntary participation, which emphasizes their right to withdraw from the study at any time. A copy of the form will be provided to the participants. Withdrawal from the study will be recorded by the researchers. Each participant (participants with stroke, significant others, and HCPs) will receive an ID number. The data will be deidentified; hence, the analysis will be performed and the results presented confidentially. Each participant will be compensated 10,000 Ugandan shillings (US $2.71) for their time at each data collection point.

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Results

As of March 2024, a total of 100 participants with stroke had been enrolled in the randomized controlled trial, of whom 2 (2%) died of natural causes. A total of 96 family members had also been enrolled. The intervention has been performed via daily reminders sent by SMS text messages and phone calls twice a week by the interventionist. Data collection was initiated on January 25, 2022. All baseline and follow-up assessments have been completed. Data analysis is planned to start in October 2024 for the randomized controlled trial and it is planned to be submitted during May 2025. Data collection for the qualitative study and the process evaluation have been completed. Data analysis for the qualitative study will be initiated in February 2025. The process evaluation has been submitted to a scientific journal.

Discussion

Summary

To our knowledge, this is the first project to include a full-scale evaluation of an ADL intervention in sub-Saharan Africa and where we will be able to demonstrate its impact. The feasibility of this intervention has been tested [33], and we are ready to take the next step. The purpose of this research project is therefore to implement and evaluate F@ce 2.0 with the intention of enabling functioning in ADLs and participation in everyday life for people with stroke and their families. Our hypothesis is that people with stroke who participate in the F@ce 2.0 intervention will increase functioning in daily activities and participation in everyday life as well as perceive their performance and satisfaction in daily activities and their self-efficacy to be higher than those of people who receive ordinary rehabilitation. The project's goals are highly relevant because they align with the United Nations' Sustainable Development Goals 2030, including goals to reduce the impact of noncommunicable diseases and to ensure healthy lives and promote well-being for all at all ages.

Building on Our Previous Feasibility Study

The previously completed feasibility study conducted in Kampala showed that the mobile phone–supported and family-centered F@ce program could, with some technical adjustments, be useful in rehabilitation [33]. The design used could be replicated in a larger trial, but improvements in recruitment, allocation concealment, randomization, and blinding of data collectors were needed. Overall, the results indicated the need for further research, which should also include participants from rural areas. Therefore, the F@ce program, in collaboration with local researchers as well as health care and rehabilitation professionals, has now been modeled to fit the actual context and is expected to positively impact stroke rehabilitation in Uganda. It is also aligned with the overarching goal of Swedish development aid to contribute to environments that support people with low socioeconomic status in their efforts to improve their quality of life.

Strengths and Limitations

Uganda has a population of 45 million, with 23% living in urban areas. The country is characterized by generally weak infrastructure, such as bad roads, poor transport systems, inadequate electricity supply, few health care units, and limited numbers of rehabilitation professionals. However, Uganda has witnessed a remarkable growth in mobile phone use, with a penetration rate of 67% as of February 2020, according to the Uganda Communications Commission. Approximately 20 million people in Uganda, representing 44% of the population, have a mobile phone subscription. Advances in technology have transformed mobile phones into all-in-one devices that can be used almost anywhere. Nearly half of all mobile subscribers also access mobile internet services. A strength of F@ce 2.0 might be the use of mobile phones to provide digital support for daily activities after stroke, which might help deliver rehabilitation services in a context with limited resources and staffing. A limitation that we have seen in our previous studies [17,34] could be that it is difficult to check and control for whether the participants have received other rehabilitation services or support that contributed to a change. Furthermore, we are aware that many of the instruments we use are self-rated or -reported instruments and that it is the participants themselves who will provide their responses via telephone to the data collectors. However, the instruments have been well tested and used in our earlier feasibility studies [17,34]. This approach was selected to make it possible to also include people living in rural Uganda.

It is expected that this research, using a randomized controlled trial design and including people from both urban and rural areas, will contribute with knowledge of the effects of the F@ce 2.0 intervention program. Furthermore, the process evaluation will provide knowledge important for future practice, particularly regarding the value, acceptability, and fidelity of the intervention.

Dissemination

Dissemination efforts will include scientific publications in open-access, peer-reviewed journals and presentations at national and international conferences, as well as reports to funders. The results will also be presented to staff and decision makers at the municipalities involved in the study, to the Ugandan public through press releases and articles in the daily press, and at conferences and fairs focused on technical solutions. A comprehensive program with suggestions for ways to implement F@ce 2.0 will be prepared for organizations such as those representing rehabilitation services (nongovernmental organizations and patient and stakeholder organizations).

Conclusions

This research study presents a unique and highly relevant opportunity to enhance knowledge and address gaps in stroke rehabilitation. The study will yield robust data on the intervention's effectiveness as well as in-depth insights into the contextual factors and mechanisms influencing its impact. Health care providers participating in the study will acquire resources to engage patients and families with digital support through mobile phones, fostering interprofessional skills in

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using ICT within rehabilitation. This will enable them to reach their patients in both rural and urban areas, meet patient needs, and improve rehabilitation support in the Ugandan context.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

SG, JTK, GE, and LvK conceived the original idea and outline of the study. SG, JTK, GE, and LvK contributed to designing the study. SG was responsible for developing the intervention in collaboration with JTK and GE. UF is responsible for the technical development and smart products used in the study in the intervention F@ce 2.0. JTK, SG, and GE will further be responsible for collaboration with the municipality and for training and supervising the health professionals, together with a research assistant. SG, GE, LvK, CY, and JTK wrote the study protocol. SG, GE, LvK, JTK, CY, UF, and TO discussed and commented on draft versions and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questions on the intervention for persons with stroke and family members.
[DOCX File , 21 KB - resprot_v13i1e60955_app1.docx]

Multimedia Appendix 2
Interview guides for the process evaluation and qualitative study.
[DOCX File , 19 KB - resprot_v13i1e60955_app2.docx]

Multimedia Appendix 3
Demographics of persons with stroke and family members.
[DOCX File , 29 KB - resprot_v13i1e60955_app3.docx]

Multimedia Appendix 4
Self-Efficacy Scale.
[DOCX File , 18 KB - resprot_v13i1e60955_app4.docx]

Multimedia Appendix 5
Peer-review report by Vetenskapsrådet - The Swedish Research Council (Sweden).
[PDF File (Adobe PDF File), 95 KB - resprot_v13i1e60955_app5.pdf]

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Abbreviations

ADL: activity of daily living
BI: Barthel Index
CBR: community-based rehabilitation
CBS: Caregiver Burden Scale
CG: control group
CONSORT: Consolidated Standards of Reporting Trials
COPM: Canadian Occupational Performance Measure
HCP: health care professional
ICT: information and communication technology
IG: intervention group
LiSat-11: Life Satisfaction Questionnaire-11
RQ: research question
SES: Self-Efficacy Scale
SIS 3.0: Stroke Impact Scale 3.0
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

The Effect of Effort During a Resistance Exercise Session on Glycemic Control in Individuals Living With Prediabetes or Type 2 Diabetes: Protocol for a Crossover Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes (T2D) is preceded by prediabetes, and these conditions place a great burden on patients and society. These conditions are significantly associated with poor glycemic control, which is improved by resistance exercise. It has been suggested that resistance exercise should be performed with a high degree of effort to improve glucose metabolism, but this is associated with negative psychological responses that might lead to lower long-term adherence.

Objective: This study aimed to investigate the effect of the degree of effort during a resistance exercise session on glycemic control and psychological responses in individuals living with prediabetes or T2D.

Methods: This study will be a crossover, 3-arm, randomized controlled trial. A total of 15 participants living with prediabetes or T2D will be thoroughly familiarized with 7 resistance exercises; afterward, they will perform 3 randomized experimental sessions, each lasting approximately 48 hours each, separated by at least 4 washout days. In 2 of these sessions, supervised resistance exercise will be performed, but the sessions will differ in the degree of effort in each set (high vs low) and will be equalized in terms of total weight lifted and session duration. For this, proximity to failure will be manipulated by changing the number of sets per exercise, the number of repetitions per set, and the resting interval between sets and exercises. Participants will also complete a sedentary (control) session, where they will not perform any exercise. In response to each session, psychological responses will be assessed (exertion, affect, enjoyment, self-efficacy, and discomfort). Glycemic control will be assessed by a continuous glucose monitoring device every 5 minutes, throughout the approximately 48 hours of each experimental session. Food and drink will be individually prescribed by a registered dietitian nutritionist and provided to participants, in order to control for the confounding effect of energy intake and diet composition. Physical activity levels will be assessed by accelerometry. Randomization will be done using the opaque, sequentially numbered envelopes technique. Participants and researchers will be blinded for continuous glucose monitoring and accelerometry data, and data will be analyzed by a blinded statistician.

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Results: This study has been funded, and data collection is expected to take place between June 2024 and May 2025. Final manuscript submission should happen by August 2025.

Conclusions: The results of this project might encourage individuals living with prediabetes and T2D to engage in resistance exercise while better informing exercise specialists on how to best incorporate resistance exercise in their client's or patient's routine.

Trial Registration: ClinicalTrials.gov NCT06208189; https://clinicaltrials.gov/study/NCT06208189

International Registered Report Identifier (IRRID): PRR1-10.2196/63598

(JMIR Res Protoc 2024;13:e63598) doi:10.2196/63598

KEYWORDS

diabetes; resistance exercise; weight training; glucose; insulin resistance

Introduction

Type 2 diabetes (T2D) is a disease in which peripheral insulin resistance associated with pancreatic beta-cell dysfunction leads to chronically elevated blood glucose levels [1]. If left unchecked over long periods of time, high glucose levels lead to vascular complications such as increased risk of cardiovascular diseases, diabetic nephropathy, neuropathy, retinopathy, and lower limb amputation [2]. In 2021, a total of 0.7 million people died due to diabetes or its complications in the United States [2], placing diabetes-related deaths as the eighth leading cause of death. T2D is preceded by prediabetes, a condition where blood glucose levels are higher than normal, but not high enough to be considered T2D [3]. The risk of individuals living with prediabetics developing T2D at some point in their life is around 50% [4], and approximately 1 in 3 Americans aged 18 years or older are currently living with prediabetes. The number of people living with diabetes in the United States was 32.2 million in 2021, and it is expected to increase to 36.3 million in 2045 [2]. Diabetes represents a great economic burden to society, as diabetes-related costs in the United States in 2021 were US$ 379.5 billion [2]. Approximately 95% of all diabetes cases are T2D [5].

It is an indisputable fact that exercise is a cornerstone for the prevention and treatment of prediabetes and T2D [6,7]. Of note, even an acute bout of exercise has profound positive effects on glucose metabolism [8]. In fact, exercise training effects on improved insulin sensitivity may be lost in as little as 6 days after the last exercise session in individuals living with T2D [9,10], suggesting the positive effects of exercise on glycemic control can be largely attributed to the acute improvements observed in the hours or days after each exercise bout [11]. Thus, understanding the acute effects of exercise on glucose metabolism is important to optimize exercise prescription for the prevention and treatment of T2D. Although aerobic exercise is usually the default choice for T2D treatment and prevention [7], resistance exercise is also a viable option for physically inactive individuals living with prediabetes and T2D [12,13].

It has been repeatedly shown that an acute bout of resistance exercise improves insulin sensitivity and glycemic control during at least the following 24 hours in individuals living with prediabetes and T2D [11,14,15]. For example, van Dijk et al [11] assessed 24-hour glycemia with a continuous glucose monitoring (CGM) device after bouts of resistance or aerobic exercise in individuals living with prediabetes not on medication, in individuals living with T2D on oral hypoglycemic medications, and in individuals living with T2D on insulin. They reported that regardless of the condition, resistance and aerobic exercise equally reduced the prevalence of hyperglycemia and improved glycemic control. Thus, resistance exercise's effects for preventing and treating prediabetes and T2D have been increasingly recognized, and prescription for muscle strengthening is highly recommended by international guidelines [7]. Despite this, while compliance with the current American College of Sports Medicine's recommendations for muscle strengthening remains low in Americans, at ~27% [16,17], the proportion of individuals living with diabetes that meet strength training guidelines is even lower, at ~13% [18].

Resistance exercise prescription entails the manipulation of many variables. These include exercise type (single- or multijoint) and order, load, number of sets per exercise, repetitions per set, repetition duration (ie, tempo), and resting interval between sets [19-22]. There are also variables that are derived from the above, such as total volume-load (load × sets × repetitions), and session density (total volume-load / session duration). Appropriate manipulation of these variables is important for targeting specific adaptations [23]. However, the literature pertaining to the manipulation of these variables for the prevention and treatment of T2D is scarce. With this in mind, in a previous study [24-26], we assessed the effect of manipulating training volume by changing the number of sets in a session of resistance exercise in individuals living with obesity on insulin sensitivity. The data showed that a session composed of 21 sets improved insulin sensitivity, while a session composed of 7 sets did not (Silva et al, 2024, unpublished data).

More recently, attention has also been directed to the degree of effort during resistance exercise sets as a potentially important variable that can be manipulated to affect adaptative outcomes [27]. In fact, it has been suggested that a high degree of effort is important for acute improvements in glucose metabolism and insulin sensitivity in individuals living with T2D [28], although direct evidence of that is lacking. In our previous study [24-26], all sets were done with a high degree of effort (perceived exertion 9-10 out of 10 for all working sets). However, performing resistance exercise sets with a high degree of effort is associated with higher perceived exertion and discomfort [29], increased muscle soreness, negative psychological responses [30], and higher neuromuscular fatigue and muscle

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damage [31]. Taken together, these negative psychological and physiological responses to resistance exercise sets performed with a high degree of effort might negatively affect enjoyment and motivation during a resistance exercise session, which could ultimately reduce long-term adherence [32]. Individuals living with prediabetes and T2D might be more susceptible to these negative responses, as they are more physically inactive than the general population [33] and identify the lack of motivation and low self-efficacy (self-perception of the ability to accomplish something) as barriers to being more physically active [34].

Resistance exercise prescriptions should be tailored to meet not only the glycemic management needs of individuals living with prediabetes and T2D but also their motivation and self-perceived capacity to engage in exercise. Thus, the aim of this study is to assess the effects of the degree of effort during a resistance exercise session on glycemic control and psychological responses in individuals living with prediabetes and T2D. The hypothesis is that the degree of effort will not affect glycemic control, but that a high degree of effort will negatively affect psychological responses.

Methods

Description of Participants

Participants aged between 18 and 75 years will be recruited through posters and flyers at strategic points and by word of mouth in order to support diversity. More specifically, we will recruit from the University of New Mexico's hospital, clinics, and facilities (both from the Main and North campuses), and from the Albuquerque area in New Mexico. After showing interest, potential participants will be thoroughly informed about the study's risks and benefits, and they will be asked to answer a medical and physical activity history questionnaire in order to assess eligibility [35]. The inclusion criteria will be presence of prediabetes (fasting glycemia between 100 and 125 mg/dL or glycated hemoglobin [HbA_{1c}] between 5.7% and 6.4%) or T2D (fasting glycemia 126 mg/dL or above or HbA_{1c} 6.5% or above), diagnosed by a medical doctor. Glycemic status will be confirmed by assessing a fasting blood sample. Exclusion criteria will be renal failure; liver disease; uncontrolled hypertension (>160 mmHg systolic and/or >100 mmHg diastolic); history of severe cardiovascular problems; inability to perform resistance exercise; being pregnant or trying to become pregnant during the course of the study; use of oral contraceptives; and in case of being treated with biguanides (metformin), being on them for less than 3 months. If eligible, before initiating participation, subjects will sign the informed consent form previously approved by the Institutional Review Board (IRB). Participants will be reimbursed for expenses incurred due to the research and resulting from it. Participation will be discontinued in case of withdrawal of consent or in case of injury or sickness (eg, skeletomuscular injury and having a cold). We will report reasons for withdrawal and discuss the reasons qualitatively. Adverse events related or nonrelated to the research protocol experienced by participants during the study will be carefully recorded and reported in the final manuscript.

Study Type and Design

This study will be a crossover, 3-arm, randomized controlled trial. The protocol description followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) [36] and the TiDieR (Template for Intervention Description and Replication) [37] guidelines (Figure 1 and Multimedia Appendices 1-4). Upon meeting eligibility criteria and agreeing to participate, participants will undergo an anthropometrics assessment, familiarization sessions, and strength assessment before randomly carrying out 3 separate experimental sessions (2 exercise and 1 control), with each session taking place over ~48 hours, over 3 consecutive days. The order of the sessions will be randomized and they will be separated by a minimum of 4 washout days.

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Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) schedule of assessments at different time points. a: Sessions order is randomized with at least a 4-day washout period.

	Study period							
	Enrolment	Before randomization	Allocation	Interventions			Post intervention	
Timepoint	$-t_1$		0	Day 1	Day ≥4	Day ≥4	Immediately	Up to 30 hours
Enrolment:								
Eligibility screen	X							
Informed consent	X							
Allocation			X					
Interventions [a]								
High-effort session				⟷				
Low-effort session					⟷			
Control session						⟷		
Assessments:								
Anthropometrics		X						
Familiarization		X						
Strength test		X						
Psychological responses							X	
Continuous glucose monitoring				X	X	X	X	X

During experimental sessions, participants' diets will be strictly controlled, and all food and drink will be provided to the participants. Glycemic control will be monitored using a CGM device throughout the experimental sessions. The exercise sessions will be matched for total volume load and session density, but proximity to concentric muscular failure (ie, incapacity to continue the set in the concentric phase of the movement) will be manipulated to vary the effort between the exercise sessions. The control session will follow identical procedures except that participants will remain sedentary for the same period of time they are to exercise in the exercise sessions.

Participants will be asked to refrain from moderate- to high-intensity physical exertion for 72 hours before the experimental sessions. The evening before the exercise or control sessions (day 1), at ~5 PM, participants will report to the laboratory to be instrumented with the CGM device and an accelerometer (to assess physical activity levels, refer to *Continuous Glucose Monitoring* subsection) and will receive dinner to be ingested at 6:30 PM and a snack to be ingested at 9:30 PM. The next morning (day 2), they will report fasted to the laboratory at 8:00 AM and ingest the provided breakfast at 8:30 AM. The exercise or control sessions will begin at 9:30 AM and will last ~50 minutes. They will perform 1 of 3 random sessions: a high-effort resistance exercise, a low-effort resistance exercise, or control session. After each session, psychological responses (perceived exertion, enjoyment, affect, discomfort, and self-efficacy) will be assessed.

After the session, participants will then be free to resume their daily activities after being given individualized meal bags and will be asked to consume lunch at 12:00 PM, a snack at 3:30 PM, dinner at 6:30 PM, and another snack at 9:30 PM, and in the following day (day 3), they will have breakfast at 8:30 AM, lunch at 12:00 PM, and a snack at 3:30 PM. After that, they will report to the laboratory between 5 and 6 PM to have the CGM device and accelerometer removed. Participants will be instructed to refrain from moderate- to high-intensity physical exertion until they are deinstrumented.

Throughout the entire study period, participants will be explicitly instructed not to alter their prescribed medication and to report any prescription changes made by their medical doctor during participation. Any adverse events whether related or nonrelated to the research protocol experienced by participants during the study (eg, skeletomuscular injury and having a cold) will be carefully recorded and reported in the final manuscript. Figure 2 depicts the study design.

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Figure 2. Study design. CGM: continuous glucose monitoring.

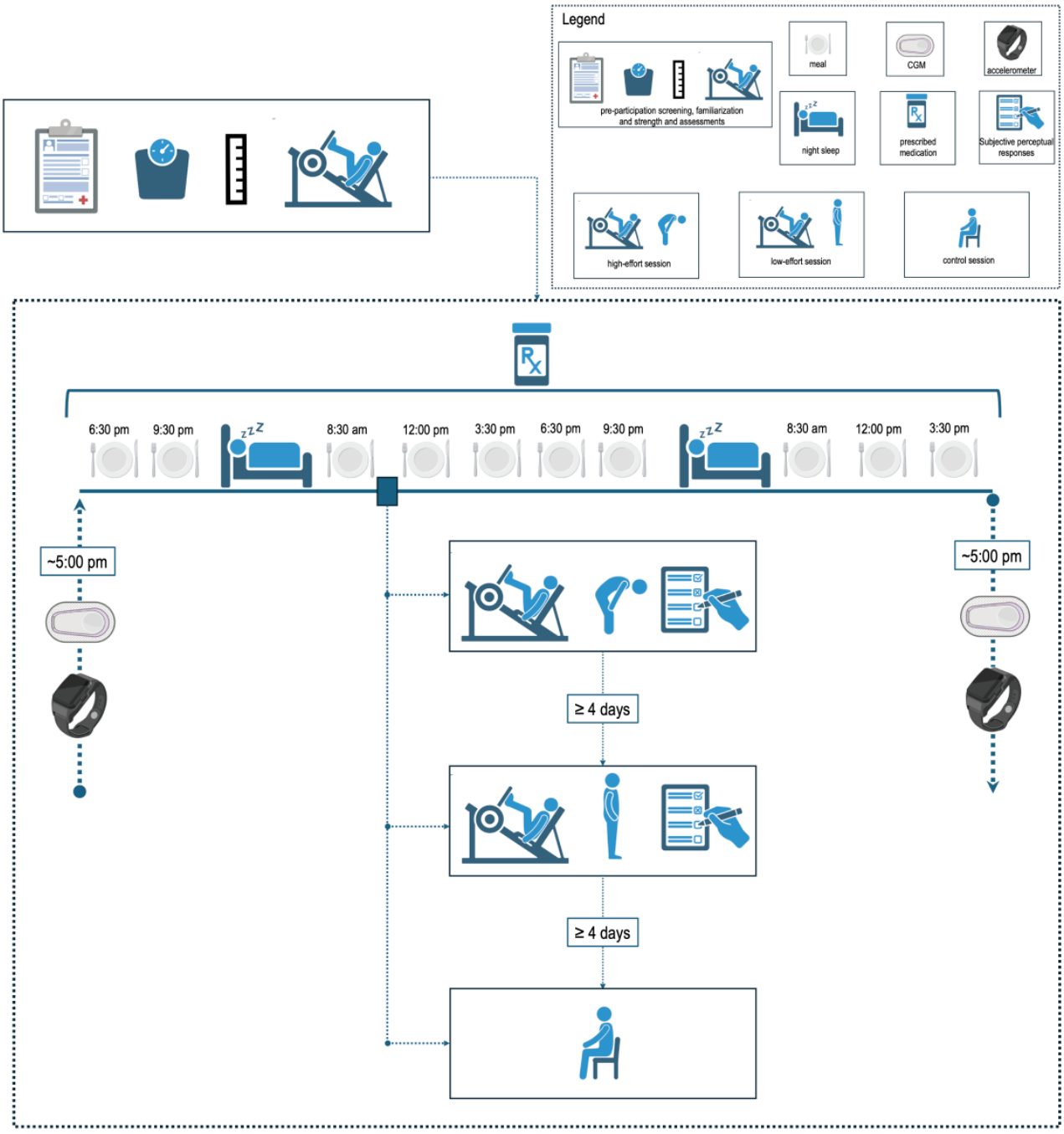

Anthropometrics

Body weight and height will be measured on an analog scale and a stadiometer, respectively, and BMI (kg/m^2) will be calculated. Subsequently, the waist circumference will be measured with a measuring tape parallel to the ground over the umbilicus. Body composition will be evaluated using multifrequency bioelectrical impedance analysis (Bioelectrical impedance analysis, InBody 770) following manufacturer instructions.

Familiarization and Strength Tests

Familiarization and strength tests will be performed as previously described [24-26]. Briefly, familiarization will consist of 5 sessions separated by at least 48 hours. In each session, participants will perform 3 sets of 8-10 repetitions of 7 exercises that target major muscle groups (hex bar squat, seated chest press, leg press, lat pulldown, leg extension, shoulder press, and leg curl; Figure 3), and load will be gradually increased throughout the familiarization sessions so that by the fifth session, participants will be able to perform the exercises with a high degree of effort (9-10 out of 10) based on the OMNI-Resistance Exercise scale [38]. Participants will also be familiarized with the psychological assessments during the familiarization period.

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Figure 3. Exercises that will be prescribed for the strength exercise sessions: (1) hex bar squat, (2) seated chest press, (3) leg press, (4) lat pulldown, (5) leg extension, (6) shoulder press, and (7) leg curl.

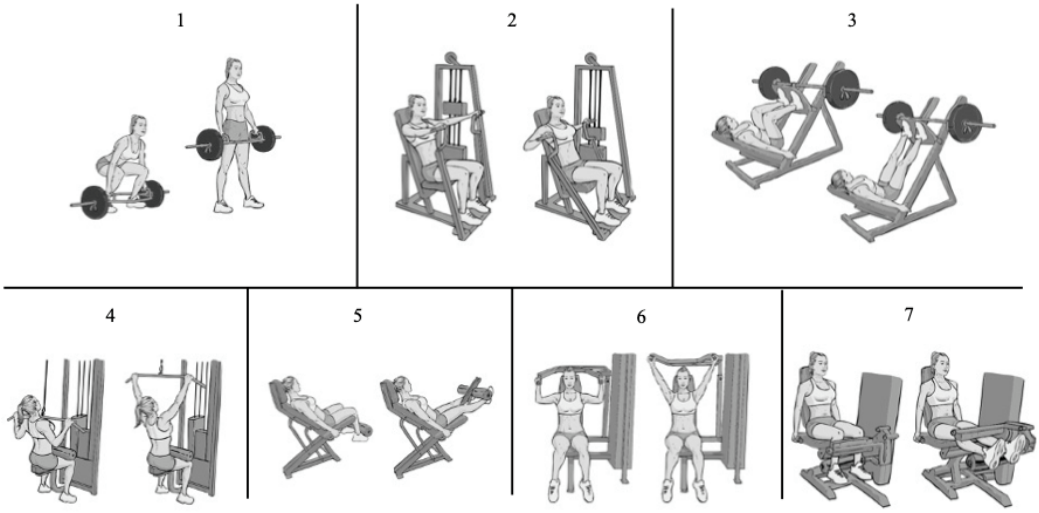

At least 72 hours after the fourth familiarization session, participants will perform the 10–repetition maximum (RM) tests [39,40] (the highest load one can lift for 10 complete repetitions with proper form) in each of the 7 exercises. After an initial 5-minute warm-up walking on a treadmill (~3-4 km/h, very light intensity) and 1 set with low load (12 repetitions, ~40%-50% 1RM, ~3-4 on the OMNI scale), the weight in each exercise will be adjusted to the weight used in the last familiarization session plus 5% to 10%, and participants will be instructed to attempt to perform 11 repetitions with good form (ie, with a full range of motion and tempo ~2:1 sec). If they perform the 11 repetitions with good form, the weight will be increased by 5% to 10%, and they will be given 180 seconds to recover and will make another attempt. Load will be increased until they can perform 10 repetitions or fewer with good form. If they perform fewer than 10 repetitions, the Brzycki equation [41,42] will be used to estimate participant's 10-RM. All tests will be performed under the supervision of the same research team member and the load corresponding to the 10-RM in each of the exercises will be used in the exercise sessions (described in *Exercise and Control Sessions* subsection).

At least 72 hours after the strength assessments, participants will perform a fifth and final familiarization session. This familiarization session will be equal to the high-effort session (described below). Participants will perform the 7 exercises, 3 sets per exercise (total of 21 sets), aiming at 8 repetitions per set, using the load corresponding to their 10-RM. Participants will be asked to rate their exertion after each set using the OMNI scale, to ensure they are performing the sets with high effort (>8 on the OMNI scale). The resting period between exercises and sets will be 120 seconds. The main outcome from the fifth familiarization session is the number of repetitions the participant can perform in each set of the 7 exercises.

Psychological Responses

After each set of each exercise, participants will be asked to rate their perceived exertion using the OMNI-Resistance Exercise scale from 0 to 10 [38]. During each session, participants will be asked to rank their feeling (before and immediately after) [43], enjoyment (immediately after) [44], self-efficacy (immediately after) [45], discomfort (5 min after the resistance exercise sessions) [46], and session rating of perceived exertion (5 min after the resistance exercise sessions) [29] using validated scales.

Randomization and Blinding

After the fifth familiarization session, random allocation of the order of the experimental sessions' participants will carry out will be performed as previously described [24-26]. The order in which the experimental sessions will be held will be randomized with the aid of the website. A collaborator not directly involved in any phase of the research (conceptualization, data collection and analysis, and reporting) will print the random orders generated by the program, insert them inside opaque, sequentially numbered envelopes, and seal them. After completing the fifth familiarization day, the envelope will be opened, and the sequence of experimental sessions will be revealed.

Due to characteristics inherent to this trial (resistance exercise), blinding of participants and researchers to exercise or control situations is not possible. However, participants and researchers will be blinded to CGM results (the blind model will be used). Furthermore, data and statistical analysis will be performed by a statistician blinded to groups and participants' identities, as previously described [24-26].

Exercise and Control Sessions

Participants will perform 2 exercise sessions and a control session, and the exercise sessions will be composed of 7 exercises (described above), both with the loads corresponding to 10-RM.

One of the exercise sessions will be a high-effort session (*high*), when participants will perform 3 sets per exercise (total of 21 sets) aiming at 8 repetitions per set. We anticipate participants will perform each repetition with a total duration of ~2.5 seconds. The resting period between exercises and sets will be 120 seconds. This will lead to a total session time of ~50 minutes.

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The other session will be a low-effort one (*low*), when participants will perform 6 sets per exercise (total of 42 sets) but perform half of the number of repetitions of the *high* session (ie, 4 repetitions). A repetition duration of ~2.5 seconds and a resting period between exercises and sets of 60 seconds will also lead to a total session time of ~50 minutes.

Both the *high* and *low* sessions will have similar total volume-load and session density but differ in perceived effort after each set [47]. Pilot data from our laboratory in healthy untrained participants show that participants were able to complete both *high* and *low* sessions as prescribed, but average OMNI score after sets (8.5 vs 5.9), session rating of perceived exertion (7.5 vs 4), and perceived session discomfort (73 vs 40) were all higher in response to *high* sessions compared with *low* sessions.

For the control session, all procedures will be identical to the *high* session, with the exception of performing the resistance exercises. However, to simulate all other procedures participants will be positioned on the equipment for ~20 seconds for each of the 3 sets in each of the 7 exercises, but will not perform any repetitions, thus, performing sham sets.

Heart Rate Assessment

To estimate cardiac work, heart rate will be assessed throughout the experimental sessions. Participants will be instrumented with a heart rate strap (Polar H10) and monitor (Polar V800), and their heart rate will be recorded continuously during the experimental situations. Data will be synced into Polar Flow and downloaded to a spreadsheet before being analyzed.

CGM Assessment

Glycemic control will be assessed by a CGM device (Dexcom G6 Pro; Dexcom) every 5 minutes, over the ~48-hour experimental sessions. Reporting of variables will follow the most recent international guidelines consensus for clinical trials [48] and will include (1) time in range: 70-180 mg/dL; (2) time in tight range: 70-140 mg/dL; (3) time below range: <70 mg/dL; (4) time in level 1 hypoglycemia: 54-69 mg/dL; (5) time in level 2 hypoglycemia: <54 mg/dL; (6) time above range: >180 mg/dL; (7) time in level 1 hyperglycemia: 181-250 mg/dL; and (8) time in level 2 hyperglycemia: >250 mg/dL. Data will be reported as a percentage of time per day and as estimated hours and minutes per day. We will also report (9) average glucose concentration and (10) area under the curve, (11) glucose management indicator (used to predict long-term glucose exposure); (12) glycemia risk index (summary of the quality of glycemia), (13) glucose coefficient of variation; and (14) mean SD glucose (both are measures of dynamic glucose variability). Variables will be reported for the entire 48-hour collection period, for the first and second 24-hour periods, and stratified over 4 different periods: morning (6 AM to 12 PM), afternoon (12 PM to 6 PM), evening (6 PM to 12 AM), and nocturnal (12 AM to 6 AM) [11]. Individual data will be analyzed only if the percentage of data obtained is >70% of the anticipated amount of data collected during the collection period [48].

Diet and Physical Activity Levels

During the ~48-hour experimental situations, diet prescription will follow American Diabetes Association recommendations [49,50] to ensure a personalized diet based on their estimated energy requirements. Meals and snacks will be provided in individualized, pre-weighted packages and will be composed of ~55% carbohydrate, ~15% protein, and ~30% fat. The timing of ingestion will be strictly controlled to ensure a standardized diet. Diet prescription will be done by a registered dietitian nutritionist. The diet will be designed to meet the energy requirements as calculated with the Cunningham equation [51] multiplied by a physical activity level of 1.2 [11].

Participants will be instructed to maintain their habitual physical activity levels, and to not perform moderate- to high-intensity physical activity 72 hours before and during the experimental sessions. Physical activity levels will be assessed using a commercially available accelerometer (GT3X, ActiGraph).

Statistical Analysis

The sample size was calculated using data from relevant literature using similar individuals and glucose-assessing tools (CGM) [11,14,52,53]. Conservative parameters were inserted in the G*Power program (Heinrich-Heine-Universität Düsseldorf, version 3.1.9.6) for a repeated measure ANOVA within interaction: effect size of 0.2 (for 24-hour average glucose concentrations), probability of error type α of 0.05, power (probability of error type 1 β) of 0.95, correlation among repeated measurements of 0.7 [54], and nonsphericity correction of 0.5 [55,56]. With these parameters, 15 individuals are required (actual power of 0.96). Considering a typical dropout rate of 25% to 40%, we will initially recruit 25 participants.

A collaborator outside the research team will double-enter data coded for allocation into a computer in separate spreadsheets, allowing the researcher responsible for data analysis to assess the data without access to allocation information. Allocation will only be revealed after statistical analyses are run. In case of doubts about data entry (missing values or values outside the reference range), the researcher responsible for data analysis will contact the collaborator outside the research team responsible for double entry of the data to check accuracy. There will be no interim analysis.

To ensure confidentiality, all study-related information will be securely stored at the study site. All participant information will be kept in locked file cabinets in areas with access controlled by the principal investigator. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. Records containing names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. No personal information from participants will be released outside the study. Full access to the complete dataset will be restricted to members of the research team.

The statistical analysis will follow the principles of intention-to-treat analysis [57]. Thus, data from participants will be assessed as randomized, regardless of whether they received the randomized treatment, meaning that even if they

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fail to follow the physical activity and diet instructions, or fail to complete the sessions as required, their data will be included in the analyses. Furthermore, we will also analyze the data "per protocol" [58], meaning that participants who deviate from instructions will be excluded from the final analyses. Differences in results stemming from intention-to-treat and per-protocol analyses will be discussed accordingly. The available variables will also be compared between participants who withdraw from the study and those who complete the study.

The effect of resistance exercise on glycemic control will be calculated as the absolute and percentage change between control and resistance exercise situations. Data will be expressed as mean and SD, with a 95% CI. For the analysis of data normality, we will perform the Shapiro-Wilk test. For normally distributed data, ANOVA will be used with 1 source of variation (experimental condition). If a significant main effect is observed, the post hoc Tukey test will be conducted. For nonnormal data, the Kruskal-Wallis test or Friedman test will be used as appropriate. The effect size will be calculated and interpreted as follows: <0.2=no effect, 0.2-0.49=low effect, 0.5-0.79=medium effect, and >0.8=large effect [59,60]. The significance level is set at 5%. The Prism program (version 10.1.1, GraphPad Software) will be used to generate graphs and analyze results. This trial will be reported following the CONSORT (Consolidated Standards of Reporting Trials) guidelines [61-63].

Data Monitoring Committee

A data and safety monitoring board will be composed of 2 medical doctors (a diabetes specialist clinician and a sports medicine specialist) and a biostatistician. The board will meet quarterly to address data and safety stemming from data collection. Specifically, they will analyze data related to adverse events related and unrelated to the study: musculoskeletal injuries (muscle strain, bruising, joint pain, back pain, etc), cardiovascular issues (increased blood pressure, arrhythmia, angina, myocardial infarction, etc), acute illnesses and symptoms (bronchitis, pneumonia, asthma attacks, flu, heart attacks, strep throat, respiratory infections sore throat, fever, cough, diarrhea, sneezing, headaches, etc), falls, syncope, aggravation of preexisting conditions (arthritis, tendinopathy, etc), hospitalizations, and death. The board will also analyze the dropout rate, as well as the reasons for dropping out. The board will make independent decisions and will have no conflict of interest regarding data collection, analysis, interpretation, and publication.

Ethical Considerations

This study's protocol and informed consent were submitted to and approved by the University of New Mexico IRB (protocol # 2310089095), and all procedures will follow the ethical standards of the IRB on human experimentation and the Helsinki Declaration of 1975, as revised in 2000. The study was prospectively registered in a public clinical trial registry [64]. Any modifications to the protocol will be submitted to the ethics committee, followed by an update of the trial registry. To promote participant retention, financial compensation (USD $200) for their time and effort will be provided.

For data sharing, all personal identifiers will be stripped from the data. Specifically, any direct identifiers (name, email addresses, phone, and cell phone numbers), date identifiers (birthday, date of disease diagnosis, and dates patients participated in data collection), location identifiers (personal or professional addresses and zip codes), links to external datasets identifiers (social media accounts) will be removed. Furthermore, participants will be represented by an ID string generated randomly, and their data will be inserted in the files in a random order, not associated with the order they were enrolled. Thus, data will be entirely deidentified before sharing, in order to protect sensitive personal information and privacy.

Results

As of June 2024, we have performed pilot studies and recruited 2 potential participants. The anticipated data collection period will be from June 2024 to May 2025, and the final manuscript is expected to be submitted for publication by August 2025.

Discussion

Potential Impact and Significance of the Study

The results of this study will contribute to a better understanding of the effects of resistance exercise in individuals living with prediabetes and T2D and will be relevant to trainers and therapists who seek to incorporate resistance exercise in their client's or patient's routine. Specifically, understanding how short-term glycemic control is affected by altering resistance exercise prescription, in the case of this study, degree of effort, and assessing how this affects psychological responses bears clinical and practical relevance. We anticipate that glycemic control will be similarly improved independently of effort, but participants will experience more positive feelings after the low-effort session. As feelings experienced during a resistance exercise session may be predictive of long-term adherence, this would suggest that correct manipulation of the degree of effort during a resistance exercise session might confer better long-term outcomes for individuals living with prediabetes and T2D.

Strengths and Weaknesses

This study will take advantage of the latest technology to track glycemic control using a CGM device and accelerometry to directly assess physical activity levels. These are much better approaches compared with other glycemic (handheld glucometers or the oral glucose tolerance test) and physical activity (self-reported questionnaires) assessments, which would increase the reliability of the data as well as its application to real-world scenarios. Also, strict dietary control will be used, and glucose-lowering medication will not be altered, in order to tease out the specific effects of resistance exercise on glycemic control. Finally, a blinded statistician not directly involved in data collection will analyze data, in order to minimize any bias and increase the significance of our findings.

In this study, we will try to anticipate participants' performance in the high-effort trial by performing a fifth and final familiarization session. This is necessary in case the low-effort trial is randomized to happen before the high-effort one, as the

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number of repetitions during the low-effort session will be prescribed as half of the high-effort session. However, if the number of repetitions performed in the high-effort session is different from the fifth familiarization session, this could introduce error. Also, to increase the external validity and scope of our results, we will include both male and female participants within a wide age range, as there is evidence that sex and age affect glycemic control [65-74] and response to glucose-lowering drugs [75-79]. Finally, because it has been demonstrated that glycemic control is worsened during the luteal compared with the follicular phase in premenopausal women [80], menstrual cycle phase might be a confounding factor in the present protocol.

Acknowledgments

This study will be based at the University of New Mexico, which will provide the equipment and space necessary for conducting the research. The authors would like to acknowledge the invaluable role played by Cintia Pimenta Lopes, a physical therapist, who will be responsible for coding data, double entering data into the electronic spreadsheets, creating the random orders, and sealing random order in opaque envelopes. This study is supported by the University of New Mexico Research Allocation Committee grant (#CmdxfJ), the University of New Mexico College of Education and Human Sciences Research Office Mini-Grants, the National Council for Scientific and Technological Development (CNPQ: Grant#407975/2018-7 and # 402091/2021-3), and the Minas Gerais State Agency for Research and Development (FAPEMIG: Grant# APQ-00008-22). The funders played no role in this study's design, conduct, interpretation of data, or reporting of results. MR is the recipient of the University of New Mexico College of Education and Human Sciences' Dean's Graduate Student Research Fellowship from the University of New Mexico College of Education and Human Sciences. This project was supported by the College of Education and Human Sciences Research Office at the University of New Mexico. The views expressed are those of the author(s) and do not necessarily reflect the views of the funders.

Authors' Contributions

All authors contributed to the concept and design of the study and established the hypothesis. FdCM wrote the first draft of the manuscript. All authors performed critical revisions of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1 [PDF File (Adobe PDF File), 77 KB - resprot_v13i1e63598_app1.pdf]

Multimedia Appendix 2 [PDF File (Adobe PDF File), 170 KB - resprot_v13i1e63598_app2.pdf]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) 2013 checklist.
[DOCX File , 23 KB - resprot_v13i1e63598_app3.docx]

Multimedia Appendix 4
World Health Organization trial registration dataset.
[DOCX File , 16 KB - resprot_v13i1e63598_app4.docx]

Multimedia Appendix 5
Approved informed consent.
[PDF File (Adobe PDF File), 259 KB - resprot_v13i1e63598_app5.pdf]

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Abbreviations

CGM: continuous glucose monitoring
CONSORT: Consolidated Standards of Reporting Trials
HbA1c: glycated hemoglobin
IRB: Institutional Review Board
RM: repetition maximum
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial
T2D: type 2 diabetes
TiDieR: Template for Intervention Description and Replication

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Protocol

The Integrating Cultural Aspects Into Diabetes Education (INCLUDE) Study to Prevent Diabetes in Chinese Immigrants: Protocol for a Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes (T2D) contributes to significant morbidity and mortality for Chinese immigrants in the United States, exacerbated by social determinants of health (SDOH) barriers such as language barriers, limited access to healthy foods, and low health literacy.

Objective: The goal of the Integrating Cultural Aspects into Diabetes Education (INCLUDE) study is to test a social media–based intervention adapting the Diabetes Prevention Program (DPP) for Chinese immigrants alongside a culturally adapted, community-supported agriculture program. Here, we report the protocol for the INCLUDE study.

Methods: INCLUDE is a 3-year randomized controlled trial (n=150). Participants with prediabetes or at risk for T2D are enrolled and randomized into either the control or intervention group (n=75 each). Participants from the intervention group receive 2-3 culturally tailored, in-language DPP videos weekly for 12 weeks, as well as biweekly phone calls from bilingual study staff to review video content, support goal setting, and assess and address SDOH-related barriers such as food insecurity. Intervention participants will also be given produce for 10 weeks as part of the community-supported agriculture program. Weight (primary outcome), self-efficacy, diet, physical activity, and food insecurity (secondary outcomes) are measured at baseline, 3-month, and 6-month intervals. Splined linear mixed models will be used to examine group differences in longitudinal weight and other secondary outcomes. The INCLUDE study was approved by the Institutional Review Board at the NYU Grossman School of Medicine.

Results: Recruitment started in May 2023, with the first cohort of 75 participants enrolled and randomized into 2 groups in July 2023. The 3-month and 6-month assessment of the first-year cohort has been completed. We have recruited 75 participants for the second cohort as of July 2024.

Conclusions: The INCLUDE study will serve as an innovative model for culturally adapted, multilevel interventions for underserved communities previously unable to access evidence-based diabetes prevention initiatives. Aligning with several

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national calls for multilevel interventions, the INCLUDE intervention will provide critical data that will inform how researchers and public health professionals address SDOH barriers faced by underserved populations and prevent diabetes.

Trial Registration: ClinicalTrials.gov NCT05492916; https://clinicaltrials.gov/study/NCT05492916

International Registered Report Identifier (IRRID): DERR1-10.2196/65455

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KEYWORDS

mHealth; mobile health; prediabetes; immigrants; prevention; diabetes; INCLUDE; T2DM; social determinants of health

Introduction

Diabetes poses a significant public health burden. Recent estimates suggest that, in 2021, more than 38 million people in the United States were living with the disease [1]. Type 2 diabetes (T2D) is the most common form of the disease, affecting 90% to 95% of those with diabetes and contributing to significant morbidity and mortality [2]. Compared with those without diabetes, people with diabetes demonstrate mortality rates that are 2 to 3 times higher and a life expectancy that is reduced by as many as 8 years [3,4]. Previous research has also identified a disproportionate burden of T2D among Asian Americans, who have the highest rate of undiagnosed diabetes (51%) among all racial and ethnic groups [5]. Moreover, Asian Americans underutilize health care services [6] and, in the wake of the COVID-19 pandemic, demonstrated the sharpest decline in screening and preventive care among all racial or ethnic groups [7]. Trends such as these point to the need for feasible approaches to address diabetes disparities observed in Asian Americans in the community setting.

As the largest Asian and Pacific Islander subgroup, Chinese immigrants bear high T2D and prediabetes burdens, particularly in New York City (NYC), where almost 1 in every 2 Chinese adults has T2D or prediabetes [8,9]. Additionally, 18% of Chinese adults in NYC who are aged 18 years and older live in poverty; this burden is particularly pronounced among those aged 65 years and older, where 30% live in poverty [10]. This burden of poverty is compounded by other social determinants of health (SDOH) barriers in Chinese immigrant communities, including high rates of limited English proficiency (LEP), lack of health insurance, and poor access to health care [11,12].

The Diabetes Prevention Program (DPP) is an evidence-based intervention to prevent or delay T2D [13]. However, many SDOH barriers limit the access of DPP to underserved Chinese immigrants, contributing to worse diabetes outcomes in Chinese immigrants with T2D compared with non-Hispanic White adults [14]. Differing cultural norms such as food representations (eg, rice vs bread as a major carbohydrate source) [15] also complicate the effective delivery of DPP following the Centers for Disease Control and Prevention's curriculum without adaptation [12,16]. Furthermore, there is a significant shortage of cultural- and linguistic-concordant providers to deliver the DPP. These barriers are further amplified by the fact that the DPP is often delivered via multiple in-person visits, which can be challenging for Chinese immigrants with LEP who often have long working hours and limited sick time [11,17].

High social media use among Chinese communities, particularly on the free and popular social media app WeChat (Tencent), suggests a promising mechanism for enhancing access to the DPP [18-20]. If shown to be efficacious, culturally and linguistically tailored DPP videos that can be widely disseminated using a free social media platform could be a transformative new model to enhance access to diabetes education and promote health equity for underserved immigrant and minority groups with LEP. This approach can address many barriers for low-income immigrant participants with LEP to accessing DPPs (eg, language and cultural barriers; transportation challenges; lack of sick time; and competing work, childcare, or family obligations) [11,12]. In earlier work, we developed 24 culturally and linguistically tailored diabetes management videos and delivered them to 30 Chinese immigrants with LEP via WeChat, successfully demonstrating feasibility, satisfaction, and potential efficacy in reducing hemoglobin A_{1c} (HbA_{1c}) and body weight in Chinese immigrants with existing T2D [18].

A mobile health (mHealth) intervention that leverages social media may have unprecedented advantages for increasing access to the DPP and holds strong promise for scalability. Yet, mHealth alone cannot address the many SDOH barriers to care [21]. According to the National Institute on Minority Health and Health Disparities Research Framework, multilevel interventions are needed to address SDOH barriers in populations with health disparity [22]. One particular issue of an area where this is the case is food insecurity and lack of access to fruits and vegetables, a major concern for Chinese immigrants with LEP [23]. Community-supported agriculture (CSA) programs, which involve a community of individuals who support a farm and in return receive distributions of the farm's produce throughout the growing season, have been demonstrated to be an effective way to improve food security in White populations and may help to address food access issues in Chinese immigrants with LEP [24,25]. Our recent pilot among 38 participants of a culturally appropriate CSA featuring Chinese produce and flexible payment structures increased vegetable intake (self-report and biomarker) and the variety of vegetables consumed [26]. As a result, we seek to adapt an existing T2D management intervention to include video content relevant to the DPP combined with a culturally appropriate CSA model, taking a multilevel approach to diabetes prevention for Chinese immigrant populations.

The Integrating Cultural Aspects into Diabetes Education (INCLUDE) study is a randomized controlled trial (RCT) within Chinese immigrants at risk of developing T2D. We aim to test a social media–based DPP video program combined with a

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culturally appropriate CSA program, both tailored for Chinese immigrants. The primary objective is to measure the efficacy of the INCLUDE intervention on body weight; in addition, patient-centered secondary outcomes and qualitative understandings of both facilitators and barriers to program implementation and intervention delivery will be explored. This report describes the INCLUDE study protocol.

Methods

Study Design

The proposed study is a 2-arm RCT. Participants are randomized equally to one of two arms (n=75 each): (1) waitlist control or (2) 12-week INCLUDE intervention. Measurements occur at baseline, 3 months, and 6 months. The waitlist control was chosen since we want to provide the INCLUDE intervention to the control group at the end of the study for health equity considerations. We followed the SBIRT (Screening, Brief Intervention and Referral to Treatment) guideline in reporting the guideline. A complete SBIRT checklist is available in Multimedia Appendix 1.

Ethical Considerations

This study was approved by the NYU Grossman School of Medicine Institutional Review Board (protocol 22-00783) and was registered at ClinicalTrials.gov (NCT05492916). The study adheres to the principles of the Declaration of Helsinki and complies with all relevant privacy and confidentiality regulations regarding participant data. Written informed consent was obtained from all participants prior to data collection. All data will be de-identified before analysis to protect participant confidentiality.

Eligibility Criteria

To be eligible for the study, participants must (1) self-identify as a Chinese immigrant or Chinese American; (2) be between 18 and 70 years old; (3) have a medical diagnosis of prediabetes or have a prediabetes risk test score [27] of greater or equal to 5; (4) have a BMI ≥23 kg/m^2 (overweight criteria for Asian individuals) [28]; (5) be willing to receive brief videos regarding diabetes prevention; and (6) possess a smartphone or, if they do not have one, be willing and able to use a study smartphone.

Individuals are excluded from participation if they meet any of the following: (1) unable or unwilling to provide informed consent; (2) unable to participate meaningfully in the intervention (eg, uncorrected sight and hearing impairment); (3) unwilling to accept randomization assignment; or (4) are pregnant, plan to become pregnant in the next 6 months or during the study, or are breastfeeding.

Recruitment

Overview

We will enroll 150 Chinese immigrants who are at risk for T2D, drawing participants from a wide array of community-based organizations and health care facilities serving the Chinese community throughout NYC. Additionally, we recruit participants from several community-based programs embedded in the NYU Langone Health systems like the Table Food Pantry and Together Growing Strong, which provide programming for underserved families in the Sunset Park neighborhood of Brooklyn, NYC.

This RCT is a 3-year study funded by the American Diabetes Association from July 2022 to June 2025.

Recruitment Strategies

This study uses multipronged recruitment strategies. We have formed a community advisory board, which includes 5 community-based organizations who have a long history of serving low-income Chinese American communities in NYC. The community advisory board provided important feedback on how to conduct outreach and engage the target population, including holding a press release, inviting local ethnic newspaper and media outlets, community events, and social media advertisement. Posters in simplified Chinese are placed at these community-based organizations and distributed during Chinese community events, in newspapers, or on social media to promote self-referrals. Recruitment materials list a contact telephone number that interested participants can call to reach bilingual staff members who speak Mandarin, Cantonese, and English or a QR code that they can scan.

Additionally, through NYU Langone Health DataCore, we use the Epic electronic medical record (Epic Systems Corporation) to generate a report of potentially eligible participants from across the NYU Langone Manhattan, Queens, Brooklyn, and Long Island campuses. The report includes demographics including name, race, ethnicity, preferred language, gender, date of birth, address, phone number, weight, height, BMI, name of primary care physician, and date of measurement. A letter in both English and simplified Chinese (front and back) describing the study, its goals, and information on how to participate are mailed to eligible participants. About 2 weeks after mailing out the letter, the study team follows up with a phone call to provide more information about the study and assess interest from potentially eligible participants.

Randomization and Intervention Groups

Screening

Potential participants are contacted by NYU bilingual study staff via phone call and provided with detailed information about the study. If participants express interest in participating, the study staff screen for eligibility by phone. Once eligibility is confirmed, staff will send participants a copy of the key information sheet in English and Chinese and schedule them for baseline data collection. Before conducting the baseline assessment, the study staff will obtain informed consent either through verbal consent via phone call or written consent through in-person sessions. The baseline data collection is conducted either in-person or via phone call. Participants will complete baseline survey consisting of self-report questionnaires with support from bilingual study staff in their preferred language (Mandarin, Cantonese, and English).

Randomization

The study biostatistician uses stratified randomization to assign participants. The matching of gender and age will be

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implemented when participants are randomly assigned to either the control group or the INCLUDE intervention group.

Intervention Description

Our mHealth intervention builds on the DPP developed by the DPP Research Group, which significantly decreased the incidence of T2D in a majority female and White cohort [13]. The DPP is primarily based on Western diet and culture and delivered in English, which has limited reach among Chinese immigrants with LEP due to language and culture barriers. Our team has culturally and linguistically adapted the DPP and developed brief videos tailored to low-income Chinese immigrants. Our video-based DPP is based on Social Cognitive Theory, the idea that self-efficacy shapes behavior and performance. Self-efficacy is influenced by 4 sources of information including mastery experiences, social modeling, verbal persuasion, and physiological states [29]. As an example of enhancing mastery experience, our intervention videos encourage participants to set incremental and achievable goals and reward themselves for reaching these goals. Further, our DPP videos address behavioral triggers, lapses, and relapses that may inhibit self-management. Our intervention also uses social modeling by featuring a Chinese immigrant community member in videos who was able to prevent or delay the onset of T2D. We also have videos guiding participants to recognize physiological states associated with diabetes prevention efforts, such as reduced body weight.

Closely aligned with the DPP curriculum, our videos cover topics from diabetes, prediabetes, nutrition, healthy eating, physical activity, stress management, sleep, and behavioral techniques (eg, goal setting, problem-solving, and social support; Table 1). These videos are designed to provide participants with important education and skills and empower them to make behavioral changes. All the videos are in Mandarin Chinese, tailored for Chinese culture and norms (eg, Chinese diet, cooking methods, recipes, cultural beliefs, and healthy eating during Chinese holidays). The videos are created with short sentences and language for lay audiences to accommodate limited health literacy reported in low-income Chinese immigrants.

Table 1. Intervention content.

Week	Content
1	Program overview and introducing the team, diabetes and prediabetes, goal setting
2	Get active to prevent T2D[a], track your activity, eat well to prevent T2D
3	Track your food and read the label, get more active
4	Burn more calorie than you take in, shop to prevent T2D, cook to prevent T2D
5	Manage stress, find time for fitness, cope with triggers
6	Keep your heart healthy, Take charge of your thoughts
7	Get support, at well away from home, stay motivated to prevent T2D
8	When weight loss stalls, take a fitness break, stay active to prevent diabetes
9	Stay active away from home, more about T2D
10	More about carbs, have the healthy food you enjoy, attending doctors' appointments
11	Navigating the US health care system, get enough sleep
12	Get back on track, prevent T2D for Life

[a]T2D: type 2 diabetes.

In addition to the educational videos, our intervention provides fresh produce to the participants via a CSA program. Bilingual study staff coordinate between the rooftop urban community farm which runs the CSA, Brooklyn Grange, and study participants. Participants receive weekly fresh and culturally appropriate fresh produce every Tuesday for 10 weeks. Each week, participants will be offered 6-7 different varieties of fresh produce, with a total weekly value of US $25. Examples of produce provided include gai lan, bok choy, and sword lettuce (Figure 1).

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Figure 1. Fresh produce pick-up.

Participants in the INCLUDE group receive standard care alongside brief DPP videos and fresh produce from the CSA program. We leverage the free and popular social media platform, WeChat, to deliver DPP videos. We send 2-3 DPP videos each week for a total of 12 weeks with each video lasting about 5 minutes in duration. Uptake of videos is further supported by biweekly phone calls from study staff trained in nutrition to review and answer any questions about the video content and support participants in both setting and reaching goals around diabetes prevention. In addition, participants are given produce for 10 weeks as part of the CSA program. Staff help participants join the CSA program and assess and address other SDOH barriers such as food insecurity.

Waitlist Control Group

Control participants continue to receive the standard of usual care with their own providers during our study. At the end of the study, the control group is provided the opportunity to

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receive DPP videos and gift cards with a value equal to the 10-week CSA program.

Procedures

A steering committee, comprised of the study principal investigator, coinvestigators, and study team, is overseeing the trial implementation. The study includes measurement visits at baseline, 3 months, and 6 months. Survey data are collected in language over the phone or in person at community site offices. After each measurement call is completed, participants are paid US $25. Further, at 6 months (the end of the program) the year-1 control group are paid US $250, the cash value of the CSA program received by the intervention group. All incentive payments are provided through ClinCard, which are provided to them at baseline visits or mailed to their home address.

Based on our initial experiences working with intervention group participants, we will develop focus group guides to characterize barriers to and facilitators of program participation and intervention delivery. We will conduct focus groups with participants, community-based organizations, study staff to gain a deeper understanding of barriers to and facilitators of program participation and intervention delivery. These are informed by the Consolidated Framework for Implementation Research (CFIR) [30], which posits five key domains affect intervention outcomes, including (1) the characteristics of the intervention, (2) the inner setting of the organization, (3) the outer setting of the organization, (4) individuals involved in the intervention, and (5) the implementation process.

We will conduct 2 participant focus groups in Chinese (n=5-8 participants each), with one group demonstrating high engagement with the INCLUDE intervention (eg, they watch at least 70% of the DPP videos or at least 70% participation rate in the CSA) and another group demonstrating low engagement (eg, watch less than 70% of the DPP videos or less than 70% participation rate in the CSA program) to understand beliefs and attitudes around diabetes prevention, perceptions of the INCLUDE program, challenges encountered, and recommendations for improving the intervention.

We will also conduct focus groups with community partners (n=5-10) to understand perceptions of the INCLUDE program's effectiveness, factors that facilitated or blocked implementation, and perceptions of their role in the INCLUDE program.

Finally, we will conduct focus groups with study staff to understand barriers and facilitators of the INCLUDE program implementation.

Measures

Primary Outcome

Weight is obtained using an electronic scale. Scales are mailed to the participants' homes. For baseline weight, most of the year-1 participants were able to attend in-person baseline measurement visit and were instructed to step on the study scale with light clothing. For 3- and 6-month follow-up data, year-1 participants completed phone-based survey and were instructed to step on the study provided scale at home and reported back the weight data.

Secondary Outcomes

As secondary outcomes, we will measure self-efficacy, dietary intake, physical activity, and food insecurity at each time point (baseline, 3 months, and 6 months).

Self-Efficacy

We will use the well-validated Weight Efficacy Lifestyle Questionnaire [31] to measure participants' confidence in resisting eating in various situations. A higher score indicates a higher level of self-efficacy. This instrument contains 20 items and asks participants to rate their confidence level in resisting eating, using a 10-point Likert scale ranging from 0 (not confident) to 9 (very confident).

Dietary Intake

Informed by a previous study and our own studies in Chinese Americans [19,32], we will use the 8-item Starting the Conversation diet scale [33] to assess dietary intake.

Physical Activity

We will use the International Physical Activity Questionnaire [34] short version to assess the frequency and duration of various physical activities undertaken by adults over the past 7 days. This scale provides an estimate of the number of minutes per week participants engage in each physical activity intensity (ie, sedentary, light, moderate, and vigorous).

Food Insecurity

We will use the 18-item San Francisco Chinese Food Security Module [35] to assess food access and insecurity in Chinese immigrants. This scale was culturally and linguistically adapted from the US Household Food Security Survey Module [36] and has been pilot-tested and validated with Chinese immigrant community members and professionals from clinical settings [35].

Covariates

We will use a sociodemographic and health questionnaire to collect basic information about participants such as age, gender, education, income, duration of residence in the United States, English proficiency, duration of prediabetes, and medical history. We also use a scale adapted from the Short Acculturation Scale for Hispanics [37] to evaluate various levels of acculturation in the sample and adjust for this in the statistical models if needed. The adapted scale has established reliability and validity in Chinese immigrants [38]. We will use the SDOH (Core) survey [39] from the National Institute of Health PhenX Toolkit to assess SDOH in Chinese immigrants.

Data Analysis

An "intent-to-treat" approach will be used to address the aims of our study regarding weight change and secondary health outcomes. A linear mixed model will be used to test time-specific differences in both primary and secondary outcomes attributable to the intervention. Randomization should obviate the need for adjustment but, in the case of unbalanced baseline covariates or for the variables that are anticipated to be associated with the outcome, these variables will be adjusted as necessary in the analyses. We will use splined linear mixed models with repeated measures to compare changing trends in

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different periods: 0-3 months and 3-6 months. In this analysis, we will adjust for the covariates as needed. Data analysts will be blinded to group allocation.

To understand barriers and facilitators of program participation, we will use NVivo software (version 14.0; Lumivero) to conduct content analysis using both deductive (CFIR theory driven) and inductive coding. We will create an initial codebook based on the constructs from the CFIR framework. Two coders will independently code the first 5 transcripts and meet to discuss agreement and disagreement to further refine the initial codebook. The 2 coders will code the remaining transcripts independently. Once coding is complete, the coders and the study team will meet to discuss relationships between codes and further identify subthemes, and themes.

Sample Size Justification

In our single-group, pre-post test, feasibility study of the diabetes management video intervention [20], we observed a significant 6.37% (95% CI 2.16%-10.58%; *P*=.005) weight loss at 6 months compared with baseline, and the SD of percent weight loss at 6 months was 10.64%. Based on these pilot data, we conservatively estimate a group difference of 5% in weight loss between the control and INCLUDE groups at 6 months; this degree of weight loss is considered clinically significant [28]. Using the observed SD of 10% in our preliminary study, based on a 2-sample, 2-sided *t* test, 64 per group will be required to detect a minimum group difference of 5% in percent weight loss with a power of 80% and a type I error of 0.05. Our prior studies have achieved ~85% to 97% retention. With a conservative retention rate of 85%, we will recruit 150 (75 per group) participants to yield a final sample of at least 128 (64 per group).

Results

Recruitment started in May 2023, with the first cohort of 75 participants enrolled and randomized into 2 groups in July 2023. The 3-month and 6-month assessment of the first-year cohort has been completed. We have recruited 75 participants for the second cohort as of July 2024. A detailed timeline is provided in Multimedia Appendix 2.

Discussion

Overview

This protocol describes the design for an RCT testing a multilevel diabetes prevention intervention, including culturally and linguistically appropriate diabetes prevention videos delivered through social media and a culturally tailored CSA produce box program, among Chinese immigrants at risk for T2D. A multilevel intervention administered through the popularly used social media platform of WeChat has great potential to support Chinese immigrants' understanding of diabetes prevention, increasing self-efficacy and promoting behavior change while decreasing the risk of developing T2D. We hypothesize that participants in the INCLUDE intervention group will achieve greater weight loss after the program and have better psychosocial and behavioral outcomes, including self-efficacy, dietary intake, physical activity, and food security than the control group.

Access to culturally tailored DPP programs is a significant public health concern for immigrants with LEP, racial and ethnic minority groups, and rural populations in the United States [40]. This project will serve as an innovative model to mitigate access issues for underserved populations. Aligning with several national calls for multilevel interventions, the INCLUDE study will provide critical data on the effect of a multilevel intervention to address SDOH barriers faced by underserved populations. This study may have important implications for other underserved immigrant populations (eg, Latino immigrants or South Asian immigrants) who also experience high chronic disease burden, face numerous SDOH barriers, and frequently use social media like WhatsApp [41].

Strengths, Limitations, and Future Directions

One major limitation of the INCLUDE intervention is that videos were only developed in Mandarin Chinese. For Chinese immigrants who only speak regionalized dialects such as Cantonese, Fujianese, or Fuzhounese but not Mandarin, this poses a barrier to understanding intervention content. However, given that Mandarin is increasingly a lingua franca spoken by most Chinese immigrants [42], our videos are still accessible to many. Further, while our sample is recruited from the NYC metropolitan area, which has a large ethnic Chinese population in the United States [43], our results may not be generalizable to other areas of the country where public health programming may differ for Chinese immigrant populations.

Despite these limitations, this study will generate important results and insights into the efficacy of multilevel, evidence-based, and culturally and linguistically concordant approaches to diabetes prevention in low-income, immigrant populations. These results will inform the development of future mHealth and multilevel interventions that target other immigrant communities facing disparate T2D burdens as well as future diabetes prevention programming for Chinese immigrant communities.

Dissemination Plan

Research findings will be presented through a variety of mediums, including both academic and community-facing outlets. These include regional venues such as the annual NYU Langone Annual Health Equity Symposium and the Biennial Asian American, Native Hawaiian, and Pacific Islander Health Conference at NYU, as well as national meetings such as the American Diabetes Association Annual Symposium. We also anticipate publishing our work in the form of manuscripts in peer-reviewed journals.

Furthermore, we will leverage our relationships with community partners in the Chinese community in NYC to report back to the general public about our findings, as well as potential implications for diabetes prevention in Chinese immigrant communities. Our reporting will take place through town hall forums at community spaces such as the NYU Langone 7th Avenue Family Health Centers or the community-based organizations; one-pagers; infographics for dissemination via

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WeChat; and short videos describing our research findings delivered in English, Mandarin, and Cantonese.

Chinese immigrants are the second-largest immigrant group in the United States, disproportionately experiencing high T2D and prediabetes burden with poor outcomes. This project aims to provide evidence on strategies to improve access to DPPs for underserved populations. It could also serve as a model for other high-risk immigrant groups with LEP with similar barriers. The study will assess the effectiveness of using an existing social media platform and CSA to improve DPP access. If successful, this approach could inform future scaling efforts and promote health equity among underserved immigrant with LEP and minoritized groups.

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Data Availability

The datasets used or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study's development. LH was responsible for conceptualization, data curation, funding acquisition, investigation, methodology, project administration, supervision, drafting the original manuscript, and reviewing and editing the final document. NL contributed to data curation, project administration, formal analysis, drafting the manuscript, and reviewing and editing. YS and JC were involved in project administration, writing the original draft, and manuscript review and editing. MAS, HL, and JB participated in conceptualization, investigation, methodology, supervision, and manuscript review and editing. KT and NL also contributed to reviewing and editing the manuscript. XX, YJ, IO, XY, YB, and LS supported data curation, project administration, and manuscript review and editing. SWC contributed to manuscript review and editing, while SY provided input on conceptualization, investigation, methodology, supervision, and manuscript review and editing. All authors were involved in refining the manuscript and have read and approved the final version.

Conflicts of Interest

LH reports holding stock in Tencent Holdings Limited. The authors declare that they have no other conflicts of interest related to this work.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 46 KB - resprot_v13i1e65455_app1.docx]

Multimedia Appendix 2
Study timeline and measures.
[DOCX File , 17 KB - resprot_v13i1e65455_app2.docx]

Multimedia Appendix 3
Peer review report from the American Diabetes Association (USA).
[PDF File (Adobe PDF File), 751 KB - resprot_v13i1e65455_app3.pdf]

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Abbreviations

CSA: community-supported agriculture
CFIR: Consolidated Framework for Implementation Research
DPP: Diabetes Prevention Program
HbA1c: hemoglobin A1c
INCLUDE: Integrating Cultural Aspects into Diabetes Education
LEP: limited English proficiency
mHealth: mobile health
NYC: New York City
RCT: randomized controlled trial
SBIRT: Screening, Brief Intervention and Referral to Treatment

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SDOH: social determinants of health
T2D: type 2 diabetes

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Protocol

Video Remote Sign Language Interpreting in Health Communication for Deaf People: Protocol for a Randomized Controlled Trial

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Abstract

Background: The current standard of interpretation provision is not efficacious or not acceptable to Deaf patients who communicate using sign language. In-person or video relay interpretation (VRI) sign language interpretation is largely unavailable. There are no clear data on the availability of VRI or in-person interpretation. Given the limited number of available sign language interpreters and the cost, VRI may be more available than in-person. Existing evidence tends to focus on assessing personal preferences of Deaf users regarding interpretation and interpreters' preferences. Although respecting preferences is essential, there is a vacuum of knowledge on how the format of access to interpretation impacts the quality of communication between Deaf persons and health personnel.

Objective: This study aims to look at the effectiveness of the VRI system in improving communication outcomes between Deaf patients and doctors versus the available standard of care of the usual communication tools, including informal interpretation, lip- or note-reading, and using their mobile phones to contact a formal or informal interpreter, for Deaf patients aged 18 years and older in Bogota, Colombia.

Methods: This is a randomized controlled trial with a total sample size of 216 participants, divided into 2 groups: an intervention group, which receives a medical appointment using VRI, and a control group, which receives a medical appointment using standard communication. Both the Deaf participants and the health care professionals will be blinded to the allocation, as they will not know whether the appointment will involve VRI or standard communication until they arrive at the office. The primary outcome measure will be an assessment of communication using a Doctor-Patient Communication Scale. This scale was translated into Colombian Sign Language following a rigorous cultural adaptation and translation procedure. Furthermore, the database contains key clinical variables and recommendations provided by the doctor during a general medicine appointment. We will compute associations.

Results: Recruitment opened on August 24, 2023. As of July 2024, 180 participants had been enrolled. The intervention and data collection were finalized in October 2024. The findings of this study are expected to be submitted for publication in early 2025.

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Conclusions: This study will provide rigorous evidence regarding information and communications technology intervention in health care, addressing empirical challenges in using inclusive research designs in public health. In addition, effective VRI models that address the challenges faced by Deaf people will be tested, implemented, and maintained in low- and middle-income countries. A disability-inclusive evaluative tool for quality communication mediated by VRI in health care is also tested. Ultimately, this will lead to evidence-based recommendations for implementing the Convention on the Rights of Persons with Disabilities (CRPD) in mobile health contexts.

Trial Registration: ClinicalTrials.gov NCT05966623; https://clinicaltrials.gov/study/NCT05966623

International Registered Report Identifier (IRRID): DERR1-10.2196/64590

(JMIR Res Protoc 2024;13:e64590) doi:10.2196/64590

KEYWORDS

assistive technology; video remote interpretation; deaf; disability; communication; healthcare

Introduction

Sign language interpretation is essential for facilitating communication between Deaf people and hearing individuals; it creates a cultural and linguistic bridge. There is growing evidence showing that communication barriers between health care staff members and Deaf patients are the main factors for health disparities. Deaf people continue to experience a lack of access to health care services in their preferred language; there is insufficient health information in sign language and insufficient knowledge and awareness by professionals of their linguistic and cultural requirements [1,2].

The current standard of interpretation provision is not efficacious or not acceptable to Deaf patients who communicate using sign language. In-person or video relay interpretation (VRI) is largely unavailable. There are no clear data on the availability of VRI or in-person interpretation. Given the limited number of available sign language interpreters and the cost, VRI may be more available than in-person interpretation. Existing evidence tends to focus on assessing personal preferences of Deaf users in regard to interpretation and interpreters' preferences. Thus, there is a vacuum of knowledge regarding whether this format of interpretation succeeds at enabling quality communication, which is core to the purpose of interpretation services. A handful of studies, all from high-income countries (HICs), predominantly the United States, provide some empirical data comparing VRI in-person interpretation [3] and show no statistical difference in their preference for VRI versus in-person interpretation for critical care, but a statistical difference for noncritical care. Myers et al [4] reported that their study participants preferred in-person interpreting due to recurrent technical difficulties with VRI. Kushalnagar et al [5] found that most people in the United States do not have access to VRI, but those with access stated that such access would meet their interpretation needs as much as in-person does [5]. Hall and Ballard [6], using a qualitative exploration of preferences, claim that Deaf people are inclined to prefer in-person interpretation, while noting that such provision is highly constrained due to shortages in the workforce. Assessing the efficiency of VRI versus the standard of care would be of more value, given that there is no other effective intervention to compare.

Access to Health Care for Deaf People

Access to health care services for Deaf people has historically been poor compared with the hearing population. Deaf people have worse mental and physical health than the hearing population [1,7]. Deaf people are at high risk of developing cardiovascular diseases, diabetes, depression, overweight, and obesity; they also have a higher risk of partner violence and depression, and there is a higher suicide rate [8,9]. They are more prompt to underdiagnosis, and undertreatment of chronic diseases can put them at risk of preventable diseases and potentially reduce their life expectancy [9]. Furthermore, those in low- and middle-income countries (LMICs) are exposed to higher health disparities than those living in HICs [10,11].

Challenges to the Provision of Sign Language Interpretation

Deaf people are more likely to avoid health care providers, partially because of the lack of means of communication with these providers and available interpreters [12,13]. Thus, even if interpreters are available, the pool of sign language interpreters tends to be relatively small, even in HICs [14]. Shortages are more acute in LMICs, where official certification is often unavailable or limited. For example, in 2015, there were approximately 42 certified sign language interpreters in Mexico [15] and 37 certified interpreters in Paraguay [16]. Sign language interpretation is often a service delivered by people who have completed a certain number of hours in sign language courses and who subsequently present themselves in institutions offering their interpreting services without an official degree and without specific studies that train them in the educational field [17]. The vacuum of available workforce and training is an issue in HICs, too. Deaf people associations in Spain and Canada have called for attention to this issue [18,19]. Furthermore, aside from the availability, the competencies of those interpreting in the health care context are a concern, as specific health communication training is mainly absent [11,20,21]. Significant progress has been made by other countries, like the United States and England, which have stabilized frameworks and regulations and standardized training systems quality standards [22].

Aside from issues of availability and competencies of the sign language interpretation workforce, a second barrier to the interpretation process is the lack of skills in health personnel. Health personnel at large tend to be unaware and unskilled in working with sign language interpreters, which, alongside

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limited awareness about deafness overall, often results in poor communication and, ultimately, patients not getting the information they need to decide on their health or treatments [14]. Good communication between health personnel is critical to patient experience and quality of care [23]. Furthermore, good communication has positively improved patient health outcomes [24].

One solution to these limitations is the growing availability of VRI, a specialized translation service that relies on a high-speed internet connection and a camera to connect a remote sign language interpreter with a health care professional and a Deaf patient to facilitate their communication [5]. VRI technology is not subject to geographical or time limitations, as the interpreter can provide their services from anywhere without having to travel to the appointment. As sign language interpreters are mainly unavailable due to workforce constraints, building capacities in this sector will take many years or generations, especially in LMICs. Therefore, VRI can be a good solution for enabling communication between health care staff members and Deaf people.

Trial Objectives and Purpose

Available data tend to focus on the evaluation of the personal preferences of Deaf users regarding interpretation, as well as the preferences of interpreters. This is useful, but knowing whether these preferences translate into better communication and health services relationships and outcomes is unknown. Furthermore, assessing the feasibility of in-person services, scalability, and sustainability are often left behind. Hall and Ballard [6] show that Deaf people prefer on-site interpretation, acknowledging the workforce shortage and operational challenges in the short term in the United States [6]. From a different angle, in Colombia, Izquierdo et al (unpublished data, 2024) documented that in tight-knit Deaf communities, some people prefer VRI, reporting a greater feeling of privacy in health-related settings. As evidence grows, and the interpretation workforce may also increase and mature in their competencies and regulation, it is pertinent to ask if VRI technology could enable health systems to make the most of the available workforce and enable Deaf communities to communicate effectively with health personnel. There are no baseline data on this issue nor evidence of the effectiveness of the technology compared with the standard of care, which includes informal interpretation, lip-reading or note-taking, or using their mobile phones to contact a formal or informal interpreter. A total of 80% of Deaf people live in LMICs; therefore, running a study in such a setting shall have more global implications.

This study is being conducted in Colombia. The following criteria were used to select this country: (1) it is a signatory country to the Convention on the Rights of Persons with Disabilities (CPRD); (2) it has demonstrated legislation, commitment, and progress of being a champion for inclusive information and communications technology (ICT; G3ICT and Zero Project International Telecommunication Union); (3) it has the necessary infrastructure to test a working model for VRI in the health care context, which includes good internet coverage throughout the country, availability of VRI for general use, and a workforce of local sign language interpreters with expertise in VRI; (4) is a high- to middle-income country, and variations within its territory are relevant for both LMICs and HICs; and (5) Deaf peoples' organizations have interest in this study and have infrastructure that could support both the survey and the intervention. The researchers are working in partnership with local and international disabled people organizations. The Ministry of Health and Universidad del Rosario are the implementing partners.

Methods

Design Based Upon the Real-Life Context in Colombia

This study trial is part of a larger study that focuses on understanding structural and societal factors alongside impairments to determine how an individual experiences health and disability (Swiss National Science Foundation, PZ00P1_186035). A steering committee governs the design of the study. The committee includes local and international Deaf organizations, leading disability and global health scholars, and public administration representatives.

A nuanced understanding of disability, which considers lived experiences, cultural differences, and intersectionality issues, is essential to inform research on the effectiveness of public health interventions. For instance, examining whether Deaf people and health providers could enable access to VRI and, therefore, mobile devices with video capabilities and the internet requires analysis at multiple levels. In the first part of the study, we ran a health priority assessment through a national e-survey in Colombian Sign Language. This survey rigorously linguistically and culturally adapted research instrument design to measure key indicators and health priorities of the Deaf community and contribute to understanding health inequities by using population comparison. Then, using qualitative interviews, the team looked at the individual-level determinant factors such as technology literacy, device adequacy, affordability, and availability. Then, we collected data on infrastructure, workforce, and health policies in tandem with interviews with health workers and sign language interpreters. This first part revealed where and how exclusion occurs within and outside the health system. Understanding their specific health care needs is paramount. This exploration enables us to determine the most effective model for such interventions, and taking action to improve VRI use across health care systems is a critical step. The design intervention addressed was developed to provide sign language with a fully qualified sign language interpreter, although formal training on health is not available in the country and region. Significant expertise in the health sector was a prerequisite to act as an interpreter in the study. Accessibility issues from the first point of contact with the health setting were considered. The design of the VRI randomized control trial (RCT) study responded to real-life contexts in Colombia.

Participants in the Sample

This study is an RCT with a total sample size of 216 participants, divided into 2 groups: an intervention group, which receives a medical appointment using VRI, and a control group, which receives a medical appointment using the standard communication (informal interpretation, lip-reading, note-taking,

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or the use of mobile phones). Both the Deaf participants and the health care professionals will be blinded to the allocation, as they will not know whether the appointment will involve VRI or standard communication until they arrive at the office.

Intervention Group

The participants were able to learn about the study through social media, advocacy organizations, and word-of-mouth. A researcher, along with a sign language interpreter, contacts each potential participant through a WhatsApp video call (the key communication channel among Deaf organizations in Colombia, using sign language) to explain the project and schedule a medical appointment. Upon arrival at the hospital, participants are greeted by a research assistant who facilitates their admission process. The participants were then guided to the consultation room.

The participants engage in a standard medical consultation known in the Colombian health system as "standard promotion and disease prevention or annual check" using VRI as the means of communication. During the consultations, the health care professional conducts a medical history assessment, performs a physical examination, and provides education and recommendations based on the findings.

The VRI is used during the appointment. A 32-inch screen displays the Colombian Sign Language interpreter, who connects through the Zoom (Zoom Video Communications) platform. A professionally accredited Colombian Sign Language interpreter with robust experience in medical interpretation facilitates communication between the health care professional and the Deaf participant during the consultation.

After the medical consultation, participants complete the Doctor-Patient Communication (DPC) scale. This scale is administered by a research assistant using a tablet and is available on the LimeSurvey platform with Spanish subtitles and Colombian Sign Language videos.

Control Group

The participants in the control group gain access to the same intervention, albeit without VRI contact. They communicate with the doctor using standard communication methods (eg, self-arranging interpretation, lip-reading, note-taking, or the use of images).

Explanation for Choice of Comparator

In-person or VRI sign language interpretation is largely unavailable. Thus, there are no clear data on the magnitude of the availability gap of VRI or in-person interpretation. In-person qualified sign language interpretation in the health care setting is considered the ideal service provision standard. Thus, it is mainly unavailable even in HICs. Furthermore, the assumption is based upon minimal available evidence on the personal preferences of Deaf people in the United States. There is no evidence that in-person interpretation is efficient in the context of weaker regulation and infrastructure, such as low sign language proficiency rates among Deaf people, lack of standard qualification of interpreters, and lack of interpreters and sustainable financing. To our knowledge, no study assesses DPC while using sign language interpretation.

Given the cost, VRI may be more sustainable than in-person care. Given that there is no other effective intervention to compare, assessing the efficiency of VRI versus the standard of care would be of greater value.

Sample Size

This study includes 216 participants who were randomized into 2 groups. As no clinical trials in the field have been undertaken, there are no previous effect sizes to consider. However, 216 participants are deemed sufficient to find clinically significant differences.

To establish that the control group that uses VRI improves concerning the variables of interest, we followed the superiority approach and computed the sample size needed using the equation given below:

Where $Z\alpha=1.64$ is the *z* score considering the level of significance to be 5%, $\alpha = .05$; $Z\beta=0.84$ is the *z* score for 80% power, $\beta = 0.2$; $\delta=0.05$ is the superiority margin (5%); p1=0.85 is the proportion in the intervention group; p2=0.65 is the proportion in the control group; d=p1–p2 is the difference between the true groups, which is 0.20; r=1 is the ratio of the sizes of the 2 groups (considering the same size for both the groups); and n is approximately 97.

Consequently, under these conditions, we expect 10% of the enrolled participants to drop out due to any circumstances that may arise and therefore not be analyzable. The final sample size was 100×(2n)/(100–10), about 216.

Inclusion, Exclusion, and Withdrawal Criteria

Inclusion criteria

To be included in the study, the participants must reside in Bogotá, Colombia, be aged at least 18 years, be fluent in Colombian Sign Language, and have the availability to attend the medical appointment. In addition, they must possess sufficient sensorimotor, cognitive, and communication skills to interact with health care personnel independently.

Exclusion criteria

Participants are excluded if they have additional impairments that affect language development or the use of sign language.

Withdrawal

Participation can be withdrawn during the treatment period without specifying a reason behind the decision.

Safety Monitoring and Reporting

The study has been registered in ClinicalTrials.gov under the identifier NCT05966623 since November 29, 2023. The data being stored will be encrypted, and all participants will receive an identification code, thus ensuring the anonymity of the participants during the analysis of the results. The LimeSurvey website is publicly accessible and allows for a wider distribution of surveys. The University of Geneva and Universidad del Rosario, partners in this research, are institutionally subscribed to this platform. The service provided by the platform meets the data protection and security requirements mandated by the

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relevant legal frameworks and ethical standards in Colombia and Switzerland. Furthermore, the transfer and storage of data comply with security guidelines. Access to the collected data is strictly restricted to research team members.

Assignment of Interventions: Blinding

To prevent selection bias, the participants will be assigned to the intervention or control group using random assignment techniques with block randomization. The randomization of participants will allow for the evaluation of treatment effects while ensuring that the observed outcomes are truly due to the treatment and not influenced by other factors. Using blocks in random assignment is a common strategy to ensure that the groups are balanced in terms of relevant characteristics, which helps minimize variability and potential biases in assigning patients to the study groups. In this case, a randomization list will be created using the website randomization.com. This site will facilitate random assignments using the block method to ensure a balanced allocation of patients between the 2 groups.

A defined procedure will be followed to define the block randomization lists.

First, determining the block size: a block size of 4 will be defined (2 patients for each group). This block size is chosen because it is a multiple of the number of groups, which in this case are 2 (intervention and control). Having a block size that is a multiple of the number of groups ensures that each group is equally represented within the blocks, which aids in maintaining a balanced random assignment of patients to the intervention and control groups. This helps ensure the validity and reliability of the study results.

Second, randomly assigning each participant within a block to a group: for example, with a block size of 4 and 2 groups (control and intervention, A and B), the assignment could be as follows:

- Block 1: ABBA
- Block 2: BAAB
- Block 3: ABAB
- Block 4: BABA

This process continues until all participants have been assigned to the different groups. To maintain concealment, the block sizes will not be revealed.

Once the participants enter the medical appointment, they will receive a box containing several envelopes. Each participant will select an envelope that will provide their participant code and the corresponding group designation (control or intervention). The researcher, the participant, the general practitioner, and the sign language interpreter will only learn the group to which the participant belongs when the envelope is opened upon entering the medical consultation.

Primary Outcomes

The primary outcome measure will be an assessment of communication using the DPC. The DPC [25] is made up of 13 questions. Each question has 4 response options, which are no, possibly no, possibly yes, and yes. The scale has high internal consistency (Cronbach α=.89) and good external validity. This is an easy-to-use and validated generic questionnaire to assess communication in the context of acute conditions, usable both in clinical research and in routine practice, which measures (1) creating a good interpersonal relationship, (2) exchanging information, and (3) making treatment-related decisions that involve the patients in decision-making. This scale was translated into Colombian Sign Language following a rigorous cultural adaptation and translation procedure [26]. The videos are hosted on the LimeSurvey platform in Colombian Sign Language, written in Spanish, and played on a tablet. The participants complete the DPC scale once they leave the medical consultation.

Secondary Outcomes

The database contains clinical variables such as age, sex, place of birth, BMI, blood pressure, heart rate, respiratory rate, personal medical history (hypertension, diabetes, alcohol consumption, tobacco, and physical activity), use of hearing aids, questions on mental health, presence of hypertension, obesity, and cardiopulmonary, musculoskeletal, and metabolic disorders, recommendations provided by the doctor during a general medicine appointment, and so on. We will compute associations.

Analyses

The participant demographics will be described both by group and overall sample. Responses for the scale were combined into 2 nominal categories (“yes, probably yes/no, probably no).

We will compute associations among the variables, such as the presence of different disorders, mental health of patients, current lifestyle, and past medical history, for both the groups, using both classic statistical methods (using the Fisher exact test) and machine learning (ML) algorithms, such as association rule learning, and then we will draw a comparison between these two approaches. We will also build suitable ML models (for instance, a regression model depicted below) to predict the occurrence of hypertension, obesity, and cardiopulmonary, musculoskeletal, and metabolic disorders based on the patient’s medical history (hypertension, diabetes, alcohol consumption, tobacco, and physical activity), place of birth, BMI, blood pressure, heart rate, respiratory rate, use of hearing aids, mental health and so on, for both the groups.

Response =predictor+age+gender+place of birth

where “predictor” denotes the patient’s medical history (hypertension, diabetes, alcohol consumption, tobacco, and physical activity), body mass index, blood pressure, heart rate, respiratory rate, use of hearing aids, mental health, and so on; and “response” denotes the occurrence of hypertension, obesity, and cardiopulmonary, musculoskeletal, and metabolic-disorders and so on.

We will report the odds ratios obtained from the regression model, as they are widely used to compare two groups. We will report the predictor-wise odds ratios obtained using the equation given below:

ORs = exp(coefficient of predictor)

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Ethical Considerations

This research has received approval from the Ethics Committee of the University of Geneva in Switzerland (CUREG_2021-05-50), the Universidad del Rosario (DVO005 1979-CV1548), and Clínica de Nuestra Señora de la Paz in Colombia (CEI-41-03-2023).

Participation will require written informed consent. During recruitment, the participants will be presented with a detailed information sheet in written Spanish and Colombian Sign Language videos. Each participant will be fully informed about the rationale, objectives, procedures, risks, benefits, and other relevant aspects of the research before enrollment. All documents used will be culturally adapted and translated into Colombian Sign Language.

The project covers the transportation costs for each participant. In addition, an incentive will be provided in the form of a COP 20,000 (US $4.50) voucher, redeemable for groceries at supermarkets.

Results

This study aims to assess the effects of VRI versus the standard of care (informal interpretation, lip-reading, written notes, and use of images) on communication between health professionals and Deaf people. Recruitment opened on August 24, 2023. The intervention and data collection are expected to be finalized by late October 2024. As of July 2024, 180 participants had been enrolled. The findings of this study are expected to be submitted for publication in early 2025.

Discussion

Principal Outcomes

VRI may enable Deaf users to overcome interpretation barriers and potentially improve communication outcomes between them and health personnel within health care services. This protocol envisions to demonstrate that a VRI intervention that is context-sensitive and addresses cultural and infrastructural challenges of health settings in LMICs enables quality communication between Deaf people and nonsigning health personnel. Evidence produced through this RCT will directly address the current knowledge gap regarding the impact of ICTs for communication, particularly sign language interpretation for health care in a case coming from the global south. There is a dearth of evidence in this area.

Available research tends to focus on personal preferences, and quality communication is often not the focus [6], which is problematic. All published literature came from HICs, but most Deaf people live in LMICs [27]. This also means that this literature overlooks the infrastructural constraints and different realities, and such findings have little relevance to LMICs.

To our knowledge, this study is the first clinical trial to examine the effects of VRI and the conventional standard of care, and we anticipate that it will provide significant knowledge about the communication of Deaf people. The study also investigates whether VRI intervention can be beneficial in removing communication barriers in the health care context.

Strengths and Limitations

The proposed study has several notable methodological strengths. First, it centered on using sign language to identify the Deaf community, drawing apart from traditional biological categorizations that tend to be highly inaccurate, for example, considering people to be Deaf when they have moderate-to-vigorous hearing loss with the use of hearing aids and communicate solely with oral language. This study addresses a linguistic cultural community that encompasses great diversity in terms of hearing functioning, while identifying as Deaf and using Colombian Sign Language as their primary means of communication. It is based upon a participatory research design that includes Deaf representatives from international and national associations, researchers, and policy makers. The study's design focused on real-life contexts in Colombia and its results will be of more direct relevance to other LMICs, where 80% of Deaf persons live.

This study has some limitations that need to be recognized. First, communication may be more complex in some circumstances, such as critical care and complex medical consultations, such as genetics consultations. Furthermore, persons who are Deaf are at higher risk of ill health and secondary impairments that may impact the capability to interact independently with health care workers or to interact with electronic devices, such as screens for VRI, and this also limits the reach of the study.

Conclusions

The Deaf community faces multiple communication barriers when accessing the health system. VRI could be a good intervention to implement in the health care context and is being evaluated in a clinical trial. This technology is rolling out worldwide and could bridge the gaps in access to health care for Deaf people. Our findings could contribute to the accessibility and quality of health care for all.

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Data Availability

The data from this research are stored in the institutional repository of Universidad del Rosario according to the data management plan [28]. The data will be stored with restricted access, and upon the project's completion, the potential for providing access to relevant data for other researchers will be assessed.

Authors' Contributions

MRV contributed as a principal investigator to design, recruitment, writing the manuscript, and acquiring funding. LCIM, JD, AM-R, and DLCR handled data collection, methodology design, and drafting. JC and NG contributed to methodology, design, review, and editing. AV-S and JI-S performed recruitment, review, and editing.

Conflicts of Interest

None declared.

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Abbreviations

CPRD: Convention on the Rights of Persons with Disabilities
DPC: Doctor-Patient Communication
HIC: high-income country
ICT: information and communications technology
LMIC: low- and middle-income country
VRI: video relay interpretation

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Protocol

Extended Reality Gaming for Exercise and Mindfulness Throughout Pediatric Cancer Rehabilitation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pediatric patients with cancer have limited options to self-manage their health while they are undergoing treatments in the hospital and after they are discharged to their homes. Extended reality (ER) using head-mounted displays has emerged as an immersive method of improving pain and mental health and promoting health-enhancing physical activity among a variety of clinical groups, but there is currently no established protocol for improving both physical and mental health in pediatric cancer rehabilitation.

Objective: This phase I, pilot, feasibility randomized controlled trial aims to investigate the potential effects of a 14-week ER program on physical activity participation and indicators of health among pediatric patients with cancer who undergo bone marrow transplantation. An ancillary aim is to evaluate the feasibility of the program through participant engagement.

Methods: This study includes a 2-arm parallel group design with a 1-group crossover (the control group will start the intervention after a waiting period). Overall, 16 pediatric patients with cancer undergoing rehabilitation (aged ≥8 years) at a children's hospital will be randomly allocated into one of two groups: (1) an immediate start group that undergoes an ER program in the hospital until discharge and then for 8 weeks at home (total duration of approximately 14 weeks), and (2) a waitlist control group that undergoes usual care in the hospital and for 8 weeks at home, before receiving the 8-week home ER program. The program will include active video gaming with rhythmic music exercises as well as mindfulness-based practices using a high-quality app. Home-based programming will include behavioral coaching calls. Physical activity will be measured daily through step counts using a tri-axial accelerometer. Health outcomes will be measured across time and include global health, measured by the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Global Health Scale Short Form 7+2, and lung function, measured by a forced expiratory volume using a peak flow meter. Feasibility will be evaluated through participant engagement metrics, such as enrollment, dropout, adverse events, and attendance rates. Descriptive statistics will be obtained for all study variables. Outcomes will be modeled using mixed modeling procedures, and changes in means will be estimated with CIs.

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Results: The study was funded in February 2024. Recruitment procedures started on June 27, 2024. All data are anticipated to be collected by February 2026. Full trial results are anticipated to be analyzed and submitted for publication by March 2026. The study's anticipated end date is March 31, 2026.

Conclusions: This trial tests an accessible remote program for improving both physical and mental health among pediatric patients with cancer. The knowledge obtained from this study will inform the development of a larger trial.

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KEYWORDS

oncology; rehabilitation; bone marrow transplant; virtual reality; VR; physical activity; exercise; extended reality; XR; pediatric cancer

Introduction

Overview of Pediatric Cancer and Physical Activity

Pediatric cancer is estimated to impact roughly 400,000 children and adolescents aged 0 to 19 years worldwide annually [1]. In the United States, it is estimated that there are about 77,000 new diagnoses each year, making up approximately 5% of all cancer cases [2]. Pediatric cancer encompasses malignancies occurring in individuals aged 19 years and younger, affecting various organs or tissues, which necessitate specialized diagnosis, treatment, and long-term follow-up care [3-5]. Notably, pediatric cancer and its treatments can diminish physical activity in children, resulting in reduced mobility, muscle weakness, fatigue, and impaired physical function [6]. Reduced activity increases their vulnerability to accelerated frailty, secondary diseases, mortality, and mental health issues, all of which can be mitigated through regular physical activity participation [7-9]. Disappointingly, physical activity levels among pediatric cancer survivors are far lower than those observed among the general pediatric population [10], which places them at high risk for cardiometabolic disease [11,12].

Role of Aerobic Exercise in Bone Marrow Transplant Rehabilitation

Bone marrow transplant (BMT) is an effective option for treatment among patients with hematological disorders, including leukemia [13,14]. However, this treatment has been associated with poor outcomes, specifically decreased cardiorespiratory capacity for months after treatment [15,16], and this leads to compromised rehabilitation, participation in daily activities, and quality of life. A systematic review has found 25 randomized controlled trials (RCTs) demonstrating that exercise is safe and critical for improving posttreatment outcomes among adult patients with cancer after BMT [17], but far fewer studies exist for children and adolescent patients [18-20]. Starting an early exercise regime in the hospital is likely beneficial for optimizing health at admission to prepare the body for BMT, as well as for preventing physical deconditioning that can occur while admitted due to an immunocompromised status requiring isolation. However, there is a paucity of physical activity research among pediatric patients with BMT [21-24].

Adulthood and Health Conditions

The transition from adolescence to adulthood is crucial for adopting healthy lifestyle behaviors, including physical activity, to manage and prevent health conditions. Pediatric cancer survivors have a high rate of severe, disabling, or life-threatening health conditions that can occur years after treatment [25]. In contrast, increased cardiorespiratory fitness and physical activity levels among pediatric cancer survivors have been linked with positive outcomes, such as a lower risk of obesity and cardiometabolic complications, improved overall health-related quality of life and social function, less cancer worry, and improved mental health (eg, cognitive function, depression, and self-body image) [26,27]. Another key impetus for promoting physical activity is to treat, manage, and prevent accelerated frailty that occurs among pediatric cancer survivors. The prevalence of frailty among this group has been found to be like that among adults 65 years and older [28].

Limited Physical Activity Options and Gaps in Knowledge

Research findings addressing physical activity interventions are nonconfirmatory and are not generalizable to the general pediatric cancer population. A recent scoping review identified only 8 RCTs of physical activity for pediatric cancer survivors [29]. A systematic review identified only 2 studies that were of high enough quality to be reviewed, indicating a need for large RCTs [30]. Hospital physical activity programs have been promising but sparse [21-24]. The limitations of these studies included small sample sizes, underpowered study designs, in-person supervision by a specialist that is difficult to access in real-world settings, and limited accessible modalities for individuals with restricted mobility and functional capacity. Moreover, the modalities of aerobic exercise training were primarily walking, jogging, and bicycling, which are difficult to perform for patients with cancer who are in the early stages of treatment recovery, are in concomitant infection isolation, are severely deconditioned, or have mobility impairments. There is a dire need for early hospital physical activity modalities that are low burden on hospital staff, which can be delivered across multiple sites to improve health outcomes among pediatric patients with cancer who undergo BMT.

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Special Needs for Physical Activity

Physical performance limitations are prevalent among pediatric cancer survivors [6]. Relevant to physical activity performance, cancer survivors have poor ambulatory function [31,32] and energy expenditure [6], and have 24% greater odds of a mobility disability [31], all of which make prolonged walking and cycling difficult to perform for prolonged periods. Given that improvements to cardiometabolic health require gradual physiological adaptations following 1-3 months of exercise training [33-35], it is important to identify programs that are not only enjoyable and accessible but also effective in maintaining the interest of pediatric cancer survivors while addressing the varied needs within this group. There is an even greater need for those who undergo surgery, radiation therapy, or chemotherapy who have experienced damage to body structures or system functions and have the greatest risk for physical disability [6]. To address this need, two lessons can be learned from the field of adapted physical activity, which represents physical activity and exercise participation among people with disabilities. First, the field includes over 30 years of research in modifying and developing exercise movements and techniques to accommodate a wide variety of functional needs [36]. Second, RCTs have transitioned from a focus on multisite, supervised, in-person interventions to remote telehealth delivery [36], accommodating the low density of people who live near disability exercise specialists. Before this change, average sample sizes were 30 people per trial [36]; this is similar to current physical activity trials in pediatric cancer rehabilitation [29].

Active Video Gaming is an Accessible and Serious Exercise

A promising area of study is the incorporation of active video gaming technology with telehealth procedures. A key benefit of active video gaming is that it provides a high level of enjoyment for children and youth. Active video gaming using an extended reality (ER) head-mounted display, the Meta Quest 3 (Reality Labs), has emerged as a promising active video gaming alternative due to its affordability and high-quality visual experiences in both virtual reality (the person is immersed in a digital environment) and mixed reality (digital objects and environments are projected into the real world through pass-through cameras). Studies have demonstrated that active video gaming with the Quest 2 (a fully virtual reality device) can achieve moderate exercise levels and provide a safe activity for various user groups, including child wheelchair users [37] and patients in intensive care [38]. In addition, virtual reality programs with psychological intervention have been found to be easy to use in clinics [39] and can improve psychological well-being among patients with cancer [40,41], which is critical given the psychological distress that can occur during and after cancer treatment [42,43]. However, to the best of our knowledge, there is no program that includes both mental health and physical activity in an intervention designed for deconditioned pediatric patients with cancer, particularly while supporting the transition across admission, BMT, and home.

Telehealth Coaching Enhances Adherence

Home-based telehealth programs that incorporate “virtual” behavioral coaching (telecoaching) are a desirable approach for promoting nonsupervised exercise behavior within the community. Telehealth interventions that use remote communication technology bypass barriers related to lack of access, time, and nearby specialists, which are common for both children with disabilities [44] and those who have had cancer [45,46]. According to the Supportive Accountability Theory [47], programs that use telehealth technology can foster strong intervention adherence by providing a sense of accountability through remote monitoring and strong relationships with specialized health professionals. The addition of behavioral coaching strategies such as goal setting, confidence building, setting reasonable expectations, and understanding benefits, underpinned by theories such as the Social Cognitive Theory [48], have been found to enhance the likelihood of promoting exercise behavior among people with disabilities [49] and cancer survivors [50]. Social Cognitive Theory provides a targeted approach toward promoting exercise behavior through 4 constructs: self-efficacy (perceived control over one’s behaviors), outcome expectations, sociostructural factors (facilitators and barriers), and goals [48,51]. A physical activity intervention that uses telehealth technology, active video gaming in the ER, and a minimal dose of behavioral coaching has the potential to promote sustainable exercise behavior among large groups of pediatric cancer survivors.

This study tests a nearly full telehealth protocol with an ER program that includes physical activity and mental health intervention using “off-the-shelf” supplies. The study will inform a larger RCT through the following aims: (1) to examine the preliminary effects of an 8-week ER gaming telehealth program on physical activity participation among 16 pediatric patients with cancer after transplantation; (2) to explore potential program effects on key physical and mental health outcomes; and (3) to evaluate the feasibility of the program and its telehealth delivery through acceptability and safety.

Methods

Study Design and Overview

This phase I pilot feasibility RCT will include a 2-arm, parallel-group design to examine the preliminary effects of an ER telegaming intervention on physical activity levels among pediatric patients with cancer from a children’s hospital, compared with a waitlist control (WC). The design also includes a single-group crossover, where the WC group will receive the ER intervention after their designated wait period. The design is displayed in Figure 1. The project will include 16 pediatric patients with cancer from a single hospital who will complete the study (enrollment targets are 8 in year 1 and 8 in year 2).

This study has 2 groups, an immediate start (IS) group and a WC group. The IS group will start the intervention as soon as possible (ideally, pretransplantation within admission for BMT). Once the IS group is discharged from the hospital, they will continue the 8-week intervention at home with remote telehealth support. The anticipated hospital stay will last approximately 6 weeks. Thus, the total duration of time for the IS group will

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be 14 weeks (6 weeks in the hospital and 8 weeks of home intervention). The WC group will undergo the usual care within the hospital (approximately 6 weeks) and for 8 weeks after they are discharged. A total of 8 weeks after hospital discharge, WC participants will start the same 8-week intervention provided to the IS group. Data will be collected remotely throughout the study through digital monitoring technology and remote testing procedures. The total duration for WC participants in the study will be 22 weeks.

Figure 1. Study procedures for both the immediate start and waitlist control groups.

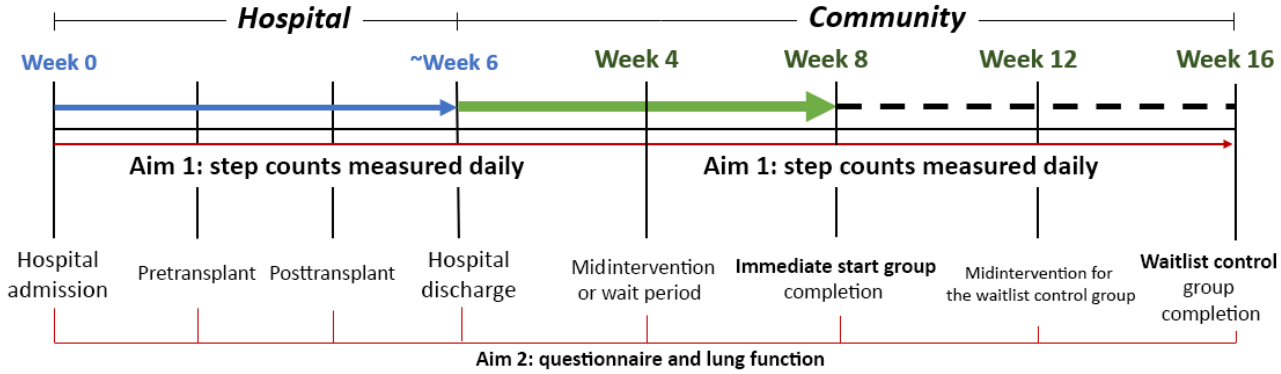

Participants

The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient at the children's hospital where the study is being conducted
- ≥8 years of age
- Medical diagnosis of malignancy or nonmalignant condition requiring hematopoietic stem cell transplant
- A caregiver who can assist the child with the study surveys and forms
- Access to a Wi-Fi Internet connection in the home through mobile phone or tablet computer

Exclusion criteria

- Complete blindness or deafness
- Inability to operate the handheld controllers
- Susceptibility to motion sickness in extended reality
- Inability to communicate in English

Screening and Recruitment

Pediatric patients with cancer are recruited from cancer clinics within the pediatric hematology-oncology department of the hospital. The recruitment strategy is physician referral through word of mouth and study flyers. Specifically, a pediatric cancer rehabilitation medicine physician team member will attend weekly BMT team meetings to scout for potentially suitable patients for the study. Prospective participants will be referred in the team meeting to the rehabilitation medicine physician, who will inform the research staff to approach the patient in their room for screening and recruitment. Research staff will screen prospective participants for the eligibility criteria and obtain informed consent and assent for participation.

Randomization and Clinical Trial Considerations

Participants will be randomized into 1 of 2 groups—IS or WC (8 per group)—with a 1:1 allocation ratio using a permuted block randomization approach. Participants will be evenly stratified into the IS or WC group based on sex. The randomization sequence will be generated by the project statistician using a computer-generated random schedule in a permuted block (SAS, SAS Institute Inc., version 9.4). Data will be entered into a secure electronic database (REDCap [Research Electronic Data Capture], Vanderbilt University) by a research assistant. The project manager will unfold the randomization sequence for successfully enrolled participants into 1 of the 2 groups. Study outcomes will be assessed by a research assistant who will be blinded to group allocation (single-blinded trial design).

Supplies

This study will include the following supplies:

1. Meta Quest 3 ER head-mounted display with handheld controllers, preinstalled with several active video games that incorporate age-appropriate themes and music and mindfulness gaming. The Quest allows gameplay in both

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virtual and mixed reality. The Quest will come equipped with accessories to enhance accessibility and usability for children with disabilities, namely, an aftermarket head strap to reduce frontal pressure on the face and pressure on the neck, and hand straps to allow gameplay for children with minimal grip strength.

2. Fitbit Flex 2 (Google) activity monitor and sleep tracker, which will be used to track daily steps.

Intervention Procedures

In summary, key features of the intervention include (1) an ER exercise intervention that has been adapted for a variety of functional abilities and fitness levels; (2) theory-based behavioral telecoaching; and (3) brief mindfulness ER gaming.

ER Intervention

IS participants will undergo an ER intervention that will last approximately 14 weeks in total. IS participants will start the ER intervention in the hospital, which will last approximately 6 weeks. They will then participate in an 8-week, home-based program with behavioral coaching. IS participants will be provided with a Quest headset within their hospital room to begin the intervention. In the hospital, IS participants will be prescribed to complete at least 15 minutes of exercise and 10 minutes of mindfulness gaming per day. Video games will be preinstalled on the headsets. Exercise games will include boxing, fitness games, and rhythmic movement-to-music games (eg, Beat Saber [Beat Games], Les Mills Body Combat [Odders], Synth Riders [Kluge Interactive], Creed: Rise to Glory [Survios]). Mindfulness gaming will include TRIPP (TRIPP, Inc.), which is a comprehensive, high-quality mindfulness ER experience that can be purchased in the digital Quest store. TRIPP includes an extensive archive of content with techniques related to breathing, meditation, yoga, pain distraction, and positive self-image. After hospital discharge, IS participants will be provided with a Quest headset and be prescribed to complete the same exercise prescription 3 times per week. The prescription will be gradually progressed through weekly behavioral coaching calls, with a goal of reaching 150 minutes of moderate-intensity ER exercise per week by the fifth week of the home intervention. The desired 150 minutes was chosen because it will likely exceed an exercise dose that could improve health in people with mobility disabilities who are physically deconditioned [52].

WC participants will receive the same intervention as those in the IS group. Participants will be given a Meta Quest 3 ER headset that will come preinstalled with the intervention games. However, WC participants will not receive the intervention until 8 weeks after hospital discharge. Thus, WC participants will be in the study for a total of approximately 22 weeks. The WC control group will undergo usual care for a total of 14 weeks (6-week hospital stay and 8-week wait period at home) before starting the 8-week intervention. Usual care consists of inpatient and outpatient rehabilitation.

Home-Based Behavioral Coaching

The home-based intervention will include behavioral coaching through phone calls with both the child and caregiver. The behavioral coaching calls will aim to enhance adherence by providing a sense of accountability [47], basic exercise knowledge, gameplay tips to increase mastery, and gradually promoting walking or community activity as a supplement to video gameplay. The rationale for promoting community physical activity is to transform a patient into a participant in their community by ER gameplay in the early intervention period to improve fitness levels that support gradual reintegration into the community. Calls will last approximately 15 minutes and will be provided weekly. Caregivers will be included in the calls since caregiver knowledge and attitude are determinants of participation.

The coaching calls will include behavior change strategies framed within the Social Cognitive Theory [48], including goal setting, confidence building, setting reasonable expectations, and understanding benefits. These strategies have been found to enhance the likelihood of promoting exercise behavior among people with disabilities [49] and cancer survivors [50]. Social Cognitive Theory provides a targeted approach toward promoting exercise behavior through 4 constructs: self-efficacy (perceived control over one's behaviors), outcome expectations, sociostructural factors (facilitators and barriers), and goals [48,51]. The coaching calls will be delivered by the lead interventionists (AW and BL).

Measures

All measures for this study will attempt to be conducted remotely, when possible. There are a total of 5 data collection time points that will be compared between groups, which are baseline (week 0), posttransplant (~week 3), hospital discharge (~week 6), the middle of the home intervention or wait (week 10), and postintervention (after week 14). WC participants will undergo 2 additional measurements, a mid- (week 18) and postintervention measure (week 22) of their home intervention. The first data collection visit will occur in person, and participants will be guided through the measurement instruments. The remaining 4 data collections will be conducted through phone or videoconference. The rationale for doing so is to simulate a remotely conducted trial and thus allow for easier replication in a future multisite trial. In addition, research staff would not have to track down participants in various clinics throughout their treatment and outpatient rehabilitation phases.

Aim 1 (Primary Outcome): Physical Activity

Physical activity level will be measured by steps per day using a Fitbit Flex 2 wrist-worn tri-axial accelerometer. The participants from both the IS and WC groups will be equipped with the Fitbit Flex as soon as they join the study. IS participants will wear the Fitbit Flex and daily steps will be measured until they complete the entire study (hospital phase, weeks 0-6; home intervention phase, weeks 7-14). WC participants will wear the Fitbit Flex, and daily steps will be measured until they complete all 3 phases that are assigned to their group: hospital phase, weeks 0-6; home wait period, weeks 7-14; and home intervention, weeks 15-22. The Fitbit Flex has evidence to support good-to-excellent validity and reliability for measuring step counts across a variety of populations, both general [53] and clinical [54], and moderate data to support validity for pediatric patients with cancer [55]. Additional rationales for the Fitbit Flex include ease of use, robust memory (30 days), water

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resistance, the small size of the monitor unit, and low cost. Although Actigraph GT3x monitors have more evidence to support their use among pediatric patients with cancer and are considered the gold standard [55], we chose not to use them due to their short storage capacity (42 days max) and an inability for both the participant and the telecoach to view and monitor their steps (app and web-based feedback; a critical component of coaching). Step counts are inversely associated with mortality [56], as well as fatigue and cumulative symptoms among patients with pediatric cancer [57].

Aim 2: Health Outcomes

Health outcomes will be measured upon joining the study at baseline (week 0), posttransplant (~week 3), before discharge (~week 6), midintervention or wait period (~week 10), and at the end of the 8-week home intervention or wait period (~week 14). WC participants will undergo additional health measurements at week 18 (midintervention) and after week 22 (postintervention). Health outcomes will include self-reported global health and lung function.

Self-reported global health will be measured by the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Global Health Scale Short Form 7+2 (PGH-7+2) survey [58,59]. The original PGH-7 has been tested for validity among representative samples in a variety of pediatric clinical groups [59-61]. The PGH-7+2 includes 7 questions from the original scale that ask about general health, general quality of life, general physical health, general mental health, the frequency of feeling sad, the frequency of having fun with friends, and the frequency of caregivers listening to ideas, along with 2 additional questions: the frequency of feeling and trouble sleeping. Lower scores indicate a poorer response. The PGH-7+2 is scored by summing the values of the first 7 questions that correspond to global health, which will be transformed into a raw T-score and an SE using tables provided by survey developers. The last 2 questions are not scored as part of global health; instead, they are reported as raw response scores. A T-score of 50 is the average for the US population, with an SD of 10. Research staff will have 2 versions of the PGH-7+2 available to account for differing abilities and preferences: a caregiver proxy report version and a pediatric self-report version. Lung function will be measured by a test of forced expiratory volume using a peak flow meter. The participants will be instructed to forcefully exhale as hard as they can into the peak flow meter. The test will consist of 3 trials, where the average will represent the final value for lung function.

Aim 3: Intervention Acceptability

Intervention acceptability will be measured through participant engagement. Participant engagement outcomes will include enrollment, dropout, adverse events, and attendance rates. Attendance to the ER prescription will be expressed as a percentage of the minutes of gaming performed, divided by the minutes prescribed. Minutes of exercise will be recorded automatically by the headset in the built-in Meta Quest Move app. Meta Quest Move tracks active minutes of play each day, which can be archived for a year and be accessed either in the headset or through the Meta mobile phone app. The Move app also allows users to set weekly goals that include built-in notification features on goal progress. Research staff will set up Move goals to match the dose of intervention prescribed in the hospital and instruct caregivers to modify the goals when participants exercise at home.

Statistical Analysis

Descriptive statistics, including means, SDs, and CIs, will be obtained for all study variables, and longitudinal smoothed scatterplots will be examined to identify temporal trends between groups, including the presence of potentially important nonlinear time trends. For aim 1 and aim 2 (measures of outcomes), outcomes will be modeled using all available measures, using mixed models with each participant included as a random effect to account for the repeated measures. Changes in means will be estimated with confidence intervals and compared between groups at 5 time points, which are baseline (week 0), posttransplant, hospital discharge (~week 6), midintervention or wait period (week 10), and postintervention (week 14) using estimated marginal means (also called least squares means). For aim 3, estimates with 95% CIs will be obtained for enrollment, dropout, and adverse event rates. Statistical tests will be 2-sided and will be performed using a significance level of $P<.05$. Statistical analyses will be performed using R (R Development Core Team) version 4.3.1 or higher (R Foundation for Statistical Computing).

Ethical Considerations

Before the enrollment of participants, this study was approved by the institutional review board of the University of Alabama at Birmingham. Written informed consent and assent documentation will be obtained from all participants before their engagement in the study. Participants will receive an electronic debit card that will be loaded for US $50 for each of the data collections completed. The IS group has 5 data collections, totaling US $250. The waitlist group has 7 data collections, totaling US $350. The rationale for this value is to account for the commitment and time required of both the child and caregiver to complete the study.

The protocol and informed consent and assent forms were approved by the Institutional Review Board for Human Use of the University of Alabama at Birmingham (IRB-300012601) on June 27, 2024. Prospective participants will provide written informed consent (signed by caregivers or patients aged 18 years or older) or assent documentation (signed by children under the age of 18 years) before joining the study. Consent and assent forms will be completed in-person during the baseline data collection visit.

Results

The study was funded in February 2024. This study started on June 27, 2024. Recruitment procedures started on June 27, 2024. This protocol paper was submitted for review before the enrollment of the first study participant. All data are anticipated to be collected by February 2026. Full trial results are anticipated to be analyzed and submitted for publication by March 2026. The study's anticipated end date is March 31, 2026.

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Discussion

Overview

This study will investigate the preliminary efficacy of a clinic-to-community ER program for improving both physical and mental health among pediatric patients undergoing cancer rehabilitation. The program incorporates off-the-shelf supplies, and most study procedures are done through telecommunications, which are 2 elements that will enhance the likelihood of scaling up the program into a multisite clinical trial. A program that can remotely link patients with pediatric cancer with ER health specialists through the internet could benefit this population. Incidence rates of cancer among pediatric patients and young adults are far lower than incidence rates among middle-aged and older adults [62]. Moreover, pediatric patients with cancer have limited options to improve their physical activity and mental health levels, particularly during their stay in the hospital [29].

Strengths and Limitations

Considering that this program can be remotely delivered, it has the potential to be carried forward in a scale-up RCT. This is important, considering that the average sample size for an RCT for pediatric patients with cancer has been found to be 24 people (7 studies, mean sample size=24, SD 9) [29]. This indicates a need for large, multisite trials. Another strength of this study is that the chosen games incorporate child-appropriate themes and music. Music-based interventions can improve mental health among pediatric patients with cancer, as demonstrated by improvements in anxiety, pain, depression, state of mind, self-esteem, and quality of life [63].

This is a preliminary pilot study with a high focus on participant engagement and a small sample size. Should this trial be successful in improving physical activity levels and health, future research efforts will be needed to confirm the study findings in larger sample sizes using objective biomarkers of health.

Conclusions

Should the findings of this study suggest that the program can improve physical activity levels, global health, and lung function, the study may discover an innovative and scalable method of intervention among pediatric patients with cancer undergoing rehabilitation.

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Data Availability

The datasets generated during and/or analyzed during this study will be made publicly available upon completion of the study and can be obtained from the corresponding author on reasonable request.

Authors' Contributions

BL, KC, AMS, AW, and JHC were responsible for conceptualization and funding acquisition. The investigation procedures were conducted by BL, KC, RY, JHR, and AW. The methodology was developed by BL, KC, AMS, AW, RY, JHR, and JHC. The authors responsible for project administration were BL, KC, AW, RY, and JHR. BL and MA wrote the initial manuscript draft. All authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by Kaul Pediatric Research Institute - KPRI Grant Program - The University of Alabama at Birmingham (USA).
[PDF File (Adobe PDF File), 325 KB - resprot_v13i1e64879_app1.pdf]

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Abbreviations

BMT: bone marrow transplant
ER: extended reality
IS: immediate start
NIH: National Institutes of Health
PGH-7+2: NIH PROMIS Pediatric Global Health scale Short Form 7+2
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WC: waitlist control

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Protocol

Exploring Medical Career Choice to Better Inform Swiss Physician Workforce Planning: Protocol for a National Cohort Study

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Abstract

Background: A medical student's career choice directly influences the physician workforce shortage and the misdistribution of resources. First, individual and contextual factors related to career choice have been evaluated separately, but their interaction over time is unclear. Second, actual career choice, reasons for this choice, and the influence of national political strategies are currently unknown in Switzerland.

Objective: The overall objective of this study is to better understand the process of Swiss medical students' career choice and to predict this choice. Our specific aims will be to examine the predominately static (ie, sociodemographic and personality traits) and predominately dynamic (ie, learning context perceptions, anxiety state, motivation, and motives for career choice) variables that predict the career choice of Swiss medical school students, as well as their interaction, and to examine the evolution of Swiss medical students' career choice and their ultimate career path, including an international comparison with French medical students.

Methods: The Swiss Medical Career Choice study is a national, multi-institution, and longitudinal study in which all medical students at all medical schools in Switzerland are eligible to participate. Data will be collected over 4 years for 4 cohorts of medical students using questionnaires in years 4 and 6. We will perform a follow-up during postgraduate training year 2 for medical graduates between 2018 and 2022. We will compare the different Swiss medical schools and a French medical school (the University of Strasbourg Faculty of Medicine). We will also examine the effect of new medical master's programs in terms of career choice and location of practice. For aim 2, in collaboration with the Swiss Institute for Medical Education, we will implement a national career choice tracking system and identify the final career choice of 2 cohorts of medical students who graduated from 4 Swiss medical schools from 2010 to 2012. We will also develop a model to predict their final career choice. Data analysis will be conducted using inferential statistics, and machine learning approaches will be used to refine the predictive model.

Results: This study was funded by the Swiss National Science Foundation in January 2023. Recruitment began in May 2023. Data analysis will begin after the completion of the first cohort data collection.

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Conclusions: Our research will inform national stakeholders and medical schools on the prediction of students' future career choice and on key aspects of physician workforce planning. We will identify targeted actions that may be implemented during medical school and may ultimately influence career choice and encourage the correct number of physicians in the right specialties to fulfill the needs of currently underserved regions.

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KEYWORDS

career choice; medical specialty; medically underserved area; motivation; professional practice; medical students; residents; prediction model; machine learning; physician workforce

Introduction

Background

The unbalanced distribution of medical staff is identified by the Global Health Workforce Alliance as the major public health challenge of the 21st century [1]. The equitable distribution of physicians in the appropriate specialties and in the appropriate regions challenges high-income countries that are currently dependent on foreign-trained physicians. The increasing pressure to supplement the physician workforce is because of the growing medical needs of an aging population coupled with an aging physician workforce [2,3]. A misdistribution of the physician workforce has been clearly predicted in recent statistics owing to increasing rates of part-time employment, difficulties in recruiting physicians to certain specialties, and growing gender gaps in certain specialties and places of practice [4,5].

This is particularly true in Switzerland, where life expectancy is high and 1 of 4 physicians is currently aged >60 years [2,3]. To increase the number of physicians, the federal and cantonal states have financed the creation of 4 new medical schools. However, there is little link, if any, between the physician and general population ratio and the distribution of the medical workforce; therefore, this strategy may be largely insufficient to meet the needs of the population [6,7].

Medical schools and postgraduate medical education policymaking bodies play a key role in this dynamic. They are responsible for the supply of an adequate medical workforce to meet demands for quality, quantity, and appropriate distribution of physicians among specialties and geographic areas [8-10]. The regulation of the Swiss medical postgraduate training system offers great flexibility to physician graduates regarding specialty selection, postgraduate program duration, and location. It is unique and differs from other systems in neighboring countries, where the specialty choice and training site are based on numerus clausus [2-4]. Beyond the regulation system, there is often an imbalance between students' wishes, the need for specialists, and the positions available, leading to shortages in some specialties and high levels of competition in others [11]. Furthermore, once specialization is achieved, concentrations in certain types of practice (private outpatient rather than hospital based) and in certain geographic areas (advantaged urban rather than rural or disadvantaged urban areas) are unbalanced [12]. Consequently, there is a growing effort to better understand what factors contribute to the physician workforce shortage and misdistribution.

These factors are impacted by the societal, political, and regulatory aspects of postgraduate medical training. The Bland-Meurer theoretical framework for medical career decision-making indicates that both specialty characteristics (eg, type of practice and person oriented) and students' career needs (eg, prestige and work-life balance) are shaped by students' individual static (eg, demographic) and dynamic (eg, motivation) features, by life experiences, and by the values and culture of the training institution [13,14]. Studies on predominately dynamic characteristics, such as motivational factors, show that students' specialty choice can be driven by internal motives ("intrinsic motivation"), such as personal abilities, interest in helping patients, intellectual challenge, and by external motives ("extrinsic motivation"), such as salary, status, and workload [15]. Their importance differs by specialty [16,17] and gender [18-21].

Various methods of artificial intelligence and machine learning have also been investigated to provide decision support for and predict individual career choice [22-28]. These career choice prediction and decision support studies have achieved some success at being able to predict career choice, with performance varying from 68% to 85% area under the receiver operating characteristic curve. To the best of our knowledge, only 1 study has used modern machine learning methods to predict a medical student's career choice [29]. To date, it remains unknown how these models perform in career choice analyses in which individual and contextual data are available. Moreover, how machine learning models perform in predictive scenarios for multiple medical career choices is yet to be explored.

Current State of Our Own Research

In our previous research, we explored the areas of intention to practice (urban and rural) of graduating students at 4 Swiss medical schools [30]. We found that 13.7% expressed an intention to practice in underserved areas (62.1% of whom intended to practice in rural areas) and 41.1% were undecided. These intentions varied from one school to another and were related to different motivational factors. Work variety and work conditions appear to be factors that might attract interested and undecided students to work in underserved areas. Among those who wished to practice in underserved areas, general practice (21.6%) was the most preferred specialty. Motivational factors influencing specialty choice were intellectual challenges, work variety, work conditions, and enthusiasm. In addition, using the same cohort at 4 Swiss medical schools, we analyzed the motivating factors that influence the choice of obstetrics and gynecology as career intentions. The results highlighted the

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importance of "experiential factors" and gender in this specialty choice. These findings provide useful information for targeted interventions to promote obstetrics and gynecology during undergraduate and postgraduate training by providing more hands-on experiences and improving the integration of male students and residents [31]. We also explored the degree of motivation for general practice, surgery, radiology, and psychiatry throughout the preclinical years. We specifically focused on personal and motivational individual characteristics correlated with general practice and surgical career intention [32-35].

The Swiss Medical Career Choice study is the continuation of 2 preliminary studies [12,36]. We will explore the role of students' individual static and dynamic features as well as that of the educational organizational context and training institution culture on career choice, that is, specialty, type, and place of practice, from medical school to postgraduate training. Thus, the present proposal seeks to understand the process of Swiss medical student career choice and attempts to predict this choice. First, we will examine the static and dynamic variables that predict the career choice of Swiss medical school graduates and their interaction. Second, we will examine the evolution of Swiss medical students' career choice and their ultimate career path.

Study Objectives

Primary Objectives

The primary objectives are to determine the current career intentions of Swiss medical students (choice of specialty and type of practice) and to assess the personal and contextual factors that determine their choice.

Secondary Objectives

The secondary objectives are as follows:

- To assess the influence of static factors such as gender and socioeconomic status
- To assess the influence of dynamic factors such as student perceptions of medical specialties and motivation
- To examine the interactions between both types of factors
- To attempt to predict career choice based on static, dynamic, and motivational factors and to design and test data-driven methods (artificial intelligence) to predict medical students' career choice
- To determine how career choice intentions vary during medical school within and across different medical school sites and during postgraduate training
- To determine how career choice intentions of Swiss medical school graduates have evolved over the last decade, considering the political strategies that have been put into place
- To compare how career choice intentions differ from the final choice in the Swiss nonregulated system and the French regulated system

Methods

Study Design

The Swiss Medical Career Choice is a 24-month longitudinal prospective national investigation implemented over 4 years (2 data collection time points) for 4 cohorts of medical students across all Swiss medical schools as well as a follow-up during postgraduate training.

For comparison purposes, this study also includes (1) a follow-up of 2 previous cohorts of medical students from Western Switzerland during postgraduate training, (2) a follow-up of the final career choice of 2 previous cohorts of medical students from 4 Swiss medical schools, and (3) a follow-up of the final career choice of 2 cohorts of medical students from Strasbourg, France.

Participants

In Switzerland, medical school consists of a 6-year curriculum divided into 3 years of bachelor's (basic science training) and 3 years of master's (clinical training). For the national prospective study, eligible participants will be medical students entering year 4 (master's 1) between 2022 and 2024 and finishing year 6 (graduates) between 2023 and 2026. The total number of eligible participants is approximately 1440 per cohort. Participants who have completed the questionnaire either in year 4 or 6 and have a response rate of >90% on the structured scale will be eligible for the follow-up study in postgraduate training year 2.

Data Collection

Data will be collected through 4 different sources: (1) a questionnaire administered during undergraduate year 4 (master's 1) and year 6 (master's 2), (2) a short survey during postgraduate training year 2, (3) data extracted from the residents' logbook of the Swiss Institute for Medical Education (SIME), and (4) exogenous contextual data extracted from the Federal Offices of Public Health and Statistics and the Swiss Medical Association (FMH).

Undergraduate participants will be invited to complete the questionnaire (approximately 30 min) during a compulsory class at the beginning of year 4 and at the end of year 6. Data will be anonymized for confidentiality reasons and for data protection issues. Participants will provide their student ID for matching purposes for the duration of the study. During the postgraduate years, participants (residents) will be invited to complete the short questionnaire (approximately 10 min) by invitation from the SIME, and relevant data will be extracted from their logbook. Data matching between the 2 data sources (undergraduate survey and data collected during residency) will be performed for each participant based on their ID number.

Ethical Considerations

The Chair of the Cantonal Commission for Ethical Research designated this study as exempt from formal review (protocol BASEC 2020-00813) as the aim of the study aim is outside the scope of the Swiss law as defined in Article 2 of the Human Research Act (HRA).

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To obtain informed consent for undergraduate data collection, eligible participants will receive an email 10 days before the survey to inform them about the research project's main goals, the content, and the testing conditions (confidential and voluntary participation). Students who agree to participate will confirm their informed consent by marking a box on the first page of the questionnaire. Comparison cohorts of medical students consented previously to this study.

Data matching will be performed by a technical administrator who is not involved in the data analysis and interpretation. Researchers will only have access to deidentified data. Anonymous responses will be collected and stored on the secure web-based server Evasys. Survey data will be extracted from Evasys and stored in a password-protected Excel (version 21; Microsoft Corporation) file that is accessible only to the central study team. The University of Geneva standards for data handling will be followed for all data management and record keeping.

Participants will not receive compensation for completing the questionnaire.

Measures

Main Outcomes

The intention of practice of the undergraduates will be assessed through a single-choice question among 6 possible options grouped into four categories: (1) hospital-based medicine (senior physician in a nonuniversity public hospital and academic and clinical career in a university hospital), (2) office-based medicine (private clinical practice in a solo practice and private clinical practice in a group practice), (3) research and teaching, and (4) undecided. The students' specialty intentions will be gathered through a single-choice question among the 46 federal specialist titles issued by the SIME plus geriatrics, emergency medicine, and an undecided option. Specialties will be further regrouped into seven categories of intentions: (1) surgical, (2) acute care, (3) diagnostic medicine, (4) preventive medicine, (5) medical subspecialties, (6) general practice, and (7) undecided. Categories 1, 2, and 3 will be grouped together in the supracategory of "technically oriented specialties." Categories 4, 5, and 6 will be grouped in the supracategory "person-centered specialties." Data collected during the postgraduate training and extracted from the SIME residents' logbook include the specialty in which the residents are currently registered, specialist title for which the resident is aiming, number of months completed in the desired specialty, and the number of months completed in different specialties. The index of change during medical school or residency will be calculated as follow: if the student does not change=0, if the student changes their intention in the same specialty category=0.5, and if the student changes for another supracategory=1. The frequency of changes will also be calculated.

Demographic Data

The demographic will include age, gender, nationality (Swiss, European, or other), medical school, high school diploma (scientific vs other), place of origin, marital status, mother tongue, and 2 indirect measures of students' socioeconomic level, that is, parents' highest educational achievement (primary, secondary, or tertiary), and parents' profession (elementary, employee, executive, or professional) [37,38].

Motivational Factors

A total of 5 global motivational factors identified in the scientific literature as influencing the choice of specialty, validated by Beaulieu et al [36], will be ranked by their importance. The degree of motivation to become a surgeon as well as a general practitioner will be measured on a 6-point Likert scale: 1=very unmotivated to 6=very motivated. The global motivational factors mentioned earlier will be broken down into 12 specific motivational factors [34] influencing the choice to become a surgeon and a general practitioner (measured on a 6-point Likert scale: 1=very dissuasive to 6=very attractive). In total, 2 single-choice questions will assess (1) students' intention to practice in medically underserved areas (yes, undecided, or no) and (2) if yes, they will be asked to specify the desired location of practice (rural, mountain, or urban areas). The desired percentage of employment will be measured as the percentage of full-time employment on a 10-point Likert scale (0=0% to 10=100%).

Individual Characteristics

The previous academic background will be identified through 2 items asking students to report the type of high school degree and the grade obtained. Personality traits will be measured through the NEO Five Factor Inventory, which is widely used to assess the major personality traits as described in the Big Five Model [39]. It consists of 60 items, 12 per trait, scored on 5-point Likert scales (0=strongly disagree to 4=strongly agree). Motivation will be measured through the Academic Motivation Scale, which is widely used to assess self-determinate motivation in educational settings [40]. It consists of 28 items scored on a 7-point Likert scale (1=strongly disagree to 7=strongly agree) assessing intrinsic motivation (12 items), extrinsic motivation (12 items), and amotivation (4 items). Students' anxiety will be measured through the State-Trait Anxiety Inventory Form Y-State. Notably, we will assess state anxiety using the state anxiety subscale [41]. It consists of 20 items scored on a 4-point Likert scale (1=yes to 4=no). The total score ranges from 20 to 80. Scores are categorized into a 3-point cutoff: below 55 (average anxiety), 56 to 65 (high anxiety), and above 65 (severe anxiety). Students' gender representation will be measured through 6 items assessing gender bias [42]. Single-item scores will be standardized into *t* scores, and a total score will be calculated.

Context Characteristics

Students' perception of learning context will be measured using a brief revised version of the students' perception of teachers in the Dundee Ready Educational Environment Measure 11-item subscale [43]. This revised version consists of 6 items scored from 0 (strongly disagree) to 4 (strongly agree) as in the original version (max score of 24). The selected questions will assess if students have identified a person they view as a role model (yes, during my medical school training; yes, but not during my medical school training; and no). If yes, 2 open-ended questions will assess (1) the function of this person and (2) in what context they met them. A total of 2 single-choice questions will assess

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(1) if the actual program location is the desired one and (2), if not, which location is the desired one. In total, 2 6-point Likert scale questions will assess (3) the degree of importance of the language of instruction and (4) the degree of importance of the cultural context.

Exogenous data collected from the Federal Medical and Population Statistics and the FMH include population density and medical density (of area of origin and of medical schools), number of professionals per specialty, specialist density per region, average specialist salary, and average number of working hours.

Table 1 summarizes domains, constructs, and measures by time points of data collection.

Table 1. Overview of domains, constructs, and measures by collection time points.

Domain and construct	Measure	Collection time point[a]		
		Master 1[b]	Master 3[c]	PGY[d]
Main outcomes				
Type or category of practice	Single-choice question	✓[e]		
Type or category of specialty	Single-choice question	✓	✓	✓
Rate of specialty or practice change	Homemade scale		✓	✓
Demographics				
Age, gender, and other demographics	Single-choice questions	✓	✓	
Marital status	Single-choice question			✓
Motivational factors				
Global motives for career choice	6-point Likert scale	✓	✓	✓
Motivation for general practice and surgery	6-point Likert scale	✓	✓	✓
Motives to choose general practice or surgery	6-point Likert scale	✓	✓	✓
Intention to practice in underserved areas	Single-choice question	✓	✓	✓
Desired percentage of employment	9-point Likert scale	✓	✓	✓
Individual factors				
Previous academic background	Single-choice question	✓	✓	
Personality	NEO-FFI[f] [39]		✓	
Motivation	AMS[g] [40]	✓	✓	✓
Anxiety	STAI-A[h] [41]	✓	✓	✓
Gender bias	Homemade scale	✓	✓	✓
Context				
Learning context	DREEM-R[i] [43]	✓	✓	✓
Role modeling	Single-choice questions	✓	✓	✓
Master's or training program location	Single-choice questions	✓	✓	✓
Exogenous data	Official records	✓	✓	✓

[a]The questionnaires will be collected annually from 2023 to 2026 from all fourth-year and sixth-year medical students and residents of Switzerland.

[b]Master 1: fourth year of medical school.

[c]Master 3: sixth year of medical school.

[d]PGY: postgraduate year.

[e]Data collection for the associated variable at the time point.

[f]NEO-FFI: NEO Five Factor Inventory.

[g]AMS: Academic Motivation Scale.

[h]STAI-A: State-Trait Anxiety Inventory Form A.

[i]DREEM-R: Dundee Ready Educational Environment Measure.

In the postgraduate survey, the selected items of individual characteristic measures will be used, except for the State-Trait Anxiety Inventory Form A. Data collection for the Western Switzerland and French comparison cohorts is similar to that

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for the prospective national cohort. For the Western Switzerland cohorts, we will conduct 2 cross-sectional data collections at 2 different time points. For all comparison cohorts, we will retrieve the career choice through the residents' logbook of the SIME and through the National Examination (Epreuves Nationales) and the National Classifying Examinations (Epreuves Classantes Nationales) official site in France.

Data Analysis

This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies [44].

Descriptive statistics will be applied to demographics, career intention, motivational factors, and individual and contextual characteristics. A chi-square test will be used to compare intentions by medical school as well as to compare previous cohorts with the national prospective cohorts. The type I error rate will be set at .05.

To examine specific motivational factors, a principal component analysis with varimax rotation will be run to aggregate the motives out of the 12, demonstrating a frequency of >10%. Data suitability will be confirmed using the Kaiser-Meyer-Olkin index of sampling adequacy. Combined criteria (ie, scree plot, eigenvalue >1.0, and interpretability) will be used to determine the number of factors [45]. The critical value for significant factor loading will be >0.40 [46]. Each factor obtained from the principal component analysis procedure will be labeled according to its content.

Appropriate statistical tests will be applied to measure changes in motivational factors, the Academic Motivation Scale, anxiety, and contextual characteristics between different time points, such as rank-order stability (Spearman correlation *r* coefficient), the Cohen *d* effect size magnitude ratios [47], and the Reliable Change Index [48].

To examine whether the demographic, motivational factors, and individual and contextual characteristics will correlate with our main outcomes, logistic regression (odds ratio and 95% CIs) and linear regression will be used. These statistical analyses will be performed using R (version 4 or above; R Foundation for Statistical Computing) and SPSS (version 27; IBM Corp).

Following a machine learning approach, the questionnaire data and exogenous contextual data from the Federal Medical and Population Statistics and the FMH will be combined in an attempt to obtain a comprehensive view of the different medical careers within the working environment. This combined data set will then be preprocessed according to the input format of the machine learning models and will link medical students and exogenous contextual data to their career intentions. To avoid issues of data bias being injected into the algorithms, data augmentation via downsampling and oversampling strategies will be assessed to reflect equal gender distribution in the training set. For the model design and experiments, different machine learning algorithms will be investigated, in particular extreme gradient boosting [49] and CatBoost [50], which provide state-of-the-art performance for categorical data, to learn career choice patterns from the collected data set. In our experiments, the data set will be randomly divided into training (60%), development (20%), and test (20%) sets to train the model parameters and hyperparameters and to evaluate the models' performance, respectively. Hyperparameter tuning and evaluation metrics will be computed using cross-fold validation to increase the robustness of the results. Standard classification evaluation metrics such as area under the receiver operating characteristic curve, F_1-score, precision, and recall will be reported. The comparison of models' predictive results will be measured using the McNemar statistical test. The type I error rate will be set at .05. The Shapley additive explanation method [51], a consistent, fast, and deterministic method for extracting feature contributions at the individual prediction level, will be used to identify factors impacting career choices.

Statistical Power

Regarding the planned analyses, all the main outcomes deal with the estimation of proportions (eg, specialty choice and practice in underserved areas). Considering the smallest subgroup population of the study (2 cohorts of residents, ie, approximately n=2880) and the proportion associated with the highest variability of the estimates (P=.50), a sample size of 864 (ie, 2×432; refer to Table 1) would allow to estimate any proportion with a precision of +2.790% to −2.790% (95% CIs derived from the hypergeometric distribution).

Results

The project has been peer reviewed and funded by the Swiss National Science Foundation in November 2022 with a start date of January 1, 2023, and an end date of December 31, 2026 (Multimedia Appendix 1). Data collection is currently underway, with the longitudinal cohort study having launched nationally on March 31, 2023. Because of organizational constraints, the postgraduate follow-up of historical cohorts will be launched from autumn 2023 to winter 2024. We expect to obtain preliminary results by mid-2024.

Discussion

Overview

This paper describes a longitudinal, prospective national investigation that will survey 4 cohorts of medical students across all Swiss medical schools as well as residents during their initial postgraduate training. The main objectives are to better understand the career choice process of Swiss medical students and to try to predict this choice.

This project will allow us to better understand the individual and contextual factors influencing Swiss medical students' career path, from students' intention at the end of medical school to postgraduate medical training and final specialization. This study will deepen preliminary findings on the relative influence and interaction of static and dynamic variables such as gender, work-life balance, and students' medical specialty perceptions [12,32-36]. The fact that the study is conducted in all Swiss medical schools will also pinpoint the differences between the various Swiss medical schools and, in particular, the effects of new medical master's programs regarding career choice and location of practice. This study will allow us to inform national stakeholders and medical schools both through prediction of

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students' future choices and key aspects of physician workforce planning. Finally, by drawing comparisons with a regulated postgraduate training system such as France's, this study will also have potential benefits at the international level.

Strengths

To the best of our knowledge, this study is the first to investigate the personal characteristics and the evolution of students' career choices during their medical studies and postgraduate training at a national level. Similarly, there is a lack of data regarding the follow-up from the initial intention to the definitive choice. This information is essential because better monitoring and understanding of career choice paths could help promote the management of physician resources and direct undergraduate and postgraduate interventions aimed at a better distribution of these resources [8-10].

We will provide information and prediction tools to meet demands for quality, quantity, and appropriate distribution of physicians among specialties and among geographic areas.

Using both individual and contextual data from medical students, we should be able to improve the predictive performance of the machine learning models as compared with questionnaire-only data [29]. By enabling better estimates than standard past averages, we expect that the predictive models will provide more effective support to decision makers for capacity planning. Moreover, by identifying the factors impacting career choice, decision makers will have data-driven information to support mitigation actions against specialty shortage. Finally, the predictive models may also help medical students in their career choice.

Limitations

Difficulties in recruiting collaborators within each medical school and coordination for survey administration may hinder response rates from students and therefore impact the realization of the study's objectives. Finally, most of the variables are self-reported and therefore subject to personal bias. However, this study will use questionnaires with established evidence to support their validity. In addition, the project has received official support from the Joint Commission of Swiss Medical Schools. This allows us to include students from all medical schools and from multiple years of study. The partnership with the Swiss postgraduate governing body, SIME, is key to enabling data collection and follow-up of subjects during the postgraduate training years. The interdisciplinary research team brings together a psychologist, a statistician, a computer engineer, and 5 medical doctors, all involved in medical education at the undergraduate and postgraduate level and holding different specialty titles.

Conclusions

Exploring the individual and contextual factors associated with the career path of all medical students in Switzerland and the establishment of a follow-up system will provide important information for improving the quality of medical workforce planning.

We will identify targeted actions that may be implemented during medical school and may ultimately influence career choice and encourage the correct number of physicians in the right specialties to fulfill the needs of currently underserved regions. Potentially, these results could contribute to better management of the medical workforce by balancing future physician distribution and, in turn, increasing the efficiency of the health care system and meeting the needs of Swiss society.

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Data Availability

The data sets generated and/or analyzed in preparation for / prior to this study that underpin a publication are available from the corresponding author on reasonable request. The data sets generated and/or analyzed as part of this study that underpin a publication will be available in due course at the Yareta, University of Geneva data repository.

Authors' Contributions

MA, MRN, DVA, DT, GLS, and NMB contributed to the initial draft of the manuscript, whereas BC, MBM, and GAS reviewed, revised, and approved the final submission. GLS and NMB contributed equally to this manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer review report from the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 293 KB - resprot_v13i1e53138_app1.pdf]

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Abbreviations

FMH: Swiss Medical Association
SIME: Swiss Institute for Medical Education
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Participatory Development and Assessment of Audio-Delivered Interventions and Written Material and Their Impact on the Perception, Knowledge, and Attitudes Toward Leprosy in Nigeria: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: In Nigeria, similar to many leprosy-endemic countries, leprosy is highly stigmatized. High levels of stigma among community members as well as internalized stigma among persons affected by leprosy often result in negative psychosocial consequences for those affected. To break this vicious cycle, it is important to conduct context-specific behavioral change activities. Although written material has been successful in improving knowledge and perception, it is not suitable for populations with low educational levels. Audio-delivered interventions are likely to be more suitable for people who are illiterate. This study proposes to assess the impact of an audio-delivered intervention on the perception (knowledge, attitudes, and beliefs) of community members with regard to leprosy in Nigeria.

Objective: This study aims to assess the impact of audio-delivered and written health education on the perception of leprosy. Specific objectives are to (1) investigate the perception (local beliefs, knowledge, and attitudes) of community members toward leprosy and persons affected by leprosy; (2) investigate whether there is a difference in impact on perception between participants who have received audio-delivered health education and those who have received written health education, with specific reference to gender differences and differences between rural and urban areas; and (3) assess the impact of the participatory development of the audio-delivered and written interventions on empowerment and internalized stigma of persons affected by leprosy who developed the interventions. Additionally, we will translate and cross-culturally validate 4 study instruments measuring outcomes in 2 major Nigerian languages.

Methods: We will use a mixed methods, cross-sectional study design for the intervention development and a 3-arm cluster randomized controlled trial for its implementation and evaluation, comprising (1) baseline assessments of knowledge, attitudes, perceptions, and fears of community members, to develop the audio-delivered content and written material, and the self-esteem and internalized stigma of persons affected by leprosy; and (2) participatory development of the audio-delivered content and written material by persons affected by leprosy and the pilot and implementation of the interventions. This will be done among

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different groups (selected using cluster randomization) that will be compared (control group, audio-intervention group, and written material group) to evaluate the intervention and the impact of developing the intervention on the persons affected.

Results: This study was funded in June 2022, and community member participant recruitment started in January 2023. Baseline data collection was completed by May 2023 (n=811). Participatory cocreation of the audio and written health education content began in July 2023, and the materials are currently under development. Study results are expected in September 2024.

Conclusions: Study findings will contribute to developing evidence-based, context-specific behavioral change interventions, which are critical to addressing stigma in many leprosy-endemic communities where leprosy is highly stigmatized, and contribute toward global triple zero leprosy efforts.

Trial Registration: Pan African Clinical Trial Registry PACTR202205543939385; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=23667

International Registered Report Identifier (IRRID): DERR1-10.2196/53130

(JMIR Res Protoc 2024;13:e53130) doi:10.2196/53130

KEYWORDS

audio health education; community perception of leprosy; health education; leprosy; Nigeria; persons affected by leprosy

Introduction

Overview

Leprosy is an infectious disease caused by *Mycobacterium leprae* [1]. Leprosy has been stigmatized since ancient times [2]. Stigma refers to a negative social response from one group toward a low-power, stigmatized group [3]. Stigma is "a social process, experienced or anticipated, characterized by exclusion, rejection, blame, or devaluation that results from experience, perception, or reasonable anticipation of an adverse social judgment about a person or group" [4]. Stigma can occur at different levels, for example, at the intrapersonal, interpersonal, community, institutional, and structural levels [5]. Many people affected by leprosy experience the negative consequences of their condition [6,7]. Stigma can have a very negative effect on employment and education opportunities, social interaction, housing, and access to health care [8]. Stigma can also indirectly cause stress and negatively impact mental well-being, quality of life, and physical health [8]. Stigma can delay seeking treatment [9] and can also impede adherence to treatment [10]. Family members and friends may experience courtesy stigma (stigma by association) [11,12].

Perception, which refers to how individuals or groups "see" an object, person, event, or institution [13-15], is an important driver of stigma [4]. The origin of stigma lies in public perceptions about people who are stigmatized. Perception comprises knowledge, beliefs, and attitudes, which are in turn influenced by personal factors (eg, personality and experience) and environmental factors (eg, culture and religion) [13,14]. Leprosy-related stigma is mainly caused by fears of contagion, external manifestations, and disabilities; religious and cultural beliefs; misconceptions; and a lack of knowledge [2,16]. Personal characteristics such as age, gender, occupation, education, and living area have also been associated with leprosy-related community stigma [17-20]. Stigma reduction (which often consists of positively influencing the perception of leprosy and increasing knowledge of leprosy) is crucial to improving the lives of people affected by leprosy and to improving leprosy services. Several interventions have successfully reduced leprosy-related stigma [21-24]. Interventions that are culture-specific and contextualized tend to be more effective [25,26].

Nigeria is among 23 global priority countries identified by the World Health Organization (WHO). In 2019, a total of 2424 new patients with leprosy were detected in Nigeria, 15% of whom had Grade 2 disabilities (G2Ds) [27]. Nigeria is among the few countries that reported more cases of G2Ds in 2019 than in previous years [27]. G2D among new patients is used as an indicator of late detection of leprosy. In addition, G2Ds (visible impairments) often exacerbate stigma and discrimination [28,29]. Leprosy is a stigmatized disease in Nigeria [30,31]. In a study among persons affected by leprosy and community members in Western Nigeria, the stigmatization of leprosy was mainly linked to perceived infectivity and perceived immoral behavior [31].

Despite progress in the control of leprosy in the last decades, the disease remains highly stigmatized [7], especially in Nigeria [30,31]. High levels of community stigma as well as internalized stigma among persons affected by leprosy may result in delayed diagnosis and disabilities [32]. To break this vicious cycle, it is important that context-specific attitude and behavior change activities are carried out. From other studies, we know that changing perceptions and improving knowledge can lead to behavior change [18,33,34]. For example, between March and June 2020, several printed materials that aimed to improve the perception of leprosy and increase knowledge about leprosy were evaluated in Uttar Pradesh, India. These context-specific materials were developed as part of NLR International's Post-Exposure Prophylaxis project. Analysis revealed an association between the number of posters seen and a positive change in knowledge and stigma scores [35].

Access to appropriate health information is an essential step in the fight against stigma and discrimination. However, written materials are not suitable for populations with low educational levels [36]. To make health information accessible to people who are illiterate in many leprosy-endemic communities of the global south (especially women and girls), it is important to provide information through modalities other than printed materials. It is believed that audio-delivered interventions would be more suitable for people who are illiterate and low-literate.

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Audio-delivered interventions, for example, radio, have been shown to be successful for different stigmatized conditions such as HIV, leprosy, and albinism [37-39].

This study aims to assess the impact of an audio-delivered intervention on the perception (knowledge, beliefs, and attitudes) of community members regarding leprosy by comparing an audio-delivered intervention with written health education. The study will be conducted in Nigeria.

Primary and Secondary Objectives

Our primary objective is to assess the impact of audio-delivered and written health education on the perception of leprosy in Nigeria. Additionally this study has the following secondary objectives: (1) to investigate the perception (local beliefs, knowledge, and attitudes) of community members toward leprosy and persons affected by leprosy; (2) to investigate whether there is a difference in impact on perception between participants who have received audio-delivered health education and those who have received written health education, with specific reference to gender differences and differences between rural and urban areas; and (3) to assess the impact of the participatory development of the audio and written interventions on empowerment and internalized stigma of persons affected by leprosy who developed the interventions.

Methods

Study Design

We will conduct a cross-sectional study (intervention development) and a 3-arm cluster randomized controlled trial (RCT; intervention implementation and evaluation). The three arms consist of (1) an intervention group who will receive the audio-delivered intervention, (2) an intervention group who will receive the written intervention (poster or flyer), and (3) a control group who will not receive any intervention.

Study Location and Setting

The study will be carried out in 6 local government areas (LGAs), 3 each in Cross River State (Boki, Calabar-South, and Obubra) and Taraba State (Jalingo, Yorro, and Zing). The 3 LGAs per area will be selected based on similarity in terms of literacy rate and prevalence of leprosy. Cross River is located in southern Nigeria, while Taraba is in the north. The total population of the study area is 940,540, estimated from the 2006 census, with 542,494 in Cross River and 398,046 in Taraba states. Both states have been selected because of the high prevalence of leprosy and G2D.

Cross River State notified a total of 106 new cases (17% with G2D) in 2019. The most common language spoken in Cross River State is Nigerian Pidgin. Over 90% of the people living in the selected LGAs in southern Nigeria speak Nigerian Pidgin. Other languages spoken in Cross River State include Efik, Ekoi, and Yala. The illiteracy rate (those with no schooling or primary or secondary education who cannot read at all) is 12.2% and 26.4% for male and female individuals, respectively. Occupations include farming, trading, and civil service employment. About 58% of women own mobile phones, compared with 71% among men [40]. Cross River State's poverty index is 0.146, and the poverty headcount rate is 36.3%. The case notification rate for leprosy is 2.76 per 100,000 people based on 2020 data.

Taraba is among the 15 high-burden states for leprosy in Nigeria; an average of 100 new cases were detected between 2013 and 2017, with an average of 6% and 5% of children and G2D cases, respectively. This figure is likely to be underreported, considering the significant presence of isolated populations such as nomadic pastoralists and internally displaced people in the state.

The most common language spoken in the selected LGAs in Taraba State is Hausa; 80% to 90% of the people living in the selected LGAs in Northern Nigeria speak Hausa. Other languages spoken in Taraba State include Mummuye and Fulfulde. The illiteracy rate is 30.1% and 64.9% in Taraba State for male and female individuals, respectively. Occupations in Taraba include farming, mainly crop production and cattle rearing, petty trading, and civil service employment. The majority of men (71%) own a mobile phone, while only 44.6% of women do. Taraba State's poverty index is 0.448, and the poverty headcount rate is 87.7%. The case notification rate for leprosy is 2.30 per 100,000 people.

Study Population

The following 2 groups of participants will be included in the study: persons affected by leprosy (for the participatory development of the interventions) and community members (the target group of the interventions).

Inclusion and Exclusion Criteria

Individuals aged 18 years or older will be included in this study. Individuals who do not speak Nigerian Pidgin or Hausa and who are unable or unwilling to give informed consent will be excluded from the study.

Study Duration and Sample Size Calculation

This study's duration will be 2 years. The sample size for the various components of the study is as follows. (1) A total of 200 community members (100 for each language per study area) will be included in the cross-cultural validation of the Explanatory Model Interview Catalogue Community Stigma Scale (EMIC-CSS) and Social Distance Scale (SDS), while 100 persons affected by leprosy (50 for each language per study area) will be included in the cross-cultural validation of the Internalized Stigma of Mental Illness (ISMI) scale and Rosenberg Self-Esteem Scale (RSES; see below). (2) A total of 770 community members will be included in the baseline and follow-up questionnaire interviews. This means a random sample of at least 385 persons in Taraba State (northern Nigeria) and at least 385 persons in Cross River State (southern Nigeria), which will consist of 114 in the audio intervention group, 114 in the written material intervention group, and 157 in the control group in each region.

This RCT will have three arms: (1) an audio-delivered intervention group, (2) a written material intervention group, and (3) a control group. The sample size calculation is based on 2 calculations. The intervention group calculation is based on an estimate of the difference in knowledge improvement

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between the audio-delivered intervention and the written material intervention groups. We used data from a perception study in India. In this study, postintervention scores improved by 12.5% after a poster intervention and community meetings. We estimate that the effect of posters alone would be an increase of 10%. We want to be able to detect an improvement of at least 15% between the audio-delivered and the written material intervention groups. The sample size of the intervention group is therefore based on a proportion 1 of 10 (estimated percentage of improvement in knowledge of leprosy in the written intervention group) and a proportion 2 of 25 (ie, an improvement of 15% or more). With a power of 80%, a significance level of .05, and a 15% loss to follow-up, 114 participants are needed in each intervention group.

We expect an increase of 2% in the knowledge score in the control group. The control group calculation is therefore as follows: proportion 1:10, proportion 2:2, power 80%, significance .05, and 15% loss to follow-up, resulting in 157 participants.

A total of 25 people will be included in the participatory development of the material [41]. In each state, these will consist of 10 persons affected by leprosy and 2-3 community members. Semistructured interviews will be conducted until data saturation is reached.

Description of the Intervention

The interventions consist of (1) an audio-delivered intervention and (2) a written or printed intervention (such as posters or flyers) for education on leprosy, awareness-raising, and stigma reduction.

We will compare the effect of the interventions with a control group. The audio-delivered and written content will be developed based on local beliefs, misconceptions, and fears about leprosy identified in the baseline study. This will be done using participatory approaches. A group of persons affected by leprosy and a few members of the community will be formed, who will be guided by a researcher to develop the messages and materials (participatory development). The key messages of the audio-delivered and written interventions will be the same. The materials will be developed in the main languages spoken in the study areas: Nigerian Pidgin (Cross River State) and Hausa (Taraba State). The majority (>80%) of our target group speaks either Nigerian Pidgin or Hausa, which will hence be the language used for this study. The audio-delivered intervention will be incorporated into Audiopedia [42]. Audiopedia's website was designed to provide access to open knowledge foremost on health, livelihood, and well-being to both community-based organizations and nongovernmental organizations and individuals. Community-based organizations and nongovernmental organizations can benefit from using Audiopedia as part of their social and behavior change communication strategy, as it enables them to search, download, embed, and share audio files. Approximately 5000 audio clips, with a total runtime of 150 hours, are available in 11 languages. Audiopedia was optimized for search engines, thus making contents easy to find. Audiopedia also provides several technological solutions to make audio-based contents accessible to both literate and illiterate audiences, such as solar-powered audio players, mobile web applications for smart (feature) phones, and Wi-Fi hotspots that can stream audio-based contents without the need for internet connectivity, etc.

Participant Recruitment and Follow-Up

Persons affected by leprosy and community members will be selected based on purposive sampling. They will develop the content of the interventions. This is therefore, ideally, a diverse group of people who represent multiple perspectives. We will select participants based on purposive sampling to ensure adequate representation of age, gender, and villages.

The intervention will be implemented in North and South Nigeria, 2 areas that are very different. Therefore, we will cluster-randomize the interventions to ensure comparable groups are included in both areas. There are three different "groups" in each site (North and South): (1) the audio-delivered intervention, (2) the written materials intervention, and (3) no intervention (control group).

We will select 3 LGAs in North and South Nigeria (6 in total); each LGA will have either the audio-delivered or the written intervention or be a control group. The three LGAs per area will be selected based on their similarity in terms of literacy rate and endemicity of leprosy.

The interventions will be randomly allocated to clusters (LGAs) based on a random numbers list. This is a 2-stage random sampling. We will select a random sample of LGAs and a random sample of participants within each LGA. The participants in each LGA will be selected using the "spin the bottle" approach: a bottle will be spun in front of the most central place in the village (rural area) or neighborhood (urban area); the direction the bottle points at is the direction we start walking and counting. The first house to be included is selected by casting a die. Participant selection will be done by proportional sampling among the clusters. We will include the same participants at baseline and follow-up (a paired sample). This study protocol is reported in accordance with the SPIRIT statement (see checklist in Multimedia Appendix 1). The timeline schedule for participants during the study period is represented in Table 1, and a schematic description of the study flow chart is depicted in Figure 1.

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Table 1. Study schedule for enrollment, intervention, and assessment.

Schedule	Study period and time point					
	Enrollment	Allocation	Postallocation			Close out
	t_{-1}	t_0 (month 0)	t_1 (baseline)	t_2 (intervention)	t_3 (6 months follow-up)	t_4
Enrollment						
Eligibility screening	✓					
Informed consent	✓					
Randomization and allocation		✓				
Intervention group						
Audio-delivered intervention				✓		
Written				✓		
Control (no intervention)						
Assessments						
Baseline variables						
KAP[a], EMIC-CSS[b], and SDS[c]			✓			
RSES[d] and L-ISMI[e] scale			✓			
CNA[f]			✓			
Outcome variables						
KAP, EMIC-CSS, and SDS					✓	
RSES and L-ISMI scale					✓	
Analysis						
Data analysis						✓

[a]KAP: knowledge, attitudes, and practices.

[b]EMIC-CSS: Explanatory Model Interview Catalogue Community Stigma Scale.

[c]SDS: Social Distance Scale.

[d]RSES: Rosenberg Self-Esteem Scale.

[e]L-ISMI: Leprosy-adapted Internalized Stigma of Mental Illness.

[F]CNA: Communication Needs Assessment.

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Figure 1. Study flow chart. LGA: local government area.

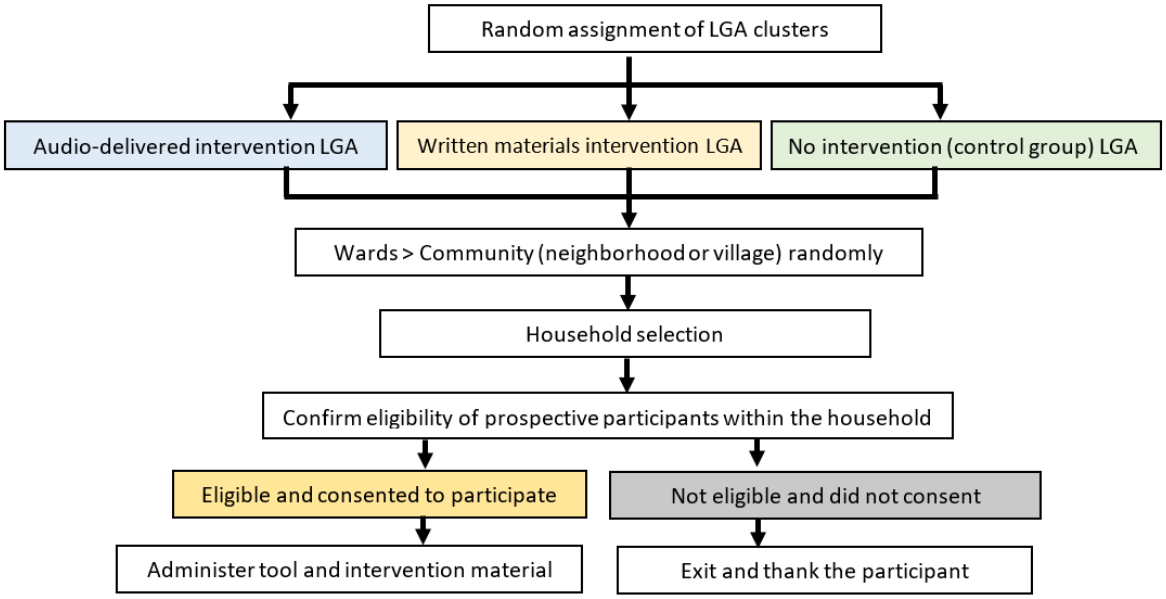

Primary and Secondary End Points

The outputs of this study will be an audio-delivered intervention and written or printed health education material for education on leprosy, awareness-raising, and stigma reduction.

In addition, all 4 scales will be translated and cross-culturally validated in Nigerian Pidgin and Hausa languages as part of this study. The qualitative outcomes are knowledge and attitudes toward (persons affected by) leprosy (eg, local beliefs, fears, and misconceptions).

Outcome measures used to be assessed at baseline and follow-up are as follows:

- Demographic information: to disaggregate data by gender, the "knowledge, attitudes, and practices" (KAP) measure includes a form to collect demographic information.
- The KAP measure, as used in a study in India [16], covers 8 main topics: early symptoms, cause, mode of transmission, treatment, prevention, curability, contagiousness when on treatment, and prevention of disabilities. The KAP is a questionnaire and has not been formally validated as a scale (nor will it be used as a scale). We will translate and pilot test the KAP measure.
- Community stigma, using the EMIC-CSS (used in Nigeria but not validated in Nigerian Pidgin and Hausa yet [17]).
- Desired social distance toward persons affected by leprosy as a proxy for attitudes and fear, using the SDS (used among persons affected by leprosy in Nigeria but not validated in Nigerian Pidgin and Hausa yet [17]).
- Self-esteem and internalized stigma of persons affected by leprosy, using the RSES (used in Nigeria but not validated in Nigerian Pidgin and Hausa yet) and the leprosy-adapted ISMI (used among persons affected by leprosy and used in Nigeria but not formally validated yet [17]).

Data Collection

Overview

We will use a mixed methods approach and collect qualitative data (in-depth interviews and focus group discussions [FGDs]) and quantitative data (the KAP measure, EMIC-CSS, SDS, communication needs assessment, RSES, and ISMI). We will also collect demographic information (including literacy levels) from each participant.

This study consists of the steps and phases outlined in the following subsections.

Step 1

None of the tools listed in step 2 have been validated in Nigerian Pidgin and Hausa yet; therefore, they will be cross-culturally validated before use. We will assess conceptual, item, semantic, operational, and measurement equivalence using a framework for cross-cultural equivalence testing based on the work of Herdman et al [43], Terwee et al [44], and Stevelink and van Brakel [45]. In addition, the interview and group discussion guides (outlined in step 2) will be pilot tested among a small sample of participants before use. The KAP measure will be translated and pilot-tested.

Step 2

A baseline study to assess the perceptions of community members using mixed methods will be conducted, consisting of both in-depth interviews and FGD sessions and questionnaires (KAP, EMIC-CSS, and SDS). A communication needs assessment will be conducted as part of the baseline study to determine the most appropriate mode of delivery of the audio intervention and the most appropriate duration and frequency of the audio intervention. We will also conduct a baseline study among the persons affected by leprosy group who will be involved in the development of the interventions. Self-esteem and internalized stigma will be assessed using in-depth interviews, RSES, and ISMI.

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Step 3

The participatory development of the audio-delivered and written content of the interventions is based on the knowledge gaps, beliefs, misconceptions, fears, and community attitudes identified in the baseline study. We will use the "6 steps in quality intervention development (6SQuID) framework [46], consisting of (1) defining and understanding the problem and its causes, (2) identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most, (3) deciding on the mechanisms of change, (4) clarifying how these will be delivered, (5) testing and adapting the intervention, and (6) collecting sufficient evidence of effectiveness to proceed to a rigorous evaluation. The final step of 6SQuID (step 6) is part of step 5 of this study—evaluation. The group of persons affected by leprosy who play a leading role in the development of the messages and materials (participatory development) will codetermine both the content of the materials (based on the knowledge gaps, beliefs, misconceptions, fears, and community attitudes identified in the baseline study) and the mode of delivery (based on the most appropriate means of communication determined by the communication needs assessment conducted as part of the baseline study).

Step 4

Implementation of the interventions in the study areas will be done in 2 groups: one intervention group will receive the audio-delivered intervention, and the other intervention group will receive the written intervention (poster or flyer). A control group will not receive any intervention. The groups will be cluster-randomized.

Step 5

Step 5 involves evaluating the impact of (1) the intervention on the community and (2) developing the intervention on persons affected, using the same mixed methods as the baseline studies (described in step 2). It should be noted that the in-depth interviews at baseline are mainly conducted to get insight into specific fears, local beliefs, and misconceptions about leprosy among community members, as well as insight into the self-esteem and internalized stigma of persons affected by leprosy. At follow-up, the communication needs questionnaire will not be administered anymore. In addition, FGDs will be held with community members at baseline and follow-up in the 6 LGAs and with the persons affected by leprosy group. In addition to further exploring themes that arose during the in-depth interviews, additional questions will be asked (at follow-up) to get insight into, among other things, awareness of, experiences with, and exposure or access to the audio and written interventions; thoughts about content; mode of delivery and frequency; and strengths and points of improvement.

Data Management and Data Analysis

Quantitative data collection will be done using electronic forms developed in the Open Data Kit, and all data will be securely stored in the cloud with access only to the research team. The recordings of the in-depth interviews and FGDs will be transcribed to the local languages, translated to English, and analyzed by 2 independent researchers using open, inductive coding and content analysis. Similar phrases with recurring themes will be coded in NVivo (QSR International). Quantitative data will be collected in the KoboCollect (Kobo Inc) mobile phone app. Data analysis will be done in the software package SPSS Statistics (SPSS Inc). Simple descriptive methods will be used to generate a demographic profile of the study sample. Differences between participants in the groups (audio, written materials, and control groups) will be evaluated using the Mann-Whitney *U* test or 1-tailed *t* test for continuous variables and the chi-square statistic for categorical variables. The mean (SD) or median (IQR), depending on the distribution of the data, of the total scores of the scales used will be calculated per intervention area. Stepwise multivariate regression with backward elimination will be done to examine what factors will have an independent effect on the outcomes. We will calculate the percentage change and corresponding 95% CI before and after the interventions are implemented and the statistical significance of this difference using a z test for differences between proportions. Effect sizes will also be calculated. If necessary, we will correct for differences in demographic information between study arms using quantile regression. We will compare the differences in follow-up assessment between the audio-delivered and written interventions. The knowledge gaps, beliefs, misconceptions, fears, etc identified in the baseline study will be summarized into a narrative review and will be used by the persons affected by leprosy group as input for the development of the content of the interventions. The most appropriate modes of delivery will be determined based on the communication needs assessment that will be conducted as part of the baseline study. The interventions will be developed using participatory methods.

Confidentiality and anonymity of data will be ensured in data collection, storage, analysis, and publication. Research assistants who will collect the data will be trained in data management, the maintenance of confidentiality, and ensuring privacy during data collection. Data will only be analyzed and shared with the Dutch and German researchers (outside of Nigeria) when they have been fully anonymized. The lead applicant will take full responsibility for ensuring the appropriate storage and security of data. Data will be kept for 5 years and destroyed after this time frame when no longer required.

Ethical Considerations

Ethical approval has been obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu (NHREC/05/01/2008B-FWA00002458-1RB00002323). In addition, appropriate clearance was sought and obtained from the respective ethics committees of both the Taraba and Cross Rivers State Ministries of Health. The confidentiality of the study participants and the data collected from them will be ensured.

Written informed consent (Multimedia Appendix 2) will be obtained from the study participants. The questionnaire will be translated into the local languages included in this study and back-translated to ensure the soundness of the translation process. The consent form explicitly states the right of the participant to refuse giving consent or withdraw from the study

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at any point. Also, he or she can decline to answer any question. Informed consent will be obtained from each participant before participation. Each participant will be given a copy of the participant information sheet and consent form to keep.

This RCT study was prospectively registered with and listed on the Pan African Clinical Trials Registry (PACTR202205543939385).

Results

This study was funded in June 2022, and community member participant recruitment started in January 2023. Baseline data collection was completed by May 2023, with a total of 811 respondents. Participatory cocreation of the audio and written health education content began in July 2023, and the materials are currently under development. Intervention will be administered after pilot-testing, and the follow-up period will last for 6 months. Neither the implementation of the study intervention nor the data analysis have commenced as of the time of submission. Study results are expected in September 2024.

Discussion

Principal Considerations

In this study, we will apply mixed methods to compare the impact of audio-delivered versus written health education intervention materials and a control group without any intervention on the perception (knowledge, beliefs, and attitudes) of community members regarding leprosy. Through a participatory cocreation process, we will develop the content of the intervention materials alongside persons affected by leprosy and implement a 3-arm cluster RCT to evaluate the effect of the intervention. The effect of the cocreation process on internalized stigma among the affected persons will also be evaluated.

Developing context-specific behavioral change intervention activities is critical to addressing stigma in many leprosy-endemic communities where leprosy is highly stigmatized. The outcome of this intervention is expected to influence knowledge and, hopefully, improve the attitudes of community members toward leprosy, as well as improve self-esteem among persons affected by leprosy. In the long run, early leprosy case finding will be boosted following stigma reduction. To the best of our knowledge, this is the first study of this kind in Nigeria. The generated educational materials (both the audio and written content) are reusable products that may be adopted or used by the national program. The audio-delivered educational content will be freely available on the Audiopedia platform, licensed under Creative Commons (CC BY).

Limitations

There are inherent limitations associated with cluster-randomized studies, such as cluster size variability. With the challenge of achieving uniform cluster sizes, variability in cluster size could impact the generalizability of the results. Additionally, there is a risk of contamination between clusters; however, this is minimal given the geographic distance between the study cluster locations.

The study sites were purposefully selected due to their similarity in having a high prevalence of leprosy and G2Ds; thus, the findings from this study may not be generalizable to the entire Nigerian populace.

Conclusion

Outputs from the research will offer policy makers, national and regional program managers, and partners reliable evidence for a new approach toward stigma reduction activities, thereby contributing toward global triple zero leprosy efforts. Content generated provides pragmatic and contextual evidence-based tools for effective health education campaigns and awareness creation, especially among populations with low literacy levels, both in Nigeria and other low- and middle-income countries.

Acknowledgments

This work is supported by the Leprosy Research Initiative Foundation (grant FP_22\15). The funding source had no role in the study design, collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

The authors deeply appreciate the contributions of persons affected by leprosy and the kind support of the central unit of the National Tuberculosis, Leprosy, and Buruli Ulcer Control Programme, Federal Ministry of Health, Abuja, Nigeria, as well as the respective team members of both Cross River State and Taraba State Tuberculosis, Leprosy, and Buruli Ulcer Control Programme.

Data Availability

This is a study protocol manuscript. Deidentified research data that support the findings from this study will be made publicly available when the study is completed and published.

Authors' Contributions

AVTN and CG conceived the original research idea. AVTN, NMO, and JC contributed to fully conceptualizing the research proposal. AVTN, NMO, JC, CN, TD, SA, CG, UAO, AM, CE, OE, and NE all contributed to the design and planning of the study. NMO wrote the draft of the study protocol manuscript and the SPIRIT (Standard Protocol Items: Recommendations for

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Interventional Trials) checklist. SA illustrated the study flow chart. All authors discussed the study protocol and contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.
[DOCX File , 45 KB - resprot_v13i1e53130_app1.docx]

Multimedia Appendix 2
Participant information sheet and informed consent form.
[DOCX File , 29 KB - resprot_v13i1e53130_app2.docx]

Multimedia Appendix 3
Peer review report by Leprosy Research Initiative (LRI), Amsterdam, The Netherlands.
[PDF File (Adobe PDF File), 117 KB - resprot_v13i1e53130_app3.pdf]

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Abbreviations

6SQuID: 6 steps in quality intervention development
EMIC-CSS: Explanatory Model Interview Catalogue Community Stigma Scale
FGD: focus group discussion
G2D: grade 2 disability
ISMI: Internalized Stigma of Mental Illness scale
KAP: knowledge, attitudes, and practices
LGA: local government area
RCT: randomized controlled trial
RSES: Rosenberg Self-Esteem Scale
SDS: Social Distance Scale
WHO: World Health Organization

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Protocol

Effectiveness of a Nursing Educational Intervention in Adults to Promote Control Behaviors Against Dengue: Protocol for a Randomized Controlled Trial

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Abstract

Background: The increase in dengue cases can be attributed to social, demographic, environmental changes, or community-driven factors. In this regard, different strategies have been established in health education, using educational interventions as necessary tools for the reduction of the disease with the aim of reinforcing and stimulating the prevention and control of dengue.

Objective: This study aims to evaluate the effectiveness of a nursing educational intervention for dengue control.

Methods: A randomized controlled trial will be conducted with adults living in rural areas and participating in health promotion and disease prevention programs. We will enroll 116 adults. Adults will be randomized 1:1, with 58 adults assigned to the educational intervention group and 58 to the usual care group. Participants will receive 4 sessions over the course of a month, 1 week apart, and will be followed up for 1 month after the end of the educational intervention. Nursing Outcome Classification labels will be used to measure the outcomes: risk control (1902) and participation in health care decisions (1606).

Results: The participants in the intervention group are expected to achieve better dengue control behaviors than those in the usual care group.

Conclusions: Risk factors are fostered by the community, largely caused by artificial reservoirs or unprotected tanks in homes; also, the lack of information hinders the identification of symptomatology and the poor implementation of effective measures, and the development of standardized educational strategies can contribute to efficient and cost-effective control of the disease.

Trial Registration: ClinicalTrials.gov NCT05321264; https://clinicaltrials.gov/study/NCT05321264

International Registered Report Identifier (IRRID): PRR1-10.2196/54286

(JMIR Res Protoc 2024;13:e54286) doi:10.2196/54286

KEYWORDS

dengue; health education; health promotion; nursing care; prevention & control

Introduction

The World Health Organization, in a report for 2023, reported that between 100 and 400 million cases of dengue occur annually [1]. It also indicates that in the Americas for the year 2021, there was an incidence of 123 cases per 100,000 inhabitants, with a case fatality rate of 0.034% [2].

Dengue in general has a global annual cost of US $8.9 billion, with an average annual cost per case of US $151 in 2013 [3] and a global burden of 1.14 million disability-adjusted life years [4]. The main burden on affected countries is the enormous

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number of hospitalizations and sick days, with older people being the most affected population [3,5]. For the economy, the negative effects are due to the high costs of controlling epidemics and absenteeism from work and school [6,7].

In addition, dengue generates indirect costs that are usually enormous. These costs are given by the consultations or medicines taken by the members of the family nucleus [8], or by the loss of income of the patients and their families due to hospitalizations and disabilities, which at the same time reflect a reduction in the supply of work from home [9,10], not to mention the distress that the patient and his family are exposed to, generated by the doubt, uncertainty, or disability that the disease can bring. Living in low socioeconomic strata in rural areas, urbanization, global warming, and increased human mobility may be factors contributing to the increased burden of the disease [11,12].

Studies in endemic countries, specifically in Latin America, reveal a low level of knowledge about dengue among the population [13]. In Peru, Gutiérrez and Montenegro-Idrogo [14] indicated that the population has a poor level of knowledge about dengue control and prevention. In Colombia, de Maria Cáceres-Manrique et al [15] reported that the knowledge of the participants about dengue is scarce, with favorable attitudes toward control but insufficient practices, and they also consider the disease to be something normal. Likewise, other studies reflect scarce knowledge about dengue, the adoption of risky practices that favor the development of the disease, and a lack of knowledge about ways to prevent dengue [16,17].

The increase of cases in these regions, apart from having behavioral and cognitive root components, such as the behavior and cultural patterns manifested by the population, essentially related to beliefs, customs, and traditions, which sometimes determine the circumstances in which the dengue virus vector lives, also presents factors that may favor the dynamics of the disease, such as socioeconomic (level of schooling, strata, overcrowding, and lack of public services), climatic, and political factors, where there is little participation of health institutions [18,19].

Research conducted in the study setting (Montería, Colombia) has related a lack of knowledge or inadequate knowledge, unfavorable attitudes, and inadequate behaviors in relation to dengue; in addition to this, people live in homes with characteristics that favor the development and multiplication of the vector, leading to recommendations for other interventions aimed at reducing contact with the vector, taking into account the conditions in which families live [20].

The presence or multiplication of dengue cases may be mostly preceded by the inadequate application of health behaviors in the management and control of the vector, having as a background the scarcity of knowledge for the appropriation and incorporation of sanitary measures in the different environments.

In view of the lack of knowledge and control measures for dengue, the literature points to several determining factors, such as sex [13], level of schooling, and socioeconomic level, since diseases such as dengue have a greater impact on low-income populations, where the conditions for the presence of vector breeding sites are more likely to occur. A low level of education generally coincides with a lack of knowledge of the disease. Other factors include residence in rural areas, occupation, overcrowding, and a lack of public services [19].

Other factors are lack of motivation and willingness, negative attitudes (low sense of belonging), inadequate habits or inappropriate cultural practices, lack of knowledge, difficult access to health services, lack of time, perception of risk, low involvement of health institutions, and limited economic and human resources allocated to public health infrastructures [21].

Thus, the evidence points to the increase in cases of dengue fever and cognitive and behavioral factors, which will be addressed in light of Nola Pender's Health Promotion Model (HPM). This model proposes that people interact with the environment, trying to achieve an adequate state of health, schematizing the nexus between personal characteristics and experiences, knowledge, beliefs, and situational aspects linked to the health behaviors or behaviors that are intended to be achieved [22], it raises dimensions and relationships that participate to generate or modify the health-promoting behavior [22], being the positive response that is expected to the actions carried out.

From the HPM perspective, the core concepts and subconcepts are used to achieve health-promoting behavior. Once the individual characteristics and experiences, cognitions, and affects related to the specific behavior are identified, the commitment to an action plan is expected, mediated in the research through the development of the nursing intervention that will generate a behavioral outcome, which is considered the expansion of skills in control behaviors in the prevention and management of dengue (Figure 1).

The objective of this study is to evaluate the effect of a nursing educational intervention to promote dengue control behaviors. We hypothesize that the participants in the intervention group will achieve better dengue control behaviors than participants in the usual care group.

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Figure 1. Description of the conceptual elements for the study of health promoting behavior.

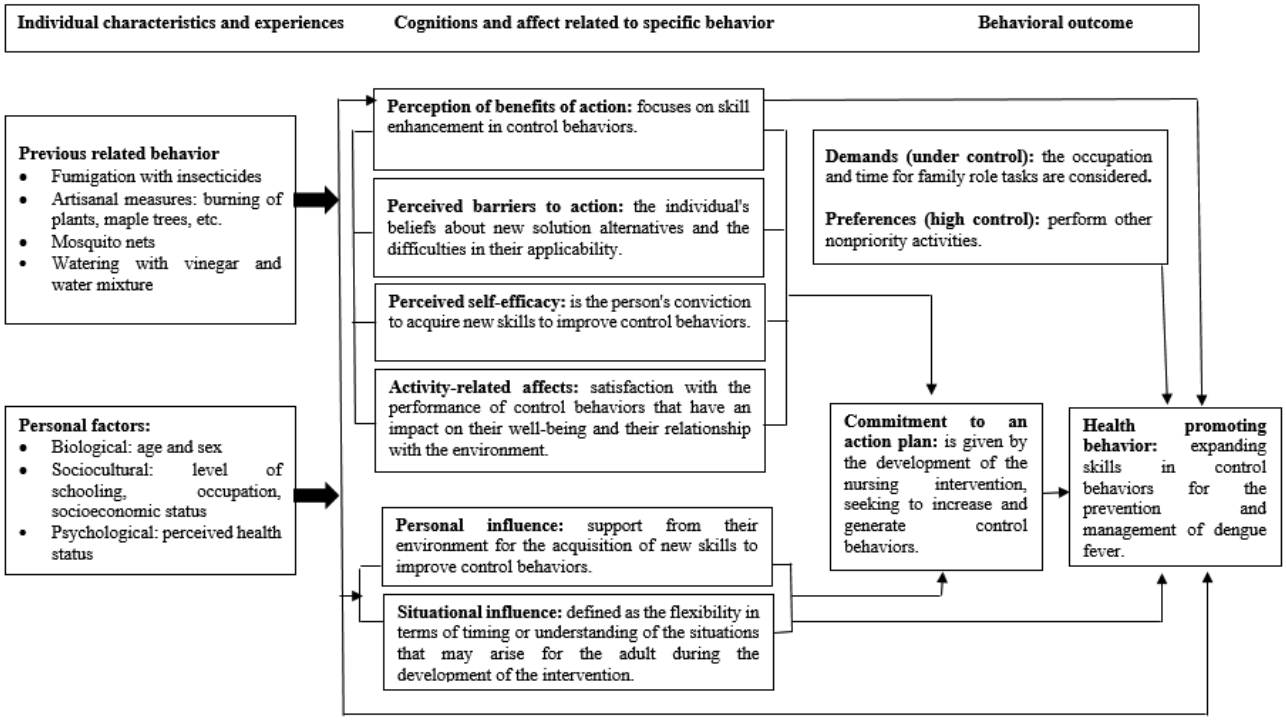

Methods

Study Design

A randomized controlled trial that follows the guidelines of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is used [23]. The study protocol was registered in ClinicalTrials.gov (NCT05321264).

Randomization and Blinding

Simple randomization into groups of equal size will be performed using the EPIDAT 4.2 program (Department of Health, Council of Galicia, Spain). Study participants will be randomized 1:1 to receive either the educational intervention or usual care. The randomization and allocation concealment will be carried out by the principal investigator. A centralized telephone randomization system will be used for masking [24]. With respect to blinding, the nurse who will perform the intervention will be blinded and will not know the outcome indicators of the study; the outcome assessors will be blinded and will not know to which group (intervention or control) the participants belong.

Participants, Setting, and Sample

The study participants are rural residents attending health promotion and disease prevention programs in a health care institution located in the municipality of Montería. It is a city in Colombia and capital of the department of Córdoba. It has 490,935 inhabitants and is considered a cattle-raising town.

Participants will be recruited during the opening hours established by the health institution. A sample size of 116 (58 participants for each group) was calculated according to the following parameters: effect size: an expected difference of 0.5 in the score of the nursing outcome labels between both groups [24], a statistical power of 90%, an α type error of 5%, a SD of the outcome scores of 1.0, an average correlation between the first and second evaluations of 0.3, an intervention/control ratio of 1:1, and a loss adjustment of 20%. Stata (version 16.0; StataCorp) software was used for this purpose.

Procedures

Eligibility Criteria

Persons older than 18 years of age, residing in a rural area of the municipality of Monteria in an endemic area with dengue or with exposure to dengue, attending health promotion and disease prevention programs of a health institution with an initial score ≤a 3.5 in the Nursing Outcome Labels (NOC) risk control (1902) and participation in health care decisions (1606), will be included in the study [25].

The Study Intervention

The educational nursing intervention in adults to promote dengue control behaviors, in terms of its structure, will follow the guidelines established by Sidani and Braden [26]. In addition, it will have as a theoretical reference Nola Pender's HPM, which is articulated for the phenomenon under study, to allow reaching a health-promoting behavior, which lies specifically in the expansion of skills in control behaviors in the face of dengue. The intervention contemplates 3 active ingredients that influence dengue control behavior: an educational component, behavioral support, and attitudinal support (Textbox 1).

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Textbox 1. Content of the intervention.

Active ingredients and components

- Session 1: educational component

General information on dengue: definition of the disease, etiological agent, mosquito life cycle, modes of transmission, period of transmissibility, and personal and environmental risk factors (tanks, flower vases, pet drinkers, and plastic containers).

- Session 2: educational component

Dengue overview: health threats, clinical manifestations, diagnostic aids, treatment, prevention and control strategies, and barriers that may prevent the implementation of effective measures.

- Session 3: behavioral support

Commitment to the implementation of preventive strategies (personal, home, and environmental care), achievements obtained with the implementation of dengue strategies, self-control in dengue decision-making, and lifestyle changes.

- Session 4: attitudinal support

Main support networks that people can find in their environment: family, friends, health, and community resources. How to take advantage of available resources?

The intervention will consist of 4 face-to-face meetings with an interval of 1 week for 1 month, each lasting 45 minutes (Textbox 2). The first session will include an educational component and address issues related to dengue, etiological agents, transmission mechanisms, and personal and environmental risk factors. The second session will cover topics such as health threats, clinical manifestations, diagnostic aids, treatment, prevention and control strategies, and barriers that may prevent the application of effective measures against dengue, also belonging to the educational component. The third session will cover personal care practices, home and environment care, and lifestyle modification, which correspond to behavioral support. Final, the fourth session covers attitudinal support, which will review support networks and the use of resources.

Textbox 2. General characteristics of the intervention.

- Objective: increase knowledge and application of dengue control behaviors.
- Duration of the intervention: 1 month
- Number of sessions: 4 sessions
- Frequency: once a week for a period of 1 month.
- Environment: institution providing health services in rural areas (promotion and prevention program).
- Delivery strategies: individual, face-to-face, standardized educational material, and use of digital tools.
- Receiver: adult who meets inclusion criteria.
- Provider: qualified and trained nurse, with previous performance verification (does not work in health institution).
- Outcome measures: risk control and participation in health care decisions.

The intervention will be delivered in a personalized, face-to-face manner [27], and standardized educational material (booklet) will be used [28-30]. It also indicates that feedback, reviews of key points, and commitments will be made in each session that is held.

Intervention Fidelity

The intervention will be delivered to adults as it is designed, seeking to generate the desired changes in the results [26]. For this, it is necessary to develop methodological strategies to ensure the application of the active ingredients (delivery mode, doses, and activities) of the intervention, called fidelity. The fidelity of the intervention contemplates 2 fundamental levels: the theoretical level and the operational level, which are described in Table 1.

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Table 1. Operationalization of intervention fidelity.

Levels and criteria	Objective	Strategies to ensure fidelity
Theoretical		
Study design control	Ensure that the intervention is consistent with the theoretical propositions of the Health Promoting Behavior.	The content of the study will be validated by experts to determine consistency between the active ingredients and the proposed theoretical component.
Operational		
Interventionist training	Ensure that the intervention is delivered in accordance with the protocol.	A course on dengue will be held and nurse training will be provided.
Delivery of the intervention	To reduce variability in the application of the intervention.	The intervention will be delivered by a trained nurse and performance will be verified. Development of the intervention protocol manual, with standardized educational material.
Treatment exposure	Ensure that all adults receive the intervention on equal terms.	Provide the intervention to all participants as defined in the intervention protocol manual: frequency, dosage, duration, delivery method, and sequence.
Treatment reception	Verify the appropriation and use of the active components of the intervention: educational, behavioral, and attitudinal support.	At the end of each session, there will be a space for feedback, review of key points, and commitments.
Follow-up of treatment compliance	Verify the implementation of health promoting behavior.	Face-to-face and telephone sessions will be held to provide feedback on the proposed objectives to achieve health-promoting behavior.

Data Collection and Measures

An intervention will be developed in 4 sessions with baseline, end line, and 2-month postintervention measures. The NOC labels chosen to evaluate the effect of the intervention are risk control (1902) and participation in health care decisions (1606).

To characterize the participants in both the intervention and control groups, a form containing variables such as age, sex, education level, marital status, actual occupation, health system affiliation, socioeconomic stratum, and dengue diagnosis will be filled out.

To evaluate the cognitive aspects or mental state of the adult, the mini mental test will be used, which is composed of 30 dichotomous items that evaluate 6 cognitive processes: temporal orientation, spatial orientation, fixation memory, evocation memory, attention and calculation, and language [31,32].

Outcomes

The outcomes of risk control and participation in health care decisions, which belong to the NOC classification, which is useful for analyzing and measuring the impact and quality of nursing interventions, will be evaluated.

Risk Control

Corresponding to code 1902, it consists of 21 indicators on a Likert-type scale with a score from 1 to 5 (1=never demonstrated, 2=rarely demonstrated, 3=sometimes demonstrated, 4=frequently demonstrated, and 5=always demonstrated) and is defined as personal actions to understand, avoid, eliminate, or reduce health threats that are modifiable [33]. It includes items that seek the implementation of behaviors by the adult.

Participation in Health Care Decisions

Defined as personal involvement in the selection and evaluation of health care options to achieve a desired outcome, it corresponds to code 1606 and consists of 15 indicators. It uses measurement scale 13, which is defined as the frequency of clarifying by report or behavior and has a score from 1 to 5 (1=never demonstrated, 2=rarely demonstrated, 3=sometimes demonstrated, 4=frequently demonstrated, and 5=always demonstrated) [33]. It contains several indicators that respond to some subconcepts of the theory, such as perceptions of benefits to action, perceptions of barriers to action, and preferences, which are the ones intended to be measured.

Follow-Up

Participants will be followed up 1 month after the end of the study intervention [34-36]. Individual and face-to-face follow-up is planned to assess the effect of the intervention over time.

Data Analysis

The information will be tabulated using the EpiData program, and the Stata software will be used for statistical analysis, following the principle of intention-to-treat analysis, which allows the patients to be analyzed as they were originally assigned or randomized [37]. Statistical hypothesis tests will be performed with an α level of 5%. A descriptive analysis of the baseline variables will be made to observe the behavior in each of the groups, using the student 2-tailed *t* test and the Fisher exact test. Categorical variables will be presented with absolute and relative frequencies. Quantitative variables with normal distribution will be presented with mean and SD, and for variables that do not comply with the principle of normal distribution, they will be presented with median and IQR (IQR=Q3–Q1). Normality will be assessed using the Kolmogorov-Smirnov test.

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Baseline variables will be compared between the control group and the intervention group. The chi-square test will be used for categorical variables. The student *t* test will be used to compare the means in the 2 groups when the normality assumption is met, and otherwise, the nonparametric Mann-Whitney *U* test will be used.

To control for possible confounding variables, a statistical adjustment will be made through an analysis of covariance with their respective 95% CIs.

The effect of the intervention will be measured through analysis of covariance by means of the delta value or difference of the NOC label score between the 2 comparison groups.

Paired *t* tests will be performed to observe separately how each group fared before and after the intervention and at follow-up.

Ethical Considerations

The trial will be conducted taking into account the ethical guidelines established in the Declaration of Helsinki, the Belmont Report (1979), the Council for International Organizations of Medical Sciences (2002), and Resolution 8430 of 1993 (Ministry of Health, Colombia, 1993). Ethical approval was granted by the Research Ethics Committee of the Faculty of Nursing of the University of Antioquia (#2021-29). Adults willing to participate voluntarily in the study will be selected, applying the principle of fairness, and the information provided by them will be maintained under strict confidentiality. Alphanumeric codes will be used to record the information, and no names or any other personal identification data will be used. The participants in the control group at the end of the research will receive the same educational intervention as the intervention group.

Results

It is expected that participants in the nursing education intervention group will have better dengue control behaviors than those in the usual care group (effect size increase of at least 0.5 of the δ score in each of the NOC outcomes). The results are expected to be published in 2025.

Discussion

Principal Result

Dengue is linked to household sanitation. The existence of breeding sites is due to specific human behaviors that favor them, whether individual, community, or institutional [15]. Insufficient knowledge about the disease is one of the factors that precipitates the application of inadequate measures [38,39]. Research indicates that risk factors are fostered by the community, largely caused by artificial reservoirs or unprotected tanks in homes [40,41]; it also indicates that the lack of information hinders the identification of symptoms [38] and the poor application of effective measures.

In the study scenario, there is evidence of inadequate knowledge and practices regarding dengue [20], aspects that this study seeks to improve in order to generate favorable changes in the behavior of the population and, therefore, of the disease.

The results of the research may serve as a basis for the identification of lines of action that should be strengthened in the prevention and control of dengue, including the induction and reinduction of the human talent necessary for health care.

Likewise, the research is a window for theoretical-practical integration in health promotion scenarios, and at the same time, it is configured as an opportunity for the visibility of care and its standardization in the rural population. It is hoped that the results will serve to strengthen the role of nursing as an active member of health risk management.

Limitations

Length of follow-up, cointerventions, and attrition during the study are anticipated limitations. To reduce these limitations, the selection of participants will be controlled by random assignment to the intervention, specific eligibility criteria for entry into the study, and intention-to-treat analysis. Both the intervention and outcome assessors will receive appropriate training. Masking and adjustments to the statistical analysis will be performed as needed. Health care professionals will be sensitized to avoid cointervention in the study. The principal investigator will be the study supervisor and will not be involved in intervention delivery or outcome assessment.

Conclusion

The scarcity of studies with a high level of evidence, such as randomized clinical trials, provides an opportunity for the development of the present research, which has a quantitative approach and aims to generate new knowledge based on the best scientific evidence for the care of vector-borne diseases in rural populations.

With the evaluation of results through the NOC, the possibility of having measurement indicators for the discipline is opened, which allow making contributions based on evidence, given that the studies carried out show scarce application of the same, so they become important work elements for the development of care processes in favor of the less favored collectivities.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Universidad de Antioquia, Colombia.
[PDF File (Adobe PDF File), 685 KB - resprot_v13i1e54286_app1.pdf]

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Abbreviations

HPM: Health Promotion Model
NOC: Nursing Outcome Classification
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e65322

Abstract

Background: Type 2 diabetes poses public health challenges for Māori and Pasifika communities in Australia. The women of these communities face a greater burden from type 2 diabetes–related mortality and comorbidities. Lifestyle modification behaviors through previous women's wellness programs have been shown to reduce the risk of developing complications in established type 2 diabetes. The Pasifika Women's Diabetes Wellness Program (PWDWP) pilot study, co-designed with Māori and Pasifika communities, was aimed at addressing late hospital presentations from diabetes-related complications.

Objective: This study (1) examines the efficacy of women with type 2 diabetes in the intervention group for improved glycated hemoglobin (HbA_{1c}) clinical levels and diabetes self-management compared with the control group from baseline (T_0) to week 12 (T_1) and week 24 (T_2; postintervention) and (2) assesses the cultural adaptability, acceptability, and feasibility of the pilot intervention for future studies.

Methods: This study uses a quasiexperimental design that involves a 24-week intervention. We recruited 50 Māori and Pasifika women with type 2 diabetes (25 in the intervention group from the south side of Brisbane and 25 in the control group from the north side of Brisbane) using participatory talanoa methodologies. The intervention group participated in face-to-face and virtual whānau education workshops (5 weeks) and had access to individual coaching and virtual support delivered by trained Māori and Pasifika health professionals and community health workers. The control group received usual care with their identified health provider. Both groups received copies of the PWDWP journal, fact sheets, and a health check passbook with tailored motivational text messages. An advisory committee was set up to oversee the program implementation, including protocols of engagement, health checks, and data collection in community settings. The quantitative data were collected at T_0, T_1, and T_2 with HbA_{1c} as the primary outcome measure. Secondary outcomes measured changes in diabetes self-care and body composition (eg, BMI, waist circumference). Qualitative data will ascertain the program's feasibility and cultural adaptability using talanoa focus groups.

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Results: This pilot study was approved by the Queensland University of Technology Human Ethic Research Committee (5609) and began in January 2023 after participant recruitment between July 2022 and December 2022. The final data collection including the health check, focus group, and survey data was completed in November 2023, and data analysis and reporting are expected to conclude in 2024.

Conclusions: This study provides a blueprint for PWDWP. Collaborative partnerships with community organizations and stakeholders are crucial for program success and suggest a potential model for targeting diabetes management for Māori and Pasifika communities, emphasizing the need for culturally relevant interventions. The findings will have significant implications for policymakers and practitioners when developing and implementing public health initiatives, particularly for communities with unique cultural nuances.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622001100785p; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384470&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/55435

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KEYWORDS

type 2 diabetes; Māori and Pasifika women; diabetes self-management; culturally co-design intervention; Pasifika diaspora; talanoa

Introduction

Background

The global prevalence of diabetes and its threat to public health continue to increase each year. Almost 90% of the estimated 537 million people currently living with diabetes worldwide have type 2 diabetes, despite it being largely preventable [1]. The Western Pacific region accounts for over one-third of the worldwide burden of diabetes, with 6 Pacific Island Countries and Territories (PICTs) among the top 10 globally with the highest prevalence of type 2 diabetes [1,2]. Additionally, PICTs face a higher prevalence of complications from debilitating diabetes as well as a higher prevalence of undiagnosed diabetes compared with other regions [2-5]. There are disparities in diabetes and diabetes-related conditions between people from PICTs and people from high-income countries, with similar disparities in Australia between Indigenous and non-Indigenous Australians [6]. As the prevalence of diabetes is positively associated with social and economic costs to individuals, families, and society, the severity and burden of type 2 diabetes are clearly highlighted [7-10].

Type 2 diabetes remains a major public health challenge for Māori and Pasifika peoples living in Queensland, which has the largest Pasifika diaspora after New Zealand [11]. Pasifika is a collective term used for Pacific peoples in Australia. Significant disparities in diabetes prevalence exist in these populations, who are 2 to 4 times more likely to be hospitalized and die from diabetes-related complications than non-Māori and Pasifika populations [12]. Evidence indicates that culturally and linguistically diverse women, in particular, face a greater burden of type 2 diabetes–related mortality and comorbidities including cardiovascular disease, kidney disease, vision impairment, and depression [12-15]. Diabetes care and support programs are less likely to be used by Māori and Pasifika women with diabetes due to low levels of health literacy, language barriers, and a strong cultural reluctance to seek help. Lack of culturally appropriate health and social services have resulted in an avoidance of engagement by Māori and Pasifika women [15]. Māori and Pasifika women carry significant cultural responsibility including expectations of acting as carers, leaders, and nurturers within their communities, often at the expense of their own chronic disease management [15]. This has significant implications for providing accessible, low-cost, and culturally appropriate diabetes care for Māori and Pasifika women with type 2 diabetes [15].

Encouraging healthier behaviors in Māori and Pasifika women with type 2 diabetes could potentially improve the health and well-being of women [15,16]. Modification of personal behaviors through women's wellness programs aimed at early intervention have been shown to reduce the risk of developing complications in established type 2 diabetes and may reduce hospitalization rates due to preventable complications [14]. A qualitative study of a multimodal behavioral intervention, the Women's Wellness with Type 2 Diabetes, found it to be effective at supporting women with developing strategies to improve their well-being and avoid complications associated with diabetes [16]. Another study with Māori and Pasifika women with type 2 diabetes in Queensland reported effective strategies to improve self-management through culturally appropriate interventions and educational resources [15,17]. Thus, the first culturally framed intervention, the Pasifika Women's Diabetes Wellness Program (PWDWP) emerged from these studies that informed the study's principles and processes, including recruitment strategies and co-design of the delivery format into a whaˉnau (family)-centered approach that harnesses digital technology [15,17]. The intervention was co-designed with Māori and Pasifika women living with type 2 diabetes in Queensland, underpinned by social cognitive theory and the Fonofale Pasifika Health Model that focuses on family, culture, community, and spirituality using talanoa, a Pacific form of dialogue, to promote sustainable self-management of type 2 diabetes [17-20]. This 24-week program is whānau-centered with 5 diabetes self-care behavior and wellness components (Figure 1) and delivered by trained Māori and Pasifika health professionals. The program takes into consideration the cultural shame associated with acknowledging the disease and tailors

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the interventions using talanoa as the key strategy to reach a shared meaning for behavioral changes [20].

Figure 1. The Pasifika Women's Diabetes Wellness Program and the "wellness" components.

The program team has previously ensured successful translation of interventions into practice through meaningful engagement with consumers, policymakers, health service managers, and clinicians [15,17,18,20-22]. This program will further consolidate collaborative partnerships between clinicians, health service providers, Māori and Pasifika communities and organizations, and consumer advocates. The study will evaluate the clinical benefits of the intervention and will target improvements in glycated hemoglobin (HbA_{1c}; measured using a point-of-care device [18]) and diabetes self-care including diet, physical activity, stress and medication management, and routine health checks of Māori and Pasifika women with type 2 diabetes from data collected via validated questionnaires using Qualtrics [24]. The study builds on a robust and systematic program of work, beginning with scoping studies, needs assessments, and early wellness trials with women [15-17].

Research Aim

The pilot study will evaluate the feasibility, acceptability, delivery, and effectiveness of PWDWP using mixed methods, in partnership with Māori and Pasifika community organizations and key stakeholders in southeast Queensland.

Objectives

The primary objective is to examine efficacy, defined as the women with type 2 diabetes in the intervention group having improved clinical HbA_{1c} levels from baseline (T_0) to week 12 (T_1) and week 24 (T_2) postintervention compared with the control group.

The secondary objective is to determine whether, compared with control participants, the intervention group achieves changes to bring body composition measurements closer to the recommended healthy range for specific cultural groups (eg, BMI ≤30 kg/m^2 and waist circumference <80 cm based on World Health Organization criteria) and improved diabetes self-care scores on diet, physical activity, routine health checks, and medication adherence assessed using the validated Summary of Diabetes Self-Care Activities scale [23,25-33].

In addition, we will assess the potential for success of the proposed intervention by examining accessibility, acceptability, uptake, and cultural adaptability of the intervention; sustainability of and adherence to the intervention over time; participants' perceptions of measurement burden; the effectiveness of the planned recruitment strategy and retention of participants; and documentation of women's experience with PWDWP through digital stories.

Hypotheses

H1 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have improved HbA_{1c} levels at 12 weeks and 24 weeks (postintervention sustainability).

H2 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have reduced waist circumference and BMI at 12 weeks and 24 weeks.

H3 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have improved diabetes self-care at 12 weeks and 24 weeks.

Data collection occurred at 3 time points: T_0 (before the commencement of the pilot program, week 1), T_1 (postintervention, week 12), and T_2 (postintervention, week 24). Data on the feasibility, accessibility, and affordability of

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the PWDWP were collected via satisfaction surveys for the intervention group at the end of the workshop (week 5), week 12, and week 24. For the control group, satisfaction surveys were completed in week 12 and week 24.

Qualitative data obtained through talanoa focus groups with participants will determine measurement burden, acceptability, potential translation, and ease of intervention access. Feasibility covers how the participants were referred to the program, time taken to complete questionnaires, any strengths or weaknesses of the intervention, its cultural relevance, experience with accessing the intervention, perceptions of the digitally delivered coaching sessions and online virtual support sessions as well as the face-to-face intervention, and any suggested improvements to the study design or intervention.

Methods

Advisory Committee

An advisory committee (AC) was established to oversee the pilot study, including its setup, ongoing management, promotion, implementation, and evaluation with outcome deliverables including appropriate dissemination. The AC includes members of the Māori and Pasifika communities including the Pasifika Women's Alliance and Pacific Island Council of Queensland and key organizations such as the Good Start Program for Māori and Pacific Islander Peoples (Children's Health Queensland) and academia (eg, Queensland University of Technology [QUT] and University of Technology Sydney through the Women's Wellness Research Program). A series of group talanoa undertaken with AC community members ensures that the pilot study is implemented and evaluated within the talanoa cultural framework. The AC meets regularly every 4 months to review the study protocols including recruitment strategies, health checks, and data collection methods and approaches and how these are disseminated. The AC provides input on the trial progress, adherence to the protocol, participant safety, and consideration of new information as well as advice on the location and place of delivery (intervention and data collection) considered to be culturally acceptable to the participants.

Participatory Talanoa Methodologies

The research uses participatory action research using co-design and talanoa methods as the theoretical and cultural framework in the collection and analysis of data.

Talanoa is a way of communicating in a Pacific context. It has been described as the co-construction of knowledge through respectful, reciprocal conversation. It is a process enabling critical discussions and knowledge construction allowing for rich contextual and inter-related information to surface as co-constructed stories [19]. Vaioleti [19] uses the following metaphor of kakala:

- "Toli" is deciding on, selecting, and picking the flowers, equating to recognizing a problem, how participants are chosen, and which data are collected and analyzed [19].
- "Tui" is the process of making and weaving the kakala, in which the stories and emotions of deep talanoa encounters are integrated and synthesized. This involves deciding on the type and amount of data to use, how the data are arranged in relation to each other, and how they are presented.
- "Luva" is the giving away of the kakala, when the research is given for the benefit of the community, where solutions can be found.

In this context, community engagement, including recruitment, data collection, and analysis processes, is a form of talanoa. All data are analyzed through talanoa with the AC and community researchers. In this context, talanoa is a method embedded within a participatory methodology [19] that informs the protocol of this study.

Study Design

This pilot study is a quasiexperimental design with 2 arms: an intervention (delivered in person and online for those who preferred virtual delivery) and an attention control arm (receiving written information and text messages). The study is being conducted to trial a 12-week intervention followed by a 12-week follow-up period (over 24 weeks) delivered by trained Māori and Pasifika health professionals (diabetes educator, clinicians, community health workers [CHWs], and community researchers). The study is conducted in southeast Queensland, Australia, with Māori and Pasifika women living with type 2 diabetes who were recruited through participatory community engagement with the Māori and Pasifika community leaders and organizations.

The study uses participatory talanoa methodologies using in-depth interviews and surveys and involves an in-person talanoa education workshop (5 weeks) as well as virtual workshops (5 weeks for those participants not in Brisbane and unable to attend in person), 3 online individual talanoa consultations (coaching) via Zoom, and an online virtual talanoa support group with motivational SMS text messages. The control participants received the usual care with their identified health professionals, a hard copy of the program materials (which includes a program journal, recipe book, fact sheets, and passbook), as well as general motivational SMS text messages. The process evaluation includes satisfaction surveys after the workshop sessions at week 5, week 12, and week 24 as well as a talanoa focus group with the participants after the intervention. Figure 2 is an overview of the PWDWP pilot study in southeast Queensland, Australia (2022-2024). The detailed intervention is described in the following sections.

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Figure 2. Overview of the Pasifika Women's Diabetes Wellness Program (PWDWP) pilot study in southeast Queensland, Australia (2022-2024).

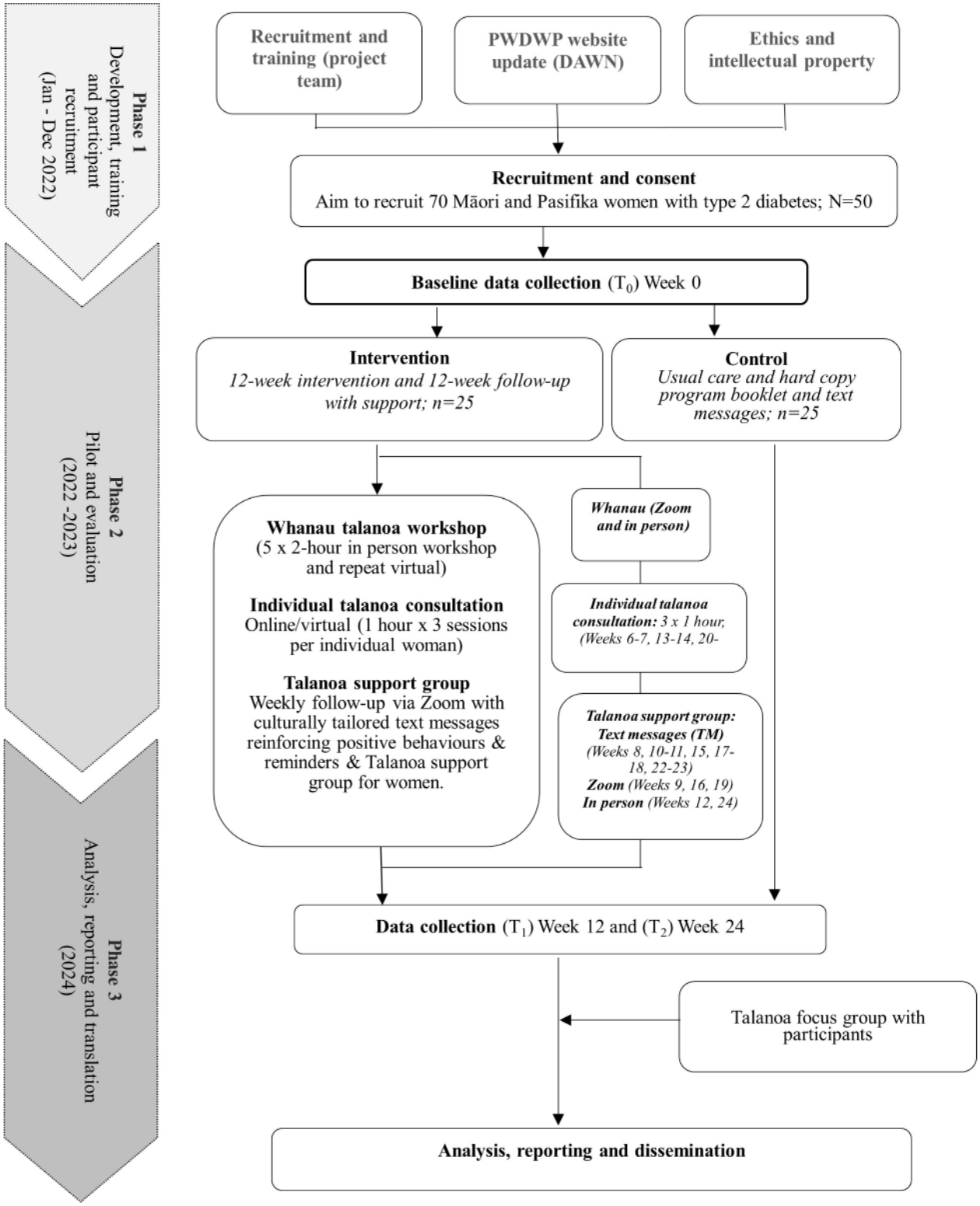

Intervention

The PWDWP intervention includes a whānau talanoa workshop, individual talanoa consultations, and a talanoa support group and text messages.

Whānau Talanoa Workshop

Five 2-hour sessions covered the wellness components. Whānau talanoa workshops provided interactive knowledge-based education on targeted health knowledge and behaviors with culturally specific tools to manage type 2 diabetes within family, community, and spiritual contexts (see Table 1).

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Table 1. Whānau talanoa education workshops on diabetes wellness components delivered by a trained Pasifika diabetes educator and community health workers.

Education component	Content delivery	Weeks delivered
Becoming Healthy	This workshop provides practical information on type 2 diabetes and its symptoms, risk factors, diagnosis, treatment and management, medication, and self-care. This session also covers practical and cultural ways to deal with issues related to the shame and stigma of developing type 2 diabetes and the impact of denial.	1
Healthy Thinking & Feeling	This workshop provides information and tools to deal and cope with stress and barriers and ways to improve wellness that incorporate elements of Pasifika values, spirituality, and faith.	2
Healthy Eating	This workshop provides information and tools for healthy eating with a self-care healthy eating plan and strategies for managing cultural hospitality requirements without losing face.	3
Staying Active	This workshop covers ways to get moving, types of exercises to do with your family, and practical tips to remain motivated to stay active while managing family and community obligations.	4
Healthy Living	This workshop encourages, motivates, and maintains healthy living including looking after your bones, eyes, kidney, and heart; sleep; and menopause with spirituality, family, and community well-being.	5

Individual Talanoa Consultations

Three 1-hour, 1-on-1 sessions were conducted. The first session consisted of a routine check-up, appropriate screenings, and a discussion to facilitate tailored education, goal setting, and specialist advice to support individualized plans and goals for a healthy weight, diet, physical activity, stress management, sleep, and medications. The second session revisited goals set during session 1 and, if necessary, discusses prevention strategies and identification of barriers. The third session reviewed participant progress including barriers to self-management, reinforcement of positive behaviors, and setting future goals for maintenance.

Talanoa Support Group and Text Messages

A virtual peer support group facilitated by CHWs encouraged and supported women with targeted topics including stress management, barriers, understanding family situations, mindfulness, nutrition and diet, importance of health checks, regular visits to general practitioners and specialists, monitoring blood glucose levels, medication adherence, and maintenance. Motivational SMS text messages were sent regularly to reinforce key messages.

Cross-Intervention and Control Conditions

The intervention group received the complete intervention over the 24 weeks and had access to an interactive program journal (hard copy and electronic), a recipe book, a passbook for health check, and fact sheets as well as text messages with reinforcing positive motivational behaviors (Table 2). The participants also had access to a website that includes culturally developed resources (such as podcasts, digital stories, and information materials).

Table 2. The intervention component for the Māori and Pasifika women with type 2 diabetes from the south side of Brisbane, Queensland, Australia.

Intervention components	Weeks (1-24)
Whānau talanoa workshops (in person and virtual)	1-5[a]
Individual talanoa consultation (coaching via Zoom)	6-7, 13-14, 20-21
Motivational SMS text messaging	8, 10-11, 15, 17-18, 22-23
Talanoa support group (via Zoom)	9, 16, 19
Data collection (T_0, T_1, T_2; in person)	0 (baseline), 12, 24
Talanoa focus group (in person)	24

[a]Offered either (1) in person (face to face) with women or (2) online (virtual) for those who cannot attend in person.

The program provided all necessary health promotion content and supported participants with logging relevant health information in the journal (either hard copy or an electronic version). A weekly diet, physical activity, and diabetes self-care checklist encouraged participants to plan ahead. The interactive website aims to reinforce educational content, enabling home monitoring of measurable health indicators, and allowed participants to fill out questionnaires and other data. The website will also be adapted for all computing platforms, including mobile phones for future studies. Figure 3 illustrates the intervention participant journey of Māori and Pasifika women with type 2 diabetes from the south side of Brisbane over 24 weeks (January 2023 to November 2023).

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Figure 3. Intervention participant journey of Māori and Pasifika women with type 2 diabetes from the south side of Brisbane, Queensland, over 24 weeks (January 2023 to November 2023), including five 2-hour education workshops (WS; either face to face or virtual), 3 individual talanoa (IT) consultations, and 3 virtual talanoa support group (VTSG) sessions with text messages (TM). DC: data collection.

The control group received their usual care with the hard copy of the program materials (ie, program journal, recipe book, fact sheets, and passbook) and SMS text messages (Table 3). At the completion of the intervention, control participants received a modified 1-day workshop covering talanoa education workshops. Figure 4 illustrates the control participant journey of the Māori and Pasifika women with type 2 diabetes from the north side of Brisbane over 24 weeks (January 2023 to November 2023).

Table 3. The control component for the Māori and Pasifika women with type 2 diabetes from the north side of Brisbane, Queensland, Australia.

Control components	Weeks (1-24)
Usual care with a hard copy program booklet (participants will be asked to document in the study journal [encouraged daily or weekly] but will be at their own discretion)	1-24
Motivational SMS text messaging	4, 8, 10-11, 15, 17-18, 22-23
Data collection (T_0, T_1, T_2; in person)	0 (baseline), 12, 24
Talanoa focus group (in person)	24

Figure 4. Control participant journey of Māori and Pasifika women with type 2 diabetes from the north side of Brisbane over 24 weeks (January 2023 to November 2023), including usual care with their preferred health provider and motivation text messages (TM). DC: data collection.

Inclusion and Exclusion Criteria

Inclusion criteria included Māori and Pasifika women with type 2 diabetes, aged ≥18 years, diagnosed with type 2 diabetes, and with access to the internet. Participants were excluded if they were pregnant and diagnosed with gestational diabetes, had a high-risk pregnancy, or were not diagnosed with type 2 diabetes.

Locations and Online Forums

Whānau Talanoa Intervention (Onsite)

The onsite face-to-face whānau talanoa sessions occurred in the community setting as recommended by the AC to ensure they were culturally acceptable to the participants in a whānau setting that is inclusive of the community.

Online Virtual Talanoa Intervention

The online sessions occurred via the Zoom platform over 5 weeks and covered the same content delivered in the face-to-face session. The Zoom setup was organized and managed through the secure QUT system, which enabled the project coordinator to host and manage each session and recordings. All the recordings and transcripts are stored with password protection and security in the QUT shared drive project folder, which can be accessed by the project team only (principal investigator and coordinator).

Individual Talanoa Consultation

The individual talanoa consultations (either via Zoom or telephone) were delivered by a trained CHW educator and managed through case notes that were uploaded (including

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Zoom recordings) to a secure project folder within the QUT shared drive.

Study Population and Setting

Study Type

This is a participatory community-based study. Māori and Pasifika women living with type 2 diabetes were recruited from the Pasifika communities in southeast Queensland through a range of organizations, representing various sectors of the Māori and Pasifika communities in Queensland. The intervention and control groups were geographically distinct to minimize cross-communication, as members within the same community socialize, and this is the design the AC recommended as culturally appropriate.

Intervention Group

The intervention participants were recruited from the south side of Brisbane, including Logan, Ipswich, and Gold Coast, and geographically separated from the control group. Inclusion criteria for intervention participants were women aged ≥18 years from the south side of Brisbane, diagnosed with type 2 diabetes, and with access to the internet.

Control Group

The control participants were recruited from the north side of Brisbane, including the Sunshine Coast. Inclusion criteria for control participants were women aged ≥18 years from the north side of Brisbane who have been diagnosed with type 2 diabetes.

The exclusion criteria for intervention and control groups were pregnant women diagnosed with gestational diabetes or with a high risk of pregnancy. Women from each arm were also excluded depending on the location (eg, South side women were excluded from the control group and vice versa).

Sample Size

The sample size was calculated based on previous studies for detecting a difference of 1% reduction in HbA_{1c} (primary outcome) with a standard deviation of 1.4% in the intervention group. A significance level (α) of .05 was considered with a study power of 80% [34]. Based on this, a sample of 64 participants was needed (32 for the control group and 32 for the intervention group), with a target sample of 90 participants to compensate for a 40% attrition rate. Although the program received approximately 90 expression-of-interest responses, challenges with community engagement, complexities arising from COVID-19, and participant dropout resulted in a total of 50 participants, with 25 in the control group and 25 in the intervention group who enrolled and completed the pilot program.

Community Settings

The program for the intervention group was provided in community settings: Pasifika Te Haus in Runcorn and Adam Gould Community Centre in Logan on the south side of Brisbane. There is a large Māori and Pasifika population in southeast Queensland. For the control group, the first health checks and data collection occurred at a Pasifika Community Church, but for the follow-up visits, home visits were undertaken as requested by the participants. The community locations were recommended by the AC.

Recruitment Strategies

Recruitment for both intervention and control groups was multimodal and through distribution of study flyers, email invitations, and advertisements via social media (Facebook, websites); local ethnic radio stations; newsletters; and community networks including church groups, organizations, and Māori and Pasifika health workers. Recruitment also occurred through presentations and dialogue with community partners and organizations, including the Pasifika Women's Alliance Inc, Oceania Pacific Health Association, and Multicultural Communities Council Gold Coast, who have representatives on the AC, and they promoted the study through their networks and social media.

Ethical Considerations

The PWDWP was approved by the QUT Human Ethic Research Committee (5609). All data will be aggregated, with no individuals able to be identified. Collected data will be coded for analysis. The anonymity and privacy of all participants will be maintained through the use of fictional names, unique participant identification numbers, and secure data storage. All data will be stored securely on a password-protected research drive as per QUT's management of research data policy and the National Health and Medical Research Council guidelines for trials, with access restricted to only the principal investigator and co-investigator.

Potential participants were contacted to discuss the study and consent processes. Those who agreed received a "participant information pack" with an introduction letter detailing the program information, timelines, demographic questionnaires, and participant consent information. The project officer conducted 2 follow-up phone calls with each participant before the intervention to finalize details regarding the program; confirm the mode of preference for participating in part 1 (in person or online) of the intervention; and discuss issues or concerns with participation, access to their own GP, and dropout as well as any other issues that the women would like to discuss. Participants who consented to participate were asked to get a medical checkup prior to the start of the program and raise any concerns with the project officer. All participants (intervention and control) who consented were allocated a unique ID number and registered in a trial database. Any reasons for nonparticipation were recorded. The original informed consent for the primary data collection allows secondary analysis without additional consent.

Any cultural, spiritual, and personal concerns about disclosure in relation to cultural and religious beliefs especially around stigma associated with a diabetes diagnosis were discussed and clarified with participants before obtaining consent to disclose or use any sensitive information. Cultural sensitivity and respect form the underpinning guiding value in this research process especially when working with Māori or Pasifika families from various ethnic and religious backgrounds. This also included talanoa style of conversations to clearly explain the reason for choosing the 2 different locations (sites) for recruitment of

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control and intervention participants and the benefits and risks with each group allocation.

Although we acknowledge that the Pasifika communities are well connected and share familial relationships, there was a possibility for the lack of confidentiality. One way this is addressed is by discussing with participants the importance of anonymity while at the same time acknowledging that this can be difficult in close-connected collective communities. This is a limitation to the study.

All participants, including control and intervention participants, were remunerated ("Koha") with gift vouchers (A$20 [US$13.05] for the health check and A$30 [US$19.57] for the talanoa focus group) to compensate for for their out-of-pocket expenses, travel time, and costs for participating at each data collection.

Data Collection and Analysis

Training of Community Health Workers, Community Researchers, and Research Team

Before the study commenced (July 2022 to December 2022), the Pasifika CHWs, health professionals, facilitators, and project team (including community researchers) received training on cultural protocols for engagement, community values, working with families across different Māori and Pasifika communities including the use of talanoa methods and approaches to coaching and delivering interventions within cultural Pasifika health model frameworks, and the protocols to be followed.

Training was undertaken by the principal investigator and diabetes educator in the form of role play, storytelling, and interactive activities using scenarios. The AC was invited to participate in the training as well as to contribute and share cultural experiences and advice in relation to working with Māori and Pasifika communities in a culturally safe and sensitive manner. All training was recorded, minutes were taken, and registration attendance was noted. The community researchers were also provided a step-by-step instruction manual on data collection.

Quantitative Outcomes

Quantitative data were collected through face-to-face or in-person sessions using online questionnaires at 3 time intervals (T_0, T_1, T_2) between January 2023 and December 2023 in a community-based location for both intervention and control participants. Data collected included anthropometric (height, weight, waist circumference, BMI), sociodemographic (age, marital status, employment status, income, post code, ethnicity), diabetes (self-care, self-efficacy), physical activity and dietary changes, and clinical (HbA_{1c} using the DVA Vantage point-of-care HbA_{1c} kit, Siemens) data [23,25-28, 31-33]. The diabetes educator and CHWs collected anthropometric and clinical data, and the community researchers completed an online Qualtrics survey [24] using a tablet. Each participant was given a unique identifier.

Quantitative Data Analysis

Quantitative data analysis will be conducted in 2 steps. Raw data will be examined for missing entries, inconsistencies, and data entry errors. Any identified problems will be corrected by checking the data against the hard copy questionnaire. To further ensure reliability and accuracy of the data entry, the researcher will randomly re-enter 10% of the collected data and compare the 2 files [34].

Data are analyzed using SPSS 24 (IBM Corp), and missing data, outliers, normality, and multicollinearity will be examined using procedures outlined by Pallant [34,35]. Methods of data analysis will include descriptive, bivariate, and logistic regression analyses. The levels of statistical significance will be set at P=.49 to reduce the risk of type 1 errors [34]. The analyses will identify changes in the primary and secondary outcomes from baseline to week 12 and week 24 for Māori and Pasifika women with type 2 diabetes who completed the intervention. Descriptive statistics will examine participants' baseline measures and characteristics and will also explore trends in the data over time. Means (SDs) will be reported for continuous variables, and percentages and frequencies will be reported for categorical variables. Independent *t* tests will be used for continuous variables, and chi - square tests for categorical variables will be used to compare mean groups. Normality of the included variables will be evaluated using the Shapiro - Wilks normality test, and a nonparametric test (Mann - Whitney *U* test) will be used if data are not normally distributed to detect differences between groups. A 2 - sided P=.49 will be considered significant for all analyses [34,35].

The study will also provide initial parameter estimates for the primary endpoint, from which sample size calculations can be performed to determine sufficient power for the main trial. The primary endpoint between group differences at 12 and 24 weeks will be estimated using a linear mixed model with a treatment-time interaction. Although aiming for an intention-to-treat analysis, we recognize there were withdrawal from the study. A prespecified multiple imputation model will be used to obtain intention-to-treat estimates. Sensitivity analyses will explore the impact of nonignorable missing data. Analysis of secondary endpoints will follow the same approach in which changes will be compared between intervention and control groups using linear mixed models.

Process Evaluation

The process evaluation includes satisfaction surveys and a talanoa focus group involving the intervention and control participants to evaluate the feasibility of the program. This includes evaluating the training of Pasifika CHWs, community researchers, and the project team; types of delivery (in person and online or virtual for education sessions); whether core messages through text messaging reinforces a positive mindset and behaviors; the talanoa approach via online and in-person delivery of the intervention; shared understanding and core messages across the project team including CHWs, community researchers, and the workshop facilitator; and satisfaction with the program assessed at T_1 and T_2. In addition, we will capture where the participants heard about the program, if accessibility to the program was easy, some of the challenges with the program, and what the participants would change about the program.

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Qualitative Outcomes

Qualitative data were collected using a talanoa focus group to gather information about the participants' experiences with the program and its acceptability, usefulness, barriers and enablers to participation, feasibility of time commitment, burden, and cultural relevance. Data gathered will explore time taken to complete data surveys, strengths and weaknesses of the intervention, perceptions of the digitally delivered sessions, and any suggested improvements to the study design or intervention as well as whether control participants had heard about the program, spoken to the intervention participants, and the influence of this on their participation.

Qualitative Data Analysis

Talanoa focus groups were conducted in a community setting, facilitated by community researchers and the principal researcher using a guide co-developed with the AC. The talanoa discussions, which lasted 90 minutes, were audio-recorded using a digital recorder and transcribed verbatim for analysis [20]. The trained community researcher took detailed notes using the guide. Immediately after the talanoa focus group session, the notetaker and community researcher summarized and prepared debrief notes that highlighted key points from the group. These were presented back to the focus group. The participants were also given the opportunity to read a copy of what they said and make any changes [20].

NVivo software will be used for data management and manual coding or identifying recurring keywords and phrases to ascertain measurement burden, acceptability, potential translation, and ease of intervention access. Co-analysis using inductive and deductive approaches will involve participatory talanoa processes with the Pasifika community researcher and participants iteratively [19,20]. The key themes from the co-analysis will be collated and presented to the AC for discussion. Patterns of meanings and interpretations during the analysis processes will be further deliberated by the AC to ensure community and cultural contexts are considered. Participants will be given progress feedback of the results and study outcomes. Giving feedback will be an integral part of the participatory research cycle in which the participants will have the opportunity to construct, reconstruct or retell, and reflect on the stories of their experience in the pilot program including both positive and negative feedback. A copy of the result findings and action outcomes will be disseminated to the participants, health providers, community organizations, and research team.

Results

Pilot Program

The pilot program began in February 2023 with 50 participants who were enrolled between January 2022 and January 2023. For the intervention group, 35 women were recruited, and there were 10 dropouts, resulting in 25 women in the intervention group. For the control group, 27 women were recruited, and there were 2 dropouts, resulting in 25 women in the control group.

Data were collected from January 2023 to December 2023. Methods of quantitative data analysis will include descriptive, bivariate, and logistic regression analyses. The focus group was conducted in November 2023, and the results are being analyzed using an inductive-deductive approach. Film and digital story production are underway and expected to be complete in April 2024. Data analysis is planned to occur from March 2024 to July 2024.

Importance of the Results

The study participants in the intervention and control groups are from diverse Pacific cultural backgrounds and include Fijians, Fiji Indians, Samoans, Māori, Tongans, Cook Islanders, and those who identify with more than one cultural group. The anticipated results from the quantitative and qualitative analyses would highlight the relevance that culturally co-designed programs could lead to improved diabetes self-care outcomes including clinical HbA_{1c} levels, positive changes in body composition measurements such as BMI and waist circumference, and enhanced diabetes self-care scores within the intervention group.

Dissemination Plan

Results are expected to be published as early as December 2024 and extend through July 2025. The study findings will be disseminated through presentations at state and national meetings (eg, Queensland Women's Health Forum, Australian Public Health), international meetings and conferences (eg, the International Diabetes Congress), and publication in peer-reviewed journals. In addition, we will work closely with Māori and Pasifika community partners to identify strategies to disseminate study findings in the community through community talanoa forums and meetings. Other social media network platforms and local community radio will be used to disseminate the study findings.

Discussion

Type 2 diabetes is a costly, rapidly growing, and largely preventable disease. Encouraging healthier lifestyles in Māori and Pasifika women with type 2 diabetes could potentially improve the health and well-being of women, prevent complications, and reduce health expenditure.

This paper describes the protocol of a quasiexperimental pilot study based on a culturally co-designed whānau-centered intervention for Māori and Pasifika women living with type 2 diabetes in Queensland, Australia [15]. The study consists of 2 arms (intervention and control) to trial a 12-week intervention followed by a 12-week follow up-period delivered by trained Māori and Pasifika health professionals and CHWs.

This study will report the clinical benefits of the intervention and will target improvements in HbA_{1c} and diabetes self-care including diet, physical activity, medication management, and routine health checks for Māori and Pasifika women with type 2 diabetes. Community-based interventions among Australian Samoans in Sydney, Australia, showed a reduction in HbA_{1c} [36], which would be promising for our study. Studies with Māori and Pasifika have shown that using community-based approaches and culturally tailored interventions are likely to

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improve health behaviors [37,38]. The qualitative data from the focus groups will inform measurement burden, acceptability, potential translation, and ease of intervention access, which has not been evaluated in other community-based studies with Māori and Pasifika communities in Australia. The potential for success of the proposed intervention will be examined using accessibility, acceptability, uptake, sustainability, adherence, participants' perceptions of measurement burden, effectiveness of the recruitment strategy and retention, and the participants' overall experience, based on women's wellness resulting from type 2 diabetes programs [16]. This will inform the program's cultural adaptability, acceptability, and feasibility for future studies.

This study recruited 50 Māori and Pasifika women with type 2 diabetes through community-led participatory approaches and with the input from the AC to ensure that the protocols of engagement with the community, recruitment of participants, and implementation and evaluation of the program were community-driven and culturally appropriate [20-22] Interventions that are specifically co-designed with communities ensure cultural relevance, effectiveness, and sustainability for addressing chronic conditions such as type 2 diabetes [22,39]. Equally important is the community-led participatory approach that embeds Māori and Pasifika cultural values within program design and implementation, which is pivotal to engaging and empowering communities to successfully improve health behaviors, particularly when tackling type 2 diabetes [21,22,39]. Developing health and lifestyle programs within communities and partnering with stakeholders including health services, governmental and nongovernmental organizations, and academic institutions have been shown to be essential to empowering underserved populations, particularly as the programs aim to understand and support behavioral changes leading to better health and well-being outcomes [21,22,38,40]. This program supports the participants in developing knowledge and practical skills for preventing and managing type 2 diabetes as well as overcoming challenges that participants and their families may face in living a healthy life [21]. As a result, this has enabled the production of 5 digital stories of women from diverse Pasifika backgrounds in the intervention, documenting their experiences and journeys, which will be used as a health promotion resource for the program in future studies.

Despite these strengths, this pilot study has limitations. One inherent limitation is the potential for cross-communication. Due to the close nature of the included communities, it is likely that they will speak to each other regarding the program. For this reason, the intervention and control groups were allocated based on geographic location to attempt to minimize this. The sample size is too small to assess the extent to which the metabolic improvements are due to self-management (eg, lifestyle change) or clinical management and may also result in nonsignificant ($P<.05$) results for some of the measurement outcomes. In addition, community-based studies are difficult to conduct in a rigorous randomized controlled trial (RCT) design without significant funding, for which pilot data are important to inform study design, including power calculations [36]. However, this study was undertaken as a pilot study to provide a proof of concept prior to undertaking a stepped-wedge RCT or multicenter RCT. Regardless of this, the outcomes of this pilot study will provide valuable information regarding culturally appropriate implementation and evaluation. The lessons learned in this pilot trial will help us to plan the larger trial with regard to recruitment strategies, intervention implementation, and data collection. The evidence-based synthesis of findings with community participants and researchers, including dissemination of the pilot study outcomes, will have future applications aimed at leading to larger studies implementing a state or nation-wide program and undertaking translation research with the potential to develop innovative digital or virtual delivery of the program with a health data collection interphase, website platform for virtual delivery, and use of a mobile app.

In conclusion, this study provides a blueprint for PWDWP and proposes a model for evaluating intervention efficacy and effectiveness in partnership with Māori and Pasifika community organizations and key stakeholders in southeast Queensland, Australia. The study findings will have significant implications for policy makers and practitioners when implementing a diabetes management program for Māori and Pasifika communities, emphasizing the need for culturally relevant interventions. Collaboration with communities and stakeholders is crucial when developing diabetes management and lifestyle programs, particularly for communities with unique cultural nuances. The findings of this study may suggest a potential model for addressing health disparities in other culturally and linguistically diverse populations.

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We would like to thank the Māori and Pasifika women with type 2 diabetes; the advisory committee members, many of whom are elders and leaders within their communities; and the Pasifika health workers for their dedication, time, and commitment to the design of this study protocol.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

The authors fulfil the criteria for authorship by contributing to the planning, development, and writing of the protocol for this study. HA is the principal investigator, and DG is the co-investigator. HA and DG drafted the preliminary protocol, ethics application, and trial registry. HA, WN, and DG contributed to the design of the study protocol. HA and WN provided Pasifika cultural oversight. MC drafted the initial paper for publication with input and advice from HA. All authors contributed to the writing of the paper, and all have read and approved the final manuscript.

Conflicts of Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and publication of this paper: DG is currently funded by the Queensland Children's Hospital Foundation via a philanthropic grant from Woolworths. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Peer Reviewed RR1 Registered Report.
[PDF File (Adobe PDF File), 111 KB - resprot_v13i1e55435_app1.pdf]

Multimedia Appendix 2
SPIRIT PROTOCOL Checklist.
[DOCX File , 21 KB - resprot_v13i1e55435_app2.docx]

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Abbreviations

AC: advisory committee
CHW: community researchers
HbA1c: glycated hemoglobin
PICTs: Pacific Island Countries and Territories
PWDWP: The Pasifika Women's Diabetes Wellness Program
QUT: Queensland University of Technology
RCT: randomized controlled trial
T0: baseline
T2: week 24

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Protocol

Inhibitory Control Training for Anxiety and Math Achievement in Primary School Children: Protocol for a Proof-of-Concept Study

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Abstract

Background: Cognitive control training (CCT) has shown potential to reduce emotional vulnerability in adults and adolescents. However, there is scant literature testing the efficacy of CCT for the reduction of anxiety and transferring the effects to educational outcomes in children. Building on the evidence that a greater ability to suppress a prepotent response (inhibitory control) is associated with higher math achievement in children, it is plausible that training inhibitory processes using a CCT paradigm may be beneficial for reducing anxiety, improving inhibitory control, and in turn increasing math achievement.

Objective: This proof-of-concept study aims to investigate the efficacy of 15 sessions of inhibitory control training for reduction in anxiety and improvement in math achievement in primary school children.

Methods: We will use a 2 (group: CCT, adaptive Go/No-Go vs active control, low-load task) multiplied by 4 (time: pre- vs posttraining vs 1-month vs 3-month follow-up) randomized design in a nonselected sample of 100 children aged 8-10 years. Both groups will complete 10 minutes of daily training for 3 weeks at school. The dependent variables will be anxiety and correlates (Spence Children's Anxiety Scale, Penn State Worry Questionnaire for Children, Revised Children's Anxiety and Depression Scale, Child Response Style Questionnaire, and Modified Abbreviated Math Anxiety Scale), inhibitory control (Go/No-Go task), shifting (color-shape shifting task), updating (*n*-back task), and math achievement (Applied Problems, Calculation, and Math Facts Fluency subtests from the Woodcock-Johnson IV Tests of Achievement).

Results: We opened enrollment in September 2023. The initial results are expected to be published in late 2024. We predict that children in the CCT group will show a reduction in emotional symptoms; improvements in inhibition, shifting, and updating performance; and advances in math achievement from pre- to posttraining, and that these effects will be maintained at 1- and 3-month follow-ups, compared to children in the active control group.

Conclusions: The CCT paradigm used in our study will provide a greater understanding of the emotional and cognitive transfer effects on children and inform future work. Specifically, the findings will advance the knowledge of deploying inhibitory control training with children and provide valuable insights into its use for reducing anxiety and advancing math achievement.

Trial Registration: Open Science Framework ofs.io/de2qa; https://doi.org/10.17605/OSF.IO/DE2QA

International Registered Report Identifier (IRRID): PRR1-10.2196/52929

(JMIR Res Protoc 2024;13:e52929) doi:10.2196/52929

KEYWORDS

cognitive control training; anxiety; inhibitory control; math achievement

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Introduction

Overview

Anxiety is the most reported mental health problem in young people across and beyond the pandemic [1,2]. Childhood anxiety is associated with excessive worry, avoidance, physical symptoms, and severe social and academic problems [3]. Interventions for anxiety in children are typically expensive to administer (eg, 1:1 psychological therapy) with long waitlists to see providers in the public health system. Hence, there is a need for novel approaches to closing the treatment gap, that is, reducing the discrepancy between the percentage of children with mental health problems and the percentage who receive treatment [4]. The focus of this proof-of-concept study is treating childhood anxiety by targeting the modifiable cognitive processes that underpin emotional symptoms. We will deliver an intervention at school as part of regular classroom routines and examine its efficacy in reducing anxiety and improving cognitive and academic outcomes (more specifically, math achievement).

Research has shown that the ability to control the focus of one's attention (attentional control or cognitive control) is vital to learning and requires top-down cognitive processes to coordinate thoughts and behaviors to achieve a goal [5]. Attentional control theory [6] proposes that anxiety upsets the balance between the top-down (goal-driven) and bottom-up (stimulus-driven) attentional processes such that it is associated with increased activation of the stimulus-driven system (ie, attention to internal and external stimuli) and decreased influence of the goal-directed system (ie, attention to task demands). Furthermore, attentional control theory posits that highly anxious individuals direct their attention toward potentially threatening information (eg, worrisome thoughts) which in turn reduces the ability to perform ongoing tasks. The theory suggests that the cognitive processes or executive functions most affected by anxiety are inhibitory control, which requires inhibiting distractors and withholding a dominant response, shifting, which entails switching between tasks or demands of a task, and updating, which requires monitoring and updating information in working memory; see Miyake et al [7]. For example, an anxious child might direct their attention to emotional thoughts and be unable to inhibit distracting worries such as "this work is too hard" or "I might fail" and have difficulty shifting their focus back to the task at hand, and when new information is presented requiring them to update their working memory, the demands of controlling attention are borne out in poorer task performance.

There is growing empirical support for targeting or training the cognitive processes most vulnerable to anxiety (ie, inhibitory control, shifting, and updating) and reducing emotional symptoms in adults [8-12] and adolescents [13]. These paradigms are known by the umbrella term, cognitive control training (CCT) or if directly targeting the inhibitory control function, inhibitory control training. A small number of CCT studies have been conducted with children. Results from a systematic review [14] highlighted that of the 8 studies that showed promise for CCT to reduce anxiety only 2 were conducted with primary school-aged children (younger than 12 years of age). Bigorra et al [15] used commercial working memory training with children of 7-12 years with attention-deficit or hyperactivity disorder (ADHD) and behavioral difficulties and Shanok et al [16] used inhibitory control training with typically developing children aged 8-12 years. Both studies reported reduced anxiety in combination with improved cognitive performance (working memory and inhibitory control, respectively); however, neither study examined the transfer of these effects to educational outcomes.

Research in math achievement in school students supports the importance of cognitive control on executive functioning. For instance, Bull and Lee [17] suggest that during math problem-solving, inhibitory control is needed to suppress unwanted information or inappropriate strategies or prepotent number representations, shifting is required to switch math operations within and between more complex problems, and updating is vital for holding and monitoring information in working memory. However, age-related variances in the development of executive function need consideration, particularly as math skill requirements change across the school years [17]. Updating is associated with math achievement in preschoolers [18] and inhibitory control and shifting have also been implicated in early math skill variability [19]. In primary school children, nonetheless, inhibitory control has been shown to be vital for math achievement [20]. Given that the development of executive functioning increases rapidly in the early years of schooling [19,21] and attenuates in adolescence [22], it is plausible that targeting inhibitory control in children aged 8-10 years may serve to boost math performance at a critical time point. The focus of this study is to use a CCT paradigm to reduce anxiety, improve inhibitory control and in turn, math achievement.

This Study

This proof-of-concept study will examine the effect of inhibitory control training in typically developing children aged 8-10 years. We will compare emotional symptoms (indexed using self-reported scales of anxiety and correlates), inhibitory control, shifting and updating skills (assessed using computerized tasks), and math achievement (measured using standardized math tests) of children completing 15 sessions of daily inhibitory control training versus an active control task from pre- to posttraining and at 1- and 3-month follow-ups. The study will be conducted in year 4 and 5 classrooms. This study aims to determine whether 10 minutes of daily inhibitory control training for 3 weeks can reduce anxiety (and correlates) and improve math achievement and whether any changes are maintained 1 and 3 months after training.

Methods

Ethical Considerations

The University of Queensland Human Research Ethics Committee provided approval to conduct this research (2023/HE000462). Gatekeeper approval was also received from participating education departments and schools. Parent consent and child assent will be gained prior to participation. The trial was registered on the Open Science Framework (ofs.io/de2qa).

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Study Design

We will use a 2 (group: CCT, adaptive Go/No-Go vs active control, low-load task) multiplied by 4 (time: pre- vs posttraining vs 1-month vs 6-month follow-up) randomized design (see Figure 1). Children in both the CCT and active control groups will train for 10 minutes each day for 3 weeks (15 sessions) as part of their daily classroom routine. Changes in the dependent variables (anxiety, worry, depression, rumination, inhibitory control, shifting, updating, and math achievement) will be examined pre- to posttraining, and compared to 1- and 3-month follow-up.

Figure 1. Study flowchart.

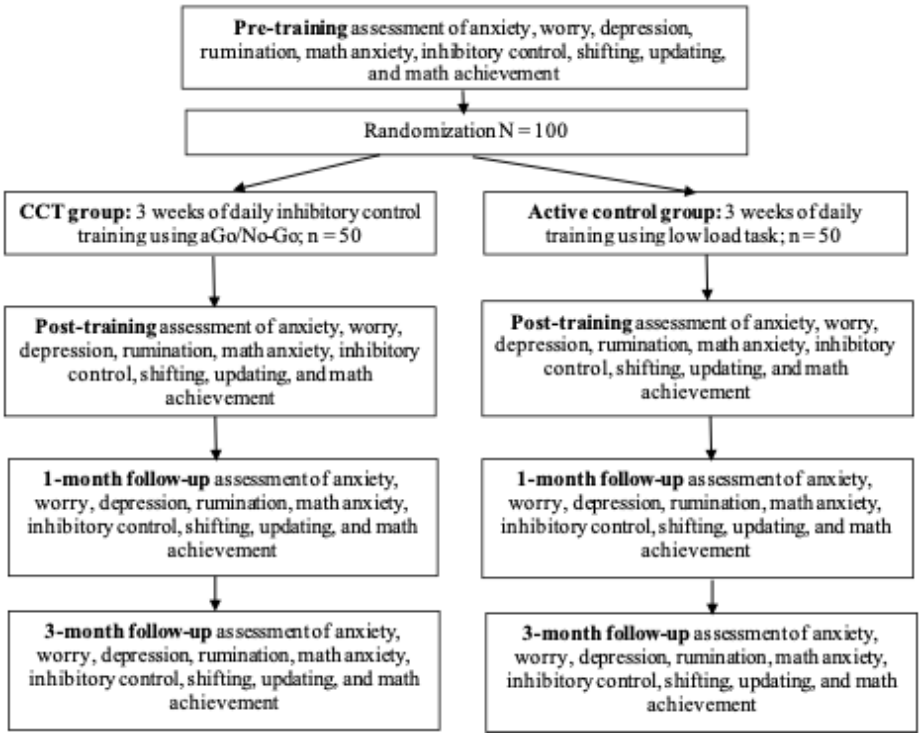

Participants

A nonselect sample of children aged 8-10 years will be recruited from primary schools. An a priori power analysis revealed that 66 participants are required to detect small effects (d=0.20) approaching those reported by previous studies with 80% or greater power on primary outcome measures relative to controls [9,23,24]. To allow for approximately 30% attrition we will recruit 100 children proportionately balanced for sex and age across 8, 9, and 10 years. To incentivize enrollment and study completion, participating children will be compensated using monetary tokens redeemed at the end of the study; Aus $ 2.00 (US $1.31) for the completed questionnaires at each of 4 time points and Aus $ 2.00 (US $1.31) for each training session (~Aus $ 40.00; US $26.14 per participant). Given that teachers are required to supervise and monitor the daily training, they will be incentivized for their class's participation (minimum 20 students) at the rate of 1 teacher relief day for each data collection time point (pre- and posttraining and 1- and 3-month follow-ups).

Primary and P-12 schools, as well as private, independent, and Catholic schools, will be approached regarding participation in the study. A recruitment package of materials (including a university ethics approval letter, gatekeeper permission request, pamphlet, study protocol, participant information sheets for parents, teachers and children, consent forms, and an information sheet about children's anxiety and depression) will be sent to the school principal to determine interest in participation. Information sessions will be held face-to-face or using a video communications platform (eg, Zoom) for principals, teachers, and parents, as required.

Measures and Tasks

Anxiety

Anxiety will be measured using the Spence Children's Anxiety Scale [25], a self-report assessment of specific anxiety symptoms in children aged 8-11 years, categorized as social phobia (6 items), panic or agoraphobia (9 items), generalized anxiety (6 items), obsessive-compulsive (6 items), separation anxiety (6 items), and physical injury fears (5 items). Children respond using a 4-point Likert scale from 0=never to 3=always. Anxiety symptoms will be examined separately (eg, social phobia, and separation anxiety) in addition to the inspection of change in an overall anxiety score calculated by summing the 38 items. Higher scores represent higher symptoms of anxiety.

Worry

Worry will be assessed using the Penn State Worry Questionnaire for Children [26], a 14-item questionnaire that measures the tendency to engage in excessive, generalized, and uncontrollable worry in children aged 7-17 years. Items are rated on a 4-point Likert scale from 0=never to 3=always. Total worry scores are calculated (after reversing 3 items) by summing the scores on all items and range from 0 to 42; higher scores represent a greater tendency to worry.

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Depression

Depression will be indexed by the Low Mood subscale from the Revised Children's Anxiety and Depression Scale [27], a self-report assessment of symptoms of major depressive disorder in children aged 8-18 years. The low mood subscale includes 10 items and children respond using a 4-point Likert scale from 0=never to 3=always. Total scores range from 0 to 30 with higher scores indicative of lower mood.

Rumination

The rumination subscale from the Child Response Style Questionnaire [28] will be used to capture repetitive negative thinking or rumination. Children respond to 13 items on a 4-point Likert scale from 0=almost never to 3=almost always. Total scores range from 0 to 39 with higher scores representing greater rumination.

Math Anxiety

The Modified Abbreviated Math Anxiety Scale [29] will be used to assess math anxiety. The 9-item self-report measure comprises 2 subscales, math evaluation anxiety (4 items), for example, thinking about a math test the day before you take it, and math learning anxiety (5 items), for example, starting a new topic in math. Children respond to statements asking how anxious they would feel during certain situations involving math using a 5-point Likert scale from 1=low anxiety to 5=high anxiety.

Inhibitory Control

A standard (ie, nonadaptive) Go/No-Go Task [30] will be used to measure inhibitory control. The Go/No-Go Task requires children to view visually presented stimuli and inhibit a dominant response based on instructions, for example, press the spacebar when they see a particular target (go) but do not press the spacebar when they see a different target (no-go). The task captures accuracy and reaction time (RT).

Shifting

The Color Shape-Shifting Task [31] will be used to assess shifting performance. In this task, children are presented with some colored shapes and are required to sort the stimuli by shape or color, as fast as they can. Children are given letter cues; for example, *S* for shape and *C* for color before each stimulus appears to indicate the characteristic to focus on. The task captures accuracy and RT.

Updating

The *n*-back Task [32] will be used to index updating performance. The task requires children to monitor letters presented in blocks of increasing difficulty (ie, *n*) and indicate when presented with a letter seen on the previous trial (1-back), after 1 intervening trial (2-back), or after 2 intervening trials (3-back). Difficulty increases with the number of intervening trials. Children indicate the same or different with a keyboard button press based on the letter 1-, 2-, or 3-back from this letter. The task captures accuracy and RT.

Math Achievement

A total of 3 subscales from the Woodcock-Johnson IV Tests of Achievement [33] will be used to assess math achievement, namely, Applied Problems, Calculation, and Math Fact Fluency. Administration and scoring will be consistent with the authors' manual. To avoid measurement error due to the practice effects, different test forms will be used at each data collection point.

Training Groups

We will randomly assign participants to 1 of the 2 training groups. Groups comprise an experimental CCT group that will train using an adaptive Go/No-Go Task (aGo/No-Go) targeting inhibitory control, and an active control group that will train using a low-load task. The active control task does not require the same cognitive load as the aGO/No-Go task; thus, we do not expect it to produce emotional or cognitive changes. Children in both groups will undertake 10 minutes of training per day for 3 weeks, allowing 15 sessions to be completed.

Inhibitory Control Training

The aGo/No-Go task requires participants to focus on desired cues related to a continuous stream of blended stimuli and press the spacebar when the desired cue appears and withhold a response when it does not appear (as per Go/No-Go). The adaptive nature of the task adjusts to the child's performance such that if the child is doing well, the task reduces the time for responding, whereas if the child is having difficulty the task allows more time for responding, thus positively reinforcing success.

Active Control Training

The low-load task presents children with a continuous stream of blended stimuli and requires them to identify target items.

Equipment and Procedure

All assessments and training will be completed on iPads (9th generation, iOS 16, 64GB; Apple Inc) specific to this project. Self-report symptom scales will be hosted on a computer-based survey platform (Qualtrics) such that the participating children can complete them under the supervision of their classroom teacher, during class time. Inquisit cognitive tasks will be deployed (retrieved from Millisecond Test Library). Math achievement tests will be administered 1:1 in a quiet room by the research team. Daily training of the aGo/No-Go and 1-back will be conducted using a computer-based experiment builder (Gorilla Experiment Builder) and include some minor gamification features to improve motivation and engagement. Training will be completed under the supervision of the classroom teacher.

Data Analytic Plan

Mixed between-within ANOVA will be used with Group (CCT, aGo/No-Go vs active control; low-load task) as the between-subjects factor and time (pre- vs posttraining vs 1- vs 3-month follow-up) as the within-subjects factor. Separate tests will be conducted with the emotional symptom scores, cognitive measures (ie, accuracy and RT), and math achievement scores as dependent variables. Intention-to-treat analyses will be used to account for missing data, as appropriate. Descriptive and inferential statistics will be performed using SPSS (IBM Corp). We will apply Bonferroni corrections to follow-up tests to control for type 1 error.

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Results

Recruitment and testing opened in September 2023 and will continue for 12 months. We will begin analyzing our data on the completion of the data collection, and the publication of results is expected by the end of 2024.

Discussion

This study will examine the effect of inhibitory control training on anxiety and math achievement in children aged 8-10 years, relative to an active control condition. We predict children in the CCT group will report reduced emotional symptoms (anxiety, worry, depression, and rumination) and demonstrate improved inhibitory control, shifting, updating, and math achievement when comparing pre- to posttraining, 1-, and 3-month follow-up, relative to controls. Results will inform whether inhibitory control training affords promise as an intervention for anxiety in this age group and advance knowledge of factors affecting math achievement. These findings would provide a foundation for the development of a training app that has the capacity to reach those not well-served, be delivered on large scale for low cost, and afford the possibility of administration across a wide range of settings [4].

This research has several limitations worth noting. We realize using a small sample of children aged 8-10 years means we may not be able to generalize our findings to a larger population or a broader age group. However, pending our results, we aim to replicate our work using a larger cohort and a randomized control design. There are constructs outside the scope of this project. For example, our design will be unable to determine whether inhibitory control training affects other educational outcomes, especially language and reading, which are linked to math achievement. With these potential shortcomings in mind, we hope this work becomes the catalyst for other research using CCT paradigms with children.

Acknowledgments

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Data Availability

Data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

EE and KLC conceptualized the project with the involvement of AC. KLC prepared the first draft and EE read and edited further versions. All authors participated in writing and reading drafts and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviews.
[PDF File (Adobe PDF File), 55 KB - resprot_v13i1e52929_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
aGo/No-Go: adaptive Go/No-Go
CCT: cognitive control training
RT: reaction time

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Protocol

The Effectiveness of Brain Injury Family Intervention in Improving the Psychological Well-Being of Caregivers of Patients With Traumatic Brain Injury: Protocol for a Randomized Controlled Trial

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Abstract

Background: Globally, traumatic brain injury (TBI) is recognized as one of the most significant contributors to mortality and disability. Most of the patients who have experienced TBI will be discharged home and reunited with their families or primary caregivers. The degree of severity of their reliance on caregivers varies. Therefore, the task of delivering essential care to the patients becomes demanding for the caregivers. A significant proportion of caregivers expressed considerable burden, distress, and discontentment with their lives. Therefore, it is critical to comprehend the dynamic of TBI and caregivers to optimize patient care, rehabilitation, and administration. The effectiveness of the Brain Injury Family Intervention (BIFI) program tailored for caregivers of patients with TBI has been widely proven in Western countries. However, the impact is less clear among caregivers of patients with TBI in Malaysia.

Objective: This study aims to assess the effectiveness of BIFI in reducing emotional distress and burden of care, fulfilling the needs, and increasing the life satisfaction of caregivers of patients with TBI at government hospitals in Malaysia.

Methods: This is a 2-arm, single-blinded, randomized controlled trial. It will be conducted at Hospital Rehabilitasi Cheras and Hospital Sungai Buloh. In total, 100 caregivers of patients with TBI attending the neurorehabilitation unit will be randomized equally to the intervention and control groups. The intervention group will undergo the BIFI program, whereas the control group will receive standard treatment. Caregivers aged ≥18 years, caring for patients who have completed >3 months after the injury, are eligible to participate. The BIFI program will be scheduled for 5 sessions as recommended by the developer of the module. Each session will take approximately 90 to 120 minutes. The participants are required to attend all 5 sessions. A total of 5 weeks is needed for each group to complete the program. Self-reported questionnaires (ie, Beck Depression Inventory, Positive and Negative Affect Schedule, Caregiver Strain Index, Satisfaction With Life Scale, and Family Needs Questionnaire) will be collected at baseline, immediately after the intervention program, at 3-month follow-up, and at 6-month follow-up. The primary end point is the caregivers' emotional distress.

Results: The participant recruitment process began in January 2019 and was completed in December 2020. In total, 100 participants were enrolled in this study, of whom 70 (70%) caregivers are women and 30 (30%) are men. We are currently at the final stage of data analysis. The results of this study are expected to be published in 2024. Ethics approval has been obtained.

Conclusions: It is expected that the psychological well-being of the intervention group will be better compared with that of the control group after the intervention at 3-month follow-up and at 6-month follow-up.

Trial Registration: Iranian Registry of Clinical Trials IRCT20180809040746N1; https://irct.behdasht.gov.ir/trial/33286

International Registered Report Identifier (IRRID): RR1-10.2196/53692

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(JMIR Res Protoc 2024;13:e53692) doi:10.2196/53692

KEYWORDS

traumatic brain injury; TBI; caregiver; randomized controlled trial; psychological well-being; Malaysia

Introduction

Background and Rationale

Traumatic brain injury (TBI) is defined as any injury sustained by the head as a result of blunt or penetrating trauma, acceleration or deceleration forces [1]. It remains as a leading cause of mortality and morbidity worldwide [2]. In Malaysia, despite investment in various preventive efforts, the incidence of TBI continues to increase yearly [3]. In 2009, as many as 166,768 trauma cases were recorded in 8 hospitals in Malaysia, most cases (76.8%) being road traffic accidents [4]. A recent study reported an extremely high cost of treatment for patients with TBI in Malaysia. The estimated annual cost of treatment for 49 patients with TBI was as high as MYR 1.5 million (US $313840) [5]. In the long term, this would lead to an adverse impact on the social and economic development of the country.

The effects of TBI depend largely on the severity and location of the injury and the age and personality of the patient [1]. TBI will affect their self-care ability, employment capacity, and social functioning. Upon discharge from hospitals, most patients with moderate to severe levels of TBI would need to move back in with their families to receive the care they need [6,7]. Patients with severe TBI are unlikely to return to their previous employment as they require a significant amount of care [8]. As most of the patients with TBI are highly dependent, their caregivers are tasked with providing the necessary physical care for them. The caregivers are also constantly involved in any ongoing rehabilitation of the patients, for example, encouraging them to perform physiotherapy exercises and reminding them to take medication. Moreover, the caregivers need to deal with difficult behaviors and challenging emotional states of patients with TBI [9-12]. These extra demands can be unfavorable to the health and well-being of the caregivers.

Many studies have highlighted the importance of understanding the dynamics of TBI on caregivers. There is an extensive body of research on the effect of TBI on caregivers globally [13-22]. However, local data are scarce, as only a few studies have been conducted to assess the effects of TBI on Malaysian caregivers [23-25]. The available studies have found that most TBI caregivers in Malaysia reported high burden and poor life satisfaction as a result of caregiving activities [25]. Similarly, there is also a lack of information regarding the needs of caregivers of patients with TBI in developing countries. It was suggested that caregivers of patients with TBI should be provided a postdischarge rehabilitation program to reduce their burden as caregivers [25]. A systematic review has suggested that caregivers of patients with TBI should be prioritized in TBI rehabilitation [26], as evidence abounds on the benefits of intervention programs tailored for caregivers toward patients with TBI [27-30].

In Malaysia, there is a lack of specific or structured intervention programs focusing on the psychological well-being of caregivers of patients with TBI. Identifying caregivers at an increased risk of burden is important for preventing emotional distress and caregiver burden to improve care for both patients and caregivers. Therefore, it is important to design a proper intervention plan to improve the quality of life of caregivers of patients with TBI. Ultimately, this will result in better care and management of patients with TBI.

Conceptual Framework

This study is based on 2 major theories, namely, the Family System Theory (FST) and Cognitive Behavior Therapy (CBT) [31].

The first theory, FST, assumes that the whole family is interconnected to one another [32]. For instance, if a family member is affected by TBI, the whole family system will also be affected [31]. Patients with TBI would most likely depend on their family members for activities of daily living, routine follow-up, rehabilitation, and financial support. This would increase the burden on the caregivers. Family members would also need to look for coping resources to overcome their problems [13,33,34]. As a result of the sudden changes in the family's functioning, family members often reported a lack of coping skills, in addition to high levels of burden, anxiety, and emotional distress [17,33,35-40], thus resulting in a decrease in psychological well-being [19,41-43]. Therefore, Brain Injury Family Intervention (BIFI) incorporates family therapy techniques such as normalization and validation to assist patients with TBI and their families.

The second theory, CBT, is widely known for its use in treating various types of psychological disorders [44]. Several studies have applied CBT to provide psychological interventions to patients with TBI and their caregivers [28,45-50]. A systematic review revealed that CBT has a significant impact on improving the psychological well-being of TBI caregivers [32,45]. CBT would equip caregivers of patients with TBI with strategies to deal with psychological problems such as depression and anxiety [44]. A specific component of CBT would also be implemented in BIFI that covers important aspects such as psychoeducation, problem-solving skills, management of emotions, setting of realistic goals and expectations, and stress management.

Aims of This Study

This study aims to assess the effectiveness of BIFI in reducing emotional distress and burden of care, besides fulfilling the needs and increasing the life satisfaction of caregivers of patients with TBI in selected hospitals.

The hypotheses of this study are as follows:

1. There is a significant association between the sociodemographic and clinical characteristics of patients with TBI and the emotional distress, burden of care, needs, and life satisfaction of caregivers of patients with TBI.

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2. There is a significant difference in the mean scores of caregivers' emotional distress, burden of care, needs, and life satisfaction between the intervention and control groups before the intervention, after the intervention, at 3-month follow-up, and at 6-month follow-up.
3. The sociodemographic and clinical characteristics of the patients are predictors of the intervention outcomes.

Methods

Study Design

This is a 2-arm, single-blinded, randomized controlled trial (RCT). All participants will be randomly assigned to the intervention group or control group. Only the investigators will be aware of the treatment allocation.

Study Setting

This study will be conducted at Hospital Rehabilitasi Cheras (HRC) and Hospital Sungai Buloh (HSB). These hospitals are the main referral hospitals for patients with TBI. A specific room in each site will be used for data collection. Figure 1 outlines the study flow according to CONSORT (Consolidated Standards of Reporting Trials) 2010.

Figure 1. Research flowchart. BIFI: Brain Injury Family Intervention; TAU: treatment as usual.

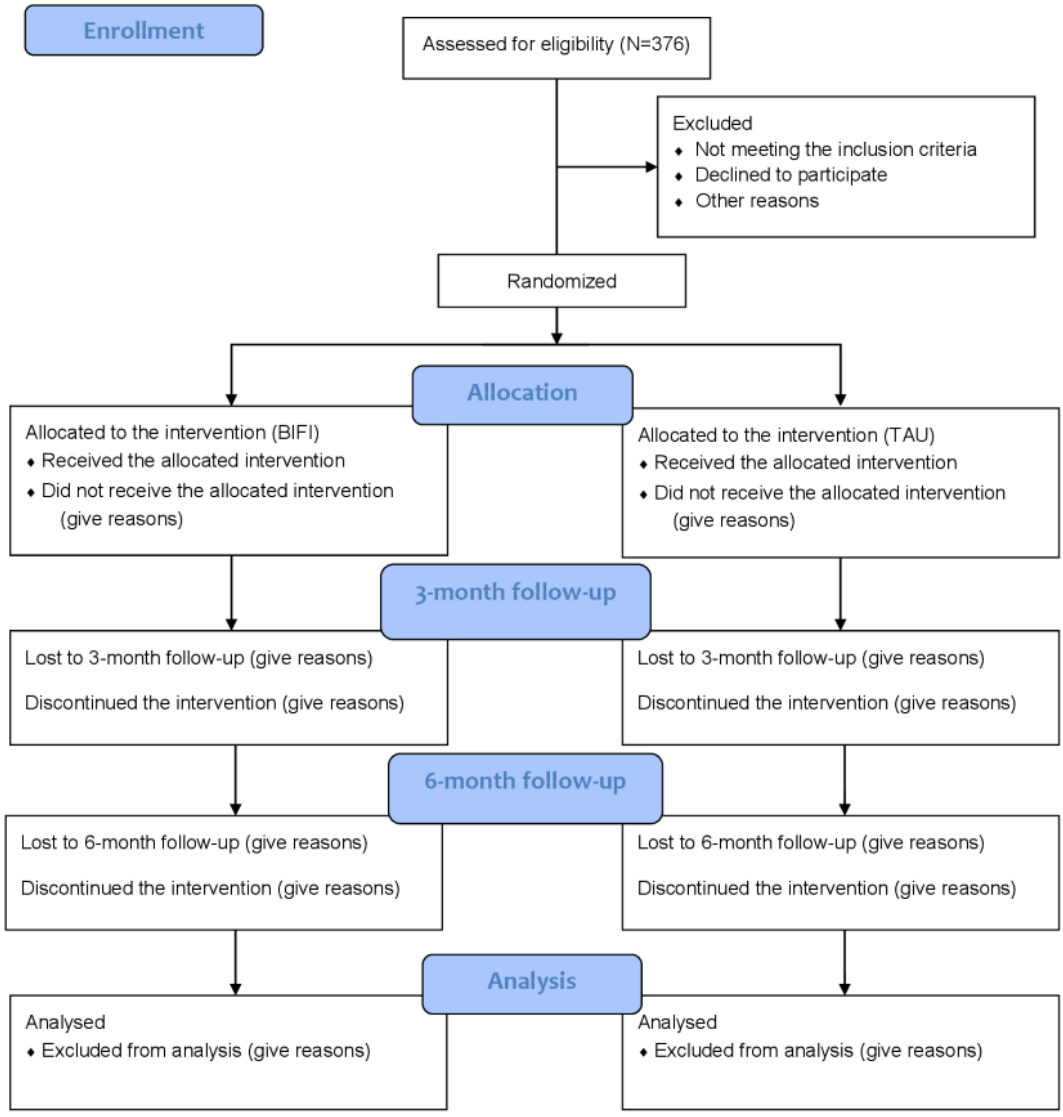

Participants

A total of 100 participants were recruited for this study. Of the 100 participants, 50 (50%) were randomly assigned to the intervention and control groups, respectively. All caregivers of patients with TBI who attend follow-up with patients with TBI at the Neuro Rehabilitation outpatient clinic of HRC and HSB were screened for eligibility to participate in this study.

Inclusion and Exclusion Criteria

To be eligible, caregivers of patients with TBI must be citizens or permanent residents of Malaysia and be aged ≥18 years, regardless of their race, ethnicity, and sex. The participants must be able to read or write in Bahasa Malaysia or English. The caregivers can be the parents, spouses, siblings, sons or daughters, or relatives of the patients with TBI. Only 1 caregiver per patient with TBI can be recruited for the program. Time

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since injury for the patient with TBI must be >3 months and time spent on caring for the patients must be at least 2 hours per day. All types of injury severity were included. However, paid caregivers were excluded.

Withdrawal Criteria

The participants may choose to withdraw at any point of time without any penalty. The participants may be withdrawn if the investigator believes that it is harmful or risky for the participants to continue.

Sample Size Estimation

Sample size estimation is based on the formula for clinical superiority trial [51]:

$$N=2x\ (Z_{1-\alpha} + Z_{1-\beta})^2 \times S^2 / (\delta-\delta_0).$$

The sample size is calculated with 80% power ($Z_{1-\beta}$=0.845) at a significance level (α) of .05, with 95% CI ($Z_{1-\alpha}$=1.96), 25% dropout rate, and medium size effect of 0.60. The parameters used in the formula will be based on a previous study [45], including δ^2=9.355 (pooled SD) and depression (Beck Depression Inventory [BDI] score) $\delta-\delta_0$=5.86 (mean difference). According to the calculation, a total of 50 participants per arm will be needed for this study.

The parameter used to compute the prevalence of caregivers of patients with TBI was taken from the paper titled "Life satisfaction and strain among informal caregivers of patients with traumatic brain injury in Malaysia" [25].

Sample Size Calculation for Prevalence Studies

In this formula, n=sample size, z=z statistic for the level of confidence, P=expected prevalence, and d^2=allowable error. This formula assumes that P and d^2 are decimal values but would also hold true if they are percentages, except that the term, 1–P, in the numerator would become 100–P [52]:

$$N=Z^2P\ (1–P) / d^2$$

Percentage of caregiver's burden=57.4%, level of significance=5%, power=80%, and d=0.05:

$$N=(1.96)^2\ 0.574\ (1 – 0.574) / 0.05^2$$

$$N=376$$

This study aimed to assess eligibility for at least 376 caregivers of patients with TBI.

Allocation

Allocation Sequence Generation

Methods of random allocation are used to ensure that all study participants have the same chance of allocation to the treatment or control group. Caregivers of patients with TBI who are eligible and consent to participate will be number coded before randomization. A simple random sampling method using computer-generated random sampling will be used to assign participants to the intervention group or control group. The procedure would be performed by following the 1:1 allocation format. Randomization will be performed by the principal investigator. All participants will have equal chance of being assigned to the intervention or control group.

Contamination Bias

To minimize contamination bias, the intervention program will be conducted outside their follow-up clinic time. The intervention program will be conducted at the seminar room of the designated hospitals. Participants are strongly encouraged not to disclose the program materials or discuss them with other caregivers of patients with TBI outside the program.

Blinding

The method of blinding in RCT is used to ensure that there are no differences in the way in which each group is assessed or managed and therefore minimize bias. In this study, only the principal investigator is aware of the treatment allocated to the participants.

Statistical Analysis

Data analysis will be performed using SPSS software (version 24.0; IBM Corp). Descriptive statistics will be used to describe the characteristics of participants. Continuous data will be reported as means and SDs or as medians and IQRs. Categorical data will be reported as percentages and frequencies. The comparison of the means between the 2 groups will be performed using a paired samples 2-tailed *t* test. In addition, 1-way ANOVA and repeated measure ANOVA will be conducted to identify any significant differences in mean scores of emotional distress (BDI), caregiver's needs (Family Needs Questionnaire [FNQ]), burden of care (Caregiver Strain Index [CSI]), and life satisfaction (Satisfaction With Life Scale [SWLS]) before the intervention, after the intervention, at 3-month follow-up, and at 6-month follow-up between the intervention and control groups. Multivariate regression analysis will be used to determine the predictors of intervention outcomes.

The intention-to-treat analysis will be performed accordingly. Assumptions of normality and homogeneity of variance will be conducted and adjusted where necessary.

Program Assessment and Translation

The BIFI manual has undergone several stages of thorough forward and backward translation, content review, and revision by a panel of local experts. The expert panel included 2 clinical psychologists, 1 certified translator (psychology content translator), and 2 rehabilitation physicians. All the panels had experience with working in the related fields for >5 years.

On the basis of the experts' feedback and comments, a few changes were made to the module. The first change was the use of a more simple Malay language. The second change was related to the pictures used in the material. The experts suggested changing to universal pictures, so that they can be adapted locally.

The final product of the manual was revised to match the local population and to ensure the intervention's fidelity.

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Pilot Study

A pilot study was conducted to assess the feasibility of the BIFI program among caregivers of patients with TBI in Malaysia. In total, 10 caregivers of patients with TBI participated, and only 8 (80%) managed to complete all 5 sessions. A caregiver withdrew owing to work commitments and another withdrew owing to personal issues. Challenges included (1) punctuality of the participants, (2) duration of the sessions, and (3) homework material.

Overall, participants were satisfied with the content and delivery of the program. Some suggested to increase the duration of the sessions and to reduce the amount of homework given. All feedback was taken into consideration, and slight alterations were performed to accommodate the participants and the program.

Intervention

BIFI will be the main intervention tool. It is a structured intervention module specifically for patients with TBI and their caregivers, developed by Professor Dr Jeffry Kreutzer and colleagues from Virginia Commonwealth University, United States. This module is based on CBT [44] and FST [53].

This module consists of several objectives: (1) providing patients and caregivers with fundamental information about brain injury, (2) helping caregivers to better understand the effects of brain injury, (3) teaching patients and caregivers about problem-solving skills, (4) teaching coping strategies, (5) recognizing progress and personal strengths and helping them to access community and professional resources, and (6) teaching effective communication skills.

BIFI was designed to be implemented in 5 sessions, with 90 to 120 minutes for each session. In total, 2 or 3 topics will be covered in each session. Using a standardized and family-focused intervention, BIFI was found to be beneficial for caregivers of patients with TBI both immediately and at 3 months after the intervention [31,54,55]. Furthermore, another study also showed that patients with TBI and caregivers reported high ratings of helpfulness, goal attainment, and satisfaction regarding the BIFI program [55].

Several measures will be taken to ensure that all participants comply with the intervention program. The program would also be conducted during weekends to accommodate the schedule of caregivers of patients with TBI. They are also allowed to choose any day during weekends at their convenience. However, they are required to complete all 5 sessions within the stipulated time frame.

Control Group

The control group or treatment-as-usual group will not receive any additional treatment during the study period. Participants in the control group will receive the usual treatment at their respective hospitals. According to the Malaysian Clinical Practice Guidelines for early management of head injury, all patients who have been discharged are recommended to attend follow-up sessions at the hospital [56]. It is recommended that patients with moderate and severe head injuries are scheduled for routine clinic follow-up. However, patients with a mild head injury can be followed up via clinic visits or telephone calls. Apart from the routine follow-up, other programs tailored for patients with TBI and their caregivers are also considered as treatment as usual in this RCT. For example, the Acquired Brain Injury Rehabilitation Unit in HRC would offer a program known as “Return to Work” for suitable patients and caregivers. A similar program is also available in HSB.

Outcomes

Overview

The outcomes of this study will be assessed using self-report questionnaires at four periods: (1) baseline, (2) 5 weeks (after the treatment), (3) 3-month follow-up, and (4) 6-month follow-up. The schedule of enrollment, interventions, and assessments are presented in Table 1.

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Table 1. Schedule of enrollment, interventions, and assessments.

	Study period					
	Enrollment	Allocation	After allocation		Follow-up	
Time point	$-t_1$	0	Baseline t_1	5-week intervention t_2	3 months t_3	6 months t_4
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Randomization	✓					
Allocation		✓				
Interventions						
BIFI[a] and TAU[b]						
TAU only						
Assessments						
Sociodemographic data		✓				
BDI[c]			✓	✓	✓	✓
PANAS[d]			✓	✓	✓	✓
CSI[e]			✓	✓	✓	✓
FNQ[f]			✓	✓	✓	✓

[a]BIFI: Brain Injury Family Intervention.

[b]TAU: treatment as usual.

[c]BDI: Beck Depression Inventory.

[d]PANAS: Positive and Negative Affect Schedule.

[e]CSI: Caregiver Strain Index.

[f]FNQ: Family Needs Questionnaire.

Primary Outcomes

The primary outcome for this study is the TBI caregiver's emotional distress, which will be measured using two scales: (1) BDI and (2) Positive and Negative Affect Schedule (PANAS). The measures are described in the Methods section.

Secondary Outcomes

The secondary outcomes will include (1) burden (CSI), (2) life satisfaction (SWLS), and (3) caregiver's needs (FNQ). The measures are described in the Methods section.

Data Collection and Time Frame

Recruitment for potential participants was conducted by the rehabilitation physicians at both hospitals, who are also the coinvestigators of the study. They screened for potential participants among the caregivers of patients with TBI who attend regular rehabilitation therapy and follow-up at their clinics. These caregivers were then invited to participate in this study. If the caregiver was interested in learning more about the study, they were led to another room, where the investigator explained the study in great detail and answered any questions that the caregivers had. At this stage, a patient information sheet about the nature of the study was provided to the potential participants.

The investigator then left the room for 10 to 15 minutes to allow the caregiver to read the information and to think about whether they would like to participate in the study. If they expressed interest in participating, they were asked to sign the consent form before completing the questionnaire. The same questionnaire used at baseline will be distributed immediately after the intervention, at 3-month follow-up, and at 6-month follow-up. The questionnaire will take approximately 30 to 40 minutes to complete. Data collection was performed between December 2018 and December 2020.

Measures

BDI Questionnaire

The original version of BDI is a self-reporting questionnaire consisting of 21 items on a 4-point scale. It is assessed using a Likert scale ranging from 0 (symptom not present) to 3 (symptom very intense). The total score can range from 0 to 63. BDI is used to measure the main symptoms of depression such as mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido [57]. Respondents who scored between 0 and 9 are considered negative for depression. In contrast, those who score >9 are screened positive for depression, whereby a score between 10

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and 18 indicates mild to moderate depression, score between 19 and 29 indicates moderate to severe depression, and score between 30 and 63 indicates severe depression (60). The BDI test is widely used globally, and its content, concurrent, and construct validity have been tested. High concurrent validity ratings are detected between BDI and other depression instruments such as the Minnesota Multiphasic Personality Inventory and the Hamilton Depression Scale. Correlation rating of 0.77 was obtained between the inventory and psychiatric ratings. BDI also showed high construct validity with the medical symptoms it measures. The study by Beck and Steer [58] reported a coefficient α rating of 0.92 for patients at outpatient clinics and 0.93 for college students. BDI has been translated into the Malay language and validated for use among the Malaysian population. Internal consistency (Cronbach α) ranged from 0.71 to 0.91, and the validity of BDI-Malay was deemed as satisfactory [59].

PANAS Questionnaire

PANAS comprises 2 mood scales that measure the positive affect (PA) and negative affect (NA), respectively. PANAS is used to assess the relationship between positive and negative effects on personality traits. Each of the PA and NA scales consists of 10 items that define their meanings. Respondents need to answer 20 items on a 5-point scale that ranges from 1 (very slightly or not at all) to 5 (extremely). The total score generated will range between 10 and 50, with low scores indicating low (positive or negative) affect and high scores indicating high (positive or negative) affect. The reliability and validity of PANAS were moderately good [60]. For the PA scale, the Cronbach α coefficient was between 0.86 and 0.90, and for the NA scale, it was between 0.84 and 0.87. Over 8 weeks, the test-retest correlations were between 0.47 and 0.68 for PA and between 0.39 and 0.71 for NA. PANAS also had strong validity with other measures of general distress and dysfunction, depression, and anxiety [61]. The Malay-translated version of PANAS had Cronbach α coefficient of 0.73 [62].

CSI Questionnaire

CSI is a self-rated, 13-item questionnaire that measures strain related to care provision. It consists of 5 major domains related to employment, financial, social, time, and physical aspects. The items can be answered as yes (score=1) or no (score=0). The maximum score for the questionnaire is 13. A score >7 is categorized as “having strain,” whereas a score <7 is defined as “no strain.” There is no age limit for the individuals who could be assessed with the tool**.** CSI has been translated into the Malay language, and the Cronbach α coefficient for the 13-item CSI-Malay was 0.79, indicating good internal consistency reliability of the scale [63].

SWLS Questionnaire

SWLS evaluates the respondents’ agreement with 5 statements on overall satisfaction with life (eg, in most ways, my life is close to my ideal). It uses a 7-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), giving rise to a range of scores between 5 and 35. A score of 20 is considered the neutral point of the scale. Scores between 5 and 9 indicate that the respondent is extremely dissatisfied with life. In contrast, scores between 31 and 35 show that the respondent is extremely satisfied. SWLS is reported as having excellent internal consistency (Cronbach α=0.88) and good test-retest reliability (r=0.68). SWLS has been translated into the Malay language and validated among the Malaysian population [64,65]. The Malay SWLS has been found to have good internal consistency (Cronbach α=0.83).

FNQ Questionnaire

FNQ is a self-administered questionnaire consisting of 37 items. It was designed to determine the family needs of patients with TBI. The family members will rate the importance of each need on a scale ranging from 1 (not important) to 4 (very important). FNQ is divided into 6 areas, namely, health information, emotional support, instrumental support, professional support, community support network, and involvement with care. It has been proven to have good content and construct validity and good internal consistency Spearman-Brown split-half reliability at 0.75 [66].

Study Procedure

All the screening procedures to identify the participants based on inclusion and exclusion criteria were performed before the intervention program by rehabilitation physicians in the respective hospitals. The recruitment started in November 2018 and was continued until the required sample size was achieved. The BIFI program will be conducted in the Malay or English language depending on the needs of the caregivers. The participants in the intervention group will be divided into smaller groups of 10 people each. Each group will receive a scheduled time and date to attend the program at the hospital. The program will be conducted by the principal investigator, who is also a clinical psychologist. The clinical psychologist must at least have 5 years of experience.

At the baseline of the program (T1), all participants are required to complete the questionnaires (BDI, CSI, PANAS, FNQ, and SWLS). The same questionnaire will be distributed immediately after the intervention program (T2), at 3-month follow-up (T3), and at 6-month follow-up (T4). The average time needed to complete the questionnaire is 30 to 40 minutes. The follow-up sessions (T3 and T4) will be scheduled by the coinvestigators. The session will be conducted at the respective hospitals by the coinvestigators to prevent any bias during follow-up. The participants were also encouraged not to share the intervention materials with other caregivers until data collection is completed.

The intervention group will undergo the BIFI program. The BIFI program will be scheduled for 5 sessions as recommended by the developer of the module. Each session will take approximately 90 to 120 minutes. The participants are required to attend all 5 sessions. A total of 5 weeks is needed for each group to complete the program, and 2 groups will be scheduled every week. All the sessions will start with an overview of the topic and end with the summary and homework assignments. Participants will be required to complete the homework given according to the module. This homework will then be reviewed by the principal investigator in the subsequent session.

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For the control group that receives the usual standard treatment, the caregivers will need to complete the questionnaires at similar time points as the intervention group.

Patient Involvement

Patients were involved during the early stage of cultural adaptation of the intervention program. The patients were invited to give their comments and feedback and review all the materials. Their valuable feedback was taken into account to ensure this program is suitable to the current culture and population.

Ethical Considerations

Approval

This study has been reviewed by the Medical Research and Ethics Committee Malaysia, Ministry of Health Malaysia (NMRR 18-2253-42951). Ethics approval has been obtained from the National Medical Research Register (NMRR-18-2253-42951-IIR) for the study to be conducted at the Ministry of Health settings. Please refer to Multimedia Appendices 1 and 2 for further details of Research Ethics comments and review. The approval letter was received on December 19, 2018. The recruitment period started in December 2018 and was completed on December 18, 2020.

Compensation

All the participants in the intervention group will be given incentives for attending the intervention program and completing the questionnaires. All participants are compensated with a travel token at the baseline (MYR 25), immediately after the program (MYR 25), at 3-month follow-up (MYR 25), and at 6-month follow-up (MYR 25).

Consent

The investigator will explain the potential risks and benefits of involvement to the participants using an information leaflet before they determine whether to participate in the study. They might ask the researcher any questions they may have regarding the study before deciding whether to participate. Once the investigator is confident that they have understood the potential risks and benefits of participating, the participant will be asked to sign a consent form. The consent forms are obtained in the written format during primary data collection and secondary data analysis is allowed to proceed without additional informed consent.

Data Management

Consent forms and paper copies of the questionnaire will be stored separately in a locked filing cabinet at University Teknologi MARA. After data collection is complete, they will be transferred to a locked filing cabinet. They will be maintained by the principal investigator for 10 years according to university regulations. Data will be accessible to the researchers and anyone authorized by Universiti Teknologi MARA to conduct a research audit.

Electronic copies of the data will be maintained by the principal investigator. These electronic files will not contain any personal identifying information and will not contain the identifying code that links the paper copies of the questionnaires with the consent forms. They will be stored only on password-protected electronic devices. Once the thesis submission and other publications are completed, these files will be destroyed. The files will be accessible to the principal investigator, the research team, and anyone authorized by Universiti Teknologi MARA to conduct a research audit.

No personal identifying details, such as names and contact details, will be recorded on the questionnaire; they will appear only on the consent form. The questionnaires will be linked to the consent forms by a unique code appearing on both documents. No digital record of the personal identifying details will be maintained, and these details will not be included in the data file. The report of the findings will also not include any such details.

Dissemination Plan

The findings of this study will be published in an academic or medical journal, and they will be presented at academic conferences. Only the research team has access to the data. As with any anonymously obtained data, the participants will not be named in any of the study's reports or publications. Permission from the Medical Research and Ethics Commission will be sought before publication.

Results

The participant recruitment process began in January 2019 and was completed in December 2020. A total of 100 participants were enrolled in this study, of whom 70 (70%) caregivers are women and 30 (30%) are men. We are currently at the final stage of data analysis. The result of this study is expected to be published in 2024.

Discussion

Anticipated Findings

In this study, we will be evaluating the effectiveness of BIFI in reducing the emotional distress and burden of care, fulfilling the needs, and increasing the life satisfaction of caregivers of patients with TBI. A total of 100 caregivers were recruited in this study. Most of the caregivers are women (70/100, 70%) and the remaining are men (30/100, 30%). The age range of the caregivers was between 22 and 55 years, with a mean age of 39.85 (SD 8.184) years. Most caregivers were Malay (65/100, 65%), followed by Chinese (21/100, 21%), Indians (12/100, 12%), and other races (2/100, 2%). Initial analysis showed promising result where there was significant reduction in emotional distress among caregivers (intervention group) immediately after the program and at the 3-month follow-up as compared with the control group.

Limitations

This study also has limitations. It was observed that during the implementation of the program, most participants (90/100, 90%) requested the program to be conducted during the weekends, whereas others wanted it to be conducted during the weekdays. This was because some of them needed to arrange for the patient's care if they were to attend the program. Hence, the program was conducted during weekends and weekdays to

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accommodate their request. The participants were allowed to choose when they wanted to attend the program. Owing to this issue, the intervention program took a long period to complete.

It is also important to address that data collection was conducted during the COVID-19 pandemic. The intervention program was halted for several months owing to Movement Control Order by the Malaysian Government. Therefore, participants were hesitant to visit the research site owing to fear of contracting COVID-19; the social distancing policy exacerbated this difficulty. It is hoped that future studies might to consider implementing intervention programs over the web to ease the participants. Web-based intervention program is another emerging approach and is more suited to current trends. However, web-based intervention versus physical intervention is still debated, and more studies are needed to answer this question.

Conclusions

To the best of our knowledge, this study would be among the first to use RCT methods to assess the effectiveness of BIFI in improving the psychological functioning of caregivers of patients with TBI in Malaysia. Perhaps, this module could be incorporated into the *Return to Work* program as standard clinical care and be made available to all. It is hoped that the results will provide more knowledge and scientific evidence to improve the rehabilitation services for patients with TBI and their caregivers.

Acknowledgments

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Data Availability

The data of this study are available upon request from the corresponding author, and it is subject to approval from the Ministry of Health Malaysia and Universiti Teknologi MARA.

Authors' Contributions

SAO is the principal investigator of this study and drafted the manuscript. FM and NSZ contributed to review of the paper and content development. All authors provided written review and feedback and revised and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Research ethics comments.
[PDF File (Adobe PDF File), 172 KB - resprot_v13i1e53692_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Medical Research and Ethics Committee Malaysia.
[DOCX File , 51 KB - resprot_v13i1e53692_app2.docx]

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Abbreviations

BDI: Beck Depression Inventory
BIFI: Brain Injury Family Intervention
CBT: Cognitive Behavior Therapy
CSI: Caregiver Strain Index
CONSORT: Consolidated Standards of Reporting Trials
FNQ: Family Needs Questionnaire
FST: Family System Theory
HRC: Hospital Rehabilitasi Cheras
HSB: Hospital Sungai Buloh
NA: negative affect
PA: positive affect
PANAS: Positive and Negative Affect Schedule
RCT: randomized controlled trial
SWLS: Satisfaction With Life Scale
TBI: traumatic brain injury

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Protocol

Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Interventions that promote adaptive emotion regulation (ER) skills reduce pain in patients with chronic pain; however, whether the effects of yoga practice on chronic low back pain (CLBP) are due to improvements in ER remains to be examined.

Objective: This study will test whether the effects of yoga on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects. In this study, pain sensitization will be assessed by quantitative sensory testing and gene expression profiles to examine whether pain sensitization moderates yoga's effects on pain or whether yoga and ER abilities reduce pain sensitization, leading to decreased pain severity and interference.

Methods: For this 2-arm parallel group blinded randomized controlled trial, we will enroll 204 adults with CLBP who will be randomized to receive the yoga (n=102) or a control stretching and strengthening (n=102) intervention, which are delivered via web-based synchronous biweekly 75-minute sessions over 12 weeks. Participants are encouraged to practice postures or exercises for 25 minutes on other days using accessible prerecorded practice videos that are sent to participants digitally. Participants will be assessed at 5 time points: baseline, midintervention (6 weeks), postintervention (12 weeks), and 3- and 6-month follow-ups. Assessments of ER, pain severity and interference, pain sensitivity including somatosensory and gene expression profiles, and physical strength and flexibility will be conducted at each visit. The fidelity of the interventions is assessed using a manualized checklist to evaluate recorded group sessions to ensure consistent instructor delivery.

Results: The primary outcome will be the mean change in pain severity as measured by the Brief Pain Inventory-Short Form at 12 weeks. The primary mechanism of action is ER measured by change in the Difficulties in Emotion Regulation Scale total score. Secondary outcomes include pain sensitivity, physical strength and flexibility, pain interference, and quality of life. A mediation path analysis and series of moderated mediation path analyses will be conducted to test the study hypotheses. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025.

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Conclusions: The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain perception and pain sensitivity as well as increased quality of life in the context of chronic pain. The study findings have important implications for determining the mechanism of action for yoga and possibly other mind-body interventions as nonpharmacological therapies for pain management. The results of the study will inform the content, delivery, and measures for intervention trials involving yoga as a modality for relieving pain and improving function.

Trial Registration: ClinicalTrials.gov NCT04678297; https://clinicaltrials.gov/study/NCT04678297

International Registered Report Identifier (IRRID): DERR1-10.2196/56016

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KEYWORDS

chronic low back pain; clinical trial; emotion regulation; mind-body interventions; pain sensitivity; yoga

Introduction

Background

Yoga has been shown to reduce pain and improve function in populations with chronic low back pain (CLBP) in multiple randomized controlled trials (RCTs) [1,2]. However, results vary, and effects are generally modest [3]. This variation is perhaps due to differences in the specific neurobiological mechanisms through which yoga exerts clinical improvements on pain that are affected by different yoga interventions. These mechanisms, which have been only minimally identified, could potentially be harnessed to achieve more consistent and optimal outcomes from yoga interventions. A study that examined mediators of yoga's effects on pain lacked strong theoretical bases for assessment of the mechanisms involved [4]. Using a comprehensive theoretical emotion regulation (ER) model of yoga [5], we will conduct the first test of ER as a primary mechanism of yoga's effects on CLBP. We will also test the role of pain sensitization using somatosensory and gene expression profiles in this model [6] and examine the specific aspects of ER.

ER refers to "extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals" [7]. Emotions strongly influence perceptions of pain intensity and predict disability [8], particularly among individuals with CLBP [9,10]. Interventions that promote adaptive ER skills reduce pain in patients with chronic pain [11]. Increasing evidence demonstrates that consistent yoga practice can promote improved ER [12,13], but research has not yet tested whether the effects of yoga practice on CLBP are due to improvements in ER.

Integrative Model of Yoga's Effects on ER

Given the importance of ER in managing chronic pain and yoga's demonstrated promotion of improved ER, we developed an integrative model of yoga's effects on CLBP that highlights the key role of ER. Previous work by our team [14,15] and others [16] demonstrated that yoga simultaneously comprises multiple components and that physical activity (poses and transitions between poses), breathwork, and meditation are all important therapeutic elements. Thus, although physical activity interventions alone have demonstrated salutary effects on negative emotion [17] and ER [18,19], yoga's inclusion of breathwork and meditation along with physical activity may more potently improve ER [5].

Yoga provides myriad opportunities to develop ER skills helpful to people managing chronic pain. Practitioners can learn how to experience sensation without negative evaluative judgments, cultivating nonreactivity. Due to cognitive priming and reinforcement during movement, yoga provides simultaneous input to cognitive, motor, and sensory pathways, which may allow practitioners to consciously influence their interpretation of sensation or pain and manage its affective dimensions. Given the myriad components of yoga that can facilitate developing ER skills, we posit that ER is a key mechanism by which yoga exerts effects on individuals with CLBP. The few studies examining links among yoga, ER, and pain support our model (Figure 1). For example, yoga practitioners were better able to tolerate experimentally induced pain compared to nonpractitioners, with corresponding greater left intrainsular white matter connectivity [20]. Further, the yoga practitioners reported coping with the pain stimulus using (adaptive) ER strategies such as relaxation, nonjudgmental focusing, and reappraisal. Thus, the ability to minimize the affective dimensions of pain may dampen physiological responses to negative emotions such as anxiety, which have been associated with the perception of pain [21,22].

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Figure 1. Model of primary and alternative mechanisms of action. Model 1 proposes that pain sensitization moderates yoga's effects on pain, in that chronic low back pain patients with higher sensitization may benefit less given that their pain is more centralized.

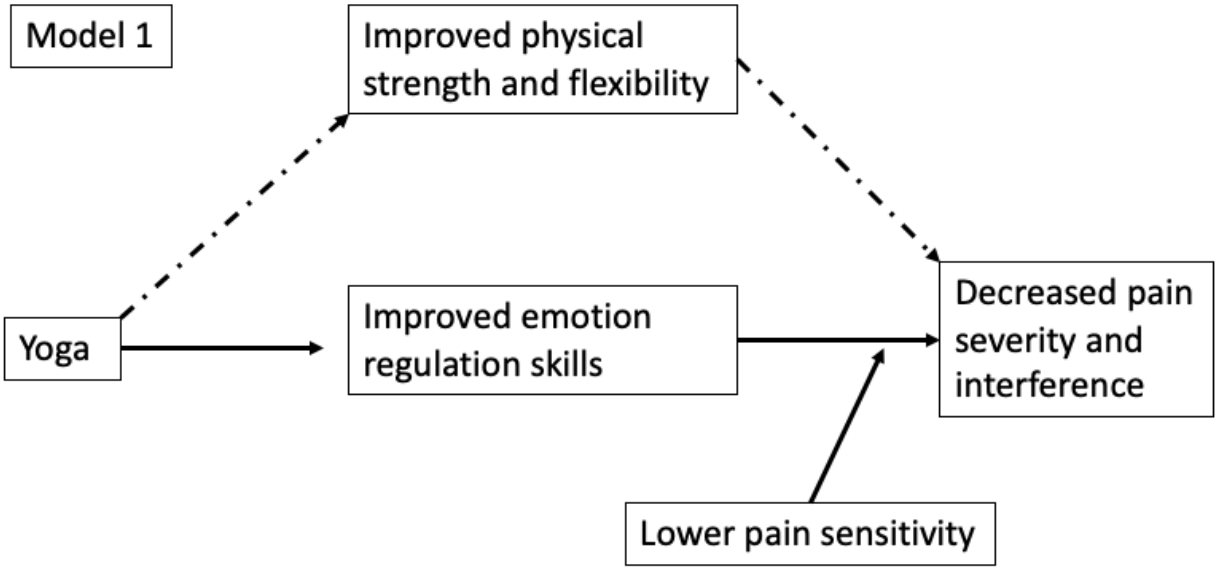

Pain Sensitivity May Influence the Effects of Yoga and ER on CLBP via Moderation or Mediation

Recent studies document that patients with CLBP demonstrate sensory and functional alterations reflecting peripheral and central nervous system sensitization associated with enhanced pain sensitivity [23-25]. Enhanced pain sensitivity as a mechanism of CLBP includes sensitization of nociceptors and neuronal circuits [26] and increased pain signaling through membrane excitability and synaptic efficacy [27], which are conferred through altered expression of pain sensitivity (and immune-related) genes [6,28]. The somatosensory changes associated with enhanced pain sensitivity in CLBP involve decreased thermal and mechanical pain thresholds at the site of pain and remote areas [25,26].

Preliminary research suggests that negative emotion is an important determinant of pain sensitivity [29,30], predicting up to 23% of the variance in CLBP-related disability [31,32]. For instance, greater pain catastrophizing and anxiety are associated with lower standardized values of heat pain threshold and tolerance in patients with chronic pain [33]. In turn, negative emotions and inability to tolerate stress have been shown to activate inflammatory pathways through the release of proinflammatory cytokines and substance P [34,35]. To date, only 2 small studies have examined whether yoga specifically influences pain sensitivity. However, in a systematic review of 15 RCTs, yoga was associated with decreases in interleukin-1β, interleukin-6, and tumor necrosis factor-α [36]. In addition, specific components of yoga (meditation, relaxation, and breathing) have been shown to alter gene expression profiles and levels of inflammatory mediators [37-39].

As shown in Figure 1, we propose that pain sensitization moderates yoga's effects on pain, where patients with CLBP with higher sensitization may benefit less [40,41], given that their pain is more centralized [42,43]. This is a fairly novel hypothesis with some supportive evidence [44,45]. We will also explore the possibility that yoga and improved ER abilities might actually *improve* sensitization and thus decrease pain (Figure 2).

Little research has demonstrated that treatments for pain, including behavioral interventions, modify sensitization once it has occurred [46,47], although a reversal of central sensitization was observed in patients with structural pain–related pathology who underwent corrective surgery [48] as well as patients with migraine and chronic pancreatitis [49,50]. We considered alternative strategies to test these linkages. For example, a systematic review of 1037 individuals with CLBP provided moderate evidence that structural brain differences in specific cortical and subcortical areas of the brain and altered functional connectivity in pain-related areas following painful stimulation differentiate chronic pain from pain-free individuals [51]. While brain imaging provides 1 way to examine changes in pain sensitivity, we assert that identifying specific cellular mechanisms through which ER affects pain sensitivity will generate greater translational capacity for the clinical care of individuals with CLBP.

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Figure 2. Moderated mediation model of emotion regulation. Model 2 will explore the possibility that yoga and improved emotion regulation abilities might actually improve sensitization and thus decrease pain.

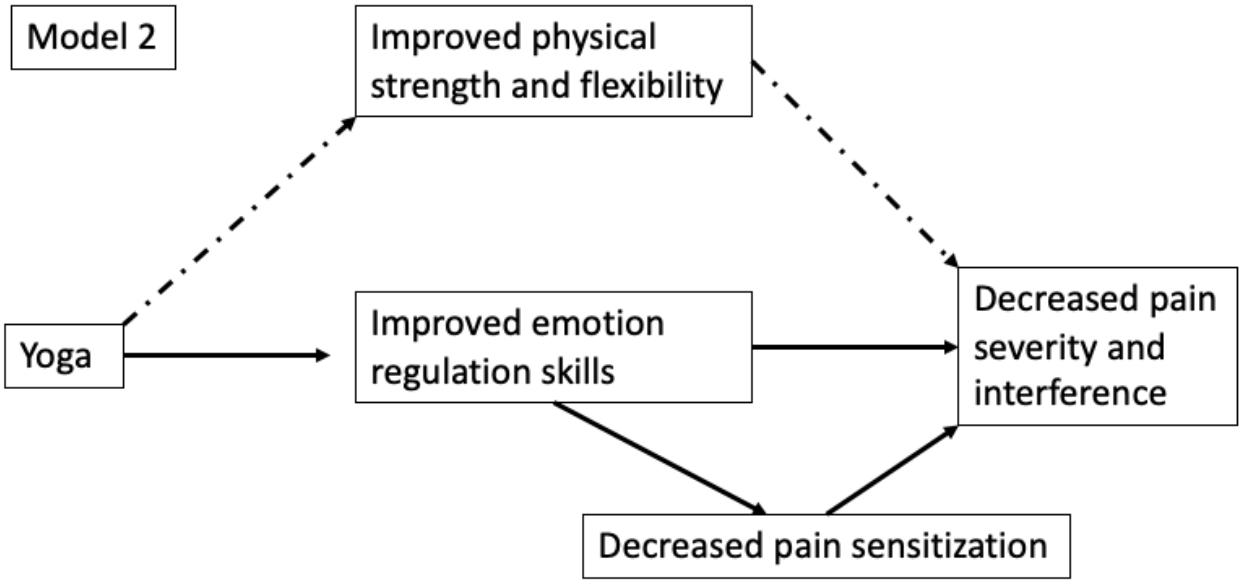

Controlling for Improvements in Physical Strength and Flexibility

To be comprehensive, our model includes improved strength and flexibility, given that improvements in these domains are common in yoga intervention trials. In fact, yoga typically shows the effects on strength, flexibility, and other physical outcomes that are as substantial as those of physical therapy or stretching-strengthening exercise groups [52,53]. Sherman et al [4] demonstrated that strength and flexibility may mediate some of yoga's effects on pain. Overall, accumulating evidence demonstrates moderate but varied effects of yoga for reducing CLBP pain and disability; much remains to be learned about *how* yoga exerts these effects and why its effects vary. Understanding the proposed mechanism of actions (MOAs) of yoga will provide not only a more solid scientific basis to assure clinicians of the value of yoga to patients with CLBP and other conditions but also important targets for intervention modification and optimization.

Objectives

To address this gap, we will test the impact of a yoga intervention on ER and pain severity and functioning compared to a general stretching or strengthening intervention. This design allows us to isolate the additional effects of yoga above and beyond more general movement practices, thereby testing ER as a key MOA underlying the clinical effects of yoga on CLBP. Specifically, we will test whether yoga's effects on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects.

For the active comparison intervention, we chose to use stretching and strengthening exercises, given that we are interested in determining not only whether yoga influences ER but also the extent to which these effects are due to aspects of yoga above and beyond nonspecific factors (eg, expectancies, time, attention, and effort) [13] as well as improvements in strength and flexibility [4]. The 2 intervention groups will be similar in many aspects, but only yoga will incorporate aspects that we hypothesize will facilitate ER (eg, breathwork, mindfulness, and relaxation). We selected the hypothesized MOA based on our extensive work regarding the therapeutic characteristics of yoga and mechanisms of CLBP [5,14]. Our 3-month and 6-month follow-ups will allow us to examine whether the effects of yoga emerge later or persist. The study is highly innovative in its approach to testing the MOA of yoga for alleviating CLBP. By identifying the specific mechanisms through which yoga may influence pain, these results will facilitate optimizing interventions to improve therapeutic accuracy for prescribing and using yoga for CLBP, a highly prevalent and costly health condition in the United States and worldwide.

Methods

Design

This study is a 2-arm parallel group blinded RCT to examine ER as a MOA of yoga in individuals with CLBP (Figure 3). In total, 204 people with CLBP will be randomized to receive yoga or the stretching and strengthening intervention with assessments of pain severity and interference; ER; pain sensitivity; physical strength and flexibility; and quality of life at baseline, 6 weeks (midway through the intervention), 12 weeks (after completion of the intervention), and 3 and 6 months after the completion of the intervention. Both groups will be instructed to continue the use of any other strategies or treatments that they have been using to manage their CLBP throughout the study.

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Figure 3. Study overview. BPI-SF: Brief Pain Inventory Short-form; DERS: Difficulties with Emotion Regulation Scale; NAPT: Negative Affective Priming Task; Pain sensitivity measured by quantitative sensory testing and blood drawn for gene expression profile; SF-36: 36-item Short Form Health Survey.

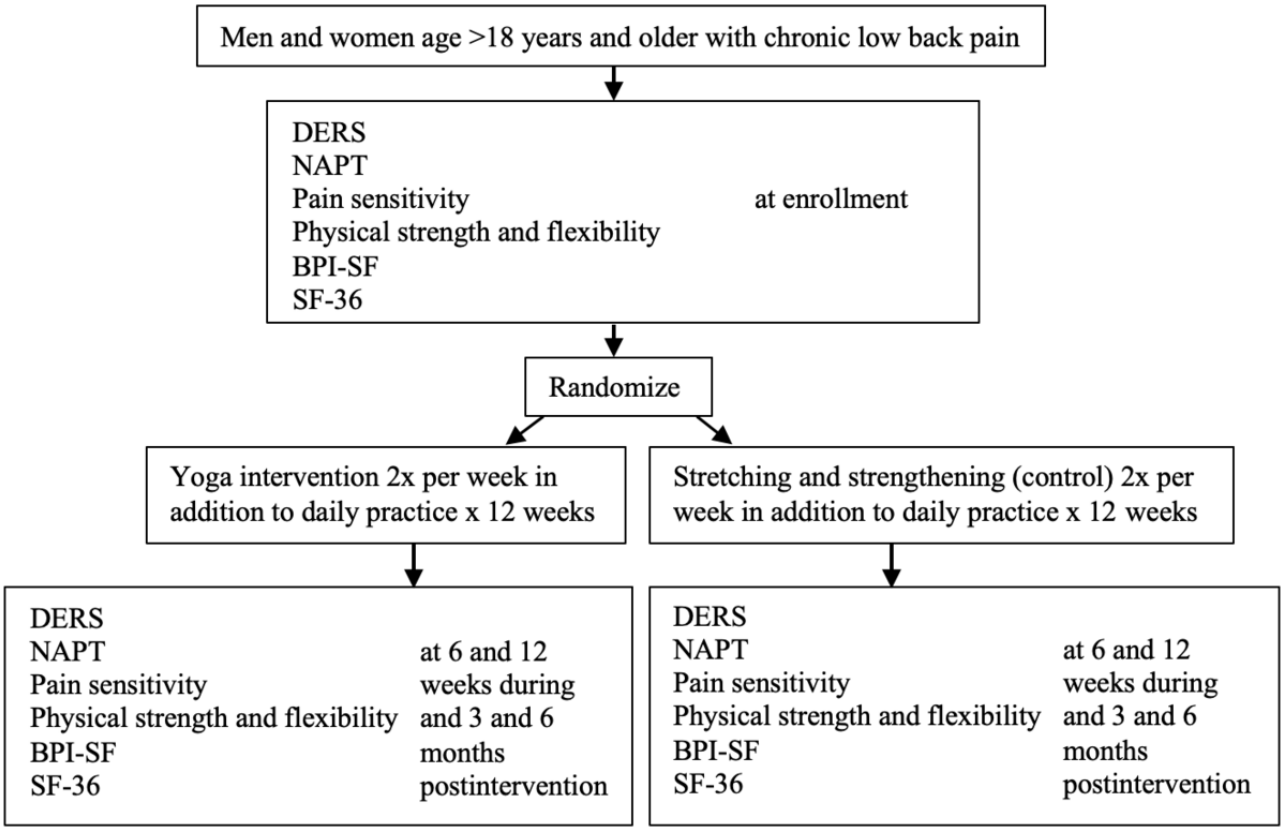

Participants

We will enroll 204 men and women aged 18 years and older with nonspecific CLBP who meet eligibility (Textbox 1). Nonspecific CLBP is defined as pain without a specific cause or need for surgical intervention that is anywhere in the region of the low back bound superiorly by the thoracolumbar junction and inferiorly by the lumbosacral junction, which has been present for more than 3 months out of the prior 6 months and is currently rated at a level of ≥2 on the numeric rating scale. Eligibility will be determined by asking the following screening questions [54]: (1) How long has back pain been an ongoing problem for you? (2) How often has low-back pain been an ongoing problem for you over the past 6 months? Responses of greater than 3 months to question 1 and "at least half the days in the past 6 months" to question 2 will define CLBP.

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Textbox 1. Inclusion and exclusion criteria to determine eligibility for study participation.

Inclusion criteria

- Aged 18 years and older
- Report low back pain for more than 3 months out of 6 months
- Willing to attend 12 weeks of yoga or stretching (twice per week)
- Willing to complete 5 assessments
- English literacy
- No changes in pain treatments in the past month
- Willing to not change pain treatments during the study unless medically necessary
- Have not practiced yoga more than 2 times in the last 3 months

Exclusion criteria

- Back surgery within the last 1 year
- Back pain due to specific systemic problem (eg, lupus)
- Lower extremity weakness (motor strength four-fifths of the quads, glutes, hamstrings, and extensor hallucis longus)
- Sciatica or (+) straight leg raise
- Coexisting chronic pain problem (migraine headaches and fibromyalgia)
- Serious or unstable psychiatric illness (eg, psychosis, mania, and history of suicide attempt) and current suicidal ideation
- Major coexisting medical illness (eg, cancer, chronic obstructive pulmonary disease, and morbid obesity)
- Positive Romberg test (with or without sensory neuropathy)

Recruitment and Retention Strategies

Active and passive recruitment strategies will be used to recruit individuals with CLBP include (1) contacting CLBP participants enrolled in an institutional review board (IRB)–approved pain registry, (2) advertisements on social media (Instagram, Facebook, Twitter, Reddit, and Craigslist), (3) placing printed advertisements in public transportation vehicles and local newspapers, and (4) distributing flyers at local outpatient clinical sites and local universities. We will recruit continuously and start a new cohort every 6 months, so that there will be cohorts in both interventions and follow-up phases throughout the study. This approach will help control for seasonal effects and other potential confounds. All participants will receive a yoga or exercise mat, block, and strap prior to their first session, and US $70 following the baseline, 6- and 12-week postintervention, and 3- and 6-month follow-up assessments with an additional US $50 for those who complete all data collection sessions.

Interested volunteers are asked to complete a web-based screening questionnaire via REDCap (Research Electronic Data Capture; Vanderbilt University), which includes questions to ensure they meet inclusion and exclusion criteria and can participate safely. Volunteers who are deemed eligible to participate are contacted by study staff to schedule their baseline appointment.

Ethical Considerations

The study was approved by the University of Connecticut IRB (#H19-191). Prior to completing any study procedures, all participants provide written informed consent on a form that was approved by the IRB at the University of Connecticut (IRB#H19-191). All study procedures are in accordance with the ethical standards described by the Helsinki Declaration. Study participants are assigned an identification number, allowing all stored records to be deidentified. Deidentified data are kept in locked file room or stored in a password-protected database on a password-protected computer. All participants are monetarily compensated for their participation up to US $400 for completing all study visits. Participants can withdraw from the study at any time.

Procedures

Randomization and Blinding

Eligible volunteers are scheduled to meet with a study staff member who will follow all informed consent procedures. After written consent is obtained, participants are randomized to the yoga or stretching and strengthening group using a stratified randomization scheme based on biological sex to ensure balance between groups, and the assigned group is known only by the study staff managing the participant and instructor schedules.

We will use blinding whenever possible. Assessments, evaluations, and data analysis will be conducted without the knowledge of participants' assigned group. We will blind the study personnel to the assigned condition of subjects when conducting data collection by using unique study identification numbers, by following a strict script to refrain from discussing participant activities, and by using different members of the study team to coordinate assigned condition activities and collect data. Deidentified data with codes for assigned condition will facilitate blinded data analysis.

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Data Collection Visits

At each study visit, venous blood samples (15 mL) will be collected in one 10-mL PAXgene vacutainer and one 6-mL K2 ethylenediaminetetraacetic acid vacutainer by a research team member experienced in venipuncture. The samples will be immediately placed in a biohazard container and transported to the laboratory where they will be processed and stored in a –80 °C freezer for bulk processing of genetic and protein measures. Physiological and quantitative sensory measurements will be conducted by a trained research assistant. Participants will be asked to complete all study questionnaires via REDCap after completion of the laboratory data collection.

Interventions

All yoga and stretching and strengthening sessions will take place on a secure web-based platform. This delivery modality will provide more inclusive participation and reduce barriers such as participant transportation and parking. For both study arms, 75-minute classes will be offered 3 times per week for 12 weeks. Participants will be asked to attend at least 2 out of 3 of the offered classes per week. The importance of attending 2 sessions per week is emphasized during the first session and throughout all subsequent sessions. Participants who repeatedly miss sessions without notifying the study personnel will be contacted to check on the reason for nonattendance and to encourage resuming participation as soon as possible. Participants are encouraged to consult with the instructor individually before or after class about problems or difficulties they are encountering at home or in the formal sessions.

Participants are asked to practice exercises at home on days they do not attend formal synchronous sessions to maximize the benefit of the intervention. Participants will be emailed daily links to prerecorded practice videos that are approximately 25 minutes in length and asked to record the amount of time they spent on the practice videos.

Yoga Intervention

Overview

The yoga intervention will be led by certified 500-hour registered yoga teachers trained in working with patients with back pain. The yoga for CLBP protocol [55] consists of classical hatha yoga with influences from vinyasa and Iyengar yoga. These yoga styles are those most commonly offered in clinical and community settings and emphasize the importance of modifications and adaptations including the use of props such as straps and blocks to minimize the risk of injury and make the poses accessible to people with health problems and limitations [56]. The manual developed to standardize the yoga classes offered in the intervention contains pictures and a description of how to perform each pose. The manual also includes suggested instructor dialogue, which may be paraphrased or varied slightly yet promotes consistent delivery, which enhances the replicability and generalization of results. The intervention includes some poses that could aggravate back conditions in some people if they are not modified; therefore, multiple modifications are suggested, and many poses are only worked up to after weeks of practice and individual attention from the instructor. The more challenging poses are never included in the home practice videos.

For each yoga class in the protocol, the instructor leads participants through a series of 23 yoga poses (32 total variations) at a slow-moderate pace. During the formal sessions, participants are instructed to take slow deep breaths, timing their inhales and their exhales with specific phases of poses. Participants are encouraged to emulate optimal alignment as demonstrated by the instructor and to focus on a goal or positive direction for their yoga practice. Yoga classes are constructed to allow optimal flow from one pose to another. Each session begins with a few minutes of deep breathing and mindfulness or meditation followed by 15 minutes of basic postures (poses 1-8) to warm up muscles by increasing circulation to provide increased flexibility as the class progresses. Most poses are conducted once per side. After the warm up, the instructor leads participants through a series of standing poses (poses 9-14) for 15 minutes. After the standing poses, the class moves into floor poses (poses 15-23) for 20 minutes. Sessions end with 5-7 minutes of complete relaxation in the standard ending pose “savasana,” during which additional positive affirmations are provided.

Stretching and Strengthening Control Intervention

This intervention is designed to require a similar amount of physical exertion (stretching and strengthening exercises only, with no extreme movement). Classes will be led by physical therapists or other skilled therapeutic exercise instructors and involve conventional exercises appropriate for patients with CLBP, including a comprehensive set of exercises that stretch all the major muscle groups, with an emphasis on the trunk and legs. The intervention will include 12 stretching exercises used in the exercise arm of previous studies that have successfully compared exercise to yoga [57,58] (ie, gastrocnemius, soleus, quadriceps, posterior and inferior shoulder, upper trapezius, hip flexor, back extension, back rotation, hamstrings, hip external rotators, and back flexion). It will also include 3 additional stretches (hip internal rotators, hip adductors, and hip flexion). Each stretch will be held for approximately 60 seconds and repeated once. In addition to a complete set of full-body stretches, the class will begin with a 5-minute warm up period consisting of basic aerobics steps (ie, 1 minute each of walking in place, marching, lateral shuffling, turning and reaching, and box step) and will also include 4 exercises that strengthen the back, abdomen, and hips (ie, squats, crunches, oblique crunches, and back extensions). Over the 12 weeks, the repetitions of each strength exercise are increased from 8 to 30. Specific strength exercises are practiced in separate sets of 5 to 10 repetitions.

Treatment Fidelity

All sessions will be recorded, and instructor fidelity to the yoga intervention or stretching intervention manuals will be evaluated using video-recordings of sessions. Instructors and participants will be aware of and consent to the recordings. We will select 1 session per week from each condition for rating by trained research assistants, who will review sessions using a manual checklist for instructor adherence to the manuals, using a 0-10 rating scale for each procedure or instruction. If the rating is

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less than 100% adherent, we will meet with the instructor to discuss the places in the session that were not adherent.

Measures

The assessments of pain intensity, pain interference, ER, and other parameters will be taken at baseline, 6 and 12 weeks, and 3 and 6 months post intervention.

Primary Outcome: Primary MOA

Pain severity will be measured with the Brief Pain Inventory-Short Form (BPI-SF) [59] at 12 weeks. The BPI-SF has been validated with CLBP and has shown good reliability [60].

ER as the primary MOA will be measured using the Difficulties in Emotion Regulation Scale (DERS) score at 12 weeks. The DERS is the gold standard self-report measure of individuals' abilities to respond to emotional experiences in a goal-oriented manner [60]. The 36-item DERS taps aspects of difficulties with ER, which we anticipate will lessen with yoga practice [61]. Participants rate the extent to which each of 36 statements currently applies to them, and the measure yields a total score comprising summed subscales. The DERS is sensitive to change over time in ER, and internal consistency reliability is high [60].

The Negative Affective Priming Task [62] will also be used to capture individual differences in emotional attention, reactivity and appraisal, and ability to inhibit negative emotion and purposefully shift attention to more positive aspects of daily life. Participants are exposed to neutral and affective words with a strong positive and negative valence in consecutive paired trials, one word serving as the "target" and the other as a "distractor." Participants are instructed to ignore the distractor and to attend to the target in both control and negative priming conditions, with "inhibition ability" operationalized as a difference score between response latencies in control and negative priming conditions. The stronger one's inhibition abilities, the longer the latency in the negative priming condition compared to the control condition (scored in milliseconds). Individuals with chronic depression and greater tendency to engage in maladaptive rumination demonstrate reduced ability to inhibit negative, as opposed to neutral, words with no difference in the ability to inhibit positive words [63,64].

Secondary Outcomes

Overview

There are 4 secondary outcomes for this study: pain sensitivity, physical strength and flexibility, pain interference, and quality of life.

Pain Sensitivity: Peripheral and Central Sensitivity

We will use a comprehensive quantitative sensory testing (QST) battery of mechanical and thermal stimuli [65]: (1) cutaneous mechanical pain sensitivity, involving measures of tolerance, threshold, temporal summation, and after sensations; (2) heat and cold pain sensitivity, involving threshold, tolerance, and ratings of suprathreshold stimuli; and (3) pressure pain thresholds. Interrater reliability of the QST protocol has been reported in several clinical trials, with each individual test achieving a CI of 0.87-0.94 [66,67].

In addition to the QST battery, we will isolate total RNA from whole blood for sequencing at each time point. We will prepare libraries per Illumina standard protocols and sequence RNA on the Illumina HiSeq2500 System (Illumina Inc) to obtain 150 base pair paired-end reads. We will examine how changes in the expression of pain sensitivity genes, as well as the entire transcriptome, differ between the experimental and control group (those with complete data from yoga vs stretching) × sex using statistical modeling and construct a database of gene expression profiles to generate a profile of change in ER, as well as identify novel therapeutic targets for better pain management. We will use a candidate approach to examine genes identified from our preliminary studies, and a hypothesis-generating approach to identify differentially expressed genes.

Physical Strength and Flexibility

Physical measures include grip strength and core stabilization and strength. Grip strength will be measured using 2 trials for each hand with a hydraulic dynamometer. The best performance is selected for each side, and the average of the left and right hand is used for analysis. Painful or injured hands or wrists are not tested, and the result of the good hand is used. Good reliability and predictive validity have been shown [68]. Core stabilization and strength will be assessed using prone and supine bridge positions [69]. Participants begin on their elbows in the prone position with shoulders, hips, and ankles aligned. The supine position is tested next, with knees flexed 90° and pelvis raised from the floor with shoulders, hips, and knees aligned. Assessors record the length of time (120 seconds maximum) that each position is held in proper form.

Pain Interference

Interference of function due to pain will be measured with the Brief Pain Inventory [60]. The pain interference score is the mean of the 7 interference items.

Quality of Life

The 36-item Short Form Health Survey [70] will be administered at each time point to gain a deeper understanding of the psychological, physical, and social limitations that participants experience as a result of pain. Subscales characterize participants' physical functioning, role functioning as impacted by physical and emotional health, energy or fatigue, emotional well-being, social functioning, pain, and general health. The 36-item Short Form Health Survey demonstrates excellent strong psychometric properties and predictive validity in a variety of diverse samples, including those experiencing chronic pain [71].

Exploratory Variables

Demographics, class attendance or home practice, expectancies, and substance use will be measured to examine the impact on the primary and secondary outcomes. A brief questionnaire (minimum data set as recommended by the National Institutes of Health Taskforce on Research Standards for CLBP) [54] will assess demographics (age, gender, race or ethnicity, education, and employment status) and medical or psychiatric history (comorbidities, medication usage, and ongoing treatments). Attendance at yoga or stretching sessions will be assessed using attendance data from the session recordings. The Essential

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Properties of Yoga Questionnaire [72] will be used to rate both interventions (yoga and stretching or strengthening) and measures the extent to which 14 different dimensions are emphasized in a mind-body intervention (eg, physical challenge, breathwork, restorative postures, and mindfulness). The Credibility Expectancy Questionnaire [73], a 6-item self-report instrument, will be used to assess treatment credibility and patient expectancy for improvement [74]. In order to assess participants' use of tobacco, alcohol, prescription medicines, cannabis, and other nonprescribed substances, the Alcohol, Smoking, and Substance Involvement Screening Test [75] will be administered by study staff at each time point.

Statistical Analysis

The primary aim of this study will test the null hypothesis that the 2 population means are equal between the yoga and stretching and strengthening groups on the primary outcome, pain severity as measured by the BPI-SF, as well as the primary MOA, ER as assessed by the DERS. Power calculations incorporated prior effect sizes from works by others. A proposed sample size of 102 per group, which adjusted for attrition, was calculated to detect statistically significant results with 80% power (estimated d=0.50). In consideration of our secondary aims, we also powered the detection of paths a and b within pain interference mediation models. This was done using simulation in R (R Foundation for Statistical Computing; N=5000). Following simulation methods (N=5000) presented in Fritz and MacKinnon [76], sample size was determined by increasing simulation sample size until 90% of simulations significantly detected both paths a and b with estimated effect size magnitudes of d=0.39 (path a) and d=0.26 (path b) at α=.05. A proposed sample size of 116 was calculated, which was already reached when powering our primary aim.

Data Analysis

All analyses will be performed in SPSS (version 29; IBM Corp). A P value of .05 or less will be considered statistically significant. The primary outcome is pain severity (BPI-SF) and the primary MOA is ER (DERS). We will examine baseline demographics and study variables descriptively and test for differences between yoga and stretching and strengthening groups. If assumptions are met, a series of 2-sided t tests, mixed effects models, and path analyses will test our hypotheses. A mediation path analysis will be conducted examining the indirect path of group and change in ER from baseline to 6 weeks (path a), and change in ER from baseline to 6 weeks and pain severity (BPI-SF) at 12 weeks (path b) controlling for baseline pain severity. The magnitude of indirect path b will be assessed controlling for path a and the direct path between group and change in pain severity at 12 weeks (path c) to test if changes in ER predict subsequent changes in pain severity. Identical models will be created with change in ER from baseline to 12 weeks and pain severity at 3- and 6-month follow-ups. The magnitude of indirect path b will be compared between groups to test if the path between ER and pain severity is greater in the yoga group than in the stretching and strengthening group. If 95% CIs of path estimates do not contain 0, they will be considered meaningful. Finally, a series of moderated mediation path analyses will be conducted, examining the measures of baseline pain sensitivity (QST scores and normalized gene expression values), strength and flexibility, pain interference, and quality of life as moderators of the identical mediation model. All analyses will also be adjusted for important covariates including, but not limited to demographics (eg, biological sex, race, and sex), cohort, instructor, and intervention components (Essential Properties of Yoga Questionnaire) and credibility or perception of success (Credibility Expectancy Questionnaire). Sensitivity analyses will examine whether treatment responders and nonresponders differ significantly in baseline ER abilities. Baseline DERS scores will also be examined as a continuous moderator in main study analyses to establish whether some individuals may enjoy greater benefit from this intervention more than others.

Results

This project is funded by the National Center for Complementary and Integrative Health and reviewed by the University of Connecticut's IRB. Recruitment began in September 2020. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025. No interim analyses are planned for evaluation of the primary and secondary outcomes. Analyses will be conducted following final data collection using a mediation path analysis and series of moderated mediation path analyses to examine the mechanisms through which yoga reduces pain.

Discussion

Yoga has been shown to decrease pain severity in individuals with CLBP. This study aims to determine whether ER is a mechanism of yoga through which a significant reduction in pain can be achieved. We will also determine whether yoga can lead to improvements in pain sensitivity, physical strength and flexibility, pain interference, and quality of life.

This will be the first study to assess ER as an MOA of yoga and interrogate plausible biological and psychological pathways that impact the contribution of ER on pain relief. The study results will provide empirical data on the role of ER as a MOA for yoga interventions and inform future studies on whether ER could be bolstered as a component of yoga or other mind-body interventions to improve pain outcomes.

Limitations of the study include that it will be performed at 1 site within the United States, and the interventions are only delivered in English. As a first step to determine whether ER is a MOA of yoga, the study may support evaluating or targeting ER in yoga interventions among more diverse populations, with delivery in other languages, and with other chronic pain conditions.

This 2-arm parallel group blinded RCT will examine ER as the MOA of yoga in individuals with CLBP. The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain, whether pain sensitization moderates yoga's effects on pain, or if yoga and improved ER abilities reduce pain sensitivity and thereby relieves pain. The study findings have important implications for future yoga

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research studies, as well as other mind-body modalities designed to improve pain management.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

ARS and CP wrote the initial manuscript, designed the tables and figures, and acquired funding. EJG designed and helped to modify the yoga intervention. All authors contributed to revisions and reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Center for Complementary and Integrative Health (National Institutes of Health).
[PDF File (Adobe PDF File), 167 KB - resprot_v13i1e56016_app1.pdf]

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Abbreviations

BPI-SF: Brief Pain Inventory-Short Form
CLBP: chronic low back pain
DERS: Difficulties in Emotion Regulation Scale
ER: emotion regulation
IRB: institutional review board
MOA: mechanism of action
QST: quantitative sensory testing

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RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

A Web-Based Physical Activity Promotion Intervention for Inactive Parent-Child Dyads: Protocol for a Randomized Controlled Trial

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Abstract

Background: Low levels of physical activity are associated with numerous adverse health outcomes, yet sedentary lifestyles are common among both children and adults. Physical activity levels tend to decline steeply among children aged between 8 and 12 years, even though children's behavioral patterns are largely governed by familial structures. Similarly, parents' activity levels have been generally reported as lower than those of nonparents of comparable age. For this reason, family-based physical activity promotion interventions are a potentially valuable and relatively underresearched method for mitigating physical activity declines as children develop into adolescents and for increasing physical activity in parents.

Objective: This study aims to assess the efficacy, feasibility, and acceptability of a novel theory-based web-based physical activity promotion intervention among parent-child dyads in Finland who do not meet physical activity recommendations at baseline.

Methods: Participants (target N=254) will be recruited from the general population using a panel company and advertisements on social media and randomly assigned to either an immediate intervention group or a waitlist control group. The intervention consists of 4 web-based group workshops over the course of 10 weeks, web-based tasks and resources, and a social support chat group. Data on physical activity behavior and constructs from the integrated behavior change model will be collected through self-report surveys assessing physical activity, autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, intention, self-monitoring, habit, and accelerometer measurements at baseline, post intervention, and 3 months post intervention. Exit interviews with participants will assess the feasibility and acceptability of the intervention procedures.

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Results: This study will reveal whether the intervention changes leisure-time physical activity among intervention participants relative to the control group and will examine the intervention's effects on important theoretical predictors of physical activity. It will also yield data that can be used to refine intervention materials and inform further implementation. Trial recruitment commenced in September 2023, and data collection should be completed by December 2024.

Conclusions: The planned intervention has potential implications for both theory and practice. Practically, the use of an entirely web-based intervention may have scalable future uses for improving physical activity in 2 key populations, while also potentially informing on the value of dyadic, family-based strategies for encouraging an active lifestyle as an alternative to strategies that target either parents or children independently. Further, by assessing change in psychological constructs alongside potential change in behavior, the intervention also allows for important tests of theory regarding which constructs are most linked to favorable behavior change outcomes.

Trial Registration: ClinicalTrials.gov NCT06070038; https://clinicaltrials.gov/study/NCT06070038

International Registered Report Identifier (IRRID): DERR1-10.2196/55960

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KEYWORDS

dyadic behavior change; family behavior change; intervention; physical activity; theory of planned behavior

Introduction

Overview

Low levels of physical activity in adult and youth populations are associated with an increased risk of physical and mental health conditions and a reduced quality of life. Conversely, regular physical activity participation is associated with reduced chronic disease risk and better psychological health and well-being [1]. Accordingly, the World Health Organization has published evidence-based guideline levels of physical activity required to realize these health benefits. The guidelines recommend that adults aged between 18 and 64 years participate in at least 75 minutes of vigorous physical activity, 150 minutes of moderate physical activity, or an equivalent combination of both per week, while children aged between 7 and 17 years are recommended to participate in at least 60 minutes of physical activity per day. Studies indicate that most people do not achieve these guideline levels of physical activity [2]. Further, studies have observed a sharp drop in physical activity participation in child and adolescent populations, followed by generally low participation levels into and throughout adulthood [3].

Given the steep decline in activity levels, as children transition into adolescence, the development and implementation of behavioral interventions to encourage an active lifestyle is a key target area for health promotion research. One strategy proposed to enhance the efficacy of behavior change strategies for children's activity levels is to target the family unit rather than children themselves. Specifically, parents of preteen children retain a strong influence on their child's behavior, both through their own activity levels [4,5] and through the opportunity to provide support for and foster motivation toward leisure-time physical activity behaviors [6,7]. Further, evidence indicates that children likely influence physical activity behaviors and beliefs in their parents, as parents tend to be less active than nonparents [8], often citing their children's lack of motivation or support as a barrier to being physically active [9]. This evidence of within-family effects indicates the potential utility of dyadic interventions for both parents and children [10], using theory-driven, group-based behavior change strategies to bolster social support, foster motivation, and reduce the perceived barriers to behavior in both the parent and child. Yet, despite evidence for the potential utility of these strategies, few physical activity interventions have been applied for parent-child dyads, and those that have tend not to have a strong basis in behavioral theory and are seldom evaluated systematically [11], inhibiting meaningful conclusions on their efficacy. In response to the relative scarcity of theory-driven, family-based physical activity intervention programs, we aim to develop and test an intervention to promote physical activity in low-active parents and their children based on the integrated behavior change model, an approach that outlines the multiple determinants and potential targets for intervention derived from multiple theoretical perspectives [12].

The Integrated Behavior Change Model

The integrated behavior change model draws from several well-established behavioral theories: self-determination theory [13], the theory of planned behavior [14], the health action process approach [15], and the reflective impulsive model [16]. Central to the model is that individuals' quality of motivation, which reflects whether their behavior is consistent with the self-endorsed reasons, is highly influential in individuals' intentions to perform physical activity and physical activity participation. This premise is derived from self-determination theory, which makes the distinction between autonomous and controlled forms of motivation. Autonomous motivation reflects an individual's performing physical activity consistent with their own interests, choices, needs, and sense of personal involvement [13,17]. By contrast, controlled motivation reflects performing activities for externally referenced reasons, such as for rewards or out of obligation to others. Of critical importance when it comes to performing physical activity, individuals who perform physical activities for autonomous motives are more likely to form intentions to perform physical activity in the future and are more likely to develop routines and habits, which can translate to long-term physical activity persistence [18]. This is because those citing autonomous reasons for performing physical activity are likely to persist because their motivation emanates from themselves, while those whose motives are controlled will only persist as long as the external contingencies

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(eg, rewards and demands from others) persist. A key tenant of self-determination theory [17,19], is that autonomous motivation for physical activity can be fostered through the support of salient others, such as parents or teachers. For example, parents who display behaviors that indicate support for children's autonomy and competence toward physical activity and demonstrate a sense of unconditional relatedness with their children for physical activities, are more likely to foster autonomous motives in their children toward performing physical activity in the future [6,7,20]. As such, enabling parents to display autonomy-supportive behaviors with respect to presenting, discussing, and performing physical activity with their children is likely an important strategy to promote physical activity participation in children and may be particularly valuable in family-based interventions aimed at promoting physical activity. It is also likely to be useful in parent-child dyads, where both parent and child can be encouraged to display behaviors that support each other's autonomous motivation. This is supported in empirical data, where autonomy-supportive parenting has been associated with autonomous motivation in children as well as positive behavioral outcomes [21], including enhanced physical activity [6].

The integrated behavior change model also specifies the processes by which autonomous motivation leads to intention toward, and actual participation in, physical activity in the future. Specifically, individuals who are autonomously motivated toward a behavior are proposed to be more likely to form adaptive beliefs in favor of performing that behavior in the future [12,22-24] and, as a consequence, form an intention to perform physical activity in the future. Such beliefs are represented in the model by the belief-based attitude, subjective norm, and perceived behavioral control constructs from the theory of planned behavior [14], a prototypical theory that identifies the antecedents of intentional behaviors such as physical activity. The theory stipulates intention is the salient predictor of subsequent behavior, and intentions themselves are a function of attitudes (beliefs about the perceived likely affective or instrumental outcomes of engaging in a behavior), subjective norms (beliefs about where important others in one's life would want them to engage in a behavior or not), and perceived behavioral control (beliefs about whether engaging in a behavior is under one's own control or within their abilities). Research has demonstrated that these beliefs tend to be reliably related to physical activity intentions and participation, signaling their potential as modifiable constructs that could be targeted in intervention strategies aimed at promoting positive intentions toward, and actual participation in, physical activity. Accordingly, interventions based on the theory and targeting the belief-based constructs have shown efficacy in changing intentions and behavior [25]. For example, interventions presenting persuasive messages that highlight the advantages of behavior and downplay the disadvantages, targeting attitude change, or prompting practice that assists individuals in successfully mastering the target behavior and overcoming obstacles, targeting perceived behavior control change, have been shown to be effective in promoting intention and behavior change in physical activity contexts [26].

While there is evidence for the utility of interventions based on the recommendations of self-determination theory (eg, use of strategies like fostering autonomy support in influential others) or the theory of planned behavior (eg, providing persuasive communications targeting belief change), the integrated behavior change model also acknowledges that these strategies are often more efficacious in changing motivation or intention than changing behavior [27]. Recognizing the shortfall in the association between motivation and behavior, such as relatively modest intention-behavior relations observed in physical activity [28-32], other strategies that bolster intentions may be useful. For example, researchers adopting action control frameworks have suggested that leveraging [28,33] intervention strategies such as planning and self-monitoring may strengthen the intention-behavior relationship and increase the likelihood that individuals act on their good intentions when performing physical activity [15,34].

Study Overview Objectives

Given the need for interventions to help children maintain physical activity levels as they transition into adolescence and to help parents become more physically active, our group used the integrated model as a starting point to develop a novel, remotely delivered dyadic physical activity promotion intervention. By applying the integrated behavior change model to a parent-child intervention, we aim to use and strengthen within-family dynamics to foster autonomous motivation and encourage physical activity in both parents and preteen children. In this protocol, we describe a planned randomized controlled trial for testing the effects of this intervention in a sample of insufficiently active Finnish-speaking parents and children.

Methods

Trial Design

The trial will adopt a randomized waitlist control design in which parent-child dyads are the unit of randomization. Families will be randomized on sign-up to either an intervention group that receives the intervention immediately after baseline data collection or to a waitlist control group that will receive the intervention after all outcome data have been collected.

Participant Recruitment and Eligibility

Parent-child dyads will be recruited from the general Finnish population through direct contact with a panel company, through social media advertisements, and through posts on parenting discussion boards and forums. Individuals who responded to the advertisements were directed to a screening survey hosted on the Webropol platform. To be eligible for inclusion, dyads must consist of a parent or guardian aged >18 years and a child aged 8-12 years, and both dyad members need to be considered sedentary. Parents are considered sedentary if they were not active for at least 30 minutes a day on 5 or more days in the past week, and children are considered sedentary if they were not active for at least 60 minutes per day in the past week. Dyads will be excluded if either the parent or child reported having a medical condition or injury likely to prevent them from safely engaging in physical activity. People meeting the inclusion criteria can continue in the Webropol survey to read information

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about the trial and are then offered the opportunity to provide their contact details to opt-in to the trial.

Power Analysis

The projected sample size was estimated from a statistical power analysis conducted using G*Power (version 3.1; Heinrich-Heine-Universität Düsseldorf). The analysis assumed a small to medium effect size (Cohen *f*=0.235) for the intervention on our primary outcome variable, leisure time physical activity, calculated from an average of effect sizes from meta-analyses of self-determination theory–based interventions (Hedges *g*=0.45 [35]) and interventions targeting self-efficacy (Cohen *d*=0.48 [36]), with α set at .05 and statistical power set at .80 reveal a projected total sample size of 178 participants. We also assumed a projected 30% attrition rate in participants through the study based on similar trials [37], resulting in a sample of 254 participants (ie, 127 dyads) to be recruited at baseline.

Study Procedures

All recruitment materials will be delivered in a web-based format with a URL forwarding participants to a screening and informed consent survey hosted on the Webropol platform. First, parents will be presented with an eligibility questionnaire to assess whether they and their children making reference to themselves and their least active child aged between 8 and 12 years, meet the inclusion criteria. Eligible parents will then be presented with information about the study and an informed consent form. Parents who provide informed consent to participate in the study will be prompted to provide their name, contact details, and the name of their least active child, aged between 8 and 12 years, and will be enrolled in the study.

After enrolling in the trial, dyads will be assigned by computerized random-digit generation to 1 of 2 groups: an immediate intervention group that receives the intervention immediately after baseline data collection, or a waitlist control group that will receive the intervention after all outcome data have been collected.

Participants in both groups will be asked to provide outcome data immediately after randomization, 3 months later, and 6 months later. Outcome data will be collected through web-based surveys hosted on the Webropol platform and through physical activity measurement devices mailed to participants' homes. For web-based surveys, parents will be emailed 2 separate URLs: 1 for themselves and 1 for their child. Parents will be instructed that they may help their child understand the survey items but should avoid influencing their child's answers to the questionnaire.

Participants in the immediate intervention group will receive the intervention between the baseline and 3-month data collection points, while participants in the waitlist control group will receive the intervention after all data collection has been completed. While data are planned to be collected at baseline, 3 months, and 6 months, the trial includes a stopping rule, such that 6-month follow-up data will not be collected if there is no effect of the intervention on the primary outcome (ie, leisure time physical activity) at the 3-month follow-up. The trial design flow diagram is presented in Figure 1.

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Figure 1. A flowchart of enrollment and data collection for the ProAct trial.

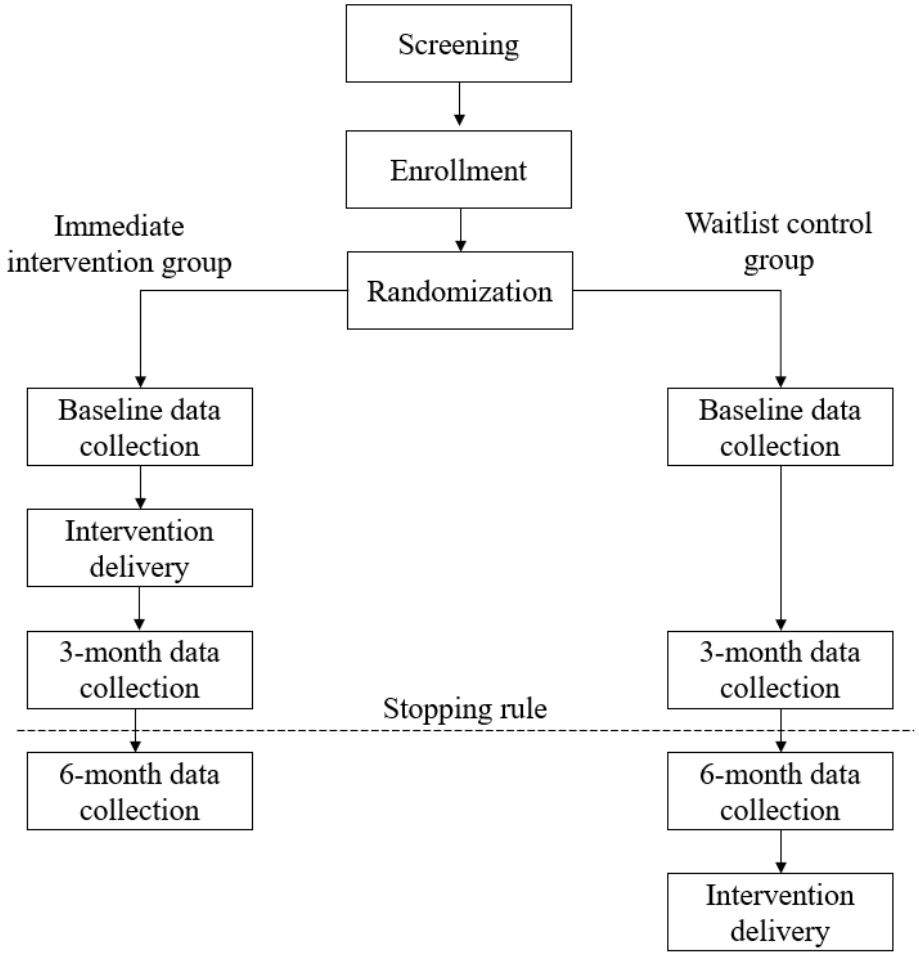

Intervention

Immediate Intervention Group

The intervention consists of 4 web-based sessions hosted through a videoconferencing platform (Zoom Inc) and facilitated by 1 or 2 members of the research team. The 4 sessions will be delivered in weeks 1, 3, 5, and 8 of the program. Summaries of each session, including the target constructs and behavior change techniques used in each session, are presented in Table 1. The first session will involve only parents and will last 90 minutes. It focuses on instructing parents in the use of autonomy-supporting parenting behaviors. The remaining 3 sessions will involve both parents and children and will last 45 minutes. Session 2 prompts a discussion of the benefits of an active lifestyle, including enjoyment and importance, and gets participants to set individual and joint physical activity-related goals. Session 3 teaches participants how to make action plans and coping plans (ie, problem-solving) when pursuing physical activity goals. Session 4 covers social norms related to physical activity, has participants specify their identity related to physical activity, and prompts social support strategies within each dyad.

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Table 1. Content and targets for each intervention session in the ProAct trial. Behavior change techniques preceded by an "M" are drawn from the Motivation and Behavior Change Techniques [38]. Behavior change techniques preceded by a "T" are drawn from the Behavior Change Taxonomy version 1 [39].

Session	Target constructs	Behavior change techniques
Session 1: 90 minutes and parents only	Autonomy supportive parenting	• M3. Use non-controlling, informational language • M5. Provide a meaningful rationale • M6. Provide choice • M7. Encourage the person to experiment and self-initiate the behavior • M10. Show unconditional regard • M12. Use empathic listening • M16. Clarify expectations • T1.1 Goal setting yeah • T1.4 Action planning • T4.1 Instruction on how to perform the behavior • T4.2 Information about antecedents • T5.3 Information about social and environmental consequences • T5.6 Information about emotional consequences • T8.1 Behavioral practice/rehearsal • T16.3 Vicarious consequences
Session 2: 45 minutes, parents, and children	Attitude	• M4. Explore life aspirations and values • M6. Provide choice • M7. Encourage the person to experiment and self-initiate the behavior • M16. Clarify expectations • M17. Assist in setting optimal challenge • M19 Help develop a clear and concrete plan of action • M20 Promote self-monitoring • T1.1 Goal Setting (behavior) • T1.3. Goal Setting (outcome) • T1.5 Review behavior goal(s) • T1.6 Discrepancy between current behavior and goal • T2.3 Prompt self-monitoring of behavior • T4.1 Instruction on how to perform the behavior • T5.6 Information about emotional consequences • T15.3 Focus on past success
Session 3: 45 minutes, parents, and children	Perceived behavioral control and self-regulation	• M15. Address obstacles for change • M19. Help develop a clear and concrete plan of action • M20. Promote self-monitoring • M21. Explore ways of dealing with pressure • T1.2 Problem-solving • T1.5 Review behavioral goals • T1.6. Discrepancy between current behavior and goal • T2.2 Feedback on behavior • T8.7 Graded Tasks • T15.1 Verbal persuasion about capability • T15.3 Focus on past success.
Session 4: 45 minutes, parents, and children	Subjective Norm and perceived autonomy support	• M2 Prompt identification of sources of pressure for behavior change • M8. Acknowledge and respect perspectives and feelings • M9. Encourage asking of questions • M14. Prompt identification and seek available social support • T1.1 Goal Setting (behavior) • T1.3 Goal Setting (outcome) • T1.4 Action planning • T1.5 Review behavioral goals • T1.7 Review Outcome Goals • T3.2 Social Support (Practical) • T3.3 Social Support (Emotional) • T6.2 Social comparison • T6.3 Information on others' approval. • T13.1 Identification of self as role model • T13.5 Identity associated with changed behavior

In addition to the web-based sessions, participants will have access to a website that includes materials that support the content of each session. This includes worksheets, slide decks and recorded versions of the sessions, a menu of physical

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activities suitable for parents and children, and further practice materials.

Between sessions, participants will receive SMS text messages that ask them to provide written feedback on their progress; offer advice, suggestions, or reminders; or prompt reflection on their motives for physical activity. Parent participants will also be granted access to a moderated web-based chat forum (WhatsApp group [Meta Facebook, Inc]) in which parents can share their experiences with the sessions and provide and receive social support from other participating parents. Intervention materials are available on the internet [40].

Waitlist Control Group

Participants assigned to the waitlist control group will complete the same data collection procedures as the immediate intervention group but will not be required to undertake any alternative intervention tasks during the data collection period. After the data collection period, participants in the waitlist control group will be invited to receive the intervention and accompanying materials.

Outcomes

Overview

Measures of psychological constructs will be assessed using multi-item scaled survey measures, while leisure-time physical activity is to be assessed using self-reported surveys and observationally through accelerometer measurements. All items were translated into Finnish by native speakers and piloted on a sample of 8- to 12-year-old Finnish children and their parents. Full measures are available on the internet [40].

Primary Outcomes (Physical Activity and Sedentary Time)

Self-reported physical activity and time spent in sedentary activities for both parents and children will be assessed using the Godin-Shepard leisure time exercise questionnaire [41], where participants will be required to report the number of occasions they engaged in light, moderate, and vigorous physical activity for 15 minutes or longer. Sedentary time will be measured using 2 items per participant, targeting weekdays and weekend days separately (eg, “In the past 7 days, how much time did you spend sitting during a typical weekday after school or weekend day?”) [42]. Items are scored on a sliding scale from “no time” upwards in increments of half an hour.

Secondary Outcomes

Device-Measured Physical Activity

Physical activity will also be assessed using a hip-worn triaxial accelerometer (Hookie AM20; Traxmeet Ltd). Each dyad will be mailed 2 accelerometers, detailed instructions on wearing the device, and a diary for recording when they wore the accelerometer, how they commuted to school or work, and any events that may have inhibited accurate data (eg, missed days and exercise done without the device). Raw data from accelerometers will be processed using the *GGIR* package in R software (R Foundation for Statistical Computing) [43], with outcome scores provided as the amount of time spent engaged in sedentary behavior, light physical activity, moderate physical activity, and vigorous physical activity.

Autonomy-Supportive Parenting

Autonomy-supportive parenting practices will be assessed using a 4-item questionnaire based on measures used in a previous study [44], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Perceived Autonomy Support

Perceived autonomy support will be assessed using the perceived autonomy support scale for exercise settings [45]. For children, the scale refers to autonomy support from parents, while for parents, the scale makes reference to autonomy support received from family. All items are scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Autonomous and Controlled Motivation

Autonomous and controlled motivation for both parents and children is assessed using 4 items each [46], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Attitude

Attitude toward engaging in physical activity is assessed using 3 items with a common stem [44,47], with responses provided on a 5-point semantic differential scale (eg, unenjoyable [1] to enjoyable [5]).

Subjective Norms

Subjective norms in parents are assessed using 3 items referring to important others [44,47]. Children answered similar items, but in specific reference to family and friends separately. All items are scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Perceived Behavioral Control

Perceived behavioral control is assessed in both parents and children using 2 items [44,47], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Intention

Intention to engage in leisure time physical activity is assessed in both parents and children through 3 items [44,47], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Self-Monitoring

Self-monitoring toward physical activity is assessed using 2 items [44,48], each scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Habit

Habits are assessed using the 4-item automaticity subscale of the self-reported habit index [49,50], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Acceptability

For participants in the immediate intervention group, the postintervention (3 months) web-based questionnaire will include survey items assessing the accessibility and feasibility of intervention procedures. Participants will also be invited to

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attend a 45-minute web-based exit interview to explore participant perceptions of the intervention content and possible improvements for future implementation.

Data Analysis

Hypotheses will be tested using R software. All analyses will initially be performed as intention-to-treat, and per-protocol analyses will also be undertaken for comparison. Patterns of missing data will be explored using the Little missing completely at random test. Missing data in the final analysis will be inferred using full-information maximum likelihood analysis. We will test the efficacy of the intervention on our primary outcome, self-reported leisure-time physical activity, using an iterative series of generalized linear models. Independent variables will include time, intervention condition, demographic covariates (eg, start date, gender, and age), delivery group clustering, within-dyad clustering, and person-intervention theory fit $P\Delta$ [51]. Each variable group will be added in a subsequent iteration of the model, and model fit statistics will be examined at each iteration. This process will be repeated for each secondary outcome variable (perceived autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, action planning, coping planning, self-monitoring, and behavioral automaticity).

We also intend to assess the effect of theory-based mediators on change in physical activity using a path model. Specifically, we aim to assess whether the effects of intervention conditions on change scores in physical activity outcomes (both primary and secondary) are mediated by change scores in each of the psychological constructs targeted by the intervention (ie, perceived autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, action planning, coping planning, self-monitoring, and behavioral automaticity).

Ethical Considerations

All study procedures have been approved by the University of Jyväskylä Human Sciences Ethics Committee (statement number 806/13.00.04.00/2023). All parents interested in participating in the study will be presented with detailed information about the intervention, potential risks to participants, the right to withdraw, and data security arrangements. Parents will have the chance to read this information and ask questions of the research team before providing their informed consent to participate. Data will be stored on secure cloud-based servers hosted by the University of Jyväskylä consistent with our data archiving and storage management plan, compliant with university guidelines. At the conclusion of data collection, participants' physical activity and data on psychological measures at each measurement point will be matched using pseudonymized codes and deidentified to the greatest extent possible. Participants will not be offered any financial or other compensation for their participation.

Results

The project team received final notification of research funding approval for the current project from the Finnish Ministry of Education and Culture, Sport Science Funds, in March 2022 (PROJECT 350904), and the trial has been preregistered on ClinicalTrials.gov (ID 806/13.00.04.00/2023). Enrollment into the trial commenced on September 20, 2023. Enrollment is scheduled to continue until March 2024, with the final collection of follow-up data scheduled for December 2024.

We expect that the research will provide valuable formative evidence for the efficacy of a theory-driven family-based physical activity intervention strategy. Further, as the proposed trial includes open materials and tests of the theory-driven mechanistic effects that may encourage behavior change, this research may also serve as a valuable stepping stone to the development of more large-scale, low-cost interventions for family behavior change.

Discussion

Overview

This protocol presents a randomized controlled trial aiming to increase physical activity levels in inactive parent-child dyads within Finland, based on the integrated behavior change model. We hypothesize in this protocol that both parents and children will show increased levels of physical activity, our primary outcome variable, both at the immediate and 3-month postintervention stage, relative to a waitlist control group. Further, we hypothesize we will observe similar changes in the trial's secondary outcomes, the psychological constructs of the integrated behavior change model (ie, autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, self-monitoring, intentions, and habit), in the intervention group relative to the waitlist control group.

Potential Findings and Implications

Children transitioning into adolescence have shown a sharp decline in activity levels [3], while parents are generally less active than similar adults without children [8]. Thus, both populations individually represent valuable targets for intervention. Recognizing this, governments and health departments have recommended behavioral interventions to promote physical activity participation in both groups. However, beyond strategies to influence physical activity in either children or parents separately, research indicates that parents and children likely have a noteworthy influence on each other's physical activity behaviors and beliefs [6,7,9]. Thus, the delivery of interventions in family contexts, such as parent-child dyads, represents a potentially highly valuable strategy to promote physical activity participation in both populations. This is supported to a degree in meta-analysis, as dyadic interventions encouraging an active lifestyle demonstrated slightly larger effects than those targeting individuals [10]. Yet, such interventions remain relatively rare compared to more traditional, individual-targeted programs, particularly those that are based on behavioral theory which may contribute to their efficacy and relevance to health sciences overall [10].

This study tests a theory-based family behavioral intervention aimed at promoting change in physical activity participation in parent-child dyads. The intervention aims to foster autonomous motivation, enhance social support, and reduce perceived barriers to exercise in an atmosphere that is accepting and open. The intervention will make a unique contribution to practice

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and theory. Given the low levels of physical activity participation in adult and child populations, demonstrating the efficacy of web-based behavioral intervention in increasing physical activity that is both replicable and potentially scalable will make a valuable contribution to practice in health care contexts. In this research, we aim to enhance the potential usefulness of this intervention in the context of informing refined, scalable interventions based on results with the use of open materials and data, including intervention content and delivery guides. Further, from a scientific perspective, the application of a theory-based intervention developed in line with current practice intervention guidelines presents a potentially valuable test of mechanistic effects presented in the integrated behavior change theory and its component models [12-15], identifying the "active ingredients" of the intervention that are associated with desired outcomes. That is, while the integrated behavior change theory has been supported in several correlational studies [22,23,52], such research only provides an indication of the likely variables most important in determining behavior and can by their correlational nature not be used for any assertions of direction or causality. Thus, a key contribution of this intervention is assessing not only whether the program is successful in changing behavior, but also in assessing which target constructs mediate the effects of the intervention on behavior change and may therefore be most valuable when refining current strategies or developing new programs.

Limitations

Beyond the expected value presented by the research, it is also important to note that the trial faces some expected and inherent challenges and limitations. For example, as the intervention does not include any reward or payment to participants beyond the benefits of the intervention itself, it is likely that parents who consent to enroll themselves and their child in the program will already be at least somewhat motivated to change their physical activity behavior. Such an issue has been noted in the previous parent-for-child interventions [53]. If this is the case, it is likely that the intervention effects will not be as strong as expected, as already motivated participants possess a lesser degree of potential for change than might be expected in families with unmotivated parents. While this nonetheless poses a challenge to the intervention, it is important to note that motivation or knowledge of the need for physical activity is commonplace [9,54], even as actual activity levels remain low. As the strategies used in this intervention include training parents in autonomy support rather than controlling strategies that may inhibit their child's autonomy and thus harm the development of active lifestyles [20,55], as well as strategies to bridge the intention-behavior gap, this trial still has bona fide value in targeting this key population. However, the problem of accessing and enrolling unmotivated families into intervention programs remains a concern for behavior change research.

Conclusions

Given the generally low levels of physical activity in Finnish parents and children, there is a notable need for intervention strategies aiming to encourage an active lifestyle in these populations. This protocol presents an upcoming randomized control trial based upon the integrated behavior change model, which aims to use a series of web-based, theory-based behavior-change strategies delivered to both parents and children as a dyadic program. In doing so, the proposed trial aims to extend upon current literature in several key aspects. First, by targeting parents and children as a dyad, the proposed study aims to add to the available literature on whether physical activity behavior change programs may be more efficacious when targeting the family unit, rather than parents or children individually. Second, as this study uses a theory-based design, testing change in both physical activity and related psychological constructs, the trial also offers an opportunity to test which beliefs and psychological factors are most associated with concomitant change in physical activity. These data, combined with the trial's open materials, may thus serve as a valuable stepping stone to the development of more large-scale, low-cost interventions for family behavior change.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Finnish Ministry of Education and Culture.
[PDF File (Adobe PDF File), 44 KB - resprot_v13i1e55960_app1.pdf]

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Protocol

Equity-Centered Postdischarge Support for Medicaid-Insured People: Protocol for a Type 1 Hybrid Effectiveness-Implementation Stepped Wedge Cluster Randomized Controlled Trial

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Abstract

Background: Disparities in posthospitalization outcomes for people with chronic medical conditions and insured by Medicaid are well documented, yet interventions that mitigate them are lacking. Prevailing transitional care interventions narrowly target people aged 65 years and older, with specific disease processes, or limitedly focus on individual-level behavioral change such as self-care or symptom management, thus failing to adequately provide a holistic approach to ensure an optimal posthospital care continuum. This study evaluates the implementation of THRIVE—an evidence-based, equity-focused clinical pathway that supports Medicaid-insured individuals with multiple chronic conditions transitioning from hospital to home by focusing on the social determinants of health and systemic and structural barriers in health care delivery. THRIVE services include coordinating care, standardizing interdisciplinary communication, and addressing unmet clinical and social needs following hospital discharge.

Objective: The study's objectives are to (1) examine referral patterns, 30-day readmission, and emergency department use for participants who receive THRIVE support services compared to those receiving usual care and (2) evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Methods: We will perform a sequential randomized rollout of THRIVE to case managers at the study hospital in 3 steps (4 in the first group, 4 in the second, and 5 in the third), and data collection will occur over 18 months. Inclusion criteria for THRIVE participation include (1) being Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) residing in Philadelphia; (3) having experienced a hospitalization at the study hospital for more than 24 hours with a planned discharge to home; (4) agreeing to home care at partner home care settings; and (5) being aged 18 years or older. Qualitative data will include interviews with clinicians involved in THRIVE, and quantitative data on health service use (ie, 30-day readmission, emergency department use, and primary and specialty care) will be derived from the electronic health record.

Results: This project was funded in January 2023 and approved by the institutional review board on March 10, 2023. Data collection will occur from March 2023 to July 2024. Results are expected to be published in 2025.

Conclusions: The THRIVE clinical pathway aims to reduce disparities and improve postdischarge care transitions for Medicaid-insured patients through a system-level intervention that is acceptable for THRIVE participants, clinicians, and their teams in hospitals and home care settings. By using our equity-focused case management services and leveraging the power of the electronic medical record, THRIVE creates efficiencies by identifying high-need patients, improving communication across

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acute and community-based sectors, and driving evidence-based care coordination. This study will add important findings about how the infusion of equity-focused principles in the design and evaluation of evidence-based interventions contributes to both implementation and effectiveness outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/54211

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KEYWORDS

health care disparities; evidence-based practice; Medicaid; transitional care; implementation science; socioeconomic disparities in health

Introduction

Background

Complex care management provides critical support in the days and weeks following hospitalization for individuals with multiple chronic conditions. This postdischarge support can be especially beneficial for nearly 80 million individuals in the United States who are insured by Medicaid [1] and experience higher rates of chronic illness [2], more frequent hospitalizations, and worse clinical outcomes following discharge [3-5]. Readmissions among adults insured by Medicaid ages 45-64 years stand at 24% compared to 20% for older adults insured by Medicare [6]. Similarly, about 34% of individuals insured by Medicaid will experience an emergency department (ED) visit annually, far exceeding the rates of those insured commercially [7]. They experience deficits in primary care assessment and treatment and fewer preventive treatments and guideline-concordant care [8,9]. Thus, Medicaid-insured patients may present to the hospital with poorly managed chronic medical conditions compared with other patients and subsequently require more intensive transitional care coordination in the aftermath of a hospitalization. The need to improve support for Medicaid-insured people following hospitalization prompted our development of the THRIVE clinical pathway. THRIVE is a clinical pathway that supports Medicaid-insured individuals with multiple chronic conditions transitioning from hospital to home by coordinating care, standardizing communication, and addressing unmet needs following hospital discharge, including the social determinants of health.

Most existing postdischarge or transitional care programs were not developed to attend to the specific needs of people insured by Medicaid and instead support older adults or patients with specific chronic illnesses such as heart failure. Other postdischarge support programs require the addition of trained health care providers such as advanced practice nurses or patient navigators to coordinate care [10-12]. At least 1 randomized controlled trial (RCT) evaluating the use of community health workers (CHWs) has demonstrated lower rates of rehospitalization for enrolled low-income individuals with significant social needs [13]. Despite facilitating important links to community-based services, CHWs are unable to manage clinical needs [13-15]. Other postdischarge support programs such as the Camden Coalition Care Model provide transitional care support to people with significant social needs with high rates of health care use, many of whom are insured through Medicaid [16]. An RCT of the Camden Coalition Care Model demonstrated no differences in readmissions at 180 days between treatment and comparison [17]. The care transitions innovation model also provides transitional care support for economically disadvantaged adults, although an RCT found no reductions in 30-day readmissions or ED use [12]. At least 3 additional studies by Liss et al [18], Balaban et al [19], and Jackson et al [20] featured weekly health coaching, self-management education, and medical home follow-up for medically and socially complex patients, although the results of these interventions have been mixed. Inconsistent findings among existing postdischarge support programs suggest the need for alternative innovations that focus on systemic and structural barriers in health care delivery.

Similar to other inequities, posthospitalization disparities among people insured by Medicaid can be traced to a long history of institutional and economic inequities impacting care delivery and outcomes. Racial and ethnically minoritized populations are overrepresented in Medicaid compared to other forms of insurance, with approximately half of Medicaid enrollees younger than 65 years of age being members of racial and ethnically diverse backgrounds [21]. With incomes 138% below the federal poverty level [22], people insured by Medicaid experience the impact of the social determinants of health, including higher levels of financial strain and concerns over out-of-pocket costs, and experience more challenges in accessing specialists and community-based care [23-28]. People insured by Medicaid are also more likely to experience the impact of systemic and institutional racism. Systemic racism refers to the distribution of goods and services in such a way that advantages one group over another or fails to provide adequate resources in the face of need. Systemic factors such as inadequate discharge planning and poor care coordination similarly contribute to unfavorable posthospitalization outcomes [21,27-29]. Interpersonal racism is often expressed through bias and discrimination and is often expressed through microaggressions and stigmatizing language. Distinct from Medicare, Medicaid has its roots in the public welfare system, which has resulted in significant social stigma. Medicaid beneficiaries have described encounters with medical professionals where they were subjected to racial and socioeconomic prejudice [29,30]. These experiences may result in the avoidance of health care settings altogether and more difficulties accessing timely specialty care, all of which paradoxically increase ED use or lead to avoidable

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hospitalizations due to delayed management of chronic illnesses [31,32].

Given the long-standing disparities experienced by people insured by Medicaid during and following hospitalization, there is a need for transitional care support focused on systemic and structural barriers to care and social determinants of health. The Centers for Disease Control and Prevention [33] defines health equity as "the state where everyone has a fair and just opportunity to attain their highest level of health." Using an equity lens draws attention to those at greatest risk to how social and economic strata shape access to material resources while also identifying the impact of marginalizing conditions such as racism and health resource constraints that intersect and result in disparate outcomes [34]. Using an equity lens also emphasizes what Peterson et al [35] refer to as the multiple, intersecting spheres of power, defined as the practices, processes, and policies that determine the distribution and access to resources and opportunities needed to be healthy. These spheres of power intersect with individual factors (eg, personal agency) to produce disparate outcomes. From this perspective, addressing postdischarge disparities requires a focus on optimizing service delivery and interdisciplinary collaborations across settings.

Codeveloping the THRIVE Clinical Pathway

Using an equity lens, our interdisciplinary team of clinicians, researchers, and community members formed to engage in meaningful action to support people insured by Medicaid and transform health care practices and processes that impeded sufficient transitional care support [36]. We began with months of participatory activities informed by an equity lens and principles of human-centered design [37], machine learning [38], and mixed methods approaches [39], which culminated in the development of THRIVE [40]. The THRIVE clinical pathway was launched in a large Level 1 Trauma Center in Philadelphia in 2019 and includes five core components: (1) the identification of individuals insured by Medicaid and coordination of home care referral during discharge planning while hospitalized; (2) provision of immediate home care services where nurses perform medication reconciliation, intensive teaching, and chronic disease management; (3) continued clinical oversight by discharging physicians; and (4) standardized communication between community and acute care providers via web-based case management that (5) prioritizes health-related social needs such as housing or food insecurity faced by Medicaid-insured patients (Figure 1). Our work as a team is anchored by our advisory board, which is comprised of community members, some of whom are Medicaid insured. The THRIVE Community Advisory Board meets quarterly to meaningfully engage past THRIVE participants, caregivers, and community members to ensure that the program goals are rooted in the vision and values of the community we serve.

In many health care settings, posthospitalization disparities among economically disadvantaged people are linked to personal deficits or behaviors. They are often referred to by their volume of health resource use, invariably referred to as "high-cost high needs," "superusers," "frequent flyers," "noncompliant," or "bounce backs," and are essentially blamed for poor outcomes. From this perspective, postdischarge disparities are often regarded as immutable social circumstances or moral failures beyond the purview of medicine's reach instead of a result of the impact of the social determinants of health, structural determinants such as failures in service delivery (eg, fragmented care coordination), and interpersonal racism [41]. In developing THRIVE, we sought to counter long-standing stigmatizing views and instead directed our focus on re-engineering service delivery and intensifying resources to those most in need while maintaining active involvement with affected community members in programmatic design and sustainability efforts.

Published results from a nonrandomized pilot of the first year of the THRIVE pathway revealed that participants experienced increased connections to postacute care services, including social support, and a 50% decrease in rates of 30-day readmissions and ED use compared to patients receiving standard care [42]. With these early findings, we are now poised to evaluate a scalable and sustainable postdischarge management process in a new setting and with a more rigorous evaluation and attention to organizational factors influencing success.

This study will deploy a type 1 hybrid effectiveness-implementation stepped wedge cluster RCT across a single hospital in Philadelphia [43]. The advantage of this trial design is that it offers an efficient and practical way to introduce THRIVE to new sites while reducing the ethical concerns of withholding an intervention that has shown benefit for economically disadvantaged populations. This study will also be guided by the Exploration, Preparation, Implementation, Sustainment framework; Proctor's outcomes framework; and the Health Equity Implementation Framework (HEIF) [44-46]. The HEIF adapts the Integrated Promoting Action on Research in Implementation in Health Services framework. The HEIF proposes determinants that are believed to predict the successful and equitable implementation of an intervention. The 3 health equity domains included in the HEIF include cultural factors, clinical encounter factors, and societal context [47]. Our use of the framework will help us to detect any factors that might lead to uneven referrals to THRIVE; disparate benefits to the intervention; and any barriers that might prevent organizations, health care providers, or administrators from engaging in the intervention. In their recently published paper, Brownson et al [48] noted that "Incorporating a strong equity focus in implementation science requires not only a deliberate emphasis on the needs, culture, and history of the populations and communities but also more critical analyses and deeper understanding of systems and policies, including care delivery and provider attitudes from which inequities might arise." They propose action steps for making health equity more prominent in implementation science. To that end, we incorporate and adapt our study design to ensure principles of equity in the approach to data collection, measures, contextual alignment, and dissemination practices (Table 1).

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Figure 1. Components of the THRIVE clinical pathway. APP: advanced practice provider; EHR: electronic health record; MD: medical doctor; OT: occupational therapy; PRN: pro re nata (as needed); PT: physical therapy; RN: registered nurse; SW: social worker.

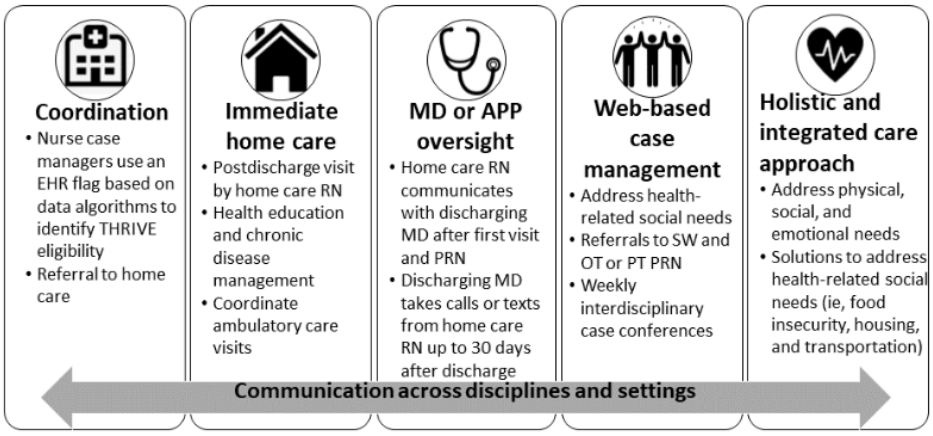

Table 1. Equity-relevant domains included in the implementation and outcome evaluation of THRIVE [48].

Domain	Recommendation	Core elements within this study
Evidence base	Link social determinants with health outcomes	Implement THRIVE for all Medicaid-insured individuals at a new study site to meet the postdischarge clinical and social needs of an economically disadvantaged population.
Methods and measures	Integrate equity into implementation models	Incorporate the 3 domains of the Health Equity Implementation Framework into the implementation evaluation.
Context	Engage organizations in internal and external equity efforts	Engage with clinical partners, administrators, and community advisory board members to implement THRIVE at a new site.
Cross-cutting issues	Focus on equity in dissemination efforts	Plan activities with THRIVE Community Advisory Board to disseminate study results.

Aims and Hypotheses

The specific aims of this research are to:

1. Examine referral patterns, 30-day readmission, and ED use patterns for participants who receive THRIVE support services compared to those receiving usual care.
   - Hypothesis 1: We anticipate that referral patterns will increase and that 30-day readmissions and ED use will decrease for THRIVE participants compared to usual care.
2. Evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Methods

Overview

Our study methods are described per the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement and the CONSORT (Consolidated Standards of Reporting Trials) extension for stepped wedge cluster RCTs [49,50]. The SPIRIT and CONSORT checklists are included as Multimedia Appendices 1 and 2.

Study Setting

The study setting includes a single site—Pennsylvania Hospital (PAH), the nation's first acute care setting in the country and 1 of 6 hospitals in the University of Pennsylvania Health System. More than 50% of PAH's patient population on the hospitalist service self-identify as racial or ethnic minority individuals, and >25% are Medicaid insured [34]. PAH provides over 40,000 ED visits and >18,000 adult admissions annually.

Design and Randomization

Overview

This is a prospective single-site type 1 hybrid effectiveness-implementation pragmatic stepped wedge cluster RCT. Our stepped wedge design will include a sequential randomized rollout of the intervention to case managers at PAH in 3 steps, and data collection will occur over 18 months. This mixed methods (quantitative and qualitative) study design involves simultaneous collection and analysis of quantitative and qualitative data, giving priority weight to the quantitative data to evaluate program referrals, outcomes, and program fidelity, while qualitative data will evaluate the process through detailed descriptions of perspectives of barriers and facilitators faced by health care providers in implementing the THRIVE intervention [51]. This study includes qualitative interviews and surveys of clinicians and administrators to assess their perspectives on appropriateness, feasibility, and acceptability of THRIVE. Nesting the qualitative interviews within an RCT of the THRIVE intervention will allow us to determine whether the intervention improved primary outcomes (referrals to home care, 30-day readmission, ED use, and connection to primary care providers) and to identify professional and organizational barriers to implementation. Combining these insights with effectiveness outcome data will allow consideration for meaningful contextual factors that are considered critical to the implementation of THRIVE and subsequent outcomes.

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Randomization

Groups of case managers (4 in the first group, 4 in the second, and 5 in the third) were randomly assigned by the study methodologist to each sequence using a random number generator. A stepped wedge design—that is, a 1-time crossover design—was used for THRIVE (Table 2).

Specifically, following a baseline data collection period, 4 case managers will be randomized to receive training on the THRIVE clinical pathway. Following training, they begin referring to the THRIVE clinical pathway. At 8-week intervals, the remaining case managers will be trained in the THRIVE intervention and will be able to begin submitting referrals. Since case managers from the sequences work within the same space, the ability to conceal allocation was limited; however, all case managers were made aware of their upcoming ability to refer to the THRIVE clinical pathway.

Table 2. Study design for the type 1 hybrid effectiveness-implementation stepped wedge cluster randomized controlled trial of the THRIVE clinical pathway.

Cluster	Baseline (3 months)	Enrollment period 1 (8 weeks)	Enrollment period 2 (8 weeks)	Enrollment period 3 (8 weeks)	Follow-up (18 months)
Sequence 1 (4 case managers)		✓	✓	✓	✓
Sequence 2 (4 case managers)			✓	✓	✓
Sequence 3 (5 case managers)				✓	✓

THRIVE Eligibility Criteria

Individuals eligible for a THRIVE referral include (1) being Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) residing in Philadelphia; (3) having experienced a hospitalization at the study hospital for more than 24 hours with a planned discharge to home; (4) agreeing to home care at partner home care settings; and (5) being aged 18 years or older. If home care services are declined at any time following discharge, THRIVE services are also discontinued. If palliative or hospice services are ordered following discharge, THRIVE services will not be offered.

Clinician Eligibility and Recruitment

Nurse case managers (CMs), home care nurses, physicians, advanced practice providers, and administrators who are actively involved in supervisory roles or in referring to THRIVE will be invited to provide feedback on the appropriateness, accessibility, feasibility, and workload involved in referring to the THRIVE clinical pathway. During the consenting process, the research coordinator will obtain preferences for the best communication method to schedule the interview (eg, email or telephone call). A total of 22 interviews and surveys are planned. Participants who complete both the surveys and interviews will receive a US $90 gift card by mail.

Ethical Considerations

This study was approved by the University of Pennsylvania's Institutional Review Board (IRB #4 approved this protocol #852910 on March 10, 2023). The study will be conducted according to the Declaration of Helsinki and national regulations. Study participation is voluntary, and written consent will be obtained prior to clinician interviews. Our IRB approval includes a HIPAA (Health Insurance Portability and Accountability Act) waiver of informed consent for THRIVE participants' clinical data. All study data collected will be deidentified, pseudonyms will be used, and data will only be accessible to the research team and stored on password-protected computers. Clinicians will be compensated US $90 by gift card for interview participation. Individual participants will not be identifiable in any published material.

Data Collection and Management

THRIVE Participants and Usual Care Group

Characteristics of THRIVE participants captured in weekly case conferences (eg, home care services, social determinants of health identified and met, and community-based services) will be stored on a Research Electronic Data Capture (REDCap; developed by Vanderbilt University) database. Data will be derived from the patient electronic health record (EHR) and hospital billing system to compare the postdischarge outcomes of participants receiving THRIVE compared to those who do not. These data will be deidentified, and a HIPAA waiver of informed consent was obtained by the University of Pennsylvania's IRB. Data will be stored on a secure password-protected data server, and access will be provided to the study statisticians (MOH), who will be blinded to the assignment of the intervention. All aspects of study design, database integrity, and study conduct will be overseen by our data and evaluation core team, which includes doctorly prepared health service researchers and statisticians.

Clinicians and Administrators

Case managers at PAH will be recruited and enrolled in the study per the stepped wedge design. At 8 weeks and 18 months, we will survey clinicians via Qualtrics (Qualtrics) and convene one-on-one interviews (or focus groups depending on clinician availability). Interviews will be conducted in the setting of the clinician's choice, either in a conference room in the hospital or via Zoom (Zoom Video Communications). During interviews, clinicians and administrators will be asked for permission to audio record the interview. If the participant agrees, all conversations from that point forward will be recorded. If the clinician or administrator consents to the interview but does not agree to recording, to retain the participant, the interviewer will take detailed notes during the conversation instead of recording. Interview documents are labeled with a unique identification number stored separately for identifying information about the participant. The study timeline is outlined in a SPIRIT diagram (Figure 2).

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram—THRIVE schedule of evaluations. ED: emergency department; PCP: primary care provider.

			Study period			
	Preallocation	Site enrollment	Post allocation (THRIVE referral period)			Follow-up
Timepoint	Retrospective data (Nov 27, 2022)	Study start (Mar 27, 2023)	Mar 27, 2023	May 22, 2023	July 17, 2023	Study end (Dec 27, 2024)
Enrollment:						
Nurse case manager		✓				
Sequence assignment		✓				
Interventions:						
Baseline data	←	→				
Sequence 1			←	—	—	→
Sequence 2				←	—	→
Sequence 3					←	→
Assessments:						
Use measures *Patient level (readmissions, ED use, PCP, and specialist appointments)			✓	✓		✓
Implementation measures *Clinician level (eg, appropriateness, acceptability, feasibility, and workload)			✓	✓		✓

Sample Size

We anticipate a sample size of 534 inclusive of THRIVE referrals and the comparison group (derived from the EHR). Based on a power analysis, a sample size of 472 (236 THRIVE participants and 236 comparisons) for the outcome of readmissions, or a sample of 534 (267 THRIVE participants and 267 comparisons) for the outcome of ED visits, will yield 80% power to detect significance at the .05 level. We will target a sample size of 534 to ensure adequate power for both outcomes. We anticipate consenting 22 clinicians and administrators to complete surveys and interviews to provide data for implementation outcomes.

The THRIVE Intervention

Current Usual Care

To provide evidence of the effectiveness and implementation of THRIVE, we will compare individuals receiving THRIVE services to patients receiving usual care. The current usual care will serve as the control condition that patients will receive during the control phases of the design. Usual care may include discharge care planning that reflects the patient's medical needs, which may or may not include referrals to home care, skilled nursing or rehabilitation facilities, and other outpatient services.

Enrollment in THRIVE

Enrollment in THRIVE begins with identification by CMs during hospitalization using a validated predictive algorithm developed by our team [31]. The algorithm is housed in the EHR and leverages principles of behavioral economics to "nudge" CMs to initiate a THRIVE referral. The THRIVE EHR flag was introduced to alleviate the need for CMs to manually identify THRIVE participants.

Once identified, THRIVE participants will receive a home care referral to Penn Medicine at home care services. The initial home care visit will be scheduled and completed by a nurse within 48 hours of discharge, at which time, medications are reconciled, discharge orders are reviewed, and person-centered goals of care are set. During the initial evaluation, home care nurses will determine the frequency of visits deemed necessary, with weekly visits ranging from 1 to 3 times depending on needs. Participants may receive additional services, such as speech or occupational therapy as required. All THRIVE participants receive a social work referral, their psychosocial needs are further assessed, and connections to community resources are provided. THRIVE participants receive a CHW referral as deemed necessary.

As a part of the THRIVE pathway, physician colleagues will extend continuity of care into the home following discharge to

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all THRIVE participants. Home care nurses will provide a brief patient status update to discharging physicians following the first home visit. During calls, nurses can raise questions about medications, clarify discharge orders, and receive guidance on emerging symptoms with the provider most recently involved with care. Extended supervision by discharging physicians will be provided for up to 30 days or until THRIVE participants have seen a primary care provider or specialist.

THRIVE participants will receive further support during discussions in our weekly interdisciplinary case management conferences for 4 weeks following discharge. During case management meetings, we will support connections to postacute primary, specialty care, behavioral health, and substance use services as needed. If a source of primary care is absent, we work to link THRIVE participants to community providers. Our intensive support addresses many of the social determinants of health that are known to influence health inequities such as housing, food insecurity, and limitations in access to behavioral health (Figure 1).

Implementation Strategies

We will use a series of implementation strategies to improve the effectiveness of THRIVE and promote its use [52]. These strategies will include (1) building and sustaining a coalition of diverse stakeholders through regular meetings and providing updates on THRIVE outcomes; (2) developing educational materials and conducting ongoing training of CMs, physicians, and advanced practice providers in the hospital and nurses and managers in home care using a scripted in-person training module to teach them about the elements of THRIVE and their role in implementing it; (3) auditing and providing feedback through the use of a referral dashboard to monitor all eligible THRIVE participants to document the individuals who were eligible for the intervention and not referred and providing feedback to case managers and document reasons for why referrals did not take place; (4) emailing reminders to case managers at weeks 2, 4, and 6; (5) identifying and preparing champions to promote the use of THRIVE; and (6) engaging of our advisory board to seek feedback for improvements.

Evaluation

Aim 1

Aim 1 is to examine referral patterns, 30-day readmission, and 30-day ED use patterns for participants who receive THRIVE support services compared to those receiving usual care.

Outcomes and Measures

The primary outcome includes the referral rate to home care made by CMs compared to baseline and the nonrandomized cluster. The secondary outcomes are 30-day readmissions and ED visits. Additional covariate data at the patient (eg, demographics and comorbidities) and unit levels (eg, type of unit and discharging team or provider) will be collected from analyses. For THRIVE participants, these outcomes will be assessed from the date of hospitalization, which resulted in a referral to THRIVE. For the usual care group, we will identify all readmissions and ED visits occurring after the first index hospitalization identified in the EHR for the calendar year of the study. Outcome measures, guiding framework, data sources, collection, and timing are described in Table 3.

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Table 3. Summary of outcomes, measures, data sources, collection method, and timing.

Construct and framework	Design	Method of collection	Timing
Aim 1: Examine referral patterns, 30-day readmission, and ED[a] use patterns for participants who receive THRIVE support services compared to those receiving usual care			
• THRIVE referrals[b] • 30-day readmissions[c] • 30-day ED visits[c] • Primary care visit within 30 days of discharge[c] • Specialty care visit within 30 days of discharge[c]	Stepped wedge cluster randomized controlled trial	Electronic health record	Baseline and at the study end
Aim 2: Evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability			
Health Equity Implementation Framework (HEIF)			
• Culturally relevant factors[d] • Clinical encounter[e] • Societal context[f]	Mixed methods approach to determine if HEIF factors are associated with uneven or disparate benefits to the intervention and to assess the implementation of THRIVE at a new site	Interviews with clinicians and administrators involved with THRIVE	8-week postintervention from the start of each sequence and at the study end
Exploration, Preparation, Implementation, Sustainment			
• Adoption[g] • Active implementation[h]	Mixed methods approach to determine the adoption and implementation of THRIVE in a new site	Interviews with clinicians and administrators	8-week postintervention from the start of each sequence and at the study end
Proctor implementation outcomes			
• Acceptability[i] • Appropriateness[j] • Feasibility[k]	Mixed methods approach to determine the Proctor implementation outcomes	Survey and interviews with clinicians and administrators	8-week postintervention from the start of each sequence and at the study end
• Fidelity[l]	Retrospective chart review	Standardized THRIVE checklist	Monthly

[a]ED: emergency department.

[b]Proportion of THRIVE referrals of those who are THRIVE eligible.

[c]Proportion of THRIVE participants experiencing the outcome within 30 days of discharge compared to usual care group.

[d]Organizational commitment to addressing disparities.

[e]Relative advantage of THRIVE to patients, degree of fit with existing practice, competing demands, and bias.

[f]Structures outside of the hospital that affect patient care.

[g]Organizational values, culture embedding, and championing adaption.

[h]Organizational priorities and goals and readiness for change and culture or climate.

[i]How fair or reasonable THRIVE is deemed.

[j]To what extent THRIVE seems suitable.

[k]The practicality and ease of delivering THRIVE.

[l]Fidelity to THRIVE's core components.

Analysis

We will develop monthly reports to monitor the referral patterns to the THRIVE clinical pathway. The target estimate and effect measure is the time-adjusted difference in participant outcomes [53,54]. The analysis of use outcomes (eg, 30-day readmissions and ED use) will use a mixed effects negative binomial regression model with random effects for the medical team and fixed effects for time to account for the stepped wedge cluster randomized design. Sensitivity analyses may be performed using logistic regression for health service use based on the distribution of the data. We will also examine the stability of effect estimates using generalized estimation equations with small sample adjustment, given the study design [55].

Equity Evaluation

Our analyses will consider several equity metrics and include interaction terms to capture racial and ethnic differences and biological sex for THRIVE participants compared to patients receiving usual care. Using all payor data obtained from the EHR, we will also conduct a secondary analysis to examine health service use across all insurance payor types for THRIVE participants and the usual care group, allowing a proxy measurement for differences across socioeconomic strata.

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Aim 2

Aim 2 is to evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Outcomes and Measures

Fidelity will be assessed using a standardized checklist and monthly report. Surveys and interviews of clinicians and administrators involved with THRIVE will be used to assess the secondary implementation outcomes of interest. These outcomes will be measured twice (at 8 weeks from the start of each sequence and at the end of the study). The surveys will use validated instruments that measure (1) feasibility, practicality, and ease of delivering THRIVE; (2) acceptability, how fair or reasonable THRIVE is deemed; (3) appropriateness, to what extent THRIVE seems suitable; and (4) clinician workload, an objective assessment of the demand of the THRIVE clinical pathway on clinician time. Clinician interviews will assess the determinants of THRIVE implementation using the HEIF [44,45]. Demographics of clinicians and administrators will also be collected.

Analysis

Summary statistics will be produced from the quantitative measures of feasibility, acceptability, appropriateness, and clinician workload. All interview data will be analyzed using constant comparative analysis to examine data across cases. Initially, we will use an iterative process of close readings and discussion of a random sample of interview transcripts and will analyze patterns in the recurrence and distribution of emergent concepts across participants. The principal investigator and research coordinator staff will then create a data dictionary and apply codes for themes that emerge while reading what the respondents say. The HEIF will inform the development of the codebook, including definitions and subsequent integration of the qualitative and quantitative data [47]. The integration of the qualitative data will help to extend and expand the findings of the quantitative findings. We will use NVivo (version 12; Lumivero) to manage our data.

Dissemination

Our team will lead several efforts to promote the dissemination and translation of our findings. First, results will be shared widely through publications, conference presentations, policy briefs, and well-established channels via the Penn School of Nursing Communication Office and the Center for Health Outcomes & Policy Research's national and international networks. Examples of print and public engagements will include up to 5 publications (at minimum 1-2 papers per aim), annual scientific presentations or conferences, infographics, and guest features on podcasts (eg, AmplifyNursing). We have built a customized THRIVE website with plans to share open-access modules on the components of THRIVE and the process for implementation. We will engage with our THRIVE Community Advisory Board to develop equity-focused dissemination efforts that are system and community focused. For example, we have previously participated in health fairs at local churches. We anticipate that the focus of this project will be of equal interest to other faith-based and community organizations and look forward to collaborating throughout the study period, not just at the end.

Results

This project was funded in January 2023. We received IRB approval on March 10, 2023. Data collection will occur from March 2023 to July 2024. Results are expected to be published in 2025.

Discussion

Expected Findings

We anticipate that patients who participate in the THRIVE clinical pathway will experience fewer 30-day readmissions and ED visits as well as more connections to primary and specialty care compared to usual care. We also expect that clinicians will value and appreciate the additional supports provided to patients with an increased burden of health-related social needs.

Comparisons With Prior Work

Most current transitional care programs were not developed to meet the needs of people insured by Medicaid and require additional personnel to implement them [10-12]. Several clinical trials of transitional care programs have resulted in mixed findings, with some noting decreased rehospitalization, while others have found no reductions in 30-day readmissions or ED use [12-17]. Similarly, other transitional care models have incorporated interventions including weekly health coaching and self-management education, though findings are inconsistent [18-20].

Strengths and Limitations

The main strength of this study is the use of a stepped wedge approach. In this design, after all of the case managers have "stepped in" to refer to THRIVE, all eligible patients will be able to receive THRIVE services. A limitation of this study is that it is a single-institution trial. However, we believe this study will yield important findings, given the rigor of the design and the focus on embedding equity-based principles throughout our implementation.

Conclusions

The goal of THRIVE is to reduce disparities and improve postdischarge care transitions for Medicaid-insured patients through a feasible system-level intervention that is satisfying for THRIVE participants, clinicians, and their teams in hospitals and home care settings. By using our equity-focused case management services and leveraging the power of the electronic medical record, THRIVE creates efficiencies by identifying high-need patients, improving communication across acute and community-based sectors, and driving evidence-based care coordination. This study will advance the field of equity-focused evidence-based interventions by testing both the effectiveness of patients' health improvement and the adoption of THRIVE by typical clinical practices. It will add important findings about how the infusion of equity-focused principles in the design and

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evaluation contributes to both implementation and effectiveness outcomes.

Acknowledgments

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Data Availability

The data that will support the findings of this study is available from the Penn Data Store and the electronic medical record and is not publicly available.

Authors' Contributions

JMBC, HB, MG-M, JB, DM, DG, KA, and MR contributed to the conceptualization and drafting of the paper. MOH, KS, AM, EF, and RC contributed to the data curation and analytic plan. All authors contributed to the editing of this paper and read and gave the final approval.

Conflicts of Interest

MOH received statistical consulting fees from Unlearn.AI and fees for editorial services from Elsevier and the American Thoracic Society, all for work unrelated to this project. JMBC, HB, MG-M, KS, AM, MR, DM, DG, JB, EF, KA, and RC have no competing interests to declare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting checklist for protocol of a clinical trial.
[DOCX File , 29 KB - resprot_v13i1e54211_app1.docx]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist for stepped wedge trials.
[DOCX File , 22 KB - resprot_v13i1e54211_app2.docx]

Multimedia Appendix 3
Peer Review Feedback from funder.
[PDF File (Adobe PDF File), 134 KB - resprot_v13i1e54211_app3.pdf]

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Abbreviations

CHW: community health worker
CM: nurse case manager
CONSORT: Consolidated Standards of Reporting Trials
ED: emergency department
EHR: electronic health record
HEIF: Health Equity Implementation Framework
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
PAH: Pennsylvania Hospital
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

High-Flow Humidified Oxygen as an Early Intervention in Children With Acute Severe Asthma: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Acute severe asthma (ASA) is a leading cause of hospital attendance in children. Standard first-line therapy consists of high-dose inhaled bronchodilators plus oral corticosteroids. Treatment for children who fail to respond to first-line therapy is problematic: the use of intravenous agents is inconsistent, and side effects are frequent. High-flow humidified oxygen (HiFlo) is widely used in respiratory conditions and is increasingly being used in ASA, but with little evidence for its effectiveness. A well-designed, adequately powered randomized controlled trial (RCT) of HiFlo therapy in ASA is urgently needed, and feasibility data are required to plan such an RCT. In this study, we describe the protocol for a feasibility study designed to fill this knowledge gap.

Objective: This study aims to establish whether a full RCT of early HiFlo therapy in children with ASA can be conducted successfully and safely, to establish whether recruitment using deferred consent is practicable, and to define appropriate outcome measures and sample sizes for a definitive RCT. The underlying hypothesis is that early HiFlo therapy in ASA will reduce the need for more invasive treatments, allow faster recovery and discharge from hospital, and in both these ways reduce distress to children and their families.

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Methods: We conducted a feasibility RCT with deferred consent to assess the use of early HiFlo therapy in children aged 2 to 11 years with acute severe wheeze not responding to burst therapy (ie, high-dose inhaled salbutamol with or without ipratropium). Children with a Preschool Respiratory Assessment Measure score ≥5 after burst therapy were randomized to commence HiFlo therapy or follow standard care. The candidate primary outcomes assessed were treatment failure requiring escalation and time to meet hospital discharge criteria. Patient and parent experiences were also assessed using questionnaires and telephone interviews.

Results: The trial was opened to recruitment in February 2020 but was paused for 15 months owing to the COVID-19 pandemic. The trial was reopened at the lead site in July 2021 and opened at the other 3 sites from August to December 2022. Recruitment was completed in June 2023.

Conclusions: This feasibility RCT of early HiFlo therapy in children with ASA recruited to the target despite major disturbances owing to the COVID-19 pandemic. The data are currently being analyzed and will be published separately.

Trial Registration: International Standard Randomised Controlled Trial Number Registry ISRCTN78297040; https://www.isrctn.com/ISRCTN78297040

International Registered Report Identifier (IRRID): DERR1-10.2196/54081

(JMIR Res Protoc 2024;13:e54081) doi:10.2196/54081

KEYWORDS

asthma; child; wheezing; oxygen therapy; high-flow humidified oxygen therapy

Introduction

Background

Asthma is a common chronic disorder of reversible airway obstruction characterized by bronchial smooth muscle contraction, airway inflammation, and increased airway secretion [1]. It is the most common noncommunicable disease in childhood, affecting 1 in 10 children worldwide [2] and causing >1000 deaths per day [3]. Children with asthma are prone to episodes of acute severe airway obstruction, characterized by wheezing and increased work of breathing, and often require hospital treatment. Acute severe asthma (ASA) is a leading cause of hospital attendance in children, accounting for up to 7% of all pediatric emergency visits [4] and 8.5% of pediatric admissions from emergency departments (EDs) [5], the most common single cause. Many preschool children who have not yet been diagnosed with asthma are admitted to the hospital with episodes of acute severe wheezing. They present identically and are treated in the same way as older children diagnosed with asthma, although they can be less responsive to therapy [6]. In this paper, the term ASA is used to describe children presenting with acute wheezing and breathing difficulty, whether they have an established diagnosis of asthma.

Therapy for ASA is directed at (1) relieving bronchoconstriction with bronchodilators, (2) decreasing airway inflammation with corticosteroids, and (3) clearing airway secretions so that they do not become thick and block the airways. Standard first-line emergency treatment [7] for ASA in children starts with burst therapy in the first hour (3 doses of high-dose inhaled salbutamol, sometimes with inhaled ipratropium, via a spacer device or nebulizer) and oral corticosteroids. During the next 1 to 4 hours, many children improve clinically and may be discharged. However, some children fail to respond to standard therapy and require hospital admission for more intensive, second-line treatment; without effective treatment, these children are at risk of fatigue, respiratory failure, and death [8]. Second-line treatment commonly includes intravenous bronchodilators (≥1 of aminophylline, salbutamol, and magnesium sulfate). However, evidence for the efficacy of such treatments is limited and inconsistent, with frequent side effects, including tachycardia, jitteriness, tremor, palpitations, nausea, vomiting, elevated lactate level, and hypokalemia [7], which can cause considerable distress to the child and family. Current guidelines [7,9] provide little guidance (because of the scarcity of evidence) regarding which second-line treatment clinicians should use. Therefore, there is a need to investigate other options for treating ASA to improve the effectiveness of the treatment and reduce adverse effects.

High-flow humidified oxygen (HiFlo) therapy is an innovative health care technology that supports breathing by supplying a warm, humidified mixture of air and oxygen at high-flow rates via fine nasal cannulae that has shown promising results in other acute respiratory conditions in children [10]. Traditional oxygen therapy uses cold, unhumidified oxygen directly from a cylinder or a wall outlet. Although this is helpful in improving oxygenation, it is uncomfortable for patients and causes drying and cooling of the nose and mouth, and potentially of the lower airways, which can cause worsening of airway obstruction and even airway damage. Therefore, unmodified oxygen therapy can only be delivered at very low flow rates. Using HiFlo technology, the air or oxygen percentage mix can be varied; it is warmed to body temperature and delivered at 100% humidity. As a result, much higher flows can be delivered without discomfort or adverse effects on the airways.

There is now considerable experience with the use of this technology in both adults and children [10]. Most of the clinical experience and evidence for the efficacy of HiFlo therapy in children is derived from studies performed in preterm neonates with surfactant deficiency. In this population, HiFlo therapy appears to be as effective as continuous positive airway pressure (CPAP) therapy and has become a standard therapy [11]. The physiological basis of its effectiveness is unclear [10,12]: HiFlo therapy itself may generate CPAP [13,14], but it may also reduce nasopharyngeal dead space, reduce upper airway resistance, and reduce the metabolic demand required to humidify inspired gases [15]. In recent years, there has been increased use of HiFlo

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therapy in infants with acute bronchiolitis [16]. Retrospective studies have suggested that introducing HiFlo therapy for acute bronchiolitis is associated with a reduced need for intubation [17,18]. Prospective trials comparing HiFlo with standard bronchiolitis therapy (low-flow 100% oxygen) have shown improved oxygen saturation levels [19], fewer treatment failures [20,21], and a nonsignificant trend toward faster weaning from oxygen [20]. A Cochrane systematic review concluded that HiFlo therapy is feasible and well-tolerated in infants with bronchiolitis but that further evidence for its effectiveness is needed [22].

To date, there have been no substantial randomized controlled trials (RCTs) of HiFlo therapy in children with ASA, although its use in ASA has been rapidly increasing [23]. The pathophysiology of ASA is very different from that of bronchiolitis. Bronchiolitis is characterized by more mechanical distal airway obstruction [22], whereas in ASA, bronchial smooth muscle constriction plays a major role [1,6]. Retrospective observational studies of HiFlo therapy in children with ASA have suggested improvements in physiological parameters and asthma severity scores [24,25] but have also raised concerns that using HiFlo therapy may delay the initiation of other forms of respiratory support [26]. There have been 2 small single-center pilot RCTs on HiFlo therapy in children with acute asthma. Ballestero et al [27] randomized 62 children with ASA with acute respiratory failure to HiFlo therapy versus conventional oxygen therapy. The asthma score of a higher proportion of children on HiFlo therapy reduced (*pulmonary score*—unreferenced) by 2 points in the first 2 hours of treatment; however, there was no difference in the need for admission or length of hospital stay. Gauto Benítez et al [28] randomized 65 children in a single center in Paraguay to HiFlo therapy or conventional oxygen therapy: the inclusion criteria were somewhat unclear, and both groups received continuous intravenous magnesium in addition to inhaled bronchodilators as a standard practice in this institution. They found no difference in the proportion reducing their asthma score (*pulmonary index score*—again unreferenced) by 2 points or in the length of hospital stay. A recent review of HiFlo in children with ASA by Chao et al [23] concluded that "large well-designed randomized controlled trials assessing the clinical efficacy of high-flow nasal cannula oxygen for children with asthma exacerbation are urgently warranted." The evidence from published studies is encouraging but mixed and is lacking in clinical outcomes. It does not provide the feasibility information required to plan an RCT on the clinical effectiveness of early HiFlo therapy in childhood ASA.

In summary, ASA in childhood is a common emergency condition with important impacts on health care costs and quality of life and presents a risk to life. HiFlo is a novel therapy that has the potential to treat patients with ASA more effectively and reduce hospital stays and intensive care admissions. However, its use is becoming widespread in clinical practice despite a lack of good evidence. If HiFlo therapy in patients with ASA is not evaluated objectively, there is a risk that a treatment without proven benefits (but with significant costs) may drift into widespread practice. Therefore, there is an urgent need for a well-designed, adequately powered RCT of HiFlo therapy in patients with ASA. To plan such an RCT, feasibility data are required. A definitive RCT would be large and expensive to run, and it is unclear whether it would be feasible, how large it would need to be, and what are the most appropriate outcome measures. This paper presents the protocol of a feasibility study designed to fill this knowledge gap, which has been successfully executed in 4 children's hospitals in the United Kingdom. The formal results will be published separately.

Study Aim and Feasibility Objectives

This feasibility study aimed to establish whether a full RCT of early HiFlo therapy in children with ASA can be conducted successfully and safely and whether recruitment to such a trial, using deferred consent, is practicable in children aged 2 to 11 years presenting to the hospital with ASA. The underlying hypothesis is that early HiFlo therapy in children with ASA will reduce the need for more invasive treatments, allow faster recovery and discharge from hospital and, in both these ways, reduce distress to children and their families. The trial was designed to generate the data required to plan a definitive RCT that would satisfy the clinical and health economic end points and the requirements of children, parents, clinicians, and health services.

Methods

Primary Feasibility Objectives and Outcome Measures

A total of 6 feasibility objectives and associated outcome measures (Table 1) were established to help determine the feasibility of progressing to a full RCT, which would require the following 4 conditions to be met:

1. At least 50% enrollment rate among eligible children (feasibility outcome 1)
2. At least 70% deferred consent rate [29] (feasibility outcome 2)
3. At least 80% of data collection is complete per participant for candidate primary outcome measures (feasibility outcome 3)
4. Confirmation that the predicted sample size, number of centers, and recruitment rates would allow an appropriately powered RCT to be conducted in the United Kingdom for 3 years (feasibility outcome 5)

Discussions with colleagues indicated that at least 15 large UK pediatric centers would be interested in participating in a definitive RCT on this question. The study has been discussed with two relevant research networks: (1) the UK National Institute for Health and Care Research (NIHR) Children Respiratory and Cystic Fibrosis Clinical Studies Group and (2) Pediatric Emergency Research in the United Kingdom and Ireland [30], a network of research-active pediatric emergency care clinicians who have indicated that they will facilitate the process of identifying appropriate centers for the definitive study.

The 2 candidate primary outcome measures recorded and evaluated are provided in Textbox 1.

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Table 1. Primary feasibility objectives and outcome measures.

Feasibility objectives	Feasibility outcome measures	Time point of evaluation
To evaluate enrollment rates	Proportion of enrolled (ie, randomized) children among eligible patients with ASA[a]	Enrollment
To evaluate deferred consent rates	Proportion of children with signed deferred consent among those enrolled into the study	Deferred consent
To assess feasibility of recording candidate primary outcome measures	Proportion of data collection completed per participant for the 2 candidate primary outcome measures	Discharge
To estimate the variability of candidate primary outcome measures	Summary statistics for the 2 candidate primary outcome measures	Discharge
To determine design characteristics for a subsequent definitive study	Proposed design, sample size, and number of centers for a definitive study	End of study
To assess the acceptability of HiFlo[b] therapy and the deferred consent model to children, parents, and staff	Satisfaction ratings on the end-of-study questionnaire	Discharge

[a]ASA: acute severe asthma.

[b]HiFlo: high-flow humidified oxygen.

Textbox 1. Candidate primary outcome measures.

- Treatment failure needing escalation of therapy as defined in the *Treatment Failure and Escalation* section.
- The time (h) between presentation to the emergency department and meeting hospital discharge criteria as defined by the following criteria:
  - The ability of the child to maintain arterial oxygen saturation (SpO_2) measured by pulse oximeter at ≥92% without supplemental oxygen or respiratory support for a 4-hour period
  - The ability of the child to remain clinically stable for a minimum of 4 hours between inhaled bronchodilator doses
  - The ability to maintain these conditions continuously until hospital discharge

Treatment Failure and Escalation

Textbox 2 lists the criteria recorded for treatment failure needing escalation in therapy.

Escalations in therapy for the primary analysis are described in Textbox 3. Pragmatically, senior clinicians on duty managing these patients had the discretion to escalate treatment if deemed clinically appropriate and justified but were asked to clearly state the reason for escalation using the abovementioned criteria. The order in which escalations are listed in Textbox 3 does not imply that they needed to be implemented in that order. The clinicians were free, for example, to implement HiFlo therapy in the standard care group before administering the second or third intravenous agent.

For the primary analysis, administering a first intravenous agent is not categorized as *treatment failure requiring escalation* in the standard care group because starting an intravenous agent would be the standard following step in a child who fails burst therapy. However, it was possible that some children randomized to the standard care group may not have received an intravenous agent directly.

Furthermore, it was useful to examine whether commencing early HiFlo therapy has an effect on the total burden of invasive treatments required. Therefore, a secondary analysis, in which escalations of therapy are defined as in Textbox 4, was carried out.

The candidate secondary outcome measures are provided in Textbox 5.

Textbox 2. Criteria for treatment failure needing escalation in therapy.

- Preschool Respiratory Assessment Measure (PRAM) score [31] rising or not falling
- Respiratory rate rising or not falling
- Heart rate rising or not falling
- Rising oxygen requirement
- Rising partial pressure of carbon dioxide (pCO_2) in capillary, venous, or arterial blood
- Other clinical concerns (specified)

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Textbox 3. Escalations in therapy for primary analysis.

High-flow humidified oxygen (HiFlo) group

- Commencing intravenous bronchodilator therapy
- Commencing the second or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with bilevel positive airway pressure (BiPAP) ventilation
- Intubation for invasive ventilation

Standard care group

- Commencing HiFlo therapy
- Commencing the second or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with BiPAP ventilation
- Intubation for invasive ventilation

Textbox 4. Escalations in therapy for secondary analysis.

High-flow humidified oxygen (HiFlo) group

- Commencing administration of the first, second, or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with bilevel positive airway pressure (BiPAP) ventilation
- Intubation for invasive ventilation

Standard care group

- Commencing administration of the first, second, or third intravenous agent
- Commencing HiFlo therapy
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with BiPAP ventilation
- Intubation for invasive ventilation

Textbox 5. Candidate secondary outcome measures.

- Time (h) between presentation to the emergency department (ED) and the actual hospital discharge
- Time (h) between presentation to the ED and achieving a Preschool Respiratory Assessment Measure (PRAM) [31] score of ≤3
- Time (h) between presentation to the ED and the ability to maintain oxygen saturation (SpO_2) at ≥92% without supplemental oxygen or respiratory support
- Need for intravenous bronchodilator therapy
- Duration of intravenous bronchodilator therapy
- Requirement for noninvasive ventilation
- Requirement for invasive ventilation (intubation)
- Treatment-related adverse effects:
  - Intravenous or inhaled bronchodilator–related side effects (eg, vomiting, tachycardia, and lactic acidosis)
  - Poor compliance with HiFlo therapy
- Hospital readmission within 48 hours of discharge
- Acceptability and comfort scores for treatment during the episode (recorded using the end-of-study questionnaire and qualitative interview following the episode). These measures were codeveloped with the Lived Experience Advisory Panel before the trial commenced.

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Study Design and Setting

This was a multicenter feasibility RCT of 50 children in the following 4 National Health Service (NHS) Trusts in England:

- The University Hospitals Sussex (UHSx) NHS Foundation Trust, Royal Alexandra Children's Hospital, Brighton
- The King's College Hospital NHS Foundation Trust, London
- The University Hospital Southampton NHS Foundation Trust, Southampton
- The University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester

Eligible children were randomized to the intervention (HiFlo therapy) or control (standard care) arms, as shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1). Screening, recruitment, and randomization were performed in the relevant EDs of the participating hospitals. Randomization was stratified by site, age (<5 years and ≥5 years), and severity of acute asthma (the Preschool Respiratory Assessment Measure [PRAM] score at study entry: <8 and ≥8, refer to the *PRAM Scoring* section), with an equal ratio between both arms.

The study was pragmatic, with HiFlo therapy being an add-on to the existing therapy in those randomized to the intervention arm, and was clearly not blinded as this would have been impossible. The children were not denied access to the existing standard second-line interventions (eg, intravenous bronchodilators) because they participated in the study. The treating clinical team was allowed to initiate intravenous bronchodilators as clinically indicated in either treatment arm. In children randomized to the intervention arm, HiFlo therapy was commenced as soon as possible after randomization as the subsequent treatment was initiated rather than intravenous bronchodilators. As the existing treatment guidelines [7,9] make no specific recommendations and because the choice of intravenous bronchodilators is physician dependent across the 4 institutions, the study protocol was physician led and did not specify which intravenous bronchodilator is initiated first. Similarly, if a child randomized to the standard care arm was failing to respond, as defined by the preset criteria, the clinical team could opt to initiate HiFlo as rescue therapy—the child remained in the study on an intention-to-treat basis. The reasons for discontinuing the intervention prematurely or for other protocol violations were recorded.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the study. HiFlo: high-flow humidified oxygen.

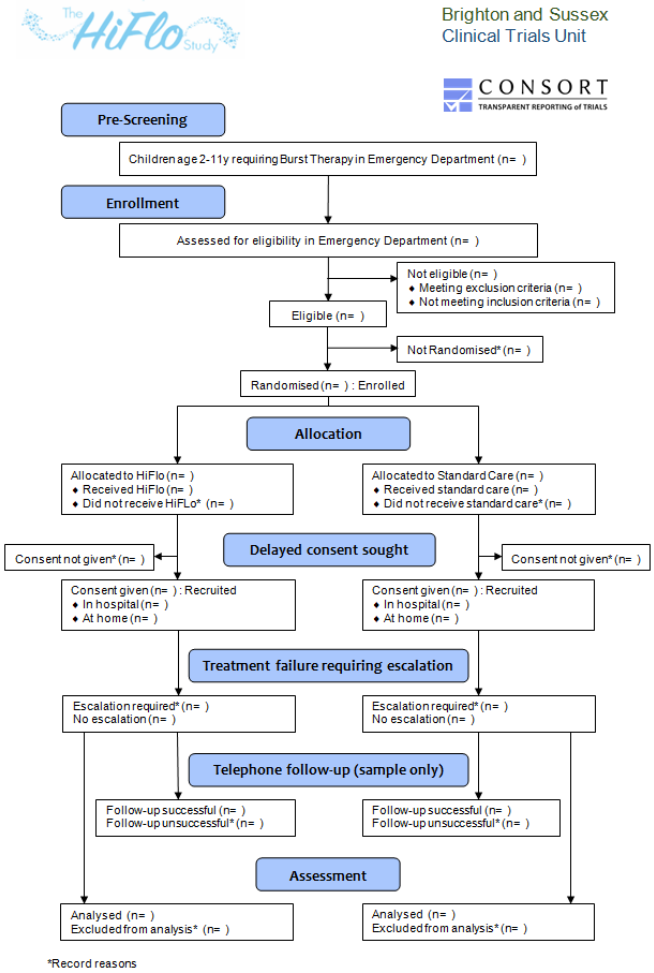

Sample Size and Planned Recruitment Rate

The size of the study was determined by the number of children required to provide an accurate estimate of the variability in the candidate primary outcome measures: recommendations for this vary between 50 [32] and 70 [33]. The larger number was chosen to allow 30% attrition to deferred consent [29]. Therefore, the study originally aimed to recruit 70 children aged

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<18 months. The recruitment target was subsequently lowered to 48 after an agreement with the NIHR Clinical Research Network that this number was sufficient to meet the objectives of the feasibility RCT. Initially, the recruitment was planned to be from 3 collaborating centers; the fourth site (Leicester) was subsequently added. The subsequent definitive RCT will determine whether HiFlo therapy is an effective intervention for children with ASA.

Participants and Eligibility Criteria

Children aged 2 to 11 years were eligible if they presented to the ED with ASA and failed to respond to standard first-line therapy (high-dose inhaled bronchodilators) based on the eligibility criteria listed in Textbox 6.

The PRAM was chosen because it has been validated across the age range of intended participants [31] and has been shown to be a good predictor of the need for admission and escalation of therapy [35]. A child with a PRAM score of 5 would typically have moderately increased work of breathing, audible wheeze, and oxygen saturation <92% but >90%. The threshold of PRAM score ≥5 was selected based on the advice of the team that designed PRAM (Professor Francine Ducharme, MD, personal communication, April 2019) and because this threshold had been successfully used as an entry criterion in a previous trial of administering nebulized magnesium to patients with acute asthma [36].

Textbox 6. Inclusion and exclusion criteria.

Inclusion criteria

- Participants having an acceptable individual capable of giving consent on their behalf (eg, parent or guardian of a child aged <16 years)
- Participants aged 2 to 11 years
- ASA, defined as respiratory distress combined with wheezing on auscultation (a formal preceding diagnosis of asthma was not necessary)
- Failure to respond to standard initial emergency management [7] with burst therapy (back-to-back 3 consecutive inhaled or nebulized doses of salbutamol with or without the addition of ipratropium bromide for a 1-h period) and systemic corticosteroids, with or without subsequent intravenous bronchodilator therapy as deemed appropriate by the treating physician. Failure to respond will be defined as a Preschool Respiratory Assessment Measure (PRAM) score of ≥5 between 1 hour and 4 hours after starting burst therapy.

Exclusion criteria

- Clinical or radiological evidence of bacterial pneumonia: fever >38.5°C and focal signs on auscultation or chest x-ray
- Signs of impending respiratory failure mandating immediate intubation. These were at the discretion of the treating clinical team but included elevated pCO_2, refractory hypoxemia, and exhaustion
- Contraindications to the use of HiFlo therapy are as follows:
  - Air leak (eg, pneumothorax, pneumomediastinum, or subcutaneous emphysema)
  - Decreased level of consciousness—AVPU (Alert, Voice, Pain, Unresponsive) score [34] P or worse
  - Recent (within 6 wk) bowel surgery
  - Intractable vomiting
- Other major respiratory, cardiovascular, or neurological condition
- Previous participation in the HiFlo ASA study during a prior hospital episode

Study Procedures

This section summarizes the procedures and evaluations conducted to support the feasibility objectives. The timing of the procedures in relation to the established study visits is given in Table 2. A detailed description of each procedure is provided in Section 6 of the study protocol in Multimedia Appendix 1 [1,4-8,10,11,13-15,17-24,27,29,31-33,37-49].

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Table 2. Schedule of events.

Study procedures	Visit				
	Screening	Enrollment	Treatment	Hospital discharge	Follow-up
Inform parents regarding the study (eg, poster and leaflet)	✓		✓		
Eligibility assessment	✓				
Demographics and medical history	✓				
Observations, including physical examination, vital signs, PRAM[a] scoring, and oxygen requirement	✓		✓		
Eligibility check and randomization		✓			
Early HiFlo[b] or standard therapy (including treatment escalation and weaning)			✓		
Deferred informed consent			✓		
Routine blood investigations			✓		
Concomitant medications			✓		
Adverse event assessments			✓		
CRF[c] completion and data query resolution			✓	✓	✓
End-of-study questionnaire				✓	
Qualitative interviews with health care professionals and parents					✓

[a]PRAM: Preschool Respiratory Assessment Measure.

[b]HiFlo: high-flow humidified oxygen.

[c]CRF: Case Report Form.

Screening

All children arriving at the participating EDs were routinely triaged by an experienced nurse and reviewed clinically during and after completing burst therapy. Children potentially eligible for the study were identified and actively screened for inclusion by ED clinical staff or research nurses according to their local capacity. Screening information included Trust ID number, age, and reasons for not being eligible for trial participation or if they were eligible but declined participation.

Enrollment and Randomization

The children who met all inclusion criteria and had no exclusion criteria were enrolled in the study and randomized to the intervention (early HiFlo therapy) or control (conventional therapy) arms only after the confirmation of eligibility by a treating clinician delegated to conduct this task. Randomization occurred at enrollment and before consent, as explained in the *Deferred Consent and Recruitment* section; it was implemented using the *Sealed Envelope* (Sealed Envelope Ltd) web-based randomization software [50] and conducted by a member of the research team trained in the study.

Treatment

The intervention was an add-on to standard care. The key difference between the groups in the 2 arms was the early use of HiFlo therapy, that is, starting HiFlo therapy as the next measure after the failure of burst therapy, and it is this strategy which was examined.

HiFlo Intervention

The use of HiFlo therapy in the study followed established practices and was standardized as far as possible while allowing for clinical judgment (Figure 2). The reasons for escalating and reducing treatment were recorded, and these data will help in defining treatment escalation and weaning pathways for the definitive RCT. The HiFlo therapy was commenced at a flow rate of 2 L/kg/min for the first 10 kg of body weight, with an additional flow rate of 0.5 L/kg/min for every kilogram of body weight >10 kg to a maximum absolute flow rate of 40 L/min, and fraction of inspired oxygen (FiO_2) was adjusted appropriately to maintain oxygen saturation ≥92%. At the discretion of the treating clinician, the flow could be increased to 3 L/kg/min but again with a maximum absolute flow rate of 40 L/min.

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Figure 2. Flowchart of the study. FiO_2: fraction of inspired oxygen; HiFlo: high-flow humidified oxygen; HR: heart rate; IV: intravenous; NIV: noninvasive ventilation; O_2: oxygen; pCO_2: partial pressure of carbon dioxide; PRAM: Preschool Respiratory Assessment Measure; RR: respiratory rate; SaO_2: arterial oxygen saturation.

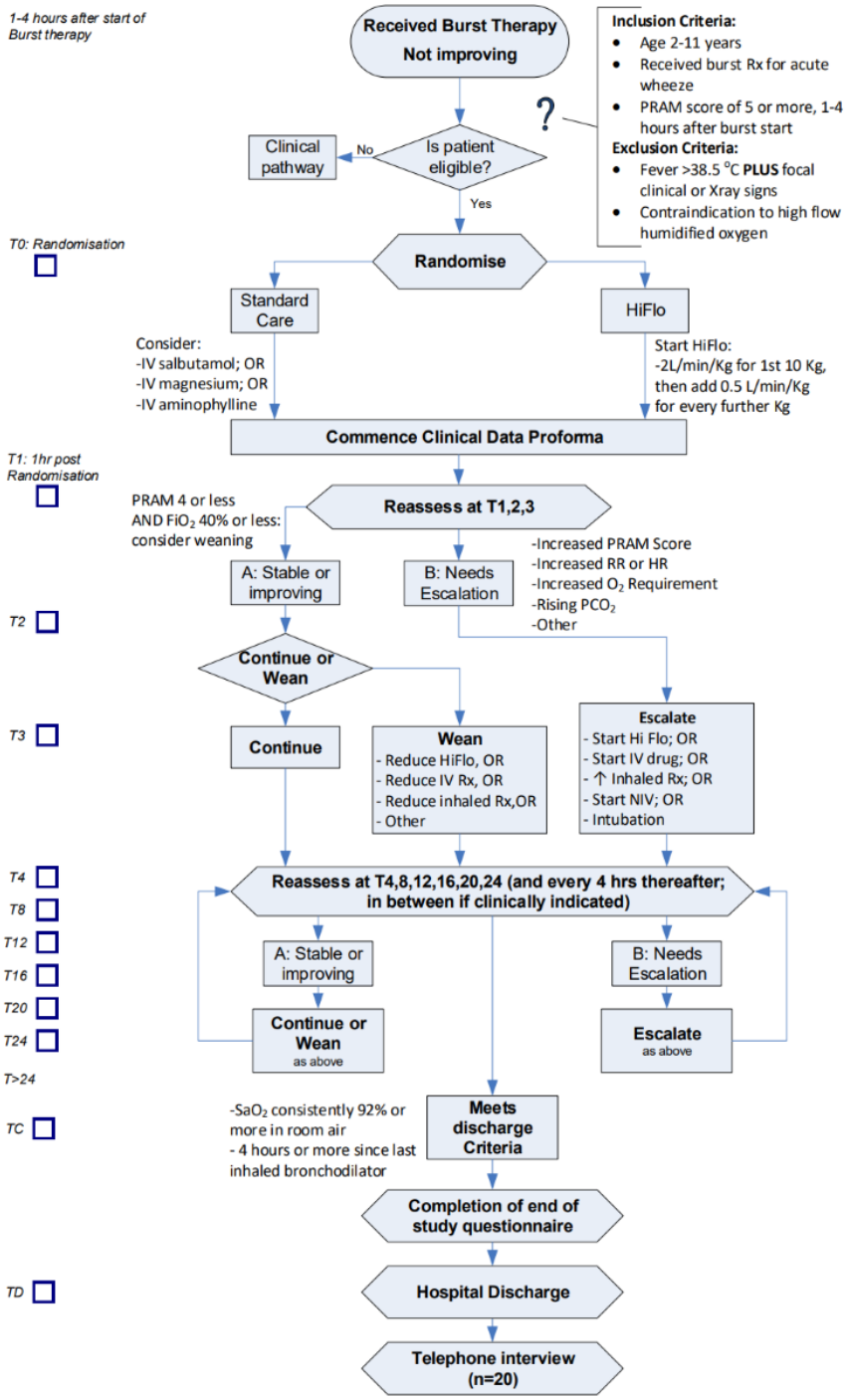

Equipment

Vapotherm, a manufacturer of portable and fixed HiFlo equipment, provided sufficient Precision Flow Plus units and consumables to make the early HiFlo intervention available free of cost in the 4 participating hospitals for the duration of the study.

Aerogen provided in-line Aerogen solo nebulizers and controller units to be used with all Vapotherm systems during the study.

HiFlo Therapy Training

HiFlo therapy was already in use in high-dependency units (HDUs, EDs) in all participating hospitals, and further staff training was undertaken in the setup period before the start of the study. HiFlo hands-on sessions were organized for staff from the EDs, HDUs, and relevant or equivalent clinical wards of participating centers by the UK Vapotherm representative Solus Medical Limited, with the aim of having at least 1 member of staff fully trained per shift. Local nursing and clinical staff members were trained as *super users* to support with

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opportunistic training, retraining, and on-site competency checks.

Weaning From HiFlo

Weaning commenced once the child was clinically stable, according to the standard criteria agreed upon across the 4 centers. The weaning strategy was not rigidly protocolized but broadly followed the schema published in the protocol for the FIRST-ABC (FIRST-line support for assistance in breathing in children) study by Richards-Belle et al [51]. Essentially, the reduction in FiO_2 occurred first, and then the flow rate was reduced in a stepwise manner once FiO_2 was consistently ≤40% (Figure 2).

Deferred Consent and Recruitment

A deferred consent model was used to avoid delay in treatment and minimize distress to families who presented to the ED with acutely unwell children. The consent process is summarized in this section (complete details are provided in section 6.4 of the study protocol in Multimedia Appendix 1).

Informed consent was not sought before randomization, but the parents were approached for informed consent within a maximum of 72 hours of randomization once their child's condition was stable. The parents were approached for informed consent by trained staff from the direct care team, who explained the study and provided information sheets to the parents and children (if age appropriate). The parents were given time to read and understand the information and the opportunity to clarify any questions regarding the study and their child's participation. Written informed consent was obtained from all the parents.

If a child was discharged from hospital before parents could be approached for deferred consent, they were contacted by a trained research nurse who explained the study via phone. Written participant information and consent forms were then sent out by post. This model was successfully used, for example, in the Emergency treatment with levetiracetam or phenytoin in status epilepticus in children (EcLIPSE) study by Lyttle et al [52], and feedback from parents was positive [37]. There was a possibility for parents to provide verbal consent via phone in special circumstances. A special process for the sensitive case of having to approach bereaved parents for consent was designed.

If neither written nor verbal consent was received, the child was not recruited into the study, and the data collected were not included in the study analysis.

Hospital Discharge

Hospital Discharge Criteria

It was recognized that the timing of discharge from hospital is affected by multiple factors in addition to the child's medical condition; therefore, criteria of fitness for discharge were defined as a more robust and reproducible candidate primary outcome measure in addition to actual hospital discharge, which was used as a candidate secondary outcome measure. Hospital discharge criteria are defined in Textbox 7.

Textbox 7. Hospital discharge criteria.

- The ability of the child to maintain arterial oxygen saturation (SpO_2) measured by pulse oximeter at ≥92% without supplemental oxygen or respiratory support for a 4-hour period
- The ability of the child to remain clinically stable for a minimum of 4 hours between inhaled bronchodilator doses
- Maintaining these conditions continuously until hospital discharge

End-of-Study Questionnaire

The study included a patient satisfaction questionnaire, tailored to children with acute severe wheezing, for all parents and their children to be collected at the time of hospital discharge.

Although validated measures of satisfaction existed within the ED setting, these were not tailored to the case of children with acute severe wheezing. Therefore, questionnaire items measuring global satisfaction outcomes were adapted with the help of patient and public involvement (PPI) groups (refer to the *PPI group* section).

The items related to treatment effectiveness, treatment satisfaction, service satisfaction, information and consent, physical comfort, pain, and communication [38] were included in the questionnaire to be rated on a Likert or visual analog scale for parents and using pictographic tools, similar to the FACES pain scale [39] and the widely used childhood Asthma-Control Test [40] for children aged ≥4 years.

Follow-Up (Telephone Interviews)

A qualitative substudy was incorporated to explore the acceptability of HiFlo therapy compared with conventional therapy and the acceptability of the deferred consent process among parents and health care professionals. Parents and health care professionals across the 4 sites were invited to participate in a semistructured telephone interview with an experienced qualitative researcher to elicit their views and opinions of the therapy and the study more generally. All telephone interviews lasted for a maximum of 30 minutes and were recorded for later transcribing. Section 6.7 of the study protocol in Multimedia Appendix 1 presents a detailed account of the recruitment and interview process and the qualitative analysis followed during this substudy. A topic guide for the interviews presented in Textbox 8 was devised with the assistance of the Lived Experience Advisory Panel (LEAP) described in the *PPI group* section.

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Textbox 8. Topic guide for qualitative interviews with parents and health care professionals (HCPs).

1. How acceptable did parents, children, and health professionals find the treatment approach used in this study?
2. What aspects of the treatment and the study more generally worked well?
3. What aspects of the treatment and the study more generally needed improvement?
4. If applicable, how did the treatment approach differ from those experienced in the past?
5. What would parents, children, and HCPs change about the therapy or study more generally?
6. Were there any outcomes which weren't measured which should have been?
7. What did parents, children, and HCPs think about the deferred consent process?
8. What would encourage other parents, children, and HCPs to participate in this study?

Clinical Data Recording

The standard of care was guided by a well-defined wheezing or asthma care pathway for children agreed upon by the participating centers, which included various observations to aid with treatment decision-making. Key observations and assessments conducted and recorded for this study are summarized in Textbox 9 (a detailed description is available in section 6.7 of the study protocol in Multimedia Appendix 1).

Textbox 9. Trial observations and assessments.

- Physical examination: this includes evaluation of suprasternal retraction, scalene muscle contraction, air entry, wheezing, work of breathing (respiratory distress), chest findings, and cardiovascular system findings.
- Vital signs: vital signs at initial assessment (triage) and during subsequent reassessments include respiratory rate, heart rate, oxygen saturation (SpO_2), capillary refill time, and temperature.
- Preschool Respiratory Assessment Measure scoring: assessments required involve a physical examination and pulse oximetry, which are all routine procedures in the participating centers.
- Oxygen requirement: this includes monitoring of oxygen (O_2) flow and fraction of inspired oxygen (FiO_2).
- Blood gases: a proportion of patients may have blood gas measurements performed routinely. Specifically, partial pressure of carbon dioxide (pCO_2) results (if available) will be used for treatment escalation decisions. In children, these will normally be measured using capillary or venous blood.

PRAM Scoring and Training

Progress was monitored regularly from hospital admission until discharge using PRAM scores (34), assessed hourly in the ED and 4-hourly after admission to an inpatient ward. PRAM scoring was included in the wheeze or asthma care pathway document adapted by the sites for local implementation. In this study, PRAM scoring was considered the standard of care and documented in the pathway document as source data to be used for patient selection (eligibility). If the pathway document could not be implemented at the ED, then the study screening and eligibility process was adapted for the recording and documentation of PRAM scores. After randomization, PRAM scoring was considered study-specific and documented in a clinical data pro forma as source data to be used for treatment monitoring.

In order to ensure consistency across all study sites, intensive training in recording PRAM scores was undertaken. Data quality was reviewed regularly, and training was updated throughout the study. The principal investigator (PI) and local investigators were responsible for promoting the clinical use of the agreed care pathway in advance of the study, for training ED staff on PRAM scoring in the context of the pathway, and for training staff in other departments (eg, HDU and ward) on the use of PRAM. Various training resources were made available to the sites, including locally produced training videos and a web-based PRAM teaching module from Centre Hospitalier Universitaire Sainte-Justine, University of Montréal [53].

Maintaining an adequate level of training for staff regarding the use of PRAM was challenging. Only one of the sites had staff who were familiar with PRAM scoring, and one of the items (palpable scalene muscle contraction) required specific training. Clinical staff had a range of opinions regarding the clinical value of asthma severity scores, and high staff turnover meant that training had to be revisited at frequent intervals.

Safety Reporting

Overview

Section 7 of the study protocol in Multimedia Appendix 1 provides standard definitions of safety reporting technology appropriate for trials other than Clinical Trials of Investigational Medicinal Products, including adverse event (AE), adverse reaction, serious AE (SAE), serious adverse reaction (SAR), and suspected unexpected SAR, and details of the safety reporting procedures (actions and required timelines) used in this study.

Recording of AEs

The operational definitions of the AEs collected from randomization to hospital discharge are given in Textbox 10 and include two types of events:

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1. Air leaks: ASA is a well-recognized risk factor for air leak. Higher HiFlo rates (>2 L/kg) can mimic the effects of CPAP, which is a theoretical additional risk factor for air leak. This study used more conservative flow levels, previously used safely in HiFlo therapy in patients with asthma [23]; therefore, the risk of air leaks was regarded as low. Air leaks in any of the following 3 manifestations were regarded as an SAE and prompted immediate reporting: pneumothorax, pneumomediastinum, or subcutaneous emphysema.
2. Standard treatment–related AE: Vomiting, tachycardia, tremor, lactic acidosis, and others are known potential side effects of intravenous or inhaled bronchodilators that could be seen in both the HiFlo and standard care groups. Documentation of their occurrences was needed to evaluate the candidate secondary outcome measures (treatment-related side effects). If serious, they could be reported as SAEs.

Textbox 10. Definitions of adverse events.

1. Pneumothorax: single episode to be reported per patient.
2. Pneumomediastinum: single episode to be reported per patient.
3. Subcutaneous emphysema: single episode to be reported per patient.
4. Vomiting: a period of sequential vomiting is considered a single episode, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
5. Tachycardia (heart rate ≥160 in children aged 2 to 4 years and ≥140 in those aged 5 to 11 years): an episode lasts for as long as the patient is in tachycardic range, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
6. Tremor: an episode lasts as long as any tremor is present, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
7. Lactic acidosis (venous or capillary lactate >2.2 mmol/L or arterial lactate >1.6 mmol/L): an episode starts every time an abnormal laboratory value is detected. The episode lactate value is recorded.
8. Hypokalemia (potassium <3.5 mmol/L): an episode starts every time an abnormal laboratory value is detected.
9. Sedation received to tolerate high-flow humidified oxygen (HiFlo) therapy: single episode to be reported per patient.
10. Patient unable to tolerate HiFlo therapy (HiFlo discontinued): single episode to be reported per patient.
11. Other: any other untoward medical occurrence or serious adverse event in a study participant.

Responsibilities of Safety Reporting

The PI at each site was responsible for reporting any SAE or SAR to the clinical trials unit (CTU). The trial manager (TM) was responsible for ensuring that all SAE and SAR reports were complete and accurate and for following up with the research teams to ensure this. The TM was responsible for maintaining and updating all the SAE and SAR records required for reporting to the sponsor and the Research Ethics Committee (REC). All AEs and SAEs were monitored by the TM at the CTU and reported and reviewed at the trial steering committee (TSC) meetings.

Statistics and Data Analysis

Statistical Analysis Plan

Participant flow through the trial will be represented in a CONSORT flowchart (Figure 1) according to the CONSORT extension for pilot and feasibility trials [41]. The available cases will be analyzed, following the intention-to-treat principles. Normally distributed variables will be summarized by means and SDs, skewed continuous variables by medians and IQRs, and categorical variables by frequencies and percentages. The difference in means between the trial arms for the primary and secondary outcomes will be estimated, together with bootstrapped 95% CIs. All analyses will be conducted using Stata (version 18; StataCorp LLC).

Qualitative Data Analysis

The interview transcripts will be anonymized and transcribed verbatim. Thematic content analysis will be performed on the interview transcripts based on a 14-stage structured approach [42]. The initial codes will be semantically clustered into subthemes, and finally, these subthemes will be clustered into main themes. The final thematic structure will be described and supported with illustrative interview quotes.

Subgroup Analyses and Participant Population

Subgroup analysis will be limited to 3 variables on which randomization was stratified: site, age, and severity of acute episode. The analysis will be conducted on an intention-to-treat basis; all the recruited participants with consent received will be included in the analysis. In addition, we will examine the screening logs at the sites to identify factors involved in the failure to recruit, which may be relevant to the design of the full RCT. Furthermore, per-protocol analysis will be performed, in which deviation from the trial protocol will result in exclusion from data analysis from that point of protocol deviation onward. Examples of protocol deviations include the following:

- A child is randomized to the HiFlo therapy arm, but for logistical reasons (eg, no equipment is available), this therapy never commenced.
- A child in the HiFlo arm is commenced on therapy, which is later discontinued or changed to another modality because of transfer to a ward area that is unable to provide this care.

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The per-protocol analysis will be interpreted cautiously because of the small sample size.

Data Management

A research team pack was used to ensure accurate data collection and included clinical observation sheets and case report forms to record the outcome data. Pseudonymized data were electronically entered by trained research nurses at each site onto a web-based, password-protected data management system (REDCap; Research Electronic Data Capture; Vanderbilt University) designed by a data manager from the Brighton and Sussex CTU (BSCTU). The data manager oversaw data quality and ensured that the database was ready for analysis. Once the data had been cleaned and the database locked, they were transferred securely to the trial statistician for descriptive analysis by the trial arm.

It was agreed that all investigators and trial site staff must comply with the requirements of the General Data Protection Regulation 2018 guidance for researchers—Health Research Authority (HRA) [54]. A specific data management plan and a monitoring plan were developed for this study (available from BSCTU). Archiving will be authorized by the sponsor following the submission of the end-of-trial report. All essential documents will be archived for a minimum of 5 years after trial completion. Destruction of essential documents will require authorization from the sponsor.

Trial Management and Monitoring

The BSCTU oversaw the management of the study. A TM worked closely with the chief investigator (CI) and research team to ensure that the timelines were met, recruitment was tracked, and remote monitoring was undertaken for quality assurance. The TM supported the setup of the sites, ensuring that all documentation and processes were in line with the research governance and HRA processes. Monthly trial management group (TMG) meetings with the CI, DM, statistician, PIs, and research nurses from the sites were conducted to oversee the study's progress.

The TSC consisted of the TMG and 3 independent members (a lay member—parent of a child with asthma, a pediatrician with relevant expertise, and a statistician). The TSC reviewed the reports from the TMG and met to oversee the overall progress. With its independent membership, the TSC also reviewed the data and safety issues, fulfilling the role of this feasibility trial of a data and safety monitoring board. Financial management for the study was overseen by the TM with institutional supervision by the head of research at the UHSx NHS Foundation Trust.

Ethical Considerations

The study protocol and all applicable documents and amendments were approved by the West Midlands–Solihull Research Ethics Committee (REC) and the Health Research Authority (HRA) according to applicable regulations (REC reference: 19/WM/0219, IRAS: 261627). This study was registered with International Standard Randomised Controlled Trial Number registry (ISRCTN78297040) [55]. The HiFlo ASA project proposal was successful in competition 35 of the NIHR Research for Patient Benefit Program after 2 stages of independent peer review by the program's designated expert advisory panel. The study protocol for this feasibility study was further developed and discussed by researchers from the participating centers, with the involvement of the BSCTU.

Dissemination

In this feasibility trial, the important aspects of dissemination concern the use of trial data in designing a full RCT and preparing an application to fund it. Therefore, dissemination will be principally among the study team, the PPI groups involved, and the stakeholders (both professional and patient or parent groups) to be involved in the full multicenter RCT. We intend to publish a protocol for this feasibility trial.

Trial Sponsorship

The sponsor was responsible for ensuring that the trial was being conducted under appropriate governance. The sponsor is the UHSx NHS Foundation Trust.

Committees

The composition, roles, and responsibilities of the TMG, TSC, and LEAP are described in the *General Information* section (part 6) at the beginning of the study protocol in Multimedia Appendix 1.

PPI Group

PPI was sought at different stages in the development of the study, with a plan for continuing input during the research and its dissemination.

The detailed involvement of the following PPI groups is described in section 11.3 of the study protocol in Multimedia Appendix 1:

- Two local patient groups from Kent, Surrey, and Sussex (KSS), funded by the NIHR, participated in the trial design and will be informed of the findings of the study: KSS young people's advisory group and KSS parent and carer advisory group (KSS, Generation R).
- A separate NIHR research support grant enabled the creation of a LEAP—a group of 6 to 8 parents whose young children have been admitted with ASA, together with 4 children with experience of ASA—to provide disease-specific PPI into the study.

Results

The trial was opened to recruitment at the lead site in February 2020, but a month later, the COVID-19 pandemic reached the United Kingdom, and the study was put on hold in March 2020. There was a 15-month pause because of a combination of factors, including general concerns about face-to-face research, specific concerns about HiFlo therapy as an *aerosol-generating procedure*, and redeployment of research staff to clinical duties during the pandemic. The trial was reopened at the lead site in July 2021 and opened at the other 3 sites between August and December 2022. The follow-up was completed in July 2023. The results are currently being analyzed and will be reported separately.

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Discussion

This paper describes the protocol for a multicenter feasibility RCT of 50 children that has been successfully executed at 4 sites in the United Kingdom. The trial aimed to establish whether a full RCT of early HiFlo therapy in ASA can be conducted successfully and safely and whether recruitment for such a trial, using deferred consent, is practicable in children aged 2 to 11 years presenting to hospital with ASA. If it is determined that a definitive RCT is feasible, the data from the study will inform the outcome measures and sample size needed for adequate power.

A total of 2 previous pilot RCTs of HiFlo therapy in acute asthma have been published [27,28], but neither provided the feasibility data required to design a definitive RCT to assess the clinical effectiveness. Both studies used an asthma severity score as the main outcome measure, but neither the *Pulmonary Score* used by Ballestero et al [27] nor the *Pulmonary Index Score* used by Gauto Benítez et al [28] were referenced, and it is unclear what any differences in these outcomes would mean for clinical management. In this protocol, we chose 2 candidate primary outcome measures that had been determined by clinicians and by parents and children to be meaningful and likely to impact practice. Both the need for escalation of therapy owing to treatment failure and the time to reach readiness for discharge are important in determining resource use and care costs.

We used an asthma scoring system and selected PRAM because it was the only asthma scoring system validated across the entire age range of 2 to 11 years. At least 17 different asthma severity scores have been published, but few EDs in the United Kingdom regularly use any of them as part of routine clinical practice [56], and only one of our sites had any prior familiarity with PRAM. The study protocol used the PRAM score in 2 ways: as one of the entry criteria (PRAM score ≥5 after first-line treatment) and as a candidate (secondary) outcome measure (time to achieve a PRAM score of ≤3). As noted above, implementing PRAM at the study sites and maintaining PRAM competency, despite high staff turnover, required considerable input of training resources. The advantage of using a validated asthma score as an entry criterion was that it standardized the severity of acute asthma in children entering the study, allowed comparison with other acute asthma trials [36], and allowed us to stratify randomization by asthma severity at entry. A potential disadvantage was that it risked reducing out-of-hours recruitment owing to PRAM-trained staff not being available.

As with many clinical trials since 2019, the conduct of this study was severely affected by the COVID-19 pandemic. It was necessary to pause recruitment for a prolonged period because of general logistic issues affecting all clinical research and specific concerns relating to the theoretical risks of aerosol generation and COVID-19 transmission from HiFlo therapy. The experience gained by the research team (both in adapting trial procedures and disseminating new research findings on aerosol generation) to allow the successful completion of the trial will be valuable in planning a definitive RCT.

Acknowledgments

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The sponsor of this study is the University Hospital Sussex NHS Foundation Trust. The sponsor's representative is Mr Scott Harfield.

We would like to acknowledge the support of Vapotherm Inc who loaned the HiFlo equipment, and Aerogen Ltd who loaned the nebuliser equipment for the study.

Conflicts of Interest

In March 2023, PS chaired an advisory board for Aerogen Ltd, who loaned nebulizer equipment for the study, and received an honorarium. ML attended the same advisory board, and received an honorarium. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Full study protocol.
[PDF File (Adobe PDF File), 1201 KB - resprot_v13i1e54081_app1.pdf]

Multimedia Appendix 2
Peer-review report from the National Institute for Health Research.
[PDF File (Adobe PDF File), 606 KB - resprot_v13i1e54081_app2.pdf]

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Abbreviations

AE: adverse event
ASA: acute severe asthma
BSCTU: Brighton and Sussex clinical trials unit
CONSORT: Consolidated Standards of Reporting Trials
CPAP: continuous positive airway pressure
CTU: clinical trials unit
ED: emergency department
FiO_2: fraction of inspired oxygen
HDU: high-dependency unit
HiFlo: high-flow humidified oxygen
HRA: Health Research Authority
KSS: Kent, Surrey, and Sussex
LEAP: Lived Experience Advisory Panel
NIHR: National Institute for Health and Care Research
PI: principal investigator
PPI: patient and public Involvement
PRAM: Preschool Respiratory Assessment Measure
RCT: randomized controlled trial
REC: Research Ethics Committee
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SAR: serious adverse reaction
TM: trial manager
TMG: trial management group
TSC: trial steering committee
UHSx: University Hospitals Sussex

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Protocol

Enhancing Psychotherapy Outcomes by Encouraging Patients to Regularly Self-Monitor, Reflect on, and Share Their Affective Responses Toward Their Therapist: Protocol for a Randomized Controlled Trial

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Abstract

Background: The quality of the therapeutic relationship is pivotal in determining psychotherapy outcomes. However, facilitating patients' self-awareness, reflection on, and sharing of their affective responses toward their therapist remains underexplored as a potential tool for enhancing this relationship and subsequent treatment outcomes.

Objective: The primary objective of this study is to examine whether and how the patients' regular self-monitoring and self-reflection (fostered by the systematic compilation of a brief postsession battery) on their affective reactions toward the psychotherapist impact the quality of the therapeutic relationship and treatment outcomes in individual psychotherapy. Secondary objectives are to (1) explore whether and how the characteristics of the patient, the therapist, and the process moderate the effect of regular self-monitoring on the therapeutic relationship and outcomes; (2) examine the relationships between the affective response of the patient, the alliance, and the result of the therapy session outcome; and (3) explore how the affective responses of the patient unfold or change throughout the course of the therapy.

Methods: We conducted a 1:1 randomized controlled trial of adults in individual psychotherapy versus individual psychotherapy plus self-monitoring. Participants will be enrolled through the web-based recruitment platforms "ResearchMatch" and "Research for Me," and data will be collected through web-based surveys. Participants in the control group will receive only their regular individual psychotherapy (treatment as usual) and will not complete postsession questionnaires. Participants in the intervention group will continue their regular individual psychotherapy sessions and complete the "in-Session Patient Affective Reactions Questionnaire" and the "Rift In-Session Questionnaire" following each therapy session in the 10 weeks of the trial. Additionally, after completion of the postsession battery, they will receive general written feedback encouraging them to discuss their feelings and reflections with their therapist. Participants in both groups will complete a comprehensive psychological assessment at baseline, midtrial (week 5), and end-of-trial (week 10). The primary outcome measure of the trial is the "Clinical Outcomes in Routine Evaluation-Outcome Measure," while the secondary outcomes are the "Real Relationship Inventory-Client-Short Form,"

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the "Working Alliance Inventory-Short Revised," and the number of scheduled therapy sessions that the patient has missed or canceled.

Results: The trial was approved by the institutional review board of the University of North Carolina at Chapel Hill. Recruitment started in September 2023. A total of 475 individuals completed the baseline assessment. Data collection was completed in February 2024. The results are expected to be published in the autumn of 2024.

Conclusions: This study could reveal key information on how regular self-monitoring and introspection can influence both the therapeutic relationship and treatment outcomes. Findings have the potential to shape interventions, enhance the efficacy of psychotherapeutic sessions, and possibly offer a cost-effective strategy for improving patients' well-being.

Trial Registration: ClinicalTrials.gov NCT06038747; https://classic.clinicaltrials.gov/ct2/show/NCT06038747

International Registered Report Identifier (IRRID): DERR1-10.2196/55369

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KEYWORDS

adult patients; evidence-based assessment; patient's perspective; psychotherapy; randomized controlled trial; systematic client feedback; therapeutic relationship; treatment outcome

Introduction

Background

Emotions lie at the core of human existence, emerging as products of evolutionary mechanisms designed to equip individuals to handle critical interpersonal interactions and life challenges [1,2]. Since the dawn of psychotherapy, the role of emotions, whether emanating from the patient or the therapist, has been recognized as crucial to the therapeutic journey [3-5].

Studies on emotional expression within the therapeutic realm emphasize their substantial influence on the outcomes of both single sessions and the entire treatment journey [2,6,7]. Emotions intertwine with both specific and generic therapeutic methodologies that underpin clinical success [8,9]. Facilitating patients to gain emotional awareness and use these emotions constructively stands central to therapeutic transformation [10,11]. For this transformative effect, therapists must engage collaboratively with the patient's in-session emotions, guiding them through recognition, acceptance, regulation, and management [12-14].

The therapeutic setting can illuminate suppressed emotions, allowing patients to confront neglected self-awareness and experience new emotional dimensions. Such insights present valuable data on patients' inherent needs and reactions, offering a platform to confront past fears and integrate new experiences [11,15]. Emotions directed toward the therapist during sessions hold significant implications for the therapeutic journey's success [16,17]. An environment characterized by empathy and affirmation determines if the emotional engagement will steer the therapy positively or detrimentally [18]. Furthermore, such an environment is both the catalyst for change and the foundation for effective psychotherapy [19].

The dawn of the new millennium saw the advent of routine outcome monitoring and feedback [20]. These systems, which track and report the patient's therapeutic progress, have seen widespread adoption and study in varied mental health contexts over recent years. These feedback mechanisms, unified by their use of standardized measures, monitor outcomes like well-being, symptomatology, and functional aspects, sometimes focusing on specific therapeutic processes like the working alliance [21]. Meta-analyses show that systematic feedback enhances therapy outcomes by reducing symptom intensity and attrition rates [22,23]. They also highlight reductions in treatment time frames and associated costs [24-26].

Given these insights, the American Psychological Association has been advocating for feedback and outcome monitoring since the early 2000s [27,28]. Feedback systems are now integral to mental health frameworks globally, especially in countries such as Australia, the Netherlands, and the United Kingdom, where monitoring outcomes is a statutory mandate for health service providers. With the capacity to tweak treatments based on progress or disruptions in the therapist-patient relationship, many experts regard progress monitoring as a pivotal strategy to enhance real-world therapy outcomes [29,30].

Study Objectives

In light of the above, the primary objective of this study is to examine the influence of a brief postsession battery, which is apt to foster patient self-monitoring and reflection on their emotional reactions toward their psychotherapist and on the quality of the therapeutic relationship and treatment outcomes.

Secondary objectives are to (1) explore whether and how the characteristics of the patient, the therapist, and the process moderate the effect of regular self-monitoring on the therapeutic relationship and outcomes; (2) examine the relationships between the affective response of the patient, the alliance, and the result of the therapy session outcome; and (3) explore how the affective responses of the patient unfold or change throughout the course of therapy.

Methods

Ethical Considerations

The institutional review board of the University of North Carolina (UNC) at Chapel Hill approved this study (23-1067) on July 31, 2023. This research was designed and executed in accordance with ethical standards for studies involving human participants.

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Before starting the baseline survey, participants will receive a detailed web-based consent form regarding the study. This form will include the purpose, rationale, and methodology of the study, as well as the contact information for both the principal investigator and the institutional review board. It will be explained to potential participants that to protect their identities, only relevant and minimally necessary information will be collected. Furthermore, it will be assured that any published results will report on groups, not individual participants. Participants will be prompted with a consent statement and given options: "I consent to participate in this study" or "I do not consent to participate in this study." Those who choose not to consent will be immediately directed to a closing page. All participants are informed that they can opt out of the study at any time without providing a reason.

Only the central research team will have access to the data until the research results are published. Once the study concludes and the primary findings are released, external applications for access to deidentified data will be entertained. These applications must adhere to data privacy rules, and the intended research must be scientifically and ethically robust. Following the publication of the research findings, the data will be publicly shared through the Open Science Framework [31].

No financial incentives were offered for participation in this trial. However, upon completing the trial, participants from both the intervention and control groups were given the opportunity to request a free copy of the scales and general feedback used in the intervention group by emailing the principal investigator.

Study Design

This study is a randomized controlled trial (NCT06038747) of 1:1 for individual psychotherapy versus individual psychotherapy plus self-monitoring. A predetermined computer-generated randomization list will be generated to assign patients to 1 of the 2 arms. Patients will not be blind to treatment allocation. Patients will be enrolled through the web-based recruitment platforms "ResearchMatch" and "Research for Me," and data will be collected through web-based surveys facilitated by the Qualtrics software hosted by the UNC at Chapel Hill.

Intervention

Participants in the intervention group will continue their regular individual psychotherapy sessions. Additionally, after each session, they will complete a brief postsession battery consisting of 2 scales on the affective reactions of the patients toward their therapist during the session and read general feedback encouraging them to discuss their feelings and reflections with their therapist. This questionnaire aims to prompt reflection on one's own experience of the therapeutic relationship.

Treatment as Usual

Patients in the control group will receive only their regular individual psychotherapy (treatment as usual) and will not complete postsession questionnaires. Additionally, they will not receive any communication encouraging them to discuss their emotional responses with their therapist during the session.

Measures

This study uses a comprehensive set of self-report instruments to collect extensive data on the therapeutic process and various patient-related factors. The data will cover 5 main domains. The sociodemographic and clinical domains capture the patient's demographic, clinical, and treatment specifics. The mental health state domain focuses on the present symptoms of anxiety and depression that impact the daily lives of respondents. The therapeutic relationship domain evaluates the specific facets of the relationship between the patient and the therapist. The last domain evaluates session and therapy outcomes.

The primary outcome measure of the trial is the "Clinical Outcomes in Routine Evaluation-Outcome Measure" (CORE-OM) [32], while the secondary outcomes are the "Real Relationship Inventory-Client-Short Form" (RRI-C-SF) [33], the "Working Alliance Inventory-Short Revised" (WAI-SR) [34], and the number of scheduled therapy sessions that have been missed or canceled by the patient.

Sociodemographic Domain

The "sociodemographic data form" collects self-reported details such as the patient's age, gender, education level, and ethnicity.

Clinical Domain

The "clinical data form A" gathers patient-provided data on the duration and frequency of the ongoing psychotherapy, session attendance method (in-person, video call, telephone, and mixed), presence or absence of a diagnosed mental disorder, any prescribed psychotropic medications, and the therapist's gender.

The "clinical data form B" records information on sessions attended, missed, and canceled over the last 5 weeks and any change in psychiatric medications during this time frame.

Mental Health State Domain

The Patient Health Questionnaire-9 (PHQ-9) [35] is a 9-item self-report depression screening tool that captures the severity of depressive symptoms during the past week. It allows the evaluation of symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depression. The PHQ-9 administered in the primary care sample showed a Cronbach α of 0.89.

The Generalized Anxiety Disorder-7 (GAD-7) [36] is a 7-item self-report anxiety screening tool with a focus on symptoms of generalized anxiety disorder. It assesses the severity and frequency of anxiety symptoms during the past week. GAD-7 showed a Cronbach α of 0.92.

Therapeutic Relationship Domain

The RRI-C-SF [33] is an 8-item self-report tool measuring the "real relationship" between a therapist and patient from the patient's viewpoint. It includes 2 subscales: "genuineness" and "realism," both of which represent closely related dimensions of authenticity and perceptual accuracy within the therapeutic relationship. The RRI-C-SF has a McDonald's ω total of 0.93.

The WAI-SR [34] is a 12-item self-report measure of the quality of the working alliance between patient and therapist from the patient's perspective. WAI-SR includes three 4-item subscales

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that focus on agreement on therapy tasks, goals, and the development of an emotional bond. Items are rated on a 6-point Likert scale, with higher scores indicating a more robust alliance. The Cronbach α for the total scale was 0.91, while the α coefficients for the subscales spanned a range from 0.85 to 0.90.

The "in-Session Patient Affective Reactions Questionnaire" (SPARQ) [37,38] is a patient-reported tool that comprises 8 items that explore the patterns of thought, feeling, and behavior activated and experienced by the patients toward their therapist during a session. It consists of 2 scales: "positive affect" and "negative affect." The positive affect scale exhibited a Cronbach α coefficient of 0.84 and an average interitem correlation of 0.51. On the other hand, the negative affect scale demonstrated an α of 0.76 and an average interitem correlation of 0.39.

The "Rift In-Session Questionnaire" (RISQ) [37] is a 4-item self-report questionnaire designed to measure the patient's risk of experiencing ruptures in the therapeutic relationship. The RISQ measures feelings of belittlement, rejection, disparagement, and attack, as well as any tendencies toward disobedience or "naughtiness" toward the therapist. The RISQ demonstrated good internal consistency with a Cronbach α coefficient of 0.73 and an average interitem correlation of 0.35.

Session and Therapy Outcomes Domain

The Session Evaluation Scale (SES) [39] assesses the quality of the therapy session from the perspective of the patient. The SES comprises 5 items rated on a 5-point Likert scale and showed Cronbach α coefficients ranging from 0.88 to 0.89.

The CORE-OM [32] is a 34-item self-report measure of change in psychotherapy that comprises 4 domains: subjective well-being, symptoms, function, and risk. The CORE-OM demonstrated good internal and test-retest reliability between 0.75 and 0.95, and convergent validity against a battery of validated measures.

Efforts to Minimize Potential Sources of Bias

In our research, extensive steps will be taken to minimize potential biases. First, participants will be sourced from ResearchMatch, a national web-based registry that boasts a broad and varied volunteer pool from all over the United States, reducing selection bias and enhancing the external validity of our study. Second, our methodology is closely tuned to gender perspectives, giving weight to nonbinary gender as a key factor in both data evaluation and result interpretation, fortifying the scientific rigor and clinical significance of the study. Third, our comprehensive set of measures covers a spectrum of therapeutic and individual aspects, from sociodemographic details to personality characteristics, providing a comprehensive snapshot of the therapeutic landscape and limiting measurement bias. Data will be gathered through Qualtrics, a trusted web-based tool that protects respondent privacy and minimizes potential biases in responses. Furthermore, great care was taken in calculating the required sample size, accounting for potential dropouts, to ensure that we had ample statistical power, thereby sidestepping the pitfalls of weak analyses or insufficient representation.

Sample Size Calculation

Assuming a power of 0.80, a 2-tailed α level of .05, an effect size (*d*) of 0.50, and an allocation ratio of 1:1, we calculated a minimum sample size of 128 patients, or 64 participants per group, using the *R package pwr* (version 1.3-0; The Comprehensive R Archive Network). However, to enhance statistical power and precision, we aim for a target total sample size of 520 participants, with 260 participants per group. This adjustment also accounts for the possibility that only 50% of participants in the intervention group will complete all postsession scales.

Inclusion and Exclusion Criteria

Participants are eligible for the study if they are aged 18 years or older, fluent in English, and currently undergoing individual psychotherapy with a minimum frequency of 2 sessions per month. Individuals with a legal guardian will be excluded from the study.

Recruitment

Patients will be enrolled through ResearchMatch and Research for Me. ResearchMatch [40] is a disease-neutral, institution-neutral, US national web-based registry designed to enroll volunteers for clinical studies. Established by various educational entities and supported in part by the National Institutes of Health's National Center for Advancing Translational Sciences, this platform provides access to more than 155,000 volunteers across the United States and has proven effective. Research for Me is a community of volunteers acting as the primary gateway for patients and local residents who wish to participate in research at the UNC at Chapel Hill. This initiative was established by the North Carolina Translational and Clinical Sciences Institute, which is the central component of the National Institutes of Health's Clinical and Translational Science Awards program at UNC at Chapel Hill. Data suggest that individuals enrolled through online research platforms reliably report their demographic and psychological details, especially when there is no monetary incentive involved [41].

Randomization

Participants will be assigned to either the intervention or control group using a pre-established computer-generated randomization list. This assignment will occur after the baseline assessment is completed.

Data Collection Process

Participants in both the intervention and control groups will undergo assessments at baseline, midtrial (week 5), and end-of-trial (week 10). Additionally, those in the intervention group will have postsession evaluations. These assessments will be delivered through Qualtrics, a secure web-based survey platform hosted by the UNC at Chapel Hill.

Baseline assessment: All participants will complete the demographic and clinical data forms in addition to the measures for mental health state, therapeutic relationship, and session and therapy outcome domains (Table 1).

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Table 1. Instruments and time line for assessment in the trial.

Domains and measures	Baseline	Midtrial[a]	End-of-trial[b]
Demographic domain			
Sociodemographic data form	✓		
Clinical domain			
Clinical data form A	✓		
Clinical data form B		✓	✓
Mental health state domain			
Patient Health Questionnaire-9 [35]	✓	✓	✓
Generalized Anxiety Disorder-7 [36]	✓	✓	✓
Therapeutic relationship domain			
Real Relationship Inventory-Client-Short Form [33]	✓	✓	✓
Working Alliance Inventory-Short Revised [34]	✓	✓	✓
in-Session Patient Affective Reactions Questionnaire [37,38]	✓	✓	✓
Rift In-Session Questionnaire [37]	✓	✓	✓
Session and therapy outcome domain			
Session Evaluation Scale [39]	✓	✓	✓
Clinical Outcomes in Routine Evaluation-Outcome Measures [32]	✓	✓	✓

[a]5 weeks after the baseline assessment.

[b]10 weeks after the baseline assessment.

Postsession assessment (only for the intervention group): participants in the intervention group will be required to complete SPARQ and RISQ [37] after each session throughout the 10-week duration of the trial. Immediately after completion of the postsession battery, participants will be presented with a general feedback statement emphasizing the importance of discussing session-related feelings with their therapist.

Mid-trial assessment: 5 weeks postbaseline evaluation, all participants will retake the scales used in the baseline assessment (Table 1).

End-of-trial assessment: 10 weeks after the baseline, all participants will again be asked to complete the initial assessment battery (Table 1).

Dealing With Missing Values

We will examine data for degree and patterns of missingness at the patient and scale level, use propensity scoring to model the pattern of missingness, and include the propensity score as a covariate in analyses if indicated [42]. Missing items will be prorated so long as at least 75% of the items are available, and otherwise the scale score will be treated as missing [43].

Planned Analysis

A comprehensive statistical strategy will be formulated and documented before starting the data analysis. R (R Foundation for Statistical Computing) will be used for data cleaning, labeling, scale scoring, and subsequent analyses. The basic characteristics of the study participants will be clearly described for each arm while also being aggregated to a sufficient level to reduce the risk of deductive identification. Baseline categorical variables will undergo a comparative evaluation between the intervention and control groups using chi-square evaluations. Continuous variables will be compared using 2-tailed *t* tests and Mann-Whitney *U* tests. Outcome metrics will be presented for each research group at various intervals. These outcomes will be detailed based on cumulative scores and the percentage of participants that demonstrate improvement from the start point.

Statistical Analysis

Analysis of covariance will be used to evaluate the influence of treatment conditions on primary and secondary outcomes since it is the most appropriate statistical method for the analysis of continuous outcomes in RCTs [44,45]. Analysis of covariance is a linear regression in which treatment assignment and baseline scores are included as covariates. Patient clinical and demographic characteristics, as well as therapist demographic and professional characteristics, will be included as exploratory variables. A total of 2 analyses will be carried out: the intention-to-treat analysis to examine the general effect and the per protocol analysis as a sensitivity analysis. The time will be measured in weeks, and the baseline is coded with the value 0. Analyses will be performed using R statistical computing software (version 4.3.1 or higher; R Foundation for Statistical Computing).

Trial Status

At the time of submission of this protocol's manuscript, recruitment is complete.

Dissemination Policy

The results of this research project will first appear as preprints and subsequently be shared through scholarly journals and

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presentations at conferences. The Open Science Framework will host a repository containing study tools and data, scoring guidelines, presentations, and preprint versions. Wikiversity pages, tailored to offer technical assets for both practitioners and researchers, will feature links directing to this repository. Furthermore, this study's conclusions could be communicated to pertinent mental health associations, contributing to future studies and potential improvements in psychotherapeutic relationships. Our goal is to adopt a comprehensive and broad-based communication approach that engages scholars, health care professionals, and the general public.

Results

Participant recruitment started in September 2023. Baseline data collection was completed in December 2023, with a total of 520 recruited participants, 475 of whom completed the baseline assessment (243 participants were assigned to the intervention group and 232 were assigned to the control group). Data was completed February 2024. Data analysis has not begun as of the time of submission. The results are expected to be published in the autumn of 2024.

Discussion

This clinical study is designed to assess the impact of introducing a concise postsession questionnaire able to trigger the self-awareness and introspection of patients about their experience of the psychotherapeutic relationship. The primary goal is to understand its influence on the effectiveness of treatment, with the CORE-OM serving as the primary outcome measure.

Should our battery prove to increase symptom reduction rates or improve overall well-being, its ease of delivery directly to patients—requiring no additional therapist involvement—suggests potential for seamless adoption across therapeutic contexts without incurring extra expenses for patients or placing added demands on therapists. This could make the system highly cost-efficient. Furthermore, the insights from this study could shed light on the nuanced interaction between specific elements of the therapeutic bond and the results of sessions or general treatment. This knowledge would empower clinicians and policy makers to recognize and prioritize those aspects of the therapeutic relationship that strengthen or hinder the efficacy of psychotherapy.

One of the main strengths of this study is its ability to gauge the benefits of regular patient self-monitoring and subsequent reflection on their emotional reactions toward their therapists in a real-world setting. The study sample accurately represents the diverse patient population within the United States, further enhancing its relevance. Other key advantages include robust statistical power, the use of an external outcome measure not related to the intervention, and a comprehensive consideration of the patient, the therapist, and treatment variables. However, there are limitations, such as the lack of information from the clinician or observer and the extended duration of data collection. Furthermore, an important potential limitation inherent in our approach concerns the adherence of the participants to the research protocol, specifically the regular completion of the battery after each therapy session, and their compliance with the recommendation to share their emotional responses toward their therapist directly and openly with the therapist.

To this day, efforts to implement and test regular self-monitoring of patient affective experiences during sessions, with systematic feedback provided directly to patients without the therapist's intervention, seem inadequate. The introduction of a newly developed systematic client feedback system for psychotherapy may offer improvements in treatment outcomes while also serving as a cost-effective tool in real-world clinical practice.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during this study protocol. The data sets generated during the actual research study will be made available in the Open Science Framework repository [31].

Conflicts of Interest

EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. EAY is the co-founder and Executive Director of Helping Give Away Psychological Science, a 501c3; he has consulted about psychological assessment with Signant Health and received royalties from the American Psychological Association and Guilford Press, and he holds equity in Joe Startup Technologies.

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Abbreviations

CORE-OM: Clinical Outcomes in Routine Evaluation-Outcome Measure
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GAD-7: Generalized Anxiety Disorder-7
PHQ-9: Patient Health Questionnaire-9
RISQ: Rift In-Session Questionnaire
RRI-C-SF: Real Relationship Inventory-Client-Short Form
SES: Session Evaluation Scale
SPARQ: in-Session Patient Affective Reactions Questionnaire
UNC: University of North Carolina
WAI-SR: Working Alliance Inventory-Short Revised

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Protocol

Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Chronic pain affects approximately 8 million Canadians (~20%), impacting their physical and mental health while burdening the health care system with costs of upwards of US $60 billion a year. Indeed, patients are often trialed on numerous medications over several years without reductions to their symptoms. Therefore, there is an urgent need to identify new therapies for chronic pain to improve patients' quality of life, increase the availability of treatment options, and reduce the burden on the health care system.

Objective: The primary objective of this study is to examine the feasibility of a parallel 3-arm pilot randomized controlled trial whereby patients are randomized to either intravenous ketamine alone, cognitive behavioral therapy (CBT) and mindfulness meditation (MM) training (CBT/MM), or the combination of intravenous ketamine and CBT/MM. The secondary outcome is to assess the durability and efficacy of combination intravenous ketamine and CBT/MM for treatment of chronic pain as compared to CBT/MM or intravenous ketamine alone (assessed at week 20 of the study).

Methods: This is a single-center, 16-week, 3-arm pilot study that will take place at the Chronic Pain Clinic at St. Michael's Hospital, Toronto, Ontario, which receives 1000 referrals per year. Patients will be enrolled in the study for a total of 20 weeks. Participants who are allocated CBT/MM therapy will receive remote weekly psychotherapy from week 1 to week 16, inclusive of health coaching administered through the NexJ Health Inc (NexJ Health) platform. Patients who are allocated ketamine-infusion therapy will receive monthly ketamine infusion treatments on weeks 2, 7, and 12. Patients who are allocated ketamine+CBT/MM will receive weekly psychotherapy from weeks 1 to 16, inclusive, as well as ketamine infusion treatments on weeks 2, 7, and 12. We will be assessing recruitment rates, consent rates, withdrawal rates, adherence, missing data, and adverse events as pilot outcome measures. Secondary clinical outcomes include changes relative to baseline in pain intensity and pain interference.

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Results: As of November 1, 2023, the recruitment process has not been initiated. Given the recruitment, consent, and intervention target of 30 participants for this feasibility study, with each patient undergoing monitoring and treatments for a course of 20 weeks, we expect to complete the study by December 2025.

Conclusions: This study assesses the feasibility of conducting a 3-arm randomized controlled trial to examine the effects of ketamine administration with the concurrent use of CBT/MM in a population with chronic neuropathic pain. The results of this pilot randomized controlled trial will inform the development of a larger-scale randomized controlled trial. Future studies will be aimed at including a sufficiently powered sample that will inform decisions about optimal treatment calibration and treatment effect duration.

Trial Registration: ClinicalTrials.gov NCT05639322; https://classic.clinicaltrials.gov/ct2/show/NCT05639322

International Registered Report Identifier (IRRID): PRR1-10.2196/54406

(JMIR Res Protoc 2024;13:e54406) doi:10.2196/54406

KEYWORDS

3-arm parallel group; cognitive behavior therapy; ketamine hydrochloride; pain intensity; pain interference; psychotherapy; randomized controlled trial

Introduction

Chronic pain affects approximately 8 million Canadians (~20%) and profoundly impacts their physical and mental health. The broad ranging consequences of this disease are evidenced by estimated health care system costs upwards of US $60 billion a year [1]. In the United States, chronic pain also affects 1 in 5 people, and the annual cost is estimated as greater than US $0.5 trillion [2]. Indeed, chronic pain is associated with poor quality of life, psychiatric symptoms, and mobility restrictions. It has significant physical, functional, social, and economic impacts at the individual and system levels. Current pain therapies aim to decrease pain to manageable levels. In most cases however, chronic pain cannot be completely eliminated. Patients are often trialed on numerous medications without adequate relief, and therapies are often limited by their lack of durability and adverse effects. There is an urgent need to identify new therapies for chronic pain to improve patients' quality of life and the availability of treatment options, while reducing health care system burdens.

Ketamine is an N-methyl-D-aspartate receptor antagonist which results in pain reduction. It is also associated with reductions in opioid-induced hyperalgesia and opioid consumption [3]. At high doses, it is an agonist at the mu receptor, the D2-R, and L-Type voltage-gated calcium channel. Current evidence supports intermittent ketamine therapy for neuropathic pain. Double-blind randomized controlled trials (RCTs) investigating the use of ketamine for neuropathic pain have demonstrated clinically significant reductions (25% to 43%) in chronic pain versus control conditions [3]. However, ketamine appears to have limited durability as studies have shown short term reductions in neuropathic pain secondary to spinal cord injury and fibromyalgia but no long-term benefits [4,5]. Although timelines and follow-ups vary significantly, the lack of durability is consistent across all ketamine infusion regimens studied [6]. Indeed, a systematic review by Cohen et al [3] indicated a lack of evidence for durable benefits, affirming the need for adjunctive therapies that improve durability and improve outcomes.

Internet-delivered cognitive behavioral therapy (CBT) for chronic pain, depression, and anxiety is associated with significant reductions in pain disability, symptoms of depression, and pain catastrophizing at 1 year follow-up [7]. Nonetheless, an integrative review [8] concluded CBT research must further address longer-term efficacy (>12 months). This same review highlighted the significant variations in the duration and total dose hours of CBT interventions and delivery methods (remote, group, or individual). Despite variations, existing studies and emergent guidelines support the synergistic effects of pharmacological therapies strategically combined with CBT-based strategies [7].

The primary objective of this trial is to study the effects of concurrent ketamine and CBT for chronic neuropathic pain relief. Biological and neurocognitive factors suggest that concurrent pharmacotherapy and psychotherapy can result in more durable and effective analgesic responses than either intervention alone. Ketamine administration induces physiological changes during and after delivery that result in powerful experiential responses with important psychological and emotional impacts [9]. The physiological changes associated with ketamine therapy are likely to influence important habitual thinking and behavior patterns. Studies suggest that ketamine alters functional brain connectivity, even to the point of disrupting spatiotemporal patterns of neural activity and increasing functional communications between brain regions typically isolated [9].

Despite the biologic plausibility of ketamine-assisted psychotherapy being an effective cotreatment for chronic neuropathic pain, there is a lack of rigorous evidence supporting its use. Our group conducted a systematic review to examine existing evidence on concurrent ketamine dosing and psychotherapy [10]. This knowledge synthesis showed substantial methodologic variations across 17 studies. The most common indications studied included posttraumatic stress disorder (6 studies), major depressive disorder (6 studies), substance use disorder (6 studies), and obsessive compulsive disorder (2 studies). Only 2 publications (a case report and a case series) examined continuous multiday ketamine infusions with concurrent psychotherapy in individuals with chronic pain.

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Ocker et al [11] described a 5-day continuous ketamine infusion regimen combined with CBT to successfully taper opioids in a patient with complex regional pain syndrome who was taking 330 mg of daily morphine equivalents. They attribute the sustained results to an observed synergism between ketamine and the outpatient CBT protocol. Keizer et al [12] described a case series of 11 patients who received ketamine-enhanced psychotherapy for comorbid neuropathic pain and posttraumatic stress disorder. A 96-hour ketamine infusion was delivered with daily bedside psychotherapy. Although it resulted in a moderate but clinically meaningful reduction in pain symptoms, the brief follow up of 5 days precluded in-depth examination of the potential synergism.

This systematic review also revealed no evidence that a single protocol or therapy strategy was decidedly more beneficial than any other. To date, no RCT has combined ketamine and psychotherapeutic intervention for patients with chronic pain. The results of this review highlight the poor methodological quality of existing studies and need for higher quality evidence on the potential impact of combined interventions. By means of this pilot study, our intention is to determine whether a customized CBT along with mindfulness and meditation (MM; ie, CBT/MM) psychotherapy regimen can be effectively and safely integrated with a ketamine-induced state in a chronic neuropathic pain sample.

The Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain study has received partial funding from the Canadian Pain Society in partnership with the Pfizer Early Career Investigator Award as well as the St. Michael's Hospital Association Innovation Fund.

Methods

Aim

The primary objective of this study is to enroll 30 participants with chronic neuropathic pain and assess the feasibility of conducting a 3-arm parallel group pilot RCT. The secondary aim of the study is to examine whether the combined effects of ketamine and CBT/MM (as delivered through the NexJ Health Inc platform by trained navigator-coaches) can reduce pain intensity and pain interference by week 20 of the study (ie, limited efficacy at week 20).

Recruitment and Randomization

Recruitment will occur at the Chronic Pain Clinic at St. Michael's Hospital, Toronto, Ontario. The clinic receives approximately 1000 referrals per year. An estimated 3% of these referrals would be eligible for inclusion in this trial.

A staff member who does not belong to the study team will be provided with the instructions to use a remote random number generator, the "Sealed Envelope" website to generate an allocation sequence at random. The allocation list will be sent to the Research Pharmacy staff at St. Michael's Hospital directly, without the knowledge of the study team, to maintain the blindness. After participant enrollment, the pharmacy staff will randomize the patient and inform a delegated research team member as to the allocated intervention arm. The delegated unblinded research team member will then notify the patient which arm they have been randomized to and will coordinate with the anesthesiologists and psychologists, who will be unblinded, to schedule in-person study visits on weeks 2, 7, and 12 according to the randomized treatment arm. For patients randomized to Arm 1 or 3, the Research Pharmacy staff will prepare ketamine-hydrochloride for weeks 2, 7, and 12. The outcome assessors are the only research staff to remain blinded to patient treatment (currently, we only have 1 delegated outcome assessor).

Participants will be randomized to receive either (1) ketamine-hydrochloride infusions alone, (2) CBT/MM alone, or (3) a combination ketamine-hydrochloride infusion and CBT/MM.

Participants will be eligible for this study as per the inclusion and exclusion criteria listed (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria regarding participant eligibility for PYSKED-NP.

Inclusion criteria

- Aged 18 years or older.
- Diagnosis of chronic neuropathic pain as determined by a pain specialist with moderate to severe neuropathic pain as per ID pain questionnaire, with mean pain scores >3 on an 11-point (0-10) Numeric Rating Scale, in the 7 days preceding inclusion.
- For participants of childbearing potential, use of highly effective or double-barrier methods of contraception. Abstinence is acceptable if it is the preferred and usual lifestyle of the participant.
- Capacity to provide informed consent

Exclusion criteria

- Patients aged younger than 18 years.
- Current or lifetime history of schizophrenia, psychotic disorder, bipolar disorder, or borderline personality disorder.
- Known history of hypersensitivity or allergy to ketamine-hydrochloride.
- Current history of dissociative disorders.
- Current concomitant use of theophylline or aminophylline.
- Current elevated intracranial pressure.
- Pregnancy or ongoing breastfeeding in female participants.
- Concomitant active substance use in the 6 months preceding enrollment (amphetamines, alcohol, and ketamine).
- Contraindication to receiving ketamine-hydrochloride (eg, current or lifetime history of cerebrovascular accident, current significant hypertension [systolic blood pressure higher than 160 mm Hg in combination with or with an isolated diastolic blood pressure higher than 100 mm Hg], and current severe cardiac decompensation [eg, presence of dyspnea, peripheral edema, elevated jugular venous pressure, hepatomegaly, pulmonary rales, and pleural effusions]).

Withdrawal Criteria

A participant will be withdrawn if the participant presents with a severe adverse event or unknown allergic reaction during the first administration of ketamine-hydrochloride or if the participant wants to withdraw from the study for any reason. The participant will receive the necessary treatment to alleviate any untoward events and will be monitored by the study physician until judged appropriate for discharge. Participants will be followed up on the following day to ascertain more details on their condition. Data from a participant who has been withdrawn will be collected up to the day following their withdrawal to ensure that the participant has no more complications. If a participant withdraws from the study at any time, the reasons for withdrawal will be collected and documented as a feasibility study outcome.

Since this is a feasibility study without a specific sample size required to analyze any outcome, participants will not be replaced or added.

Intervention

Intervention Description

Participants will be randomly assigned to one of 3 arms. Arm 1: Ketamine-hydrochloride infusions alone, Arm 2: CBT in combination with MM (CBT/MM), or Arm 3: Ketamine-hydrochloride infusions in combination with CBT/MM.

Ketamine-hydrochloride will be delivered intravenously for patients in Arm 1 and Arm 3. For this study, 1 mg/kg of ketamine intravenous will be dosed by total body weight and administered over 2 hours up to a maximum dose of 100 mg as per our local institutional protocol.

Arm 1: Ketamine-Hydrochloride Infusion Alone

Patients in Arm 1 receiving a ketamine-hydrochloride infusion alone will receive ketamine infusions on weeks 2, 7, and 12 of the study. After the study intervention, participants will have their vital signs and adverse events monitored for one hour. The anesthesia provider will be responsible for assessing the participant before discharge. Participants will not be allowed to drive after the intervention; therefore, measures will be taken to ensure the participant has an adequate plan of transportation (ie, a companion or suitable transportation).

For safety reasons, the anesthesia provider administering the medication will not be blinded. However, the study personnel designated to collect the outcome data will be unaware of the treatment assignment. Patients will not be blinded to their therapy for the purposes of this feasibility study.

Arm 2: CBT/MM Alone

Participants in Arm 2 receiving CBT/MM alone will receive weekly CBT/MM treatment in collaboration with NexJ Health Inc and supplemented by the designated psychotherapist trained for and experienced in previous studies [13]. About 16 hours of CBT/MM therapy will be delivered over 16 weeks. Participants will be assigned to a 3-hour CBT/MM workshop remotely, to be administered by the delegated psychotherapist. The CBT-MM programming will combine exposure to smartphone- and computer-accessible workbooks with phone-based mental health counseling (16 hours in 16 weeks)

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that coordinates with ongoing software interactions (eg, secure text messaging) [14,15].

The software for delivering the CBT/MM therapy is a standalone platform, called "Connected Wellness Platform," developed by NexJ Health Inc. Connected Wellness Platform is a customized, secure (2-level log-in with 128-bit encryption) interface accessible through both a smartphone and a computer.

Arm 3: Ketamine-Hydrochloride Infusion in Combination With CBT/MM

Finally, participants in Arm 3 receiving ketamine infusion+CBT/MM will receive both the standard CBT/MM and ketamine-hydrochloride infusion protocols as described above. Participants in this arm will have psychotherapy delivered concurrently with their ketamine infusions on weeks 2, 7, and 12 in person by the delegated psychotherapist. Participants in Arm 3 will also receive 16 weeks of CBT/MM remotely.

Hypothesis

In line with the primary aim of this study, this pilot study will prove to be feasible for a large-scale clinical trial. We expect that we will be able to successfully meet our recruitment target (30 participants) within the 1-year time frame of the study and expect this study withdrawal rate to be less than 10% (3/30 patients). Feasibility of this study will be determined by the following set variables and cutoff percentages; recruitment success with the specific aim to recruit all necessary patients within the first year of the trial period, adequate consent rate (30/100, >30% of eligible patients consent to participate in the study), intervention adherence as define by the percentage of patients who complete all medication and psychotherapy visits (27/30, >90%), percentage of patients who withdraw from the study (ie, due to side effects; 6/30, <20%), percentage of patients with incomplete pain intensity and pain interference data at 1 month, (eg, withdrawal due to side effects, loss to follow up, or missing data; 3/30, <10%), and rate of adverse outcomes. We do not foresee any issues arising with the protocol of the study or the delivery of each arm.

While not powered to examine these effects, we hypothesize that patients allocated to the combination ketamine and CBT/MM arm of this study will have the greatest reduction in pain intensity and pain interference.

Blinding Mechanism

The intervention delivery providers (anesthesiologists and psychologists) and other members of the research team will be aware of each participant's assigned intervention. Within the research team, blinded members will be responsible for inputting all of the data into the REDCap (Research Electronic Data Capture; Vanderbilt University) database, with the exception of any ketamine-specific data, that is, semistructured interviews after the ketamine intervention and any adverse events. Following data collection, we will request blinded staff to record their "best guess" of each patient's intervention to assess blinding efficacy. The research team currently has 1 blinded member who will serve as the outcome assessor and be responsible for data input.

Emergency Unblinding

To optimize study quality, emergency unblinding will only occur when knowledge of the intervention is essential for participant care, as determined by the principal investigator. In the case of emergency unblinding, the timing, reason for doing so, and personnel involved will be recorded in the case report form, while blinding is maintained by as many other study personnel as possible.

Outcome Measures

Primary Outcome

The primary outcome of this pilot trial is to determine the feasibility of a large-scale multicenter trial. Feasibility outcomes will include the following variables, with all thresholds listed in parentheses:

1. Recruitment success (with the specific aim of recruiting all necessary patients within the first year of the trial period).
2. Adequate consent rate (>30% of eligible patients consent to participate in the study).
3. Percentage of patients who complete all medication and psychotherapy visits (ie, intervention adherence; >90%).
4. Percentage of patients who withdraw from the study (eg, due to side effects or other reasons; <20%).
5. Percentage of patients with incomplete pain intensity and pain interference data at 1 month and stated or ascribed reason (eg, withdrawal due to side effects, loss of follow-up, or missing data; <10%).
6. Rate of adverse outcomes (ie, 0 serious adverse events).

Based on the result for each primary feasibility outcome, we will determine whether the definitive study is feasible as proposed (ie, all feasibility targets are met), feasible with protocol modifications (modifications specified), or not feasible because feasibility targets could not be met even with protocol modifications. These cutoffs, identified in the parentheses above, will help determine whether protocol changes are required before proceeding with a definitive trial.

Secondary Outcome

The secondary outcomes chosen for the definitive trial follow consensus recommendations of core domains that should be addressed in studies examining chronic pain. Information will be collected in these domains as part of the pilot trial using survey-based outcome assessments, either in person during study visits or over the telephone by trained research personnel. The following pain score questionnaires will be used:

1. Pain intensity on an 11-point (0-10) Numeric Rating Scale.
2. Pain interference on the Patient-Reported Outcomes Measurement Information System (PROMIS-PI) scale.
3. Catastrophic thinking about pain, as measured by the Pain Catastrophizing Scale (PCS).
4. Features of depression, as measured by the Patient Health Questionnaire-9 (PHQ-9).
5. Features of anxiety, as measured by the Generalized Anxiety Disorder-7 (GAD-7).
6. Patient Global Impression of Change Scale (PGIC).

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Secondary clinical outcomes will include changes relative to baseline assessment in pain intensity and pain interference at week 20 (4 weeks post-completion of treatment; Figure 1). Scores for all outcomes at weeks 2, 7, 12, 16, and 20 will be compared to baseline scores to assess any progressive additive effects between the treatments. For any patients who withdraw before week 20, their last documented responses will be used as a comparison against baseline data. Patients will be allowed to adjust the dosages of other analgesic medications in conjunction with their primary physician. Analgesic medication use and doses will be tracked at the above time points to assess changes over time. Semistructured interviews will be conducted at 2 points within the study period: at weeks 1 and 20 and after the ketamine infusions (Table 1). The interviews will be audio-recorded to ensure the responses are accurately captured. In-person interviews will be recorded with an encrypted device, and phone interviews will be recorded through the Unity Health Zoom (Zoom Video Communications Inc) recording option. The audio recording files will be saved on St. Michael's Hospital secure and restricted servers, and the files will be labeled by the study number. The recordings will be transcribed by the research team, and after verifying that the transcriptions are accurate, the audio recordings will be destroyed. Questionnaires will be delivered to patients at prespecified time points, as outlined in the study timeline below.

Figure 1. Overview of study design with primary and secondary outcomes. CBT/MM: cognitive behavior therapy/mindfulness and meditation.

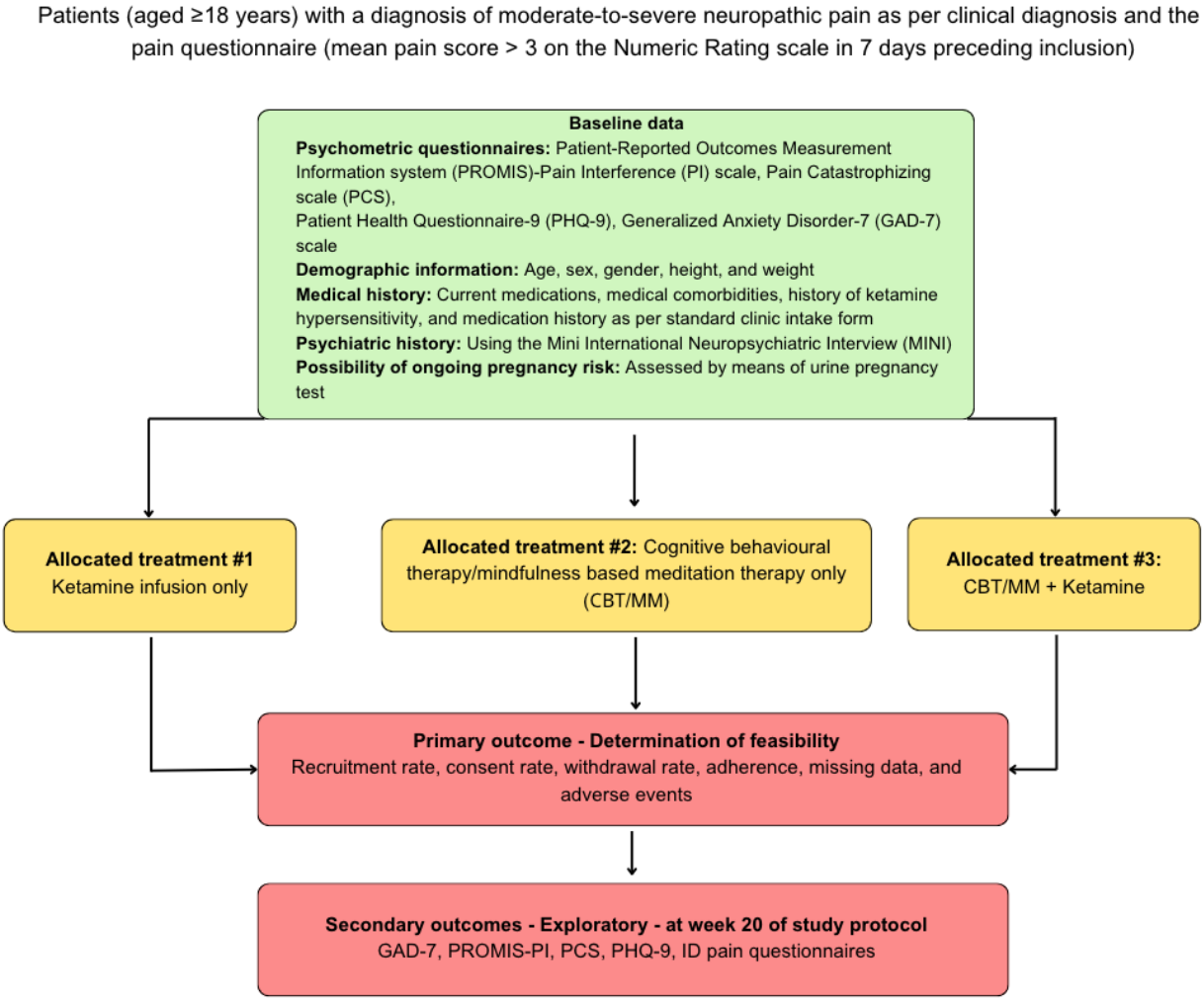

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Table 1. Study timeline from weeks 1-20.

Time point	Screening	Week 1	Week 2	Week 7	Week 12	Week 16	Week 20
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
MINI[a]	✓						
Randomization		✓					
Interventions							
Ketamine-hydrochloride infusion (arm 1 and arm 3)			✓	✓	✓		
Remote CBT/MM[b] (arm 2 and arm 3)		✓	✓	✓	✓	✓	
In-person CBT/MM (arm 2 and arm 3)			✓	✓	✓		
Assessments							
Baseline data		✓					
Semistructured interviews		✓[c,d]	✓[d]	✓[d]	✓[d]		✓[c,d]
Pregnancy test (if applicable)[e]			✓	✓	✓		
Questionnaires: PROMIS-PI[f], PGIC[g], GAD-7[h], PHQ-9[i], and PCS[j]		✓	✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓

[a]MINI: Mini International Neuropsychiatric Interview.

[b]CBT/MM: cognitive behavior therapy/mindfulness and meditation.

[c]Participants randomized to receive CBT/MM alone (arm 2), will receive a semistructured interview on weeks 1 and 20.

[d]Participants randomized to receive ketamine-hydrochloride infusion + CBT/MM (arm 3) will receive a semistructured interview on weeks 1 and 20 as well as a semistructured interview during the ketamine infusion on weeks 2, 7, and 12.

[e]Only female participants randomized to receive ketamine-hydrochloride alone (arm 1) or the ketamine-hydrochloride infusion + CBT/MM (arm 3) will require a pregnancy test on the day of infusion.

[f]PROMIS-PI: Patient-Reported Outcomes Measurement Information System.

[g]PGIC: Patient Global Impression of Change Scale.

[h]GAD-7: Generalized Anxiety Disorder-7.

[i]PHQ-9: Patient Health Questionnaire-9.

[j]PCS: Pain Catastrophizing Scale.

Ethical Considerations

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki, the protocol, Good Clinical Practice guidelines, and applicable regulatory requirements. This study received a “No Objection Letter” from Health Canada on October 13, 2022, indicating the study protocol was deemed acceptable.

Full written informed consent will be obtained from participants before conducting any study activities. The study was reviewed and approved by the Research Ethics Board at St. Michael’s Hospital on May 5, 2023 (22-217). This trial was designed and will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) clinical trials statement checklist and the CONSORT-Outcomes 2022 extension [16].

Results

Prestudy Screening

Eligible participants will be screened at the Chronic Pain Clinic at St. Michael’s Hospital. Participants diagnosed with chronic neuropathic pain that meet the criteria from the ID pain questionnaire will be approached and asked to consider study participation.

After participants have provided informed consent, they will be asked about their medical comorbidities, psychiatric history as based on the Mini International Neuropsychiatric Interview, history of ketamine hypersensitivity, and concomitant medications to confirm eligibility. If a participant is eligible to participate in the study, the participant will be enrolled in the study, and the study coordinator will book an appointment for the participant’s study intervention.

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At this current point, November 1, 2023, the study has not started enrolling and consenting patients.

Baseline Data

After initial screening and informed consent are obtained, the following data will be collected at baseline (week 1):

1. Demographic information: age, sex, gender, height, and weight.
2. Detailed data regarding current medications and medical comorbidities, as well as medication history, is collected by our standard intake form.
3. Chronic neuropathic pain severity and other relevant covariates will be assessed at baseline using:
    - PROMIS-PI
    - PCS
    - PHQ-9
    - GAD-7
    - PGIC

Follow-Up Data

In all arms, at each follow-up visit, participants will complete the PROMIS-PI scale, PCS, PHQ-9, GAD-7, and the PGIC to assess outcome measurements. Follow-ups will be conducted every 4 weeks over the phone to maintain the blindness of the research team.

For females, a urine pregnancy test will be required for those randomized to the ketamine-hydrochloride infusion alone or the ketamine-hydrochloride infusion+CBT/MM arms in order to confirm that the patient is not pregnant before each ketamine infusion treatment.

Outcome Analysis

Based on the primary end points, we will determine whether or not this pilot study is as follows:

1. Feasible: all feasibility outcomes are met; no protocol modifications are needed,
2. Feasible with modification: all feasibility outcomes are met or can be met with protocol modifications, and
3. Not feasible: Even with protocol modifications, some feasibility outcomes cannot be met.

In terms of statistical analyses for this feasibility study, preliminary analyses will consist of univariate tests to compare clinical and demographic variables of interest. Linear regression analysis will be used to quantify the strength and magnitude of the relationship between the intervention and the coprimary outcomes. Secondary outcomes will be analyzed as continuous measures using generalized linear regression models.

For any missing data where patients do not attend the allocated sessions or do not complete all components of the relevant questionnaires, this will be noted and documented to assess the overall feasibility of this study. Data will not be extrapolated or interpreted for these missing data sets.

Study Status As of Date

As of the current date, November 1, 2023, the study has not started to recruit patients.

Discussion

It is hypothesized that concurrent pharmacotherapy and psychotherapy have combined effects on the analgesic response. In addition to ketamine's anesthetic-analgesic properties, it also uniquely alters the individual's level of consciousness at variable doses. Some researchers posit that the therapeutic experience of psychotherapy may be augmented by ketamine's alteration of conscious awareness [10]. As demonstrated by this systematic review, few studies have examined ketamine-assisted psychotherapy (KAP) for chronic neuropathic pain. RCTs have not been published on this topic. In addition, there appears to be wide variability in the indication, dosage, and patient treatment setting, such that the current literature is inconclusive.

The 3-arm design allows us to compare the feasibility of KAP with ketamine alone and CBT/MM. We will track feasibility outcomes, including recruitment rate and adverse event rate, to estimate the acceptability of this intervention compared to controls. There are also limitations to this study. Due to the participatory nature of CBT/MM, we are unable to blind patients and the research team to patients' assigned interventions. To mitigate this, the outcome assessors will be blinded to minimize bias, and we will request and report their "best guess" estimate of each patient's assigned intervention at the end of the study. We also recognize that there may be different patient outcomes based on the mode of CBT/MM delivery. Patients in arm 1 receiving ketamine alone will have no CBT/MM as part of the trial design. Patients assigned to CBT/MM alone (Arm 2) will be receiving their intervention sessions remotely rather than in-person for 16 weeks. Patients in Arm 3 will be receiving ketamine on weeks 2, 7, and 12 and in-person CBT/MM at this time. They will also be involved with remote CBT/MM sessions from weeks 1 to 16 (except for weeks 2,7, and 12). This hybrid intervention will allow us to collect data on the feasibility of in-person versus remote psychotherapy for this patient population.

This study will inform the development of a larger-scale multicenter RCT. Our results will help inform the sample size calculation to ensure an adequately powered, definitive RCT. We anticipate that the psychotherapy and ketamine protocols developed in this study will be easily replicable and scalable should they show clinical and statistical benefits in the chronic neuropathic pain population. Furthermore, future studies developed by our research team will aim to study longer-term outcomes associated with KAP and the need for ongoing therapy in this patient subset.

Acknowledgments

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the Department of Anesthesiology and Pain Medicine at the University of Toronto. Joel Katz is supported by a Canadian Institutes of Health Research Canada Research Chair in Health Psychology at York University. PR is currently funded by the Canadian Institutes of Health (2021-2025). He coordinates research with NexJ Health Inc which provides software to convey the programming he develops and assesses.

Authors' Contributions

KL, H Clarke, JK, PR, JPC, ZT, GM, and AG were responsible for conception and design. BK, H Chan, KP, and AG were responsible for drafting the manuscript. All the authors were responsible for revising the manuscript for intellectual content and final approval of the completed manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Canadian Pain Society in partnership with the Pfizer Early Career Investigator Award.
[PDF File (Adobe PDF File), 742 KB - resprot_v13i1e54406_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder-7
KAP: ketamine-assisted psychotherapy
MM: mindfulness and meditation
PCS: Pain Catastrophizing Scale
PGIC: Patient Global Impression of Change Scale
PHQ-9: Patient Health Questionnaire-9
PROMIS-PI: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Quantifying Bone and Skin Movement in the Residual Limb-Socket Interface of Individuals With Transtibial Limb Loss Using Dynamic Stereo X-Ray: Protocol for a Lower Limb Loss Cadaver and Clinical Study

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Abstract

Background: Relative motion between the residual limb and socket in individuals with transtibial limb loss can lead to substantial consequences that limit mobility. Although assessments of the relative motion between the residual limb and socket have been performed, there remains a substantial gap in understanding the complex mechanics of the residual limb-socket interface during dynamic activities that limits the ability to improve socket design. However, dynamic stereo x-ray (DSX) is an advanced imaging technology that can quantify 3D bone movement and skin deformation inside a socket during dynamic activities.

Objective: This study aims to develop analytical tools using DSX to quantify the dynamic, in vivo kinematics between the residual limb and socket and the mechanism of residual tissue deformation.

Methods: A lower limb cadaver study will first be performed to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin to simultaneously assess dynamic tibial movement and residual tissue and liner deformation. Five cadaver limbs will be used in an iterative process to develop an optimal marker setup. Stance phase gait will be simulated during each session to induce bone movement and skin and liner deformation. The number, shape, size, and placement of each marker will be evaluated after each session to refine the marker set. Once an optimal marker setup is identified, 21 participants with transtibial limb loss will be fitted with a socket capable of being suspended via both elevated vacuum and traditional suction. Participants will undergo a 4-week acclimation period and then be tested in the DSX system to track tibial, skin, and liner motion under both suspension techniques during 3 activities: treadmill walking at a self-selected speed, at a walking speed 10% faster, and during a step-down movement. The performance of the 2 suspension techniques will be evaluated by quantifying the 3D bone movement of the residual tibia with respect to the socket and quantifying liner and skin deformation at the socket-residuum interface.

Results: This study was funded in October 2021. Cadaver testing began in January 2023. Enrollment began in February 2024. Data collection is expected to conclude in December 2025. The initial dissemination of results is expected in November 2026.

Conclusions: The successful completion of this study will help develop analytical methods for the accurate assessment of residual limb-socket motion. The results will significantly advance the understanding of the complex biomechanical interactions between the residual limb and the socket, which can aid in evidence-based clinical practice and socket prescription guidelines.

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This critical foundational information can aid in the development of future socket technology that has the potential to reduce secondary comorbidities that result from complications of poor prosthesis load transmission.

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KEYWORDS

biplanar fluoroscopy; dynamic stereo x-ray; lower limb loss; transtibial limb loss; prosthetic sockets; amputation; lower extremity

Introduction

Background

For individuals with lower limb loss who use a prosthesis, relative motion between the prosthetic socket and the residual limb, including vertical translation and axial rotation, is a common problem that can lead to skin integrity concerns [1]. Excessive motion between the residual limb and socket can lead to discomfort, pain, and gait deviations that can limit mobility [2], which has been correlated with worse quality of life [3]. Up to 40% of individuals with transtibial limb loss experience issues involving the residual skin and soft tissue, which can be directly attributed to the movement of the residuum relative to the prosthetic socket and liner during dynamic activities [4]. Restricting residual bone motion within the socket may therefore help improve the quality of life and comfort for individuals with lower limb loss. Although some efforts have been made to advance socket technology [5-7] and improve suspension techniques [8], clinical practice has been slow to adopt these new technologies and continues to primarily rely upon unscientific methods for socket fabrication [9,10]. The challenge of developing enhanced socket technology and suspension techniques can be partially attributed to the multifactorial nature of socket fit, which is complicated by the complex mechanical interaction between the residual limb (bone and tissue), the liner, and the socket during dynamic activities. Furthermore, there has traditionally been a lack of accurate analytical techniques to quantify the complex, dynamic biomechanics of the socket-residual limb interface.

Although biomechanical assessments of the relative motion between the residual limb and the prosthetic socket have been performed, the existing data are suboptimal or lack an appropriate resolution. Radiological methods have been widely used to measure the relative motion of the bone and socket in 2 dimensions, but these methods have only provided static analyses of the residual limb-socket relationships [11,12]. Ultrasound has been used to monitor residual limb motion in individuals with above-knee limb loss [13], but the mounting technique has been found to be too cumbersome to implement on a clinical basis. Advanced imaging methods including computed tomography (CT) and spiral x-ray CT offer higher spatial resolution, but imaging must be performed in the supine position, resulting in non–weight-bearing, static assessments [14-16]. Roentgen stereophotogrammetric analyses have been used to characterize the motion between the residual limb and socket in 6 degrees of freedom (DOF) by using biplanar imaging [17]; however, these techniques use static loading protocols. Dynamic assessments of 3D in-socket residual limb-socket kinematics are currently only possible using dynamic stereo x-ray (DSX), which can provide submillimeter bone pose [18-21] and in vivo strain analysis. Currently, only 1 study performed a dynamic investigation of residual tibia motion in participants with transtibial limb loss [10], but the methods relied on subjective input and were time intensive, which can affect accuracy [22] and sample size. In individuals with transfemoral limb loss, Maikos et al [23] used DSX to compare 3D residual femur kinematics between 2 different prosthetic socket types. Gale et al [3] also used DSX for 3D markerless tracking of the residual femur for individuals with transfemoral limb loss during late swing and early stance to calculate the 6 DOF kinematics of the residual femur relative to the socket but did not include terminal stance. DSX may help fill the substantial gap in our understanding of the complex mechanics of the residual limb-socket interaction during dynamic activities that limit the ability to improve prosthetic design.

During the cyclical loading and unloading of the residual limb during the gait cycle, the skin of the residual limb is exposed to nonphysiological stresses and strains, including excessive shear forces [24]. Although the skin is well adapted to compressive force, excessive shear force can be damaging, leading to abrasions, wounds, and ulcers [25,26]. Understanding in-socket skin strain biomechanics is critical for enhancing prosthetic socket fit, limb health, and overall comfort. However, whole-limb skin strain analysis is complicated by the heterogeneous composition of the skin and its anisotropic mechanical properties. Some investigations have used 3D digital image correlation (DIC) to create full-field deformation and strain maps of an unsupported residual limb [27]. Lin et al [28] examined skin strain in a flexed biological residual limb from an individual with transtibial limb loss and showed that the anterior patella region of the limbs exhibited predominantly tensile strains, whereas the posterior patella region exhibited predominately compressive strains. Although 3D DIC evaluations have provided critical data to help improve the mechanical interface of sockets and liners to limit relative motion and shear forces on the skin surface, these investigations only considered strain on an unloaded residual limb. Whole-limb strain fields can drastically change during dynamic, weight-bearing activities while using a prosthetic interface. Furthermore, 3D DIC and other imaging techniques are further complicated by the need for transparent biomechanical interfaces to accurately compute the strain analysis. Other techniques, such as magnetic resonance imaging and CT, can be used to evaluate in vivo strains, but they are also limited by static protocols, low resolution, motion artifacts, and shape distortion [29]. Gale et al [30] used DSX to measure residual limb skin strain and strain rate for individuals with transfemoral limb loss during gait and found that shear strain increased from proximal

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to distal regions of the residual limb. The proposed investigation will use time-efficient and highly accurate analytical techniques to measure in-socket residual limb skin strain for individuals with transtibial limb loss during dynamic activities.

Study Objectives and Aims

There remains an unmet need to fill the gap of accurate, biomechanical evaluations of residual limb-socket kinematics, which can then be effectively translated into evidence-based clinical practice. Furthermore, quantifying dynamic shear and tissue deformation is yet to be efficiently evaluated to determine the exact mechanism of tissue strain. Therefore, the objective of this investigation is to develop quantitative, dynamic analytical tools to quantify both 3D bone movement as well as soft tissue and liner deformation at the socket-residual limb interface for individuals with transtibial limb loss. To meet the study objective, the following aims will be addressed: (1) to optimize the DSX procedural setup for the accurate tracking of the prosthetic socket, skeletal kinematics, and tissue and liner deformation; (2) to quantify the relative motion between the residual tibia and the prosthetic socket during dynamic activities; and (3) to measure the deformation of the skin and liner in the prosthetic socket during dynamic activities. The proposed investigation will use a state-of-the-art DSX system to accurately quantify 3D in vivo residual limb-socket kinematics during dynamic activities. To verify the sensitivity of this technique and its relevance to individuals with transtibial limb loss, residual limb-socket kinematics will be evaluated in 2 different socket suspension systems: elevated vacuum (EV) and traditional suction. It is hypothesized that an efficient and highly accurate method to quantify the dynamic interaction between the residual limb and the prosthetic socket will be sensitive enough to distinguish between different types of prosthetic socket suspension systems, which will further enhance the biomechanical understanding of residual limb-socket kinematics.

Methods

Study Overview

To address the study aims, first an iterative cadaver study will be conducted to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin to simultaneously assess both dynamic skeletal movement and residual skin and liner deformation. Using a gait simulator, stance phase gait will be simulated using cadaver limbs during each DSX session to induce bone movement as well as skin and liner deformation. The number and placement of markers will be evaluated after each session to refine the marker placement to best track skin and liner deformation and skeletal movement. Once an optimal marker setup is identified, 21 participants with transtibial limb loss will be fitted with a socket capable of being suspended via both EV and traditional suction. Participants will undergo a 4-week acclimation period using the new socket and will then be evaluated at the DSX facility at Rutgers New Jersey Medical School. DSX will be used to track skeletal, skin, and liner motion under both suspension techniques during 3 dynamic activities: treadmill walking at a self-selected speed, treadmill walking at fast walking (10% faster), and a step-down movement. The performance of the 2 suspension techniques (active EV and traditional suction) will be tested by quantifying the 3D bone movement of the residual tibia with respect to the prosthetic socket and quantifying liner and skin deformation at the socket-residuum interface. This study has been registered on ClinicalTrials.gov (NCT05287646).

Cadaver Study to Optimize DSX Setup

The aim of the cadaver study is to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin, which will then be used in the human trial to accurately measure the dynamic skeletal movement and residual tissue and liner deformation simultaneously during functional tasks. Five cadaver limbs will be used in an iterative process to develop an optimal marker setup to distinguish markers placed on the socket, liner, and skin as well as to visualize the tibia. The number, size, shape, and placement of markers will be evaluated after each cadaver test to determine the optimal marker set for the measurement of skin and liner deformation and bone movement. The goal is to develop a skin and liner marker set that is free of occlusion during tracking while also not interfering with bone tracking. Although it is understood that the cadaveric tissue may not produce accurate tissue displacement and deformation profiles compared to living tissue, the main intent of cadaver testing is to accurately position the skin and liner markers during an iterative process to reduce or eliminate occlusion during tracking.

Cadaver Preparation and Socket Casting

Five fresh-frozen, whole, lower extremity cadaveric specimens without a history of significant trauma or major surgery at or below the knee will be used. Lower extremity cadaver specimens will be from individuals aged <80 years and with a BMI of <38 kg/m^2 to account for the predicted upper limits of the human trials. Cadavers will be thawed at room temperature for 24 hours and will be transected at the midthigh to keep the knee intact. The cadaver specimens for the initial assessments will be amputated below the knee to a length between 12.5 cm and 17.5 cm below the medial joint line, which is considered an ideal length for transtibial amputation [31]. Myodesis will be performed to stabilize the muscles, and the remaining skin flap will be sutured in place. After initial cadavers of ideal length have been used to determine an optimized marker set, subsequent cadaver limbs will be amputated at shorter lengths to ensure that the marker set does not need to be modified to account for different residual limb lengths. A liner will be placed over the amputated cadaver limbs and then cast with fiberglass to create a negative mold. The negative mold will be filled with plaster to create a positive cast, which will be used to fabricate a ThermoLyn socket. Cadavers will be fitted with the socket and prosthetic componentry, including a pylon and prosthetic foot. A rocker bottom shoe will be placed on the prosthetic foot to aid in simulating dynamic gait.

Cadaver CT Scans

A single CT scan will be acquired for each cadaver experiment. The residual limb will be marked with radiopaque paint. A silicone liner will be applied to the residual limb, and a thermoformed plastic socket marked with solid, 2-mm diameter embedded brass spheres will be placed on the limb before

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scanning. The socket will maintain the unloaded 3D shape of the residual limb and the relative positioning of the radiopaque makers. The CT scan will be used to create gray-scale volumes and high-resolution 3D bone surface models required for computing all outcome variables in DSX. CT volume images will be acquired at a resolution of 512×512×0.625 mm^3 (120 kVp; SMART mA).

Experimental Design

To determine the areas of highest strain on both the skin and inner liner surface (to serve as a starting point for appropriate marker placement), the first cadaver experiment will use a grid of circular radiopaque markers distributed across the circumference of the residual limb and the inner surface of the liner (in separate experiments). Although this grid pattern will cover the entire surface to help quantify areas of highest strain on the liner and skin, the high density of radiopaque markers will make it unlikely to track the movement of the residual tibia, liner, skin, and socket accurately and simultaneously. Therefore, this initial cadaver experiment will serve only to help determine areas of importance for subsequent cadaver studies. However, previously reported skin strain findings from the scientific literature will be considered to ensure that areas of interest are included [10,27]. For clarity, the procedures will be first carried out with markers on the skin and no markers on the liner. The experiment will then be repeated using a liner with no markers on the skin.

A custom grid stencil will be fabricated by cutting specific patterns of circles on a thin vinyl sheet using an electronic die-cutting machine (Cricut, Inc). The circles on the grid will be cut to diameters of either 2 mm or 4 mm and spaced 2 cm apart within each row and column. Each row and column of circles will alternate between the larger and smaller circles, which will help uniquely identify them during marker tracking. The stencil will then be applied to the cadaver limb or liner (in separate experiments), and radiopaque paint will be applied to the pattern to transfer the grid onto the residual limb or liner. The liner will then be placed over the limb, the socket will be donned, and the limb will be placed in the DSX capture volume. Averaging the DSX data collected from 10 to 20 frames from the unloaded-donned socket in the static pose will produce the relative resting grid positions, which will account for any skewness after donning the liner and socket. The circles will then be digitized in dynamic trials to relate their dynamic positions to the resting grid.

Stance Simulation

An electromechanical stance simulator will be designed to apply a compressive load on a cadaver limb through simulated stance phase (Figure 1). The framework will be designed to interface with the DSX system while allowing for remote control of the load and trajectory of a cadaver limb during DSX data capture. Using this setup in conjunction with DSX data capture, simulated stance phase will be performed to determine areas of highest strain on both the skin of a cadaver leg and the inner liner surface, while simultaneously tracking tibial movement during dynamic activities during the clinical trial. To ensure accurate results, the system will be able to apply 100% body weight in compression to induce tissue deformation. The applied load will be monitored using a force plate (AMTI Inc).

Figure 1. Overview of the stance simulator design for simulation of the stance phase for cadaver testing. (A) Isometric view of the stance simulator assembly. (B) Detailed view of the force applicator mechanism.

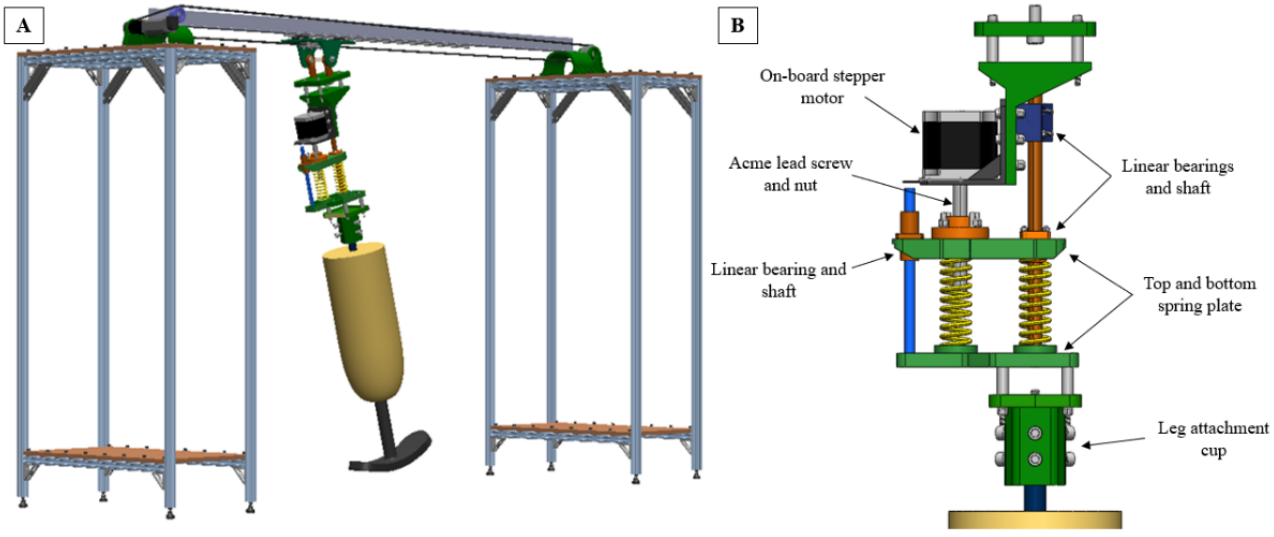

To avoid interference with the DSX system, the main support structure of the simulator will consist of 2 stands with an angle bar spanning the length between them (Figure 1A). Weights placed on the outer stands will ensure that the system remains fixed despite varied applied loads. A linear track attached to the beam will provide a low friction path for the leg to travel along the plane of forward progression, and the beam will ensure minimal deflection of the track. The leg will pivot around this attachment point, allowing it to attain a full range of motion to mimic heel-strike to toe-off. The drive motor will be placed off-board and will move the leg with a timing belt and pulley. A second, on-board motor will control the deflection of 2 springs to actuate the load applied to the leg. The force applicator mechanism (Figure 1B) will include a stepper motor with a built-in Acme lead screw and nut to add spring compression, allowing for consistent control of applied forces at high loads.

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In addition, 3 linear bearings in the assembly allow the assembly to compress without direct control from the on-board motor because of the natural compression of the springs as the leg rolls over in stance under the fixed-height track. The cadaver leg will be placed in extension to limit bending of the knee or the knee will be fixed in place with a titanium rod, increasing the lever arm and ensuring that the springs apply a compressive force. A 3D-printed cup fixture will be secured to the exposed femur of the leg by tightening 6 separate bolts. This attachment method will allow for alignment flexibility, varying the load path through the leg. The entire system will be controlled electronically by 2 separate motor drivers, 1 each for the off-board motor and on-board stepper motor.

Marker Tracking

For each cadaver trial, the images will be analyzed using Locate3D (C-Motion, Inc), which is an application in the DSX suite of software. Locate3D tracks radiopaque markers in x-ray trials by locating the weighted center of circular regions on the images. The circles will be digitized in both the unloaded (resting) and loaded dynamic conditions to relate dynamic positions to the resting grid. Each circle will be tracked throughout the simulated stance phase to calculate the 3D position of each circle in the socket reference frame during dynamic movement. Point clouds will then be calculated in a common frame. Vector fields (ie, movement of the circles) will be computed between the loaded and the resting trial. The distance between each circle and its 8 closest neighbors will be calculated and measured from the resting to the loaded conditions during dynamic trials. From these measurements, the circle clusters that have the largest changes in distance will be determined. The displacement field on the limb surface will be calculated by correlating the time series of images during the dynamic movements. From the correlated skin displacement field, the Green-Lagrange strain and Euler-Almansi strain will be calculated. The areas of the highest strain from these trials will provide a strong estimate of the most appropriate placement of markers on the skin and liner for the human trials.

Subsequent Cadaver Experiments

The results from the initial cadaver experiment will help inform the placement of markers on the liner and skin for subsequent cadaver experiments. Figure 2 illustrates example marker shapes (Figure 2A) and the setup on a cadaver limb (Figure 2B). To track the pose of the socket, brass beads (2 mm diameter) will be secured to the socket. The initial marker shapes on the skin will be lines (10×3 mm) of radiopaque paint that will be placed in a circular pattern (6 cm in diameter—black lines in Figure 2A). Lines organized in the shape of a circle were chosen because the end points of each line in each marker cluster will be able to be independently tracked. However, there is a possibility that there may be a substantial overlap between markers on the surface of the skin, particularly on opposite sides, which would limit their ability to be tracked throughout the movement trials. Therefore, additional shapes (eg, triangles and stars) will also be tested during initial cadaver experiments to determine which marker types are easiest to track throughout the movement trials. Overall, these sizes and shapes were chosen to provide a large surface area on the skin while also permitting visualization of the tibial bone edges. For the inner surface of the liner, radiopaque paint consisting of double lines (10×3 mm) in the shape of a square will be used (Figure 2A). The number of markers, marker shape, placement, and size will be evaluated after each testing session to determine the optimal placement to avoid any overlapping or occlusion of the bone edges. If the markers overlap or interfere with DSX, the sizes will be reduced, the placement of the markers will be changed, or different shapes will be used. An initial, sample cadaver marker set was tested in the DSX system under static conditions to determine if the DSX software had the ability to distinguish markers placed on the socket, skin, and liner (Figure 3). Brass beads were embedded in the socket and radiopaque markers were placed on the skin and liner (similar to that presented in Figure 2). The anteroposterior and oblique x-ray views were fused with the CT imaging into a 3D entity with coregistration of the socket markers, liner markers, skin markers, and bone geometry. It was confirmed that the DSX software could distinguish markers on all surfaces. Subsequent cadaver testing will be performed under dynamic conditions while the skin, liner, and socket markers are tracked in conjunction with bone tracking throughout the simulated stance phase.

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Figure 2. Example skin marker shape and setup for the cadaver trials. (A) Circles (lines: 10 mm in length, 3 mm wide) and squares (lines: 10 mm in length, 3 mm wide) will be placed on the skin and liner, respectively. (B) Example marker placement on the skin on a scanned, translucent residual limb in the anterior-lateral view.

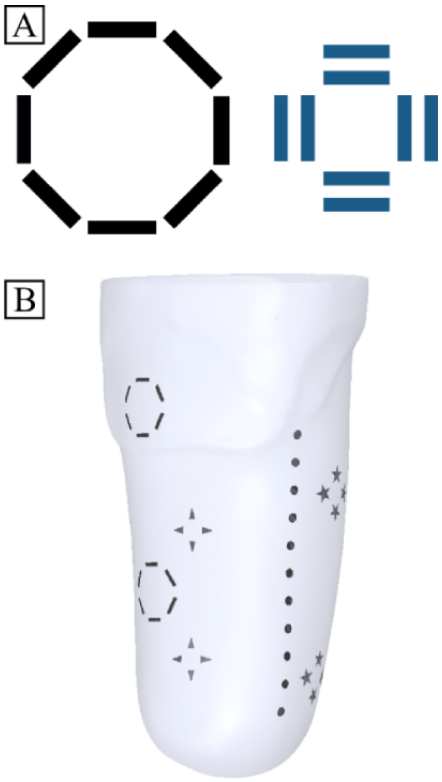

Figure 3. Static testing of a sample cadaver marker set in the dynamic stereo x-ray system. (A) and (B) X-ray images of the residual tibia, socket, and skin markers from the inline and offset x-ray views. Note the cluster of skin (lines in the shape of a circle), liner (triangles), and socket (beads) markers and the bone edges. (C) The x-ray and computed tomography images are fused to create a 3D model with coregistration of the socket and skin markers and bone geometry.

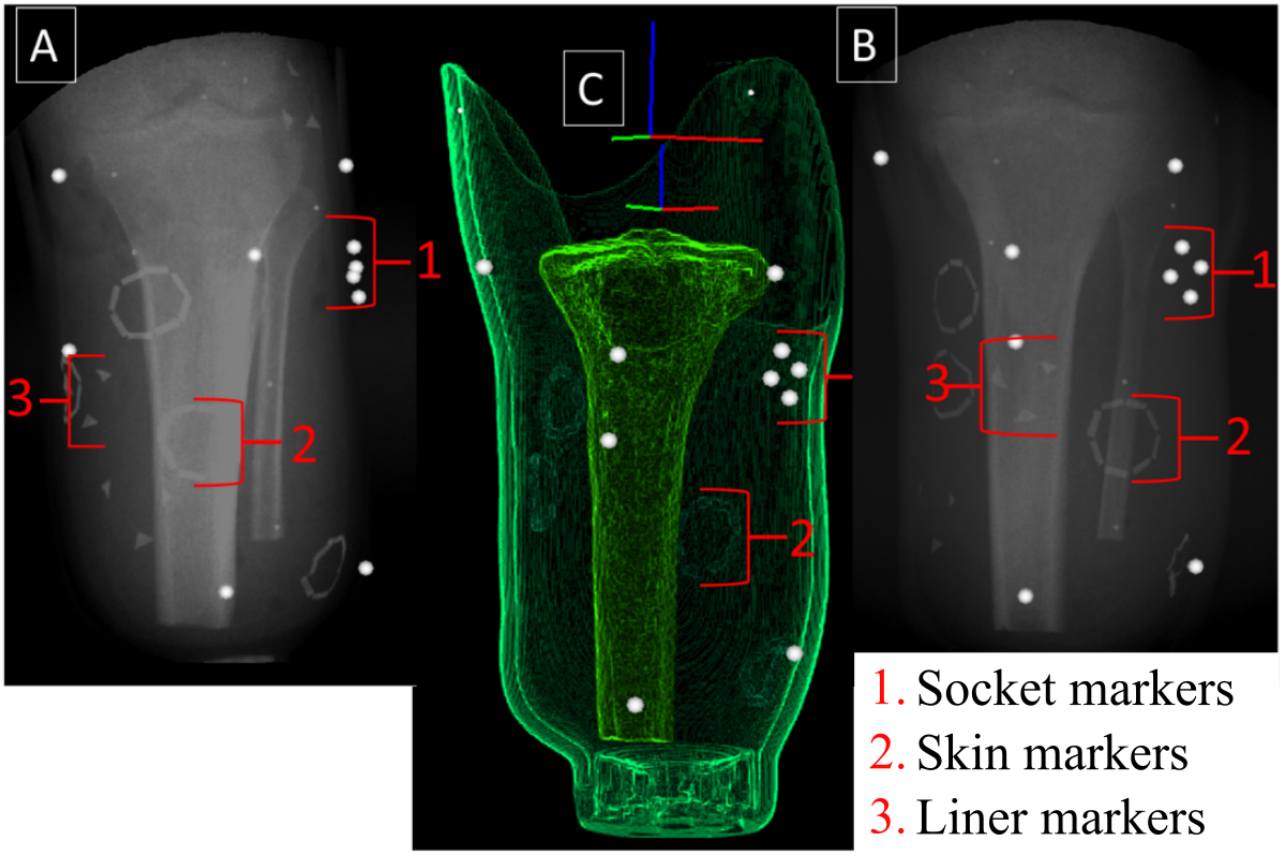

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Optimization of the Marker Set

An iterative, heuristic approach will be used with the goal of accurately tracking all end points of each line for the skin and liner marker sets without (or minimal) occlusion while simultaneously tracking the underlying tibial movement. Notably, if there is too much overlap of the lines and tracking is not possible with the lines, additional shapes will be evaluated, and the centroid of each shape will be tracked. Cadaver trials will be sequential, and the marker set will be evaluated through tracking of each marker and performing preliminary deformation analysis after each cadaver trial. Once an acceptable marker protocol has been achieved heuristically, it will be tested on subsequent cadavers to ensure that it is robust for differing anatomies and residual limb lengths. Shorter residual limbs could potentially limit the number of markers that could be applied to the skin. As such, a minimum length may be required for skin and liner marker tracking, which would be then reflected in the inclusion and exclusion criteria.

Deformation Analysis

The markers on the cadaver skin and the inner surface of the liner will be tracked during the simulated stance phase, and their trajectories in both the socket and tibia coordinate systems will define the motion of the skin relative to the socket and tibia, respectively. Their positions in the socket and tibia coordinate systems during the static trial will serve as their baseline positions. Visual3D (C-Motion, Inc) contains the tools to define the socket and tibia coordinate systems and track the motion of the skin and liner markers within these reference frames. Two metrics will be used to quantify skin and liner deformation. The first, shear, is defined as the change in angle between the lines painted on the skin and liner from the baseline position. The end points of the lines forming the circles and squares will be digitized, and the 3D trajectories will be used to reconstruct the 3D shape of the line at each time frame. The angles between the lines will be measured in the static pose to quantify the baseline skin shear. The change in angles will be measured during the simulated stance phase. Shear will be measured as the change in angle relative to the angle in the static position. The second, compression, will be quantified by calculating the change in distance between the lines and a neutral position. As with shear, baseline distances will be calculated from the static trial. From these values, 3D strain maps of the highest areas of deformation will be developed for both the liner and the skin.

Validation of DSX Strain Measurements

In conjunction with the cadaver experiments, to validate the accuracy of proposed methods to measure skin deformation, a customized, mechanical testing setup (Acumen 3AT axial-torsion system, MTS Systems Corp), which can directly interface with the DSX system, will be used. This system permits mechanical testing of soft tissue to be simultaneously performed during DSX data captures (Figure 4). This setup will be used to apply displacements to cadaveric lower limb tissue (mimicking tissue deformation in the socket) to validate the measurements from the proposed DSX analysis. To perform this validation test, 5 segments of cadaveric skin and subdermal tissue will be dissected to be mechanically tested in conjunction with DSX imaging. Each tissue sample will be affixed in tension between the opposing rings of a radiolucent plastic fixture with the skin held taut between the rings using radiolucent hardware. To validate the deformation analysis, radiopaque markers used in the cadaver experiments will be painted on the tissue. A CT scan, as previously described, of each tissue sample with applied markers will be obtained before testing to model the tissue specimen and locate the markers in a 3D space. The DSX apparatus will be angled at a maximum of 30° to distinguish the markers on the horizontal surface to avoid occlusion by the metal structures of the mechanical testing system. The mechanical testing compression rings will allow translation while the center of the fixture below the sample will be open to allow the tissue to freely deform with the applied force. Both the plastic circular fixture attachment and compressive bending fixture will be fabricated from polylactic acid thermoplastic, which is radiolucent. The Acumen 3AT axial-torsion system will be used for mechanical testing with a maximum axial testing capacity of 3 kN. To remove the effects of tissue freezing, the samples will be preconditioned at 0.1 mm/s with an axial displacement loading between 0.1 and 0.5 cm, for 50 cycles, based on the results of a previous study [32]. This displacement (0.5 cm) corresponds to the minimum bone-socket displacement associated with patellar straps, sleeves, or suspension liners [11]. Following this, the displacements associated with vacuum (1.3 cm) and traditional suction (1.8 cm) for the bone-socket interface [11] will be tested for 10 cycles each in compression at a displacement rate of 1 mm/s [32]. The axial displacement, axial force, and time will be recorded with high-speed data acquisition while the tissue is simultaneously imaged by the DSX system. A digital input-output connection will be used to synchronize the 2 systems. The compressive force on the skin tissue is proportional to the distance from the origin of the bending load, and the skin strain and shear stress can thus be calculated for a given symmetric, circular geometry. The skin strain will be compared directly to the strain calculations derived from the position of the markers collected by the DSX system. To account for the asymmetry present in the skin, the geometries, boundary conditions, material properties, and the loading regimen will be simulated using finite element analysis (Ansys, Inc). This analysis will be compared to the mechanical testing results along the skin to determine the degree to which the asymmetry of the skin affects the strain measurements.

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Figure 4. Validation apparatus setup. (A) The mechanical testing system interfaces with the dynamic stereo x-ray system. (B) Full view of the testing setup showing testing inclination. (C) Single static biplanar x-ray images of the skin deflected during compressive testing.

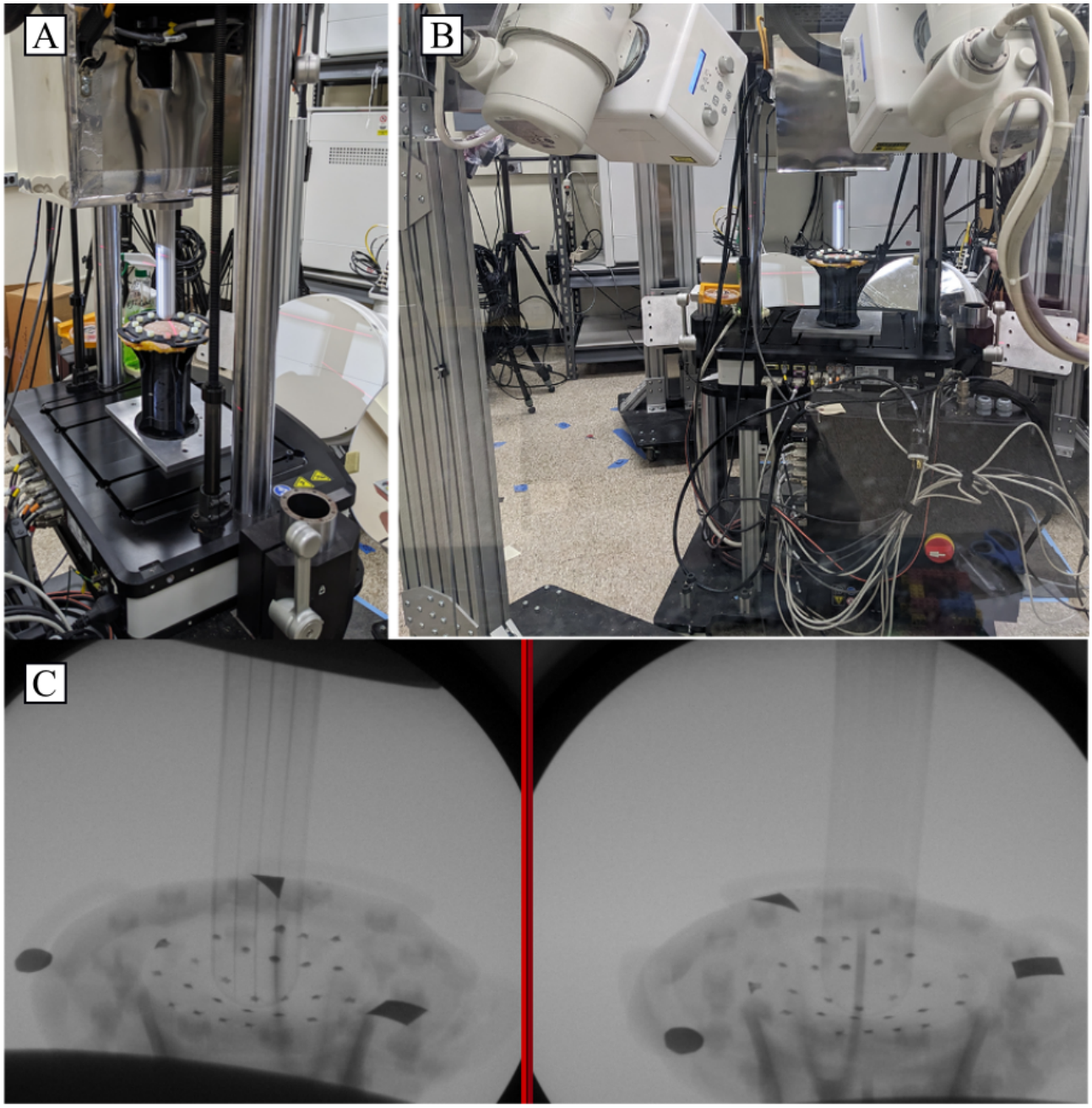

Clinical Experiment

Upon completion of the cadaver trials, a robust marker set will have been developed to evaluate skin strain and residual tibial movement for human participants as part of the clinical experiments. The residual tibial motion will be compared relative to the prosthetic socket for individuals with transtibial limb loss while separately using 2 suspension methods: EV suspension and traditional suction (EV system not activated). Participants will be assessed while walking at a self-selected speed on a treadmill, at a speed 10% faster, and during a step-down task. These activities were chosen for three distinct reasons: (1) their relevance to normal activities [33], (2) the fact that the forces exerted on the lower limb during stepping and walking can displace the prosthetic socket relative to the residual limb, and (3) these movements are suitable for recording by the DSX system. These 2 common suspension conditions (EV and traditional suction) were chosen because of their clinical relevance and expected measurable differences between these conditions.

Recruitment and Enrollment

The study sample will consist of 21 individuals with unilateral transtibial limb loss recruited from Veterans Affairs New York Harbor Healthcare System. The inclusion and exclusion criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Veteran, service member, or civilian with unilateral transtibial limb loss of any etiology
- Aged ≥18 years
- ≥6 months after limb loss
- Current prosthesis users for ≥6 hours per day

Exclusion criteria

- Inability to tolerate socket suspension
- Length of the residual limb prohibits socket fitting, marker placement, or dynamic stereo x-ray data capture
- Mental impairment that impedes study compliance
- Cognitive deficits or mental health problems that would limit the ability to participate fully in the study protocol
- Skin conditions and those with severe contractures that prevent prior prosthetic wear
- Neuropathy, uncontrolled diabetes, receiving dialysis, insensate feet, severe phantom pain, a history of severe skin ulcers, or any other significant comorbidity that would interfere with the study
- Severe circulatory problems including peripheral vascular disease and pitting edema
- Women who are pregnant or who plan to become pregnant during participation in the study

Ethical Considerations

This study was approved by the Veterans Affairs New York Harbor Healthcare System institutional review board (protocol ID 1655582) and the Rutgers University institutional review board (protocol ID Pro2022001576). All participants will provide informed consent before participating in any study activity. No research data will be acquired until the informed consent form has been signed. The principal investigator or study staff will explain the protocol, and participants will be given adequate time to review and comprehend all information before agreeing to participate in the study. After the informed consent form is signed, the study prosthetist will then screen each participant to confirm all inclusion and exclusion criteria and will inspect the residual limb to ensure that there are no issues that could prevent socket fitting. The appropriate residual limb measurements will be taken, and the residual limb will be cast to prepare for socket fabrication. Each participant's involvement will last approximately 8 weeks, including 4 weeks for socket fabrication and fitting, a 4-week acclimation period, and a data collection visit for CT scans and DSX testing on both socket suspension conditions. Study participants will be compensated US $50 for each of the socket fitting visits (up to 4 maximum) and US $100 for the 1-day data collection and testing at Rutgers. Compensation will be given in the form of a direct deposit voucher, processed through the Veterans Affairs New York Harbor Healthcare System fiscal department.

To protect the privacy and confidentiality of the human participants, each participant will be given a unique identification number that will be used in all study-related paperwork. The specific code system will not contain any personally identifiable information. All information collected throughout the study will be methodically recorded, handled, and stored to allow for accurate reporting, interpretation, and verification. Veterans Affairs (VA) complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all applicable laws that protect the privacy of research participants. The principal investigator and study staff will ensure that research records are stored in a manner that protects the confidentiality of human participant information. All electronic data collected will be deidentified and will not contain any Health Insurance Portability and Accountability Act identifiers, and the physical study forms (ie, signed consent forms and data collection forms) will be stored in secured and locked filing cabinets at the on-site office of the principal investigator. Computer files will be secured through password protection. Throughout the study, deidentified data (video data and electronic data) will be shared using VA information security office–approved secured VA computer systems with password protection and firewall. The study materials will be stored in accordance with the VA record control schedule.

Prosthetic Suspensions

Individuals with transtibial limb loss will be provided with a prosthesis capable of being suspended via both EV and traditional suction, with the prosthetic ankle-foot devices they currently use. Participants will be tested under 2 conditions: with the EV suspension active and with the EV inactive (traditional suction suspension). The order of the conditions will be counterbalanced.

Socket Fitting and Prosthetic Alignment

Before fitting the prosthetic socket, the study prosthetist will capture measurements of the residual limb (eg, length, circumference, and percentage of the sound limb). The study prosthetist will also document any areas of potential concern on the residual limb (eg, excessive redness, scar tissue, redundant tissue, heterotopic ossification, sensitivities, or evidence of previous wounds). A total of 2 to 3 preliminary "check" sockets will then be fabricated to ensure proper fit before the fabrication of the definitive socket. Each socket will

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be fitted with a Harmony vacuum pump (Ottobock Inc). Continued fittings will occur, as needed, to get to a comfortable, consistent daily volumetric fit throughout several consecutive days. Each participant will use their own ankle-foot device. Once a consistent, comfortable fit is achieved, fabrication of a definitive, laminated study socket will occur. Participants will use the study socket for a minimum period of 4 weeks before DSX testing occurs. Participants will be asked to use each suspension method equally during the 4-week acclimation period.

Subjective Surveys

Following the 4-week acclimation period, participants will complete 3 surveys for each suspension method. Participants will complete the Prosthesis Evaluation Questionnaire (PEQ), which is a self-reported visual analog-style survey for individuals with lower limb loss [34]. The PEQ has 9 independent domains as well as separate, non–domain-specific questions that can be evaluated individually. For this investigation, the domains for utility, appearance, sounds, residual limb health, and ambulation will be used. The PEQ questions on satisfaction and pain will also be assessed. In addition, participants will complete the PEQ Addendum, which asks 2 open-ended questions regarding any falls and stumbles that the participant may have experienced over the previous 4 weeks [35]. To specifically assess socket comfort, participants will complete the socket comfort score scale, which is a numerical scale of socket comfort that has shown good repeatability and sensitivity to change [36].

DSX Experimental Design

Following the 4-week acclimation period, the participants will be evaluated at the Rutgers New Jersey Medical School DSX facility. To evaluate the 6 DOF kinematics of the residual limb within the socket, participants will separately walk on a treadmill at a self-selected speed, at a speed 10% faster, and during a step-down task from an 18 cm–high platform. The DSX system will be oriented such that all tasks can be recorded with the same configuration. These movement tasks will be completed under 2 conditions: with the EV suspension active and with the EV system inactive (traditional suction). For testing with the traditional suction suspension (EV inactive), the vacuum connector will be replaced with a PushValve (Ottobock, Inc) [11]. A randomized block, crossover design will be used to evaluate the residual limb-socket fit. A group of 11 participants (group 1) and a group of 10 participants (group 2) will be formed. Participants in group 1 will first be tested in the DSX system with the EV on, and then, they will repeat all procedures with the EV inactive. Participants in group 2 will first be tested in the DSX system with the EV inactive, and then, they will repeat the tasks with the EV active. After each suspension method is applied, participants will be instructed to perform normal daily activities for 2 hours to allow for acclimation and for transient changes (eg, volume loss) to manifest. A period of 2 hours was chosen so that both conditions can be tested on the same day while still capturing 90% of the volume loss during socket use [1]. Up to 4 trials of DSX will be conducted for each task for each socket condition, giving a maximum of 24 trials per participant. For each task, DSX data will be collected and analyzed to determine the underlying bone movement and skin strain with respect to the socket. Separate CT scans of the residual limb and socket will also be captured for each participant to generate participant-specific socket and bone models of the residual limb for tracking kinematics.

DSX technology has a limited field of view (about the size of a basketball). Careful placement of the x-ray sources will permit a view of the knee, tibia, and socket. Because participants will be walking on a treadmill, the DSX setup will likely be able to capture the entire gait cycle; but at a minimum, stance phase will be collected. The 3D kinematics of the thorax, pelvis, lower limbs, and prosthesis will be recorded synchronously using a 6-camera motion capture system (Qualisys Inc). Marker-based motion capture will be used to record the overall position and orientation of the body segments that are out of the viewing volume of the DSX during the movement to establish the participants' overall movement patterns.

Clinical Study CT Scans

After the radiopaque markers have been applied to the residual limb and liner, the socket with embedded brass beads will be donned by the participant and a single CT scan of the residual knee joint and tibia will be acquired while participants lie in the supine position with their socket and liner on and with the knee extended. CT scans provide gray-scale volumes for use with DSX and high-resolution 3D surface models required for computing all outcome variables. CT volume images will be acquired at a resolution of 512×512×0.625 mm^3 (120 kVp; SMART mA). Surface3D (C-Motion Inc) will be used to segment 3D models of the socket, liner, and tibia from the CT volumes.

Quantification of the Relative Motion Between the Residual Bone and the Prosthetic Socket

Quantification of the 3D position and orientation of the residual limb has been previously described in detail [23]. In brief, the residual tibia will be tracked throughout the gait cycle, with the coordinate system defined in the CT space using a morphology-based coordinate systems adapted from previous studies [37,38]. These coordinate systems will be registered between Visual3D (C-Motion, Inc) and CT space using the coregistration transformation matrix. The position and orientation (pose) of the socket will also be tracked with 2-mm brass beads secured to the exterior of the prosthetic socket. To provide a context for the relative motion of the residual tibia and socket, 3D infrared motion capture will synchronously be recorded with the DSX data for each participant. Anatomical frames of the thorax, pelvis, and thigh will be constructed by placing retroreflective markers on anatomical locations. Visual3D will be used to establish the anatomical reference frames, estimate the position and orientation of all segments, and compute the kinematics. The reference frames for the socket will be established based on the sagittal plane of the prosthesis. The sagittal plane will be defined by the long axis of the foot. The axial direction will be defined by the pylon. The lateral direction will be perpendicular to the sagittal plane. The anterior direction will be the cross-product of the axial and lateral directions.

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To use the same reference frames for both imaging techniques, the global coordinate systems of the optical motion capture and DSX systems will be coregistered by simultaneously capturing the static position of a rigid lattice consisting of 11 radiopaque, spherical markers outfitted with retroreflective tape. The transformation matrix for the coregistration of each global coordinate space will be computed and applied to the respective kinematic data sets. The pose of the socket will be estimated using a standard 6-DOF pose estimation with a set of beads as tracking markers implanted into the socket. The socket reference frame will be established by structural landmarks on the prosthesis in the CT image.

Data Processing

Validation of DSX systems for 3D volumetric model-based tracking has been previously reported [39-41]. For each participant, the residual tibia will be segmented from the CT volume to construct a polygonal mesh of the tibia surface. Digitally reconstructed radiographs (DRRs) created from participant-specific CT scans will be matched to the DSX images in the inline and offset views to calculate the 3D pose of the tibia (Figure 5) [18,41]. DRRs will be generated by positioning the segmented CT volume within a virtual x-ray system and projecting rays through it to create a simulated x-ray image [23]. The optimal position and orientation of the bone will be defined as the pose that maximizes the similarity between the pair of DRR images and their corresponding x-ray images. To track each trial, the tibia will first be manually positioned in every fourth frame of data. Subsequently, a cubic spline will be fitted to the set of manual positions and orientations of the bone, which can be interpolated by the model-based tracking algorithm to determine a pose of the bone in every frame.

Figure 5. A 3D representation of the synchronized x-rays. The inline x-ray image is the red frame (A), whereas the offset x-ray image is the green frame (B). The 3D residual tibia (C) is reconstructed from computed tomography (CT) data. The red and green lines are the perpendiculars from the x-ray image planes to the x-ray sources. The outlines of the tibia (shown in yellow) superimposed over each x-ray image are created by casting rays from each x-ray source through the CT tibia to the x-ray planes.

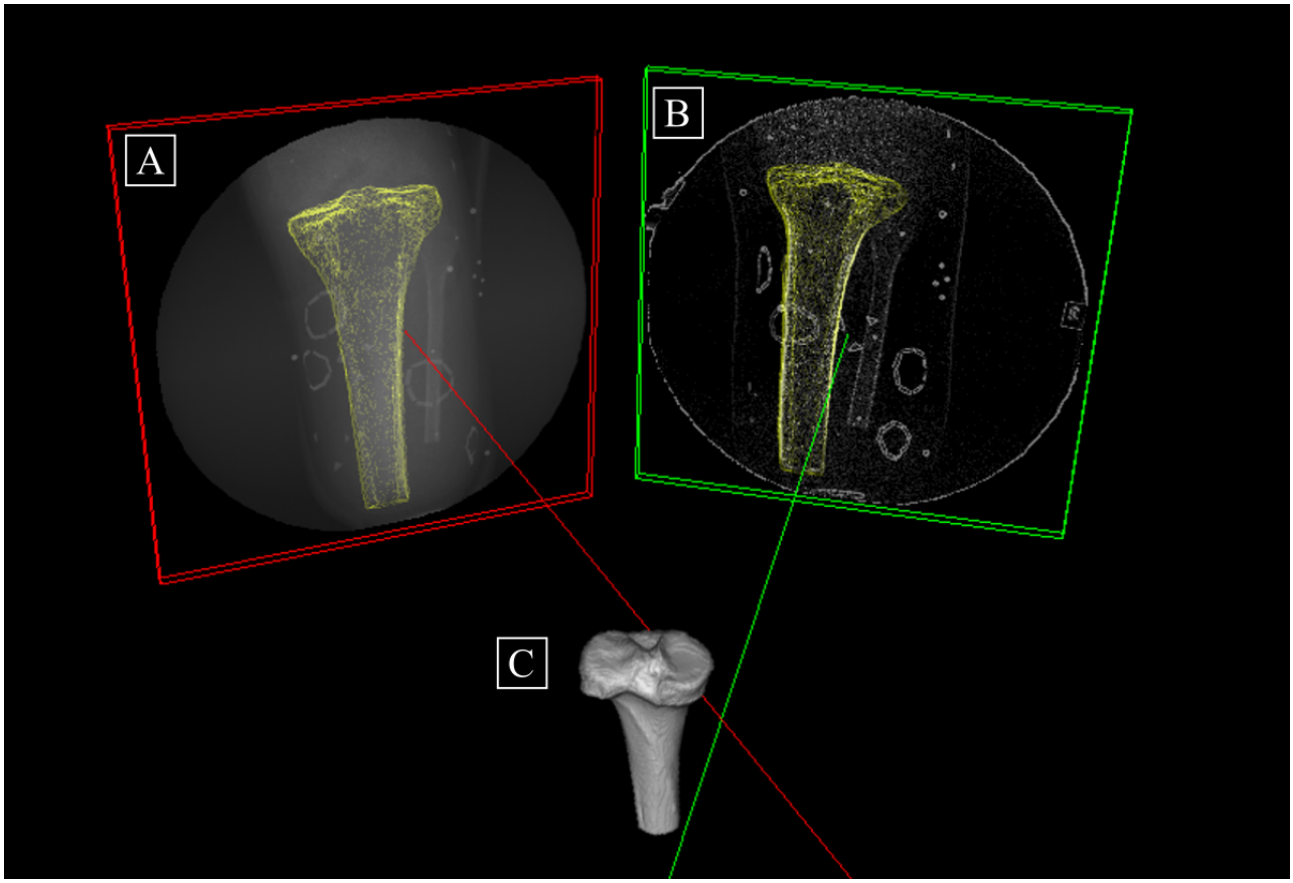

The algorithm output will be a set of 4×4 transformation matrices representing the pose of the residual tibia. The position and orientation of the socket will be calculated using beads placed on the rigid socket for each time frame. Excursions for relative tibial rotations and translations will be defined as the difference between the maximum and minimum values for each variable within the gait cycle. The differences between the residual bone movement with the EV and traditional suction will be determined in 6 DOF for each participant. Group differences for tibial rotations and translations will be compared at initial contact, toe-off, and swing phase as well as for the total excursions of the residual tibia during the gait cycle.

Quantification of Skin and Liner Deformation

Motion between the bone and the skin (skin deformation) and motion between the skin and the inner surface of the liner will be examined simultaneously with bone movement in the prosthetic socket. Motion between these interfaces can be directly associated with discomfort while wearing a prosthesis [3,30]. In addition, motion between the socket and both the skin

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and inner surface of the liner will be examined for a complete understanding of the motion between the limb and the prosthesis.

The results from the cadaver experiments will inform the final placement of markers on the liner and skin. The final number, sizes, shapes, and placement of markers will be based on the results of the cadaver experiments and any potential overlap or bone occlusion. However, the proposed shapes will make identification of the markers in the x-ray images easier and will foster the ability to examine both shear and compression. The ends of each line will be digitized manually from the 2 sets of x-ray images. Reconstruction of the 3D trajectories of the markers will be performed using the DSX software (C-Motion Inc). Visual3D will be used to estimate the deformation of the skin and liner from the relative movement of the markers in the socket reference frame.

Motion of the Skin and Interior of the Liner Relative to the Socket and Residual Tibia

The ends of the lines on the skin and liner will be tracked during the dynamic trials, and their trajectories in the socket coordinate system will define the motion of the skin and liner relative to the socket. Their positions in the socket coordinate system during the static trial will serve as the baseline positions. Visual3D contains the tools to define the socket coordinate system and track the motion of the skin markers within this reference frame. The motion of the lines will also be calculated in the coordinate system of the residual tibia. Their positions in the tibia coordinate system during the stationary trial will serve as their baseline positions. The tibia coordinate system will be defined to track the motion of the skin and liner markers within this reference frame.

Deformation of the Skin

Deformation of the skin will be evaluated in the same way as in the cadaver experiments. In brief, 2 primary metrics will be used to quantify skin deformation: shear and compression. For shear, the end points from the lines will be digitized and the 3D trajectories will be used to reconstruct the 3D shape of the line at each time frame. The angles between the lines will be measured in the static pose to quantify the baseline skin shear. The change in angle will be measured during each dynamic task. Shear will be measured as the change in angle relative to the angle in the static position. Compression will be calculated by the change in distance between lines as well as a neutral position. As with shear, baseline distances will be calculated from the static trial.

Data and Statistical Analysis

Overview

Descriptive statistics will be used to summarize demographic and continuous baseline variables. Median and IQR will be used to classify nonnormal or ordinal data. For the clinical experiment, a between-participant factor at 2 levels (EV on and EV off) will be used. The interaction of the suspension condition (EV on or off) will determine the efficacy of the EV system on the outcome measures.

Bone Movements

The differences between the residual bone movement with the EV and the traditional suction suspension will be determined in 6 DOF for each participant. Briefly, group differences for tibial rotations and translations as well as total excursions of the bone for each suspension condition will be compared during the gait cycle. Paired *t* tests will be performed and a between-participant factor at 2 levels (EV on and EV off) will be used. A hierarchical linear model will be used to evaluate the tibial range of motion (ie, maximum translation and rotation) as a function of tibial position and potential confounding factors (eg, gender, age, etiology, and time since limb loss). The hierarchical linear model will also be used to evaluate the tibial motion path and the effect of rate during the 3 different activities.

Skin and Liner Deformation

The characterization of 3D skin deformation will be performed by comparing the 3D position of the skin markers at rest, or unloaded position, to the 3D positions of the markers when deformed during each task to produce relative strain assessments for marked regions of the residual limb. The characterization of 3D deformation will be measured between the suspension methods. Paired *t* tests will be performed as previously described for bone movements. Linear regression models will be used to evaluate the potential confounding factors.

Power Analysis

Table 1 outlines the sample size estimate required to achieve 90% power for the key variables of interest. A previous pilot investigation for individuals with transfemoral limb loss [23] indicated an effect size of 0.77 for residual femur axial translation. Assuming an α of .05, using paired *t* tests, 21 participants are required to achieve 90% power to detect a 0.5 cm difference in axial translation. Owing to the paucity of highly accurate data on movement between the residual tibia and socket, data from Board et al [1] were used to calculate an effect size for tibia translation (1.75) for suction and EV suspension. Given an effect size of 1.75 and an α of .05 for a paired *t* test, a sample size of 21 will be powered at >99% to detect differences between EV on and off. For skin strain, Gale et al [30] found a maximum shear strain of approximately 0.08. Assuming a shear strain of 0.08 with a moderate effect size of 0.75 (α=.05), a sample size of 21 will be required to achieve 90% power to detect differences between EV on and off.

Table 1. Power analysis.

Measure	Values, mean (SD)	Sample size for achieving 90% power, n
Femur distal translation (cm)	2.0 (0.6)	21
Tibial translation (cm)	4.0 (0.4)	6
Skin shear strain	0.08 (0.02)	21

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Results

This study was funded in October 2021. Cadaver testing began in January 2023. Enrollment began in February 2024. Clinical data collection is expected to be completed in December 2025, and the study is expected to be completed in April 2026. Data analysis of the full data set will begin after final data collection. Initial dissemination of results is expected in November 2026, with subsequent publication of secondary analyses in 2027.

Discussion

Expected Outcomes and Anticipated Principal Findings

It is expected that the outcomes of this investigation will significantly contribute to the understanding of the complex mechanics of the residual limb-tissue-socket interfaces during dynamic activities for individuals with lower limb loss. It is also expected that by using DSX in combination with novel mathematical algorithms, relative movement between the residual limb and socket and skin deformation can be accurately measured during dynamic motions for individuals with lower limb loss. Ultimately, this foundational information can be critical for developing a database of biomechanical socket parameters deemed important for socket fit, limb health, and comfort. By using the techniques developed in this investigation to perform future comparative effectiveness research of current prosthetic socket technology, better information about the benefits, risks, and costs of different socket options can be generated to provide health care decision makers (eg, patients, clinicians, and policy makers) with highly accurate, evidence-based information. Furthermore, the methodology detailed in this study should speed up the processing time, which, to date, has been burdensome for researchers. This will allow for faster dissemination of information and greater throughput of data to inform clinical guidelines for prosthetic suspension systems. Finally, this investigation can provide vital foundational information that can be used by leading manufacturers in prosthetic design to create enhanced socket technology that has the potential to reduce long-term secondary physical comorbidities and degenerative changes [42].

As the number of individuals with limb loss continues to grow [43], substantial resources will be required for rehabilitation and prosthetic services for this population. Effective outcomes-based clinical practice will be necessary to reduce long-term disabilities associated with prosthetic use. As such, it is the objective of this investigation to examine the dynamic in vivo kinematics between the residual limb and prosthetic socket in 6 DOF of motion, as well as to quantify residual tissue and liner deformation for individuals with transtibial limb loss.

Dissemination Plan

For large-scale dissemination in the Department of Veterans Affairs and Department of Defense, results will be presented through webinars offered by the Extremity Trauma and Amputation Center of Excellence, which are available across the entire Department of Veterans Affairs and Department of Defense health care networks. These webinars are offered to researchers and health care professionals who provide care for individuals with limb loss. For stakeholders in the civilian health care systems, the outcomes and important techniques developed in this study will be published in highly rated peer-reviewed scientific journals (eg, *Gait & Posture, Clinical Biomechanics, Journal of Biomechanics, Frontiers,* and *Orthotics and Prosthetics International*). The results will also be presented at professional conferences that are specific to clinical limb loss care teams (eg, the American Academy of Orthotists and Prosthetists, American Society of Biomechanics, and Military Health System Research Symposium). The findings and methods of this study will also be directly distributed to industry partners. Because most prosthetic technologies used by veterans and service members with limb loss are developed by industrial entities, sharing new evidence-based information with industry leaders will support the development of future products to better meet the needs of individuals with lower limb loss.

Limitations

The heterogeneity of the population, including varied ages, etiology of limb loss, prosthesis experience, and time since limb loss, may limit the generalizability of the outcomes to a more diverse population. However, the statistical analysis models will adjust for these specific confounding factors. Although participants will use the same type of prosthetic socket, the ankle-foot devices will not be prescribed, which could introduce additional variability. The tibia and skin markers will likely be manually positioned at every fourth to tenth time frame, which may cause intratracker errors that could be improved with automated algorithms. Finally, the limited field of view for DSX may restrict collecting data for the entire gait cycle and will be unable to record the overall position and orientation of the lower limbs and pelvis that are out of view.

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the design of this study and will not have any role during its execution, analyses, and interpretation of the data or in the decision to submit results.

Data Availability

All data generated or analyzed during this study are included in this published paper. The final results will be available via a publicly available data repository.

Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the authors, the Department of Veterans Affairs, or any component agency.

Authors' Contributions

JTM, JPL, and SED participated in the conceptualization of the study. JTM, JMC, DVH, DNP, CW, JPL, and SED participated in methodology development. JTM, JMC, DVH, DNP, and CW participated in data collection. JTM, JMC, DVH, DNP, CW, JPO, MJH, JPL, and SED participated in writing, review, and editing of the manuscript. JTM, JPO, and MJH participated in project administration. JTM and JPO participated in supervision of the project and staff. JTM, DNP, JPL, and SED participated in funding acquisition. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewed summary statement from the Congressionally Directed Medical Research Programs, Orthotics and Prosthetics Outcomes Research Program.
[PDF File (Adobe PDF File), 89 KB - resprot_v13i1e57329_app1.pdf]

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Abbreviations

CT: computed tomography
DIC: digital image correlation
DOF: degrees of freedom
DRR: digitally reconstructed radiograph
DSX: dynamic stereo x-ray
EV: elevated vacuum
PEQ: Prosthesis Evaluation Questionnaire
VA: Veterans Affairs

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Protocol

Social Transfers for Exclusive Breastfeeding (STEB) Intervention in Lao People's Democratic Republic: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children in Lao People's Democratic Republic (Lao PDR) receive suboptimal nutrition because of low breastfeeding rates, undermining their developmental potential. While major public health campaigns have attempted to increase breastfeeding rates, they have been largely unsuccessful. One explanation for these unsuccessful interventions is the economic and financial constraints faced by mothers. A potential solution for alleviating these pressures is providing social transfers to support breastfeeding; defined as a cash or in-kind transfer. Capitalizing on key strategies used in previous social transfer programs, we will assess the effectiveness of social transfer intervention for increasing exclusive breastfeeding rates in Vientiane, Lao PDR.

Objective: This study aims to conduct a randomized controlled trial (RCT) designed to assess whether social transfers can increase exclusive breastfeeding rates in Vientiane Capital, Lao PDR.

Methods: A prospective, parallel cluster-RCT was conducted among 300 mothers who recently gave birth and initiated breastfeeding. Enrolling 100 participants for each intervention arm provided us with 80% power to detect an increase in exclusive breastfeeding from the anticipated 21% in the control arm to 40% in either of the 2 intervention arms. Mother-infant dyads were enrolled at approximately 1 month post partum. Follow-up visits will occur at 6 months, 1 year, 2 years, and 3 years post partum; with the ambition to extend the follow-up period. Mother-infant dyads were enrolled between August 2022 and April 2023 with follow-up until 3 years post partum (2026). A local study team comprised of 2 nurses and 2 laboratory technicians is responsible for enrollment and follow-up of participants. Participants were randomly assigned to one of three groups during the baseline, 1-month visit: (1) control group, no social transfer; (2) intervention group 1, an unconditional social transfer at 6 months post partum; and (3) intervention group 2, a social transfer at 6 months post partum conditional upon mothers exclusively breastfeeding. All groups received educational materials supporting mothers to exclusively breastfeed. The primary end point will be exclusive breastfeeding at 6 months post partum. Secondary end points will include exclusive and complementary breastfeeding duration, childhood wasting and stunting, child growth, maternal and infant stress, predictors of early breastfeeding cessation, intestinal inflammation, anemia, maternal weight loss, maternal blood pressure, maternal anxiety, and GRIT personality score. Questionnaires and physical examinations were used to collect information.

Results: As of November 2023, the study has enrolled 300 participants. Study participation is ongoing until December 2026 at minimum. Over the study lifetime, 93% have completed all visits.

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Conclusions: We see potential for a long-term program that may be implemented in other low- or lower-middle-income countries with only minor modifications. The RCT will be used as a basis for observational studies and to investigate the impact of human milk on child fecal microbiota and growth.

Trial Registration: ClinicalTrials.gov NCT05665049; https://clinicaltrials.gov/study/NCT05665049

International Registered Report Identifier (IRRID): DERR1-10.2196/54768

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KEYWORDS

breastfeeding; lactation; human milk; breastmilk; child; infant; health; growth and development; cash transfer; incentive; intervention

Introduction

Breastfeeding provides important benefits for infants and societies [1,2]. Despite its well-known and widespread benefits, breastfeeding rates remain low in many parts of the world. In Vientiane, the capital of Lao People's Democratic Republic (Lao PDR), only 21% of children aged 0-5 months were exclusively breastfed, and less than half (42.3%) were predominantly breastfed in 2017 [3]. Complying with the World Health Organization's breastfeeding recommendations can help countries meet the United Nation's sustainable development goals with respect to good health and well-being, economic growth, and reduced inequalities [4].

Even though most mothers recognize the benefits of breastfeeding, they also face a complex web of factors that make breastfeeding difficult, including formal labor commitments without sufficient parental leave or breastfeeding support, and television ads promoting infant formula [5,6]. Over the last 30 years, the Ministry of Health in Lao PDR has attempted to increase breastfeeding rates through standard public health behavior change campaigns, including a safe motherhood program and a large United Nations children's fund supported exclusive breastfeeding promotion campaign; however, these programs were largely unsuccessful [5].

One probable explanation for these unsuccessful interventions is the economic and financial constraints faced by mothers. A potential solution for alleviating these pressures is providing social transfers to support breastfeeding; defined as a cash or in-kind transfer. Evidence suggests that social transfers have helped increase breastfeeding rates in other settings. In a previous experiment, Puerto Rican mothers were provided US $25 per month after successful observation of breastfeeding (ie, conditional cash transfer), which resulted in significantly higher breastfeeding rates at 6 months postpartum compared with mothers who did not receive the cash transfer [7]. A similar model providing a social transfer with a letter encouraging mothers to spend time with their infant (ie, labeled social transfer) in a US neonatal intensive care unit increased the daily provision of breastmilk [8]. However, all evidence on social transfer programs for breastfeeding comes from high-income countries. In fact, no study has implemented a social transfer program for breastfeeding promotion in low- or middle-income countries despite a large number of successful social transfer programs targeting other health behaviors in these settings [9].

Capitalizing on key strategies used in previous social transfer programs, we will assess the effectiveness of social transfer programs for increasing breastfeeding rates in Vientiane, Lao PDR. A previous qualitative, community-engaged project in Vientiane focused on identifying breastfeeding norms and social transfers that would support breastfeeding mothers (unpublished data). Using the results from this study, we designed a culturally grounded social transfer program that is responsive to the identified needs of new mothers.

The overall objectives of this project are to assess (1) the effect of social transfers on exclusive and complementary breastfeeding duration and (2) the long-term impacts of breastfeeding on child development.

Methods

Overview

The Social Transfers for Exclusive Breastfeeding (STEB) is a prospective, parallel cluster-randomized trial in the Vientiane Capital, of Lao PDR. Mother-infant dyads will be enrolled at approximately 1 month post partum and followed for 3 years; with the ambition to extend the follow-up period. The study period runs from August 2022 to December 2026.

Participants and Recruitment

Our study is nested within an ongoing birth cohort (the Vientiane Multigenerational Birth Cohort [VITERBI]). Women were recruited for VITERBI if they (1) lived in one of the following districts of Vientiane: Chanthabuly, Sikhottabong, Sangthong, or Mayparkngum; (2) had an expected due date/or gave birth between July 1, 2022, and June 30, 2023; (3) did not plan to permanently move outside the study area; (4) did not have a medical, intellectual, or psychological disability; and (5) agreed to participate and sign an informed consent; if younger than 18 years, a legal representative had to agree to sign the informed consent.

The target sample size for the STEB randomized control trial was 300 mothers and their children. All pregnant women enrolled in VITERBI were eligible to participate in our study if they gave birth within the last 4 weeks, were exclusively breastfeeding at the time of recruitment, had no illnesses that contraindicate breastfeeding, and had a healthy singleton infant of 37 weeks or more gestation with a birth weight of at least 2500 g.

A local study team comprised of 2 nurses and 2 laboratory technicians was responsible for enrollment and follow-up of participants. Using pregnancy records from VITERBI, a list of potential participants was created. In order to identify women

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who recently gave birth (≤1 month), the following data were used: (1) approximate due date or (2) weeks gestation when an approximate due date was not provided. When both variables were missing, the average week of gestation was set at 40 weeks and added to the interview date to provide the latest possible birth date. All potential participants were screened on a telephone call to ensure they met the eligibility criteria. If the participant met the inclusion criteria and agreed to participate in the study, a baseline visit was scheduled.

Sample Size Calculation and Power

Enrolling 100 participants for each intervention arm provided us with 80% power to detect an increase in exclusive breastfeeding from the anticipated 21% in the control arm to 40% in either of the 2 intervention arms.

Study Logistics

During the baseline visit, if informed consent was given, a random number was generated within the Open Data Kit (ODK) platform that assigned the mother to a control or intervention group. If they were randomly assigned to an intervention group, mothers were allowed to choose from the following social transfers: (1) money (US $75); (2) developmental toys, clothes, and diapers for the child; or (3), a combination of money and developmental toys, clothes, and diapers for the child (Figure 1). We created a shopping catalog with different toys and clothes for them to choose from. At the end of the visit, the study team encouraged intervention group 1 to meet their breastfeeding goals and told them that the social transfer would be provided at 6 months post partum to show our support for their breastfeeding efforts. Mothers randomly selected for the third intervention arm were told that they would only receive their social transfer if they exclusively breastfed and nurses could observe breastmilk expression at the 6-month visit. All intervention and control groups received educational material about the benefits and recommendations of exclusive breastfeeding.

During a follow-up visit when the child is 6 months of age, nurses will collect an end-line survey from mothers, collect infant fecal samples, and observe breastmilk expression.

Figure 1. Screenshot from shopping catalog for Social Transfers for Exclusive Breastfeeding (STEB) participants.

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Data Collection Instruments

Overview

STEB has a total of five questionnaires: (1) a screening questionnaire to assess eligibility; (2) baseline enrollment conducted at approximately 1 month post partum; (3) an endline questionnaire at 6 months post partum; (4) a follow-up visit at 1 year post partum; and (5) a follow-up visit at 2 years post partum. All source documents were created in English and translated into Lao. We briefly describe each questionnaire below.

Screening Questionnaire

A screening questionnaire was conducted on the telephone in order to assess the inclusion and exclusion criteria. A maximum of 10 questions were asked. If an answer to one of the questions rendered them ineligible for the study, no further questions were asked. Questions included date of birth and expected birth date in order to determine prematurity of the infant, birth parity, birthweight, current breastfeeding status, breastfeeding exclusivity, long-term medical problems of the infant, and if the mother experiences galactosemia, human immunodeficiency virus, human T-cell lymphotropic virus type 1 or 2, illicit drug use (ie, cocaine), Ebola, artificial breast implants, or infectious tuberculosis.

Baseline—1 Month Postpartum

The baseline questionnaire is conducted at approximately 1 month post partum and includes employment questions, the short Grit scale [10], family and gender roles, child health and vitamin, mineral or other medicine intakes, breastfeeding and infant feeding, Breastfeeding Self-Efficacy Scale–short form [11], and maternal diet. The Demographic and Health Surveys household characteristics questionnaire. Hemoglobin levels of the mother and infant were taken using the HemoCue Hb 301. Biospecimen samples included infant feces, human milk, and a saliva sample from the mother and infant. Anthropometric measurements of the child included skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, mid-upper arm circumference (MUAC), and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

Endline—6 Months Postpartum

The endline questionnaire is conducted at approximately 6 months post partum and includes employment questions; child health; vitamin, mineral, or other medicine intake; breastfeeding and infant feeding; maternal diet; participation in cultural postpartum activities (eg, hotbeds and mother roasting); perceived stress scale [12]; Postpartum Specific Anxiety Scale [13]; and caregiver-reported early development instruments [14]. A variety of additional health measurements were assessed. Hemoglobin levels of the mother and infant were taken using the HemoCue Hb 301. Biospecimen samples include infant feces, human milk, and a saliva sample from the mother and infant. Anthropometric measurements of the child included skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, MUAC, and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

1- and 2-Year Follow-Up

Visits will occur at 1, 2, and 3 years post partum (SD 1 month). The questionnaire includes child health and vitamin, mineral or other medicine intake; breastfeeding and infant feeding; maternal diet; alcohol consumption; Postpartum Specific Anxiety Scale [13]; Edinburgh Postnatal Depression Scale [15]; and the brief infant sleep questionnaire–short form [16]. At 1 year post partum, child development will be assessed using caregiver-reported early development instruments [14]. At 2 and 3 years post partum, child development will be assessed using the Global Scale for Early Development [17]. Hemoglobin levels of the mother and infant will be taken using the HemoCue Hb 301. Biospecimen samples include infant feces and human milk. Anthropometric measurements of the child included foot length, skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, MUAC, and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

Retention of Participants

In order to reduce participant dropout, we collect a variety of contact information. Participants provide their first and family name, address, phone number, email address, village leader name, temple or religious organization, and the contact information of a family member or close friend. In addition, we provide a small incentive. Immediately after the physical examination, all participants receive the test results for both the mother and child and can track their progress over time at each visit. Test results include blood pressure, hemoglobin levels, and all anthropometric values. Results are explained in person and written on an information pamphlet. All participants who complete the baseline questionnaire receive a small gift that equates to approximately US $1.

Outcomes

The primary end point will be exclusive breastfeeding at 6 months postpartum. Secondary end points will include exclusive and complementary breastfeeding duration, childhood wasting and stunting, child growth (height and weight), maternal and infant stress, predictors of early breastfeeding cessation, intestinal inflammation, anemia, maternal weight loss, maternal blood pressure, maternal anxiety, and GRIT personality score.

Data Management

The ODK is used for all questionnaires and data management. All study staff have access to an Android tablet with the ODK Collect app. Data collection is completed offline on password-protected devices. Data connectivity is only used to send the final questionnaire data.

Project data will only be accessible to authorized personnel who require the data to fulfill their duties within the scope of the research project. On the case report forms and other project-specific documents, participants are only identified by a unique participant number. The unique participant number will be taken directly from VITERBI, and is a combination of

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the household number, district, village, and individual within the household. Health-related data will be stored for 15 years, following institutional storage and safety policies. Only samples will be kept for an unidentified amount of time if the separate consent for reuse of health data has been signed. Data storage is on a locally secured server using the ODK Aggregate server and secured via a secure sockets layer.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel. The biological specimens will be stored with their code at Lao TPHI and Swiss TPH.

Ethical Considerations

Ethical approval for the study was obtained from the Ethics Commission of Northwestern and Central Switzerland (EKNZ, 2020-00037) and from the National Ethic Committee for Health Research (044/NECHR; June 30, 2021). This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Swiss Human Research Act, and the Swiss Human Research Ordinance [1], as well as other locally relevant regulations. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Eligible participants will be visited initially by study staff. The purpose of the study and its procedures will be explained to participants and written informed consent will be obtained. Pregnant women will be giving consent for themselves and their newborns. For minors (aged <18 years), both the pregnant woman and her parents will provide consent. For participants who are illiterate, there will be an additional witness who is not part of the study team. Participation is voluntary and patients have the right to withdraw from the study at any given point in time with no further obligations. If the participant withdraws at any time, all data will be deleted and biospecimen samples destroyed. Confidentiality of information will be assured to the participants. All participants younger than 18 years are considered vulnerable populations according to the Lao PDR legislation. If the respondent is underage and agrees to participate, he or she needs the authorization of a parent or legal guardian, who cosigns the study informed consent.

Results

As of November 2023, the study has enrolled 300 participants. Study participation is ongoing until December 2027 at minimum. Over the study lifetime, 93% have completed all visits. Primary results from the 6-month visit are expected in early 2024.

Discussion

Conditional cash transfer programs have been used in a wide range of settings to reduce poverty, with proven benefits for short- and long-term health [18]. STEB is to our knowledge the first longitudinal and randomized social transfer program evaluation for breastfeeding in a low- or middle-income country. We will follow participants for a minimum of 3 years post partum—providing an excellent platform to investigate the short- and long-term benefits of a breastfeeding social transfer program.

During the first year of the program, we encountered a variety of barriers. To start, enrolling new mothers at approximately 1 month post partum was difficult due to the high rates of infant formula use. We strategically enrolled at 1 month post partum to reduce coercion among mothers who did not want to breastfeed. However, a large majority of mothers provided infant formula before 1 month post partum. Enrolling mothers earlier in the postpartum period who want to exclusively breastfeed may reduce the early introduction of infant formula. Second, distances between the 4 study districts in Vientiane, Lao PDR are large. Transportation of staff to the rural districts is a major challenge because of the time spent traveling and the high burden of transportation costs. For example, during the rainy season, many streets become impassable—reducing the capabilities of the study staff to reach participants. Collection of infant fecal samples at 1-month was also difficult because of the irregularity of bowel movements at this age.

Despite the substantial size of the social transfers made, we believe that interventions that include financial support for breastfeeding can be highly cost-effective in this setting. In 7 Southeast Asian countries alone, the short- and long-term benefits of breastfeeding are estimated at US $1.9 billion a year [1]. We believe that social transfer programs focused on breastfeeding have the potential to be more effective in low- or middle-income countries, where monetary compensation may reduce additional barriers not present in high-income countries.

STEB has some limitations worth noting. The small sample size will prohibit more nuanced data analysis. Enrollment does not occur immediately after birth; instead, all participants are enrolled at 1-month post partum. Many mothers face significant barriers to exclusive breastfeeding during the first month postpartum; therefore, the study population of STEB may be slightly different. Recall of the exact timing of complementary foods provided is likely biased; yet, previous research has shown that recall bias for breastfeeding is minimal.

STEB was designed to provide a unique platform to investigate the short- and long-term impacts of exclusive and complementary breastfeeding on child health and development. Further, the longitudinal sampling of human milk and infant feces provides a unique opportunity to study human milk as a biological system and how this impacts the gut microbiome. If proven effective, we see potential for a long-term program that may be implemented in other low- or lower-middle-income countries with only minor modifications.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

SK and GF made substantial contributions to the conception and design of the study. S Sonephet, LZ, PV, S Sayasone, PO, and LS contributed to the acquisition of data and revised the manuscript. JTW made a substantial contribution to the conception and design of the study, the acquisition of data, and drafted the manuscript. All authors approve the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 272 KB - resprot_v13i1e54768_app1.pdf]

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Abbreviations

Lao PDR: Lao People's Democratic Republic
MUAC: mid-upper arm circumference
ODK: Open Data Kit
RCT: randomized controlled trial
STEB: Social Transfers for Exclusive Breastfeeding
VITERBI: Vientiane Multigenerational Birth Cohort

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Protocol

The Effect of Prebedtime Behaviors on Sleep Duration and Quality in Children: Protocol for a Randomized Crossover Trial

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Abstract

Background: It is recommended that children should avoid eating dinner, being physically active, or using screens in the hour before bed to ensure good sleep health. However, the evidence base behind these guidelines is weak and limited to cross-sectional studies using questionnaires.

Objective: The aim of this randomized crossover trial was to use objective measures to experimentally determine whether recommendations to improve sleep by banning electronic media, physical activity, or food intake in the hour before bed, impact sleep quantity and quality in the youth.

Methods: After a baseline week to assess usual behavior, 72 children (10-14.9 years old) will be randomized to four conditions, which are (1) avoid all 3 behaviors, (2) use screens for at least 30 minutes, (3) be physically active for at least 30 minutes, and (4) eat a large meal, during the hour before bed on days 5 to 7 of weeks 2 to 5. Families can choose which days of the week they undertake the intervention, but they must be the same days for each intervention week. Guidance on how to undertake each intervention will be provided. Interventions will only be undertaken during the school term to avoid known changes in sleep during school holidays. Intervention adherence and shuteye latency (time from getting into bed until attempting sleep) will be measured by wearable and stationary PatrolEyes video cameras (StuntCams). Sleep (total sleep time, sleep onset, and wake after sleep onset) will be measured using actigraphy (baseline, days 5 to 7 of each intervention week). Mixed effects regression models with a random effect for participants will be used to estimate mean differences (95% CI) for conditions 2 to 4 compared with condition 1.

Results: Recruitment started in March 2024, and is anticipated to finish in April 2025. Following data analysis, we expect that results will be available later in 2026.

Conclusions: Using objective measures, we will be able to establish if causal relationships exist between prebedtime behaviors and sleep in children. Such information is critical to ensure appropriate and achievable sleep guidelines.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000206527; https://tinyurl.com/3kcjmfnj

International Registered Report Identifier (IRRID): DERR1-10.2196/63692

(JMIR Res Protoc 2024;13:e63692) doi:10.2196/63692

KEYWORDS

screen time; digital device; diet; physical activity; objective measurement; wearable camera; sleep; mobile phone

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Introduction

Ensuring children and youth receive sufficient good-quality sleep is paramount for optimal health and well-being [1,2]. However, poor sleep health is a major issue worldwide [3], including in New Zealand [4]. Children with poor sleep are at increased risk of excess weight [5], do not do as well at school [6], are less resilient [7], and have poorer mental health [8]. Thus, advisory groups worldwide [9-11] endorse several "sleep hygiene" behaviors that are thought to promote good sleep health, encompassing sleep habits, environments (eg, bedding and temperature), and prebed behaviors (limiting the use of electronic media, vigorous exercise and active play, or the consumption of food in the hour before bed). However, the evidence base illustrating that these strategies actually influence sleep is variable. Strong support exists for some aspects including consistent bed and wake times, age-appropriate sleep duration, bedtime routines, sleep independency, and no bedroom electronics [12,13]. By contrast, evidence supporting any effect of screen time, physical activity, or food intake in the hour before bed is less definitive [12-15].

While a potential relationship between electronic media and subsequent sleep has received the most attention, the evidence on which these guidelines are based is mainly from cross-sectional studies that cannot determine causality [16,17]. The much smaller evidence base of prospective studies reports inconsistent findings, with most research not showing any significant relationship between screen time and sleep [18,19]. Using stronger temporal analyses that examine the effect of screen time on sleep each night have also reported a limited impact of evening screen use [20,21]. Furthermore, most studies to date have used recalls of screen use, which are prone to bias and are likely unable to measure screen time in the modern world [22,23]. While evidence is emerging that has used objective measures of screen time, this has often been restricted to individual devices (predominantly phones) [24,25]. This precludes the measurement of behaviors including multitasking where more than 1 device is used simultaneously [26,27]. A further limiting aspect is that most studies have examined the impact of whole-day screen time, rather than that more immediate to bedtime, thought to be more detrimental to sleep [16,28]. Although some, but not all, questionnaire-based analyses by Hartley et al [29] and Belmon et al [30] have reported that the use of evening electronic media was associated with poorer sleep, objective measurement of bedtime smartphone usage (tracking app) did not support these findings [24].

A recent review suggested that interventions to reduce screen time can improve sleep. However, there are many issues with this literature. Interventions have often included day screen use [31], or not specified evening screen use only [32], or included changes to other behaviors that might also influence sleep such as diet and exercise [31]. Much of the assessment has also been through questionnaires, which have produced conflicting findings [33,34].

Although daytime physical activity is beneficial for evening sleep in some studies [35-38], how physical activity before bedtime impacts sleep (the actual recommendation) in youth is unclear, with very limited data. Matsuyama et al [39] showed no difference in accelerometer-measured physical activity of any intensity between those who went to bed earlier versus later. However, the period examined (after school until bedtime) was considerably longer than the guidelines (1-2 hours before bed), and sleep duration was not examined. While others have reported that youth with morning chronotypes tend to have higher levels of physical activity and lower levels of sedentary behavior [40], such data do not analyze a direct relationship between evening physical activity and subsequent sleep. Presumably, the recommendation about evening activity was developed based on experimental work in adults. However, examination of that research also suggests that evening exercise of moderate to vigorous intensity either has no detrimental effect, or is even protective, improving a range of sleep health outcomes [41-44]. Comparable findings have also been reported in large observational studies using objective measures of both behaviors [45]. Given the dearth of research on youth, who may respond differently to adults, experimental evidence directly designed to answer whether evening physical activity impedes sleep is required.

The final recommendation refers to avoidance of large amounts of food close to bedtime. However, as with screens and activity, relatively few studies appear to have investigated associations between the timing of the evening meal (hereafter referred to as dinner) and sleep outcomes in youth. Cross-sectional data in children show that later dinner meals are associated with parental-reported later bedtimes [46] and shorter sleep duration [47]. However, objective measures of sleep have produced mixed results, with studies showing associations between later evening mealtimes and shorter total sleep time (TST) [48] or later sleep midpoint [49], or no difference in sleep duration between early and late dinner eaters [50]. To date, no experimental evidence analyzing meal timing and sleep appears to have been conducted in youth, although comparable data show no effects in adults [51].

Thus, it appears that very little experimental evidence has directly examined whether any of these prebedtime behaviors adversely affect sleep; critical data for producing evidence-based sleep hygiene guidelines. This is particularly relevant considering that implementation of such guidelines might be challenging for families. For example, both parents and children may find the current blanket ban on screen time before bed difficult, if not impossible, to implement regularly, despite more than half of all parents viewing excessive screen time as their top health concern [52]. Given almost ubiquitous engagement in evening screen use by adolescents [53] and the potential for further stress and conflict in families from screen time "bans" [54,55], an examination of the practicality of such guidelines seems warranted. Encouraging children not to eat late or be physically active in the evenings might also be challenging, given they do not see these behaviors as important for sleep [56]. Whether parents also find the recommendations to restrict food and vigorous activity before bedtime difficult, appears not to have been examined. It is also important that sleep hygiene recommendations do not harm children. For example, given that inadequate physical activity is a major issue for children

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worldwide [57], restricting children from being active close to bedtime is a misguided effort to improve sleep, and may have unintended consequences on overall activity. Such analyses do not appear to have been examined.

Therefore, the primary aim is to use objective measures to experimentally determine whether screen time, physical activity, or a meal in the hour before bed affects TST.

The secondary aims are to determine (1) whether screen time, physical activity, or a meal in the hour before bed affects sleep onset, wake after sleep onset (WASO), shuteye latency, sleep onset latency, sleep disturbances, and sleep impairment; (2) whether screen time, physical activity, or a meal in the hour before bed affects health-related quality of life; (3) whether restricting physical activity before bed influences physical activity during the day; and (4) how participants and families found the interventions and how realistic they considered them to be.

Methods

Study Design

The helpful activities before it is time to sleep (HABITS) study is a randomized crossover trial to experimentally determine whether banning electronic media, physical activity, or food intake in the hour before bed actually impact children's sleep quantity and quality. Wearable cameras will be used to obtain objective measures of prebed behaviors and accelerometers for objective measures of sleep. The study will be conducted in participants' homes and at the University of Otago in Dunedin, New Zealand.

All children will undergo a baseline week to establish usual prebedtime behavior and set bedtimes for the intervention weeks. Each participant will follow 4 experimental prebedtime conditions in a randomized order (Figure 1). The comparison or ideal week will be condition A. In condition B (screens week), participants can use any device and undertake any screen behavior. In condition C (exercise week), suitable options will be suggested for both indoor (eg, wrestling and dancing) and outdoor (tag, sports, and walking) activities. In condition D (food week), participants will be asked to eat a large meal in the hour before bed.

Families will follow each intervention condition on the same consecutive 3 days of each intervention week (days 5-7). In total, 3 days will provide sufficient data to determine how each behavior influences sleep, allows a washout between each condition, and is a pragmatic choice to limit participant or researcher burden. As we are examining the effect of the condition on sleep the same night, this amounts to 3 observations/participant/condition, which should give more reliable estimates than 1 observation or condition. Each family can choose what days of the week are days 5-7 for them, as long as the same days apply across all 5 weeks. All interventions will occur during the school term to limit known changes in sleep caused by holidays [58]. Daylight savings will be avoided and lunar patterns will be recorded to examine the potential for confounding across the different phases.

Figure 1. The helpful activities before it is time to sleep study design using Williams Latin square randomization design.

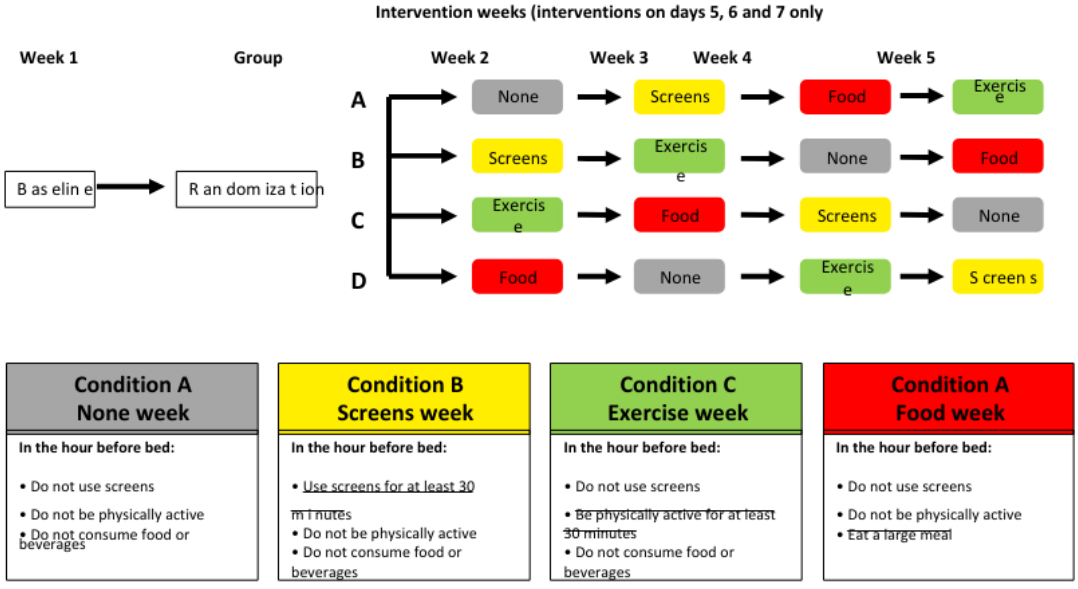

Ethical Considerations

The HABITS study was approved by the University of Otago Health Ethics Committee (H23/039) and is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12624000206527; www.anzctr.org.au). Written informed consent will be obtained from adult and child participants before the first appointment. We also follow ethical frameworks for the use of wearable cameras in research [59]. In brief, this includes discussing with participants and families about privacy considerations (eg, everyone in the household needs to be happy to be recorded, remove the camera when toileting or someone asks), families get to view the footage before the research team does and can delete any footage without explanation, and that footage is deleted from cameras as soon as it is uploaded to our high-capacity secure storage system.

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Sample Size

To detect a difference of 15 minutes (assuming within-person SD of 35 minutes) in TST [60], with 90% power at a .05 α level, a sample size of 60 participants would be required. We will recruit 72 children, allowing for 20% nonadherence, dropout, or incomplete data.

Recruitment and Eligibility

Overview

Recruitment will take place through social media and community networks. Interested families will complete an eligibility screening questionnaire online (assessing whether their child has, or previously had, a sleep disorder, any medications that may impact sleep, and ability to undertake physical activity), which they will access through local Facebook (Meta) pages or email from the researchers. Children will be eligible to participate if they are 10-15 years old and live in the Dunedin area. Children will be excluded if they have been diagnosed with a sleep disorder or issue or are on medication that may affect sleep. Children who are not eligible will be sent a standardized text or email by their caregiver. We aim to recruit a sample that is broadly representative of the New Zealand population [61].

Before attending the baseline appointment, potentially eligible participants will be asked to select 3 consecutive nights in the week that would work best for them to complete the intervention (eg, Mondays, Tuesdays, and Wednesdays). These days will be classified as days 5-7 for participant baseline (week 1) and intervention (weeks 2-5) weeks. The researchers will then book their baseline appointment on day 1 of the baseline week.

Baseline (Week 1)

At the baseline appointment, researchers will explain the study protocol to potential participants and their caregivers (mainly parents), with opportunities for questions throughout. If the child and their caregiver indicate that they would like to be involved, they will be given a paper version of the assent (child) and consent (caregiver) form to sign. Once consent and assent are signed, caregivers will complete an online demographics questionnaire assessing the child's date of birth, household address, and ethnicity. Weight (using Tanita electronic scales HD351) and height (using Wedderburn Portable Height Rod, WS-HRP) will be measured by trained researchers using standard procedures [62].

Participants will be given an accelerometer (AX3 [Axivity]) to wear on their nondominant wrist for 7 nights, 24 hours per day, to measure usual sleep (more details are discussed in the *Intervention Adherence* section). To determine usual bedtime practices in terms of screen time, physical activity, and food consumption, participants will be asked to wear a wearable video camera from 90 minutes before bedtime until bedtime on their 3 "intervention" nights (more details are discussed in the *Intervention Adherence* section). A second stationary camera in the child's bedroom will face the bed and allow researchers to measure in-bed electronic use or eating, and to measure when the participants attempt sleep (shut-eye time; more details are discussed in the *Sleep* section). Participants will be asked not to change their behavior during the baseline week. Information from the cameras will also be used to give researchers insight into how the participants might be able to adapt their nighttime behavior to complete the intervention weeks. Researchers will talk to participants (and families) at the baseline visit about their usual eating, physical activity, and screen time habits to help develop personalized suggestions for completing the intervention weeks.

Randomization

Overview

Once the baseline appointment is completed, participants will be randomized using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module [63] to one of 4 intervention group orders using a computer-generated sequence, stratified by age (from 10 to less than 13 years or from 13 to 15 years), with random block sizes of 4 or 8. The 4 group orders are from a Williams Latin square balanced for first-order carryover effects. Usual bedtimes will be discussed with families, based on camera footage from baseline. While bedtime for each night of intervention (ie, nights 5-7 of each intervention week) can be different, each day of the week must be consistent between all 4 intervention weeks.

Intervention (Weeks 2-5)

At the start of each intervention week, a trained researcher will visit the participants at home to inform them which intervention (screens, physical activity, food, or none week) they are completing that week. The researchers will discuss potential ideas with the participants based on their baseline week information on how to adhere to that week's protocol.

As the participants will potentially be asked to do less (ie, not use screens) or more (ie, eat dinner close to bedtime) than they usually would do before bed, they will be given ideas for filling in the time while avoiding their usual prebedtime activities. For example, researchers will suggest games or reading for the nonscreen weeks and discuss rescheduling of the family dinner during the food week. These strategies will be put in place specifically to encourage adherence, so that we can determine the true effect of each prebed behavior on sleep. During the physical activity week, we will give each participant a Fitbit Inspire 3 (Google) to measure their heart rate while exercising. Participants will be able to see their heart rate and asked to aim for a target heart rate of 65% of their maximum ([208-0.7*age]*0.65) [64] during the 30 minutes of activity. Participants and their caregivers will receive regular text reminders, letting them know what intervention to complete each night, and when to turn the cameras on.

Intervention Adherence

Objective and subjective measures will be used to assess adherence. On days 5-7 of each intervention week, participants will wear a PatrolEyes Max (StuntCams) camera on a chest harness from 90 minutes before bedtime until bedtime. These cameras (weighing 160 g and having dimensions 79×57×27 mm) provide time-stamped footage, face outwards, record audio and video (including overnight use through infrared), and quantify when and how much screen use has occurred [65]. We

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will also be able to determine when and what food or beverages were consumed, supplemented with a brief questionnaire (text message) on mornings 6, 7, and 8, asking them whether they consumed any food or drinks in the hour before bed last night, as well as any caffeine intake. We will use the wearable cameras to code for moderate-to-vigorous physical activity (Compendium of Physical Activity metabolic equivalent values >4 [66]) using a reliable video coding protocol that codes free-living physical activity behavior, supplemented with information from heart rate monitors and accelerometers. Since the wearable cameras can be removed before bedtime (eg, bathing), a second stationary camera will be set up in the participant's bedroom 10 minutes before bedtime. This "back-up" camera would detect any time-stamp missing from the wearable camera (as long as the participant is in their bedroom) and is also used to assess some aspects of sleep (more details are discussed in the *Sleep* section). It will not be possible to blind coders (as they are looking for specific behaviors) or participants (as they know what behaviors they need to do), but statistical analysis will be undertaken blinded to the intervention order.

The following predefined cut-offs will be used to classify participants as "adherent" for the per-protocol analysis (ie, those who followed the HABITS protocol):

1. Condition A: children use screens and engage in physical activity for less than 5 minutes and do not consume any food or beverages other than water in the hour before bed.
2. Condition B: children spend at least 30 minutes on screens in the hour before bed (and engage in physical activity for less than 5 minutes and do not consume any food or beverages other than water).
3. Condition C: children spend at least 30 minutes being physically active (light, moderate, or vigorous activity) in the hour before bed (and use screens for less than 5 minutes and do not consume any food or beverages other than water).
4. Condition D: children consume their dinner meal in the hour before bed (and use screens and engage in physical activity for less than 5 minutes).

Video data will be examined to describe how children are spending this time, based on a reliable ($\kappa \geq 0.8$) coding schedule previously developed by our team [65].

Outcome Measures

Sleep

The primary outcome is TST, with secondary outcomes of sleep onset, WASO, shuteye latency, sleep onset latency, sleep disturbances, and sleep impairment assessed using objective and subjective measures (Figure 2). AX3 accelerometers will be worn on the nondominant wrist, 24 hours a day, for 7 days during the baseline week and 3 days during intervention weeks 2-5. These accelerometers provide accurate measures of our sleep variables in this age group, as determined against the gold standard polysomnography [67]. These devices are smaller than a watch, waterproof, unobtrusive, and do not need to be removed for sport or bathing, ensuring high wear time compliance rates [68]. After initialization of the accelerometer, the data will be downloaded with OmGui software (version 1.0.0.30; Open Movement), saved in raw format as .cwa files, then converted into ActiGraph counts for data processing [69]. Sleep variables are obtained using an automated script developed in MATLAB (MathWorks) that uses a count-scaled algorithm to estimate sleep and wake epochs for each individual for each day [70]. Sleep onset is then determined as the start of the first 15 continuous minutes of sleep preceded by 5 minutes of awake. Sleep offset is determined as the last of 15 continuous minutes of sleep followed by 5 minutes of awake. WASO is determined as the number of minutes from the sum of all movement epochs that occur over 5 continuous minutes of awake between sleep onset to offset. TST is determined as the number of minutes from sleep onset to sleep offset minus WASO. The remaining sleep variables of interest will be measured from the stationary video data. Bedtime is determined as the first time the participant gets into bed and under the covers. Shuteye time is determined as the first time the participant stops interacting with any device or person and appears to close their eyes to try and go to sleep. Shuteye latency is calculated as the difference between bedtime and the first shuteye time. Sleep latency is calculated as the difference between shuteye time from the video camera data until sleep onset time from the accelerometer. Sleep disturbances (difficulties falling and staying asleep) and sleep impairment (daytime alertness and sleepiness) will be measured using 2, 8-item PROMIS (Patient-Reported Outcomes Measurement Information System) questionnaires [71]. The questionnaires were originally designed with a 7-day recall and will be used in this context to assess usual sleep disturbances and impairment during the baseline week on day 8 (therefore covering the previous week). An adapted version assessing the previous night only, will be used to measure sleep disturbances on the previous night and will be administered on the morning of days 6, 7, and 8 of each intervention week, asking about "Last night…" rather than "Over the past 7 days." An adapted version assessing sleep impairment over the previous 3 days will be administered on the evening of day 8 of each intervention week, with the anchors for these questions changing from "Over the past 7 days" to "Over the past 3 days."

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Figure 2. Outline of the measurement schedule. PROMIS: Patient-Reported Outcomes Measurement Information System.

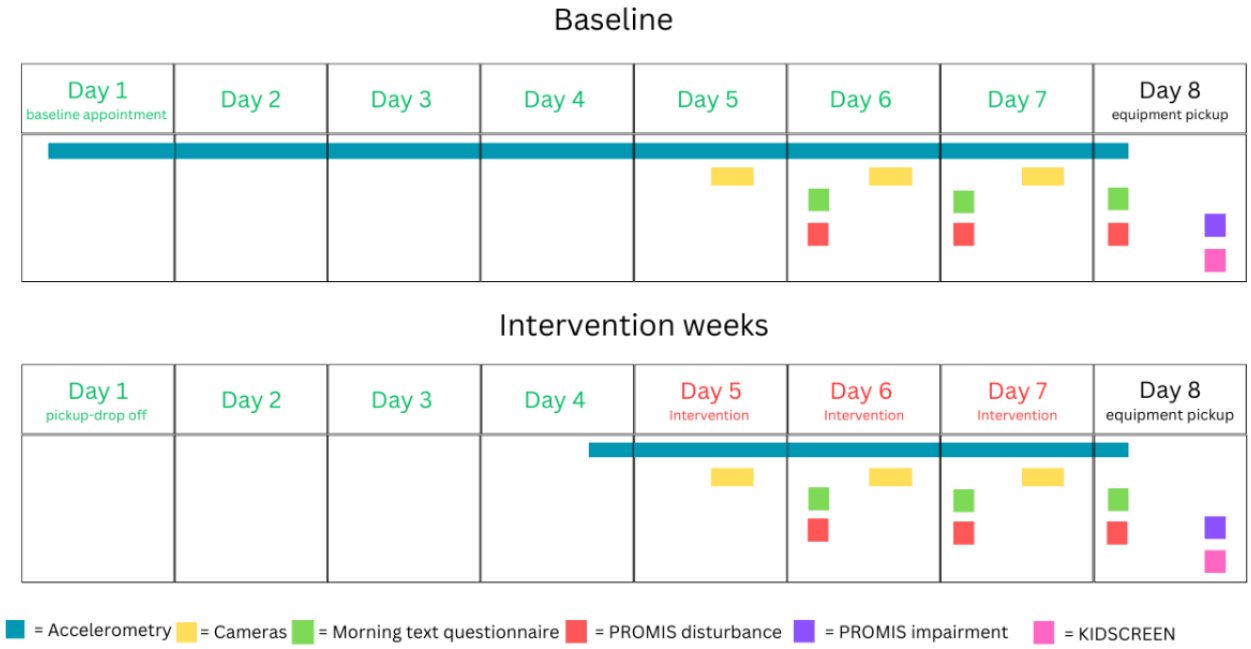

Health-Related Quality of Life

Participants will complete the 10-item KIDSCREEN questionnaire that assesses health-related quality of life over the past week [72] at the end of the baseline week. As with the PROMIS impairment questionnaire, an adapted version of the KIDSCREEN questionnaire will be completed in the afternoon of day 8 of each intervention week. The adapted version changes the answer anchors from "Thinking about the last week..." to "Thinking about the last 3 days..."

Participant and Family Experiences

At the end of each intervention week, participants and families will provide brief feedback on their experiences, rating the ease of activity on a scale of 1 to 5, and providing reasons for their rating. In addition, 16 participants and families will take part in semistructured interviews upon study completion, offering detailed qualitative feedback on each intervention activity, its feasibility for integration into daily routines, and any changes in sleep resulting from the activities.

Statistical Analyses

Siblings in the same family may wish to participate, and they would be convenient participants, given their familiarity with the intensive intervention protocols. However, siblings represent family clustering that must be statistically accounted for. We examined the intraclass correlation coefficient (ICC) for families in our recent observational repeated-measures study of screen use and sleep in teens [73], which was low (ICC=0.005). Using this ICC and an average family cluster size of 2, the design effect is 1.005 [74], which has a negligible effect on the required sample size (60*1.005=60.3). Therefore, siblings may be recruited but will be assessed at different times throughout the year, will be individually randomized, and will contribute to no more than half the sample (ie, n=36 participants must not have siblings in the study).

Primary statistical analyses will be undertaken using data from adherent days; secondary analyses will use all data. Mixed effects regression models with a random effect for participants nested within a family cluster will be used to estimate mean differences, 95% CI, and *P* values for conditions 2, 3, and 4 compared with condition 1. Residuals will be plotted and visually assessed for homoskedasticity and normality. Adjustments for within-person confounding (eg, lunar phases) will be undertaken as sensitivity analyses. Results will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) statement extension to crossover trials. Descriptive analyses will also be undertaken to explore participants' experiences with the interventions as well as their adherence. Relationships between sleep and quality of life measures will be assessed using repeated measures mixed effects analyses.

Results

Data collection commenced in February 2022, and the first results are expected to be submitted for publication in 2026.

Discussion

Ensuring children receive enough good-quality sleep is paramount, given the number worldwide who do not get sufficient sleep for their needs [3]. In fact, it has been argued that addressing sleep health may be a viable way of reducing many health inequities [3]. Therefore, ensuring suitable guidelines exist that are both evidence-based and achievable for families is critical to ensure health impact. At present, we do not have strong evidence that using screens, being physically active, or eating the dinner meal in the hour before bed even impact sleep. In addition, we know that there are many barriers to implementing these behaviors in households. Based on the limited experimental evidence available, we believe that these 3 behaviors might have a limited effect on sleep outcomes in

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children. It is possible that some, particularly physical activity before bed, might even be beneficial for sleep.

Our proposed trial has several strengths. We have chosen a strong experimental design, are using objective measures of key behaviors to overcome many of the limitations of the current evidence base, and have adequately powered our study to answer our research questions of interest. The HABITS study has been specifically designed to show if these prebedtime behaviors truly influence sleep so that the relevant sleep guidelines can be evidence-based. However, it also has some potential limitations. We will need to ensure that we can recruit a diverse sample, to enable generalizability of findings to a broad demographic. Ideally, we would assess each behavior over the course of a full week, but this was considered inappropriate because of respondent burden. There will be some variation in how families interpret the evening meal and exercise routines suggested, but this should reflect the real world and is appropriate for our pragmatic trial.

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Data Availability

The deidentified data sets used or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

RJ, JH, KM-J, BG, JC, DB, and RT designed the research and obtained funding. RJ and CG will conduct the research. JH designed and will undertake the analyses. RJ, CG, and RT wrote the first and subsequent versions of the manuscript. All authors read and approved the final manuscript. RT has final responsibility for final content of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Te Kaunihera Rangahau Hauora o Aotearoa / Health Research Council of New Zealand.
[PDF File (Adobe PDF File), 516 KB - resprot_v13i1e63692_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
HABITS: helpful activities before it is time for sleep
ICC: intraclass correlation coefficient
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
TST: total sleep time
WASO: wake after sleep onset

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Protocol

Effectiveness of Aerobic Training for Adverse Symptoms Related to Chemotherapy During Treatment: Protocol for a Randomized Controlled Trial With Cost-Effectiveness Assessment

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Abstract

Background: One strategy to prevent adverse effects resulting from chemotherapy treatment is to perform physical exercises during treatment. However, there is still no consensus on the best type and intensity of exercise, nor when it should be started. Most studies have been carried out in patients with breast cancer, usually a few weeks after starting chemotherapy, on an outpatient basis 2 to 3 times a week. The main differences in our study are that we carried out physical training in hospitalized patients undergoing a cycle of chemotherapy for cancer treatment and that this training was carried out 5 times a week and was not restricted to a specific type of cancer.

Objective: We aimed to evaluate the effects of aerobic training on symptoms related to chemotherapy (nausea, vomiting, asthenia, and sensation of weakness), fatigue, mobility, clinical complications, and length of hospital stay of patients during the drug treatment cycle. We also evaluated patient satisfaction with the proposed intervention, the adverse effects of aerobics training, and the cost-effectiveness of this intervention.

Methods: This is a controlled and randomized trial with blinded evaluation that will include 94 hospitalized patients with cancer for 1 or more cycles of chemotherapy. The intervention group will perform aerobic training during a cycle of chemotherapy. The control group will receive a booklet with guidelines for staying active during the hospitalization period. The groups will be compared using a linear mixed model for fatigue, mobility, and chemotherapy-related symptoms before and after the intervention. The length of hospital stay will also be compared between groups using Kaplan-Meier survival analysis. The incidence of complications will be compared using the χ^2 test. Cost-effectiveness and cost-utility analyses will be performed for the impact of exercise and quality-adjusted life years with the EQ-5D-3L-21 quality of life trials. The implementation variables (acceptability, suitability, and feasibility) will be evaluated by frequencies.

Results: The clinical trial registration was approved in March 2023. Recruitment and data collection for the trial are ongoing, and the results of this study are likely to be published in late 2025.

Conclusions: Chemotherapy has side effects that negatively impact the quality of life of patients with cancer. Aerobic exercise can reduce these side effects in a simple and inexpensive way. The field of work of physical therapists could be expanded to oncology if the intervention works.

Trial Registration: Registro Brasileiro de Ensaios Clínicos RBR-6b4zwx3; https://tinyurl.com/39c4c7wz

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KEYWORDS

cancer; exercise; chemotherapy; physical therapy; cost benefit analyses; economic evaluation

Introduction

Cancer is already the biggest public health problem in the world. In Brazil, the estimate for the 2023-2025 period is that there will be 704,000 new cases of cancer per year (excluding cases of nonmelanoma skin cancer) [1]. One of the main forms of treatment for cancer is chemotherapy, which consists of a systemic treatment in which a drug is used to interfere with cell proliferation, targeting its DNA or RNA and its metabolism [2]. The costs of cancer treatment in the United States already reach US $158 billion per year [3], and in Brazil, they exceed R $3.5 billion (US $700 million) [4]. The application of these resources requires health care staff, medications used directly and indirectly in treatment, equipment, and hospitalization days.

Treatment with chemotherapy involves a series of side effects, including nausea, vomiting, diarrhea, and febrile neutropenia, which are treated with supplementary medications. These adverse effects have a major impact on patients' lives, as well as on adherence and compliance with the recommended dose of treatment, and they are also associated with an increase in the rate of hospitalization. At least one-third of women undergoing adjuvant chemotherapy treatment for breast cancer are unable to complete the prescribed dose of treatment due to adverse effects, thus compromising the prognosis of the disease [5].

Physical exercise in patients with cancer during chemotherapy has been tested in randomized trials [5-11] and appears to improve physical function, fatigue, symptom burden, and the quality of life of patients, in addition to allowing the nonreduction of chemotherapy doses. However, most studies have been carried out on an outpatient basis, involved patients with breast cancer, used 3 weekly exercise sessions, and evaluated fatigue as the primary outcome. There are still no clinical trials testing the effect of exercise in a hospital environment with daily sessions (Monday to Friday) carried out during the chemotherapy cycle.

Therefore, our objective is to evaluate the effects of aerobic training on chemotherapy-related symptoms (nausea, vomiting, asthenia, and sensation of weakness), fatigue, mobility, clinical complications, and length of hospital stay in patients during the drug treatment cycle. Furthermore, we also aim to evaluate the adverse effects of aerobic training, patient satisfaction with the proposed intervention, its implementation, and its cost-effectiveness.

Our hypothesis is that aerobic training will decrease chemotherapy-related symptoms, fatigue, clinical complications, and length of hospital stay, in addition to not increasing mobility. In addition, we hypothesize that the proposed intervention will be cost-effective from the point of view of the patient and society due to the preservation of quality of life and lower health costs related to the treatment of adverse effects from chemotherapy.

Methods

Design

This is the protocol for a randomized controlled trial with 2 parallel groups, 1:1 allocation, and blind evaluation that will be conducted in the oncology ward of the Instituto de Assistência Médica ao Servidor State Public, São Paulo-SP, Brazil, in accord with the CONSORT (Consolidated Standards of Reporting Trials) checklist [12]. The trial has been registered on the Registro Brasileiro de Ensaios Clínicos (RBR-6b4zwx3).

Ethical Considerations

This study protocol was approved by the research ethics committees of the Universidade Cidade de São Paulo and Instituto de Assistência Médica ao Servidor (50436221.7.3001.5463). All participants will provide written informed consent before participating in this study. This will be collected and stored securely by one of the clinical data collection team members.

Participants

Patients older than 18 years diagnosed with cancer and hospitalized in the ward to undergo at least 1 cycle of chemotherapy will be eligible for this study. Patients will be included in the study if they do not have musculoskeletal, cognitive, or clinical limitations that interfere with the proposed assessments and interventions, such as heart disease (eg, moderate to severe aortic or pulmonary stenosis, decompensated heart failure, advanced cardiac arrhythmias, myocarditis, and unstable coronary insufficiency), lung diseases (eg, chronic obstructive pulmonary disease or decompensated asthma), diabetes mellitus, and decompensated systemic arterial hypertension with serum hemoglobin <8g/dL or hematocrit <25% or platelets <30,000 mm [5,13-15].

Patients who require transfer to the intensive care unit, or for whom chemotherapy treatment has been contraindicated or discontinued for any reason, will be excluded from the study.

Procedures

During the protocol period, all patients admitted to the oncology ward who are identified and meet the eligibility criteria will be invited to participate in the study by the evaluating physiotherapist. These eligible patients will be informed about the objectives of the study and invited to sign the informed consent form. Next, the patients will be evaluated regarding anthropometric and clinical characteristics, fatigue, and mobility, as well as the occurrence, frequency, intensity, and discomfort of the main adverse effects of chemotherapy. After the initial assessment, patients will be randomized into an intervention

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group, which will perform aerobic exercise sessions, and a control group, which will receive a booklet with guidelines (the same booklet will be given to the patients in the intervention group). The next day, the intervention will begin. Aerobic training will be carried out from Monday to Friday while the patients are hospitalized for the chemotherapy cycle in the oncology ward. Before carrying out the day's aerobic exercise session, the patients will be asked if they feel any type of discomfort that is related to the previous day's training (for example, muscle or joint pain in the lower limbs). If for any reason chemotherapy is interrupted for a patient, the exercises will also be interrupted, and as soon as chemotherapy treatment is resumed, the exercise will also be resumed. The booklet will be given to the patients and explained by a trained physiotherapist. Patients will be re-evaluated on the day following the last day of the chemotherapy cycle regarding the occurrence, frequency, intensity, and discomfort of adverse effects of the treatment, as well as fatigue, mobility, and satisfaction with the proposed intervention.

After the study intervention period, patients who need it will receive routine physiotherapeutic care provided by the physiotherapy team at the hospital. The incidence of clinical complications from chemotherapy and the length of hospital stay will be assessed as outcomes until hospital discharge. All data will be collected by a blinded assessor. Additionally, data will be coded and entered into a Microsoft Excel spreadsheet and will be double-checked before analysis. A visual representation of the study design is presented in Figure 1.

Figure 1. Clinical trial flowchart. BFI: Brief Fatigue Inventory; DEMMI: De Morton Mobility Index; MSAS-BR: Memorial Symptom Assessment Scale, Brazilian version.

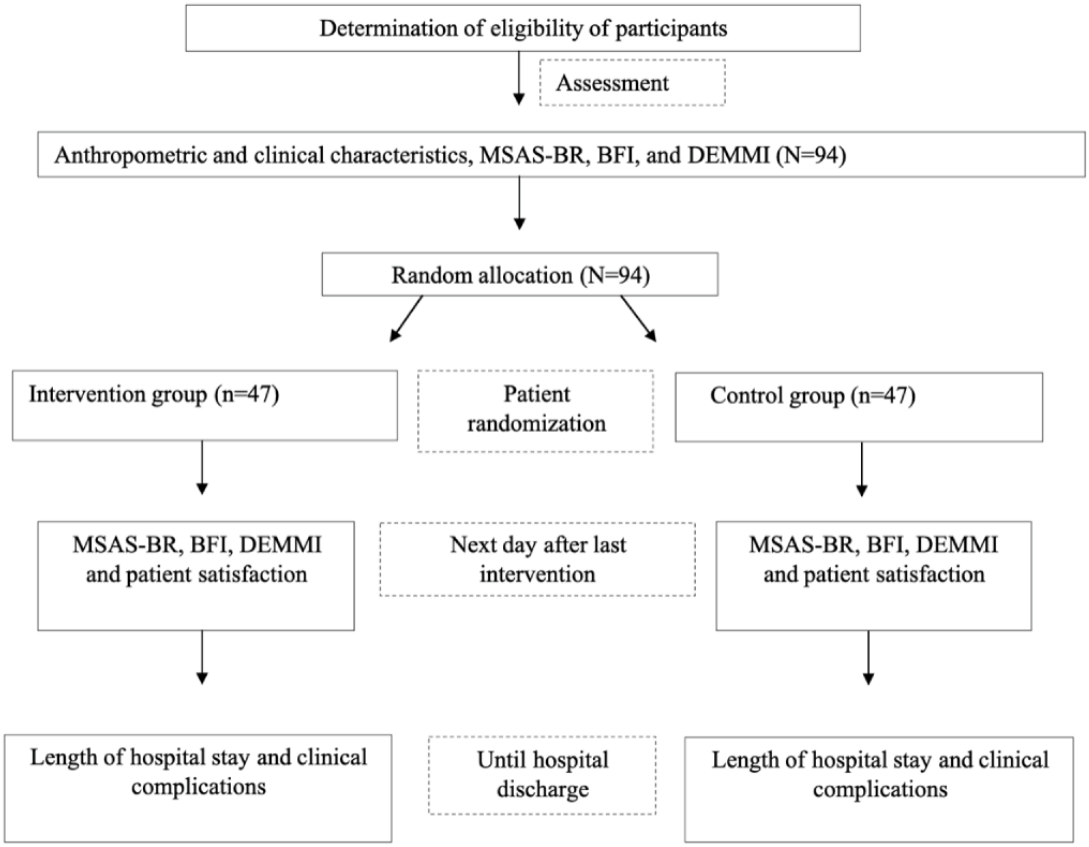

Randomization

Immediately after baseline assessments and before starting the intervention, patients will be randomly allocated to 1 of 2 groups: intervention or control. The allocation will be conducted by a researcher who will not be involved in the selection or evaluation of patients or in the intervention; it will follow a randomization schedule generated by a website [16] with a 1:1 allocation rate. The rooms in the ward accommodate 2 to 4 patients (beds); therefore, randomization will be carried out by group or cluster [17]. The rooms will be randomized, because although the intervention is directed to one patient, it can affect another patient in the same room, contaminating those who should not receive the intervention and reducing the estimated result [17]. The researcher responsible for randomization will place a written document inside a sealed opaque envelope indicating which group (intervention or control) each room belongs to in order to ensure the confidential allocation of patients to the blinded evaluator [18]. Before starting the intervention, the physiotherapist responsible for the intervention will open the envelope in front of the patient and disclose which group the room the patient is in corresponds to.

Due to the nature of the study, it will not be possible to blind the physiotherapist responsible for the intervention or the patients. However, the evaluator will be blinded to the groups (intervention and control). After the intervention and assessments, the physiotherapist responsible for the intervention will ask the blinded evaluator to which group (intervention or

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control) he believes each patient belonged to evaluate the evaluator's blinding.

Assessments

First of all, a standardized printed form will be used that will include personal data (name, age, sex, place of birth, contact telephone number, education, monthly family income, marital status, and occupation) and anthropometric data (height and weight, measured as recommended by the National Institute of Health, Heart, Lung, and Blood) [19]; diagnosis of current illness; preexisting illnesses; current or past smoking history; history of alcohol consumption and medications used; previous chemotherapy or radiotherapy; whether the current chemotherapy is neoadjuvant, adjuvant, treatment of choice, or palliative; and whether the patient is or was a practitioner of physical activity and how often they performed such activity.

The primary outcome will be assessed via frequency and intensity. Discomfort caused by the main adverse symptoms of chemotherapy (such as pain, nausea, and dry mouth) will be assessed using the Memorial Symptom Assessment Scale, Brazilian version (MSAS-BR) [20]. This scale consists of 32 symptoms that are scored by the patient according to their frequency and intensity (1-4 points, with 1 being less intense and frequent) and the discomfort (0-4, zero being no discomfort) that this symptom caused the previous week. This scale gives us a final index, which consists of the average of the 3 domains (frequency, severity, and bother) and all items, in addition to 4 subscales: Psych, which assesses psychological symptoms (with six items); Phys H, which assesses the most prevalent physical symptoms (with 12 items); Phys L, which assesses the less prevalent physical symptoms (with 14 items); and the Global Distress Index, which measures 4 psychological and 6 physical symptoms [20,21]. This scale will be applied in the initial and final assessments by an evaluator blind to which group the patient belongs.

Other outcomes will be assessed, such as fatigue, level of patient mobility, length of hospital stay, and clinical complications. Fatigue will be assessed using the Brief Fatigue Inventory, Brazilian version. This inventory consists of 9 items that are rated from 0 to 10 on a visual numeric scale. The first question is a dichotomous question about whether the patient has felt tired or fatigued in the last 7 days. Three items refer to the severity of fatigue at the time of assessment, the usual fatigue in the last 24 hours, and the worst fatigue in the last 24 hours, where 0 represents no fatigue and 10 "the worst fatigue imaginable." The other 6 items refer to how fatigue interfered with different aspects of the patient's life in the last 24 hours; these items are "general activities," "mood," "ability to walk," "work" (including work outside and at home and daily tasks), "relationships with other people," and "enjoying life," where 0 means that it does not interfere and 10 means that it interferes completely [22,23]. This inventory will be applied in the initial and final assessments by an evaluator blind to which group the patient belongs.

The level of mobility will be assessed using the De Morton Mobility Index. This scale is made up of 15 activities, where 11 are classified as 0 or 1 (incapable or capable, respectively) and 4 are classified as 0, 1, or 2 (incapable, partial, and capable, respectively). Of the 15 activities, 3 are performed in bed, 3 in a chair, 4 involve static balance, 2 involve walking, and 3 involve dynamic balance. The scale was translated and validated in Brazilian Portuguese [24,25] and ranges from a score of 0, which represents low mobility, to 100, which represents high mobility. This index will be applied by an evaluator who is blind to which group the patient belongs and will be applied in the initial and final assessments.

In addition, the total number of days of hospital stay, possible clinical complications (cardiac, pulmonary, infectious, or neurological) arising from chemotherapy treatment, and the need for transfer to the intensive care unit will be accessed through the medical records of the patient.

The adverse effects of aerobic training, such as muscle pain, will be collected in the form of a question, developed by the researchers themselves, that will be answered every day before starting a new aerobic exercise session. In the same way, the patients' subjective perception of satisfaction and discomfort in relation to the proposed protocol will be assessed through 2 questions developed by the researchers themselves that will be answered on the day of the patients' final assessment. The patients' responses to the questions will be on a scale of 0 to 10. In the question about satisfaction with the treatment, 0 will indicate "complete dissatisfaction" and 10 "maximum satisfaction." When the question is about the discomfort of the treatment, 0 will indicate "no discomfort" and 10 will indicate "maximum discomfort."

At the end of the treatment, the acceptability, suitability, and feasibility outcomes will be assessed using the Weiner scale [26], which was translated and adapted into Brazilian Portuguese [27]. The answer options for all questions are "completely disagree" (1 point), "disagree" (2 points), "neither agree nor disagree" (3 points), "agree" (4 points) and "completely agree" (5 points).

Acceptability is the perception among parties interested in implementing a given treatment that it is pleasant or satisfactory. It will be evaluated in terms of patient satisfaction in the intervention group according to their responses to the following statements: (1) "Physical exercise during chemotherapy treatment has my approval"; (2) "Physical exercise during chemotherapy treatment is attractive to me"; (3) "I enjoyed physical exercise during chemotherapy treatment"; and (4) "I recommend physical exercise during chemotherapy treatment."

As for suitability, it is the relevance or compatibility of the proposed innovation (ie, treatment) for a given clinical practice environment. It will be evaluated by the following statements addressed to health professionals who care for patients included in this study, such as doctors, nurses, and physiotherapists: (1) "Physical exercise during chemotherapy treatment seems appropriate"; (2) "Physical exercise during chemotherapy treatment seems adequate"; (3) "Physical exercise during chemotherapy treatment seems applicable"; and (4) "Physical exercise during chemotherapy treatment seems to be a good option."

Feasibility is defined as the extent to which a new treatment can be implemented within a given environment. It will be

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evaluated by the following statements addressed to physiotherapists and patients included in this study: (1) "Physical exercise during chemotherapy treatment seems implementable"; (2) "Physical exercise during chemotherapy treatment seems possible to perform"; (3) "Physical exercise during chemotherapy treatment seems feasible"; and (4) "Physical exercise during chemotherapy treatment seems easy to use."

Economic evaluation will be monitored during the hospitalization period [28]. The index year will refer to the year of data collection. The costs of the intervention used will be assumed through the estimated value of the instruments used (oximeter and cycle ergometer), as well as the booklets and the in-hospital physiotherapy sessions (using the reference fees from the Physiotherapy Council table). The assessment of health care costs corresponds to the individual's costs to the health care system and the costs of lost productivity due to total days of hospitalization. This assessment will be carried out using cost information obtained at the hospital. The cost-effectiveness analysis will be carried out by evaluating the effects of the intervention using the MSAS-BR-16 questionnaire, while the cost-utility analysis will be measured by quality-adjusted life years (QALYs) using the quality-of-life questionnaire EQ-5D-3L [29]. Sensitivity analysis will test uncertainty in key parameters, such as selection of cost weights and statistical variation in quality-of-life scores.

Interventions

The patients allocated to the intervention group will participate in an aerobic training protocol on a cycle ergometer during the period in which they are hospitalized and undergoing the chemotherapy cycle. The training will be carried out with daily sessions for 4 days lasting 40 minutes as long as the chemotherapy cycle continues. Exercise on the cycle ergometer will begin with a 5-minute warm-up and will progress to 30 minutes of exercise at a speed corresponding to 40%-60% of the heart rate reserve calculated by the Karvonen formula [30]: (220 – age) – (heart rate of rest × % intensity) + resting heart rate. The exercise will end with 5 minutes of recovery. The objective will be to maintain the patient at a score of 12 for the perception of dyspnea and physical fatigue, as measured by the Borg scale [31] (12 indicates that the patient's dyspnea and physical fatigue is above "relatively easy" and below "slightly tiring"), during exercise on the cycle ergometer. The Borg scale presents a range of scores from 6 (no effort) to 20 (maximum effort). Therefore, if the patient is considered fit by the physiotherapist, the speed on the cycle ergometer will be gradually increased until the patient reaches 60% of the heart rate reserve. We will record heart rate and peripheral oxygen saturation (Palmsat 2500 pulse oximeter; Nonin), dyspnea and physical fatigue (Borg scale) [28], and blood pressure (Premium Aneroid Sphygmomanometer and Littmann Classic II Stethoscope) before, during, and after each physical training protocol session. The session may be interrupted at any time if the patient presents signs or symptoms such as dizziness, dyspnea, fatigue, or nausea. If the patient requires any emergency assistance during the period in which they are undergoing physical training supervised by the study physiotherapist, the same physiotherapist will contact the medical team on duty responsible for the patient in the oncology ward to provide the necessary assistance to stabilize the condition of the patient. To assist in blinding the evaluator, a booklet titled "Why do I need to move when I am hospitalized" [32] will be given to patients in both groups. The cycle ergometer will always be removed from the patient's room after the training session to ensure blind evaluation.

The patients allocated in the control group will receive the same booklet ("Why do I need to move when I'm hospitalized"), which uses illustrations and short texts to encourage patients to spend more time in their chair, walk, and go up and down stairs (with a companion) [32]. This booklet will be delivered and explained by a trained physiotherapist and the participant will keep it for any questions and consultations.

Statistical Design

The calculation to determine the sample size was carried out based on a previous randomized clinical trial that also compared the effect of aerobic training compared to usual care on the deleterious effects of chemotherapy in patients with breast cancer [11]. Our study was designed to detect a difference of 2.7 (SD 4) points in the physical fatigue score, in addition to a difference of 6.2 (SD 7) episodes of vomiting or nausea between the groups. A power of 80%, an α of 5%, and a loss to follow-up of 15% of the sample were considered. A sample of 94 patients (47 patients in each group) was estimated.

After the data collection, all analyses will be conducted following intention-to-treat principles and will be performed by a researcher who will not be involved in the study assessments and intervention.

For analyzing the effect of the intervention, after a descriptive analysis and the Shapiro-Wilk normality test with a visual analysis, the groups will be compared using a linear mixed model for fatigue, mobility, and chemotherapy-related symptoms before and after the intervention. The length of hospital stay will also be compared between groups using Kaplan-Meier survival analysis. The χ^2 test will be used to compare the clinical complication rates between groups. Descriptive analysis will be used for recruitment, completion, and adherence rates and potential adverse events. The significance level will be set at 5%. For all these analyses, SPSS (version 21.0; IBM Corp) will be used.

For economic evaluation, the analysis will be performed using chemotherapy-related symptoms, fatigue, and mobility as outcomes, and the cost-utility analysis will use QALYs. Missing data will be handled using multiple imputation by chained equations. Ten complete data sets will be created (efficiency loss <5%). Pooled estimates will be calculated according to the Rubin rules [33]. Average cost differences between groups will be calculated for total and disaggregated costs. Incremental cost-effectiveness and cost-utility rates will be calculated by dividing the difference in total costs by the difference in effects. Uncertainty surrounding cost differences and incremental cost-effectiveness and cost-utility ratios will be estimated using corrected and accelerated bootstrap techniques (5000 replications). The latter will be presented graphically in cost-effectiveness plans [34]. Cost-effectiveness acceptability

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curves will be estimated to indicate the probability of interventions being cost-effective compared to each other at different willingness-to-pay values [35]. Sensitivity analyses will be performed to assess the robustness of the results. The first sensitivity analysis will be performed from a health care perspective, and the second sensitivity analysis will be performed per protocol. The economic evaluation will be carried out using Stata (version 14; StataCorp).

Results

In March 2023, the clinical trial registration was approved. Recruitment and data collection for the trial is ongoing, and the results of this study are likely to be published in late 2025.

Discussion

Anticipated Findings

To our knowledge, this will be the first controlled trial with an economic analysis that will be carried out to test the acute effects of aerobic exercise in patients undergoing a cycle of chemotherapy. However, based on previous studies conducted in the outpatient phase of cancer treatment [36], we believe that aerobic training will be cost-effective and will lead to a lower incidence of adverse effects from chemotherapy treatment, less fatigue, maintenance of mobility, shorter hospital stays, and lower incidence of clinical complications when compared to the control group.

Despite the potential beneficial effects of physical exercise for patients with cancer, a decline in activity level has been reported in this population [37]. This decline appears to have an impact on quality of life and to lower performance in activities of daily living in women with breast cancer. A possible hypothesis for this decrease in physical exercise may be the relationship with psychosocial barriers in these patients [37].

Smith and colleagues [38] conducted a study that aimed to assess exercise behavior, barriers, facilitators, and motivators for exercise participation and the different exercise support needs of cancer survivors living in a rural Canadian community. They observed that the main barriers reported were cost, time, distance, transportation, and side effects. Still, the study described above was able to observe that patients reported that access to a gym, equipment, social support, transportation, and information on physical exercise were facilitators [38].

The Clinical Oncology Society of Australia and Exercise and Sport Science Australia encourage health care professionals who work with patients with cancer to seek to know more about the relationship between physical activity and cancer and understand how they must guide their patients to practice physical activity [39]. They also advise health professionals to refer patients to professionals who are more prepared and who better understand the practice of exercise in patients with cancer.

In the study by Park and colleagues [40], the authors analyzed the influence of doctors on their patients among 162 people who overcame early-stage breast and colorectal cancer and who completed primary and adjuvant treatment. Only 80.7% (n=130) of participants in the study remained until the end. Three groups were stratified: the first was the control group (n=59); the second group received exercise recommendations from oncologists (n=53); and the third group received physical activity recommendations from oncologists and an exercise motivation package (n=50). Participants were assessed at the beginning of the study and after 4 weeks [40].

The motivation package provided exercise DVDs, a pedometer, an exercise diary, and a 15-minute physical education session. In the recommendations, the oncologists said, “Studies have shown that engaging in moderate PA [physical activity] more than 150 minutes per week could significantly reduce the recurrence of breast and colorectal cancer. Therefore, it is highly recommended that breast and colorectal cancer survivors participate in at least 150 minutes of moderate-level PA and twice-weekly strengthening exercises” [40].

We have seen in the current literature the importance of understanding how much physical exercise can impact the treatment and quality of life of patients with cancer undergoing chemotherapy treatment. Studies have shown that incorporating adequate and supervised exercise can help combat fatigue, improve physical fitness, reduce anxiety and depression, and help maintain functionality. However, it is important that the exercise program is individualized, taking into account the stage of the disease, as well as the patient’s age, needs, and limitations. Supervision by specialized professionals is essential to ensure safety and effectiveness. In summary, physical exercise can be a valuable tool in managing symptoms and promoting well-being in patients with cancer, complementing conventional treatments and providing both physical and emotional improvements during the cancer treatment journey.

Conclusion

Chemotherapy has side effects that negatively impact the quality of life of patients with cancer. Aerobic exercise can reduce these side effects in a simple and inexpensive way. Oncology could be a way to expand the field of work for physical therapists if the intervention works.

Acknowledgments

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Data Availability

The data obtained in this study will be available from the corresponding author (ACL) upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from the Pró-Reitoria de Pós-Graduação, Pesquisa e Extensão (PRPGPE) - Universidade Cidade de São Paulo (UNICID) - São Paulo Research Foundation (FAPESP) (Brazil).
[PDF File (Adobe PDF File), 153 KB - resprot_v13i1e60828_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
MSAS-BR: Memorial Symptom Assessment Scale
QALY: quality-adjusted life year

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Protocol

Effectiveness of an mHealth App That Uses Financial Incentives and Gamification to Promote Health Behavior Change in Adolescents and Caregivers: Protocol for a Clinic-Based Randomized Controlled Trial

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Abstract

Background: Adolescent and adult obesity continues to be a public health epidemic in the United States. Despite the popularity of mHealth apps with gamification among adolescents, there are insufficient studies to evaluate the efficacy of gamified mHealth apps and financial incentives to motivate sustained health behavior change in adolescents or their adult caregivers.

Objective: This study aims to evaluate the effectiveness of gamification techniques and financial incentives used in the novel "CommitFit" mHealth app to motivate health behavior change and improve various mental and physical health metrics in adolescents and their caregivers.

Methods: This study is a 3-month randomized controlled trial (RCT) with 30 adolescents (aged 13-15 years) and their adult caregivers (N=60). It evaluates "CommitFit," which uses gamification including points and leaderboards to motivate logging and achievement of self-selected health behavior goals (eg, more water, sleep, physical activity, fruits, or vegetables or fewer sugary beverages). The RCT had three arms, each with 10 dyads: (1) CommitFit-only users; (2) CommitFit$, where adolescents were paid US $0.05 for each point they earned; and (3) waitlist control. Intervention dyads used the app for 3 months and had the option to use it for the fourth month without prompts or extra financial incentives. User analytic software was used to evaluate the frequency of user logs and goal achievement. Monthly surveys evaluated self-reported change in the 5 CommitFit health behaviors. Changes in BMI and blood pressure were evaluated for all participants at 3 clinical visits. Mental health, gamification, and behavior economics surveys were completed during the clinical visits.

Results: Recruitment began in August 2023 and was completed in 10 weeks. The research team successfully recruited and enrolled 30 dyads. Researchers emailed and called 89 caregivers on a physician-approved adolescent patient list, a 33% recruitment rate. Data collection and analysis will be conducted in the spring and summer of 2024. The results of this study are anticipated to be published between late 2024 and early 2025.

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Conclusions: This RCT will expand knowledge of the effectiveness of gamification techniques, financial incentives, and mHealth apps to motivate sustained health behavior change among adolescents and caregivers. These results may offer new opportunities to caregivers, health insurers, health care systems, and clinicians to motivate health behavior change in adolescents and caregivers, with the ultimate goal of preventing or reducing obesity and obesity-related diseases. Additional gamification, mental health surveys, and app user analytics included in the study may provide further insight into the characteristics of adolescents or caregivers who would benefit the most from using a gamified mHealth app like CommitFit.

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KEYWORDS

mHealth; adolescents; apps; caregivers; obesity; healthy lifestyle; CommitFit; mobile health

Introduction

Background and Rationale

Adolescent obesity continues to be a significant public health problem in the United States. In 2020, 20% of children (aged 12-19 years) had obesity [1]. Adolescents with obesity are more likely to have obesity as adults [2], consequently facing an increased risk of developing obesity-related diseases such as heart disease, type 2 diabetes mellitus, hypertension, and some types of cancer [3].

Children with obesity are more likely to have parents or caregivers who also have obesity [4]. However, current obesity research generally focuses on the adolescent or caregiver with obesity independently and fails to design interventions that engage both the adolescent and caregiver. Family-based treatment is more effective for weight loss and other positive health outcomes [5]. An approach that includes both the adolescent and caregiver is more likely to result in weight loss for the adult caregiver [6]. Additionally, evidence supports bidirectional improvement; children lose more weight when their parents lose weight through family-based treatment [7]. Yet, there is a lack of studies that evaluate the inclusion of parents or caregivers in adolescent interventions [8].

mHealth apps offer a promising opportunity to address adolescent and adult obesity; however, there are significant deficits in the literature about how to best use this technology. An estimated 50% of the 3.4 billion global smartphone users have downloaded at least 1 mHealth app [9]. mHealth apps are a preferred intervention delivery method for adolescents because of their use of gamification or "game design elements in nongame contexts" [10], such as points, leaderboards, badges, avatars, and challenges to motivate health behavior change [9]. mHealth apps show promise for short-term reductions in adolescent weight [11] but have not been evaluated long-term or with concurrent use by adult caregivers [12,13]. Additionally, although 64% of American adolescents report having ever used an mHealth app, few report consistently using them [14], due to their lack of financial and gamification incentives to maintain their motivation and attention [15,16]. We developed the "CommitFit" mHealth app and conducted the current randomized controlled trial (RCT) to address these gaps.

The CommitFit mHealth app uses gamification techniques and financial incentives to motivate adolescents to set and achieve their health behavior goals. While the CommitFit mHealth app may improve adolescent and caregiver weights, it was intentionally designed not to be a weight loss app and does not ask users to log or track their weight. Rather it focuses on improving health behaviors for adolescents and adult caregivers. CommitFit was developed with significant adolescent, caregiver, and health care provider input received from focus groups, interviews, and a feasibility study in which the adolescent used CommitFit for 2 weeks and then provided qualitative and quantitative feedback regarding the app [17,18], all of which were integrated based on the user-centered design process [19].

This project will evaluate the use of the CommitFit app through a clinic-based RCT. Our primary objective is to evaluate the effectiveness of gamification techniques in CommitFit and financial incentives to motivate health behavior change in adolescents and their caregivers.

Conceptual Framework

Behavioral economics (BE) seeks to understand why humans sometimes do not act in a rational fashion that is in their long-term self-interest [20]. Similar to intervention studies based on self-efficacy theory [21], previous BE-based intervention studies have been encouraging successful increases in physical activity and improved child nutrition [22]. Based on social cognitive theory [23], social ranking is a BE concept that uses peer-normative feedback to influence individual health behaviors [24]. CommitFit uses social ranking by allowing users to earn points through daily health behavior logging and self-selected goal achievement and then ranking users on a leaderboard based on these points.

Financial incentives or paying participants who achieve a predetermined goal in an effort to make the task more attainable [25] is another BE approach that has successfully increased physical activity [26] and resulted in short-term weight loss in adults [24]. mHealth apps offer a convenient and effective modality to evaluate BE concepts [27]. What remains to be ascertained is whether these concepts can be operationalized in an intervention aimed at modifying health behaviors, and whether adolescents and caregivers will use the mHealth app for a duration sufficient to enact meaningful health behavior changes.

Study Aims

The aims and hypothesis are as follows.

- Specific aim 1: Evaluate the effectiveness of behavior change in adolescents using CommitFit for 3 months

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(primary outcome) compared to the waitlist usual care, and at the 4-month follow-up.

- Hypothesis 1: Compared to the waitlisted usual care group of adolescents, CommitFit users will have a greater improvement in their health behaviors at 3 months, and at the 4-month follow-up.
- Specific aim 2: Evaluate the effectiveness of behavior change in adult caregivers using CommitFit for 3 months (secondary outcome) compared to the waitlist usual care group, and at the 4-month follow-up.
- Hypothesis 2: Compared to the waitlisted usual care group of adult caregivers, CommitFit users will have a greater improvement in their health behaviors at 3 months, and at the 4-month follow-up.
- Specific aim 3: Evaluate the effectiveness of financial incentives (cash per point) to increase the frequency that adolescents log in and achieve their health behavior goals.
- Hypothesis 3: The CommitFit user group with the additional financial incentives (CommitFit$) will have a higher frequency of logging and achieving their health behavior goals compared to the group without incentives (CommitFit).

Methods

Study Design

We planned to conduct the 3-arm RCT with a total of 30 adolescents and 30 adult caregivers (30 dyads) of all weights at baseline. Participants were randomized into 3 arms, each with 10 dyads: CommitFit, CommitFit$ with an extra financial incentive, and waitlist control. The CommitFit intervention groups were encouraged to use the app consistently for 3 months. Adolescents in the CommitFit$ group were paid US $0.05 for each point they earned in the app, which the CommitFit group did not receive. After 3 months, both CommitFit groups had the option to continue to use the app if they chose but without extra financial incentives or encouragement from the research team. All participants returned for a 4-month visit, after which, control participants were given the option to download and use CommitFit (waitlist control; Figure 1).

Figure 1. CommitFit randomized controlled trial.

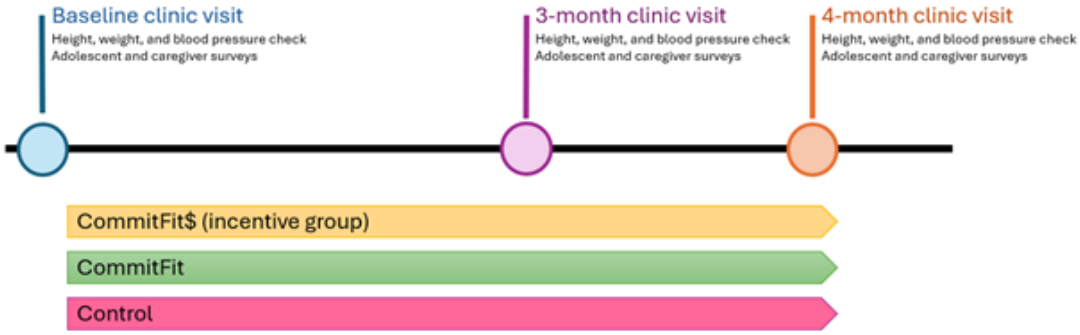

Study Setting

The study was conducted at the University of Missouri outpatient primary care clinic during after-school and work hours (from 4 PM to 7 PM). One of the principal investigators (AB) practices family medicine at this clinic and was able to obtain the support of clinic staff, nurses, leadership, and clinicians to conduct the study at this location. The initial enrollment visit (baseline) and 3- and 4-month follow-up visits all took place in private clinic exam rooms at this clinic with stadiometers, weight scales, and sphygmomanometer (blood pressure machine).

The CommitFit app, secured server, and user data analytic software were fully programmed and tested before and during the study with no major malfunctions. The principal investigators met with IT security and compliance officers to develop a plan regarding Health Insurance Portability and Accountability Act (HIPAA) compliance and IT security.

Participants

The inclusion criteria for both caregivers and adolescents are as follows.

- Aged 13-15 years (adolescent) or over 18 years (adult caregiver)
- Speak English fluently and able to read at the sixth grade level or higher
- Self-reported proficiency with iOS Apple devices (eg, iPhone or iPad)
- Access to email for survey data collection (caregiver)

The exclusion criteria are as follows.

- Previous or current diagnosed eating disorders (adolescents or adult caregivers)
- Participants with self-reported severe or uncontrolled anxiety or depression (adolescent only; Participants with mild or controlled anxiety or depression were not excluded)

Recruitment

After obtaining a HIPAA waiver, researchers generated a patient list of adolescents aged 12-15 years followed by the University of Missouri family medicine and pediatric primary care physicians (PCPs) at the clinic. PCPs screened their list and removed any adolescents they did not believe would be appropriate for the study. All further recruitment was done by research staff to reduce the burden on clinicians and clinic staff. Adolescents who met age inclusion criteria and approval from PCPs and had their caregiver's contact information in their electronic health record were emailed and then called (up to twice) by research staff to inform them of the study. An

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additional screening was conducted over the phone. Interested dyads who met screening criteria after the phone screening were scheduled for a baseline intake visit in the clinic where they completed informed consent and assent and enrolled in the study (Figure 2).

Figure 2. Research flowchart. PCP: primary care physician.

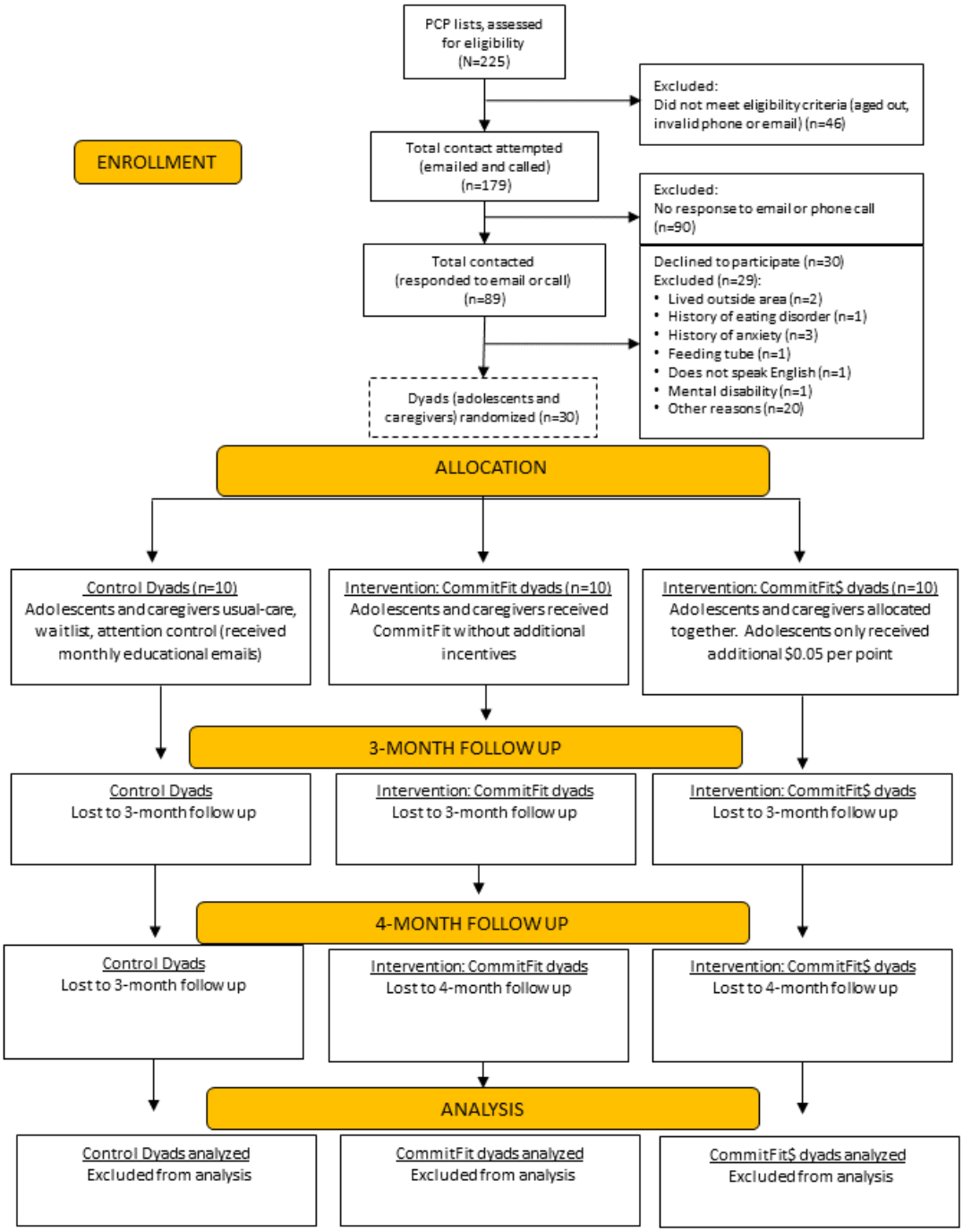

Allocation

After being consented, adolescents were randomized into 1 of 3 arms (CommitFit, CommitFit$, or waitlist control groups) by selecting an opaque envelope with the assignment group printed on a piece of paper. Caregivers were assigned to the same arm as their adolescent, although caregivers did not receive the extra financial incentives (US $0.05/point) in the CommitFit$ group.

Study Procedure

At each clinic visit, all adolescents and caregivers had their height, weight, and blood pressure (BP) recorded by the study team in private exam rooms or conference rooms. Nurses and health care providers provided the research staff with training on how to measure accurate blood pressures and weights on the clinic's equipment, which included Seca stadiometers and scales (model 2841300109) and Welch-Allyn sphygmomanometers. The study team used the American Heart Association protocol [28] for checking and rechecking BP when indicated. BPs were

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checked with participants' feet flat on the floor, after they had been sitting for several minutes, using an appropriately sized upper arm cuff with the BP cuff at heart level. Adolescent or adult participants with values consistent with stage 1 hypertension (≥130/≥80 mm Hg) [28] were notified by one of the principal investigators (AB), who is also a family medicine physician, and encouraged to follow up with their PCP. The PCPs were also contacted by the principal investigator (AB) to notify them of the elevated BPs.

In addition, participants completed electronic (via REDCap, Vanderbilt University) or paper surveys (Table 1) at each clinic visit. The caregivers and PCPs of adolescents who reported moderate or severe anxiety (score of greater than 10) on the 7-item General Anxiety Disorder [29] scale were notified by the principal investigator (AB) to follow up.

Table 1. Outcome measures.

Domain and measurement	Items, n	Respondent	Baseline	1 month	2 months	3 months	4 months
Anthropometrics							
BMI%/BMI (height, weight)	2	Caregiver and adolescent	✓			✓	✓
Blood pressure	1	Caregiver and adolescent	✓			✓	✓
Health behaviors							
5 CommitFit behaviors	5	Caregiver and adolescent	✓	✓	✓	✓	✓
Modifiers							
Demographics		Caregiver and adolescent	✓				
Behavioral economics survey	5	Caregiver and adolescent	✓				
Gamification survey	7	Caregiver and adolescent	✓				
Health psychology surveys							
GAD-7[a]	7	Adolescent	✓			✓	✓
PedQL[b]	11	Adolescent	✓			✓	✓
Reasons for health	9	Adolescent	✓			✓	✓
CommitFit surveys							
CommitFit use	8	Caregiver and adolescent, intervention groups only				✓	
Commercialization	6	Caregiver and adolescent, intervention groups only				✓	

[a]GAD-7: 7-item General Anxiety Disorder.

[b]PedQL: Pediatric Quality of Life Inventory.

CommitFit mHealth App

The CommitFit app (Figure 3) uses gamification techniques to motivate adolescents and caregivers to set and achieve health behavior goals. An in-app tutorial teaches users how to choose a health behavior goal (eg, eat more fruits or vegetables, increase water intake, decrease sugary beverage intake, increase physical activity, or increase overnight sleep), set a time period for that goal, and set a target amount (level) within that goal behavior. The app asks for the user's current level of the specific targeted behavior and makes a modest recommendation to set the behavior goal 2 levels above their current level. For example, an adolescent who reported consuming no fruits or vegetables currently per day would be recommended to consume 2 servings of fruits or vegetables per day. Users are not required to follow this recommendation; however, they must set a behavior goal level equal to or higher than their current level but below a maximum threshold based on current clinical and evidence-based guidelines [30], aiming to prevent excessive behaviors. Users can choose up to 2 health behaviors to work on at once and can work on the same goal multiple times during the study period if they choose. Once a health behavior has been optimized (the user has chosen and achieved the recommended level for that health behavior for 2 goal periods), the user will be required to choose a different goal. The user can choose to work on a goal for 1, 2, 3, or 4 weeks. They will receive a reminder, which can be turned off or modified, in the morning and afternoon to log their health behavior. Users receive 1 point for each daily goal they log, an extra 1 point if they achieve the user-selected goal level, 6 points when they complete their goal period, and 10 points if they achieve, on average, the goal level at the end of the goal period. Users are then ranked by total points and points per week (to allow new users to be competitive). Families have the option to form teams and can also see their team points (averaged by 2 team members). Users earn CommitFit coins through the same methods which can be used to unlock gear and clothing (headphones and jewelry) for their customizable avatars (Figure 3). A variety of skin colors, hair textures, and style options for the avatars were intentionally included in the CommitFit app. In addition, CommitFit provides educational resources to support users in achieving their health

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behavior goals, and a weekly and monthly progress graph of their logged behaviors.

Figure 3. Selected screenshots of CommitFit app.

CommitFit Group

Ten of the adolescents and their caregivers were randomly selected to use the CommitFit app, as described above, with full use of gamification features such as points and leaderboard, but without extra monetary incentives. All groups were compensated US $50 e–gift cards, which were emailed to each adolescent and caregiver after each clinic visit. Participants in the CommitFit group were assisted in downloading the CommitFit app through the TestFlight service (Apple, Inc), guided through logging in, and were provided training in how to use the app, including picking their first goal, setting a behavior level and time period (1-2 weeks for the first time period), logging their behavior daily, and setting notifications. Participants were educated on the leaderboard, avatar, progress report, gear store, and resources. A handout was also provided to each family with instructions on the functions of the CommitFit app.

Participants in the CommitFit group were asked to use the app consistently for 3 months, and they were allowed to continue to use CommitFit before and after their 3-month visit if they were interested in doing so. However, app use after the 3-month visit was not emphasized. There were no penalties if they did not use the app for the entire duration or used it infrequently.

If participants did not have access to an iOS device, the study team provided them with 1 loaner iPad and charger per family at the first clinic visit. Participants were asked to return the iPad and charger at their 4-month clinic visit to receive their last e–gift cards.

CommitFit$ Group

Ten randomly selected adolescents and their caregivers used the CommitFit app just as the CommitFit group. In addition to the participant compensation of e–gift cards for completing clinic visits, adolescents in the CommitFit$ group received an extra US $0.05 for every point they earned using the app during the 3-month period. The maximum amount an adolescent can earn in a 3-month period is US $52.50 (equivalent to 1050 points). The purpose of this extra financial incentive is to evaluate if an external financial reward will provide enough motivation to encourage adolescents to log their daily health behaviors and achieve their health behavior goals. No extra financial incentives were given at the 4-month visit to determine how often the CommitFit$ adolescents would log and achieve their goals when the financial incentives were no longer provided.

The research team decided to provide additional financial incentives exclusively to the adolescents in the CommitFit$ group, rather than also to the caregivers. This decision was based on the likelihood that adolescents would be more motivated by such incentives. Additionally, there is a potential business model where caregivers could pay to incentivize positive health behaviors for their children. Further, we were interested to see how giving financial incentives solely to adolescents, not

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caregivers, would influence caregiver logging and goal achievement.

Control or Waitlist Usual Care Group

The control dyads (n=10, 30%) received monthly emailed handouts with healthy lifestyle recommendations that are available and provided as electronic or paper handouts in the primary care clinics as an attention control. Topics for these handouts included healthy fruits and vegetables, tips on physical activity for teens, tips on sleeping habits, and tips on healthy eating. All groups were instructed to continue their routine medical care. After the 4-month clinic visit, the waitlist control group was provided the link and assistance to download and use the CommitFit app, if desired.

Clinic Visits

Thirty dyads from all 3 arms (N=60) were scheduled to be seen for three research clinic visits: (1) baseline visit for screening, consent or assent, and randomization (caregivers completed a demographics survey for themselves and their adolescents at the baseline visit); (2) 3-month visit after CommitFit and CommitFit$ groups had used the app for 3 months; and (3) 4-month follow-up clinic visit.

Outcomes

Primary Outcome

Our primary outcome was to evaluate changes in the 5 health behaviors that were promoted in the CommitFit app (fruits or vegetables, water, physical activity, decreased sugary beverages, and sleep) in adolescents and caregivers. Between the initial baseline and 3-month clinic visit (at 1 month and 2 months), caregivers were emailed surveys for themselves and the adolescent to fill out which consisted of the 5 CommitFit target health behaviors. Adolescents and caregivers completed the CommitFit behavior surveys in person during the clinic visits at baseline, 3 months, and 4 months. This allowed for monthly assessments of CommitFit health behavior changes in adolescents and caregivers.

Secondary Outcome

Our secondary outcome was to determine if the additional financial incentives received by CommitFit$ groups increased user daily logging and achievement of their health behavior goal. These data were collected internally through user analytic software programmed by the research team. The research team received monthly reports of each activity conducted by each user including when a goal was set, what the goal was, each time the user logged a health behavior, and the level of that logged behavior. The research team was able to use this user data to determine the percentage of days the user logged at least 1 behavior (% logged) and the percentage of days the user achieved their self-selected health behavior goals (% goal achieved).

Additional Anthropometric Outcomes

Height and weight for the adolescent and caregiver were measured by the study team at their baseline and the 3- and 4-month clinic visits, and these were used to calculate BMI% for the adolescent and BMI for the caregiver. These metrics were used over other weight metrics because they have been shown to be highly correlated with adiposity change in children over time [31,32]. BP was also measured at each clinic visit for adolescents and caregivers.

Additional Surveys

At baseline, all participants completed behavior economics and gamification surveys created by the research team to evaluate the participants' self-awareness of potential motivating factors. Other mental health surveys included the 7-item General Anxiety Disorder, which evaluates symptoms of anxiety; the Pediatric Quality of Life Inventory, which assesses health-related quality of life [33]; and a Reasons for Health survey, which the research team created to evaluate adolescent's motivation to be healthy. These surveys were completed at baseline, 3 months, and 4 months by adolescent participants.

Ethical Considerations

Institutional Review Board Approval

This study was approved by the University of Missouri Health Science Institutional Review Board (2092610). This RCT has not been registered in a trial registry because it was not required by the funder based on the small sample size and exploratory nature of the study.

Minimizing the Risk of Harm

The harm associated with weight-based discomfort or eating disorders was minimized in the CommitFit app by focusing on behavior change strategies rather than weight or calorie restriction. CommitFit was programmed to set limits on health behavior goals to prevent extreme or unhealthy goal-setting and behaviors. CommitFit does not collect or display any personal or sensitive information from users. The risk of harm associated with undiagnosed or untreated anxiety or hypertension was mitigated by contacting the caregiver and the user's PCP.

The potential risk of harm from an accidental breach of personal health information and data was minimized by removing identifying information before analyzing, sharing, or publishing any results. We maintained the participant's data and participation status confidentially on a password-protected laptop and server. All potential risks were disclosed on the consent forms.

Consent

The study team obtained consent by having the caregiver review and sign consent forms for themselves and their child. Additionally, the adolescents reviewed and signed the child assent form for themselves. Initially, we attempted to obtain signed consent before the baseline clinic visit, via Docusign (Docusign, Inc). However, this was logistically challenging, and after the first few dyad clinic visits, all consents were obtained in-person at the in-person baseline clinic visit. This allowed the research staff to explain the study and answer questions in person. Participants were provided electronic copies and offered paper copies of all consent forms.

Compensation

All study participants (both adolescents and caregivers) each received a total of US $150 e–gift cards for full participation

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in the study. The planned study protocol was to provide two US $50 e–gift cards (one for the caregiver and one for the adolescent) to be sent to the caregiver's email after each of the 3 clinic visits. However, due to an administrative error, the first 2 rounds of e–gift cards (4 e–gift cards) were sent out after the first clinic visit. The study protocol was thus changed to require participants to attend the 3-month and 4-month clinic visits to receive their last two US $50 e–gift cards. Despite this protocol deviation, attendance at the 3- and 4-month clinic visits was still high.

Data Management

All surveys completed during clinic visits were either conducted on laptop computers directly into RedCap or, if this was not available, through paper surveys and then entered by research staff into RedCap. Monthly CommitFit health behavior surveys were generated and emailed through RedCap for months 1 and 2. Paper surveys and consent forms were stored in locked research or clinic offices and destroyed after being digitally stored. Results were stored and shared with the research team using password-protected Microsoft Teams folders on network-secured servers. All databases are HIPAA compliant. The principal investigator will maintain electronic copies of data that have been deidentified on password-protected, network-secured laptops for 10 years or until all related publications and submissions have been completed.

Data Analysis Plan

Descriptive statistics were used to examine baseline demographics and will be used to examine study outcomes over time. Chi-square analysis will be used to compare group differences for categorical outcomes and 2-tailed *t* test or ANOVA for continuous outcomes. Cronbach α will be used when evaluating the internal reliability of study-developed scales. All analyses will be conducted using SAS version 9.4 (SAS Institute).

Results

The research team successfully recruited and enrolled 30 dyads (60 total adolescents and caregivers) in 10 weeks (from August 2023 to October 2023) by emailing and calling 89 caregivers of PCP-approved adolescent patient lists, achieving a 33% recruitment rate. Data collection, including CommitFit user analytics, and statistical analysis of primary and secondary study outcomes are being conducted in the spring and summer of 2024. The results of this study are anticipated to be published in late 2024 and early 2025.

Discussion

Expected Outcomes and Potential Impact

The purpose of this study was to evaluate the effectiveness of the CommitFit mHealth app, which uses gamification and financial incentives to motivate sustained health behavior change in adolescents and adult caregivers. The results from this study will inform future mHealth lifestyle and adolescent and adult obesity interventions. It will help researchers and app developers design programs that appeal to users and sustain their attention and motivation long enough to result in sustained health behavior changes and improved health outcomes. This RCT was also designed to evaluate the influence of including an adult caregiver with the adolescent mHealth intervention.

Dissemination Plan

The results of the study will be disseminated through publications, presentations, and meetings with stakeholders. We will use contacts through our advisory boards and funders to identify key stakeholders to disseminate the results of this and future studies to facilitate the further development and dissemination of CommitFit. With the assistance of these stakeholders, we will identify additional funding and resources to support implementation and dissemination.

Limitations

This study has some limitations. Anthropometrics (BMI%, BP) were collected in the study. However, because most of the adolescents included in the study had a healthy weight at baseline (overweight or obesity was not an inclusion criterion in this study) and because of the small sample size, a significant improvement in these measurements is not anticipated in adolescents or caregivers. Our next fully scaled study will only include adolescents and caregivers with overweight or obesity and will be conducted for 6 months to evaluate the effectiveness of CommitFit to improve BMI over an extended period of time.

Two server errors occurred during the study, which caused the CommitFit app to be unusable. The first occurred around 1 month and another close to 3 months after the study had begun. The first server error lasted a few days and the second lasted a day. Within 8 hours of the server error occurring, all participants in the intervention groups were emailed regarding the malfunction, steps to mitigate it, and a request to physically log their health behaviors. After server errors were fixed and the app was running again, the study team sent a follow-up email to all participants in the intervention groups letting them know the app was working again and a request to email the study team their health behaviors so their total points could be recorded, and the appropriate financial incentives could be provided to the CommitFit$ adolescents at the end of the study. Because the server errors lasted a short time relative to the duration of the study (4/120 days) and because we manually recorded the logged health behaviors that participants emailed to the study team, we do not feel these server errors significantly affected data collection or the intervention; however, we will evaluate this when conducting primary analyses. The rapid and thorough response to the server errors seemed to be appreciated by the participants.

Strength

We attribute the high recruitment rate (N=60) in a short period of time (11 weeks) to a strong recruitment strategy. Two of the principal investigators are family medicine physicians with good relationships with the PCPs, nurses, and clinical staff where the study visits occurred. This helped to expedite the PCP approval of the prescreened adolescent recruitment list. Researchers also leveraged the relationship between the PCP and participants when recruiting them for the study. For this research strategy to be effective, trust must be maintained

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between the participant, the research team, and the PCP. Researchers should consider collaborating with clinicians for their clinical research studies.

Because it takes time for recruitment lists to be generated, for institutional review board amendments to be approved, and for study startups to occur, and because adolescents on the original list may age out of the inclusion age range, the research team found it useful to include adolescents a year younger than the inclusion criteria in the initial list (aged 12-15 years, rather than 13-15 years) and to check the adolescent's current age before contacting their caregiver for recruitment. Once the recruitment list was approved by the PCP, the research team found that the most effective recruitment method was to email caregivers, wait 2 days, then call them, up to twice. Including both the adolescent and caregiver in the study and providing both with compensation individually also seemed to increase recruitment.

This RCT will expand knowledge regarding the use of gamification and BE techniques including financial incentives to motivate health behavior change among adolescents and their caregivers. These results may offer new opportunities to parents or caregivers, health insurers, health care systems, and clinicians to motivate health behavior change in adolescents and caregivers, with the ultimate goal of preventing or reducing obesity and obesity-related diseases and morbidities. Additional gamification, BE, mental health surveys, and app use analytics included in the study may provide additional insights into the characteristics of adolescents or caregivers who would most benefit from using a gamified mHealth app like CommitFit.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AB conceptualized the study and wrote the initial draft of the manuscript. AB, PG, EM, CL, JG, MP, KK, CG, KTB, and RJK contributed to the design and development of the study and the design and programming of the CommitFit app. AB, PG, EM, and NH recruited participants, conducted the study, and contributed to the initial drafts of the manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Editorial Notice

This randomized study protocol was not registered, explained by authors that it was not required by the funder based on the small sample size and exploratory nature of the study. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials, because the risk of bias appears low and the study protocol was considered formative and exploratory. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness.

Multimedia Appendix 1
Peer review report by the Oversight Committee - University of Missouri (MU) Coulter Biomedical Accelerator (USA).
[PDF File (Adobe PDF File), 205 KB - resprot_v13i1e63505_app1.pdf]

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Abbreviations

BE: behavioral economics
BP: blood pressure
HIPAA: Health Insurance Portability and Accountability Act
PCP: primary care physician
RCT: randomized controlled trial

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Protocol

Quantification of Urinary Exosomal Prostate-Specific Antigen for the Diagnosis of Prostate Cancer Using Clinical Laboratory–Based Techniques: Protocol for a Case-Control Study

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Abstract

Background: Prostate cancer is the most common cancer in men and represents a major public health problem. The current method for the diagnosis or screening of prostate cancer is invasive and costly. There have been renewed and innovative studies searching for urinary biomarkers to aid in the diagnosis of prostate cancer, especially with technologies based on urinary exosomes. However, technologies based on urine exosomes usually need expensive machines such as an ultracentrifuge and they are difficult to standardize, which hinder their application in clinical laboratories. We have optimized and standardized the isolation of urinary exosomes with the precipitation method. We have found that urinary exosomal prostate-specific antigen (PSA) can be quantified by automatic Elecsys total PSA technique.

Objective: In this study, our objective is to utilize urinary exosomes from prostate cancer for the development of a test to aid in its diagnosis.

Methods: Exosomes from the prostate cancer cell line LNCaP was used to set up the technique. To analyze urine samples from patients, the methods include the collection of first-void urine using the Colli-Pee device, the isolation of urine exosomes using the optimized precipitation method, and the quantification of exosomal PSA by Elecsys total PSA.

Results: This will be a 2-year study. We will start including patients and controls in the last quarter of 2024. We expect the results to be published in the second quarter of 2027.

Conclusions: This is the first study to quantify urinary exosomal PSA using the Elecsys total PSA technique for the diagnosis of prostate cancer. This study emphasizes techniques that are suitable for implementation in clinical laboratories, which will facilitate the application of urinary exosomes to simplify and improve the diagnosis and screening of prostate cancer.

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KEYWORDS

liquid biopsy; urinary exosome; diagnosis; PSA; prostate-specific antigen; prostate cancer

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Introduction

With 50,000 to 70,000 new cases per year, prostate cancer is the most common cancer in men [1]. The current method for the diagnosis or screening of prostate cancer is based on a biopsy of prostate tissue following an elevated blood concentration of prostate-specific antigen (PSA; >4.0 ng/mL). This method has some drawbacks. Prostate tissue biopsy is invasive and painful with possible side effects for patients. PSA is not a specific marker for prostate cancer. In addition to prostate cancer, other factors can lead to an elevated PSA, including age, prostate infection, and benign prostatic hyperplasia. According to the PSA threshold (usually 4.0 ng/mL), its estimated sensitivity ranges from 67.5% to 80% and its estimated specificity ranges from 60% to 70% [2-4]. Consequently, 20% to 30% of cancers go undetected when only the PSA blood test is considered, and it is not feasible to perform prostate biopsies on a large number of patients. It is more worthwhile to improve the diagnosis and screening of prostate cancer.

Extracellular vesicles are characterized by a lipid bilayer membrane and are subcategorized into small extracellular vesicles (exosomes) and large extracellular vesicles [5]. The size of exosomes is between 30 to 150 nm. Exosomes form within multivesicular bodies and are then released into the extracellular medium by exocytosis [5]. Almost all cell types can secrete exosomes. Exosomes are involved in multiple processes of tumorigenesis and development, including the promotion of angiogenesis, differentiation and infiltration, regulation of immunity, and response to treatment [6,7]. They are widely present in bodily fluids, including blood, saliva, urine, breast milk, pleural fluid, and ascites [6,7]. Since exosomes carry tumor markers such as nucleic acids, proteins, and lipids, they can serve as a liquid biopsy to aid in the diagnosis of tumors.

Urine has the advantage of containing an abundance of exosomes. Because the prostate and urine are in close proximity, prostatic exosomes can be secreted into urine. The characterization of exosomes released by tumor cells and collected in urine could be a new tool to improve the diagnosis of prostate cancer. Recently, we used the exosomes isolated from the prostate cancer cell line LNCaP to set up the techniques. We have optimized and standardized the isolation of urinary exosomes with the precipitation method. We have found that the urinary exosomal PSA can be quantified by automatic Elecsys total PSA technique. Therefore, our objective is to utilize urinary exosomes from prostate cancer for the development of a test to aid in its diagnosis. We hypothesize that urinary exosomal PSA may be a new tool for the diagnosis of prostate cancer.

Methods

Overview and Study Design

This is a case-control, single-center study. The study team is composed of urologists, oncologists, and biologists from Centre Hospitalier Universitaire (CHU) Saint-Etienne, which is a public and university medical center for patient care and medical research. CHU Saint-Etienne supports medical research projects and provides complete administrative guidance and methodological aid to implement medical research. Before the project began, many meetings were held to discuss the methodological issues as well as administrative issues such as informed consent. Research assistants will be engaged in document collection and sample collection. The study scheme is presented in Figure 1.

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Figure 1. The study scheme. PSA: prostate-specific antigen.

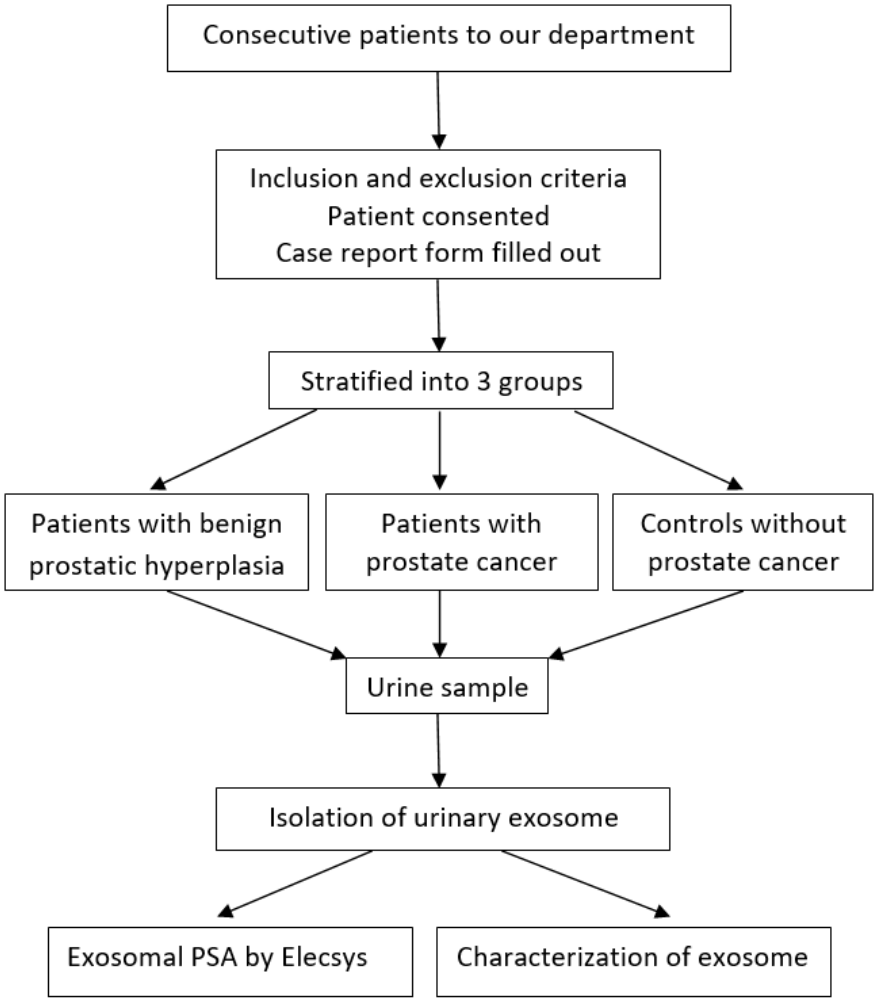

Primary Objective

The primary objective of this study is to quantify urinary exosomal PSA from prostate cancer with clinical laboratory–based techniques.

Secondary Objective

The secondary objective of this study is to compare the use of transmission electron microscopy (TEM), flow cytometry (FCM), and reverse transcription–quantitative polymerase chain reaction (RT-qPCR) for the detection of tumor urinary exosomes from patients with prostate cancer.

Primary End Point

The primary end point is to quantify urinary exosomal PSA.

Secondary End Point

The secondary end point is to compare the percentage of detection according to the different techniques (TEM, FCM, and RT-qPCR).

Inclusion of Patients With Prostate Cancer

Patients who meet the following criteria are eligible for inclusion into the group of patients with prostate cancer: (1) aged >50 years; (2) a positive biopsy for prostate cancer; (3) without urinary tract infection; (4) benefiting from social security; and (5) having accepted and signed the consent form.

Inclusion of Patients With Benign Prostatic Hyperplasia

Patients who meet the following criteria are eligible for inclusion into the group of patients with benign prostatic hyperplasia (BPH): (1) aged >50 years; (2) a histologically confirmed diagnosis of BHP; (3) without urinary tract infection; (4) benefiting from social security; and (5) having accepted and signed the consent form.

Inclusion of Controls

Patients who meet the following criteria are eligible for inclusion into the control group: (1) aged >50 years; (2) normal PSA levels; (3) no clinical evidence of BPH or prostate cancer; (4) prostate volume less than 30 cm^3; (4) without urinary tract infection; (5) benefiting from social security; and (6) having accepted and signed the consent form.

Exclusion of Patients and Controls

Patients meeting any of the following criteria are excluded from the study: (1) aged <50 years; (2) taking treatment or hormones known to modify the level of serum PSA in the 3 to 6 months preceding inclusion; (3) a urinary tract infection or history of prostate cancer; (4) history of invasive therapeutic procedures for BPH or for symptoms of urinary tract disorders within 6 months prior to inclusion; (5) a history of concurrent bladder

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or renal tumors in the 6 months preceding inclusion; and (6) no signature of the consent form.

Patient Procedure

After checking the inclusion and exclusion criteria, the study information leaflet will be given to patients. Patients will have a 1-hour reflection period. A 20-mL first-void urine sample will be collected using the Colli-Pee device in the department before oncological treatment. Urine collection corresponds to the end of a patient's participation in this study.

Urine Sample Processing

Urine samples are kept in refrigerator and processed within 24 hours after collection. Urine is centrifuged at 3000 g for 15 minutes at 4 °C to remove the exfoliated urinary cells. The supernatant is aliquoted and used for the isolation of urinary exosomes.

Isolation of Urinary Exosomes

To isolate urinary exosomes, 5 mL of the urine supernatant will be used. Urinary exosomes are isolated using the polyethylene-glycol (PEG)–based precipitation method. We have optimized the PEG-based technique for the isolation of urinary exosomes. After the adjustment of urine pH, a solution of PEG is mixed with urine. The mixture is incubated at 4 °C for 2 hours. The mixture is centrifuged at 4500 g at 4 °C to collect urinary exosomes. The exosome pellet is suspended in 200 µL of phosphate buffered saline (PBS) solution for the quantification of PSA.

Quantification of Urinary Exosomal PSA

In both exosomes isolated from the prostate cancer cell line LNCaP and those isolated from urine samples, the concentration of total PSA is determined in the automatic analyzer Cobas 8000 (Roche Diagnostics). In the Cobas 8000, total PSA is measured in a c602 module using Elecsys total PSA reagent kits based on electrochemiluminiscent immunoassays in a "sandwich" configuration. The concentration of total PSA is expressed in µg/mL.

Urinary Exosome Characterization

We will characterize urinary exosomes using TEM, FCM, and nanoparticle tracking analysis. TEM is performed on the exosome pellets, which are suspended in PBS. A 10-µL urinary exosome suspension is placed on 200 mesh copper grids (AGS138; Oxford Instruments) and allowed to adhere for 20 minutes. The excess sample is wicked off using a piece of filter paper. The grids are washed 3 times with distilled water. The grids are incubated with a drop of staining solution Uranyless (Delta Microscopy) for 20 seconds and blotted with a filter paper. The urinary exosomes are observed at an accelerating voltage value of 100 kV using a Hitachi electron microscope (H800; Hitachi).

For FCM analysis, the technique uses Aldehyde/sulphate latex beads (A37304; ThermoFisher). First, 1 µL of Aldehyde/sulphate latex beads is added to 100 µL of exosome suspension and mixed well. Second, 900 µL of PBS is then added, and the mixture is incubated for 2 hours at room temperature on a rotary wheel. Third, 100 µL of 100 mM glycine is then added, and the mixture is incubated at room temperature for 30 minutes. The mixture is then pelleted by centrifugation at 2650 g for 5 minutes, and the supernatant is removed. The pellet is washed by the addition of 1mL PBS+0.5% fetal bovine serum solution. The mixture is centrifuged at 2650 g for 5 minutes. Finally, the pellet is resuspended in PBS, and the antibody of antihuman CD63-FITC (IM1165U; Beckman Coulter), CD81-FITC (B25329; Beckman Coulter), or CD9-FITC (IM1755U, Beckman Coulter) or the antibody of isotype control (A07795; Beckman Coulter) is added. The incubation with antibody is performed for 30 minutes in the dark. After twice washing with PBS, the staining is observed by using conventional FCM.

Nanoparticle tracking analysis for urinary exosomes is performed using NanoSight LM10 fitted with a 488-nm laser and 500-nm long-pass filter (Malvern Instruments). The urinary exosome sample is diluted in PBS to a final volume of 1 mL. The diluted sample is then injected into the laser chamber. Particle counts per mL and size distribution of particles in solution are collected and calculated.

Sample Size

To calculate the necessary number of patients with prostate cancer needed for inclusion, our hypotheses were as follows: 75% detection is considered insufficient (P0=0.75) and 90% is sufficient (P1=0.90), unilateral α=5%, and power=95%. Based on these assumptions, using the 1-step Fleming method, 65 participants are required. To verify the specificity, we will also include 65 patients with BPH and 65 controls.

Statistical Analysis

For quantitative analysis, the number of observations available, mean, SD, median, minimum, and maximum will be calculated and compared. For qualitative analysis, absolute and relative frequencies (expressed in percentages) will be calculated and compared. Sensitivity and specificity will be calculated. The area under the receiver operating characteristic curve will be determined.

Data Sources

The sponsor (via the research technicians or the investigators) aims to respond to any request for access to data within a maximum of 1 month. Furthermore, only personnel authorized by the sponsor (investigators, research engineers, and research technicians) and representatives of the health authorities will have access to this information.

Study data will be collected directly in observation notebooks. These data will be validated by the investigator, who will sign (electronically) the observation notebooks.

The information collected as part of this study includes (1) demographic data (age, gender, weight, and height); (2) medical history (stage and grade of cancer); and (3) results of different analysis techniques.

Missing data will need to be justified. Any correction made in the case report form must be traceable.

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Ethical Considerations

This study has received ethics approval by the ethics committee of CHU Saint-Etienne (IRBN262024/CHUSTE). No compensation will be provided to the participants.

Results

This will be a 2-year study. We will start including patients and controls in the last quarter of 2024. We expect the results to be published in the second quarter of 2027.

Discussion

The study of urinary markers for the diagnosis of prostate cancer is a renewed and innovative research area in the contemporary era [8,9]. Liquid biopsy using urinary exosomes is promising for the diagnosis of prostate cancer. According to recent studies, tumor can discharge more exosomes into bodily fluids. We expect the quantity of urinary exosomes from patients with prostate cancer to be significantly increased compared to that of controls. Therefore, the exosomal PSA level would be significantly increased in patients with prostate cancer. The increased exosomal PSA level may be a new tool for the diagnosis of prostate cancer. A recent study supports that the level of urinary exosomal PSA is increased compared to that of patients with BPH or normal controls [10]. However, to implement the urinary exosomal PSA testing into clinical laboratories, improvement or optimization is necessary for every step, such as urine collection, the isolation of urinary exosomes, and the quantification of urinary exosomal PSA. This study is the first one to optimize and standardize the precipitation method for isolating urinary exosomes.

This study presents some unique characteristics: the collection of first-void urine using a standardized Colli-Pee device, the isolation of urine exosomes using an optimized precipitation method, and the quantification of exosomal PSA by Elecsys total PSA. First-void urine is important because it contain more exosomes from the prostate. In this study, first-void urine is to be collected without digital prostate message, whereas a previously published study required a digital prostate message before the collection of urine [10]. At present, there has been no consensus on the isolation method. Methods that are suitable for clinical laboratories are preferable. In this study, we decided to adapt the precipitation method. The precipitation technique using PEG for the isolation of exosomes is considered suitable for clinical laboratories [11]. Many commercial kits such as the commercial ExoQuick kit use this technology. We have optimized and standardized the precipitation method to isolate urinary exosomes. We recently found that urinary exosomal PSA could be detected by the Elecsys total PSA automatic assay in a clinical laboratory. To the best of our knowledge, it is the first study to detect urinary exosomal PSA from prostate cancer using the Elecsys total PSA technique.

Urinary exosomes from prostate cancer express many tissue markers. The contents in urinary exosomes are relatively stable because of the protection by a lipid bilayer membrane. Many tumor markers including PSA, prostate-specific membrane antigen, and prostate cancer antigen 3 have been identified in urinary exosomes as being of potential interest [12-14]. Recent results show that urinary exosomes are particularly useful for those who need a prostate biopsy, that is, men with a PSA level between 2-10 ng/mL [15,16]. By avoiding unnecessary tissue biopsy, it is considered as a major advancement in the diagnosis of prostate cancer [15,16]. To characterize urinary exosomes from prostate cancer, we will use the RT-qPCR, FCM, and TEM techniques to study the exosomal markers. Conventional FCM seems to not be suitable for the detection of exosomes because of the size detection limit. For FCM, we will use the bead-assisted technique [17,18] and the classic technique of detection by FCM on a DXFLEX cytometer. The bead-assisted technique is interesting. The RT-qPCR technique is routine in clinical laboratories. We will perform RT-qPCR according to the TaqMan technique [17,18]. We have worked on cancerous exosomes in biological fluids for several years [17-22]. Recently, we have developed an immunostaining and TEM observation test to identify exosomes from clear cell kidney cancer [19]. We wish to use this technique to characterize tumor exosomes in the urine of patients with prostate cancer. In this project, we will use immunolabeling of exosomal and tumor biomarkers and observation of exosomes under TEM to further confirm our objective.

In conclusion, this is the first study to quantify urinary exosomal PSA using the Elecsys total PSA technique for the diagnosis of prostate cancer. This study emphasizes techniques that are suitable for implementation in clinical laboratories, which will facilitate the application of urinary exosomes to simplify and improve the diagnosis and screening of prostate cancer.

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Data Availability

The datasets generated and analyzed during this study are not publicly available to maintain participant confidentiality but will be available from the corresponding author upon reasonable request.

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Conflicts of Interest

None declared.

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Abbreviations

BPH: benign prostatic hyperplasia
CHU: Centre Hospitalier Universitaire
FCM: flow cytometry
PBS: phosphate buffered saline
PEG: polyethylene-glycol
PSA: prostate-specific antigen
RT-qPCR: reverse transcription–quantitative polymerase chain reaction
TEM: transmission electron microscopy

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Protocol

Effect of Semaglutide on Physical Function, Body Composition, and Biomarkers of Aging in Older Adults With Overweight and Insulin Resistance: Protocol for an Open-Labeled Randomized Controlled Trial

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Abstract

Background: Older adults with type 2 diabetes mellitus (T2DM) or prediabetes are at increased risk of adverse changes in body composition, physical function, and aging-related biomarkers compared to those with normal glucose tolerance. Semaglutide is a glucagon-like peptide 1 receptor agonist that has been approved for T2DM and chronic weight management. Although semaglutide is effective for weight loss and T2DM management, its effects on lean body mass, physical function, and biomarkers of aging are understudied in older adults.

Objective: This study aims to compare the effects of lifestyle counseling with and that without semaglutide on body composition, physical function, and biomarkers of aging in older adults.

Methods: This is an open-label randomized controlled trial. A total of 20 adults (aged 65 years and older) with elevated BMI (27-40 kg/m^2) and prediabetes or well-controlled T2DM (hemoglobin A_{1c} 5.7%-7.5%) are recruited, stratified by sex, and randomized 1:1 to one of 2 groups (semaglutide plus lifestyle counseling vs lifestyle counseling alone) and followed up for 5 months. Those in the semaglutide group are titrated to 1 mg weekly, as tolerated, for 12 weeks. Lifestyle counseling is given by registered dietitians and based on the Diabetes Prevention Program Lifestyle Change Program. Our primary outcomes include changes in lean mass, physical function, and biomarkers of aging. Body composition is measured by dual-energy x-ray absorptiometry and includes total fat mass and lean mass. Physical function is measured by 6-minute walk distance, grip strength, and short physical performance battery. Biomarkers of aging are measured in blood, skeletal muscle, and abdominal adipose tissue to include C-reactive protein, interleukin-6, tumor necrosis factors α, and β galactosidase staining.

Results: The study was funded in December 2021 with a projected data collection period from spring 2023 through summer 2024.

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Conclusions: Despite the elevated risk of adverse changes in body composition, physical function, and biomarkers of aging among older adults with glucose intolerance and elevated adiposity, the benefits and risks of commonly prescribed antihyperglycemic or weight loss medications such as semaglutide are understudied. This study aims to fill this knowledge gap to inform clinicians about the potential for additional clinically meaningful, nonglycemic effects of semaglutide.

Trial Registration: ClinicalTrials.gov NCT05786521; https://clinicaltrials.gov/study/NCT05786521

International Registered Report Identifier (IRRID): DERR1-10.2196/62667

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KEYWORDS

glucagon-like peptide; lean body mass; physical function; biomarkers of aging; semaglutide

Introduction

Background

Glucose intolerance affects many older adults in the United States with 49% having prediabetes and an additional 29% having type 2 diabetes mellitus (T2DM) [1]. The mechanisms that lead to age-related glucose intolerance and T2DM are unknown, but age-dependent decreases in β-cell function and insulin sensitivity are thought to be important in the deterioration of glucose homeostasis with age [2]. Unfavorable changes in body composition observed with aging can contribute to insulin resistance, including redistribution of fat from peripheral subcutaneous areas to a central location [3] and loss of lean muscle mass [4]. Overall, changes observed with aging appear to lead to glucose intolerance and T2DM.

Although T2DM complications are primarily thought of as nephropathy, neuropathy, and retinopathy, T2DM is associated with detrimental changes in physical function and body composition, and biomarkers of aging. A recent meta-analysis reports a 50%-80% increased risk of mobility disability; defined as walking speed, chair stand time, and balance test; for those with T2DM compared to people without T2DM [5]. In multiple longitudinal studies, older adults with T2DM have a greater decline in lean mass compared to those without T2DM [6-8]. Additionally, those with prediabetes compared to normoglycemia appear at increased functional risk [9]. These data suggest that insulin resistance, even in the early stages, is associated with adverse changes in body composition and physical function.

Historically, glycemic control has been the focus of T2DM management but the nonglycemic cardiovascular, renal, and weight benefits of some classes of antihyperglycemic agents lead to increased individualization of T2DM therapy regimen based on a patient's co-morbidities even after glycemic goals are reached. Semaglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist. GLP-1 receptor agonists use the physiologic action of the incretin GLP-1 to increase insulin secretion and suppress glucagon release in response to meals. These drugs reduce hemoglobin A_{1c} (HbA_{1c}) by 1.45%-1.55%, depending on dose [10,11]. Semaglutide additionally has nonglycemic benefits, including chronic weight management and reduction of cardiovascular events. A recent meta-analysis determined that semaglutide has an average weight loss of 12% with 54% of participants achieving at least 15% weight loss [12]. Currently, semaglutide is approved by the Food and Drug Administration not only for T2DM management, to decrease cardiovascular events in adults with T2DM, and for chronic weight management for those with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with at least 1 weight-related comorbidity Therefore, a significant portion of older adults may be prescribed GLP-1 receptor agonists considering that 29% of them have T2DM and 42.8% of them have a BMI of ≥30 kg/m^2 [1,13].

With significant weight loss resulting from semaglutide use, concomitant lean body mass losses may occur. However, the results on lean mass appear mixed, with most trials indicating that semaglutide results in reductions in total fat mass and lean mass with most of the weight loss resulting from fat mass loss [14-17], while others revealed that lean body mass remained stable [18-20]. The effect of semaglutide on physical function has been infrequently studied in older adults. One study found the preservation of grip strength [14] but have not evaluated other validated measures of function in older adults such as short physical performance battery and 6-minute walk distance. Additional measures of muscle quality such as histology and mitochondrial respiration have not been completed in humans. Of note, these trials have an average studied population younger than 65 years, limiting the ability to extrapolate the results to older adults. These data suggest a gap in the literature related to the effects of semaglutide on body composition and physical function in older adults.

Since semaglutide has positive changes in glycemic control, cardiovascular system, and weight management; there are possible changes to the aging process as well. Although there is no standard set of biomarkers to obtain for evaluation of aging, systemic interleukin (IL)-6, tumor necrosis factors α (TNFα), C-reactive protein (CRP), and GDF15 are proposed biomarkers that are used in geroscience guided clinical trials [21]. A process that contributes to aging is cellular senescence, which is a stable cell cycle arrest triggered in normal cells that can lead to impaired tissue regeneration and chronic age-associated disease [22]. Cellular senescence can be detected by staining tissues for senescence-associated β-galactosidase and senescence-associated secretory phenotype [22]. Although semaglutide has not been widely studied, the class of GLP-1 receptor agonists shows evidence of improvement in CRP and TNFα [23] with 1 study indicating that CRP has a significant decline following 68 weeks of treatment with semaglutide [24]. Therefore, this underscores the necessity for further research in this field.

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Objectives

This study aims to (1) ascertain the potential ramifications of semaglutide on the lean mass profiles and physical functionality of individuals with prediabetes or T2DM and (2) to assess the impact of semaglutide on molecular biomarkers of aging in blood, adipose, and skeletal muscle tissues. We hypothesize that semaglutide will induce favorable alterations in body composition, particularly for lean and adipose body mass quantified via dual-energy x-ray absorptiometry, and improve physical function, as assessed by metrics such as the short physical performance battery, handgrip strength, and walking speed. Additionally, clinical changes are associated with positive changes in systemic and tissue-specific biomarkers of aging.

Methods

Trial Design

This is a randomized, open-label pilot study. The institutional review board is notified of any deviations from the approved protocol or breaches of confidentiality.

As shown in Table 1, this study involves 8 visits, which include screening and baseline assessments (visit 1 and visit 2), randomization (visit 2), intervention follow-up (visits 3-5), end-of-study assessments (visits 6a and 6b), and a postintervention telemedicine follow-up visit (visit 7). The intervention phase occurs over 20 weeks. Participants are contacted before in-person visits to ensure they are able to attend or reschedule if needed. All in-person visits are conducted at the Sam and Ann Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio.

Table 1. Schedule of events.

	Screening	Intervention start, T=0 week	T + 3 weeks (±7 days)	T + 7 weeks (±7 days)	T + 11 weeks (±7 days)	T + 20 weeks (±7 days)	T + 20 weeks (±7 days)	T + 21 weeks (± 7 days)
Visit	V1	V2	V3	V4	V5	V6a[a]	V6b[a]	V7
Medical history and physical exam	X					X		
Vitals, anthropometric measurements	X	X	X	X	X	X	X	
Clinical labs	X					X		
Randomization		X						
DXA[b] scan	X					X		
ECG[c]	X							
SPPB[d], grip strength, 6-minute walk	X					X		
Surveys (SF-12[e], CNAQ[f])	X					X		
Blood, muscle, and adipose biopsy		X					X	
Start of semaglutide for treatment group		X						
Semaglutide dispensed to treatment group		X	X	X	X			
Lifestyle education		X	X	X	X			
Assessment of adverse events		X	X	X	X	X	X	X

[a]Visits 6a and 6b are the end-of-study visits but are split into 2 visits.

[b]DXA: dual-energy x-ray absorptiometry.

[c]ECG: electrocardiogram.

[d]SPPB: short physical performance battery.

[e]SF-12: Short-Form 12.

[f]CNAQ: The Council on Nutrition Appetite Questionnaire.

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Participants and Inclusion and Exclusion Criteria

The study is recruiting 20 older adults from San Antonio, Texas. Overall, for this pilot, our population is generally healthy older adults who are eligible to receive semaglutide for either indication of T2DM or chronic weight management. The inclusion criteria are as follows: (1) men and postmenopausal women; (2) aged 65 years and older; (3) BMI: 27-40 kg/m^2; (4) HbA_{1c} 5.7%-7.5% or fasting blood glucose greater than 100 mg/dL; (5) community-dwelling; (6) willingness and ability to comply with protocol requirements. The exclusion criteria are as follows: (1) glomerular filtration rate≤29 mL/min/1.73 m^2 [25]; (2) hematocrit≤33%; (3) thyroid stimulating hormone>7 mIU/L with abnormal free thyroxine; (5) use of medications known to lower blood glucose besides metformin; (6) history of cardiovascular events; (7) systolic blood pressure≥170 mm Hg or diastolic blood pressure≥95 mm Hg; (8) active inflammatory, autoimmune, infectious, hepatic, gastrointestinal, malignant, or uncontrolled psychiatric disease; (9) ≥5% change in weight during the 3-month period prior to screening; (10) personal or family history of medullary thyroid cancer [26]; (11) personal or family history of multiple endocrine neoplasia syndrome type 2 [26]; (12) previous history of pancreatitis [26]; (13) electrocardiogram with QTc prolongation (QTc>470 ms in men or >480 ms in women) or evidence of ischemic changes; (14) personal history of diabetic retinopathy [26]; (15) allergy to semaglutide; and (16) type 1 diabetes or other insulin dependent diabetes. Individuals who initially fail their initial screening are eligible to be rescreened 12 weeks after their initial screening.

Recruitment

Recruitment methods include electronic medical records and Barshop Call Center Registry queries, community engagement activities, and web-based advertisements (including social media). Potential participants undergo a prescreening questionnaire to ensure they meet the inclusion and exclusion criteria for enrollment. Those who qualify from the prescreening questions are scheduled for a full in-clinic screening evaluation and sent an advance copy of the consent form.

Screening

We conduct an in-clinic evaluation consisting of medical and social history, current medications, vital signs, anthropometric measurements, and physical examination. Additionally, a fasting blood profile is collected to assess a complete metabolic panel, complete blood count, HbA_{1c}, thyroid stimulating hormone, and coagulation panel. Body composition analysis, evaluation of physical function, and completion of patient-reported measures, as detailed below, also are carried out during this visit.

Baseline and Postintervention Assessment Measures

Assessments are performed at baseline (screening or visit 1) and the end of the study (visits 6a and 6b) for both groups (Textbox 1).

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Textbox 1. Study assessment measures.

Laboratory tests

Clinical labs: After fasting overnight, whole blood is collected for the assessment of complete blood count, comprehensive metabolic panel, hemoglobin A_{1c}, lipid profile, thyroid stimulating hormone, prothrombin time, and partial thromboplastin time.

Research laboratories: After fasting overnight, a credentialed research team member obtains blood, skeletal muscle, and abdominal adipose samples. Blood is drawn by staff well-versed in phlebotomy to reduce the number of attempts needed for venipuncture. Vastus lateralis muscle biopsy are obtained with a Bergstrom needle after location anesthesia is achieved. Assessments of inflammation and cellular senescence in muscle, adipose tissue, and blood samples are conducted within the clinical research unit. In adipose tissue, we perform staining for β-galactosidase [27]. For muscle tissue, histological processing and measurement of mitochondrial respiration are carried out immediately, followed by freezing additional tissue for the analysis of interleukin (IL)-6, tumor necrosis factor α (TNFα), TNFα receptors 1 and 2, p12, and p16 concentrations. We also investigate changes in SIRT1 activity within muscle tissue. Plasma samples obtained from whole blood are used to measure concentrations of IL-6, TNFα, and C-reactive protein.

Anthropometric measurements

BMI: Weight is measured on a standard, calibrated scale at baseline and throughout the study without shoes and with light clothing. Standing height (cm) is measured using a stadiometer at screening. BMI is calculated as weight (kg)/ height (m^2).

Waist circumference: Waist circumference is measured with a tape measure at the level of the iliac crest.

Body composition: dual-energy x-ray absorptiometry scans are used to measure whole-body adipose and lean mass and total bone mineral density.

Physical function

Short physical performance battery: A standardized and validated assessment developed by the National Institute on Aging for use in the Established Population of the Epidemiologic Studies of the Elderly, which is used to evaluate the physical function of older adults independently from their self-reported abilities [28]. The tests fall under 3 categories: balance, gait speed, and chair stand tests. The entire battery of tests can be finished within 10-15 minutes. The administrator begins by demonstrating all the activities to the participant. The balance assessment comprises side-by-side, semitandem, and tandem stands. The gait speed test involves walking along a 4-meter path at their usual pace, repeated twice. Finally, participants are assessed on their ability to rise from a chair without arm assistance, followed by completing 5 timed chair rises. The maximum score is 12. We will classify a score <10 as an increased risk of all-cause mortality [29].

Grip strength: Hand grip strength of both the dominant and nondominant arms ware assessed using a handheld dynamometer [30]. The participant's hand grip strength is assessed and the average grip strength from the 3 trials recorded. This test takes less than 5 minutes. Grip strength for women <16 kg and men >26 kg will be classified as at risk [31].

6-minute walk: Participants are asked to walk as quickly as they can, for as many times as they can over a 40-foot track for a total of 6 minutes. The total distance walked is obtained [32]. Values will be compared to normative values for healthy older adults: 367 m for women and 400 m for men [33].

Patient-reported outcomes

The Council on Nutrition appetite questionnaire (CNAQ): Validated as an evaluation of appetite in older adults to predict anorexia before weight loss [34]. The CNAQ consists of 8 items within a single domain, with responses rated on a 5-point scale. The total score is calculated by summing the scores of all 8 items, ranging from 8=indicating the poorest appetite to 40=indicating the best appetite.

The Short- Form 12: A validated tool for assessing health-related quality-of-life in older adults. A higher score indicated better health with a score of 50 indicating the average score in the general US population [35].

Intervention

Randomization

Eligible participants are randomized to either the lifestyle counseling group (control) or the semaglutide with lifestyle counseling group (1:1) after their blood draw and muscle and adipose biopsies during visit 2. Randomization is performed by the principal investigator at the end of the visit 2 through tables that were stratified by sex in sequential order at the time of randomization. A total of 10 participants are to be enrolled in each group, with 20 overall enrolled. Due to cost restrictions, placebos are not used, and the principal investigator and the participants are unblinded.

Lifestyle Counseling

All participants meet with a registered dietitian for an hour-long diet, exercise, and behavior modification sessions at visits 2-5. When in-person classes are not feasible, web-based sessions are made available. Behavior modification is based on the Diabetes Prevention Program Lifestyle Change Program [36]. Aligned with the Diabetes Prevention Program participants receive instructions for changing their dietary composition based on the US Department of Agriculture's MyPlate guidelines, which focus on fruit, vegetables, low-fat dairy, and whole grains. MyPlate reinforces small feasible and affordable changes that result in sustainable eating patterns that promote good health [37].

Participants are given detailed written and verbal instructions to achieve these guidelines. During these sessions, education materials are provided on budget-friendly nutrition for optimal aging: nutrition basics (ie, healthy dietary patterns, calorie balance, food labels, and hydration), recipe modification, and mindful eating. In addition, based on the American College of Sports Medicine physical activity recommendations (duration, intensity, and mode) participants are encouraged to perform moderate-intensity physical activity at least 150 minutes per week [38]. Physical activity instruction also focuses on how to

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safely exercise in their home environments. We also cover topics based on participants' questions, which we anticipate may include managing common comorbidities (ie, sleep behaviors, preventing and managing diabetes, avoiding excessive sitting, and managing stress), and available community resources. At each follow-up lifestyle session, weight is obtained, and previously made goals are assessed to determine success or additional modifications required to achieve goals.

Semaglutide

Participants are given verbal and written instructions on appropriate preparation and subcutaneous injection of semaglutide are self-administered once a week. At visit 2, a semaglutide pen that administers 0.25-0.5–mg dose is provided and participants are monitored as they self-administer their first dose of 0.25 mg. They continue semaglutide 0.25 mg for additional 3 weeks, then increase as tolerated to 0.5 mg on visit 3 for 4 weeks, and 1 mg once a week on visit 4 for 4 weeks and continue 1.0 mg on visit 5 for an additional 8 weeks. The titration planned is as follows: complete 4 weeks of 0.25 mg, 4 weeks of 0.5 mg, and 12 weeks of 1.0 mg. If titration is not tolerated, then the participant is kept on the tolerated dose for a longer period with a retry of the higher dose at the next visit.

At each visit, participants are given a semaglutide pen, along with a schedule for the date of the next planned self-administered injection. Participants are asked to bring their study medication to every visit to determine if the appropriate weekly dose has been administered. Participants are withdrawn from the study for noncompliance with semaglutide injections or inability to increase the weekly dose.

Statistical Analysis

The primary outcomes include changes in lean mass, 6-minute walk distance, grip strength, and short physical performance battery after the 20-week intervention between the semaglutide and lifestyle compared to lifestyle alone groups. We use intention-to-treat principles per the Consolidated Standard of Reporting Trials for analysis [39]. Experimental results are expressed as means (SEM). Comparisons of means between groups are performed by analysis of variance for repeated measures and general linear model are used to add covariates. Associations, within a group, between aging-related biomarkers versus body composition and physical function outcomes are determined by Pearson correlation. For tests of correlation coefficients between groups, we use Fisher *Z* transformation. Multiple regression analysis was used to determine the relationship between aging-related biomarkers and body composition and physical function outcomes. Covariates include age, sex, ethnicity, and BMI. Alpha equal to .05 is used to determine significance. We plan for 20 participants, 10 per group, to accomplish this pilot study within the funding mechanism timeframe. The data generated through this study are used to guide sample size and power calculations for further studies. The Biostatistics Core of the San Antonio Claude D Pepper Older Americans Independence Center is assisting with statistical analyses. Planned software analysis program is SAS (version 9.4; SAS Institute).

Monitoring Adverse Events

Adverse events are assessed during set interactions with the participants. This includes in-person visits at the research facility and a telemedicine encounter during visit 7. They will also be provided with information on how to contact the research team if they have concerns about medication adverse reactions between visits. All adverse events are logged and reported to the institutional review board. Additionally, adverse events are reviewed by a medical doctor to determine the severity, the event's relationship to the study intervention, and what action should be taken.

Data Management

Each participant is assigned a study code not associated with their name. Data are saved and stored using REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data management system, which is a secure, password-protected, local area network hosted at the University of Texas Health Science Center at San Antonio. Participants' charts, which will include all the visits' documents, are kept inside a locked cabinet located in the clinical research space.

Ethical Considerations

The study is approved by the University of Texas Health Science Center San Antonio institutional review board (20220256HU) in accordance with the ethical standards of the responsible committees on humane experimentation and the Declaration of Helsinki. Eligible participants sign the informed consent after a research staff member has explained the study and answered all questions. Participants may choose to leave or opt out of the study at any time without penalty. Participants receive compensation for their time up to US $425 through a ClinCard if all visits are completed. Privacy and confidentiality are maintained by having only authorized research staff accessing patient health information, keeping participant files in a locked cabinet, and providing access to REDCap to the minimum authorized research staff. The study is registered with ClinicalTrials.gov (NCT05786521).

Results

The study was funded in December 2021, with a projected data collection period lasting from Spring 2023 through Summer 2024. Data analysis and results are aimed to be published in late 2024.

Discussion

Summary

The purpose of this study is to investigate the effect of semaglutide in addition to lifestyle counseling compared to lifestyle alone on body composition, physical function, and systemic and local biomarkers of aging. We hypothesize that semaglutide therapy will improve body composition and physical function and that these clinical improvements are supported by positive changes to biomarkers of aging.

GLP-1 receptor agonists are a relatively novel group of antihyperglycemic agents that are prescribed in increasing

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frequency [40]. Thus far, glycemic control, cardiovascular benefits, and whole-body weight reduction have been observed in people treated with semaglutide [10,11,41]. The majority of studies on GLP-1 receptor agonist use suggest a loss of lean mass, though this is not universally observed [18,19]. With the popularity of these medications, the additional effects on health parameters especially important to older adults such as function and lean body mass need to be thoroughly evaluated.

Although there have been few studies examining the effect of semaglutide on measures of health span in older adults, several preclinical studies have been conducted. Semaglutide treatment in obese mice resulted in an increase of type I/II muscle fibers, muscle fiber density, mitochondrial mass, and decline of TNFα, IL6, and IL-1β compared to untreated obese mice, resulting in the semaglutide-treated mice having a muscle quality similar to the nonobese control group [42]. In a mouse model of sarcopenic obesity, where mice were fed a high-fat diet, treatment with semaglutide led to enhancements in muscle strength, muscle fiber characteristics, and markers of muscle atrophy when compared to mice that did not receive treatment. [43]. The improvements in muscle quality and strength seen with semaglutide may be through the SIRT1 pathway, which is a key regulator of skeletal muscle biology and function. SIRT1 has also been associated with the ability of GLP-1 receptor agonists to improve hepatic steatosis and skeletal muscle insulin resistance [44,45]. This study intends to add to this mechanistic research by providing an insight into the effects of semaglutide on biomarkers of aging. These findings may be especially relevant to older adults as clinical targets for future evaluation and potential intervention.

Limitations

Although this is a randomized controlled trial, there are potential limitations. As this is an open-label trial, the lack of blinding can lead to ascertainment bias [46]. The small sample size for this pilot may lead to a type II error. Given the 5-month duration of the trial, it is possible that maximum weight loss may not be attained. Consequently, we lack a comprehensive understanding of the full impact of this class of medication under conditions of maximum weight loss.

Conclusions

Based upon the known glycemic, cardiovascular, and body weight loss effects of GLP-1 receptor agonists in the treatment of T2DM and chronic weight management, we are conducting a clinical trial to expand this work by examining the effects of semaglutide on body composition, physical function and biomarkers of aging in older adults with prediabetes and well-controlled T2DM. This study fills a significant gap by focusing on the effect of frequently used medication in older adults and infrequently studied outcomes of clinical significance in this population. The findings will serve as valuable insights for future research endeavors, potentially shaping the treatment approaches using GLP-1 receptor agonists among older adults.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed for this article. The data sets analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

TMC, LV, and RR wrote the initial draft of the manuscript. All authors have reviewed and edited the manuscript. All authors have approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from San Antonio Older Adult Independence Center .
[PDF File (Adobe PDF File), 205 KB - resprot_v13i1e62667_app1.pdf]

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Abbreviations

CRP: C-reactive protein
GLP-1: glucagon-like peptide 1
HbA1c: hemoglobin A1c
IL: interleukin
REDCap: Research Electronic Data Capture
T2DM: type 2 diabetes mellitus
TNFα: tumor necrosis factors α

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Protocol

Education Program for Enhancing Health Care Students' Attitudes Toward People Living With Dementia: Protocol for a Single-Arm Pre-Post Study

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Abstract

Background: Health care students are instrumental in shaping the future of dementia care. Cultivating a positive attitude and understanding toward people living with dementia is crucial for diminishing the stigma associated with the condition, providing effective and person-centered care, and enhancing the quality of life for people living with dementia. Educational programs about dementia are increasingly recognizing the potential of gaming tools.

Objective: This study aimed to evaluate the effectiveness of gaming-based dementia educational programs in improving attitudes toward people living with dementia among health care students.

Methods: This single-arm pre-post study will be conducted among health care students in Indonesian universities. This educational program based on gaming tools will consist of a lecture on dementia, the use of N-impro (gaming tool), and the enactment of short dramas depicting desirable and undesirable communication with people living with dementia behaviors. We will assess attitudes toward people living with dementia, intention to help people living with dementia, knowledge of dementia, and the stigma associated with people living with dementia. The gaming-based dementia education program will be integrated into the curriculum of the health care students. The program will be implemented once with a duration of 90 minutes.

Results: Data collection will occur from August 2023 to March 2024. Analysis of the data will be finalized by May 2024, and the outcome will be determined by July 2024. The impact of the gaming-based dementia educational program on improving attitudes toward people living with dementia will be reported. The study findings will be published in a peer-reviewed journal.

Conclusions: The gaming education program demonstrates significant potential in enhancing attitudes toward people living with dementia across various countries, introducing an innovative method for the community-based support of people living with dementia.

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KEYWORDS

ageism; dementia; health professional; education program; long-term care

Introduction

The global increase in the aging population has increased the number of people living with dementia [1]. In Indonesia, the adjusted weighted people living with dementia rate is 27.9%, indicating a potential population of over 4.2 million people living with dementia [2]. Consequently, global policies have been established to foster a "dementia-friendly" society [3,4]. Dementia-friendly initiatives aim to enhance the quality of care for patients with dementia [5]. Distinguishing ageism from carefully reasoned clinical decisions can be challenging [6]. Health care professionals such as medical doctors, public health workers, nurses, dentists, pharmacists, and nutritionists may inadvertently perpetuate ageism, as it can be deeply embedded in daily procedures. As a result, older adults may not receive the same level of care as younger patients [7]. Therefore, health care professionals must improve their ability to provide dementia care to address the diverse needs of older adults and combat ageism.

A previous study found that medical students had neutral attitudes toward older individuals and lacked knowledge about dementia [8]. Whereas, a study in Indonesia found low knowledge but high attitudes toward dementia among nursing students [9]. Bachelor's degree courses are offered to help health care professionals understand health care subjects, including holistic care for older adults with dementia. Health care students may struggle to care for older adults with dementia due to a lack of understanding of how to respond to specific symptoms of dementia and challenges in visualizing actual care scenarios [10]. Thus, it is necessary to pursue effective educational methods that enhance knowledge and attitudes toward older adults.

Health care professionals can provide quality care by combining integrated learning, critical thinking, and optimal decision-making skills. The integration of simulation into the educational process facilitates the attainment of this goal. A previous study has suggested that simulated education is beneficial for content that is challenging to convey through traditional classroom instruction [11]. One such method of simulation education is a gaming-based education program, which allows students to engage with and enjoy the learning process [12,13]. The implementation of dementia education through a game- and simulation-based program has been shown to effectively enhance knowledge and attitude toward dementia among health care students [14-17]. Therefore, an educational approach that introduces dilemmas through gaming, is needed [18].

In recent years, we have developed a dementia gaming-education program known as N-impro [19,20]. This program is designed to influence attitudes toward supporting older adults and foster community networks that promote an age-friendly environment within Japanese communities. Given the rapidly increasing demand for health care professionals and long-term care facilities to care for the older adults in Indonesia [21], the N-impro program will be adapted for health care students in Indonesia with necessary modifications to improve attitudes toward supporting older adults. Therefore, this study aims to assess the effectiveness of gaming-based dementia educational programs in enhancing health care students' attitudes toward people living with dementia.

Methods

Study Design

This study will use a single-arm pre-post design to assess the effectiveness of gaming-based dementia educational programs for health care students. The study will be conducted in collaboration with the Faculty of Health at an Indonesian University. The programs will be integrated into courses related to dementia care, such as the Gerontological Nursing Care course, the Psychiatric Nursing course, and the Health Assessment course. Participation in the study is open to all students in these classes. However, there will be no penalties for students who choose not to participate. The study will continue until participant inclusion is completed, which is anticipated to be around March 2024.

Participants and Settings

Participants in this study will be health care students at an Indonesian University. For this study, we will invite nursing and public health students. A participant must meet the following inclusion criteria: they must be a health care student enrolled in the semester for which we have designated the course for the implementation of this educational program. For instance, nursing students at Airlangga University will be selected from those in the fifth semester. While public health students are in the sixth semester, both are third-year grade health care students with class topics related to dementia. Prospective participants will be assigned a new ID number to ensure their student ID numbers remain confidential. The sample size was calculated using a power analysis for differences between two dependent means (matched pairs). The total sample size is 68 health care students with an effect size of d=0.5 (Reference from N-impro study: d=0.5, α=0.05, power=0.80). In conducting a matched pair t test analysis, this study will collect sufficient data from the participants; the sample size will exceed the calculated sample size.

This study will be conducted at Indonesian universities with health-based faculties. Health education activities will be implemented in various classrooms within the university. Each classroom will accommodate approximately 50 participants and will be equipped with chairs and tables to facilitate discussion. The classrooms will be divided into 4 parts, each comprising up to 10 chairs.

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Recruitment

Prospective participants will be identified using information from the e-learning portal of the university. We will document the data of the students enrolled in the designated course for the execution of this educational program at the start of the odd semester for the 2023-2024 academic year. Individuals who meet the eligibility criteria will receive detailed communications about the study and invitations to participate in the program.

The course coordinator and principal investigator (PI) will comprehensively explain the learning plan or syllabus for the designated course at the beginning of the semester. Generally, an overview of the execution of the research session will be presented, and detailed research procedures will be presented shortly before the research begins. An announcement regarding the research implementation will be distributed approximately 1 week in advance, and the recruitment process will be conducted through a Google form. Following the explanation of the research procedure, potential participants can freely choose whether or not to participate in the research. Those who express interest will receive a new ID for this study and will be notified of the schedule and location of the educational program through a class announcement 3 days before it commences.

On the event day, prospective participants will gather at the designated venue and formally record their attendance by signing an attendance sheet with their newly assigned ID. The PI overseeing this research will clarify all study phases, highlighting the participants' right to withdraw at any point. Participation in this research will be entirely voluntary. Students who choose not to participate will continue to receive standard dementia-related materials through the e-learning portal of the university, with the exception of the game-based education program. All participants who consent to participate will express informed consent at the beginning of the Google form. Furthermore, we will state that we would regard the completion and submission of the questionnaires as consent to participate.

Implementation

The intervention of this study is a gaming education program, which will be conducted once for each participant. The program will be implemented at various times, with each session accommodating a maximum of 60 participants. These participants will be divided into small groups of approximately 7-8 individuals within the same room, each group led by a facilitator. The facilitators, who will be either research team members or health lecturers, will be recruited and trained jointly by the Japanese and Indonesian research teams. The program's instructors include the PI of this study, assisted by a research team serving as co-instructors.

Development of Gaming Education Program

The gaming education program was developed based on previous study [19,20,22]. The authors modified the study outline based on the participants and purpose of this study. The gaming educational program in this study comprises 3 primary components, as outlined in Table 1. The sequence of the short film (undesirable communication with people living with dementia), lecture, N-impro gaming, and the desirable communication with people living with dementia scenarios is determined based on insights from previous studies. The gaming education program is designed to be conducted within 90 minutes. The 3 primary components of the gaming education program are as follows.

Table 1. Overview of the gaming educational program.

The content of the education program	Time
Introduction of the study	
Principal investigator explained the overall of study and content of inform	5 min
Pretest	
Participants will receive a QR code providing access to information regarding Informed Consent and the online questionnaire.	10 min
Short film (Undesirable communication with people living with dementia scenario)	
Observing a narrative featuring a woman people living with dementia, participants reflect on her background and the reactions of those around her.	10 min
Lecture	
The lecture consists of dementia, treatment of people living with dementia, person-centered care, and social support. The lecture included questions and answers.	25 min
N-impro gaming	
In the gaming setting, students will participate as a group alongside a facilitator. The game is structured with components such as "situation cards," "answer cards," and "point cards." All groups will be provided with identical sets of situation cards.	20 min
Short film (Desirable communication with people living with dementia scenario)	
Participants identify differences in the emotional experiences of people living with dementia and the reactions of individuals in their immediate surroundings between the two given scenarios.	10 min
Posttest	
Participants will be issued a QR code to access the online posttest. In addition, there will be a designated space for participants to provide free-form comments expressing their opinions and feedback on the gaming education program.	10 min

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Short Drama Portraying Undesirable and Desirable Scenarios

Participants will view a short drama depicting an older woman who may be experiencing dementia. The narrative explores her life history, values, and interactions with family, friends, and community members. In total, 2 parallel scenarios are presented, showcasing both desirable and undesirable communication methods. This contrast enables the participants to subjectively experience the emotional responses of the main character to different types of communication; thus, the participants can naturally learn the appropriate method of communicating with people living with dementia. The scenario of the short drama was created based on interviews with people living with dementia and their families, a review of scholarly articles, and consultations with experts in dementia care. The research team translated a Japanese drama into Indonesian and added subtitles. The drama was projected onto a screen, akin to the setting of a movie theater.

A Lecture About Dementia

Lectures form the foundational framework of this educational program, which is based on the established curriculum for dementia-related health education. Furthermore, the contents of these lectures have been fashioned from the condensed dementia supporter training program in Japan [23,24]. These include the definition of dementia, diagnostic procedures, the various types of dementia, underlying causes, symptoms, treatment and prevention strategies, person-centered care and social support for people living with dementia, and the point of nursing care and how to support the people living with dementia.

Japanese researchers will curate the content outline, followed by their Indonesian counterparts, who will generate the presentation slides and conduct the lectures. A proficient senior lecturer will deliver the courses. The lessons will be systematically recorded and subsequently projected onto screens during class sessions to ensure uniformity across all instructional content in the various class settings.

N-Impro (Gaming Tool)

We developed the gaming tool based on the methodology of a disaster education program [25] and modified it to discuss dilemmas that can occur in a convenience store [19]. The game comprises “situation cards,” “answer cards,” and “point cards.” The situation cards present a 3-part scenario: (1) assigning a role to the participant (eg, you are a convenience store manager), (2) describing a relevant dilemma, and (3) prompting the participant to choose a course of action (yes or no). We developed eleven situation cards, each depicting a unique dilemma based on episodes from the interviews. For instance, the following situation card was created:

> *You are a convenience store manager. You suspect a customer has dementia and are concerned for his well-being. You have previously consulted a welfare volunteer about the customer; however, she said she can do nothing until the name or address of the customer is identified. The customer visits your store irregularly, and you are unable to learn his name because of his unintelligible.*

Other situation cards were similarly crafted to reflect various dilemmas. The N-impro cards are available in Japanese and English. The professional translator translated into Indonesian (Multimedia Appendix 1).

The N-impro game will be played for about 25 minutes during the third session. The research team will provide 6-7 cards with the same scenario and order for each group. Each N-impro game group will consist of 7-8 students with 1 facilitator. The facilitators are teachers in the faculty of health care. The facilitator has undergone 2 training sessions. In the first session, training was conducted by a Japanese team, which included video demonstrations of the N-impro game and slides explaining the game rules. Then, in the second session, the research PI in Indonesia completed offline training for all facilitators to present the game rules and further discuss and role play the N-impro game.

Data Collection

Data will be collected from November 2023 to March 2024 through an online questionnaire. Participants will be informed to prepare a mobile phone or personal computer before joining the class. For the online questionnaire, participants need to access the form, enter the required information, complete the questionnaire, and submit the form. Participants do not need to log into their Google accounts to access the link. They will only provide the new ID number at the beginning of the form. The link to the questionnaire will be shared through a QR code displayed on the classroom screen.

Measurement

This study assesses the pre- and posttest outcomes of a gaming-education program focused on dementia. We aim to measure the effectiveness of the education program by evaluating attitudes toward people living with dementia, intentions to assist people living with dementia, knowledge of dementia, and stigma associated with people living with dementia. This study hypothesizes that a gaming-based education program will foster positive attitudes toward people living with dementia and an intention to help people living with dementia. Furthermore, we anticipate that the knowledge gained from the lectures and discussions during the gaming education will enhance the confidence of health care students in caring for people living with dementia.

This study uses the model by Lane and Yu, which encompasses 3 primary concepts contributing to dementia-friendly communities: knowledge of dementia, attitudes toward people living with dementia, and the intention to assist people living with dementia [26]. The model is underpinned by 2 theories: first, an increase in dementia knowledge is directly linked to a high intention to help people living with dementia, and second, attitude is an intermediary factor between knowledge and intention, influencing the formation of intention and potentially enhancing tangible supportive actions. Therefore, according to this model, improvements in both knowledge and attitude should strengthen the intention to assist.

The questionnaire used in this research is in Indonesian (Bahasa). The questionnaire was originally in English and Japanese. We performed a forward and backward translation

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into Indonesian using the standard method [27]. The translation process involves 2 stages. First, a health care professional who is fluent in both Japanese and Indonesian, has expertise in dementia, and possesses knowledge of Japanese and Indonesian culture performs an initial forward translation. Second, a professional translator who is proficient in Japanese-Indonesian language performs the back translation. Afterward, the Japanese research team validated the translations. Subsequently, we sought input from an Indonesian lecturer, an associate professor in the Department of Japanese Studies, Department of Gerontological Home Care and Long-term Care Nursing, University of Tokyo to ensure the fluency and uniqueness of sentences in Indonesian. The following are the measurements.

Primary Outcomes: Attitudes Toward People Living With Dementia

The primary focus of this study is the attitude toward people living with dementia, as it is intrinsically linked to the concept of attitude. The main objective of education aimed at fostering a dementia-friendly community is to enhance attitude. Attitude, as a concept, is a mental and neural state molded by experience, which influences the responses of individuals to various objects and situations and exerts a directive or dynamic impact on their behavior [28,29]. Consequently, numerous previous studies have used attitude as the primary outcome in educational research [22,30-32].

People's perceptions of people living with dementia are related to stigma. Stigma is a societal phenomenon characterized by others perceiving an individual as deviating from the norm [33]. There are significant obstacles to creating communities that are supportive of people living with dementia, including stigma and social isolation. Stigma can impede the provision of care and support, frequently manifesting in behaviors such as excluding people living with dementia from health care [34,35]. Stigma can significantly influence the attitudes and behaviors of health care students. Therefore, measuring attitudes toward people living with dementia is important among health care services and students, as it relates to people's perceptions of people living with dementia.

Attitudes toward people living with dementia were assessed using a 14-item measurement tool developed using information from previous research. This tool uses a 4-point Likert scale, ranging from 1 (disagree) to 4 (agree), and comprises 4 subscales: tolerance (5 items), refusal (4 items), feeling of distance (3 items), and affinity (2 items). The total score ranged from 14 to 56, with high scores indicating favorable attitudes. Tolerance was assessed with the statement, "I am open to having more interactions with people living with dementia in my daily life." Refusal was measured by "I prefer to minimize interactions with people living with dementia as much as possible." The feeling of distance was gauged with "If a family member were to develop dementia, I would be concerned about what people around me would think." Affinity was evaluated by "If someone with dementia requires assistance, I would readily offer help."

Secondary Outcomes

Knowledge of Dementia

Knowledge of dementia will be measured using the 15-item Dementia-Related Knowledge Scale developed by Kim and Kuroda [36], which assesses the knowledge of dementia: its symptoms, treatments, and diagnosis. This scale will require respondents to provide answers using a 3-point Likert scale ranging from agree, disagree, and don't know. The author will calculate the total dementia knowledge score, with a high score indicating a high level of knowledge about dementia.

Ageism Among People Living With Dementia

Ageism is stereotyping, prejudice, and discrimination against individuals based on their age [37]. Dementia is often associated with advanced age. To develop dementia-friendly services by health care professionals, it is crucial to investigate the prevalence of ageism among people living with dementia. Thus, we will use the Fraboni's Scale of Ageism (FSA) short version to assess the level of ageism among people living with dementia [38,39]. The FSA short version comprises 19 items that measure negative opinions toward older people using a Likert scale (1=strongly disagree, 2=disagree, 3=agree, and 4=strongly agree). Items that represent positive opinions toward older adults have reversed scoring (items 13-16). The possible FSA scores ranged from 19 to 76, with the high scores indicating high levels of ageism.

Intention for Helping Behaviors Toward People Living With Dementia

Based on previous research, methods aimed at raising awareness about dementia and providing education to individuals can enhance the probability of individuals engaging in supportive actions through 2 mechanisms. Individuals tend to develop favorable attitudes toward people living with dementia, and they improve their capacity to recognize signs indicating a need for assistance [40]. Therefore, the intention to help will be measured using 4 vignettes derived from the previous study. The vignettes describe situations in which people living with dementia may require assistance. For example, consider a scenario where you are a clerk in a supermarket. An older woman, a regular customer, arrived this morning to buy 2 bunches of bananas; however, it is now evening, and she has returned to purchase 2 more bunches. She also visited the supermarket twice yesterday for bananas and is appropriately dressed. Participants will read each vignette and, for each one, will be asked to indicate their answer to the item "You will help her." The intention to help will be scored using a Likert scale (1=strongly disagree, 2=disagree, 3=agree, and 4=strongly agree). A high score indicates a high intention to help people living with dementia.

Demographic Data

Demographic information will be collected, including participants' age, sex, affiliation, relationship to people living with dementia, experience in assisting and caring for elderly individuals (including people living with dementia), and history of attending dementia-related lectures, whether through a formal course or a dementia-focused organization.

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Data Analysis

Statistical analyses will be performed as follows: initially, descriptive analyses will be conducted to outline the characteristics of the participants. Subsequently, we will evaluate changes in total and subscale scores for attitudes toward people living with dementia, intention to help people living with dementia, knowledge of dementia, and stigma associated with people living with dementia before and after the program using paired *t* tests and the Wilcoxon rank sum test. To determine the effectiveness of the program, we will calculate effect sizes using Cohen *d*, classifying differences between pre- and postprogram scores as small (d=0.2), medium (d=0.5), or large (d=0.8). We will set the threshold for statistical significance at P<.05 (2-tailed). The statistical analysis will be conducted using IBM SPSS Statistics (version 26.0).

Ethical Considerations

The study protocol of this study has been reviewed and approved by the ethical committee of the Faculty of Nursing at Universitas Airlangga (2377-KEPK).

Results

Data will be collected from November 2023 to March 2024. Data analysis will be completed by May 2024, and the final results will be completed by July 2024. The impact of gaming-based dementia educational programs on enhancing attitudes toward people living with dementia remains unknown. The study findings will be disseminated through publication in a peer-reviewed journal.

Discussion

Principal Findings

Our study results will highlight the impact of gaming-based dementia educational programs on enhancing attitudes toward people living with dementia. The model by Lane hypothesized that knowledge influences attitudes and, indirectly, a helping behavior [26]. We will explore the relationships among these variables in our study findings.

The game-based educational program focuses on real-life situations for helping older adults with dementia. Integrating this program with other educational initiatives may amplify its beneficial effects [22,41]. We hypothesize that the results of our study will support the development of positive attitudes and understanding toward people living with dementia. This is crucial for providing effective, person-centered care that improves the quality of life for people living with dementia and diminishes the stigma linked to their condition.

Limitations

The limitations of the study include its single-arm pre-post design, which impedes the establishment of causation due to the lack of a control group. Without a control group, attributing the observed outcomes exclusively to the gaming-based intervention is challenging, as other variables may influence the results. Furthermore, the impracticality of setting up a control group, owing to the limited number of facilitators, further complicates the isolation of the intervention's effects. Addressing these limitations is essential for future research to ensure more reliable conclusions regarding the effectiveness of the interventions.

Furthermore, it is important to note that the study's exclusive emphasis on health care students may restrict its generalizability, and the absence of objective behavioral assessments poses a challenge in evaluating actual changes in behavior. Therefore, to enhance the reliability and applicability of the findings, future research should address these limitations by considering diverse populations, using more robust study designs, and incorporating objective measures.

Conclusions

To the best of our knowledge, this study represents the inaugural gaming education program among health care students at Indonesian universities, specifically targeting dementia education. This program shows considerable potential as a method to enhance attitudes toward people living with dementia globally, offering a novel approach for the community-based support of people living with dementia.

Acknowledgments

We extend our gratitude to the Dean of the Faculty of Nursing and the Faculty of Public Health at Universitas Airlangga for granting us permission to collect data from their students. The author expresses gratitude to all translation teams for their work on the Japanese and Indonesian tools used in this study.

Data Availability

The data from this study will be stored by the corresponding author and will not be published online.

Authors' Contributions

DWS, HK, AI, EMMH, and NYM contributed to conceptualization. DWS, HK, AI, MT, EMMH, and NYM performed the methodology. DWS, IAN, and EMMH conducted analysis, DWS, MT, HS, JW, RF, IAN, and EMMH performed investigation. DWS, HK, AI, HM, JW, RF, IAN, EMMH, and NYM handled resources. DWS, HS, JW, RF, and EMMH contributed to data curation. DWS and EMMH wrote the original draft. AI, MT, HM, and NYM conducted the manuscript review. DWS, IAN, and EMMH managed the project administration. DWS handled the funding acquisition.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of The Gaming Educational Program.
[PDF File (Adobe PDF File), 104 KB - resprot_v13i1e62654_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Research and Community Service Institute, Universitas Airlangga (Indonesia).
[PDF File (Adobe PDF File), 434 KB - resprot_v13i1e62654_app2.pdf]

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Abbreviations

FSA: Fraboni's Scale of Ageism
PI: principal investigator

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Protocol

Effectiveness of a Bullying Intervention (Be-Prox) in Norwegian Early Childhood and Education Care Centers: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: A new and growing body of research has studied bullying among children in early childhood education and care centers (ECECs). The Bernese Program (Be-Prox) is designed to systematically prevent and handle bullying between children in Swiss ECECs. However, the effectiveness of the Be-Prox intervention has not yet been explored in a Norwegian ECEC setting.

Objective: This study aims to evaluate the effectiveness of Be-Prox in preventing and handling bullying among peers in Norwegian ECECs.

Methods: ECECs from 2 Norwegian municipalities were invited to participate in a cluster randomized controlled trial (RCT) to evaluate the effectiveness of the Be-Prox intervention on peer bullying in Norwegian ECECs. After baseline measures were taken, project ECECs were randomized to either an intervention or a control arm. The Be-Prox intervention was introduced to ECECs in the intervention arm through 6 modules over a 9-month period immediately after the randomization. ECECs in the control arm participated in the data collection and were offered the Be-Prox intervention the following year. The primary outcome of the effect evaluation is the mean sum of negative behavior between peers after the Be-Prox training is completed in the intervention arm. Secondary outcomes include child bystander behavior, teacher self-efficacy, and ECEC's authoritative climate. An extensive implementation and process evaluation, as well as cost-effectiveness analyses, will be conducted alongside the RCT.

Results: Baseline data collection was conducted in September 2023, and the postintervention data collection started in May 2024. At baseline, we collected data on 708 children and 413 personnel from 38 project ECECs in the 2 Norwegian municipalities. The results from the study will be available in late 2024 at the earliest.

Conclusions: The proposed project includes a comprehensive evaluation of the effectiveness of Be-Prox in Norwegian ECECs directly targeting the prevention and handling of bullying, including implementation and cost-effectiveness evaluations. The results from the project have the potential to fill in identified knowledge gaps in the understanding of negative behavior and bullying between peers in ECECs, and how these may be prevented. If proven efficient, our ambition is to offer Be-Prox to Norwegian ECECs as an evidence-based practice to prevent and handle bullying among preschool children.

Trial Registration: ClinicalTrials.gov NCT06040437; https://clinicaltrials.gov/study/NCT06040437

International Registered Report Identifier (IRRID): DERR1-10.2196/60626

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(JMIR Res Protoc 2024;13:e60626) doi:10.2196/60626

KEYWORDS

peer bullying in early childhood education and care; The Bernese Program; cluster randomized controlled trial; bullying; child; preschool; program evaluation

Introduction

According to the Norwegian Kindergarten Act (sections 41-43), Norwegian early childhood education and care centers (ECECs) should work systematically to prevent bullying and social exclusion, including adopting a zero-tolerance for violations, such as exclusion, bullying, violence, discrimination, and harassments [1].

Intentionally exposing other children to negative behavior is regarded as aggressive behavior [2,3]. Children with difficulties in regulating and understanding emotions are at greater risk of displaying aggressive behavior [4,5], as they may often misunderstand the emotions of others and are more inclined to interpret others' intentions as aggressive [6]. Aggression can also be more planned and proactive, which is instrumental in reaching a goal, such as dominating others [7]. Children struggling to regulate emotions and behavior require developmental support from adults to function in interactions with their peers [8,9]. Preventing trajectories of aggressive behavior early gives a better prognosis later in life [10], and social and cognitive skills that children acquire in early childhood lay the foundation for later peer interactions and relationships [3,11]. Efforts to reduce the number of children exposing others or being exposed by others to aggression, as early as preschool years, are, in other words, important measures to promote social participation that may prevent social exclusion later in life.

A systematic review of universal social and emotional learning interventions for children in ECECs through 12th grade showed that children who participated in these interventions experienced improved academic achievement, school climate, school functioning, social and emotional skills, attitudes, and prosocial and civic behaviors, and reduced internalizing and externalizing problems [12]. The findings specifically suggest the value of teaching emotional skills before social skills, contributing to the strongest effects of the social and emotional learning programs [13,14]. In Norway, Fossum et al [15] used a randomized controlled between-group design to identify the preventive effects of the Incredible Years Teacher Classroom Management program on social competence and behavior problems of preschoolers. These findings suggested an increase in social competence and a reduction in aggression, internalizing, and attention problems among children. In addition, significant improvements in social competence were observed in a subsample of children who exhibited baseline aggressive behavior scores at or above the 90th percentile [15].

Aggressive behavior does not constitute bullying in itself. The term peer bullying is conventionally defined as aggressive behavior that occurs repeatedly over time and where there is a power imbalance between the child exposing others and the child being exposed [16]. While bullying is well-described in school-age children, a new and growing body of research also describes bullying among children in ECECs. Estimating the prevalence of bullying among children in ECECs based on previous studies is challenging, however, due to differences in how bullying is defined and operationalized in this age group, differences in informants, instruments used, and the modes of data collection [17]. Moreover, the concept of bullying among preschool children in ECECs is debated [2,18,19]. Some argue that children in this age group (ie, under 6 years) seem to aggress toward their peers in a rather indiscriminative way, and do not repeatedly target peers who have less power than themselves, which generally is considered an important criterion to discriminate bullying from aggression [3]. Hence, terms such as "unjustified aggression" [2] and "peer victimization" [20] have been suggested instead of bullying in this age group. Through results from their studies, Alsaker and Valkanover [21] argue that bullying also exists among children in kindergartens. In the Pathways to Victimization study, they used the concepts of teacher-reported physical, verbal, relational, and object-related negative acts and categorized children as victims, bullies, bully victims, and noninvolved [21].

Studies specifically targeting bullying between preschool peers are few and often limited by a low sample size [9]. In the Pathways to Victimization study, 6% of the children were found to be victims of bullying (ie, exposed to negative acts by other children at least once a week over a 3-month period), 11% were bullies (ie, exposing others to negative acts), 10% were bully victims (ie, both exposed and exposing others), and 46.5% were not involved [21,22]. Two Finnish studies found that 12.6% of children aged 3-6 years in ECECs were involved in bullying [23] and almost 30% of 4-year-olds [11], as reported by teachers and parents, respectively. From a Norwegian context, a scoping review found the prevalence in Norwegian ECECs varied from 6% to 20% in various studies [17]. A recent study, including approximately 900 children aged 1-5 years from Norwegian ECECs, used the concepts of physical, verbal, relational, and object-related negative acts to study negative behavior between peers and found that, across age, almost half of the children were involved in negative behaviors between peers, either as a victim, perpetrator, or both, 2-3 times a month or more often, based on teacher reports (unpublished data, ME Solberg et al, 2024). The prevalence varied markedly across age and the specific acts; however, with the prevalence of all types of negative acts increasing between those aged 1 and 2 years, after 3 years of age, the prevalence of physical negative acts declined, whereas the verbal and relational acts were attenuated.

There are limited evidence-based interventions described in the literature directly targeting bullying between peers in ECECs [3,17]. The Bernese Program (Be-Prox), designed to systematically prevent and handle bullying between children in Swiss ECECs, is one of the few interventions with supported evidence [24]. In Be-Prox, the aim is to increase understanding

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and skills among ECEC personnel through a 6-module training. An evaluation of the Be-Prox program in Swiss ECECs found a decrease in the number of children victimized after introducing the intervention, and that the risk of being victimized in the control ECECs was 1.5 times higher compared with ECECs where Be-Prox was introduced [25]. In a pilot study, Be-Prox was translated, adjusted, and evaluated for a Norwegian context, providing teaching materials and tools for ECECs in a Norwegian municipality. From this pilot, our experience is that Be-Prox is well accepted among Norwegian ECEC personnel and that the 6 modules were feasible in the effort to prevent and handle negative behavior and bullying in Norwegian ECECs, in accordance with the Norwegian Kindergarten Act [1]. However, whether the intervention leads to changes in the frequency of negative behavior and bullying in a Norwegian context is not known. To evaluate the effectiveness of the Be-Prox intervention to prevent and handle bullying in Norwegian ECEC, there is, therefore, a need for a sufficiently powered randomized controlled trial, preferably including several municipalities in different parts of Norway to increase the generalizability of the findings.

For successful implementation of an intervention in educational systems, such as ECECs, evidence should go beyond the solid empirical documentation of the effect of an intervention (evidence-based intervention) and incorporate the empirically based knowledge with the practitioner's experience-based knowledge and the needs and wishes of the end users [26]. To be able to say with a reasonable degree of certainty that an intervention will be effectively used in ordinary practice, both positive results from good efficiency studies and evaluation of systems that ensure implementation quality when the intervention is used in ordinary practice are necessary. Therefore, the assessment of the implementation quality, fidelity, and usefulness of the program in question should be included in the study evaluation [27]. This is referred to as evidence-based practices, and the goal is to base decisions on useful interventions, measures, or programs on the best available scientific evidence aligned with the views and needs of the practitioners and end users [28]. More attention is also currently being directed to the economic evaluations of an intervention when implemented to, for instance, the educational system. These evaluations assess alternative program options in terms of cost and consequences. A core question is whether resources on interventions are optimally spent in terms of benefits gained, compared with the current practice [29]. Cost-effectiveness analysis compares the costs (monetary units, such as Norwegian Krone) and benefits (nonmonetary units, such as the prevalence of bullying) of the intervention with the standard practice [30].

The current project aims to evaluate the effectiveness of the evidence-based antibullying intervention, Be-Prox, in a cluster randomized controlled trial (RCT) in Norwegian ECECs with an overall aim to ensure a safe and sound ECEC environment for Norwegian children. We hypothesize that the Be-Prox intervention will be effective in preventing and handling bullying among peers in Norwegian ECECs and that it is possible to successfully implement the intervention in Norwegian municipalities.

We will reach the project aim through the project objectives in Norwegian ECECs, which are (1) to evaluate the effectiveness of the Be-Prox intervention to prevent and handle bullying among peers, (2) to examine implementation factors that promote or inhibit the effectiveness of the Be-Prox intervention, (3) to examine the cost-effectiveness of the Be-Prox intervention, and (4) to generate knowledge on how the Be-Prox intervention can be aligned and implemented in Norwegian municipalities.

Methods

Study Design and Setting

The fundamental pillar of the project is the effect evaluation, using an RCT design, with longitudinal follow-ups in 2 Norwegian municipalities (Figure 1). The primary outcome for the effect evaluation will be measured after the training is complete in the intervention arm (T1). The implementation and process evaluation and economic evaluation will be conducted alongside this trial, benefitting from the stringently conducted RCT in a real-world setting, combining the advantages of minimizing selection bias and increasing the external validity of the findings [29].

The study is set in 2 mid-sized Norwegian municipalities, Bjørnafjorden and Narvik, with approximately 25,000 and 19,000 inhabitants and 24 and 28 ECECs, respectively [31]. Both public and private ECEC institutions were invited to participate in the study. The project adopts a pragmatic approach and includes all ECECs that were available and consented to participate.

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Figure 1. Overview of the Be-Prox study. Be-Prox: The Burmese Project; ECEC: early childhood education and care center.

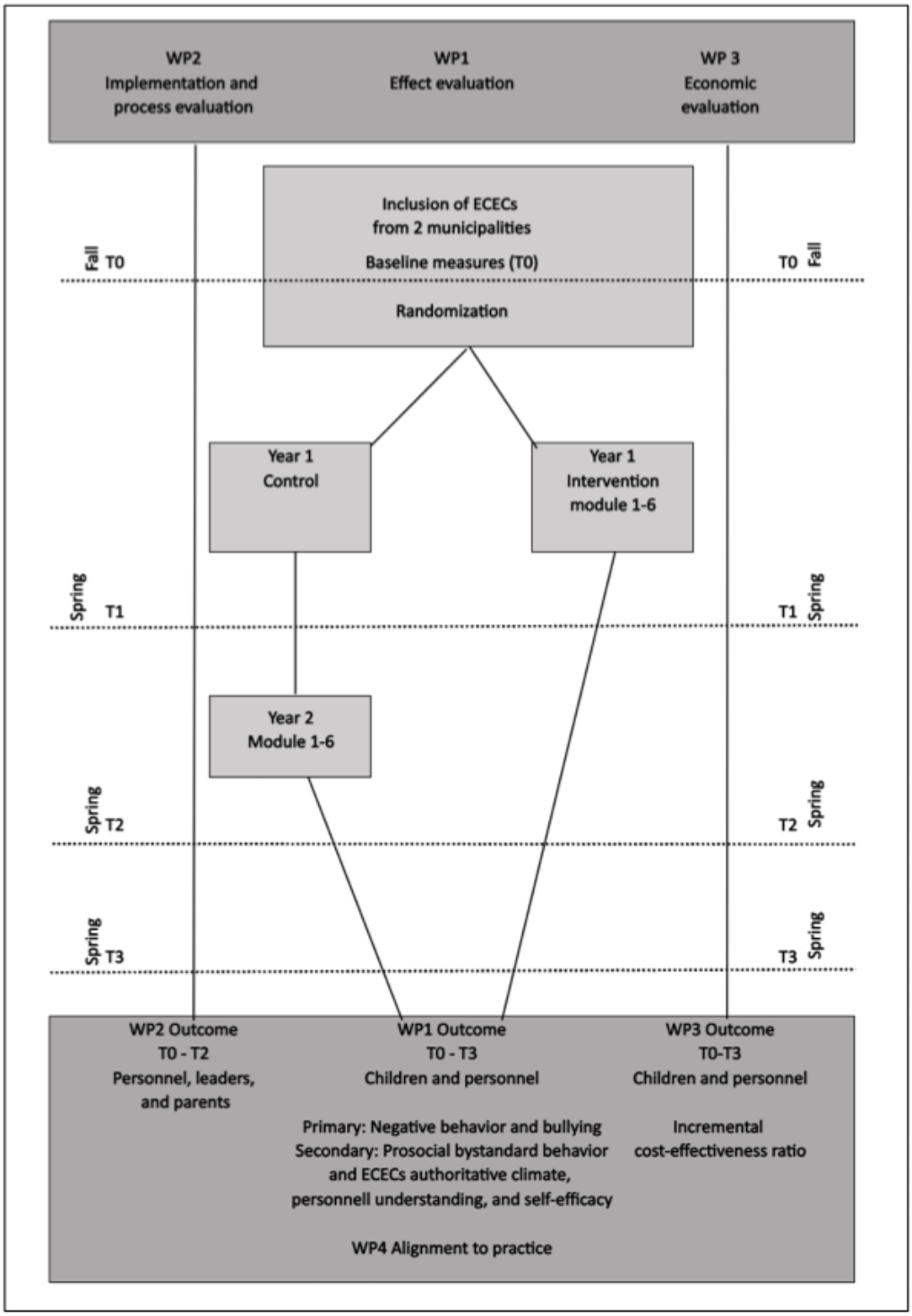

Participants and Recruitment

All ECECs in the 2 municipalities received information about the project in meetings with the municipality and participants from the project group (Figure 2). While all public ECECs were included through the municipality, private ECECs consented to participation on their own after this initial meeting.

In ECECs consenting to participate (in the following referred to as project ECECs), parents of children that turned 3 years of age or older in project year 1 (ie, when ECECs in the intervention arm received the training) were asked to consent for the participation of their child to the study. Children were included if they belonged to a project ECEC, turned 3 years of age in project year 1 or were older, and if at least 1 parent consented to their participation. Children were excluded if they were younger than 3 years or if one parent specifically opposed the participation of their child.

All personnel in project ECECs that attended the Be-Prox training, as appointed by the head of the ECEC, were invited to participate in a general survey and evaluations of the Be-Prox

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training. Personnel who did not consent to participation were excluded.

All Be-Prox instructors in both municipalities were invited to fill in a self-evaluation following each Be-Prox training session.

When training was completed in ECECs in the intervention arm (T1), all parents of children in the project ECECs were invited for an anonymous survey.

Figure 2. Study procedures in the Be-Prox study. Be-Prox: The Burmese Project; ECEC: early childhood education and care center.

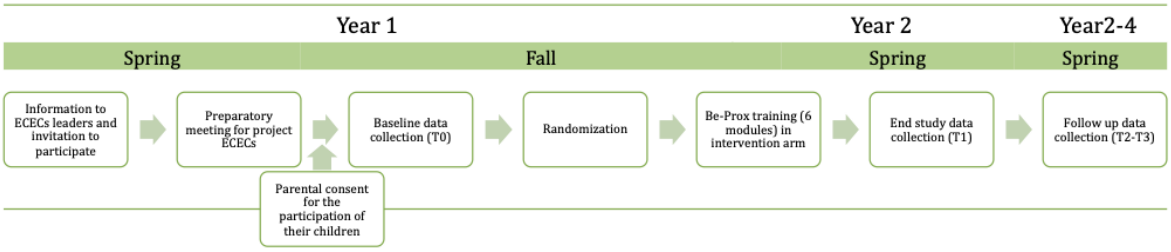

Randomization and Allocation to Study Arms

Project ECECs were randomized to the intervention or control arm after baseline measures (T0) were completed about 1 month after the start of the ECEC year following the summer holidays (Figures 1 and 2). Randomization was stratified by municipality, the size of the ECEC (small or large), and public or private ECEC. Randomization was done by a statistician at UiT the Arctic University of Norway not otherwise involved in the project. A random number of 0 and 1 was generated using SPSS version 29.0 (IBM Corp) and assigned to each project ECEC.

Intervention and Cointervention

Be-Prox Intervention

Drawing from an ecological approach focusing on the quality and context of the child's environment [32], the Be-Prox intervention regards bullying among peers as a social phenomenon that requires both the presence of aggressive children and the passivity of other children and adults to develop into chronic patterns [25,33,34]. This intervention aims to lower the levels of bullying through a positive ECEC environment characterized by shared values and beliefs about behavior among children and ECEC personnel. Moreover, Be-Prox fosters an adult authoritative approach combining a high degree of support toward the children with a high degree of disciplinary structure.

ECEC personnel, and in this regard, all adults working in ECECs independent of their profession, are, therefore, the main target group for the Be-Prox intervention [25]. The focus is on a 6-module training to increase understanding and skills in managing bullying among all personnel and encourage positive interactions between the children [34]. The goal is to prevent occurrences of negative behavior and bullying at an early stage, talk about bullying and victimization, strengthen prosocial resources in the group of children, and intervene when negative behavior and bullying occur [25].

The principles of Be-Prox, as described above, are introduced to ECEC personnel in 6 modules over a 9-month period [34] (Table 1). The Be-Prox training is conducted during personnel meetings throughout the ECEC year (usually modules 1 and 2 in 1 full day in early fall, then modules 3-6 in approximately 2.5-hour meetings, 2 in the fall and 2 during spring).

All participants in the training have access to the Be-Prox material and tools through the Be-Prox home page. Between the module training, there are assignments where the personnel try out and practice activities with the children. These assignments are discussed with colleagues at the start of the next module. After the training is completed, there is a final meeting in the ECEC leader team on the implementation of a quality system to ensure the sustainability of the program in the ECECs after training is completed.

Table 1. Be-Prox modules and program elements.

Modules	Title	Program elements
Module 1	Mobilize	To raise awareness of negative behavior and bullying among kindergarten peers
Module 2	Look at it	Uncover negative behavior and bullying among kindergarten peers
Module 3	Let's talk about it	Discuss negative behavior and bullying with children, colleagues, and parents
Module 4	The contract	Involve children in making common rules of behavior
Module 5	Act and monitor	Kindergarten personnel are consistent in their follow-up of common rules
Module 6	Strengthening resources	Strengthening resources and prosocial bystander behavior
Program appendices	(1) Collaboration with parents. (2) Quality control systems to ensure the sustainability of the program	—[a]

[a]Not applicable.

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Preparations

The leaders of all ECECs participated in a preparatory meeting (April and May in year 1) before the start of data collection, randomization, and training in the intervention arm (Figure 2). This meeting included brief information on the project, including data collection and randomization procedures, how to structure the training in the ECECs, and the importance of investing in the Be-Prox training in the first year for successful adoption of the program.

Instructor Training

The Be-Prox intervention was delivered to ECECs by local, trained instructors in pairs of 2. These local instructors were trained and supervised by senior advisors (AS, MH, MA, and JGE) throughout the intervention period.

Eligible candidates with competence at the bachelor's or master's level and relevant experience were identified within the municipalities to be trained as Be-Prox instructors. The instructor training was held over 6 days, with 3 days of introduction (August, year 1), 2 days of follow-up (January year 2), and a final digital 3-hour meeting summarizing and discussing the way forward (May and June year 2). The trained instructors (3 pairs in each municipality) are responsible for the Be-Prox training in the ECECs and receive digital supervision from senior advisors at the partner institutions, timed according to each module throughout the ECEC year.

Intervention Arm

In the intervention arm, a preparatory meeting with the ECEC leader team was conducted. After filling in the baseline measures (T0), ECECs randomized to the intervention arm continued with the full Be-Prox training over a period of about 9 months.

Cointervention Arm (Control)

In the cointervention arm, a preparatory meeting with the ECEC leader team was conducted and baseline measures (T0) were filled identical to the intervention arm. ECECs in the control arm will be offered the Be-Prox training in year 2.

Data Collection

All data in the project are collected by questionnaires created with Nettskjema, a survey solution developed and hosted by the University of Oslo. Data are stored within the same system (TSD, Services for Sensitive Data, University of Oslo) designed for the storing and postprocessing of sensitive data in compliance with applicable regulations [35].

Data on child behavior are collected by 2 ECEC personnel who know the children well (as appointed by the ECEC leader). The questionnaire takes approximately 10 minutes to fill in for each child. These personnel received an introductory video on how to fill in the questionnaire. The personnel in all project ECEC will complete questionnaires on child behavior at baseline (T0) and following the end of the Be-Prox training in the intervention arm (T1). Data will also be collected after 1 (T2) and 2 (T3) years following the end of the Be-Prox training in the intervention arm (longitudinal follow-ups; Figures 1 and 2).

For personnel, we collect survey data at baseline (T0) and after completion of the training in the intervention arm (T1), and 1 (T2) and 2 (T3) years after the end of the Be-Prox training in the intervention arm (Figures 1 and 2). At each time point, questionnaires take approximately 30 minutes to fill in. During the intervention year, personnel will also fill in questions related to the training modules (fidelity) and the instructors will be requested to anonymously fill in fidelity checklists connected to each training module.

During the spring of year 2 (T1), we will invite all parents to fill in an anonymous user satisfaction survey.

Outcomes

Effect Evaluation

Negative Behavior Between Peers

The frequency of negative behavior between peers will be rated by ECEC personnel using 4-item scales on physical, verbal, relational, and object-related negative acts, where 1 scale is on exposing peers to negative acts, and 1 scale is on being exposed to negative acts by peers [21]. These scales are adapted from the Pathways to Victimization study, have shown acceptable construct validity [36,37], and will have the following response categories in this study: "never or seldom" (0), "once per month" (1), "2-3 times per month" (2), "1 time per week" (3), and "more than once a week" (4) using the last month as the reference period.

In this study, the scales will be used as sum scores (ie, "exposing peers to negative behavior" and "being exposed to negative behavior by peers," range 0-20), itemized by the different negative acts (ie, physical, verbal, relational, object-related, range 0-5) and as the frequency of children exposing peers and being exposed by peers to negative behavior more than 2-3 times per month. For each of the 8 negative acts, the questionnaire will also include an identical item assessing whether there was a power imbalance involved in the negative acts with the response categories no (0), yes (1), and yes and no (2).

The primary outcome of the effect evaluation are the mean sum of negative behavior (range 0-16), exposing peers and being exposed by peers, post intervention. This is also what forms the basis for the power calculations.

Child Bystander Behavior

Bystander behavior, that is, trying to help the exposed child, withdrawing from the situation, or joining in on the bullying will be assessed by a 12-item questionnaire adapted from the Pathways to Victimization study [38], with the response categories "never" (0), "seldom" (1), and "always" (2).

ECECs Personnels' Self-Efficacy

Personnels' self-efficacy and the probability that they will intervene will be assessed by adapted items from the Bullying Intervention Self-Efficacy Scale, developed and validated for a German school setting [39,40]. The original 5-item scale was translated to Norwegian for this study and wordings changed from school peers to ECEC peers. We also changed the response category from 4 to 7 points on the Likert scale, where high scores indicated high self-efficacy in handling bullying situations.

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Authoritative Climate

Authoritative climate will be measured through an adapted version of a scale constructed and validated for Norwegian schoolteachers [41]. In this study, we have included 10 items where the personnel evaluate the degree of support and control in the ECEC environment on a 7-point Likert scale. From the original 8-item scale, adaption for the current ECEC environment included changing from using "I" to "Adults in our unit" and adding 2 items related to the ECEC context. In this scale, higher scores indicate a higher degree of authoritative ECEC climate.

Implementation and Process Evaluation

To identify factors that promote or inhibit the implementation of the Be-Prox program, the study will investigate issues regarding the personnel's work environment, intervention fit, and organizational readiness for change [42,43]. Questions were rephrased to be more relevant to this study setting. For example, in addition to questions phrased in the first person (I), questions in the third person (them) were added. Wordings were also rephrased to address the current theme of "bullying" within this specific ECEC context. Questions related to employees' perception of workload, work conflict and work-family conflict, and autonomy and leadership, as well as job satisfaction, were adjusted to this study and included [44]. Factor structure and psychometric properties of the Norwegian versions are supported in previous studies [45,46]. In addition, questions about employees' intention to quit [47] and employees' perceptions of burnout and engagement [48,49] will be examined. Questions are rated on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree) or assessed from 1 (not at all) to 7 (to a very large extent).

Implementation quality, fidelity, and usefulness of the program will be assessed through checklists to Be-Prox instructors and module evaluations to personnel. Checklists and module evaluations were developed for this study based on Be-Prox materials and tools [34], and distribution was timed according to each training module, as well as a final evaluation after the last training module.

This study will also explore parents' experiences of how the personnel addresses negative behavior and bullying, as well as parents' confidence and ability to raise concerns about these issues through a user satisfaction survey. Questions are assessed on a 5-point scale ranging from 1 (to a very large extent) to 5 (to a very small extent) and are supported in previous Norwegian studies [50,51]. The survey will be distributed electronically to the parents after the program completion at the end of the first year (T1).

Economic Evaluation

The economic evaluation of Be-Prox will consist of a cost-effectiveness analysis from a societal and ECEC perspective. A cost-effectiveness analysis compares the costs and consequences of different programs, such as antibullying interventions, and estimates the value of the program [30]. The aim of the current study is to evaluate the cost-consequences for each gained unit effect of the Be-Prox intervention.

In the cost-effectiveness analysis, we will use the primary outcome as outlined above. The cost data for the cost-effectiveness analysis will include both direct and indirect intervention costs. Direct costs include material and labor costs for extra staff or extra labor hours used to implement the program incurred by the ECECs [30,52]. Indirect costs include labor costs that are not directly incurred by the kindergarten but compensate for the time used to implement the program that could have been otherwise spent on other core activities. These costs are relevant economic costs ("alternative costs") and often constitute the largest part of the overall costs for similar intervention programs. The cost information will be collected from ECEC leaders at T3. Information on time resources and workload connected to the Be-Prox implementation will be collected as part of the fidelity measures.

Demographic Variables

Information on the child's age and gender and parental country of birth will be collected from parents while asking for consent for child participation (before T0, Figure 2). Demographic information of the personnel, such as age, gender, nationality, educational background, current position in the ECEC, and years of experience from ECEC work will be collected in the survey at baseline (T0). Based on the leader's report, organizational variables of the ECECs (eg, number of employees, children, and departments, type of organization and structure in the ECEC, and previous competence-enhancing courses and measures) will also be examined [45].

Sample Size Estimations

A 2-level random intercept multilevel model will be used to detect group mean differences (intervention vs control) on posttest scores. Pretest scores aggregated at the cluster level will be included as covariances to increase power [53]. Based upon interclass correlations and cluster sizes from the pilot study, power calculation using the Optimal Design Software (Version 3.01) [54] shows that with a .05 level of significance, power of 0.80, expected ICC at kindergarten level at 0.12, a cluster size of 45 (children), and pretest cluster-level covariate explaining 30% of the posttest score, 39 kindergartens are needed to detect effect sizes equal to or larger than Cohen *d* 0.30m representing a medium effect [55]. Given the potential risk of dropout during the trial and potential contamination bias, we have decided to recruit at least 44 of the 52 available kindergartens.

Statistical Analyses

For the effect evaluation (primary outcomes), 2-level random intercept multilevel models will be used to detect group mean differences in negative behavior (intervention versus control) on posttest scores. Pretest scores aggregated at the cluster level will be included as covariates to increase power [53]. Multilevel growth curve analyses will be conducted to explore whether potentially positive gains from the RCT are maintained at 1 and 2 years after the end of the intervention. Multilevel analyses will also be used in other analyses when data clustering must be accounted for. Missing data will be handled with multiple imputations and full information maximum likelihood [56].

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Demographic information provides important descriptions of the samples and can facilitate measurements of potential effect modifications (eg, by age, gender, position, and educational background).

The implementation evaluation will examine whether implementation fidelity and quality (eg, mean evaluation of the Be-Prox training received by employees and mean evaluation of the training delivered by the Be-Prox instructors) predict the effectiveness of the Be-Prox intervention (ie, the difference in frequency of negative behaviors between baseline and T1). Multilevel models with ECEC as a cluster variable will be used. The experiences of the parents will also be analyzed with multilevel analyses (with ECEC as a cluster variable) to investigate which factors predict their satisfaction with how the personnel address negative behavior and bullying. The effect of the Be-Prox intervention on the employees' attitudes and experiences of the work environment (eg total workload, attitude toward evidence-based programs, and autonomy) will be evaluated using 2-level random intercept multilevel models that will compare changes in the control and intervention groups through time (T0, T1, and T2).

The economic evaluation will calculate the cost-effectiveness of the intervention based on estimates from the incremental cost-effectiveness ratio (ICER). The ICER indicates the additional investments needed for the intervention to gain one extra unit of effect compared with control ECECs with no intervention, which can be interpreted as the monetary cost for 1 less child victim or offender [29]. When ICERs are estimated, we will use nonparametric bootstrapping with 4000 replications to estimate 95% CIs around cost differences and the uncertainty surrounding ICERs. To account for the clustering of data, bootstrap replications will be stratified by ECECs. Bootstrapped cost-effect pairs will be plotted on a cost-effectiveness plane and used to calculate cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves display the probability that a treatment is cost-effective compared with control ECECs with no treatment. We will also carry out deterministic and probabilistic sensitivity analyses to establish the uncertainty of the cost-effectiveness results.

We will also use other statistical approaches, such as simple descriptive statistics, regression analyses, factor analysis, and structural equation models, to answer secondary research questions in the project.

User Involvement

User knowledge is essential in the process of building knowledge for evidence-based practice [26]. In the current project, the perspectives of the end users will be incorporated through parent representatives and antibullying professionals in the reference group meeting yearly. The project will also involve ECEC practitioners in the planning of the study and interpretations of results and alignment to practice.

Ethical Considerations

The study will be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Due to the nature of the study, formal approval from an ethics committee was deemed not necessary. All participants were thoroughly informed about the study purpose and procedures and consent was collected through the Nettskjema. Participation in the study is voluntary and consent can be withdrawn at any time. Data will be handled according to recommendations from the Norwegian Data Protection Service (reference number 705199), with the public interest as the legal basis for processing personal data (ie, Art. 6 (1)(e) of the General Data Protection Regulation). All data will be collected and stored within systems designed for storing and postprocessing of sensitive data in compliance with applicable regulations (ie, Nettskjema and TSD). Only a restricted number of members from the project team will have access to raw data. The remaining project members will have access to anonymized data only. A Data Protection Impact Assessment has been conducted by the Norwegian Agency for Shared Services in Education and Research and the Data Protection Officer at NORCE, in collaboration with the principal investigator (IK) and co–principal investigator (MA). The processing of personal data was evaluated to be in line with the personal data protection regulations. The project is registered at ClinicalTrials.gov (NCT06040437).

Results

The project secured funding in June 2022, started in January 2023, and received recommendations from the Norwegian Data Protection Service in July 2023. Baseline data collection was conducted in September 2023, and the postintervention data collection started in May 2024. From baseline, we have data from 708 children from 38 project ECECs in the 2 Norwegian municipalities and 413 of the personnel, constituting a response rate of 70% and 80% of all available participants, respectively. Results from the study will be available in late 2024 at the earliest and will be published in peer-reviewed international and national journals, as well as presented at relevant conferences.

Discussion

Principal Findings

The proposed project includes a comprehensive evaluation of the effectiveness of Be-Prox in Norwegian ECECs directly targeting the prevention and handling of bullying. The evaluation includes a stringent RCT design in a real-world municipality setting with implementation and cost-effectiveness evaluations.

Be-Prox is one of the few interventions described in the literature with scientific evidence for an effect on negative behavior and bullying between peers in kindergartens [9,24]. Through the existing project outputs, we will be able to measure whether such an effect also can be found in Norwegian ECECs. Including a wider range of outcome measures, we will be able to examine important mechanisms involved, such as the effect on negative behavior as such or on bullying as conventionally defined, the mediation by personnel factors, and the potential modification by age and gender. Hence, findings from the current project will represent an important contribution to the research field, both in providing scientific evidence as to whether Be-Prox is effective beyond Switzerland and on important mechanisms involved.

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From the described project, we will also obtain comprehensive data on negative behavior and bullying between preschool peers in a large population-based sample from Norwegian ECECs. Data will be collected on multiple levels, including children, parents, personnel, and ECEC leaders. The concept of bullying in this age group is debated [2,3], and data from the current project can contribute to an increased understanding of the concept of bullying among ECEC children.

The importance of the project outputs is underlined by the additions to the Norwegian Kindergarten Act in 2021, introducing the right of all children to a safe and sound ECEC environment [1]. Although, increasingly also in Norway, there is a consensus that bullying exists among preschool children in ECECs, few interventions are available directly targeting bullying behavior in this setting [17]. The lack of evidence-based practice represents a challenge for Norwegian ECECs as well as the municipalities responsible for ECECs being run in accordance with applicable laws and regulations. Going beyond measuring the effect of Be-Prox to prevent and handle bullying; the current project also incorporates essential factors for successful implementation and to whether Be-Prox is a cost-effective alternative. In this regard, project outputs will provide practitioners and decision makers with information on whether the intervention fulfills its purpose and, in addition, inform on whether Be-Prox may be implemented in practice and at what cost. If effectiveness is proven with an effect size that is judged to be of practical significance, Be-Prox can be offered to ECECs and municipalities nationwide.

The negative consequences for children being exposed to bullying are well-described [57], and the available evidence suggests that this can also be generalized to ECEC children [58]. Research findings point to the importance of preventing trajectories of aggressive behavior early [10] and that social skills acquired in early childhood lay a foundation for later relationships [3]. Reducing the number of children experiencing or exposing others to negative acts or bullying may therefore be an important measure in a common effort to promote social participation and prevent social exclusion among the rising generation. In this regard, the project is not only answering to the United Nations Convention on the Rights of the Child stating the right for all children to be protected from all forms of physical and mental violence [59], but also to several of the Sustainable Development Goals (SDGs), including SDG 3 to ensure healthy lives and promote well-being at all ages and SDG 4 to ensure inclusive and equitable quality education to all [60].

Strength and Limitations

To the best of our knowledge, this is one of few RCTs investigating the effect of an anti-bullying intervention in Norwegian ECECs. Strengths of the study include being a well-powered cluster randomized trial enrolling a large sample of children aged 3 to 5 years and adopting a pragmatic approach in a real-world setting increasing the external validity of our findings. The study setting of 2 Norwegian municipalities representing different geographical areas (western and northern Norway) should also be considered a study strength. The project adopts an interdisciplinary approach, with project group members from different disciplines (eg, psychology, kindergarten, pedagogy, and economics) and representing different work areas such as kindergarten authorities at the municipality level, scientists, and senior advisors. The project setup, with the evaluation of effect, implementation, process, and economics, facilitates a large data collection with the potential to not only increase the knowledge of peer bullying in Norwegian kindergartens but also to what extent the Be-Prox intervention may be implemented in Norwegian municipalities and to what cost.

Limitations to the study include the risk of loss of follow-ups of project ECECs, children, and personnel and loss of power to identify meaningful effects. Moreover, since control ECECs are offered the Be-Prox intervention in year 2 of the project, it is not possible to measure the long-term effects of the intervention using the RCT design. We will, however, through state-of-the-art statistical methods measure associations between the Be-Prox intervention and relevant outcomes in a longitudinal design.

National and International Collaboration

The study is a collaboration between 2 regional centers in Norway working on mental health problems among children and adolescents: RKBU West/NORCE and RKBU North/UiT and 2 Norwegian municipalities: Bjørnafjorden and Narvik. The project is also conducted in close collaboration with the developer of the Be-Prox intervention, Professor Emerita Francoise Alsaker from the Department of Psychology, University of Bern, Switzerland.

Conclusion

Results from the project have the potential to fill in identified knowledge gaps in the understanding of negative behavior and bullying between peers in ECECs and how these may be prevented. If proven efficient, our ambition is to offer Be-Prox to Norwegian ECECs as an evidence-based practice to prevent and handle bullying among preschool children, in accordance with the Norwegian Kindergarten Act [1]. In a broader context, the findings will have the potential to inform future strategies for combating bullying in kindergartens, and how, through a systematic measure, to promote social participation and avoid social exclusion later in life, thereby contributing to a safer and more inclusive learning environment for children in Norway.

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Bern, Switzerland and Mona Solberg, previous senior researcher at RKBU-West, for their valuable support with the Be-Prox program. The project was funded by the Research Council of Norway (RCN; grant 336181). RCN was not involved in the design of the study; data collection, analysis, and interpretation of results; and writing the manuscript.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

IK, FA, KB, EK, HK, MM, and MA contributed to the study conception. IK, FA, RCA, KB, JGE, IKF, MH, BMH, GEH, EK, HK, MM, AM, KM, AS, LRS, and MA contributed to the study design. IK and KB performed statistical planning. FA, JGE, HK, MM, AM, AS, and MA performed implementation and process evaluation planning. RCA and EK contributed to economic analysis planning. IK, FA, RCA, KB, EK, HK, MM, AM, LRS, and MA performed data collection. IK and MA contributed to manuscript writing. FA, RCA, OLB, KB, JGE, IKF, JJ, MH, BMH, GEH, EK, HK, MM, AM, KM, AS, and LRS performed article review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Forskingsrådet - Research Council of Norway.
[PDF File (Adobe PDF File), 65 KB - resprot_v13i1e60626_app1.pdf]

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Abbreviations

Be-Prox: The Bernese Program
ECEC: early childhood education and care center
ICER: incremental cost-effectiveness ratio
RCT: randomized controlled trial
SDG: Sustainable Development Goals

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Protocol

Transitional Care Support for Medicaid-Insured Patients With Serious Mental Illness: Protocol for a Type I Hybrid Effectiveness-Implementation Stepped-Wedge Cluster Randomized Controlled Trial

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Abstract

Background: People diagnosed with a co-occurring serious mental illness (SMI; ie, major depressive disorder, bipolar disorder, or schizophrenia) but hospitalized for a nonpsychiatric condition experience higher rates of readmissions and other adverse outcomes, in part due to poorly coordinated care transitions. Current hospital-to-home transitional care programs lack a focus on the integrated social, medical, and mental health needs of these patients. The Thrive clinical pathway provides transitional care support for patients insured by Medicaid with multiple chronic conditions by focusing on posthospitalization medical concerns and the social determinants of health. This study seeks to evaluate an adapted version of Thrive that also meets the needs of patients with co-occurring SMI discharged from a nonpsychiatric hospitalization.

Objective: This study aimed to (1) engage staff and community advisors in participatory implementation processes to adapt the Thrive clinical pathway for all Medicaid-insured patients, including those with SMI; (2) examine utilization outcomes (ie, Thrive referral, readmission, emergency department [ED], primary, and specialty care visits) for Medicaid-insured individuals with and without SMI who receive Thrive compared with usual care; and (3) evaluate the acceptability, appropriateness, feasibility, and cost-benefit of an adapted Thrive clinical pathway that is tailored for Medicaid-insured patients with co-occurring SMI.

Methods: This study will use a prospective, type I hybrid effectiveness-implementation, stepped-wedge, cluster randomized controlled trial design. We will randomize the initiation of Thrive referrals at the unit level. Data collection will occur over 24 months. Inclusion criteria for Thrive referral include individuals who (1) are Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) reside in Philadelphia; (3) are admitted for a medical diagnosis for over 24 hours at the study hospital; (4) are planned for discharge to home; (5) agree to receive home care services; and (6) are aged ≥18 years. Primary

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analyses will use a mixed-effects negative binomial regression model to evaluate readmission and ED utilization, comparing those with and without SMI who receive Thrive to those with and without SMI who receive usual care. Using a convergent parallel mixed methods design, analyses will be conducted simultaneously for the survey and interview data of patients, clinicians, and health care system leaders. The cost of Thrive will be calculated from budget monitoring data for the research budget, the cost of staff time, and average Medicaid facility fee payments.

Results: This research project was funded in October 2023. Data collection will occur from April 2024 through December 2025. Results are anticipated to be published in 2025-2027.

Conclusions: We anticipate that patients with and without co-occurring SMI will benefit from the adapted Thrive clinical pathway. We also anticipate the adapted version of Thrive to be deemed feasible, acceptable, and appropriate by patients, clinicians, and health system leaders.

Trial Registration: ClinicalTrials.gov NCT06203509; https://clinicaltrials.gov/ct2/show/NCT06203509

International Registered Report Identifier (IRRID): DERR1-10.2196/64575

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KEYWORDS

serious mental illness; health care disparities; Medicaid; evidence-based practice; implementation science; socioeconomic disparities in health

Introduction

Background

Approximately 10 million adults in the United States have a serious mental illness (SMI; ie, major depressive disorder, schizophrenia, and bipolar disorder) [1]. Medicaid, as the largest payer of mental health services, covers 26% of nonelderly adults with SMI [2]. However, up to half of Medicaid-insured individuals with comorbid SMI experience unmet treatment needs [3]. Our population of interest is Medicaid-insured individuals who are hospitalized for a medical condition but live with comorbid SMI. They experience worse health outcomes, particularly following hospitalization due in part to care fragmentation and a lack of connection to community-based services [4,5]. Such disparities are rooted not only in the complexities of their psychiatric conditions but also in a health care system that often fails to provide comprehensive and integrated care. Hospital-to-home transitional care programs can improve postdischarge outcomes through a focus on continuity of care; however, most of these programs often focus on specific medical conditions and lack comprehensive plans to address co-occurring mental health diagnoses [6-8]. Similarly, SMI-focused transitional care programs often exhibit a critical gap; they do not also have a comprehensive plan to address co-occurring chronic medical conditions [9-11]. This oversight is significant given the complex needs of individuals with SMI, who frequently face concurrent medical conditions that require integrated care approaches. In addition, existing transitional care models for patients with SMI who are admitted for psychiatric or nonpsychiatric reasons do not adequately address the social determinants of health (SDOH), a critical driver of optimal health and well-being [12,13]. The SDOH, including factors such as housing stability, employment, social support, and access to nutritious food, significantly influences health outcomes yet remains peripheral in many transitional care strategies. The absence of a holistic approach in these transitional care models underscores the necessity for integrating SMI care with physical health management and addressing the SDOH.

The Thrive clinical pathway addresses the SDOH for Medicaid-insured individuals with multiple chronic conditions transitioning from hospital to home through intensive virtual case coordination, home care services, connections to community-based services, and supervision provided by the discharging clinician for up to 30 days (Figure 1).

Through this process, Thrive increases connections to community-based services and providers (ie, primary and specialty care) and decreases unfavorable posthospital use (ie, readmissions and emergency department [ED] visits). In a pilot study comparing 42 Thrive participants to 437 patients receiving usual care, we found a 50% reduction in 30-day hospital readmissions and a 50% increase in access to postdischarge primary care and specialty care [14].

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Figure 1. Components of the Thrive clinical pathway. APP: advanced practice provider; EHR: electronic health record; MD: medical doctor; OT: occupational therapy; PRN: pro re nata (as needed); PT: physical therapy; RN: registered nurse; SW: social worker.

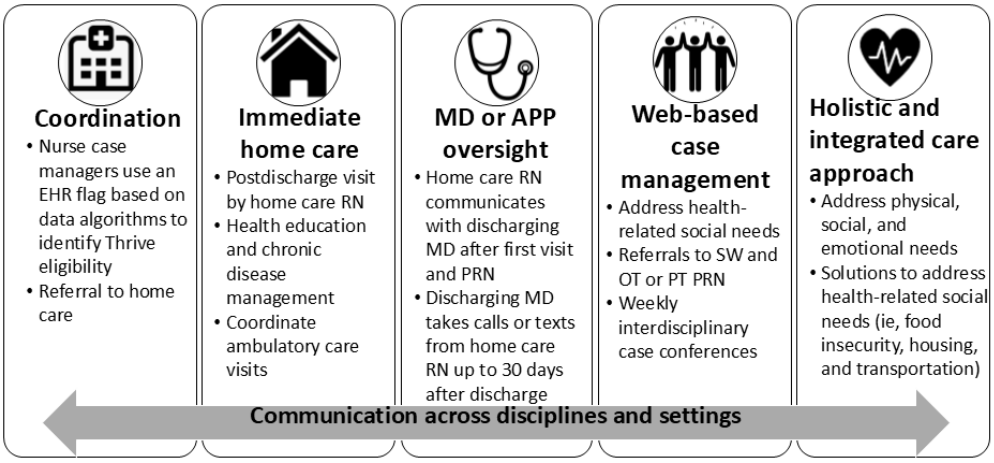

Enhancing Thrive: Integrating Serious Mental Illness

During the successful launch of Thrive at a single site, we also noted a sizable co-occurrence of SMI among our Thrive participants. This raised concerns over additional barriers they might face following hospitalization [15] and whether they experienced similar benefits from the Thrive intervention compared with participants without an SMI diagnosis. In an observational pilot study comparing utilization outcomes of Thrive participants with and without SMI, there were no statistically significant differences between the groups for 30-day readmissions and ED use. However, in qualitative interviews, Thrive participants revealed that while they were happy with the care provided for their medical conditions and with connections to social services, their behavioral health needs were not fully assessed or addressed (JM Brooks Carthon, 2024, unpublished data).

Building on these pilot findings, we now seek to adapt Thrive to ensure suitability for all patients insured by Medicaid including those with co-occurring SMI. Therefore, we are conducting a type I hybrid effectiveness-implementation, stepped-wedge, cluster randomized controlled trial at a new clinical site [16]. Our study is informed by Woodward's Health Equity Implementation Framework (HEIF), which centers equity within the implementation process and focuses on the culturally relevant factors of recipients, the patient-provider interaction, and the societal and organizational context [17].

Aims and Hypotheses

The specific aims of this research are to engage staff and community advisors in participatory processes to (1) prioritize additional components to the current Thrive care model suitable for participants with co-occurring SMI and evaluate the context required for adaptation of the intervention; (2) examine utilization outcomes (ie, Thrive referral; readmission; and ED, primary, and specialty care visits) for Medicaid-insured individuals with and without SMI who receive Thrive compared with usual care—we hypothesize that individuals with SMI who receive usual care will have worse utilization outcomes compared with those without SMI and that all individuals receiving Thrive with and without SMI will have better outcomes compared with those with usual care; and (3) evaluate the acceptability, appropriateness, feasibility, and cost-benefit of an adapted Thrive clinical pathway that is tailored for Medicaid-insured patients with co-occurring SMI.

Methods

Overview

This study will use a prospective, type I hybrid effectiveness-implementation, stepped-wedge, cluster randomized controlled trial design. The advantage of this trial design is that it offers an efficient and practical way to introduce Thrive at a new clinical site while reducing the ethical concerns of withholding an intervention that has shown benefit for economically disadvantaged populations [14]. We will conduct our study in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement and the Consolidated Standards of Reporting Trials (CONSORT) extension for stepped-wedge cluster randomized trials [18,19]. These guidelines ensure rigorous and transparent reporting of our trial design and outcomes and the checklists are included as Multimedia Appendices 1 and 2. Our use of a mixed methods (quantitative + qualitative) study design prioritizes quantitative data to evaluate program referrals, outcomes, and fidelity. Qualitative data will enrich our understanding of barriers and facilitators faced by health care providers in implementing the expanded Thrive intervention, particularly with the addition of mental health services [20]. Taken together, the findings from both the quantitative and qualitative approaches will allow for future intervention refinement if needed and determining the implementation strategies associated with adoption and sustainability. Multimedia Appendix 3 provides a study overview, and the methodology of each aim will be described.

Study Setting

This study is set at the Cedar location of the Hospital of the University of Pennsylvania (HUP), part of the University of Pennsylvania Health System and a new site to implement Thrive. HUP-Cedar is located in West Philadelphia and serves as a safety net primarily treating the most socially at-risk residents of Philadelphia. Over half the patients at this 45-bed hospital

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are Medicaid or dually Medicare and Medicaid insured, and the majority are from diverse racial and ethnic minority backgrounds.

Aim-1 Methods

Aim 1 is to engage staff and community advisors in participatory processes to (1) prioritize additional components to the current Thrive care model suitable for participants with co-occurring SMI and (2) evaluate the context required for adaptation of the intervention. The preimplementation process used to meet aim 1 is described extensively elsewhere (JM Brooks Carthon, 2024, unpublished data).

Aim-2 Methods

Aim 2 is to examine utilization outcomes for Medicaid-insured individuals diagnosed with and without SMI who receive Thrive services compared with usual care.

Design and Randomization

The stepped-wedge cluster design accounts for the proportion of the study period that each group spends in the control and intervention periods (Table 1).

Randomization will occur at the unit level. There are 2 units at HUP-Cedar; using a random number generator, the first unit will be chosen. Eight weeks later, the second unit will begin Thrive referrals. Each unit has 1 case manager and 1 social worker responsible for discharge planning and initiating Thrive referrals. Due to the small number of clinicians and their shared workspace, all 4 will be trained simultaneously, and concealing allocation will not be feasible.

Table 1. Study diagram for the type I hybrid effectiveness-implementation, stepped-wedge, cluster randomized controlled trial of the adapted Thrive clinical pathway for serious mental illness.

Cluster	Baseline (3 months)	Enrollment period 1 (two months)	Enrollment period 2 (two months)	Follow-up (17 months)
Sequence 1 (first unit)		✓	✓	✓
Sequence 2 (second unit)			✓	✓

Study Population

Eligibility criteria for Thrive referral include individuals who (1) are Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) reside in Philadelphia; (3) are admitted for a medical diagnosis for over 24 hours at the study hospital; (4) are planned for discharge to home; (5) agree to receive home care services; and (6) are aged 18 years or older. Patients with SMI will be identified using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes for major depressive disorder, bipolar disorder, or schizophrenia in secondary diagnoses [21]. Exclusion criteria include referral to palliative or hospice home care services at discharge.

Current Usual Care

Usual care includes a discharge to the patient's home with standard discharge care planning that addresses the patient's medical needs. This may or may not encompass referrals to home care and other outpatient services as appropriate.

Thrive Intervention Group

Patients are referred to Thrive by nurse case managers or social workers during the hospital discharge planning process. They are alerted to a potential Thrive referral by an electronic health record (EHR) flag developed by our team [22]. Thrive participants agree to home care services through Penn Medicine at Home. A home care nurse visits the patient within 72 hours of discharge. This visit includes medication reconciliation, review of discharge orders, setting person-centered goals, and referral to other home care services (eg, physical therapy) as deemed necessary. The nurse also determines the visit frequency based on the patient's needs, ranging from 1-3 visits per week. All Thrive participants receive a social work referral, and their psychosocial and mental health needs are further assessed and connections to community resources are provided. Home care nurses provide patient updates to the discharging provider (eg, a medical doctor or advanced practice provider) following the first home visit. Extended supervision by the discharging provider is provided for up to 30 days or until Thrive participants have been seen by their primary care provider. A key feature of Thrive is the intensive, equity-focused, 30-day case management provided during weekly virtual interdisciplinary case conferences. These meetings focus on assessing and addressing the SDOH such as housing, food insecurity, and substance use services as needed. If a source of primary care is absent, we work to link Thrive participants to community providers. Additional Thrive services will be provided as determined by the work group (Aim 1).

Data Collection and Sources

Clinical data, outcome metrics, and postacute care service use will be derived from the EHR at baseline and throughout the Thrive referral period. The characteristics of Thrive participants will be captured in weekly case conferences and stored in a University of Pennsylvania REDCap (Research Electronic Data Capture; Vanderbilt University) system database. Data for the usual care group will be derived from the EHR. The study timeline is outlined in the SPIRIT diagram (Figure 2).

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram—Thrive schedule of evaluations. ED: emergency department; PCP: primary care provider.

			Study period		
	Pre-allocation	Site enrollment	Post allocation (Thrive referral period)		Follow-up
Timepoint	**Retrospective data (Jan 15, 2024)**	**Study start (Apr 15, 2024)**	**Apr 15, 2024**	**June 17, 2024**	**Study end (Dec 31, 2025)**
Enrollment:					
Nurse case manager		✓			
Sequence assignment		✓			
Interventions:					
Baseline data	←	→			
Sequence 1			←	→	
Sequence 2				←	→
Assessments:					
Use measures *Patient level (readmissions, ED use, PCP, and specialist appointments)			✓	✓	✓
Implementation measures *Clinician level (eg, appropriateness, acceptability, feasibility, and workload)				✓	✓

Variables and Measures

The primary independent variable is participation in Thrive. The outcome variables include Thrive referral rates; 30-, 60-, and 90-day readmissions and ED visits; and receipt of primary and specialty care within 30 days of index hospitalization [23-25]. For Thrive participants, these outcomes will be assessed from the date of hospitalization that resulted in a referral to Thrive. For the usual care group, we will identify all readmission and ED visits occurring after the first index hospitalization identified in the EHR from the calendar year of the study. Additional covariate data at both the patient (eg, demographics, comorbidities, or mental health diagnoses) and unit levels (eg, type of unit, discharging team, or provider) will be collected.

Analysis

Monthly reports will be generated to monitor referral patterns to the Thrive clinical pathway. The primary analysis will use a mixed-effects negative binomial regression model, accounting for both medical team and time effects, to evaluate readmission and ED utilization patterns comparing those with and without SMI who receive Thrive to those with and without SMI who receive usual care [26,27]. Sensitivity analyses may include logistic regression, depending on data distribution.

Power Analysis

Based on a power analysis, a sample size of 472 (236 Thrive participants and 236 usual care) for the outcome of readmissions, or a sample of 534 (267 Thrive participants and 267 usual care) for the outcome of ED visits, will yield 80% power to detect significance at the $P<.05$ level. Our goal is a sample size of 534 to ensure adequate power for both outcomes. This assumes a 20% (106/534) loss to follow-up rate. Furthermore, assuming at least a third of the patients will have SMI and an overall 30-day readmission rate of 28% (44/160), a sample of 534 patients will have 80% power to detect an odds ratio as small as 1.46, comparing those with and without SMI, to be statistically significant at the $P<.05$ level. Power analyses were conducted using Power Analysis and Sample Size 2021 (NCSS Statistical Software) [28].

Aim-3 Methods

Aim 3 is to evaluate the acceptability, appropriateness, feasibility, and cost-benefit of an adapted Thrive clinical pathway that is tailored for Medicaid-insured patients with co-occurring SMI.

Design

Guided by Woodwards' HEIF and using a mixed methods approach, we will survey and interview patients, organizational leaders, and health care providers to determine if HEIF domains including cultural factors, clinical encounters, and societal context are associated with uneven or disparate benefits to the intervention.

Sample

Patients

Using a convenience sampling approach, the project manager (PM) will invite patients referred to Thrive to provide feedback on their experiences with the interventions. If Thrive participants agree, the PM will enroll and obtain consent shortly after discharge. Refusal to participate in an interview does not exclude

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the patient from getting Thrive services. We will attempt to recruit up to 40 patients for interviews (20 with SMI and 20 without). For participants with a history of psychosis, we will complete the Evaluation of the Capacity to Sign Consent to assess their ability to participate in the interviews or survey. Thrive participants will be excluded from interviews if they are (1) incapable of participating in a group discussion or understanding content as determined by the Evaluation of the Capacity to Sign Consent or (2) experiencing an acute cognitive impairment or intellectual disability.

Clinicians

Fifteen clinicians (eg, physicians, advanced practice providers, nurse case managers, and home care nurses) will be recruited to participate in interviews at the end of the study. These professionals will provide critical insights into the feasibility, appropriateness, and workload involved in referring patients to the expanded Thrive clinical pathway.

Health Care Leaders

We will recruit 5 leaders at HUP-Cedar and Penn Medicine at Home to assess the broader contextual factors affecting the acceptability and implementation of Thrive. These will take place at the end of the study.

Data Collection

Qualitative Data Collection

Interview guides will be developed using our previous experience piloting Thrive, the domains of the HEIF, and Proctor's implementation outcomes. Questions will be tailored for patients and clinicians and may include perceptions of bias, culturally relevant care, discrimination, acceptability of Thrive, and feasibility of its delivery. During interviews, participants will be asked for permission to audio record the interview. If the participant consents to the interview but does not agree to recording, the interviewer will take detailed notes during the conversation. Demographics of clinicians and administrators will also be collected. Directly following the interview, the interviewer will record field notes to add details not apparent from a transcript. Audio recordings will be labeled with a unique ID number. They will be uploaded to a secure server and transcribed by ADA Transcription, a transcription company with considerable experience in qualitative research, HIPAA (Health Insurance Portability and Accountability Act) regulations, and confidentiality. Cleaned transcripts will be entered into NVivo 14 (Lumivero) for coding and analysis. All interview participants will receive a US $50.00 gift card for participation.

Quantitative Data Collection

At the beginning of their interviews, clinicians and patients will be asked to complete a 12-item survey based on Proctor's implementation outcomes, assessing acceptability (how fair or reasonable Thrive is deemed), appropriateness (to what extent Thrive seems suitable), and feasibility (the practicality and ease of delivering Thrive). Each construct has a 4-item instrument with a 5-point Likert scale that asks participants to rate the degree of agreement or disagreement with each item. Each instrument is averaged with higher scores indicating greater acceptability, appropriateness, or feasibility [29].

Cost-Benefit Data

The cost of Thrive will be calculated from budget monitoring data for the research budget and the cost of staff time [30]. Postdischarge use (ie, readmissions and ED use) will be derived from the EHR. Average Medicaid facility fee payments per admission will be obtained from the Pennsylvania Health Care Cost Containment Council, an independent state agency responsible for addressing health costs [31].

Analysis

In our concurrent mixed methods approach, surveys and interviews will be collected at the same time. Summary statistics will be produced from the quantitative measures of acceptability, appropriateness, and feasibility. All interview data will be stored and analyzed on NVivo version 14 using constant comparative analysis to examine data across cases.

Triangulation of Quantitative and Qualitative Data

Using a convergent, parallel, mixed methods design [32-34], analyses will be conducted simultaneously for the surveys and interviews. This design will allow us not only to compare the quantitative and qualitative findings but also to validate and expand our quantitative results using qualitative data. Integration of the results will occur during analysis and interpretation to confirm or cross-validate findings. Using the HEIF as an organizing framework, we will look for linkages between our findings from the quantitative analysis and related themes that emerge from the qualitative data [35].

Cost-Benefit Analysis

The cost of Thrive will be calculated from budget monitoring data for the research budget and the cost of staff time [30]. We will use the number and acuity of inpatient admissions to estimate the costs paid by Medicaid for patients who received Thrive compared with usual care. In Pennsylvania, Medicaid pays by hospital admission; so, to estimate inpatient costs, we will use the average Medicaid facility fee payment per admission reported by the Pennsylvania Health Care Cost Containment Council and increase it by 17.7% to reflect typical Medicaid professional fees as a percentage of facility fees [36,37]. We will adjust this inpatient admission cost estimate to reflect the acuity of admissions as follows. First, we will estimate the acuity of each admission by multiplying its diagnostic-related group code by standardized case-mix weights published by the Centers for Medicare and Medicaid Services [31]. We will average these case-mix weights by study arm and divide them by the average case-mix weight for all Medicaid discharges in our dataset. We will multiply these arm-specific adjustment factors by the Medicaid cost per admission to arrive at an acuity-adjusted average cost of admission for each arm.

Ethical Considerations

The study has received approval from the University of Pennsylvania institutional review board (#8, Protocol 854422 on October 4, 2023), including a HIPAA waiver of informed consent for clinical data derived from the EHR. All study data collected will be deidentified, and participants will be assigned

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a pseudoidentifier. No individual participant will be identifiable in any published materials. Data will only be accessible on password-protected computers available to the study team. Written consent will be obtained before patient, clinician, and health system leader interviews. Interview participants will be compensated US $50.00 by gift card. The study will be conducted according to national regulations and the Declaration of Helsinki**.**

Dissemination

Our team will lead extensive efforts to disseminate our findings, emphasizing the expanded scope of Thrive to thoroughly address the mental health needs of patients with co-occurring SMI. We will use various channels, including publications; conference presentations; policy briefs; and engagement with both national and international networks through the Penn School of Nursing Communication Office, Leonard Davis Institute of Health Economics, and the Center for Health Outcomes and Policy Research. Planned dissemination activities include (1) up to 5 publications (at least 1-2 per aim); (2) annual scientific presentations and conferences; (3) infographics and guest appearances on relevant podcasts (eg, Amplify Nursing); and (4) development of a comprehensive Thrive website, featuring open-access modules on the components and implementation processes of the expanded program. We will also engage with our Thrive Community Advisory Board quarterly to ensure our dissemination efforts are equity-focused and resonate with health system and community stakeholders.

Results

Our research was funded in October 2023. Data collection began in April 2024 and is expected to continue through December 2025. As of October 17, 2024, a total of 46 patients have been referred to Thrive. We will conduct data analysis early in 2026. We anticipate publishing results in 2025-2027.

Discussion

Expected Findings

We anticipate that patients with and without co-occurring SMI will benefit from Thrive enrollment and experience less unfavorable use (ie, readmissions and ED visits) and more favorable use (ie, primary care, specialty, and connections to community-based resources) than those receiving usual care. We also anticipate the adapted version of Thrive to be deemed feasible, acceptable, and appropriate by patients, clinicians, and health system leaders.

Comparisons with Previous Work

Transitional care programs that focus on patients with SMI most often do not include a comprehensive plan to address integrated medical and psychiatric conditions [9-11]. In addition, there is a lack of focus on addressing SDOH, which are driver of both physical and mental health outcomes. For example, programs like the mobile health transitions of care program for adults with schizophrenia spectrum disorders aim to support patients with SMI in the critical period following hospital discharge through mobile health technologies [38]. Similarly, models such as the Depression and Coleman Care Transitions Intervention focus specifically on mental health conditions like depression, without integrating care for co-occurring physical health issues [9].

Strengths and Limitations

The major strength of our study is the use of a stepped-wedge, cluster randomized controlled trial design. This allows all eligible patients at our study hospital the opportunity to be referred to Thrive during the study window. One limitation is the use of EHR data for our usual care group, as we can only capture use that occurs within our health system.

Conclusion

This study is poised to advance the field of equity-focused, evidence-based interventions by testing the effectiveness of Thrive in improving care transitions for patients with Medicaid insurance and co-occurring SMI and examining Thrive's implementation at a new site. The infusion of equity-focused principles in the design and evaluation of Thrive is anticipated to contribute substantially to both implementation and effectiveness outcomes, offering critical insights into how these principles can enhance health care delivery for patients with the highest health-related social needs.

Acknowledgments

Funding for this research project was provided by the Agency for Healthcare Research and Quality (GRANT 1R18HS029815; JMBC, principal investigator), the Center for Health Outcomes & Policy Research (CHOPR), the Office of Nursing Research (ONR), the University of Pennsylvania School of Nursing, and the National Institutes of Nursing Research T32-NR-007104 (McHugh, principal investigator). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, or the Agency for Healthcare Research and Quality.

Data Availability

The datasets generated and analyzed during this study are not publicly available due to their inclusion of patient identifiers and would need to be requested through the Penn Data Store, as they are derived from the electronic health record (EHR).

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Authors' Contributions

JMBC, HB, MG-M, PC, MOH, KA, DG, AB, JN, and KBL contributed to the conceptualization and drafting of the paper. MOH, MG-M, KA, and DG contributed to the data curation and analytic plan. All authors contributed to the editing of this paper and read and gave the final approval.

Conflicts of Interest

JMBC, HB, MG-M, PC, AB, KA, DG, JN, and KBL have no competing interests to declare.

Multimedia Appendix 1
Reporting checklist for protocol of a clinical trial based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.
[DOCX File , 29 KB - resprot_v13i1e64575_app1.docx]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist for stepped wedge trials.
[DOCX File , 23 KB - resprot_v13i1e64575_app2.docx]

Multimedia Appendix 3
Summary of outcomes, measures, data sources, collection method, and time.
[DOCX File , 17 KB - resprot_v13i1e64575_app3.docx]

Multimedia Appendix 4
Peer Review Feedback from the Agency for Healthcare Research and Quality.
[PDF File (Adobe PDF File), 164 KB - resprot_v13i1e64575_app4.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
ED: emergency department
EHR: electronic health record
HEIF: Health Equity Implementation Framework
HIPAA: Health Insurance Portability and Accountability Act
HUP: Hospital of the University of Pennsylvania
ICD-10: International Classification of Diseases, Tenth Revision
PM: project manager
SDOH: social determinants of health
SMI: serious mental illness
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Collaborative Care to Improve Quality of Life for Anxiety and Depression in Posttraumatic Epilepsy (CoCarePTE): Protocol for a Randomized Hybrid Effectiveness-Implementation Trial

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Abstract

Background: Anxiety and depression in people with epilepsy are common and associated with poor outcomes; yet, they often go untreated due to poor mental health specialist access. Collaborative care is an integrated care model with a strong evidence base in primary care and medical settings, but it has not been evaluated in neurology clinics. Evaluating implementation outcomes when translating evidence-based interventions to new clinical settings to inform future scaling and incorporation into real-world practice is important.

Objective: The Collaborative Care for Posttraumatic Epilepsy (CoCarePTE) trial aims to evaluate the effectiveness (improvement in emotional quality of life) and implementation of a collaborative care intervention for people with anxiety or depressive symptoms and posttraumatic epilepsy.

Methods: CoCarePTE is a 2-site, randomized, single-blind, hybrid type 1 effectiveness-implementation trial that will randomize 60 adults to receive either neurology-based collaborative care or usual care. Adults receiving neurological care at participating centers with anxiety or depressive symptoms and a history of at least mild traumatic brain injury before epilepsy onset will be enrolled. The collaborative care intervention is a 24-week stepped-care model with video or telephone calls every 2 weeks by a care manager for measurement-based anxiety and depression care, seizure care monitoring, and brief therapy intervention delivery. This is supplemented by antidepressant prescribing recommendations by psychiatrists for neurologists via case conferences and care manager–facilitated team communication. In step 2 of the intervention, individuals with <50% symptom reduction by 10 weeks will receive an added 8-session remote cognitive behavioral therapy program. The study is powered to detect a moderate improvement in emotional quality of life. As a hybrid type 1 trial, effectiveness is the primary focus, with the primary outcome being a change in emotional quality of life at 6 months in the intervention group compared to control. Secondary effectiveness outcomes are 6-month changes in depression, anxiety, and overall quality of life. Implementation outcomes, including fidelity, acceptability, feasibility, and appropriateness, are evaluated before implementation and at 3 months. The primary effectiveness

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analysis will compare changes in emotional quality of life scores from baseline to 6 months between the intervention and control arms using multiple linear regression modeling, adjusting for study site and using an intent-to-treat approach.

Results: Enrollment commenced in 2023, with modifications in the inclusion and exclusion made after the first 6 enrollees due to slow recruitment. Enrollment is expected to continue at least into early 2025.

Conclusions: The CoCarePTE trial is novel in its use of a hybrid effectiveness-implementation design to evaluate an evidence-based mental health intervention in epilepsy, and by incorporating seizure care into a collaborative care model. If a significant improvement in emotional quality of life is found in the intervention group compared to usual care, this would support next step scaling or clinical implementation.

Trial Registration: ClinicalTrials.gov NCT05353452; https://www.clinicaltrials.gov/study/NCT05353452

International Registered Report Identifier (IRRID): DERR1-10.2196/59329

(JMIR Res Protoc 2024;13:e59329) doi:10.2196/59329

KEYWORDS

integrated care; mental health; seizures; psychiatric comorbidity; neurology clinic; epilepsy

Introduction

Background

Anxiety and depression in epilepsy are highly prevalent, and they are stronger independent predictors of poor quality of life than seizure frequency [1]. They are particularly relevant to people with posttraumatic epilepsy (PTE), including veterans. Anxiety and depression are significantly more common among people with epilepsy than the general population, with pooled point prevalence of 20.2% for anxiety and 22.9% for depression in a recent meta-analysis [2] and lifetime prevalence of 30% to 35% demonstrated in a population-based study [3]. In addition to being associated with poor quality of life, anxiety and depression in epilepsy are associated with increased mortality from suicide, higher health care costs, cognitive dysfunction, adverse effects from medication, and poor seizure outcomes [1,4-8].

PTE (epilepsy caused by traumatic brain injury [TBI]) is more common in prevalent versus incident epilepsy samples, indicating a tendency for greater chronicity or severity than many other causes of epilepsy, and it is common, accounting for up to 20% of prevalent epilepsies [9]. PTE is a significant predictor of anxiety and depression 2 years after moderate to severe TBI [10]. Despite the impact of anxiety and depression in epilepsy on quality of life and other outcomes, including suicide risk, these comorbidities are underrecognized and undertreated [11-13]. Neurologists face significant barriers to arranging specialty mental health access for people with epilepsy; however, most are willing to prescribe antidepressants [14,15]. Prior work demonstrates that usual neurology care for anxiety and depression in epilepsy does not improve quality of life [16], and symptoms may persist despite a prescribed antidepressant [17]. However, people with epilepsy desire treatment for anxiety and depression in the neurology setting and are willing to participate in research [18,19]. Thus, to improve quality of life among individuals with PTE and anxiety or depression, enhanced care interventions should be studied in the neurology setting.

Collaborative care models for managing anxiety and depression are highly effective in nonpsychiatric settings and improve quality of life [20]. These models were successfully implemented in US Department of Veterans Affairs (VA) primary care and various subspecialty settings [21-23], and a home-based depression program in epilepsy was beneficial [24]; yet, collaborative care has not been investigated in neurology clinics. As anxiety and depression in epilepsy are particularly relevant to people with PTE and considering the particular risk for anxiety and depression in PTE, it is important to study neurology collaborative care implementation to improve quality of life, anxiety, and depression in PTE.

Effectiveness-implementation hybrid trial designs are optimal for studying interventions (such as collaborative care) that have a strong evidence base in other health conditions but are being translated to a new setting and disease area [25]. This approach can speed the dissemination of evidence-based interventions into new settings by initially testing effectiveness in that setting (the degree of benefit derived in real-world circumstances rather than in the ideal conditions typical of efficacy trials). Moreover, hybrid type 1 effectiveness-implementation designs can further support future dissemination of effective interventions by emphasizing effectiveness outcomes and also collecting information on implementation [25]. This study design is a good fit for evaluating collaborative care in the new setting (neurology clinics) and population (individuals with PTE). Thus, we describe a protocol for a hybrid 1 randomized trial to evaluate collaborative care for PTE (CoCarePTE) to test the hypotheses outlined in the next subsection.

Hypotheses

The primary hypothesis to be tested in this study is whether collaborative care improves emotional quality of life at 6 months in adults with anxiety or depressive symptoms and PTE compared with usual neurology care (effectiveness). A clinically significant improvement in emotional quality of life (defined as a moderate change—20 units [26]—in the emotional quality of life subscale of the Quality of Life in Epilepsy-31 [QOLIE-31] scale), compared to control, would warrant immediate clinical implementation of the intervention. The secondary hypothesis overall (implementation) is that the fidelity of the intervention, defined as the proportion of those receiving the collaborative care intervention who attend a majority of care management video or telephone calls in 12 weeks, is very good (ie, >60%). This level of fidelity was chosen based on the

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clinical judgment of the investigators because it was felt that a fidelity of <60% would definitely warrant modification of the intervention as a next step.

Aims

The aims of the CoCarePTE trial are as follows:

1. To evaluate the effectiveness of a neurology-based, video and telephone delivered, 24-week stepped collaborative care intervention adapted from existing local programs among 60 adults with PTE and anxiety or depressive symptoms (the primary effectiveness outcome is group-level change in emotional quality of life at 6 months; and secondary effectiveness outcomes are group-level changes in depressive symptoms, anxiety symptoms, and overall quality of life at 6 months)
2. To assess early implementation outcomes of the neurology-based collaborative care intervention, with primary implementation outcome being intervention fidelity (patient participant attendance at intervention visits in the first 12 weeks; patient- and provider-level acceptability, feasibility, and appropriateness of the intervention will also be evaluated)
3. To explore potential mediators and moderators of the effectiveness of collaborative care (primary and secondary effectiveness outcomes), including seizure factors (seizure frequency and severity) and treatment factors (medication adherence and side effects)

Methods

Study Design

This is a single-blind, 2-site civilian and VA randomized type 1 hybrid effectiveness-implementation trial comparing a 24-week neurology-based, stepped collaborative care intervention for anxiety and depression with usual neurology care. The study will include adults with epilepsy, anxiety or depressive symptoms, and history of a mild (or worse) TBI before their first seizure. Individuals will undergo site-stratified randomization at a 1:1 ratio to receive either collaborative care or usual neurology care. Effectiveness outcomes will be collected remotely by blinded outcome assessors.

The study has been registered at ClinicalTrials.gov (NCT05353452).

Settings

This study is being conducted at Atrium Health, a large academic medical center in the southeastern United States affiliated with the Wake Forest University School of Medicine, and at the WG (Bill) Hefner Salisbury VA Medical Center. Both the civilian and VA sites have multiple neurology or epilepsy clinic locations that serve patients from western and southwestern North Carolina along with surrounding areas. Separate intervention teams and research staff recruit participants and deliver the intervention to randomized enrollees at each main site, but the overall study principal investigator (PI) and blinded outcome assessors serve roles at both sites via dual credentialing. Overall study oversight is based at Atrium Health Wake Forest Baptist Neurology, the major academic hub for Wake Forest University School of Medicine neurology research.

Ethical Considerations

The study has been approved by the institutional review boards (IRBs) of the Wake Forest University School of Medicine (00084191) and the WG (Bill) Hefner Salisbury VA Medical Center (1679395-14). As the study is funded by the Department of Defense (W81XWH2210630), the study protocol was also reviewed and approved by the Department of Defense Office of Human Research Oversight; and the study protocol was also reviewed and approved by the Department of Defense Office of Human Research Oversight; protocol amendments were approved by both IRBs and communicated to the Office of Human Research Oversight. The trial will be carried out in accordance with the International Council for Harmonisation Good Clinical Practice. Full informed consent is obtained from participants before enrollment and baseline data collection and includes permission to transmit deidentified data to the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository for data sharing. All research activities are conducted in as private a setting as possible, and study data are securely stored at each clinical site in locked offices or password-protected secure data systems to which only approved study team members have access. Individual participants and their research data are identified by a unique study ID number, with linkage code stored securely in local site files with password-protected access limited to appropriate study team members. REDCap (Research Electronic Data Capture; version 14.0.21; Vanderbilt University), a 21 Code of Federal Regulations Part 11–compliant data capture system, is used for data collection and storage for analysis. Participants receive a US $40 incentive for completing enrollment and randomization and US $20 each for completing 3- and 6-month outcome procedures.

Participants and Recruitment Methods

Inclusion and Exclusion Criteria

Textbox 1 summarizes the study inclusion and exclusion criteria. Adults receiving neurology care at participating centers are included if they meet the study definition of PTE and exhibit sufficient anxiety or depressive symptoms at screening. To meet study criteria for PTE, the following two criteria must be met: (1) diagnosis of epilepsy by the treating neurology provider based on their clinical impression or ictal or interictal electroencephalogram findings (epileptologist investigator review of documented medical record required for verification) and (2) mild or worse TBI before the first seizure. The presence of mild or worse TBI is assessed based on the Mid-Atlantic Mental Illness Research, Education, and Clinical Center assessment of TBI screener [27], and the temporal relationship of the earliest TBI with seizure onset is evaluated using 3 questions from the National Institute of Neurological Disorders and Stroke (NINDS) PTE screening form. The Mid-Atlantic Mental Illness Research, Education, and Clinical Center assessment of TBI screener is a 5-question validated screener to detect a history of mild or worse TBI [27]. The presence of anxiety or depressive symptoms is determined by scores on the Generalized Anxiety Disorder-7 (GAD-7) and Neurological

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Disorders Depression Inventory for Epilepsy (NDDI-E) instruments, which are well-validated anxiety and depression screeners in epilepsy. Initial cutoffs for inclusion were GAD-7 score ≥10 or NDDI-E score >15, based on original validation literature [28,29], but these were modified to GAD-7 score ≥8 and NDDI-E score >13 after the first 6 enrollments to facilitate recruitment and to align with more recent meta-analyses of these instruments in epilepsy suggesting refined optimal cutoffs [30-32]. Individuals are excluded if they are not good candidates for collaborative care based on having a prior suicide attempt or active suicidal ideation, active psychiatry care without the ability to benefit from the collaborative care intervention, inadequate cognition to complete self-report instruments as part of measurement-based care and research participation, unstable medical problems, or unstable substance misuse. Individuals currently participating in an intervention research study are also excluded.

Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- Diagnosis of posttraumatic epilepsy based on neurology clinician impression or electroencephalogram-based diagnosis and at least mild traumatic brain injury before seizure onset
- Anxiety or depressive symptoms (initial inclusion cutoffs of Generalized Anxiety Disorder-7 [GAD-7] score ≥10 or Neurological Disorders Depression Inventory for Epilepsy [NDDI-E] score ≥16 were active during enrollment of the first 6 participants but were reduced to GAD-7 score ≥8 or NDDI-E score ≥14 thereafter)
- Aged ≥18 y
- Willing and interested in participating
- Neurology care at a study site

Exclusion criteria

- Inadequate cognition to complete self-report instruments
- Active suicidal ideation
- Past suicide attempt
- Unstable drug or alcohol misuse
- Unstable or progressive medical condition
- Current participant in an intervention study
- Active ongoing psychiatry treatment *without potential to benefit from collaborative care intervention* (the additional component of this exclusion, presented in italics, was added after enrollment of the first 6 participants; this was determined based on investigator judgment as to whether the pre-enrollment psychiatry care was less intensive than the potential study intervention; individuals receiving less intensive psychiatry care [eg, stable medication or medication with no case management or therapy intervention] were considered eligible)

Recruitment Methods and Informed Consent Process

Multiple recruitment methods are used at both sites, including neurology clinician referrals; prescreening of scheduled neurology clinic visits with previsit communication to neurologists or follow-up letters and telephone calls; flyers, brochures, cards, and posters advertising the study in neurology clinics; engagement with epilepsy nursing and patient advocacy stakeholders to refer potential participants; electronic recruitment messages in the patient portal (civilian site only); and education and information about the study disseminated to neurology providers via virtual meetings, email, and other communications. Other tools for clinicians available at the civilian site include a patient visit instructions text tool to enable patient self-referral and electronic screening for eligibility, clinician letters mailed to potentially eligible patients identified via data warehouse data pull, and study screening consent and initial screening in the electronic health record (EHR) and embedded in standard care procedures (GAD-7 and NDDI-E screeners attached to all visits at the adult epilepsy clinic) using methods similar to the research team's prior work [33]. At the VA site, prior participants in the Veterans Integrated Service Network 6 Mid-Atlantic Mental Illness Research, Education, and Clinical Center Post-Deployment Mental Health Study [34] who agreed to be contacted for future studies are also screened for potential eligibility and contacted if potentially eligible.

Individuals referred for screening or who express interest will first complete a very brief electronic or verbal screening consent followed by electronic or verbal study screening questions to determine eligibility. Electronic screening questions may be initiated in the EHR for individuals who expressed interest via EHR screening consent or in REDCap [35]. Those individuals found to be fully eligible and interested then complete a full informed consent process, either on paper at the start of an in-person enrollment visit (primarily at the VA) or via local ethics board–approved electronic (DocuSign) or mailed remote informed consent procedures.

Research Procedures and Randomization

Overview

Figure 1 shows an overview of the study procedures. After full informed consent, baseline data collection procedures are conducted by the main site study coordinator either in person

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or remotely (via telephone and, in some cases, via electronic survey for the self-report instruments). Immediately after baseline data collection is completed, participants are randomized by the study coordinator (via a randomization button in REDCap [35], with the site-stratified blocked randomization scheme having been uploaded by the study statistician in REDCap and concealed from all other study team members until the moment of randomization). Variable block sizes are used, with the randomization sequence generated using R (R Foundation for Statistical Computing) [36]. Participants randomized to the collaborative care intervention group then complete the preintervention implementation outcomes. All participants undergo remote 3- and 6-month effectiveness outcome assessment by a blinded outcome assessor, and this blinded outcome assessment is followed by a supplementary unblinded outcome collection by the main site study coordinator. Blinded assessors have restricted access to the study database and other electronic files to prevent unblinding, and scripts are used by the unblinded staff at outcome reminder calls and by the blinded assessors at the start of outcome assessments to remind participants to refrain from mentioning study group allocation. Data collected by the unblinded coordinator during unblinded assessments include implementation outcomes, medications, and information about any changes in mental health treatment. During the study design and planning process, efforts were made to select study measures aligned with NINDS epilepsy or TBI common data elements.

Figure 1. Study design and outcome assessment for patient-level outcomes. QOL: quality of life.

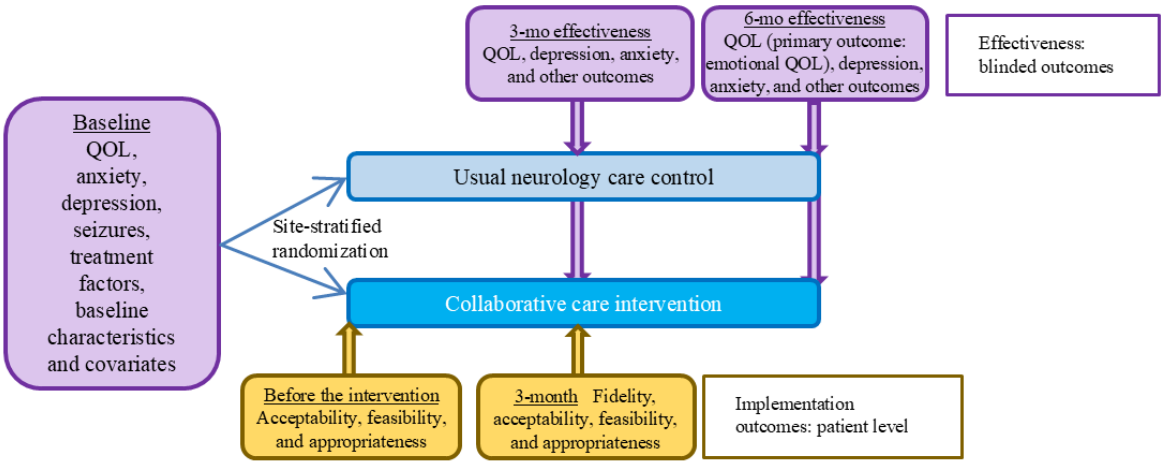

Baseline Data Collection Instruments

At baseline, all effectiveness measures and potential mediators (Table 1) not already collected during screening are administered. The following additional baseline information is also collected: detailed demographics; epilepsy history, including epilepsy type, prior antiseizure medications, cause or risk factors, and prior epilepsy surgeries (aligned with the NINDS epilepsy common data elements). TBI history is assessed via the Ohio State University TBI Short Form [37], while additional core common data elements are evaluated from the FITBIR injury history form and general medical history. The Ohio State University TBI Short Form is a reliable and valid brief structured interview evaluating a history of exposure to TBI, including 5 initial screening questions, and gathering additional information on loss of consciousness, memory gap, and age at injury for each specific incident and any repeated injuries [37]. In addition to the injury history, general medical history and demographics are collected using components of the respective FITBIR forms, including the TBI core common data elements [38]. Epilepsy type (focal, generalized, or unknown) and seizure types are aligned with the current International League Against Epilepsy seizure type and epilepsy classification and the American Academy of Neurology quality measure for seizure type [39-41]. Substance use is evaluated using the Alcohol, Smoking, and Substance Involvement Screening Test, a reliable and valid measure that has 11 screening items for any use across different substance categories, followed by up to 6 additional questions to assess for problematic use among those categories having a positive screen [42]. For each substance area, scores are rated as lower, moderate, or high risk on a scale ranging from 0 to 39, with scores of <4 categorized as lower risk, 4 to 26 as moderate risk, and >26 as high risk. Cognition is evaluated using 5 items from the Brief Test of Adult Cognition by Telephone, a validated cognitive instrument and highly recommended NINDS TBI common data element designed specifically for remote administration via telephone [43]. These items take 5 to 15 minutes to administer.

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Table 1. Effectiveness end points and exploratory potential mediators (seizure and treatment factors).

Concept	Measure	Administration or collection method	Number of items	Score range[a] (if applicable)	Notes about administration
Effectiveness (aim 1)					
Emotional quality of life: primary effectiveness outcome	QOLIE-31[b] (emotional quality of life subscale) [44]	Self-report	5	0-100	—[c]
Epilepsy quality of life[d]	QOLIE-31 [44]	Self-report	31	0-100	—
Depressive symptoms[d]	Beck Depression Inventory–Second Edition [45]	Self-report	21	0-63	—
Anxiety symptoms[d]	Beck Anxiety Inventory [46]	Self-report	21	0-63	—
Depression and anxiety diagnoses	Mini International Neuropsychiatric Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[e] [47]	Structured diagnostic interview	Modules A, C-H, K, N, and O	—	—
Major depressive episode screener	Neurological Disorders Depression Inventory for Epilepsy[f] [29]	Self-report	6	6-24	—
Generic quality of life	SF-36[g] [48]	Self-report	36	0-100	10 items are identical to QOLIE-31 items; these are administered with QOLIE-31, and the responses are used for SF-36 scoring along with the other 26 SF-36 items
Potential mediators (exploratory aim 3)					
Seizure frequency	Seizure diary: NINDS[h] common data elements diary [49]; seizure frequency: American Academy of Neurology epilepsy quality measures seizure frequency categories [41]	Participant paper diary entries reported to study coordinator via interview; interview	—; 2 per seizure type	—	Date, number, and seizure type for each seizure during the time frame; seizure frequency and time since last seizure categories for each seizure type
Seizure severity	Liverpool Seizure Severity Scale [50]	Self-report	1-13	0-100	—
Adverse effects	Liverpool Adverse Events Profile [51]	Self-report	19-21	19-48	—
Medication adherence	Pharmacy records	Record review	—	—	Number of actual refills and number of refills expected for 6 months before enrollment and in each 3-month follow-up time frame

[a]Higher scores indicate higher quality of life for the Quality of Life in Epilepsy-31 (QOLIE-31) emotional quality of life subscale, total QOLIE-31, and Short Form Health Survey-36. Higher scores on the other scaled instruments indicate worse depression, anxiety, seizure severity, or adverse effects.

[b]QOLIE-31: Quality of Life in Epilepsy-31

[c]Not applicable.

[d]Secondary effectiveness outcomes.

[e]Administered only at baseline and 6 months (other measures administered at baseline and at 3 and 6 months).

[f]Screener for the presence of a current major depressive episode.

[g]SF-36: Short Form Health Survey-36.

[h]NINDS: National Institute of Neurological Disorders and Stroke.

Measures and End Points

Effectiveness: Quality of Life, Anxiety, and Depression

The primary outcome is the emotional quality of life subscale of the QOLIE-31 [44], which is identical to the emotional quality of life subscale of the Short Form Health Survey-36 [48] generic quality of life measure; thus, the outcome is of relevance to communities of people with TBI consisting of both those with epilepsy and those without epilepsy. The specific primary outcome is group-level change in emotional quality of life from

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baseline to 6 months. Secondary effectiveness outcomes are depressive symptoms measured by the Beck Depression Inventory–Second Edition [45], anxiety symptoms measured by the Beck Anxiety Inventory [46], and overall epilepsy-specific quality of life (QOLIE-31 total score) [44]. Similar to the primary outcome, these secondary outcome measures will be evaluated as group-level changes at 6 months. Table 1 outlines details of the effectiveness outcome measures, including the number of items and administration characteristics.

Exploratory effectiveness outcomes include generic overall quality of life (Short Form Health Survey-36) [48]; *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, anxiety and depression diagnoses measured by the Mini International Neuropsychiatric Interview (MINI) [47] for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; and epilepsy-specific depression screening status measured by the NDDI-E [30]. At baseline, we administer the mood disorder MINI modules (A [depression], C [manic episodes related to bipolar disorder], and K [psychosis]) as well as the following anxiety and anxiety-related modules: D (panic disorder), E (agoraphobia), F (social anxiety disorder), G (obsessive-compulsive disorder), H (posttraumatic stress disorder), and N (generalized anxiety disorder), along with module O to rule out organic causes. At 6 months, the mood disorder–related modules as well as the panic, generalized anxiety, and posttraumatic stress disorder modules are readministered along with module O for all participants. The agoraphobia and social anxiety disorder modules are repeated at 6 months if a current diagnosis is present at baseline.

Potential Mediators: Seizure Frequency, Seizure Severity, and Treatment Factors

Seizure frequency and severity measures are collected at baseline and at 3 and 6 months to explore as potential mediators of the effect of collaborative care. Seizure frequency is collected via a daily seizure diary (NINDS common data elements seizure diary) provided to participants at enrollment, with diary entries collected by telephone at outcome assessments by the blinded outcome assessor. Seizure frequency and time since last seizure are also classified using the American Academy of Neurology epilepsy quality measures seizure frequency categories at baseline and each outcome assessment [41]. Seizure severity is rated using the Liverpool Seizure Severity Scale [50]. Table 1 contains additional information about the administration characteristics of these seizure- and treatment-related end points.

Medication adherence and side effects are also collected to explore as potential mediators. The Liverpool Adverse Events Profile [51] is used to evaluate medication side effects, and pharmacy records are reviewed to evaluate medication adherence for all standing antiseizure medications and psychotropic medications during the study. Past adherence is assessed at baseline based on a review of prescription fills in the 6 months before enrollment; actual refills will be compared to expected refills in both the pre-enrollment and on-study periods.

Other Exploratory Health Outcomes, and Other Measures Collected at Follow-Up

Major health care use events, including hospitalizations and emergency visits, will be collected at 3 and 6 months via participant report and supplemented by EHR review. Mental health treatments received as part of the intervention or outside of the intervention will be collected and tracked by an unblinded study team member. The GAD-7 and Patient Health Questionnaire-9 (PHQ-9) are valid and reliable measures of anxiety and depression severity with 7 and 9 scored items, respectively [28,52]. These instruments are used for symptom monitoring in the intervention group and collected at screening and baseline and at 3- and 6-month outcome assessments for all participants. Scores range from 0 to 21 and 0 to 27 for the GAD-7 and PHQ-9, respectively, with higher scores indicating worse symptoms.

Implementation

The implementation data collected emphasize early implementation outcomes, with a focus on fidelity (primary implementation outcome), feasibility, acceptability, and appropriateness (Table 2). The primary fidelity measure is the proportion of intervention group participants who attend at least 50% of the care management calls in the first 12 weeks of intervention delivery. This 50% metric was determined based on the consideration of the investigators because it was felt that individuals attending <50% of the visits would be very unlikely to benefit from the intervention. Rates of overall attendance at collaborative care calls are also collected along with various process measures at the level of the patient participant, intervention team, and neurologist. Patient- and provider-level acceptability, feasibility, and appropriateness are collected via very brief validated quantitative measures [53]. Patient participants in the intervention group complete these measures before receiving the intervention and at the 3-month outcome assessment.

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Table 2. Implementation (aim 2) end points and levels of measurement.

Concepts and measures	Levels
Fidelity (primary: intervention adherence)	
Proportion meeting minimum adherence metric of 50% call participation at 12 weeks: primary implementation measure	Patient
Percentage attendance: secondary implementation measure	Patient
Process measures	Neurologist, patient, and intervention team
Feasibility[a]	
Feasibility of Intervention Measure	Patient and neurologist
Acceptability[a]	
Acceptability of Intervention Measure	Patient and neurologist
Appropriateness[a]	
Intervention Appropriateness Measure	Patient and neurologist

[a]Four-item self-report scales that produce a continuous score ranging from 4 to 20, with higher scores indicating higher feasibility, acceptability, and appropriateness for the respective instrument [53].

Neurology providers at the study sites are offered a brief (<30 min) collaborative care training session in person or virtually, delivered by the PI along with members of the local intervention team. They are then offered the opportunity to participate in the implementation measure survey [53] after providing consent through a brief information sheet. Initial neurology provider training sessions were held before the study launch at the initial study sites. Additional training sessions and survey participation are offered on a rolling basis to new neurology provider staff and staff at newly participating neurology clinics within the study site networks. Neurology providers will have the opportunity to complete follow-up acceptability, feasibility, and appropriateness surveys at the study midpoint. Neurology care provider–level process measures will be collected, including whether psychotropic medication prescribing recommendations conveyed by the intervention team were carried out by the neurology providers.

Study Intervention

Overview

The intervention is characterized by a neurology-oriented, remotely delivered collaborative care team model for anxiety and depression management lasting 24 weeks (Figure 2). The team is composed of a care manager (either a nurse or a licensed clinical social worker) who monitors patient symptoms, seizures, and medications and provides care management support and brief therapy interventions via video or telephone calls every 2 weeks; a psychiatrist who primarily provides recommendations at virtual team meetings occurring between care management calls; and a therapist (psychologist or licensed clinical social worker) who delivers an 8-session cognitive behavioral therapy (CBT) program in step 2 of the intervention, if needed. This team communicates with the patient's primary neurologist or neurology provider and provides recommendations for mental health medication interventions to the neurologist. This intervention is grounded in primary care and nonneurology subspecialty collaborative care models demonstrated to be more effective than usual care [20] and adapted from existing primary care and general programs at the study sites, with study intervention team members having expertise in these existing programs (family medicine–based collaborative care at the Wake Forest University School of Medicine and the VA's Whole Health and Primary Care Mental Health Integration programs).

Figure 2. Intervention schema. CBT: cognitive behavioral therapy.

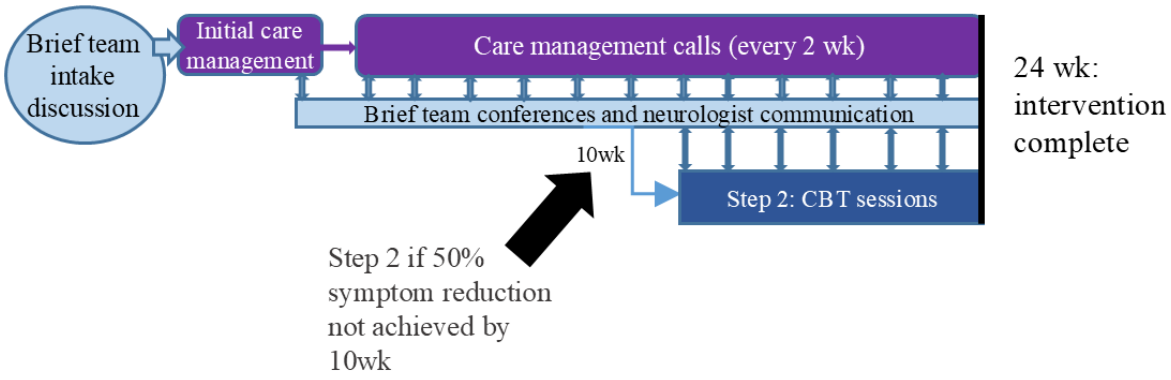

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Care Management Calls and Conferences

A preintervention care conference meeting is held before each participant's first intervention visit with the care manager, typically 1 to 2 weeks after randomization. These meetings are initial brief virtual team intake discussions that review the following information: key aspects of the enrollment MINI [47] results, baseline PHQ-9 and GAD-7 scores, and current and past psychiatric treatment history from the enrollment interview (the collection of this information at baseline serves the care team in the process of understanding what formal information could help in diagnosis and management). In addition, preliminary treatment recommendations are formulated by the collaborative care team (including the use of selected brief therapy interventions), and care management begins at the first intervention appointment that occurs a few days to a week after the initial care conference. The information provided for the initial virtual team case discussion is meant to help frame information that could be gathered by self-report as an initial step in the intervention in clinical practice or by the care manager at an initial care management visit. This provides an opportunity for the experienced mental health clinicians leading the intervention team (psychiatrists and psychologist) to prepare non–mental health care manager clinicians (nurses with coaching experience at the VA site) to deliver the intervention and collect subsequent appropriate mental health assessment information.

The initial care management session is conducted by video, in which the care manager verifies the current symptoms and past and current treatment history with the patient, reviews medication management for both anxiety and depression as well as epilepsy, establishes patient-centered treatment goals, and initiates the treatment recommendations of the collaborative care team. Medication education, when applicable and appropriate, and reinforcement of medication adherence are delivered.

Care management continues with telephone calls or video visits every 2 weeks for 24 weeks in which anxiety and depression scale scores are collected or reviewed (GAD-7 and PHQ-9 instruments for anxiety or depressive symptom severity, respectively, available electronically or on paper for completion before scheduled calls or visits or administered by interview during the call); and response to treatment, any side effects, and barriers to treatment are discussed. The mode of these visits or calls (video or telephone) is determined based on participant preference. The PHQ-9 and GAD-7 instruments were chosen because of their common use in collaborative care models and their ability to characterize symptom severity for depression and anxiety, as well as because they are NINDS epilepsy common data elements. At each intervention call, brief therapy interventions are also delivered to enhance behavioral health. Seizure frequency, side effects of antiseizure medications, and barriers to seizure medication adherence are also assessed during care management calls or visits. To enhance adherence to the intervention calls, telephone or electronic reminders occur the day before each scheduled call.

Team care includes care management conferences between care management calls or visits. These are brief meetings in which the care manager discusses updates on intervention participants since their prior care management call with the intervention team psychiatrist (and psychologist when applicable), and updated recommendations are formulated for the content of care management calls (especially the brief therapy interventions), antidepressant or psychotropic medication management recommendations to be relayed to the neurologist, and potential referrals or direct psychiatry care recommendations. The care manager facilitates communication between the collaborative care team and the neurologist and assists as needed with referrals and medication access. In addition to relaying antidepressant prescribing recommendations to the neurologist, the care manager relays information on seizure status or antiseizure medication side effects to the neurologist or neurology provider if patients are not free from seizures and side effects. Communication with the intervention care manager or psychiatrist can also be initiated by the neurologist at any time.

Brief Therapy Interventions for Care Management Calls

Brief therapy interventions, selected during the intervention team care management conferences, include wellness-based interventions, psychoeducation, problem-solving therapy, behavioral activation, relaxation, mindfulness, or mindful movement. A combination of these is applied, tailored to each participant. Wellness-based interventions focus on the holistic well-being of the participant, identifying areas where they feel they are doing well and where they may need some assistance [54]. Psychoeducation involves informing patients about their symptoms and diagnosis and providing relevant information on these topics throughout collaborative care [55]. Problem-solving therapy helps define areas of concern in the patient's life and supports brainstorming potential solutions to their problems [56]. Behavioral activation involves incorporating positive activities or experiences into daily life, aiming to help participants identify positive activities they could engage in between calls to increase activity levels and decrease anxiety or depressive symptoms [57]. Relaxation techniques teach participants skills related to deep breathing, imagery, and muscle relaxation to assist with grounding and calming, providing temporary relief from tension, stress, or mental or physical pain [58]. Mindfulness encourages participants to live in the present moment by observing current thoughts and feelings, rather than dwelling on the past or worrying about the future [59]. Mindful movement involves checking in with the body and moving in a way that can help lower stress, release stagnant energy, and strengthen the mind-body connection [60]. To assist with the introduction and practice of these topics, participants are provided with related handouts from Therapist Aid (a fair-use free web-based resource for therapists, counselors, clinicians, and care managers) and freely available documents from the VA Whole Health program that are referenced during calls.

Step 2 CBT Intervention

If symptoms for which the participant met criterial for enrollment fail to decrease to 50% of the initial GAD-7 and PHQ-9 measures by week 10, participants move to step 2, which involves 8 sessions of brief, remote CBT by the team psychologist or clinical social worker. At the 10-week collaborative care conference, whether step 2 of the intervention is indicated will be evaluated by examining baseline and the

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most recent scores for the symptom category or categories for which the participant met study inclusion criteria at enrollment (anxiety only, depression only, or both anxiety and depression). If the most recent scores are not ≤50% compared to the baseline and enrollment scores, the CBT step will typically be added to ongoing care management calls. This intervention is used as a more-intensive level of care for those not showing a significant reduction in symptoms since beginning the care management calls. Each 30-minute CBT session is delivered by a licensed psychologist or licensed clinical social worker and includes the following component activities: a review of symptom screening tools (typically the GAD-7 and PHQ-9 from the most recent care management call), teaching of the main CBT topic area for the session, teaching of a technique to use at home as a tool to manage symptoms, and discussion of homework assignments for the period after the session. The first session also includes an initial content element: goal setting, identifying the targeted symptoms, and desired change if the intervention is successful. Sessions 2 to 8 include a review of homework practice from the prior session early in the appointment schedule. The main topics covered across the 8 sessions are an introduction to the CBT model (how thoughts, feelings, and behaviors interact), the use of thought records (tracking daily thoughts and feelings and reframing), the cycle of anxiety or depression through a CBT lens, the role of automatic negative thoughts or automatic thoughts, behavioral intervention through a CBT lens (behavioral activation and exposure and response inhibition), core beliefs and how they impact our thoughts and feelings, situations or stressors (antecedents) applied to thought record use, and creating a plan for the independent use of CBT concepts and tools after the conclusion of the study [61].

Interventionist Training and Fidelity Assessment

To minimize bias in the results from using distinct care managers and therapists for CBT delivery at the 2 sites, checklists and a manual with scripts were provided to intervention team members at both sites, and members at both sites underwent a uniform training process, including manual self-study, live training sessions delivered by intervention team lead investigators, and rating of competencies using the checklists. Care managers also completed the American Psychiatric Association web-based module "Applying the Integrated Care Approach: Skills for the Behavioral Health Care Manager" before intervention delivery. A demonstration of adequate competency on all checklist items is required before study intervention delivery by a team member. During intervention delivery, care management calls and CBT sessions are recorded using secure methods acceptable per local study site policies, and some sessions are randomly selected for review to evaluate adherence to the key components on the checklists. Further training will be provided if needed to team members to maximize the consistency of intervention delivery.

Comparator

The control group receives usual neurology care, meaning ongoing neurology provider–recommended clinic visits, prescriptions, testing, and referrals. Mental health referrals or prescribing of antidepressants may potentially occur in this group; these types of interventions will be tracked at outcome assessments.

Safety

To ensure study safety, individuals with active suicidal ideation, past suicide attempt, or unstable substance misuse are excluded. If there is a need for immediate treatment (eg, active suicidal ideation or active psychotic symptoms) at any point in time, staff will notify the PI or designated investigator and follow established study safety procedures [62,63] to evaluate and respond. All study team members having participant contact receive specific live training on site-specific safety procedures, along with IRB-approved safety procedure instruction documents. If needed, participants may be referred for psychiatric care, including emergent psychiatric care. Study psychiatrists and the psychologist or social worker at each site are available for input and guidance as needed. As an additional safety precaution, we will ask each participant upon study entry to identify and provide emergency contacts and their contact information. All participants will receive information about safety precautions and procedures to follow in the event that a participant becomes imminently suicidal. They will also be given telephone numbers for site-specific urgent psychiatric care and a crisis hotline. As an additional safety precaution, if any participant indicates a significant worsening in anxiety or depression scores (an increase of >1 SD on the Beck Depression Inventory–Second Edition or Beck Anxiety Inventory from baseline, 12 and 10 points, respectively [45,46]), the computer software system will facilitate identifying the worsening, and an email will be sent to the site coordinator, PI, and site psychiatrist or psychologist. Staff will be instructed to follow the study-specific safety procedures in follow-up and review with the investigator any need for additional action, such as referral for psychiatric care or to other physicians as appropriate. Safety monitoring will be conducted by the Wake Forest University School of Medicine Institutional Data Safety Monitoring Board.

Sample Size and Power

Given the emphasis on effectiveness in our trial, we estimated the total sample size using the primary effectiveness outcome, that is, change in emotional quality of life from baseline to 6 months. With a total sample size of 60, we will have 80% statistical power to detect a moderate clinically important difference in mean change equal to 20 units [26] in the collaborative care group, compared to usual care, assuming a dropout rate as high as 13% at 6 months in the intervention group and a common SD of 24 units [24] (2-sample 2-tailed *t* test, α=.05). For our secondary outcome overall (primary implementation outcome), we will have 80% statistical power to detect a true proportion of participants of 0.8 who attend a majority of the collaborative care management calls in the first 12 weeks, assuming a sample size of 30 in the intervention group (exact binomial test, α=.10, one-sided testing vs the null proportion of 0.6) [64].

Statistical Analysis Plan

To evaluate the primary effectiveness outcome, we will test the hypothesis that there is a clinically significant change in

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emotional quality of life (QOLIE-31 emotional quality of life subscale) at 6 months with the collaborative care intervention compared to usual care. The primary analysis will compare changes in subscale scores from baseline to 6 months between the intervention and control arms using multiple linear regression modeling, adjusting for study site and using an intent-to-treat approach. If the data are incomplete due to withdrawal of consent or dropout, missed visits, or missed individual data items, missing data methods will be used to compare results; specifically, a sensitivity analysis and maximum likelihood repeated measures analysis will be conducted under the missing-at-random assumption. Secondary effectiveness outcomes (anxiety, depression, and epilepsy-specific overall quality of life) will be evaluated using similar methods.

In exploratory effectiveness analyses, we plan to extend this modeling to evaluate the moderators and mediators of the collaborative care intervention effects. Potential moderators will include baseline medication adherence, cognition, and social factors such as employment and marital status. Mediators will include factors related to patient seizures (seizure frequency and severity) and treatment (medication adherence and side effects). We believe analysis of these factors to be a logical next step in follow-up of the primary and secondary results, with good potential for identifying important mechanisms to help us improve our implementation strategies and increase the effectiveness or efficiency of future interventions.

To evaluate the primary implementation outcome, we will test the hypothesis that the fidelity of the intervention, as measured by the proportion of participants in the intervention group who attend a majority of the collaborative care management calls in the first 12 weeks, is >0.6 using exact binomial testing (type I error rate ≤0.10). The corresponding CI (90% level) will be calculated based on the Wilson score method [65]. The data analysis for this project will be generated using R and SAS or STAT software (SAS Institute Inc) [36].

Results

Enrollment for the study commenced in 2023. Due to initial slow recruitment, the inclusion and exclusion criteria were adjusted after the first 6 participants enrolled, as mentioned previously. The civilian site is initiating plans to expand enrollment beyond the Atrium Health Wake Forest Baptist region of the primary study's health system to include neurology and epilepsy care sites throughout the Atrium Health enterprise (after EHR harmonization efforts across the 2 enterprise regions). Enrollment is expected to continue at least into 2025.

Discussion

Summary

This hybrid type 1 effectiveness implementation trial will evaluate a 24-week collaborative care intervention adapted from existing civilian and VA programs among adults with anxiety or depressive symptoms and PTE. The analysis of the primary outcome will demonstrate whether the collaborative care intervention results in a moderate improvement in emotional quality of life compared to usual care and thus merits immediate clinical implementation, or whether it instead merits further investigation, such as a larger trial powered to detect a minimal clinically significant difference. The implementation results will help demonstrate whether additional refinement of the intervention or implementation strategy is needed.

Comparison to Prior Work

This study builds on a vast body of data supporting collaborative care to improve anxiety, depression, and emotional quality of life in medical samples [20] by testing it in a neurology clinic setting among patients with epilepsy. In contrast to the Program to Encourage Active, Rewarding Lives intervention in epilepsy, which involved master's-level therapists delivering eight 50-minute in-home sessions of problem-solving therapy emphasizing physical and social activity, our study intervention targets anxiety and depression rather than depression alone and includes additional brief therapy options tailored to individual goals [24]. Collaborative care is directly aligned with existing billing codes, in contrast to various evidence-based epilepsy self-management programs for which funding uncertainty was identified as a key barrier to implementation and sustainment [66]. Our collaborative care intervention also builds on the study team's prior work demonstrating that while many patients with epilepsy may prefer to receive mental health care in a neurology setting [18], many individuals in this setting have inadequate symptom relief despite existing antidepressant prescribing [17], arguing for neurology clinic–based interventions that include specialized mental health input, such as collaborative care. Our collaborative care intervention incorporates elements previously reported to be preferred anxiety and depression management modalities by patients in this epilepsy care setting (wellness-based interventions, antidepressants prescribed by a neurologist, therapy, and complementary or integrative techniques such as mindfulness) [18], and the collaborative care model was also well received by patients with epilepsy in a semistructured interview study [67].

Strengths and Limitations

This is an innovative application of a hybrid effectiveness-implementation trial design and validated quantitative implementation outcome measures in the field of epilepsy. The intervention is fully remotely delivered, which may facilitate participation for patients with epilepsy, and it is grounded in an intervention that can be billed to government and commercial insurance carriers, which may facilitate next step clinical implementation if demonstrated to be effective. The seizure care–related components of the intervention are an innovative disease-specific adaptation of collaborative care for epilepsy; these components may potentially benefit overall epilepsy care.

The limitations of this study include the small, 2-site design, which may limit generalizability but which does have the advantage of including participants from 2 very different practice settings—the VA and a civilian university site—which may mitigate this limitation. The intervention teams are small, and the intervention is adapted from local programs at these clinical sites; further evaluation in a larger multisite context may be beneficial. In addition, the teams are somewhat distinct

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at the VA (nurses with coaching experience, psychologist, and psychiatrist) versus the civilian site (licensed clinical social worker and psychiatrist), but we attempted to mitigate this via standardized training and checklist use as well as fidelity assessment using intervention recordings and the checklist during intervention delivery. Another limitation of this trial as an implementation study is that multiple research instruments are used to collect data, which incurs a participation burden distinct from routine care practice collaborative care and may result in selection bias and deter recruitment.

Future Directions

Depending upon the results of this trial, the next steps could include refining the intervention or implementation strategy and further testing in a larger trial or preparation for dissemination and clinical implementation. Ultimately, the future directions include using the implementation data collected in this trial to consider implementation characteristics and build toward scalability. Future testing focused on the impact of collaborative care on seizure outcomes and testing of similar interventions in mixed neurological disease samples may be warranted. Other future directions related to health policy could include examining the impact of integrated mental health care program availability on neurologist burnout and potential advocacy for increased access and resources for mental health screening and treatment. This advocacy could include specific action to advocate for more payers to cover the collaborative care billing codes, as well as other funding and resources for mental health care in specialty clinics.

Conclusions

CoCarePTE is an innovative hybrid type 1 effectiveness-implementation trial testing a collaborative care intervention for anxiety or depression in PTE. The main results may support immediate clinical implementation of this intervention versus further refinement and testing, and the implementation results will inform implementation strategy refinement and potential planning for scalability.

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Data Availability

Datasets generated and analyzed during this study will be submitted to the Federal Interagency Traumatic Brain Injury Research data repository [68] and may be requested by accessing the repository.

Authors' Contributions

HMMC was responsible for conception, design, and drafting the manuscript. BMS was responsible for conception, design, drafting parts of the manuscript, and critical review for important intellectual content. CC was responsible for conception, design, and drafting the manuscript. RK, JNK, HBA, GAB, JBM, and RAH were responsible for conception, design, and critical review for important intellectual content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from Department of Defense Congressionally Directed Medical Research Programs Epilepsy Research Program.
[PDF File (Adobe PDF File), 118 KB - resprot_v13i1e59329_app1.pdf]

Multimedia Appendix 2
CONSORT checklist.
[PDF File (Adobe PDF File), 126 KB - resprot_v13i1e59329_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CoCarePTE: Collaborative Care for Posttraumatic Epilepsy
EHR: electronic health record
FITBIR: Federal Interagency Traumatic Brain Injury Research
GAD-7: Generalized Anxiety Disorder-7
IRB: institutional review board
MINI: Mini International Neuropsychiatric Interview
NDDI-E: Neurological Disorders Depression Inventory for Epilepsy

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NINDS: National Institute of Neurological Disorders and Stroke
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
PTE: posttraumatic epilepsy
QOLIE-31: Quality of Life in Epilepsy-31
REDCap: Research Electronic Data Capture
TBI: traumatic brain injury
VA: US Department of Veterans Affairs

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Protocol

Community Versus Facility-Based Services to Improve the Screening of Active Hepatitis C Virus Infection in Cambodia: The ANRS 12384 CAM-C Cluster Randomized Controlled Trial—Protocol for a Mixed Methods Study

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Abstract

Background: In Cambodia, hepatitis C constitutes a significant public health challenge, particularly among older adults (>45 years) for whom prevalence is estimated to be 5%. To facilitate the elimination of hepatitis C among the general population, enhancing access to screening and treatment is imperative. In this regard, the evaluation of community-based screening programs emerges as a crucial step toward improving health care accessibility.

Objective: This study aims to assess the comparative efficacy of a community-based versus a facility-based approach in enhancing the uptake of hepatitis C antibody testing among the general population older than 40 years of age in Cambodia.

Methods: The CAM-C (Community Versus Facility-Based Services to Improve the Screening of Active Hepatitis C Virus Infection in Cambodia) study uses a cluster-randomized controlled trial design across two Cambodian provinces to compare community-based and facility-based hepatitis testing interventions. Sampling involves a multistage cluster approach, targeting individuals older than 40 years of age due to their higher prevalence and risk of chronic hepatitis complications. This study incorporates a qualitative analysis of acceptability and a cost-effectiveness comparison. Interventions include facility-based testing with subsequent referral and community-based testing with direct in-home assessments. Follow-up for positive cases involves comprehensive management and potential direct-acting antiviral treatment. This study aims to identify a significant increase in testing uptake, requiring the screening of 6000 individuals older than 40 years of age, facilitated by a structured sampling and intervention approach to minimize contamination risks.

Results: The final protocol including the quantitative, qualitative, and cost-effectiveness part of the study was registered and was approved in 2019 by the National Ethical Cambodian for Health Research. Inclusions were completed by mid-2024, with analyses starting in May 2024.

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Conclusions: Using a mixed methods approach that combines a robust methodology (cluster-randomized controlled trial) with a cost-effectiveness analysis and qualitative research, such a study should provide invaluable information to guide the Ministry of Health in its hepatitis C virus screening strategy and move toward elimination.

Trial Registration: ClinicalTrials.gov NCT03992313; https://clinicaltrials.gov/study/NCT03992313

International Registered Report Identifier (IRRID): DERR1-10.2196/63376

(JMIR Res Protoc 2024;13:e63376) doi:10.2196/63376

KEYWORDS

hepatitis C virus; HCV; community-based intervention; cluster randomized controlled trial; Cambodia; cost-effectiveness analysis; qualitative analysis

Introduction

Hepatitis C virus (HCV) infection is a major public health concern, affecting millions of individuals worldwide. In recent years, several countries have launched ambitious national programs aiming at eliminating HCV as a public health threat [1,2]. These programs use a range of strategies including widespread screening, access to affordable treatment, harm reduction measures, and public awareness campaigns. Current efforts to eliminate hepatitis C at the national level vary in scope and implementation strategies. Countries, like Egypt, Australia, Georgia, and Iceland, have emerged as leaders in the global fight against HCV, demonstrating significant reductions in disease prevalence and incidence [3,4]. These countries have adopted multifaceted approaches that encompass mass screening, treatment access, harm reduction interventions, and public engagement [4]. Successful outcomes have been achieved through proactive government policies, collaboration with health care providers and community organizations, and innovative financing mechanisms [1,5].

One of the significant recent advancements is the availability of direct-acting antivirals (DAA), with cure rates approaching 90% to 95% along with their good tolerance. These treatments are expected to change the dynamic of HCV infection worldwide and give hope for eradication. However, the impact of DAA in the general population is completely related to the population-level cascade of care: screening programs must reach undiagnosed individuals, diagnosed individuals must be linked with care, and people engaged with care must be assessed, receive treatment, and be cured. In 2016, in the Western Pacific region, according to the World Health Organization (WHO), only 21% of people living with HCV have been diagnosed and 2% started treatment. There is a need to address how different interventions apply to the context of well-tolerated, simple, oral treatment regimens. The Georgia HCV elimination program has recently reported promising results [6] highlighting that “high-quality screening, innovative linkage-to-care strategies, and cost-effective and simplified diagnostic and treatment regimens are needed” to reach the elimination target.

In Cambodia, the burden of viral hepatitis exceeds the combined burden of HIV and tuberculosis. Estimates suggest that 3% of the population (approximately 475,000 individuals) live with chronic hepatitis B virus (HBV), and 1.6% (around 257,000 individuals) with chronic HCV [7]. These infections are the predominant causes of liver cirrhosis and liver cancer–related fatalities in the country, leading to roughly 2300 deaths annually. Liver cancer, primarily attributed to viral hepatitis, has become the foremost cause of cancer death in Cambodia [8]. A 2018 seroprevalence survey by Médecins Sans Frontières (MSF) nongovernmental organization and Epicentre highlighted a critical awareness gap; 64% of respondents and 57% of seropositive participants had never heard of HCV. Moreover, the prevalence among older adults (>45 years) was significantly higher (5.1%) compared to those younger than 45 years old (0.6%) [9].

A recent study indicated that people living with HIV are at a heightened risk of contracting HCV, with a prevalence rate of 6.8%. This study also identified two significant risk factors for HCV infection: having a family member positive for HCV and the use of intravenous medication in the past 5 years [10]. These efforts underscore the complexity of the hepatitis epidemic in Cambodia and the multifaceted approach required to address it. The challenges in eliminating hepatitis in Cambodia include not only the provision of medical treatments but also the need for increased public awareness, improved diagnostics, and the integration of hepatitis screening and care into the broader public health infrastructure including communities’ health care workers.

While there has been considerable progress in access and affordability to diagnostic and treatments for lower-middle-income countries there is a sheer lack of international or domestic financing for a robust program for patients chronically infected with hepatitis B or C [10,11]. In 2018, a modeling study led by Bristol University using data from the MSF pilot project demonstrated the cost-effectiveness of a public health intervention [12]. This analysis was made at the time of higher prices of HCV commodities and estimated the cost for the elimination of about US $60 million by 2030 [13]. The 12-week DAA treatment for HCV chronic patients would not only prolong thousands of lives but also offer a direct cost saving of US $18.3 million. Discussions with UNDPA (United Nations Department of Political Affairs) are underway to help Cambodia benefit from lower prices. In the past 2 years, the Cambodian government has committed to the national elimination program by 2023, allocating US $1 million per year for screening tests and treatment.

We hypothesize that enhancing hepatitis care necessitates identifying and tailoring effective screening strategies for the general population, particularly prioritizing those older than 40 years of age due to their vulnerability to severe hepatitis

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outcomes. Our approach advocates for integrating serological and virological assessments to boost the precision of active infection detection. Additionally, we advocate for a community-based testing model, leveraging rapid diagnostic tests (RDT) and dried blood spot (DBS) synergies, to potentially surpass traditional facility-based methods in accessibility and patient engagement. The main objective of this study is to compare the effectiveness of a community-based intervention to a facility-based intervention to improve the antibody-testing uptake of HCV infection among the general population older than 40 years of age in Cambodia.

Methods

Study Design

The CAM-C study is a 2-arm cluster randomized controlled trial, in which clusters are defined as a group of 50 households corresponding to the service population of the community health care workers (CHWs). This study includes a qualitative investigation of the acceptability of both strategies, as well as a cost-effectiveness analysis comparing the community-based and facility-based arms with each other and with the status quo.

Study Overview and Sampling

This protocol outlines a cluster randomized controlled trial designed to evaluate the effectiveness of facility-based testing interventions (Arm 1) compared with community-based interventions (Arm 2) in improving the detection of people with HCV active infection.

The research was conducted across two separate provinces in Cambodia: Siem Reap and Kampong Cham. Both provinces have a population of approximately 1 million, each served by a provincial hospital. Siem Reap is organized into 4 operational districts (ODs), 103 communes, 5 referral hospitals, and 88 health centers. Kampong Cham, on the other hand, comprises 9 ODs, 107 communes, 9 referral hospitals, and 98 health centers (Figure 1).

Figure 1. Study area Siem Reap and Kampong Cham provinces.

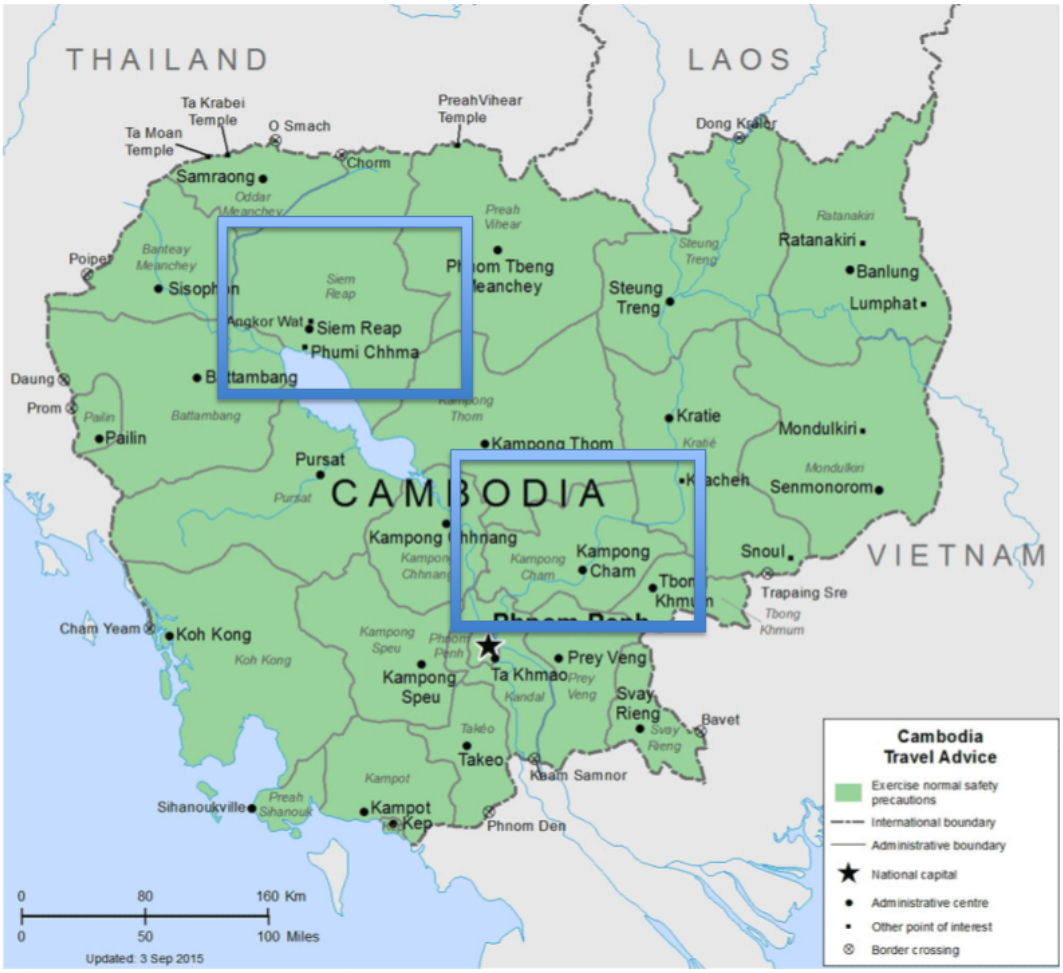

For the purpose of this study, one OD in Siem Reap and two ODs in Kampong Cham have been selected. These districts have a comparable number of villages and inhabitants and are equidistant from their respective provincial health departments. Each district is further segmented into communes, which are then divided into villages, and subsequently into groups, typically consisting of 50 households each. One such group will be designated as a cluster.

To further reduce contamination risks between arms in terms of intervention-related activities, four geographically distinct areas, separated by nonparticipating communes, have been chosen in each province. These areas were randomly assigned to either Arm 1 or Arm 2. A multistage cluster sampling

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approach was used for participant selection within each geographic area. Initially, a probability proportional to size sampling method was used to select 10 villages in each geographic area. A preliminary mission allowed us to verify the locations of households within these villages, during which demographic data, including inhabitants' ages, were collected. Subsequently, a simple random sampling method was applied to select 100 households per village from the 10 chosen villages. Finally, all individuals older than 40 years of age within these households were invited to participate in the study. This structured approach ensures a comprehensive assessment of the proposed testing interventions within the target populations. The inclusion and exclusion criteria are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- All persons older than 40 years of age
- Residing in the study area
- Informed consent obtained with oral information given and explained and the consent form signed by the participant

Exclusion criteria

- Known hepatitis C virus (HCV) status with previous HCV treatment
- Severe disease present at inclusion involving life-threatening
- Concurrent participation in any other clinical study without written agreement of the two study teams

For the qualitative part of the study, key participants for the interviews included leaders in the health sector, such as heads of health centers and ODs, alongside health care providers directly involved in the intervention, including health centers staff, community health workers, and village health support groups.

Sample Size

The objective was to discern a significant increase in testing uptake from 60% in facility-based settings to 80% in community-based settings among individuals older than 40 years. The calculation was based on data from the 2014 Cambodia Demographic and Health Survey report, which indicates an average rural household size of 4, with 25% of individuals being older than 40 years, resulting in an estimated cluster size of 50 [14].

Key assumptions for this calculation included an intraclass correlation of 0.01, a significance level of 5% (α=.05), and a study power of 80% (1-β). The design effect was set at 1.5, reflecting the expected variance inflation due to cluster sampling.

To achieve the desired power for detecting the anticipated difference in testing uptake between the two study arms, the study required screening at least 300 patients for HCV RNA. This implied screening at least 6000 individuals older than 40 years by RDT on the basis of an estimated 5% positivity rate for HCV antibodies. Given an expected median testing uptake of 60%-70%, the study plans to propose testing to 8000 participants, distributed across 160 clusters (80 clusters per intervention arm), to ensure reaching the target of 6000 screened participants.

Intervention

The study design of both interventions is resumed in Figure 2.

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Figure 2. Study design of the intervention. CHW: community health care worker; DAA: direct-acting antiviral; DBS: dry blood spot; HCV: hepatitis C virus; RDT: rapid diagnostic test; UHS: University of Health and Science, Phnom Penh.

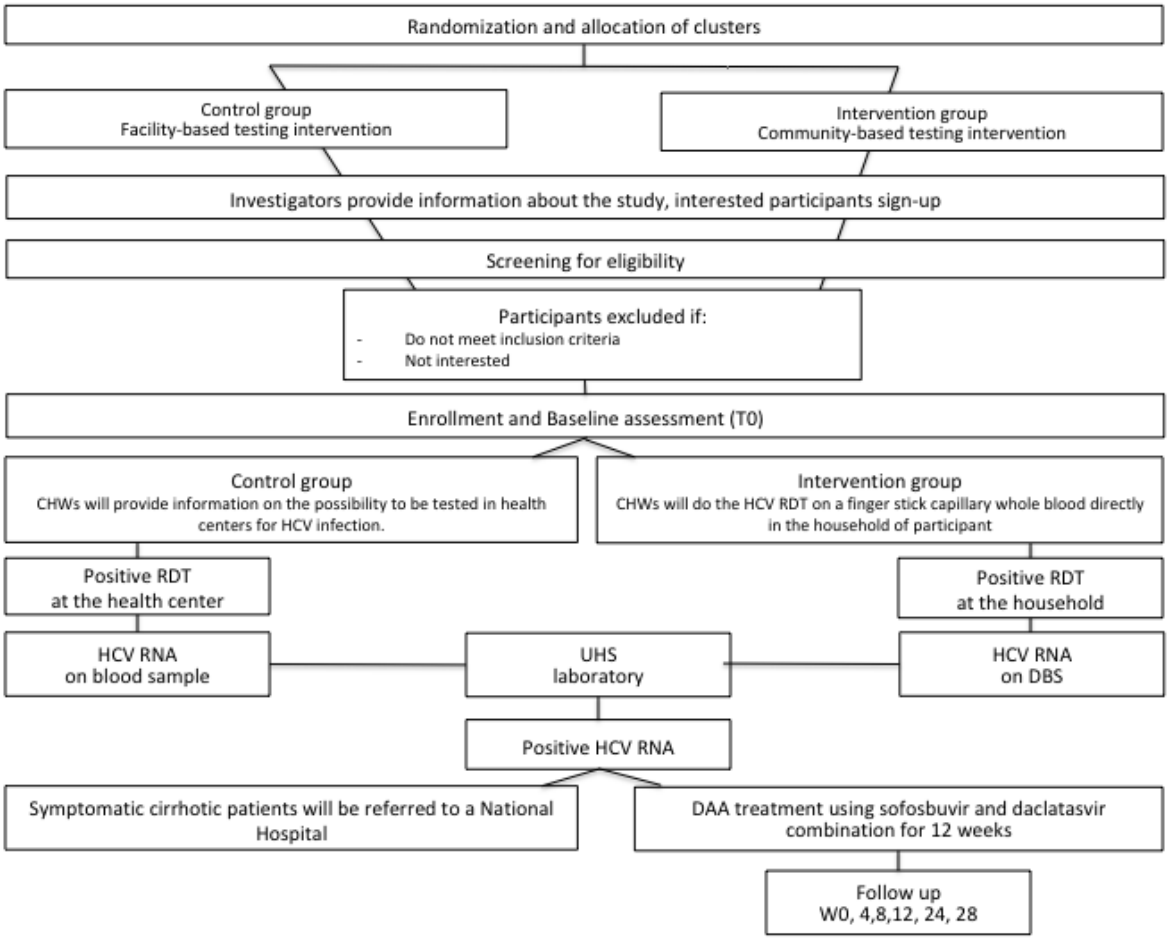

Arm 1: Control Group, Facility-Based Testing Intervention

In this arm, CHWs disseminated face-to-face information in selected households about HCV testing opportunities at health centers through information sheets and dedicated leaflets. Interested participants received a voucher to attend a referral health center for HCV testing. Upon consenting formally at the health center, individuals underwent HCV testing via RDT using finger stick capillary whole blood, with results available within 15 minutes. Positive RDT participants had an immediate collection of a 5-mL whole blood sample (using an ethylenediaminetetraacetic acid tube) at the health center, which was forwarded to the provincial hospital laboratory for plasma extraction. The plasma was sent to the Pasteur Institute of Cambodia for HCV RNA analysis, with the outcomes relayed back to the health center. Health center nurses communicated the results to the participants and facilitated referrals for those with active infections, ensuring follow-up through systematic appointments and phone calls for nonattendees.

Arm 2: Intervention Group, Community-Based Testing Intervention

In this arm, CHWs, after receiving specialized training, performed HCV RDTs directly in participants' homes using finger stick capillary whole blood. Information was provided through the same information sheets and leaflets as the facility arm, and consent was obtained prior to testing in participants' homes. Should household testing face structural or societal hurdles, alternate testing locations within the village may be used. Coordination with village heads ensured population awareness, with a provision for a second visit for absentees during the initial visit; no further attempts were planned after a missed second visit. For participants testing RDT positive, 5 blood spots were collected immediately on DBS cards, securely packaged with the participant's ID number, and dispatched to the Pasteur Institute of Cambodia for HCV RNA extraction and amplification. Results were communicated back to each village's referral health center, where nurses were responsible for result disclosure to participants and subsequent referral for those with active infections, supplemented by systematic appointments and phone calls for those who did not attend.

Follow-Up

Participants with negative HCV RNA results received specific counseling tailored to their situation. Participants with positive HCV RNA were scheduled for a consultation at the provincial hospital. If a consultation was not attended within 4 weeks, an SMS text message reminder was dispatched to the participant. Trained general practitioners, with potential phone support from hepatologists, conducted the consultations. The initial assessment for these participants encompassed questionnaires

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covering risk behaviors and socioeconomic status, a clinical examination, blood sampling, and a liver ultrasound.

Patients displaying symptoms indicative of cirrhosis, such as ascites, collateral circulation on the abdominal wall around the umbilicus, encephalopathy, jaundice, or those with hepatocellular carcinoma, were referred to the hepatology unit in a national hospital in Phnom Penh (Calmette hospital).

For other patients, DAA treatment was offered, pending a review of creatinine levels and potential drug-drug interactions. The study used nonexperimental drugs, specifically a daily regimen of sofosbuvir (400 mg) and daclatasvir (60 mg) for 12 weeks. WHO-prequalified generic drugs from Hetero Labs Limited, comprising a daily dose of Sofosbuvir (400 mg) and Daclatasvir (60 mg) were used. DAA treatment was initiated at the first provincial hospital consultation, with monthly follow-ups thereafter. All adverse events were assessed by the investigator and documented regardless of the possible causality with the concomitant treatments. Adherence was evaluated every month using a questionnaire and visual analog scale. Biological follow-up during the treatment is reported in Multimedia Appendix 1.

Blood Sample Collection and Tests

Upon confirmation of HCV RNA positivity, further tests were conducted at the initiation of DAA therapy, including screenings for HBsAg, HIV syphilis duo, and a range of blood and biochemical analyses. The rapid tests used in the study were Alere Determine, HBsAg, Bioline HCV test, and Bioline HIV/Syphilis Duo test.

Subsequent tests are scheduled at weeks 4, 8, 12, and 24, with varying focuses, such as complete blood counts, serum transaminases, and serum creatinine levels, culminating in a plasma HCV-RNA viral load test at week 24.

The study differentiates between Arm 1 and Arm 2 in terms of HCV RNA testing methods, with Arm 1 using plasma and Arm 2 using DBS for sample collection and transport to the Pasteur Institute laboratory for analysis. Post screening, all samples are slated for destruction, except for those designated for the biobank.

For the biobank, samples collected during therapeutic follow-up at weeks 0, 12, and 24 were stored at the University of Health and Science's Rodolphe Merieux laboratory. Plasma from these samples was aliquoted and frozen, with a dedicated database for sample registration. These samples are preserved for 15 years post participant consent, facilitating future research and analysis.

Data Collection

Clinical research assistants who obtained signed informed consent from participants in their native language collected data for this study on the field. For qualitative data, interviews were recorded, transcribed, and translated from Khmer into English for analysis. The data collection encompassed various aspects, including the cost-effectiveness analysis of the two study arms (community-based and facility-based interventions). This included detailed cost data such as the time spent by human resources, salaries, the costs of tests, and the treatments in each study arm. All collected data were then anonymized to ensure participant confidentiality and privacy.

Statistical Plan

The demographic and socioeconomic characteristics of participants at inclusion will be detailed for the total sample and comparatively between arms by using chi-square, Student *t* test, or Wilcoxon tests as applicable (eg, comparing proportions, means, or medians). The comparison between arms in terms of demographic, socioeconomic characteristics, and the distribution across provinces will provide information about potential significant differences between arms. In this case, statistical methods, such as inverse probability weighting, will be implemented in order to ensure the comparability of arms, that is, avoiding sampling or selection biases introduced by implementation issues, participants' behaviors, etc [15,16]. The primary outcome will focus on the percentage of participants tested for HCV RDT and informed of their status within the total eligible population in the intervention regions, with comparisons drawn between the two arms. Secondary outcomes will assess the percentage of persons tested for both HCV RDT and HCV RNA, the number of individuals with active HCV infection who received and understood their results, and the number of persons with at least one consultation at the provincial hospital, all compared between the study arms. The ANOVA will be used to identify significant differences in primary and secondary outcomes between the clustered trial arms, supplemented by confidence levels, intervals, and effect sizes to elucidate the data. An Analysis of Covariance model will analyze the main outcome by considering the baseline as a covariate and will test for associations between covariates to provide a thorough understanding of the intervention's impact. A logistic mixed model will be used to assess the associated factors (odds ratio and 95% CI) for the primary outcome. This will allow accounting for cluster intraclass correlation and disentangle the variability of the outcome due to geographical (eg, provincial) and individual differences [16,17].

Cost-Effectiveness Analysis

The cost-effectiveness analysis of this study compares the value of mobile HCV testing services versus incentivizing health center testing, focusing on individual and societal benefits. It tackles methodological challenges by carefully evaluating costs associated with DAA, the analysis perspective (ie, health system and individual), time horizon, and HCV-related diseases including nonmedical expenses. Costs are broken down by intervention arm, covering community information, HCV RDTs, blood sample collection, and transportation, with additional costs for CHWs mobilization in community-based screening. Common costs across both arms include further biological tests, DAA treatment, concomitant drugs, outpatient consultations, and inpatient care. Special attention is given to cirrhotic patients and nonresponders, accounting for specific tests and treatments. The main effectiveness criterion corresponds to the primary outcome of the study (ie, the proportion of participants with HCV RDT tests and informed of their status among the total eligible population). This analysis aims to provide a detailed understanding of the economic implications of each testing strategy.

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Qualitative Study

The qualitative component of the study aims to explore the acceptability of both facility-based and community-based HCV testing strategies, engaging approximately 94 participants. The methodology includes semistructured interviews with about 30 health sector leaders and health care providers, including heads of health centers, community health workers, and village health support groups, to understand their perspectives on HCV testing's context, strengths, and challenges. Additionally, 8 focus group discussions will be conducted, involving around 64 participants from the community, divided equally between those who accepted and those who declined HCV testing. These discussions aim to gather diverse viewpoints on testing strategies, barriers to testing, and suggestions for increasing testing uptake in Cambodia. The study's structured approach, using a mix of interviews and focus groups, is designed to offer comprehensive insights into the feasibility and acceptability of HCV testing interventions, thereby informing effective HCV management and control strategies.

Ethical Considerations

In this study, patient participation was strictly voluntary, with comprehensive information provided about the study's aims, procedures, duration, risks, benefits, and possible discomforts. This information was conveyed both verbally and through a written sheet in Khmer language. Consent was given before any study-related exams, with participants signing a consent form, a process overseen by the investigator. Consent forms were securely stored, and participants received a copy. The process varies slightly between the 2 study arms, with consent collected at health centers for Arm 1 and in participants' households for Arm 2. A separate consent process was also in place for the therapeutic phase at the provincial hospital and the qualitative part of the study. The protocol received approval from the National Ethical Cambodian for Health Research on February 25, 2019 (approval 047). This protocol has also been registered with ClinicalTrials.gov (NCT03992313).

Results

This project has received funding from the ANRS Emerging Infectious Diseases (ANRS MIE) award ANRS 12384. The final protocol including quantitative, qualitative, and cost-effectiveness parts of the study was registered and approved in 2023 by the National Ethical Cambodian for Health Research. Participant enrollment was completed by mid-2024, and analyses commenced in May 2024. We will publicize our findings through peer-reviewed studies, conference presentations, and recommendations to the local and national public health institutions.

Discussion

Expected Benefits of the Study

The Royal Government of Cambodia, in alignment with the WHO's global objectives, has committed to the ambitious goal of eliminating HCV and HBV by 2030. Since the 1990s, the Cambodian government has expanded access to systematic screening of blood donations for HBV and HCV, as well as the widespread adoption of single-use syringes. The latter measure is especially critical, given that HCV transmission is predominantly associated with parenteral interventions, surgeries, or endoscopies prior to the year 2000 [18]. Populations at greatest risk appear to be individuals older than 40 years of age [19]. In June 2018, the Ministry of Health established a Viral Hepatitis Technical Working Group, led by the Director of the Communicable Disease Control Department. This group was tasked with developing a Viral Hepatitis National Strategic Plan and guidelines policies based on scientific evidence and enhancing the accessibility of diagnostics and treatments within the public health system. Hepatitis was listed as a priority area for action within Cambodia's most recent national strategic health plan (2016-2020), and in 2017, the National Center for HIV/AIDS, Dermatology and STDs secured funding from the Global Fund (using underspend on their grant) to diagnose and cure HIV/hepatitis C coinfected patients enrolled in their antiretroviral therapy program.

One of the main issues identified within the National Technical Working Group was the difficulty in reaching at-risk people for HCV screening. In 2020, using a health center-based approach, the MSF project reached a screening coverage of 40% of the adult population older than 45 years of age estimated in need of HCV treatment in 3 ODs of the province of Battambang [20]. This excellent result in the context of the COVID-19 pandemic is, however, insufficient to reach the 80% coverage target required for elimination. A community-based approach, offering screening directly in the homes of those concerned, could therefore be an effective strategy for increasing screening coverage.

Within this ambitious framework, this project aims to provide innovative data on the effectiveness of a community-based screening method, as well as the characteristics and factors associated with screening effectiveness in households or health centers. Additionally, qualitative data will complementarily highlight the barriers and facilitators to scaling up and implementing such interventions through a multi-level evaluation that includes participants, those who opt out of testing, community workers, and health care providers. Finally, the cost-effectiveness study will offer updated and robust data to support advocacy and cost estimation for scaling up, contributing to the national eradication strategy.

Limitations and Strengths

The mixed method study protocol on community versus facility-based services for HCV screening in Cambodia presents a robust design, yet it encompasses inherent limitations and strengths.

One limitation is the potential for selection bias, as the study relies on voluntary participation, which might not fully represent the broader population's perspectives on HCV testing. Additionally, the qualitative component's reliance on self-reported data may introduce response bias, where participants might provide socially desirable answers. The study's cluster-randomized design could also face operational challenges, such as logistical issues in remote areas, which might affect the uniformity of intervention implementation.

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On the other hand, the study's strengths are significant. The mixed methods approach allows for a comprehensive understanding of the acceptability and feasibility of HCV testing strategies, combining quantitative data's robustness with qualitative insights' depth. The inclusion of a diverse participant pool from different health sectors and the community enhances the generalizability of the findings. Moreover, incorporating a cost-effectiveness analysis will allow for better scalability and sustainability of the interventions based on the results, directly addressing the practical challenges of HCV screening in Cambodia and providing valuable data to inform national health strategies. This approach, grounded in local realities, positions the study to offer actionable recommendations for enhancing HCV care and control in Cambodia and similar settings.

Comparison With Prior Work

The question of "who to test" and "how to test" in low and middle-income countries was discussed in a recent study [21]. WHO recommended that "HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure or behavior" [22]. This recommendation includes persons who have received medical or dental interventions in health care settings where infection control practices are substandard which was the case in Cambodia before the 2000's. Targeted HCV testing interventions to individuals who are a part of risk groups for HCV infection or who have a history of HCV risk behaviors seems to be effective in diagnosing cases and increasing treatment uptake [23] but the reported programs are mainly heterogenic, and the majority did not use a comparison group [24]. However, many countries in Europe and the United States recommend a systematic population-based screening for groups at risk of infection. In the United States, excepting classic at-risk groups (injecting drug use, hemodialysis, and prisoners), HCV infection is most prevalent among individuals born between 1945 and 1965 (baby-boomer population) [25]. Since 2012, Communicable Disease Control has recommended HCV screening in this population. In France, recommendations changed in 2014: HCV screening must be done for all men aged 18-60 years, with also a particular warning for the baby-boomer population, as many persons are still undiagnosed in 2014 in this population [26]. Screening could be done in different medical structures [27-30] and could easily be integrated into routine primary care [31].

Nevertheless, all these studies were conducted in high-income countries, and data in low-income countries are scarce. Rapid diagnosis tests are available in the majority of these countries but targeted testing interventions are related to the country's epidemic situation and the health care structures. Community approach with testing at a household level was reported effective in Egypt to ensure both high uptake of testing, and equity in access regardless of sex, age, income level, or stage of disease [32]. As recommended by WHO, operational research is needed to evaluate different approaches to increase the reach and uptake of simplified screening services close to the population [33]. Indeed, a comprehensive and integrated approach to the elimination of HCV at a community level must incorporate both preventive approaches to reduce transmission and new infections, and testing and treatment to reduce both the burden of disease and associated morbidity. A prompt linkage to care to ensure access to treatment is essential.

Conclusions

The CAM-C study aims to gather data on the effectiveness of a community-based screening strategy for hepatitis C in a high-prevalence general population country. These findings will be used to tailor public health interventions and to inform the national hepatitis elimination program, as well as broader eradication plans in resource-limited settings. Using a mixed methods approach that combines a robust methodology (cluster-randomized controlled trial) with a cost-effectiveness analysis and qualitative research, this study seeks to provide a comprehensive view of the impact of such strategies and the feasibility of their implementation and scaling-up.

Acknowledgments

The authors would like to thank all the study participants, as well as the representatives from the various hospitals and health centers in the area, and the villagers who assisted with the investigation. We would also like to express our gratitude to the project managers at ANRS MIE in Paris who assisted in sponsoring this study: Ms Diana Molino, Ms Laure Amélie De Monteynard, and Dr Ventzislava Petrov-Sanchez. The cluster-randomized controlled trial is supported by the ANRS Emerging Infectious Diseases (ANRS MIE) award (ANRS 12384).

Data Availability

The datasets generated during or analyzed during this study are available from the principal investigators upon reasonable request, subject to approval from the National Ethical Cambodian for Health Research.

Authors' Contributions

EM wrote the first draft of the manuscript and participated in the clinical investigation as medical investigator, OS wrote the protocol submitted to the ethics committee and supervised the clinical investigation, SN coordinated the study, DK designed and coordinated the qualitative part and will participate in the analysis, LS-T designed and coordinated the cost-effectiveness part, CLP supervised the biological analyses, SM contributed to the study setup, CC and KH was in charge of the study's operational implementation, JCDV and VS are the principal investigators of the study and contributed to its design and implementation and will participate to the analysis and dissemination.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Study schedule.
[DOCX File , 15 KB - resprot_v13i1e63376_app1.docx]

Multimedia Appendix 2
Peer review report by France Recherche Nord&Sud Sida-HIV Hépatites (L'ANRS) Maladies infectieuses émergentes (MIE).
[PDF File (Adobe PDF File), 149 KB - resprot_v13i1e63376_app2.pdf]

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Abbreviations

CAM-C: Community Versus Facility-Based Services to Improve the Screening of Active Hepatitis C Virus Infection in Cambodia
CHW: community health care worker
DAA: direct-acting antiviral
DBS: dried blood spot
HBV: hepatitis B virus
HCV: hepatitis C virus
MSF: Médecins Sans Frontières
OD: operational district
RDT: rapid diagnostic test
WHO: World Health Organization

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Protocol

Respiratory Strength Training Versus Respiratory Relaxation Training in the Rehabilitation of Physical Impairment, Function, and Return to Participation After Stroke: Protocol for a Randomized Controlled Trial

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Abstract

Background: Persistent disability in chronic stroke survivors is often attributed to arm or leg weakness; however, respiratory muscle weakness also impedes poststroke rehabilitation, reduces quality of life, and increases the risk of health complications. Respiratory complications are common after stroke and place patients at risk for both prolonged functional disability and mortality. In addition, stroke survivors face ongoing cardiovascular disease that places them at risk for recurrent stroke.

Objective: The study aims to compare the effects of 2 respiratory training programs, paired with individualized flexibility, strengthening, and cardiovascular exercise programs, on physiologic, activity, and societal participation outcomes in chronic stroke survivors.

Methods: This study will be a randomized controlled trial. Participants are 80 community-dwelling adults with chronic stroke. In conjunction with a 24-session (3 times/week for 8 weeks), American Heart Association–informed, whole-body exercise program, participants will be randomized to receive either respiratory strength training or respiratory relaxation training. Study intervention will be directed by a physical therapist and take place in a community fitness center. Outcome assessments will occur in a clinical research center. The primary outcome measure is maximal respiratory pressure. Secondary outcome measures include airway clearance, walking endurance, spatial-temporal gait characteristics, community walking, functional strength and fatigue, depression, and societal participation measures. Longer-term societal participation is a complex domain that may be influenced by other factors beyond physical function. Participants' health status will be monitored for 1 year following the intervention for falls, respiratory illness, and hospitalizations. Additional subanalyses will evaluate the effect of smoke exposure on short- and long-term outcomes. Outcome assessors are blinded to group assignments. Respiratory relaxation training is an active comparator, but no pure control group is included.

Results: This study was funded in March 2020 with enrollment commencing in November 2020. Completion of enrollment is projected for May 2025 with a study projected end date of April 2026. Published results are anticipated in Fall 2026.

Conclusions: Results from this study will improve our understanding of the additive benefits of respiratory exercises on short- and long-term physiologic, functional, and societal gains for these individuals. These data will be instructive to meet a current unmet rehabilitative need to promote patient-centered care and contribute to decreasing morbidity and mortality in chronic stroke survivors.

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Trial Registration: ClinicalTrials.gov: NCT05819333; https://clinicaltrials.gov/study/NCT05819333
International Registered Report Identifier (IRRID): DERR1-10.2196/59749

(JMIR Res Protoc 2024;13:e59749) doi:10.2196/59749

KEYWORDS

stroke; rehabilitation; exercise; clinical trial; respiration; wellness; community based

Introduction

Background

Stroke is the leading cause of serious long-term disability in the United States [1]. A decrease in stroke mortality (36.9% decrease from 1999 to 2009), has led to a subsequent increase in those living with the consequences of stroke [2]. As such, it impacts the financial status of patients, families, and health care systems [3]. A retrospective study of inpatient stroke care costs from 2000 to 2020 revealed mean hospital costs per stay were US $15,781 (SD US $330) [4]. The mean lifetime cost of ischemic stroke is approximately US $140,048 in the United States, placing stroke among the top 10 most costly conditions among Medicare beneficiaries [5]. Recurrent stroke, cardiac disease, and respiratory complications are the leading causes of mortality in stroke survivors. Given these financial and health costs, there is therefore a critical need to prevent further cardiovascular and cardiorespiratory decline and reduce the incidence of cardiac and respiratory disease and functional disability.

Although stroke sequelae affect numerous body systems, automatic control of resting ventilation is typically spared in the majority of stroke cases, affected only in more severe brainstem strokes. Motor deficits are often the most debilitating to mobility and return to participation in life roles. Motor processing and the voluntary control of muscles of respiration engaged when speaking, upon exertion, coughing, or with exercise may be weakened following damage directly to the cerebral cortex or the descending axonal projections. Consequently, individuals after stroke may exhibit prolonged exercise intolerance, dyspnea, and airway clearance dysfunction. It is upon this conceptual framework we propose that respiratory muscle training is an important component in the rehabilitation of individuals following stroke. The purposes of this study are to (1) evaluate the effect of a combined exercise program (EP) with respiratory strength training (RST) on measures of impairment, activity, and participation; (2) evaluate its ability to maintain prospective respiratory health; and (3) explore the effect smoking history may have on these outcomes.

Study Objective and Aims

The primary objective of this trial is to test the hypothesis that a combined EP with RST improves physiologic, activity, and societal participation outcomes in chronic stroke survivors. In addition to limb and respiratory weakness, up to 78% of patients after stroke present with dysphagia [6], a significant risk factor for aspiration. Cough is a critical mechanism to guard against aspiration and is often impaired after stroke [7], resulting in greater incidences of aspiration and chest infection [8,9]. Furthermore, pneumonia is the leading cause of nonvascular death in acute [10] and chronic [11] phases after stroke. RST could improve airway clearance as a protective function. The adoption of interventions capable of preventing the occurrence of respiratory complications may substantially improve the long-term outcomes of these patients [12]. Several small-scale studies have demonstrated that inspiratory [13-16] and expiratory [14] muscles respond to strength training in patients after stroke, but the impacts of respiratory strengthening on function are less clear. In a systematic review of poststroke respiratory muscle training randomized controlled trials, Menezes et al [17] reported there were insufficient data to determine whether the benefits of respiratory muscle training are realized in gains in functional activity level or participation, concluding that future trials are needed to assess the effects of training on one's activity and participation in life roles. RST for individuals after stroke has the potential to facilitate a return to these important societal roles.

Our secondary objective is to prospectively monitor health status for 1-year following the exercise intervention. There is a clear link between the presence of respiratory dysfunction in individuals after stroke and the incidence of respiratory complications such as aspiration or respiratory infections [18-20]. Menezes et al [17] revealed that respiratory muscle training reduced the relative risk of respiratory complications immediately and 6 months after the commencement of the intervention. Others have reported that expiratory muscle strength training exercises improve respiratory strength, cough, and swallowing function in stroke [21-23]. A 2016 meta-analysis [17] revealed that respiratory muscle training reduced the relative risk of respiratory complications immediately and 6 months after the commencement of the intervention. However, this conclusion was based on just 2 trials, and procedures for detecting the occurrence of respiratory complications were not sufficiently robust.

An exploratory objective will evaluate potential differential responses to respiratory muscle training based on smoke exposure. Cigarette smoking negatively impacts respiratory health and increases the risk of cardiovascular events. While direct cigarette smoking is a known risk factor for stroke and poststroke complications, individuals exposed to secondhand smoke also face high health risks. There is a strong, dose-dependent association between passive smoking and stroke [24].

Methods

Trial Design

This is a single-blind randomized controlled trial. Participants will be assessed at Brooks Rehabilitation Clinical Research Center and receive intervention sessions at the Brooks Family

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YMCA. Health status will be monitored monthly for 1 year following the intervention. This study is registered at ClinicalTrials.gov (NCT05819333). The trial will be reported according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), TIDieR (Template for Intervention Description and Replication), and CONSORT (Consolidated Standards of Reporting Trials) guidelines (Figure 1).

Figure 1. Flowchart of clinical trial. EP: exercise program; RRT: respiratory relaxation training; RST: respiratory strength training.

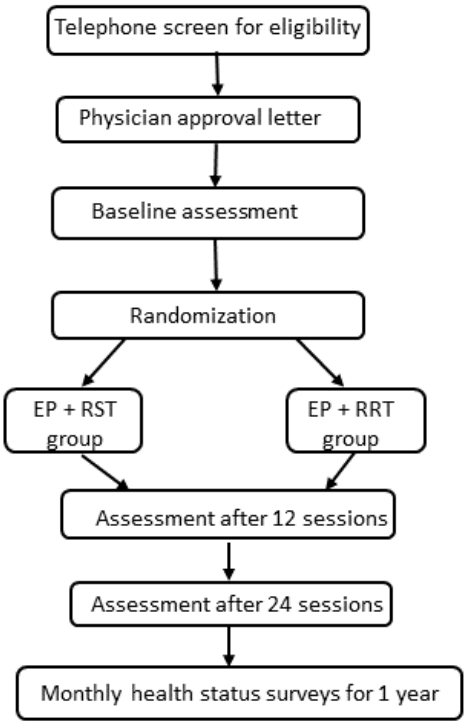

Ethical Considerations

This protocol and Informed Consent Form were reviewed and approved by the University of Florida's institutional review board (IRB; #202000810). Participants will sign the IRB-approved informed consent form before enrollment. Participants will be assigned a unique numerical identifier to deidentify and assure the privacy and confidentiality of all collected data. Compensation of US $15/study visit will occur in the form of a debit card, with a total compensation of US $405.

To evaluate not simply how many steps participants take but to understand where those steps are taken (ie, within the confines of their home or actually outside their home in the community), participants will wear a GPS device for 7 days. These deidentified longitude and latitude coordinate data are not collected in real-time but rather will be downloaded to a password-protected computer at the completion of the 7-day wearing period. Safety of trial intervention and assessments will be monitored by reporting to the IRB any adverse events that occur from enrollment to trial completion at 12 months following the intervention.

Participants

Participants will be recruited from an IRB-approved clinical research registry and study flier. Power calculations determined a study population of 80 participants and are presented below. We will enroll up to 95 participants to allow for a potential attrition rate of up to 15% (14/95). Specific inclusion and exclusion criteria for study enrollment are presented in Textbox 1. The cardiovascular and respiratory exclusion criteria were adopted from a previous exercise study with individuals poststroke [25,26].

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Textbox 1. Inclusion and exclusion criteria for enrollment into the trial.

Inclusion criteria

- Diagnosis of stroke >6 months after onset
- Signed letter of medical approval from primary care physician to participate
- Community dwelling
- Ability to attend the exercise program 3 times/week for 8 weeks
- Ability to follow directions or mimic exercises
- Ability to communicate adverse effects such as pain or fatigue or the need for assistance
- Able to ambulate 20 feet (6.1 m) with no more than contact guard assist, with or without an assistive device or orthotic device
- Able to access exercise equipment independently or with caregiver assist
- Older than 18 years of age

Exclusion criteria

- Neurologic conditions other than stroke (ie Parkinson disease or multiple sclerosis)
- Severe, functional limiting arthritis
- Orthopedic condition that limits mobility
- Severe weight-bearing pain
- Current participation in other physical rehabilitation services or exercise programs
- Serious cardiac conditions (hospitalization for myocardial infarction or heart surgery within the past year, history of congestive heart failure, documented serious and unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living). Anyone meeting New York Heart Association criteria for Class 3 or Class 4 heart disease will be excluded.
- Severe hypertension with systolic >200 mm Hg and diastolic >110 mm Hg at rest, that cannot be medically controlled into the resting range of 180/100 mm Hg
- Use of supplemental oxygen
- Severe obstructive pulmonary disease (Classification of Global Initiative for Chronic Obstructive Lung Disease 3 or higher, indicating forced expiratory volume 1 <50% predicted)
- Treatment for pneumonia or lower respiratory infection within the past month
- Able to run one-quarter mile (402 m) without stopping

Randomization, Allocation, and Blinding

Participants will be randomized to the EP plus RST group or EP plus respiratory relaxation training (RRT group) using the Microsoft Excel (Microsoft Office Professional Plus 2016) *RAND* function. Participants and the intervention physical therapist will be aware of the group assignment due to the nature of the intervention; however, study evaluators will remain blinded.

Interventions

In total, 24 intervention sessions will be delivered 3 times a week over 8 weeks. Intervention therapists will undergo standardized training and a structured intervention log with the 3 aspects of the EP, and the respiratory training outlined will be followed each session to assure intervention fidelity.

EP Components

Both groups will participate in the EP consisting of 3 components recommended by American Heart Association (AHA) poststroke exercise recommendations [27], directed by the intervention physical therapist, and individualized to the participants' ability.

Strengthening Exercise

Resistance exercises will address primary muscle groups of the upper and lower limbs and trunk. Graded resistance will be provided through weight machines or resistance bands.

In terms of progression, the ability to perform an exercise with appropriate kinematics will determine initial resistance. Once the participant can perform 2 sets of 10 repetitions, resistance will be increased.

Cardiovascular Exercise

Exercise modalities may include treadmill, recumbent cross trainer, recumbent bicycle, stairs, elliptical stepper, upper-extremity ergometer, arc trainer or provided through overground gait, sit-to-stand repetitions, shallow knee bends, step-ups, and marching in place.

In terms of progression, participants will wear a heart rate monitor and exercise between 40% and 70% of heart rate reserve. The exertion will be subjectively reported using the rate of perceived exertion scale [28]. Progression will occur by increasing exercise duration, resistance, or speed.

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Flexibility Exercise

Static stretching of the trunk and upper and lower extremities, 2 repetitions of each stretch held for 20 seconds. Muscles groups will be individualized according to participants' needs.

Respiratory Training

Participants will be randomized to the RST or RRT group.

RST Group

RST will consist of a bout of inspiratory strength training at the start of each EP session, plus a bout of expiratory strength training at the conclusion of each EP session. RST devices (Orygen Dual Valve, Forumed SL) provide up to 70 cm H_2O of inspiratory and 80 cm H_2O of expiratory pressure threshold loads. RST bouts include 5 sets of 5 maximal volume and speed breaths of both inspiratory and expiratory muscle training 2 times during each session. The initial intensity will be 25% of the maximal inspiratory and expiratory pressures the subject can generate. In terms of progression, the inspiratory setting of the training device will be increased up to 10% of the training load from the first set each session, to achieve a rate of perceived exertion of 6-8 (Modified 10-point Borg scale) [29] with complete valve opening. Expiratory settings will be progressed similarly.

RRT Group

RRT will consist of bouts of relaxation breathing at the start and conclusion of each EP session. Participants will be guided to breathe slowly through a respiratory training device (Threshold PEP, Respironics), with minimal resistance. RRT bouts include 5 sets of 5 breaths, 2 times during the session. While the effects of relaxation breathing exercises may include a modest lowering of systolic blood pressure in some hypertensive patients [30], this group serves as an active control. In terms of progression, there will be no progression for this group.

Outcome Measures

Participants will be assessed (1) at baseline, (2) after 12 sessions, and (3) after 24 sessions by a physical therapist blinded to group assignment. Blinded assessors will undergo standardized training to assure assessment fidelity. Following intervention completion participants will complete monthly health status questionnaires.

Primary Objective Outcomes

The World Health Organization's International Classification of Functioning, Disability, and Health model [31] recognizes that functioning and disability as a result of a health condition (stroke, in this trial) are multidimensional concepts, relating not simply to impairment at the level of one's body (ie, muscle strength) but to limitations in activity one might experience, as well as one's restrictions in societal participation. To assess more broadly how addressing respiratory muscle weakness can improve quality of life after stroke, we will examine outcomes across these dimensions (Figure 2).

Figure 2. Outcome measures across World Health Organization's International Classification of Functioning, Disability and Health model. 5XSTS: Five Times Sit to Stand; 6MWT: Six Minute Walk Test; FACIT-D: Functional Assessment of Chronic Illness Therapy – Dyspnea; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FEV1: Forced Expiratory Volume in 1 second; FSS: Fatigue Severity Scale; FVC: Forced Vital Capacity; MEP: Maximum Expiratory Pressure; MIP: Maximum Inspiratory Pressure; Neuro-QOL: Neuro Quality of Life; PCF: Peak Cough Flow; PHQ-9: Patient Health Questionnaire -9; PROMIS-10: Patient-Reported Outcomes Measurement Information 10; SIS-P: Stroke Impact Scale – Participation; WHO-QOL BREF: World Health Organization Quality of Life Brief Version.

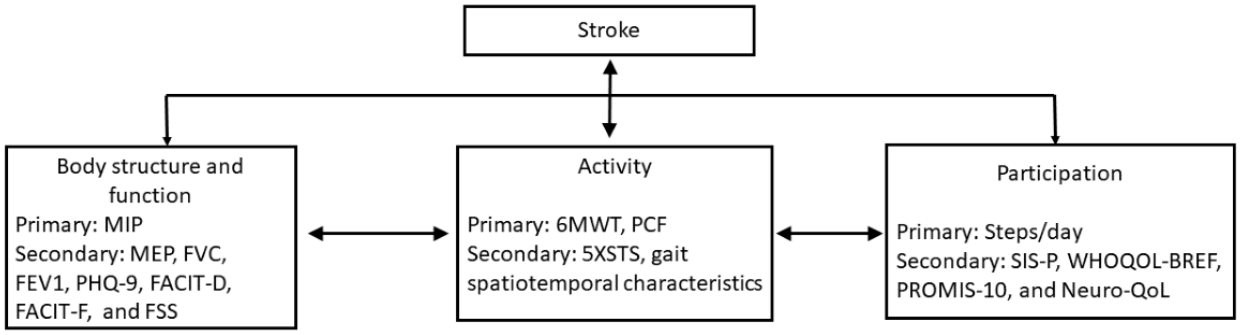

Our primary outcome is maximum inspiratory pressure (MIP). MIP is a measure of the strength of inspiratory muscles, primarily the diaphragm [32]. Participants will perform a seated MIP maneuver using a respiratory pressure manometer, from residual volume, in accordance with American Thoracic Society testing guidelines for respiratory muscle testing [33]. Additional respiratory measures include maximal expiratory pressure (measure of the strength of expiratory muscles, primarily the abdominals and intercostals) [33], forced vital capacity (the total volume of air blown out of the lungs during forced exhalation after maximal inspiration) [33], forced expiratory volume in 1 second (a measure of the amount of air that can be forced out of the lungs in one second following a full inhalation) [33], and peak cough flow (maximum expiratory flow during the compressive phase of a cough) [34]. Open circuit spirometry will provide breath-by-breath cardiopulmonary data while participants complete the 6-minute walk test [35]. Additional measures of physical function include the 5-times sit-to-stand test [36] and spatiotemporal gait characteristics captured while walking across an instrumented walkway. Steps per day and GPS data will be obtained at baseline and intervention conclusion for 1 week. A portable accelerometer will record participants' steps, and a GPS device will record location. A walk score [37,38] and an area deprivation index [39] score will objectively characterize the "walkability" and the socioeconomic status of the participant's neighborhood.

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Finally, self-report measures of participation and quality of life will also address our primary objective. These include the Participation subsection of the Stroke Impact Scale [40]; the abbreviated World Health Organization Quality of Life instrument [41], which measures the domains of physical health, psychological health, social relationships, and environment; the Functional Assessment of Chronic Illness Therapy Dyspnea [42] and Fatigue [43] Scales; the Fatigue Severity Scale [44]; the Patient Health Questionnaire-9 depression assessment [45]; the Patient Reported Outcomes Measurement Information-10, an assessment of health status after stroke [46]; and the satisfaction and ability to participate in life roles subscales of the Neuro Quality of Life [47] (Table 1).

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Table 1. Outcome measures.

Assessment	Outcome measured	Time to complete	Scoring	Psychometrics
MIP[a]	Maximum pressure created during inspiration measured with a manometer	8 minutes	Pressure measured in cm H_2O	• Reliability [48] • Validity [48]
MEP[b]	Maximum pressure created during expiration measured with a manometer	8 minutes	Pressure measured in cm H_2O	• Reliability [48] • Validity [48]
PCF[c]	Strength of cough	5 minutes	Liters of air breathed out per minute; L/min	• Reliability [49] • Validity [49]
FVC[d]	Maximum amount of air exhaled after fully inhaling and making a maximal effort.	5 minutes	Volume measured in liters	• Reliability [50,51] • Validity [50,51]
FEV_1[e]	The volume of air exhaled in the first second during forced exhalation after maximal inspiration	1 minute	Volume measured in liters	• Reliability [50,51] • Validity [50,51]
6MWT[f]	Participants walk for six minutes covering as much ground as possible. Participants were permitted to stop and rest at any time during the test.	6 minutes	Distance measured in meters	• Reliability [52] • Validity [53]
5XSTS[g]	Participants stand up and sit down from a 16” solid seat as quickly as possible 5 times, with their arms folded across their chest.	1 minute	Time is measured in seconds	• Reliability [54] • Validity [54]
Steps/day	Number of steps taken over a seven-day period measured with an activity monitor	7 days	Number of steps completed each day	• Reliability [55] • Validity [56]
PHQ-9[h]	Self-report questionnaire to assess depressive symptoms	6 minutes	Nine items scored on a 0-3 Likert scale	• Reliability [57] • Validity [57]
SIS-P[i]	Self-report questionnaire to assess ability to participate in meaningful life activities	3 minutes	Eight items scored on a 1-5 Likert scale	• Reliability [58] • Validity [58]
WHO-QOL BREF[j]	Self-report questionnaire to assess four QOL domains: physical health, psychological health, social relationships, and environment.	12 minutes	26 items rated on a 5-point Likert scale. Each domain score is transformed into a scaled score, with a higher score indicating a higher QOL.	• Reliability [59] • Validity [59]
FSS[k]	Self-report questionnaire to assess the impact of fatigue on life and functional activities	8 minutes	Nine items scored on a 1-7 Likert Scale; one item scored on a 0-10 visual analog scale.	• Reliability [60] • Validity [60]
FACIT-D[l]	Self-report questionnaire to assess dyspnea severity during activities of daily living	5 minutes	Ten items scored on a 0-3 Likert scale	• Reliability [42] • Validity [42]
FACIT-F[m]	Self-report questionnaire to assess fatigue experience and impact on daily life	5 minutes	Thirteen items scored on a 0-4 Likert scale	• Reliability [61] • Validity [61]
Neuro-QOL[n]	Two self-report questionnaire subscales to assess 1) the Ability to Participate in Social Roles and Activities and 2) Satisfaction with Social Roles and Activities	10 minutes	A total of 16 items scored on a 1-5 Likert scale	• Reliability [47] • Validity [47]
PROMIS-10[o]	Self-report questionnaire to assess multiple domains of health	5 minutes	Ten items scored on a 1-5 Likert scale	• Reliability [62] • Validity [62]

[a]MIP: maximum inspiratory pressure.

[b]MEP: maximum expiratory pressure.

[c]PCF: peak cough flow.

[d]FVC: forced vital capacity.

[e]FEV1: forced expiratory volume in 1 second.

[f]6MWT: 6-Minute Walk Test.

[g]5XSTS: Five Times Sit-to-Stand.

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[h]PHQ-9: Patient Health Questionnaire-9.

[i]SIS-P: Stroke Impact Scale–Participation.

[j]WHO-QOL BREF: World Health Organization Quality of Life Brief Version.

[k]FSS: Fatigue Severity Scale.

[l]FACIT-D: Functional Assessment of Chronic Illness Therapy–Dyspnea.

[m]FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue.

[n]Neuro-QOL: Neuro Quality of Life.

[o]PROMIS-10: Patient-Reported Outcomes Measurement Information 10.

Secondary Objective Outcomes

To investigate if RST in the chronic poststroke period impacts the rate of respiratory complications, we will follow participants for 1 year after intervention. Respiratory complications will be defined as the onset of respiratory symptoms that require the evaluation and treatment by a medical provider or hospitalization for respiratory causes. If the participant reports a respiratory complication, medical records will be obtained and a blinded assessor will review the record to confirm diagnosis.

Exploratory Objective Outcomes

To address this objective, participants will provide a urine cotinine test and complete a subset of key questions from the Global Adult Tobacco Survey, a validated self-report of tobacco consumption and passive smoking [63]. From the cotinine test results, participants will be categorized as either (1) no significant smoke exposure or (2) significant smoke exposure. Cotinine is a metabolite of nicotine and indicates exposure to tobacco products within the past 48 hours. The Global Adult Tobacco Survey is a household survey created as a way to globally monitor adult tobacco use and indirectly measure the impact of tobacco control and prevention initiatives. A subset of questions will be asked about current and past tobacco use (if any) and exposure to secondhand smoke. We will compare the outcome measures described above from our primary and secondary objectives to investigate differences between those categorized as no significant smoke exposure and significant smoke exposure.

Data Analysis

Power Calculations

Our primary outcome measure is MIP. The power calculation was based on work by Messaggi-Sartor et al [14], who examined the effect of RST on respiratory strength and respiratory complications following subacute stroke and measured MIP as the primary outcome. MIP mean gain was 18.9 (SD 15.1) cm H_2O in the experimental RST group and the mean MIP change was 9.3 (SD 10.1) cm H_2O in the control (sham RST) group. With a total of 80 participants (40 in each group) in this study, a 2-sided repeated measures ANOVA comparing 2 treatments across 3-time points, using a pooled SD of 12.8 would detect a difference at power >0.8 (f=0.16, F=3.067, =0.5, =.5). For our secondary objective, the RST effect on lung infections may be even more robust. Messaggi-Sartor et al [14] reported a 70% lower lung infection rate for subjects who completed RST during subacute stroke rehab, compared with subjects allocated to the control group. The number needed to treat to prevent one lung infection event was seven [14]. The effect of RST on respiratory complications for those with chronic stroke is not yet known. Our exploratory objective is to distinguish responses to RST, based on smoking exposure. The primary intent of this objective is to collect data to power a future, larger study. Specifically, baseline function is lower in current smokers without neurological disease, and their tolerated exercise training volume may be reduced. A sample size of 80 will provide an opportunity to evaluate whether smoking influences responses to the exercise interventions.

Statistical Analysis

To analyze the data for each objective and investigate the intervention effects for EP+RST versus EP+RRT, we will adopt a mixed effects model [64] to account for the correlation of repeated measurements within each participant. Depending on the outcome for each objective, we will include the baseline value as an independent covariate in addition to other independent variables including intervention effects at 4 weeks and 8 weeks, age, gender, and BMI by using a robust covariance matrix, that is, unstructured covariance matrix.

Results

This study was funded in March 2020 with enrollment commencing November 2020. As of July 2024, a total of 69 participants were enrolled. Completion of enrollment is projected for May 2025 with a study projected end date of April 2026. Published results are anticipated in Fall 2026.

Discussion

Anticipated Findings

Results from this study will improve our understanding of the additive benefits of respiratory exercises on short and long-term physiologic, functional, and societal gains for these individuals. We hypothesize that the combined RST+EP will be more effective than the EP alone for stroke survivors with and without a smoking exposure history. Specifically, we hypothesize that combined RST+EP will be more effective in restoring poststroke maximal respiratory pressure, in restoring both physical (walking endurance) and respiratory (airway clearance) function, and in restoring poststroke life and social roles. We also hypothesize that RST+EP will be more effective than EP alone in reducing 1-year postintervention incidence of adverse respiratory events.

Wellness Approach

While multiple studies indicate the potential for respiratory muscle training to improve respiratory strength, airway protection, and dyspnea during acute stroke rehabilitation

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[14,65,66], limited information is available pertaining to the benefits of respiratory training in community-dwelling adults with chronic stroke [13,21,67]. This study approaches the research aims from a wellness perspective, as opposed to a medical model of rehabilitation. The AHA-informed EP and respiratory training sessions occur in a community-based gym that emphasizes wellness and secondary prevention of stroke. Previous respiratory training research has emphasized respiratory strength, with fewer studies reporting effects on activity-based metrics such as cough force, gait speed, or walking endurance [16,68]. This trial uses an impairment-based primary study outcome measure (MIP) as a comparator to other published respiratory training studies in stroke. However, activity- and participation-based outcome measures were also included to account for functional limitations participants might experience after stroke and to further quantify restrictions in their societal roles. Further, this study moves beyond patient-reported participation, by directly measuring impacts of the respiratory training on gains in community activity and societal roles for up to 1 year following the completion of the intervention. The carryover from a gain in body function or activity to improved community and societal participation is a recognized need in stroke rehabilitation research [17].

Effects of Smoke Exposure

This research will also contribute novel exploratory information regarding effects of the EP and respiratory training in people with chronic stroke with and without daily cigarette smoke exposure. Smoking is an independent risk factor for stroke that directly increases the relative risk of stroke in a dose-dependent fashion [69]. Smoking induces vascular inflammation and endothelial dysfunction to accelerate the progression of atherosclerosis [70,71]. Secondhand smoke exposure also independently increases both the risk of stroke and obstructive pulmonary disease [72,73] and no level of passive smoke exposure is considered safe [24]. Chronic smoke exposure increases the work of breathing through dynamic hyperinflation and heightened airway resistance, despite an increased inspiratory neural drive, leading to dyspnea and airway clearance dysfunction [74,75]. Despite the negative impacts of smoking on cardiovascular and respiratory health, its impact on poststroke respiratory rehabilitation is poorly understood. Older adults with obstructive lung disease who completed 6 weeks of inspiratory strength training achieved significant improvements in MIP and dyspnea, and reported physical quality of life, yet in contrast to adults without lung disease, no gains in walking endurance occurred. These results suggest that individuals with lung disease recovering from stroke may require additional training time or combinatorial exercises to improve walking [76].

Limitations

We recognize some limitations of the study design. The study was powered to distinguish the 8-week effects of RST from RRT on MIP. We acknowledge that societal participation is multidimensional, and longer-term changes may be influenced by many contributing factors beyond respiratory strength and walking endurance [77,78]. The use of patient-reported outcome measures and assessment of the Area Deprivation Index will help identify some factors that contribute to societal participation. Since group assignment will be based on the type of respiratory training, it is possible there may be unequal proportions of smoke-exposed and nonsmoking participants in each group. The monitoring of smoke exposure will enable us to explore whether the combined respiratory and whole-body exercise approaches offer distinct benefits to cigarette smoke-exposed individuals. While study assessors will be blinded to group assignment, patients and exercise supervisors will know their respiratory exercise assignment. A true control or “sham” respiratory training intervention was not included; rather, the RRT serves as an active comparator. The volume of respiratory exercises during exercise sessions will be the same for both groups, even though the physiological effects of RST and RRT exercises likely differ.

Dissemination Plan

Since findings from this study may influence the health promotion, wellness, and secondary prevention societal roles of the physical therapy profession, dissemination efforts will be directed toward physical therapists and other rehabilitation providers. Study results will be presented at scientific conferences and published in peer-reviewed journals used by physical therapists and rehabilitation scientists.

Conclusion

This trial is an investigator-initiated, single-blind, randomized controlled trial designed to evaluate the effects of an AHA-informed EP and respiratory training on measures of impairment, activity, and societal participation. Implementation of this trial will help identify modes of exercise that lead to the greatest short- and long-term functional and societal gains in smoke-exposed and nonexposed, community-dwelling adults with chronic stroke.

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Data Availability

All data generated or analyzed during this study, once available, will be included in the published results.

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Authors' Contributions

DR and BS conceptualized and designed this study and obtained external funding. GB, KC, JBH, and HS contributed to the study intervention, assessment, and data acquisition. WX conceptualized the statistical approach. All authors read, edited, and approved the submitted manuscript and are personally accountable for their contributions and will investigate and resolve any questions regarding the accuracy or integrity of any part of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report 1 from the Florida Department of Health James and Esther King Research Program 18-19 (USA).
[PDF File (Adobe PDF File), 124 KB - resprot_v13i1e59749_app1.pdf]

Multimedia Appendix 2
Peer-review report 2 from the Florida Department of Health James and Esther King Research Program 18-19 (USA).
[PDF File (Adobe PDF File), 447 KB - resprot_v13i1e59749_app2.pdf]

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Abbreviations

AHA: American Heart Association
CONSORT: Consolidated Standards of Reporting Trials

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EP: exercise program
IRB: institutional review board
MIP: maximum inspiratory training
PROMIS-10: Patient Reported Outcomes Measurement Information 10
RRT: respiratory relaxation training
RST: respiratory strength training
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication

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Protocol

Frontal Pole Neuromodulation for Impulsivity and Suicidality in Veterans With Mild Traumatic Brain Injury and Common Co-Occurring Mental Health Conditions: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Suicide remains a leading cause of death among veterans in the United States, and mild traumatic brain injury (mTBI) increases the risk of suicidal ideation (SI) and suicide attempts (SAs). mTBI worsens impulsivity and contributes to poor social and occupational functioning, which further increases the risk of SI and SAs. Repetitive transcranial magnetic stimulation is a neuromodulatory treatment approach that induces neuroplasticity, potentially repairing neurodamage. Intermittent theta burst stimulation (iTBS) is a second-generation form of transcranial magnetic stimulation that is safe, shorter in duration, displays a minimal side effect profile and is a promising treatment approach for impulsivity in mTBI. Our novel proposed treatment protocol uses frontal pole iTBS to target the ventromedial prefrontal cortex, which may reduce impulsivity by strengthening functional connectivity between the limbic system and frontal cortex, allowing for improved top-down control of impulsive reactions, including SI and SAs.

Objective: The objectives of this study are to (1) develop an iTBS intervention for veterans with mTBI, impulsivity, and SI; (2) assess the feasibility and tolerability of the intervention; and (3) gather preliminary clinical outcome data on SI, impulsivity, and functions that will guide future studies.

Methods: This is a pilot, double-blinded, randomized controlled trial. In developing this protocol, we referenced the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. We will enroll 56 participants (28 active iTBS and 28 sham iTBS). The iTBS intervention will be performed daily, 5 days a week, for 2 weeks. We will collect 10 validated, psychometric, quantitative outcome measures before, during, and after the intervention. Measures included will assess functioning, impulsivity, suicidality, posttraumatic stress disorder, and depressive symptoms. We will collect qualitative data through semistructured interviews to elicit feedback on the participants' experiences and symptoms. We will perform quantitative and qualitative analyses to (1) assess the feasibility, tolerability, and acceptability of the treatment; (2) gather advanced neuroimaging

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data to assess neural changes elicited by treatment; and (3) assess improvements in outcome measures of impulsivity and suicidality in veterans with mTBI.

Results: This study protocol was approved by the Edward Hines, Jr. VA Hospital Institutional Review Board (Hines IRB number 14-003). This novel treatment is a 5-year research project (April 1, 2023, to March 31, 2028) funded by the Veterans Administration Rehabilitation Research and Development service (CDA2 award IK2 RX002938). Study results will be disseminated at or before the project's end date in March 2028.

Conclusions: We will provide preliminary evidence of the safety, feasibility, and acceptability of a novel frontal pole iTBS treatment for mTBI, impulsivity, SI and SAs, and functional deficits.

Trial Registration: ClinicalTrials.gov NCT05647044; https://clinicaltrials.gov/study/NCT05647044

International Registered Report Identifier (IRRID): PRR1-10.2196/58206

(JMIR Res Protoc 2024;13:e58206) doi:10.2196/58206

KEYWORDS

mild traumatic brain injury; transcranial magnetic stimulation; intermittent theta burst stimulation; suicidality; suicidal ideation; impulsivity; neuromodulation; social and occupational functioning

Introduction

Background

The prevalence of suicide among veterans who served in the US military is devastatingly high. Veterans die by suicide at almost double the rate of civilians in the United States [1]. The prevalence of suicide among veterans with traumatic brain injury (TBI) is even higher. Veterans with TBI are 1.5 times more likely to die by suicide than veterans without TBI, even when controlling for comorbid psychiatric conditions [1,2]. These statistics are particularly concerning given that there have been >400,000 new TBI diagnoses among US service members since the beginning of operations Enduring Freedom, Iraqi Freedom, and New Dawn, of which >80% are mild traumatic brain injury (mTBI) [3]. Overall, between 16% and 20% of all operations Enduring Freedom, Iraqi Freedom, and New Dawn veterans have a history of mTBI, and among them, up to 22% report suicidal ideation (SI) [4].

TBI consists of any external force applied to the head of any individual, resulting in vascular and axonal damage, edema, and neuronal death [5]. TBI is clinically further subcategorized by the severity of the injury as either mild, moderate, or severe. mTBI is defined as a loss of consciousness for <30 minutes, postconcussive altered mental status or amnesia for <24 hours, a Glasgow Coma Score, following injury of 13 to 15 (15 being the maximum score), and lack of abnormalities on standard clinical magnetic resonance imaging (MRI) or computed tomography [6]. TBI is an extremely common injury, resulting in an estimated 4.8 million independent emergency room visits throughout the United States annually [7-9]. TBI results in a significant economic burden: the cost of nonfatal TBI amounts to >US $40 billion per year in the United States [10]. Globally, TBI resulted in the loss of 246.7 million disability-adjusted life years between 1990 and 2013 [11].

Given the high suicide rate among US veterans, suicide prevention is a high-priority issue for the US Veterans Administration (VA) [12]. The US VA has assembled task forces that have created clinical practice guidelines for the assessment and management of veterans at risk for suicide [13]. These guidelines establish substantial risk factors to help providers identify which veterans are at the highest risk. The guidelines specifically cite having a history of TBI, functional deficits, past SI, and a history of impulsivity as independent risk factors for developing SI [13]. TBI predisposes individuals to functional deficits [14,15] and impulsivity [16], and those with impulsivity likely struggle with functional deficits [17]. Given these findings, we hypothesize that these conditions may be interrelated and could serve as meaningful behavioral targets in the treatment of SI.

Transcranial magnetic stimulation (TMS) therapy was first described by Barker et al [18]. Seminal studies by George et al [19] demonstrated the efficacy of TMS in the treatment of depression in large, multisite sham-controlled trials. TMS was subsequently approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of major depressive disorder [20]. TMS was first hypothesized as a treatment for TBI by Pape et al [21]. It was later shown to be effective in treating several TBI sequelae, including depression [22]. TMS also has demonstrated efficacy in the treatment of posttraumatic stress disorder (PTSD), chronic pain, cognitive deficits, and headaches in individuals with mTBI [23-27]. A second-generation form of TMS, intermittent theta burst stimulation (iTBS), was first shown to treat depression in 2009 in a study by Holzer and Padberg [28]. In a large, noninferiority study comparing iTBS and TMS, patients with treatment-resistant depression show similar safety and adverse event (AE) profiles and exhibit improvements in their depressive symptoms to both interventions [29].

This study aims to create a novel iTBS intervention to reduce impulsivity and SI among veterans with mTBI while improving overall social and occupational functioning. This study will be conducted at the Edward Hines, Jr. VA Hospital in Hines, Illinois. We are interested in stimulating the ventromedial prefrontal cortex (VMPFC) with iTBS because the VMPFC appears to exhibit less functional connectivity with the limbic system in individuals with mTBI [30]. This diminished connectivity is suspected to be responsible for impulsivity and SI in individuals with mTBI [30-32]. To the best of our knowledge, no established treatment approach has used VMPFC iTBS to improve social and occupational functioning, SI, and

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negative urgency impulsivity among individuals with mTBI and comorbid mental illness. A list of the common terms used in the study and their definitions are provided in Textbox 1.

Textbox 1. Terms and definitions used in the study.

- Mild traumatic brain injury: a type of brain injury resulting from mechanical forces defined by loss of consciousness for <30 minutes, Glasgow Coma Score of 13-15, post-concussive altered mental status or amnesia <24 hours, and normal findings on neuroimaging
- Negative urgency impulsivity: a form of impulsivity in which an individual exhibits poor behavioral control or aggression in the setting of a negative event or affect
- Neuromodulation: a category of brain treatments that modulate or alter neuronal activity through direct electrical or chemical stimulation
- Transcranial magnetic stimulation: a non-invasive brain treatment that applies a magnetic field directly to the scalp, activating neuronal activity and neuroplasticity to specific cortical regions of the brain
- Intermittent theta burst stimulation: a novel second-generation form of transcranial magnetic stimulation that utilizes bursts of magnetic energy known as theta bursts

Rationale

SI Epidemiology and Current Treatment

SI is a severe and prevalent condition among veterans and civilians alike and can prove lethal. The Centers for Disease Control and Prevention estimates that from 2015 to 2019, 4.3% of the general adult US population had SI, and 5% to 10% of these individuals advanced to making a suicide attempt (SA) [33]. Consequently, focusing treatment on individuals with SI before they advance to making an SA gives providers an opportunity at suicide prevention.

Current evidence-based treatment options for SI include pharmacotherapy and psychotherapy. Pharmacotherapeutic treatment (primarily antidepressants) can take 6 to 8 weeks or more to become effective [34]. A recent meta-analysis suggested that only two-thirds of the published studies demonstrated a reduction in SI with any pharmacotherapy compared to placebo [35]. Furthermore, many patients will require multiple medication trials and may take months to experience any symptomatic improvement [36]. Given the latency of these treatment options, individuals with SI require more suicide prevention interventions that are designed to exhibit better and faster resolutions toward promoting resilience.

mTBI and Suicide: The Role of Impulsivity

Impulsivity is associated with TBI of all severities [16,37,38]. For this study, we will focus on veterans with mTBI. Veterans with mTBI make up the majority (>80%) of the veteran population with TBI in the United States [3]. A form of behavioral impulsivity, negative urgency impulsivity, is particularly prevalent in this population [38]. Negative urgency impulsivity refers to poor behavioral control in the setting of negative events or affect [39]. It is associated with excessive agitation, irritability, low moods, and a greater tendency for aggression toward oneself or others immediately following a negative event [40]. Unsurprisingly, negative urgency impulsivity increases the likelihood of SI [41] and is associated with significant risk factors for suicide, such as social and occupational functional deficits [42]. Our laboratory's previous work built upon these findings and completed a chart review study that found negative urgency impulsivity most strongly mediated the relationship between a history of TBI and SI and SAs [43].

Post-TBI negative urgency impulsivity is presumed to be secondary to disinhibition of the limbic system from TBI-related damage to the prefrontal cortex, specifically the VMPFC, medial orbitofrontal cortex, or both [16]. The VMPFC, which serves as an inhibitory control center for the limbic system, is particularly vulnerable to damage in all severities of TBI as this region abuts the cranial floor and frontal cranial bone, making it susceptible to coup and contrecoup forces from nearly all directions [31,44,45]. Uninhibited limbic effect can manifest as poor frustration tolerance, fear, and aggression [46]. These characteristics of negative urgency impulsivity can reduce the quality of life and worsen community and social functioning, predisposing individuals to SI and SAs (Figure 1) [46].

To the best of our knowledge, no neuroimaging evidence implicates specific brain regions in mTBI-related impulsivity and SI. The presented study will help address this knowledge gap using within-participant neuroimaging data to identify brain regions predisposed to these conditions.

Figure 1. Relationship between impulsivity, functionality outcomes, and suicidal ideation.

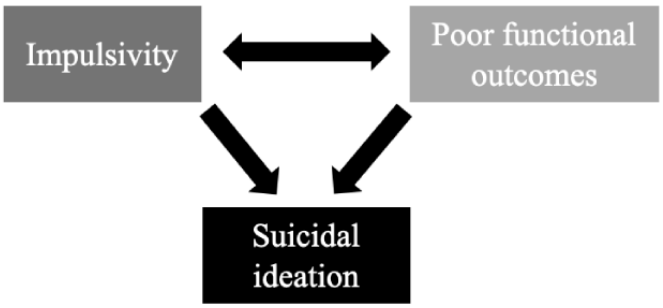

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mTBI and Suicide: The Role of Functional Deficits

TBI itself predisposes individuals to social and occupational functional deficits [47]. A meta-analysis of psychosocial factors found that difficulties in social and occupational functioning were strongly tied to increased levels of SI, social isolation, and low socioeconomic status and are directly associated with increased incidences of SI and completed suicides (Figure 1) [48]. Among individuals with TBI, those who were unemployed in the past year were at the highest risk for SI when compared to individuals who had been employed [17]. Given that TBI and impulsivity are both (1) independent risk factors for developing SI and (2) associated with impaired social and community functioning, it appears that TBI, SI, impulsivity, and functional deficits are intertwined and should be considered in tandem. However, the evidence is scarce to directly support biological treatments for SI, impulsivity, and functional deficits following mTBI. This study aims to address this knowledge gap by providing further evidence to support the development of a novel neuromodulatory treatment to improve functioning for those with impulsivity, SI, and mTBI symptoms.

TMS in Neuropsychiatry

TMS is a noninvasive neuromodulatory technique that involves placing an insulated electric coil on the scalp [49]. The electrical current flowing through the coil produces alternating magnetic fields. These fields pass through the skull, inducing electric currents in the brain tissue beneath the coil [50]. In large, multisite, double-blinded, sham-controlled trials, TMS applied [51,52] to the left dorsolateral prefrontal cortex (DLPFC) was shown to effectively treat depression. TMS was subsequently approved by the FDA to treat treatment-resistant depression in 2008 [53-55]. In 2020, a nationwide clinical TMS program was implemented in the US VA after completing a multisite clinical trial. Thus, the VA health care system is well-positioned to offer novel TMS treatment approaches for veterans in need.

iTBS is a second-generation FDA-approved form of TMS designed to mimic endogenous brain rhythms with the added benefit of markedly reduced treatment time [28,56]. In iTBS, 50 Hz triplets are applied at a theta rhythm (5 Hz), which is thought to facilitate long-term potentiation in less time and with fewer pulses than standard TMS, which generally is administered at 5 to 10 Hz [57]. Using this approach, iTBS can be administered in 3 to 10 minutes, compared to the standard 37.5-minute protocol for first-generation TMS [58]. One of the most prevalent and widely known iTBS treatment protocols is based on a study by Li et al [58] and delivers 1800 pulses of iTBS per day for 10 days. This amount of stimulation appears to be well tolerated and shows a good effect on depressive symptoms, even in a treatment-refractory group [58]. Studies demonstrate that this number of pulses results in an optimal "window" of cortical excitability, and additional pulses may have an inhibitory effect [59-61]. The result of significant symptomatic improvement in a short period is particularly interesting and relevant in treating SI, where a shorter latency to treatment response is of the essence and could potentially be lifesaving.

TMS as a Treatment for TBI Sequelae

TMS has an established safety record as a treatment for individuals with mTBI [23]. There is accumulating evidence supporting the safety and efficacy of TMS for sequelae of mTBI and related neuropsychiatric conditions, including depression, cognitive deficits, and chronic pain or headaches [23-26]. TMS also improves PTSD symptoms among those with co-occurring mTBI [22,27]. Further, multiple studies and meta-analyses demonstrate that TMS, administered to a variety of brain locations, including the DLPFC, does not induce more significant numbers of AEs among individuals with mTBI than among individuals without mTBI [23,25,62,63]. Specifically, in a national US VA TMS study of 770 veterans receiving TMS, nearly half had mTBI, and TMS was demonstrated to be equally safe in veterans with and without mTBI [64].

An overall estimate of 70% of individuals with mTBI struggle with at least one psychiatric comorbidity [65]. Thus, it is essential to consider TBI and comorbid mental illness simultaneously, as they frequently co-occur. Comorbid conditions include substance use disorders, PTSD, and depression [66-68]. Moreover, neuroimaging studies of individuals diagnosed with PTSD and substance use disorder (2 conditions that are also associated with impulsive behavior and SI) demonstrate diminished volume and hypoactivity in the VMPFC [69,70]. Therefore, it is likely that when mental illness diagnoses such as PTSD and substance use disorders co-occur with mTBI, they have an additive effect on brain functioning in the VMPFC, further worsening negative urgency impulsivity [69,70].

TMS as Treatment for Suicidality

Encouraging meta-analyses suggest that TMS may also effectively treat suicidality [71,72]. For example, a randomized controlled trial (RCT) reported a 44% decrease in individuals experiencing "thoughts of suicide" after high-dose left-sided DLPFC TMS treatment [73]. In addition, a study of pooled sham-controlled trials reported that bilateral TMS is associated with a decline in SI [74].

However, drawing overall conclusions from the existing literature on TMS for suicidality remains challenging because of the heterogeneity of the data. Studies are often limited by small sample sizes, inconsistencies in how suicidality is measured across studies, and contradictory findings [75,76]. Interestingly, an analysis suggests that changes in SI may be statistically independent of depression outcomes, underscoring the importance of studying SI separately from depression in contrast to many previous studies [77].

Post-TBI negative urgency impulsivity is presumed to arise from limbic system disinhibition because of damage to the VMPFC [16]. In mTBI, thinning of the right VMPFC is evident when compared to healthy controls [78]. Individuals exhibiting this volume loss report increased aggression, anxiety, and depression following injury [79]. Uninhibited limbic effect can manifest as poor frustration tolerance and aggression, characteristics of negative urgency impulsivity [80]. Interestingly, individuals without a history of mTBI who attempted suicide or have a history of SI also show diminished

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VMPFC volume and reduced connectivity between the prefrontal cortex and the limbic system, further supporting it as a potential therapeutic target [31,81]. Our study will collect MRI data to support our hypothesis that iTBS increases neuroconnectivity between the VMPFC and limbic system.

Frontal pole stimulation is a recent TMS and iTBS site of interest for reducing impulsive behaviors, including substance abuse [82] and compulsions in obsessive compulsive disorder [83]. iTBS can be applied to the frontal pole to target the VMPFC, and iTBS to the frontal pole is tolerable, with no more subjective pain than TMS [63]. This approach allows for more direct stimulation of the VMPFC and modulation of the limbic system [63,82].

This study proposes inducing neuroplasticity to the VMPFC by stimulating the frontal pole to treat SI and impulsivity in veterans with mTBI. We selected the frontal pole and associated right VMPFC as a treatment target as volumetric data demonstrates thinning of the right medial orbitofrontal cortex and VMPFC when compared to healthy controls [78]. Individuals exhibiting this volume loss also report increased aggression, anxiety, and depression following injury [79]. The role of the VMPFC in negative urgency impulsivity is also supported by evidence that individuals with penetrating TBI to the VMPFC are significantly more likely to become aggressive than those with penetrating TBI elsewhere [44]. By inducing modulation and neuroplasticity to the VMPFC and limbic system, iTBS at the frontal pole offers a promising means of mitigating impulsive behaviors and decreasing SI by increasing connectivity and undoing limbic damage caused by mTBI. However, more research is essential to ensure safety, tolerability, and efficacy of this treatment approach.

Objectives

This pilot study aimed to (1) determine the safety, feasibility, tolerability, and efficacy of frontal pole iTBS for veterans with mTBI, negative urgency impulsivity, and SI; (2) collect advanced neuroimaging data from veterans with mTBI, impulsivity, and suicidality to further our understanding of what neural changes are occurring when treatment is effective; and (3) gather preliminary clinical outcome data on impulsivity, SI, and social and occupational functioning of veterans receiving iTBS. The results of these objectives will help to guide future studies on neuromodulation as a treatment for impulsivity and SI among patients with mTBI.

Hypotheses

Our central hypotheses are that frontal pole iTBS will be safe, feasible, and tolerable among veterans with mTBI based on existing literature that suggests frontal pole iTBS is as safe and tolerable as iTBS performed elsewhere [23,25,62]. Similarly, iTBS, when administered to individuals with mTBI is as safe and tolerable as in individuals without mTBI [63]. Given that we are using an established iTBS protocol within the established TMS safety guidelines [84], we do not anticipate significant AEs.

We further hypothesize that social and occupational functioning, negative urgency impulsivity, and SI will be improved for individuals who receive active-iTBS compared with those who receive sham-iTBS. Even if only a single domain improves, we consider this a positive finding.

In addition, we hypothesize that resting-state functional connectivity between the VMPFC and the limbic system (especially the amygdala and anterior cingulate cortex) will be strengthened for the active-iTBS group compared with the sham-iTBS group. We also expect that veterans with increased connectivity between these regions of interest (ROIs) will likely show the most functional improvements.

Pending the results of this pilot trial, larger-scale RCTs may be warranted to establish the efficacy of frontal pole iTBS for social and occupational functional deficits, negative urgency impulsivity, and SI.

Methods

Study Design

The proposed study is a pilot, prospective, randomized, double-blinded, sham-controlled study to develop a frontal pole iTBS intervention. We will examine the safety, feasibility, tolerability, and efficacy of 10 sessions of iTBS over 2 weeks. Preliminary impulsivity, SI, and social and occupational functioning data will be collected before and after receiving active or sham treatment. In developing this protocol, we referenced the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [85]. We used the CONSORT (Consolidated Standards of Reporting Trials) checklist when writing our report [86]. Refer to Multimedia Appendix 1 for the CONSORT flow diagram.

Ethical Considerations

The study protocol was reviewed and approved by the Edward Hines, Jr. VA Hospital Institutional Review Board (Hines IRB number 1716074) and the University of Illinois, Chicago Institutional Review Board. The study is registered on ClinicalTrials.gov (NCT05647044). This study is designed in accordance with the ethical standards of the US VA Office of Research and Development, based on those from the Declaration of Helsinki, the Belmont Report, US Common Rule and Regulations from the Council for International Organizations of Medical Sciences. The study will be overseen by the institutional review boards of the both Edward Hines, Jr. VA Hospital and the University of Illinois, Chicago. This research study is designed on a 5-year research plan.

A Health Insurance Portability and Accountability Act (HIPAA) authorization waiver will be obtained to enable electronic medical records review of potential participants before obtaining consent. The HIPAA waiver allows research staff to access information about the patient's medical history and demographics, as well as history of drug or alcohol abuse to determine study eligibility. If a potential participant declines to participate in the study, no further contact will be made.

If the potential participant consents to the study, they will then begin the informed consent process. Informed consent will be obtained in English by trained research staff. Research participants will have access to research staff and the principal investigator to assist with any questions or concerns until

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understanding is achieved. A consent note is made in the participant's medical record either electronically or on paper. The original consent is then placed in the medical record, a copy is given to the participant, a copy is filed with the Edward Hines, Jr. VA Hospital Institutional Review Board and the original informed consent is placed in the participant's research binder and maintained in a locked file cabinet at Hines VA Hospital. Once the informed consent process is completed, a note will be documented in the electronic medical record system and the participant will be flagged as a research participant.

Any identifiable information about the participant, including their signed consent form, is stored in a different location than study data, on encrypted VA servers in files that are only accessible to approved study team members. The collected, deidentified research data are also stored on encrypted VA servers elsewhere, in password-protected folders, only accessible to approved study team personnel. Any participant information obtained in the study will be treated as confidential and safeguarded in accordance with the Privacy Act of 1974. Information published or presented about the results of the study will be done such that no individual identifying information is shared.

Participants will be compensated up to US $350 for their participation, prorated for their time.

Participants

We will enroll 56 veterans aged between 22 and 65 years with a history of mTBI and impulsivity. They must also report that they have experienced SI within the last 3 months. mTBI will be defined according to the VA and Department of Defense guidelines [87] and use aspects of the mTBI symptom attribution and classification algorithm [88] when determining eligibility. mTBI must have occurred at least 1 year before enrollment to ensure that the injury has stabilized. Though it is not mandatory, veterans may also have diagnoses of depression, PTSD, or bipolar spectrum illness (without a history of psychosis). Recent SI (within the past 3 months) will be defined as a score of ≥1 on the Columbia Suicide Severity Rating Scale [89]. Impulsivity will be defined as having any mentions of impulsive behavior in the medical chart and any positive results on the Urgency, Premeditation (lack of), Perseveration (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale–Negative Urgency subscale (UPPS-P) [41]. For safety, we will exclude persons with contraindications to TMS or MRI because of increased risk of AEs. We will also exclude participants whose SI is active, with intent and plan, as they require emergency psychiatric intervention. We will not exclude individuals based on sex, gender identity, ethnicity, or race. To enhance generalizability, we will include veterans regardless of previous combat or deployment experience. As cannabis and alcohol use is prevalent among veterans, intermittent or low amounts of cannabis or alcohol consumption will not be considered exclusionary if the use does not meet the criteria for a moderate substance use disorder. Detailed information on inclusion and exclusion criteria is listed below (Textbox 2).

Textbox 2. Participant inclusion and exclusion criteria.

Inclusion criteria

- Aged between 22 and 65 years
- Can read and speak English
- Mild traumatic brain injury (mTBI) criteria: Symptom Attribution and Classification Algorithm [88] criteria for mTBI (without the requirement of clinical neuropsychological impairment).
- Columbia Suicide Severity Rating Scale score of ≥1 within 3 months
- History of impulsivity documented in the chart and exhibited on the Urgency, Premeditation (lack of), Perseveration (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale—Negative Urgency subscale (Urgency score >20) [41]

Exclusion criteria

- Contraindications to intermittent theta burst stimulation or transcranial magnetic stimulation (eg, epilepsy)
- Contraindications to magnetic resonance imaging (eg, claustrophobia, ferromagnetic metal implants)
- Active substance use disorder per DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria
- Active suicidal ideation with intent and plan (these participants will be brought to the emergency department for emergent psychiatric care)
- History of moderate to severe traumatic brain injury
- History of nontraumatic neurological injury (eg, stroke, neurosurgery, hemorrhage)
- History of or current psychosis not due to an external cause (eg, due to illicit drug use)
- Pregnant or breastfeeding
- Within 12 weeks of a major surgery
- Active, unstable health condition (ie, decompensated heart failure, recent severe heart attack)
- Within 1 year of mTBI

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Power Analysis and Sample Size Justification

To ensure we have adequate power to detect a difference in our primary outcome, the Social and Occupational Functioning Assessment Scale (SOFAS), we conducted a power analysis. Assuming a significance level of 0.05, a mean SOFAS score of 44.6, and a SD of 15, with 50 veterans, we will have 82% power to detect a significant interaction between time and treatment assuming no change over time in the sham-iTBS group and a change of 13 points in the active iTBS group [90]. On the basis of similar studies of iTBS protocols for patients with depression and PTSD, receiving treatment of similar duration, attrition rates are expected to be low—under 10% [58,90,91]. As such, we plan to enroll participants to ensure we have an adequate sample size considering 10% attrition. Thus, our total sample size will be 56 with 28 in the active iTBS group and 28 in the sham iTBS group.

Recruitment

We will recruit veterans receiving care from the TBI and polytrauma program, primary clinic, women's health clinic, and the Mental Health Service Line at Edward Hines, Jr. VA Hospital in Hines, Illinois, United States. Personnel at all mentioned clinics will be educated on the study and encouraged to give institutional review board (IRB)–approved flyers containing contact information to veterans who may be a good fit for the study. We will be added as cosigners in the electronic medical records of Hines VA patients who may be deemed a good fit for this study. We will also mail informational letters to veterans who have completed past TBI studies and permit us to contact them about future studies through a TBI Data Repository (Hines IRB number14-003), which currently includes >300 veterans. Research candidates at the Hines VA will also be identified using administrative electronic health record data available through the VA Informatics and Computing Infrastructure. The VA Informatics and Computing Infrastructure database will search for TBI within the past 10 years (FY2013-FY2023) according to appropriate *International Classification of Diseases* (ninth and tenth editions), clinical modification, codes reflecting study inclusion criteria. All potentially eligible veterans will receive an informational letter and phone call to gauge interest and perform initial eligibility screens.

Data Collection and Measures

MRI Data Acquisition, Neuronavigation, and Motor Thresholding

All participants will undergo an MRI of their brain before and after iTBS administration. Before iTBS, a high-resolution, 3D, T1-weighted, multigradient-echo sagittal anatomical scan (voxel size=0.8 mm isotropic resolution) will be collected at the University of Illinois, Chicago Center for Magnetic Resonance Research to allow for iTBS treatment site neuronavigation for each participant. Participants will also complete a resting-state functional MRI (fMRI) and diffusion tensor imaging before and after iTBS administration to examine treatment-induced connectivity changes. Participants will be asked to complete a standardized MRI safety screening form before starting the study to ensure the MRI safety procedures are followed (Multimedia Appendix 2).

Each participant's T1 MRI will be loaded into a TMS Neural Navigator TS system (version 3.3.22, Localite), consisting of a camera and computer system that allows a TMS provider to superimpose an individual's MRI onto where they are in space, allowing for very precise placement of the TMS coil. Electrodes will be placed on the thumb over the abductor pollicis brevis (ABP) muscle and connected to an electromyograph (MagVenture) to measure motor-evoked potentials (MEPs). To determine each participant's motor threshold (MT) for iTBS (to determine at which intensity the iTBS stimulation should be delivered), a MagProX100 with MagOption stimulator and Magpro Cool Coil B65 A/P (MagVenture) will be used. Single pulse TMS will be administered to the left motor cortex at the hand knob. The location of this part of the motor cortex will be estimated using the participant's MRI and then confirmed using TMS to identify the ABP muscle neural coordinates. The resting MT is the lowest stimulus intensity necessary to produce MEPs of the peak-to-peak amplitude of ≥50 μV in 5 of 10 trials. MEPs of the ABP will be recorded using surface electrodes on the right thumb. The right frontal pole will be identified and mapped using the TMS Neural Navigator (Localite) system. The anatomical location is easily identifiable using anatomical landmarks and correlates with electrode frontal polar cortex (FP; FP2) on a 10 to 20 electroencephalogram, a region overlapping with the right VMPFC [22,63,82]. Refer to Multimedia Appendix 3 for the equipment list.

Data Collection

Data collection is expected to take approximately 18 to 20 hours per participant over the intervention period of 2 weeks. Assessments will be collected at 4 time points in the study: screening, baseline, midpoint, and end point (Table 1).

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Table 1. Assessment timeline and purpose.

Assessment name	Assessment purpose	Items	Scoring	Validity and reliability
Phone screening assessments				
Ohio State TBI[a] Identification Method [92] (rater administered)	mTBI[b] eligibility determination	Structured interview	Determination of the likelihood TBI sustained based on the participant's detail recollection	Interrater reliability >90% (very high) [92]
Columbia Suicide Severity Rating Scale [89] (rater administered)	History of suicidality, eligibility determination—secondary outcome	Five items measuring the presence of SI[c], intensity of SI, presence of suicidal behaviors, lethality of behaviors	Ideation: 0-5; intensity: 2-25; suicidal behaviors: yes or no; lethality: 0-2, higher scores=more severe	Internal validity a=0.95 and test-retest reliability r_{tt}=0.90-1.0 (very high) [93,94]
Urgency, Premeditation (lack of), Perseveration (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale—Negative Urgency subscale [41,95] (rater administered)	Negative urgency impulsivity, eligibility determination—secondary outcome	Fifty-nine items measuring 4 traits–urgency, lack of premeditation, lack of perseveration, and sensation seeking [96]	4-point Likert scale questions, scored by each trait, some reverse-coded. Higher score=more severe [97]	Cronbach α=0.91 (very high) [41,97]
Demographics (rater administered)	Sample characterization	__[d]	—	—
UIC[e] CMRR[f] MRI[g] Safety Form (Multimedia Appendix 2; rater administered)	MRI safety, compatibility, and eligibility determination	—	—	—
TMS[h] Safety Form (Multimedia Appendix 4; rater administered)	TMS safety compatibility, eligibility determination	—	—	—
In-person screening assessments				
Structured diagnostic interview [88] (rater administered)	mTBI symptoms, eligibility determination	Structured interview	Likelihood symptoms owing to TBI sustained	—
Neurobehavioral Symptom Inventory [98] (rater administered)	mTBI symptoms, eligibility determination	Twenty-two items asking about the severity of postconcussive symptoms	Severity: 0=never to 4=very severe, symptom always present; higher score=more severe symptoms	Cronbach α=0.81-0.96 (very high) [98]
Clinically Administered PTSD[i] Scale for DSM-5[j] [99] (rater administered)	PTSD diagnosis	30-item questionnaire corresponding to DSM-5 PTSD criteria	Severity: 0=absent to 4=extreme, total symptom severity 0-80, higher score=more severe symptoms	Interrater reliability *K*=0.78-1.0 (high) discriminant validity: rs=0.02−0.54 (moderate) [100]
Alcohol Use Disorder Identification Test [101] (participant self-administered)	Active alcohol use disorder, eligibility determination	10-item questionnaire about the frequency and amount of alcohol used	Questions 1-8 (0-4 points), 9-10 (0,2,4 points, range of 0-40 points, higher score=more severe symptoms)	AUROC[k]=0.891 (high) [101]
Drug Use Disorders Identification Test [102] (participant self-administered)	Active substance abuse disorder, eligibility determination	11-item questionnaire about the frequency and number of drugs of abuse used	Questions 1-9 (0-4 points), 10-11 (0,2,4 points, total score 0-44, higher score=more severe symptoms)	Cronbach α=0.93 (very high), convergent validity *r*=0.76 (high) [102,103]
Structured Clinical Interview for DSM-5, Research Version [104] (rater administered)	Active mental illness diagnosis	Structured interview	—	*K*>0.4 (above average) sensitivity of identifying diagnosis >0.8 (good) [105]
Baseline, midpoint, and follow-up assessments				

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Assessment name	Assessment purpose	Items	Scoring	Validity and reliability
Social and Occupational Functioning Assessment Scale [106] (rater administered)	Functioning in the community–primary outcome	Single item 100-point scale assessing social activities, relationships, self-care, aggressive behavior	0-100 (0=not functioning, 100=superior functioning)	Weighted *K*=0.95 (very high) [107]
Columbia Suicide Severity Rating Scale (rater administered)	As described in "phone screening assessments"	As described in "phone screening assessments"	As described in "phone screening assessments"	As described in "phone screening assessments"
Urgency, Premeditation (lack of), Perseveration (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale—Negative Urgency subscale (participant self-administered)	As described in "phone screening assessments"	As described in "phone screening assessments"	As described in "phone screening assessments"	As described in "phone screening assessments"
Buss-Perry Aggressiveness Scale [108] (participant self-administered)	Aggression symptoms	29-item scale of true or false statements about aggressive and stable behaviors, including measures of physical aggression, verbal aggression, anger, and hostility	Scale of 1-5, 1 being "extremely uncharacteristic," to 5 being "extremely characteristic." Some reverse coded (stability statements), higher score=more aggressiveness	Test-retest reliability r_{tt}=0.80 (high), Cronbach α=0.68-0.8 for each subscale (moderate-high) [108]
Patient Health Questionnaire-9 [109] (participant self-administered)	Depression symptoms	9-item scale of DSM-5 depressive disorder symptoms (ie, low mood, sleep disturbance, SI)	Scale of 0-3, 0="not at all," 3="always." Higher score=more severe depression	Cronbach α=0.9 (very high) [110]
Veteran's RAND [111] (participant self-administered)	Perceived community functioning	36 items across 8 subscales of health including physical health, limitations owing to health, energy, social health, etc	0-100, higher score=more favorable health state	Cronbach α=0.78-0.93 depending on the domain (high-very high) [112]
Beck Suicide Scale [113] (participant self-administered)	Suicidal ideation measurement	21 items about recent thoughts of death, recent suicidal behaviors	Scale of 0-2, higher number=more severe SI	Cronbach α=0.89 (very high), strong predictive validity [114]
PTSD Checklist for DSM-5 [115] (participant self-administered)	PTSD symptoms	20 items corresponding to DSM-5 criteria for PTSD symptoms (eg, hypervigilance, flashbacks)	Scale of 0-4, 0=not at all, 4=extremely, score >33=probable PTSD diagnosis	Cronbach α=0.94 (very high) and test-retest reliability (r_{tt}=0.82) (high) [116]
Inventory of Depressive Symptomatology, Self-Report [117] (participant self-administered)	Depression symptoms	30 items assessing DSM-5 depressive symptoms	Scale of 0-3, 0=not present, 3=severe symptoms, higher score=more severe symptoms	Cronbach α=0.94 (very high) and test-retest reliability r_{tt}=0.82 (high) [118]
Difficulties in Emotion Regulation Scale [119] (participant self-administered)	Perceived struggles with emotion modulation	36-item scale, 6 subscales of emotion regulation	Scale of 1-5, 1=almost never, 5=almost always. Higher score=more difficulty with regulation	Cronbach α=0.90 (very high) [120]
Delayed Discounting Task [121] (administered on computer)	Impulsivity inhibition measure	Behavioral assessment of impulsivity, 27 items where participant chooses smaller immediate rewards vs larger delayed reward	Tendency to choose smaller immediate rewards consistent with more impulsivity	Test-retest reliability r_{tt}=0.89 (very high) [122]

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Assessment name	Assessment purpose	Items	Scoring	Validity and reliability
Stroop Color & Word Test [123] (rater administered)	Impulsivity inhibition measure	Behavioral assessment of processing speed and inhibition of cognitive interference	Measure the number of correct answers versus incorrect answers	Reliability estimates range from a=0.83 to a=0.91 and test-retest reliability ranges from r_{tt}=0.79 to r_{tt}=0.97 (all high-very high) [124]

[a]TBI: traumatic brain injury.

[b]mTBI: mild traumatic brain injury.

[c]SI: suicidal ideation.

[d]Not applicable.

[e]UIC: University of Illinois, Chicago.

[f]CMRR: Center for Magnetic Resonance Research.

[g]MRI: magnetic resonance imaging.

[h]TMS: transcranial magnetic stimulation.

[i]PTSD: posttraumatic stress disorder.

jDSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[k]AUROC: area under the receiver operating characteristic curve.

Eligibility measures and information collected during the preenrollment phone screen administered by authorized clinical researchers include The Ohio State University TBI Identification Method [92], the Columbia Suicide Severity Rating Scale [89], the UPPS-P [41], self-reported age, the ability to read and speak English, the Center for Magnetic Resonance Research safety form (Multimedia Appendix 2), and TMS safety form (Multimedia Appendix 4). If deemed eligible, participants will be asked to complete an in-person screening.

The in-person screening will consist of completing additional assessments to ensure eligibility and baseline characteristics. They include the structured diagnostic interview from the symptom attribution and classification algorithm, created by individuals involved in this study to determine likelihood and severity of prior TBIs [88], the Neurobehavioral Symptom Inventory, to determine TBI-related symptom presence [98], the Clinician-Administered PTSD Scale for DSM-5 to determine preexisting diagnosis of PTSD [99], the Alcohol Use Disorder Identification Test-Consumption Questions to determine if an alcohol use disorder is present [101], the Drug Use Disorders Identification Test to determine if a drug use disorder is present [102], and the Structured Clinical Interview for DSM-5–Research Version to determine the presence of other psychiatric disorders [104].

Once the listed diagnostic and screening measures are completed and participants meet eligibility criteria, participants will be asked to complete self-reported measures at their baseline, midpoint, and end point visits (Table 1).

Feasibility completion rates will be described according to the reasons participants did not complete the 2-week intervention and the rates of missed sessions. Study completion is defined as completing all 10 sessions. Safety measures will follow procedures used in prior TMS studies [125] and will be scored using the *Medical Dictionary for Regulatory Activities*. Side effects, AEs, and the TMS data safety sheet will assess change severity throughout the intervention. Tolerability will be measured through the number of patients who complete the treatment course and via self-report.

Safety and AE Monitoring

Participants will participate in safety monitoring using the Data Safety Monitoring Scale. This scale will measure rate changes from baseline vitals (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus (ringing in the ears), sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, and substance use.

Participants will be asked about AEs at each iTBS session, which will be logged to ensure safety throughout the intervention. These will be coded using the current version of the Medical Dictionary for Regulatory Activities, following procedures used in previous TMS studies [82]. The TMS safety sheet (Multimedia Appendix 4) will be collected and scored regarding severity and change from baseline. Data on every side effect and AE will be collected, rated on a score of 0 to 5 to assess severity, and reported.

All iTBS sessions will be videotaped to monitor for safety and allow for review in case of an AE. Acknowledgment for pictures and videos will be completed as part of our informed consent procedure.

AEs can be nonserious and serious. A serious AE is when the changes are life-threatening and may be disabling, require hospitalization, or require intervention to prevent impairment. We will measure deleterious changes in (1) neurological status and cognitive symptoms, (2) somatic and vestibular symptoms, (3) and depression. AE will be tracked using the AE log.

All unanticipated AEs related to this research study will be reported to the IRB, the study sponsor, and the research director within 5 business days. Serious AEs will be reported to these entities within 24 hours. If any unanticipated problem occurs, such as deviation from this protocol that involves risks or has the potential to recur, the investigator will report this information to the IRB. All AE information will be reported within 2 to 5 business days of the investigator or staff becoming aware of the event.

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The study will take place at the Edward Hines, Jr. VA Hospital in Hines, Illinois, a full-service, tertiary-care hospital. Our laboratory is located within the rapid response area, meaning a team of specialized nurses and doctors can be called at any time to emergently assess a patient, should the need arise. Participants will be clinically monitored for seizure by trained research staff. In the event of a seizure, the research team member will call the on-site rapid response team (RRT) to provide emergent medical care to the participant. Cardiopulmonary resuscitation–trained research staff will assess the participant's airway, breathing, and circulation until the RRT team arrives. RRT will then take over the participant's care, including administering seizure-abating medications and airway protection, and transport the participant to the emergency department. Any seizure will result in stopping the intervention and withdrawal from the study.

Experimental Intervention

Each participant will be randomized to receive active or sham treatment throughout the protocol, with 50% (28/56) receiving active treatment and 50% (28/56) of participants receiving placebo. We will use a T1 MRI to localize the FP stimulation site. This region is correlated with electrode FP2 on a 10 to 20 electroencephalogram, a region overlapping with the right VMPFC [22,82]. To ensure precise and repeatable coil positioning over the frontal pole FP2 site, the Localite (neuronavigation) system and an MRI instrument marker will be used at every iTBS session.

Our 9-minute iTBS protocol will be delivered using the MagVenture Mag-Pro X100 with the MagOption stimulator, including active and placebo coils (C-B60 Butterfly coils). The consensus in the literature is that iTBS can safely deliver 1800 pulses at 110% of the MT to the frontal pole [82,83]. iTBS parameters include 3 pulses of stimulation at 50 Hz, repeated every 200 miliseconds. The interpulse interval is 20 miliseconds. A 2-second train of TBS is repeated every 10 seconds for a total of 570 seconds, equaling a total of 1800 pulses delivered over 9 minutes. To ensure that the participants can tolerate the treatment, stimulation intensity will begin at 60% to 70% of the MT intensity and will slowly increase as the patient tolerates to 110% of the patient's MT intensity over the first few treatment sessions [42].

Study Procedures

A partial HIPAA waiver and waiver of informed consent for screening purposes will provide regulatory approval to screen potential candidates to determine study eligibility. Once identified as a potential research candidate, candidates will be contacted for an initial phone screening to determine eligibility criteria. Demographics, mental illness diagnosis, current medication use, and history of impulsive behaviors (eg, history of fights, violence, anger, and irritability) will be cross-verified in the patient's electronic medical record. A thorough chart review will be completed to cross-reference current medications with study eligibility criteria to identify antiepileptics or medications that could lower the seizure threshold. If review findings indicate possible contraindications to TMS or MRI related to a metal implant, then the model and manufacturer of the implant will be obtained to determine whether it is safe to expose the implant to a strong magnet. Manufacturer recommendations regarding safety will be followed. If potential participants meet all eligibility criteria, they will be invited for their first research visit, an in-person screening (visit 1). There will be 14 visits for this research study (Figure 2).

Figure 2. Study visit diagram. iTBS: intermittent theta burst stimulation; MRI: magnetic resonance imaging.

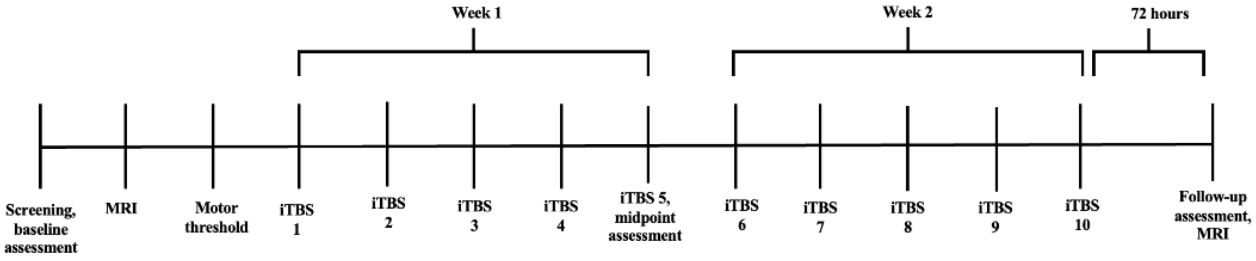

After meeting with the research staff and signing the informed consent, participants will complete several baseline diagnostic and screening measures (Table 1). These measures will be used to track changes in symptoms of impulsivity, suicidality, depression, anger, aggression, and social and occupational functioning throughout the study. If the participant is a woman, sexually active, and not on any form of physician-prescribed birth control, they will be asked to take a urine pregnancy test at this visit. Veterans who have completed baseline measures and have met eligibility criteria will be asked to complete a pretreatment resting-state fMRI at the University of Illinois, Chicago, an institution partnering with us for this study (visit 2). After the pretreatment MRI, participants will be invited back to the Hines VA to complete their MT and brain mapping using the TMS Neural Navigator (Localite) system (visit 3).

Participants will be randomized to either active or sham treatment. Blinding procedures for active and sham iTBS will be delivered with the MagProX100 with MagOption stimulator and Magpro Cool Coil B65 A/P (MagVenture), which can be switched to active or sham. The coil is identical visually for the sham and active conditions. Veterans and researchers will wear headphones connected to the noise generator during treatment to hear active iTBS for both conditions, thereby maintaining the blind. The sham coil and scalp electrodes will be placed in the same location for all participants and will mimic the sensation produced by the active coil but will not alter brain physiology. Thus, the sham stimulation looks, sounds, and feels like active stimulation. A single unblinded study team member will determine which participants are randomly placed in the active or sham groups.

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After the MRI and MT have been completed, participants will be randomized, and the intervention will begin (visits 4-13). Intervention sessions will occur once daily for 10 business days, with each session lasting 30 minutes to 1 hour. Research staff will complete a TMS safety rating scale before and after every iTBS session to assess for changes from baseline for vital signs, sleep duration, fatigue level, recent seizures, and tinnitus. Pain and tolerability measures will be completed at the end of every session to assess daily pain and session tolerability. After iTBS session 5 (visit 8), each participant will be asked to complete the self-report rating scales and neurocognitive testing they completed at baseline.

All veterans who have completed the iTBS treatment course of 10 sessions will be asked to return to the University of Illinois, Chicago's Center for Magnetic Resonance Research to obtain a second resting-state fMRI for their final research visit. Posttreatment MRI data collection is expected to be completed 72 hours after the iTBS course. This time spacing between stimulation and imaging has been done in similar studies [78] and is thought to be a long enough gap post-iTBS completion not to represent the immediate effects of the most recent stimulation.

Analytic Plan

A statistical significance level corresponding to α=.05 will be used to test hypotheses.

Descriptive statistics of feasibility, safety, and tolerability measures will be computed for all participants and compared between active- and sham-iTBS groups. We will calculate the categorical variables' frequencies and compare them using chi-square analyses for the descriptive statistics [126]. For the continuous variables (ie, daily pain ratings), we will compute mean, median, range, and SDs and compare using 2-tailed *t* tests.

For functional outcome measures, we will estimate a mixed model ANOVA to measure differences within-participants (how the SOFAS changes over time), between-participants (how the SOFAS differs between active and sham iTBS), and whether there is a significant interaction between time and treatment [127]. We will assume equal variance between test and control groups [128]. If the variance is unequal, we may transition to a generalized linear mixed (GLM) effects model [129].

For our neuroimaging analysis, to evaluate the VMPFC to the amygdala and anterior cingulate relationships and how they change before and after treatment, we will define ROIs for the amygdala and anterior cingulate with clear anatomical boundaries identified using Freesurfer [130]. Average time-series data will be extracted, and GLM will be used to quantify the relationship between the seeds and targets. The GLM results will yield individual *r* values (ie, correlations), which will be normalized into *Z* scores using Fisher R-to-Z transformation [131]. The individual maps of *Z* scores will be the primary measure of connectivity between the seed and target ROIs. We will then implement an ROI-to-ROI analysis within the connectivity toolbox to evaluate resting-state functional connectivity between the amygdala, anterior cingulate, and VMPFC [132]. We will assume a normal distribution and use Fisher's *Z* test to compare active-iTBS and sham-iTBS groups, both before and after treatment [133]. We will adjust for a priori covariates, including age, sex, and baseline psychiatric diagnoses. All analyses will be corrected for multiple comparisons using false-discovery rate correction. We will use linear mixed models to test how connectivity changes correspond to functional and mental health outcome changes, with functional and behavioral measures included as the dependent variables [134].

To inform future research studies, we will estimate regression models that include additional covariates such as demographics, psychotropic medication use, comorbid psychiatric diagnoses, and scores on the Inventory of Depressive Symptomatology, Self-Report and the PTSD Checklist for DSM-5, in addition to testing our hypotheses for the primary and secondary outcomes.

Results

This study was funded in April 2023 and began enrolling participants in July 2024. As of July 2024, there are 2 participants enrolled in the study. Data will be analyzed and study results will be disseminated on or before the project's end date in March 2028.

Discussion

Principal Findings

This novel protocol represents the first pilot RCT for frontal pole iTBS for mTBI, negative urgency impulsivity, and suicidality. We hypothesize that iTBS administered to the frontal pole in US veterans with mTBI, impulsivity, and suicidality will be safe and well tolerated as studies show that both TMS and iTBS appear safe and effective when administered to other anatomical sites in individuals with mTBI [23-26]. Furthermore, studies demonstrated frontal pole iTBS is tolerable with good safety outcomes in individuals without mTBI [63].

We hypothesize that we can improve social and occupational functioning, impulsivity, and SI among US veterans with mTBI. Other studies have specifically found meaningful change in both the UPPS-P and SOFAS over a 2-week neuromodulation intervention period among individuals with major depression [90,135]. Several repetitive TMS (the precursor to iTBS) trials among individuals with SI and major depression have shown reductions in suicidality [71-74]. We anticipate these results will generalize to individuals with mTBI when treated with iTBS [72,136].

Finally, we hypothesize that we will be able to identify changes in neural connectivity among individuals who respond to our iTBS protocol by comparing pretreatment fMRIs with posttreatment fMRIs. Several studies on both iTBS and TMS, administered to the DLPFC, of a variety of treatment durations, showed increased connectivity between the frontal cortex and areas of the limbic system [137]. We expect to see similar results with iTBS administered to the VMPFC.

We will add to the existing literature in several ways. First, there are no widely established treatments for poorer functional outcomes, suicidality, or impulsivity that occur in the context

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of mTBI. If we can develop an effective intervention that targets all of these likely interrelated conditions, we will be adding important findings to the literature base and we could also improve the quality of life and treat SI among people with mTBI. By further establishing the frontal pole as a tolerable and effective iTBS stimulation site, we could also encourage other researchers to explore this site for potential therapeutic benefit for a variety of conditions. Finally, by identifying fMRI connectivity changes before and after iTBS treatment, we will add to the literature base regarding how neuromodulation works mechanistically, which is still unclear. Moreover, if we can identify specific fMRI connectivity changes correlating to symptomatic changes, it may help us identify future neuromodulatory treatment sites of interest, to continue to further explore this very promising treatment modality.

Strengths of the Study

The proposed study has several key strengths. First, the study uses an established FDA-approved device readily available in both VA and civilian health care systems throughout the United States. Compared with traditional pharmacological and behavioral approaches, iTBS has a reduced latency to treatment response, which could be lifesaving among individuals with SI. Our approach also differs from previous studies that primarily focused on improving SI via the treatment of depressive symptoms. We provide a novel framework for understanding and ultimately treating SI, which could be helpful for individuals who have yet to respond to past evidence-based treatments for this condition. Finally, by targeting the VMPFC and including neuroimaging from before and after treatment, this study has the potential to identify a novel target for iTBS, increase insight into the underlying neurological mechanisms of SI, and identify which individuals are more likely to respond to a neuromodulatory intervention.

Limitations of the Study

There are several limitations to consider. The small sample size reduces the study power, which may limit the detection of statistically significant outcome differences. However, this sample size reflects the pilot nature of the study and funding mechanism. Variability in the baseline characteristics of the patient population (ie, co-occurring psychiatric and somatic conditions, coadministration of other medications, etc) that are being studied in detail in this project may impact our findings. Covariates will be explored; however, given the small sample size, only select covariates can be added to the final models. The relatively short follow-up time of 72 hours after the final iTBS treatment will not provide insight into the long-term effects of our intervention. Future studies would benefit from additional follow-up outcomes assessments and imaging several months after the treatment to assess the intervention's durability. Although prior studies used a dose of 110% MT and a time frame of 10 sessions, we are still determining if these parameters are optimal. A future dosing study would help optimize the treatment parameters. This study does not select targets based on resting-state data; however, in collecting these data in tandem using neuronavigation, we can potentially target more specific sites in the future.

Conclusions

The proposed study integrates past findings from impulsivity, TBI, neuroanatomical, neuroimaging, neurorehabilitation, and neurostimulation research to create a novel, but highly informed treatment strategy. In this study, we hope to induce neuroplasticity in the connections between the VMPFC and limbic system, through neuromodulation at the frontal pole. In inducing neuroplasticity with iTBS, in an effort to repair damaged neural connections, we hope to mitigate the development of impulsive behaviors, improve social and community functioning, and decrease SI, as we believe all 3 of these conditions would benefit from strengthening the VMPFC-limbic system network. Data obtained by using validated scales will inform future studies.

Moreover, the collection of pretreatment neuroimaging may help us understand what neural signatures predispose individuals to respond favorably to frontal pole iTBS, so we might be able to predict who is most likely to benefit from treatment, following comparable work in predicting response to neurostimulation in individuals with major depression [138]. Thus, findings from the proposed project are expected to have the capacity to (1) help identify which individuals are more likely to respond to a neurostimulation intervention for impulsivity and suicidality related to mTBI and (2) better understand what neural changes we are eliciting. Advancing knowledge in both areas will inform future studies and enable a more rapid determination of which treatments will be most effective for a given individual and determining where connectivity changes are occurring may allow us to further optimize treatment effects.

Acknowledgments

This study is funded by the Veterans Affairs Rehabilitation Research and Development Career Development level 2 grant (grant IK2RX004298), which began on April 1, 2023. The authors of this project gratefully acknowledge the Edward Hines, Jr. VA Hospital, with special thanks to the Mental Health Service Line and Research Service Line for supporting the research team. They also thank the Department of Psychiatry and the Center for Magnetic Resonance Research at the University of Illinois, Chicago. The contents of this paper do not represent the views of the US Department of Veterans Affairs or the US government.

Data Availability

The datasets generated during and analyzed during this study are not publicly available due to legal restrictions the US Department of Veterans Affairs places on access to veteran data, including both identifying data and sensitive patient information, but are

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available from the corresponding author on reasonable request with the completion of an approved data use agreement. For more information, please visit the VA website [139].

Authors' Contributions

AB and AA led the writing of this manuscript. AA conceived the project and obtained funding to support the project. All other authors contributed to the study design and reviewed the manuscript.

Conflicts of Interest

CH has served as a consultant for Magstim and is currently employed by BrainsWay.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) flow diagram—anticipated.
[DOC File , 40 KB - resprot_v13i1e58206_app1.doc]

Multimedia Appendix 2
University of Illinois–Chicago Center for Magentic Resonance Research magnetic resonance imaging safety form.
[DOCX File , 27 KB - resprot_v13i1e58206_app2.docx]

Multimedia Appendix 3
Equipment list.
[DOCX File , 13 KB - resprot_v13i1e58206_app3.docx]

Multimedia Appendix 4
Transcranial magnetic stimulation (TMS) safety form.
[DOCX File , 14 KB - resprot_v13i1e58206_app4.docx]

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Abbreviations

ABP: abductor pollicis brevis
AE: adverse event
CONSORT: Consolidated Standards of Reporting Trials
DLPFC: dorsolateral prefrontal cortex
FDA: Food and Drug Administration
fMRI: functional magnetic resonance imaging
FP: frontal polar cortex

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GLM: generalized linear mixed
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
iTBS: intermittent theta burst stimulation
MEP: motor-evoked potential
MRI: magnetic resonance imaging
MT: motor threshold
mTBI: mild traumatic brain injury
PTSD: posttraumatic stress disorder
ROI: region of interest
RRT: rapid response team
SA: suicide attempt
SI: suicidal ideation
SOFAS: Social and Occupational Functioning Assessment Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TBI: traumatic brain injury
TMS: transcranial magnetic stimulation
UPPS-P: Urgency, Premeditation (lack of), Perseveration (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale–Negative Urgency subscale VA: US Veterans Administration
VMPFC: ventromedial prefrontal cortex

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Protocol

Adaptive Intervention to Prevent Respiratory Illness in Cerebral Palsy: Protocol for a Feasibility Pilot Randomized Controlled Trial

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Abstract

Background: This study will pilot-test an innovative just-in-time adaptive intervention to reduce severe respiratory illness among children with severe cerebral palsy (CP). Our intervention program, Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT), delivers timely customized action planning and rapid clinical response when hospitalization risk is elevated.

Objective: This study aims to establish RE-PACT's feasibility, acceptability, and fidelity in up to 90 children with severe CP. An additional aim is to preliminarily estimate RE-PACT's effect size.

Methods: The study will recruit up to 90 caregivers of children with severe CP aged 0 to 17 years who are cared for by a respiratory specialist or are receiving daily respiratory treatments. Participants will be recruited from pediatric complex care programs at the University of Wisconsin–Madison (UW) and the University of California, Los Angeles (UCLA). Study participants will be randomly assigned to receive usual care through the complex care clinical program at UW or UCLA or the study intervention, RE-PACT. The intervention involves action planning, rapid clinical response to prevent and manage respiratory illness, and weekly SMS text messaging surveillance of caregiver confidence for their child to avoid hospitalization. RE-PACT will be run through 3 successively larger 6-month trial waves, allowing ongoing protocol refinement according to prespecified definitions of success for measures of feasibility, acceptability, and fidelity. The feasibility measures include recruitment and intervention time. The acceptability measures include recruitment and completion rates as well as intervention satisfaction. The fidelity measures include observed versus expected rates of intervention and data collection activities. The primary clinical outcome is a severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization. The secondary clinical outcomes include hospital days and emergency department visits, systemic steroid courses, systemic antibiotic courses, and death from severe respiratory illness.

Results: The recruitment of the first wave began on April 27, 2022. To date, we have enrolled 30 (33%) out of 90 participants, as projected. The final wave of recruitment will end by October 31, 2023, and the final participant will complete the study by April 30, 2024. We will start analyzing the complete responses by April 30, 2024, and the publication of results is expected at the end of 2024.

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Conclusions: This pilot intervention, using adaptive just-in-time strategies, represents a novel approach to reducing the incidence of significant respiratory illness for children with severe CP. This protocol may be helpful to other researchers and health care providers caring for patients at high risk for acute severe illness exacerbations.

Trial Registration: ClinicalTrials.gov NCT05292365; https://clinicaltrials.gov/study/NCT05292365

International Registered Report Identifier (IRRID): DERR1-10.2196/49705

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KEYWORDS

just-in-time adaptive intervention; respiratory illness; cerebral palsy; action planning; digital health

Introduction

Background

Children with severe cerebral palsy (CP) have spastic quadriplegia and are classified in level IV or V on the Gross Motor Function Classification System (GMFCS), often resulting in little or no independent mobility and serious respiratory consequences [1]. The mechanisms of respiratory illness in severe CP vary, paralleling those of other neuromuscular diseases [2], and include respiratory muscle weakness, recurrent infections and aspiration with inflammatory fibrosis, impaired airway clearance from altered tone, upper airway abnormalities, and poor chest wall compliance [3,4].

Respiratory illness is consistently the leading cause of death and hospitalization in severe CP [5,6]. Respiratory illness accounts for 59% of the deaths [5,7] and 25% of the hospitalizations [8-10] in severe CP. Moreover, respiratory illness strongly predicts future risk: respiratory hospitalization risk is 10-fold higher with a respiratory illness in the past year. Nevertheless, respiratory illness risk factors in severe CP are considered modifiable [11]. The prevention of these events is a significant need and a key to improving the quality of life and decreasing mortality [1,12].

Preventing hospitalization requires the opportunity for families and clinical teams to connect early enough to change trajectory [13-15]. Parents of children with CP have expressed the need for interventions focused on crisis management and self-efficacy [9,13,16]. However, respiratory illness in severe CP has broad comorbid triggers (eg, emesis, dysphagia, aspiration, and seizures). Because of this complexity, simple action plans or coaching alone may not address the breadth of respiratory illness triggers or potential responses; for example, if a parent of a child with severe CP follows an action plan directed toward bronchospasm, it would not effectively address an acute infectious lower respiratory infection. Parents of children with severe CP need comprehensive action planning and coaching; they also need an efficient direct extension to their clinical team for a just-in-time (JIT) adaptive clinical response directed specifically to acute real-time problems.

Currently, difficulty identifying when JIT care is needed is a barrier to effective illness response. Concerns may not reach clinical teams until an emergency department (ED) visit or hospitalization is inevitable. A national expert panel to identify interventions to prevent the hospitalization of children with complex diseases concluded that enhanced access, proactive crisis planning, and support for caregiver technical skills were crucial strategies to lower hospital use [17]. Prior postdischarge research has confirmed that admissions and ED visits could be better predicted by identifying when parents were not confident that their child with chronic conditions could avoid hospitalization or an ED visit than by other clinical or demographic indicators [18,19]. Preliminary work with a cohort that included children with severe CP demonstrated that parent confidence, monitored prospectively and repeatedly by SMS text message, is feasible, is acceptable, and predicts hospitalization within 2 weeks. This program of research will drive care forward by providing JIT care triggered by parents' self-reported period of low confidence, thus matching the intervention to the immediate clinical need and preventing respiratory crisis.

Prior Work

This team developed the earlier Plans for Action and Care Transitions (PACT) intervention to prevent hospitalizations for children with complex chronic diseases, including severe CP. After integrating a systematic literature review [20], parent interviews [21], and a national expert panel [17], each focused on preventing hospitalization, the team designed PACT to leverage evidence-based strategies from different populations: asthma action planning [22-24], health coaching [25-27], and feedback from parent advisory group meetings. The PACT intervention delivered action planning and coaching activities to children with diverse complex diseases, including severe CP, and observed 40% lower hospitalization rates for intervention versus control patients [28]. Simultaneously, our prior multisite research observed that confidence to avoid hospitalization, measured through repeated SMS text messaging, predicted hospitalization over the subsequent 2 weeks. Our clinical team and family partners hypothesized that periods of low confidence might be a useful tailoring variable to prompt intervention delivery [29].

The pact intervention has now been adapted to prevent severe respiratory illness in children with severe CP and to integrate SMS text messaging as a tailoring variable within a JIT adaptive intervention framework [29,30].

Objectives

This pilot study (ClinicalTrials.gov: NCT05292365) is designed to establish the feasibility, acceptability, and fidelity of our intervention program, Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) in up to 90 children with severe CP and to establish a preliminary effect size of RE-PACT to inform a future efficacy study to reduce severe

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respiratory illness. This intervention consists of three related parts: (1) universal action planning, (2) an ongoing assessment of hospitalization risk, and (3) an algorithm to determine when to increase clinician contacts and tailor action plans. The study period will be divided into 3 waves; after each wave, feasibility, acceptability, and fidelity data will be reviewed against predefined measures of success to adjust the protocol and overcome implementation barriers. We describe the design and protocol of this trial in the following sections.

Methods

Participants and Setting

This intervention will recruit primary caregivers of children with severe CP. Up to 90 caregivers of children with severe (GMFCS level IV or V) CP aged 0 to 17 years and cared for by a respiratory specialist or receiving daily respiratory treatments will be enrolled. Participants will be recruited from pediatric complex care programs at the University of Wisconsin–Madison (UW) and the University of California, Los Angeles (UCLA). These programs were established to deliver care to children with medical complexity. The key components of each program include pediatric clinicians, care coordinators, and extended visit lengths, which aid in delivering comprehensive care to children with CP. Both clinical programs have been described in more detail elsewhere [28,31].

Inclusion Criteria

Participants are caregivers of children with severe CP. Individuals must meet all inclusion criteria to be eligible to participate in the study. Caregiver criteria include (1) being aged at least 18 years, (2) being the primary caregiver to an eligible child, (3) ability to speak English or Spanish well enough to be interviewed, and (4) having a mobile phone capable of sending and receiving SMS text messages. Child criteria include (1) age 0 to 17 years, (2) GMFCS level IV or V CP [32], and (3) being cared for by a respiratory specialist or receiving daily respiratory treatments (oxygen, ventilation, airway clearance device, and medications).

Exclusion Criteria

During this study, participants are asked to reply to SMS text messages when received at random times during daytime hours and connect with an intervention clinical responder either at home, in person at a mutually agreeable location, by mobile phone, or over the internet. Any individual lacking the ability or willingness to engage in SMS text messaging or clinical responder interactions during the study will be excluded from participation in the study.

Recruitment and Screening

We will recruit caregivers of children with severe CP aged between 0 and 17 years. We will recruit up to 90 participants (n=45, 50% at each site) divided across 3 waves. In each wave, there is a 1- to 2-month enrollment period. We anticipate that approximately 80% of those screened will enroll, requiring approximately 110 individuals to be screened.

Using diagnostic codes for CP (International Classification of Diseases, Tenth Revision [ICD-10]: G80-83), we will identify potential participants by reviewing clinic registries and electronic health record data, which contain detailed information about children and their diagnoses. We will send an *opt-out* letter that alerts families that a research study is being conducted and their child may be eligible, with a contact number to call if they wish to opt out of the research or if they wish to receive additional information or have any questions. Potentially eligible caregivers will be contacted by telephone to screen for eligibility and interest.

If the research team is not notified that a family wishes to opt out of the research, the study research personnel will attempt to call the families (or meet them at an upcoming visit) to complete screening, informed consent, baseline questionnaires, and random group assignment. CP status and additional eligibility criteria will be determined with a reliable and valid parent questionnaire and screener conducted at the beginning of the initial telephone contact [32].

Individuals who do not meet the criteria for participation in this trial (screen failure) because they meet ≥1 exclusion criteria that are likely to change over time may be rescreened. Theoretical examples might include a child developing a need for respiratory treatment or families acquiring a mobile phone capable of sending and receiving SMS text messages.

All study participants will undergo informed consent, including authorization to view the child's medical record and participate in action planning, rapid clinical response, and weekly SMS text message surveillance.

Study Design

This is a 2-site pilot randomized controlled clinical trial to establish the RE-PACT protocol's feasibility, acceptability, and fidelity as well as an estimate of effect size. We anticipate being underpowered to assess the efficacy of the intervention in this pilot study; however, to inform future randomized controlled trial power estimates, we will test differences between the intervention and control groups in primary and secondary clinical outcomes.

Study participants will be randomly assigned to receive usual care through the complex care clinical program at UW or UCLA or the study intervention, RE-PACT. Random allocation will be concealed from the research staff conducting recruitment and will use a 1:1 allocation with random block sizes of 2 and 4. Block randomization will be achieved with a computer-generated random number list prepared by the study biostatistician without clinical involvement in the trial. Randomization will be stratified by site to account for site-specific study characteristics.

RE-PACT will be run through 3 successively larger 6-month trials (*waves*), allowing ongoing protocol refinement between waves, guided by prespecified definitions of success for feasibility, acceptability, and fidelity measures. Each wave has a specific protocol refinement focus (wave 1: onboarding, training, recruitment, and data collection; wave 2: randomization and intervention activities; and wave 3: rapid enrollment and the conduct of all protocol activities with high fidelity). Participants in both groups will undergo assessments of demographic, clinical, and caregiving measures using

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questionnaires and medical record review case report forms at baseline and at 6 months after enrollment. Intervention feasibility, acceptability, and fidelity data will be collected from parent reports, medical records, and research team logs using case report forms.

Description of the Intervention

RE-PACT uses a dynamic JIT adaptive intervention design [33] to deliver proactive intervention based on risk modeling and partnership between the care team, patients, and families. Although the causes of respiratory illness in severe CP are modifiable, they are also broad and require distinct responses, even for the same child, over time. RE-PACT assumes that (1) every patient with severe CP has a risk of hospitalization, (2) some risks are knowable via the ecosystem of data generated around patient care, and (3) an intervention delivered when risk is increasing can reduce hospitalizations. RE-PACT's design addresses the changing needs of a child and family. RE-PACT involves action planning, rapid clinical response to prevent and manage respiratory illness, and weekly SMS text messaging surveillance of caregiver confidence for their child to avoid hospitalization.

Action Planning

Overview

All intervention families will receive respiratory illness action plans within 1 month of study entry. The action plan format and process are adapted from the original PACT study, and the contents include (at minimum) recognizing, describing, and managing the child's known contributors to respiratory illness. The three main components of the action plans are (1) *focus area* for the action plan (eg, asthma, aspiration, and seizures); (2) *severity levels* corresponding to objective and subjective indicators of baseline (*green*), concerning (*yellow*), and severe (*red*) statuses (eg, >2 L/min of oxygen); and (3) *specific actions* that caregivers should take to manage each status (eg, increase vest therapy, albuterol, suction every 4 hours, and use oxygen up to 4 L/min). As needed, JIT plans are also created at times of low confidence by parent request or by clinician determination during the study period. Any plan created will be developed with families, target an issue that plausibly will recur and lead to respiratory illness–related ED or hospital visit, and, when relevant, be harmonized with prior plans and reflect pulmonologist agreement.

Mobile Health Platform

The mobile health (mHealth) platform is built from an earlier study, *Assessing Confidence at Times of Increased Vulnerability* (ACTIV) [29], which was designed to elicit a SMS text rating of confidence to avoid hospitalization in the next month (ratings range from 1 to 10, where 1 is lowest confidence, and 10 is highest confidence; Figure 1). The platform supports English and Spanish languages. Beginning on the Sunday after enrollment, families will start receiving weekly SMS text messages asking them to rate their confidence for their child to avoid hospitalization in the next month. SMS text messages are programmed to be sent at random days and times to caregivers, averaging once weekly (Sunday to Thursday) between 8 AM and 9 PM (local time). The Sunday-to-Thursday time frame was chosen to support a feasible response during business days and hours. After 2 hours of nonresponse, a reminder is sent, and this is repeated up to 2 times at 2-hour intervals. Clinical responders will receive an email notification in real time if a participant reports low confidence. In addition, clinical responders will receive an SMS text message notification between 9 AM and 6 PM with the report of low confidence. If a response comes outside of these hours, it will be delayed until the next day.

Figure 1. Schematic of the mobile health (mHealth) SMS text message process in which all study participants receive weekly SMS text messages asking them to rate their confidence for their child to avoid hospitalization in the next month.

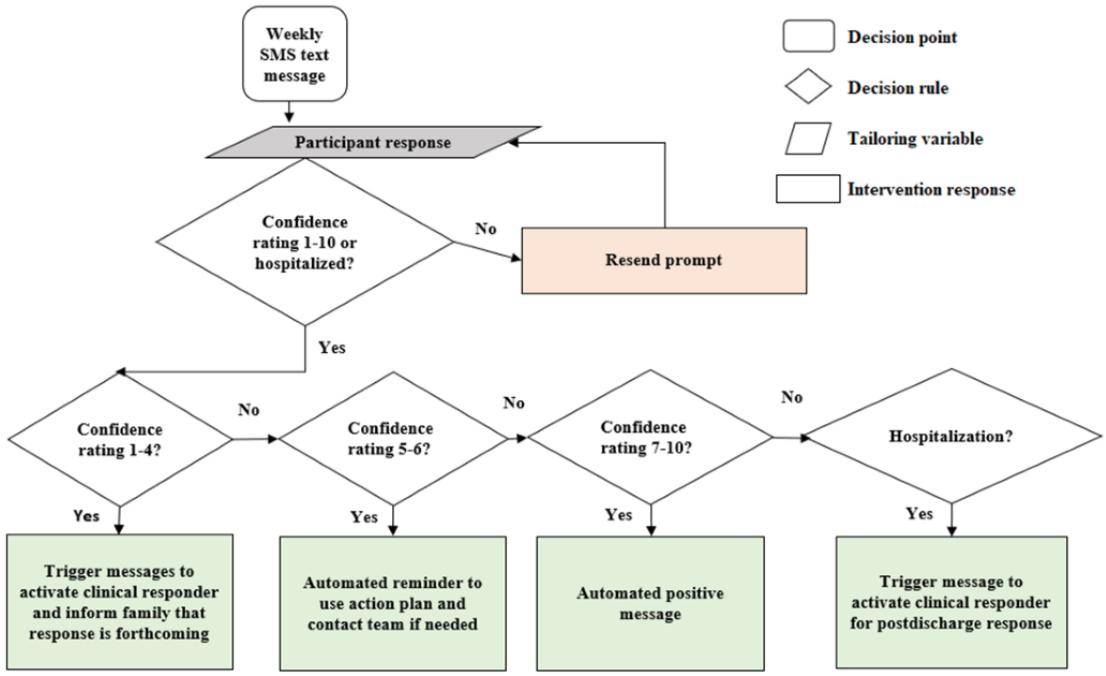

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Rapid Clinical Response

This response is adapted from our prior intervention (PACT) [28]. In RE-PACT, a clinical responder guides the JIT response, adapting to the current child and family situation. Triggers for the clinical responder include (1) low family-reported confidence (a confidence rating of <5) during mHealth messaging, (2) hospital discharge, and (3) family call or electronic message to the clinic owing to acute respiratory concerns (Figure 2). Clinical responders are clinicians, including medical doctors, nurse practitioners, registered nurses, and care coordinators (or equivalent). The same responder intends to work with the family throughout study enrollment.

Figure 2. Summary of the Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention. The figure illustrates low-confidence SMS text messages as the trigger of rapid clinical response. Other triggers include hospital discharge or family-expressed respiratory concerns through telephone call or electronic message to the clinic.

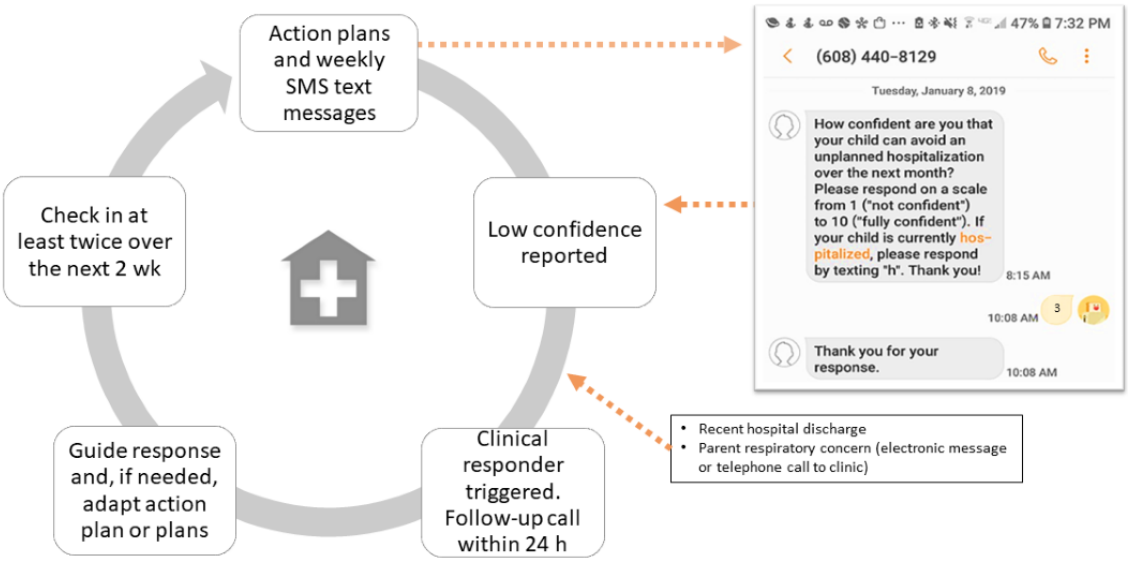

Rapid clinical responses include 3 interactions between family participants and clinical responders. First, a triage contact occurs within 24 hours of a trigger (during business hours). The triage contact goals are to determine the nature of the trigger, whether an action plan exists for the situation, and whether the issue is within the clinical responder's clinical practice scope. If not within the scope, the issue is referred to the relevant support (eg, a specialty physician or clinic social worker). Second, a response planning visit occurs either as a component of the triage contact or at a mutually agreed upon time within 72 hours of the trigger. Third, at least 2 follow-up contacts occur within 2 weeks of the trigger, with additional follow-ups as indicated by ongoing need until the issue is resolved. All contacts can occur through any of the following, at the preference of the family: telephone call, clinical encounter (telehealth, clinic, and hospitalization), or a home visit. The follow-up contacts can occur through electronic communication if the clinical responder and family determine this to be appropriate. At each contact point, there are two goals: (1) ensuring that the family understands red flags, relevant medications, and whom to call and when and keeps notes about the issue; and (2) coaching and skill transfer for the family to generate solutions and lead actions, with the responder intervening if the family is stuck or if clinical needs dictate intervention. Each contact point has scripting to guide the clinical responder as well as electronic health record documentation templates. At the end of a clinical responder event, the responder determines whether the issue affects respiratory health, is likely to recur, and poses a risk for future ED or hospital visits. If all of these are true, the responder either updates existing action plans or creates a new one to address the issue. A participant is considered to have completed the study if they have completed the baseline and 6-month follow-up assessments (Table 1; Figure 3).

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Figure 3. Schematic of the study design of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention enrollment period, enrollment visit, postenrollment evaluation, and protocol refinement. The protocol is refined between each of the 3 waves of the RE-PACT study. JIT: just-in-time; mHealth: mobile health; REDCap: Research Electronic Data Capture; UCLA: University of California, Los Angeles; UW: University of Wisconsin–Madison.

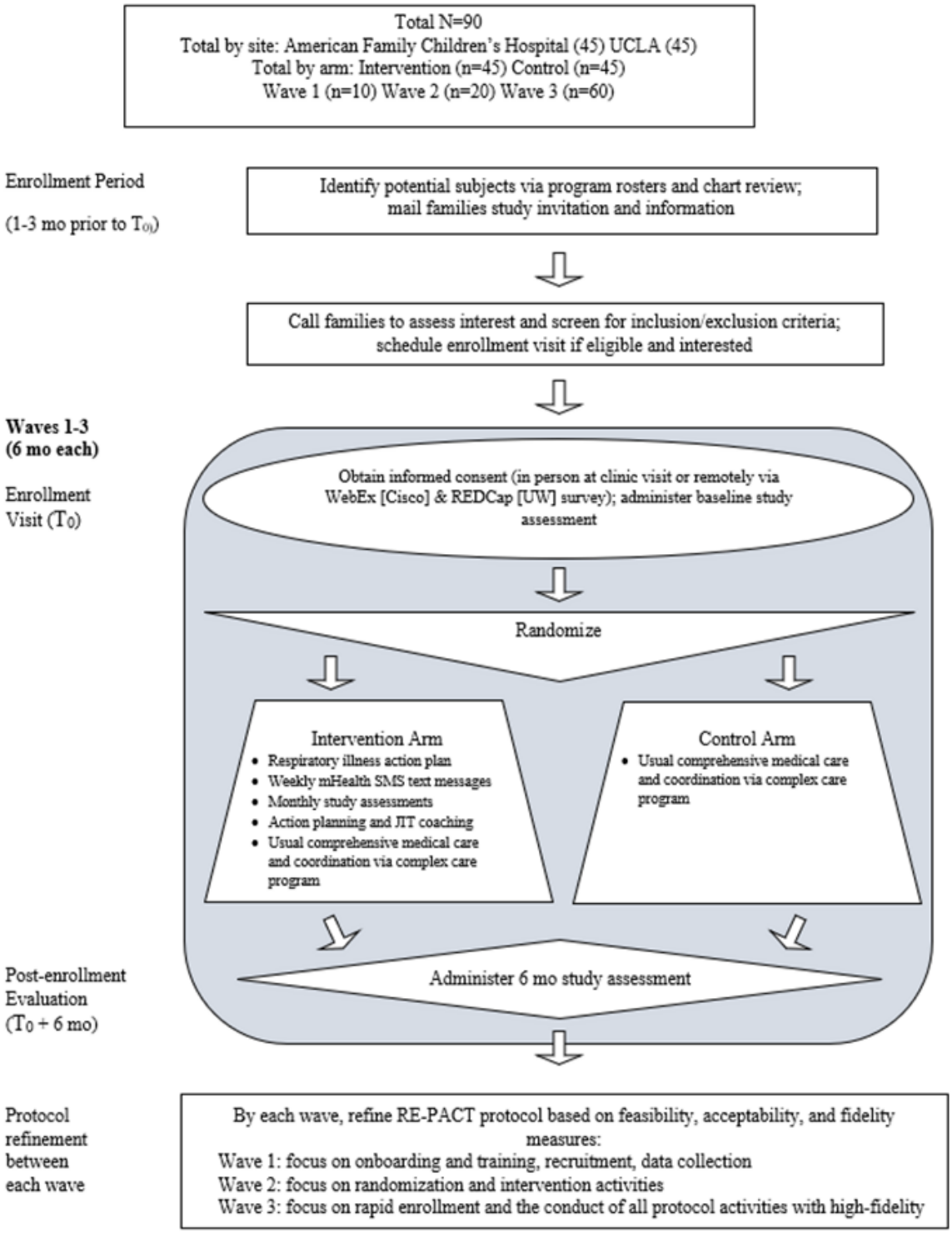

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Table 1. Schedule of activities of the Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention throughout the study period, with the depiction of personnel involved.

Activities	Study period (personnel involved)							
	Enrollment visit (research coordinator)	RE-PACT intervention period (clinicians)						Final visit (research coordinator)
	0 (T_0)[a]	1 (T_1)[a]	2 (T_2)[a]	3 (T_3)[a]	4 (T_4)[a]	5 (T_5)[a]	6 (T_6)[a]	End of month 6 (T_7)[a]
Confirm eligibility	✓							
Informed consent	✓							
Baseline assessment	✓							
6-mo assessment								✓
Randomization	✓							
Participant compensation	✓							✓
Usual comprehensive medical care and coordination via complex care program		✓	✓	✓	✓	✓	✓	
Intervention arm only								
SMS text message training	✓							
Weekly mHealth[b] text message and response		✓	✓	✓	✓	✓	✓	
Intervention overview		✓						
Create action plan		✓						
Action planning		✓	✓	✓	✓	✓	✓	
Rapid clinical response when triggered		✓	✓	✓	✓	✓	✓	
Monthly study assessments		✓	✓	✓	✓	✓	✓	

[a]Month (time point).

[b]mHealth: mobile health.

Outcomes

Primary Study End Points: Feasibility, Acceptability, and Fidelity

The specific measures and prespecified definitions of success for primary study end points, including feasibility, acceptability, and fidelity, are listed in Table 2. These measures will be summarized between each of the 3 waves, with protocol adjustments made for any measures that do not meet the definition of success.

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Table 2. Primary study end points to evaluate the feasibility, acceptability, and fidelity of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT; n=90).

Measure and measure detail		Success definition
Feasibility		
Recruitment	Days to enroll target, mean (SD)	<14 (1)
Intervention onset	Days between randomization and "T_0[a]" intervention activities, mean (SD)	<7 (1)
Time to action plan	Days to action plan creation	<30
Intervention time	Time logged (min) for action planning and for coaching activities, mean (SD)	N/A[b]
Intervention costs	Mileage and travel costs; personnel salary; training costs; and other incurred costs, total	N/A
Intervention triggers	Number per patient (annualized), both respiratory and nonrespiratory focused	N/A
Acceptability		
Enrollment	Enrollment rate (number of patients enrolled/number approached)	>80%
Consent refusal	Categorized reasons for refusal	N/A
Loss and dropouts	Dropout rate (active or passive) before 6 mo (number of dropouts/number enrolled)	<10%
Action plan, SMS text messaging and clinical responder satisfaction	Do caregivers use the action plan, coaching, and texting? How could it be improved? Would caregivers recommend this to another family?	N/A
Fidelity		
Enrollment duration	Time (mo) of participant enrollment in the study, mean (SD)	6 (1)
Action plan creation	Number of respiratory and overall action plans per patient and action plan focus areas	≥1
Rapid clinical response: home or web-based visit	Success rate (number of visits completed and number expected); stratify by trigger and by "respiratory" and "nonrespiratory"	>80%
mHealth[c] texting	Response rates (number of SMS texts responded and number expected); "respiratory" and "nonrespiratory"	>90%
Crossover	Number of patients inappropriately receiving any intervention component	0
Data collection	Complete entry and exit questionnaire, monthly questionnaire, and chart review data (number of data collection events completed and number of total data collection events)	>95%

[a]a: Enrollment visit

[b]N/A: not applicable.

[c]mHealth: mobile health.

Clinical End Points

The study's secondary objective is to estimate the effect size of RE-PACT. The clinical end points are listed in Textbox 1. The primary clinical end point is severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization. *Respiratory diagnosis* is defined as a discharge diagnosis of any of the following: asthma, pneumonia (community or hospital acquired), bronchiolitis, influenza, upper or lower respiratory tract infection, tracheitis, aspiration pneumonia and pneumonitis, chronic lung disease, and respiratory failure [34]. *Hospitalization* is defined as a nonelective, unscheduled hospital encounter (inpatient or *observation* status), accompanied by both an admission history and physical examination as well as a discharge summary note signed by a physician or advanced practice provider. Field-testing the assessment of this end point with trained research personnel at study sites demonstrated high interrater reliability (κ>0.9).

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Textbox 1. Clinical end points of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT).

Primary clinical end point

- Severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization

Secondary clinical end points

- Hospital days during severe respiratory illness
- Systemic steroid courses (systemic steroids [exclude inhaled or topical steroids for the purposes of defining an illness]: hydrocortisone, prednisone, prednisolone, dexamethasone, methylprednisolone, and triamcinolone acetonide; common inhaled steroids: fluticasone, budesonide, mometasone, beclomethasone, and triamcinolone [14-16,35])
- Systemic antibiotic courses (antibiotics: amoxicillin or amoxicillin/ and clavulanate, ampicillin, ampicillin and sulbactam, azithromycin, cefdinir, cefepime, cefixime, cefpodoxime, ceftazidime, ceftriaxone or cefotaxime, ceftibuten, cefuroxime, cephalexin [Keflex], clarithromycin, clindamycin, ciprofloxacin, doxycycline, erythromycin, ertapenem, imipenem, levofloxacin, linezolid, meropenem, metronidazole, moxifloxacin, oseltamivir, penicillin, piperacillin and tazobactam, rifampin, and vancomycin [14-16,35])
- Respiratory emergency department visits
- Death

The secondary clinical outcomes (Textbox 1) include total hospital days during severe respiratory illness; the number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits; and death. Hospital days are calculated through resolution if admission occurs in the study time frame, even if discharge occurs after the study exit date. *Systemic corticosteroid course* is defined by oral or parenteral corticosteroids prescribed for respiratory diagnosis, including hydrocortisone, prednisone, prednisolone, methylprednisolone at least 1 mg/kg/d (or 30 mg/d) × minimum 3 days, or dexamethasone at least 0.15 mg/kg/d (or 10 mg/d) × ≥1 days. Physiologic or stress replacement doses in adrenal insufficiency are excluded. *Systemic antibiotic course* is defined by oral or parenteral antibiotics prescribed for respiratory diagnosis for a minimum of 3 days. The specific antibiotics are derived from the Infectious Diseases Society of America pediatric pneumonia guidelines [36] and published literature [35]. Respiratory ED visits are any ED visits not resulting in admission and having a discharge respiratory diagnosis.

Exploratory Study End Points

The objectives of the tertiary study are to explore the mediating relationships between RE-PACT and capability, opportunity, motivation, and behavior (COM-B) measures [37]. By blending our foundational research on preventing hospitalizations [17,21] with behavioral intervention theory [38], our conceptual model suggests that decisions to seek care (behaviors) are influenced by capability (family capacity), opportunity (health system and susceptibility), and motivation (confidence). A theorized mechanism of RE-PACT's effect is that combining action planning, mHealth surveillance, and coaching will increase caregiver COM-B measures to manage respiratory illness in severe CP. The tertiary end points are listed in Textbox 2.

Textbox 2. Exploratory study end points of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT).

Capability

- Family Caregiver Activation in Transition (FCAT) tool [39]: mean composite score
- Caregiver General Self-Efficacy Scale (GSES) [40]: mean composite score

Opportunity

- Family Experiences with Care Coordination (FECC) [41]: percentage top-box score for selected items

Motivation

- Confidence responses mobile health SMS text messaging: mean weekly score

Assessment Procedures

Data about research participants (children and their families) will be collected by study research assistants on case report forms using electronic family self-administered questionnaires, structured interviews with research personnel by telephone or in person with enrolled caregivers, and abstraction of child medical record data. Family and child measures will be recorded at baseline, and end points will be recorded at study exit (6 months after the enrollment visit [T_0]). Caregiving measures, which may change as a result of the intervention, will be collected at baseline and study exit. Clinical responders will enter data for intervention group families into a clinical response event case report form.

Feasibility, acceptability, and fidelity end point data will be collected during each of the 3 waves by research personnel reviewing study logs, conducting monthly chart reviews, and administering surveys (by telephone, in person, or sending electronic self-administered links) with caregivers randomized to the intervention. For control group participants, the feasibility

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of assessments will be evaluated by completion rates at study exit. In addition, intervention and control participants will be debriefed at study exit on their experiences in the study and asked for feedback on the strengths and weaknesses, as well as any concerns about the protocol. Between each wave and after the third wave, clinical teams at each site will be debriefed on the strengths and weaknesses, as well as concerns about the protocol.

The CP GMFCS measures and all caregiving measures have been well documented as reliable in the literature [39-45]. We have separately established the reliability of identifying respiratory illnesses in our preliminary research (κ>0.9). We will ensure reliability in data collection through direct observation, data auditing, establishing clear data dictionaries and definitions, using uniform variable definitions, and use of a central data repository coordinated and maintained by UW.

Data Collection, Storage, and Protection

Clinical data (including adverse effects) and clinical laboratory data will be entered into Research Electronic Data Capture (REDCap; UW) managed by the University of Wisconsin, a 21 Code of Federal Regulation Part 11–compliant data capture system provided by the UW Institute for Clinical and Translational Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify inconsistent, incomplete, or inaccurate data. Clinical data will be entered directly from the source documents or entered directly from secure self-administered questionnaires (surveys) sent via REDCap to participants.

Sample Size Considerations

We will enroll up to 90 participants. On the basis of this team's preliminary work, we estimate that half (45/90, 50%) of the participants will experience at least 1 respiratory illness during the enrollment period. We expect to be able to maintain contact and collect data from ≥90% (≥81/90) of the participants at the final follow-up, evenly divided between the intervention and control groups. We assume that this sample will not be powered to establish the efficacy of the intervention; however, it will provide a sufficient sample to determine feasibility and estimate effect sizes, which will be used for power calculations in the future large randomized clinical trial. Attainable power levels were calculated for detecting differences in severe respiratory illness rates (primary clinical outcome) between the study arms at the 2-tailed <.05 significance level based on a negative binomial (NB) regression model with an overdispersion parameter of ϕ=1.0 (Table 3). Hence, large effect sizes with relative risks ranging between 3.0 and 5.0 for comparing the severe respiratory illness rates between the study arms will be detected with 19% to 88% power at the 2-tailed <.05 significance level.

Table 3. Attainable power levels for detecting differences in severe respiratory illness rates between the study arms, assuming a sample size of 45 participants per arm with a missing value rate of ≤10%.

Relative risk (control vs intervention)	Number of severe respiratory illnesses in the intervention arm over the 6-mo follow-up period				
	5 (λ=0.02)[a], %	10 (λ=0.40)[a], %	15 (λ=0.06)[a], %	20 (λ=0.08)[a], %	25 (λ=0.10)[a], %
3.0	19	29	38	45	52
4.0	31	41	59	68	75
5.0	42	62	74	83	88

[a]Severe respiratory illness rate per patient-month.

Statistical Analysis Plan

The primary outcome data will assess the RE-PACT intervention's feasibility, acceptability, and fidelity using descriptive statistics. Categorical variables will be displayed as percentages and continuous variables as means with SDs (if normally distributed) or medians with IQRs (if skewed). We will compare observed values with the prespecified definitions of success for each of our feasibility, acceptability, and fidelity measures. We will also determine overall positive, neutral, and negative reports of feasibility and acceptability using content analysis of qualitative (open-ended comments) data. We will explore any patterns if challenges emerge (eg, enrollment refusal or dropout or low reported use of the intervention activities).

We anticipate being underpowered to assess efficacy using the clinical end points of the intervention in this pilot study. Analyses will also estimate the effect size estimates of clinical end points to allow precise sample size calculations for a future large-scale efficacy trial. We will compare differences between the intervention and active control group outcomes at 6 months. The primary clinical outcome is the severe respiratory illness rate, defined as the total number of severe respiratory illnesses divided by the person-months over the 6-month follow-up period. The severe respiratory illness rate will be analyzed using an NB regression model to account for overdispersion in the count data. For the primary analysis, univariate NB regression analysis will be conducted with a study arm as a predictor variable. The study site will be included as a stratification factor in the primary analysis to account for stratified randomization. The observed effect size of the analysis will be quantified in terms of relative risk and reported along with the corresponding 95% CI. As a secondary analysis, multivariate NB regression analysis will be performed to compare the severe respiratory illness rates between the study arms. This analysis will include clinical and demographic characteristics as covariates in an initial nonparsimonious model. The least absolute shrinkage and selection operator and elastic net penalty methods for NB regression models will be used to identify a parsimonious model with independent covariates.

Longitudinal changes in the severe respiratory illnesses within and between study arms will be evaluated with a generalized linear mixed effects model with a logit link function and

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participant-specific random effects. An autoregressive correlation structure will be used to account for within-participant correlations. In this analysis, the presence or absence of severe respiratory illness at the monthly assessments will be the dependent variable, the study arm will be included as a predictor variable, and the study site will be included as a stratification variable to account for the stratified randomization.

The secondary clinical outcomes include total hospital days during severe respiratory illness; the number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits; and death. The number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits over the 6-month follow-up period will be analyzed using NB regression analysis as described previously for the primary outcome. Observed effect sizes and the corresponding 95% CIs will be reported. The presence or absence of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits will be documented at the monthly assessments, and longitudinal changes within and between study arms will be analyzed using generalized linear mixed effects modeling with a logit link function and patient-specific random effects. The total number of hospital days over the 6-month follow-up period will be analyzed using ANOVA with the study site as a stratification factor. In a secondary analysis, an analysis of covariance (ANCOVA) will be performed where clinical and demographic baseline characteristics will be included as covariates, and the least absolute shrinkage and selection operator method will be used to identify a parsimonious model. Longitudinal changes in the number of hospital days per hospitalization will be analyzed using a normal mixture linear mixed effects model with patient-specific random effects. The normal mixture component will be included in the model to capture the probabilities of hospitalization at the monthly follow-up. Parameter estimation will be performed using the expectation-maximization algorithm, the standard method for the parameter estimation of mixture models.

Two-tailed P values of <.05 will be considered statistically significant. Missing values (eg, owing to loss of follow-up and missing monthly visits) will be evaluated by conducting a sensitivity analysis comparing the results obtained from the complete case analysis with those obtained from imputation-based analyses. Specifically, multiple imputations will be used to impute the missing values of the primary and secondary clinical outcomes. For monotonic missing value data structures, we will use regression-based multiple imputation techniques. By contrast, we will use Markov Chain Monte Carlo–based imputation techniques for nonmonotonic missing value data structure.

Although we anticipate that the intervention and control groups will be similar owing to random assignment, we will adjust for any variables in our analysis that are not equal between the groups, given the small sample size. In addition, we will analyze for any effect of primary home language on the study outcomes because this may affect families' ability to navigate the systems of care in the United States.

Finally, as a planned exploratory analysis, we will test the mediating effect of caregiver COM-B measures on the relationship between intervention and respiratory illness outcomes. The mediating effects will be evaluated by conducting a multistep analysis approach. In the initial step, NB regression analyses will be conducted to examine whether there are differences in respiratory illness outcomes (the number of severe respiratory illnesses, systemic steroid courses, systemic antibiotic courses, and respiratory ED visits) between the intervention and control arms. In the next step, we will conduct a sequence of univariate analyses by regressing each potential mediator variable (caregiver capability COM-B measures) on the binary study arm variable. If significant associations between the potential mediator variables and the study arm are detected, we will regress the respiratory illness outcomes on both the mediator variables and study arm indicator variables using ANCOVA. The mediation effect for each potential mediator variable will then be tested using the Sobel z test based on the slope parameter estimates from the corresponding regression models.

Ethical Considerations

This study received initial approval from the UW health system's institutional review board on January 19, 2022 (20211532). All participants will provide informed consent before taking part in the study. Informed consent materials will be provided in private spaces in both written and verbal formats and will review in detail the study design, including random assignment to the intervention and control groups, potential risks of participation, protections against risk, and the rights of human research subjects. The informed consent process will also include review and signing of the Health Insurance Portability and Accountability Act waiver, allowing researchers to review the child's medical records. Parents will be able to decline parts of the study and still participate in other parts and can revoke their consent at any point. Any identifying information kept for the purpose of contacting participants will be kept secure, in REDCap, a locked filing cabinet or in a password-protected electronic file and will be destroyed when the study is complete. The study is monitored by the Data Monitoring Committee at the UW-Madison Institute for Clinical and Translational Research. All participants receive an incentive of US $200, divided in 2 parts: US $100 at enrollment and US $100 after the exit survey, in the form of a gift card, check, or cash.

Results

The recruitment of the first wave began on April 27, 2022. To date, we have enrolled 30 (33%) out of 90 participants, as projected. The final wave of recruitment will end by October 31, 2023, and the final participant will complete the study by April 30, 2024. We will start analyzing the complete responses by April 30, 2024, and the publication of results is expected at the end of 2024.

Discussion

Summary

We describe the protocol for a pilot clinical trial of RE-PACT, a JIT adaptive intervention to reduce respiratory illness in severe

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CP. A recent expert consensus statement on preventing and managing respiratory disease in young people with CP highlighted the need for 4 activities: early identification of risk factors; regular assessment of risk; effective partnerships among multidisciplinary teams, families, and individuals with CP; and proactive treatment of respiratory disease [46]. The RE-PACT intervention protocol aligns with each of these 4 critical areas.

For children with severe CP, RE-PACT was designed by families and clinicians from promising earlier interventions to manage health crises with proactive action planning, simple surveillance of family confidence to avoid hospitalization through frequent SMS text messaging, and JIT adaptive rapid clinical responses. This intervention breaks down barriers to equitably connect families and clinical teams precisely when it matters most. This approach is innovative because we tailor the intensity of the response (eg, telephone call and clinic visit) and its content to family- and illness-specific needs. The adaptive nature of the intervention ensures that it meets caregiver needs for that specific instance, flexibly changing for individuals over time in response to each intervention trigger. RE-PACT is also designed to acknowledge that respiratory illness in severe CP is driven by both respiratory and nonrespiratory comorbid and social conditions [11,46] (eg, neuromuscular weakness, seizures, dysphagia, feeding intolerance, health system navigation barriers, and coordination problems).

By conducting successively larger waves of the RE-PACT protocol, we expect to produce a final high-quality protocol that has been developed sufficiently to support the implementation of a large-scale multisite clinical efficacy trial.

Limitations

This study has several limitations. Although we anticipate achieving a feasible, acceptable, and high-fidelity protocol by the end of the third wave, it is possible that some challenges may remain. We anticipate being underpowered to assess intervention efficacy. Despite the randomized design, allocation concealment is not possible. As randomization occurs at the level of the family, inadvertent intervention contamination to nonintervention patients in the same clinical program may occur. This risk will be minimized by having research staff (not clinical staff) manage action planning and SMS text messaging procedures. In future studies, we will consider alternative designs (such as a stepped wedge trial), randomizing at the clinic level to avoid this threat. Threats to external validity will reflect the relatively narrow population of families recruited from 2 complex care programs. Although it is a strength that the intervention will be conducted in English and Spanish, future expansion to populations of children with CP outside of complex care programs and from more geographically and culturally diverse settings will be helpful. As research continues, it will be important to examine whether this intervention design, which relies in part on the use of digital technology, addresses disparities in access to care and inequities in outcomes.

Conclusions

Despite the limitations, our pilot RE-PACT intervention represents an innovative and promising strategy to reduce severe respiratory illness among children with severe CP. RE-PACT operationalizes universal action planning, mobile SMS text messaging, and a JIT adaptive rapid clinical response to deliver timely customized care to families of children with severe CP. This protocol describes detailed methods to assess intervention feasibility, acceptability, and fidelity. This line of research may be relevant to other researchers and health care providers who wish to adopt a similar early intervention strategy for patients with chronic and complex conditions at high risk of future hospitalization.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RC, the principal investigator of this study, obtained grant funding and conceived the study. CL, HK, TK, PC, CC, DG, BK, ME, and SI participated in the design of the study. AF and RC drafted the manuscript. RC, CL, GW, KH, LP, RD, SI, and TW are responsible for recruitment and major study activities. All authors contributed to the intellectual content of the manuscript and the development of the trial protocol, and all authors have read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACTIV: Assessing Confidence at Times of Increased Vulnerability
ANCOVA: analysis of covariance
COM-B: capability, opportunity, motivation, and behavior
CP: cerebral palsy
ED: emergency department
GMFCS: Gross Motor Function Classification System
***ICD-10*:** *International Classification of Diseases, Tenth Revision*
JIT: just-in-time
mHealth: mobile health
NB: negative binomial
PACT: Plans for Action and Care Transitions
RE-PACT: Respiratory Exacerbation–Plans for Action and Care Transitions
REDCap: Research Electronic Data Capture
UCLA: University of California, Los Angeles
UW: University of Wisconsin–Madison

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Protocol

Feasibility, Acceptability, and Preliminary Effectiveness of a Combined Digital Platform and Community Health Worker Intervention for Patients With Heart Failure: Protocol for a Randomized Controlled Trial

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Abstract

Background: Interventions focused on remote monitoring and social needs care have shown promise in improving clinical outcomes for patients with heart failure (HF). However, patient willingness to use technology as well as concerns about access in underresourced settings have limited digital platform implementation and adoption. There is little research in HF populations examining the effect of a combined digital and social needs care intervention that could enhance patient engagement in digital platform use while closing gaps in care related to social determinants of health. Here, we describe the protocol for a clinical trial of a digitally enabled community health worker intervention designed for patients with HF.

Objective: This study aims to describe the protocol for a randomized controlled trial assessing the acceptability, feasibility, and preliminary effectiveness of an intervention that combines remote monitoring with a digital platform and community health worker (CHW) social needs care for patients with HF who are transitioning from hospital to home. Given the elevated morbidity and mortality, identifying comprehensive and patient-centered interventions at the time of hospital care transitions that can improve clinical outcomes, impact cost, and augment the quality of care for this cohort is a priority.

Methods: This trial randomized adult inpatient participants (n=50) with a diagnosis of HF receiving care at a single academic health care institution to the 30-day intervention (digital platform+CHW pairing+usual care) or the 30-day control (CHW pairing+usual care) arms. All study participants completed baseline questionnaires and 30-day exit interviews and questionnaires. The primary outcomes will be acceptability, feasibility, and preliminary effectiveness.

Results: This clinical trial opened for enrollment in September 2022 and was completed in June 2023. Initial results are expected to be published in the spring of 2024, and analysis is currently underway. Feasibility outcome measures will include the use rates of the biometric sensor (average hours per day), the digital blood pressure monitor (average times per day), the weight scale (average times per day), and the completion of the symptoms questionnaire (average times per day). The acceptability outcome will be measured by the patients' response to the truthfulness of the statement that they would be willing to use the digital platform in the future (response options: very true, somewhat true, or not true). Preliminary effectiveness will be measured by tracking 30-day clinical outcomes (hospital readmissions, emergency room visits, and missed primary care and cardiology appointments).

Conclusions: The results of this investigation are expected to contribute to our understanding of the use of digital interventions and the implementation of supportive home-based social needs care to enhance engagement and the potential effectiveness of

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clinically focused digital platforms. These results may inform the construction of a future multi-institutional trial designed to test the true effectiveness of this intervention in HF.

Trial Registration: ClinicalTrials.gov NCT05130008; https://clinicaltrials.gov/study/NCT05130008

International Registered Report Identifier (IRRID): DERR1-10.2196/55687

(JMIR Res Protoc 2024;13:e55687) doi:10.2196/55687

KEYWORDS

heart failure; digital platform; remote monitoring; home-based care; health worker; social needs care; community health worker

Introduction

Background

Heart failure (HF) is one of the most common causes of 30-day readmissions and is a morbid and burdensome disease for patients [1]. Factors related to clinical complexity [2,3] and unmet social needs [4] have been identified as key culprits contributing to rising costs of HF care associated with HF exacerbations and recurrent hospitalizations [5]. While individual interventions focused on digital solutions to augment either clinical care [6-8] or home-based care [9-11] to address unmet social needs have the potential to improve HF clinical outcomes, these interventions are challenged by specific barriers that limit their effectiveness.

Digital platforms with remote monitoring capabilities can track fundamental biometrics, such as heart rate, blood pressure, and body weight, which are critical for the home management of HF [12-15]. These biometrics can be used to evaluate clinical status at home with automated reporting back to patient teams [16-19]. Some platforms also offer daily symptom questionnaires and even embed artificial intelligence algorithms with the ability to tailor alerts to individual patient norms, which can improve platform accuracy and precision [13]. These digital platform capabilities have improved the detection of markers signaling clinical decline (eg, changes in weight, activity tolerance, heart rates, blood pressure, and symptomatology), and a number of studies have demonstrated an early benefit of digital platform use for clinically complex patients, including those managing HF at home [6,8,20,21].

However, the integration of digital platforms among patients with HF has been incremental, at best, for reasons ranging from infrastructure limitations of health care institutions to patient-related barriers [22,23]. Specifically, several patient care barriers have been identified including knowledge gaps, lack of willingness to gain familiarity with technology, reduced health care access, and marginal internet connectivity [22,23]. Concordantly, valid concerns about the exclusion of digital platform use in low-resourced, aging, or less technology-facile populations exist [19]. A number of these challenges could be resolved by integrating a home-based human resource, with basic knowledge of the digital platform who could also deliver social needs care.

Home-based care that focuses on social needs is often delivered by community health workers (CHWs) [24,25]. CHWs, with basic knowledge of chronic conditions, can address unmet social needs and reinforce clinical care plans in ways that improve outcomes by bolstering connections to clinical care teams [26]. Specifically, CHW outreach includes telephone calls; home visits; health care coaching; accompaniment to clinic visits; and identification of low or no-cost resources to close gaps in care related to food insecurity, transportation, rental assistance, or other unmet social needs. CHWs can also provide elbow-to-elbow support with the completion of insurance forms or agency applications. Through motivational interviewing, goal setting, and psychosocial support, CHWs can work closely with patients to identify and address logistical barriers to care [27]. While the evidence base for CHW-focused interventions to improve outcomes and reduce readmissions for patients with chronic diseases including HF is robust [10,11,28-31], CHWs generally rely on one-to-one in-person or phone or text-based patient interactions without symptom or biometric monitoring [32]. In this way, CHW care remains largely siloed without the tools needed to care for larger, clinically complex populations. As such, CHWs inadvertently spend more time with patients who are healthier and engaged in care and less time with patients who are harder to reach and would benefit from early intervention [33,34]. While manageable in smaller cohorts and studies, this can stifle the impact of CHWs on clinical outcomes when scaled.

A combined intervention with a digital platform and CHW care (ie, digitally enabled CHW care) could address important barriers associated with platform use. Specifically, CHW care, through home visits, phone calls, and connections to care teams, can address digital platform knowledge gaps and connectivity issues [27]. CHWs can also act as navigators for digital platforms by encouraging use and engagement that can improve platform usability and adoption. In this way, CHWs are uniquely positioned to enhance the use and reach of digital platforms. In addition, pairing patients at high risk for readmission, especially those with HF, with a CHW and a digital platform could address key barriers to CHW care delivery related to the historical reliance on one-to-one outreach [35]. Digital platforms can better inform the timing and prioritization of CHW outreach with real-time access to streamlined basic biometric data (weights, steps taken per day, or a daily clinical score) and patient response data (collected in a daily questionnaire). This access can augment the ability of CHWs to connect patients to clinical care teams earlier for interventions that can potentially prevent hospital readmissions or emergency department (ED) visits.

This trial, based on a single-arm observational study performed prior [27], will study the effect of a digitally enabled CHW intervention created for patients with HF. In this way, the study addresses a gap in current knowledge of home-based care for patients with HF as one of the first randomized controlled trials

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(RCTs) examining the effect of a digital platform combined with social needs care delivery from a CHW in patients with HF. This work is important because it seeks to reduce hospital readmissions for HF, which is imperative for Centers for Medicare and Medicaid stakeholders [36]. This study intervention also occurs at the time of hospital discharge, a particularly vulnerable time point as patients are transitioning out of the hospital. The results of this clinical trial may also contribute to a novel and innovative model for home-based care in a high-risk HF population. Specifically, this study will add value to ongoing conversations about the applications and implementation of digital solutions and unmet social needs, particularly in chronic disease populations with serious illness.

The goal of this trial is to determine if a remote monitoring and social needs care intervention deployed at the time of hospital discharge is feasible, acceptable, and can demonstrate preliminary effectiveness relevant to clinical outcomes (hospital readmissions, ED visits, and missed appointments). We expect to see a higher degree of engagement and adherence to clinical care among those assigned to digitally enabled CHW care compared to those assigned to CHW care alone. The methodology described here will add insight into the implementation of similar digital interventions for patients transitioning from hospital to home with HF.

Primary Objective

The objective of this trial is to assess the acceptability, feasibility, and preliminary effectiveness of a digitally enabled CHW intervention.

Hypothesis

The central hypothesis is that pairing patients with a digitally enabled CHW intervention that addresses clinical, social, and behavioral barriers to HF care will (1) be feasible for patients with HF at home, (2) be acceptable for patients with HF at home, and (3) demonstrate preliminary effectiveness in improving clinical outcomes.

Methods

Study Overview and Design

An RCT design was applied to evaluate the intervention (digital platform+CHW+usual care) group compared to the control (CHW+usual care) group during the 30 days after discharge from the hospital to home. Figure 1 describes the study's procedural flow. Eligible patients were screened via the electronic medical record (EMR) on 8 inpatient study floors (6 internal medicine floors and 2 cardiology floors) in a single health care institution. Research staff approached patients after obtaining permission from bedside nursing. After verifying eligibility and introducing the study design, interested patients completed consent processes and all enrollment questionnaires. Participants were randomized to the intervention or the control arm for the 30-day intervention and study period. Both intervention and control participants were contacted by their assigned CHW within 24 weekday hours of enrollment and received teaching via an American Heart Association–sponsored HF patient education tool (educational control). Intervention participants received study equipment and were oriented to the use of all platform components by research staff prior to hospital discharge. All enrolled participants completed an exit questionnaire and interview via phone at the end of the 30-day intervention.

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Figure 1. Trial design, study arm assignment, and outcomes of a pilot randomized controlled trial. CHW: community health worker. PCP: primary care provider. Rx: medical prescription. HF: heart failure.

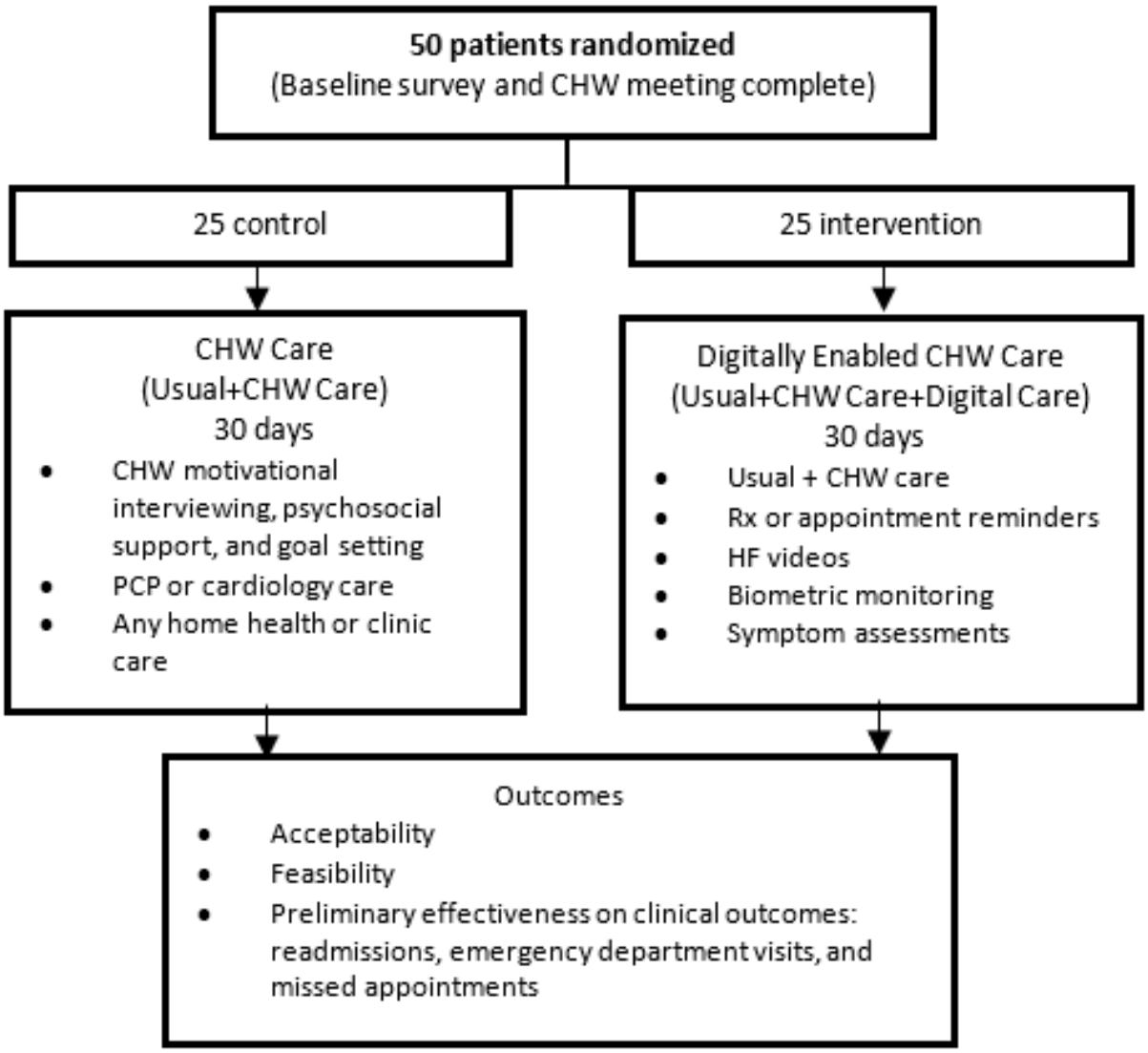

Clinical Setting of Patient Population

Massachusetts General Hospital (MGH) is a 999-bed academic medical center in Massachusetts with 75,000 to 100,000 hospital admissions each year. The MGH Corrigan Minehan Heart Center serves over 27,000 patients with cardiac disease each year, many of whom have HF. As an accountable care organization and medical home in partnership with the Mass General Brigham system, MGH inpatient teams are comprised of full and part-time staff clinicians, including board-certified internists or cardiologists, residents, fellows, nurses, advanced clinicians (nurse practitioners and physician assistants), and students. The majority of inpatients are supported by Medicare or Medicaid-based insurance products.

Subject Eligibility and Recruitment Strategy

Eligibility criteria were established based on prior clinical trials and qualitative studies focused on care transitions from hospital to home [27,37-39]. Eligibility criteria for participants who were approached and introduced to the study while hospitalized included the following: being 18 years and older, living within a 50-mile radius of MGH, having a diagnosis of HF listed in the EMR problem list, a history of ≥1 hospitalization within the previous 12 months, a clinician managing their HF, cognitive ability to participate in the intervention, and English fluency. Patients were ineligible if they had an active alcohol or substance use disorder, were living in a long-term care facility, were unable to provide consent, had invoked health care proxy, or had prisoner status. Research staff attempted to enroll patients up to 3 times if they were unsure or unable to be engaged in the initial approach.

CHW Training and Supervision

Extensive experience training CHWs gained during our prior CHW clinical trial was applied for CHW training purposes [9]. CHW staff participating in the trial were trained in the core competencies of CHW care delivery for HF and other common diagnoses associated with hospital readmissions (eg, pneumonia, atrial fibrillation, and pulmonary disease). These CHW core competencies included motivational interviewing, behavioral change, and psychosocial support. Additional skill sets and

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activity building occurred for medication reconciliation, common management and postdischarge follow-up plans, general American Heart Association guideline–concordant care, patient educational tools, and commonly used community resources. CHW supervision was led by a CHW manager experienced in supervising CHWs caring for clinically, socially, and behaviorally complex patients. Supervision occurred through daily huddles (with the CHW staff supervisors) and weekly meetings with the CHW staff supervisors and the principal investigator (JC). All clinical aspects of CHW care were also supervised by the principal investigator.

For the intervention arm, CHW staff were also trained on the use of the digital platform. The training was fulfilled using participatory methods, case scenarios, and video clips for optimal teaching and application for the patient-facing mobile app as well as the team dashboard. Specific training on the digital platform features (Figure 2) was designed to enhance communication and monitoring in concert with the application of core competencies and skill sets associated with traditional CHW care. This occurred during multicomponent didactics involving feedback, consultation, and supervision. Extensive role play and case studies with simulation experiences for troubleshooting and technology-based challenges were performed over a 14-day period. After training, simulation and behavioral interviewing–based proficiency testing were used to evaluate both CHW best practices and digital platform proficiency. CHW staff were also trained on how to interpret digital platform symptom assessments and biometric monitoring. In the platform, these symptoms and biometrics were translated into a color-coded schematic (Figure 3: green=no new symptoms or biometric variance or clinical symptom score of ≤0.7; yellow=1 new symptom or clinical score of 0.8-0.9; red= more than 1 new symptom or a clinical score of ≥1.0). For any participants with a yellow categorization on any given day, CHWs (1) contacted the participant to verify symptoms and ask probing questions, (2) contacted the participant's designated care clinic, and (3) coordinated a patient visit with CHW staff or a visiting home nurse for expedited clinical evaluation. For participants with a red categorization, all yellow categorization steps were followed and CHWs partnered with the clinical care team to arrange for expedited transfer to MGH or in-home evaluation if clinically indicated per the clinical care team providers.

Figure 2. Procedural workflow overview for study participants. CHW: community health worker.

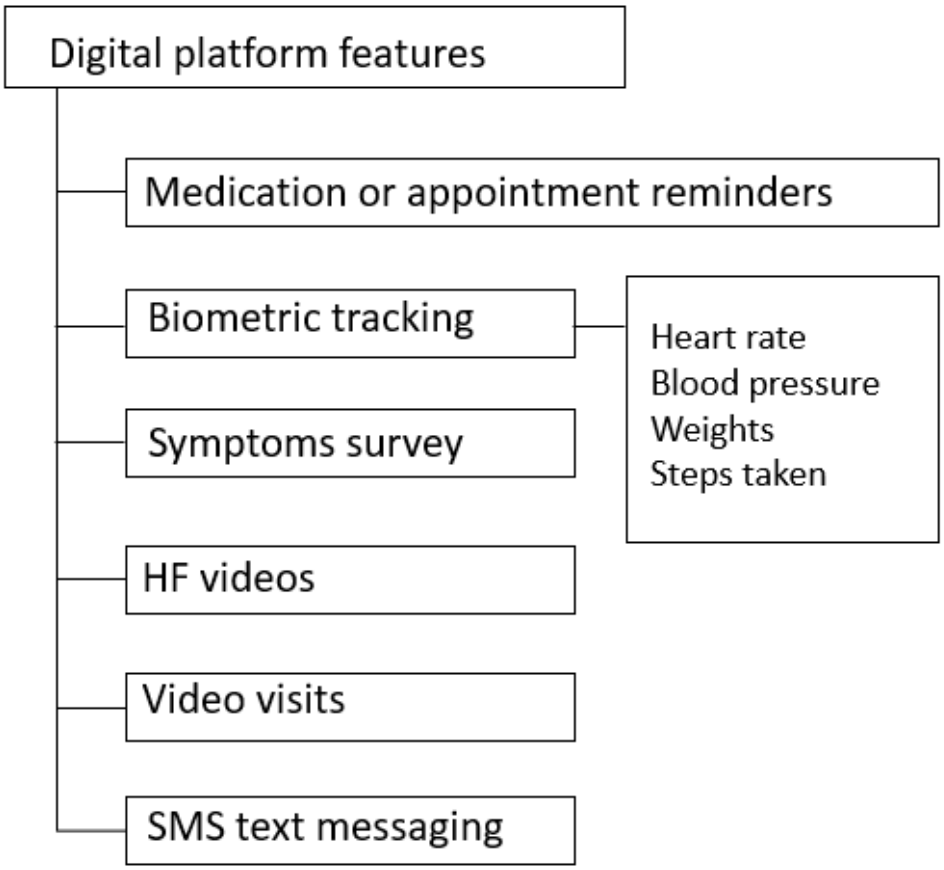

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Figure 3. Digital platform components (intervention arm only). HF: heart failure.

Digital platform biometric algorithm			
Digital platform biometric data score and color key			CHW action taken
≤0.7	Green	• No new symptoms or biometric variation	• Continued CHW care
0.8-0.9	Yellow	• 1 new symptom or • 1 biometric variant change by ≤7% baseline	• Contact patient; call clinic care team, arrange for clinical eval with CHW staff
≥1	≥1 Red	• >1 new symptom • ≥1 biometric variant change by >7% baseline	• See "Yellow" action taken + arrange for timely MGH transfer if deemed indicated by providers

Control

Participants were contacted routinely by CHW staff to review medication adherence, nutrition, physical activity, symptoms, and clinic appointments and discuss any unmet social needs. CHW staff (n=1) paired with enrolled participants reviewed individual participant's discharge care plans and integrated the patient's clinical, social, and behavioral goals with clinical care plans. As such, CHWs also identified resources to reduce gaps in care caused by unmet social needs and connected patients to clinical care teams for clinical questions. One CHW with expertise in CHW core competencies [25] (motivational interviewing, goal setting, behavior change, and psychosocial support) delivered the control arm treatment. Daily huddles occurred to discuss patient interactions and plans for goal achievement. CHW staff documented all participant encounters in the EMR. In addition, all CHW interactions were logged in a web-based research team REDCap (Research Electronic Data Capture; Vanderbilt University) database. All social, behavioral, and clinical activities (clinical care team and community agency interactions, as well as time spent engaged in phone, in-person, and email modalities) were tracked. Pre-existing clinical team members were copied on all EMR notes and contacted directly, when necessary, by the CHW or supervisory staff during the intervention. Figure 4 shows an overview of the study participant workflow.

Figure 4. Color schematic depicting the relationship between the biometric clinical status score generated by the digital platform algorithm and the action taken by CHW staff. CHW: community health worker; MGH: Massachusetts General Hospital.

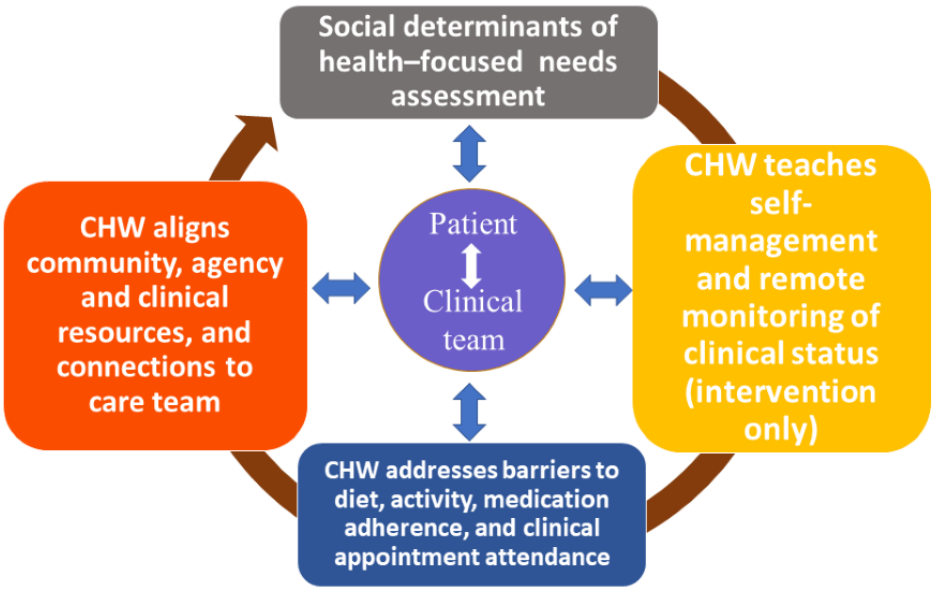

Intervention

Enrolled intervention participants were introduced to the digital platform features prior to hospital discharge: an HF mobile phone app within a smartphone (Android) that included a daily checklist for patients, educational HF videos, a portal CHW video visits, and a daily symptom questionnaire. In addition, participants were given a digital blood pressure monitor, a digital weight scale, and a sensor attached to a lightweight armband to be worn on the nondominant arm tracking basic biometric data (heart rates, oxygenation, and steps taken). As described, CHWs were trained to assist patients with technology setup and troubleshooting. Any unreconciled technical difficulties were addressed by research study staff and the platform vendor as needed. An artificial intelligence algorithm within the mobile app generated a daily score along with alerts sent to the CHW team dashboard, indicating if participants were at or moving away from their clinical baseline in terms of symptoms,

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biometrics, and functionality. This team dashboard was used in conjunction with a color schematic described (Figure 3). Any scores or alerts indicating that participants were moving away from their baseline were discussed with a CHW project manager. When indicated, CHWs notified clinical team staff during weekday office hours within 2 hours of a biometric or other clinically related concern (ie, significant change in heart rate, blood pressure, body weight, or patient-reported symptoms). Participants were instructed to engage with clinical care teams or urgent or emergent care as they would normally if they experienced symptomatic changes or other concerns outside weekday hours of operation.

Participants were contacted routinely by CHW staff to review medication adherence, nutrition, physical activity, symptoms, and clinic appointments and discuss any unmet social needs as described in the control treatment arm. All elements of other CHW outreach activities were performed as described in the control arm.

Data Collection and Measures

All study participants completed an enrollment questionnaire focused on health habits and patient experience with home self-care. This questionnaire was developed based on prior patient qualitative interviews and CHW focus groups with those caring for patients with HF [37,38]. These questions were adapted by study investigators for interviewer-assisted administration with inpatients prior to hospital discharge. We used a qualitative process to identify core domains through key informant interviews with patients, community-based primary care physicians, cardiologists, and internal medicine hospitalists. This was coupled with a review of the literature on patient experience in hospitalized settings along with consultations with survey and health services research experts. Draft surveys were pretested with 3 patients with the opportunity for revision prior to study administration. The enrollment questionnaire included 59 items from 7 distinct categories: health-related habits, understanding of the care plan, smartphone knowledge, quality of life (Kansas City Cardiomyopathy Questionnaire) [40], perceptions of physical and mental health, unmet social needs, loneliness (Three-Item Loneliness Scale) [40], and depression (Patient Health Questionnaire-2) [40]. Additional domains included confidence in the ability to perform self-care after discharge and patient-predicted likelihood of readmission within 30 days. Open-ended questions were asked to patients regarding anything that would help them manage their health outside the hospital.

An exit questionnaire administered at the study end (after 30-day enrollment) was also developed. This questionnaire mirrored domains in the enrollment questionnaire to assess any changes (eg, health-related habits and care plan understanding) associated with intervention or control arm assignments. Intervention participants also completed an acceptability questionnaire focused on the digital platform (adapted from components of the Technology Assessment Model Measurement Scales [41] as described by Ben-Zeev et al [42]). Similarly, the exit questionnaire was initially pretested with 3 patients, and no additional changes were made (all pretested questionnaire data will be included in the final analysis).

Separately, participants also completed an exit interview after completion of the 30-day enrollment period. The exit interview was conducted via phone and prompted participants to describe their experience with the digital platform and CHW staff interactions. Specific questions included: *What was it like to work with a CHW for the last month? What was it like using this technology in your home for the last month?* and *Are there things that could have made your time in the study better for you?* Semistructured interviews occurred via phone at times designated by participants and lasted 5-12 minutes. All semistructured interviews were audio-recorded and transcribed verbatim.

Process Measures, Source, and Timeframe Associated With Primary Outcomes of Feasibility, Acceptability, and Primary Effectiveness

The primary outcomes of feasibility, acceptability, and preliminary effectiveness will be tracked (Table 1). We will report feasibility outcome measures including daily use rates of the biometric sensor (mean hours per day), the digital blood pressure monitor (mean times per day), the weight scale (mean times per day), and completion of the symptom questionnaire (mean times per day). The acceptability outcome measure will be patient responses to the truthfulness of a statement indicating willingness to use the intervention in the future (response options: very true, somewhat true, or not true). Preliminary effectiveness will be measured by tracking 30-day clinical outcomes (hospital readmissions, emergency room visits, and missed primary care and cardiology appointments). Demographic data and survey item responses were captured in REDCap. These items will be summarized, and univariate analysis will be completed for any domains connected to the outcomes. Structured medical record review data extracted from the EMR will also be captured in the REDCap database.

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Table 1. Outcome measures or covariates for the digitally enabled CHW[a] intervention.

Outcomes and process measures	Source	Timing
Feasibility		
Use of the digital platform (wearing the biosensor[b], use of the blood pressure monitor[c], use of the digital weight scale[c])	Platform database	At 30 days
CHW engagement (number of CHW interactions, types of CHW interactions)	CHW interaction log	At 30 days
Acceptability		
Willingness to use the intervention again	Patient exit questionnaire	At 30 days
Preliminary effectiveness		
30-day readmissions	Electronic health record	At 30 days
Emergency department visits	Electronic health record	At 30 days
Missed appointments	Electronic health record	At 30 days

[a]CHW: community health worker.

[b]Hours worn per day.

[c]Number of times recorded per day.

Statistical Analysis

All standards for trial design, analysis, and reporting will be adhered to per the CONSORT (Consolidated Standards on Reporting Trials) checklist [43]. Univariate analysis will include demographic covariates of participants as well as intervention use frequencies, means, and SDs related to feasibility and acceptability outcomes. For the 30-day clinical outcomes of readmission, ED visits, and missed primary care and specialty appointments, we will use the proportion with any readmissions, emergency visits, or missed clinic visits will be compared between the 2 arms using Pearson ^{2} tests. We will also use a logistic regression model to include other potential predictors of the outcome to improve the precision of the estimate. The number of readmissions, ED visits, or missed appointments will be compared using Poisson models.

For exit interviews, we will use a framework analysis to identify main themes along with verbatim transcription for coding and analysis. Interview transcripts will be uploaded into Dedoose (version 8.3.47b.exe; SocioCultural Research Consultants, LLC). An analytic framework will be developed based on the major domains of the patient interview guide. To help facilitate reliability, 2 members of the research team (JC and NS) will serve as coders and familiarize themselves with the raw transcription data. They will then independently identify key themes raised by respondents. An iterative reapplication of this thematic framework will be used to identify all transcript components mapping to these specific themes. Coders will identify associations between themes, user characteristics, and outcomes for all interviews prior to achieving intercoder reliability. Any discrepancies unable to be resolved through discussion by the 2 coders (JC and NS) will be reviewed by a third researcher with expertise in qualitative data. These methods will be completed in concordance with the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist standards [44]. All trial procedures will also be in concordance with ClinicalTrials.gov regulations (NCT05130008).

Ethical Considerations

Institutional review board approval (2018P002014) was obtained from the Mass General Brigham Human Research Committee on September 22, 2020. All patients interested in enrollment participated in an informed consent process with the opportunity to ask questions and review all study procedures, data collection, and data analysis processes (primary and secondary) prior to signing an informed consent form. Privacy and protection standards were upheld with secure and password-protected database storage for all study data (which will be presented in deidentified form on publication). All participants were offered US $250 for remuneration for study participation.

Results

Between September 2022 and June 2023, enrollment was completed (n=50) with participants from inpatient general internal medicine and cardiology study floors at the MGH. The analysis is expected to be completed by January 2023, with results published in the spring of 2024. The study was approved by the IRB on June 4, 2019.

Discussion

Anticipated Findings

Here, we describe the protocol of an RCT designed to assess the feasibility, acceptability, and preliminary effectiveness of a novel digitally enabled CHW intervention for patients managing HF at home. The results of this trial are expected to deepen our understanding of experiential barriers patients with HF patients face while living at home and underline the potential value of a home-based CHW-supported digital platform solution. Assessment of the intervention's ability to augment patient engagement, adherence to care plans, and impact clinical outcomes will be addressed. Given the rising cost of care for patients with HF and heightened morbidity and mortality, the findings of this study may also carry important economic lessons in terms of designing value-based care that can assist in avoiding

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preventable readmissions for patients with HF who are at high risk for hospitalization.

This study may also add context to our understanding of how digital interventions for patients with HF and other serious illnesses are best implemented. Numerous barriers to adoption have been well documented, and the results generated from this study may aid in the development of a framework, leading to best practices for addressing individual clinical and social barriers that may arise for patients engaging with digital platforms at home. The use of qualitative exit interviews adds to the patient centeredness of the study by highlighting the patient perspective and experience that may generate important solutions for the home management of HF and for unmet social needs. These results may also demonstrate how home-based CHW care can potentially advance patient use and engagement with digital platforms, adherence to clinical care plans, and connections to clinical homes. These study results may be used to strengthen and inform the feasibility and adoption of future digital interventions. Finally, this study also will provide opportunities to clarify our understanding of which types of interactions and resources provided to certain patients with HF by CHWs are most beneficial with regard to clinical outcomes.

Comparison to Prior Work

Remote monitoring studies have shown some improvements in outcomes for patients with HF. In a large trial with 1571 patients randomized to remote monitoring versus usual care, intervention patients had fewer days lost to unplanned cardiovascular admissions (4.88% vs 6.64%; 95% CI 0.65-1.0; *P*=.046) and decreased all-cause death rate (7.86 vs 11.34; hazard ratio 0.70, 95% CI 0.5-0.96; *P*=.028). However, most studies of remote monitoring have demonstrated mixed results [6]. A large study randomized 1437 participants to a combined health coaching and telemonitoring intervention for 180 days but showed no significant difference in readmission (50% vs 49%; *P*=.74) [45]. Similar outcomes were seen in other large-scale studies [46-48]. Nevertheless, systematic reviews have been suggestive of improved outcomes. In a systematic review analysis of 25 studies inclusive of structured telephonic support and telemonitoring (n=9332), telemonitoring reduced all-cause mortality (n=3740; RR 0.80, 95% CI 0.68-0.94) and HF-related hospitalization (n=2148; RR 0.71, 95% CI 0.6-0.83) [20]. However, all-cause 30-day readmission rates were unchanged. Concordantly, in a meta-analysis of 21 analyzed RCTs assigning patients to different remote patient monitoring interventions (n=6317) with medical personnel support or telephone support, results showed that those interventions that included staff delivering some home-based support (either clinically or administratively) reduced mortality (HR 0.77, 95% CI 0.55-1.08) [49].

While the majority of CHW studies are focused on cancer, there is a growing evidence base demonstrating the impact of CHWs on chronic disease and HF populations. In an RCT (n=426) pairing CHWs with patients who have chronic disease insured by Medicaid at the time of hospital discharge, adherence to posthospital care was improved (60% vs 47%; *P*=.02) [10], but no difference in 30-day readmissions was seen. Another RCT that focused on patients with 2 or more chronic diseases (n=322) demonstrated a reduction in systolic blood pressure associated with a 6-month CHW postdischarge intervention (–11.2 mm Hg vs 1.8 mm Hg; overall *P*=.08) [11]; a 28% reduction in 1-year hospitalizations was also seen, although it did not achieve statistical significance. A large RCT (n=525) testing a nurse practitioner and CHW intervention among patients with cardiovascular disease showed reductions in reduced total cholesterol (difference 19.7 mg/dL), low-density lipoprotein cholesterol (difference 15.9 mg/dL), triglycerides (difference 16.3 mg/dL), systolic blood pressure (difference 0.2 mm Hg), and glycated hemoglobin (difference 0.5%), as compared to enhanced usual care [50]. Some smaller studies have also supported these outcomes. In a study with 28 patients with HF paired with CHWs at the time of hospital discharge, participants paired with a CHW for 12 months saw a decrease in HF-related ED visits (0.71 vs 0.18; *P*<.001), and an 89% decrease in HF readmission (0.64 vs 0.07; *P*<.005) [51]. No significant difference in 30-day readmissions or ED visits was seen compared to matched controls. Systematic review data have also been positive. In a meta-analysis of 16 CHW-focused RCTs, 5 RCTs demonstrated a significant reduction in ED visits (23%-51% reduction; *P*=.05), hospitalizations (21%-50% reduction; *P*<.05), and urgent care visits [52]. We expect that this study will build on this knowledge by filling knowledge gaps related to adoption and adherence to a digitally enabled CHW intervention that has yet to be studied in a clinical trial powered to test its effect.

Strengths and Limitations

This methodology describes a small pilot trial performed at a single, urban, academic health care center. Since there are limited survey instruments designed to assess user experience with this particular digital platform, we adapted a prior questionnaire with established generalizability to assess this digital platform [37]. While formal patient-reported outcome measure scales were unable to be incorporated for all patient questionnaire covariates due to burdensome instrument length, Patient Health Questionnaire-2, Kansas City Cardiomyopathy Questionnaire, and the Three-Item Loneliness Scale were included as well as a number of items related to health behaviors and satisfaction used in our previous studies [27]. The study strengths include the RCT design focused on a unique intervention for an at-risk cohort of patients facing a burdensome and morbid condition. We also believe that the inclusion of feasibility as an outcome adds strength to the structure and actionability of the trial methodology in 2 ways: by further informing implementation science and strategic deployment of the intervention and by identifying potential barriers and facilitators of this intervention delivery and engagement for future larger trial performance. Additionally, the use of patient response data gathered from questionnaires and exit interviews adds a quasi-mixed methods design element that not only contributes to our understanding of the patient experience with living with HF at home but can also add depth and context to the study outcomes. While this trial will not be adequately powered to assess the true effectiveness of the intervention and our sample size will be limited to a single academic institution that may not be generalizable to other settings, the methodological quality and integrity of the study performance

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may generate preliminary results that may later be tested in a large multisite clinical trial powered to assess the intervention's effect on clinical outcomes in larger populations.

Conclusions and Future Directions

The findings of this trial are expected to contribute to the implementation of digital platforms, as well as the role of CHWs in supporting digital care for a patient with HF. In this way, these findings may improve the performance of a large-scale and multisite RCT and help determine the true effectiveness of this intervention with regard to clinical outcomes. In addition, this trial may answer important questions about what types of CHW interactions can offer the greatest value for patients relevant to demographic, clinical, and social domains. As total medical expenditures for those affected by HF are expected to grow exponentially in the next decade, creating value-based and patient-centered solutions is a fundamental priority for health care institutions and stakeholders alike.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to the small number of participants at a single institution but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CHW: community health worker
CONSORT: Consolidated Standards on Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Research
ED: emergency department
EMR: electronic medical record
HF: heart failure
MGH: Massachusetts General Hospital
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Clinical Remote Monitoring of Individuals With Spinal Cord Injury at Risk for Pressure Injury Recurrence Using mHealth: Protocol for a Pilot, Pragmatic, Hybrid Implementation Trial

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Abstract

Background: Pressure injuries are one of the most challenging secondary conditions for individuals with spinal cord injuries and related disorders (SCI/D) owing to inherent, lifelong risk factors that include a lack of sensory and motor function below the level of injury and reliance on a wheelchair for daily mobility, resulting in prolonged periods of sitting. Although many factors contribute to the development of pressure injuries, the pressure between the skin and a surface is always a factor and the development of injury is dependent on the magnitude and duration of the pressure. Clinically, broad recommendations for relieving pressure are used because we know very little about the unique day-to-day life patterns of the individual wheelchair user. Typically, it is after the occurrence of a pressure injury that the therapist will check equipment fit and the effectiveness of pressure offloading and ask about other surfaces they sit on in their home and community. This time-lapsed, largely self-reported data are fraught with recall bias and inaccuracies that the therapist incorporates into a plan of care.

Objective: This study's objective is to pilot-test the implementation and clinical effectiveness of a telehealth model of care combined with our mobile health (mHealth) Assisted Weight-Shift device for remote monitoring of factors related to maintaining skin health and wheelchair setup. Our overall hypothesis is that this study will result in an effective implementation plan, and the enhanced connected model of care using remote monitoring of pressure management will result in pilot-level, improved clinical outcomes for adults with spinal cord injury at high risk for pressure injury recurrence.

Methods: For all aims, we will use a mixed methods design using an exploratory, sequential approach to include the strengths of both qualitative and quantitative data. For aims 1 and 2, we will iteratively collect qualitative data from therapists, patients with SCI/D, and other stakeholders. For aim 3, we will perform a hybrid effectiveness-implementation randomized controlled trial to pilot-test the intervention. The projected results include an iteratively developed and tested implementation plan that meets moderate to high levels of acceptability, feasibility, and appropriateness. Additionally, the pilot trial results are expected to show positive trends in relevant clinical outcomes related to reduced pressure injury incidence, recurrence, and improved healing when compared with the standard of care.

Results: Currently, 6 participants have been recruited for our aim-1 qualitative study.

Conclusions: This study will expand upon our previous study to move the Assisted Weight-Shift system into routine clinical care, which was a strong desire of adults with SCI/D for improved individualized care plans to prevent pressure injuries. The results of this study will guide the next steps in a full, hybrid effectiveness-implementation trial with the goal of improving care to prevent pressure injuries.

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KEYWORDS

wheelchair user; seating and mobility; weight shift behavior; pressure injury; mobile phone

Introduction

Background

Pressure injuries are one of the most challenging secondary conditions for individuals with spinal cord injuries and related disorders (SCI/D) owing to inherent lifelong risk factors that include a lack of sensory and motor function below the level of injury and reliance on a wheelchair for daily mobility, resulting in prolonged periods of sitting. A 2022 report stated that the incidence of pressure injuries in adults with SCI/D was 25% to 38%, with incidence increasing with time after SCI/D onset [1,2]. Recurrence rates as high as 80% [3-5] have been reported. Pressure injuries are also the second most common reason for rehospitalization at a rate of 11% to 20%, and these numbers are also increasing with time since SCI/D onset [1]. Pressure injuries are the only secondary condition consistently correlated with mortality risk [1,6], and they cause a significant negative impact on the individual, health care system, and society owing to the costs to manage them once they are present.

Interface Pressure Is a Major Risk Factor for Pressure Injuries

Although many factors contribute to the development of pressure injuries [7,8], the pressure between the skin and a surface is always a factor and the development of injury is dependent on the magnitude and duration of pressure [9,10]. An individual's pressure versus time curve is based on their ability to physiologically tolerate mechanical loads over time [11]. The longer the pressure is applied without mitigation, the higher the risk for tissue damage. Some individuals can tolerate more load over longer periods of time than others; therefore, individualization is important for prevention.

Individualized Solutions Are Necessary for Effective Prevention

Unique risk factors are present for individuals with SCI/D, including motor and sensory impairment; changes to muscle and bone tissues; and for up to 80% of those with SCI/D, the reliance on a wheelchair for mobility [1]. Individuals with more complete injuries have more impaired sensory function [12] and tend to fare worse in their ability to prevent pressure injury over time [13-15]. Movement is a key mechanism in offloading pressure, and there is high variability in daily movement patterns across the SCI/D population [16], which makes it difficult to standardize the recommendations for performing weight shifts. In addition, some individuals are physiologically better able to tolerate more or longer duration of pressure than others [17]. Each person has unique levels of risk awareness, daily routines, habits, and contexts within which they function, and these influence their ability to adhere to preventative behaviors [18]. Thus, for preventative behaviors to be added successfully to daily life, they need to be customizable and individualized to fit within each person's unique scenarios.

Standard of Care for Pressure Injury Prevention Is Individualized but Includes Limited Data About Daily Life

For the occupational or physical therapy seating specialists, care is provided in a client-centered manner such that education, treatments, and recommendations are individualized to the person as much as possible. This client-centered approach includes education about minimizing prolonged pressures under bony areas [3,11,19,20], with movement strategies to redistribute pressures [21-26] that are specific to the individual's injury level, functional level, body habitus, and so on. However, although the wheelchair, seating surface, and mechanism of pressure offloading (leaning or tilt) are specialized to the person, the clinical recommendations for the frequency and duration of skin-protective movement patterns are broadly applied to all people and range from performing weight shifts every 15 minutes to every hour and holding them for up to a 2-minute duration [3,7,19]. Broad recommendations are used because we know very little about the unique day-to-day life patterns of the individual wheelchair user. If a patient returns to their therapist after the occurrence of a pressure injury, the therapist can check equipment fit and the effectiveness of pressure offloading, and they can ask about other surfaces they sit on in their home and community. This time-lapsed, largely self-reported data are fraught with recall bias and inaccuracies that the therapist does their best to incorporate into an effective care plan.

However, based on the rates of pressure injury incidence and recurrence, there is a gap in the care we can provide to individuals with SCI/D. We hypothesize that this gap is largely owing to the limited availability of data about the patient's daily life. On the basis of our own preliminary data, we know that therapists want to know the following objective and contextual data about their patients: (1) frequency and duration of daily pressure offloading behaviors, (2) effectiveness of pressure offloading during their daily weight shifts, and (3) pressure distribution on the other sitting surfaces the patient interacts with (chair, car seat, commode, etc). Without the necessary client-centered data gathered in context, the therapist is significantly limited in developing an individualized care plan.

The Assisted Weight-Shift System Monitors Factors of Individualized Pressure Management

In our Department of Defense (DoD) Spinal Cord Injury Research Program–funded project (W81XWH-15-1-0484), our group, in collaboration with veterans with SCI/D, developed the Assisted Weight-Shift (AW-Shift) system (formerly called the comprehensive mobile assessment of pressure system) to capture objective data regarding pressure management during daily life to be used by the patient or consumer and clinical partners to better prevent pressure injuries [27]. In a current National Institute of Health (NIH)–funded project (R01 AG056255), we have improved the hardware and software design of the AW-Shift system and are performing a clinical trial of the system in a consumer-use model. The AW-Shift system provides real-time pressure mapping visualization

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(Figure 1), tracks weight shift behaviors, and provides weight shift reminders and high-pressure alerts. The data provided by the AW-Shift system offer unique, client-centered information to drive individualized goals and intervention plans. With this level of information about daily life, each person's unique daily occupations, routines, and rituals that influence their pressure management profile can be directly integrated into individualized care. Through DoD and NIH funding, we have demonstrated the efficacy of the system in terms of improving pressure injury prevention awareness, self-efficacy, and pressure management behavior in a consumer-use model. The proposed project advances our past studies through implementation of the AW-Shift system and evaluation of its impact on the clinical care of adults with SCI/D.

Figure 1. Assisted Weight-Shift (AW-Shift) real-time pressure map and countdown to next weight shift. PPI: Peak Pressure Index.

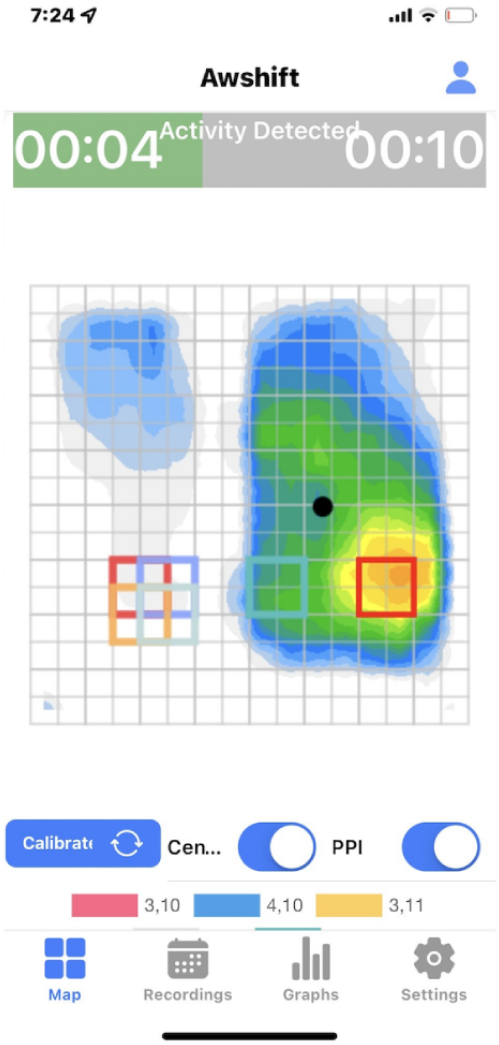

Structured Implementation Studies Are Necessary for Clinical Practice Improvement

Implementation research is the study of methods to optimize the systematic uptake of evidence that has been shown to be efficacious (has the intended effect) and effective (has the intended effect in the intended setting). As noted, emerging technologies such as AW-Shift may provide safe, efficient, and effective pressure injury prevention, but additional studies are needed to determine what approaches are optimal for integrating this technology and individualized data into clinical practice. The implementation of the AW-Shift system into routine clinical practice is far more complex than simply providing proof that the system works in a research setting.

Implementation into practice requires the commitment and active involvement of practitioners and patients, collaboration with relevant stakeholders who influence care delivery, and modifications to the intervention that meet the needs of providers and patients in dynamic practice settings. We have designed this project to assess the current clinical practices, iteratively modify the intervention to meet the clinical practice needs, and identify what factors may influence its uptake.

Overall Objective and Specific Aims

Overview

Our long-term objective is to facilitate the effective prevention of seating-related pressure injuries throughout the lifetime of individuals with SCI/D with the use of our evidence-based, real-time pressure management solution, the AW-Shift system (Figure 1). Our short-term objective for this study is to pilot-test the implementation and effectiveness of a telehealth model of care combined with our mobile health (mHealth) AW-Shift

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device for remote monitoring of factors related to maintaining skin health and wheelchair setup. Our overall hypothesis is that our development plan will result in an effective implementation plan, and the enhanced connected model of care using remote monitoring of pressure management will result in pilot-level improved clinical outcomes (wound recurrence, early identification of wounds, and wound healing) for adults with spinal cord injury (SCI) at high risk for pressure injury recurrence. We will pursue our objective through the following specific aims.

Aim 1: Clinical System Development (Develop mHealth Report and Integrate Within the Medical Electronic Environment)

The current remote monitoring interface was built for research use. Through a user-centered, mixed methods design, we will engage with patients and clinicians through focus groups, interviews, and surveys to determine the optimized design for the capture and reporting of data to the patient and the clinician through a connected care model. After the capture and reporting method is developed, the data flow will be integrated within electronic medical record infrastructure.

Aim 2: Rapid Cycle Quality Improvement (Integrate System Into Connected Care and Telemedicine Infrastructure)

Using best practices for rapid cycle quality improvement, we will integrate our connected care solution into a current telehealth infrastructure. We will test the ability of our connected care solution to perform patient visits and short-term remote monitoring of pressure management focused on the system integration aspects to cycle through improvements in a 3-month time frame to prepare for aim 3.

Aim 3: Pragmatic, Hybrid Implementation Trial (Implement the Connected Care Solution via a Pilot, Pragmatic Trial Comparing Clinical Outcomes Between the Connected Care Model and Standard Practice)

Patients identified as having high risk for pressure injury recurrence will be randomized to either the connected care model (Figure 2) or the standard model of care for a 1-year follow-up time frame. Our implementation outcomes include important stakeholders' assessment of feasibility, acceptability, appropriateness, costs, and improved monitoring. Our pilot effectiveness outcomes are rate of wound healing for prevalent cases, incidence and recurrence of pressure injuries, early identification of wounds, and hospital admissions or readmissions.

Figure 2. Through a connected care model and the Assisted Weight-Shift mobile health system, the provider guides the patient to change high-risk pressures (phone image on the left) into safe pressures (phone image on the right).

Methods

Study Design

For all aims, we will use a mixed methods design using an exploratory, sequential approach to include the strengths of both qualitative and quantitative data. For aims 1 and 2 of the study, in an iterative manner, we will collect qualitative data from therapists, patients, and other stakeholders. For aim 3, using both qualitative and quantitative data, we will perform a hybrid effectiveness-implementation randomized controlled trial to pilot-test the intervention. For implementation outcomes, we will assess the feasibility, acceptability, and appropriateness for the in-home use by the patients and the feasibility, acceptability, and appropriateness of the previsit information from clinical stakeholders. For pilot effectiveness, we will assess the clinical outcome measures of wound recurrence, early identification of wounds, and wound healing.

Ethical Considerations

All research activities for aims 1 to 3 will be performed under institutional review board (IRB) oversight and with IRB approval. At the time of the writing of this manuscript, aim 1 was approved by the University of Texas Medical Branch IRB (22-0280) as an exempt study that waives the requirement for informed consent. The study is no more than minimal risk and fits the second exemption category (interviews), including recording data in such a manner that the identity of the human participants cannot be readily ascertained through identifiers linked to the participants. IRB approval for aims 2 and 3 will be sought under the minimal risk category. We expect that owing to the iterative nature of aims 2 and 3, modifications will be

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required throughout the study to accommodate updates to the protocol and procedures, motivated by study staff and participant experiences and feedback. Participants for aim 1 are compensated for their participation with a gift card worth US $50. Participants for aims 1 and 2 will be compensated for their time with payment commiserate with the time required to complete the study.

Rationale for Hybrid Effectiveness-Implementation Study Design

Hybrid designs were developed to improve efficiency in moving promising interventions along the efficacy-effectiveness-implementation continuum, as implementation research focuses on the adoption of evidence-based interventions by systems of care. Integrating implementation planning into the study design helps to promote the full adoption of an intervention into the practice in which it was tested. We propose to use a hybrid-1 design [28], wherein the study is designed to test a pilot clinical intervention while gathering information about its delivery during the effectiveness trial and about its potential implementation in "the real world" of clinical practice. We will simultaneously plan for implementing AW-Shift into practice while testing its effectiveness in changing clinical outcomes. Our design includes formative evaluations of clinical staff during the study period, which will provide a rigorous assessment of what potential internal and external influences are critical for a successful implementation and add qualitative data to enrich the data analysis and evaluation.

Rationale for Using Consolidated Framework for Implementation Research Implementation Model to Guide Implementation

We propose to use Consolidated Framework for Implementation Research (CFIR) to inform which implementation targets will be critical for successful implementation. CFIR is a meta-theoretical framework that is based on a synthesis of 19 implementation frameworks and models with a goal to "foster knowledge-building into why implementations succeed or fail." It includes 5 domains: outer setting, inner setting, intervention characteristics, individual characteristics, and process. Each domain includes common constructs, 39 in total, associated with successful implementation. The framework does not specify hypotheses or causal pathways, allowing flexibility in evaluating constructs that are unique to a study. It has been described as a "menu of constructs" that enables systematic and comprehensive exploration and identification of potential factors that can influence implementation [29]. In general, the framework helps researchers and interventionists to assess the structural capacity for an intervention, culture for change, perceptions from stakeholders about the need for change, quality of the proposed solution, and way in which the intervention should be planned and executed. Regarding the qualitative work for aim 1, we will explore the potential constructs in each domain (eg, design quality and packaging, patient needs and resources, compatibility, relative priority, leadership engagement, and self-efficacy) from the CFIR model that will inform the efforts for the rapid cycle assessment in aim 2 and pilot trial in aim 3.

Specific Aim-1 Methods: Clinical System Development

The goal of aim 1 is to define the scope of the implementation of the AW-Shift system into a connected care model and operationalize that scope into a testable plan for aim 2. Each step of the plan will be guided by the end users and other key stakeholders through qualitative and survey feedback.

Patient and Clinician Needs Assessment

Overall, 2 focus groups, 1 for adults with SCI/D and 1 for clinicians from the Seating Clinic and Wound Care, will be conducted to determine the needs and priorities of each group for improving the assessment of seating and mobility needs. A focus group guide, drawn from CFIR's Interview Guide Tool [30], will be used for each group to better understand how expanded seating pressure information captured during the daily life of patients could better inform seating and mobility therapy visits. The discussion will include brainstorming of types of information that would be of value and identifying barriers to and facilitators of attaining the information. There will be an emphasis on understanding the concerns about the complexities of a new process as it relates to the outer setting, inner setting, and individual characteristic constructs of the CFIR model [31]. The focus groups will be conducted through a Health Insurance Portability and Accountability Act–compliant web-based meeting format (Zoom; Zoom Video Communications). The discussion will be recorded for analysis.

Qualitative Outcome Measures and Data Analysis

The qualitative data from the focus groups will be transcribed by a transcriptionist. Investigators will import transcripts and field notes into computer-assisted coding software such as NVivo (Lumivero) to structure the transcripts and enable them to be "openly coded" by the researchers. The CFIR constructs will guide the development of the code book, as these constructs are key to effective implementation. Qualitative analysis of the interview transcripts will combine deductive and inductive approaches using an initial coding template structured around the interview guide topics and then refined through full data set coding [32]. The coding template refinement process will include an element of reflexivity owing to clinical expertise of coders, thus offering an efficient process to generate high-value design requirements layered with contextual rationale. Through memo-taking and iterative meetings to discuss data, the team will reach consensus about the code book and the assignment of text segments to particular codes. Investigators will independently review the transcripts and codes to provide a measure of internal validation. A coalescence of major themes from the coders will be used for the interpretation of findings and the subsequent theory development. The survey data will be used to define the areas of strengths and weaknesses of the intervention and implementation plan.

Sample Size

For focus groups, we will follow the recommended practice by having no more than 10 participants per group [33]. For the patient focus group (n=10), we aim to purposively sample patients with various levels of SCI/D, wheelchair type (power and manual), history of pressure injuries, and age to seek a wide breadth of user experiences. For the therapist focus group

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(n=10), we aim to purposely sample therapists with a range of years of experience, to seek a breadth of perspectives about providing seating and mobility care to patients with SCI/D.

Draft Plan and Follow-up Focus Group

Needs assessment will be used to refine the draft implementation plan (Figure 3). Following the refinement of the draft plan, a follow-up focus group with clinicians and patients will be conducted, wherein the draft plan will be presented along with a description of the AW-Shift system. Through this focus group, we seek to understand the specific types of data and activities to measure during daily life that can inform the clinical assessment. In addition, the participants may be queried about specific aspects of the plan using survey responses that will likely use a Likert scale for assessing the level of satisfaction or acceptability with aspects of the plan. We will learn from these focus groups and survey responses regarding what needs to be adapted in the draft plan and what data will be used in the mHealth report. We will operationalize the implementation plan based on the participant feedback and use the CFIR constructs to increase the usability and acceptance of the AW-Shift system by participants or patients with SCI/D.

Figure 3. Implementation outline with example implementation steps. AW-Shift: Assisted Weight-Shift.

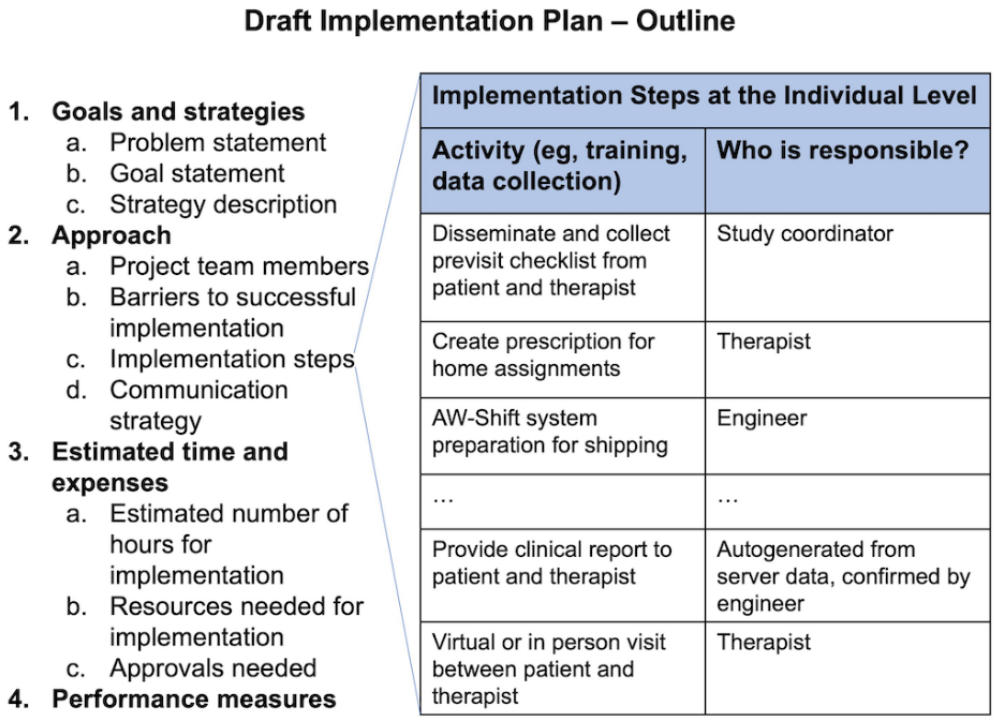

mHealth Report

The mHealth report will provide summary data and visualizations that provide an informative snapshot of the home testing period (a partial example is shown in Figure 4).

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Figure 4. Example of a partial mobile health report. AW-Shift: Assisted Weight-Shift.

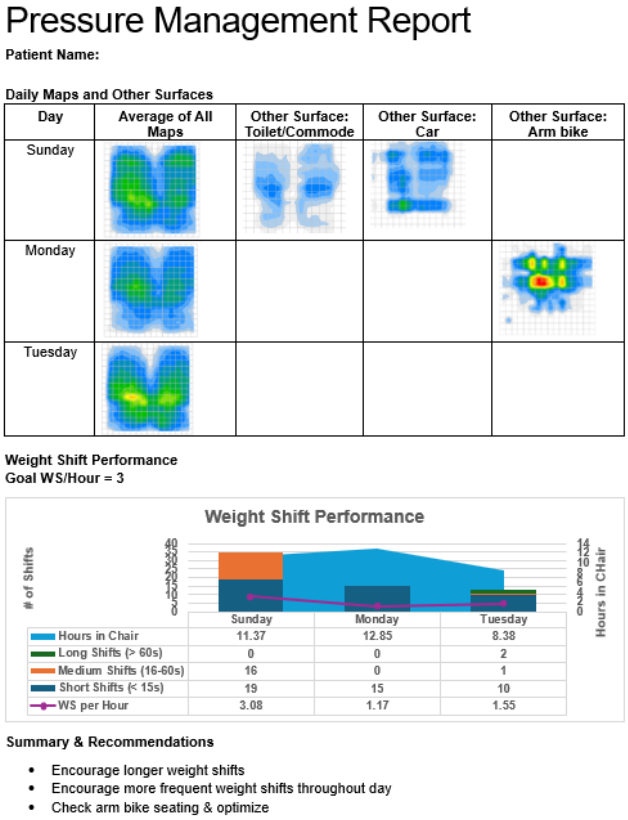

Integration of the mHealth Report Into the Clinical Electronic Environment

On the basis of the focus group findings, the team will perform the following tasks in collaboration with necessary stakeholders. We will adapt the current, remote data capture process and infrastructure to meet the patient and therapist priorities and requirements for use during the clinical visit. A likely solution for communication of the data will involve the mHealth report being autogenerated on the server and provided back to the patient through the mobile app before the telehealth visit. The patient, being the ultimate owner of their data, will then send their report to their therapist through a secure patient website or mobile app that allows direct communication to the care team and patient access to their web-based medical record. With this data flow plan, the report would be available to the therapist for easy viewing during their visit. In addition, the patient will have full awareness of the data that the clinician is viewing.

Iterative Process for User-Designed Implementation of the AW-Shift System Into Clinical Care

Through a series of iterative focus groups and further refinement steps, the team, along with the users of the system (patients and therapists), will co-design the full implementation plan that will be ready for testing in aim 2. We estimate this step will take 2 to 3 iterations of focus groups and refinement steps.

Specific Aim-2 Methods: Rapid Cycle Quality Improvement

Overview

Rapid quality improvement assessment of the implementation plan will be completed in aim 2 by testing the plan with an estimated 10 patients with SCI/D. For the first 3 to 5 patient participants, each participant will be run 1 at a time through the implementation plan. Rapid adjustments will be made as each participant goes through the steps of the plan. For the final 6 to 8 participants, participants will be scheduled in pairs such that at least 2 participants will be run in parallel to test the ability of the implementation plan to adjust to concurrent use of the system in the participants' home and community. After each participant set, we will make rapid adjustments to optimize the implementation plan. Owing to participant heterogeneity, we will be mindful about how plans will need to be optimized differently depending on patient characteristics such as injury level and whether a caregiver or personal aid is required by the patient to use the system.

Protocol for Connected Care Model

Although the specific details of this protocol may change, we propose an outline of the procedures that will occur after participant consent and enrollment.

Individualized AW-Shift Prescription

A seating clinic therapist will review the clinical notes of the participant for their seating and mobility history. We presume from our preliminary data from therapists and the knowledge of the clinical team members in this project that a simple initial checklist will be effective in determining the possible "home

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assignments" that therapists could give to patients to gather the pertinent information specific to the patient, including recording pressure across different surfaces, using weight shift reminders, and recording weight shifts performed during specific tasks. In addition, the patient will be asked to complete a checklist to identify their seating and mobility concerns including, for example, new areas of concern about their skin, seat cushion, weight shifting habits, pressure on other surfaces, sitting posture, or weight relief quantity or quality. On the basis of the checklist information, an individualized prescription will be developed for the participant to fulfill (with extensive team support) during the 2-week daily life testing period.

System Setup and Prescription Delivery

The participant will be shipped an AW-Shift system and scheduled for a virtual visit to set up the system by the study coordinator. The system will include the hardware components, a user manual, and a study-provided smartphone or tablet if the participant does not have their own device. If the participant is using their own phone, they will be instructed to download the AW-Shift mobile app from the Apple App Store or Google Play Store. During the system setup visit, the participant will be provided with training regarding how to use the AW-Shift system with the study coordinator and engineering and therapy experts on the study team. The team will review the individualized prescription with the participant, and knowledge about system use will be tested to determine sufficient mastery of using the system.

Home and Community Use of the AW-Shift System

Participants will use the system for an estimated 2 weeks before their clinical visit. Participants will have easy access via phone; secure, web-based format; email; and SMS text message for technical and therapy support. A potential prescription could include (but not be limited to) mapping the variety of surfaces the participant sits on in the home and community (the system can be used on any surface), completion of daily weight shift protocols to assess participant positioning on their cushion, measurement of how the participant performs weight shifts with and without reminders provided by AW-Shift, and measurement of the effectiveness of the weight shifts to offload pressure.

Summary Report

Before the telehealth clinic visit, the prepared mHealth report will be delivered via the AW-Shift mobile app to the participant. The participant will be instructed about how to upload the report 1 day before their telehealth clinical visit. The therapist will view the mHealth report via the participant's medical records during the clinical visit.

Telehealth Clinical Visit

During the visit, the therapist will use the standard clinical notes and the data provided on the mHealth report to guide the patient participant through the typical steps of a therapy visit focused on the seating and mobility needs related to pressure injury prevention. The telehealth visit will be completed using the standard Zoom interface. The therapist will use all the information they have available to determine the next steps in the patient's care plan. The clinic visits will be recorded, so that the study team can provide additional observations for use in process improvement. The therapist will ask for confirmation of a skin check performed on the day of the visit with assistance from a caregiver, if necessary.

Assessment

Following the telehealth visit, both the patient participants and the therapists will complete a series of surveys to assess usability (System Usability Survey [34]), acceptability (Unified Theory of Acceptance of Use of Technology [35,36]), feasibility (Feasibility of Intervention Measure [37]), and appropriateness [37] of the procedures, and each of them will participate in a short interview to gather qualitative feedback to improve the implementation plan.

Rapid Assessment Procedure

Rapid assessment procedures are a pragmatic option for producing timely, contextually rich evaluative information about complex interventions implemented into dynamic clinical settings [38]. We will use rapid assessment procedures after each participant in the first 3 to 5 participants or after each pair of the final 6 to 8 participants to improve the plan for the next set of participants.

Stakeholder Input About Case Summaries

The findings from aim 2 will be written as a case summary that will be presented to the patient and therapist focus groups from aim 1 to gather additional stakeholder input about the optimization process. Any points regarding necessary improvement or inconsistencies will be discussed by the research team until consensus is achieved for the final plan for aim 3.

Outcome Measures and Data Analysis

The qualitative data from focus groups and interviews will be managed and analyzed as described for aim 1. The quantitative data from the survey scores will be used to define the areas of strengths and weaknesses of the intervention and implementation plan for further refinement.

Sample Size

For the rapid assessment testing for aim 2, we provide a robust approach by cycling the process through single and paired visits. Similar to the focus groups, we will sample to attain a breadth of user experiences. A total of 10 participants for each round is an effective sample size to be able to narrow down and optimize the process [33].

Data Management

All study data will have unique identifiers removed before the final analysis. Study data will be imported from the various clinical data sets into a central REDCap (Research Electronic Data Capture; Vanderbilt University) database that can be accessed by the study team. The study coordinator managing the database will keep the electronic key secure in accordance with Health Insurance Portability and Accountability Act and patient privacy regulations.

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Potential Limitations and Alternative Strategies

Failure of the System in the Field

We will monitor system use and will be available for troubleshooting. We currently have 25 full systems and will be able to accommodate equipment swapping by mail.

Recruitment

We have experienced very little difficulty in reaching our goals for participation in past studies with similar methodology. We will continue to collaborate closely with clinical staff and consumer groups to ensure successful recruitment.

Skin Safety

We will continue to track skin safety during the study and will discontinue use if we notice any signs of skin issues.

Sensing Technology

The current resistive sensors used in the selected pressure map have inherent limitations including a tendency to creep under prolonged loaded states, but we mitigate this through specific calibration protocols. The mat was selected because it stretches and is durable for whole day use.

Specific Aim-3 Methods: Pilot

Pragmatic Hybrid Implementation Trial

The proposed pilot randomized controlled trial will test whether our novel AW-Shift system intervention adds value to the clinical care of adults with SCI/D to inform our next steps in translation.

Study Design

This single-site randomized controlled trial will use a modified intention-to-treat analysis. Randomization will be a stratified, block randomization with stratification based on wheelchair type (manual vs power) and current wound severity (no wound or stage 1 vs stage 2 or stage 3). The intervention group (26/52, 50%) will receive the connected care model that used AW-Shift in combination with telehealth. The control group (26/52, 50%) will receive the standard of care that uses telehealth when appropriate. The statistician will be masked to the group allocation information for the outcome measure analysis.

Randomization

We will stratify based on wheelchair type (2 groups: power and manual), and current wound severity (2 groups: no wound or stage 1 and stage 2 or stage 3). We will block randomize in groups of 4. This randomization scheme will ensure distribution of important confounders between arms of the study. Furthermore, the blocking will ensure equal distribution of group assignment during the study.

Study Population

Adults with SCI/D with high risk of recurring pressure injury who answer "yes" to one of the following questions are eligible: (1) I get pressure ulcers about every couple of years; (2) I get at least 1 pressure ulcer a year; and (3) I always seem to have sores, often requiring surgery or hospitalization [39]. Our rationale for choosing individuals at high risk for recurring injury is that once a person has one pressure injury, their chances are significantly high to have another; hence, it has been recommended that interventions focus on this group of individuals [39].

Initiating and Conducting the Pilot Clinical Trial

The principal investigators (PIs), coinvestigators, and study staff will manage the process of study initiation with a modified standard checklist that covers essential items. Pilot clinical trial initiation meeting will occur early in mid–year 1, wherein all the steps will be reviewed, and the specific timeline will be determined. Standard operating procedures and field guidebooks will be developed to follow throughout the trial period. Weekly phone calls or web-based meetings among all study members will be used for study management. Any urgent communication regarding the pilot clinical trial will be managed with a phone call to the PI made within 18 hours of the event and reported to the IRB.

Study Procedures

For initiation and administration of the intervention, the following procedures will be followed:

1. Project initiation: The project will be initiated following a study initiation checklist by the PI and local site investigators.
2. Staff training for the intervention: Staff will be instructed about how to use the AW-Shift system, view and use the mHealth report, and administer data collection elements as is appropriate for each study role. Data collection procedures will be standardized and tested for consistency across study team members.
3. Participant recruitment: Recruitment and enrollment during year 2 will occur primarily through clinical staff in collaboration with the study coordinator.
4. Intervention study period: The intervention will begin with 2 weeks of AW-Shift use at home by the patient with SCI/D, followed by a web-based clinical visit with a seating clinic therapist. Before mailing AW-Shift to participants, individualized tasks will be assigned by the seating specialist. The tasks are meant to inform the seating assessment process during the clinical visit. Participants and seating specialists will complete surveys after the seating clinic visit and participate in a guided interview.

Intervention Protocol

The planned intervention protocol is similar to that described for aim 2, for the rapid quality assessment as described in the *Protocol for Connected Care Model* section. We expect that the protocol will be improved through the iterative process we are using to optimize the implementation of our intervention. Full demographic variables relevant to SCI/D will be collected during the consent visit. The same surveys and structured interview will be completed after each visit by the intervention group participants and the therapists including assessment of usability (System Usability Survey [34]), acceptability (Unified Theory of Acceptance of Use of Technology [35,36]), feasibility (Feasibility of Intervention Measure [37]), and appropriateness [37] of the procedures.

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Control Protocol

If participants are randomized into the control group, the standard of care protocol will be followed as used in the seating clinic. Demographic and additional variables will be collected from participants similar to those in the intervention group, and their clinical visit will be recorded for assessment of the visit.

General Statistical Methods

All tests are 2 sided, with a 0.05 type-1 error rate. Analysis will be conducted using SAS (SAS Institute) and R software (GNU Project). Mean and SD or median and IQR will be reported for all demographic, predictor, and outcome variables, as appropriate. For all outcome measures, the effect of relevant biological variables including sex, age, level of sensation, and pressure injury history will be assessed as covariates in the analysis. In addition, wheelchair type will be included as a covariate. Variables will be transformed as necessary to meet the appropriate distributional assumptions for modeling (eg, normality). For missing data, mixed models can be used to handle missing data naturally, so that all available data points may be analyzed, irrespective of whether the participant had some outcome data missing. However, analyses of data with multiple imputation for missing data may be attempted if the data are likely to be missing at random.

Primary Pilot Clinical Trial Effectiveness Outcomes

The primary effectiveness of the intervention will be captured via the collection of the following clinical outcomes: wound recurrence, early identification of wounds, wound healing, and hospital admission or readmission. The data for these metrics will be abstracted during the full year (365 days) after the study-related clinical visit for both the control and intervention group participants. Then, 2 independent therapist team members will abstract the medical records of each participant to search for the occurrence of an incident wound, stage at which wounds are identified, time frame of wound healing, and occurrence of a hospital admission or readmission directly related to a seating area pressure wound. Comparisons between groups for the primary outcome measures will be made using a 2-tailed *t* test. Additional comparisons will be made with regression and mixed effect models to explore the role of covariates on the study findings.

Secondary Pilot Clinical Trial Effectiveness Outcomes

As a proxy outcome measure for clinical effectiveness, each clinical visit for the control and intervention groups will be assessed using the review of visit checklist shown in Figure 5 by the therapists leading the clinical visit. Then, 2 independent raters, who are seating specialists, will assess the checklist for each participant and will be blinded to the identities of the patients and therapist. The reviewers will rate the visit information on a 5-point Likert scale (eg, “Rate the effect of AW-Shift data on clinical recommendations: (1) significantly diminished, (2) diminished, (3) neither improved nor diminished, (4) improved, or (5) significantly improved”). The reviewer ratings will be analyzed with a 2-sample Mann-Whitney *U* test to determine if the ratings are different between groups to test our hypothesis that the AW-Shift data will significantly improve clinical recommendations. Effectiveness will also be assessed qualitatively in the interviews.

Figure 5. Clinical visit review checklist.

Clinical Visit Checklist

Used for retrospective chart reviev and for study visit video observation.

Participant ID:

Visit Date:

Does the documentation indicate that:	Yes	No
o Participant has a concern regarding pressure?		
o Pressure mapping completed during the visit?		
o There were concerns about pressure management?		
o Mention of surfaces other than the seat cushion/wheelchair used during the visit?		
o There is a need for further evaluation of pressure on other surfaces?		
o New equipment or modification of current equipment needed?		
o A change in daily routine or daily activities is needed?		
o There is a need for change in weight shift practice		
o Frequency		
o Duration		
o Consistency		
o Method for improved pressure distribution		

Comments (indicate the recommendations and strategies that were documented):

Implementation Outcome Measures

Implementation success will be assessed using feasibility, acceptability, and appropriateness surveys regarding the in-home system use of participants and therapists. This information will guide the broad implementation of the intervention.

Additional Study Variables, Controls, and End Points

Demographic variables relevant to SCI/D will be collected and used in the analysis as appropriate. Additional metrics include self-efficacy in managing pressure, assessed using the Skin Care Belief Scales [40]; consistency of weight shift performance, as measured by the AW-Shift system during home use; and the SCI–Quality of Life scale.

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Feasibility Study Variables

For future clinical trial planning, the study variables of screening rate, recruitment rate, enrollment rate, and retention rate will be measured. In addition, the treatment adherence rate and treatment fidelity rates will be measured, and the assessment process will be evaluated. The assessment process includes documenting the planned assessments and data collection instruments that are completed in addition to the duration of the visits.

Sample Size

The sample size for this pilot study (N=52; n=26, 50% per group) is based on guidance that for a trial with 90% power and 2-sided 5% significance, pilot trial sample size of 25 participants per treatment arm is sufficient for an expected small, standardized effect size (0.2) [39]. We do not have the needed data for our primary outcomes to directly determine the power of our planned study design; however, this pilot study will be used to power the full clinical trial. Furthermore, we have used approaches to optimize our statistical power including blocking within the design itself that adjusts for covariates during randomization to reduce imbalance and triangulating the findings of quantitative analyses with qualitative data in mixed methods designs [41].

Potential Limitations and Alternative Strategies

In addition to the potential limitation described for aim 2, aim 3 has the added potential of loss to follow-up. As the long-term follow-up data are passively extracted from the medical record, we acknowledged that patients may seek care outside the original health system they were recruited from. In addition, for participants who have data that we cannot access, we will seek the approval of the participant to access their medical records from other medical systems.

Human Participants

Study Population

Focus groups and structured interviews will be conducted for all aims. Qualitative methods will include adult patients with SCI/D and seating and mobility therapy specialists. Adults with a SCI/D will be the participants for aims 2 and 3. As needed, we will capture additional input from other stakeholders involved in the proposed implementation process to ensure that we are gathering views from a broad range of affected individuals as per the CFIR framework. These individuals may include therapy managers, IT staff, data security staff, scheduling staff, and industry representatives.

Recruitment

Following IRB guidelines, manual and power wheelchair users with traumatic or atraumatic SCI/Ds will be enrolled for the study. The inclusion and exclusion criteria were chosen to include wheelchair users with SCI/D who are at risk for pressure injury development. Recruitment will be purposeful in achieving the desired equal distribution of power and manual wheelchair users and individuals with paraplegia and tetraplegia. For study randomization in aim 3, we will use a stratified, blocked randomization method to ensure even distribution of important predictor and confounding variables in the intervention and control groups. Announcements for participation in this study will be made by personnel directly to patients through mailed letters, phone calls, and word of mouth. Upon determining a person's eligibility, an appointment (via phone or in person) will be made with the study coordinator to explain the research project, confirm eligibility, and collect the necessary demographic data.

Inclusion and Exclusion Criteria

We will enroll adult men and women, aged between 18 and 80 years, with SCI/D at C4 or below, who have a lack or absence of sensation, are primary wheelchair users, and are at high risk for pressure injury. For aims 2 and 3, participants must have had a seating clinic visit or be scheduled for a seating clinic visit. Participants must demonstrate the ability to independently access the AW-Shift system app on a mobile phone or tablet and be able to participate in web-based visits or meetings with the research team. Participants will be excluded if they are unable to consent, have an active stage-4 wound at the seating surface site, do not have adequate resources or support for use of the AW-Shift technology in their home environment, or are currently receiving palliative care. We will enroll current occupational or physical therapy staff for aim-1 qualitative and survey feedback.

Potential Risks

There is the potential for skin irritation from sitting on a pressure mat for long periods. Participants may sit on the pressure mat throughout the day or may simply use it for short periods while performing their prescribed activities. Participants will be instructed to do a skin check every day and log their findings.

Participants are instructed to call the study coordinator if a new area of skin breakdown or wound occurs while they are using the pressure mat or if a current wound worsens. The participant will be asked to remove the mat until the skin breakdown or wound resolves. If the area does not resolve and worsens further, the participant will again contact the study coordinator and will then be referred to their typical clinical care provider in the case of a potential, new-onset incidence of pressure ulcers of stage 3 or 4. Initializing and deploying the AW-Shift system will require performing transfers and weight shifts. Transfers always have some risk of injury or fall, and the participant will be advised to transfer in their usual manner. Weight shifts will include typical functional movements, such as leaning forward and sideways, but participants will be instructed to only perform weight shifts with which they are comfortable. Risks from transferring on their own while the sensors are on the wheelchair are no different than transferring without the sensors present.

Focus Group Guide

Questions were created for the clinicians' structured interviews and focus groups. A sample of the question list is shown in Textbox 1.

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Textbox 1. Sample of question list.

- What are some of the challenges you come up against when teaching a patient with spinal cord injuries and related disorders (SCI/D) about pressure relief?
- On the basis of feedback from our patients of how very useful real-time information is to their pressure relieving behavior. What do you think about the having the real-time image available all the time to the patient?
  - Do you think having that image available will assist you in monitoring and teaching seating behavior?
- What other information, or data, would you want to be readily available to you to monitor the patients' learning of pressure injury prevention behaviors?
  - For example, would it help you to know how many pressure reliefs the patient conducted during the previous hour?
- Would you like the data available for you to be in a particular format?
  - For example, an average number of pressure reliefs conducted over the past four hours, or the percentage of offload over a certain period?
  - How far back would you want data available for monitoring or educating pressure relieving behaviors?
  - Do you want the information pushed to you?
- Can you think of any data that would not be helpful for you to be able to access?
  - For example, when reviewing the patients pressure relieving behavior would you find it useful to know the actual peak psi's that occurred over the previous period of monitoring, or would that be too much information?

Implementation Strategies

We developed the draft of our study-specific implementation strategies (Table 1). From this chart, a refined, operational implementation guide would be created.

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Table 1. Implementation strategies chart.

Study phase	Implementation strategies
Prestudy	• Conduct local needs assessment • Conduct local consensus discussions • Fund and contract for the clinical innovation • Use an implementation advisor • Develop an implementation glossary • Identify and prepare champions • Identify early adopters • Inform local opinion leaders • Build a coalition • Assess for readiness and identify barriers and facilitators • Promote network weaving • Develop and organize quality monitoring systems • Develop and implement tools for quality monitoring
Aim 1: Clinical system development: define scope of implementation of AW-Shift[a] into a Connected Care model	• Develop a formal implementation blueprint • Build a coalition • Conduct educational meetings • Distribute educational materials • Promote adaptability • Prepare patients or consumers to be active participants • Involve patients or consumers and family members • Obtain and use patients or consumers and family feedback • Shadow other experts • Use data warehousing techniques
Aim 2: Rapid cycle quality improvement: rapid quality improvement assessment of the implementation plan	• Facilitation • Conduct educational meetings • Conduct cyclical small tests of change • Provide ongoing consultation • Provide local technical assistance • Provide clinical supervision • Organize clinician implementation team meetings • Prepare patients or consumers to be active participants • Involve patients or consumers and family members • Purposely reexamine the implementation • Obtain and use patients or consumers and family feedback • Tailor strategies • Remind clinicians • Intervene with patients or consumers to enhance uptake and adherence • Shadow other experts • Facilitate relay of clinical data to providers • Use data warehousing techniques
Aim 3: Hybrid pilot clinical and implementation trial: randomized controlled trial to test whether AW-Shift system adds value to clinical care of people with SCI/D[b]	• Stage implementation scale up • Provide ongoing consultation • Provide local technical assistance • Provide clinical supervision • Remind clinicians • Recruit, designate, and train for leadership • Use data warehousing techniques • Obtain formal commitments

[a]AW-Shift: Assisted Weight-Shift.

[b]SCI/D: spinal cord injuries and related disorders.

Results

This study was funded in January 2023, and the IRB approval for Aim 1 of the study was December 5, 2022. We have recruited 6 participants into the clinician arm of our Aim 1 qualitative study as of manuscript submission. Expected results for Aim 1 to be published in winter 2024.

Discussion

Expected Outcome

Pressure mapping performed in rehabilitation clinics can effectively determine appropriate equipment and positioning in a wheelchair [42-44], but the translation of the same information from daily life into clinical care has not been previously tested. The day-to-day uncertainty of ulceration leads to patient

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appointments simply to “be mapped” as a preventative action often involving long distances and, sometimes, with an active pressure injury. A system such as AW-Shift can be integrated into a connected care model to allow for the integration of real-world data into the clinical practice of wheelchair users with SCI/D. The system has the potential to enhance the prevention of pressure injuries. Our mapping system has the ability to address and correct the contributors to pressure ulceration that have been observed in seating and mobility clinics: undetected cushion failures; caregivers who are unexpectedly late or absent, leaving the patient in the chair longer than necessary; frequent caregiver turnover; inexperienced caregivers; and caregivers who struggle with positioning the patient. AW-Shift can provide meaningful information about the daily life of people with SCI/D to the patient, caregivers, and clinicians to significantly improve the management of patient needs.

This project will demonstrate the ability to use an mHealth solution for improvement in pressure injury clinical outcomes. The success of this project will have sustained, powerful influence in the field of SCI/D through enhanced evidence of pressure injury risks that are present in a wheelchair user’s daily routine and environment that are not identifiable through routine, in-person evaluations in the clinic. It will further demonstrate the opportunity for the clinician and individual with SCI/D to work together to plan effective strategies for more expeditious interventions.

We hypothesize that an enhanced connected model of care using remote monitoring of pressure management will result in improved clinical outcomes (wound recurrence, early identification of wounds, and wound healing) for adults with SCI at high risk for pressure injury recurrence. We have performed extensive studies assessing the acceptability, usability, and efficacy of the AW-Shift system with adults with SCI/D. We now need to partner with patients and clinicians (therapists) to capture seating pressure information during daily life to inform clinical visits for individualized seating and skin health recommendations. On the basis of our projects funded by DoD, NIH, and Veterans Administration, we know that adults with SCI/D and therapists who treat them have the strong desire for a visual system and expanded access to data from daily life. Changing current clinical practices will require engagement and collaboration with providers and patients about what information is critical and how it should be used with clinical guidelines. This project will expand upon our previous study to move the AW-Shift system into routine clinical care, which was a high desire of adults with SCI/D for improved individualized care plans to prevent pressure injuries.

Acknowledgments

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Conflicts of Interest

TLV-D, MMM, and Mayo Clinic have a financial interest related to this study. MMM and TLV-D are inventors of the Assisted Weight-Shift system. The previous study reported in this paper has been reviewed by the University of Minnesota and Mayo Clinic Conflict of Interest Review Board and has been conducted in compliance with both policies.

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Abbreviations

AW-Shift: Assisted Weight-Shift
CFIR: Consolidated Framework for Implementation Research
DoD: Department of Defense
IRB: institutional review board
mHealth: mobile health
NIH: National Institute of Health
PI: principal investigator
REDCap: Research Electronic Data Capture
SCI/D: spinal cord injuries and related disorders
SCI: spinal cord injury

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Protocol

Evaluating the Feasibility, Acceptance, and Beneficial Effects of Online Occupational Therapy for Post–COVID-19 Condition: Protocol for a Randomized Controlled Trial (ErgoLoCo Study)

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Abstract

Background: Post–COVID-19 syndrome (PCS; also known as “long COVID”) is a relatively novel disease comprising physical, psychological, and cognitive complaints persisting several weeks to months after acute infection with SARS-CoV-2. Approximately 10% of patients with COVID-19 are affected by long-term symptoms. However, effective treatment strategies are lacking. The ErgoLoCo (Occupational Therapy [Ergotherapie] for Long COVID) study was designed to develop and evaluate a novel occupational therapy (OT) concept of online delivery of therapy for long COVID.

Objective: The primary study objective is to assess the feasibility of the online OT intervention in PCS. Secondary aims include the evaluation of online OT concerning cognitive problems, occupational performance, and social participation.

Methods: This randomized controlled interventional pilot study involves parallel mixed methods process analyses and a realist evaluation approach. A total of 80 clients with PCS aged at least 16 years will be recruited into two interventional groups. The control cohort (watch and wait) comprises 80 clients with long COVID. Treatment is provided through teletherapy (n=40) or delivery of prerecorded videos (n=40) using the same standardized OT concept twice weekly over 12 weeks. Analyses of quantitative questionnaires and qualitative interviews based on the theoretical framework of acceptability will be performed to

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assess feasibility. Focus group meetings will be used to assess how acceptable and helpful the intervention was to the participating occupational therapists. Standardized tests will be used to assess the initial efficacy of the intervention on neurocognitive performance; limitations in mobility, self-care, and everyday activities; pain; disabilities; quality of life (QoL); social participation; and anxiety and depression in PCS, and the possible effects of online OT on these complaints.

Results: The German Ministry of Education and Research provided funding for this research in March 2022. Data collection took place from October 2022 to August 31, 2023. Data analysis will be completed by the end of April 2024. We anticipate publishing the results in the fall of 2024.

Conclusions: Despite the enormous clinical need, effective and scalable treatment options for OT clients who have PCS remain scarce. The ErgoLoCo study will assess whether online-delivered OT is a feasible treatment approach in PCS. Furthermore, this study will assess the effect of the intervention on cognitive symptoms, QoL, and occupational performance and participation in everyday life. Particular emphasis will be placed on the experiences of clients and occupational therapists with digitally delivered OT. This study will pave the way for novel and effective treatment strategies in PCS.

Trial Registration: German Clinical Trial Registry DRKS00029990; https://drks.de/search/de/trial/DRKS00029990

International Registered Report Identifier (IRRID): PRR1-10.2196/50230

(JMIR Res Protoc 2024;13:e50230) doi:10.2196/50230

KEYWORDS

SARS-CoV-2; COVID-19; post COVID-19 condition; pandemic; occupational therapy; cognitive deficits; online treatment; long Covid; RCT; randomized controlled trial; controlled trials; internet based; digital health; digital intervention; video; prerecorded; feasibility; acceptability; effectiveness; online therapy

Introduction

Background

Post–COVID-19 syndrome (PCS; also known as post–COVID-19 condition or long COVID) is defined as chronic health challenges persisting for more than 4 weeks after an acute SARS-CoV-2 infection. PCS affects a substantial proportion of COVID-19 survivors [1], with an estimated risk of approximately 10% after each infection [2-5]. PCS is a heterogeneous condition that can include symptoms of respiratory impairment, prolonged fatigue, and neurocognitive sequelae [6-8]. Systemic, endothelial, and neuroinflammatory processes, along with reactivation of latent pathogens are suspected contributors to PCS development. However, the immunological and pathological mechanisms of PCS remain unclear and specific treatment options are scarce [9]. Importantly, due to the large number of individuals faced with this condition, PCS considerably impacts communities and health care systems worldwide [10].

Patients with PCS report substantial limitations in their everyday lives [11]. Classic PCS symptoms include problems in concentration and cognitive function, often described as “brain fog,” fatigue, and postexertional malaise. Individuals living with PCS often struggle to participate in everyday contexts such as in work, leisure, self-care, and social interaction [7,12]. Therapy guidelines such as the British National Institute for Health and Care Excellence recommend an integrative, multidisciplinary approach to treating PCS, aiming at symptom management and reduction of functional impairments [11]. Occupational therapy (OT) is central in this multidisciplinary approach [13-15], as it has been shown to improve quality of life (QoL) for individuals with PCS by enabling self-management and coping strategies and accelerating the return to relevant everyday activities in self-care, productivity, and leisure [16].

In most fields of medicine, isolation measures during the COVID-19 pandemic led to further development of online care provision [17-19]. Digital treatment strategies hold great promise for individuals with PCS, who often experience impaired mobility, as these strategies facilitate therapy access and adherence [20].

The ErgoLoCo (Occupational Therapy [Ergotherapie] for Long COVID) study will evaluate the role of digitally delivered OT treatment strategies for clients with PCS. This unblinded, randomized pilot study tests the feasibility and effect of a digitally delivered 12-week online OT program in PCS. The program is delivered either via personal digital visit sessions (teletherapy) or through prerecorded videos (video therapy), focusing on symptom management for cognitive impairment in PCS and improvement of occupational performance in relevant activities of daily life. Our purely digital and scalable approach may help bridge health care gaps and facilitate treatment access for clients with PCS.

Objectives

This pilot study hypothesizes that an online-administered OT treatment program for individuals affected by PCS is a suitable form of intervention to reduce symptoms and improve occupational performance and QoL. The primary objective is to assess the feasibility of the ErgoLoCo concept by collecting data on participation rates, participant satisfaction, and experience. Secondary aims include analyzing changes in cognitive performance, occupational performance, QoL, and social participation. We here outline the study design and protocol according to the CONSORT (Consolidated Statement of Reporting Trials) guidelines [21].

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Methods

Study Setting

The ErgoLoCo study centers are located in Lower Saxony, Germany, at the Department for Rheumatology and Immunology of Hannover Medical School and the Department of General Practice of the University Medical Center Goettingen. Data analyses will be conducted at the Ostfalia University of Applied Sciences in Braunschweig. Lower Saxony is Germany's second-largest federal state with approximately 8 million residents [22]. The number of people affected by PCS in this federal state is unclear. Based on data from a study on cases of illness and death associated with COVID-19 in Lower Saxony, approximately 3,528,782 people had experienced a reported infection with SARS-CoV-2 by the end of 2022 [23].

Study Design

This pilot study is a 12-week unblinded randomized controlled trial with two intervention groups (group 1: teletherapy/live online; group 2: video on demand) in comparison to a control group (group 3: watch and wait). The study is designed to evaluate feasibility and acceptability, as well as to obtain preliminary evidence on efficacy. The observational period comprises 24 weeks: a baseline assessment (T0) and a 12-week intervention phase with subsequent online questionnaire and testing (T1). At week 24 (T2), study participants will be asked to fill out questionnaires and participate in interviews, and a second round of online testing will be conducted. Given the digital nature of ErgoLoCo, the entire study process, including enrollment, treatment, interviews, and testing, will be performed through online visits.

Participants

The study will enroll individuals 16 years and older with PCS symptoms persisting at least 4 weeks after confirmed SARS-CoV-2 infection. We will enroll a convenience sample of 120-150 participants.

Eligibility Criteria

Inclusion criteria are as follows: (1) 16 years or older, (2) affected by persisting health problems beyond 4 weeks after SARS-CoV-2 infection (confirmed either by polymerase chain reaction or rapid antigen testing), (3) personal reporting of subjective cognitive symptoms such as brain fog and fatigue ≥5/10 on a Likert scale, (4) having access to an appropriate technical device to participate in the intervention (eg, PC, tablet, or smartphone with internet access), and (5) provision of written informed consent to participate in the study (in clients <18 years of age, additional written consent is to be provided by legal guardians). Individuals not meeting the above-mentioned inclusion criteria and those lacking the willingness or ability to complete the program consisting of either teletherapy or video sessions will be excluded from the study.

Recruitment

Potential participants will be recruited via the homepage of participating hospitals and research departments and a prior observational study on PCS (DEFEAT Corona study) [24,25]. Moreover, local private practices and clinics throughout Northern Germany and beyond will be asked to share information on the study with affected clients in their care. Clients interested in participating in the study are asked to register on the DEFEAT study webpage [25].

Participant Screening

Study eligibility will be evaluated by online questionnaires on self-perceived PCS-related cognitive impairment (eg, brain fog and fatigue scores ≥5/10 or higher on a Likert scale). Eligible participants will receive comprehensive study information as well as an invitation to book an online appointment by email. Upon the first digital visit, study staff will provide further information, discuss possible questions, and recheck eligibility criteria. After obtaining written informed consent by digital signature on an online study inclusion form (including signature of a legal guardian for participants below the age of 18 years), data on age, gender, and health status are collected. Furthermore, information on social participation and subjective well-being are obtained. Participants are also tested for cognitive functions and impairments in daily life (Table 1).

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Table 1. Schedule for enrollment and assessment.

Stage and outcome	Instrument	Time point
Eligibility screen	Online questionnaire	Enrollment
Informed consent	Digital visit	Enrollment
Randomization	Digital visit	Enrollment
Mixed methods study on acceptability and feasibility (primary outcome)		
Acceptance and feasibility of the online program	Semistructured interviews with 12 participants of each treatment group	Week 6 and week 12
Acceptance and feasibility of the online program	Questionnaire assessing 35 Likert-scaled items developed based on the theoretical framework of acceptability in all participants [26]	Week 24
Acceptance and feasibility of the online program	Focus group meeting notes on acceptance and feasibility of the online program by occupational therapists providing live-online sessions	Week 12
Neurocognitive and occupational impairments (secondary outcomes)		
Self-perception of occupational performance in everyday life	Canadian Occupational Performance Measure [27]	Enrollment and week 12
Memory and cognitive impairment	Wilde-Intelligence test-2, modules MF[a] and ER[b] [28]	Enrollment, week 12, and week 24
Impairment in daily life activities, family and social life, stress, and sexual activity	Index for the Assessment of Health Impairments [29]	Enrollment, week 12, and week 24
Physical, mental, and social effects of neurological conditions	Quality of Life in Neurological Disorders [30]	Enrollment, week 12, and week 24
Deficits in concentration, attention [31], and mental speed	D2 test of attention-revised [31]	Enrollment, week 12, and week 24
Mobility, self-care, usual activities, pain, disabilities, anxiety, and depression	EQ-5D-5L [32]	Enrollment, week 12, and week 24
General and health information		
Date of enrollment, demographic data (eg, age, sex, education level, residential and housing status, care level, disabilities, migration status)	Online questionnaire	Enrollment
Preexisting health conditions, medication, smoking, SARS-CoV-2 infections	Online questionnaire	Enrollment
Vaccination status (time point and type of COVID-19 vaccinations)	Online questionnaire	Enrollment

[a]MF: memory function.

[b]ER: embedded math exercises.

Randomization

Directly after enrollment, urn randomization will be carried out to ensure a balanced distribution of the participants across groups, as shown in Figure 1. Randomization will be performed by an independent study group member not involved in the study design or OT delivery.

Figure 1. Process flowchart of the ErgoLoCo study. OT: occupational therapy.

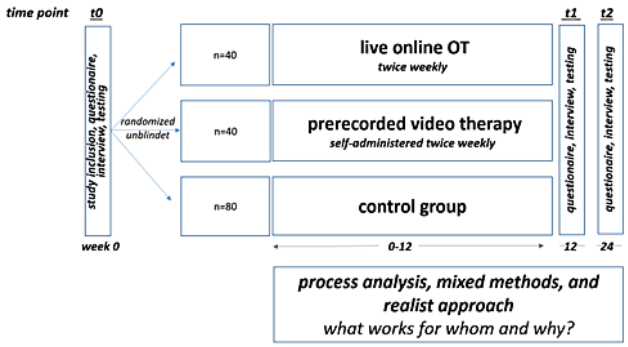

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Intervention

The OT concept was designed using the Medical Research Council Framework, ensuring evidence-based and theory-based OT-specific approaches [33]. These approaches will be identified using a literature review, including the English, Dutch, and German literature. Furthermore, we will include stakeholder experiences in treating clients with PCS in inpatient and outpatient settings in Germany, Austria, and Switzerland. The OT concept will include 24 30-minute standardized therapy sessions. Each session will be delivered twice a week over 12 weeks. Therapy sessions consist of OT-specific instructions for managing PCS symptoms, which will be tailored to individual aims defined for each OT recipient upon entering and throughout the program. Participants will receive an accompanying workbook with materials to support therapy transfer into everyday life.

Intervention Delivery

After randomization, each participant is interviewed by an occupational therapist to assess occupational performance challenges in their everyday occupations, using the German version of the Canadian Occupational Performance Measure (COPM) [27]. The COPM has been validated in various OT intervention studies, which provides metrics on changes in occupational performance, satisfaction and importance, and enhancing transparency in OT outcomes [26,34-37].

The teletherapy/live online group (group 1; n=40) will undergo online OT by a professional occupational therapist via teletherapy twice week using the medical communication and conference software medflex, which ensures data security compliant with the German General Data Protection Guidelines, Datenschutz-Grundverordnung. Video group participants (group 2; n=40) will receive digital OT through prerecorded videos twice weekly. Group 2 participants will receive emails every 2 weeks with links to four online videos illustrating the next intervention module. The participants in this group are asked to watch two videos per week. Intervention groups 1 and 2 will receive both a printed and digital version of a workbook that visualizes and supports all tasks performed throughout the program. The control group (group 3; n=80) is a watch-and-wait group, and these participants will receive the video-on-demand-materials after study completion.

Outcomes

Primary Study End Points: Feasibility and Acceptability

To assess feasibility and acceptability, we will use a realist evaluation approach [38]. Realist evaluation emphasizes the interplay of contexts through social interactions that engage with the intervention. In alignment with this method, this study aims to assess the effects and influences of the digitally provided OT program on the health status of the study participants and the feasibility and acceptance of both digital approaches from the user's perspective. Therefore, we will collect quantitative data regarding participant rates in the follow-up examinations, participant surveys, and qualitative in-depth interviews about the participants' participation experiences.

All participants in both intervention groups (n=80) will be asked via email to complete an online questionnaire with four closed (Likert-scaled) questions and two open questions on handling the digital intervention after each of the six intervention modules. This approach will enable the individual evaluation of different program parts. Questions include: "Were you able to apply the content of the last module in your everyday life?" "What was particularly beneficial for you in the last module?" and "How satisfied were you with the last module?".

Moreover, all participants will be asked to complete an online questionnaire including 35 Likert-scaled items developed within discursive circles by research team members based on the theoretical framework of acceptability (TFA) [39,40]. The TFA proposes a theoretical framework for assessing the acceptability of health interventions and consists of seven component constructs: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy [40].

To enrich quantitative data with the first-hand experiences of the study participants, a subsample of at least 12 study participants of intervention groups 1 and 2 will be invited to share their personal experiences regarding the acceptability and feasibility of the program at week 6 and week 12. These semistructured interviews will last approximately 45 to 60 minutes.

To capture the occupational therapists' experiences with OT teletherapy, an online focus group interview will be conducted with all occupational therapists working in the study (N=8). A moderation guide will be developed to help facilitate the engagement of participants in a discussion on the feasibility of the treatment concept, acceptance, and recommendations for further intervention development. All conducted interviews, as well as the audio-recorded focus group meeting, will be transcribed according to the simplified rules of Dresing and Pehl [41] and will be analyzed using thematic content analysis [42] by a team of three researchers.

Secondary End Points

Secondary outcomes will involve the analysis of possible efficacy outcomes such as cognitive performance, health-related QoL, social participation, occupational performance and satisfaction in daily life, and memory and concentration abilities. All measurements used for data collection and the time points at which they will be collected are depicted in Table 1.

Analytical Approach

Power and Sample Size

The main focus of this study is to assess the feasibility and acceptability of the intervention. Therefore, efficacy analyses with regard to secondary outcomes will only be exploratory. The pilot study is not sufficiently powered to evaluate the effectiveness of the intervention. However, exploratory analyses will address potential differences in outcomes of cognitive function, QoL, occupational performance, and social participation between the intervention and control groups. No previous reports on OT concepts in PCS or online OT in general were available that could have been used to estimate sample

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sizes. As current practice standards suggest that formal sample size calculations are unsuitable for feasibility trials, the convenience sample of 120-150 participants was selected pragmatically [43].

Statistical Analysis Plan

All quantitative data will be prepared using Microsoft Excel or SPSS software and analyzed with R statistical packages. Data visualizations will be created using GraphPad Prism and R software tools. Analysis of the following items is planned from the time points 0 weeks (T0), 12 weeks (T1), and 24 weeks (T2): impairments in daily life activities, family and social life, stress, and sexual activity, and deficits in concentration, attention, and mental speed, particularly focusing on visual attention, physical, mental, and social symptoms of PCS, including concentration, attention, mental speed, mobility, self-care, usual activities, pain, disabilities, anxiety, and depression. An intention-to-treat approach will be used. Estimates and 95% CIs will be computed for the mean, median, and selected lower quantiles. To compare time points, *t*, Wilcoxon-Mann-Whitney, and Kolmogorov-Smirnov tests will be applied, including corrections for multiple testing. Scores derived from questionnaires will be analyzed concerning change over time using *t* and Wilcoxon-Mann-Whitney tests, including corrections for multiple testing. Effect sizes will also be computed. Furthermore, at T0, T1, and T2, we will assess whether certain factors such as age or education influence the feasibility of therapy experiences using *t*, Wilcoxon-Mann-Whitney, and Fisher exact tests as appropriate.

Analysis of Qualitative Data

All interviews and the focus group will be audio-recorded, pseudonymized, transcribed verbatim, and analyzed using thematic content analysis following the approach of Kuckartz and Rädiker [42], assisted by the MAXQDA analysis software.

Data Management

All assessment measures will be completed online. The data collected will be categorized in four data sets: (1) personal data such as name and email address; (2) sociodemographic data (eg, clinical characterization, age, gender, migration background, health status, and symptoms), as well as attitudes toward vaccination and experiences with COVID-19 vaccination; (3) test results (scores in cognitive assessments and occupational performance assessments); and (4) qualitative data such as interview transcripts and written interview documentation. Data from the first 3 categories will be incorporated into two independent databases, which are stored separately for data protection reasons.

Ethical Considerations

The study is registered at the German Clinical Trial Register (DRKS00029990), an approved primary study registry within the World Health Organization network, and has been reviewed by the institutional review boards of participating sites (eg, Hannover Medical School; DEFEAT Corona No. 9948_BO_K_2021). The study is designed as an interventional online pilot study. Interested participants will obtain information about participation in advance on the internet and will be fully informed personally by a study team member about possible benefits and risks of study participation before inclusion. Written informed consent will be obtained from all study participants (as well as from their legal guardians for those younger than 18 years). Additionally, each participant will receive detailed written information on the study and data management procedures. All participants will be informed that their study participation is entirely voluntary and that they can withdraw participation consent at any time without disclosing reasons. Contact information to reach out to the study team for questions via email, telephone, or online meetings at any point during the study will be provided upon enrollment. All data will be collected in pseudonymized form and designated data safety measures have been developed to ensure the privacy of each participant. Personal data will be separated from all other collected data and stored in encrypted form. Qualitative data will be exclusively processed at the University Medical Center Göttingen, and other project team members cannot access these data. Following the transcription of interview notes, transcripts will be pseudonymized and any information (such as location and names of participants) that could enable retrograde identification will be eliminated (ensuring factual anonymization). Audio raw data/video data will be subsequently destroyed. Transcripts will be stored on digital media with password protection in a lockable file cabinet. If a participant does not consent to the use of factually anonymized data for further research projects, transcripts will be destroyed after 10 years. Study participation can be realized entirely from home without any physical or infection risk.

Results

In this study, we aim to evaluate the feasibility of digital OT as a treatment for clients with PCS. Exploratory analyses will address possible cognitive and performance improvements, QoL, and social participation. The German Ministry of Education and Research provided funding for this research in March 2022 (FKZ 01EP2103A). Data collection is scheduled to take place from October 2022 to August 2023, followed by data analysis between September 2023 and April 2024. We anticipate publishing the results in the fall of 2024.

Discussion

The ErgoLoCo study is a randomized controlled interventional pilot study designed to gain insight into new therapy options for people affected by long COVID. The intervention was developed to improve occupational performance in relevant everyday occupations and the self-management of PCS-related challenges. As a pilot study, ErgoLoCo is not powered to show treatment efficacy. However, it will provide the first insights into the acceptance and feasibility of a novel OT intervention. The mixed methods approach will provide detailed information on which parts of the intervention will likely impact the well-being of clients with PCS.

Although the current study focuses on long COVID, other medical conditions with similar symptoms, such as myalgic encephalomyelitis or chronic fatigue syndrome, may also benefit from our approach in the future.

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A short description of the ErgoLoCo study design will be included in each publication by the study group and this protocol will be referenced. If changes in the study design are necessary, these will be brought to the attention of the institutional review board and will be amended to the study protocol.

The ErgoLoCo pilot study will contribute to developing treatment strategies in PCS, an emerging disease with increasing prevalence, strong socioeconomic impact, and high clinical need.

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The authors would like to thank all study participants recruited thus far for their participation. The authors also thank the entire DEFEAT Corona team for access to the DEFEAT Corona cohort and database. This study is funded by the German Ministry of Education and Research (FKZ 01EP2103A). The funder had no influence on the design of this study.

Data Availability

The results of this study will be published, preferably in open access journals. Further data and information can be obtained by the study team upon reasonable request.

Authors' Contributions

All authors designed and coauthored the protocol substantially. The study was conceptualized by ADJ, FM, CH, and SS, and CM designed the qualitative study component. FK and SK were responsible for biometric supervision. AS, DS, SR, and SH managed the data of the study. CH, AS, and ADJ were responsible for participant recruitment. The first draft of the manuscript was written by CM and CH, and all authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Statement of Reporting Trials
COPM: Canadian Occupational Performance Measure
ErgoLoCo: Occupational Therapy (Ergotherapie) for Long COVID
OT: occupational therapy
PCS: post–COVID-19 syndrome
QoL: quality of life
TFA: theoretical framework of acceptability

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Protocol

Feasibility and Preliminary Efficacy of α–Calcium Sulfate Hemihydrate in Socket Preservation: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Tooth extraction procedures often lead to bone resorption, which can have adverse effects on the dimensions of the alveolar ridge. Research has shown that socket preservation techniques using bone graft substitutes can effectively minimize early bone loss in such cases. α–calcium sulfate hemihydrate (α-CSH) has garnered significant attention as a potential bone graft material due to its favorable properties, including osteoconductivity, angiogenic potential, and biocompatibility. Considering these facts, we developed a preliminary protocol for applying α-CSH in addressing alveolar bone loss following tooth extraction.

Objective: This research's general objective is to evaluate the feasibility and initial effectiveness of α-CSH as bone-inducing graft material for socket preservation after tooth extraction.

Methods: This preliminary clinical trial will involve 30 fresh extraction sockets from individuals aged 18-35 years. The participants will be divided into 2 groups: one group will receive α-CSH graft material after tooth extraction for socket preservation, while the other group will not receive any graft material. Throughout the study, the participants will be closely monitored for safety measures, which will include clinical examinations, radiographic imaging, and blood tests. Radiographic imaging will be used extensively to assist the progress of bone formation.

Results: The study commenced enrollment in August 2022 and is scheduled to conclude post assessments and analyses by the end of 2023. The results of the study are anticipated to be accessible in late 2024.

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Conclusions: This clinical study represents the initial investigation in humans to assess the feasibility and efficacy of α-CSH in alveolar bone regeneration. We hypothesize that the inclusion of α-CSH can greatly expedite the process of bone formation within fresh sockets, resulting in a swift restoration of bone height without the disadvantages associated with harvesting autogenous bone graft.

Trial Registration: Indonesia Registry Center INA-D02FAHP; https://tinyurl.com/2jnf6n3s

International Registered Report Identifier (IRRID): DERR1-10.2196/49922

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KEYWORDS

α–calcium sulfate hemihydrate; α-CSH; bone graft; bone regeneration; socket preservation; pilot; feasibility; efficacy; impacted tooth; tooth extraction; radiographic imaging; bone; dentist; dentistry; dental; bone resorption; graft; bone loss; alveolar bone; regeneration

Introduction

Bone resorption is an ongoing and irreversible process that leads to changes in both hard and soft tissue dimensions, particularly occurring immediately after tooth extraction [1,2]. Various factors, such as chronic periodontitis, alveolar cleft, prolonged edentulous state, and tooth morphology, can contribute to alveolar bone resorption [3,4]. In addition, anatomical, prosthetic, functional, and metabolic factors have been identified as influencing factors in alveolar ridge resorption [5,6]. A previous study reported an average of 50% vertical resorption and 20% horizontal bone resorption occurring 8 weeks after tooth extraction [7]. Considering these findings, the dimensional changes in the alveolar bone following tooth loss raise significant concerns in oral rehabilitation [6,7].

In recent years, there has been a growing emphasis on developing techniques to preserve alveolar bone volume following tooth extraction [2,6,8]. Socket preservation procedures are recommended when tooth extraction significantly impacts the height of the buccal bone [9,10]. These techniques aim to minimize the biological resorption of the buccal bone, which facilitates implant placement and reduces the need for future bone augmentation procedures. Studies have shown that socket preservation techniques lead to greater bone volume compared to procedures without socket preservation [8,11]. In the future, sites that undergo grafting after tooth extraction are likely to require fewer bone augmentation treatments, particularly if implantation is planned [1,10]. Various biomaterials have been used to graft fresh extraction sockets, and most have demonstrated positive clinical outcomes [8,12,13].

α–calcium sulfate hemihydrate (α-CSH) has gained significant recognition as a bone graft substitute material with outstanding biocompatibility [14,15]. It has successfully repaired various bone defects, including resorbed maxilla, postextraction socket preservation, and significant segmental bone defects [14-16]. The α-CSH is regarded as a leading bone replacement material due to its ability to promote bone ingrowth and its resemblance to autologous bone [14,15,17]. Notably, it exhibits excellent workability, high self-setting strength, impressive osteoconduction properties, and the capacity to induce hemostasis and angiogenesis [14,17,18]. Despite these remarkable biological characteristics, this material still has to function better in clinical settings [15]. This study aims to evaluate the feasibility and preliminary efficacy of α-CSH as a bone-inducing graft material in socket preservation procedures following tooth extraction. Our hypothesis suggests that α-CSH will serve as a safe, efficient, and effective alternative to conventional autografts, as its regenerative properties complement its osteoconductive nature.

Methods

Ethical Considerations

The clinical trial was approved by the Ethics and Research Committee of Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, with code number 504/UN4.6.4.5.31/PP36/2022. The study was designed according to the principles of the Declaration of Helsinki and will conform to the CONSORT (Consolidated Standards on Reporting Trials) statement [19].

Before participating in the study, all individuals must provide written informed consent, signifying their voluntary agreement to participate. Participants will have the opportunity to seek clarification on any aspects of the study and review all procedures, data collection methods, and data analysis protocols before signing the consent form. The informed consent document will comprehensively outline the research's purpose, procedures, potential risks and benefits, as well as the confidentiality and security measures pertaining to the collected data. Participants will be explicitly informed of their entitlement to withdraw from the study at any point without experiencing any adverse consequences on their treatment.

Strict privacy and security protocols were implemented, and all study data were stored in a password-protected secure database. Each participant will receive a unique study code, and data sharing with operators and research assessors will be done in an encrypted format that maintains patient privacy. Participants will not be provided with any form of remuneration for their involvement in the study. Nonetheless, they will receive complimentary examination and treatment related to the trial without incurring any costs.

Recruitment

Figure 1 presents a simplified diagram that outlines the study protocol based on the CONSORT diagram. The recruitment of participants and the implementation of the trial will take place

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at Hasanuddin Dental Hospital, Makassar, Indonesia. This hospital is the primary institution in the designated region that handles the majority of oral surgery cases. To identify eligible participants, all individuals presenting to the Department of Oral and Maxillofacial Surgery with a chief complaint related to the mandibular third molar will undergo screening conducted by the study investigators.

Before enrollment, all participants will be provided with detailed information regarding the risks and potential complications associated with the procedure, such as bleeding, infection, cheek asymmetry, parotid duct injury, potential injury to facial nerve branches, and the unlikely event of nonclosure. Informed consent will be obtained from each participant after ensuring their understanding and agreement.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart diagram. α-CSH: α–calcium sulfate hemihydrate; PPD: probing pocket depth.

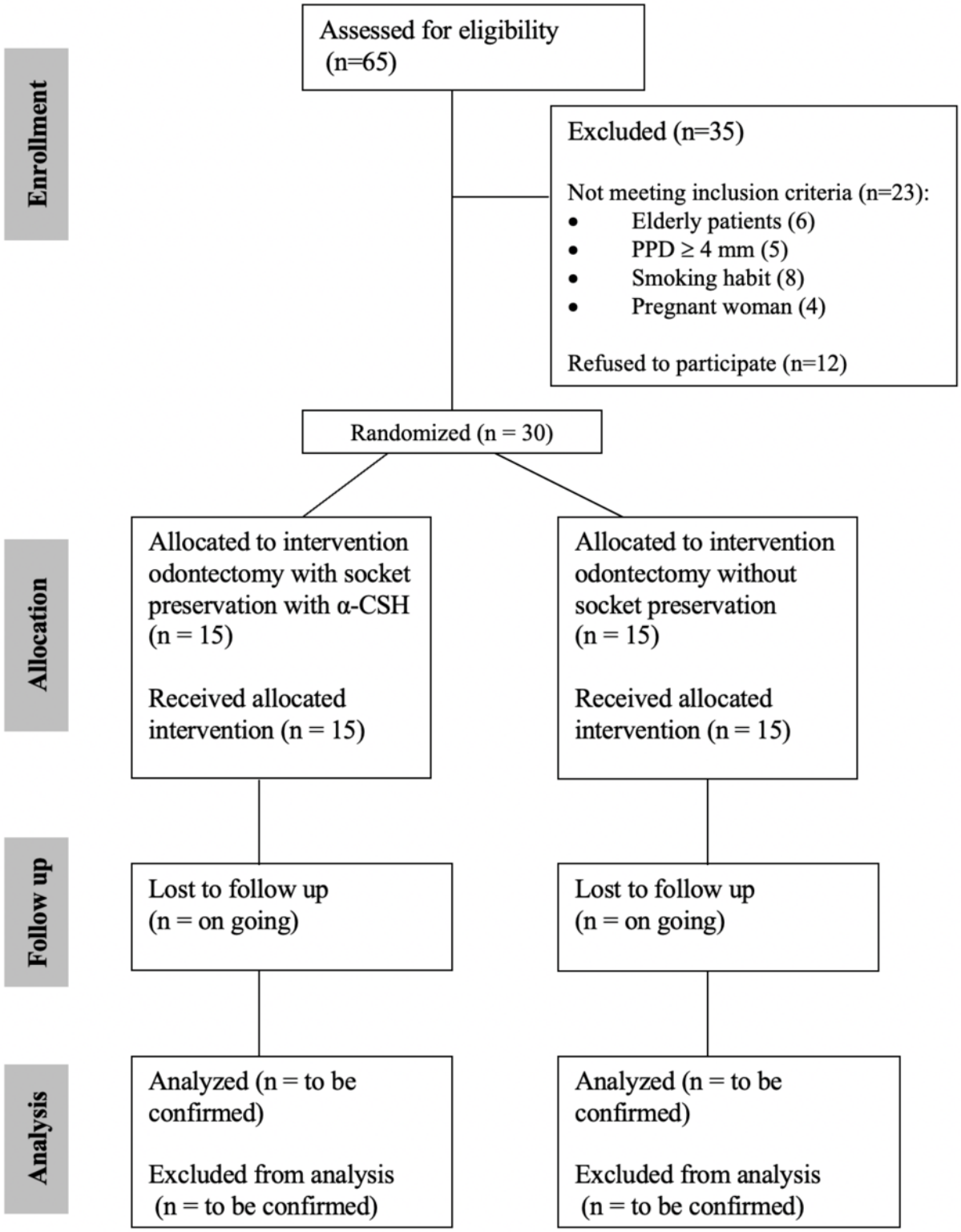

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Study Design

This prospective control clinical trial will be conducted at a single center and will involve 30 targeted extraction sockets after the removal of impacted mandibular third molars. This case is chosen as it represents a common scenario requiring extraction and often involving the removal of a significant amount of bone, making it an ideal model for studying human alveolar bone loss for socket preservation. The study aims to evaluate the efficacy of a high-purity α-CSH bioceramic ($CaSO_4 \cdot 0.5H_2O$), synthesized from calcium sulfate dihydrate (CSD) without the use of chemical reagents, as a bone graft material in the alveolar bone loss case.

The 30 extraction sockets will be randomly assigned into 2 groups: 15 will receive α-CSH as a bone graft, while the other 15 will not receive any graft material. The main end point will be evaluated 6 months into the procedure. During follow-up visits, any adverse events or serious adverse events will be carefully documented, and clinical assessments will be conducted as specified in the "intervention section." All patients will undergo regular monitoring through clinical examinations, radiographs, lab tests, and any additional necessary procedures. Ultimately, the study will publish a comprehensive report on the feasibility and potential efficacy of the α-CSH approach in promoting bone formation, regardless of the outcome.

Inclusion and Exclusion Criteria

To be eligible for participation in this clinical trial, patients must meet specific inclusion criteria, which are as follows: being a healthy male or female; aged 18-35 years old; providing written informed consent to participate in the trial; having an average blood count within normal range; presenting with impacted mandibular third molars that require extraction. The diagnostic indications for tooth extractions include caries, orthodontic, and preventive measures. In particular, based on the relation of the impacted mandibular third molar to the ramus, the impacted teeth will be restricted to Class I and Class II as per the Pell and Gregory classification [20,21]. Patients had to demonstrate good oral hygiene, maintain healthy periodontium, and have a clinical attachment loss score of ≤2 mm and a probing pocket depth (PPD) of <4 mm. Clinical and radiographic images taken before the operation are depicted in Figure 2.

Figure 2. Preoperative image of the clinical and radiographic condition of the patients.

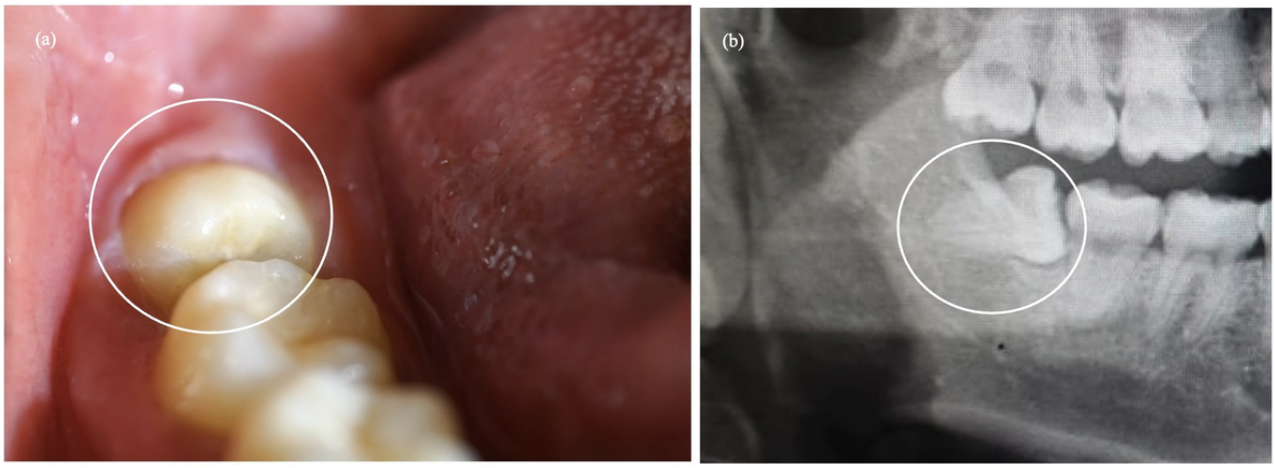

Patients will be disqualified from participating in the study if they meet any of the following exclusion criteria: impacted teeth concerning their position relative to the occlusal plane fall within the Pell and Gregory classification's level C category [20,21]; presence of uncontrolled or untreated periodontal disease; existence of acute abscesses or active infections that occur close to the targeted surgical site; presence of systemic diseases or systemic/local infections; recent receipt of chemotherapy, radiotherapy, immunosuppressant medications, or anticoagulants that could potentially interfere with the healing process; previous administration of bone growth–inducing substances, malnutrition, or current active influenza; regular smoking habit of more than 10 cigarettes per day; being pregnant, breastfeeding, or participating in a fertilization program.

Withdrawal of Participants

Participants have the right to withdraw from the study at any time and for any reason without facing any negative consequences. In cases where a participant has urgent medical needs, the researcher may choose to exclude them from further participation in the study. Participants who choose to discontinue the study before completing all surgical procedures and follow-up visits will be considered dropouts.

Material Preparations

The high-purity α-CSH bioceramic was synthesized from calcium sulfate dihydrate (Acros Organics, Morris Plains, NJ) using a microwave irradiation technique, following the methodology outlined in our previous study [14,17]. In brief, 2 g of CSD powder were mixed with 10 mL of deionized water. Following this procedure, the resulting mixture, along with a magnetic stirring bar, was placed in a 55-ml Teflon pressure tube at approximately 350 pounds per square inch (psi). The mixture was then subjected to microwave irradiation at 800 watts and 160 °C for 10 minutes. After synthesis, the sample was filtered, washed with ethanol, then dried in an oven at 60 °C for 8 hours, and finally ground into a powder.

Interventions

Prior to the surgical procedures, a preoperative panoramic x-ray and cone-beam computed tomography (CBCT) scan will be conducted to evaluate the tooth position and the surrounding

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bone structure. A complete blood count (CBC) will also be performed to ensure the safety of all patients undergoing surgical procedures and receiving bone grafts. Furthermore, the PPD score will be measured using a periodontal probe (BPWHO: Single, Osung, South Korea) to evaluate the periodontal condition. Patients exhibiting a significant amount of calculus will be referred for scaling and root planning procedures. Skilled oral and maxillofacial surgeons will carry out the interventions following standardized operating procedures. Video demonstrating the clinical and surgical procedures will be presented during the initial calibration meeting to ensure consistency across all operators.

The extraction of mandibular third molars will be carried out in a sterile environment under local anesthesia, minimizing damage to both the soft tissue (gingiva) and the hard tissue up to the crest of the bone. The surgery will adhere to the principle of minimally invasive techniques, using a split technique. To preserve the integrity of the marginal alveolar bone, an elevator will be used carefully to avoid any harm to the bone margins. Initially, a triangular access flap was created, with a releasing incision made on the tuberosity and another distal to the second molar. Then, the third molars will be split, and extraction will be performed using forceps or a dental elevator. After removing the tooth, a thorough sharp curettage will be performed to eliminate any remnants of the periodontal ligament and other soft tissues. Special attention will be given during the procedures to protect the socket walls and interproximal papillae from damage.

The fresh extraction sockets will be treated differently based on the assigned groups. In the experimental group, α-CSH material will be used to fill the socket, while no bone graft material will be applied in the control group. The amount of α-CSH used will depend on the size of the socket. Using a periosteal elevator, the material will be carefully placed and gently packed into the extraction site until it reaches the top of the socket. The graft material will be applied up to 2 mm apical to the soft tissue edge, with a maximum total dose of 3 g per patient. A membrane will be used to cover the upper side of the socket, and primary wound closure will be achieved using absorbable sutures.

Postoperatively, patients will be prescribed appropriate antibiotics and pain relievers for a duration of 7 days. They will be provided with instructions to follow a soft food diet, gargle after meals, and limit physical activities for the first 3 days following surgery. Clinical follow-up examinations will be conducted at 7 days and 14 days after the procedure. Control assessments will include panoramic radiography and CBCT scans within 3 and 6 months after the surgery to monitor the progress of bone formation.

Adverse Event and Severe Adverse Event Assessment

Adverse events encountered during the study will be classified as serious or nonserious based on severity using the classification system established by the World Health Organization [22]. Participants who experience any adverse events will receive comprehensive medical care to address their needs. Any changes in the participant's health status that occur between

the screening examination and the initial administration of α-CSH or associated procedures will be documented in their medical records. In the event of a severe adverse event, the principal investigator will be promptly notified within 24 hours of its occurrence. If the severe adverse event is determined to be associated with severe toxicity or infection at the transplant site, the experiment will be immediately halted to ensure participant safety.

Sample Size

As this study focuses on feasibility rather than achieving statistical significance, formal power calculations were not conducted prior to its initiation. Instead, the emphasis lies on assessing safety, feasibility, and generating preliminary data.

With no prior data on the use of this bone graft material in humans, the sample size was determined based on practical considerations, including resource availability, feasibility of recruitment within the study timeline, and ethical concerns regarding participant risk exposure. The aim was to enroll a sample size, allowing for meaningful observations and providing valuable preliminary insights into safety and efficacy.

Furthermore, following a common rule of thumb for pilot studies, which typically suggest around 30 participants, we decided on a sample size of 30 extractions, with 15 extraction sockets in each group. The number of sockets per patient varies based on individual clinical circumstances. This sample size was deemed appropriate for assessing safety, feasibility, and generating preliminary efficacy data.

Randomization and Blinding

The allocation of participants into the treatment and control groups will be determined through randomization. This process will be conducted using a secure computer system for central randomization. Each patient will be assigned a unique study code, and their data will be provided to the operators and research evaluators in a format that preserves patient confidentiality through coding. When evaluating the data, the radiologist and the statistician will be blinded to the treatment.

Data Collection and Access

The study team will receive detailed guidelines and responsibilities. The medical professionals within the research team will collect the required information as outlined in Table 1. Training sessions will be conducted for the entire research team to ensure consistent data collection at each study visit. The clinical assessors and investigators will receive the data in a format that maintains patient confidentiality through coding. The participants will be monitored for a maximum duration of 6 months. The data manager will prioritize the confidentiality and security of the participant's data.

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Table 1. Assessment of clinical trial.

	Consent form	Clinical photograph	Panoramic	CBCT[a]	Blood test	Probing	Physical examination
Preoperatively	✓	—[b]	✓	✓	✓	✓	✓
Operative day	—	✓	—	—	—	—	✓
Postop day 7	—	✓	—	—	—	—	✓
Postop day 14	—	✓	—	—	—	—	✓
Postop day 90	—	✓	✓	✓	—	✓	✓
Postop day 180	—	✓	✓	✓	—	✓	✓

[a]CBCT: cone-beam computed tomography.

[b]Not applicable.

Outcomes

Feasibility Assessment

The assessment of α-CSH safety in the present context will focus on the occurrence of serious adverse events. To deem α-CSH as safe, it should not result in a higher frequency of adverse events compared to standard treatment (without socket preservation). Additionally, any adverse events that do arise should be manageable through established noninvasive procedures such as analgesics and antibiotics. The evaluation of safety will play a crucial role in determining the suitability and viability of α-CSH in the study.

Feasibility evaluation was conducted using intraoral clinical examination and photographs to assess potential complications such as inflammation, infection, dehiscence, and graft loss. Graft loss will be evaluated in the early postoperative period, within the first week, and late postoperative period. The progress of wound healing at the surgical sites will be assessed with the Landry wound healing index [23]. This index considers factors such as the color of the soft tissue (pink or red), presence of suppuration, amount of bleeding, presence of granulation tissue, and exposure of connective tissue. Based on these criteria, the healing process was categorized into 5 distinct categories, namely very poor, poor, good, very good, and excellent [23]. Patients were also asked about any pain in the surgical site or adjacent areas during the follow-up period.

Quantitative Bone Formation Evaluation

CBCT scans obtained before extraction, 3 months and 6 months post extraction were analyzed using Digora software (Digora for Windows 2.8.107.458 Network Client, Soredex Orion Corporation) to evaluate bone density and formation characteristics. The region of interest, corresponding to the socket preservation and grafting site, was identified based on the grafted area. The view was adjusted axially to align with the angulation of the alveolar ridge. The contours of the crestal bone were delineated, taking into account any apical recession of the alveolar crest on the buccal or lingual aspect. The buccolingual width of the alveolus was then measured 2 mm below the alveolar crest level before tooth extraction and at the follow-up time point. Changes in ridge width were calculated by subtracting the preoperative measurements from the postoperative ridge width measurements.

Monitoring

Continuous monitoring will be conducted by internal monitors from the Hasanuddin University Faculty of Medicine's Ethics and Research Committee to ensure the study's compliance with ethical guidelines. A separate Data Safety Monitoring Board will not be established as the study is associated with minimal risk. However, an annual safety report will be submitted to the Medical Research Ethics Committee of the Faculty of Medicine at Hasanuddin University.

Statistical Analysis

Statistical analysis will be performed using SPSS 16.0 (IBM Corp). Student *t* test will be used to analyze the difference between groups and different follow-up points. The statistical significance level will be set at a *P* value of .05 or lower.

Amendments

Any significant changes that arise during the course of the trial will be promptly reported to the ethical committee and the relevant authority. This ensures the participant's safety and well-being, maintains the trial's integrity, and upholds its scientific value.

Posttrial Care

In order to ensure the safety of participants and monitor any potential long-term adverse effects of the α-CSH graft material, secondary follow-up will be conducted for all participants at 1 and 2 years. This extended follow-up period will allow for thorough evaluation and observation of any potential late-onset complications or concerns related to the use of α-CSH.

Results

The project secured funding in 2022 and is currently in the enrollment phase, with participants being recruited and awaiting the follow-up period. The initial findings of the study are expected to be submitted for publication in late 2024.

The trial's outcomes will be disseminated through diverse strategies, encompassing academic publications, research reports, and participation in international conferences. The results pertaining to the primary objective will be detailed in a primary manuscript designated for submission to a distinguished, high-impact, peer-reviewed journal.

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Discussion

This clinical investigation serves as the inaugural examination of human subjects to evaluate the feasibility and effectiveness of α-CSH in the regeneration of alveolar bone. Our hypothesis posits that the incorporation of α-CSH may significantly accelerate bone formation within fresh sockets, leading to a rapid restoration of bone height while mitigating the drawbacks associated with autogenous bone graft harvesting.

In dentistry, bone grafts and substitute materials are commonly used to regenerate missing hard tissue structures [24,25]. In recent years, there has been a growing interest in the use of bone graft substitutes, driven by concerns over potential immune reactions associated with allografts [1,2,18]. Challenges remain, particularly regarding graft versus host responses associated with nonautograft-derived materials [24,26]. Furthermore, one significant obstacle encountered is the limited research conducted on the safety and effectiveness of newer bone grafting materials [26,27]. Existing information about these materials is primarily derived from case reports or experimental animal models, which may raise concerns about the reliability of such data [8,26,28]. It is crucial to conduct more standardized, well-documented preclinical and clinical studies to gain a comprehensive understanding of the clinical viability and advantages of each material. This will facilitate the introduction of a wider range of commercially available products based on reliable evidence.

The α-CSH, a substance with remarkable characteristics such as high self-setting strength, excellent osteoinductive properties, biocompatibility, and angiogenesis capabilities, has emerged as a popular alternative to traditional bone grafts [29-31]. Previous in vitro and in vivo studies conducted by our team have demonstrated the ability of α-CSH to promote angiogenesis and enhance osteogenesis [14,17,29]. Given the strategic development of α-CSH as a potential biomaterial for bone regeneration, it holds promise as a unique biocomposite bone graft material to be investigated in this study [30,31]. This clinical trial represents a pioneering effort to investigate the potential regenerative capacity of α-CSH in the context of alveolar bone loss, specifically in post-extraction sockets following an odontectomy procedure.

This study aims to provide initial evidence regarding the viability of α-CSH as a bone graft material, specifically its suitability for human transplantation. The effectiveness of the intervention will be evaluated by measuring bone parameters such as bone volume, graft volume, and bone height over a 6-month period. In previous studies, histomorphometric and histological analysis has typically been used to assess the new bone formation and remineralization of the grafted sites [25,32,33]. Unfortunately, it is not feasible in the case of postodontectomy third molar due to an ethical concern for the second operation. Instead, we expect that both panoramic and CBCT imaging will provide a clear visualization of bone volume and density in the evaluated area as it has been used in previous bone regeneration studies [24,34,35]. By using radiographic techniques, we can evaluate bone production and quantify various parameters associated with bone formation [34-36]. The anticipated outcomes of this study will have significant scientific and clinical implications, enhancing our understanding of the feasibility and early efficacy of α-CSH. These findings can guide the approach to socket preservation following tooth extraction, particularly in cases involving bone augmentation for implant placement. Furthermore, this research has the potential to contribute to the development of biomaterials for clinical use, advancing the field and ultimately improving patient outcomes.

Our research encounters several limitations that warrant consideration, including the challenge of recruiting patients who meet our stringent inclusion and exclusion criteria, which poses a significant hurdle. Relying solely on hospital patients for recruitment may limit the generalizability of our findings, underscoring the need for broader sampling strategies in future studies. Additionally, the absence of previous studies to estimate sample size leaves us navigating uncharted territory, potentially impacting the precision and adequacy of our sample size determination. Despite these limitations, our study presents compelling initial data on the accelerated bone formation observed with α-CSH in fresh sockets. These findings will provide a foundation for further exploration and offer valuable insights that can inform the design and execution of larger clinical trials or studies in the future.

This protocol outlines our approach to assessing the feasibility and initial efficacy of α-CSH as a promising grafting material for alveolar bone loss, specifically in cases involving postodentectomy mandibular third molars. We aim to evaluate the potential of α-CSH as a graft material and determine its suitability in this clinical scenario.

Acknowledgments

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Data Availability

Data from this clinical trial will be available to the corresponding author upon reasonable request.

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Authors' Contributions

MR, NH, and AT contributed to conceptualization. ASHY, RN, and DSNK contributed to data collection. YYA and MNA contributed to visualization and project administration. MR, CML, and KLO contributed to supervision, resources, and funding acquisition. All authors contributed to methodology, and writing the original draft as well as reviewing and editing it.

Conflicts of Interest

None declared.

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Abbreviations

α-CSH: α–calcium sulfate hemihydrate
CBC: complete blood count
CBCT: cone-beam computed tomography
CONSORT: Consolidated Standards of Reporting Trials
CSD: calcium sulfate dihydrate

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PPD: probing pocket depth

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Protocol

Physical Activity Mobile App (CareFit) for Informal Carers of People With Dementia: Protocol for a Feasibility and Adaptation Study

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Abstract

Background: Physical activity is a critical component of both well-being and preventative health, reducing the risk of both chronic mental and physical conditions and early death. Yet, there are numerous groups in society who are not able to undertake as much physical activity as they would like to. This includes informal (unpaid) carers, with the United Kingdom national survey data suggesting that 81% would like to do more physical activity on a regular basis. There is a clear need to develop innovations, including digital interventions that hold implementation potential to support regular physical activity in groups such as carers.

Objective: This study aims to expand and personalize a cross-platform digital health app designed to support regular physical activity in carers of people with dementia for a period of 8 weeks and evaluate the potential for implementation.

Methods: The CareFit for dementia carers study was a mixed methods co-design, development, and evaluation of a novel motivational smartphone app to support home-based regular physical activity for unpaid dementia carers. The study was planned to take place across 16 months in total (September 1, 2022, to December 31, 2023). The first phase included iterative design sprints to redesign an initial prototype for widespread use, supported through a bespoke content management system. The second phase included the release of the "CareFit" app across Scotland through invitations on the Apple and Google stores where we aimed to recruit 50 carers and up to 20 professionals to support the delivery in total. Partnerships for the work included a range of stakeholders across charities, health and social care partnerships, physical activity groups, and carers' organizations. We explored the implementation of CareFit, guided by both Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) and the Complex Intervention Frameworks.

Results: Project processes and outcomes were evaluated using mixed methods. The barriers and enablers for professional staff to signpost and use CareFit with clients were assessed through interviews or focus groups and round stakeholder meetings. The usability of CareFit was explored through qualitative interviews with carers and a system usability scale. We examined how CareFit could add value to carers by examining "in-app" data, pre-post questionnaire responses, and qualitative work, including interviews and focus groups. We also explored how CareFit could add value to the landscape of other online resources for dementia carers.

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Conclusions: Results from this study will contribute new knowledge including identifying (1) suitable pathways to identify and support carers through digital innovations; (2) future design of definitive studies in carer populations; and (3) an improved understanding of the Reach, Effectiveness, Adoption, Implementation, and Maintenance across a range of key stakeholders.

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KEYWORDS

carers; dementia; physical activity; sedentary; cross platform app; caregivers; mobile phone

Introduction

Background

Recent estimates suggest that in the United Kingdom, 10.6 million family members and friends look after a family member or friend due to a disability, frailty, or a mental or physical condition [1]. The collective impact of this group (often termed "informal carers") in the United Kingdom is a saving to health and social care services of £162 billion (US $206 billion, 1£=US $1.27) per year [2], a figure comparable to the entire budget for the National Health Service England [3]. However poignant this contribution is, the support does not come without personal costs to carers. Many carers report poor mental and physical health, a finding also supported by systematic review evidence [4,5]. Poor carer health is a concern for everyone in society and has been associated with a reduced quality of life and increased mortality in the person being cared for [6,7].

As global populations continue to age, our health and social care systems are beginning to reform, driven through a combination of factors (eg, staff shortages, risk of infection in hospital settings, and cost savings) to pivot further toward care in the community [8,9]. With this shift, there is a growing call to build more holistic approaches around health and well-being in carers [10,11]. Achieving such major reform looks certain to embrace digital components, including building up evidence into digital interventions that could both alleviate pressure on health and social care staff and empower carers. Yet, realizing such digital implementation remains challenging, not least because the requirements for successful implementation of digital solutions are both long and intricate [12,13]. For example, this includes not only technical and operational readiness or rigor but also the development of a strong evidence base [14], an inclusive and authentic co-design approach (ideally early and including a wide variety of key stakeholders [15]), and early recognition and management of risks around nonadoption and abandonment [16,17].

Across a wide array of carer innovations and research [18,19], the development of digital supports for carers of people with dementia continues to be of significant societal interest [20-22]. For example, the pioneering work of the World Health Organization (WHO)–led "iSupport" platform for carers of people with dementia [23] has facilitated evidence-based theories on personhood and cognitive reframing [24,25] to become accessible to a global audience through web-based training and support, with anticipated impacts including reducing burden and anxiety. The content delivered is multidimensional, including an introduction to dementia, reducing stress, supporting activities of daily living, being a carer and caring for yourself, and dealing with behavior changes. As the evidence base for iSupport continues to grow (including adaptation and evaluation in 33 countries [26]), there remains scope to complement and augment global resources such as iSupport across other unmet needs of carers. This includes areas of physical activity where the UK national survey data suggest that 81% of carers are not able to do as much physical activity as they would like to [2], with a lack of digital innovations in development for this specific group. An added challenge is that, owing to their caring role, many of the carers spend much time indoors, limiting the value of location- and step count–based approaches that are more accessible to other population groups) [27,28].

We previously reported on our initial "CareFit" progress [28,29], after building the first version of the app as an Android Package Kit (APK) and testing a minimum viable concept during the COVID-19 pandemic lockdown across Scotland. The original app was designed to support carers to undertake early steps in physical activity, informed by the UK national physical activity guidelines and is based on the transtheoretical model of behavioral change [30]. While initial results identified the acceptability, usability, and feasibility of the app and concept, the work marked only the first step to develop an evidence base for future use and explores a relatively new area of research around sedentary behavior in informal carers. We demonstrated limited implementation findings around the reach (the app was only available on Android phones), the sustainability (the app was designed for 3 weeks of use only), and the lack of wider engagement with health and social care professionals and providers. Thus, we concluded that significant insights could be gained from a redesigned version of the app (eg, a completely new build using React Native [Meta]), introducing a higher quality user experience covering multiple platforms, a more personalized user journey, and establishing how we could design a future definitive study for sustainable use with implementation. Further insights that remain critical include those relating to future study design (eg, relating to the MRC Complex Intervention Framework [15,31,32]) through the lens of a single postdiagnostic pathway such as dementia.

Study Aims and Objectives

This work aimed to improve current uncertainties around social care pathways to implementation and gain an understanding of facilitators and barriers to the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) [33] of "CareFit" in a real-world setting. Our objectives were to (1) expand an initial 3-week intervention to an 8-week intervention to support maintenance of physical activity; (2) develop understanding of

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recruitment pathways and explore barriers and enablers to recruitment for a future definitive trial, including recruiting more deprived socioeconomic groups; (3) improve understanding of usage adherence and develop understanding of the most reliable methods to regularly measure physical activity and sedentary behavior within dementia carers; (4) explore how "CareFit" could provide added value for dementia carers with the existing solution of other digital interventions (such as "iSupport") through qualitative interviews or focus groups with key stakeholders; and (5) to explore unexpected benefits including whether people with dementia also see the benefits of CareFit.

Methods

Study Design

The CareFit for dementia carers study was a mixed methods evaluation of a novel motivational smartphone app to support home-based regular physical activity for unpaid dementia carers. The study took place across 16 months (September 1, 2022, to December 31, 2023) and formed a "stand-alone" element of an existing randomized controlled trial on "iSupport" [26]. Initial co-design and adaptation of an existing prototype [28] facilitated this feasibility study. In brief, the co-design sessions for adaptation and expansion involved 3 development sprints: gaining feedback from a range of stakeholders such as carers, professionals who support carers (eg, charity partners) and researchers, and developers to create priority areas for app development. At the conclusion of participation in the CareFit feasibility study (designed for up to 8 weeks of use), all carers completing their final evaluation survey received information about regional support services and a shopping voucher as a token of appreciation for their participation in this work.

Participant Recruitment: Feasibility Study

Professional study collaborators and organizations were sent a media pack of adverts across text, image, and video formats. Informal carers of people with dementia were identified and recruited through our partner organizations' networks, the Join Dementia Research (JDR) [34] database, and were supported by other stakeholders through advertising through posters, emails, social media, and center referrals, as required. Staff from our partner organizations were invited to contribute to the evaluation across this work, along with a broader group of stakeholders (eg, including organizations who did not take an active role in recruitment) at the conclusion of the work, for "round table" stakeholder meetings and interviews. Throughout, staff were not obliged to participate in the evaluation even where their organization was a collaborator in this work. All participants were free to withdraw at any time without any impact on their future health and care or working role. Participant data collected to the point of withdrawal were used in the analysis unless consent for this was specifically withdrawn (Textbox 1).

Textbox 1. Feasibility study inclusion and exclusion criteria.

- Feasibility study inclusion criteria for carers
  - Adults (18+) living in Scotland who self-identify as an unpaid carer (partners, children, friends, etc) of a person with dementia (self-reported)
  - Contemplating or preparing to undertake physical activity
  - Ability to undertake simple exercises such as arm raises or stretching
  - Be able to read and write in English
  - Have access to a smartphone (Android or Apple) and access to the internet
  - Normal or corrected to normal eyesight
- Feasibility study inclusion criteria for social care professionals
  - Adults aged 18 and older
  - Based in Scotland
  - Working as a health and social care professional
  - Willing to engage with the study (eg, share information about "CareFit" with carers of people with dementia) through their professional role for a period of at least 3 months (to ensure timely follow-up)
- Feasibility study exclusion criteria for carers
  - Anyone advised by a clinician not to undertake physical activity or make any change in their present level of exercise
  - Are already regularly exercising to a significant level outside the home (eg, running or cycling)
  - Residing outside Scotland at the time the study is conducted
  - Currently part of a related "iSupport" study
- Feasibility study exclusion criteria for social care professionals
  - Working exclusively within the National Health Service

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CareFit Intervention

"CareFit" is a smartphone app designed to support carers of people with dementia. It was designed to be accessible on both Android and Apple smartphones and tablet devices. It was developed to support the early steps in physical activity in line with the transtheoretical model of behavior change [30] and co-designed with carers, health and social care professionals, and physical activity experts over a series of phases.

For participants who did join the study, they were sent an "invitation only" link to download the app on their own smartphone or tablet device and were supported to do this over a number of email steps and correspondence with the research team, as part of a "closed" study on Google and Apple stores.

Ethical Considerations

Human Participant Ethics Review

Ethical approval for feasibility work was obtained through the Bangor University School of Medical and Health Sciences academic ethics committee (approval number 2021-16915). The initial co-design and adaptation work was supported through approval in 2022 from the Department of Computer and Information Sciences, University of Strathclyde.

Informed Consent

For the feasibility study, both carers and professionals were provided with online information sheets before involvement in the study. Informed consent was demonstrated by the online signing of a consent form in Qualtrics [35]. Participants electronically selected individual items in the online form, corresponding to the paper consent form, in order to confirm they had read and agreed with each item. Their electronic signature was achieved by entering their first name and surname, and then either typing or drawing their signature next to a declaration. During the consent process, potential participants were supported by a researcher in an online meeting (eg, Skype [Microsoft Corporation] and Zoom) or telephone call wherever requested and any questions were answered. They then completed an online form, or the form registered that they declined.

Privacy and Confidentiality

The research team and app developers undertook a number of steps to ensure the security of the information collected. While the use of secure, General Data Protection Regulation–compliant online survey forms are standard for such studies, privacy for the development and use of the app was ensured through the development of a secure content management system to store pseudonymized "top-level" information from participants about overall app use. Information that is personal to the participant, such as barriers and enablers to physical activity, was kept on the individual handset, was not shared further, and did not cross between devices, even when the user remained the same. Any information stored by the University of Strathclyde was stored within university-approved, password-protected encrypted storage sites.

Compensation Details

Carers who participated in this work were offered a £20 (US $25.40 [1£=US $1.27]) shopping voucher to thank them for their involvement.

Data Collection, Management, and App Download Process

There were four key areas of data collection (1) study advertisement and recruitment impact (including proactively contacting carers through the JDR platform), (2) online surveys, (3) "In-app" data collection (namely the usage across the different domains of the app such as the "activity," "planner," "resources," or "sharing" elements, including a "time stamp" at the time and date of use), and (4) interviews and focus groups. For online surveys, the online platform "Qualtrics" was used. Study adverts (in both paper-based and digital formats) were shared with study partners alongside the use of the JDR platform. Carers who consented to the study were directed to a bespoke hyperlink within the Google Play and Apple stores, where an individual pseudonymized ID was entered after download. The CareFit research team offered support to individuals at any stage as requested through email or telephone or video call support. Focus groups and interviews both took place to understand a subsample of the participants' experiences and were used in the closing stages of the project as "round stakeholder" meetings, which explored, in conversation, future steps around key themes and points identified through the use of the RE-AIM methodology.

Evaluation Outcomes

Our mixed methods evaluation was underpinned by a number of different data sources, including (1) baseline carer demographic survey (eg, age group, gender, and number of years caring and hours caring per week) and 8-week follow-up (eg, International Physical Activity Questionnaire Short Form, [IPAQ-SF] [36], EQ5D [37], and system usability scale [SUS] [38]), (2) professional survey (eg, elements of RE-AIM and how CareFit could integrate into working role), (3) "in-app" collected data, and (4) interviews and focus groups. Following the format of the RE-AIM framework, our outcomes were guided wherever possible by the elements of Reach, Effectiveness, Adoption, Implementation, and Maintenance and were also interpreted with support of the Complex Intervention Framework [15,31,32]. Further information is listed in Table 1.

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Table 1. Example research questions and example data sources based on the RE-AIM framework.

RE-AIM[a] component and example research questions	Example data sources
Reach	
• What is the participation rate within the study? • What is the dropout rate within the study? • What are the key barriers or facilitators to reach?	• Registry data for "Join Dementia Research" • Study monitoring of overall numbers of interviews or focus groups or roundtable discussions
Effectiveness	
• What are the indications around the usability of "CareFit"? • What are the early indications of effectiveness for increasing physical activity/reducing sedentary behavior and increasing knowledge of physical activity? • What (if any) are the unintended consequences of using the app? • What is the overall caregiver engagement with the app?	• Patient-reported outcome measures (eg, system usability scale, International Physical Activity Questionnaire Short Form, individual items, and bespoke measures including sedentary, knowledge, and support outcomes) • Interviews or focus groups and roundtable discussions • "In-app" collected data (eg, "activity," "planner," "resources," or "sharing" elements including a "time stamp" at the time or date of use)
Adoption	
• What are the characteristics of organizations that support the work • What is the organizational staff's understanding of why CareFit was/was not adopted?	• Interviews or focus group questions that focus on the experience of adoption activities
Implementation	
• What are the key barriers and facilitators to implementation? • How can we measure the cost implications (eg, financial and time for organizations)?	• Interviews or focus groups and roundtable discussions • Patient-reported outcome measures (eg, EQ5D).
Maintenance	
• What are the facilitators and barriers to maintaining the program? Do participants continue engaging with the app across 8 weeks of use? • What could encourage the use of the app beyond 8 weeks?	• Interviews or focus groups and roundtable discussions. • "In-app" collected data (eg, "activity," "planner," "resources," or "sharing" elements including a "time stamp" at the time and date of use)

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

Analysis

Our approach to mixed methods [39] was to analyze qualitative and quantitative results individually to form conclusions. Where possible, we synthesized further interpretations of the quantitative results through the qualitative findings. Interviews were recorded through the use of an encrypted Dictaphone or University-approved video software where Braun and Clarke's [40] thematic analysis was followed. For quantitative outcomes, basic statistics relating to feasibility were gathered (eg, description of key recruitment numbers, adherence to CareFit from our "in-app" data included summaries across the "activity," "planner," "resources," and "sharing" elements, including a "time stamp" at the time and date of use). Indicators of usability were underpinned by SUS total scores and, on occasion, individual questions were used to support the interpretations of qualitative data. For all outcomes assessed, differences in measures between baseline and follow-up were analyzed primarily around metrics that support our understanding of feasibility and suitability of outcomes, such as completeness of information and correctness of data gathered, such as percentage completion and error value rate. Secondary analyses may be used at a later time point (eg, app engagement vs outcome improvements) for hypothesis generation but were not a primary purpose of this study.

Results

At the time of publication (July 2024), we have recruited 41 participants into the CareFit study, with a peer-reviewed publication with the results to follow.

Discussion

Principal Findings

Here we aimed to expand, personalize, and evaluate the implementation potential of a cross-platform digital health app (ie, accessible on both Google and Apple stores) to support regular physical activity in carers of people with dementia for a period of 8 weeks. The results build significantly on existing research across the breadth of materials offered (eg, number and range of physical activity videos) and the new functionalities, look and feel, and interaction capabilities of the app overall. The publication of this protocol serves a number of functions to help benefit others in the field including maximizing the transparency, accountability, and reproducibility of the work, particularly given that CareFit constitutes a complex intervention [15,31,32]. For the first time, we have explored different implementation pathways and will be in a position to report on how well different routes to "marketing" for carers

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performed in detail—an important outcome given that carers are often difficult to identify and support in society. Furthermore, our use of both implementation focus groups guided by the RE-AIM framework provides a comprehensive understanding of how carer-focused digital health approaches (including those in dementia) can move forward at both local and national levels.

We anticipate that results will contribute new knowledge in a number of ways, including (1) recommendations of suitable pathways to identify and support carers through digital innovations; (2) future design of definitive studies in carer populations (eg, suggestions for dropout levels and suitable measures of physical activity); and (3) an improved understanding of the reach, effectiveness, adoption, and maintenance for a range of key stakeholders. Such results support the future design of this work, including the identification of an optimal and sustainable route forward for CareFit, including a pilot randomized trial for use over an extended period. This is likely to also include furthering our understanding of costs; we are currently exploring options for CareFit or future iterations to be free and as low cost as possible for carers at the point of use (July 2024).

Limitations

There were a number of limitations of this study. First, our routes for implementation and recruitment were varied and included not only stakeholders directly advertising the study but also the JDR online registry for carers of people with dementia. Registry routes may not always reflect the wider carer demographic; however, these are increasingly recognized and used by charity partners, and it was pragmatic to use JDR within a time-limited recruitment period. Furthermore, our work identified the strengths and limitations of these different recruitment approaches. Second, there were a number of steps involved in downloading and accessing the "CareFit" app (eg, email exchanges with the CareFit research team were required to onboard participants). Such steps would not take place if the app was freely available in app stores, but we opted to design our study for "closed" testing so that we only collected app usage data from consented participants and could build up evidence in an iterative way. Finally, there were some limitations regarding our analysis of the study data. While our mixed methods approach consists of many comprehensive data sets, we opted not to analyze the personal goals, barriers, and enablers participants expressed, in order to protect their privacy. Should future research be conducted in this project or similar projects, it may be of use to expand these opportunities with the full consent of study participants as an opt in or out selection.

Conclusions

As the role of community care in health and wellness continues to grow, new opportunities are emerging to support the role of the informal carer. Our mixed methods approach to adapting, implementing, and evaluating CareFit will not only inform the design of future similar studies but also give early indications about a wide array of impacts, such as marketing, reach, acceptability, and the feasibility of implementation.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

KE, RM, MDD, AK, GW, JS, GF, BF, BM, and WH contributed to the conceptualization, writing, and editing of the study. KE handled the methodology. KE, MDD, BM, and WH performed the formal analysis. KE, RM, MDD, AK, GW, JS, and BF managed funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

APK: Android Package Kit
IPAQ: International Physical Activity Questionnaire
JDR: Join Dementia Research
NIHR: National Institute for Health Research
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SUS: system usability scale
WHO: World Health Organization

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Protocol

Brief Mobile App–Based Mindfulness Intervention for Indonesian Senior High School Teachers: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The COVID-19 pandemic has increased the level of anxiety among Indonesian senior high school teachers, who face challenges to treat their mental disorder symptoms that arise during their working hours, as mental health services in Indonesia are limited. Therefore, it is vital to equip schoolteachers in Indonesia with early interventions that are easily available, private, and affordable, and 1 feasible approach is to deploy a smartphone mobile app.

Objective: The objectives of this study are (1) to evaluate the feasibility of a brief mindfulness–based mobile app (BM-MA) for Indonesian senior high school teachers experiencing anxiety and stress and (2) to examine the effects of using the BM-MA on anxiety, stress, life satisfaction, self-efficacy, trait mindfulness, self-compassion, and physical and social dysfunction among the participants.

Methods: We followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement for this feasibility randomized controlled trial (RCT) protocol. A total of 60 Indonesian senior high school teachers were recruited for this study and randomly assigned to either the intervention group (BM-MA) or a wait-list control group (CG) in a 1:1 ratio. The BM-MA group was required to engage in mindfulness practices using the app for 10-20 minutes per day for 3 weeks. All participants were assessed with a battery of self-report measures at baseline, postintervention, and at 1-month follow-up. Validated scales used to measure the outcome variables of interest included the Satisfaction With Life Scale (SLS), the Teachers' Sense of Efficacy Scale (TSES), the Self-Compassion Scale—Short Form (SCS-SF), Generalized Anxiety Disorder-7 (GAD-7), General Health Questionnaire-12 (GHQ-12), and the Five Facet Mindfulness Questionnaire (FFMQ). The practicality and acceptability of the app will be evaluated using the Client Satisfaction Questionnaire-8 (CSQ-8) and structured qualitative interviews. Data from the interviews will be analyzed with the deductive thematic analysis framework as a process of qualitative inquiry. Repeated measures ANOVA with groups (intervention vs control) as a between-subject factor and time as a within-subject factor (baseline, postintervention, and 1-month follow-up) will be used to examine the effects of the BM-MA on the outcome variables. The data will be analyzed using an intent-to-treat approach and published in accordance with CONSORT (Consolidated Standards of Reporting Trials) recommendations.

Results: Participants were recruited in December 2023, and this pilot RCT was conducted from January through March 2024. Data analysis was conducted from March through May 2024. The results of this study are expected to be published in December 2024. The trial registration of this protocol was submitted to the Chinese Clinical Trial Registry.

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Conclusions: This study aims to determine the feasibility and efficacy of the BM-MA, a digital mental health intervention developed using an existing mindfulness-based app, and assess its potential for widespread use.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300068085; https://tinyurl.com/2d2x4bxk

International Registered Report Identifier (IRRID): DERR1-10.2196/56693

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KEYWORDS

digital mental health; telemedicine; anxiety; stress; self-efficacy; life satisfaction; self-compassion; mindfulness; feasibility study; mobile app; mindfulness-based stress reduction; stress management

Introduction

Background

During the COVID-19 epidemic, 79.1% of government senior high school teachers in Jakarta, Indonesia, experienced stress due to workload, work engagement, work routine, and the workplace environment [1]. The higher stress level of schoolteachers during the pandemic was closely tied to the increased workload caused by a shift in the teaching format [2]. The educational strategy during the COVID-19 pandemic was ambiguous, leading to differences in how teaching was implemented. Teachers often interpreted the policy based on their existing knowledge and teaching skills [3]. Another ambiguity in the online school period was that teachers perceived a lack of explicit consequences, whether positive or negative, for the quality of their online teaching delivery [3,4].

Teachers between the ages of 36 and 45 years were found to experience greater levels of stress and anxiety than older teachers, since younger teachers were required to perform more technology-related duties that the older teachers could not perform [5]. Malini [5] also reported that schoolteachers lack a means of coping with their mental health. The condition of schoolteachers does not improve, and they receive less assistance in managing stress and depression. After 2 years of the pandemic, Indonesian senior high school teachers reported elevated levels of anxiety and somatic and social dysfunction [6].

In general, mental health services in Indonesia are limited, with psychologists, psychiatrists, and therapists being more accessible in major cities and not covered by national insurance [1-3]. There are significant disparities in the level of mental health literacy among those engaged in the health care system throughout various regions of Indonesia. The guidelines and allocation of support for mental health practitioners still present unresolved concerns. In certain regions of Indonesia, accessing the nearest community health clinics for mental health services can be challenging and costly due to a lack of competent and knowledgeable human resources in this field [7]. As a result, Indonesian senior high school teachers face challenges to treat the symptoms of mental disorders that arise during their working hours, because there are few public hospitals that have a psychology/psychiatry department [6,7]. Teachers can also get professional mental health services at a private hospital. However, private hospitals charge 4 times more than public hospitals for 1 psychotherapy season [6,7].

In view of the aforementioned circumstances, it is vital to equip schoolteachers in Indonesia with early interventions that are easily available, private, and affordable, and 1 feasible approach is to deploy a smartphone mobile app. A smartphone has multiple capabilities, such as presenting on-demand video resources and opportunities for live engagement with users. Consequently, it can be used to provide schoolteachers with accessible, inexpensive, and extended psychological interventions. Research has found that individuals with stress management skills and favorable living conditions are likely to have more long-term happiness [8]. Mindfulness-based interventions are 1 category of interventions that may be effective in improving well-being and stress management skills [9]. One popular mindfulness-based intervention is “Mindfulness-Based Stress Reduction” (MBSR). The MBSR was originally developed to address a variety of diseases in clinical and nonclinical populations. The program consists of 8 weekly sessions, plus approximately 45 minutes of daily home practice [10].

Much research has examined the effectiveness of the MBSR and other forms of mindfulness meditation in addressing mental health symptoms. Studies have revealed that the effect sizes for the MBSR are larger than those for other kinds of mindfulness meditation, likely due to the fact that the MBSR uses a variety of processes, such as formal meditation practices and live instruction by a trained facilitator [10-12]. Several studies have demonstrated the efficacy of mindfulness interventions for schoolteachers’ stress and anxiety [13-18], as well as stress related to COVID-19 [16]. However, relatively few studies have examined the effects of mindfulness training–based mobile apps for schoolteachers. One of the few empirical studies examined the effects of a 5-week standardized meditation program consisting of weekly offline classes and a suggested dose of 2 daily 20-minute home and school practice sessions [17]. The types of meditation practices included in this intervention included mantras and breath observation. The sample consisted of elementary, middle, and high school teachers who were randomly allocated to intervention (n=45) and control (n=46) groups. Findings indicated improvements in state and trait anxiety, reduction in emotional weariness (a component of burnout), and reduction in stress posttest, and lowered depersonalization (another component of burnout) at 1-month follow-up. Another study of the MBSR for primary school teachers [19] showed improvements in melancholy and stress, as well as increased tolerance and lowered prejudice (a component of the mindfulness scale) among schoolteachers following engagement in the intervention.

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This feasibility study comprises 3 weeks of daily use of a mobile phone app. The lessons are organized based on components of the MBSR, and mobile apps are used to provide instructions for exercises requiring 10-20 minutes of daily home practice. Existing mindfulness interventions for general populations based on mobile apps for smartphones are primarily given in English, with rating stars based on user reviews [20]. There have been studies on the efficacy of mindfulness-based mobile apps in broad populations [20-22]. Several studies based in Iran have suggested the use of online and digital mindfulness programs as an efficient method to alleviate the stress related to COVID-19 and enhance psychological resilience [23]. To summarize, mindfulness-based mobile interventions have been demonstrated to be effective in reducing stress and enhancing well-being in a variety of settings [10,22,24].

To date, mobile app–based mindfulness interventions have not yet been implemented in the Indonesian language for senior high school teachers. According to the 2019 Global Economy Survey [5,6], which ranked Indonesia 72nd out of 97 countries in terms of the senior high school teacher-student ratio, there appears to be a decline in teacher supervision and student attention. As a result, schoolteachers are facing increased workloads, leading to higher levels of stress and physical complaints [4]. To support Indonesian senior high school teachers in managing anxiety and stress symptoms effectively and in a user-friendly manner, it is crucial to develop a brief mindfulness–based mobile app (BM-MA) intervention in Indonesia. Since such an app has not yet been implemented in Indonesia, this study aims to assess the feasibility and acceptability of the BM-MA to determine its suitability for further testing through a randomized controlled trial (RCT) [25].

Study Objectives

This feasibility study will evaluate the possible adoption of the BM-MA in real-world contexts. The secondary objectives are to determine the effectiveness of BM interventions based on mobile apps in enhancing life satisfaction, self-compassion, and a sense of self-efficacy and in reducing participant-reported anxiety and stress symptoms. The following scientific questions will be addressed:

- Can the BM-MA be accepted into the community practice of Indonesian senior high school teachers to enable scale-up?
- Throughout the study, could the BM-MA be applied as intended?
- Could the BM-MA implementation be continued throughout the conclusion of the research?
- Does the BM-MA reduce stress and promote life satisfaction, self-compassion, and a sense of self-efficacy, as stated by participants?
- Does the BM-MA reduce participant-reported anxiety symptoms?

Methods

Overview of Study Design

This feasibility study will use a repeated-measures, between-group RCT design and adhere to the CONSORT (Consolidated Standards of Reporting Trials) statement (Multimedia Appendix 1). The feasibility protocol presented followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement (Multimedia Appendix 2) [26]. As determined by an initial screening instrument, participants were only recruited if they exhibited good overall health, had no past experience with mindfulness practice, and had not recently experienced any adverse life events. Individuals who matched the inclusion criteria (explained further in the subsequent section) and responded within the recommended time frame of 2 weeks were routed to a webpage and a participant information sheet via the Qualtrics platform. Participants from 2 public senior high schools were informed that they would be randomly assigned to a treatment group or a wait-list control group (CG) and were asked to provide written informed consent (see Multimedia Appendix 3) prior to completing a brief demographic questionnaire. The participants were subsequently randomly assigned to either the BM-MA group or the CG. Participants in the CG were notified that they were on a waiting list and were asked to answer questionnaires at baseline, postintervention, and at 1-month follow-up before being allowed access to the BM-MA intervention for an additional 21 days (if they wished to use it).

At the end of the waiting period, the CG received thorough instructions regarding downloading and using the BM-MA intervention via a smartphone. In the meantime, the BM-MA group was instructed to complete questionnaires at baseline, postintervention, and at 1-month follow-up of the BM-MA intervention. After the baseline measures were completed, participants in the BM-MA group were provided with an access code and details of how to download the BM-MA to their smartphone. During the 21-day study period, they were urged to use the app daily. At baseline, postintervention, and at 1 month follow up of the BM-MA intervention, both groups were invited to attend a Zoom session to finish the measurements in real time, monitored by random assignments. Both groups were reminded about their right to withdraw from the study at any moment if they so chose. The follow-up evaluation was conducted 1 month postintervention for both groups. The intervention tries to ensure that no participant will face stigma as a result of participation by removing any potentially objectionable language according to the feedback from the local government partner, the Dinas Pendidikan Kepemudaan dan Olahraga Provinsi (Province Youth and Sports Office). The overview of the BM-MA pilot RCT study design following CONSORT guidelines is presented in Multimedia Appendix 1.

Timeline and Study Setting

This feasibility study was conducted among schoolteachers from 2 public senior high schools in Indonesia over a 21-day period (Multimedia Appendix 4). A total of 30 participants per group (BM-MA and control) were adequate to establish feasibility [27]. A demographic survey of senior high school teachers in Indonesia [4] revealed that the median monthly pay for schoolteachers was IDR 5,000,000 (~US $321). Almost all the participants have a smartphone (n=55, 91.7%) and internet access on their smartphone (n=60, 100%), and only 17 (28%) said they had no intention of obtaining mental health treatment.

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To the best of our knowledge, there has been no formal record of senior high school teachers in Indonesia using mental health treatments. Nevertheless, the remarkable progress of Indonesia's mental health care system is still restricted to a few major cities on Java Island [7].

Local Stakeholder Partner

This study will be conducted in partnership with local education authorities in a number of Indonesian provinces, specifically the Dinas Pendidikan Kepemudaan dan Olahraga Provinsi (Province Youth and Sports Office). The government education authorities are responsible for the following:

- The creation of education-related technological policy
- The implementation of educational policy and the growth of language, literacy, and literature
- Education administration in the realm of education
- Implementation of program planning, assessment, and reporting
- The execution of other functions assigned by the governor that are linked to their duties and responsibilities

On the basis of the aforementioned capabilities, the local government partners made a major contribution to recruiting participants to take part in this feasibility study by sending invitations over email to prospective participants.

Intervention

The BM-MA consists of audio guides of BM practices derived from mindfulness exercises available in the MBSR and mindfulness-based cognitive therapy (MBCT), an intervention adapted from the MBSR for preventing relapse in major depression. Examples of mindfulness practices that are included in the BM-MA are mindfulness of breathing, mindfulness of sounds, body scan meditation, mindful stretching, mountain meditation, and loving-kindness meditation. The audio guides for these mindfulness practices were developed (in the Indonesian language) by qualified MBCT teachers based in Indonesia and professionally recorded in an authorized recording studio. Each audio guide lasts between 5 and 20 minutes, and participants will be expected to engage in 10-20 minutes of mindfulness practice in total daily.

A progression of mindfulness practices was recommended to the participants in the first 10 days of practice, beginning with brief, introductory mindfulness exercises (eg, mindfulness of breathing), followed by practices that are lengthier and more open ended in nature (eg, mountain meditation, choice-less awareness meditation). After the first 10 days of practice, the participants were allowed to daily engage in any practice tracks that they like. The app also contains a feature that allows participants to track the overall duration and frequency of practice over a period of 21 days. Prior to downloading the app, the participants received an orientation to mindfulness practice by a trained mindfulness teacher via a Zoom meeting, and the session consisted of an introduction to the practice of mindfulness, stigma related to mental health, common myths about mindfulness practice, setting up a suitable environment for mindfulness practice, and troubleshooting potential difficulties that may arise during mindfulness practice (eg, dealing with difficult thoughts and emotions). The orientation session served the purpose of establishing a common level of mindfulness knowledge among the participants and ensuring their comprehension of how to use the BM-MA. They were asked to set aside time daily to commit to home mindfulness exercises using the app.

Recruitment and Sample Size

This study's sample comprised Indonesian high school teachers. The sample was drawn from 2 public senior high schools after a request for volunteers was sent over email by local government partners. Individuals who answered within 1 week were directed to a webpage on Qualtrics that describes the study and screening process. In addition, recruiting advertisements based on the opinion of the school principals were distributed via the schools' social media. Individuals who passed the screening process were included in the participant pool.

The inclusion criteria for the feasibility study were Indonesian certified senior high school teachers (1) who are aged 18 years and older, (2) can read and write in Indonesian, (3) have access to a smartphone, and (3) have a total Generalized Anxiety Disorder-7 (GAD-7) score of no more than 14 and a total General Health Questionnaire-12 (GHQ-12) score of no more than 20. The exclusion criteria for the feasibility study were (1) regular practice of mindfulness meditation (eg, 15-20 minutes per day, 2-3 times per week), (2) a history of ongoing and present treatment for a mental disorder, (3) a positive response to GHQ-12 questions regarding suicidal ideation, and (4) refusal to provide written informed consent. These criteria were designated to recruit participants without prior regular experience in mindfulness practice and with no severe symptoms of depression and anxiety. The criteria also contributed to a more homogenous selection of participants across conditions.

Random sampling was used in the 2 public senior high schools in Indonesia, with the unit that was randomized being the senior high schools themselves. The sample size for this feasibility study was 30 participants for each study arm, with 95% CIs and small standardized effect sizes [27].

Acceptability and Feasibility

A mixed methodological study was used to evaluate the BM-MA's feasibility and acceptability. Acceptability is defined as the extent to which an app is suitable [28], and is assessed by analyzing participants' qualitative responses to structured interviews. The quantitative scale used to measure feasibility was the Client Satisfaction Questionnaire-8 (CSQ-8) [28]. Each item in the CSQ-8 is rated on a scale of 1-4, and total scores range from 8 to 32. More than 70% of participants must receive a score of 24 or above on the CSQ-8 [28], given a 10% acceptable error rate [29], and participate in structured qualitative interviews for acceptance to be determined.

Feasibility is defined by Feeley et al [30] as the ease of deployment of an app among adults. In this study, on the basis of app scores, feasibility will be evaluated descriptively by examining the ease of recruitment, enrollment rate, and attrition rate. Participants will also be required to complete an in-person final evaluation. End-of-line evaluations will involve the viability and acceptance of the mobile app, as well as structures qualitative interviews.

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Randomization and Blinding

Participants from 2 public senior high schools were randomly assigned to the BM-MA group or the CG in a 1:1 ratio. The app arbitrarily selected a block size (2, 4, or 6) and assigned a random order within the block. For example, we randomly allocated 30 participants to each group in this scenario. The BM-MA group was denoted as "M" and the CG as "C." The possible groupings were MCCM, MMCMCC, CM, MC, and CMCM. As part of the screening consent procedure, participants were informed that this will be an interventional study in which they might be randomized to a variety of BM-MA groups.

The prior online mindfulness intervention revealed a substantial potential for attrition. To proactively address this problem, we identified all potential avenues for recruiting and factored in the attrition rate when determining the appropriate sample size [27,30]. Considering the features and design of this pilot project, it would not be possible to blind the treatment assignment and result evaluation. However, participants were provided with information regarding the significance of a 2-arm study design following the CONSORT checklist (can be seen in Multimedia Appendix 1) and were strongly advised against disclosing their group allocation to their coworkers. Although there may be possible problems, this strong methodology will guarantee that the BM-MA intervention is carried out with a high level of academic excellence.

Assessments Tools

There were 4 points of measurement: screening, baseline, end line, and follow-up. In Table 1, following the SPIRIT 2013 statement [26], an overview of the evaluation instruments used in this study is presented. Both groups received compensation for the time they spent and the internet data they used throughout the baseline, end line, and follow-up periods. The compensation amounts were ~US $3 for baseline, US $7 for the end line, and US$ 10 for follow-up, which is equivalent to the average cost of obtaining internet data in Indonesia. The act of providing monetary compensation as reimbursement is noncontroversial and commonly acknowledged [31].

Table 1. Study outcomes and time points of measurement.

Outcome	Instrument	Screening	Baseline	End line	Follow-up
			Day 1	Day 21	Day 41
Sociodemographics (age, education level, sex, marital status, occupation, years as schoolteacher, salary, schoolteacher status)	Demographics	Y[a]	Y	—[b]	—
Source of obtaining BM-MA[c] information	Demographics	Y	—	—	—
Mental health care service history	Demographics	Y	Y	Y	Y
Smartphone ownership	Demographics	Y	Y	—	—
Internet access	Demographics	Y	Y	—	—
Contact details	Demographics	Y	—	—	—
Convenient contact times	Demographics	Y	—	—	—
Perceived stress	PSS[d]	—	Y	Y	Y
Depression symptoms	GHQ-12[e]	Y	Y	Y	Y
Anxiety symptoms	GAD-7[f]	Y	Y	Y	Y
Well-being	SLS[g] and SCS-SF[h]	—	Y	Y	Y
Self-efficacy	TSES[i]	—	Y	Y	Y
Mindfulness trait	FFMQ[j]	—	Y	Y	Y
Engagement and experiences with the BM-MA	Questionnaires	—	Y	Y	Y
Qualitative interview of feasibility and acceptability	Interview guideline	—	—	Y	Y

[a]Y: measured.

[b]Not measured.

[c]BM-MA: brief mindfulness–based mobile app.

[d]PSS: Perceived Stress Scale.

[e]GHQ-12: General Health Questionnaire-12.

[f]GAD-7: Generalized Anxiety Disorder.

[g]SLS: Satisfaction With Life Scale.

[h]SCS-SF: Self-Compassion Scale—Short Form.

[i]TSES: Teachers' Sense of Efficacy Scale.

[j]FFMQ: Five Facet Mindfulness Questionnaire.

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Sociodemographic and Personal Information

During the screening session, participants' sociodemographic and personal information was collected using a combination of questions. The open questions inquired about participant age, years as a teacher, and salary, whereas the closed questions required participants to select from a list of options, such as the education level and internet access on a smartphone (yes/no). To ensure participants' eligibility, sociodemographic and personal data were requested once again at baseline.

Measurement of Primary Outcome

The evaluation of the BM-MA implementation in real-world contexts will be the primary outcome for this study. This study will evaluate the adoption of the BM-MA with an engagement and experience questionnaire. On the basis of Howell et al's [22] findings, a questionnaire will be designed to allow participants to rate their experience using the app.

Measurement of Secondary Outcomes

Anxiety was measured with the GAD-7 as a secondary outcome. The GAD-7 is a brief, self-administered scale with a few measures for measuring anxiety that was first administered to primary care patients [32,33]. The scale has been translated into other languages. People have adjusted the items to suit different contexts. It has high psychometric qualities, which enables it to detect anxiety and depression quickly and precisely [32]. Items are rated from 0 (absence of anxiety) to 3 (anxiety is felt most of the days) [33], and the overall score ranges from 0 to 21. Higher scores indicate that the respondent exhibits more anxiety symptoms. In this study, the GAD-7 demonstrated strong reliability and validity in terms of criteria, the concept, and factorial and procedural measures. An optimal cut-off was set that maximized sensitivity (89%) and specificity (82%) [32].

To determine the psychological well-being of participants, we measured their life satisfaction, sense of self-efficacy, and self-compassion. Life satisfaction was measured with the Satisfaction With Life Scale (SLS). Perceived self-efficacy was measured with the Teachers' Sense of Efficacy Scale (TSES) [34]. For the TSES, higher scores show a higher sense of self-efficacy. The reliability of the TSES subscales was 0.91 for instruction, 0.90 for management, and 0.87 for engagement. The intercorrelation among the instruction, management, and engagement subscales was 0.60, 0.70, and 0.58, respectively, with a significance level of $P<.001$ [34]. Self-compassion was measured with the 12-item Self-Compassion Survey—Short Form (SCS-SF) [35]. The SCS-SF includes 3 subscales: self-kindness versus self-judgment, common humanity versus isolation, and mindfulness versus overidentification. Higher scores indicate higher self-compassion. The internal consistency of the SCS-SF was found to be satisfactory, with Cronbach α of .86 or higher in all samples [35].

In addition, depression symptoms of the participants were measured using the GHQ-12. This scale has been psychometrically validated for use as a screening instrument for depression symptoms in primary health services in numerous countries and has high validity and reliability [36]. Reliability analysis revealed a respectable outcome, with Cronbach α of .87 [37]. The most common scoring methods are bimodal (0-0-1-1) and Likert scoring styles (0,1,2,3) [37]. For the GHQ-12, higher scores indicate depression and physical and social dysfunction. The perceived stress condition was assessed using the 10-item Perceived Stress Scale (PSS) [38]. This scale examines the responses of participants to a variety of potentially stressful circumstances with 2 variables. The reliability coefficients for the scores on these 2 variables were 0.87 and 0.73, respectively [38]. Higher scores indicate a higher level of perceived stress.

The mindfulness trait was assessed using the Five Facet Mindfulness Questionnaire (FFMQ). This instrument was created on the basis of a factor analytic assessment of 5 independently developed mindfulness questionnaires [39]. The FFMQ has repeatedly demonstrated strong psychometric qualities, including high levels of construct validity and reliability. The subscales of the FFMQ have Cronbach α ranging from 0.73 to 0.91, indicating good internal consistency [40]. Baer et al [39] identified 5 parameters that appear to represent mindfulness aspects as they are currently conceived: observing, describing, acting with awareness, not judging the inner experience, and not reacting to the inner experience. Higher scores indicate a greater level of mindfulness in individuals.

Ethical Considerations

Ethical Approval

The BM-MA is a digital nonpharmaceutical mental health intervention whose content was adapted from 1 of the existing mindfulness-based apps that has been shown to be safe for treating anxiety [41]. The trial protocol was approved by the Research Ethics Committee at Universitas Pendidikan Ganesha (1828/UN48.16/LT/2022) and publicly registered (Chinese Clinical Trial Registry with protocol number ChiCTR2300068085). The intervention also ensured that no participant will be stigmatized for their participation. An introduction meeting was held on Zoom to address the potential stigma around mental health interventions and explore strategies for effectively managing this stigma. We will be communicating to the research committee in the case of any important protocol modifications. Written informed consent was obtained from each participant. The intervention content, which includes an activity to learn and practice mindfulness exercises via a mobile app, was rewritten or sensitive or potentially objectionable terms were eliminated.

Data Management

Data collection was conducted electronically. The data were securely stored on password-protected computers, and only members of the study group have access to them. To ensure the confidentiality of the participants, distinct, unique study numbers were used for data storage, tracking, and reporting. An encryption protocol used complex algorithms to obscure data, which it then decoded using an encryption key that the interaction's sender provided. The data cleaning procedure systematically and proactively identified mistakes. Errors were deliberately and methodically sought out through the data cleaning procedure. Repeated imputation was used to manage missing data due to its reliability in dealing with missing data

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in a feasibility study and its availability for the vast majority of data types [42].

Data Analyses

The sociodemographic characteristics of the participants (eg, age) will be analyzed descriptively. Missing data, including participants who dropped out, will be treated using the intention-to-treat principle with multiple imputations of missing values [42]. Intention-to-treat analysis is a statistical method used in prospective randomized studies. It involves including all individuals who were randomly assigned to a group, regardless of whether they received any sort of treatment. These participants are then examined on the basis of their initial group assignment. This methodology enables the researcher to derive precise and impartial judgments regarding the efficacy of an intervention. This approach maintains the advantages of randomization, which cannot be presumed when using alternative methods of analysis.

The data will be examined using repeated-measures ANOVA with groups (BM-MA vs control) and 3 time periods as factors (baseline, day 21, day 41). In addition, Pearson correlation analysis will be undertaken to determine whether the subjective ratings of involvement and experience with the BM-MA by participants correlate with any potential improvements in well-being experienced by the BM-MA group. The variation in findings between the 2 groups will be encompassed by the 95% CI range for the significance of the effect. The amount of effect (Cohen d) will be calculated by dividing the median variation (from baseline, monitoring, and end line to follow-up) obtained from the results of the linear mixed model by the pooled SD at baseline.

Transcription will be conducted for all records of structured qualitative interviews. The qualitative data will undergo deductive theme analysis using a framework and will be used to create an initial codebook. The qualitative data will be analyzed using an iterative method by 2 coders, who will independently code all transcripts and then discuss any inconsistencies until consensus is established. The resulting comprehensive codebook will be input into qualitative analysis software.

Results

This protocol funding started in May 2023. Participants for this pilot RCT were recruited in December 2023, and the RCT was conducted from January through March 2024. Data analysis was conducted from March through May 2024. Paper writing based on the data analysis is ongoing. The expected results of this study will be published in December 2024. The BM-MA display can be seen in Figures 1-3.

Figure 1. Screenshot 1 of the brief mindfulness–based mobile app (BM-MA).

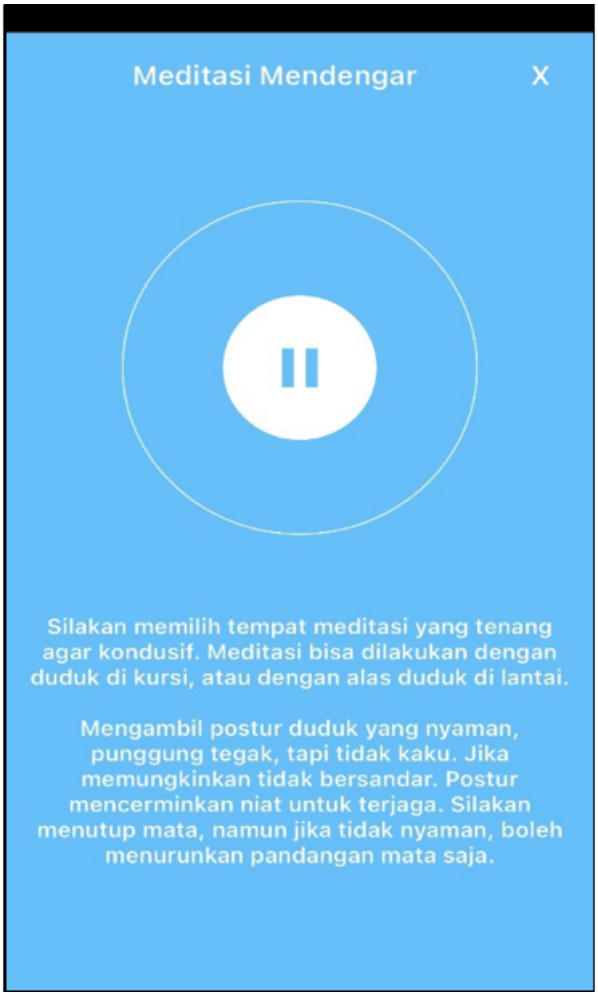

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Figure 2. Screenshot 2 of the brief mindfulness–based mobile app (BM-MA).

Figure 3. Screenshot 3 of the brief mindfulness–based mobile app (BM-MA).

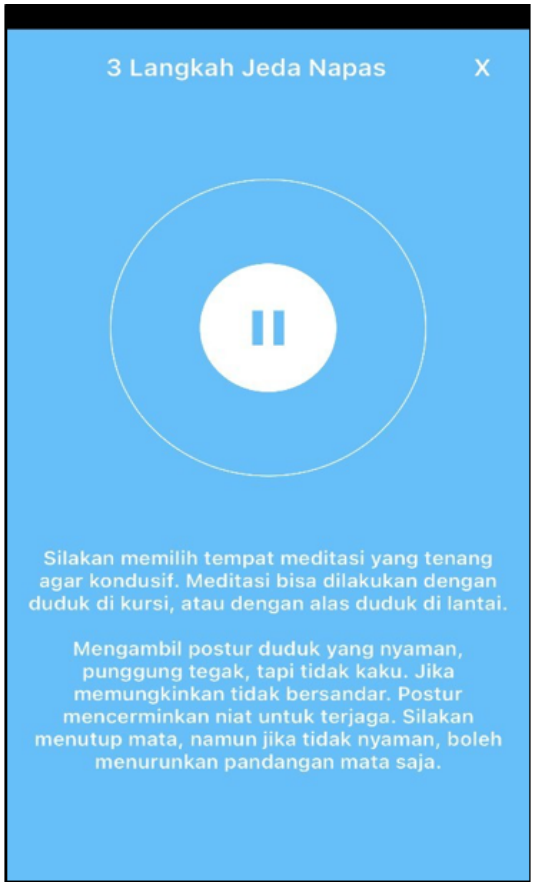

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Discussion

Summary of Findings

This study seeks to explore the feasibility, acceptability, and efficacy of the BM-MA for Indonesian high school teachers. According to our understanding, the BM-MA is the first evidence-based nonpharmacological intervention in the Indonesian language aimed toward communities, particularly senior high school teachers, in order to address the difficulties in accessing mental health treatments in Indonesia. This protocol provides exhaustive details on how the intervention will be carried out. The reason for the study design, including its overview and context, has been provided.

This protocol offered extensive information regarding the execution of the trial. The study design's explanation has been clarified, comprising its overview and setting. Furthermore, theoretical and pragmatic reasons for the implementation of recruitment, screening, intervention, and assessment have been acknowledged, including primary and secondary assessments, as well as follow-up evaluation. Efforts have been made to address both ethical and safety concerns in order to uphold the integrity of the research and ensure the safety of the participants. The protocol implementation has been additionally enhanced by the participation of teacher communities in recruitment and the significant degree of enthusiasm among participants in digital mental health interventions.

The BM-MA intervention feasibility protocol will investigate multiple outcomes, such as teachers' life satisfaction, self-efficacy, self-compassion, anxiety, stress, and mindfulness state, among senior high school teachers in Indonesia. The outcome of this feasibility study will also examine pre- and postintervention measures to detect any significant changes. The consequences of the findings will determine whether a BM-MA intervention should be recommended for efficacy testing [25]. This feasibility study aims to assess the potential implementation of the BM-MA in practical applications.

Nonetheless, any trial may encounter difficulties, particularly with attrition, a typical issue in clinical trials [43]. To anticipate the problem of attrition, all teacher communities, including the local government partner (Dinas Pendidikan Kepemudaan dan Olahraga Provinsi, Province Youth and Sports Office), that contribute to the recruitment process were discovered and the rate of attrition accounted for in the sample size calculation [43]. The participants were provided with an explanation of the relevance of the study. Attrition can be solved with the condition that 72% of participants in the preliminary survey [6] had a strong interest in using digital mental health interventions.

The study findings have practical implications for the adoption of digital mental health interventions in Indonesia, particularly among schoolteachers. The preparedness of the BM-MA to be publicly accessible, in partnership with local government partners in the education sector, is a key factor. Undoubtedly, the potential impact of the BM-MA in addressing the mental health needs of schoolteachers is highly important. Therefore, it is imperative to consider collaborating with the Indonesian government to enhance treatments.

The potential future research directions based on the study findings could involve performing larger-scale efficacy trials or investigating the long-term benefits of the BM-MA for the wellness of schoolteachers. It is necessary to evaluate potential areas for improving or adapting the intervention based on feedback from participants and recent research, such as integrating functionalities within the app to guarantee its accessibility for users with specific requirements.

Hence, we believe that the BM-MA intervention passes rigorous academic criteria. We will publish the findings of the feasibility study in both an international journal and an international conference. We will use the Contributor Roles Taxonomy (CRediT) to evaluate the authorship and provide a detailed description of each author's data set and statistical code.

Conclusion

This study will establish essential information regarding the feasibility and efficacy of the BM-MA, a digital mental health intervention modified from 1 of the existing mindfulness-based apps, as well as its scalability. This research is crucial for developing knowledge and practice in the field of digital mental health. If the BM-MA demonstrates a considerable positive effect on life satisfaction, self-efficacy, self-compassion, anxiety, and stress among Indonesian senior high school teachers, it will have the potential to be used by Indonesian schoolteachers who might also develop anxiety symptoms and find it challenging to seek expert mental health services. This feasibility study's findings will be published in an international journal and also presented at a conference. Moreover, the future application the BM-MA could be through collaborative efforts with the Indonesian government.

Acknowledgments

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Authors' Contributions

GRD, NMA, AL, NKAS, and SLK conceived and designed the research; GRD, NMA, and AL contributed materials/analysis tools; GRD, NMA, AL, NKAS, and NWSM wrote the paper; and GRD, SLK, and NWSM reviewed the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 65 KB - resprot_v13i1e56693_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 132 KB - resprot_v13i1e56693_app2.pdf]

Multimedia Appendix 3
Informed consent.
[DOCX File , 14 KB - resprot_v13i1e56693_app3.docx]

Multimedia Appendix 4
Figure S1. Overview of BM-MA pilot randomized controlled trial study design following CONSORT diagram. BM-MA: brief mindfulness–based mobile app; CONSORT: Consolidated Standards of Reporting Trials.
[DOCX File , 42 KB - resprot_v13i1e56693_app4.docx]

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Abbreviations

BM: brief mindfulness
BM-MA: brief mindfulness–based mobile app
CG: control group
CONSORT: Consolidated Standards of Reporting Trials
CSQ-8: Client Satisfaction Questionnaire-8
FFMQ: Five Facet Mindfulness Questionnaire
GAD-7: Generalized Anxiety Disorder-7
GHQ-12: General Health Questionnaire-12
MBCT: mindfulness-based cognitive therapy
MBSR: Mindfulness-Based Stress Reduction
PSS: Perceived Stress Scale
RCT: randomized controlled trial
SCS-SF: Self-Compassion Scale—Short-Form
SLS: Satisfaction with Life Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TSES: Teachers' Sense of Efficacy Scale

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Protocol

Efficacy and Safety of the Natural Killer T Cell–Stimulatory Glycolipid OCH-NCNP1 for Patients With Relapsing Multiple Sclerosis: Protocol for a Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system that causes myelin sheath damage and axonal degeneration. The glycolipid (2S, 3*S*, 4*R*)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol (OCH-NCNP1 or OCH) exerts an immunoregulatory action that suppresses T helper (Th)1 cell–mediated immune responses through natural killer T cell activation, selective interleukin-4 production, and Th2 bias induction in human CD4-positive natural killer T cells.

Objective: This trial aims to investigate the efficacy and safety of the immunomodulator OCH in patients with relapsing MS through 24-week repeated administration.

Methods: This protocol describes a double-blind, multicenter, placebo-controlled, randomized phase II clinical trial that was initiated in September 2019. The participants were randomly assigned to either a placebo control group or an OCH-NCNP1 group and the investigational drug (3.0 mg) was orally administered once weekly for the 24-week duration. Major inclusion criteria are as follows: patients had been diagnosed with relapsing MS (relapsing-remitting and/or secondary progressive MS) based on the revised McDonald criteria or were diagnosed with MS by an attending physician as noted in their medical records; patients with at least two medically confirmed clinical exacerbations within 24 months prior to consent or one exacerbation within 12 months prior to consent; patients with at least one lesion suspected to be MS on screening magnetic resonance imaging (MRI); and patients with 7 points or less in the Expanded Disability Status Scale during screening. Major exclusion criteria are as follows: diagnosis of neuromyelitis optica and one of optic neuritis, acute myelitis, and satisfying at least two of the following three items: (1) spinal cord MRI lesion extending across at least three vertebral bodies, (2) no brain MRI lesions during onset (at least four cerebral white matter lesions or three lesions, one of which is around the lateral ventricle), and (3) neuromyelitis optica–immunoglobulin G or antiaquaporin-4 antibody-positive. Outcome measures include the primary outcome of MRI changes (the percentage of subjects with new or newly expanded lesions at 24 weeks on T2-weighted MRI) and the secondary outcomes annual relapse rate

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(number of recurrences per year), relapse-free period (time to recurrence), sustained reduction in disability (SRD) occurrence rate, period until SRD (time to SRD occurrence), no evidence of disease activity, and exploratory biomarkers from phase I trials (such as gene expression, cell frequency, and intestinal and oral microbiome).

Results: We plan to enroll 30 patients in the full analysis set. Enrollment was closed in June 2021 and the study analysis was completed in March 2023.

Conclusions: This randomized controlled trial will determine whether OCH-NCNP1 is effective and safe in patients with MS as well as provide evidence for the potential of OCH-NCNP1 as a therapeutic agent for MS.

Trial Registration: ClinicalTrials.gov NCT04211740; https://clinicaltrials.gov/study/NCT04211740

International Registered Report Identifier (IRRID): DERR1-10.2196/46709

(JMIR Res Protoc 2024;13:e46709) doi:10.2196/46709

KEYWORDS

OCH-NCNP1; natural killer cell; multiple sclerosis; clinical study; randomized controlled trial; autoimmune inflammatory disease; degeneration; clinical efficacy; biomarker; relapse; disability; imaging; autoimmune; RCT; Expanded Disability Status Scale; EDSS; neuromyelitis optica; optic neuritis; acute myelitis; Fisher exact test; MRI; magnetic resonance imaging; myelin sheath; demyelinating lesion; aminotransferase; clinicopathology; pathology

Introduction

Multiple sclerosis (MS) is considered to be an autoimmune disease triggered by environmental factors that act on a genetically susceptible host. Both major histocompatibility complex (MHC) and non-MHC genes are risk factors for the development of MS. In addition, environmental factors such as low vitamin D, low ultraviolet radiation exposure, cigarette smoking, obesity, and Epstein-Barr virus exposure can increase the risk for both the development of MS and a more severe disease course. Accumulating evidence suggests that dysregulation of the intestinal microbiome (dysbiosis) constitutes an important factor contributing to MS pathogenesis. The microbiome regulates T cell function, with both regulatory and pathogenic effects, thereby playing an important role in autoimmune responses [1].

MS is a cell-mediated autoimmune disease directed against central nervous system (CNS) myelin antigens involving both CD4+ and CD8+ T cells, especially the so-called pathogenic T helper (Th)17- and Th1-type and CD8 myelin autoreactive T cells. The development of MS is likely triggered or promoted by breakdown of the delicate balance between autoreactive T cells and regulatory lymphocytes [1].

Although MS has historically been considered a demyelinating disease of the CNS and white matter, in recent years, neurodegeneration of the cortical and deep gray matter has been recognized to play a role in the pathogenesis of MS. Cortical atrophy is associated with disease progression, which has emerged as one of the best predictors of neurological disability in MS [1].

According to a recent worldwide epidemiological study, the number of patients with MS is estimated to be 2.8 million, which has been increasing in every world region since 2013 [2]. The estimated total economic burden of MS in the United States is US $85.4 billion, with a direct medical cost of US $63.3 billion and indirect and nonmedical costs of US $22.1 billion [3].

Relapsing-remitting MS (RRMS) initially involves clinical relapses with near or complete recovery; however, recovery over time may be incomplete and disability often worsens [4]. Approximately 20% of patients with RRMS develop a progressive form of MS accompanied by chronic neuroinflammation. Such cases are referred to as secondary progressive MS (SPMS). The term “relapsing MS” (RMS) is used to describe the condition of patients with repeated relapses of either RRMS or SPMS.

As understanding of the pathomechanism of MS progresses, various disease-modifying drugs have been used in clinical practice, including sphingosine-1-phosphate receptor modulators (fingolimod, siponimod), a monoclonal antibody that selectively binds the α4 integrin subunit (natalizumab), and CD20 monoclonal antibodies (ofatumumab, ocrelizumab), resulting in an overall improvement of patient prognosis. However, there are patients for whom current treatments are ineffective and there are cases where current treatments are intolerable due to side effects. Furthermore, progressive MS remains refractory to current drugs and constitutes an unmet medical need [4]. These observations highlight the need for new, safer therapeutic oral agents.

In 1997, Kawano et al [5] reported the discovery of sponge-derived α-galactosylceramide (α-GC) as a glycolipid ligand that stimulates natural killer T (NKT) cells. However, because this glycolipid stimulates NKT cells and induces the production of both interleukin (IL)-4 and interferon (IFN)-γ, a search for glycolipids that selectively induce IL-4 production was initiated to treat Th1 cytokine–dependent autoimmune diseases such as MS. These efforts led to the discovery of (2*S*, 3 *S* , 4*R*)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol (OCH-NCNP1; hereafter referred to as OCH), which was detected during screening for glycolipids that selectively induce the production of Th2 cytokines [6].

OCH is a derivative (synthetic glycolipid) of α-GC with a shortened fatty-acid chain (sphingosine chain). The compound is a white to slightly yellow powder that is extremely insoluble in methanol or ethanol and is practically insoluble in water. OCH exhibits an immunoregulatory action that suppresses Th1 cell–mediated immune responses through NKT cell activation,

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selective IL-4 production, and Th2 bias induction in human CD4+ NKT cells [7].

Although the mechanism by which OCH induces Th2 bias in NKT cells is not fully understood, it has been suggested to involve both cell intrinsic and extrinsic factors [8,9]. As a cell intrinsic mechanism, IFN-γ production by NKT cells was reported to be more susceptible to the sphingosine length of the glycolipid ligand compared to IL-4 production, and the length of the sphingosine chain determined the half-life of NKT cell stimulation by CD1d-associated glycolipids. As an extrinsic regulatory mechanism, OCH suppresses the production of IFN-γ, not only by NKT cells but also by NK cells, compared with that of α-GC. OCH induced lower IL-12 production due to ineffective primary IFN-γ and CD40 ligand expression by NKT cells, which resulted in lower secondary IFN-γ induction.

Animal studies verified that OCH can be administered orally to control Th1 cell–mediated autoimmune pathology in mice, with efficacy against autoimmune disease models such as experimental autoimmune encephalomyelitis, collagen-induced myelitis [10], nonobese diabetes [11], and inflammatory enteritis [12].

We here describe a protocol for a feasibility study that will be conducted in patients with RMS to investigate the efficacy and safety of OCH immunomodulators. Through 24 weeks of weekly administration, this trial was performed to confirm changes in exploratory T cell and NK cell biomarkers that fluctuated in the phase I trial [13], as well as measures of efficacy, including recurrence, dysfunction, and magnetic resonance imaging (MRI) changes, and their association with combined endpoints. In alignment with past clinical trials [14,15] and European Medical Agency guidelines, the primary outcome will be the percentage of subjects with new or newly expanded lesions at 24 weeks on T2-weighted MRIs.

Methods

Study Design

This is a double-blind, multicenter, placebo-controlled, randomized phase II clinical trial with a 24-week duration. This trial investigates the efficacy and safety of the immunomodulator OCH in patients with RMS through 24-week repeated administration. The protocol was also designed to confirm exploratory biomarkers of T cells and NK cells that fluctuated in the phase I trial [13], as well as efficacy-related clinical endpoints, including relapses, disability, and MRI changes, and their association with combined endpoints. Recruitment opened in September 2019 and concluded in June 2021, with participants randomly assigned to either a placebo control group or an OCH group using a clinical-based management system (Translational Research Center for Medical Innovation, Kobe, Japan). The researchers were blinded to the participant group assignments, and the packaging appearance of the control and investigational drugs was confirmed to be indistinguishable.

An independent data monitoring committee will regularly audit all available data, including safety, and recommend trial continuation to the principal investigator.

Selection Criteria

Inclusion and exclusion criteria for this study are provided in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients who provided written consent for trial participation
- Patients had been diagnosed with relapsed multiple sclerosis (MS), including relapse-remitting MS and/or secondary progressive MS, based on the revised McDonald criteria or were diagnosed with MS by an attending physician as noted in their medical records
- Patients with at least two medically confirmed clinical exacerbations within 24 months prior to consent or one exacerbation within 12 months prior to consent
- Patients with at least one lesion suspected to be MS on screening magnetic resonance imaging (MRI)
- Patients with 7 points or less in the Expanded Disability Status Scale during screening
- Patients who were 20-65 years old at the time of consent
- Patients who can practice contraception until 90 days after final administration of the investigational drug
- Patients with no clinical or test findings suggesting acute recurrence based on evaluation by a neurologist

Exclusion criteria

- Diagnosis of neuromyelitis optica and one of the three following three criteria: optic neuritis, acute myelitis, and satisfied at least two of the following three items: (1) spinal cord MRI lesion extending across at least three vertebral bodies, (2) no brain MRI lesions during onset (at least four cerebral white matter lesions or three lesions, one of which is around the lateral ventricle), and (3) neuromyelitis optica–immunoglobulin G (IgG) or antiaquaporin-4 antibody-positive
- Currently pregnant or nursing
- Contraindication for MRI (eg, those with metal implants or a pacemaker) or cases in which MRI is difficult to perform (eg, claustrophobia)
- History of allergic or hypersensitive reaction to gadolinium contrast
- History of liver disease, including liver transplantation, viral hepatitis, autoimmune hepatitis, cirrhosis, and hepatic malignancies
- Liver dysfunction determined by the screening test or baseline test (alanine aminotransferase, aspartate aminotransferase, γ-guanosine triphosphate, or alkaline phosphatase) exceeding twice the upper limit of normal and total bilirubin exceeding 1.5-fold the upper limit of normal
- History of malignant tumors in the past 5 years (however, patients deemed to have no recurrence for at least 5 years prior to consent can be enrolled)
- Varicella-zoster virus IgG antibody–negative
- Positive for syphilis serum reaction (treponema pallidum latex agglutination, rapid plasma reagin)
- positive for β-D glucan (exceeding the standard value) or T-spot
- positive for antiaquaporin-4 antibody
- history of human immunodeficiency virus infection or who have been confirmed positive by a screening test
- History of hepatitis B infection (hepatitis B surface antigen–positive or hepatitis B core antibody–positive), or patients who have been confirmed positive by a screening test
- History of stem cell transplantation, organ transplantation, and treatment for rejection
- Physical, mental, or social condition affecting the ability to provide consent to or complete the trial
- Participation in other clinical trials that received the investigational drug within 4 months prior to enrollment
- Blood donation (200 mL within 2 months, 400 mL within 3 months) prior to enrollment
- Peripheral blood lymphocyte count <600/mm^3 by screening or baseline examination
- With or suspected of having an infectious disease
- Immunocompromised patients
- Inflammatory bowel disease
- Use of the following prohibited concomitant therapies:

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interferon-β preparation (prohibited 1 month before trial enrollment); fingolimod hydrochloride (prohibited 6 months before trial enrollment); natalizumab (prohibited 3 months before trial enrollment); glatiramer acetate (prohibited 1 month before trial enrollment); dimethyl fumarate (prohibited 3 months before trial enrollment); drugs other than azathioprine that have immunosuppressive, immunostimulatory, or myelosuppressive effects (prohibited 3 months before trial enrollment); pulse therapy using corticosteroids (prohibited 1 month before clinical trial registration, except when MS recurs); plasmapheresis, immunoadsorption therapy, lymphocyte depletion therapy (prohibited from the time of consent acquisition); immunoglobulin preparation (prohibited 2 months before trial enrollment); vaccines (prohibited 1 month before trial enrollment, except when permitted by the investigator); other investigational drugs (prohibited 4 months before trial enrollment); nonsteroidal anti-inflammatory drug (liver damage at the time of screening should be checked, and for patients who take it regularly, this drug can be used in combination by fixing the dosage and administration. Additionally, when used for adverse events, it should be possible to use this drug within the minimum necessary range)

Additional exclusion criteria:

- Patients with evident prolongation of the QT/QTc interval prior to the trial (eg, patients with repeating QTc interval>450 ms)
- Patients with a history of other risk factors for torsades de pointes (eg, family history of heart failure, hypokalemia, and long QT syndrome)
- History of severe drug or food allergy
- Patients with drug or alcohol dependence in the past or present
- Asthma (excluding patients with no history of treatment or attack for at least 10 years)
- Diagnosis of epilepsy or patients with a history of seizures (excluding febrile seizures)
- Other pathological symptoms, illnesses, or history that may affect this trial
- Other factors resulting in unsuitability for this trial as deemed by the principal investigator; if such exclusion occurs, the specific rationale will be described in the trial results

Sample Size Estimate

The target number of participants was 30 (15 per group) based on feasibility. The detection power was calculated when the primary outcome (proportion of subjects with new or enlarged existing lesions detected on T2-weighted images) was compared using the Fisher exact test. With 60% of patients placed in the placebo group based on the results of the domestic phase II study (D1201 study) at the time of fingolimod development [16] and assuming a 5% proportion in the OCH group, the detection power was 86.5%. Furthermore, when the OCH group was set to 10%, the detection power was 74.6% (the significance level was set to 5% using a two-tailed test).

Patient Clinicodemographic Characteristics

The following clinicodemographic information was recorded for each participant: (1) subject background (eg, birth date, sex, body height, body weight); (2) urine pregnancy test; (3) infectious disease or antibody test; (4) vital signs (blood pressure, pulse rate, body temperature, and breathing rate); (5) neurological symptoms rating scale (Expanded Disability Status Scale [EDSS] or functional disability scale); (6) clinical tests (hematological test, hematobiochemical test, or urine test); (7) 12-lead electrocardiogram; (8) echocardiography; (9) chest or abdominal X-ray; (10) abdominal computed tomography; (11) MRI; (12) peripheral blood gene expression level (reverse transcription–polymerase chain reaction); (13) frequencies of NK, NKT, T cells, or other lymphocyte subsets; (14) frequencies of Th1, Th2, or Th17 cells; (15) intestinal and oral microbiome; (16) adverse events; (17) combination drugs and important nondrug therapies; and (18) Columbia Suicide Severity Rating Scale.

Outcome Measurements and Study Timeline

The outcomes that will be measured repeatedly throughout the trial and the corresponding time points are shown in Multimedia Appendix 1. The main outcome is MRI changes (the percentage of subjects with new or newly expanded lesions on T2-weighted MRI). In addition, the annual relapse rate, cumulative number of new or newly expanded lesions on T2-weighted MRI, percentage of subjects who did not have lesions at 12 and 24 weeks on T2-weighted images of head MRI compared to those at the preobservation period at 24 weeks, brain atrophy in T1-3D images, percentage of subjects with no contrast-enhanced lesions on gadolinium-enhanced T1-weighted images, number of contrast-enhanced lesions on gadolinium-enhanced T1-weighted images, changes in volume of demyelinating lesions on fluid-attenuated inversion recovery 3D images, diffusion tensor imaging changes in myelin sheath lesions, and changes in myelin sheath lesions by a myelin map will be assessed. Additional outcomes include the relapse-free period (from randomization to earliest relapse), sustained reduction in disability occurrence rate, period until sustained reduction in disability (from randomization), no evidence of disease activity, and exploratory biomarkers from phase I trials (peripheral blood gene expression, frequencies of lymphocyte subsets, and intestinal and oral microbiome) [13].

Adverse Events

Adverse events, defined as any undesired or unintended sign (including abnormal fluctuations in each test value), symptoms, or illness that occurs between the start of investigational drug administration and end or discontinuation of the investigational drug (regardless of its association with the study drug), will be recorded. The recordings will include the degree of symptoms on a 1-5 scale (1=asymptomatic or mild adverse events, 5=death due to the adverse event), outcomes from 1 to 6 (1=event disappeared or normalized, 6=death), and association with the

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investigational drug from 1 to 4 (1=associated, 4=not associated).

Discontinuation Criteria

Discontinuation of involvement in the clinical trial may occur for any patient because of voluntary withdrawal or for any of the following reasons: (1) serious adverse events; (2) pregnancy; (3) alanine aminotransferase and aspartate aminotransferase >5-fold higher than the standard value upper limit; (4) total bilirubin exceeding 2.0 mg/dL; (5) number of peripheral blood lymphocytes <500/mm^3 and administration of the investigational drug is stopped three times in a row without recovery, even after three tests; (6) occurrence of a grade-3 event based on Common Terminology Criteria for Adverse Events v4.0-JCOG; (7) new neurological symptoms with unpredictable MRI findings observed from the course of MS; (8) more than one recurrence of MS; (9) at least three courses of pulse steroid therapy performed; (10) an important management problem is discovered (subject noncompliance); (11) significant deviation from the protocol; (12) administration of the investigational drug is stopped at least three times, regardless of the reason; and (13) at the discretion of the principal investigator. If discontinuation occurs because of this final criterion, justification will be provided in the results report.

Administration of Trial Compound

The investigational drug OCH (3.0 mg) in the form of granules (total of 0.3 g) or placebo granules alone (0.3 g) was orally administered with approximately 150 mL of water 30 min before breakfast once weekly for the 24-week trial duration. The white granules were composed of crystalline cellulose, mannitol, sodium croscarmellose, low-substituted hydroxypropyl cellulose, and polysorbate 80.

Statistical Methods

Patient clinicopathological data will be summarized using descriptive statistics for each group. The proportion of subjects with new or enlarged existing lesions on T2-weighted MRIs in each group will be calculated and compared using the Fisher exact test with 95% CIs. The proportion of data between groups related to the primary endpoint will also be compared using the Fisher exact test with 95% CIs. For time-to-event data such as relapse-free periods, Kaplan-Meier estimates will be calculated for each group and groups will be compared using the log-rank test. The expression rates of safety-related outcomes and adverse events will be calculated for each group. For various test values, a list of measured values will be created for each group. The summary statistics for each group and measurement time point will also be calculated.

Patient and Public Involvement

Patients were first involved in this study during the recruitment and screening processes. Based on previous experiences with patients with MS, the importance of the outcomes measured in this study was evaluated and determined based on their medical importance and impact on the patients' quality of life. The patients recruited for the study agreed to the methods of disseminating the aggregate results when providing informed consent.

Ethical Considerations

This study was conducted in compliance with the Declaration of Helsinki and all applicable local and national regulatory laws with approval from the National Center of Neurology and Psychiatry institutional review board (approval number II-013). The legal representatives of each patient provided written informed consent prior to participation in the study. Copayment reduction fees were paid to the trial participants in accordance with the regulations of the implementing medical institution.

Dissemination

The results will be disseminated in peer-reviewed journals and presented at relevant conferences.

Results

The first patient completed registration in December 2019 and the last patient completed registration in June 2021. The full analysis set comprised 30 cases and the study analysis was completed in March 2023. Preliminary analysis suggests that OCH may be effective for RMS (particularly SPMS).

Discussion

Principal Results

This will be the first randomized double-blind placebo-controlled trial to study the efficacy and safety of OCH. This randomized controlled trial will determine whether OCH is effective and safe in patients with MS. The results of this trial are expected to provide evidence for the potential of using OCH as a therapeutic agent for MS.

A single-dose trial (STEP 1) trial was conducted in healthy adults from November 2012 to July 2013 and a repeated-dose trial (STEP 2) was conducted in patients with RRMS from March 2014 to August 2017 [13]. In a phase I trial consisting of STEP 1 and STEP 2, OCH was administered to 28 patients (STEP 1: 3 patients×5 groups in all cohorts, STEP 2: 7 patients×1 group in a cohort, 3 patients×2 groups in a cohort).

Grade-1 adverse events and side effects were noted in STEP 1 and there were no serious adverse events or discontinuations. In STEP 2, serious side effects (acidosis and altered state of consciousness, depression, muscle weakness, and malaise) were reported in three patients in the 0.3 and 3 mg groups. Two patients discontinued treatment; however, all patients recovered. No other serious events were observed, confirming that the patients tolerated doses of 0.3, 1, and 3 mg. After OCH administration, there was no significant change in the neurological symptom evaluation scale score (EDSS or functional disability scale) even in STEP 2 because of the short observation period. MRI revealed clinically significant abnormalities in one patient in the 0.3 mg group; this patient discontinued the study.

A phase I physician-led clinical trial, conducted as an early exploratory clinical trial, determined that the dose was likely to have pharmacological action (fluctuations in some biomarkers) in humans. The dose at which pharmacological action was observed in experimental autoimmune

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encephalomyelitis model mice was 0.4-0.5 mg/kg. Considering that the area under the curve $(AUC)_{0-\infty}$ following oral administration of 5 mg/kg to mice was 2922 ng·h/mL, the $AUC_{0-\infty}$ following oral administration of 0.5 mg/kg (dose at which pharmacological action was observed) was estimated as 292.2 ng h/mL. Assuming a correlation between systemic exposure ($AUC_{0-\infty}$) and pharmacological effects and systemic exposure in monkeys ($AUC_{0-\infty}$ after oral administration of 10 mg/kg was 2376, SD 1164 ng), pharmacological action may be expected in humans if at least approximately 1.2 mg/kg is orally administered.

In STEP 1 of the phase I trial, administration of OCH at doses of 0.3, 1, 3, 10, 30, 100, and 300 mg to healthy adults was planned. However, STEP 1 was completed at 30 mg; in the subsequent STEP 2, OCH at 0.3, 1, and 3 mg was administered to patients with MS. Importantly, no tolerability problems were noted.

The following changes in exploratory biomarkers were observed. In analysis of the immune cell subsets using flow cytometry, (1) inhibitory T cells (Foxp3+T cells) and effector regulatory T cells (CD45RA-$FoxP3^{high}$ T cells) tended to increase and (2) granulocyte-macrophage colony-stimulating factor–producing Th cells transiently decreased in both healthy subjects and patients with MS. Recently, granulocyte-macrophage colony-stimulating factor–producing Th cells were identified as pathogenic cells in MS [17]. These changes suggest that oral OCH administration can correct the proinflammatory changes linked with disease activity in MS. Moreover, by conducting DNA microarray analysis of whole blood cells, we identified upregulation of several immunoregulatory genes and downregulation of several inflammatory genes in both healthy subjects and patients with MS, further supporting the immunoregulatory effect of OCH.

Based on the above safety profile and biomarker analysis results, a dose of 3 mg was selected as the investigational dose for this trial.

Limitations

The primary limitation of our trial design is the small sample size. The sample size in this study was determined to be 30 participants based on the results of the previous phase I study. This study was limited to a small cohort of patients over a 24-week timeline and involved weekly administration of one dose of OCH. Although necessary in this early stage of the investigation, the small sample size could limit the ability to identify potential adverse events that may be rare or related to specific clinicodemographic traits of patients not captured in this study. However, the robust and clinically relevant nature of our primary outcome measure and sample size determined in prior studies are expected to provide indications of drug efficacy.

Conclusions

This article describes an NKT cell–stimulatory glycolipid (OCH) protocol. This randomized controlled trial will determine whether OCH is effective and safe in patients with MS. The results of the trial are expected to provide evidence for the potential of OCH as a therapeutic agent for MS.

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Data Availability

Data are not included in this protocol, but will be presented in an upcoming paper summarizing the results of this clinical trial. The data sets are available from the corresponding author upon reasonable request taking into account our patent strategy.

Authors' Contributions

TO, TI, RS, YA, HN, WS, and T Yamamura conceived and designed the study and were involved in protocol development. TI, RS, YA, and HN were involved in administrative and regulatory aspects of the study. TI and HN wrote the first draft of the manuscript. YS and YN were involved in patient recruitment. TO, YN, T Yokota, YL, and WS were responsible for data acquisition.

Conflicts of Interest

TO, WS, and T Yamamura disclose that royalties were received from EA Pharma Co, Ltd based on a license agreement. The other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Observation, examination, and survey schedule.
[DOCX File , 26 KB - resprot_v13i1e46709_app1.docx]

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Abbreviations

α-GC: α-galactosylceramide
AUC: area under the curve
CNS: central nervous system
EDSS: expanded disability status scale
IFN: interferon
IL: interleukin
MHC: major histocompatibility complex
MRI: magnetic resonance imaging
MS: multiple sclerosis
NKT: natural killer T cells

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OCH: (2S, 3S, 4R)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol
RMS: relapsing multiple sclerosis
RRMS: relapsing-remitting multiple sclerosis
SPMS: secondary progressive multiple sclerosis
Th: T helper

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Protocol

Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep in Individuals With Insomnia Symptoms: Protocol for a Double-Blind Randomized Controlled Trial

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Abstract

Background: Cortical hyperarousal and ruminative thinking are common aspects of insomnia that have been linked with greater connectivity in the default mode network (DMN). Therefore, disrupting network activity within the DMN may reduce cortical and cognitive hyperarousal and facilitate better sleep.

Objective: This trial aims to establish a novel, noninvasive method for treating insomnia through disruption of the DMN with repetitive transcranial magnetic stimulation, specifically with continuous theta burst stimulation (cTBS). This double-blind, pilot randomized controlled trial will assess the efficacy of repetitive transcranial magnetic stimulation as a novel, nonpharmacological approach to improve sleep through disruption of the DMN prior to sleep onset for individuals with insomnia. Primary outcome measures will include assessing changes in DMN functional connectivity before and after stimulation.

Methods: A total of 20 participants between the ages of 18 to 50 years with reported sleep disturbances will be recruited as a part of the study. Participants will then conduct an in-person screening and follow-on enrollment visit. Eligible participants then conduct at-home actigraphic collection until their first in-residence overnight study visit. In a double-blind, counterbalanced, crossover study design, participants will receive a 40-second stimulation to the left inferior parietal lobule of the DMN during 2 separate overnight in-residence visits. Participants are randomized to the order in which they receive the active stimulation and sham stimulation. Study participants will undergo a prestimulation functional magnetic resonance imaging scan and a poststimulation functional magnetic resonance imaging scan prior to sleep for each overnight study visit. Sleep outcomes will be measured using clinical polysomnography. After their first in-residence study visit, participants conduct another at-home actigraphic collection before returning for their second in-residence overnight study visit.

Results: Our study was funded in September 2020 by the Department of Defense (W81XWH2010173). We completed the enrollment of our target study population in the October 2022 and are currently working on neuroimaging processing and analysis. We aim to publish the results of our study by 2024. Primary neuroimaging outcome measures will be tested using independent components analysis, seed-to-voxel analyses, and region of interest to region of interest analyses. A repeated measures analysis of covariance (ANCOVA) will be used to assess the effects of active and sham stimulation on sleep variables. Additionally, we will correlate changes in functional connectivity to polysomnography-graded sleep.

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Conclusions: The presently proposed cTBS protocol is aimed at establishing the initial research outcomes of the effects of a single burst of cTBS on disrupting the network connectivity of the DMN to improve sleep. If effective, future work could determine the most effective stimulation sites and administration schedules to optimize this potential intervention for sleep problems.

Trial Registration: ClinicalTrials.gov NCT04953559; https://clinicaltrials.gov/ct2/show/NCT04953559

International Registered Report Identifier (IRRID): DERR1-10.2196/51212

(JMIR Res Protoc 2024;13:e51212) doi:10.2196/51212

KEYWORDS

continuous theta burst stimulation; transcranial magnetic stimulation; default mode network; sleep; insomnia; cTBS; randomized controlled trial

Introduction

Overview

The sleep disturbances of insomnia include difficulty falling asleep, staying asleep, or inability to fall back to sleep after premature awakenings, or any combination of these, along with daytime sleepiness and dysfunction. Difficulty falling and remaining asleep affected nearly 30% of the US population, with approximately 20% of the general population experiencing occasional difficulties and an additional 10% meeting the clinical criteria for an insomnia disorder [1]. However, this protocol was conducted during the COVID pandemic, when the prevalence of insomnia symptoms increased to 53% and insomnia disorder prevalence jumped from 10% to 17% [2]. Insomnia symptoms have been linked with poorer health across multiple domains and exacts a high societal cost in the workplace, on the health care system, and on an individual's and family's quality of life [3-5]. Moreover, side effects from medications used to manage insomnia increase these factors in some cases. Novel approaches that facilitate sleep are critically needed, and some potential neural mechanisms of insomnia create a viable treatment target [6].

The most widely accepted theory of primary insomnia is the hyperarousal hypothesis, which suggests that problems with sleep initiation and maintenance are due largely to the disruptive effects of somatic or cognitive hyperarousal [7,8]. In particular, cortical hyperarousal can emerge from excessive focus on repetitive negative thoughts, including intensive problem-solving, self-reflective rumination, and worry [9-11]. Subjectively, people who struggle with insomnia often make comments such as "I wish I could just turn my mind off" or "I just keep replaying conversations over in my head." In fact, one of the major features of insomnia is the tendency toward self-reflective rumination and worry [9,12-15]. This internal dialogue contributes to a cycle of self-referential thought and hyperarousal that appears to hinder sleep onset and maintenance [9,16-18]. In fact, worry and sleep disruptions are associated in the general population [3]. In individuals with insomnia, cortical hyperarousal contributes to difficulty initiating and maintaining sleep [19].

Neuroimaging research has shown that internally focused self-reflective processes of this type tend to activate an interconnected system within the brain known as the default mode network (DMN) [20,21]. Moreover, negative ruminative thinking is associated with changes in DMN connectivity and other brain regions associated with cognitive arousal or negative emotion [22]. Patients with insomnia often show abnormalities in the functioning of the DMN that are consistent with the hyperarousal hypothesis [23-25]. The core nodes of the DMN typically include the medial prefrontal cortex, posterior cingulate cortex, precuneus, and bilateral inferior parietal cortex regions but can also include several ancillary smaller regions, including the hippocampus, medial temporal lobes, and other subcortical structures [26]. Individuals with insomnia disorder tend to have increased resting-state functional connectivity (FC) between spatially segregated nodes of the DMN [27,28]. Increased connectivity and activation of the DMN could contribute to the ongoing self-referential processing and internal dialogue that maintains a hyperaroused state and perpetuates difficulties falling and remaining asleep [27,29]. Individuals with insomnia disorder show greater activation of the DMN compared with healthy controls while viewing word lists associated with past, present, and future worries, particularly when the words are self-referential [29].

Mainstream approaches to treating primary insomnia include cognitive behavioral therapy for insomnia and pharmacologic sleep aids, such as hypnotic sedatives [30-33]. While cognitive behavioral therapy for insomnia often helps to reduce ruminative cognitions and is effective at improving sleep for many individuals, there are many who fail to achieve meaningful benefits [34,35]. Similarly, pharmacologic sleep aids also tend to have modest effect sizes [36] and are often associated with unwanted side effects (eg, daytime drowsiness and memory problems) and health-related morbidities [37]. Various noninvasive neuromodulatory approaches have been shown to improve insomnia symptoms, including repetitive transcranial magnetic stimulation (rTMS) [38]. However, low-frequency rTMS has a cortical inhibition effect that has been shown to improve insomnia symptoms, which may be due to hyperarousal across multiple psychological and physiological domains [39].

The proposed protocol aims to bridge the gap between cognitive and neuromodulatory interventions to facilitate sleep onset and longer maintenance by temporarily inhibiting the brain FC that is associated with cortical hyperarousal and presleep ruminative cognitions. Our proposed approach will involve using rTMS prior to bedtime to briefly disrupt the strength of FC among cortical regions of the DMN. As we propose to inhibit connectivity within the DMN, we will use continuous theta burst stimulation (cTBS), which induces long-term depression of cortical neural firing following a sustained stimulation period of 40 seconds [40]. Thus, we hypothesize that the application

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of cTBS to an easily accessible node of the DMN will suppress the local neural activity of that node and propagate inhibition throughout the DMN, thereby reducing ruminative thinking and worry prior to sleep onset. Decreased DMN connectivity is expected to improve sleep quality and quantity. An increase in slow-wave and rapid eye movement sleep stages has been proposed as mechanisms of rTMS in increasing restorative sleep in individuals with insomnia, so polysomnography (PSG) parameters are the primary outcome measures in the outlined protocol [41]. This phase 1 clinical trial will be the first study to investigate the effects of cTBS targeted to the left inferior parietal node of the DMN on objectively measured sleep outcomes.

Research Aims and Hypotheses

This study aims to explore the effects of cTBS on (1) the activation and connectivity of the DMN and (2) sleep outcomes. We hypothesize that modulating the DMN by stimulating a targeted region of the left inferior parietal lobule with a single cTBS administration will decrease FC within the DMN and thereby improve sleep parameters (ie, PSG) relative to an identical sham administration.

Study Design and Randomization

This phase 1 clinical trial (ClinicalTrials.gov NCT04953559) will be conducted with a randomized, double-blind, sham-controlled, counterbalanced, crossover design. Participants serve as their own controls as they undergo 2 identical study sessions separated by at least 5 days (ie, washout period). Participants and study personnel who interact with the participants will be blind to the specific condition (active cTBS vs sham) the participant receives during each study visit. Using a prespecified, equally balanced, block randomization procedure, participants will be assigned to the order in which they receive active cTBS and sham stimulation conditions. The randomization list will be generated by a computer random number generator, with the constraint that half of the participants of each biological sex will receive sham first and half will receive the active cTBS first. This design will allow us to examine the intraindividual effects of the active cTBS and establish the superiority of active cTBS compared with sham stimulation in improving PSG sleep outcomes.

Methods

Study Procedures Overview

The study procedures were completed over 3 separate visits. Screening to determine eligibility and baseline assessments was conducted during visit 1. Eligible participants were asked to wear a wrist actigraph for at least 5 days prior to their first in-laboratory overnight visit (visit 2). Based on a preestablished counterbalanced crossover randomization schedule, participants were then assigned to receive either the active cTBS or sham stimulation for their first overnight visit (visit 2) followed by the alternative intervention during their second overnight visit (visit 3) at least 5 days later. As shown in Figure 1, each in-laboratory session lasted 18 hours, including a 2-hour cognitive testing block, 1 hour of preintervention magnetic resonance imaging (MRI), followed by either active cTBS or sham stimulation, and a postintervention hour of neuroimaging. Participants were then fitted with PSG electrodes and were permitted 8 hours of sleep while undergoing PSG sleep monitoring in the lab. The next morning, participants completed another 2-hour cognitive testing block before being released.

The full study execution takes approximately 38-40 hours with 2-3 hours allocated for baseline screening and enrollment (visit 1) and 18 hours allocated for each overnight visit (visits 2 and 3). Table 1 presents the specific assessment measures administered at each visit.

Figure 1. Overview of the pilot randomized controlled trial study design. Participants first complete a web-based eligibility survey screening for sleep disturbances. Potentially eligible volunteers complete an in-lab enrollment process and baseline assessment (visit 1) at a large Southwestern University medical research center. Participants are then randomized to a stimulation order condition. After at least 5 days with actigraphically measured sleep, participants return for an 18-hour overnight session involving 2 MRI scans and overnight sleep (visit 2) at the medical research center. Depending on their condition assignment order, they either receive active cTBS or sham intervention. Participants then undergo a washout period of at least 5 days that includes actigraphically measured sleep. They then return for an identical overnight visit that involves the alternate intervention condition. cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging.

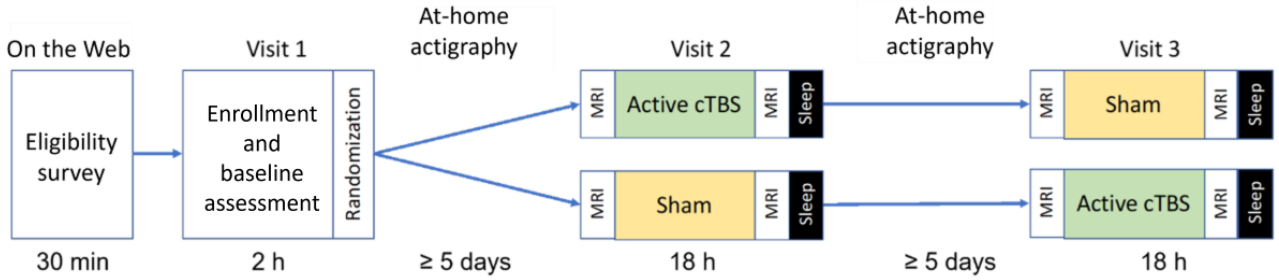

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Table 1. List of study activities and assessments performed during study visits during a pilot randomized controlled trial evaluating the preliminary effectiveness of continuous theta burst stimulation in improving sleep in individuals with reported sleep disturbances.

Study activities and assessments	Baseline screening and enrollment (visit 1)	At home	Overnight visits (visits 2 and 3)
Screening			
Consent form	✓		
Eligibility screening (TMS[a], health background, MRI[b], PSQI[c], ISI[d], and ESS[e])	✓		
Pregnancy test	✓		
Covariates			
Demographics	✓		
Anxiety (STAI-S[f] and STAI-T[g])	✓		✓
Depression (BDI-II[h])	✓		✓
Sleep preoccupation (SPS[i] and GCTI[j])	✓		✓[k]
Caffeine consumption questionnaire	✓		
Intelligence (WASI-II[l])	✓		
Actigraphy (Phillips Actiwatch)		✓	
Sleep quality (Sleep diaries)		✓	
Primary Outcomes			
Functional connectivity in DMN[m]			✓
Sleep (PSG[n])			✓
Secondary Outcomes			
Information processing speed (GNG[o])			✓
Attention (PVT[p])			✓
Verbal memory (CVLT-3[q])			✓
Immediate and delayed memory (RBANS[r])			✓
Self-reported sleepiness (KSS[s])			✓
Mood (VAMS[t])			✓
Side effects (pre- and post-TMS assessment)			✓

[a]TMS: transcranial magnetic stimulation.
[b]MRI: magnetic resonance imaging.
[c]PSQI: Pittsburgh Sleep Quality Index.
[d]ISI: Insomnia Severity Index.
[e]ESS: Eppworth Sleepiness Scale.
[f]STAI-S: State-Trait Anxiety Inventory-State.
[g]STAI-T: State-Trait Anxiety Inventory-Trait.
[h]BDI-II: Beck Depression Inventory.
[i]SPS: Sleep Preoccupation Scale.
[j]GCTI: Glasgow Content of Thoughts Inventory.
[k]Only GCTI.
[l]WASI-II: Wechsler Abbreviated Scale of Intelligence.
[m]DMN: default mode network.
[n]PSG: polysomnography.
[o]GNG: go/no-go task.
[p]PVT: psychomotor vigilance task.

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[q]CVLT-3: California Verbal Learning Task 3.

[r]RBANS: repeatable battery for the assessment of neuropsychological status.

[s]KSS: Karolinska Sleepiness Scale.

[t]VAMS: Visual Analogue Mood Scale.

Ethical Considerations

All study activities and study personnel were approved by the University of Arizona's Institutional Review Board (IRB) and by the Department of Defense Office of Human Research Oversight (OHRO) in March 2021 (approval 2007900971). Any protocol amendments and reportable new information were disseminated to both IRB and OHRO. All participant information was deidentified for confidentiality. Participants were compensated 500 dollars via check for their participation in the study if they were fully compliant with the study procedures. The study team maintains dissemination control of the final deidentified data set. Final results will only report cumulative population data to respective regulatory and scientific reporting agencies and along with peer-reviewed publications. Access to the deidentified data set will be available upon request to the principal investigator and in conjunction with proper regulatory requirement.

Participants and Recruitment

A total of 20 otherwise healthy adults with self-reported sleep disturbances were recruited from the greater Tucson and Phoenix metropolitan areas. Recruitment strategies include flyers posted on community boards, advertisements in local newspapers, sponsored social media posts, and email lists at local universities. Individuals who were recruited from the community were directed to complete a web-based survey in a HIPAA (Health Insurance Portability and Accountability Act)–compliant server. If participants met the initial inclusion criteria, a study member then completed a preliminary phone screening with the participant. Study personnel then scheduled an in-person screening visit for eligible individuals.

Power Analyses

During the study design, we conducted a power analysis to determine the sample size necessary to compare mean changes in DMN connectivity before and after cTBS using a within-subjects ANOVA approach. From prior cited work on transcranial magnetic stimulation (TMS) and FC, a total sample of 20 was found to have sufficient power to answer the research questions to include analysis of 2 groups (within-subject active and sham), 2 repeated measurements (before and after TMS), and a correlation between the change in DMN activation and sleep outcome metrics [42,43].

Inclusion and Exclusion Criteria

Individuals between the ages of 18-50 years with reported sleep disturbances were included in the study. Individuals were excluded if they reported or exhibited any health conditions beyond insomnia-related symptoms. Exclusionary criteria were based on one or more of the following considerations: the criterion in question is (1) known to alter sleep, (2) known to substantially increase interparticipant variability, (3) known to put the volunteer outside the range of what is considered healthy, or (4) required by regulation. Detailed inclusion and exclusion criteria are referenced in Textbox 1.

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Textbox 1. A detailed description of inclusion and exclusion criteria of a pilot randomized controlled trial evaluating the preliminary effectiveness of continuous theta burst stimulation in improving sleep in individuals with reported sleep disturbances.

Inclusion criteria

- 18-50 years old
- Self-reported sleep disturbances on 2 of 3 inventories:
  - Pittsburgh Sleep Quality Index ≥6
  - Insomnia Severity Index ≥15
  - Epworth Sleepiness Scale ≥11

Exclusion criteria

- Unwillingness to provide informed consent
- Presence of a metal implant or medical device which poses a safety risk for magnetic resonance imaging or transcranial magnetic stimulation
- Self-reported past or present medical diagnosis of sleep- or breathing-related disorders
- Travel outside the time zone within 1 week prior to the enrollment visit or while active during the study
- Self-reported major medical or neurological problems
- Self-reported past or present history of cardiovascular disease
- Self-reported past or present history or first-degree family history of any seizures or seizure disorders
- Self-reported underlying acute or chronic pulmonary disease
- Self-reported history of fainting spells or syncope
- Self-reported past or present psychiatric problems
- Self-reported suicidal ideation
- Self-reported current use of prescription medications
- Self-reported current use of supplements that affect sleep
- Self-reported caffeine use in excess of 300 mg per day on average
- Self-reported regular nicotine use
- Self-reported or suspected heavy alcohol indicated on the Alcohol Use Disorders Identification Test (AUDIT) as greater than or equivalent to 14 drinks a week for male individuals and 7 drinks a week for female individuals
- Self-reported use of illicit drugs
- Speaking English as a nonprimary language
- Less than a ninth-grade education
- Engaged in overnight shift work
- Female individuals only: positive urine pregnancy test
- Female individuals only: self-reported current breast-feeding or collecting breast milk

Study Activities

Enrollment and Baseline Assessment (Visit 1)

Eligible participants were invited for an in-person screening and baseline data collection session lasting approximately 2-3 hours. After participant consent was obtained by trained study staff members, the participants underwent a baseline assessment, including measurement of intellectual capacity with the Wechsler Abbreviated Scale of Intelligence by a certified administrator, subjective sleep assessment including the Pittsburgh Sleep Quality Index and Insomnia Severity Index, and other cognitive assessments.

At-Home Actigraphy Week

Upon the completion of the enrollment visit, participants were fitted with a wrist actigraphic sleep monitor that they wear for at least 5 days prior to returning for the in-laboratory assessment sessions and continued to wear the device during the intervening washout week between the 2 in-residence laboratory stays. Participants also completed a web-based sleep diary each morning. Throughout the entire period of enrollment, participants were required to maintain a regular sleep schedule and were not permitted to use caffeine products for 48 hours prior to the in-laboratory overnight stays.

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Overnight In-Residence Laboratory Sessions (Visits 2 and 3)

Participants completed 2 overnight in-residence laboratory stays according to a double-blind counterbalanced crossover design, with each session separated by at least 5 days. Figure 2 provides a graphical overview of the in-residence laboratory activities.

Figure 2. Timeline of the in-residence laboratory testing for the pilot randomized controlled trial. Participants arrive at the lab at 1500 and undergo cognitive testing followed by a preintervention MRI scan. The intervention is administered between 1900 and 2000 and is randomly assigned as either active cTBS stimulation or an identical appearing sham condition. After stimulation, participants complete a postintervention series of MRI scans, followed by a brief cognitive testing battery. At 2200, they are escorted to the sleep lab and PSG electrodes are applied. Lights out occur at 2300 and the participant is provided with an 8-hour undisturbed period for PSG-monitored sleep. Following wake-up at 0700 the next morning, the participant is provided a light breakfast and completes a final battery of cognitive tests. This procedure is repeated on separate weeks for the active cTBS and placebo conditions. cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging; PSG: polysomnography.

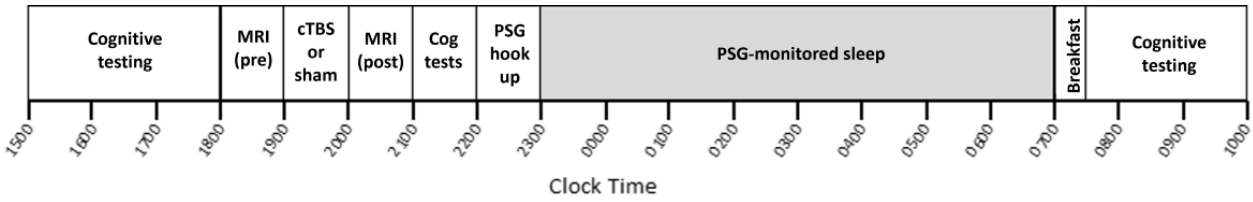

Cognitive Testing Block

Participants arrived at 3 PM and completed approximately 3 hours of cognitive testing with a trained and certified administrator, including the 10-minute psychomotor vigilance testing (PVT) and Karolinska Sleepiness Scale (KSS) at 3 time points separated by an hour, in addition to the Visual Analog Mood Scale, State-Trait Anxiety Inventory-State only (STAI-S), Beck Depression Inventory (BDI-II), California Verbal Learning Task 3 (CVLT3), go/no-go task (GNG), repeatable battery for the assessment of neuropsychological status (RBANS) symbol digit test, RBANS digit span, RBANS story memory test, and Glasgow Content of Thoughts Inventory (GCTI).

Prestimulation Neuroimaging

MRI scans were collected on a Siemens MAGNETOM Skyra 3T scanner (Siemens) using a 32-channel head coil. Participants completed a series of scans that included structural (magnetization-prepared rapid gradient-echo), functional (10-min eyes open) resting state, and proton magnetic resonance spectroscopy (^{1}H MRS) scans, with voxels placed in (1) the anterior cingulate gyrus and (2) posterior cingulate or precuneus. Functional MRI data will be preprocessed with standard neuroimaging packages, including statistical parametric mapping 12, FSL, and the functional connectivity toolbox (CONN v17f or later; focusing on DMN network connectivity) following standard published pipelines [44].

Intervention: cTBS Versus Sham

Following the first MRI scan, participants exited the scanner and underwent either cTBS stimulation or sham stimulation according to their preassigned double-blinded condition. The stimulator was preprogrammed prior to the start of the session and the participants and technicians that administered the stimulation procedure were blind to the administered condition. Each individual was expected to have a different sensitivity to the magnetic fields generated by the stimulation coil, and the stimulation intensity was adjusted based on each individual's resting motor threshold (RMT). The real-time, motor-evoked potential of muscle contraction is provided to ensure consistent force production. Once the RMT was identified, the stimulation intensity for TBS was set to 70% of each participant's RMT.

For primary rTMS stimulation, we located a predetermined node in the inferior parietal lobe, localized by coregistering the participant's head, structural T1-weighted MRI image, and TMS coil in the same space using a TMS 3D Neuronavigation System. Once coregistration was complete, the Neuronavigation system provided real-time feedback on the TMS coil location and recorded the coil position and orientation relative to the head. The cTBS was applied using a figure-of-8 coil with an active cooling system connected to the MagPro magnetic stimulator (MagVenture Cool-B65). The same coil has 2 sides, 1 designed for active TMS stimulation, and the other is equipped with a magnetic shield that effectively blocks any stimulation and is used for the sham condition. The rTMS setup is shown in Figure 3.

For this project, we selected an easily accessible node of the DMN located on the left lateral parietal (LLP) cortex. The exact spatial location for stimulation is based on the Yeo et al [45] probability atlas. We downloaded this atlas into the Mango 4.1 visualization program (and identified the centroid of the LLP node of the DMN at the MNI coordinates of x (–48), y (–61.5), and z (32.5). These coordinates are converted into the same stereotaxic space as the participant's brain to allow precision localization of the LLP node as the target for stimulation. Once this site was localized for the participants, a 40-second cTBS stimulation train (600 stimuli/session) or identically matched sham stimulation was administered using a MagVenture MagPro X100 stimulator (MagVenture Inc) connected with a figure-of-8 magnetic coil with active cooling.

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Figure 3. Transcranial magnetic intervention system set-up for the pilot randomized controlled trial. Left: (A) the continuous theta burst stimulation is administered with a MagVenture Cool-B65 stimulator that included an active and sham side; (B) the resting motor threshold was determined using a MagPro X100 stimulator with a figure-of-8 coil; (C) the transcranial magnetic stimulation system is maintained at a constant temperature using an active cooling system. Middle: the stimulation is directed by a computerized system that detected the orientation of the head in space using (D) an antenna camera and correlate it with the individual's coregistered magnetic resonance imaging scan. Right: An image showing the Neuronavigation system used to administer the transcranial magnetic stimulation to the precise default mode network locations.

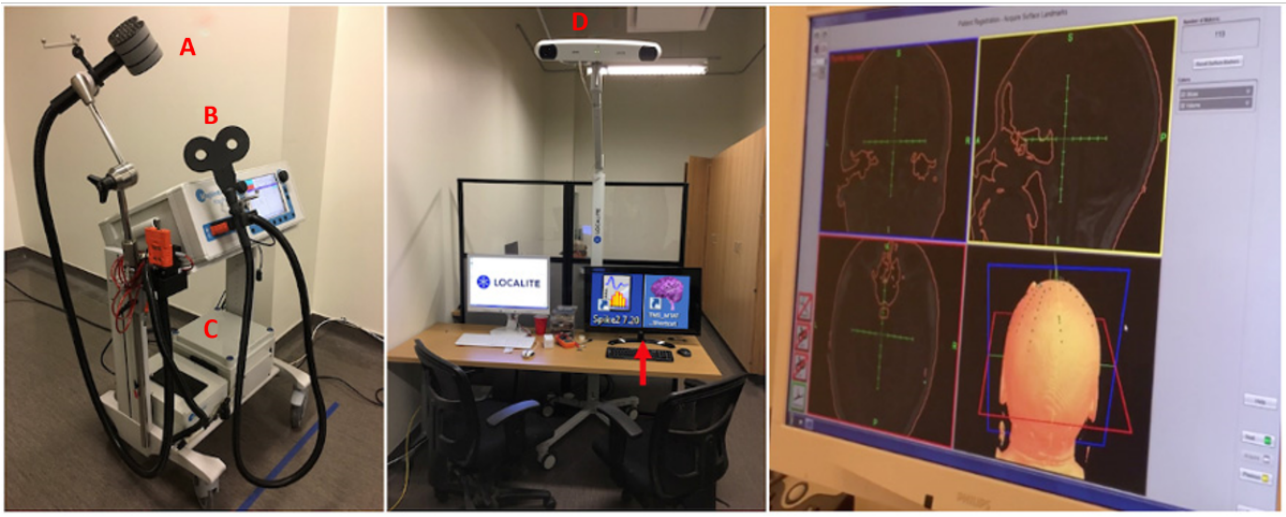

Poststimulation Neuroimaging

Immediately following the cTBS or sham stimulation period, each participant underwent a second neuroimaging session that was identical to the prestimulation MRI session previously described.

PSG Recording

Participants slept undisturbed in a light- and temperature-controlled private bedroom while continuously monitored by a trained technician with a Nihon Kohden JE-921 PSG recording system using standard 10-20 electrode placement. Data from PSG were scored using Polysmith software according to the standard Rechtschaffen and Kales approach by a trained and certified sleep technician who was blind to the participant's condition and status. The primary outcome metrics include sleep onset latency (SOL), latency to N1, N2, N3, and REM, total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), and number of awakenings and arousals, as well as time and percentage of time spent in each sleep stage.

Monitoring

Participants were assessed both prior to stimulation and after receiving stimulation for any adverse somatic, cognitive, or physical symptoms. Any presence of symptoms was logged in a HIPAA-compliant server and the participant was assessed by the study physician to determine if enrollment needed to be discontinued. All adverse events were reported to both IRB and OHRO. All study activity was subject to independent, random auditing from the Department of Psychiatry at the University of Arizona and study sponsors.

Data Management

All collected data were deidentified and stored within HIPAA-compliant, password-protected servers immediately after collection. Study data were only accessible to IRB-approved study staff. All data were checked and double-entered by study personnel no more than 1 week after data collection. Data quality checks were conducted every quarter by staff members for additional data assurance. Any data collected after participants' consent were included in the study database for both compliant and noncompliant participants. However, following a per-protocol analysis, we are only using data from participants who fully completed the study due to within-subjects analysis.

Primary Outcomes: FC Changes in the DMN

We hypothesize that active cTBS will disrupt the within-network and between-network connectivity of the DMN. This hypothesis will be assessed from a 10-minute resting-state FC scan and analyzed using standard procedures in the CONN (v17f or higher). Standard pipelines for preprocessing will be used. Within-network connectivity will be determined by first conducting an independent components analysis of the intrinsic activation patterns across the brain. Twenty independent components will be extracted. Mean activation clusters from each component will be examined for intercorrelation to determine within-network connectivity. Additionally, between-network, region-to-region, and seed-to-voxel analyses will be conducted to compare changes in FC between the 2 stimulation conditions.

Analysis Plan

FC Changes to the DMN

First-level whole brain connectivity analyses will be undertaken in CONN for each subject at each of the 4 sessions (ie, active prestimulation, active poststimulation, sham prestimulation, and sham poststimulation). This will result in an FC map for each participant at each session, indicating the magnitude and direction of intrinsic correlation between each seed region (eg, lateral parietal cortex of the DMN) and all other voxels in the brain. For our primary analysis, we will estimate the effects of active cTBS on FC within the DMN using multimodal neuroimaging data including resting state FC. Raw NifTI images

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will be preprocessed using standard functional preprocessing pipelines in CONN [46].

The first-level connectivity maps will be combined in subsequent second-level analyses in CONN to explore the effects of cTBS stimulation on brain connectivity to include (1) independent components analysis, (2) seed-to-voxel analyses, and (3) region of interest to region of interest analyses [44]. Statistically significant differences in FC of the DMN between sham and active conditions will be the minimal important change to confirm the primary hypothesis. Next, PSG parameters measuring sleep stage duration and onsets, arousals, and awakenings will be added as covariates of FC change from before to after stimulation, comparing sham and active cTBS conditions.

PSG Analysis

We will assess the effects of active cTBS on sleep and whether participants demonstrated greater sleep quality during their active cTBS session compared with their sham stimulation session. Analyses will be conducted on sleep variables including total sleep time; N1 latency; N2 latency; N3 latency; REM latency; SOL; persistent SOL; SE; WASO; total number of awakenings; spontaneous arousals; wake duration; and stage duration for N1, N2, N3, and REM. Analyses will include repeated measures ANOVA controlling for covariates. Statistically significant difference between sham and active conditions will be the minimal important change to confirm this hypothesis.

Exploratory Analysis

We will examine the effects of active cTBS on secondary outcomes of cognitive performance, mood, and side effects compared with sham stimulation using repeated measures ANOVAs and nonparametric tests accordingly.

Results

Our study was funded in September 2020 by the Department of Defense (W81XWH2010173). We completed the enrollment of our target population of 20 participants in October 2022. As of July 2023, we will initiate extensive neuroimaging data analysis and anticipate that the full results of the study will be published by 2024.

Discussion

Study Rationale

With a growing number of people reporting greater sleep disturbances, identifying effective nonpharmacological interventions is an important step in providing more innovative and noninvasive approaches for improving sleep outcomes. While the sample size for this study is small, this is the first study to investigate cTBS effects on the DMN to improve sleep outcomes.

Experimental Clinical Design Rationale

Double-blind randomized controlled trials are the gold standard for scientific inquiry. Therefore, each participant will serve as their own control in a counterbalanced crossover design. Implementing a crossover design in which every participant receives both active and sham cTBS stimulation permits comparison of intraindividual differences in DMN connectivity and sleep quality parameters, as each participant acts as their own control. Because the goal was to examine the effects of cTBS on individuals with sleep problems, no healthy control samples were recruited or necessary to test our hypotheses. Blinding study personnel to the TMS condition also reduces systematic differences in the administration of the stimulation interventions and ostensibly reduces the influence of expectations about treatment effects.

Brief cTBS of the LLP Lobule

Continuous theta burst was selected as the intervention based on its previously demonstrated inhibitory effects on the cortex [47]. A single 40-second cTBS session inhibits, or suppresses, neural excitability in the cortex for up to 50 minutes or longer [47]. Stimulation of a single node of the DMN is expected to inhibit local activity, with further suppression of cortical excitability propagating throughout the network overall. Inhibition of the left inferior parietal lobule was selected for two primary reasons: (1) prior research showed reduced metabolic activity in this region when individuals were falling asleep and (2) this region facilitates an easy-to-access node of the posterior DMN [48].

The localization of specific brain regions requires prestimulation imaging to account for individual variability in brain structure. For this reason, a critical element of that project was to show that stimulation of a single, easily accessible surface node of the larger DMN could lead to significant alterations in FC within this network. Prior investigations using cTBS have focused primarily on the stimulation of brain regions associated with the prefrontal areas of the DMN. Sleep-related parameters have rarely been collected as outcome measures for cTBS. One prior study examining rTMS effects on the right parietal cortex showed reduced anxiety and insomnia symptoms [49]. However, that study used a stimulation session (of three 1-Hz stimulations every 10 minutes) spread across 10 days. The presently proposed cTBS protocol is aimed at establishing initial research outcomes of the effects of a single burst of cTBS on disrupting network connectivity of the DMN to improve sleep. Thus, only a single stimulation session of both active cTBS and sham is needed to identify the intraindividual effects of cTBS on sleep outcomes.

Limitations and Future Directions

Targeting a single node of the DMN and conducting only 1 stimulation session are limitations of this protocol to sufficiently answer the research questions and aims proposed regarding DMN and insomnia improvement. Future work could determine the most effective stimulation sites within the DMN and the optimal number of pulses and administrations to optimize this potential intervention for sleep problems. Larger samples are also needed than the small pilot sample collected for this protocol to examine the effects of sex observed in previous studies [38].

Summary and Conclusions

Insomnia symptoms linked with many other psychiatric and physiological morbidities have become an increasingly prevalent

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and important health care and societal concern. Noninvasive neuromodulation can be inexpensive and is a technique accessible to many types of treatment providers. The protocol presented here unifies the prominent aspects of insomnia—physiological and psychological hyperarousal—by targeting a unique neural network, known to be associated with proposed mechanisms of insomnia [8,50].

Acknowledgments

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Authors' Contributions

LH carried out the data collection, data management, wrote the initial draft of the manuscript, and contributed to revisions. AH contributed equally to the initial drafting of the manuscript, provided revisions, and contributed to the ongoing statistical analysis of the study. ND assisted with the study design and executed data collection. SJ and KHA contributed to data collection, data management, and regulatory reporting, and reviewed drafts of the manuscript. CT, YCC, and YHC provided training in transcranial magnetic stimulation (TMS), provided the TMS study equipment, and oversaw TMS data collection. WDSK was responsible for the initial conceptualization and design of the project, obtaining the research funding, providing oversight of the study, contributing to ongoing statistical analysis and interpretation of the findings, and contributing to initial drafting and revisions of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
BDI-II: Beck Depression Inventory
CONN: Functional Connectivity Toolbox
cTBS: continuous theta burst stimulation
CVLT-3: California Verbal Learning Task 3
DMN: default mode network
FC: functional connectivity
GCTI: Glasgow Content of Thoughts Inventory
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
LLP: left lateral parietal
MRI: magnetic resonance imaging
OHRO: Office of Human Research Oversight
PSG: polysomnography
PVT: psychomotor vigilance task
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RMT: resting motor threshold

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rTMS: repetitive transcranial magnetic stimulation
SE: sleep efficiency
SOL: sleep onset latency
TMS: transcranial magnetic stimulation
TST: total sleep time
WASO: wake after sleep onset

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Protocol

Psychostimulant Medications for Physical Function and Spasticity in Children With Cerebral Palsy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cerebral palsy (CP) is a prevalent nonprogressive disorder that leads to impaired movement (ie, spasticity), posture, and balance, which affects functions such as walking and upper extremity tasks. Current medical treatments show efficacy in improving motor performance but have considerable side effects. Emerging off-label use of central nervous system (CNS) medications for improving motor performance has shown promising results in children with CP and other populations.

Objective: The aim of this study is to describe a protocol for a pilot randomized controlled trial (RCT) to examine the safety, tolerability, and efficacy of methylphenidate (MPH) and modafinil on spasticity and motor performance in children with CP.

Methods: This will be a protocol study for a pilot, triple-masked, placebo-controlled RCT (a class I trial following the American Academy of Neurology criteria) with blinded patients, outcome assessors, and intervention delivery team. Eligible children should be diagnosed with CP levels I or II based on the Gross Motor Function Classification System and be aged between 7 and 12 years. Thirty-six children with CP will be randomized into 3 groups to receive (1) MPH (2.5 mg of MPH + 100 mg placebo), (2) modafinil (100 mg modafinil + 2.5 mg placebo), or (3) a placebo (2.5 mg placebo + 100 mg placebo), in addition to physical therapy for 12 weeks. Primary outcomes include the Gross Motor Function Measure–66 and the Modified Ashworth Scale. Secondary outcomes include the Timed Up and Go test, 5 Time Sit to Stand test, Modified Clinical Test for Sensory Interaction of Balance, and 10-Meter Walk Test.

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Results: The protocol has been accepted by Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). The inclusion of participants will start in June 2024.

Conclusions: The combination of CNS stimulant medications and controlling for rehabilitation has not been studied yet. The findings of this study may determine if using CNS stimulant medications is beneficial for the reduction of spasticity and improvement of physical function in children with spastic CP.

Trial Registration: ClinicalTrials.gov NCT05675098; https://clinicaltrials.gov/study/NCT05675098

International Registered Report Identifier (IRRID): PRR1-10.2196/53728

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KEYWORDS

cerebral palsy; CNS stimulants; spasticity; motor performance; gross motor function; psychostimulant; medications; physical function; CP; children; child; pediatrics; pediatric; impairment; movement; central nervous system; safety; tolerability; efficacy; methylphenidate; modafinil; Kuwait; rehabilitation; physical therapy

Introduction

Background

Cerebral palsy (CP) is a group of disorders that cause permanent, nonprogressive damage to the developing brain [1], leading to impairments in movement and posture, as well as balance deficits [2,3]. These impairments could affect gross motor skills [4], such as gait [5], upper limb tasks (eg, reaching) [6], and oral motor function (eg, eating and swallowing) [7], which could contribute to limitations across a variety of life domains, including self-care, education and work, and recreational activities [8].

CP is one of the leading causes of disability [2], affecting about 1 in 500 children, with estimated prevalence of 17 million individuals globally [9]. CP can be classified into different categories based on motor impairments, including spasticity (increased muscle excitability) [10], dyskinesia (uncontrollable random movement) [11], ataxia (impaired coordination) [12], or mixed movement disorders [3].

Spastic disorders are the most common type of CP that affects motor activities essential for activities of daily living (ADL) [3]. Treatment of CP spastic disorders includes pharmacological medications (oral and injected), surgical therapy, and nonpharmacological therapy (ie, rehabilitation or constraint-induced movement therapy [13,14]). Pharmacological medications with different mechanisms of action can be used to reduce spasticity in children with CP. For instance, using botulinum toxin type A (BoNT-A) injections is efficacious in reducing spasticity of the upper extremities (UEs) [15] and lower extremities (LEs) [16], which helps in improving the overall motor function in children with CP [17]. BoNT-A inhibits acetylcholine production from the presynaptic terminal, causing a decrease in muscle excitability [17]. Based on the current CP clinical practice guidelines, BoNT-A is considered a safe and effective intervention for spasticity in children and adolescents with CP [18-21]. However, BoNT-A effects are peripheral, targeting specific muscles, and have a temporary influence on spasticity [15,16]. Importantly, BoNT-A has been criticized due to its potential to induce muscle weakness in a condition that is characterized by motor impairments [17].

Other pharmacological medications can reduce spasticity in children with CP, such as baclofen (tablets or intrathecal injections) and diazepam (tablets) [20]. These medications reduce spasticity by improving the affinity of gamma-amino butyric acid (GABA) on its receptors, which in turn blocks excitatory neurotransmitters [22,23]. Notably, these medications have shown effectiveness in both reducing spasticity and improving motor performance in children with CP [24,25]. Nevertheless, baclofen and diazepam have potential side effects that could impact their use, including drowsiness and potential muscle weakness [20]. These medications counter a key factor in improving motor performance by decreasing the rate of motor firing [20]. Therefore, there is a critical need to explore the effects of medications that could both improve motor performance and reduce spasticity but also exhibit minimal side effects in children with CP.

In the past 2 decades, central nervous system (CNS) stimulants such as methylphenidate (MPH) have been reported to improve motor performance when used in children with attention-deficit/hyperactivity disorder (ADHD) [26,27]. Furthermore, a case report documented that a woman aged 44 years with CP (mixed type—choreoathetosis with spasticity) consumed another CNS stimulant (amphetamine) recreationally and observed a remarkable reduction in her spasticity, which encouraged her physician to prescribe MPH for spasticity reduction [28]. This woman had a considerable long-term decline in spasticity and choreoathetosis with MPH use [28]. Another CNS stimulant (modafinil) showed improvements in gait and spasticity among children with CP [29-31]. Nevertheless, the effects of modafinil on spasticity and motor improvement have been inconsistent [32]. Consequently, potential CNS stimulants such as MPH and modafinil are hypothesized to reduce spasticity and improve motor performance in children with CP due to alteration in neurochemicals in the brain (ie, changes in neuroplasticity) [33].

Rehabilitation interventions for children with CP produce changes in neuroplasticity [34], which could lead to long-term improvements in motor function. Specifically, early interventions for spasticity and motor function may be associated with improved motor performance due to enhancement of sensory feedback plasticity [35]. Sensory feedback is an essential modifiable factor for motor learning by iteration, which alters

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connections between primary motor and somatosensory cortices [36,37]. Therefore, the use of CNS stimulants, in addition to rehabilitation interventions, could offer long-term improvements in spasticity and motor performance in children with CP. Using CNS stimulants may offer advantages over existing pharmacological treatments, primarily because they do not induce muscle weakness [17]. Given the limited studies that have examined the effects of CNS stimulants on motor performance, with or without rehabilitation, in children with CP, a pilot experimental research study is warranted.

Objective

We designed a triple-masked pilot randomized controlled trial (RCT) that aims to examine the safety and tolerability of MPH and modafinil (aim 1) as well as to assess trends in changes in gross motor function and spasticity with the use of MPH and modafinil in children with CP (aim 2). In this placebo-controlled study, participants will be randomized into 3 groups that will receive MPH, modafinil, or placebo tablets. We hypothesize that using MPH or modafinil will be tolerable and safe for children with CP. We also hypothesize that there will be trends toward improvement in gross motor function and spasticity in children with CP.

Methods

Ethical Considerations

Ethical approval for this study has been obtained from Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). Prior to initiation of this study, participants and their legal guardians will be informed about the study and written consent and assent will be obtained from each participant. We followed the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) guidelines for the preparation of this protocol [38]. The SPIRIT guidelines are a 33-item checklist that allows researchers to draft and plan high-quality RCTs and describe elements of the content of the RCT. The protocol of this study has been registered at ClinicalTrials.gov (NCT05675098).

Study Design

This study will be a single-center, prospective, triple-masked, placebo-controlled pilot RCT. The study design is informed by the American Academy of Neurology (AAN) criteria for evidence classification as a class I study [39]. To meet these criteria, this study will (1) be triple-masked (blinded) to minimize the risk of bias (ie, patients and legal guardians, treatment providers, and outcome assessors will be blinded), (2) use the intent-to-treat principle to account for dropouts, (3) have only 2 primary outcomes (the Gross Motor Function Measure [GMFM] and Modified Ashworth Scale [MAS]), (4) have a prespecified minimal clinical detectable change in the primary outcomes, and (5) use a powerful method to correct for multiple comparisons for secondary outcomes. This study will also use a placebo-control group as an active control; this is due to the fact that there are no medications that possess CNS-stimulant qualities that have been tested for the purpose of the study. This study will examine the effects of a 12-week administration of MPH, modafinil, or placebo with the GMFM and MAS, with a testing session in the middle of the study period (ie, at the 6-week mark). This is integral, as it will allow for monitoring changes in the primary outcomes at multiple time points. The study will also examine the long-lasting effects of these medications (MPH and modafinil) at 12 weeks after the conclusion of the intervention (ie, at 24 weeks) to assess if any detected trends of improvement last beyond the period of the intervention. This study will be guided by the CONSORT (Consolidated Standards of Reporting Trials) guidelines for recruitment (Figure 1).

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Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the proposed randomized controlled trial.

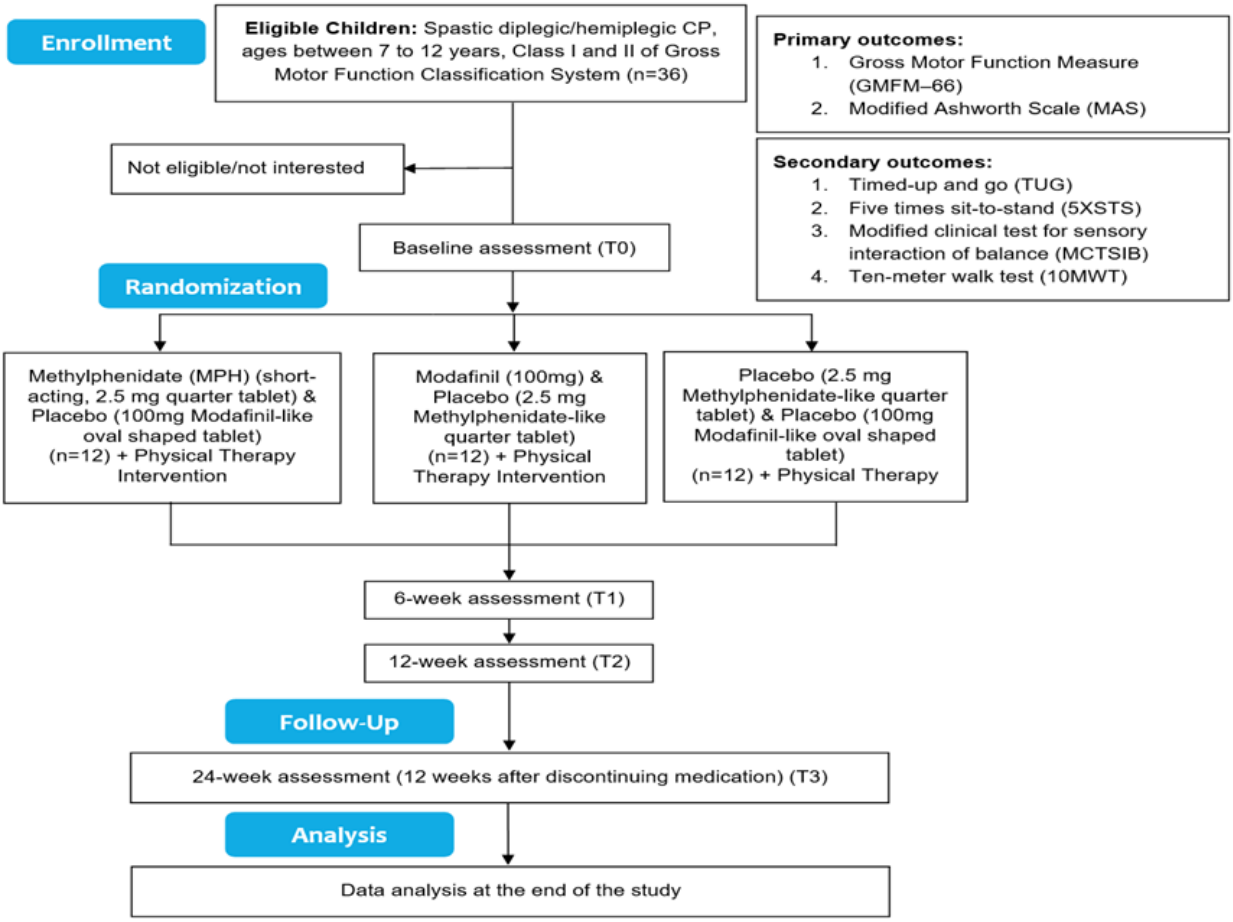

Recruitment

Participants

Formal power calculation will not be carried out because this is a pilot study. Children with CP (N=36) aged 7 to 12 years will be enrolled (ie, 12 children per group). Children will be recruited from hospitals around Kuwait using several advertisement methods, including flyers, email notifications to health care providers, and social media advertisements (eg, on X, formerly known as Twitter). Additionally, we will use the snowball recruitment method for this study. The study will be conducted at Jaber Al-Ahmad Hospital, Kuwait.

Inclusion Criteria

Children will be screened and considered for eligibility if they are diagnosed with spastic diplegic or hemiplegic CP by a pediatric neurologist with at least 5 years of experience with this population, aged 7 to 2 years, male or female, classified as level I or II on the Gross Motor Function Classification System (GMFCS), (ie, they are able to walk independently with or without limitation) [40], and have received physical therapy for at least 3 months. GMFCS level will be determined by the treating therapist of the participant according to the expanded and revised version of the GMFCS [41]. If eligible, participants will only follow the rehabilitation intervention described in this protocol. Medicine management will continue as prescribed by the treating physician.

Exclusion Criteria

Children will be excluded if they have had a seizure in the past 6 months, have been diagnosed with ADHD, have had any surgery within the last 6 months, use medications that interfere with spasticity (eg, baclofen), are unable to follow simple commands, or have LE (hip, knee, and ankle) contractures determined by the passive range of motion (ROM). Contracture measurement will follow the CP Follow-up Program (CPUP) measurement manual, based on the guidelines of Norkin and White [42]. Measurements will be done using a universal goniometer and in standardized positions. Decreases in passive ROM are considered contractures if they fall within the red level of the “traffic light” system of the CPUP [42]. For the hip joint, abduction and extension ROM will be measured with the Ely test [43]. For the knee joint, extension along with popliteal angle will be measured [44]. Finally, for the ankle joint, dorsiflexion with knee flexed and extended along with plantarflexion will be measured. Assessors will be consistent across data collection points (screening, baseline, at 6 weeks, at 12 weeks, and at 24 weeks). Interrater reliability will be measured on 25% of the sample, chosen randomly to ensure consistency among assessors.

Randomization

Match or pair randomization will be used in this study to control for confounding effects of sex and GMFCS level. Children will be allocated to the MPH, modafinil, or placebo group using a concealed centralized electronic allocation application. Children

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will be matched for sex (male or female) and GMFCS (level I or II).

Sample Size

This study will include 12 children in each group (N=36). Due to the design of the study (ie, a pilot trial), power calculation will not be performed to estimate the sample size. Upon the completion of this study, our findings will provide effect sizes that are essential for future studies to conduct a power analysis.

Blinding Procedures

This study will be triple-masked (blinded), where treatment providers, outcome assessors, and participants (children and their legal guardians) will be unaware of the study group allocation. Two pharmacists and 1 study coordinator will be the only personnel exposed to the group allocation. The 2 pharmacists will carry out the randomization process and prepare the medication using a concealed nontransparent envelope and send it to the nursing staff, who will provide the treatment approximately 90 minutes before the physical therapy session. The study coordinator will track group allocation and deliver the prescriptions to the nursing staff before the administration of the drug. Physicians who prescribe MPH, modafinil, or placebo will use a customized sham form to ensure blinding. All primary and secondary outcomes will be collected by 2 physical therapists (PTs), who will be also blinded to the group allocation.

Intervention

Medication

Participants will receive 2 medications based on their group assignment. The MPH group will receive a quarter tablet of short-acting MPH (2.5 mg) and an oval-shaped placebo (100 mg) tablet that looks like a modafinil tablet. The modafinil group will receive a modafinil (100-mg) tablet and a circle-shaped quarter tablet of placebo that looks like an MPH tablet (2.5 mg). The placebo group (the active control) will receive 2 placebo tablets (a circle-shaped quarter tablet of MPH placebo and an oval-shaped tablet of modafinil placebo). All delivered medications (MPH, modafinil, and placebo) will be administered approximately 90 minutes before the physical therapy session, to use the peak medication effect to augment the outcomes of physical therapy [45]. The medication will be administered by a registered nurse and will be controlled by the pharmacy department at Jaber Al-Ahmed Hospital. The medication will be only prescribed on the day of a physical therapy session, which means that children will receive 3 medication doses per week over 12 consecutive weeks (the duration of the study). Since children need to receive the medication 90 minutes before their PT session, appointments will be scheduled on Sundays, Tuesdays, and Thursdays during the daytime (ie, from 8 AM to 1 PM; Figure 2). Any missed appointment will be documented, and the prescribed medication will be returned to the pharmacy. After 12 weeks of medication administration, participants will stop receiving the prescribed medication in this study, whether it was the active agent or placebo. A follow-up assessment session will be performed 12 weeks after the discontinuation of medication to examine the potential for long-lasting benefits from the received medication. Further analysis will be done to compare compliant versus noncompliant children.

All MPH (Ritalin, 10 mg; Novartis), modafinil (Provigil, 100 mg; Apotex), and placebo (circle-shaped MPH placebo, 10 mg; oval-shaped modafinil placebo, 100 mg; Kuwait Saudi Pharmaceutical Industries Co) bottles that will be used in this study will adhere to labeling requirements to ensure traceability and accountability, containing the following information: (1) the full name of the supplier of the medication and placebo bottles, (2) the batch number, and (3) the manufacturing and expiration dates. In addition, the medication and placebo tablets will be extracted from their original bottles and secured in individual containers with the aforementioned information and a patient identifier. The study coordinator is responsible for ensuring compliance with these labeling requirements, which will be recorded and will be made available for inspection upon request.

Figure 2. Illustration of the timing of the administration of the medication and physical therapy sessions.

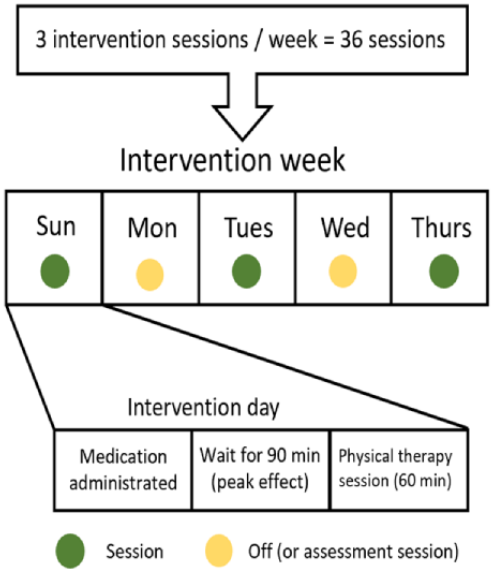

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Physical Therapy Intervention

The physical therapy intervention will include therapeutic exercises that target different domains of the International Classification of Functioning, Health, and Disability (ICF), including body structure, activity, and participation. The dose of the physical therapy intervention will be as follows: (1) the frequency will be 3 sessions per week for 12 weeks; (2) the session time will be 60 minutes; (3) the type and intensity will be treatment activities that focus on joint ROM and muscle strength (body structure domain), locomotion training (body structure [endurance], activity [gait training], and participation [locomotive abilities] domains), reaching training (activity and participation domain), and motor control and motor learning training (activity and participation domain) (Table 1). A detailed manual will be provided to the treating PTs to ensure consistency in the treatment delivered to each child. After 12 weeks of receiving the physical therapy intervention, participants are entitled to enroll into any other rehabilitation program. At week 24, participants will complete an assessment session and provide information on whether they received rehabilitation after stopping the medication, if any, including duration of the session per day, frequency of sessions per week, and compliance to these sessions in the past 12 weeks.

Table 1. Detailed physical therapy plan.

ICF[a] domain and type	Details
Body structure and function	
Joint range of motion	• Active and passive stretching (eg, squats and stepping up)
Muscle strength	• Active and resistive training (85% of 1-repetition maximum—build up to 3 sets of 10 repetitions)
Activity	
Locomotion training	• Treadmill walking—build up to 1.2 m/s with a 0.2 m/s increase per week or as tolerated • Overground walking—over and around obstacles for 10 m or as tolerated
Reaching training	• Bimanual activities—reaching in all directions (with both hands or switching between hands)
Postural control	• Equilibrium reaction training— moving from a stable to an unstable surface with eyes open, then repeated with eyes closed
Participation	
Motor control and learning	• Training for activities of daily living—standing progression, walking progression, and higher function progression (stair climbing, running, and jumping)

[a]ICF: International Classification of Functioning, Health, and Disability.

Implementation of the Intervention

Data collection sessions (assessment data points) will be held on Sundays, Tuesdays, and Thursdays during the daytime (ie, 8 AM to 1 PM). Two PTs will be assigned to deliver physical therapy interventions throughout the study. Each PT will treat a range of 3 to 6 children per intervention period (n=36 intervention sessions). Two experienced investigators will supervise the physical therapy treatment and track the participants' compliance. The expected time commitment for each child for each session is about 2 to 2.5 hours, with the first hour waiting for the medication's peak effect and the remaining time for the physical therapy intervention.

Outcomes

Primary Outcomes

After obtaining the consent and assent forms, caregivers will complete a questionnaire on demographic information, followed by a body weight and height assessment of each child. The primary outcomes of this study will be the GMFM-66 and MAS scores for the LEs and UEs to assess changes in functional motor performance and spasticity, respectively. The assessment session will be done by a trained PT who is different from the PTs that will deliver the intervention. There will be 4 examination sessions (baseline, at 6 weeks, at 12 weeks, and at 24 weeks) that will last approximately 2 hours—for both primary and secondary outcomes. These assessment sessions will be scheduled separately from the intervention sessions. The GMFM-66 is designed to examine gross motor activities in five domains: (1) lying and rolling, (2) sitting, (3) crawling and kneeling, (4) standing, and (5) walking, running, and jumping [46]. The GMFM-66 scores range between 0 to 3, where 0 corresponds to "does not initiate," 1 corresponds to "initiates," 2 corresponds to "partially completes," and 3 corresponds to "completes" [46]. Items that a child refuses to perform or that are not administered are scored as "not tested" [46]. Scoring will be done using the Gross Motor Ability Estimator (GMAE), where each score is entered and then converted into an internal level to calculate the total score for each child's gross motor function. The GMFM-66 is a valid and reliable tool to assess gross motor function in children with CP [47]. In addition, we will use the MAS for the LE (hip extensors and adductors and ankle plantar flexors) and UE (shoulder internal rotators and flexors and elbow flexors) musculature as the second primary outcome. The MAS scores range from 0 (no increase in resistance to stretch) to 4 (complete rigidity) [48]. Children will lay supine on a flat bed with their head at midline and the arm beside the trunk [48]. Each extremity will be examined

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separately. The examiner will rapidly move the child's extremity throughout the range within 1 second [48]. The examiner will determine the MAS score after applying 3 passive movements [48]. This MAS has been shown to have a good intrarater reliability for the LEs (intraclass correlation [ICC]=0.644; Cohen κ=0.488) [49]. The minimum clinically important differences (MCIDs) for the GMFM-66 are 1.7 and 1.0 for GMFCS levels I and II, respectively [50].

Secondary Outcomes

The secondary outcomes will include the Timed Up and Go (TUG) test, 5 Times Sit to Stand (5XSTS) test, Modified Clinical Test for Sensory Interaction of Balance (MCTSIB), and 10-Meter Walk Test (10MWT). For the TUG, participants will stand up from a 45-cm height armchair, walk at their typical, comfortable pace around a cone that will be placed 3 meters away from the chair, then walk back to the chair and sit down. Time(s) to complete the task will be recorded as the score of this test using a stopwatch. The TUG has excellent test-retest reliability in children with CP (ICC=0.91-0.99) and MCIDs of 0.36 and 0.87 for GMFCS levels I and II, respectively (ie, a large effect size) [51].

For the 5XSTS, participants will stand up from a 45-cm armchair and sit down as fast as they can. Time(s) will be used for scoring this test. This test has excellent test-retest reliability in children with CP (ICC=0.91) [52]. Of note, MCID data are not available for children with CP; however, the minimal detectable change for this test is 0.06 seconds [53].

The MCTSIB measures balance in 4 conditions, measured for a maximum of 3 trials of 30 seconds for each condition: firm floor with eyes open, then closed; and foam (unstable surface) with eyes open, then closed [54]. This test has excellent test-retest reliability (ICC=0.91) [54].

For the 10MWT, participants will be instructed to walk at their comfortable pace for 10 meters; time(s) will be recorded as the score of this test. This test is to measure gait speed and variability and has fair test-retest reliability (ICC=0.81) [55].

Statistical Analysis

SPSS (version 29; IBM Corp) will be used to conduct all the data analyses in this study. For changes in the primary outcomes, we will use a repeated-measures ANOVA to examine changes in the GMFM-66 between the 3 intervention groups across all testing time points (ie, baseline, at 6 weeks, at 12 weeks, and at 24 weeks). To examine changes in MAS between the 3 intervention groups, we will use Kruskal-Wallis *H* test because MAS is an ordinal scale. Finally, we will use multivariate linear mixed models to determine changes in the associated secondary outcomes between the 3 intervention groups.

Adverse Events

At the beginning of each intervention week, a questionnaire will be administered by the PTs inquiring about adverse effects. Any adverse events will be addressed immediately by the research team. Any potential risks of using CNS medications will be recorded in the informed consent and assent forms and will be explained to the caregiver of each child. In case of an adverse event, we will refer the participant directly to the emergency department to receive medical care and record the incident of the adverse event. Additionally, we will notify the institutional review board office at Kuwait University and the Ministry of Health of Kuwait about any potential incidents. Finally, should we encounter 2 or more incidents per medication group, we will stop the intervention for that specific group and document it in our records.

Data Collection and Management

Data collection will be performed at baseline (before randomization), 6 weeks, and 12 weeks, as well as at 24 weeks (as a test of long-lasting effects) after starting the intervention. A data monitoring committee (DMC) will be assigned that will include a research assistant and a pharmacist. Members of the DMC will be exposed to the randomization process and will manage adverse events throughout the protocol. Compliance to medication and physical therapy will be collected every session by the PTs, using an online Google form; Microsoft Excel sheets and participant ID numbers will be used to identify each participant. Only the DMC members will have access to this sheet, in which no identifiable information of participants will be included.

Confidentiality

All identifiable data of participants will be protected and decoded in the data collection sheet. After agreement to participate, signed consent and assent forms will be stored in a locked locker at the principal investigator's office. All other study documents (eg, data collection sheet, randomization and mediation prescriptions, and demographic data questionnaires) will use a participant ID number that will replace the name of the child.

Ancillary and Posttrial Care

Due to the pilot nature of this study, the results will not provide definite findings regarding the effectiveness of CNS stimulant medications in reducing spasticity and improving motor function in children with CP. Therefore, we are unable to recommend the prescribing of any CNS medication for children with CP until the findings of advanced phases of this project indicate their efficacy and effectiveness.

Results

The protocol has been accepted by Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). The inclusion of participants will start in June 2024. The findings of this study are intended to be disseminated at several scientific meetings, including the American Academy of Cerebral Palsy and Developmental Medicine and the AAN annual meetings. Additionally, the findings of this study will be submitted for publication to scientific journals specialized in the field of CP and developmental medicine.

Discussion

Principal Findings

This study protocol details the background and design of a pilot RCT to determine changes in motor performance and spasticity

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as a result of the use of CNS stimulant medications in children with CP. We expect the findings of this study to document the safety and tolerability of using these medications in children with CP. We also expect that there will be a trend of improvements in the GMFM-66 and MAS in the CNS stimulant groups (ie, MPH and modafinil) compared to the placebo group. We anticipate that these changes will impact quality of life and the overall function of children with CP, demonstrated by improvement trends in secondary outcomes, where these improvements could document positive effects of CNS stimulants in improving the health of patients with CP.

The findings of this study will be shared and disseminated through multiple scientific mediums, including annual conferences and scientific meetings, as well as peer-reviewed scientific journals. The functional and motor improvements that could result from using CNS stimulants in this population could reduce the consequences of impairments associated with CP. Therefore, using CNS stimulants could help in reducing the financial burden associated with treating CP functional impairments on the health care system.

Limitations

The complexity of CP and the heterogeneity of motor impairments may contribute to variations in response to medication in this study. However, we limited participation in this study to participants with GMFCS levels I and II to minimize the effect of severe motor impairments. Although not an issue in pilot studies, dropout across the study groups may occur. Nevertheless, this concern could be mitigated by providing physical therapy sessions to all groups in addition to medications. Regardless, CP motor treatment is valued across parents of children with CP and could help in reducing attrition. Finally, information obtained from the physical therapy intervention will be important for revising the conceptual model for the intervention and will inform the next step of the trial.

Conclusions

Evidence suggests promising results of using CNS stimulant medications for reducing spasticity and improving physical function in children with spastic CP. The combination of CNS stimulant medications and controlling for rehabilitation has not been studied yet. The findings of this study may suggest positive effects of using CNS stimulant medications for reducing spasticity and improving physical function in children with spastic CP.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

M Alotaibi and ABA conceptualized the idea and methodology and contributed to manuscript preparation and revision. SA and NA improved the methodology, provided an overall framework, and revised the manuscript. AA, M Alharbi, and AT managed the pharmacological planning and placebo design in accordance with the study requirements and revised the manuscript. BA, LV, and MMA helped refine the protocol and provided critical feedback for improving the quality of this protocol. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

10MWT: 10-Meter Walk Test
5XSTS: 5 Times Sit to Stand
AAN: American Academy of Neurology
ADHD: attention-deficit/hyperactivity disorder
ADL: activity of daily living
BoNT-A: botulinum toxin type A
CONSORT: Consolidated Standards of Reporting Trials
CP: cerebral palsy
CPUP: cerebral palsy follow-up program
CNS: central nervous system
GABA: gamma-amino butyric acid
GMAE: Gross Motor Ability Estimator
GMFCS: Gross Motor Function Classification System
GMFM: Gross Motor Function Measure
ICC: intraclass correlation
ICF: International Classification of Functioning, Health, and Disability
LE: lower extremity
MAS: Modified Ashworth Scale
MCID: minimum clinically important difference
MCTSIB: Modified Clinical Test for Sensory Interaction of Balance
MPH: methylphenidate
PT: physical therapist
RCT: randomized controlled trial
ROM: range of motion
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
TUG: Timed Up and Go
UE: upper extremity

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Original Paper

Design and Rationale of Prolonged Nightly Fasting for Multiple Myeloma Prevention (PROFAST): Protocol for a Randomized Controlled Pilot Trial

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Abstract

Background: Obesity is an established, modifiable risk factor of multiple myeloma (MM); yet, no lifestyle interventions are routinely recommended for patients with overweight or obesity with MM precursor conditions. Prolonged nightly fasting is a simple, practical dietary regimen supported by research, suggesting that the synchronization of feeding-fasting timing with sleep-wake cycles favorably affects metabolic pathways implicated in MM. We describe the design and rationale of a randomized controlled pilot trial evaluating the efficacy of a regular, prolonged nighttime fasting schedule among individuals with overweight or obesity at high risk for developing MM or a related lymphoid malignancy.

Objective: We aim to investigate the effects of 4-month prolonged nightly fasting on body composition and tumor biomarkers among individuals with overweight or obesity with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or smoldering Waldenström macroglobulinemia (SWM).

Methods: Individuals with MGUS, SMM, or SWM aged ≥18 years and a BMI of ≥25 kg/m^2 are randomized to either a 14-hour nighttime fasting intervention or a healthy lifestyle education control group. Participants' baseline diet and lifestyle patterns are characterized through two 24-hour dietary recalls: questionnaires querying demographic, comorbidity, lifestyle, and quality-of-life information; and wrist actigraphy measurements for 7 days. Fasting intervention participants are supported through one-on-one telephone counseling by a health coach and automated SMS text messaging to support fasting goals. Primary end points of body composition, including visceral and subcutaneous fat (by dual-energy x-ray absorptiometry); bone marrow adiposity (by bone marrow histology); and tumor biomarkers, specifically M-proteins and serum free light-chain concentrations (by gel-based and serum free light-chain assays), are assessed at baseline and after the 4-month study period; changes therein from baseline are evaluated using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. Feasibility is assessed as participant retention (percent dropout in each arm) and percentage of days participants achieved a ≥14-hour fast.

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Results: The PROlonged nightly FASTing (PROFAST) study was funded in June 2022. Participant recruitment commenced in April 2023. As of July 2023, six participants consented to the study. The study is expected to be completed by April 2024, and data analysis and results are expected to be published in the first quarter of 2025.

Conclusions: PROFAST serves as an important first step in exploring the premise that prolonged nightly fasting is a strategy to control obesity and obesity-related mechanisms of myelomagenesis. In evaluating the feasibility and impact of prolonged nightly fasting on body composition, bone marrow adipose tissue, and biomarkers of tumor burden, this pilot study may generate hypotheses regarding metabolic mechanisms underlying MM development and ultimately inform clinical and public health strategies for MM prevention.

Trial Registration: ClinicalTrials.gov NCT05565638; http://clinicaltrials.gov/ct2/show/NCT05565638

International Registered Report Identifier (IRRID): DERR1-10.2196/51368

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KEYWORDS

MGUS; smoldering myeloma; cancer prevention; intermittent fasting; fasting; myeloma; cancer; oncology; oncological; overweight; weight; obese; obesity; tumor; tumors; RCT; randomized; controlled trial; controlled trials; body mass index; BMI; blood; hematology; hematological; gammopathy; eating; diet; dietary

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is preceded by well-defined precursor conditions called monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) [1,2]. MGUS and SMM are asymptomatic conditions that have an annual progression rate to overt MM of 1% and 10%, respectively, but can be as high as 58% in 20 years in certain risk groups [3,4]. Despite the increasingly strong interest in intervening at the precursor stage for the early interception and prevention of MM, safe and cost-effective interventions are lacking. Although clinical trials have shown that earlier initiation of anti-MM therapies at the precursor stage (eg, lenalidomide-based regimen for high-risk SMM [5]) may alter the natural disease course and improve survival [5,6], early treatment remains highly controversial due to high costs and toxicity risks to patients, limiting its use to only a subset of patients at the highest risk strata [7-10].

Lifestyle interventions targeting excess adiposity and metabolic health in precursor patients may have an important role in MM prevention. Obesity is a well-established, potentially modifiable risk factor of MM [11], and there is accumulating evidence that obesity may also increase the risk of MGUS and its progression to overt MM [12-14]. Although current dietary and weight control guidelines for cancer prevention focus largely on calorie restriction and optimizing intake of specific food groups [15], challenges related to their integration into individuals' daily lives for a sustained period of time remain a consideration [16-19]. Time-restricted feeding, a form of intermittent fasting whereby ad libitum energy consumption is constrained to a window of time (typically between 4 and 12 hours daily), may be a simple, feasible alternative for weight loss and cancer risk reduction [16,20]. When food intake timing occurs during the wake phase of the 24-hour day, time-restricted feeding may benefit metabolic health and cancer risk by synchronizing feeding-fasting regimens with daily circadian rhythms, which, in turn, improve oscillations in the circadian clock expression of numerous genes important for glucose metabolism and overall cellular homeostasis (eg, autophagy and DNA damage repair) [16,21,22].

The PROlonged nightly FASTing (PROFAST) study is a randomized controlled pilot trial investigating the clinical benefit of a 4-month prolonged nightly fasting regimen in individuals with overweight or obesity with MGUS, those with SMM, and those with smoldering Waldenström macroglobulinemia (SWM). The intervention is supported by evidence that prolonged nighttime fasting is not only a simple and sustainable behavior change [16,23] but also improves metabolism and body weight regulation [24-29]. Here, we describe the study design, rationale, and framework for assessing the potential clinical significance of a low-risk, cost-effective lifestyle intervention in patients with MM precursor conditions.

Methods

Design of PROFAST

PROFAST is a pilot randomized controlled trial of our 4-month prolonged nightly fasting intervention in patients with overweight or obesity with MGUS, SMM, or SWM. The goal of the trial is to acquire preliminary outcome data for the efficacy of prolonged nightly fasting on body composition and clinical markers of disease progression in precursor patients. Participants are randomly assigned to (1) a theory-based intervention designed to promote a 14-hour fast during the nighttime hours or (2) the healthy lifestyle education control group.

Ethical Considerations

All study procedures and materials have been approved by the institutional review board at the Dana-Farber Cancer Institute (22-071).

Participants and Eligibility

Eligible participants are at least 18 years old, have a BMI of ≥25 kg/m^2, and have a documented diagnosis of MGUS, SMM, or SWM via the review of their electronic medical records. As shown in Textbox 1, inclusion criteria include individuals who (1) are currently fasting for <14 hours per night as assessed via

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self-report and using 24-hour food recalls and (2) own a cell phone and are capable of sending and receiving SMS text messages comfortably. Exclusion criteria are patients with (1) overt MM; (2) other cancers requiring active therapy; (3) diabetes mellitus, which may increase the risk of hypoglycemia with a prolonged fast, unless the physician who manages their clinical care provides consent that they may enroll; or (4) any other condition or circumstance that, in the investigators' judgment, would be a contraindication to nightly fasting or interfere with trial participation (eg, night shift work, night eating syndrome, taking weight loss medication, and participation in another weight loss program). Participants are primarily recruited from the Dana-Farber Cancer Institute Center for Early Detection and Interception of Blood Cancers, a clinic focused on evaluating patients diagnosed with precursor conditions of hematologic malignancies and which works with patients to manage their risk of disease progression.

Textbox 1. Study eligibility criteria.

Inclusion criteria

- Age ≥18 years
- BMI ≥25 kg/m^2
- Diagnosis of monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or smoldering Waldenström macroglobulinemia
- Currently fasting for <14 hours per night, as assessed by 24-hour food recalls
- Owns a cell phone capable of sending and receiving SMS text messages comfortably
- Ability to understand and willing to sign a written informed consent document

Exclusion criteria

- Diagnosis of overt multiple myeloma
- Diagnosis of another malignancy requiring active therapy
- Diagnosis of diabetes mellitus, unless consent from the patient's physician managing the participant's clinical care
- Any medical or lifestyle condition contraindicated in or would interfere with study intervention (eg, night eating syndrome and night shift work)
- Currently taking medications intended for weight loss or participating in other weight loss programs

Clinic Visits and Randomization

On completion of the consent form, participants attend a baseline clinic visit that includes laboratory, self-report, and physical assessments, as shown in Figure 1. In particular, participants have their height and weight measured and receive a dual-energy x-ray absorptiometry (DXA) scan to evaluate body composition. Participants provide biospecimen samples (ie, blood and bone marrow aspirate or biopsy). For each blood draw, approximately 30 to 60 mL of blood per participant is collected into EDTA and serum separator tubes for immediate plasma and serum preparation, respectively, and aliquots of plasma and serum in 1.8-mL cryovials are placed in a –80 °C freezer for storage. As for bone marrow samples, approximately 20 mL of bone marrow is collected into EDTA tubes for immediate processing, and the processed samples are placed in cryovials in a slow freezing cryostorage for 1 to 7 days before moving to storage in a liquid nitrogen tank.

Participants' current diet and lifestyle patterns are characterized through two 24-hour dietary recalls: (1) questionnaires ascertaining demographic, comorbidity, lifestyle, and quality-of-life information; and (2) the wearing of an ActiGraph accelerometer (GT3XP-BTLE; ActiGraph Corp) on their wrists for 7 days for baseline assessment of sleep, physical activity, and circadian rhythm.

Within 28 days of completing baseline assessments, participants are randomized in a 1:1 manner to either the nighttime 14-hour fast intervention group or the healthy lifestyle education comparison group. Once randomized, participants initiate the intervention or control condition ideally no later than 28 days of baseline screening assessments.

A clinic visit is scheduled 4 months after initiating and ideally within 7 days of completing the intervention or control condition. At this final visit, participants' weight, biospecimens and clinical labs, DXA scan, and self-reported outcome measures are reobtained.

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Figure 1. Schematic of the study design. Timeline of participant recruitment, baseline visit, randomization to intervention or control arm, and end-of-study visit, with assessments that include tumor biomarkers, body composition, 24-hour food recalls, quality-of-life and lifestyle survey, and ActiGraph.

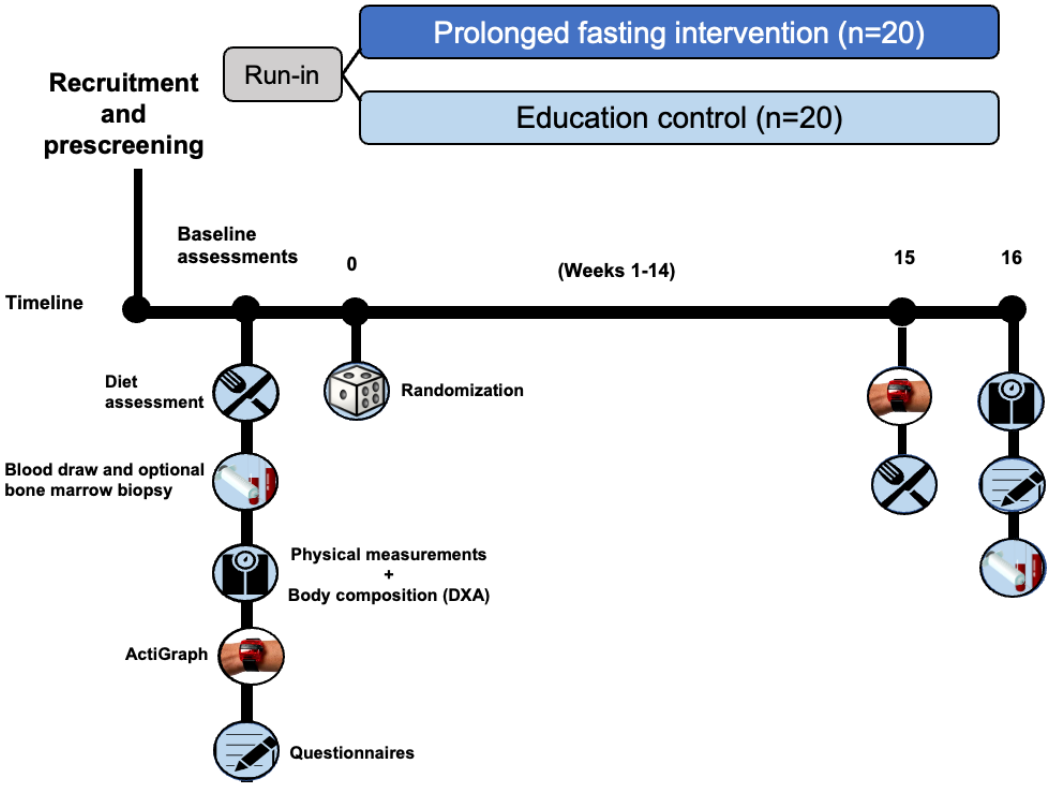

Details of the Intervention

The intervention's goal is to achieve a 14-hour nightly fast. Fasting goals during the initial weeks of the study are individualized, allowing participants to gradually adopt a 14-hour fasting duration on or before the third week of study. A 14-hour window was selected because it has been demonstrated to be an achievable intervention target in other populations of adults with chronic health conditions, and studies to date suggest that it is a sustainable intervention target [29,30]. Specifically, previous interventions have reported elective continuation of the intervention beyond the intervention period, resulting in sustained health benefits including weight loss [29,30]. The overnight fasting period is defined as the longest interval of time overnight in which no calorie-containing foods or beverages are consumed. Given prior findings that fasting may be more beneficial when aligned with the biological night [26], participants are encouraged to begin their nightly fast by 8 PM. To maximize acceptability and adherence to the intervention protocol, participants are allowed to consume noncaloric beverages including water, plain coffee, plain tea, zero-calorie sodas, and calorie-free sweeteners.

The intervention delivery consists of one-on-one telephone counseling by a health coach and an SMS text messaging system to support this target. Participants are supported through telephone counseling during the initial phase (weeks 1-3) of the interventional period and gradually transition to activities that promote self-reliance for behavioral maintenance from week 4 until the end of the study. The intervention incorporates a number of theory-based behavior change strategies in its design [31-33], including those grounded in social cognitive theory and its central tenet of self-efficacy [31].

SMS Text Messaging System

An SMS text messaging system was developed in collaboration with Mosio, Inc, and is introduced to participants during week 3 of the study for the purpose of self-monitoring, tracking adherence, and encouraging maintenance of prolonged nightly fasting. Participants are asked to text the study team to indicate when they began and ended their overnight fast. Participants receive an automated response to their SMS text messages, with positive reinforcement if the fasting goal was successfully achieved or corrective tools, such as a behavioral strategy, that may help them achieve a longer fast. The messages sent back to participants also contain feedback about their cumulative adherence to the prolonged overnight fasting pattern, calculated as the percentage of the successful overnight fasts during the past week. Participants also receive an SMS text message each day to remind them of their target end time of the overnight fast as well as encouraging SMS text messages to promote adherence that are customized to past performance. An example of SMS text messages sent to and received from participants through the automated SMS text messaging system is provided in Table 1.

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Table 1. Example of an interaction in which a participant in the intervention arm submits SMS text messages to indicate the beginning and end of overnight fast and, in turn, is provided with automated, encouraging messages promoting cumulative adherence and achievement of the fasting goal.

Time stamp	Message status	Message content
February 17, 2013, 6:00 PM	Sent	Remember: Calories break a fast! Once you start, you need be calorie-free
February 17, 2013, 7:28 PM	Received	FAST
February 17, 2013, 7:29 PM	Response	Thanks! You are now running calorie free! Check back in the morning for your end time.
February 18, 2013, 7:00 AM	Sent	Your fast ends at 9.28 am. You can do it!
February 18, 2013, 9:55 AM	Received	EAT
February 17, 2013, 10:05 AM	Response	Congratulations! Your success rate is 100%. Nice work!

Healthy Lifestyle Education Control

Participants in the control arm receive educational information regarding healthy lifestyle to enhance retention of participants randomized to this group. At baseline, control participants receive an educational session with the health coach and a workbook containing brief information about topics about a healthy lifestyle (eg, sun safety, sleep, hydration, and sitting less). It is notable that research indicates that a single education session has only modest and temporary impacts on behaviors among most individuals [34,35]. To support sustained engagement throughout the 4-month study period, control group participants also receive 1 email and 1 SMS text message per week by the same SMS text messaging system used for participants in the interventional arm. These SMS text messages contain a mixture of educational information and potential personalized touch points to help participants feel valued.

Primary End Points

A challenge in assessing the clinical benefit of short-term interventions in MGUS, SMM, and SWM is that precursor patients are expected to have a relatively small number of progression events over months to years, limiting the ability to evaluate these events as the outcome. In this study, we focus on body composition, bone marrow adipose tissue, and biomarkers of tumor burden, which are accessible outcome measures in evaluating the efficacy of our lifestyle intervention.

Body Composition and Bone Marrow Adiposity

Most investigations evaluating the association of obesity and MGUS and MM have used BMI as a surrogate measure of obesity [12,13,36,37], and although BMI is a convenient, inexpensive measurement [38], it has low specificity for identifying excess adipose tissue and does not account for the type and distribution of fat (visceral and subcutaneous fat) [39,40]. These shortcomings of BMI limit our understanding of the relationship between obesity and the development of MM, as different adipose tissue compartments are known to have differential influences on obesity-related diseases [41-43]. For example, visceral fat is a metabolically active tissue type that releases fatty acids and proinflammatory substances and, in comparison with subcutaneous tissue, is more strongly associated with components of metabolic syndrome [41-43]. Thus, in our study, DXA scan (Horizon W DXA; Hologic, Inc) is used to measure body composition, differentiating not only fat mass from lean mass but also among adipose tissue types (visceral and subcutaneous fat). Furthermore, bone marrow adipose tissue is an understudied adipose depot with endocrine and paracrine signaling functions linked with the proliferation of nearby MM cells [44]. In our study, total marrow lipid content is quantified in bone marrow aspirate samples. Adipocyte-lipid content is analyzed using histology, flow cytometry, and lipidomics on adipocyte-enriched fractions. By measuring and comparing these adiposity measures between baseline and end of study, our study is able to evaluate whether prolonged nightly fasting possibly improves the body composition profile of participants.

Clinically Available Tumor Biomarkers

Serum protein electrophoresis supplemented by immunofixation (SPEP/IFX) and serum-free light chains (SFLCs) are the most commonly used clinical tests used to monitor patients at all stages of the disease continuum (MGUS, SMM, and MM). Monoclonal immunoglobulin (M-protein) and light-chain concentrations, as measured by SPEP/IFX and SFLCs, correlate with overall tumor burden and importantly decrease after treatment with a range of mild and aggressive MM therapies [45-47]. These biomarkers are sensitive and measurable variables of tumor response to treatment [48] and, therefore, serve as clinically relevant disease end points for our lifestyle-related intervention pilot study.

Other End Points

Metabolomics

Metabolomics—the high-throughput identification and quantification of small-molecule metabolites—is the study of metabolic changes in biological systems and provides the small-molecule fingerprints that reflect the complex relationships among diet, lifestyle (obesity), genes, and disease processes [49]. Metabolomics can yield novel insights into pathogenesis and risk of cancer and chronic disease [49,50]. Particularly important categories of metabolites in cancer and metabolic disease are metabolites of glycolysis and the tricarboxylic acid cycle [51,52]. These are of interest to this study because of their critical role in tumor growth and because they have been shown to be related to obesity [53]. Metabolomics-based data of MGUS, SMM, and MM are limited to only a small number of studies, including one by Ludwig et al [54] that identified 25 bone marrow metabolites that differed between 10 patients with MGUS and 10 patients with MM [55-59]. Of all molecular entities in the body (eg, genes, transcripts, proteins, and metabolites), metabolites as the final products of biochemical processing have the closest relationship

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to expressed phenotype [60]. Thus, we believe that metabolomics offers a unique lens to study progression of MM precursors.

Quality of Life

Given the high rates of anxiety and distress document in individuals with MGUS and SMM and lack of evidence-based risk reduction strategies available for preventing disease progression to MM [61,62], we aim to evaluate the psychosocial benefits of offering a low-risk lifestyle intervention to this patient population as an exploratory objective. Quality of life is assessed using the well-validated PROMIS (Patient-Reported Outcomes Measurement Information System) global health survey [63-65]. Cancer worry is assessed using a 4-item scale adapted from Lerman et al [66].

Baseline Dietary and Lifestyle Assessment

Participants undergo two 24-hour dietary recalls to assess food and beverage consumption (ideally for 1 weekday and 1 weekend day), which are conducted through the Behavioral Measurement and Interventions Shared Resource at the University of Arizona Cancer Center. Participants also complete a baseline survey querying sociodemographic variables (eg, age, sex, race, ethnicity, highest level of education attained, and annual family income), medical comorbidities (eg, hypertension, hyperlipidemia, and diabetes mellitus), and lifestyle factors (eg, smoking, physical activity, sleep impairment, and disturbance) measured by well-validated instruments [67-72]. Finally, participants are asked to wear an ActiGraph accelerometer (GT3XP-BTLE; ActiGraph Corp) on their wrists for 7 days for a baseline assessment of physical activity, sleep, and circadian rhythm parameters [73-75].

Feasibility, Acceptability, Fidelity, and Safety

Feasibility is assessed as participant retention (percent dropout in each arm) and percentage of days participants achieved a ≥14-hour fast. Acceptability is assessed as perceived effectiveness of intervention components, plans to continue to engage in a prolonged nightly fast, elements of intervention liked or disliked, and satisfaction with program delivery and staff. Items are rated on a scale from 1 to 5. Finally, fidelity is assessed as percentage of days participants recorded fasting duration via the SMS text messaging system, percentage of SMS text messages read, and percentage of calls with the health coach.

Safety is monitored and assessed by the number and severity of adverse events, according to the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Individuals with any medical or lifestyle condition (eg, diabetes mellitus) that is deemed to elevate their risk of adverse events from the intervention are excluded from the study (Textbox 1). Participants are informed of expected side effects related to fasting (eg, lightheadedness, headaches, restlessness, irritability, and low blood glucose), and adverse events that vary in nature, intensity, and frequency from what is expected are reported.

Analysis Plan

The key outcomes evaluated in this trial are changes in body composition (with a focus on visceral and subcutaneous adiposity), M-protein concentrations, and bone marrow adiposity. Changes in these end points are evaluated from baseline to follow-up in the 2 groups using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. The baseline values of the dependent variables (eg, weight and M-protein level) and disease subtype are included as covariates in the regression models. Group-by-time interaction terms are included as fixed effects in the regression model. Model fit is assessed using standard methods.

Results

The PROFAST Study was funded in June 2022. Participant recruitment commenced in April 2023, after developing and testing the text messaging system. As of July 2023, a total of 6 participants consented to the study. The study is expected to be completed by April 2024, and data analysis and results are expected to be published in the first quarter of 2025.

Discussion

The PROFAST study provides important preliminary data regarding the impact of prolonged nightly fasting on body composition, bone marrow adipose tissue, and biomarkers of tumor burden (SPEP/IFX and SFLCs) in patients with MM precursor conditions, thereby generating hypotheses on how targeting obesity-related mechanisms of carcinogenesis may help prevent MM development.

Obesity is a well-established, potentially modifiable risk factor of MM [11], and there is accumulating evidence that obesity may also increase the risk of MGUS and its progression to overt MM [12-14]. A study of 3 large prospective cohorts of US-based adults followed over 5 million person-years observed a 17% increase in MM risk per 5 kg/m^2 increase in BMI [36]. In another study of 7818 patients with MGUS in the US Veterans Health Administration database, being overweight and obese were associated with an increased risk of transformation to MM (hazard ratio [HR] for overweight 1.55, 95% CI 1.16-2.06; HR for obesity 1.98, 95% CI 1.47-2.68) [12]. Concordant with these findings, a more recent analysis of patients with MGUS identified through a population-based screening study in Olmstead County, Minnesota, between 1995 and 2003 observed that having a BMI ≥25 was also associated with increased progression to MM or other plasma cell or lymphoid disorders in univariate analysis (HR 2.14, 95% CI 1.05-4.36) and in a multivariable model accounting for clinical factors [13].

These epidemiological studies are supported by mechanistic evidence that obesity may lead to chronic low-grade inflammation and dysregulation of endogenous growth factors linked to myelomagenesis [76,77], together suggesting that weight control may be an effective MM prevention strategy. Indeed, according to a compelling 2016 consensus statement, an expert panel convened by the International Agency for Research on Cancer concluded that there is sufficient

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mechanistic evidence that a preventative relationship has been established between the "absence of body fatness" and MM [76]. In obesity, adipose tissue, including adipocytes in the bone marrow, is altered in ways that may promote carcinogenesis, including by creating an unfavorable tumor microenvironment in which MM can engraft and grow [44,78]. Notably, the adipose tissue of obese individuals leads to excess free fatty acids as well as altered levels of proinflammatory cytokines (eg, tumor necrosis factor α and interleukin 6), adipokines (eg, adiponectin and leptin), and metabolic peptide hormones (eg, insulin and insulin-like growth factor 1) [44,78,79]. Dysregulated levels of these biological compounds may fuel tumor initiation and influence the genetic characteristics of MM cells in ways that increase cell proliferation [80], reduce apoptosis [81], and contribute to immune cell evasion [82,83]. The implication of these factors is that weight loss may curb the contribution that excess adiposity-associated chronic inflammation and metabolic dysregulation have on MM development.

Beyond weight loss, the PROFAST study tests the hypothesis that "when we eat," not just "what or how much we eat," is relevant to cancer prevention [24,25,84,85]. There is evidence suggesting that chronic exposure to circadian rhythm disturbances may lead to metabolic dysregulation, upregulation of proinflammatory cytokines, and abnormal cell proliferation [21,86]. As food intake contributes to the setting of circadian clock rhythms in peripheral organs, such as by inducing changes in body temperature and through the action of hormones such as insulin and nutrient-sensing enzymatic and nuclear receptor signaling systems [21,87], the synchronization of feeding-fasting patterns with circadian rhythms may be important for preventing chronic diseases [24,26,27]. This hypothesis is supported by a large prospective study of patients with early-stage breast cancer, which observed that a short nightly fasting duration (<13 hours per night), compared with a nightly fasting of ≥13 hours, was associated with an increased risk of breast cancer recurrence [25]. In that same study, each 2-hour increase in the nightly fasting duration was associated with lower hemoglobin A_{1c} levels and a longer duration of nighttime sleep [25]. These findings are consistent with the results of population-based studies [24,26,27], including a large case-control study in Spain that observed that diurnal eating patterns, specifically in maintaining longer time intervals between the last meal of the day and initiation of sleep, were inversely associated with risk of breast and prostate cancer [27]. Similarly, two US-based studies of 2009-2010 National Health and Nutrition Examination Survey data evaluating biomarkers of breast cancer risk observed that a longer duration of nighttime fasting was associated with improved measures of glycemic control and systemic inflammation [24,26], aligning with pathophysiological mechanisms underlying cancer risk [76].

Results from these human observational studies are consistent with rodent studies demonstrating that mice subjected to a time-restricted (16-hour) fasting regimen of a high-fat diet during the sleep phase were protected against weight gain, abnormal glucose metabolism, and inflammation, all of which were associated with cancer outcomes [22,88-91]. Notably, protective effects were observed despite these mice having the same caloric intake as those that had ad libitum access to food and ate frequently throughout day and night [22], suggesting that the beneficial effects of this fasting regimen were partly mediated through mechanisms independent of calorie restriction. Together, these data provide a strong basis of our intervention aimed to curb the inflammatory and metabolic mechanisms shown to contribute to myelomagenesis [44,77].

Finally, and importantly, prolonged nightly fasting represents a lifestyle modification that is safe, practical, and acceptable for patients who otherwise are managed by a "watchful waiting" strategy. Patients with MM precursor conditions are reported to have diminished quality of life, increased comorbidities, and heighted anxiety and a sense of loss of control regarding their MM risk [61,62,92,93]. There is, therefore, a need to identify lifestyle-based interventions that patients can safely and practically adopt into their daily lifestyles and ultimately help curb disease progression. Fasting, as a practice, developed independently among different people groups and religions (eg, Ramadan in Islam) around the world [94], and intermittent fasting has become one of the most common dietary patterns reported in the United States [95]. Prolonged nightly fasting is attractive because of its simplicity and feasibility, as supported by evidence from clinical trials of time-restricted eating strategies [16,23], and, thus, may be a potentially effective disease prevention strategy at the population level [16].

The limitations of this study include the relatively small sample size of the study and the potential lack of sociodemographic and geographic diversity of participants due to recruitment occurring at a single academic institution, thus, possibly impacting generalizability of findings. Also, participants willing to participate in a 4-month prolonged overnight fasting intervention may not be representative of the general population of patients with overweight or obesity with MM precursors, and selection bias for patients who are motivated to participate in PROFAST could increase the study adherence rate. Furthermore, although participants in the intervention group are prescribed solely a prolonged overnight fasting regimen with no other recommendations regarding lifestyle patterns, it is theoretically possible that participants may change their dietary, physical activity, and sleep habits due to paying closer attention to the timing of their eating and evaluations of their body composition before and after the intervention. These changes may also impact outcomes.

In summary, the study described herein serves as an important first step in exploring the premise that prolonged nightly fasting is a practical, effective strategy to control obesity and intercept disease progression in individuals with MM precursor conditions. By evaluating the impact of this lifestyle intervention on relevant biomarkers of excess adiposity and myeloma tumor burden, this pilot study may generate hypotheses and inform further investigations in identifying clinical and public health strategies for MM prevention.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

IMG has served as a consultant for AbbVie, Adaptive, Amgen, Aptitude Health, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Menarini Silicon Biosystems, Novartis, Pfizer, Regeneron, Sanofi, Standard Biotools, Takeda, The Binding Site, and Window Therapeutics; received honoraria from Vor Biopharma and CurioScience; and received support for attending meetings from Amgen, Bristol-Myers Squibb, Novartis, Menarini Silicon Biosystems, and Pfizer. IMG's spouse, William Savage, is Chief Medical Officer and equity holder at Disc Medicine.

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Abbreviations

CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
DXA: dual-energy x-ray absorptiometry
HR: hazard ratio
MGUS: monoclonal gammopathy of undetermined significance
MM: multiple myeloma
PROFAST: PROlonged nightly FASTing
PROMIS: Patient-Reported Outcomes Measurement Information System
SFLC: serum-free light chain
SMM: smoldering multiple myeloma
SPEP/IFX: serum protein electrophoresis supplemented by immunofixation
SWM: smoldering Waldenström macroglobulinemia

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Protocol

Community Health Workers as Mental Health Paraprofessionals: Protocol for a Mixed-Methods Pilot Feasibility Study

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Abstract

Background: Community health workers (CHWs) are effective in delivering behavioral activation (BA), especially in low-resource settings. In an area with a lack of Spanish-speaking mental health counselors, such as southwest Montana, CHWs can provide needed care.

Objective: The goal of this pilot study protocol is to test the feasibility, acceptability, and preliminary efficacy of a model of care that engages CHWs as providers of BA.

Methods: We will train 2 CHWs in BA methodology. We will enroll 20 participants who screen positive for depression in a 12-week telephone intervention for BA. Preliminary efficacy will be tested in pre- and postscores of the Beck Depression Inventory and semistructured interviews. Feasibility and acceptability will be measured through participant retention and treatment adherence. The Therapeutic Alliance with Clinician Scale will be used to measure the strength of the therapeutic relationship. Descriptive statistics will measure alliances and repeated measures ANOVA will measure trends and changes in depression scores.

Results: Enrollment began in October 2023. A total of 12 participants completed at least 10 BA sessions and all study measures by the time the study concluded in May 2024. In August 2024, data analysis occurred with an anticipated manuscript to be submitted for publication in October 2024.

Conclusions: Results from this study will inform future studies into the implementation of an evidence-based mental health intervention in a limited resource setting for Latino people with limited English proficiency.

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KEYWORDS

behavioral activation; community health workers; implementation science; Latino; mental health provider shortage area; pilot study; evidence-based treatments

Introduction

Background

Latino people with limited English proficiency (LEP) experience persistent and preventable mental health disparities. According to the National Alliance on Mental Illness, 18% of Latino people in the United States have a mental illness, but only 33% of those received professional services (compared to 50% of non-Hispanic Whites with mental illness) [1]. In Montana and other Mountain West regions with rapidly increasing LEP populations, the mental health infrastructure has not kept pace with the growing need. Existing English-speaking providers are only able to meet 11% of the need in rural and frontier counties of Montana [2]; however, in Montana counties where the LEP population has grown by as much as 200% [3], access to

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culturally and linguistically congruent mental health providers is even more dire. Through 3 years of data collection using a community-engaged approach, our team found depression in 15% of the LEP population [4]. Working with a community advisory board, we found the primary mental health concern of the LEP community to be depression and a lack of Spanish-speaking providers [5]. Montana leads the nation in suicide rates [6], making access to mental health services an urgent concern.

An evidence-based approach to increasing mental health services is the use of community health workers (CHWs) who can be specially trained to deliver mental health interventions [7]. CHWs are generally from the same community as the population they work with, and while traditional models leverage their ability to provide a bridge to health and other resources, CHWs can provide evidence-based treatments (EBTs), including preventive care and early interventions in low-resource settings, capitalizing on their language and cultural skills [8]. Evidence suggests that CHW-provided EBTs produce mental health outcomes that are comparable to professionally delivered treatments [9]. In an area with a lack of Spanish-speaking mental health counselors, such as southwest Montana, CHWs can provide much-needed services. Indeed, in preliminary work by our team, we found improvements in depression scores in patients who engaged in 6 telehealth motivational interviewing sessions with a trained CHW (Montana State University, unpublished).

CHWs have a positive impact on health outcomes and the ability to address disparities in mental health treatment in a cost-effective, community-focused way. This is especially important in a low-resource setting with a lack of Spanish-speaking providers. Therefore, the goal of this study is to test the feasibility and acceptability of a model of care that engages CHWs as providers of the evidence-based mental health intervention of behavioral activation (BA).

Previous Studies

The theoretical underpinnings of BA suggest that depression results when a person disengages from pleasurable activities and experiences a negative mood [10]. To combat this, the BA protocol helps a client identify activities that provide pleasure and increase positive feelings. Practitioners assist the client to target core problems by scheduling specific activation activities assigned as homework [11]. Persons in BA participate in activities that are enjoyable and monitor their mood while engaging in these activities to increase their awareness of how the activity influences their mood [12]. Clients learn the connections between their activities and their moods and schedule activities to help increase engagement in activities that create positive moods [13]. Clients are also taught to identify behaviors that interfere with their goals ("depressed behaviors") and learn ways to replace these behaviors with positive ones [14]. BA allows clients to explore personal values and goals and to identify positive behaviors that are consistent with meeting those goals. Pleasurable activities are scheduled into the daily routine, and the client tracks mood changes in response to those activities. Clients are also supported in identifying persons who may help support them in accomplishing these activities [15].

Research shows BA is an effective intervention to address depression in Latino people with LEP when delivered by Spanish-speaking mental health professionals. In a randomized hybrid efficacy and effectiveness trial, Kanter and colleagues [11] saw increased engagement and retention from the intervention group receiving BA versus the treatment-as-usual group. In another efficacy study, Latino patients diagnosed with major depressive disorder experienced a greater reduction of depressive symptoms with the implementation of BA-centered treatment when compared to treatment as usual [16]. Other comparable studies found similar results when comparing BA to treatment as usual [17,18].

However, studies on the effect of BA delivered by CHWs are limited. In one study, Magidson and colleagues [19] successfully implemented BA treatment for torture survivors in Iraq with the use of CHWs to deliver the intervention. The procedure was modified to include relevant cultural elements and account for low literacy, and researchers saw improvements in depression. A total of 2 pilot studies—one with veterans and another including the target population (US Latino people)—reported efficacy and fidelity with the use of CHWs as the public-facing component of a multidisciplinary care team [20,21].

This study will address the gap in the existing science of the effect of CHW-delivered BA intervention on depression among Latino people with LEP by testing its acceptability, feasibility, and preliminary efficacy. We will also address a disparity in mental health outcomes for Latino people with LEP in southwest Montana by increasing the supply of Spanish-language mental health resources.

Methods

Intervention

In total, 2 bicultural/bilingual CHWs will be recruited and trained in the administration of BA through the University of Washington's Advancing Integrated Mental Health Solutions Center. The training, specifically designed for CHWs and other patient-facing practitioners, consists of 8 hours of training over the course of 4 months and includes both web-based asynchronous work and 5 hours of web-based training sessions with the BA professional. CHWs learned the principles of BA, how to help participants identify rewarding activities and apply activity scheduling, and how to evaluate progress. The CHWs will be supervised by a nurse who has been trained in supervising CHWs for the duration of the study. As needed, a licensed professional counselor, well versed in working with the Latino population, will be available for further supervision and case management support.

The trained CHWs will deliver a 12-week program of BA over the phone. Individual 50-minute sessions will be scheduled based on participant preference and will consist of creating a plan of activation activities, self-monitoring, identifying avoidance behaviors, setting goal-oriented behaviors, and recording mood changes with activation activities [22]. During sessions, CHWs will discuss the cycle of depression and how

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activities influence moods. Together, CHWs and participants will identify participant goals, create "activating" activities that help work toward those goals, and develop strategies to schedule pleasurable activities. Participants will employ identified activities as homework and track their moods with a daily log. CHWs will record participant progress, homework, and changes in mood in REDCap (Vanderbilt University).

Participants

We aim to recruit 20 participants for this pilot study. Recruitment will occur through a variety of community-based means: in-person community health screening events conducted by our team in Southwest Montana, referrals from the federally qualified health center (Community Health Partners) and the Gallatin City-County Health Department [4], contacts with nonprofit and service providers who work with the Latino population, and word of mouth through our community advisory boards and previous research partners. Eligible participants will be monolingual Spanish speakers with a score of at least 5 on the Patient Health Questionnaire-9 and who have the ability to participate in a phone intervention. The exclusion criteria will include current treatment by a behavioral health specialist and proficiency in English. The study enrollment goal will be 20 with an anticipated attrition rate of 20%, for a final n=16. Studies with attrition rates higher than 20% may be influenced by attrition bias [23]. Participants will be randomly assigned to one of 2 CHWs, so that each will manage a caseload of 10 participants (Figure 1). Participants will schedule their own sessions with the CHW and do not have to meet weekly. Participants who complete 10 of the 12 sessions will be considered to have completed the interventions.

Figure 1. Proposed recruitment. CHW: community health worker; PHQ9: Patient Health Questionnaire-9.

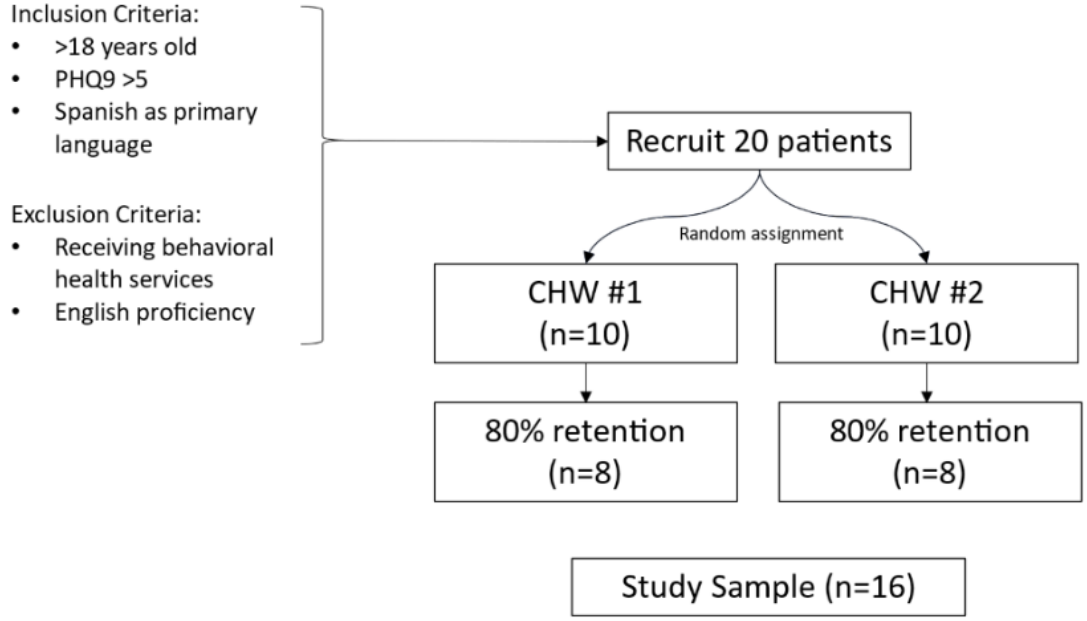

Data Collection and Analysis

We will use a mixed-methods approach to determine the acceptability, feasibility, and preliminary efficacy of the intervention. Acceptability will be measured through participant retention (number of total sessions completed of 12) and treatment adherence (percent of homework assignments completed). We will also use the Therapeutic Alliance with Clinician Scale, a 9-item Likert scale used to estimate the strength of the therapeutic relationship [24]. It has been validated in a Spanish-speaking population with an internal consistency of 0.96 [25]. Descriptive statistics will be used to determine alliance, with higher scores signaling higher estimates of alliance.

The goal of analyzing feasibility is to determine factors that contributed to the implementation of the study. For example, if the attrition rate exceeds 20%, the retention rate in the study would suggest low feasibility for participation. We will assess our methods, including participant recruitment and retention, and test the acceptability of study questionnaires. We will do this through a quantitative analysis of the counts of the number of participants who express interest versus those who enroll versus those who complete the BA sessions. One month after the study concludes, we will conduct qualitative interviews with both CHWs and a subset of participants (expected n=8). Participants who complete at least 1 session will be randomly selected by a research assistant, who will conduct interviews via telephone using a semistructured interview guide. Interviews will be audio recorded and transcribed in Spanish. We will analyze Spanish transcripts through thematic analysis [26]. Potential questions will include how participants heard about the study and why they decided to join, what aspects of the study made it easy or difficult to participate (including reasons for not completing any sessions), facilitators and barriers to completing study questionnaires, and recommendations for improvement to the study protocol. Study measures are shown in Table 1.

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Table 1. Study implementation measures.

Outcome	Measurement	Analysis
Acceptability	Participant retention	Total sessions completed/12
	Treatment adherence	Percentage of homework assignments completed
	Therapeutic Alliance with Clinician Scale	Descriptive statistics
Efficacy	Beck Depression Inventory-II	Linear regression with repeated measures
Feasibility	Qualitative interviews	Thematic analysis

We will measure preliminary efficacy in 2 ways. First is through the semistructured interviews. We will ask participants what effect the intervention had on their general mood and if they felt the study helped improve their depression. We will also measure changes in depressive scores through the Beck Depression Inventory-II [27]. This 21-item self-report inventory is widely used to measure depression severity and has been tested in Spanish with internal consistency between 0.91 and 0.95 [28]. We will administer the Beck Depression Inventory-II at baseline, after 3 sessions, after 6 sessions, after 9 sessions, and upon completion of the BA intervention. We will use repeated measures ANOVA to estimate the trends or changes in depression scores over treatment.

Ethical Considerations

The study was approved by the Institutional Review Board (2023-819) at Montana State University. Participants will complete a translated consent form in Spanish for participation in human studies designed by Montana State University upon enrollment in the study. They will be informed of the study objective, the logistics of the intervention, risks of participation, benefits of participation, privacy and data security protocol, and their rate of compensation. Participants in this study will be paid $200 via a prepaid VISA card upon completion of at least 10 sessions.

Results

The study began in June 2023, and the CHWs were trained in the ethical conduct of research and BA in the fall of 2023. We began enrollment in October 2023. A total of 12 participants completed at least 10 BA sessions and all study measures by the time the study concluded in May 2024. In August 2024, data analysis occurred with an anticipated manuscript to be submitted for publication in October 2024.

Discussion

Anticipated Findings

We hypothesize that this study will contribute to the current science of using nonprofessionals to deliver mental health interventions to a traditionally underserved population. While CHWs have shown promise in delivering BA in many settings and are emerging as part of the evidence base for increasing access to mental health resources [8], their use in the LEP Latino population has not yet been documented. For example, a recent study by Vazquez and colleagues [29] showed that cognitive behavioral therapy delivered by CHWs among a Spanish-speaking population was feasible and acceptable. They also found reductions in depressive scores for study participants. Similarly, Steinman and colleagues [21] adapted a CHW-delivered mental health intervention that included, among other treatment modalities, BA for use with older Latino adults and found the intervention to be feasible and acceptable. In a study of an adapted BA intervention among refugees in Iraq, Bolton and colleagues found reductions in depressive scores for study participants [30]. Our project is innovative in 2 distinct ways. First, it engages a previously underserved community in the delivery of an EBT to address depression among Latino people with LEP. While BA successfully relieves depressive symptoms in Latino people with LEP, most studies use a clinical or primary care practice setting to test the intervention. Our approach is innovative and advances what we know about BA delivered by CHWs in that it engages the community itself and leverages the unique roles of CHWs to deliver an intervention outside of a traditional clinic setting via telephone. The CHWs we will employ as part of this study are currently working as CHWs in the community. They are native Spanish speakers (1 from Colombia and 1 from Peru) and work to connect community members with health services following health screening events. Second, this study will be the first of its kind to address an unmet need in Montana, where very few professional counselors have the Spanish-language skills required to develop truly therapeutic relationships with patients.

Potential Limitations

It is conceivable that participants in our study will require a higher level of care than that which can be provided by a CHW. During our regular team meetings, if we determine that a participant requires more mental health support, they will be referred to a local federally qualified health center that provides professional mental health services, albeit through interpreters. All participants will also be counseled in the use of the 2-1-1/9-8-8 crisis line, which has services in Spanish.

Stigma impacts demand for mental health services, and stigma in the LEP Latino population [5] may be a limitation that will affect study participation. We will work closely with our community advisory boards throughout the project to address potential stigma through social media and other messaging to the community.

Expected Impact

Successful completion of this pilot project will have a significant impact on the potential for increasing the mental health workforce for Latino people with LEP in Montana. Findings from this study—and subsequent findings from larger-scale projects—will help inform practices designed to train, employ, and reimburse CHWs. We hope to demonstrate the efficacy and

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feasibility of implementing an EBT approach delivered by paraprofessionals. We anticipate that a well-trained CHW workforce can help reduce mental health disparities across Montana for Latino people with LEP.

Acknowledgments

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Data Availability

The data sets that will be generated and analyzed during this study will not be publicly available due to confidentiality concerns and required compliance with informed consent protocols but will be available from the corresponding author on reasonable request.

Authors' Contributions

SM contributed to the study concept, design, and methodology; both authors contributed to the drafting of the manuscript and participated in manuscript revision; both authors read and approved the final manuscript. The final version was reviewed and approved by both authors.

Conflicts of Interest

None declared.

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Abbreviations

BA: behavioral activation
CHW: community health worker
EBT: evidence-based treatment
LEP: limited English proficiency

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Protocol

Family-Centered Treatment Program for Problematic Gaming and Excessive Screen Use in a Clinical Child and Youth Population (FAME): Protocol for a Feasibility Pilot Mixed Method Study

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Abstract

Background: Screen time among children and adolescents has increased dramatically, raising concerns about its impact on development and mental health. While research highlights both potential benefits and risks, excessive use has been linked to issues like anxiety, depression, and gaming addiction. Despite growing concern, effective interventions are scarce. Recognizing the importance of family dynamics in child development, we propose a family-centered program to address problematic gaming and excessive screen use in a clinical population. By involving both children and parents, we aim to create a more comprehensive approach to prevention and treatment.

Objective: This study aims to determine the possibility of distributing and evaluating a family-centered group program for problematic gaming and excessive screen use (FAME) in a clinical child and adolescent psychiatry (CAP) population. We will monitor the recruitment rate; track the retention and attendance rates of both parents and children; and assess whether each session's objectives are met, the content is delivered within the allotted time, and the necessary resources (eg, facilitators and materials) are available. Additionally, we will gather qualitative and quantitative feedback from participants through postprogram surveys and individual interviews with both children and parents.

Methods: A total of 10 families with ongoing contact with CAP in Skåne, Sweden, will be recruited and offered participation in a family-centered group program targeting children aged 10-18 years with reported difficulties regarding screen gaming or screen use. The intervention to be tested is a newly developed, family-centered, psychoeducational, cognitive behavioral therapy–based intervention addressing both positive and negative aspects of screen use; setting boundaries; the connection between thoughts, feelings, and behaviors; conflict triggers; and sleep hygiene. The primary goal of the pilot study is to test the feasibility of the program, as well as recruitment and the analysis of participants' experiences with the program.

Results: A total of 11 children and their parents were enrolled during first quarter of 2024. A 4-session pilot was delivered in first quarter of 2024, and the first results are expected in the third quarter of 2024.

Conclusions: The overarching goal of this pilot study is to determine the possibility of distributing and evaluating a family-centered group program for problematic gaming and excessive screen use (FAME) in a clinical CAP population. The insights gained from this study will guide our future research, which will focus on conducting a larger-scale evaluation of the intervention's impact on family screen time conflicts and inform future strategies for the implementation of family-centered interventions in child and youth clinics.

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International Registered Report Identifier (IRRID): DERR1-10.2196/56387

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KEYWORDS

gaming; family program; family intervention; pilot study,; adolescent; problematic gaming; excessive screen time; children; screen use; child-parent relationship; motivational interviewing

Introduction

During the past 10 years, the use of screens, as in social media and video games, has become one of the most common leisure activities for children and adolescents. According to the Swedish Internet Foundation, 94% of children in Sweden between ages 8 and 12 use screens every day [1], with boys playing video games while girls being more active on social media [2]. The growing trend of children and youth spending excessive amounts of time engaged with screens has been perplexing adults. Parents and professionals who work closely with children and youth are particularly concerned about the potential negative impacts of screen time on their overall development [3-5]. Some research suggests that screen time in general and gaming in particular is an educational and skills training activity that can stimulate the user's cognitive abilities and ability to solve problems [6]. Other research has concerns that screen use can become a potentially pathological activity that interferes with everyday life with risks of developing psychiatric disorders such as social media disorder or internet gaming disorder (IGD) [7]. Indeed, while there is currently no official diagnosis for social media disorder, IGD is included in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, as a condition necessitating further clinical experience and research before inclusion as a formal disorder. The World Health Organization, on the other hand, has included gaming disorder in the *International Classification of Diseases, 11th Revision*, as a formal diagnosis [8].

Screen time for adolescents is a complex issue. While it is often associated with gaming, it encompasses a wider range of activities like social media, communication, and even creative pursuits through apps. Social media use, for instance, can foster positive digital behavior and a sense of belonging [9,10]. However, research also indicates that excessive screen time can negatively impact mental health, leading to anxiety and depression in young people [11]. The increasing presence of social media in teenagers' lives presents a double-edged sword. Moderate use can be beneficial for social-emotional development and peer relationships. However, problematic social media use, characterized by addictive tendencies and an inability to regulate use, has been consistently linked to depression, anxiety, and stress [12,13]. While not a formal diagnosis, it is often evaluated based on such addictive symptoms [14].

There is a general consensus among school health professionals, social workers, child and adolescent psychiatrists, and even parents that excessive screen time can impact childhood development [15]. However, clear recommendations remain elusive. Many parents allow their children's current behavior, believing that media content can be educational and that screen time offers a readily available, affordable form of entertainment [16].

Experiencing addictive problems as a child may pose a threat to future psychosocial development [17], including mental health and socioemotional development. In that sense, child and youth mental health services need to put more effort into developing interventions that target children at risk to prevent the development of mental health problems among children and youth. To date, there are no evaluated preventive programs for children and youth with excessive screen time, including problematic gaming, in Sweden.

Our research group from Lund University and Region Skåne has evaluated relapse prevention as an individual treatment for problematic gaming in a randomized controlled trial among children aged 12-18 years in a child and adolescent psychiatry (CAP) setting [18]. This was one of the first treatment studies for children with problematic gaming in Europe. Although we discovered that the individual treatment of children and youth has a promising effect on their gaming, we also found that important pieces were lacking when providing treatment for children with problematic gaming. The most prominent one was the lack of family, including parents, involvement in the treatment. Indeed, children and their development need to be seen from a system perspective [19]—children develop interaction with their environment or family. For children, parents are the closest socializing agents in their environment, who, with their parenting behaviors and practices, pave the way for child developmental transitions. In that sense, the development of certain behaviors, such as gaming and excessive screen use, may, at least to some extent, be related to family factors [20,21]. It is then possible that a child's problematic screen time or gaming is not only attributed to the child itself, but to the family as a system. Therefore, we believe that parents need to be included in the preventive interventions targeting children and their families. Instead of only focusing on the child, changing the family environment, including parent-child interactions at home, may pose significant changes in the child's screen behavior. This is a recognized logic from other family interventions such as the Strengthening Families program targeting families with children with behavioral problems [22] and the Cool Kids program [23] targeting families with children with anxiety. In fact, parents whose children have undergone the relapse prevention treatment in our project state that they need to and want to be involved in the child's treatment. Arguments for family-centered interventions in the treatment of IGD have been presented in previous compilations and emphasize experiences from addiction conditions, where family system involvement has been shown to be important in bringing about behavioral changes in the child [24]. Additionally,

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group-based treatment shows promise for adolescents with problematic gaming [25], although the underlying mechanisms need further exploration. Problematic screen use, not the least gaming, is particularly shown in children with neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder and autism spectrum disorder [3,26], and we, therefore, consider it crucial to evaluate the intervention in a clinical setting where these children are present.

The objective of this study is to determine the possibility of distributing and evaluating a family-centered group program for problematic gaming and excessive screen use (FAME) in a clinical CAP population. We will examine the feasibility of the program including treatment delivery and recruitment of the participants. Additionally, we also aim to examine the participants' experience of the program, as well as the relevance of the selected measuring instruments. The conclusions drawn from this study will serve as the foundation for a larger, quasi-experimental study in a clinical setting to follow.

Methods

Overview

The family-centered program for problematic gaming and excessive screen use in a child and youth population (FAME; S Kapetanovic, unpublished data, 2024) is a group-centered, family program developed and based on theoretical and empirical knowledge of parenting and child and youth development [19-21]; knowledge from the previous randomized controlled trial study on individual treatment of child and youth gaming problems [18]; and findings from interviews with the parents regarding their needs and content aspirations relating to gaming and excessive screen use.

The program specifically targets families where the child exhibits excessive screen use including problematic gaming and social media use. Both the child and at least 1 parent participate in the program, with the main goals being (1) to reduce problematic and excessive screen use in children and (2) to strengthen parent-child relationships. The logic model behind the program (Textbox 1) illustrates that these goals are achieved through various components such as psychoeducation, cognitive restructuring, and social and emotional learning. The theoretical framework is based on systemic theory [27], social cognitive theory [28], and emotion socialization theory [29]. The psychoeducational elements consist of information on screen-related health, sleep hygiene, and supportive interactions with children with mental health issues and are conveyed and illustrated through video clips, the use of a shared whiteboard, and illustrative example situations. The program uses different activities, including storytelling and on-site and home assignments, to help children and parents understand the positive and negative aspects of screen use, recognize cognitions and emotions, and prevent problems and family conflicts (proximal goals). Additionally, the program aims to teach participants how to handle emotions and behaviors as mediating mechanisms, ultimately leading to the attainment of the main or distal goals.

The program includes an initial individual session (session 0) where the child and the participating parent or parents meet with a clinician for goal setting and a motivational interview. This is followed by four group sessions with the following content: (1) positive and negative aspects of screen use and structure for setting boundaries; (2) psychoeducation on how thoughts, feelings, and behaviors influence each other and strategies for emotion regulation; (3) identifying triggers and preventing conflicts; and (4) psychoeducation on sleep hygiene and continued work moving forward.

Group session 1, conducted separately for children and parents, begins 1 to 2 weeks after session 0. Although the themes in both child and parent groups are aligned, the activities and outputs are tailored to be age appropriate and meet the specific needs of children and parents.

The sessions will take place at a CAP clinic that serves both subclinical and clinical groups of patients. The program will be delivered by clinicians, who could be doctors, psychologists, or health counselors, all possessing competence in cognitive behavioral therapy and having completed a 2-day FAME program education.

Each session is expected to last approximately 90 minutes, including a 15-minute break. This timeframe allows for a comprehensive and effective delivery of the treatment.

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Textbox 1. Logic model of the FAME program.

Target group

- Families seeking support for problematic screen use in children

Theory

- Family system theory
- Social cognitive theory
- Theory of emotion and emotion-focused therapy

Components

- Psychoeducation
- Cognitive restructuring
- Emotional knowledge and regulation
- Parenting skills

Activities

- Meeting sessions
- Discussions
- Storytelling
- Practice and homework

Outputs

- One individual meeting with the clinician
- Four group sessions with children and parents in separate groups
- Homework
- Booklets

Proximal goals

- Understanding the positive and negative sides of screen use
- Recognizing feelings and emotional and behavioral triggers
- Preventing emotional tantrums and family conflicts

Mediating mechanisms

- Children learn to control their behavior
- Parents learn to handle (child) feelings and behaviors
- Enhanced parenting skills

Distal goals

- Less problematic screen use
- Better parent-child relationships

Enrollment

Primary care patients (*Första linjen*) seeking treatment at CAP units in Skåne for problematic gaming or excessive screen time will be given the opportunity to participate in our treatment program. Patients contact CAP Skåne through En Väg In, a call center managed by psychiatry nurses and health care counselors. During the standard intake interview, patients are asked “Does your child (or “do you” if the child calls themselves) have any problems related to gaming or screen use?” As part of the existing procedure, parents or children who call En Väg In are also asked if they consent to be contacted for participation in research programs. The responses are tagged by the staff, and these tags are analyzed weekly by research administrators. Families with both tags are then contacted and provided with oral and written information about the study and the program. Families can be included in the study in 2 ways: either by being contacted by the research team during the initial contact with CAP, following the procedure described above, or by their therapist at CAP. Therapists at CAP can contact the study if

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families have described screen-related family conflicts in the context of receiving other care and have consented to be contacted by the research team for further information about the study. Regardless of the contact method used, research team staff will contact guardians by phone in an initial call to provide information about the study, assess motivation and consent, and verify inclusion and exclusion criteria. If all inclusion criteria are met and no exclusion criteria are present, the family will be scheduled for session 0, the content of which has been described above. For this pilot study, we will enroll 10 families, involving both the child and parent or parents. The inclusion and exclusion criteria are provided in Textbox 2.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Age between 10 and 18 years
- Reported problems in the family regarding computer gaming or screen use
- Children or youth and guardians can read, write, and communicate in Swedish
- An available guardian who can participate in the program
- Possibility to participate in program sessions on-site

Exclusion criteria

- Observed or suspected intellectual disability

Measures

The following data will be collected within the framework of this pilot study. The usability of the scales will be evaluated in future analyses. The data given below will be collected from the children:

- SCREENS-Q screening form, for valuing children and adolescent's screen time (adapted version, including questions targeting extent, type of activity, boundary setting, and positive and negative consequences of the child's screen use): It has shown good internal consistency (Cronbach α 0.61-0.90) [30].
- Game Addiction Scale for adolescents, for the diagnosis of computer game addiction targeting questions in accordance with the proposed Diagnostic and Statistical Manual of Mental Disorders criteria for IGD [5]: The instrument has shown good internal consistency (Cronbach α 0.81-0.86) [31].
- The Kessler Psychological Distress Scale (Kessler-6) screening for depression and anxiety over the past 6 months, including questions regarding feelings of hopelessness and nervousness: It is a widely internationally used measure of psychological distress. The instrument has shown a sensitivity of 0.36 (0.08) and a specificity of 0.96 (0.02) in predicting severe mental illness in a general population [32,33].
- Parenting Children and Adolescents Scale (PARCA) for assessing aspects of the parent-child relationship and parenting practices (adapted version including questions regarding encouraging positive behaviors and setting boundaries) [34]: This is originally a 19-item measure with each item rated on a 5-point scale. The instrument includes 3 subscales: encouragement of positive behaviors, setting limits, and proactive parenting behaviors, and has shown good psychometric properties (Cronbach α 0.86-0.91) [34].
- Adult-Child Relationship Scale—Family Check-Up (FCU): It measures warmth and conflict with 8 items rated on a 5-point scale targeting questions such as the tendency to involve parents in the child's thoughts and feelings and 3 items measure parent-child conflicts and conflict behaviors. Scale α values in previous studies have shown good internal consistency (Cronbach α 0.74-0.85) [35].
- The Insomnia Severity Index Adolescent for assessing sleep problems: It is a well-established tool for measuring sleep problems in adolescents, including questions targeting the child's perception of the consequences of their sleep patterns. Scale α values in previous studies have shown good internal consistency (Cronbach α 0.83) [36,37].
- Background data: gender, age, length, weight, family constellation, parental education level, and diagnosis at CAP.

Baseline data that will be collected from the parents before treatment are:

- SCREENS-Q screening form for valuing children and adolescents' screen time (adapted version, including questions targeting extent, type of activity, boundary setting, and positive and negative consequences of the child's screen use) [30].
- PARCA for assessing aspects of the parent-child relationship and parenting practices (adapted version including questions regarding encouraging positive behaviors and setting boundaries) [34].
- FCU: 5 items measure parent-child warmth such as questions about the parent's perception of the child's openness about their thoughts and feelings, and 3 items measure parent-child conflicts and conflict behaviors [35].

Given our expectation that a larger evaluation will be able to determine whether the intervention has any impact on screen-related conflicts within families, we will pay particular attention to the usability of the PARCA and FCU instruments. The follow-up data will be collected in connection with the last session of the program. Interviews with children and parents will be conducted approximately 2 weeks after the end of the program. The interviews will focus on the participant's experience of the program. The quantitative data will be

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analyzed with SPSS (IBM Corp), and the interview data will be analyzed with thematic analysis [38].

Analysis

In our analysis, we will be addressing several key indicators such as (1) monitoring the recruitment rate by tracking the number of eligible participants approached versus the number enrolled in the study; (2) tracking the retention and attendance rates of both parents and children; (3) evaluating whether each session's objectives are met, the content is delivered within the allotted time, and the necessary resources (eg, facilitators and materials) are available; and (4) gathering qualitative and quantitative feedback from participants through postprogram surveys and individual interviews with both children and parents. By assessing these criteria, we will determine if the program and recruitment processes are feasible and ready for expansion into a larger, quasi-experimental study. In order to capture the participants' experience of the program, semistructured interviews will be conducted and analyzed using thematic analysis [38]. For the statistical analysis, we will use 2-tailed paired sample *t* tests to address potential differences in pre- and postprogram measures. However, if data are not normally distributed, a nonparametric Wilcoxon signed rank test will be used. After each session, group leaders together with the project owner will assess compliance and pay particular attention to any adverse events such as deterioration in family relationships or increasing ill health of the participants. What constitutes an adverse event in psychotherapy can be difficult to define [39], although it could constitute severe illness, parental divorce, etc. We will, therefore, pay particular attention to any of the changes within the individuals and their families in the various parts of the data collection.

Ethical Considerations

The study was reviewed and approved by the Swedish Ethical Review Authority (2023-05533-01; November 13, 2023). The study has been registered at ClinicalTrials.gov (NCT06098807) and approved on October 23, 2023. We have calculated that the risk for patients to participate in the study is low. Mental illness among young people causes great distress and costs both on individual and societal levels. The knowledge and understanding of mental illness among young people are low in general society and particularly low regarding screen behaviors among youth. Hence, new knowledge about treatment of excessive screen use is of uttermost importance and the benefits will be greater than the risks of this project. The trial intervention is similar to other clinical practices offered in child and youth psychiatric clinics, which is why we consider the risks with the trial as minimal. Participants will not receive any economic compensation for their participation in the study. After eligibility is confirmed, written and verbal information about the study will be provided to all participants according to the Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). All patients and their carers who verbally agree to take part in the project will be provided with a consent form enabling them to provide written consent. According to Swedish law on research ethics, for patients younger than 15 years of age, written consent from a parent or guardian is also required for their children to participate in the study. All participants will be informed that their partaking in the study is voluntary; their data will be handled with strict confidentiality; results will be reported solely on a group level, which means that individual participants will not be identifiable; and that they are free to withdraw from the study at any time without reporting a reason for withdrawal. Personal and identifiable data will be collected from patients. Data will be kept confidential and managed in accordance with the Data Protection Act, General Data Protection Regulation policies, and the Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). Data will be held on services located within the Region Skåne databases, stored and secured both physically (in locked cabinets designed for the purpose) and electronically (behind firewalls), and be accessible to the research team only.

Results

A total of 11 children and their parents were enrolled during the first quarter of 2024. A 4-session pilot was delivered in the first quarter 2024, and the first results are expected in the third quarter 2024. The results are intended for publication in international peer-reviewed scientific journals and presentation at international and national scientific conferences. A primary publication is planned for the first quater of 2025. Additional secondary publications may follow. Whenever possible, the results will be presented in open-access journals.

Discussion

Expected Outcomes

This study aims to evaluate the delivery and feasibility of the newly developed family-centered group program (FAME) designed to address problematic gaming and excessive screen use among children and adolescents aged 10-18 years within a CAP setting. The program is based on established empirical knowledge in the field (Textbox 1) and our own experiences from previously completed studies [18,40,41]. We anticipate that (1) the program will demonstrate feasibility in terms of treatment delivery and participant recruitment, (2) participants' experiences with the program will provide valuable insights for further development and testing, and (3) the selected measurement instruments will be relevant and effective in evaluating program outcomes.

Our intention is that both the quantitative and the qualitative exploration of the pilot study will form an important basis for refining the program, as well as for the development of a larger study. Based on the low number of participants, it will not be possible for us to draw any conclusions regarding the program's effect. However, we expect to observe a decrease in children's problematic screen use, including a reduction in the amount of time spent using screens. Additionally, we anticipate improvements in the parent-child relationship, characterized by reduced conflict and increased family cohesion. If these criteria are met, we will consider modifying the program as needed and proceed to a fully powered study.

Despite the huge interest in children and adolescents' screen behavior in both popular science and more clinical and scientific contexts, to date, there is neither consensus regarding what is

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acceptable screen time nor evaluated family interventions for problem gaming and excessive screen use. Child screen use is generally seen as both a cause and a consequence of problematic parent-child relationships [42,43], and family interventions, where both the child and the parents are included, are both recommended [24] and requested [40]. Therefore, this would be the first intervention of a kind that could be of help to both children and their parents. Such an intervention could be beneficial for individual families, but it could also be an effort that would contribute to reduced health inequalities among children and families.

Limitations

One limitation is the small number of families included in the pilot study. Notably, this pilot study is primarily exploratory in nature and our focus is on assessing the format and practical implementation of the intervention rather than drawing conclusions about its efficacy. Another potential challenge that arises involves differing perceptions between parents and children concerning the child's health and the dynamics of the parent-child relationship [44]. To address this issue, we approach it by soliciting perspectives from both the child and parent regarding screen use and their parent-child relationship, without biasing our interpretation toward either viewpoint. Additionally, based on our observations and past clinical encounters, we anticipate potential differences in motivation between parents and children, with parents often showing greater enthusiasm for participation in our program than their children. Our strategy involves proactively addressing and managing such scenarios during the initial individual session with the therapist prior to commencing group sessions.

Conclusions

This unique intervention involves both the child and at least 1 parent, with the multiple aims of reducing problematic screen use, enhancing parent-child interactions, and mitigating conflicts related to screen use. The findings from this study will inform subsequent research efforts, which will aim to conduct a larger-scale evaluation of the intervention's effectiveness in reducing family conflicts associated with screen time. Such an early intervention targeting both children and their parents has the potential to be an important support for many families and be relevant to several of society's support functions.

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Data Availability

The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SK and ECK designed this study, and together with MW, contributed to the recruitment and data collection. MW drafted the protocol. All authors read and approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

CAP: child and adolescent psychiatry
FCU: Family Check-Up
IGD: internet gaming disorder
PARCA: Parenting Children and Adolescents Scale

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Protocol

Effects of Electronic Nicotine Delivery Systems Substitution on Body Weight Status: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Weight gain following smoking cessation is a well-documented concern, often attributed to the absence of nicotine's metabolic influence. The adoption of Electronic Nicotine Delivery Systems (ENDS) has been used to achieve smoking cessation, with claims of aiding weight control. However, existing reviews present conflicting conclusions on ENDS' impact on weight status, necessitating a rigorous evaluation.

Objective: We aim to conduct a systematic review with meta-analysis to assess the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking. The primary goal is to provide clinicians with evidence-based insights into the potential effects of ENDS use as a smoking substitute on weight control.

Methods: Adhering to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines, our systematic review will analyze randomized and nonrandomized controlled trials, clinical trials (quasi-experimental), and prospective or retrospective cohort studies on the weight status effects of ENDS among individuals who have either quit or reduced smoking. Searches will include PubMed, Scopus, and Cochrane Library, covering the period from 2010 to January 2024. A gray literature search and supplementary searches will be performed. Data will be extracted independently by 2 reviewers and quality assessments will be conducted concurrently. Quality assessments will use Joanna Briggs Institute tools, 2020 version, along with bias assessments for internal validity and reporting bias based on the Catalogue of Bias. The included studies will be examined for any internal data reporting discrepancies by using Puljak's checklist. Meta-analysis and subgroup analyses (ie, general ENDS usage, ENDS use coupled with a reduction in smoking exceeding 50%, and exclusive ENDS use for achieving smoking cessation) are planned. Certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Results: The protocol has been registered in PROSPERO (CRD42023494974) and the entire systematic review is expected to be completed by April 2024. The main goal of this review is to retrieve all current human research studies investigating the influence of ENDS on weight management among individuals who have quit or reduced smoking. Furthermore, the review will assess the quality of these studies and examine potential biases to identify the most dependable evidence available. Dissemination strategies will include traditional journal publications, social media announcements, and a white paper. The latter, available for download and distributed at conferences, aims to reach a broad audience, including clinicians and ENDS users.

Conclusions: The review will address the importance of informing health care professionals and patients about the current and robust evidence regarding the effects of transitioning to ENDS for smoking cessation on weight status.

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Trial Registration: PROSPERO CRD42023494974; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=494974
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KEYWORDS

Electronic Nicotine Delivery Systems; body weight; smoking cessation; tobacco harm reduction; systematic review; meta-analysis

Introduction

Background

The phenomenon of weight gain following smoking cessation is a well-documented concern in scientific research [1]. Typically, individuals who quit smoking experience an average weight increase ranging from 4.67 to 4.8 kg after 1 year, with more than 10% experiencing a rise exceeding 10 kg [2,3]. This weight gain can primarily be attributed to the lack of nicotine's influence on metabolic processes, which includes appetite suppression and alterations to both lipolysis and lipogenesis [4,5].

In the past few years, there has been a notable increase in the adoption of Electronic Nicotine Delivery Systems (ENDS), commonly known as e-cigarettes, among individuals attempting to cease tobacco use [6]. Some who use ENDS do so for weight loss or weight management. The use of ENDS for weight loss was most prevalent among individuals with eating disorders, at 32% (n=178) [7]. This usage drops considerably in the general ENDS-using population. In the United States, 15% (13/84) of college students and 13.5% (62/459) of adults reported using ENDS for weight control [8,9]. Among US military recruits, 5.1% (11/223) of males and 6.0% (4/61) of females have used ENDS for this purpose [10]. In England, the figure stands at 4.6% (18/394) of current ENDS users [3].

Observational studies have also noted the practice of using vaping as a dietary substitution, where individuals vape flavored liquids to mitigate food cravings. This behavior, while less prevalent in England [3], has been reported in various surveys and interviews conducted in the United States [11,12].

Commercial entities have recognized these consumer patterns, resulting in the development and marketing of vaping products that claim to support weight loss. Numerous patents have been filed globally, and several companies have marketed vapor devices that propose to offer benefits such as fat burning, appetite suppression, and rapid weight loss [13,14]. These claims, often promoted through online sites and aggressive marketing strategies [13,15], are claims that have not been verified.

Previous Reviews

Recent reviews assert that there is insufficient evidence to draw definitive conclusions on the impact of ENDS on weight control in people who have ceased or reduced conventional smoking. The systematic review of Hod et al [16] of human and in vitro studies concluded that ENDS use is prevalent among the obese, although the authors state that causality cannot be determined due to the cross-sectional design of human studies. Moreover, the data are conflicting, with in vivo studies suggesting weight loss effects, but in vitro studies do not support this claim Thus, the authors underlined the need for further investigation to determine the impact of ENDS on weight control [16]. Another review by Hartmann-Boyce et al [17] found 2 ENDS studies, 1 involving ENDS as an adjunct to nicotine replacement therapy and the other comparing them to varenicline, both with wide CIs at all measurement time points. The CIs of weight change (kg) at the end of the treatment and 12 months encompassed both clinically significant weight loss and weight gain [17]. Therefore, the authors stated that "data are needed on whether using e-cigarettes to quit smoking affects post-cessation weight change" [17].

Research Question

Given the rise of ENDS as an alternative to traditional smoking, and their associated perceived benefits for weight control, we aim to rigorously evaluate the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking. For this purpose, we intend to conduct a systematic review with meta-analysis to analyze human clinical studies that provide longitudinal data on body weight among participants who have replaced cigarette smoking with ENDS use.

Population, Intervention, Comparator, and Outcomes Criteria

The research strategy follows the Population, Intervention, Comparator, and Outcome (PICO) approach as follows: population—adults who smoke cigarettes, intervention—complete or partial substitution of ENDS for cigarettes, comparator—within-subject changes baseline to the end of the study, and outcomes—changes in body weight.

Objectives

We will conduct a systematic review with a meta-analysis to critically assess and synthesize available human studies on the weight status effects of ENDS among individuals who have either quit or reduced smoking. Our goal is to critically evaluate and synthesize the available evidence to offer clinicians high-quality insights into the potential effects of ENDS use as a substitute for smoking, specifically concerning weight control. Thus, our aim is to equip clinicians with robust evidence to enhance their treatment recommendations and strategies for individuals who smoke, aiding them in making informed decisions and plans.

Methods

Overview

In adherence to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) requirements

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[18], this protocol is registered with PROSPERO (CRD42023494974), and any deviations will be transparently reported within the review. The review team (GRMLR, MAQ, LF, EA, and RP), led by RP, has substantial expertise in conducting literature reviews and an expert background in tobacco control, tobacco harm reduction, and ENDS.

Database Search and Secondary Searches

The databases to be included are PubMed, Scopus, and CENTRAL Cochrane Library. Using the keywords specific to each database (ie, weight, BMI, "body mass index," "electronic cigarette," "e-cigarette," and "electronic nicotine"), searches will be performed in the title and abstract fields in PubMed, and in the title, abstract, and keywords in Scopus. Cochrane Library will be searched for trials. The search will include the period from 2010 to January 2024, in line with the date of the first peer-reviewed research studies on ENDS. Language restrictions will not be applied. In compliance with PRISMA-P, the search strategy example is detailed in Multimedia Appendix 1. Retrievals will be downloaded into EndNote (Clarivate), and duplicates will be removed.

A secondary search of the existing reviews, conducted independently by 2 reviewers, will be conducted to identify any additional studies. Next, the references of the included studies will be scrutinized to identify additional studies. Finally, the included studies will be citation chased (ie, snowball search) through Google Scholar. The studies excluded during the thorough full-paper review will be documented.

The list of selected studies will be forwarded to 2 medical experts to validate that all pertinent studies have been included. In addition, a comprehensive gray literature search will be conducted on the websites of 16 weight-related medical organizations (Multimedia Appendix 1).

Inclusion and Exclusion Criteria

The selected study designs will include randomized and nonrandomized controlled trials, clinical trials (quasi-experimental), and prospective or retrospective cohort studies. The initial exclusion will be based on titles and abstracts reviewed. Exclusion criteria will be by publication types (ie, editorials, letters, commentaries, protocols, narrative reviews, conference abstracts, and dissertations), study designs (ie, vitro, animal studies, inhalation toxicology, biomarker studies, surveys, and qualitative studies), adolescent populations, and studies lacking baseline or follow-up weight data. A total of 2 reviewers will independently conduct the exclusion process, with any discrepancies resolved through discussion.

The next process will involve a thorough review of full papers, guided by 3 inclusion criteria, including study designs, availability of data before and after testing participants who substituted ENDS for smoking, and outcome data on weight. All 3 criteria will have to be satisfied for a study to be included.

Review team members will undergo training on the inclusion criteria through analysis of 3 included studies. Two independent reviewers will then conduct the inclusion and exclusion assessments on the studies, resolving any disparities through discussion. The objective is to attain a high level of agreement between reviewers on the study selection process. The project leader will make the final decision regarding the inclusion and assessment of the studies.

Data Extraction

Using a standardized form derived from Joanna Briggs Institute (JBI) and Cochrane Collaboration inventories [19,20], data extraction will be conducted by 2 reviewers independently, followed by cross-checking for accuracy. The full data extraction form is provided in Multimedia Appendix 1. The data extraction form includes bibliographic details, study population demographics, intervention descriptions, and weight measurements. The form will be pilot-tested and revised as necessary.

In cases where the published data are insufficient or absent, an email requesting additional details will be sent to the corresponding author. Findings from the included studies will be reported in a dual format. First, individual studies will be summarized with a concise narrative description. Second, study tables will be formulated incorporating elements derived from the data extraction and quality assessments (refer to the subsequent section).

Quality Assessment and Risk of Bias

Quality assessments will use JBI tools, 2020 version [21], along with bias assessments for internal validity and reporting bias based on the Catalogue of Bias [22] (Multimedia Appendix 1). Examination of studies for any internal data reporting discrepancies will be conducted using the checklist proposed by Puljak et al [23] (Multimedia Appendix 1). The data extraction forms will be pilot-tested and revised if necessary. The comprehensive evaluation of study quality will involve calculating an overall rating through a rubric that integrates the JBI score and biases checklist. The overall study quality will be categorized according to the Cochrane guidelines—low risk of bias, some concerns, and high risk of bias [20]. Quality assessment will be conducted concurrent with the data extraction, and 2 reviewers will independently perform assessments. Discrepancies will be resolved through discussion or decided by the project leader.

No studies will be excluded on the basis of their quality assessment or bias. Studies deviating from the JBI quality assessment criteria or exhibiting biases will be documented in the study table. These limitations will be explicitly identified during the data analysis and referenced in the discussion section of the review.

Data Analysis and Synthesis

Studies will be categorized by risk of bias, and summaries will include study design, participant and intervention characteristics, and main findings. A meta-analysis of change scores is planned, where the change score is defined as mean kg at the end of the study minus mean kg at the baseline. Three subgroup analyses will be performed, focusing on (1) general ENDS usage, (2) ENDS use coupled with a reduction in smoking exceeding 50%, and (3) exclusive ENDS use with the goal of smoking cessation. Publication bias will be assessed if a minimum of 10 studies are included.

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Grading of Recommendations Assessment, Development, and Evaluation

Certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [24].

Results

The protocol has been registered in PROSPERO (CRD42023494974) and the entire systematic review is expected to be completed by April 2024. The primary objective of this review is to compile all existing human research studies concerning the impact of ENDS on weight control in people who ceased or reduced smoking. In addition, the review will rigorously evaluate the quality of these studies and scrutinize potential biases to emphasize the most reliable and available evidence. The planned review will also identify studies that may exhibit reporting bias, thereby enabling a more accurate representation of the effects of ENDS on weight control within the ongoing discourse on tobacco harm reduction.

Discussion

Principal Findings

This protocol is intended to provide the methodological framework for a systematic review and meta-analysis of the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking.

Many research protocols lack comprehensive planning for dissemination and knowledge translation activities beyond the conventional approach of publishing the review in a peer-reviewed journal and presenting findings at conferences. Naturally, this review will be disseminated through these traditional channels. Following an approach previously described [25], some additional strategies will be adopted. Briefly, upon acceptance, the project protocol will be published in JMIR Research Protocols and the final review with meta-analysis will be published in a peer-reviewed journal. In addition, efforts will be made to translate the review's abstract into several languages. To enhance visibility, the availability of the review will be disseminated via social media platforms.

A white paper will be produced and made available for download on a dedicated website, and we anticipate disseminating it to medical associations and distributing it at conferences. The goal is to ensure the widespread of findings among clinicians and individuals currently using or considering ENDS. Given that a significant number of physicians and health care providers harbor misconceptions regarding the health impacts of nicotine [26,27], the white paper will incorporate a dedicated section focusing on nicotine. Infographics drawn from the white paper will be disseminated to current and potential ENDS users via user advocacy organizations [25]. Traditional review publication methods may not effectively reach the stakeholders who will benefit from clear and accessible updated sources of information. The objective of these activities is to ensure broad dissemination of the review findings to multiple audiences.

It is crucial to acknowledge the potential limitations arising from both the number and the quality of the studies that will be included in this systematic review. The limited quantity of available studies can restrict the scope and depth of conclusions drawn, leading to gaps in understanding and potentially biasing the overall assessment. Furthermore, the quality of the studies significantly impacts the reliability of the review's conclusions. If the included studies exhibit methodological flaws, biases, or insufficient rigor, the overall evidence may be weakened, resulting in tentative or inconclusive findings.

Conclusions

In conclusion, tobacco consumption constitutes a significant public health burden. Electronic cigarettes may represent a viable option for those attempting to quit smoking. Furthermore, there is a growing interest in these devices due to their potential benefits for weight control, especially for counteracting the short-term weight gain associated with smoking cessation. Therefore, it is essential to inform both patients and health care professionals about the most current and robust evidence regarding the effects of switching to electronic cigarettes for smoking cessation on weight status. This review, including meta-analysis, aims to contribute to this objective.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study.

Authors' Contributions

GRMLR, MAQ, and RP designed the study and wrote the original draft. LF and EA contributed to the study and reviewed the final study for accuracy and completeness. All authors have read and approved the final study.

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Conflicts of Interest

GRMLR, MAQ, LF, and EA declare no conflicts of interest. RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) and AIR-PROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling), Integral Rheumatology and Immunology Specialists Network (IRIS), Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp and Dohme, Boehringer Ingelheim, Novartis, Arbi Group srl, Duska Therapeutics, Forest Laboratories, Ministero dell Universita' e della Ricerca (MUR) Bando Piano Nazionale di Ripresa e Resilienza (PNRR) 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU), and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell Universita' e (MUR)—PNRR EU Community. He is founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and Gerson Lehrman Group (GLG) Group. He receives textbooks royalties from Elsevier. He is also involved in a patent application for ECLAT srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO); and he is Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).

Multimedia Appendix 1
(A) Sample PubMed bibliographic search. (B) Weight medical organizations grey literature search. (C) Data extraction form. (D) Data discrepancies form. (E) Bias report. (F) PRISMA-P 2015 checklist.
[DOCX File , 39 KB - resprot_v13i1e56324_app1.docx]

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Abbreviations

ENDS: electronic nicotine delivery systems
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
JBI: Joanna Briggs Institute
PICO: Population, Intervention, Comparator, and Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Best Practices and Recommendations for Research Using Virtual Real-Time Data Collection: Protocol for Virtual Data Collection Studies

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Abstract

Background: The COVID-19 pandemic and the subsequent need for social distancing required the immediate pivoting of research modalities. Research that had previously been conducted in person had to pivot to remote data collection. Researchers had to develop data collection protocols that could be conducted remotely with limited or no evidence to guide the process. Therefore, the use of web-based platforms to conduct real-time research visits surged despite the lack of evidence backing these novel approaches.

Objective: This paper aims to review the remote or virtual research protocols that have been used in the past 10 years, gather existing best practices, and propose recommendations for continuing to use virtual real-time methods when appropriate.

Methods: Articles (n=22) published from 2013 to June 2023 were reviewed and analyzed to understand how researchers conducted virtual research that implemented real-time protocols. “Real-time” was defined as data collection with a participant through a live medium where a participant and research staff could talk to each other back and forth in the moment. We excluded studies for the following reasons: (1) studies that collected participant or patient measures for the sole purpose of engaging in a clinical encounter; (2) studies that solely conducted qualitative interview data collection; (3) studies that conducted virtual data collection such as surveys or self-report measures that had no interaction with research staff; (4) studies that described research interventions but did not involve the collection of data through a web-based platform; (5) studies that were reviews or not original research; (6) studies that described research protocols and did not include actual data collection; and (7) studies that did not collect data in real time, focused on telehealth or telemedicine, and were exclusively intended for medical and not research purposes.

Results: Findings from studies conducted both before and during the COVID-19 pandemic suggest that many types of data can be collected virtually in real time. Results and best practice recommendations from the current protocol review will be used in the design and implementation of a substudy to provide more evidence for virtual real-time data collection over the next year.

Conclusions: Our findings suggest that virtual real-time visits are doable across a range of participant populations and can answer a range of research questions. Recommended best practices for virtual real-time data collection include (1) providing adequate equipment for real-time data collection, (2) creating protocols and materials for research staff to facilitate or guide participants through data collection, (3) piloting data collection, (4) iteratively accepting feedback, and (5) providing instructions in multiple forms. The implementation of these best practices and recommendations for future research are further discussed in the paper.

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KEYWORDS

real-time data collection; remote research; virtual data collection; virtual research protocol; virtual research visits

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Introduction

Overview

Research visits with participants are a fundamental tool for data collection across multiple disciplines. Research visits can include a wide array of activities, including the assessment of eligibility, consenting, intervention administration, and baseline and follow-up data collection. Participation in in-person research visits can often be challenging for individuals limited by distance, disability, and access to transportation. Historically, most research visits have been conducted in person, face-to-face, between study participants and study staff. However, in response to the immediate need to halt in-person visits due to the COVID-19 pandemic, researchers adapted their research protocols to include remote data collection, allowing them to continue research projects without interruption [1]. The goal of this paper is to review the virtual real-time data collection research protocols used in the past 10 years to identify and propose best practices for continuing to use virtual real-time methods when appropriate for data collection going forward.

Research Conducted Before and During COVID-19

The body of research using remote data collection methods conducted before the COVID-19 pandemic indicates that many types of data collection were conducted remotely but not necessarily in real time. Common remote data collection methods included: online survey data collection [2], online focus groups [3], video-recorded instructions for data collection [4], self-collection of biometric data (eg, taking weight at home) [5,6], and remote qualitative interviews [7,8]. The emergence of the COVID-19 pandemic in March of 2020 resulted in the sudden need for research teams to stop in-person research and move to virtual or remote data collection options that they may have never done before. Thus, many researchers shifted their data collection protocols to use remote research protocols that could be done in real time with a participant and study team member. For many study teams, these changes to revise their data collection approach to be remote and real time came quickly with limited guidance.

Findings from studies conducted both before and during the COVID-19 pandemic suggest that many types of data can be collected virtually or remotely, and, in many cases, the same type of data can be collected in several different ways. For example, multiple research teams collected anthropometric data (eg, height, weight, and waist circumference) remotely through real-time videos [5,6,9-28], while others collected anthropometric data by using recorded videos, telephone instructions, and multiple modes of instruction to assure data quality. Clinical research studies researching long-term illnesses and diagnoses (ie, Parkinson disease, Huntington disease, autism spectrum disorder, HIV, etc) used telehealth and videoconferencing during the COVID-19 pandemic [11-13,20,24,25,29]. Additionally, studies collected biospecimen samples or anthropometric data, whereas other studies administered fitness tests or surveys. These previous studies show remote data collection was occurring before COVID-19 to a limited degree, but it is still important to learn more about how research was adapted virtually during COVID-19 because of the numerous studies that shifted remotely and engaged in virtual remote data collection.

The Value of Using Virtual Research Moving Forward

While remote data collection may no longer be a necessity dictated by the COVID-19 pandemic, there are multiple reasons to support the continuation of virtual real-time data collection. For example, remote data collection may be more accessible to some rural and limited mobility populations with a stable internet connection [30,31]. Having to attend research visits in person poses several accessibility issues, such as transportation issues, mobility problems, and the lack of childcare. Allowing participants to engage in data collection remotely removes these barriers to participation. Additionally, remote data collection is more affordable in some circumstances, as there is no need to reimburse participants for mileage. Many remote visits are shorter in duration as compared to in-person visits, thus requiring study staff to work fewer hours and therefore lowering the cost of the study. Finally, the need for specialized equipment and on-campus office space can be reduced when research is conducted remotely, as a larger study space is not needed for in-person gatherings and participants can often use their own materials from home [8]. In many cases, remote research improves opportunities to recruit a more representative study population as accessibility (ie, location) study costs and time barriers can be reduced. Reducing study costs in terms of office space, research staff costs, and mileage reimbursement allows for the funds to be used toward higher compensation for participants or to cover more study objectives and research questions. Moving forward, identifying ways to continue high-quality virtual real-time data collection visits would be a beneficial asset to many research studies.

Study Aims

As suggested above, some researchers have been conducting virtual data collection for several years before the pandemic; however, most research using remote data collection methods were conducted during the COVID-19 pandemic. This sudden shift in the research approach meant that much of this data collection was done with little empirical guidance. Reflecting now on the various virtual real-time data collection practices' researchers have used enables an analysis of the benefits and drawbacks of various practices used. We can evaluate how we can use learnings from protocols and approaches that were developed before the COVID-19 pandemic and those developed in response to the pandemic to facilitate decisions we make about best practices for future remote data collection. This paper aims to (1) summarize the literature over the last decade on virtual research visit protocols involving real-time data collection; (2) evaluate current practices and methods used for virtual, real-time research visits; (3) identify gaps in the current methods used for virtual, real-time research visits; and (4) provide insight on the best practice protocols for carrying out virtual, real-time research visits. The findings from this paper will offer insights on how to best carry out remote real-time data collection and improve the access and quality of research for underserved populations, which will enable study teams to pivot to various forms of data collection as needed for various

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circumstances that arise in the future. Remote and virtual data collection are used interchangeably throughout this paper.

Methods

A 10-year literature review was conducted to identify past and present studies engaging in remote real-time data collection to identify strengths and weaknesses of these approaches and inform best practices for virtual real-time data collection in the future.

Identifying Relevant Studies: Inclusion or Exclusion

A search of the published literature was carried out to identify original research articles that collected data for research purposes in remote real-time settings. The inclusion and exclusion criteria used to determine which articles could be included in this paper are described in Textbox 1.

Every article conducting real-time virtual data collection was reviewed for inclusion and exclusion criteria. The first author (JS) systematically conducted a decade-long review by searching PubMed and Google Scholar for articles published between January 1, 2013, and June 23, 2023. The 10-year span was chosen to ensure results included articles that were from before and after the pandemic. The search was conducted from April 2023 through July 2023.

The databases were searched using Boolean operators of terms derived from three concepts: (1) remote data collection, (2) virtual real-time data collection, and (3) assessment or measurement. The following search terms were used in various combinations to identify articles: “anthropometry,” “anthropometrics,” “methods,” “telemedicine,” “telehealth,” “remote consultation,” “remote visit,” “remote research,” “live,” “real-time,” and “virtual research.” The search was limited to only articles published between 2013 and 2023.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Original research was conducted in “real time” when research staff actively engaged in data collection with a participant through a live medium such as videoconferencing (eg, Zoom or Google Chat) or telephone, where a participant and research staff could talk to each other back and forth.

Exclusion criteria

- Reviews
- Research that is not original
- Research that does not collect data in real time
- Research intended exclusively for medical purposes (eg, telehealth or telemedicine or describing a clinical encounter)
- Articles that solely described research protocols and did not include actual data collection and results
- Articles collecting participant or patient measures for the sole purpose of engaging in a clinical encounter as part of a health care visit or assessment
- Research visits that were only engaging in qualitative interview data collection
- Data collection that relied solely on self-report measures (ie, without virtual or remote guidance from the study team)
- Articles that described research interventions but did not involve the collection of data via a web-based platform.

Study Selection

The selected studies underwent 3 levels of review. First, the lead author (JS) independently reviewed each article for inclusion. Articles were labeled for potential relevance as “yes,” “maybe,” or “no” based on eligibility criteria. Then, an independent reviewer also reviewed the articles and worked with the lead author to make final decisions on which articles should be included based on the previously described eligibility criteria. Third, the additional 2 coauthors (AT and JB) reviewed the studies selected after the initial reduction of studies. At each level of review, the authors reviewed article inclusion and exclusion criteria before excluding an article. A total of 22 unique articles met the eligibility criteria for inclusion in the current review (see Multimedia Appendix 1 [5,6,9-28]). Some articles (n=7) focused on collecting anthropometric data. This review included articles with study populations of different genders, different dyad types (ie, parent-child, participant-partner, and 2 adults), different racial or ethnic identities (ie, White, Black, Hispanic or Latinx, etc), and different medical conditions and abilities (ie, cancer, Huntington disease, autism spectrum disorder, HIV, and Parkinson disease). The articles involved data collection on child participants (n=9), individuals with Parkinson disease (n=4), and Huntington disease (n=1), cancer survivors (n=3), individuals with autism spectrum disorder (n=1), and adults with HIV (n=1). A total of 11 articles reported collecting data on samples that were predominantly college-educated. A total of 19 articles were composed of majority White samples, with 12 articles on White women and 7 articles on White men. One article collected anthropometric data and corrected this data in an effort to make it more accurate, using an equation that was developed using previous data [16].

Data Collection

The data were independently extracted by the first author (JS) and reviewed by an independent reviewer. The following information was extracted from eligible studies: participant demographic data, study variables, study methods (ie, remote measurement variables), study findings, recommendations, study mode, the level of instructions provided (ie, real-time, recorded, written, etc), the level of interaction between study

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staff and participants, technology used to guide data collection, equipment used, accessibility features enabled, and the reason for virtual data collection. The extracted data were organized and reviewed to identify best practices. Multimedia Appendix 1 shows a detailed description of all the collected articles.

Results

Results from the protocol review will be summarized under the themes of: (1) "modality of data collection," (2) "equipment for data collection," (3) "guided visit instruction or materials," (4) "participant-staff interaction," and (5) "reliability and validity of measures" (see Multimedia Appendix 2 [8-10,17,21-24,27-29,32]). Results and best practice recommendations from the current protocol review will be used in the design and implementation of a substudy to provide more evidence for virtual real-time data collection. We will examine the concordance between virtual real-time collection of height, weight, and neck circumference collected by participants while guided by research team members and in-person collection of height, weight, and neck circumference collected by a research team member on a sample of over 600 families. These results will add more concrete evidence to virtual real-time data collection methods that were assessed in this protocol review. We expect to carry out this substudy over the next year.

Discussion

Overview

This study aimed to review the different protocols and approaches used to conduct virtual real-time data collection visits over the past 10 years and during COVID-19 to identify best practices in virtual real-time data collection. Our review identified four areas in which there were both similarities and differences across studies using remote real-time data collection: (1) mode, (2) equipment, (3) guided visit instruction or materials, and (4) participant-staff interaction. We found that remote data collection approaches were used successfully across a range of different populations. A variety of approaches were used to collect data and maintain participant engagement, depending on populations and the type of data collection.

Several studies reported that providing as much equipment as possible within budget constraints resulted in successful data collection and a more representative study population. For example, multiple studies explained that providing hotspots was particularly effective in reducing barriers to participation, especially for racially or ethnically diverse and low-income populations [5,6,14,26]. Other studies that did not provide hotspots cited a lack of internet as an exclusion factor as well as a study limitation [11,15,21,23,24,28]. Studies that excluded participants without access to the internet limited the generalizability of their study population. Providing hotspots also allowed for the inclusion of rural [9] and low-income populations, for whom reliable internet may not be as readily accessible. The mode of instruction and level of interaction between staff, researchers, and participants were also emphasized as important considerations across studies. Several studies suggested that providing real-time instructions through videoconferencing was particularly helpful for specific types of data collection; in particular, real-time instructions were helpful for obtaining height and weight data as researchers could see the way participants were measuring themselves and provide real-time corrections to participants approaches to self-measurement with the goal of improving the reliability and validity of these measures.

Recommendations

Based on findings from this review, we propose some best practice protocol recommendations to move the field forward regarding virtual real-time data collection (see Multimedia Appendix 1).

Create Protocols and Materials for Research Staff to Facilitate or Guide Participants Through Data Collection

Protocols and materials should be created for research staff to facilitate and guide participants as much as possible through data collection. Protocols should be as detailed as possible to ensure research staff are able to provide the same detailed instructions to all participants. While remote research removes some barriers to data collection, it also makes data collection more difficult for certain measures (ie, height); therefore, research staff should go through a thorough training process and certification so they are able to provide the same level of instruction to all participants. All materials (scales, electrocardiogram equipment, spirometers, etc) necessary to adhere to the research protocols should also be provided to reduce bias among participant results and to improve participation across diverse populations for increased generalizability of study findings. Troubleshooting guides should be provided for research staff so they are able to help participants through any issues (ie, videoconferencing not working) that may arise.

Provide all Necessary Equipment to Participants

Researchers should aim to provide as much necessary equipment (eg, web cameras and tablets) as possible to participants to ensure all participants have access to the same research equipment. For example, hotspots should be provided to those without access to a stable internet connection (low-income participants, rural participants, etc) so that all interested participants can fully engage in data collection. Providing scales and tape measures to participants is also beneficial, as previous studies have found results differ when using home equipment [33]. More complex studies, such as those involving electrocardiogram equipment, should provide the equipment, as this is not easily accessible to participants. It may be best to include the various types of equipment in a "toolkit" so that participants have all their needed equipment, including directions, in the same packages. Given that providing the equipment necessary to participants at their home address is costly, researchers should budget for these materials and shipping expenses when requesting funding packages.

One other key consideration that researchers need to address when conducting remote real-time data collection is exclusion criteria based on equipment requirements. For example, our review of the literature revealed that some studies chose to exclude participants that did not have reliable internet access or access to a device that could connect to the internet [5,21].

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This was done because having internet services and access to internet-capable devices was deemed necessary to conduct research at a distance. However, requiring participants to have access to reliable internet and internet-capable devices can impact how representative the study population is of the population of interest.

Pilot Data Collection

Collecting pilot data from actual participants before starting official data collection should be strongly considered. Having a shorter pilot previsit before the official data collection visit allows participants to become familiar with the protocols and videoconferencing software, troubleshoot any technological issues, and build rapport with the research staff before data collection. This can also be an opportunity to ask for feedback from participants.

Iteratively Accept Feedback

Researchers should accept feedback from participants in an iterative manner that allows for adaptations of study protocols as the study advances. Accepting feedback results in meeting the needs of participants better and increases the likelihood of adherence to the research protocols.

Provide Instructions for Participants in Multiple Formats

Instructions for participants should be provided in multiple forms (ie, oral, written, and video instructions) to assure that all different styles of learning are accounted for and that participants understand the protocol and can look back at the directions if any questions arise. Additionally, across studies, the more that staff interacted with participants, the better the data collection visit went regarding flow and quality of data collected. This is particularly true for certain types of data collection, such as height and weight, where research staff can offer real-time corrections and guidance as the data are being collected. Textbox 2 shows best practices for virtual data collection.

Textbox 2. Recommended best practices for virtual data collection.

Proposed best practice protocol recommendations for virtual real-time data collection

- Create protocols and materials for research staff to facilitate or guide participants through data collection.
  - As many details as possible should be provided through protocols, infographics, and simplified figures or visuals to ensure research staff can provide detailed instructions to participants for successful data collection.
  - Research staff should undergo thorough training and a certification process.
  - Provide troubleshooting guides for research staff.
- Provide adequate equipment for participants.
  - Technology necessary for research should be provided (ie, hotspots, tablets or internet-capable devices, and web cameras).
  - Complex equipment that is not easily found at home should be provided (ie, electrocardiogram equipment).
- Pilot data collection
  - Have a short pilot visit before data collection to troubleshoot and familiarize participants with protocols.
  - Ask for participants' feedback during pilot visits.
- Iteratively accept feedback.
  - Accept feedback iteratively and adapt study protocols as the study advances.
- Provide instructions in multiple forms to participants.
  - Provide instructions in multiple forms (ie, oral, written, and video instructions) to meet differing learning styles.
  - The more interactive the research staff can be, the easier it is for participants to follow directions successfully.

Strengths and Limitations

This review had both strengths and limitations. This is the first review that we are aware of that synthesizes studies using remote or virtual real-time data collection to inform best practices for future virtual data collection. There are also limitations to consider. One limitation was that studies conducting virtual or remote visits were not representative of the general population. The studies reviewed were composed of a majority of White, highly educated individuals with above-median incomes. Many studies reported using strict inclusion and exclusion criteria (ie, access to internet capable devices, access to high-speed internet, ability to use technology, and ability to download apps), which prevented individuals without access to these requirements from participating. Considering that the strict requirements to participate in research involved materials that were costly, we can assume that participants with lower incomes were not always included in these studies. Thus, we know that the recommendations listed work well for White, highly educated, and economically stable populations, but we cannot say for certain that they work for the general population. These recommendations can be used as starting points when

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developing accessible research, but future research should aim to include a more representative sample of the US population. Recommendations need to be created using a population that is representative of the general population to expand accessibility. Additionally, not all the methods used were validated against gold standard approaches (see Multimedia Appendix 1). Therefore, it is uncertain whether these research methods are valid and reliable. Researchers need to compare virtual methodology and measurements to gold-standard approaches to confirm that virtual research is valid and reliable.

Conclusions

Our findings suggest that virtual real-time data collection visits are doable across a range of participant populations and to answer a range of research questions. Top considerations that emerged while reviewing the literature were that researchers should keep in mind how staff will engage with participants throughout virtual visits, the importance of creating materials and protocols that will facilitate measurement collection, piloting protocols ahead of time, encouraging feedback from participants throughout data collection, and that inclusion or exclusion criteria needed to be balanced to ensure a representative population of participants can fully engage in remote data collection protocols. Recommended best practice protocols were developed based on these identified considerations: (1) creating protocols and materials for research staff to facilitate or guide participants through data, (2) providing adequate equipment, (3) piloting data collection, (4) iteratively accepting feedback, and (5) providing instructions in multiple forms.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of articles reviewed by population, measurement type and approach, and feasibility.
[DOCX File , 26 KB - resprot_v13i1e53790_app1.docx]

Multimedia Appendix 2
Themes on the logistics of collecting data from participants remotely.
[DOCX File , 16 KB - resprot_v13i1e53790_app2.docx]

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Protocol

Patterns of Use of e-Cigarettes and Their Respiratory Effects: Protocol for an Umbrella Review

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Abstract

Background: Electronic nicotine delivery systems (ENDS)—e-cigarettes or vapes—have been shown to substantially reduce or eliminate many toxins compared with cigarette smoke, but simultaneously ENDS use also produces their own unique toxins. Yet the patterns of use among people who use ENDS are not homogeneous. Some people who use ENDS also smoke cigarettes (dual use). Other people who formerly smoked cigarettes are completely substituting ENDS (exclusive use). A small number of people who have never smoked cigarettes are using ENDS (naïve use of nicotine). Each of these patterns of use results in different exposures to toxins. Unfortunately, epidemiological studies routinely group together any ENDS use regardless of other tobacco use.

Objective: This umbrella review primarily aims to present all the evidence available on the respiratory effects of ENDS use by adults based on their pattern of use: dual use, exclusive use, and naïve use. With each of these patterns of use, are there benefits, no changes, or harmful effects on respiratory functioning? Our objective is to provide clinicians with a detailed analysis of how different patterns of ENDS use impact respiratory functioning and to point to the best sources of evidence.

Methods: This umbrella review follows the Methods for Overviews of Reviews framework and the PRIOR (Preferred Reporting Items for Overviews of Reviews) statement. Systematic reviews published since 2019 will be searched across 4 databases and 3 gray literature sources. Additional searches will include citation chasing, references lists, and referrals from respiratory specialists. The quality of included reviews will be evaluated using the AMSTAR2 (A Measurement Tool to Assess Systematic Reviews) checklist. We will document biases in 3 areas: protocol deviations, biases from the Oxford Catalogue of Bias, and internal data discrepancies. Two reviewers will independently conduct the search and quality assessments. Our analysis will focus on reviews rated as moderate or high confidence by AMSTAR2. We will use the Vote Counting Direction of Effect method to manage expected data heterogeneity, assessing whether ENDS use is beneficial or detrimental, or has no effect on respiratory functions based on the pattern of use.

Results: The review is expected to be completed by December 2024. The database search was concluded in April 2024, and data extraction and bias assessment were completed in June 2024. The analysis phase is planned to be completed by October 2024.

Conclusions: A thorough and comprehensive assessment of the evidence will better inform the contentious debate over the respiratory effects of ENDS providing much needed clarity by linking their effects to specific usage patterns. This analysis is particularly crucial in understanding the risks associated with continued cigarette smoking.

Trial Registration: PROSPERO CRD42024540034; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=540034

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KEYWORDS

dual use; electronic nicotine delivery systems; naïve use; respiratory; smoking cessation; umbrella review

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Introduction

Background

Electronic nicotine delivery systems (ENDS)—e-cigarettes or vapes—have been shown to substantially reduce or eliminate many toxins compared with cigarette smoke [1,2]. Although limited in number, ENDS use does produce their own unique toxins, such as metal exposure [3], and others that are present in tobacco smoke, such as carbonyls, although at much lower levels [4]. In terms of risk, most e-cigarette analyses show the cancer potencies of ENDS to be less than 1% of that of cigarette smoke [5]. Furthermore, the lung cancer risk from vaping is estimated to be 5 orders of magnitude lower than smoking [6].

Yet the patterns of use among people who use ENDS are not homogeneous. Some people who use ENDS also smoke cigarettes (dual use). Other people who formerly smoked cigarettes are completely substituting ENDS (exclusive use). A small number of people who have never smoked cigarettes are using ENDS (naïve use of nicotine). Unfortunately, epidemiological studies routinely group together any ENDS use regardless of other tobacco use [7], and this grouping together of populations with different patterns of use confounds the findings of studies [3].

For each of these discrete groups, ENDS exposure will have differing effects on their respiratory health and functioning. In dual use, ongoing exposure to tobacco smoke, even from as few as 1 or 2 cigarettes a day, continues to generate high risks for tobacco-related diseases [8-10]. Daily use of cigarettes and less than daily use of ENDS is the most common pattern of dual use, but there are differing patterns [11,12]. For exclusive use, smoking history (smoking career) may have already impacted respiratory functioning [9], regardless of the subsequent reduction in exposure to toxins. Advocates of tobacco harm reduction stress complete abstinence from cigarettes to obtain potential benefits from ENDS use [3]. Although the numbers of nicotine-naïve individuals using ENDS are small (for example, 0.6% to 0.7% of English adults who never smoked use ENDS [3]), evidence on the respiratory effects of ENDS use by these individuals is crucial for their health care and their lifestyle choices. Data on the effects of naïve use contribute to the research by identifying potential risks or harms of vaping that are not a consequence of prior smoking history [3].

Numerous systematic reviews have examined the respiratory effects of ENDS use with varying conclusions [13-16]. For instance, one systematic review found that vaping increases sensitive measures of airway resistance but does not appear to affect standard measurements of lung function test (eg, forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], or the FEV1/FVC ratio) [14]. However, this review primarily focused on the acute effects of vaping. Another review by Alqahtani et al [15] highlighted the heterogeneity and inconsistencies in existing studies, underscoring the need for further research using robust study designs. Given the diverse findings and methodological differences in the existing literature, conducting an umbrella review is essential for a comprehensive and critical synthesis of the current evidence.

Research Question

The primary purpose of our umbrella review is to present all the evidence available on the respiratory effects of ENDS use by adults based on their pattern of use: dual use with continued cigarette smoking, exclusive use after abstaining from cigarettes, and use by adults who have never smoked cigarettes. With each of these patterns of use, are there benefits, no changes, or harmful effects on respiratory functioning? Our secondary purpose is to identify the higher quality systematic reviews through a rigorous assessment of both their conduct and reporting. Our objective is to provide clinicians with a detailed analysis of how different patterns of ENDS use impact respiratory functioning and to point to the best sources of evidence.

Methods

Overview

Our umbrella review was developed with the Methods for Overviews of Reviews (MOoR) framework [17,18] and the PRIOR (Preferred Reporting Items for Overviews of Reviews) statement [19].

Population, Intervention, Comparator, and Outcomes Criteria

The PICO (Population, Intervention, Comparator, and Outcome) criteria below define the scope of our umbrella review.

- Population: adults (≥18 years old) who smoke cigarettes, adults who have quit smoking, and adults who have never smoked (<100 cigarettes lifetime)
- Intervention: ENDS use
- Comparator: within-subject changes, control group or arm (including placebo), or longitudinal cohort
- Outcome: any self-reported or clinically measured change in respiratory function

Respiratory function outcomes include both respiratory symptoms and test measurements. The symptoms include breathlessness, dyspnea, breathing difficulties, wheeze, cough, sputum, and phlegm. Tests include spirometry (ie, FEV1, FVC, forced expiratory flow at 25%-75% of forced vital capacity, peak expiratory flow, and FEV1/FVC%), airway resistance, impulse oscillometry, impaired mucociliary clearance, and lung function (ie, total lung capacity, residual volume, and expiratory reserve volume). Other outcomes include but are not limited to computed tomography findings of emphysema, airway remodeling, and small airway loss; respiratory-related quality of life and exercise limitations; incidence or prevalence of respiratory disease; and exacerbations of previous respiratory disease. Finally, outcomes include health care resource utilization for respiratory disease–related ambulatory care, emergency department visits, and hospitalization [14]. Other respiratory outcomes not in this list will be added as reported. E-cigarette or vaping use–associated lung injury (EVALI) data, if available, will be evaluated as a separate class of outcome.

Search and Selection Processes

Databases for the search include Scopus (Elsevier), MEDLINE (via PubMed), Cochrane Database of Systematic Reviews,

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International Prospective Register of Systematic Reviews (PROSPERO), and Epistemonikos, and the gray literature databases MedNar, National Technical Information Service, and WorldWideScience.org.

We will include systematic reviews published from 2019. Restricting the time frame is justified by 2 main reasons. First, these systematic reviews included the latest primary studies conducted with the most advanced devices. Second, these devices have evolved significantly over time, leading to considerable changes in their designs, making older models outdated and no longer available in the market [20,21]. A newer style model is the single-use disposables that were introduced to the market in 2019 [22]. The modifications in newer models have played a role in reducing exposure to silicon and solder [21], while alterations in ENDS liquids exhibit potential for lowering carbonyl emissions [23]. Therefore, it is imperative that our findings and conclusions are grounded in the most up-to-date evidence derived from tests conducted with these newer models.

Terms such as "electronic nicotine," "e-cigarette," and "vaping" will be combined with respiratory-related keywords such as "respiratory," "lungs," and "pulmonary" using Boolean operators (ie, OR for synonyms and AND for combining intervention and outcome). Title, abstract, and keywords fields will be selected for the search. For each database, the search terms and syntax will be adjusted according to the database-specific requirements, such as MeSH (Medical Subject Headings) terms for PubMed. A filter for detecting only systematic reviews will be applied where possible. As an example, the search strategy for the Scopus database is as follows: TITLE-ABS-KEY (("e-cig*" OR "vaping" OR "e-cigarette" OR "vapers" OR "Electronic nicotine delivery systems") AND ("respiratory" OR "pulmonary" OR "lungs" OR "breathlessness" OR "dyspnea" OR "wheeze" OR "cough" OR "sputum" OR "phlegm" OR "spirometry") AND ("systematic review" OR "meta-analysis")) AND PUBYEAR > 2018 AND PUBYEAR < 2025. Each search will be meticulously documented by screenshots of the database pages displaying the search syntax and the number of results, and all retrieved records will be exported into an EndNote library, where duplicates will be identified and removed. Two researchers will independently screen the records for all PICO criteria in the title and abstract (or summary); publications lacking any PICO criterion will be excluded. Discrepancies in the exclusions will be decided by the project leader, and the interrater agreement reported.

After the database searches are completed, we will conduct a second round of secondary searches. One search will be a citation chase (snowball search) in Google Scholar. The second search will be a check of the references of the included systematic reviews. These 2 searches will be conducted by 2 reviewers independently. Secondary search publications will be included or excluded based on the full paper criteria. Finally, the list of included systematic reviews will be checked by two experts in respiratory diseases.

Inclusion and Exclusion Criteria

After the title and abstract exclusion process, a full paper review will be conducted by 2 researchers independently for the inclusion and exclusion criteria shown in Table 1.

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Table 1. Inclusion and exclusion criteria.[a]

Criteria	Inclusion	Exclusion
Article type	• Systematic review with a minimum search of 2 databases	• All other study designs
Language	• All languages	• Reviews for which translation is unavailable
Publisher	• Academic journals • Government reports • Medical organizations	• Predatory journals (not indexed in PubMed or Directory of Open Access Journals) • Conference abstracts
Primary study designs	• Clinical trials (randomized or nonrandomized) • Experimental studies • Longitudinal cohort studies	• Cross-sectional study data • Surveys • Case studies • Qualitative studies • Animal studies • In vitro studies
Population	• Adults who smoke cigarettes, adults who have quit smoking, and adults who have never smoked	• Youth
Data	• Changes in disease symptoms • Clinical test measurements • Self-reported health status	• Passive or second-hand exposure • Only 1 primary study from included study designs
Bias assessment of primary studies	• Individual primary studies assessed with any method	• No bias assessment of individual primary studies • Inappropriate bias tool
Analysis-synthesis method	• Meta-analysis • Tabulation • Narrative assessment	• Solely summary of individual primary studies

[a]Studies excluded at the full paper examination will be listed in an appendix and will note the reason for exclusion.

Data Extraction

For efficiency, the data extraction and quality assessments of a systematic review (including its supplementary materials and protocol) will be conducted concurrently.

The specific items for data extraction will be chosen by the research team and pilot-tested on 2 systematic reviews. The planned data items are included in Textbox 1. For systematic reviews that include multiple study designs, data will be selected solely from those that fulfill the inclusion criteria. One researcher will perform the data extraction, and a second reviewer will 100% cross-check it.

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Textbox 1. Data items for the data extraction.

- Bibliographic information
- Funders and conflicts of interest
- Databases searched and dates
- Secondary searches performed
- Inclusion-exclusion criteria of the systematic reviews
- Population demographics
- Intervention description including the electronic nicotine delivery system device and nicotine strength
- Outcome definition and measurement
- Primary studies with their bias assessments
- Narrative assessment (if applicable)
- Data analyses (including sensitivity analyses)
- Meta-analyses
- Any subgroup analyses
- GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) or authors' assessment of confidence in the evidence
- Limitations identified by the systematic review authors
- Conclusions quoted

Quality Assessment

We will use the AMSTAR2 (A Measurement Tool to Assess Systematic Reviews) checklist [24] to assess the quality of the systematic reviews and identify the higher quality ones. The review team will designate AMSTAR2 item 7 (a list of excluded studies) as a *noncritical weakness* and not a *critical flaw* because PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [25], a widely used reporting standard, does not require an excluded studies list. Two reviewers will independently complete the checklist, and the project leader will decide any unresolved discrepancies. For the overall confidence rating, the project leader will score its confidence rating as *high*, *moderate*, *low*, or *critically low* as per the AMSTAR2 criteria except for item 7 as noted above.

A second quality assessment of the reviews will be an examination for reporting biases in 3 areas. The first will be unreported deviations from the protocol. The second will be a checklist of reporting biases drawn from the Oxford Catalogue of Bias [26]: spin bias of nonsignificant findings, omitted findings, one-sided reference bias, framing by over- or underemphasis of outcomes, and overreliance on *P* values (as compared with clinical relevance). The third examination will check for internal data reporting discrepancies within the systematic review publication with the checklist proposed by Puljak et al [27].

We expect that this umbrella review will include a systematic review of ENDS substitution of cigarette smoking that we published with coauthors [16]. To preclude the possibility of bias, 2 neutral third-party reviewers will conduct the AMSTAR2 and reporting bias assessments for this systematic review.

The search processes and results will be displayed in a PRIOR flow diagram. A study table will report the systematic reviews, a second table will display their AMSTAR2 scoring and rating, and a third table will record reporting biases. A citation matrix will list all the primary studies included in the systematic reviews. Analyses will be presented based on the pattern of use: dual use, exclusive use, and naïve use. Subgroup analyses are planned for populations with asthma or chronic obstructive pulmonary disease.

Planned Analyses

In our review, heterogeneity presents a challenge to select the appropriate method of analysis. The evidence base of primary studies is expected to be highly heterogeneous. Particularly notable are the variations in ENDS devices, nicotine strengths, the duration of the intervention, and the duration of follow-up. Heterogeneity occurs also between the systematic reviews, primarily from differences in their inclusion and exclusion criteria. Heterogeneity also arises from earlier and later search dates resulting in different primary studies analyzed in the systematic reviews.

For these reasons, a statistical meta-analysis will most likely not be feasible. Our analysis method will be a Vote Counting Direction of Effect, which is appropriate for heterogeneous data [28]. This analysis will indicate if ENDS use is beneficial, detrimental, or has no effect on respiratory functions. To reduce the risk of bias for the synthesis, only systematic reviews rated at AMSTAR2 moderate or high confidence will be analyzed. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) or bias description rating of the findings made in the systematic reviews will be included in the Vote Counting Direction of Effect.

As a component of our analyses, we will calculate the overlap of primary studies between the systematic reviews. This analysis is necessary to determine if certain primary studies are overrepresented and therefore would result in these studies being

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overweighted in the findings. We will apply the *corrected coverage area* calculation [29] to determine which, if any, primary studies could skew the findings of our umbrella review.

Respiratory functioning outcomes (see PICO above) will be ranked in importance for clinical care by a respiratory physician.

A sensitivity analysis will compare findings in the analyses with those from the systematic reviews rated at low confidence. If necessary, a sensitivity analysis will compare results from commercially funded systematic reviews (including tobacco industry, vape companies, pharmaceutical companies, and medical equipment manufacturers) with all others.

The observations of reporting biases will be reported in a table. The impact of reporting biases on the research literature will be explored in the Discussion and will contribute to our recommendations for future research

If 10 or more systematic reviews are included, publication bias will be investigated with a tabulation of the conclusions of the systematic reviews on the respiratory effects of ENDS usage.

Any deviations from the protocol will be reported in the published umbrella review.

Results

The protocol has been registered in PROSPERO (CRD42024540034), and the umbrella review is expected to be completed by December 2024, followed by the submission of the review for journal publication. The database search was concluded in April 2024, and data extraction and bias assessments were completed in June 2024. The analysis phase is planned to be completed by October 2024.

Discussion

This will be the first umbrella review to provide a comprehensive overview of respiratory symptoms in ENDS users. Based on the current evidence, exclusive ENDS use is expected to significantly improve respiratory outcomes after completely switching away from cigarette smoking. In contrast, dual use with concurrent tobacco cigarette consumption may experience less improvement than exclusive ENDS use. Additionally, we anticipate a deterioration or no effect on respiratory symptoms in naïve use of vapes.

This umbrella review is expected to have a potential significant impact thanks to its methodological rigor, grounded in the MOoR framework and the PRIOR statement. However, the scarcity of data on the respiratory health effects of ENDS in never smokers is a possible limitation that may affect the robustness of the study findings.

Methodological rigor is crucial in a highly polarized research field [30-32]. A rigorous and comprehensive evaluation of the evidence will clarify some of the key controversies surrounding the respiratory impacts of ENDS, correlating their effects with specific usage patterns, particularly the risks associated with ongoing cigarette smoking.

The intention is to widely disseminate the publication of the study protocol and the completed review through articles in peer-reviewed journals and conference presentations. The link to the publication will be shared via our email list to hundreds of academic experts in the field and to general media with a press release. Dissemination will also occur via social media platforms.

A summary of the results will be available on the study website for public access. The anonymized data will be available to researchers on reasonable request.

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Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during this study.

Authors' Contributions

GRMLR contributed to the conceptualization, writing of the original draft, and the reviewing and editing of the manuscript. RO was involved in the conceptualization, writing of the original draft, and the reviewing and editing of the manuscript. RP contributed to the conceptualization, secured funding, and participated in the reviewing and editing of the manuscript.

Conflicts of Interest

GRMLR is currently a research fellow at the University of Catania and, at the time of drafting this paper, was supported by ECLAT srl, a University of Catania spin-off that has received funding from the Global Action to End Smoking (formerly known as Foundation for Smoke-Free World). RO is supported by a contract with ECLAT, srl. ECLAT has received funding from the

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Global Action to End Smoking (formerly known as Foundation for Smoke-Free World). She declares no conflicts of interest. RP is a full tenured professor of internal medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same university. He has received grants from U-BIOPRED and AIR-PROM, Integral Rheumatology & Immunology Specialists Network, Global Action to End Smoking (formerly known as Foundation for Smoke-Free World), Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group srl, Duska Therapeutics, Forest Laboratories, and Ministero dell Universita' e della Ricerca Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU, the European Union economic recovery package. He is founder of the Center for Tobacco Prevention and Treatment at the University of Catania and the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, and Sermo Inc. He is being paid textbook royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo and the International Network of Nicotine Consumers Organizations. He is chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).

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Abbreviations

AMSTAR2: A Measurement Tool to Assess Systematic Reviews
ENDS: electronic nicotine delivery systems
EVALI: e-cigarette or vaping use–associated lung injury
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
MOoR: Methods for Overviews of Reviews
PICO: Population, Intervention, Comparator, and Outcome
PRIOR: Preferred Reporting Items for Overviews of Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Epidemiology of Syphilis in Pregnancy and Congenital Syphilis in Brazil and the Risk or Associated Factors: Protocol for a Systematic Review

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Abstract

Background: Syphilis in pregnancy and congenital syphilis are growing public health issues worldwide. Several factors can influence their occurrence in the population. Therefore, understanding the epidemiology of this condition and the factors that influence its occurrence is fundamental for decision-making by clinicians and health managers. However, so far, no systematic review has summarized and analyzed data on the incidence, prevalence, and predictors of these diseases in Brazilian cities, considering different sociocultural, demographic, economic, sanitary, and spatial-temporal characteristics presented across locations.

Objective: We propose a systematic review protocol to gather and analyze data on the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil, taking into account different local or regional contexts.

Methods: Searches will be conducted in CINAHL, MEDLINE, LILACS, Embase, and Web of Science databases. We will include observational studies (ie, cross-sectional, longitudinal, or case-control studies), analyzing the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil from primary data. The diagnosed syphilis will be assessed based on direct pathogen detection tests or through immunological, treponemal or nontreponemal tests, following Brazilian protocols for diagnosing syphilis. The studies are currently undergoing screening in the databases, and after this step, 2 reviewers will perform all identified documents. The Newcastle-Ottawa Scale and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system will be used to assess methodological quality and quality of evidence of studies, respectively. The Kappa coefficient will assess the agreement between researchers in each study stage. Cochran Q test will assess the heterogeneity among studies. Then, a random-effects meta-analysis will be performed.

Results: Results will be discussed based on subgroup analysis, which is as follows: (1) type of syphilis (in pregnancy or congenital), (2) type of study (case-control and cross-sectional studies for analysis of associated factors and longitudinal studies for risk factors), and (3) contextual factors (ie, region of country, socioeconomic and demographic characteristics, and year of study). This systematic review is expected to be completed by December 2023, and our results will be disseminated through publication in peer-reviewed journals and scientific events.

Conclusions: This systematic review aims to assist health care managers and professionals in their decision-making to control these diseases in Brazil, considering location heterogeneity. Furthermore, countries with health systems and demographic and socioeconomic contexts similar to those of Brazil may benefit from this information.

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KEYWORDS

sexually transmitted diseases; epidemiology; prevalence; incidence; Brazil; syphilis; pregnancy; sociocultural; economic; congenital syphilis; heterogeneity; decision-making

Introduction

Syphilis is a sexually transmitted infection caused by *Treponema pallidum* and is a major public health issue worldwide [1]. Despite the efforts of health care professionals to control this infection in Brazil, cases of syphilis have increased in recent years [2-4], impacting public and private health care systems and highlighting the need to improve disease surveillance [5,6]. Globally, 2 million out of 36 million syphilis infections occur in pregnant women [7], resulting in congenital syphilis (infection of the fetus) and adverse events (eg, early fetal death, stillbirth, premature birth, low birth weight, and neonatal death) [8,9].

Recently, an outbreak of syphilis has been observed among men and women in more economically developed countries, which can be explained by changes in the sexual behavior of individuals and increased exposure to the risk of infection due to a false sense of security stemming from new treatments and an increased search for sexual partners over the internet [10]. In this context, understanding the epidemiology and control of this disease becomes more complex and difficult.

Syphilis in pregnancy and congenital syphilis can be controlled with health care measures, such as access to prevention services, early diagnosis, and treatment [4,11,12]. Conversely, these measures require the analysis of epidemiological data and predictors [4,11]. Although studies in Brazilian cities analyzed the incidence, prevalence, and predictors of syphilis in pregnancy and congenital syphilis [13-17], each city presented different sociocultural, demographic, economic, sanitary, and spatial-temporal characteristics, hindering data extrapolation to the national territory.

Summarizing and analyzing the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis must take into account location heterogeneity. This type of analysis enables a broader understanding of the problem, improves control strategies and equity in disease management, and establishes reference data to help disease screening efforts in Brazil. Despite the relevance of the theme, no systematic review has been conducted to date on the epidemiological data of gestational and congenital syphilis or its predictors, subgrouping and analyzing this information from different contexts.

Thus, we propose a systematic review protocol to gather and analyze data on the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil, taking into account different local or regional contexts.

Methods

Study Design

This systematic review protocol was developed according to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [18], which will also guide the systematic review. The protocol has been registered in PROSPERO (CRD42022329329).

Eligibility Criteria

Observational studies whose sample comprised cases of syphilis in pregnant women or newborns in Brazil will be included in the systematic review. Table 1 [2,19,20] presents the eligibility criteria used in the review.

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Table 1. Eligibility criteria for the systematic review.

Variables	Inclusion criteria	Exclusion criteria
Study design	• Cross-sectional, longitudinal, or case-control studies conducted in Brazil • Studies based on primary data	• Reviews, opinion articles, editorials, or publications without primary data or not peer-reviewed • The most complete and recent data will be used if studies report the same data in multiple sources [19,20].
Population and location	• Studies in which the sample involved pregnant women or newborns with syphilis • Studies with residents in Brazil	• Studies with samples involving other populations (non-pregnant women or men)
Outcomes	• Studies reporting the prevalence or incidence of Treponema pallidum (syphilis) infection or its risk or associated factors in pregnant women or neonates • Studies that diagnosed syphilis based on direct pathogen detection tests or through immunological, treponemal, or non-treponemal tests, in accordance with Brazilian protocols for diagnosing syphilis [2]	• Studies presenting the incidence or prevalence of combined infections (ie, syphilis with other sexually transmitted infections) and not allowing isolated analysis
Language	—[a]	• No restriction regarding language or year of publication
Time frame	—	• No restriction regarding to year in which the study was carried out or published

[a]Not applicable.

Study Selection

Textbox 1 presents the search strategy. Searches will be conducted in the CINAHL, MEDLINE, LILACS, Embase, and Web of Science databases. Grey literature will be also searched using the reference lists of relevant studies in addition to using databases such as Open Gray and Google Scholar. Further, reports with epidemiological data on syphilis in the country will be screened in the electronic database of the Brazilian Ministry of Health.

Two researchers will independently search, identify potentially eligible studies, and remove duplicates. Then, inclusion and exclusion criteria will be applied to titles and abstracts, eligible studies will be read in full, and reasons for exclusion will be recorded. Disagreements between researchers will be resolved by discussion or with a third researcher. The flowchart of the study selection is described in Figure 1.

Textbox 1. Search strategy.

#1 “syphilis” [Title/Abstract] OR “congenital syphilis” [Title/Abstract] OR “treponemal infections” [Title/Abstract] OR “T. pallidum” [Title/Abstract] OR “pallidum” [Title/Abstract] OR “serosyphilis” [Title/Abstract] OR “sexually transmitted diseases” [Title/Abstract]

#2 “pregnant” [Title/Abstract] OR “women” [Title/Abstract] OR “congenital” [Title/Abstract]

#3 “incidence” [Title/Abstract] OR “prevalence” [Title/Abstract] OR “prevalence study” [Title/Abstract] OR “cross-sectional study” [Title/Abstract] OR “observational study” [Title/Abstract]

#4 “risk factors” [Title/Abstract] OR “associated factors” [Title/Abstract] OR “measures of association, exposure, risk or outcome” [Title/Abstract]

#5 “brazil” [Title/Abstract] OR “brazilian” [Title/Abstract]

#6 #1 AND #2 AND #3 OR #4 AND #5

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Figure 1. Flowchart of the study. The numbers are to be confirmed.

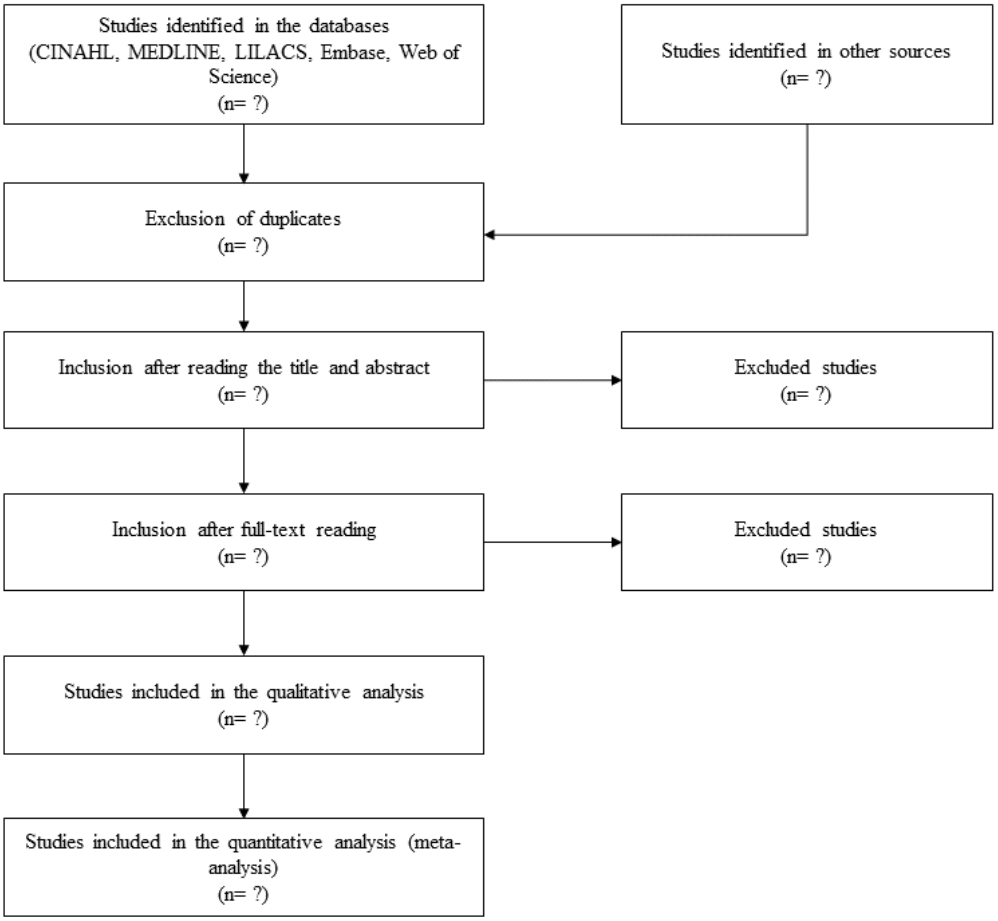

Assessment of Methodological Quality and Quality of Evidence

The Newcastle-Ottawa Scale will be used to assess the methodological quality of studies [21]. This scale includes 8 items categorized into 3 domains (ie, selection, comparability, and outcome or exposure) to assess the risk of bias in nonrandomized studies. The Newcastle-Ottawa Scale has specific tools for cohort and case-control studies. Thus, adaptations will be made to allow the proper assessment of the potential sources of bias in cross-sectional studies. In addition, quality of evidence will be analyzed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system, which classifies evidence as high, moderate, low, and very low [22,23].

Data Extraction and Synthesis

The following data will be extracted and entered into a Microsoft Excel spreadsheet: first author, year of publication, type of study (eg, longitudinal, cross-sectional, or case-control), type of syphilis (eg, in pregnancy or congenital), the diagnostic method used, study location (eg, city and state), participants (eg, sample size, age, type of population, and presence of co-infection), population setting (eg, community, health care centers, schools, neighborhoods, and the environmental context of the participants), date of data collection, sampling method, and main results (eg, incidence, prevalence, and risk or associated factors).

After summarizing the studies, results will be discussed based on subgroup analysis, as follows: (1) type of syphilis (eg, in pregnancy or congenital), (2) type of study (eg, case-control and cross-sectional for analysis of associated factors and longitudinal for risk factors), and (3) contextual factors (eg, region of country, socioeconomic and demographic characteristics, and year of study).

Statistical Planning

Kappa coefficient will assess the agreement between researchers [24]. The unadjusted incidence or prevalence and the standard error will be recalculated based on the numerator and denominator values presented in each study. Furthermore, the prevalence or incidence may be reported using the direct method of standardization, adjusted for the variables of age, study location, and presence of co-infection. If the study does not provide data for calculating adjusted incidence or prevalence, the researchers will request this information from the study authors.

Additionally, a meta-analysis will be performed using a random-effects model due to the potential heterogeneity among studies. The random-effects model is applied when the aim is to combine several studies that have similar objectives but are conducted in different ways (ie, exhibiting methodological

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heterogeneity) [25]. Moreover, the Freeman-Tukey double arcsine transformation will stabilize variances to maintain the estimates of individual effects of each study [26]. Cochran Q test will assess the heterogeneity among studies [27]. I^2 values of 25%, 50%, and 75% will represent low, medium, and high heterogeneity, respectively [28].

Studies will undergo a subgroup analysis using clustering variables (eg, study location, study population, method of syphilis diagnosis, mean sample size, year of data collection, sampling methods, and methodological quality) to investigate possible sources of heterogeneity [20].

Analyzes will be performed using the Review Manager (RevMan) software (version 5.4; Cochrane Collaboration) and the R software (R Core Team), considering a 95% CI.

Results

The protocol has been registered in PROSPERO (CRD42022329329). The screening of the studies in the databases has already started, and the entire systematic review is expected to be completed by December 2023. The results of the study will provide evidence that can support decision-making regarding strategies to control syphilis in Brazil and countries with similar health, demographic, and socioeconomic profiles. Results will be disseminated through publication in peer-reviewed journals and presentation at scientific events.

Discussion

Expected Results and Practical Implications

After a preliminary search, we found studies in Brazilian cities that analyzed epidemiological data and predictors of syphilis in pregnancy and congenital syphilis [13-17,29]. However, no study has organized and summarized data to perform a broader analysis of this public health issue.

Summarizing local studies will allow the analysis and discussion of epidemiology and risk or associated factors of syphilis in pregnancy and congenital syphilis, considering sociocultural, demographic, spatial-temporal, economic, and sanitary differences in each location. Thus, this systematic review will help in the decision-making of health care managers and professionals to control these diseases in Brazil according to location heterogeneity.

Limitations

Some limitations that may compromise the quality of evidence can be found in the systematic review, such as heterogeneity among studies, wide CIs, and uncertainty of estimated effects.

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Data Availability

All data generated and analyzed in this study are available upon request from the corresponding author.

Authors' Contributions

YTP, JCD, and ANAF designed the study and wrote the original draft; JRRH and RARS designed the study and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Blockchain-Based Dynamic Consent and its Applications for Patient-Centric Research and Health Information Sharing: Protocol for an Integrative Review

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Abstract

Background: Blockchain has been proposed as a critical technology to facilitate more patient-centric research and health information sharing. For instance, it can be applied to coordinate and document dynamic informed consent, a procedure that allows individuals to continuously review and renew their consent to the collection, use, or sharing of their private health information. Such has been suggested to facilitate ethical, compliant longitudinal research, and patient engagement. However, blockchain-based dynamic consent is a relatively new concept, and it is not yet clear how well the suggested implementations will work in practice. Efforts to critically evaluate implementations in health research contexts are limited.

Objective: The objective of this protocol is to guide the identification and critical appraisal of implementations of blockchain-based dynamic consent in health research contexts, thereby facilitating the development of best practices for future research, innovation, and implementation.

Methods: The protocol describes methods for an integrative review to allow evaluation of a broad range of quantitative and qualitative research designs. The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) framework guided the review's structure and nature of reporting findings. We developed search strategies and syntax with the help of an academic librarian. Multiple databases were selected to identify pertinent academic literature (CINAHL, Embase, Ovid MEDLINE, PubMed, Scopus, and Web of Science) and gray literature (Electronic Theses Online Service, ProQuest Dissertations and Theses, Open Access Theses and Dissertations, and Google Scholar) for a comprehensive picture of the field's progress. Eligibility criteria were defined based on PROSPERO (International Prospective Register of Systematic Reviews) requirements and a criteria framework for technology readiness. A total of 2 reviewers will independently review and extract data, while a third reviewer will adjudicate discrepancies. Quality appraisal of articles and discussed implementations will proceed based on the validated Mixed Method Appraisal Tool, and themes will be identified through thematic data synthesis.

Results: Literature searches were conducted, and after duplicates were removed, 492 articles were eligible for screening. Title and abstract screening allowed the removal of 312 articles, leaving 180 eligible articles for full-text review against inclusion criteria and confirming a sufficient body of literature for project feasibility. Results will synthesize the quality of evidence on blockchain-based dynamic consent for patient-centric research and health information sharing, covering effectiveness, efficiency, satisfaction, regulatory compliance, and methods of managing identity.

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Conclusions: The review will provide a comprehensive picture of the progress of emerging blockchain-based dynamic consent technologies and the rigor with which implementations are approached. Resulting insights are expected to inform best practices for future research, innovation, and implementation to benefit patient-centric research and health information sharing.

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KEYWORDS

best practices; blockchain; clinical trial; data reuse; data sharing; dynamic consent; health care data; integrative research review; scientific rigor; technology implementation

Introduction

Rationale

Blockchain has been proposed as a critical technology to advance patient engagement and facilitate a shift toward improved patient centricity in health research [1]. For instance, in addition to being used as a means to enhance the integrity and transparency of data in clinical trials [2,3], research indicates that it can be applied to coordinate and document dynamic consent for patient-centric health information sharing [4,5] in which patients' needs, wants, and perspectives are optimally considered [6].

Dynamic consent is a procedure that allows patients and research participants to continuously review and renew their consent to use their private health information. Compared to conventional one-time obtainment and documentation of informed consent, dynamic consent strives to give individuals greater control over their data and to ensure their preferences are respected throughout their participation [7,8]. Moreover, dynamic consent can facilitate ongoing engagement for the secondary use of data (ie, for purposes other than the initial purposes for which consent was given). Thus, dynamic consent may open up novel opportunities for ethical and compliant research, data sharing, and longitudinal researcher-patient engagement beyond the scope of the original agreement [9].

Blockchain technology offers functionality and efficiencies that are difficult to achieve with traditional data systems. First, it can be applied to facilitate dynamic consent by establishing a privacy-preserving, universally verifiable, and immutable record of the consent process [9]. The decentralized nature of blockchain ensures that these records cannot be altered by a single party, safeguarding the integrity of the participant's documented consent independent of any 1 system or device. Moreover, blockchain offers means for mathematical and privacy-preserving verification of (consent) records and associated user identities, with no dependence on trusted intermediaries for reliable recordkeeping [10]. Such can be used for decentralized authentication and authorization, bolstering individual autonomy. In addition, using blockchain in dynamic consent can enhance the transparency of the process. Research participants can track how their data are used and can be provided with means to readily revise their consent [11]. The use of dynamic consent can inspire more people to participate in clinical research by fostering trust between participants and researchers [8]. Additionally, dynamic consent allows for continuous engagement and communication with research participants throughout and after a study, registry, or repository participation [12]. Last, blockchain technologies are currently used to automate downstream researcher access to data based on individuals' preferences without the burden and expense of manual curation [9].

While promising, dynamic consent based on blockchain technology is a relatively new concept, and it is unclear how well it functions in real-world health research environments. Although numerous studies and pilot projects have been conducted to describe the potential application of blockchain technology to facilitate dynamic consent capabilities [13-15], it is necessary to critically evaluate the articles' scientific methodology and results. Further, there are few best practices published about implementation methodology for blockchain-based dynamic consent. Moreover, there is a need for critical appraisal of approaches that capitalize on blockchain's abilities to empower individuals in managing their digital data and identities. For example, self-sovereign identity (SSI) seems particularly pertinent for ongoing authentication and authorization in patient-centric research collaborations [16].

Yet, as of December 2022, the authors could not locate any published systematic or scoping review to examine the current state of blockchain-based dynamic consent features and implementations. Additionally, no reviews of blockchain-based dynamic consent are currently registered as "in progress" with PROSPERO (International Prospective Register of Systematic Reviews), the systematic review registry [17]. Therefore, there is a need for a systematic review to capture a wide range of literature to establish the scope and quality of evidence for blockchain-based dynamic consent features and implementations in clinical settings.

Objectives

We aim to conduct a systematic integrative research review to synthesize a wide range of evidence regarding blockchain-based dynamic consent solutions, thereby informing future innovation research and practice in this domain. The goal is to identify blockchain-based dynamic consent implementations, the technology's impact, and potential best practices for research, innovation, and implementation.

Research Questions

The following research questions (RQs) will be used to guide the analysis and critical appraisal:

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- RQ1: What are the current implementations of dynamic consent involving blockchain and their objectives for health information sharing and health research? What empirical evidence is provided for these implementations?
- RQ2: What are the risks, challenges, and opportunities of applying blockchain-based dynamic consent for health information sharing and health research?
- RQ3: What are the technical, spatial, and temporal aspects of SSI for different blockchain-based dynamic consent systems for health information sharing and health research?
- RQ4: What are the future research directions for research, innovation, and implementation of blockchain-based dynamic consent systems for health information sharing and health research?

A summary of how RQs are addressed by the various research methods is provided in Table 1.

Table 1. Research questions and methods to address them.

Research questions	Associated research methods
RQ1: What are the current implementations of dynamic consent involving blockchain and their objectives for health information sharing and health research? What empirical evidence is provided for these implementations?	• Include only publication years since 2016 (current), and only Technology Readiness Level 6 or higher (actual implementations). • Use integrative design that considers different sources and varied research methodologies. • Perform systematic data extraction and evaluation on implementations' development status and empirical evidence.
RQ2: What are the risks, challenges, and opportunities of applying blockchain-based dynamic consent for health information sharing and health research?	• Perform systematic data extraction and evaluation on implementations' effectiveness, efficiency, satisfaction, compliance, challenges, and limitations.
RQ3: What are the technical, spatial, and temporal aspects of self-sovereign identity for different blockchain-based dynamic consent systems for health information sharing and health research?	• Perform systematic data extraction and evaluation on implementations' consideration of self-sovereign identity standards and capabilities.
RQ4: What are the future research directions for designing, implementing, and validating blockchain-based dynamic consent systems for health information sharing and health research?	• Systematic data extraction and evaluation of articles' future research suggestions and description of best practices regarding design, implementation, and validation. • Critical appraisal and synthesis of collected data from RQ1-4 into best practices for research and innovation.

Methods

Protocol and Registration

This protocol demonstrates a priori development of the research plan. It was registered at PROSPERO on February 15, 2023 (registration number CRD42023396983) [18], before initiating literature review activities. In addition, a timestamped and immutable cryptographic record of the protocol was generated using blockchain-anchoring technology by Triall (Clinblocks BV), allowing for indisputable and independent verification of the protocol and its exact contents at the registered time.

The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist [19,20] was referenced to prepare this protocol.

Study Design

The review will accumulate and synthesize the global published literature about blockchain-based dynamic consent, including quantitative, qualitative, and mixed methods research articles. We will use integrative research review methodology for a comprehensive review of diverse literature [21]. Specifically, integrative reviews aim to provide a comprehensive and holistic understanding of a particular phenomenon or problem by synthesizing evidence from diverse research methodologies. For example, an integrative review may include case studies, observational studies, mixed methods, and qualitative methods that inform theory. By synthesizing a combination of diverse research methodologies, an integrative review allows researchers to develop new theories or models as well as identify gaps in the literature that need to be addressed by future research [22,23]. We plan to identify literature gaps and suggest methods for strengthening future research designs accordingly [24]. By critically appraising current implementations of blockchain-based dynamic consent, we also plan to inform best practices for future innovation and implementation.

To ensure precision, we will adopt the following definitions:

A blockchain is a decentralized, distributed ledger that records information about transactions or activities across a network of computers. Blocks consist of interconnected, encrypted groups of records [25].

Dynamic consent is a method of electronic consent that is flexible, configurable, and can honor an individual's consent preferences across a spectrum of choices over time [7,8].

The protocol is organized to use the integrative review methodology proposed by Whittemore and Knafl [21] and augmented by the PRISMA-P checklist [19,20].

Problem Identification

To progress with blockchain-based dynamic consent, it is critical to advance high-quality research and establish guidance for innovation and implementation. However, most papers to date

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have concentrated on theoretical applications and proofs of concept. Despite the acknowledged requirement for high-quality data and scientific rigor [26], evidence collection has received little attention.

Literature Search

The integrative review will focus on published articles about blockchain-based dynamic consent. Databases selected to search the indexed peer-reviewed academic literature include CINAHL, Embase, Ovid MEDLINE, PubMed, Scopus, and Web of Science (all databases). Gray literature (which is described in various ways but typically includes nearly everything not published in a peer-reviewed journal [27]) will be included in the literature review because a significant portion of relevant research and innovation in this fast-moving field takes place outside of academia. Further, gray literature allows for a more comprehensive assessment of the field's progress [28]. While gray literature can be captured in some of the indices listed above, additional search engines selected to identify gray literature include Electronic Theses Online Service, ProQuest Dissertations and Theses, Open Access Theses and Dissertations, and Google Scholar.

Eligibility Criteria

Eligibility criteria reflect PROSPERO questions and requirements [29]. Not all PROSPERO data fields are pertinent for this integrative review. The eligibility criteria are summarized and presented in Textbox 1.

Textbox 1. Article inclusion and exclusion eligibility criteria.

Inclusion criteria

- Original research articles (architecture, system designs, framework, scheme, model, platform, approach, protocols, test results, and algorithms)
- Any type of research methodology, including quantitative, qualitative, mixed methods, and descriptive narratives
- Describes an actual blockchain-based dynamic consent system (technology readiness level 6 or higher)
- Solutions are implemented in, or intended for, human health-oriented care or research contexts
- Publication years since 2016
- English language articles

Additional sources of gray literature for inclusion criteria

- Scientific or government reports
- Books and book chapters
- Conference papers or proceedings
- Theses

Exclusion criteria

- Review articles that summarize a body of existing literature (although review articles will be examined to perform backward literature tracking)
- Abstracts only
- Letters to the Editor
- Non-English articles
- Secondary research where an author describes work from another publication
- Articles discussing only proposed, potential, or theoretical applications of blockchain-based dynamic consent
- Articles unrelated to the topic

Additional sources of gray literature for exclusion criteria

- Magazine publications
- Interviews
- White papers
- Patents
- Preprints self-posted by the author

Types of Articles to Be Included

Inclusion and exclusion criteria reflect academic and gray literature sources to capture a vast body of literature for the integrative review. These criteria are deliberately broad because few empirical studies are available for inclusion. Therefore, we will include quantitative, qualitative, mixed methods, and descriptive articles from various sources. Further, review articles are included to permit backward citation tracking. A population,

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intervention, control, and outcomes format was used to guide the article selection criteria as follows.

Participants and Population

Articles must feature participants who would use a blockchain-based dynamic consent solution. Populations may include—but are not limited to—patients, research participants, providers, staff members, and research administrators. Some studies may not assess the actual users.

Interventions and Exposures

Rather than a health intervention, participant exposure involves interaction with a dynamic consent solution. The blockchain-based dynamic consent solution must demonstrate sufficient development progress for evaluation. We evaluated the technology described in each article using a modified Technology Readiness Level (TRL) framework that includes technology descriptions from both the US Government Accountability Office [30] and the US Department of Defense [31]. TRL frameworks provide guidelines about the nature of evidence and progress expected for each level of technology development on a scale of 1 (idea formulation and review of scientific literature) to 9 (ready for full-scale production and commercialization). Government Accountability Office guidelines allow consideration and early negotiation with vendors whose products meet the criteria of TRL 6 (representative model or prototype in a relevant environment) or higher. Therefore, for this integrative review, descriptions of dynamic consent solutions must meet the criteria for TRL 6 or higher for inclusion. Our preliminary examination of the full-text articles has confirmed a sufficient body of literature with blockchain-based dynamic consent products at and above this threshold.

Comparators and Control

While we would like to capture comparisons of blockchain-based systems to other comparator systems, we are unaware of any published head-to-head comparisons. Therefore, we included studies without comparators if they meet all other eligibility criteria.

Context

The studies must apply to a health research context, which is, they must describe intended or actual application to the sharing and use of health information for research purposes. Publication years must be 2016 or later to capture the modern implementations of blockchain in this context.

Main Outcome

The review is intended to capture evidence of progress with blockchain, and dynamic consent technology related to health research. Several components will be collected about the implementation or commercialization stage, effectiveness, efficiency, satisfaction, regulatory compliance, and methods of managing identity.

Search Terms

The search strategies were determined through team discussion and were reviewed by an experienced academic librarian at the University of Colorado Denver Auraria Library.

The blockchain-based dynamic consent search strategy includes 2 primary blocks of search terms: “blockchain” and “dynamic consent” within a health care or health research setting. The blocks of terms include synonyms and related concepts, such as using the search term “distributed ledger” for “blockchain.”

Because exact terms, such as “dynamic consent,” may not be used in the desired articles, a list of synonyms was generated for “dynamic,” including: “progressive,” “personalized,” “customized,” “interactive,” “modify,” “modifiable,” “revocation,” “revocable,” and “revoking.” These synonyms will be searched within the proximity of other pertinent terms. For example, we propose using synonyms of “dynamic” within 5 words of terms representing “consent” as a verb or noun, including: “consent,” “permission,” “grant,” “authorize,” “authorization,” “allow,” “agree,” and “agreement.”

Search strategies used character substitutions, such as “decentrali?ed,” to capture American and British English spelling variations (eg, decentralized and decentralised, respectively). Further, word truncations were used to capture related word endings, such as “consent*,” to capture “consent,” “consents,” and “consenting.” The search strategy was customized for each index or database’s unique syntax and capabilities. The complete search terms and syntax are presented for a sample MEDLINE search in Multimedia Appendix 1.

Additional scientific articles were identified using manual backward and forward citation tracking of review articles obtained during the search. Backward citation tracking, also referred to as “backward chaining,” “footnote chasing,” and “reference list searching,” is an umbrella term for finding articles directly or indirectly from the reference section of articles being reviewed [28]. Forward citation tracking, also called “forward chaining,” aims to identify additional literature among the articles that cite one of the selected articles [32]. These additional abstracts were obtained and reviewed for inclusion.

Several gray literature articles were incidentally identified using the search process described above. Theses and dissertations were identified with iterations of the search terms to augment the gray literature search process. Google Scholar was searched using the advanced search screen and Boolean operators. Forward citation tracking was facilitated by clicking the “cited by” option.

Article Selection and Screening

Search results were imported and deduplicated using Covidence Systematic Review Management software (Veritas Health Innovation Ltd). A total of 2 reviewers (WMC and MBW) independently reviewed titles and abstracts (and keywords, when applicable) to determine potential eligibility for inclusion in the review. Any abstracts considered too ambiguous or where reviewers disagreed were resolved by a third reviewer (JF) or by examining the full text.

To facilitate full-text review and abstraction, Covidence automatically imported the open-access articles, and the remaining articles were manually imported. The articles selected for abstraction were also imported into EndNote (version X9; Clarivate) citation management software to facilitate manuscript preparation.

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Full-Text Review

A total of 2 reviewers (WMC and MBW) will independently review the publications to verify that eligibility criteria are met. While the articles do not specify a TRL level, the reviewers will attempt to discern whether the blockchain-based dynamic consent technologies described in the articles meet the criteria for TRL 6 or higher. Any reviewer disagreement will be resolved by a third reviewer (JF) or by discussions between reviewers.

Data Extraction and Evaluation

Although integrative reviews do not typically include a quality appraisal, we have elected to use the validated Mixed Method Appraisal Tool (MMAT) [33] to capture data on the studies' quality. This aligns with established guidelines for organizing and synthesizing a wide range of literature [22,23]. Moreover, we recognize that there is an increased risk of bias in articles where the authors describe their own products with the goal of future commercialization. The MMAT is brief (only 5 yes or no questions per article) and is designed to assess the methodological strength of studies with diverse designs, consistent with an integrative review. Questions pertain to methodological quality, interpretations, and risks of bias. This tool has been assessed and updated for reliability [34] and content validity [35]. A total of 2 reviewers (WMC and MBW) will independently address the MMAT quality appraisal questions of the eligible literature and will extract all pertinent information from each article. A third reviewer (JF) will integrate the reviews from the 2 reviewers or request collaborative discussions among all reviewers.

The remaining data extraction questions were developed by WMC and MBW and refined by the other team members. Questions were programed into Covidence and tracked with an audit trail. Key information planned for extraction includes: (1) article characteristics: author or authors, year of publication, title, and journal; (2) context and setting for actual or intended blockchain-based dynamic consent implementation: country of intended implementation, setting of implementations (eg, hospital, clinic, or research organization), and intended users; (3) details about blockchain-based dynamic consent solution: name given to the technology (if any), stated purposes or objectives of the product, blockchain platform used (if specified), capabilities of integrations with other data sources, maturity of the technology, stated compliance with regulations, SSI capabilities; (4) evidence about the blockchain-based dynamic consent solution: comparisons with other technologies, evaluation with patients or research participants, nature, and scope of evidence presented; and (5) additional questions about scientific integrity and future research: descriptions of challenges and limitations, whether evidence is presented objectively, descriptions of best practices, and recommendations for future research.

Data Synthesis

Categorical data will be summarized by the percentage of articles or blockchain-based dynamic consent products by category.

Information pertaining to the research questions will be organized using qualitative summary narratives—comparing and contrasting blockchain-based dynamic consent approaches [36]. If necessary, a coding manual will be developed to increase the consistency of coding categorization and the synthesis of subthemes [37,38]. The interpretations will consider article quality, representativeness, and bias or objectivity [36].

Results

Article Selection and Screening

Using the search strategies and databases described above, 637 articles were identified. A total of 145 duplicates were removed, resulting in 492 articles eligible for preliminary screening. Title and abstract screening removed 312 articles. A total of 180 articles are available for full-text review against inclusion criteria, confirming a sufficient body of literature for project feasibility.

Presentation

The review will present data as a narrative, supported by tables and graphs to display the characteristics of included articles and implementations of blockchain-based dynamic consent. The structure of the narrative synthesis will reflect the objective and research questions. The flow of information through the review phases will be generated by Covidence and displayed as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram [39].

Discussion

Key Findings

While the results will not be known until we complete the integrative review, we plan to interpret the findings and their implications in the context of the 4 research questions. In discussing findings and implications, we will refer to the subthemes synthesized by evaluating data extracted from the articles.

Potential Impact of the Review

Individual patients and research participants are increasingly given more rights to control the uses of their data through privacy regulations [40-42] and health information interoperability requirements [43,44]. In addition, patient-centric research initiatives are considered by industry, academia, and regulatory stakeholders globally as a promising means to overcome clinical research and development delays, inefficiencies, and high failure rates [45]. Therefore, technologies that facilitate patient-centricity, such as blockchain-based dynamic consent, are increasingly relevant for health care and health research organizations. It underscores the importance of rigorously reviewing these technologies and their impact, elevating scientific rigor, and establishing best practices for research, innovation, and implementation.

Elucidating Technology Benefits

Extant studies that suggest blockchain-based technologies for health care settings typically involve prototypes, proof-of-concept technologies, or minimum viable products, where nearly all purported results are theoretical [46]. This protocol and subsequent integrative review publication highlight

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the relevance and methods for evaluating technology readiness and empirical evidence. Similarly, some studies promote blockchain products and possible benefits but do not explain how products are designed to address specific problems. For example, Durneva et al [47] performed a systematic review of blockchain-based systems for health care and examined how well-proposed solutions aligned with organizational goals. In their review, the authors noted that only 10% (7/70) of products were designed to reduce inefficiencies. As organizations publish more literature about these technology developments, this protocol provides methodology that facilitates critical appraisal of studies and presented evidence.

With the recognition that it is necessary to manage users' identities for a digital consent solution used over time [48]—and possibly across multiple devices—we believe this literature review will also shed light on the identity management features that blockchain could underpin.

Elevating Scientific Rigor

This work can inform and improve future research designs on blockchain-based dynamic consent. In 2019, Treiblmaier [26] noted that the quality of blockchain research was lagging, and he offered guidelines for designing and publishing case studies to improve evidence quality. Years later, authors still emphasize that blockchain research must have more scientific rigor for the work to be respected [49-51]. When addressing blockchain-based dynamic consent literature quality, we will offer deeper insight into gaps, weaknesses, and ways to address these.

Offering Best Practices

This integrative review is expected to identify optimal approaches to implementing and evaluating the effectiveness of blockchain-based dynamic consent technologies. While blockchain products are being developed for health research environments, few implementation models exist [52]. Additionally, few articles describe their products' limitations or weaknesses, contributing to narrow and unrealistic perspectives [53]. Based on the data, we plan to discuss how blockchain-based dynamic consent solutions must be designed to address specific issues in health information sharing and health research. This review will aggregate all information from the articles about strengths and weaknesses—plus draw from our real-world experience—to offer best practices for blockchain technology implementation in this domain. To enhance understanding and practical relevance, we intend to discuss these best practices in an exemplary implementation case, for example, blockchain-based dynamic consent for collecting and exchanging health information and managing informed consent across research centers in the context of longitudinal cardiovascular research projects with extensive and diverse participant cohorts.

Limitations

This integrative research review has several limitations. First, we acknowledge that this is a relatively new area of research and innovation. As a result, the literature base is still relatively small and may not facilitate a comprehensive understanding of the technology and its potential applications. Another limitation is that many published studies on blockchain-based dynamic consent describe early stages of development rather than being based on real-world implementations [14]. This means that they may not reflect the challenges and limitations encountered in practical applications of the technology. Last, some published studies on blockchain-based dynamic consent may be based on small-scale or pilot projects, which may not represent how the technology would perform in a larger, more complex health research setting [47]. To mitigate these limitations, we have conducted a preliminary full-text examination of eligible articles to confirm a sufficient body of literature on implementations at a sufficiently progressed technology readiness level (ie, TRL 6 or higher). The quality of studies and their focal implementations will be appraised systematically using the MMAT. Besides, the early stages of this research arguably increase the relevance of critically evaluating current approaches and synthesizing best practices for future research, innovation, and implementation.

Conclusions

The review will provide a comprehensive picture of the progress of emerging blockchain-based dynamic consent technologies and the rigor with which implementations are approached. Resulting insights are expected to inform best practices for future research, innovation, and implementation to benefit patient-centric research and health information sharing.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed Search Syntax.
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Abbreviations

MMAT: Mixed Method Appraisal Tool
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RQ: research question
SSI: self-sovereign identity
TRL: Technology Readiness Level

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Protocol

The Effectiveness of Digital Health Lifestyle Interventions on People With Prediabetes: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression

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Abstract

Background: There has been an increasing interest in the use of digital health lifestyle interventions for people with prediabetes, as these interventions may offer a scalable approach to preventing type 2 diabetes. Previous systematic reviews on digital health lifestyle interventions for people with prediabetes had limitations, such as a narrow focus on certain types of interventions, a lack of statistical pooling, and no broader subgroup analysis of intervention characteristics. The identified limitations observed in previous systematic reviews substantiate the necessity of conducting a comprehensive review to address these gaps within the field. This will enable a comprehensive understanding of the effectiveness of digital health lifestyle interventions for people with prediabetes.

Objective: The objective of this systematic review, meta-analysis, and meta-regression is to systematically investigate the effectiveness of digital health lifestyle interventions on prediabetes-related outcomes in comparison with any comparator without a digital component among adults with prediabetes.

Methods: This systematic review will include randomized controlled trials that investigate the effectiveness of digital health lifestyle interventions on adults (aged 18 years or older) with prediabetes and compare the digital interventions with nondigital interventions. The primary outcome will be change in body weight (kg). Secondary outcomes include, among others, change in glycemic status, markers of cardiometabolic health, feasibility outcomes, and incidence of type 2 diabetes. Embase, PubMed, CINAHL, and CENTRAL (Cochrane Central Register of Controlled Trials) will be systematically searched. The data items to be extracted include study characteristics, participant characteristics, intervention characteristics, and relevant outcomes. To estimate the overall effect size, a meta-analysis will be conducted using the mean difference. Additionally, if feasible, meta-regression on study, intervention, and participant characteristics will be performed. The Cochrane risk of bias tool will be applied to assess study quality, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach will be used to assess the certainty of evidence.

Results: The results are projected to yield an overall estimate of the effectiveness of digital health lifestyle interventions on adults with prediabetes and elucidate the characteristics that contribute to their effectiveness.

Conclusions: The insights gained from this study may help clarify the potential of digital health lifestyle interventions for people with prediabetes and guide the decision-making regarding future intervention components.

Trial Registration: PROSPERO CRD42023426919; http://tinyurl.com/d3enrw9j

International Registered Report Identifier (IRRID): PRR1-10.2196/50340

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KEYWORDS

digital health; effectiveness; lifestyle intervention; meta-analysis; meta-regression; prediabetic state; systematic review; type 2 diabetes prevention; weight loss

Introduction

Diabetes is a major global health care challenge. In 2021, an estimated 10.5% of the world's population aged between 20 and 79 years had diabetes, and the prevalence is expected to increase to 12.2% by 2045 [1]. Type 2 diabetes (T2D) is the predominant form of diabetes, representing approximately 90% of diabetes cases worldwide, and is one of the most common metabolic disorders [1,2]. T2D results in abnormally high levels of plasma glucose due to insulin resistance and gradual impairment of pancreatic beta-cell function [2,3]. Continuously high levels of plasma glucose can lead to several micro- and macrovascular complications, such as retinopathy, nephropathy, and cardiovascular diseases, increasing the risk of premature mortality, morbidity, and reduced quality of life [2,3]. This poses a major economic burden to the health care system and society [3-5].

The development of T2D is affected by both environmental and genetic factors but living with overweight and having a sedentary lifestyle are prominent risk factors [2,6]. Before the diagnosis of T2D, an intermediate stage of elevated plasma glucose usually exists [7,8]. This intermediate stage, where a person has abnormally high glucose levels but not high enough to be diagnosed with T2D, is called prediabetes [1,9]. Prediabetes is characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated hemoglobin A_{1c} (HbA_{1c}) levels [9,10]. Depending on the organization, diagnostic test, and cutoff criteria used, different definitions of prediabetes exist, which makes global prevalence estimates challenging and varying [8,11]. According to the International Diabetes Federation, an estimated 10.6% of the global population aged between 20 and 79 years had IGT in 2021 and an estimated 6.2% of adults had IFG, based on the criteria established by the World Health Organization. The global prevalence of IGT and IFG is expected to increase to 11.4% and 6.9%, respectively, by 2045 [1].

Most people with prediabetes are unaware of the condition, as it is frequently asymptomatic [10]. People with prediabetes are at increased risk of developing T2D. Approximately 70% of people with prediabetes will develop T2D during their lifetime and about 25% will progress to T2D within 3-5 years [10,11]. Additionally, elevated plasma glucose in the range of prediabetes leads to an increased risk of developing micro- and macrovascular complications usually associated with T2D [12-14]. Several studies have demonstrated that progression from prediabetes (mainly IGT) to T2D, as well as complications, can be prevented and delayed through intensive lifestyle interventions that focus on diet and physical activity [15-18]. These studies have found that intensive lifestyle interventions reduced the risk of progression to T2D by 28%-58% over a 2.5- to 6-year period [15-18]. Prediabetes thus represents a time of opportunity to prevent or delay progression to T2D, potentially slowing down the increase in the prevalence of people with T2D [10,11,19].

Despite the effect of resource-intensive lifestyle interventions observed in clinical trials, these interventions may not be scalable and accessible in clinical practice because of restricted health care resources [8,20,21]. Digital health interventions have the potential to reduce the resources of intensive lifestyle interventions and thereby make them more scalable and accessible in clinical practice [21-23]. Digital health defines the use of digital technologies in support of health care and includes technologies such as mobile apps, videos, websites, and wearable devices [24,25]. Previous reviews have demonstrated that digital health interventions are effective in reducing body weight among people with overweight or obesity [26,27] and reducing HbA_{1c} among people with diabetes [28-30]. These findings indicate that digital health interventions have the potential to improve various health-related outcomes. However, more research is still required to determine whether digital health lifestyle interventions can effectively improve prediabetes-related outcomes (eg, weight loss and glycemic status) to clarify their potential for people with prediabetes. In addition, an evaluation of characteristics associated with effects on outcomes is crucial to guide the development of future interventions and inform decision-making on intervention components.

Previous systematic reviews have investigated the effect of digital health lifestyle interventions on people with prediabetes [20,21,31-33]. However, the reviews had limitations. They focused on specific types of digital interventions [32], including a relatively small number of data sources [32,33], lacking a meta-analysis [20,21,33], or pooling results from different study designs [31]. Furthermore, previous meta-analyses did not include a broader subgroup analysis exploring the association between intervention characteristics and effects on outcomes [31,32]. As a result, the specific characteristics that are associated with effects on prediabetes-related outcomes remain relatively unknown. Additionally, given the rapid development of digital interventions, several new research papers have likely emerged since the conduct of previous reviews.

The considerations mentioned above indicate the need for an updated and comprehensive systematic review, meta-analysis, and meta-regression in the field to synthesize and evaluate the effectiveness of digital health lifestyle interventions on people with prediabetes.

Methods

Study Design

The conduct and reporting of this review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [34]. The review process will

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be conducted based on this review protocol, which adheres to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [35]. The protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) on July 5, 2023 (CRD42023426919), in accordance with the PRISMA guidelines.

Objective

The objective of this systematic review, meta-analysis, and meta-regression is to systematically investigate the effectiveness of digital health lifestyle interventions on weight loss and other prediabetes-related secondary outcomes in comparison with any comparator without a digital component among adults with prediabetes.

Review Questions

This systematic review, meta-analysis, and meta-regression is guided by the following research questions: What is the effectiveness of digital health lifestyle interventions on weight loss and other prediabetes-related outcomes among adults with prediabetes, and how do variations across study, intervention, and participant characteristics contribute to differences in the observed effect?

Inclusion Criteria

Participants

Studies including adults aged 18 years or older meeting criteria indicative of prediabetes will be considered for inclusion in this systematic review, meta-analysis, and meta-regression. The criteria for meeting prediabetes will be defined by the presence of IFG, IGT, or raised HbA_{1c}. According to the criteria of the American Diabetes Association, IFG is defined as fasting plasma glucose levels between 5.6-6.9 mmol/L, IGT as 2-hour plasma glucose (75-gram oral glucose tolerance test) between 7.8-11.0 mmol/L, and raised HbA_{1c} as HbA_{1c} levels between 39-47 mmol/mol [9].

Studies that are restricted to adults with T2D, type 1 diabetes, or gestational diabetes will be excluded. In addition, studies that investigate the effect of a combined lifestyle and pharmacological intervention will be excluded. Studies that examine combined age groups (eg, adults and adolescents) will also be excluded unless the data for the adult population are reported transparently and separately. Similarly, studies that do not report separate data when considering prediabetes in conjunction with any type of diabetes (eg, T2D) or metabolic syndrome will also be excluded.

Interventions

Studies that examined the effectiveness of digital health lifestyle interventions (diet or physical activity interventions) on adults with prediabetes will be considered for inclusion. These studies may encompass both independent digital solutions and interventions that combine in-person meetings with a digital component. The digital component may include different technologies such as SMS text messaging, smartphone apps, email, automated phone calls, mobile phones, websites, computer-based programs, and video. Studies will be deemed ineligible for inclusion if the intervention does not incorporate a digital component.

Comparators

This systematic review, meta-analysis, and meta-regression will examine studies that compare digital health lifestyle interventions to any comparator without a digital component.

Settings

Studies investigating the effectiveness of digital health lifestyle interventions on adults with prediabetes will be considered without any restrictions on the setting.

Outcomes

Studies that report the effectiveness on relevant outcomes related to prediabetes (eg, weight loss, glycemic status, and incidence of T2D) will be considered in this systematic review, meta-analysis, and meta-regression. The primary outcome will be a change in body weight (kg). Secondary outcomes will include changes in the following variables: (1) glycemic status, (2) body composition, (3) incidence of T2D, (4) markers of cardiometabolic health (eg, blood pressure and lipids), (5) patient-reported outcomes (eg, quality of life), and (6) feasibility outcomes (eg, differential retention rate, adherence, and acceptance).

Study Types

Randomized controlled trials with a parallel design will be eligible for inclusion in the systematic review, meta-analysis, and meta-regression. Additionally, studies will be eligible for inclusion if the researchers assess that the study was conducted using a parallel randomized controlled trial design, regardless of whether the paper itself describes the design using a different terminology. Systematic reviews or meta-analyses will be excluded but inspected for potentially eligible studies. Only full-text studies that have undergone peer review and are available in English, Norwegian, Danish, or Swedish will be included. The present review will not impose any restrictions on the publication year of included studies, as older as well as more recent interventions will be evaluated to offer valuable insights.

Search Strategy

The systematic search will be conducted by the first author (TFH) across various databases with the aim of systematically identifying studies investigating the effectiveness of digital health lifestyle interventions for adults with prediabetes. The following bibliographic databases will be searched: Embase, PubMed, CINAHL, and CENTRAL (Cochrane Central Register of Controlled Trials). Assistance in the performance of the systematic search will be provided by a research librarian experienced in systematic review searching.

To identify search terms of relevance, encompassing controlled vocabulary and keywords, an initial limited search will be conducted in PubMed and Embase. The systematic search will involve the identification and incorporation of related terms and synonyms associated with the identified search terms. Additionally, a series of search functions, such as truncation and phrase search, will be used, and the identified search terms

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will be combined using Boolean operators. The systematic search approach will be tailored and adjusted to suit each database included in the study. The complete search strategy for PubMed is presented in the Multimedia Appendix 1. If relevant, for example, in case of inaccessibility of a study or questions during the selection process, the authors of the study in question will be contacted.

Reference search and citation tracking of eligible studies will be performed to identify additional potentially relevant studies. Citation tracking will be conducted in Web of Science and SCOPUS.

A follow-up search will be conducted in each included database before final submission to prevent selection bias and to ensure that all newly published papers are included.

Study Selection

The identified studies will be collected and imported into RefWorks. First, any duplicate studies will be removed in RefWorks. Second, the titles and abstracts of remaining studies will be screened for inclusion against the review eligibility criteria by the first author. Third, the studies that meet eligibility criteria, as well as those where uncertainty persists, will undergo full-text screening. The first author will assess their inclusion against the predetermined eligibility criteria with assistance from a coauthor. In case of any disagreement between the reviewers regarding study selection, the reviewers will engage in discussion to resolve the issue. If necessary, a third coauthor will be involved to reach a consensus. Data extraction, quality assessment, and, if feasible, statistical analysis will be conducted for all eligible studies.

A PRISMA flowchart [34] will be used to demonstrate the screening process for each stage and the results of the systematic search, as depicted in the Multimedia Appendix 2. The PRISMA flowchart will also comprise exclusion reasons of full-text studies.

Risk of Bias Assessment

The Cochrane risk of bias tool will be applied to facilitate the quality assessment of the included studies by the first author with assistance from a coauthor. In case of disagreements, the reviewers will resolve them through discussion, and a third coauthor may be involved if needed. If necessary, for example, if items are missing or unclear for the risk of bias assessment, the authors of the studies in question will be contacted.

Data Extraction

A standardized spreadsheet in Excel (Microsoft Corporation) will be used to extract data from included studies, facilitating data synthesis and analysis while ensuring consistent data extraction. The first author will perform the data extraction with assistance from a coauthor. In case of any disagreement between the reviewers regarding data extraction, the reviewers will engage in discussion to resolve the issue. If necessary, a third coauthor will be involved to reach a consensus.

The data items that will be extracted include the following four categories:

1. Study characteristics, including first author, year of publication, study design, and country.
2. Baseline characteristics of study participants, including sample size of each group, percentage male participants, ethnicity, age, body weight, BMI, HbA_{1c}, and fasting plasma glucose.
3. Outcomes of the study intervention and control group, including primary and/or secondary outcomes when available.
4. Characteristics of the digital health lifestyle intervention, including duration of follow-up, setting, resources used, intervention components, mode of delivery, provider, contact type (eg, face-to-face, fully automated, or remote), and frequency of contact.

Data Synthesis

A statistical meta-analysis will be conducted using Stata (version 17; StataCorp 2021) by pooling data from included studies to estimate the overall effect size of digital health lifestyle interventions on adults with prediabetes. The mean difference between the digital intervention group and the comparator group will be used to present the effect size for continuous data, along with a 95% CI. Primary outcomes presented in other units will be scaled to the same unit if possible (eg, a change in body weight reported as percentage or in pounds will be transformed into kilograms). Standardized mean difference will be used to present the effect size for secondary outcomes presented in different units unless it is possible to scale them to the same unit. Traditional methods will be used to convert results reported as medians and interquartile ranges into means and SDs [36]. For dichotomous data, the effect size will be presented as an odds ratio with a 95% CI. In cases where statistical pooling is impossible, the results will be presented narratively, accompanied by tables and figures where applicable. Feasibility outcomes will also be summarized narratively, eventually supported by tables and figures.

Both qualitative and statistical assessments will be conducted to evaluate the heterogeneity of the included studies. Qualitative assessment will involve comparing the characteristics of the studies, while the I^2 test will be used for statistical analysis. If heterogeneity is present, as determined by an I^2 value of more than 50%, a random-effects model will be used to statistically pool the data. Otherwise, a fixed-effect model will be used. The results of the meta-analysis will be presented in a forest plot. If possible, meta-regression on study characteristics (eg, variations across countries), intervention characteristics (eg, human-to-human interventions vs fully automated interventions), and participant characteristics (eg, gender) will be conducted to uncover common patterns among effective interventions and identify knowledge gaps within the research field. If conducting a meta-regression is impossible due to data limitations, alternative subgroup analyses based on study-, intervention-, and participant characteristics will be performed.

To visually evaluate the potential presence of publication bias, a funnel plot will be created and included in the presentation of the results. If the number of studies included in the meta-analysis is more than 10, a statistical test (Egger test) will be performed to detect funnel plot asymmetry.

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Certainty of Evidence Assessment

The certainty of evidence will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [37]. The assessment will consider the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on these considerations, the evidence will be classified as high, moderate, low, or very low certainty. A summary of findings table will be generated using the web-based software GRADEpro Guideline Development Tool to summarize the strength and reliability of the evidence [38].

Results

The results of this review intend to provide insights into both the overall effectiveness of digital health lifestyle interventions and the characteristics that contribute to their effectiveness. The results will undergo peer review and be submitted for publication.

Discussion

This systematic review, meta-analysis, and meta-regression will review current evidence to address a lack of comprehensive research within the field of digital health lifestyle interventions for people with prediabetes.

As this publication represents a preliminary stage of the systematic review, specific comparisons with key studies are currently lacking. However, the protocol emphasizes conducting a comprehensive review of relevant literature to allow for meaningful comparisons once the results are obtained. Furthermore, the forthcoming discussion aims to assess the applicability of the findings in clinical practice and their potential implications for real-world implementation. Evaluating the resources used in the included interventions may be crucial for this assessment, considering their potential limitations in expanding digital health lifestyle interventions into real-world settings.

The insight gained from this study may help clarify the potential of digital health lifestyle interventions in the management of prediabetes and offer guidance for future development decisions. The planned systematic evidence assessment, using the GRADE methodology, is expected to indirectly inform and guide future recommendations and development decisions for digital health solutions [39]. These recommendations will be enriched by insights obtained from the meta-regression or subgroup analysis. We intend to explore these aspects in the forthcoming discussion.

However, it is crucial to acknowledge the anticipated limitations within this review. Studies investigating digital health interventions are expected to vary in factors such as mode of delivery, intervention type, population, and duration, resulting in notable heterogeneity among the included studies. This diversity might complicate the comparison and statistical pooling of results. Moreover, the upcoming discussion intends to highlight additional limitations and knowledge gaps identified during the review, with the aim of informing and enhancing further work in this field.

Acknowledgments

The authors would like to express their gratitude to research librarian Conni Skrubbeltrang for competent assistance with the search strategy and the literature search. No specific funding will be allocated to support this systematic review, meta-analysis, and meta-regression.

Authors' Contributions

The protocol was drafted by TFH. TFH and SH constructed the search strategy in collaboration with a research librarian experienced in systematic review searching. All authors contributed to the developed eligibility criteria and data extraction strategy. FWU provided statistical expertise. All authors contributed to the final manuscript by reading it, providing feedback, and critically revising it for important intellectual content. The final protocol was approved by all authors.

Conflicts of Interest

KF and BJvS are full-time employees and own shares at Novo Nordisk A/S (joint-stock company). MHJ owns shares at Novo Nordisk A/S. No conflicts of interest were declared by the remaining authors.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v13i1e50340_app1.docx]

Multimedia Appendix 2
Study selection process.
[DOCX File , 59 KB - resprot_v13i1e50340_app2.docx]

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Abbreviations

A/S: joint-stock company, in Danish
CENTRAL: Cochrane Central Register of Controlled Trials
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HbA_{1c}: hemoglobin A_{1c}
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
T2D: type 2 diabetes

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Protocol

Implementation of Chatbot Technology in Health Care: Protocol for a Bibliometric Analysis

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Abstract

Background: Chatbots have the potential to increase people's access to quality health care. However, the implementation of chatbot technology in the health care system is unclear due to the scarce analysis of publications on the adoption of chatbot in health and medical settings.

Objective: This paper presents a protocol of a bibliometric analysis aimed at offering the public insights into the current state and emerging trends in research related to the use of chatbot technology for promoting health.

Methods: In this bibliometric analysis, we will select published papers from the databases of CINAHL, IEEE Xplore, PubMed, Scopus, and Web of Science that pertain to chatbot technology and its applications in health care. Our search strategy includes keywords such as "chatbot," "virtual agent," "virtual assistant," "conversational agent," "conversational AI," "interactive agent," "health," and "healthcare." Five researchers who are AI engineers and clinicians will independently review the titles and abstracts of selected papers to determine their eligibility for a full-text review. The corresponding author (ZN) will serve as a mediator to address any discrepancies and disputes among the 5 reviewers. Our analysis will encompass various publication patterns of chatbot research, including the number of annual publications, their geographic or institutional distribution, and the number of annual grants supporting chatbot research, and further summarize the methodologies used in the development of health-related chatbots, along with their features and applications in health care settings. Software tool VOSViewer (version 1.6.19; Leiden University) will be used to construct and visualize bibliometric networks.

Results: The preparation for the bibliometric analysis began on December 3, 2021, when the research team started the process of familiarizing themselves with the software tools that may be used in this analysis, VOSViewer and CiteSpace, during which they consulted 3 librarians at the Yale University regarding search terms and tentative results. Tentative searches on the aforementioned databases yielded a total of 2340 papers. The official search phase started on July 27, 2023. Our goal is to complete the screening of papers and the analysis by February 15, 2024.

Conclusions: Artificial intelligence chatbots, such as ChatGPT (OpenAI Inc), have sparked numerous discussions within the health care industry regarding their impact on human health. Chatbot technology holds substantial promise for advancing health care systems worldwide. However, developing a sophisticated chatbot capable of precise interaction with health care consumers, delivering personalized care, and providing accurate health-related information and knowledge remain considerable challenges.

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This bibliometric analysis seeks to fill the knowledge gap in the existing literature on health-related chatbots, entailing their applications, the software used in their development, and their preferred functionalities among users.

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(JMIR Res Protoc 2024;13:e54349) doi:10.2196/54349

KEYWORDS

artificial intelligence; AI; bibliometric analysis; chatbots; health care; health promotion

Introduction

Chatbots are software applications that use computerized algorithms to simulate conversations with human users through text or voice interactions [1,2]. Since their inception in the 1960s, chatbots have found applications in various settings, such as airlines, banks, hotel chains, and information technology companies, serving as digital agents to handle and streamline customers' queries and needs [3]. Compared to human agents, chatbots can efficiently respond to a large number of users simultaneously, conserving human effort and time while still providing users with a sense of human interaction [4]. Due to this advantageous feature, chatbots have been implemented in health care settings to automatically resolve or deflect repetitive calls, thereby reducing waiting times for health care consumers and enabling health care professionals to focus on more complex cases. Driven by the evolution of Industry 4.0, characterized by the integration of digital technologies, data, and automation to create more efficient and responsive societal systems, the future of high-quality health care hinges on the automation and digitalization of data exchange. Against this social-technological backdrop, artificial intelligence (AI) chatbots, also known as conversational AI, hold substantial promise as innovative tools for advancing our health care systems [5].

AI chatbots have been developed to automate and streamline various tasks for health care consumers, including retrieving health information, providing digital health support, and offering therapeutic care [6]. The literature reveals that AI chatbots commonly fulfill roles such as assisting individuals in scheduling medical appointments, identifying health clinics, and providing health educational information [7,8]. Research has also shown that health care professionals, patients, and families exhibit favorable attitudes toward the use of chatbot technology to enhance health outcomes [7,9-12].

While AI chatbots hold considerable potential to drive significant advancements and improvements in health care [13,14], their application in health care is still in its early stages. A significant barrier to the deployment of chatbot technology in health care systems is the lack of sophisticated AI algorithms capable of facilitating precise and personalized human-chatbot interactions to meet the expectations of health care providers or fulfill the needs of health care consumers [11]. For instance, in the United States, health-related chatbots have been developed to monitor the health status of patients with chronic heart failure [15], screen for osteoporosis in menopausal women [16], and detect colorectal cancer in the general population [17]. However, their effectiveness in clinical trials was found to be limited when compared to health professional assessments. To fully realize the potential of chatbot technology in health care systems, more studies are needed to develop more sophisticated AI algorithms that are culturally tailored, theoretically informed, and trained based on clinical needs [18-21]. Creating such sophisticated AI chatbots presents a challenge for both health scientists and chatbot engineers, necessitating iterative collaboration between the 2 [22]. Specifically, after chatbot engineers develop a chatbot prototype, health scientists evaluate it and provide feedback for further refinement. Chatbot engineers then upgrade the chatbot, followed by health scientists testing the updated version, training it, and conducting further assessments. This iterative cycle can impose significant demands in terms of time and funding before a chatbot is equipped with the necessary knowledge and language skills to deliver precise responses to its users.

Bibliometric analysis is a quantitative research method to discern publication patterns within a specific timeframe [23]. Scholars use this type of analysis to elucidate the intellectual structure of a particular area within the realm of existing literature [24]. Despite the increasing popularity of health-related chatbots, no bibliometric analysis has been conducted to examine their application. Studies on the coverage of health-related chatbot research have predominantly been conducted in the form of scoping or systematic reviews [19,25,26]. The current body of research papers lacks the breadth of a comprehensive scientific performance mapping analysis. Hence, this bibliometric analysis aims to identify the current status and emerging trends in chatbot technology research, serving as an initial stride for researchers worldwide to gain a comprehensive understanding on the landscape of health-related chatbots. This overview will facilitate the identification of areas for improvement and promote the integration of chatbot technology into health care systems.

Chatbot technology should be promoted in the health care system because many digital health interventions have proven effective but are not implemented in real clinical settings, as they often require high-intensity and sustained human inputs. For example, they often require researchers to regularly and manually send personalized reminders, provide real-time guidance, and initiate referrals [27,28]. To bring population-level effects, digital health intervention needs to be automating personalized messages, modifying them based on responses, and providing new outputs in real time [29]. AI chatbots have the potential to achieve these goals. For example, our previous formative research indicates a high level of acceptance toward the use of chatbot technology among vulnerable populations who are at high risk for HIV [2]. Additionally, we have conducted beta testing for chatbot technology in promoting HIV testing and prevention and found that participants believed chatbot technology provided them with a platform to protect their safety and privacy. This was particularly important in

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environments where stigma and discrimination toward HIV exist, and where same-sex behaviors are criminalized. Compared with the conventional health care use model, where people need to face stigma and discrimination from health care providers, chatbots can provide them with a safe platform to ask questions and receive consulting services. Therefore, promoting chatbot technology holds significance for enhancing the current health care system and an anonymous user setting in chatbots is necessary to protect health consumers' privacy [2].

Methods

Bibliographic Search

We will conduct searches in the following databases: CINAHL (EBSCOHost), IEEE Xplore (IEEE), PubMed, Scopus (Elsevier), and Web of Science (Clarivate) to ensure a comprehensive coverage of research on health-related chatbots. We have identified a set of consensus search keywords related to chatbots and health care through a review of previous systematic reviews [18-21] and consultations with university librarians who possess expertise in informatics and digital health. Our search strategy includes keywords such as "chatbot," "virtual agent," "virtual assistant," "conversational agent," "conversational AI," "interactive agent," "health," and "healthcare." A retrieval search string, including the keywords with Boolean operators listed in Multimedia Appendix 1, will be used.

Selection of Studies

We will include papers on chatbots that are used to promote health outcomes. All interventional and observational studies published as journal papers or conference proceedings will be included. To offer a holistic view of the evolving usage of chatbots in health care, we will not set restrictions on the year of publication. Moreover, we will not exclude papers published in non–English language to incorporate research findings from low- and middle-income countries [30]. Studies that do not discuss the use of chatbots to promote health or wellness will be excluded. Systematic reviews pertaining only to chatbot designs and development, purposes, or features will be excluded. Papers such as editorials, dissertations, preprints, and letters to the editor will also be excluded.

Search results from each database will be imported into Covidence (Veritas Health Innovation Ltd), a systematic review management software. Duplicate papers will be identified and removed. Five researchers will independently screen the titles and abstracts of all papers and categorize them as either "include," "exclude," or "unsure" based on the following inclusion criteria related to (1) chatbot and (2) health promotion. To provide a comprehensive overview of the current research on health-related chatbots, we will include papers about chatbots designed for various populations, including patients, clinicians, policy makers, or the general population. We will not exclude papers based on their study design. Papers marked as "unsure" will be downloaded and assessed for eligibility. The eligibility assessment will be performed by 2 authors (VB and VT) who are an AI consultant and a clinician. In the event of disagreements, the 2 authors will discuss in team meetings with the corresponding author (ZN) to reach a consensus.

Data Extraction

Selected studies will be downloaded from Covidence and imported into VOSViewer (version 1.6.19; Leiden University), a Java-based bibliometric analysis visualization software application. We will use VOSViewer to analyze data related to chatbot publication patterns, encompassing the number of annual publications, the distribution of countries and institutions involved in chatbot research, the number of annual grants that supported chatbot research, the number of funders, the number of journals publishing chatbot research, the number of journal citations, the most prolific authors in the field of chatbots, author network maps, and the most frequently used keywords related to chatbots. Additionally, using Excel (Microsoft Corp), we will manually extract data regarding the number of interventional and observational studies, the methodologies used in creating chatbots, the number of chatbots deployed worldwide, and the usage of chatbots.

Data Analysis

Research Characteristics

In this bibliometric analysis, we will analyze the characteristics of chatbot research based on the topics of the selected studies, identified through their reported keywords, such as primary functions and disease domains. We will report the frequency and percentage of the top keywords and topics by following the framework in previous research to measure the centrality of a keyword using its frequency scores [31].

Publication Patterns

We will report the trend of yearly number of publications and showcase the growth rate of publication by computing the monthly publication rate each year from the earliest publication selected to the latest. To control for the "publication noise," a surge in publications following the releases of ChatGPT, we will stratify the data by publication date before and after the emergence of ChatGPT and conduct sensitivity analyses to distinguish between the direct impact of ChatGPT and other trends in chatbot research. This approach will help to ensure that our findings reflect the broader trends in chatbot technology research and are not disproportionately influenced by the recent increase in publications related to a single event or development. We will calculate the frequencies and percentages of publications for each journal and country in each publication year, whereby we identify the countries and institutions associated with the publication based on the affiliations of the corresponding authors. We will report the trend of research support by identifying the number of grants and funders as reported under each study's source of funding. Moreover, we will compute the distribution of the following two indicators including (1) the methodology used to create chatbots and (2) the implementation of health chatbots.

Research Hot Spot and Connectedness

We will use the number of journal citations to construct bursts, whereby clusters will be sorted by the keywords used by the study. We will further report the most prolific authors based on a combined metric of the number of publications and citation frequency. We will present 2 author network maps using author names and research institutions affiliated with the listed authors.

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Authors and affiliated institutions will be the nodes within each network connected by edges representing the coauthorship of publications [32]. Edges will be weighted by the number of coauthorships between the same listed authors and their affiliated institutions.

Ethical Considerations

This analysis does not involve recruiting human participants or providing interventions; therefore, ethical review and consent forms are not required. We hope that the findings from the manuscript will aid researchers, engineers, health professionals, funders, and policy makers in their future implementation of chatbot technology to facilitate innovative and efficient health care systems.

Results

The preparation for the bibliometric analysis began on December 3, 2021, with the initial steps involving the research team familiarizing themselves with VOSViewer and CiteSpace, followed by digital consultations with 3 librarians from Yale University. Tentative searches in the databases yielded a total of 2340 papers. The official search phase began on July 27, 2023. Our goal is to complete the screening of papers and perform the analysis by February 15, 2024. We anticipate a significant increase in chatbot research following the emergence of ChatGPT.

Discussion

AI chatbots hold strong potential to transform the field of health care. For example, ChatGPT, an AI chatbot developed by OpenAI, has sparked numerous discussions within the health care industry regarding the impact of AI chatbots on human health [13,14,33-38]. Our team has been developing an AI chatbot since June 2019, and we have discovered that developing a sophisticated AI chatbot capable of precise interaction with health care consumers, delivering personalized care, and providing accurate health-related information and knowledge remains a considerable challenge. One of the major obstacles faced by health scientists interested in chatbot research is their lack of familiarity with chatbots' underlying technologies, such as the computational systems, software platforms, and underlying algorithms that train chatbots and enable their automation and individualization. Similarly, chatbot engineers may have limited insight into the challenges faced by patients and health care providers in real-world clinical settings, making it difficult for them to fully grasp the nuances and directions of chatbot technology. Such information asymmetry in interdisciplinary collaboration hinders health-advancing chatbot technology from reaching its full potential. More literature that can offer diverse stakeholders, ranging from health scientists, health care providers, to chatbot developers, insights into a holistic roadmap to creating effective chatbots to meet health care needs is thus urgently needed to facilitate such interdisciplinary endeavors.

Chatbot technology holds immense potential to enhance health care quality for both patients and professionals through streamlining administrative processes and assisting with assessment, diagnosis, and treatment. Used for health information acquisition, chatbot-powered search, as we anticipate, will become an important complement to traditional web-based searches. This trend is primarily driven by the convenience of chatbot-powered search for users, as it eliminates the need for users to manually sift through search results as required in traditional web-based searches. However, no recognized standards or guidelines have been established for creating health-related chatbots. We believe that with theory-informed and well-trained algorithms, chatbots can also be used as health care digital assistants to provide consumers and patients with quick, precise, and individualized answers. As demonstrated by the widespread adoption of ChatGPT in recent times, it is reasonable to anticipate that the development and implementation of AI chatbots will substantially enhance the efficiency and convenience of health care consumers' information search. Existing studies have also shown that AI chatbots can increase health appointment volume by automating the scheduling process for health care consumers, achieved through a user-friendly platform that enables appointment scheduling, verification, and cancellation with ease, further leading to reduced no-show rates. For example, Weill Cornell Medicine reported a 47% increase in appointments booked digitally through the use of AI chatbots [39]. Moreover, chatbot technology can enhance the work efficiency of nurses, physicians, and other health care professionals by delivering prompt responses to inquiries related to clinical practice standards, eliminating the need to navigate prolonged websites or extensive clinical guidelines for specific information.

Despite the obvious benefits of chatbot technology in health care, several potential risks of using chatbots exist, including breaching privacy, providing misinformation, and generating systematically biased responses [2,7-9]. These risks are relevant to the nature of chatbot technology, in which chatbot developers need to maximize a personalized experience and enable chatbots to provide users with precision answers through training chatbots [12]. However, training chatbots requires chatbot technology to have access to a wealth of users' personal data. This poses a major threat to using chatbots in health care. To address privacy issues, chatbot developers and researchers must ensure that users' data are protected using encryption during human-chatbot interactions or when a chatbot needs to retrieve backend data [2]. Second, misinformation originates from the immature or flaws of the chatbot algorithms. Training a chatbot is an iterative process that demands a large data set and vetting of the outputs by researchers. During a chatbot creation, the earlier versions of the chatbot often provide redundant and impersonalized information that may prevent users from using the chatbot. To increase chatbot usability, a chatbot must be precise enough in its communications with users or can connect users to a human agent if necessary [11,12]. Third, even well-trained chatbots can provide biased responses or solutions to users [13]. This is particularly true if the data sets used to train chatbots are biased. To minimize these risks of using chatbots in health care, it is necessary for researchers to validate chatbot outputs and reduce biases in the data sets used to train a chatbot. Only by adopting this approach, quality chatbots with high usability can be used to promote health care.

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To fully realize the potential of chatbot technology in improving health outcomes for everyone, sustained collaborative efforts from an interdisciplinary research team comprising chatbot engineers and health scientists are essential. To the best of our knowledge, this is the first study aimed at summarizing the current status and future trends of chatbots in the health care field. This study will provide a broad overview of publications on health-related chatbot research and bridge the knowledge gap in the existing literature, including software used for chatbot development, popular functionalities, and chatbots' applications in health care. This study includes papers published since the inception of the chatbot and is not confined by the language of publication. Consequently, it offers a global perspective on the evolution of chatbots within the health care domain. One limitation of this study is its nature as a bibliometric analysis, which does not explore topics in the same depth as a systematic review.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

ZN, VT, MLP, and VB conceived the study and wrote the first draft of the manuscript. MLP and VB helped to develop the bibliographic search and bibliometric analysis. All authors contributed to the development of the study protocol, revised the subsequent version of the manuscript, and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
A retrieval search string.
[DOCX File , 15 KB - resprot_v13i1e54349_app1.docx]

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Abbreviations

AI: artificial intelligence

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Protocol

Nutritional Interventions for the Prevention of Cognitive Decline in Patients With Mild Cognitive Impairment and Alzheimer Disease: Protocol for a Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Mild cognitive impairment (MCI) is the stage between cognitive decline due to physiological aging and the severity of decline seen in neurodegenerative disorders like Alzheimer disease (AD), which is among the most prevalent neurodegenerative disorders characterized by cognitive impairment. People with MCI are at increased risk of developing AD. Although MCI and AD are incurable, nutritional interventions can potentially delay or prevent their onset. Consequently, effective interventions used to decelerate or alleviate the progress of cognitive impairment in older people are a significant focus in geriatric care. Given the synergistic effects of nutrition on health, assessing the effectiveness of nutritional supplements or dietary composition in preventing MCI or AD is essential for developing interventional strategies.

Objective: Our study aims to assess the effectiveness of various nutritional interventions, including special dietary types, dietary patterns, specific foods, nutritional intake, and nutritional supplements, in preventing cognitive decline among patients diagnosed with MCI or AD. To achieve this, we will use a comprehensive approach, including network meta-analysis, pairwise meta-analysis, and systematic review of randomized controlled trials (RCTs).

Methods: The review will follow the Population, Intervention, Comparison, Outcome (PICO) model and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. Two investigators will independently search PubMed electronically. Data extraction will follow the inclusion criteria, and data will be assessed for risk of bias using a revised tool. Additionally, evidence quality will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. The outcomes of interest are assessing the cognitive outcomes in patients with MCI or AD. A systematic literature search will be conducted, identifying randomized controlled trials that investigate the impact of these nutritional interventions on cognitive function decline in individuals with MCI and AD. Network meta-analyses (random-effects model) and pairwise meta-analyses will then estimate the relative effectiveness of different nutritional interventions.

Results: We included 51 studies, published between 1999 and 2023 (27 studies for AD and 24 studies for MCI) and involving 8420 participants. We completed data extraction for all 51 studies by December 2023. Currently, we are actively engaged in data analysis and manuscript preparation. We plan to finalize the manuscript and publish the comprehensive results by the end of 2024.

Conclusions: Our study holds significant clinical relevance given the rising prevalence of AD and the potential influence of nutritional interventions on cognitive function in individuals with MCI and AD. By investigating this relationship, our research aims to inform evidence-based decision-making in the development of prevention strategies for MCI and AD. The outcomes are

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expected to contribute to the establishment of reliable recommendations for MCI or AD management, providing substantial support in the field.

Trial Registration: PROSPERO CRD42022331173; http://tinyurl.com/3snjp7a4

International Registered Report Identifier (IRRID): PRR1-10.2196/47196

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KEYWORDS

network meta-analysis; cognitive impairment; Alzheimer disease; Alzheimer; neurodegenerative disorders; geriatric care; nutritional interventions; older patient; geriatric; cognitive decline; aging; older people; nutrition; cognitive; aging; intervention; Alzheimer disease; dementia; acute confusional senile dementia; Elder Nutritional Physiological Phenomena; Nutrition Physiology; nutrition; meta-analysis; meta-analyses; systematic review; systematic reviews

Introduction

Cognitive decline, particularly associated with mild cognitive impairment (MCI) and Alzheimer disease (AD), represents a significant and growing public health concern worldwide [1]. As the aging population continues to increase, the prevalence of MCI and AD is also on the rise, leading to substantial personal, societal, and economic burdens [2]. One study indicated that the occurrence of MCI was higher than 22.5 per 1000 person-years among people aged 75 years and older [3]. Patients with MCI are also at a high risk of developing AD [4,5]. Therefore, identifying effective interventions to prevent or delay cognitive decline in individuals with MCI and AD is of utmost importance.

Currently, MCI and AD are incurable; however, delay and prevention of MCI or AD are possible [6]. Modifiable factors such as metabolic conditions (eg, diabetes), vascular issues (eg, hypertension), mental health concerns (eg, depression), social factors (eg, isolation), and lifestyle choices (eg, nutritional intake [7], dietary type [8], and physical inactivity) have been frequently linked with the risk of MCI and AD [9]. As such, it is critical to understand how modulating health and lifestyle factors may prevent cognitive decline. In recent decades, nutritional interventions have gained attention as potential strategies for cognitive decline prevention [10,11]. Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential benefits in cognitive function and neuroprotection. Multiple types of intervention have been applied to these populations to reduce the decline of cognitive function, such as the Mediterranean diet and the ketogenic diet as well as the regulation of fatty acids, antioxidants, vitamins, and micronutrients [12-15]. Andrews et al [16] conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of dietary patterns, food, and nutritional supplements on cognitive function in individuals with MCI. The findings of this review demonstrated that few nutritional interventions convincingly improved the cognition of individuals with MCI [16]. Vlachos et al [17] conducted a systematic review and found folate, vitamin E, omega-3 fatty acids, and certain multinutrient formulations have shown some preliminary promising results [17]. However, the evidence regarding the effectiveness of different nutritional interventions remains inconclusive, with conflicting findings reported across individual RCTs.

To address the limitations of traditional pairwise meta-analyses and provide a comprehensive synthesis of the available evidence, we propose conducting a network meta-analysis (NMA). An NMA is a type of meta-analysis that extends beyond regular meta-analyses [18,19]. By using this approach, we aim to provide more precise and robust estimates of the effects of different nutritional interventions on cognitive decline in patients with MCI and AD. In this protocol, we outline the methodology for conducting an NMA of RCTs on nutritional interventions for the prevention of cognitive decline in patients with MCI and AD.

Methods

Experimental Approach

This protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist [20]. This protocol has been registered with the PROSPERO database (CRD42022331173).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be determined according to the principle of the Population, Intervention, Comparison, Outcome (PICO) design. The inclusion and exclusion criteria are presented briefly in Table 1.

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Table 1. Inclusion and exclusion criteria for studies in the meta-analysis.

Variables	Inclusion criteria	Exclusion criteria
Study design	RCTs[a] reported as comparing one nutritional intervention with another or a placebo	Non-RCTs
Participants	Participants with MCI[b] or AD[c] older than 50 years	Participants with vascular dementia; Parkinson disease–related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid hemorrhage
Diagnosis of MCI or AD	Diagnosis according to NINCDS-ADRDA[d] DSM[e] or assessed by MMSE[f] with scores between 10 and 26	N/A[g]
Nutritional intervention assessment	Any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake, and nutritional supplements at all doses or ingested amounts with a duration of more than 12 weeks	No definitive preventative impact was evaluated, or the effects were evaluated for less than 12 weeks.
Outcome measurement	The primary outcome will be assessed by the MMSE. The secondary outcomes will be assessed with other scales like the ADAS-Cog[h], CDR[i], and WAIS-R[j] scores.	N/A

[a]RCTs: randomized controlled trials.

[b]MCI: mild cognitive impairment.

[c]AD: Alzheimer disease.

[d]NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

[e]DSM: Diagnostic and Statistical Manual of Mental Disorders.

[f]MMSE: Mini-Mental State Examination.

[g]N/A: not applicable.

[h]ADAS-Cog: Alzheimer's Disease Assessment Scale cognitive subscale.

[i]CDR: Clinical Dementia Rating Scale.

[j]WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Inclusion Criteria

Type of Study

All RCTs that compared one nutritional intervention with another or a placebo for the prevention of cognitive decline in patients with MCI or AD will be included.

Participants

Participants with MCI or AD older than 50 years, regardless of gender, ethnicity or race, geography, dwelling, or chronic diseases, will be included in the analysis.

Inclusion of Patients With Different Degrees of MCI or AD

Participants will be considered as having AD by fulfilling the requirement of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) [21,22]. Participants will be evaluated for MCI using the Mini-Mental State Examination (MMSE) [23].

Nutritional Interventions Assessment

Experimental interventions included any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake, and nutritional supplements at all doses or ingested amounts. Interventions lasted more than 12 weeks and were with or without medication as cointervention. The control group received a placebo intervention.

Outcome Measurements

Both the primary outcome and secondary outcomes involve the assessment of the cognitive function. The primary outcome will be assessed by the MMSE and the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog). The secondary outcomes will be assessed using other scales, such as the Clinical Dementia Rating Scale (CDR), and the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The standard mean difference (SMD; Cohen *d*) will assess the effect sizes of the continuous variables. A small-sample (n<20) correction will be applied to SMD, leading to an effect size called Hedges *g*.

Exclusion Criteria

The following studies were excluded:

- Studies were non-RCTs or in the form of a letter, editorial, commentary, or case report.
- There was no definitive preventative impact evaluated, or the effects were evaluated for less than 12 weeks.
- Participants had vascular dementia; Parkinson disease–related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid hemorrhage.

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Search Strategy

Two investigators (QH and KCHW) will independently perform the search strategy, and disagreements will be resolved by discussion or by a third investigator (JYZ). We will search for all the relevant citations published from the date of the respective database onset until Dec 31, 2023, in 3 English databases (ie, PubMed, Embase, and Cochrane Library). We will establish search strategies that combine keywords and indexed terms indicative of MCI or AD, nutritional intervention, and RCTs. Furthermore, the reference lists of the listed papers will be manually examined to seek new studies that are related. Any controversies will be resolved through dialogue. Multimedia Appendix 1 includes the search techniques.

Data Extraction

Two investigators (QH and KCHW) will independently extract the data from all eligible studies published in English using standardized spreadsheets that are predefined. Any discrepancies will be resolved through consensus by discussion between the 2 investigators or, if necessary, arbitrated by a third investigator (JYZ). The following information will be extracted from every study: first author, publication year, detailed trial information (ie, randomization, sequence concealment, blinding, nutritional intervention protocols, number of treatment arms, as well as the dose and frequency of interventions), the diagnosis criteria, characteristics of the patient (eg, age, gender, race, and baseline MMSE or ADAS-Cog scores), sample size, follow-up MMSE or ADAS-Cog scores, number of completed interventions, as well as the duration of the intervention and follow-up. We will contact the authors via email to obtain the raw data when the data on outcomes are incomplete in the original article; otherwise, we will not include studies lacking such data. At last, 2 investigators will cross-check all retrieved data to verify their accuracy.

Quality Assessment

The quality of the included studies will be evaluated by the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) [24]. Various biases, such as selection bias (randomized sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (dealing with incomplete outcome data), reporting bias (selective reporting), and overall biases will be assessed in our study. The trials will be categorized into 3 types: low risk of bias, unclear risk of bias, and high risk of bias. Assessment of bias of the trials will be conducted by 2 investigators (QH and KCHW), and disagreements will be resolved through discussion with a third investigator (JYZ). Moreover, we will contact the authors asking for detailed allocation concealment and other characteristics when they are not available in the study.

Statistical Synthesis

Characteristics of Included Studies and Information Flow in the Network

For the eligible trials included in our analysis, we will generate descriptive statistics to provide a comprehensive overview of the population characteristics and key variables across all trials. These descriptive statistics will encompass factors such as age, disease subtype, and other relevant risk factors that may impact the outcomes of interest. To visually represent the network of evidence, we will construct a network diagram. The edges connecting different interventions will be depicted with widths proportional to the inverse of the variance of the summary impact for each direct treatment comparison. The size of the nodes in the diagram will correspond to the quantity of evidence accumulated for each treatment, represented by the total number of studies contributing to that node. In addition, we will use a contribution matrix to explore the direct comparisons that have a substantial influence on the relative effects within the network [21,22]. This matrix will help identify the specific comparisons that contribute significantly to the overall findings.

Assessment of the Transitivity Assumption

The transitivity assumption will be assessed by evaluating the distribution of modifiable variables, such as age and mean baseline cognitive function, between the intervention and the control group [23].

Pairwise Meta-Analyses and Network Meta-Analyses

By conducting the pairwise meta-analysis, we can quantitatively assess the effectiveness of interventions that have direct evidence. This analysis allows for a comparison of the treatment effects within individual studies, providing valuable insights into the efficacy of each intervention. To ensure transparency and facilitate interpretation, we will present the results of the pairwise meta-analysis using forest plots.

The NMA will be conducted using a Bayesian framework, pooling data from all included studies [24]. To provide a visual representation of the network of evidence, we will generate network plots, which summarize the geometry of the network. These plots will help illustrate the connections between different interventions and highlight the available evidence for each comparison. For the estimation of effect sizes, we will use contrast-based methods within the NMA framework. The surface under the cumulative ranking curve will be used to estimate the relative rank of the different nutritional interventions [25].

All data will be analyzed using the R 4.0.3 (R Core Team) software, specifically using the gemtc package. Estimates will be reported as SMDs and 95% credible intervals (CrIs). We will use 3 Markov chains with 100,000 iterations after an initial thinning of 10,000 and a thinning of 10. The convergence of the model will be estimated by checking trace plots and the Brooks-Gelman-Rubin statistical value.

A systematic review will be considered when studies are scarce, typically involving less than 2 available studies. Additionally, if the heterogeneity observed among the included studies is exceptionally high, typically exceeding 95%, a systematic review approach will be adopted.

Assessment of Inconsistency for Network Meta-Analysis (NMA)

Consistency refers to the statistical manifestation of transitivity while a lack thereof is known as inconsistency [26]. Inconsistency suggests a disagreement between these estimates and indicates potential issues with the consistency of evidence

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across the network of studies. We will use the node-splitting method to assess inconsistency [27,28]. The presence of inconsistency between different estimates using direct and indirect evidence can be evaluated by assessing the *P* value. Inconsistency in the network is indicated by $P<.05$.

Assessment of Heterogeneity and Sensitivity Analyses

To quantify between-study heterogeneity, we will calculate the I^2 statistics with 95% CrI and τ^2 to convey the heterogeneity. τ^2 represents the variability in intervention effects across studies, while I^2 quantifies the proportion of total variability that is due to heterogeneity rather than chance. If I^2 >50%, it will be considered as moderate to substantial heterogeneity; in such cases, the effect sizes will be estimated using a random-effects model [29]. Moreover, we will estimate the outlier and influential study when I^2>50%, and then, we will perform the NMA or pairwise meta-analysis again, excluding the outliers and influential studies. Study-specific estimates and 95% CrIs, will be presented by forest plots. Subgroup meta-analyses and meta-regression analysis will be performed to estimate the source of heterogeneity. Subgroup analyses by different groups allow us to test specific hypotheses and describe why certain types of studies produce lower or higher effects than others. Performing subgroup analysis would help estimate if the interventional effects for the primary outcomes are robust. Meta-regression analysis could help quantify the effects by including covariates in the network meta-analysis models, if suitable. Then we will run subgroup and meta-regression with the following criteria: cognitive dysfunction severity at baseline, study year, sample size, risk of bias, duration of intervention, and number of recruiting centers (ie, single-center or multicentric studies).

Sensitivity analyses will be conducted to assess the robustness of the primary outcome results in the meta-analysis. These analyses will involve examining the impact of outliers, influential studies, risk of bias, and sample size by using the leave-one-out method. Specifically, each study will be systematically removed from the meta-analysis, and the pooled effect will be re-evaluated both in pairwise meta-analysis and NMA for each iteration. Studies with changes in the effect size exceeding 10% will be noted.

Assessment of Publication Bias

The comparison-adjusted [26] and contour-enhanced funnel plots [30] will be used to find out whether the results in imprecise trials differ from more precise trials. In addition, network meta-regression models and the Egger test will be performed to detect the effects between study size and effect size and to assess the asymmetry of the funnel plot, respectively.

Results

The initial search yielded 30,269 citations, of which 248 articles were identified as potentially eligible and will undergo evaluation for eligibility. Among these, a total of 197 articles were excluded for various reasons. This exclusion consisted of 3 duplicates, 39 articles without full-text availability, 45 articles lacking an assessment of cognitive function, 40 articles not meeting the criteria of being RCTs, 28 articles not in English, and 42 articles unrelated to the study objective. Ultimately, 51 studies meeting the inclusion criteria were included in our NMA. These studies, published between 1999 and 2023, consisted of 27 studies focusing on AD and 24 studies focusing on MCI. In total, these studies involved 8420 participants. We completed data extraction for all 51 studies by December 2023. Currently, we are actively engaged in data analysis and manuscript preparation. We plan to finalize the manuscript and publish the comprehensive results by the end of 2024.

Ethical approval was not required in the meta-analysis. Our study is merely based on the published literature, for which ethical approval has been obtained. To disseminate the evidence obtained, we will publish our results in an international peer-reviewed journal to improve preventive applications with scientific evidence.

Discussion

The global phenomenon of population aging has led to a significant increase in the prevalence of cognitive impairment, particularly AD and MCI [31]. This demographic shift has garnered substantial attention from health care providers, researchers, and policy makers due to the immense personal, societal, and economic implications [32]. As the current treatments for MCI and AD are limited and primarily focused on symptom management, identifying effective preventive strategies is of paramount importance [15]. The potential benefits of nutritional interventions for cognitive health have been a subject of considerable interest [2]. Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential neuroprotective effects and cognitive function improvement. Therefore, through this study, we aim to consolidate the available evidence and provide a rigorous and comprehensive synthesis using the NMA approach. Moreover, identifying the most effective interventions will help guide future research efforts and resource allocation toward the most promising strategies.

It is important to acknowledge the limitations of this study. Although an NMA provides a robust statistical framework for synthesizing evidence, it is reliant on the quality and availability of data from included RCTs. Furthermore, potential sources of bias and heterogeneity among the studies may affect the robustness of the results.

In conclusion, the findings of this study will have significant implications for clinical practices as well as for informing public health strategies and policy making.

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Authors' Contributions

QH and KCHW participated in the study design and data collection; they also analyzed the data and wrote the manuscript. ANB participated in the discussion of the study design and data analysis; he also edited the manuscript. JYZ participated in the independent quality checking of all data included in the analysis. KHKC conceived the study, designed and coordinated the study, and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search techniques.
[PDF File (Adobe PDF File), 60 KB - resprot_v13i1e47196_app1.pdf]

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Abbreviations

AD: Alzheimer disease
ADAS-Cog: Alzheimer's Disease Assessment Scale cognitive subscale
CDR: Clinical Dementia Rating Scale
CrI: credible interval
DSM: Diagnostic and Statistical Manual of Mental Disorders
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
MCI: mild cognitive impairment
MMSE: Mini-Mental State Examination
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMA: network meta-analysis

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PICO: Population, Intervention, Comparison, Outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
SMD: standard mean difference
WAIS-R: Wechsler Adult Intelligence Scale-Revised

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Protocol

The Effectiveness of a Telenutrition Intervention to Improve Dietary Behavior and Physical Activity Among Adolescents With Obesity: Protocol for a Systematic Review

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Abstract

Background: The global obesity pandemic among adolescents is becoming a public health issue throughout the world. Telehealth use has significantly increased during and after the COVID-19 pandemic, including its application in adolescent obesity prevention and treatment.

Objective: This review aims to synthesize the evidence on the effectiveness of telenutrition in improving dietary behavior and physical activity in adolescents with obesity.

Methods: The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guideline will be used to structure this protocol. The focus of the systematic review is guided by the population, intervention, comparator, and outcome (PICO) framework. A systematic search of Science Direct, PubMed, Cochrane, Embase, JMIR, ProQuest, and Google scholar databases will be conducted. Two authors will screen the titles and abstracts of identified studies independently and select studies according to the eligibility criteria. The full-text reading will be done independently by 2 reviewers to assess final eligibility. Any discrepancies will then be discussed and resolved. The Cochrane Collaboration Risk of Bias tool was used to assess the risk of bias; a descriptive analysis will summarize the effectiveness of the telenutrition or any type of telehealth intervention used.

Results: The systematic review is expected to be completed by the end of March 2024. The ongoing screening and review of the articles are currently being conducted.

Conclusions: This systematic review aims to summarize the effectiveness, features, design process, usability, and coherence of a telenutrition intervention using behavior change theory to improve dietary patterns and physical activity among adolescents with obesity. It will identify areas for improvement and best practices, informing the development of more useful and engaging telenutrition interventions for adolescents.

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KEYWORDS

telehealth; obesity; telenutrition; adolescent; behavior change; virtual counseling; teenager; young adult; food intake; dietary pattern; intervention

Introduction

The global obesity pandemic is becoming a public health issue, particularly among children and adolescents aged 5 to 19 years [1]. Between 2013 and 2018, the trend of adolescent obesity nearly doubled in Indonesia [2,3]. Obesity is caused by unhealthy lifestyles, such as most adolescents not meeting the daily fruit and vegetable recommendation and engaging in less physical activity; additionally, approximately 65% of adolescents skip breakfast, and 56% of adolescents aged 15-19 years have regular daily consumption of sugar-sweetened beverages [4,5].

To address this issue, various programs and interventions have been implemented. Nutrition literacy interventions combined with behavior change communication interventions in a school-based setting have shown to be promising for improving BMI and reducing unhealthy food choices. The school environment has been identified as a strategic channel for health promotion among school-age adolescents [6,7]. However, certain gaps have been identified that explain why health and nutrition programs in school settings in Indonesia have not been as effective as desired. Some schools encountered competing priorities in supporting the program, such as a lack of teachers and time due to teaching constraints. Additionally, 21% of adolescents were not going to school, compounded by insufficient parental support [8,9].

Telehealth is an alternative method for increasing access to adolescents, as the target population, and their parents. A previous systematic review revealed that there is great potential in digital platforms for universal health promotion, especially among school-age children and adolescents [10]. Digital nutrition literacy combined with a behaviour change program delivered via a telehealth platform could be a promising solution to bridge the gap. The International Organization for Standardization defines telehealth intervention for children as "the use of telecommunication techniques for the purpose of providing telemedicine, medical education, and health education over a distance" [11]. A review was carried out to assess the use of digital health interventions, such as websites, short-text messages, gamification, social media, and multidigital component interventions, aimed at improving adolescent diet and physical activity. The review revealed that website interventions can influence behavior change in adolescent diet and physical activity. However, due to variability in engagement, these changes often are not sustained in the medium or long term [12]. Meanwhile, there is less evidence supporting the effectiveness of other digital platforms, such as apps, text messages, and social media [12].

During and after the COVID-19 pandemic, there has been an increase in evidence supporting the impact of telehealth interventions in improving health [13,14]. This medium provides more engagement features compared to other forms of digital intervention. Therefore, a systematic review is required to address the following:

- Synthesize the evidence on the effectiveness of telenutrition in improving dietary behavior and physical activity in adolescents with obesity.
- Identify specific intervention components that characterize the more successful telenutrition intervention, particularly in adolescent populations.

Methods

Overview

We will use the population, intervention, comparator, and outcome (PICO) framework to identify appropriate Medical Subject Headings (MeSH) terms for the literature search. Meanwhile, the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) 2015 guideline will be used as the standard reporting protocol guideline checklist. The PRISMA-P 2015 guideline will aid in describing the rationale, hypothesis, and planned methods of the review [15]. The checklist is provided in Multimedia Appendix 1.

This systematic review will comprise a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis. The protocol of this systematic review was prospectively registered on PROSPERO (CRD42023458336).

Eligibility Criteria

The PICO framework presented in Table 1 is derived from the research questions previously mentioned.

Table 1. The eligibility criteria based on the population, intervention, comparator, and outcome (PICO) framework.

Criteria	Detailed information
Population	Adolescents or young adults aged 13-18 years with overweight or obesity.
Intervention	Any digital health promotion intervention with any type of telehealth (including but not limited to either educational or personalized feedback or monitoring services).
Comparator	Other digital health promotion interventions delivered by other methods, such as social media, websites, and short-text messengers or studies with control groups without an intervention.
Outcomes	Healthy behavior and nutritional outcome, such as changes in dietary behavior, physical activity level, and BMI.

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Search Strategy

We will search the following databases: Science Direct, PubMed, Cochrane, Embase, JMIR, ProQuest, and Google Scholar. Key terms relating to telehealth and telenutrition were extracted from an initial review of the literature. Specific search terms, such as "obesity," "adolescent," "dietary behaviors," and "physical activity," were identified in a preliminary scan of the literature and chosen in consultation with a medical librarian. Search terms will include MeSH terms and related keywords and are grouped into 3 themes presented in Table 2. All the MeSH terms and Keywords are included in Table 2 with the following structure: Obesity (MeSH OR keywords) AND Adolescent (MeSH OR keywords) AND Telenutrition (MeSH OR keywords). To broaden the scope of the article collection, we will not limit the publication period or language of publication in our search strategy. In addition to exploring these databases, a manual search will be performed to identify the reference lists of included studies. Authors of conference and poster abstracts selected for inclusion will be contacted to see if a full text is available to be included.

Table 2. Search terms.

Number	Category	MeSH[a] terms and keywords in titles or abstracts
1	Obesity	"Obesity"[Mesh] OR "Pediatric Obesity"[Mesh] OR "overweight"[MeSH Terms] OR "overweight"[All Fields]
2	Adolescent	("Adolescent" OR "Adolescent Behavior" OR "Adolescent Health" OR adolesce*)
3	Telenutrition	("Telenutrition" OR "Mobile Health" OR "mHealth" OR "Telehealth" OR "eHealth" OR "Short Message Service" OR "SMS" OR "Text Messag*" OR "cell phone" OR "telephone" OR "smartphone" OR "cellular" OR "mobile" OR "social media" OR "social network")
4	All categories	1 AND 2 AND 3

[a]MeSH: Medical Subject Headings.

Inclusion Criteria

Only human intervention studies, either quasi-experimental studies or randomized controlled trials, will be included in this review. This review will evaluate original research articles using digital health promotion interventions delivered via any type of telehealth and involving adolescents aged 13-18 years with overweight or obesity. Overweight and obesity among adolescents aged 5-19 years are defined by their BMI per age *z* score, as outlined in the World Health Organization growth chart references [16]. We will include any study that categorizes participants with a BMI per age *z* score >1 SD as overweight and those with a BMI >2 SD as obese.

Exclusion Criteria

The review focused mainly on the changes in healthy behaviors and nutritional outcomes, including dietary behavior, physical activity levels, and BMI. Any outcomes other than these will be excluded from our review. In addition, articles for which full texts cannot be obtained despite requests to the corresponding authors will be excluded.

Screening and Article Selection

All articles found through database searches will be saved in the citation and article management software Mendeley and Rayyan AI, which will be used to eliminate duplicates and screening. The titles and abstracts of all studies will be reviewed independently by 2 reviewers. Studies that do not meet the eligibility criteria will be excluded, and any disagreements will be discussed until a consensus is reached. The full text of the remaining studies will then be examined by 2 reviewers independently to determine final eligibility, with any disagreements resolved by a third and fourth reviewer. A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be replicated.

Data Extraction and Management

One reviewer will read the full text of all the papers included in the final selection to extract the predetermined outcomes, which will be validated by a second reviewer. The outcomes will be extracted into a standard extraction form, which will be designed in Covidence (Veritas Health Innovation). The detailed extraction custom-built form is summarized in Table 3. Disagreements will be resolved through discussion, and if consensus cannot be reached, a third and fourth reviewer will be consulted. Missing data will be considered in the risk of bias assessment, but due to time constraints, authors will not be contacted.

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Table 3. Summary of the data extraction template.

Information	Detail extraction
General study information	• Year of publication • Study setting (including the time frame before or after the COVID-19 pandemic, if available) • Analyzing the sample size • Sample demographics (including age, gender, and target population) • Intervention design information (including type, duration, and follow-up periods, if any)
Behavioral and nutrition literacy intervention	• Target health behaviors and intervention focus • Theory of the intervention • Behavior change technique
Telehealth and telenutrition	• Area of health care used • Name of the platform • Developers • Media platform • Design process or steps • Component and design features (ie, gamification, families' involvement, and SMS reminder)
Evaluation	• The outcomes measured • Any kind of effectiveness measurement • Participant health outcomes • Participant engagement or adherence rates (including participation or drop-out rates) • Feasibility and usability • Challenges and limitations (including ethical concerns and barriers during the experiment)

Quality Appraisal and Risk of Bias Assessment

Following the final selection of studies, 2 reviewers will independently assess the risk of bias in all papers included in the final selection. If there is a disagreement in judgment, the reviewers will discuss it before consulting the third and fourth reviewers. The Cochrane Collaboration Risk of Bias tool will be used to assess the randomized controlled trials included in the review and assign low, unclear, or high risk to the studies for each of the potential biases [17]. Studies will be classified as low risk if the identified bias is unlikely to significantly alter the results, and they are classified as high risk if the bias clearly has the potential to significantly alter the results. Unclear risk occurs when the bias imposes some doubt on the outcome. The risk of bias assessment will cover 6 domains: selection, performance, detection, attrition, reporting, and other bias [17].

Meanwhile, ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) will be used for evaluating the risk of bias in estimates of the comparative effectiveness of interventions from studies that did not use randomization to allocate units to comparison groups [18]. A table will be created that summarizes the quality of all included studies.

Data Analysis and Synthesis

A meta-analysis is unlikely to be conducted due to the expected diversity of study aims, methods, and reported outcomes. As a result, we will conduct a descriptive analysis to summarize the extracted data. Each outcome will be coded as having no (0), some (+), or significant evidence (++) of effectiveness in both outcomes. Significant evidence will be coded only when the intervention (ie, nutritional literacy and behavior change communication via telehealth delivery) outperforms a comparator or control. The intervention will be considered to have some evidence of effectiveness if there is a significant difference over time but not between groups or a significant improvement in only a subgroup of the population. Studies will be grouped by target health behavior (eg, dietary pattern only, physical activity only, or both) and analyzed together to describe the effectiveness of telehealth or telenutrition interventions in general for both those target behaviors; in particular, the analysis will focus on either dietary pattern or physical activity. The discussion will synthesize the data to describe specific intervention components that characterize a successful telenutrition intervention, such as the type of digital platform, engagement features, theory, method, and behavior change strategy used. The theory, method, and behavior change strategy will be analyzed and presented based on the intervention mapping approach and its taxonomy, as described by Bartholomew et al [19] and Kok et al [20]. Furthermore, the information regarding the identified barriers and challenges of telehealth interventions will be summarized to give directions for future research and development.

Ethical Considerations

There will be no involvement from patients or the public in this study. This study synthesizes data from studies that were already peer reviewed and published. Thus, no ethical approval will be required.

Results

The systematic review is expected to be completed by the end of March 2024. The ongoing review and data extraction of the articles is currently being conducted. The findings of this study will be outlined in the following subsections: (1) study selection,

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(2) study characteristics, (3) synthesis of results (behavior change strategy and method or telehealth development and intervention), as well as (4) impact and evaluation, including challenges and barriers of study implementation.

Discussion

A systematic and transparent review of the literature will provide a better understanding of the current state-of-the-art telehealth or telenutrition approaches, how they are used, and their effectiveness. Strengths, limitations, and implications for the interaction of technology and behavioral health management will help inform and improve the development, acceptability, and effectiveness of future telehealth approaches in managing adolescent obesity for clinicians, telehealth providers, and relevant stakeholders. Based on the data, we will outline the conclusions, the strengths and limitations of our systematic review, and important directions for future research. Telehealth has grown over the past decade, with its popularity increasing during the COVID-19 pandemic. In addition, our review aims to differentiate findings between before and after the COVID-19 pandemic, if possible. Furthermore, the findings will be interpreted carefully, taking into consideration the potential scalability to other areas or countries with similar contexts. Our study has some potential limitations due to limited resources; we were unable to conduct manual searching and identification of reference lists of included studies. The review also could not provide a clear effect estimate between the telehealth intervention and health outcomes, as a meta-analysis could not be conducted.

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Authors' Contributions

MRA and FSTD conceived the study topic and designed the review protocol. MRA and NK performed article screening, reviewed by AAPP and FSTD. MRA prepared the first draft of the protocol, and revisions were made by NK, AAPP, and FSTD. The manuscript was submitted after all authors reviewed and agreed to it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 150 KB - resprot_v13i1e53282_app1.pdf]

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Abbreviations

MeSH: Medical Subject Heading
PICO: population, intervention, comparator, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions

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Protocol

Patients' Experiences of Digital Health Interventions for the Self-Management of Chronic Pain: Protocol for a Systematic Review and Thematic Synthesis

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Abstract

Background: Chronic pain is a highly prevalent condition that requires multidisciplinary treatment. However, in the United Kingdom, access to specialist pain clinics where patients can receive medical multidisciplinary treatment is limited, and provision varies between health boards. As such, self-management of chronic pain using digital tools has been gaining traction recently, but evidence of its effectiveness from clinical-based trials focuses mainly on quantitative outcomes.

Objective: This systematic review aims to identify, appraise, and synthesize qualitative evidence on patients' experiences with digital health interventions (DHIs) for the management of chronic pain.

Methods: This systematic review will consider qualitative and mixed methods studies that explore the experience of patients (aged 18 years and older) with chronic pain engaging in DHIs to manage their pain. MEDLINE Ovid, PubMed, Embase, CINAHL, PsycINFO, and Scopus databases will be searched for published studies. The systematic review will be conducted in accordance with the ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) guidelines. Following the 3-step thematic synthesis methodology of Thomas and Harden, titles and abstracts will be screened by 2 independent reviewers (AM and HM), and a third reviewer (MI or FM) will resolve any conflict that arises before the full-text screening. The Critical Appraisal Skills Programme checklist tool will be used to critically appraise the included studies. The extracted data will be imported to NVivo (QSR International), where thematic synthesis will be used to derive analytical themes from the included studies.

Results: Themes that encapsulate the patient experience will be identified from qualitative evidence, and these themes will shed light on the perceived benefits and disadvantages, usability, acceptability, and the overall impact digital tools can have on the lives of those with chronic pain.

Conclusions: This systematic review will identify, appraise, and synthesize the overall experience of patients engaging in DHI to manage a diverse range of chronic pain conditions. By elaborating the patient experience through qualitative analysis, the findings from this review will enhance our current understanding of the experiences of patients with chronic pain using digital tools for the self-management of their pain and highlight what person-centered elements are essential for future DHI development.

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KEYWORDS

chronic pain; digital health; digital tool; digital health intervention; mHealth; eHealth; pain-management; person-centered; experience; protocol; patients' experiences; patient experiences; self-management; systematic review; thematic synthesis; protocol.

Introduction

Background

Chronic pain is a major public health condition affecting more than 30% of the world's population [1]. Defined as pain that persists beyond the expected recovery period of 12 weeks [2], chronic pain is a complex phenomenon, and the root causes are only partially understood [3]. Following recent developments, the *International Classification of Diseases* has adapted its definition of chronic pain to encompass both primary and secondary chronic pain. Chronic secondary pain is initially regarded as a symptom caused by an underlying condition or disease (such as cancer, rheumatoid arthritis, or endometriosis), whereas in chronic primary pain, pain emerges without any history of an injury or operation (eg, fibromyalgia, headache, and musculoskeletal pain) [2].

Chronic pain is a complex condition pertaining to biological, psychological, and social components [4]. A UK-based population study found that of 28 million adults affected by chronic pain, around 12% of people described their pain to be moderately or severely disabling [5]. In addition to the physical burden, psychological challenges are frequently associated with chronic pain with many individuals reporting a significantly deteriorated quality of life [6]. Chronic pain can also have a considerable socioeconomic impact, with pain impacting work effectiveness, which in many cases leads to unemployment [7].

To successfully manage the multifaceted nature of chronic pain, a multidisciplinary treatment approach is required. Substantial evidence supports that combining approaches across disciplines is the most effective treatment in addressing the biopsychosocial nature of chronic pain [8-12], although access to evidence-based multidisciplinary treatment is not always readily available [13]. Many patients with chronic pain rely on their general practitioner for advice [14], and those who do get referred to specialist pain clinics can wait months to years for assessment and treatment [13].

A means of overcoming the barriers of accessibility to multidisciplinary health care could be the delivery of self-management strategies using digital tools, which have become more prevalent than ever since the COVID-19 pandemic. Digitization has transformed the health care landscape by offering more accessible alternatives to conventional medical treatment [15]. Digital health interventions (DHIs) use a range of digital tools, such as smartphone apps, websites, and social media campaigns, to deliver self-management programs remotely [16]. Self-management strategies for chronic pain management include symptom tracking, physical activity, education, relaxation techniques, and cognitive behavioral therapy [17-20]. According to the Office of National Statistics, approximately 90% of private UK households have computers and mobile phones in 2022; therefore, digital health is accessible to almost everyone [21].

Research regarding the impact of digital tools has grown exponentially in recent years. A number of systematic reviews have evaluated the effectiveness of digital tools in areas such as chronic pain in general [16,22], specific chronic pain conditions [23,24], the impact of individual modalities such as smartphones [25,26], and specific age groups [27]. It is widely considered that such tools are effective in improving clinical outcomes such as pain intensity, pain interference, and improvements in quality of life [28].

Although there is substantial evidence on the positive effect digital tools can have on chronic pain patients' symptoms, most research focuses on quantitative outcomes. Quantitative research is essential in supporting evidence-based practice, which emphasizes findings from well-designed research to provide high-quality patient care [29]. However, it has been argued that quantitative evidence from clinical trials does not take into account patients' individual experiences, thus overlooking the complex nature of chronic pain [30]. In response to standard evidence-based practice, there has been a shift to person-centered care, which has transformed the health care system. Person-centered care was first described as "understanding the patient as a unique human being" [31], where the sole focus is on the individual, and treatment can be tailored to a patient's needs. The World Health Organization (WHO) guidelines advise person-centered care as a core element of good quality health care [2], and studies have shown that person-centered care significantly improves clinical outcomes [32].

A systematic review of qualitative studies by Fernandes et al [33] evaluated enablers and barriers to telehealth interventions for individuals with musculoskeletal pain, and Svendsen et al [34] explored engagement strategies, facilitators, and barriers to the use of DHIs for low back pain management. However, both qualitative reviews focus on barriers and facilitators to DHI engagement rather than overall patient experience, and both studies target a specific condition as opposed to a diverse range of chronic pain conditions. Despite the abundance of qualitative literature exploring the experiences of patients with chronic pain with DHIs, the evidence that encapsulates the experience as a whole has yet to be synthesized.

To address this gap in the research, this review will identify, appraise, and synthesize qualitative data, through a thematic synthesis approach, to provide a detailed account of how patients with chronic pain experience DHIs, and if and why they experience changes and improvements in patient-reported outcomes. Thematic synthesis was developed to address questions concerning intervention need, appropriateness, and acceptability and can produce results that have the potential to inform the design and practice of interventions [35]. Descriptive explanations of patients with chronic pain views could uncover a better understanding of DHI lived experiences from the point of view of the end user—for whom the treatment is designed. Therefore, the findings from this review could have the potential

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to enhance our understanding of how DHIs impact patients with chronic pain and emphasize what patient-centered aspects are important for future DHI development.

Objectives

This review aims to identify, appraise, and synthesize existing qualitative evidence on patients' experiences with a DHI for the self-management of chronic pain.

Methods

Overview

The proposed review will be conducted in accordance with "ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) guidelines [36].

Search Strategy

The search strategy and eligibility criteria will be based on the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation and Research) framework [37]. This framework was deemed the most suitable for answering the research question as it has been adapted for clarity in nonquantitative research by outlining key characteristics of qualitative research questions [37].

Keywords used in the search strategy adhere to each of the key characteristics of the SPIDER framework. These include chronic pain as the sample ("fibromyalgia" and "rheumatoid arthritis"), DHIs as the phenomenon of interest ("mHealth" and "telemedicine"), qualitative methods as the design and research type ("qualitative" and "thematic analysis"), and patient experience as the evaluated outcomes ("patient satisfaction" and "patient attitudes").

The search strategy will involve an initial search of electronic databases, followed by the analysis of keywords in the titles and abstracts of each database search. The search will then continue to the reference lists of selected articles to identify additional studies not located through the electronic database search. The strategy will aim to locate published articles—gray literature and unpublished articles will be excluded from the review. Due to the rapidly evolving nature of digital technology, the search will be limited to articles published within the last 10 years in order to capture the most relevant literature (2013-2023). The search will also be limited to articles published in the English language. The search strategy will be adapted for each electronic database. A detailed search strategy for each database is presented in Multimedia Appendix 1.

Information Sources

A literature search for qualitative and mixed methods studies will be conducted on the following electronic databases: Embase, MEDLINE, PubMed, CINAHL, PsycINFO, and Scopus. These databases have been chosen as they encompass nursing, medicine, social sciences, and psychology literature, which are deemed the most appropriate for answering the research question concerning patient experience and chronic pain.

Eligibility Criteria

Inclusion criteria will follow the SPIDER [37] framework. Textbox 1 shows the list of inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria based on the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation and Research) framework.

Inclusion criteria

- Papers reporting on participants (aged ≥18 years old) with a diagnosis of chronic pain
- Papers that report on digital health interventions to deliver self-management strategies for chronic pain
- Qualitative studies and mixed methods studies with a qualitative component
- Papers that report on patient experience of participating in a digital health intervention through qualitative data
- Papers published in the English language

Exclusion criteria

- Papers reporting on participants <18 years old
- Papers that have not specified that the participants have a chronic pain diagnosis
- Papers that include participants with chronic pain that does not exceed 12 weeks
- Papers that report on digital health interventions that incorporate external involvement
- Quantitative studies, quantitative components from mixed methods studies, gray literature, protocols, dissertations, and other reviews
- Papers that report data from participants who did not actively participate in the intervention
- Papers published in a language other than English

Sample

The review will include studies that involve patients older than age of 18 years with a diagnosis of chronic pain, who have participated in a DHI that delivered self-management strategies. Studies exploring the experience of children, adolescents, clinicians, or health professionals will be excluded. The definition of chronic pain will be aligned with the revised *International Classification of Diseases, 11th Revision* classification: pain that persists or recurs for more than 3 months [2], including both primary and secondary chronic pain. The included conditions are based on the National Institute for Health

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and Care Excellence guidelines for assessing and managing both primary and secondary chronic pain [3].

Phenomenon of Interest

The phenomenon of interest explored in this review will be DHIs that deliver self-management strategies for chronic pain. Digital interventions regardless of platform (eg, telephone, web-based smartphone app, and social media) or self-management strategy (eg, exercise, education, relaxation, and meditation) will be included. Due to the terminological inconsistency existent in the current literature, the review will not distinguish among telehealth, telemedicine, eHealth, mobile health, or other similar terms. This review will use the term "digital health" to encompass all related terms.

Design and Research Type

The review will consider studies that explore patients' experiences of participating in a DHI. Qualitative data regarding patient experience collected through surveys, questionnaires, focus groups, group and individual interviews, and observational data will be examined, and this may have been collected remotely or face-to-face or in a group or one-to-one setting. Mixed methods studies with a qualitative component will be included; the quantitative data from these studies will not be used in this review. Protocols, dissertations, gray literature, and other reviews will be excluded.

Evaluated Outcomes

The outcome evaluated in this review will be patients' experiences of participating in DHIs. This will be in the form of qualitative data collected via questionnaires, focus groups, surveys, observational data, and interviews. Patients must have participated in the intervention either entirely or partially, for example, patients who started a digital intervention and followed through until completion, and patients who started a digital intervention and did not complete it in its entirety. Studies exploring patients' opinions or perceptions of what an intervention should involve without active participation will be excluded.

Data Extraction

Articles identified from the database search will be uploaded to EndNote (version 20; Clarivate), and any duplicates will be removed. Two independent reviewers (AM and HM) will then screen the titles and abstracts in Rayyan for papers that meet the inclusion criteria. The data extracted will adhere to the SPIDER tool, specifically outlining the sample, phenomenon of interest, and outcomes of significance to the objective of this review [37]. Any uncertainty between reviewers will be resolved by discussion, and if necessary, a third reviewer (MI or FM) will be requested to resolve any disagreements that persist. This process will be repeated for the papers included for full-text screening. Subsequently, the remaining papers will be included in the review. Each paper will be uploaded to NVivo (version 12) as this will facilitate the researcher's ability to perform data synthesis systematically and rigorously. The full data extraction table will include the author, year of publication, country design, data collection method, participant characteristics, type and description of the intervention, and potential themes.

Strategy for Data Synthesis

The results and discussion section of each included paper will be imported verbatim to NVivo, where a 3-step thematic synthesis approach based on the methodology described by Thomas and Harden will be used [38].

1. The first step will involve line-by-line coding of the results and discussion sections to identify contextual information on patient experiences with DHIs for the self-management of chronic pain.
2. Subsequently, similarly coded data will be clustered together to generate "descriptive themes." Descriptive themes will be based on verbatim data from the selected studies. Reviewers will reassess these codes to ensure the data are captured accurately.
3. Consequently, using inductive reasoning to make inferences from previous codes, reviewers will identify "analytical themes" about the experiences captured in the descriptive themes. These themes will be relevant to the key aim of this meta-synthesis. These themes are comprised based on inferences made from the data and, therefore, will be conducted independently by 1 reviewer (AM).

Risk of Bias or Critical Appraisal for Included Studies

The Critical Appraisal Skills Programme (CASP) checklist tool will be used to assess the methodological quality of the included studies. The CASP tool was deemed appropriate for the context of this review as it is endorsed by Cochrane and the WHO [39] and is the most frequently used tool for quality appraisal in health-related qualitative evidence syntheses [40]. Two reviewers (AM and HM) will assess the quality of the included papers independently, and any discrepancies that arise between reviewers will be resolved through discussion. If an agreement is not met, an additional reviewer (MI or FM) will be consulted until a consensus has been reached.

Ethical Considerations

Ethical approval is not required for conducting the systematic review as the research does not directly involve human participants or access to personal or identifiable data. The findings from this review will be disseminated to a broad range of stakeholders, including academics, clinicians, and policy makers. The findings will also be published in accredited peer-reviewed journals. This protocol is part of a larger PhD project; therefore, the findings will also be included as part of the thesis.

Results

This review will synthesize qualitative literature on patients' experiences of participating in a DHI for the self-management of chronic pain. Using thematic synthesis, an adapted version of Braun and Clark's thematic analysis developed for the purpose of secondary data synthesis [38,41], analytical themes will be derived from the included studies. We anticipate that the results from this review will characterize the patient experience of DHIs for the self-management of chronic pain and explain the impact digital tools have on the lives of those with chronic pain. These findings will emphasize what patient-centered aspects are essential for future DHI

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development, such as how they engaged with DHIs, perceived advantages and disadvantages, which aspects of DHIs they felt worked well and which could be improved, and insights on acceptability and usability. Evidence-based practice emphasizes evidence from well-designed research. However, it has been argued that this approach does not value individual experience and subsequently does not effectively represent the complexity of the chronic pain experience [38]. The results of this qualitative systematic review will enhance our understanding of the way patients experience DHIs for the self-management of chronic pain by emphasizing individual experience from a person-centered approach.

Discussion

Principal Findings

Previous systematic reviews have demonstrated the effectiveness of DHIs in improving patients' outcomes across various health conditions, including chronic pain in general [16,22] as well as specific chronic pain conditions like musculoskeletal pain [23]. However, there is a lack of research evaluating qualitative studies that explore how patients with chronic pain experience such improvements in DHIs. A qualitative exploration of experiences has the potential to generate an in-depth, representative, conceptual understanding of how patients exhibit such improvements in outcomes. Themes that characterize the patient experience of participating in DHIs for the self-management of chronic pain will be identified to capsulate the impact DHIs have on individuals living with chronic pain.

Strengths and Limitations

The comprehensive systematic approach to the current review is a major strength of this research. The search strategy and inclusion criteria are based on SPIDER, a framework adapted for clarity in qualitative research by defining crucial characteristics of qualitative research questions [37]. The search strategies for each database were developed with the help of 2 specialist librarians (see Multimedia Appendix 1), and search terms regarding chronic pain were taken from the National Institute for Health and Care Excellence guidelines for the management of chronic pain [3]. The review will be guided by the ENTREQ checklist to ensure a rigorous systematic approach is taken to synthesize the qualitative evidence [36]. The quality of included studies will be assessed using the CASP checklist tool, which has been endorsed by Cochrane and the WHO [39]. Following the 3-step thematic synthesis approach based on the methodology described by Thomas and Harden, extracted data will be reviewed by 2 independent researchers (AM and HM), and a third reviewer (MI or FM) will be consulted to resolve any issues that arise.

Limitations of this review include the exclusion of studies published in a language other than English, as well as gray literature, both of which could have valuable contributions to the research outcomes. Furthermore, although thematic synthesis is a powerful method that can draw overall conclusions on a specific topic, the raw data from each included study are not analyzed, which could undermine the richness of the data from each primary study.

Conclusions

This systematic review will be the first to synthesize the overall experience of patients engaging in DHIs to manage a diverse range of chronic pain conditions. The in-depth analysis provided by qualitative data will enhance our current knowledge, representing the point of view of the end user—for whom the digital interventions are designed to treat. By elaborating the patient experience through qualitative analysis, the findings from this review have the potential to inform the future development of DHIs by highlighting which person-centered aspects are crucial to effectively manage symptoms of chronic pain.

Acknowledgments

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Data Availability

Data sharing is not applicable to the current article as no data were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for each database.
[DOCX File , 17 KB - resprot_v13i1e52469_app1.docx]

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Abbreviations

CASP: Critical Appraisal Skills Programme
DHI: digital health intervention
ENTREQ: Enhancing Transparency in Reporting the Synthesis of Qualitative Research
SPIDER: Sample, Phenomenon of Interest, Design, Evaluation and Research
WHO: World Health Organization

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Protocol

AI as a Medical Device for Ophthalmic Imaging in Europe, Australia, and the United States: Protocol for a Systematic Scoping Review of Regulated Devices

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Abstract

Background: Artificial intelligence as a medical device (AIaMD) has the potential to transform many aspects of ophthalmic care, such as improving accuracy and speed of diagnosis, addressing capacity issues in high-volume areas such as screening, and detecting novel biomarkers of systemic disease in the eye (oculomics). In order to ensure that such tools are safe for the target population and achieve their intended purpose, it is important that these AIaMD have adequate clinical evaluation to support any regulatory decision. Currently, the evidential requirements for regulatory approval are less clear for AIaMD compared to more established interventions such as drugs or medical devices. There is therefore value in understanding the level of evidence that underpins AIaMD currently on the market, as a step toward identifying what the best practices might be in this area. In this systematic scoping review, we will focus on AIaMD that contributes to clinical decision-making (relating to screening, diagnosis, prognosis, and treatment) in the context of ophthalmic imaging.

Objective: This study aims to identify regulator-approved AIaMD for ophthalmic imaging in Europe, Australia, and the United States; report the characteristics of these devices and their regulatory approvals; and report the available evidence underpinning these AIaMD.

Methods: The Food and Drug Administration (United States), the Australian Register of Therapeutic Goods (Australia), the Medicines and Healthcare products Regulatory Agency (United Kingdom), and the European Database on Medical Devices (European Union) regulatory databases will be searched for ophthalmic imaging AIaMD through a snowballing approach. PubMed and clinical trial registries will be systematically searched, and manufacturers will be directly contacted for studies investigating

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the effectiveness of eligible AIaMD. Preliminary regulatory database searches, evidence searches, screening, data extraction, and methodological quality assessment will be undertaken by 2 independent review authors and arbitrated by a third at each stage of the process.

Results: Preliminary searches were conducted in February 2023. Data extraction, data synthesis, and assessment of methodological quality commenced in October 2023. The review is on track to be completed and submitted for peer review by April 2024.

Conclusions: This systematic review will provide greater clarity on ophthalmic imaging AIaMD that have achieved regulatory approval as well as the evidence that underpins them. This should help adopters understand the range of tools available and whether they can be safely incorporated into their clinical workflow, and it should also support developers in navigating regulatory approval more efficiently.

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KEYWORDS

AIaMD; artificial intelligence as a medical device; artificial intelligence; deep learning; machine learning; ophthalmic imaging; regulatory approval

Introduction

Overview

There is a growing capacity-demand mismatch within ophthalmology, increasing the risk of sight loss from treatment delays [1,2]. Artificial intelligence (AI) has the potential to help address these challenges. AI's strength lies in its ability to produce high-throughput analyses and glean meaningful insights from complex multimodal and multidimensional data sets through pattern recognition. This is well aligned with ophthalmology services, where disease diagnosis and management depend heavily on multimodal imaging [3]. AI therefore has the potential to help improve speed and access to care at reduced costs.

However, despite the exponential increase in the number of AI as a medical device (AIaMD) being developed and receiving regulatory approval, relatively few have been seamlessly integrated into routine clinical practice [4-6]. This so-called "AI chasm" limits the deployment of AIaMD to achieve patient benefit at scale [7]. This AI chasm results from a wide range of interdependent factors at the policy, organizational, and individual levels [8-13]. Key elements include ensuring adequate clinical evaluation to support regulatory decisions, such that the evidence base underpinning such tools is aligned with their intended use and is safe for the target population, and also clarifying how these regulatory requirements align with commissioners' needs.

The evidential requirements for software (including AIaMD) may be more ambiguous compared to more established interventions, making it more difficult for AI developers to explicitly understand the nature and extent of evidence they need to generate to gain regulatory approval. Attempts to study regulator approved AIaMD are impeded by the usability of public databases as well as the private nature of much of the information submitted by applicants, making it difficult for researchers, clinicians, or commissioners attempting to understand the evidence underpinning approved AIaMD. A review of Food and Drug Administration (FDA) approvals in the United States found that few submissions included comparisons between AI and human performance and that only a small proportion reported prospective data [14]. The reporting of sample size and number of sites in the validation studies was generally poor. The review did not assess whether participant characteristics such as gender and ethnicity were reported. Although guidelines for performing and presenting AI studies have been developed [15-18], there is no clear "best practice" for providers to ensure the safety and effectiveness of the AIaMD they adopt [14].

Review Objectives

This scoping review will focus on AIaMD that contributes to clinical decision-making (relating to screening, diagnosis, prognosis, and treatment) using ophthalmic imaging as an input. The aim is to identify and characterize AIaMD for ophthalmic imaging, which have received regulatory approval in 4 countries with established regulatory pathways for clinical use, in order to support providers in procurement decisions and developers in generating evidence to support applications to regulators.

The objectives are as follows:

1. To identify regulator-approved AIaMD for ophthalmic imaging in Europe, Australia, and the United States
2. To report the characteristics of those AIaMD and the regulatory approvals granted to them
3. To report the available evidence for the effectiveness and efficacy of approved AIaMD

Methods

Protocol Registration and Reporting

The protocol and subsequent review will adhere to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [19] and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [20] reporting guidelines, respectively (note that PRISMA-AI [21] is still in development). The protocol was registered with the Open Science Framework's website.

Eligibility Criteria

This review will focus on AIaMD for ophthalmic imaging that helps inform clinical management. All AIaMD for ophthalmic

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imaging where the AIaMD or its manufacturer are recorded in the US FDA, Medicines and Healthcare products Regulatory Agency (MHRA), European Database on Medical Devices (EUDAMED), or Australian Register of Therapeutic Goods (ARTG) databases will be included. All 4 countries are members of the International Medical Regulators Device Forum and have a track record of admitting AIaMD to their markets. No restrictions will be placed on the type of ophthalmic imaging modality involved or the intended use of the AIaMD.

The AIaMD will have a partial or fully data-led mechanism (eg, regression modeling, random forest, or convolutional neural networks). Any AIaMD that exclusively uses rule-based mechanisms (eg, a priori decision trees, best practice alerts, and normal or abnormal threshold alerts) will be excluded.

With regard to the evidence underpinning each AIaMD, only original research that comprises a clinical evaluation of the AIaMD in human participants will be included. This may include randomized controlled trials or prospective or retrospective observational studies. Systematic reviews and meta-analyses, case series, case reports, commentaries, and expert opinions will not be eligible. No date or language restrictions will be applied to the electronic search.

Search Strategy and Sources of Information

To identify potentially eligible AIaMD, the FDA (United States), ARTG (Australia), MHRA (United Kingdom), and EUDAMED (European Union) regulatory databases will be searched through a snowballing approach [22]. This will involve an exhaustive review of the product class codes and predicate devices (if applicable) with which each known eligible device is associated. This strategy has been adopted due to limitations in the search functionality of these databases. No AI tools will be used to assist the search.

The snowball search will commence with a list of 15 AIaMD for ophthalmic imaging (Textbox 1). This represents the sum of the authors' awareness of regulated products and a pragmatic search of relevant academic literature [23].

Textbox 1. Initial list of ophthalmic imaging artificial intelligence as a medical device (AIaMD) used in snowball search.

Ophthalmic imaging AIaMD

- LumineticsCore (previously known as IDx-DR), Digital Diagnostics
- Eyeart, Eyenuk Inc
- RetmarkerDR, Retmarker SA
- SELENA+, eyRIS Pte Ltd
- Automated Retinal Disease Assessment, Verily Life Sciences
- Medios AI, Remidio
- OphtAI, Evolucare, ACDIS
- RetCAD, Thirona Retina B.V.
- DeepDee AI, DeepDee
- MONA DR, MONA
- Eyetelligence, Eyetelligence Pty Ltd
- CARA, Diagnos
- RetinaLyze, RetinaLyze System A/S (Ltd)

Next, PubMed, ClinicalTrials.gov, and the International Clinical Trials Registry Platform will be systematically searched for each eligible AIaMD and its manufacturer by combining both search terms with an "OR" Boolean operator. These searches will be limited to relevant ophthalmology-specific studies using relevant key terms such as "retin*" for AIaMD relating to diabetic retinopathy screening.

In addition, manufacturers' websites will also be reviewed for any peer-reviewed publications. The manufacturers of all eligible AIaMD will be contacted directly for clarification and as an additional source of peer-reviewed publications and ongoing studies. A preliminary scoping search highlighted that not all studies mention the AI device name or manufacturer, and some devices undergo a name change from one version to the next. Hence, this additional search will ensure that the data captured are as comprehensive as possible.

Study Selection

Two authors will search the regulatory databases independently. They will come to a consensus decision about the eligibility of any AIaMD identified. Any unresolved disagreements will be arbitrated by a third author. There may be instances where an AIaMD's eligibility or its regulatory approval status cannot be determined with publicly available evidence, as eligible devices may use proprietary AI that is kept confidential. If this is the case, correspondence with the manufacturer will be undertaken to seek clarification. If further clarification is not possible, the ambiguity about the AIaMD's eligibility and the rationale for including or excluding it will be recorded.

The search for evidence will be undertaken by an independent author. After deduplication, the titles and abstracts will be independently screened by 2 authors to assess their relevance to the eligible AIaMD. Discrepancies will be resolved by discussion and by arbitration with an additional author if

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necessary. The full texts will be screened, and a further round of arbitration will take place as needed.

Data Extraction

Data extraction will be undertaken in 2 phases, using standardized data extraction forms designed and piloted for the purposes of this review.

Phase 1

The characteristics of each eligible AIaMD for ophthalmic imaging with regulatory approval in Europe, Australia, and the United States at the time of the search will be obtained. Where available, this will include:

1. Type of regulator approval and date of approval
2. Class assigned under FDA, TGA, UK MDR (Medical Devices Regulations 2002) and/or EU MDR (Regulation (EU) 2017/745)
3. Intended use statement
4. Ophthalmic imaging modality
5. Model type and architecture (eg, deep learning with machine learning)
6. Recall indications on the regulatory databases, as available

Some AIaMD may be approved in 2 or more jurisdictions, and the data will be extracted accordingly. Google searches will be used to supplement data extraction if the required data are unavailable from the FDA, EUDAMED, MHRA, or ARTG databases.

Phase 2

Published evidence underpinning the effectiveness and efficacy of each eligible AIaMD will be obtained. The following data will be extracted from each included study:

1. Study characteristics: title, author name, publication status, funding source, conflicts of interest, and author affiliations with manufacturers
2. Study methodology: study duration, study design (randomized, prospective observational, and retrospective observational), etc
3. Validation: external validation, reference standards, and comparison between AI and humans
4. Data set or cohort details: source of data set, size of data set or number of participants, setting, number of countries, number of centers, and participant demographics (age, gender, and ethnicity)
5. Model performance: metrics including sensitivity, specificity, area under the curve, etc, with 95% CIs; clinical outcomes as described

Assessment of Methodological Quality

Two review authors will independently assess the methodological quality of each included clinical validation study. Appropriate quality assessment tools will be used for each study type, for example, the QUADAS-2 tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies [24], the Cochrane risk of bias-2 tool for randomized controlled trials [25], and the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) tool for nonrandomized studies [26]. QUADAS-AI (quality assessment tool for artificial intelligence-centered diagnostic test accuracy studies) [27] and PROBAST-AI (Prediction Model Risk of Bias Assessment Tool for Artificial Intelligence) [28] are under development at the time of writing but will be used where appropriate if available. Any disagreements will be resolved through discussion or by involving a third reviewer where consensus cannot be reached.

Data Synthesis

Study-Level Data

The extracted data will be synthesized using narrative and tabular approaches. A summary of the findings will be presented, using descriptive statistics to describe the characteristics of the included studies. For example, mean and SD will be used to describe continuous variables, while percentages will be used to describe proportions. If appropriate, a meta-analysis of AIaMD diagnostic accuracy will be considered, but this may not be feasible if there is significant heterogeneity in study methods and AI methodology.

AIaMD-Level Data

The data for each AIaMD will be synthesized to give an overview of the characteristics of its regulatory approval or approvals and its clinical validation studies, again through narrative and tabular approaches.

Ethical Considerations

Ethical approval is not required, as this is a protocol for a systematic scoping review. All relevant data have been published, and no primary or proprietary data will be collected. This decision has been verified with the Newcastle University Ethics Committee.

Results

Preliminary searches were conducted in February 2023, and screening is underway. Data extraction, data synthesis, and assessment of methodological quality commenced in October 2023. We anticipate that the scoping review will be completed and submitted for peer review by April 2024.

Discussion

This will be the first review to examine and synthesize evidence on AIaMD for ophthalmic imaging. The key aim is to better understand the landscape of AIaMD for ophthalmic imaging on the market and the level of evidence that supports their regulatory approval.

Strengths and Limitations

Due to the limited and variable functionality of regulatory databases, it was not possible to conduct searches with standard systematic review methodologies based on research databases. This has necessitated several design considerations. We have sought to minimize publication bias and improve the completeness of the search process by undertaking a snowballing approach informed by expert knowledge, in combination with a database search. This was necessitated by limitations in the search functionality of the regulatory databases, but we

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acknowledge that this approach facilitates the mitigation rather than the removal of these limitations. In addition, our PubMed search strategy may be hampered by incomplete reporting or no mention of the AI device's name or manufacturer. We have attempted to mitigate this by supplementing our search with reviewing manufacturers' websites, corresponding with manufacturers, and performing adjunct searches of major clinical trial registries in order to ensure that our search is as comprehensive as possible.

Strengths include the international scope of the review. We recognize that there may be differences in regulatory requirements across territories (and in the transparency of reporting of data supporting those applications) and have therefore included 4 major jurisdictions. We have also assembled an international team of authors with representation from the United States, Europe, and Australia to support the interpretation of the data. The inclusion of critical appraisal to identify any methodological variations or shortcomings of existing clinical validation studies is a further strength not common to previous regulatory reviews of AIaMDs, and will help guide any future improvements.

Conclusion

We describe the protocol for a systematic scoping review that seeks to map and examine AIaMD for ophthalmic imaging that has received regulatory approvals for commercial use. We anticipate that our findings may be of interest to ophthalmic professionals, AI model developers, health care commissioners, and policy makers, with the overall aim of improving transparency to help inform safe AIaMD implementation, thereby optimizing patient care.

Data Availability

Data sharing is not applicable to this article, which is a protocol for a scoping review, as no data sets were generated or analyzed.

Conflicts of Interest

HDJH is funded by the National Institute for Health Research through a doctoral fellowship award (NIHR301467) and is on the advisory board for Siloton, an optical coherence tomography imaging equipment manufacturer. PAK has received personal fees from AbbVie, Google Health, Roche, Apellis, Novartis, RetinAI, Bitfount, and nonfinancial support from Bayer outside the submitted work. The remaining authors do not have any conflicts of interest or financial disclosures to declare.

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Abbreviations

AI: artificial intelligence
AIaMD: artificial intelligence as a medical device
ARTG: Australian Register of Therapeutic Goods
EUDAMED: European Database on Medical Devices
FDA: Food and Drug Administration
MHRA: Medicines and Healthcare products Regulatory Agency
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROBAST-AI: Prediction Model Risk of Bias Assessment Tool for Artificial Intelligence
QUADAS-AI: quality assessment tool for artificial intelligence–centered diagnostic test accuracy studies

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ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions

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Protocol

Factors Underlying Vaccine Hesitancy and Their Mitigations in Saudi Arabia: Protocol for a Systematic Review

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Abstract

Background: Vaccine hesitancy is a growing concern in Saudi Arabia, impacting even well-educated parents. The decision-making process involves various factors such as accessibility, trustworthy information, and the influence of social networks, reflecting a complex interplay of emotional, cultural, social, spiritual, and political dimensions.

Objective: This review seeks to evaluate the prevalence and trends of vaccine hesitancy, identify contributing factors, and explore potential solutions to enhance immunization rates. This review aligns with global concerns, as the World Health Organization has identified vaccine hesitancy as a top global health threat.

Methods: Our systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria for comprehensive assessment. We will conduct a thorough search across various databases, encompassing a wide range of vaccines, and pay special attention to vaccination campaigns and refusals. Inclusion criteria involve descriptive, observational, and analytical studies focusing on factors influencing vaccine acceptance or hesitancy. The study will use the Crowe Critical Appraisal Tool for quality assessment and perform a narrative synthesis to summarize findings thematically.

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Results: This systematic review is expected to unveil the prevalence and trends of vaccine hesitancy in diverse populations in Saudi Arabia, shedding light on cultural, religious, and social factors contributing to hesitancy. It aims to assess the effectiveness of implemented strategies, enable regional and global comparisons, and provide implications for tailored vaccination policies. Additionally, the review may pinpoint research gaps, guiding future investigations to address and mitigate vaccine hesitancy effectively.

Conclusions: The findings are expected to have direct policy implications and guide interventions to strengthen vaccination programs and improve public health outcomes.

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KEYWORDS

acceptance; campaigns; effectiveness; factors; hesitancy; immunization rates; immunization; intervention; literature analysis; misinformation; mitigations; prevention; protocol; public health; review methodology; review methods; Saudi Arabia; search; searching; syntheses; synthesis; systematic review; systematic; vaccination; vaccine hesitancy; vaccine

Introduction

Vaccines have consistently proven to be among the safest and most effective methods for preventing a wide range of infectious diseases [1,2]. Despite the proven safety and effectiveness of vaccines, vaccine-preventable diseases continue to persist in various parts of the world. In recent years, there have been outbreaks of infectious diseases, even when effective vaccines are available to combat them. One significant contributing factor to this phenomenon is “vaccine hesitancy” [3,4]. Vaccine hesitancy is defined as a reluctance or delay in accepting or agreeing to receive vaccines, even when vaccination services are readily available. Vaccine hesitancy is a complex and multifaceted phenomenon influenced by a wide range of factors. These factors encompass cognitive, psychological, sociodemographic, political, and cultural elements, among others. Moreover, the specific factors contributing to vaccine hesitancy can vary significantly across different populations and communities [5]. The reasons for vaccine hesitancy are intricate and can vary over time, across different locations, and depending on the specific type of vaccine in question. Similarly, vaccine hesitancy arises from a multitude of factors, including religious beliefs, geographic barriers, the quality of the parent-provider relationship, concerns about adverse events of immunization, limited knowledge about vaccination, and perceptions of disease risk [6].

In 2019, the World Health Organization (WHO) identified vaccine hesitancy as one of the top 10 global health threats [7]. Vaccine hesitancy refers to the reluctance of certain individuals or communities to accept vaccines, and it poses a substantial challenge to public health efforts. This reluctance is influenced by various factors, including misinformation, distrust in health care systems, personal beliefs, and a perceived low risk of vaccine-preventable diseases [7,8]. Vaccine hesitancy is not a recent challenge in disease prevention. It has been a significant issue for years, and examples of it can be found in the context of seasonal influenza vaccination and the response to the 2009 H1N1 pandemic [9-11]. Recent research in the literature over the past decade has indicated a concerning trend: vaccine hesitancy appears to be on the rise among various populations, including health care workers [12,13]. According to Olive et al [14], a social movement opposing public health vaccines has been gaining traction in the United States. This movement, among various other factors, has played a role in the increasing percentage of the population in both the United States and Europe that is refusing vaccination efforts in recent years [14]. Vaccine hesitancy indeed poses a substantial challenge to public health experts as it leads to significantly reduced vaccination rates within populations. This challenge becomes even more critical in the context of combating infectious diseases [1]. According to a survey conducted by the WHO and UNICEF (United Nations Children’s Fund), vaccine hesitancy started to emerge as a significant concern approximately a decade ago [15]. This trend of vaccine hesitancy has been observed in several countries around the world, including the United Kingdom, the United States, and India [16,17]. Vaccine hesitancy across Gulf Cooperation Council countries varied between 11% and 71%, with notable discrepancies observed based on the type of vaccine, with the highest reported hesitancy recorded for the COVID-19 vaccine at 70.6% [18].

Vaccine hesitancy has also become a concern in Saudi Arabia. According to Alabbad et al [19], 17% of their study population expressed hesitance to receive the influenza vaccine. Additionally, Alsubaie et al [20] found that vaccine hesitancy among Saudi parents reached 20%. Even well-educated parents have the same behavior. Alzahrani and Alghamdi [21] reported a vaccine hesitancy rate 20%-27 % against COVID-19 immunization [21]. A study conducted by Thabit et al [22] determined that factors such as the convenience of receiving the vaccine, the availability of trustworthy information from authorities, and the positive influence of family and friends played significant roles in motivating the public to get vaccinated. Al-Mohaithef and Padhi [23] reported that concerns about vaccine safety (17%), worries about potential side effects (35%), and perceptions of receiving too many injections (28%) are critical factors contributing to vaccine hesitancy. Alaamri et al [24] conducted a cross-sectional study in Saudi Arabia, which stated that decision-making for vaccination is a multifaceted process that encompasses emotional, cultural, social, spiritual, and political dimensions. These various aspects can significantly influence an individual’s or a community’s choice regarding vaccination. In-depth literature analysis reveals the current absence of a systematic review on vaccine hesitancy factors specific to Saudi Arabia. This review aims to (1) assess

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the prevalence and trends of vaccine hesitancy, (2) identify factors contributing to vaccine hesitancy, and (3) explore potential solutions to enhance immunization rates.

These findings will be instrumental in shaping a comprehensive vaccination policy for Saudi Arabia.

Methods

Basic Strategy

This systematic review will adhere to the quality standards outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines [25,26] and will be structured according to the PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria for comprehensive and transparent reporting [27], as given in Textbox 1 and Table 1. Before conducting this review, the protocol will be submitted to PROSPERO (the International Prospective Register of Systematic Reviews) for approval [28,29].

A comprehensive search will be conducted across multiple databases, including Cochrane, PubMed (MEDLINE), Web of Science, Google Scholar, Scopus, Science Direct, and Springer Links, to identify peer-reviewed literature. The search will not be limited by a specific time period because no previous review on the factor has been conducted. If it is time-limited, there is a chance of missing some factor that may affect the prospective work. It will also encompass literature with search terms present in the title, abstract, and full text. Furthermore, the search will be restricted to publications available in the English language.

Textbox 1. Title and checklist items for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

Title

- Determine whether the report is categorized as a systematic review, a meta-analysis, or a combination of both.

Background: objectives

- The research inquiry encompasses elements such as comparators, interventions, outcomes, and participants.

Methods: eligibility criteria

- Criteria for inclusion are based on the characteristics of the study and the report.

Methods: sources of information

- The databases that were searched and the dates of those searches.

Methods: potential for bias

- Methods for evaluating the potential for bias in research studies.

Results: studies inclusion

- The quantity and nature of incorporated research studies, the participants involved, and pertinent attributes of these studies.

Results: report of findings

- Summary of primary results, ideally with a breakdown of the number of studies and participants for each outcome.

Results: description of the effect

- The direction of the impact (ie, which group benefits) and the magnitude of the effect expressed in terms that are meaningful to health care professionals and patients.

Discussion: limitations and strengths of available evidences

- Concise overview of the advantages and drawbacks of the evidence, including factors like inconsistency, imprecision, indirectness, or risk of bias, along with any corroborating or conflicting evidence.

Discussion: interpretation

- Overall interpretation of the findings and significant implications.

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Table 1. PICOS (Population, Intervention, Comparison, Outcomes, and Study) inclusion and exclusion criteria.

PICOS criteria	Inclusion criteria	Exclusion criteria
Participants	The community of Saudi Arabia	Research studies will intentionally exclude certain subgroups, such as those with comorbidities, complex patients, or health care providers
Intervention	The qualitative and quantitative studies and randomized controlled trials	Studies pertaining to other topics and those involving statistical, mathematical, or predictive methods will not be covered in this context
Comparison	When applicable, this comparison of specific subgroups may also extend to studies conducted in multiple cities or locations	N/A[a]
Outcomes	To assess the factors that influence individuals' decisions regarding vaccine acceptance or vaccine hesitancy	Studies that do not aim to identify or analyze the factors influencing vaccine acceptance or hesitancy
Study design	Observational or descriptive and analytical studies conducted at a national level, or those with an adequately justified sample size and calculations	Pilot studies for tool assessment or improper sampling

[a]N/A: Not applicable.

Searching Approaches

To optimize search results and ensure comprehensive coverage, a combination of medical subject headings and natural language keywords will be used. Boolean and proximity operators will also be used to refine search queries and uncover relevant studies. Additionally, truncation (*) and wildcards ($) will be used to account for variations in search terms and enhance the chances of identifying a wide range of relevant literature.

The search strategy has been configured to align with the specific vocabularies and indexing systems used by each database, ensuring that the search is optimized for each platform's unique structure and content. This approach enhances the precision and relevance of search results within each database.

The search strategy will be formulated using the vocabularies and indexing systems specific to each database. This tailored approach ensures that the search is optimized for the unique characteristics and content of each database. The terms "vaccine," "immunization," "vaccine hesitancy," "vaccine trust," "vaccine resistance," "vaccine concern," "vaccination," "vaccine intervention," "vaccine side effects," "vaccine confidence," "vaccine impact," "vaccine strategy," "vaccine hesitant," "vaccine refusal," "adverse effect of vaccines," and "vaccine rejection" will be applied alone or combined as operators.

Eligibility Criteria

While conducting our search for vaccine hesitancy, we will take into account universally recommended vaccines for individuals across various age groups, including children, adolescents, and adults. These vaccines encompass a range of preventable diseases and include: "seasonal influenza vaccine," "hepatitis B vaccine," "tuberculosis (Bacillus Calmette-Guerin [BCG] vaccine)," "measles, mumps, and rubella (MMR) vaccine," "diphtheria-pertussis-tetanus (DPT) vaccine," "Haemophilus influenzae type b (Hib) vaccine," "human papillomavirus (HPV) vaccine," "poliomyelitis vaccine," "oral polio vaccine," "varicella vaccine," "meningococcal vaccine," "pneumococcal vaccine," and "COVID-19 vaccine." These vaccines are typically recommended as part of immunization programs to protect individuals from various infectious diseases. In addition, we will pay particular attention to the results of vaccination campaigns aimed at promoting and expanding vaccination programs in Saudi Arabia. This will also involve a detailed examination of the various campaigns, their objectives, strategies, and outcomes, as well as their impact on increasing vaccine coverage and public health in the region.

In this review, we will include both descriptive and analytical studies that provide insights into the impact of strategies aimed at addressing vaccine hesitancy. These studies should offer a clear description of the strategies used and their effects on vaccine hesitancy.

However, we will exclude studies that are opinion-based or studies that do not primarily focus on populations eligible to receive vaccines or their parents. Additionally, studies that do not allow for the extraction of relevant information related to vaccination will also be excluded from our analysis.

Selection of Studies and Critical Appraisal

Our research review process should be robust, and it should be designed to ensure the quality and relevance of the studies included in the analysis [30]. The following sections provide a summary of the key steps.

Initial Screening

A total of 2 researchers will independently review the titles, abstracts, and keywords of the identified studies. This step will ensure the segregation of eligible studies from those that are not relevant.

Full-Text Retrieval and Screening

After the initial screening, studies that pass this stage will have their full texts retrieved and reviewed. This allows for a more detailed assessment of their eligibility.

Data Extraction

A total of 2 researchers will independently perform data extraction from the selected studies. This process involves extracting relevant information and data from the studies.

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Consensus on Unmatched Studies

In cases where there is a disagreement between the 2 researchers regarding the inclusion or exclusion of a study, a third researcher will be involved to reach a consensus. This ensures that the final selection of studies is based on consensus and reduces bias.

This screening process, along with independent data extraction and consensus resolution, will help to enhance the reliability and validity of our research findings. It also minimizes the potential for bias in the selection and extraction of data from the identified studies.

Quality Assessment

This study will undergo quality assessment using the Crowe Critical Appraisal Tool (CCAT) [31,32]. This tool focuses on 8 domains for evaluating quality, encompassing preliminaries (title, abstract, and text), introduction (background and objective), design (research design, intervention, treatment, exposure, outcome, output, predictor, measure, and bias), sampling (sampling method, sample size, sampling protocol), data collection (collection method, collection protocol), ethical considerations (participant ethics, researcher ethics), results (analysis, integration, interpretation method, essential analysis, outcome, output, predictor analysis), and discussion (interpretation, generalization, and concluding remarks). The CCAT tool will be used to evaluate the quality of all the included articles across these 8 domains. A cumulative score will be computed for each article and then converted into a percentage. The percentage scores will be categorized into three groups: (1) high quality (≥80%), (2) medium quality (60%-79%), and (3) poor quality (<60%). This assessment of quality will be carried out independently by the authors, with any disagreements being resolved through consensus.

Analysis and Synthesis

According to the methodological nature of our systematic review, conducting a narrative synthesis of the results will be a suitable approach. A narrative synthesis will involve summarizing and interpreting the findings of the included studies. This approach is common when the included studies are diverse in terms of methodology, outcome measures, or data presentation [33].

Thematic Analysis

We will organize the findings thematically. Focus on the common themes, patterns, or trends across the studies. We will create categories, themes, and subthemes that capture the key aspects of vaccine hesitancy and the impact of strategies.

Narrative Description and Synthesis

We will describe the findings of each study within the context of the identified themes that provide a clear and concise summary of each study. We will synthesize the findings by drawing connections between different studies and themes.

Results

We can anticipate potential results that may emerge from this systematic review.

Prevalence and Trends of Vaccine Hesitancy

The review is expected to reveal the prevalence and trends of vaccine hesitancy among different populations. It may show whether vaccine hesitancy rates have been increasing or decreasing over time and how this compares to global trends.

Factors Contributing to Vaccine Hesitancy

Identification of specific factors contributing to vaccine hesitancy in the Saudi Arabian context. Insights into cultural, religious, and social influences on vaccine hesitancy within Saudi Arabia.

Impact of Strategies on Vaccine Hesitancy

Evaluation of the effectiveness of strategies implemented to address vaccine hesitancy and the identification of successful interventions and areas where improvements are needed.

Regional and Global Comparisons

Discover potential comparisons between vaccine hesitancy factors and strategies in Saudi Arabia and those in other countries, particularly within the Middle East region, and understand whether Saudi Arabia faces unique challenges or shares common issues with other nations.

Implications for Vaccination Policy

The review is likely to have implications for public health policy in Saudi Arabia and provide recommendations for tailored vaccination strategies to improve acceptance rates and combat vaccine hesitancy.

Identifying Research Gaps

The review may identify gaps in the existing literature on vaccine hesitancy in Saudi Arabia and highlight areas where further research is needed or not to address vaccine hesitancy.

Discussion

Impact

Vaccine hesitancy poses a substantial threat to public health worldwide [34], and Saudi Arabia is no exception [19-24]. Understanding the prevalence and factors contributing to vaccine hesitancy in Saudi Arabia is crucial for developing targeted interventions to increase vaccination rates and prevent outbreaks of vaccine-preventable diseases [35,36]. Moreover, the causes of vaccine hesitancy and its consequences will be helpful to mitigate [37].

Like the United States, the findings will help tailor an individualized educational program for vaccine-hesitant parents [38]. Alternatively, childhood vaccination will increase, as it is reported to be very low in Saudi Arabia [39-41]. Delays in vaccination were influenced by factors such as parental education, nutrition preferences, and vaccine-related beliefs, while prematurity was associated with a decreased likelihood of delays. As a mandatory requirement, children in Saudi Arabia are expected to be fully vaccinated before starting school at the age of 6 years [42].

In Saudi Arabia, the vaccination program commenced in 1979 with the administration of DTP vaccines, and it has since been

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expanded to encompass a broader range of vaccines [20]. The Saudi National Immunization Program advises administering several vaccines within the first 24 months of life. These vaccines include the hepatitis B vaccine at birth, as well as the pneumococcal conjugate, rotavirus, inactivated poliovirus vaccine (IPV), meningococcal vaccine (MCV), diphtheria, tetanus, polio, Hib vaccine, BCG vaccine, MMR vaccine, and hepatitis A vaccines [20,42].

According to the WHO, vaccination coverage rates in Saudi Arabia have shown significant variation in recent years. In 2019, the coverage rate for BCG vaccination was reported to be 52%, a notable decrease from the 98% coverage rate observed in 2018 [42,43]. While in 2022, it was similar to 2022 [44]. On the other hand, the coverage rates for DPT and MMR vaccines remained high, with rates of 98% and 96%, respectively. Despite the generally high immunization rates, there were concerning numbers of reported cases in 2019. Measles, for instance, had 1035 reported cases, mumps had 187 reported cases, pertussis had 326 reported cases, and rubella had 62 reported cases. These figures indicate that, despite high vaccination coverage rates for some vaccines, there are still significant challenges in preventing these vaccine-preventable diseases in certain populations or regions within Saudi Arabia [42,43].

The study aligns with global concerns about vaccine hesitancy, which the WHO identified as a top 10 global health threat [7]. By exploring vaccine hesitancy in Saudi Arabia, this research contributes to the global understanding of this phenomenon and may shed light on whether Saudi Arabia faces unique challenges or shares common issues with other nations [45,46].

By analyzing the predictors from different stakeholders [47-51], the study's findings are likely to have direct policy implications. Tailored vaccination strategies can be developed based on the identified factors contributing to vaccine hesitancy [41-43,52]. Policy recommendations can help improve acceptance rates and strengthen vaccination programs in Saudi Arabia, ultimately enhancing public health outcomes. Identifying specific factors contributing to vaccine hesitancy in Saudi Arabia is essential for designing targeted interventions. For instance, if religious beliefs are a significant factor [53,54], interventions may involve engaging religious leaders to promote vaccination [55].

Conclusions

This systematic review will investigate Saudi Arabia's vaccine hesitancy, examining prevalence, trends, and contributing factors across diverse populations. It evaluates the effectiveness of implemented strategies and draws regional and global comparisons, shedding light on unique challenges or shared issues within the Middle East. The findings hold implications for Saudi public health policy, suggesting tailored vaccination strategies to combat hesitancy. Additionally, by identifying research gaps, the review provides direction for future studies, pinpointing areas where further investigation is crucial for a comprehensive understanding of vaccine hesitancy in Saudi Arabia.

Conflicts of Interest

None declared.

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Abbreviations

BCG: Bacillus Calmette-Guerin
CCAT: Crowe Critical Appraisal Tool
DPT: diphtheria-pertussis-tetanus
Hib: Haemophilus influenzae type b
HPV: human papillomavirus
IPV: inactivated poliovirus vaccine
MCV: meningococcal vaccine
MMR: measles, mumps, and rubella
PICOS: Population, Intervention, Comparison, Outcomes, and Study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Applications of Artificial Intelligence in Emergency Departments to Improve Wait Times: Protocol for an Integrative Living Review

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Abstract

Background: Long wait times in the emergency department (ED) are a major issue for health care systems all over the world. The application of artificial intelligence (AI) is a novel strategy to reduce ED wait times when compared to the interventions included in previous research endeavors. To date, comprehensive systematic reviews that include studies involving AI applications in the context of EDs have covered a wide range of AI implementation issues. However, the lack of an iterative update strategy limits the use of these reviews. Since the subject of AI development is cutting edge and is continuously changing, reviews in this area must be frequently updated to remain relevant.

Objective: This study aims to provide a summary of the evidence that is currently available regarding how AI can affect ED wait times; discuss the applications of AI in improving wait times; and periodically assess the depth, breadth, and quality of the evidence supporting the application of AI in reducing ED wait times.

Methods: We plan to conduct a living systematic review (LSR). Our strategy involves conducting continuous monitoring of evidence, with biannual search updates and annual review updates. Upon completing the initial round of the review, we will refine the search strategy and establish clear schedules for updating the LSR. An interpretive synthesis using Whittemore and Knafl’s framework will be performed to compile and summarize the findings. The review will be carried out using an integrated knowledge translation strategy, and knowledge users will be involved at all stages of the review to guarantee applicability, usability, and clarity of purpose.

Results: The literature search was completed by September 22, 2023, and identified 17,569 articles. The title and abstract screening were completed by December 9, 2023. In total, 70 papers were eligible. The full-text screening is in progress.

Conclusions: The review will summarize AI applications that improve ED wait time. The LSR enables researchers to maintain high methodological rigor while enhancing the timeliness, applicability, and value of the review.

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KEYWORDS

emergency department; ED; wait time; artificial intelligence; AI; living systematic review; LSR

Introduction

Background

Extended emergency department (ED) wait times are a major health care system problem worldwide [1-4]. Long wait times in the ED can threaten patients' well-being, leading them to depart the ED without receiving the essential care they require. Additionally, this situation contributes to overcrowding within the ED and fosters a sense of dissatisfaction among both patients and ED personnel [2]. Previous studies have investigated many initiatives to reduce ED wait times. Among them, a new approach is the use of artificial intelligence (AI) [3,4].

AI is one of the most important technological advancements of the Fourth Industrial Revolution [5]. AI refers to the use of technology and computers to mimic human-like critical thinking and intelligent behavior. In 1956, the word AI was first used by John McCarthy to refer to the science and engineering of creating intelligent machines AI refers to the use of technology and computers to mimic human-like critical thinking and intelligent behavior. As mentioned by Amisha et al [6], John McCarthy used the word AI for the first time in 1956 to refer to the science and engineering of creating intelligent machines. Recent years have seen exponential growth in the technological and scientific aspects of AI as well as machine learning, one of its main subcategories [7]. Notable benefits include increased productivity and innovation. Significant progress has been made to date in several fields, including computer vision, natural language processing, audio analysis, smart sensing, and many more [8]. Therefore, modeling based on AI is the key to creating automated, intelligent, and smart systems that meet today's needs. Different forms of AI, including analytical, functional, interactive, textual, and visual AI, can be used to improve an application's intelligence and capabilities to solve problems in the real world [5]. Although many of AI's practical applications are still in the early stages and require further research and development, the technology has the potential to revolutionize medicine in ways that have not yet been considered [6].

Harnessing the power of AI holds promising potential to improve the quality of care within EDs by effectively tackling challenges such as overcrowding by offering advanced clinical decision-making tools [9,10]. By developing an AI-assisted module, a significant reduction in wait times for outpatient services was demonstrated in the ED, according to a retrospective cohort study [4]. Furthermore, a prospective study revealed a notable decrease in the wait time for receiving care services through digital automation [11].

All AI methods that enable computers to learn from data without explicit programming are included in machine learning [12]. An Italian study used 2 large data sets of EDs to test several machine learning methods using predictive analytics. The findings demonstrate the viability of a real-time performance monitoring system that supports operational decision-making and has major practical implications for EDs and hospitals [13]. An Australian study showed that wait time forecasts for low-acuity ED patients assigned to the waiting room were improved through machine learning techniques and a wide range of queuing and service flow features. Machine learning models surpass the best rolling average in terms of mean absolute prediction error using queuing and service flow characteristics along with knowledge of daily fluctuations, and quantile regression lowers the proportion of patients with significantly underestimated wait times [14].

Deep learning is a subclass of machine learning defined primarily by neural network models with more layers and, in general, more neurons than typical machine learning neural networks. Additionally, deep networks, relative to traditional neural networks, achieve increased performance with increasingly large amounts of data, becoming practically realizable due to modern advances in computing power [15]. In a study conducted in Saudi Arabia, deep learning was used to forecast the length of time patients would wait in the ED's queue system. The findings of this study demonstrated the applicability of deep learning models for predicting patient wait times in the ED [16].

By looking at current developments in ED operations and clinical patient management, the authors of a review paper summarized the applications of AI in emergency medicine. They came to the view that the areas of prehospital emergency management, patient acuity, triage, and disposition, prediction of medical diseases and conditions, and ED management are where AI applications in ED are most prevalent [2]. Another systematic review study sought to show how AI was applied in ED and how it changed how ED practitioners' work was organized. Most AI applications, according to the study's findings, involved AI-based tools to support clinical judgment and reduce the pressure on overburdened EDs. Additionally, AI support was primarily provided during triage, the decision-making stage that determines a patient's course, and there is strong evidence that AI-based apps could enhance clinical decision-making [10].

Based on our understanding of the literature, the systematic reviews that encompassed studies involving AI applications in the context of EDs were comprehensive and addressed diverse aspects of AI implementation. However, these reviews were limited in their usefulness due to the absence of a plan for regular updates on AI progress, rendering them less applicable across some contexts. It is crucial to recognize that AI development is a revolutionary field with a rapidly evolving landscape. As such, reviews in this domain must undergo frequent updates to stay relevant. As a result of AI, computer programs can answer questions intelligently and infer facts based on real-world data. AI will become a core component of all contemporary decision-making in the immediate future. To keep up with the ongoing changes and revolutions in this field, we plan to conduct living systematic reviews (LSRs). Our

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review will be regularly updated. We will incorporate relevant new evidence when it is available.

Study Goals and Objective

The study aims to summarize the available evidence on how AI can impact ED wait times; describe the applications of AI in reducing wait times; and examine the depth, breadth, and quality of evidence related to the application of AI in reducing wait time in the ED.

Methods

Rationale for LSR

LSR enables researchers to maintain high methodological rigor while enhancing the timeliness, applicability, and value of the review. Our strategy involves conducting continuous monitoring of evidence, with biannual search updates and annual review updates. Upon completing the initial round of the review, we will refine the search strategy and establish clear schedules for updating the LSR.

Type of Review

This will be an integrative review. Integrative reviews stand out as the most exhaustive form of systematic review methodology. They offer the flexibility of diverse sampling strategies and a broad scope of objectives, enabling them to provide a comprehensive representation of complex ideas, theories, or significant health care issues [17]. We selected this type of review since we aimed to examine the full breadth of techniques, methods, algorithms, and modalities of AI used to improve wait time in EDs from various academic sources. As mentioned by Hopia et al [18], according to Whittemore and Knafl's methodological steps, the integrated review method can use diverse data sources, thereby creating a comprehensive understanding of the topic of interest by presenting the state of the science and contributing to theory development. Whittemore and Knafl [17] approach consists of 5 stages and is based on Cooper's theoretical framework, which is one of the methodological approaches used in integrative reviews. These steps generally include problem identification, literature search, data evaluation, data analysis, and presentation [17].

Systematic Review Team

Research team members participating in the systematic review include researchers, physicians, and nurses with expertise in emergency medicine, librarians, learners, patients, AI specialists, and review methodologists.

Patient Engagement

Our research plan and related materials will be showcased to SurgeCon's [19] patient engagement working group, comprising individuals from diverse backgrounds, including people of different gender identities residing in urban and rural areas of Newfoundland and Labrador. This approach aims to comprehensively gather the needs, desires, and firsthand experiences of those who stand to gain from the implementation of AI in improving ED wait times.

Protocol of the Integrative Review

Overview

Our designed integrative review protocol will include 5 stages summarized in Figure 1, which will be explained in the following. Furthermore, to ensure transparent and accurate reporting, we will use PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in this review [20].

Figure 1. Visual representation of the 5 key stages in an integrative review protocol.

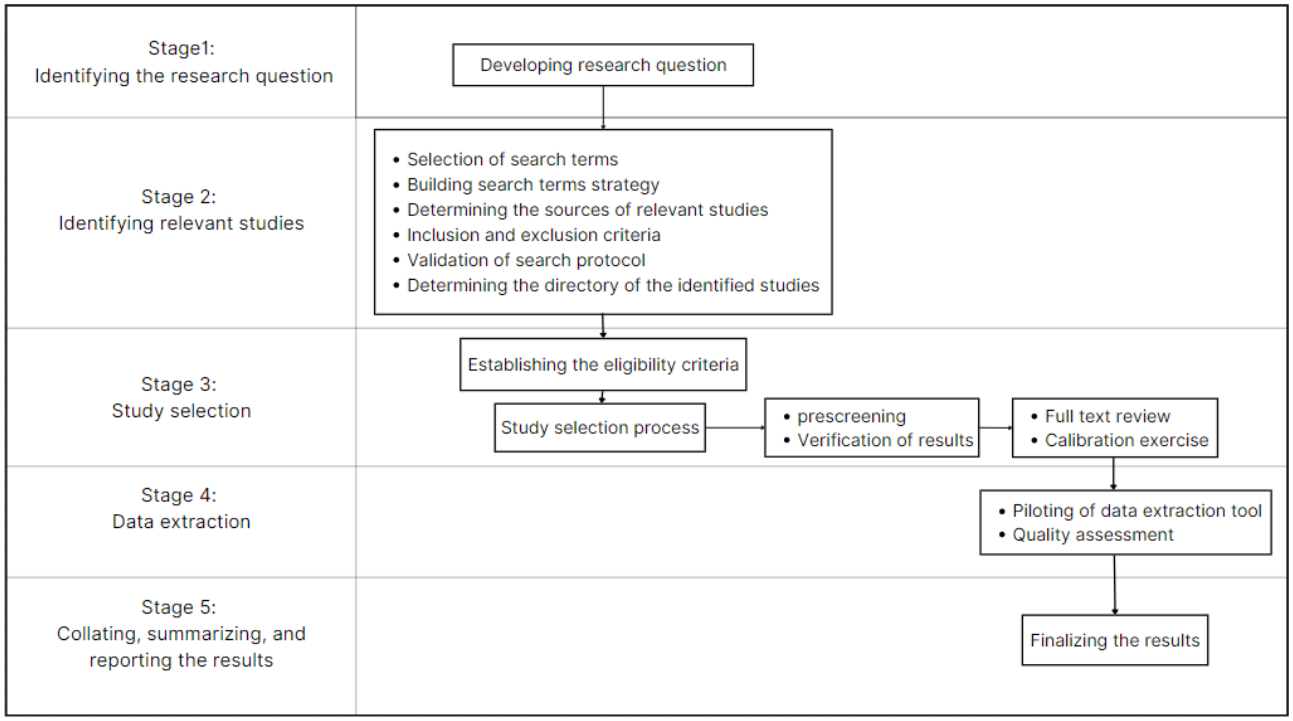

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Stage 1: Identifying the Research Question

Our research questions will be developed and refined by a team of researchers and clinicians, including physicians and nurses with expertise in emergency medicine, patients, and librarians. “How does the application of AI reduce ED wait times, as supported by evidence from current literature?”

Stage 2: Identifying Relevant Studies

Selection of Search Terms

The search terms will be developed by content experts and patients. These terms include general variations on “ED,” “wait times,” “AI,” “machine learning,” “deep learning,” and any more specific terms related to algorithms and methods used in the field of AI and indicators related to wait times in the ED. Once completed, the research question’s key terms will be chosen by relevant stakeholders, which will be compiled alongside a list of potential synonyms or other terms identified by a librarian. The optimal search phrases will be determined by searching for Medical Subject Heading (MeSH) terms, the MeSH tree, and related words in keywords and references.

Building Search Terms Strategy

A librarian will assist in exploring various word combinations in databases to discover the most effective search method. When searching relevant literature, search phrases are iteratively improved by evaluating various terms, merging new terms, and finding new relevant citations. The MeSH and keywords will be combined in the search. For other data sets, different search techniques will be applied as needed.

Sources of Relevant Studies

We initiate the review process by conducting a comprehensive examination of peer-reviewed papers cited in electronic databases. This meticulous approach allows us to identify and encompass all relevant, available information sources. A librarian will provide support in completing the search for research studies in the following databases for studies that were published between January 1, 1946, and August 17, 2023: Embase, MEDLINE via Ovid, CINAHL, Cochrane, and Scopus. The search strategy for MEDLINE is available in Multimedia Appendix 1.

Inclusion and Exclusion Criteria

During our search for relevant research papers, we will incorporate peer-reviewed papers and published PhD dissertations from reputable repositories. Studies that focus on AI-related concepts, including AI algorithms and techniques, in the context of EDs to improve wait times will undergo a full-text review. We have categorized all the AI-related concepts and terminology we want to explore in reducing ED wait times in Multimedia Appendix 2. Since AI and its applications are evolving, we will reevaluate the inclusion and exclusion criteria in the next review to ensure new terminologies for AI will be included in our research. Our inclusion criteria will consist of studies that specifically concentrate on the application of AI techniques in the ED to decrease wait times. These studies must include wait times as an outcome measure and present relevant results. We will exclude studies that do not directly address the use of AI or do not primarily focus on reducing wait times in the ED. Additionally, master theses and conference abstracts will also be excluded from our selection.

Validation of the Search Protocol

The gold standard papers and journals recommended by subject matter experts will be used to test the search methodology and calibrate our search technique. The eligibility requirements will be changed as necessary. The search strategy for this LSR will be iteratively revised, and new search terms may supplement future searches if required.

Directory of Identified Studies

Covidence software (Veritas Health Innovation) will be used to manage the review and build a directory of publications.

Stage 3: Study Selection

Overview

The process of inclusion studies will be iterative and involve searching the literature, adjusting the search strategy, determining eligibility, prescreening, reviewing the full text of the literature for inclusion, and keeping only studies that discuss the use of AI to reduce ED wait times.

Eligibility Criteria

Members of our team who are knowledgeable about AI and ED and who will be blinded to the study results in question will make decisions about the review process methodology. Inclusion criteria will ensure a wide range of literature from various sources.

We will include patients, regardless of gender or age, who have been analyzed by AI algorithms. Audits or anecdotal information, planning-stage research, pilot studies, undergraduate dissertations, book reviews, gray literature, such as unpublished theses and reports from relevant websites, and policy assessments are among the exclusion criteria. We will look at both qualitative and quantitative studies. If the paper is a systematic review, all included studies in the review will be examined, and the related ones will be included in our review. In addition, we will conduct backward and forward citations of all studies eligible for data extraction in our review.

Study Selection Process

Prescreening

Papers will be digitally stored and managed in Covidence software, and duplicates will be removed by Covidence software. After training team members, they will independently review the titles and abstracts of all publications found through database searches to determine eligibility. Conflicts will be resolved through a discussion between the 2 reviewers (BA and AG); a third team (SA) member will provide feedback when necessary. If studies or abstracts do not address the topic of the search, or if the studies are commentaries or editorials, they will be deemed unrelated and excluded.

Verification of Results

One of the 2 reviewers (BA and AG) will then reevaluate a random sample of 5% (n=875) of the papers that were rejected based on title and abstract to make sure that all pertinent studies were considered. All excluded papers will be reexamined if

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more than 5% (n=44) of the sample is determined to be relevant. We will also provide reviewers with retraining as needed.

Full-Text Review

Two research team members (BA and AG) will independently review all full texts. Only English papers are subject to full-text reviews, although the total number of studies considered appropriate by title, abstract, and full text will be noted for future use.

Calibration Exercise

We will conduct a calibration exercise before the process begins and then continue the calibration exercise throughout the review. Five percent of the listed citations will be randomly chosen. Two reviewers (BA and AG) will independently assess the full text against the eligibility criteria provided in Covidence. They will then discuss their rationale for including or excluding each article, and a third team member (SA) will provide feedback if necessary. Using an iterative process, if the level of agreement between the 2 reviewers is low (0.5), the eligibility criteria for screening and full-text review and the exclusion criteria for full-text review will be revised on Covidence. Then, the remaining citations will be evaluated by the reviewers (BA and AG), and a third reviewer (SA) will settle any disagreements. Furthermore, we will schedule biweekly team meetings to assess the review process. We will examine the reviewers' understanding of the eligibility criteria during these meetings and provide training if needed. The reviewers need to maintain a 0.8 agreement during the process.

Stage 4: Data Extraction

Overview

A data extraction tool for systematic data gathering from the indicated studies will be prepared in Excel (Microsoft Corporation). The tool will be made to extract data based on citation type (eg, original research), country, study date, study methodological features, study design, study population, sample size, AI techniques used, input variables, wait time metrics, outcomes measured, results performance, performance measure, and any limitations or challenges reported by the authors.

Piloting of the Data Extraction Tool

The team evaluates the data extraction tool by using a random sample of 5% (2) of the included studies. If required, the data extraction tool will also undergo frequent revisions. The data will be reviewed and extracted separately by 2 independent reviewers (BA and AG).

Quality Assessment

A scoring system for systematic reviews of mixed research will be used to evaluate the quality of primary studies (both quantitative and qualitative) [21]. The goal of the quality assessment is to determine the overall caliber of the studies in the sample rather than to identify or reject weaker studies. The quality of the screened studies will be reported.

Stage 5: Collating, Summarizing, and Reporting the Results

We will use a complex strategy to understand and combine the results of many studies for an interpretive synthesis. A descriptive summary of the identified and relevant studies will be reported. The frequency of research with study designs that match the criteria included in the data extraction tool will be provided [22]. In addition to collecting results, we seek to uncover underlying meaning, patterns, and relationships in the data. The framework developed by Whittemore and Knafl [17] is a useful resource for accomplishing this interpretative synthesis. Detailing the documented outcomes of AI interventions and the kinds of AI methods used by our data extraction tool's specifications will be part of the interpretive synthesis. We aim to identify commonalities or patterns in the studies by categorizing their results according to their impact on various wait time metrics. We will classify the findings of the identified research according to how they affect different wait time metrics in the ED using interpretive synthesis. These metrics include length of stay, number of patients leaving without being seen by a physician or their delegate, time to the initial physician assessment, and others. We will list the reported effects of AI interventions and the types of AI techniques implemented based on the criteria included in our data extraction tool. For an in-depth visual representation, the outcomes of the interpretative synthesis will be presented using descriptive tables, frequency tables, and diagrams. To develop a combined estimate of the effectiveness of AI initiatives in lowering ED wait times, the integrative review will evaluate the included papers' suitability for conducting a meta-analysis. If the selected studies show sufficient homogeneity in their methods and findings, a meta-analysis could be possible and provide a quantitative synthesis of the findings. We improve the breadth and clarity of this study's results by integrating these components into our interpretive synthesis approach, offering a robust analysis of the effect of AI interventions on ED wait times.

Knowledge-User Consultation

The review will be carried out using an integrated knowledge translation strategy, and knowledge users will be involved at all stages of the review to guarantee applicability, usability, and clarity of purpose. This strategy aims to engage content experts and the community advisory committee within our team through multiple consultations. The objective is to actively involve them in shaping the study's outcomes, action plan, and research agenda while also fostering opportunities for knowledge exchange [22,23]. We will organize regular meetings with the knowledge users' group to provide an opportunity to receive their feedback throughout the review. In addition, we will regularly update the progress of the review to notify them. By adopting these strategies, we can ensure that feedback from consultations is systematically integrated into the integrative review process, enhancing the relevance and applicability of the study outcomes. This team includes researchers and clinicians, including physicians and nurses with expertise in emergency medicine, learners, patients, AI specialists, and review methodologists. A practical understanding of the difficulties and possible advantages of applying AI to reduce wait times can be gained by speaking with ED physicians, nurses, administrators, and other health care workers who have firsthand experience working in the ED. Speaking with those in charge of planning the ED system and allocating resources

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can give us an understanding of the broader effects of using AI in the ED. They can provide viewpoints on financing priorities, legislative considerations, and the viability of incorporating AI solutions into current health care systems. Speaking with professionals involved in the development and application of AI in similar contexts will help us comprehend the technical facets and capabilities of AI systems on a deeper level. These professionals can offer perceptions of the promise of AI technologies, the difficulties in putting them into practice, and factors to consider for successful integration into the ED environment. This LSR aims to provide updated information on the application of AI to improve ED wait times. Initial review findings will be regularly communicated to our team to validate our conclusions and help direct the completion of the review [22]. In addition to scientific papers and academic presentations, a summary of potential clinical practice implications will be created using the study's findings, including any areas that might call for medium- or long-term action. The summary will be distributed in our biweekly meetings with ED stakeholders to generate ideas, formulate research questions, and decide on suitable approaches for the SurgeCon ED wait time improvement team in Newfoundland and Labrador, Canada.

Results

The literature search was completed by September 22, 2023. We identified 17,569 studies. The title and abstract screening was started independently by 2 reviewers (BA and AG) on September 23, 2023, and ended on December 9, 2023. The full-text review phase started with 70 eligible papers on January 22, 2024, and is in progress.

Discussion

Recognizing the dynamic nature of AI research and its impact on health care decision-making in emergency medicine, we propose the use of LSRs. The major goal of LSRs is to keep our reviews up-to-date and relevant by including new information and revolutions in the field of AI as they become available. Using LSRs, we propose a methodological innovation that maintains rigor and assures that reviews remain relevant and applicable over time, reflecting the continual progress of AI applications in EDs.

Our research aimed to analyze the published studies examining AI applications in EDs, with a particular emphasis on reducing wait times. The analysis of the literature found that studies of AI applications in EDs to improve wait times cover a wide range of topics in emergency medicine [4,9,11,13,14,16]. We also found a few systematic reviews showing that scholars and specialists in the field have been proactive in synthesizing the available knowledge [2,10]. Despite their comprehensiveness, these systematic assessments have 1 significant limitation: no plan for regular updates. Since the field of AI is characterized by rapid change and continual progress, this issue jeopardizes the use of these studies in future settings. AI technologies are continually improving, and their applications in health care, including EDs, are no exception.

The study has several limitations. Implementing an LSR strategy may necessitate changes to existing review procedures as well as potential challenges in gathering and synthesizing constantly emerging data. Furthermore, the feasibility and practicality of conducting living reviews must be carefully considered. In addition, like other types of systematic reviews, the LSR is prone to publication bias, and the quality of the synthesis could be affected by the quality of the included studies.

In conclusion, our study illuminates the current state of AI applications in EDs and addresses a crucial gap in systematic review methods. LSRs emerge as a timely solution to the challenge of obsolescence amid rapid AI growth and advancements. Embracing LSRs ensures timely information for health care decision makers and sets a precedent for enhancing review techniques in the dynamic realm of AI research. As major technological shifts loom, our study highlights the methodological evolution needed to fully harness AI's potential in health care.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Search strategy.
[PDF File (Adobe PDF File), 76 KB - resprot_v13i1e52612_app1.pdf]

Multimedia Appendix 2
Related concepts and terms.
[DOCX File , 17 KB - resprot_v13i1e52612_app2.docx]

Multimedia Appendix 3
The original ChatGPT transcript.
[DOCX File , 17 KB - resprot_v13i1e52612_app3.docx]

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Abbreviations

AI: artificial intelligence
ED: emergency department
LSR: living systematic review
MeSH: Medical Subject Heading
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Effectiveness and Experiences of Quality Improvement Interventions in Older Adult Care: Protocol for a Mixed Methods Systematic Review

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Abstract

Background: Quality improvement (QI) interventions are designed to resolve the recurring challenges of care for older individuals, such as working conditions for staff, roles of older individuals in their own care and their families, and relevant stakeholders. Therefore, there is a need to map the impacts of QI interventions in older adult care settings and further improve health and social care systems associated with older adults.

Objective: This review aims to compile and synthesize the best available evidence regarding the effectiveness of policy and practice QI interventions in older adult care. The secondary aim is to understand the care of older individuals and QI intervention-related experiences and perspectives of stakeholders, care providers, older individuals, and their families.

Methods: The mixed methods review will follow the standard methodology used by Joanna Briggs Institute. The published studies will be searched through CINAHL, MEDLINE, PsycINFO, ASSIA, and Web of Science, and the unpublished studies through Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. This review included both qualitative and quantitative analyses of patients undergoing older adult care and any health and care professionals involved in the care delivery for older adults; a broad range of QI interventions, including assistive technologies, effects of training and education, improved reporting, safety programs, and medical devices; the experiences and perspectives of staff and patients; the context of older adult care setting; and a broad range of outcomes, including patient safety. The standard procedure for reporting, that is, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, will be followed.

Results: A result-based convergent synthesis design will be used in which both quantitative and qualitative studies will be analyzed separately, and the results of both syntheses will be then integrated during a final (convergent) synthesis. The integration will compare the findings of quantitative and qualitative evidence using tables in light of the results of both syntheses.

Conclusions: This comprehensive review is expected to reflect on the insights into some QI interventions and their impact, outline some common challenges of quality for older adult care, and benefit both the practical usefulness of care service activities and the society at large.

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KEYWORDS

patient safety; acceptability; accessibility; appropriateness; timeliness; equitability; social care

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Introduction

Overview

Quality improvement (QI) intervention has been defined as "a systematic and continuous approach that designs, tests and implements changes using real-time measurements to improve the safety, effectiveness and experience of care" [1]. There are QI interventions designed to illuminate and resolve the current challenges in the care of older individuals that arise within health care and social care systems. This may include the challenges regarding working conditions for staff and the organization as a whole [2]; the roles of older individuals in their own care, including support from their relatives and families [3]; and the roles of clinical and public health researchers, academics, engineers and planning experts [4-7] to make changes in improving health and social care systems for older adults [4,8]. For the readers' convenience, the definition of QI will be used throughout this protocol to indicate the care of older individuals associated with health and social care systems.

The older population worldwide is growing with increased life expectancy and improving public health. These individuals are expected to live longer with multiple needs and circumstances [9]. Despite the challenge regarding adequate funding, care for older individuals in Sweden has been established because everyone should have equal access to care services [10]. Over 18% of the Swedish population is 65 years or older, and this number is expected to grow and be over 20% by the year 2030 and 25% by 2040 [11]. Sweden's health and care burden was moved to homecare in 1992 by implementing the ÄDEL reform, which focuses on minimizing complications for older adult care. Even though this strategy turned out to be a success for the Swedish health and social care system, achieving better accessibility by providing home health services to 90% of the aging population [10,12], the challenges around older adult care still remain. For example, a Swedish study found that while government agencies were very positive about the implementation of new technology in older adult care, the unstructured implementation process (without proper planning) and incoherent evaluation model (without compatible designing) indicated inequality of access to such new technology [13,14].

Several QI programs have shown promising results in improving the aging population's health and social care quality. For example, the QI program, that is, Acute Care for Elders, improved the outcomes for older adults, that is, significant reductions in cost and length of stay with greater comorbidity scores [15]. Other QI interventions, such as education sessions/toolkits, improved the impact of accurate and suitable medicines supply to the residents of residential aged-care facilities [16]. A discharge planning intervention increased the feasibility and effectiveness of facilitating the transition of older adults from hospitals to their homes [17]. An intervention comprising technical and social components reduced preventable harm in care homes [18,19]. Such QI programs may also involve collaboration between geriatricians and primary care physicians, further reducing hospitalization risk and total health and care costs among vulnerable older adults [20].

The review will consider various dimensions of care quality, such as accessibility, appropriateness, safety, efficacy, effectiveness, timeliness, patient-centeredness, and equitability [21,22]. Each subsection will also be covered to obtain a comprehensive insight into health and care quality. For example, the 5 dimensions of accessibility, that is, approachability, acceptability, availability and accommodation, affordability, and appropriateness, will be considered and explored [23,24]. This is because the care provided should be adequate for all these dimensions, that is, 1 or more missing aspects of the care do not complete the entirety of the quality [25,26]. For instance, providing inappropriate or ineffective care should be unacceptable even if it is safe and provided in a timely manner [27,28].

A recent comprehensive or mixed methods systematic review of QI interventions in the radiology setting has demonstrated expected results, that is, improvements in outcomes, such as improved workflow efficiency, report turnaround time, and teamwork and communication [29,30]. We believe that a similar review in the setting of older adult care would develop new knowledge for the health and social care system as well as for older individuals and care providers. Therefore, the findings of the review will generate insights that have wider relevance in creating a model for improved older adult care systems and to meet today's societal challenges.

Several systematic reviews have been performed for older adult care focusing on health and care quality and its dimensions, such as patient safety [31], appropriateness [32], and accessibility [23], including recent reviews on the interventions of eHealth [33] and training [34]. However, none of these reviews constitutes a comprehensive systematic review focusing on both quantitative and qualitative studies for looking through multiple lenses into the health and social care system of older adult care with broader perspectives that would further facilitate analyzing the issues and devising recommendations. A preliminary search has been performed on Campbell Systematic Reviews, the Cochrane Database of Systematic Reviews, PROSPERO (International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) evidence synthesis, and we have not identified any systematic reviews on QI interventions in older adult care settings using either qualitative or quantitative methodology.

Aim and Review Questions

The primary purpose of this review is to compile and synthesize the best available evidence regarding the effectiveness of QI interventions in older adult care. Provided that QI initiatives ultimately target the beliefs and perspectives of clinicians, in a broader sense, the organization and its resources, the secondary objective of this review is to understand the experiences and perspectives of care providers, older individuals and their families, and relevant stakeholders undergoing a QI initiative. Specifically, the review questions are as follows:

- What kind of QI interventions have been used to improve the quality of older adult care?
- How effective are interventions in relation to policy and practice that target improvements in the quality of older adult care?

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- What are the experiences and perspectives of care providers, older individuals and their families, and relevant stakeholders about these interventions?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for systematic (mixed methods) reviews [35].

Search Strategy

Databases will be searched for both published and unpublished studies. The approach to searching for studies for a scoping review will follow the standard 3-step method. The first step will be an initial limited search of a selection of relevant databases, followed by an analysis of text words in the title and abstract and the index terms used to describe the article. The search for published studies will include a 2-way search strategy. One is to search the journal and reference databases, such as CINAHL, MEDLINE, PsycINFO, ASSIA, and Web of Science. Another is to search article-based (journal) databases, such as ACM digital library, IEEE Xplore, and BMJ Journals. The search for unpublished studies (gray literature) will include Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. A second search using all identified keywords (see Textbox 1) and index terms will be undertaken across all included databases. Additional search strategies, that is, citation search—specific researcher or article (for example, gold-standard article), and chain search—review reference list of the systematically selected articles will be included to complement the search for published and unpublished papers. Studies, such as reviews (systematic, scoping, umbrella) and editor letters, will be excluded. Any studies that lack ethical concerns will also be excluded.

Textbox 1. A list of keywords for search strategy.

Participants: Old people (patient), older people (patient), elderly people (patient), elderly people (patient), elderlies, aging population, geriatricians, social workers, and domiciliary workers (Using OR Boolean operator).

Context: elderly care, aged care, primary care, private hospital, public hospital, clinic, geriatric ward, old-age home, nursing homes, domiciliary care, and home care (Using OR Boolean operator).

Interventions: Technology, training, education, staff arrangement, incident reporting, peer review, clinical audit, teamwork intervention, communication intervention, team training, safety checklist, local governance, and quality improvement intervention. (Using OR Boolean operator).

Outcomes: Patient safety, incident, event, near miss, adverse event, safety culture, safety effectiveness, timeliness, patient-centeredness, equitability, decision-making, communication, teamwork, leadership, report turnaround, patient experience, patient perspective, staff experience, and staff perspective. (Using OR Boolean operator).

Types of Studies: Randomized controlled trials, cluster randomized controlled trials, quasi-experimental, controlled before and after trials, interrupted time series analysis, qualitative, grounded theory, ethnography, phenomenology, case study, narrative model, and historical model (Using OR Boolean operator).

Studies published in English will be considered. Studies published from 1990 onward (when the first substantive patient safety research study, "Harvard Medical Practice," was published) [36,37] will be considered for inclusion in this review. The search strategy results will be depicted through the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [38].

Inclusion Criteria

Research Background

The inclusion criteria of this review will follow the mnemonics of PICO (for quantitative studies) and PICo (for qualitative studies)—which stands for Population, Phenomena of Interest, and Context. These mnemonics are used as a guide (not policy); therefore, the inclusion criteria of this systematic review will include a detailed description of types of participants/population, types of interventions, phenomena of interest, context, outcomes, as well as types of studies, search strategies, assessment of methodological quality, and synthesis of results.

Types of Participants/Population

This review will include studies of older individuals (65 years or older) undergoing older adult care irrespective of gender and diversity, including age, ethnicity, socioeconomic status, and disability, and any health and care professionals (care providers) and stakeholders involved in the care delivery for older individuals, such as nurse practitioners, registered nurses, enrolled nurses, specialist nurses, and geriatricians.

Types of Interventions

The included studies should concentrate on the implementation of a QI intervention, that is, defined as the systematic and continuous approach that designs, tests, and implements changes using real-time measurements to improve the safety, effectiveness, and experience of older adult care. Given the complexities of the health and social care system, a range of QI interventions will be included in this review. The interventions will include but not are limited to ton technology; training and education; improved reporting and management; safety programs; changes in staffing arrangements (staffing levels, and skill, grade and qualification mix); improved regulation; peer review; and revalidation, clinical audit, and changes to local governance.

Phenomena of Interest

The phenomena of interest will be the effects on outcomes and workflow processes and the experiences and perspectives of care providers and older individuals undergoing or being exposed to the QI interventions. These experiences or perspectives included descriptions of the quality and safety concerns, the contexts and cultures of the workplaces (including factors such as conflict and how it was managed, teamwork

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behaviors, and the attitudes of care providers), and the management of adverse events and near misses.

Context

The systematic review will consider studies in older adult care settings, such as geriatric wards of primary health care, hospitals or clinics, old-age homes, nursing homes, and home care facilities for older people.

Outcomes

The outcomes will include validated measures of safety culture decision-making, communication, teamwork, leadership, report turnaround time, and timeliness of care. Further outcomes will be patient satisfaction and patients' perceptions of the quality of older adult care [39].

Types of Studies

Quantitative and qualitative studies will be included to report empirical evidence and the human experience. Quantitative studies include randomized controlled trials or Cluster Randomized Controlled trials; nonrandomized controlled trials; quasi-experimental, controlled before-after trials; and interrupted time series studies. Qualitative studies included interpretive work focusing on, but not limited to, designs such as content analysis, phenomenology, grounded theory, ethnography, case study, narrative model, and historical model. Mixed methods and descriptive studies will also be eligible for inclusion.

Assessment of Methodological Quality

Two independent reviewers for methodological validity prior to inclusion will assess selected quantitative and qualitative papers for retrieval, reducing the risk of methodological issues, such as subjective bias. This will be done using the standardized critical appraisal criteria from the critical appraisal instruments by the JBI. Any discrepancies that may arise between reviewers' assessments will be resolved by consensus through discussion.

A critical appraisal of the selected papers will be conducted after screening. The formal process of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) and the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) will be used to rate the quality of scientific evidence and confidence to place in findings from systematic reviews of both quantitative and qualitative studies, respectively. For example, 3 grades of quality may be used for each study, based on the score achieved in the critical appraisals: low quality (less than 33% or equal to 33%), medium quality (34%-66%), and high quality (more than 66%).

Data Extraction

Quantitative data will be extracted from papers included in the review using the standardized JBI data extraction tool. Qualitative data will be extracted from papers included in the review using the standardized JBI data extraction tool. The data extracted for quantitative and qualitative studies will include specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives.

Results

A result-based convergent synthesis design [40] will be used in which quantitative and qualitative studies will be analyzed separately, and the results of both syntheses will be then integrated during a final (convergent) synthesis. The integration will compare the quantitative and qualitative evidence findings using tables in light of the results of both syntheses. This will help us address overall review questions with subquestions (if possible).

Quantitative papers will, where possible, be pooled in a statistical meta-analysis using the appropriate JBI tool. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% CIs will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square and I-square. It will also be explored using subgroup analyses based on the different quantitative study designs included in this review. Where statistical pooling is impossible, the findings will be presented in narrative form, including tables and figures, to aid in data presentation where appropriate.

Qualitative research findings will, where possible, be pooled using the appropriate JBI tool. This will involve the aggregation or synthesis of findings to generate a set of statements that represent that aggregation through assembling the findings rated according to their quality and categorizing them based on similarity in meaning. These categories are then subjected to a meta-synthesis to produce a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice. Where textual pooling is impossible, the findings will be presented in narrative form.

Discussion

Principal Findings

Health and social care systems embrace welfare broadly and include institutions, organizations, and resources to maintain or promote health and social care. The resources may consist of funds for the training and education of care providers and welfare technologies used for older adult care services [41,42]. During the COVID-19 pandemic, the quality and safety of care for older individuals have been a top priority [43]. A future pandemic situation can be overcome through sustainable health and social care systems for older individuals by dealing with the challenges found at the system and organizational levels.

This review is designed to be a mixed methods systematic review that will contain evidence of and bring together the results of single-method reviews (including quantitative and qualitative), which has the potential to produce reviews of direct relevance to policy makers and practitioners. As this review covers a wide range of interventions and outcomes and the experiences and perspectives of both care providers and older individuals, the results are expected to reflect on and offer insights into some QI interventions and their impact and some common quality challenges for older adult care. The challenges may include accommodation and availability, the role of the

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families, friends, and relatives; working conditions and staffing arrangements; and the practical usefulness of the patients and care service activities and the society at large.

It is essential to cover a diversity perspective in the review; for example, older individuals of different cultural backgrounds may have different needs for QI. As we cover as many health and care quality dimensions as possible, we believe that issues of diverse perspectives will be included in the literature. For example, the dimension of "acceptability" is defined as the relationship between clients' attitudes about personal and practice characteristics of existing providers, including age, sex, location, and type of facility or religious affiliation of the provider or facility, as well as provider attitudes about acceptable personal characteristics of clients, including ethnicity and source of payment [23,24,44].

This review will include studies of individuals undergoing older adult care irrespective of gender, diversity, ethnicity, socioeconomic status, and disability. This review will evaluate if older adult care facilities worldwide are equipped enough to deal with the challenges of gender sensitivity and cultural diversity. For example, the review may cover the issues of gender sensitivity, especially when a family experiences feelings of shame when receiving care from a nonfamily member or the opposite gender [23,45].

Strengths and Limitations of the Review

The results of this systematic review will need to be treated with caution since our search is restricted to language and publication period. To minimize the effect of such limitations, a comprehensive strategy, that is, a standard 3-step method, will be followed. For example, the inclusion of gray literature will provide additional insights into the review findings. There may be other limitations, for instance, the possibility pertaining to the results associated with limited included studies, introducing a layer of bias for the selected studies. The evidence-based practice center methods guide proposed by the Agency for Health Care Research and Quality will be used to risk the risk of bias in individual studies [46].

To ensure the review produces generalizable findings, discussions with older adults and their families and the relevant public will be channeled to support the interpretation and dissemination of the review findings.

Conclusion

No current or underway systematic reviews on the topic were identified. This comprehensive review will uncover the shreds of evidence requiring diligent attention to address the effectiveness of interventions in relation to policy and practice in older adult care settings. The review will also reflect on the insights into the impact of QI interventions, outline some common challenges of quality for older adult care, and benefit both the practical usefulness of care service activities and the society at large.

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Data Availability

All data generated or analyzed during this study will be included in this published article and its supplementary information files.

Conflicts of Interest

None declared.

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Abbreviations

CERQual: Confidence in the Evidence from Reviews of Qualitative Research
GRADE: Grading of Recommendations Assessment, Development and Evaluation
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
QI: quality improvement

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Protocol

Impact of Digital Interventions on the Treatment Burden of Patients With Chronic Conditions: Protocol for a Systematic Review

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Abstract

Background: There is great potential for delivering cost-effective, quality health care for patients with chronic conditions through digital interventions. Managing chronic conditions often includes a substantial workload required for adhering to the treatment regimen and negative consequences on the patient's function and well-being. This treatment burden affects adherence to treatment and disease outcomes. Digital interventions can potentially exacerbate the burden but also alleviate it.

Objective: The objective of this review is to identify, summarize, and synthesize the evidence of how digital interventions impact the treatment burden of people with chronic conditions.

Methods: The search, selection, and data synthesis processes were designed according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015. A systematic search was conducted on October 16, 2023, from databases PubMed, Scopus, Web of Science, ACM, PubMed Central, and CINAHL.

Results: Preliminary searches have been conducted, and screening has been started. The review is expected to be completed in October 2024.

Conclusions: As the number of patients with chronic conditions is increasing, it is essential to design new digital interventions for managing chronic conditions in a way that supports patients with their treatment burden. To the best of our knowledge, the proposed systematic review will be the first review that investigates the impact of digital interventions on the treatment burden of patients. The results of this review will contribute to the field of health informatics regarding knowledge of the treatment burden associated with digital interventions and practical implications for developing better digital health care for patients with chronic conditions.

Trial Registration: PROSPERO CRD42023477605; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=477605

International Registered Report Identifier (IRRID): DERR1-10.2196/54833

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KEYWORDS

chronic illness; treatment burden; eHealth; mHealth; digital health; mobile health

Introduction

Background

Digital technologies are now commonly used in daily life, bringing many new possibilities for connecting people and providing services. The use of mobile- and web-based digital health care interventions has increased during the COVID-19 pandemic and has been found to have high efficacy, accessibility, and cost-effectiveness in the self-management of chronic diseases [1-3].

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As the global population is growing, the prevalence of chronic diseases has increased significantly [4]. The World Health Organization [4] has estimated that if this trend continues, by 2050 chronic diseases will be the cause of 86% of the 90 million deaths each year. This means a 90% increase in absolute numbers since 2019. Therefore, there is a continuous need for new interventions for the management of chronic diseases.

Chronic diseases often require regular long-term management, which requires patients to not only cope with their symptoms but also navigate services, interact with health professionals, and adhere to treatments, creating a significant burden for many patients [5]. Treatment burden is defined as both the workload required for self-management of disease and the impact treatment regimens have on the patient's function and well-being [5]. Treatment burden can affect many domains: burden of taking medications, traveling to appointments, financial burden, impact on social life and emotions, and burden of accessing health care services [6,7]. A high treatment burden has been associated with poor adherence and worse disease outcomes [6].

The variety of available digital interventions can be tailored to meet the diverse needs of patients. For example, telemedicine and remote visits can reduce the need for traveling to medical appointments [8]. Mobile health apps, wearable technologies, and remote monitoring systems can track patients' health data and alert health care professionals (HCPs) if intervention is required [9,10]. Electronic health records offer a central repository for patients' history to minimize the paperwork and speed up the adherence process [11], while electronic prescription management improves patient safety as well as the efficiency and costs of prescribing medications [12]. Furthermore, patients' portals, web-based support groups, and forums provide emotional and social support for patients [13].

The World Health Organization Classification of Digital Interventions, Services and Applications in Health [14] highlights a variety of digital health technologies for different types of services. In this study, we will focus on the point of service category of digital interventions. The point of service category includes those digital interventions that facilitate and deliver health care services to the patients, making it easier to see the connection between the treatment burden of the patient and the digital intervention. This category includes communication systems, community-based information systems, decision support systems, diagnostics information systems, electronic medical record systems, laboratory information systems, personal health records, pharmacy information systems, and a variety of telehealth systems. These digital interventions can include many different components, such as monitoring tools, decision aids, behavior change support, communication with HCPs, and web-based peer support groups.

Digital interventions may affect the treatment burden in multiple ways. With limited resources, digital interventions may be used to reduce the burden on the health care system, and staff end up offloading the burden to patients [15-18]. Patients may also find digital systems inaccessible or difficult to use [19] and struggle with digital stress [20]. However, digital interventions can expedite and simplify health care processes in a way that patients may receive treatment more efficiently, reducing the treatment burden for patients. For example, they can reduce the need for medical appointments and travel to hospitals [8] and make self-management easier and more motivating for patients [21,22].

Many systematic reviews have been conducted to investigate the treatment burden on patients with chronic conditions [6,7,23-26]. These reviews have provided insights into the definition, prevention, and patient's experience of treatment burden. In addition, recent systematic and umbrella reviews about digital interventions have found that most digital interventions in health care are mobile- or computer-based [27-29]. The findings of the recent research are mostly focused on effectiveness, and the largest targeted condition group is mental illnesses [27,29]. However, we have observed a gap in the literature regarding systematic reviews combining these 3 concepts: treatment burden, digital interventions, and chronic conditions.

Objective

The aim of this review is to identify gaps in the literature and summarize and synthesize currently available evidence of how digital interventions impact the treatment burden of people with chronic conditions. The impact can be a positive or negative effect on any domain of treatment burden. We aim to investigate if the results differ between chronic conditions with different levels of treatment burden or between interventions with different components.

Research Questions

We have two primary research questions: (1) How can digital interventions impact the treatment burden on people with chronic conditions? (2) What kind of support can digital interventions provide for people with chronic conditions with their treatment burden?

Methods

Ethical Considerations

We followed the University of Oulu ethics process as defined in the guidelines from the Ethics Committee of Human Sciences [30]. According to the guidelines, an ethics board review is not needed for this protocol.

Study Design

This protocol is reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 [31]. We registered the protocol on the International Prospective Register of Systematic Reviews (PROSPERO CRD42023477605).

The systematic review will use a convergent design for systematic mixed studies reviews [32]. The mixed method approach was selected because qualitative results can help us to understand the phenomenon of treatment burden in the context of digital health care, and quantitative results can be used to generalize the qualitative findings by measuring their magnitude, trends, causes, and effects [33]. The convergent design was

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most suitable for this review since the research questions can be answered by both qualitative and quantitative findings.

Information Sources and Search Strategy

A systematic search for papers published between January 1, 2013, and October 16, 2023, was conducted from bibliographical databases PubMed, Scopus, Web of Science, ACM, PubMed Central, and CINAHL. The following search string was used: ("Chronic illness" OR "chronic disease" OR "chronic diseases" OR "chronic illnesses" OR "chronically ill" OR "diabetes" OR "asthma" OR "cancer" OR "cystic fibrosis" OR "epilepsy" OR "rheumatoid arthritis" OR "HIV" OR "patient") AND ("Digital" OR "Remote" OR "Mobile" OR "smartphone" OR "smartwatch" OR "smart ring" OR "smart device" OR "smart devices" OR "app" OR "mHealth" OR "eHealth" OR "web-based") AND ("Treatment burden" OR "Burden of treatment" OR "Treatment impact" OR "Treatment workload" OR "Treatment inconvenience" OR "Treatment acceptability" OR "Illness burden" OR "Burden of illness" OR "Medication burden"). To identify relevant papers, a search strategy was conducted in an iterative way. The creation of the search strings for treatment burden was informed by previous systematic reviews on the topic [23,24]. Scoping searches were conducted in several potential databases focusing on health and biomedicine, information technology, nursing, psychology, or multiple disciplines (PubMed, Scopus, Web of Science, ACM, PubMed Central, CINAHL, IEEE, and APA PsycINFO). Scoping searches were conducted on October 15, 2023, in CINAHL and on October 12, 2023, in other databases. Searches conducted on IEEE and APA PsycINFO databases revealed no relevant results, so databases were excluded from the search strategy. Including only certain chronic conditions, for example, epilepsy or neurological conditions, was considered, but there was a limited number of studies found during the initial scoping searches. For example, in the scoping search for epilepsy conducted on October 12, 2023, only 3 relevant papers were identified. Therefore, we decided to keep the scope wide and include all chronic conditions in the search string.

The MeSH term "chronic disease" and search terms "coronary heart disease," "heart disease," "MS," and "multiple sclerosis" were tested during a scoping search in PubMed, but they brought no new results and therefore were removed from the search terms. A supplementary search will be conducted from the citations contained in systematic literature reviews and scoping reviews that were found during the literature searches.

Inclusion Criteria

We have included original publications written in English and accepted in peer-reviewed journals or conference proceedings. Qualitative, quantitative, and mixed method studies are included. The studies can be clinical trials, nonrandomized controlled trials, cross-sectional studies, longitudinal studies, observational studies, case studies, and other types of qualitative studies. Study design will be classified based on the tool from Grimes and Schulz [34]. Conference proceedings are included, but reviews, protocols, and book chapters are excluded.

We limited our search to publications after 2013 to include the last 10 years of research. Although digital health technology has developed quickly in recent years, the use of digital interventions in health care for chronic conditions goes farther than 10 years [35]. To the best of our knowledge, there are no previous systematic reviews relating to both digital health and treatment burden. However, studies before 2013 referred mostly to apps created only for research purposes, which were not available to the public at that time. Therefore, we decided to include papers published after 2013 to cover all relevant publications.

The study population in the included publications must consist of patients who have a chronic condition, their caregivers, or HCPs treating patients with chronic conditions. All ages and ethnicities are included. Only studies with outcomes regarding treatment burden for the patients are included. Studies that do not specifically mention the phrase "treatment burden" or "burden of treatment" but still discuss the impact of health care on the workload and burden for patients are also included. Only studies regarding a digital intervention that facilitates and delivers health care services to patients with chronic conditions are included.

Selection of Studies

After the searches, all titles and abstracts from search results were uploaded to a web-based Covidence screening tool (Veritas Health Innovation), where duplicate records will be removed. All titles and abstracts were screened and selected for inclusion independently by 2 authors (MP and PK or OK). Full-text papers from the selected papers will also be screened and selected for inclusion independently by 2 authors (MP and PK or OK). Disagreements will be resolved by discussion.

Data Extraction

Data on population characteristics, study design, aims, intervention characteristics, measures, and main results will be extracted using a predefined data extraction form in Covidence. Study design will be classified based on the tool from Grimes and Schulz [34]. Before proceeding with data extraction, MP will pilot the data extraction form with 5 papers to identify possible adjustment needs. Data extraction will be performed independently by 2 reviewers (MP and PK or OK). Disagreements will be resolved by discussion.

Risk of Bias

The quality of the included studies will be assessed using Joanna Briggs Institute Critical Appraisal tools. Two reviewers (MP and PK or OK) will assess the quality of each included study independently. Based on the design of the eligible studies, we will use Joanna Briggs Institute checklists designed for randomized controlled trials, quasi-experimental studies, analytical cross-sectional studies, case-control studies, case series, and qualitative studies.

Data Synthesis

A convergent integrated approach to synthesis and integration will be used [32]. This involves converting quantitative data into qualitative data followed by integration of the qualitative and quantitative evidence [36].

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Results

Currently, we have performed searches in the 6 selected databases, and 241 studies have been identified. Screening based on title and abstract excluded 192 studies. Overall, 69 studies have been included in the second round of study selection, which is ongoing. The review is expected to be completed in 2024.

Discussion

This systematic review is performed to investigate the impact of digital health care on the treatment burden of patients with chronic conditions. This review is important because the world is currently facing increasing amounts of chronic diseases, and digital solutions are needed to improve the management of chronic diseases, which pose a significant burden on both health care systems and the patients themselves. However, it is essential to design the digital interventions in a way that helps patients to deal with their existing treatment burden and avoids further increasing the treatment burden. To the best of our knowledge, this will be the first review that covers the impact of digital health care on the treatment burden of patients with chronic conditions. The outcomes are expected to cover the positive and negative impacts of digital interventions on treatment burden and the different types of support digital interventions can provide to people with chronic conditions struggling with treatment burden. We aim to categorize different types of interventions and their components and find potential differences between interventions with different components and chronic conditions with different levels of treatment burden.

For the limitations of this review, the findings will depend on the number of eligible studies we will be able to identify and the quality of these studies. In addition, the studies identified for this review may be heterogeneous in terms of design, interventions, participant groups, and outcomes. Furthermore, our search will be restricted to peer-reviewed studies published in English.

Authors' Contributions

MP developed the initial research questions; design of the review, search, and selection strategies; and drafted the paper. PK and OK contributed to the refining of the research questions; design of the review, search, and selection strategies; and writing and editing of the paper. WB and MI contributed to the editing and approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

HCP: health care professional
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Family Involvement in the Care of Hospitalized Older Adults: Protocol for a Qualitative Evidence Synthesis

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Abstract

Background: Older adults are frequently hospitalized. Family involvement during these hospitalizations is incompletely characterized in the literature.

Objective: This study aimed to better understand how families are involved in the care of hospitalized older adults and develop a conceptual model describing the phenomenon of family involvement in the care of hospitalized older adults.

Methods: We describe the protocol of a qualitative evidence synthesis (QES), a systematic review of qualitative studies. We chose to focus on qualitative studies given the complexity and multifaceted nature of family involvement in care, a type of topic best understood through qualitative inquiry. The protocol describes our process of developing a research question and eligibility criteria for inclusion in our QES based on the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research type) tool. It describes the development of our search strategy, which was used to search MEDLINE (via Ovid), Embase (via Elsevier), PsycINFO (via Ovid), and CINAHL Complete (via EBSCO). Title and abstract screening and full-text screening will occur sequentially. Purposive sampling may be used depending on the volume of studies identified as eligible for inclusion during our screening process. Descriptive data regarding included individual studies will be extracted and summarized in tables. The results from included studies will be synthesized using qualitative methods and used to develop a conceptual model. The conceptual model will be presented to community members via engagement panels for further refinement.

Results: As of September 2023, we have assembled a multidisciplinary team including physicians, nurses, health services researchers, a librarian, a social worker, and a health economist. We have finalized our search strategy and executed the search, yielding 8862 total citations. We are currently screening titles and abstracts and anticipate that full-text screening, data extraction, quality appraisal, and synthesis will be completed by summer of 2024. Conceptual model development will then take place with community engagement panels. We anticipate submitting our manuscript for publication in the fall of 2024.

Conclusions: This paper describes the protocol for a QES of family involvement in the care of hospitalized older adults. We will use identified themes to create a conceptual model to inform further intervention development and policy change.

Trial Registration: PROSPERO 465617; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023465617

International Registered Report Identifier (IRRID): PRR1-10.2196/53255

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(JMIR Res Protoc 2024;13:e53255) doi:10.2196/53255

KEYWORDS

systematic review; family; patient participation; hospital medicine; aged; geriatrics; qualitative research

Introduction

Older adults comprise less than 20% of the US population [1], yet they account for over 40% of hospitalizations at 13.2 million per year [2]. These hospitalizations confer increased risks of infection, functional decline, and cognitive disability [3-7]. There is an urgent need to identify strategies to mitigate the negative sequelae associated with these hospitalizations both by preventing those that are preventable and attenuating the harmful effects of those that are not. Improving family involvement in care may be one strategy to mitigate negative downstream consequences of hospitalization for older adult patients [8-10]. For example, systematic family involvement in the discharge planning process reduces the risk of readmission for hospitalized older adults and is now written into policy in 42 states by the Care Act [11,12]. Implementation of the Care Act is associated with measures of improved patient experience, such as communication with nurses and physicians and receipt of discharge information [12]. There is a critical need to better understand family involvement in the full range of care for hospitalized older adults in addition to discharge planning.

Family involvement in older adults' care has been better described in community and outpatient settings. Up to 36 million family members and friends provide care to community-dwelling older adults in the United States through medication management, care coordination, personal care, and nursing assistance [13]. This work totals roughly 30 billion hours of care annually [14]. A meta-analytical review showed that roughly 40% of adult patients are accompanied by family to primary care visits [15]. This review showed that the presence of family is associated with greater biomedical information giving while increasing the average visit length by 20%, findings that may contribute to patient-centered outcomes like satisfaction with care and that have consequences for workflow and reimbursement [15]. Other work has shown that families participate in ways that can be both helpful and harmful to communication, satisfaction, and the delivery of care in outpatient visits [15-19]. There was some national attention to the importance of family for the delivery of care for hospitalized patients (eg, in information exchange and decision-making) with the imposition of hospital visitor restrictions at the onset of the COVID-19 pandemic [20-22]. However, the full range of extant qualitative evidence describing the roles, tasks, experiences, and outcomes of family involvement in care for hospitalized older adults has not been systematically reviewed, and a conceptual model for this topic has not been developed in the peer-reviewed literature.

Our objective in this study is to better understand how families are involved in the care of hospitalized older adults. An improved understanding of the interactions of family members and the professional medical team can inform future process innovation and policy change. To accomplish our objective, we chose to conduct a systematic review of qualitative studies, known as a qualitative evidence synthesis (QES), regarding family involvement in the care of hospitalized older adults. We chose to focus on qualitative research given that the complex nature of family involvement may be incompletely described through quantitative data. The themes identified in the review will be used to develop a conceptual model of family involvement in the care of hospitalized older adults, building on a prior model of family involvement in other settings (Figure 1) [15]. We anticipate that our refined model will establish a shared language for future multidisciplinary work, inform future intervention development and testing, and motivate workflow and policy changes [23]. This paper describes the protocol for our QES.

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Figure 1. Preliminary conceptual model of family involvement in the care of hospitalized older adults (adapted from Wolff and Roter [15] with permission from Elsevier). Triadic relationships among patients, families, and clinicians in the hospital setting occur within the broader context of the financial and organizational resources and structure of health care within a community and are affected by prehospitalization patient factors, family factors, and clinician factors. The nature of the triadic involvement of patients, families, and clinicians in the hospital setting may affect proximal outcomes during a hospitalization and more distal outcomes post discharge.

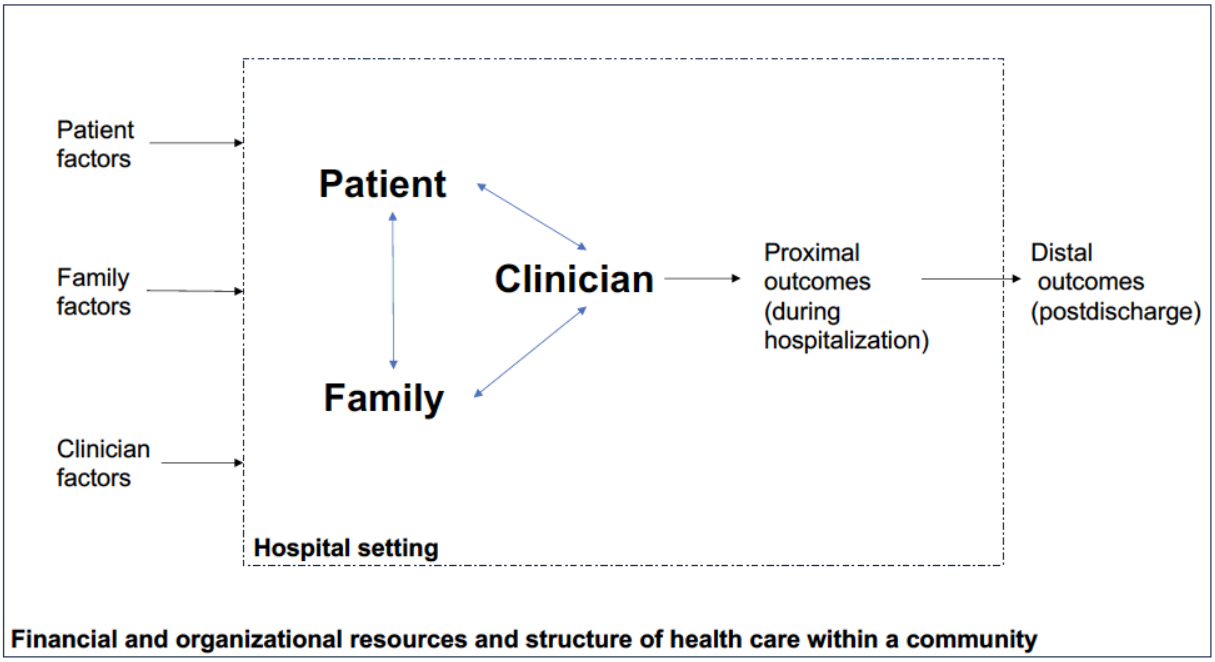

Methods

Overview

The research question of this review is as follows: How are families involved in the care of hospitalized older adults? Qualitative research provides in-depth understanding of human experience and multifaceted social phenomena that cannot be conveyed as richly with quantitative data alone [24]. Family involvement in the care of hospitalized older adults is this kind of complex social phenomenon. We chose a QES, a systematic review of qualitative evidence, for this study given our goal to be comprehensive in characterizing the existing literature on the complex phenomenon of family involvement in the care of hospitalized older adults [25]. We have submitted our review protocol on PROSPERO (ID 465617) and adhere to PRISMA-P (Preferred Items for Reporting Systematic Reviews and Meta-Analyses Protocols) guidelines in this protocol (Multimedia Appendix 1) [26,27]. The review results will be reported in the final paper using the ENTREQ (Enhancing Transparency in Reporting Synthesis of Qualitative Research) guidelines [24].

Eligibility Criteria

Key elements of eligibility for inclusion in the review were specified using the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) tool, a standardized approach to systematic review eligibility criteria for qualitative systematic reviews as an alternative to the PICOT (Population, Intervention, Comparison, Outcome, Time) tool used for quantitative systematic reviews [28]. We define older adults as adults 65 years of age or older or as defined by an individual study's authors as studying "older adults." We use the term family broadly to refer to any family member, friend, or neighbor who is involved in a hospitalization of an older adult motivated by a personal relationship rather than financial remuneration [29]. For the purposes of eligibility in our QES, we do not distinguish between "family members" and "family caregivers" or require that this person be involved in the care of the older adult before or after a hospitalization. We define involvement broadly as inclusion in care processes and include search strategy cognate concepts such as engagement, participation, teamwork, collaboration, and coproduction [30,31]. Only original research studies using primary qualitative data collection and analysis methods and published in peer-reviewed journals are eligible for inclusion. Reference lists of reviews or protocols identified in our search will be manually checked to identify completed original studies that may be eligible in our review. Full inclusion and exclusion criteria, based on our SPIDER question, appear in Table 1.

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Table 1. Sample, Phenomenon of Interest, Design, Evaluation, Research type criteria of eligibility for inclusion in our qualitative evidence synthesis.

Element and definition	Inclusion criteria	Exclusion criteria
Sample		

Who is the sample or population of interest?	• Family of hospitalized older adults:
	  • A study is eligible for inclusion if the majority (>50%) of included patients are older than 65 years if the average age of patients is older than 65 years, or if the study authors define the patient population of interest as being "older adults" (eg, if a study purports to examine hospitalized older adults which authors define in their study as being age 60 years or older)
	  • If age of patients is not specified in the abstract but is otherwise appropriate for inclusion, the title and abstract will advance to full text review
		• Hospitalized older adult patients without family involvement
		• Majority or average of included patients are not older adults (as defined by individual study authors or older than 65 years)

Phenomenon of interest		

What do you hope to understand?	• Family involvement in the care of hospitalized older adults
	• The term family broadly refers to any family member, friend, or neighbor who is involved in a hospitalization of an older adult motivated by a personal relationship rather than financial remuneration
	• Family involvement in care is defined broadly as any type of participation, engagement, interaction with the professional medical team, support, or caregiving
	• The settings of interest include the following:
	• • Emergency department prior to inpatient admission
	  • Medical ward
	  • Medical or cardiac intensive care unit
	• Transitions of care will be included if they include care prior to hospital discharge. If exclusively concerning care after discharge, it will not be included
		• Involvement in the care of older adults in in nonemergency department, nonmedical, or nonmedical or cardiac intensive care unit settings, such as the following:
		• • Surgical ward
		  • Surgical intensive care unit
		  • Emergency department encounters not leading to hospital admission
		  • Outpatient encounters
		  • Hospital at home
		  • Trauma centers
		  • Long-term acute care
		  • Burn units
		  • Inpatient rehabilitation
		  • Urgent care visits
		  • Psychiatric units
		  • Inpatient hospice
		• If patient and family involvement are not at all considered separately (eg, "patient and family engagement" is considered as a single entity rather than distinguishing between patient engagement and family engagement), the paper will be excluded

Design		

What types of study methods are you interested in?	• Qualitative designs:
	  • Phenomenological studies
	  • Ethnographies
	  • Grounded theory studies
	  • Case studies
	  • Narrative inquiries
	  • Discourse analyses
	  • Conversation analyses
	• Qualitative data collection techniques:
	  • Interviews
	  • Participant observation
	  • Focus groups
	  • Review of documents or artifacts
	  • Open-ended surveys
	• Qualitative data analysis techniques:
	  • Thematic analysis
	  • Framework analysis
	  • Content analysis
	• Qualitative components of mixed methods studies will be retained in the review
		• Quantitative studies:
		• Experimental study studies
		• Quasi-experimental studies
		• Descriptive quantitative studies
		• Reviews (though will identify primary research papers from references for consideration of inclusion)
		• Protocols (although will use protocols to search for completed studies that meet inclusion criteria)
		• Nonresearch:
		• Editorials
		• Personal essays
		• Comments
		• Gray literature

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Element and definition	Inclusion criteria	Exclusion criteria
Evaluation		

What are the evaluation outcomes? (These may be subjective such as feelings, attitudes, opinions, etc)	• All outcomes, including the following:
	  • Roles of family
	  • Tasks performed by family
	  • Experiences of family in care delivery
	  • Impacts of family on patient care
	  • Perceptions of family by professional staff
		• None

Research type		
What type of research best suits your question? (qualitative, quantitative, and mixed methods)	• Qualitative • Mixed methods (qualitative aspect)	• Quantitative studies
Language		
Language of publication	• Any	• None • Non-English publications will not be included in the analysis, but citations will be included in the appendix.
Years		
Year of publication	• Any	• None
Countries		
Country where research took place	• Any	• None
Publication types		
Type of publication	• Original research studies in a peer-reviewed journal	• Non-peer reviewed journals • Dissertations • Conference abstract • Gray literature • Lay press • Books • Multimedia

Information Sources

Our review uses the following databases: MEDLINE (via Ovid), Embase (via Elsevier), PsycINFO (via Ovid), and CINAHL Complete (via EBSCO).

Search Strategies

The search strategies used a mix of database-specific subject headings and keywords searched in the title and abstract for the following concepts: family, informal caregivers, older adults, acute care, and the hospital setting. The search was developed and executed by an expert medical librarian, with input on keywords from other authors. The search strategy was peer-reviewed by another expert librarian using a modified PRESS (Peer Review of Electronic Search Strategies) checklist [32]. The search was executed in all 4 databases on August 23, 2023 and yielded 8862 citations in total. The full reproducible search strategies for all databases are included here as a Multimedia Appendix 2.

Study Records

Data Management

Citations resulting from the database searches were uploaded to Covidence (Veritas Health Innovation) [33] and duplicates were removed.

Study Selection

We first piloted our title and abstract screening process by having 4 members of the study team (JBV, BPG, MRS, and MHG), each independently screen the first 50 titles and abstracts according to the inclusion and exclusion criteria specified in our SPIDER criteria; we discussed discrepancies as a group until we reached consensus. We are currently in the title and abstract screening stage in which each title and abstract will be screened in Covidence by 2 reviewers (JBV, BPG, MRS, and MHG) from the study team. When disagreements cannot be resolved by discussion between the 2 reviewers (JBV, BPG, MRS, and MHG), a third study team member will adjudicate. Full texts of papers included for the next stage of screening will then be retrieved and uploaded to Covidence. Each full-text paper will be read by 2 reviewers from the study team and assessed for eligibility based on the inclusion and exclusion

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criteria, with disagreement again resolved through discussion. If the 2 reviewers are unable to reach consensus, a third reviewer from the study team will adjudicate. If data from a single research study are presented and analyzed in multiple papers, we will retain each paper in our review and will denote when a single study is included multiple times. We will include a PRISMA flow diagram in our final paper, which will include reasons for exclusion of papers at the full-text stage [34]. If a study team member has been involved in one of the papers being considered for inclusion in the review, that team member will not be involved in decisions regarding its inclusion or quality (ie, will not be involved in screening its eligibility for inclusion, data extraction, or methodological assessment).

Data Collection Process

A data extraction tool will be created (using Microsoft Excel or similar software) and piloted for use with 2 full-text publications by 2 members (JBV, BPG, MRS, and MHG) of the study team. After piloting and subsequent modification of the data extraction tool, data will be extracted by 1 team member for each included publication, with a second member auditing the data extraction for accuracy.

Data Extraction Items, Outcomes, and Prioritization

Data elements to extract will include characteristics such as journal, journal discipline, publication date, study location, sample size, research design, data collection techniques, data analysis techniques, study setting, funding sources, and theoretical or conceptual framework. This descriptive data will be entered into the data extraction tool. The results section of each included study will also be extracted. All qualitative results related to family involvement in care will be extracted; we do not prespecify or prioritize particular outcomes of interest.

Sampling of Studies

Should the number of eligible studies exceed our ability to perform a high-quality synthesis, we will use purposive sampling to select a sample of studies for synthesis and analysis [35]. We expect to use purposive sampling if the number of eligible studies after full-text review exceeds 40. We will prioritize studies that (1) take place in the United States (the review authors' country), (2) include older adult patients with cognitive impairment (given the greater need for family involvement for patients with impaired decision-making capacity) [36], and (3) are data rich [37]. Data richness will be determined using a previously published data richness scale to score studies on a data richness scale ranging from 1 to 5, with a score of 4 or higher being considered data rich [37].

Assessing the Quality of Included Studies

Two independent reviewers will independently assess the methodological quality of the included studies using the QualSyst tool for qualitative studies [38], with the resolution of final quality assessments reached through discussion. Quality assessments will be entered into Excel along with data extraction. We will report the findings of our quality assessment for each study in a table in the final manuscript.

Data Synthesis

Descriptive data about the studies (eg, journal name, journal discipline, and publication date) will be presented in a table and summarized narratively. We will analyze and synthesize the results from included studies using qualitative methods. Specifically, the results will be uploaded from into qualitative data analysis software such as Dedoose (SocioCultural Research Consultants, LLC), which we will use to facilitate our synthesis [39]. We will choose a synthesis method appropriate to the available pool of evidence, guided by published guidance on doing so, with the expectation that we will likely use thematic synthesis [40-42]. Thematic synthesis includes coding the text of each study's results to develop descriptive themes, which are then used to generate analytical themes [41]. We anticipate using both inductive and deductive methods to identify themes. Deductively, we will consider domains identified in prior models of family involvement in outpatient and long-term care settings and in decision-making including caregiving context; facility context; family tasks, actions, and roles (eg, information exchange, emotional support, and relationship rapport); and patient and family outcomes [15,18,43]. We will meet as a team regularly to discuss review progress and iterate on emerging themes and will present a summary of our findings in a Summary of Qualitative Findings table.

Conceptual Model Development

Once we have formulated a list of themes, we will use them to develop a conceptual model of family involvement in the care of hospitalized older adults to inform intervention development, measurement approaches, and policy needs. We will build on previously published conceptual models of family involvement in health care processes to refine our conceptual model for family involvement in care during hospitalizations of older adults [15,43]. As lead author, JBV will draft the initial model from themes identified in our synthesis of included papers. The study team will then meet iteratively to refine the model. Afterwards, we will obtain community input by eliciting feedback on our themes and conceptual model from family caregiver informants as a form of member checking [44,45]. We plan to perform this step through the Duke Clinical and Translational Science Institute Community Engaged Research Initiative and the Durham VA Veteran Research Engagement Panel to gather feedback and further refine themes and the conceptual model. We expect this step to take place in the spring or summer of 2024.

Review Author Reflexivity

Our multidisciplinary review team includes members with expertise in hospital medicine, general internal medicine, geriatric medicine, nursing, information science, evidence synthesis, social work, and health services research. Throughout all stages of the review process and subsequent model development, we will each be cognizant of how our own backgrounds, views, and beliefs could influence our decisions regarding study eligibility decisions and the interpretation of the data. We will include discussions of potential bias in our regular team meetings. As a review team, we have a variety of backgrounds, which may help to overcome systematic bias in decision-making and analysis. Seven have clinical backgrounds

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(4 in medicine: JBV, BPG, KMG, SNH; 2 in nursing: MHG and TOO; 1 in clinical social work: MRS). Five are family caregiving researchers (JBV, BPG, TOO, CVH, and MHG) and 4 of us have formal training in qualitative methods (JBV, BPG, MHG, and TOO). One is a senior medical librarian (SC) and 1 is a health economist (CVH). Four have formal training in evidence synthesis (JBV, SC, KMG, and TOO). Six have been involved in the care of hospitalized older adults as family members (JBV, MHG, MRS, SNH, KMG, and CVH). We all work in academic settings. As lead author, JBV will keep an account of the review process and decisions made to document and reflect as the project progresses.

Results

The study was submitted for registration in PROSPERO (ID 465617). As of September 2023, we have assembled a multidisciplinary team, developed the research question and inclusion and exclusion criteria, and finalized our search strategy. We executed the search for all 4 databases (MEDLINE, Embase, PsycINFO, and CINAHL Complete), yielding 8862 citations. We are currently screening titles and abstracts and anticipate that full-text screening, data extraction, quality appraisal, and synthesis will take place by January 2024. Conceptual model development will then take place, with initial drafting by the study team followed by community input via Community Engaged Research Initiative and Durham VA Veteran Research Engagement Panel in the spring of 2024. We anticipate submitting our review manuscript in the fall of 2024.

Discussion

Summary

The importance of family involvement in health care delivery has been increasingly recognized [9,10,15,18,29], but family roles, tasks, and interactions with the professional clinical team in the hospital have received less attention than in the outpatient and community settings. Systematic review of family involvement in discharge planning for hospitalized patients supported policy implementation of the Care Act in the majority of US states requiring systematic family involvement in discharge planning [11]. More comprehensive evidence synthesis of how families are involved with other aspects of care for hospitalized older adults has the potential to similarly impact intervention development and policy change that can positively affect public health. The proposed work aims to complete this synthesis via a systematic review of existing qualitative literature regarding family involvement in the care of hospitalized older adults, followed by the development of a conceptual model of family involvement in the care of hospitalized older adults.

Strengths and Limitations

The strengths of the proposed study include its comprehensive approach and the focus on an incompletely understood phenomenon of interest. Systematic reviews of qualitative research are growing in use, but our QES method can still be considered an innovative strength [46]. The multidisciplinary team, including physicians, nurses, a librarian, a social worker, a health economist, and health services researchers with expertise in qualitative methods, evidence synthesis, and clinical care, is another strength of the proposed study. Limitations will likely stem from ambiguity in the phenomenon of interest, which may lead us to miss relevant studies that exist in the literature. This ambiguity surrounding the similar concepts of involvement, engagement, participation, teamwork, and other terms has been previously described [30,32]. We attempt to ameliorate this potential limitation by including as many cognate concepts in our search strategy as keywords based on prior work. Another limitation is intentional and that is the lack of inclusion of quantitative research. It is possible that prior experimental or observational studies that collected quantitative data only would give important information about the experiences of family involvement in the care of older adults that we will not be able to assess in a review of qualitative data alone. However, we maintain that a qualitative approach will identify richer data than that available with existing quantitative data. We anticipate that our included studies will identify roles that family members play. This will help identify narrower topics of interest within the larger phenomenon of family involvement, which will be better suited to a systematic review of quantitative studies in the future (eg, a systematic review of interventions designed to involve families for the purposes of delirium prevention for older adults).

Conclusions

This paper describes the protocol for a QES of family involvement in the care of hospitalized older adults. Themes identified through this review will be used to develop a conceptual model of the phenomenon of interest. We anticipate that the review and conceptual model will be used in the future to improve the health and well-being of hospitalized older adults and their families through optimizing family involvement.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JBV led the study conceptualization and development of the methodology, recruited collaborators, wrote the original draft of the manuscript, and led manuscript editing and revision. BPG contributed to the conceptualization of the study, development of the methodology, and manuscript editing and revision. SC led the development of the search strategy and contributed to manuscript editing and revision. MHG contributed to the conceptualization of the study, development of the methodology, and manuscript editing and revision. SNH contributed to the development of the methodology and manuscript editing and revision. TOO contributed to the development of the methodology and manuscript editing and revision. KMG contributed to the conceptualization of the study, development of the methodology, and manuscript editing and revision, and provided supervision. CVH supervised the conceptualization of the study, development of the methodology, and manuscript editing and revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.
[DOCX File , 17 KB - resprot_v13i1e53255_app1.docx]

Multimedia Appendix 2
Search strategies.
[DOCX File , 46 KB - resprot_v13i1e53255_app2.docx]

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Abbreviations

ENTREQ: Enhancing Transparency in Reporting synthesis of Qualitative Research
PICOT: Population, Intervention, Comparison, Outcome, Time
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Items for Reporting Systematic Reviews and Meta-Analyses Protocols
QES: qualitative evidence synthesis
SPIDER: Sample, Phenomenon of Interest, Design, Evaluation, Research type

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Protocol

Human-Centered Design and Benefit Realization Management in Digital Health Care Solution Development: Protocol for a Systematic Review

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Abstract

Background: Earlier research shows that a significant number of resources are wasted on software projects delivering less than the planned benefits. It has, however, been evidenced that adopting a human-centered design approach when designing health devices can be beneficial. This understanding from earlier research has raised our interest in investigating how human-centered design might contribute to realizing the potential benefits of health care software projects. To our current knowledge, this intersection of human-centered design and benefit realization management has not yet comprehensively and consistently been researched within the context of digital health care solutions. Therefore, there is a need for evidence synthesis using systematic reviews to address this potential research gap.

Objective: The objective of this study is to examine if human-centered design helps benefit realization management processes in the development of digital health care solutions and thereby enables better benefit realization. We explore the evidence of assumed or confirmed benefits of using human-centered design in the health care domain and whether better results have been reported when the benefit realization management process is followed.

Methods: This protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. The proposed review would use a planned and systematic approach to identify, evaluate, and synthesize relevant and recent studies (reported in English) to see if there is evidence that using human-centered design and benefit realization management has a positive effect on realizing set benefits in those projects. We will commence a systematic literature search using human-centered design, benefit realization management, and health care–related search terms within 5 repositories (ACM Digital Library, PubMed Central, Scopus, PubMed, and Web of Science). After removing duplicate results, a preliminary scan for titles and abstracts will be done by at least 2 reviewers. Any incongruities regarding whether to include articles for full-text review will be resolved by a third reviewer based on the predefined criteria.

Results: Initial queries of 2086 records have been executed and papers are being prescreened for inclusion. The search was initiated in December 2023 and the results are expected in 2024. We anticipate finding evidence of the use of human-centered design in the development of digital health care solutions. However, we expect evidence of benefitting from both human-centered design and benefit realization management in this context to be scarce.

Conclusions: This protocol will guide the review of existing literature on the use of human-centered design and benefit realization management when developing digital health care solutions. The review will specifically focus on finding evidence of confirmed benefits derived from the use of human-centered design and benefit realization management. There may be an opportunity to gain a broader understanding of the tools or approaches that provide evidence of increased benefit realization within the health care domain.

International Registered Report Identifier (IRRID): DERR1-10.2196/56125

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(JMIR Res Protoc 2024;13:e56125) doi:10.2196/56125

KEYWORDS

human-centered design; digital health care solution; electronic health record; benefit realization management; digital health care; health care software; digital health; information technology; IT; usability

Introduction

Background

Throughout the last decades, IT investments have grown significantly in all industries. Smaller portions of IT service providers´ budgets are often allocated to seeking improvements in their product or service development practices. Human-centered design (HCD) or user-centered design (UCD) belongs to this portion.

Discussion on Human-Centered Design and User-Centered Design

British Standards Institution defines HCD as "an approach to interactive systems development that aims to make systems usable and useful by focusing on the users, their needs, and requirements, and by applying human factors/ergonomics, and usability knowledge and techniques" [1]. On the other hand, R Kling [2] states UCD is an approach that bases the design, testing, and development of a product or a service on the needs of the users affected by it. UCD can thereby be described as offering a set of principles and strategies to guide the design from the perspectives of (and with input from) those humans who eventually use that product or service. When discussing UCD in the context of digital health care solutions, "user" can refer to many different groups. A user in that context can mean a clinician (eg, a doctor or a nurse), other health care professionals, care givers, or a patient. Given that, it may be more appropriate to talk about HCD, rather than UCD in the health care context, since multiple user groups are of interest here, rather than just one. In addition, Walters [3] and Steen et al [4] differentiate UCD and HCD. They argue that HCD places more emphasis on different stakeholders' varying needs and broader contexts. This definition aligns well with the different user groups we are interested in within the health care context, particularly those who use digital health care solutions.

Digital Health Care Solution

By digital health care solutions, we mean a wide range of technologies used to improve the delivery, efficiency, and accessibility of health care services using digital tools and IT. Some examples of digital health care solutions include telehealth solutions (eg, video conferencing platforms for doctor-patient consultations), electronic health records (ie, electronic systems that store and manage patient health information), and mobile health apps (eg, medication reminder apps and mental health apps).

On Benefits and Related Disciplines

As noted by earlier research [5-7], a significant number of resources are wasted on software projects delivering less than the planned benefits. Furthermore, Tursunvayeva et al [8] discuss how a range of sociotechnical challenges often hamper the benefit realization processes, with many expected improvements (or benefits) either not being realized or only partially realized. These studies also discuss benefits management (BM) and explain that BM is a topic of discussion due to overlapping disciplines within BM, such as benefit realization, benefit realization management (BRM), and value management. Looking back to earlier publications on BM, BM is described as the overall process of evaluating and realizing IT benefits. Ward et al [9,10], on the other hand, define BRM as "the process of organizing and managing such that potential benefits arising from the use of IT are actually realized." In addition, BRM can be described as a comprehensive management idea. The definition of BRM usually focuses on either the benefits lifecycle or the realization of potential investment benefits in change. One often used definition of BRM is "the process of organizing and managing, so that potential benefits, arising from investment in change, are actually achieved" [11]. Tursunbayeva et al [8] also discuss how benefits can be divided into 2 groups when associated with IT projects—expected benefits and realized benefits. The former can have an important role in shaping the enablement of the latter.

Health care professionals have been studied regarding their adaptation to health care technology, and the study showed that technological anxiety had a negative influence on behavioral intention [12]. Furthermore, as noted by Persson [13] in her study on technology-centered versus human-centered perspective in the design and development process, reducing the focus on technical advancements in favor of the needs of the health care user community was found to be favorable. It has also been evidenced that taking an HCD approach when designing health devices, particularly for older adults, can be beneficial and can increase the likelihood of technology acceptance [14]. Consequently, earlier research has shown that planned benefits can be misleading in digital transformation projects unless they are consistently followed up regularly throughout the process.

Establishment of Interest and Consideration

This understanding from earlier research has raised our interest in investigating how HCD might contribute to organizing, managing, and realizing the planned benefits within health care software projects. To our current knowledge, this intersection of HCD and BRM has not yet been comprehensively and consistently researched within the context of health care IT. It is, however, recognized that benefits may not appear as a direct consequence of the implementation of a digital health care solution and those benefits are necessarily not financially measurable (eg, patient or clinician experience) [15]. It is worth noting that there may be multiple reasons for the translational gap in digital health care solution development. We, therefore, value understanding and providing evidence of whether there is already an established correlation and dialogue between design techniques and software development in realizing the

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targeted benefits (both quantitative and qualitative) in the health care context.

Toward the goal of successfully identifying, analyzing, and summarizing these existing studies, we aim to systematically review design and development approaches in the health care domain. This includes examining their design techniques, exploration of BRM, and capabilities to realize the planned benefits. The theoretical assumption of this study is that when HCD is used in digital health care solutions' development projects, the set and planned benefits are better realized. Additionally, it will be controversially considered whether we can assume that a technology-centered approach in the health care sector has contributed to the realization of disbenefits.

Research Questions

In this paper, we examine if HCD helps the BRM process in the development of digital health care solutions**,** thereby enabling better benefit realization.

To address our aims, we have set the following research questions:

- Is HCD used in the design and development of software solutions for health care domain? What are the assumed or confirmed benefits of HCD?
- Is BRM used in the process of developing health care software solutions? Have better results been reported when BRM is included in the process?
- Have there been studies on whether HCD helps the BRM process in the development of digital health care solutions? What is the evidence that planned benefits have been better realized with the help of HCD?

Objectives

To answer our research questions, we have identified the following objectives for the study:

1. to explore the evidence of assumed or confirmed benefits of using HCD in the development of digital health care solutions.
2. to investigate whether there is evidence that better results have been reported when BRM is included in the development process of digital health care solutions.
3. to identify whether there is evidence that planned benefits have been better realized with the help of HCD and BRM in health care context.

Methods

Design of the Study

For the design of the systematic review, we will use the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [16]. PRISMA-P consists of a literature search, article selection and screening, data extraction and analysis, as well as an assessment of study quality and bias. Figure 1 depicts the study structure, which is explained in more detail in the next sections.

Figure 1. Illustration of the study structure.

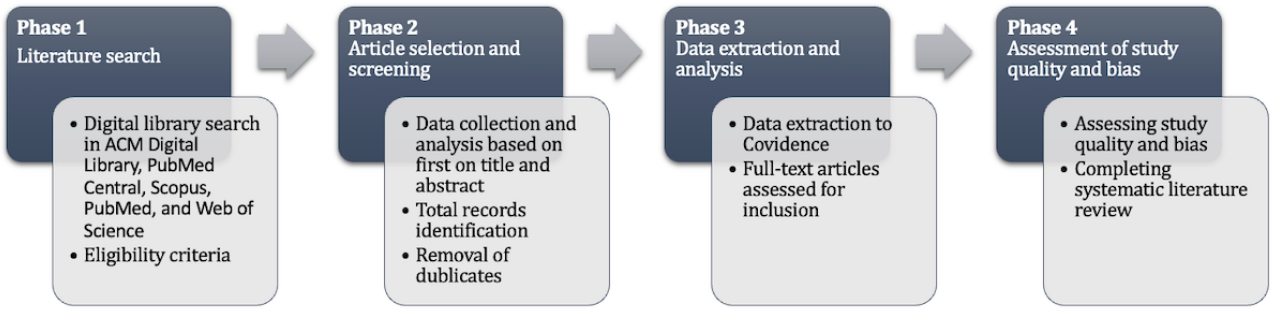

Literature Search

We will survey 5 large databases of digital literature—ACM Digital Library, PubMed Central, Scopus, PubMed, and Web of Science—using keywords and terms presented in Table 1.

Search strings need to be adapted to suit the specific requirements of the different databases and electronic libraries.

Search terms focus on 3 key areas: HCD terms (eg, human-centered and user-centered), BRM terms (eg, benefit management, benefit realization management, and benefit realization), and health care–related terms (eg, electronic health record and health care IT). An initial digital library search has provided 2086 papers.

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Table 1. Used search terms for data collection.

Field of interest	Search string
Human-centered design and related terms (in first round, titles and abstracts are in focus)	"human-centered design" OR "human centered design" OR "human-centred design" OR "human centred design" OR "user-centered design" OR "user centered design" OR "user-centred design" OR "user centred design"
Benefit realization management and related terms (in first round, titles and abstracts are in focus)	"assumed benefits" OR "confirmed benefits" OR "benefit realisation management" OR "benefit realization management" OR "benefit realisation" OR "benefit realization" OR "benefit management"
Health care–related terms (in first round, titles and abstracts are in focus)	e-health OR ehealth OR "health information system" OR "healthcare information system" OR "hospital information system" OR "clinical information system*" OR "electronic health record" OR "digital health" OR "mobile health application" OR mhealth
Combined search strings	("human-centered design" OR "human centered design" OR "human-centred design" OR "human centred design" OR "user-centered design" OR "user centered design" OR "user-centred design" OR "user centred design") AND ("assumed benefits" OR "confirmed benefits" OR "benefit realisation management" OR "benefit realization management" OR "benefit realisation" OR "benefit realization" OR "benefit management") AND ("human-centered design" OR "human centered design" OR "human-centred design" OR "human centred design" OR "user-centered design" OR "user centered design" OR "user-centred design" OR "user centred design") AND (e-health OR ehealth OR "health information system" OR "healthcare information system" OR "hospital information system" OR "clinical information system*" OR "electronic health record" OR "digital health" OR "mobile health application" OR mhealth) AND ("assumed benefits" OR "confirmed benefits" OR "benefit realisation management" OR "benefit realization management" OR "benefit realisation" OR "benefit realization" OR "benefit management") AND (e-health OR ehealth OR "health information system" OR "healthcare information system" OR "hospital information system" OR "clinical information system" OR "electronic health record" OR "digital health" OR "mobile health application" OR mhealth)

Eligibility Criteria

Eligibility will be described by defining the criteria for including articles in the review and the criteria for excluding found publications from further processing. Studies will be selected according to the criteria described in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Only peer-reviewed articles, conference proceedings, and book chapters.
- Papers that describe only quantitative, qualitative, or mixed methods.
- Papers that describe the use of human-centered design methodologies when designing digital health care solutions, such as co-design, cocreation, design sprint, or usability testing.
- Papers that describe the use of benefit realization management when developing digital health care solutions.
- Papers that describe if and how benefits have been realized with the help of human-centered design or benefit realization management when developing digital health care solutions.

Exclusion criteria

- Papers that are purely study protocols, systematic literature reviews, abstracts, posters, short papers, or scoping reviews.
- Papers that are not in English.
- Papers that are not research articles or publication or are otherwise off topic.
- Papers not related to digital health care solutions.
- If human-centered design or benefit realization management is explained but not applied in the digital health care solution.
- Papers that discuss fitness applications, well-being applications, and sport applications (we will only focus on applications and solutions related to therapeutic areas, such as cardiology, neurology, or oncology, that directly affect patient care, either through use by clinicians or together with patients' care givers; therefore, in this review, we will exclude more consumer-targeted applications).

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Article Selection and Screening

After implementing the search strategy on the named databases, the results will be imported into Covidence (Veritas Health Innovation) to initiate the selection and screening process. Covidence automatically identifies duplicates and supports reviewers to execute their screening simultaneously and independently.

In the initial search and screening, the focus will be on titles and abstracts only. Three people will be involved in the screening. Each paper will be reviewed by at least 2 independent reviewers. All reviewers have backgrounds in digital health and information processing science. After completing the initial search and screening phase of the study, reviewers will move on to screening the full texts of the selected articles.

If the reviewers face disagreement in either the initial screening or during the full-text screening, reasons for disagreement will be discussed. If no resolution is found during the discussions, a fourth reviewer may act as an arbitrator to review the disagreed article and decide whether the article will be included or excluded. The disagreement will be documented together with the eventual outcome and its reason.

Data Extraction and Analysis

The key information of the included articles will be extracted using the Data Extraction Form function available on Covidence. The extraction task will be completed by the 2 initial reviewers. The data extraction form within Covidence will assist in the extraction of relevant information from the selected studies.

Assessment of Study Quality and Bias

Quality assessment will be produced in parallel to the data extraction process using a quality assessment form that will be included in Covidence. The quality assessment form will follow the checklist proposed by Dybå and Dingsøyr [17,18]. The checklist highlights the following main focus areas:

- The paper is based on research and research aims are clearly stated.
- Context, where research was carried out, is adequately described.
- The research design and recruitment strategy were appropriate for the aims of the research.
- The data were collected to address the research issues, and the data analysis was rigorous enough.
- The study is of value for research or practice.

Data Synthesis

The included studies may be a collection of qualitative and quantitative data that will need to be transformed into a qualitative format. For data synthesis, narrative synthesis will be used, and therefore, a narrative form with an appropriate table format will be used. The table will consist of categories, such as the use of HCD, the use of BRM, evidence of assumed benefits (quantitative or qualitative), therapeutic areas (eg, cardiology, neurology, or oncology), modality of digital user interfaces (eg, desktop, mobile, or smartwatch), targeted user groups (eg, clinicians, patients, or care givers).

With the help of thematic coding, we will organize the extracted data into categories based on similarities and patterns. The categories will be further developed into a framework that will be used to construct a narrative addressing the proposed research questions and objectives of the review. Overall, the entire search strategy from the search and article selection to data synthesis will be piloted with 3-5 studies to address any need to change the approach.

Results

As of January 2024, we have identified 2086 papers that have met our initial screening criteria. These papers are now being further analyzed to exclude those that do not exactly match our inclusion criteria described in Textbox 1.

Discussion

The objective of this study specifically is to explore whether there is evidence that the use of HCD in the development of digital health care solutions helps the BRM process and enables better benefit realization.

Based on the initial search results and incomplete full paper screening, we can already see that there is evidence of using HCD in the creation of digital health care solutions, and by doing so, the benefits of the chosen design principle have been reported. However, the actual use of BRM in the context of digital health care solutions' development does not seem so evident.

The large number of found papers in the initial search may be considered as a limitation of the study, potentially resulting in a broad sequence of alternative perspectives. We plan to critically review the inclusion and exclusion criteria while screening the remaining abstracts and titles and when reviewing selected full papers. This approach will increase the study's quality level.

This review will enable the critical appraisal and synthesis of evidence on the successful use of HCD and BRM when developing digital health care solutions, leading to a better realization of the benefits set at the beginning of those projects. Controversially, if there is no evidence of both activities and causation, there is an opportunity for new knowledge creation going forward.

Acknowledgments

We would like to acknowledge the Tauno Tönning fund for financing the development of this work.

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Authors' Contributions

KK designed the study and wrote the original draft; PK and SK contributed to the content and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BM: benefits management
BRM: benefit realization management
HCD: human-centered design
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
UCD: user-centered design

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Protocol

Preconception Care Interventions for Adolescents and Young Adults to Prevent Adverse Maternal and Child Health Outcomes: Protocol for an Evidence Gap Map

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Abstract

Background: Preconception is the period before a young woman or woman conceives, which draws attention to understanding how her health condition and certain risk factors affect her and her baby's health once she becomes pregnant. Adolescence and youth represent a life-course continuum between childhood and adulthood, in which the prepregnancy phase lacks sufficient research.

Objective: The aim of the study is to identify, map, and describe existing empirical evidence on preconception interventions that enhance health outcomes for adolescents, young adults, and their offspring.

Methods: We will conduct an evidence gap map (EGM) activity following the Campbell guidelines by populating searches identified from electronic databases such as MEDLINE, Embase, CINAHL, and Cochrane Library. We will include interventional studies and reviews of interventional studies that report the impact of preconception interventions for adolescents and young adults (aged 10 to 25 years) on adverse maternal, perinatal, and child health outcomes. All studies will undergo title or abstract and full-text screening on Covidence software (Veritas Health Innovation). All included studies will be coded using the Evidence for Policy and Practice Information (EPPI) Reviewer software (EPPI Centre, UCL Social Research Institute, University College London). Cochrane Risk of Bias tool 2.0 and Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) tool will be used to assess the quality of the included trials and reviews. A 2D graphical EGM will be developed using the EPPI Mapper software (version 2.2.4; EPPI Centre, UCL Social Research Institute, University College London).

Results: This EGM exercise began in July 2023. Through electronic search, 131,031 publications were identified after deduplication, and after the full-text screening, 18 studies (124 papers) were included in the review. We plan to submit the paper to a peer-reviewed journal once it is finalized, with an expected completion date in May 2024.

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Conclusions: This study will facilitate the prioritization of future research and allocation of funding while also suggesting interventions that may improve maternal, perinatal, and child health outcomes.

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KEYWORDS

preconception health; adolescent; young adult; maternal health; perinatal outcomes; child health; infant health; evidence gap map; EGM; interventions; perinatal health; preconception; young woman; woman; evidence gap; perinatal; map; gap; offspring; maternal; infancy; prepregnancy

Introduction

Preconception health influences the reproductive, perinatal, and child health outcomes of women who are planning their pregnancy [1]. According to the United Nations Population Fund, nearly half of all pregnancies worldwide are unplanned [2,3]; thus, risk factors that can potentially lead to adverse perinatal, maternal, and child outcomes are identified and addressed in the initial prenatal appointment, which usually marks the midpoint of the critical first trimester [4].

Existing literature focuses on identifying risk factors and interventions to prevent adverse maternal, perinatal, and child outcomes among women of reproductive age, who are either pregnant or in their postpartum period [5,6]. However, exposures occur a relatively long time before conception (during adolescence), which has indeed received very limited attention [7]. Adolescence, a phase from childhood to adulthood (from ages 10 to 19 years), marks a critical period of growth and development physically, socially, psychologically, and intellectually. This period also includes the social preparation for marriage or partnering and maturity before reaching adulthood [8]. Since adolescents have fully developed their life skills, they are at greater risk of indulging in risky behaviors such as substance abuse and unsafe sex, leading to adverse outcomes such as unintended pregnancies, pregnancy complications, sexually transmitted diseases, preterm birth, low birth weight (LBW), congenital anomalies, intrauterine growth restriction, behavioral problems, and infant and maternal mortality [9-11].

Preconception care focuses on identifying health problems, poor lifestyle habits, and social health before, during, and after pregnancy, as well as during adolescence [12]. Preconception health interventions can modify behavioral, biomedical, and social risks pertinent to women's health via prevention and management strategies [13]. It increases the need for optimal health before conceiving a baby [14]. Preconception care is a broader umbrella comprising several components such as risk assessment or screening, health promotion and counseling, interventions targeting the identified risks, and referral to specialized preconception care if indicated [15-17].

Screening and risk assessment as part of preconception care helps to assess and gauge a holistic picture of the risk factors that can adversely affect perinatal outcomes [18]. Evidence suggests that perinatal screening and risk assessment help identify the trend of perinatal mortality [19], congenital anomalies [20,21], and general health [21]. Family planning, psychosocial counseling, empowerment of women, health promotion, and education are also important components of preconception care, which aim to increase awareness and modify an individual's behavior, preventing risky behaviors such as substance abuse and unsafe sex [7]. It can also help reduce the risk of unintended pregnancies [22], unsafe abortions [23], sexually transmitted infections, maternal morbidity, and mortality [24]. Another important aspect of psychosocial counseling and health promotion is around healthy weight and nutritional supplementation [25]. Interventions targeting poor outcomes due to inadequate nutrition include social protection programs, food fortification, nutrition counseling, lifestyle modification, and both macro- and micronutrient supplementation [7,25-27]. For example, folic acid supplementation reduces the risk of neural tube defects [28], and iron supplementation reduces the risk of maternal anemia [29]. Multiple micronutrient supplementation in pregnancy has also been shown to reduce the likelihood of a baby who is LBW [27,30], is small for gestation age (SGA) [31], and is premature [27,32]. Social support and social protection programs, such as safe spaces for adolescents and young people, food baskets, conditional cash transfers, and food vouchers, have contributed to improving the mental health and health and nutrition of adolescents, mothers, and their families [33-35]. These programs have also contributed to alleviating issues faced due to poverty and low socioeconomic status and have helped reduce the risk of infant mortality, preterm, LBW, and SGA babies [33]. These interventions have also contributed to reducing the risk of psychosocial stressors, incidence of domestic and sexual abuse, female genital mutilation, and substance abuse among adolescents [34,36].

Despite all the identified interventions in preconception care, the target of positive health outcomes in adolescents and their children has not yet been achieved. Given that many exposures can lead to adverse outcomes in pregnant adolescents and developing fetuses, targeted interventions to improve overall health are understudied. Therefore, we aim to identify, map, and describe the gaps in the existing empirical evidence on preconception health interventions implemented to improve the health and well-being of adolescents and young adults (10 to 25 years of age) and their children.

Methods

Overview

We will undertake an evidence gap map (EGM) exercise to identify the gaps in existing evidence on preconception health

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interventions for adolescents and young adults. EGM analysis visually presents the existing evidence, presenting different types of interventions and outcomes evaluated. EGM is an intuitive tool widely used for identifying gaps in evidence and for decision-making of policy [37]. For the EGM exercise, Campbell's checklist will be followed for reporting standards of the EGM [38,39], and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will also be followed for reporting the purposes [40]. The EGM is also registered at Open Science Framework [41].

Eligibility Criteria

The eligibility criteria for the EGM exercise have been briefly discussed below.

Topic of Interest

In this EGM, studies that have reported on preconception health interventions among adolescents and young adults to prevent adverse maternal and child health outcomes will be included.

Population

We will include studies involving nonpregnant adolescents and young adults aged 10 to 25 years (of all genders) at the time of intervention. We will exclude studies conducted on women of reproductive age older than 25 years; however, we will include studies that report subgroup or disaggregated data on adolescents and young adults. Additionally, we will consider studies on a case-by-case basis if the majority of participants were adolescents and young adults, as determined by assessing the median age at the time of intervention.

Study Design

Systematic reviews of interventions will be included, but for systematic reviews including both interventional and observational studies, data will be extracted from the evidence coming from interventional studies included in the review.

We will also include experimental studies (such as individual or cluster randomized and nonrandomized controlled trials, including quasi-randomized, controlled before-after, and interruptive time series) focused on preconception interventions. Observational studies, qualitative studies, descriptive reviews, narrative reviews, literature reviews, and gray literature will be excluded.

Initially, we will search for systematic reviews on the topic. A separate search will be conducted for experimental studies that did not have a published systematic review on the topic.

Intervention

We will include studies reporting on any intervention intended to improve preconception health compared to any other intervention, standard of care, or no intervention. Previously published reviews and reports served as a guiding road map for preconception intervention [13,42,43]. These interventions include general preconception care, health promotion, sex education, family planning services (including counseling, contraceptive distribution, and birth intervals), nutrition counseling and supplementation, social protection programs, lifestyle modification, vaccination or immunization, screening and management of chronic diseases, prevention of domestic violence, genetic monitoring and testing, social support, telemedicine, vocational training for youth development and empowerment, smoking cessation, prevention of alcohol and substance use (including drug therapy, rehabilitation, and psychosocial support), dental care and hygiene practices, prevention from chemical and environment risk, mental health programs, and prevention and treatment of infections (including sexually transmitted infections). We will exclude studies on infertility treatment.

Outcomes of Interest

We will only include studies that have reported on the impact of preconception health interventions on maternal, perinatal, and child health outcomes, regardless of whether the assessments occurred during adolescence or at any subsequent point following the intervention. We will exclude studies that have not reported on the following outcomes: (1) maternal outcomes include maternal morbidity (as reported by the authors but mainly include outcomes like anemia, gestational weight gain, pre-eclampsia, and postpartum hemorrhage), maternal mortality, pregnancy complications, and mode of delivery (vaginal or cesarean section); (2) perinatal outcomes include miscarriage or spontaneous abortions, stillbirth, perinatal mortality, neonatal mortality, preterm birth, SGA or large for gestation age, intrauterine growth retardation, LBW (<2500 g) or macrosomia (>4000 g), mean birth weight, and congenital anomalies or birth defects; and (3) child and infant outcomes include infant mortality (death under 1 year), child mortality (death under 5 years), early childhood morbidity (as reported by the authors but mainly include outcomes like fever, diarrhea, pneumonia, and other infections), poor growth outcomes, developmental outcomes (eg, poor motor skills), sexually transmitted diseases (transferred through mothers, eg, HIV or AIDS), and mental health issues or disorders

Search Strategy and Databases Search

A search strategy was developed using keywords and MeSH terms on preconception health interventions, adolescents, young adults, and maternal, perinatal, and child health outcomes (Multimedia Appendix 1). The following databases will be used to search the relevant papers: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, and Web of Science. All the systematic reviews will be cross-referenced to retrieve studies that would have been missed during the initial search. The searches will be limited to language and date, that is, studies published in English from 2010 onward. We plan to search data from 2010 because the World Health Organization started a momentum to improve preconception health and address poor maternal and perinatal outcomes through stakeholder meetings across different regions worldwide [13,44]. Through this meeting, the World Health Organization addressed the need for a continuum of care from preconception through pregnancy, aiming to reduce maternal and childhood mortalities by advocating the integration of preconception care into global health strategies.

Screening and Data Extraction

All studies identified from the search will be imported to the Covidence software (Veritas Health Innovation), and 2 independent reviewers will screen the studies at the title or

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abstract and full-text stages, after removing the duplicate studies. The senior reviewer (ZSL) will resolve any disagreements. The final list of included studies will be subject to forward and backward citation chaining to ensure no relevant eligible papers have been missed. A diagram showing the flow of literature will be produced and reported in accordance with PRISMA guidelines [45]. Data will also be extracted in the framework matrix, and mapping will be done independently. Data will be extracted on study design, participants, study setting, intervention, comparison groups, and the outcome assessed.

Quality Assessment of Included Studies

We will appraise the quality of systematic reviews using Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) [46] and Cochrane Risk of Bias 2.0 tool for randomized controlled trials and cluster randomized controlled trials [47], and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for quasi-experimental studies [48]. Two independent reviewers will assess the quality of the included studies, and discrepancies will be resolved through discussion or by contacting the third reviewer (ZSL). The risk of bias assessment of the included studies will highlight the quality of the included trials and reviews, which will help researchers and policy makers to plan studies and programs strategically in the future.

Analysis Approach

The EGM will be created on Evidence for Policy and Practice Information (EPPI) Reviewer (EPPI Centre, UCL Social Research Institute, University College London) and EPPI Mapper software (version 2.2.4; EPPI Centre, UCL Social Research Institute, University College London), where we will use the 2D intervention outcome framework to provide a visual representation of evidence gaps in the literature related to the interventions implemented to improve preconception health. The 2D EGM framework will be formed following the eligibility criteria, in which the interventions would be set as rows and outcomes as columns, and the bubble in the cells of the table will show the studies reporting on that particular intervention and outcome. Empty cells in the table will highlight no evidence on that particular intervention and outcome. The size of the bubble will signify the number of studies, while the color of the bubble will show the quality of the study, gender, or any other selected variable. The maps will be populated based on quality assessment of included studies, gender, age of participants at the time of intervention (adolescents: 10 to 18 years, young adults: 19 to 25 years, and both adolescents and young adults), and country by income. A visual example of EGM is given in Figure 1. The key findings from the EGM will be reported narratively.

Figure 1. A visual example of an evidence gap map.

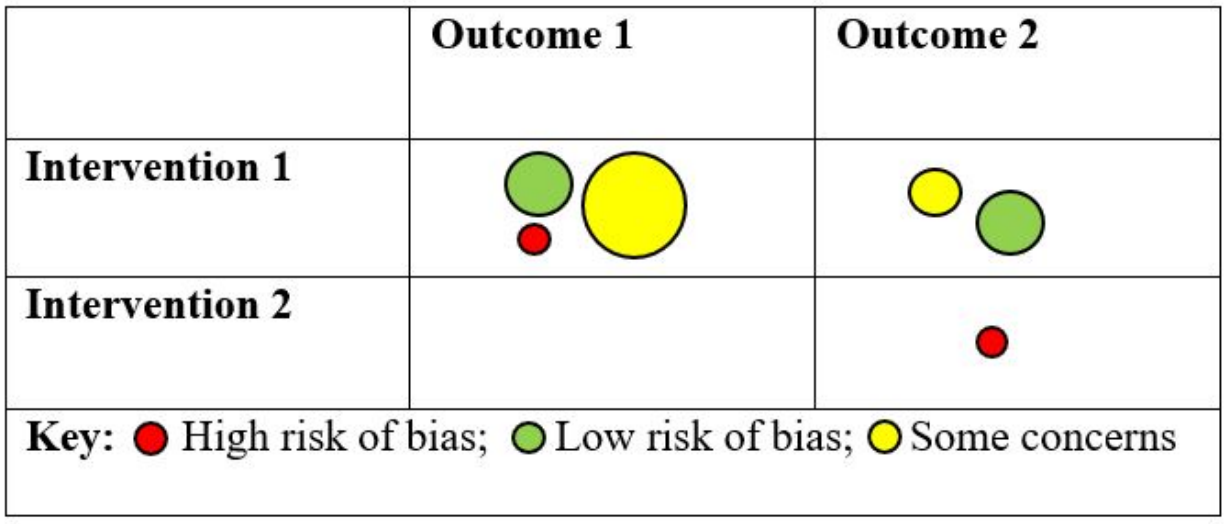

Ethical Considerations

Ethics approval is not required, as this paper is an EGM of publicly available and published literature.

Results

This EGM exercise began in July 2023. Through electronic search, 131,031 publications were identified after deduplication, and after the full-text screening, 18 studies (124 papers) were included in the review. Data analysis and summarization are currently under process. We plan to submit the paper to a peer-reviewed journal once it is finalized, with an expected completion date in May 2024. The findings of this study will identify and highlight the research gaps in preconception health interventions in different contexts and geographical settings. The results of the study will be disseminated among researchers and other stakeholders through publication in a peer-reviewed journal and presentation at national and international conferences. Additionally, we will promote the study's findings on various social media platforms, including Twitter and LinkedIn, and we will also write blogs and newspaper articles to share the results with a broader audience.

Discussion

Overview

To the best of our knowledge, this is the first EGM that will collate all the existing evidence on preconception health

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interventions targeted to adolescents and young adults to prevent adverse maternal, perinatal, and child health outcomes. The 2D matrix of interventions and outcomes will help identify gaps in evidence and will inform policy and funding agencies for further specific areas of research.

Strengths and Limitations

The limitation of this EGM is that it will include studies published after the year 2010 and those published in the English language, thus leading to a loss of studies published prior to 2010 and those published in other languages. The strength of this study is that we will follow the Campbell checklist to report the study findings. We will also follow a systematic approach to search papers, which also involves dual screening and data extraction process. We will also conduct a risk of bias assessment to judge the quality of included trials and systematic reviews.

Conclusions

Adolescents and young adults are a part of an underresearched population. It is also a global health priority to identify, target, and engage adolescents and young adults at preconception in healthy lifestyle interventions to improve health outcomes. The EGM will help map out the spread of preconception care interventions and programs specifically planned and carried out for adolescents and young adults. It will also highlight the evidence on effective preconception interventions for adolescents and young people to improve their health and the health of their future generation and will identify the research gaps in the current evidence base to point out areas in preconception care that underscore research attention for further work. The proposed project is the first step toward identifying interventions that have health and economic benefits for the larger younger population.

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Authors' Contributions

ZAP, GAT, JCA, JAB, SM, and ZSL contributed to the study conception and design. ZAP and KAR built the search strategy, which was reviewed and approved by GAT, JCA, and ZSL. The first draft of the paper was written by ZAP and KAR, which was reviewed by all the other authors. Feedback from all the other authors was incorporated by ZAP.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for MEDLINE.
[DOC File , 34 KB - resprot_v13i1e56052_app1.doc]

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Abbreviations

AMSTAR-2: Assessing the Methodological Quality of Systematic Reviews-2
EGM: evidence gap map
EPPI: Evidence for Policy and Practice Information
LBW: low birth weight
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I: Risk of Bias in Non-Randomized Studies of Interventions
SGA: small for gestation age

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Protocol

Evaluation of Artificial Intelligence Algorithms for Diabetic Retinopathy Detection: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus. The global burden is immense with a worldwide prevalence of 8.5%. Recent advancements in artificial intelligence (AI) have demonstrated the potential to transform the landscape of ophthalmology with earlier detection and management of DR.

Objective: This study seeks to provide an update and evaluate the accuracy and current diagnostic ability of AI in detecting DR versus ophthalmologists. Additionally, this review will highlight the potential of AI integration to enhance DR screening, management, and disease progression.

Methods: A systematic review of the current landscape of AI's role in DR will be undertaken, guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) model. Relevant peer-reviewed papers published in English will be identified by searching 4 international databases: PubMed, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials. Eligible studies will include randomized controlled trials, observational studies, and cohort studies published on or after 2022 that evaluate AI's performance in retinal imaging detection of DR in diverse adult populations. Studies that focus on specific comorbid conditions, nonimage-based applications of AI, or those lacking a direct comparison group or clear methodology will be excluded. Selected papers will be independently assessed for bias by 2 review authors (JS and DM) using the Quality Assessment of Diagnostic Accuracy Studies tool for systematic reviews. Upon systematic review completion, if it is determined that there are sufficient data, a meta-analysis will be performed. Data synthesis will use a quantitative model. Statistical software such as RevMan and STATA will be used to produce a random-effects meta-regression model to pool data from selected studies.

Results: Using selected search queries across multiple databases, we accumulated 3494 studies regarding our topic of interest, of which 1588 were duplicates, leaving 1906 unique research papers to review and analyze.

Conclusions: This systematic review and meta-analysis protocol outlines a comprehensive evaluation of AI for DR detection. This active study is anticipated to assess the current accuracy of AI methods in detecting DR.

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KEYWORDS

artificial intelligence; diabetic retinopathy; deep learning; ophthalmology; accuracy; imaging; AI; DR; complication; retinopathy; Optha; AI algorithms; detection; management; ophthalmologists; early detection; screening; meta-analysis; diabetes mellitus; DM; diabetes; systematic review

Introduction

Diabetic retinopathy (DR) has a profound presence in medicine and ophthalmology. It is one of the most common complications of diabetes mellitus (DM), attacking many areas of the body and causing issues like end-stage renal disease and cardiovascular illness [1]. DR's pathophysiology involves hyperglycemia, loss of capillary structural integrity, inflammation, and neurodegeneration as contributors to the condition's development; eventually, patients will notice signs of visual impairment and potential vision loss [1]. These symptoms burden many people globally, with DR having a prevalence of 8.5% among the world's adult population [2]. Patients with diabetes have an increased DR prevalence of 34.6% [3]. The commonality of this pathology makes careful observation of DM progression and potential DR a priority [3].

DR has a wide distribution in populations, with symptoms ranging from mild to proliferative, and its impact can be detrimental to people's lives. Thus, it is good practice for patients with diabetes to be frequently screened for clinical signs of DR. As of their 2017 update, the American Diabetes Association states patients with type 1 DM are to be initially screened for DR within 5 years of onset, and patients with type 2 DM are to be initially screened at the time of diagnosis; then, they are to be checked annually unless no clinical signs exist, in which they can alternatively be screened every 2 years [4]. As a result, physicians should be well-equipped to screen for DR in their clinics. Done traditionally with a dilated funduscopic examination, there have been increasingly more talks to include artificial intelligence (AI) in DR screening and general clinical decision-making.

AI involves the use of computers to perform tasks that typically require human intelligence. It has taken the world by storm, with industries increasingly exploring its capabilities [5]. The 2017 PwC report on AI projected that AI could significantly increase global gross domestic product, estimating an impact of US $2 trillion to US $4 trillion by 2022, and potentially reaching US $4 trillion to US $8 trillion by 2024 [6]. This growing trend sparked discussions about its potential within health care and medical subspecialties. Ophthalmology is ever growing in technology and innovation; therefore, it is of no surprise to see an initiative for AI integration into this field. Previous advancements in ophthalmic care include integrating telemedicine into DR screenings to decrease appointment wait time adherence difficulties [7]. Wilson et al [8] tackled the increasing demand for screenings by proposing teleophthalmology within primary care clinics. Now, the focus is on AI. Gulshan et al [6,9] used deep convolutional neural networks to grade 128,175 fundus images with remarkable specificity and sensitivity. Furthermore, population demographics are changing, with the median age rising globally and conditions like retinopathy of prematurity becoming more prevalent [10]. The AI revolution is finding ways to improve disease assessment and diagnosis in the field.

Following the course of action shown in Figure 1, this systematic review aims to identify the current and trending use of AI in ophthalmology and their effectiveness in diagnosing, specifically for patients with DR. Factors considered are the sensitivities and specificities of AI versus gold standard diagnostics, accuracy and reliability of mentioned modalities, and their efficiency and economics. Understanding the status of its discussion and integration will help trend industry standards and identify qualms and achievements in the current time. Overall, this systematic review and meta-analysis will critically examine the current body of knowledge regarding the use of AI methods for detecting DR and define its accuracy in comparison to ophthalmologists, or other health care professionals. In addition, this review will evaluate the potential use of AI within the clinical setting to improve DR screening, monitoring, and patient outcomes. Ultimately, this study will provide a detailed understanding of AI's current role in ophthalmology and highlight its potential future applications.

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Figure 1. Steps for inception and conduction of the project. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

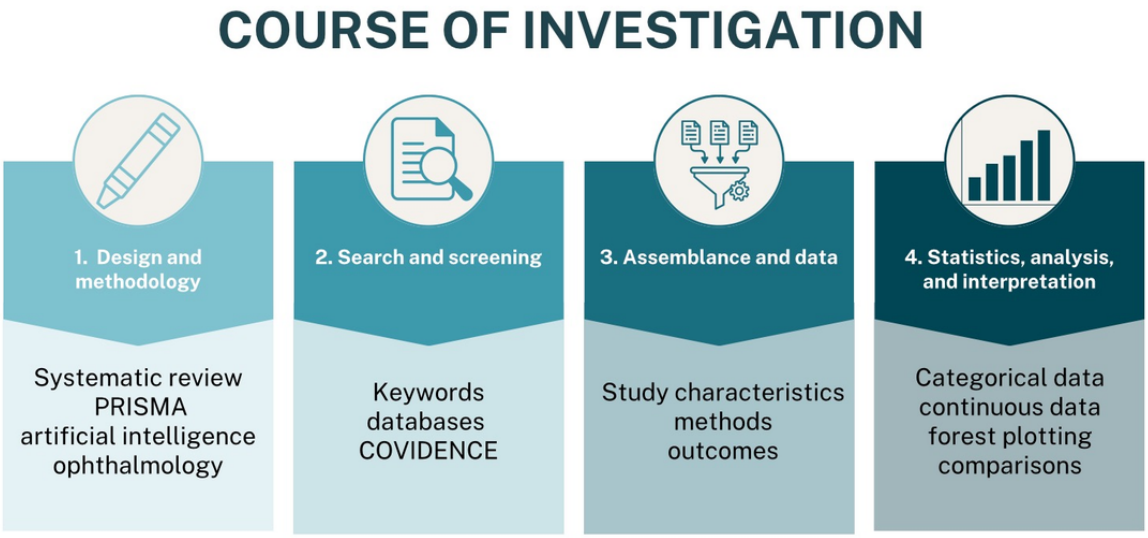

Methods

Overview

A systematic review and meta-analysis will be conducted in concordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [11]. The scope of this systematic review will examine the current body of literature and provide an update regarding the performance and accuracy of AI or machine learning algorithms at detecting DR. Published full-text papers including randomized controlled trials, controlled experiments, or cohort studies are included. Publications that are not original research in nature, such as abstracts, editorials, or review papers will be excluded. In the event of future amendments to this protocol, these changes and the date of implementation will be documented.

Study Design

This systematic review will use multiple web-based databases and perform a quantitative meta-analysis all while following the PRISMA guidelines [11].

Eligibility Criteria

The inclusion and exclusion criteria for the systematic review are given in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
Population	
Individuals 18 years or older	Individuals younger than 18 years
Diverse populations	Populations with specific comorbidities
Intervention	
AI[a] methods in retinal image analysis	Studies with nonimage-based applications
Comparison	
Studies with clear reference for DR[b] diagnosis	Studies without a direct comparison group
Comparisons with ophthalmologist or optometrist	N/A[c]
Outcome	
Measurement of diagnostic accuracy	Outcomes unrelated to DR detection
Study characteristics	
Peer-reviewed studies published on or after 2022	Studies published before 2022
Randomized controlled trials, case-control, or cohort studies	Incomplete or unclear research methodologies

[a]AI: artificial intelligence.

[b]DR: diabetic retinopathy.

[c]N/A: not applicable.

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Search Strategy

Relevant peer-reviewed papers published in English will be identified by searching the international databases: PubMed, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials. The following search queries will be used: ("Diabetic Retinopathy" AND "Artificial Intelligence"), ("Deep Learning" AND "Diabetic Retinopathy"), ("Computer Vision" AND "Diabetic Retinopathy Detection"), ("AI" AND "Accuracy" AND "Diabetic Retinopathy"), ("AI" AND "Sensitivity" OR "Specificity" AND "Diabetic Retinopathy"), ("AI Algorithms" AND "Ophthalmology Workflow"). Only papers published in or after 2022 will be included. Subsequently, the identified studies will be imported and managed as citations using the reference manager EndNote 21 (Clarivate Analytics) [12]. Furthermore, to facilitate the paper screening process, authors will use the systematic review manager software Covidence (Veritas Health Innovation) [5].

Data Management

Study Selection

In the initial screening phase, 2 authors (JS and DM) will independently review the titles and abstracts of the selected studies. They will rigorously evaluate these studies against the predefined inclusion and exclusion criteria, using a designated assessment form. In cases where the selected abstracts lack sufficient information, the full texts of the studies will be retrieved and thoroughly assessed to determine their eligibility. Should any discrepancies arise between the 2 authors (JS and DM) during this process, a third author (VS) will be consulted for their perspective to resolve any disagreements. In situations where data are unclear or missing from the selected studies, the authors of those respective studies will be contacted for clarification.

Data Extraction

The data extraction process will be performed independently by 2 authors (JT and MA) using a standardized data protocol developed by the review authors. The extracted data will include the authors' name, publication year, publishing journal, study location, study characteristics (research design and AI methods), and study outcomes (accuracy, sensitivity, and specificity). The standardized data collection form is summarized in Textbox 1. Any discrepancies arising during data extraction will be resolved through a discussion involving the third author (JSC).

Textbox 1. Components of data extraction.

- Study characteristics
  - Author, year
  - Country
  - Study design
  - Sample characteristics
- Artificial intelligence methods
  - Model
  - Image modality
  - Data source
- Comparator (ophthalmologist, optometrist, and manual grading)
- Outcome measures
- Quality assessment
- Notes

Quality Assessment

A total of 2 review authors (JS and DM) will independently perform a critical appraisal and determine the risk of bias in studies. Using the Quality Assessment of Diagnostic Accuracy Studies tool for systematic review, the methodological quality of eligible studies will be graded for risk of bias as high, low, or unclear risk [13]. Similarly, concerns regarding the applicability of studies will be graded as high, low, or unclear concern of applicability. In case of discrepancies in study evaluation, the resolution will be facilitated by a third author (VS) to reach a consensus.

Data Synthesis and Statistical Analysis

Upon completion of the systematic review, data synthesis will be considered. If among the selected studies, there is sufficient homogeneity for comparison, a meta-analysis will be performed. This will consist of a quantitative approach. The quantitative synthesis will comprise a random effects meta-analysis model to account for between-study variability in addition to within-study variability. Data summarization for dichotomous outcomes will be displayed using odds ratio, relative risk, or hazard ratio with their respective 95% CIs. Data summarization for continuous outcomes will be displayed using the standardized mean difference with 95% CI.

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Heterogeneity will be assessed quantitatively using the I^2 statistic and chi-square test. Values of I^2 greater than 50% will indicate substantial heterogeneity and will be further explored. To address publication bias, funnel plots will be created for each meta-analysis containing 10 or more studies. Any asymmetry in plots will be investigated with the Egger test. If publication bias is detected, the trim-and-fill method will be used to estimate the effect of bias on meta-analysis results.

The statistical analysis will be performed using the Review Manager (RevMan) software (version 5.9.7; The Cochrane Collaboration). For statistical processes not supported on RevMan, STATA (StataCorp) will be used.

Ethical Considerations

The study will involve a secondary analysis of research data. All data compiled from the web-based databases and used for the study are open-access and available to the public. As such, institutional review board or ethics committee approval was not required. Study data will be deidentified to ensure no use of individually identifiable health information.

Results

With the results of this systematic review and meta-analysis, we provide key insight into the trends and advancements in AI algorithms for DR detection, assessing their diagnostic accuracy, sensitivity, and specificity compared to traditional ophthalmological evaluations. We expect to highlight the potential of AI to enhance DR screening and management, emphasizing improvements in efficiency and cost-effectiveness.

Using selected search queries across multiple databases, we accumulated 3494 studies on our topic of interest, of which 1588 were duplicates, leaving 1906 unique research papers to review and analyze. The methods and procedures are conducted in concordance with the PRISMA guidelines, quality assurance is guaranteed with 2 review authors (JS and DM) independently appraising each study, and the process is expected to be completed by the end of January 2025.

Discussion

Principal Findings

DR is one of the most common complications of DM and affects a significant portion of the population. Patients with diabetes should be screened annually for DR. In general, diabetic retinopathy is diagnosed using a dilated fundoscopic examination, and there are discussions about integrating AI, an exponentially growing innovation, into the practice. With an ever-aging population, researchers and clinicians are looking for ways to improve the standard of care. As this is a protocol outlining a study that is yet to be completed, direct comparisons with existing research are not currently available. Future iterations of this work will include a comprehensive comparison with prior studies to contextualize our results within the existing body of literature on AI applications in DR screening and management. This study will look into the sensitivities and specificities of DR detection using AI and compare the results to ophthalmology-trained clinician interpretations. This study will also analyze the efficiency and economics of the tool. It will be possible to obtain all these data when performing a thorough systematic review following the PRISMA guidelines. Key Boolean pairs like “Diabetic Retinopathy” and “Artificial Intelligence” will be used to filter in publications useful for the study.

We expect to find multiple growing trends. For one, the quality of AI is expected to have improved significantly within the last 2 years. Parameters to be improved include the sensitivity and specificity of DR detection in fundoscopy along with its accuracy and reliability. This expectation would match increasing demands for AI use and regulation in our society. Furthermore, the use of AI in DR detection is expected to perform comparably to gold-standard diagnostics, if not better. In addition, the cost of using AI in clinics is expected to have decreased in recent years and be a more cost-effective alternative to the status quo. These expected findings will follow the trend of previous systematic reviews looking into AI performance in health care.

Limitations

Although our goal with the study is to provide a current update on the status of AI in DR screening, the extent of data extraction is limited to English-written papers, leaving out data from papers written in other languages. Our study’s scope is confined to the selected search queries and databases. Therefore, the data compiled will not be truly comprehensive. The final systematic review and meta-analysis may encounter further limitations in data homogeneity and study quality across the diverse array of research papers. Furthermore, the data cannot necessarily inform clinicians how to specifically use AI in their own practice but rather provide an overarching trend of AI capabilities and usage within the field of ophthalmology.

Strengths

AI continues to grow in effectiveness and utility; therefore, updates on its trend have been made constantly. This study will provide the most up-to-date findings on AI’s ability to screen for DR. The use of large-scale databases and multiple variations of search criteria will help filter in the most relevant publications and become very thorough in nature.

Conclusions

This systematic review will review the most up-to-date data on AI functionality in ophthalmic DR screenings. We expect the data to portray AI as a growing and more accurate tool for ophthalmic care. Through analysis of the current state of AI in ophthalmology, a realization of AI’s current and future role in the field will be better understood. In turn, the discovery of trends would help choose decisions on how to evolve clinical practices hereafter.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
DM: diabetes mellitus
DR: diabetic retinopathy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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Protocol

The Experience of Cancer-Related Cognitive Impairment Across Common Cancers: Protocol for a Qualitative Systematic Review

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Abstract

Background: Cancer-related cognitive impairment (CRCI) is commonly experienced by patients with cancer during treatment, and 35% of patients experience cognitive impairment after treatment completion. Impairments in memory, attention, executive functioning, and information processing speed are most reported and often negatively impact daily functioning and quality of life (QoL). Despite the large scale of reports, this adverse side effect is underinvestigated across common cancer types, and there is a lack of insight into the CRCI experience.

Objective: This qualitative synthesis aims to explore the evidence in relation to the experience of CRCI across common cancers. It also aims to understand the prevalence of CRCI across various cancer types, cognitive domains, and its impact on QoL and functional ability.

Methods: A comprehensive search of databases, including PubMed, American Psychological Association PsycINFO, CINAHL, and Scopus, will be conducted. A total of 2 independent reviewers will screen titles and abstracts for inclusion, followed by full-text screening. A third reviewer will resolve any arising conflicts in the process of data screening and inclusion. Subsequently, data extraction and quality assessment using the Critical Appraisal Skills Programme (CASP) tool will be conducted. The results will be analyzed using thematic analysis.

Results: This review is part of a PhD program funded in January 2023. The review commenced in June 2023, and data analysis is currently in progress. The qualitative synthesis will explore the experiences of CRCI across common cancers. The included studies are expected to report on numerous cancer types such as breast cancer, prostate cancer, leukemia, and lung cancer. The included study types are most likely to be interviews, focus groups, and surveys with qualitative components.

Conclusions: This protocol highlights the need for a qualitative synthesis that will explore the experience of CRCI across common cancer types. It will provide valuable insight into the lived experience of CRCI and the cognitive domains that may be disproportionately affected. There is a growing demand for further management interventions and clinically tested treatments of CRCI and the qualitative exploration of patient experience is crucial for their development. This qualitative synthesis will inform future developments and will contribute to improving QoL after cancer.

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KEYWORDS

cancer; neoplasms; cancer survivors; cancer-related cognitive impairment; chemotherapy-related cognitive impairment; qualitative research; executive function; cognition; cognitive impairment; quality of life; common cancer; qualitative synthesis; adult; young adult; functional ability; functional outcome; qualitative; cognitive impairments; cancer survivor; survival rates

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Introduction

Background

The global cancer population is growing rapidly with an estimated 19.3 million new cases and almost 10 million deaths annually [1]. Fortunately, with advances in cancer treatment, survival rates have improved significantly. Despite their well-recognized side effects (eg, joint pain, nausea, depression, and anxiety) [2], treatments, such as chemotherapy, radiotherapy, and targeted cancer drugs, all play a major role in decreasing the incidence and risk of death [3]. Around 75% of patients experience quantifiable cognitive impairment throughout treatment and 35% go on to experience cognitive impairment posttreatment for months and years to follow [4].

Cancer survivors often report problems with memory, attention, executive functioning, and information processing speed [5]. These symptoms associated with cancer treatment are referred to as cancer-related cognitive impairment (CRCI), "chemobrain," or "chemotherapy-induced cognitive impairment (CICI)" [6]. There is currently no standard definition or description of CRCI and the mechanism behind this phenomenon remains unknown [7]. Although not all patients will experience CRCI, some risk factors increase susceptibility such as low cognitive reserve, older age, genetics, and lifestyle factors [8]. The long-term toxic impact of cancer treatments on neurological functioning is a crucial area to investigate in terms of quality of life (QoL).

There is limited literature surrounding CRCI but from current research, we now understand the daily challenges associated with it and the negative impact on QoL [9]. Existing qualitative studies investigating the experience of CRCI in the breast cancer population discovered that patients report feeling "less sharp," which often becomes apparent when returning to routine activities. This has an adverse impact on their ability to function in everyday life [6]. Despite increasing numbers of survivors managing to return to work, CRCI is commonly reported but is not well managed in corporate workplaces. The most reported problems involve planning and executing work and many survivors described feeling fatigued and experiencing psychological distress [10]. Remaining in employment while experiencing CRCI is associated with better QoL than resigning from employment. Therefore, developing management strategies for CRCI in the workplace is of interest to both patients and employers [11]. Furthermore, cognitive symptoms, such as language deficits, also impact interpersonal relationships by causing confusion and miscommunication between family and friends. There are also reports of family members downplaying the severity of symptoms and others report their authority being challenged due to their impairments [12].

There are currently no effective treatments for CRCI; however, there are some interventions that can be implemented to alleviate symptoms. In severe cases, pharmaceutical options, such as antidementia drugs, can be administered to manage cognitive impairment but there is limited clinical evidence of their efficacy [13]. Patients with breast cancer with CRCI were administered donepezil, an antidementia drug, in a trial that found no significant improvements in memory and other cognitive functions [14]. In most cases, these drugs are not required and various management techniques, such as physical exercise, mindfulness, and cognitive training, are implemented [15]. Engaging in aerobic exercise and strength training over a period of 6 months has been shown to improve self-reported cognitive issues, fatigue, and QoL [16]. However, physical exercise may not be feasible for all patients with cancer as treatment side effects often include chronic illnesses such as joint pain [2]. Management techniques often involve introducing prompts such as setting alarms, making notes, writing lists, and implementing a healthy diet can also help. Nonetheless, there is a growing need and demand for alternative evidence-based CRCI treatment and management from patients [17].

Despite the large scale of reports, this adverse side effect is underinvestigated across common cancer types and there is a lack of insight into the CRCI experience. There is insufficient qualitative evidence relating to the experience of CRCI. Existing research primarily focuses on breast cancer compared with other cancers which are often overlooked (eg, prostate, lung, colorectal, and kidney). CRCI is a serious difficulty that has negative implications on daily functioning and QoL and there is currently no sufficient intervention. This review will aim to fill the gap in this field by exploring qualitative and mixed method evidence of the CRCI experience across common cancers. Such a review has not been previously conducted. The findings will provide insights into the prevalence of CRCI, consolidate current knowledge, and identify gaps in the research area. The outcomes could also define specific cognitive domains, cancer types, or treatments that may be disproportionately affected. This review will inform further developments of resources to support the maintenance and management of CRCI.

Objectives

This qualitative synthesis aims to (1) explore the qualitative evidence in relation to the experience of CRCI across common cancers, (2) understand the prevalence of CRCI across various cancer types, (3) understand the impact of CRCI on QoL and functional ability, and (4) understand the impacted cognitive domains.

The research question is as follows: "What are cancer survivors' experiences of cancer-related cognitive impairment across common cancers?"

Methods

Design

The data collection and analysis of this qualitative synthesis will be conducted and reported in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [18] and will adhere to the "Enhancing Transparency in Reporting the Synthesis of Qualitative Research" (ENTREQ guidelines) [19].

Eligibility Criteria

The population phenomenon of interest and context (PICo) framework will be applied to evaluate studies and guide inclusion and exclusion criteria (Textbox 1) [20].

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Interviews
- Focus groups
- Only qualitative components of mixed method surveys including verbatim quotes
- Qualitative data exploring patient experience of cancer-related cognitive impairment
- Qualitative data extracted from mixed method studies

Exclusion criteria

- Gray literature
- Reviews
- Quantitative data including questionnaires with scales or any data without verbatim quotes
- The experience or perception of caregiver or practitioners
- Conditions other than cancer
- Cases where there is no mention of cognitive impairment

Population

The qualitative synthesis will include studies involving patients aged 18 years or older, who are currently undergoing or have completed any cancer treatment and experienced cognitive impairment. There will be no restriction on gender, tumor type, or comorbidities.

Phenomenon of Interest

The phenomenon of interest in this protocol is the experience of CRCI. As there is no definitive term used to describe CRCI across the literature, the following terms will be included: CRCI, cognitive impairment, dementia, mild cognitive impairment, cognitive dysfunction, and cognitive decline. The definition of cognitive impairment aligns with the American Psychological Association Dictionary of Psychology, which defines it as any impairment in perceptual, learning, memory, linguistic, or thinking abilities [21].

Context

This qualitative synthesis will not place any restrictions on the context of patient experiences of CRCI and will include all geographical locations. Contexts are likely to include community-based settings such as the patient's home, residential care facilities, or charitable organizations. Primary care settings may also be included such as general practitioner surgeries, pharmacies, or hospitals.

Search Strategy

A literature search for qualitative and mixed methods studies will be conducted on the following web-based databases: PubMed, American Psychological Association PsycINFO, CINAHL, and Scopus. These databases were selected as they include a wide range of research fields deemed suitable to answer the objectives of this review. A librarian was consulted when forming the search terms to ensure no relevant terms were omitted. The search strategy has been adapted for each database to capture far-reaching and relevant studies. The specific search terms for each database are provided in Multimedia Appendix 1. The search terms were developed based on the PICo framework. The terms included the population of cancer survivors and the phenomenon of CRCI and its experience. There was no condition relating to context, therefore, there were no such terms included in the strategy.

Data Extraction

The results from each database will be uploaded to Rayyan (Qatar Computing Research Institute), an artificial intelligence web-based tool for systematic reviews, where deduplication, collaborative title and abstract screening, collaborative full-text screening, and conflict resolution will be conducted. The remaining titles and abstracts will be screened to identify papers that adhere to the inclusion criteria. Screening will be performed by 2 independent reviewers; any uncertainty will be resolved by discussion. If necessary, a third reviewer will be requested to resolve disagreements. The included papers will then be retained for full-text screening. Subsequently, 2 reviewers will pilot the data extraction together by discussion, selecting 10% of the included studies to verify the agreement between reviewers. This will ensure that the data extracted will adhere to the PICo guidelines, specifically outlining the population, phenomenon of interest, and context relevant to the objective of this review. The included papers will be uploaded to NVivo (version 1.3; Lumivero) which will facilitate systematic and rigorous data synthesis [22]. The following data will be included in the data extraction table: author, year of publication, geographical location, design, data collection method, cancer type, impacted cognitive domains, management techniques, and possible themes. References will be stored in EndNote.

Data Synthesis

The results section will be directly imported to NVivo for data synthesis. Data synthesis will be based on Thomas and Harden's [23] 3-step thematic synthesis methodology. First, line-by-line coding will take place in the results section of each included study to interpret key concepts. These concepts surrounding patient experiences of CRCI will be translated from one study to another. Second, similar codes will be grouped to generate

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"descriptive themes." These themes will be based on verbatim data from the selected studies. The codes and themes will be further reviewed to ensure that the data have been interpreted accurately. Finally**,** inductive reasoning will be used to determine "analytical themes" based on the descriptive themes to capture the patient experience of CRCI. These themes will directly relate objectives of this qualitative synthesis. The analytical themes will be based on the data interpretation of an independent reviewer.

Critical Appraisal for Included Studies

Quality assessment of the included studies will be conducted using the Critical Appraisal Skills Programme (CASP) checklist tool, recommended for use in qualitative synthesis by Cochrane [24]. The CASP tool will be implemented by 2 independent reviewers to evaluate the quality of each of the included studies. Any potential disagreements between reviewers will be resolved verbally until a resolution is reached. An additional reviewer will be consulted if there is significant disagreement until the matter is resolved.

Results

This qualitative synthesis will determine the current studies exploring the experience of CRCI across common cancers in adults aged 18 years or older. The results will presumably report on numerous cancer types such as breast cancer, prostate cancer, leukemia, and lung cancer. However, due to the heavy focus on breast cancer in the existing literature, this cancer type is expected to appear the most. The experiences of CRCI may be varied due to the broad definition of "experience" which could be used to describe many aspects of daily functioning. The management techniques adopted by the patients may also vary due to the different cognitive domains that may be impacted, as well as their employment status.

Although the inclusion criteria involve surveys, most of the qualitative data are likely to be derived from interviews and focus groups. Despite there being no evidence to suggest that CRCI only occurs after treatment, many of the current studies involve patients post treatment. Therefore, it is also reasonable to assume that the included studies will involve patients who have completed treatment rather than those during treatment. Despite reports of CRCI occurring during treatment, many papers report cases after treatment [25,26]. The results of this qualitative synthesis will be a novel addition to the literature and the results will clarify which cancer types and cognitive domains if any, are disproportionately impacted. We will also be able to determine the shared aspects of patients' daily experiences of CRCI across common cancers.

Discussion

Principal Findings

To our knowledge, there is no other qualitative synthesis that explores the experience of CRCI across common cancer types. This qualitative synthesis will be one of a kind as it will collate the experiences of CRCI across cancer types and will identify common themes. From this, we can infer that the experience of CRCI is similar across all cancer types. If there are significant disparities across CRCI experiences, we can deduce which cancer types if any, are affected disproportionately. With global cancer survival rates rapidly increasing, it is essential to explore the long-lasting toxic impact of cancer treatments on neurological functioning. Patients need and are demanding effective CRCI interventions. This qualitative exploration will play a pivotal role in informing further developments of resources to support the maintenance and management of CRCI. There is vast literature surrounding cancer causes and treatment; however, this protocol will bridge the gap in the knowledge as it will provide useful insight into the collective experience of CRCI.

The results of this qualitative synthesis will be submitted for publishing in peer-reviewed scientific journals and will be included in a PhD thesis.

Strengths and Limitations

The selected databases encompass a broad range of disciplines such as medicine, psychology, and nursing. The search strategy for this qualitative synthesis was defined with the assistance of an experienced librarian which allowed for comprehensive and systematic searching of the databases. A total of 2 reviewers will conduct systematic blind screening to decrease the risk of bias and ensure all relevant papers are included. A possible limitation of this qualitative synthesis is that papers were limited to the English language; therefore, some relevant papers may be omitted.

Conclusion

This protocol summarizes the approach for a qualitative synthesis which aims to explore the experience of CRCI across common cancer types. With the rapid rise in global cancer survival, it is essential to explore life after cancer and the potential long-term toxic impact of cancer treatment on survivors' neurological functioning and QoL. This qualitative synthesis will provide valuable insight into the lived experience of CRCI and the cognitive domains that may be disproportionately affected. There is growing demand for further management interventions and clinically tested treatments of CRCI and the qualitative exploration of the experience of CRCI is crucial for their development. This qualitative synthesis will inform future developments and will contribute to improving QoL after cancer.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 16 KB - resprot_v13i1e56888_app1.docx]

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Abbreviations

CASP: Critical Appraisal Skills Programme
CICI: chemotherapy-induced cognitive impairment
CRCI: cancer-related cognitive impairment
ENTREQ: Enhancing Transparency in Reporting the Synthesis of Qualitative Research
PICo: population phenomenon of interest and context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
QoL: quality of life

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Protocol

Incidence, Risk, and Clinical Course of New-Onset Diabetes in Long COVID: Protocol for a Systematic Review and Meta-Analysis of Cohort Studies

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Abstract

Background: COVID-19, an infectious disease pandemic, affected millions of people globally, resulting in high morbidity and mortality. Causing further concern, significant proportions of COVID-19 survivors endure the lingering health effects of SARS-CoV-2, the pathogen that causes COVID-19. One of the diseases manifesting as a postacute sequela of COVID-19 (also known as “long COVID”) is new-onset diabetes.

Objective: The aim of this study is to examine the incidence of new-onset diabetes in patients with long COVID and assess the excess risk compared with individuals who tested negative for COVID-19. The study also aims to estimate the population-attributable fraction for COVID-19 as a risk factor for new-onset diabetes in long COVID and investigate the clinical course of new-onset diabetes cases.

Methods: This is a protocol for a systematic review and meta-analysis. PubMed, MEDLINE, Embase, Scopus, and Web of Science databases will be systematically searched to identify articles published between December 2019 and July 2024. A comprehensive search strategy for each database will be developed using a combination of Medical Subject Headings terms, subject headings, and text words to identify eligible studies. Cohort studies and randomized controlled trials (only control arms) involving patients with COVID-19 of any age, with follow-up data on new-onset diabetes in long COVID, will be considered for inclusion. Controls will comprise individuals who tested negative for COVID-19, with or without other respiratory tract infections. Three independent reviewers (AST, NB, and TT) will perform article selection, data extraction, and quality assessment of the studies. A fourth reviewer (ST) will review the identified studies for final inclusion in the analysis. The random-effects DerSimonian-Laird models will be used to estimate the pooled incidence proportion (%), incidence rate of diabetes (per 1000 person-years), and risk ratio (with 95% CIs) for diabetes incidence.

Results: A total of 1972 articles were identified through the initial search conducted in August 2023. After excluding duplicates, conducting title and abstract screening, and completing full-text reviews, 41 articles were found to be eligible for inclusion. The search will be updated in July 2024. Currently, data extraction is underway, and the meta-analysis is expected to be completed in August 2024. Publication of the study findings is anticipated by the end of 2024.

Conclusions: The study findings should provide valuable insights to inform both clinical practice and public health policies regarding the effective management of new-onset diabetes in patients with long COVID.

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KEYWORDS

COVID-19; SARS-CoV-2; type 1 diabetes; type 2 diabetes; new-onset diabetes; long COVID; incidence; cohort studies; postacute sequela; systematic review; meta-analysis

Introduction

Overview

The COVID-19 caused by SARS-CoV-2 has had devastating effects on people's health [1,2]. Globally, as of September 25, 2023, there have been more than 770 million confirmed cases of COVID-19, including nearly 7.7 million deaths [2].

While COVID-19 is primarily an infectious disease, its bilateral relationship with diabetes is of significant concern [3-5]. Diabetes, a global pandemic that has persisted for decades, is projected to affect 1.31 billion individuals worldwide by 2050 [6]. This chronic and debilitating condition affects multiple organs and systems, including the eyes, kidneys, nerves, heart, and blood vessels, consequently leading to increased morbidity and mortality [6]. Research has consistently shown that individuals with diabetes, whether preexisting or newly diagnosed, incur an increased risk of severe COVID-19, characterized by respiratory distress necessitating intensive care unit admission or mechanical ventilation, sepsis, or multi-organ failure [3,7,8]. Conversely, mounting evidence suggests that COVID-19 may precipitate the onset of diabetes during the acute phase of the illness [4,9,10] and the post-recovery phase [11-17], often referred to as "long COVID" [18].

Long COVID refers to a range of symptoms or conditions that persist or emerge 30 days or more after the initial infection or following hospital discharge (a proxy for clinical recovery) [18]. Research indicates that approximately 43% of individuals who recover from the acute phase of COVID-19 may develop long COVID [19]. Besides new-onset diabetes, patients with long COVID may experience other disorders such as myocarditis, arrhythmias, depression, anxiety, gastrointestinal disturbances, insomnia, muscle fatigue, and cognitive difficulties [19]. The development of diabetes in patients with long COVID can significantly affect their quality of life [20] and is likely to place additional strain on health care systems. Therefore, it is crucial to understand the extent of the risk of developing new-onset diabetes in patients with long COVID for early detection and effective management of this complication. Moreover, this understanding is essential for health care planning and resource allocation.

Previous systematic reviews examining the incidence and excess risk of new-onset diabetes in patients with long COVID (compared to individuals without COVID-19) are subject to several limitations. These limitations include the inclusion of new-onset diabetes cases that occurred during both the acute and post–COVID-19 phases [14], a small number of studies included in the meta-analysis [11,14,15], reliance solely on a single definition for COVID-19 diagnosis (such as the *International Classification of Diseases, Tenth Revision* [*ICD-10*] codes) [16], the absence of meta-analysis [13], and a focus limited to a specific type of diabetes [14]. Moreover, none of these studies have provided data on the clinical trajectory of new-onset diabetes cases or quantified the impact of COVID-19 as a risk factor for new-onset diabetes during the long COVID phase.

Objectives

Our systematic review and meta-analysis objectives are (1) to examine the incidence of new-onset diabetes in patients with long COVID, (2) to evaluate the excess risk of new-onset diabetes in patients with long COVID compared with individuals who tested negative for COVID-19, (3) to estimate the population-attributable fraction (PAF) for COVID-19 as a risk factor for new-onset diabetes in long COVID, and (4) to investigate the clinical course of new-onset diabetes cases.

Methods

Overview

This protocol was developed following standard guidelines, including the Cochrane Handbook for Systematic Reviews [21] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [22]. The PRISMA-P checklist is provided in Multimedia Appendix 1. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42020200432) [23].

Ethical Considerations

As this study does not have the direct involvement of human participants, an ethics committee approval is not required.

Eligibility Criteria

Overview

This study followed the Population, Exposure, Comparator, Outcome, and Study Design (PECOS) framework [24] to formulate the eligibility criteria. All the criteria outlined apply to both the systematic review and meta-analysis, except for those pertaining to the clinical course of new-onset diabetes cases, which are not relevant to the meta-analysis.

Population

Patients of any age diagnosed with COVID-19, either clinically, using diagnostic codes (eg, *ICD-10* codes) [25], or by a positive SARS-CoV-2 test are included.

Exposure

Patients exposed to the SARS-CoV-2 virus infection are included.

Comparators

Comparators will consist of individuals who tested negative for SARS-CoV-2, either with or without other respiratory tract infections.

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Outcomes

Overview

In the long COVID phase, as defined by the US Centers for Disease Prevention and Control (CDC) as 30 days or more after a COVID-19 diagnosis [18] or hospital discharge (a proxy for clinical recovery), the following outcomes will be assessed.

Primary Outcomes

The primary outcomes were, first, the incidence of new-onset diabetes, defined as the absence of previous diabetes history and meeting 1 of the following criteria: fasting plasma glucose (FPG) ≥126 mg/dL, 2-h post-load glucose (2-h PG, or postprandial glucose) ≥200 mg/dL, random blood glucose (RBG) ≥200 mg/dL, or hemoglobin A_{1c} (HbA_{1c}) ≥6.5% [26,27], or diagnosed using *ICD-10* or similar codes for diabetes [25]. Second, the risk ratio for diabetes incidence in patients with COVID-19 compared with controls.

Secondary Outcomes

Secondary outcomes were PAF for COVID-19 as a risk factor for new-onset diabetes and clinical course of new-onset diabetes cases. To investigate the clinical course of new-onset diabetes cases during follow-ups in the post-COVID-19 phase, we will assess (1) persistence and regression of diabetes: the proportion of patients who remained diabetic ("persistence of diabetes") and those who regressed to prediabetes or normoglycemia. Prediabetes is defined as FPG 100 or 110 to 125 mg/dL, 2-h PG 140 to 199 mg/dL, RBG 140 to 199 mg/dL, HbA_{1c} 5.7% or 6.0% to 6.4% [26,27], or diagnosed using *ICD-10* codes or similar codes [25]. Normoglycemia is defined as FPG <100 or 110 mg/dL, 2-h PG <140 mg/dL, RBG <140 mg/dL, HbA_{1c} <5.7% or 6.0% [26,27], or diagnosed using corresponding *ICD-10* codes or similar codes [25]); (2) antidiabetes medication use: the proportion of patients newly initiated on antidiabetes medications (oral drugs or insulin), those who continued, and those who discontinued such medications; (3) diabetes-related complications: the proportion of patients who developed diabetes-related complications such as retinopathy, neuropathy, nephropathy, or foot ulcers; (4) hospitalizations: the proportion of patients hospitalized due to diabetes-related reasons; (5) mortality: the proportion of patients who died due to poor glycemic control or diabetes-related complications; and (6) glycemic control: changes in mean glucose and HbA_{1c} levels over time.

Study Design

Cohort studies and randomized controlled trials (only control arms) with follow-up data on new-onset diabetes in patients with long COVID will be considered. Cross-sectional and case-control studies, case reports, case series, letters, editorials, opinion articles, and comments will be excluded.

Data Sources, Search Terms, and Search Strategy

PubMed, MEDLINE, Embase, Scopus, and Web of Science databases will be systematically searched to identify articles published from December 2019 to July 2024. Using the PECOS framework, a comprehensive search strategy for each database will be developed using a combination of Medical Subject Headings (MeSH) terms, subject headings, and text words to identify eligible studies. In PubMed, the MeSH terms will include "COVID-19," "SARS-CoV-2," "diabetes mellitus," "cohort studies," "longitudinal studies," "follow-up studies," "prospective studies," "retrospective studies," and "randomized controlled trial." Additionally, the reference lists of selected studies, relevant narrative and systematic reviews, and the World Health Organization (WHO) COVID-19 research database [28] will be searched for additional relevant studies. No language restrictions will be applied. If articles written in languages other than English are identified, they will undergo translation by qualified translators. The search strategy utilized for the PubMed database is given in Multimedia Appendix 2.

Study Selection

Three independent reviewers (AST, NB, and TT) will screen the titles and abstracts of studies retrieved from the database search. Afterward, they will screen the full text of the selected studies using the a priori inclusion and exclusion criteria to identify eligible studies. A fourth reviewer (ST) will review the identified studies for final inclusion in the analysis. The percent agreement for study selection between the three independent reviewers will be presented.

Data Extraction

Data will be summarized as means (SDs) or medians (IQRs) for continuous variables and as frequencies (%) for categorical variables. We will design a data extraction form as per the Cochrane Handbook for Systematic Reviews [21]. Data on first author's name, country, data sources, study design, study setting (community or hospital), number of participants with COVID-19, number of participants without COVID-19 or with other respiratory tract infections, age, sex, follow-up time, post–COVID-19 period, number of new cases of diabetes, diagnostic criteria for COVID-19, diagnostic criteria for diabetes, reported risk estimates, type of diabetes, covariates adjusted in regression models, and level of COVID-19 severity will be extracted by 3 independent reviewers (AST, NB, and TT). The reviewers will also collect data on the clinical course of new-onset diabetes cases, as listed under the eligibility criteria section. This includes data on the persistence of diabetes, regression to prediabetes or normoglycemia, mean glucose and HbA_{1c} levels, medication usage, development of diabetes-related complications, and hospitalizations and deaths due to diabetes-related reasons in the long COVID phase. Disagreements in the data extraction between the reviewers will be resolved by discussion or by a fourth reviewer (ST).

Data Management

Articles retrieved from databases and other sources will be imported into the EndNote software (Clarivate), and a separate EndNote file will be created for each data source. These EndNote files will then be exported as "XML" files, which will be imported into the web-based Covidence (Veritas Health Innovation) platform [29]. The Covidence software will be used to remove duplicate records, screen articles, resolve disagreements between the reviewers, conduct data extraction using a customized template, perform risk of bias assessment, create a PRISMA (Preferred Reporting Items for Systematic

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Reviews and Meta-Analysis) flowchart, and export the eligible studies for conducting meta-analysis in RevMan Web (Cochrane) [30] and Stata software (version 18.0; StataCorp) [31].

Risk of Bias and Certainty of Evidence

Three independent reviewers (AST, NB, and TT) will assess the risk of bias in the included studies using the Newcastle-Ottawa Scale (NOS) [32], and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [33] framework to determine the certainty of the evidence. Consensus between the reviewers will be achieved by discussion or by a fourth reviewer (ST).

Data Synthesis

The variances of incidence proportions (%) will be stabilized using the Freeman-Turkey Double Arcsine Transformation method [34]. The random-effects DerSimonian-Laird models [16,35] will then be used to pool the incidence proportion (%) and the incidence rate (per 1000 person-years) of diabetes across studies [35]. Meta-analysis to estimate the risk of developing new-onset diabetes among patients with long COVID compared with controls will use a 2-stage approach [21]. In the first stage, the aggregate effect estimate in each study will be extracted or derived. Subsequently, in the second stage, these estimates will be pooled using DerSimonian-Laird random-effects models [35] to compute pooled hazard ratios and their corresponding 95% CIs for diabetes incidence.

PAF in each study will be estimated using the below formula [36], and the PAFs across studies will be pooled using the random-effects models [35].

Where *P* stands for the proportion of patients with COVID-19 in the entire study population, RR stands for the risk ratio, and PAF is the proportion of all cases of a specific disease in a population attributable to a specific exposure [36]. The degree of between-study heterogeneity will be assessed using the Cochran *Q* test ($P<.01$ for heterogeneity) and Higgins I^2 statistic (low: <25%, moderate: 25%-50%, and high: >50%) [37]. A meta-regression analysis will be performed to identify the sources of heterogeneity. Based on the data availability, subgroup analyses by age, sex, disease severity, hospitalization, follow-up time, the pandemic phase, time since the diagnosis of diabetes, type of diabetes, comorbidities, glycemic status (normal glucose tolerance or prediabetes), controls (no COVID-19 or those with other respiratory tract infections), race or ethnicity, and country will be performed. Publication bias will be assessed by funnel plots [38] and Egger test [39] if 10 or more studies are included in the meta-analyses. A sensitivity analysis will be conducted by excluding low-quality studies to assess the robustness of the primary findings, given the potential variability in study quality and risk of bias. A 2-sided $P<.05$ will be considered statistically significant. Analyses will be performed using RevMan Web (Cochrane) [30] and Stata (version 18.0; StataCorp) [31].

Results

Figure 1 displays the PRISMA flowchart. The initial search was conducted in August 2023. A total of 3306 articles were identified through the database search, with an additional 10 articles from citation searching and the WHO COVID-19 database. After removing 1279 duplicates, the titles, and abstracts of 693 articles were screened. Among these, 606 articles were excluded as they did not meet the eligibility criteria. Subsequently, 87 articles underwent full-text reviews, with 46 articles excluded for various reasons, resulting in 41 eligible articles. Considering the dynamic nature of ongoing research on long COVID, we will be updating the search in July 2024 to retrieve articles that may have been published between August 2023 and July 2024 Table 1 shows the study timeline. Data extraction is currently underway, and the meta-analysis is expected to be completed in August 2024. Publication of the study findings is expected by the end of 2024.

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Figure 1. PRISMA flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

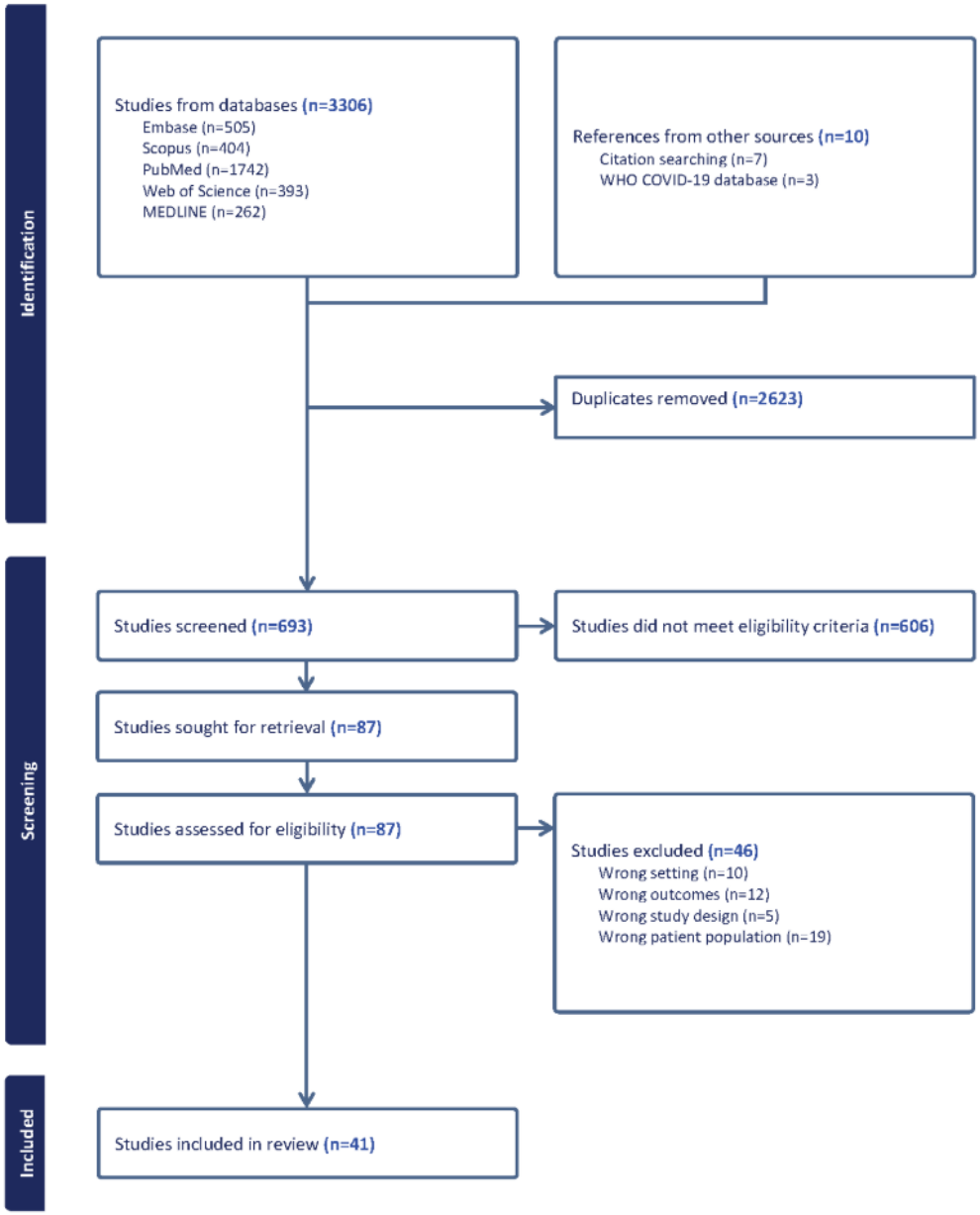

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Table 1. Study timeline.

Tasks	2023								2024							
	May	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July to Sep	Oct to Dec
Formulation of study objectives	✓															
Development of search terms and strategies		✓	✓													
Database search				✓												
Title and abstract screening					✓	✓										
Full-text screening							✓	✓								
Data extraction									✓	✓	✓	✓				
Risk of bias and certainty of evidence assessment									✓	✓	✓	✓				
Database search update												✓			✓	
Meta-analysis														✓	✓	
Paper writing															✓	
Submission of paper for publication																✓

Discussion

Principal Findings

Our systematic review and meta-analysis aim to examine the incidence and excess risk of new-onset diabetes in patients with long COVID compared with controls. The study will also estimate the PAF for COVID-19 as a risk factor for new-onset diabetes and investigate the clinical course of new-onset diabetes cases.

Comparison With Previous Studies

Previous systematic reviews [11-16] have provided data on the burden of new-onset diabetes among individuals experiencing long COVID. However, each of these previous studies was constrained by certain limitations. The study conducted by Zhang et al [16] exclusively included studies where new-onset diabetes was diagnosed solely based on *ICD-10* codes. This methodology may have led to an underestimation of occurrences by overlooking cases identified through blood tests, potentially limiting the study's accuracy in assessing the true burden of new-onset diabetes in patients with long COVID. In the meta-analysis by Bellia et al [12], a deviation from the widely accepted definition of long COVID was observed. By defining long COVID as 60 or more days from the diagnosis, instead of the recommended threshold of 30 or more days postdiagnosis [18], the study excluded potential diabetes cases occurring between 30 and 60 days postdiagnosis. Furthermore, Bellia et al's [12] focus on the prevalence, rather than the incidence, of new-onset diabetes further narrows the scope of the study and limits its applicability in understanding the full extent of diabetes burden in patients with long COVID. The study conducted by Rahmati et al [14] is notable for its inclusion of both acute and patients with long COVID, potentially obscuring the unique risks and outcomes associated with the prolonged phase of COVID-19. The study by Banerjee et al [11] comprised a small number of studies (n=7), potentially constraining the statistical power of the subgroup analyses. Finally, the systematic review by Harding et al [13] lacked a meta-analysis component. While systematic reviews without meta-analyses still provide valuable insights by summarizing and synthesizing existing evidence, the absence of a quantitative synthesis may limit the study's ability to quantify the overall effect size. In summary, these studies have contributed valuable insights into the burden of new-onset diabetes in the context of long COVID. However, their limitations underscore the need for further research efforts to address these gaps and provide a more comprehensive understanding of the impact of long COVID on diabetes incidence and outcomes.

Potential Implications

Our study findings are expected to provide valuable insights for the effective management of patients with long COVID and new-onset diabetes. This includes the development of targeted interventions and therapies aimed at enhancing patient outcomes, along with tailoring interventions to subgroups at higher risk. Additionally, the insights garnered from our study have the potential to inform public health strategies, including vaccination campaigns, preventive measures, and postpandemic planning. Furthermore, our research is anticipated to contribute to the more effective allocation of health care resources.

Strengths and Limitations

Our study will represent the largest investigation conducted to date in estimating the burden of new-onset diabetes in patients with long COVID. Furthermore, it will be the first to derive pooled estimates of the PAF for COVID-19 as a risk factor for new-onset diabetes in long COVID, while also examining the clinical trajectory of new-onset diabetes cases among patients with long COVID. Finally, standard statistical analysis will be

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used for conducting the meta-analysis per the Cochrane Handbook of Systematic Reviews [21]. However, our study also has some limitations. Heterogeneity among the included studies is expected due to potential variations in methodology, study settings, participant characteristics, diagnostic criteria for COVID-19 and new-onset diabetes, and the severity of COVID-19 cases. To address this, we will use random-effects meta-analysis and perform meta-regression and subgroup analyses to identify sources of heterogeneity. Despite our efforts to provide a comprehensive review, the dynamic nature of ongoing research on the long-term effects of COVID-19 may lead to additional studies emerging post-publication of our review. In conclusion, our research holds significant potential to provide valuable insights that can guide both clinical decision-making and public health policies for the effective management of new-onset diabetes in patients with long COVID.

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Data Availability

All data generated or analyzed in this study are included in the published paper and Multimedia Appendices 1 and 2.

Authors' Contributions

ST performed conceptualization. AST, NB, TT, and ST contributed to methodology. AST, NB, and ST contributed to writing—original draft preparation. AST, NB, TT, and ST contributed to writing—review and editing. ST managed project administration and funding acquisition. All authors have read and agreed to the published version of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[DOCX File , 26 KB - resprot_v13i1e54853_app1.docx]

Multimedia Appendix 2
Search strategy employed in PubMed.
[DOCX File , 17 KB - resprot_v13i1e54853_app2.docx]

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Abbreviations

2-h PG: 2-h post load glucose
CDC: Centers for Disease Prevention and Control
FPG: fasting plasma glucose
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
HbA_{1c}: hemoglobin A_{1c}
***ICD-10*:** *International Classification of Diseases, Tenth Revision*
NOS: Newcastle-Ottawa Scale
PAF: population-attributable fraction
PECOS: Population, Exposure, Comparator, Outcome, and Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RBG: random blood glucose
WHO: World Health Organization

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Protocol

Multivisceral Oncological Resections Involving the Pancreas: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: With the continuous advancement of cancer treatments, a comprehensive analysis of the impact of multivisceral oncological pancreatic resections on morbidity, mortality, and long-term survival is currently lacking.

Objective: This manuscript presents the protocol for a systematic review and meta-analysis designed to summarize the existing evidence concerning the outcomes of multivisceral oncological pancreatic resections across diverse tumor entities.

Methods: We will conduct a systematic search of the PubMed or MEDLINE, Embase, Cochrane Library, CINAHL, and ClinicalTrials.gov databases in strict accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The predefined outcomes encompass postoperative mortality, postoperative morbidity, overall and disease-free survival (1- to 5-year survival rates), the proportion of macroscopically complete (R0) resections (according to the Royal College of Pathologists definition), duration of hospital stay (in days), reoperation rate (%), postoperative complications (covering all complications according to the Clavien-Dindo classification), as well as pancreatic fistula, postpancreatectomy hemorrhage, and delayed gastric emptying (all according to the definitions of the International Study Group of Pancreas Surgery).

Results: Systematic database searches will begin in July 2024. The completion of the meta-analysis is anticipated by December 2024. Before completion, the literature search will be checked for new publications that must be considered in the context of the work.

Conclusions: The forthcoming findings will provide an up-to-date overview of the feasibility, safety, and oncological efficacy of multivisceral pancreatic resections across diverse tumor entities. This data will serve as a valuable resource for health care professionals and patients to make well-informed clinical decisions.

Trial Registration: PROSPERO CRD42023437858; https://tinyurl.com/bde5xmfw

International Registered Report Identifier (IRRID): PRR1-10.2196/54089

(JMIR Res Protoc 2024;13:e54089) doi:10.2196/54089

KEYWORDS

meta-analysis; systematic review; multivisceral resection; pancreatic resection; oncological resection; surgery; outcomes; mortality; morbidity; survival; cancer; tumor; pancreas

Introduction

Complete resection stands as the principal curative recourse for nonmetastatic solid malignancies. However, in instances of locally advanced stages, often involving encroachment of adjacent organs or structures, the mere excision of the tumor's origin may prove insufficient. In such scenarios, a multivisceral resection is necessary, entailing the removal of proximate organs [1-4].

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Among abdominal tumors in locally advanced stages such as sarcomas, colon cancer, pancreatic cancer, and gastric cancer, the organs most frequently subjected to resection encompass the colon, gallbladder, stomach, liver, kidney, and notably, the pancreas [1,3,5,6]. While isolated pancreatic operations are acknowledged as intricate interventions bearing considerable risks, including considerable mortality and morbidity rates [2,4], a noteworthy proportion of patients, roughly one-third, undergo pancreatic resection as part of a multivisceral resection [7]. If oncological multivisceral resections include high risk interventions such as a pancreas resection, this can be associated with an additional increase in complication rates [2,3,5,8].

The adoption of such aggressive resections can potentially enhance the prospects of achieving negative resection margins, longer survival times, and even cure [5,9,10]. However, due to the increased surgical trauma, these interventions also introduce supplementary hazards that can compromise outcomes and diminish survival prospects [2,6,8].

The evidence concerning the impact of multivisceral oncological pancreatic resections on morbidity, mortality, and long-term survival across varied tumor entities is characterized by heterogeneity [5,11]. Consequently, formulating evidence-based decisions becomes a formidable challenge.

We plan to conduct a systematic review with meta-analysis to summarize the currently available evidence on morbidity, mortality, and long-term survival in these extensive interventions.

Methods

The literature search and data analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12]. The study has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42023437858) [13].

Search Strategy

With a predefined search strategy (Multimedia Appendix 1), publications will be identified from the databases PubMed or MEDLINE, Cochrane Library, CINAHL, and ClinicalTrials.gov. The search will be performed on articles that were published between database inception and a defined search date. The search strategies used in the individual databases will be documented. Furthermore, the reference list of the included studies will be manually searched to find relevant articles. Titles and abstracts will be evaluated independently in a standardized manner by 2 authors to assess eligibility for inclusion or exclusion. All the potential studies identified from the search will be coded as either “retrieve” (eligible, potentially eligible, or unclear) or “do not retrieve.” For studies coded “retrieve,” 2 reviewers will independently screen the full text and recommend inclusion or exclusion. Disagreements between reviewers will be resolved by consensus. If no agreement can be reached, a third reviewer will decide whether to include the study.

Inclusion and Exclusion Criteria

Publications of observational studies and randomized controlled trials of patients undergoing multivisceral pancreatic resection will be considered. The incorporation of both observational studies and randomized controlled trials may introduce heterogeneity in study designs, potentially impacting the overall quality of evidence. Nevertheless, the inclusion of only one of the 2 study designs may result in insufficient statistical power to reliably detect treatment effects. By defining inclusion and exclusion criteria and assessing the risk of bias, we try to ensure the highest quality and reduce variability. Concerning pancreatic malignancies, multivisceral pancreatic resection refers to the excision of organs beyond the pancreas or spleen in cases of distal pancreatectomy. For multivisceral pancreaticoduodenectomies or total pancreatectomies, the resection encompasses additional organs other than the distal two-thirds of the stomach, the duodenum with the first jejunal loop, the bile duct including the gallbladder, and the spleen. It is important to note that additional procedures like portal vein resection or splenectomy are not categorized as multivisceral resections within the respective resection types. In cases involving nonpancreatic malignancies, any surgical procedure that includes resection of the pancreas along with other organs will be classified as a multivisceral resection. Notably, patients who underwent isolated pancreatic resection for pancreatic metastasis or revision pancreatectomies will be excluded from this analysis. Patients who were not undergoing oncological resections (eg, surgery for traumatic lesions) or those who did not undergo surgery with “curative intent” will also be excluded from the study.

Reviews, clinical case reports or case series, and other scientific papers reporting on fewer than 10 patients, as well as comments and letters, will not be considered. There are no language restrictions. The details of the study selection process will be summarized in a flowchart (Figure 1).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram.

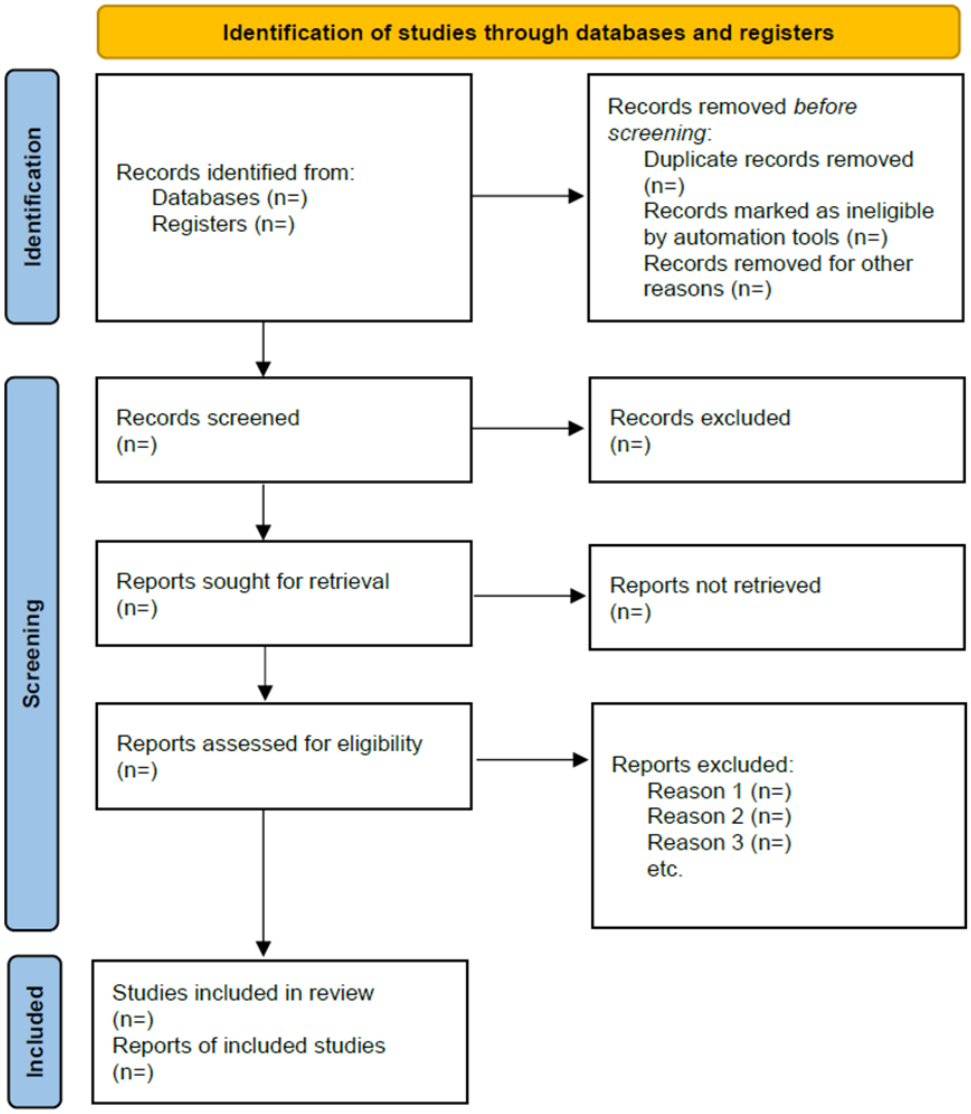

Data Collection

Data from the individual included studies will be extracted separately by 2 authors and collected in a dedicated database. The following descriptive data will be documented for each selected study: first author, year of publication, inclusion period of the study, country where the study was conducted, study size, and median follow-up time.

The distribution of the following patient and operation characteristics will be documented: age (in years), sex (male or female), comorbidities (according to the Charlson Comorbidity Index), American Society of Anesthesiologists classification (6 categories), Eastern Cooperative Oncology Group performance status (scale 0 to 5), tumor entity (eg, pancreatic adenocarcinoma, pancreatic neuroendocrine tumors, cystic pancreatic lesions, lymphoma, sarcoma, gastrointestinal stromal tumors, cholangiocarcinoma, other type of carcinoma, and nonpancreatic-neuroendocrine tumors), tumor stage (according to TNM-classification), neoadjuvant, adjuvant or radiotherapy (yes, no, or regimen), type of pancreatic resection (total pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, or central pancreatectomy), resected organs and structures, date and duration of surgery (in minutes), type of surgical access (open surgery, laparoscopic surgery, or robotic assisted surgery), intraoperative complications (according to Satava's classification and type), as well as blood loss (in milliliters, method used).

The following predefined outcomes will be extracted: mortality (in-hospital, 30-day, or 90-day), morbidity, overall survival (1- to 5-year survival rates), duration of follow-up, recurrence-free survival, proportion of macroscopically complete resection (%), duration of hospital and intensive care unit stay (days), reoperation rate (%), and postoperative bleeding. Postoperative complications are scored and classified using the Clavien-Dindo classification of surgical complications [14]. When the Clavien-Dindo classification is not available, complications will be categorized as major and minor when possible. Resection margins, including transection and circumferential margins of the pancreas, are categorized according to the definition of the Royal College of Pathologists and classified into R0 (distance margin to tumor ≥1 mm), R1 (distance margin to tumor <1 mm), and R2 (macroscopically positive margin). Complications, readmissions, and mortality are all recorded up to 90 days postoperatively. Pancreatic fistula, postpancreatectomy

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hemorrhage, and delayed gastric emptying are categorized according to the definitions of the International Study Group of Pancreas Surgery (Multimedia Appendices 1 and 2) [15].

For each study, the risk of bias will be assessed using the ROBINS-I (risk of bias in nonrandomized studies of interventions) tool suggested by the Cochrane collaboration [16]. An ideal randomized controlled trial on the pertinent research question will be conceived and emulated. The actual studies included in the meta-analysis will be compared with this emulated trial regarding their risk of bias in the following domains:

1. Preintervention domains: bias due to confounding and bias in the selection of participants for the study.

2. Intervention domain: bias in the classification of interventions.

3. Postintervention domains: bias due to deviations from intended interventions, bias due to missing data, bias in measurement of the outcome, and bias in selection of the reported result.

For each domain, the tool foresees signaling questions whose response options are yes, probably yes, probably no, no, and no information. Based on the responses, the risk of bias for each domain will be judged as low, moderate, serious, critical, or no information. From the risk of bias for the single domains, an overall risk of bias for the study will be ascertained according to Textbox 1.

For randomized controlled trials, the risk of bias 2 (RoB 2), the Cochrane risk-of-bias tool for randomized trials, will be used [16]. Like the ROBINS-I tool, RoB 2 is structured into domains of bias, with signaling questions for each domain. Based on the responses and the risk of bias for the single domains, an overall risk of bias for the study will be ascertained (Table 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Article or study type: observational studies and randomized controlled trials of patients undergoing multivisceral pancreatic resections.
- Study population
  - Concerning pancreatic malignancies: resection of organs beyond the pancreas or spleen in cases of distal pancreatectomy or resection of additional organs other than the distal two-thirds of the stomach, duodenum with the first jejunal loop, bile duct including the gallbladder, and spleen for multivisceral pancreaticoduodenectomies or total pancreatectomies.
  - Concerning nonpancreatic malignancies: any surgical procedure that includes resection of the pancreas along with other organs will be classified as a multivisceral resection.
- Reported outcomes: at least one of the following:
  - Mortality (in-hospital, 30-day, or 90-day)
  - Morbidity
  - Long-term survival (1-5–year survival)
  - date of last follow-up and status
  - Recurrence-free survival
  - Proportion of macroscopically complete resection
  - Resection margins, including pancreatic transection and circumferential margins
  - Duration of hospital or intensive care unit stay
  - Reoperation rate
  - Postoperative complications (eg, pancreatic fistula, delayed gastric emptying, or postpancreatectomy hemorrhage)
- Language: all languages.

Exclusion criteria

- Article or study type:
  - Reviews
  - Case reports
  - Case series with fewer than 10 patients
  - Commentaries
  - Letters
- Study population:
  - Additional procedures like portal vein resection or splenectomy are not categorized as multivisceral resections in the case of distal pancreatectomy, multivisceral pancreaticoduodenectomies, or total pancreatectomies.
  - Patients who underwent isolated pancreatic resection for pancreatic metastasis or revision pancreatectomies.
  - Patients who were not undergoing oncological resections or did not undergo surgery had “curative intent.”
- Reported outcomes: none of the outcomes mentioned as inclusion criteria.

Table 1. Bias judgment [16].

Overall risk of bias judgment	Interpretation	Criteria
Low risk of bias	The study is comparable to a well-performed randomized trial.	The study is judged to be at low risk of bias for all domains for this result.
Moderate risk of bias	The study appears to provide sound evidence for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial.	The study is judged to be at low or moderate risk of bias for all domains.
Serious risk of bias	The study has one or more important problems.	The study is judged to be at serious risk of bias in at least one domain but not at critical risk of bias in any domain.

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Statistical Analysis

As stated, all studies will undergo a qualitative analysis by examining data through techniques like coding and thematic analysis to uncover patterns and meanings. It aims to provide a rich understanding of the subject by considering context, multiple perspectives, and researcher reflexivity. An analysis will be performed for all comparative trials. A separate analysis will be performed for randomized trials. Furthermore, a meta-analysis will be conducted exclusively for comparative studies, which involve a cohort of patients undergoing nonmultivisceral oncological resections for direct comparison. Subgroup analyses will be executed for each distinct tumor entity encompassed within the study, including sarcoma, colon cancer, pancreatic cancer, gastric cancer, and other oncological conditions. Also, a stratification according to different tumor types, for example, pancreatic ductal adenocarcinoma or pancreatic neuroendocrine tumors, will be conducted.

The Review Manager software (version 5.4; The Cochrane collaboration) will be used. A random effects model will be used to assess the effect estimate. Visualization will be facilitated through forest and funnel plots to illustrate the magnitude of the effect. Dichotomous data will be subjected to odd ratio analysis with 95% CIs. Continuous data will undergo mean difference calculations alongside 95% CIs, and if continuous outcomes are assessed on different scales, a standardized mean difference with corresponding 95% CIs will be determined. When the studies do not report mean difference and standardized mean differences, these will be calculated using the methods described by the guidelines of the Cochrane collaboration [17] and Hozo et al [18]. If hazard ratios are not reported, the team may digitize the curve and calculate them. If the proportional hazards assumption is not met, the team might explore alternative statistical methods such as stratified analysis or time-dependent covariate analysis to appropriately handle the violation. The 95% CI, heterogeneity, and statistical significance will be reported for each outcome. The chi-square and Kruskal-Wallis tests will be used for the evaluation of statistical significance. A value of $P<.05$ will be considered statistically significant. The outcome "postoperative complications" will be assessed when possible, according to the Clavien-Dindo classification [14].

Sensitivity analyses will be conducted according to the risk of bias ascertained as previously described. For these, all studies with a high or serious risk of bias will be excluded, and the analyses of the outcomes, as previously described, will be conducted. To determine the quality of the evidence, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria (study limitations, consistency of effect, imprecision, indirectness, and publication bias) will be used. In accordance with GRADE, evidence will be distinguished between high, moderate, low, or very low [19].

Ethical Considerations

Due to the nature of the data used in this meta-analysis, which involves aggregate information from previously published studies, ethical approval is deemed unnecessary.

Results

Database searches will commence in July 2024. The meta-analysis will be completed by December 2024. Before completion, the literature search is checked for new publications that must be taken into account in the context of the work.

Discussion

This systematic review with meta-analysis will synthesize all available evidence on the feasibility, safety, and oncological effectiveness of multivisceral pancreatic resections in various tumor diseases. Due to the limited number of eligible studies, we include both observational studies and randomized controlled trials, which may introduce heterogeneity in the study designs, potentially affecting the overall quality of the evidence. Nevertheless, the inclusion of only one of the 2 study designs may result in insufficient statistical power to reliably detect treatment effects. Additionally, inherent limitations in retrospective studies might impact the overall quality of the evidence. Hence, we enhance the statistical power by consolidating the findings from both study methods. Through the establishment of clear inclusion and exclusion criteria and rigorous assessment of bias risks, our aim is to uphold the highest quality standards and reduce variability. Furthermore, minor differences in skill levels and learning curves among surgeons, as well as the focus on specific academic research institutions, may impact the generalizability of the findings. We will thoroughly address these limitations in the discussion section and, if feasible, conduct subgroup analyses to enhance the quality of our analysis. This systematic review and meta-analysis will be conducted according to the defined protocol presented here and will be reported following the recommendations stipulated in the PRISMA [12,20] statement, thus ensuring the highest quality standards and minimizing the risk of possible bias. The expected results will provide new information on the prognostic value of multivisceral pancreatic resections in various tumor diseases and thereby support health care professionals and patients in their decision-making.

Acknowledgments

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Authors' Contributions

All authors conceived the concept and design. MG conducts the literature search strategy. MN, JF, and AR will conduct article screening and data extraction. JU, J Klose, J Kleeff, UR, and AR act as surgical experts. All authors drafted this manuscript, revised it for content, and provided the final approval of this version. AR, the corresponding author, is the guarantor of the review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 41 KB - resprot_v13i1e54089_app1.docx]

Multimedia Appendix 2
Variables.
[DOCX File , 15 KB - resprot_v13i1e54089_app2.docx]

Multimedia Appendix 3
Index, scores, and definitions.
[DOCX File , 18 KB - resprot_v13i1e54089_app3.docx]

Multimedia Appendix 4
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist.
[DOCX File , 29 KB - resprot_v13i1e54089_app4.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RoB 2: risk of bias 2
ROBINS-I: risk of bias in nonrandomized studies of interventions

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Protocol

Efficacy and Safety of Remimazolam Versus Etomidate for Induction of General Anesthesia: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Postinduction hypotension (PIHO) is a hemodynamic abnormality commonly observed during the induction of general anesthesia. Etomidate is considered a safer drug for the induction of anesthesia because it has only minor adverse effects on the cardiovascular and pulmonary systems. Recent evidence indicates that the novel benzodiazepine remimazolam has minimal inhibitory effects on the circulation and respiration. However, the efficacy and safety of remimazolam versus etomidate in the induction of anesthesia are unclear.

Objective: To further understand the potential of remimazolam in anesthesia induction, it is necessary to design a meta-analysis to compare its effects versus the classic safe anesthetic etomidate. The aim of this study is to determine which drug has more stable hemodynamics and a lower incidence of PIHO. Our study will also yield data on sedation efficiency, time to loss of consciousness, time to awakening, incidence of injection pain, and postoperative nausea and vomiting with the two drugs.

Methods: We plan to search the Web of Science, Cochrane Library, Embase, PubMed, China National Knowledge Infrastructure, and Wanfang databases from the date of their creation until March 31, 2025. The language is limited to English and Chinese. The search terms are “randomized controlled trials,” “etomidate,” and “remimazolam.” The incidence of PIHO is the primary outcome measure. Secondary outcomes include depth of anesthesia after induction, sedation success rate, time to loss of consciousness, hemodynamic profiles, recovery time, incidence of injection pain, and postoperative nausea and vomiting. Reviews, meta-analyses, case studies, abstracts from conferences, and commentaries will not be included. The heterogeneity of the results will be evaluated by sensitivity and subgroup analyses. RevMan software and Stata software will be used for data analysis. We will evaluate the quality of included studies using version 2 of the Cochrane risk-of-bias tool. The confidence of the evidence will be assessed through the Grading of Recommendations, Assessments, Developments, and Evaluations system.

Results: The protocol was registered in the international PROSPERO (Prospective Register of Systematic Reviews) registry in November 2023. As of June 2024, we have performed a preliminary article search and retrieval for further review. The review and analyses are expected to be completed in March 2025. We expect to submit manuscripts for peer review by the end of June 2025.

Conclusions: By synthesizing the available evidence and comparing remimazolam and etomidate, we hope to provide valuable insights into the selection of anesthesia-inducing drugs to reduce the incidence of PIHO and improve patient prognosis.

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Trial Registration: PROSPERO CRD42023463120; https://tinyurl.com/333jb8bm
International Registered Report Identifier (IRRID): PRR1-10.2196/55948

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KEYWORDS

general anesthesia; anesthesia induction; postinduction hypotension; remimazolam; etomidate; meta-analysis

Introduction

As medical care advances worldwide, the number of patients undergoing surgery under general anesthesia has increased [1]. Postinduction hypotension (PIHO) is a hemodynamic abnormality commonly observed during induction of general anesthesia [2], which is defined as hypotension occurring within 20 minutes after anesthesia induction or before surgical incision. The incidence of PIHO was reported to reach 45%-55% [3-5]. Common PIHO risk factors include methods and dosages of anesthesia, poor baseline condition of the patient, hypovolemia, and poor cardiac function [6]. Because circulatory reserves weaken with age, older patients are especially vulnerable to the development of PIHO [7]. Acute renal damage [8], neurocognitive dysfunction [9], and perioperative cardiovascular events [10] are all linked to PIHO. Moreover, PIHO has been associated with increased mortality (8.8%), intensive care unit admission (7.9%), and requirement of postoperative mechanical ventilation (20.7%) [8,11]. Therefore, it is important to find safer and more effective anesthesia-inducing drugs to avoid PIHO.

Most intravenous anesthetics have a direct inhibitory effect on circulatory function [12]. Previous studies have found that etomidate has minimal adverse effects on the cardiovascular and pulmonary systems [13-15]. Etomidate is considered to be a somewhat safer drug for the induction of anesthesia in patients undergoing heart surgery because of the reduced risk of hypotension [16,17]. However, the drawbacks of etomidate, including adrenocortical depression and myoclonus, have limited its clinical use [18].

Remimazolam is a novel drug in the benzodiazepine class [19], and its effects initiate and end more rapidly than achieved with the common benzodiazepine midazolam. Remimazolam can be continuously infused owing to its ultrashort-acting profile [20]. Additionally, its clearance is not dependent on liver or renal function because the drug is metabolized by tissue esterase [21,22]. Recent research has shown that remimazolam and propofol have comparable rates of sedative success but that remimazolam is associated with less respiratory and circulatory depression [23-25].

However, the evidence comparing remimazolam and etomidate for induction of general anesthesia is conflicting. Huang et al [26] found that the remimazolam group had a higher incidence of PIHO and a lower heart rate during induction than the etomidate group. However, some studies have found that low-dose remimazolam is hemodynamically more stable and has fewer adverse effects than etomidate in noncardiac and cardiac surgery [27,28].

Therefore, to further understand the potential of remimazolam, it is necessary to design a meta-analysis to compare the effects of remimazolam versus the classic, safe anesthetic etomidate in the induction of general anesthesia. These results can help to determine which drug has more stable hemodynamics and a lower incidence of PIHO. In addition, our study will yield data on sedation efficiency, time to loss of consciousness, time to awakening, incidence of injection pain, and incidence of postoperative nausea and vomiting with the two drugs.

Methods

Study Registration

This meta-analysis is registered in the international PROSPERO (Prospective Register of Systematic Reviews) registry (CRD42023463120). The protocol is reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [29] (Multimedia Appendix 1)

Search Strategy

We plan to search the Web of Science, Cochrane Library, Embase, PubMed, China National Knowledge Infrastructure, and Wanfang databases from the date of their creation until March 31, 2025. The language is limited to English and Chinese. We will identify additional relevant studies by screening the references of related research and the International Clinical Trials Registry platform. Multimedia Appendix 2 displays the complete PubMed search strategy.

Eligibility Criteria

Studies are considered eligible for inclusion in the systematic review and meta-analysis based on the Patients/Population, Intervention, Comparison, Outcomes, and Study design (PICOS) criteria as follows: patients aged 18 years or older undergoing surgery under general anesthesia, remimazolam as the intervention delivered at the induction of anesthesia compared to anesthesia induction with etomidate, primary outcome is the incidence of PIHO, and the effect of the intervention is assessed in randomized controlled trials.

Study Selection

Two authors will independently determine the articles retrieved from the databases that are eligible for inclusion by screening the titles and abstracts of prospective eligible papers and then examining the full texts of the publications. Disagreements will be settled through dialogue with a third author. Studies will be selected according to the PRISMA selection process.

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Data Extraction

Two authors will independently extract the following information from the included studies: first author, year of publication, patient characteristics, sample size, dosage of remimazolam, type of surgery, incidence of PIHO, time to loss of consciousness, and recovery time. We will attempt to contact the corresponding author for raw data if the results are reported as the median and range. If there is no response, the median and range values will be converted to the mean and standard deviation according to the methods described by Hozo et al [30]. Any disagreements will be resolved through discussion with a third author.

Risk of Bias Assessment

We will evaluate the quality of the included studies using version 2 of the Cochrane risk-of-bias tool [31]. The judged domains include the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each domain is judged as high, low, or some concern.

Statistical Analysis

The meta-analysis will be carried out using RevMan software and Stata software. For continuous data, we will use the mean difference and 95% CI, whereas for dichotomous data, we will calculate the risk ratio and 95% CI. The I^2 statistic will be used to analyze study heterogeneity. When there is insignificant heterogeneity (I^2<50%), a fixed-effects model will be used; otherwise, a random-effects model will be used. In addition, if high heterogeneity is encountered, sensitivity analysis or subgroup analysis will be performed to determine the underlying reasons. Methods for sensitivity analysis will include, but are not limited to, the single-study exclusion method and meta-regression. Subgroup analysis will be performed based on the final included studies, focusing on patient age, sex, type of surgery, intervention dosage, and other factors. When more than 10 studies are included, publication bias will be assessed using Stata software for the Egger test or Begg test [32]. For all analyses, two-tailed tests assessed at a significance level of P<.05 will be used. The Grading of Recommendations, Assessments, Developments, and Evaluations approach will be used to assess the confidence of the evidence [33].

Results

The protocol was registered in the PROSPERO registry in November 2023. As of June 2024, a preliminary article retrieval step has been performed (see Multimedia Appendix 2). The review is expected to be completed by March 2025. We expect to submit manuscripts for peer review by the end of June 2025.

Discussion

PIHO is more common in older patients owing to decreased vascular elasticity, autonomic nerve reflexes, and cardiac function reserve with age [34]. PIHO may lead to disastrous outcomes such as myocardial ischemia, cerebral infarction, kidney injury, neurocognitive impairment, and even death [35]. A recent large-sample (409 cases) multicenter randomized controlled trial found that induction of general anesthesia with remimazolam significantly reduced the incidence of PIHO and the use of vasoactive drugs compared with propofol. In addition, the incidence of bradycardia was significantly lower in patients in the remimazolam group [36].

Although etomidate has a relatively reduced effect on the circulation compared with other anesthesia drugs, several recent studies have found a lower incidence of PIHO with remimazolam than with etomidate [27,28,37]. However, these studies had small sample sizes and were single-center studies. Therefore, a meta-analysis is necessary to pool the results of the current studies. Many anesthetic drugs used during induction of anesthesia can trigger PIHO, including opioids. Considering the impact of opioids on PIHO, we will ensure that the same opioids are used across studies for comparison or we will perform subgroup analyses on this factor to help reduce the potential impact of opioids on the primary outcome of PIHO in our analysis.

This study also has some limitations. First, only articles published in English and Chinese are included in the search. Second, due to the novelty of this topic, a limited number of studies are available for analysis. Despite this limitation, it is necessary to synthesize the current studies on the incidence of PIHO during the induction of general anesthesia with remimazolam and etomidate to inform evidence-based clinical decision-making and plan future studies.

By synthesizing the available evidence and comparing the effects of remimazolam and etomidate, we hope to provide valuable insights into the selection of appropriate anesthesia-inducing drugs to reduce the incidence of PIHO and improve patient prognosis.

Acknowledgments

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Authors' Contributions

LZ and YG designed the study and wrote the manuscript. XZ produced the appendix tables. LL critically supervised the protocol, and evaluated and validated the article. All authors contributed to writing and review of the manuscript and agreed with the submitted version.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist.
[DOC File , 74 KB - resprot_v13i1e55948_app1.doc]

Multimedia Appendix 2
Complete PubMed search strategy.
[DOCX File , 14 KB - resprot_v13i1e55948_app2.docx]

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Abbreviations

PICOS: Patients/Population, Intervention, Comparison, Outcomes, and Study design
PIHO: postinduction hypotension
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: Prospective Register of Systematic Reviews

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Protocol

The Relationship Between Physical Activity and Mental Health Among Individuals With Spinal Cord Injury: Protocol for a Scoping Review

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Abstract

Background: Spinal cord injury (SCI) is a devastating condition that often leads to significant impairments in physical function, leading to disability and mental health disorders. Hence, understanding the prevalence of SCI and the relationship between physical activity and mental health in individuals with SCI is crucial for informing rehabilitation strategies and optimizing outcomes.

Objective: This study aims to comprehensively analyze existing research on the link between physical activity and mental health and identify the level of physical activity and mental health status, the barriers to physical activity, and SCI's impacts on psychological well-being in individuals with SCI.

Methods: An electronic search strategy will be used to identify prevalence studies published since 1993 in health-related databases such as PubMed, MEDLINE, COCHRANE Library, and Wiley Library using the following query: "Spinal Cord Injury" OR "Paraplegia" OR "Tetraplegia" AND "Physical Activity" OR "Exercise" AND "Mental Health" OR "Mental Illness" OR "Mental Disorder." Bibliographies of primary studies and review articles meeting the inclusion criteria will be searched manually to identify further eligible studies. The risk of bias in the included studies will be appraised using the Joanna Briggs Institute checklist for prevalence studies by 2 review authors. Any disagreement will be resolved by reaching a consensus.

Results: Funding was received in October 2023, data collection will commence in July 2024, and the results are expected by 2025. We will summarize the selection of the eligible studies using a flowchart. The data from the studies will be extracted and tabulated. This scoping review will be published in a peer-reviewed journal in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

Conclusions: This scoping review underscores the complex relationship between physical activity and mental health among individuals with SCI, highlighting the level of physical activity and mental health status, barriers to physical activity engagement, and psychological implications. Understanding these dynamics is crucial in devising tailored interventions aimed at enhancing mental well-being. This synthesis of evidence emphasizes the need for personalized strategies to promote physical activity, addressing unique challenges faced by this population to foster improved mental health outcomes and overall quality of life.

Trial Registration: Open Science Framework osf.io/ugx7d; https://osf.io/ugx7d/

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International Registered Report Identifier (IRRID): PRR1-10.2196/56081

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KEYWORDS

access barriers; depression; disability; exercise interventions; mental health; mobility limitations; physical activity; psychological outcomes; quality of life; spinal cord injury; SCI; mobility; scoping review; exercise; effectiveness; mental health; well-being; impairments; physical function; disability; prevalence

Introduction

Spinal cord injury (SCI) is a devastating event that often leads to significant issues with physical function and mobility and is defined by varying degrees of sensory and motor dysfunction [1,2]. SCI can result from traumatic events such as motor vehicle accidents [3,4], falls [4,5], sports and recreation [6], or nontraumatic events such as degenerative disc diseases [7,8], cancer, myelopathy [9], and other diseases [10]. Individuals with SCI face numerous daily obstacles, including pain [11], neurogenic bowel and bladder [12], restrictions in strength, endurance, cardiovascular fitness, flexibility, and functional mobility, which affect physiological function [13,14], their return to work [15], and quality of life (QOL) [16].

Physical activity is any movement that requires energy expenditure and engages our musculature. Regular physical activity provides numerous advantages, including improved cardiovascular health, increased strength, and flexibility [17], improved mental well-being, weight management, and a decreased risk of chronic diseases such as diabetes and hypertension [18,19]. Depression is an example of a mental health disorder characterized by persistent sadness, loss of interest or delight in activities, and a spectrum of emotional and physical symptoms [20,21]. It can affect daily functioning, employment [22], and QOL [23].

A review has been conducted to determine the effects of physical activity on mental health after SCI [24]. However, this review's findings have limited generalizability to broader populations or settings [25,26] and difficulty in establishing causality [27] compared to a review of prevalence studies. Therefore, a review of prevalence studies to determine the level of physical activity and mental health as well as their association, including the barrier and psychological impacts, is essential and useful particularly for conducting future intervention studies or trials and informing health care professionals, researchers, policy makers, and rehabilitation specialists to improve the QOL and care for individuals with SCI. By providing a holistic overview, this study seeks to bridge gaps in understanding and informing more personalized rehabilitation strategies, thereby enhancing the overall QOL for individuals with SCI. The rationale for this study lies in the necessity to comprehensively understand the relationship between physical activity and mental health among individuals with SCI. The objectives of this study are to (1) determine the association between physical activity and mental health level, (2) address the level of physical activity and mental health status, and (3) identify barriers to physical activity and their impact on psychological well-being as well as QOL after SCI.

Methods

Search Strategy

The first author WO will conduct a scoping review in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines with a literature search using MeSH (Medical Subject Headings) terms in various health-related databases such as PubMed, COCHRANE Library, MEDLINE, Web of Science, and the Wiley Online Library (January 1993 to December 2023). A starting point of 1993 will be selected for exploring a wide array of research findings and trends, providing valuable insights into the evolution of knowledge and practices in the field over the past 3 decades. Databases such as the aforementioned ones were selected for their comprehensive coverage of biomedical and health-related research. PubMed and MEDLINE offer extensive coverage of peer-reviewed biomedical literature, while COCHRANE Library specializes in clinical trials. In addition, a bibliography and gray literature search will be performed to locate additional potential studies that are already relevant. Bibliography searching, also known as citation searching or reference chaining, involves examining the reference lists of relevant articles that may not have been captured during the initial database search. The gray literature search will be conducted in the ProQuest Dissertations & Theses Global database.

The search terms or keywords used were based on the population, such as "Spinal Cord Injury" OR "Paraplegia" OR "Tetraplegia" and outcomes such as "Physical Activity" OR "Exercise" AND "Mental Health" OR "Mental Illness" OR "Mental Disorder." The elements from the databases were then combined using the Boolean operator (Table 1).

The inquiry was restricted to studies published in the English language from 1993 to 2023 and involving only human participants. The flowchart of the study is shown in Figure 1. The search will be modified for each database, and the obtained references will be managed using the EndNote reference management software (Clarivate).

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Table 1. Search strategies to obtain eligible studies on mental health among individuals with spinal cord injury.

Criteria	Databases
Databases	PubMed, MEDLINE, COCHRANE Library, Web of Science, and Wiley Online Library
Bibliography searching	Reference lists of relevant articles
Gray literature	ProQuest Dissertations & Theses Global
Keywords	(Spinal Cord Injury OR Paraplegia OR Tetraplegia) AND (Physical Activity OR Exercise) AND (Mental Health OR Mental Illneses OR Mental Disorder)
Limiters	Humans, English language, adults (19-65 years old), 1993, 2003, and academic journals
Search modes	Boolean/Phrase

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart of study searching and selection to obtain eligible studies to be included in the review of mental health outcomes among individuals with spinal cord injury.

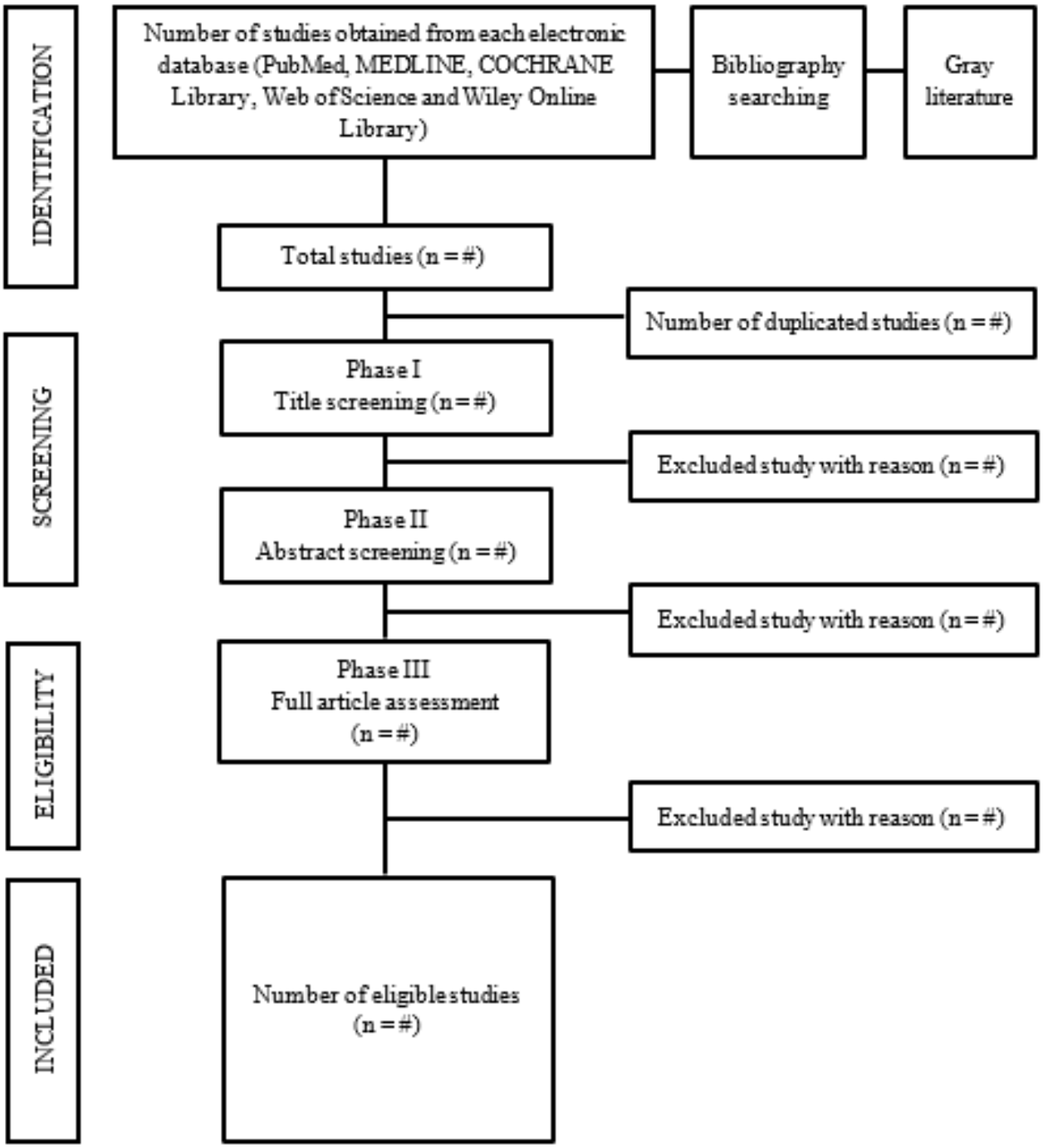

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Selection Criteria

Inclusion Criteria

Studies will be included if they were published between January 1993 and December 2023 and if they are cross-sectional, prospective, or retrospective cohort studies, and any other study designs except for randomized or nonrandomized controlled trials, systematic or scoping reviews, and meta-analyses, qualitative studies, regardless of age, gender, ethnicity, severity of injury, level of injury, socioeconomic status, level of education, socioeconomic, or study setting.

Exclusion Criteria

To maintain the integrity and relevance of the review by ensuring that only studies with well-defined objectives and methodologies are included, studies will be excluded if they do not report the primary outcome and do not provide a clear description of the case definition, full-text articles are unavailable, full-text access is unavailable, and are animal studies. Additionally, systematic reviews and meta-analyses will be excluded because they represent secondary analyses rather than primary research studies. In this scoping review, qualitative data will be excluded from the analysis. The decision to exclude qualitative data is based on the scope and objectives of the review, which will primarily focus on synthesizing quantitative evidence to address the research question effectively. By excluding qualitative data, the review aims to maintain a clear and focused approach, ensuring that the synthesis process remains manageable and aligned with the predetermined research objectives.

Outcomes

Our outcomes include the participants' characteristics, studies' characteristics, and risk-of-bias assessment.

The Review and Data Extraction Process

Inclusion and exclusion criteria will be used to determine the admissibility of studies. The 3-phase filtration procedure will commence with the title (first phase), followed by the abstract (second phase), and finally the full text (third phase). Duplicate studies will be eliminated. Author WO will screen and select pertinent research from the database and the reference lists of selected articles for inclusion in the review. Authors WO and NAO will extract data on the demographic characteristics of the study populations, including age, gender, years since injury, level and severity of injury, and type of injury, ethnicity, province or district, study setting (community or health facility-based), setting (urban or rural), sample size, response rate, and prevalence of physical capacity. The following data will also be extracted: study title, study design, duration, objective, intervention, and outcomes. After completion, the data will be compared, and any discrepancies will be resolved through a consensus discussion between the 2 examiners or in consultation with a third reviewer.

The data extraction process will involve systematically collecting relevant information from each included study to address the research objectives. Key variables to be extracted include (1) demographic characteristics (age, gender, and severity of injury), (2) study characteristics related to physical activity and mental health (study design, intervention details, and outcome measures), (3) the level of physical activity and mental health status, (4) the level of association between physical activity and mental health, (5) barriers or facilitators to participation in physical activity among individuals with SCI. Additionally, data on the prevalence of physical activity and mental health outcomes will be recorded. To handle missing data, a pragmatic approach will be adopted. Initially, attempts will be made to contact study authors for additional information or clarification regarding missing data. If missing data are to be obtained, author WO will document the missing data and the steps taken to address them in the final review report.

Assessment of Risk of Bias

A checklist created by the Joanna Briggs Institute (JBI) will be used to evaluate the quality of methodology of each prevalence study to determine the extent to which each study addressed the possibility of bias in its design, conduct, and analysis [28]. The JBI Scientific Committee authorized the JBI checklist after a thorough peer review. The JBI checklist has high face validity and acceptability levels, is easy to administer, and requires less evaluation time. In addition, the JBI checklist is presently being evaluated for its other clinometric properties, including construct validity and interrater reliability, as part of a larger-scale study. The JBI checklist uses the following criteria to evaluate studies: (1) a representative sample; (2) an appropriate apparatus; (3) an adequate sample size; (4) an appropriate description and study report, subjects, and setting; (5) adequate data coverage; (6) measurement of the condition's validity; (7) measurement of the condition's dependability; (8) appropriate statistical analysis; and (9) the adequacy of the response rate. To assess studies for low or moderate risk of bias, reviewers examine each criterion based on predefined thresholds or criteria. A study with a representative sample that adequately reflects the target population may be considered as having a low risk of bias, while a study with significant sampling limitations may be classified as having a moderate risk of bias. Two evaluators will evaluate the eligible studies, and any disagreements will be resolved by consensus discussion or a third reviewer will be consulted. Additionally, reviewers should document the rationale for their risk-of-bias assessments, including any limitations or concerns identified during the evaluation process. This transparency helps ensure the reliability and credibility of the scoping review findings.

Ethical Considerations

Since the scoping review will use published research with deidentified data, no approval from an ethics committee is required. Numerous studies have been conducted on the prevalence of physical capacity in individuals with SCI, but this review is the first to collect and consolidate all these studies. It will also provide policy makers, stakeholders, and health care professionals with epidemiological data to help them in planning health care and policy. The PRISMA-ScR guidelines will be adhered to when publishing the review's findings in journal articles and academic reports.

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Results

This study was funded in October 2023. Data collection will commence in July 2024, and the results are expected to be published in 2025. A narrative description will be provided for investigations with a low or moderate risk of bias. Clinical heterogeneity will be investigated by examining the characteristics of the study participants, method of diagnosis, and definitions of the cases. If sufficient data are available, subgroup analyses will be conducted for the study population (age, gender, population group, years since injury, level, severity, and type of SCI) and study characteristics (study design, settings, outcome measurement, and the level of physical activity and depression).

Discussion

Principal Findings

In this scoping review, we seek to comprehensively analyze the relationship between physical activity and mental health among individuals with SCI. The objective of this study is to comprehensively analyze existing research on the link between physical activity and mental health, identifying the level of physical activity and mental health status, barriers to physical activity, and their impact on psychological well-being in individuals with SCI.

Physical activity plays a crucial role in the mental health of individuals with SCI [29]; however, several barriers to physical activity are associated with mental health. These barriers include the challenges to the management of secondary complications of SCI, which can make recovery complex and difficult [30]. Additionally, individuals with SCI may face mobility limitations and disability, which can hinder their ability to engage in physical activity and negatively impact their mental health [31]. Furthermore, the busy and sedentary lifestyle of modern society can contribute to decreased physical activity levels and an increased risk of depression [31]. It is important to address these barriers and promote physical activity among individuals with SCI to improve their mental health outcomes. It is important to note that further research is needed to fully understand the impact of physical activity on mental health among individuals with SCI.

Building upon our main findings, the scoping review will reveal several noteworthy insights into the relationship between physical activity and mental health among individuals with SCI. First, we expect to observe a positive association between engagement in physical activity and improved mental well-being in this population. Studies would consistently report that regular exercise is correlated with reduced symptoms of depression, anxiety, and stress among individuals with SCI. This finding will align with those of existing literature in the broader context of physical activity and mental health, indicating that similar principles will apply to individuals with SCI.

Furthermore, our review will highlight the multifaceted nature of barriers hindering participation in physical activity among individuals with SCI. These barriers will encompass both internal factors, such as motivation, self-efficacy, and knowledge, as well as external factors, including accessibility, transportation, and financial constraints. Understanding these barriers will be crucial for developing targeted interventions aimed at overcoming these obstacles and promoting physical activity engagement in this population.

Moreover, our findings will underscore the importance of tailored exercise programs that address the unique needs and challenges faced by individuals with SCI. Adaptive exercise equipment, accessible facilities, and personalized exercise regimens will be essential components of effective interventions. Collaborative efforts among health care professionals, rehabilitation specialists, and community organizations will be needed to develop and implement such programs.

Comparing our findings to those in existing literature, our review will corroborate previous studies that have highlighted the beneficial effects of physical activity on mental health outcomes among individuals with SCI. However, it will also extend existing knowledge by identifying specific barriers and challenges that are unique to this population. By elucidating these factors, our review will provide valuable insights for designing targeted interventions and support services tailored to the needs of individuals with SCI.

In summary, our detailed analysis will underscore the importance of promoting physical activity as a means to enhance mental well-being among individuals with SCI. By addressing barriers, developing tailored interventions, and fostering collaborative partnerships, health care professionals and policy makers can work toward improving the overall QOL for this population.

Limitations

Despite the valuable insights provided by this scoping review, several limitations should be acknowledged. First, the inclusion criteria may lead to the exclusion of relevant studies that do not meet the specified criteria, potentially limiting the comprehensiveness of the review. Additionally, the quality of included studies may vary, leading to potential biases in the synthesis of findings. Furthermore, the reliance on published literature may introduce publication bias, as studies with statistically significant results are more likely to be published. Moreover, the heterogeneity of study designs and methodologies across included studies may pose challenges in synthesizing and interpreting findings. Finally, the scope of the review is limited to studies published in English, which may result in the exclusion of relevant research published in other languages.

Conclusions

This review of existing studies sheds light on how physical activity relates to mental health in individuals dealing with SCI. Different exercise methods have shown potential in helping individuals who are feeling low, but obstacles such as limited access to facilities and physical challenges still pose significant hurdles. Understanding how exercise affects mood highlights the need for specific plans that address the unique struggles of this group. This emphasizes the importance of personalized approaches to boost mental well-being and enhance the overall quality of life for individuals with SCI. By recognizing the impact of physical activity on mental health outcomes among

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individuals with SCI, health care providers can prioritize interventions that promote both physical and psychological well-being. Implementing personalized exercise programs tailored to the needs and preferences of individuals with SCI can lead to more effective rehabilitation outcomes and improved QOL. Ultimately, these efforts contribute to a more comprehensive and holistic approach to SCI rehabilitation, fostering greater independence, social participation, and overall well-being for individuals living with SCI.

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Data Availability

No data sets were generated or analyzed during this investigation, so data sharing is not applicable. Data sharing will be applicable after the full review study is conducted.

Authors' Contributions

AZ and HH conceptualized the study and designed the scoping review approach with support from the Centre for Rehabilitation and Special Needs Study (ICaRehab) research working group. WO and NAO wrote the first draft of the scoping review protocol with support from LHW, ATXE, MFA, and AZ. The manuscript was revised and critically reviewed by HM, BH, MA, NAMN, and HH. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
QOL: quality of life
SCI: spinal cord injury

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Protocol

Effects of Lifestyle Interventions on Cardiovascular Disease Risk and Risk Factors Among Individuals at High Risk for Type 2 Diabetes: Protocol for a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Individuals at high risk for type 2 diabetes are also at an increased risk for developing cardiovascular disease (CVD). Although there are separate trials examining the effects of lifestyle interventions on absolute CVD risk among people at high risk for type 2 diabetes, a comprehensive evidence synthesis of these trials is lacking.

Objective: We will systematically synthesize the evidence on the effects of lifestyle interventions in reducing absolute CVD risk and CVD risk factors among people at high risk for type 2 diabetes.

Methods: We adhered to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement in reporting the details of this protocol. Randomized controlled trials of diabetes prevention that examined the effects of lifestyle interventions for at least 6 months on absolute CVD risk and CVD risk factors among individuals at high risk for type 2 diabetes will be eligible. We will systematically search the MEDLINE, Embase, PsycINFO, CENTRAL, and Scopus databases and ClinicalTrials.gov using a mix of Medical Subject Headings and text words. Two authors will independently screen the abstract and title of the articles retrieved from the search, followed by full-text reviews using the inclusion and exclusion criteria and data extraction from the eligible studies. Article screening and data extraction will be performed in the Covidence software. The primary outcome will be the changes in absolute 10-year CVD risk, as estimated by risk prediction models. The secondary outcomes are the changes in CVD risk factors, including behavioral, clinical, biochemical, and psychosocial risk factors, and incidence of type 2 diabetes.

Results: An initial database search was conducted in July 2023. After screening 1935 articles identified through the database search, 42 articles were considered eligible for inclusion. It is anticipated that the study findings will be submitted for publication in a peer-reviewed journal by the end of 2024.

Conclusions: This study will provide up-to-date, systematically synthesized evidence on the effects of lifestyle interventions on absolute CVD risk and CVD risk factors among individuals at high risk for type 2 diabetes.

Trial Registration: PROSPERO CRD42023429869; https://tinyurl.com/59ajy7rw

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KEYWORDS

diabetes; prediabetes; cardiovascular disease; CVD; CVD risk; CVD risk factors; lifestyle interventions; systematic review; meta-analysis

Introduction

Cardiovascular diseases (CVDs), mainly ischemic heart disease and stroke, are the leading causes of premature deaths and disability among adults worldwide [1]. In 2019, CVDs accounted for an estimated 18.6 million deaths and 34.4 million years lived with disability [1].

Hyperglycemia is a well-established risk factor for CVDs [2,3]. Individuals with a high risk of developing type 2 diabetes, such as those with prediabetes, also face an elevated risk of experiencing CVD events [4], with higher incidence rates than the general population [5,6]. Consequently, it is imperative to implement interventions for the primary prevention of CVDs among those at high risk for type 2 diabetes [7,8].

Behavioral risk factors such as an unhealthy diet, heavy alcohol drinking, and physical inactivity lead to increased BMI, plasma glucose, and serum lipids and the development of CVD events [1,9]. Studies have also shown that psychosocial factors, such as anxiety, depression, stress, social isolation, and the lack of social support, can independently influence absolute CVD risk [10,11].

Assessing an individual's CVD risk is the initial step in the primary prevention of CVDs [12]. The international clinical guidelines from the World Health Organization (WHO) and the American Heart Association recommend estimating a person's 10-year absolute risk of developing CVD events using risk scores that quantify the cumulative impact of multiple risk factors [12,13]. The predicted 10-year CVD risk not only informs treatment strategies but also assists in assessing the effectiveness of those strategies [14]. Furthermore, treatment options vary based on the levels of CVD risk. For example, the European Society of Cardiology guidelines recommend using the Systematic Coronary Risk Evaluation 2 (SCORE2) algorithm, which includes age, sex, current smoking, systolic blood pressure (BP), total cholesterol, and high-density lipoprotein cholesterol. This algorithm helps determine an individual's CVD risk category as "low-to-moderate," "high," or "very high" [9,14]. Although the guidelines advocate for smoking cessation and the adoption of healthy lifestyle choices for individuals in any risk category, treatment for high systolic BP and cholesterol is specifically recommended for those with "high" or "very high" scores [15].

Randomized controlled trials (RCTs) focusing on adopting a healthy diet, increasing physical activity, quitting smoking, and addressing stress and other psychosocial risk factors have shown significant reductions in absolute CVD risk [16,17] and CVD events [8,12] among individuals at high risk for type 2 diabetes. However, there have also been lifestyle-based RCTs that did not report significant results [18]. These discrepancies in the outcomes of trials underscore the importance of conducting a systematic review to provide a comprehensive summary of the existing evidence. Previous systematic reviews and meta-analyses on reduction in absolute CVD risk with lifestyle interventions included people with type 2 diabetes, the general population, or high-risk groups for CVD (eg, individuals with hypertension or obesity) [17,19], but not those at high risk for type 2 diabetes. Notably, although previous systematic reviews have examined the effects of lifestyle-based diabetes prevention trials on traditional CVD risk factors (eg, obesity and high total cholesterol) [17,19-21], none specifically examined the impact of such trials on psychosocial risk factors. This is despite studies showing that psychosocial risk factors influence absolute CVD risk and risk factors [13,22].

The proposed systematic review will thus fill a substantial gap in the existing literature by focusing on individuals at high risk for type 2 diabetes and assessing the effects of lifestyle interventions on absolute CVD risk and not only traditional CVD risk factors but also psychosocial risk factors.

Methods

Overview

We adhered to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement in reporting the details of this protocol [23]. The PRISMA-P checklist has been included in Multimedia Appendix 1 [23]. The proposed systematic review and meta-analysis will be conducted per the *Cochrane Handbook for Systematic Reviews of Interventions* [24] and will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline for reporting [25]. This review has been registered in PROSPERO (CRD42023429869).

Inclusion Criteria

The following PICOS (Population, Intervention, Comparator, Outcome, and Study Design) framework [26] will be considered to determine the eligibility of studies (Table 1).

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Table 1. PICOS (Population, Intervention, Comparator, Outcome, and Study Design) framework.

Criteria	Description
Population	• Adults (aged ≥18 years) at high risk of developing type 2 diabetes: 1. Impaired fasting glucose, defined by the ADA[a] criteria (FPG[b] 100 mg/dL [5.6 mmol/L] to 125 mg/dL [6.9 mmol/L]) [27] or the WHO[c] criteria (FPG 110 mg/dL [6.1 mmol/L] to 125 mg/dL [6.9 mmol/L]) [28] or 2. Impaired glucose tolerance, defined as 2-hour plasma glucose 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) on a 75-g oral glucose tolerance test [27] or 3. Elevated hemoglobin A_{1c}: 5.7%-6.4% (39-46 mmol/mol) [29] or 6.0%-6.4% (42-47 mmol/mol) [30] or 4. High diabetes risk scores: for example, the Indian Diabetes Risk Score ≥60 [31], the Finnish Diabetes Risk Score ≥12 [32], the ADA risk test ≥5 points [33], and the Leicester Risk Assessment Score ≥16 [34]
Intervention	• Structured lifestyle intervention programs for 6 months or more that aimed to improve diet quality, increase physical activity, help participants quit smoking, reduce alcohol consumption, or provide advice on other healthy lifestyle choices
Comparator	• Usual or standard care with or without minimal intervention (eg, providing health education booklets)

Outcome	• *Primary outcome*: Changes in absolute 10-year CVD[d] risk, as estimated by risk prediction models, and the incidence of fatal and nonfatal CVD events (myocardial infarction, angina, stroke, peripheral artery disease, need for coronary bypass grafting, or heart failure)
	• *Secondary outcomes*: Changes in behavioral, clinical, biochemical, and psychosocial risk factors and incidence of type 2 diabetes
	  • Behavioral risk factors include an unhealthy diet (includes poor diet quality or increased consumption of processed foods that are high in sugars and saturated fat), physical inactivity, alcohol consumption, tobacco use, and sleep time and quality
	  • Clinical measures are weight, BMI, waist circumference, and systolic and diastolic blood pressure
	  • Biochemical measures are FPG, hemoglobin A_{1c}, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides
	  • Psychosocial measures are stress, depression, and anxiety

Study design	• Randomized controlled trials

[a]ADA: American Diabetes Association.

[b]FPG: fasting plasma glucose.

[c]WHO: World Health Organization.

[d]CVD: cardiovascular disease.

Exclusion Criteria

Studies conducted among individuals with diagnosed type 2 diabetes or gestational diabetes will be excluded. Studies testing pharmacological or surgical interventions, non-RCT studies, and articles not published in English will also be excluded.

Data Sources and Search Strategy

Bibliographic databases, such as Ovid MEDLINE, Embase, CENTRAL, PsycINFO, and Scopus, and ClinicalTrials.gov will be searched for articles reporting on the effects of lifestyle interventions on absolute CVD risk and CVD risk factors among individuals at high risk of developing type 2 diabetes. Our search strategy will include a combination of Medical Subject Headings and free-text terms. The search terms are "cardiovascular disease," "lifestyle interventions," "diet," "physical activity," "prediabetes," "impaired fasting glucose," "impaired glucose tolerance," "diabetes risk score," "diabetes prevention," "cardiovascular disease risk score," "cardiovascular risk factors," "psychosocial risk factors," "stress," "depression," and "anxiety." A comprehensive search strategy for each bibliographic database will be developed in consultation with a librarian and experts in the field of diabetes and CVD. As an example, the search strategy for MEDLINE is given in Multimedia Appendix 2.

Study Selection

All identified studies will be exported to the Covidence software (Veritas Health Innovation), and duplicates will be removed. Two independent reviewers will screen the titles and abstracts of eligible studies. The full-text reviews will be performed against the inclusion and exclusion criteria by the same 2 reviewers. Disagreements arising between the reviewers at any stage of study selection will be resolved by discussion or consultation with a third reviewer.

Data Extraction

Two independent reviewers will extract data from eligible studies using a template designed by the Covidence software. The data extracted will pertain to specific details about study participants, lifestyle interventions, study methods (eg, study setting and follow-up time), and outcomes. Any reviewer conflicts will be resolved through discussion or consultation with a third reviewer. The authors of the papers will be contacted to obtain missing or additional data if needed.

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Risk of Bias and the Certainty of Evidence

Two reviewers will independently assess the potential sources of bias specific to RCTs using the revised Cochrane risk-of-bias tool for randomized controlled trials (RoB 2) [35]. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework [36] will be used to determine the certainty of the evidence. Consensus between the reviewers will be achieved by discussion or consultation with a third reviewer.

Data Synthesis

After the selection of eligible studies and data extraction, the included studies will be described in a narrative form focusing on the following: income status of the countries (high-income or low- and middle-income countries) where the studies were conducted, study setting (community, hospital, or workplace), age and sex distribution of the study participants, components of the lifestyle intervention programs (eg, diet, physical activity, sleep, stress, and smoking), duration of the interventions, duration of follow-up, and outcomes.

Where possible, outcomes data across studies will be pooled using the DerSimonian-Laird random-effects models for meta-analysis [37]. Effect sizes will be expressed as risk ratios (for categorical variables) and standardized mean differences (for continuous variables) with 95% CIs. The degree of between-study heterogeneity will be assessed using the Cochran Q test (P<.01 for heterogeneity) and Higgins I^2 statistic (low: <25%, moderate: 25%-50%, and high: >50%) [38]. I^2 quantifies the percentage of variability in effect estimates due to heterogeneity rather than sampling error [24]. Subgroup analyses will be considered if there are sufficient data to examine the effects of lifestyle interventions by types of high-risk individuals (impaired fasting glucose, impaired glucose tolerance, elevated hemoglobin A_{1c}, and high diabetes risk score) and different prediabetes definitions. Publication bias will be assessed by funnel plots [39] and Egger test [40] if 10 or more studies are included in the meta-analysis [38]. A 2-sided P<.05 will be considered statistically significant. Analyses will be performed using RevMan (version 5.4.1; The Cochrane Collaboration) and Stata software (version 17.0; StataCorp).

Ethical Considerations

This is a systematic review and meta-analysis based on previously published studies and will not involve individuals. Therefore, ethical approval is not required.

Results

Figure 1 shows the PRISMA flowchart. An initial database search was conducted in July 2023, identifying a total of 1935 articles. After removing 122 duplicates, 1813 articles remained. The titles and abstracts of these articles were screened, resulting in 124 studies selected for full-text review. Following this review, 82 studies were excluded for various reasons. Finally, 42 studies were included for data extraction. Currently, 2 independent reviewers are extracting data from these studies and conducting a quality assessment of the studies. We anticipate that the results of the study will be submitted for publication in a peer-reviewed journal by the end of 2024. The study findings will also be disseminated through presentations at scientific conferences and meetings.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the study selection. RCT: randomized controlled trial.

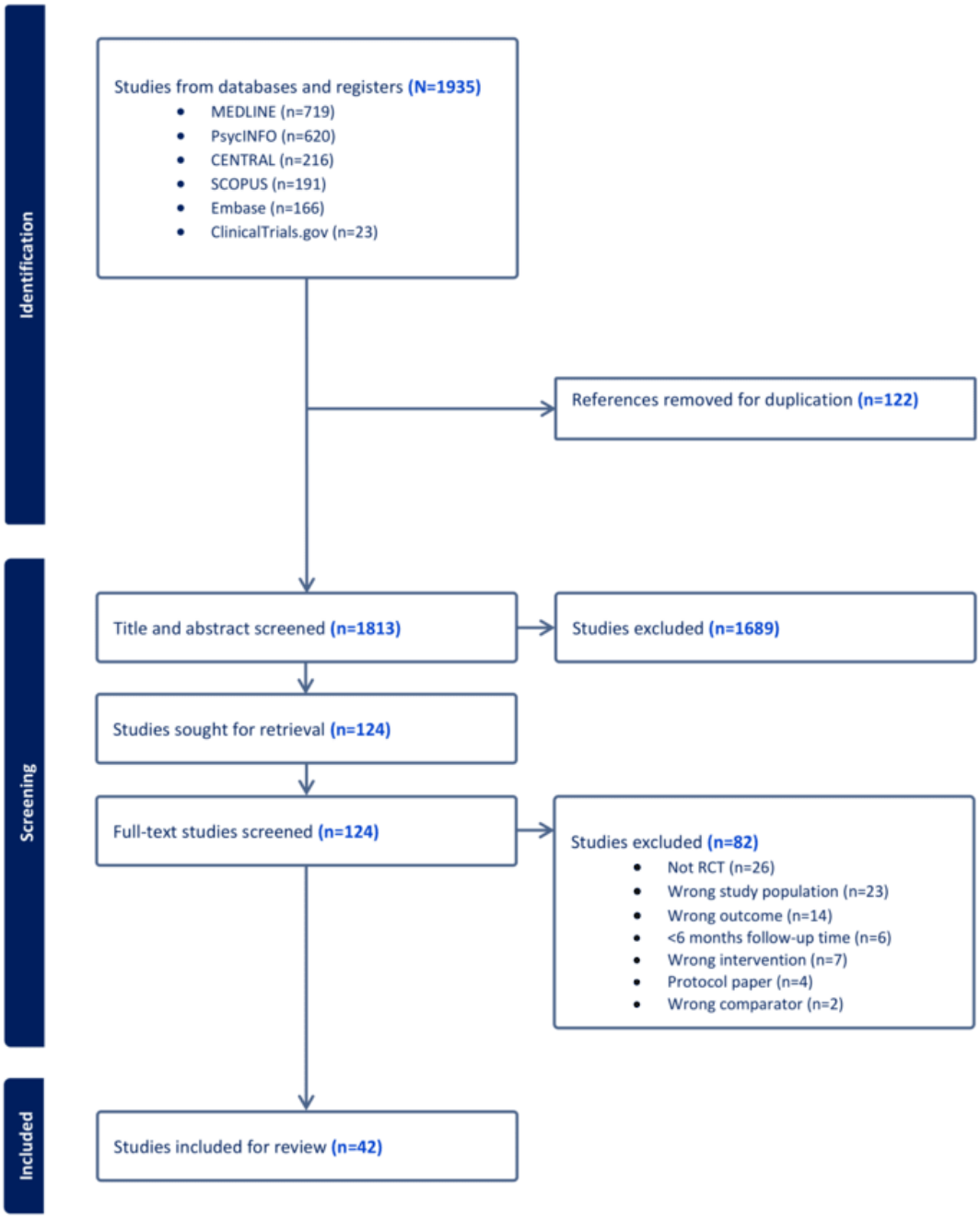

Discussion

Novelty and Expected Findings

This study aims to provide up-to-date and summarized evidence on the effects of lifestyle interventions in reducing absolute CVD risk and CVD risk factors among individuals at high risk for type 2 diabetes. By specifically focusing on individuals at high risk for developing type 2 diabetes, this study aims to bridge a significant gap in the existing literature. Previous systematic reviews and meta-analyses have predominantly centered around people with established type 2 diabetes or the general population, making this study distinctive in its targeted approach.

Limitations

One of the limitations of this study is that our search is specific to the English language; studies published in other languages may be missed, and this may lead to an incomplete representation of the available evidence. Although we used a comprehensive search strategy, if relevant studies are still missed during the search process, the review's conclusions may be biased.

Potential Implications

The study results are expected to provide valuable insights that can contribute to shaping future guidelines about the reduction of CVD risk and the prevention of CVD events.

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Acknowledgments

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Data Availability

All data generated and analyzed for this study are included in the paper and its supplementary files.

Authors' Contributions

GDD, TH, ST, and BO designed this protocol. GDD and ST drafted the manuscript. JB, TH, ST, and BO critically reviewed the manuscript. All authors approved the final version for submission to the journal.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOC File , 85 KB - resprot_v13i1e53517_app1.doc]

Multimedia Appendix 2
Search strategy for MEDLINE.
[DOCX File , 20 KB - resprot_v13i1e53517_app2.docx]

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Abbreviations

BP: blood pressure
CVD: cardiovascular disease
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
PICOS: Population, Intervention, Outcome, Comparator, and Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
SCORE2: Systematic Coronary Risk Evaluation 2
RCT: randomized controlled trial
WHO: World Health Organization

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Protocol

Experiences of Governments and Public Health Agencies Regarding Crisis Communication During the COVID-19 Pandemic in the Digital Age: Protocol for a Systematic Review of Qualitative Studies

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Abstract

Background: Governments and public health agencies worldwide experienced difficulties with social media–mediated infodemics on the internet during the COVID-19 pandemic. Existing public health crisis communication strategies need to be updated. However, crisis communication experiences of governments and public health agencies worldwide during the COVID-19 pandemic have not been systematically compiled, necessitating updated crisis communication strategies.

Objective: This systematic review aims to collect and organize the crisis communication experiences of senders (ie, governments and public health agencies) during the COVID-19 pandemic. Our focus is on exploring the difficulties that governments and public health agencies experienced, best practices in crisis communication by governments and public health agencies during the COVID-19 pandemic in times of infodemic, and challenges that should be overcome in future public health crises.

Methods: We plan to begin the literature search on May 1, 2024. We will search PubMed, MEDLINE, CINAHL, PsycINFO, PsycARTICLES, Communication Abstracts, and Web of Science. We will filter our database searches to search from the year 2020 and beyond. We will use a combination of keywords by referring to the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research type) tool to search the abstracts in databases. We intend to include qualitative studies on crisis communication by governments and public health agencies (eg, officials, staff, health professionals, and researchers) to the public. Quantitative data–based studies will be excluded. Only papers written in English will be included. Data on study characteristics, study aim, participant characteristics, methodology, theoretical framework, object of crisis communication, and key results will be extracted. The methodological quality of eligible studies will be assessed using the Joanna Briggs Institute critical appraisal checklist for qualitative research. A total of 2 independent reviewers will share responsibility for screening publications, data extraction, and quality assessment. Disagreement will be resolved through discussion, and the third reviewer will be consulted, if necessary. The findings will be summarized in a table and a conceptual diagram and synthesized in a descriptive and narrative review.

Results: The results will be systematically integrated and presented in a way that corresponds to our research objectives and interests. We expect the results of this review to be submitted for publication by the end of 2024.

Conclusions: To our knowledge, this will be the first systematic review of the experiences of governments and public health agencies regarding their crisis communication to the public during the COVID-19 pandemic. This review will contribute to the future improvement of the guidelines for crisis communication by governments and public health agencies to the public.

Trial Registration: PROSPERO CRD42024528975; https://tinyurl.com/4fjmd8te

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KEYWORDS

COVID-19; health communication; infodemic; misinformation; social media; SARS-CoV-2; coronavirus; pandemic; infectious; digital age; systematic review; internet; public health; government; governments; crisis communication; qualitative; methodology; disinformation; eHealth; digital health; medical informatics

Introduction

The COVID-19 pandemic has been one of the most devastating health crises in human history. The pandemic forced governments and public health agencies to deal with a dizzying array of diverse and complex challenges including disruptions to daily life, economic crises, and rapidly mutating viruses. Governments and public health agencies needed to communicate effectively to the general public to encourage people to restrict their activities and take preventive actions to stop the spread of the virus [1]. Even before the COVID-19 pandemic, the World Health Organization published guidelines for crisis communication [2-4], and public health researchers considered emergency communication strategies based on lessons learned from past public health crises [5-9]. However, once the COVID-19 pandemic broke out, governments and public health agencies worldwide realized that they lacked systematic preparation and training in communicating with the public in the midst of a rapidly changing and confusing situation [10-15].

During the COVID-19 pandemic, governments and public health agencies worldwide experienced great difficulties with crisis communication, represented by an "infodemic" on social media [16]. The flood of information and misinformation made it difficult for people to find reliable sources of information and guidelines for necessary actions to take [17]. For governments and public health agencies, social media was a new and important means of delivering accurate information to the public quickly and widely [18]. At the same time, however, the infodemics allowed misinformation to spread through social media as quickly as the virus [19]. Governments and public health agencies had to fight both the virus and the infodemic. Even before the COVID-19 pandemic, the management of misinformation was recognized as an important public health issue, and many studies were conducted and coping measures proposed [20-23]. However, the COVID-19 pandemic highlighted the inexperience and the failure of governments and public health agencies to develop strategies to deal with the spread of misinformation during an emergency with infodemics [24,25].

Thus, the COVID-19 pandemic presented governments and public health agencies with unprecedented challenges and necessitated updates to existing crisis communication strategies. Our study will collect and organize data on the difficulties experienced and lessons learned by governments and public health agencies worldwide in crisis communication to the general public during the COVID-19 pandemic. This work is essential for updating future crisis communication strategies of governments and public health agencies. To this end, we will conduct a systematic review of qualitative studies on governments and public health agencies in diverse countries. We will focus on the difficulties that governments and public health agencies experienced, best practices of crisis communication from governments and public health agencies to the public during the COVID-19 pandemic in times of infodemic, and challenges to overcome in future public health crises.

Methods

Overview

We will conduct and report this systematic review following the guidelines provided in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Multimedia Appendix 1) [26]. As this will be a systematic review of qualitative studies, we will refer to the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research type) tool for the synthesis of qualitative evidence [27]. This protocol is registered with PROSPERO; the registration number is CRD42024528975. We plan to begin the literature search after this protocol is peer-reviewed on May 1, 2024, and finish the analysis by September 30, 2024.

Literature Search

We will search PubMed, MEDLINE, CINAHL, PsycINFO, PsycARTICLES, Communication Abstracts, and Web of Science. We will filter our database searches to include only papers from the year 2020 and beyond. We will use a combination of keywords with reference to previous studies to search the abstracts in databases [28-30]: ((government*) OR (ministr*) OR (department*) OR (office*) OR (municipalit*) OR (prefecture*) OR (province*) OR (state*) OR (count*) OR (organization*) OR (institution*) OR (center*) OR (agenc*) OR (sector*) OR (authorit*)) AND ((covid-19) OR (coronavirus) OR (sars-cov-2)) AND ((interview*) OR (focus group*) OR (questionnaire*) OR (survey*)) AND ((communicat*) OR (messag*) OR (inform*) OR (recommend*) OR (announce*)) AND ((qualitative) OR (mix method)). All publications collected from the start to the end of the database search will be included. The reference lists of eligible studies will be searched to identify further potentially eligible publications.

Eligibility Criteria

The inclusion and exclusion criteria for the review are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Qualitative studies of communication to the public by governments and public health agencies
- With regard to design, qualitative studies with qualitative data such as interviews, documents, and free-text responses to the questionnaire
- Content analysis of qualitative data that meets our study aim
- A review of qualitative studies that meet our study aim
- Mixed methods studies with qualitative results that meet our study aim
- With regard to study participants, studies on individuals such as officials, staff, health professionals, and researchers working for governments and public health agencies
- Studies on participants of any age, gender, ethnicity, or country
- Gray literature (information produced outside traditional publishing and distribution channels such as conference proceedings and theses) that provides sufficient information to assess eligibility (ie, full-length description of research objectives, methods, results, discussion, and conclusions)
- Papers written in English
- Studies conducted in January 2020 and beyond

Exclusion criteria

- Quantitative studies with quantitative data such as observational and interventional studies
- Studies on journalists in media companies and members of the public
- Studies not published in full-text format
- Papers written in languages other than English
- Studies that do not meet our study aims such as content analysis of media information, studies on information searches by the public, studies on handling patients with COVID-19 in hospitals, patient-provider communication, telehealth, and digital transformation technology

Study Selection

Rayyan software [31] will be used for screening studies. Duplicates will be removed automatically using this software. First, titles and abstracts will be screened to identify eligible studies using the selection criteria. The titles and abstracts of the literature will be independently screened by both the first (TO) and second (MT) reviewers. Disagreements will be discussed until a consensus is reached. When a consensus cannot be reached, a third reviewer (HO) will be involved in resolving the disagreement. Second, the full text of the remaining literature will be screened independently by both the first (TO) and second (MT) reviewers. If they disagree, the third reviewer will be consulted to resolve it through discussion. The screening process will be displayed using a PRISMA flow diagram.

Data Extraction

The first reviewer (TO) will extract descriptive data from eligible studies using Microsoft Excel, and the second reviewer (MT) will review the eligible studies for errors in the extracted data. The extracted data will consist of study characteristics (eg, author, year of publication, country, title, year and month of data collection, and type of paper), study aim, participant characteristics (eg, number of participants, workplace, and job title), methodology (eg, study design, methods of analyzing qualitative data, type of data, and setting), theoretical framework (when used), and object of crisis communication (eg, lockdown, behavioral restrictions, preventive behavior, and vaccination). The first reviewer (TO) will extract key results (eg, categories, themes, and quotations) using Microsoft Word, and the second reviewer (MT) will review the eligible studies for errors and bias in the extracted data. The third reviewer (HO) will be consulted if necessary for this validation.

Quality Assessment

To assess the methodological quality of eligible studies, the first reviewer (TO) will use the Joanna Briggs Institute (JBI) critical appraisal checklist for qualitative research [32], which is a trusted tool used for critical appraisal of qualitative studies [33]. Each of the 10 items on the checklist can be evaluated as "yes," "no," "unclear," or "not applicable." The JBI checklist assesses the descriptive, interpretative, theoretical, and evaluative validity of qualitative studies. The second reviewer (MT) will validate the results of the quality assessment using the JBI checklist, and the third reviewer will be invited if necessary. Our review will not exclude the included studies because of the results of the quality assessment.

Data Synthesis

The first reviewer (TO) will synthesize data using thematic synthesis [34]. Thematic synthesis, recommended by Cochrane, is a systematic method for synthesizing qualitative evidence [35]. According to the thematic synthesis method, in the first stage, TO will conduct free line-by-line coding of texts and quotations in the Result section of each of the included studies. In the second stage, the first (TO) and second (MT) reviewers will independently group similar codes generated in the previous stage and develop data-driven descriptive themes. They will reach a consensus through discussion, and the third reviewer (HO) will be consulted if necessary. In the third stage, TO will develop analytical themes by interpreting the descriptive themes generated in the previous stage. Those analytical themes will

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include new insights beyond the results of individual studies. The process of generating analytical themes will involve discussions between TO, MT, and HO. Those codes and themes will inductively be generated through the data-driven data synthesis process.

Results

We will summarize our findings in a table and a conceptual diagram and discuss them in a descriptive and narrative review form. We will discuss the implications for future research, policies, and practices. Our findings will be presented at a relevant conference and published in a peer-reviewed journal. We expect our review to be submitted for publication by the end of 2024.

Discussion

Expected Findings

Many studies have already been conducted worldwide on the infodemic experienced by patients and citizens during the COVID-19 pandemic [36-44], and systematic reviews of those studies already exist [45,46]. However, no systematic review to date has collected data on the experiences of governments and public health agencies regarding crisis communication during the COVID-19 pandemic. To fill this gap, our systematic review of qualitative studies will collect and organize data on the difficulties and challenges experienced by governments and public health agencies worldwide in crisis communication during the COVID-19 pandemic. Our systematic review will describe how communication strategies were developed and implemented by government and public health agencies during the pandemic, and how they were disrupted, called into question, and changed by the infodemic. It will also reveal outstanding attempts to overcome communication difficulties regarding lockdowns, recommendations for preventive behaviors, and the safety and efficacy of rapidly developed vaccines by governments and public health agencies.

Our systematic review will shed light on the experiences of information senders during the COVID-19 pandemic. By cross-checking studies on the experiences of patients and citizens on the receiving end of information with our systematic review of the experiences of governments and public health agencies on the sending end of information, we will be able to capture a fuller picture of crisis communication experiences during the COVID-19 pandemic. A literature review that provides such a complete picture of crisis communication experiences during the COVID-19 pandemic will be an essential resource for professionals and the public to learn from the COVID-19 pandemic and address future public health crises.

Limitations

Although we will use a comprehensive search strategy, we may miss relevant studies. To review qualitative studies, such as papers published in international academic journals, we will, as a first step in our research, include full-length literature written in English, which may exclude relevant studies published in languages other than English. Future studies will be expected to collect more comprehensive findings from various countries' literature written in various languages. This review will include qualitative analyses but exclude quantitative results of previous studies. That is because a quantitative survey using a questionnaire reveals the quantitative distribution of already known or inferred items. Our study objective is to examine the unprecedented difficulties that governments and public health agencies experienced during the pandemic involving the first web-based infodemics in human history, and it attempts to address these difficulties. To this end, it is important to begin with a review of qualitative studies that shed light on the lived experiences of governments and health professionals. We will include analyses of qualitative data, such as interviews, documents, and free-text responses to the questionnaire, to meet our study objective as comprehensively as possible.

Conclusion

To our knowledge, this will be the first systematic review to describe the experiences of governments and public health agencies around their crisis communication to the public during the COVID-19 pandemic. This review will provide important information for the future improvement of the guidelines for crisis communication of governments and public health agencies to the public. Based on this systematic review, we will examine the communication challenges for governments and public health agencies in the COVID-19 pandemic and provide recommendations for managing future global public health crises.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed in this study protocol.

Authors' Contributions

Conceptualization, methodology, and writing of the original draft were done by TO. Funding acquisition was done by HO. TK did the supervision. All authors contributed to reviewing and editing the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[PDF File (Adobe PDF File), 51 KB - resprot_v13i1e58040_app1.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPIDER: Sample, Phenomenon of Interest, Design, Evaluation, and Research type

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Protocol

Detecting Algorithmic Errors and Patient Harms for AI-Enabled Medical Devices in Randomized Controlled Trials: Protocol for a Systematic Review

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Abstract

Background: Artificial intelligence (AI) medical devices have the potential to transform existing clinical workflows and ultimately improve patient outcomes. AI medical devices have shown potential for a range of clinical tasks such as diagnostics, prognostics, and therapeutic decision-making such as drug dosing. There is, however, an urgent need to ensure that these technologies remain safe for all populations. Recent literature demonstrates the need for rigorous performance error analysis to identify issues such as algorithmic encoding of spurious correlations (eg, protected characteristics) or specific failure modes that may lead to patient harm. Guidelines for reporting on studies that evaluate AI medical devices require the mention of performance error analysis; however, there is still a lack of understanding around how performance errors should be analyzed in clinical studies, and what harms authors should aim to detect and report.

Objective: This systematic review will assess the frequency and severity of AI errors and adverse events (AEs) in randomized controlled trials (RCTs) investigating AI medical devices as interventions in clinical settings. The review will also explore how performance errors are analyzed including whether the analysis includes the investigation of subgroup-level outcomes.

Methods: This systematic review will identify and select RCTs assessing AI medical devices. Search strategies will be deployed in MEDLINE (Ovid), Embase (Ovid), Cochrane CENTRAL, and clinical trial registries to identify relevant papers. RCTs identified in bibliographic databases will be cross-referenced with clinical trial registries. The primary outcomes of interest are the frequency and severity of AI errors, patient harms, and reported AEs. Quality assessment of RCTs will be based on version 2 of the Cochrane risk-of-bias tool (RoB2). Data analysis will include a comparison of error rates and patient harms between study arms, and a meta-analysis of the rates of patient harm in control versus intervention arms will be conducted if appropriate.

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Results: The project was registered on PROSPERO in February 2023. Preliminary searches have been completed and the search strategy has been designed in consultation with an information specialist and methodologist. Title and abstract screening started in September 2023. Full-text screening is ongoing and data collection and analysis began in April 2024.

Conclusions: Evaluations of AI medical devices have shown promising results; however, reporting of studies has been variable. Detection, analysis, and reporting of performance errors and patient harms is vital to robustly assess the safety of AI medical devices in RCTs. Scoping searches have illustrated that the reporting of harms is variable, often with no mention of AEs. The findings of this systematic review will identify the frequency and severity of AI performance errors and patient harms and generate insights into how errors should be analyzed to account for both overall and subgroup performance.

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International Registered Report Identifier (IRRID): PRR1-10.2196/51614

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KEYWORDS

patient safety; adverse events; randomized controlled trials; medical device; systematic review; algorithmic; artificial intelligence; AI; AI health technology; safety; algorithm error

Introduction

Background

Artificial intelligence (AI), the use of machines to undertake complex processes that would usually require human intelligence, has the potential to transform health care [1,2]. The potential benefits of such data-led technologies include a wide range of clinical applications, such as faster diagnosis, prognostics, digital therapeutics, and even the detection of novel signals [3-5]. Although there has been a great deal of enthusiasm around AI medical devices, performance in computer-based test environments is often different from that in the real world [6-8]. There is an urgent need to investigate how such technologies can be evaluated and monitored to ensure clinical benefit and avoid patient harm [9-12].

AI Errors and Patient Harms

The translation of AI medical devices from "code to clinic" is complex and, if planned poorly, can lead to serious safety concerns [13,14]. Safety assessments involve understanding risks associated with AI medical devices, including what AI errors can arise, how these might lead to patient harms, and what failure modes may exist. These concepts are defined in Textbox 1.

Textbox 1. Glossary of terms.

Adverse events

- "An unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it" [15,16]

Artificial intelligence (AI) errors

- "Any outputs of the AI system which are inaccurate, including those which are inconsistent with expected performance and those which can result in harm if undetected or detected too late." [9]

Failure modes

- "The tendency to malfunction in the presence of certain conditions. Whereas an error can be a single occurrence, failure modes represent errors which will repeatedly occur and often have similar consequences." [9]

Patient harms

- "Injury or damage to the health of people" (as defined in International Organization for Standardization [ISO] 14971- application of risk management for medical devices) [17]
- "The totality of possible adverse consequences of an intervention or therapy" [18]

Performance Evaluation and Monitoring of AI Medical Device

AI medical device safety and effectiveness evidence can be generated at various stages in the evaluation process, which can be broadly divided into pre- and postmarket evaluations. Premarket evaluation includes a range of study types such as test accuracy studies and randomized controlled trials (RCTs). Postmarket evaluation on the other hand includes these study types in addition to local assurance practices and ongoing monitoring. Several study designs exist for the generation of effectiveness evidence, with the most robust evidence in terms of minimizing bias and objectively measuring the effect of AI interventions on clinical outcomes being derived from prospective RCTs [19]. Recent literature demonstrates the importance of in-depth performance error analysis including the identification of "inhuman errors" (eg, highly displaced fractures missed by AI), testing for algorithmic encoding of

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protected characteristics, and conducting exploratory error analyses to identify cases of hidden stratification [20-22]. An AI medical device might be shown to perform well overall; however, without more rigorous error analysis including exploratory and subgroup analysis, it is not possible to truly understand the clinical impact on patients as individuals. The concept of performance error analysis has been outlined in the recent AI extension reporting guidelines for clinical trials and trial protocols (Consolidated Standards of Reporting Trials-AI [CONSORT-AI] and The Standard Protocol Items: Recommendations for Interventional Trials-AI) [23,24]. Recent systematic reviews demonstrate that the quality of reporting of RCTs remains both suboptimal and variable [25,26]. The reviews demonstrated poor adherence of published RCTs to the CONSORT-AI reporting guidelines. There is still minimal literature specifically describing the reporting and analysis of errors and adverse events (AEs), and how performance error analysis is being conducted. There is a need to conduct a literature review in this area to inform future clinical evaluations of AI medical devices and real-world AE reporting. This systematic review aims to explore AI errors and AE reporting in RCTs of AI interventions.

Purpose

This systematic review will assess the frequency and severity of AI errors and AEs in RCTs investigating AI medical devices as interventions in clinical settings. Where reported, data regarding AI system risks, reported errors, and how these errors were analyzed will be extracted. Our research question is, what are the characteristics (including frequency and severity) of AI errors and AEs in RCTs and how are these performance errors analyzed?

Aim

The primary aims of this review are to assess the frequency, severity, and types of errors and AEs reported in RCTs of AI medical devices. The secondary aims of the review include (1) identifying what analyses are conducted when errors or harms are reported and (2) reporting the error and AE detection methods used.

Methods

Protocol

This systematic review protocol is written in compliance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) guidelines [27]. The completed systematic review will be reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance (Figure 1) [28]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Artificial Intelligence (PRISMA-AI) will be used if published before the submission of this systematic review [29].

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Figure 1. PRISMA flow diagram outline to be populated during the systematic review process. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO: World Health Organization.

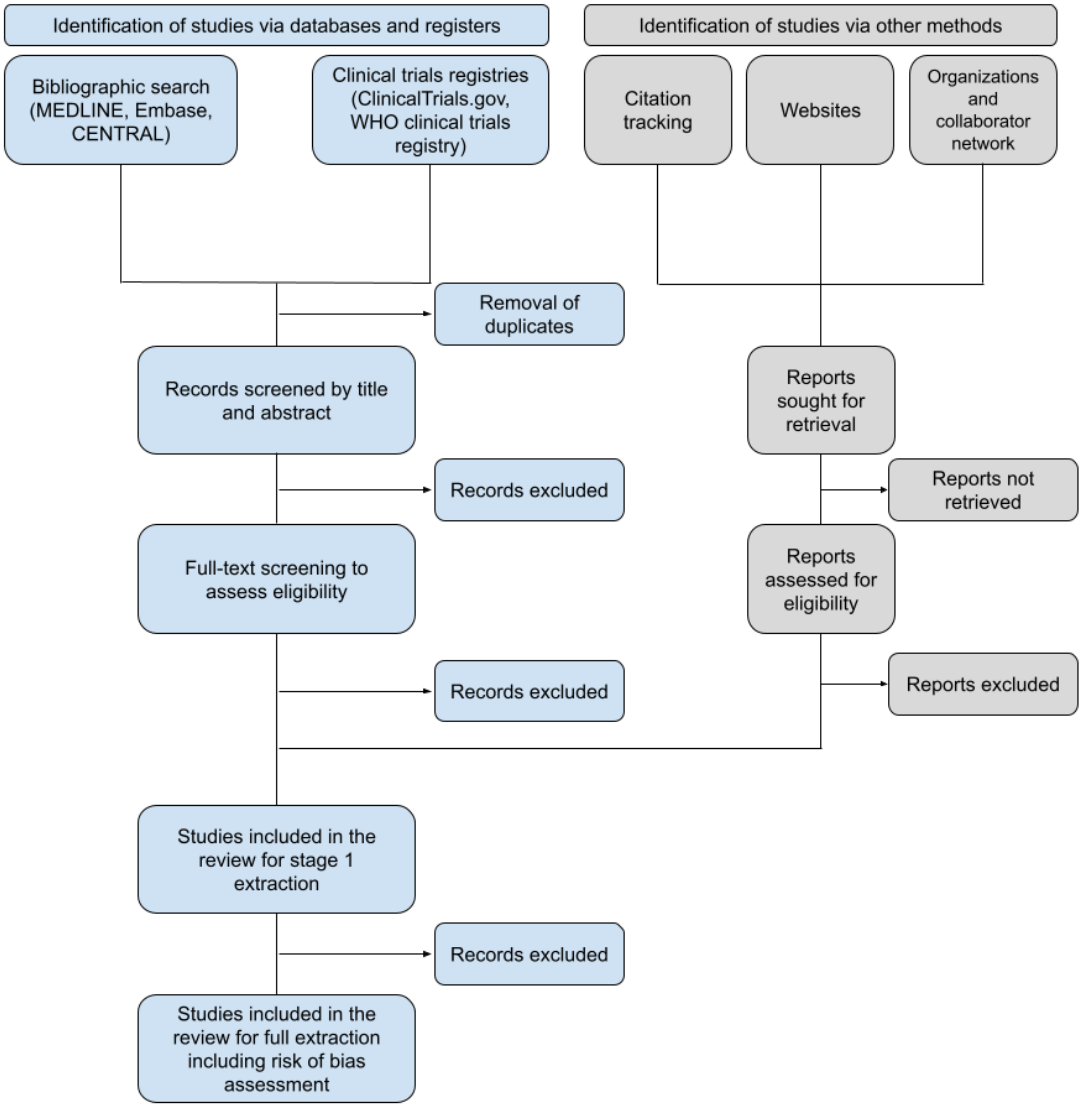

Systematic Review Registration

This systematic review protocol is registered on PROSPERO (CRD42023387747).

Information Sources

The search strategy will be used to search 3 online bibliographic databases, in addition to clinical trial registries, to identify RCTs evaluating AI interventions in clinical settings. Literature searches will not be limited by year to ensure that all AI medical device RCTs are identified. The bibliographic databases of published studies are MEDLINE, Embase, and Cochrane CENTRAL. The registers of clinical trials are ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP portal).

Search Strategy

In bibliographic databases, free text, and index terms will be used to search for RCTs of AI medical devices. Clinical trial registries will be searched using in-built filters to identify RCTs with results. RCTs identified in bibliographic databases will be cross-referenced using clinical trial registries to ensure that all harms data are captured. The search strategy has been developed in consultation with an information specialist (AC) and further details are included in Multimedia Appendix 1 [26,30-33]. The searches were executed on June 30, 2023. No date cutoff was applied. The full search strategies are available in Multimedia Appendix 2. Reference lists of included reports will be checked to capture additional RCTs. Additionally, experts in the field will be contacted to identify reports that were not available from the databases listed above.

Selection Criteria

Overview

The selection criteria are structured using the Studies, Data, Methods, Outcome measures (SDMO) framework for methodological systematic reviews that were deemed most appropriate and adapted for this study [34]. Studies not published in the English language will be included where the translation is available.

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Types of Studies

Only RCTs will be included in this systematic review. Other study types including nonrandomized clinical trials, observational studies, and case studies will be excluded. The review will include trials where randomization happens at any level (such as cluster randomization and crossover RCTs).

Types of Data

AI medical device interventions that directly affect patient care will be included, for example, diagnostic, prognostic, or therapeutic tasks. AI medical devices will be included if their function, as described within the trial, is consistent with the function of a medical device, that is, within the range of functions attributed to medical devices as defined by the International Medical Device Regulators Forum (IMDRF) [35]. AI medical devices that are deployed for nonclinical tasks will be excluded. RCTs evaluating robotic interventions will also be excluded.

Types of Methods

RCTs with control arms involving a non-AI standard of care will be included. RCTs with only AI-enabled control arms will be excluded. Additionally, the review will include trials where error analysis has been conducted.

Outcomes

RCTs reporting AEs and patient harms (not explicitly reported as AEs) will be included in the final analysis. Studies not involving these outcomes will be examined to extract data related to the RCT design and characteristics of the AI medical device.

Selection Process

Once papers have been identified through the search strategy, the studies will be screened for relevance by title and abstract. The Rayyan systematic review tool will be used to screen results [36]. Irrelevant studies will be removed. This process will be carried out by 2 reviewers independently and any discrepancies will be resolved by discussion or referral to an arbitrator.

Papers identified as potentially relevant will then be retrieved and the full text will be assessed for inclusion against the selection criteria described above. During full-text screening, the studies will also be assessed for the presence of patient harm data or any form of performance error analysis. Those with these data present will be marked for full extraction and risk of bias assessment, and those that do not report these data will be marked for the extraction of the RCT design and AI technology characteristics only. This will again be done by 2 reviewers independently with recourse to arbitration if required .

If included RCTs do not report errors or AEs, only data relating to the type of AI medical device and trial design will be extracted. This is signposted as stage 1 extraction in the PRISMA diagram. Further details are included in the data extraction section.

Data Extraction

The data extraction process will be undertaken using a standardized, piloted data extraction form. Data will be entered into the data extraction form in Microsoft Excel. This will be done by 2 reviewers who will complete data extraction independently using the agreed data extraction template. Authors of papers will be contacted for further information and clarification where required. Where available, the following items will be extracted (Textbox 2).

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Textbox 2. Data points for extraction using piloted data extraction form.

Study characteristics

- Title, authors, publication year, journal, and country
- Specialty (medical discipline, eg, radiology, ophthalmology, or cardiology)
- Study context (eg, primary care or hospital care)
- Study design
- Sample size
- Study length (time period)
- Control arm comparator (overview of workflow)
- Baseline characteristic subgroups (eg, sex, age, ethnicity, and socioeconomic details)
- Primary and secondary endpoints

Characteristics of the artificial intelligence (AI) medical device

- Name of AI medical device
- AI developer (and manufacturer where relevant)
- AI subtype, for example, "recurrent neural network"
- AI-intended use and clinical pathway (context)
- AI autonomy level (ie, the extent to which human oversight is expected). The autonomy level will be graded from 1 to 5 based on the classification described in the literature [37]
- Input data
- AI output
- Role in clinical decision-making
- Characteristics of the end user (eg, clinician or patient)

Outcomes and findings

- Primary outcomes (to satisfy primary objectives of systematic review):
  - Frequency of AI errors
  - Frequency and severity of adverse events (AEs; as classified by relevant regulatory documents including International Organization for Standardization [ISO] 14971-application of risk management for medical devices) in all study arms [17]
  - Characteristics of error, patient harm, and AEs identified
- Secondary outcomes (to satisfy secondary objectives of systematic review):
  - Types of performance error analysis, for example, subgroup analysis by patient or task characteristics
  - Error and AE detection methods described in the study and risk mitigations in place during the randomized controlled trial (RCT)

Reporting of AEs and Performance Error Analysis

Characteristics of the AI medical device being evaluated will be extracted for all included RCTs. Full data extraction will only be completed for studies reporting some form of AEs (or possible patient harms not explicitly reported by authors) or details of performance error analysis (item 19 of the CONSORT-AI extension) [23]. Performance error analysis is defined as any of the following: (1) exploratory error analysis, (2) subgroup analysis, or (3) adversarial testing [9].

Quality Assessment

Assessment of quality will be carried out for all included studies. Version 2 of the Cochrane risk-of-bias tool (RoB2) for randomized trials will be used to assess studies [38]. Assessment will be undertaken by 2 reviewers independently with arbitration by a third reviewer where required. The risk is categorized into "low," "high," or alternatively "some concerns."

Data Synthesis

Overview

Findings will be synthesized in both narrative and tabular formats. Included studies will be divided into 3 groups (1, 2a, and 2b as shown) for within-group (and between-group where possible) comparison, based on the AI medical device type and RCT study design

1. Studies assessing therapeutic AI medical devices (eg, drug-dosing algorithms and AI-enabled psychological therapies)

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2. Studies assessing diagnostic or predictive AI medical devices
    a. With ground truth (where ground truth is a reference test, for example, biopsy result or clinician opinion)
    b. Without ground truth

The synthesis of data will be divided into 2 sections consistent with the aims outlined in this protocol. The first section is focuses on the primary aims of the review—the frequency, severity, and types of AI errors and patient harms. The second section is focused on the secondary aims of the review: (1) the reporting of harms data based on the CONSORT harms extension, (2) the types of performance error analysis described, and (3) identified subgroups of interest for each health area.

Analysis to Achieve Primary Aims

AI error and patient harm rates will be calculated for each RCT. These data will be compared between and within the identified groups. The analyses that will be considered are as follows:

- First, reported AEs with comparison between AI and control arms, such as (1) frequency and severity of AEs for each technology, with comparison between AI medical device groups listed; (2) whether the AE was directly linked to the AI medical device (as assessed by RCT authors); and (3) severity of AEs will be based on guidance from international standards (ISO 14971-application of risk management for medical devices) [17].
- Second, the frequency of errors, for example, false positives or false negatives for diagnostic AI medical devices. If the AI output is reported as likelihood distribution, then the analysis will be directed by the subsequent clinical action taken in response to the AI output. If a ground truth is present in the study, then a comparison can be made, such as (1) a comparison within and between AI medical device groups listed. The type of algorithm used by the AI medical device will also be included for comparison, and (2) if appropriate, a meta-analysis will be conducted investigating harms as a proportion of total outputs for intervention versus control arms. Appropriateness will be defined by assessing the heterogeneity of trial characteristics. Assessment of heterogeneity will include the consideration of trial design, primary outcomes, and the types of reported AEs.
- Third, the characterization of errors and harms for AI medical devices, such as (1) comparison between AI medical device error rate and erroneous clinical action. For example, if the AI medical device output incorrectly suggests the administration of a drug, is this drug actually administered? (2) Harms that are identified but not explicitly reported by authors will also be extracted where possible.

Analysis to Achieve Secondary Aims

Failure Modes

The number of studies describing subgroup and exploratory error analysis will be recorded. First, subgroup analysis of AI medical device performance for the clinical task will be documented. Subgroups of interest described in RCTs will be documented for each medical specialty. Second, exploratory error analysis will be documented with a specific focus on the types of scenarios most likely to cause errors for each clinical use case. Described failure modes will be documented for each medical specialty and clinical task. Third, the types of performance analysis conducted for each type of AI medical device and clinical discipline will be compared to identify groups with high rates of failure.

Error and AE Detection Methods

Error and AE detection methods will be recorded for each study. The extraction of AI medical device characteristics for all identified RCTs (including those excluded from full extraction) will demonstrate trends in AI medical devices with no AEs or implicit patient harms. This will allow for the identification of areas where AE detection methods are particularly underdeveloped or less frequently used. An example of an AE detection method is the use of questionnaires to allow patients to self-report AEs after interaction with an AI-enabled mental health chatbot.

Results

The project was registered on PROSPERO in February 2023. Preliminary searches have been completed and the search strategy has been designed in consultation with an information specialist and methodologist (AC and DJM). Searches were conducted in June 2023. Title and abstract screening began in September 2023 and finished in February 2024. After deduplication, 11,913 papers were screened resulting in 423 eligible studies for full-text screening. The full-text screening was completed in April 2024. Data extraction commenced in April 2024. Data analysis and paper drafting will be conducted from May 2024 to July 2024.

Discussion

The potential value of AI medical devices is well recognized, and numerous studies have been published recently relating to model development and evaluation [30,31]. Although AI medical devices show promise, there are still barriers to their deployment at scale. One of the most important related challenges is ensuring that these technologies are effective, safe, and inclusive. As an interventional study, RCTs allow the measurement of clinically relevant outcomes including patient harms that would not be possible in an in silico study. As a randomized clinical trial, the study design minimizes bias and is, therefore, considered the gold standard of clinical evidence.

This systematic review aims to assess the frequency and severity of AI errors and AEs. Data will be extracted regarding how AEs and AI errors are analyzed such as subgroup analysis and identification of failure modes. Investigating the severity and frequency of errors and AEs in addition to how these are reported in RCTs may provide insights into study design, real-world impacts, and methods for evaluating unintended effects of AI medical devices. The systematic review will not only shed light on which AI medical devices or RCT designs most commonly report AEs, but also on the methods used for AE detection. A summary of these methods will be an important part of the insights generated by this study. The main anticipated limitation of this systematic review is the heterogeneity of

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outcomes across the different medical disciplines and types of AI medical devices. This will be addressed by grouping RCTs based on the type of AI medical device and medical specialty where appropriate. The benefits of a broad review in this instance outweigh the limitations given the lack of consensus in the analysis and reporting of AI errors and AEs. Furthermore, recent literature reviews have demonstrated poor adherence to CONSORT-AI guidelines which indicates a reporting limitation. This means that if no AI errors or AEs are reported, this will not necessarily stipulate that none had occurred in the study. Finally, AI error may or may not lead to clinical error and there will be other instances where clinical error is introduced by human involvement in the workflow. Mapping clinical workflows and analyzing work system elements will be important; however, there might be reporting limitations. Where relevant, authors may be contacted for further information.

There is a growing unmet need for methods enabling the detection, analysis, and reporting of AI errors and AEs related to AI medical device usage. This systematic review aims to be the first of its kind focused on errors and AEs associated with AI medical devices in health care. The impact of this systematic review will be 2-fold. First, it will demonstrate current practices in error and AE detection, analysis, and reporting, forming the basis for further work around best practices for AI harms in RCTs. Second, we hope that this work will inform the real-world deployment of AI medical devices, particularly safety monitoring and risk mitigation practices, which is an area of significant interest globally. This will be achieved through the signposting of best practices for AE detection and performance error analysis identified through the review. This is part of a wider program of work looking at postmarket safety monitoring of AI medical devices. A complementary systematic review focusing on AEs reported in regulatory databases is also being conducted.

Acknowledgments

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Authors' Contributions

All authors have contributed to the design and development of this systematic review. AUK, XL, DJM, and AKD contributed directly to the drafting of the paper. AUK, XL, AC, AKD, and DJM developed the search strategy. All authors contributed to reviewing and redrafting of this paper. AKD and DJM are joint senior authors.

Conflicts of Interest

BG is a part-time employee of HeartFlow and Kheiron Medical Technologies. XL was a health scientist at Apple and a consultant for Hardian Health and Conceivable Life Sciences.

Multimedia Appendix 1
Development of search strategy for MEDLINE and Embase.
[DOCX File , 21 KB - resprot_v13i1e51614_app1.docx]

Multimedia Appendix 2
Search strategies.
[DOCX File , 25 KB - resprot_v13i1e51614_app2.docx]

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Abbreviations

AE: adverse event
AI: artificial intelligence
CONSORT-AI: Consolidated Standards of Reporting Trials-Artificial Intelligence
ICTRP: International Clinical Trials Registry Platform
IMDRF: International Medical Device Regulators Forum
ISO: International Organization for Standardization
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-AI: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Artificial Intelligence
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol
RCT: randomized controlled trial
SDMO: Studies, Data, Methods, Outcome measures
WHO: World Health Organization

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Protocol

AI as a Medical Device Adverse Event Reporting in Regulatory Databases: Protocol for a Systematic Review

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Abstract

Background: The reporting of adverse events (AEs) relating to medical devices is a long-standing area of concern, with suboptimal reporting due to a range of factors including a failure to recognize the association of AEs with medical devices, lack of knowledge of how to report AEs, and a general culture of nonreporting. The introduction of artificial intelligence as a medical device (AIaMD) requires a robust safety monitoring environment that recognizes both generic risks of a medical device and some of the increasingly recognized risks of AIaMD (such as algorithmic bias). There is an urgent need to understand the limitations of current AE reporting systems and explore potential mechanisms for how AEs could be detected, attributed, and reported with a view to improving the early detection of safety signals.

Objective: The systematic review outlined in this protocol aims to yield insights into the frequency and severity of AEs while characterizing the events using existing regulatory guidance.

Methods: Publicly accessible AE databases will be searched to identify AE reports for AIaMD. Scoping searches have identified 3 regulatory territories for which public access to AE reports is provided: the United States, the United Kingdom, and Australia. AEs will be included for analysis if an artificial intelligence (AI) medical device is involved. Software as a medical device without AI is not within the scope of this review. Data extraction will be conducted using a data extraction tool designed for this review and will be done independently by AUK and a second reviewer. Descriptive analysis will be conducted to identify the types of AEs being reported, and their frequency, for different types of AIaMD. AEs will be analyzed and characterized according to existing regulatory guidance.

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Results: Scoping searches are being conducted with screening to begin in April 2024. Data extraction and synthesis will commence in May 2024, with planned completion by August 2024. The review will highlight the types of AEs being reported for different types of AI medical devices and where the gaps are. It is anticipated that there will be particularly low rates of reporting for indirect harms associated with AIaMD.

Conclusions: To our knowledge, this will be the first systematic review of 3 different regulatory sources reporting AEs associated with AIaMD. The review will focus on real-world evidence, which brings certain limitations, compounded by the opacity of regulatory databases generally. The review will outline the characteristics and frequency of AEs reported for AIaMD and help regulators and policy makers to continue developing robust safety monitoring processes.

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KEYWORDS

adverse event; artificial intelligence; regulatory science; regulatory database; safety issue; feedback; health care product; artificial intelligence health technology; reporting system; safety; medical devices; safety monitoring; risks; descriptive analysis

Introduction

Background

Patient safety has been defined as one of the 6 key indicators of health care quality by the Institute of Medicine [1]. In a landmark report published in 2001, the Institute of Medicine identified that approximately 100,000 adverse events (AEs) resulted in patient death each year in the United States, with sources suggesting that medical error is third on the list of leading causes of death [2,3]. In the UK's National Health Service, it is estimated that 8%-12% of hospital admissions may involve an AE resulting in harm to the patient [4,5].

Whereas administration errors and AEs have been extensively explored in the context of medication, there has been much less attention given to similar issues in the context of medical devices [6]. Suboptimal reporting exists due to a range of factors such as failure to recognize the association of AEs with medical devices, lack of knowledge of how to report AEs, as well as a common culture of not reporting events [7]. Evidence shows that a significant proportion of AEs in hospitals (including drug and device AEs) are indeed preventable and that transparency of AE reporting to generate insights into device safety issues is essential [8-10].

Artificial intelligence as a medical device (AIaMD) is an important new tool for improving health care most notably in the areas of diagnosis, screening, prognosis, and clinical decision support systems. There is however an increasingly recognized performance gap between the initial proof-of-concept studies and what may be observed in the more challenging deployment in the real world where there is a greater diversity of setting and population and much less control of external factors [11-13]. An important factor in the wider adoption of AIaMD will be to have adequate systems of safety signal detection, attribution, and reporting that are transparent and can be trusted by health systems and the patients and the public they serve. One key component of existing safety systems is AE reporting. An AE is defined as "An unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it" [14,15]. It is important to note that definitions of AEs are often centered around the use of medicines rather than medical devices. For the purposes of this review, relevant regulatory guidance such as that from the International Medical Device Regulators Forum (IMDRF) [16] will be used to guide the classification of AEs.

AE reports can be submitted by different stakeholders including device manufacturers, clinical staff or patients, and members of the public. The AE reporting processes vary by country; however, in general, each regulatory body has an AE or safety notice database, of which some are publicly available and searchable. There are currently no specific AIaMD AE reporting processes; and therefore, existing processes for medical devices are currently used.

Guidance from the Medicines and Healthcare Products Regulatory Agency (MHRA) was recently released, aiming to aid manufacturers in understanding what events should be reported [17]. There still remains an urgent need to develop robust safety monitoring processes to ensure that patients, professionals, health systems, and regulators can have confidence that AIaMDs are safe for patients. AE reporting is an important component of safety monitoring and aims to ensure that any AIaMD that is found to be unsafe after reaching the market is swiftly detected and either corrected or removed.

Purpose

AE reporting is a cornerstone of safety monitoring in medical devices and other health care products and will be a key component of the safe introduction of AIaMD. There are concerns, however, that current AE reporting systems are inadequate with many AEs remaining hidden. Even when AEs are reported, the details are not publicly available, leading to a lack of transparency, and reducing the opportunity for these and other health systems to learn and act early. Even for regulatory territories with stronger AE infrastructure (openly accessible dedicated AE databases), it is unclear how well AEs are reported and recorded within those databases. The systematic review described in this protocol aims to identify reported AEs and data relating to frequency and severity for different types of AIaMD.

The secondary aims of the review described in this protocol are (1) to compare the number of AEs reported for different AIaMD risk classes, (2) to compare AE reporting across 3 jurisdictions with publicly available AE databases, and (3) to identify the

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level of clinical evidence available for devices with reported AEs.

Methods

Reporting of Protocol and Systematic Review

The reporting of this protocol follows the guidelines of PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [18]. The PRISMA-P checklist is included in Multimedia Appendix 1. Reporting of the subsequent review will adhere to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) reporting guideline for systematic reviews [19] and the PRISMA-AI guideline (if available as this is still in development) [20].

Systematic Review Registration

This systematic review has been registered in the Open Science Framework.

Information Sources

The search strategy for this review has been designed to identify reported AIaMD AEs. We have identified searchable AE databases through scoping searches across three different jurisdictions: (1) the Manufacturer and User Facility Device Experience (MAUDE)—available from the US Food and Drug Administration (FDA), United States [21]—contains reported AEs associated with FDA-approved medical devices. AEs can be reported by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters (eg, health professionals, patients, and consumers) [21]; (2) The Database of Adverse Event Notifications (DAEN)—available from the Therapeutic Goods Administration (TGA), Australia [22]—similar to MAUDE, contains AE data for medicines and medical devices approved for use by the TGA; and (3) Field Safety Notice (FSNs) website—available from the MHRA, United Kingdom [23]—describes corrective actions taken by device manufacturers in response to an identified safety issue. These notices are not reported AEs; however, they can contain relevant device safety data that can be extracted. FSNs may be disclosed by manufacturers in response to AEs.

Scoping searches have demonstrated that there are relatively fewer information sources for medical device AEs compared to AEs associated with medicines. The 3 databases mentioned earlier have been identified as being searchable to yield details regarding safety events. In addition to the AE or FSN databases, each of the 3 regulatory bodies outlined earlier will be searched to identify any product recalls for AIaMDs.

Search Strategy

We have undertaken an initial feasibility assessment of searching AE databases. Given that each database is unique to its own regulatory body, different search strategies are required. Search strategies cannot be transferred between AE databases due to inconsistencies in terminology, device names, and search capabilities. It is important to note that the common thread in the search strategies is searching for AIaMDs for which AEs have been reported. The following search strategies are specific to each database listed:

- MAUDE (provided by the FDA)
  - This database will be searched using the openFDA application programming interface (API). The openFDA was set up by the first Chief Health Information Officer in March 2013 and enables public access to relevant data including drug and medical device AEs.
  - The API can be searched to request several data points. This approach has been used in previous studies to identify AEs for both drugs and devices [24,25].
  - The database will be searched to find AEs reported for artificial intelligence (AI) or machine learning (ML)–enabled devices listed on the FDA website [26].
- DAEN (provided by the TGA)
  - The DAEN website allows for searches of medical device AEs. Due to a lack of AI- or ML-specific search terminology, it is not possible to search the database using these terms. However, the word “software” is indexed and will be used to search for relevant events. Events specific to AIaMDs will be identified through manual screening.
- FSNs website (provided by the MHRA)
  - The MHRA FSN website has an in-built search function, and the database will be searched using a similar approach to the search of DAEN. As mentioned earlier, following the identification of software-related FSNs, manual screening will be undertaken to identify AIaMD-related FSNs.

For devices where events are identified in one of the 3 information sources, web searches will be used to identify the device manufacturer’s website. Where available, details for clinical evaluations will be identified from the device manufacturer’s website. Data will be extracted for analysis including the type of study, sample size, reported demographics, and whether or not any AEs were identified and reported. Further information regarding the extracted data is listed below, and a PRISMA flow diagram is shown in Figure 1 to be populated during the review process.

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Figure 1. PRISMA flowchart to be populated during the systematic review process. AE: adverse event; AI: artificial intelligence; DAEN: Database of Adverse Event Notifications; FSN: Field Safety Notice; MAUDE: Manufacturer and User Facility Device Experience; MHRA: Medicines and Healthcare Products Regulatory Agency; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis.

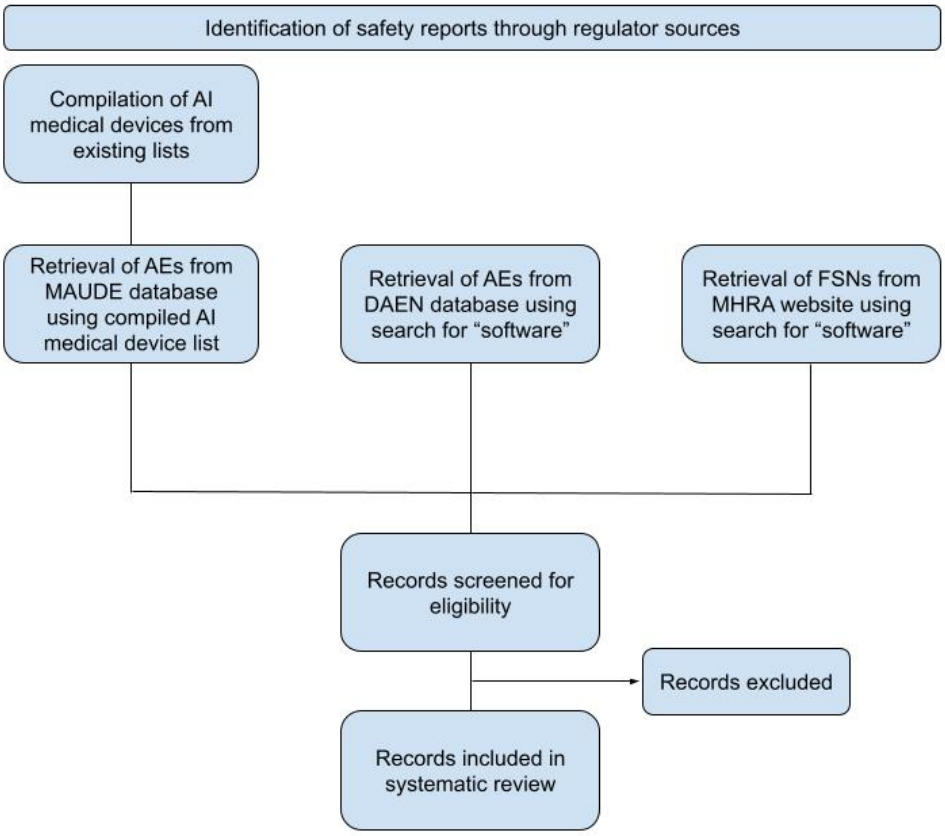

Selection Criteria

Intervention

All regulatory-approved AIaMDs will be included in this systematic review. AUK and a second reviewer will independently screen identified AE reports to ensure that the medical device in question is an AI medical device.

Types of Documentation

The following documentation will be reviewed to ensure appropriate selection of medical devices:

- MAUDE (provided by the FDA)
  - The full AIaMD AE or incident report will be downloaded and cross-referenced with the FDA summary document. The summary documents include details regarding evidence submitted for approval and the date of regulatory approval. This documentation often includes the intended use and type of the AIaMD.
- DAEN (provided by TGA)
  - The full AE report will be downloaded and assessed to ensure that the medical device in question is AIaMD. This will be cross-referenced with web-based sources where required, such as the device manufacturer's website.
- FSNs (provided by MHRA)
  - The full FSN will be downloaded and assessed to ensure the medical device is AIaMD. As with the Australian database (DAEN), devices will be cross-referenced with web-based sources as required.

Selection Process

Once AIaMDs are identified through searches, the AE reports or FSNs will be screened to ensure that the medical device is AI- or ML-enabled. Publicly available regulatory documents and web-based sources will be used to screen devices. Where required, manufacturers will be contacted for additional details. This will be undertaken independently by AUK and a second reviewer. The main inclusion criterion is that the AE report concerns an AIaMD. The exclusion criteria are AE reports for AI health technologies that are not medical devices and AE reports for software as a medical device with no use of AI.

Risk of Bias Assessment and Confidence in Cumulative Evidence

This systematic review focuses on real-world data reported in regulatory databases. There are no formal risk-of-bias assessment tools for these data; however, the review will include a measure of the completeness of data reported in AE reports. There will be no formal evaluation of confidence in cumulative evidence, as the items included in this review are not research papers.

Data Extraction

The data extraction process will involve 3 stages. The first stage relates to the MAUDE database (FDA). The openFDA API will be used to extract all AIaMD-related reports into a local

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database. The data will then be tabulated and displayed in Excel (Microsoft Corp). The second stage relates to the DAEN (TGA) and FSN (MHRA) information sources. For these, the data extraction process will be undertaken using a standardized data extraction form. Data will be entered into the extraction form using Excel. AUK and a second reviewer will extract these data independently using the agreed template, and any disagreements will be escalated to a third arbitration reviewer (AKD or XL). Finally, regulatory data will also be extracted where available for AIaMDs with reported AEs (such as device classification and route to approval). For AIaMDs with reported AEs, published clinical evaluation studies will also be identified where available.

The following data will be extracted based on documentation available from the FDA, the IMDRF, and published literature [27,28]. Data points directly relating to safety reports are type of report, date of event, date of report, patient demographics, patient outcome (death, injury, or malfunction without patient harm), description of the event (free text entry regarding the incident), device brand name (brand name of AI medical device involved in the AE report), manufacturer name (name of the manufacturer for the AI medical device in question), unique device identifier if available, operator of device, reporter occupation, response to AE from the manufacturer where available (details regarding any investigation), latency of response from the manufacturer (time from AE report to manufacturer response), and recall data if available. Further data regarding the AIaMD will be identified from clinical evaluation data submitted to the respective regulatory body (Textbox 1).

Textbox 1. Data points relating to the medical devices in question.

- Approval number (if Food and Drug Administration approved): Unique approval number assigned to devices acquiring regulatory approval.
- Approval pathway: The name of the regulatory pathway through which artificial intelligence as a medical device (AIaMD) was approved. For example, for the Food and Drug Administration, this will be 510k, de novo or premarket approval.
- Manufacturer origin country: The country of origin of the manufacturer.
- Medical specialty: The medical discipline which the device is intended for.
- Type of artificial intelligence: The type of artificial intelligence system, for example, deep learning.
- Autonomy level of AIaMD: Autonomy level will be graded based on the intended use of the device.
- Intended use of AIaMD: Intended purpose of the device and associated details such as the intended population and setting.
- Risk classification: The risk class of the AIaMD as approved by the regulator.
- Risk level: The risk level of the AIaMD determined according to International Medical Device Regulators Forum guidance.
- Validation sample size: The sample size of the validation cohort if available.
- Retrospective or prospective validation: The type of validation study that was conducted prior to regulatory approval.
- Reported demographics in validation: Any reported patient demographics reported in the validation study.
- Adverse events reported in clinical validation study: Whether or not any adverse events were reported within the validation study prior to regulatory approval.

Data Synthesis

A descriptive analysis of extracted data will be undertaken. Analysis of the variables described earlier will include comparison across (1) types of intended use (and risk level), (2) specialty areas, and (3) regulatory territories (the United Kingdom or the United States or Australia). The comparison aims to identify whether there are certain types of AIaMD intended use (and risk level), specialty, or regulatory territory within which AEs are more commonly reported. The types of intended use for AIaMDs will be grouped into 2 broad categories based on clinical tasks. These will include (1) diagnostic and prognostic AIaMD and (2) therapeutic AIaMD. Detected AEs and FSNs will be characterized according to AE terminology available from the IMDRF [29].

Once AEs and FSNs have been characterized using AE terminology, rates of each type of AE will be quantified and compared between the groups described earlier. The following further analyses will also be considered:

- The number of AEs reported per year to identify trends in reporting
  - Rates of AEs reported for AIaMDs across the 3 jurisdictions mentioned will be calculated. This will be calculated for each group but also across groups to quantify trends in AE reporting.
- Completeness of AE reports
  - AE reports often vary in their completeness. For example, some reports may not contain who reported the event or what the final patient outcome was. Completeness of AE reports will be assessed against reference criteria, developed using existing guidance and AE reporting forms. The IMDRF (which has membership of several international regulators) provides guidance relating to AE reporting. This assists in the standardization of AE reports across the globe. Therefore, it is likely that the findings generated will apply to AE reporting both within and outside the 3 jurisdictions included in this study.
- AE reporting party

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    - The source of the AE will be compared across groups to understand how reporting characteristics vary. For example, reporting by manufacturers versus clinical staff versus patients.
- Availability of clinical evaluation data for medical devices with reported AEs
    - Where AEs are reported for AIaMD and clinical evaluation data are available (from regulatory or manufacturer websites), further analysis will be conducted. The types of AEs that are reported across different clinical studies will be identified and compared with AEs detected in AE databases.

The analysis aims to generate insights into the frequency of reporting of AIaMD-associated AEs but also the characteristics of the AEs in order to inform real-world safety monitoring practices for AIaMD. Additionally, this systematic review aims to generate insights into how AE reporting may vary by region and regulatory authority. By understanding what types of AEs have been reported, systems to detect relevant patient harms can be implemented in real-world AI safety monitoring strategies.

Results

Scoping searches are being conducted with screening to begin in April 2024. Data extraction and synthesis will commence in May 2024, with planned completion by August 2024. The review will highlight the types of AEs being reported for different types of AI medical devices and where the gaps are. It is anticipated that there will be particularly low rates of reporting for indirect harms associated with AIaMD. The results are expected to be submitted for publication in quarter 4 of 2024.

Discussion

Overview

The systematic review outlined in this protocol aims to identify and characterize AEs arising from AIaMDs as estimated through AE reporting systems. The review will highlight the types of AEs being reported for different AI medical devices and more importantly where the gaps are. It is anticipated that reporting will be poor overall with particularly low rates of reporting for indirect harms associated with AIaMD. AEs are often poorly reported in the literature and are usually not the primary outcome of clinical research studies [30]. Once a medical device has gained regulatory approval and is in active use, AE reporting is an essential component of postmarket safety monitoring. There is variable reporting of AEs for medicines and medical devices, and reporting can often be sporadic for the latter [6,31]. AIaMD has gained much interest recently, with many new commercially available AIaMDs ready for deployment. However, there remains a lack of consensus on how to ensure robust safety monitoring post deployment. One key aspect is AE reporting for AIaMDs.

Anticipated Principal Findings

There is minimal awareness around what consists of an AE for AIaMDs and how these AEs should be reported. This systematic review protocol describes the methodologies for searching AE databases and highlights relevant information sources. The systematic review will outline the methodology for searching AE databases and highlight all reported AEs for AIaMD. The review will provide insights into the types of AEs that may occur for AIaMDs, the completeness of reporting, and the frequency of AE reports. Given the often-variable AE reporting for many other types of medical devices, it is likely that AE reporting for AIaMDs will be equally variable if not even poorer. The data points listed in the previous section will allow the analysis of frequency and types of AEs being reported, in addition to the types of AI medical devices for which AEs are more commonly identified. Furthermore, for devices where validation data are available from regulators, the analysis will highlight the potential correlation between the level of evidence submitted for regulatory approval and the likelihood of AEs being reported.

Limitations

There are several limitations that need to be considered. First, the review described in this protocol focuses on real-world evidence in the form of AEs, which have been reported through postmarket surveillance pathways. This means that there will be variations in the quality of reports. As part of this review, the completeness of the report will be assessed; however, there will not be a formal risk of bias assessment. Second, the scope of this review is focused on AIaMD. There will be numerous AEs reported for software as a medical device without AI. Many of the AEs related to this group of devices could provide relevant insights for AI medical devices, and there might be value in a review for these devices in the future. Finally, this study only examines publicly available data, as access to additional data is reserved for medical device regulators only. It is anticipated that the review will highlight the need for transparent databases, providing a foundation for further work with regulators to reduce the opacity of such data sources.

Conclusions

This review of AE databases comes at a key milestone in AIaMD regulation reform and aims to inform regulators and policy makers of the current state of AE reporting. The review will provide information such as the devices and types of algorithms for which AEs are most commonly reported, whether any use cases or specialties are frequently involved, and potentially the level of clinical validation associated with frequent AE reports if this is available. A companion systematic review is being conducted by our group investigating AE reporting in randomized controlled trials of AI medical devices. The companion review aims to assess the types of AEs being reported in randomized controlled trials but also how algorithmic performance error analysis is conducted. Together, these systematic reviews will identify the current status of AE reporting across both clinical trials and real-world deployment phases. This work aims to generate insights into how AIaMD safety signals could be monitored going forward while informing the decision-making of multiple stakeholders including

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manufacturers, AIaMD deployment teams, regulators, and policy makers.

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Authors' Contributions

All authors have contributed to the design and development of this systematic review. AUK, XL, DJM, and AKD contributed directly to the drafting of the manuscript. AUK and RD developed the search strategy including application programming interface–based searches of the openFDA database. All authors contributed to reviewing and redrafting of this manuscript. They have all approved the final version and agreed to be held accountable for all aspects of the work. AKD and DJM are joint senior authors.

Conflicts of Interest

BG is a part-time employee of HeartFlow and Kheiron Medical Technologies. XL was a Health Scientist at Apple and has received consultancy fees from Hardian Health and Conceivable Life Sciences.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 27 KB - resprot_v13i1e48156_app1.docx]

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Abbreviations

AE: adverse event
AI: artificial intelligence
AIaMD: artificial intelligence as a medical device
API: application programming interface
DAEN: Database of Adverse Event Notifications
FDA: Food and Drug Administration
FSN: Field Safety Notice
IMDRF: International Medical Device Regulators Forum
MAUDE: Manufacturer and User Facility Device Experience
MHRA: Medicines and Healthcare products Regulatory Agency
ML: machine learning
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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TGA: Therapeutic Goods Administration

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Protocol

Estimating the Global and Regional Burden of Streptococcus pneumoniae Meningitis in Children: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: *Streptococcus pneumoniae* (Spn) has been a leading cause of bacterial meningitis in children. The most recent estimation of the global burden of Spn meningitis indicates a positive trajectory in eliminating Spn through the implementation of pneumococcal conjugate vaccines. However, continuous monitoring and assessment of the disease burden are necessary due to the evidence of serotype replacement, antibiotic resistance, and the impact of the recent COVID-19 pandemic.

Objective: The aim of this systematic review is to provide an updated and focused assessment of the global and regional burden of Spn meningitis in children, which can guide policies and strategies to reduce the disease burden.

Methods: Population-based studies published from January 1, 2000, to January 1, 2022, were preliminarily searched from the electronic databases PubMed, Embase, Global Health (CABI), and CINAHL Plus without any language restrictions. Studies were included if they reported the incidence, prevalence, mortality, or case-fatality ratio (CFR) for Spn meningitis in children aged 0-4 years; meningitis was confirmed by cerebrospinal fluid culture; the study period was a minimum of 1 year; the number of reported cases was at least 10; and the study had no methodological ambiguities. The article screening process follows the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. Characteristics including study period, setting, World Health Organization region, income level, vaccination information, and participant data (age, number of cases, deaths, sequelae, and risk factors) will be extracted from the included studies. Search results will be updated and incorporated into our review prior to finalizing the extraction of data. Generalized linear mixed models meta-analysis will be performed to estimate the pooled incidence and CFR. We will further assess the risk of bias and heterogeneity, and will perform subgroup and sensitivity analyses to provide a meaningful interpretation of the current burden and literature for pneumococcal meningitis.

Results: Our preliminary search in December 2021 yielded 9295 articles. Out of 275 studies that were assessed with our eligibility criteria, 117 articles were included. Data extraction and analysis are expected to be complete by January 2025. We plan to publish the results from the full study, including an updated search in 2024, by March 2025.

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Conclusions: Given that the major burden of Spn meningitis affects children under the age of 5 years, this systematic review will provide a thorough understanding of the global burden of Spn meningitis in this vulnerable population over a span of 2 decades. Insights into incidence trends, geospatial distribution, risk factors, and sequelae will be valuable for stakeholders, policy makers, and the academic community. This information will aid in the ongoing monitoring of the disease and in enhancing targeted vaccine programs to further mitigate the impact of the disease on children worldwide.

Trial Registration: PROSPERO CRD42021293110; https://tinyurl.com/kc3j5k4m

International Registered Report Identifier (IRRID): DERR1-10.2196/50678

(JMIR Res Protoc 2024;13:e50678) doi:10.2196/50678

KEYWORDS

Streptococcus pneumoniae; meningitis; streptococcal meningitis; pneumococcal meningits; global burden; pediatric meningitis; infectious disease; pneumonia; sepsis; infection; infection prevention and control; IPC; child health; global health; systematic review; pneumococcal

Introduction

Streptococcus pneumoniae (Spn) is a gram-positive, encapsulated coccus; the World Health Organization (WHO) has identified diseases caused by Spn as a serious public health concern [1]. Indeed, Spn infection is a major cause of morbidity and mortality worldwide and is a leading cause of bacterial meningitis in children [2]. There were an estimated 103,000 cases of Spn globally with a case-fatality ratio (CFR) of 59% in 2000 [3]. With the introduction of pneumococcal conjugate vaccines (PCVs), the most recent study into the global burden of Spn in 2015 reported a decrease in burden to 83,900 cases (range 36,100-169,000) of pneumococcal meningitis with a CFR of 44% in children regardless of HIV status [4].

In 2007, the WHO recommended including the 7-valent polysaccharide-protein conjugate vaccine (PCV7) in national immunization programs, particularly in countries with high mortality rates from pneumococcal disease in children under 5 years [1]. PCV7 has been widely used for providing protection against 65%-85% of serotypes associated with invasive pneumococcal disease in young children [1]. However, since 2009, the WHO has recommended PCV10 or PCV13 depending on the country's serotype prevalence, financial budget, and vaccine supply; thus, PCV7 is no longer in use [5]. Multiple notable trials worldwide have been conducted and are currently ongoing [6-11] to provide evidence for the preferred product and dosage schedule, which is currently recommended to be 3+0 or 2+1 [12]. As of December 2021, 147 countries (114 with PCV13, 26 with PCV10, and 7 with PCV10&PCV13) have implemented PCV into their national immunization programs, 60 of which are financially supported by the Global Alliance for Vaccines and Immunization [13]. The universalization of PCV has been estimated to have prevented 250,000 deaths in children from 2000 to 2015 [4].

Despite such continuous endeavors to globally implement PCV, the emergence of COVID-19 and associated pandemic measures affected a shift in the paradigm of Spn meningitis. The mass distancing measures contributed to a sharp decline in pneumococcal infections at the start of the pandemic [14]; however, disruption of vaccination programs has become prevalent and concerning [15,16]. Evidence forecasts that this phenomenon will lead to a detrimental increase in the cases of Spn meningitis [17]. The true impact of COVID-19 on the current Spn disease burden is yet to be determined. Therefore, an updated estimation of Spn meningitis will be an important comparator for future investigations and guide strategies to mitigate the pandemic's negative impacts on Spn immunization programs.

Although the introduction of the vaccine has contributed to a decreasing trend in the burden of pneumococcal meningitis, the reported figures show a marginal reduction within the 15-year period [3,4]. Recent evidence highlights a concerning outlook for the future burden of the disease. Although vaccination has reduced the incidence of Spn for PCV serotypes, there has not been a uniform decrease in the incidence and CFR of Spn meningitis, revealing an issue of serotype replacement [18-21]. This predicament is exacerbated by the increasing antibiotic resistance to Spn meningitis [20,22,23]. Heterogeneity of serotypes and antibiotic resistance are persistent challenges facing other causes of bacterial meningitis, which demands the Spn burden to be scrutinized to a similar degree [24]. Ultimately, Wahl et al [4] reported that their study did not account for the outbreaks of pneumococcal meningitis, possibly leading to an underestimation. Furthermore, the current literature concurs with these authors' concern about the countries that are yet to implement a national pneumococcal immunization program [4,14]. These problems call for further rigorous efforts in determining and monitoring the disease burden to direct policies to counter the numerous cases and deaths [4].

This review aims to provide the most up-to-date estimate of the global and regional burden of Spn meningitis in children under the age of 5 years. Our objective is to provide meaningful data regarding the global and regional incidence, CFR, and risk factors to guide policies in preventing and minimizing the burden of the disease.

Methods

Study Design and Registration

A systematic review of the literature will be performed to estimate and understand the global and regional burden of Spn meningitis in children under the age of 5 years. This protocol was developed in accordance with the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols) checklist [25]. The review was registered with the

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International Prospective Register of Systematic Reviews (PROSPERO) on December 3, 2021. Any amendments to the protocol will be subsequently published on the register (CRD42021293110).

Inclusion Criteria

This review will include studies published between January 1, 2000, and January 1, 2024, based on a search of the following databases: PubMed, Embase, Global Health (CABI), and CINAHL Plus. The initial search was conducted for literature published from January 1, 2000, to December 1, 2021, and the search will be reconducted to include the most recent papers prior to final data extraction and analysis. Meningitis cases that we will include in the review will be defined as an acute bacterial illness with symptoms consisting of severe headache, nausea, neck stiffness, vomiting, photophobia, and high fever. Clinical presentations denoted in the studies will be compared to the definitions from the *International Classification of Diseases, Tenth Revision* [26] and WHO [27-29].

Population-based studies will be included if they (1) reported the incidence, prevalence, mortality, or CFR for pneumococcal meningitis (the papers have to specify or have clear suggestions that *Streptococcus* was referring to Spn); (2) confirmed meningitis by cerebrospinal fluid culture in a facility-based laboratory; (3) had a minimum study period of 1 year (or multiples of 1 year); (4) reported a minimum of 10 cases of confirmed Spn meningitis during the study period; (5) reported results for a participant age group of 0-4 years; and (6) contained no methodological ambiguities about how the study was conducted and no systematic errors in the design in the research that could affect the results of the study.

Search Strategy

We plan to use the following search strategy to capture all relevant studies without any restrictions for the language of publication: Meningitis AND (*Streptococcus pneumoniae* OR invasive pneumococcal disease OR streptococcal OR pneumococcal) AND (burden OR incidence OR prevalence OR deaths OR mortality OR morbidity OR sequela* OR case fatality OR risk factor OR vaccination OR immunisation) NOT (case reports OR animals OR adults). This search was performed on December 3, 2021. The search strategies used in each database are provided in Multimedia Appendix 1.

Study Records

The screening process will be performed on EndNote20 (Clarivate Analytics). Two reviewers (JT and MMA) will independently screen the studies for titles and abstracts that are relevant to this review. Subsequently, the reviewers will only discuss their screening results when applying eligibility criteria for the retrieved full texts. A third reviewer (JJP) will check for final inclusions and settle any disagreements when applying the eligibility criteria. Any decisions that are outstanding will be discussed with a fourth reviewer (DA).

Data Items

Our data extraction proforma (Table 1) has been developed to fully answer our review question according to the condition, context, and population (CoCoPop) framework [30]. This proforma has been drafted according to a pilot form that has been completed by two independent reviewers (JJP and JT). Once screened for all studies that are relevant, data extraction for the systematic review will be performed by three authors (JT, SN, and MMA) and verified by a fourth author (JJP). Any disagreements will be settled by these four authors through consensus-based discussion, and subsequent unsettled decisions will be discussed with the fifth author (DA). All data extracted from included studies will be managed and stored in an Excel spreadsheet.

The items in Table 1 will be extracted from all included studies. Missing data that are unavailable in the retrieved full texts will be acquired by contacting the authors of the studies. If unreported details remain, we will report the missing data. Case ascertainment of pneumococcal meningitis will have to be available for the study to be included in our review.

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Table 1. Data extraction proforma to outline and define specific data to be extracted from included studies.

Data to be extracted	Definitions
Study characteristics	
Authors	Authors of the study
Date of publication	Year in which the study is published
Study period	Year(s) in which the study was conducted
Study era	Whether the study was conducted before or after 2010
Study setting	Community-based study versus hospital-based study
Study site	Country in which the study was conducted (and city if defined in study)
WHO[a] region of the study	WHO classification of the region in which the study is conducted [31]
Income level of the study site	World Bank classification of the income level of the study site [32]
Study design	Retrospective versus prospective studies
Study duration	Duration of the study in months
Study quality	Quality of the study (ie, high, moderate, low, very low)
Vaccination	
Vaccination era	Pre- versus postvaccination implementation
Vaccine introduction year	Year in which vaccination program has been implemented
Vaccination program	Type of vaccination program at the time of study (ie, PCV[b]7, PCV10, PCV13, PCV10&13)
Dosage	Dosage plan of the vaccination at the time of study (ie, 3+0, 2+1, or 3+1)
Participants	
Diagnostic criteria	How the diagnosis is made (ie, latex agglutination, cell count, polymerase chain reaction, isolation from the cerebrospinal fluid, isolation from the blood serology, enzyme-linked immunosorbent assay)
Age range	Age range of the participants in months
Number of cases confirmed	The number of pneumococcal meningitis cases confirmed within the study
Number of deaths confirmed	Number of deaths due to pneumococcal meningitis confirmed within the study
Population denominator	Total samples in the study; catchment population of the surveillance
Sequelae	The long-term consequences due to Spn[c] meningitis
Number of patients with sequelae	Number of patients that experienced specific long-term consequence due to Spn meningitis
Risk factors	
Risk group	Type of risk identified in the study (eg, age, sex, hospital-acquired, comorbidities)
Risk reference (comparator)	Variable that the risk is being compared to
Risk	Risk factors identified within the study
Measure of effect	Measure of effect for the risk factor (eg, odds ratio, relative risk)
Upper confidence interval	Maximum value of the confidence interval
Lower confidence interval	Minimum value of the confidence interval

[a]WHO: World Health Organization.

[b]PCV: pneumococcal conjugate vaccine.

[c]Spn: *Streptococcus pneumoniae.*

Outcomes and Prioritization

The primary outcome of this review will be the global and regional incidence and CFR of pneumococcal meningitis in children. Our secondary outcomes include exploring the different subgroups and their impact on the incidence and CFR. In addition, if sufficient data for risk factors are identified from the included studies (10 or more), our objective is to produce meaningful multivariable risk factors of Spn meningitis.

Risk of Bias

The quality of the included studies will be appraised by two independent reviewers (JJP and SN). Any disagreements regarding the quality of the study will be discussed among four

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reviewers (JJP, SN, JT, and MMA). If necessary, an opinion will be sought from a fifth reviewer (DA).

A consensus on a quality assessment tool for observational studies, and especially incidence/prevalence studies, is yet to be established [33,34]. Therefore, we have improved upon our own quality assessment criteria that have been adapted from the validated checklists/quality assessment tools from the Joanna Briggs Institute Critical Appraisal Tools; Checklist for Prevalence Studies; National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies; and GRADE (Grading of Recommendations Assessment, Development, and Evaluation). We will no longer be using a scoring system to assess the quality but rather a scale from "good" to "very low," according to the recommendations in the literature [24,34]. This scale has been adapted so the questions are specific to the studies of inclusion (see Multimedia Appendix 2).

Data Synthesis

The pooled incidence and CFR of Spn meningitis will be estimated by performing generalized linear mixed models meta-analysis in the case of determining mortality and the population denominator from all included studies. For our additional outcome, we will also construct a multivariable metaregression model to produce a pooled odds ratio for multivariable risk factors of Spn meningitis. Meta-analyses will be performed with the meta, metaphor, and dmetar packages of R statistical software (version 4.1.2).

Heterogeneity among studies will be assessed using I^2 statistics, and heterogeneity will be further explored by performing subgroup analysis on the following extracted items: WHO region, income level of the study site, study period, and vaccination period.

We will be performing the Egger regression test to assess for publication bias. A funnel plot of standard error by incidence will be produced and visually inspected for asymmetry. Sensitivity analysis will be performed to assess the impact of the study design, study setting, and quality of the studies on the incidence/CFR.

Ethical Considerations

Formal ethical approval will not be required as this study will not involve primary data collection or patients.

Results

The search from 4 databases resulted in 9295 articles, as shown in the PRISMA flowchart in Figure 1.

A total of 3213 articles were removed as duplicates and 326 studies were further removed due to the participants being adults or nonhuman or the articles being case reports. After the screening process, we included a total of 117 articles that met our eligibility criteria. We are currently undergoing the data extraction process, which will soon be followed by a meta-analysis. The expected completion date for extraction and analysis is January 2025 and the results are planned to be published by March 2025. The results of the completed study will be disseminated through international conferences and publication in a peer-reviewed journal.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart to demonstrate the screening process for studies included in this systematic review. CFR: case fatality ratio.

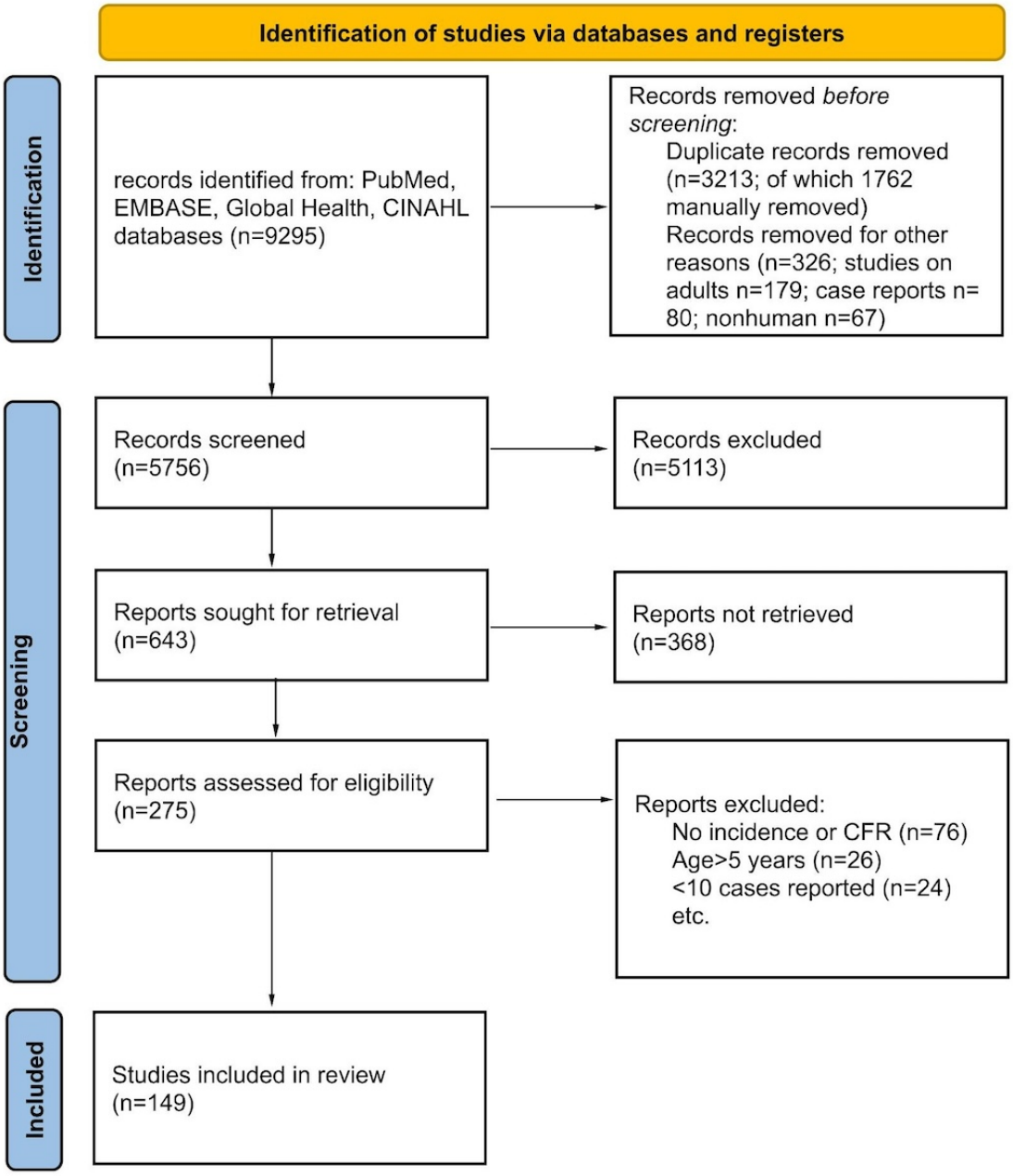

Discussion

This systematic review will identify the most recent global burden of Spn meningitis in children under 5 years of age, while providing important insights into factors that may contribute to a greater or lesser disease burden. Moreover, considering the frequency of sequelae following Spn meningitis, our study will comprehensively capture the types and incidence of the long-term clinical consequences associated with Spn meningitis in children [35].

Findings from our previous systematic review on *Haemophilus influenzae* type B (Hib) meningitis concurred with a long-standing challenge in the epidemiological literature [36,37], which is the scarcity of surveillance data in countries where such data are most needed. The least amount of data were acquired from the Southeast Asia Region and Eastern Mediterranean Region, which may have impacted the accuracy of our estimation. Therefore, this review will aim to assess and highlight the gaps in the evidence of Spn meningitis in children. For the same reason, we will include an assessment of outcomes and the body of evidence through the GRADE approach, using the GRADEpro Guideline Development Tool. Two independent reviewers (JJP and SN) will assess the quality of the outcomes. The third reviewer will adjudicate any disagreements that are unsettled between the two reviewers.

Although recent evidence indicates the decrease in language bias due to the trend of studies being published in English [37], our review on Hib meningitis had 6 studies that were published in a non-English language out of the 33 studies that were included. As a result, one of the major strengths of this review is including studies of all languages. We will be using Google Translate to acquire data from non-English studies and, similar

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to our previous review, we will seek advice from external individuals who speak the corresponding languages as necessary. This is to improve the accuracy of extracting data by understanding subtle nuances within the publication.

There are, however, some limitations to this review. We will not be including unpublished data from registers such as the WHO Invasive Bacterial Disease Surveillance Network, which may lead to an underestimation of the disease burden. In addition, we will focus on providing a crude estimate, which may be different from the adjusted values when factors such as HIV prevalence and vaccination have been considered. Nevertheless, this systematic review and meta-analysis will provide data that are comparable to the burden reported in the previous literature and will further expand our knowledge of the current global disease burden of Spn meningitis in children and the impact of universal vaccination programs.

With a specific focus on Spn meningitis in the pediatric population, this review is positioned to offer deeper insights into the disease burden and provide valuable guidance for managing Spn at a policy level for this vulnerable patient group.

Authors' Contributions

JJP, DA, and IR contributed to the conception of the study. JJP designed the study, wrote the study protocol, and is the protocol guarantor (in detail, JJP proposed the study to IR and DA; conducted the background scoping review; and determined the study inclusion criteria, study outcomes, search strategy, risk of bias assessment, and data extraction proforma). JJP and SN wrote the Introduction section. JJP wrote the Methods and Discussion sections. JJP and JT piloted the data extraction proforma. BMA, JJP, and DA determined the statistical methods. BMA developed the statistical model. IR, DA, and BMA are the study supervisors. All authors contributed to reviewing and approving the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms and strategy.
[PDF File (Adobe PDF File), 261 KB - resprot_v13i1e50678_app1.pdf]

Multimedia Appendix 2
Quality assessment criteria for assessing risk of bias.
[PDF File (Adobe PDF File), 349 KB - resprot_v13i1e50678_app2.pdf]

Multimedia Appendix 3
Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.
[PDF File (Adobe PDF File), 349 KB - resprot_v13i1e50678_app3.pdf]

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Abbreviations

CFR: case-fatality-ratio
CoCoPop: condition, context, and population
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
Hib: Haemophilus influenzae type B
PCV: pneumococcal conjugate vaccines
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: Prospective Register of Systematic Reviews
Spn: *Streptococcus pneumoniae*
WHO: World Health Organization

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Protocol

Effectiveness of Mobile App Interventions to Improve Periodontal Health: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Periodontal health plays a key role as a shared reference point for evaluating periodontal diseases and identifying significant treatment outcomes. Providing adequate instruction and enhancing the motivation of patients to maintain proper oral hygiene are crucial factors for successful periodontal treatment, with self-performed regular oral hygiene identified as a critical factor in improving the outcomes of treatment for periodontal diseases. Recently, mobile health (mHealth) solutions, especially mobile apps, have emerged as valuable tools for self-management in chronic diseases such as periodontal disease, providing essential health education and monitoring capabilities. However, the use of mHealth apps for periodontal health is complex owing to various interacting components such as patient behavior, socioeconomic status, and adherence to oral hygiene practices. Existing literature has indicated positive effects of mHealth on oral health behaviors, knowledge, attitude, practice, plaque index score, and gingivitis reduction. However, there has been no systematic review of mobile apps specifically targeting patients with periodontal disease. Understanding the design and impact of mHealth apps is crucial for creating high-quality apps.

Objective: The aim of this systematic review and meta-analysis is to evaluate the effectiveness of existing mobile apps in promoting periodontal health.

Methods: A comprehensive search strategy will be performed in multiple electronic databases (PubMed, EBSCOhost, CINAHL Plus, Dentistry & Oral Sciences, ScienceDirect, Scopus, and Cochrane Central Register of Controlled Trials) with the following keywords in the title/abstract: “mobile application,” “mobile health,” “mHealth,” “telemedicine,” “periodontal health,” “periodontitis,” and “text message.” Only randomized controlled trials will be included that assessed the following outcomes to measure periodontal health improvement: gingival index, bleeding index, periodontal pocket depth, and clinical attachment loss. Covidence will be used for data collection, and a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart will be used to describe the selection process of the included, identified, and excluded studies. The Confidence in Network Meta-Analysis approach will be used for meta-analysis of the extracted data from the included studies.

Results: This review will not require ethical approval since no primary data will be included. As of July 2024, a total of 83 articles retrieved from various databases have been imported to Covidence with 13 articles deemed eligible for inclusion in the review. The review is currently ongoing and is expected to be complete by the end of 2024 with the results published in early 2025.

Conclusions: This systematic review and meta-analysis will contribute to developing mobile apps with enhanced criteria to improve periodontal clinical outcomes. The review emphasizes the importance of mHealth and preventing periodontal disease, which can set the stage for informed global health care strategies.

Trial Registration: PROSPERO CRD42022340827; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=340827

International Registered Report Identifier (IRRID): DERR1-10.2196/50479

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KEYWORDS

mobile app; periodontal health; text messages; application; effectiveness; physical well-being; mental well-being; social well-being; oral hygiene; oral disease; disease prevention; periodontal; health education; systematic review

Introduction

Background

Periodontal health is essential to overall oral health and well-being [1]. Periodontal health is generally defined as the absence of inflammatory periodontal disease [2], encompassing the health of the surrounding support system for the tooth, which includes the gingiva, periodontal ligament, and alveolar bone [3]. A standard definition of periodontal health is crucial for identifying a reference point to determine and assess treatment outcomes [2]. Building upon this understanding, periodontal health is classified into the following 4 levels, as proposed by Lang and Bartold [2], based on various factors such as the condition of the periodontium, the ability to control modifying factors, predisposing factors, and treatment outcomes:

1. Pristine periodontal health, representing the absence of clinical inflammation, usually with no bleeding on probing, bone loss, or attachment loss involvement, making it difficult to measure clinically.
2. Clinical periodontal health (intact periodontium), referring to minimal or absent gingival inflammation, which is clinically detectable with bleeding on probing.
3. Periodontal disease with stability in the reduced periodontium, defined as major plaque-associated periodontal diseases such as periodontitis, with the condition being effectively treated and no apparent worsening of clinical signs despite a reduced periodontium.
4. Periodontal disease in remission or under control, characterized by a reduction in the severity of symptoms, although they may not be resolved entirely.

Furthermore, the two primary periodontal conditions, gingivitis and periodontitis, play significant roles in oral health. Gingivitis, the mildest form of periodontal disease, is characterized by localized, reversible inflammation of the gingiva caused by dental plaque [4], whereas periodontitis is a microbe-associated, host-mediated inflammatory condition leading to progressive attachment loss [5]. Chronic conditions such as periodontal disease and dental caries can cause severe pain in advanced stages and may result in challenges with speaking and eating [6]. Additionally, there is a strong association between oral diseases and noncommunicable conditions such as diabetes [7] and cardiovascular disease [8].

In response to the evolving understanding of periodontal diseases, a global workshop was convened in 2017 to develop a new classification system to simplify diagnosing and treating these diseases in general dental practice [9]. This updated classification system addresses the form, severity, and extent of periodontitis and formally incorporates recognized risk factors and their associations with systemic diseases. Critical components of this classification system include staging, which categorizes the severity and extent of the disease, and grading, which predicts future risks and potential health impacts. This classification system allows for precise and focused definitions of periodontal health and gingivitis as follows: (1) patients with an intact periodontium, (2) patients with a reduced periodontium due to causes other than periodontitis, and (3) patients with a reduced periodontium due to periodontitis [9].

The previous classification was formally introduced in 1999 [10]; the notable distinction between the two classifications was the use of the term “periodontitis” instead of “aggressive and chronic periodontitis” [9]. Furthermore, smoking and diabetes were identified as major potential risk factors that could influence the staging of periodontal disease in the new classification [9].

As part of an accurate diagnosis and appropriate treatment strategy, having clear and focused definitions in a classification system is fundamental in promoting periodontal health. This understanding is vital as neglecting periodontal health can lead to significant conditions such as periodontal disease, bone loss, and ultimately tooth loss [10]. A combination of effective oral hygiene practices, routine dental examinations, and a healthy lifestyle is essential to maintain optimal periodontal health. Daily brushing and flossing help eliminate plaque, while professional scaling can remove calculus buildup [1]. The importance of effective self-performed oral hygiene in preventing oral diseases is well-established [11], including the integration of mobile health (mHealth) interventions to promote the self-management of oral health [12].

Indeed, the combination of mHealth technology in periodontal care has significantly impacted the field, offering a promising avenue for promoting oral health awareness and empowering patients to take control of their periodontal health [13,14]. mHealth is a medical and public health practice supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices [15]. These mobile apps gather users’ health data, offer customized guidance, and facilitate remote patient data monitoring, thereby fostering collaborative relationships between dental professionals and individuals [16]. The increasing interest in chronic disease management has created opportunities to enhance self-management capabilities [17].

In light of these developments, Toniazzo et al [12] performed a systematic review to summarize the role of mHealth in improving oral health, with the measured outcomes being the plaque index and gingival index (GI). The review findings demonstrated a significant improvement in dental plaque and gingivitis resulting from the use of mobile apps, suggesting that these tools may enhance oral health behaviors. However, the lack of regulation during app development increases the risk of patients accessing inaccurate information [18]. Therefore, this review is designed as a preliminary step prior to the development of an mHealth-promotion app. To our knowledge, no other

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systematic review has been performed to specifically evaluate mobile apps targeting patients with periodontal disease.

Overall, integrating mHealth technology in periodontal care presents exciting opportunities for advancing oral health promotion and disease management. By embracing these innovations, dental professionals can enhance patient care and improve oral health outcomes while maintaining a comprehensive understanding of periodontal diseases.

Review Objective

The aim of this systematic review and meta-analysis is to evaluate the effectiveness of existing mobile apps or text messages designed to enhance periodontal health among patients compared to the outcomes of patients without any mobile app or digital intervention to support their treatment.

Methods

Study Registration and Framework

This systematic review has been registered in PROSPERO under registration number CRD42022340827.

The Participants, Interventions, Comparators, Outcomes, and Study design (PICOS) framework is used to guide the eligibility criteria [19,20]. *Participants* include all patients, regardless of age or sex, with or without periodontal disease, except those who cannot participate independently. The *intervention* of interest is the use of mobile apps available on Android or iOS devices and mobile phones for sending SMS text messages or web-based interventions. As *comparators*, this review considers studies that compare the intervention to standard or usual care such as a placebo or control group without using mobile technology. The main *outcome* is improvement in the periodontal health of participants based on signs of progress in the following indicators: GI, bleeding index (BI), clinical attachment loss (CAL), and periodontal probing depth (PPD). All of these periodontal clinical parameters (described in further detail below) are considered crucial for assessing periodontal health because they provide valuable information about the condition of the gingiva and surrounding tissues [2].

Outcome Measures

Gingival Index

The GI is a clinical examination tool used to assess the condition of the gingival tissue and differentiate the lesion severity. To perform the examination, the alterations in 4 areas around the tooth are located. Each area (mesial, distal, buccal, palatine, or lingual) is assigned a score ranging from 0 to 3. The overall score is calculated by summing the scores from the 4 areas and dividing the total by 4. [21]: a total score of 0 indicates a normal gingiva; a score of 1 represents mild inflammation, characterized by a slight color change and edema with no bleeding on probing; a score of 2 signifies moderate inflammation, characterized by redness and edema; and a score of 3 indicates severe inflammation marked by pronounced redness, edema, ulceration, and a tendency toward spontaneous bleeding [21,22].

Bleeding Index

The BI is a tool to assess and reflect the histological and bacterial factors associated with the severity of periodontal diseases [23]. The BI is typically determined using a Williams periodontal probe inserted into the gingival crevice to a depth of approximately 2 millimeters. The probe is angled at approximately 60° to the tooth's longitudinal axis. The presence or absence of bleeding is then assessed within 30 seconds after probing [24].

Clinical Attachment Loss

CAL is one of the most important tools to measure periodontitis, which is crucial in diagnosing and managing periodontal diseases. CAL is calculated as the distance from the cementoenamel junction or the border of restoration to the bottom of the periodontal pocket [25].

Periodontal Probing Depth

PPD represents a deepened gingival sulcus around a tooth at the gingival margin due to pathological causes. The PPD is an important marker to indicate the presence of inflammation or infection and to monitor the progress of periodontal treatment [26]. The values are recorded in millimeters at 6 sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual) to measure the distance between the base of the pocket and the gingival margin [25].

Inclusion and Exclusion Criteria

All published randomized controlled trials (RCTs) published in English will be included in the review. Studies aimed at improving tooth mobility and the grey literature will be excluded from this review. There will be no limitations on the time frame for measuring the outcome of the intervention.

Search Strategy for Identification of Potential Studies

The search strategy for identifying potential studies will be designed by 3 team members (RM, DE, and FKD) to ensure a comprehensive exploration of eligible studies. This will involve performing a thorough search across various electronic databases, including PubMed, EBSCOhost, Dentistry & Oral Sciences, ScienceDirect, CINAHL Plus, and Scopus. The search will use combinations of Medical Subject Headings (MeSH) key terms in the title or abstract, including "mobile applications," "periodontal health," "periodontitis," "mHealth," "smartphone application," and "app-based intervention." These terms will be combined using Boolean operators such as "AND" and "OR" to capture relevant studies. Additionally, databases such as the Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform [27], and ClinicalTrials.gov [28] will be searched. A final rerun of the search will be performed before the final meta-analysis to include any additional studies. An example of the search strategy for PubMed is provided in Multimedia Appendix 1.

Study Selection Process

Two independent reviewers (RM and DE) will review all included articles. The selection will be based on the eligibility criteria and discrepancies will be resolved through consultation with a third reviewer (FKD). The identified articles will be

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imported to Covidence software [29], which is a web software system that assesses the data management process by reviewers during the systematic review process. The screening process will be performed independently by the two reviewers in 2 stages: (1) screening the abstract and (2) screening the full texts. Duplicate records will be removed automatically by Covidence.

Ongoing trials with no results will be flagged and recorded in an "Ongoing studies" table. Articles not meeting the eligibility criteria will be excluded and listed in a "Characteristics of excluded studies" table along with the reasons for exclusion. The study selection process will be described in a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart [30]. This protocol adheres to the PRISMA Protocols checklist (see Multimedia Appendix 2).

Data Extraction and Management

Two independent reviewers (RM and DE) will extract data into Covidence using a specific form designed for this purpose. Data categories to be extracted include the field of research, sample size, setting, authors, publication year, countries, number of participants, app name and platform, app purpose, intervention period, and outcomes. Any disagreements will be resolved through discussion between the two reviewers. In cases where disagreements are unresolved, the third reviewer (FKD) will be consulted to reach a consensus through discussion.

Assessment of Risk of Bias of Included Studies

Two independent reviewers (RM and DE) will assess the methodological quality of the included RCTs using the Cochrane Risk of Bias tool [31]. Any disagreements with quality ratings will be settled by consensus-based discussion.

The following domains for the risk of bias will be assessed for *all* included studies: random sequence generation (selection bias); allocation concealment (selection bias); blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment; incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias [31].

The risk of bias for each domain will be categorized as high, low, or unclear. The risk of bias assessment outcomes will be documented in a table with a justification of the decision. A description of the criteria for a decision of "low risk," "high risk," or "unclear risk" will be documented [31].

Meta-Analysis

Measures of Treatment Effect

If there is a probability that data are skewed with a fixed upper and lower limit, a "rule of thumb" calculation will be used to detect the distribution of the data. This calculation will follow the method proposed by Higgins et al [31], who suggested that if the SD doubled is greater than the mean, the assumption that the data are normally distributed cannot be made (ie, that the mean is at the center of the distribution). If the outcomes are dichotomous data, the data will be presented as risk ratios, odds ratios, or risk difference values. Data that include continuous outcomes will be presented as means or standardized mean differences. All significance tests will be judged at the 5% α level with 95% CIs. Time-to-event outcomes will be reported as hazard ratios and 95% CIs [31].

Assessment of Heterogeneity

The heterogeneity of results among studies will be interpreted by considering the variation of participant characteristics (eg, age) and trial characteristics such as randomization and allocation concealment in the different studies. Heterogeneity will be generally assessed by visually inspecting the forest plots to detect the proximity of the point estimates and the overlapping of CIs. Specifically, heterogeneity will be examined using the I^2 statistic with a P value threshold of <.10, which quantifies inconsistency across studies to assess its impact on the meta-analysis. The I^2 statistic will be classified as follows: 0%-40%, negligible to minor heterogeneity; 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity.

Heterogeneity will further be investigated using sensitivity analysis. This involves assessing the robustness of the findings to different decisions or ranges of values made during the study. This process helps ascertain whether the findings are dependent on specific decisions or if they are robust and reliable [32,33]. If heterogeneity is found to be significant, the Mantel-Haenszel method will be used for the fixed-effects model. The random-effects model will be selected if $I^2 \geq 50\%$ or $P<.10$.

Assessment of Reporting Biases

When the outcomes are reported in 10 or more studies, a funnel plot will be constructed to investigate the possibility of reporting bias according to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions [31].

Confidence of Study Findings

The results of the meta-analysis will be analyzed using the Confidence In Network Meta-Analysis (CINeMA) tool if there are more than 2 interventions included in the analysis; CINeMA is a software based on the framework developed by Salanti [34] and refined by Nikolakopoulou [35-37]. This framework's efficiency lies in combining direct and indirect evidence from included studies in a meta-analysis when comparing more than one intervention.

Specifically, the CINeMA framework evaluates network meta-analysis through the following 6 domains: (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity, and (6) incoherence. The evaluation of each domain determines the level of concern, categorized as having no, some, or major concerns. These judgments across the domains are combined into a single confidence rating of "high," "moderate," "low," or "very low."

CINeMA serves as an alternative to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, which has traditionally been used to assess confidence in the outcomes of systematic reviews and meta-analyses [33].

Data will be narratively synthesized when a meta-analysis is unsuitable according to the nature of included studies.

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Sensitivity Analysis

A sensitivity analysis will be performed to determine the possible effect of loss to follow-up on the effect estimates for the primary outcomes. The results of the sensitivity analysis will be matched to the overall findings. However, for continuous data, the sensitivity analysis will be aligned with the methods described by Ebrahim et al [38,39]. These methods involve 5 sources of data for imputing means for participants with missing data: (1) best mean score among intervention arms, (2) best mean score among control arms, (3) mean score of the same trial among the control arms, (4) worst mean score among intervention arms, and (5) worst mean score among control arms [38].

Dissemination of Findings and Data Sharing

All data, regardless of publication quality, will be included in the review. If study details cannot be obtained, the librarian will be consulted. If the study remains unobtainable, it will not be included in the meta-analysis.

Results

Of the 159,214 publications identified, 83 were imported into Covidence to remove duplicates and perform the screening. This was followed by full-text reviewing and data extraction, resulting in 13 included articles. CINeMA analysis of the data is underway. This review is expected to be completed by the end of 2024, and we plan to publish the results in a peer-reviewed journal.

Discussion

The significance of this systematic review and meta-analysis lies in its contribution to the development of mobile apps with enhanced criteria specifically aimed at improving periodontal clinical outcomes. To enhance the quality of new apps, a comprehensive understanding of the design and impact of mHealth apps is essential in improving treatment outcomes.

Using mHealth apps to improve periodontal health represents a complex intervention due to the numerous interacting components involved (eg, patient behaviors, socioeconomic status, and adherence to oral hygiene practices). The existing literature in this field has mainly focused on promoting oral health, hygiene, practices, and adherence to orthodontic treatment.

In a previous systematic review, Toniazzo et al [12] evaluated the effects of mobile apps on oral hygiene, revealing significant improvements in reducing dental plaque and gingivitis and in promoting better oral health behaviors. Another systematic review on the impact of digital media for promoting oral health showed improved knowledge, attitude, practice, and plaque index scores, along with overall gingivitis reduction [40].

Chen et al [41] performed a systematic review with a thematic focus on the prevention of dental caries through mobile apps aiming to improve oral hygiene, encourage adequate fluoride usage, and regulate dietary intake, while addressing adherence to orthodontic treatment. However, the authors concluded that dental caries outcomes management could have been more precise. In another systematic review and meta-analysis, Al-Moghrabi et al [42] assessed behavioral changes in orthodontic patients, covering aspects such as adherence to appliance use, oral health–related behaviors, hygiene levels, periodontal outcomes, appointment attendance, and knowledge, finding very low to moderate evidence supporting the effect of digital health; the authors thus recommended designing a well-constructed mobile app to enhance orthodontic outcomes.

Limiting our review to studies published in the English language may introduce bias. Nevertheless, we acknowledge that studies with significant findings are often published in English to enhance their visibility and citation potential. Furthermore, this review exclusively includes RCTs and we are excluding the grey literature. An important recommendation for future systematic reviews will be to assess the applicability and feasibility of the mHealth apps.

Finally, the broader implication of this systematic review and meta-analysis is its pivotal contribution to advancing the global integration of mobile apps for oral health by highlighting the positive impact of these tools on periodontal outcomes and emphasizing the importance of periodontal health management. These findings can help to enhance our understanding of mHealth interventions, elevate the quality of life among the target population, and set the stage for informed health care strategies in periodontal care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy sample from PubMed.
[DOCX File , 17 KB - resprot_v13i1e50479_app1.docx]

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Multimedia Appendix 2
PRIMSA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 20 KB - resprot_v13i1e50479_app2.docx]

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Abbreviations

BI: bleeding index
CAL: clinical attachment loss
CINeMA: Confidence In Network Meta-Analysis
GI: gingival index
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
MeSH: Medical Subject Heading

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mHealth: mobile health
PICOS: Participants, Interventions, Comparators, Outcomes, and Study design
PPD: periodontal pocket depth
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT: randomized controlled trial

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Protocol

The Effectiveness of Medical Adherence Mobile Health Solutions for Individuals With Epilepsy: Protocol for a Systematic Review

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Abstract

Background: Epilepsy requires continuous management and treatment to optimize patient outcomes. The advancement of digital health has led to the development of various mobile health (mHealth) tools designed to enhance treatment adherence among individuals with epilepsy. These solutions offer crucial support through features such as reminders, educational resources, personalized feedback, assistance with managing costs, shared decision-making, and access to supportive communities. To design effective medication adherence mHealth solutions, it is essential to evaluate the effectiveness of existing mHealth tools, understand the unique circumstances of different patients, and identify the roles of health care professionals within the digital care pathway. Existing studies on epilepsy primarily focus on self-management, whereas the effectiveness and usability of medical adherence mHealth solutions often remain overlooked. Furthermore, the involvement of health care professionals in digital care pathways for epilepsy as well as the impact of adherence mHealth solutions on the patient experience have not been adequately explored.

Objective: This study aims to assess the effectiveness of current mHealth solutions designed to improve medical adherence among patients with epilepsy. Furthermore, the study will examine the experiences of patients using mHealth solutions for maintaining medical adherence in epilepsy care. Finally, this review intends to determine the roles of health care professionals within mHealth systems aimed at supporting adherence to medication among patients with epilepsy.

Methods: A systematic literature review has been selected as the appropriate method to address the research questions, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The inclusion and exclusion criteria have been carefully selected, and both qualitative and quantitative analyses will be used to analyze the results. The expected results will mainly focus on the comparison, classification, and analysis of the effectiveness of current medical adherence mHealth tools. Moreover, the patient experiences using available medical adherence mHealth tools for epilepsy will be assessed. Finally, the role of health care professionals in the epilepsy digital care pathway will be explored, with emphasis on medical adherence.

Results: The initial search, full-text screening, and data extraction have been carried out. Thirty-three papers were included in the final stage of the review. The study is expected to be completed by October 2024.

Conclusions: To enhance the digital care pathway for epilepsy, a medical adherence mHealth solution should be personalized, manage medications, include an alarm system, track seizures, support consultations, and offer updated treatment plans. This study aims to understand how findings from the research questions can improve mHealth solutions for individuals with epilepsy. Insights from this research on the effectiveness of current mHealth adherence solutions will provide guidance for developing future mHealth systems, making them more efficient and effective in managing epilepsy.

Trial Registration: PROSPERO CRD4202347400; https://tinyurl.com/48mfx22e

International Registered Report Identifier (IRRID): DERR1-10.2196/55123

(JMIR Res Protoc 2024;13:e55123) doi:10.2196/55123

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KEYWORDS

digital care pathway; epilepsy; mHealth; mobile health; effectiveness; systematic review; management; medical adherence; patient outcomes; digital health; design; eHealth solutions; health care professionals

Introduction

Epilepsy is considered a chronic neurological condition that has to be consistently managed and treated to optimize patient outcomes [1]. With the advancement of digital health technologies, various mobile health (mHealth) solutions have been developed to improve the adherence of patients with epilepsy to treatment [2]. Medication adherence mHealth solutions can offer significant assistance to individuals with epilepsy, including reminders and alerts, education, personalized feedback, cost management, support, and community engagement [3-6].

When designing medication adherence mHealth solutions, it is crucial to understand the unique circumstances of different patients. Patients can have many potential reasons for nonadherence. Previous research identified common barriers for medication adherence for children with epilepsy, including disliking the taste of the medication, difficulty remembering to give epilepsy medications up to 4 times per day, lower family support, and lower family socioeconomic status [1,2]. For adults, common reasons for nonadherence include the beliefs about medications, being depressed or anxious, poor self-management, uncontrolled seizures, demanding medication routine, poor relationship with physician, and perceived social support [2,4,6]. Some patients may also find digital systems inaccessible or difficult to use [5]. Understanding the diverse needs, preferences, and barriers of patients is crucial, as these factors can impact the effectiveness of mHealth interventions. Similarly, previous studies have identified that patients frequently report a perceived lack of communication with their health care professionals as a barrier to understanding their health conditions and using available tools for epilepsy self-management [7].

Reviewing studies related to digital health solutions for epilepsy is essential for the determination of effective interventions and how they could be leveraged beyond individual use in the health care context. Existing reviews on this topic [7-10] have mainly focused on overviewing the digital tools for epilepsy and self-management; however, mHealth solutions specifically designed for medical adherence were neglected. Accordingly, data on the usability, acceptance, and effectiveness of these mHealth solutions remain scattered across individual studies.

Previous studies have shown that health care professionals in epilepsy care are using smartphone apps with their patients, and they largely perceive that data from wearables might be useful to enrich their understanding of a patient's health state in between consultations and for improving adherence to medications; however, further analysis showed that the data generated by these solutions were rarely or never used or discussed in the clinic during consultations [11]. This suggests that the role of health care professionals in mHealth interventions for epileptic care has not been properly addressed. The active participation of health care professionals is required for a digital care pathway to optimize the medical adherence of patients to mHealth solutions. Furthermore, the existing reviews [6,12] have not thoroughly assessed the patient's experience of using digital solutions for medical adherence in epilepsy. Therefore, a thorough synthesis of the body of research assessing the benefits and drawbacks of mHealth adherence solutions for individuals with epilepsy is required.

In this regard, this systematic review aims to collate, synthesize, and summarize the existing studies to provide a clear understanding of the current state of mHealth solutions for treatment adherence in epilepsy and to identify areas for future research. Based on the limitations and shortcomings of existing studies on the topic, the following 3 research questions were formulated to be answered in this systematic review:

1. What are the effects of medical adherence mHealth solutions on individuals with epilepsy in managing their condition?
2. What are the effects of medical adherence mHealth solutions on the patient's experience?
3. What are the effects of health care professionals on the medical adherence of individuals with epilepsy using mHealth solutions?

The overall goal of this study is to systematically review the existing research related to mHealth solutions for medical adherence among individuals with epilepsy. To address the research questions, this systematic review aims to address 3 main objectives. First, it explores the effectiveness of various medical adherence mHealth solutions for individuals with epilepsy, assessing how these technologies assist in managing their condition. Second, the review investigates the experiences of patients using these mHealth solutions, focusing on how the technology impacts their adherence behaviors and overall treatment engagement. Lastly, the study aims to identify the roles and responsibilities that health care professionals are expected to assume within the context of mHealth solutions designed to improve medical adherence for epilepsy. This comprehensive approach can help to illuminate the multifaceted impacts of mHealth technologies in the management of epilepsy. This review can consequently provide insights for improving the quality of medical adherence mHealth solutions for individuals with epilepsy. Therefore, this study represents a critical stepping stone for future research on mHealth solutions for individuals with epilepsy.

Methods

Study Objectives and Design

This study aims to provide a comprehensive overview of the available evidence and prior research on medical adherence mHealth solutions for individuals with epilepsy. For this reason, a systematic literature review (SLR) was selected to answer the research questions. The SLR will be carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, which provides a reliable

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methodology to perform SLRs in the fields of medicine. The process flow of the protocol is illustrated in Figure 1.

The first step involves the formulation of the 3 research questions based on the shortcomings of existing studies. The review is then planned to be carried out using Covidence according to the Joanna Briggs Institute (JBI) guideline for a systematic review of effectiveness evidence [13]. In the next step, the search string along with inclusion and exclusion criteria are defined. Subsequently, the full-text screening step is performed for the included papers. Each paper will be reviewed by at least 2 reviewers and conflicts will be resolved through discussion and using Covidence. After finalizing the included full papers, the analysis and synthesis are carried out along with interpretation of the results.

Figure 1. The protocol process flow. ACM: Association for Computing Machinery; IEEE: Institute of Electrical and Electronics Engineers; JBI: Joanna Briggs Institute; mHealth: mobile health; SLR: systematic literature review.

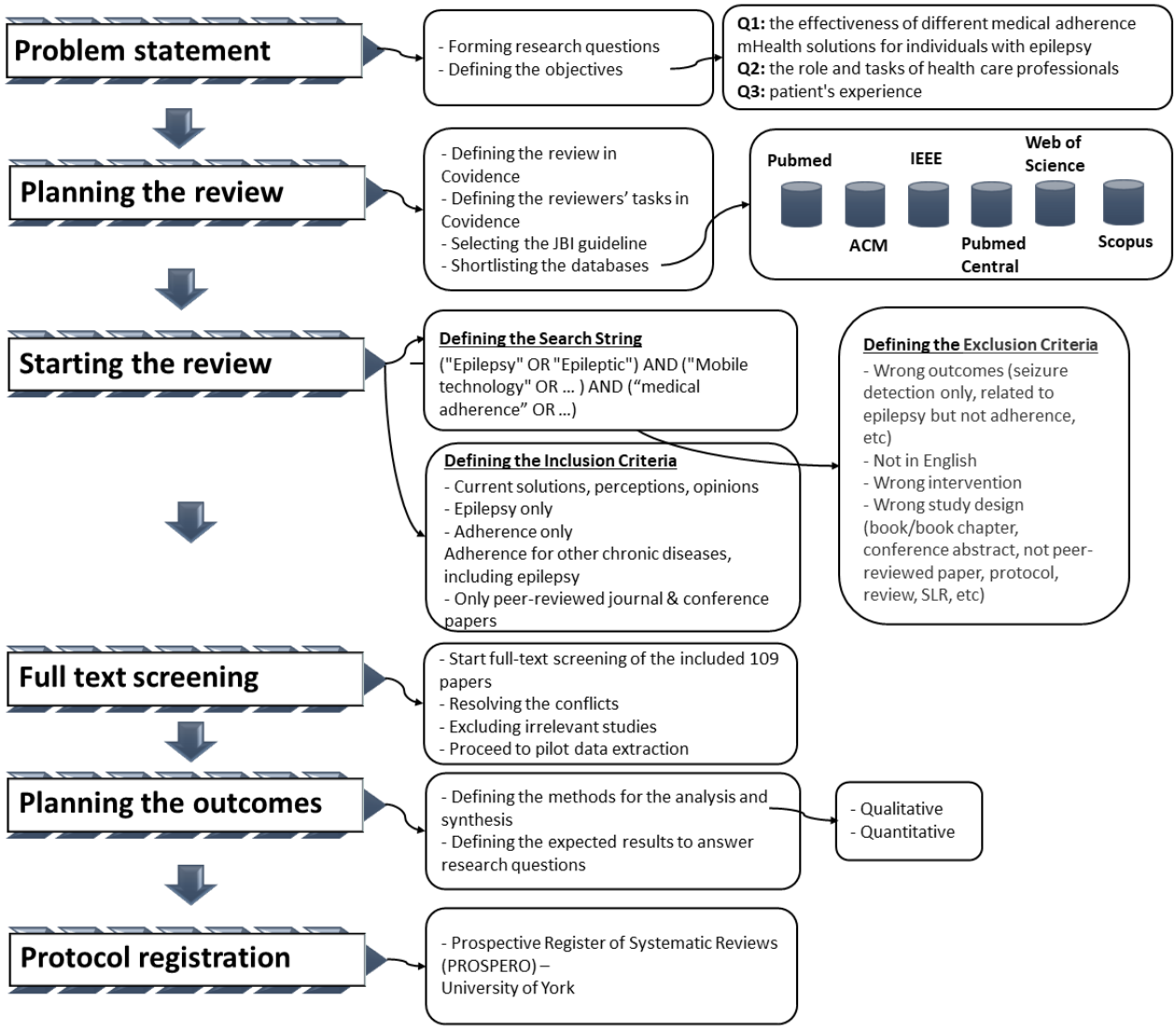

Information Sources and Search Strategy

Extensive searches were carried out for relevant literature in digital databases specializing in the fields of information technology, biomedical engineering, and health to find the eligible studies, including PubMed, ACM Digital Library, IEEE Xplore, PubMed Central, Web of Science, and Scopus. The main search string used for searching in the digital databases includes terms related to epilepsy, digital interventions, and medical adherence, including the Boolean operators "AND" and "OR," as follows: ("Epilepsy" OR "Epileptic") AND ("Mobile technology" OR "Mobile technologies" OR "mobile phone" OR "mobile device" OR "mobile phones" OR "mobile devices" OR "smart device" OR "smartphone" OR "smartwatch" OR "smart ring" OR "smart device" OR "smart devices" OR "mobile app" OR "health app" OR "mobile health intervention" OR "mobile health solution" OR "mHealth" OR "mHealth" OR "mobile health tool") AND ("medical adherence" OR "adherence" OR "medication" OR "adherence to medicines" OR "medicine adherence" OR "medicine compliance" OR "medical advice" OR "adhering to medical advice" OR "adherence to medical advice" OR "treatment"). The corresponding Medical Subject Headings (MeSH) terms and keywords were combined for the search strategy, especially in PubMed.

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Selection of Studies and Eligibility Criteria

This systematic review will include original research articles focused on current medical adherence mHealth solutions for individuals with epilepsy. The eligible publications for this review are restricted to those published in peer-reviewed journals and conference proceedings written in English. The publication period of the included studies was restricted from 2013 to 2023. Although mHealth technologies started to become more accessible in the first half of the 2010s, their impact on the health care scene started to become evident only several years later. In 2013, it was acknowledged that only a few studies had assessed the impact of mobile apps in the health context, and all of those studies referred to apps that had been created only for research purposes and were not available to the public at that time [14]. Therefore, we limited our search to articles with publication dates starting only after 2013. Furthermore, articles based on perceptions, opinions, and futuristic solutions, especially those focusing on medical adherence for epilepsy, will be reviewed for this study. The methods used for data collection are varied, including qualitative, quantitative, and mixed methods approaches. Review papers, SLRs, and abstracts are excluded from study selection. Moreover, articles that are focused on a technical approach of epileptic seizure detection rather than on mHealth solutions as an intervention for epilepsy management are excluded from the review.

The included articles will be imported into Covidence (Veritas Health Innovation). The screening process is divided into two stages, which are carried out independently by at least 2 researchers with computer science and health psychology backgrounds along with previous research experience in the field. At the initial stage, the screening is limited to titles and abstracts. Before starting this stage, the reviewers complete a joint exercise to validate the methodology and ensure the inclusion and exclusion criteria were correctly understood. Any disagreements that arise during the initial screening stage are discussed and resolved between the 2 reviewers before starting the second stage. The second screening stage includes the review of the full text of the articles that are preliminarily included from the initial stage.

Risk of Bias and Quality Assessment

Assessing the quality of reviewed literature and the risk of bias is necessary to ensure the reliability of any conclusions made for an SLR [1]. This study will follow the quality assessment guideline provided by Yang et al [1]. In addition, the quality assessment checklist designed by Dybå and Dingsøyr [15] will be used to evaluate the risk of bias and the quality of the studies included in the data extraction process.

Data Extraction and Analysis

A data extraction form created in Covidence will be used to gather and extract the relevant information from the included articles. The study design will be classified based on the tool from Grimes and Shulz [16]. Three reviewers will work on the data extraction task.

A mixed methods approach will be used to analyze the included studies to determine the overall evidence of the effectiveness of mHealth interventions for individuals with epilepsy. To answer the first research question, the effectiveness of mHealth interventions will be assessed using the guideline provided by the JBI [13] based on both qualitative and quantitative analyses. Furthermore, using quantitative analysis, the efficacy of the mHealth solutions will be evaluated and classified according to various features and phases.

The second research question will be addressed through qualitative studies regarding the experiences of patients and their caregivers with using mHealth interventions for medical adherence. The qualitative data will provide insights on patients' needs, preferences, challenges, and barriers of using mHealth interventions. The information about patients' experiences will complement the quantitative results and help us to better understand the results regarding the effectiveness of the mHealth interventions.

To maximize the benefits of mHealth solutions for medical adherence, health care providers must actively participate in the digital care pathway. Hence, the last research question will be addressed through qualitative analysis to explore the effectiveness, role, and responsibilities of health care professionals on medical adherence mHealth solutions for individuals with epilepsy.

Specifically, quantitative data such as year of publication and number of adherence criteria will be analyzed. Descriptive analysis and thematic synthesis will also be used to describe the effectiveness of the mHealth solutions. A coding strategy will be applied using NVivo software to simplify the synthesis of qualitative data. Furthermore, textual analytics will be used for clustering purposes. The effectiveness of the mHealth solutions will be categorized and grouped based on different characteristics and stages using quantitative analysis, while different categories will be labeled and classified quantitatively.

Results

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; University of York) under registration number CRD42023474008. As of July 2024, the initial searches have been carried out, the manuscripts have been imported into Covidence, and the full-text screening process has begun. Based on the initial search in the electronic databases, 4873 relevant articles published from 2013 to 2023 were identified. After applying the exclusion criteria; filtering; and removing review papers, SLRs, abstracts, and technical papers related to seizure detection, 477 papers were imported into Covidence. A total of 120 duplicates were removed from Covidence. In the first screening stage, the titles and abstracts of 357 articles were screened. From the initial screening, 109 papers were selected for full-text screening as they fulfilled the inclusion criteria. After full-text screening, a total of 33 papers were included in this review. This systematic review is anticipated to be completed by the end of 2024.

Discussion

To enhance the current epilepsy digital care pathway, a medical adherence mHealth solution is needed that personalizes the care plan, manages medication, sets an alarm system, monitors and

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tracks seizures, facilitates consultations, and provides updated treatment plans. Therefore, this study aims to determine the effectiveness of various medical adherence mHealth solutions for individuals with epilepsy. By addressing this aspect, effective mHealth solutions can improve the quality of care, enhance treatment adherence, and consequently yield better health outcomes. Patient experience plays a crucial role in determining effective medical adherence through mHealth solutions for individuals with epilepsy, as it leads to treatment plans and the overall management of the digital care pathway. Furthermore, clearly defining the role and effect of health care professionals is crucial in enhancing medical adherence to mHealth solutions for epilepsy. Health care professionals can significantly affect patient engagement, trust, and adherence to the treatment plan.

Several key points can be addressed by this study to elaborate on the findings, integrate them with existing knowledge, and outline future research directions. First, the results of this systematic review will confirm, extend, or challenge existing knowledge about mHealth solutions for epilepsy. The effectiveness of various mHealth solutions in enhancing medical adherence among patients with epilepsy will be interpreted, highlighting any significant trends or unexpected outcomes observed in the literature. Furthermore, the results will provide a detailed analysis of patient experiences with mHealth technologies and discuss factors that influence patient engagement and adherence to treatment, such as usability, accessibility, and personalized features of mHealth solutions. Finally, the findings of this study can provide new insight into the evolving roles and responsibilities of health care professionals in deploying and managing mHealth solutions, while highlighting the training needs, challenges, and opportunities for health care providers to effectively integrate mHealth into a digital care pathway for epilepsy.

After addressing the research questions, this study will explore how insights derived from the research findings can inform improvements in the design of medical adherence mHealth solutions for individuals with epilepsy. Drawing from the critical insights obtained regarding the effectiveness of existing solutions, future mHealth systems can be refined to provide a more efficient and sustainable digital care pathway for individuals with epilepsy [17,18]. Finally, the outcomes of this study are expected to encourage collaborative, patient-centered care that may improve adherence to the same degree as other digital tools. However, accurate measurement of medical adherence and the effectiveness classification might be challenging, which are identified as the main limitations of this study.

Acknowledgments

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Authors' Contributions

PK formulated the initial research questions; developed the design, search, and selection methodologies of the review; and drafted the manuscript. MP and SGM enhanced the research questions; contributed to the review's design, search, and selection methodologies; and participated in the writing and editing of the manuscript. MI was involved in reviewing and editing the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
SLR: systematic literature review

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Protocol

Engagement With Conversational Agent–Enabled Interventions in Cardiometabolic Disease Management: Protocol for a Systematic Review

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Abstract

Background: Cardiometabolic diseases (CMDs) are a group of interrelated conditions, including heart failure and diabetes, that increase the risk of cardiovascular and metabolic complications. The rising number of Australians with CMDs has necessitated new strategies for those managing these conditions, such as digital health interventions. The effectiveness of digital health interventions in supporting people with CMDs is dependent on the extent to which users engage with the tools. Augmenting digital health interventions with conversational agents, technologies that interact with people using natural language, may enhance engagement because of their human-like attributes. To date, no systematic review has compiled evidence on how design features influence the engagement of conversational agent–enabled interventions supporting people with CMDs. This review seeks to address this gap, thereby guiding developers in creating more engaging and effective tools for CMD management.

Objective: The aim of this systematic review is to synthesize evidence pertaining to conversational agent–enabled intervention design features and their impacts on the engagement of people managing CMD.

Methods: The review is conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Searches will be conducted in the Ovid (Medline), Web of Science, and Scopus databases, which will be run again prior to manuscript submission. Inclusion criteria will consist of primary research studies reporting on conversational agent–enabled interventions, including measures of engagement, in adults with CMD. Data extraction will seek to capture the perspectives of people with CMD on the use of conversational agent–enabled interventions. Joanna Briggs Institute critical appraisal tools will be used to evaluate the overall quality of evidence collected.

Results: This review was initiated in May 2023 and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in June 2023, prior to title and abstract screening. Full-text screening of articles was completed in July 2023 and data extraction began August 2023. Final searches were conducted in April 2024 prior to finalizing the review and the manuscript was submitted for peer review in July 2024.

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Conclusions: This review will synthesize diverse observations pertaining to conversational agent–enabled intervention design features and their impacts on engagement among people with CMDs. These observations can be used to guide the development of more engaging conversational agent–enabled interventions, thereby increasing the likelihood of regular intervention use and improved CMD health outcomes. Additionally, this review will identify gaps in the literature in terms of how engagement is reported, thereby highlighting areas for future exploration and supporting researchers in advancing the understanding of conversational agent–enabled interventions.

Trial Registration: PROSPERO CRD42023431579; https://tinyurl.com/55cxkm26

International Registered Report Identifier (IRRID): DERR1-10.2196/52973

(JMIR Res Protoc 2024;13:e52973) doi:10.2196/52973

KEYWORDS

cardiometabolic disease; cardiovascular disease; diabetes; chronic disease; chatbot; acceptability; technology acceptance model; design; natural language processing; adult; heart failure; digital health intervention; Australia; systematic review; meta-analysis; digital health; conversational agent–enabled; health informatics; management

Introduction

Cardiometabolic diseases (CMDs) are a group of interrelated conditions, including heart failure and diabetes, that increase the risk of cardiovascular and metabolic complications [1]. The number of Australians managing CMDs is increasing, necessitating new approaches to better manage these conditions [2,3]. Approximately one-quarter of people globally are estimated to be living with metabolic syndrome and approximately 1 in 13 are living with cardiovascular disease [4,5]. The self-management of CMDs requires individuals to adhere to treatment regimens such as taking prescribed medications, maintaining a healthy diet, and performing regular physical activity to effectively manage their condition [6]. As these lifestyle modifications can be complex and ongoing, digital health interventions have emerged as an integral part of a scalable and accessible strategy to support individuals self-managing CMD [7,8].

In CMD contexts, the prolonged course of illness, often spanning decades, increases the difficulty of sustained engagement with self-management, where the risk of relapse remains a significant concern over time [9,10]. Therefore, it is essential that interventions aiming to improve self-management must be able to sustain user engagement over long time periods [10]. Indeed, low engagement rates undermine the effectiveness of digital health interventions; a recent review found an average participant dropout rate of 43% in studies assessing digital health interventions applied to the self-management of chronic diseases [11].

A recent systematic review identified improving personalization and interactivity as effective approaches to improving long-term engagement rates of digital health interventions [12,13]. This is particularly crucial in managing CMDs, where ongoing engagement and sustained behavior change are necessary for the effective attenuation of CMD complications [10]. As components within digital health interventions, conversational agents could greatly enhance the effectiveness of these self-management interventions by contextualizing information, offering constructive feedback, and fostering critical reflection [14-18]. A conversational agent is a technology that interacts with people using natural language, whether text-based or spoken, enabling accessibility to broader populations, including people with motor or cognitive disabilities [19]. Use of conversational agents could also reveal a linguistic dimension to a person's health status, which could improve the personalization and effectiveness of digital health interventions [16,20].

Within the emerging research field of conversational agent–enabled interventions, the majority of existing tools are text-based, driven by machine learning algorithms, and delivered through mobile apps [21]. The literature on conversational agent–enabled interventions that support individuals with chronic diseases, including CMDs, to manage their condition is mainly composed of qualitative studies, quasiexperimental studies, pilot tests, and a limited number of randomized controlled trials, which all primarily examine prototypes of these interventions [22-25]. In clinical contexts, mental and physical wellness are the primary domains for the application of conversational agents, where they often provide emotional support [26,27]. In contrast, conversational agents applied to CMD self-management tend to provide a modality for monitoring symptoms and to deliver patient education [26]. However, recent trends indicate a shift from these basic functions to more complex and long-term end points in future applications, such as motivating behavior change [21]. This shift has occurred in parallel with technological advancements in cloud computing and transformer models, which have enabled a new generation of conversational agents termed large language models.

Large language models use deep neural networks to handle complex language tasks such as summarizing, generating, and translating natural language [28]. These tasks are achieved not by large language models understanding the prompts but rather by repeatedly predicting the word that is statistically the most likely to follow a sequence of words given as a prompt until a full response is offered [29,30]. However, this predictive approach means that large language models are potentially unsafe in clinical contexts, as they are liable to misinterpret prompts or generate unforeseen and inaccurate content [31-33]. Additionally, the opacity of this predictive approach hinders the ability to anticipate all possible outputs, making it challenging to establish safeguards that effectively prevent the dissemination of harmful or misleading information [34,35].

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Furthermore, integrating these models into health care systems can involve transmitting sensitive, patient-identifiable data to third-party servers for processing, thereby imposing significant legal and ethical risks on health care providers [36,37].

Evidence indicates that the design features of conversational agent–enabled interventions impact the engagement of people with mental health issues in managing their condition [38,39]. For example, studies indicate that specific design features such as enhancing the anthropomorphic qualities of conversational agent–enabled interventions can improve engagement by reducing the monotony of repeated interactions [38,40]. Additionally, a recent review explored how design features pertaining to conversational architecture, such as delaying responses, proactive dialogues, and self-disclosures, affected user perceptions of conversational agents [41]. However, to date, there has not been a synthesis of evidence pertaining to conversational agent–enabled intervention design features (eg, personality) and their impacts on the engagement of people managing CMDs. In filling this gap, this review will contribute to the broader developer community making better informed choices when developing conversational agents, leading to more engaging, and therefore effective, conversational agent–enabled interventions for CMD self-management.

Methods

Protocol and Registration

This protocol is reported in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist [42,43]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023431579) in June 2023.

Eligibility Criteria

Population

The review will include studies of adult participants (aged≥18 years) with a CMD diagnosis. CMDs are a group of interrelated conditions, including heart failure and diabetes, that increase the risk of cardiovascular and metabolic complications [1]. Populations reported with comorbidities such as mental health disorders or multiple CMDs will also be included.

Intervention

The review will include studies reporting on conversational agent–enabled interventions to assist people with CMD in managing their condition, such as by offering emotional or educational support and assisting individuals to monitor their symptoms.

Outcomes

The review will include studies reporting engagement outcomes such as ratings, interviews, analytics, and focus groups.

Study Design

The review will include primary research studies, including qualitative studies, quasiexperimental studies, observational studies, and randomized controlled trials. Reviews, editorials, protocols, and non-English publications will be excluded.

Information Sources

We systematically searched the Ovid (Medline), Web of Science, and Scopus databases for relevant articles from inception until April 2024. Ovid (Medline) was selected owing to its medical and health science focus, which is useful for capturing research on the topic of CMDs. Web of Science and Scopus were both selected for their broader focus, which is useful for capturing research on conversational agents and engagement topics. To ensure a manageable scope, several databases were ruled out during preliminary searches. For example, Embase was ruled out because it had redundancy with Medline. In addition, the Cochrane Library was too specific, with 4 of the 5 exemplar papers present in all other databases not found in the Cochrane Library database. As this is a rapidly developing field, final searches will be conducted prior to the submission of a manuscript and additional studies that meet the inclusion and exclusion criteria will be incorporated into the review. Reference list searches will be conducted on all articles included in the full-text review.

Search Strategy

An extensive set of search terms will be used related to the three central topics of the review: CMD, conversational agents, and engagement. Boolean operators will be used to combine search terms, including the following search string: (“Cardiovascular Diseases”[MeSH Terms] OR metabolic) AND (“conversational agent*” OR chatbot*) AND (accept* OR perceived). This approach is intended to yield a comprehensive collection of literature that explores the intersection of these central topics. An example of a complete search strategy is provided in Multimedia Appendix 1.

Data Management

All search results will initially be imported into PaperPile, followed by removal of duplicate entries. The deduplicated library will then be exported from PaperPile and imported into Covidence (Veritas Health Innovation). Covidence (cloud-based software) will be used to store PDF files of articles considered during the full-text review. Additionally, Covidence will be used to store data extraction and quality appraisal forms, study selection results, and reviewer comments. Covidence will be used for data extraction and management and then the data will be exported to Microsoft Excel.

Study Selection

During initial screening, two reviewers (NK and ATS) will independently examine the titles and abstracts of all studies collected from the search strategy. Assessments will be based on the defined inclusion and exclusion criteria. If conflicts arise, they will be settled during meetings between the two reviewers. If a conflict is not able to be resolved in this manner, the matter will be arbitrated by a third reviewer to achieve consensus.

During full-text screening, the remaining studies will be independently assessed by two reviewers to determine inclusion or exclusion using defined inclusion and exclusion criteria. Any

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conflict between the two reviewers will be settled during meetings, with arbitration by a third reviewer when required.

Data Extraction

Data extraction from all included studies, including any supplementary material, will be performed and documented by two independent reviewers. Where more detailed information is required, authors will be contacted once for clarification.

The data extraction form will be designed to capture a wide array of details necessary to achieve the outcomes described above, primarily by capturing the perspectives of people with CMD on the use of conversational agent–enabled interventions. These details will include bibliographic information, study design, participants and population, intervention, and design features in terms of engagement outcomes.

Quality Appraisal

The following Joanna Briggs Institute critical appraisal tools will be used: Checklist for Qualitative Research for qualitative research [44], Checklist for Quasi-Experimental Studies for quasiexperimental studies [45], and Assessment of Risk of Bias for Randomized Controlled Trials for randomized controlled trials [46]. The quality of evidence assessment results will be presented in a summary of findings table.

Data Synthesis

An adapted version of the thematic synthesis analysis method developed by Thomas and Harden [47] will be used. This method will focus on data extracted from studies that detail design features and engagement outcomes. During the initial phase, these data will be categorized under multiple domains. Following the extraction, these domains will be iteratively consolidated until further merging would detract from the descriptive accuracy of the domains regarding their respective data sets. Subsequently, within each primary domain, the data will be further sorted into subdomains in a similar manner of iterative consolidation. Tables will be used to detail various aspects of the extracted studies, including study design, population, conversational agent characteristics, and design feature domains. Analysis of these themes will contribute to informing design choices for conversational agent–enabled interventions and to identify research gaps in how engagement tends to be reported in the literature.

Results

The review was initiated in May 2023 and, prior to title and abstract screening, was registered with PROSPERO in June 2023. Full-text screening of articles was completed in August 2023, followed by data extraction. Final searches were conducted in April 2024 (Figure 1) and the completed review was submitted to *Digital Health* in July 2024. Data pertaining to study design and sample size have been extracted and are summarized in Table 1.

Figure 1. Flowchart illustrating the study selection process.

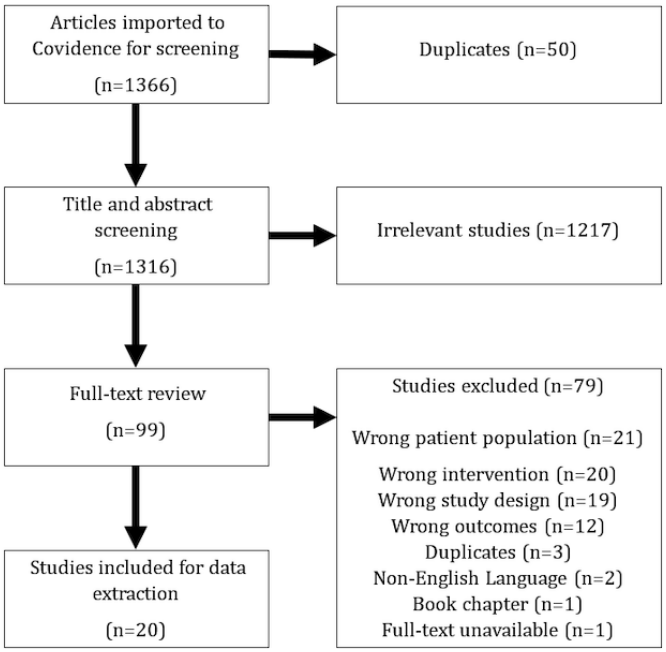

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Table 1. Characteristics of included studies.

Reference, publication year	Study design	Conversational agent role
Apergi et al [22], 2021	Quasiexperimental	To ask the patients the same series of questions related to their heart failure treatment and symptoms and provide feedback
Balsa et al [48], 2019	Qualitative	To assist older people with type 2 diabetes mellitus in medication adherence and lifestyle changes
Balsa et al [49], 2020	Qualitative	To support older people with type 2 diabetes mellitus in medication adherence and lifestyle changes
Baptista et al [23], 2020	Quasiexperimental	To deliver self-management education and support to adults with type 2 diabetes mellitus
Cheng et al [24], 2018	Qualitative	To provide a less cumbersome way for older patients with type 2 diabetes mellitus to effectively adhere to guidelines
Echeazarra et al [50], 2021	Randomized controlled trial	To help patients with hypertension self-monitor their blood pressure
Epalte et al [25], 2023	Qualitative	To counsel, educate, and train patients and family members with stroke with regard to rehabilitation, care, and other related issues
Gingele et al [51], 2023	Qualitative	To evaluate patients' health status, provide patient education, and enable communication with heart failure nurses
Gong et al [52], 2020	Randomized controlled trial	To provide more accessible and engaging self-management support, monitoring, and coaching to adults with type 2 diabetes mellitus in Australia
Guhl et al [53], 2020	Quasiexperimental	To augment patient-centered health care by providing health education, monitoring, and problem-solving for users
Kimani et al [54], 2016	Quasiexperimental	To provide education on atrial fibrillation and promote adherence to daily heart rhythm monitor readings
Magnani et al [55], 2017	Quasiexperimental	To promote education, motivation, and monitor patient symptoms and adherence to behaviors
Roca et al [56], 2021	Quasiexperimental	To improve medication adherence in patients with comorbid type 2 diabetes mellitus and depressive disorder
Sagstad et al [57], 2022	Qualitative	To educate women with gestational diabetes mellitus
ter Stal et al [58], 2021	Qualitative	To support users in the self-management of chronic diseases in a long-term, daily life setting
Tongpeth et al [59], 2018	Qualitative	To improve patients' knowledge of and response to acute coronary syndrome symptoms
Tsai et al [60], 2022	Qualitative	To support patients with chronic kidney disease manage their condition
Zhang et al [61], 2015	Qualitative	To counsel patients on their diagnoses and medications specified by a clinician, as well as increasing physical activity, improving diet, decreasing stress, and motivating them to be more involved and proactive in their own care

Discussion

The effectiveness of digital health interventions in supporting people with CMD is dependent on the extent to which users engage with the digital tool [17,18]. Augmenting digital health interventions with conversational agents, technologies that interact with people using natural language, may enhance engagement because of their human-like attributes [24,25,57]. This protocol outlines a systematic review that aims to synthesize evidence pertaining to conversational agent–enabled intervention design features and their impacts on the engagement of people managing CMDs. The anticipated outcomes of the analysis include the identification of specific design features or themes within various domains that improve engagement with digital health interventions. Additionally, the quality appraisal process is expected to uncover research gaps on conversational agent–enabled interventions, thereby providing a clearer direction for future studies applied to investigating the design of conversational agent–enabled digital health interventions.

This synthesis will provide guidance on how best to embed engagement strategies within these interventions, thereby facilitating more engaging and effective strategies for supporting people managing CMDs. Additionally, characterizing the literature, in terms of how engagement tends to be reported, will have the benefit of identifying research gaps and highlighting areas for future exploration. These outcomes can in turn support researchers in developing a greater understanding of user engagement with conversational agent–enabled interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 13 KB - resprot_v13i1e52973_app1.docx]

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Abbreviations

CMD: cardiometabolic disease
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

The Effectiveness of Collaborative Care Interventions for the Management of Patients With Multimorbidity: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression Analysis

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Abstract

Background: Collaborative care interventions have been proposed as a promising strategy to support patients with multimorbidity. Despite this, the effectiveness of collaborative care interventions requires further evaluation. Existing systematic reviews describing the effectiveness of collaborative care interventions in multimorbidity management tend to focus on specific interventions, patient subgroups, and settings. This necessitates a comprehensive review that will provide an overview of the effectiveness of collaborative care interventions for adult patients with multimorbidity.

Objective: This systematic review aims to systematically assess the effectiveness of collaborative care interventions in comparison to usual care concerning health-related quality of life (HRQoL), mental health, and mortality among adult patients with multimorbidity.

Methods: Randomized controlled trials evaluating collaborative care interventions designed for adult patients (18 years and older) with multimorbidity compared with usual care will be considered for inclusion in this review. HRQoL will be the primary outcome. Mortality and mental health outcomes such as rating scales for anxiety and depression will serve as secondary outcomes. The systematic search will be conducted in the CENTRAL, PubMed, CINAHL, and Embase databases. Additional reference and citation searches will be performed in Google Scholar, Web of Science, and Scopus. Data extraction will be comprehensive and include information about participant characteristics, study design, intervention details, and main outcomes. Included studies will be assessed for limitations according to the Cochrane Risk of Bias tool. Meta-analysis will be conducted to estimate the pooled effect size. Meta-regression or subgroup analysis will be undertaken to explore if certain factors can explain the variation in effect between studies, if feasible. The certainty of evidence will be evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Results: The preliminary literature search was performed on February 16, 2024, and yielded 5255 unique records. A follow-up search will be performed across all databases before submission. The findings will be presented in forest plots, a summary of findings table, and in narrative format. This systematic review is expected to be completed by late 2024.

Conclusions: This review will provide an overview of pooled estimates of treatment effects across HRQoL, mental health, and mortality from randomized controlled trials evaluating collaborative care interventions for adults with multimorbidity. Furthermore, the intention is to clarify the participant, intervention, or study characteristics that may influence the effect of the interventions. This review is expected to provide valuable insights for researchers, clinicians, and other decision-makers about the effectiveness of collaborative care interventions targeting adult patients with multimorbidity.

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Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42024512554; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=512554

International Registered Report Identifier (IRRID): DERR1-10.2196/58296

(JMIR Res Protoc 2024;13:e58296) doi:10.2196/58296

KEYWORDS

multimorbidity; comorbidity; multiple chronic conditions; patient care team; multidisciplinary teams; collaborative care; quality of life; systematic review; meta-analysis

Introduction

Multimorbidity lacks a universally accepted standard definition but is most commonly defined as the presence of 2 or more coexisting chronic conditions in one individual [1]. Multimorbidity is distinguished from the related concept of comorbidity by treating all conditions equally as opposed to prioritizing or designating an index condition in the case of comorbidity [1].

Multimorbidity is highly prevalent on a global scale [2,3]; however, the prevalence shows substantial variation across studies conducted in different countries and age groups [4]. Approximately 37% of adults worldwide are estimated to have multimorbidity [3]. The number of patients with multimorbidity has been rising worldwide and is expected to continue to increase in the future [3,5]. This is partly due to changing lifestyle risk factors and the aging population [3]. A range of lifestyle factors are associated with a higher risk of developing multimorbidity, such as smoking, excessive alcohol intake, lack of physical activity, obesity, and poor diet quality [6-8]. The prevalence of multimorbidity also commonly increases with age [9] and the majority of patients with multimorbidity are typically 65 years and older [2,10]. However, multimorbidity is also associated with gender [9,10], socioeconomic status [9], and educational level [10,11].

Multimorbidity leads to increased resource use due to a higher health care demand and treatment complexities. Patients with multimorbidity face a higher likelihood of hospital admissions, extended hospital stays, and premature mortality compared to those with a single condition [12,13]. The economic burden of managing patients with multimorbidity is substantial and increases in proportion to the number of additional conditions [14-17]. Multimorbidity is also associated with an increased risk of mental disorder, psychological distress [18], impaired quality of life [19-21], and poorer physical function [22]. Depression is especially common among patients with multimorbidity, being 2-3 times more common than among people with no or only one chronic condition [23]. Thus, multimorbidity negatively impacts quality of life [21].

Collaboration between sectors, specialties, and professions has been proposed as a promising approach to improve health care for patients with multimorbidity. Typically, the health care teams involved in these interventions are composed of a range of different types of professionals (eg, nurses, physicians, or social workers) or professionals from different disciplines or specialties (eg, general practice or endocrinology) [24]. Despite previous systematic reviews exploring the effects of using collaborative care interventions in the management of patients with multimorbidity [25-33], these reviews have generally been limited to a certain type of intervention, subpopulation, or setting. The general findings in these systematic reviews are further subject to uncertainties regarding the effectiveness of collaborative care interventions for managing multimorbidity due to mixed results, insufficient data, and evidence gaps [25-28,31]. Multiple explanations have been suggested for these findings. The current definitions of multimorbidity result in the inclusion of a substantial number of diverse patients, some of whom may not require collaborative care interventions [34]. One plausible explanation is that the effect of collaborative care interventions depends on the target subpopulation, implying that studies involving patients with limited room for improvement demonstrate less effectiveness [25,35]. This emphasizes the importance of identifying the patients who would generally benefit the most from collaborative care interventions.

Collectively, this situation leads to a fragmented overview of the collaborative care interventions used for patients with multimorbidity, necessitating a comprehensive review of these interventions and their corresponding effects. This calls for a new systematic review with a meta-analysis incorporating specific analyses such as meta-regression or subgroup analysis that is capable of handling differences between studies with regard to participant and intervention characteristics. This need is underlined by the rapid development in research within the field of collaborative care interventions for patients with multimorbidity.

Therefore, this systematic review aims to assess the effectiveness of collaborative care interventions compared with usual care on health-related quality of life (HRQoL), mental health, and mortality among adult patients with multimorbidity.

The main research question is: What is the effectiveness of being assigned to collaborative care interventions compared to usual care for adult patients with multimorbidity?

The secondary research question is: Can differences in effectiveness between studies be explained by participant, intervention, or study characteristics?

Methods

Study Design

The development of this protocol is based on the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [36]. The proceeding systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses) guidelines [37]. This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024512554) on February 15, 2024.

Eligibility Criteria

Participants

Participants must be adults, defined as being at minimum 18 years of age. The included participants must have multimorbidity, defined as at least 2 chronic conditions in one individual [38]; chronic diseases will be considered according to the World Health Organization definition of "health problems that require ongoing management over a period of years or decades" [39]. Studies with subgroups of patients with multimorbidity, presented in separate subgroup analyses, will be considered for inclusion.

Intervention

The definition of collaborative care is based on the systematic review by Gunn et al [40]. The intervention must involve any type of collaborative care activity in addition to the delivery of patient care. The intervention should include at least one health care professional (HCP) and the collaboration must involve at least 2 different health or social professions (eg, nurses, social workers, or pharmacologists) or similar HCPs from at least 2 different specialties (eg, collaboration between 2 physicians specialized in cardiology and endocrinology). Alternative professions such as "health coordinators" or "clinical care managers" will be considered when these professionals actively contribute as independent participants in the intervention, providing coordination or insight from social or health care perspectives. Furthermore, the intervention must encompass a structured management plan and scheduled patient follow-ups [40].

Comparator

The comparison must be usual care. For this review, usual care is defined as the level of collaboration expected as part of normal practice, without explicitly mentioning a higher degree of collaboration, inspired by the study of Pascucci et al [41].

Outcomes

Prioritization of outcomes in this systematic review is based on the core outcome set for multimorbidity proposed by Smith et al [42]. The primary outcome is HRQoL, given its highest rank in the core outcome set [42]. The secondary outcomes will cover various elements such as mental health outcomes (encompassing general mental health, depression, and anxiety scales) and mortality due to their status as essential outcomes in the core outcome set [42].

Study Design

Randomized controlled trials (RCTs) with a parallel design will be considered in this review. Feasibility studies with an RCT design presenting results on effectiveness will also be considered for inclusion. Other criteria encompass inclusion of articles written in English, Danish, Swedish, and Norwegian. The articles must be available in full text. All studies available up to the submission date will be considered for inclusion. Only peer-reviewed articles will be included.

Information Sources

The systematic research will be conducted in the following scientific databases: CENTRAL, PubMed (including the MEDLINE database), CINAHL, and Embase. All included articles will undergo reference screening and a citation search to ensure relevant papers are captured. Citation searches of relevant articles will be carried out in Scopus, Web of Science, and Google Scholar.

Search Strategy

The search strategy was developed by conducting an initial search in CENTRAL and PubMed to identify the relevant literature. The retrieved literature from the initial search was then used to identify relevant keywords that were integrated into the search strategy. The search will be performed through a block search structured according to the Population, Intervention, Comparator, and Outcome (PICO) framework, encompassing terms related to the population and intervention. The search strategy will be tailored to the specific database used. Synonyms, similar terms, and variations in spelling will be considered in the searches. The databases' built-in search functions will also be used, such as the inherent thesaurus, Boolean operators, and filtering options. The search strategies are planned in collaboration with a research librarian. The complete search strategy used in all databases is provided in Multimedia Appendix 1. Prior to submission, a follow-up search in all databases will be performed to ensure inclusion of all newly published studies.

Study Records

Data Management

Following the search, all references will be uploaded into Zotero version 6.0.30 [43]. The function *merge duplicates* in the *duplet section* will initially be used. Subsequently, the references will be exported to the web-based software Covidence [44], facilitating collaborative inclusion and exclusion of studies.

Selection Process

Potential studies will be evaluated for inclusion in this review based on the presented eligibility criteria. Two authors will independently assess all studies from the block search. Initially, the studies will be screened by title and abstract, and those not aligning with the eligibility criteria will be excluded. The remaining studies will undergo a full-text assessment, and only those meeting the eligibility criteria will be included. In case of disagreement, a third author will be involved in the decision-making process. Additional citation and reference searches will be performed by the first author. A PRISMA flow diagram will be provided to ensure transparency in the selection of articles (see Multimedia Appendix 2).

Data Collection Process

Data extraction will be performed using a customized Microsoft Excel form. In cases where usable data extraction is hindered due to incomplete representation of study details or results in some articles, the authors of these studies will be contacted for clarification.

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Data Items

The information relevant for this review includes elements of the study design, participant characteristics, intervention details, and main outcomes. The data extracted from the studies will encompass various elements, including author details, publication year, country, study design, baseline characteristics, total sample size, intervention specifics, intervention team, setting, comparator, and study outcomes. A table summarizing the key characteristics of each study will be provided. Concerning the type of participants in the study, a distinction will be made between comorbidity studies, focusing on patients with specific combinations of conditions, and multimorbidity studies, encompassing participants with diverse combinations of conditions [45]. Baseline characteristics will include elements such as age, gender, BMI, or body weight. Details about the interventions will encompass aspects such as the setting, intervention duration and frequency, and the types of professionals and specialties represented in the collaborative care teams. Furthermore, it will be noted whether the intervention incorporates a digital element. The collected data items pertaining to the study outcomes will include details such as outcome scores or values, statistical precision metrics, assessment tool, sample size in each group at the time of assessment, and time of assessment. In the meta-analysis, results related to the latest time of assessment will be collected. The authors of the included studies will be contacted to provide additional information if characteristics or results at the study level are not available.

Risk of Bias Assessment

The included studies will be assessed for limitations according to the Cochrane Risk of Bias tool version 2 [46], with independent assessments conducted by 2 authors. In cases where differences in assessment occur, a discussion involving a third author will be initiated to reach agreement. All eligible studies will be included in this review, regardless of their quality. Only studies with an overall risk of bias judged to be “low risk of bias” or “some concerns” will be included in the meta-analysis. If missing information makes risk of bias assessment impossible, corresponding authors will be contacted to obtain the necessary information. The results of the risk of bias assessment will be presented in a risk of bias chart.

Data Synthesis

Meta-Analysis

A meta-analysis will be performed to analyze the available data. The analysis will be performed in RStudio using the Meta-Analysis Package for R (Metafor package) enabling the creation of a data frame containing various measures for the meta-analysis model (eg, effect size, *t* statistics, or *P* values). However, if the measures differ due to discrepancies in the data provided by some studies, supplementary calculations to standardize the data for analysis will be performed. These adjustments will adhere to the equations outlined in the Cochrane Handbook [47]. Outcome scores or values given as the absolute mean difference from baseline or absolute mean at follow-up, along with statistical precision metrics (eg, SD, CI, or SE), will be used to estimate the overall effect size for continuous variables. For studies where these data are not reported, the between-group estimates that quantify the effect of the intervention on the outcome and their precision will be used. If results are presented as medians and IQRs, the means and SDs will be estimated [48]. The article with the largest sample will be used for the meta-analysis if 2 or more articles present data from the same study for a particular outcome.

The meta-analysis will be based on the standardized mean difference for continuous variables sharing the same construct but different outcome measures. There is no rule as to when certain outcomes measures can be combined, which is generally determined by clinical judgment [49]. The decision to combine different outcome measures will involve at least 2 authors. Should disagreement arise, a third author will be consulted to reach agreement. Conversely, the weighted mean difference will be applied for continuous variables sharing the same outcome measure.

As it is difficult to make assumptions about the underlying distribution of effect sizes, the meta-analysis will follow the pragmatic approach proposed in the Cochrane Handbook regarding the choice of model [50]. This means that both the random- and fixed-effects models will be used in this meta-analysis because the included studies are expected to vary in multiple parameters [51]. One parameter is the samples in the studies, which do not originate from the same population. Although the overall population is patients with multimorbidity, the selected samples in the studies are expected to vary considerably. Consequently, the effects estimated across the studies may not be identical but rather follow a similar distribution. The findings from both models will be presented using forest plots and tables, accompanied by a sensitivity analysis. The effect estimate of continuous variables will be presented as a pooled mean difference or pooled standardized mean difference with 95% CIs. Odds ratios will be given for dichotomous variables with 95% CIs. Two-sided *P* values <.05 will be considered statistically significant. Interpretation of the pooled effect size will be guided by the principles outlined in the Cochrane Handbook [52]. To test for heterogeneity, the Higgins I^2 statistic will be calculated. The interpretation of I^2 will also be made according to the Cochrane Handbook [50].

Sensitivity Analysis

Sensitivity analysis will be performed, including variations in statistical models (random vs fixed effects) as well as assessments of risk of bias. If relevant, sensitivity analysis will also be performed by excluding studies that only report medians and IQRs. Other potential sensitivity analyses may consider a range of parameters such as sample size or follow-up length, with the purpose of evaluating the potential impact of these factors on the overall findings. A summary table will showcase the results of any sensitivity analyses performed [50].

Meta-Regression and Subgroup Analysis

Meta-regression or subgroup analysis will be performed to explore if certain factors can explain the variation in effect between studies. To explore associations between the primary outcome and various factors in the meta-analysis, a meta-regression analysis will be performed. In the analysis,

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participant characteristics will be examined by distinguishing between comorbidity and multimorbidity studies. Other participant-related factors to be explored include demographics, socioeconomic status, health indicators, lifestyle factors, and treatment variables. Interventions will be examined across multiple dimensions, including setting, duration, and frequency. Additionally, the types of professionals and specialties represented in the collaborative care teams will be evaluated to understand their influence on intervention outcomes. Furthermore, the presence of digital components will be considered to assess if they contribute to variations in effectiveness across studies.

Subgroup analysis may be performed if the meta-regression is impossible due to limitations related to the data. This may be due to the limited availability of continuous variables if studies predominantly report variables categorically (eg, in case of age groups instead of age as a continuous variable). Additionally, meta-regression analysis will not be considered if there are fewer than 10 studies in a meta-analysis [50].

Narrative Format

A table containing a narrative description of the key characteristics and findings of all studies will be provided. Due to heterogeneity or high risk of bias, meta-analysis may not be feasible for certain outcomes. In these cases, a narrative description will be provided. The results of the quantitative synthesis will be presented in a table with a summary of findings.

Assessment of Meta-Biases

To assess potential publication biases, a funnel plot with a regression line will be created. The funnel plot will be complemented by a statistical test for funnel plot asymmetry, such as the Egger test. The funnel plot will only be constructed for evaluation if the specific meta-analysis contains results from at least 10 studies [53].

Confidence in Cumulative Evidence

The GRADE (The Grading of Recommendations Assessment, Development, and Evaluation) system will be used for grading the certainty of evidence [54]. The GRADE evaluation will be performed independently by 2 authors. In case of disagreement, a third author will perform an additional GRADE evaluation. The web-based GRADEpro Guideline Development Tool software (Evidence Prime) will be used to perform the evaluation [55]. The results from the GRADE evaluation will be presented in a summary of findings table. This grading will be based on risk of bias, directness, heterogeneity, precision, and risk of publication bias.

Results

This systematic review and meta-analysis is ongoing. Results from the preliminary search, performed on February 16, 2024, can be found in Multimedia Appendices 1 and 2. A total of 6730 records were retrieved, of which 1475 were duplicates. This resulted in 5255 unique records remaining for initial title and abstract screening. A follow-up search across all databases will be conducted prior to submission. The findings will be visually presented through forest plots and in a summary of findings table where meta-analysis is feasible, and in cases where it is not, through narrative comparisons. This systematic review and meta-analysis is expected to be completed in late 2024. Following completion, the results will undergo peer review before being submitted for publication.

Discussion

This systematic review aims to assess the treatment effect on HRQoL, mental health, and mortality in collaborative care interventions compared to usual care in adult patients with multimorbidity. The presented systematic review will have both strengths and limitations. The strengths are rooted in the comprehensive exploration and broad scope undertaken. This review aims to investigate the impact of heterogeneity in participant and intervention characteristics on the pooled effect size. Such exploration holds the potential to provide valuable insights into the effectiveness of collaborative care interventions and to identify the factors that influence this effect. This may contribute to determining the optimal selection of patients with multimorbidity expected to derive the greatest benefit from collaborative care interventions. Additionally, this review may reveal intervention characteristics that prove meaningful to investigate further. Conducting a subsequent qualitative analysis may offer a deeper understanding of aspects that quantitative data alone may not capture. Triangulating these findings therefore ensures a thorough investigation of the complexities inherent in collaborative care interventions for patients with multimorbidity.

Nevertheless, limitations are expected due to the high degree of clinical diversity. This variability extends across the population, encompassing diverse conditions and diagnoses, as well as within the intervention characteristics, where differences stem from factors such as the composition of the collaborative care teams and the settings where the interventions are implemented. The planned comparison is therefore expected to be complicated due to the lack of homogeneity within the field. Hence, the forthcoming discussion will also encompass the consideration of confounders and methodological limitations to ensure meaningful conclusions. Further limitations will be examined and elucidated in the discussion section of the review to contribute valuable insights for guiding future research efforts.

Acknowledgments

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Authors' Contributions

AMK wrote the initial protocol draft, while the other authors provided substantial revisions, ensuring a comprehensive and informed final version of this protocol. Each author contributed significantly to the design of this study, defining the aim and objectives, formulating the eligibility criteria, and planning the data extraction. AMK and ACDD developed the search strategy in collaboration with a research librarian. The final version of this protocol was collectively reviewed and approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 24 KB - resprot_v13i1e58296_app1.docx]

Multimedia Appendix 2
Study selection flow diagram.
[DOCX File , 55 KB - resprot_v13i1e58296_app2.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HCP: health care professional
HRQoL: health-related quality of life
PICO: patient, intervention, comparison, outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial

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Protocol

Training of Community Health Workers in Diabetes Lead to Improved Outcomes for Diabetes Screening and Management in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Diabetes is a growing concern worldwide, particularly in low- and middle-income countries (LMICs). Type 2 diabetes mellitus constitutes a significant proportion of cases and is associated with debilitating microvascular complications. Type 2 diabetes mellitus is steadily increasing among the LMICs where many barriers to health care exist. Thus, task shifting to community health workers (CHWs) has been proposed as a solution to improve diabetes management in these settings. However, CHWs often lack the necessary training to manage diabetes effectively. Thus, a systematic review is required to present evidence of the highest degree for this intervention.

Objective: This study aims to establish the protocols for a systemic review.

Methods: Using the Participants Intervention Comparator Outcome Time Study Design (PICOTS) framework, this study outlines a systematic review aiming to evaluate the impact of training programs for CHWs in diabetes management in LMICs. Quantitative studies focusing on CHWs, diabetes training, focusing on diabetes management outcomes like hemoglobin A_{1c} levels and fasting blood glucose levels, between January 2000 and December 2023 and found on databases such as PubMed, Ovid MEDLINE, Evidence Based Medicine Reviews, BASE, Google Scholar, and Web of Science will be included. We will include randomized controlled trials but will also include observational studies if we find less than 5 randomized controlled trials. An author committee consisting of 3 reviewers will be formed, where 2 reviewers will conduct the review independently while the third will resolve all disputes. The Cochrane Methods Risk of Bias Tool 2 will be used for assessing the risk of bias and the Grading of Recommendations, Assessment, Development and Evaluation approach for the meta-analysis and narrative synthesis analysis will be used. The results will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.

Results: The review will begin in May 2024 and conclude in 3 months.

Conclusions: The review will synthesize existing evidence and provide insights into the effectiveness of such programs, informing future research and practice in diabetes care in LMICs.

Trial Registration: PROSPERO CRD42022341717; https://tinyurl.com/jva2hpdr

International Registered Report Identifier (IRRID): PRR1-10.2196/57313

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KEYWORDS

community health workers; diabetes training; community health worker training; systematic review; diabetes management; community training; low-and-middle-income countries; diabetes; type 2 diabetes mellitus; prevalence; rural; health care professionals; barriers

Introduction

Diabetes is a global epidemic that is threatening to grow exponentially and impact the lives of those affected. The International Diabetes Federation estimates that 463 million people will have diabetes globally and projects this number increasing to 700 million by 2045 [1]. Almost 80% of the world's patients with diabetes reside in low- and middle-income countries (LMICs) [2]. Type 2 diabetes mellitus (T2DM) constitutes a majority of patients with diabetes (almost 90%) and it severely affects them by causing microvascular complications that are often debilitating and morbid [3]. The condition itself is a risk factor for many other conditions such as stroke, cancer, and tuberculosis and causes damage to critical organs such as the heart, kidneys, eyes, and the limbs [4,5]. The immunocompromised nature of the patients makes them susceptible to infections and overall contributes to poorer health outcomes.

The LMICs are also gradually witnessing a rise in the prevalence of the disease in rural areas [6]. The LMICs are also plagued with barriers like availability of trained health care professionals who are required to cater to this growing number of patients with diabetes, long distances to the health centers, and lack of transportation facilities which often cause poorer uptake of health services [7-9].

The T2DM disease burden has increased exponentially in LMICs due to continuous upward growth in the trajectory of common risk factors responsible for T2DM. These have caused an increase in the comorbidities associated with the T2DM condition across the LMICs [10]. Similarly, the age-standardized death rates over the past decade have seen a 2- to 3-fold increase in the LMICs, when compared to the upper- or middle-income countries [11]. Recent studies have shown an increase in the prevalence of T2DM in lower socioeconomic areas of LMICs [12,13]. They also show that the increase in the prevalence of prediabetes is greater in these areas than the rate of increase in the urban areas [6,14]. Hence, the burden is set to increase among populations that have remote access to health care services or cannot afford the life-long management costs associated with T2DM [8,12,13,15,16].

Thus, a potential method of overcoming these barriers has been the use of community health workers (CHWs) for task shifting in LMICs for both infectious diseases and noncommunicable diseases [17-24]. All such task shifting initiatives need to ensure that the participating CHWs are provided with requisite training. Most CHW studies have found them to be deficient in knowledge and associated skills, and hence training them for any task-shifting initiative is critical for its success [25-28].

Where training has been provided, the results have generally been encouraging. However, such training programs have been few, and their evaluations have been rare. Evidence is found wanting for the efficiency of trained CHWs in LMICs in screening and managing patients with diabetes. Hence, a systematic review is required to present evidence of the highest degree for this intervention, and we propose to conduct the systematic review to understand if training of CHWs in diabetes would lead to improved outcomes for diabetes screening and management in LMICs.

Thus, the objective of this paper is to establish the protocols for the systematic review.

The systematic review has been registered with PROSPERO at PROSPERO 2022 (CRD42022341717).

Methods

Study Design

The criteria for considering studies for the systematic review would be done according to Participants Intervention Comparator Outcome Time Study Design (PICOTS) framework. Therefore, we would be considering the studies under the following conditions, the participants, the intervention, the comparators, the outcomes, the types of studies, and the timing of the study. Along with these, the databases to be used for the search will also be considered.

Description of Condition

T2DM will be the condition of interest. It accounts for almost 90% of diabetes globally and thereby affects a larger proportion of the population suffering from it. We will consider the World Health Organization (WHO) cutoff value of 126 mg/dl for fasting plasma glucose or 200 mg/dl for 2-hour post food plasma glucose to classify a person with diabetes [29].

Description of Participants

CHWs of LMICs will be considered participants for the studies or trials to be included in this review. The WHO defines CHWs to be "members of the communities where they work, should be selected by the communities, should be answerable to the communities for their activities, should be supported by the health system but not necessarily be a part of its organization, and have shorter training than professional workers" [30]. Hence, we will include all studies with CHWs in LMICs. The LMICs will be defined according to the World Bank definition of economies as those with a gross national income per capita between US $1136 and US $4465, calculated using the World Bank Atlas method [31]. A detailed list of the countries is given in Multimedia Appendix 1.

Description of the Intervention

The CHWs employed for task shifting have been found to have deficient knowledge. This can be corrected by providing them

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with the requisite training as that has been evidenced as an effective instrument for improving their knowledge, skills, and practices in LMICs [32,33]. Training in T2DM management includes the systematic application of formal processes to impart knowledge and help people acquire the skills necessary for them to perform their jobs satisfactorily. Hence, studies reporting any training related to the knowledge, skills and performance of the CHWs will be included. Some of the common aspects of training might include the screening of glycemia, lifestyle advice and education for patients, measurement of glycemia, and referral indications related to the aforementioned items.

Description of the Comparator

Standard training given to CHWs will be considered as the comparator. Therefore, any such training (whether focused on diabetes or even no training) provided to the CHWs would be included as the comparator.

Description of Studies

For the review, we will include randomized controlled trials (RCTs) as the first choice of studies, conducted between January 2000 to December 2023, in LMICs and published in English. This is due to the fact they present the highest degree of scientific evidence, and WHO and the World Medical Association published their guidelines and resolutions on task shifting respectively [34,35] around this time period. If there are less than 5 such studies, we will then include observational studies as well. For high scientific evidence, we will exclude qualitative studies. The included studies will focus on the training of CHWs in diabetes and look at diabetes management as their outcome. The details about the outcomes are detailed in the Description of Outcomes section.

Description of Outcomes

As we wish to study the effect of the training on diabetes management, we will include studies reporting any of the following outcomes with the respective measures of effect: (1) referral for diabetes (change in the number of referrals), (2) screening for diabetes (change in the number of screenings), (3) hemoglobin A_{1c} (HbA_{1c}) values (change in the mean HbA_{1c} values), and (4) fasting blood glucose values (change in the mean fasting blood glucose values).

Databases and Other Sources

For our review, we would search for appropriate studies on the following databases: Ovid MEDLINE, PubMed, Scopus, Cochrane Central, and Evidence Based Medicine Reviews. Additionally, we will also search the bibliographies of all the trials included based on our search strategies to identify further relevant studies. We will also be searching for all pertinent grey literature as this will help us identify the case studies and reports in greater detail. This will include a search of the databases about gray literature such as BASE, Google Scholar, WHO International Clinical Trials Registry Platform, and WorldCat. These will help us identify reports of studies conducted by private and civil society organizations or by other PhD students. The provisional search strategy for PubMed has been described in Multimedia Appendix 2.

Study Selection for the Review

Study titles and abstracts, which will be obtained through electronic source search, will be independently read by the reviewers (AGG and RD). The papers would then be selected for eligibility, based on the criteria. Papers that the authors find to be eligible will be retrieved in the full-text form. In case any of these papers are later found to be unsuitable for inclusion in our review, they would be mentioned separately in detail in a tabular manner, titled table of excluded studies. The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocols) [36] guidelines have been adhered to for this protocol and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will be adhered to for the conduct of the review (Multimedia Appendix 3). The full-text review will be carried out independently by 2 reviewers (AGG and RD). The third reviewer (GRB) will resolve any disagreements, which might arise.

Data Extraction and Synthesis

The data extraction will be done by 2 reviewers independently. They will first develop a custom-made data extraction form using the Cochrane collaboration template for RCTs and non-RCTs. This form will first be piloted with a small sample of study designs included in the review. The data will be extracted to prespecified and preapproved sheets using Microsoft Excel. These forms will be prespecified by the authors to include a recording of the study characteristics, the outcomes of interest and all relevant information. Furthermore, these forms will be shared with the author committee members for their feedback and for them to further pilot it put on a small number of studies. Based on this, the forms would either be revised or finalized. In this manner, these forms would be preapproved and finalized. The final version of the form will be used to extract and subsequently collect data from all included studies by the reviewers. Any disagreements will be resolved by the third reviewer.

If the data extracted are found to be limited, then we will contact the study authors for further information. Finally, we will also contact the authors of the included trials or studies to ascertain if they would like to answer any questions regarding the trials or studies. All the results will be presented in an appendix. Any missing or otherwise relevant information will be obtained from the primary authors of the original trials or studies (if needed).

Finally, in case of multiple publications, we will consider the final or the updated version of each study as the primary reference. This will ensure that the latest evidence is included in the review.

The following information will be extracted from the included studies:

- Training characteristics: we will extract characteristics such as the duration of training, frequency of training, the content of training, and location of training.
- The outcomes as reported by the study authors will include the following: (1) referral for diabetes, (2) screening for diabetes, (3) HbA_{1c} scores, and (4) fasting blood glucose values.

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We will use the desktop version of software like Covidence (Veritas Health Innovation Ltd) or Sysrev (Insilica LLC) for the extraction process.

Risk of Bias (Quality) Assessment

We will follow the revised risk of bias version 2 tool [37], which is a modified version of the Cochrane risk-of-bias tool to assess the internal validity of the included RCTs. The tool includes an assessment of sequence generation and allocation concealment; blinding of participants and outcome assessment; and incomplete outcome data and selective outcome reporting.

We will use ROBINS risk of bias tool in nonrandomized studies (if included) of intervention for assessing the risk of bias in nonrandomized studies included in the review. This will be done at the outcome level. All 3 reviewers (AGG, RD, and GRB) will be a part of the review. The first 2 reviewers will be conducting the review and in case of any disagreement which cannot be resolved between them, the third reviewer will resolve the disagreement and his decision will be final. If the information available from the sources is inadequate, then we will contact the primary authors of the studies to include details to request any missing data on items that could have contributed to the risk of bias. The individual bias items will be evaluated based on the items described in the *Cochrane Handbook for Systematic Review of Interventions* [38].

Strategy for Data Synthesis

A preliminary search for studies showed a lot of heterogeneity, in terms of the training, like the study settings, participant education, professional experience, training frequency, training duration, and training content. Expecting this trend in the studies to be extracted and included, the authors will synthesize the training component narratively as per the suggestion in *Cochrane Handbook for Systematic Review of Interventions*.

The preliminary search also showed homogeneity in terms of the outcome results, like the mean change in fasting blood glucose values and the mean change in HbA_{1c} values. We will perform a meta-analysis and report the results in a PRISMA diagram [39].

The following are the data points which the reviewers would look for in synthesis. First, the effect of the intervention. Authors will determine if studies are estimating the same underlying treatment or intervention effect. As our review focuses on CHW training as the intervention, we will be looking if the studies are estimating the intervention effect in terms of knowledge, skills, and performance of the CHWs related to diabetes, that is, the interventions focus on screening, referral, HbA_{1c} levels, and fasting blood glucose levels. Additionally, the methodology and participants being studied will also be studied. Second, the factors affecting the implementation of the study interventions.

For the continuous data points, we would use the mean difference method for meta-analysis while we would use the odds ratio and the risk ratio methods for the discrete data points. In both cases, the confidence intervals would be 95%.

The narrative synthesis will be carried out by developing a general framework using a set of tools such as Microsoft Excel and Mendeley (Elsevier) or EndNote (Clarivate Analytics). This will be executed using the following steps:

- Develop a theory of change to understand how the intervention works, why it works, and for whom it best works.
- Development of preliminary synthesis of findings of all the studies to be included
- Exploration of relationships across the entire data from the included studies.
- Assessment of the robustness of the synthesis.

The main narrative findings will be reported in a table titled "Summary of Findings" by using the Grading of Recommendations, Assessment, Development and Evaluation approach as mentioned in the *Cochrane Handbook for Systematic Review of Interventions*. The within-study risk of bias to assess the methodological quality, the directness of the evidence, the heterogeneity, the precision effect estimates, and the risk of publication bias will also be considered.

Eventually, a rating system to rate the quality of the evidence for each of the outcomes in terms of high, moderate, low, and very low will be created. The same Grading of Recommendations, Assessment, Development and Evaluation method will also be used for the meta-analysis findings.

Analysis of Subgroups or Subsets

We plan to perform subgroup analysis according to the following factors: (1) types of community health workers (nurses and lay health workers) and (2) demographic factors of health workers (education and work experience).

These factors will be analyzed for homogeneity or heterogeneity using the chosen software. All data would be entered in the software and tabulations would be carried out concerning each of the factors mentioned earlier to assess the heterogeneity or homogeneity. We would be using the Q statistic and I-square methods for assessing the heterogeneity. Further relationships will be explored within the data using the aforementioned factors and the predefined outcomes. A statistical test of significance will be carried out for each of the mentioned factors and an eventual summary will be presented to showcase statistical significance (if present) based on the *P* value of the association using the 1-tailed *t* test for each factor and its relationship with each outcome.

Results

The review will start in May 2024 and will be completed in a time frame of 3 months. This will include the screening, abstract review, full-text review, data extraction, and data synthesis. The results are expected to be published before the end of 2024.

Discussion

Diabetes is a pressing global health challenge, particularly affecting LMICs, where the prevalence is rapidly increasing among sections that are unable to afford or access quality health care. These patients are at high risk of developing complications which will affect the critical organs of the body. These combined with the delayed wound healing and their immunocompromised

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status, contributes to poorer outcomes for them. This underscores the importance of developing effective strategies for managing T2DM, particularly in LMICs where access to health care services are limited.

One such strategy is the use of CHWs for task shifting. CHWs, who are often members of the communities they serve, play a vital role in delivering health care services, including diabetes management in LMICs. However, CHWs lack the necessary knowledge and skills to manage diabetes and thus require training to improve their capacities. While there is some evidence to suggest that such training programs are successful in improving the CHWs knowledge, skills, and performance in diabetes management, such studies are few and their evaluations are rare. Therefore, there is a need for a systematic review to assess the impact of training programs for CHWs on diabetes outcomes in LMICs.

Possible findings from the review may include evidence supporting the effectiveness of training programs in improving CHWs' ability to screen for diabetes, refer patients for further care, and manage diabetes-related outcomes such as HbA_{1c} levels and fasting blood glucose values. The review may also identify gaps in the existing literature, such as the lack of rigorous evaluations of training programs or the need for more studies in certain geographical regions or among specific populations.

The limitations of the study would be possible deviations from the protocols due to unexpected results in terms of number of studies, language restrictions, type and number of studies, and the quality of studies.

In conclusion, our protocol aims to establish a systematic review that will have the potential to influence future efforts of CHW training for effective diabetes management in LMICs.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

The study was conceptualized by AGG, SK, GRB, NCS, and OCPVS. AGG wrote the manuscript, which was validated by GRB, NCS, and OCPVS. The manuscript was further edited by GVSM in addition to the above authors. The tables were prepared by AGG and SK and were reviewed by GRB, GVSM, NCS, and OCPVS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List of Low-Middle-Income-Countries defined by World Bank 2024.
[DOCX File , 15 KB - resprot_v13i1e57313_app1.docx]

Multimedia Appendix 2
Provisional Search Strategy for PubMed.
[DOCX File , 14 KB - resprot_v13i1e57313_app2.docx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocol) checklist.
[DOCX File , 19 KB - resprot_v13i1e57313_app3.docx]

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Abbreviations

CHW: community health worker
HbA_{1c}: hemoglobin A1c
LMIC: low- and middle-income country
PICOTS: Participants Intervention Comparator Outcome Time Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocols
RCT: randomized controlled trial
T2DM: type 2 diabetes mellitus
WHO: World Health Organization

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Protocol

University Food Environment Assessment Methods and Their Implications: Protocol for a Systematic Review

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Abstract

Background: While the retail food environment has been well studied, research surrounding the university food environment is still emerging. Existing research suggests that university food environments can influence behavioral outcomes such as students' dietary choices, which may be maintained long-term. Despite a growing interest in assessing university food environments, there is no standardized tool for completing this task. How researchers define "healthy" when assessing university food environments needs to be clarified. This paper describes the protocol for systematically reviewing literature involving university food environment assessments.

Objective: This paper aimed to describe the protocol for a systematic review of the assessments of university food environments. The review will summarize previously used tools or methods and their implications.

Methods: Electronic databases, including PubMed (NLM), Cochrane Library (Wiley), Web of Science (Clarivate), APA PsycINFO (EBSCO), CINAHL (Cumulative Index to Nursing & Allied Health) Complete (EBSCO), ProQuest Nursing and Allied Health, and Google Scholar were searched for papers published between 2012 and 2022 using combinations of related medical subject headings terms and keywords. The electronic databases were supplemented by reviewing the reference list for all included papers and systematic reviews returned with our search results. The review will include all study types, including randomized controlled trials, observational studies, and other pre-post designs. Papers that examine at least 1 aspect of the university food environment, such as cafeterias, campus convenience stores, and vending machines, were considered for inclusion. A total of 2 reviewers will independently screen titles and abstracts, complete a full-text review, extract data, and perform a quality assessment of included papers, with a third reviewer resolving any conflicts. The Quality Assessment for Diverse Studies (QuADS) tool was used to determine the methodological quality of selected studies. A narrative and tabular summary of the findings were presented. There will not be a meta-analysis due to the methodological heterogeneity of the included papers.

Results: The initial queries of 4502 records have been executed, and papers have been screened for inclusion. Data extractions were completed in December 2023. The results of the review were accepted for publication in May 2024. The systematic review generated from this protocol will offer evidence for using different assessment tools to examine the campus food environment.

Conclusions: This systematic review will summarize the tools and methods used to assess university food environments where many emerging adults spend a significant part of their young adult lives. The findings will highlight variations in practice and how "healthy" has been defined globally. This review will provide an understanding of this unique organizational food environment with implications for practice and policy.

Trial Registration: PROSPERO CRD42023398073; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=398073

International Registered Report Identifier (IRRID): DERR1-10.2196/54955

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(JMIR Res Protoc 2024;13:e54955) doi:10.2196/54955

KEYWORDS

universities; nutrition assessment; nutrition policy; health behavior; young adult; food environment; retail food; university food environment; university food; dietary choice; food assessment; tool; university; lifestyle habit; diet; obesity; United States; weight gain

Introduction

Rationale

An optimal time to encourage healthy lifestyle habits is during young adulthood, specifically between the ages of 18 and 25 years [1-4]. This transitional period from adolescence to young adulthood is critical for developing self-identity, self-efficacy, and long-term behaviors and lifestyles [4]. Research suggests diet quality, activity patterns, and overall health decline during this transition with exposure to unfamiliar environments and routines [5-7]. For many emerging adults, this period also means transitioning to college and shifting interpersonal influences [8].

The obesity rate among young adults in the United States has risen in the past decade from 24% to 29% [9]. This increase is partially due to unhealthy dietary and physical activity behaviors [10-12], which are modifiable. Since college students make up a considerable proportion of the emerging adult population globally, university campuses may be an optimal intervention point. For instance, 38% of emerging adults in the United States attended college in 2021 [13]. Many studies suggest that the transition to college is associated with poor dietary intake and excess weight gain, especially in the first year [14-18].

Poor dietary behaviors among college students are associated with decreased health, lower academic outcomes, and lower socioeconomic outcomes [19-22]. Thus, college students are ideal for interventions designed to improve dietary choices and promote healthy lifestyles. Adopting healthy nutritional practices by young adults might persist throughout adulthood, resulting in a reduced risk of chronic diseases later in life [23,24].

The social cognitive theory emphasizes reciprocal determinism and provides a valuable framework for exploring how environmental factors or changes influence the attitudes and behaviors of college students [25]. The social cognitive theory and other related theories, such as the socio-ecological model, have been applied in several initiatives implemented within higher education in an attempt to promote healthy and environmentally sustainable campus communities [15,26,27]. Research indicates that these interventions have a significant role in shaping health behaviors among students, and college administrators play a critical part in developing and implementing policies that encourage healthy choices [26].

Beyond the design and implementation of health promotion interventions, research in this domain has examined the healthfulness of food environments [28-30], dietary and food purchasing behaviors of college students [31-34], food security among college students [35], nutrition security [36,37], food accessibility [38], menu diversity [39], and food sustainability [14,40]. These studies cut across different countries and postsecondary school contexts, providing valuable insights for designing effective nutrition policies on university campuses. An overlapping objective of most of these studies is to improve the healthfulness of campus food environments and fight the obesity epidemic among young adults.

The existing evidence regarding campus food environments and their impact on healthy eating behavior is still emerging. Recent literature suggests that university food environments offer less nutritious food options [41,42] and college students endure food and nutrition insecurity [43]. Notably, the COVID-19 pandemic altered the student experience and increased food insecurity among young adults [44]. At an institutional level, many university campuses have yet to develop policies to encourage the consumption of sustainable food options [26,45] or fail to co-ordinate efforts to improve access to safety net programs (eg, the SNAP [Supplemental Nutrition Assistance Program] program enrollment) for students experiencing food insecurity with limited resources [46]. Furthermore, opinions on improving the healthfulness of food environments, menu diversity, food security, and food accessibility are diverse and context-specific [47]. Studies on the effects of environmental changes on dietary choices provide mixed findings. For example, research on the impact of calorie posting and nutritional labeling on dietary behaviors and choices of college students suggests both significant and nonsignificant positive effects [48-52]. Despite the burgeoning body of literature on campus food environments, research on the methods used to assess campus food environments and their healthfulness is broadly lacking.

Further investigation is warranted because of the increasing interest in emerging adult health [53], campus food security, and university food environment research [54]. Universities are a unique type of organizational food environment in which they function as a “mini city” [55,56]. Many students, typically first-year students, are required to buy meal plans to obtain food on campus. As a result, these students may be limited to the options available on campus [8]. Such factors set university campuses apart from other consumer food environments and provide a unique setting for understanding its relationship with the dietary behaviors of emerging adults.

Systematic reviews of the broad retail food environment, including vending machines, exist [57-64]. In addition, researchers have conducted systematic reviews of the impact of the campus food environment or food environment interventions on students’ dietary behaviors [65-67]. However, no systematic review has investigated how universities assess their food environments, how “healthy” is defined, and the behavioral and environmental implications of conducting this type of assessment. As a result, there is a need for a concise understanding of the methods currently used to evaluate the healthfulness of university food environments to address

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variations in practices and understand how researchers define "healthy."

Objectives

This paper aimed to describe the protocol for a systematic review of the assessments of university food environments. The review will summarize previously used tools or methods and their implications. Researchers, practitioners, and policymakers can review these tools when determining how to evaluate their campus food environment in the best way. Furthermore, public health nutrition researchers and university administrators can better understand how to look at campus food environments and determine areas for improvement. The systematic review will answer the following questions: (1) How are university food environment assessments conducted? (2) How is "healthy" being defined? What guidelines are researchers using to determine "healthy?"

This systematic review would help researchers assess their campus food environments and may support the development of policies to create healthier university food environments. These actions may positively impact students' dietary behaviors or food choices.

Methods

Registration and Reporting

This protocol was registered with the PROSPERO (International Prospective Register of Systematic Reviews; CRD42023398073), and was prepared following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [68]. The entire systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 guidelines [69].

Eligibility Criteria

Types of Studies

In addition to papers that focus on reporting the development or validation of measures, there are no restrictions on the type of study to allow our research team to capture assessment results that may be included as a component of behavioral or experimental studies. The review may include randomized controlled trials, observational studies, cross-sectional, nonrandomized studies, feasibility and acceptability trials, and other pre-post designs.

Types of Participants

The review will include studies that assess at least 1 aspect of the university food environment, including campus convenience stores, dining halls, quick-service restaurants, and vending machines. In addition, it will include studies examining the perceptions of the food environment from students, university employees, and other campus dining stakeholders.

Types of Interventions

This review is not solely focused on interventional studies. Instead, it will synthesize evidence from peer-reviewed, published literature on the assessments of university food environments over 10 years (between 2012 and 2022).

Comparators

Given the proposed focus on a descriptive summary of existing literature on university food environment assessments, studies with any comparison group and no comparison group are eligible for inclusion.

Types of Outcomes

The proposed review will focus only on assessment methods. Studies were included in the review if there is a tool or method detailed for how data on the campus food environment can be collected and if original research findings were included. Secondary outcomes were the guidelines or standards used to define "healthy" within these assessments (eg, federal guidelines) and any policy recommendations provided as part of the publication (eg, added sugar limits on vending machine products). Studies with no nutritional focus were excluded from the review.

Timing

The date range of published papers to be included in the review is from 2012 to 2022.

Setting

The setting includes all university, college, and campus food environments (ie, public, private, multisite, or unspecified). University medical centers may also be included. The countries of origin were unrestricted.

Language

We will include papers written in the English language.

Exclusion Criteria

Regarding the criteria listed above, papers may be excluded from the review if they do not describe an assessment of the food environment. Dissertations, theses, and conference abstracts without an associated peer-reviewed publication will also be excluded from the final review.

Information Sources

We will search the databases, such as PubMed (NLM), Cochrane Library (Wiley), Web of Science (Clarivate), APA PsycINFO (EBSCO), CINAHL (Cumulative Index to Nursing & Allied Health) Complete (EBSCO), ProQuest Nursing, and Allied Health. We will not have any restrictions when searching the databases. The electronic database searches were supplemented by reviewing the reference list for all included papers and systematic reviews returned with our search results. We will also search the gray literature on Google Scholar by examining the first 10 pages of results yielded from our search.

Search Strategy

Both qualitative and quantitative studies were included in this systematic review search. No study design, date, or language limits were imposed on the search. At the conception of the research question, a librarian (RH) with literature-searching expertise worked to identify appropriate concepts and terminology for the research question. Our team identified 3 main areas for the search, such as food choice and eating behaviors, food environment and caloric information, and the college environment. A variety of terms were included for each

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concept. For food choice and environments, meal behavior, food choice, and purchasing behaviors were some of the included terms. For the concept of the food environment, a sample of included terms were meal plans, nutrition information, and food access. The college environment search included terminology such as university, college, and postsecondary. Subject term and keyword searching were applied to all searches when appropriate, depending on the database being used. The database search strategies can be found in Table S1 in Multimedia Appendix 1.

In addition, spelling variations, phrase searching, and truncation were applied to allow for a comprehensive search. The librarian (RH) conducted an initial search in November 2022, for the team to review and refine the search. All library database searches were completed in January 2023. The Google Scholar search was completed in July 2023, to capture publications that may have been indexed late for 2022.

Data Management

Literature search results were uploaded to Covidence, an internet-based software program for systematic reviews [70]. The team used Covidence for the screening and full-text review process. At each stage, a team discussion occurred to review and revise the criteria as needed.

In total, 2 review authors (SF and LA) independently screened the titles and abstracts in Covidence to determine if they meet the inclusion criteria. A third author (AD) resolved any conflicts that arose during the screening process. Next, the papers that met the inclusion criteria were downloaded for review. Then, all reviewing authors (AD, SF, and LA) first independently reviewed 6 papers and discussed the rationale for inclusion or exclusion before moving through the full-text review process. Once the full-text review had been completed by 2 authors (SF and LA), a third author (AD) resolve any conflicts through discussion. None of the authors were blind to the journal titles, study authors, or institutions.

Data Extraction

Based on quantitative and qualitative data, this review investigates the types of assessments used to determine the healthfulness of a university food environment. We are examining how assessments have been conducted (eg, observational and focus groups) and how "healthy" is defined or what they are using as a guide (eg, USDA [United States Department of Agriculture] guidelines and menu labeling or best practices). A total of 2 reviewers (SF and LA) extracted the information regarding the paper title, DOI (digital object identifier), author names, year, geographic location, subjects included, setting, assessment type, study design, sample size, sample type, sample characteristics, duration, study objective, primary outcome, secondary outcome, type of assessment, benchmark criteria for "healthy," and summary of findings. A third review author (AD) reviewed the extracted data, and any adjustments or updates recommended were discussed among the reviewers. The data extraction sample tables are provided in Multimedia Appendices 2-4.

Quality Assessment of Included Studies

The Quality Assessment for Diverse Studies (QuADS) tool was used to assess the methodological quality of selected studies (ranked on a scale of 0-3) in each of the areas, such as (1) theoretical or conceptual underpinning to the research, (2) statement of research aims, (3) clear description of the research setting and target population, (4) whether the study design is appropriate to address the stated research aims, (5) appropriate sampling to address the research aims, (6) the rationale for the choice of data collection tools, (7) whether the format and content of data collection tool is appropriate to address the stated research aims, (8) description of data collection procedure, (9) recruitment data provided, (10) justification for analytic method selected, (11) whether the method of analysis was appropriate to answer the research aims, (12) evidence that the research stakeholder have been considered in research design or conduct, and (13) strengths and limitations critically discussed [71]. In total, 2 reviewers (SF and LA) conducted quality assessments, and any discrepancies were brought to a third reviewer (AD) for additional feedback to reach a consensus. Also, these ratings were presented in a table to aid in contextualizing the narrative summary.

Data Synthesis

A summary of findings was provided in narrative and tabular format (Multimedia Appendices 2-4) based on the outcomes reported in the studies reviewed, along with an indication of the quality of the studies resulting from our use of the QuADS tool. Since the methods used to assess university campus food environments are considerably heterogeneous, we will not perform a meta-analysis of outcomes associated with the assessments.

Software Used

Paper screening was completed using Covidence [70]. Data extraction and synthesis were conducted using Google Sheets.

Results

The research protocol was registered with PROSPERO (CRD42023398073) on February 8, 2023. As per the protocol, the initial queries resulting in 4502 total records have been screened by 2 reviewers (SF and LA), with conflicts resolved by a third reviewer (AD). Data extraction and analysis were completed by January 2024. This protocol will lead to a systematic review of findings that offer evidence about existing measurements and opportunities for assessing college food environments. The results may provide researchers and academic institutions with a report of best practices for examining the healthfulness of the organizational food environment. Potential implications include informing policy and programs to improve the overall campus food environment. The results have been disseminated through a peer-reviewed publication in 2024 [72].

Discussion

Principal Findings

The university campus food environment has been identified as a contributing factor to the emergence of an obesogenic

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generation [17,26]. Existing research on university food environments has focused on describing their healthfulness or evaluating population interventions aimed at improving college students' food choices and dietary behaviors [26,27,73,74]. This study is unique in that it will provide a comprehensive picture of tools that have been used in assessing food environments where emerging adults, specifically college students, spend a significant part of their young adult lives. Compared with other review papers that broadly assess the college food environment to understand its implications for young adults' individual dietary behaviors and risk for chronic health outcomes, this study would provide a more nuanced understanding of the tools used for such assessments at an organizational level.

This systematic review will have many significant strengths. First, it will provide a broad spectrum of methodologies for assessing the healthfulness of university food environments, including validated and nonvalidated instruments within and outside the United States. Second, we partnered with an experienced university librarian (RH) to develop a comprehensive search strategy of peer-reviewed and gray literature to identify studies that meet our inclusion criteria. Third, the study also considered all relevant study designs; qualitative and quantitative designs were considered in the inclusion criteria. Studies from different countries and regions were included to provide a global perspective of methods used for university food environment assessments. Fourth, 2 reviewers (SF and LA) were used for every stage of the systematic review, from title screening to data extraction. A third reviewer (AD) resolved conflicts as the review progressed. Finally, the study was registered with PROSPERO and followed the PRISMA protocol for systematic reviews [68].

Despite the many strengths highlighted above, an obvious limitation of the study is the use of an established time frame of publication dates as an inclusion criterion; only papers published between 2012 and 2022 were selected for the data extraction. As a result, papers that have not yet been indexed at the time of our search or more recent papers published with unique methodologies may be excluded. Further, the initial search results indicated that most of the studies included in the systematic review were conducted in developing countries. Thus, the generalizability of the findings may be limited globally.

Conclusions

This review will contribute helpful information to address variation in practice and improve our understanding of how researchers evaluate the campus food environment designed to influence the dietary behaviors of emerging adults. As a result, this systematic review will be informative for a broader and more nuanced understanding of these terms with implications for practice and policy. Finally, we plan to provide wide-ranging consequences or recommendations that would benefit practitioners and researchers in nutrition policy design and evaluation. Notably, there is an opportunity to digitize objective campus food environment assessments to improve the data collection procedures and expand efforts to collect and compare data across institutions [75]. While this review focuses on assessing the food environment offerings, there is an opportunity to develop digital approaches to capture subjective perceptions of college students and food hall patrons [76]. Overall, this systematic review will provide a comprehensive and updated body of evidence that will contribute to designing, implementing, and evaluating interventions to improve the nutritional choices and behaviors of emerging adults, specifically college students.

Acknowledgments

Support for this project was made possible by the UNC Charlotte College of Health and Human Services-Atkins Library Systematic Review Collaboration Pilot program, which provided access to Covidence software to conduct the systematic review.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

AAD, LA, and SF were responsible for conceptualization, methodology, validation, formal analysis, investigation, data curation, writing original draft, and visualization. RH performed the software search. AAD and RH contributed to resources. AAD, LA, SF, and RH conducted the review and editing for the report. AD contributed to supervision, project administration, and funding statement.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the databases included in the review.
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Multimedia Appendix 2
Data extraction for descriptive statistics of articles included in the study.
[DOCX File , 14 KB - resprot_v13i1e54955_app2.docx]

Multimedia Appendix 3
Data extraction for methods or tools used for the assessment of university food environments.
[DOCX File , 14 KB - resprot_v13i1e54955_app3.docx]

Multimedia Appendix 4
Data extraction for healthfulness definitions or benchmarks used in included studies.
[DOCX File , 15 KB - resprot_v13i1e54955_app4.docx]

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Abbreviations

CINAHL: Cumulative Index to Nursing & Allied Health
DOI: digital object identifier
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
QuADS: Quality Assessment for Diverse Studies
SNAP: Supplemental Nutrition Assistance Program
USDA: United States Department of Agriculture

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Protocol

Electroacupuncture and Transcutaneous Electrical Acupoint Stimulation for Perioperative Neurocognitive Disorder in Older Patients Undergoing Cardiac Surgery: Protocol for Systematic Review and Meta-Analysis

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Abstract

Background: Perioperative neurocognitive disorder (PND) is a critical concern for older patients undergoing cardiac surgery, impacting cognitive function and quality of life. Electroacupuncture and transcutaneous electrical acupoint stimulation (TEAS) hold promise for mitigating PND. This protocol outlines a systematic review and meta-analysis to thoroughly assess the efficacy of electroacupuncture and TEAS in older patients undergoing cardiac surgery with PND, providing up-to-date evidence for PND prevention and treatment.

Objective: This study aimed to thoroughly assess the efficacy of electroacupuncture and TEAS in older patients undergoing cardiac surgery with PND, providing up-to-date evidence for PND prevention and treatment.

Methods: A comprehensive and systematic approach will be used to identify eligible studies from a diverse range of electronic databases, including 9 major sources such as PubMed (NLM) and Cochrane (Wiley), as well as 2 clinical trial registration websites. These studies will focus on investigating the effects of electroacupuncture and TEAS on PND in older patients undergoing cardiac surgery. The study selection will adhere to the criteria outlined in the patient, intervention, comparison, outcome, and studies (PICOS) format. Data extraction will be carried out by 2 independent researchers (YP and LS), using established tools to evaluate the risk of bias. The primary outcome will be PND incidence, with secondary outcomes including Mini Mental State Examination scores, neuron-specific enolase, S100β, interleukin-1β, interleukin-6, tumor necrosis factor-α, time to first flatus, first defecation, bowel sound recovery, and hospitalization duration to be selectively reported. Adverse events linked to acupuncture, such as bleeding, needle site pain, and local reactions, rather than serious adverse events, will also be considered. Meta-analysis will be performed using appropriate statistical methods to assess the overall effect of electroacupuncture and TEAS on PND prevention, treatment, or other relevant outcomes. The Cochrane Collaboration Risk of Bias tool will be used for assessment, and data synthesis will be executed using the RevMan 5.4 software (Cochrane).

Results: We plan to summarize the eligible studies through the use of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. The findings will be showcased in the form of a summary table of evidence. Figures and forest plots will be used to illustrate the outcomes of the meta-analysis.

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Conclusions: The impacts of electroacupuncture and TEAS interventions on PND in older patients undergoing cardiac surgery have not yet been established. This protocol addresses a critical gap by thoroughly assessing electroacupuncture and TEAS for PND in older patients undergoing cardiac surgery, enhancing understanding of nonpharmacological interventions, and guiding future research and clinical practices in this field. Its strength lies in rigorous methodology, including comprehensive search strategies, independent review processes, and thorough assessments of the risk of bias.

Trial Registration: PROSPERO CRD42023411927; https://tinyurl.com/39xdz6jb

International Registered Report Identifier (IRRID): PRR1-10.2196/55996

(JMIR Res Protoc 2024;13:e55996) doi:10.2196/55996

KEYWORDS

perioperative neurocognitive disorder; cardiac surgery; elderly patients; systematic review; meta-analysis

Introduction

Perioperative Neurocognitive Disorder

Perioperative Neurocognitive Disorder (PND) remains a significant concern in the context of cardiac surgery [1]. PND encompasses a spectrum of cognitive deficits that manifest during the perioperative period, ranging from mild cognitive impairment to delirium and overt dementia [2]. These deficits impact a range of cognitive areas, encompassing memory, concentration, executive skills, and language abilities [3,4]. The manifestation of these impairments becomes evident in the aftermath of surgery [5], typically peaking within the initial postoperative week and occasionally enduring for an extended duration [3,6]. These cognitive changes carry substantial implications for patients' quality of life, functional independence, health care expenditure, and postoperative outcomes [7-9].

PND in Older Patients Undergoing Cardiac Surgery

The relationship between PND and older patients undergoing cardiac surgery is of particular interest, given the vulnerability of this population to cognitive decline [10,11]. As the worldwide population ages and surgical methods and anesthetic practices advance, the volume of individuals undergoing cardiac surgery is on the rise, prompting a greater focus on enhancing their perioperative management. The exact pathophysiological mechanisms of PND are multifactorial and complex, remaining elusive. Factors such as age-related physiological changes, surgical anesthesia stress, increased susceptibility to inflammation, and potential pre-existing cognitive deficits may render older patients more susceptible to PND [12-19]. Furthermore, cardiac surgery introduces potential risks of neurocognitive complications due to cardiopulmonary bypass and associated factors [20,21]. Epidemiological studies have indicated that the occurrence rates of PND in older individuals undergoing cardiac surgery vary between 25% and 50% [22-25]. This wide variability underscores the complexity of PND's etiology and the need for comprehensive investigation and intervention strategies [26].

Related Management Methods of PND

Current conventional approaches for managing PND primarily focus on mitigating risk factors through neuroprotective agents, refined anesthesia management, and inflammation minimization [16,27]. Nevertheless, these strategies have limitations in preventing PND occurrence or effectively treating established cases, and many medications exhibit side effects, falling short of addressing the disorder's multifaceted nature and potential adverse effects [28]. To bridge these gaps in the treatment landscape, exploring alternative or supplementary therapeutic interventions targeting PND's multifaceted nature is compelling to attenuate cognitive decline. Among emerging alternative approaches, acupuncture has garnered attention as a potentially promising intervention for PND. Rooted in traditional Chinese medicine, acupuncture is suggested to offer advantages such as modulating neuroinflammation, enhancing cerebral perfusion, and promoting neural plasticity [29-35]. Furthermore, acupuncture's favorable safety profile aligns with the older adult population's increased susceptibility to pharmacological agents' adverse effects [36]. Particularly, electroacupuncture and transcutaneous electrical acupoint stimulation (TEAS), involving noninvasive application of electrical currents to modulate neural activity, hold promise as nonpharmacological interventions that may prevent or ameliorate cognitive decline. The results of a randomized controlled trial (RCT) revealed that the acupuncture group exhibited a shorter time to first remission of delirium and a significantly higher number of delirium-free days compared with the standard treatment group in the treatment of older patients with delirium, with no observed adverse safety events [37].

Limitations of Previous Studies

While previous studies have explored various interventions for PND, previous meta-analyses have primarily focused on the overall population without distinguishing between surgical types, resulting in considerable heterogeneity [38,39]. Currently, there is a recognized gap in the literature regarding the impact of electroacupuncture and TEAS, specifically on PND in older patients undergoing cardiac surgery, with no systematic reviews or meta-analyses available. A previous meta-analysis included 18 RCTs to evaluate the impact of TEAS on cognitive function in older individuals after general anesthesia. Despite this effort, it was not possible to analyze the incidence of postoperative delirium due to the limited number of original studies and poor methodology [40]. In 2021, a review of 16 RCTs involving 1241 patients suggested that acupuncture appears to be a promising adjunct intervention for the treatment and prevention of postoperative cognitive dysfunction. However, the evidence is insufficient and has limitations [41]. Another systematic review and meta-analysis in 2023 included 12 studies with a total of 1058 patients to explore the use of acupuncture-related

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techniques in treating postoperative cognitive complications. Nonetheless, the enrolled studies varied in surgical types, and no definitive conclusions could be drawn [42]. Consequently, the acupuncture research landscape for PND remains intricate with varied study methodologies, inconsistent intervention protocols, and divergent outcome measures contributing to fragmented evidence, lacking a comprehensive synthesis. The curative effect of acupuncture on PND remains controversial, and the optimal acupuncture regimen for preventing or treating PND is unclear.

Aims

Given the gaps in knowledge and potential implications for clinical practice, this systematic review and meta-analysis protocol aims to consolidate current research findings on electroacupuncture and TEAS interventions' potential effectiveness in preventing or ameliorating PND in older patients undergoing cardiac surgery. By synthesizing available evidence, we endeavor to provide a comprehensive overview of the existing literature, identify key research gaps, and offer insights into potential mechanisms. Specifically, our objective is to offer a comprehensive perspective by comparing treatment outcomes and phenomena associated with acupuncture and addressing the questions, such as (1) what is the impact of electroacupuncture and TEAS on the incidence and severity of PND in older patients undergoing cardiac surgery? (2) What are the effects of electroacupuncture and TEAS on serum biomarkers in older patients undergoing cardiac surgery? Through addressing current knowledge gaps, these insights have the potential to inform clinical practice, clarify controversies, and shape future research endeavors. In addition, they contribute to the development of evidence-based strategies aiming to optimize perioperative care for older patients undergoing cardiac surgery, ultimately leading to improvements in postoperative cognitive outcomes.

Methods

Study Registration

The meta-analysis protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews; registration CRD42023411927). In addition, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol guidelines have been used to report this protocol (Multimedia Appendix 1) [43]. Our systematic review will be conducted following the guidelines outlined in the Cochrane Collaboration Handbook [44], and we will ensure transparency in reporting by adhering to the PRISMA 2020 guidelines [45].

Study Design

We intend to incorporate a range of study designs, such as RCTs, quasi-experimental approaches, and prospective cohort studies, as well as controlled clinical trials, that assess the effectiveness and safety of electroacupuncture and TEAS in PND in older patients undergoing cardiac surgery [46].

Type of Participants

Incorporating patients who are 60 years of age or older, this study endeavors to investigate the inclusion of individuals scheduled for elective cardiac surgery, ensuring that they do not exhibit any preexisting neurocognitive disorders. It is worth noting that participants' eligibility will not be restricted by factors such as gender, race, surgical history, or underlying medical conditions.

Type of Intervention

The treatment groups will undergo electroacupuncture and TEAS therapies. The study will not impose any limitations on the sample size, intervention duration, perioperative care, or the underlying treatment modalities used. This inclusivity will facilitate a comprehensive exploration of the treatment's efficacy.

Type of Control Groups

To provide a comparative framework, the control groups may encompass a range of approaches. These include the application of general anesthesia as part of conventional care, sham acupuncture, as well as pharmacotherapy involving Western medicine. It is crucial to note that interventions deviating from these specified approaches will be excluded from the comparator groups, ensuring a coherent and consistent comparison.

Types of Outcome Measures

To assess the impact of the chosen interventions, a comprehensive set of outcomes has been strategically determined. Primary outcomes will focus on evaluating the incidence of PND. Emphasizing the significance of a comprehensive evaluation, a host of secondary outcomes will be collected and subjected to meticulous analysis. These encompass evaluating neurocognitive function through the use of Mini Mental State Examination (MMSE) scores, alongside measuring serum levels of neuron-specific enolase, S100β, interleukin-1β, interleukin-6, and tumor necrosis factor-α. In addition, vital secondary outcomes include evaluating the time to first flatus, first defecation, bowel sound recovery, and the duration of hospitalization. It is crucial to highlight that adverse events associated with acupuncture, such as bleeding, needle site pain, and other localized reactions will be documented and analyzed, while serious adverse events will be addressed separately [47].

Search Strategy

To perform a thorough review of the literature, we have formulated an expansive search approach, encompassing the exploration of 9 distinct databases, specifically PubMed (NLM), Embase (Elsevier), Cochrane Library (Wiley), Web of Science (Clarivate), Scopus (Elsevier), China National Knowledge Infrastructure (Tongfang Knowledge Network Technology), Chinese Biomedical Literature Database (SinoMed), Wan Fang Database, and VIP Database. In addition, 2 registered websites [48,49] will also be explored. To maximize the scope of the review, reference lists from relevant articles will be manually examined. Importantly, there will be no limitations placed on the publication status, source country, or publication year. To ensure a comprehensive search, a predefined list of search terms, including "electroacupuncture," "TEAS," "PND," 'cardiac surgery," "elderly," and "RCTs," will be used in combination with the subject words unique to each database [50]. Notably, the comprehensive search approach used within PubMed can

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be found in Table 1, with specific search strategies tailored for individual databases accessible in the Multimedia Appendix 2. To further enhance this comprehensive approach, additional sources, such as dissertations, conference papers, gray literature, and unpublished research from relevant entities, will also be assessed and advice will be sought from experts in acupuncture and cardiac surgery. To streamline this process, EndNote 20 (Clarivate) will be used to manage the literature and eliminate any duplicate studies. In order to uphold research integrity, the eligibility of studies will be independently screened and evaluated by 2 researchers, YP and LS. Any disagreements will be resolved through deliberation with other members of the research team. Both Chinese and English language studies will be retrieved and considered in this study. The manuscript screening process is shown in Figure 1.

Table 1. The search strategy for PubMed.

Order	Strategy
#1	"Postoperative Cognitive Complications" [MeSH[a]]
#2	""postoperative delirium" [MeSH]
#3	""perioperative neurocognitive disorder" [Title/Abstract]
#4	""cognit*[b]" [Title/Abstract] OR "cognition disorder" [Title/Abstract] OR ""cognition impairment" [Title/Abstract] OR ""cognition decline" [Title/Abstract] OR "cognitive dysfunction" [Title/Abstract] OR ""cognitive function" [Title/Abstract] OR "delirium" [Title/Abstract] OR "neurocognitive disorder" [Title/Abstract]
#5	"postop*[b]" [Title/Abstract] OR "postoperative*[b]" [Title/Abstract] OR ""postoperative" [Title/Abstract] OR "postoperative period" [Title/Abstract]
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	"acupuncture" [MeSH Terms] OR "acupuncture therapy" [MeSH Terms] OR "acupuncture therapy" [MeSH Terms] OR "electroacupuncture" [MeSH Terms]
#9	"Acupuncture" [Title/Abstract] OR "Electroacupuncture" [Title/Abstract] OR "EA[c]" [Title/Abstract] OR "transcutaneous electrical acupoint stimulation" [Title/Abstract] OR "TEAS[d]" [Title/Abstract]
#10	#8 OR #9
#11	((((((((((Thoracic Surgery [MeSH Terms]) OR (Cardiac Surgical Procedures [MeSH Terms])) OR (Surgery, Thoracic)) OR (Surgery, Cardiac)) OR (Surgery, Heart)) OR (Heart Surgery)) OR (Cardiac Surgery)) OR (Procedure*[b], Cardiac Surgical)) OR (Surgical Procedure*[b], Cardiac)) OR (Surgical Procedure*[b], Heart)) OR (Cardiac Surgical Procedure*[b])) OR (Heart Surgical Procedure*[b])) OR (Procedure*[b], Heart Surgical)
#12	elderly OR older OR geriatric
#13	#7 AND #10 AND #11 AND #12

[a]MeSH: Medical Subject Headings.

[b]*: special character that represents zero or more characters in wildcard searching.

[c]EA: electroacupuncture.

[d]TEAS: transcutaneous electrical acupoint stimulation.

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Figure 1. PRISMA flow diagram of study identification and selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses [43].

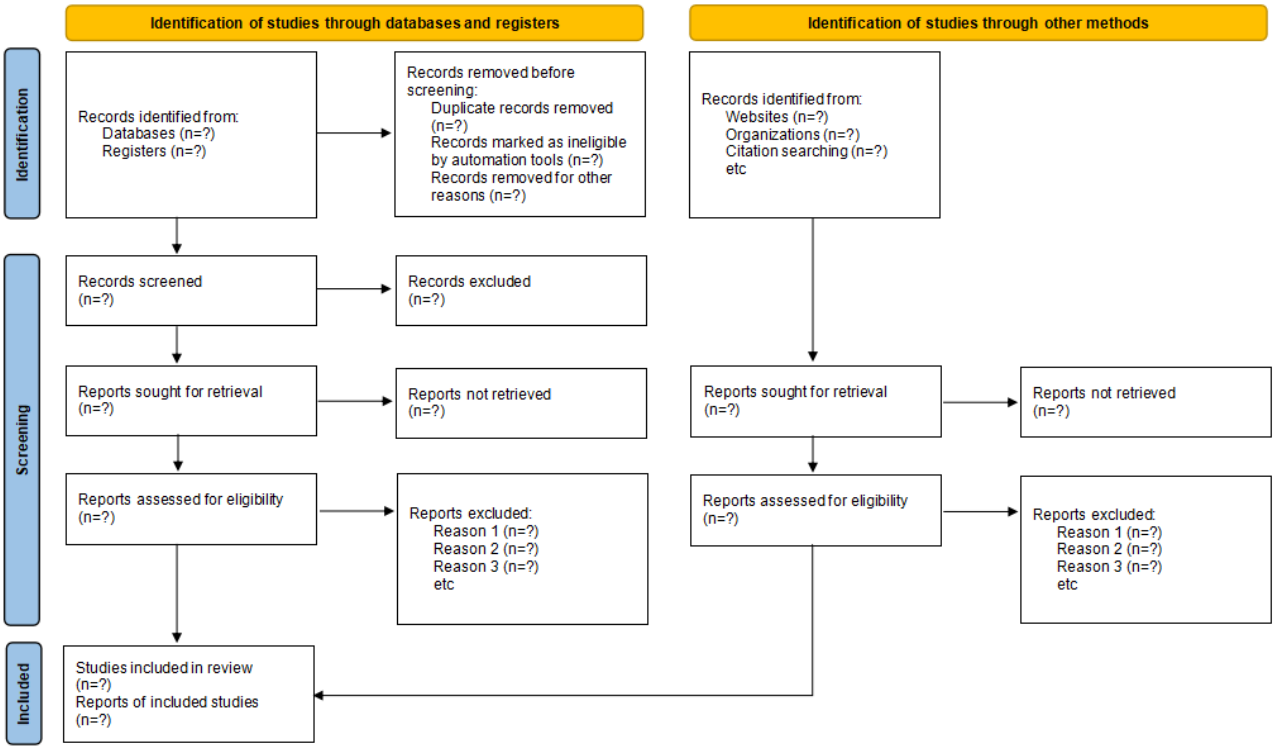

Inclusion and Exclusion Criteria

The criteria for inclusion in this review were established following the patient, intervention, comparison, outcome, and studies (PICOS) framework (Textbox 1). There were no language restrictions and the publication date considered was up to June 15, 2024.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- The study's target population comprises older individuals (aged 65 years or older) undergoing cardiac surgery. These patients may exhibit a range of cardiac conditions necessitating surgical procedures, including coronary artery bypass grafting, valve replacement, or a combination of interventions.
- The primary intervention of interest is electroacupuncture or transcutaneous electrical acupoint stimulation (TEAS). Studies using either of these interventions as a therapeutic modality in the perioperative period will be considered. The interventions may involve varying frequencies, intensity, waveform, durations, and acupoint selections. Research that involves other forms of acupuncture or nonacupuncture interventions will be excluded unless they are used within the context of a comparative group.
- Eligible studies will encompass those incorporating an appropriate comparative group. This may involve sham or placebo interventions, standard care lacking any electroacupuncture and TEAS application, or alternative interventions designed to mitigate perioperative neurocognitive disorder. Studies comparing different forms of electroacupuncture and TEAS protocols will also be considered, including studies comparing different frequencies, intensities, waveforms, acupoints, or durations of electroacupuncture and TEAS interventions.
- Primary outcome: incidence of perioperative neurocognitive disorder. Secondary outcomes: the Mini Mental State Examination scores, neuron-specific enolase, S100β, interleukin-1β, interleukin-6, and tumor necrosis factor-α, time to first flatus, first defecation, bowel sound recovery, and duration of hospitalization will be selectively reported. Adverse incidents linked to acupuncture, such as bleeding, discomfort at needle insertion sites, and local reactions, will be considered, with a focus on non-serious adverse events.
- The eligible studies will encompass randomized controlled trials, quasi-experimental designs, prospective cohort studies, as well as controlled clinical trials.

Exclusion criteria:

- Research focusing on patients who are not older adults (aged <65 years) or those undergoing surgeries unrelated to cardiac procedures.
- Studies lacking proper cognitive assessment as an outcome measure.
- Studies involving animals, retrospective investigations, case reports, commentaries, literature reviews, duplicate publications, and articles with unavailable full text.
- Studies where electroacupuncture and TEAS is combined with other interventions that cannot be adequately isolated for analysis.

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Data Extraction and Risk of Bias Assessment

The extraction of data will be carried out independently by 2 researchers (YP and LS). Throughout the process, any differences will be resolved through discussion or by involving another researcher (KW). The essential data extracted from the papers include the author's name, publication year, country, sample size, gender distribution, age distribution, disease duration, treatment duration, intervention details, and study outcomes. The inclusion or exclusion of electroacupuncture and TEAS interventions in each article will be itemized meticulously in accordance with the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) checklist [51,52]. A predesigned data collection form will be used to conduct data extraction for each study, with a prime focus on extracting the PICOS components and funding details.

A total of 2 evaluators (YP and LS) will individually evaluate potential biases in each study by applying the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions. Any discrepancies will be resolved through constructive dialogue or by enlisting the participation of another author (KW). We will assess the literature's quality using the "bias risk assessment tool" recommended by the Cochrane Collaboration. The bias risk will be documented in a table, where high risk will be indicated in red, low risk in green, and uncertain risk in yellow. We will add annotations to the tables to supplement information about the risk of bias and unpublished data sources obtained by contacting trial authors. Each item in the risk of bias assessment will be considered independently without assigning an overall score. We will consider the potential impact of bias in each study when assessing the effectiveness of the treatment, as it could affect the results.

Data Synthesis and Analysis

We will use RevMan 5.4 software to conduct the meta-analysis and generate the risk of bias graph. For binary data, we will use risk ratios and Mantel-Haenszel tests, along with a 95% CI analysis. Continuous variables will be represented as the mean difference, effect value, and 95% CI. In cases where outcome measures vary across studies, the mean SD will be used. To assess statistical heterogeneity, we will perform tests including the I^2 statistic, which ranges from 0% to 100%. Statistical heterogeneity will be evaluated using the standard chi-square test (α=.1) and the I^2 test [53]. If $I^2 \leq 50\%$, the fixed-effects model will be used. If $I^2 > 50\%$, the random-effects model will be applied [54]. In instances of conspicuous clinical heterogeneity, the random-effects model will be used. The forest plots will display the results of the meta-analysis, where a P less than .05 indicates statistical significance. If a study is not amenable to quantitative synthesis, a descriptive analysis will be conducted and presented using a summary table.

Management of Missing Data

Efforts will be made to reach out to the primary author or corresponding author of the initial publication for the acquisition of any absent or inadequate data. In cases where such data cannot be obtained, an examination of the available data will be performed.

Subgroup and Sensitivity Analyses

If excessive heterogeneity is observed, we will conduct grouping and sensitivity analyses to investigate the potential sources of major inconsistencies or heterogeneity. Subgroup analysis will be performed based on different types of acupuncture and PND. The type of acupuncture, surgical methods, anesthesia, and other complicating factors will be analyzed if there are a sufficient number of studies and a variety of regimens are used [47]. During the sensitivity analysis, certain trials will be omitted to pinpoint potential origins of bias and evaluate the uniformity of the meta-analysis findings. Specifically, studies that did not report an intention-to-treat analysis, experienced high rates of participant dropout, or had other missing data will be excluded [55]. In addition, sensitivity analysis will be performed to evaluate the potential influence of any missing data on the outcomes.

Evaluation of Publication Bias

In cases where there are more than 10 studies included for each outcome, we will use funnel plots generated in RevMan to visually assess the presence of publication bias and assess the quality of evidence.

Grading of Recommendations Assessment, Development, and Evaluation Quality of Evidence

We will use the Grading of Recommendations Assessment, Development, and Evaluation criteria to rank the quality of evidence. We will then evaluate the level of evidence and strength of recommendations for the outcomes under consideration. The levels of evidence certainty encompass 4 categories, that are "high," "moderate," "low," or "very low." These categories signify the degree of confidence in the effect estimate, with "high certainty" denoting a robust level of confidence and "very low certainty" indicating minimal confidence [56]. Confidence levels may be adjusted based on considerations such as risk of bias, imprecision, inconsistency, indirectness, or publication bias. Since only RCTs will be included in the review, reasons for updating the study (eg, large effects, dose-response relationships, and confounders) do not apply [57].

Sample Size Evaluation

Trial sequential analysis (TSA) will be used for sample size estimation in systematic reviews or meta-analyses. TSA overcomes the limitations of classical systematic reviews or meta-analyses [58]. It reduces the occurrence of incorrect positive outcomes resulting from random errors in situations where the number of cases included in a meta-analysis is insufficient. TSA refers to the required information size, which denotes the minimum number of cases necessary to achieve statistically significant distinctions in a meta-analysis. Generally, the sample size requisite for meta-analysis is regarded as no smaller than what is needed for a properly designed and statistically robust individual RCT. In this study, the TSA program version 0.9.5.10 Beta (Copenhagen Trial Unit) will be used to control the risks of type I and type II errors by estimating RIS (required information size) and monitoring testing sequences [59].

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Patient and Public Involvement

The design, execution, reporting, and dissemination plans of this research will not involve the participation of patients and the public, given the nature of the systematic review and meta-analysis. Nevertheless, upon completion of the research, our findings will be disseminated and shared through peer-reviewed journals, conferences, and seminars focusing on the care and treatment of older patients undergoing surgery.

Ethical Considerations

Ethical clearance is not required for this systematic review, as it relies on previously published data. Because no original data will be collected, this study does not require ethical approval. The results will be presented at conferences and published in journals with peer review.

Validity, Reliability, and Rigor

Our systematic review will present findings in accordance with the best practice PRISMA guidelines, and meta-analyses will be carried out using a random-effects meta-analytic approach, as recommended for synthesizing study outcomes [60].

Amendments

The protocol for this systematic review will be amended when necessary.

Results

The results of this study will be presented at conferences and published in journals with peer review. We will maintain regular updates to our searches across all databases every 2 months to incorporate any newly available data into the systematic review.

Discussion

Hypothesized

Due to increasing cardiovascular issues, there is a growing demand for cardiac surgeries [61]. In accordance with traditional Chinese medical principles, which emphasize the interconnectedness of the heart and the brain, it is suggested that the "heart and brain co-govern spirit," wherein the spirit encompasses both the nervous system and mental faculties. Consequently, patients with cardiac surgery are more susceptible to cognitive impairment [62,63]. Research has indicated that reduced cardiac ejection fraction can activate the autonomic nervous system, elevate catecholamine and endothelin levels, disrupt cerebral autoregulation, and subsequently cause insufficient cerebral perfusion, diminished cerebral blood flow, damage to nerve cells, onset of cognitive deficiencies, and changes in mental conditions. These factors align with some of the underlying factors associated with acupuncture [64]. Our study hypothesizes that electroacupuncture and TEAS can significantly reduce the incidence of PND in older patients undergoing cardiac surgery.

Potential Effect of Acupuncture on PND

To date, no interventions are offering a complete cure for PND, and common pharmacotherapies may pose challenges due to patient compliance and potential adverse reactions [65,66]. Measures aimed at enhancing patients' understanding and acceptance of the disease and its treatment, such as electroacupuncture and TEAS, have gained prominence in recent years. These simple, convenient, cost-effective, and safe modalities empower patients to proactively monitor and manage PND. The empirical use of acupuncture in treating cognitive impairments spans millennia [28]. Previous research suggests that acupuncture may serve as an effective adjunctive therapy for neurological conditions such as depressive symptoms [67], mild cognitive impairment [68], poststroke cognitive impairment [69,70], vascular dementia [71], schizophrenia [72] and Alzheimer disease [73]. Electroacupuncture and TEAS represent novel acupuncture therapies that combine electrical stimulation with acupuncture point stimulation. As nonpharmacological interventions, they offer advantages such as there are no drug-related side effects and minimal invasiveness, making them widely used in clinical practice, especially in perioperative management [74-76]. Numerous emerging trials presently demonstrate the clinical efficacy of electroacupuncture and TEAS in managing PND [38,39,68,77]. Currently, theories related to the pathogenesis of PND include central inflammatory responses, reduced central cholinergic system function, synaptic dysfunction, abnormal protein function, and disturbances in gut microbiota [78,79]. Among these, the central inflammatory response mechanism is of particular concern [80-82]. Early studies have suggested that electroacupuncture and TEAS can alleviate both central and peripheral inflammatory responses, inhibit microglial cell activation, suppress neuronal apoptosis, and provide significant neuroprotection through various pathways, thereby delaying the pathological progression of PND [83,84]. Furthermore, numerous emerging trials have also demonstrated that adjunctive use of electroacupuncture and TEAS in the perioperative period has regulatory effects on the gastrointestinal system, improves circulation, reduces anesthesia requirements, enhances immunity, decreases inflammation, and alleviates stress. This leads to shorter patient recovery and hospitalization times, ultimately improving patient quality of life and indicating the potential efficacy of electroacupuncture and TEAS in treating PND [85,86]. Regrettably, despite certain systematic reviews having assessed the effectiveness of electroacupuncture and TEAS-related approaches in PND management, these reviews invariably manifest limitations encompassing diversities in terms of race, age, gender, intervention methodologies, and acupuncture treatment protocols. Such diversification might engender heightened clinical and statistical heterogeneity [87]. In addition, some of the earlier studies lacked standardized protocols for assessing PND, leading to inconsistencies in the definition and diagnosis of the condition. These constraints have posed challenges in developing an extensive comprehension of the efficacy of approaches such as electroacupuncture and TEAS in preventing or mitigating PND. Therefore, as of the present, no compelling evidence has materialized, thereby limiting the applicability of acupuncture.

Outcome Indicator Selection Reasons

In light of the limitations in previous research, our meta-analysis concentrates on a specific aspect—the impact of electroacupuncture and TEAS on PND in older patients

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undergoing cardiac surgery. By narrowing our scope to this particular intervention and patient population, we aimed to provide a more comprehensive and normative approach to evaluating the evidence for electroacupuncture and TEAS in preventing or treating PND. This approach allows for a more homogeneous pool of studies, which enhances the comparability and generalizability of our findings. The primary outcome measure (ie, the incidence of PND), was chosen as it represents the most direct and fundamental outcome of cognitive dysfunction postcardiac surgery. It facilitates an assessment of whether electroacupuncture and TEAS have the potential to reduce the risk of cognitive impairment. The inclusion of the MMSE as a secondary outcome measurement is motivated by its widespread use as a highly sensitive, standardized, and reliable tool for assessing cognitive function. MMSE scores will enable a detailed examination of specific cognitive domains, allowing for a more nuanced analysis of the impact of electroacupuncture and TEAS on cognitive performance. Neurobiological markers such as neuron-specific enolase, S100β, and proinflammatory cytokines including interleukin-1β, interleukin-6, and tumor necrosis factor-α are selected as secondary outcomes to explore the potential mechanisms underlying observed cognitive effects. Monitoring these biomarkers will provide insights into the neuroinflammatory response and neuronal damage associated with PND, helping to elucidate the pathways through which electroacupuncture and TEAS may exert their influence. In addition to cognitive outcomes, we are also attentive to impacts on certain clinical manifestations, with gastrointestinal function being a crucial aspect of overall recovery after cardiac surgery. This study will assess postoperative parameters of gastrointestinal recovery, including the first flatus time, the first defecation time, and the recovery of bowel sounds. Electroacupuncture and TEAS are considered to potentially accelerate intestinal function recovery through their effects on the neuroendocrine and autonomic nervous systems, thereby influencing these indicators. These measures offer a comprehensive perspective on the impact of acupuncture-based interventions on postoperative physiological recovery, potentially influencing patient comfort and overall surgical outcomes. Furthermore, prolonged hospitalization is associated with increased medical costs and potential complications. Evaluating the impact of electroacupuncture and TEAS on the length of hospital stay provides valuable insights into the overall recovery trajectory and cost-effectiveness of the intervention. To summarize, the selection of these primary and secondary outcome measures was driven by the need to capture a holistic picture of the intervention's multifaceted impact on cognitive function, neuroprotection, inflammatory response, and overall postoperative recovery in older patients undergoing cardiac surgery. These outcomes collectively aim to contribute to the existing knowledge base, provide scientific information for clinical practice, and potentially improve patient outcomes in this vulnerable population.

Implications and Conclusions

If our meta-analysis can demonstrate the effectiveness of electroacupuncture and TEAS in preventing or ameliorating PND in older patients undergoing cardiac surgery, its significance will be profound. Firstly, patients undergoing cardiac surgery might experience better cognitive results and an improved quality of life postoperatively. This finding offers significant hope for older patients who are particularly prone to PND. Frontline health care providers, including cardiac surgeons and anesthesiologists, can benefit from our research results by considering the inclusion of electroacupuncture and TEAS in their perioperative care protocols. This may result in enhanced patient results, diminished health care expenses linked to the treatment of complications related to PND, and increased patient contentment. In addition, our research may inspire additional exploration in the realm of safeguarding cognitive function during the perioperative period. It may encourage researchers to explore other complementary interventions, refine protocols, and conduct RCTs to establish causality and optimize clinical practices. In conclusion, our meta-analysis represents a critical step toward addressing the limitations of previous research on PND in older patients undergoing cardiac surgery.

Limitations

It is essential to acknowledge the limitations of the proposed systematic review and meta-analysis. Variability in acupoint selection and the heterogeneity of cardiac surgical procedures may introduce challenges in synthesizing the evidence. In addition, publication bias and the quality of included studies may impact the robustness of the conclusions drawn. Building upon the results of this protocol, future research avenues could explore the optimal timing, duration, and frequency of electroacupuncture and TEAS interventions. Moreover, investigating the mechanisms underlying the observed effects may provide valuable insights into the neurobiological processes influenced by acupuncture-based therapies. To conclude, by focusing on electroacupuncture and TEAS and adopting a more standardized approach, we hope to contribute valuable insights for clinicians and researchers, positioning acupuncture as a viable treatment option for PND. This, in turn, can provide better choices for patient management and guide future research efforts to improve perioperative cognitive outcomes.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors directly participated in this study. Conceptualization was performed by KW and JZ, methodology was performed by XW, systematic review registration was contributed by YP and LS, quality assessment was done by YP and XW, and manuscript writing was contributed by YP, XW, and LS. All authors have read and agreed to the published version of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist.
[DOCX File , 30 KB - resprot_v13i1e55996_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 36 KB - resprot_v13i1e55996_app2.docx]

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Abbreviations

MMSE: Mini Mental State Examination
PICOS: patient, intervention, comparison, outcome, and studies
PND: Perioperative Neurocognitive Disorder
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
TEAS: transcutaneous electrical acupoint stimulation
TSA: trial sequential analysis

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Protocol

Impact of Biological Sex on Emotional Perception Among Adults With Schizophrenia Spectrum Disorders: Protocol for a Systematic Review

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Abstract

Background: It is well established that individuals with schizophrenia experience deficits in emotional perception that can impact long-term social and occupational functioning. Understanding the factors that impact these impairments is important for targeting interventions to improve recovery. In the general population, compared with males, females tend to show greater perception of emotions. Whether this sex difference persists in schizophrenia is less clear. In contrast to males, females diagnosed with schizophrenia tend to have a higher age of disease onset and better premorbid functioning but do not necessarily have better outcomes. Effective treatments for social cognitive impairments are highly relevant to long-term functional rehabilitation. A greater understanding of the cognitive deficits in emotional perception within females and males living with schizophrenia may assist interventions to be better tailored to individuals.

Objective: This systematic review aims to collate, synthesize, and critically appraise evidence considering the influence of biological sex (female and male) on the emotional perception of individuals with schizophrenia.

Methods: This is a systematic review protocol based on the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. The electronic databases MEDLINE, Embase, CENTRAL, CINAHL, and PsycINFO will be systematically searched. To be included in this review, studies must compare the emotional perceptions of male and female participants older than 18 years who have a primary diagnosis of a schizophrenia spectrum disorder. Qualitative studies, case reports, case series, unpublished manuscripts, and studies not reported in English will be excluded. Key search strategies will include combinations of the following terms: “men,” “male,” “man,” “female,” “women,” “woman,” “sex,” “gender,” “emotional perception,” “emotional processing,” “schizophrenia,” “schizophren,” “psychotic disorders,” “psychosis,” “psychoses,” “psychotic,” “schizoaffective,” “schizotypal personality disorder,” and “schizotyp.” Identified studies will be uploaded to the web-based Covidence systematic review management software. The risk of bias for individual studies will be assessed using the relevant Joanna Briggs Institute checklist tools. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will also be used to evaluate the strength of the evidence base. Findings will be synthesized to provide a systematic summary of the existing literature. If sufficiently comparable data to permit meta-analysis emerges, a random-effects meta-analysis will be performed.

Results: This systematic review was registered with the PROSPERO (International Prospective Register of Systematic Reviews) in October 2023. The search and screening of study titles and abstracts are currently underway. Data are expected to be extracted and analyzed in July 2024.

Conclusions: Results will contribute to an improved understanding of the social cognitive profiles of males and females with schizophrenia. This knowledge is expected to inform the adaptation of interventions to improve functional outcomes.

Trial Registration: PROSPERO CRD42023463561; https://tinyurl.com/34sr3rnf

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KEYWORDS

schizophrenia; emotional perception; systematic review; sex differences; psychosis; social cognition; emotional processing

Introduction

Schizophrenia spectrum disorders (SSDs) are estimated to affect 24 million (or 1 in 300) people globally [1]. Overall mortality rates for people with schizophrenia are 3 times greater than for the general population [2], with life expectancy reduced by an average of 14.5 years [3]. These disorders are characterized by both positive (ie, hallucinations, delusions, and disorganized thoughts and behavior) and negative (ie, reduced speech and emotional expression, social withdrawal, and anhedonia) symptoms [4], which can contribute to significant distress and functional impairment across multiple life domains. Deficits in cognition are also a key feature of SSD, and their presence is predictive of poor functional outcomes [5,6]. Current pharmacological treatments have relative success in reducing positive psychiatric symptoms; however, they have limited capacity to target cognitive impairments [7,8]. These cognitive deficits extend not only to neurocognitive domains (eg, memory and attention) but also to social cognitive processes (ie, those involved in social interactions) [9-12]. In particular, it is well established that individuals with SSD have problems with emotional perception [13], the mental operations involved in the ability to understand and recognize the emotions of others [9].

There is strong evidence that individuals with schizophrenia perform significantly worse on tasks of emotional perception when compared with healthy individuals [13,14]. These deficits have been found to persist across different stages of the illness, worsen with the number of psychotic episodes, and be present in those at risk of developing schizophrenia [15-17]. It is noteworthy that previous meta-analyses of emotional perception in schizophrenia have tended to focus on facial emotion perception (FEP) [14]. This is unsurprising given that emotional perception is often conceptualized as the information conveyed in facial expressions. However, it can include other nonverbal (eg, body posture, movement, and physical touch) and verbal communication cues (eg, speech rate, vocal pitch, and voice intensity) [18]. Meta-analyses that have looked at the recognition of emotional perception in speech [19,20] have demonstrated significant deficits in individuals with schizophrenia, suggesting that emotional perception impairments extend across both verbal and nonverbal channels of communication. These impairments in emotional perception mean that individuals with schizophrenia can find adjusting and responding to social situations more challenging than healthy individuals. This can negatively impact a range of functional outcomes, including the ability to work and live independently [21], as well as the ability to demonstrate effective social skills and social problem-solving [22], both of which are important for developing meaningful social connections and support.

Despite emotional perception deficits being well established in the literature, there is still a lack of consensus regarding the specific factors contributing to impairments in this social cognitive domain [9]. For instance, in nonclinical populations, there appears to be a relationship between emotional perception and sex, such that females tend to perceive emotions better than males [23-25]. However, it is unclear whether this female advantage exists in schizophrenia [26-29]. Females with schizophrenia typically present with disease onset later than males and thus have higher premorbid functioning, although not necessarily better long-term outcomes [30-32]. There are a range of sex-related differences in the prevalence, presentation, and management of schizophrenia; however, these differences are still poorly understood, and research in this field is still in its infancy [33]. We identified 1 systematic review and meta-analysis [34] on the sex differences in FEP in a schizophrenia population. The sample included adults with chronic schizophrenia, individuals with early or recent onset of schizophrenia, and individuals with a first-degree relative with schizophrenia. This review found limited studies that reported sex differences in FEP, although those that did tended to show that females performed better than males. This study's authors emphasized the importance of future research into the potential sex differences in FEP to improve the long-term outcomes of individuals with schizophrenia. Indeed, biomedical research, more generally, has tended to demonstrate sex disparity in participant recruitment (ie, males favored over females) [35]; there is a need for more research into sex-related differences in SSD [33]. Indeed, the inclusion of sex-specific clinical practice guidelines to guide the treatment of schizophrenia has been considered [35] as a potential step in managing the disorder.

Social cognition is significantly associated with long-term function, irrespective of factors such as symptom severity and length of illness [36]. It can also act as a mediator between neurocognition and functional outcomes [5,37]. Effective treatments for social cognitive impairments are highly relevant to long-term functional rehabilitation. We argue that a greater understanding of the deficits in emotional perception, a key aspect of social cognition, is needed to assist such interventions to be better tailored to individuals with schizophrenia. We also argue that understanding the role individual variables, such as biological sex, play on emotional perception task performance is important in developing the social cognitive profile of schizophrenia, particularly for females with the disorder, that has typically been underresearched. Previous systematic reviews and meta-analyses have studied emotional perception impairments in schizophrenia; however, preliminary searches in the PROSPERO (International Prospective Register of Systematic Reviews), CENTRAL, and the Joanna Briggs Institute Database of Systematic Reviews revealed no recent systematic reviews that have examined the role of biological sex on this social cognitive domain and no previous systematic

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reviews that have looked at the impact of biological sex on emotional perception outside of FEP tasks. This study aims to systematically review and critically appraise the quantitative literature considering the impact of biological sex on emotional perception in adults with SSDs. Our primary goal is to identify differences in emotional perception performance between males and females to contribute to the knowledge of the social cognitive profile of schizophrenia.

Methods

This protocol was developed in consultation with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [38,39]. This systematic review is registered with PROSPERO (ID: PROSPERO 2023 CRD42023463561).

Eligibility Criteria

Participants

Participants must be older than 18 years with a primary diagnosis of SSD, as diagnosed by any recognized diagnostic criteria, such as the *DSM-V* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) or the *ICD-11* (*International Classification of Diseases, 11th Revision*). Studies that include animals, children, or adolescents will be excluded. Participants who are at high risk of schizophrenia or who have experienced a first episode of psychosis but do not yet meet the full criteria for an SSD diagnosis will be excluded from this review. Studies that group adolescents and young adults together will also be excluded unless it is possible to separate participants who are older than 18 years.

Intervention

Studies will not need to include an intervention to be included in this systematic review. However, studies will need to examine at least 1 measure of emotional perception (eg, Bell Lysaker Emotion Recognition Task [28]; Penn Emotion Recognition Test [29]). We will define emotional perception as the social cognitive processes involved in comprehending and recognizing emotions in others. We will include any aspect of emotional perception (ie, verbal, and visual). Studies that are attempting to validate new tasks will be excluded.

Comparator

There will be no restriction on the inclusion of comparator groups (eg, intervention, treatment-as-usual, and healthy controls); however, studies must include male and female participants. Studies that combine participants (both males and females) into 1 group can also be included if the available data allow us to separate these participant groups. Studies that do not report the biological sex of participants will be excluded.

Outcomes

This systematic review will include quantitative, empirical studies with no restrictions on the type of setting or timing of publication. The exclusion criteria include qualitative studies, case reports, case series, unpublished manuscripts or abstracts, and papers not available in English. Studies must provide performance outcomes on the emotional perception task. These may be primary or secondary outcomes of the included studies.

Search Strategy

Initial search terms will be developed and piloted by the research team. Key search terms will include “men,” “male,” “man,” “female,” “women,” “woman,” “sex,” “gender,” “emotional perception,” “emotional processing,” “schizophrenia,” “schizophren,” “psychotic disorders,” “psychosis,” “psychoses,” “psychotic,” “schizoaffective,” “schizotypal personality disorder,” and “schizotyp.” Boolean operators “OR” and “AND” will combine these keywords. We will build a search terms and limits table to consider the keywords, terminology, and search limits. This table will also capture these keywords’ synonyms, abbreviations, alternative spellings, and collective nouns. We will use the MeSH (Medical Subject Headings) Browser to search for our topics and review the MeSH tree structures for each keyword to see whether there are any narrower terms to include in our search. We will then use this table to develop a preliminary search strategy with MEDLINE (PubMed; Multimedia Appendix 1). Peer review will be sought from a health services librarian with expertise in systematic reviews and meta-analyses. We will use the Polyglot search translator to adjust and translate our search strategy syntax to different databases [40]. The following electronic databases will be searched: MEDLINE, Embase, CENTRAL, CINAHL, and PsycINFO. Reference lists of included studies will also be manually scanned. Databases will continue to be searched for new publications until the end of June 2024. Study authors may be contacted to request full-text publications and clarify questions about study results. We will also search, at minimum, the first 3 pages of Google and Google Scholar to test our search strategy.

Selection Process

The literature search results will be uploaded to the web-based Covidence systematic review management software (Veritas Health Innovation) [41]. Abstracts that meet the search terms will be imported into Covidence, and titles and abstracts will be screened to determine whether they meet the inclusion criteria for a full-text review. Any duplicates will be removed during the screening process. Full-text papers will be uploaded for the formal reviewing process. If full-text versions are unavailable, the researchers will attempt to contact the study authors to request a copy of their paper via a maximum of 3 email attempts. Researchers (FD and GR) will independently screen titles and abstracts based on the study selection criteria. Before this screening process, screening questions will be developed to assist reviewers. Covidence software will flag any conflicts between reviewers at each of these stages. Reviewers will meet to discuss and resolve these conflicts. A third reviewer (HN) will be sought if a consensus cannot be reached. Full-text versions of studies that are considered relevant will then be formally reviewed by at least 3 researchers. Again, any conflicts during this process will be flagged, and reviewers will meet to seek consensus. Another reviewer will be contacted if an agreement cannot be reached. Eligible full-text publications will be stored in Endnote referencing software using smart groups. These selected papers will be checked for retractions

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and errata. Before data extraction, a search will be rerun to identify any new studies to be retrieved for inclusion. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will record search results during the study selection process [42].

Methodological Quality Assessment

Two reviewers will independently critically appraise the quality of studies included in the systematic review for risk of bias using the relevant Joanna Briggs Institute checklist tools [43]. These tools provide checklists for a range of study designs, including randomized and nonrandomized controlled trials. Assessment will consider potential sources of bias for each study, such as in the selection of participants, reliability in the measurement of outcomes, appropriateness of the statistical analysis undertaken, and potential selective reporting of results. Reviewers will meet to resolve any discrepancies in these ratings. A third reviewer will be sought if required. No reviewers will be blind to journal titles, study authors, or institutions. We will report the results of this quality assessment in tabular format in the systematic review.

Data Extraction and Synthesis

One researcher will extract the data from the selected full-text publications using the web-based Covidence systematic review management software [41]. This process will be reviewed by a second researcher. A data extraction template will be developed, piloted, and reviewed by the researchers before formal data extraction. If any data are unclear, the researchers will attempt to contact study authors to clarify their findings via a maximum of 3 email attempts over 28 days. We expect to extract the following data from the selected full-text publications as available: author and institution details, publication information (including study title, journal title, publication date, and study location), participant demographic and clinical information (including age, biological sex, primary and secondary mental health diagnoses, mean duration of onset of symptoms, premorbid functioning, current stage of illness, any other cognitive or physical impairments, and current medications), study methodology (including trial design, trial size, and emotional perception task), and all quantitative data on dynamic perception task performance including any dropouts or missing data.

The characteristics of the included studies will be presented in tabular format and summarized in narrative synthesis as appropriate. If sufficiently comparable data to permit meta-analysis emerges, this will be completed using the random-effects model. Both continuous (eg, standardized mean difference) and categorical outcomes (eg, odds ratio and relative risk) in the extracted studies will be assessed and compared. The heterogeneity of effect sizes of pooled studies will be measured via forest plots using chi-square and I^2 values. If appropriate, a funnel plot and Egger test will be used to report publication bias. No subgroup analyses are planned at this stage. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will be used to consider the strength of the evidence available [44]. Two reviewers will rate their level of confidence (ie, very low, low, moderate, or high) in the quality of evidence for outcomes. A third reviewer will be sought if consensus cannot be reached in these ratings. We will report this evaluation of the evidence in tabular format in the systematic review.

Ethical Considerations

This study does not require ethics approval and consent to participate. No data used for analysis or reported in the systematic review will be identifiable.

Results

This systematic review was submitted to PROSPERO in September 2023 and registered in October 2023. As of January 2024, preliminary searches and piloting of the study selection process have been completed. Formal screening of study titles and abstracts against eligibility criteria has commenced, with 973 studies imported to Covidence management software for screening. Data are expected to be extracted and analyzed in July 2024, and we aim to submit results for peer-reviewed publication by December 2024. This study is self-funded.

Discussion

Principal Findings

This study will systematically review the impact of biological sex on emotional perception in adults with SSD. In comparison with the general population, deficits in emotional perception in schizophrenia are well established [13,14], but there is very little research into the potential impact sex has on performance. We did identify 1 systematic review and meta-analysis [34] that found only limited evidence of a female advantage for emotional perception. However, it is important to note that this construct was restricted to FEP tasks, and the study authors highlighted the need for future research into this area. We hypothesize that our review may provide support to these findings. In healthy adults, females tend to perform better at emotional perception tasks. Our review aims to understand whether this advantage extends to females with schizophrenia or whether the advantage is attenuated. The social cognitive profile of schizophrenia, more generally, is still largely heterogeneous and how it differs to other psychiatric disorders is still under investigation [9]. We hope to provide a greater understanding of how sex-related differences in emotional perception may explain some of this variation and, in turn, inform future treatment that targets functional outcomes in these individuals. The need for more research into sex-related differences in schizophrenia has been emphasized as a new but important field of research [33].

Limitations

The main limitation anticipated in this review relates to the lack of consensus within the literature on how to measure emotional perception [12], compounded by the limited availability of well-validated and reliable tools. Often, attempts have been made to adapt measures from other participant samples to a schizophrenia population but with limited research on the psychometric properties of these measures in SSD [9]. A similar critique relates to existing social cognitive tasks' lack of cross-cultural validity [9]. These restraints may limit the ability to draw conclusions and pool outcomes from comparable

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studies. If this is the case, we plan to provide a narrative synthesis and group studies by the type of emotional perception task, reporting on the reliability and validity of these measures. The study researchers must also acknowledge the cultural biases we bring to this review and be cautious in generalizing any conclusions drawn to other cultures, especially given the limit to studies available in English included in our study criteria. We also plan to measure the quality of evidence to assess the confidence in the available data and report these findings in the systematic review.

Conclusions

This study will review the evidence for sex differences in emotional perception within SSD. The results will provide a greater understanding of the social cognitive profile of schizophrenia and, in turn, inform future interventions tailored to improve long-term rehabilitation.

Acknowledgments

FD is the guarantor. All authors read and approved the final manuscript. No professional writers or generative artificial intelligence was used in any portion of the manuscript writing.

Data Availability

Access to research data is restricted and governed by the Queensland Health Government; however, extracted data may be available upon request. All researchers will have access to the final data set. Extracted data will be made publicly available as multimedia appendices.

Authors' Contributions

GR participated in the methodology, investigation, writing original draft, and writing review and editing; HN participated in the investigation, writing review, and editing; SP participated in the methodology, writing review, and editing; and FD participated in the conceptualization, methodology, investigation, writing review and editing, and supervision.

Conflicts of Interest

FD has received honorariums from Janssen and Lundbeck for delivering lectures at clinician education events. In the past 5 years, SP has received research funding from the Common Good Foundation, Johnson & Johnson, Metro North Foundation, PA Foundation, RANZCP, and Suicide Prevention Australia; and honoraria from Johnson & Johnson, RANZCP, Queensland Psychotherapy Training, CSL Seqirus, and Tasmania Health. The other authors declare no conflicts of interest.

Multimedia Appendix 1
Draft MEDLINE search—PubMed interface.
[DOCX File , 13 KB - resprot_v13i1e56977_app1.docx]

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Abbreviations

***DSM-V*:** *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*
FEP: facial emotion perception
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
***ICD-11*:** *International Classification of Diseases, 11th Revision*
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol Statement
PROSPERO: International Prospective Register of Systematic Reviews
SSD: schizophrenia spectrum disorder

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Protocol

Supporting Carers: Study Protocol of a Meta-Review of Psychosocial Interventions for Carers of People With Cancer

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Abstract

Background: While there is a clear need for psychosocial interventions that promote the well-being of carers of patients with cancer, the corresponding evidence base is disparate, complex, and difficult for end users to navigate and interpret. Carers remain undersupported with a lack of dedicated, effective, evidence-based programs. We will conduct a meta-review to synthesize this evidence and determine the state of science in this field.

Objective: This study aims to address the question, "what psychosocial interventions are available to promote the well-being of carers for people with cancer?"

Methods: A meta-review will synthesize the relevant reviews of psychosocial interventions that have been developed and evaluated with carers for people with cancer. A total of 4 electronic databases (PsycInfo, MEDLINE, CINAHL, and Cochrane Database of Systematic Reviews) will be searched for reviews published between January 2013 and December 2023. A team-based approach will be taken for screening and assessment of the returned records against the eligibility criteria to determine inclusion. Included reviews will be critically appraised using the Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews and Research Syntheses. Relevant data on study characteristics, carer and patient populations, intervention details, and psychosocial outcomes will be extracted, synthesized, and the findings will be presented in a narrative format.

Results: It is anticipated that the study will be completed by October 2024.

Conclusions: Ensuring that carers have access to evidence-based programs that promote their well-being as they care for loved ones is critical. This meta-review will contribute to program development and translation efforts by providing a clear picture of the intervention evidence base of carers of patients with cancer and identifying notable strengths, weaknesses, and gaps across the literature. The findings are anticipated to offer future directions to advance research in the field.

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Trial Registration: PROSPERO (CRD42023403219); https://tinyurl.com/4tnzv49s
International Registered Report Identifier (IRRID): DERR1-10.2196/56403

(JMIR Res Protoc 2024;13:e56403) doi:10.2196/56403

KEYWORDS

cancer; carer; caregiver; psychosocial; supportive intervention; psychosocial interventions; carers; caregivers; study protocol; well-being; wellbeing; end-users; evidence-based; evidence-based program; mental health

Introduction

Background

Family and friend carers serve as the core, yet underacknowledged, members of the health team in coordinating and providing care for loved ones diagnosed with cancer [1]. The partners, parents, siblings, children, and friends of patients often fulfill this role, which spans pragmatic, clinical, and emotional domains of support [2-4]. Shifts in oncology care delivery, increasingly toward outpatient, community, and home settings have widened the scope of carers' roles and responsibilities [1,4-6]. Carers of people with cancer may assume significant responsibilities in not only coordinating and organizing care, but also in providing direct clinical care (eg, administering medications) [4,6].

Becoming a carer is a role that many feel unprepared for, and are overwhelmed by, with implications for health and well-being [7,8]. Carers experience depression, anxiety, and distress, commonly at higher rates than the general population [9-11]. Furthermore, both the quality-of-care and clinical outcomes of the patient are linked to the well-being of carers [6]. There has been a growing interest in identifying psychosocial interventions that may be effective in supporting this population [7,12].

While there appears to be a large volume of literature reporting on studies of psychosocial interventions for carers of patients with cancer, this body of work is complex and fragmented, and it is challenging to draw clear conclusions about the evidence for specific types of programs or carer groups. The result is that carers remain undersupported, with limited evidence of the effective interventional approaches. Key issues within the evidence base of carers of patients with cancer that limit advancement in practice are the divergent scope and focus of current interventions (eg, in-person therapy for carers, web-based interventions for patient-spouse dyads [13], compared with psychological interventions for parents of children and adolescents with chronic illness [14]), all of which may be included in a single review.

A potential weakness in the current literature is that interventions have not necessarily been designed for carers as the target primary population; programs may be developed for patients and extended to include carers [15]. In such cases, carer-specific needs may not be met. In addition, the nature of relationships between carers and the person being cared for is not always sufficiently considered in the collation of intervention evidence. While findings suggest that distress and stress can arise while providing health care and with a loved one being ill [3,16], this appears underexplored. These limitations, with the divergences in the literature described, pose barriers for end users of this evidence [17].

Review Aim and Question

Undertaking a meta-review was identified as a useful first step in addressing the abovementioned barriers to enable the development of targeted interventions that may offer greater impacts to reduce carer distress and enhance support [18]. A meta-review offers a means to develop an overall, coherent picture of a large volume of evidence [19,20], that is useful for those wishing to navigate this literature and identify the evidence relevant to them. This study aims to synthesize the evidence from reviews of psychosocial interventions designed to support the well-being of carers of people with cancer.

This study will address the question, "what psychosocial interventions are available to promote the well-being of carers for people with cancer, as reported in the evidence from reviews?"

Methods

Overview

Please revert back to the original text or alternatively revise to read: "A meta-review was selected as a method that offers a systematic and rigorous approach to the identification and review of relevant evidence in the form of various types of reviews [21]. The protocol for this study is registered with the PROSPERO (International Prospective Register of Systematic Reviews; CRD42023403219). In the absence of a method-specific protocol reporting framework, the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines are used to report this study protocol (Multimedia Appendix 1) [22].

Eligibility Criteria

The following eligibility criteria will be used to determine study inclusion (Textbox 1).

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Population
  - Carer for a family member (adult or child) or a person with whom they have a personal relationship who has received a diagnosis of cancer.
  - People who are providing care on an "informal" basis, which they have not been professionally contracted to provide.
- Intervention
  - Nonpharmacological interventions that are designed to positively impact some aspect of the psychosocial well-being of carers of people with cancer (such as interventions focused on improving mental health, health-related quality of life, or life satisfaction).
  - Psychosocial interventions can include educational, informational, and therapeutic activities designed to promote well-being (eg, cognitive behavioral therapy).
  - Remote, in-person, and hybrid modes of intervention delivery will be eligible for inclusion.
  - Both facilitated and self-directed interventions will be eligible for inclusion.
- Outcome
  - Primary
    - Psychosocial outcomes of carers: quality of life, depression, anxiety, resilience, psychological distress, and any other psychosocial outcomes reported on.
  - Secondary
    - Patient or family well-being outcomes associated with the intervention (eg, patient psychological distress).
    - Implementation-related outcomes, such as acceptability, feasibility, and uptake into practice.
- Context
  - Care in the home, community, health care, or any other setting.
- Study methods
  - Any type of review (eg, scoping reviews, narrative reviews, integrated reviews, systematic reviews, meta-reviews, reviews of qualitative evidence, meta-syntheses, and meta-analyses) of interventions including controlled trials, quasi-experimental studies, pilot studies, feasibility studies, pre-post studies, and evaluation studies.
  - Reviews of studies using any methods are eligible—quantitative, qualitative, and mixed- and multimethods.
- Publication type
  - Peer-reviewed publications.
- Publication date
  - January 1, 2013-December 31, 2023.
- Language
  - English.

Exclusion criteria

- Intervention
  - Interventions in which psychosocial well-being (eg, reduced psychological distress and improved quality of life) is not a stated outcome.
  - Studies that do not report the data and results separately for carers of people with cancer.
- Study methods
  - Nonreview studies.
- Publication type
  - Conference abstracts, editorials, opinion pieces, non–peer-reviewed research, and nonempirical research will be excluded.

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Information Sources

Systematic searching of PsycInfo, MEDLINE, CINAHL, and Cochrane Database of Systematic Reviews will be performed. In addition, the reference lists of relevant reviews will be audited to identify other potentially eligible reviews. The search will cover a 10-year period from January 1, 2013, to December 31, 2023.

Search Strategy

The search strategy for the databases listed was developed through consultation with a medical research librarian. The search was developed based on the search strategy used in the study by Treanor et al [23] Cochrane review of the psychosocial interventions for informal carers of people living with cancer and informed by concepts encompassed in Fletcher et al [24] model of the cancer family carer experience. Search terms were updated as required, including terms related to the study type (eg, "systematic review"). The search period was selected to identify recently published reviews and capture the current evidence landscape. The finalized search strategy uses a combination of MeSH (Medical Subject Headings) terms and keywords and as an example, the strategy developed for the MEDLINE database is included in Multimedia Appendix 2.

Selection Process

Records retrieved from the searches will be imported into EndNote X9 (Clarivate, citation management software) [25], and duplicates will be subsequently removed. The remaining records will then be uploaded to Covidence (literature review management tool) [26], which will be used to manage the screening of records. The titles, abstracts, and keywords of records will be screened by 1 of the team members against the criteria to determine inclusion. The full texts for included records will then be retrieved and 2 team members will independently assess each text against the eligibility criteria. Disagreements will be resolved by team discussion, with discrepancies discussed with a third team member until a resolution is reached. The search results will be documented and reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [27], with adaptations made as needed to reflect the meta-review method.

Data Collection Process

A draft data extraction template will be developed, and 2 team members will independently extract data for a shared 10% of the included reviews to identify any amendments needed to the template. Once finalized, a team-based approach to data extraction will be taken where data will be extracted by one team member, all of which will be subsequently cross-checked by another member of the team. Discrepancies will be resolved through discussion. Microsoft Excel will be used to manage the data extraction process [28]. Data will be extracted in the areas of study characteristics, populations of carers and patients, intervention details, and reported impact (if any) on the outcomes of interest (Table 1).

Table 1. Data items for extraction.

Areas of data collection	Data item details
Study characteristics	Year, review aims, types of review, any geographical restrictions of review, conditions of those cared for methods, study types and designs included in review, total number of included studies (and articles, if different), participants' total number or sample size details, search period, synthesis method, critical and quality appraisal tool used, and any other notable details
Population	Population focused in the review, target carer population, target, patient population, and any other notable details
Intervention details	Details about intervention development, mode of delivery, theoretical bases, settings, facilitators, details about frequency, duration or length of interventions, and any other notable details
Outcomes of interest	
Carer psychosocial outcomes	Quality of life, depression, anxiety, resilience, psychological distress, and any other psychosocial outcomes reported on
Implementation-related outcomes	Acceptability, feasibility and uptake into practice, and other implementation-relevant outcomes
Patient or family well-being outcomes	Patient or family well-being outcomes associated with the intervention such as patient psychological distress

Data Synthesis

The extracted data will be collated and organized. A narrative approach will be taken to describe the results, study characteristics, populations, interventions, outcomes, and any other details of interest. Data will be categorized and grouped (eg, by types of intervention facilitators) and where possible, a quantitative description will be provided (eg, the total number of studies reported across reviews). The narrative will provide a mapping and organization of the data to promote a coherent picture of the body of evidence. Data permitting salient groupings and dimensions of differences in the evidence, such as types of interventions, populations, and outcomes will be explored. For example, a reader would be able to glean the evidence for psychosocial interventions for couples.

Critical Appraisal

The risk of bias and quality of methodological results for the included reviews will be evaluated using a standardized appraisal tool specifically designed for the appraisal of systematic reviews and research syntheses [29]. One team member will initially conduct an appraisal that will be cross-checked by a second team member. Any discrepancies will be discussed by team members and resolved.

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Ethical Considerations

Ethical approval is not required for this manuscript. The manuscript does not contain any data.

Results

To date, the search and study selection process is underway, with a search to be rerun in January 2024 to encompass the full search period. A preliminary extraction method has been developed, tested, and discussed among the team to help refine the process. It is anticipated that the study will be completed by October 2024.

Discussion

Principal Findings

The study outlined in this paper is anticipated to reveal the state of the science of cancer caregiver psychosocial support interventions. While informative meta-review research has been conducted in related areas (eg, a more broadly focused study of support for carers of people with a wide range of conditions [30], or a review specifically focused on family-based interventions in palliative cancer care [31]), these studies were not targeted to address the aim of the current research. The proposed synthesis of the evidence from reviews of psychosocial interventions designed to support the well-being of carers of people with cancer is expected to result in the formation of a coherent picture of a vast and fragmented literature base. These findings will offer a novel and valuable point of view conducive to understanding the quality of this evidence, the strengths, and weaknesses, and identify research priorities for supporting evidence-based programs.

Attention in the synthesis to the grouping of particular outcomes, carer populations, and intervention characteristics (and any other important groupings) will help end users identify the review evidence most pertinent to them, in addition to serving as a useful foundation for others interested in further studying the evidence about particular carer populations or interventions. The findings from this meta-review will be reported in a scholarly publication, presented at conferences, and disseminated through professional networks. Any variations to the protocol will be advised of in the record of the protocol and reports of the findings.

Strengths and Limitations

This is a well-designed study that had input in the development of the search strategy from a research librarian in addition to team members' subject matter and methodological and clinical expertise. The process is guided by an established method with inbuilt procedures to promote rigor and transparency. Meta-review findings are limited by the quality of the included reviews and the primary research reported therein [17,18,32]. Furthermore, as the study is designed to capture review evidence, this means that recent findings reported in newly published primary research will not be captured [33].

Conclusion

There is a clear need to ensure that carers have access to evidence-based programs that can effectively support their well-being as they care for their loved ones. Current models of cancer care rely heavily on the work of carers, and, given the growing burden of cancer worldwide [30], this caregiving work is also vital to health system sustainability. This meta-review will facilitate an improved understanding of the evidence base, enabling better identification of research strengths, limitations, and gaps. It will also enhance the navigation of the literature, allowing researchers, clinicians, and policymakers to more readily review evidence relevant to them [18,19], in turn supporting the translation of evidence into practice.

Acknowledgments

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Data Availability

All data used during this study will be included in this published article and its Multimedia Appendices.

Authors' Contributions

BNGE, BN, JJ, and RH contributed to the conceptualization. BNGE, BN, JJ, KS, and RH managed funding acquisition. BNGE, BN, RLP, USD, KS, and RH conducted the investigation. All authors contributed to the methodology. BNGE, BN, JJ, SM, and KS handled project administration. SM managed the data curation, software, and validation. BNGE wrote the original draft. BN, JJ, RLP, USD, LJ, LK, SM, KS, and RH contributed to writing- review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[PDF File (Adobe PDF File), 108 KB - resprot_v13i1e56403_app1.pdf]

Multimedia Appendix 2
Search Strategy.
[PDF File (Adobe PDF File), 69 KB - resprot_v13i1e56403_app2.pdf]

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Abbreviations

MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Reviews
PRISMA- P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Metagenomics in the Diagnosis of Pneumonia: Protocol for a Systematic Review

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Abstract

Background: Causative pathogens are currently identified in only a minority of pneumonia cases, which affects antimicrobial stewardship. Metagenomic next-generation sequencing (mNGS) has potential to enhance pathogen detection due to its sensitivity and broad applicability. However, while studies have shown improved sensitivity compared with conventional microbiological methods for pneumonia diagnosis, it remains unclear whether this can translate into clinical benefit. Most existing studies focus on patients who are ventilated, readily allowing for analysis of bronchoalveolar lavage fluid (BALF). The impact of sample type on the use of metagenomic analysis remains poorly defined. Similarly, previous studies rarely differentiate between the types of pneumonia involved—community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP)—which have different clinical profiles.

Objective: This study aims to determine the clinical use of mNGS in CAP, HAP, and VAP, compared with traditional microbiological methods.

Methods: We aim to review all studies (excluding case reports of a series of fewer than 10 people) of adult patients with suspected or confirmed pneumonia that compare metagenomic analysis with traditional microbiology techniques, including culture, antigen-based testing, and polymerase chain reaction–based assays. Relevant studies will be identified through systematic searches of the Embase, MEDLINE, Scopus, and Cochrane CENTRAL databases. Screening of titles, abstracts, and subsequent review of eligible full texts will be done by 2 separate reviewers (SQ and 1 of AL, CJ, or CH), with a third clinician (ES) providing adjudication in case of disagreement. Our focus is on the clinical use of metagenomics for patients with CAP, HAP, and VAP. Data extracted will focus on clinically important outcomes—pathogen positivity rate, laboratory turnaround time, impact on clinical decision-making, length of stay, and 30-day mortality. Subgroup analyses will be performed based on the type of pneumonia (CAP, HAP, or VAP) and sample type used. The risk of bias will be assessed using the QUADAS-2 tool for diagnostic accuracy studies. Outcome data will be combined in a random-effects meta-analysis, and where this is not possible, a narrative synthesis will be undertaken.

Results: The searches were completed with the assistance of a medical librarian on January 13, 2024, returning 5750 records. Screening and data extraction are anticipated to be completed by September 2024.

Conclusions: Despite significant promise, the impact of metagenomic analysis on clinical pathways remains unclear. Furthermore, it is unclear whether the use of this technique will alter depending on whether the pneumonia is a CAP, HAP, or VAP or the sample type that is collected. This systematic review will assess the current evidence base to support the benefit of clinical outcomes for metagenomic analysis, depending on the setting of pneumonia diagnosis or specimen type used. It will identify areas where further research is needed to advance this methodology into routine care.

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Trial Registration: PROSPERO CRD42023488096; https://tinyurl.com/3suy7cma
International Registered Report Identifier (IRRID): DERR1-10.2196/57334

(JMIR Res Protoc 2024;13:e57334) doi:10.2196/57334

KEYWORDS

pneumonia; metagenomics; CAP; community-acquired pneumonia; HAP; hospital-acquired pneumonia; VAP; ventilator-associated pneumonia; diagnosis; respiratory tract infection; systematic review

Introduction

Background

Pneumonia is an acute infection of lung parenchyma [1]; it is of key importance globally with high incidence and mortality [2]. Lower respiratory tract infections, encompassing pneumonia, are the leading infectious cause of death worldwide [3], although figures for incidence and mortality rates vary significantly with the population being studied. In adults, pneumonia is predominantly a disease of aging, with incidence rising from 1.1 to 4.8 per 1000 persons per year in all adults to 6.7 to 42 per 1000 persons per year in those older than 65 years old [2]. At extreme age, this increases further: a UK analysis found the rate of pneumonia episodes among 85- to 89-year-olds was 7 times that among 65 to 69-year-olds [4]. With populations aging in many countries, there is an urgent need to improve outcomes for patients with pneumonia.

The diagnosis of pneumonia is not pathogen specific, encompassing a range of infections by varied bacterial, viral, and fungal causes [5]. Prognoses and optimal treatments vary depending on the causative organism, and the likely pathogens change depending on the setting in which infection occurs, with pneumonia usually categorized into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP). Identifying the responsible pathogen carries importance in allowing targeted effective treatment. However, with existing microbiological methods, an organism is only identified in around half of cases of CAP [6] and between 4% and 27% of patients with HAP [7-9]. In addition, traditional culture-based techniques have a relatively slow turnaround time of 2-5 days from sample collection to antimicrobial sensitivity results [10]. As a result, treatment is largely empirical, based on common organisms and resistance patterns, with the risk of antibiotic prescriptions that are unnecessary, ineffective, or harmful [11]. Empiric treatment, especially with broad-spectrum antibiotics as recommended for HAP and VAP [12], also drives antimicrobial resistance, which is a growing societal concern with an estimated 4.95 million deaths associated with antibiotic resistance in 2019 [13]. With lower respiratory tract infections being the largest contributor to this total [13], antibiotic resistance is both a consequence and cause of inappropriate antibiotics in pneumonia. Timely identification of causative organisms and potential resistance patterns could lead to early rationalization or escalation of antibiotics, to improve outcomes and limit the impact on antimicrobial resistance.

Metagenomic next-generation sequencing (mNGS) is an emerging technology that is of considerable promise in pneumonia [14]. Current techniques to identify a causative pathogen in pneumonia rely largely on microscopy and culture. These traditional methods have significant limitations which contribute to the low rates of pathogen identification. Not all pathogens grow readily in standard culture media, and where organisms are identified results often take several days to be reported, leading to delays in optimizing antimicrobials [10,15]. Metagenomic sequencing offers a nonbiased approach to pathogen identification by sequencing all nucleic acid present in a sample and so, in addition to identifying organisms, has the potential to provide data on likely resistance patterns or virulence. It also offers potential improvement in laboratory turnaround times, with 24 hours having been achieved in clinical practice [16], with a 6-hour turnaround from sample to result in a research environment, suggesting what may become possible with scale and optimization [17].

Increasingly, studies are considering the role of metagenomics in pneumonia diagnosis [18-20]. This has led to a systematic review of the sensitivity and specificity of metagenomics for pneumonia diagnosis [21]. However, work assessing the clinical use of metagenomics is more limited. Lv et al [22] performed a recent systematic review assessing relative pathogen detection rates, with some clinical outcomes; however, this only considered severe pneumonia with the majority of included studies based exclusively within intensive care. Similarly, a recent pilot of metagenomics within a clinical service showed a significant impact on antimicrobial prescribing but was again based solely on intensive care [14]. Most patients with pneumonia are not treated in the intensive care unit, and it is important to assess the potential benefit of metagenomic methods outside this setting. In addition, the Lv et al [22] review also made no distinction between CAP, HAP, or VAP. Given that CAP, HAP, and VAP result from a different range of pathogens, among differing cohorts of patients, it is possible that metagenomics may have clinical use in one disease but be ineffective in another.

Studies have predominantly looked at the impact of metagenomic analysis of bronchoalveolar lavage samples, and the relative sensitivity and specificity of other bodily fluids (such as expectorated sputum, pharyngeal swabs, or peripheral blood sampling) remains uncertain for patients with pneumonia. Lower respiratory tract sampling may improve pathogen identification but is impractical to obtain for many patients. Understanding the relative use of less invasive sampling methods is important.

While previous work has looked specifically at the sensitivity and specificity of metagenomics, the clinical relevance of this methodology remains unclear. To be routinely adopted,

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metagenomics will need to identify a causative pathogen from nonsterile samples, improve the timeliness of laboratory turnaround times, impact clinical prescribing, and be associated with improvements in clinical outcomes. These may differ in CAP, HAP, and VAP.

Objectives

This systematic review aims to determine the clinical use of mNGS in CAP, HAP, and VAP among an adult population, compared with traditional microbiological methods. This will be through assessing the impact of mNGS on the frequency and speed of pathogen identification, as well as evidence of this translating to clinical outcomes, such as change in antibiotic therapy. It will also include subgroup analyses on how the use of mNGS is affected by the sample type used for metagenomic analysis.

Methods

The review will be conducted and reported in keeping with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [23], and a completed PRISMA checklist will accompany any published results.

Eligibility Criteria

Studies comparing metagenomic analysis for identifying pathogens with traditional microbiological methods (to include culture, serum, and urine antigen testing and polymerase chain reaction–based approaches) will be included (Textbox 1). As clinical use of metagenomic analysis is an emerging field, case series and observational studies will be included, as well as randomized controlled trials. No date or language restrictions will be applied. The primary and secondary outcomes included in the systematic review are shown in Textbox 2.

Textbox 1. The inclusion and exclusion criteria.

Inclusion criteria

- Randomized controlled trials, observational studies, and case series of more than 10 patients
- Studies comparing metagenomic analysis with alternative methods of microbiological diagnosis
- Studies report data for hospitalized patients with suspected pneumonia (community-acquired pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia)
- Studies that include adult patients only (aged 18 years old and older)

Exclusion criteria

- Case series of less than 10 patients
- Studies describe respiratory infection, but where the definition does not require any radiological changes in keeping with pneumonia
- Animal or environmental studies

Textbox 2. Primary and secondary outcomes.

Primary Outcome

- Pathogen positivity rate of metagenomic analysis in confirmed community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia compared with standard methods (to include culture, antigen testing, and polymerase chain reaction)

Secondary Outcomes

- The primary outcome analyzed in subgroups based on sample type (blood, sputum, or bronchoalveolar lavage fluid
- Laboratory turnaround time (defined as the time from sample receipt to report of organisms identified, with antimicrobial sensitivities where available)
- Impact on clinical decision-making (to include proportion of patients in which antimicrobials were changed or rationalized based on metagenomic results)
- Length of stay (hospital admission)
- 30-day and 90-day mortality
- Sensitivity and specificity of metagenomic methods for diagnosing community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia

Search Strategy

A comprehensive search of Embase, MEDLINE (through the PubMed interface), Scopus, and Cochrane CENTRAL databases will be performed, with the support of a health care librarian, as well as gray literature. Reference lists will also be manually searched for appropriate studies. No date or language restrictions will be applied.

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Search Terms

Exact search strings will be optimized for the database being searched. The full search strategy used will be provided as supplementary material with the completed review.

The following provides the core terms around which searches will be based: (pneumonia OR CAP OR HAP OR VAP OR "lung infection" OR "respiratory infection" OR "pulmonary infection") AND (metagenomic* OR "next generation sequencing" OR "NGS" OR "mNGS").

Screening, Data Management, and Data Extraction

Studies identified by searches will be stored and processed using the "Covidence" software program package (Covidence). Retrieved titles and abstracts will be independently assessed for eligibility by 2 reviewers (SQ and 1 of AL, CJ, or CH), with a third independent clinician (ES) providing adjudication in cases of disagreement. Full text of eligible articles will be retrieved, and data relevant to our primary and secondary outcomes will be extracted and recorded onto predesigned forms. Where studies that provide separate data for CAP, HAP, or VAP, or explicitly study only 1 of these, this will be recorded and combined outcomes will be reported for each pneumonia type. If the type of pneumonia is not clear or the criteria used to define pneumonia do not allow separation into subtypes, data will still be collected to avoid the loss of meaningful information. These data will only be included in outcomes looking at the use of metagenomics in pneumonia as a whole. Where reported, data relevant to diagnostic test accuracy (true positive, false positive, true negative, and false negative) will be recorded to enable pooled sensitivity and specificity calculations. Information will also be extracted regarding study design, including sample size, definitions of pneumonia used methods for randomization where appropriate, and the criteria used for a reference standard of positive diagnosis, as well as declared funding sources.

For papers where the sample type used for analysis is not stated or only statistics of combined sample types are given, attempts will be made to contact the authors to retrieve this missing information. If this is not available, these data will not be used when analyzing subgroups by sample type but will still be included for other outcomes. Other missing data will be recorded and reported on when discussing results.

As this is a systematic review of a diagnostic tool, the quality of included studies and risk of bias will be assessed using the QUADAS-2 tool (University of Bristol), as determined by 2 independent reviewers (SQ, AL, CJ, or CH). Again, any disagreement during data extraction or in the assessment of study quality will be discussed with a third reviewer (ES) and a consensus decision reached.

Analysis of Results

Statistical analyses will be conducted using R version 4.2 (The R Collaboration). For outcomes where insufficient data are available to conduct a meta-analysis, this will be highlighted, and the data will be combined in a narrative synthesis.

Reporting of Outcome Measures

Data from eligible studies will be pooled, and if possible, random effects meta-analyses of outcome measures will be performed. For dichotomous outcomes, we will calculate odds ratios with 95% CIs where possible. Laboratory turnaround times, as a continuous outcome, will be converted to standard units (hours) and the mean difference will be calculated. Subgroup analyses will be performed to look at the type of sample used for metagenomic analysis, and analysis will also be performed separately for CAP, HAP, and VAP.

Missing Data

Where SDs are not provided for continuous outcome data (such as laboratory turnaround time), study authors will be contacted up to 3 times in an attempt to obtain these. If this is not possible, attempts will be made to estimate SDs using recognized formulae from statistics provided (eg, standard error or *P* values), or if there is insufficient information to allow this, an SD value will be imputed based on that of other included studies. Where this is necessary, a sensitivity analysis of the results will be performed to identify if this has a meaningful impact.

Assessing Heterogeneity

A funnel plot will be performed to assess for publication bias, and statistical heterogeneity of studies will be calculated using I^2. Where substantial heterogeneity is found (I^2>50%), data entry will be assessed for accuracy. Possible reasons for the observed heterogeneity will be investigated by identifying studies that are obvious outliers on visual inspection of the graphical data and assessing for any methodological or population characteristics that account for the heterogeneity. These will be discussed alongside the results.

Results

Searches were completed on January 13, 2024, returning 5750 records. Screening of returned papers and data extraction are anticipated to be completed by September 2024. The review is registered prospectively on the PROSPERO database (CRD42023488096) and will be updated once complete. The results will be submitted for publication in peer-reviewed journals and presentation at local and international conferences.

Discussion

A systematic review of the literature on the use of metagenomics in the management of pneumonia should clarify the current understanding of this topic of importance in terms of clinical burden and current existing unmet needs. Metagenomic sequencing has been shown previously to improve the rate of pathogen identification [21]. However, how to interpret this in light of a nonsterile respiratory tract and lack of gold-standard comparators is challenging. The clinical significance of this increased analytical sensitivity remains unclear. Assessing the impact on clinical outcomes will highlight the potential clinical relevance or otherwise of metagenomics in this context and highlight where future studies may be needed to develop this further. Similarly, it will clarify if mNGS may be of particular benefit in certain pneumonia subtypes, and by investigating the

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impact of different sample types, it may identify the least invasive method to provide meaningful clinical data, given that existing reviews have focused on the use of BALF [21]. If insufficient data currently exist to make clear conclusions, this will be highlighted by the review and so direct where future research is needed.

We feel these are questions of clinical importance, and this review will offer a valuable contribution to shaping the use of emerging technologies in clinical practice. The results will be submitted for publication in peer-reviewed journals and presented at both local and international conferences. If, for any outcome, we are unable to identify sufficient studies to derive meaningful results, this will be reported to help direct future avenues for research.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed. On completion of the study, datasets generated as part of the study will be included in any submissions for publication.

Authors' Contributions

SQ participated in planning the review and drafting the manuscript. ES participated in planning the review and providing critical appraisal of the manuscript. AL, CJ, CH, AS, DT, DP, and AM provided critical appraisal of the paper.

Conflicts of Interest

ES reports funding from the National Institute for Health and Care Research, Welcome Trust, UK Research and Innovation, Health Data Research UK, and Asthma + Lung UK. AM reports funding from UK Research and Innovation and Welcome Trust. SQ and CJ are funded by the National Institute for Health and Care Research Birmingham Biomedical Research Centre (BRC). CH is funded by the Midlands National Institute of Health and Care Research (NIHR) Patient Safety Research Collaborative.

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Abbreviations

BALF: bronchoalveolar lavage fluid
CAP: community-acquired pneumonia
HAP: hospital-acquired pneumonia
mNGS: metagenomic next-generation sequencing
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
VAP: ventilator-associated pneumonia

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Protocol

Effect of Addition of Metal Oxide Nanoparticles on the Strength of Heat-Cured Denture Base Resins: Protocol for Systematic Review and Meta-Analysis of In Vitro Studies

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Abstract

Background: Metal oxide nanoparticle–reinforced polymethyl methacrylate (PMMA) has been shown to improve mechanical properties, such as strength. Different types of metal oxide nanoparticles have been used previously, but the comparative effect on the strength of heat-cured denture base resins remains unclear.

Objective: This is a protocol for a systematic review and meta-analysis that will aim to pool evidence to compare and analyze the effects of the addition of different metal oxide nanoparticles, with varied sizes and concentrations, on the strength (flexural, impact, transverse, compressive tensile strength, and fracture toughness) of heat-cured PMMA. In addition, this review aims to analyze methodological factors, such as adherence to testing and sample-making guidelines, and the effects of surface treatments of the nanoparticles on the strength of heat-cured denture base resins.

Methods: The protocol has been registered in the Open Science Framework. Search strategies to identify studies on the effect of metal oxide nanoparticles on the strength of heat-cured PMMA were developed by the subject matter expert in library science. Following this, a systematic search of 5 electronic databases (PubMed [NCBI], Scopus [Elsevier], Cochrane Library [Wiley], CINAHL Plus with Full Text [EBSCO], and Dimensions Free Web App) was conducted to retrieve in vitro studies published in English from January 2012 to October 2023. Along with this citation chasing, other online sources and gray literature were also searched. Furthermore, papers will be screened, and appropriate data elements will be extracted in a standardized manner. A risk-of-bias assessment will be performed using a modified Cochrane Risk of Bias Tool. A meta-analysis will be performed using a random-effects model.

Results: Search in databases resulted in 1837 papers, of which 1752 were duplicates, leaving 85 records that were screened for titles and abstracts based on the eligibility criteria. A similar search run on other online sources identified 129 papers that will be

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further analyzed for inclusion. The study was initiated in November 2023 and research questions and search strategies were formulated. The proposed study is expected to be completed by December 2024.

Conclusions: This systematic review will comprehensively analyze the effects of the incorporation of metal oxide nanoparticles in heat-cured denture base resins on the strength of the material. We anticipate gaining a deeper understanding of the effects and method of use of metal oxide nanoparticles to improve the strength of PMMA denture base resins.

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KEYWORDS

nanoparticles; strength; denture base resins; polymethyl methacrylate; denture; dentures; resin; resins; metal oxide

Introduction

Acrylic resins used in dentistry are composed of compounds that are natural or artificial in origin and have several repeating structural units or monomers that form the macromolecules or polymers [1]. Although there have been recent technical advances in denture base materials (DBMs), such as computer-aided design and computer-aided manufacturing, heat-cured polymethyl methacrylate (PMMA) continues to remain as one of the most widely used DBMs [2-4]. Even with its prevalent use, it continues to have poor mechanical properties (eg, strength). Heat-cured dentures are known to fracture under repeated occlusal and functional loads [5,6]. For optimum clinical usage and longevity, denture base resins should withstand masticatory forces and, thus, must have good mechanical properties (eg, strength). Overall, dentures are subjected to a combination of tensile, compressive, and shear forces and are susceptible to sudden drop, which may result in denture base fracture [7,8].

Furthermore, DBMs should have high flexural strength to withstand the mastication forces, showing no deformation or fracture [9]. To improve the mechanical properties of PMMA, reinforcement with nanoparticles has been shown to have promising results. Nanoparticles affect the mechanical properties of materials due to their potential to create new and strong bonds and make them more reactive when compared with macro- or microparticles [10]. With the recent advances in nanotechnology, various metal oxide nanoparticles, such as copper oxide (CuO), titanium dioxide (TiO_2), zirconium dioxide (ZrO_2), zinc oxide (ZnO), silicon dioxide (SiO_2), and others, have been developed to enhance the properties and clinical performance of denture base resins [11-18].

Previous research has shown that the properties of nanocomposite can be influenced by factors, such as the type, size, shape, concentration of nanoparticles, and interaction of the nanoparticles with the polymer matrix [17,19-21]. Although few systematic reviews have attempted to analyze the effect of the addition of nanoparticles on the mechanical properties [22-25], they were limited to a single type of metal oxide nanoparticle. Furthermore, while the effect of metal oxide nanoparticles on certain aspects of strength, such as flexural and impact strength, has been reviewed, collective evidence of different types of clinically relevant strengths remains unclear. Therefore, the primary objective of this review is to systematically synthesize the evidence to compare and analyze the effects of the addition of metal oxide nanoparticles on the strength (flexural, impact, transverse, compressive tensile strength, and fracture toughness) of heat-cured PMMA denture resins. The secondary objective is to determine the optimum size and concentration of nanoparticles to provide improved strength of PMMA. In addition, this review also aims to analyze methodological factors, adherence to testing and sample-making guidelines, and surface treatments of nanoparticles on the strength of heat-cured denture base resins. The findings of this review will serve as recommendations for the optimum use of metal oxide nanoparticles to improve the mechanical properties of heat-cured PMMA.

Methods

Ethical Considerations

This study is a review of existing in vitro studies, not involving human subjects, and thus an institutional ethical clearance was not necessary.

Protocol Registration

To have robust methodology and transparency in reporting, the protocol of the review has been registered in the Open Science Framework (OSF) [26]. Open Science Framework is an open and free platform that supports research by helping in protocol registration and collaborations. This study will be conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses [27].

Review Question

This systematic review and meta-analysis attempts to answer the following research questions: (1) What is the effect of different metal oxide nanoparticles on the strength (impact, compressive, flexural, tensile, transverse strength, and fracture toughness) of heat-cured denture base resins? (2) What is the optimum size and concentration of addition of metal oxide nanoparticles to achieve improved impact, compressive, flexural, tensile, transverse strengths, and fracture toughness of heat-cured denture base resins? and (3) Do methodological factors, such as the treatment of nanoparticles and following testing and sample fabrication guidelines, influence the strength of denture base resins?

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Eligibility Criteria

The eligibility criteria of studies for inclusion are defined using the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria (Figure 1).

Figure 1. PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework for eligibility criteria. NP: nanoparticle; PMMA: polymethyl methacrylate.

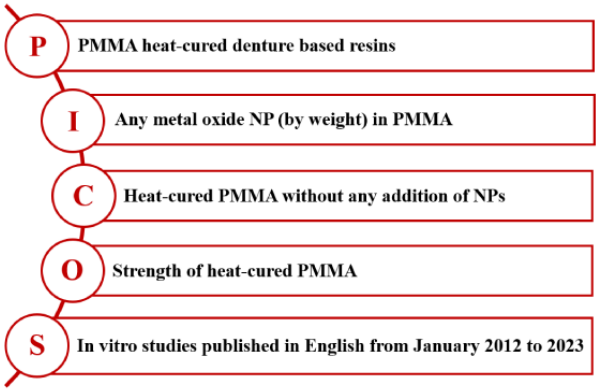

In Figure 1, population (P) denotes PMMA heat-cured denture base resins. Studies using veined, autoclaved, or microwave-cured denture base resins will be excluded. Intervention (I) denotes the addition of any metal oxide nanoparticle in PMMA only by weight. Studies based on nanotubes, fillers, fibers, coating, or hybrid nanoparticles in PMMA will be excluded. Studies that do not mention weight or volume, units of measurement, and method of mixing or dispersion of the nanoparticles will be excluded. Control (C) denotes heat-cured PMMA without any addition of nanoparticles. Outcome measure (O) denotes the strength of heat-cured PMMA. Strength was interpreted as all important parameters of strength that can affect the denture base resins, which include flexural, impact, transverse, compressive, tensile strength, and fracture toughness. Studies in which the dimensions of the samples tested were not mentioned, or if testing was done on dentures and studies in which the units of measurement were not mentioned, will be excluded. Study designs (S) denote in vitro studies published in English from January 2012 to 2023 will be considered. Thus, in vivo studies, case reports, systematic and narrative reviews, letters to the editor, short commentaries, pilot studies, or studies with preliminary results will be excluded.

Information Sources and Search Methods for Identification of Studies

The search strategy was formulated for each database by an experienced librarian (CP) and was sent for peer reviewing to another qualified librarian using PRESS (Peer Review of Electronic Strategies) guidelines [28]. Electronic searches in 5 databases will be performed: PubMed (NCBI), Scopus (Elsevier), Cochrane Library (Wiley), CINAHL Plus with Full Text (EBSCO), and Dimensions Free Web App. Reporting of the search methods shall be done using the PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses search extension), wherein searches will be done in databases, study registries, gray literature, and other online sources.

Other online sources that will also be searched include Google Scholar, ResearchGate, and one source for gray literature (OpenGrey). Citation chasing and manual citation searching will be done by 2 researchers (AP and AT). The details of the search strategies used can be found in Multimedia Appendix 1.

Screening and Selection of Studies

After using the formulated search strategy in all databases and other online sources, papers or records will be imported to Rayyan (Rayyan Systems Inc) for screening. Deduplication will be performed using the same software. Two researchers (PK and AH) will independently screen the titles and abstracts of the exported papers sequentially. Full-text papers of potentially eligible studies will be retrieved to determine their final inclusion and data extraction (Figure 2 [27]). If papers are to be eliminated, the reasons for elimination will be documented.

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Figure 2. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram to describe the study selection process.

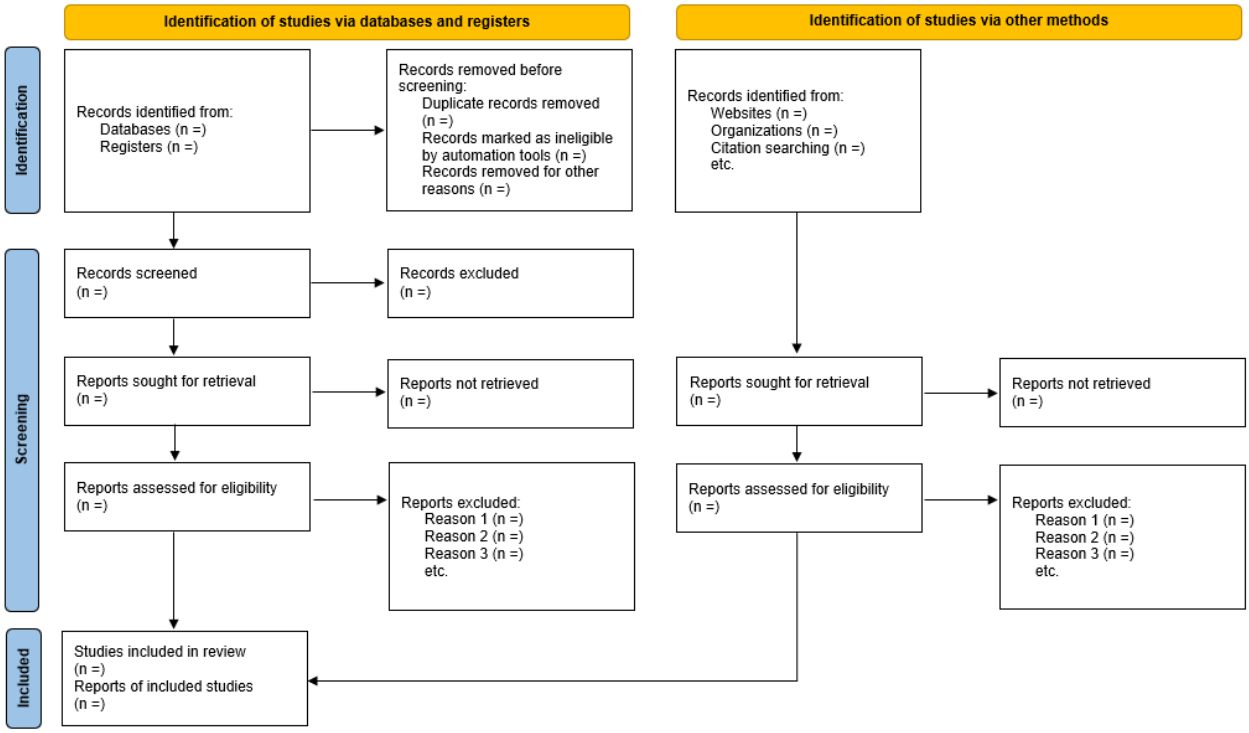

In case of disagreements, conflicts will be resolved; however, for papers where conflicts cannot be resolved, 2 reviewers (AP and AT) will be consulted for the final decision (Figure 2).

Process of Data Extraction

Two researchers (AP and AT) will analyze each of the included papers and extract the relevant data elements. To ensure precision, error-free, and complete extraction of data elements, extraction will be done independently. The extracted data will be tallied, and disparities will be resolved by discussions with the other 2 reviewers (PK and AH). Corresponding authors of papers will be contacted for more information or missing information in the published record if required.

Elements of Data Extraction

Elements of data are summarized in Textbox 1. Data not stated shall be reported as **“**NS,” and unclear data shall be reported as **“**unclear.” A pilot test of the 2 researchers shall be done to ensure uniformity in understanding and procedure.

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Textbox 1. Data elements to be extracted for the data summarization and analysis.

Headings and subheadings

- Study details
  - Study title
  - Study author
  - Year of publishing
- Details of the added metal oxide nanoparticle
  - Type of nanoparticle used
  - Size of nanoparticle used
  - Concentration of nanoparticles used
  - Effect of metal oxide nanoparticle morphology on the strength
- Methods of sample fabrication
  - Treatment of nanoparticles
  - Method of dispersion of nanoparticles
  - Details of used acrylic used
  - Method of acrylization
  - Method of sample finishing
  - Storage of samples before testing
- Testing and sample details
  - Testing or sample fabrication guidelines followed
  - Sample size used
  - Sample dimensions
  - Details of testing mechanism
- Results and conclusion
  - Mean and SD of the strength tested
  - Conclusions

Methodological and Risk-of-Bias Assessment

The assessment of the quality of the included papers will be performed using the modified CONSORT (Consolidated Standards of Reporting Trials) guidelines [29]. The risk of bias will be assessed individually by 2 researchers (PK and AH), and any disagreements will be resolved by the third reviewer (AP) based on the modified Cochrane Risk of Bias tool; scoring will be done as described in a previous study [26].

Data Extraction

The extracted data will be presented in tabular form. The table will report the extracted variables as listed above in the *Elements of Data Extracted* section. Following data extraction, narrative as well as quantitative analyses will be performed.

Data Analysis and Summarization

The results of all finally included studies will be described succinctly in the form of a summary table. A random-effects model will be used to calculate pooled estimates, as this is a more robust estimate regardless of heterogeneity [30]. Cochran Q and I^2 statistics will be used as indicators of heterogeneity. The pooled estimates of the primary end points will be calculated as the weighted mean differences with 95% CIs using the Comprehensive Meta-analysis Package (CMA version 3.0). Sensitivity analysis will be conducted to identify studies that may have severely affected the pooled estimates. Exploratory subgroup analyses by different moderator variables will also be conducted to examine sources of heterogeneity. A funnel plot and Egger linear regression test will be used to assess publication bias [31]. The significant level will be set as 2-sided and $P<.05$. Forest plots will be used to present the data.

Results

After running the search in the 5 databases, a total of 1837 papers were found. Of these, 1752 were found to be duplicates, leaving 85 potential records that will be screened for titles and abstracts, and analyzed based on the inclusion and exclusion criteria. A similar search was conducted on other online sources, resulting in the identification of 129 papers that will be further

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analyzed based on inclusion and exclusion criteria. Citation chasing will be done on the finally selected papers. These numbers may slightly vary, once we update our search. The study was initiated in November 2023, where the research questions were clearly defined and search strategies were formulated. The proposed study is expected to be completed by December 2024.

The results of this systematic review and meta-analysis will be disseminated to the academic community through possible avenues, such as scientific conferences and publication in a peer-reviewed journal. A full timeline of the systematic review process is shown below in Figure 3.

Figure 3. Dissemination plan of the systematic review and meta-analysis. Colored cells depict the timeline of completion of the proposed work.

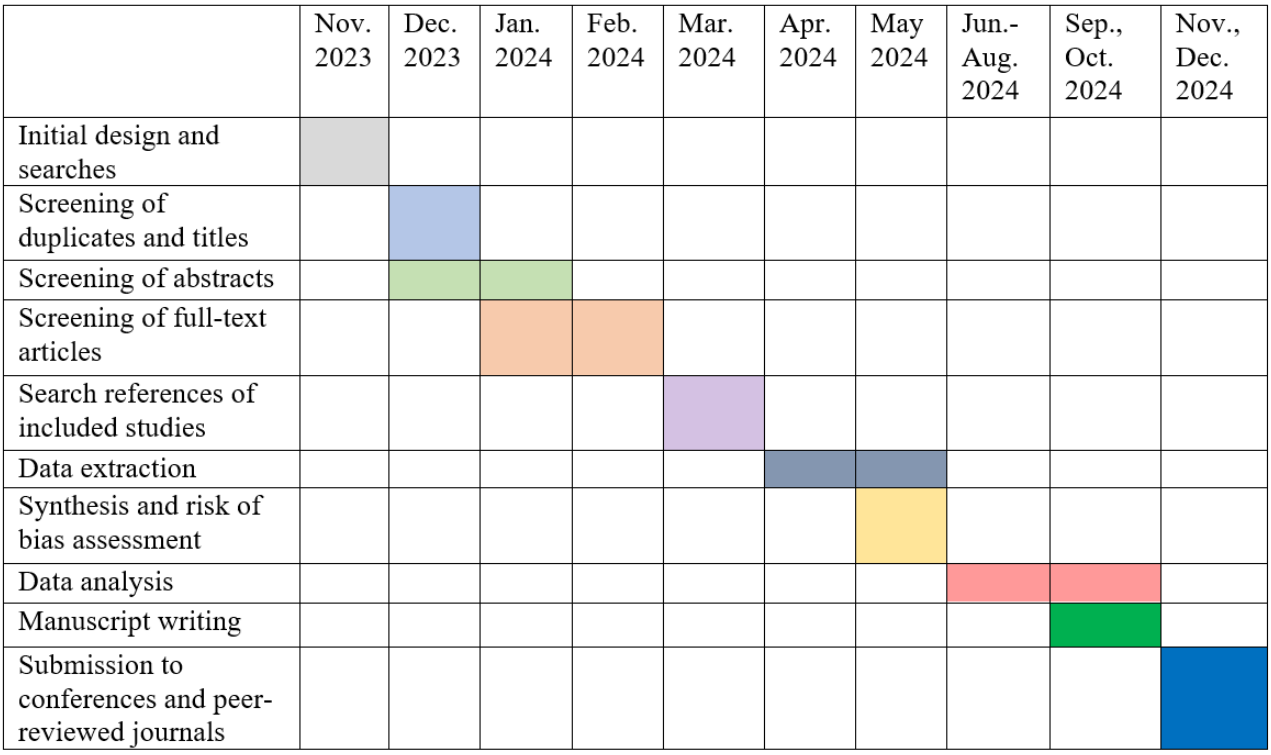

Discussion

Principal Findings

The proposed systematic review will provide collective evidence that evaluates the effects of the addition of metal oxide nanoparticles on the different types of strength of heat-cured PMMA. It further attempts to analyze different methodological factors that can affect the strength of metal oxide nanoparticle–reinforced, heat-cured PMMA.

Previous research has shown that even though metal oxide nanoparticles can improve the mechanical properties of PMMA, they do so at certain concentrations and particle sizes [24,32-35]. Therefore, this systematic review further aims to analyze the effect of different sizes of metal oxide nanoparticles that can affect the strength. Similarly, the concentration of the nanoadditive plays a significant role in the mechanical properties, as with increased percentages, there are agglomerates formed that adversely affect the properties of the nanocomposite [23].

Other methodological factors, such as surface treatment of the nanoparticles, have also been shown to affect the properties of the nanocomposite. The use of a silane coupling agent improves the bonds between the matrix and the filler [36]. Surface treatments have also been shown to lower the surface energy of the nanoparticles, thereby preventing agglomeration or cluster formation [37]. On similar lines, following standard guidelines for testing or sample fabrication can play a crucial role in determining the robust methodology followed in the study as well as affect the results obtained. Over the years, an optimized methodology has been followed by standard organizations across countries [38].

With the advances in nanotechnology, there are several types of metal oxide nanoparticles being used and tested for their effects. To the best of the authors' knowledge, no systematic review has attempted to evaluate and compare the effect of these different metal oxide nanoparticles on the different strengths (flexural, impact, transverse, compressive, tensile strength, and fracture toughness) of the heat-cured PMMA. We anticipate determining the optimum metal oxide nanoparticle addition conditions to heat-cured PMMA to achieve the most favorable mechanical properties about strength.

The results of the review can be used to fabricate heat-cured dentures reinforced with metal oxide nanoparticles with improved mechanical properties, subsequently improving the longevity of the dentures reducing fractures and deformation. The results of this review would also generate relevant consideration for future research to improve the quality of DBM used and continued improved quality of life for patients with dentures.

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Strengths and Limitations

The strength of the review is in the rigorous methodology that will be followed. To enhance the likelihood of locating relevant papers on this topic, a medical librarian was involved in developing a thorough search strategy. Second, robust inclusion and exclusion criteria will be followed, which will also ensure scientific rigor in answering the specific research question. Finally, all variables that can affect the strength of nanoparticle-reinforced PMMA will be analyzed either qualitatively or quantitively.

This systematic review will have some limitations that should be taken into consideration. The studies chosen for this systematic review and meta-analysis may exhibit a degree of heterogeneity due to variations in the acrylic used and the strength testing techniques. This review is limited to heat-cured PMMA resins only and does not consider other types of resins such as light-cured, autopolymerizing resin; 3D printed resins; and computer-aided design and computer-aided manufacturing denture materials. This review is restricted to pure metal oxide nanoparticles and does not consider hybrid nanoparticles. This review will not include studies published in languages other than English. Although an exhaustive literature search was performed, there may be a possibility of missing literature pertinent to the research question, due to the vast measure of articles published on this topic.

Conclusions

This systematic review will analyze the impact of the incorporation of metal oxide nanoparticles on the different types of strength of heat-cured denture base resins. This review shall determine the optimal size and concentration of metal oxide nanoparticles to enhance the strength of heat-cured denture base resins. This study may also provide insights into the optimal methodology for adding metal oxide nanoparticles, such as following guidelines and surface treatments of the nanoparticles, to enhance the strength of heat-cured denture base resins.

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Data Availability

Data sharing is not applicable to this paper, as no datasets were generated or analyzed during this study.

Authors' Contributions

PK, AP, and KB managed the conceptualization of the study. PK, AH, AP, CP, and KB contributed to the methodology. PK, AH, and AP performed data curation. KB performed formal analysis and funding acquisition. PK, AH, AP, AT, CP, VG, HK, JK, and KB handled the investigation. PK, AH, AP, AT, and KB contributed to the project administration. PK and KB managed the resources. PK, AH, AP, AT, VG, and KB managed the software. PK and KB performed supervision. PK, AH, AP, AT, CP, VG, HK, JK, and KB performed validation. VG and HK performed visualization. PK, AH, AP, AT, CP, VG, HK, JK, and KB contributed to writing–original draft. PK, AH, AP, AT, CP, VG, HK, JK, and KB contributed to writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies used in different databases.
[DOCX File , 14 KB - resprot_v13i1e59999_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CuO: copper oxide
DBM: denture base material
OSF: Open Science Framework
PICOS: Population, Intervention, Control and Outcome Study
PMMA: polymethyl methacrylate
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses search extension
SiO2: silicon dioxide
TiO2: titanium dioxide
ZnO: zinc oxide
ZrO2: zirconium oxide

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Protocol

Psychoeducational Burnout Intervention for Nurses: Protocol for a Systematic Review

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Abstract

Background: Nurses face high levels of stress and emotional exhaustion due to heavy workloads and demanding work environments. Prolonged exposure to these stressors predisposes nurses to burnout, which can adversely affect patient care. Addressing burnout among nurses requires a multifaceted approach, involving both personal and organizational strategies. While organizational strategies target systemic workplace issues, personal interventions are often favored for their ease of implementation, immediate benefits, and empowerment of health care workers through stress management and resilience-building. Prioritizing evidence-based interventions to mitigate burnout among nurses is crucial for managing occupational stress and promoting well-being. Person-directed psychoeducation is an effective personal intervention strategy used to equip nurses with the appropriate knowledge and skills to handle stressors, thereby safeguarding their mental health and ensuring high-quality patient care.

Objective: This protocol proposes a systematic review that aims to identify and assess the effectiveness of person-directed psychoeducational interventions for nurses. The review aims to pinpoint effective interventions that can be implemented to manage burnout and support the mental health of nurses.

Methods: This systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. In total of 5 electronic databases (PubMed-MEDLINE, EBSCOhost, Ovid MEDLINE, Scopus, and ScienceDirect) will be searched for studies published between January 1, 2014, and December 31, 2023. The search will encompass 3 main keywords: “nurses,” “burnout intervention,” and “burnout.” Predefined eligibility criteria will guide the screening process. Data will be extracted to address the objectives of the review. The risk of bias for each study will be assessed using Joanna Briggs Institute Critical Appraisal Tools.

Results: Preliminary searches have been initiated since February 2024, with the review expected to be completed by June 2024. The expected results will include a comprehensive list of psychoeducational interventions and their effectiveness in reducing burnout among nurses. The review will highlight interventions that demonstrate significant impact in published studies from various countries.

Conclusions: Given the rising prevalence of burnout among nurses and its detrimental effects on individuals and health care organizations, the findings from this systematic review are expected to inform health care policy and practice. By evaluating different interventions, it will provide insights into the most effective strategies, contributing to evidence-based practices that support nurses’ mental health and well-being. The findings can support stakeholders in developing and implementing targeted strategies to combat nurse burnout, ultimately enhancing the quality of patient care and health care delivery. In addition, the findings will also offer valuable information for researchers, guiding future practice and research in this area.

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Trial Registration: PROSPERO CRD42024505762; https://tinyurl.com/4p84dk3d
International Registered Report Identifier (IRRID): DERR1-10.2196/58692

(JMIR Res Protoc 2024;13:e58692) doi:10.2196/58692

KEYWORDS

burnout intervention; burnout; psychoeducation; nurse; systematic review; protocol; evidence-based intervention; effectiveness; psychoeducational intervention; mental health.

Introduction

Background

In recent decades, health care systems have undergone significant transformations characterized by increased complexity and heightened demands in patient care [1]. This evolution is marked by a surge in the severity of medical conditions experienced by patients in hospitals, necessitating a more intricate and intensive approach to their treatment [2]. Health Care Professionals (HCPs), the frontline professionals responsible for delivering medical care, find themselves immersed in a work environment that has become more challenging and fast-paced, necessitating them to enhance their skills and expertise to meet the escalating demands of medical practice. Consequently, the responsibilities undertaken by HCPs have multiplied, requiring them to juggle multiple facets of patient care with higher precision and efficiency [3]. Long working hours and heavy workloads have become the norm, placing an extraordinary burden on HCPs. As a result, the intense nature of their work has contributed to a pervasive issue known as burnout [4].

The *ICD-11* (*International Classification of Diseases, 11th Revision*), defined burnout as a syndrome stemming from chronic workplace stress that is not effectively managed. It encompasses feelings of exhaustion, depersonalization, and a decreased sense of personal accomplishment [5]. The dimension of exhaustion is described as a feeling of physical and emotional fatigue, leading to a significant decrease in energy levels due to prolonged work-related stress. Next, the depersonalization dimension involves a sense of detachment or disengagement from one's work, often resulting in negative attitudes or cynicism toward work, colleagues, and the organization. Finally, the reduced sense of personal accomplishment refers to a perceived decline in competence and effectiveness in professional roles, often manifesting as diminished productivity and motivation. Burnout is different from stress and other psychological disorders because it involves the coexistence of these 3 elements. In addition, burnout is characterized by a prolonged experience of these symptoms, distinguishing it from stress [6].

Nurse burnout is a significant concern in health care settings. Work-related stress is a prominent factor contributing to this issue [7]. Nurses, often considered the backbone of health care provision, face high levels of stress and emotional exhaustion that can lead to burnout. The development of burnout in nurses is a complex issue influenced by various factors [8], including excessive workload, inadequate staffing, and interpersonal conflicts involving patients, guardians, and medical staff [9]. Furthermore, the lack of control over their work and decision-making with a need to provide efficient care in a limited timeframe can create a stressful environment that further predisposes them to burnout [10]. Moreover, the absence of good leadership support [11], and access to resources and guidance, can amplify stress levels and contribute to burnout among nurses.

Globally, numerous studies with varying burnout prevalence rates have been reported in different regions, highlighting the magnitude and severity of the problem worldwide. A systematic review conducted in 2013 found that burnout prevalence ranged from 22% to 40% among nurses in 10 European countries [12]. Asian countries were not spared of the same burnout epidemic among nurses. A meta-analysis conducted by Woo et al [13] revealed that the Southeast Asia and Pacific regions recorded the highest prevalence (13.7%) of burnout among all 6 global regions. A study conducted in Malaysia by Abd Wahab et al [14] highlights the prevalence of work-related stress among health care workers, particularly nurses, with a prevalence of 24.3%. Similarly, another national-level survey revealed that approximately 1 in 4 (24.4%) nurses in the public sector experienced burnout, with hospital nurses having a slightly higher prevalence (25.8%) than primary care nurses (19.3%) [15].

The consequences of nurse burnout are extensive [16], ranging from impact on individual physical and psychological well-being, job satisfaction, organizational commitment, and health care quality [17,18]. On a personal level, it can lead to increased stress, anxiety, depressive symptoms, reduced attention to detail, and impaired decision-making abilities, all of which can manifest as organizational issues such as increased medical errors, compromised care quality, and lower patient satisfaction [19,20]. In addition, absenteeism and high turnover rates from burnout can contribute to workforce shortages and economic implications for health care systems [21]. Hence, it is crucial to mitigate the burnout epidemic among HCPs, including nurses. Research has shown that effectively managing nurse burnout translates into significant economic benefits for health care systems. In a recent study, a hospital's annual expenses associated with turnover attributable to nursing burnout were estimated to be US $16,736 per nurse. However, it dropped to US $11,592 per nurse annually at institutions with a burnout reduction program [22].

Tackling burnout among HCPs demands a multifaceted approach encompassing person- and organization-directed interventions. A holistic solution is often the most effective [23]. Organization-directed interventions target systemic factors such as workload and organizational culture within the work

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environment [24]. It is undeniable that organizational-directed interventions remain important in addressing systemic issues contributing to burnout and fostering a supportive work environment. Nevertheless, they are difficult to implement and maintain due to inherent challenges such as resistance to change and the complexity of altering organizational structures [25] as well as the need for strong evidence in terms of long-term benefits and sustainability [26].

Consequently, person-directed interventions emerge as a favorable option for addressing burnout among HCPs, especially nurses. Person-directed interventions enhance individual skills, resilience, and coping mechanisms by offering practical tools and strategies for HCPs to manage burnout proactively [24]. Some examples of these interventions include stress management techniques and mindfulness training [27] that empower individuals to recognize and address burnout symptoms early on. They are easier to implement and can yield immediate improvements in well-being by providing the right tools, techniques, and self-care strategies [28] and fostering a sense of personal agency in managing burnout. Prioritizing person-directed interventions in the absence of organizational-directed strategies can provide practical solutions to improving well-being and job satisfaction among HCPs [29]. A physically and emotionally healthier workforce that is better equipped to navigate the complexities of the health care landscape [30] can ultimately enhance patient outcomes and overall health care quality [31].

Review Questions

Burnout represents a significant challenge within the health care sector, particularly among nurses. Despite the critical need for effective burnout interventions, the optimal strategies for addressing nurses' burnout remain unclear, primarily due to inconclusive evidence on the effectiveness of specific burnout interventions for nurses. Although several reviews have been published on interventions to reduce nurse burnout, their target groups are different from ours. For instance, Zhang et al [32] focused on nurses as well as physicians, whereas Lee and Cha [33] targeted clinical nurses solely.

Our review will examine a wider range of psychoeducational burnout interventions, including but not limited to mindfulness training, in contrast to the reviews by Suleiman-Martos et al [34] and Sulosaari et al [35], both of which focused on the effects of mindfulness training on burnout among nurses. In addition, a recent comprehensive evaluation of the efficacy of individual-based methods to lessen nursing burnout was carried out by Hsu et al [36]. Our systematic review seeks to close this gap by offering a thorough study of numerous psychoeducational interventions, assessing their efficacy in various nursing contexts, and identifying significant moderators and mediators that affect intervention results. This approach will provide a more comprehensive understanding of how various strategies can be combined to synergistically reduce burnout symptoms among nursing personnel.

In response to this evidentiary gap, we aim to systematically review and analyze published studies on person-directed psychoeducational burnout interventions and evaluate their effectiveness in mitigating burnout symptoms among nursing staff. Guided by a comprehensive analytical framework, this investigation will address the following research questions: (1) What available person-directed psychoeducational burnout interventions are used across various health care settings to reduce nurses' burnout levels? (2) Which of these interventions has effectively managed burnout among nurses? (3) What are the challenges and facilitators of these interventions?

Ultimately, we aimed to provide a comprehensive overview of effective person-directed psychoeducational burnout interventions tailored to nurses based on existing research evidence. In addition, this review seeks not only to delineate effective strategies but also to identify gaps within the existing literature and areas that require further investigation in the context of psychoeducational burnout interventions for nurses in the current health care setting. Using an inclusive methodological approach, this review will critically evaluate a broad spectrum of studies and settings, ensuring a thorough assessment of intervention strategies.

Methods

Overview

The systematic review will adhere to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 checklist (Multimedia Appendix 1) [37] to ensure a rigorous and transparent approach. These guidelines provide a standardized framework for conducting systematic reviews, ensuring that the review process is comprehensive and replicable with minimal bias. The review protocol has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42024505762) [38]. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication and promotes transparency, thereby reducing reporting bias. The final review will be reported following the PRISMA statement [39]. Necessary amendments to this protocol will be reported and published with the review results.

Search Strategy

To ensure a thorough and comprehensive literature retrieval, we will screen 5 electronic bibliographic databases, that consist of PubMed-MEDLINE, EBSCOHost, Ovid MEDLINE, Scopus, and ScienceDirect. These databases are known for their comprehensive inclusion of medical and scientific publications. Our search strategy, designed for maximal sensitivity, will leverage a meticulously curated combination of Medical Subject Headings terms, subject-specific headings, and keywords. These terms are strategically chosen to encapsulate core concepts and variables pertinent to our research inquiry. Furthermore, Boolean operators ("AND" and "OR") will be used to refine the information retrieval process. These operators allow for the combination of different search terms, enabling precise modification of the search scope to either expand or narrow down the results according to the specific requirements of the study.

The PICO (Population, Intervention, Comparison, and Outcomes) framework guides our search strategy. This

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framework facilitates the organization of our search strategy by identifying the relevant elements of the research question and aligning them with corresponding search terms. The application of the PICO framework in orchestrating our search strategy underscores our commitment to a systematic and evidence-based review process. The detailed application of the PICO framework and the corresponding search terms and strategies is outlined in Table 1. This structured and strategic approach to literature search is pivotal in ensuring the exhaustive coverage of relevant studies, thereby contributing to the rigor and comprehensiveness of our systematic review.

Table 1. Search strategy using the PICO (Population, Intervention, Comparison, and Outcomes) framework.

PICO elements	Keywords	Search terms	Search strategies
Population	Nurses in health care settings	Nurse	(nurse*) AND
Intervention	Psychoeducational burnout intervention	Burnout intervention	((psychoeducation) OR (coping) OR (burnout intervention*) OR (cognitive behavioral therapy) OR (cognitive behavioural therapy) OR (mindfulness) OR (stress reduction)) AND
Comparison	—[a]	—	—
Outcomes	Reduce burnout	Burnout	(burnout)

[a]Not applicable.

Eligibility Criteria

Table 2 outlines the eligibility criteria based on the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) model [40]. The focus will be on nurses working in health care settings worldwide. “Nurse” encompasses all licensed nursing professionals, considering international variations in terminology while “health care setting” refers to institutions where nursing care is administered. This approach embraces countries with diverse income levels, ensuring inclusivity across low-, middle-, and high-income economies. By incorporating studies from varied health care systems and contexts, we hope to obtain a comprehensive understanding of the issue at hand, accounting for differences in nursing practices, resources, and cultural factors impacting burnout and its interventions.

In addition, the review will also analyze delivery modalities, evaluation tools, and implementation challenges of burnout interventions among nurses. It aims to assess the impact of interventions on reducing burnout and address implementation hurdles, such as limited resources or resistance to change. Identifying these challenges provides insights for future interventions.

The search will only include studies with quantitative research methods, allowing for objective measurement and statistical analysis of burnout levels, hence ensuring that findings are based on measurable outcomes rather than subjective interpretations [41]. Quantitative research provides consistency and replicability through standardized tools [41], enhancing the generalizability of results to a broader population of nurses. The search will prioritize studies reporting baseline and postintervention burnout changes, allowing for a thorough evaluation of intervention effectiveness over time. Burnout assessment will form the main outcome. Validated self-reported questionnaires must be applied in the studies to ensure reliability and validity in measuring burnout, enabling standardized and objective data collection across studies. Studies within the past decade will be targeted to ensure that recent publications with updated research findings are retrieved. The review will exclude gray literature as the preliminary scan by the researchers revealed a sufficiently large number of studies with good quality and reliability and have undergone a rigorous peer-review process. The decision to exclude gray literature was made because of limited accessibility, inconsistent indexing, and difficulties in assessing the quality and reliability of information [42].

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Table 2. Eligibility criteria based on the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) model.

PICOS model categories	Description
Population	• Nurses working in health care settings across any country
Intervention	• All studies on interventions focused on person-directed psychoeducational approaches to address burnout among nurses in health care settings
Comparison	• An inactive control group that did not receive an intervention or received usual care, OR • An active control group that received an alternative intervention for burnout
Outcomes	The following elements will be examined: • Characteristics of burnout interventions • Changes in burnout levels from preintervention to postintervention, including evaluation tools • Implementation challenges of burnout interventions
Study design	• Publications that are written in the English language with full text and are peer-reviewed journal papers • Studies conducted between January 1, 2014, and December 31, 2023 • All quantitative studies that involve case and control groups (randomized controlled trials, nonrandomized experimental studies, and cohort studies)

Data Management

Study Selection

Our systematic review protocol will use a meticulous multilevel screening approach to streamline the process of identifying relevant literature on psychoeducational burnout interventions for nurses. In the initial stage, study titles and abstracts will be screened, followed by a thorough examination of the full texts of the selected studies to determine the eligibility criteria. Searches, eligibility assessments, and data extraction will be performed independently in an unblinded standardized manner by all team members working in pairs. Any discrepancies will be resolved by seeking the consensus of a third team member. Next, the full-text appraisal will be performed on selected articles before the list of included studies is finalized. Similarly, any discrepancies between each pair of reviewers will be resolved through broader team discussions and mutual agreement. Subsequently, all selected studies will subsequently be imported into Google Sheets, a web-based spreadsheet editor, to facilitate organization and further review. This collaborative approach ensures a comprehensive and impartial selection of studies. Outcomes from both screening levels will be meticulously documented, adhering to the PRISMA guidelines. The screening process will be recorded through the PRISMA flow diagram in Figure 1, including the reasons for study exclusion at each stage, ensuring transparency and accountability of the study selection process. This systematic and collaborative approach to study selection and data management is crucial to ensure the integrity and validity of our systematic review.

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Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram.

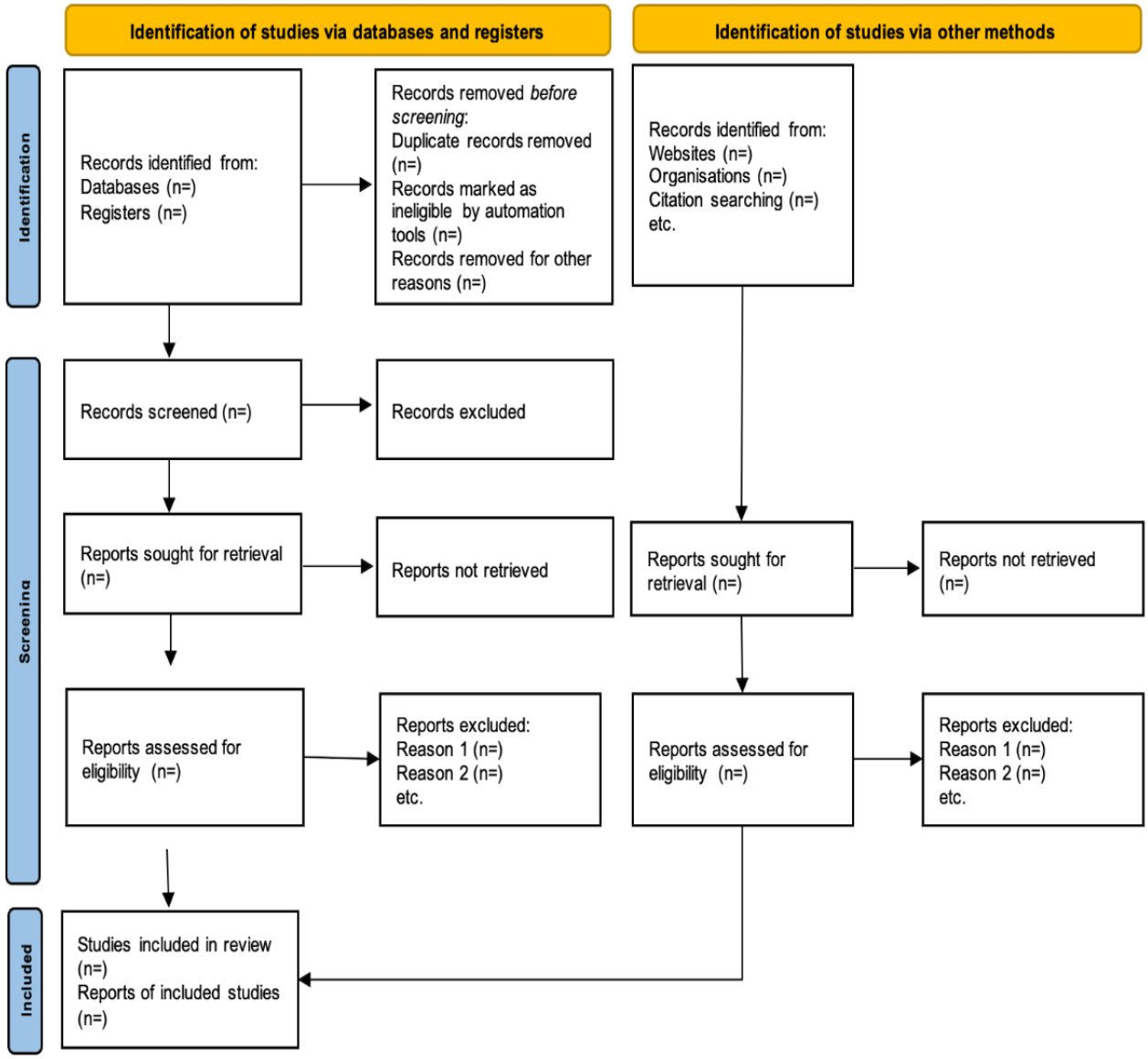

Data Extraction

Data extraction will be conducted independently and in an unblinded, standardized manner by all team members working in pairs. This approach ensures a thorough and accurate data extraction from the finalized paper. This process will use a standardized data extraction form to capture comprehensive information pertinent to our research question. Any reviewer disagreement regarding the extracted data will be resolved through discussion and consensus among all team members. To further validate any unclear data, the corresponding authors of the studies may be contacted to provide any missing information or additional details. This step is crucial to generate a more comprehensive understanding of the interventions and enhance the overall quality of the systematic review. The extracted data will encompass various aspects relevant to the current review (Table 3).

All extracted data will be documented in Google Sheets to enable efficient collaboration between all team members in organizing and analyzing the data. This approach ensures that all team members have real-time access to the data, facilitating a transparent and efficient review process. No external software or tool will be used for data extraction and management, underscoring our commitment to a straightforward and accessible method of handling the data gathered in the review. This structured approach to data extraction is designed to ensure the reliability, accuracy, and comprehensiveness of our review findings.

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Table 3. Data extraction template.

Sections	Description
Section 1: Bibliometric details	
Authors name	For example, Smith J.
Year of publication	For example, YYYY
Title	Title of the study
Journal	Name of the journal
Country	For example, Africa
Section 2: Study characteristics	
Study design	Provide the study design used in the study
Study location	Provide the location where the study was conducted
Sample size	Provide the total number of participants in the intervention and control group
Target population	Provide the target population in the study
Section 3: Intervention characteristics	
Name of intervention	Provide the name of the intervention
Content of intervention	Describe the content of the intervention
Implementer	Provide the facilitator of the intervention
Frequency of intervention	Provide frequency of implemented intervention to participants of the study
Duration of intervention implemented	Provide duration from the start of intervention until the end
Comparison control group	Provide information if the comparison group was given any intervention
Burnout measurement tool	Provide the name of the burnout measurement tool used in the study
Follow-up frequency	Provide a timeline of when pre- and postintervention follow-up is done
Section 4: Outcome	
Outcome of intervention	Describe reported burnout level pre- and post-intervention
Facilitator factors	Provide facilitators identified, if available
Barrier factors	Provide barriers identified, if available
Limitation of study	Provide limitations of study, if available

Quality Appraisal

The methodological quality of the studies included in our review will be rigorously assessed using the critical appraisal tools developed by the Joanna Briggs Institute (JBI), an esteemed international research organization that has developed various tools for evaluating the effectiveness and appropriateness of health care interventions. Specifically, the JBI Critical Appraisal Tool for Assessment of Risk of Bias for Randomized Controlled Trials [43] and JBI Critical Appraisal Checklist for Quasi-Experimental Studies [44], which feature 13 and 9 questions respectively, will be used to evaluate the reporting quality of the papers. These tools will facilitate a detailed examination of internal validity aspects, including biases related to selection and allocation, administration of intervention or exposure, assessment, detection and measurement of outcomes, participant retention, as well as statistical conclusion validity. The responses to the questions are categorized as “yes,” “no,” “unclear,” and “not applicable.” A study is considered “unclear” if it does not provide explicit information for a specific question. If a question is irrelevant to the study’s context, it is labeled as “not applicable.” A scoring system will be applied, where when a question is answered with “yes,” it is assigned a score of 1 point. However, if the answer is “no,” “unclear,” or “not applicable” no points are awarded. Based on these responses, the quality scores will be organized and displayed in a table format. To ensure a comprehensive and objective evaluation, 2 reviewers will evaluate the quality of each study independently, with their ratings remaining confidential to each other to maintain impartiality. Any discrepancies in the assessment of the studies will be addressed through discussion among the reviewers until a consensus is reached. A third reviewer will be consulted to provide additional input and facilitate resolution if necessary. In addition to assessing the risk of bias in individual studies, the overall quality of evidence across all the papers will also be evaluated. This meticulous quality appraisal process aims to provide a robust understanding of the methodological strengths and limitations of the included studies, bolstering confidence in the review findings.

Data Synthesis

In the data synthesis phase, all the included studies will be examined comprehensively. Study characteristics and quality, as well as the effects of the interventions on nurse burnout, will

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be tabulated. This process will be underpinned by a narrative synthesis approach to organize and summarize and organize the extracted information from each study thematically. This approach enables the identification of effective psychoeducational interventions for managing nurses' burnout levels.

An integral part of our data synthesis will involve conducting subgroup analyses to assess the differential effectiveness of psychoeducational programs among nurses. This analysis is designed to discern specific characteristics that may influence the outcomes of psychoeducational interventions. We will categorize subgroups based on the type of psychoeducational intervention received, including online programs, in-person workshops, and blended learning formats. Through this meticulous approach, we aim to determine how the mode of delivery impacts intervention effectiveness, thus contributing valuable insights into optimizing burnout management strategies within the nursing profession.

To ensure transparency and adherence to reporting standards, the PRISMA guidelines will be followed when reporting the results. These guidelines provide a structured framework for reporting systematic reviews and meta-analyses, ensuring the findings are presented comprehensively and standardized. By adhering to these guidelines, the review will maintain a high level of methodological rigor and enhance the credibility and reproducibility of the results.

Results

The study was initiated in February 2024 by forming a research team and assigning respective roles. The systematic literature review was commenced in February 2024, and data synthesis was expected to be concluded by May 2024 and the review by June 2024. The findings will be used in developing a psychoeducation program tailored for nurses in our country. Further dissemination to an international audience will also be undertaken through peer-reviewed journal publications and scientific presentations (PRISMA flowchart provided in Figure 1).

Discussion

Expected Results and Practical Implications

This systematic review is important because it comprehensively maps existing research and literature pertaining to psychoeducation as a tool for managing burnout among nurses. By systematically analyzing a wide range of intervention strategies across diverse health care settings, this review will explore the most effective methods and contribute to a deeper understanding of burnout intervention, providing valuable insights for health care practitioners and policymakers. This systematic review marks the initial phase of a comprehensive research effort to develop a person-directed psychoeducational burnout intervention package tailored for nurses within our country. The primary objective of this review is to identify and evaluate person-directed psychoeducational interventions that have demonstrated effectiveness in mitigating burnout among nurses. This review will serve as a foundational framework for developing comprehensive intervention packages tailored to nurses' specific needs in various health care settings. By incorporating diverse methodologies, durations, and delivery formats, the review aims to offer a holistic view of effective strategies.

To the best of our knowledge, no other work has systematically reviewed the effectiveness of psychoeducational intervention in mitigating burnout among nurses. This review is anticipated to provide multi-faceted outcomes that contribute to research and practice in nursing and health management. As a start, we will identify effective psychoeducation-based person-directed intervention strategies tailored to address burnout among nurses that can be incorporated as pivotal components of the intervention package to reduce burnout and promote well-being among nurses. Highlighting the challenges and successes inherent in implementing these interventions will offer detailed insights into their practical implementation alongside real-world applicability and scalability considerations. Furthermore, this review places great focus on the practical implications of applying these interventions in real-world settings. Understanding the challenges and accomplishments of these interventions will provide valuable insights into their feasibility, scalability, and applicability. This knowledge is critical for health care organizations that want to incorporate evidence-based methods into their daily operations to help nurses' mental health and well-being.

Empowering nurses and other HCPs with the knowledge and resources is a prerequisite for proactive burnout mitigation. Thus, the insights garnered from this review will inform the development of evidence-based interventions and policies for seamlessly integrating psychoeducation and person-directed approaches into existing practices that prevent and manage burnout among nurses. This review may stimulate improvements in job satisfaction, retention rates, and overall patient care quality. Furthermore, effective burnout interventions hold the potential to yield substantial cost savings for health care systems by mitigating turnover rates, absenteeism, and medical errors associated with burnout, thereby enhancing the standard and safety of patient care delivery. Empowering nurses with knowledge and resources for proactive burnout mitigation is essential. The findings from this review will inform the development of evidence-based interventions and policies, integrating psychoeducation and person-directed approaches to prevent and manage burnout among nurses. These insights could lead to improved job satisfaction, retention rates, and overall patient care quality. Effective burnout interventions also hold the potential to yield substantial cost savings for health care systems by reducing turnover rates, absenteeism, and medical errors associated with burnout.

Last but not least, this review will identify notable gaps in this literature and areas and guide future research endeavors. In-depth investigations into the efficacy and implementation of psychoeducation-based person-directed interventions for burnout prevention and management among nurses will foster continuous progress and innovation in the field, besides providing insight into similar adaptation for other HCPs.

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Limitations

This review is subjected to certain limitations. First, since our search was conducted solely using electronic databases, the exclusion of unpublished or gray literature may potentially result in the oversight of some studies. The omission of gray literature might lead to losing valuable insights or unpublished findings regarding burnout interventions among nurses. However, including gray literature may complicate systematic retrieval and quality assessment, potentially affecting overall reliability and introducing heterogeneity.

Second, our decision to restrict the review to English-language publications could narrow its scope by possibly excluding relevant studies in other languages. We opted for English-language studies due to practical considerations, that is the broader accessibility of English publications and limited translation resources. In addition, our focus on studies from the past decade was intended to capture this landscape of burnout interventions, but this approach may introduce selection bias.

Conclusion

Given the increasing prevalence of burnout among nurses and its adverse effects on both individuals and organizations, this systematic review is timely and crucial. The findings are expected to provide a robust evidence base for health care policy makers and practitioners to develop and implement effective psychoeducational interventions tailored to the specific needs of nurses. By identifying successful strategies and understanding the barriers to their implementation, this review aims to support the development of targeted approaches to manage nurse burnout. In the long run, enhancing nurses' well-being will lead to improved patient care quality and overall health care delivery, benefiting both health care providers and recipients.

Acknowledgments

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Data Availability

All data generated and analyzed in this study are available upon request from the corresponding author.

Authors' Contributions

All authors made equal contributions to this work. All authors have reviewed and approved the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 34 KB - resprot_v13i1e58692_app1.docx]

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Abbreviations

HCP: Health Care Professional
***ICD-11*:** *International Classification of Diseases, 11th Revision*
JBI: Joanna Briggs Institute
PICO: Population, Intervention, Comparison, and Outcomes
PICOS: Population, Intervention, Comparison, Outcomes, and Study design
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Racial and Ethnic Differences in Traumatic Brain Injury Outcomes From 2009 to 2023: Protocol for a Systematic Review

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Abstract

Background: In 2009, Gary and colleagues reviewed prior research examining racial and ethnic differences in outcomes after traumatic brain injury (TBI). Over the past 15 years, advances in research and changes in the demographic composition of the United States warrant a comprehensive understanding of racial and ethnic disparities after TBI.

Objective: A systematic review will be conducted to examine racial and ethnic differences in TBI outcomes from 2009 to 2023.

Methods: Preliminary searches and study screening processes will identify relevant English-language articles published from January 2009 to December 2023 using the CINAHL, Gale OneFile, PsycINFO (Ovid), and PubMed electronic databases. Relevant articles will include quantitative or mixed method approaches, involve individuals with TBI or their caregivers, and compare 2 or more groups by race or ethnicity on post-TBI outcomes. Quality will be assessed using the Newcastle-Ottawa Scale. This systematic review protocol was developed following PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. Results will be summarized, and a subgroup analysis may be conducted based on demographics (eg, age, gender, or sex).

Results: We have already identified abstracts using the search strategy for all 4 of the included electronic databases. We recently updated the search and will begin abstract screening of the additional abstracts identified from the last search completed in January 2024. This systematic review is anticipated to be completed by fall 2024, and its findings will be disseminated to the scientific community, persons with TBI, caregivers, and the lay audience.

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Conclusions: This systematic review will advance our understanding regarding outcome disparities among minoritized individuals with TBI, examine progress over the past 15 years in minimizing barriers encountered by these racial and ethnic groups, and provide professionals with a roadmap illustrating existing gaps in rehabilitation care, making way for further development and implementation of evidence-based interventions to improve health equity in TBI outcomes.

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KEYWORDS

traumatic brain injury; TBI; health disparities; racial and ethnic differences; injury outcomes; outcomes assessment; social determinants of health; neurorehabilitation; evidence-based interventions

Introduction

The estimated global prevalence of traumatic brain injury (TBI) is over 55 million, a number that has continued to grow over the past 3 decades [1]. From 1990 to 2016, the incidence of TBI increased by 3.6% and prevalence increased by 8.4%; in 2016 alone, there were 27 million new cases [1]. From these estimates, approximately 0.7% of the world's population live with a medically treated brain injury. TBI is prevalent among all age groups and commonly causes long-term functional, cognitive, behavioral, and social challenges that require a multidisciplinary approach to rehabilitation [2,3]. As emphasized by the 2022 US National Academies of Sciences, Engineering, and Medicine report [4], one's ability to access appropriate care and maximize functional recovery is dependent upon numerous personal and social factors. These factors include race, ethnicity, age, gender, socioeconomic status, geographical location, preinjury status, and the presence of comorbidities, among others [5]. Of these social determinants of health (SDoH), racial and ethnic disparities are the most reported health disparities following TBI [6].

Earlier studies of racial and ethnic health disparities following TBI rehabilitation using large databases focused primarily on adults categorized as "minorities versus Whites." The seminal paper written by the early pioneer in the TBI field examined the impact of *minority status* on functional outcomes using the TBI Models Systems national database, which included 586 African American (37%), Hispanic (7%), and White (53%) individuals categorized as "minority versus Whites" [7]. Rosenthal et al [7] used the Community Integration Questionnaire and determined that minority status affected long-term community integration (CI), with adults with TBI from racial and ethnic minority groups faring worse in long-term productivity and social integration compared to White adults. With time, the TBI field began to conduct more rehabilitation research focused mainly on adults.

In the early and mid-2000s, TBI researchers began centering on race as a moderator of functional outcomes following TBI [8-10]. By the mid- to late 2000s, research on racial and ethnic minority status and TBI exploded, and numerous studies narrowed around postinjury outcomes such as CI, competitive employment, job stability, and life satisfaction. In these studies, "minority," "Hispanic," or "Black" adults reported worse outcomes in regard to functioning, employment, life satisfaction, and CI relative to White adults with TBI [11-17] and without significant differences between minority groups [11], even after accounting for income [17].

When exploring outcomes after TBI, the needs of caregivers of persons with TBI are important factors that must be addressed. Racial differences in kinship patterns have been identified, with African American caregivers spending significantly more time in direct caregiving and reporting more depression than White caregivers [18]. Black and Hispanic caregivers made greater use of emotion-focused coping skills and used more traditional ideology with a greater sense of obligation and family duty. Interestingly, caregiving did not lead to greater perceived burden [19]. By 2009, there were no studies specifically examining racial and ethnic differences among older adults with TBI. However, within the past decade, more studies have examined disparities in care and outcomes among older adults with TBI.

In more recent years, interest has increased in understanding how racial and ethnic minority groups are differentially impacted by a TBI. While TBI sequelae largely depends on specific aspects of the brain injury itself and patient characteristics (eg, age, premorbid medical health, and psychiatric health), the effects from the brain injury occur in a social and cultural context. Recent systematic reviews have tried to shed light on racial and ethnic disparities in TBI outcomes. Their findings align with many of the conclusions by Gary et al [14], suggesting that racial and ethnic disparities exist across acute care, rehabilitation, and long-term outcomes and in domains of community reintegration, degree of disability, and return to work when compared to non-Hispanic White individuals [20]. Race and ethnicity are also the most prevalent SDoH implicated in the incidence of TBI [6]. We recognize that both interpersonal and structural racism are often the drivers of disparities experienced by minoritized racial and ethnic groups [21].

Prior reviews have either been non-TBI specific, included other clinical groups such as stroke and cardiac arrest [22], excluded patients with mild TBI [23], focused exclusively on health utilization during acute care [22], or included studies that had narrow outcomes such as mechanisms of injury and other pathophysiology in racial and ethnic minority groups [24]. Although not a systematic review, the work by Gary et al [14] inspired our proposed work. Therefore, we aim to conduct a rigorous comprehensive analysis of the literature over a 15-year period focused on racial and ethnic disparities in TBI outcomes (eg, treatment, functional, psychosocial, emotional or behavioral,

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and caregiver) across the lifespan and including all injury severities. We hypothesized that racial and ethnic disparities in outcomes persist across all outcome domains and across the continuum of care regardless of age or injury severity.

Methods

Study Design

Following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines (Multimedia Appendix 1) [25], we outline an updated systematic review of quantitative and mixed methods studies reporting racial and/or ethnic differences in TBI outcomes across the lifespan. The systematic review protocol is registered in PROSPERO (CRD42023394529).

Eligibility Criteria

The PICOS (Patient, Intervention, Comparison, Outcomes, and Study Design) framework was used to develop our systematic review question and guide the development of the literature search strategies [26]. The elements are detailed below:

- Participants (P): Individuals with a TBI of any age and any severity. Studies including people with an acquired brain injury (eg, stroke, tumor, and hypoxic injury) in addition to TBI may be included if the results for persons with TBI are separated. If there are sufficient studies using pediatric, adult (age >18 years), or older adult (aged 55+ years) populations or caregivers, then we will decide if we want to separate the findings and develop separate review articles for each population.
- Intervention (I): Not applicable.
- Comparison (C): Racial or ethnic group identity, where 2 or more ethnic or racial groups must be compared. Comparisons between “majority” and “minority group” and between “non-Hispanic White” and “ethnic or racial minority group” are examples of other comparisons that may be included. We will acknowledge the earlier race or ethnicity language used in earlier studies, but our review will use current, inclusive race or ethnicity language.
- Outcomes (O): Outcomes following TBI, such as treatment, function, psychosocial, cognition or neuropsychological, and emotional or neurobehavioral. Studies may also address caregiver outcomes.
- Study design (S): All quantitative or mixed methods studies (eg, observational research, cohort study, prospective, and longitudinal) will be included. Qualitative studies, abstracts, editorials, review articles, commentaries, dissertations or theses, case reports, policy statements, and epidemiological studies will be excluded. All included papers will be in the English language and published from January 1, 2009, to December 31, 2023.

The Determinants of Inequities in Neurological Disease, Health, and Well-being framework by the National Institute of Neurological Disorders and Stroke will be used to also identify the individual-to-structural determinants of health reported in the included studies [21]

Information Sources

We have performed preliminary searches and piloted the study screening process using the CINAHL, Gale OneFile, PsycINFO (Ovid), and PubMed electronic databases to identify relevant quantitative or mixed method articles published in English. On January 9, 2023, we conducted a preliminary database search to ensure the inclusion of literature from January 1, 2009, to December 31, 2022. We recently conducted our final search on January 10, 2024, to identify relevant articles published since the last search through December 2023. We will hand search the reference lists of relevant systematic reviews and articles to identify additional studies not previously identified. All references identified through the searches will be exported into the online review software Covidence. Duplicates are removed automatically by the Covidence software.

Search Strategy

A variety of Medical Subject Headings and relevant key words were developed and used by a medical librarian with significant experience in performing literature searches. The full search strategies for each database are included in Multimedia Appendix 2. Results were filtered by dates and English language.

Study Selection

Using Covidence, at least 2 of the 7 reviewers will independently screen each reference according to the title and abstract. All disagreements will be resolved either by the pair or by the inclusion of a third reviewer. During the initial preliminary search, we were able to identify 1746 records that were imported for screening (693 from CINAHL, 507 from PubMed, 326 from PsycINFO, and 220 from Gale OneFile). Of these, 520 duplicate references were automatically removed by Covidence. An additional 326 records were identified and added to Covidence (61 from CINAHL, 200 from PubMed, 21 from PsycINFO, and 44 from Gale OneFile) during the updated search through December 2023, and 103 duplicates were removed. We updated our search criteria to include Alaska Native, resulting in an additional 47 records identified (11 from CINAHL, 22 from PubMed, 10 from PsycINFO, and 4 from Gale OneFile). As a result, we added 12 additional abstracts after 35 duplicates were removed. We will begin the review of the 235 additional abstracts included. Upon abstract review completion and resolving any disagreements, we will begin the full-text screening phase. The full-text articles will be uploaded to Covidence to facilitate the review. Each full-text reference will be reviewed for inclusion by 2 independent reviewers out of the 7 total reviewers. Any disagreements will be resolved as a group. Full-text articles will be included in the data abstraction or collection phase. We will hand search the reference lists of relevant review articles that were flagged during the abstract and full-text screening phase, as well as review the references of the included full-text articles. We will also use hand searching methods to manually identify any relevant studies not identified through our included databases. A PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram will document the selection process, including the reasons for exclusions.

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Data Collection

The review team will meet to reflect on the full-text review process and included articles, then finalize the data extraction form and its elements for inclusion in Covidence. We will pilot test the data extraction form on at least 4 of the included articles before completing the process with the remaining included full-text articles. We will follow the same review process as before by having the reviewers work independently in pairs to extract data for each included article within Covidence. A third reviewer will resolve any discrepancies. If needed, the group will discuss the discrepancies to finalize the included data. If data are not clear in the article, the investigators will contact the authors to confirm.

Data Items

The following data will be extracted from each of the included articles: source reference; publication year; population (ie, pediatric populations, adults aged ≥18 years, or older adults aged ≥55 years); race or ethnicity; sex or gender; geographic setting (eg, within or outside of the United States); study setting (eg, acute or inpatient, rehabilitation, outpatient, or community); sample characteristics; sample size; nature of study (descriptive, quantitative, or mixed methods); study design (eg, cross-sectional, cohort, or longitudinal); description and type of individual-, interpersonal-, institutional-, community-, or structural-level factors discussed (eg, socioeconomic status, health care coverage, housing, citizenship status, neighborhood location, or food security); measures of effect (eg, proportions, relative risks, odds ratios, or hazard ratios); outcome measures; and summary of author interpretations or conclusions.

Risk of Bias and Quality Assessment

Two investigators out of the 7 will independently assess the methodological quality of each individual article based on the Newcastle-Ottawa Quality Assessment Scale [27]. A third reviewer will address any disagreements, or the team will meet to discuss and decide as a group. If needed, study authors will be contacted to provide additional details or clarification.

Outcomes

Primary post-TBI outcomes include treatment outcomes (eg, emergency department, discharge disposition, rehabilitation placement or access, and rehabilitation treatment), mortality, functional outcomes (eg, functional status at admission, discharge, and 1+ years follow-up using the Functional Independence Measure, Disability Rating Scale, and Functional Status Examination instruments), psychosocial outcomes (eg, employment or productivity, community integration, marital status, quality of life or life satisfaction, and driving), cognitive or neuropsychological outcomes (eg, executive functioning, processing speed, and working memory), and emotional or neurobehavioral outcomes (eg, posttraumatic stress, postconcussion disorder, depression, anxiety, and aggression). Studies may also address as secondary outcomes those of caregivers of people with TBI (eg, caregiver burden, family functioning, psychological symptoms, posttraumatic stress disorder, and quality of life). However, if sufficient studies are identified based on caregiver outcomes, then we will report the findings in a separate review.

Data Synthesis

We plan to conduct a narrative synthesis instead of a meta-analysis due to the high likelihood of heterogeneity and the diversity of confounding variables and the data included in the studies. For the narrative synthesis, we will synthesize the types of studies, methodologies used, methodological considerations, findings of the studies (particularly regarding racial and ethnic differences in outcomes), evidence of findings, limitations of methods, and a summary of author conclusions. If sufficient data are identified, we will conduct a subgroup analysis by age (eg, older adults or pediatric populations) or by sex or gender.

Ethical Considerations

No ethical approval from an institutional review board was required for this systematic review.

Results

As mentioned previously, the initial protocol has been registered in PROSPERO (CRD42023394529). We have already identified abstracts using the search strategy for all 4 of the included electronic databases. We recently updated the search and will begin abstract screening of the additional abstracts identified from the last search completed in January 2024. We will then begin full-text review, and we anticipate that entire systematic review will be completed by fall 2024. The study results will be disseminated through an open-access publication in a peer-reviewed journal, and we will present our findings at an international or national meeting. We also hope to develop a nontraditional dissemination product that can be shared with persons with TBI, their families, and the lay audience.

Discussion

Expected Findings

The goal of this work is to seek and review additional literature regarding outcomes of minoritized populations with TBI across the recovery process. Outcomes of interest are broad and inclusive of physical and cognitive functioning, as well as emotional and behavioral outcomes. This work will also review treatment outcomes in studies examining differences between minoritized and nonminoritized communities. This comprehensive review builds upon and updates decades-long research examining racial and ethnic disparities in TBI outcomes as the field continues to investigate ways to achieve health equity in the population with TBI.

This work is especially appropriate currently as many fields of research increase focus on SDoH [21,28], which affect all areas of a person's environment, from education to health care access and quality, to economic stability and the social context. With the increased awareness and inclusion of SDoH in research since 2009, this review can contribute to the identification of higher-level intervention opportunities in terms of clinical and community programming, as well as policy changes affecting treatment across numerous points in the continuum of care. With this review, we expect to gain additional insight into progress or continuing barriers to health equity and be able to

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identify any gaps in the literature in the science of treatment and recovery for minoritized populations with TBI.

Study Limitations

Limitations of our study include the use of only English-language studies, which can limit the representativeness of the review. Our study is also limited by the validity of the articles we include. The heterogeneity of the articles can make it difficult to draw conclusions; however, to facilitate interpretation, we will summarize the findings based on outcomes of interest. The definitions of race and ethnicity are informed socially and are continuously changing; these definitions could change in the future and alter the implications of our review. The treatment of racial and ethnic groups as homogenous could also lead to erroneous conclusions. We focused only on racial and ethnic social identities; therefore, we must acknowledge that there are multiple dimensions of social identities that may influence disparities in outcomes after TBI.

Conclusions

The results of this updated systematic review could provide greater insights into ethnic and racial disparities experienced following TBI across the lifespan. We hope that the results of this updated systematic review will not only corroborate the findings of Gary et al [14] and others, but also add to the knowledge base regarding post-TBI outcome differences by race or ethnicity. It will also include a comprehensive analysis of disparities across the various stages of recovery, outcomes, and settings and will use rigorous and systematic processes of review, data collection, and extraction. Instead of being one of many disparities-focused reviews, we hope that our findings will be serve as foundational knowledge to inform clinical practice; guide the development of patient-centered and culturally-guided services, programs, and interventions to address identified disparities; as well as to inform policy and practice changes to address systemic inequities that continue to perpetuate health disparities for marginalized communities with TBI.

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Authors' Contributions

MRP, KGT, PG, MS, and AHL designed the study. MRP and KGT supervised the study. MRP, KGT, PG, CRA, CKO, MS, and AHL wrote the original draft and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies for the CINAHL, Gale OneFile, PsycINFO (Ovid), and PubMed databases.
[PDF File (Adobe PDF File), 184 KB - resprot_v13i1e58763_app1.pdf]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.
[PDF File (Adobe PDF File), 137 KB - resprot_v13i1e58763_app2.pdf]

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Abbreviations

CI: community integration
PICOS: Patient, Intervention, Comparison, Outcomes, and Study Design
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
SDoH: social determinants of health
TBI: traumatic brain injury

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Protocol

A Comparison of Conventional Root Canal Sealers With Ones That Use Green Synthesized Nanoparticles for Antimicrobial Activity: Protocol for a Systematic Review

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Abstract

Background: Root canal failure and secondary endodontic infection are frequent clinical scenarios in dentistry. The main microorganisms implicated in root canal therapy failure are persistent *Enterococcus faecalis*, *Candida albicans*, and *Staphylococcus aureus*. To combat the impact of disease resistance, scientists are concentrating on alternative antimicrobial root canal sealers. Nanomaterials are a recent development in endodontic materials that exhibit great antimicrobial properties, making them an ideal material choice for root canal sealers.

Objective: This systematic review aims to compare the antimicrobial properties of conventional root canal sealers to those incorporating green synthesized nanoparticles between 2010 and 2024.

Methods: A well-constructed protocol was established and registered with PROSPERO (CRD42021286373). Ethics approval was obtained from the Biomedical Research and Ethics Committee from the University of the Western Cape (UWC; BM22/1/4). PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) reporting guidelines were followed. The included criteria demonstrate the green synthesized nanoparticles studies where the nanoparticles (NPs) are incorporated in root canal sealers. MeSH (Medical Subject Headings) terms were used for the search strategy of the systematic electronic databases for articles published in English between 2010 and 2024. The selected databases included Scopus, PubMed, Web of Science, Science Direct, EBSCOhost, SpringerLink, and Wiley Online. A quality assessment tool for laboratory studies will be used to critically appraise the included studies. If applicable, statistical measures (mean, SD, etc) will be used for data analysis and presentation of the results.

Results: The protocol is registered with PROSPERO. A preliminary search was conducted using a determined search strategy across 8 electronic databases, and the review is now complete.

Conclusions: It is anticipated that the results of this systematic review may reveal the increased interest and application for nanoparticle-enhanced root canal sealers. This will aid in the future development of root canal sealants and mitigate the risk of endodontic failure.

Trial Registration: PROSPERO CRD42021286373; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=286373

International Registered Report Identifier (IRRID): DERR1-10.2196/51351

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KEYWORDS

root-canal sealers; nanoparticles; antimicrobial activity; root canal; antimicrobial; dentistry

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Introduction

Background

In the United States, more than 20 million root canal treatments are completed annually [1]. Worldwide, the international prevalence of people having at least one tooth with a root canal filling is 55.7% (95% CI, 49.6%-61.8%) [2]. Conventional nonsurgical endodontic treatment has a success rate of around 80% [3-5]. However, 22.8% of treated teeth may develop clinical and radiological findings known as apical periodontitis, and 10% of these may require retreatment [6]. The most common reason for endodontic failure is secondary or persistent endodontic infection [7].

Due to numerous and challenging anatomical variances, complete eradication of microbes from the root canal system is not always possible. The root canal system cannot always be completely cleaned of bacteria and their by-products by mechanical and chemical preparation. As a result, an efficient antimicrobial sealer is paramount for a successful root canal treatment [8,9].

In root canal obturation, a variety of sealers with similar properties have been used. Biocompatibility and a potent antimicrobial effect are the main criteria for developing a root canal sealer [10,11]. Conventional root canal sealers exhibit mild to strong antibacterial properties, but once set, the materials possess a diminished antimicrobial capacity [12,13]. Zinc oxide eugenol sealers, for example, have high antibacterial effects at first because of eugenol leaching. However, the antibacterial activity fades with time as eugenol gradually dissipates [14]. A systematic review found that most conventional root canal sealers exhibit strong antibacterial effects immediately after mixing, but these effects gradually decrease and disappear as the sealer hardens over time [13]. The antimicrobial effect of the commercially available bioceramic sealers revealed diverse degrees of antimicrobial capacities of compared sealers [15,16]. A newer root canal sealer with a more potent antimicrobial effect is sought. In recent years, nanomaterials have been used widely in dental materials. Nanoparticles (NPs) are characterized by a small size that is reflected by a large surface area to mass ratio. In addition, its chemical reactivity is improved when compared with the large size of the original material [17,18]. New strategies to improve the success rates of root canal treatment include modifying root canal sealers with strong antimicrobial agents such as nanomaterials [19,20]. Research has shown that the integration of nanomaterials into root canal sealers may result in a drop in the bacterial count penetrating the dentinal tubules [21,22].

Description of the Secondary Endodontic Infection

The failure of endodontic treatment is defined as the “recurrence of clinical symptoms along with the presence of a periapical radiolucency” [23]. Therefore, clinical presentation and radiographic findings are used to evaluate endodontic failure. The following clinical and radiological criteria are used to diagnose endodontic failure: (1) the presence of clinical signs and symptoms, (2) enlargement of the pre-existing apical radiolucency, (3) formation of a new apical radiolucency related to the tooth, and (4) persistent apical radiolucency related to a tooth that had root canal therapy before 4 years [24]. Failure may occur due to multiple factors, predominantly the presence of persistent intracanal and extracanal microorganisms. Inadequate cleaning and shaping, poor canal obturation, overextension of filling material, poor apical and coronal seals, missed canals without treatment, inadequate access cavity, and some procedural errors such as broken files, ledges, and perforations are other factors contributing to root canal treatment failure [25]. Microbes isolated from teeth undergoing endodontic retreatment include *Enterococcus faecalis*, *Staphylococcus aureus*, and *Candida albican*s [26-29].

Description of the Intervention

In biomedical applications, the use of nanotechnology has developed as an encouraging technique for future applications**.** NPs are considered microscopic particles with dimensions ranging from 1 to 100 nm [30]. Different types of NPs have been produced in the last decade. Metal and metal oxide NPs, including silver and zinc oxide, revealed strong antimicrobial effects against endodontic pathogens [31,32]. Furthermore, NPs also exhibit low cytotoxicity to oral tissues [33-35]. In dentistry, NPs are considered effective antimicrobial agents and are superior in comparison to other materials, with a low capacity for bacterial resistance [36].

However, the synthesis of NPs is a complex procedure. There are 2 major pathways for NPs synthesis. The first one is a top-down approach, whereby NPs are synthesized by reducing the size of the desired material from its initial bulk state into smaller particles [37]. Different chemical and physical techniques are used in the reduction, such as mechanical milling, chemical etching, laser ablation, sputtering, thermal ablation, and explosion processes [37]. The second is a bottom-up approach where small structures such as atoms and molecules are joined into larger building blocks and assembled to form the final NPs [37]. Chemical and biological techniques are used in the formation of NPs using the bottom-up approach.

In the biological technique, a green synthesis method involves using plants and their extracts, microorganisms such as bacteria, fungi, actinomyces, and algae [38]. The green synthesis or biosynthesis method is favored over chemical and physical techniques as it is considered to be more environmentally friendly, economical, consumes less amount of energy, biocompatible, and nontoxic [39].

The Clinical Significance of This Systematic Review

Inflammation of the pulpal tissues and resultant endodontic infection occur when microbes find a convenient portal of entry into the pulpal space [40]. Primary endodontic infection ensues when the microorganisms attack the healthy pulp, causing pathological changes that are followed by pulp necrosis [41]. Secondary endodontic infection is caused when the endodontically treated teeth get reinfected as a result of microorganism invasion into the root canal system [41]. The secondary endodontic infection might happen due to an inadequate coronal seal leading to coronal leakage and intraradicular and extraradicular infection [42,43]. Persistent endodontic infection is observed because of the presence of microorganisms that are part of either primary or secondary

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endodontic infection. The microorganisms resist the chemo-mechanical preparation as well as the root-filling materials and become a source of persistent infection [44].

This review will have great clinical significance because it will help clinicians choose a more effective root canal sealer for endodontic treatment and identify new areas for dental materials development.

Aim

This systematic review aims to compare the antimicrobial properties of conventional root canal sealers to those incorporating green synthesized NPs between 2010-2024.

The research question for this systematic review was formulated following the PICO (Population, Intervention, Comparator, and Outcome) format as seen in Table 1: "Do root canal sealers with green synthesized nanoparticles exhibit better antimicrobial efficiency than conventional root canal sealers?"

Table 1. PICO[a] format for the research question.

Frame	Search terms
P (types of sample or participants)	Root canal sealers.
I (types of intervention)	Root canal sealers containing green synthesized NPs[b].
C (types of control or comparators)	Conventional root canal sealers.
O (type of outcome measures)	Antimicrobial effect or the resolution of infection.

[a]PICO: Population, Intervention, Comparator, and Outcome.

[b]NPs: nanoparticles.

Objectives

Our objectives are as follows:

- Objective 1: determine the antimicrobial efficacy of 2 root canal sealers (conventional vs those with NPs) in preventing secondary endodontic infection.
- Objective 2: determine the antimicrobial efficacy of root canal sealers with NPs microbiologically.
- Objective 3: determine what other research on root canal sealers with NPs was completed.
- Objective 4: determine how root canal sealers with NPs are prepared (in vitro studies).
- Objective 5: determine how antimicrobial efficacy is investigated.

The goals of this systematic review include gathering research that discusses the use of green synthetic NPs in root canal sealers and comparing their antibacterial efficacy to that of conventional root canal sealers in primary endodontic infection.

Methods

PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; Multimedia Appendix 1) reporting guidelines were followed in this study [45]. A well-constructed protocol was established and registered with PROSPERO (CRD42021286373; Multimedia Appendix 2).

According to this type of study, participants, interventions, outcome measures, and the criteria for selecting studies are described. The setting or context includes any laboratory study where green synthetic NPs were used in root canal sealers.

Types of Studies

The included studies are laboratory studies (in vitro) conducted between 2010 and 2024, where green synthesized NPs are incorporated in root canal sealers used in endodontics.

Types of Samples

All in vitro studies, the description of root canal sealers with NPs (material) preparation will be reported.

Types of Intervention

Intervention

Any green synthesized NPs included in root canal sealers.

Control

Conventional root canal sealers with no addition of green synthesized NPs.

Type of Outcome Measures

The outcomes are prespecified and include:

Primary Outcome

Resolution of infection with common endodontic microbes with the incorporation of green synthesized NPs in root canal sealers.

Secondary Outcome

The antimicrobial activity of root canal sealers modified with NPs can be measured with a variety of methods. These include Kirby Bauer tests, assay tests, direct contact tests, and colony counting. The efficacy of green synthesized NPs on microbes is reported by a clear reduction in colony numbers while measuring the colony-forming units (CFU).

The Identification of Study Searching Methods: Electronic Searches

A thorough computer search will be carried out for the primary and ongoing studies relevant to the search topic. PubMed, EBSCOhost, Science Direct, Web of Science, Scopus, Wiley Online, BioMed Central, and SpringerLink are the databases that will be used. Studies published between 2010 and 2024 will only be included in their English-language versions. Boolean operators will be used to combine key terms and database-specific functions will be developed to create search

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strategies for each database. In databases that support this function, MeSH (Medical Subject Headings) terms will be used. Duplicate results from the electronic searches will be eliminated using EndNote (Clarivate) software. Thereafter, title, abstract, and full-text screening will be performed. Searched studies will be managed through Rayyan's QCRI (Rayyan Systems Inc), an electronic online tool designed to support researchers in conducting systematic reviews.

A comprehensive search strategy focusing on the comparison of the antimicrobial effect of the root canal sealers incorporated with the green synthesized NPs and the conventional root canal sealers will be used. The following is an example of our search strategy: (antibacterial OR antimicrobial) AND (green synthesis OR plant-mediated synthesis OR biosynthesis) AND (nanoparticles OR nanomaterials) AND (root canal sealers OR root canal filling materials) AND (2010-2024).

For further references, all retrieved studies' reference lists will be observed manually by carrying out meticulous hand-searching for each study. If complete texts are inaccessible, authors will be contacted for the full texts. The PRISMA-P flowchart will be followed in reporting the search results [46].

Data Collection and Analysis: Study Selection

The data obtained through the database search will be recorded on Rayyan QCRI and subsequently screened for titles and abstracts by 2 review authors (AM and RA) independently. A data extraction sheet will be developed during these phases. The studies found to be relevant or potentially related to the search terms will be obtained and then read and analyzed by 2 different authors (AM and RA) for eligibility criteria. Any disagreement during the 2 phases of screening data will be managed by discussing with a third author (EI).

All selected and screened primary studies that do not meet the eligibility criteria will be excluded and the exclusion reasons will be shared. Secondary studies, including all types of reviews, will be omitted.

Data Management and Extraction

Using a specifically created prepiloted data extraction form, 2 review authors (AM and RA) will independently collect data on research methodology, participants, interventions, results, and conclusions from each included study. A risk-of-bias evaluation tool will be used by the 2 authors to evaluate the methodological value of all included papers [47]. Results will be reported using Tables and Figures. The retrieved information from all studies will include the following extracted data: (Authors, the title, year of publication, country, study methods, type of materials, type of NPs used, size and concentration of NPs, NPs synthesis routes, the chemicals used, the microorganisms used for antibacterial testing, specimen size, settings, sources of publication, inclusion and exclusion criteria, study methodologies, and statistical analysis). Furthermore, information regarding research funding sources, ethical approval, conclusions, comments, and other necessary correspondence will be retrieved and reported. Any ambiguous or missing data will be reported to the study authors, and any issues will be settled by consensus with the other review authors.

PRISMA-P

This tool is designed for the standardization of systematic reviews and meta-analysis protocol reporting. Poor systematic review reporting may affect the power and value of the systematic review and will be an unreliable source for clinicians and policymakers. In this systematic review protocol, the PRISMA-P checklist (Multimedia Appendix 1) will be followed. The importance of following PRISMA-P is to ensure all the steps during systematic review construction are strictly respected, this will be done by reporting every single step using the checklist [45].

Study Quality Assessment: Quality Assessment of Laboratory Studies

For laboratory studies, a critical appraisal tool that was developed by Adam and Khan [47], will be used. In this tool, the following five parameters were used: (1) sampling technique standardization, (2) explanation of sample size estimate, (3) sample calibration in agreement with ISO (International Organization for Standardization) before experimenting, (4) Validity and reliability of outcome measures, and (5) the use of statistical analysis tools (Table 1). Each of the 5 parameters will be scored using a scale from 0-2, as depicted in Table 2. A score of 0 means that the particular parameter is clearly stated in the study. A score of 1 means that the parameter is reported, but it was unclearly reported, or there is a lack of some details regarding the parameter. A score of 2 means the parameter is not reported or hard to find information related to the parameter.

For overall scoring, the total score for each study will be calculated and explained as follows: A score of 0-3 means a low risk of bias. A score of 4-7 means a moderate risk of bias. A score of 8-10 means a high risk of bias for the assessed study; hence, the study is considered of poor quality.

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Table 2. Quality assessment tool of included laboratory studies [47].

	Assessment criteria	Scores			Total score
		1	2	3	—[a]
1	Sampling technique standardization	—	—	—	—
2	Explanation of sample size estimation	—	—	—	—
3	Sample calibration in agreement with ISO[b]	—	—	—	—
4	Validity and reliability of outcome measures in agreement with ASTM[c] or ISO	—	—	—	—
5	The uses of proper statistical analysis tools.	—	—	—	—

[a]Not available.

[b]ISO: International Organization for Standardization.

[c]ASTM: American Society for Testing Materials.

Data Synthesis

If possible, the findings will be compiled, synthesized, and reported in a meta-analysis following a critical evaluation of each of the included studies. When combining data across studies, we will use inverse variance weighting and perform meta-analyses using the DerSimonian and Laird methods. To explore the consistency of effects across studies, we will calculate the I^2 statistic, which quantifies the proportion of total variation attributable to heterogeneity. In addition, we will use Kendall's τ to assess the relationship between effect sizes and study characteristics. Forest plots will be generated to visually represent the pooled estimates and individual study results. If substantial heterogeneity is detected (I^2>50%), we will conduct subgroup analyses and meta-regression to investigate potential sources of inconsistency. That will be reported in the included studies. If not, a narrative report will be generated.

Managing Missing Data

The authors of the studies will be contacted for any missing data to get any relevant missing data.

Assessment of Reporting Biases

In case of publication bias. If possible, a funnel plot will be constructed to report publication bias.

Ethical Considerations

Ethics approval was obtained from the Biomedical Research and Ethics Committee, University of the Western Cape (UWC; BM22/1/4).

Results

This systematic review protocol, as seen in Figure 1, aims to compare the biological activity of root canal sealers incorporated with nanoparticles to the conventional ones. Following the use of preset inclusion criteria, a preliminary search will be conducted using a determined search strategy across the databases, the final laboratory studies will be identified, and the data will be extracted. If possible, a meta-analysis will be constructed, or a narrative presentation of the findings will be finalized. The review process is expected to be completed by December 2024. The systematic review findings will be disseminated and submitted for publication in a peer-reviewed journal.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flowchart.

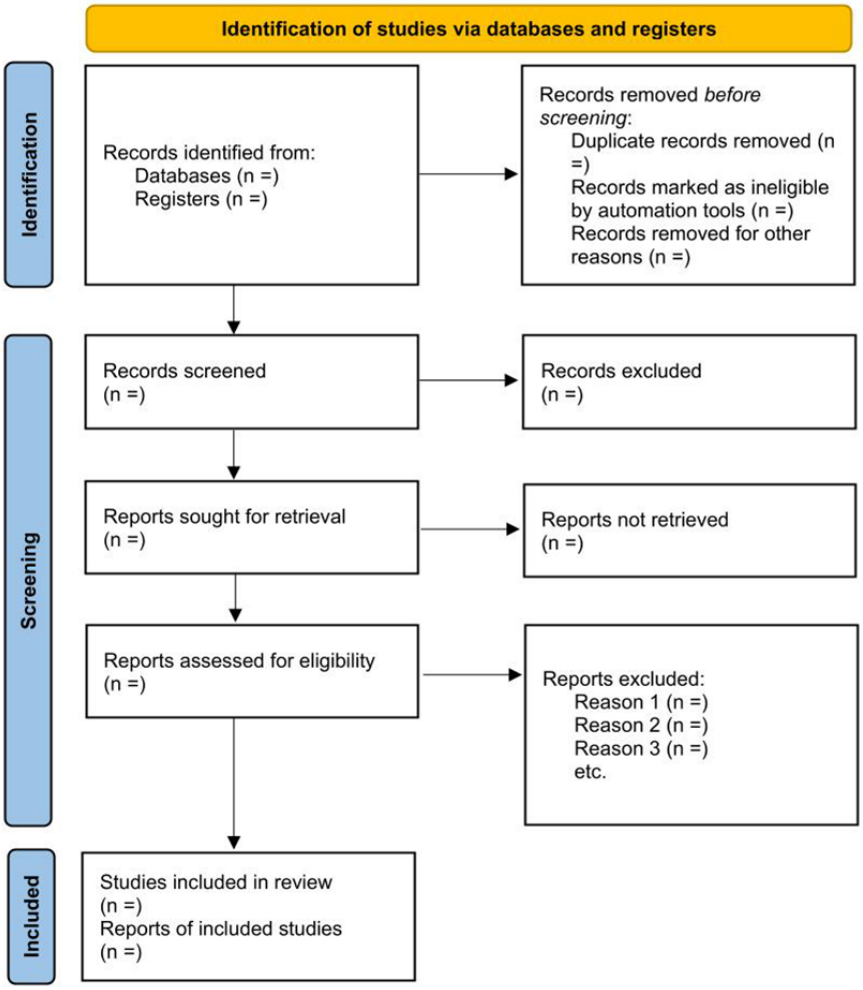

Discussion

This systematic review will comprehensively look at the antimicrobial activity of root canal sealers incorporated with green synthesized nanoparticles compared with conventional root canal sealers. We anticipated that the use of green synthesized NPs could enhance the antimicrobial activities of root canal sealers. In the literature, the incorporation of chemically or physically synthesized nanoparticles in root canal sealers revealed superior biological properties [11,48,49]. Thus, the findings of this systematic review may highlight the significance of green synthetic nanoparticles in endodontics.

Evidence-based practice is formed by the assimilation of good-quality clinical knowledge and patient values mixed with the most excellent research evidence. Systematic reviews are secondary research used to detect, appraise, and recapitulate the findings of the primary research, including laboratory and clinical trials, in order to inform the decision makers about health care–related topics. Thus, systematic review findings can be interpreted and implemented in clinical settings [50]. Conducting systematic reviews is important as it synthesizes data from many studies into 1 report [51]. Up-to-date research knowledge regarding prognostic factors, diagnostic tests, and interventions is gained by conducting precise, systematic reviews [52].

Laboratory studies involving dental materials are not often transformed into clinical trials. Commonly, the high cost of these in vitro studies means a significant financial investment is required. In addition, the production of feasible clinical research outcomes is doubtful as the translation of laboratory findings into clinical research may take longer than expected due to ethical issues. Long follow-up and observation periods during clinical trials may also play a role. The translation of laboratory findings into clinical studies is primarily caused by all the aforementioned problems.

The state of the included studies and the strength of their findings will determine whether this systematic review will have an impact on the investigator's choice regarding the use of nanomaterials in endodontics.

The anticipated limitation of this systematic review is mainly around the type of included studies. Since the subject of the search is entirely novel to the field of endodontics, there are not likely to be enough clinical studies using the necessary intervention. High-quality clinical trials with rigorous designs and a controlled setting are required for the conversion of knowledge from research into clinical practice. Furthermore, it is argued that the comparability of laboratory investigations is significantly impacted by the lack of procedure standardization across various study designs.

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Another restriction is the usage of many databases for searching; each database has its specific constraints and functionality. It is not always possible to use the same search string across all databases; some databases may not accept long search keywords. Furthermore, the different search engines use various sets of filters. In conclusion, the use of green synthesized NPs in endodontic sealers is still new. Thus, the expected transformation of laboratory studies into clinical trials will not be enough to be included in this systematic review.

Conclusion

In conclusion, this systematic review protocol aims to provide a comprehensive evaluation of the antimicrobial properties of endodontic sealers incorporated with green synthesized NPs compared with conventional root canal sealers. Using robust techniques, such as specific inclusion and exclusion criteria and using the suitable search string across various databases, leads to the inclusion of relevant laboratory and clinical studies. Finding out the quality of the acquired data will be made easier by using the proper critical appraisal tool. This review will provide useful insights into the possible advantages of using green synthesized NPs in endodontic treatment and enhance clinical practice by gathering available information and critically evaluating study methods.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RZA performed conceptualization. AM wrote the original draft. EI and RZA performed visualization. AM, EI, and RZA wrote, reviewed, and edited the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 144 KB - resprot_v13i1e51351_app1.pdf]

Multimedia Appendix 2
Prospero.
[PDF File (Adobe PDF File), 184 KB - resprot_v13i1e51351_app2.pdf]

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Abbreviations

CFU: colony-forming unit

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ISO: International Organization for Standardization
MeSH: Medical Subject Headings
NP: nanoparticle
PICO: Population, Intervention, Comparator, Outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
UWC: University of the Western Cape

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Protocol

Auricular Therapy to Control Pain in Women With Breast Cancer: Protocol for Systematic Review and Meta-Analysis

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Abstract

Background: The increased incidence of breast cancer implies the appearance of frequent symptoms associated with disease and treatments, such as pain. For the management of this issue, auricular therapy has been used in a complementary manner, especially for its safety and analgesic action.

Objective: This systematic review aims to summarize available evidence on the effects of auricular therapy on pain in women undergoing breast cancer treatment.

Methods: This is a systematic review that includes randomized controlled trials that evaluated the effects of auricular therapy on pain in women with breast cancer, as compared with other interventions (sham or placebo auricular therapy, other nonpharmacological interventions, and routine pain treatments) during the treatment of the disease. Pain, whether induced or not by cancer treatments, is the main outcome to be evaluated. The search for the studies was performed in the following databases: MEDLINE through PubMed, CINAHL, CENTRAL, Embase, Web of Science, Scopus, VHL, TCIM Americas Network, CNKI, and Wanfang Data. The reviewers have independently evaluated the full texts, and in the near future, they will extract the data and assess the risk of bias in the included studies. The certainty of the evidence will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), and a meta-analysis will be carried out to evaluate the intervention, considering the homogeneity of the results, using the Cochran Q test and quantified by the Higgins inconsistency index. The guidelines of the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) have been respected in the elaboration of this protocol.

Results: The records screening stage has been completed, and the synthesis and meta-analysis were conducted in February 2024. We hope to have finished the preparation of the paper for publication by September 2024. Review reporting will follow standard guidelines for reporting systematic reviews. The results will be published in peer-reviewed scientific journals.

Conclusions: This review will compile the strength of evidence for the use of auricular therapy in the management of pain in women with breast cancer during the treatment of the disease, identifying gaps in the available evidence as well as assisting health professionals in indicating the intervention for clinical practice.

Trial Registration: PROSPERO CRD42022382433; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=382433

International Registered Report Identifier (IRRID): DERR1-10.2196/55792

(JMIR Res Protoc 2024;13:e55792) doi:10.2196/55792

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KEYWORDS

breast neoplasms; cancer pain; pain; auricular acupuncture; auricular therapy; systematic review; meta-analysis

Introduction

Pain is a symptom commonly associated with patients with cancer [1]. Considering breast cancer, the most common in the global female population [2], it is estimated that between 40% and 89% of this population will experience pain at some point during the disease [3,4], which is why it is important to consider effective therapeutic strategies for the management of this clinical condition.

Although there have been advances in the treatment of pain in patients with cancer [5], most feel pain at some moment of the disease [6]. This symptom may or may not be associated with antineoplastic treatments, such as chemotherapy, hormone therapy, and radiotherapy; have varied intensity; be acute or chronic; and generate physical and emotional distress that negatively impacts the patients' quality of life [7-9]. Therefore, pain in patients with cancer demands special care from health care teams.

In that context, in recent years, complementary and alternative medicine (CAM) has gained ground in the area of oncology [10]. The desire to treat complications or cure cancer with holistic approaches, which influence health as a whole, enabling greater control over the treatment, is the main reason that leads these patients to seek these therapies [11]. On average, 51% of all patients with cancer use CAM, and this prevalence is even higher in women [11] with breast cancer [12,13].

There is a wide variety of therapies that encompass CAM, among which acupuncture is recognized as a complement to cancer treatment [14,15], especially breast cancer treatment [16]. Studies show that acupuncture is associated with the relief of disease-related adverse effects, such as pain [17-19].

Auricular therapy is a practice from traditional Chinese medicine, which includes, but is not limited to, acupuncture and acupressure [20,21]. According to the World Health Organization, auricular acupuncture is a microacupuncture capable of influencing the entire body [15]. This therapy was described in 500 BC in the classic text *Huang Di Nei Jing* and was later modified and updated by the French physician Paul Nogier in the 1950s [20,22].

Auricular therapy involves the relationships between the ear with the energy channels (the meridians) and the regions of the body through the theory of somatic reflexology, considering that diseases or symptoms of the body are projected onto areas of the ear [20,21]. Moreover, according to the perspective of traditional Chinese medicine, illnesses of the body are caused by an imbalance of energy (qi) in a person. Thus, auricular therapy treats health problems by stimulating points in the ear to equilibrate qi and activating the body's meridians [21,23]. This stimulation can occur through different types of needles, seeds, spherical materials, electricity, lasers, and digital pressure [20,21,23].

The number of works involving auricular therapy has grown since the 1980s [23]. Studies show that this therapy is safe, effective, and cheap for the treatment of pain in people with cancer, revealing significant advantages in its application for the relief of this symptom [24-26]. In addition, auricular therapy can help to reduce analgesic consumption and treatment adherence [24]. When applied to women with breast cancer who experience pain, the therapy demonstrates benefits in reducing this pain, in addition to improving fatigue, sleep disorders [27], constipation [28], and quality of life [29].

Thus, considering that estimates point to a significant increase in the number of cases of breast cancer and a consequent increase in cases of pain in this population [30], auricular therapy can be a safe, inexpensive, and effective complementary treatment option for that complaint. However, the effects of this intervention on pain relief, specifically in women with breast cancer, are not fully elucidated in the literature. Therefore, this investigation is necessary.

Although previous reviews have evaluated the effects of auricular therapy in patients with cancer, particularly in relation to cancer pain [18,25], the effectiveness of this intervention, specifically in women with breast cancer, is still not completely clear, as studies have included populations with different types of malignant neoplasms.

To the best of our knowledge, no previous review has evaluated the effects of auricular therapy on pain management in women with breast cancer. Thus, our objective will be to identify available evidence on the effects of auricular therapy on pain in women undergoing breast cancer treatment. In addition, we intend to evaluate (1) the effects of this auricular therapy on pain intensity, (2) the risks and safety of auricular therapy in the treatment of pain in women with breast cancer, (3) whether there are auricular therapy protocols for this clinical condition, (4) the profile of professionals who apply the therapy, and (5) at which levels of care this treatment has been offered.

Methods

Protocol and Registration

The protocol of this review is registered in the PROSPERO (CRD42022382433) and has been developed according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [31-33]. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [34] will be used to disclose future results.

Development of the Research Question

The Population, Intervention, Comparator, and Outcomes strategy was used to develop the research question [35] (Textbox 1).

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Textbox 1. Research questions were developed according to the Population, Intervention, Comparator, and Outcomes strategy.

Population, Intervention, Comparator, and Outcomes and their components

- Research question
  - What is the efficacy of auricular therapy in controlling the pain induced or not by antineoplastic treatment in women with breast cancer, as compared with sham auricular therapy (a simulated intervention that may not be physiologically inert, as it stimulates tissue and the peripheral and central nervous system, even at minimal doses, such as nonspecific or superficial needling), or the treatment of routine pain or other nonpharmacological interventions?
- Population
  - Women with breast cancer undergoing cancer treatment
- Intervention
  - Auricular therapy with seeds, metallic points, magnetic points, plastic points (crystals), radionic crystals, needles (semipermanent and systemic), stiper, electrostimulation, laser therapy, and chromotherapy
- Comparator
  - Sham or placebo auricular therapy [36], other nonpharmacological interventions, and routine treatment
- Outcomes
  - Pain control induced or not by cancer treatment and adverse events originated from the uses of auricular therapy as a pain treatment for women with breast cancer

Eligibility Criteria

Types of Studies

Studies that are a randomized controlled trial of auricular therapy to treat pain in women with breast cancer were included.

Types of Participants

The participants included women, 18 years of age and older, with breast cancer, regardless of the type of tumor and staging, including those in palliative care, and experiencing pain as adverse effects induced by cancer treatment or unrelated to the treatment.

Types of Interventions/Exposure and Comparison

Studies using auricular therapy as an intervention with any kind of device (mustard seeds or Vaccaria, metallic points, magnetic points, plastic points [crystals], radionic crystals, needles [semipermanent and systemic], stiper, electrostimulation [electroacupuncture, hai hua], laser therapy, and chromotherapy) were included. The intervention may be used by itself or in combination with other methods. The control included (1) sham or placebo auricular therapy or placebo, (2) conventional routine treatment with conventional drugs, and (3) other nonpharmacological interventions.

Types of Outcomes

The primary outcome was the intensity of pain presented during cancer treatment, evaluated through the Numerical Rating Scale, the Visual Analog Scale, and the McGill Pain Questionnaire, among other tools that may appear in the studies. The secondary outcomes, such as one's quality of life, anxiety, and depression, among others, were also identified and evaluated.

Another variable investigated in the selected study outcomes was the possible adverse effects of using auricular therapy.

Setting

The study setting was public or private health care services.

Information Sources

The literature search was performed using MEDLINE through PubMed, CINAHL, CENTRAL, Embase, Web of Science, Scopus, VHL, TCIM Americas Network, CNKI, and Wanfang Data. No time and language restrictions were applied. Abstracts and full papers were obtained for each selected study based on the inclusion criteria. Additional studies were identified through the reference list of included papers and other systematic reviews that evaluated the effects of acupuncture on pain in people with cancer. The search for gray literature was performed on Google.

Search Strategy

To determine eligible studies for inclusion in the review, 2 reviewers independently assessed the English titles and abstracts of the papers; another 2 reviewers independently assessed the Chinese titles and abstracts of the papers. The search strategy was developed with the contribution of a librarian. We used Medical Subject Headings, keywords, and free text search terms. The key search terms were as follows: ("Acupuncture, ear" OR "Ear acupuncture" OR "Auriculotherapy" OR "Auricular therapy" OR "Ear therapy" OR "Ear therapies" OR "Auricular acupuncture" OR "Ear acupressure" OR "Auricular acupressure" OR "Auricular plaster" OR "Auricular electroacupuncture" OR "Ear electroacupuncture" OR "Laser auriculotherapy" OR "Auricular point*" OR "Ear point*" OR "Acupoint*") AND ("Breast neoplasms" OR "Breast neoplasm" OR "Breast cancer" OR "Breast tumor*" OR "Breast tumors" OR "Breast carcinoma" OR "Breast diseases" OR "Mammary cancer" OR "Mammary tumor" OR "Mammary carcinoma"). The Chinese literature search terms were "疼痛," "乳癌," and "耳穴."

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Study Records

Data Management

Searches in the databases were uploaded into the Covidence [37] to aid in the selection and management of papers. This software was used to manage the references obtained through database searches, the inclusion and exclusion of papers, and the removal of duplicates.

Selection Process

The selection of the papers was performed by 4 authors independently. Initially, the titles and abstracts of the papers were read considering the eligibility criteria. The preselected papers were then read in their entirety and evaluated for eligibility to confirm inclusion in the review. When there was disagreement between the authors regarding the eligibility of the paper, a third author was called, and the 3 authors came to a consensus regarding the inclusion or exclusion of the paper. The review selection process will be presented through the PRISMA flow diagram.

Data Collection Process

Data from the included studies will be extracted by 4 independent authors. To ensure consistency of the interpretation among these authors, they will undergo initial training. The differences found in the data extracted from studies will be resolved through discussion between these 2 authors and, in case of disagreement between them, a third author will aid in the decision. One of the authors will cross the data extraction forms in order to create a final single form, filled out completely with the data.

Data Items

We prepared a form for data extraction, which will be finalized after the consensus of all authors. This form will extract data from the included studies (Table S1 in Multimedia Appendix 1). The intervention data will be extracted based on the methodological guideline for evaluating clinical trials with acupuncture STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) [38].

Risk of Bias in Individual Studies

The Cochrane Collaboration Risk of Bias Tool [39] will be used to evaluate the risk of bias in the included studies. Methodological quality will be assessed by 2 independent authors considering random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data results, selective reports, and other biases. Each of these domains will be rated based on the risk of bias as low risk, high risk, and unclear risk. Methodological biases identified by STRICTA will be related to the intervention bias. Disagreements regarding the risk of bias will be discussed and resolved by another author.

Data Synthesis and Analysis

The meta-analysis will be carried out using the program R (version 4.2.2; R Foundation for Statistical Computing) with the package *metafor*, considering the evaluations carried out before and after the intervention. Dichotomous and continuous variables will be estimated, respectively, as relative risk and mean difference, with 95% CI. For missing data, an attempt will be made to contact the corresponding authors, twice at most, with an interval of 15 days between them in order to recover them. To describe the percentage of variation among studies due to heterogeneity, the Cochran Q method and the Higgins method (I^2 statistics) [40] will be used. I^2 with values of 25%, 50%, and 75% will be considered of low, average, and high heterogeneity, respectively [41]. If the heterogeneity presents high values (I^2>50%), the authors will reach a consensus on the inclusion or exclusion of the meta-analysis in the study. The result will be presented through the forest plot [42]. If the meta-analysis is not included in the review, the selected studies will be presented through a systematic narrative synthesis.

Certainty of Evidence

We will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to evaluate the certainty of evidence [43]. Two authors will carry out this evaluation independently. When there is a disagreement between them, a third author will be consulted to resolve the disagreement.

Results

The systematic review is ongoing. On June 11, 2023, we identified 1309 records, and after title and abstract screening, 47 reports were assessed for eligibility. The risk of bias analysis and meta-analysis were completed in February 2024, and we plan to release the results of the study by submitting the paper to a peer-reviewed journal in September 2024.

Discussion

Overview

An increase in pain complaints in women with breast cancer is expected in the upcoming years, given the growing incidence in the number of cases of this disease. As a result, more effective, cheaper, and safer treatments will be a priority in health services that involve this type of health care. In this context, auricular therapy can be a complementary option for pain management. However, the evidence for its use in controlling this symptom in women with breast cancer is not fully elucidated. In addition, the lack of protocols and knowledge about the profile of professionals who work with this practice, as well as the level of health care in which it is offered, can make it difficult for patients to adhere to and use the therapy in clinical practice. Therefore, we believe that this review is extremely important, as it will provide a comprehensive review of studies already published on the subject, identifying gaps in this knowledge and presenting the evidence available to date.

Conclusions

This systematic review will provide evidence for the use of auricular therapy in the management of pain in women with breast cancer during the treatment of the disease. We believe this is an important question to assist health professionals in recommending and using the intervention in clinical practice, as well as benefiting the patients. Its results may provide direction for future studies.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data were generated or analyzed for this research protocol. Data extracted from the literature and generated during the systematic review will be included in the published paper or made available upon request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extracted from the included studies.
[DOCX File , 14 KB - resprot_v13i1e55792_app1.docx]

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Abbreviations

CAM: complementary and alternative medicine
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture

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Protocol

Effects of Injury Registry Data on Policy Making, Hospitalizations, and Mortality: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Initiated in 2021, a Brazilian project aims to establish a national injury registry, compiling comprehensive data on events and individuals across the country, irrespective of injury severity. The registry integrates information from prehospital and hospital care, diverse health systems lacking interoperability, and sectors such as firefighters and the police. Its primary goal is to enhance health surveillance by providing timely, high-quality information, guiding prevention strategies, and informing policy making. The project still aims to reduce long-term morbidity and mortality associated with injuries.

Objective: A knowledge gap remains regarding the effects of injury registries in relation to policies and injury outcomes. This protocol outlines a systematic review and meta-analysis to answer "What is the effect of implementation and use of injury registry data on policy making, hospitalization, and mortality?"

Methods: The systematic review follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, focusing on studies reporting results related to the implementation and use of injury registries, including trauma registries. Outcomes of interest include policy making, hospitalization rates or duration, and mortality. Registries within well-defined administrative boundaries will be included. Data will be collected from PubMed, Embase, Scopus, Web of Science, Lilacs, and references. Records will be independently screened by 2 reviewers, with any disagreements resolved through arbitration by a third reviewer. Homogeneous studies, with 3 or more evaluating the same outcome, may undergo meta-analysis. Subgroup analyses by registry type, injury groups, and other selected variables of interest will be conducted. Sensitivity analysis, risk of bias assessment, publication bias evaluation, and quality appraisal will also be performed.

Results: This systematic review will run from November 2023 to June 2024. No identical review was found. Search strategies were finalized, the bibliographic search started, duplicates were eliminated, and title and abstract screening began. Of 35 studies retrieved, 85 were excluded due to duplication, leaving 50 for selection.

Conclusions: This study is timely, aligning with ongoing national efforts to implement an injury registry. By synthesizing available evidence, we will identify the potential of injury registries to guide the decisions of Brazilian policy makers.

Trial Registration: PROSPERO CRD42023481528; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=481528

International Registered Report Identifier (IRRID): PRR1-10.2196/55029

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KEYWORDS

injury registry; trauma registry; policy making; health policy; wounds and injuries; outcome assessments, health surveillance; hospitalizations; mortality

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Introduction

Injuries arising from various incidents, such as accidents, falls, drownings, burns, poisonings, and acts of violence directed at oneself or others, represent a global concern. Of the 4.4 million injury-related deaths, an annual toll of 3.16 million is attributed to unintentional injuries, while injuries linked to acts of violence account for 1.25 million casualties annually. Approximately one in 3 fatalities result from road accidents, 1 in 6 from suicides, 1 in 2 from homicides, and 1 in 61 from armed conflicts. According to data from the World Health Organization, globally, approximately 200,000 young individuals aged 10 to 29 lose their lives each year, with homicides ranking as the fourth leading cause of death within this age group [1].

In Brazil, injuries and violence have consistently ranked as the third or fourth leading cause of death among Brazilians, surpassed only by cardiovascular diseases and cancer until 2015, by respiratory diseases between 2016 and 2019, and by COVID-19 during the pandemic. In 2021, there were 149,322 fatalities attributed to injuries in Brazil, equating to approximately 70 deaths per 100,000 Brazilians. Among these causes, homicides prevailed (30.5%), followed by traffic accidents (23.5%), other accidental causes (23.2%), and suicides (10.4%). Studies highlight the significance of injuries among young individuals and males in premature mortality and disabilities, making it a top-priority issue in the country [2,3].

Every year, tens of millions of individuals around the world endure nonfatal injuries, resulting in visits to emergency rooms, acute care facilities, or hospitalizations [1]. In Brazil, in 2021, the number of hospitalizations within the public health system due to injuries was 8.4 times higher than the number of deaths. That year witnessed nearly 600 injury-related hospitalizations per 100,000 Brazilians, totaling 1,247,109 hospitalizations. Among these hospitalizations, falls were the most common (34.6%), followed by other accidental injuries (24.9%), and traffic accidents (18.9%) [4].

The National Policy for the Reduction of Morbidity and Mortality from Accidents and Violence emerged as a response to the challenge of injuries as a public health problem in Brazil, given their magnitude and significance [5]. As a result of this policy, the National Policy for Emergency Care was launched in 2003 [6]. In 2004, the proposal for the creation of the National Network for the Prevention of Violence and Health Promotion was introduced [7]. Two years later, in 2006, the Violence and Accident Surveillance System in Sentinel Services (Viva) was implemented [8]. In 2010, the Life in Traffic Project was initiated, representing an innovative initiative for intersectoral coordination and data integration for the surveillance and intervention in traffic accidents, executed by 54 Brazilian municipalities [9-11].

In 2021, a project under the framework of the Institutional Development Support Program of the Unified Health System (PROADI-SUS), a collaboration between the Brazilian Ministry of Health and the Hospital Israelita Albert Einstein (HIAE), was initiated with the goal of establishing a national injury registry. This initiative aims to facilitate the integration and improve data quality from prehospital and hospital care, as well as various existing health information systems that currently lack interoperability. In addition, it seeks to incorporate data from multiple sectors involved in the topic of injuries and violence, such as firefighters and police. The primary objective of this project is to strengthen health surveillance capacity, providing timely and high-quality information, thus guiding the development and evaluation of prevention strategies and policy making in this field, incorporating data from across the country. Ultimately, these efforts aim to reduce morbidity and mortality associated with injuries [12].

An injury registry is a systematic and standardized database that records detailed information about events and individuals who have sustained injuries, regardless of their severity or whether they result from accidents, falls, violence, or other causes. These databases can encompass a wide range of injuries, from minor ones that may not require hospitalization to more serious injuries that do [13]. Traumatic injuries that require acute care delivered to hospitalized patients, typically resulting from high-impact events such as car accidents, severe falls, or gunshot wounds, are usually included in trauma registries [14]. Both types of registries play important roles in injury prevention, research, and health care management. The primary distinction lies in the scope and severity of injuries each type of registry deals with. They include but are not limited to patient demographic data, the circumstances, characteristics, and outcomes of each injury case, prehospital care, hospital management, and outcomes, with the aim of providing a comprehensive view of the injury landscape in a given region, country, or health care system. These registries often leverage information technology systems to efficiently collect, store, and analyze data. Their primary objectives include enhancing understanding of injury trends, identifying high-risk populations, and evaluating the effectiveness of injury prevention initiatives and trauma care systems. In addition, they allow policy makers to efficiently target resources and implement evidence-based interventions [15-17].

The success of trauma systems has been reported in various localities, with their effectiveness well-established [15,17-19]. Estimates indicate a 15% reduction in the odds of mortality [20,21]. Furthermore, the implementation of trauma registries has been well-documented, and these registries are consistently recognized as essential tools for improving trauma systems and policy making [16,22]. However, a substantial knowledge gap remains regarding the effects of injury registries that include all injuries, irrespective of their severity [22].

Considering the current efforts to implement an injury registry in Brazil, there is an urgent need to establish an evidence base in this context. Therefore, this protocol outlines a systematic review and meta-analysis aimed at investigating the effect of injury registries on policy making and injury outcomes, particularly in terms of reducing hospitalizations and mortality. Hence, the research question guiding this review is “What is the effect of implementation and use of injury registry data on policy making, hospitalization, and mortality?”

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Methods

The development of this protocol adhered to the reporting recommendations outlined in the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015. The checklist is filled in Multimedia Appendix 1 [23]. The systematic review report itself will comply with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for 2020 [24].

Eligibility Criteria

To formulate the eligibility criteria for this systematic review we used the PICOS (Population, Intervention, Comparison, Outcomes, and Study) structure, as shown in Table 1. Included articles must report results or effects related to the implementation and use of data from injury registries, including trauma registries, for at least one of the outcomes described in Table 1. These registries should be established within cities, states, provinces, countries, hospitals, or other well-defined administrative boundaries. Nonrandomized intervention studies or analytical observational studies will be included, such as cohort studies, case-control studies, before-and-after studies, and interrupted time series studies, among others. Descriptive observational studies will be included exclusively for the policy making outcome.

Table 1. Eligibility criteria are presented in the PICOS (Population, Intervention, Comparison, Outcomes, and Study) structure.

Acronym	Description	Criteria
P	Population	Cities, states, provinces, countries, hospitals, or other well-defined administrative boundaries with injury surveillance.
I	Intervention	Implementation and use of injury registries, including trauma registries.
C	Comparison	No restrictions on comparators.
O	Outcomes	Policy making (changes and design, including preventive measures, health care improvements, surveillance actions, among others), hospitalization rates or duration, and mortality.
S	Study	Nonrandomized intervention studies or observational studies

Studies will be excluded if they do not provide any description of the injury or trauma registry or are based on sources other than an injury or trauma registry. Furthermore, studies with a specific focus solely on the registry of a particular body part or a specific age group, or those that do not involve human participants, will be excluded. Articles without full-text availability will also be excluded, as well as opinion articles, editorials, letters to the editor, conference abstracts, systematic or literature reviews, and any other studies that lack empirical research regarding the effects of injury registries. Also, studies using decision models or other estimation methods for outcomes will be excluded. The excluded studies will be documented in an attached table within the systematic review.

There will be no restrictions on publication date, country, or language. Studies published in languages other than English, Portuguese, or Spanish will be translated using Google Translate.

Information Sources

The search will be conducted in the MEDLINE databases through PubMed, Embase, Lilacs through the Virtual Health Library, Scopus, and Web of Science databases. To ensure comprehensive literature coverage, we will also review the reference lists of included studies and relevant systematic or literature reviews identified through the search.

Search Strategy

The implemented search strategies are presented in Multimedia Appendix 2. The search terms used were defined for the population, intervention, and outcomes, as outlined in the PICOS structure. These terms include controlled vocabulary terms specific to each database, as well as uncontrolled vocabulary terms, synonyms, natural language, related terms, expressions, and truncations, all aimed at broadening the scope of the search.

The strategies were developed by a librarian (ETR) experienced in conducting systematic review searches. First, the MEDLINE strategy was developed with input from the research team and was subsequently reviewed by a specialist (BZdO) with expertise in the research topic. Once the MEDLINE strategy was finalized, it was adapted to the syntax and subject headings of the other databases.

Data Management

Literature search results will be uploaded to Rayyan (Qatar Computing Research Institute), a free web platform that expedites the elimination of duplicates and the initial screening of abstracts and titles through a semiautomated process [25]. Comments and notes relevant to inclusion and exclusion criteria will be recorded on this platform. After the initial screening, the remaining studies will undergo a full-text review and data extraction, which will be performed using a Microsoft Excel spreadsheet. Excluded studies will also be organized in a Microsoft Excel spreadsheet.

Selection Process

Adhering to PRISMA recommendations [23], 2 independent reviewers (ACMdS and LESL) will perform the initial screening of titles and abstracts based on the eligibility criteria. The reasons for study exclusions will be documented. Any disagreements not resolved through discussion between the reviewers will be arbitrated by a third reviewer (BZdO).

Data Collection Process

Using a predefined Microsoft Excel spreadsheet, the same independent reviewers (ACMdS and LESL) will extract the

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data of interest for the systematic review from each included publication with available data. To ensure consistency among reviewers, calibration exercises will be conducted before starting the review. The data extracted by each researcher will be compared and merged into a single Microsoft Excel spreadsheet. Reviewers will resolve disagreements through discussion, and a third reviewer (BZdO) will adjudicate unresolved disagreements. Authors of the studies will be contacted to address any uncertainties.

Data Items

The information that will be extracted from each study are publication title, authorship, corresponding author's contact, publication year, URL, language, summary, objectives, methodology, study type, time horizon, study location, study population, sample size, statistical significance, comparator (if applicable), outcome measures, conflicts of interest, and methodological quality. Concerning the registries, included information will encompass registry type (if injury or trauma registry), registry age, geographical scope, participation and inclusion criteria, number of participating centers, and recorded data. In cases where any data cannot be identified, the authors will be contacted. Additional data items, considered relevant for this systematic review, may also be included if available in eligible studies.

Outcomes and Prioritization

Recognizing that injury registries are acknowledged for their support in evaluating and designing public policies, thereby enhancing surveillance capabilities and service quality to reduce morbidity and mortality from injuries and violence, the primary outcomes will encompass policy changes and designs, including preventative measures for injuries, health care improvements, surveillance actions, stakeholder partnerships, among others. The secondary outcomes under investigation will involve hospitalization rates or duration, and mortality.

Risk of Bias in Individual Studies

Risk of bias assessment for each study will be conducted using the ROBINS-I ("Risk Of Bias In Non-randomized Studies-of Interventions") [26] tool, which is applicable to studies that did not use randomization to allocate interventions, including observational studies. The risk of bias due to confounding, bias in the selection of participants into the study, bias in the classification of interventions, bias due to deviation from intended interventions, bias due to missing data, bias in outcome measurement, and bias in the selection of reported results will be independently assessed by 2 reviewers (ACMdS and LESL). This assessment will categorize the overall risk of bias across the outcomes as low, moderate, serious, critical, or no information. Any unresolved disagreements will be adjudicated through arbitration by a third reviewer (BZdO).

Data Synthesis

Summaries of study characteristics will be presented in tables and data synthesis will be explored based on outcomes. If studies are sufficiently homogeneous in terms of design and methods, and if 3 or more studies have evaluated the same outcome, a meta-analysis will be conducted using random effects models adapted to the scale of measurement and reported in forest plots. Depending on the available studies, the synthesis method adopted may be changed. Subgroup analyses will be conducted by registry type, whether it is an injury or trauma registry, categorized by injury groups: all injuries, transport accidents, falls, homicides, suicides, and others according to authors' definitions, as well as by other selected variables of interest. In addition, sensitivity analysis will be carried out, excluding studies of low methodological quality. These analyses will be performed on RStudio software (Posit PBC).

If quantitative synthesis is not appropriate, results will be presented using a standardized narrative synthesis. All relevant findings from the studies will be summarized in the text.

Meta-Bias

Publication bias, resulting from selective publication or reporting, will be investigated through visual inspection of funnel plots. Statistical tests for assessing symmetry will be explored if 10 or more studies have evaluated the same outcome. These analyses will also be conducted using the RStudio software.

Confidence in Cumulative Evidence

To evaluate the quality of evidence presented in the meta-analysis, which pertains to the confidence in the effects derived by the set of evidence for a specific outcome, we will adopt the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [27]. Reviewers (ACMdS and LESL) will independently classify evidence as high, moderate, low, or very low quality, considering all factors that determine the reliability of the results presented in the studies. Any disagreement will be settled by consensus or adjudication with a third author (BZdO), if necessary.

Results

This systematic review will be conducted from November 2023 to June 2024. A preliminary literature search for systematic reviews, both completed and in progress, related to this topic was performed in the Cochrane Database of Systematic Reviews (CDSR) [28] and the Prospective Register of Systematic Reviews (PROSPERO) [29]. No identical review to the proposed study was found. The study was then submitted to PROSPERO on November 10, 2023 (registration number CRD42023481528). The search strategies were finalized, and the bibliographic search commenced on November 6, 2023. The elimination of duplicates and screening of titles and abstracts began in November 2023 as well. In total, 35 studies were retrieved, of which 85 were excluded due to duplication, leaving 50 studies for the selection process. Upon completion, the results of the review will be published in the second half of 2024.

Discussion

Principal Findings

This systematic review and meta-analysis is particularly timely, given the current national efforts to implement an injury registry. We strongly believe that our findings will be of crucial importance for anticipating the effects of implementing an injury

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registry, including trauma registries, on policies and injury outcomes.

Our findings may identify and offer a holistic view of policies and opportunities for intervention that can be established using injury registries. In addition, they may highlight the political partnerships with other sectors involved in the field of injuries and violence, such as firefighters and police, enabling effective intervention strategies based on identified needs. Furthermore, we aim to assess the impact of injury records on reducing hospitalization rate and duration, as well as mortality.

To our knowledge, this is the first systematic review to use evidence intending to map these effects using injury or trauma registry data, preferably with proven causality. Previous research has predominantly focused on this relationship with trauma systems, as evidenced by a meta-analysis that demonstrated a 15% reduction in mortality in favor of the presence of a trauma system [21], as well as by another systematic review that sought to identify which components contributed to its effectiveness [20]. We can also mention another study that exclusively addressed the research dimensions of trauma registry data regarding the formulation of health policies, though it did not encompass all types of injuries [16]. While trauma registries have demonstrated considerable success, particularly in high-income countries, our study addresses a notable gap in the literature by examining the broader implications of injury registries, which encompass a wider spectrum of injuries, regardless of severity.

One of the strengths of our study lies in its transparency and methodological rigor, as it adheres to PRISMA guidelines for systematic reviews and meta-analyses, ensuring the reliability of our findings. However, as with any systematic review, certain limitations need to be anticipated. One potential limitation is the possibility of a shortage of available primary studies on the topic. Furthermore, variability in study designs, data sources, and methodological approaches may pose challenges to data synthesis and drawing conclusive results. This variability can limit the ability to perform robust statistical analyses. The quality or risk of bias of the included studies also needs to be recognized, as this may affect the reported results. In addition, some registries implemented in specific contexts, such as high-income countries, may not be directly comparable to the effects observed in low- and middle-income countries.

To ensure the widespread dissemination of our findings, we plan to publish our results in peer-reviewed journals and present them at relevant congresses and seminars. In addition, we aim to engage policy makers, health care professionals, and stakeholders through targeted dissemination activities, such as interactive workshops and meetings, to facilitate the translation of our findings into practice.

Conclusion

In conclusion, this systematic review and meta-analysis contribute to the growing body of evidence on the effectiveness of injury or trauma registries in informing policy making and improving health outcomes. By synthesizing available evidence, we will identify the potential of injury registries to enhance health surveillance, reinforce and guide Brazilian policy makers' decisions, and ultimately reduce the burden of morbidity and mortality associated with injuries in the country. However, further research will be warranted to focus on the impact of injury registries and address the methodological challenges inherent in evaluating their effectiveness causally, even through primary studies.

Acknowledgments

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Authors' Contributions

ACMdS and BZdO contributed to the conception and design of the study. ACMdS and LESL defined the systematic review and meta-analysis methods. ETR developed the search strategy. ACMdS and LESL drafted the manuscript. BZdO, ETR, and LRC provided feedback and revised the final manuscript.

Conflicts of Interest

The authors are employees of HIAE, the entity that provides funding for the project discussed in this article.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*.
[DOCX File , 42 KB - resprot_v13i1e55029_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 43 KB - resprot_v13i1e55029_app2.docx]

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Abbreviations

CDSR: Cochrane Database of Systematic Reviews
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HIAE: Hospital Israelita Albert Einstein
PICOS: Population, Intervention, Comparison, Outcomes, and Study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol
PROADI-SUS: Institutional Development Support Program of the Unified Health System
PROSPERO: Prospective Register of Systematic Reviews
ROBINS-I: Risk Of Bias In Non-randomized Studies-of Interventions

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Protocol

Effectiveness of Self-Management Programs Among Athletes With Patellofemoral Pain Syndrome: Protocol for a Systematic Review

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Abstract

Background: Patellofemoral pain syndrome is a highly prevalent overuse knee injury in athletic populations associated with pain and functional limitations, exacerbated by activities such as running, pivoting, cycling, and jumping. Self-management programs empowering athletes to take an active role in controlling their symptoms for chronic musculoskeletal conditions such as patellofemoral pain syndrome have grown in popularity. However, the efficacy of self-management programs specifically for athletes with patellofemoral pain syndrome is unclear due to limited and heterogeneous evidence.

Objective: The systematic review study will evaluate the effectiveness of self-management programs on pain and function, in athletes with patellofemoral pain syndrome.

Methods: PubMed/MEDLINE, Cochrane Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO databases will be systematically searched using terms related to “patellofemoral pain syndrome,” “self-management,” and “athletes.” Interventional studies that are randomized and nonrandomized controlled trials will be included, comparing self-management programs to other treatments or control conditions among athletes with patellofemoral pain syndrome. Four reviewers will independently screen studies, extract data using the COVIDENCE software, and assess the quality of the study and evidence using the Pedro scale of risk of bias tool and GRADE approach, respectively. If feasible, a meta-analysis will be performed using the RevMan (version 5.4; the Cochrane Collaboration).

Results: The systematic review is currently in the search phase, with the authors refining search strings for the selected databases. The final search strings are expected to be ready by March 2024, and the review is projected to be completed by July 2024.

Conclusions: This systematic review protocol outlines a rigorous methodology for evaluating the effectiveness of self-management programs among athletes with patellofemoral pain syndrome. The findings will inform clinical practice and guide the development of tailored interventions to optimize outcomes for athletes with patellofemoral pain syndrome.

Trial Registration: PROSPERO CRD42023492746; https://tinyurl.com/c5jze9ca

International Registered Report Identifier (IRRID): PRR1-10.2196/58340

(JMIR Res Protoc 2024;13:e58340) doi:10.2196/58340

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KEYWORDS

patellofemoral pain syndrome; athletes; self-management; chronic pain; pain management; systematic review

Introduction

Background

Patellofemoral pain syndrome (PFPS) is a common and prevalent musculoskeletal disorder affecting athletes, particularly those engaged in repetitive knee flexion, such as running, jumping, and cycling. Sports participation often entails rigorous training regimens and competitive demands, leading to overuse injuries and biomechanical stress on the patellofemoral joint. Additionally, athletes may exhibit specific risk factors predisposing them to PFPS, such as quadriceps muscle weakness, hip muscle dysfunction, patellar malalignment, and foot biomechanical abnormalities [1]. These factors can disrupt patellofemoral joint mechanics, alter load distribution, and contribute to the onset and persistence of PFPS symptoms among athletes.

The prevalence of PFPS is about 25% of knee injuries seen in sports rehabilitation clinics, with incidence rates ranging from 9% to 40% among active individuals in United States, England, and Belgium [2]. Despite its high prevalence, effective management strategies for PFPS remain elusive, often leading to prolonged pain, functional limitations, and decreased athletic performance [3].

The management of PFPS typically involves a multimodal approach, including rest, activity modification, physical therapy, and, in some cases, surgical intervention [4]. However, recent emphasis has been placed on self-management strategies to empower athletes to take an active role in their recovery process [5]. Esculier et al [6] affirmed that self-management programs (SMPs) aim to educate individuals about their condition, promote self-efficacy, and provide tools and techniques for symptom management and functional improvement. While there is growing interest in self-management approaches for PFPS, the evidence supporting their effectiveness among athletes remains limited and heterogeneous [7].

Several studies have investigated the efficacy of various self-management interventions, including exercise therapy, taping, bracing, and education, but findings have been inconsistent, and the optimal combination and delivery of these interventions remain unclear [8-10]. This systematic review will, therefore, aim to synthesize the current evidence regarding the effectiveness of self-management programs among athletes with PFPS. By critically evaluating the existing literature, we seek to identify the most effective self-management strategies for pain reduction, functional improvement, and return to sport among this population. Cowan et al [1] stated that such systematic review findings provide insights that are essential for informing clinical practice and optimizing outcomes for athletes with PFPS. This is important as less is known about the self-management program and its impact on individuals with chronic dysfunction. Similarly, there is limited knowledge of how other stakeholders, such as caregivers, health experts, and researchers, view self-management programs in the context of disability, chronic health conditions, and assistive technologies [11]. Hence, the present study is proposed to evaluate the existing evidence on the effectiveness of SMP in reducing knee pain and improving function among athletes with PFPS.

Objectives

This study will identify, appraise, and synthesize the existing evidence on the effectiveness of self-management programs among athletes with patellofemoral pain syndrome.

Methods

Overview

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol will be used to design the systematic review as described by Souto et al [12].

Eligibility Criteria

Inclusion Criteria

Study Design

Randomized clinical trials (RCTs) and non-RCTs that compare self-management program (SMP) as an intervention with a control group (placebo, adjunctive treatment, or alternative therapy alone) will be eligible for the study.

Type of Population

The current systematic review will include articles involving athlete participants clinically diagnosed with PFPS, using the main criteria of pain around or behind the patella, which increases by running, jumping, squatting, kicking, jogging, riding, and other sporting activities.

Type of Intervention

Self-management programs concerning PFPS treatment interventions, including nonpharmacological interventions such as patellofemoral knee orthoses (bracing), patellar taping, foot orthoses, weight loss, psychological therapy, exercises, education, behavioral changes, and other complementary therapies will be included in the study.

Comparison of Interest

Studies with or without a comparator group will be considered. Comparators may include PFPS standard care, no intervention, placebo, or an alternative treatment.

Outcome Measures

Studies that assess pain intensity and functional ability as primary outcomes through validated measures within the PFPS population will be included. The secondary outcome will be compliance and adherence to self-management programs, treatment satisfaction, no recurrence of PFPS, and no adverse effects. Both short-term and long-term assessments would be considered.

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Exclusion Criteria

Review studies and protocols will be excluded in this study. Studies that examine other knee conditions such as osteoarthritis, patella dislocation, and sports injuries (anterior cruciate ligament, meniscus, and unhappy triad), leading to ligamentous instability or knee pain will be removed. Studies of participants with previous knee, hip, ankle, or low back surgeries will be excluded.

Search Strategy

Overview

The search strategy and eligibility criteria will be based on the PICOS (Participant, Intervention, Design, Comparator, Outcomes and Study design) framework. The search will include a combination of keywords and MeSH (Medical Subject Headings) terms related to PFPS, self-management programs, and pain measurements. Keywords used in the search strategy adhere to each of the key characteristics of the PICO framework. These include patellofemoral pain as the participant ("Patellofemoral pain syndrome," Anterior Knee Pain Syndrome) self-management as the intervention ("Self-management," "Exercise therapy" OR "Biofeedback"), experimental controlled studies as the design and research type ("RCT"), and pain and function as the outcomes ("pain intensity" and "Pain Severity"). The Boolean operators "AND" and "OR" will be used to refine the search strategy. A sample search strategy for PubMed (MEDLINE) is outlined below:

1. ("Anterior Knee Pain Syndrome" OR "Patellofemoral Syndrome" OR "Patellofemoral Pain" OR "Patellofemoral Pain Syndrome") AND
2. ("Self-management program" OR "Exercise therapy" OR "Biofeedback" OR "Muscle strengthening" OR "Education") AND
3. ("Pain Intensity" OR "Pain Severity" OR "Pain Measurement" OR "Pain Assessment")

The search strategy will involve an initial search of electronic databases, followed by the analysis of keywords in the titles and abstracts of each database search. The search will then continue to the reference lists of selected articles to identify additional studies not located through the electronic database search. The strategy will aim to locate published articles—gray literature and unpublished articles will be excluded from the review. The search will not be limited to specific period but it will include all articles published from inception of the database till the start of the search in March 2024. The search strategy will be adapted for each electronic database. The search strategy for each data source will be developed by 4 researchers (BB, NC, NM, and AM). Language will not be used to filter publication during the search.

Information Sources

A literature search for experimental controlled studies will be conducted on the following electronic databases: PubMed (MEDLINE), Cochrane Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and PsycINFO. These databases have been chosen as they encompass nursing, medicine, social sciences, and psychology literature, which are deemed the most appropriate for answering the research question concerning self-management of patellofemoral pain.

Data Management

The search results will be loaded into COVIDENCE, a systematic review reference management program, to find and eliminate duplicates.

Study Selection

The selection process will be performed by the 4 independent reviewers (BB, NC, NM, and AM) who will screen the titles and abstracts. The researchers will independently apply the inclusion and exclusion criteria after thoroughly reading the selected studies. In disagreements, consensus will be sought; however, a fifth reviewer (UU) will be consulted if disagreement persists. The reviewer (AM) will contact the study authors if the complete information is unavailable. The study will be excluded if the authors cannot provide the full article or fail to reply to the request after 3 attempts.

Data Extraction

After selection of the primary studies, the 4 reviewers (BB, NC, NM, and AM) will work independently. Consensus will resolve disagreements; should they persist, an independent reviewer (UU) will be consulted. Data relevant to the research question and predefined criteria will be extracted from the selected studies. Extracted data will include author, population, age range, study design, participant characteristics, details of the self-management intervention, controls, outcomes measured, adverse effects, results, and conclusion.

A pilot testing of the data extraction form will be conducted using a subset of studies for accuracy purpose. Reviewers will meet regularly to discuss and resolve any uncertainties or discrepancies in the data extraction process. The extracted data will be cross-checked between reviewers to minimize errors and enhance reliability. The extracted data will be saved and stored in COVIDENCE allowing easy access and retrieval during the synthesis and analysis stages. A version control system will be implemented to track any updates or modifications made during the data extraction process. Authors will be contacted for missing or unclear information. If data cannot be obtained, the potential impact of missing data will be addressed and reported in the systematic review. The collected data will be reported transparently and comprehensively in the final systematic review, including tables summarizing critical characteristics of the included studies and their findings. These processes are aimed to enhance the reliability and validity of the systematic review's findings.

We aim to start reviewing articles in March 2024 and completing data extraction in June 2024.

Data Analysis

The results will be synthesized through a narrative approach using qualitative thematic analysis of the studies via line-by-line coding of the results and discussion sections to identify contextual information on self-management of patellofemoral pain, clustering the coded data to generate "descriptive themes," identifying "analytical themes" about the data captured in the

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descriptive themes [13]. These themes will be relevant to the key aim of this study.

When appropriate, all self-management program effects will be converted to standardized mean difference for ease of comparison. For each program, pooled standardized mean difference values and measures of heterogeneity (such as I2 and assessment of publication bias) will be calculated using the random-effects meta-analysis model. The heterogeneity may come from varied designs, participant demographics, interventions, and result measures. If substantial heterogeneity exists, sensitivity analyses will be conducted to explore potential sources. The "R" program will be used for data synthesis. A significance level of α=.05 will be applied to determine statistical significance. The general quality of evidence will be evaluated using the GRADE system to provide a transparent evaluation of the strength of the findings. The selection process, including the number of studies screened, reasons for exclusion at each stage, and the included studies, will be reported as PRISMA flow diagram.

Quality Appraisal

The assessment of bias for the studies included will be conducted using the PEDro scale and Cochrane risk of bias tool (if needed). The reliability of this tool is fair to good [14]. While the scale comprises 11 items, the inclusion of eligibility criteria specifications will be omitted from the final score, resulting in a scale range of 0-10. Each affirmative answer will receive one point, which will be added to obtain the final score [14]. The evaluation of studies listed in the PEDro database will be upheld, while nonindexed studies will undergo independent assessment by 2 reviewers (BB and AM). Ratings will categorize studies as having low risk if they score ≥7/10, moderate risk (4-6/10), or high risk of bias (≤3/10) according to this scale [15].

Missing Data

If feasible, we will reach out to authors to acquire any absent data, particularly information crucial for conducting a meta-analysis. If authors are unable to furnish the missing data or do not respond after 3 attempts, the study will be excluded from subsequent statistical analyses.

Regarding documentation of significant protocol alterations, this section will log the date of each amendment along with a description of the modification and its rationale. These changes will be recorded without integration into the protocol itself.

Results

This systematic review protocol was developed in November 2023 to assess the effectiveness of SMP for athletes with PFPS. To our knowledge, this will be the first systematic review focused specifically on SMPs for PFPS in athletes. The review aims to synthesize evidence on the effects of SMPs on outcomes such as pain and function, in athletes with PFPS. Upon completion (anticipated by June 2024), the outcome of this study will be submitted for publication in an academic journal that uses expert peer review process to evaluate research manuscripts.

Findings of the current study will fill the knowledge gap in front of researchers, physiotherapists, and athletes with patellofemoral pain syndrome as well regarding the effective and evidence-based self-management strategies that can be used by the patients or advised by the practitioners to their patients to reduce their pain and disability.

Discussion

Overview

It was hypothesized that there will be enough literature for both qualitative and quantitative synthesis and analysis that shows positive effects for the self-management programs on treatment of pain and disability in athletes with patellofemoral pain syndrome. The aim of this systematic review protocol will be to evaluate the current evidence on SMPs for treating PFPS in athletes. This review will synthesize evidence on the effects of SMPs on outcomes such as pain and function in athletes with PFPS.

Principal Findings

Previous RCTs and systematic reviews have demonstrated the effectiveness of some self-management strategies in improving clinical outcomes in general population with patellofemoral pain [3,6,8-10]. Multiple studies have examined the effectiveness of SMPs for reducing pain and improving function in athletes with PFPS [16,17]. However, there is a lack of research collectively evaluating experimental controlled studies that explore how athletes with patellofemoral pain can self-manage themselves and the impact of this self-management on their pain and disability.

Strengths and Limitations

The comprehensive approach of this systematic review gives it its strength. PICO framework will guide the eligibility criteria and search strategy. Search terms and strategies will be determined with the help of librarian and from PubMed MeSH terms. The review will follow the PRISMA checklist to report and synthesize the systematic evidence. The quality of included studies will be assessed using the 2 most recommended and strong checklist tools: PEDro and Cochrane. Data extraction will be performed by 5 independent researchers, and another reviewer will resolve any disagreement if present. Furthermore. this review will not limit search by year of publication or language. However, this review is limited by excluding grey literature, which may affect results and conclusions.

The discussion will summarize the components of SMPs that were effective for athletes with PFPS based on the studies reviewed. This systematic review will summarize the components of SMPs and clarify the evidence of their effectiveness in reducing pain and disability in athletes with PFPS. Based on the findings, this will inform future research, such as improving the quality of future studies, increasing treatment duration, improving adherence, and so on. It can also inform clinical practice recommendations.

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Acknowledgments

Authors thank the librarian who helped with setting keywords and search strategy. This research received no external funding.

Data Availability

All data will be available via contacting the corresponding author upon request.

Authors' Contributions

NC and NM were involved in the conceptualization, writing of the draft, and analysis. BB and UU supervised, analyzed, and interpreted the results. All authors were involved in the review of the draft and final approval of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature
MeSH: Medical Subject Headings
PFPS: Patellofemoral pain syndrome
PICOS: Participant, Intervention, Design, Comparator, Outcomes and Study design
PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trail
SMP: self-management program

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Protocol

Effectiveness of Computer-Based Psychoeducational Self-Help Platforms for Eating Disorders (With or Without an Associated App): Protocol for a Systematic Review

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Abstract

Background: Access to psychological health care is extremely difficult, especially for individuals with severely stigmatized disorders such as eating disorders (EDs). There has been an increase in children, adolescents, and adults with ED symptoms and ED, especially following the COVID-19 pandemic. Computer-based self-help platforms (± associated apps) allow people to bridge the treatment gap and receive support when in-person treatment is unavailable or not preferred.

Objective: The aim of this systematic review is to evaluate the effectiveness of computer-based self-help platforms for EDs, some of which may have associated apps.

Methods: The proposed systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This review will report and evaluate the literature concerning the efficacy of self-help platforms for EDs. Articles were obtained from the Ovid MEDLINE, Embase, Global Health, and APA PsycInfo. The inclusion criteria included research with original data and gray literature; research evaluating the efficacy of web-based psychoeducational self-help platforms for EDs; people with an ED diagnosis, ED symptoms, at risk of developing EDs, or from the general population without ED-related behaviors; pre– and post–computer-based ± associated apps intervention clinical outcome of ED symptoms; pre– and post–computer-based ± associated apps intervention associated mental health difficulties; and literature in English. The exclusion criteria were solely guided self-help platforms, only in-person interventions with no computer-based ± associated apps comparison group, only in-person–delivered CBT, self-help platforms for conditions other than eating disorders, systematic reviews, meta-analyses, posters, leaflets, books, reviews, and research that only reported physical outcomes. Two independent authors used the search terms to conduct the initial search. The collated articles then were screened by their titles and abstracts, and finally, full-text screenings were conducted. The Cochrane Risk of Bias 2 tool will be used to assess the risks of bias in the included studies. Data extraction will be conducted, included studies will undergo narrative synthesis, and results will be presented in tables. The systematic review will be submitted to a peer-reviewed journal.

Results: The authors conducted a database search for articles published by May 31, 2024. In total, 14 studies were included in the systematic review. Data charting, synthesis, and analysis were completed in Microsoft Excel by the end of July 2024. Results will be grouped based on the intervention stages. The results are expected to be published by the end of 2024. Overall, the systematic review found that computer-based self-help platforms are effective in reducing global ED psychopathology and ED-related behaviors.

Conclusions: Self-help platforms are helpful first-stage resource in a tiered health care system.

Trial Registration: PROSPERO CRD42024520866; https://tinyurl.com/5ys2unsw

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International Registered Report Identifier (IRRID): DERR1-10.2196/60165

(JMIR Res Protoc 2024;13:e60165) doi:10.2196/60165

KEYWORDS

self-help; online self-help; eating disorders; anorexia nervosa; psychoeducational intervention; psychoeducation; binge eating; anorexia; bulimia; access to care; patient education; patient self-help

Introduction

Background

Eating disorders (EDs) are a group of heterogeneous psychiatric disorders that are characterized by irregular eating behaviors [1]. Research demonstrated that between 5.5% and 17.9% of women and 0.6% and 2.4% of men meet the *DSM-5* (*Diagnosis and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria for EDs [2]. Furthermore, gender and sexual minorities are demonstrated to be particularly at risk for developing EDs, with anorexia nervosa and bulimia being the most prevalent [2-4]. Compared with any other psychiatric conditions, anorexia nervosa has the highest suicidality and mortality rates and lowest quality of life levels, highlighting the importance of urgency of care [5,6]. Despite this, merely one-fourth of individuals with ED symptoms or developed EDs access care [7]. EDs have been demonstrated to negatively impact the psychological, cognitive, physical, and social development of individuals, which evidences the need for accessible resources, such as self-help platforms, which support individuals and prevent, treat, and avoid the relapse of EDs [8].

During the COVID-19 pandemic, there was an increase in children and adolescents struggling with ED symptoms and EDs, leading to a surge in waiting times [9,10]. Whilst face-to-face treatments such as ED-focused family therapy, CBT-E have been demonstrated to effectively reduce ED symptoms for eating disorders, many previously in-person psychoeducational support systems transitioned to computer-based self-help platforms [11,12]. Computer-based self-help platforms ± associated apps are stand-alone support websites or mobile apps which do not require the presence or assistance of trained professionals [8]. Self-help platforms overcome issues related to the help-seeking stigma, geographical isolation, and time constraints, which have been demonstrated as factors which prevent help-seeking [13], though they rely on the individual's motivation to access support. Health care systems have evolved to provide a resource-efficient framework for communities to provide stepped support for individuals depending on their level of need. One such framework is the THRIVE framework [14].

THRIVE provides service providers with a set of principles to help guide their care approaches by distinguishing between 5 stages of care provision: "thriving," "getting advice," "getting help," "getting more help," and "getting risk support." Self-help platforms are the initial stage of accessing support, and when more support is needed, then the initial stage of "getting advice" to "getting help" [14]. Self-help platforms are available for the general public and provide psychoeducational information for those requiring additional resources or support [14]. Although self-help platforms are good prevention strategies, research has demonstrated that individuals are significantly more satisfied when self-help platforms are provided in combination with in-person interventions [15].

Psychoeducational self-help computer-based platforms ± associated apps aid the understanding of ED's causes, risk factors, and potential consequences for individuals and their families with the aim of developing effective coping mechanisms [16,17], but they need to be able to recognize the problem and be motivated to seek help. Self-help platforms allow for early recognition and early skills development to people who identify with at risk or disordered eating symptoms. [18]. A variation of approaches can be used in addition to the psychoeducation, such as implementing cognitive behavioral therapy (CBT) techniques, dissonance-based interventions (DBI), and motivation enhancement therapeutic techniques (MET). The specific aims and target groups for the therapeutic techniques can be found in Table 1.

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Table 1. Cognitive behavioral therapy, dissonance-based intervention, and motivation enhancement therapy.

Therapeutic design	Aim	Target group
CBT[a]	Focuses on the relationship between thoughts, behaviors, and feelings. For ED[b], it addresses one's thoughts and behaviors related to their irregular eating patterns [19].	Effective for all age groups, targets a variety of disorders, including ED.
DBI[c]	Challenges society and media-propagated body ideals [20]. It is often most effective when implemented during key developmental stages.	Effective for all age groups, most effective for individuals who have maladaptive and conflicting attitudes and behaviors, often used for EDs and substance abuse issues.
MET[d]	Urges people with ED's to make changes to their behaviors and cognitive processes [21].	Effective for all age groups, MET often combined with CBT to enhance individuals' motivation to change maladaptive behaviors and relationship with food.

[a]CBT: cognitive behavioral therapy.

[b]ED: eating disorder.

[c]DBI: dissonance-based intervention.

[d]MET: motivation enhancement therapy.

Previous systematic reviews have demonstrated guided computer-based self-help platforms ± associated apps as effective in reducing ED core symptoms and ED-related behaviors by altering maladaptive behaviors and changing the individual perseverative thinking, thin idealization, body dissatisfaction, depression, quality of life, and lack of motivation to change [17,22]. However, to the knowledge of the authors, there has not yet been a systematic review evaluating the effectiveness of solely self-help platforms for EDs [17,23,24]. Therefore, the current systematic review aims to evaluate the literature on the effectiveness of ED self-help platforms. The effectiveness of self-help platforms will be primarily measured by the platform's ability to reduce ED symptomology. Second, the effectiveness will be evaluated based on the platform's ability to decrease ED-related behaviors such as perseverative thinking, thin idealization, body dissatisfaction, depression, quality of life, and resistance to change.

Objective

This systematic review aims to explore literature which has evaluated the following research questions:

1. Are computer-based psychoeducational self-help platforms ± associated apps effective in preventing the onset of EDs?
2. Are computer-based psychoeducational self-help platforms ± associated apps effective in reducing the core ED symptoms?
3. Are computer-based psychoeducational self-help platforms ± associated apps effective in improving the long-term effects of EDs?

This systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to evaluate the literature regarding the effectiveness of web-based psychoeducational and self-help platforms for EDs.

Methods

Overview

A systematic review was conducted to explore the literature regarding the effectiveness of computer-based psychoeducational self-help platforms ± associated apps for people with ED symptoms and developed EDs. The reporting of this systematic review abided by the PRISMA guidelines [25].

Eligibility Criteria

Population

This systematic review did not have a set age restriction for the population. The systematic review considered research that had screened participants at baseline level, before the intervention, and following intervention. The population included individuals with no ED behavioral patterns, individuals who were at-risk of developing ED's, and individuals with any diagnosed ED.

Intervention

This review included literature examining the clinical effectiveness of computer-based psychoeducational self-help platforms ± associated apps. The comparison groups were treatment as usual.

Outcome

Clinical effectiveness was defined as a decrease in ED symptoms, ED related behaviors, and increase in weight for those with a restrictive eating disorder.

Context

This review considered studies conducted in any geographical context using any computer-based intervention platforms ± associated apps for EDs.

Types of Evidence Source

This review considered studies with all types of research designs (eg, randomized controlled trials, quasi-experimental and case-control studies, clinically on-controlled studies, and observational studies) and studies using qualitative, quantitative, or mixed methods. Gray literature was analyzed and included as appropriate. Furthermore, only studies published in English was included.

The inclusion and exclusion criteria are mentioned in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Research with original data, including gray literature.
- Research evaluating the efficacy of web-based psychoeducational self-help platforms for eating disorders (EDs).
- People with ED diagnosis.
- People with ED symptoms.
- People at risk of developing EDs.
- People from the general population without ED-related behaviors.
- Research which examined the pre- and post-computer-based intervention ± associated apps clinical outcome of ED symptoms.
- Research which examined the pre– and post–computer-based intervention ± associated apps associated mental health difficulties.
- Literature in English.

Exclusion criteria

- Guided self-help platforms.
- Only in-person interventions with no computer-based ± associated apps comparison group.
- Only in-person delivered cognitive behavioral therapy.
- Self-help platforms for conditions other than Eds.
- Systematic reviews.
- Meta-analyses.
- Posters.
- Leaflets.
- Books.
- Reviews.
- Research that only reported physical outcomes.

Search Strategy

A systematic search was conducted using Ovid MEDLINE, Embase, Global Health, and APA PsycInfo up to the established date of May 31, 2024. A manual search of references was conducted using Google Scholar to identify alternative literature. Furthermore, a reference list search will be conducted to identify any other potential literature that can be included.

Author AG conducted an initial search using Ovid on May 31, 2024, using preliminary search terms developed by AG and YYK and reviewed by EC. AG used the search terms “Eating Disorder* OR Anorexia OR Anorexia Nervosa OR Bulimia OR Binge eating OR Avoidant restrictive food intake disorder OR ARFID OR Otherwise specified feeding or eating disorder OR OSFED” and “Intervent* OR Treatment* OR Psychoedu*” and “ICBT OR Internet cognitive behavioral therapy OR self-help OR digital OR online.” The search terms were identified based on previous literature and key relevant terms relating to ED self-help platforms. The table depicting the search terms and the results can be seen in the Multimedia Appendix 1.

Study Selection

After the completion of the search, studies were exported to EndNote and duplicates were removed. Articles were then initially screened independently by AG and YYK by titles and abstracts. Following this, the authors full text screened the literature and collected research which abided by the inclusion and exclusion criteria. The reviewers met to discuss the pertinent articles. EC was contacted to provide further insight and resolve any disagreements when AG and YYK could not reach an agreement following the discussion. Literature that did not meet the inclusion criteria was excluded from the systematic review.

Data Extraction

Data extraction will be completed by the researchers capturing key aspects of studies that fit the inclusion criteria. The key aspects will be initially recorded on a Microsoft Excel spreadsheet. The aspects extracted will include primary author name and published date, sample population demographics, follow-up times and sample size, outcome measure, intervention, key findings, and overall risk of bias. A draft of the table is presented in Textbox 2. However, this draft may be modified in the final review. The data will be inputted by AG and YYK independently for each included study, to assess the studies eligibility. In cases of any disagreements, the reviewers will discuss to reach a consensus. EC will be consulted in the case of uncertainty or unsolved disagreement.

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Textbox 2. Table components draft.

Components

- Authors, date.
- Baseline sample (N), female %, and mean age.
- Follow-up times and sample size (% of initial sample).
- Outcome measure.
- Intervention.
- Key findings.
- Risk of bias.

Data Synthesis and Quality Assessment

The findings of the systematic review will be initially summarized in a Microsoft Excel table and then narratively synthesized and analyzed based on the guidelines specified by Popay et al [26]. Included studies used diverse methods to analyze primary and secondary outcomes (ie, clinical effectiveness and associated mental health difficulties). Therefore, the reliability of the questionnaires will be analyzed and reported. Quality assessment will be performed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Risk of Bias

Following the initial search, the primary author found all included literature was randomized controlled trials; therefore, the Cochrane Risk of Bias 2 tool was selected. If additional research methods are detected in the included literature, the risk of bias tool may be revised. The Cochrane Risk of Bias 2 tool will be used to ensure that all questionnaires are approximately similar in validity and reliability. Detailed information regarding the selection procedure will be presented in a PRISMA flow diagram. Where applicable, common findings amongst the research will be identified and reported.

The primary outcomes will be reported in terms of the web-based self-help platforms' effectiveness in decreasing the clinical symptoms of eating disorders in participants. Secondary outcomes will be analyzed in terms of associated mental health difficulties (ie, perseverative thinking, body dissatisfaction, thin idealization, fear of becoming fat, preoccupation of food and weight, motivation to change their weight, self-esteem, depression, and quality of life).

AG and YYK will independently analyze potential biases of the studies using the Cochrane Risk of Bias tool. The risk of bias tool assessment examined 5 domains of potential risk of bias namely, randomization, divergence from the intended intervention, analysis of missing data, measurement of outcomes, and selection of reported results.

Missing Values

Self-help platforms have been demonstrated to have high dropout and attrition rates. Therefore, the bias caused by missing values will be determined at the discretion of the authors. The authors will reflect the impact of the missing values on the Cochrane Risk of bias 2. Meta-analysis will not be performed due to high heterogeneity of the outcomes of studies.

Ethical Considerations

No patients or members of the public were involved in the development of this protocol or will be involved in the final scoping review. Nevertheless, including qualitative studies should give a valuable insight into patient and carer perceptions and experiences with intensive community and home treatments. Ethical approval will not be required for this review as the data will be obtained from publicly available sources.

Results

This systematic review explores the effectiveness of web-based self-help interventions for the prevention and management of EDs. Data collection was conducted until May 31, 2024. Overall, 14 studies were collated, which were in line with the inclusion and exclusion criteria of this systematic review. Due to varying population groups, the data will be divided based on the stepped intervention approach taken. Studies conducted with the general population participants will be grouped under primary prevention, studies conducted with participants who are at risk of developing EDs will be grouped under secondary prevention, and studies conducted with participants who have clinically significant ED symptoms will be grouped under tertiary prevention. Data charting is provided in Textbox 2 above. The studies will be narratively synthesized, and the results will be presented in the form of a systematic review report. Data analysis and write-up were completed by the end of July 2024, and the result is expected to be published by the end of 2024. The PRISMA flow chart can be seen in Figure 1.

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Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

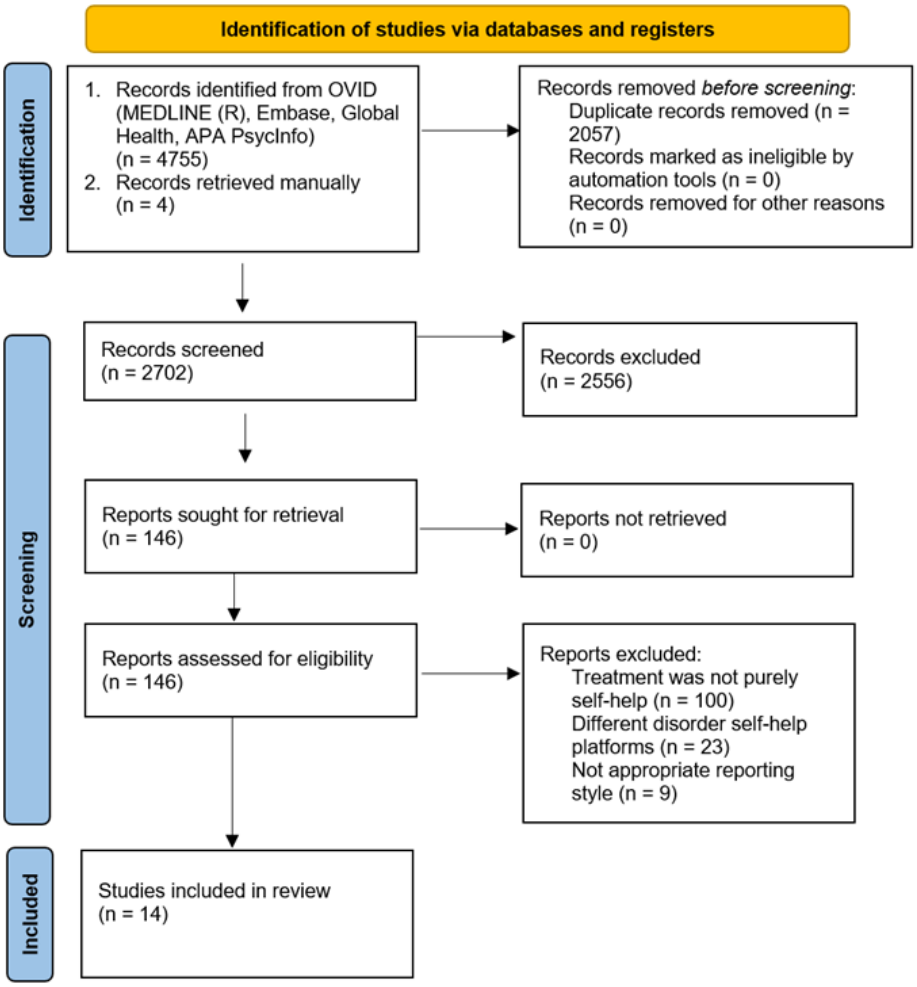

Discussion

This is the first systematic review solely exploring existing literature the effectiveness of unguided computer-based psychoeducational self-help platforms ± associated. Whilst previous systematic reviews compared guided with nonguided computer-based psychoeducational self-help platforms ± associated apps, this systematic review evaluates the effectiveness of self-help platforms across the age range.

One of the biggest challenges in conducting unguided computer-based psychoeducational self-help platforms ± associated apps is the high dropout rate. This systematic review discusses the issue and mentions the effectiveness of the treatment in different ethnic population. The effectiveness of different unguided self-help platforms to ED psychopathologies and ED-related behaviors will be analyzed.

There are some strengths related to this systematic review. This systematic review will provide an overview of the effectiveness of the computer-based psychoeducational self-help platforms ± associated apps and the feasibility of implementing the platforms in clinical settings. It is expected that this systematic review will provide directions for future research and tactics to improve already existing web-based self-help platforms. Furthermore, the findings of this review will be reported according to the rigorous guidelines for systematic reviews outlined in the PRISMA. In addition, 2 independent researchers conducted searches and data extraction, increasing the findings' internal validity. As a limitation to the systematic review, there is a high dropout rate found from the studies included. Consequentially, the systematic review will have a limited overview of the validity of the efficacy of computer-based psychoeducational self-help platforms ± associated apps. Furthermore, a meta-analysis might not be performed due to the high risk of heterogeneity in the studies. The review's findings will be disseminated through conference presentations and peer-reviewed publications.

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transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data Availability

The datasets used after this systematic review results are completed will be available from the corresponding author upon reasonable request.

Authors' Contributions

EC conceptualized the systematic review topic and is the main supervisor for the project. AG developed the research questions, search strategy, data charting tool, and formal data analysis plan with supervision from EC. AG and YYK wrote the protocol and curated the data. EC provided constructive feedback. AG and YYK developed the original draft, which was further edited following EC's feedback. All authors wrote, read, and approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search results from OVID databases (MEDLINE, Embase, Global Health, and APA PsycInfo).
[PDF File (Adobe PDF File), 74 KB - resprot_v13i1e60165_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
DBI: dissonance-based intervention
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*
ED: eating disorder
MET: motivation enhancement therapy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Efficacy of Electroacupuncture in the Treatment of Mild to Moderate Female Stress Urinary Incontinence: Protocol for a Systematic Review and Network Meta-Analysis

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Abstract

Background: Stress urinary incontinence (SUI), the most common form of urinary incontinence, is a condition that affects many women. It is characterized by involuntary urine leakage during activities that increase abdominal pressure, such as sneezing, coughing, or physical exertion, according to the International Continence Society. SUI affects patients' quality of life and causes depression and emotional disorders, which negatively influences physical and mental health. The participants in the studies in this review comprised women with mild to moderate SUI, because there are more female patients than male patients, and most patients with severe SUI are treated surgically. Moreover, after retrieval, there were no systematic reviews or network meta-analyses (NMAs) of conservative treatments, such as electroacupuncture (EA), in women with mild to moderate SUI.

Objective: This study aims to investigate the efficacy of electroacupuncture among women with mild to moderate SUI using an NMA.

Methods: Randomized clinical trials related to conservative treatments for SUI will be searched in 5 English and 3 Chinese literature databases: EMBASE, PubMed, Cochrane, Web of Science, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), WanFang, and the Chinese BioMedical Literature Database. The search period for these 8 electronic databases will be from 2002 to 2022. The PROSPERO database and the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) database will also be searched. Two reviewers will independently complete the research selection. After screening the studies, 2 other researchers will extract the data, and the quality of the included studies will be evaluated according to the quality standards specified in the Cochrane Collaboration Tool (version 2). The primary outcomes will be the change in urine leakage determined by a 1-hour pad test and International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) scores at baseline and at the conclusion of the follow-up. The secondary outcomes will be 72-hour incontinence episodes, residual bladder volume, effective rate, urodynamic indexes, and other reported measurements. Stata (version 14.0; StataCorp) and Review Manager (RevMan version 5.3; Cochrane) will be implemented for data synthesis and meta-analysis.

Results: The results are not yet accessible because this is a protocol for a systematic review and meta-analysis. The protocol was registered on INPLASY on February 22, 2023. By April 6, 2023, we had completed the literature search of the 8 databases and completed the selection and data extraction of the articles.

Conclusions: The results of this systematic review will demonstrate the efficacy of EA among women with mild to moderate SUI. The results will provide evidence for clinicians and guideline makers to choose suitable treatments for SUI.

Trial Registration: International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) 202320098; https://inplasy.com/inplasy-2023-2-0098/

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KEYWORDS

stress urinary incontinence; electroacupuncture; drugs; pelvic floor muscle training; systematic review; network meta-analysis

Introduction

Stress urinary incontinence (SUI), the most common type of urinary incontinence (UI), is defined by the International Continence Society as an involuntary loss of urine on physical exertion, sneezing, or coughing [1]. The incidence of UI is 2-3 times higher in women than in men [2]. Epidemiological studies have demonstrated that SUI is a common health problem worldwide, affecting 23% to 45% of the female population [3]. The prevalence of SUI in China is 18.9% [4], with the highest prevalence (28%) in the age group of 50-59 years [5].

Although SUI is not a life-threatening disorder, it reduces quality of life in both the physical and mental health domains, and the condition is an independent risk factor for anxiety and depression, which may negatively impact work function [6]. According to urodynamic examination, involuntary urine leakage occurs when the bladder pressure exceeds the maximum urethral pressure, in the presence of increased abdominal pressure and no detrusor contraction. In the anatomical pathogenesis of SUI, the urethra itself, the periurethra, and the pelvic floor nerves all play significant roles [7]. Vaginal delivery is a significant risk factor for developing pelvic floor diseases such as SUI [8]. The levator ani muscle plays an important role in supporting the pelvic organs, and women are most likely to damage this muscle during pregnancy and childbirth because of overstretching. In addition to other anatomical factors, the external urethral sphincter and the levator ani muscle's joint contraction play important roles in urinary continence, and they can result in the formation of a urethral bend angle and the urethra being forcibly closed. When the external urethral sphincter and levator ani muscle are dysfunctional, the urethra cannot be forcibly closed, which causes urinary incontinence [7].

SUI is divided into mild, moderate, and severe levels with the Ingelman-Sundberg scale. Mild UI occurs when coughing or sneezing, with no need to use a urinary pad; moderate UI occurs in daily activities such as running, jumping, and brisk walking and requires the use of a urinary pad; severe UI occurs with slight activity and the change to a supine position [9].

SUI, irrespective of its severity, has a great impact on patients' quality of life. But due to the embarrassment of describing their symptoms, only the most severely affected women seek help [10]. In the past 20 years, scholars worldwide have conducted research on various aspects of SUI, encompassing its etiology, diagnostic methodologies, and therapeutic interventions. Chinese scholars have found 20 risk factors for SUI, including old age, high BMI, heavy labor intensity, a history of drinking alcohol, hypertension, constipation, a history of urinary system disease, a history of respiratory system disease, a history of gynecological disease, giving birth more than once, heavy birth weight of the first child, perineal laceration, a history of pelvic surgery, menopause, vaginal delivery, and uterine prolapse [11].This extensive list underscores the multifactorial nature of SUI and highlights the need for a comprehensive understanding of the condition to inform effective clinical management strategies.

The International Consultation on Urological Diseases recommends that treatment methods for mild and moderate SUI include lifestyle intervention, behavior therapy, and pelvic floor muscle training (PFMT). [12]. PFMT has been demonstrated to be effective in alleviating symptoms of SUI across a spectrum of age groups, including young, middle-aged, and older women who have either SUI or mixed urinary incontinence (MUI) [13].

Although PFMT has a significant impact on female SUI, traditional PFMT is based on one-on-one training sessions with pelvic floor physical therapists or other licensed health care specialists. This form of intense, individual rehabilitation therapy is expensive, and the community's availability of licensed pelvic floor therapists is restricted [14].

In addition to conservative treatment, many women also opt for surgery. The standard surgery for SUI includes retro-pubic urethropexy or a pubovaginal sling. Mid-urethral slings are currently the most regularly performed surgical option [15]. Women younger than 60 years rate the outcome of mid-urethral sling surgery better than older women. And women aged 60 to 79 years have a slight but statistically significant increased risk of surgical complications, such as bladder perforation and urine retention, as well as an increase in urgent urinary incontinence (UUI) symptoms and de novo UUI [16]. Surgical treatment of female SUI is effective, but there is a risk of pain, infection, and dysuria-related complications [17]. As a result, many patients are hesitant to have surgery. Therefore, other safe and effective conservative therapies are needed.

There are clinical trials showing that electroacupuncture (EA) is more effective than PFMT in the treatment of SUI [18]. However, the efficacy of PFMT at home heavily depends on adherence and standard movements, whose quality is more difficult to control than EA.

Recently, many clinical studies and reports have revealed that the effectiveness of simple EA therapy or EA-related therapies for treating SUI is relatively high. A randomized clinical trial [19] showed that EA involving the lumbosacral region in women with SUI resulted in less urine leakage after 6 weeks compared to sham EA. In another trial [20], based on the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) score, EA showed better results than sham EA in improving quality of life, indicating that EA had sound short-term and long-term specific effects. EA continued to work even after treatment was stopped.

Although current clinical trials have shown the effectiveness of EA, meta-analysis assessing its efficacy and safety is constrained by limitations inherent in previous clinical studies, such as small sample sizes, suboptimal study designs, and significant risk of bias [21]. Consequently, a rigorous scientific and systematic assessment of EA's efficacy remains needed. This study aims to compare the efficacy of EA with other conservative therapies in treating female SUI of mild and moderate severity by using

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network meta-analysis (NMA), providing evidence for clinical decision-making.

Methods

Study Registration

This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY). The registry number is INPLASY 202320098 [22], and any revisions to the program will be documented on the INPLASY platform.

Search Strategy

We will electronically search (search period: 2002 to 2022) the following international and domestic databases: EMBASE, PubMed, Cochrane, Web of Science, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), WanFang, and the Chinese Biomedical Literature Database (CBM). The PROSPERO database and the INPLASY database will also be searched. The search strategy will use a combination of terms from Medical Subject Headings (MeSH) and keywords including *SUI*, *EA*, *drugs*, *PFMT*, *systematic review*, and *NMA* (Multimedia Appendix 1). The search words in the Chinese databases have the same meaning as those used in the English databases. Protocols and conference reports will be excluded. The document languages will be limited to Chinese and English.

Criteria for Studies

Types of Studies

All randomized controlled trials (RCTs) will be included. Protocols, observational research, animal experiments, qualitative research, letters, news, communications, and review articles will not be included. Duplicate articles, irrelevant research, articles with missing data and/or methodology issues, and articles whose full text could not be found will be excluded.

Types of Participants

Female patients of any age or ethnicity with a clinical diagnosis of SUI in accordance with the diagnostic criteria of the International Continence Society [23] will be included. Postpartum female patients will be included. Male participants with SUI will be excluded. Patients who have undergone surgery will be excluded. Patients diagnosed with mild or moderate SUI will be included, while those with severe SUI and other types of UI, such as UUI and MUI, will be excluded. Patients who have undergone other previous treatments, such as surgical treatment and drug treatment, will be excluded.

Types of Interventions

The studies will be included if they use EA or transcutaneous electric nerve stimulation (TENS) as the treatment for SUI.

Types of Comparators and Controls

Studies will be included if they used medicine exclusively (for example, selective adrenoceptor agonists, midodrine hydrochloride, duloxetine hydrochloride, and topical vaginal estrogen therapy) or any PFMT exclusively. Studies will be excluded if they (1) do not incorporate a comparison group or condition or (2) use EA (including TENS) as an adjuvant therapy.

Outcome Measures

Primary Outcome

The primary outcome is the change from baseline to the end of follow-up in urine leakage, measured by a 1-hour pad test and the ICIQ-SF score.

Secondary Outcomes

The secondary outcomes include 72-hour incontinence episodes, residual bladder volume, effective rate, urodynamic indexes, and other reported measurements with sufficient data for synthesis.

Data Collection and Analysis

Selection of Studies

The search results from the above databases will be exported to EndNote (Clarivate) [24] for article screening. Duplicate articles will be filtered and removed. Two reviewers (JS and JL) will independently select articles by screening their titles and abstracts. Full texts will be searched for further evaluation when necessary. Then, the reviewers will examine the full-text articles according to the inclusion criteria. In cases of conflicting opinions, a third reviewer (BX) will be consulted to resolve any disagreement.

Data Extraction and Management

Three reviewers (PL, YZ, and YW) will independently extract parameters from functional studies, including identification information (eg, publication year and first author), general information (eg, country, number of centers, and sample size), baseline characteristics of the participants (eg, age, BMI, SUI severity, and mode of child delivery), interventions (type of acupuncture, as well as frequency, sessions, and duration), comparator (if there are any; this will include details of the treatment, such as its name, dosage, frequency, and course), and outcomes (data and time points for each measurement, safety of the treatments, and adverse effects).

Risk of Bias (Quality) Assessment

Two researchers (PL and YZ) will independently evaluate the literature's quality, mainly according to results obtained with the Cochrane Risk of Bias 2 assessment tool [25]. The main factors considered include the randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, selective outcome reporting, and other sources of bias. Two researchers will grade the above content as "low bias risk," "high bias risk," or "unclear bias risk" and cross-check the obtained results. Any conflicts or discrepancies will be solved by discussion; otherwise, a third researcher (BX) will be consulted to achieve agreement. Finally, a bias risk diagram will be drawn using Microsoft Excel 2019.

Quality of Evidence Assessment

Additionally, if possible, we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [26] to assess the certainty of evidence. We will assess the quality of the evidence in 4 levels: high

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quality, moderate quality, low quality, and very low quality. Moreover, the official GRADE Pro software will be used to conduct this process.

Statistical Analysis

Overview

Review Manager (RevMan version 5.3; Cochrane) will be used to perform statistical analysis. A pairwise meta-analysis will be used to assess treatments against direct evidence. Considering the expected between-study heterogeneity, we will use a random effects (RE) model for each intervention comparison. We will pool the data from each outcome separately using a Bayesian RE model. A risk ratio with 95% CIs will be used to analyze dichotomous outcomes. The continuous data will be expressed as means and SDs for each study. The mean difference, or standardized mean difference if different metrics are used across studies, will be calculated with their respective 95% CIs. We will calculate the rate ratio with a 95% CI for count outcomes.

Heterogeneity will be evaluated with the χ^2 test and the I^2 statistic [25]. Statistical heterogeneity will be categorized as follows: (1) $P>.05$ and $I^2\leq 50\%$ indicates low or moderate heterogeneity, and a fixed effect model can be used for the analysis; (2) $P<.05$ and $I^2=50\%$-75% indicates substantial heterogeneity; and (3) $P<.05$ and $I^2\geq 75\%$ indicates considerable or high heterogeneity [27].

We will perform an NMA for each outcome to compare multiple interventions in a single model using Stata (version 14.0; StataCorp). We will preferentially pool direct evidence; however, indirect comparisons will be used to estimate the effect in the absence of direct comparisons. For analysis, the Markov chain Monte Carlo method can be used. In addition, we will evaluate convergence using Gelman-Rubin diagnostics and inspection of Monte Carlo errors [28].

The intervention effect estimates will be presented along with their corresponding 95% CIs, and surface under the cumulative ranking curve (SUCRA) will also be shown. The best treatment is expected to have high SUCRA values, while the worst will have low values. We will present the direct, indirect, and network estimates for each comparison.

Sensitivity Analysis

The effect of studies with a high risk of bias on the overall estimate of the intervention's effect will be determined using sensitivity analysis.

Subgroup Analysis

To investigate sources of heterogeneity, we will conduct subgroup analyses according to the following factors: age, disease course, severity of SUI, acupoints, waveform, frequency of EA parameters, and treatment duration.

Dealing With Missing Data

Should clarification or additional data be necessary from the included articles, the corresponding authors of these studies will be contacted via telephone or email.

Assessment of Reporting Bias

If more than 10 studies are included, a funnel plot will be used to construct the reporting bias. Otherwise, we will use Stata 14 to assess reporting bias with the Egger test [29].

Results

Results are not yet available because this is a protocol for a systematic review and meta-analysis. The protocol was registered on INPLASY on February 22, 2023. By April 6, 2023, we had completed the literature search of 8 databases and completed the selection and data extraction of the articles. The specific analysis has not been completed yet. The search and selection process is illustrated by the flow diagram in Figure 1.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 flow diagram for new systematic reviews, including searches of databases and registers only. CNKI: Chinese National Knowledge Infrastructure.

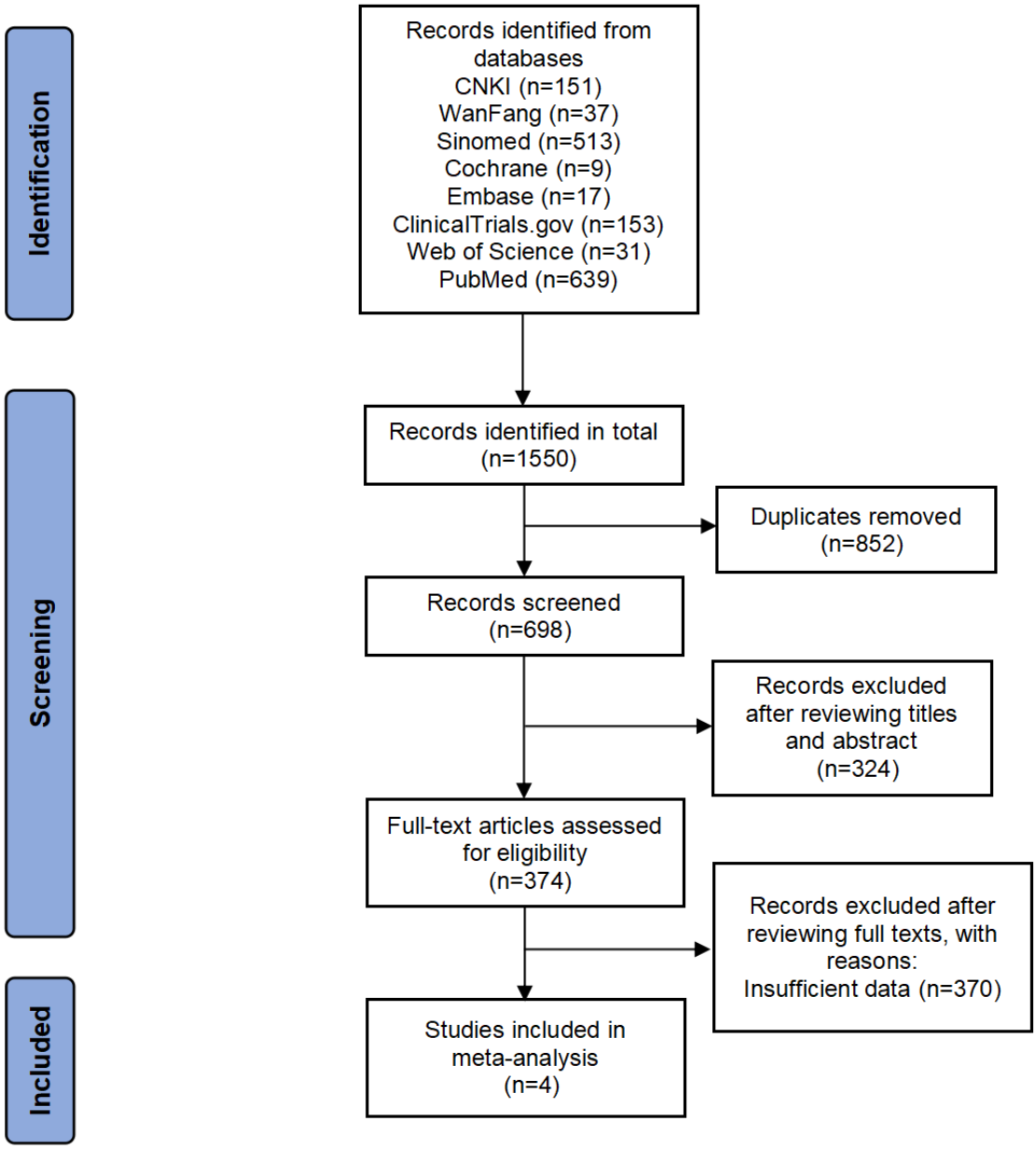

Discussion

Principal Findings

SUI is a significant problem that seriously affects people's health. The prevailing theory explaining SUI is that leakage from the urethra occurs when the intra-abdominal pressure exceeds the urethral pressure [30]. Intrinsic urethral sphincter deficiency and urethral hypermobility caused by weak pelvic floor muscles have been proposed as the main pathophysiologies [31].

EA is a treatment in which a small amount of low-frequency pulse current is applied by an acusector to a filiform needle inserted into an acupoint during acupuncture. Although the treatment mechanism of acupuncture for SUI is currently unknown, EA may facilitate the reinnervation and strengthening of the pelvic floor muscles, improving symptoms of SUI [19]. Moreover, the cost of acupuncture treatment is generally lower than that of Western medicine [32,33].

Summary

To sum up, this review aims to determine whether EA is an effective, safe, and affordable treatment for women with mild to moderate SUI when compared with other conservative treatments, such as drug therapy and PFMT.

Previous research [3,19,34] has shown that EA is frequently used in the clinical treatment of SUI and is an efficient and safe treatment. Based on preliminary screening and data extraction results for the change in urine leakage from baseline to the end of the follow-up, as measured by a 1-hour pad test, the ICIQ-SF score, 72-hour incontinence episodes, and effective rate measurements, it appears that EA therapy is more effective in treating mild to moderate SUI in women compared to drug therapy or PFMT.

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Comparison to Prior Work

Most current meta-analyses have extensively searched and analyzed conservative treatment methods for female SUI, despite the low consistency and high heterogeneity among the included studies. Compared with other meta-analyses for conservative treatment of female SUI [34-37], we narrowed the range of interventions and limited the severity of female SUI to mild to moderate, making the analysis more targeted.

Strengths and Limitations

This systematic review and meta-analysis of the research should provide an integrated understanding of the current state of treatment for mild to moderate SUI in women, offer more ideas to clinicians for treating the condition, and provide a basis for patients to choose more effective, safer, and more convenient and affordable treatment options. Our NMA will be the first to compare the efficacy of EA or TENS with drugs or PFMT in the treatment of women with mild to moderate SUI.

Nevertheless, there may also be some potential limitations in this review. Due to limited language ability, financial resources, and personnel, only papers written in English or Chinese will be included. This limitation may inadvertently restrict the breadth of available data or introduce a linguistic bias.

Since the quality of the original literature will affect the quality of this evaluation, we will include the literature in strict accordance with outcome indicators and screening criteria to reduce the impact of literature quality on the risk of bias.

Future Directions

The findings of this systematic review will be used as evidence to determine if EA treatment can be used to intervene effectively in women with mild to moderate SUI. This NMA will also help clinicians make evidence-based clinical choices and provide guideline makers with high-quality updated evidence for recommending EA.

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Authors' Contributions

Conceptualization: BX, YW, JS, JL, PL, YZ.
Data curation: JS, YW, JL.
Formal analysis: YW, PL, YZ.
Resources: BX.
Software: PL, YZ.
Writing (original draft): JS.
Writing (review and editing): BX, PL, YZ, JS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full search strategies.
[PDF File (Adobe PDF File), 95 KB - resprot_v13i1e55870_app1.pdf]

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Abbreviations

CBM: Chinese Biomedical Literature Database
CNKI: Chinese National Knowledge Infrastructure
EA: electroacupuncture
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form
INPLASY: International Platform of Registered Systematic Review and Meta-Analysis Protocols
MeSH: Medical Subject Headings
MUI: mixed urinary incontinence
NMA: network meta-analysis
PFMT: pelvic floor muscle training
RCT: randomized controlled trial
RE: random effects
SUCRA: surface under the cumulative ranking curve
SUI: stress urinary incontinence
TENS: transcutaneous electric nerve stimulation
UI: urinary incontinence
UUI: urgent urinary incontinence

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Protocol

Accuracy Standards of Wearable Technologies for Assessment of Soccer Kicking: Protocol for a Systematic Literature Review

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Abstract

Background: Wearable technology is widely applied in performance monitoring, an integral part of sports and exercise sciences. The kick movement in soccer exemplifies a sports technique that could benefit from appropriate biomechanics assessment methodologies. However, the accuracy of wearables in quantifying soccer kick mechanics, particularly under field conditions, remains unclear.

Objective: This study aims to present a protocol for a systematic review to discuss the measurement properties (validity, reliability, and/or accuracy aspects) of wearable technology systems explicitly used to measure ball-kicking features in soccer.

Methods: This review protocol was preregistered in the Open Science Framework. A total of 2 authors will perform searches in major electronic databases using specific keyword combinations in PubMed, Physical Therapy and Sports Medicine, Web of Science, ProQuest, IEEE Xplore, EBSCOHost, and Scopus. Following a specific population, intervention, comparison, outcome framework (population: soccer players and/or collected human data in a football-related environment; intervention: at least 1 wearable used; comparator: criterion measures, repeated testing sessions and/or actual values; outcome: ball kicking data), studies will be screened based on predetermined inclusion and exclusion criteria. The methodological quality of the included studies will be assessed using the "consensus-based standards for the selection of health measurement instruments" checklist (in studies concerning validity or reliability) or the "quality assessment of diagnostic accuracy studies" tool (in studies concerning accuracy). Data extraction will be conducted to determine the level of evidence according to the "best evidence synthesis method," and an evidence gap map will be constructed. The Cohen κ coefficient will be used to estimate the interevaluator agreement.

Results: This ongoing systematic review has completed database searches and is currently in the screening phase. Depending on the number and consistency of studies, results may be presented by meta-analysis or qualitative synthesis, with subgroup analyses considering factors such as gender, age, and playing level. The final results are expected by July 2024, with manuscript submission anticipated by November 2024.

Conclusions: Our study will provide a comprehensive summary of the highest level of evidence available on the use of wearables for the assessment of soccer kick mechanics, providing practical guidance for athletes and sports sciences professionals regarding the validity and reliability aspects of using wearable technology to measure ball-kicking features in soccer.

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KEYWORDS
skill-related performance; shooting; team sports; sports engineering; measurement error; validity; reliability; quality control

Introduction

Soccer is well-known as one of the most practiced and watched sports around the world, with an estimated 5 billion have engaged in the last edition of the FIFA (Fédération Internationale de Football Association) World Cup Qatar 2022 [1]. A main action in soccer is the kicking. Kicking is defined as a form of striking in which the foot is used to deliver force against an object [2]. In the case of soccer, the ball is the desired object for kicking (eg, for passing or shooting). Despite the evident importance of ball kicking to soccer performance, the quantity and quality of investigations are not proportional to its relevance to the game. The lack of sufficient evidence to assist practice is evidenced, for example, by the limited number of investigations available in the form of scientific studies assessing practical interventions and their effects on ball-kicking movement [3]. While adopting field paradigms is desired when measuring or testing kicking skills in soccer [4], the difficulty of capturing player movement kinematics under field conditions may justify in part the scarcity of literature (eg, large time-frame from data collection to results report) [5-7]. In this context, the emergence of technologies that can overcome such limitations is therefore necessary.

Wearables represent a range of devices that can be worn or attached to the body to record data and comprise, in general, 2 categories: independent running devices (primary) or devices that require offline transference to a primary wearable device [8]. Wearables have been extensively used to measure load demands (internal and/or external). At the same time, this can also be used in additional sport-specific movements, such as evaluating technical aspects of gameplay [9], including but not restricted to ball kicking. Examples of wearables used to monitor soccer kicking data (eg event detection and release velocity) include inertial measurement unit [10], accelerometer [11], GPS-embedded accelerometer [12], or LPS (local positioning system) [13]. One advantage of wearable devices, which provide kinematic outputs, as compared with traditional video-based tracking techniques, refers to their generally reduced cost and time effectiveness [6].

Defining some further concepts in advance is necessary when proposing a protocol for a systematic review of the measurement properties (eg, validity and reliability) of wearables used to measure ball kicking. The first one refers to the validity term, which can be assumed as whether one given instrument measures the characteristic it was designed to quantify. Concerning kinematics variables, there is a traditional acceptance that high-speed optical systems (eg VICON; Oxford Metrics Ltd) represent the “gold standard” [14]. Reliability (eg test-retest) represents more the variation of the tool, protocol, or human system [15]. Accuracy can be defined as the closeness between a measured value and the actual value [16,17]. In the case of wearables applied to capture soccer kicking features, this can be exemplified by the number of kick occurrences registered by the device or system compared with known values derived from offline observational analysis of video recordings (ie human operator labeling). Finally, while there is a knowledge base [18-20], to the extent of our knowledge, no previous systematic reviews addressed solely the measurement properties, such as validity aspects of wearable technologies specifically applied to compute ball kicking indices.

Therefore, this study aims to provide a protocol for a systematic review focused on analyzing the measurement properties (validity, reliability, and accuracy) of wearable technology systems used explicitly to measure ball-kicking features in soccer. The future review using the protocol described here will assist in answering the following question: Are the available wearables accurate enough to quantify soccer kick mechanics, especially under field conditions?

Methods

Electronic Databases and Search Strategy

Searches will be performed by 2 authors (LV and FM) in the following electronic databases: (1) PubMed (National Library of Medicine), (2) Physical Therapy and Sports Medicine (Gale OneFile), (3) Web of Science (Clarivate), (4) ProQuest (ProQuest LLC), (5) IEEE Xplore (Institute of Electrical and Electronics Engineers), (6) EBSCOHost (Elton B. Stephens Company, EBSCO Information Services LLC), and (7) Scopus (Elsevier BV). No restrictions will be imposed concerning the date of publication; that is, studies will be considered for inclusion when published, even online ahead of print, from inception up to the date of searches. The searches will be updated—carried out once again—when necessary (ie, if the time interval separating literature search and manuscript acceptance for publication exceeds 12 months). The Zotero software (version 6.0.30; Corporation for Digital Scholarship, Roy Rosenzweig Center for History and New Media at George Mason University) will be used to manage reference entries from the initial search to the final inclusion steps. According to a specific Population, Intervention, Comparison, Outcome (PICO) framework [21], studies will be screened looking for those in which “P” participated able-bodied soccer players and/or collected human data in the football-related environment, “I” evaluated with at least one wearable device or system (regardless of their category, ie, commercially available or patent or research not yet commercialized), “C” that was compared against criterion measures (ie, tested validity), between testing sessions (ie, tested reliability) and/or against actual values (ie, tested accuracy) and “O” reported data for ball kicking action.

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Thus, search terms attempted to respect such defined PICO framework and are presented in Table 1 using a Boolean search strategy, also considering those key terms used previously in existing systematic reviews [3,14,20]. The search string formulated across the databases focused on searching using 3 major fields (title, abstract, and keywords). There was one exception of the Physical Therapy and Sports Medicine database in which a broader field of search was needed, due to a particular word limit imposed when entering the search terms in such database. After performing the last step of selection, the reference list of included studies will also be checked, aiming to identify additional studies potentially eligible for inclusion in this review.

Table 1. Search strategy formulated for each specific database considered for the present study protocol.

Database	Search string
PubMed	((((soccer[tiab]) OR football*[tiab]) OR association football[tiab]) OR 11-a-side[tiab]) AND ((((((((((((wearable*[tiab]) OR inertial measurement unit[tiab]) OR IMU[tiab]) OR acceleromet*[tiab]) OR microtechnology[tiab]) OR micro-electrical mechanical system[tiab]) OR MEMS[tiab]) OR global positioning system[tiab]) OR global navigation satellite system[tiab]) OR local positioning system[tiab]) OR GPS[tiab]) OR GNSS[tiab]) OR LPS[tiab]) AND (((((validity[tiab]) OR reliability[tiab]) OR measurement error[tiab]) OR accuracy[tiab]) OR precision[tiab]) AND (((((kick*[tiab]) OR shoot*[tiab]) OR pass*[tiab]) OR skill[tiab]) OR technical[tiab])
Web of Science	TS=(((((soccer) OR football*) OR association football) OR 11-a-side) AND ((((((((((((wearable*) OR inertial measurement unit) OR IMU) OR acceleromet*) OR microtechnology) OR micro-electrical mechanical system) OR MEMS) OR global positioning system) OR global navigation satellite system) OR local positioning system) OR GPS) OR GNSS) OR LPS) AND ((((((validity) OR reliability) OR measurement error) OR accuracy) OR precision) AND ((((kick*) OR shoot*) OR pass*) OR skill) OR technical))
EBSCOHost	TI ((soccer OR football OR association football OR 11-a-side) AND (wearable* OR inertial measurement unit OR IMU OR acceleromet* OR microtechnology OR micro-electrical mechanical system OR MEMS OR global positioning system OR global navigation satellite system OR local positioning system OR GPS OR GNSS OR LPS) AND (validity OR reliability OR measurement error OR accuracy OR precision) AND (kick* OR shoot* OR pass* OR skill OR technical)) OR AB ((soccer OR football OR association football OR 11-a-side) AND (wearable* OR inertial measurement unit OR IMU OR acceleromet* OR microtechnology OR micro-electrical mechanical system OR MEMS OR global positioning system OR global navigation satellite system OR local positioning system OR GPS OR GNSS OR LPS) AND (validity OR reliability OR measurement error OR accuracy OR precision) AND (kick* OR shoot* OR pass* OR skill OR technical)) OR KW ((soccer OR football OR association football OR 11-a-side) AND (wearable* OR inertial measurement unit OR IMU OR acceleromet* OR microtechnology OR micro-electrical mechanical system OR MEMS OR global positioning system OR global navigation satellite system OR local positioning system OR GPS OR GNSS OR LPS) AND (validity OR reliability OR measurement error OR accuracy OR precision) AND (kick* OR shoot* OR pass* OR skill OR technical))
SCOPUS	(TITLE-ABS-KEY (soccer OR football OR “association football” OR 11-a-side) AND TITLE-ABS-KEY (wearable* OR “inertial measurement unit” OR imu OR acceleromet* OR microtechnology OR “micro-electrical mechanical system” OR mems OR “global positioning system” OR “global navigation satellite system” OR “local positioning system” OR gps OR gnss OR lps) AND TITLE-ABS-KEY (validity OR reliability OR “measurement error” OR accuracy OR precision) AND TITLE-ABS-KEY (kick* OR shoot* OR pass* OR skill OR technical))
ProQuest	TI,AB,IF(soccer OR football OR association football OR 11-a-side) AND TI,AB,IF(wearable* OR inertial measurement unit OR IMU OR acceleromet* OR microtechnology OR micro-electrical mechanical system OR MEMS OR global positioning system OR global navigation satellite system OR local positioning system OR GPS OR GNSS OR LPS) AND TI,AB,IF(validity OR reliability OR measurement error OR accuracy OR precision) AND TI,AB,IF(kick* OR shoot* OR pass* OR skill OR technical)
Physical Therapy and Sports Medicine	Entire Document: soccer OR football OR association football OR 11-a-side AND Entire Document: wearable* OR inertial measurement unit OR IMU OR acceleromet* OR microtechnology OR micro-electrical mechanical system OR MEMS OR global positioning system OR global navigation satellite system OR local positioning system OR GPS OR GNSS OR LPS AND Entire Document: validity OR reliability OR measurement error OR accuracy OR precision AND Entire Document: kick* OR shoot* OR pass* OR skill OR technical
IEEE Xplore	(“All Metadata”:soccer OR “All Metadata”:football OR “All Metadata”:association football OR “All Metadata”:11-a-side) AND (“All Metadata”:wearable* OR “All Metadata”:inertial measurement unit OR “All Metadata”:IMU OR “All Metadata”:acceleromet* OR “All Metadata”:microtechnology OR “All Metadata”:micro-electrical mechanical system OR “All Metadata”:MEMS OR “All Metadata”:global positioning system OR “All Metadata”:global navigation satellite system OR “All Metadata”:local positioning system OR “All Metadata”:GPS OR “All Metadata”:GNSS OR “All Metadata”:LPS) AND (“All Metadata”:validity OR “All Metadata”:reliability OR “All Metadata”:measurement error OR “All Metadata”:accuracy OR “All Metadata”:precision) AND (“All Metadata”:kick* OR “All Metadata”:shoot* OR “All Metadata”:pass* OR “All Metadata”:skill OR “All Metadata”:technical)

Inclusion and Exclusion Criteria

This review will include studies presented in the form of (1) original research articles (independent of its design), (2) written in the English language, (3) published in scientific journals with peer-review policy, (4) with full-text available for download, and (5) abstract available for screening in the respective database. Suppose there is no option to obtain full-text in its original database, in that case, additional searches can be conducted in Google Scholar, allowing for potential inclusion

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of studies from ResearchGate (ResearchGate GmbH). As an additional inclusion criterion, (6) studies will be only considered for inclusion in the present systematic review project when they have respected the fundamental ethical principles consistent with the Declaration of Helsinki by including the full text, such information that an institutional research ethics committee approved the investigation with human subjects [22] or otherwise whether there is an explicit statement indicating that evaluations were done as a part of traditional athletes routine measurements (eg, occupationally based work or given a requirement of employees) which may allow the absence of previous approval by an appropriate body [23].

Those studies (1) examining only the application or feasibility of wearable device, (2) observations/experiments only addressing football codes movements other than ball kicking, (3) reported as grey literature, conference proceedings, books, thesis, dissertations, literature reviews, opinion pieces, case studies, (4) where a ball was not kicked, (5) with outcomes only concerning motion/flight of the ball, (6) without mention of the location where the wearable system/device was attached to the body of evaluated subjects, and (7) retracted studies will be excluded. A third researcher with long-term experience in the area (FMC) will resolve cases if no consensus is reached by the 3 authors in charge of searches/selection of studies.

Methodological Quality and Risk of Bias Assessments

The methodological quality of the included studies will be determined using the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) checklist, specifically the forms B (for studies assessing reliability) and H (for studies assessing validity) [24,25] or the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool (for studies assessing accuracy) [17,26]. In addition, the Risk of Bias (RoB) of results or inferences will be computed for each study included separately through the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS; Kim et al [27]). Each item will be assessed as having low, high, or unclear risk concerning criteria of selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Review Manager software (RevMan, version 5.3; The Cochrane Collaboration) [28] will be used to construct the RoB graphs for individual studies as well as all results of all studies pooled. In addition, 2 authors (WMRO and KRVV) will perform the processes independently.

Data Extraction and Evidence Synthesis

Data extraction will be made (by LHPV and KRVV) using a specific spreadsheet, and parameters considered to be included will be selected after piloting, with approximately 3 studies among those included. In general, we expected to extract the following data from included studies: correlation coefficients, intraclass correlation coefficient, root-mean-square error [20], F-measure, and accuracy [29] in addition to study characteristics, including, for example, device employed, time used, kick protocol, measured variable, and concluding remarks [30]. The corresponding authors of included studies will be contacted by email—those provided together with the publication—in cases where the full text lacks sufficient data or if the information presented is unclear. In the absence of a response (or negative), data will be indicated in the tables of results with the symbol "--". Following on, the "best evidence synthesis method" will be applied to classify the level of evidence across included studies [31]; consistency has been defined when ≥75% of studies reported results in the same direction, while inconsistency when <75% of studies reported results in the same direction [3,32,33]. Thus, the following thresholds will be used:

1. Strong evidence: consistent findings obtained from multiple high-quality studies;
2. Moderate evidence: consistent findings obtained from multiple moderate-quality and/or 1 high-quality study;
3. Limited evidence: findings obtained from 1 moderate-quality and/or only low-quality studies;
4. Conflicting evidence: inconsistent findings obtained from studies;
5. No evidence: no study found.

To assist the graphical presentation of the strength of evidence, an evidence gap map will also be constructed [34,35]. For all steps where 2 evaluators are requested above (ie, literature search/selection, methodological quality/bias, and data extraction), interevaluator agreement will be assessed using Cohen κ coefficient, and then the average value across measures will be reported in the final systematic review paper.

Ethical Considerations

The review protocol was preregistered in the Open Science Framework Registries/Generalized Systematic Review Registration (Registry ID: #ZM3J6) [36]. This protocol, as presented in full here, follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist [37] (Multimedia Appendix 1). Some updates to the original protocol registration were done based on the *JMIR Research Protocols* external reviewer's suggestion. The projected future systematic review is also intended to contain the items proposed by the 2020 version of the PRISMA statement [38]. This study has been carried out under authorization from the Institutional Research Ethics Committee (Comité de Ética en Investigación de las Escuelas Profesionales de Educación Inicial y Ciencias del Deporte de la Universidad César Vallejo), project number 2761 (ANEXO N.º 3).

Results

This systematic review project is ongoing. From an initial search (February 2024) conducted to find previous analyses on wearables in the context of sport (data found from inception to 2023; Table 2), there were no existing reviews, amongst those identified, which have aimed at examine solely the application of wearables to investigate ball kicking in soccer [7,9,14,18-20,39-44] (Table 3). Given the importance of the subject, a dedicated analysis is therefore justified. At the moment of submission, database searches were completed (ie, identification step), and the present authors are beginning the screening step. If there is a sufficient number of studies (ie, 3 or more on a given dependent variable) and no substantial variations are detected concerning methods used across studies, results can also be presented through a meta-analysis

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(quantitative synthesis). Subgroup analysis, if pertinent, will consider, for example, gender, age, and playing level. Finally, independent of whether the final manuscript will qualify for quantitative synthesis or not, qualitative synthesis will be performed using the best evidence synthesis method. In addition, a table in attachments containing the main study characteristics will be included (eg, aim, results, and findings). Results are predicted to be completed by July 2024, and the final systematic review manuscript submission by November 2024.

Table 2. Some methods of review studies potentially address wearable technology and soccer kicking assessment.

Reference	Type of review	Guidelines	Date of searches or inclusion	Databases considered
Adesida et al [18]	Systematic	__[a]	From inception to October 31, 2018	Scopus, MEDLINE, Embase, Cochrane Library, IEEE Xplore, Web of Science (Core Collection), and Engineering Village
Camomilla et al [19]	Systematic	PICOS[b] framework	Until April 12, 2017	Web of Science, Scopus, PubMed, and Sport Discus
Cardinale and Varley [39]	Brief (narrative)	—	Search on July 2016	PubMed
Chambers et al [9]	Systematic	—	Published between 2008 and 2014	Academic Search Complete, CINAHL, PsycINFO, PubMed, SPORTDiscus, and Web of Science.
Crang et al [14]	Systematic	PRISMA[c] statement	From earliest record to March 2020	SPORTDiscus, CINAHL, and MEDLINE
De Fazio et al [40]	Overview (narrative)	—	—	—
Fong and Chan [41]	Systematic	—	From 1966 to July 2010	MEDLINE, ISI Web of Knowledge (Science Citation Index Expanded), Social Sciences Citation Index, Arts & Humanities Citation Index, SportDiscus, and IEEE Xplore
Liu & Zhang [44]	Narrative	—	—	—
Lutz et al [42]	Overview (narrative)	—	—	—
Poitras et al [20]	Systematic	PRISMA	From 2005 to July 2018	PubMed, CinAHL, Ergonomic abstract, Compendex, and Embase
Rana and Mittal [7]	Narrative	—	—	—
Seçkin et al [43]	Narrative	—	Published between 2015 and 2023	Web of Science

[a]Information not reported or unclear.

[b]PICOS: Population, Intervention, Comparison, Outcome, Study design.

[c]PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Table 3. Results of an initial search for review studies potentially addressing wearable technology and soccer kicking assessment.

Reference	Year	Aim	Results related to measurement properties of wearable technologies to measure soccer kicking
Adesida et al [18]	2019	Comprehend the application of wearables in sports to optimize performance and mitigate the risk of injury	Good concurrent validity between MVN Link/Xsens inertial measurement system and Vicon, despite the higher error in segments showing fastest movements (1 study); Approximately 99% accuracy of a wearable sensor to detect kicks (1 conference proceeding); Descriptive data of application of wearables in kick investigations (2 studies)
Camomilla et al [19]	2018	Assessing the existing evidence and the prospective role of wearables in evaluating sport performance	Mention of devices assessing the accuracy of wearable sensors to detect kicks (2 studies); Descriptive data of application of wearables in kick investigations (1 study)
Cardinale and Varley [39]	2017	Review applications, obstacles, and potentials of different wearable technologies in training monitoring	—[a]
Chambers et al [9]	2015	Evaluate the use of microsensors in quantifying movements specific to sports	—
Crang et al [14]	2021	Analysis of research examining the validity/reliability of wearables in measuring actions of intermittent team sports	—
De Fazio et al [40]	2023	Offer a thorough examination of wearable technologies used for tracking the physiological aspects of patients during post-surgery recovery and athletes' training	—
Fong and Chan [41]	2010	Examine the existing body of literature concerning the application of inertial sensors in studies focused on the biomechanics of the human lower limbs	—
Liu and Zhang [44]	2022	Provides a holistic view of recent developments in flexible/wearable sensor technologies for sports	—
Lutz et al [42]	2020	Look into contexts where wearables find application for both individual and team performance assessments, emphasizing aspects such as reliability and validity	—
Poitras et al [20]	2019	Evaluate the criterion validity and reliability of inertial measurement units according to body joint across tasks of varying levels of complexity	Mention of validity results to Xsens MVN BIOMECH (Xsens Technologies B.V., Enschede, the Netherlands) (1 study)
Rana and Mittal [7]	2021	Examining wearable technology/sensors used for performance analysis in sports	Mention of devices assessing the accuracy of wearable sensors to detect kicks (2 conference proceedings); Descriptive data of application of wearables in kick investigations (3 conference proceedings)
Seçkin et al [43]	2023	Explores the use of wearables in the measurement/monitoring of athletic components (performance, injury prevention, rehabilitation, and performance optimization)	—

[a]Not available.

Discussion

In this study, we set out to provide a detailed protocol for a future systematic review of the measurement properties of wearables adopted to investigate ball kicking. Ensuring data quality through the integration of new technological devices is crucial for minimizing bias in research publications and the decisions derived from using such instruments in daily practice. Therefore, scientific publishing must prioritize valid metrics, as measured in concurrent-validity studies, and reliability [45]. Based on the exploratory analysis conducted in our initial search, the majority of publications indicate that wearables help quantify soccer kick mechanics. This finding would instill confidence in their use in real-world scenarios.

Recognizing the increasing demand for ecologically focused soccer drills [46] and acknowledging the opportunities presented

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by new technologies for incorporating measurement systems into training, the use of wearables in ecological scenarios emerges as a high-value proposition. Indeed, this approach offers a viable solution to overcome the constraints associated with gold-standard motion-based devices, which are typically limited to specific locations, predominantly within laboratories.

With the progress in microsensors, we anticipate observing satisfactory levels of concurrent validity in wearable inertial measurement units, as supported by previous original research [47,48]. The majority of kinematic measures exhibiting acceptable concurrent validity and reliability are expected to be associated with ball release velocity [48], representing an outcome of the kicking process. Meanwhile, other outcomes will be linked to the inherent quality of movement, seeking to characterize the kinematic profile of players [12,47] by measuring linear, angular, or joint velocities. It is important to note that the judgment on whether individual wearable types/brands present sufficient research evidence to be used in practice will be based on both the quality and quantity of published studies available in the form of scientific articles, as per the rigorous synthesis method adopted.

The reliability levels observed in the wearable microsensors, as mentioned above, may enable ecological-based research and practical scenarios. Despite their accuracy and precision being comparable to gold-standard vision-based instruments, the latter are, in general, significantly limited in their ability to track kinematics in confined spaces, thereby failing to provide context and real-world applicability to practice.

As a limitation, this study focuses solely on the kicking process, thereby excluding the examination of other wearable technologies that are currently being observed for upper limb movements and throws. However, it is conceivable that these technologies may become applicable to kicking in the near future. Furthermore, the limited number of articles identified in this research field, coupled with its niche nature, may constrain the generalization of findings. Nonetheless, our study addresses a specific research and practice issue within one of the most widely practiced sports globally. Consequently, it has the potential to assist provide insights into the quality of data derived from these devices for numerous coaches.

The outcomes of this systematic review will offer researchers and practitioners a means to comprehensively summarize the evidence regarding the quality of data extracted from wearable devices for measuring kicking performance. This will enable the identification of the most accurate and reliable devices, pinpoint gaps in current research, and identify new research directions and developments that need attention in the coming years. From a practical standpoint, coaches and sports scientists can confidently use wearable technology to analyze the kinematics of kicking. Such analyses can inform the design of tasks aimed at enhancing kicking performance while also providing valuable feedback to soccer athletes to improve this skill.

Conclusions

To our knowledge, this will be the first systematic review of scientific literature to attempt to collate knowledge derived from peer-reviewed articles that covered the measurement properties related to the use of wearable devices to capture ball-kicking features. A systematic review of scientific studies addressing this issue will potentially help, for example, to (1) highlight which instruments are effective in day-to-day testing or monitoring of kicking performance, (2) to understand the potential sources of variability (eg, specific environmental properties), and (3) to clarify the operator attitudes (eg, configurations) that could be adopted as a way of capturing adequately the event of interest – ball kicking – which itself is not a trivial task. Thus, it is possible to conclude that the protocol proposed here will benefit practitioners and football scientists, together with the final results from the systematic review with the best evidence synthesis.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study protocol. A brief literature overview is presented and all data reported are from previous published studies, which have been cited and included in the reference list.

Authors' Contributions

LHPV, FACM, and WMRO contributed to conceptualization. LHPV, FMC, and FPC contributed to the methodology. LHPV and KRVV performed the investigation. LHPV, FMC, and FPC contributed to the writing (original draft preparation). LHPV, FMC, FACM, WMRO, KRVV, and FPC contributed to writing (reviewing and editing). LHPV contributed to supervision, data curation, project administration, and funding acquisition.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist for the present systematic review protocol.
[DOC File , 99 KB - resprot_v13i1e57433_app1.doc]

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Abbreviations

COSMIN: COnsensus-based Standards for the selection of health Measurement Instruments
FIFA: Fédération Internationale de Football Association
GPS: global positioning system
LPS: local positioning system
PICO: Population, Intervention, Comparison, Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies
RoB: Risk of Bias
RoBANS: Risk of Bias Assessment Tool for Nonrandomized Studies

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Protocol

Clinical and Biochemical Outcomes in Transgender Individuals Undergoing Hormone Therapy: Protocol for a Systematic Review

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Abstract

Background: Monitoring of various clinical outcomes and parameters, such as lipid levels, is recommended in transgender individuals undergoing hormone therapies. However, comprehensive data to inform these recommendations is scarce.

Objective: This study aims to conduct a systematic review and meta-analysis to synthesize evidence from existing literature on the effect of exogenous hormone therapy on clinical and biochemical outcomes for transgender adolescents and adults.

Methods: We will search multiple electronic databases and will include prospective and retrospective observational studies with and without a control group. The study population will include transgender individuals undergoing hormone therapy with testosterone or estrogen. Comparisons will include age-matched, cisgender individuals and changes from baseline. Primary outcomes include changes in or the development of abnormal lipid parameters. Secondary outcomes include BMI, weight, height, and blood pressure for age, serum testosterone or estrogen levels, and development of disease including hypertension, diabetes, fatty liver disease, obesity, adverse cardiac events, as well as all-cause mortality. The meta-analysis will pool the studies where applicable, and meta-regressions will be conducted to evaluate effect modifiers. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach will be used to evaluate the overall certainty of evidence.

Results: We will summarize the selection of the eligible studies using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. The results will be presented in a table summarizing the evidence. Data collection is ongoing, and the paper is expected to be published in Spring 2025.

Conclusions: This systematic review will summarize and evaluate the evidence of the clinical and biochemical outcomes associated with hormone therapies for transgender individuals.

Trial Registration: PROSPERO CRD42024483138; https://tinyurl.com/yc4sfvnb

International Registered Report Identifier (IRRID): PRR1-10.2196/57931

(JMIR Res Protoc 2024;13:e57931) doi:10.2196/57931

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KEYWORDS

transgender; lipid levels; hormone therapy; biochemical outcomes; clinical outcomes; comprehensive data; systematic review; meta-analysis; adolescent; adults; electronic databases; testosterone; estrogen

Introduction

An estimated 1.6 million adolescents and adults identify as transgender in the United States [1]. For those seeking hormone therapy as part of their gender-affirming care, the World Professional Association for Transgender Health (WPATH) recommends initiation and continuation of gender-affirming hormone therapy in eligible transgender and gender-diverse individuals who require treatment based on demonstrated improvement in quality of life and psychosocial functioning [2]. The Endocrine Society guidelines recommend a testosterone therapy regimen consisting of intramuscular or subcutaneous testosterone at an initial dose of 25 mg/m^2 every 2 weeks with a gradual increase in the dose every 6 months until an adult dose of 100-200 mg every 2 weeks is achieved [3]. For transfeminine adolescents, the recommendation is an initial dose of 5 µg/kg per day of oral 17B-estradiol gradually increased every 6 months until an adult dose of 2-6 mg per day is achieved or an initial dose of 6.25-12.5 µg transdermally until an adult dose of 50-200 µg/24 hours is achieved [3].

Abnormal lipid levels have been associated with an increased risk of atherosclerosis and cardiovascular disease throughout life [4]. The pathophysiology of testosterone's and estradiol's effect on lipid metabolism is complex and has remained largely unknown [5,6]. However, recent studies have examined the relationship between sex hormones and lipid metabolism in an attempt to establish causation. A review published by Zhang et al [7] in 2022 postulates that in human adipocyte cells, estrogen increases the expression of certain enzymes that inhibit lipogenesis. A different study from 2022 showed a similar relationship between testosterone and lipid metabolism, stating that low testosterone leads to major changes across various metabolic functions [8]. Despite these findings, the extent of the association between testosterone and estrogen on lipid metabolism remains largely unknown. Figure 1 shows a conceptual framework for the association between these hormones and lipid metabolism. Currently, treatment guidelines recommend monitoring lipid levels in those taking gender-affirming testosterone therapy. However, the recommended frequency of such monitoring is unclear [2,3]. Monitoring of lipid levels is not currently recommended for those taking gender-affirming estrogen therapy, despite inconsistencies in existing literature [9]. The Endocrine Society reports a wide variety of possible adverse effects when undergoing testosterone therapy, including coronary artery disease and hypertension [3]. Individuals undergoing estrogen therapy face similar potential adverse outcomes, including the development of thromboembolic disease, coronary artery disease, and hypertriglyceridemia [3].

Figure 1. A conceptual framework for the association between estrogen and testosterone use and lipid metabolism.

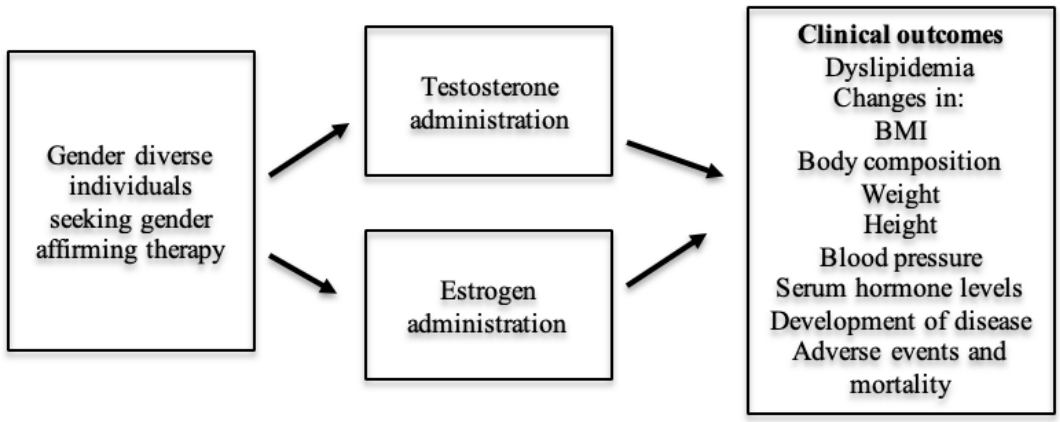

There has been a recent increase in research investigating the effects of gender-affirming testosterone therapy on lipid levels in transgender and gender-diverse adolescents and adults. A recent systematic review and meta-analysis published by Tienforti et al [10] reviewed 39 existing studies. It concluded that testosterone-based gender-affirming hormone therapy in individuals assigned female at birth was statistically associated with changes in body composition, body fat distribution, and the cardiovascular lipid profile. This study described the results comprehensively; however, it did not use any method that can incorporate the risk of bias into the conclusion, such as methods described by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group. Furthermore, this systematic review excluded studies that compare the clinical and biochemical outcomes for age-matched, cisgender females. Our study seeks to describe the totality of evidence using the GRADE methods and includes studies that make use of an age-matched, cisgender female population. In addition, we plan to include studies that discuss clinical outcomes in transfeminine adolescents undergoing estrogen hormone therapy matched with similarly aged cisgender males. We also plan to do additional analyses, such as evaluating associations of age with clinical and biochemical outcomes, with separate analyses for adolescent and adult populations. Separate analyses for these populations are necessary, given the differences in reference lipid values seen in adult versus adolescent populations [3,11].

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Methods

Objective

To assess the effects of testosterone and estrogen therapies on select clinical and biochemical outcomes of transgender and gender-diverse adolescents and adults.

Inclusion Criteria

Study Type

We will include prospective and retrospective observational cohort studies with and without a control group. We will exclude case-control studies, reviews, case reports, cross-sectional studies, and qualitative studies.

Population

Our population will include transmasculine and transfeminine individuals taking gender-affirming testosterone or estrogen therapy. We will include all individuals irrespective of age.

Intervention and Exposure

Our primary exposure is exogenous testosterone or estrogen hormone therapy, which will be categorized as yes or no (any exposure to hormone therapy for at least one year). We will record the duration of exposure, and studies that include a duration of therapy of less than 6 months will be excluded. We will include studies of multiple methods of exogenous hormone administration, including subcutaneous, transdermal, and intramuscular routes for testosterone, as well as oral, transdermal, and intramuscular routes for estrogen. Subcutaneous injections are administered under the skin, often in the abdomen or thigh, typically with a 5/8-inch needle [12]. Intramuscular injections are administered into the muscle, frequently the thigh muscle, with a larger needle (often 1 inch) [12]. Transdermal routes include patches that may be applied to the back, abdomen, stomach, thighs, or arms [13]. Transdermal routes of administration may also incorporate solutions or gels [13]. We will exclude studies where testosterone or estrogen were administered for reasons aside from gender-affirming care.

Comparison

We will include studies that include age-matched cisgender populations as comparisons, but studies that follow individual changes from baseline data will be included as well. Any study that allows for the determination of an association between the exposure and a relevant outcome will be considered for inclusion, regardless of the presence of absence of a control group (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Study type: prospective and retrospective observational studies.
- Population: transmasculine and transfeminine individuals of all ages.
- Intervention (exposure): testosterone or estrogen therapy administered transdermally, intramuscularly, subcutaneously, or orally for >6 months.
- Comparison: age-matched cisgender populations or changes from baseline.

Exclusion criteria:

- Study type: case-control, reviews, case reports, cross-sectional, and qualitative studies.
- Intervention (exposure): therapy administered for reasons aside from gender-affirming therapy or for a mean duration of <6 months.

Outcomes

The primary outcome of interest will be changes in lipid levels. Secondary outcomes of interest include a variety of clinical and biochemical variables. Values will be measured at baseline, 1 year, and longest follow-up. Studies will be included if they report data for any of the primary or secondary outcomes. Studies need not report every potential outcome to be included in the analysis. The following values will be included for consideration (Textbox 2).

Lipid levels will be compared with reference ranges for healthy adolescents and adults (more details in Tables 1 and 2). Reference ranges were adapted from the NIH and Cleveland Clinic's guidelines for cardiovascular health [3,11]. Lipid levels will be measured at baseline, one year, and longest follow-up. Any values outside of the acceptable ranges shown in Tables 1 and 2 will be considered abnormal. We will assess mean differences and mean changes from baseline levels and include relative and absolute risk measures when relevant.

Each lipid parameter will be evaluated as a dichotomous outcome (abnormal, yes or no), and the mean difference and mean changes from baseline will be continuously assessed. Any values outside of the acceptable normal ranges given in the above tables will be considered an abnormal outcome.

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Textbox 2. The primary and secondary outcomes.

Continuous outcome:

- Total cholesterol (TC), a measure of the cumulative amount of cholesterol in the blood [14].
- Low-density lipoprotein (LDL), often referred to as "bad" cholesterol, or the main source of buildup in the arteries [14].
- High-density lipoprotein (HDL), referred to as "good" cholesterol. HDL helps in the removal of other forms of cholesterol from the bloodstream [14].
- Non-HDL cholesterol (non-HDL), a measure of the total cholesterol minus the HDLs [14].
- Triglycerides (TGs), the most common type of fat found in the body [14].
- BMI for age (kg/m^2 or *z* scores).
- Body composition (visceral fat, body fat, bone density, and muscle mass).
- Weight for age (kg or *z* scores).
- Height for age (cm or *z* scores).
- Blood pressure for age (mmHg).
- Serum testosterone levels (ng/dL or nmol/L).
- Serum estrogen levels (pg/mL).

Dichotomous outcome:

- Development of hypertension.
- Development of type-2 diabetes.
- Development of fatty liver disease.
- Development of obesity (Defined by age and sex-specific BMI in the 95th percentile or greater for adolescents [15], or a BMI of 30 or higher for adults older than 20 years) [16].
- Presence or absence of any adverse cardiac advents.
- All-cause mortality.

Table 1. Acceptable lipid parameter ranges in cisgender adolescents aged 10-19 years [3].

Category	Acceptable range (mg/dL)
TC[a]	<170
LDL[b]	<110
Non-HDL[c]	<120
HDL[d]	>45
TG[e]	<90

[a]TC: total cholesterol.

[b]LDL: low-density lipoprotein.

[c]Non-HDL: non–high-density lipoprotein.

[d]HDL: high-density lipoprotein.

[e]TG: triglycerides.

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Table 2. Acceptable lipid parameter ranges in cisgender adults [11].

Category	Acceptable range (mg/dL)
TC[a]	125-200
LDL[b]	<100
Non-HDL[c]	<130
HDL[d]	>40 (Males) >50 (females)
TG[e]	<150

[a]TC: total cholesterol.

[b]LDL: low-density lipoprotein.

[c]Non-HDL: non–high-density lipoprotein.

[d]HDL: high-density lipoprotein.

[e]TG: triglycerides.

Literature Search

Systematic searches will be conducted electronically on several databases, including PubMed, Scopus, Embase, Web of Science, the Cochrane Central Register for Controlled Trials, the World Health Organization Global Index Medicus, and CINHAL. We will also examine the references of formerly published reviews for possible inclusion. The citation tracking function of included studies through PubMed will be reviewed for eligible studies. ClinicalTrials.gov will be used to identify any studies that are currently ongoing. No restrictions will be applied to initial searches based on study design, publication date or status, language, or outcomes. We will include studies published to date. A full search strategy, including search terms, can be found in Multimedia Appendix 1.

Data Extraction and Synthesis

Selection of Studies

A 3-stage process will be used to screen studies for inclusion. To begin, 2 individuals will screen study titles and abstracts yielded from the systematic searches independently. Any studies selected during this stage will advance to a full-text review, which constitutes the second stage. Finally, eligible studies will undergo data extraction during the final stage. A coding software, Covidence (Veritas Health Innovation), will be used to assist with screening and data extraction [17]. Any conflicts that arise during the study selection process will be resolved with discussion. For any studies that are only available in abstract form, we will write to the authors or use the interlibrary loan system to obtain the full text. If any included studies are available in a language other than English, we will use local resources for translation. Multiple publications of the same study will be counted as one, and data will be extracted from all available sources as needed.

Data Extraction

A data extraction sheet will be designed and used to collect information on selected studies. Similar to screening methods, 2 individuals will use the data extraction sheet independently, followed by a comparison of their findings. Any conflicts or questions will be resolved by discussion, and a senior author will be involved if necessary. For each study, the following data will be extracted: type of study, study site and year, study population characteristics including mean age, exposure (exogenous sex hormone therapy, including route of administration, dose, duration, and frequency), comparisons, primary and secondary outcomes, confounding factors, and risk of bias. Confounding factors that will be considered include sex assigned at birth, ethnicity, age, and familial history, as these variables may all play a role in lipid metabolism [11,18]. If both adjusted and unadjusted values are available, we will use the adjusted values for analysis.

Assessment of Risk of Bias in Included Studies

The Cochrane risk of bias in non-randomized studies (ROBINS-1) tool will be used to assess the risk of bias in included studies [19]. A total of 2 authors will assess the risk of bias independently before coming to a consensus. Any disagreements will be resolved by discussion, with a senior author consulting if no agreement can be reached. In addition, 5 domains of signaling questions will be addressed, including bias in the selection of participants, bias due to confounding, bias due to missing data, bias in selecting the reported result, and bias due to measurement of outcomes. Each domain will be judged individually and will be awarded a label of low, moderate, or critical risk of bias. The overall risk of bias will be determined from the highest risk label across the domains.

Data Synthesis

Findings from this systematic review will be reported qualitatively and quantitatively. Qualitatively, we will use a narrative synthesis to report our results and the characteristics of the included studies. Quantitively, meta-analyses will be conducted to synthesize data across studies so long as clinical and methodological homogeneity exists. Relative risk effect sizes, along with their 95% CIs, will be used to measure dichotomous outcomes. Mean difference effect sizes and their corresponding 95% CIs will be used to measure change from baseline for continuous outcomes. The mean difference will be calculated using the absolute difference between the mean values between the 2 groups in the study. If the study contains a cisgender comparison group, mean differences will be calculated between the intervention and control groups. If the study does not contain a cisgender comparison group, the mean difference will be calculated using the pre- and post-values from the

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intervention group. Data from these 2 study types will be analyzed separately throughout the analysis, including in measures of relative and absolute risk. Random effect models will be used to pool data using the generic inverse variance method of meta-analysis. Data from studies that measured change over time will be pooled along with data matched to cisgender controls. Studies that make use of multiple intervention groups will be combined and analyzed as a single study. In addition, a meta-regression will be conducted to isolate effect modifiers and evaluate differential effects based on factors such as mean age of study (continuous outcome), duration of exposure in days, and route of administration. To attain these statistics, we will make use of RevMan (Cochrane) [20] and STATA software (StataCorp LLC) [21].

Dealing With Missing Data

Attrition will be documented during the data extraction process. We will contact the trial authors to request full datasets if data is missing for some cases. If the SDs are not reported for continuous outcomes, we will request this data from the study authors. In the event of a nonresponse or unavailability, we will attempt to use an SD value from a similar study with a similar population. In the event that final values are not available but values are given for the difference between the study start and end, we will use the difference to calculate the final values.

Assessment of Heterogeneity

Heterogeneity, or any variability among studies, can be assessed with measures of clinical, methodological, or statistical heterogeneity. We will analyze the statistical heterogeneity of effect sizes in the total data by using statistics such as Tau^2, chi-square, and I^2. We will also visually inspect forest plots and assess *P* values. Significant statistical heterogeneity will be achieved at $P<.10$ and an I^2 value exceeding 50%. We would also expect our forest plots to show substantial variability in the effect of the intervention. In addition, subgroup analysis will be conducted to determine the reasoning behind any identified statistical heterogeneity. These subgroups may assess differences in study populations, exposure routes, and outcomes.

Assessment of Reporting Bias

Biases resulting from small study size or publication bias will be evaluated using funnel plots. Given an asymmetrical funnel plot, weighted linear regression (Egger) tests will be used to determine the presence of bias when at least 10 studies are included in the meta-analysis.

Subgroup Analysis

Subgroup analysis will be done by age group (adolescents <19 years of age vs adults ≥19 years of age), route of exposure, and duration of exposure (>2 years vs <2 years).

Sensitivity Analysis

We will remove studies with a high risk of bias in order to complete sensitivity analysis. Results will be compared between random effects and fixed-effect models.

Rating of Overall Quality of Evidence

The GRADE approach will be used to evaluate the overall quality of evidence [22]. The GRADE approach uses characteristics such as study design, risk of bias, heterogeneity of effect, directness of evidence, publication bias, and precision of effect estimates to assess the overall quality of evidence for an outcome [22]. The GRADEpro software (GRADE Working Group) [23] will be used to rate the overall quality of evidence as very low, low, moderate, or high. The GRADE assessment results will be presented in a summary of findings table that will include quality ratings for the primary and secondary outcomes of total cholesterol, LDL, HDL, obesity, hypertension, and quality of life scores.

Results

The results of this review intend to provide insights into various clinical and biochemical outcomes that result from the use of hormone therapies in transgender individuals. The results will undergo peer review and be submitted for publication. Data collection is ongoing and the review is expected to be published in spring 2025.

Discussion

The protocol for this systematic review describes a comprehensive approach to a review of the literature in order to draw meaningful conclusions. It is our hope that this review will serve to inform future clinical guidelines and practices for this marginalized group. The strengths of this review include the use of 2 authors for screening for all papers, the inclusion of literature from multiple electronic databases, and the inclusion of a wide variety of outcomes. In addition, GRADE criteria will enable us to assess the overall strength and quality of evidence. It is possible that all included studies will not report data for all the outcomes of this review, which is a limitation of this study.

Even though we defined the methods of data extraction and analysis for this systematic review a priori, data may not be available for all outcomes in all included studies, which would be a limitation of this systematic review. An ideal comparison to assess the effect of hormone therapy in transgender individuals includes a cisgender without the hormone supplements. However, studies may not include a cisgender comparison group, and in that case, we will consider the analysis for pre- and post-hormone supplementation in transgender individuals. We, however, plan to analyze the data separately for cisgender comparison and pre-post intervention data in the same individual.

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annotated literature review, as well as Paul Casella for his help in editing the manuscript. No generative artificial intelligence was used in any portion of the manuscript writing.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ES, KT, CP, and AI contributed to conceptualization. ES, KT, CP, AS, JE, and AI contributed to the methodology. ES contributed to writing–original draft preparation. ES, KT, CP, and AI contributed to writing-review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 52 KB - resprot_v13i1e57931_app1.pdf]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-1: risk of bias in non-randomized studies
WPATH: World Professional Association for Transgender Health

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Protocol

Influence of Psychological Stress on the Response to Periodontal Treatment: Protocol for a Systematic Review

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Abstract

Background: The interaction between stress and periodontal treatment is a topic of growing interest. It stands out as a field of research that sheds light on the complexity of oral health in individuals subjected to high levels of emotional stress.

Objective: This paper aims to provide a protocol for a systematic review to examine the scientific evidence related to the influence of psychological stress on the response to periodontal treatment.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be followed, and the study is based on a formulation of PECO (Participants, Exposure, Comparators, and Outcomes) questions. This systematic review will involve a literature search covering studies published from January 2000 to May 2024. It will include searching the PubMed, Web of Science, EBSCOHost, Scopus, and ProQuest databases to identify relevant studies. After selection, data extraction and quality assessment (using the Ottawa-Newcastle Scale) of the included studies will be carried out. The objective is to integrate high-quality evidence on how psychological stress impacts the outcomes of periodontal treatment. Depending on the number and methodological consistency of included studies, the results may be presented by meta-analysis or qualitative synthesis.

Results: The current stage of the study consists of selecting studies for the systematic review as outlined by this protocol. The search, screening, and data extraction began in January 2024. The final results are expected by July 2024, with final manuscript submission planned for November 2024.

Conclusions: This review will help clarify how psychological factors, such as stress, influence the results of periodontal treatment, providing valuable guidelines for future research and helping clinicians make decisions about the best treatment options for patients.

Trial Registration: Open Science Framework (OSF) Registries qfs6p; https://osf.io/qfs6p

International Registered Report Identifier (IRRID): PRR1-10.2196/56765

(JMIR Res Protoc 2024;13:e56765) doi:10.2196/56765

KEYWORDS

periodontal disease; periodontal therapy; integral health; oral health; evidence-based; periodontitis; inflammatory diseases; inflammatory response; anxiety; stress; depression; periodontal health

Introduction

Psychological stress represents an emotional and physiological response of the body to adverse stimuli, which occurs when a person perceives a situation or event as threatening to his or her coping resources [1]. It can be derived from various sources in everyday life, such as work problems, personal relationships, and adverse economic situations, and these stressors influence

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well-being, behavior, and general health [2]. In its acute manifestation, its effect originates in the immune system [2,3], while in its chronic form, it can lead to prolonged inflammatory processes that negatively impact both the immune and endocrine systems [4]. These effects contribute to the development of diseases such as diabetes mellitus, cardiovascular diseases, cold sores, lichen planus, and periodontitis [4-6].

Periodontitis is a chronic inflammatory disease that affects the supporting tissues of the teeth. In its development and progression, dysbiosis (imbalance in the microbiota) and the host's immune-inflammatory response play fundamental roles [7]. Research has indicated a positive relationship between psychological stress and periodontal diseases [2,8-10]. Stress can trigger changes in the immune system [2], characterized by an increase in the inflammatory response and a decrease in the body's immune defenses [3]. The presumed biological mechanisms affect the activity of stress axes, namely, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to a subsequent dysregulation of the immune system [6]. In addition, it has been observed that stress can lead to a reduction in saliva flow and its acidification, which, in turn, may increase the prevalence of periodontal diseases [8,9].

Simultaneously, research has also demonstrated that stress has an adverse effect on periodontal treatment [2,11,12] and delays healing [13], indicating that stressed individuals do not show a reduction in periodontal clinical parameters [11]. Studies also suggest that stress triggers the production of substances such as cortisol, dehydroepiandrosterone [14], and catecholamines [3,4], which can modulate bacterial growth in periodontal disease and the expression of virulence factors [4]. In addition, factors like stress and anxiety can induce behavioral changes, such as poor oral hygiene, low-quality sleep, increased smoking [2,3], as well as an inadequate diet [9] that includes foods rich in carbohydrates, sugar, and acids, further exacerbating periodontitis [9]. In this context, it seems crucial to consider and address psychological factors as an integral part of periodontal therapy [15].

Currently, there are systematic reviews on the impact of psychological factors, such as stress and anxiety, on periodontal health [16,17], as well as on stress and depression as risk factors for periodontal diseases [8,18]. However, systematic reviews addressing how psychological stress specifically affects the outcomes of periodontal treatment have not yet been conducted. Therefore, it is imperative to delve into this aspect and understand how this factor may influence periodontal treatment; that is, the impact of psychological factors such as stress on periodontal treatment constitutes a highly relevant and complex aspect that demands a comprehensive approach to understanding how stress affects the immune response and patient behavior, which may influence the severity of periodontitis [5] and in the recovery capacity of periodontal tissue [13,14].

The objective of this paper is to provide a protocol for a systematic review intended to evaluate the influence of stress on the clinical outcome of periodontal treatment. The addressed PECO (Participants, Exposure, Comparators, and Outcomes) question will focus on "What is the influence of psychological stress on the response to periodontal treatment?"

Methods

Registration

This protocol was preregistered in the Open Science Framework (OSF) Registries (ID: qfs6p) [19]. This protocol, as presented in its entirety below, follows the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols) checklist (Multimedia Appendix 1) [20]. It is also intended that this systematic review will contain the items of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, 2020 version [21].

Electronic Databases and Search Strategy

The search will include all articles indexed in the PubMed, Web of Science Core Collection (Clarivate), EBSCOHost, Scopus, and ProQuest databases published in the English language from January 2000 to May 2024. In addition, we will also consider an additional exploration of the reference lists and bibliographies of all potential full-text articles. EndNote software (version X7.0.1; Clarivate) will be used to facilitate reference management.

In Table 1, the search terms are presented exactly as they will be used in each specific database. A Boolean search strategy was elaborated, considering also those key terms previously used in existing systematic reviews [8,16]. For the PubMed database, Medical Subject Headings terms were used to ensure a more comprehensive and precise search.

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Table 1. The search strategy used exactly as entered into each specific database considered in this review. The PubMed strategy included MeSH (Medical Subject Headings) terms.

Database	Search strategy
PubMed	(((((((periodont*[Text Word]) OR periodontal therapy[MeSH Terms]) OR non-surgical periodontal therapy[MeSH Terms]) OR scaling[Text Word]) OR periodontal debridement[Text Word]) OR mechanical debridement[Text Word]) OR plaque removal[Text Word]) AND (((((stress[Text Word]) OR psychological stress[MeSH Terms]) OR emotional stress[Text Word]) OR chronic stress[Text Word]) OR job-related stress[Text Word]) AND (((control*[Text Word]) OR baseline[Text Word]) OR *stressed group*[Text Word]) AND (((probing depth[Text Word]) OR clinical attachment level[Text Word]) OR bleeding of probing[Text Word])
Web of Science	Periodont* OR Periodontal therapy OR Non-surgical periodontal therapy OR Scaling OR Periodontal debridement OR Mechanical debridement OR Plaque removal (Topic) AND Stress OR Psychological stress OR Emotional stress OR Chronic stress OR Job-related stress (Topic) AND Control* OR Baseline OR *Stressed group* AND Probing depth OR Clinical attachment level OR Bleeding of probing (Topic)
EBSCOHost	(Periodont* OR Periodontal therapy OR Non-surgical periodontal therapy OR Scaling OR Periodontal debridement OR Mechanical debridement OR Plaque removal) AND (Stress OR Psychological stress OR Emotional stress OR Chronic stress OR Job-related stress) AND (Control* OR Baseline OR *Stressed group*) AND (Probing depth OR Clinical Attachment level OR Bleeding of probing)
Scopus	(TITLE-ABS-KEY (“periodont*” OR ”periodontal therapy“ OR ”non-surgical periodontal therapy“ OR scaling OR ”periodontal debridement“ OR ”mechanical debridement“ OR ”plaque removal“) AND TITLE-ABS-KEY (stress OR ”psychological stress“ OR ”emotional stress“ OR ”chronic stress“ OR ”job-related stress“) AND TITLE-ABS-KEY (control* OR baseline OR ”*stressed group*“) AND TITLE-ABS-KEY (”probing depth“ OR ”clinical attachment level“ OR ”bleeding of probing“))
ProQuest	noft(Periodont* OR Periodontal therapy OR Non-surgical periodontal therapy OR Scaling OR Periodontal debridement OR Mechanical debridement OR Plaque removal) AND noft(Stress OR Psychological stress OR Emotional stress OR Chronic stress OR Job-related stress) AND noft(Control* OR Baseline OR Stressed group*) AND noft(Probing depth OR Clinical Attachment level OR Bleeding of probing)

Inclusion and Exclusion Criteria

Type of Studies to be Included

Cohort or cross-sectional studies, case-control studies, and studies published in English are considered eligible. A targeted research query designed to enhance the literature search was formulated, outlining the assigned PECO measures as shown in Textbox 1.

Textbox 1. PECO (Participants, Exposure, Comparators, and Outcomes) measures.

- Participants (P): Adult patients diagnosed with periodontitis and undergoing periodontal treatment (prophylaxis and scaling and root planing [ultrasonic devices, curettes, and polishing]).
- Exposure (E): Psychological stress (assessed by psychometric instruments, validated questionnaires to measure stress levels, or studies that used biomarkers to assess stress [eg, salivary cortisol]).
- Comparators (C): Patients with periodontitis without psychological stress (assessed by psychometric instruments, validated questionnaires to measure stress levels, or studies that used biomarkers to assess stress [eg, salivary cortisol]).
- Outcomes (O): Clinical outcome of periodontal treatment.
  - Primary outcomes:
- Changes in probing pocket depth (PPD) and clinical attachment level (CAL) were measured in millimeters.
- Changes in bleeding on probing (BOP) are measured in percentage.
  - Secondary outcomes
- Changes in plaque index (PI) are measured in percentage.

Variables that will be considered for extraction include, for example, probing pocket depth, clinical attachment level, bleeding on probing, and plaque index. Null-hypothesis significance tests may include independent-samples *t* test, Mann-Whitney *U* test, Kruskal-Wallis test, analysis of covariance (ANOVA) with post hoc, linear regression models, logistic regression models, and multivariable ANCOVA. For this review synthesis, the threshold for the significance will be preset at $P \leq .05$.

Type of Studies to be Excluded

The following types of studies will be excluded: observational studies (without mechanical debridement or professional plaque removal); studies where patients received other adjuvant therapies (eg, laser, probiotics, or antibiotic use) or any type of

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periodontal treatment in the last 6 months; studies on patients with systemic or autoimmune disorders, which influence treatment outcomes such as diabetes; studies on patients who are pregnant or breastfeeding; studies on patients using immunosuppressive drugs or drugs that affect the oral microbiome (eg, antineoplastic or antiepileptic drugs); studies that did not go through ethics committee; letters, case reports, and short communications; and studies in animal models and in vitro studies.

Selection of Studies

The selection process will be in accordance with PRISMA guidelines. Data collection will be carried out using a specific spreadsheet, with parameters selected after a pilot study involving approximately 10 included studies. In addition, 2 reviewers, identified as participating researchers, will conduct the assessment independently. In case of disagreement, a third researcher with expertise in the field will resolve discrepancies.

If there is unclear or omitted information from the selected studies, such as missing data or incomplete text, the authors will be contacted by email, and weekly attempts will be made for a maximum of 5 weeks. If there is no response from the authors, the study will be excluded.

Studies meeting the inclusion criteria will undergo validation and data extraction.

Data Extraction and Evidence Synthesis

The relevant data extracted from each study will describe the designated PECO measures: author's name and date of publication; country; study design; participant characteristics; periodontal treatment; definition of psychological stress; stress diagnosis (stress scale or biomarkers used); clinical parameters (probing depth, clinical attachment level, bleeding on probing, and plaque index); monitoring and outcome measures of interest to the review (regular clinical monitoring to monitor the effectiveness of treatment); authors' conclusions; and source of funding.

Subsequently, the "best evidence synthesis method" will be applied to classify the level of evidence [22]. It will be considered strong (consistent findings observed among multiple high-quality studies), moderate (consistent findings observed among multiple moderate-quality studies and/or 1 high-quality study), limited (findings provided by 1 moderate-quality study and/or only low-quality studies), conflicting (when inconsistent findings were observed), or "no evidence"(when there were no available studies) [22]. Consistency will be defined as ≥75% of studies report results in the same direction, and inconsistency will be defined as <75% of studies report results in the same direction.

Methodological Quality and Risk of Bias Assessments

A total of 2 authors (KRVV and KOS) will independently evaluate the methodological quality of each included study using the Newcastle-Ottawa Scale [23]. This scale is specifically designed for nonrandomized studies. The authors will use a "star" system for each study, considering 3 main components: (1) quality of study participant selection, (2) comparability, and (3) exposure and outcome. The maximum score is 9 points for case-control studies and 10 points for cross-sectional studies. The total score will categorize the studies into three groups: (1) high quality (total score: 7 to 9 or 10), (2) moderate quality (total score: 4 to 6), and (3) low quality (total score: 0 to 3). To determine consistency, the interrater agreement will be calculated using the Cohen κ coefficient.

Furthermore, the risk of bias in the outcomes or interpretations will be independently determined for each included study. This will be done using the Risk of Bias Assessment Tool for Non-Randomized Studies [24]. Each element will be evaluated as presenting low, high, or unclear risk concerning participant selection criteria, potential confounding variables, accuracy of exposure measurement, blinding of outcome assessments, handling of incomplete outcome data, and selective outcome reporting.

Data Synthesis

If there are a sufficient number of studies and no substantial variations in the methods used among them, the results may also be presented through a meta-analysis (quantitative synthesis). Regardless of whether the final manuscript meets the criteria for a quantitative synthesis, a qualitative synthesis will be conducted using the best evidence synthesis method. In addition, a table with the main characteristics of the studies will be included.

We will also consider the statistical analyses used in the selected studies, including different types of regression models to adjust for confounding variables. This may include multiple linear regression for continuous dependent variables, multiple logistic regression for binary stages, and multivariable ANCOVA. In addition, we will also include other statistical analyses, such as clarification analysis, as applicable.

Results

The search, screening, and data extraction began in January 2024, following the established protocol. From the initial search to find previous reviews on the influence of psychological stress on periodontal treatment, no reviews were identified that had this objective, although we did find reviews on the association of psychological stress on periodontitis and about stress as a risk factor for periodontitis (Tables 2 and 3).

The results are expected to be completed by July 2024, and the final manuscript of the systematic review is anticipated to be submitted in November 2024.

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Table 2. Some review studies that potentially address the influence of stress on periodontal treatment.

Reference	Type of review	Guidelines	Date of searches	Databases considered
Peruzzo et al [18]	Systematic	__[a]	January 1, 1990, to April 1, 2006	MEDLINE and the Cochrane Oral Health Register
Botelho et al [25]	Systematic and meta-analysis	PRISMA[b]	Up to September 2017	Electronic general, open access, regional, and gray literature databases
Decker et al [8]	Systematic	PECOS[c] framework	Up to December 2017	MEDLINE (OVID), Embase (OVID), and CENTRAL (Cochrane Library); gray literature at the New York Academy of Medicine Grey Literature Report
Castro et al [16]	Systematic	PRISMA	Until March 2018	PubMed, Scopus, Web of Science, Lilacs, and Cochrane Library; Google Scholar and OpenGrey were used as gray literature sources
Badia et al [26]	Systematic and meta-analysis	PRISMA	Until June 2021	MEDLINE, Embase, and the Cochrane Library
Aggarwal et al [17]	Systematic and meta-analysis	—	Until December 2019	PubMed, Embase, and Scopus

[a]Not available.

[b]PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

[c]PECOS: Participants, Exposure, Comparators, Outcomes, and Study Design.

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Table 3. Results of the initial search for review studies that potentially address the influence of stress on periodontal treatment.

Reference	Year	Aim	Results
Peruzzo et al [18]	2007	Review the evidence on the influence of stress and psychological factors on periodontal disease	In total, 8 (57.1%) studies found a positive outcome between psychosocial factors of stress and periodontal disease, 4 (28.5%) studies observed a positive outcome for some characteristics and a negative outcome for others, and 2 (14.2%) studies found a negative outcome between psychosocial factors of stress and periodontal disease.
Botelho et al [25]	2018	To systematically assess whether periodontitis has a meaningful effect on salivary cortisol, reflecting changes in free blood cortisol levels	A network meta-analysis was performed comparing salivary cortisol response between chronic and aggressive periodontitis patients. Although the indirect estimates were not statistically significant, the results were consistent with the Bucher test (P=.99) and favored aggressive periodontitis regarding salivary cortisol response. Overall, the salivary cortisol response in patients with aggressive periodontitis is, on average, 42% higher than in patients with chronic periodontitis (mean ratio 1.42 95% CI 0.97-2.06; P=.99).
Decker et al [8]	2020	To evaluate the impact of stress-related disorders on the progression of periodontal disease and evaluate the growing body of evidence of stress as a risk indicator for periodontal disease progression	Relationships between stress-related disorders and serum and salivary biomarkers such as cortisol, dehydroepiandrosterone, chromogranin A, and proinflammatory cytokines were identified.
Castro et al [16]	2020	To explore the relationship between psychological stress and periodontitis by analyzing cortisol levels and periodontal clinical parameters	3 articles were selected by full text. Among them, 2 articles reported a positive association between psychological stress and periodontitis. All articles were classified as low risk of bias. Even though 2 articles highlighted an association between psychological stress and the presence of a possible modulatory pattern of cortisol levels in clinical parameters of periodontitis, more studies are necessary to elucidate this question.
Badia et al [26]	2022	To evaluate the literature on the impact of psychological stress on periodontitis and its progression and to evaluate current evidence of psychological stress as a risk factor for periodontal disease using psychological questionnaires	The results of the meta-analysis did not show statistically significant differences between the 2 groups. There is a relationship between psychological stress and the severity of periodontitis. This relationship must be considered a possible risk factor.
Aggarwal et al [17]	2022	To assess the association between psychologic stress, anxiety, and periodontitis	A total of 25 studies were selected for systematic review, and only 14 studies could be used for meta-analysis in 3 subsets. The pooled odds ratio for stress and periodontitis was 1.78, which was statistically highly significant (I^2=98.6%, P=.00). Mean salivary cortisol levels as a measure of stress in patients with periodontitis was 4.81 nmol/L (I^2=98%, P=.08). State-Trait Anxiety Inventory score was –1.28 (I^2=0%, P=.06) for state anxiety and –0.11 (I^2=0%, P=.85) for trait anxiety in patients with periodontitis.

Discussion

Principal Findings

Studies have shown a correlation between psychological stress and various inflammatory diseases [27,28]. Research in the field of dentistry shows systematic reviews that explore the association between psychological stress and periodontitis [16,17,25] or psychological stress as a possible risk factor for periodontal diseases [8,18,26]. However, to date, no systematic review has focused on understanding how psychological stress specifically influences periodontal treatment outcomes.

There is evidence that psychological stress affects the body's inflammatory response [29,30], which together may increase susceptibility to periodontal disease [16,17,31,32] and hinder adherence to periodontal treatment, resulting in slower healing and less favorable clinical outcomes [32,33]. Therefore, it is hypothesized that the results of the selected studies confirm a significant influence of psychological stress on periodontal treatment. Patients with high levels of stress are likely to show worse periodontal treatment outcomes compared with those with lower levels of stress. A study [34] evaluated the effects of psychological stress on periodontitis healing in rats and the contribution of baseline fibroblast growth factor expression to the healing process; it observed that psychological stress could delay periodontitis healing, which may be mediated in part by down-regulation of baseline fibroblast growth factor expression in the periodontal ligament. Therefore, it is important to investigate whether patients with elevated levels of psychological stress may require personalized, lifestyle-changing interventions to optimize treatment outcomes.

A strength of this review is the rigorous methodology, which reinforces the validity of the results. In addition, this review will provide an updated, specific, and detailed view of how psychological stress directly affects periodontal treatment outcomes, highlighting the importance of considering psychosocial factors. However, there may be limitations to

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consider, such as variability in the measurement of psychological stress among the included studies, which may introduce bias.

For future research, it would be useful to explore the effectiveness of psychological interventions integrated into periodontal management to improve clinical outcomes. In addition, this review will identify other knowledge gaps, encouraging further studies to fill these gaps and thus improving the overall understanding of the topic, which will benefit clinical practice in the future.

To maximize the impact of these findings, several dissemination strategies are planned. These include publication in high-impact scientific journals and collaborations with dental professional societies to promote the integration of these findings into clinical practice. In addition, educational materials and workshops for oral health professionals will be developed, highlighting the importance of addressing psychological stress in periodontal treatment.

Conclusions

This review will provide current information on how psychological stress affects the outcome of periodontal treatment, the results of which can serve as a basis for creating broader health strategies aimed at addressing psychosocial factors in promoting oral health.

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Authors' Contributions

KRVV contributed to conceptualization. KRVV, LHPV, and KOS contributed to the methodology. KRVV, LHPV, and KOS performed the investigation. KRVV and LHPV contributed to writing—original draft preparation. KRVV, LHPV, and KOS contributed to writing—review and editing. KRVV contributed to supervision, data curation, project administration, and funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols) checklist.
[DOC File , 100 KB - resprot_v13i1e56765_app1.doc]

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Abbreviations

ANCOVA: analysis of covariance
OSF: Open Science Framework
PECO: Participants, Exposure, Comparators, and Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols

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Protocol

Mental Health Monitoring for Young People Through Mood Apps: Protocol for a Scoping Review and Systematic Search in App Stores

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Abstract

Background: The researchers have used mobile phones to assist in monitoring, analyzing, and managing moods to acquire insight into mood patterns. There is a lack of evidence in their use as clinical tools and interventions, which necessitates a comprehensive review and quality assessment to understand barriers and facilitators for app implementation as an impactful clinical intervention.

Objective: This review aims to (1) provide an overview of the recent evidence on mobile mood-monitoring apps that are intended for facilitating self-management and support of mental health in children, adolescents, and young people; and (2) investigate the quality of publicly available apps.

Methods: The study will first involve a scoping review of the literature on mood-monitoring apps for children, adolescents, and young people followed by an evaluation of features of the apps available in the marketplace. The scoping review will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and search 6 databases— Embase, CINAHL, PubMed, ACM Digital Library, Scopus, and Springer LNCS—for relevant studies and reviews published in the last 3 years. The author will then screen the references, extract data from the included studies, and analyze them to synthesize the evidence on mood apps. Next, the Apple App Store and Google Play Store will be searched for mood apps. A total of 2 independent reviewers will screen the apps based on eligibility criteria, and disagreements will be resolved through consensus. The features of the selected apps will then be evaluated using the Mobile Health Index and Navigation framework, and descriptive analysis will be used to synthesize the findings.

Results: Literature search and screening began soon after submission of the protocol and is expected to be completed by September 2024. The app evaluation will be completed by October 2024.

Conclusions: Combined, the scoping literature review and app evaluation will provide an in-depth overview of the most recent scientific evidence related to mood apps and the quality of apps actually available for use.

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KEYWORDS

digital health; mental health; mood apps; mobile apps; mobile phone

Introduction

Globally, there has been a surge in mental health concerns over the past decade. In 2019, there were over 970 million reported cases of depression and anxiety disorders worldwide [1]. This is particularly the case for children, adolescents, and young people, who are vulnerable to mental health difficulties as they grow [2]. Simultaneously, the use of smartphones, especially among children, adolescents, and young people, has become ubiquitous, where popularity and ownership have exponentially increased and their potential for health promotion has heralded a new era of digital health products [3,4]. There has been a movement toward technology that embraces the support for mental health through digital solutions [5]. Such digital health apps hold the potential to overcome barriers faced by individuals seeking mental health support. This approach brings health support within reach of diverse users, including those residing in geographically remote or underserved regions and individuals with limited financial resources [6,7]. Interest in these tools by children, adolescents, and young people, who seek assistance through mood-monitoring apps for mental health support, has significantly grown [7]. As children, adolescents, and young people typically exhibit a reluctance to seek professional help and often contend with the high prevalence of mental health issues [8], digital health apps can ease concerns related to the stigma associated with mental health challenges [9].

Mental health is a large area of product development within digital health [10]. Many mental health apps have entered the market with the aim of providing methods for addressing symptoms of mental health conditions, such as depression or anxiety and improving overall quality of life and well-being [11]. A subset of these apps includes mood-monitoring features, often in addition to self-management interventions, such as cognitive behavioral therapy or educational content. Some apps have also been developed with the sole purpose of monitoring mood through tools such as daily mood ratings and free-text journaling. This feature is becoming increasingly popular as it has the potential to help increase self-awareness, improve engagement, and facilitate better diagnosis of mood disorders [12-14].

The landscape of currently available apps is diverse, with an estimate of over 20,000 mental health apps available in app stores [15,16]. Only a small fraction of these apps have undergone empirical or clinical scrutiny, suggesting limited evidence of their effectiveness, with less than 5% of all mental health apps confirmed to have clinical evidence [17]. While published evidence is not required for medical device registration, it plays a significant role in the regulatory approval process and the adoption of medical devices in clinical practice [18]. The lack of a comprehensive understanding of validated mood apps may confuse both users and clinicians in selecting apps to meet their personal and professional needs [19].

Previous research has explored the perspectives of people using mood-tracking apps [13,14]. One study found an overall preference for features of personalization and visualization of previously tracked moods among users, while the lack of app-facilitated recommendations for how to interpret user data to improve mood was seen as a missing element [14]. An and Lee [20] used the Mobile App Rating Scale (MARS) to determine which features should be modified to improve the quality of apps [20]. The review demonstrated that most mood management apps received high scores for functionality and aesthetics, but low scores for subjective quality and specific app characteristics, underlining the need for additional refining of evidence-based principles. Rickard et al [3] used the American Psychiatric Association's 5-step criteria assessment tool to assess the quality and integrity of the most visible 100 apps for "depression," "anxiety," and "mood" on the Google Play Store and Apple App Store with a wider scope of general mental health apps and their function types, for example, mental health promotion, prevention, and intervention. The study reveals that out of 10 included and analyzed apps, only 3 met the criteria for clinical base and ease of use. App quality did not significantly vary across function types, with no correlation between app quality and app visibility. The results highlight the risks of insufficient synopsis of "high quality" mood apps for vulnerable users.

To mitigate risks of misinformed decision-making, missed self-help, or the risk of worsening the user's emotional well-being, various app assessment hubs like the Mobile Health Index and Navigation Database (MIND), Open mHealth, Beacon, or Mindtools.io were established [21,22]. MIND is a publicly available and cost-free repository comprising more than 650 mental health apps that have been assessed using 105 different criteria, with particular emphasis on accessibility, privacy, evidence-based efficacy, user engagement, and therapeutic objectives. Users have the capability to apply various filters to find apps that match their specific requirements and can access detailed information on apps across 9 distinct categories. The apps listed on MIND undergo regular updates, ensuring that the information provided remains current and offers insights into how these apps evolve over time, typically within a span of 100 to 180 days [23].

While there is previous research on the evaluation of quality features of general mental health apps drawn through different measures, common findings indicate that apps offering engaging designs and user-friendly aesthetics are most likely to attract users and improve satisfaction [18]. There is an overall gap in standardized app quality and effectiveness measures on mood apps specifically, app guidance for clinicians and consumers to interpret data, and the improvement of evidence-based mood apps that incorporate consumer preferences [24]. This review aims to bridge this gap by offering an overview of currently available mood-tracking apps on the Google Play Store and Apple App Store as well as the available evidence on mood

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apps, identifying the strengths and limitations of the apps through a quality evaluation and the gaps in the research through a scoping literature review. The review will focus on mood apps designed for children, adolescents, and young people.

Methods

Design

We will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [25] guidelines to guide the search and selection of studies and apps for evaluation (Multimedia Appendix 1). This evaluation will be composed of an app and literature search, screening and app selection, data extraction, data analysis, and data synthesis. The study will begin with a literature review, the results of which will be used to inform a review of features of mood-monitoring apps for young people. The Population, Intervention, Comparator, Outcome, Study (PICOS) framework will be used to develop the search strategy for both the literature review and app search (Table 1) [26,27].

Table 1. The Population, Intervention, Comparator, Outcome, Study (PICOS) framework.

Category	Description
Population	Children, adolescents, and young people
Intervention	Mood-monitoring apps (mobile smartphone apps that allow daily mood log and monitoring)
Comparator	—[a]
Outcomes	The primary outcome of the literature review will be an overview of the recent literature on mood-monitoring apps for children, adolescents, and young people. The app search will be an overview of the features and content of mood apps available in the marketplace, updated in the last 3 years (refer to the *Exclusion Criteria* section of phase 2). The secondary outcomes will include a classification of mood apps that test for clinical outcomes and their used measures for the app evaluation and clinical scales used in evaluations for the literature review, as well as a quality evaluation of the 50 most downloaded mood apps.
Study types (only literature review)	Qualitative, quantitative, and mixed methods studies in English that presents studies on mood apps, their review of clinical outcomes, applied measuring methods, and quality assessment of features are eligible for inclusion. Preprints, protocols, abstracts, and meta-analyses with no full-text access and those older than 3 years will be excluded.

[a]Not applicable.

Scoping Literature Review

Search Strategy

The first phase will be a scoping review of the literature on mood-monitoring apps targeted at children, adolescents, and young people. We will search 6 databases—Embase, CINAHL, PubMed, ACM Digital Library, Scopus, and Springer LNCS—using the search structure that includes mental health or mood (Medical Subject Headings OR Keywords) AND mobile apps (Medical Subject Headings OR Keywords) AND children, adolescents, and young people (Medical Subject Headings OR Keywords); Multimedia Appendix 2 provides the full search strings.

Inclusion Criteria

The review will include studies evaluating mood-monitoring apps targeted at children, adolescents, and young people. To avoid excluding relevant literature, any app that had mood monitoring as a feature will be included in the review. All types of study designs will be included as long as the study evaluates at least 1 mood-monitoring app. As the scope of the review covers apps targeting children, adolescents, and young people, our search terms will focus on this population; however, to ensure the inclusion of all relevant papers and due to a variety of definitions of "young people" in the literature, we did not specify an age limit.

Exclusion criteria

Any study that does not evaluate mood-monitoring apps, including reviews, conference proceedings, reports, posters, and protocols will be excluded. Literature older than 3 years, those in languages other than English, and papers for which the full texts are unavailable will also be excluded from this review. Studies describing a mood-monitoring app without evaluating it will be excluded. Finally, studies of apps that focus on mental health in general without reference to mood monitoring, and those designed for use by health care professionals, will also be excluded.

Screening and Paper Selection

References will be exported and stored in the citation management software, EndNote 21 (Clarivate). EndNote will then be used to remove duplicates and conduct automatic screening based on keywords from the search strategy. The titles and abstracts and then the full texts of the remaining papers will be screened by the author (SB) to determine final eligibility. To ensure transparency, the details of this process will be charted in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Data Extraction

SB, AS, and CC will read the full text of all included papers and extract data into a predetermined form (Textbox 1). Specific attention will be given to clinical rating scales used to evaluate the apps. Chosen based on clinical consensus, Textbox 2 lists the categories of the rating scales (refer to Multimedia Appendix 3 for a detailed list of typically used validated scales for each category).

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Textbox 1. Data extraction items for literature review.

Literature

- Author
- Title
- Year of publication

App

- Name of app
- Platform (iOS or Android)
- Allows mood monitoring? (yes or no)
- Targeted age group
- App category
- Focus of app
- Clinical outcomes
- Evaluation measures

Textbox 2. Extraction items of clinical rating scales.

- Types of clinical rating scales
- Bipolar disorder
- Mania or hypomania
- Depression
- Measures of functioning and quality of life

Data Analysis and Synthesis

A descriptive analysis will be used to provide an overview of the research on mood-monitoring apps for children, adolescents, and young people. If applicable, a thematic analysis will be conducted on available qualitative data to better understand user perspectives about the apps.

App Search and Evaluation

Search Strategy

The selection of mood apps will be conducted by searching 2 app marketplaces (Apple App Store and Google Play). A systematic search will be conducted using the keywords “mental health,” “mood,” “depression,” “bipolar disorder,” “mania,” “hypomania,” “mental coach,” and “mood journal”. The executed search through search terms will automatically be displayed by popularity (given the app store’s traffic algorithm) and limited to apps with at least 100,000 downloads. This will ensure that the apps being evaluated are the ones that are most used.

Inclusion Criteria

Apps will be eligible if they meet all of the criteria, such as (1) the app’s primary focus is mood tracking, (2) the app operates as self-reporting (no passive sensing), (3) the app has been updated in the last 3 years (due to the disruption of digital mental health support during and after the pandemic), (4) the app is in English, and (5) the app has at least 50 total ratings and reviews on the Apple iOS and Google Play Store. We will include apps regardless of whether they are paid, contain in-app purchases, or are free, and the apps must be designed as a standalone service, without the need for human support (eg, telehealth counselors or web-based service) or additional devices (eg, wearable heart rate monitor).

Exclusion Criteria

We will exclude duplicates of apps (if an app is available for both iOS and Android operating systems, we will include the iOS version only) and apps that are not in the English language. Considering the significant change in health app usage during and after the pandemic, we will consider apps that take the disruptive mental health consequences of the COVID-19 pandemic into account and, therefore, exclude apps that have not been updated in the past 3 years [24]. As we focus on mood-tracking apps that focus on the improvement of the user’s well-being, we will exclude any apps that do not provide the mood-tracking feature. To achieve the research objective of offering a holistic overview of existing mood-tracking apps specifically for children, adolescents, and young people, mood apps that are specifically designed for elderly people will also be excluded as they do not fit the population type.

Screening and App Selection

All mood apps found through the app marketplaces will be recorded in a Microsoft Excel document and duplicates will be removed, including Android apps that also have an iOS version. Preliminary screening by AS and CC will determine the initial

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eligibility for the evaluation, using the information provided in the app summaries on the Apple App Store and Google Play Store. Apps that are deemed eligible will be purchased, and, if necessary, downloaded to an iOS device and Android device. Apps that, upon closer examination, do not meet the inclusion criteria will be excluded. Any disagreements between the reviewers will be discussed and, if necessary, settled by CC. All apps identified as being eligible for inclusion will be reviewed. An adapted PRISMA flow diagram will be used to record the details of the search, screening, and selection processes so that the evaluation can be reproduced.

App Evaluation

The quality of the apps will be evaluated using the MIND framework, which is based on the American Psychiatric Association's app evaluation model. This framework includes 105 questions that assess various aspects of apps across 6 domains. The framework covers areas such as functionality, accessibility, inputs and outputs, privacy and security, data sharing, and evidence and clinical foundation. It also evaluates features and engagement styles. It helps assess app features, such as goal setting, psychoeducation, data tracking, cognitive behavioral therapy, and engagement elements, such as chat features and gamification [23,24]. MIND was chosen as an evaluation tool, as the platform offers richer data compared with other manual app rating frameworks. The literature highlights that digital navigators who use tools such as MIND, aid in the deployment of a more standardized approach to create lists of tested, approved, and authorized mood apps for clinicians to use and decrease barriers to app implementation in the clinic environment [25]. The list of data to be extracted to aid the quality evaluation is presented in Textbox 3.

Textbox 3. Full data charting list for app evaluation.

General

- Name
- Year of launch
- Platform (iOS and Android)
- Cost
- Target population
- Number of downloads
- App store rating (1-5 stars)
- Clinical outcome (measurable change in health or quality of life)
- Evaluation measures (which evaluation measure is used)
- Published evaluation of app (yes or no)

Features

- Interface (use of audio, video, and images)
- Support (use of support buddy)
- Emergency (lifeline or SOS feature)
- Notifications (possibility to set different notifications on mobile device)
- Trends (possibility to display mood trends)
- Notes (possibility to take in-app notes)
- Reminders (possibility to set in-app reminders)
- Security (use of personal identification number protection to access the app)
- Information (possibility to access educational material)
- Research (option to use data for research purposes with permission)
- Data erasure (possibility of erasing full or partially selected data)
- Data export (possibility to export data including electronic health care records)

Ethical Considerations

No ethical approval is required as exclusively secondary data will be used.

Results

The literature search and screening began soon after the submission of this protocol in January 2024, and the review is expected to be completed by September 2024. As of September

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2024, the app search and evaluation has begun and is expected to be completed and published by October 2024.

Discussion

Summary of Expected Findings

This review will provide an overview of the current landscape of mood apps targeted toward children, adolescents, and young people available in the market and the evidence on these mood apps. We will examine the apps' features, usability, and scientific evidence base. The findings of this review will improve knowledge about not only the state of the literature on mood apps but also the quality of mood apps in active use and shed light on areas that require further research and improvement. The review will place a special emphasis on the end users of these mood apps, understanding the benefits of use for young people by examining the clinical base or publication of evidence of the apps. In addition, we will explore any interventions or strategies that have been used to enhance the quality and responsible development of mood apps.

Implications and Comparison to Previous Work

By summarizing the existing features, strengths, and weaknesses of mood apps, as well as examining user experiences and satisfaction, we aim to contribute to the development of more effective and user-centered mood app frameworks. While previous research has analyzed the quality and literature on general apps for mental health, a similar synthesis about mood-monitoring apps is lacking [17,18,24]. We expect that the findings of this review will provide deeper insights into apps that specifically monitor mood and highlight evidence about digital self-monitoring of mood. The review will serve to inform the future development of mood-monitoring apps and, on a broader scale, enable a better understanding of the clinical use of regular mood monitoring for mental health management. In addition, we anticipate that this evaluation will play a crucial role in addressing ethical and usability concerns and promoting the responsible advancement of mood app technology.

Limitations

The exclusion of literature published earlier than 3 years ago (ie, before 2021) is a potential limitation of phase 1 of this review. Although the time frame was chosen with the rapid evolution of technology in mind and enables a comprehensive analysis of the most recent evidence, we risk excluding relevant and good-quality apps evaluated earlier. Another limitation is that the exclusion of apps and studies not available in English may bias the findings of the review.

Conclusions

The primary aims of this review are to provide an overview of the recent evidence on mood-monitoring apps and to assess the quality of the mood apps currently available in the marketplace and active use. Together, these analyses will help us understand the current landscape of mood apps targeted toward children, adolescents, and young people and potentially highlight the strengths and limitations of the research and the apps themselves. We expect that the outcomes of this review will inform the future development of mood apps for young people as well as scientific research into these apps. The results of the review will be disseminated through a peer-reviewed publication.

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Authors' Contributions

The review protocol was conceptualised and supervised by MMI and EM. Clinical review and editing were provided by DA and AS. SB drafted the protocol including the research question, PICOS, and search strategy. SB, AA and CC responded to peer review and restructured methods and narratives under the supervision of EM. All authors contributed to the review and edits of manuscript revisions.

Conflicts of Interest

AS received an honorarium for speaking at an educational event from Angelini Pharma. EM is an Editor in Chief of JMIRx Med.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[DOCX File , 84 KB - resprot_v13i1e56400_app1.docx]

Multimedia Appendix 2
Search strings.
[DOCX File , 16 KB - resprot_v13i1e56400_app2.docx]

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Multimedia Appendix 3
Clinical outcomes and measurement methods.
[DOCX File , 23 KB - resprot_v13i1e56400_app3.docx]

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Abbreviations

MARS: Mobile App Rating Scale
MIND: M-Health Index and Navigation Database
PICOS: Population, Intervention, Comparator, Outcome, Study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Effects of Interprofessional Education on Readiness for Interprofessional Learning in Rehabilitation Science Students From Professional Health Care Programs: Protocol for a Systematic Review

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Abstract

Background: The World Health Organization defines interprofessional education (IPE) as a process in which students from different health care programs work together to provide effective care while deepening their knowledge of each other's roles. Previous literature shows a strong argument for early exposure to IPE as a facilitator for high quality patient care. The goal of IPE is to improve interprofessional collaboration (IPC), the "gold standard" of care to enhance patients' quality of life, functional ability, and health status, especially for patients who require expertise from a variety of health care professionals. IPC has shown improvements in quality of life, functional ability, and health status. IPE can occur in the form of structured interventions or spontaneously in student placements. Literature has demonstrated that IPE facilitates skill, knowledge development, teamwork, communication skills, and mutual respect among health care professional students.

Objective: This systematic review aims to examine IPE outcomes, including readiness for IPC, IPE perceptions, attitudes toward collaborative learning, student confidence, practice efficiency, and team dynamics after IPE interventions in rehabilitation science students.

Methods: The study will be conducted as outlined by the Cochrane Handbook for Systematic Reviews and will be reported per the PRISMA (Preferred Reporting of Items for Systematic Reviews and Meta-Analyses) 2015 guidelines. Students have performed literature searches across the databases MEDLINE, Embase, CINAHL, ERIC, Web of Science, and AMED. Studies will be included if their IPE intervention included multiple prelicensure health care professional students in a health care or health care education setting. Based on timelines presented in the Institute of Medicine's report on the impacts of IPE, relevant studies from 2016 to the present will be included. The Risk of Bias 2 tool will be used to study sources of bias. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group's methods will be used to evaluate the quality of the evidence presented. The final 3 authors are assisting as supervisors, providing oversight and feedback as needed. Any deviations from this protocol will be reported in the final paper.

Results: The search strategy was finalized and searched across the databases by March 8, 2024. The systematic review was registered with PROSPERO on March 31, 2024. A total of 10,692 citations were retrieved for abstract and title screening, beginning in March 2024, and 756 were eligible for full-text screening in April 2024. Six articles were considered for inclusion and data extraction, which began in July 2024. Finalization of the extracted data and paper will occur in September 2024.

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Conclusions: This systematic review will provide a summary of the effects of IPE interventions in prelicensure rehabilitation science students. It will provide educators, health care providers, and students with valuable information for understanding the relevance of IPE. It will also shed light on research gaps and highlight areas for further study.

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KEYWORDS

interprofessional education; rehabilitation science; health care students; interprofessional collaboration; prelicensure health care professionals; patient care; interdisciplinary education; rehabilitation education; curriculum development; team-based learning

Introduction

Chronic diseases currently affect 1 in 3 Canadians and the World Health Organization (WHO) predicts that this will result in 52 million deaths by 2030 [1]. The high multisystemic impact of chronic diseases on patients and health care systems underscores the critical need for top-tier health care [1,2]. Top-tier health care can be facilitated with the early integration of interprofessional education (IPE) in health care students' curricula [3].

Various definitions of IPE exist in the literature. A widely accepted, global definition from the WHO defines IPE as the collaboration among students from different health care professionals to deepen their understanding of each other's roles and who work together to provide safe and effective care [4]. This form of education can occur in structured activities integrated into the curriculum or arise spontaneously during student placements [4]. IPE aims to enhance clinical practice by facilitating knowledge and skills development in teamwork, communication skills, and mutual respect among health care professional students [5-8]. Therefore, IPE should be considered pivotal in providing comprehensive care.

In educational settings, systematic reviews have found that students and licensed health care professionals participate in IPE in several ways [9-11]. This includes small group discussions, simulations, and workshops, which led to improved attitudes and perceptions of IPE, confidence, and self-efficacy associated with team-based performance and communication skills [9,11]. Notably, over half the studies in both reviews showed significant improvements in positive attitudes, suggesting the effectiveness of these interventions [9,11]. While treatments have been proven effective, a review looking at a follow-up period reported that improvements were only sustained for a short period [9]. Moreover, the same review saw improvements in patient outcomes such as patient safety, time from arrival to care, and pressure ulcers, but no differences in length of stay, mortality rate, and complications in the hospital setting with the implementation of IPE [9]. Although many positive improvements were noted, these reviews reported very low quality of evidence and heterogeneity across studies, due to the lack of randomized controlled trials (RCTs), a high proportion of loss to follow-up, and a high risk of bias (RoB) [9,11]. These IPE effects were predominantly reported in nursing and medical students [9,11], with very few studies focusing on other health care professional students, such as those enrolled in rehabilitation programs.

Rehabilitation consists of interventions aimed at optimizing the quality of life in individuals with health conditions [12]. Along with increasing independence and promoting participation in meaningful activity, rehabilitation contributes to healthy aging through disease management and helps reduce morbidity and mortality [12]. According to WHO, rehabilitation professionals include "physiotherapists, occupational therapists, speech and language therapists and audiologists, orthotists and prosthetists, clinical psychologists, physical medicine and rehabilitation doctors, and rehabilitation nurses" [12]. Exploring the effects of IPE on rehabilitation science students is crucial, as it can contribute to improved chronic disease management and enhanced quality of health care delivery through collaboration among various professionals.

Thus, the goal of this systematic review is to explore the effects of IPE on prelicensure rehabilitation science students' readiness toward interprofessional collaboration (IPC). Secondary outcomes will also be explored, including but not limited to team dynamics, confidence levels, closed-loop communication, and practice efficiency.

Methods

Overview

This systematic review will be conducted as outlined by the Cochrane Handbook of Systematic Reviews and reported as per the updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2015 statement [13-15]. The protocol has been registered in PROSPERO (CRD42024506081) and the PRISMA Protocols (PRISMA-P) checklist was used to guide this protocol submission [15]. If any deviations occur from this protocol, this will be reported in the final manuscript.

Eligibility Criteria

Studies will be selected according to the population, intervention, comparison, and outcome (PICO) framework and will be limited to those conducted between 2000 and 2024 to reflect contemporary educational practices and the prominence of IPE in rehabilitation professions' curricula. This was aligned with the rise in implementation of IPE initiatives in the 2000s across health care systems—such as in Canada where IPE and collaboration began to gain traction and were reported to be "essential to achieving effective delivery of health care" [16]. Furthermore, prelicensure rehabilitation training program

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curricula underwent stark changes in the 2000s, as seen with the World Confederation for Physical Therapy developing new guidelines for entry-level physical therapy education between 2003 and 2011 [16,17].

For title and abstract screening, inclusion criteria were defined by whether the abstract and title addressed the following three questions: (1) “Was there an IPE intervention performed?” (2) “Were multiple health care professions' prelicensure students represented in the study?” (3) “Did the study take place in a health care or health care education setting?” Studies that did not answer “yes” to all 3 statements were excluded. These 3 qualifying questions were derived from the PICO framework to facilitate the screening process. Similarly, in full-text screening, all 3 questions must be satisfied (eg, “yes”) before the studies could be included in this review (Multimedia Appendices 1 and 2).

Participants

Studies evaluating prelicensure students in entry-to-practice rehabilitation training programs will be included. Rehabilitation disciplines will be defined according to the WHO, including “physiotherapists, occupational therapists, speech and language therapists and audiologists, orthotists and prosthetists, clinical psychologists, physical medicine and rehabilitation doctors, and rehabilitation nurses” [12]. Studies with participants including only practicing rehabilitation professionals will be excluded. For example, registered physiotherapists involved in an IPE opportunity for their professional development requirements.

Intervention

IPE interventions will be included if presenting two or more rehabilitation science students engaging in an active exchange of information and participation in activities aimed at improving communication and collaboration skills, as per the WHO and the Cuff 2013 definitions [4,18]. Interventions may take place within various settings including large group classes, small group tutorials, clinical settings, and digital platforms [3]. Models of learning may include team-based learning, simulation, and student-led interprofessional clinics [3]. Additional IPE settings and modes of learning not mentioned above may still be included, as long as they satisfy the IPE intervention criteria mentioned above [4,18].

Comparison

Having a control or comparator group is not a requirement for inclusion in this review. If the study has a control group, the intervention may include usual teaching, learning practice, or any other type of intervention, excluding IPE.

Outcome

The primary outcome of this review will be IPE interventions' effect on rehabilitation science students’ readiness for IPC, defined by their interest and ability to work with other professional teams [7,18,19]. This primary outcome was also an important learning outcome outlined in the Interprofessional Learning Continuum model published by the Institute of Medicine [7]. Readiness for IPC may be captured using various measurement tools, which may include but are not limited to, the Readiness for Interprofessional Learning Scale [20], the Student Perceptions of Interprofessional Clinical Education-Revised, the Interdisciplinary Education Perception Scale, the Entry Level Interprofessional Questionnaire [21], and Brief Attitudes Survey for Interprofessional Collaborative Learning [22]. There are numerous outcome measures to assess IPE competencies, but for the purposes of this review, the foci will be tools that evaluate students’ attitudes and abilities for IPC and teamwork [19]. Secondary outcomes that will be examined include students’ perception of IPC, students’ appreciation for the role and scope of complimentary rehabilitation disciplines, closed-loop communication, confidence levels, practice efficiency, and team dynamics. The secondary outcomes may be measured by tools such as the Anesthetists' Non-Technical Skills checklist and purpose-built questionnaires [23]. Outcome measures used to assess primary and secondary outcomes will not be limited in this review.

Study Design

This systematic review will include randomized and non-RCTs, cohort studies, and case-control studies published in peer-reviewed journals. Narrative reviews, scoping reviews, and systematic reviews will be excluded; however, their references will be searched for relevant articles. Other documents that will be excluded from this systematic review include abstracts, dissertations, theses, editorials, conference proceedings, magazines, news, and any other non–peer-reviewed papers (Multimedia Appendix 3).

Search Strategy

A search strategy was developed in consultation with a health sciences librarian at McMaster University to ensure it captured the PICO elements of the research question. To develop this search strategy, the authors identified a set of MeSH (Medical Subject Headings) terms and keywords by examining previous systematic reviews for topics related to IPE, rehabilitation health care personnel, and learning, to find terms linked to these 3 concepts [10,24]; these were then verified with the health sciences librarian. The combination of terms, including the necessary vocabulary and targeted MeSH terms, were trialed in MEDLINE and was similar to: (“health science learners” OR “health science students”) AND (“interprofessional education” OR “interprofessional learning”). The full search string for MEDLINE is available in Multimedia Appendix 4. MEDLINE was chosen as the database to trial the initial search as it is widely considered to be the gold standard for health-related literature searches [25]. Additionally, MEDLINE is most often used as a starting point in systematic review searching due to its extensive collection of biomedical and health-related literature [13,25].

Following the initial search on MEDLINE in February 2024, the search was translated to 4 additional databases including Embase, CINAHL, ERIC, and AMED. These additional databases were selected as they contain education and rehabilitation profession-specific literature relevant to this review. The databases were searched between January 1, 2000, and March 8, 2024, to include IPE interventions and studies after the implemented changes in prelicensure rehabilitation training program curricula in the 2000s [17].

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Study Selection

Literature search results were downloaded from the databases and imported into EndNote 21 (Clarivate) for a first line of duplication removal. The remaining citations were uploaded into Covidence (Veritas Health Innovation) for further duplication removal, followed by title or abstract, and full-text screening. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews.

Before engaging in the formal screening process, title and abstract screening were pilot-tested by all authors by reviewing the first 30 texts as a group, ensuring agreement and consistency between all reviewers. According to the recently published best practice guidelines for conducting systematic reviews, it is recommended that abstract screening take place by screening 20 to 30 abstracts to ensure the review team reaches consensus [26]. Three pairs of reviewers (ED, GD, JP, KD, RC, SF, and ET) screened the remainder of the titles and abstracts for inclusion criteria (Multimedia Appendix 1). Each study required consensus between 2 blinded reviewers before a final decision to include or exclude was made. Disagreement resolution was first attempted by discussion, followed by a decision by a third reviewer (SQ, SW, and AO) if consensus cannot be achieved. Following the completion of the title and abstract screening, the full-text screening process included pilot testing, independent reviews, and disagreement resolution using the same framework as the title and abstract screening (Multimedia Appendix 2).

Data Extraction

Data extraction was pilot-tested by all reviewers by reading the first 10 studies as a group and inputting relevant information into the data extraction table. The data extraction table was reviewed such that all authors are in consensus for the data extraction of the remaining studies. This clarified discrepancies and ensured adequate interrater reliability with data extraction [13,27]. Ten studies were piloted for extraction to ensure that relevant information for data analysis and synthesis was captured. After pilot testing was completed, 3 groups of 2 authors (ED, GD, KD, SF, ET, and RC) were involved in data extraction for all full texts included in the review. The 2 reviewers independently assessed each paper into a predefined data extraction table as outlined in Multimedia Appendix 5. Disagreements were resolved first by discussion, followed by a decision by a third reviewer (SQ, SW, and AO) if consensus could not be achieved.

The chosen information to be extracted aligns with the Cochrane Handbook of Systematic Reviews [13]. Once data extraction was piloted, the tool was modified to ensure all relevant data were captured. The following information will be extracted from studies that met the inclusion criteria: title, author, year, country of publication, study design, and sample size (total and per group). Participant characteristics to be extracted include age (mean and SD), gender, previous IPE experience, previous degrees conferred, and educational programs. Intervention characteristics to be extracted are the level of study, setting, frequency, and duration for both experimental and control groups as well as the timing of data collection. For all of the primary and secondary outcomes, the following data will be extracted: total and subscale scores of the included outcome measures, baseline score and postintervention scores (mean and SD) in both the experimental and control groups, mean group difference and SD, group *P* value, effect size, and a summary of the results. If any of the earlier information is missing from the included studies, authors will be contacted to request missing data. If the data are reported only in figures and the authors do not provide the requested data, WebPlotDigitizer will be used if possible.

RoB Assessment

The Cochrane RoB tool will be used (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) for RCTs within this review [28]. For non-RCTs, the RoB in Non-Randomized Studies of Interventions will be used [29]. Two authors will independently perform the RoB assessment for each citation, any disagreements will be resolved through discussion. If no consensus can be established, a third reviewer will be consulted (SQ, SW, and AO). For this review, RoB will be performed at a study level.

Confidence in Included Results

Prior to assessing the quality of evidence for each outcome, each study will be assessed for inclusion using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework for quality assessment [30]. The quality of evidence will be assessed across the domains of RoB, consistency, directness, precision, and publication bias. The overall quality of outcomes in the studies will be assessed using GRADE, and results will be stratified as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect) [31]. GRADE will be conducted by 3 pairs of authors in which each pair will be independently performing the GRADE assessment for each citation with any disagreements resolved through discussion. If no consensus can be established, a third reviewer will be consulted.

Data Synthesis

Tables will be constructed to describe the types of studies, populations, characteristics of the IPE intervention, professions involved in the intervention, comparator, and outcomes. Meta-analysis will be conducted if at least 2 studies reported the same outcome. The standardized mean difference will be the summary measure collected if applicable and measures of consistency will be explored via the I^2 statistic. If the estimated I^2 statistic is equal to or greater than 50% this would be interpreted as a large amount of heterogeneity [32]. Furthermore, due to the abundance of variability in IPE research concerning participants, interventions, comparators, and study designs, a random-effects model that inherently allows more heterogeneity will be used. If meta-analysis cannot be performed, the data will be synthesized through a narrative approach.

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Subgroup analysis may be conducted if sufficient data are available from two or more studies to examine outcome variability and population affected by the outcome (patient-reported outcomes, clinician outcomes, and student outcomes) or exposure variability (setting, frequency, and duration; including the potential total number of exposure hours and whether hours came from patient-facing vs nonpatient-facing exposure experiences). Potential subgroup analyses may include examining the impact of an IPE intervention between different prelicensure rehabilitation science students. These subgroup analyses, if conducted, might inform the authors and readers further on the aspects of IPE that should be prioritized, and potentially some of the current best methods by which to measure the outcomes of interest from a collaborative and potentially patient experience perspective.

Results

This project was initiated in November 2023, a search strategy was drafted on January 17, 2024, and trialed in a preliminary search in MEDLINE, before consulting with the Health Sciences Librarian at McMaster University on February 7, 2024. The search strategy was finalized on March 8, 2024, and this study was registered on PROSPERO on March 31, 2024 (CRD 42024506081). The final search across the 5 databases resulted in 10,692 citations for abstract and title screening. 756 citations were eligible for full-text review, which started in April 2024. From the eligible citations, 6 citations were considered for data extraction. Data extraction began in July 2024 and is ongoing. Data extraction will be finalized for knowledge synthesis by September 2024. This project is expected to be completed and finalized by October 2024 and a paper will be prepared for publication by November 2024.

Discussion

To the authors' knowledge, this is the first time a review focusing on IPE with prelicensure rehabilitation science students will be performed. Previous studies show the potential of IPE in improving collaboration, communication, and role clarity among interprofessional peers [8-10]. It is hypothesized that students in professional rehabilitation sciences programs will experience similar benefits. As there are limited synthesis reviews on this subgroup of students, our study will bring forward their perspectives on IPE effectiveness, possibly identifying the necessary IPE components for successful implementation. Rehabilitation professions play a crucial role in facilitating the prevention, treatment, and overall management of various health conditions [1,12], emphasizing the need for this study. Evaluating the effectiveness of these IPE interventions provides a greater understanding of students' readiness and its associated improvement for IPC upon entering the workforce.

There are numerous IPE interventions described in the literature, and considerations for their implementation are usually generally described [3]. Comprehensive IPE activities need to consider each participating student's role and responsibilities under relevant circumstances to allow for skill development in conflict resolution, skillful communication, and collaborative practice for improving patient care [3,6,10]. However, these contexts and nuances are rarely reported, especially from the perspective of rehabilitation science students. Thus, this review may also provide clarity on future learning environments, delivery methods, or implementation, which could be implemented to formalize rehabilitation science students' awareness of their interprofessional identity and contributions to patient care [19].

Furthermore, the knowledge gained from this review may impact education for prelicensure rehabilitation science students by bringing forward the essential components and direction for IPE in their curriculums. There are several interprofessional competencies including role clarity, team-based collaborations, IPC, and values in interprofessional practices [7,33]. These competencies are interdependent and are necessary to facilitate high-quality patient care [5,6,33]. Thus, IPE delivery must be continuously reviewed for alignment with these outlined competencies to ensure prelicensure students are gaining the necessary experiences to facilitate their IPE readiness [7,19,34]. In addition, the promotion and implementation of IPE opportunities should be evaluated to ensure they address prelicensure rehabilitation science students' needs as their roles differ from those of physicians and nurses [8,9,11]. By identifying the current IPE structure, delivery, and implementation, this information can identify rehabilitation science students' knowledge gaps in core competencies, informing the future development of IPE in rehabilitation professional programs. Subsequently, this knowledge growth will supplement WHO's mandate of using innovative approaches to teach health care students across the world to optimize IPE readiness in future generations of health care providers [4].

The proposed systematic review will have many strengths including the registration of the protocol prior to study commencement and the use of the Cochrane Handbook and PRISMA guidelines to optimize rigor and reporting transparency [13,31]. These outlined steps will facilitate the authors' progress at all stages to mitigate errors, and risk of bias. This review will also include rehabilitation science students who participate in IPE interventions, where we used an international definition outlined by the WHO, a global health organization [12]. Since there are common outcome measures for interpreting perspectives on IPE interventions, there may be an opportunity for meta-analysis and determination of standardized outcome measures for IPE, an identified need in IPE research. This systematic review will include a variety of study designs and include studies published after 2016 to reflect the Institute of Medicine's report on the impacts of IPE [7], capturing the most relevant and current evidence in IPE literature.

Potential limitations may include studies lacking long-term follow-up, varying populations included, and varying intervention methods. Furthermore, the included studies may not use the same outcome measures, reducing the possibility for further analyses via a meta-analysis. Our search is also limited by using the search term "healthcare" instead of "health" as the term "health" broadened our initial search by over 20,000 results in comparison to the term "healthcare." With a high-level review of the search results using "health," the scope of the papers was not directly applicable to this proposed systematic review, and the term "healthcare" was therefore used instead

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to optimize study feasibility and relevancy to professional health care programs.

Acknowledgments

The authors would like to acknowledge the Health Sciences Librarian at McMaster University, Stephanie Sanger, for their facilitation in developing and finalizing the search strategy.

Data Availability

All data generated or analyzed during this study are included in this article and additional information may be available from the corresponding author upon reasonable request.

Authors' Contributions

AO, SW, and SQ were involved in study conceptualization, literature search, abstract screening, data analyses, and manuscript preparation. ED, JP, KD, RC, GD, SF, and ET were involved in literature search, abstract screening, data collection and analyses, and manuscript preparation. All authors reviewed the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Title and abstract tool.
[PDF File (Adobe PDF File), 263 KB - resprot_v13i1e60830_app1.pdf]

Multimedia Appendix 2
Full text screening tool.
[PDF File (Adobe PDF File), 262 KB - resprot_v13i1e60830_app2.pdf]

Multimedia Appendix 3
Inclusion and exclusion criteria.
[PDF File (Adobe PDF File), 216 KB - resprot_v13i1e60830_app3.pdf]

Multimedia Appendix 4
MEDLINE search strategy.
[PDF File (Adobe PDF File), 210 KB - resprot_v13i1e60830_app4.pdf]

Multimedia Appendix 5
Data extraction tool.
[PDF File (Adobe PDF File), 470 KB - resprot_v13i1e60830_app5.pdf]

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Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
IPC: interprofessional collaboration
IPE: interprofessional education
MeSH: Medical Subject Headings
PICO: population, intervention, comparison, and outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
RCT: randomized controlled trial
RoB: risk of bias
WHO: World Health Organization

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Protocol

Using Artificial Intelligence to Detect Risk of Family Violence: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Despite the implementation of prevention strategies, family violence continues to be a prevalent issue worldwide. Current strategies to reduce family violence have demonstrated mixed success and innovative approaches are needed urgently to prevent the occurrence of family violence. Incorporating artificial intelligence (AI) into prevention strategies is gaining research attention, particularly the use of textual or voice signal data to detect individuals at risk of perpetrating family violence. However, no review to date has collated extant research regarding how accurate AI is at identifying individuals who are at risk of perpetrating family violence.

Objective: The primary aim of this systematic review and meta-analysis is to assess the accuracy of AI models in differentiating between individuals at risk of engaging in family violence versus those who are not using textual or voice signal data.

Methods: The following databases will be searched from conception to the search date: IEEE Xplore, PubMed, PsycINFO, EBSCOhost (Psychology and Behavioral Sciences collection), and Computers and Applied Sciences Complete. ProQuest Dissertations and Theses A&I will also be used to search the grey literature. Studies will be included if they report on human adults and use machine learning to differentiate between low and high risk of family violence perpetration. Studies may use voice signal data or linguistic (textual) data and must report levels of accuracy in determining risk. In the data screening and full-text review and quality analysis phases, 2 researchers will review the search results and discrepancies and decisions will be resolved through masked review of a third researcher. Results will be reported in a narrative synthesis. In addition, a random effects meta-analysis will be conducted using the area under the receiver operating curve reported in the included studies, assuming sufficient eligible studies are identified. Methodological quality of included studies will be assessed using the risk of bias tool in nonrandomized studies of interventions.

Results: As of October 2024, the search has not commenced. The review will document the state of the research concerning the accuracy of AI models in detecting the risk of family violence perpetration using textual or voice signal data. Results will be presented in the form of a narrative synthesis. Results of the meta-analysis will be summarized in tabular form and using a forest plot.

Conclusions: The findings from this study will clarify the state of the literature on the accuracy of machine learning models to identify individuals who are at high risk of perpetuating family violence. Findings may be used to inform the development of AI and machine learning models that can be used to support possible prevention strategies.

Trial Registration: PROSPERO CRD42023481174; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=481174

International Registered Report Identifier (IRRID): PRR1-10.2196/54966

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KEYWORDS

family violence; artificial intelligence; natural language processing; voice signal characteristics; public health; behaviors; research literature; policy; prevalence; detection; social policy; prevention; machine learning; mental health; suicide risk; psychological distress

Introduction

Family violence is a major public health problem and can include behaviors such as physical, sexual, and verbal abuse; coercive control; and emotional, spiritual, religious, and financial abuse perpetrated by 1 adult partner to another. Definitions of family violence vary in the research literature, which has implications for reported rates of family violence and, importantly, policy [1]. For this article, family violence will be defined by Section 4AB (1) of the Australian Family Law Act 1975 as "threatening or other behavior by a person that coerces or controls a member of the person's family (the family member) or causes the family member to be fearful." Family violence is most commonly, but not exclusively, perpetrated by men against women [2], and these experiences can have considerable mental health impacts, such as depression, posttraumatic stress disorder and anxiety [3], and physical consequences for survivors, including serious injury and death [4]. Recent estimates suggest that globally 27% of women aged between 15 and 49 years old have experienced intimate partner violence [5]. In Australia, the most recent statistics suggest that approximately 20% of adults have experienced family violence at some point since the age of 15 years [6].

The prevalence and impact of family violence underscores the importance of early detection and prevention. Addressing family violence requires prevention strategies across a range of contexts, such as social policy, culture, health care as well as the familial level [7]. Prevention of family violence has relied primarily upon education strategies, with a large emphasis on educating survivors of family violence [8], which have reported mixed results. For instance, Noughani and Mohtashami [9] found that dissemination of an educational booklet to women did not change the reported incident rate of family violence in their sample. However, a significant reduction in family violence after three 60-minute educational classes for women was reported by Taghdisi et al [10]. Education strategies have also targeted health professionals such as nurses [11]. Given the varying levels of success of these initiatives and the often-hidden nature of family violence, novel approaches for detecting family violence are needed.

Family violence increased during the COVID-19 pandemic, exacerbating the mental and physical health difficulties experienced by individuals, families, and communities [12]. Telehealth services and online mental health support tools proliferated during the COVID-19 pandemic [13,14]. The use of technology in psychology has been found to be useful across a range of settings. For instance, telehealth is effective in treating several mental health disorders [15] and previous research has examined the use of technology regarding family violence screening and interventions [16]. According to a review by El Morr and Layal [16], information and communication technologies facilitate greater levels of disclosure of family violence victimization than is achieved though in-person screening; however, only standardized screeners were studied and alternate means of disclosure (eg, free-text questions and voice signals) were not considered.

Progress in information technology, particularly artificial intelligence (AI) has led to some significant advancements in medical and public health interventions. In a recent systematic review, Qui et al [17] found that large AI models have been used in bioinformatics, medical diagnoses, imaging, informatics, education, robotics, and public health. These models include large language models, large vision models, and large multimodal models. The authors caution that large language models are not yet reliable and may generate information that can mislead users. Further challenges and risks identified by the review include bias, privacy issues, the resource intensive requirements associated with updating large models, and emphasize the importance of situating the models in line with human ethics.

Recent research has examined the use of machine learning in mental health, including screening for suicide risk [18], assessment of psychological distress [19], and detection of family violence in medical records [20,21] as well as using voice signal informed classification [22]. Voice signal data such as vocal pitch [23] and articulation [24] have been found to distinguish between the voice recordings of distressed and nondistressed individuals. Similar approaches using text-based analysis have been developed to identify and to detect reports of family violence on Twitter [25]. The analysis of social media content can provide valuable insights into risk factors, in particular textual markers of family violence. A similar approach has been taken where advanced AI models, such as transformer architecture have been applied to the analysis of annotated clinical notes to detect family violence [20]. In a review by Iyer and Meyer [18], timing patterns of speech were able to detect high risk of suicide callers compared with their comparison group with a median accuracy of 95%. Other vocal characteristics such as power spectral density sub-bands and mel-frequency cepstral coefficients demonstrated at least 80% accuracy in differentiating groups.

Machine learning and AI have also been used in predictive analytics across a range of settings, including crime and policing using Tweets [26] and mobile phone behavioral data [27] with high degrees of accuracy (70%-81%). Historically, predictive analysis regarding family violence has relied on police responses to questionnaires such as the Domestic Violence Safety Assessment Tool, and has poor predictive accuracy [28]. Given the success and accuracy previous AI tools have demonstrated at identifying psychological distress across both vocal and text-based settings, as well as predictive accuracy in some settings, research into predictive analytics and the use of AI to detect risk of family violence may have real world consequences, particularly in terms of prevention. However, to

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date, no research has amalgamated these findings to assess the accuracy of AI models in identifying the risk of family violence.

Detecting individuals who are at risk of perpetrating family violence is critical for the implementation of prevention strategies. The primary aim of this systematic review is to assess the accuracy of AI models in differentiating between individuals at risk of perpetrating family violence, versus those who are not, using textual or voice signal data. The following questions will inform this review: (1) What research using AI and machine learning has used textual or voice signal data to identify risk of family violence? and (2) What is the accuracy of such tools in differentiating between individuals at risk of perpetrating family violence versus those who are not?

Methods

Inclusion and Exclusion Criteria

An overview of inclusion and exclusion criteria is presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Include human participants.
- Involve adult participants.
- Use machine learning methods.
- Differentiate between low and high risk of family violence perpetration.
- Use voice signal data or linguistic (textual) data.
- Nonexperimental and experimental studies.
- Reporting metrics of classification accuracy.

Exclusion criteria

- Animal models.
- Child or adolescent perpetrators.
- Reviews (eg, narrative, systematic, meta-analysis, and meta-regression).
- Comments and editorials.
- The treatment of family violence.
- Involving child abuse.
- Involving elder abuse.
- The focus of enquiry is a condition other than family violence.

Additional inclusion criteria are that the papers are available in full text, and published in peer reviewed journals. Theses and dissertations will also be eligible for inclusion to yield the most exhaustive search possible. Languages other than English will be considered and translations conducted, subject to time and resource availability.

The decision to restrict the study population to adult participants is consistent with most research that recognizes adults as the key perpetrator population.

Search Strategy

The search strategy and terms were informed by a preliminary search for relevant publications. The search will be restricted to the following databases: IEEE Xplore, PubMed, PsycINFO, EBSCOhost (Psychology and Behavioral Sciences Collection), and Computers and Applied Sciences Complete. ProQuest Dissertations and Theses A&I will also be used to search the grey literature. The full text will be searched using the following representative syntax (ie, Pubmed) ((("Domestic Violence"[Mesh] NOT ("Child Abuse"[Mesh] OR "Elder Abuse"[Mesh])) OR "family violence"[All Fields] OR "domestic violence"[All Fields] OR "domestic abuse"[All Fields] OR "intra-familial violence"[All Fields] OR "spousal violence"[All Fields] OR "spousal abuse"[All Fields] OR "interpersonal violence"[All Fields] OR "interpersonal abuse"[All Fields] OR "intimate partner violence"[All Fields]) AND (("natural language processing"[Mesh] OR "natural language processing"[All Fields] OR "word embeddings"[All Fields]) OR ("signal processing, computer-assisted"[MeSH Terms] OR "speech analysis"[All Fields] OR "acoustic"[All Fields] OR "emotional speech"[All Fields] "voice"[All Fields] OR "MFCC"[All Fields]))) NOT "review"[publication type]. The reference lists of all articles included for review will be searched for any additional publications as well as relevant reviews.

Study Selection

Retrieved studies will be loaded into NVivo (Lumivero) and title and abstract screening will be conducted by 2 researchers. A full-text review will be conducted by 2 authors and will resolve any discrepancies through discussion, or a third reviewer as needed. An overview of the study selection process is provided in Figure 1.

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Studies that meet all inclusion criteria will be included in the review. An overview of the participant, intervention, comparator, outcomes, and time (PICOT) [29] is provided below (Textbox 2) and forms the basis of data extraction. Screening and reporting of included publications will be in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (refer to Multimedia Appendix 1 for PRISMA checklist).

Figure 1. Overview of study selection. Searches are yet to be performed.

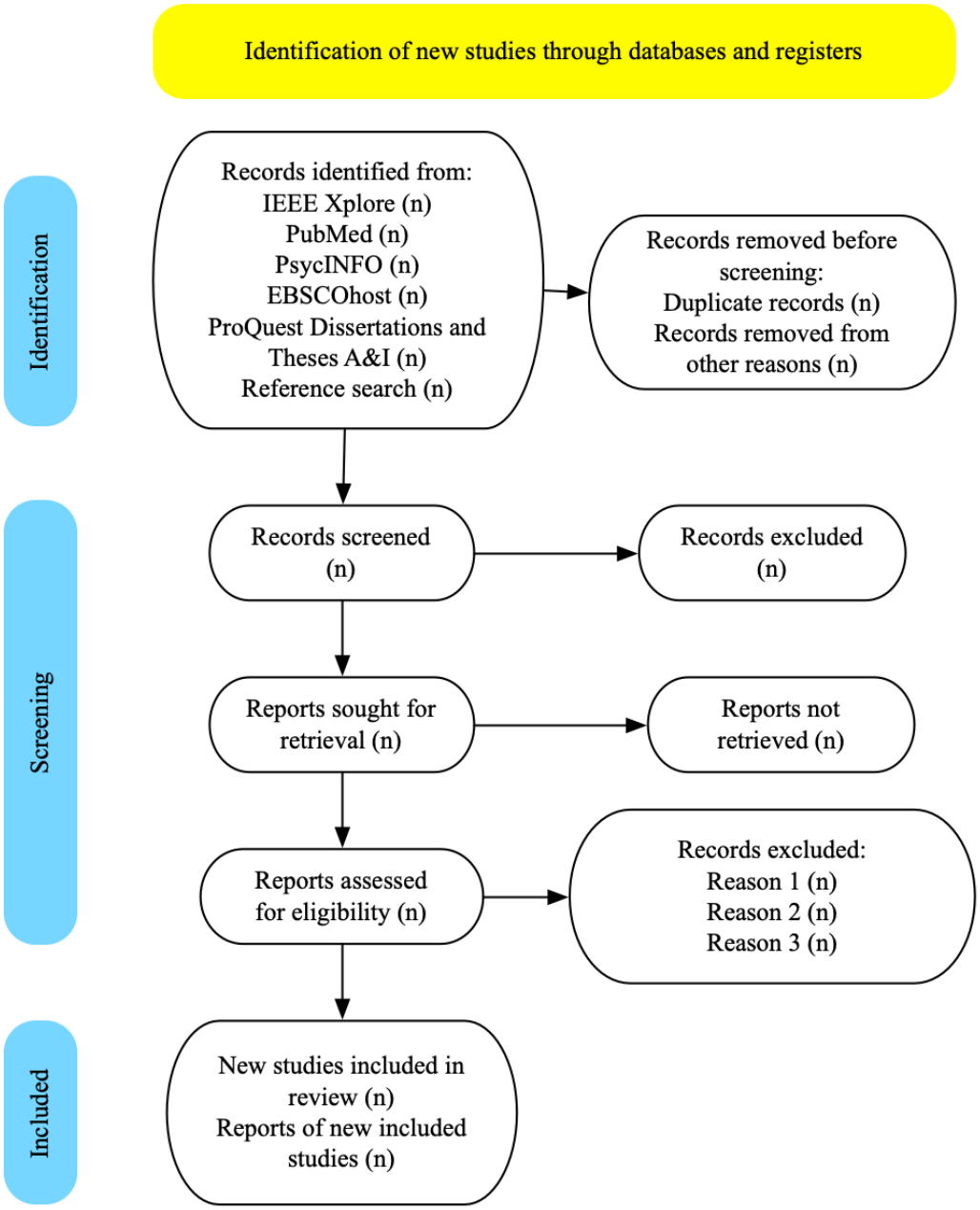

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Textbox 2. Summary of the participant, intervention, comparator, outcomes, and time requirements.

Patient population

- >18 years of age.

Intervention of interest

- Reviewing the use of text and voice signal-based machine learning tools used to predict risk of family violence.

Comparison interventions

- Not applicable.

Primary outcomes

- Accuracy of classification between low and high risk of family violence.

Time (Year published)

- 2000 and above.

Other considerations

- Language: all languages.
- Study designs: quantitative, experimental, and nonexperimental.
- Population: nonanimal investigations.

Quality Assessment

Quality assessment will be performed by 2 researchers using the risk of bias tool in nonrandomized studies of interventions [30]. Included studies will be rated across the 7 domains including bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes (eg, reporting training versus test dataset accuracy), and selection of the reported result. A final rating of risk of bias will then be assigned to each included publication and across included publications as either low, moderate, serious, critical, or no information provided. This step is essential to ensure the validity and reliability of reported findings.

Data Extraction

Data extraction will be conducted on NVivo and will be performed by 2 researchers, with regular meetings to discuss results. If there is disagreement regarding extraction, a third researcher will be involved in mediating. The following categories will be used to extract the data: study characteristics, participant characteristics, intervention and comparator characteristics, and outcome characteristics. Specific information will also be extracted relevant to vocal signal characteristics used, natural language processing methods, and machine learning methods.

Synthesis Method

Initially, included studies will be synthesized using a narrative synthesis following guidelines proposed by Rodgers et al [31]. Data will be tabulated based on the information described above. The tabulated data will then be analyzed and clustered into groups based on various characteristics, such as population demographics and data type (eg, text or speech). Short summaries of each included paper will also be developed. Throughout the synthesis process, the research team will meet to critically evaluate the process and to resolve issues that may arise during the synthesis.

A random-effects meta-analysis will be conducted using the area under the receiver operating curve (AUC) and its SE, as reported in the included studies. Where an AUC value is not reported, a point estimate for the AUC will be obtained from the confusion matrix [32]. To be included in the analysis, the SE or CI must be reported. In the absence of SE values, these will be computed by the equivalence of the AUC to the Wilcoxon statistic or derived from reported CIs. If not provided, the corresponding authors will be contacted with a request to provide the necessary data. Separate random-effects meta-analyses will be performed by classification algorithm subgroup (eg, deep learning, gradient boosting random forest etc), where enough studies (>3) are available. Higgins I^2 test will be used to evaluate the level of heterogeneity between included studies, with a level >56% indicating substantial levels of heterogeneity between included studies [33]. Publication bias will be ascertained through Egger regression and funnel plot analyses [34]. All analyses will be conducted using R software (version 4.2.0; R Foundation for Statistical Computing) and the “metafor” (ie, meta-analyses and funnel plots).

Ethical Considerations

No participants will be involved in this review, as data will be extracted from existing published studies. Thus, ethics review is not required for this study. This review aims to contribute to a paucity of research in the areas of family violence risk prediction that uses textual and voice-signal based data. Findings from this review will be of particular importance internationally to health care providers such as telehealth services that leverage verbal cues to assess risk. Given the reported high incidence of family violence in the community, this will clarify the state of

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the literature, providing meaningful information that may be of interest to law enforcement, health care providers, and policy makers and may clarify the next steps needed to advance research in this area. In addition, this review will provide important information about the relevance of specific voice and text features in risk detection for the development of future algorithms.

Results

As of October 2024, preliminary searches have not been conducted. Data will be extracted in line with the aims of this review. The results will include a narrative summary. The meta-analysis results will be presented using a forest plot. It is expected results will be published with the established protocol in a peer-reviewed journal.

Discussion

The primary aim of this systematic review is to assess the accuracy of AI models in differentiating between individuals at risk of perpetrating family violence versus those who are not. Given that previous research has been accurate at identifying other forms of risk for example, suicide risk [18], and based on preliminary searches [22], it is anticipated that these models may report a high degree of accuracy in identifying individuals who are at high risk of perpetrating family violence.

Given that this is a nascent area of research, it is possible that there may be a high level of heterogeneity across the included studies, differences in the definitions used to identify family violence and there may be diversity in the vocal or textual characteristics used to discriminate high and low risk, as has been found in previous reviews [18]. Despite these potential limitations, the results of this review will clarify the state of the literature on the accuracy of machine learning models to identify individuals who are at high risk of perpetuating family violence. Importantly, they may contribute to the development of machine learning and AI models that can accurately predict individuals at risk of perpetrating family violence, thus contributing to the development of potential prevention and intervention strategies. In addition, the findings from this review will summarize what systems are involved in the detection of family violence.

Findings from this review may inform the development of surveillance models and contribute to evolving dialogue concerning ethical and political considerations on surveillance on domestic spaces, abusers co-opting smart speakers and the privatization response to family violence as outlined by Sparrow and colleagues [35].

Results from this literature review will be disseminated through academic journals and will likely be presented at academic conferences.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

KdB, RI, and DM were involved in conceptualization and development of the methodology. KdB and RI wrote the original draft. DM, JLM, and MN contributed to reviewing and editing drafts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic analyses and Meta-Analyses) checklist.
[PDF File (Adobe PDF File), 133 KB - resprot_v13i1e54966_app1.pdf]

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Abbreviations

AI: artificial intelligence
AUC: area under the receiver operating curve
PICOT: participant, intervention, comparator, outcomes and time
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

The Relationship Between Self-Compassion and Resilience in the General Population: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Resilience can protect individuals from the negative impact of adversity, facilitating a swift recovery. The exploration of protective factors contributing to resilience has been a central focus of research. Self-compassion, a positive psychological construct that involves treating oneself with kindness, holds the potential to bolster resilience. Although several studies have indicated an association between self-compassion and resilience, there is a lack of systematic reviews and meta-analyses examining this relationship and the potential moderators and mechanisms.

Objective: This study aimed to systematically review the literature on the relationship between self-compassion and resilience in the general population, perform a meta-analysis to quantify the effect size of their association, and explore potential moderators (eg, age, gender, culture, and health status) and mediators.

Methods: We will search the Web of Science, PsycINFO, MEDLINE, Scopus, CINAHL, and CNKI databases for peer-reviewed studies (including observational and experimental studies) that examined the relationship between self-compassion and resilience, with no language restrictions. There are no restrictions regarding participants' age, gender, culture, or health status. Qualitative studies, conference abstracts, review articles, case reports, and editorials will be excluded. Two reviewers (XL and JH) will independently screen the literature, extract data, and assess the quality of the eligible studies. If possible, the pooled effect size between self-compassion and resilience will be meta-analyzed using a random-effect model. Meta-regression and subgroup analysis will be conducted to examine the moderating roles of age, gender, culture, health status, and other potential moderators. The characteristics and main findings of eligible studies will be summarized in tables and narrative descriptions. Results from the meta-analysis, meta-regression, and subgroup analysis will be presented quantitatively.

Results: We registered our protocol with PROSPERO, conducted the search, and initiated the screening in April 2024. We expect to start data analysis in October 2024 and finalize the review by March 2025.

Conclusions: The systematic review and meta-analysis will provide evidence on the protective role of self-compassion in resilience under adversity. Our investigation into potential moderators will highlight the contexts and groups where the benefits of self-compassion can be maximized. The findings are expected to provide valuable insights for health care professionals and stakeholders, informing the development of interventions aimed at enhancing resilience by fostering self-compassion.

Trial Registration: PROSPERO CRD42024534390; https://tinyurl.com/3j3rmcja

International Registered Report Identifier (IRRID): PRR1-10.2196/60154

(JMIR Res Protoc 2024;13:e60154) doi:10.2196/60154

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KEYWORDS

self-compassion; resilience; resiliency; adversity; compassion; coping; coping styles; health status; meta-analysis; meta-regression

Introduction

Background

Individuals in the modern era face a multitude of adversities that can negatively impact their mental well-being, physical health, and social functioning [1-4]. Such adverse life events may contribute to the development of stress-related disorders, including anxiety, depression, and posttraumatic stress disorders [5], and can increase the risk of substance use, eating disorders, and internet addiction [6]. In addition, prolonged activation of the stress response system due to adversity can increase the risk of cardiovascular diseases [7]. However, not all individuals experiencing adversity exhibit negative outcomes. Some individuals possess the capacity to maintain their health or recover swiftly when confronted with adversity, effectively demonstrating resilience in such challenging circumstances. Promoting resilience is vital to prevent stress-related disorders by prioritizing the cultivation of personal strengths [5]. This approach can benefit individuals across different age groups; for instance, it can help prevent children and adolescents from internalizing problems amid interpersonal tensions and academic pressures [8,9], as well as mitigate work-related burnout in adults [10,11]. Therefore, enhancing resilience could be a promising strategy to combat stress-related disorders and facilitate well-being despite pervasive stressors.

Resilience can be conceptualized and operationalized in various ways, with no consensus yet reached among researchers. A total of 3 common approaches are applied to define resilience, including the trait-oriented, process-oriented, and outcome-oriented perspectives [12,13]. Resilience can be defined as a stable trait or ability to recover from adversity; as a dynamic process during which an individual deploys internal and external resources to maintain well-being in adversity; or as adaptive outcomes despite adversity, such as maintained psychological well-being and the absence of psychopathology. Accordingly, as a trait, resilience can be measured using psychometric scales [14]; as a process, it could be modeled as an adaptive trajectory following adversity [15]; and as outcomes, it could be evaluated through measures of mental or physical health accounting for stressor loads [5]. To accommodate various approaches, we define resilient individuals as those possessing the capacity to leverage personal, social, and environmental resources to cope with stressors, thereby facilitating adaptive responses and health outcomes during and after adversity [5,13].

Since the inception of resilience research, considerable attention has been devoted to identifying protective factors that may enhance resilience. One such potential protective factor is self-compassion [16]. Self-compassion refers to treating oneself with warmth and kindness in the face of failures, personal inadequacies, or adversities [17]. According to the self-compassion framework developed by Neff [18], self-compassion contains six components distributed across three dimensions, which are (1) self-kindness versus self-judgment, (2) common humanity versus isolation, and (3) mindfulness versus over-identification. Self-kindness refers to treating oneself with understanding, warmth, and kindness, instead of judging oneself harshly. Common humanity involves recognizing suffering as shared experiences in human beings, rather than perceiving it as isolating and unique to oneself. Mindfulness involves developing an awareness of one's pain and approaching it with a balanced perspective, thereby avoiding excessive immersion in or over-identification with negative emotions or experiences. Higher levels of self-kindness, common humanity, and mindfulness, and reduced levels of self-judgment, isolation, and over-identification, jointly contribute to a self-compassionate state of mind.

Self-compassion has been proposed to be a potential resilience factor in light of its positive roles in promoting mental health and aiding in the management of stressful situations [19]. Research indicates that self-compassion is positively correlated with psychological well-being and the use of adaptive coping strategies [20,21] while being negatively associated with detrimental symptoms, such as rumination, stress, depression, and anxiety [22]. Furthermore, self-compassion appears to be particularly beneficial during stressful events [23,24]. Evidence suggests that self-compassion could buffer the impact of perceived stress on depression, anxiety, and negative affect up to 6 months later [25], and reduce the negative effect of poor physical health on psychological health [23]. Collectively, these findings indicate that self-compassion could possibly promote resilience under stressful life events.

Preliminary evidence has supported this claim by demonstrating positive correlations between self-compassion and resilience in various populations, including adolescents, college students, and adults [26-28]. Moreover, Gilbert's [29] affect-regulation model could offer an evolutionary perspective to understand the role of self-compassion as a protective resilience factor. According to this model, self-compassion originates from the safeness system, an evolved mechanism that fosters affiliative affects and a sense of calmness. The safeness system has the capacity to downregulate the threat system, which is hypothesized to activate in potentially threatening situations and elicit arousal responses [29,30]. Gilbert's [29] theory suggests that self-compassion could mitigate threat-related reactions and induce soothing feelings in stressful situations, thereby promoting resilient adaptation and recovery from adversity.

Potential pathways through which self-compassion is linked to resilience may involve emotion regulation and stress coping [20,31]. First, self-compassion has been shown to reduce negative emotions and enhance positive emotions [21], indicating its potential effectiveness as an emotion regulation strategy. A systematic review identified emotion regulation as a mechanism through which self-compassion contributes to mental health [31]. Second, as suggested in Gilbert's [29] model, self-compassion may mitigate stress-related reactions, and promote adaptive coping strategies [20,29]. Biological evidence

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also suggested that self-compassion could reduce stress-related reactions, as indicated by lower levels of salivary alpha-amylase [32], reduced daily cortisol levels, and baseline inflammation [33,34].

The association between self-compassion and resilience may differ across different demographic groups, taking into account characteristics such as age, gender, culture, and health status. Some evidence suggests that self-compassion has a more pronounced effect on well-being as individuals age [35], is more effective in reducing rumination in adult women compared with men [36], and has a greater impact on psychological health in adults with poorer health status [23]. In addition, a cross-cultural study found that self-compassion was a stronger predictor of life satisfaction in Taiwan than in Thailand, indicating a moderating role of cultural backgrounds such as Confucianism and Buddhism [37].

To date, one scoping review has provided an initial overview of the association between self-compassion and resilience in work situations [19]. However, the nonsystematic nature of the search, the practice-oriented focus, and the specific context of this review have limited its ability to comprehensively investigate the evidence. It is also crucial to extend this investigation to other populations, such as emerging adults and the retired population, due to the unique challenges they face [19,38]. Furthermore, despite the existence of meta-analyses assessing the link between self-compassion and well-being or psychopathology [21,39], there is still a lack of quantitative synthesis on the effect size between self-compassion and resilience. In addition, the specific associations between different components of self-compassion and resilience have not been systematically explored. Such an analysis is essential to determine the inclusion of self-compassion in resilience-enhancing interventions and to identify which components of self-compassion should be targeted. Finally, there is limited knowledge about how this relationship may vary across different subgroups, such as those defined by age, gender, culture, and health status. Addressing this gap could help identify which groups are most likely to benefit from self-compassion, thereby informing the design of more targeted and effective interventions.

Objectives

The primary aim of the systematic review and meta-analysis is to investigate the relationship between self-compassion and resilience. The relationship between 6 components of self-compassion (ie, self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification) and resilience, and self-compassion and resilience measured with different methods (eg, measured using scales or as health outcomes related to the stressor), will also be investigated. The secondary aim is to explore the moderating effects of age, gender, culture, and health status in the relationship between self-compassion and resilience, along with other potential moderators. Finally, the potential mechanisms between self-compassion and resilience will be investigated.

Methods

Design and Registration

The protocol was developed following the PRISMA-P (Preferred Reporting Systematic Review and Meta-Analysis Protocols) guidelines [40] and the standardized Joanna Briggs Institute approach for conducting systematic reviews of association [41]. The checklist for PRISMA-P can be found in Multimedia Appendix 1. A brief version of this protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO; protocol ID: CRD42024534390).

Ethical Considerations

This study is a systematic review and meta-analysis based on secondary analysis of publicly available data from previously published studies. No new data collection or direct interaction with human participants will be involved. Therefore, ethical approval will not be required for this study.

Eligibility Criteria

We developed the inclusion and exclusion criteria following the PEO (Population, Exposure of interest, and Outcome) framework [41], which is applicable in reviews addressing associations between variables. Inclusion and exclusion criteria are summarized in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Study types
  - Peer-reviewed empirical studies using quantitative methods and full texts that explore the association between self-compassion and resilience
- Population
  - General population
- Exposure
  - Self-compassion assessed using validated scales
- Outcome
  - Resilience measured using validated scales, and self-compassion measured as a moderator between a stressor and health outcomes, or other validated measurements
  - Resilience explicitly stated as the study focus or framework

Exclusion criteria

- Study types
  - Qualitative studies, conference abstracts, review articles, case reports, and editorials
- Population
  - Nonhuman subjects
- Exposure
  - Studies without a validated measure of self-compassion; studies measuring compassion as a broad concept rather than focusing specifically on self-compassion
- Outcome
  - Studies with no validated measurements of resilience
  - Studies that do not explicitly state resilience as the primary focus or framework

Type of Studies

Only peer-reviewed empirical studies using quantitative methods will be included. The study designs will cover observational studies (eg, cross-sectional surveys and longitudinal studies) that investigated the relationship between self-compassion and resilience, and experimental studies involving the manipulation of self-compassion levels. Experimental studies will be synthesized separately to examine the causal relationship between self-compassion and resilience. Qualitative studies, conference abstracts, review articles, case reports, and editorials will be excluded. No restrictions will be applied regarding the language of the studies.

Population

We will explore the general population, including individuals of different ages (including children, adolescents, youth, and adults), genders, cultures, and health statuses. Studies involving nonhuman subjects will be excluded.

Exposure of Interest

The exposure of interest in this study is self-compassion. The eligible studies should adopt a validated measure of self-compassion, such as the Self-Compassion Scale [18], its short version [42], or youth version [43], and may include measurements of its components (eg, self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification). Experimental studies manipulating levels of self-compassion should include manipulation checks using validated scales, such as the State Self-Compassion Scale [44]. Randomized controlled trials (RCTs) will be eligible for inclusion if the interventions are specifically designed to target self-compassion, such as the Mindful Self-Compassion intervention [45]. For studies in which compassion is a key variable, data specifically relating to compassion directed toward oneself, or self-compassion, should be reported. For instance, if the Compassionate Engagement and Action Scales [46,47] were used, the study should include data on the self-compassion subscale. Studies that discuss compassion solely as a broad concept without a focus on self-compassion will be excluded.

Outcome

This review will focus on resilience as the primary outcome. We will not limit the definitions or measurements of resilience and will include studies explicitly indicating resilience as a study focus and using validated measurements to assess resilience, such as using resilience scales (eg, the

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Connor-Davison Resilience Scale [47], the Resilience Scale for Adults [48], Resilience Scale [49], and the Brief Resilience Scale [14]). It is noteworthy that 1 common method to assess resilience is to examine health outcomes related to specific stressful events or stressor loads [12,15]. In this context, the role of self-compassion in promoting resilience may be observed through its moderating effect on the adverse effect of stressful events on health outcomes, even if resilience is not directly measured. We will include studies that use this approach to measure self-compassion as a resilience factor but will exclude those that apply this approach without explicitly focusing on resilience.

Search Strategy

We will perform a systematic literature search in electronic databases, including Web of Science Core Collection (Clarivate), PsycINFO (Ovid), MEDLINE (Ovid), Scopus, CINAHL (EBSCO), CNKI (Chinese database). No filters will be used during the search stage. Search strings will encompass 2 categories, which are (1) self-compassion, and (2) resilience. For self-compassion, the search terms could be "self-compassion* OR (compassion near/5 (self OR oneself))." For resilience, the search terms could be "resilient*." The Boolean operator "AND" will be applied between (1) and (2). The detailed search strategies can be found in Multimedia Appendix 2. Furthermore, we will complement the search by screening similar articles (eg, those recommended by PubMed) and using backward- and forward-chain searching using the top 10 relevant studies to identify any overlooked literature.

Screening Procedure

Abstract and title screening and full-text screening will be conducted in Covidence, which is a web-based systematic review tool. All search results will be imported into Covidence and deduplicated automatically. The titles and abstracts will be screened independently by 2 reviewers (XL and JH) to evaluate their initial eligibility. The full text of a publication will be retrieved if at least 1 of the reviewers deems it potentially eligible. Following this, 2 reviewers will independently screen the full text according to the eligibility criteria and note down the exclusion reasons. Any disagreement in the screening process will be resolved through discussions between 2 reviewers, and consultation from a senior researcher (GZ). Cohen κ will be calculated to assess the consistency between the 2 reviewers. A flowchart will be drawn to demonstrate the process of screening according to PRISMA [40].

Data Extraction

A total of 2 reviewers (XL and HX) will independently extract information from the eligible literature in Covidence using a standardized information extraction form. The form will be developed following the PRISMA guideline and revised by piloting on the first few literature. The extracted information will include study characteristics (ie, author and year, title, journal, country, study design, and relevant study aim), population information (ie, demographic information, health status, age range, and mean, and gender proportion), exposure of interest (ie, measurement of self-compassion and its Cronbach α, unadjusted and adjusted effect size, CI and *P* value, and confounders), outcome (measurement of resilience and its Cronbach α, definition, and domain of resilience), main findings, and potential moderators and mediators. In addition, if the literature reported an RCT study, the intervention type, timing, and duration will be extracted. If there are missing data necessary for effect size calculation or quality assessment, the authors will be contacted up to 3 times within a month to request the information.

Risk of Bias Assessment

The risk of bias of all individual studies and overall evidence will be assessed independently by 2 reviewers (XL and HX). Cohen κ will be calculated to evaluate the interrater reliability. Any discrepancy will be addressed through discussions between 2 reviewers and consultation from a senior reviewer (GZ). Standardized critical appraisal checklists developed by the Joanna Briggs Institute will be applied to evaluate the methodological quality of each study [50]. Different checklists will be adopted based on study design, covering observational study (ie, cross-sectional and longitudinal study), quasi-experimental study, experimental study, or RCT study. The appraisal of observational studies will take into account selection bias, information bias, and confounding, while the appraisal of experimental or quasi-experimental studies will consider selection bias, performance bias, attrition bias, detection bias, and reporting bias [51]. The quality of each study will be rated as high, low, or unclear in each domain. Exclusion will not be implemented based on study quality, but the appraisal outcome will be incorporated in the sensitivity analysis (by omitting studies rated as high risk of bias) to assess the influence of risk of bias on results.

The overall publication bias of evidence in the systematic review will be assessed by drawing a funnel plot and conducting sensitivity analyses using publication bias tests if there are at least 10 studies [52,53]. If the publication bias is identified, the trim-and-fill method will be used to compensate for it [54].

The overall certainty of evidence will be assessed using the GRADE (Grading of Recommendation Assessment, Development and Evaluation) [55]. The GRADE assesses the overall certainty of evidence using 5 indices: risk of bias, inconsistency, indirectness, imprecision, and publication bias [55]. The quality of the evidence will be categorized into 4 degrees: high, moderate, low, or very low.

Data Synthesis

First, a narrative synthesis will be reported, showing study characteristics, such as year of publication, country, participants and sample size, and study design. Studies with similar study designs and measurement of the outcome (ie, resilience) will be grouped together and summarized in tables. The potential moderators and mechanisms between self-compassion and resilience will be summarized narratively.

A meta-analysis will be conducted on relatively homogeneous studies stratified by study designs and measures (eg, by using scales or calculating moderating effects), if there are at least 5 studies in each analysis [56]. We will assess the heterogeneity of studies in each analysis using I^2 statistic, with a value of larger than 75% indicating a considerable heterogeneity [57].

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Due to the broad populations that are eligible for inclusion, heterogeneity is assumed to exist. Therefore, to account for between-study variance, we will apply a random-effect meta-analysis to calculate the pooled effect sizes (ie, correlation coefficients for observational studies, and Cohen *d* for experimental studies) between self-compassion and resilience. The average connection between each component of self-compassion and resilience will also be calculated for studies providing necessary data. The Cronbach α will be used to correct the effect sizes, accounting for measurement unreliability. A forest plot will be drawn to illustrate the confidence interval of the relationship of interest in each study.

Furthermore, subgroup analyses and meta-regression will be conducted to identify potential moderators in this relationship and to address heterogeneity in the evidence. Subgroup analyses will be stratified by age groups (adolescents, young adults, and older adults), gender (women vs men), cultural backgrounds (eg, cultures influenced by Buddhism vs Confucianism; Western vs Eastern cultures), and health status (clinical vs nonclinical populations). In addition, we will compare effect sizes across studies with different study designs and varying methodological quality. A meta-regression will be used to further investigate potential moderators, including age, gender proportion, culture, health status, and risk of bias. As for the potential mediators, if there are multiple studies investigating the same mediator, we will use the meta-analytical structural equation modeling method to synthesize the mediation effect quantitatively [58]. All the statistical analyses will be conducted in R (R Core Team, version 4.2.0), using packages such as metaphor [59] or meta [60].

We will document the search and screening process using the PRISMA flowchart and present the characteristics and main findings of eligible studies through tables and narrative descriptions. The results obtained from meta-analysis, meta-regression, and subgroup analysis will be reported in a quantitative manner.

Results

We registered our protocol with PROSPERO, conducted the search, and initiated the screening in April 2024. We expect to start data analysis in October 2024 and finalize the review by March 2025.

Discussion

To the best of our knowledge, this study will be the first systematic review and meta-analysis to comprehensively examine the association between self-compassion (overall and its components) and resilience in the general population. In addition, it aims to explore the moderating influences of age, gender, cultural background, and health status, as well as potential mediators in this relationship. Given the established role of self-compassion in coping with adversity, we anticipate finding a positive association between self-compassion and resilience, along with insights into the relevant moderators and mediators.

Enhancing resilience in the general population is crucial for maintaining psychological and physical well-being amidst diverse stressors and adversities [61,62]. Resilience-focused interventions targeting children and adolescents have been effective in reducing internalizing symptoms, such as anxiety and depressive symptoms [8]. By strengthening their ability to cope with adversity, such as experiences of maltreatment, these interventions can help reduce the intergenerational transmission of depression and provide long-term benefits throughout their lives [63]. Similarly, enhancing resilience in older adults has pronounced effects in promoting successful aging, longevity, and reducing depression [64].

Although there are valuable studies aiming to address the associations between adversity, or risk factors and resilience [65,66], identifying modifiable resilience factors like self-compassion and understanding the underlying mechanisms could offer insights into preventing stress-related disorders in challenging situations before they develop. Considering the conducive role of self-compassion on well-being, coping, and reducing psychopathological symptoms in adversity, it could be a protective factor to promote resilience [16,20].

To date, although there is one scoping review exploring their relationship in work contexts [19] and a chapter providing a narrative overview of this relationship [53,67], a systematic and quantitative examination of this association has not yet been conducted. The absence of such a synthesis could lead to insufficient evidence supporting the targeted use of self-compassion as an intervention for enhancing resilience, as well as an unclear understanding of its potency and the specific roles of its components. Specifically, discerning which component has a stronger connection with resilience and in which group the benefits of self-compassion are more pronounced could inform the design of targeted interventions, maximizing effectiveness and efficiency. The findings of this systematic review and meta-analysis will be applied in practice by disseminating results and insights on intervention design to health care professionals and stakeholders.

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We would like to express our gratitude to Carolyn Smith, an outreach librarian from the University of Oxford, for her assistance with the search strategies, inclusion and exclusion criteria. XL would like to express appreciation for the scholarship and support provided by the Institute of Population Research and Office of International Relations at Peking University, for the exchange program with the University of Oxford.

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Data Availability

The datasets generated and analyzed during the systematic review and meta-analysis will be available in the Open Science Framework repository.

Authors' Contributions

XL, the guarantor of the study, conceived the study idea and design and drafted the protocol. MAM, TDC, and GZ contributed to the critical revision of the draft. All authors contributed to developing the eligibility criteria, search terms, strategies for information extraction, and data analysis. All authors have read and approved the protocol before submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 28 KB - resprot_v13i1e60154_app1.docx]

Multimedia Appendix 2
Search strategies for electronic databases.
[DOCX File , 16 KB - resprot_v13i1e60154_app2.docx]

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Abbreviations

PEO: Population, Exposure of interest, and Outcome
PRISMA: Preferred Reporting Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
GRADE: Grading of Recommendation Assessment, Development and Evaluation

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Protocol

Global and Regional Prevalence of Domestic Violence During the COVID-19 Pandemic and Its Determinants: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Domestic violence is one of the most significant global public health priorities. This social problem could be accelerated by global catastrophes such as the COVID-19 pandemic. The structural changes due to the imposition of health measures, combined with personal and social problems, may worsen the situation.

Objective: This study aims to investigate the global and regional prevalence of domestic violence during the COVID-19 pandemic and its determinants.

Methods: We will perform a comprehensive review of the literature in PubMed, PsycINFO, Embase, Cochrane COVID-19 Register, and Applied Social Sciences Index and Abstracts, up to July 2024. This review will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines. Observational studies will be considered eligible if they have a population-based design, report the number of cases or prevalence of domestic violence during the COVID-19 pandemic, and report potential determinants. Studies in languages other than English, those with unclear data, case reports, conference proceedings, reviews, and letters will be excluded. To assess the methodological quality, a standardized critical appraisal checklist for studies reporting prevalence data will be used. A robust Bayesian approach will be applied using the STATA software package (version 14; STATA Inc) and JASP 0.19.1 (GNU Affero General Public License [GNU AGPL]) software.

Results: The search and screening for the systematic literature review are anticipated to be finished in October 2024. Data extraction, quality appraisal, and subsequent data synthesis will begin in November 2024. The review is expected to be completed by April 2025, and the study results will be published in 2025.

Conclusions: This systematic review and meta-analysis will address significant gaps in understanding the pandemic's impact on domestic violence, providing a comprehensive assessment of its prevalence and contributing factors. Despite some limitations, the study incorporates diverse data sources and vulnerable groups to offer a detailed and accurate picture. The findings will inform targeted interventions and policy responses to mitigate the impact of future global crises on domestic violence rates.

Trial Registration: PROSPERO CRD42022351634; https://tinyurl.com/yth37jkx

International Registered Report Identifier (IRRID): PRR1-10.2196/60963

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(JMIR Res Protoc 2024;13:e60963) doi:10.2196/60963

KEYWORDS

COVID-19; domestic violence; systematic review and meta-analysis; lockdowns; pandemic effects; intimate partner violence; elder abuse; child abuse; vulnerable populations

Introduction

Domestic violence (DV) is one of the most important global public health priorities. It can include physical, sexual, psychological, and financial dimensions, as well as controlling or coercive actions and behaviors by one or more members against others of a household [1]. Usually, women are survivors of DV by their intimate partners [2]. It is showed that 1 in 3 women will be a survivor of physical or sexual violence during her life [3]. Despite efforts to decrease it, DV still occurs worldwide and may be amplified by factors such as natural disasters and socioeconomic crises [4-7].

The COVID-19 pandemic, as a global health crisis, brought the greatest challenges in all aspects of human life. It has caused structural changes in the category of human communication and has resulted in many adverse psychosocial effects [8-10]. Evidence shows that the levels of DV increased globally as the COVID-19 pandemic escalated. According to the World Health Organization (WHO) Eastern Mediterranean Region (EMRO), the prevalence of violence against women in the region is the second highest in the world at 37% [11]. The National Commission on COVID-19 and Criminal Justice also reported that DV incidents in the United States increased by 8.1% after the enforcement of the lockdown [12].

Factors such as quarantine, staying at home, remote work, and many other imposed conditions, in addition to personal and social crises, put pressure on people beyond the threshold of tolerance, which may exacerbate DV [13-19]. DV during the COVID-19 pandemic remains as an important health concern and a serious human rights violation, and addressing it is still a global issue. In addition, identifying critical gaps of knowledge to develop response strategies, principles, and recommendations for controlling DV during long- and short-term catastrophic events like COVID-19 is essential for public health emergencies [20-23]. There are some review studies that addressed this issue [24-29]. However, our study would be the first to provide pooled estimates of global and regional prevalence of DV during COVID-19 and measure the effect of determinants using strong statistical methodology.

The purpose of this systematic review and meta-analysis is to investigate the global and regional prevalence of DV during the COVID-19 pandemic and its associated determinants.

Methods

Overview

This study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines. The study protocol was followed PRISMA-Protocol (PRISMA-P; Multimedia Appendix 1). The protocol of this study was registered in PROSPERO (CRD42022351634)

The review question was framed based on the PICO (Population, Intervention, Comparison, and Outcomes) statement as follows:

- P: Populations affected by COVID-19, as defined by the studies, will be included. There will be no limits in terms of gender or ethnicity.
- I: This review will consider studies that report on the prevalence of DV during the COVID-19 pandemic.
- C: This study does not include a comparison.
- O: The primary outcome of study is pooled prevalence of DV during COVID-19. This includes physical violence, sexual, psychological, controlling behavior violence, and economic violence.

As secondary outcomes, all factors and determinant associated with DV will be extracted. The determinants can be but are not limited to age, gender, educational status, decision-making power, social support, wealth index, and unemployment. In cases of missing data or articles with no available full text, we will contact the corresponding author 3 times. Articles will be excluded if no response is received.

Eligibility Criteria

Observational studies will be considered eligible if they have a population-based design, report the number of cases or prevalence of DV during the COVID-19 pandemic, and report potential determinants. Studies in languages other than English, those with unclear data, case reports, conference proceedings, reviews, and letters will be excluded.

Search Strategy

We will conduct a comprehensive literature review using databases such as PubMed (including Medline), Embase, PsycINFO, Google Scholar, Cochrane COVID-19 register, and Applied Social Sciences Index and Abstracts, up to July 2024. In addition, we will manually search the reference lists of selected studies and other relevant reviews to maximize the identification of eligible studies and consider results from gray literature.

Search String

To identify relevant studies for our systematic review and meta-analysis, we will develop and execute a comprehensive search strategy across multiple electronic databases. Our search will incorporate Medical Subject Headings (MeSH), keywords, and specific search terms as outlined in Table 1. The search strategy will be tailored to each database to ensure optimal retrieval of relevant articles. The search strategy will be adapted to align with the database's indexing and search capabilities. Specifically, in PubMed we will use MeSH terms in combination with keywords. The search string will incorporate MeSH terms and keywords to capture the breadth of literature related to DV during the COVID-19 pandemic ("Domestic Violence"[MeSH] OR "Spouse Abuse"[MeSH] OR "Elder Abuse"[MeSH] OR "Child Abuse, Sexual"[MeSH] OR "Intimate Partner

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Violence"[MeSH] OR "Physical Abuse"[MeSH]) AND ("child*" OR "Infant" OR "adolescen*" OR "young people" OR "adults" OR "Women" OR "Frail Elderly" OR "Aged") AND ("Coronavirus" OR "COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus") AND ("prevalence" OR "incidence" OR "rate" OR "diagnosis" OR "disease burden" OR "epidemiology" OR "frequency" OR "determinants" OR "predictors" OR "correlates" OR "risk factors" OR "protective factors"). For other databases, keywords and subject headings relevant to each database's search functionality will be used.

Table 1. Keywords and search strategy.

Search query	Search topic	Search keywords (titles, abstracts, general keywords, and subject headings)
1	Condition or outcome of interest	"Domestic Violence" OR "Spouse Abuse" OR "Elder Abuse" OR "Child Abuse, Sexual" OR "Child Abuse" OR "Intimate Partner Violence" OR "intimate terrorism" OR "coercive controlling violence" OR "Physical Abuse" OR "Homicide" OR "verbal abuse" OR "sexual abuse" OR "Sexual assault" OR "physical assault" OR "verbal assault" OR "Family violence" OR "Intimate Partner Aggression" OR "intrepersonal violence" OR "partner violence" OR "Domestic harassment"
2	Population	No limitation
3	Exposure or context	"Coronavirus" OR "COVID-19" OR "COVID19" OR "SARS-CoV-2" OR "2019 novel coronavirus" OR "2019-nCoV" OR pandemia OR "global pandemic" OR lockdown
4	Phenomenon	No limitation
Final search query	Intersection of 4 topics	1 AND 3

Study Selection and Data Extraction

The titles, abstracts, and full texts of selected studies will be screened independently by 2 authors based on the eligibility criteria. The following data will be extracted from eligible studies: the first author's name, publication year, study design, sample size, characteristics of population, determinants, and outcome measurements. The accuracy of data before the meta-analysis will be assessed by double-checking the data extraction process to ensure no bias in the data extraction and data entry. Any discrepancies will be resolved through discussion with the senior review author.

Assessment of Methodological Quality

We will use the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [30] for Prevalence Studies, which includes criteria for evaluating aspects such as study design, sample selection, measurement methods, and statistical analysis. Two independent reviewers will conduct the methodological quality assessment of each included study. Each reviewer will assess the studies separately to ensure a thorough evaluation. Any disagreements between the reviewers regarding the appraisal of study quality will be resolved through discussion. If consensus cannot be reached, a third reviewer, who is not involved in the initial assessment, will be consulted to adjudicate and provide a final decision. The results of the quality assessments will be documented and used to inform the interpretation of the review's findings. Studies will be classified based on their methodological quality to help in the synthesis and analysis of data.

Statistical Analysis

The STATA software package (version 14; STATA Inc) and JASP 0.19.1 (GNU Affero General Public License [GNU AGPL]) software will be used to conduct statistical analysis. Heterogeneity will be evaluated using the chi-square test and I^2 index. Publication bias will be assessed using funnel plots and statistical tests. In case of significant results, the robust Bayesian approach will be applied. The random effect model will be used for the estimation of the pooled prevalence via the meta-prop method with a pooled estimate after Freeman-Tukey double arcsine transformation to stabilize the variances. Forest plots for each outcome and by any extracted subgroups such as gender, regions, type of DV, educational level, etc, will be illustrated as well. Meta-regression analysis will be run to assess the effect of extracted determinants as the potential sources of heterogeneity. Sensitivity analysis will be applied to find influential studies in case.

Ethical Considerations

The protocol of this study was registered in PROSPERO (CRD42022351634). This is a systematic review of published papers, which does not require informed consent. In addition, this study was considered by the ethics committee of the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (ethics code: IR.USWR.REC.1401.140).

Results

The search and screening for the systematic literature review are anticipated to be finished in October 2024. Data extraction, quality appraisal, and subsequent data synthesis will begin in November 2024. The review is expected to be completed by April 2025, and the study results will be published in 2025.

Discussion

Principal Findings

The results of this systematic review and meta-analysis will estimate the prevalence of DV and its determinant in the COVID-19 pandemic and is poised to address critical gaps in the existing literature. It is anticipated that the study will reveal a significant increase in DV rates both globally and regionally, driven by pandemic-related conditions such as lockdowns, economic stress, and restricted access to support services. The analysis is expected to identify critical determinants contributing to this rise, including socioeconomic status, household size, and

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preexisting conditions of abuse. By illuminating these factors, the study seeks to inform effective interventions and policy responses to mitigate DV in the context of ongoing and future public health crises.

The occurrence of a natural disaster typically leads to an increased risk of social health problems [31]. Disease outbreaks such as COVID-19 pandemic necessitate emergency prevention and control measures in the community; however, they also result in psychosocial side effects [29,32-34].

Generally, there are several potential factors associated with DV, including individual traits such as age; ethnicity; previous history of exposure or experience of violence; psychological disorders such as depression, anxiety, substance abuse, and suicidality; as well as sociocultural factors that foster a culture of violence against women and social norms supporting male authority and control over women [24,35,36].

Evidence showed that COVID-19 preventive interventions such as physical distancing, lockdown, and social isolation were also associated with psychiatric problems, including anxiety, depression, suicidal thoughts, and DV [25,26,37-39]. A systematic review study that included 18 studies showed an increase in reported incidents of DV due to COVID-19–related restrictions, such as stay-at-home and lockdown orders [12]. Another integrative review that included 38 studies also indicated some factors increasing women's vulnerabilities to violence, such as social distancing and lockdown [40]. It seems that COVID-19 preventive and controlling policies as a mediator factor can exacerbate potential related factors, leading to an escalation of violence and abusive behaviors. Therefore, results of studying the dynamics of this violent behavior, its associated factors, and COVID-19 measures can be extrapolated to global disaster situations [41].

In addition, Kifle et al [42], in a systematic review of 14 observational studies, estimated the prevalence of intimate partner violence on women during the COVID-19 pandemic. They reported that nearly 1 in 3 women experienced intimate partner violence during the COVID-19 pandemic. Subgroup analysis based on region showed that the highest prevalence of intimate partner violence was in resource-limited regions (33%). All forms of intimate partner violence (physical, sexual, emotional, and economic) were prevalent.

However, some limitation in those studies, such as narrow inclusion criteria, often focusing exclusively on women, thereby neglecting other vulnerable groups such as older individuals. Furthermore, important databases such as Embase were not included in some available studies, potentially limiting the scope and robustness of their findings. In addition, most of them did not report the determinants and risk factors for DV.

Crisis management organizations, health care providers, and policy makers should be aware of the potential increase in rate of DV during state of emergency. They should provide suitable health care facilities such as local referral pathways of services, support and counseling services, protection services, hotlines, and shelters. Humanitarian and nongovernment organizations could also step up to provide necessary services to support DV survivors during crises.

The strength of our study lies, first, in the breadth of evidence it produces. Bayesian meta-analysis will be applied to address potential publication bias, a critical mythological concern in prevalence meta-analysis [43,44]. Second, we will identify significant determinants through a meta-regression approach. Additionally, we will ensure high methodological quality by adhering to the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guideline. However, our study has limitations. DV is widely underreported worldwide, and obstacles to data collection during COVID-19 intensify this issue [45,46]. One limitation regarding the control of violence could be the lack of accurate data and evidence. Therefore, response organizations and authorities need to include support services to facilitate the safe collection of data on reported cases of DV in their crisis plans. Studies included in the meta-analysis may use different definitions and methodologies to assess DV, which could contribute to heterogeneity and affect the reliability of pooled prevalence estimates. DV prevalence and its determinants may vary significantly across different global regions and cultural contexts. Addressing this heterogeneity adequately in the meta-analysis could be challenging but crucial for accurate regional estimates. Access to the full text of the articles may be restricted, which will be resolved by corresponding with authors. In addition, strong heterogeneity among studies may exist, which will be addressed using random effect models and appropriate subgroup analyses.

Conclusion

This systematic review and meta-analysis will address significant gaps in our understanding of the pandemic's impact on DV. Although there are some limitations, prior research has highlighted the increase in DV incidents linked to COVID-19 restrictions. This study will provide a comprehensive assessment and analysis, encompassing a broader range of vulnerable groups and incorporating diverse data sources. By doing so, it seeks to offer a more detailed and accurate picture of the prevalence and factors contributing to DV during the pandemic. The findings will be crucial in informing targeted interventions, shaping policy responses, and ultimately mitigating the impact of future global crises on DV rates.

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Authors' Contributions

RB-Y conceived the idea. The protocol is written by RB-Y, SB-G, AB, FNN and PR. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflicts of Interest

None declared

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.
[PDF File (Adobe PDF File), 135 KB - resprot_v13i1e60963_app1.pdf]

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Abbreviations

AMSTAR: Assessing the Methodological Quality of Systematic Reviews
DV: domestic violence
EMRO: Eastern Mediterranean Region
JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PICO: Population, Intervention, Comparison, and Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
WHO: World Health Organization

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Protocol

Barriers and Facilitators of International Health Care Students' Well-Being in Higher Education: Protocol for a Systematic Integrative Review

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Abstract

Background: International health care students encounter unique hurdles as they pursue education in foreign countries. These challenges, stemming from adjustment to new cultural environments and stressful academic programs, significantly impact their well-being. Understanding the barriers and facilitators experienced by international health care students is crucial for ensuring their successful integration into academic and professional spheres. Most existing reviews focus on specific populations or disciplines, thus limiting their generalizability.

Objective: This systematic integrative review aims to provide a comprehensive understanding of barriers and facilitators of international health care students' well-being in higher education.

Methods: The protocol follows the Joanna Briggs Institute's guidance for a mixed methods systematic review. The main information sources will include PubMed, Scopus, Web of Science, and EBSCOhost, supplemented with manual reference search and citation tracking using Google Scholar. The study selection will be done independently by 2 reviewers based on predetermined eligibility criteria. The study population will consist of international higher education students enrolled in human health–related disciplines including medicine, pharmacy, nursing, and allied health care fields. Qualitative and quantitative data relating to barriers and facilitators of international health care students' well-being will be extracted using a customized data extraction template in Covidence review management software. Quantitative data will be "qualitized" and integrated with qualitative data using a convergent integrated approach, as described in the Joanna Briggs Institute's guidance. The integrated data will then be synthesized using a thematic analysis approach to provide a comprehensive understanding of barriers and facilitators of international health care students' well-being.

Results: The initial literature search yielded 2408 papers from the selected databases. The findings of this review will be presented in a narrative format, supported by visualizations such as tables and diagrams. The review is expected to be completed by December 2024.

Conclusions: This systematic integrative review will identify barriers and facilitators of international health care students' well-being in higher education. The findings could inform the development of targeted interventions and support initiatives in higher education institutions globally, with the ultimate goal of enhancing the well-being as well as the academic and professional success of international health care students.

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Trial Registration: PROSPERO CRD42024372785; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024372785

International Registered Report Identifier (IRRID): PRR1-10.2196/59927

(JMIR Res Protoc 2024;13:e59927) doi:10.2196/59927

KEYWORDS

integrative review; higher education; international students; educational migrants; barriers; facilitators; well-being; mixed methods synthesis; health care students; health care education

Introduction

Background

International health care students face unique compound stressors as they navigate the demands of health care education while adjusting to a new cultural environment [1]. Research indicates that health care students, for example, medical students, report significantly higher rates of depression, anxiety, and burnout compared to the general population [2]. As international students, these challenges are further compounded by the stress of addressing emerging challenges in the transition to culturally new environments [3,4]. Reports show that international students have significantly lower satisfaction with their student experiences, poorer global life satisfaction, less social support, higher rates of mental health issues and various addictions, and are less likely to seek help [5,6]. In addition, international students face persistent language barriers, cultural disparities, different health care systems, a lack of sense of belonging, and potential discrimination [7-10]. Thus, they are often allocated the identity of minority or vulnerable groups [10,11]. The enduring impacts of the COVID-19 pandemic, along with future crises and uncertainties, further threaten their overall well-being [12].

Moreover, poor well-being among international health care students can have profound consequences for patient care in professional settings. Poor well-being may increase the likelihood of burnout or mental health issues, which in turn can heighten the risk of medical errors [13]. This is possibly due to insufficient resilience, weak coping mechanisms during early career development, or a lack of adequate support. These issues can persist over time, leading to suboptimal patient care and professional dissatisfaction in the later stages of their careers [14]. Therefore, prioritizing the well-being of international health care students is crucial not only for their personal welfare but also for maintaining the quality and safety of health care services for patients [15].

The well-being of international health care students is a critical issue that requires comprehensive support systems and targeted interventions. Evidence suggests that some interventions have shown promise in reducing symptoms of depression, anxiety, and burnout among students, such as mindfulness-based programs or peer support programs [16,17]. These interventions not only enhance international health care students' well-being during their academic journey but also equip them with resilience-building tools that benefit their future careers. Understanding barriers and facilitators of international health care students' well-being could inform the development of effective interventions to promote their well-being. By understanding the unique challenges and needs of these students, this review will provide valuable insights that might support the next generation of health care students and in turn, professionals to develop sustainable resilience in their academic journey, future career, and ever-changing social environments. By investigating their barriers and facilitators of well-being, stakeholders will be able to identify areas for improvement within the educational and health care systems and develop culturally sensitive, inclusive interventions to address their unmet needs. Continued research in this field can provide insights for crafting tailored interventions and implementing systemic changes to bolster the well-being of upcoming health care professionals.

Numerous studies and systematic reviews have investigated the well-being of international students in higher education [18-20]. These studies predominantly address the stressors and psychological challenges faced by international students, especially during the COVID-19 pandemic [19]. Findings from these reviews consistently indicate a high prevalence of anxiety, depression, and stress among these student populations globally [18]. Factors such as self-esteem, emotional regulation, and social relationships that significantly influence student well-being [19] have been highlighted. School-based, well-being interventions have shown small to moderate positive effects on students' social-emotional and behavioral adjustments [21]. However, these interventions may not fully address the specific needs and experiences of international students, particularly those in health care settings where stressors may differ.

The majority of reviews focus on specific populations, such as Chinese international students, or specific professions, such as nursing, thus limiting the generalizability of the findings [18]. For example, a scoping review identified common challenges of international nursing students in major host countries as language and communication barriers, cultural barriers, lack of familiarity with the health system, social exclusion, discrimination, financial struggles, and inability to maintain work-life balance [22]. The review also identified coping strategies including support from family and friends, peer support, seeking clarifications, maintenance of home countries' cultural values, and development of language proficiency. There is a need for more reviews that encompass a broader range of international student experiences across different cultural backgrounds and health care disciplines [18,20]. Given the stressful nature of health care education, further exploration in this area is critical to develop targeted support mechanisms [23].

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Objective

This systematic integrative review aims to provide a comprehensive understanding of the barriers and facilitators of international health care students' well-being in higher education.

Review Question

What are the barriers and facilitators of international health care students' well-being in higher education?

Methods

Study Design

To explore the well-being of international health care students, an integrative review approach was selected to address the research objective. This approach is particularly effective for synthesizing diverse types of research, including both experimental and nonexperimental studies [24]. The integrative review method was chosen for the following reasons:

- It is a flexible and iterative method that explores a complex phenomenon [25] from diverse sources with a more holistic approach [26].
- An integrative review is one of the more suitable approaches for identifying barriers and enablers [27,28] and evidence-based practice [24]. This aligns with the review question.

The overall design consulted the Joanna Briggs Institute's guidance for a mixed methods systematic review, using a convergent integrated approach to synthesis and integration of the data [29].

Protocol and Registration

The protocol was registered on May 1, 2024, with PROSPERO (CRD42024372785).

Search Strategy

The search strings for this integrative review were developed in consultation with an experienced university librarian to enhance rigor and trustworthiness [24,30]. The search will use truncation and wildcard techniques to cover spelling variations and address information needs. A search log will be maintained for documentation purposes. Boolean operators will be used to combine the selected terms and formulate search strings based on the research question. The search strings are therefore based on search terms relating to international health care students, barriers and facilitators, and well-being. Search strings will be adjusted based on the specific characteristics of each database. This approach ensures that the search strategy aligns with the nuances and indexing systems of individual databases. We will conduct iterative running and testing before finalizing the search strings. In addition, further studies will be identified by a manual search of references and citation tracking of relevant studies using Google Scholar.

Information Sources

Web of Science and Scopus are widely recognized databases spanning diverse scientific disciplines, frequently used for literature searches [31,32]. PubMed primarily focuses on biomedical and life sciences literature, making it an invaluable resource for health-related topics [33]. Moreover, EBSCOhost functions as an academic search engine, providing an interface to access numerous databases [34]. The databases searched through EBSCOhost in this review include Academic Search Complete; AgeLine; British Education Index; Business Source Complete; CINAHL Complete; eBook Collection (EBSCOhost); ERIC; European Views of the Americas: 1493 to 1750; GreenFILE; Historical Abstracts; Hospitality & Tourism Complete; Library, Information Science & Technology Abstracts; Psychology and Behavioral Sciences Collection; Regional Business News; SocINDEX with Full Text; Teacher Reference Center; UK & Ireland Reference Centre; MLA Directory of Periodicals; MLA International Bibliography; RILM Abstracts of Music Literature; APA PsycArticles; APA PsycInfo; APA PsycBooks; APA PsycExtra; and EconLit.

To supplement the review, a limited number of relevant and high-quality gray literature sources such as websites of the World Health Organization, United Nations, and relevant government agencies will be searched using a combination of terms relating to international health care students, barriers and facilitators, and well-being.

Eligibility Criteria

To minimize the bias and ensure this systematic integrative review is transparent, predetermined inclusion and exclusion criteria will be applied based on Population, Phenomenon of Interest, and Context, as recommended in the Joanna Briggs Institute's guidance for a mixed methods systematic review [29].

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Population: (1) International health care students who move to another country to study in a cross-cultural context; (2) they are formally enrolled as full-time students in higher education institutions within the host countries; and (3) they undertake undergraduate or postgraduate academic health care programs, for example, master's and PhD students
- Phenomenon of interest: Barriers and facilitators of international health care students' well-being
- Context: The context for this review includes higher education institutions where international health care students pursue their studies at a third-level education including universities, colleges, medical schools, nursing schools, pharmacy schools, public health schools, and other relevant third-level educational institutions offering programs in health care–related fields
- Type of literature: (1) Qualitative studies such as interviews, focus groups, ethnographic studies, or qualitative surveys; (2) quantitative studies using surveys, questionnaires, or other quantitative methods; (3) mixed methods studies combining qualitative and quantitative approaches; and (4) peer-reviewed journal papers and gray literature including scientific or government reports, thesis, and conference papers
- Publication language: English
- Time period: No time restriction

Exclusion criteria

- Population: (1) International health care students studying part-time or through distance learning programs; (2) students enrolled in pre–health care or preparatory programs; and (3) health care students who work with animals
- Phenomenon of interest: Studies not relating to the well-being of international health care students
- Context: Postgraduate training solely based in health care institutions such as residency training or internship
- Type of literature: Case reports; editorials; opinion pieces; abstracts only; protocols; reviews; and posters
- Publication language: Non-English
- Time period: No time restriction

Study Selection

All the studies from different databases will be uploaded into Covidence, which allows multiple reviewers to work simultaneously. Covidence will be used to remove duplicates and select eligible studies in 2 steps.

- Step 1 (title and abstract screening): Two reviewers (YX and JOD) will screen the study titles resulting from the finalized search strings. Irrelevant titles and abstracts will be excluded from further consideration.
- Step 2 (full-text screening): Two reviewers (YX and JOD) will conduct a full-text screening of studies selected from title and abstract screening based on the eligibility criteria already discussed.

Conflicts during the study selection will be resolved by mutual consensus. When consensus cannot be reached, a third reviewer (KPF) will be consulted.

Quality Assessment

The Mixed Method Appraisal Tool (McGill University) will be used to appraise the quality of included studies [35]. This tool is chosen because it is suitable for appraising different types of primary studies including randomized controlled trials, observational studies, qualitative studies, and mixed method research. The outcome of the quality assessment will not be used to inform the inclusion of studies but will provide an overview of the methodological quality of the included papers.

Data Extraction

The review will be a data extraction template in Covidence, developed based on the research question, to extract the following data items.

- Study characteristics: Author(s), type of study, year of publication, aim or purpose, study design, setting, sample size, and methods
- Participant characteristics: Demographics, country of origin, health care field of study, host country(s), student profile, gender, and target second language(s)
- Barriers: These refer to obstacles that hinder international health care students from achieving desired outcomes or accessing resources. This review focuses on identifying specific obstacles, difficulties, and limitations experienced by international health care students in pursuing their education in health care–related fields outside their home countries.
- Facilitators: These are elements that ease the path for international health care students to attain their goals such as supportive structures, enabling environments, interventions, services, programs, technologies, strategies, skills, or behaviors that lead to positive outcomes.
- Well-being indicators: According to the Organization for Economic Cooperation and Development, student well-being refers to the psychological, cognitive, social, and physical functioning and capabilities necessary for living a happy and fulfilling life [36].

This review adopts the Organization for Economic Cooperation and Development's Programme for International Student Assessment indicators of well-being framework, examining 4

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key dimensions of international health care students' well-being: psychological, social, cognitive, and physical [37].

Data Transformation and Integration

The extracted quantitative data will be transformed into qualitative data by providing narrative interpretations of the quantitative results to further describe the barriers and facilitators of international health care students' well-being [29]. The transformed quantitative data ("qualitized" data) will then be integrated with the qualitative data to provide a comprehensive understanding of barriers and facilitators of international health care students' well-being using a convergent integrated approach [29].

Data Synthesis

The integrated data from the included studies will be synthesized using a thematic analysis method, which involves coding and categorizing data to identify common themes, patterns, and relationships [29]. A reflexive approach will be adopted for the thematic analysis [37]. This process will be carried out in 3 main stages: coding of primary data, development of descriptive themes, and generation of analytical themes [37]. After familiarizing with the data, coding will be done independently by 2 reviewers (YX and JOD) to identify distinct ideas (codes) in the integrated data using the highlight function of NVivo (Lumivero). Each group of similar codes will be aggregated, and a descriptive theme will be created to capture the meaning of each group by mutual agreement of the 2 reviewers (YX and JOD). Descriptive themes will be developed by comparing and contrasting the codes to identify areas of convergence, divergence, or complementarity. Analytical themes will be generated based on a third-order analytical interpretation of the descriptive themes by all the reviewers and this will go beyond the original data [37]. The generation of analytical themes will be iterative, involving regular discussion among the review team to refine interpretations and ensure coherence.

Ethical Considerations

Ethical clearance is not deemed necessary for this integrative review, as it solely involves the synthesis of existing literature.

Results

The review is expected to be finished by December 2024. Using the search strategy and databases discussed previously, an initial total of 2408 papers were identified, consisting of 427 papers from PubMed, 1125 papers from Scopus, 784 papers from Web of Science, and 72 papers from EBSCOhost (Multimedia Appendix 1). The synthesized findings will be presented thematically, supported by illustrative quotes, tables, or figures to enhance clarity and transparency. The study selection process will be depicted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [38]. The review is expected to be completed by December 2024.

Discussion

Anticipated Findings

This systematic integrative review aims to contribute to a deeper understanding of the factors influencing the well-being of international health care students. The anticipated findings from the synthesis of data extracted from primary studies will include barriers and facilitators of international health care students' well-being. It is expected that the barriers will be structural, systemic, environmental, or personal in nature [9,39,40]. On the other hand, facilitators will highlight factors that contribute to the well-being of international health care students in higher education such as supportive structures and interventions [41].

Strengths and Limitations

This study, to the best of our knowledge, is the first systematic integrative review that focuses on barriers and facilitators of international health care students' well-being in higher education. The integration of both qualitative and quantitative data is also an advantage as it will ensure a holistic and comprehensive coverage of factors influencing the well-being of international health care students [24-27].

Although a systematic integrative review is a rigorous approach, it does have inherent methodological shortcomings that can be challenging to overcome [25]. Combining diverse data sources can lead to complexity and potential bias, affecting the accuracy of the results [25]. To address potential bias, each stage of this review will be conducted by multiple independent reviewers to ensure a balanced assessment. In addition, the inclusion of only studies published in English could potentially lead to the exclusion of relevant studies conducted in other languages. However, we hope that English-language papers will provide sufficient depth and breadth as majority English-speaking countries such as the United States, United Kingdom, Canada, and Australia are the top host destinations of international students [22].

Conclusions

The review will contribute to a deeper understanding of the challenges and support needs of international health care students. The findings may inform the development of appropriate interventions and support systems tailored to the specific needs of international health care students in a manner that supports their overall well-being.

Acknowledgments

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

YX contributed to the manuscript draft, study concept, design, and methodologies. JOD contributed to the study concept and design, and KPF to the editing, methodologies, and design. All authors reviewed and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Initial search result.
[DOCX File , 3269 KB - resprot_v13i1e59927_app1.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Connecting Actors With the Introduction of Mobile Technology in Health Care Practice Placements (4D Project): Protocol for a Mixed Methods Study

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Abstract

Background: The learning process in clinical placements for health care students is a multifaceted endeavor that engages numerous actors and stakeholders, including students, clinical tutors, link teachers, and academic assessors. Successfully navigating this complex process requires the implementation of tasks and mentorships that are synchronized with educational and clinical processes, seamlessly embedded within their respective contexts. Given the escalating number of students and the rising demand for health care services from the general population, it becomes imperative to develop additional tools that support the learning process. These tools aim to simplify day-to-day clinical practice, allowing a concentrated focus on value-based activities. This paper introduces a project funded by the European Commission that involves 5 European countries. The project's objective is to comprehensively outline the entire process of development and ultimately implement mobile technology in practice placements. The project tackles the existing gap by constructing tailored mobile apps designed for students, teachers, tutors, and supervisors within each participating organization. This approach leverages practice-based learning, mobile technology, and technology adoption to enhance the overall educational experience.

Objective: This study aims to introduce mobile technology in clinical practice placements with the goal of facilitating and enhancing practice-based learning. The objective is to improve the overall effectiveness of the process for all stakeholders involved.

Methods: The "4D in the Digitalization of Learning in Practice Placement" (4D Project) will use a mixed methods research design, encompassing 3 distinct study phases: phase 1 (preliminary research), which incorporates focus groups and a scoping review, to define the problem, identify necessities, and analyze contextual factors; phase 2 (collaborative app development), which involves researchers and prospective users working together to cocreate and co-design tailored apps; and phase 3, which involves feasibility testing of these mobile apps within practice settings.

Results: The study's potential impact will primarily focus on improving communication and interaction processes, fostering connections among stakeholders in practice placements, and enhancing the assessment of training needs. The literature review

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and focus groups will play a crucial role in identifying barriers, facilitators, and factors supporting the integration of mobile technology in clinical education. The cocreation process of mobile learning apps will reveal the core values and needs of various stakeholders, including students, teachers, and health care professionals. This process also involves adapting and using mobile apps to meet the specific requirements of practice placements. A pilot study aimed at validating the app will test and assess mobile technology in practice placements. The study will determine results related to usability and design, learning outcomes, student engagement, communication among stakeholders, user behavior, potential issues, and compliance with regulations.

Conclusions: Health care education, encompassing disciplines such as medicine, nursing, midwifery, and others, confronts evolving challenges in clinical training. Essential to addressing these challenges is bridging the gap between health care institutions and academic settings. The introduction of a new digital tool holds promise for empowering health students and mentors in effectively navigating the intricacies of the learning process.

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(JMIR Res Protoc 2024;13:e53284) doi:10.2196/53284

KEYWORDS

practice-based learning; practice placement; technology enhanced learning; mobile learning; co-design; cocreation; higher education; health professionals; health students.

Introduction

Background

Practice-based learning encompasses the educational process in which students acquire knowledge within a service delivery environment tailored to their educational level and competencies. Health profession students, such as nurses, physicians, and physiotherapists, cultivate skills through hands-on experience in various settings. Learning occurs through observation and subsequent participation in clinical tasks.

Conceptually, learners in practice settings acquire "knowledge-in-action" [1] through interaction with experienced professionals, patients/clients, and their peers. For health profession students, practice-based learning provides an opportunity for direct engagement with "real" patients in authentic settings where actual health care is delivered. Health profession students cannot grasp the full complexity of the health care environment until they acquire the specific knowledge, skills, and attitudes that demonstrate competency in their area of practice [2].

The learning process in clinical placements typically involves a diverse array of individuals, including tutors, supervisors, mentors, teachers, and students. Throughout this intricate process, tasks and mentorships must be implemented in a manner that aligns with both educational and clinical processes and is well-embedded in the respective contexts [3].

The learning process, connecting the academic environment with health care centers, encompasses a broad variety of scenarios and contexts. Numerous factors are involved in this complex and challenging practical training for health profession students, affecting both the respective actors and institutions. These factors can result in an inefficient process, causing dissatisfaction and frustration. Much of the effort is directed toward coordinating the involved parties rather than focusing on the learning process itself and its quality.

The interplay between learning and education at the university, along with practical training in placements, constitutes core elements of health care degree programs at universities, such as nursing or medicine [4]. The purpose of education in practice placements is to equip future professionals with the ability to manage their learning, make decisions that enable effective action in their future professional practice, and enhance the quality of care provision [5]. To attain these objectives, practice-based learning becomes indispensable as it necessitates students to scrutinize and assess their patient care, evaluate and integrate scientific evidence, and consistently enhance patient care through ongoing self-evaluation. Students are expected to cultivate skills and habits that enable the practical application of clinical and transversal competencies acquired at the university.

Practice-based learning in health care settings is defined and characterized by several key aspects [6]. These include the contexts in which practices occur [7], their purpose or objective [8], the methods used to assess students [9], the overall commitment within health care degree programs, the practice education model [10-13], and the various actors involved [3,14].

Elements of Practice Placement in Health Care Education

According to Jokelainen et al [15], the 2 fundamental aspects of mentorship in practice placement involve establishing a supportive learning environment and addressing aspects related to the mentorship process itself. Delving into the establishment of learning support environments, 2 elements are identified as facilitators of learning and indicators of clinical practice environments. These elements are (1) the preparation of the practice setting for learning, which involves planning the training and practice placement, ensuring the implementation of training in the practice setting, and providing opportunities for individualized support during placement; and (2) the organization of interpersonal learning practices, encompassing becoming familiar with the workplace as a work environment, promoting equal participation in practices through teamwork, and collaborating with other stakeholders involved in training.

In delving into the mentorship process within a practice placement, 2 elements that serve as facilitators of learning and indicators of clinical practice placement are recognized. These are (1) facilitating student learning by establishing a supportive

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learning environment and fostering individualized learning processes; and (2) enhancing the professionalism of students by encouraging the development of professional attributes and identity, ultimately improving the attainment of professional competence.

Furthermore, Thomson et al [16], in a qualitative phenomenological study, identified 5 significant aspects of the experience in tutoring and follow-up in nursing student practice environments. These mentoring and follow-up aspects were (1) being more independent, (2) receiving support, (3) a sense of belonging to the profession, (4) feedback on the learning process, and (5) anticipatory anxiety.

In this intricate scenario involving various actors, institutions, placement contexts, and mentoring approaches, among others, numerous processes are undertaken, requiring substantial resources and time investments. Given that the primary goal of practice-based learning is student learning and the enhancement of their clinical practice, it becomes crucial to develop innovative approaches that can enable more efficient resource management. In this context, the integration of mobile technology in practice settings has the potential to support and enhance students' learning process while concurrently reducing the resources required for administrative processes in practice placements.

Introducing Mobile Technology in the Learning Process

Contemporary health systems are shifting toward more integrated and person-centered care models [17], with the use of technology becoming increasingly common in various processes related to care provision. Within this context, health care higher education institutions are incorporating technology into their degree programs with the goal of equipping students with essential skills in digital health [18] and preparing them for their future workplaces. The integration of mobile technologies, coupled with advancements in digital literacy, is expected to empower professionals to confront the intricate challenges presented by contemporary health systems [19]. Additionally, these technologies should facilitate student learning, particularly during clinical practice periods. The education of health students is grounded in the preparation of future professionals capable of navigating this evolving context. Therefore, a key objective of training and learning is the transition from acquiring established knowledge to educating for an unknown future. This shift in learning necessitates the adoption of new approaches and the utilization of innovative teaching and learning technologies [20]. Hence, the utilization of information and communication technologies and Web 2.0 environments in the context of learning during practice placements plays a pivotal role in preparing for this uncertain future in education. Technology-enhanced learning encompasses the application of technology to support any learning-related activity, concentrating on various pedagogical domains that leverage technology [21-23].

The evolution of the Web 2.0 concept has seen a shift in learning from eLearning to mobile learning (mLearning). mLearning is characterized as learning that occurs in diverse contexts, involving social interactions and content consumption, using personal electronic devices as a means of distance education. In this approach, mLearners (students) use educational technology through mobile devices [24] at their convenience [25]. The application and utilization of mLearning in education are contingent on the specific learning needs, context, and objectives to be accomplished [26,27].

In practice placements, where the learning needs involve reinforcing and applying competencies acquired at the university, mLearning serves as a valuable tool for consulting reference materials. Its accessibility virtually anywhere and anytime allows students to enhance their understanding. Furthermore, students can share experiences and knowledge gained in the practice setting with mentors and peers, enabling instant feedback and suggestions. This highly interactive process has demonstrated a 22% reduction in abandonment rates in technical environments, accompanied by an increase in evaluation scores from the 50th percentile to the 70th percentile [28]. In the context of mobility, mLearning facilitates student movement, offering excellent content portability by replacing traditional books and notes with small, personalized devices filled with learning materials. Its convenience stems from its accessibility from almost anywhere.

To effectively tackle current issues in teaching and learning, integrate technologies into their respective practices, and enhance user acceptance, mLearning solutions must be collaboratively designed with all stakeholders. This includes researchers, teachers, students, and administrative staff. Achieving a sustainable digitization and transformation of higher education demands a human-centered approach [29,30] that fosters adoption and ensures a lasting impact on practices. Applying this approach to the digitization and transformation of practice-based learning in health care can aid in comprehending the determinants and factors contributing to the successful introduction of mLearning in practice placements. To bridge the gap between the various actors in these learning contexts (university and clinical practice placement) and enhance the overall experience in practice-based learning in health care settings, it becomes essential to implement mLearning approaches in practice placements and gain insights into their tangible benefits and optimal usage strategies.

This paper outlines the protocol for a study focused on the implementation of mobile technology in practice placements. The study protocol aligns with the research vision of an innovation project in higher education known as the "4D in the Digitalization of Learning in Practice Placement" (4D Project; Multimedia Appendices 1 and 2), involving participants from 5 European countries, namely, Spain, Germany, The Netherlands, Austria, and Poland [31] (Multimedia Appendix 3).

The project aims to fill this gap by creating personalized mobile apps for students, teachers, tutors, and supervisors in each participating organization. This will be achieved through the integration of practice-based reflective learning, mobile technology, and the adoption of technology. The aims are as follows:

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- To determine the key factors (barriers, facilitators, and solutions) to introduce mobile technology in practice placements.
- To cocreate design learning practices, materials, and adapt or adopt mLearning technology in practice placements using various co-design methods. This approach aims to respect users' core values and address their needs.
- To test and assess the introduction of this mobile technology in practice placements in 3 different health institutions in European countries.

Methods

Study Design and Methodological Framework

The research will follow a mixed methods research design, incorporating 3 distinct study phases, each utilizing different methodologies.

In phase 1, the focus is on comprehending the facilitators and barriers associated with the integration of mobile technology into clinical education during practice placements for medical and health care students. The goal is to identify potential strategies and approaches to overcome the identified barriers.

During phase 2, the emphasis is on collaborative creation and design with users, involving various design methods. The objective is to cocreate and co-design an mLearning technology specifically tailored for practice placements. This phase aims to incorporate user input and preferences into the development process.

In phase 3, the research moves to the practical testing of the mLearning technology in a real-world environment. The focus is on evaluating the impact, usability, design effectiveness, interactive learning features, and overall user satisfaction. This phase involves assessing how well the developed technology performs in a real setting and gathering feedback to refine and improve its functionality.

Theoretical Framework

The study will be guided by a design-based research framework, which aligns with the principles of design-based research [32-34]. This framework acknowledges that initial research and theoretical review are essential for understanding the problem, identifying needs, and analyzing the context (as seen in phase 1). Subsequently, during the next phase, researchers actively engage in the cocreation of the solution using various design methods (as in phase 2). The final phase involves testing the solution in a real-world environment to assess its impact on students' learning (as in phase 3). This iterative process allows for the continuous refinement and improvement of the developed solution. The study includes a reflecting phase that directs researchers to reflect on the outcomes and use this reflection to redesign the solution. The iterative research process involves designing, testing, evaluating, and reflecting, leading to a new research cycle aimed at refining and redesigning the solution [35] (Figure 1). This cyclical approach allows for continuous improvement and adaptation based on the insights gained from each iteration.

The following sections detail methodological considerations for each phase:

Figure 1. 4D Project conceptual model approach for implementation research [35].

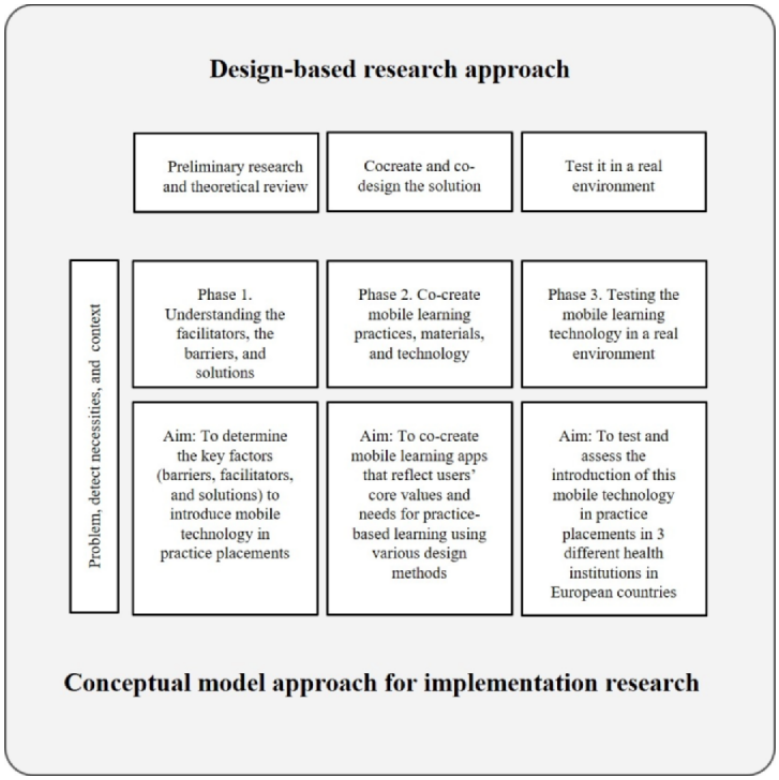

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Phase 1: Understanding the Facilitators, the Barriers, and Solutions

Overview

During this initial phase, the primary objective is to comprehend the facilitators and barriers associated with the integration of mobile technology into clinical education during practice placements for medical and health care students. The focus is on identifying potential solutions to overcome the identified barriers, laying the foundation for subsequent phases of the research.

Aim

The aim of this phase is to determine the key factors (barriers, facilitators, and solutions) to introduce mobile technology in practice placements. We describe 3 research questions to ensure and support the objective's consecution:

- What are the facilitators for introducing mobile technology into clinical education in the practice placement of medical and health care students?
- What are the barriers to introducing mobile technology into clinical education in the practice placement of medical and health care students?
- What are the solutions to overcome barriers for introducing mobile technology into clinical education in the practice placement of medical and health care students?

Research Design

To carry out the assessment, we will use 2 methods. First, a scoping literature review will analyze and synthesize existing research evidence. Simultaneously, focus groups will be conducted to capture the perspectives of undergraduate health profession students and stakeholders on the barriers and facilitators associated with the introduction of mobile devices in practice placements. The scoping literature review adheres to the recommendations of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) statement [36]. The review process follows the framework established by Arksey and O'Malley [37], further refined by Levac and colleagues [38], encompassing the following stages: (1) identification of research questions; (2) identification of relevant studies; (3) selection of studies; (4) data charting; and (5) collation, summarization, and reporting of results.

Focus groups will be conducted to analyze the barriers, facilitators, and needs associated with introducing mobile technology in practical training for future health care students. This qualitative data collection method aims to offer an in-depth understanding of the phenomena. The findings will be reported following the guidelines outlined in the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [39]. The content for the focus groups will be collaboratively developed through consensus among the research team and subject matter experts. Research questions have been formulated in alignment with the research's purpose by experts representing all partners involved in the 4D Project. This collaborative approach ensures a comprehensive and well-informed set of questions for the focus groups.

Sampling Procedures of Focus Groups

Participants for the focus groups will include undergraduate health care students and stakeholders from Tecnocampus, Pompeu Fabra University, the Medical University of Lublin (Poland), the University of Duisburg Essen (Germany), and the Germans Trias i Pujol University Hospital (Spain). The selection of participants will be carried out using purposive sampling with the aim of achieving maximum variation. Students eligible for participation should be enrolled in degree programs such as nursing, medicine, physiotherapy, or midwifery. Stakeholders will also be included based on the following criteria: involvement in the practical training of future nurses, midwives, physiotherapists, or doctors in roles such as clinical mentors; link teachers; practical training coordinators; hospital ward managers; or staff in the nursing, midwifery, and medical fields.

In each country, we have scheduled 2 focus groups with 8-10 participants each. Overall, we plan to conduct 3 focus groups with undergraduate students (nurses, physiotherapists, midwives, or medical students) and 3 focus groups with stakeholders, including clinical mentors, link teachers, practical training coordinators, hospital ward managers, staff, and other relevant stakeholders.

Analysis

In the scoping literature review, the study screening will follow a structured process [40] involving a sequential review by title, abstract, and full text. Two pairs (pair 1: BD and Agnieszka Chrzan-Rodak; pair 2: Cristina Casanovas Cuéllar and Ariadna Huertas Zurriaga) of experienced researchers will participate in this screening process. Initially, study titles will undergo independent screening by paired reviewers to identify studies that meet the inclusion criteria. Subsequently, researchers will assess the abstracts for inclusion, reviewing a distinct group of articles from the previous step. Following this, the researchers will rigorously evaluate the full text of the remaining articles, strictly adhering to the inclusion and exclusion criteria. In each round, a third researcher will scrutinize the work of each reviewing pair for potential errors. In case of any disagreement between the paired researchers, the document will be referred to the next researcher in the process to mitigate deselection bias. The third researcher will additionally assess the level of agreement between review pairs for both the title and abstract phases, aiming for a 95% agreement level.

The analysis of focus group data will adhere to Koole's FRAME (Framework for the Rational Analysis of Mobile Education) model [41]. The FRAME model delineates 3 principal aspects influencing mLearning and specifies factors (device usability, interaction learning, and social technology) that impact the successful integration of these aspects. For this study, the FRAME model will be adapted to encompass all the findings generated throughout the research.

The initial phase of analysis involves 1 of the researchers (BD) reading the transcripts multiple times to gain familiarity with the content and identify initial units of meaning. Subsequently, the texts will be coded using descriptive codes based on their content. These codes will then be organized into categories according to similarities in the codes. At this juncture, the

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preliminary results will be discussed within the research group. Through reflective thinking and critical reasoning, adjustments will be made until a consensus is reached. The themes derived from the analysis will be organized under the learning aspects outlined in Koole's original model. Subsequently, the resulting report will be discussed with 2 participants to validate the meaning and coherence of the interpretations. To enhance the trustworthiness of the data, considerations will be given to credibility, dependability, conformability, and transferability [42]. The participants for this discussion will be selected through purposive sampling with maximum variation to bolster credibility. The information from the focus groups will undergo thorough examination by at least two members (SH and CMG) of the research team, and the results will be compared to evaluate dependability. To ensure conformability, all information provided by participants will be presented transparently. For the transferability of the study's data, a comprehensive and detailed description of the data and context will be provided.

Phase 2: Cocreate Mobile Learning Practices, Materials, and Technology

Overview

This phase is dedicated to collaboratively creating mLearning practices, materials, and technology for practice-based learning using various (co-)design methods.

Aim

The objective is to cocreate mLearning apps that align with users' core values and needs for practice-based learning. This involves collaborative design and production of mLearning practices and materials. Additionally, it includes the adaptation and appropriation of existing mobile apps to bridge the gap between the academic and practice contexts in health care practice placements.

Research Design

This section of the study utilizes collaborative design methods to comprehend the core values and needs of health care students and stakeholders. The goal is to develop embedded mLearning apps for practice placements. To facilitate the coordination of the innovation process within the design team and with domain representatives, the university innovation canvas (UIC) is used. The UIC elucidates the key factors fostering digital transformation and sustainable innovation. This will help to plan the selection and application of more specific co-design methods and tools such as the value proposition canvas (VPC), personas, storytelling, and use case definitions.

University Innovation Canvas and Value Proposition Canvas

The UIC draws inspiration from the business model canvas by Osterwalder and Pigneur [43] and the lean canvas by Maurya [44]. While the business model canvas primarily explores the creation of value for businesses, the UIC [30] is designed to reflect how "value" is generated within a university setting. This adaptation aligns the canvas with the specific context and objectives of fostering innovation within the university environment. In our scenario, the aim is to establish a shared understanding of enhancing collaboration between universities and their affiliated practice placement organizations, involving all relevant stakeholders (eg, students, teachers, and nurses). The UIC comprises 11 elements organized into 3 dimensions: the technology-enhanced learning concept (value creation), stakeholder relationships (value delivery), and foundation and scaling (value capture). This framework provides a structured approach to addressing key aspects of innovation and value creation in the university setting. The specific elements and dimensions within the canvas serve as tools for various stakeholders from diverse contexts to refine their collective focus. They facilitate reflection on crucial factors related to planned sustainable innovation, particularly in the context of enhancing practice placements. The canvas provides a structured framework that encourages stakeholders to align their perspectives and contribute to the development of innovative solutions.

To precisely define the value proposition within the UIC and align it with the technologies available for adoption within the consortium, we opted for the VPC [45]. This tool concentrates on how to generate value for all stakeholders involved (eg, students, teachers, nurses), or more precisely, how these stakeholders can benefit from the anticipated learning intervention. The VPC offers a structured approach to articulate and understand the unique value that the proposed innovations bring to each stakeholder. The VPC consists of 2 parts: First, the *stakeholder profile*, which aims at (1) describing the things or tasks they must do during their work; (2) related pains during the work including risks, potential bad outcomes, or obstacles related to their job; and (3) desired gains including the outcomes and benefits they would like to have. Second, the *value map*, which aims at creating value for the stakeholders by identifying the following: (1) pain relievers in the form of an innovation to reduce/eliminate the stakeholder's pains, (2) innovations that could be built around the value proposition, and (3) gain creators that describe how the innovation creates gains for the stakeholders.

Participants

The participants involved in this process are all members of the 4D Project partner teams, particularly those working at universities or in hospitals. This inclusive approach aims to gather perspectives and insights from both the education side at the university and the practice placements, ensuring a comprehensive representation of stakeholders involved in the project.

Procedure and Analysis

The application of the UIC and VPC will follow a 2-step approach, commencing with a "top-down" approach and subsequently transitioning to a "bottom-up" approach. In the initial step ("top-down" approach), the UIC will be distributed to all 4 distinct practice placements. The stakeholders engaged in the practice placements will receive an introduction to the UIC along with a clear explanation of the purpose behind this activity. The objective is to illuminate the addressed problems, identify value propositions and measures, and identify all involved stakeholders from various perspectives. After the completion of the UICs for each of the 4 practice placements,

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the analysis will focus on uncovering commonalities across all of them. In the subsequent step (ie, the "bottom-up" approach), 3 of the identified commonalities will undergo a more detailed analysis. Hence, in a face-to-face setting, the pertinent stakeholders will be invited to vote for the most significant commonalities and collaboratively complete the VPC. The objective is to explore, from a value proposition perspective, how potential innovations could assist them in creating value for their stakeholders (eg, students, lecturers, and nurses). After the completion of the VPCs, the input will be analyzed and used to generate new UICs. This process aims to establish a shared understanding of possible solutions that align with all 4 practice placements and to emphasize how such innovations can be applied across all 4 settings. Based on the outcomes, subsequent co-design activities using personas, storytelling, and use case definition will be used to further refine the elicited innovation. This may involve creating mock-ups and developing application scenarios in practice. The process includes collaborative efforts to cocreate mLearning practices, materials, and suitable tools within the consortium and with all stakeholders. The overarching goal is to support the practice-based learning of health care professionals in education through innovative and tailored solutions.

Phase 3: Testing the Mobile Learning Technology in a Real Environment

Overview

This phase is dedicated to testing the mLearning technology in a real environment, evaluating its impact, usability, design, interactive learning, social technology, and overall satisfaction.

Aim

The objective is to test and assess the introduction of this mobile technology in practice placements within 3 distinct health institutions located in Spain, Germany, and Poland.

Research Design

In this phase of the study, the descriptive method, specifically a survey, will be used. The underlying premise is that the primary users, namely, the students and clinical mentors, can provide valuable information on aspects related to the use of mobile devices in a practice placement.

The proposed data collection method involves designing and crafting a questionnaire to ensure a comprehensive exploration of the subject. A self-administered questionnaire will be formulated, comprising distinct sections, including a participant information sheet; consent form; demographics information; and segments focusing on usability, design interaction, learning, social technology, and satisfaction. The questionnaire has been created by the authors of the study and draws upon the insights gained from the literature review [41,46,47] and the outcomes obtained in phase 2. Response options will consist of a 5-point Likert scale (ranging from 5=strongly agree to 1=strongly disagree), short responses, or free-text answer options. To assess the feasibility of the questionnaire, it will undergo a pilot phase with a group of students and stakeholders engaged in clinical education. Subsequently, the questionnaire will be revised, if necessary, based on the feedback received during the pilot testing. All participants will be provided with information about the study, including the study protocol, a digital consent form, and a questionnaire. Only those who agree to participate in the study will be directed to the questionnaire. Participants retain the right to withdraw from the study at any point. The online survey is estimated to take approximately 15 minutes to complete. The collected data will be securely stored on a password-protected computer, with access restricted to designated research staff or other authorized personnel who are obligated to maintain the confidentiality of the information. It is important to note that the data will be anonymized.

Participants

The study sample will consist of participants from Tecnocampus, Pompeu Fabra University (Spain), the Medical University of Lublin (Poland), the University of Duisburg Essen (Germany), and the Germans Trias i Pujol University Hospital (Spain). The questionnaire will be completed by students, teachers, tutors, and supervisors who use the developed apps. Moreover, all other individuals engaged in clinical education (practice placement) will be invited to participate in the study.

Analysis

The survey will be designed and implemented using REDCap (Research Electronic Data Capture), a secure, web-based application specifically designed to facilitate data capture for research studies [48].

The analysis in this phase will use inferential statistics to draw conclusions regarding the integration of mobile technology in practical placements. The statistical package used for this analysis will be SPSS, version 23.0 (SPSS Inc.). However, we do not exclude the possibility of using MS Excel (Microsoft Corporation) to facilitate and expedite the data collection and analysis process.

The methodology for describing and analyzing open free-text answers (unstructured data) will involve the use of Dcipher Studio (Dcipher Analytics), an artificial intelligence–powered tool designed to identify topics and sentiments in free-form text responses [49]. Using sentiment analysis and tonality detection will prove valuable in quantifying the emotional tones expressed in the responses.

The analysis of mobile app usage will involve reviewing computer-generated event logs to identify bugs and security threats, ensuring compliance with regulations, and gaining insights into user behavior.

Ethical Issues

At every stage of the planned research, strict adherence to the ethical principles outlined in the Declaration of Helsinki will be maintained. In research involving individuals, such as students and stakeholders, each partner will submit an application containing a comprehensive description of the research protocol to the relevant Ethics Committee. The focus groups and questionnaire studies will adhere to the principles of voluntary participation, anonymity, and respect for the decision to withdraw from the study at any stage. The gathered data will be used solely for purposes associated with the implementation of the 4D Project.

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Ethics Approval

The study has received approval from the ethics committees of the respective institutes in each country: the Bioethical Commission at the Medical University of Lublin in Poland (protocol code KE-0254/152/06/2022 approved on June 30, 2022), the University of Duisburg Essen's Ethics Committee in Germany (protocol code 22-10783-BO approved on October 19, 2022), and the Fundació Tecnocampus Mataró-Maresme's Ethics Committee in Spain (protocol code CEI2/2022 approved on October 7, 2022). Informed consent will be obtained from all study participants.

Results

Phase 1: Understanding Facilitators and Barriers

The scoping literature review commenced in April 2022 and concluded in July 2022, while the focus groups were conducted from October to December 2022. It is anticipated that the outcomes of phase 1 will reveal (1) the identification of factors supporting the successful integration of mobile technology in clinical education for medical and health care students; (2) the acknowledgment of obstacles and challenges impeding the effective use of mobile technology in practice placements; (3) practical solutions proposed to address the identified barriers and challenges, and (4) insights derived from the focus groups, which will provide a deep understanding of the perspectives and experiences of health care students and stakeholders regarding the integration of mobile technology.

Phase 2: Cocreating Mobile Learning Practices

The design process commenced in July 2022 and concluded in November 2023. The outcomes of phase 2 revealed (1) the development of innovative and customized mLearning apps that resonate with the core values and requirements of health care students and stakeholders; (2) the adaptation and proficient utilization of preexisting mobile apps to fulfill the distinct needs of practice placements; and (3) the recognition of how collaboratively crafted mLearning practices can yield value for a diverse range of stakeholders, encompassing students, educators, and health care professionals.

Phase 3: Testing Mobile Learning Technology

The pilot study is set to commence in January 2024. It is anticipated that the outcomes of phase 3 will reveal (1) results pertaining to the usability and design of the collaboratively created mLearning apps obtained through surveys; (2) the impact of mobile technology integration on various aspects including learning outcomes, student engagement, and communication among stakeholders; (3) an examination of the emotional tones expressed by participants in relation to the implementation of mobile technology; and (4) findings from the analysis of computer-generated event logs from mobile apps, providing insights into user behavior, identifying potential issues, and ensuring compliance with regulations.

Discussion

Principal Findings

The primary objective of this study is to bridge the gap in practice-based learning by developing personalized mobile apps tailored for diverse actors and stakeholders. The study aims to assess the integration of mobile technology in practice placements within European health care institutions.

This study aims to showcase the transformative potential of mobile technology in reshaping practice placements within health care education. Through targeted efforts to overcome significant barriers, engaging stakeholders in co-design processes, and integrating mobile apps, the study will concentrate on enhancing both the learning and administrative aspects of practice placement. The overarching goal is to ensure the effective clinical education of health care students in higher education.

Identifying key factors, including barriers, facilitators, and potential solutions, for the introduction of mobile technology in practice placements will unveil a spectrum of elements. Literature reviews and insights from focus groups suggest that factors facilitating the use of mLearning in practice placements may include improved access to clinical resources; enhanced communication and collaboration among health care professionals, students, and stakeholders; and the facilitation of self-directed learning. Barriers to the integration of mobile technology in practice placements are concerns about the design of the product being beyond the control of learners and their teaching staff. Additionally, challenges arise when cultural acceptance and adherence to social norms regarding the use of mobile devices in clinical settings are not taken into account. Moreover, the absence of clear policies further contributes to impediments in this context [50-52].

The co-design of an mLearning app, aligning with users' core values and needs, is crucial for the effective adoption of mobile technology in practice-based learning [53]. The outcomes will offer valuable insights into users' needs, values, and preferences, guiding the design process to ensure a user-centered application [54].

Ultimately, the testing and assessment of mobile technology in clinical practice placements are poised to yield promising results across various dimensions, including usability and design, learning outcomes, student engagement, communication among stakeholders, user behavior, identification of potential issues, and compliance with regulations. The integration of mobile apps holds the potential to have a positive impact on the learning process, streamlining day-to-day clinical practice, and enhancing value-based activities.

The impact of this study underscores the necessity for sustained investment in technology-enhanced learning and the crucial role of user-centered design in health care education. Extending beyond the immediate scope of this study, the findings will emphasize broader implications for health care education, particularly in clinical practice placements.

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Limitations

It is important to note that the findings of this study may have limited generalizability beyond the participating European countries due to variations in educational contexts and health care systems. Moreover, the assessment of learning outcomes and intervention effectiveness in complex educational settings poses challenges, potentially impacting the comprehensiveness and quantifiability of our results.

Conclusions

The 4D Project endeavors to address the existing gap between academic contexts and clinical placements in higher education. Its objective is to introduce mobile technology as a solution to enhance the learning process in this context. The project actively supports the examination of communication and interaction processes among various stakeholders within and across different organizations and countries. This is achieved through a meticulous methodology used in the design of a mobile app.

The study will use a multiphase approach. Initially, a systematic review and qualitative methodology involving focus groups will be used to identify barriers and facilitators to the introduction of mobile technology in practice placements. Subsequently, a design-based research methodology will be implemented, enabling the cocreation of mLearning apps that align with users' core values and needs for practice-based learning. Finally, a pilot study using both quantitative and qualitative methods will be conducted to validate and test the mLearning technology in a real-world environment. This phase will evaluate its impact, usability, design, interactive learning, social technology aspects, and user satisfaction.

The long-term benefits of the "4D Project" are centered around improving communication, interaction, and collaboration among the diverse stakeholders engaged in the educational process. By addressing current challenges in practice placements, the project aims to fortify the connection between these stakeholders in the digital era. It seeks to foster new forms of collaboration through the strategic integration of mobile technology.

Health care education, encompassing disciplines such as medicine, nursing, midwifery, and others, encounters ongoing challenges in clinical training. The imperative task of bridging the divide between health care institutions and academic settings is crucial. The introduction of a novel digital tool holds the potential to empower health students and mentors, providing a means to navigate the complexities inherent in the learning process.

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Authors' Contributions

All authors have had substantial intellectual contributions to this protocol. CMG and EC conceptualized this study and wrote the first and final drafts of the protocol. All the authors participated in writing, reviewing, and editing the protocol. All authors have contributed to revising the protocol for intellectual content. All authors have read and approved the final manuscript and given final approval for the manuscript to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Selected projects 2021-KA220-HED-s.
[PDF File (Adobe PDF File), 1271 KB - resprot_v13i1e53284_app1.pdf]

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Multimedia Appendix 2
Eligibility outcome for the 4D Project. 4D Project: 4D in the Digitalization of Learning in Practice Placement.
[PDF File (Adobe PDF File), 68 KB - resprot_v13i1e53284_app2.pdf]

Multimedia Appendix 3
4D Project grant agreement. 4D Project: 4D in the Digitalization of Learning in Practice Placement.
[PDF File (Adobe PDF File), 1360 KB - resprot_v13i1e53284_app3.pdf]

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Abbreviations

4D Project: 4D in the Digitalization of Learning in Practice Placement
COREQ: Consolidated Criteria for Reporting Qualitative Research
FRAME: Koole's Framework for the Rational Analysis of Mobile Education
mLearning: mobile learning
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
REDCap: Research Electronic Data Capture
UIC: university innovation canvas
VPC: value proposition canvas

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Protocol

Digital Knowledge Translation Tools for Disseminating Sexual and Reproductive Health Information to Adolescents: Protocol for an Evidence Gap Map Review

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Abstract

Background: Digital or eHealth knowledge translation (KT) interventions have been identified as useful public health tools, particularly to advance sexual and reproductive health (SRH) among adolescents. Existing literature reviews on digital health interventions for adolescents' SRH demonstrate limitations, including shortcomings in reporting and comprehensiveness that limit the utility and trustworthiness of findings. However, there is a lack of evidence synthesis on the effectiveness of available digital or mobile health KT tools to promote SRH interventions for adolescents.

Objective: We aim to identify, map, and describe existing empirical evidence on the digital KT tools developed to improve adolescent SRH outcomes globally.

Methods: This study will be conducted using an evidence gap map (EGM) approach to address the objectives, including reviewing relevant literature and a landscape analysis of the outcomes of interest. The following electronic databases will be searched for retrieval of literature: MEDLINE (1946-present), Embase (1974-present), and Global Health (1910-present) via OVID; CINAHL (1936-present) via EBSCOhost; Scopus (1976-present); and Cochrane Library (1993-present) via Wiley. We will include only those studies that focused on adolescents aged 10-19 years and addressed SRH outcomes. We will include experimental studies (randomized or cluster randomized and nonrandomized controlled trials, including quasi-randomized, controlled before-after, and interruptive time series) and observational studies, that is, including prospective cohort and case-control studies. The experimental and observational studies will only be included in the presence of control or comparison arms. Studies with a historical control arm will be excluded. The systematic review software, Covidence (Ventas Health Innovation), will be used to screen and select the studies. Further, 2 independent reviewers will complete the first and second levels of screening of studies and any conflicts arising will be resolved by consensus between the 2 reviewers or by involving the third reviewer. We will conduct the quality assessment of all included studies using the Risk of Bias tool for randomized controlled trials and nonrandomized controlled trials, and AMSTAR2 for systematic reviews.

Results: Papers screening, data extraction, and synthesis will be completed by March 2024. We will use EPPI-Mapper (The International Public Policy Observatory) software to generate an online evidence map and to produce the tables and figures for the descriptive report. This EGM review will identify areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization).

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Conclusions: This protocol focused on mapping eHealth KT tools that have been used in the literature to address SRH among adolescents. This will be the first EGM exercise to map digital KT tools to promote adolescents' SRH and will incorporate a range of published sources.

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KEYWORDS

adolescents; sexual and reproductive health; digital tools; knowledge translation; mobile phone

Introduction

Background

Adolescence is a critical period in the transition from childhood into adulthood, during which young individuals aged 10 to 19 years experience substantial physical, psychological, social, and emotional changes [1]. Adolescents are vulnerable because of their age-related psychosocial and biological changes and the challenges associated with navigating these changes [2]. As part of their physical, psychological, and social development, it is common for adolescents to explore their sexual orientations and feelings through sexual experimentation [3]. Depending on their knowledge about sexuality and social support, some may experience unintended consequences such as unplanned pregnancy and sexually transmitted infections. Neglect of specific adolescents' sexual and reproductive health (SRH) needs can affect their physical and mental health, future employment, economic well-being, and ability to reach their full potential [4-6].

SRH issues pose serious concerns for adolescents including the lesbian, gay, bisexual, transgender, queer, and gender diverse population. Adolescents have the highest rates of contracting sexually transmitted infections, including HIV [7,8]. Approximately 16 million girls aged 15-19 years and 2 million girls younger than 15 years become pregnant each year around the world [9]. Pregnancy-related complications are the second leading cause of death among girls aged 15-19 years [10]. Furthermore, adolescents have less access to information and services. Access to contraception also remains low among females 15-24 years compared to women older than 30 years [11]. This is primarily due to a lack of awareness, social stigma, policies, and procedures inhibiting the provision of contraception and abortion services to girls, and judgmental attitudes of health care professionals [12-14]. Young people have special SRH education needs that remain unmet, and to address these specific SRH needs, innovative and novel approaches are required to ensure access to evidence-based SRH information and acceptable SRH services [13].

To maximize health system resources and improve SRH outcomes for adolescents, it is increasingly important to close the research-practice gap by ensuring that research knowledge translates into action—a process called knowledge translation (KT). KT is the synthesis, exchange, and application of knowledge to improve the health of individuals, provide more effective health information, services, and products, and strengthen health care systems [15]. KT is the process of translating knowledge into action to provide more effective health services and strengthen the health care system [15,16]. The goal of KT is to ensure that individuals, such as patients, health professionals, and policymakers, can access and use research evidence to inform their health-related decision-making [17].

KT is a dynamic process that uses tools and methods to increase the use of evidence in decision-making while considering policy rationales in the process of generating evidence [18]. On the other hand, KT tools are a subgroup of KT interventions that facilitate moving research-based information to clinicians and patients or health care consumers in user-friendly language and formats to provide explicit recommendations or meet knowledge or information needs [16,17,19]. KT tools to transfer health information to health care consumers can be presented using a multitude of formats, including but not limited to videos, infographics, apps, practice guidelines, and decision-aiding tools to aid consumers in the synthesis, dissemination, and implementation of research [19]. Digital KT tools offer a promising approach to improving health literacy and communicating complex health information to health care consumers. Digital KT tools such as mobile phone websites, mobile apps, mobile health (mHealth), SMS text messaging, and social media platforms have been identified as useful public health tools, particularly to promote SRH among adolescents. The use of digital technology for SRH promotion offers privacy [20-25], access to personalized information [20,22,24,26], and convenience [20,25,27] making it a valuable way to provide accurate information about sexual health to adolescents [20-24].

Several research studies tested the effect of technology-based tools on improving adolescents' knowledge, attitudes, and practices regarding sexual health [22-27]. Cornelius and Lawrence [23] used text messaging through mobile phone technology to increase awareness of adolescents to prevent sexually transmitted infections (HIV) and improve safe sexual practices [28]. The study reported that adolescents found text messaging to be an excellent source of information exchange and a reminder to have safe sex practices [27]. Another study evaluated the prevalence and effectiveness of using chatbot (chat agent) inquiries related to sex, drugs, and alcohol use among adolescents. The study reported that adolescents found chatbots a confidential and user-friendly tool to answer their queries related to topics around sex and sexual activities [28]. Additionally, Guse and colleagues [21] conducted a systematic review to summarize evidence on the effectiveness of digital media-based sexual health intervention for adolescents aged 13-24 years [29]. The review included 10 studies in total, while the majority of the included studies were conducted in the United States. The findings of the review study reported the

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effectiveness of digital media-based interventions in improving sexual behavior and health among adolescents.

However, despite the availability of digital KT tools, there is a lack of evidence of synthesis on the available digital or mHealth KT tools to promote SRH interventions for adolescents. Not all KT tools are equally effective and trustworthy sources of SRH information. Therefore, this study using an evidence gap map (EGM) exercise aims to synthesize evidence on the usefulness of digital KT tools to improve adolescents' SRH. EGM is an emerging approach to mapping and synthesizing evidence from empirical studies to implement effective strategies and inform policymakers [30]. EGM is a systematic way of gathering scientific evidence and summarizing the evidence in a graphical format for researchers and practitioners to understand what is known and where the gap is in a particular sector. Another key advantage of using the EGM framework is that this guide is designed for nonspecialist audiences to distill key findings and provide implications for practice and policy [30].

Study Purpose and Objective

This review aims to identify, map, and describe existing empirical evidence on the digital KT tools developed to improve adolescent SRH outcomes globally. In this EGM, we will assess and report on empirical studies describing the development, implementation, or evaluation of SRH digital KT tools to identify current aims, processes, methods, frameworks, tools, user roles, disciplinary and geographic domains of application, as well as to document existing knowledge gaps. The specific objectives of this EGM are to, first, identify, assess, and report on empirical studies of any design that describe the development, implementation, or evaluation of adolescent SRH digital KT tools; second, to identify current uses, purposes, and methods in the development of digital KT tools; third, to describe the characteristics of digital KT tools; and finally, to identify research gaps in the literature.

We will conduct an EGM to address the objectives, including reviewing relevant literature and a landscape analysis of the outcomes of interest. The EGM will be presented on a web-based platform and accompanied by a published paper with an analysis of the available evidence. An EGM aims to establish what we know and do not know about the effects of interventions in a thematic area [31]. The map is populated through systematic searching, screening, and data extraction of all relevant completed, and ongoing, impact evaluations and systematic reviews.

Methods

Study Design

This study is conducted in alignment with standard methodologies for the development of EGM [30]. The protocol for this work is registered with PROSPERO (CRD42022373970). We started this review in May 2023 and will complete it by April 2024.

Scope of EGM

The scope of the EGM was determined through a consultative workshop organized by SM to discuss the interventions and strategies to improve the adolescents' SRH and rights and on how to meet the information needs of adolescents related to SRH. We invited the stakeholders from Option for Sexual Health and Action Canada for Sexual Health and Rights to the consultative workshops for research team members of World Universities Network and members of the Contraception and Abortion Research Team. This workshop identified the need for the EGM and informed the general inclusion criteria and the framework of the EGM. We found EGM as the most appropriate and suitable framework for this review as we aim to map the available evidence on the effectiveness of digital interventions in the form of a table or matrix that provides a visual presentation of the evidence [32].

Eligibility Criteria

The eligibility criteria for the evidence map are summarized in Textbox 1 and detailed below:

- *Study types:* We will include experimental studies (randomized or cluster randomized and nonrandomized controlled trials, including quasi-randomized, controlled before-after, and interruptive time series) and observational studies, that is, including prospective cohort and case-control studies. The experimental and observational studies will only be included in the presence of control or comparison arms. Studies with a historical control arm will be excluded. Studies such as cross-sectional studies, case reports and series, editorials, commentaries, and narrative reviews will not be included.
- *Topics of interest:* We will include studies that have reported KT tools on SRH topics such as family planning and contraception use, healthy timings and spacing of pregnancy, teenage pregnancy, abortion, HIV and AIDS and other sexually transmitted infections, intimate partner violence or dating violence, menstruation, feminine hygiene, child marriage, and female genital mutilation associated with the above topics.
- *Population:* We will include primary studies conducted on adolescents aged 10-19 years. Studies and reviews on populations younger and older than adolescents but inclusive of adolescents will be included if they separately report outcomes on adolescents. We will report the studies separately if they do not report outcomes on adolescents separately.
- *Exposure or intervention:* We will include studies assessing digital KT tools for disseminating SRH information to adolescents. If a digital KT tool is meant for dissemination in wider age groups, it will be included, and these KT tools will consist of websites, mobile apps, mHealth, SMS text messaging, pamphlets, and brochures over email, podcasts, mass media such as radio messages or videos on television, and social media such as Instagram, TikTok, Facebook, Twitter, YouTube, and over-the-top platforms.
- *Comparison:* We will include studies comparing the abovementioned KT tools with no interventions, the standard of care, or other interventions.
- *Setting:* We will include studies conducted globally regardless of the settings or context of its conduct.

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Textbox 1. Eligibility criteria for the evidence map.

Population

- Adolescents aged 10-19 years

Exposure or intervention

- Digital knowledge translation tools for disseminating sexual and reproductive health information such as websites, mobile apps, mobile health (mHealth), SMS text messaging, pamphlets, and brochures over email, podcasts, radio messages, videos on television, and social media such as Instagram, TikTok, Facebook, and Twitter

Comparison

- Any comparison is eligible

Geography

- Global evidence, that is, studies from high-income and low- and middle-income countries

Topics of interest

- Family planning and contraception use
- Healthy timings and spacing of pregnancy
- Teenage pregnancy
- Abortion
- HIV and AIDS and other sexually transmitted infections
- Intimate partner violence or dating violence
- Menstruation and feminine hygiene
- Child marriage
- Female genital mutilation
- Rights, norms, education, and empowerment associated with the above topics

Study type

- Experimental and observational studies, including systematic reviews

Timeframe

- Studies and reports published from 2010 onwards as internet and digital or social media usage increased from 2010

Language

- English language only given the prominence of the English language in science

Search Strategy

The search strategy for this review will be reported in adherence to the PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Searching) extension [33]. The search strategy will be developed by an experienced health sciences librarian (MK) in consultation with the research team. The following databases will be searched individually from inception to present: MEDLINE (1946-present), Embase (1974-present), and Global Health (1910-present) via OVID; CINAHL (1936-present) via EBSCOhost; Scopus (1976-present); and Cochrane Library (1993-present) via Wiley.

The search strategy will be derived from four main concepts: (1) adolescents, teenagers, or young adults; (2) SRH or health services including vocabulary related to contraception, family planning, pregnancy, sexually transmitted infections, and gender-based violence; (3) digital communication tools such as websites, web-based messaging, smartphones, mobile apps, social media, podcasts, television, or digital information; and (4) KT including vocabularies such as information dissemination, research innovation, knowledge transfer, implementation science, research into practice, knowledge into practice, and evidence-based practice. Bibliographic databases will be searched using a combination of natural language (keywords) and subject headings, such as Medical Subject Headings, wherever they are available. Items such as books, book chapters, editorials, conference materials, and opinion pieces will be removed from the results and a publication date limit of 2010 to the present will be applied. A preliminary search for OVID Medline was developed and executed in October 2022 to determine the feasibility of this project and test the scope (see Multimedia Appendix 1 for the MEDLINE search strategy). The systematic review software, Covidence, will be used to manage this review. Covidence will be used for the

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deduplication of database search results and will be used to facilitate the title or abstract screening and full-text screening phases.

Screening and Extraction

All the studies identified from the databases will be imported to Covidence (a digital screening software), and 2 independent reviewers will screen the studies in title or abstract and full-text stages. Disagreements, if any, will be resolved by consensus. The reference list of all the included studies will be scanned and searched to include any relevant study that may have been missed during the search of databases. The final list of included studies will be subject to forwarding and backward citation chaining to ensure no relevant eligible papers have been missed. A diagram showing the flow of literature will be produced and reported by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [33]. For data extraction, we will use a standardized data extraction form to extract descriptive data from all studies meeting our inclusion criteria. Data extracted from each study will include bibliographic details, KT tool types and descriptions, outcome types and descriptions, study design, context or geographical information, and details on the outcome and quality of the KT tool. Further, 2 review authors will independently extract data, and discrepancies will be resolved through discussion until consensus has been achieved or by consulting a third reviewer if required. Attempts will be made to contact the authors of the included studies to obtain clarifications or additional data. We will extract data on the following study characteristics presented in Textbox 2:

Textbox 2. Extraction of data on this study's characteristics.

Publication information

- Journal, publication year, study location, and study setting

Population

- Number of participants, sex, mean age, age range, and sociodemographic status

Digital knowledge translation (KT) tool

- Digital KT tool description, purpose, setting, and any other important detail

Intervention (if studies used digital KT tool as an intervention to improve sexual and reproductive health [SRH] information and outcome of adolescents)

- Intervention description, the composition of the intervention, duration of intervention, a platform for delivery (school-based or community-based, peer-support, mobile health [mHealth]), and comparison group description

Control

- Standard of care or control

Outcomes

- Outcomes specified earlier, time points of outcomes reported, and evaluation methods used

Study design

- Type of study design

Other information

- Funding sources, study limitations, and conflicts of interest

Data Synthesis

Data from the review will be visually synthesized in an EGM using EPPI-Mapper [34] with an accompanying narrative. Rows of the EGM list digital KT strategies and columns components of outcomes and other relevant data coding. Each cell shows the number and quality of evidence for digital KT strategies. We will conduct the quality assessment of the included studies using Risk of Bias for interventional studies including randomized controlled trials and nonrandomized controlled trials and AMSTAR2 tool for systematic reviews [31,35]. The EGM identifies areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization) An example of the layout of the evidence map matrix can be found in Multimedia Appendix 2 (developed in consultation and discussion with experts in the area of adolescents SRH).

Patient and Public Involvement

Patients will not be involved in the design, conduct, reporting, or dissemination of the EGM exercise.

Ethical Considerations

No ethical review was required, as we included published data which is accessible and available for the public in this review. We will disseminate findings from the EGM through summary reports and publications; present our findings at conferences to

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facilitate research reach; list project descriptions and associated outputs on investigator-affiliated websites and professional web-based accounts; and concurrent dissemination through professional social media accounts. The EGM has the potential to inform researchers and decision makers about user-centered innovation by highlighting current practices and opportunities for further KT tools development. Findings will inform the development of future projects with the principal investigators and coprincipal investigators' research program aimed at developing, implementing, and evaluating digital KT tools and associated projects in various receptive adolescent SRH contexts. Findings will directly inform a concurrent project by the lead investigator (SM) focused on co-designing a mobile app to improve the SRH of immigrant adolescents in Canada.

Results

Overview

Paper screening, data extraction, and synthesis will be completed by March 2024. We will use EPPI-Mapper software to generate a digital evidence map and to produce the tables and figures for the descriptive report. EPPI-Mapper will consist of rows representing digital KT interventions and column components presenting outcomes. Each cell shown within the matrix will present the number and quality of evidence for digital KT strategies. This EGM review will identify areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization). This EGM exercise will offer a novel knowledge synthesis tool (a web-based EGM), mapping all of the digital KT tools currently available to promote the SRH of adolescents. The information will be available in a usable format to enable efficient and effective use by multi-stakeholder audiences.

Discussion

Principal Findings

The purpose of this review is to create an EGM to guide multi-sectoral stakeholders regarding digital KT tools to better understand and use the evidence-based digital KT tools to improve the SRH of adolescents. Digital KT tools have the potential to advance the SRH of adolescents, yet there is a dearth of knowledge regarding the quality and uptake of these digital KT tools. Digital technologies have the potential to facilitate innovative, efficient ways of meeting growing global health needs. A global 2019 report [36] indicated that over 5 billion mobile phone users, 4 billion internet users, and 3 billion active social media users, with most accessing the internet through mobile devices. The anonymity, convenience, and accessibility afforded by SMS, web access, and video streaming enhance the potential for SRH interventions to reach persons disconnected from mainstream SRH services.

Existing literature reviews on digital health interventions for adolescents' SRH demonstrate limitations, including shortcomings in reporting and comprehensiveness that limit the utility and trustworthiness of findings. An EGM of digital KT tools is therefore warranted. Innovative ways to deliver sexual health information and services are more important than ever before due to the impact of the COVID-19 pandemic on access to SRH services globally [37]. Interruptions in SRH information and service delivery seriously impact vulnerable adolescents' health and well-being. The absence of adolescent SRH services from "essential" health services during COVID-19 amplifies the potential role of technology in meeting the SRH needs of vulnerable groups like adolescents. Amidst the pandemic, technology has primarily provided the means to support the recalibration of health systems, service provision, and information delivery [38]. Digital health tools play an important role in preserving the continuity of SRH services for adolescents and youth during a crisis. Using digital health tools in the pandemic and climate change context would improve adolescents' access to information which might support them in having the knowledge and motivation to access services.

Guidelines and policies are increasingly focused on adolescents as a specific population for modifying health behaviors [39], and the global community is calling for further research in this area [40]. However, it is important to first map out all the available digital KT tools for improving behavior related to SRH among adolescents. Digital or eHealth KT interventions have been identified as useful public health tools, particularly to advance SRH among adolescents. The use of digital technology for SRH promotion offers privacy [21-26], access to personalized information [21,23,25,27], and convenience [21,26,28] making it a valuable way to provide accurate information about SRH to adolescents [21-26].

Despite the high level of SRH information consumption via a digital platform, evidence of the successful use of SRH digital KT tools is limited. EGM provides a novel knowledge synthesis approach that can accelerate the uptake of digital KT tools to promote adolescent SRH outcomes. This study will map all the digital KT tools currently available and identify the key evidence gaps in digital KT tools that may not be obvious from quick snapshots of the literature. Systematically mapping evidence for digital KT tools will provide valuable insights to inform practice, policy, research, or investment for future adolescent SRH research agendas.

Strengths and Limitations of This Study

This will be the first EGM exercise to map digital KT tools to promote adolescents' SRH and will incorporate a range of published literature sources. An independent dual-reviewer process will be used throughout to reduce the risk of bias and increase the likelihood of comprehensive study identification and inclusion. The 2D matrix of interventions and outcomes will help identify and inform policy and funding agencies for further specific areas of research. Publication bias is a possible limitation as non-English and gray literature will be excluded, which may underrepresent the digital KT tools available and used across geographically diverse contexts.

Conclusions

This project will offer a novel knowledge synthesis tool (a digital EGM), mapping all of the digital KT tools currently available to promote the SRH of adolescents. The information will be available in a usable format to enable efficient and

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effective use by multi-stakeholder audiences. This work is timely as innovative ways to deliver SRH information are more important than ever before due to the impact of digital media on accessing SRH information and services globally. In addition, key policies will be enacted to encourage and support research initiatives in underrepresented regions as this would promote a more comprehensive global understanding of SRH among adolescents. This review will report on the gaps identified in the research and quality assessment of included studies and recommendations will be set forth for future robust research studies. We will disseminate the findings of our study, via community symposiums, and public training sessions, and present at academic conferences and publish in open-access, peer-reviewed journals, advancing the body of knowledge on available digital KT tools to promote SRH and the rights of adolescents.

Acknowledgments

Thank you to stakeholders from Option for Sexual Health and Action Canada for Sexual Health for providing their expert feedback in preparing an evidence map matrix for this study. This study is funded through an Endowment Fund for the Future: Support for the Advancement of Scholarship (EFF-SAS) Research Fund (ZLD 23).

Authors' Contributions

SM and ZSL conceptualized this study, including leading the associated grant application and drafting this study's protocol. All authors contributed to the protocol and will be involved in conducting the proposed research. All authors provided final approval of this paper before submission and agree to be accountable for all aspects of this study as described here.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary Medline search strategy.
[PDF File (Adobe PDF File), 27 KB - resprot_v13i1e55081_app1.pdf]

Multimedia Appendix 2
Example evidence map matrix.
[DOCX File , 23 KB - resprot_v13i1e55081_app2.docx]

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Abbreviations

EGM: evidence gap map
KT: knowledge translation
mHealth: mobile health
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Searching
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SRH: sexual and reproductive health

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Protocol

Identifying Person-Specific Drivers of Depression in Adolescents: Protocol for a Smartphone-Based Ecological Momentary Assessment and Passive Sensing Study

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Abstract

Background: Adolescence is marked by an increasing risk of depression and is an optimal window for prevention and early intervention. Personalizing interventions may be one way to maximize therapeutic benefit, especially given the marked heterogeneity in depressive presentations. However, empirical evidence that can guide personalized intervention for youth is lacking. Identifying person-specific symptom drivers during adolescence could improve outcomes by accounting for both developmental and individual differences.

Objective: This study leverages adolescents' everyday smartphone use to investigate person-specific drivers of depression and validate smartphone-based mobile sensing data against established ambulatory methods. We describe the methods of this study and provide an update on its status. After data collection is completed, we will address three specific aims: (1) identify idiographic drivers of dynamic variability in depressive symptoms, (2) test the validity of mobile sensing against ecological momentary assessment (EMA) and actigraphy for identifying these drivers, and (3) explore adolescent baseline characteristics as predictors of these drivers.

Methods: A total of 50 adolescents with elevated symptoms of depression will participate in 28 days of (1) smartphone-based EMA assessing depressive symptoms, processes, affect, and sleep; (2) mobile sensing of mobility, physical activity, sleep, natural language use in typed interpersonal communication, screen-on time, and call frequency and duration using the Effortless Assessment of Risk States smartphone app; and (3) wrist actigraphy of physical activity and sleep. Adolescents and caregivers will complete developmental and clinical measures at baseline, as well as user feedback interviews at follow-up. Idiographic, within-subject networks of EMA symptoms will be modeled to identify each adolescent's person-specific drivers of depression. Correlations among EMA, mobile sensor, and actigraph measures of sleep, physical, and social activity will be used to assess the validity of mobile sensing for identifying person-specific drivers. Data-driven analyses of mobile sensor variables predicting core depressive symptoms (self-reported mood and anhedonia) will also be used to assess the validity of mobile sensing for identifying drivers. Finally, between-subject baseline characteristics will be explored as predictors of person-specific drivers.

Results: As of October 2023, 84 families were screened as eligible, of whom 70% (n=59) provided informed consent and 46% (n=39) met all inclusion criteria after completing baseline assessment. Of the 39 included families, 85% (n=33) completed the 28-day smartphone and actigraph data collection period and follow-up study visit.

Conclusions: This study leverages depressed adolescents' everyday smartphone use to identify person-specific drivers of adolescent depression and to assess the validity of mobile sensing for identifying these drivers. The findings are expected to offer novel insights into the structure and dynamics of depressive symptomatology during a sensitive period of development and to

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inform future development of a scalable, low-burden smartphone-based tool that can guide personalized treatment decisions for depressed adolescents.

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(JMIR Res Protoc 2024;13:e43931) doi:10.2196/43931

KEYWORDS

adolescents; depression; idiographic assessment; network modeling; treatment personalization; ecological momentary assessment; mobile sensing; digital phenotyping; actigraphy; smartphones

Introduction

Background

Adolescents experience escalating risk of developing clinical depression, with lifetime prevalence rates doubling from age 13 years (8%) to 18 years (15%) [1]. Depression impairs young people's academic, social, and physical functioning [2]; often continues into adulthood [2]; and increases the risk of developing other disorders [2] and suicide attempts [3]. Puberty brings a host of changes, including significant developmental changes in the brain, physical growth spurts and sexual maturation, metabolic and circadian changes, along with an emerging identity, increasingly complex social contexts, and increased learning capacity [4]. These changes may contribute to the risk of developing depression but also signal an opportunity for high-impact intervention [5]. Mastering mood management skills during adolescence can alter the developmental course of depression, thereby improving long-term outcomes. Unfortunately, existing therapies fail to sufficiently capitalize on this developmental window. Meta-analyses revealed significantly smaller effects of psychotherapy for depressed adolescents than for adults [6] and for youth depression than for anxiety or conduct problems [7]. The efficacy of evidence-based psychotherapies such as cognitive behavioral therapy (CBT) may be limited by their fixed, linear delivery to all individuals. Personalizing intervention selection, sequencing, and combination may maximize therapeutic benefit [8], especially for a disorder as heterogeneous as depression. However, empirical support on how to do so is lacking.

One promising avenue for informing personalization is to identify symptoms that are *influential* in the onset and maintenance of dynamic variability in depressive symptoms (ie, short-term, temporal relationships among symptoms), that are *modifiable* through intervention, and that *vary across individuals*—referred to here as *person-specific drivers of depression*. Most evidence-based approaches to therapy, such as CBT, attempt to teach individuals coping skills that will allow them to moderate these dynamics in real time. As such, understanding these drivers can inform personalized intervention that focuses on the specific skills most relevant to an individual's own affective dynamics. Extant theory suggests possible drivers, such as negative affect, rumination, avoidance, social isolation, and anhedonia. Empirical research with 3000+ adults with major depression has documented sadness, loss of energy, interest, and pleasure; concentration problems; sympathetic arousal; and panic as the most *central* (ie, strongly interconnected) among a network of depressive and nondepressive symptoms [9]. Moreover, in never-depressed adults, central depressive symptoms prospectively predicted the onset of depression [10]. Importantly, some central symptoms predicted subsequent changes in other symptoms among depressed or anxious adults, and marked heterogeneity was found in these temporally-ordered predictive relationships [11,12], with no 2 persons sharing the exact number or nature of predictive relationships. Similarly, a large internet-based CBT trial showed that >90% of depressed adults had unique patterns of treatment response, with certain symptoms impacted directly by treatment, which then influenced the reduction of other symptoms [13]. Modeling these person-specific patterns may uncover the mechanisms by which symptoms are maintained and resolved with treatment, providing powerful tools for personalizing treatment. Researchers have led efforts to select and sequence CBT modules to target person-specific drivers identified by idiographic models early in therapy [12,14], which is purportedly more efficacious and efficient due to the drivers' downstream effect on other symptoms. An open trial [15] of personalized CBT returned effect sizes 1.5-2 times larger, achieved over a shorter duration, compared to a historical benchmark [16]. However, no published studies have examined person-specific drivers of depression among adolescents. To our knowledge, only group-level central internalizing symptoms have been studied among youth [17-19]. An idiographic approach is needed to obtain novel insights about symptom dynamics among depressed adolescents in order to inform interventions that account for both developmental and individual differences and that can shift the trajectory of depression onset, maintenance, and recurrence.

To model symptom dynamics, ecological momentary assessment (EMA) is often used [11,20]. Participants are prompted to provide subjective self-report of experiences and events through brief web-based or text surveys daily or repeatedly throughout the day. Whereas EMA involves *active* input from participants, *passive* assessment uses a mobile or wearable device to unobtrusively record participants' behavior or physiology. Wrist-worn actigraphs are research-grade devices containing accelerometers and sometimes other sensors (eg, a light sensor) to estimate behavioral indices of sleep and physical activity [21], which relate to key symptoms of depression (ie, hypersomnia or insomnia, fatigue, and psychomotor retardation or agitation). Actigraphy has been validated against gold standard lab-based measures of sleep (ie, polysomnography [22]) and physical activity (ie, indirect calorimetry [23]). Smartphone-based EMA and wrist actigraphy have been successfully used with youth [24-26] and can be feasibly used to examine person-specific drivers with depressed adolescents.

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Smartphone-based mobile sensing may offer advantages over established methods—especially for adolescents—but needs validation. Mobile sensing or digital phenotyping [27,28] minimizes response burden while leveraging adolescents' near universal (95%) smartphone ownership [29] and usage to obtain objective, fine-grained data about their everyday behaviors. Systematic reviews [30,31] have documented promising evidence for using mobile sensor data (sometimes with EMA) to monitor mood by measuring behaviors related to depression, including sleep (through light sensors, accelerometers, and screen time), physical activity (through accelerometers), mobility (through GPS), and social activity (through call and text frequency or duration). Moreover, a national study of depressed adults showed that idiographic models of GPS-based mobility and other sensor data predicted daily mood at the individual level but not at the group level [32], suggesting the utility of such data for elucidating person-specific symptom dynamics. However, there are very few published studies using mobile sensing to collect data or monitor mood among depressed youth, and of these studies, participant samples tend to be small (range 11-37) [33-36], and large amounts of missing data that affect prediction modeling have been reported [33-37]. More validation studies—especially those with larger samples of depressed adolescents—are needed to demonstrate that mobile sensor data collected from depressed adolescents are correlated with, or predictive of, their EMA and actigraph data before mobile sensing can supplement or substitute these established methods.

Baseline predictors of person-specific drivers could distinguish subgroups with different treatment targets. Identifying between-subject characteristics that predict within-person drivers could facilitate efficient assessment and treatment decisions. For example, a study examining a network of positive and negative emotions, stress, and physical activity found that high arousal positive affect (eg, enthusiastic) was the strongest driver (ie, reduced stress and negative affect) among nonanhedonic individuals, whereas low arousal positive affect (eg, relaxed) was the strongest driver among anhedonic individuals [38]. These findings suggest different optimal intervention targets for the 2 subgroups of depressed adults. Exploring baseline markers that predict person-specific drivers and within-person symptom dynamics is an initial step toward the development of strategies to tailor interventions to optimize outcomes.

Objectives

This study will leverage adolescents' everyday smartphone use for the purpose of evaluating the contributions of these data to understanding person-specific drivers of depression and to further validate smartphone-based mobile sensing data against established ambulatory methods such as EMA and actigraphy. We plan to address three specific aims in this study after data collection is complete. Aim 1: model idiographic, within-subject networks of EMA symptoms to identify person-specific drivers of depression. We hypothesize that most (≥50%) adolescents will have person-specific drivers: (1a) symptoms strongly associated with, or (1b) prospectively predict change in other symptoms in an idiographic network, and (1c) differ markedly across adolescents. Aim 2: (2a) compute correlations among EMA, mobile sensor, and wrist-worn actigraph measures of sleep, physical, and social activity; and (2b) conduct data-driven analyses of core depressive symptoms (ie, self-reported mood and anhedonia) to assess the validity of mobile sensing for identifying person-specific drivers. Aim 3: explore between-subject baseline characteristics as predictors of these person-specific drivers. For this protocol report, the objectives are to describe the methods of this study and provide an update on the status of this study.

Methods

Participants and Recruitment

A total of 50 adolescents who are (1) aged between 12 and 18 years, (2) have one parent or legal guardian willing to participate, (3) report elevated levels of depressive symptoms (a score of ≥16 on the Center for Epidemiologic Studies Depression (CES-D) [39]), and (4) own a smartphone will be included in the study. The targeted age range covers the period when depression rates start to climb until they peak, and when the sex difference in prevalence widens [40]. Thus improved, personalized treatment is likely to be most impactful at these ages. Adolescents of these ages are also likely to own a smartphone—mobile sensing research assumes typical phone use, and research found that adults often did not carry study phones with them or use them as they would use personal phones [31]. Exclusion criteria include the following: (1) if receiving pharmacotherapy or psychotherapy for depression, the type or dose of therapy or dosage of medication has not been stable for at least the past 4 weeks; (2) current psychotropic medication taken as needed that could influence mood and related symptoms; (3) acute suicidality (ie, past-month method, plan, intent, access, perceived ability and probability of carrying out attempt); (4) past-year suicide attempt or serious nonsuicidal self-injury (NSSI), or history of suicide attempt over a year ago and not currently receiving mental health services; (5) history of mania or psychosis; (6) adolescent is not fluent in English; and (7) parent or legal guardian is fluent in neither English nor Spanish. Before December 2022, adolescents who reported any history of suicide attempt were excluded, and before February 2022, adolescents who reported any history of serious NSSI were also excluded, and the cutoff score was ≥20 on the CES-D to be included in the study. However, we broadened the inclusion criteria to address challenges with recruitment.

To account for expected attrition of 15%, 59 participants will be recruited from multiple sources, which include a university youth mental health clinic and local middle and high schools within south Florida in the United States, as well as social media posts, advertisements, and community referrals. Interested families are contacted to complete a brief phone screen where they will be assessed for eligibility. Adolescents are screened with the CES-D, which has been validated extensively with adolescents aged between 12 and 18 years [41], including those of Hispanic ethnicity [42], expected to comprise roughly 70% of our sample. The CES-D can discriminate severity at lower levels of depression [43], and 40%-50% of adolescents are likely to meet our cutoff score of ≥16 [44], making this an appropriate measure to select a sample of adolescents with elevated symptoms of depression.

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Ethical Considerations and Informed Consent

Study procedures were approved by the Florida International University Institutional Review Board in April 2020 (IRB-20-0257) and renewed annually thereafter. Due to the sensitive nature and large amount of data collected by the smartphone app from a vulnerable youth population, informed consent is required from both legal guardians (if applicable) of adolescents under the age of 18 years to participate in the study. Adolescents aged 18 years (ie, legal adults in the United States), as well as caregivers, provide informed consent for themselves to participate.

Safety Planning and Daily Safety Surveys

All families who consent to participate in the study are given brief psychoeducation about depression. Given the increased risk of adolescents with depression having thoughts of suicide [45], adolescents also complete a suicide risk assessment and safety plan [46] with a member of the research team during baseline assessment. The adolescent's assessment and safety plan are then reviewed with the participating caregiver, who is engaged to provide additional information and feedback and encouraged to support the adolescent in following the safety plan whenever needed, and a copy of the safety plan is provided to the family. Adolescents with elevated risk are excluded from the study and connected to crisis support services as appropriate. In addition, all adolescent participants complete a daily safety survey as part of our EMA procedures. Adolescents are asked whether they have experienced abuse or suicidal ideation since the last survey. Endorsement of abuse will prompt an automated reminder to call 911 or contact a trusted adult, as well as a call from the research team to the youth within 24 hours. Endorsement of suicidal ideation will prompt an automated reminder to use the safety plan or call 911, as well as a call from the research team to the caregiver within 24 hours. Families are instructed not to use the safety survey or other mobile data collected as a way to seek help in an emergency, as it is not feasible for data to be reviewed frequently throughout the day. The adolescent and parent participating in the study then complete a brief quiz to demonstrate that they understand risk procedures in the event that the adolescent reports suicidal ideation or abuse on their daily surveys. All research team members who interact with families receive training and ongoing supervision by the principal investigator, a licensed clinical psychologist, in risk and mandated reporting procedures. In addition, research team members are instructed to contact the principal investigator or an on-call licensed mental health clinician at the university mental health clinic shortly after receiving any report of suicidality or possible abuse from adolescents to ensure that appropriate steps are taken to ensure the safety of the adolescents.

Data Collection

All assessments take place remotely [47]. The wrist-worn actigraph is mailed to participants in advance of the baseline assessment. During the baseline assessment, caregivers and adolescents who meet all inclusion criteria complete a series of questionnaires measuring demographics, depressive symptoms, and depressogenic processes (Table 1). Adolescents are guided to install the Effortless Assessment of Risk States (EARS) mobile app [27,48] on their smartphones, and, for the next 28 days, the app collects EMA and mobile sensor data, and adolescents wear the actigraph device. EARS was developed for both iPhones and Android phones, is updated to maintain compatibility with newer operating systems, and uses rigorous data security features. During the 28-day smartphone and actigraph period, the app presents feedback to adolescents about their survey completion and bonuses earned and uses gamification features (eg, graphics and trophies) to reinforce adherence. Smartphone data will be continuously uploaded to a cloud server and monitored; those who uninstall the app or miss consecutive surveys will be called or texted and offered assistance. Families receive up to US $191 for study completion, including bonuses for completion of all surveys per day and 80%-90% overall adherence to EMA and actigraph procedures. At follow-up, families complete measures and a user feedback interview (Table 1). EARS is then uninstalled, and the actigraph is mailed back to the research team.

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Table 1. Measures completed by adolescents and caregivers at baseline and follow-up assessment.

Measures	Baseline	Follow-up
Demographics, ethnic identity, and pubertal development		
Demographic information and adolescent self-reported smartphone habits	Adolescent and caregiver	—[a]
Multigroup Ethnic Identity Measure [49,50] validated with diverse samples of adolescents and adults [51]	Adolescent and caregiver	—
Pubertal Developmental Scale [39,52]	Adolescent	—
Adolescent depression and related symptoms, and caregiver depression		
Center for Epidemiologic Studies Depression Scale [39] measures adolescent and caregiver self-reported depression	Adolescent and caregiver	Adolescent and caregiver
Youth Self-Report and Child Behavior Checklist [53] measures internalizing and externalizing problems	Adolescent and caregiver	Adolescent and caregiver
Affective Reactivity Index [54] measures irritability	Adolescent and caregiver	Adolescent and caregiver
Children's Reports of Sleep Patterns [55] measures sleep problems, validated with polysomnography	Adolescent	Adolescent
Top problems assessment [56] measures problems youth or caregivers identify as most important	Adolescent and caregiver	—
Use of services and impact of COVID-19		
Adolescent Medication, Therapy, and Services assesses mental health service use	Adolescent and caregiver	Adolescent and caregiver
Epidemic-Pandemic Impacts Inventory [57] measures the impact of the COVID-19 pandemic on various domains of personal and family life	—	Caregiver
University of Florida Life Space Mobility rates the frequency of movement before and after the COVID-19 pandemic	—	Adolescent
Environmental Influences on Child Health Outcomes COVID-19 Scale measures the impact of the COVID-19 pandemic on school, stress, activity levels, and other domains	—	Adolescent
Adolescent depressogenic processes and Research Domain Criteria constructs		
Rumination Response Scale [58] measures negative perseverative cognitions	Adolescent	Adolescent
Automatic Thoughts Questionnaire [59] measures negative automatic cognitions	Adolescent	Adolescent
Behavioral Activation/Inhibition Scale [60] measures reward responsiveness and potential threat response	Adolescent	Adolescent
Responses to Stress Questionnaire [61] measures coping and involuntary stress responses. Adolescents select the version of the questionnaire that corresponds to the stressor that is most applicable to them. Adolescents can select from peer stress, maternal depression, paternal depression, family stress, academic problems, COVID-19, or financial problems	—	Adolescent
Multidimensional Scale of Perceived Social Support [62,63] measures affiliation with friends, family, and significant other	Adolescent	Adolescent
Berkeley Expressivity Questionnaire [64] measures social communication through the production of facial expression	Adolescent	Adolescent
Snaith-Hamilton Pleasure Scale [65] measures anhedonia	Adolescent	Adolescent
Feedback interview about ecological momentary assessment, mobile sensing, and actigraphy. Rate how enjoyable, easy to use, disruptive, acceptable; privacy concerns and changes in phone use during the study; describe likes or dislikes, suggested improvements, and health-related apps currently used	—	Adolescent and caregiver

[a]Measures not given to adolescents and caregivers.

EMA

Symptom surveys are administered 5 times a day on weekdays and 6 times a day on weekends, over 28 consecutive days. Prompts are delivered randomly within 2-hour blocks in the morning (9 AM-11 AM), around noon (11 AM-1 PM), early afternoon (1 PM-3 PM), late afternoon (3 PM-5 PM), and evening (5 PM-7 PM), with a late evening (7 PM-9 PM) block on weekends. Each block includes a 0.5-hour buffer to separate adjacent surveys. A similar sampling schedule has been used successfully (>80% compliance) with adolescents [24]. Adolescents rate on a 0-100 visual analogue scale 21 items adapted from previous studies [11,12,25]: depressive symptoms ("felt down or depressed," "felt hopeless," "felt irritable or cranky," "felt like you don't enjoy things," "felt

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bored/uninterested in things," "felt worthless or guilty," "had difficulty concentrating," "felt tired," "felt restless"), depressogenic processes ("dwelled on the past," "avoided people," "avoided activities," "procrastinated"), negative affect/anxiety symptoms ("felt angry," "felt worried," "felt nervous or anxious," "felt afraid," "felt tense in your muscles"), and positive affect ("felt happy or positive," "felt energetic," "felt enthusiastic"). Once per day, adolescents also report their attempted sleep time, sleep onset latency, and wake time; their subjective sleep quality on a 0-100 visual analog scale; and whether they had a “fixed” or “free” wake-up (by alarm or caregivers, noise, or naturally).

Mobile Sensing

We selected 12 sensor variables to be analyzed based on previous literature [30,32,35,37]. These include raw data on battery status, calls (frequency×duration), as well as extracted features on mobility (percentage of time spent at home and distance traveled from GPS), physical activity intensity from accelerator, sleep duration and efficiency (from ambient light and accelerometer), and natural language use in social communication (from all text typed into email, text, and social media apps, captured by a keyboard logger). Specifically, we will assess word count and word sentiment through the Linguistic Inquiry and Word Count [66] Positive Emotion and Negative Emotion dictionaries, and the use of first-person pronouns (eg, “I”) and absolutist words (eg, “never”) associated with mental health [67-69], in English and Spanish.

Actigraphy

Adolescents wear on their nondominant wrist a research-grade actigraph, a wearable wrist monitor used to capture and record continuous, high resolution physical activity and sleep and wake information. The wGT3X-BT device (ActiGraph) is widely used in research studies and has been validated against indirect calorimetry and polysomnography [22,23]. It also features a light sensor; thus, this model was initially used with participants. However, feedback interviews from early in the study revealed a strong preference for a less conspicuous device to avoid drawing unwanted attention. A total of 15 adolescents wore the wGT3X-BT model, with an average wear time of only 74.3% for the 13 adolescents who completed 28 days of actigraphy. To maximize adherence to wearing the actigraph, we replaced the initial model (encased in a bright red plastic shell) with the newer GT9X Link model (ActiGraph), which resembles a black smartwatch with a digital display of the time, in August 2022. Since then, 24 adolescents have used or are using the GT9X Link model, resulting in an increased average wear time of 80.2% for the 21 adolescents who completed 28 days of actigraphy using this model. Both models use a triaxial accelerometer and ActiGraph’s proprietary filtering algorithm to assess total sleep time, sleep latency onset, wake after sleep onset, sleep efficiency, sedentary bouts, and physical activity intensity in participants’ natural environments, and were designed to give comparable results. The primary differences between the wGT3X-BT model and the GT9X Link model are that the GTX9 Link model has a liquid-crystal display and a gyroscope, and the other model does not, whereas the wGT3X-BT has an ambient light sensor, and the other model does not. The data will be analyzed with the ActiLife companion software using the Sadeh algorithm to distinguish between sleep and wake states [70].

Data Analysis

Sample Size

The numbers of observations (t=148) and participants (n=50) were estimated based on previous research using similar idiographic models [4,6]. Given the mean response rate (78%) in smartphone EMA with youth [71], 115/148 observations per adolescent are expected; thus, up to 23 EMA items can be included in an idiographic model with ≥5 observations per item.

Aim 1 Analyses: Idiographic Dynamic Models of EMA Data to Identify Person-Specific Drivers

EMA will yield a multivariate time series for each adolescent to be submitted to network analysis [11,12]. The graphical vector autoregressive (VAR) model will be used to identify contemporaneous and lag-1 directed effects. The graphical VAR function in R [72] models the autocorrelations and cross-predictions in a lag-1 VAR model as directed paths in the temporal portion of the network model, and the residual correlations as associations in the contemporaneous network. Regularization is applied through the least absolute shrinkage and selection operator (LASSO) algorithm, and model selection is performed by the extended Bayesian information criterion [73]. Hypotheses are supported if ≥50% adolescents (1) have contemporaneous networks in which ≥1 item has greater strength centrality at a given time t, (2) temporal networks in which ≥1 item has greater outstrength (ie, time t values that strongly predict other items at time t+1), and (3) if items with the greatest centrality and outstrength vary across adolescents. Because idiographic networks are a new area, there is no established threshold for identifying drivers and distinguishing significant differences among adjacent-ranked items for the same adolescent, other than selecting items with a CI that does not include zero. We will thus explore and consider using novel methods that may facilitate the identification of drivers. For example, a recently developed approach that ranks the items by their controllability (ie, how efficient it is to intervene on each item, taking into account downstream changes in the symptom network [74]) might be helpful for addressing this aim if it can be extended from group analyses to idiographic analyses. In addition, results may not generalize beyond the items in the measure used to generate the network, prompting recommendations to avoid multiple items measuring the same construct and to examine latent variables before estimating networks [75]. Person-specific dynamic factor analysis is another approach to identifying person-specific drivers by examining latent variables of symptoms that predict other latent variables of symptoms over time [76].

Aim 2 Analyses: Validation of Mobile Sensing to Identify Person-Specific Drivers

First, we will sample mobile sensor and actigraph data collected during the 15-minute intervals just before and just after each EMA response. (2a) Because of our idiographic focus and previous research showing high between-subject heterogeneity [34], N-of-1 correlations will be computed with the equivalent

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or conceptually similar actigraph and EMA measures: (1) sleep duration and efficiency, physical activity intensity with EMA items "felt energetic," "felt tired" (2) communication word count and calls with EMA item "avoided people." Our a priori thresholds for correlations are r=0.32 (minimum acceptable), r=0.50 (moderate), and r=0.71 (strong), corresponding to 10%, 25%, and 50% of overlapping (shared) variance. Among the various metrics, we believe that overlapping variance represents the degree to which the EMA, sensor, and actigraph data signals stem from the same data-generating process. Moderate to strong correlations support the utility of sensor-measured behaviors as proxies for self-reported tiredness, energy, and social interaction, providing empirical support for replacing these EMA items in idiographic symptom network models. (2b) Second, we will assess the 12 mobile sensor variables as predictors of self-reported mood ("felt down or depressed," "felt hopeless," "felt irritable or cranky") and anhedonia ("felt bored/uninterested in things," "felt like you don't enjoy things") using random forests [77], which has been used successfully to analyze mobile sensor data for N-of-1 models [32]. The 5 EMA items will be assessed as separate outcomes in N-of-1 models, a high R^2 indicates that the model closely predicted and could substitute the EMA scores. The same R^2 thresholds of 10%, 25%, and 50% overlapping variance will be used. The robustness of these predictions is assessed with repeated sampling of 100 random training-test data splits, with a 70/30 split of training and test data per sample [32]. This approach accommodates nonlinear relationships and complex interactions, minimizes overfitting the data, and selects the most important predictors [78]. Moreover, random forests perform well in smaller samples without hyperparameter tuning [79] and when the number of trees does not exceed the number of observations [80,81]. Random forest is an ensemble method combining bootstrapped data sets into a final model, and although predictor importance is indicated, the lack of regression coefficients can be challenging for interpretation [32]. Thus, if necessary, we propose an alternative with similar advantages (eg, selects important variables, minimizes overfitting)—elastic net regularization. A k-fold cross-validation with 20 folds will be used to select the optimal model with the minimum mean cross-validated error. This approach produces fewer prediction errors than comparable methods (eg, LASSO and ridge regression).

Aim 3 Analyses: Exploration of Baseline Predictors of Person-Specific Drivers

From the idiographic models in aim 1, ≥50% of adolescents are expected to have drivers (1 or 2 out of 18 EMA symptoms with the greatest strength centrality and outstrength). A wide range of baseline adolescent characteristics (demographic, developmental, and clinical) will be examined as predictors of driver status (yes vs no) in a between-subjects (all participants) random forest classification model for every symptom. An area under the curve >0.50 indicates that the predictors can predict driver status of a given symptom better than chance. The robustness of classification is assessed with a 70/30 split of participants into a training set and a testing set [32]. If necessary, we propose elastic net regularization as an alternative due to the reasons described in aim 2, and good performance even though the number of participants is small compared to the number of predictors [82].

Results

Recruitment began in May 2021. As of October 2023, we have contacted 1069 families; 22% (n=235) expressed interest in participation and completed a phone screen, of whom 36% (n=84) were eligible to enroll in the study. Of the 84 eligible families, 70% (n=59) provided informed consent, 63% (n=53) completed a baseline assessment, and 46% (n=39) met all inclusion criteria. Of the 25 families who were eligible but elected not to participate in the study, 52% (n=13) did not provide a reason, 28% (n=7) were unable to be reached, 16% (n=4) were not comfortable with the amount of data collected or frequency of surveys, and 4% (n=1) were only able to get consent from one of their 2 caregivers in order to participate. A total of 6 families provided informed consent but did not continue with the study, of whom 66% (n=4) did not provide a reason, 17% (n=1) stated their schedule was not compatible with the study, and 17% (n=1) were unable to be reached. During baseline assessment, 17% (n=14) of families were excluded from the study, of whom 36% (n=5) were excluded for acute suicidality, and the remaining 64% (n=9) were excluded due to a history of serious NSSI, suicide attempt, or both. Of the 39 included families, 85% (n=33) completed the 28-day smartphone data collection period and follow-up study visit, 8% (n=3) lost the actigraph, 5% (n=2) stopped participation early, and 3% (n=1) is currently in the process of completing the study.

Discussion

Overview

In this protocol report, we describe the methods of a study using smartphone-based EMA and passive sensing with the goal of identifying person-specific drivers of depression in adolescents. We have provided a status update on data collection for this ongoing study. Of the 59 adolescents targeted for recruitment, two-thirds (n=39) have started the study, and half have completed all phases of the study (n=33). After data collection is complete, we plan to address the 3 specific aims of this study. First, we will investigate whether there is evidence for person-specific drivers of depression among this sample of adolescents. That is, we will identify symptoms that strongly predict change in other symptoms for each adolescent and examine whether these driver symptoms differ across adolescents. Second, we will validate mobile sensor data against EMA and actigraph measures. We will assess whether smartphone-measured sleep, physical activity, and social interaction variables are correlated with conceptually similar actigraph-measured variables and EMA responses, and whether mobile sensor data can predict EMA responses about the key depressive symptoms of low mood and anhedonia within each adolescent. Third, we will explore whether baseline adolescent characteristics can predict which symptoms are drivers for which adolescents.

Empirical findings suggesting that person-specific drivers of adolescent depression exist would offer a plausible explanation

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for individual differences in clinical presentation and treatment response in this population. These findings would also support the need for a personalized approach to assessment and intervention, where treatments or their component modules are selected and sequenced to target each adolescent's specific drivers [14,15]. Indeed, emerging research suggests that depressed youth display heterogeneous responses to individual CBT modules [83,84]. Moreover, the particular symptoms identified as drivers in our adolescent sample could be compared to those identified in adult samples. Differences in driver symptoms between adolescents and adults may provide clues as to why depressed adolescents do not benefit as much from psychotherapy as do adults [6], thereby informing the generation of hypotheses about developmental considerations in the treatment of adolescent depression for future testing.

Our efforts to validate mobile sensor data for predicting depressive symptoms in adolescents will add to the small but growing literature on this topic [33-36]. Recent studies have demonstrated promising results in predicting depressive symptom scores [33,35] and diagnosis [36] using smartphone and wearable sensor data. One study [34] found good prediction of elevated anger and anxiety but more modest prediction of sadness from mobile sensor data—a finding that is particularly relevant to this study's focus on assessing and predicting the severity of individual depressive symptoms. Accurately predicting individual symptom severity with mobile sensor data obtained with minimal user effort can make the assessment of person-specific drivers more feasible to use with adolescents in clinical practice.

If adolescent characteristics measured at baseline are found to predict each adolescent's driver symptoms reasonably well, then a preliminary assessment of drivers could be made early in the evaluation, shortening the lag time from intake to the initiation of treatment. The month-long smartphone tracking phase may be used to confirm the preliminary assessment results or perhaps even be skipped entirely. Although identifying drivers focuses on intrapersonal symptom dynamics, examining between-subject characteristics that predict those drivers could shed light on interpersonal differences in psychopathology and begin to illuminate subgroups of adolescents with different optimal treatment targets. A future direction is to use the data generated by this study to inform the development and testing of a scalable, low-burden smartphone-based tool and treatment algorithm to select and sequence therapy modules targeting person-specific drivers in depressed adolescents with potential public health impact.

Limitations

This study is recruiting participants from the community who generally have mild depressive symptoms and low risk of suicide and self-harm. We focused on this population due to practical reasons relating to recruitment and our capacity for responding to emergent crises. However, adolescents with severe depressive symptoms and higher risk of suicide and self-harm may be in greatest need of effective treatment. In order to inform personalized treatment for the adolescents who may benefit the most from it, further research on person-specific drivers of depression needs to be conducted with this population.

In addition, this study cannot establish whether identified drivers cause changes in other depressive symptoms, only whether they are associated with changes in depressive symptoms. It is thus possible that a third variable is causing changes in both driver and nondriver depressive symptoms. Moreover, contemporaneous networks cannot determine the direction of association between central symptoms and other symptoms; changes in other symptoms may in fact precede changes in central symptoms, or the association may be bidirectional. A related concern is that the temporal networks' ability to capture directional change is constrained by the EMA sampling intervals of 2 hours—directional change that occurs during a shorter or much longer time frame will not be detected.

Furthermore, data were collected during the COVID-19 pandemic, a time when adolescents had to deal with multiple stressors, including fears about themselves or their loved ones being infected, losses (eg, of life, job, or relationships) experienced by themselves or family members, disruptions to schooling and social activities, and isolation at home due to safe distancing measures [85]. Studies have documented increased depressive symptoms and loneliness, as well as poorer academic functioning among adolescents during the pandemic, with notable heterogeneity in pandemic impact attributed to differential access to resources and preexisting vulnerabilities [86]. To assess how the pandemic may influence the associations between adolescents' behavior assessed by mobile sensors and their depressive symptoms, we have included several measures of pandemic impact on adolescents and their parents.

Conclusions

As one of very few studies examining depressive symptom networks among adolescents, this study is expected to offer novel insights into the structure and dynamics of depressive symptomatology during a sensitive period of development. A better understanding of what drives depression during this high-risk, high-impact window of development could lead to assessments and interventions that better address developmental and individual differences, ultimately producing greater benefit over the life course. Finally, this study is expected to contribute to the growing literature supporting a shift from standardized to personalized assessment and treatment of adolescent depression.

Acknowledgments

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Data Availability

The data sets generated during this study are available from the National Institute of Mental Health Data Archive at the National Institutes of Health. The National Institute of Mental Health Data Archive is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Data set identifier is 10.15154/88w5-4029. This manuscript reflects the views of the authors and may not reflect the opinions or views of the National Institutes of Health.

Authors' Contributions

MYN is the principal investigator of this funded study; AJF, JWP, and DLM are coinvestigators who contributed to the study design and ongoing implementation of the study; NBA is a consultant providing expertise on smartphone data collection methods; and JAF is a graduate research assistant serving as study coordinator.

Conflicts of Interest

NBA is the cofounder and CEO of, and has an equity interest in, Ksana Health, the company that developed and maintains the EARS platform used in this study. JWP receives royalties from New Harbinger Publications and the American Psychological Association. All other authors declare no conflicts of interest.

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Abbreviations

CBT: cognitive behavioral therapy
CES-D: Center for Epidemiologic Studies Depression Scale
EARS: Effortless Assessment of Risk States
EMA: ecological momentary assessment
LASSO: least absolute shrinkage and selection operator
NSSI: nonsuicidal self-injury
VAR: vector autoregressive

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Protocol

A Digital Communication Intervention to Support Older Adults and Their Care Partners Transitioning Home After Major Surgery: Protocol for a Qualitative Research Study

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Abstract

Background: Older adults (aged ≥65 years) account for approximately 30% of inpatient procedures in the United States. After major surgery, they are at high risk of a slow return to their previous functional status, loss of independence, and complications like delirium. With the development and refinement of Enhanced Recovery After Surgery protocols, older patients often return home much earlier than historically anticipated. This put a larger burden on care partners, close family or friends who partner with the patient and guide them through recovery. Without adequate preparation, both patients and their care partners may experience poor long-term outcomes.

Objective: This study aimed to improve and streamline recovery for patients aged ≥65 years by exploring the communication needs of patients and their care partners. Information from this study will be used to inform an intervention developed to address these needs and define processes for its implementation across surgical clinics.

Methods: This qualitative research protocol has two aims. First, we will define patient and care partner needs and perspectives related to digital health innovation. To achieve this aim, we will recruit dyads of patients (aged ≥65 years) who underwent elective major surgery 30-90 days prior and their respective care partners (aged ≥18 years). Participants will complete individual interviews and surveys to obtain demographic data, characterize their perceptions of the surgical experience, identify intervention targets, and assess for the type of intervention modality that would be most useful. Next, we will explore clinician perspectives, tools, and strategies to develop a blueprint for a digital intervention. To achieve this aim, clinicians (eg, geriatricians, surgeons, and nurses) will be recruited for focus groups to identify current obstacles affecting surgical outcomes for older patients, and we will review current assessments and tools used in their clinical practice. A hybrid deductive-inductive approach will be undertaken to identify relevant themes. Insights from both clinicians and patient-care partners will guide the development of a digital intervention strategy to support older patients and their care partners after surgery.

Results: This study has been approved by the Massachusetts General Hospital and Harvard Institutional Review Boards. Recruitment began in December 2023 for the patient and care partner interviews. As of August 2024, over half of the interviews have been performed, deidentified, and transcribed. Clinician recruitment is ongoing, with no focus groups conducted yet. The study is expected to be completed by fall 2024.

Conclusions: This study will help create a scalable digital health option for older patients undergoing major surgery and their care partners. We aim to enhance our understanding of patient recovery needs; improve communication with surgical teams; and ultimately, reduce the overall burden on patients, their care partners, and health care providers through real-time assessment.

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KEYWORDS

mHealth; geriatric; surgery; care partner; qualitative study; digital intervention; intervention development

Introduction

Background

Older adults aged 65 years and older account for over 30% of the population of inpatients undergoing operations in the United States [1]. Older adults and their care partners typically begin their interaction with the surgical system as outpatients in an episodic fashion as they prepare for elective surgery. After surgery, the time spent in the hospital after many operations has shortened dramatically with the use of Enhanced Recovery After Surgery protocols [2]. Being prepared and informed prior to transitioning home is an important process that can improve patient and care partner's confidence during their hospital stays and beyond. Unfortunately, communication during surgical discharge is often inadequate. Up to 80% of patients do not recall the information provided, 71% of nurses say they do not have enough time to meet patient engagement and education needs, and 50% of patients recall incorrect information [3,4]. Once home, older patients often depend on care partners, close family, or friends who partner with the patient and help guide them through recovery and who often take on this role with little or no training by the surgical care team.

This transition to home earlier in their recovery can be difficult for the older adult patient. Delirium [5,6], functional decline [7], and loss of independence [8,9] occur frequently in this patient population in the early postoperative period. These changes to a patient's baseline function as well as sleep disturbance and medical burdens lead to anxiety and stress for patients and care partners, who are helping patients with activities of daily living during their recovery [10]. These compounded effects impact transitions to home and contribute to adverse outcomes, including mental health challenges, the need for hospital readmission, and loss of independence [11]. There is a critical need to address gaps in care quality to improve outcomes of older adults recovering from major surgery at home and support their care partners.

One possible and scalable way to address these gaps is through technology. It is a common misconception that most of the older population is resistant to technology; about 61% of adults aged ≥65 years owned a smartphone in 2021, and many more own a computer/laptop (90%) and use the internet (75%) [12,13]. Our current work strives to lay the groundwork for the development of a future digital health intervention to improve the outcomes of older adults and their care partners transitioning home by addressing unmet communication needs [14] and focusing on the perioperative period. We hypothesize that this qualitative study will yield critical information from all participants interviewed (patients, care partners, and clinicians) to create a useful digital health tool that addresses communication gaps and improves care coordination, thereby improving patient quality of life and reducing caregiver burden after surgery.

Objectives

The overall goal of this study is to identify and understand the obstacles older adults and their care partners face while recovering at home after major surgery and to receive input from clinicians involved in their care regarding current geriatric conditions, assessments, and potential interventions. These findings will inform a future digital intervention that addresses shortcomings in current systems of care and is designed for older adults undergoing elective surgery along with their care partners.

Methods

Study Design

We will conduct an exploratory qualitative analysis to investigate the communication needs of patients, care partners, and clinicians and the potential role of a digital health tool to address these needs. We will conduct interviews with adults (aged ≥65 years) who have undergone major surgery as well as their identified care partners (through a separate 1:1 interview) to understand unmet needs and challenges they encountered during recovery. We will explore how they responded to these obstacles and the types of intervention they anticipate would be the most helpful. Subsequently, we will seek additional input from key clinical stakeholders, specifically geriatricians, surgeons, and nurses, to explore the assessment tools and approaches that they feel would support the needs of older patients and their care partners during postoperative recovery and specifically how a digital tool could facilitate that support. A hybrid deductive-inductive approach will be undertaken to identify relevant themes [15]. Results will be used to inform the future development of a digital solution to support these patients after surgery and their care partners.

Inclusion and Exclusion Criteria

Patients and Care Partners' Semistructured Interviews

Surgical clinic patients from an urban academic medical center and community surgical center who underwent colorectal, orthopedic, and thoracic surgery will be considered for inclusion. To be included, patients must also be 65 years or older, have undergone recent (within 90 days) elective major surgery, and speak English. As for their care partners, they will be 18 years or older and be English speakers. Both patients and their respective care partners will need to be recruited (a dyad) for inclusion in the study. Exclusion criteria include cognitive impairment causing an inability to perform teach-back for consent to interview, as outlined in prior National Institutes of Health–funded studies [16]. If one-half of the dyad does not complete the requirements of the study, the other half's information and data will not be included in the study analysis.

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Clinician Focus Groups

We will include English-speaking health care workers within the clinician focus groups. These participants will be derived from the following populations nationwide: geriatricians, surgeons, anesthesiologists, advanced practice providers, physical therapists or occupational therapists, social workers or case managers, and nurses with experience with older adults recovering from surgery. Exclusion criteria include having less than 1 year of clinical experience, having no or limited experience with the older adult surgical patient population, and practicing outside of the United States.

Recruitment and Sampling

Patients and Care Partners' Semistructured Interviews

Older adults presenting to the Massachusetts General Hospital or North Shore Medical Center Surgical clinics (both part of the Mass General Brigham integrated health system) and their care partners meeting eligibility criteria will be recruited. The research team will query the operative list from the colorectal, thoracic, and orthopedic surgery patient population.

Eligible patients will be approached by the research fellow, who will review the study purpose, eligibility criteria, and informed consent documents using standard processes. Purposive sampling will ensure a diverse group of older surgical patients, with the inclusion of patients aged 80 years or older, to capture patients across an age spectrum [17]. In addition, the team will partner with the Massachusetts General Hospital Community Access, Recruitment, and Engagement Center to recruit patients from minority communities and those with low socioeconomic status (ie, education less than a high school diploma) to ensure the evaluation of recovery needs among a diverse patient population.

We expect to recruit 5 patients and their care partners from each of the 3 specialties, with a total of 30 interviews to reach saturation [18].

Clinician Focus Group Recruitment

Among clinicians currently practicing in the United States, we will recruit a nationally representative sample of clinician participants by email in which we outline the study purpose and attach the consent form for participation in focus groups. We will leverage personal contacts in nursing, surgery, and geriatrics as well as national professional society meetings (such as the American Society of Colon and Rectal Surgeons, American Geriatrics Society, and American College of Surgeons) to obtain email addresses and optimize recruitment. Once participants are identified, we will schedule focus groups aligned by specialty to optimize group dynamics and encourage psychological safety as described in similar studies. We will plan to recruit 8 clinicians per group to account for nonattendance. We will conduct interviews and focus groups until thematic saturation is reached, with an initial estimate of 24 participants across 4 focus groups needed based on past studies and practical limitations of available clinicians [19,20]. Focus groups of around six members have been described as optimal for meaningful discussion [21].

Ethical Considerations

Ethical approval was obtained from the Harvard TH Chan School of Public Health Institutional Review Board (IRB23-0790). Survey information is collected and saved securely on REDCap (Research Electronic Data Capture). Informed consent is obtained prior to starting the interviews. Participants are informed of any intent to record prior to the start of the recording. Recordings are then transcribed, deidentified, and uploaded to a secure server. For each patient and care partner who completes both the survey and interview, they will receive US $20 for their efforts. Concerted efforts are made to purposefully recruit patients from varying sociodemographic, cultural, and ethnic backgrounds to obtain diverse perspectives from patients across surgical subspecialties.

Interviews

Patients and Care Partners' Semistructured Interviews

Prior to the qualitative interview, we will send out an electronic survey via email through REDCap to both the patient and designated care partner; each participant will answer demographic and quality of life questions (the latter is based on the World Health Organization Quality of Life questionnaire [WHOQOL-BREF]) [22,23]. The care partner will answer additional questions based on the Zarit Burden Interview [24,25]. These survey emails take 15 minutes or less to complete. The WHOQOL-BREF questionnaire is scored based on a predefined scoring system that is then calculated into domain scores, which range from 0 to 100, with a higher score representing a better health state. Each question on the Zarit Burden Interview is scored based on the Likert scale, with a higher composite number representing a greater burden to the care partner. Both questionnaires are highly validated tools that have been used for decades [23,25].

During the virtual or phone qualitative interview, we will (1) characterize patients' and care partners' perceptions of the surgical experience and how they cope with its challenges; (2) identify appropriate intervention targets, such as the 5 Ms of geriatrics (ie, mind, mobility, medications, what matters most, and multicomplexity); (3) assess patients' and care partners' preferences for the structure or mode of delivery (including video, phone, in-person, or via an application or desktop platform), the timing of the intervention, and the number of sessions; (4) review potential module content and the resources used; and (5) assess patients' and care partners' perception about their usefulness (Multimedia Appendices 2 and 3).

Clinician Focus Groups

Prior to the qualitative interview, clinicians will fill out an electronic survey via REDCap that will capture demographic data. During the virtual focus groups, we will (1) evaluate geriatric conditions affecting outcomes from major surgery among older adults, (2) discuss geriatric assessments performed to evaluate these needs, (3) rate assessments and tools, and (4) discuss procedures for intervention delivery (Multimedia Appendix 4).

Remote interviews will be conducted using Health Insurance Portability and Accountability Act–compliant video conference

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software (eg, Microsoft Teams; version 24004.1304.2655.7488). We will use audio and video to record the interviews and transcribe them.

Analysis

Interviews will be coded using a multistep approach [26,27]. First, 2 members of the research team will create an a priori codebook, drawing codes directly from the interview guide. A priori themes will include (1) presurgery experiences, (2) clinical care team communication, (3) postsurgical challenges, and (4) description and use of a digital intervention. A set of 2 transcripts will be coded using this codebook. At least 2 members of the research team will then meet to discuss and resolve discrepancies and update the codebook accordingly. Next, at least 2 members of the research team will inductively code 2 additional transcripts to identify additional themes not included in the a priori codebook. Based on this open coding, inductive codes will be added to the codebook. All transcripts will be coded against this codebook. All coding will be conducted in the NVivo 20 software. At least 2 members of the research team will code all transcripts, meeting periodically to discuss discrepancies and ensure a consensus is reached. NVivo software's coding comparison feature will be used to compare coding and identify any major discrepancies that emerge in the coding process. We will compare each researcher's coding across all transcripts and resolve discrepancies on a regular basis until all coding is complete [28].

Clinician, patient, and care partner interviews and focus groups will guide intervention development. Our research team will meet weekly to discuss the analytic plan and intervention development.

Results

This study is funded by the Agency for Healthcare Research and Quality grant (R01HS029454). The study was approved by the institutional review board of the Massachusetts General Hospital and Harvard. Recruitment began in December 2023 for the patient and care partner interviews. As of August 2024, over half of the proposed patient-care partner interviews have been performed, deidentified, and transcribed. A proposed codebook has been developed and the coding process is underway but not yet completed. Clinicians are currently being recruited and no focus groups have been performed yet.

Discussion

Expected Outcomes

The overall goals of this qualitative study are to identify and understand the obstacles older adults, care partners, and clinicians face when transitioning home after major surgery and to use this understanding to inform a potential intervention that addresses the needs of these groups during this critical time. This protocol will outline stakeholder perspectives on clinically important geriatric conditions, assessments, and interventions to meet the currently unmet needs of this growing patient population. The results of these semistructured interviews and focus groups will inform the development of a digital health intervention aimed at improving the quality of life for patients and reducing care giver burden during surgical recovery by addressing communication gaps and current shortcomings in care coordination.

Given the increasing use of the internet and mobile-based technologies for delivering health care during and following the COVID-19 pandemic [12], it is imperative that clinicians and surgical systems leverage digital health applications to improve transitions of care, particularly for vulnerable populations, including older adults [29]. For example, if participants identify physical and neurocognitive decline after major surgery as a challenge for patients, the digital intervention we develop could use personalized, timely assessments to identify and address these findings to optimize care for older adults transitioning home after surgery [30]. If participants note challenges with coordinating access to care after surgery (eg, presenting to the emergency room versus the surgical clinic for wound concerns), we can develop tailored communication to improve care coordination through the intervention. In addition, timely anticipatory guidance based on participant feedback can ensure patients and care partners prepare their homes and obtain supplies helpful during their recovery. By designing the intervention with input from both academic and community surgical practices, we propose to develop an intervention that is acceptable, usable, and based on the best evidence. This design process should ensure that the resulting tool will be readily adopted by a wider audience.

Despite the burgeoning use of technology to facilitate remote health monitoring, older adults are sometimes excluded from the benefits that these technologies provide [31]. Lack of access to health care–related technology is a barrier to adoption and is influenced greatly by both exposure and cost [32]. The social and professional environment and personal preferences of older adults may not inspire or influence them to follow and adopt this technology as readily as their younger counterparts. It is often the role of the younger care partner or family member to learn and then teach older adults how to use newer technologies. If the older adult does not have access to this information (by owning the necessary technology or having the baseline skills required of digital literacy, such as using a computer or smartphone) or someone to teach them (a care partner who has this knowledge or access to newer technologies), then the patient will often resort to a more traditional or antiquated alternative. These new technologies can also be cost prohibitive, especially for older adults who have limited resources. Buying the latest gadget or health monitor may not be in their budget [33].

Another obstacle is that digital health options are often designed for young populations with excellent vision and manual dexterity in addition to advanced digital literacy [34]. It is not uncommon for older adults to require large and bolded text on their phones because of the loss of visual acuity. In addition to small text, many electronic applications have inappropriately colored or contrasted text that older adults have trouble reading [35]. In addition, these devices and applications may have functions that may rely on a preexisting familiarity with the technology's functionality unfamiliar to older adults not fully immersed in the digital ecosystem.

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This qualitative study will strive to consider all these diverse factors. If an interview participant does not have internet access or knowledge of videoconferencing, then a phone interview will be conducted. It will gauge patient and care partner challenges and their current solutions. It will identify the resources they had (before and after surgery) and those they wished they had. It will assess current effective and unproductive modes of communication. Most importantly, it will gauge their direct sentiments about a digital health option that could potentially address the shortcomings identified in their interview answers. This protocol will ensure that any digital health option generated in the future will take into account older adults' perspectives as well as those of their care partners and clinicians. This will minimize waste, ensure the tools developed are designed within the targeted audience's physiological and biopsychosocial restrictions, and increase the probability of adoption and utility. Importantly, this study will also explore how digital technologies can be used by the adjacent care partner to support an older adult during recovery. Care partners may have differing needs from the patients and different degrees of engagement with digital technology. This study may ultimately identify opportunities for novel digital health capabilities through technology that links the patient-care partner dyad with the health care team.

Strengths and Limitations

There are several strengths to this study. This is one of the first studies to evaluate communication barriers of the older adult population undergoing major surgery and explore how a digital intervention might improve transitions home after surgery. It will also consider the care partner perspective, who may be of the same generation (oftentimes spouses or close relatives). The study will include diverse clinician perspectives, particularly those professionals who interact with older patients frequently. This information can then be leveraged to develop a prototype digital health intervention that is useful and acceptable using a human-centered design approach. The application will then undergo refinement to further improve acceptability. Smartphone-based education and remote self-monitoring are scalable solutions that can improve outcomes in this growing high-risk patient population. This protocol outlines the foundational development of a future digital health solution to support the needs of older adults undergoing major surgery as well as the needs of their care partners. The findings from this work can be scaled and spread to increase the value of care provided for a variety of health conditions and will drive future efforts to improve transitions home after major surgery, particularly for current and future generations of older adults—by the end of this decade a fifth of Americans will be aged older than the 65 years [36].

Limitations of this study include potential limits in generalizability based on our recruitment of patients from the geographic northeast of the United States. To overcome this limitation, we will intentionally recruit a diverse patient population. Another limitation of this study is that all patients and care partners will be English speakers. Future work will need to address this shortcoming with multilingual qualitative interviewers to culturally adapt content of the planned intervention. We will include patients from 3 major surgical specialties that service a large older adult patient population. Although this study is based in the United States, it reflects the same concerns addressed in countries globally that are looking to adopt digital health technology. Our findings may have generalizability to other countries that are comparable in terms of economic development and digital technology adoption. We will also strive to include the perspective of patients and care partners with low income and those below the poverty threshold and reflect on the particular limitations encountered by these groups. It will be important to note the possibility that benefits derived from future interventions based on this work may deepen the digital divide that already exists, as it can leave behind those who, for financial, health, or geographic reasons, cannot benefit from more real-time assessment [37,38]. Possible solutions proposed have been for governments to subsidize basic or newer technologies [39] to facilitate adoption and to be purposeful when building new or reinforcing internet infrastructures with a focus on marginalized populations [40].

Conclusions

This qualitative research protocol will improve our understanding of the obstacles older adults and their care partners face while recovering at home after major surgery. The described approach will yield critical data to inform the development of a digital health intervention that is tailored to all those involved in the care of the older adult surgical population with a particular focus on care partners that are often provided limited support from the surgical care team. These findings will inform a future digital intervention that addresses shortcomings in current systems of care and will be designed to support older adults undergoing major surgery, their care partners, and clinician team members.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer-review reports from the Healthcare Information Technology Research (HITR) - Agency for Healthcare Research and Quality (USA).
[PDF File (Adobe PDF File), 133 KB - resprot_v13i1e59067_app1.pdf]

Multimedia Appendix 2
Questions to be asked during the patient qualitative interview.
[DOCX File , 20 KB - resprot_v13i1e59067_app2.docx]

Multimedia Appendix 3
Questions to be asked during the care partner qualitative interview.
[DOCX File , 20 KB - resprot_v13i1e59067_app3.docx]

Multimedia Appendix 4
Questions to be asked during the clinician focus group interview sessions.
[DOCX File , 184 KB - resprot_v13i1e59067_app4.docx]

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Abbreviations

REDCap: Research Electronic Data Capture
WHOQOL-BREF: World Health Organization Quality of Life questionnaire

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Proposal

Problematic Social Media Use Among Italian Midadolescents: Protocol and Rationale of the SMART Project

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Abstract

Background: Social media (SM) use constitutes a large portion of midadolescents' daily lives as a way of peer interaction. A significant percentage of adolescents experience intense or problematic social media use (PSMU), an etiologically complex behavior potentially associated with psychological distress. To date, studies longitudinally testing for risk or protective factors of PSMU, and collecting qualitative data are still scarce among midadolescents. Self-help interventions specifically targeting PSMU in this population and involving midadolescents in co-creation are needed.

Objective: The 2-year SMART multicenter project aims to (1) advance knowledge on PSMU; (2) co-design an unguided self-help app for promoting awareness and functional SM use; and (3) test feasibility and provide preliminary findings on its effectiveness to further improve and adapt the app.

Methods: The SMART project is organized in 3 phases: phase 1 will focus on knowledge advancement on PSMU and its risk and protective factors using a longitudinal design; phase 2 will explore adolescents perspectives using qualitative approach and will co-design an unguided self-help app for reducing PSMU, which will be evaluated and adapted in phase 3. Around 1500 midadolescents (aged 14-18 years) will be recruited in northern, central, and southern Italy to investigate the potential intra- and interpersonal psychological risk and protective factors for PSMU and define specific PSMU profiles and test for its association with psychological distress. Subjective (self-report) PSMU's psychosocial risk or protective factors will be assessed at 3 different time points and Ecological Momentary Assessment (EMA) will be used. Moreover, focus groups will be performed in a subsample of midadolescents to collect the adolescents' unique point of view on PSMU and experiences with SM. Those previous results will inform the self-help app, which will be co-designed through working groups with adolescents. Subsequently, the SMART app will be deployed and adapted, after testing its feasibility and potential effectiveness in a pilot study.

Results: The project is funded by the Italian Ministry of University and Research as part of a national grant (PRIN, "Progetti di Rilevante Interesse Nazionale"). The research team received an official notice of research funding approval in July 2023 (Project Code 2022LC4FT7). The project was preregistered on Open Science Framework, while the ethics approval was obtained in November 2023. We started the enrollments in December 2023, with the final follow-up data to be collected within May 2025.

Conclusions: The innovative aspects of the SMART project will deepen the conceptualization of PSMU and of its biopsychosocial antecedents among midadolescents, with relevant scientific, technological, and socioeconomic impacts. The advancement of knowledge and the developed self-help app for PSMU will timely respond to midadolescents' increased loneliness and psychological burden due to COVID-19 pandemic and humanitarian crisis.

Trial Registration: OSF Registries; https://osf.io/2ucnk/

International Registered Report Identifier (IRRID): DERR1-10.2196/58739

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KEYWORDS

adolescents; social media; problematic social media use; psychological distress; wellbeing promotion; eHealth interventions; co-creation; qualitative research; biomarkers

Introduction

Background

According to the World Health Organization, one-sixth of the global population is composed of adolescents, and this number is expected to rise through 2050 [1]. Unfortunately, 1 in 7 adolescents experience mental health conditions, which remain largely unrecognized and untreated. Also, given the widespread use and pervasiveness of new technologies among adolescents, it is not surprising that 60.43% of Italian adolescents report an intense or a problematic social media (SM) use (PSMU) [2] and, although to our knowledge, no estimations regarding the direct or indirect financial cost or societal burden of PSMU are currently available, it has been hypothesized that PSMU may have relevant costs both for individuals (eg, mental and physical health, social functioning) and societies (eg, direct health care costs and indirect costs following productivity losses).

SM is made up of various digital user-driven platforms (eg, Facebook, TikTok, Instagram) that facilitate connectivity and engagement between individuals as well as allow to create and share user-generated content [3]. PSMU is considered an etiologically complex behavior associated with psychological distress, although this relation is far from being completely understood [4] and the conceptualization of PSMU is still debated. To date, the absence of a commonly accepted definition could be linked to the rapidly changing nature of SM as well as to the inconsistent results obtained by prior research on PSMU among adolescents [5]. Technology and SM are an integral part of the daily life of today's teenagers, who use them to create a virtual space to satisfy their needs for communication, social contact, belonging, comparison, and self-realization. However, some scholars defined PSMU as an "addictive-like" behavior (eg, associated with salience, tolerance, withdrawal, and relapse) [6], hierarchically arranged (ie, with different levels of excessive or disordered use) and whose main characteristic is a lack of self-regulation in one's own SM use [4].

Nonetheless, the adoption of an addiction paradigm to describe PSMU has been criticized [7].

Further, recent findings have highlighted how PSMU cannot be defined solely by the so-called screen-time ("how much"), but rather by "how" the SM is used [8]. More specifically, a high intensity of screen time and SM use may be a normative adolescent behavior that does not necessarily interfere with life domains relevant to adolescents' mental health (eg, offline socializing with friends or family) [2]. Core aspects of the way in which SM are used are active versus passive use [9], social support [10], fear of missing out [11], and types of activities individuals engaged in when using SM [12]. Yang et al [13] proposed an integrative model in which the previous multiple dimensions of SM use are considered. The Multidimensional Model of Social Media Use [13] suggests that individual platforms differ by activities (eg, interactive or directed communication, active posting to an unspecified audience, passive browsing), motives for use (eg, enhancement or compensation), and communication partners (eg, strong or weak ties) and that each dimension is associated with better or poorer well-being among youth. However, despite these differences in SM platform activities and interaction partners, surprisingly research usually focuses on overall or generic SM use and few studies have examined how adolescent characteristics may be more relevant to some platforms than others [14,15].

Previous research has also investigated several potential intra- and interpersonal psychological predictors of PSMU, clearly evidencing its multifactorial and complex etiology [16]. Among others, secure attachment [17], self-esteem [18], self-control [19], emotion regulation [20], life satisfaction [21], and parental variables (such as low levels of parents' own SM use and parental phubbing) [22] are some of the established protective factors for PSMU. Despite such efforts, the mechanisms underlying the development and maintenance of PSMU are still underinvestigated [4,23] due to the lack of (1) well-performed longitudinal studies designed to test for a temporal precedence of specific risk and protective factors for PSMU, (2) qualitative studies collecting adolescents' unique perspectives and needs, and (3) psychophysiological studies on PSMU. Indeed, 2 biomarkers of psychopathological risk, namely a lower parasympathetic activity over heart at rest [24], and the presence of specific polymorphisms for serotonin gene transporter 5-HT1AR and 5-HT2AR [25], may be associated with increased odds of PSMU among adolescents.

Finally, there is a call for effective prevention or early intervention programs which are tailored to the substantial risk and protective factors for PSMU to promote awareness of PSMU phenomenon and functional SM use and to overcome less effective abstinence-based protocols [26]. Smartphone apps could be an innovative way to reach young people. There is increasing evidence that unguided mobile self-help apps and web-based interventions offer a powerful solution for promoting public health and life skills interventions [27,28], especially among young digital natives [29,30]. The use and the engagement of such self-help apps may also increase thanks to a co-design process that involves end users (ie, midadolescents) [27,30,31].

Objectives of the SMART Project

The 2-year project "problematic Social Media use among Italian mid-Adolescents: from the identification of Risk/proTective factors to the co-design and evaluation of a self-help app" (namely "SMART project") aims to: (1) advance knowledge on PSMU and its risk and protective factors using a longitudinal design; (2) exploring adolescents unique perspectives on PSMU and co-design an unguided self-help app for promoting awareness and functional SM use; and (3) test feasibility and

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provide preliminary findings on its effectiveness to further improve and adapt the app.

As for the first aim, we hypothesize that intrapersonal (ie, higher difficulties in emotion regulation, negative affect, adjustment difficulties, and fear of missing out, as well as lower self-esteem, self-control, and satisfaction with life) and interpersonal (ie, attachment insecurity, higher preference for online social interactions, and parental phubbing and parents' dysfunctional SM use) risk factors will predict higher adolescents' PSMU (primary outcome), as well as higher emotional distress and passive SM use (secondary outcomes).

As for the second aim, the research questions that guide the study are: what are the adolescents' experiences and perspectives on SM and PSMU, the SM impact, and the possible strategies for promoting positive SM use? As for the app, we hypothesize to include several interactive modules, including an informative and awareness section and a psychoeducational section, to promote both (1) emotional awareness and skills, and (2) adolescents' personal and interpersonal resources, so to prevent PSMU and promote a functional SM use.

As for the last aim, we hypothesize a good feasibility for the SMART app, and that greater app use will be associated with an increase in functional SM use.

Methods

Study Design

The SMART project is organized in 3 consequential phases, each including different integrated actions: phase 1—prospective longitudinal study with repeated-measures design [32] for the advancement of knowledge on PSMU through quantitative approaches; phase 2—qualitative focus group study for exploring adolescents' perspectives on PSMU and functional use of SM and co-design approach for developing the unguided self-help SMART app; phase 3—pilot study to evaluate feasibility and signal of effectiveness of the intervention throughout the self-help app.

The project is conducted by researchers and clinical psychologists in four Italian Universities (University of Verona, University of Palermo, University of Perugia, and University of Bergamo), thus including a large population of midadolescents in diverse regions of north, central, and south of Italy (see Figure 1 for an overview of the project phases and Table 1 for a synthetic description of general objectives, research aims, and methods of each phase).

Figure 1. SMART project: General overview of the 3 phases.

Phase 1: Longitudinal study	T0 M3-5	T1 M8-10	T2 M13-15
Self-report questionnaires evaluation	X	X	X
Ecological momentary assessment	X		
Biological markers evaluation	X		

Phase 2: Qualitative study and co-design	M5-7	M8-15
Focus groups study	X	
Co-design workshops		X
SMART app development		X

Phase 3: Pilot feasibility study	M16-17	T3 M18-20	M21-24
SMART app use	X		
Self-report questionnaires evaluation		X	
SMART app adaptation			X

M = Month

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Table 1. General description of the 4 study phases: objectives, research aims, and main methodologies.

Phase	General objectives	Research aims	Main methodologies
Phase 1: Longitudinal prospective study	• Improving the conceptualization of PSMU[a] • Longitudinally identifying the intra- and interpersonal risk, protective and maintenance factors of PSMU • Longitudinally analyzing the associations between PSMU and psychological distress • Exploring the presence of specific profiles of PSMU among adolescents • Informing the development of SMART self-help app	• Which are the main risk or protective factors of PSMU among adolescents? • What are the longitudinal associations between PSMU and psychological distress? Is PSMU predicted by a higher distress, or is it a change in distress for that specific participant to predict it? • Are there specific sub-groups of PSMU? If yes, what characterizes them?	• Prospective longitudinal study with repeated-measures design (3 waves) using self-report questionnaires • Collection of biological markers • EMA[b]
Phase 2: Qualitative study and co-design of the SMART app	• Exploring adolescents' experiences, examples and perspectives on PSMU and functional use of SM[c] • Informing the development of SMART self-help app • Co-designing the beta version of a self-help app aiming to promote awareness and functional SM use	• Which are the adolescents' experiences and perspectives on PSMU and functional use of SM? • Which are the adolescents' opinions and perspectives on what is useful to promote awareness and functional SM use? • Which are the adolescents' perspectives, suggestions, and preferences on an app to promote functional SM use?	• Focus groups • Thematic analysis of the transcripts to identify and analyze patterns in qualitative data • Co-design working groups with the adolescents involved
Phase 3: Feasibility and pilot study	• Investigating the feasibility and acceptability of the SMART self-help app • Preliminary evaluating its effectiveness • Incorporating user feedback and study results during the app development	• Which are the perspectives of adolescents on the SMART self-help app feasibility and acceptability? • Is there preliminary evidence that the SMART self-help app is effective?	• Single-arm pilot feasibility study to explore feasibility and preliminary data on effectiveness (pre-post evaluation)

[a]PSMU: problematic social media use.

[b]EMA: ecological momentary assessment.

[c]SM: social media.

Participant Recruitment and Setting

The target group (adolescents aged 14-18 years) will be actively involved in the various actions of each phase. Participants will be recruited from schools (ie, secondary school), in the north, central, and south Italy. Each research team will select schools (on a voluntary basis or following previous collaborations) and interact with stakeholders (regional and local school offices, school communities) to obtain their availability for participation. Attention will be given to contacting schools located in particularly disadvantaged areas and to include students with different sociodemographic and cultural backgrounds and levels of vulnerability. At each participating school, adolescents may participate in the different phases of the study.

The following inclusion criteria will be followed for participation in each included school: (1) having an age between 14 and 18 years, (2) having signed the consent form for the study participation (ie, consent to participate for adolescents less than 18 years signed by both parents—or legal representatives—or by the adolescent when 18 years); having sufficient knowledge of the Italian language.

Procedure and Measures

Longitudinal 3-Waves Evaluation (Phase 1)

The longitudinal evaluation study (phase 1) will be articulated across 3-time points of assessment: baseline (T0: around months 3-5), at around 5 months (T1: months 8-10), and at around 10 months follow-up (T2: month 13-15). At each time point, a survey composed by a battery of self-reported questionnaires will be delivered through a dedicated web-based platform during regular school hours.

Diverse theoretical models of PSMU are operationalized in those battery of questionnaires (see Table 2 and Multimedia Appendix 1 for a detailed description of measures and questionnaires) to explore potential intra- and interpersonal psychosocial risk or protective factors of PSMU.

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Table 2. Self-report questionnaires adopted in the SMART project[a].

Role of the dimension in the longitudinal study ad questionnaire name	Investigated dimension	Questionnaire's characteristics	Time
Intrapersonal risk factors			
Difficulties in Emotion Regulation Scale-Short Form [33]	Emotion dysregulation	18 Items, 5-points Likert scale	T0, T1, and T2
Rosenberg Self-Esteem Scale [34]	Self-esteem	10 Items, 5-points Likert scale	T0, T1, and T2
Brief Self-Control Scale [35]	Self-control	13 Items, 5-points Likert scale	T0, T1, and T2
Satisfaction With Life Scale [36]	Satisfaction with life	5 Items, 7-points Likert scale	T0, T1, and T2
Strengths and Difficulties Questionnaire [37]	Adjustment difficulties and strengths	25 Items, 3-points Likert scale	T0, T1, and T2
Fear of Missing Out Scale [38]	Apprehension that others might be having rewarding experiences from which one is absent	10 Items, 5-points Likert scale	T0, T1, and T2
Interpersonal risk factors			
Inventory of Parent and Peer Attachment—Revised [39]	Attachment relationships toward mother, father, and peers	25 Items, 5-points Likert scale	T0
Preference for Online Social Interaction Scale (subscale of the Generalized Problematic Internet Use Scale 2) [40]	Preference for online social interaction	3 Items, 5-points Likert scale	T0, T1, and T2
Parental Phubbing Scale [41]	Perceived parental phubbing	9 Items, 5-points Likert scale	T0, T1, and T2
Primary outcome			
Bergen Social Media Addiction Scale [42]	Core addiction elements regarding SM[b] use	6 Items, 5-points Likert scale	T0, T1, T2, and T3
Secondary outcomes			
Social Emotional Distress Scale—Secondary [43]	Emotional distress	10 Items, 4-point Likert scale	T0, T1, T2, and T3
Passive Social Networking Site Use Questionnaire [44]	Passive SM use	5 Items, 5-points Likert scale	T0, T1, T2, and T3

[a]Time: time of administration; T0 (baseline) corresponds to months 3-5, T1 to months 8-10, and T2 to months 13-15. T3 is an additional time point (at the end of the app intervention) explained in phase 3.

[b]SM: social media.

Moreover, in a subsample of participants, momentary emotions or feelings (eg, happy, sad, tired, relaxed, nervous, quiet, each rated on a visual analogue scale) as well as the subjective use of SM during the past 2 hours will be recorded at 1 time point through an ad hoc app, using an ecological momentary assessment approach [45]. Momentary questions will be randomly delivered during nonschool hours (ie, from 3 to 10 PM), for a total of 4 times per day, for 2 weeks.

At baseline, 2 additional biological markers of PSMU will be randomly collected in vivo in a subsample of participants. First, the autonomic activity of the participants will be collected with the aim of testing whether a greater PMSU is associated with a decreased vagal (ie, parasympathetic) activity at rest. This autonomic parasympathetic activity—considered a physiological index of emotion dysregulation [24]—will be investigated through specific indices of heart rate variability (HRV) such as the high frequencies and the root mean square of successive differences between normal heartbeats [46]. The HRV will be continuously recorded during 10-minute resting condition using a wearable electrocardiogram device. The second biomarker is the presence of specific polymorphisms for serotonin gene transporter 5-HT1AR and 5-HT2AR that—according to the bipartite model of brain serotonin functions [25]—seem to be associated with a greater risk of developing internalizing disorders [47], such as PSMU. The presence of these polymorphisms will be tested through saliva samples, collected with a saliva stick and processed by the University of Perugia.

Qualitative Focus Group Study and Co-Design Approach (Phase 2)

Focus groups (FGs) have been widely used as a method for exploring people's perspectives and experiences by using the group interaction to encourage the participants to explain, disagree, and share their views [48]. This method is particularly useful in research with adolescents [49]. Through FGs, we will explore the adolescents' point of view regarding the following topics: the adolescents' perspectives regarding the main purposes and modalities of SM use; the link between SM use, psychological distress, and well-being; risk factors associated with PSMU and protective strategies and resources that may be activated to promote functional use of SM. Each FG will be led by a moderator and an assistant (both with expertise in conducting FGs and in clinical psychology) and will last around 90-120 minutes each. Each FG will include around 8 to 10 adolescents, recruited through purposive sampling in the

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participating schools and balanced for sociodemographic variables, according to the suggestions of Palinkas et al [50], and the availability of the participating schools.

FGs will be conducted following a shared interview guide, including a set of open-ended questions and following a semistructured approach. While conducting the FGs, researchers will also pay attention to the group dynamics, ensuring that a good atmosphere is maintained. Before the FG, participants will fill out a brief questionnaire to collect background information (eg, sociodemographic information, emotional distress, and SM use) to describe the sample.

Co-designing of the app involves "a process of collective creativity" based on active collaboration between researchers, developers, and end users (ie, midadolescents) as "experts of their experiences" [31,51]. Originating from the field of participatory design, the co-design process allows to maximize engagement, satisfaction, and use of eHealth interventions for potential users [29]. General guidelines for the application of co-design methods and previous research experiences of the research team will be followed to organize and structure the co-design workshops [27,51,52], adopting agile design, design thinking, and user-centered design approaches (ie, cycles of design, develop, and test) [29]. The timeframe and duration of the workshops will be agreed with participating schools. Specifically, a "designing group" (ie, 2 researchers in clinical psychology, 1 computer engineer, and a subsample of midadolescents) will be established at the beginning of the second phase of the project. Members will be involved in a series of interactive workshops (organized in presence or through digital platform meetings) to define the main functionalities, features and contents of the app (alpha version) on the basis of: preexisting conceptual models on PSMU, existing evidence-based interventions for, preliminary evidence from the sample of Italian midadolescents, including their experiences, suggestions, and needs. During the workshops, the facilitators will encourage midadolescents to discuss the topic presented through practical techniques (eg, use of visual materials, scenario thinking, playful activities, participants' interactions with prototypes and discussion on them) [53] for facilitating co-design while promoting meaningful engagement among adolescents [29]. Ideally, in the first workshop, midadolescents will be asked to discuss the general aims, functionalities, features, and contents of the self-help app, while the subsequent workshops will aim to collect inputs for adapting the alpha version to a beta version.

Feasibility and Pilot Study (Phase 3)

In phase 3, the co-designed self-help app will be delivered to all recruited midadolescents, who will be free to download the app on their personal iOS or Android device. For 1 month, participants will be invited to use the self-help app exploring the different contents and functionalities weekly, and to adopt these newly learned competencies in their daily life.

At the end of the self-help app use (T3; postintervention), feasibility will be investigated: (1) administering an adolescent-adapted version of the "Mobile App Rating Scale user version" (uMARS) [54], together with open-ended questions exploring the adolescents' opinion about the app (eg, "Can you tell me about your experiences using the App?"; "What did you like most/least?"). The uMARS is a 20-item self-report measure of the perceived quality of apps, which includes 4 objective quality subscales (ie, engagement, functionality, aesthetics, and information quality) and 1 subjective quality subscale.

At this last time point (T3; around months 18-20), we will gather preliminary data on the effectiveness of the app intervention, administering the self-report questionnaires measuring the primary and secondary outcomes mentioned in phase 1. Given that the latter time point for the longitudinal study (ie, T2) falls a little before the start of phase 3, data on outcomes collected at that time point will be used as preintervention scores.

As a last step of this project, the app (eg, contents, features, and design) will be adapted on the basis of the emerging results.

Sample Size Estimation

For the longitudinal study (phase 1) a convenient sample of 1216 adolescents will allow detection of a small effect size for regression-based models according to potential predictors (α=.05; power=0.80). After a 25% increase to account for potential dropouts, the estimated final number of participants will be 1520 adolescents.

For the HRV measure, to detect a medium effect size with 80% of power [55], at least 61 healthy adolescents need to be recruited. For the analysis of the genotyping serotonin transporter polymorphisms 5-HT1AR and 5-HT2AR, based on the effect sizes reported in Matsunaga et al [47], an a priori power analysis estimated that 191 participants would be necessary to detect a small-to-medium effect size (α=.05; power=0.80).

For phase 2, applying the criteria of data saturation, around 12 FGs distributed across schools in Italy are expected to be sufficient to explore all the relevant topics. The final number will be adjusted according to the data saturation criteria. As for the co-design workshops, a purposive sample of around 20 midadolescents is evaluated sufficient.

For phase 3, all the adolescents who took part in phase 1 of the project will be invited to participate in this phase. Considering that longitudinal studies on unguided self-help interventions report up to 63% of drop-out rates [56] and that this phase will start after several months from the first recruitment, we expect a final sample of around 400 adolescents participating in this phase, which is considered sufficient for feasibility and pilot aims.

Intervention

The SMART app will aim to promote awareness and functional SM use. The app will use unguided web-based self-help approaches, that is a self-help program that does not include any contact with a therapist or researcher during its use, although it may include automatic reminders through app notifications (eg, to motivate the app use, or to complete an app session).

The app will be created according to the co-design described above and contents based on the more recent literature in the field, considering the evidence-based interventions already

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developed for PSMU and the empirical data derived from quantitative and qualitative data collected during the current project. To date, to the best of our knowledge, among the most widely used approach we have cognitive behavioral therapy, psychoeducational, positive psychology, and multifamily group therapy ones [57]. Among the preexisting theoretical models of PSMU, the systemic and cognitive-behavioral psychological models emerged. Specifically, the compensatory internet use theory [7] posits that PSMU could be conceptualized as a maladaptive coping mechanism that allows individuals to manage their negative emotions, to escape from disturbing issues and to regulate negative moods.

Although all the contents will be adapted according to the collected results and co-design, ideally the core features of the app will prioritize strategies aimed at improving emotional awareness, emotions regulation and interpersonal skills, specifically in relation to the context of SM use. Based on both theoretical and clinical knowledge and experience in the field, the app will ideally include several interactive modules, including: (1) an informative and awareness section with different educational contents (eg, information regarding SM use, consequences of PSMU, and SM role in defining individuals' identity); and (2) a psychoeducational section aimed at promoting emotional awareness and skills and adolescents' personal and interpersonal resources in order to prevent PSMU and promote functional SM use (eg, how to manage the pervasive apprehension that others might be experiencing rewarding activities that one could miss out; how to change negative thinking patterns; problem-solving strategies). Videos, practical scenarios, and examples (collected during FGs or co-created with adolescents during workshops) will be potentially used to promote engagement. The tone and contents of messages will be adapted according to the feedback from adolescents to ensure informative, nonjudgmental, and supportive communication as well as to motivate adolescents to use the app. Moreover, the app developers will use some specific tools to foster the readability and comprehensibility of the app (including, for example, the Simple Measure of Gobbledygook Index, Hemingway app).

Ethical Considerations

In compliance with the ethical standards for research outlined in the Ethical Principles of Psychologists and Code of Conduct [58], approval by the Ethics' Committee have been required and obtained by the Ethical Committee of the Umbria Region (protocol 4637/23). In order to participate in the study, written consent from parents or legal guardians and oral assent from midadolescents will be obtained. The informed consent will inform parents or legal guardians and midadolescents around the purposes of the research, the expected duration, the procedures, the absence of potential risks including physical, mental, and social injury, and participants' right to withdraw at any time from the study if not willing to continue. Participation will be voluntary, and no monetary incentive will be given. In all the different phases of the study, data will be collected to assure participant's privacy and confidentiality protection (eg, pseudonymization during the data collection and anonymization during the dissemination phase). All research teams will also protect the values, rights, and interests of the participants and respect basic ethical principles such as nonmaleficence, informed consent, and fair treatment. All data will be collected according to the EU General Data Protection Regulation.

Statistical Analyses

Quantitative data will initially be screened for assumptions, including univariate and multivariate normality, and tested for the presence of outliers. Further, quantitative analyses will be complemented with effect sizes (which will be reported and interpreted according to guidelines) [59].

As for phase 1, we will test the longitudinal changes over time in PSMU as well as its psychosocial predictors, or the interactions between psychological distress (anxiety and depression) and PSMU, through 3-level mixed models (with repeated measures nested within participants, nested within classes) [60]. Ecological momentary assessment data will be examined through multilevel regression models, to test the interaction effects between SM use and emotional experiences over time. Finally, longitudinal profiles of participants will be examined through latent growth curve analyses [61]. Due to the relevant changes within adolescence, sensitivity analyses (based on sociodemographic variables, including age groups such as 14-15 years and 16-18 years) will also be carried out.

As for phase 2, each FG will be audio-recorded and transcribed verbatim. The transcribed text will be thematically analyzed using a 6-phase process for data engagement, coding, and themes development [62-64]: (1) familiarization with data and starting to create initial observations; (2) generation of initial codes; (3) searching for themes and discussion on how to combine and cluster different codes to form an overarching theme; (4) reviewing the themes checking them against the original data; (5) defining and naming themes; and (6) for each theme, representative quotes to contextualize and exemplify the themes will be selected to tell the reader a coherent story about the data. Analyses will be conducted by considering the recurrence but also meaningfulness as main criteria during the coding process. An inductive approach will be predominant [65,66]. However, to ensure that results will be meaningful to the research questions, in addition codes might be developed keeping in mind the main theoretical models of PSMU (such as the Multidimensional Model of Social Media Use [13], the Interaction of Person-Affect-Cognition-Execution model [67], and the pathway model [68]). To enhance rigor and trustworthiness of these procedures and analyses [69], and in accordance with Lincoln and Guba [70] credibility, transferability, dependability, and confirmability criteria, multiple strategies will be introduced. These will include prolonged engagement; persistent observation; 2 independent researchers will analyze the data separately; investigator triangulation by involving several researchers as research team members and presenting analysis at data group meetings; detailed descriptions of the research context to facilitate the assessment of its relevance and applicability to other contexts; purposeful sampling to ensure a diverse range of participants; reflexivity and researcher positionality; and maintaining an audit trail; and using transparent approaches to data analysis [69].

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Finally, examples and scenarios will be stimulated during the discussion and might be used to inform the app (eg, collecting real-life examples of PSMU; situations in which negative experiences with SM are associated with well-being; protective strategies to PSMU).

In line with a mixed methods approach [71], quantitative and qualitative results will be synthesized and merged in order to achieve a better understating of the PSMU. Indeed, qualitative results will be used to deepen our understanding of the PSMU phenomenon, corroborating the findings from the quantitative design and/or adding potential different topics.

As for phase 3, feasibility (ie, uMARS mean scores and app usage) will be investigated through simple descriptives, examining whether participants met the thresholds for good feasibility: (1) mean uMARS subscale scores≥70% of the total will be considered indicative of good feasibility [72]; examining the app use (with ≥75% of participants with ≥10 app sessions considered indicative of a good feasibility) [72]. We will have a deeper understanding of the app feasibility by synthesizing the qualitative results. We will further examine whether the self-help app led to an actual change in primary and secondary outcomes through 3-level piecewise regression models, using the 4-time points from baseline (as defined in phase 1; T0) up to posttreatment (T3; M18-M20). To further strengthen these analyses, we will compute both a Reliable Change Index and a Clinically Significant Change for each participant [73,74]. These methods are used to test whether a change over time (in our case, from pre- to posttreatment) may be considered reliable (ie, taking into account the measure's internal reliability) and clinically significant (eg, the posttreatment scores are within the boundaries of nonpathological scores).

Quantitative analyses will be performed using SPSS (version 29; IBM Corp), Hierarchical Linear Models (version 8.2; Scientific Software International, Inc), and MPLUS (version 8.4; Muthén & Muthén).

Results

The project is funded by the Italian Ministry of University and Research as part of a national grant (PRIN, "Progetti di Rilevante Interesse Nazionale"), with the research team receiving an official notice of research funding approval for the current project in July 2023 (Project Code 2022LC4FT7). The study was preregistered on Open Science Framework, while the ethical approval was obtained in November 2023. We started the enrollments in December 2023, with the final follow-up data collected within May 2025.

As of July 2024, we completed 2 data collections (T0 and T1) and conducted the qualitative FGs of phase 2.

Discussion

Expected Findings

The innovative SMART project replies to crucial existing knowledge gaps on PSMU. First, to date, the conceptualization of PSMU is still debated. The SMART project emphasizes a person-centered approach since it underlines the need to focus not only on "how much" the SM is used, but also on "how" adolescents engage in this behavior. Second, a comprehensive evaluation of risk or protective factors for PSMU is still lacking. Thus, the potential effect of diverse variables at intra- and interpersonal psychological and biological levels, collected at several time points, is examined. Adopting complex longitudinal data analyses represents a third innovative aspect—as literature in the field relied mostly on cross-sectional designs—allowing us to test several hypotheses whose final aim is to disentangle the longitudinal associations between supposed risk or protective-factors, psychological distress, and the changes over time in PSMU. For example, the definition of different longitudinal profiles of primary or secondary PSMU outcomes will orient the scientific community about new research lines of inquiry and the development of tailored interventions. The adoption of EMA—a promising naturalistic and ecologic research method that provides longitudinally valid data and investigates SM use in real time—will additionally provide a fine-grained picture of adolescents' experiences in their natural contexts, capturing both the variability over time in SM use, emotional experiences, and their interactive dynamic patterns. Third, an additional strength lies in the use of a mixed-methods design, combining quantitative and qualitative approaches to enrich the understanding of PSMU and of the relationships between the investigated variables.

In terms of impact, the project investigates a stage of life that has been strongly affected by the pandemic of COVID-19 [75]. The latter negatively impacted midadolescents' need for autonomy and social interaction, causing anger and loneliness that some of them self-regulated through an increased use of SM. Therefore, the SMART project results may help better understand an actual adolescents' need, worsened by the COVID-19 pandemic's mental health burden. The SMART project invites adolescents to critically discuss SM use habits and needs and encourages them to share (eg, during FGs or co-design workshops) difficulties that adolescents might present as connected to SM use as well as the potential coping strategies adopted to face them. Even if this is not the aim of the FG, this may indirectly lead to a potential psychological benefit for adolescents in terms of normalization of the experience and reduction of isolation. The participatory approach actively engages adolescents to fully participate in designing an age- and culturally appropriate app-based self-help intervention. Empowering youths to play an active role in their well-being is one of the key foci of the participatory approach in promoting healthy communities [76].

Within the project, we will develop and evaluate an unguided self-help app, thus contributing to the advancement of knowledge on eHealth interventions for SM use and PSMU in adolescence. This simple and easy-to-use app, including interactive and supportive contents, will be based on adolescents' preferences and inputs and on evidence-based intervention models, and will: (1) promote a healthier use of SM among midadolescents; (2) help them to become more aware of a potential PSMU; (3) mitigate the impact of psychosocial and biological risk factors on PSMU; and (4) boost their confidence through the use of more adaptive coping strategies while facing stressful events. The results from the pilot study

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may guide future multinational RCT studies for the evaluation of app effectiveness. Finally, in future research, the self-help app may be adapted to the special needs of adolescents with different PSMU profiles.

It is well known that untreated mental health problems, including psychological distress linked to PSMU-, have visible (eg, due to treatments) and invisible (eg, school dropouts, lower academic achievements) socioeconomic costs [77,78]. An unguided self-help intervention, such as SMART self-help app, may then be a cost-effective solution for promoting a better use of SM within this specific population, and which could be additionally included by schools and mental health professionals as a specific strategy in already existing interventions targeting psychological well-being of midadolescents.

Several dissemination activities maximize the impacts of the project, targeting the scientific community, schools, policy makers, and civil society. As regards schools, the project involves midadolescents and, potentially their caregivers and teachers, promoting interest around the PSMU. If, as suggested by some scholars [79], PSMU represents escapism from anxiety and depressed mood, informing, raising awareness, and sharing experiences about PSMU may have positive and substantial effects on psychological well-being, social exclusion, discrimination, educational difficulties, risk-taking behavior, and cyberbullying. Moreover, dissemination activities with caregivers (ie, organized at schools' level at the end of the project) will be strategic, considering that provision of advice to parents has been scant and this kind of communication has not been specifically endorsed by governments or local communities. Dissemination events targeting policy makers will also contribute to informing policy recommendations on the apparent mismatch between perception of PSMU problems (by decision makers and adults in general) and real problems experienced by midadolescents. For example, attention has been primarily focused on digital safety (ie, cyberbullying, privacy issues) rather than on the psychological risk factors or impacts affecting adolescents and the promotion of functional SM use [80].

This study has some limitations. First, data will only be collected among Italian participants, thus our results may not be generalizable to other populations and cultures. Second, most of the measures used in this protocol are self-report, thus subjected, among the others, to response and social desirability biases [81]. The effectiveness of the SMART app will be tested through a nonrandomized design, thus limiting our possibility to make causal inferences. Finally, we have chosen to investigate only a fraction of the potential biopsychosocial predictors of PSMU among adolescents, thus we may have missed other important determinants of this problematic behavior.

Conclusions

The SMART project contributes to the conceptualization of PSMU and deepens on its biopsychosocial antecedents among midadolescents, offering relevant scientific, technological, and socioeconomic impacts. The advancement of knowledge and the developed self-help app for PSMU responds to midadolescents' increased loneliness and psychological burden due to COVID-19 pandemic and humanitarian crisis.

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Data Availability

The data sets generated during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table S1. Additional information about the self-report measures adopted in the SMART Project.
[DOCX File , 29 KB - resprot_v13i1e58739_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the Italian Ministry of University and Research (Ministero dell'Università e della Ricerca, MUR).
[PDF File (Adobe PDF File), 67 KB - resprot_v13i1e58739_app2.pdf]

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Abbreviations

FG: focus group
HRV: heart rate variability
PSMU: problematic social media use
SM: social media
uMARS: Mobile App Rating Scale user version

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Protocol

Toward a Clinical Decision Support System for Monitoring Therapeutic Antituberculosis Medical Drugs in Tanzania (Project TuberXpert): Protocol for an Algorithm' Development and Implementation

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Abstract

Background: The end tuberculosis (TB) strategy requires a novel patient treatment approach contrary to the one-size-fits-all model. It is well known that each patient's physiology is different and leads to various rates of drug elimination. Therapeutic drug monitoring (TDM) offers a way to manage drug dosage adaptation but requires trained pharmacologists, which is scarce in resource-limited settings.

Objective: We will develop an automated clinical decision support system (CDSS) to help practitioners with the dosage adaptation of rifampicin, one of the essential medical drugs targeting TB, that is known for large pharmacokinetic variability and frequent suboptimal blood exposure. Such an advanced system will encourage the spread of a dosage-individualization culture, including among practitioners not specialized in pharmacology. Thus, the objectives of this project are to (1) develop the appropriate population pharmacokinetic (popPK) model for rifampicin for Tanzanian patients, (2) optimize the reporting of relevant information to practitioners for drug dosage adjustment, (3) automate the delivery of the report in line with the measurement of drug concentration, and (4) validate and implement the final system in the field.

Methods: A total of 3 teams will combine their efforts to deliver the first automated TDM CDSS for TB. A cross-sectional study will be conducted to define the best way to display information to clinicians. In parallel, a rifampicin popPK model will be developed taking advantage of the published literature, complemented with data provided by existing literature data from the Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (panACEA), and samples collected within this project. A decision tree will be designed and implemented as a CDSS, and an automated report generation will be developed and validated through selected case studies. Expert pharmacologists will validate the CDSS, and finally, field implementation in Tanzania will occur, coupled with a prospective study to assess clinicians' adherence to the CDSS recommendations.

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Results: The TuberXpert project started in November 2022. In July 2024, the clinical study in Tanzania was completed with the enrollment of 50 patients to gather the required data to build a popPK model for rifampicin, together with a qualitative study defining the report design, as well as the CDSS general architecture definition.

Conclusions: At the end of the TuberXpert project, Tanzania will possess a new tool to help the practitioners with the adaptation of drug dosage targeting complicated TB cases (TB or HIV, TB or diabetes mellitus, and TB or malnutrition). This automated system will be validated and used in the field and will be proposed to other countries affected by endemic TB. In addition, this approach will serve as proof of concept regarding the feasibility and suitability of CDSS-assisted TDM for further anti-TB drugs in TB-burdened areas deprived of TDM experts, including second-line treatments considered important to monitor.

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KEYWORDS

TDM; therapeutic drug monitoring; pharmacometrics; tuberculosis; model-informed precision dosing software; clinical pharmacology; clinical decision support system; Tanzania; mobile phone

Introduction

Even though tuberculosis (TB) is curable, it remains one of the leading causes of death from a single bacterial infection worldwide. The World Health Assembly declared the end of TB with a drastic reduction in death and incidence; however, the decrease is at a suboptimal pace, only 11% and 9.2%, contrary to at least 20% and 35% by 2020, respectively [1,2]. Sub-Saharan Africa contributes around 25% of the global TB burden, with a higher death rate than other World Health Organization (WHO) regions at 22% [3]. Significant and commonly coexisting comorbidities in patients with TB, which include HIV coinfection [4], enteric pathogens [5], malnutrition [6], and diabetes mellitus (DM) [7], increase the risk of unfavorable treatment outcomes. This is primarily driven by incomplete adherence and pharmacokinetic variability of first-line antitubercular (anti-TB) drugs, leading to insufficient circulating drug exposure and development of drug-resistant TB or excessive exposure and toxicity, resulting in treatment interruption.

Precision dosage of medicines based on drug concentration monitoring is an essential patient-centered approach for optimizing adherence and efficacy and preventing adverse effects. There are available tools for helping pharmacologists with the dosage adaptation process. However, they are difficult to use for nonspecialists and would benefit from automation. Real clinical decision support systems (CDSS), that have the potential to assist practitioners, not necessarily pharmacologists, in the dosage adaptation of anti-TB drugs in patients with TB, are yet to be available in TB endemic settings. Deployment of such an advanced system will encourage the spread of a dosage-individualization culture among practitioners not specialized in pharmacology while bridging the gap by adapting those novel technologies for optimizing TB care [8].

In that context, as part of the Adaptive Diseases Control Expert Programme in Tanzania, the TuberXpert project aims to develop an automated CDSS to help practitioners with the dosage adaptation of rifampicin. Being one of the essential medical drugs targeting TB, rifampicin is known for its significant pharmacokinetic variability and frequent suboptimal blood exposure [9].

This project shows the field application of such an automated CDSS for the dosage adaptation of rifampicin in Tanzania with underpinned applied research questions to address scientific implementation for sustainability. The 3 project partners are the University of Applied Sciences and Arts Western Switzerland (HEIG-VD), the University Hospital of Lausanne (CHUV), and the Kibong'oto Infectious Disease Hospital (KIDH). HEIG-VD is bringing computer science expertise, CHUV pharmacometrics expertise, and KIDH clinical expertise.

Methods

Overview

An automated CDSS software requires an embedded population pharmacokinetic (popPK) model for rifampicin to predict drug concentrations and propose meaningful adjustments correctly. The software will be based on the core computing engine of Tucuxi [10,11], a model-informed precision dosing software for Bayesian forecasting that was already developed and that helps clinicians adapt medical drug dosages. These software computations are based on the popPK models implemented within the software and the model-identified influential patient covariates, potential drug concentration measurements, and specific drug pharmacokinetics (PK) targets validated by therapeutic drug monitoring (TDM) experts for dose optimization. The CDSS will be implemented in 5 phases, as shown in Figure 1. In brief, the first phase includes developing an appropriate popPK model for rifampicin for Tanzanian patients and implementing it within Tucuxi. The second phase will optimize reporting relevant information to practitioners for drug dosage adjustment. The third phase will automate the delivery of the report in line with the measurement of the drug concentration [12]. The fourth phase will validate the system, and the final step will implement the system in the field. Details of each stage and associated research questions are summarized in the next subsections.

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Figure 1. TuberXpert protocol PERT diagram decomposed into 5 phases. CDSS: clinical decision support system; popPK: population pharmacokinetic; panACEA: Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics; PERT: program evaluation and review technique; TDM: therapeutic drug monitoring.

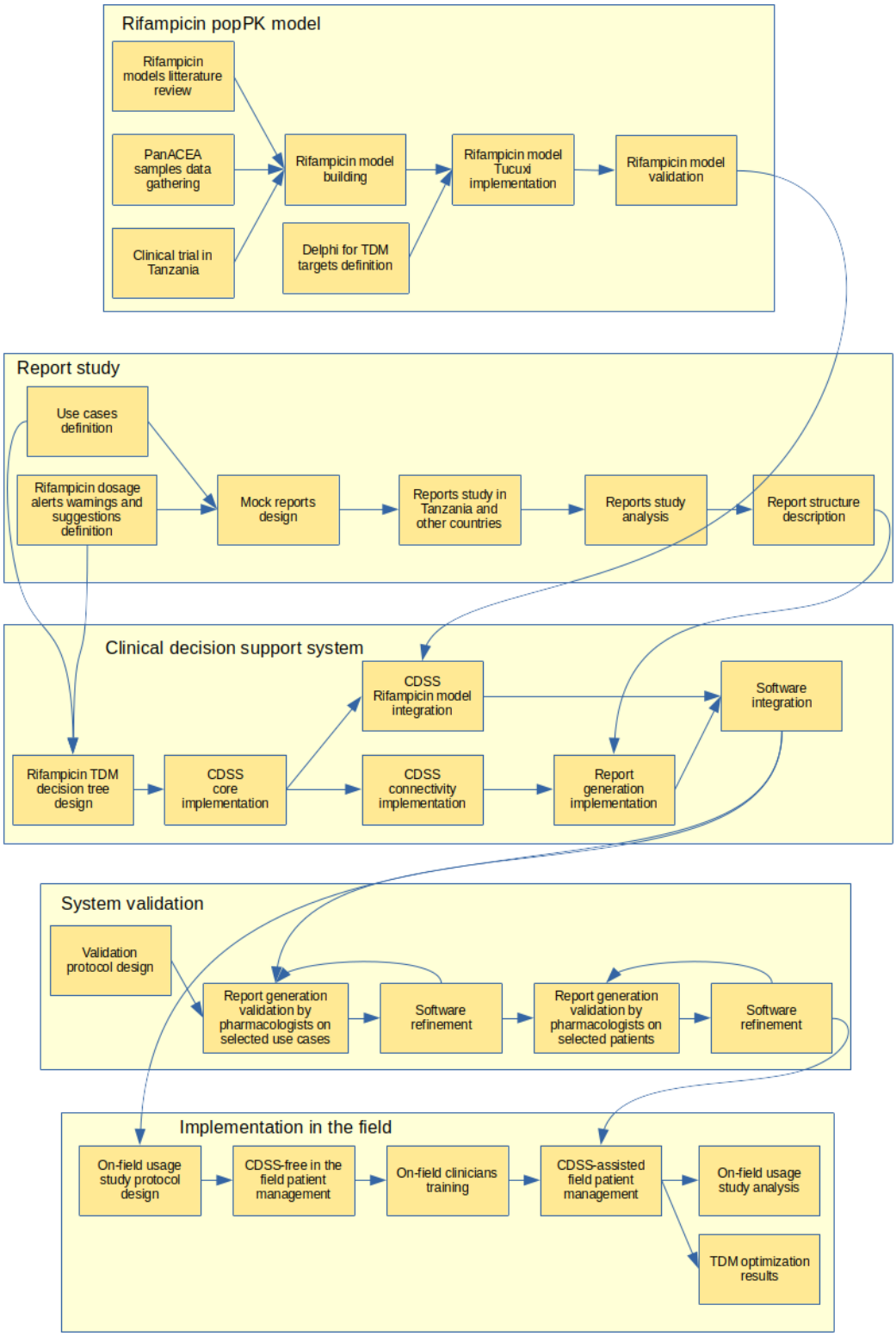

Model Selection, Development, and Calibration

Predicting the concentration of a medical drug in blood for dosage adjustment using Tucuxi crucially requires the selection of a popPK model, as the latter determines the ability of the software to propose the correct dosage regimen for each patient. An extensive literature search will be conducted to identify the published popPK models of rifampicin in patients with TB [13-15], developed using NONMEM (ICON) [16] or Monolix (Lixoft) [17], both widely used computer programs for parametric popPK analyses. Models describing rifampicin PK in patients with TB with the previously mentioned comorbidities, that is, DM, malnutrition, and HIV, will be included to investigate their impact on the anti-TB drug PK. The number of participants in the studies, as well as that of available

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observations distributed over time, will be considered. The description of the model development steps (eg, structural and statistical considerations, and inclusion of covariates) will be carefully reviewed, and the study results will be judged using standard procedures in population analysis (eg, diagnostic goodness-of-fit plots and type of validation) to ensure the quality of the model and the completeness of the information provided. The available models will be ranked according to a cumulative score based on the previous elements, and the best one will be selected for implementation. Because of the autoinduction and the nonlinear processes underlying rifampicin absorption and elimination, we expect a complex nonlinear popPK model to characterize its PK best (which will require software updates to encompass specific kinetics). If the best-identified model fails to capture essential PK characteristics of rifampicin, the opportunity to use a model-based meta-analysis approach will be investigated to build a comprehensive popPK model using all available pertinent literature. Model refinement will be attempted if the selected model proves to be computationally prohibitive for its implementation in Tucuxi, verifying that the simplified model's prediction for the targeted exposures is comparable to the original ones. Whatever the choice made for this step, the model will undergo formal validation and adjustment to Tanzanian patients using rifampicin concentrations available through the Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (panACEA) network and those collected in Tanzania within this project. To achieve this aim, a prospective study will be conducted on 50 patients with TB (including those with HIV coinfection, coexistent DM, or malnutrition) followed at the KIDH or in neighborhood clinics during the early stage of the TuberXpert project. These patients will provide 3 samples randomly on 2 separate occasions, that is, at the treatment start and approximately after 1 week of treatment. We will elaborate and then strictly follow a study protocol. We will also conduct a study comparing dried blood spot analysis [12] to HPLC-UV laboratory analysis [18] on these samples. Finally, we will conduct a Delphi study, as suggested in reference [19], to define the optimal therapeutic target, as this is critical for therapy individualization and there is currently no definitive consensus for rifampicin (various propositions [13,20-22]).

Before using Tucuxi in therapy individualization, we have to conduct further essential preliminary validation step. It will consist of verifying that the dosage regimen propositions made by the software are in line with those made by experienced pharmacologists to perform TDM in their clinical practice. Pharmacologists of the service of clinical pharmacology of CHUV and clinicians at KIDH will be in charge of such clinical validation of the software using selected patients of this study. Data on rifampicin dosage history and concentrations, administration, and sampling times, and all necessary clinical information on the selected patients will be collected. Experienced pharmacologists will choose the most appropriate dosage regimen to achieve the target according to the patient clinical status among those proposed by the software using the graphical user interface (GUI) of Tucuxi. The correctness of the forecasted dosing schedule will be validated against the dosage recommendations made by the TDM experts at CHUV and clinicians at KIDH. After this vital validation step, the model will be made available within the standalone Tucuxi software, allowing users to exploit this new model.

The research question components are as follows: (1) What is the appropriate popPK model that includes the structural and statistical considerations, as well as the influential individual factors, to be incorporated in Tucuxi for optimizing rifampicin dosage in patients with TB in Tanzania? (2) What is the Tucuxi-guided rifampicin dosage adjustment accuracy for anti-TB therapy individualization against experienced pharmacologists in the TDM clinical practice?

Report Design Specifications

Report generation, specifically the report structure and visual content, is essential to help clinicians with decision-making. It shall be easily understandable by inexperienced TDM pharmacologists. The displayed information must be carefully selected and structured to not lose the prescriber with a too complex presentation and terminology [23]. It should contain the appropriate information presented visually. In addition, alerts shall be issued, if necessary, in a form following the Instrument for Evaluating Human Factors Principles in Medication-Related Decision Support Alerts (I-MeDeSa) principles [24].

The definition of the report layout will be elaborated through the following process. We will prepare mock reports showing various layouts based on use cases. The designs will be done after reviewing the literature to identify good practices. We will then, in Tanzania, expose a cohort of clinicians to these reports and collect their input through semistructured interviews. We expect to reach 10 clinicians from different facilities, in Tanzania. We also aim to ask 10 non-Tanzanian clinicians to obtain helpful information about varying preferences regarding information representation depending on culture or background. Thus, pharmacologists with strong expertise in dosage adjustment will be included to get their specific needs compared to general medical doctors. We will improve the report's rendering over 2 cycles of interviews, with thorough attention to the clinicians' feedback. The output of this study will allow for the design of the final report. This study will also illustrate the differences between TDM expert pharmacologists and general medical doctors and, hopefully, between other countries and Tanzania for report design acceptance.

The research question components are as follows: (1) What information and how this information shall be displayed to clinicians for an efficient decision-making process concerning dosing regimen? (2) What are the differences in terms of expectations about reports data and design among expert pharmacologists and medical doctors, both in Tanzania and the Western world?

CDSS

Tucuxi offers a GUI, graphs with drug concentration predictions surrounded by percentiles, and dosage adaptation propositions. The software uses Bayesian inference to find the most likely individual parameters integrating information from the underlying popPK model and the observations obtained on the patient. Currently, the user has to decide by himself or herself on the dosage adjustment among those proposed by the software

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and write some sentences to fill up a report. Experienced pharmacologists do this manually, but this practice requires particular skills related to this specialized medical discipline. Clinicians who make final decisions about the drug dosage rely on monographs, experience, or a consultation with a pharmacologist for dosage adaptation. In that context, a CDSS can bring much-needed information to decision makers [25] in locations where expert pharmacologists are not readily available.

The CDSS that will be developed in TuberXpert will offer various features and they are (1) assess the expectedness (likelihood) of a drug concentration result, taking into account the patient's characteristics; (2) assess the adequateness (target attainment) of the current dosage; (3) propose a dosage adjustment if required; (4) present clear and meaningful messages within the report to help the clinician with the decision-making process; and (5) generate alerts when data seem suspicious or erroneous.

While the current Tucuxi software allows the necessary computations, this project will add a new level to the computing engine. Research is needed to ensure the system is extensible enough to address other medical drugs without colossal refactoring. Therefore, a perfect balance between genericity and rifampicin-specific features has to be found. The system must also be easily integrated into existing IT systems thanks to a generic interface. It will also need to be highly reliable and deployable in the field.

Common and uncommon use cases (eg, type of patient, under or over drug exposure, and standard or strange observed drug level) will be identified in both Switzerland and Tanzania, to increase case heterogeneity. Indeed, the patients with TB treated in Switzerland are usually exceptional cases compared to the daily routine patients with TB in Tanzania. Artificial use cases will complete this panel to cover as many borderline cases as possible. We will carefully analyze every patient and use case scenario to design a formal decision tree [26] that will lead to software development. This decision tree will be required to create the software and will be published as a guide for clinicians doing the job by hand. Special attention will be given to appropriate corrective actions [27]. For instance, if a measured drug level appears out of range, an alert shall identify either a potential error in the data or a lack of adherence whenever such sources of bias can be identified with sufficient certainty. In less clear situations, an estimation of the likelihood of common artifacts versus a definite individual PK alteration in the patient should be issued.

The report to be generated shall display proper values and graphs and offer readable sentences. In close relation with the decision tree, a set of standard customizable sentences will have to be defined. They will then be integrated to offer medically meaningful reports as if a human professional had written them. These sentences will be related to TB and rifampicin. Still, the software will be developed keeping in mind that it should be straightforward to define new sentences for other diseases and medicinal drugs. Thanks to established configurations, the core components will be generic, and a parametrization will enable repurposing as efficiently as possible.

We will conduct a short survey in Tanzania to address the availability of computer infrastructures, printers, and connectivity in clinics and at the doctor's desk. We also will ensure that the system can be connected to the laboratory information system that manages the transmission of drug concentration measurement results. In addition, having a version of the CDSS where computations are running remotely could be an option if the clinicians in the field do not own computers with enough computing power. If this approach is required, the patient's data could stay on the clinician's computer to ensure data privacy.

The research question components are as follows: (1) What data processing leads to the most accurate suggestions based on the available data of a specific patient? (2) What setup is most appropriate for rural clinics where access to computer infrastructures is not ideal?

System Validation

TuberXpert will then be validated after the CDSS and report generation are completed, considering the rifampicin popPK model has already been validated and calibrated to the target population. We will assess the correctness of the generated reports based on use cases designed within the project among patients on rifampicin followed at CHUV and on the data gathered in Tanzania (retrospective data of patients from CHUV and 25 from Tanzania, ie, randomly selected 50% among hospital or study patients). CHUV patients necessitating a TDM intervention often present an overly complex clinical situation, allowing for report-generation testing in extraordinary cases. Experienced pharmacologists will generate a manual report using the GUI of Tucuxi to individualize the therapy of the selected patients. Such a "standard" document will contain all the essential information to justify the chosen dosage adjustment, including the patient clinical situation, data nonreliability, or inconsistencies. It will serve as the gold standard for the TuberXpert report, which will be compared to it to identify any discrepancies. We will verify the correctness of the provided guidance and the presence of all the necessary clinical information, justifications, and warnings. This step will also allow for the refinement of the report to guarantee the reliability of the information for the final user, that is, a clinician without strong TDM expertise. Before conducting this project phase, we will elaborate a detailed protocol to ensure the most reliable validation.

After this first validation step, we will update the CDSS and the report generation based on the study results and specifically on the feedback of the pharmacologists. Indeed, the CDSS development will be driven by the use cases defined in the project beginning, while the validation will be conducted on another set of retrospective data. As such, some adjustments will likely be required.

After the software update, we will conduct a second validation, following the same protocol but on another set of patients (25 from Tanzania and 15 from CHUV). This second step should end with very few differences between the pharmacologists' outputs and the generated reports, and we only expect minor software modifications to be necessary after that. Finally, we will again run TuberXpert against all the use cases to validate

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it against the pharmacologists' choices made during the 2 validation steps. The research question component is—is the CDSS developed reliable enough in comparison with a human pharmacologist?

Implementation in the Field

The last project phase consists of the CDSS implementation in the field and a prospective study following a strict protocol that will be elaborated according to Tanzania laws on human research. The goal will be to observe the relevance of the generated reports for the clinicians in Tanzania. KIDH will select a cohort of clinicians actively involved in TB treatment with rifampicin that will identify patients to enroll in the study. This step will assess the benefit of CDSS use versus standard practice in Tanzania. Thanks to the existing network of KIDH, we expect to have at least 30 patients in the cohort treated in 10 facilities in the field.

Before introducing TuberXpert to the clinicians, the selected panel will follow their patients according to standard clinical management while collecting all the needed information for a TDM procedure using a dedicated form that will be elaborated according to CDSS specificities. In addition, the possible dosage adjustments, the patient's health status evolution (ie, clinical features and pragmatic microbiology parameters), and all other relevant data about the patients will be collected. Blood analysis will be implemented and centralized at Kilimanjaro Clinical Research Institute (KCRI) or at KIDH. The KIDH will use this information to feed the CDSS to determine the correspondence between the CDSS output and the clinicians' decisions. The CDSS will be used in this phase without interfering with the patient's treatment.

Then, the consortium will train the clinicians in the field about CDSS usage and report interpretation. This training will not only be beneficial for this project but also for spreading the TDM culture throughout Tanzania.

After the training session, the CDSS will be available at the clinics participating in the study. We will deploy the software in facilities where such deployment is feasible, in a setup that still has to be defined, and also set up a direct communication channel with the Swiss team to help the clinicians with any questions regarding software usage or TDM in general. More clinicians will be involved in this second phase, including but not limited to those who participated in the previous non-CDSS phase, as participation in the first phase is not mandatory to be part of the second one. The study protocol will be written during the project and will strongly focus on the clinical relevance of the CDSS and the acceptance of the software tool [28]. The clinicians will be asked to collect the same information as in the first implementation phase, including clinical features during the patients' follow-up and pragmatic microbiology parameters. Likewise, we will establish the baseline information on the safety of TDM by observing and assessing patients' clinical evolution between the 2 phases, which will subsequently offer the opportunity to determine the overall benefit of CDSS-assisted versus standard patient management in Tanzania. This second part will also help identify the cases where TuberXpert has influenced the clinicians, why they would not be keen to follow the suggested regimens, and if the outcome of the dosage adjustment has been positive for the patient. If clinicians scarcely follow the CDSS suggestions, we will investigate the barriers and bottlenecks that hinder its implementation to increase the accessibility of benefits of the TuberXpert technology. The analysis will then be performed by comparing the subgroup of clinicians who followed the CDSS recommendations versus those who were reluctant and included in the first phase to assess the CDSS benefits. The research question component is—are clinicians keen to adhere to the suggestions of an automated CDSS?

Patient and Public Involvement

The development of this protocol aligns with the patient-centered care approach [29]. This project was designed based on the results of a series of TB research studies in Tanzania that showed individual patients with TB differ and may need different treatment strategies and duration due to variations of disease severity and comorbidities [30-34]. Findings from the described project will be shared with organizations involved in TB management for further refinement before subsequently contributing to shaping the agenda of effective integration of communicable and noncommunicable diseases for policy makers.

Ethical Considerations

The patient enrollment has been approved at the local health research committee serving Kibong'oto Infectious Diseases Hospital and National Health Research Committee with reference KNCHREC003 and NIMR/HQ/R.8a/Vol.IX/2988. Furthermore, the Ministries of Health and Regional Administrative and Local Government Authority have endorsed implementing this protocol. Dissemination will be done mainly through scientific publications for all project parts. Social media will also be used to gain more visibility. Finally, spreading the usage of the system is a goal envisioned at the end of the project.

Results

The TuberXpert project started in November 2022. During its first phase, and as of July 2024, a total of 50 patients have been enrolled to gather the required data to build a popPK model for rifampicin. In addition, the panACEA consortium agreed to share and already provided individual rifampicin data collected in three different studies (trial numbers NCT01392911, NCT00760149, and NCT01785186), allowing preliminary popPK model development based on these data. A review of TDM practices for TB treatment in Tanzania has also been conducted within the same timeframe. From January to December 2023, we carried out the report design study. We started with a literature review concerning the best way to present information to clinicians. Then we created mock-up reports and conducted a qualitative study with 2 rounds of interviews (13 Tanzanian and 27 non-Tanzanian clinicians) to end up with the final report layout. In September 2023 we started to CDSS general architecture. In July 2024 the first prototype of the CDSS core system was finalized.

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Discussion

Principal Findings

The TuberXpert project is a multidisciplinary study blending information technology, clinical expertise, and modeling approaches to deploy precision pharmacotherapy of first-line anti-TB medicine through dosage optimization in TB treatment, thanks to an automated CDSS system. To the best of the authors' knowledge, there is no existing system offering the same functionality. Some TDM software are available, but they require specific skills and do not end up with a fully automated report generation.

After 18 months, interesting information emerged from the project's first phases. As seen in other low-resource settings, TB in Tanzania is complicated by socioeconomic factors, comorbidities, and a rigid health care system unsuited to patients who are dual-diseased. Significant pharmacokinetic variability of rifampicin between and within subjects further complicates TB management, potentially leading to unfavorable treatment outcomes. Hence, TDM stands as a considerable asset for addressing the limitations of the generalized "one-size-fits-all" approach by tailoring treatment to patient characteristics. While this personalized approach is appealing, the highly complex pharmacokinetic profile of rifampicin significantly complicates straightforward TDM for nonexpert clinicians. Implementation of TDM is further hindered by features exacerbated by low-resource settings, such as logistical barriers, lack of funding, analytical equipment, or trained pharmacologists suited to TDM. If well implemented in the Tanzanian health care landscape, a CDSS coupled with TDM can provide a practical medical tool facilitating personalized medicine in resource-limited settings contributing to alleviating the TB burden.

The report study emphasized the importance of designing accessible and engaging medical reports, particularly in the context of TDM and CDSS. Simplifying and standardizing report formats can improve comprehension and action ability for clinicians, especially those who are nonexperts. As the TuberXpert project aims to create user-friendly TDM reports for TB treatment, it highlights the necessity of clear visuals and appropriate terminology. Interviews with health professionals revealed that simplicity, clear structure, and effective visuals are crucial, though balancing detailed information with simplicity remains challenging. The study also addressed the complexities of multinational collaboration, stressing the need for consistent and understandable communication across diverse health care environments.

Future Directions

In July 2024 the team will start with the development of the popPK model based on the acquired data and in parallel prepare and validate the CDSS. These phases are expected to last a year. Finally, the implementation of the system in the field will enable the team to assess the adherence of the clinicians to the proposed adjustments and to observe the real impact of the TuberXpert setup. Shall the conclusions be positive, the system could be deployed in other countries, and extended to other medical drugs.

Strengths and Limitations of This Study

To our knowledge, this is the first study to investigate the application of CDSS technology at varying health care delivery systems levels to guide TDM in patients with TB in TB-endemic settings, especially where pharmacologists are not available. In the future, routine implementation of TDM-CDSS, particularly for rifampicin, a backbone for TB treatment, is expected to transform TB's clinical management in resource-limited settings. Anti-TB dosage optimization will improve treatment outcomes of patients who would otherwise succumb or develop drug-resistant TB because of suboptimal drug exposure. This will considerably contribute to the end TB strategy, particularly with arduous forms of TB with either HIV coinfection or coexistent DM or malnutrition.

While the project's expected impacts are important, some limitations could arise. A lack of computer infrastructure in health facilities may prevent the implementation of a centralized system in resource-limited countries. If such computers are not available, if the network is stable enough, we envision using smartphones thanks to a web server offering the TuberXpert service.

Conclusions

This game-changing transdisciplinary 3-year project combines technology and pharmacometrics to enable appropriate dosages of anti-TB drugs in patients with TB at various levels of the health care system in TB-endemic settings. TuberXpert thus provides an unprecedented opportunity to optimize and individualize the clinical management of patients with TB in resource-limited settings. Moreover, TDM tends to be increasingly recommended, particularly for treating multidrug-resistant TB with second-line chemotherapeutic agents, when achieving effective and safe concentration exposure is of vital importance [35]. In the end, TuberXpert could be adapted beyond rifampicin and holds promise far beyond TB alone, with indirect benefits in other therapeutic areas such as HIV, cancer, and so forth. At the project half-life, it is too early to draw definitive conclusions, but a set of contributions are expected, for the field of dosage adjustment, TDM, and especially for the patients.

Contribution to the Field

Findings from this project will provide broad knowledge on the feasibility and appropriateness of dosage correction for individuals with suboptimal drug exposure to medicinal drugs critical for the treatment of a life-threatening condition. The project will concretely validate a model-based dosage adjustment of rifampicin in patients with TB. Through publications, it will enhance evidence-based information applicable in different countries.

Routine implementation of the TDM-CDSS particularly for rifampicin, which is a backbone for TB treatment, will transform the clinical management of TB. The current WHO rifampicin dosage of 10 mg/kg was designed rather empirically without prior evidence derived from preclinical or clinical trials [36]. Researchers have documented rifampicin suboptimal drug levels in at least 50% or more of the TB-treated population [30,37]. However, there is limited evidence on the use of technology to

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address the gaps [8]. This project will also improve the education of medical doctors in Tanzania concerning the dosage adjustment of rifampicin. The expertise will be made available in remote areas where there is a considerable number of patients with TB.

Contributions to Patient Care, Disease Management, and Public Health

The project will contribute considerably to the end TB strategy by improving patients' treatment, particularly with arduous forms of TB (either with HIV coinfection or coexistent DM or malnutrition). It might definitely improve treatment outcomes of patients who would otherwise succumb or develop drug-resistant TB as a result of suboptimal drug exposure [22]. A priori dosage recommendations made in this project as a function of specific patient's characteristics will already limit the use of dangerous subtherapeutic doses in these fragile populations. Furthermore, TDM can decrease the occurrence of adverse drug reactions in patients by favoring appropriate dosages and preventing overdoses [38]. This project challenges the status quo of empirical treatment toward individualization of therapeutics, a patient-centered approach regarded as an important arsenal for the end TB strategy [39].

Contribution Toward Implementation of TDM-CDSS as an Innovative Technology

The TuberXpert project fosters collaborations with African or European countries that will enable Tanzania to produce high-quality research on pharmacotherapy while strengthening research capacity, and Switzerland will benefit as well on innovation, science, and entrepreneurship. The proof-of-concept will pave the way to a user-friendly TDM-CDSS that has a good chance of proving applicable to other medicinal drugs.

Contribution Toward the Community of TDM Users

At the end of the project, the source code of the CDSS and report generator will be publicly available, with a license allowing to use it for nonprofit purposes (possibly to use it for helping clinicians, but not to sell a software). If at some stage in the future a company is interested in commercializing a software embedding parts of the existing source code, a specific license with royalties will be considered as an option for further closed-source exploitation. Both the core engine and the GUI of Tucuxi are available in Open Source [40]. The result of TuberXpert will be proposed within this framework to help as many institutions and countries as possible. The vision is to build a community of institutions revolving around TDM, with participants from various countries able to take advantage of each other to improve patient care. This will be of particular interest to African countries that could have access to such tools for free.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to patients' data privacy concerns, but are available from the corresponding author on reasonable request. The source code that will be generated during this study will be shared on GitHub as Open Source, allowing anyone to reuse and improve it in the future.

Authors' Contributions

YT, MG, and SGM conceptualized, designed, and supervised the research proposal. YT wrote the paper with input from all the authors. YT is leading the project, specifically the software part of it. MG is leading the popPK rifampicin model development and coordinating the University Hospital of Lausanne (CHUV) team. SGM is leading the study in the field. AEC is in charge of conducting the report study and the clinical decision support system (CDSS) development. YJP is developing the rifampicin popPK model and is working on the therapeutic drug monitoring (TDM) implementation. BS is in charge of the studies in the field (enrollment of patients and implementation). MLS is responsible for the laboratory analysis. CC is cosupervising AEC and YJP PhDs. All authors have approved the final version and agreed to be accountable for all aspects of the work related to accuracy and integrity.

Conflicts of Interest

None declared.

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Abbreviations

CDSS: clinical decision support system
CHUV: University Hospital of Lausanne
DM: diabetes mellitus
GUI: graphical user interface
HEIG-VD: University of Applied Sciences Western Switzerland
I-MeDeSa: Instrument for Evaluating Human Factors Principles in Medication-Related Decision Support Alerts
KCRI: Kilimanjaro Clinical Research Institute
KIDH: Kibong'oto Infectious Disease Hospital
panACEA: Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics
PK: pharmacokinetics
popPK: population pharmacokinetic

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TB: tuberculosis
TDM: therapeutic drug monitoring
WHO: World Health Organization

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Protocol

The Impact of the Ecosystem on Health Literacy Among Rural Communities in Protected Areas: Protocol for a Mixed Methods Study

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Abstract

Background: Protected areas are crucial for the maintenance of human health and well-being. They aim to preserve biodiversity and natural resources to secure various ecosystem services that are beneficial to human health. Their ecological characteristics can influence local health literacy. Typically, communities surrounding protected areas have limited economic opportunities due to restriction policies to protect the ecosystem, resulting in socioeconomic disparities. The local community faces obstacles in gaining access to health care facilities and health information due to these limitations. It is difficult for them to locate, comprehend, and apply information and services to make better health-related decisions for themselves and others.

Objective: This study protocol examines the impact of the ecosystem on health literacy among rural communities in protected areas.

Methods: This study comprises 5 phases. In phase 1, we conduct a systematic review to identify the issue of health literacy in protected areas. In phase 2, we will collect data from stakeholders in a protected area of Pahang National Park and analyze the results using Net-Map analysis. In phase 3, we will conduct a survey among the adult community in Pahang National Park related to health literacy, socioeconomic status, health expenditure, and quality of life. In phase 4, informed by the results of the survey, we will determine suitable intervention programs to improve health literacy through a focus group discussion. Finally, in phase 5, we will conduct a costing analysis to analyze which intervention program is the most cost-effective.

Results: This study was funded by Universiti Sains Islam Malaysia (USIM) and strategic research partnership grants, and enrollment is ongoing. The first results are expected to be submitted for publication in 2024.

Conclusions: This is one of the first studies to explore health literacy among rural communities in protected areas and will provide the first insights into the overall level of health literacy in the protected community, potential determinants, and a suitable intervention program with expected cost analysis. The results can be used to promote health literacy in other protected areas and populations.

Trial Registration: International Standard Randomized Controlled Trial Number Registry ISRCTN40626062; http://tinyurl.com/4kjxuwk5

International Registered Report Identifier (IRRID): PRR1-10.2196/51851

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KEYWORDS

ecosystem; health literacy; protected areas; Net-Map; quality of life; rural communities; protocol

Introduction

Good health and well-being can be achieved with adequate health literacy [1,2]. Adequate health literacy indicates that the individual can obtain, process, understand, and apply basic health information and services needed to make appropriate health decisions [3]. Higher levels of health literacy allow people to make better health decisions [4], be more committed, and do their jobs more efficiently [5]. Patients must have enough information about their health to leverage it and make well-informed decisions regarding getting health treatments and medicine. In the context of preventive health care, an adequate level of health literacy helps ensure that patients get the most out of their health investments and make the best use of resources [6]. According to the World Health Organization (WHO), people residing in rural areas often experience socioeconomic inequity and lower educational attainment due to imperfect living conditions. These areas are cut off from urban centers and have limited facilities [7,8]. The varying ecosystems within the population may influence different levels of health literacy.

People living in the protected areas often have limited health literacy [9]. The government designates protected areas for conservation purposes. Thus, less emphasis is placed on new land development for farming, housing, and infrastructure [10-12]. As a result, populations encounter challenges in gaining better access to networks, health facilities, the internet, and other resources. This limitation, in turn, adversely affects their quality of life [9]. The health outcomes, living conditions, and education levels of the population residing in rural areas lag significantly behind those living near urban centers. This disparity places people in rural areas at a disadvantage when it comes to making informed health decisions, as they have limited knowledge in this regard.

Accordingly, policy makers are putting in place and advocating for health programs and awareness campaigns to improve the health literacy status among populations in rural and protected areas [13]. However, this strategy is hard to implement in communities that live in protected areas as they have limited educational backgrounds. They struggle to access, obtain, understand, and apply health information in their daily lives. Moreover, they are often unable to access health information when they are sick. Indigenous people often turn to traditional remedies, consult shamans, or opt for inaction with the hopes that the illness will recover on its own [14]. The limited knowledge of hygiene among indigenous people has prompted the government to develop a specialized syllabus for indigenous children at primary school. This curriculum focuses on teaching essential practices, such as washing hands, proper toilet usage, and dental hygiene. Understanding the impact of protected areas on health literacy in local communities is crucial to sustaining their way of life and health. However, the level of health literacy and its response to protected areas varies, depending on factors such as the type of protected area, how policies are planned, and how they are implemented [15].

Research on health literacy among people who live in protected areas is important for understanding their needs for access to health care, disease prevention, health promotion, and health care. It will also help elucidate how to meet these needs in the best and most effective way. Nevertheless, thus far, there has been limited research on health literacy and health issues among people in protected areas considering 4 perspectives (ie, that of government entities, knowledge institutions, civil agencies, and local communities). Accordingly, this paper proposes a study that will examine health literacy and health status of communities in protected areas. The study protocol can serve as a model for similar investigations in protected areas in other countries.

Based on the available evidence, this study aims to (1) conduct a systematic review to understand the health literacy status among rural communities surrounding protected areas; (2) explore stakeholders' perceptions of health literacy status among rural communities surrounding protected areas; (3) determine the health literacy status and its associated factors among rural communities located near protected areas; (4) develop a new health literacy intervention program for rural communities near protected areas; and (5) conduct a cost structure analysis of the new health literacy intervention programs for rural communities surrounding protected areas.

Methods

Background and Conceptual Model

This study adopts a mixed methods approach to investigate health literacy.

Our understanding of health literacy is underpinned by the four core dimensions of the Health Literacy Model [16]: (1) accessing, (2) understanding, (3) appraising, and (4) applying health information. Based on this model, this study will explore the impact of the ecosystem on health literacy among rural communities in protected areas. Figure 1 explains the conceptual model for this study.

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Figure 1. Conceptual model of the study.

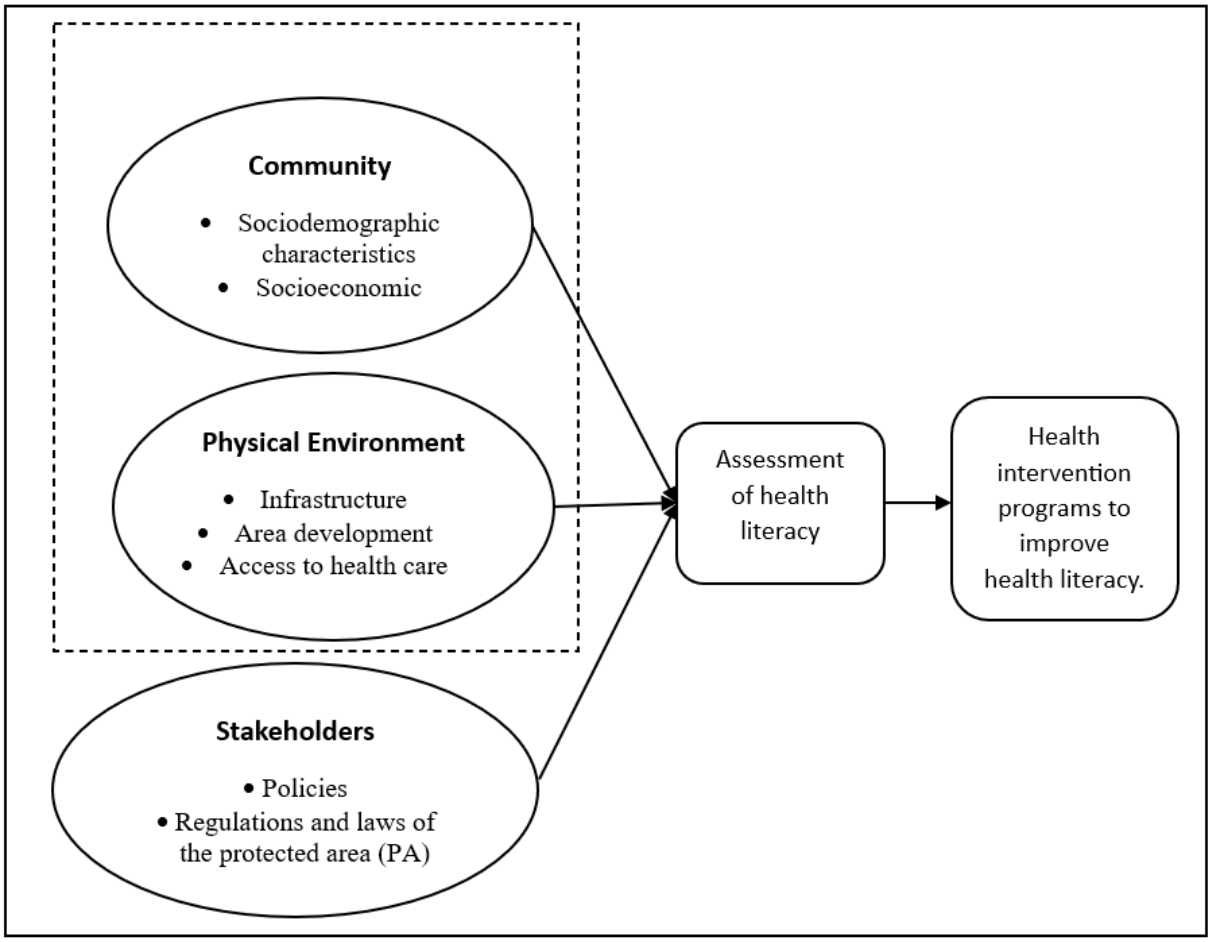

Study Site

This study comprises one of Malaysia's protected areas, Pahang National Park (PNP). There are 53 national and state parks in Malaysia, with PNP being among the country's most important and best-protected conservation areas. The region has diverse populations, including Malay and indigenous communities. As per the Jabatan Kemajuan Orang Asli (JAKOA; translated to Department of Orang Asli Development) [17], Pahang has the highest number of indigenous communities (37.9%) in Malaysia. Because the PNP site fulfills the criteria for this research (ie, the implementation of a protected area and the presence of legal or other formal mechanisms promoting such an area), we selected it as our study area.

Research Design

This study contains 5 phases consisting of identifying the health literacy issues in this area, confirming the issues, testing the issues, and preventing and analyzing the issues. The 5 phases will be carried out based on the 5 objectives.

Phase 1: Identifying Issues Through a Systematic Review

Overview

In phase 1, we will review the literature to understand the health literacy status among rural communities surrounding protected areas. This phase will involve conducting a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Approach

The systematic review will use a standard search string using the PICO (Population, Intervention, Comparison, and Outcome) structure. For the keyword search, we will use PubMed, Scopus, and Web of Science databases. Later, 2 reviewers will be appointed to appraise all selected studies. The result will compile the highest quality studies relevant to the study objectives.

Eligibility

The selection of results will be based on the following eligibility criteria: (1) full articles written in English and (2) articles published between 2012 and 2022. The exclusion criteria include (1) gray literature and (2) articles outside the scope of our research. The screening process will consider the qualifying requirements established.

Quality Assessment

First, 2 reviewers will conduct a quality assessment using a set of study quality assessments checklist. The checklist consists of eight evaluation criteria: (1) research goals, (2) study design, (3) study outcomes, (4) sample size calculations, (5) analysis of findings, (6) variance estimates for the primary results, (7) adequate reported results, and (8) conclusions. A quality score is one way to incorporate quality into the review process [18]. The reviewers will assign 2 points to articles that meet all

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criteria, 1 point if they fulfill some requirements, and 0 points if they do not. Subsequently, the quality score will be calculated by aggregating all elements from the quality assessment tool to provide an overall single score. In case of disagreements, a third reviewer will be appointed.

Data Coding and Analysis

This study employs a thematic synthesis, utilizing a 2-step coding procedure wherein reviewers will code each line of text from the articles separately for its meaning and substance. Before finishing this step, we will analyze every text associated with a particular code to ensure that the interpretation is consistent.

Phase 2: Exploring Stakeholders' Perceptions of Health Literacy Status in Rural Communities Surrounding Protected Areas

Overview

Phase 2 will use focus group discussions (FGDs) and in-depth interviews to achieve objective 2, which is to obtain stakeholders' opinions on health literacy issues among the community in PNP. The results will support the findings for objective 1.

Sample Selection

The selection of the stakeholders will be based on 3 categories, namely, government entities, knowledge-generating institutions, and civil society organizations [19,20]. However, the number of these actors will vary. This method will use purposive sampling to obtain a precise sample size. The expected actors can nominate any other actors with potential contributions to PNP's health literacy issue. This process will be halted when the answers given by the respondents are saturated [21].

Data Coding and Analysis

Data extraction and coding will be done for all Net-Map exercises, with a focus on thematic analysis utilizing information from the interviews. This analysis will mainly involve mapping activities and explaining the impact of protected areas on health literacy. The thematic analysis will follow a 2-step coding process. First, a line-by-line review of the interview data will be conducted to identify the key impacts related to the study objectives. Subsequently, each article will be assigned a code label to cluster all the information into a common theme.

Phase 3: Identifying Health Literacy and Its Associated Factors in Rural Communities Surrounding Protected Areas

Participants and Sampling

This study will focus on the PNP. It covers 2477 square kilometers and was the country's first national park established in Malaysia between 1938 and 1939, originally known as the King George V National Park. Following Malaysia's independence from British rule in 1957, the park was renamed. It is comprised of 3 protected areas in the states of Pahang, Kelantan, and Terengganu to form the central spine of Peninsular Malaysia. The national park has a reputation for being one of the world's oldest tropical rainforests, with an estimated age of 130 million years and a size of 4343 square kilometers.

Local communities in PNP are composed of Malay and Orang Asli (Batek and Semak Beri ethnicities). This location meets the criteria for this study because a protected area has been established and legal and other institutional measures have been established to promote them. The Pahang Department of Wildlife and National Parks (PERHILITAN) manages the PNP. The area is not open to the public except for those who have received prior approval from the authority for research purposes and minimal tourism activity at Kuala Tahan. Currently, the wildlife reserve contains a single research center that serves 2 distinct goals. The national park was originally established at Ulu Tembeling, with the first superintendent's office situated at Kuala Tahan. The southern section of PNP features a river boundary of over 80 kilometers along Sungai Tembeling, the Hulu Tembeling basin's principal river. Indigenous people inhabit the national park, while the Malay community resides near the river. For this study, respondents were drawn from the Malay and indigenous communities from the provinces of Hulu Tembeling and Tembeling Tengah. Table 1 shows the total number of respondents.

Respondents aged 18 years and above may vary in health status, including those with disabilities. A stratified random sampling approach (based on villages) will be employed for both the Hulu Tembeling and Tembeling Tengah provinces. All villages will be identified and visited. The choice of houses in the village will be selected randomly based on the number of houses given by the head of the village (Tok Empat and Tok Batin) and the inclusion criteria among the respondents, such as being able to read, having no cognitive disabilities, and being willing to participate in the survey.

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Table 1. The total number of respondents and sample in Pahang National Park (PNP).

Name of village	Race	Province	Head of households (N=2525), n (%)	Sample (N=400), n (%)
Kg Pagi	Malay	Hulu Tembeling	95 (3.8)	15 (3.8)
Kg Kuala Sat	Malay	Hulu Tembeling	142 (5.6)	22 (5.6)
Kg Bantal	Malay	Hulu Tembeling	155 (6.1)	25 (6.1)
Kg Gusai	Malay	Hulu Tembeling	70 (2.8)	11 (2.8)
Kg Bukit Mat Daling	Malay	Hulu Tembeling	141 (5.6)	22 (5.6)
Kg Kuala Tahan	Malay	Tembeling Tengah	657 (26.0)	104 (26.0)
Kg Gol/Lik	Malay	Tembeling Tengah	40 (1.6)	6 (1.6)
Kg Merting/Lubok Payung	Malay	Tembeling Tengah	111 (4.4)	18 (4.4)
Kg Labu/Jong Berlabuh	Malay	Tembeling Tengah	163 (6.5)	26 (6.5)
Kg Pasir Sia/Air Hitam	Malay	Tembeling Tengah	86 (3.4)	14 (3.4)
Kg Selimbar/Chebong	Malay	Tembeling Tengah	58 (2.3)	9 (2.3)
Felda Sg Retang	Malay	Tembeling Tengah	509 (20.2)	81 (20.2)
Kuala Atok	Batek	Tembeling Tengah	35 (1.4)	6 (1.4)
Sungai Tiang	Semoq Beri	Tembeling Tengah	60 (2.4)	10 (2.4)
Sungai Tekal	Semoq Beri	Tembeling Tengah	83 (3.3)	13 (3.3)
Bukit Gam	Batek	Tembeling Tengah	22 (0.9)	3 (0.9)
Sg Keniam	Batek	Tembeling Tengah	35 (1.4)	6 (1.4)
Jeram Aur	Batek	Tembeling Tengah	13 (0.5)	2 (0.5)
Jeram Dedari	Batek	Tembeling Tengah	17 (0.7)	3 (0.7)
Sungai Yong	Batek	Tembeling Tengah	18 (0.7)	3 (0.7)
Sg Tabung/ Teresek	Batek	Tembeling Tengah	15 (0.6)	2 (0.6)

Sample Size

Two approaches will be considered to calculate the optimal sample size (ie, using the odds ratio [OR] and prevalence). The selection will be based on the method producing the higher sample size. For the OR, the sample size will be calculated using the OR of health literacy in Malaysia [22], identified as 3.41 with a 95% CI. We will use the Open Epi Software (version 3.01) to calculate the sample size. With an OR of 3.41, the estimated sample size is 310 as shown in Table 2. Furthermore, Table 3 shows the comparison of sample sizes for exposed and nonexposed groups in Kelsey and Fleiss methods.

In contrast, the second method uses prevalence. In Malaysia, the health literacy prevalence among individuals aged 18 years and above is 35.5% [23]. Using this percentage, the minimum sample size calculated for this study is 323 people for a 95% CI. Since the prevalence sample size is higher than the OR, we decided to use it as our sample size. Considering a dropout probability of approximately 10%, the total sample size needed for this study is about 355 people. However, we will distribute a sample size of 400 people based on the ratio calculated. We estimate that out of 400 adults, approximately 200 households will need to be interviewed based on the assumption that 1 household has 2 adults. To ensure that the provinces within the national park are well represented, the percentage of the selected population is determined to be 24%, 64%, and 12% for Malay in Hulu Tembeling, Tembeling Tengah, and indigenous people, respectively. Using the stratified random sampling techniques, the number of samples allocated for each village is outlined in Table 1.

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Table 2. The estimated sample size.

Variables	Values, n
Sample size, n	310
Two-sided significance level (1-alpha)	95
Power (1-beta, % chance of detecting)	80
Ratio of sample size, unexposed/exposed	1
Percent of unexposed with outcome	5
Percent of exposed with outcome	15
Odds ratio	3.4
Risk/prevalence ratio	3
Risk/Prevalence difference	10

Table 3. Comparison of sample sizes for exposed and nonexposed groups in Kelsey and Fleiss methods.

Variables	Kelsey (n=274), n (%)	Fleiss (n=272), n (%)	Fleiss with CC[a] (n=310), n (%)
Sample size, exposed	137 (50)	136 (50)	155 (50)
Sample size, nonexposed	137 (50)	136 (50)	155 (50)

[a]CC: continuity correction.

Inclusion and Exclusion Criteria

Participants in this study are required to be adults aged 18 or above and will be recruited after providing consent. Age verification will be based on their ID cards. Potential respondents may either be healthy or have various physical disabilities and demonstrate a willingness to participate. Additionally, they must be able to communicate in the Malay language. However, people with cognitive impairments will be excluded from the study.

Tools and Instruments

This study will comprise 3 evaluations: health literacy, health, and socioeconomic status. There are 8 parts to the questionnaire, which are outlined in Table 4.

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Table 4. Components of the questionnaire.

Component	Description
Part 1: Housing and the environment (head of household only)	Part 1 will capture family structure, household transportation, and water supply.
Part 2: Household income (head of household only)	Part 2 will record the household's annual income from all sources.
Part 3: Sociodemographic characteristics (all household members, including the head of household)	Part 3 will capture sociodemographic information such as date of birth, ethnicity, education, employment status, relationship status, and so on.
Part 4: Health care expenditure and utilization (all household members, including the head of household)	Part 4 questions will capture data on health payments, health care service utilization, traditional and complementary medicine practice, and health care expenditure.
Part 5: Modifiable lifestyle factors (all household members, including the head of household)	Part 5 will ask about tobacco consumption, nutrition, physical activity, and medical conditions.
Part 6: Medical information (all household members, including the head of household)	Part 6 will measure the height, weight, waist circumference, and hip circumference. The calibrated vertical SECA portable 217 stadiometer (SECA GmBH & Co KG) will be used to measure respondents' height, the calibrated SECA 813 digital electronic weighing scale will measure weight, and the SECA 201 ergonomic measuring tape will measure waist (abdominal) and hip circumferences.
Part 7: Quality of life (all household members, including the head of household)	Questions in part 7 will assess the participant's quality of life using standard and generic methods.
Part 8: Health literacy status	Health literacy status will be determined using the HLS-SF-Q12[a] [24]. The perceived difficulty of each health-related task is rated on a 4-point Likert scale (1=*very difficult*, 2=*difficult*, 3=*easy*, and 4=*very easy*), with a possible lowest mean score of 1 and a possible highest mean score of 4. The questions consider the 4 competencies of an individual when dealing with health-relevant information (access/obtain, understand, appraise/judge/evaluate, and apply/use health information) to form a judgment and make health-related decisions for the 3 domains of health care, disease prevention, and health promotion.

[a]HLS-SF-Q12: 12-item Short-Form Health Literacy Questionnaire.

Reliability, Validity, and Trustworthiness

Reliability indicates whether the results can be consistently reproduced or not. In this study, internal consistency is evaluated through the Cronbach α value, with a threshold set at greater than or equal to .70 for satisfactory reliability. At the same time, validity will measure the validity and accuracy of the questionnaire. Face and content validity will be used to measure the validity of the questionnaire. Notably, this study incorporates established questionnaires with preestablished reliability and validity from different sources [22,25].

Data Collection Procedure

A total of 8 interviewers will be required to conduct the survey, working in pairs. For security and dialect reasons, a local representative will be appointed to accompany each team. Before the data collection, the ground staff will introduce the interviewers to the household members to ensure that the head of the household and other members are present and grant permission for the interviewers to enter their personal premises. Once approval is obtained, the interviewer will explain the nature of the study based on the participants' information sheet, which outlines the key details. Subsequently, the information sheet will be provided to the participants for their reference. In addition, the interviewers will reassure the participants that the information provided in the study will remain confidential and their participation is entirely voluntary. The face-to-face interview will begin shortly after the head of the household and other household members have signed the consent form. During the interview, the respondents' height and weight will be measured, contingent on suitability and participant preference. If the head of the household is absent during the visit, the house will be marked on the map, and a second visit will be arranged for the next day. However, the house will be excluded if the head of the household is still not present during the second visit.

Data Analysis Procedure

The data analysis procedure will involve both descriptive and analytical analyses. Initially, a descriptive analysis will focus on the sociodemographic characteristics of the study population. We will examine the distribution of study variables by calculating frequency and percentage, along with reporting mean and SD. Since the outcome of interest is categorical, nonparametric tests will be used. Following the approach outlined in [26], responses categorized as inadequate and problematic will be grouped as inadequate (0), while those categorized as sufficient and excellent will be classified as adequate (1) during the analysis.

For the analytical analysis, we will carry out both bivariate and multivariate analyses to explore the determinants of health literacy among both the study population residing whining the

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PNP and the population living outside the PNP. This comparative approach will aim to determine which ecosystem has adequate health literacy. The significance level has been set to $P<.05$. The analytical analysis will be conducted using SPSS software (version 28.0, IBM Corp).

Phase 4: Developing a New Health Literacy Intervention Program for Rural Communities in the Protected Area

Overview

Phase 4 will be conducted via FGD discussion among the stakeholders.

Data Collection Procedure

The data collection process will be based on the opinions of the stakeholders and field experts. We will invite them to the seminar and sharing session to discuss the sustainability of the community near PNP. An invitation letter will be sent to the stakeholders and experts to confirm their willingness to participate in the discussion. They will include representatives from the Ministry of Health, JAKOA, Department of Wildlife and National Parks, heads of villages (Tok Empat and Tok Batin), nongovernmental agencies (NGOs), and academicians who are Taman Negara community health experts. During the seminar and sharing session, they will discuss mitigation measures that are suitable and effective in enhancing the health literacy status of the rural community.

Eligibility

The eligibility criteria for the intervention programs will be based on several factors, including the capacity of these programs, the financial support they received, their geographical location, prior experience in conducting health literacy programs, and willingness to participate. To account for differences in intervention activities, epidemiology, and target populations, we will limit our selection to only interventions that target communities located within the protected areas.

Data Analysis Procedure

During the discussion session, stakeholders will provide information regarding suitable intervention programs to improve health literacy at PNP using Logical Framework Analysis (LFA). The core components of LFA are outlined in Table 5.

Table 5. The core components of Logical Framework Analysis (LFA).

Component	Description
General objectives (goal)	This is the project's overarching goal. The project's benefits are laid forth in the objective goal for the beneficiaries.
Project purpose	The target group's plan of action to effect the desired change is expressed in the purpose. The project purpose frequently refers to modifying the target group's behavior because they use the services or goods the project offers.
Output	The project offers the products, services, and goods to the intended audience. The project is accountable for these outputs.
Activities	The project's processes for delivering the various goods, services, and products are outlined.

Phase 5: Conducting a Cost Structure Analysis of the New Health Literacy Intervention Programs for Rural Communities Surrounding the Protected Area

Overview

Phase 5 is a continuation of Phase 4. We will conduct a cost analysis for every intervention program listed in Phase 4.

Data Collection Procedure

The cost structure will be prepared based on advice from experienced agencies or individuals in the field. A list of intervention activities will be presented as an alternative to the policy makers or any agencies who are interested in improving health literacy among the PNP community.

Economic data on providers' costs will be collected for the financial year 2021 to 2022. The data obtained will contain information on the costs incurred at the intervention and funding agency levels. When valuing economic costs, the opportunity cost of each resource will be considered, encompassing all resources used in the intervention, including those that are donated or subsidized. This approach ensures a uniform method of data collection, enabling reliable cost comparisons among the various interventions.

Data Analysis Procedure

The cost analysis will analyze expenses based on the cost unit, source data, and frequency, with comparisons made across the intervention programs. The cost unit pertains to the expenses associated with each intervention per patient per year. Simultaneously, the sources of data serve as evidence for the interventions, and frequency refers to the number of interventions required annually.

Data Management and Analysis

Data Security

At the end of each day of data collection, the project manager will gather all interviewers and conduct a postmortem session. Any loopholes identified during the process will be addressed immediately to avoid further mistakes and invalidate the collected data. In addition, the project manager will verify if the number of answer booklets corresponds with the number of households surveyed. Upon verification, the answer booklets will be placed in a safe box, while the consent form will be kept in a separate secure box to avoid any information breach. Only the project manager and the principal investigator have access to these secured boxes. Similarly, all recorded videos and voices from FGD and interviews will be safely placed in a Dropbox (Evenflow Inc) for analysis.

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Data Entry and Analysis

Data entry from the survey form will be completed within 2 to 4 weeks after completing the groundwork, depending on the number of respondents. Once all data have been entered into SPSS software, we will perform a random cross-checking of the data set to maintain data accuracy. The cross-checking will be set at 20% of the overall questionnaires entered [25]. Data analysis will comprise both descriptive and analytical analyses. Descriptive analysis will be performed on the population's sociodemographic characteristics, BMI measurements, expenditure, utilization of health care goods and services, modifiable lifestyle factors, and reported quality of life. The analytical examination will be conducted to determine the association between sociodemographic characteristics, health status, and socioeconomic status with health literacy status. The results will be analyzed using SPSS software. The data and results will be presented to and validated by field experts and stakeholders of PNP in the form of reports and seminar-sharing sessions.

Ethical Considerations

Ethics approval for this study was granted by the Universiti Sains Islam Malaysia (USIM) Research Ethics Committee (USIM/JKEP/2022-216). Each respondent will sign a written informed consent form before the interview. Academic journals, conferences, and stakeholder seminars will be used to communicate the findings of this research. The protocol received approval from the International Standard Randomized Controlled Trial Number Registry (ISRCTN; 40626062).

Results

The project was funded by USIMl and strategic research partnership grants. Enrollment for the overall project is ongoing. We are conducting a systematic review of health literacy in protected areas and conducting a cross-sectional study based on the survey results to determine the determinants of health literacy in protected areas. Findings from this study will be used to develop a sustainable health intervention module with an effective cost that may be adopted in all protected areas in Malaysia. The first results are expected to be submitted for publication in 2024.

Discussion

Anticipated Findings

The conservation policy of the protected areas has limited opportunities for local communities to harvest natural resources from the ecosystem. Their quality of life has been affected due to inferior education, health, and living conditions compared to communities living in urban areas. This disparity has resulted in challenges for the community in accessing health facilities and infrastructure, thereby limiting their health literacy level. Their remote location and distance from main roads have contributed to this low health literacy. To our knowledge, few studies have been conducted on health literacy and health issues among individuals in protected areas from 4 perspectives: government entities, knowledge institutions, civil agencies, and local communities. Accordingly, this paper proposes a study to investigate the health literacy and health status of communities within and near PNP. In accordance with the recommendations made by the PNP shareholders, this study aims to develop a health intervention program that is efficient and appropriate for community implementation. Health literacy research among people living in protected areas is essential for a deeper understanding of their needs for access to health care, illness prevention, health promotion, and health care. This understanding will guide the development of effective strategies to meet these requirements.

Strengths and Limitations

This study's strength lies in its mixed methods analysis, employing a triangulation process to converge and validate both qualitative and quantitative data [27]. Moreover, this study will be conducted in multiple phases to discuss the issue comprehensively. This structured approach facilitates incremental progress [28]. Phases 1 and 2 are conceptual phases where the issue is identified and validated through a systematic review by stakeholders in PNP, such as government agencies, knowledge institutions, and civil society organizations. Phase 3 will design and plan the questionnaire and examine the health literacy status and its influencing factors among the community. The stakeholders in the FGD in phase 4 will validate the results of phases 1 to 3. Using these results, the stakeholders will discuss and design an effective health literacy intervention program. Finally, phase 5 will involve the dissemination of the health literacy intervention program to improve the health literacy status in the community. Moreover, a cost analysis will be calculated to analyze the cost of the program.

The study's limitations became apparent during the FGD session with the stakeholders, as the invited participants did not attend. Consequently, we missed capturing unique macro-level perspectives. Another limitation is that the stakeholders' views may not be representative of all who live inside or near the protected area in Malaysia or globally. Additionally, the study did not address the distinctions between locals and outsiders. Access to rural areas is difficult logistically, and the potential presence of wildlife, such as tigers, elephants, and bears, further complicates the research process.

Conclusions

In conclusion, this study will determine how different ecosystems, especially in protected areas, impact the health literacy of the local community using a mixed methods approach. The phases of the data collection process, incorporating both qualitative and quantitative methods, aim to comprehensively address the issue of health literacy in the local community. We will use these findings to disseminate a health intervention program, along with a cost structure, to improve health literacy among the protected area's community. The mixed methods study serves as a structured investigative model for evaluating and improving health literacy, health status, and well-being among all protected areas and communities worldwide.

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Data Availability

The data sets generated in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

The conceptualization of the project was led by AA, MHJ, and MIMN. The data collection was led by NAAK, and the development of the questionnaire was a collaborative effort involving NAAK, AA, MHJ, and MIMN. Supervision was provided by AA, MHJ, MIMN, and ZK. NAAK wrote the original draft, which was then reviewed by AA and MIMN.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Universiti Sains Islam Malaysia (USIM).
[PDF File (Adobe PDF File), 520 KB - resprot_v13i1e51851_app1.pdf]

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Abbreviations

FGD: focus group discussion
ISRCTN: International Standard Randomized Controlled Trial Number Registry
JAKOA: Jabatan Kemajuan Orang Asli
LFA: Logical Framework Analysis
NGO: nongovernmental agency
OR: odds ratio
PERHILITAN: Pahang Department of Wildlife and National Parks
PICO: Population, Intervention, Comparison, and Outcome
PNP: Pahang National Park
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
USIM: Universiti Sains Islam Malaysia

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Proposal

Meaningful Social Inclusion and Mental Well-Being Among Autistic Adolescents and Emerging Adults: Protocol for a Community-Based Mixed Methods Study

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Abstract

Background: In the United States, autistic people face high rates of co-occurring mental illnesses and premature death due to self-harm, which are indicators of threats to mental well-being. Social inclusion may enhance mental well-being and resilience among autistic people. According to Simplican and colleague's (2015) model of social inclusion for people with intellectual and developmental disabilities, social inclusion is an interaction between community participation and interpersonal relationships. There is limited research on social inclusion that includes the integration of interpersonal relationships and community participation among autistic people or the impact of social inclusion on the well-being of autistic people. Additionally, little evidence exists regarding how autistic people prefer to be included in the community or form interpersonal relationships.

Objective: The long-term objective of this project is to improve social inclusion factors to support the mental well-being of autistic people. This protocol describes a community-based, mixed methods pilot study to develop a definition of meaningful social inclusion for autistic people and to understand the relationship between meaningful social inclusion and mental well-being among autistic adolescents and emerging adults.

Methods: The project uses a community-based, sequential mixed methods design with a formative phase (Phase 1) that informs a survey phase (Phase 2) and concludes with a process evaluation of the community engagement process (Phase 3). During Phase 1, we will recruit 10 community partners (autistic adults and stakeholders) and conduct sharing sessions to cocreate a definition of meaningful social inclusion and a survey of meaningful social inclusion and well-being. During Phase 2, we will recruit 200 participants (100 autistic adolescents and emerging adults and 100 caregivers) to complete the survey. We will examine whether meaningful social inclusion predicts well-being given sociodemographic factors using ordered logistic regression, with well-being categorized as low, medium, and high. During Phase 3, the community partners from Phase 1 will complete a survey on their experiences with the project.

Results: Ethics approval was obtained for this project in March 2023. We have recruited community partners and started the Phase 1 focus groups as of September 2023. Phase 2 and Phase 3 have not yet started. We expect to complete this study by March 2025.

Conclusions: Using a community-based, mixed methods approach, we intended to develop a definition of meaningful social inclusion for autistic people and understand the role meaningful social inclusion plays in the well-being of autistic people.

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KEYWORDS

autism; community-based; mixed methods; social inclusion; well-being

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Introduction

Overview

Mental well-being is a holistic conceptualization of mental health characterized by a lack of symptoms of mental conditions and the presence of positive feelings [1]. Compared to nonautistic people, autistic people often experience poor mental well-being [2], reduced quality of life [3], higher rates of suicidality and premature death due to suicide [4-6], and greater rates of mental health conditions [7-9]. Worldwide, across decades, and across age groups, autistic people have a twofold increase in mental health issues compared to people without autism. For example, rates of mental health issues among the general population in the United States hit an all-time high during the COVID-19 pandemic, with an estimated 40% reporting mental health challenges [10], while rates of co-occurring mental health issues among autistic adolescents and emerging adults during a "typical" time period are as high as 82% [11]. The total size of the autistic population is unknown due to women, gender-diverse people, and people of color being historically underdiagnosed and adult-diagnosed autistic people not being captured in prevalence rates. Even so, current estimates suggest that 1 in 44 children in the United States are diagnosed with autism [12]. The impact of poor mental well-being among autistic people impacts a substantial proportion of the US youth population. The burden of poor mental well-being in the autistic community increases with age [13,14] and shortens life expectancy [5].

A complex interplay of internal and external factors may explain disparities in mental well-being between autistic people and nonautistic people. While endogenous factors such as genetics and neurology play a role, systemic, compounding stressors exogenous to the autistic person can also influence mental well-being. These modifiable, external factors include experiences such as being bullied, masking, and feeling accepted. Autistic people experience higher rates of bullying compared to nonautistic people, and these experiences are linked to a greater risk of mental health issues [15]. Masking (also known as camouflaging) describes the efforts of autistic people to hide autistic traits and avoid negative experiences such as bullying. Similar to bullying, masking is also associated with poorer mental well-being [16-19]. Conversely, when autistic people feel accepted, they report better mental well-being. Higher levels of acceptance by nonautistic people are associated with lower levels of mental distress [20]. Contrary to stereotypes of autistic people, research confirms that interpersonal relationships are important to the autistic well-being [20], and higher levels of community participation are associated with better mental well-being [21,22].

However, current research suggests that autistic people face individual-level social inclusion barriers [20,23] and are less likely to participate in the community [24] or form interpersonal relationships [25] compared to nonautistic people. Additionally, this literature primarily focuses on how autistic people should change to adapt to communities and other people, rather than on how communities and other people could adapt to include autistic people [26]. Because they do not center on the experiences of autistic people, many of these studies focus on independence rather than autonomy and conformity to neurotypical standards as criteria for social inclusion and enforced normalization. Given the historic emphasis on children [7], it is imperative to focus on the mental well-being of autistic adolescents and emerging adults. Social inclusion may hold the key to implementing sweeping changes to improve mental well-being for autistic adolescents and emerging adults [23,27], particularly as identification with social groups is associated with higher levels of mental well-being among autistic people [1]. Social inclusion and mental well-being are research priorities for the autistic community [28], as is shifting the focus from "fixing" the individual to addressing systemic issues external to the autistic person [29].

To the best of our knowledge, no study has integrated both aspects of social inclusion, included the voices of autistic people, and focused on mental well-being. These 2 relationship contexts (interpersonal relationships and community participation) are instrumental in promoting adaptive mental and physical health among autistic people. Interpersonal relationships are important to the well-being of autistic people [20], and higher levels of community participation are associated with better mental well-being [21,22]. This project fills a critical need to develop an understanding of meaningful social inclusion that includes both interpersonal relationships and community participation for autistic people and use this to understand the impact of social inclusion on mental well-being. Without an understanding of how social inclusion factors shape mental well-being, we cannot identify and implement effective and efficient community-level change to improve the well-being and quality of life of autistic people. In the absence of this knowledge, rates of co-occurring mental health conditions, the resulting diminished quality of life, and premature deaths will remain high. Filling this gap with this study is critical, as this information is necessary for policy and planning to improve mental health parity among autistic people.

Conceptual Framework

There is no agreed-upon conceptual framework for social inclusion. However, the ecological model of social inclusion for people with intellectual and developmental disabilities by Simplican and colleagues [30] provides a road map for understanding, measuring, and modifying social inclusion. According to this model, social inclusion is defined as the interaction of interpersonal relationships (family, staff, friends, acquaintances, and partners) and community participation (leisure activities, political and civic activities, employment and education, access to goods and services, and religious and cultural activities).

Study Aims

The long-term objective of this project is to improve social inclusion factors to support the mental well-being of people with autism. Our goal is to address the problem of high rates of poor mental well-being by understanding how social inclusion is associated with this phenomenon. We focus on adolescence and emerging adulthood because this is a key developmental period for autistic people and a challenging time for mental well-being [31,32]. We will meet our goal through two specific

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aims: Aim 1: develop a working definition of meaningful social inclusion for autistic people living in the community that is cocreated with the autistic community; and Aim 2: delineate variation in mental well-being by social inclusion (interpersonal relationships and community participation) among autistic adolescents and emerging adults. Our hypothesis is that higher levels of social inclusion will be associated with higher rates of mental well-being.

Methods

All protocols and materials will follow the Academic Autism Spectrum Partnership in Research and Education practice-based guidelines for research coproduced with autistic people [33].

Study Design

Overview

The project uses a community-based, sequential mixed methods design with a primary formative phase that will inform a subsequent secondary survey phase [34] and a tertiary phase that consists of a process evaluation of the community engagement process. This design has been used successfully to capture community member experiences and influence policy changes [35]. In Phase 1, we will conduct sharing sessions with members of the autistic community to cocreate (1) a working definition of meaningful social inclusion and (2) an adaptation of a survey of social inclusion and well-being. In Phase 2, we will deploy the cocreated survey in the autistic community to gather data on their level of social inclusion and mental well-being. In Phase 3, we will evaluate the research processes. Findings from each phase will be integrated using triangulation with the autistic community. We will consider where findings from each part agree (convergence), result in complementary information (complementarity), or disagree (discrepancy).

Phase 1: Formative Research

Sharing sessions will be held virtually through Zoom (Zoom Video Communications), recorded, and transcribed for analysis. Sharing sessions will be facilitated through a series of open-ended questions developed to capture the lived experiences of meaningful social inclusion of autistic community members. Community members participating in the sharing sessions will be provided with informed consent, a 1-page description of the study, the open-ended questions, the draft survey, and the background of the research team. Multiple meetings will be scheduled to (1) develop an understanding of meaningful social inclusion, (2) select and refine survey items, (3) review analysis results, and (4) determine the best ways to disseminate the results that align with the community's agenda. Over the course of the project, the timing, number, and format of the meetings will be negotiated with community partners [36].

Phase 2: Adapted Survey of Social Inclusion and Mental Well-Being

This aspect of the project follows a cross-sectional survey design in which data are captured at a single point in time. Autistic adults living in the community will report on social inclusion and mental well-being using adaptations of existing survey instruments created with community members during the sharing sessions. Data will be gathered through an anonymous web-based questionnaire hosted through the Qualtrics (Silver Lake) platform.

Phase 3: Process Evaluation

Satisfaction with community engagement will be measured by asking community partners at the end of the study to report on their experiences with the community engagement process.

Measures

Overview

Our main variables of interest are meaningful social inclusion and mental well-being. We will measure the identity of autistic people and address potentially confounding variables through sociodemographic variables associated with social inclusion and mental well-being. Whenever possible, short-form versions of instruments will be used to reduce the burden on participants. Items will also be adapted for completion by caregivers reporting on autistic adolescents and emerging adults in their care. Caregivers will be asked if the autistic adolescents and emerging adults in their care also completed the survey to create a subgroup of caregivers providing proxy responses and caregivers providing additional responses.

Identity of Autistic People

The identity of autistic people will be measured using current guidelines for establishing rigor to generalize to autistic people [37], through self-identification, age at diagnosis, diagnosis status (self vs community), and the Ritvo Autism Asperger Diagnostic Scale-14 [38]. This measure will be used for autistic people who will complete the survey. Caregivers will be asked if they care for an autistic adolescent or emerging adult, whether the autistic adolescent or emerging adult was professionally diagnosed, the current age of the person they provide care for, and the age the person was diagnosed.

Social Inclusion

Social inclusion will be assessed using adaptations of the Temple University Community Participation (TUCP) measure [39] for community participation and the Friendship Questionnaire (FQ) for interpersonal relationships [40]. The TUCP contains 26 items that measure independent and self-directed community participation over the last 30 days in the following domains: community activities, employment, education, and volunteering. The TUCP asks (1) for the number of days in the past 30 days that the person engaged in a community activity (0-30); (2) if the activity is important to the person (1=yes or 0=no); and (3) if the activity was done enough, not enough, or too much (−1=not enough, 0=enough, or 1=too much). Although initially created for use with people with complex and chronic mental health conditions, the TUCP has been used to assess community participation among autistic adults [24,41,42].

The FQ contains 35 items that measure multiple aspects of interpersonal relationships, such as having best friends ("I have one or two particular best friends") and the characteristics of friends ("In terms of interests, how similar to your friends do you tend to be?"). The FQ was designed for use with nonautistic and autistic adults [40].

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Mental Well-Being

Mental well-being will be captured through the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) [43] and the Depression Anxiety Stress Scales-21 (DASS-21) [44]. The WEMWBS is a 14-item questionnaire measuring positive mental well-being through positive emotions, positive mental health, and psychological functioning. Each item is a positively worded statement (eg, "I've been feeling good about myself") with a 5-point Likert-type scale (1=none of the time to 5=all the time) indicating how often the statement applied to the person over the past 2 weeks. An overall score is calculated by totaling the scores for each item. Higher scores indicate higher levels of mental well-being. The WEMWBS has good content and construct validity, face validity, cross-cultural validity, test-retest reliability (intraclass correlation =.83), and internal consistency, with Cronbach α ranging from 0.89 to 0.93 [43,45]. The WEMWBS has been extensively used to measure mental well-being among autistic adults [1,46]. The DASS-21 contains 3 self-report scales measuring depression, anxiety, and stress. The DASS-21 has been found to function well as a measure of psychological distress among autistic people [47].

Sociodemographic Variables

Sociodemographic variables will include age, gender, race and ethnicity, rurality, income, education, employment status, co-occurring conditions, level of support need, and social functioning using the Social Functioning Questionnaire [48]. Gender, education, race and ethnicity, and co-occurring conditions are items derived from the National Survey on Health and Disability. Gender will include options for gender-diverse people. Employment status is based on items used in the 2021 Behavioral Risk Factor Surveillance System. Participants will be asked to estimate their household income and will be presented with multiple-choice income options. The level of support needed will be determined using items representing assistance needed for activities of daily living and instrumental activities of daily living.

Rurality will be identified using the self-reported residence zip code of the participant's permanent residence and categorized based on Rural-Urban Commuter Area (RUCA) codes. RUCA codes classify US census tracts on a continuum of rural to urban categories using patterns of daily commuting, population density, and measures of urbanization. Whether a participant originated from a rural community will be determined based on residence in a zip code associated with large rural, small rural, or isolated RUCA codes.

Satisfaction With Community Engagement

Satisfaction with community engagement will be measured by asking community partners who participated in the sharing sessions to complete a Community Engagement Questionnaire [36] describing their experiences with the project: (1) What has been your experience with participating in this research study? (2) How satisfied were you with your contribution to this research study? (3) How could your experience be improved? and (4) Is there anything else you would like to add?

Study Participants and Recruitment

Participants will be recruited on the web through groups such as the Autism Foundation of Oklahoma, Autistic Adults of Oklahoma, AutismStillwater's website, AutismOKC's website, tribal organizations, and state department health services caseworkers. Our community partners will leverage their community contacts in each of these groups for the recruitment of participants for the study.

The intended participants for Phase 1 are autistic adults and caregivers of autistic young people. The participants will be older than 18 years and reside in Oklahoma. For Phase 2, the intended participants are (1) autistic adolescents (aged between 10 and 18 years) and emerging adults (aged between 19 and 25 years) residing in Oklahoma, fluent in English, who have a community diagnosis of autism or meet the Ritvo Autism Asperger Diagnostic Scale-14 cutoff for autism and (2) caregivers of autistic adolescents and emerging adults. Phase 3 participants are the same participants from Phase 1. Exclusion criteria include communication impairment and an inability to consent.

For Phase 1 and Phase 3, we will recruit up to 10 autistic community partners to participate in the sharing sessions, and each partner will be paid US $400 for their participation. For Phase 2, we will recruit 100 autistic adolescents and emerging adults living in the community and 100 caregivers to complete the adapted survey. The most recent electronic survey deployed by the Autism Foundation of Oklahoma resulted in 270 respondents. Based on this, we believe 200 respondents is feasible. We will not incentivize the survey. Recent web-based surveys deployed by the research team that were incentivized (ie, had a gift card raffle) resulted in a high number of bots and scammers completing the survey for monetary gain. This, combined with the relatively high number of participants the Autism Foundation of Oklahoma had on their surveys who were not incentivized, led the research team to drop the use of incentives.

Data Analysis

Phase 1: Formative Research and Phase 3: Process Evaluation

The data from the sharing sessions and community engagement questionnaire will be analyzed and interpreted using iterative inductive and deductive thematic analyses. Data will be developed through verbatim transcription of audio recordings, analyzed using Dedoose (SocioCultural Research Consultants), and transformed into concept maps. The transcripts and texts will be reviewed several times and coded based on themes to reduce and display the data and draw conclusions. This process involves (1) familiarizing the research team with the data, (2) coding the data, (3) using the codes to develop initial themes, (4) reviewing the themes as a team, (5) defining the themes, and (6) writing up the results. Inductive codes will be based on emerging codes from the data, and deductive codes will be based on the literature and the open-ended sharing session and process evaluation questions. The credibility of the outcomes will be verified with community members to help ensure we capture the experiences of the community members.

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Phase 2: An Adapted Survey of Social Inclusion and Mental Well-Being

We will examine whether meaningful social inclusion predicts well-being given sociodemographic factors using ordered logistic regression, with well-being categorized as low, medium, and high [49]. Models will be adjusted using participant characteristics to hold influences outside of social inclusion constant.

Power Analysis

Qualitative data will be collected until saturation is reached. For quantitative analysis, logistic regression is a nonlinear model, and thus, probability at the mean and 1 SD above the mean is necessary for the power analysis. These values are not available in the literature. We will develop these probabilities through this pilot study for use in a larger study. However, in general, a sample size over 100 with cell counts over 10 is necessary for logistic regression.

Ethical Considerations

Ethics approval for Phase 1 was obtained for this project in March 2023 from the Institutional Review Board of Oklahoma State University (IRB-23-46). Phase 2 and Phase 3 of this protocol will be reviewed and approved, and electronic informed consent or assent, where appropriate, will be attained before beginning any aspect of the study.

Results

The study was funded by Oklahoma Center for the Advancement of Science and Technology in January 2023. Ethics approval was obtained for this project in March 2023. We have developed Phase 1 materials, recruited community partners, developed a draft of the survey, and started the Phase 1 focus groups as of September 2023. Phase 2 and Phase 3 have not started yet. We expect to complete this study by March 2025.

Discussion

Expected Outcomes and Potential Impact

The expected outcomes of this protocol include a definition of meaningful social inclusion for autistic people and an enhanced understanding of the role meaningful social inclusion plays in the well-being of autistic people. The research findings may generate new knowledge on meaningful social inclusion that addresses community-level needs and limited social inclusion among autistic adolescents and emerging adults. This project could advance our understanding of how to improve social inclusion, reduce poor mental well-being among autistic adolescents and emerging adults, and advance our scientific understanding of facilitating social inclusion and integration of autistic people in communities.

Results will be integrated into the Autism Foundation of Oklahoma's training and awareness programs on, for example, employment, education, and criminal justice. The results will also be used to develop new training and awareness programs focused on social inclusion. The proposed study will provide preliminary data for developing interventions for testing (eg, modifying the Autism Foundation of Oklahoma's current training program for employers to hire autistic people) and lay the groundwork for larger studies on enhancing quality of life and social inclusion factors such as interpersonal relationships and community participation for autistic adolescents and emerging adults.

Potential Difficulties and Limitations

We assume that social inclusion is associated with better mental well-being. However, it could be that better mental well-being is associated with higher levels of social inclusion; that is, better mental well-being leads to more social inclusion. This is an issue of endogeneity—when the outcome variable is a predictor and not simply a response (simultaneity bias). We can test for this relationship using the Hausman test for endogeneity, and we also included variables that can be used as statistical instruments should we need to use an instrumental variable analysis to control for endogeneity.

Strength of the Study

Most research on social inclusion and autistic people focuses on exclusion rather than inclusion. This research is typically conducted on autistic children in primary school settings and often excludes the lived experiences of autistic people. This can result in outcomes and recommendations that do not align with the experiences and goals of the autistic community. As such, several strengths of this study lie in our focus on social inclusion rather than exclusion, our centering of the experiences of autistic adolescents and emerging adults, and our use of a community-based mixed methods approach to engage the autistic community. By focusing on the lived experiences of autistic people, we increase the likelihood that the outcomes of this project will have a meaningful impact on the well-being of autistic people.

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Authors' Contributions

DJM and MC designed the study protocol and wrote the manuscript. DN provided content experience. EP and DJM developed the community member engagement materials. DJM, EP, AM, and CL are leading community member engagement and focus

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groups. All authors are developing the survey. CL programed the draft survey. All authors provided input for the study protocol, reviewed the manuscript, and will participate in implementing the study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 171 KB - resprot_v13i1e52658_app1.pdf]

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Abbreviations

DASS-21: Depression Anxiety Stress Scales-21
FQ: Friendship Questionnaire
RUCA: Rural-Urban Commuter Area
TUCP: Temple University Community Participation
WEMWBS: Warwick-Edinburgh Mental Well-being Scale

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Protocol

Nonspecific Effects of the Bacillus Calmette-Guérin Vaccine in Portuguese Children Under 5 Years of Age: Protocol for a Population-Based Historical Birth Cohort Study

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Abstract

Background: The Bacillus Calmette-Guérin vaccine (BCG) against tuberculosis (TB) shows beneficial nonspecific effects, which are likely related to innate immune training. Until 2016, a single BCG dose was administered to all newborns in Portugal. In July 2016, a clinical guideline established that only children under 6 years belonging to high-risk groups should receive BCG. This might have prevented nonvaccinated children from developing trained immunological responses as effectively as BCG-vaccinated children.

Objective: This study aims to investigate if there is variation in TB-related and all-cause mortality, and severe, moderate, or mild morbidity in children under 5 years of age, and whether such variation might be explained by the BCG vaccination policy change in 2016.

Methods: This population-based historical birth cohort study includes children under 5 years of age born in Portugal between July 1, 2010, and June 30, 2021. Newborns with low birth weight, premature status, or known or suspected HIV infection are excluded. The follow-up period is until the completion of 5 years of age or the end of follow-up (June 30, 2021). The study will use secondary data from the National Health Service user registry, death certificate database, vaccination registry, communicable diseases surveillance system, TB surveillance system, diagnosis-related group information system for hospital admissions and emergency department visits, and primary health care information system. The data will be linked. Primary outcomes include person-time incidence rates of death (all causes and TB), TB diagnosis, and all causes and some specific causes of severe, moderate, or mild morbidity, and the incidence rate ratio of nonvaccinated to BCG-vaccinated children. We will compare the probability of surviving the first and fifth years of life or of not having severe, moderate, or mild morbidity during the follow-up period according to exposure (BCG vaccinated or nonvaccinated, number of doses, and time from birth until the first dose), using the log-rank test for assessing differences in survival rates between exposed and nonexposed children and hazard ratios for quantifying the differences. Moreover, we will perform a proportional hazards regression analysis.

Results: Ethics approval has been obtained. In March 2022, database owners were contacted to present the project and discuss the request for data. A unique identifier will be used. In July 2023, a process of redefinition of the variables per database was initiated. Data were received in October and November 2023. In November 2023, further work was conducted. By April 2024, we expect to start analyzing the full data set.

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Conclusions: The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy. Data linkage can contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policy decision-making.

Trial Registration: ClinicalTrials.gov NCT05471167; https://clinicaltrials.gov/study/NCT05471167

International Registered Report Identifier (IRRID): DERR1-10.2196/55332

(JMIR Res Protoc 2024;13:e55332) doi:10.2196/55332

KEYWORDS

BCG; Bacillus Calmette-Guérin vaccine; policy; Portugal; nonspecific effects; vaccines; heterologous immunity

Introduction

Background

Immunization has led to a significant decrease in mortality in children under 5 years of age. Several studies have demonstrated that the reduction in mortality and morbidity due to vaccination extends beyond the targeted infections. This seems to result from broader nonspecific effects (also termed heterologous immunity) stemming from the synergistic effects of several live vaccines [1-4]. The vaccines demonstrated to have nonspecific effects include the Bacillus Calmette-Guérin vaccine (BCG), polio vaccine, and measles vaccine [5]. Overall, the nonspecific effects of vaccines vary according to age, sex, time to administration, last vaccine administration, previous and concurrent infections and immunizations, interval between vaccines, genetic factors, nutritional state, season, and co-administration of other immunomodulating agents [1].

BCG is a live attenuated vaccine against tuberculosis (TB), which is administered to newborns ideally at birth or before the seventh day of life. Despite its low efficacy for preventing primary infection or reactivation of latent pulmonary infection and TB infection, BCG is effective against childhood tuberculous meningitis and miliary disease [6]. Hence, BCG at birth is recommended in settings with a high incidence of TB, and it is parsimoniously administered in countries with a low incidence and has been removed from routine vaccination schemes in high-income countries with a low TB incidence [7].

BCG was introduced in the 1920s in Sweden, where it quickly became apparent that the all-cause mortality was lower in BCG-vaccinated children than in those not vaccinated [8]. In England and the United States, the same pattern was observed between the late 1940s and early 1960s, where a reduction in mortality from diseases other than TB was estimated in 25% of vaccinated children (95% CI 6%-41%) [1,9]. Later studies showed the same pattern in infant mortality and morbidity [10], as well as in morbidity in the neonatal period [11]. Furthermore, BCG is used as a standard treatment for carcinoma of the bladder and influences the natural history of infectious and neoplastic diseases [1]. More recently, the effect of BCG was tested in viremia after SARS-CoV-2 exposure [12].

Further studies in children from Denmark and Greenland failed to show a decrease in hospitalization due to infectious diseases in vaccinated children [13,14]. On the contrary, a cohort study of children from 19 different countries revealed that BCG-vaccinated children under 5 years of age had a lower risk of suspected acute lower respiratory infection [15]. In Spain, hospitalization rates due to respiratory infection were lower in BCG-vaccinated children, with an attributable fraction of 32% for children under 1 year of age, and a similar finding was noted for sepsis, with an attributable fraction of 53% [16].

A systematic review concluded that BCG has a beneficial effect on mortality in children, with differential effects according to age (earlier administration of the vaccine is associated with greater effects) [5]. Nevertheless, there has been a call for more research on the nonspecific effects of BCG [5,17]. Currently, studies are seeking to further investigate the nonspecific effects of BCG [18] in terms of the effects on allergy and infection [7], severe morbidity, nonaccidental hospital admission, and all-cause consultation in children under 5 years of age [19].

BCG Vaccination in Portugal

In Portugal, BCG began to be routinely administered to all newborn children in 1965. Until 2016, a single BCG dose was administered to all newborns, typically before discharge from the maternity ward (most births in Portugal are hospital-based) or as early as possible thereafter [20].

In June 2016, a clinical guideline established that only children under 6 years of age who belong to high-risk groups (those originating from countries with high TB incidence; having contact with active cases or persons under prophylaxis; having HIV-positive mothers; having parents with a alcohol or drug abuse problem and antecedents of TB; having parents who have been in prison in the last 5 years; living in high-risk TB communities; or traveling to high-incidence countries) should be vaccinated as close to birth as possible [21]. Some of these risks were not considered individually but by proxy, with some parishes (freguesias) thus considered high risk for the criteria defined.

In 2016, 42% of children under 1 year of age had received BCG (compared to 98% in the previous year) [20]. Between 2016 and 2018, the incidence of TB increased by 16% in children under 1 year of age (from 7.0 to 8.1 per 100,000 inhabitants) and 192% in children aged 1 to 5 years (from 2.6 to 7.6 per 100,000 inhabitants) [20].

Between the adoption of the high-risk strategy for BCG vaccination in 2016 and 2018, the infant mortality rate (IMR) remained stable at 3.2‰ to 3.3‰, with important variations between the considered years [20]. In 2019, there was a decrease to 2.8‰. The mortality rate in children under 5 years of age decreased from 3.4‰ in 2016 to 3.0‰ in 2019, but not constantly in this period (eg, during 2018 it was 3.5‰) [20]. No death in children under 5 years of age has been attributable

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to TB since the implementation of the high-risk strategy for BCG [20]. Nevertheless, the number of severe cases of TB in children under 5 years of age decreased in 2020 compared to 2018 (4 cases) and 2019 (7 cases), with just 1 case registered in a child without BCG vaccination [22].

Evaluation of the BCG Vaccination Policy

Since the implementation of the high-risk strategy for BCG in 2016, no assessment has been conducted regarding the impact of the BCG policy shift on severe, moderate, or mild morbidity and on mortality in children. It is a common problem that vaccination practices are changed without evaluating the overall health effects of the change and that the nonspecific effects of vaccines are not included in the considerations regarding vaccine policies.

In 2021, the first cohort of children not vaccinated for BCG completed the fifth year of life, and evidence is needed regarding the impact of this strategy, especially given fluctuations in the IMR, a decline in the TB notification rate not accompanied by a decline in the incidence, a higher TB incidence in greater metropolitan areas, and a high median number of days from symptoms to diagnosis [22].

No data have been gathered on overall hospital admissions and morbidity patterns. Similarly, no data have been compiled on the BCG strains used in the country and their differences in terms of efficacy. This evidence will have a bearing on the continuity of the current strategy.

The need for more and better evidence is paramount, especially given that besides deciding on the inclusion of BCG in the country's immunization plan, arguments on the nonspecific effects of vaccines (and not only of BCG) can help overcome vaccine hesitancy. In high-income countries, including Portugal, vaccine hesitancy has been responsible for a decline in coverage rates and for the re-emergence of severe cases of vaccine-preventable diseases such as measles [23,24].

Hypothesis

Given the described effects of BCG on overall mortality, immune and atopic conditions including asthma, and incidence of respiratory tract infections; its nonspecific protection against nonrelated pathogens; and its protective effects that are apparent shortly after immunization and sustained for at least 1 year [2,25], we hypothesize that some of the variations in mortality among children under 5 years of age, in the incidence of TB, and in severe, moderate, and mild morbidity among children under 5 years of age might be partially explained by a reduction in the coverage rate of BCG since 2016. The reduction in the coverage rate of BCG, which resulted from only high-risk children receiving BCG at birth, might have prevented nonvaccinated children from developing trained immunological responses as effectively as BCG-vaccinated children.

Objectives

We aim to investigate the incidence of the specific and nonspecific effects of BCG by comparing the incidences of TB disease and infection; mild, moderate, and severe morbidity; and mortality in the first 5 years of life among children born in Portugal between 2010 and 2021, according to their BCG status.

Methods

Study Design

This population-based historical (retrospective) birth cohort study will compare the incidence of all-cause mortality (including due to TB disease); TB disease; and severe, moderate, and mild morbidity between BCG-vaccinated and nonvaccinated children born between July 1, 2010, and June 30, 2021.

Setting

This study will investigate the specific and nonspecific effects of BCG based on the shift in the BCG vaccination policy that occurred in Portugal in July 2016, when a consistently low incidence of TB led to the revision of the National Immunization Plan. Since then, BCG has been administered only to newborns considered to be at higher risk of TB infection, thus creating an opportunity to compare BCG-vaccinated and nonvaccinated children.

The approach adopted by Portuguese public health authorities to define the high risk for TB was based on geographical risk, with, for instance, all children born in some parishes in the metropolitan areas of Lisbon and Porto being offered BCG independent of socioeconomic status, country of origin, or vulnerability. We believe that this type of risk definition has guaranteed enough variability between BCG-vaccinated and nonvaccinated children, thus allowing comparisons of health outcomes between exposed and nonexposed children.

Participants

The study will include children under 5 years of age born and registered in Portugal between July 1, 2010, and June 30, 2021. We have chosen this period because it will allow us to (1) compare the cohorts before and after the change in the BCG immunization strategy (Figure 1); (2) characterize children not vaccinated with BCG and their health outcomes (when universal BCG at birth was recommended); and (3) compare children exposed and not exposed to BCG after the 2016 change in the BCG vaccination strategy.

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Figure 1. Lexis graph. BCG: Bacillus Calmette-Guérin vaccine.

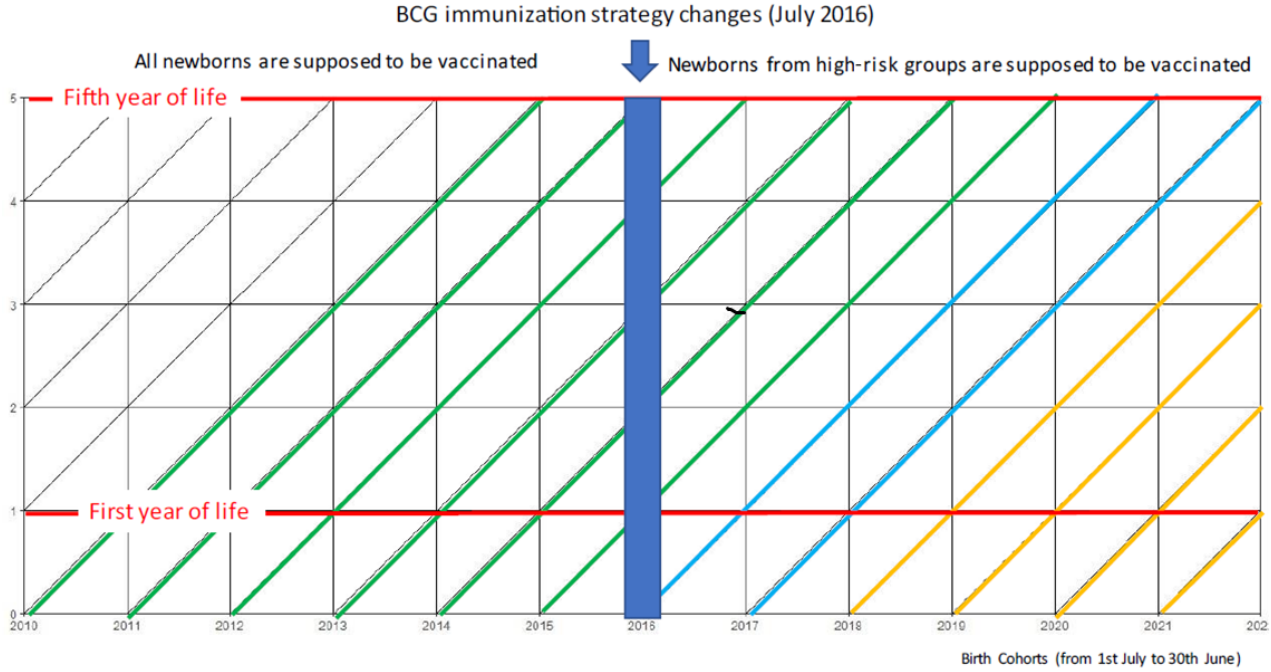

Eligibility Criteria

The study will include children born alive in Portugal (births coded as diagnosis-related group [DRG] 795 [normal newborn]).

Exclusion Criteria

The study will exclude newborns who have a weight of <2 kg, are premature (<37 weeks of gestation), or are known or suspected to have HIV infection.

The follow-up period will be until the completion of 5 years of age or the end of follow-up (June 30, 2021) (Figure 2).

Figure 2. Flowchart. DRG: diagnosis-related group; NHS: National Health Service.

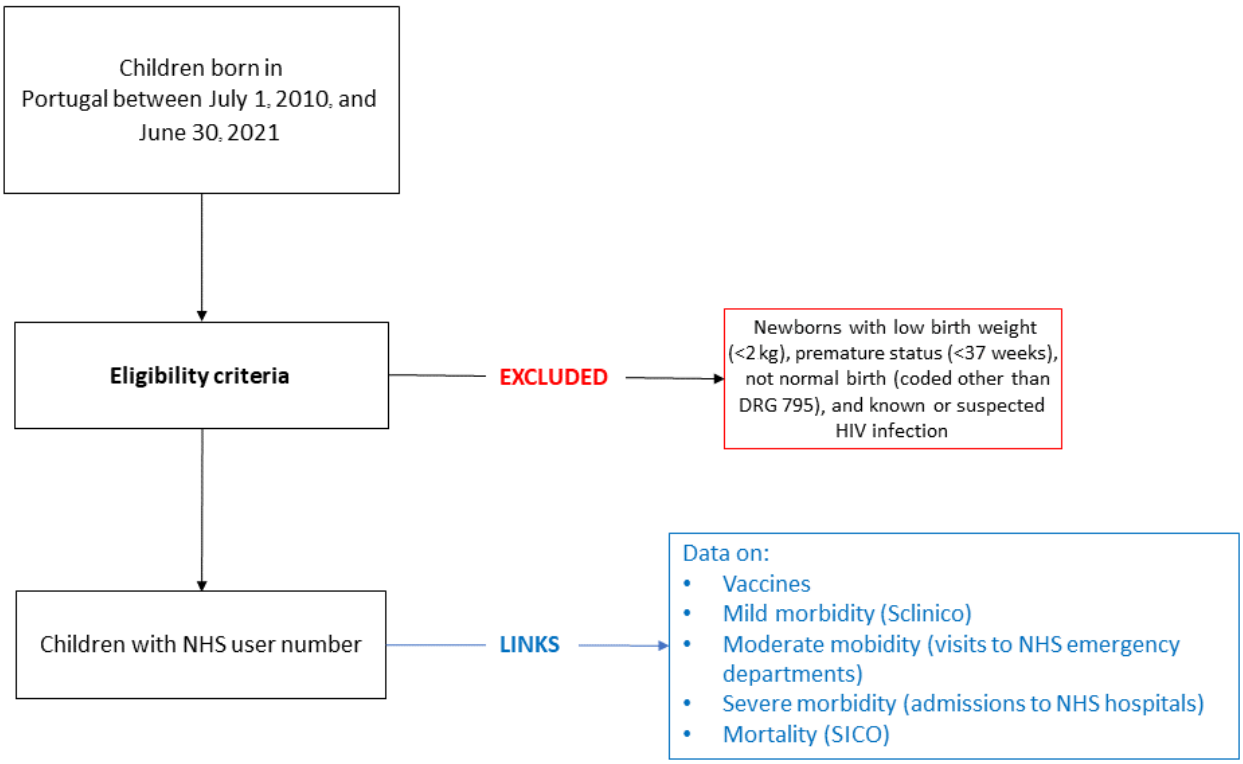

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Data Sources

The study will be based solely on secondary data. The data sources are the National Health Service (NHS) user registry (RNU), Death Certificate Information System (SICO), vaccination registry, communicable diseases surveillance system (Sistema Nacional de Vigilancia Epidemiologica [SINAVE]), surveillance information system for TB (Svig-TB), DRG information system for hospital admissions and visits to the emergency department (Base de Dados de Morbilidade Hospitalar [BDMH]), and primary health care (PHC) information system (SClínico) of children born between July 1, 2010, and June 30, 2021.

The birth registry database (RNU) contains data on gender, age, PHC center where the child is to be followed up, nationality, and place of residence. The SICO database provides data on the cause and date of death. The vaccination registry includes data on the vaccines administered, date of vaccination, and place of residence. The BDMH database gathers data on hospital admissions and emergency department visits to NHS hospitals, including the date of admission and discharge, diagnosis, type of admission, motive for admission, weight at birth, DRG code, major diagnostic category (MDC) code, complications of pregnancy and delivery, and type and place of delivery. Data from admissions at private hospitals are not included. The SClínico database contains data on socioeconomic status and visits (including motive and diagnosis) to NHS PHC units. Svig-TB is a database for notification and follow-up of TB cases, and SINAVE is the general surveillance information system for communicable diseases, including TB, and regarding TB, it contains data on symptoms at presentation, date of diagnosis, type of treatment, other diseases before TB, risk groups, and outcomes of the infection.

Measurements

Exposure is defined as having received the BCG vaccine during the first year of life and is measured using the vaccination registry. Variables include BCG (yes or no, and number of doses) and time from birth to BCG (in days).

Outcomes

Primary Outcomes

In this study, the primary outcomes for BCG-vaccinated and nonvaccinated infants and children under 5 years of age include the incidence of all-cause death and death due to TB; the incidence of mild, moderate, and severe morbidity; and respective relative risks.

The primary outcomes will be measured as person-time incidence rates of death (all causes and TB); TB diagnosis; and severe, moderate, and mild morbidity in the follow-up period, and the incidence rate ratio of nonvaccinated to BCG-vaccinated children (Table 1). For the outcome of death, data will include death (yes or no), age at the time of death (in days), and cause of death (eg, diseases of the respiratory system and diseases of the skin and subcutaneous tissue). Data on TB diagnosis will include confirmed case (yes or no), presentation of TB, age at diagnosis (in days), duration of treatment, and outcomes of treatment. Severe and moderate morbidity will be measured based on hospitalization and visits to the emergency department of the NHS. Outcomes will be characterized by age at presentation (in days), frequency of admissions or visits to the emergency department, length of stay for hospital admission (in nights), and MDC code for hospitalization and emergency department visits. We will include the outcome of hospital admission (discharged alive or died) in case fatality risk analyses. The outcome of mild morbidity is defined as contact with a medical doctor or nurse at a PHC unit owing to disease or ill health during the follow-up, as well as contact related to a recommended child surveillance scheme or other reasons besides health. It will be characterized through visits to the PHC center owing to disease or ill health (yes or no, and number), age at the visits (in days), and diagnosis (International Classification of Primary Care-2 [ICPC-2]). Mortality and morbidity pertaining to external causes and accidents will not be included in the analysis.

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Table 1. Predictable analysis per cohort and outcome.

Analysis[a]	Outcomes
Exposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2010 to 2015, 2016, 2017, 2018, 2019, 2020, and 2021	Primary outcomes in the first year of life
Exposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2010 to 2015, 2016, and 2017	Primary outcomes in the first 5 years of life
Exposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021 compared to nonexposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021	Primary outcomes in the first year of life
Exposed children in birth cohorts 2016 and 2021 compared to nonexposed children in birth cohorts 2016 and 2017	Primary outcomes in the first 5 years of life
Nonexposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2016 to 2021	Secondary outcome profile of nonvaccinated children before and after the 2016 BCG[b] vaccination change
Children in birth cohorts 2010 to 2015, 2016, and 2017	Secondary outcomes of the mortality and morbidity profile of children under 5 years of age, and NHS[c] hospital and primary health care utilization profiles
Exposed children in birth cohorts 2010 to 2015 compared to exposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021	Secondary outcomes of the mortality and morbidity incidence according to BCG strains administered per cohort in the first 5 years of life and first year of life
Exposed children in birth cohorts 2010 to 2015 compared to exposed children in birth cohorts 2016 and 2017	Secondary outcomes of the mortality and morbidity incidence according to BCG strains administered per cohort in the first 5 years of life

[a]Between 2010 and 2015, Bacillus Calmette-Guérin vaccine (BCG) coverage varied between 98.2% and 98.4%. In 2016, BCG coverage was 41.6%.

[b]BCG: Bacillus Calmette-Guérin vaccine.

[c]NHS: National Health Service.

Secondary Outcomes

The secondary outcomes include the mortality and morbidity profiles of children under 5 years of age between 2010 and 2021, including causes of death and morbidity, the profiles of nonvaccinated children, and the NHS hospital and PHC utilization profiles of children under 5 years of age before and after 2016 (Table 1).

Statistical Methods

Through data linkage, we will create a single database that links data from the birth registry, SICO, vaccination registry, SINAVE, Svig-TB, BDMH, and PHC database (SClínico) to reconstruct chronological sequences of morbidity and mortality events from birth until the completion of 5 years of life or the end of follow-up (for the 2018 cohort onwards).

In each of the databases, we will identify the data needed and whether a unique identifier (UI) exists and can be provided with the data set. After having access to the requested data and in case a UI is provided (and common to all databases), we will combine information based on that UI.

In case a UI is not provided, we will link data from several data sets using a range of proxy identifiers (eg, date and place of birth, sex, and place of residence) to identify probable matches.

The type of data linkage method to be used will depend on the type and quality of the linkage variables available in the data sets. However, we anticipate having to use a combination of deterministic and probabilistic methods. Before applying linkage methods, we will clean and standardize the data, thus identifying and removing errors and inconsistencies. Given the expected size of the data sets, we will then select sets of block attributes (eg, sex, date of birth, and initials) and compare record pairs with the same matched attributes within blocks. Subsequently, record pairs will be compared for each linkage variable, and an agreement score will be computed. This score will be used to weigh the probability of a record pair belonging to the same child [26,27].

After obtaining the final database, we will compute person-time incidence rates for primary outcomes in BCG-vaccinated and nonvaccinated children. Using the Kaplan-Meier method, we will compute and compare the probability of surviving the first and fifth years of life or of not having a hospitalization, emergency department visit, or mild morbidity episode during the follow-up period according to exposure. Additionally, we will use a log-rank test for assessing differences in survival rates between exposed and nonexposed children and hazard ratios (and corresponding CIs) for quantifying the differences. To explore the effects of several variables on the survival outcomes, we will use proportional hazards regression analysis. If missing data are below 5%, we will use complete case analysis. Otherwise, the frequency and patterns of missing data will be analyzed, and if appropriate, we will use multiple imputation techniques.

Confounders to be measured and controlled for are sex, health unit, completeness and timeliness of vaccination status and scheme, socioeconomic status, and BCG strain (over the years, administered BCG has been provided by different producers, with different strains).

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Ethical Considerations

This study has received ethical approval from the Ethics Committee of Instituto de Higiene e Medicina Tropical (IHMT) – Instituto de Tecnologia Química e Biológica António Xavier (ITQB) NOVA – NOVA School of Law (NSL) – Instituto Gulbenkian de Ciência (IGC) (11.23) [28].

The project protocol was submitted to the Ethics Committee of IHMT – ITQB NOVA (11.23), which issued a conditional authorization in July 2022 [29] that became definitive in December 2023.

Results

This project was approved as an exploratory project by the Portuguese Foundation for Science and Technology in the 2021 competitive call for R&D projects (reference: EXPL/SAU-EPI/0067/2021). It was granted approximately €50,000 (US$ 53,869) and was started in January 2022.

During the first month of the project's implementation, administrative and financial activities were carried out, with a summary of the project sent to members of the Scientific Advisory Board, including the planned activities.

In March 2022, database owners were contacted to present the project and discuss how to officially request the data. A document detailing all the data needed to carry out the study was prepared and sent to the Directorate General of Health. After approval from this body, Serviços Partilhados do Ministério da Saúde (SPMS) and Administração Central do Sistema de Saúde (ACSS) also had to provide authorization to access the data, with the last authorization given in October 2023.

We were informed that a UI would be provided for each database, based on the NHS user number, from the RNU, thus allowing direct linkage of records. However, some of the requested variables had to be reviewed and replaced given the Data Protection Law. In July 2023, a process of redefinition of the variables per database was initiated, with some of the variables requested not being supplied owing to legal restrictions (eg, date of birth had to be replaced by days from birth until the event and information if the child had been born before or after 2016) (Multimedia Appendix 1).

Data were received during October and November 2023. By mid-December, data from SINAVE had not yet been provided. No data were obtained from Svig-TB as we were not granted access. Some of the variables requested from this database were replaced by equivalent or proxy variables from SINAVE (Multimedia Appendix 1).

In November 2023, work was conducted in the databases already provided to restructure the databases, perform quality checks and cleaning, compute exposure variables, transform string variables into numeric variables, and perform coding.

By April 2024, we expect to start analyzing the full data set, which is expected to include around 970,000 children.

Discussion

Principal Findings

If the change in the BCG strategy in 2016 is proven to influence the health outcomes of children in their first year of life and during the first 5 years of life, it would further contribute to evidence that BCG primes the immune system against unrelated pathogens and even other health conditions, strengthening the arguments regarding the nonspecific effects of BCG. Additionally, it would provide evidence of the impact of the high-risk strategy for BCG vaccination and inform future decisions regarding BCG vaccination for children in Portugal and other high-income countries. The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy.

The use of data linkage can also contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policies. The project will demonstrate the feasibility of conducting large-scale epidemiological register-based vaccine studies in Portugal.

Limitations

The main limitation of this project involves the use of secondary data collected for purposes other than research. The RNU database, which provides the basis for creating a UI, only includes children who have a user number for the NHS. The user number is assigned to each person to identify them when accessing the services of the public health care units of the NHS. People with Portuguese citizenship obtain their user number automatically when they apply for a Citizen's Card. Foreigners with a residence or stay permit in Portugal have to apply for an NHS user number. Most but not all infants are registered shortly after birth.

In August 2016, the Portuguese government created the program "Nascer Utente" (translated to "Born as a User") that allowed for immediate registration in the RNU database, assigning the respective user number. This process is conducted by the hospital (public and private) where the child is born, immediately after birth [30]. We therefore expect a bias toward children born after this date in the RNU database.

The electronic registry of vaccines was started in 2017, and all data before this point had to be back introduced in the database, which could have increased the number of typing errors and other issues. We can again have a bias toward the most recent years in terms of the quality of data.

The number of deaths of children under 5 years of age might be underestimated since very young children tend not to have an NHS user number, especially before August 2016. In this case, we can also expect to have a bias in the age of children who died between July 1, 2010, and June 30, 2021, toward older ones.

The BDMH database only pertains to public hospitals. It does not include data from emergency department visits or hospital admissions in the private sector. The same is true for SClínico, which contains data from PHC centers in the NHS. Children using the private sector are not captured by this database.

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Additionally, the case mix (severity) of admissions in public hospitals is usually greater than that in private hospitals, which might introduce a bias toward higher case fatality rates in hospital admissions.

In 2020, 32% of Portuguese people had voluntary health insurance (in 2010, the proportion was less than 20%), and the proportion is dependent on household income, with those in higher income groups showing a higher probability of having voluntary health insurance. As such, we expect a bias toward lower income groups, especially in the last years of the study period [31].

Comparison With Prior Work

This is one of the first studies conducted in Portugal linking several databases. During the COVID-19 pandemic, several data linkage studies were conducted [32,33].

To our knowledge, this is the first population-based study that gathers data on mild, moderate, and severe morbidity and mortality among children under 5 years of age and addresses the nonspecific effects of BCG.

In Portugal, this is the first study to assess the impact of the BCG vaccination policy change on the health of children.

Conclusions

The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy. The use of data linkage can also contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policy decision-making.

Acknowledgments

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Data Availability

The data sets analyzed during this study are not publicly available owing to Portuguese Law but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data on variables (variables requested per database, variables provided per database, number of records in original data sets, actions taken, and final number of records to be linked).
[DOCX File , 30 KB - resprot_v13i1e55332_app1.docx]

Multimedia Appendix 2
Peer-review report from the Fundação para a Ciência e Tecnologia.
[PDF File (Adobe PDF File), 196 KB - resprot_v13i1e55332_app2.pdf]

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Abbreviations

BCG: Bacillus Calmette-Guérin vaccine
BDMH: Base de Dados de Morbilidade Hospitalar
DRG: diagnosis-related group
IHMT: Instituto de Higiene e Medicina Tropical
IMR: infant mortality rate
ITQB: Instituto de Tecnologia Química e Biológica António Xavier
MDC: major diagnostic category
NHS: National Health Service
PHC: primary health care
SINAVE: Sistema Nacional de Vigilancia Epidemiologica
TB: tuberculosis
UI: unique identifier

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Protocol

Linking Dementia Pathology and Alteration in Brain Activation to Complex Daily Functional Decline During the Preclinical Dementia Stages: Protocol for a Prospective Observational Cohort Study

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e66438/

Abstract

Background: Progressive difficulty in performing everyday functional activities is a key diagnostic feature of dementia syndromes. However, not much is known about the neural signature of functional decline, particularly during the very early stages of dementia. Early intervention before overt impairment is observed offers the best hope of reducing the burdens of Alzheimer disease (AD) and other dementias. However, to justify early intervention, those at risk need to be detected earlier and more accurately. The decline in complex daily function (CdF) such as managing medications has been reported to precede impairment in basic activities of daily living (eg, eating and dressing).

Objective: Our goal is to establish the neural signature of decline in CdF during the preclinical dementia period.

Methods: Gait is central to many CdF and community-based activities. Hence, to elucidate the neural signature of CdF, we validated a novel electroencephalographic approach to measuring gait-related brain activation while participants perform complex gait-based functional tasks. We hypothesize that dementia-related pathology during the preclinical period activates a unique gait-related electroencephalographic (grEEG) pattern that predicts a subsequent decline in CdF.

Results: We provide preliminary findings showing that older adults reporting CdF limitations can be characterized by a unique gait-related neural signature: weaker sensorimotor and stronger motor control activation. This subsample also had smaller brain volume and white matter hyperintensities in regions affected early by dementia and engaged in less physical exercise. We propose a prospective observational cohort study in cognitively unimpaired older adults with and without subclinical AD (plasma amyloid-β) and vascular (white matter hyperintensities) pathologies. We aim to (1) establish the unique grEEG activation as the neural signature and predictor of decline in CdF during the preclinical dementia period; (2) determine associations between dementia-related pathologies and incidence of the neural signature of CdF; and (3) establish associations between a dementia risk factor, physical inactivity, and the neural signature of CdF.

Conclusions: By establishing the clinical relevance and biological basis of the neural signature of CdF decline, we aim to improve prediction during the preclinical stages of ADs and other dementias. Our approach has important research and translational

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implications because grEEG protocols are relatively inexpensive and portable, and predicting CdF decline may have real-world benefits.

International Registered Report Identifier (IRRID): DERR1-10.2196/56726

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KEYWORDS

EEG; electroencephalographic; mobility; preclinical dementia stages

Introduction

Background

Progressive difficulty in performing everyday functional activities is a key diagnostic feature of dementia. Yet not much is known about the neural underpinnings of functional decline, particularly during the very early stages of dementia. Early intervention before impairment in everyday functions is observed offers the best hope of reducing the burdens of Alzheimer disease (AD) and other dementias. However, to justify early intervention, those at risk need to be detected earlier and more accurately.

The decline in complex daily function (CdF) such as managing medications and finances has been reported to precede impairment in basic activities of daily living (eg, eating and dressing). Our goal is to establish the neural signature of decline in CdF during the preclinical dementia period. We recently reported that limitations in CdF were more prevalent or declined faster in those who converted to mild cognitive impairment (MCI) [1]. We compared CdF profiles at baseline in 59 community-dwelling older individuals with normal cognitive performance who went on to develop incident MCI ("pre-MCI") with 284 older individuals who remained cognitively normal over follow-up. While limitations in CdF were reported to be subtle, the mean number of limitations at baseline was 3.1 (SD 3.0) in the pre-MCI cases and 2.0 (SD 2.4) in normal controls (P=.003). This is in line with studies using amyloid-β (Aβ), phosphorylated τ, neurofilament (also referred to as AT(N) classification system) [2] to stratify dementia risk in cognitively normal older adults, showing the presence of AT(N) biomarkers to be associated with more limitations in CdF [3,4].

While combining behavioral (eg, cognition and CdF assessment) with biological (eg, AT(N)) markers has further improved early risk assessment, it is insufficient to justify intervention during the preclinical dementia stages. For example, up to one-third of older individuals with significant accumulation of AD-related and vascular pathology will not progress to MCI and dementia stages [5,6]. In this proposal, we seek to further improve risk assessment by establishing the neural signature of CdF. We posit that abnormal patterns of neurophysiological activation precedes and can serve as a robust predictor of change in CdF, which in turn increases the risk of conversion to dementia [7]. To test this hypothesis, we designed complex gait tasks. Gait has physical and cognitive contributions. We showed that gait performance (eg, gait speed) during normal and dual-task conditions is associated with scores on the Activities of Daily Living–Prevention Instrument (ADL-PI) [8], which includes questions about abilities to manage money, drive, do the laundry, and use appliances [9,10]. We applied a novel electroencephalographic-based mobile brain-body imaging approach to measure gait-related brain activation while participants perform complex gait-based functional tasks [11-19]. Raising the complexity of the gait task may allow early distinction of individuals with and without the risk of developing limitations in CdF by increasing the cognitive demands of the task. We designed simple (walking-only) and complex (dual-task walking) gait-based tasks to measure differential activation (complex minus simple gait). This proposal builds on and extends 2 decades of work by our team showing that changes in gait (eg, slowing of walking speed) during simple and complex walking conditions are robust predictors of decline in CdF, cognitive decline, and progression to dementia [9,10,20-30].

Hypothesis

Our overarching hypothesis illustrated in Figure 1 is that the presence of dementia-related pathology during the preclinical period of dementia is associated with a unique gait-related electroencephalographic (grEEG) pattern that predicts a subsequent decline in CdF. The first aim of this study is to establish the neural signature of CdF. Our preliminary findings show that individuals reporting CdF limitations can be characterized by weaker pre as well as postcentral gyrus and stronger fronto-medial activation during complex gait (eg, dual-task walking). This unique grEEG activation pattern (neural signature) will predict CdF decline longitudinally. Our second aim is to determine the association of dementia-related pathology with the incidence of the neural signature of CdF in individuals without the neural signature at baseline. Specifically, we hypothesize that plasma-based assays of Aβ, T, and white matter hyperintensities (WMH) at baseline will independently and in combination predict the incidence of the neural signature of CdF. We also need to understand if and how behaviors are known to increase dementia risk (eg, physical inactivity) and may modify the neural signature of CdF as a prelude to developing interventions. Our third aim is to determine whether physical inactivity is associated with the prevalence and incidence of the neural signature of CdF in our sample.

This project is part of a larger effort at the Division of Cognitive and Motor Aging at Albert Einstein College of Medicine (AECOM) to go beyond memory-centered depictions of AD and consider cognitive processes related to motor and sensory abilities as important additional characterization of AD and related dementias. We are partnered with an ongoing investigation (R01AG075679-01) that seeks to establish visual-somatosensory integration (VSI study) as a novel marker of preclinical AD. With Aβ accumulation occurring early in sensory association areas [31], the VSI study (principal

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investigator [PI] JRM) seeks to define multisensory integration as a preclinical marker of AD and related dementias (see [32] for more details). The VSI study serves as a parent study for cross-enrollment and includes older adults across the cognitive spectrum from cognitively normal to MCI. Participants in the VSI study with confirmed preclinical AD diagnosis (defined as Aβ positive) will undergo positron emission tomography testing. Collectively, these studies will broaden the scope of our investigations in synergistic ways to deepen our understanding of the very early preclinical dementia period.

Figure 1. Sequence of events leading to decline in CdF. CdF: complex daily function; Cog.: cognitive; MCI: mild cognitive impairment; Unimp.: unimpaired.

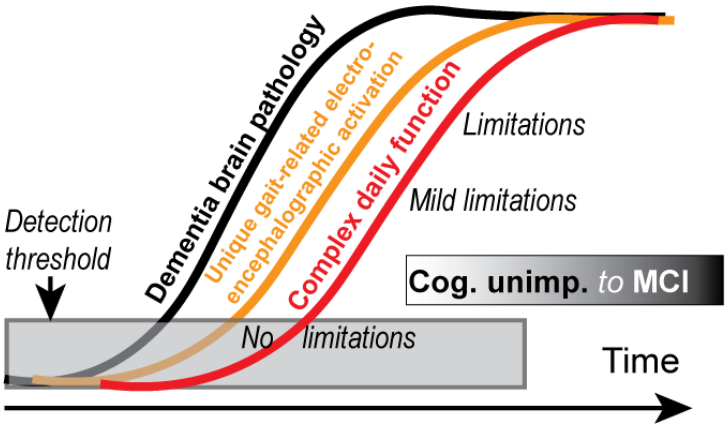

Methods

Study Design and Recruitment

We propose a prospective observational cohort study of 180 older adults who are cognitively unimpaired. Figure 2 shows the recruitment and timeline of procedures. We will cross-enroll participants from an active study (R01AG075679, PI JRM). We will use telephone-based screening procedures to enroll and follow a community-based cohort. Potential participants aged 65 year and older from the greater New York City area are first contacted by mail and then by telephone to explain the purpose and nature of this study. The telephone interview includes verbal consent, a brief medical history questionnaire, and 2 brief cognitive screens [33,34]. We will ensure that enrollment reflects the race and ethnic diversity of our catchment area. Following the interview, potential participants are invited for further evaluation at our research center. If eligible, written informed consents are obtained at study visits as per institutional review board (IRB) guidelines. This study is approved by the AECOM IRB.

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Figure 2. Recruitment and procedures conducted under this proposal. Aβ: amyloid beta; CdF: complex daily function; CU: cognitively unimpaired; fun.: function; max.: maximum; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; T: phosphorylated τ; WMH: white matter hyperintensities.

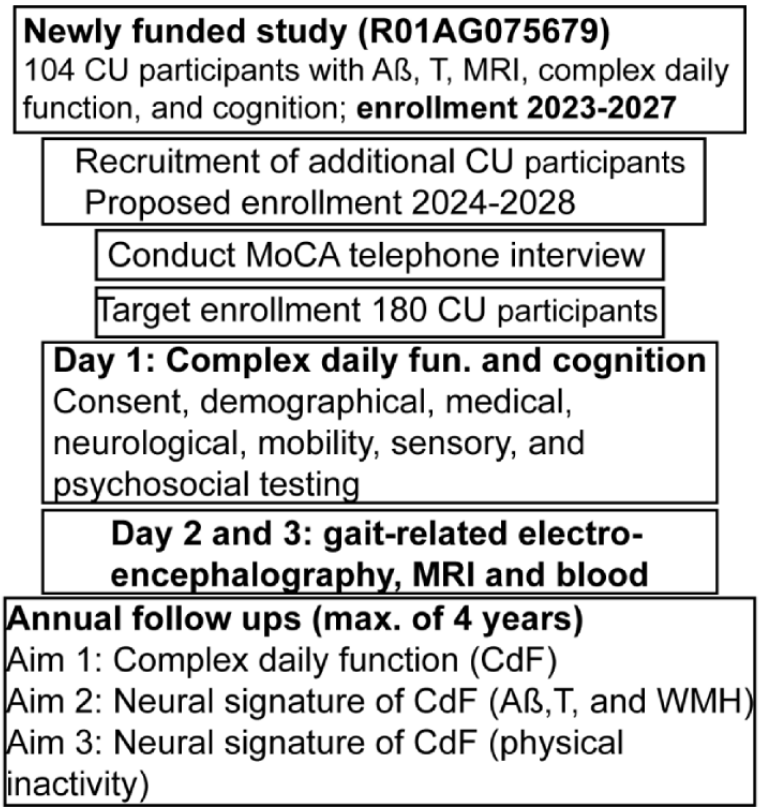

Study Criteria

Inclusion Criteria

Adults are included who are aged 65 years and older, can speak and write in English, reside in the New York metropolitan area, plan to be in the area for the next 3 or more years, and are ambulatory.

Exclusion Criteria

Exclusion criteria were previous MCI or dementia diagnosis, reported severe sensory impairments, chronic medication use (eg, neuroleptics) that influence cognitive functioning, terminal illness with life expectancy <12 months, existing diagnosis of neurodegenerative diseases (eg, Parkinson disease or amyotrophic lateral sclerosis), presence of clinical disorders that overtly alter attention like delirium, or major psychiatric disorder such as schizophrenia. Additional electroencephalographic and magnetic resonance imaging (MRI)–specific exclusion criteria are seizure medication, stroke, traumatic brain injury, claustrophobia, and MRI contraindications such as pacemakers or any permanent magnetic metal implants.

Assessments

Table 1 lists instruments used to assess function and other domains. The ADL-PI will serve as our primary outcome measure. It is a 15-item questionnaire that was developed to target the earliest changes in complex daily activities [8]. A performance-based instrument, the Everyday Problems Test [35], will serve as our secondary CdF outcome measure. It is a 42-item paper-pencil test that examines abilities to understand and execute complex daily activities (eg, write a check).

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Table 1. Measurements conducted under this proposal.

Domain and measures		Time
Independent variables		
Aim 1: neural signature of CdF[a] (mobile electroencephalographic)		2.5 h including rest
Aim 2: MRI[b] white matter hyperintensity and plasma-based Aβ42[c]/Aβ40/τ		1 h
Aim 3: Physical Activity Scale for the Elderly [36] and accelerometry		5 min and 7-d period
Outcomes (yearly assessed)		
Aim 1: Activities of Daily Living–Prevention Instrument [8]—primary		5 min
Aim 1: Everyday Problem Test—secondary		45 min
Aims 2 and 3: Incident neural signature of CdF		2.5 h including rest
Covariates		
Cognition (moderator)	Montreal Cognitive Assessment [37] (moderator aim 1) Wechsler Adults Intelligence Scale IV [38]	55 min
Physical function	Quantitative Gait Assessment (ProtoKinetics Movement Analysis Software) [39-41], hand grip strength [42]	15 min
Psychosocial	Geriatric Depression Scale [43]; Beck Anxiety Inventory [44]	15 min
Dementia risk factors	*ApoE*, obesity, diet [45], social isolation [46], cognitive engagement [47], depression	30 min
Medical	Medical history, comorbidities, or medication [30,48]	20 min
Sensory	Visual sensory screen [49], Shoebox auditory testing, Vibratron [50], Michigan Neuropathy Screening Instrument [51,52]	15 min

[a]CdF: complex daily function.

[b]MRI: magnetic resonance imaging.

[c]Aβ: amyloid-β.

Neuroimaging and plasma-based blood testing will be conducted during baseline visits for each participant. C2N Diagnostic will quantify plasma τ217 (nonphosphorylated and phosphorylated) and plasma amyloid (Aβ42, Aβ40), and provide plasma *ApoE* prototyping using liquid chromatography-tandem mass spectrometry platforms (PrecivityAD) [53-55]. Blood samples will be collected and stored in the biorepository at AECOM. Physical activity will be assessed at baseline and during annual in-person visits using the Physical Activity Scale for the Elderly [36] as well as objectively using accelerometry [56] over 7 days (AX3; Axivity Ltd). The Physical Activity Scale for the Elderly [57,58] and AX3 [59] are reliable and valid measures of physical activity.

Cognitive Diagnoses

Established clinical consensus case conference procedures [60], where participants' demographic, neuropsychological, neurological, psychosocial, and functional test results are reviewed by a multidisciplinary clinical team consisting of neurologists and neuropsychologists, will be used to determine normal cognitive status. Cognitively unimpaired individuals testing positive for Aβ are classified as preclinical AD [2]. Cognitive status—normal, MCI, and dementia—will be assigned at baseline and during yearly follow-up visits. Individuals with MCI and dementia at baseline are excluded from this project.

Outcomes

For aim 1, the primary outcome is complex daily functional limitations measured with the ADL–PI, as reported in our previous publication [8]. For aims 2 and 3, the outcome is the incidence of the neural signature of CdF (see section below for definition). All outcome measures are assessed annually over a maximal period of 4 years.

Ethical Considerations

Protocols for the proposed research project are approved by the AECOM's IRB (2023-14773). Before enrollment, written consent is obtained from all interested persons who meet the inclusion criteria at the time of the visit. Confidentiality will be preserved by the use of unique ID codes for identification. ID and name associations will be password-protected in an encrypted master file to which only the PI and study coordinator have access. Participant data, including computer data disks, will be kept in a locked room. Participants will receive monetary compensation (US $20 per hour), free lunch, and transportation for participating in this study.

grEEG Protocol

We designed simple (walking-only) and complex (dual-task walking) gait tasks to measure differential activation (complex minus simple gait). We provide preliminary findings showing that individuals reporting CdF limitations can be characterized by a unique grEEG pattern: weaker sensorimotor activation, measured by pre or postcentral gyrus 13-28 Hz desynchronization, and stronger motor control activation, measured by fronto-medial 3-7 Hz synchronization. Figure 3 shows an individual performing the visual-perturbed walking task. The participant walking on a treadmill wearing an

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electroencephalographic cap is immersed into a large-scale visual flow field designed to destabilize posture [61]. We superimpose sideway shifts onto a display of dots radiating outward from a central point of extension to create visual perturbations. We validated the task in prior studies [12,15]. Participants wore harnesses for safety.

Figure 3. Participant during the visually perturbed walking task.

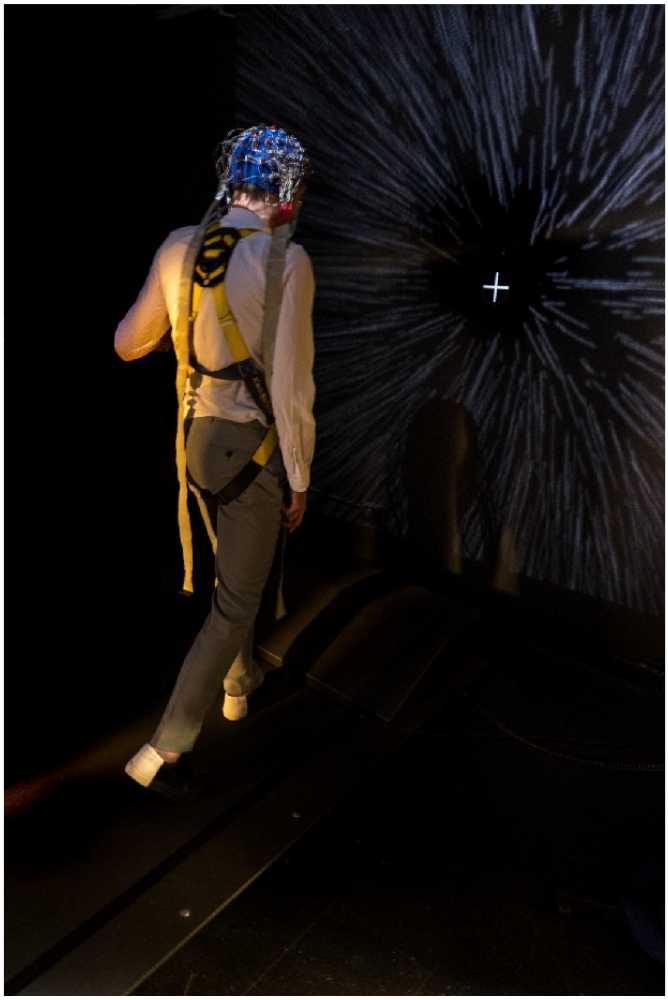

Neural Signatures—Starting With Cognition and Switching to CdF

In our first attempt to identify the neural signature of CdF, we stratified individuals by their cognitive performance [19]. Cognitively normal individuals (Montreal Cognitive Assessment [MoCA] ≥ 22 [62,63]) were dichotomized into low (score of 22-26; n=10) and high (score 27+; n=16) performing groups. We discovered a unique grEEG activation pattern time-locked to the gait cycle in low-cognitive performers: weaker central gyrus β (13-28 Hz) desynchronization paired with stronger fronto-medial θ (3-7 Hz) synchronization during visually perturbed compared to unperturbed walking. We also found correlations between θ synchronization and worse MoCA scores and between β desynchronization and better MoCA scores. Amplitude suppression (ie, desynchronization) of brain oscillatory activity within 8 to 28 Hz over pre as well as postcentral gyrus during movement is considered a neurophysiological marker of sensorimotor activation related to preparation and execution of movement [64-70]. We suggest that posterior parietal and sensorimotor activation during gait adjustment is related to prioritizing inputs from visual, somatosensory, and vestibular systems based on reliability to build accurate proprioception subserving motor output [19]. On the other hand, increased θ activity (ie, synchronization) over the fronto-medial cortex is thought of as a mechanism by which the need for cognitive or motor control is realized and signaled across brain regions [71,72]. In the context of movement, we and others observed fronto-medial θ in moments of postural instability [12,15,73-78].

Neural Signature of CdF

To test whether this unique grEEG activation pattern also associates with the limitation in CdF, we dichotomized our sample in the following way: (1) compute the difference in activation between unperturbed and perturbed walking; (2) use inverse source localization techniques to estimate intracranial sources of scalp-recorded activity; (3) separate individuals with source localized to fronto-medial regions into groups of weak and strong θ synchronizers using the median; (4) separate individuals without sources in fronto-medial and with sources in sensorimotor region into groups of weak and strong β desynchronizers using the median (we chose right sensorimotor β because effects where strongest for that region and frequency: P=.04) [19].

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Figure 4 shows preliminary findings in support of our hypothesis: Individuals characterized by a unique grEEG pattern report limitations in CdF to a higher degree.

Figure 4. The neural signature of limitations in CdF and unique gait-related electroencephalographic activation. CdF: complex daily function; med.: medial; pert.: perturbed; PP: posterior parietal; SM: sensorimotor; unpert.: unperturbed; V.: visually.

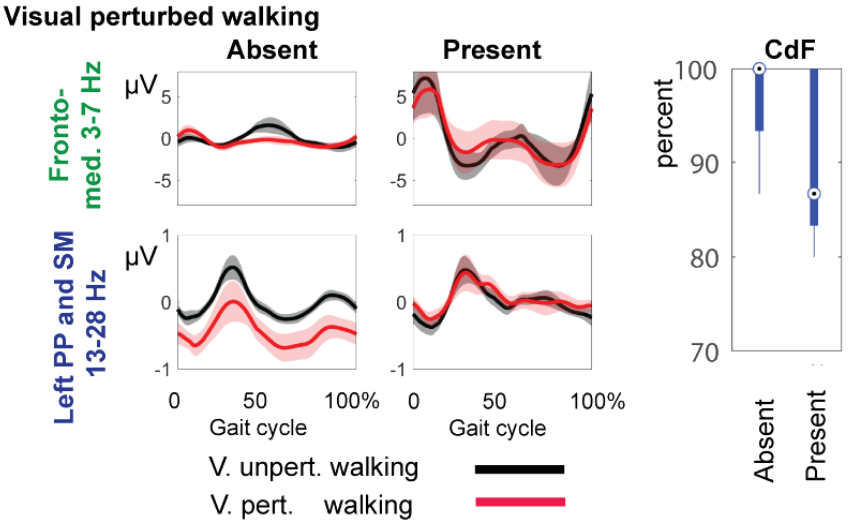

Results

Aim 1—Establish the Neural Signature of CdF

Overview

Figure 4 shows individuals with and without the unique grEEG pattern and associations with mild complex daily functional limitations measured with ADL-PI [8,79]. A score of 100% in Figure 5 indicates all activities are performed without difficulties. In both walking tasks, individuals with the unique grEEG pattern expressed nominally more difficulties performing complex daily activities.

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Figure 5. Analysis pipeline for separating brain activity from non–brain related artifacts during MoBI recording. ERSP: event-related spectral perturbation; IC: independent components; ICA: independent component analysis; LH: left heel strike; LTO: left toe off; MoBI: mobile brain body imaging; RH: right heel strike; RTO: right toe off.

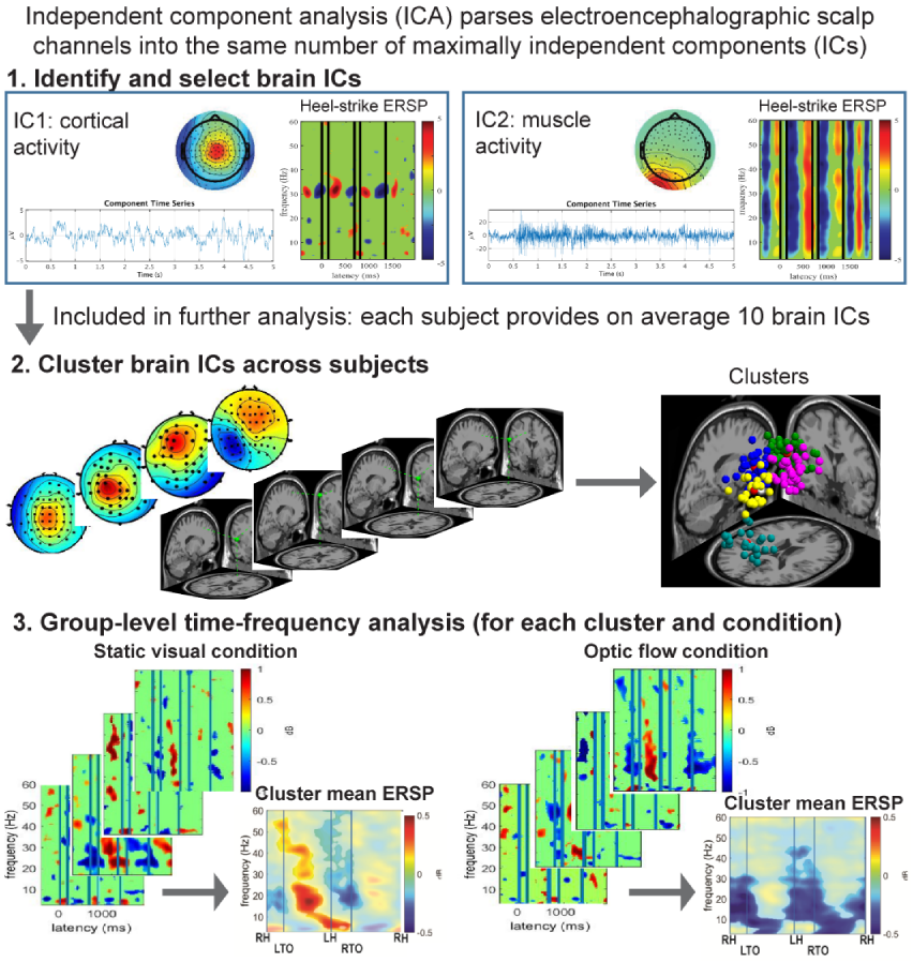

Walking Tasks

Participants will familiarize themselves with walking on the treadmill and are asked to determine their preferred walking speed before starting the experiment. For the VPW, participants will perform 4 visual perturbed and 4 unperturbed walking blocks randomized within participants. During perturbed stimulation, a large-scale visual field of dots is projected centrally onto a black wall in front of the participant. The stimulation consisted of 200 randomly placed white dots emanating outward from a central area of expansion. Superimposed to the outward motion is a sinusoidal perturbation in the mediolateral direction. A static image of dots placed randomly across the visual field serves as a control condition (ie, unperturbed walking). For the DTW, participants will perform the Go/No-Go task standing (4 blocks) and walking (4 blocks). Blocks are randomized within participants. The Go/No-Go stimuli consist of images from the International Affective Picture System [80]. Participants were instructed to click a wireless computer mouse button with the right hand each time a new image appeared (Go trials) but to withhold their response if the same image was shown twice in a row (No-Go trials). Each block consists of 180 trials and the probability of Go and No-Go trials will be 0.85 and 0.15, respectively. They will also walk wearing a safety harness.

Kinematics Recordings

The Optitrack infrared motion capture system with 9 cameras is used to collect kinematic data in the X/Y/Z direction at a sample frequency of 100 Hz (Arena version 1.5 acquisition software, Natural Point).

Electrophysiological Recordings

Continuous electroencephalography is recorded with a 64-channel BioSemi ActiveTwo system (digitized at 512 Hz; 0.05 to 100 Hz passband, 24 dB/octave). Data are high-pass filtered at 2 Hz and an automatic channel rejection procedure [81] is applied to exclude noise channels followed by visual inspection. Time-synchronized acquisition of electroencephalographic and motion tracking is conducted with Lab Streaming Layer software (Swartz Center for Computational Neuroscience, University of California San Diego).

Prevalence of Unique grEEG Activation

To estimate the prevalence of grEEG abnormalities in aging, we reanalyzed previously published data [16]. Using event-related potentials measured in control participants (ie, young adults), we defined a threshold (1.5 SD from the mean 2.2 µV) to calculate the percentage of unique grEEG (event-related potential, ERP_{young}>1.5 SD, mean 2.2 µV) in

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older participants. The prevalence of grEEG abnormality in older adults was 25% (4 out of 16).

Data Analysis

Gait Kinematics

Spatiotemporal features of gait kinematics are determined by computing the velocity profile for each foot (for a detailed description, see De Sanctis et al [19]).

Integrated Gait-Electroencephalographic Analysis

Figure 5 shows the basic steps to identify or correct artifacts and model spatially resolved brain dynamics tied to the gait cycle that we apply in our proposal. We have validated and applied this analysis pipeline in prior work [12,15,61]. Independent component (IC) analysis will be used to parse electroencephalographic signals into ICs. The resulting ICs are source-localized using inverse source modeling [82,83]. Only dipoles located within the brain, with a fit accounting for at least 80% of the variance for a given IC scalp projection, are retained [84,85]. Cortical IC clustering will be used to cluster brain ICs across subjects using feature vectors coding for IC differences in power spectral density, dipole location, and scalp projection [86,87]. Event-related spectral perturbations (ERSPs) are computed from single trial spectrograms for each IC, time-locked to the right heel strike [88]. ERSPs are computed by determining the power spectra over a sliding latency window and normalizing the spectrogram by their respective mean spectra (averaged across the latency window) [88]. To average across all strides taken and compute gait cycle ERSPs, we time-warped single trial spectrograms applying a linear interpolation function to align left toe off, left heel strike, right toe off, and right heel strike across epochs following the methods introduced by Gwin and colleagues [87].

Statistical Plan Aim 1

Primary Analyses

grEEG measures will be compared between individuals with and without limitations in CdF using the 2-sample *t* tests to assess which grEEG measure is associated with limitations in CdF. Pearson correlation will be computed between grEEG measures and CdF scores.

Longitudinal Analyses

The time-to-event analyses including Kaplan-Meier survival curves, log-rank tests, and Cox proportional hazards regression models will be used to assess whether unique grEEG patterns predict a decline in CdF longitudinally.

Power Analysis

With the sample size of 180 older adults who are cognitively unimpaired, we estimate that there will be 54 individuals classified with CdF limitations based on our preliminary studies. With a significance level (α) of .05, using a 2-sided 2-sample *t* test, this study achieves 80% power to detect a minimal difference of 0.5 SD in the grEEG measure between CdF limitation groups. The minimum detectable hazards ratio for CdF decline between older adults with and without unique grEEG pattern ranges from 1.52 to 1.69 (assuming event rate between 0.30 and 0.48) with a power of 0.8 and a 2-sided type I error rate of 5% [89].

Aim 2—Determine Association of Dementia-Related Pathology With Incidence of Neural Signature of CdF

Overview

Figure 6 shows preliminary findings in support of our hypothesis that Aβ burden [90] as well as MRI-regions impacted early during AD and cerebrovascular pathology are nominally associated with the presence of unique grEEG activation. Figure 6 shows the volume and white matter differences in brain regions between participants with and without unique grEEG patterns during DTW (15/28). Further, when grouping participants in tertiles based on amyloid probability score (APS) [90]—APS accounts for Aβ 42/40 ratio, age, and *ApoE* phenotype - we find that high APS is nominally associated with the increased presence of unique grEEG activation (1st tertile: 1 out of 5; 2nd tertile: 3 out of 6; 3rd tertile: 3 out of 5).

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Figure 6. Individuals with unique grEEG pattern have smaller cuneus, lingual, ant. cingulate, and increased white matter burden of the fimbra, which connects the hippocampus. Act.: activity; ant.: anterior; Anteri.: anterior; grEEG: gait-related electroencephalographic; MRI: magnetic resonance imaging; WMH: white matter hyperintensities.

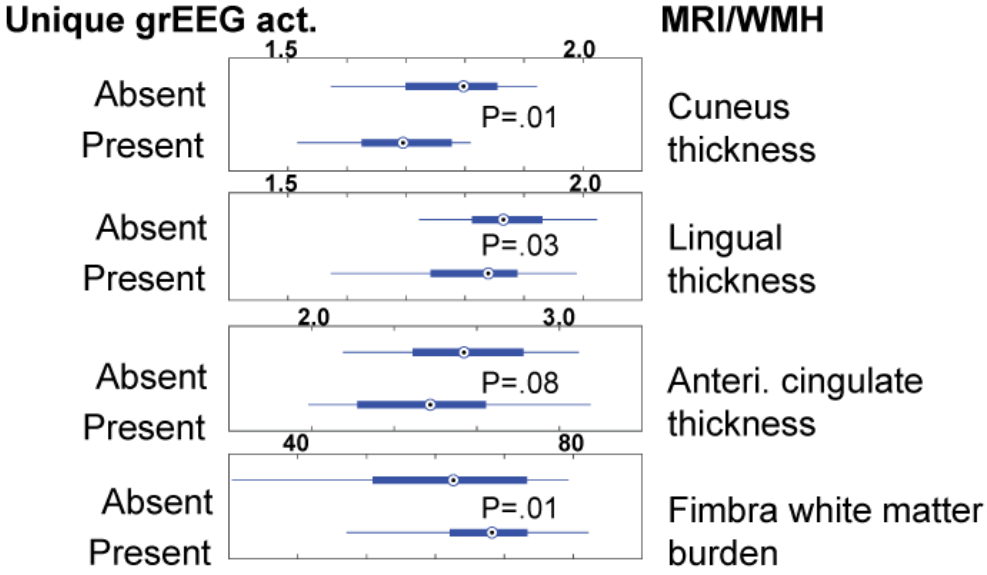

MRI Image Acquisition

All images will be acquired at the Gruss Magnetic Resonance Research Center at Einstein, using a Philips 3T Elition multinuclear MRI/magnetic resonance spectroscopy system. Our noninvasive MRI imaging procedures are reliable and extensively used in aging and dementia studies. T1-weighted images will be acquired using axial 3D-magnetization-prepared rapid acquisition with gradient echo parameters over a 240 mm field of view; 1.0 mm isotropic resolution, echo time/repetition time=4.6/9.9 ms, α= 8o, and SENSE factor 2.6. 3D-FLAIR images will be acquired with repetition time/inversion time=4800/1650 ms, echo time=335 ms, 240 × 238 acquisition matrix, and 0.46 mm voxel size. Functional (resting-state and task-based), diffusion-weighted, arterial spin labeling, and susceptibility-weighted images will also be acquired as part of the parent study (for additional details see [32]). A radiologist will review each MRI scan and confirm that there are no clinically significant findings for any of the participants. WMH will be quantified from 3D-FLAIR using the lesion segmentation toolbox [91] (implemented with SPM12/MatLab). T1-weighted images will be reconstructed using FreeSurfer (version 7.2; FreeSurfer). FreeSurfer's subcortical segmentation and cortical parcellation are comparable to manual labeling [92]. Parcellation of the T1-weighted data into anatomical brain regions is important for examining cortical thickness and volume associated with the grEEG pattern during visually perturbed walking or dual-task walking. Gray matter volumes and cortical thicknesses of 68 cortical regions will be extracted from this pipeline and entered into subsequent statistical models.

Statistical Plan Aim 2

Primary Analyses

The time-to-event analyses will be used to assess whether Aβ and WMH predict the incidence of the neural signature of CdF. Prevalent cases—that is, older adults with the unique grEEG pattern at baseline—will be excluded. Time to the neural signature will be defined as the time interval between baseline and the date when the participant demonstrates the unique grEEG pattern during the longitudinal follow-up.

Power Analysis

Preclinical Aβ/WMH prevalence is estimated at 24% to 45% among older adults who are cognitively unimpaired [93-95]. With a baseline sample size of 180 and a conservative attrition rate of 20%, the minimum detectable hazards ratio for incident neural signature of CdF between older adults with and without dementia-related pathology is 1.75 (assuming an event rate of 0.25) with a statistical power of 80% and a 2-sided type I error rate of 5%.

Aim 3: Establish Associations Between Physical Inactivity and Neural Signature of CdF

Overview

Figure 7 shows preliminary findings in support of our prediction that less exercise (assessed with the Late Life Function and Disability Instrument [96,97]) is nominally associated with 13-28 Hz less desynchronization during DTW.

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Figure 7. Less exercise is related to less β desynchronization during DTW. DTW: dual-task walking; W: walking.

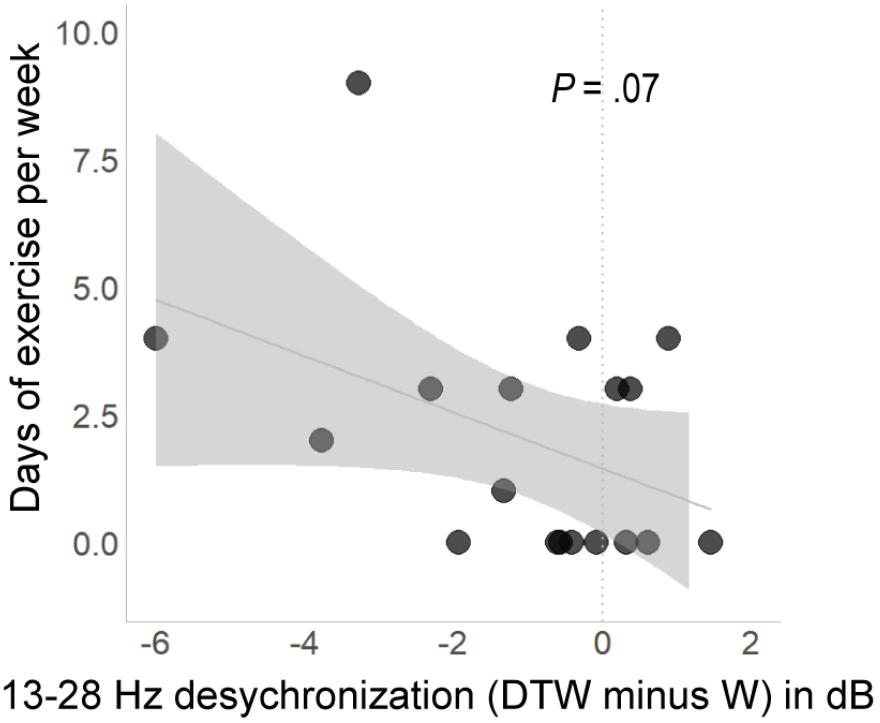

Statistical Plan Aim 3

Overview

The time-to-event analysis will be used to assess whether physical activity at baseline predicts the presence of the neural signature of CdF longitudinally.

Power Analysis

The minimum detectable hazards ratio for incident neural signature of CdF between older adults with less physical activity and normal level physical activity is 1.78 (assuming an event rate of 0.25) with a power of 0.8 and a 2-sided type I error rate of 5%.

Discussion

Principal Findings

A major effort aimed at curbing the rapid rise of dementia revolves around early intervention. To substantiate early intervention, it is crucial to enhance the accuracy of early detection. We focus on the neural signature of early limitations in CdF to improve detection. Walking is central to many instrumental and complex activities [9,10]. To determine the neural signature of CdF, our team [11-19] and others [73,87,98-104] have established the validity and reliability of neurophysiological recordings while participants are in motion. We designed novel grEEG protocols for this proposal and selected walking as an activity that, compared to other daily activities (eg, preparing a meal), allows for the use of standardized, reproducible, reliable, and well-tolerated study protocols across participants [30,39,105,106].

Our preliminary findings in 28 older adults without MCI/dementia show that reporting of CdF limitations is associated with a unique grEEG activation pattern: 13-28 Hz central gyrus desynchronization paired with 3-7 Hz fronto-medial synchronization. We term this electroencephalographic activation pattern the neural signature of CdF. This subsample also had higher Aβ burden, smaller brain volume, and WMH in regions affected early by dementia and engaged in less physical exercise.

Some limitations are important to note. The ceiling effect with a majority reporting no limitations in CdF is a concern (eg, in Marshall et al [79] study only 16% reported limitations). However, in our study, 30% of individuals reported limitations [1]. To optimize detection, we choose 2 validated and reliable instruments (self-report [107] and paper-pencil test [35] with numerous dependent variables such as self-assessment, time-to-complete, and number and type of errors to quantify performance) covering a broad range of complex daily activities. Further, different processes denoted by Aβ deposition and WMH and their respective roles in the etiology of AD and other dementias are matters of ongoing debates. The prevalence of amyloid deposition in normal aging warrants consideration of Aβ in concert with phosphorylated τ and neurofilament light assays to recognize the multitude and temporal order of pathological processes leading up to clinical signs.

In summary, establishing a noninvasive neurophysiological signature of prevalence and incidence of CdF decline will refine pre-MCI stage characterization. As our recent study shows [1], both individuals who progress and do not progress to MCI may report mild limitations in CdF during the preclinical period, though more limitations are reported in the individuals who go on to develop MCI. By establishing the clinical relevance and biological basis of the neural signature of CdF decline, we aim to improve prediction during preclinical stages of ADs and other dementias.

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Acknowledgments

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Data Availability

The data set generated in this study is available from the corresponding author upon reasonable request and with the completion of the data user agreement.

Conflicts of Interest

JRM has a financial interest in JET Worldwide Enterprises Inc, a digital health startup spun out of research conducted at the Albert Einstein College of Medicine that is not related to this project. All other authors report no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this paper apart from those disclosed.

Multimedia Appendix 1
Peer review summary by NIA study section.
[PDF File (Adobe PDF File), 139 KB - resprot_v13i1e56726_app1.pdf]

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Abbreviations

Aβ: amyloid-β
AD: Alzheimer disease
ADL-PI: Activities of Daily Living–Prevention Instrument
AECOM: Albert Einstein College of Medicine
APS: amyloid probability score
AT(N): amyloid-β, phosphorylated τ, neurofilament
CdF: complex daily function
ERSP: event-related spectral perturbation
grEEG: gait-related electroencephalographic
IC: independent component
IRB: institutional review board
MCI: mild cognitive impairment
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
PI: principal investigator
VSI: visual-somatosensory integration
WMH: white matter hyperintensities

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Protocol

Communication and Contextual Factors in Robotic-Assisted Surgical Teams: Protocol for Developing a Taxonomy

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Abstract

Background: Robotic-assisted surgery (RAS) has been rapidly integrated into surgical practice in the past few decades. The setup in the operating theater for RAS differs from that for open or laparoscopic surgery such that the operating surgeon sits at a console separate from the rest of the surgical team and the patient. Communication and team dynamics are altered due to this physical separation and visual barriers imposed by the robotic equipment. However, the factors that might comprise effective communication among members of RAS teams and the contextual factors that facilitate or inhibit effective communication in RAS remain unknown.

Objective: We aim to develop a taxonomy of communication behaviors and contextual factors that influence communication in RAS teams. We also aim to examine the patterns of communication behaviors based on gender.

Methods: We will first perform a scoping review on communication in RAS to develop a preliminary taxonomy of communication based on the existing literature. We will then conduct semistructured interviews with RAS team members, including the surgeon, assisting surgeon or trainee, bedside or first assistant, nurses, and anesthetists. Participants will represent different disciplines, including urology, general surgery, and gynecology, and have a range of experiences in RAS. We will use a reflexive thematic analysis to analyze the data and further refine the taxonomy. We will also observe live robotic surgeries at Royal College of Surgeons in Ireland (RCSI)–affiliated hospitals. We will observe varying lengths and conditions of RAS procedures to a capture a wide range of communication behaviors and contextual factors to help finalize the taxonomy. Although we anticipate conducting 30 interviews and 30 observations, we will collect data until we achieve data sufficiency. We will conduct data collection in parallel with data analysis such that if we identify a new behavior in an interview, we will follow up with questions related to that behavior in additional interviews and/or observations.

Results: The taxonomy from this project will include a list of actionable communication behaviors, contextual factors, their descriptions, and examples. As of May 2024, this project has been approved by the RCSI Research and Ethics Committee. Data collection started in June 2024 and will continue throughout the year. We plan to publish the findings as meaningful results emerge in our data analysis in 2024 and 2025.

Conclusions: The results from this project will be used to observe and train surgical teams in a simulated environment to effectively communicate with each other and prevent communication breakdowns. The developed taxonomy will also add to the knowledge base on the role of gender in communication in RAS and produce recommendations that can be incorporated into training. Overall, this project will contribute to the improvement of communication skills of surgical teams and the quality and safety of patient care.

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KEYWORDS

communication; teams; robotic surgery; robotic-assisted; simulation

Introduction

There has been exponential growth in establishing and integrating robotic-assisted surgery (RAS) into surgical practice and training in the last few decades. For example, the use of RAS for all general surgery procedures increased from ~2% to ~15% from 2012 to 2018 [1]. Compared with open or laparoscopic surgery, RAS reduces postoperative pain, promotes faster recovery time, and provides better patient outcomes [2]. However, the introduction of a robotic system into the operating theater changes the spatial configuration of the surgical team and patient. In RAS, the surgeon sits at a console and is physically separated from the surgical team and patient who remain in the sterile field. As the surgeon places their head inside the console to look at the video feed of the surgical site, they no longer have a direct view of physical movements and nonverbal cues from the surgical team. The surgical team also faces the robotic operating equipment, which obstructs their views of each other. Consequently, the surgeon and the rest of the surgical team are dependent on explicit, descriptive communication not only to give and respond to instructions and requests but also to provide updates on the status of the patient and robotic system. Thus, RAS entirely changes communication and team dynamics in the surgical team, raising the potential for miscommunication and misunderstandings that may threaten the potential for enhanced outcomes.

Nontechnical skills such as communication are critical for improving surgeons' performance, operative workflow, and patient outcomes and for reducing adverse events [3,4]. Although communication has been identified as one of the essential nontechnical skills in robotic surgery [3,5], little is known about how the surgical teams communicate most effectively in RAS. This limited understanding about what constitutes effective communication in RAS is problematic because failed communication is the second most common factor contributing to surgical errors [6]. Thus, this protocol describes a project that aims to develop a taxonomy of communication behaviors and contextual factors that facilitate or inhibit effective communication in RAS.

Previous studies have developed assessment or rating tools for nontechnical skills in RAS using behavioral marker methodology [3,5]. Schreyer et al [4] identified leadership and management, teamwork and cooperation, problem-solving and decision-making, and situational awareness as essential nontechnical skills. However, their rating tool did not focus specifically on communication but rather on nontechnical skills as a whole. In contrast, Manuguerra et al [3] and Raison et al [5] identified communication as an essential nontechnical skill. However, their behavioral markers were not actionable from the perspective of training, including "effective verbal communication whilst at the console," "appropriate interaction with beside assistant surgeon," and "presence of feedback" [3,5]. As an example, team members cannot coordinate with each other if they do not effectively communicate their needs. Therefore, this project goes beyond the current state of this field and further examines communication specifically as a key nontechnical skill in RAS as it is fundamental to other nontechnical skills.

Moreover, Manuguerra et al [3] and Raison et al [5] developed rating tools only for surgeons. However, RAS changes existing roles not only for surgeons but also for other surgical team members. For example, nurses in RAS are expected to have more technical knowledge and coordination than required in traditional surgery [7]. They are also expected to speak up and share information pertaining to issues occurring outside of the surgeon's field of vision that might help improve efficiency in the operating theater or patient safety [8]. As a result, there are changes in role-based communication needs and expectations that must be considered. Therefore, this project goes beyond previous studies that examined nontechnical skills only for surgeons by further examining communication among all RAS team members.

Gender also influences the perceptions, experiences, teamwork, and performance of health care professionals in the operating theater, thereby affecting patient care and outcomes. For example, compared to men, women are generally less listened to when they speak up and share concerns about the patient in the operating theater [9]. In addition, male and female health care professionals engage in their clinical practices differently, which leads to different patient outcomes. Examples of this difference include evidence that female physicians are more likely to follow clinical guidelines and engage in more patient-centered communication compared to male physicians, and patients treated by female physicians experience lower mortality and readmission rates than those treated by male physicians [10]. Thus, it is important to understand how gender influences surgical teams' training, learning, teamwork, and performance in RAS. However, the role of gender in robotic surgery has not been studied in previous research. As there are changes in team roles and dynamics in robotic surgery, this project addresses this research gap and examines the role of gender in communication among robotic surgical teams.

This project has two important contributions to RAS. First, the taxonomy developed from this project will include a list of actionable communication behaviors along with contextual factors and their associated descriptions and examples. We anticipate that the taxonomy will be used for behavioral observations and training surgical team members to effectively communicate with each other and prevent communication failures. Second, this project will answer important questions related to the gender dimension (eg, male vs female surgical team members engaging in a specific communication behavior) that can be taken into consideration in their training.

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Methods

Scoping Review

Literature Search

We will first perform a scoping review to examine the existing literature on communication in RAS and identify the gaps in the literature according to the methodological guidance of Peters et al [11]. The review will be reported based on the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guideline and checklist [12].

We will search the following databases: PsycINFO, CINAHL, PubMed, Cochrane, Embase, MEDLINE, and Web of Science. We will also search the grey literature in the Scopus and Google Scholar databases. The search terms and strategy are outlined in Textbox 1.

Textbox 1. Search strategy for the scoping review.

1: Title/abstract

- robotic surg* OR “robotic surgery” OR “robot-assisted surgery” OR “robot assisted surgery” OR “robotic assisted surgery” OR “robotic-assisted surgery” OR robotic surgical procedure* OR robotic surg* team* OR “minimally invasive surgery”

2: Medical Subject Heading (MeSH) terms or subject terms

- robotic surgery

3: 1 OR 2

4: Title/abstract

- “non-technical skills” OR “non technical skills” OR “nontechnical skills” OR communicat* OR coordinat* OR cooperat* OR collaborat* OR teamwork OR team process* OR interpersonal skill* OR “information sharing” OR non-technical skill* OR team dynamic*

5: MeSH terms or subject terms

- communication

6: 4 OR 5

7: 3 AND 6 with the following syntax:

(“robotic surg*”[Title/Abstract] OR “robotic surgery”[Title/Abstract] OR “robot-assisted surgery”[Title/Abstract] OR “robot-assisted surgery”[Title/Abstract] OR “robotic-assisted surgery”[Title/Abstract] OR “robotic-assisted surgery”[Title/Abstract] OR “robotic surgical procedure*”[Title/Abstract] OR ((((“robot”[All Fields] OR “robot s”[All Fields] OR “robotically”[All Fields] OR “robotics”[MeSH Terms] OR “robotics”[All Fields] OR “robotic”[All Fields] OR “robotization”[All Fields] OR “robotized”[All Fields] OR “robots”[All Fields]) AND “surg*”[All Fields]) AND “team*”[Title/Abstract]) OR “minimally invasive surgery”[Title/Abstract] OR “robotic surgical procedures”[MeSH Terms]) AND (“non-technical skills”[Title/Abstract] OR “non-technical skills”[Title/Abstract] OR “nontechnical skills”[Title/Abstract] OR “communicat*”[Title/Abstract] OR “coordinat*”[Title/Abstract] OR “cooperat*”[Title/Abstract] OR “collaborat*”[Title/Abstract] OR “teamwork”[Title/Abstract] OR “team process*”[Title/Abstract] OR “interpersonal skill*”[Title/Abstract] OR “information sharing”[Title/Abstract] OR “non technical skill*”[Title/Abstract] OR “team dynamic*”[Title/Abstract] OR “communication”[MeSH Terms])

Study Selection and Data Extraction

We will select studies for the review based on the inclusion and exclusion criteria outlined in Table 1. We will then extract information relevant to our research focus (ie, communication in RAS) using a charting table. We will analyze the data using descriptive statistics (eg, frequency). Finally, we will report the results according to PRISMA-ScR guidelines as well as in diagrams and/or tables as appropriate. This scoping review will result in the preliminary taxonomy of communication and contextual factors in RAS teams.

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Table 1. Inclusion and exclusion criteria in the scoping review.

Category	Inclusion criteria	Exclusion criteria
Publication date	Between January 2010 and December 2023	Before 2010
Population	Health care professionals	Medical students
Context	Simulation, hospitals, medical centers; teaching/learning environment; effects of environmental, external, or contextual factors (eg, stress, audio and video issues) on communication	Community
Type of surgery	Robotic-assisted surgery or comparison of robotic surgery to other types of surgery	Laparoscopic, open
Sources	Peer-reviewed articles, conference proceedings, theses, and dissertations	Books, periodicals, magazines, policy documents, and websites
Language	English	Non-English
Study design	Quantitative, qualitative, and mixed methods; training, assessment, rating tool, checklist, protocol	All types of reviews

Interviews

This project will take place at the Royal College of Surgeons in Ireland (RCSI). We will use purposive and convenience sampling to recruit participants. We will invite participants through the RCSI's surgical networks. We will conduct one-on-one semistructured interviews with members of the surgical teams, including the consultant/attending surgeon, assisting surgeon or trainee, bedside or first assistant, nurses, and anesthetists. Participants will represent different disciplines, including urology, general surgery, and gynecology, and have a range of experiences in robotic surgery. The interviews will take place in person or virtually and will be audio-recorded and transcribed. A sample interview questions is "In robotic-assisted surgery, what does it look like when communication is effective in the team?"

Although we anticipate conducting 30 interviews, we will collect data until we achieve data sufficiency (ie, sufficient data to answer the research questions capturing both the uniqueness of the communication experience and its socially constructed meaning) [13] and an equal representation of male and female voices. In qualitative research, sample size depends on several factors such as study purpose, sample specificity, and quality of exchange between researchers and participants. For example, if participants offer rich accounts of their experiences, the sample size required may be lower than otherwise. By contrast, a study with a broad aim and limited theoretical background requires a higher sample size.

We will analyze the data in parallel to data collection. We will use reflexive thematic analysis, an iterative process where researchers interpret and analyze patterns of behaviors while being aware of their own assumptions, experiences, and social positions (eg, with regard to gender) [14]. We will identify and develop themes of communication and contextual factors. We will also calculate interrater agreement with an adequate proportion of the data. If we find a new theme, we will clarify or ask further questions in the following interviews. Through this iterative process, we will further refine the taxonomy.

Observations

We will conduct interviews and observations in parallel to allow these findings to inform each other as the period of data collection and iterative data analysis proceeds. We will observe live robotic surgical procedures at hospitals affiliated with the RCSI. The RCSI Group is comprised of several hospitals, including Beaumont Hospital, which provides a national and regional service to Dublin and the eastern and northern regions of Ireland. We will invite participants through the RCSI's surgical networks. A researcher will be present in the operating theater and take notes at an optimal distance to hear any communication occurring among the surgeon, assisting surgeon, first assistant, nurses, and anesthetist. Excel spreadsheets will be used to record the frequency of the behaviors observed. Moreover, we will observe varying lengths of robotic surgical procedures to capture a wide range of communication behaviors, as certain parts of a procedure are more challenging and create conditions that require different strategies of management and communication. Although we anticipate observing 30 robotic surgical procedures, we will collect data until we achieve data sufficiency.

We will analyze the data and further refine the taxonomy. We will also calculate interrater agreement with an adequate proportion of observations. If we find a new behavior or event during an observation, we will follow up with additional interviews and/or observations. We will pursue this iterative process until we achieve data sufficiency. The final outcome of the iterative process is a valid and reliable taxonomy of communication behaviors and contextual factors, their descriptions, and examples that can be used for behavioral observations.

Ethical Considerations

The study was approved by the RCSI Research and Ethics Committee in May 2024 (reference number: REC202309006). We will seek informed consent from the surgical team members and patients, and they can withdraw from the study at any point without repercussions. Participants will not receive any compensation. Data will be pseudonymized and stored on the secure, encrypted RCSI OneDrive that only the research team has access to. The data sets, including raw data, will not be

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openly available as they contain personal information of participants (eg, gender) and their personal experiences that are confidential.

Dissemination and Secondary Use of Data

The taxonomy resulting from this project will serve as the metadata that will include codes used in data analysis, their description, and examples. Researchers can use the taxonomy to replicate the study or for future research. The taxonomy will be published in open access journals and/or made publicly available via appropriate repositories (eg, Zenodo, RCSI Repository, Open Research Europe). Request for access to the data may be considered if individuals have received training on research ethics and General Data Protection Regulation and approvals from appropriate research ethics committees.

Results

The data collected will include interviews (audio files, transcripts, and a codebook) and observational notes (Excel sheet). The taxonomy will include a list of communication behaviors and contextual factors, their descriptions, and examples. This project has been funded by a Marie Skłodowska-Curie Actions Fellowship (grant 101107170) of the European Union from September 2023 to September 2025. As of June 2024, we have screened abstracts and titles of 5024 articles and the full texts of 182 articles. We are preparing to assess 79 included articles. Moreover, we have conducted one interview and will continue data collection and analysis throughout the year. We aim to publish the findings as meaningful results emerge throughout our data analysis in 2024 and 2025.

Discussion

Anticipated Results

RAS differs from open or laparoscopic surgery mainly because of the surgeon's separation from the rest of the surgical team and the patient and the presence of the robotic operating equipment in the operating theater. This setup inherently changes communication and team dynamics in RAS teams. This protocol describes a project that aims to develop a taxonomy of communication and contextual factors that facilitate or inhibit effective communication in RAS. The taxonomy will include a list of communication behaviors and contextual factors in RAS, their descriptions, and examples. We also anticipate obtaining results related to the gender dimension, such as whether and/or how male and female surgeons engage in similar or different patterns of communication behaviors.

Comparison With Prior Work

Compared with previous studies that examined mainly nontechnical skills in RAS [3-5], this project focuses specifically on communication and its contextual factors that facilitate or inhibit effective communication in RAS teams. As communication is fundamental to other nontechnical skills, the taxonomy of communication developed from this project can be used for behavioral observations and training focusing specifically on communication. In addition, previous studies have used behavioral marker methodology to develop rating tools for nontechnical skills in RAS. Behavioral marker methodology categorizes various behaviors into broad behavioral classes [15]. Although this approach provides an overall assessment of nontechnical skills, some behaviors in a given behavioral class may not occur frequently and this method is susceptible to observer bias [15]. For example, one behavior might stand out to an observer who then rates the entire behavioral class favorably. Alternatively, the taxonomy from this project will focus on specific and defined communication behaviors that are easier to observe and train and less susceptible to observer bias. Thus, this project has unique contributions to improving communication skills in RAS teams.

Limitations

We acknowledge possible limitations in this project. We are collecting data in the da Vinci robotic surgical system (Intuitive Surgical), as it is the platform most surgeons are currently familiar with. However, there are other robotic systems such as the Hugo RAS System (Medtronic) and Versius (CMR Surgical). There might be differences in communication according to different system setups. Moreover, we will only examine core communication behaviors that can be trained across different disciplines or specialties. There might be discipline-specific communication as well as contexts (eg, emergency situation) that need to be incorporated into training. Therefore, future research should further examine RAS team communication in different contexts.

Conclusions

The results from this project will serve as training materials to observe and train surgical teams in a simulated environment to effectively communicate with each other and prevent communication failures. Simulation provides a safe environment that mimics a real hospital for learning and practicing surgical skills and techniques. Thus, the results will be applied in simulation training focusing on communication for surgical teams. We will also answer important questions related to the gender dimension. The results will inform behaviors and contexts that need to be emphasized in simulation training and address gender gaps. In conclusion, this project aims to improve the communication skills of RAS teams so that they are competent and responsible in effectively communicating with each other and using robotics to deliver safe patient care.

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Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the European Commission - Horizon Europe Framework Programme - Royal College of Surgeons in Ireland.
[PDF File (Adobe PDF File), 1434 KB - resprot_v13i1e54910_app1.pdf]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
RAS: robotic-assisted surgery
RCSI: Royal College of Surgeons in Ireland

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Protocol

Identifying Interventions to Improve Diagnostic Safety in Emergency Departments: Protocol for a Participatory Design Study

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Abstract

Background: Emergency departments (EDs) are complex and fast-paced clinical settings where a diagnosis is made in a time-, information-, and resource-constrained context. Thus, it is predisposed to suboptimal diagnostic outcomes, leading to errors and subsequent patient harm. Arriving at a timely and accurate diagnosis is an activity that occurs after an effective collaboration between the patient or caregiver and the clinical team within the ED. Interventions such as novel sociotechnical solutions are needed to mitigate errors and risks.

Objective: This study aims to identify challenges that frontline ED health care providers and patients face in the ED diagnostic process and involve them in co-designing technological interventions to enhance diagnostic excellence.

Methods: We will conduct separate sessions with ED health care providers and patients, respectively, to assess various design ideas and use a participatory design (PD) approach for technological interventions to improve ED diagnostic safety. In the sessions, various intervention ideas will be presented to participants through storyboards. Based on a preliminary interview study with ED patients and health care providers, we created intervention storyboards that illustrate different care contexts in which ED health care providers or patients experience challenges and show how each intervention would address the specific challenge. By facilitating participant group discussion, we will reveal the overlap between the needs of the design research team observed during fieldwork and the needs perceived by target users (ie, participants) in their own experience to gain their perspectives and assessment on each idea. After the group discussions, participants will rank the ideas and co-design to improve our interventions. Data sources will include audio and video recordings, design sketches, and ratings of intervention design ideas from PD sessions. The University of Michigan Institutional Review Board approved this study. This foundational work will help identify the needs and challenges of key stakeholders in the ED diagnostic process and develop initial design ideas, specifically focusing on sociotechnological ideas for patient-, health care provider–, and system-level interventions for improving patient safety in EDs.

Results: The recruitment of participants for ED health care providers and patients is complete. We are currently preparing for PD sessions. The first results from design sessions with health care providers will be reported in fall 2024.

Conclusions: The study findings will provide unique insights for designing sociotechnological interventions to support ED diagnostic processes. By inviting frontline health care providers and patients into the design process, we anticipate obtaining unique insights into the ED diagnostic process and designing novel sociotechnical interventions to enhance patient safety. Based on this study's collected data and intervention ideas, we will develop prototypes of multilevel interventions that can be tested and subsequently implemented for patients, health care providers, or hospitals as a system.

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KEYWORDS

emergency departments; participatory design; diagnostic process; multilevel interventions; sociotechnical interventions; mobile phone

Introduction

In emergency departments (EDs), diagnosing and managing patients require highly complex processes involving multiple stakeholder interactions (eg, physicians, nurses, trainees, consultants, caregivers, and patients). A unique aspect of EDs is that various stakeholders make crucial medical decisions in a time-pressured environment. Because of this unique nature, health care providers in EDs face significant challenges in making accurate and timely diagnoses, often causing patient safety issues. While precise error rates are unknown, a conservative estimate of 5% of errors in adults of the 131 million annual ED visits translates to about 7 million cases of ED-based diagnostic errors, with nearly half of them having potential for patient harm [1].

Numerous interventions have supported health care providers' work and promoted patient safety in clinical settings. For instance, recent artificial intelligence (AI) systems have been proposed and designed to help nurses and physicians in various aspects, such as an AI-assisted autocomplete system [2] for increasing the quality and efficiency of documentation and data entry and an AI-based smartphone app, Face2Gene developed by FDNA Inc [3], for helping health care providers in the diagnostic process of rare congenital disorders. Patient-facing technologies have also been developed, such as an indoor navigation and communication system [4] for estimating patients' location and helping patients send request messages to health care providers (eg, "Can I have medicine now?") and a mobile display [5] presenting a digital report on patients' progress, care plans, and care teams' work throughout their ED stay. While these technological interventions provide efficiency in health care providers' cognitive work and patient safety efforts, direct input from patients and health care providers is often overlooked when developing such solutions.

Participatory design (PD) [6] is a design methodology that engages all stakeholders in the design process to create a functional solution that addresses their needs. PD has been used in prior works in health care and medical domains to design technology that meets the specific needs of health care providers. Despite the benefits of PD in designing health technology, there has been limited adoptions of a user-centered PD approach to develop technology interventions for the ED. Østervang et al [7] conducted PD workshops with health care providers and patients to design an ED information system. They presented how the PD approach helps yield insights from ED health care providers and patients to create a more person-centered system. Yet ED patients had limited participation since the workshops were conducted one-on-one, and patients were only asked to provide feedback on intervention ideas developed by health care providers.

This proposed study aims to design ED-based diagnostic error prevention interventions by incorporating key stakeholders' needs, preferences, and perspectives. Our study will bring key stakeholders together to understand the perspectives of both patients and health care providers and seek to incorporate their input into the design process for future interventions. To involve the stakeholders in the design process, we will deploy a co-design approach using PD methods with patients, caregivers, and clinicians to gather their insights, generate and critique design ideas, and co-design interventions. Through this, we aim to ultimately identify at least 1 intervention for further development at each of the following levels: patient-involved, clinician-focused, and health care system–oriented.

Methods

Overview

To accomplish our research goal, we assembled a research team with diverse expertise in emergency medicine, cognitive psychology, systems engineering, informatics, human-computer interaction and design, anthropology, and public health. We are creating a research project group, Improving Diagnosis in Emergency and Acute Care-Learning Laboratory, to investigate ED diagnostic processes and study system vulnerabilities and develop and iteratively test patient-, health care provider–, and system-oriented interventions to mitigate diagnostic error.

This study is part of a larger mixed methods project aiming to identify the challenges of ED health care providers and patients and design multilevel interventions for them. This study has 2 specific parts (Table 1), focusing on developing intervention ideas by inviting ED health care providers and patients to the design process. The study will be conducted in 2 academic medical centers: the University of Michigan and the Mayo Clinic. Participants will be recruited from each center's ED. We will conduct separate study sessions for ED health care providers and patients. Combining findings from both groups, we will develop multilevel (patient-involved, clinician-focused, and health care system–oriented) intervention ideas to enhance the ED diagnosis process. Ultimately, we will create prototypes of those interventions for future evaluations.

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Table 1. Overview of the previous and proposed studies. The proposed study has two parts: participatory design with (1) ED[a] health care providers and (2) ED patients or caregivers to explore their needs and generate design ideas for technological interventions for the ED care process.

	Previous study [8]	Proposed study	
		Part 1	Part 2
Purpose	To understand the current ED care process and preliminarily assess the challenges faced by ED health care providers and patients or caregivers in the diagnostic process	To explore health care providers' needs and generate design ideas for technological interventions for the ED care process	To explore patients' or caregivers' needs and generate design ideas for technological interventions for the ED care process
Research questions	What are the needs and challenges of ED health care providers and patients or caregivers related to the diagnostic process, patient safety, and overall experience during ED care?	How do ED health care providers perceive suggested technological interventions? What are the expected impacts of the intervention?	How do ED patients or caregivers perceive suggested technological interventions? What functions do they expect from the interventions?
Approach	Field observation and interviews	Participatory design	Participatory design
Results or expected outcomes	Scenarios that describe technological interventions to address challenges in the ED process	A ranked list of design ideas that address health care providers' challenges in the ED process and improve or refine ideas	A ranked list of design ideas that address patients' and caregivers' challenges in the ED process and improve or refine ideas

[a]ED: emergency department.

Idea Generation on ED Care Intervention Design

The findings from our previous study [8] (described in Table 1) using direct observation and participant interviews have helped us identify key needs and challenges health care providers and patients encountered in the ED diagnostic process. For instance, our analysis showed that ED health care providers need a better representation of patients' statuses to enhance their triage process. They want a system for enhanced collaboration within the care team in the fast-paced ED context. Notably, we identified different challenges stratified by health care provider role (nurses, physicians, and both nurses and physicians), as shown in Textbox 1.

Textbox 1. A list of identified problem categories from the previous study's emergency department (ED) health care provider interview data. We identified 2 problems from nurses, 4 from physicians, and 4 from both nurses and physicians.

Nurses

- Forgetting to perform patient reassessments due to heavy workloads.
- Difficulty in remembering timely patient reassessment and keeping track of their conditions.

Physicians

- Clinicians' high levels of stress can impede decision-making and focus on ED work.
- Physicians' high cognitive load may interfere with their ED diagnosis work.
- Lack of decision support tools that aid in diagnostic decision-making for increased accuracy.
- Difficulty accessing scattered patient history in a concise and easy-to-read format.

Both nurses and physicians

- Insufficient communication between physicians and nurses about orders and next steps in patient care and a lack of electronic health record support for such communication.
- Insufficient communication between physicians and nurses about the patient's diagnosis and no established opportunity to discuss diagnoses before discharge.
- Lack of notification and information about incoming patients with critical care needs.
- Acuity level differs between nurses and physicians. Physicians sometimes have to reassign acuity levels mentally.

For patients, one of the major challenges was limited time spent with the caregiver team, which was perceived as the absence or lack of support. The patients often received less attention, care, or information about the ED process than expected or needed. Based on these challenges, we identified 7 problem categories that previous study patients experienced (described in Textbox 2).

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Textbox 2. A list of 7 identified problem categories from the previous study's patient and caregiver interview data.

Waiting room general challenges

- Patients feel forgotten in the waiting room because health care providers do not check on them.
- Patients are left in pain or experience other unresolved symptoms in the waiting room.

Overcrowding challenges

- General overcrowding problems (eg, there are patients with mild symptoms who make emergency department [ED] more crowded).

Information presentation and overload challenges

- Patients are not sufficiently informed of the ED process during the visit (lack of ED process literacy).
- Test results can be confusing for patients to understand because of the use of medical terminology.

Information sharing challenges

- Patients often feel that there are errors in the doctor's notes (which are different from what was discussed during the visit).
- Health care providers at hospitals sometimes wait for information transfer from the patient's original hospital, which can take time.

Communication challenges

- Patients find it hard to recount all personal medical details in the ED because they are sick, stressed, or unaware.
- Patients sometimes have trouble communicating with health care providers because of challenges such as being a nonnative English speaker.

Contagious disease transfer in ED

- Crowded waiting rooms can have many sick patients in close proximity, which makes patients concerned.
- Contact with surfaces can cause disease transfer.

Discharge and postvisit challenge

- Lack of postvisit resources for patients.
- Patients feel that they have been wrongly discharged.

We have developed various initial ideas for ED care interventions based on the identified challenges that the ED health care providers and patients faced in the ED diagnostic process. These design ideas describe technological solutions that can serve as probes to identify the challenges and needs of ED health care providers and patients. For health care providers, the design ideas include automated tools to support health care providers in triaging patients, visualization tools to help monitor patients' conditions, wearable devices to track and manage health care providers' stress, and communication tools for the ED care team. For patients or caregivers, intervention idea categories include robots to alleviate patient anxiety in the waiting room, visualization tools to inform them about the procedures, and systems to enhance their communication with health care providers. Based on these design ideas, we will select novel ideas to develop them into intervention scenarios. Those scenarios describe how each intervention can resolve a specific challenge for ED health care providers or patients. The scenarios will be used to facilitate discussions in the PD sessions with ED health care providers (part 1) and patients or caregivers (part 2).

Part 1: PD With ED Health Care Providers

Sampling, Eligibility, and Recruitment of ED Health Care Providers

We will recruit ED health care providers with different roles (eg, emergency medicine and pediatric emergency medicine–trained physicians, fellow physicians, and nurses) and explore how different roles engage in the ED care process. Eligible health care providers will be ED physicians and nurses who have worked a minimum of a year in the ED setting. We will recruit 3-4 health care providers for each session. In total, 4-5 sessions are planned, and additional sessions may be conducted if data saturation is not reached. The health care providers will be recruited in 2 medical centers, as described earlier. A study coordinator will recruit health care providers through email or in person on the day of a shift. Once they express their interest in participating in our study, we will obtain electronic informed consent via email before each session. We will offer a US $100 gift card to health care providers for their participation in a design session. All PD sessions will be audio-recorded and transcribed for data analysis.

Data Collection Instruments

Before conducting design sessions, we will create storyboards that describe our design ideas about potential technological interventions and their use scenarios. The storyboards will be

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based on health care providers' challenges in seeking and using the information necessary for the ED diagnostic process, as shown in Textbox 1. For instance, a storyboard will describe how an AI-based dashboard can compute the patient care priority based on the risk factors of each ED patient and visualize the priority with simple graphs (Figure 1).

Figure 1. A sample storyboard presenting our design idea from the session with ED health care providers: an artificial intelligence–based dashboard that visualizes patients' risk levels so that health care providers can prioritize patient care more efficiently. ED: emergency department.

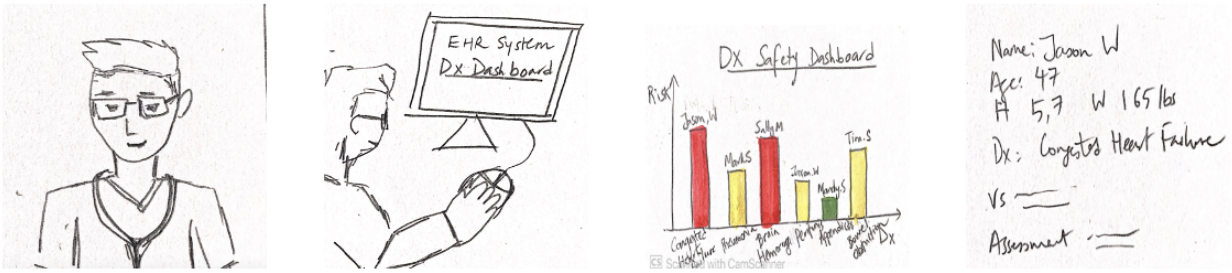

Activity 1: Design Idea Critique With Health Care Providers

Each PD session will involve 3 or 4 ED health care providers with the same role (eg, physician or nurse) from the same medical organization to avoid any impact of power dynamics between different roles [9]. Depending on the health care providers' availability, each session will be conducted in person in a private conference room at one of the medical organizations or remotely through a web-based platform (Zoom; Zoom Video Communications). Each PD session will have two major activities: (1) design idea critique and (2) co-design activity. For the critique activity, we will use storyboards to present the intervention ideas to participants. Participants will review the storyboards and have a group discussion about the appropriateness, feasibility, and applicability of each intervention idea and features that should be added. We will prepare follow-up questions to facilitate group discussions (eg, "How do you want the AI system to present the emergency severity index about patients?"). Besides those questions, participants can also freely share their thoughts and perspectives on each storyboard.

Activity 2: Co-Design With Health Care Providers

In the second activity, among the storyboards they discussed, participants will be asked to choose the most helpful intervention idea and improve or modify it individually. Then, they will share their ideas with other participants and reflect on the ideas together as a group. For the in-person sessions, we will prepare drawing materials (eg, pencils, colored pencils, and paper) to make the co-design activity more engaging and effective. For the remote sessions, we will ask participants to prepare their drawing materials in advance (at least a pencil and a piece of paper). As a group, all participants will combine their ideas into 1 intervention idea that everybody agrees upon. All sessions will be audio- and video-recorded for data analysis. Participants' drawings will be collected after design sessions. For the remote sessions, participants will be asked to take a picture of their design and send it to one of the researchers, who will share the design with all the participants.

Data Analysis

We will use a thematic analysis approach [10] to analyze the transcripts from design sessions. Thematic analysis is a methodical tool for discovering repeating themes in the text by finding common topics or ideas that keep coming up. It represents the structured outcome of a collaborative brainstorming session. Adopting the thematic analysis, the research team members will code the transcripts separately first. We will also analyze and code our observation notes from each session and participants' designs from the activity. Photos and recorded videos will capture detailed participant interactions during each session. Then, the researchers will combine the codes, compare their codes, and identify recurring themes. The research team will discuss the themes to identify which aspects of each intervention participants like or dislike. The research team will also analyze potential differences between 2 sites or roles (eg, physician vs nurse). This analysis will help us better understand participants' nuanced technology preferences and provide insights into how to balance different perspectives in designing future technologies to support ED health care providers.

Part 2: PD With ED Patients or Caregivers

Sampling, Eligibility, and Recruitment of Patients or Caregivers

We will recruit ED patients and caregivers from the adult and pediatric EDs at the University of Michigan. Eligible participants are those 18 years or older or whose caregivers have visited an

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ED (either pediatric or adult) in the last 6 weeks. We will recruit 4-6 patients or caregivers for each session. The expected number of sessions will be 4-5, but we may conduct more sessions if data saturation is not reached. A few well-trained researchers will visit the ED and introduce the study to patients in the waiting room. We will collect their contact information for follow-up scheduling once they express interest in participating in our study. We will contact interested patients and ask them to complete a digital poll to provide their availability. This information will be used to find a suitable time to conduct a session with 4-6 participants. We will also post a flyer with a study description and our contact information at the hospital. Our research team staff will contact the eligible participants through calls, SMS text messages, or emails. Patients and caregivers will receive a US $100 gift card for participating in a design session. We will obtain electronic informed consent from all patient or caregiver participants by emailing the form before each session. If they do not fill out the digital form, we will obtain a paper copy of the consent form and ask them to sign it at the beginning of the in-person session. All PD sessions will be audio-recorded and transcribed for data analysis.

Data Collection Instruments

Like part 1, we will create storyboards describing our design ideas about potential technological interventions and their use scenarios. The storyboards will be based on patients' challenges in seeking and using the information necessary for the ED diagnostic process, as shown in Textbox 2. For instance, a storyboard will present how a wearable device for ED patients in a waiting room can track patients' real-time conditions and notify health care providers if a patient need immediate attention (Figure 2).

Figure 2. A sample storyboard presenting our design idea from the session with patients and caregivers: a wearable device for ED patients in a waiting room that tracks patients' real-time conditions and notifies health care providers if the patients need immediate help. ED: emergency department.

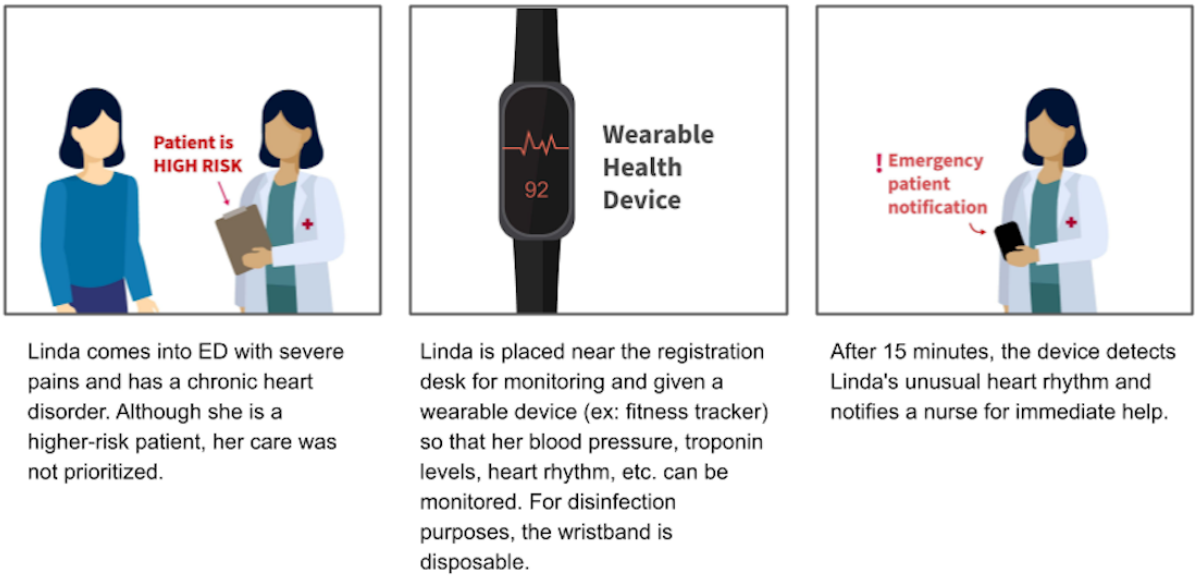

For patients, we will also provide a paper copy of a typical timeline of the ED care process (Figure 3). We created this timeline based on our previous study [8] and prior work on the ED care framework [11]. Unlike health care providers, patients may need more information about the step-by-step ED care process. Thus, the timeline will help patients understand the structure of the process and remind them of their own recent ED experiences. We will ask participants to share the challenges they experience throughout the timeline.

Figure 3. An ED care process timeline that illustrates the steps before, during, and after ED care. We created this timeline based on prior studies. ED: emergency department.

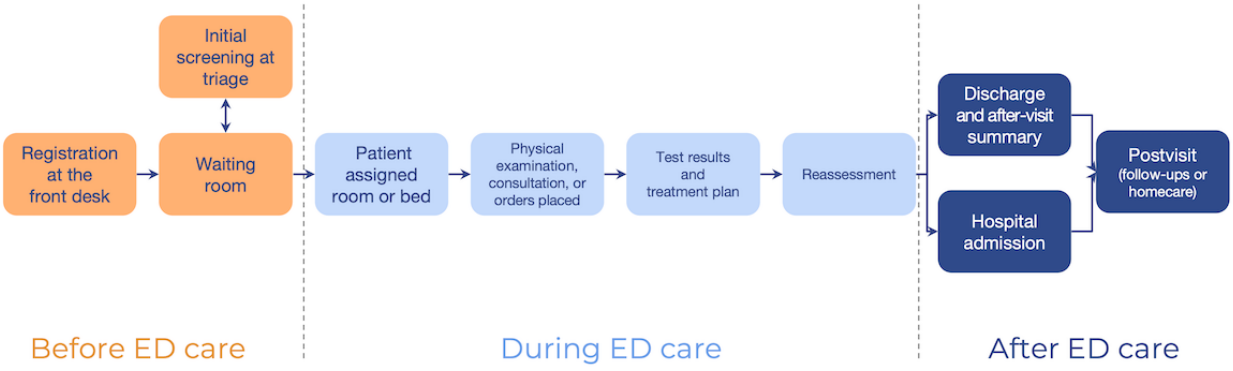

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Activity 1: Design Idea Critique With Patients and Caregivers

Each session will involve 4-6 patients or caregivers. Caregivers will include patients' family members or friends who visited an ED with the patient. The sessions will be conducted in person in a private room at one of the medical organizations, following a format similar to the activities described in "PD with ED health care providers." Participants will also be given a handbook that includes a paper copy of each storyboard, the ED care process timeline, and additional pages for their notes. Before the main activity, we will begin the sessions with patients by introducing the ED process timeline so they can easily remember the experiences and challenges they faced during their recent ED visits.

Similar to part 1, the first activity will be critiquing design ideas. We will use storyboards to present the intervention ideas to participants. Participants will review the storyboards and have a group discussion about the appropriateness, feasibility, and applicability of each intervention idea and additional features that should be added. We will prepare follow-up questions to facilitate group discussions for each intervention idea (eg, "What types of information can the chatbot provide?"). In addition, we will verify the problem described in each storyboard by asking participants specific questions (eg, "Have you ever felt that providers needed to explain more about test results or processes but were too busy?"). Besides those questions, participants can also freely share their thoughts, perspectives, and experiences related to the problem described in each storyboard. During this activity, participants can take notes on their handbook, which has a paper copy of each intervention.

Activity 2: Co-Design With Patients and Caregivers

In the second part of the PD workshop, participants will choose their favorite storyboards based on their ED experiences and knowledge, and they will share their reasoning with the group in order to choose one storyboard as a group. Then, all participants will design their ideas as a group to improve or modify the intervention idea. We will prepare drawing materials (eg, pencils, colored pencils, and paper) and whiteboards for the design activity. The participants will then present their ideas to the research team members, and the researchers will ask follow-up questions to probe the group's reasoning for each design decision. All sessions will be audio- and video-recorded for data analysis. Participants' drawings will be collected after the design sessions.

Data Analysis

Like part 1, we will use a thematic analysis approach [10] to analyze transcripts, participant notes, and observation notes from the sessions. To circumvent biases of subjective interpretation of the qualitative data, at least 2 research team members will code the transcripts separately. Photos and recorded videos will also capture detailed participant interactions during each session. Then, the research team members will combine the codes, compare their codes, and identify recurring themes. The team will discuss the themes related to patient needs, challenges, and aspects of each intervention. This analysis will help us better understand participants' nuanced intervention ideas and provide insights into possible future technologies to improve patients' experience of ED visits.

Prototype Development

By combining data collected from both health care providers and patients, we will explore potential intervention ideas at 3 levels: patient-focused, health care provider–focused, and system-focused interventions. This co-development process with participants will initially allow user input and flexibility but ultimately lead to a concrete version of a technological intervention that provides effective support to patients, ED health care providers, and hospitals as a system.

Drawing on the results from the analysis, we will develop prototypes of the top intervention ideas from participants, using an iterative approach. The iterative approach has been used in various design projects and proven its effectiveness in improving the quality of prototype designs [12-14]. The iterative process will have 3 main steps. First, we will develop a series of low-fidelity prototypes based on the 3-level interventions. Second, we will conduct usability evaluations with health care providers and patients or caregivers. Third, we will revise the prototypes based on the feedback and return to the second step. Through this iterative process, we will identify the most feasible and helpful intervention ideas for future implementation.

Ethical Considerations

We will comply with the following ethical considerations. First, we will get consent from all participants before the study sessions as described in the multisite institutional review board protocol approved by the University of Michigan (HUM00156261). Second, we ensure that the transcription data is deidentified, and participants' faces in photos or videos will be blurred. All collected data will be stored in a secure storage facility that requires University of Michigan accounts. Third, all researchers will complete research compliance training on best practices and ethical considerations of interacting with health care providers and patients, such as those offered by the Collaborative Institutional Training Initiative or the Program for the Education and Evaluation in Responsible Conduct of Research.

Results

The recruitment of participants for ED health care providers and patients is complete. We are currently preparing for PD sessions. The results from design sessions with health care providers and patients will be reported separately in fall 2024. The results of this study will be disseminated through journal publications and presentations at national and international meetings.

Discussion

Anticipated Findings

PD is a useful methodology for incorporating stakeholders' needs in the early stage of the intervention development process by verifying the overlap between the needs a design research team observed during fieldwork and the needs target users perceive in their own lives as well as their preferences for new

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technology. Specifically focusing on the ED care contexts, the proposed study will contribute to extending the understanding of the challenges experienced by ED health care providers and patients and their expectations for interventions to improve the diagnostic process and patient safety.

The proposed study has 3 anticipated contributions. First, the study findings will reflect the nuanced needs of patients and health care providers during PD sessions. These user ideas will help us and other researchers to understand their needs and the barriers encountered in the ED decision-making process, which will inform the design of technological interventions to meet these needs. Second, recruitment of participants from 2 sites with varying characteristics may provide diverse perspectives and broader intervention insights. The findings may show differences between participants from different sites, which may provide design insights for mitigating conflicting user needs when developing technological interventions for the ED decision-making process. Third, this study will present how the PD approach can be used to develop health technologies that support the diagnostic process in the ED, thereby extending findings from previous work on PD in hospital settings by focusing on the distinction between the needs of the ED health care providers and those of the patients. A few prior studies conducted PD in hospital settings. For instance, Kusunoki et al [15] conducted PD workshops with trauma team members to understand the different needs of awareness support among the various roles of team members and identify concrete design strategies to manage the differences in their awareness needs. Pollack et al [16] organized a design session with 11 clinicians to develop a clinical information tool using PD techniques. Based on the session's findings, the authors identified benefits (eg, a high level of domain knowledge can be used to anticipate how design ideas can be applied to clinical processes and workflow) and potential challenges (eg, power dynamics between physicians). The authors also outlined guiding principles for implementing these methods in health care organizations interested in advancing their use of health information technology. These prior studies have presented how PD is helpful and effective for designing human-centered technology in health care settings. Along with these previous studies, this proposed study will provide insights for conducting PD with multiple stakeholders, particularly extending the involvement of ED patients whose roles were often limited [7]. In addition, the proposed study findings will provide rich insights into design implications for technology to support decision-making in the ED diagnostic process by incorporating perspectives and ideas from patients and health care providers.

Limitations

This study has several limitations. First, given its qualitative nature, the findings are specific to the participating sites, as health care providers and patients from other EDs may face different challenges. Yet, we anticipate our findings will contribute to identifying such challenges and potential interventions to address the challenges through a PD approach. Second, even though we leveraged evidence from preliminary interview data, some intervention ideas we developed are novel technologies, with which some participants may have no prior experience (eg, tabletop robots). Thus, it may be challenging for the participants to contextualize using these nonexistent technologies without a tangible prototype.

Conclusions

The study findings will provide unique insights into designing sociotechnological interventions to support ED diagnostic processes. Inviting ED health care providers and patients into the design process will facilitate the design of sociotechnological interventions to address the specific needs of ED health care providers and patients. Finally, we will develop prototypes based on this study's findings and intervention ideas, which will be developed iteratively in future evaluation studies.

Acknowledgments

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Data Availability

The data sets generated in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

HS is co-chair of the Leapfrog Group project Recognizing Diagnostic Excellence.

Multimedia Appendix 1
Peer review report from the Agency for Healthcare Research and Quality (AHRQ).
[PDF File (Adobe PDF File), 179 KB - resprot_v13i1e55357_app1.pdf]

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Abbreviations

AI: artificial intelligence
ED: emergency department
PD: participatory design

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Proposal

Suicidal Ideation and Attempts Among Youth With Physical-Mental Comorbidity in Canada: Proposal for an Epidemiological Study

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Abstract

Background: Evidence suggests that having a chronic physical illness (CPI; eg, asthma, diabetes, and epilepsy) is an independent risk factor for suicidality (ie, suicidal ideation or attempts) among youth. Less is known about the mechanisms linking CPI and suicidality. Some evidence suggests that mental illness (eg, depression and anxiety) or neurodevelopmental disorder (eg, attention-deficit/hyperactivity disorder) mediates or moderates the CPI-suicidality association. Missing from the knowledge base is information on the association between having co-occurring CPI and mental illness or neurodevelopmental disorder (MIND) on youth suicidality.

Objective: This study uses epidemiological data from the 2019 Canadian Health Survey of Children and Youth (CHSCY) to study the intersection of CPI, MIND, and suicidality in youth. We will estimate prevalence, identify predictors, and investigate psychosocial and service use outcomes for youth with CPI-MIND comorbidity versus other morbidity groups (ie, healthy, CPI only, and MIND only).

Methods: Conducted by Statistics Canada, the CHSCY collected data from 47,850 children (aged 1-17 years) and their primary caregiving parent. Measures of youth CPI, MIND, family environment, and sociodemographics are available using youth and parent informants. Information on psychiatric services use is available via parent report and linkage to national administrative health data found in the National Ambulatory Care Reporting System and the Discharge Abstract Database, which allow the investigation of hospital-based mental health services (eg, emergency department visits, hospitalizations, and length of stay in hospital). Questions about suicidality were restricted to youths aged 15-17 years (n=6950), which form our analytic sample. Weighted regression-based analyses will account for the complex survey design.

Results: Our study began in November 2023, funded by the American Foundation for Suicide Prevention (SRG-0-008-22). Access to the linked CHSCY microdata file was granted in May 2024. Initial examination of CHSCY data shows that approximately 20% (1390/6950) of youth have CPI, 7% (490/6950) have MIND, 7% (490/6950) seriously considered suicide in the past year, and 3% (210/6950) had attempted suicide anytime during their life.

Conclusions: Findings will provide estimates of suicidality among youth with CPI-MIND comorbidity, which will inform intervention planning to prevent loss of life in this vulnerable population. Modeling correlates of suicidality will advance understanding of the relative and joint effects of factors at multiple levels—information needed to target prevention efforts and services. Understanding patterns of psychiatric service use is vital to understanding access and barriers to services. This will inform whether use matches need, identifying opportunities to advise policy makers about upstream resources to prevent suicidality. Importantly, findings will provide robust baseline of information on the link between CPI-MIND comorbidity and suicidality in

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youth, which can be used by future studies to address questions related to the impact of the COVID-19 pandemic and associated countermeasures in this vulnerable population of youth.

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(JMIR Res Protoc 2024;13:e57103) doi:10.2196/57103

KEYWORDS

adolescents; children; chronic disease; epidemiology; mental health; suicidality

Introduction

Background

Suicide remains a leading global cause of mortality among youth aged 15-19 years [1], and findings show that the prevalence of suicide thoughts and attempts has increased from 14% to 18% and from 6% to 9%, respectively, in the past decade [2,3]. There is a disproportionate risk of suicidality in youth with risk factors grouping into several domains: sociodemographic and educational (male sex, sexual minority, low socioeconomic status, and low educational attainment), negative life events and family stressors (marriage dissolution, parental death, adverse childhood experiences, family history of mental illness, or suicidal behavior), and psychological and personality (mental or neurodevelopmental disorder, substance misuse, and hopelessness) [4-6]. There is also accumulating evidence that having a chronic physical illness (CPI; eg, asthma, diabetes, and epilepsy) is an independent risk factor for youth suicidality, with odds ratios (ORs) ≥2.0 compared with youth with no CPI in epidemiological studies [7-11]. Less is known about the mechanisms linking CPI and suicidality among youth. Some research shows abnormal hypothalamic-pituitary-adrenal axis functioning or increased disability [10,12] among those with CPI who have experienced suicidality. Some evidence suggests that mental illness, specifically major depression, mediates the association between CPI and suicidality [13], and other research has found mixed findings regarding the moderating effect of mental illness on the CPI-suicidality association [11,14].

Rationale

Missing from the knowledge base is information on the association between having co-occurring CPI and mental illness or neurodevelopmental disorder (MIND) on suicidality among youth (or any other developmental group). Our forthcoming research in a small clinical sample of youth with CPI has shown increased suicidality among those with co-occurring MINDs. It is unknown the extent to which this preliminary finding can be extrapolated to the general population of youth. Other reports have adjusted for the presence of MIND when investigating suicidality among youth with CPI; however, such approaches do not allow for testing dose-response relationships. One study showed that youth with ≥2 disabilities had a higher likelihood of past-year suicide attempts (16%) than those with 1 (7%) or no disabilities (2%) [15]. Unfortunately, this work did not report the types of comorbidities. Furthermore, there is no information on psychosocial, academic, or substance use outcomes among youth with CPI-MIND comorbidity (or CPI only) who experienced suicidality.

Addressing knowledge gaps regarding the burden of suicidality among youth with CPI-MIND comorbidity and determinants and outcomes associated with suicidality, as well as use of psychiatric services, is desperately needed to inform the provision of timely and appropriate health services to reduce the incidence of suicidality in this vulnerable group. To do this, we need robust contemporary epidemiological data on a representative sample of youth. Our study meets these key criteria and is poised to maximize the impact of the findings. Importantly, information gained from this study can influence practice and policy in terms of best practices in the context of family-centered care and for ensuring successful transition from the pediatric to the adult health system. We describe the protocol for the first study to comprehensively investigate suicidality among youth with CPI-MIND comorbidity.

Objectives and Hypotheses

This study uses epidemiological data from the 2019 Canadian Health Survey of Children and Youth (CHSCY) to study the intersection of CPI, MIND, and suicide ideation and attempts (herein suicidality) in youth. First, we will estimate the prevalence of suicidality among youth with CPI-MIND comorbidity. We hypothesize that youth with CPI-MIND comorbidity will have the highest prevalence of suicidality compared with other morbidity groups: CPI only, MIND only, and healthy controls (youth with no CPI or MIND). Epidemiological evidence of suicidality prevalence stratified by these morbidity groups is lacking; thus, we are unable to hypothesize specific prevalence estimates. However, we anticipate that likelihood of suicidality among youth will show a dose-response effect: CPI-MIND comorbidity > MIND only > CPI only > healthy youth.

Second, we will quantify magnitudes of association between CPI-MIND comorbidity and suicidality, adjusting for sociodemographic or economic factors. We hypothesize that the association between CPI-MIND comorbidity and suicidality will remain strong (OR ≥2.0) after covariate adjustment, indicating the persistence and importance of CPI-MIND comorbidity over and above other factors.

Third, we will identify multilevel correlates (individual, family, and neighborhood) of suicidality among youth with CPI-MIND comorbidity. We hypothesize that correlates of suicidality will include older age, male sex, transgender identity, increased levels of disability, parent psychopathology, strained parent-youth relationships, lower household income, and neighborhood disadvantage. We expect that these correlates will be similar to those found in other morbidity groups, although the magnitudes of association will be larger for those

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with CPI-MIND comorbidity, further highlighting their vulnerability.

Fourth, we will contrast patterns of psychiatric services use among youth with CPI-MIND comorbidity who have versus have not experienced suicidality. We hypothesize that youth with CPI-MIND comorbidity who experienced suicidality will have fewer psychiatric outpatient visits but more psychiatric inpatient and emergency department visits, as well as report more barriers to accessing services. Given the lack of research in this population of youth, we are unable to hypothesize whether associations will be similar to youth with CPI or MIND only.

Finally, we will test whether CPI-MIND comorbidity moderates associations between suicidality and health outcomes. Given the anticipated compounding effect of CPI-MIND comorbidity versus other morbidity groups, we hypothesize that suicidality will be associated with poorer psychosocial and academic outcomes and increased use of substances, and that these associations will be substantially larger for youth with CPI-MIND comorbidity.

Methods

Design and Sample

The CHSCY was conducted by Statistics Canada with data collected (in both official languages, English and French) between February and June 2019 and made available to researchers in July 2020 [16]. The target population was children and youth aged 1-17 years living in the 10 provinces and 3 territories. The sampling frame was the 2018 Canada Child Tax Benefit file, which covers approximately 98% of the target population. The study sample was selected by multistage, stratified, and random sampling of households within the Canada Child Benefit file. The sample is primarily stratified by province, with 2 exceptions: the 3 territories are grouped into a single stratum (“North”), and in Ontario (the most populous Canadian province), the subregions of the Administrative Health Regions within the province form the geographic strata.

From the identified households, there were a total of 47,850 participants aged 1-17 years who were included. Survey weights based on the probability of selection, adjusted for nonresponse and stratification, were created by Statistics Canada to ensure unbiased estimates and a representative sample. Field interviewers contacted households by telephone or in person to speak with the person most knowledgeable (PMK) about the household, described the study, confirmed eligibility, and invited eligible children and youth within the household to participate. The PMK provided self- and proxy-reported data for all children and youth in the study (aged 1-17 years). Youth aged 12-17 years were eligible to provide self-reported data (13,650/47,850, 29% of the CHSCY sample); however, measures of suicidality were asked only of youth aged 15-17 years; thus, we restrict our analyses accordingly (6950/47,850, 15% of the CHSCY sample) [17]. Sample proportions are based on rounded frequencies provided by Statistics Canada prior to data access and vetting of results [16]. Thus, it is reasonable to expect some differences in these values and those available in the master microdata file.

Participants were provided the opportunity to complete the survey on the web. If the e-survey was not completed by March 31, 2019, a Statistics Canada interviewer called and asked the participant to complete the survey over the telephone. The CHSCY also asked the participants to consent to the sharing of their personal information to facilitate data linkage with administrative health data (98% consented) [17].

Ethical Considerations

Participant confidentiality is provided under the Statistics Act and data fidelity is guaranteed by Statistics Canada. Informed consent, collected by Statistics Canada, included the provision for secondary data analysis. All data in the analytic file that will be used by our research team are deidentified. As such, this study is exempt from ethics review by our institutional research ethics board in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), which states, “Research does not require [research ethics board] review when it relies exclusively on information that is publicly available through a mechanism set out by legislation or regulation and that is protected by law” [18].

We will access the CHSCY microdata file via the Canadian Research Data Centre Network, which is an example of information made available through legislation or regulation. According to the TCPS2, “Exemption from REB review for research involving this type of information is based on the presence of a custodian/steward designated in accordance with access to information and privacy legislation who protects privacy and proprietary interests associated with the information (eg, an access to information and privacy coordinator or a guardian of Canadian census data)” [18]. Our application to Statistics Canada to initiate this study was approved (#7327).

Measures

The measures described will be used to address our research objectives. In asking about the physical and mental health of youth, the PMKs are instructed that “long-term conditions are those that are expected to last or have already lasted six months or more and that have been diagnosed by a health professional.”

Physical Health

CPIs in youth were assessed using a self-administered questionnaire. The PMK was asked, “Has this child been diagnosed with any of the following long-term conditions?” Binary responses were provided for the following CPIs: headache, allergies (including food, animal, dust mites, mold, pollens or grasses, chemicals, medicine, or other), hay fever or nasal allergy, asthma, diabetes, and epilepsy. The CHSCY also included PMK-reported height and weight of children, which was used to calculate BMI and subsequently used to classify youth with overweight or obesity according to the World Health Organization [17,19]. These conditions represent the most common CPIs affecting youth [20-23], and the estimated proportions in the CHSCY range from 1% to 20%. Furthermore, a final question asked to the PMKs was whether their children were diagnosed with “any other long-term physical, mental,

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developmental or intellectual conditions" (6%). Because this question aggregated CPIs and MINDs, the PMKs who positively endorse this question, but no other CPI, will be excluded from the analysis.

Mental Health

Using the same leading statement and response options for the assessment of CPI, MINDs in youth were ascertained by asking the PMK about the following: anxiety disorder (including phobia, obsessive-compulsive disorder, or panic disorder), mood disorder (including depression, bipolar disorder, mania, or dysthymia), attention-deficit/hyperactivity disorder, autism spectrum disorder (including autism, autistic disorder, Asperger disorder, or pervasive developmental disorder), and eating disorder (including anorexia or bulimia). The CHSCY also asks the PMKs about whether children have been diagnosed with fetal alcohol spectrum disorder or with a learning disability or disorder. These conditions represent the most common MINDs among youth [24,25], and the estimated proportions in the CHSCY range from 1% to 7%.

Suicidality

Suicidal ideation and attempts were measured by asking youth to respond to 2 standardized questions. These questions align closely with the suicidal ideation and attempt modules of the Self-Injurious Thoughts and Behaviors Interview, a gold standard instrument for assessing suicidality [26]. In the first question, youth were asked, "In the past 12 months, did you ever seriously consider attempting suicide or taking your own life?" In the second question, youth were asked, "Have you ever attempted suicide or tried taking your own life?" Estimates provided by Statistics Canada suggest that nearly 7% and 3% of youth aged 15-17 years positively endorsed the question on suicidal ideation and attempts, respectively.

Disability/Functioning

The CHSCY included the PMK-reported UNICEF/Washington Group child functioning module as a measure of youth disability across the broad domains of physical, behavior, communication, emotions, cognition, and social [27]. This module is psychometrically robust with a strong track record [28-30]. Evidence shows that constructs of functioning, disability, or pain are independently associated with poorer mental health in youth with CPI [31,32] and suicidality [11,13,14,33,34]. Thus, youth disability may confound the association between CPI-MIND comorbidity and suicidality and will be adjusted for in statistical models.

Psychosocial Health

Aligned with self-determination theory and adapted from the Intrinsic Need Satisfaction Scale [35], the CHSCY included 3 need subscales (autonomy, competence, and relatedness). Satisfaction with each need is assessed in 3 different contexts (home, school, and with friends), based on 6 items reported for the past week. Each item is a statement (eg, "I feel I have a choice about when and how to do my schoolwork" for autonomy, "I feel I do things well at home" for competence, and "My friends like me and care about me" for relatedness). Youth reported the extent to which the statements are true or false for them. Higher scores indicate higher levels of need satisfaction and are associated with youth well-being [35]. The CHSCY also included Statistics Canada standardized measures of perceived current life satisfaction using a 10-point scale, usual life stress using a 5-point scale, and usual level of happiness using a 5-point scale.

Education and Extracurricular Activities

Youth academic achievement was measured using an approximate overall grade for the current school year in which response options included percentages (eg, "80%-100%") and associated letter grades (eg, "mainly A"). Youth were asked whether they had educational accommodations at school for the following: permanent physical disability; cognitive, behavioral, or emotional disability; gifted; or other. Past-week school absences and perceptions of how often youth look forward to going to school were assessed using a 4-point scale (never to always). Participation in extracurricular activities related to physical activities with a coach or instructor; music, drama, or art clubs or sessions; and other organized clubs or community groups was assessed using no or yes response options.

Victimization

Past-year bullying was asked of youth using a 5-point scale, which measured the frequency (never to daily) for 10 experiences (eg, made fun of, called names, or insulted; threatened with harm; pushed, shoved, tripped, or spit on; and hurtful information posted on the internet). A composite bullying score will be computed with higher scores indicating greater frequency of bullying.

Physical Activity and Substance Use

Statistics Canada generated derived variables to measure whether youth in the CHSCY adhered to the physical activity standards from the Canadian 24-hour movement guidelines [36-39] over the past week. Variables were derived for low physical activity and moderate to vigorous physical activity, which were dichotomized as meeting versus not meeting the Canadian guidelines.

Youth reported the frequency of their alcohol consumption over the past year (never, once a month or less, 2-3 times a month, and at least once a week) and frequency of past 30-day binge drinking. Statistics Canada also derived a variable that classified youth according to alcohol use (regular, occasional, did not drink in the past year, and never drinker). Questions are also asked regarding 30-day and lifetime cigarette smoking and a derived variable was computed (current or former smoker, experimental smoker, and never smoked). Also included is a measure of past 30-day e-cigarette use, which categorized youth according to use (<1 time per week, 2-3 times per week, 3-5 times per week, daily, or almost every day). Youth reports were also collected to measure frequency of past-year and past 3-month cannabis use (never, once or twice, 1-3 times per month, weekly, daily, or almost daily). The substance use measures are consistent with those derived from previously validated self-report measures appropriate for youth populations including other representative child and adolescent health surveillance studies in Canada [40-43], or measures specifically recommended by the Substance Use and Addictions Program at Health Canada. Consistent with previous research, the

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substance use measures can be used as either frequency or categorical measures.

Psychiatric Service Use

The PMKs were asked about whether their children required or received services for health-related concerns. We restrict our focus to the 3 health services listed in the CHSCY that are in the sphere of mental health care—focusing or controlling behavior, mental health, and learning. For those services that were endorsed by the PMK, questions were asked whether families experienced any of the following barriers to accessing each of the endorsed services: wait time too long, not available, cost, child not eligible, or other reason. The PMKs were also asked about required or received services from specific health professionals. In focusing on mental health professionals, we limit our analyses to "psychiatrists" and "psychologists or counselors" (as listed in the CHSCY). The same questions regarding barriers to accessing these mental health professionals were asked.

The CHSCY also collected individual health numbers of youth participants to link to databases to ascertain detailed health services use data [16,44]. These include the National Ambulatory Care Reporting System and the Discharge Abstract Database, which allow for the investigation of hospital-based mental health services (number of emergency department visits and hospitalizations, length of stay in hospital). As the data custodian, Statistics Canada will conduct the data linkages within their Social Data Linkage Environment and deposit the CHSCY-linked microdata file in our institutional Research Data Centre.

Parent and Family Health

The PMKs provided self-reports of perceived mental health using a 5-point scale, as well as life satisfaction and usual life stress using the same standardized questions described for youth. Canadian low-income cutoffs based on community size and number of individuals within the household will be used as a proxy of socioeconomic disadvantage [45].

Sex, Gender, and Sexual Attraction

Youth and their PMK reported on their individual (1) sex at birth and (2) current gender identity. Regarding gender identity, the CHSCY included the following for participants: "Gender refers to current gender which may be different from sex assigned at birth and may be different from what is indicated on legal documents." Available response options are male, female, or please specify. Statistics Canada then used these 2 variables (sex at birth and current gender identity) to derive a variable for cisgender and transgender participants. This 2-step consideration of gender identity is the current gold standard [46]. Sexual minority status will be measured using youth and PMK-reported gender (male, female, and other) and sexual orientation using an instrument recommended by the Sexual Minority Assessment Research Team and included in the CHSCY [47]. Following previous work [48], we will construct the following sexual minority categories: heterosexual (only opposite gender attraction), boys who were only or mostly attracted to boys, girls who were only or mostly attracted to girls, those attracted to >1 gender (equally attracted to female and male individuals or mostly attracted to opposite gender), and unsure.

Community Factors

The CHSCY included an urban and rural area classification based on standardized thresholds for community size. This community-level characteristic will be used as a proxy for mental health service availability [49]. The PMKs are asked about whether their neighborhood is safe for children to play outside during the day (very unsafe to very safe). Neighborhood safety has been shown to influence child and adolescent health and health behaviors [50-53] but has not been used to examine differential effects for youth with versus with no CPI-MIND comorbidity.

Demographic Factors

Youth and their PMK reported on several demographic characteristics for themselves and their family, including, age, educational attainment, marital status, household income, number of people in the household, ethnicity, country of birth, and year of immigration.

Analysis

Youth CPI-MIND comorbidity will be operationalized as the co-occurrence of ≥1 PMK-reported CPI and ≥1 PMK-reported mental illness. The complex design of the CHSCY requires that along with sampling weights, bootstrap weights be used to produce unbiased population estimates of variances for prevalence and model parameters, respectively [16]. Our approach will be to include youth and parent sex, gender identity, and sexual orientation as covariates in all our statistical models. If any of these variables are found to moderate any associations outlined in our research objectives, we will follow best practices [54], whereby sex- or gender-stratified models will be computed, reported, and interpreted to ensure that findings are broadly applicable.

Prevalence of suicidality across morbidity status (CPI-MIND comorbidity, CPI only, MIND only, and healthy controls) will be computed, along with associated 95% CIs for objective 1. The Rao-Scott χ^2 test will assess whether prevalence differs across morbidity groups. Where possible, analyses will be conducted separately for suicidal ideation and suicide attempts, although we recognize that because the prevalence of suicide attempts is rare (3%), such investigations are likely to be underpowered and thus, exploratory.

Logistic regression, adjusting for relevant covariates, will be used to compute ORs and 95% CIs for the association between CPI-MIND comorbidity and suicidality (objective 2). Contrasts will be specified to determine whether ORs are different across morbidity groups. Covariates will be added to the unadjusted model sequentially in blocks that correspond to these levels: (1) youth: age, sex, gender identity, sexual attraction, immigrant, ethnicity, disability, victimization, and strained relationships with parents; (2) PMK: sex, gender identity, sexual attraction, education, immigrant, ethnicity, perceived mental health, and low-income household; and (3) community: size and neighborhood safety.

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A multinomial logistic regression model will be used to address objective 3, correlates of youth suicidality with CPI-MIND comorbidity, whereby risk factors for morbidity groups will be compared with reference to healthy controls. Contrasts will be specified to determine whether ORs for statistically significant correlates of suicidality are different across morbidity groups—an important effort to identify morbidity-specific suicidality profiles among youth. Covariates from objective 2 will be added to the model in a single block as main effects. A second block will include product-term interactions that will be explored as potential moderators of the hypothesized associations between CPI-MIND comorbidity and suicidality.

To address objective 4, logistic regression models will be computed to examine potential differences in use of psychiatric services between youth with CPI-MIND comorbidity who have experienced suicidality and youth with CPI-MIND comorbidity who have not experienced suicidality. These logistic regression models will examine the independent outcomes of psychiatric service use or health professional consultations as listed in the CHSCY, as well as emergency department visits or hospitalizations for mental health as recorded in the National Ambulatory Care Reporting System and Discharge Abstract Database in the year prior to and the 2 years after the CHSCY. Poisson regression models will examine differences in the number of reported barriers for using psychiatric services, number of emergency department visits and hospitalizations, and associated lengths of stay in hospital between youth with CPI-MIND comorbidity who have versus have not experienced suicidality. Our approach follows definitions and codes used in the Mental Health and Addictions Scorecard and Evaluation Framework at the Institute of Clinical and Evaluative Sciences [55].

To determine whether CPI-MIND comorbidity moderates associations between suicidality and health outcomes in objective 5, product-term interactions will be included in a series of independent linear or logistic regression models. Outcomes include psychosocial health, physical activity, substance use, academic achievement, extracurricular activities, and victimization. In the presence of a statistically significant interaction, post hoc moderator analyses will be conducted to identify the direction of the effects [56].

Study Power

The focus on youth aged 15-17 years suggests that an anticipated sample size (n=6950) will be available for analysis. Given the estimated proportions of suicidality and CPI-MIND comorbidity in the CHSCY, recent simulation studies for logistic and multinomial regression [57-60], as well as our calculations for linear regression [61], suggests that our proposed analyses are adequately powered at $1–\beta=.80$ and $\alpha=.05$ to address our research objectives. Specifically, χ^2 tests used in objective 1 require a total sample size of 2268 to detect small differences across morbidity status ($\omega=0.1$). Logistic regression models used to address objectives 2, 4, and 5 require a total sample size of 2262 to detect an OR of 2.0 for a main effect and a sample size of 6691 to detect an OR of 2.5 for product-term interactions. Similarly, linear regression models with ≤30 covariates will be adequately powered to detect very small effects ($f^2=0.01$) with sample sizes of 1785 and 4195 for main and interaction effects, respectively. The multinomial regression model with unequal morbidity group sizes, 16 covariates, and 30 events per variable that will be used to address objective 4 requires a sample size of 5085. To maximize the analytical sample, an appropriate imputation technique, such as multiple imputation or full information maximum likelihood, will be used to account for data missing at random. Based on our previous experience working with epidemiological data in this field of study (which detected small to large effect sizes) [10,11,32,62-65], we expect that the sample size available in the CHSCY is sufficient.

Results

Our study began in November 2023, funded by the American Foundation for Suicide Prevention (SRG-0-008-22), with linkage of the CHSCY to National Ambulatory Care Reporting System and Discharge Abstract Database in collaboration with Statistics Canada. Access to the CHSCY microdata file was made available to our research team in May 2024. Initial examination of CHSCY data shows that approximately 20% (1390/6950) of youth have CPI, 7% (490/6950) have MIND, 7% (490/6950) seriously considered suicide in the past year, and 3% (210/6950) had attempted suicide anytime during their life.

Discussion

Principal Outcomes

In this study, we will estimate the prevalence of suicidality among youth with CPI-MND comorbidity; quantify the magnitudes of association between CPI-MND comorbidity and suicidality, adjusting for relevant sociodemographic and economic factors; identify multilevel correlates of suicidality among youth with CPI-MND comorbidity; contrast patterns of psychiatric services use among youth with CPI-MND comorbidity who have versus have not experienced suicidality; and test whether CPI-MND comorbidity moderates associations between suicidality and health outcomes. Each of these objectives will be examined in reference to other morbidity groups (ie, healthy, CPI only, and MIND only) in the sample.

Limitations

We anticipate some limitations to this study. First, the CHSCY relies upon PMK-reported diagnoses of a nonexhaustive list of CPIs and MINDs in youth. This can be problematic for chronic conditions with very low prevalence [66], leading to misclassification and attenuation of measures of association. However, evidence suggests that this bias is negligible [67]. Furthermore, the most common CPIs and MNDs affecting youth were included in the CHSCY, suggesting that coverage will be acceptable [20-25]. Concordance checks with diagnostic codes in the linked administrative health databases will also be conducted, if feasible. Second, given some evidence that associations between suicidality and CPIs may be heterogenous [9], we will test whether prevalence of suicidality across CPI-MIND comorbidities (eg, asthma-anxiety and diabetes-depression) is different. If this test is nonsignificant, then it would indicate support for the noncategorical approach to understanding suicidality among youth with physical-MND

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comorbidity [68,69]. The noncategorical approach posits—and has empirical evidence to support—that while differences in mental health or suicidality outcomes are large between youth with and with no CPI, differences across illnesses are relatively small [11,31,70]. Aggregating CPI-MIND comorbidities into a single variable will ensure model parsimony and statistical efficiency in addressing the research objectives. If the noncategorical approach is not supported, then CPI-MIND comorbidities will be included as dummy variable covariates in our models. Third, temporal ordering of study variables in relation to CPI and MIND onset, as well as suicidality, is limited in the CHSCY, thus preventing inferences on causality. We will explore opportunities to use PMK-reported age of diagnosis for physical and mental illnesses to untangle temporal associations; however, missing data for these variables are likely; thus, possible misclassification and subsequent bias induced by the timing of diagnoses are anticipated.

Conclusions

The CHSCY is a large representative study and is the most contemporary national pre–COVID-19 pandemic data set in Canada. As a study led by Statistics Canada, the data are of the highest quality and primed for immediate use. Importantly, findings will provide a standardized baseline of information on the link between CPI-MIND comorbidity and suicidality in youth, which can be used by future studies to address questions related to the impact of COVID-19 and associated countermeasures in this vulnerable population. Furthermore, linking the CHSCY to national administrative health records provides an unprecedented opportunity to compare and contrast patterns of psychiatric service use among youth who have experienced suicidality across morbidity groups. Not only do such data provide accurate accounts of actual service use by avoiding recall biases associated with self-reported services use but linkage also permits the examination of potential barriers to psychiatric service use. There is a pressing need for this information to inform policies related to integrated physical-mental health services, as well as ensuring that supportive resources are available as youth transition from the pediatric to adult health system.

Acknowledgments

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Data Availability

The microdata file used in this study is made available by Canadian Research Data Centre Network. An application for data access can be made on the web [71].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the American Foundation for Suicide Prevention.
[PDF File (Adobe PDF File), 230 KB - resprot_v13i1e57103_app1.pdf]

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Abbreviations

CHSCY: Canadian Health Survey of Children and Youth (CHSCY)
CPI: chronic physical illness
MIND: mental illness or neurodevelopmental disorder
OR: odds ratio
PMK: person most knowledgeable
TCPS2: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

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Protocol

Rehabilitation at Home With the Development of a Sustainable Model Placing the Person's Needs and Environment at Heart: Protocol for a Multimethod Project

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Abstract

Background: Each year, more than 1.5 million people in Europe have a stroke, and many experience disabilities leading to activity and participation restrictions. Home-based rehabilitation is the recommended approach for stroke rehabilitation, in line with the international shift to integrated care. Despite this, rehabilitation often focuses on the person's physical functions, not the whole life situation and opportunities to live an active life. Given that rehabilitation today is often provided in the person's home, there is a need to develop new models that consider the rehabilitation process as situated in the everyday living environment of persons with stroke. This project is grounded in experiences from our ongoing research, where we study the importance of the home environment for health and participation among persons with stroke, rehabilitated at home. This research has shown unmet needs, which lead to suboptimal rehabilitation outcomes. There is a need for studies on how to use environmental resources to optimize stroke rehabilitation in the home setting.

Objective: The overarching objective of the project is to develop a new practice model for rehabilitation where the needs of the person are the starting point and where the environment is considered.

Methods: The project will be conducted in partnership with persons with stroke, significant others, health care professionals, and care managers. Results from a literature review will form the base for interviews with the stakeholders, followed by co-designing workshops aiming to create a new practice model. Focus groups will be held to refine the outcome of the workshops to a practice model.

Results: This 4-year project commenced in January 2023 and will continue until December 2026. The results of the literature review are, as of April 2024, currently being analyzed. The ethics application for the interviews and co-design phase was approved in October 2023 and data collection is ongoing during spring 2024. We aim to develop a practice model with stakeholders and refine it together with care managers and decision makers. The outcome is a new practice model and implementation plan, which will be achieved in autumn 2026.

Conclusions: The project contributes with a prominent missing puzzle to optimize the rehabilitation process by adding a strong focus on user engagement combined with integrating different aspects of the environment. The goal is to improve quality of life and increase reintegration in society for the large group of people living with the aftermath of a stroke. By co-designing with

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multiple stakeholders, we expect the model to be feasible and sustainable. The knowledge from the project will also contribute to an increased awareness of the importance of the physical environment for sustainable health care. The findings will lay the foundation for future upscaling initiatives.

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KEYWORDS

co-design; early supported discharge; home; integrated care; life space mobility; multi-methods; physical environment; person-centered care; social environment; stroke rehabilitation

Introduction

Background

This project (InHome) focuses on developing an implementable practice model that uses person-centered care principles. Our primary goal is to improve the quality of life of people with stroke by integrating their environment into the rehabilitation process. The intervention is complex and requires careful development, evaluation, and formulation of practical implementation strategies before scaling up. In InHome, the concept of the physical environment is fundamental. It consists of the built environment (eg, stairs or doors), natural environment (outdoor surfaces), and social factors such as human interactions [1]. The environmental impact on a person's health and ability to perform daily activities depends on the person's cognitive and physical ability and the demands of the environment. The same environment can facilitate one activity for one person and be an obstacle for another.

Life After Stroke

Each year, more than 1.5 million Europeans will have a stroke [2]. The number is expected to rise partly due to an aging population and improved survival rates [3,4]. Many stroke survivors face lasting cognitive, physical, emotional, and psychological challenges. This can be manifested as memory loss, communication difficulties, reduced mobility, and emotional impact such as depression and anxiety [5-7]. Such impairments can lead to decreased social interactions and limited community mobility, resulting in diminished participation in meaningful activities (eg, activities outside the home and leisure activities) and social engagements. This constrained living space not only impacts daily living and well-being but also poses a risk of isolating persons with stroke from essential social resources and services [8,9]. Moreover, studies have shown that people who have had a stroke tend to make fewer social trips compared with healthy adults in general [9,10]. These limitations have profound implications for daily life, health, and overall well-being, highlighting the critical importance of community integration in the rehabilitation of stroke survivors [11].

The overall complexity of life after stroke is often underestimated and requires a holistic and integrated support system [11,12]. This research underscores the necessity of including factors of the physical environment at home and in the neighborhood in rehabilitation, recognizing the profound influence of the environment on recovery and everyday life [11,13,14]. Issues, such as accessibility challenges and fall risks, are common [5], with an inaccessible living environment correlating with poorer health perceptions and recovery outcomes [13]. Addressing these environmental challenges is crucial, but equally important is the recognition of the individual's role and agency in the recovery process. This dual focus on environmental adaptability and personal empowerment is essential for a comprehensive approach to poststroke care.

The recovery process poststroke extends beyond the hospital, and many feel abandoned and excluded from decision-making and rehabilitation planning, demonstrating a strong need for more person-centered approaches [5,15,16]. Research shows that recovery after a stroke is best supported when the person and family feel that they can manage daily life and control the rehabilitation and recovery process and activities with the support of resources in the person's environment [17,18].

The environment plays a crucial role in supporting individuals who have experienced a stroke. An environment that allows individuals to control their choices and activities fosters a sense of autonomy, which is closely related to self-efficacy. Self-efficacy, an individual's belief in their capabilities to execute behaviors necessary to make specific performance achievements [19], can significantly impact their motivation, well-being, and recovery outcomes. In that sense, an accessible environment reduces physical barriers, enabling individuals to perform daily tasks more independently. This sense of independence can enhance self-efficacy as the person recognizes their ability to manage daily life. Moreover, an environment that can be easily modified to suit the individual's changing needs supports ongoing engagement in activities, promoting a sense of control and competence. A safe and secure environment reduces the fear of injury or fall, allowing the individual to engage in activities confidently, thus fostering a sense of self-efficacy. An environment that facilitates social interactions and support networks can provide encouragement, feedback, and assistance, all of which can bolster an individual's self-efficacy.

Stroke Care and Rehabilitation

In Sweden, a person with a stroke will meet a decentralized, fragmented, and complex health care system, with specialized rehabilitation managed by regional health care providers. After the acute phase, the responsibility for long-term support is shifting to the municipalities [20]. To mitigate these challenges and enhance integrated care, early supported discharge (ESD), an internationally recommended approach in stroke rehabilitation, is practiced in certain regions in Sweden. ESD involves persons with mild to moderate stroke continuing their rehabilitation at home guided by a multidisciplinary team [17].

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Concurrently, there is a transformative shift in stroke care, with shorter hospital stays. This shift necessitates a broader responsibility for individuals and their families in managing poststroke recovery at home [21]. This transformation emphasizes the importance of patient empowerment, self-management of health, and collaborative decision-making with health care providers. Ensuring stroke survivors and their families are well-equipped to navigate these complexities is essential for optimizing recovery and quality of life [22,23]. Moreover, it highlights the crucial role of the home environment, which can simultaneously serve as a support and present a unique challenge [16,24]. For example, being at home in a familiar place can support the recovery process. It creates opportunities for rehabilitation in an environment meaningful to the person rather than the hospital, allowing problem-solving and planning in a meaningful context. However, people with stroke report that health service providers rarely ask about their home environment, and its impact on their ability to reintegrate into society after stroke is often overlooked during the rehabilitation process [16]. Instead, existing rehabilitation models focus on functional abilities rather than participation in meaningful activities. Further, the role played by the environment is regarded as a side finding in stroke research [25].

To sum up, after a stroke, individuals may face challenges spanning cognitive, physical, emotional, and psychological domains, often leading to reduced social interactions, limited mobility in society, and a subsequent reduction in participation in meaningful activities. The trend toward shorter hospital stays has shifted responsibility for poststroke care to the home environment, requiring robust support networks and resources. However, existing care models cannot meet these needs, especially when it comes to integrating the physical environment to support the person recovering from a stroke at home.

Thus, there is a critical gap in the rehabilitation process that addresses the complex and multifaceted needs of stroke survivors in their physical environment. This gap highlights the need for innovative and holistic models of care that are co-designed with input from people with stroke, relatives, and health care professionals. Such models must integrate the physical environment of the stroke survivor, ensuring tailored and practical support. To ensure feasibility and scalability, the Medical Research Council (MRC) recommends a step-by-step approach to the development, evaluation, and implementation of interventions. This approach ensures that interventions are robust, research-based, and ready for large-scale implementation [26]. In this new era of person-centered care, our initiative aims to bridge this gap, developing a holistic, co-designed practice model for poststroke rehabilitation in which the physical environment is integrated, and preparing it for widespread use and implementation.

Study Objectives and Research Questions

InHome aims to develop a new practice model that integrates environmental factors in rehabilitation after a stroke for a more person-centered service. Following the MRC's [23] recommendations for developing complex interventions, we will involve key stakeholders to develop and evaluate a new intervention aiming to improve health-related outcomes and support new effective working methods for rehabilitation services in the home.

The specific research questions are as follows: How do physical (ie, built, natural, and social) environmental factors contribute to supporting a person-centered rehabilitation process in the individual's activity space? What methods and activities for integrating environmental factors to support a person-centered rehabilitation process are described in the literature? What experiences and expectations do persons with stroke, significant others, health care professionals, and care managers have of integrating environmental factors into the rehabilitation process? (2) How could a practice model that integrates physical environmental factors be designed to meet the expectations and requirements of persons with stroke and health care services, to make efficient use of resources for rehabilitation in the home? What environmental factors should be integrated into a new practice model to support a person-centered care rehabilitation process? How should a feasible practice model be designed? (3) What are the critical mechanisms for integrating environmental factors into stroke rehabilitation at home? How is the model perceived and evaluated by decision makers regarding its sustainability, for example, potential benefits including health outcomes, cost-effectiveness, resources, feasibility, and acceptability? What are the most important facilitators and obstacles to implementing the new practice model?

Theoretical Framework

Several theoretical models focusing on person-environment interactions underpin InHome. The person-environment-occupation model [27], the Ecological Theory of Aging [28], and the International Classification of Functioning, Disability, and Health (ICF) [29] show that the environment comprises a multitude of facilitating or hindering factors external to the person. The models describe that a good fit between a person's (P) functional abilities and the demands of environmental factors (E) leads to positive outcomes such as increased independence and overall well-being (P-E fit). Hence, to optimize rehabilitation outcomes, it is important to make use of a person's environment and be aware of facilitating and hindering factors.

InHome is also grounded in Bandura's social cognition theory and the key constructs of self-efficacy and collective self-efficacy [19]. These concepts see individuals as capable with unique experiences and resources and describe people's or group's beliefs about their ability to achieve specific performance levels, which then affects their control over life events [30].

Furthermore, we will use the concept of activity space, which has been defined as "the subset of all locations within which an individual has direct contact as a result of his or her day-to-day activities" [31] to operationalize the term physical environment. The value of the idea of activity space for our project lies in the fact that it is person-centered: it encompasses the area and locations that an individual uses, for different activities, such as work and leisure, using different modes of transport such as the car or bicycle. An individual's activity space is likely to

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consist of different important nodes or locations from which activities are undertaken [32]. Typically, the most important node is the home, especially in populations who experience impairments in everyday life such as older adults [33]. The same is likely to apply to people affected by stroke. Figure 1 provides an abstract representation of an activity space.

Figure 1. An example of how a person's activity space might decrease in case of an illness like a stroke. Dotted blue lines represent meaningful places that are no longer accessible due to functional limitations and barriers related to the mode of transportation or the physical environment. Nondotted lines represent places that are still accessible.

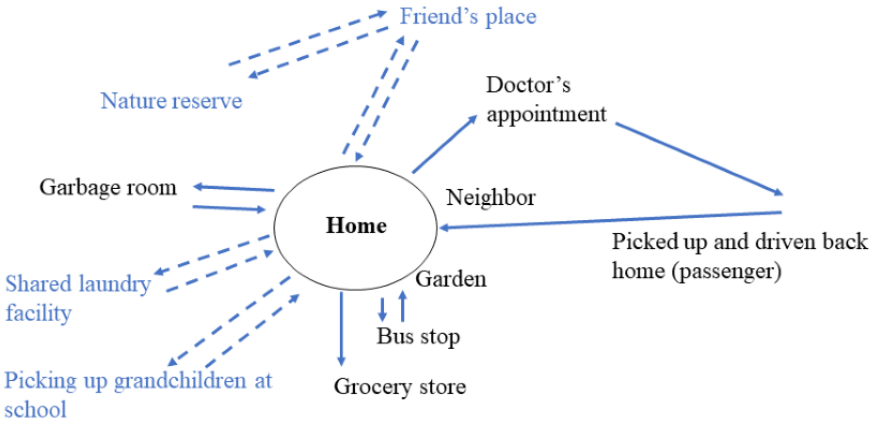

Methods

Overview

InHome has a multimethod approach across 3 studies (Figure 2). We will use a research design that combines knowledge synthesis, and qualitative and co-design methods to investigate important environmental factors and implementation strategies for a new practice model that integrates environmental factors in the rehabilitation of people with stroke. To ensure a successful co-design process, we will use the PRODUCES (Problem Objective Design (end-) Users Co-creators Evaluation Scalability) [34] framework, which provides a systematic planning method for conducting, evaluating, and reporting research findings with specific stakeholder involvement and scientific consistency.

The first study, a knowledge synthesis, involves a scoping review which along with interviews aims to identify the critical factors for integrating environmental factors to support the person-centered rehabilitation process in the home. The knowledge synthesis will inform the following co-design of the intervention and implementation strategies, which is the second study. In the third study, we will involve the perspectives of decision makers to refine the model further. Figure 2 provides an overview of the project.

Figure 2. Illustration of the 3 studies in the multi-method project, InHome, aiming to develop a new working model for person-centered, home-based stroke rehabilitation integrating environmental factors.

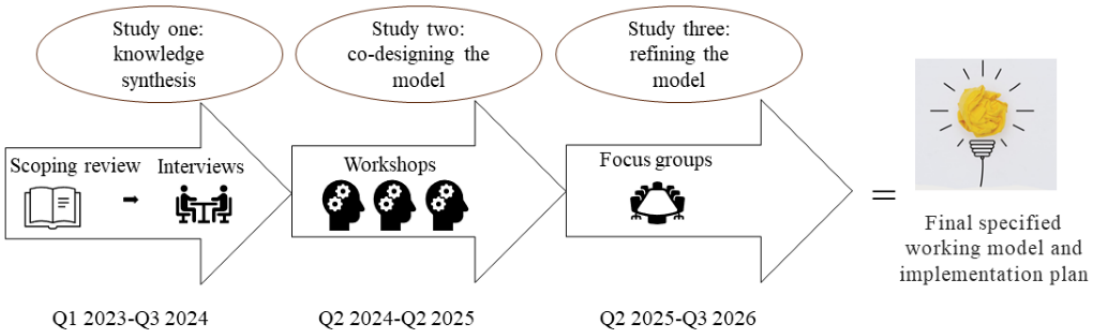

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Addressing Research Question 1: Knowledge Synthesis

Scoping Review

A total of 2 sources of data will be used to learn about essential environmental factors in the rehabilitation process and how those could be integrated into the process. First, we will conduct a scoping review [35] to update the evidence on the key environmental factors that are important to support a person-centered rehabilitation process in the home. The completeness of the review will be constrained by the availability of relevant published research, policy, and gray literature within the last 10 years (2012-2023). The search strategy will focus on the sensitivity of terms relating to rehabilitation at home (eg, ESD, integrated care) and environmental factors (eg, physical, natural, and built) to identify and capture the most relevant and up-to-date research, policy, and gray literature. A systematic process will be used for item searching, selection, screening, coding, critical appraisal, and synthesis, building on methods outlined by Arksey and O'Malley [35] and recommendations by Levac et al [36].

Participants

Second, we will perform individual interviews with a strategic sample of 25 recruited stakeholders: people with stroke (n=5), significant others (n=5), health care professionals (n=10), and care managers (n=5). We will recruit people with stroke and significant others through stroke wards and outpatient wards. Persons with stroke meet the inclusion criteria if they have a diagnosed moderate stroke and have a focal neurological deficit when discharged, are 18 years or older, and can communicate and formulate answers to questions. We will also ask the persons with stroke to name a significant other if possible. We will recruit health care professionals (ie, occupational therapists, physiotherapists, nurses, and health care assistants) and care managers through collaboration with stroke units and municipalities that deliver home rehabilitation after stroke in Sweden. We will strive to balance the different occupational groups from the whole chain of care (ie, professionals employed in regions, as well as in municipalities).

Interviews

An interview guide will be designed by the research team, with the details aimed at the different target groups. First, participants will be encouraged to discuss their own rehabilitation experiences at home after a stroke, with a particular focus on the physical environment and participation. Second, participants will be invited to (1) discuss the results of the review; (2) comment on their views and understanding of critical environmental factors; and (3) recommend optimized strategies that include the environment and are likely to improve rehabilitation outcomes after stroke (eg, increased participation, self-efficacy, and mobility outside the home). For the persons with stroke, we will also use place-mapping. This is a participatory visualization technique that has been developed for studying persons with stroke. By reflecting on important places and modes of transport together, the interviewers and participants develop a place map together. Through the participatory process, the researchers can ensure that the collected data are comprehensive and valid. A place map represents the participant's activity space in a schematic manner (see Meijering et al [14] for a detailed description of the method). The interviews will be audio recorded and transcribed verbatim.

Analysis

We will use qualitative content analysis [37], facilitated by the NVivo software (Lumivero) [38] to analyze the data. The output from the knowledge synthesis is a specification of important environmental factors for a person-centered rehabilitation process and implementation strategies.

Addressing Research Question 2: Co-Designing the Intervention

Participants

In a second step, the same participants (who participated in the interviews) will be invited, with additional recruitment in case of dropout. The participants will then be divided into 2 groups.

Co-Designing Workshops

The 2 groups will participate in workshops in a co-designing process [39] guided by the "double diamond" method [40]. This means that we together with the participants (1) "discover," that is, develop a deeper understanding of the problem or challenges that exist, (2) "define," further define the problem and brainstorm about potential solutions, (3) "develop," develop a prototype or model, and (4) "deliver," deliver a model. The method has been frequently used in the research group. The 2 parallel co-design processes will encompass 3 half-day workshop meetings (in person or via the web), facilitated by people in the research team. We will use an iterative process of collecting data, moving between data collection, analysis, modifications to the intervention, and then further data collection. Data will be collected through participatory observations (ie, reactions, interactions, and potential conflicts), interviews, field notes, and photos of, for example, notice boards used during the workshop. The meetings will be audio recorded.

Analysis

Meeting minutes, interviews, and field notes will be transcribed and analyzed between workshop meetings using qualitative content analysis to reveal patterns or underlying themes in the content [37]. Findings will be brought to the following meeting. The output from co-designing the intervention is a first draft of the practice model and implementation plan.

Addressing Research Question 3: Refining the Intervention

Participants

To refine the developed practice model and produce an intervention and implementation plan (output of the project), we will collect data from a series of focus groups with decision makers in health care and spatial planning. A notable advantage of this approach lies in the collaborative dynamics created within a group [41], fostering momentum and facilitating the concurrent emergence of opinions, beliefs, feelings, and attitudes alongside individual experiences [42]. We will recruit 8 people for each focus group (n=16) [42], through the research group's

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established networks. Heterogeneity will be attained in diverse occupations, age, sex, and geographical factors (ie, urban or rural) to mirror both similarities and differences to enable diverse perspectives to emerge.

Focus Groups

A total of 2 focus groups with decision makers in health care and spatial planning, such as officials responsible for the operation of health care environments in the region and municipalities, will be formed and meet 2 times each. The interview guide will be developed based on the draft from the co-design phase. In total, 2 moderators will lead each group; 1 will lead the discussions; and 1 will observe group interactions and listen to the discussions. The observing moderator will take field notes on settings and group dynamics, as well as pose clarifying questions. At the end of each focus group session, the observing moderator will give a summary of the core issues discussed and allow participants to comment and suggest amendments. The meetings will be audio recorded. After round 2, audiotapes will be transcribed verbatim.

Analysis

Analyses will be accomplished according to Krueger and Casey [42]. The moderators will read the transcripts and listen to the recordings to get a feeling for the dynamics of the discussions and independently code the data. After the coding, the units of meaning will be categorized, and then themes will be formulated for further analysis.

Ethical Considerations

All parts of InHome will be conducted following the Helsinki Declaration of Ethics in research. Ethical approval for the first study, the knowledge synthesis, was obtained from the Swedish Ethical Review authority in October 2023 (ID 2023-05164-01). Data will be registered and stored under the Personal Data Act and Dalarna University rules. We will comply with international agreements and rules. A data management plan will be developed according to Dalarna University rules. The individual data will be treated confidentially and if participants wish to withdraw their participation, their data will be removed from the database. Data from all phases will be treated on a general level, that is, individuals will not be identified in any publications. Finally, data of personal information and registration of databases will follow the General Data Protection Regulations. The research group has extensive experience in performing research on persons with frail health such as older persons or persons with neurological illnesses. Informed consent from the person considered to be included in the study will be obtained. Written and oral information on the study purpose and what participation would entail will be given before the informed consent. No compensation will be provided. The participants will also be informed about confidentiality and their right to withdraw from the study at any time.

Results

This 4-year project commenced in January 2023 and will continue until December 2026. The scoping review is ongoing, and the results are, as of April 2024, currently being analyzed. The interviews, based on the results, started during the last quarter of 2023. The co-designing workshops, based on the interviews, are planned for autumn 2024, and refinement of the intervention in spring 2025. A final practice model and implementation plan is planned to be achieved in autumn 2026.

Discussion

Principal Findings

This project sets out to coproduce a new practice model that integrates environmental factors in rehabilitation after a stroke for a more person-centered service. We expect that the new model will lead to improved quality of life and increased reintegration in society for the large group of people who are rehabilitated at home after a stroke. In the long run, the knowledge from the project contributes to an increased awareness of the importance of the physical environment for sustainable health care and thus supports improved, strategic, and sustainable planning of living environments.

In Sweden and many other countries, care and rehabilitation are increasingly transferred to the local community and people's ordinary homes [43]. The Government and Sweden's Municipalities and County Councils (Sveriges Kommuner och Regioner) have emphasized the need to address the physical environment's potential for the success of this new reform of health care. Even so, research seldom considers the role of the physical environment; instead, the focus is on how biomedical and a person's physical functions influence participation and life after stroke [5]. Given that current rehabilitation models are far from adequately supporting persons with stroke after hospital discharge [44], future research and stroke health care policy initiatives should focus on the diverse and long-term needs of this population [45] and consider how the environment can be integrated to support these needs [5]. This is important because stroke survivors constitute a large group in society and today many of them report feeling abandoned and excluded from decision-making and rehabilitation planning, demonstrating a strong need for more person-centered approaches [5,15,16].

The qualitative data from the interviews will provide valuable insights into which strategies and environmental factors to focus on to improve rehabilitation outcomes after stroke (eg, increased participation, self-efficacy, and mobility outside the home). This participatory approach addresses the often-reported gaps in patient engagement in care and rehabilitation planning described above, fostering a model that is both practical and implementable. Moreover, the co-design process will occur in several iterative activities to inform the practice models' development, design, and evaluation. It enables an accumulation of knowledge and increased mutual understanding between stakeholders and researchers and contributes to nonlinear learning that provides solid knowledge production [46]. Participation is crucial for designing user-friendly new methods, processes, or products as people participate in shaping models that represent their needs, experiences, and preferences.

Turning to place mapping, previous research has shown that this method is useful for gaining information about a person's important places that are no longer accessible [14]. Our approach to using this method as part of the interviews will improve our

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understanding of barriers in the physical environment, as well as enhance the validity of the in-depth interview data. Moreover, using visual representations of a person's activity space can facilitate a dialogue around meaningful places and how health care best can support access to them.

In Sweden, a high prevalence of environmental barriers in ordinary housing has been shown, and since persons with stroke often have functional limitations, they might experience accessibility problems, which can hinder activities in daily life and thus have negative consequences for health and well-being [47,48]. Many barriers in the home can easily be removed yet a large proportion of persons poststroke (range 5%-39%) report home adaptation needs as unmet [5]. Unmet needs related to access to transportation and mobility are also evident in the literature, for example, [49] highlighting a need for considering and supporting out-of-home mobility in the rehabilitation process.

The dissemination of results includes a range of activities such as conferences and seminars and published results in traditional open-access high-impact journals, and popular science articles in public press. In addition, our research method involves a continuous and integrated knowledge translation process because the project will be carried out in close collaboration with relevant actors. It enables knowledge and competence sharing between researchers and users of the results. We will also use our established networks of end user organizations for stroke care to spread findings in newsletters and on the organizations' websites.

Strengths and Limitations

InHome is conducted in Sweden, but the knowledge gained from the project is expected to have international health care policy relevance. Hence, the trend of shorter hospital stays, and continued care and rehabilitation is a global phenomenon that requires organizational change, as well as new approaches to meeting with persons with stroke and their relatives.

Our goal is to develop a practical and implementable model that is based on users' needs. Co-designing is a fruitful method but there is a risk it is found too demanding. The participants may also come to insight into shortcomings in their rehabilitation process, but this is something we are prepared for. In addition, following MRC and PROCEDURES will support the quality and standardization of the development.

The small sample can be seen as a limitation. However, the focus of this project is on developing a new practice model; future studies with larger sample sizes are needed to evaluate the intervention through stages of feasibility testing and to establish effects and cost-effectiveness, knowledge needed for implementation (MRC). Finally, we will include participants with stroke receiving ESD, meaning they had mild to moderate stroke; experiences of those with severe stroke are yet to be investigated.

Conclusions

InHome contributes with a prominent missing puzzle to optimize the rehabilitation process by adding a strong focus on user engagement combined with the integration of different aspects of the environment. The goal is to improve the quality of life and increase reintegration in society for the large group of people living with the aftermath of a stroke. InHome goes beyond traditional rehabilitation models that focus on physical functions and less on the whole life situation and opportunities to live an active life. We expect that the co-design method will make the model feasible and sustainable. In addition, the knowledge from the project will contribute to an increased awareness of the importance of the physical environment for sustainable health care. The findings will lay the foundation for future upscaling initiatives.

Acknowledgments

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Data Availability

The data sets generated during this study are not publicly available due to privacy or ethical reasons, but anonymized data are available from the corresponding author on reasonable request.

Authors' Contributions

MK and ME generated the project idea, designed the project, and wrote the proposals for funding in close collaboration with all coauthors except LN. LN wrote the manuscript, assisted by MK and ME, with critical reviews from all coauthors. LM provided details regarding activity space and place mapping. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Assessment of application.
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e56996_app1.pdf]

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Abbreviations

ESD: early supported discharge
ICF: International Classification of Functioning, Disability, and Health
MRC: Medical Research Council
PRODUCES: Problem Objective Design (end-) Users Co-creators Evaluation Scalability

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Protocol

Developing Evidence to Support Policy: Protocol for the StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT)

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Abstract

Background: All federal agencies are required to support appropriation requests with evidence and evaluation (US Public Law 115-435; the Evidence Act). The StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) is 1 of 6 centers that help the Department of Veterans Affairs (VA) meet this requirement.

Objective: Working with the existing VA evaluation structure, SALIENT evaluations will contribute to (1) optimize policies and programs for veteran populations; (2) improve outcomes regarding health, equity, cost, and provider well-being; (3) advance the science of dissemination and knowledge translation; and (4) expand the implementation and dissemination science workforce.

Methods: We leverage the Lean Sprint methodology (iterative, incremental, rule-governed approach to clearly defined, and time-boxed work) and 3 cores to develop our evaluation plans collaboratively with operational partners and key stakeholders including veterans, policy experts, and clinicians. The Operations Core will work with evaluation teams to develop timelines, facilitate work, monitor progress, and guide quality improvement within SALIENT. The Methods Core will work with evaluation teams to identify the most appropriate qualitative, quantitative, and mixed methods approaches to address each evaluation, ensure that the analyses are conducted appropriately, and troubleshoot when problems with data acquisition and analysis arise. The Knowledge Translation (KT) Core will target key partners and decision makers using a needs-based market segmentation approach to ensure that needs are incorporated in the dissemination of knowledge. The KT Core will create communications briefs, playbooks, and other materials targeted at these market segments to facilitate implementation of evidence-based practices and maximize the impact of evaluation results.

Results: The SALIENT team has developed a center infrastructure to support high-priority evaluations, often to be responsive to shifting operational needs and priorities. Our team has engaged in our core missions and operations to rapidly evaluate a high-priority areas, develop a comprehensive Lean Sprint systems redesign approach to training, and accelerate rapid knowledge translation.

Conclusions: With an array of interdisciplinary expertise, operational partnerships, and integrated resources, SALIENT has an established and evolving infrastructure to rapidly develop and implement high-impact evaluations. Projects are developed with sustained efficiency approaches that can pivot to new priorities as needed and effectively translate knowledge for key stakeholders

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and policy makers, while creating a learning health system infrastructure to foster the next generation of evaluation and implementation scientists.

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KEYWORDS

evidence-based policy-making; policy evaluation; knowledge translation; veterans; implementation science

Introduction

Background and Center's Overall Goal

The US Public Law 115-435—The Evidence Act—requires the Department of Veterans Affairs (VA) to support appropriation requests with evidence and evaluation [1]. The Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative (QUERI), developed the Evidence-based Policy Evaluation Center Award mechanism to develop an infrastructure of centers that specialize in rigorous, independent evaluations focused on national priorities that are informed by the Foundations for Evidence-Based Policymaking Act (Evidence Act, US PL 115-435) of 2018 (Multimedia Appendix 1).

The current protocol presents the proposed StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT), with the goal to conduct evaluations that support the adoption of programs and policies aligned with VA priorities and VA's goal to be a high-reliability organization and learning health system. SALIENT will generate, disseminate, and implement evidence-based policy recommendations and best practices in accordance with the Evidence Act. To accomplish this, we propose 4 objectives. For objective 1, the SALIENT team will develop and conduct comprehensive evaluations using a wide range of approaches (quantitative, qualitative, mixed methods, policy analysis, economic, clinical informatics, and implementation science) specifically tailored to VA's strategic mission goals and priority areas. For objective 2, the SALIENT team will develop and deploy knowledge translation resources such as communication briefs, playbooks, and other materials for key stakeholders to accelerate the implementation of evidence-based practices and impact. For objective 3, the SALIENT team will use evaluation methods to develop best practices in policy evaluation and implementation. For objective 4, the SALIENT team will train diverse evaluation scientists to democratize evaluation, implementation, and knowledge translation expertise.

In 2022, to align with 2021-2025 QUERI strategic goals and accelerate rapid knowledge translation in the pursuit of transforming VA into to a learning health system, QUERI launched an initiative to include a funding mechanism for evidence-based policy evaluation centers to support innovation in policy evaluation [2,3]. SALIENT was selected to support the enterprise-wide effort in policy planning and evaluation, due to the team's capability to foster advancements in VA priority areas.

SALIENT Areas of Expertise Related to FY23 Evaluation Priorities

Our interdisciplinary team has broad and deep expertise across VA evaluation priorities. Table 1 illustrates our expertise in these priority areas and details resources of our multisite center, including leadership from the Informatics, Decision Enhancement, & Analytics Sciences Center and James A. Haley Veterans' Hospital, and collaborators from the Center of Innovation for Complex Chronic Healthcare (Hines VA), the Center for Innovation for Veteran-Centered and Value-Driven Care, the Center for Care Delivery and Outcomes Research, and the War Related Illness and Injury Study Center. This expertise uniquely positions us to address 6 national evaluation priorities, identified by QUERI's multistakeholder process, that are linked to Veterans Health Administration Performance Plan metrics (eg, Strategic Analytics for Improvement and Learning).

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Table 1. StrAtegic PoLicy EvIdence-Based Evaluation CeNTer investigator expertise in Quality Enhancement Research Initiative 2023 priority areas.

Priority area	SALIENT[a] investigators
Military environmental exposures	Hunt, McAndrew, Mohanty, Samore, Knight, Smith, and *Pugh*[b]
Integration of care	Gordon, Hunt, Butler, Brooke, Nelson, McAndrew, A Jones, and *Haun*[b]
Improve long-term care, aging in place, home-based services, and so forth	Bouldin, Rupper, Butler, French, and *Pugh*[b]
Strategies to mitigate impact of COVID-19	Samore, M Jones, McAndrew, Hunt, Mohanty, Knight, Smith, and *White*[b]
Assess quality and cost of VA[c]-purchased community care	Vanneman, Smith, and *Haun*[b]
Assess MISSION Act standards of care and impacts on QI[d] and policy changes	Vanneman and *White*[b]

[a]SALIENT: StrAtegic PoLicy EvIdence-Based Evaluation CeNTer.

[b]Italicized names indicate SALIENT multiple principal investigators leading each priority area.

[c]VA: Department of Veterans Affairs.

[d]QI: Quality improvement.

Evaluate Strategies and Inform Policy to Mitigate Military Environmental Exposures on Veterans

SALIENT investigators are uniquely positioned to evaluate environmental exposures [4], including airborne hazards [5], which are high priorities of the President and Congress [6]. Our team conducted foundational studies to document the impact of military exposures and improve health care, demonstrating our operational partnerships and "big data" resources. This includes pioneering the use of the electronic health record to examine exposure concerns, that is, chronic multisymptom illness (AFM, LMM, and MHS), and conducting the first hybrid effectiveness implementation trial for exposure concerns: chronic multisymptom illness (LMM) [7-11]. VA's Health Outcomes Military Exposure program office called on us to lead the use of the electronic health record and individual longitudinal exposure record to connect phenotypes with military exposures (MJP), evaluate Health Outcomes Military Exposure/War Related Illness and Injury Study Center initiatives and clinical services (AFM and LMM), and lead and support educational efforts (LMM and SCH).

Optimize Integration of Care for Primary, Mental Health, Specialty, and Urgent Care Services

SALIENT is uniquely positioned to evaluate and optimize care for veterans with complex conditions that require integration of care across providers. Dr Gordon leads the Vulnerable Veteran Innovative Patient-Aligned Care Team Service & Research, Veteran Innovative Patient-Aligned Care Team Initiative, which has developed and implemented integrative care models for vulnerable veterans, including the implementation of medication treatment for opioid use disorder in 36 VA facilities across the nation (SCOUTT). Dr Brooke implemented a multidisciplinary program, the Transitional Pain Service, in Veterans Integrated Services Networks-19 coordinating pain management for patients at risk for opioid use disorder at the time of surgery [12,13]. This includes implementation for primary care providers to identify and refer high-risk patients to Transitional Pain Service. Our team is also a leader in integrating care for exposures into primary care. Dr Hunt is the national director of the postdeployment integrated care initiative, which is the office of primary care initiative to integrate deployment and exposure care into primary care, and Dr McAndrew is conducting multiple evaluations of education and consultation services to support primary care in addressing these concerns.

Improve Long-Term Care, Aging in Place, Geriatric Care, and Home Care Service

National efforts have focused on rebalancing long-term support services to promote care for veterans in their homes rather than institutional settings. This priority area is aligned with our expertise leading the Data and Policy Core of the Elizabeth Dole Center of Excellence for Veteran and Caregiver Research (Dole CoE). The Dole CoE helps veterans age in place. The Dole CoE team works with operations partners in Geriatric Extended Care to identify health services trajectories associated with quality home care and those predicting institutionalization using Geriatric Extended Care–Data Analysis Center VA Medicare and national survey data. The data resources (Multimedia Appendix 2) and expertise of SALIENT investigators in evaluation and geriatrics [14] are a strong foundation to address this VA priority.

Evaluate Strategies to Mitigate the Long-Term Impact of COVID-19 Including Reducing Adverse Outcomes Associated With Delayed or Suppressed Care

SALIENT investigators have played an instrumental role in the COVID-19 response for multiple federal agencies and local and state health departments [15,16]. Our contributions to efforts to mitigate the adverse impacts of COVID-19 highlight our expertise in epidemiology and control of infectious diseases. We developed new data resources for case ascertainment, clinical classification, and assessment of outcomes [17-19]. Combining clinical expertise with advanced analytical techniques, we have addressed key questions around short- and long-term management of COVID-19 infection [20]. We lead studies funded by the Food and Drug Administration and the Centers for Disease Control and Prevention on veteran COVID-19–related health inequities. In VA Health Systems

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Research (HSR), QUERI, and Department of Defense funded studies, we use mixed methods to evaluate problems of vaccine hesitancy and trust, and the impact of COVID-19 on veterans' health and well-being [21]. Building on our HSR-funded work on colon cancer screening, we evaluated the impact of the pandemic on veteran access to endoscopy [22,23]. Working with our VA operational partners, the SALIENT team proposed the COVID Post-Exposure Evaluation and Symptomatology Center, which addresses critical knowledge gaps concerning the post–acute sequelae of COVID-19 (ie, post–COVID-19 condition) and underscores our focus on advancing COVID-19 research and improving care for veterans living with COVID-19.

Assess and Improve the Quality and Cost of VA-Purchased Community Care, Including Enhancing Community Care and Digital Care Coordination to Improve Veteran Health

SALIENT is uniquely positioned to evaluate quality and cost of VA-purchased community care across a broad set of domains, including mental health and disparities. Dr Vanneman is a VA HSR Career Development Award recipient and a national expert in measuring access, quality, and cost of VA-purchased community care, with an emphasis on access, patient experience, and behavioral health [24-31]. Dr Vanneman is a multiple principal investigator (MPI) of the Access and Community Care Engagement Network Team COnsortium of REsearch. Dr Haun leads research and operations-based projects on implementation and evaluation of digital care resources to improve VA employee workflows and care coordination for veterans and their informal caregivers. Her work has driven the implementation and redesign of My HealtheVet, Secure Messaging [32], and the Veterans' Delegation tool, and extended integration of digital resources in primary care [32-38].

Assess MISSION Act Standards of Care and Impacts on Quality Improvement and Policy Changes

The MISSION Act (Section 1703C of title 38, Section 104) required VA to establish standards for quality for VA and VA-purchased community care health care services [39]. Published studies, including those by Dr Vanneman and collaborators, show similar or better quality of care at the national level for VA-delivered versus VA-purchased community care and are consistent with findings from prior studies that have compared VA and non-VA care (eg, Medicare). As Dr Vanneman is one of the few HSR investigators with extensive expertise in policy and analysis of community care data, SALIENT is well positioned to evaluate MISSION Act standards of care and impacts on quality improvement and policy.

SALIENT Is an Integral Part of the Existing VA Program Evaluation Structure

Figure 1 shows the interrelationships of VA operations and leadership, QUERI, the Partnered Evidence-Based Policy Resource Center (PEPReC), and SALIENT stakeholders.

We will work with these partners and other evaluation centers to conduct evaluations that support VA programs and policies. We will continually communicate research findings to other VA evaluators and synthesize learning across SALIENT and other groups to enhance the quality of evaluations conducted by the VA more broadly and develop best practices in policy implementation, impact, and evaluation.

Figure 1. Interrelationships of Veterans Affairs operations and leadership, Quality Enhancement Research Initiative, the Partnered Evidence-based Policy Resource Center, and StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) stakeholders. PEPReC: Partnered Evidence-Based Policy Resource Center; QUERI: Quality Enhancement Research Initiative; VA: Department of Veterans Affairs.

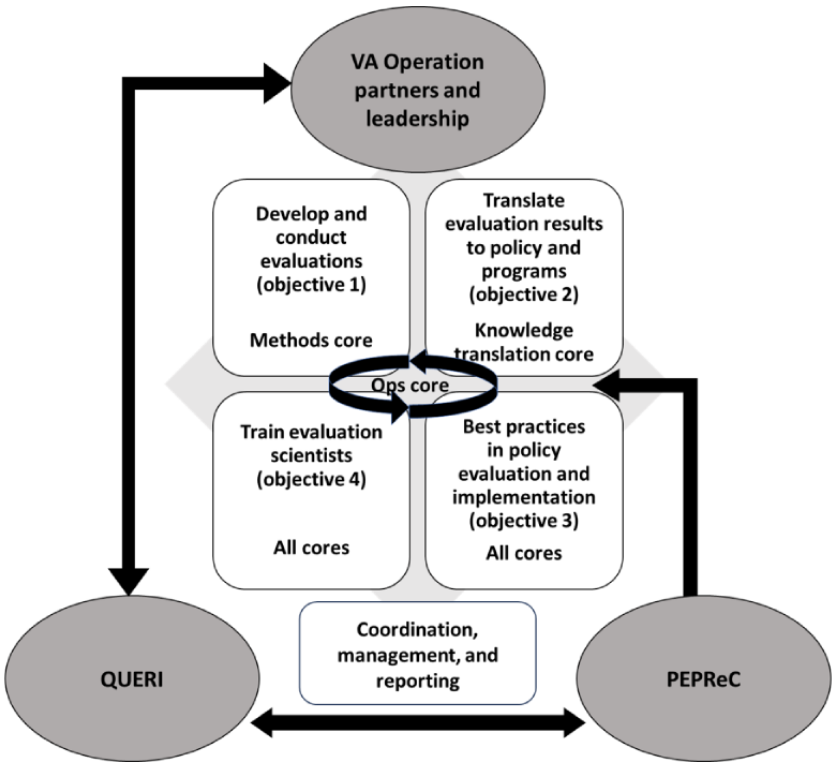

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Methods

Guiding Frameworks

SALIENT will conduct evaluations that support the adoption of programs and policies aligned with VA priorities and its goal to be a national learning health system. Our evaluation approach is anchored by key tenets of implementation science, quality improvement, and learning health systems (Figure 2).

Following the steps outlined by the QUERI Implementation Roadmap [40], and ACTION (Alignment with multilevel priorities, Commitment from operational partners, Tailoring to the local context, Informing the field, Observing health care changes, and generating New questions or projects) Impact Framework [41], SALIENT researchers will (1) identify problems and solutions, (2) engage stakeholders, (3) develop an implementation research logic model, (4) help implement relevant interventions as needed for a given project, (5) monitor data, and (6) perform ongoing reflection and evaluation. Through this process, we will develop best practices in policy evaluation (Figure 2). The theoretical frameworks guiding our project evaluations include the Consolidated Framework for Implementation Research (CFIR) and the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM). CFIR organizes factors that influence implementation outcomes across 5 domains—intervention, outer setting, inner setting, individuals, and implementation process [42]. The RE-AIM framework focuses explicitly on issues and steps in the implementation process that may improve or impede desired impact [43,44]. The principles of Lean Six Sigma and the Learning Health Systems Knowledge to Action Framework ensure a continual feedback loop of lessons learned [45].

Figure 2. StrAtegic PoLicy EvIdence–Based Evaluation CeNTer (SALIENT) conceptual framework for conducting evaluation. CFIR: Consolidated Framework for Implementation Research; IRLM: Implementation Research Logic Model; RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance.

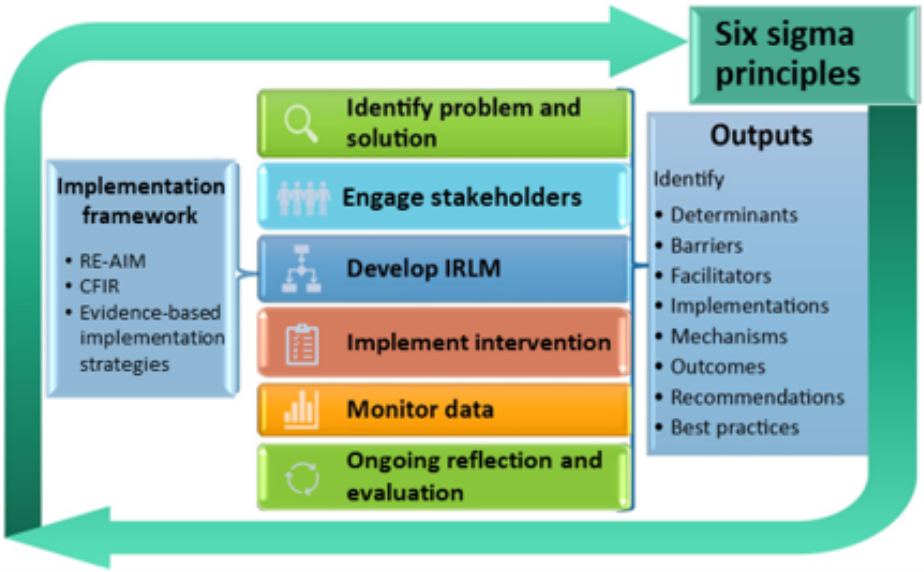

Ethical Considerations

This policy center was funded by a QUERI quality improvement center award mechanism and as such, the center and projects are to be conducted as quality improvement nonresearch. In alignment with regulatory guidelines, this center application was reviewed by the VA Salt Lake City Human Research Protection Office and received approval as quality improvement. It is notable that QUERI projects and centers are funded as quality improvement; research-regulated projects are funded by other services within the Veterans Health Administration, Office of Research and Development. Participants' identities are kept confidential, and data are stored behind VA fire walls. All methods are performed in accordance with relevant guidelines and regulations. Informed consents, compensation for participants, and institutional review board oversight are not applicable for quality improvement projects funded as part of SALIENT.

Consent has been provided by coinvestigators and project leads to use names in text, tables, and figures within this protocol.

Overarching Processes: SALIENT Core Integration

After PEPReC assigns evaluations [46], the Operations Core (Lead Cochran) will coordinate work using Lean methodologies in addition to managing contracts and external reporting (eg, QUERI, PEPReC, other VA stakeholders, and the Office of Management and Budget). The Methods Core (Leads Vanneman and Zickmund) will ensure that appropriate methodologies are used for each evaluation (objective 1). The Knowledge Translation (KT) Core (Lead Fagerlin) will use state-of-the-art translation of evaluation results into action and policy. KT Core team integration will enhance impact through guidance as evaluations are developed and implemented and products such as executive summaries and playbooks are produced (objective 2). All cores will prioritize the development of best practices in evaluation science (objective 3) and training of diverse implementation scientists (objective 4).

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Objective 1: Develop and Conduct Evaluations

Overview

As described in "Lean Sprint and Lean Six Sigma in Evaluation Processes" section, SALIENT begins each evaluation with a Lean Sprint to scope the evaluation topic, articulate evaluation objectives, develop evaluation questions, match methods to the questions, and identify possible pitfalls and potential contingency plans required to ensure high-quality evaluations. The mission of the Methods Core is to support and conduct evaluations by ensuring that appropriate, rigorous methods are used to address all assigned evaluations. SALIENT proposes a Methods Core with extensive expertise to apply qualitative, quantitative, and mixed methods to assigned evaluations. Multimedia Appendix 3 identifies investigators and leads affiliated with each methodological focus.

Lean Sprint and Lean Six Sigma in Evaluation Processes

We used Lean Sprint and Lean Six framework process to successfully complete an extensive evaluation of post-9/11 women veterans unemployment in 9 months (Table 2) and will continue this model integrating Lean methods within our implementation framework.

Using our established expertise, SALIENT will use Lean Sprint (iterative, incremental, time-boxed iteration cycle for sourcing, ranking, and testing new ideas) [47] and Lean Six Sigma (hereafter Lean Six) processes to conduct evaluations and inform continuous development for each evaluation and the center as a whole. Lean Six includes 5 operational stages (Define, Measure, Analyze, Improve, and Control) to manage the operations of each evaluation. Lean Six processes are management strategies for process improvement that have been applied in industry sectors including health care [48] for improvement of management processes and outcomes [49]. Evidence also shows the value of using Lean Six processes for planning [38] and producing improvements for clinical and translational research center workflow [50]. Because VA continues to train operations and medical center staff in Lean Six principles, this will facilitate alignment with operational partners and subsequent translation and implementation of policies and programs on completion of each evaluation.

On evaluation assignment, SALIENT MPIs will identify an evaluation team (ET) lead based on requirements of the evaluation and expertise to complete the evaluation. The ET lead will conduct a Pre-Sprint meeting with MPIs, core leads, operational partners, and other stakeholders to identify Lean Sprint needs and objectives, identify the ET investigators and staff, and assemble other key stakeholders and participants for the Lean Sprint team based on the evaluation content, appropriate methods, policy implications, and relationship to the phase of the QUERI Implementation Roadmap.

Table 2. Timeline of completed evaluation of women veterans' unemployment.

Lean Six method	Evaluation task	Months											
		1	2	3	4	5	6	7	8	9	10	11	12
Define	Lean sprint	✓											
Measure	Data collection		✓	✓	✓	✓	✓	✓					
Analyze	Analysis					✓	✓	✓	✓				
Improve	After-action evaluation									✓	✓		
Control	After-action integration											✓	✓

We Will Use Lean Sprint to Develop the Evaluation Plan (Define)

The Operations Core will facilitate the Lean Sprint, with engagement from MPIs, ET, and core leads. The Lean Sprint team will meet weekly for ~5 weeks, with individual core teams meeting between to inform decision-making (Figure 3). The goals of each phase are as follows. In phase 1, the team will develop a common understanding of the evaluation required and evaluation questions to be addressed and identify possible approaches for each question, potential pitfalls, and other critical stakeholders and team members for the evaluation. In phase 2, the team will evaluate options (pros, cons, and pitfalls) of approaches and identify additional team members. In phase 3, the team will create a short list of evaluation approaches. In phase 4, the team will evaluate options on the short list. In phase 5, the team will finalize the evaluation plan (Figure 3).

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Figure 3. Use of Lean Sprint and Lean Six methodology to develop implementation evaluation plans. KTC: Knowledge Translation Core; MC: Methods Core; OC: Operations Core; QUERI: Quality Enhancement Research Initiative; VA: Department of Veterans Affairs.

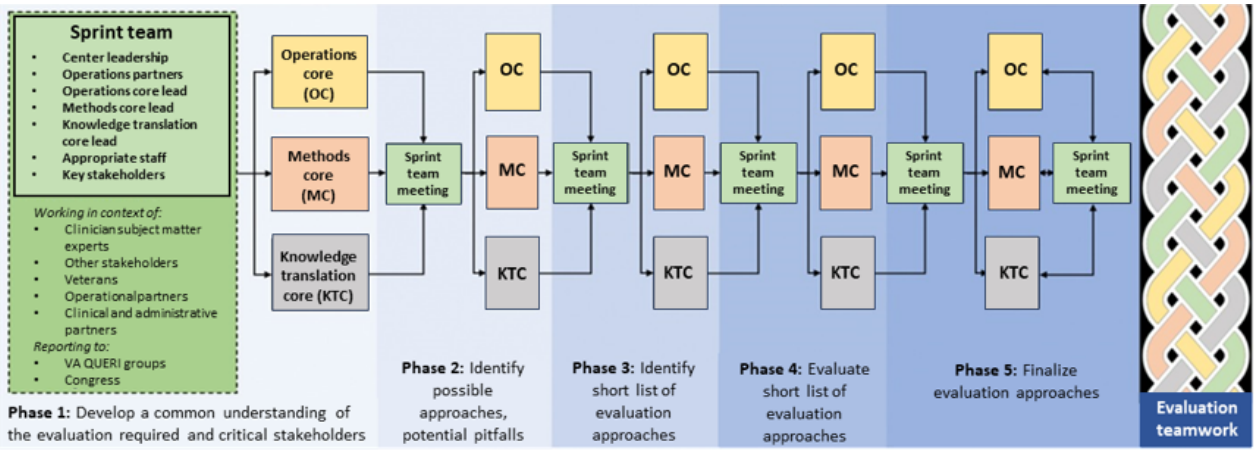

Complete Evaluation Plan Using Lean Six Management Model

The cross-core collaborations in the 5 operational stages of Lean evaluation operations [50,51] are depicted by the braid on the right side of Figure 3. This symbolizes the close interaction among cores in biweekly ET meetings throughout the evaluation as they measure (conduct analysis), analyze (synthesize results for reports), improve (after action evaluation) and control (develop improved processes for future evaluations) stages. Throughout evaluations, the Operations Core will facilitate communication with and between the Methods and KT Cores including milestones and timelines to monitor performance of evaluations. The Operations Core will provide feedback to the ET and core leads on timelines, needs, and actionable performance monitoring to ensure that ETs meet contractual and stakeholder expectations. Evaluation facilitators will be assigned to an ET as it is formed and provide substantive support and guide research analysts assigned to each evaluation. Dr Cochran (Operations Core Lead with Greenbelt certification in Lean Six Sigma) will maintain communication using short huddles (1-2 times per week or as needed) with SALIENT leadership.

Objective 2: Develop and Deploy Knowledge Translation Resources

Overview

The mission of the KT Core is to translate findings produced by SALIENT into useful and informative formats for stakeholders and policy makers and to inform best practices in policy evaluation and implementation. Led by Drs Fagerlin and MPI Haun, the KT Core will identify items essential to any knowledge translation process: (1) Stakeholders—priorities, capabilities, strengths, weaknesses, and incentives; (2) Actions—potential policy changes and operational changes; and (3) Outcomes—help VA achieve better health outcomes for veterans. SALIENT investigators have expertise in knowledge translation at the patient, provider, and system levels; development of plain language patient and clinical educational tools; and training postdoctoral fellows. The coleads of the KT Core will leverage Dr Haun's experience integrating key stakeholders in the evaluation process and Drs Haun's and Fagerlin's experience in communication of results. Together they will support stakeholder engagement in projects and lead knowledge dissemination.

KT Approach

The KT Core will be involved in all phases of the evaluation (Figures 3 and 4).

As the evaluation plan is developed, the KT Core will begin development of key components of a playbook based on the QUERI Implementation Roadmap and ACTION Impact Framework [40,41]. For each evaluation, playbook development will carry out and adapt 4 steps to determine stakeholders, actions, and outcomes; create dissemination tools; disseminate findings; and evaluate dissemination outcomes. Multimedia Appendix 4 gives an example of a playbook overview developed for another QUERI project (MPIs: Haun and Pugh).

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Figure 4. Structure of StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) team. Projects and leads were subject to change upon the start of SALIENT funding. MPI: multiple principal investigator; PI: principal investigator; UU: The University of Utah; VA: Department of Veterans Affairs.

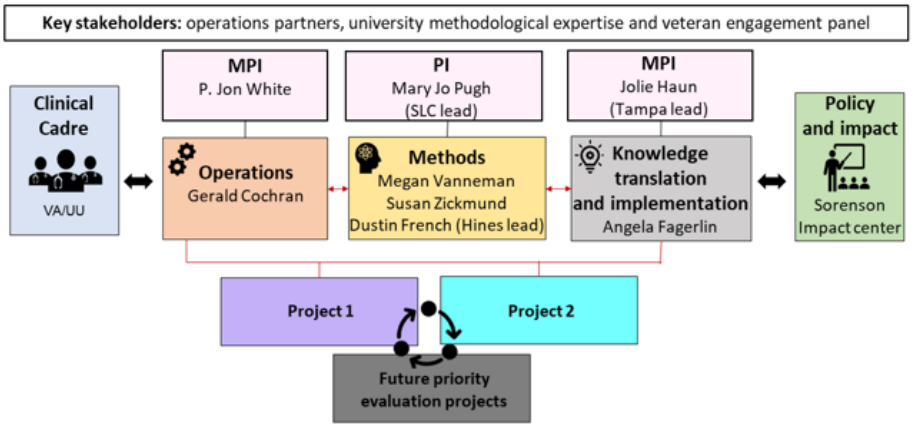

Determine Key Stakeholders, Actions, and Outcomes

The KT Core will provide an initial list of key stakeholders who would implement or be impacted by evaluation findings (Pre-Sprint) by (1) systematic review of VA operational partners and VA leadership, (2) Veteran Engagement Panel review, and (3) discussion with relevant VA and non-VA experts. This list will be finalized during the Sprint. We will create a table defining the priorities, capabilities, strengths, weaknesses, and incentives of each stakeholder group (eg, VA leaders, clinicians, veterans) and the role of each stakeholder for the specific evaluation. We will work with stakeholders to create feedback channels, report progress regularly, adjust strategy, and make data accessible.

Create Dissemination Tools

Throughout evaluations, the KT Core will collaborate with project teams to create dissemination tools tailored to each stakeholder and their priorities, capabilities, strengths, weaknesses, and incentives with feedback from Veteran Engagement Panels (Veterans Administration Salt Lake City and others), evaluation Clinical Cadre, and Declarative. Declarative will help identify communications strategies across stakeholder groups, business case analyses, and implementation plans. For each stakeholder, we will develop a formal briefing document, infographics, a "talking points memo," and a list of suggested resources and methods to use findings to make changes to VA priorities, regulations, processes, budgets, and (as appropriate) national law. The briefing document will describe the problem, the outcome of the evaluation including possible impact of outcomes on a federal level (as possible) (using "plain language" and figures to make outcomes simple to digest), stories of veterans affected, case studies, and suggested changes to VA due to outcomes (regulations, processes, and budgets). We will create tailored infographics [52] and design each dissemination tool considering (1) key information for each stakeholder, (2) key points to be emphasized that will illustrate outcomes and benefits of implementing strategies, and (3) how each tool should be tailored for stakeholders [53].

Dissemination of Findings

The KT Core will facilitate communication for 2 types of stakeholders. General operations will inform VA leadership, VA operational partners, QUERI, PEPReC, and other QUERI programs about SALIENT expertise, evaluations, and staff development and enrichment. Content-specific partners include those described in the section titled "Determine Key Stakeholders, Actions, and Outcomes." The KT Core will respond to knowledge translation inquiries from operations partners, policy makers, and the broader research community. Specific outputs and evaluation of specific approaches for each type of stakeholder may include a SALIENT web page, a VA-approved YouTube channel, monthly SALIENT leadership teleconferences with stakeholders, distribution of tailored dissemination tools, peer-reviewed publications, and conference presentations. Topics covered will include SALIENT team expertise and evaluations, training on priority topics, and alignment with QUERI and VA priorities.

Evaluation of Dissemination

In the evaluation sustainment phase, we will evaluate whether our results had an impact on veterans' health and well-being and the VA (eg, impact on regulations, processes, budgets, and laws). Annually, we will examine relevant VA processes, regulations, laws, and budgets to determine whether they reflect findings from our evaluation and whether our findings and dissemination tools are described. As part of the playbook, each evaluation will receive a scorecard that will include a short list of high-priority policy or programmatic goals (3-5) to implement from the evaluation, operations partners, and QUERI Central Office. Scorecard goals, and additional impacts, will be aligned with the QUERI Action Impact Framework domains [41]. The playbooks and scorecards will be planned in the initial Lean Sprint. As an evaluation progresses and data are gathered and analyzed, analogous to the QUERI Implementation Framework [40], evidence-supported strategies, resources, interventions, and benchmarks that support solutions will evolve.

Objective 3: Develop Best Practices in Policy Evaluation and Implementation

We propose a multilayered theoretical approach, using rigorous mixed methods that relies on implementation science

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frameworks, Lean Six processes and a strategic process across SALIENT project conceptualization, data collection, analysis, implementation strategy development, reporting, synthesis, and dissemination over time. RE-AIM, CFIR, evidence-based implementation strategies, and the Implementation Research Logic Model process will inform our conceptual lens across projects to standardize our approach to policy evaluation and implementation over time.

Consistent with Lean Six [48] the Operations Core is charged with continuous and sustained improvement of center operations to ensure that performance is meeting stakeholders' expectations and the SALIENT team improves work processes and optimizes efficiencies during and after each evaluation. The Operations Core will facilitate the feedback loop with stakeholders, cores, and ETs using periodic reflections [54], throughout evaluations, allowing rapid feedback from stakeholders on aspects of design and execution that will inform the direction of the project, modifications, and development of a learning health system (Analyze and Improve phases). We will facilitate a continuous feedback loop to avoid misalignment in goals and expectations, allow rapid and strategic course corrections throughout the evaluation, and ensure that the end user can optimize use of evaluation results.

To develop best practices in policy evaluation and implementation across projects over time, we will develop a SALIENT Policy Evaluation Catalog of projects to document project factors (ie, policy type, stakeholders, constructs, implementation strategies, communication and dissemination strategies, and mechanisms). We also propose to collaborate with other centers to collect these data on their evaluations to inform large-scale synthesis of policy evaluation and implementation best practices. Data from our inventory can be used by SALIENT, other centers, and the coordinating center for cross-project observations and learning, which is a broader opportunity for overall QUERI development. To accomplish this, the Operations Core will conduct after-action evaluations including operations partners (see left side of Figure 3), investigators, and end users of the evaluation to discuss successes or concerns observed during the evaluation documented by detailed field notes and recordings. A quantitative postevaluation assessment (Multimedia Appendix 5) will capture operations successes and barriers.

Using the SALIENT Evaluation Policy Catalog data we will brainstorm alternatives, overcome barriers experienced, and inform future evaluation development and processes. These data will be used to create Lean Six tools, such as Value Stream Maps (schematics used to identify activities that have value to stakeholders as well as waste, delays, and inefficacies), to identify strengths and weaknesses of SALIENT activities. Examples of wastes, delays, or inefficiencies could include team members from one core unnecessarily waiting for completion of entire components of evaluations (batches) instead of working continually as smaller components are completed (single-piece workflow); a highly inefficient approach to collaborative work processes. These schematics and proposed priorities will be discussed with center and core leads. The group will come to consensus on priorities and their rank order. Sustaining improvements are ensured by this type of regular review and use of audit checklists for continued monitoring. These analyses will synergize findings and processes across cores and evaluations to develop best practices in policy evaluation and implementation.

Objective 4: Train Diverse Evaluation and Implementation Scientists

Overview

We aim to recruit, train, and retain highly skilled investigators in evaluation and implementation science. We will recruit "SALIENT Scholars" to participate in the Advancing Diversity in Implementation Leadership (ADIL) program in addition to graduate students and postdoctoral fellows who can grow our ADIL program. We will leverage our suite of advanced fellowships to provide a cohort and peer support for ADIL participants. We will also leverage The University of Utah (UU) Vice President's Clinical and Translational Research Scholars Program for junior investigators, career development, and leadership training (eg, weekly seminars and a 3-day career development retreat) led by the director of career and leadership training at UU and early career coaching designed specifically for underrepresented scientists. These targeted programs will assist ADIL participants in identifying additional career and near-peer mentors who are also scientists who identify as underrepresented in science. Our team includes such junior investigators (Naranjo).

As we do in other fellowships, we will use a Matrix Mentoring Model [55] where each fellow has a content mentor, a senior scientific mentor, and a KT mentor. Mentees will meet with MPIs and core leads to establish mentoring teams and complete career development plans (CDPs). Mentees will meet twice monthly with their scientific mentors and twice per year with mentor teams to review productivity, plan for the next 6 months, and track progress toward program and career goals. Mentees will write and submit annual progress reports to the MPIs, who will review them with the mentees. Mentees will also follow a personalized CDP while working on evaluations guided by their mentoring team. The mentoring program will parallel that of the Combatting Antimicrobial Resistance through Rapid Implementation of Available Guidelines & Evidence QUERI, which includes didactic training, group learning, leadership development, external engagement (eg, Center for Evaluation and Implementation Resources, for consultation, instruction, and guidance related to their project, participation in the Implementation Research Group, a national learning collaborative), dissemination support, and tracking of performance considering person goals and CDPs. Dr Rubin, lead of the Combatting Antimicrobial Resistance through Rapid Implementation of Available Guidelines & Evidence QUERI mentoring core and the UU Vice President's Clinical and Translational program, and Dr Knight (co–primary investigators of Informatics, Decision Enhancement, & Analytics Sciences HSR fellowship) and Dr Fagerlin (PI of UU TL1 pre- and postdoctoral training programs) will integrate SALIENT Scholars (and SALIENT mentors) into their existing training programs. In addition to these fellowships, SALIENT will include training in Lean Six methods using existing VA training mechanisms and training with Operations and KT Core faculty.

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Training will also be offered to other fellows and trainees (eg, graduate students, faculty) from partnering programs and sites.

Center Management Plan

Upon proposal resubmission to address reviewer comments (Multimedia Appendices 6 and 7) and funding acceptance, the MPIs, site leads, core leads, and investigators attended a dual digital and in-person hybrid kickoff meeting in December 2022. At this kickoff, we attended to all preliminary start-up issues and collaborated to initiate projects and core efforts. The kickoff provided the setting for connecting all 3 sites, setting the standard and logistics, to continue their effective multisite communication. After the kickoff meeting, we initiated team's meetings and shared project folders and other relevant logistics for communication and collaboration. Second, the entire SALIENT team attends quarterly meetings with operational and veteran stakeholders on projects to address evaluation activities, benchmarks, project issues, and ultimately subsequent implementation efforts. This ongoing communication facilitates changes or operations-prompted amendments to the projects, as sometimes occurs. In this case, the MPIs consult with operations and reconceptualize project activities and deliverables as needed. Third, we conduct digital biweekly meetings with the MPIs and project teams during which each team will report on progress, roadblocks, and findings. Fourth, we conduct digital project-specific weekly meetings, attended by the MPIs, leads, coinvestigators, and project managers to address day-to-day activities. Fifth, the MPIs and site and project leads formulate email updates to send to all SALIENT members—updates will include project progress, training opportunities, and other content relevant to other ongoing meetings. These updates are summarized in quarterly reports to operational partners. Sixth, team members communicate as needed via email, phone, and videoconference as done during the development of this proposal. Given the long-standing collaboration among the MPIs and site leads, and our current digital collaboration practices, we do not anticipate any concerns. SALIENT sites will use 6 primary means for center management and communication (Figure 5).

Figure 5. Evaluation timeline and deliverables. MOU: memorandum of understanding.

Results

Funding and start-up activities for SALIENT began in October 2022. Current SALIENT evaluation projects are underway, and funding is expected to continue through September 2027. Anticipated project evaluation results will be disseminated as projects end on their projected timelines. Reporting will be performed at funding, operational, and congressional levels as appropriate. SALIENT KT Core efforts will support rapid dissemination to key partners and organizations.

Discussion

Principal Considerations

The goal of this evaluation center is to support the successful identification and implementation of VA high-priority operational evaluation projects that are aligned with VA population and system needs. This protocol illustrates a multilevel theoretical and Lean Sprint methodology to conduct rapid rigorous operations-based policy evaluation in a learning health system. To our knowledge, this protocol is unique in that it informs a center-wide Lean Sprint methodology to conducting quality improvement to evaluate priority policies. Our impact will be to accelerate the generation, dissemination, and implementation of evidence-based policy recommendations pursuant to the Evidence Act, develop best practices in policy evaluation and implementation, and train diverse evaluation and implementation scientists.

Strengths and Limitations

This center protocol contributes to the field in four distinct ways by (1) using a Lean Sprint methodology (iterative, incremental, rule-governed approach to clearly defined, and time-boxed work) to develop our evaluation plans collaboratively with operational partners and key stakeholders including veterans, policy experts, and clinicians; (2) using a multicore approach (operations, methods, and knowledge translation) to conduct evaluations and rapidly disseminate findings to inform knowledge translation; (3) developing a center infrastructure to train diverse evaluation scientists to democratize evaluation, implementation, and knowledge translation expertise; and (4) identifying best practices in policy evaluation and implementation to inform learning health systems.

Potential weaknesses of the center should also be considered. First, given geographic diversity, communication breakdowns across sites are a risk; however, a comprehensive center management plan and digital communication methods ensure continuity in communication and center-site interactions. Second, given the size of the center and rapid nature of projects, there is a risk of diffuse efforts or mismanagement of resources; however, the multicore approach of the center ensures infrastructural, administrative, and resource support from an administrative, operational, and methodological perspective. Third, with shifting topical and funding priorities, continuity in resources and staffing could pose challenges across projects over time; however, SALIENT leadership is engaged with QUERI, other QUERI Evidence Act evaluation centers, and operational leadership to anticipate and respond to the changing

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climate to allow for symbiotic reciprocity. Furthermore, SALIENT's Lean Sprint systems redesign approach maximizes resources and sustained efficiency of projects. Fourth, often operations-based projects require data sets and resources that may not be readily available, particularly on the rapid timeline of high-priority projects. SALIENT subject matter experts have a highly developed network of resources and collaborations within and beyond VA to ensure currency and continuity across data resources.

Conclusions

In summary, the SALIENT environment has exceptional evaluation and training resources; has established infrastructure with a proven track record of rapid evaluation and dissemination of results; and strong, lasting operational partnerships and collaborations. The SALIENT team is poised to rapidly conduct state-of-the-science evaluations to support the broad VA response to the Evidence Act and high-priority legislative requirements related to environmental hazards and airborne exposures. SALIENT evaluations will contribute to (1) optimized policies and programs for veterans; (2) improved outcomes regarding health, equity, cost, and provider well-being; (3) advances in the science of policy evaluation and knowledge translation by synthesizing learning across SALIENT and other center evaluations; and (4) expansion of the implementation and dissemination science workforce.

Acknowledgments

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Data Availability

Data for center projects are available from the authors upon reasonable request. Requests can be made to the corresponding author for referral to appropriate SALIENT project lead.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Department of Veterans Affairs funding opportunity announcement request for applications. VA: Department of Veterans Affairs, VA-ORD: Office of Research and Development; QUERI: Quality Enhancement Research Initiative; RFA: Request for Applications.
[PDF File (Adobe PDF File), 839 KB - resprot_v13i1e59830_app1.pdf]

Multimedia Appendix 2
Data resources compiled by StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) investigators to be used in future evaluations and scientific investigation.
[PDF File (Adobe PDF File), 115 KB - resprot_v13i1e59830_app2.pdf]

Multimedia Appendix 3
StrAtegic PoLicy EvIdence-Based Evaluation CeNTer (SALIENT) team methodological expertise with selected references.
[PDF File (Adobe PDF File), 274 KB - resprot_v13i1e59830_app3.pdf]

Multimedia Appendix 4

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Playbook overview developed for another Quality Enhancement Research Initiative project (multiple principal investigators: Haun and Pugh).
[PDF File (Adobe PDF File), 2688 KB - resprot_v13i1e59830_app4.pdf]

Multimedia Appendix 5
Quantitative post-project team evaluation template.
[PDF File (Adobe PDF File), 162 KB - resprot_v13i1e59830_app5.pdf]

Multimedia Appendix 6
Request for applications reviewer comments.
[PDF File (Adobe PDF File), 97 KB - resprot_v13i1e59830_app6.pdf]

Multimedia Appendix 7
Request for applications resubmission responses to reviewer comments.
[PDF File (Adobe PDF File), 141 KB - resprot_v13i1e59830_app7.pdf]

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Abbreviations

ACTION: Alignment with multilevel priorities, Commitment from operational partners, Tailoring to the local context, Informing the field, Observing health care changes, and generating New questions and projects
ADIL: Advancing Diversity in Implementation Leadership Program

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CDP: career development plan
CFIR: Consolidated Framework for Implementation Research
ET: evaluation team
HSR: Health Systems Research
KT: Knowledge Translation
MPI: multiple principal investigator
PEPReC: Partnered Evidence-Based Policy Resource Center
QUERI: Quality Enhancement Research Initiative
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
SALIENT: StrAtegic PoLicy EvIdence-Based Evaluation CeNTer
UU: The University of Utah
VA: Department of Veterans Affairs

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Protocol

Applying the Multiphase Optimization Strategy for the Development of a Culturally Tailored Resilience-Building Intervention to Facilitate Advance Care Planning Discussions for Chinese Americans: Protocol for a Survey and Qualitative Study

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Abstract

Background: Newly arrived Chinese Americans face difficulties engaging in advance care planning (ACP) discussions with their family caregivers. Avoiding such discussions and failing to complete advance directives can delay palliative and hospice care. Yet, timely palliative care is essential to maintaining the quality of life at the end of life. Currently, there is a lack of interventions to help Chinese Americans diagnosed with cancer or heart disease overcome the barriers to engaging in ACP discussions via effective use of resilience.

Objective: This study aims to develop a culturally tailored, resilience-building intervention for Chinese Americans with cancer or heart disease.

Methods: The development of this intervention will be guided by the 3-phase multiphase optimization strategy. In the first phase of preparation, we will examine the prespecified components of the intervention through pilot studies to understand the necessity of each component. First, a qualitative study will be conducted to understand the experiences of 10 religious or spiritual leaders who have provided pastoral or spiritual care to Chinese Americans in Chicago, United States. The interview findings will be categorized as facilitators and barriers and integrated into the development of the intervention's resilience-building guide. Second, a cross-sectional study will be conducted to assess the readiness of Chinese Americans to engage in ACP discussions with their family using surveys. Third, think-aloud interviews will be conducted to understand the experiences of 18 pairs of Chinese Americans and their family caregivers regarding the prototype of the culturally tailored, resilience-building intervention. Finally, we will examine the feasibility and acceptability of the intervention prototype along with issues related to the study's implementation process.

Results: Recruitment for the qualitative study began in November 2023. As of October 2024, a total of 7 participants have been recruited, enabling a preliminary qualitative analysis to evaluate the analytical framework developed from the literature. Recruitment for the cross-sectional study began in April 2024, and as of October 2024, a total of 63 Chinese Americans have participated. The potential participant recruitment lists for the think-aloud interviews have been received, enabling recruitment to begin after the preliminary qualitative analysis is completed.

Conclusions: The proposed culturally tailored, resilience-building intervention is an innovative way to facilitate ACP discussions among Chinese Americans, particularly those diagnosed with serious chronic diseases. The findings from all 3 study methods will inform the development of the proposed intervention and identify effective recruitment strategies for this underserved and hard-to-reach population to be used in future research.

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KEYWORDS

resilience; Chinese Americans; multiphase optimization strategy; protocol; advance care planning; feasibility studies

Introduction

Advance care planning (ACP) is an iterative process that helps adults reflect on their personal values and preferences regarding future medical care and document those preferences in advance directives to share with their health care agents and health care providers [1]. ACP encompasses 3 main components, including designating a health care agent, discussing ACP with the health care agent, and completing an advance directive with the health care agent [2]. The well-known benefits of ACP include its ability to (1) help individuals increase satisfaction with care, patient-family communication, and quality of death; and (2) improve the mental health of family caregivers by reducing anxiety, depression, and caregiver decisional burden [3]. Despite the proven benefits of ACP, however, only 13.7% of Chinese Americans (defined for this study as individuals who self-identify as of Chinese descent, including foreign-born immigrants from regions such as China, Hong Kong, Taiwan, and other East Asian countries, as well as the descendants of these first-generation immigrants; hereafter referred to as Chinese Americans) have completed advance directives [4]. This rate is less than half of the 37% completion rate in the US general population [5]. This disparity in the use of ACP between Chinese Americans and non-Hispanic White Americans (defined as US residents with origins in Europe, the Middle East, or North Africa) [6] may relate to known disparities between these groups in palliative and end-of-life care, including in rates of hospice care use, the prevalence of unwanted aggressive treatments at the end of life, and end-of-life expenditures [7-10]. For example, Chinese Americans are twice as likely as White Americans to be administered mechanical ventilation in their last 30 days of life (17% compared to 8%) and significantly more likely to die in a hospital (49% compared to 36%) [9]. In addition, the mean end-of-life Medicare expenditures claimed by Asian Americans (US $15,388) are significantly higher than those claimed by White Americans (US $10,761) [10]. In other words, the lack of completion of advance directives among Chinese Americans may contribute to aggressive and extravagant care that significantly worsens their quality of life at the end of their lives.

The leading causes of death among Chinese Americans—similar to those for non-Hispanic White Americans—are cancer and heart disease [11]. Yet, newly arrived Chinese Americans' health behaviors regarding access to care, specifically end-of-life care, may contribute to health disparities at the end of life. When Chinese Americans face a diagnosis of serious chronic diseases, such as cancer or heart disease, their coping behaviors are deeply affected by four cultural beliefs: (1) fatalism; (2) respect for elders; (3) harmony; and (4) respect for authority figures, such as health care providers and religious leaders [12].

Chinese Americans may hold the fatalistic belief that life is predetermined by destiny and beyond one's control [12]. This fatalistic belief may reduce Chinese Americans' willingness to adopt healthy behaviors, including ACP discussions and prevention-focused cancer screening [12-14]. Some may even deny their cancer diagnosis as a coping mechanism [15], and others may turn to religious or spiritual practices as a way to cope with serious disease [16]. Their family caregivers, a role usually served by adult children, may show respect for elders by protecting and promoting their parents' well-being [12]. However, when adult children know that taboo topics like ACP may offend their parents, they may avoid these uncomfortable conversations, even if their parents initiate them [17]. To maintain family harmony, adult children may wait for authority figures, especially health care providers, to initiate ACP discussions [17]. In situations where ACP topics have not been initiated by health care providers, adult children who practice filial piety (ie, the obligation felt by children to ensure the well-being of their parents in order to promote longevity) may decide to prolong their parents' lives by selecting life-sustaining therapy during end-of-life care decision-making [12,18]. However, this decision, despite being based on goodwill, may contradict the Chinese cultural value related to a good death, in which being pain-free and maintaining dignity in death are preferred [12,19]. These cultural beliefs, combined with other common barriers, including misconceptions about ACP [20] and low levels of acculturation and health literacy [21,22], may exacerbate the low completion rate of advance directives among Chinese Americans.

Making end-of-life decisions requires constant coping with barriers while considering cultural beliefs. One promising approach to helping Chinese Americans appraise and cope with the barriers to ACP is building resilience. In this study, we define resilience as the process by which an individual learns to use their resources to sustain physical and psychological well-being in the face of adversity [23,24]. Resilience may enable individuals to buffer against stress, and it can be developed through practice [25]. Individuals with resilience skills can effectively use and apply their external resources (eg, social support from families and health care providers), internal resources (eg, individual strengths and coping skills), and existential resources (eg, meaning-making and finding gratitude) to address the stress they face [26]. Individuals with resilience skills may see a serious illness diagnosis as a challenge instead of a threat and use suitable coping strategies such as self-awareness of personal strengths and cultivating positive emotions and positive relationships with health care agents to facilitate psychological adaptation [27]. Continuous adaptation, through accurate appraisals and evaluation of coping strategies, is an important process for building the resilience necessary to overcome the stress experienced in ACP discussions.

Previous clinical trials of interventions have consistently shown positive effects of resilience on reducing psychological distress, increasing personal growth, and improving the quality of life in people with cancer [28,29]. Patients with breast cancer who participated in a pilot randomized controlled trial (RCT) showed

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improved resilience and decreased anxiety and perceived stress after 12 weeks of resilience training, including training in finding gratitude, meaning-making, and interpreting the cancer experience flexibly [28]. Family caregivers of patients with cancer can also benefit from the protective effects of resilience. One study found resilience to be negatively associated with caregiving burden, anxiety, and depression among family caregivers of patients with advanced cancer [30]. Resilience was also found to be a predictor of a caregiver's readiness for surrogate decision-making [31]. These studies suggest that strengthening the resilience of people with cancer or heart disease and their family caregivers may help reduce the emotional impact of ACP discussions and improve the process of completing advance directives.

Currently, most ACP interventions developed for Chinese Americans in the United States have been examined for effectiveness at the patient level only [32-34], overlooking the collective family decision-making process emphasized in Chinese culture and the ongoing evaluations needed to stay current with evolving preferences and values for end-of-life care [22]. In addition, despite the need for spiritual support, especially during difficult times [16], very few studies have included religious leaders in the development of interventions to understand how they address the barriers faced by Chinese Americans regarding ACP and death-related issues. Additionally, most prior interventions examined changes in knowledge and attitudes among community-dwelling Chinese Americans [32-34], not those currently experiencing serious chronic diseases such as cancer or heart disease. While these interventions have demonstrated improvements in knowledge and attitudes toward ACP [32], they may not adequately address the evolving preferences and values regarding end-of-life care when Chinese Americans confront their own mortality. A diagnosis of cancer or heart disease may prompt a greater need for resilience skills to successfully engage in ACP discussions with their family caregivers [13,16].

As a first-generation Chinese American nurse scientist specializing in palliative and hospice care in the United States, the first author (LL) is acutely aware of the challenges adult children face in discussing death and dying with their parents. These challenges are compounded by barriers related to health literacy and misconceptions about hospice and palliative care. The first author's cultural background influenced her research interest in developing a culturally tailored, resilience-building intervention to help Chinese Americans engage in ACP discussions.

This feasibility study has 3 aims for intervention development, each of which uses a different study design. Aim 1 is to conduct a qualitative content analysis of semistructured interviews with 10 religious or spiritual leaders to identify barriers and facilitators to discussing ACP and death-related topics among Chinese Americans in Chicago, United States. Aim 2 is to collect survey data to assess the readiness of Chinese Americans aged 18 years and older and living in Chicago to engage in ACP discussions with their families. Aim 3 is to conduct think-aloud interviews with 18 pairs of Chinese Americans and their family caregivers (9 pairs with cancer and 9 pairs with heart disease) living in Chicago to collect feedback on the content of a culturally tailored, resilience-building intervention prototype. We expect that incorporating the strategies used by religious or spiritual leaders to discuss ACP and death-related topics (aim 1) into the intervention prototype will enhance the acceptability of the intervention among Chinese Americans and their family caregivers (as measured in aim 3). This intervention, in turn, may potentially address Chinese Americans' readiness for ACP discussions (as identified in aim 2) and increase the completion rate of advance directives.

Methods

Study Design

In this study, we will use the multiphase optimization strategy (MOST) to guide the development of the culturally tailored, resilience-building intervention. MOST is an engineering-inspired framework that aims to develop a multicomponent behavioral intervention that is most efficient, affordable, and scalable [35]. It consists of 3 phases: preparation, optimization, and evaluation. In the preparation phase, intervention components are selected for inclusion and then examined through various study designs to understand the necessity of each. In the optimization phase, the final necessary components are combined and examined using a factorial experimental design to assess their individual and combined effects. In the evaluation phase, the intervention that was refined based on the results of the optimization phase is evaluated in an RCT to examine its effectiveness [36].

The proposed study will focus on the preparation phase of MOST. Based on previously reported barriers to ACP among Chinese Americans, we selected the following intervention components: (1) knowledge related to ACP [20], (2) end-of-life education [12], (3) check-ins by research staff, (4) family caregiver involvement [22], and (5) resilience skills [25]. Each component targets only one proximal mediator (Multimedia Appendix 1): (1) ACP knowledge; (2) cultural beliefs; (3) concrete support from health care providers; (4) social support from family caregivers during ACP discussions; and (5) use of adequate coping skills.

The intervention development will be informed by the interview and survey findings collected in the 3 aims. The intervention prototype will consist of five components (Multimedia Appendix 1): (1) provision of an advance directive (Five Wishes) to introduce ACP; (2) end-of-life education to overcome cultural barriers; (3) regular check-ins from a trained research staff member; (4) family caregiver involvement; and (5) a six-module resilience guide. The resilience skills taught in this intervention center around Five Wishes, a widely used advance directive that combines a living will, health care power of attorney, comfort care, and spirituality [37,38]. Patients and family caregivers will be provided with Five Wishes and the resilience guide. They will first be educated about ACP and end-of-life care, then review 1 wish from Five Wishes per module and use the resilience guide to learn 1 resilience skill to cope with that particular wish. Each module also includes a short activity to help patients and family caregivers accurately appraise the stressors and flexibly use different coping strategies for barriers related to ACP discussions.

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Ethical Considerations

This study was approved by the University of Illinois Chicago (2023-0354) and Rush University Medical Center institutional review boards (IRBs; 23061205-IRB01). Informed consent will be obtained after participants are informed that any identifiable data collected for the study will only be disclosed to others with their written permission. Participants will be compensated upon the completion of data collection (aims 1 and 3: US $50/person/hour; aim 2: US $20/person). The findings will be shared at national and regional scientific conferences, such as the American Public Health Association Annual Meeting and Society of Behavioral Medicine Annual Meeting, as well as in peer-reviewed journals and with other investigators interested in health disparities, end-of-life care, and positive psychology.

Aim 1

Setting and Sample

For aim 1, we will conduct a qualitative content analysis to understand the experiences of religious or spiritual leaders and facilitate the development of the intervention prototype. The research gap in understanding ACP from the perspective of religious or spiritual leaders led to the following research question: What are the barriers and facilitators experienced by religious or spiritual leaders, including chaplains, when addressing ACP or death-related issues with Chinese Americans in Chicago? Religious or spiritual leaders play a key role as authority figures in providing spiritual care to Chinese Americans, especially following a diagnosis of serious chronic disease [16]. We will use snowball sampling to recruit 10 religious or spiritual leaders to participate in semistructured interviews, meeting the suggested minimum sample size needed to reach saturation in qualitative research [39]. Religious or spiritual leaders, regardless of their affiliation, will be eligible for inclusion in the study if they (1) are aged 18 years and older; (2) serve as a chaplain, pastor, or monk at a health care setting or religious organization in Chicago; (3) have experience providing pastoral or spiritual care to Chinese Americans living in Chicago; and (4) are able to read and respond to questions in English or Mandarin. Religious or spiritual leaders will be excluded from the study if they are not willing to provide consent.

Procedure

For the snowball sampling, the recruitment chain will begin with 1 chaplain and 2 pastors in the Chicago region. Considering the potential bias from snowball sampling, we will purposefully select the first 3 religious or spiritual leaders who do not have a prior relationship with the interviewer (LL). Religious or spiritual leaders will be contacted by phone or email to arrange a meeting at their preferred location and mode (either in-person or via videoconference call on Zoom [Zoom Video Communications]). During initial contact, a research team member will use a telephone script to determine if the potential participant meets the eligibility criteria. Those eligible will be given an informed consent form in either paper-and-pencil or electronic format to provide the purpose, procedures, benefits, and risks of the study. Participants will be given time to review the consent form and will be encouraged to ask questions or express any concerns about the study. In addition, they will be informed that the interview will be audio and video recorded to document their verbal and nonverbal communication, including voice, tone of voice, facial expressions, gestures, body language, and posture. After consent is obtained, participants will be asked to provide their demographic information at the start of the interview. Then, a 40- to 45-minute, one-on-one, semistructured interview will proceed to ensure a rich and detailed insight into participants' experiences by asking the following open-ended questions: "Tell me about your end-of-life discussions with Chinese Americans living in Chicago"; "What barriers did you encounter when you addressed ACP and/or death-related topics with Chinese Americans?"; "Tell me about the strategies you used for ACP discussions and death-related issues"; and "Tell me about your experiences in providing end-of-life education to Chinese Americans." As one of the strategies to enhance credibility, participants will be encouraged to provide examples to support their statements regarding barriers and facilitators [40]. At the end of each interview, participants will be asked to identify other religious or spiritual leaders who have similar experiences providing spiritual care to Chinese Americans in Chicago. On interview completion, each participant will receive US $50 (cash or gift card) for their time and effort. To further enhance credibility, each participant will be contacted again with an opportunity to review their own transcripts and the interpretation of the interview data and provide feedback [40]. We have already planned for the recruitment of 10 religious or spiritual leaders, with the possibility of continuing as needed until data saturation is achieved.

Qualitative Data Analysis

To identify barriers and facilitators of ACP, all interviews will be transcribed verbatim and entered into NVivo 14 qualitative data analysis software (Lumivero). At the beginning of the content analysis, we will use an iterative process of reading transcripts to confirm their accuracy and enhance immersion in the data [41]. The first author (LL) will analyze the qualitative data using the 6-stage framework method while developing an analytical framework. The initial analytical framework will consist of two categories: (1) barriers to death and dying discussions encountered by Chinese Americans, and (2) facilitators used by religious or spiritual leaders. Under the barriers category, predefined codes will be developed based on previous literature, including cultural beliefs, indirect communication, fear, lack of knowledge, language barriers for health care, and others. Codes under the facilitators category will be derived from the open coding process [41].

The first author will then read 2 transcripts to pilot-test the codes and revise the analytical framework should any new codes arise during this process. She will then independently read the remaining 8 transcripts and highlight all text deemed to address barriers to or facilitators of end-of-life discussions. The third author (CT) will independently code line-by-line. After the first round of coding, the authors will discuss the initial analytical framework, use interrater coding tools to compare coding differences, reconcile any disagreements, and recode the transcripts if needed. Throughout this process, we will practice reflexivity by keeping a reflexive journal, conducting peer

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debriefing, and engaging in critical self-reflection [42]. The first author, who will conduct all interviews, will also specifically assess whether her religious affiliation may influence the research process, including data collection and analysis.

After completing the data analysis, we will assess the necessity of recruiting additional participants based on the consensus regarding the barriers and facilitators encountered by the 10 participants. Recruitment will cease when data saturation is achieved (ie, no further addition of information) [39]. Then, we will contact the participants and share the final interpretation of data with them for clarification, feedback, and accuracy of the data interpretation, which will then be used to refine the proposed intervention. When reporting and disseminating the findings, we will use the Joanna Briggs Institute checklist for qualitative research to ensure transferability, providing a detailed description of the research process that readers will be able to apply to their own populations and settings [40].

Aim 2

Setting and Sample

For aim 2, we will conduct a survey to understand the readiness of Chinese Americans to participate in ACP discussions with their family. Participants will be recruited from Chinese community events in Chicago. We will recruit 100 Chinese Americans who (1) are aged 18 years and older; (2) are able to read and respond to questions in English or Mandarin; and (3) self-identify as first- or second-generation Chinese Americans.

Procedure

We will approach potential participants at events specifically organized for Chinese Americans in Chicago. We will use a research information sheet to introduce the study to any potential participants we meet during the events. If they express interest in participating in the study, they will be encouraged to thoroughly read the information sheet and ask any questions they may have. After providing their verbal consent, they will proceed to complete the 34-item paper-and-pencil Chinese or English version of the ACP Engagement Survey, which assesses 4 behavior change constructs, including knowledge, contemplation, self-efficacy, and readiness within 4 ACP domains [43]. In addition, they will be asked to complete a demographic survey regarding their educational attainment, marital status, and employment status. They will also be invited to provide their contact information if they have any interest in participating in future research studies focusing on Chinese Americans.

Data Analysis Plan

Descriptive statistics, including frequencies, percentages, means, and SD, will be performed to describe the participants' demographic characteristics and their readiness for ACP discussions.

Aim 3

Setting and Sample

For aim 3, we will conduct think-aloud interviews to refine a culturally tailored, resilience-building intervention developed for and with Chinese Americans with cancer or heart disease and collect feedback on the intervention's content. Patients and family caregivers will be recruited from 2 hospitals in Chicago, which serve at least 150 Chinese Americans with cancer or heart disease every year. We will use convenience sampling to recruit 18 pairs of patients and family caregivers (9 pairs each for cancer and heart disease; N=36) for think-aloud interviews. Patients will be eligible for the think-aloud interviews if they (1) are aged 18 years and older; (2) have a cancer or heart failure diagnosis documented in the electronic medical record; (3) are able to read and respond to questions in English or Mandarin; and (4) have a family caregiver who is responsible for the care and willing to participate in the study. Family caregivers will be eligible if they are (1) aged 18 years and older; (2) able to read and respond to questions in English or Mandarin; and (3) identified by the patient as a family caregiver. Patients who (1) have cognitive impairment per a Short Portable Mental Status Questionnaire with more than three errors; (2) have received heart transplantation or a left ventricular assist device; (3) have completed an advance directive; or (4) were born in the United States will be excluded from the study.

Procedure

For aim 3, after approval by the affiliated IRBs, we will request a list of potential participants who are aged 18 years or older and have cancer or heart failure diagnosis documented in the electronic medical record from each hospital. Our recruitment process will begin by sending potential patient participants an introductory email. Following the email, we will wait for a period of 2 weeks before initiating contact with them via telephone. For individuals who have only a telephone number as contact information, we will initiate a phone call to inquire about their interest in participating in the study using a telephone script. If they express interest in participating during our initial contact through email or phone call, we will use the Short Portable Mental Status Questionnaire to assess cognitive function. After the screening, we will inform eligible participants that a family caregiver responsible for their care is required in order to participate in the study. They have the option to either provide us with the contact information of their family caregiver or have their family caregiver contact us directly through email or phone. For those who share the contact information with us, we will first recruit their family caregiver by sending an email. We will then wait for 2 weeks before initiating contact via telephone. For family caregivers who only have a telephone number as their contact information, we will initiate a phone call to inquire about their interest in participating in the study and screen for their eligibility. Eligible participants will then be given a brief description of the research and asked if they wish to learn more. If they agree, a 1-hour usability test will be arranged at a time convenient for both the patient and the identified family caregiver to meet a research team member at the University of Illinois Chicago College of Nursing Behavioral Research Core Laboratory.

Prior to the usability test, participants will first be asked to review the consent form with a research team member. They will be encouraged to ask questions they may have regarding the study during this process. Once we receive their consent, we will proceed with the 1-hour usability test. Participants will be provided with a survey regarding their demographic

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information, a copy of the Chinese version of Five Wishes, and a resilience-building guide. While participants are reading the guide, we will encourage them to verbalize their impressions of the guide and activities. The think-aloud interviews will be audio and video recorded, along with their facial expressions and movements. Participants' responses and expressions will be used for later refinement of the intervention. To assess the acceptability of the intervention, each participant, at the end of each interview, will be asked to complete the Theoretical Framework of Acceptability. The constructs included in the Theoretical Framework of Acceptability are affective attitude, burden, ethicality, opportunity costs, intervention coherence, perceived effectiveness, and self-efficacy, which can help us assess the acceptability of the intervention during both its development and modification [44]. On interview completion, each patient and family caregiver will receive US $50 in cash (a total of US $100 per pair) for their time and effort.

The culturally tailored, resilience-building intervention prototype will be evaluated and refined upon completion of each group of 3 patient and family caregiver pairs. Appropriate changes will be implemented based on the input and responses from the Theoretical Framework of Acceptability. The resilience-building guide will undergo a review by IRB before each subsequent round of participants reviews it for any changes made.

Data Analysis Plan

Data obtained through the think-aloud interviews will be transcribed verbatim; summative content analysis will be used to identify any recurrent issues. Two members of the research team will independently review the transcripts and document the occurrences of the issues. The findings will be compared until a consensus is reached between the 2 team members. All issues identified during each round of think-aloud interviews and the responses from the Theoretical Framework of Acceptability will be discussed based on the categories of the MoSCoW (Must Have, Should Have, Could Have, and Will Not Have) criteria [45]. The research team will use the MoSCoW criteria to help prioritize the necessary modifications needed, which can ensure that the intervention provides understandable and meaningful information. These modifications will contribute to a revised version of the culturally tailored, resilience-building intervention that leads to the completion of an advance directive to be optimized in the second phase of MOST.

Descriptive statistics will be calculated to assess the acceptability of the intervention through the Theoretical Framework of Acceptability. Study feasibility will be examined through (1) the number of potential patient participants who approached, screened, and consented for the aim 3 think-aloud interviews; (2) reasons for refusal to participate; (3) characteristics of the patients and family caregivers who consented versus those who refused; (4) the number of patients and family caregivers who visited the Behavioral Research Core Laboratory for the think-aloud interviews; (5) the number of tasks completed for each module during the think-aloud interviews; (6) the number of participant reminder calls completed; and (7) the facilitators and barriers to implementation and how they were addressed.

Results

Recruitment for the qualitative study (aim 1) began in November 2023 following the IRB approval. As of October 2024, a total of 7 participants have provided consent and shared their experiences during the semistructured interviews. The response rate was initially low due to the holiday season at the end of the year, and it improved after the holidays. The snowball sampling method was not as effective as expected among the population of religious or spiritual leaders, likely due to the additional workload placed on them. Instead, contacting religious or spiritual leaders by phone using the lists of religious organizations identified on the internet in Chicago made recruitment more feasible. A preliminary qualitative analysis is currently being conducted to examine the coding guide developed from previous research.

The IRB approval for conducting surveys (aim 2) has been obtained, allowing recruitment to commence in April 2024. As of October 2024, a total of 63 participants have completed the ACP Engagement Survey. Furthermore, the process and implementation of conducting and recruiting participants for the think-aloud interviews have been approved by the affiliated IRBs, and a list of potential participants has been provided by each hospital. Recruitment may begin upon completion of preliminary qualitative analysis of aim 1.

Discussion

This feasibility study presents a unique and innovative strategy to facilitate engagement in ACP discussions. Our use of multiple study designs allows us to anticipate that Chinese Americans diagnosed with cancer or heart disease and their family caregivers will accept the resulting prototype of the culturally tailored, resilience-building ACP intervention. Three aspects of the study are particularly innovative: (1) the intervention will include family caregivers, not just patients; (2) we will involve religious or spiritual leaders in developing the resilience-building intervention to address barriers to ACP; and (3) the study will use MOST as a guide for intervention development to optimize the effectiveness, affordability, scalability, and efficiency of the intervention. Completing the first phase of MOST prior to an RCT for intervention effectiveness can pinpoint practical intervention components in terms of the demand and resources needed for implementation [35]. This essential process will offer an opportunity to attain greater public health effects by reaching more underserved Chinese Americans through an affordable and scalable culturally tailored, resilience-building ACP intervention.

It should be noted that, in the development of a culturally tailored, resilience-building intervention, consideration should be given to participants' acculturation [22]. Chinese Americans in Chicago tend to be low acculturated [46]; thus, the proposed intervention aims to offer support to individuals with low acculturation by providing them with exposure to ACP and methods for resolving conflicts between their health care preferences and traditional cultural values. In fact, many cultures and communities consider the topic of ACP or death to be taboo, and while the majority of the modules in the resilience guide

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will be tailored specifically for Chinese Americans, some modules will be useful for the general population.

Finally, when using in-person observation for the think-aloud interviews, the Hawthorne effect, which happens when participants become conscious of being observed, can occur. To prevent this, we will encourage participants to think aloud about what they see and feel about the resilience guide, and the inclusion of a survey at the end of the think-aloud interview to gather additional information can help ensure that participants' feedback aligns with their responses during the interview. While the issues related to acculturation and in-person observations are beyond the scope of this study, they will be included in the design of future studies for the second phase of MOST.

Acknowledgments

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LTHL wrote the manuscript; LTHL and AD are responsible for the protocol and intervention development; CCL provides consults on intervention refinement and study implementation; and LTHL, CYT, and AD are responsible for data analysis. All authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Components of the resilience-building intervention to facilitate ACP discussions. ACP: advance care planning.
[DOCX File , 15 KB - resprot_v13i1e59343_app1.docx]

Multimedia Appendix 2
Peer-review report by the Chicago Chronic Condition Equity Framework (Chicago, USA).
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e59343_app2.pdf]

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Abbreviations

ACP: advance care planning
IRB: institutional review board
MoSCoW: Must Have, Should Have, Could Have, and Will Not Have
MOST: multiphase optimization strategy
RCT: randomized controlled trial

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Protocol

Personalized Deep Learning for Substance Use in Hawaii: Protocol for a Passive Sensing and Ecological Momentary Assessment Study

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Abstract

Background: Artificial intelligence (AI)–powered digital therapies that detect methamphetamine cravings via consumer devices have the potential to reduce health care disparities by providing remote and accessible care solutions to communities with limited care solutions, such as Native Hawaiian, Filipino, and Pacific Islander communities. However, Native Hawaiian, Filipino, and Pacific Islander communities are understudied with respect to digital therapeutics and AI health sensing despite using technology at the same rates as other racial groups.

Objective: In this study, we aimed to understand the feasibility of continuous remote digital monitoring and ecological momentary assessments in Native Hawaiian, Filipino, and Pacific Islander communities in Hawaii by curating a novel data set of longitudinal Fitbit (Fitbit Inc) biosignals with the corresponding craving and substance use labels. We also aimed to develop personalized AI models that predict methamphetamine craving events in real time using wearable sensor data.

Methods: We will develop personalized AI and machine learning models for methamphetamine use and craving prediction in 40 individuals from Native Hawaiian, Filipino, and Pacific Islander communities by curating a novel data set of real-time Fitbit biosensor readings and the corresponding participant annotations (ie, raw self-reported substance use data) of their methamphetamine use and cravings. In the process of collecting this data set, we will gain insights into cultural and other human factors that can challenge the proper acquisition of precise annotations. With the resulting data set, we will use self-supervised learning AI approaches, which are a new family of machine learning methods that allows a neural network to be trained without labels by being optimized to make predictions about the data. The inputs to the proposed AI models are Fitbit biosensor readings, and the outputs are predictions of methamphetamine use or craving. This paradigm is gaining increased attention in AI for health care.

Results: To date, more than 40 individuals have expressed interest in participating in the study, and we have successfully recruited our first 5 participants with minimal logistical challenges and proper compliance. Several logistical challenges that the research team has encountered so far and the related implications are discussed.

Conclusions: We expect to develop models that significantly outperform traditional supervised methods by finetuning according to the data of a participant. Such methods will enable AI solutions that work with the limited data available from Native Hawaiian, Filipino, and Pacific Islander populations and that are inherently unbiased owing to their personalized nature. Such models can support future AI-powered digital therapeutics for substance abuse.

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KEYWORDS

machine learning; precision health; Indigenous data sovereignty; substance use; personalized artificial intelligence; wearables; ecological momentary assessments; passive sensing; mobile phone

Introduction

Background

Methamphetamine abuse is highly prevalent in Hawaii, especially among Indigenous Pacific Peoples [1]. Since the 1980s, Hawaii has been considered the methamphetamine capital of the United States. Data from the Pacific Health Analytics Collaborative show that from 2015 to 2018, in total, 1.5% of Hawaiian residents used methamphetamine annually [2]. This was more than twice the national rate of 0.6%. According to the Bureau of Alcohol, Tobacco, Firearms, and Explosives, 71% of all drug cases in Hawaii were related to methamphetamine [3]. There are major methamphetamine-related disparities between Native Hawaiian, Filipino, and Pacific Islander individuals and people of other races in Hawaii, with Native Hawaiian, Filipino, and Pacific Islander individuals exhibiting elevated rates of illicit substance abuse [4]. According to the Centers for Disease Control and Prevention, Native Hawaiian and Pacific Islander high school students exhibited lifetime methamphetamine use of 7.7% versus 3.7% in White students, 2.7% in Black students, 3.1% in Asian students, and 5.7% in Hispanic and Latino students, and these disparities continued into adulthood [5]. Digital interventions powered by artificial intelligence (AI) have the potential to reduce these disparities by aiding clinicians in remotely providing care and monitoring patients between visits, especially among populations living in rural areas in Hawaii. Furthermore, such technology could be useful in relapse prevention for those hoping to maintain abstinence. In Hawaii in 2021, a total of 96% of residents possessed at least 1 piece of hardware with internet capacity, with only 4% lacking access to such equipment, indicating widespread internet access among the population [6].

AI-based detection of substance abuse using biometric signals measured by wearables is an active field of research across several research laboratories globally, as documented in a 2022 review paper by Rumbut et al [7]. Studies in this field tend to collect prediction labels through the remote administration of an ecological momentary assessment (EMA), a methodology in which participants are periodically asked to answer questions about their psychiatric or behavioral state while living as usual [8-10]. Notably, previous AI models suffered from clinically unacceptable performance. The primary reason for this lackluster performance is that prior methods attempted to train models using data from many patients, which is the status quo in deep learning because of the requirement of massive data sets for successful training. In contrast to these prior works, we will develop personalized AI models using a method developed in PW's laboratory, which are capable of learning baseline patterns of human behavior and transferring this knowledge to prediction tasks with very few labeled examples to learn from.

Our research laboratory is particularly qualified to carry out this project as we are already developing computer science methods to support the personalization of AI models for large and mostly unlabeled data streams, with promising preliminary data and publications in preparation supporting this methodology. As a T1 (covering basic discovery) or T2 (initial human trials) project, our proposed study is significant both in terms of equitable substance abuse therapeutics and as a general methodology for clinical and translational research in other domains. There are countless situations in health care where vast amounts of unlabeled data are collected from a single patient. Annotations for the event of interest (eg, substance abuse) are frequently sparsely dispersed. The development of predictive supervised models is infeasible in such circumstances because classical approaches cannot handle the complexity of data, and modern deep learning approaches require vast amounts of data.

Innovation

To support machine learning (ML) development in situations where vast longitudinal data are collected with minimal human-provided annotations, we propose the development of personalized ML models, which are trained solely on an individual's unlabeled data to learn feature representations that are specific to their baseline temporal dynamics. We are creating a novel method and framework that has never been explored in health care, consisting of pretraining neural networks to learn the temporal dynamics of a patient's biosignals. This method will enable deep networks to be trained using relatively small data sets, which would not be possible without the self-supervised approach proposed in this study. This technique is particularly well-suited for massive data sets with few labels.

The application of personalized AI to a diverse population of persons using substances is unique. Native Hawaiian, Filipino, and Pacific Islander communities have been understudied and could benefit from novel treatments to address methamphetamine use. Although we will apply this technological innovation toward the prediction of methamphetamine use, multimodal time-series personalization can be applied to a variety of other biological and health problems where (1) multiple signals are sparsely emitted, (2) the baseline signal patterns are specific to each individual, and (3) it is infeasible to acquire the vast amounts of labels required to train a supervised deep learning model.

This method has the potential to dramatically advance the field of precision health care by enabling reliable AI predictions from massive but mostly unlabeled data sets, which are trained in a self-supervised manner on data from a single user. This setting of large, unlabeled data sets with sparse supervision appears frequently in the field of digital health care. Notable examples include passive mobile sensing studies for mental health and well-being [11-20], digital therapeutics for children with autism spectrum disorder that record videos of the child [21-37], and passive brain sensors for brain-computer interfaces [38-46]. As such, this study protocol can be considered as one of the first tests of a broader emerging paradigm in precision health.

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Methods

Overview

The long-term methodological goal of the proposed work is to develop novel AI methodologies for predicting health events (eg, methamphetamine use and cravings) using biosensors in a personalized manner. This technical innovation will be applied toward the detection of drug use events from wearable device sensors. The inputs to the proposed AI models are Fitbit (Fitbit Inc [47]) biosensor readings, and the outputs are predictions of methamphetamine use or craving (Figure 1). The methods developed can be applied to a variety of biomedical domains.

Figure 1. In many biomedical domains, there exist large data sets with sparse annotations of health events. We propose a "personalized self-supervised learning" method that can support the training of deep neural networks in such scenarios. We will evaluate our method primarily on the prediction of methamphetamine use events using biosignal data from a Fitbit device.

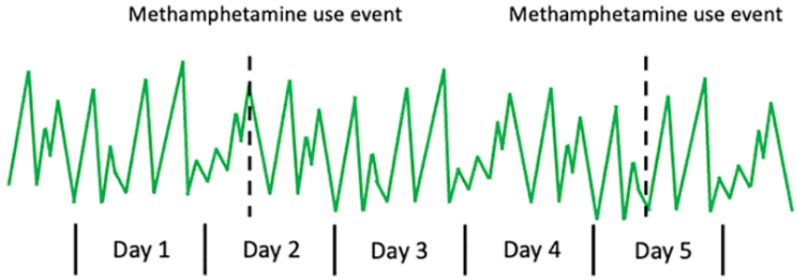

Diagnostic ML models are typically trained and deployed at a population level. In this traditional scenario, a single model is developed to make predictions for all individuals within a population. However, in several health contexts, an event of interest occurs repeatedly for an individual. For example, patients with diabetes have repeated blood glucose spikes, and chronically stressed individuals might have repeated blood pressure spikes. In these cases, ML models can be developed by conducting supervised training on the individual's data only, resulting in a separate personalized model per individual. Although deep learning models have achieved state-of-the-art performance in a variety of health contexts, neural networks require massive data sets that are infeasible to collect for an individual. However, recent advances in self-supervised learning (SSL), or the subfield of ML focusing on pretraining models without any human-provided labels, have made it possible to realize the personalized ML diagnostics paradigm using deep learning by pretraining the weights of a neural network such that it can learn the baseline temporal dynamics without any labels. The pretrained model can then use transfer learning on relatively few labels that are acquired solely from the individual in question. This methodology can work particularly well in scenarios where massive amounts of unlabeled data are collected, such as with continuously worn devices.

Aim 1: To Understand the Feasibility of Remote Digital Monitoring and EMAs in Native Hawaiian, Filipino, and Pacific Islander Communities by Curating Longitudinal Fitbit Biosignals With the Corresponding Substance Use and Craving Labels

Description

We will recruit 40 carefully selected Native Hawaiian, Filipino, and Pacific Islander participants who are either in treatment or have received services from one of our community partners to participate in a 4-week remote Fitbit data collection and concurrent EMA study. EMA studies, which involve periodic digital self-reports about psychiatric and behavioral outcomes *in the wild*, have often been used to understand substance abuse [48], including among persons who use methamphetamine [49]. We expect ≥80% complete data from approximately 25% (10/40) of the participants (refer to the *Recruitment* section for justification). Each participant will wear a study-provided Fitbit Charge 5 watch during all waking hours for at least 15 hours each day. Apart from wearing the device and periodically recording an EMA about their methamphetamine use via a mobile smartphone app (Figure 2), participants will be asked to follow their normal routine throughout the study.

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Figure 2. User interface of the ecological monitoring app provided to participants.

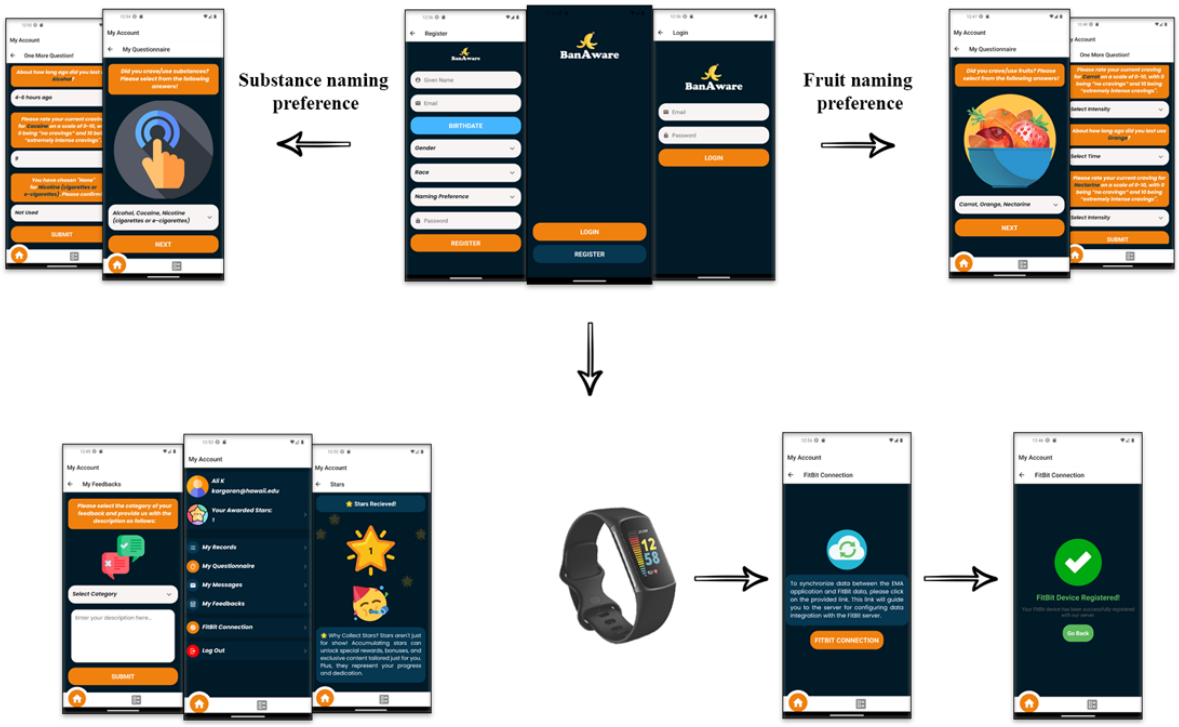

Participant Recruitment and Management

We will recruit participants from a combination of sites, including the Hawaii Health and Harm Reduction Center and other sites where the clinical collaborators have connections (ie, Hina Mauka). Potential participants will be eligible for the study if they (1) are aged ≥18 years, (2) self-report consumption of methamphetamine on ≥2 different days per week on average, (3) have no plans to leave Oahu for at least 1 month, and (4) own a smartphone with either a data plan or regular access to a Wi-Fi connection. Potential participants will be excluded if they (1) are homicidal or suicidal, (2) cannot provide informed consent, (3) are not able to complete interviews in English, (4) are expecting incarceration or plan to leave Oahu within the next month, or (5) are unable to provide names and contact information for at least 2 verifiable locator persons for retention purposes.

We will recruit 40 participants in total. A secondary analysis of EMAs for methamphetamine abuse monitoring measured the percentage of participants who reached ≥80% compliance at different frequencies of methamphetamine use, finding that approximately 50% of persons who use methamphetamine 1 to 3 times per month met this 80% compliance bar, and 40% using 1 to 2 days per week met the bar, and 25% using 3 to 4 days per week met the bar [50]. Therefore, we anticipated that approximately 25% (10/40) of the participants will reach ≥80% compliance rate, which is sufficient to demonstrate the feasibility of our AI method, as a separate analysis will be conducted for each participant (ie, 1 model per participant).

Data Collection

We will leverage the existing application programming interface provided by Fitbit to record the user's watch sensor readings and upload the data to the cloud. The Fitbit application programming interface provides access to heart rate (HR), gyroscope and accelerometer readings, breathing rate, blood oxygen saturation (SpO_2) level, and skin temperature sensor readings. These biosensors have previously been used to predict substance abuse and cravings using AI [51-55]. The data will be managed on each participant's smartphone device through an app, implemented for both iOS and Android, which we are actively developing. The study team will install the app on the user's smartphone and configure the Fitbit device during study onboarding.

We will run the study with 8 (20%) of the 40 participants at a time as we have 8 Fitbit Charge 5 devices, resulting in 5 batches of data collection periods. We will record background characteristics, substance use, and treatment history during study intake, and we will record questions pertaining to the tolerability and obtrusiveness of the app during study outtake (Textbox 1). The smartphone app will record EMA responses from the participants throughout the 1-month study period (Textbox 1). At each EMA, we will ask participants to list the approximate times (eg, date, hour, and minute) of their methamphetamine intake in the past 24 hours via a user interface on the smartphone app. Participants will be asked to do the same for cravings. Participants will be prompted to provide EMA responses both when drastic signal changes are detected (ie, event-triggered EMA) and every 24 hours (ie, fixed-interval EMA).

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Textbox 1. Study intake and outtake measures and ecological momentary assessment (EMA) questions collected from each participant.

Background characteristics (intake)

- To better describe the sample, participants will be asked about their gender, sexual orientation, age, race or ethnicity, marital status, education, income, employment, housing, and health insurance status.

Substance use and treatment history (intake)

- Questions will be developed to assess current and history of substance use and participation in treatment services.

Tolerability (study conclusion)

- How comfortable was the device?

Obtrusiveness (study conclusion)

- Did the device change your daily routine? Do you have any concerns with continuously Fitbit usage?

Methamphetamine use (EMA)

- Have you used meth since the last time we contacted you?
- Approximately what time did you last use meth?
- How did you use meth the last time you used?

Craving (EMA)

- Please rate your current craving or desire to use methamphetamine at this exact moment on a scale of 0-10, with 0 being “no cravings” and 10 being “extremely intense cravings.”

We will institute procedures to reduce the burden associated with EMA and increase compliance as suggested by Burke et al [56]. To reduce the burden related to time commitment, we are compensating for every signal-contingent response and providing additional compensation when participants respond to >80% of prompts. Participants will be trained extensively on the EMA protocol at baseline, and if they experience any technology-related issues, our research assistants will help troubleshoot these issues remotely. Participants who experience technology-related problems will not have their compensation reduced because of missing prompts.

We will store the curated data from each participant (Figure 2) on a centralized server hosted on Amazon Web Services (AWS; Amazon). Data uploaded from both wearable systems and the smartphone will first run through a preprocessing server hosted on an elastic cloud computing (EC2) instance with data stored on DynamoDB (Amazon). Each table will have columns for the participant ID and timestamp. To ensure privacy and Health Insurance Portability and Accountability Act (HIPAA) compliance, we will encrypt all server-side data and require secret access keys for data access. DynamoDB tables are automatically encrypted on the server side. To add an additional layer of security, we will implement client-side encryption on the mobile app, ensuring encrypted data transmission across an https connection to move data between the devices and AWS. The data will not be accessible without a secret access key. All data will be anonymized.

An anonymized version of participant data will be made available to other computational researchers as a publicly available data set. This data set will be stored on AWS on a HIPAA-compliant server and will be password protected. Researchers will only gain access to this data set by signing a data use agreement. Such data sets exist for activity and emotion recognition from wearable data, but the prediction of methamphetamine use from these measurements will be a challenging task, and other ML practitioners can improve upon our initial AI models with the release of the deidentified data set. This will be the first publicly available data set that includes substance use self-reports alongside wearable sensor readings.

Data Analysis and Interpretation

We will measure the success rate of the remote data collection procedure using the response rate to EMA notifications. We hypothesize that we will observe higher compliance rates with event-triggered EMAs than fixed-interval EMAs. Furthermore, we will document qualitative challenges with the data collection process, tolerability, and unobtrusiveness (Textbox 1). We will conduct an interview with the participants at the study conclusion when the devices are returned. The research team will qualitatively code interview responses to derive recurring themes and design insights.

Potential Pitfalls and Mitigation Strategies

This analysis plan is uniquely robust to incomplete data collection because a separate AI model will be trained and evaluated for each participant. There is no requirement for equivalent data streams between participants nor will the analysis be prevented if the full 28-day data collection period is not achieved. The ML strategy can work with only a few logged methamphetamine use events. We expect approximately 25% (10/40) of the participants to complete the study at a sufficient level of compliance to support personalized ML analysis. This will provide sufficient data to demonstrate the feasibility of personalized ML analysis.

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We have budgeted a 4-month buffer period beyond the 5 months required for complete data collection to account for participant delays and no-shows. Because participant data will be uploaded to AWS daily, we will remotely monitor participants through an automated tracking system already developed in our research laboratory and will cease the study if compliance is not logged after 4 days. Another possible issue is Fitbit theft or loss. To minimize this risk, participants will be compensated a minimum of US $135 for study completion and a maximum of US $210, which will be paid when the Fitbit device is returned. In the case of Fitbit device breakage or loss, our laboratory will purchase additional devices with funds separated from Center for Pacific Innovations, Knowledge, and Opportunities, up to a limit of 6 additional devices along the course of the study period.

Aim 2: To Develop Real-Time Personalized AI Models Predicting Methamphetamine Use and Craving With Fitbit Sensor Data

Description

On the basis of extensive support from prior literature, we hypothesize that AI solutions can detect periods of both methamphetamine use and cravings with high sensitivity through the personalization of ML models. Such models will achieve high performance on a single individual through the finetuning of each model using only the data curated from the person of interest for model training. These personalized predictions can trigger the onset of digital therapy. We will develop two AI models per participant: (1) a model that detects methamphetamine use in real time and (2) a model that predicts methamphetamine craving in real time. We hypothesize that model personalization using novel self-supervised pretraining strategies will outperform traditional state-of-the-art AI techniques with <5% of the required label data.

ML Model Training

The inputs to the models will consist of a separate 1D convolutional backbone pretrained for each biometric modality. The convolutional features will be fused upstream into a shared joint dense representation space and finally a dense prediction layer with linear activation for regression prediction (Figure 3). We will implement all models using TensorFlow (Google Brain) [57].

Figure 3. The key methodological computer science innovation of this protocol is the personalization of machine learning models that make predictions from biosignals time-series data without user-provided labels. In this figure, we depict a neural network that is trained to predict a heart rate signal given SpO_2 levels and accelerometer signals from a single participant. SpO_2: blood oxygen saturation.

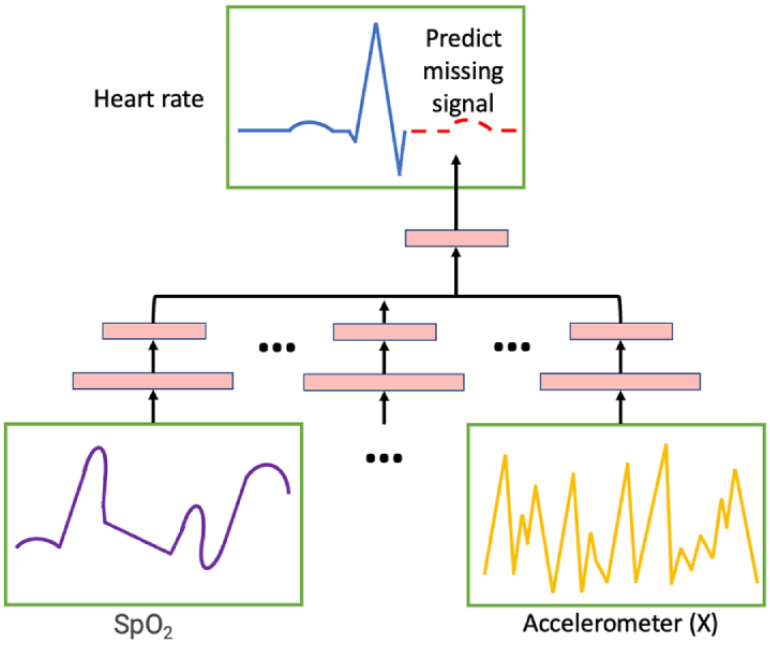

The data augmentation techniques that we apply to the signals will be domain specific, keeping in mind the inherent dynamics of each sensor. For example, for accelerometer data, rotations simulate different sensor placements, and cropping is used to diminish the dependency on event locations [58]. Across several modalities, sensor noise can be simulated through scaling, magnitude warping, and jittering [58]. We will be careful not to apply augmentation strategies that might change the meaning of the underlying signal.

Model Personalization

SSL is usually used to pretrain an entire data set with no explicit labeling by humans to guide the supervision task. We propose to redesign the SSL paradigm toward the task of model personalization. By pretraining a model only on the vast amounts of data curated from a single individual, the weights of the neural network will learn to make predictions using the inherent structure of each participant's biosignals. This is essential because baseline HR, SpO_2, skin temperature, and movement patterns, regardless of stress, will vary drastically across individuals, limiting the performance of general-purpose ML models.

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We plan to exploit the multimodal time-series nature of the collected data to perform novel SSL pretraining. We will use ≥1 signal to predict the value of another signal source (Figure 4). The motivation for this approach is that the biometrics of interest recorded by Fitbit are correlated [59-62].

Figure 4. Depiction of the proposed data set, consisting of continuous Fitbit Charge 5 sensor readings and the corresponding methamphetamine use and craving annotations from 20 participants collected over a 4-week period. HR: heart rate; SpO_2: blood oxygen saturation.

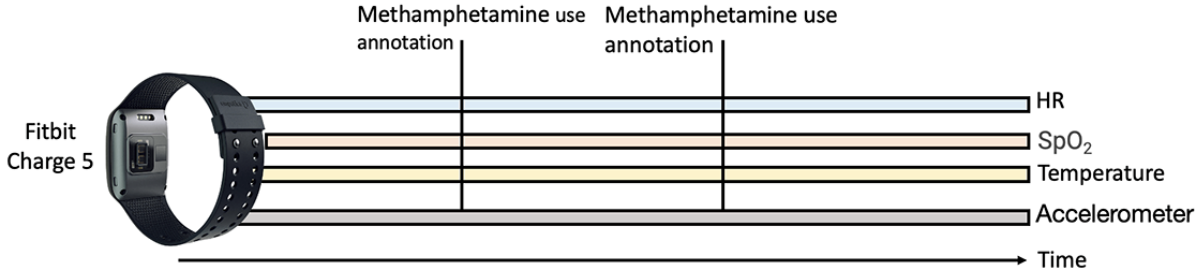

Data Analysis and Interpretation

We will train the model on the first 75% of the data (by time) and calculate the balanced accuracy, precision, recall, F_1-score, and area under the receiver operating characteristic curve for the final 25%. This evaluation pattern mimics real-world use, where a model will be calibrated by a user before real-world deployment. It is important to emphasize that we will train and test a separate personalized ML model for each individual (up to 40 separate models).

In a manner similar to our preliminary data, we will evaluate the models by comparing the performance with respect to the number of labeled examples used for supervised finetuning. A plot of this comparison will elucidate the number of methamphetamine annotations required for model calibration to an individual. We will create a separate plot for each study participant as the ML portion of this protocol tests the personalization of ML models rather than a general-purpose one-size-fits-all ML model, which is more typical in ML evaluations.

Feasibility

Self-supervised pretraining has been successfully demonstrated in several contexts in computer science and even health care [59,63,64], although not in the personalized context that we will explore, except for preliminary results that we have recently published [65-68]. Multimodal SSL has demonstrated success in prior literature [69-72], although not in the personalized manner in which we will innovate.

Ethical Considerations

This protocol was approved by the University of Hawaii Institutional Review Board (protocol #2022-01030). In addition, this study has received further scrutiny and approval from the University of Hawaii Data Governance Process (request #230410-3).

Informed consent will be provided by the participants on paper during the intake session of the study.

Participants will provide information about their substance use on a smartphone app that we have created and will install on the phones of each participant. Because Fitbit is owned by Google, participants' Fitbit data will be uploaded directly to Google's cloud servers, which uses the same level of security as other Google products, such as Gmail.

Access to each participant's Fitbit data on Google's cloud servers is implemented through OAuth, which provides clients with secure delegated access to server resources on behalf of a resource owner (ie, the participants of this study). This mechanism is used by companies such as Amazon, Google, Facebook, Microsoft, and X (X Corp, formerly known as Twitter) to permit the users to share information about their accounts with third-party apps or websites. In this case, the "third party" is the study team.

Access to each participant's annotations of substance use and craving from their smartphone app will be immediately uploaded to our secure and encrypted server on AWS, which is HIPAA compliant [73]. The participant's data will be immediately removed from their smartphone after successful uploading to AWS.

All participant data will be analyzed on AWS. A fully anonymized version of the data set will be released to researchers who sign a data use agreement, which will be approved by the University of Hawaii Data Governance Office.

As a precaution, the interface on the app will not be labeled as "substance consumption" and "substance use" but rather as "banana consumption" and "banana use." Furthermore, our data will be stored and labeled as "fruit" rather than "substance use."

The participant's data that will be accessible to the study team will include biometrics data from Fitbit, labels of "banana consumption" and "banana use" with the corresponding timestamps, and a unique participant ID. Digital data will only contain participant IDs rather than identifiable information. A paper copy of the participant's mapping from the participant ID to the name and contact information will be stored on paper and securely locked in a lockbox hidden in PW's desk. The lockbox in PW's desk is secured with a key that only PW has access to, and his desk is in his office, which is secured with another key that only PW has access to. PW's office is located within a suite of offices, which is secured by a third key that only professors in the Information and Computer Sciences Department have access to and which currently only PW has access to.

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We will anonymize all the collected data. We will be provided with a Federal Certificate of Confidentiality from the National Institutes of Health, which will protect participants and assure confidentiality and privacy. KTP, a member of the mentorship and community teams, has found that having a Certificate of Confidentiality helps retain participants in lengthy projects.

Compensation Type and Amount

We will provide the participants with US $135 for participation in the study. This amount is commensurate compensation for the requested work (wearing a smartwatch during all waking hours of the day for 4 weeks while continuously annotating their craving events). In addition, this compensation amount is above the market rate of a Fitbit device, helping to mitigate the risk of device theft by study participants.

US $20 will be provided to the participants to cover their transportation expenses for attending 2 in-person meetings on campus.

Furthermore, we will use snowball sampling as a form of recruitment, where participants can choose to refer their acquaintances to the study. Enrolled participants will be encouraged to refer other eligible participants to the study and will receive US $5 each for up to 3 referrals who enroll. The participants will be given 3 recruitment cards to distribute to eligible participants. When a new and eligible enrollee presents the card, the recruiting participant will receive US $5 compensation. If the recruiting participant has already completed the study, they will be contacted via their assigned study phone number (eg, by phone or SMS text messaging) or email to receive the compensation. If this proves unsuccessful, we will reach out to locator contacts or send a letter notifying the participant that they are eligible for the additional compensation.

Finally, we can compensate participants an extra US $40 as an incentive for providing responses on schedule and consistently throughout the study period.

Results

Starting from November 2023, a total of 5 participants visited our laboratory and received Fitbit devices, including 4 (80%) male individuals and 1 (20%) female individual, aged between 22 and 63 years, representing 3 different ethnicities: 3 (60%) are White, 1 (20%) is Mexican, and 1 (20%) is Filipino Hawaiian.

Among the 5 participants, 178 logs have been collected. They completed an average of 8.6 days of EMA activity reporting, with each participant logging their data approximately 4 times per day. In total, the participants reported 40 instances of substance craving and 61 instances of substance use, including methamphetamine, alcohol, cannabis, and nicotine.

Fitbit devices recorded sensor data, including HR, number of steps, SpO_2, HR variability, and breathing rate. HR and number of steps were tracked throughout the day, whereas SpO_2 level, HR variability, and breathing rate were monitored during sleep.

Challenges related to EMA prompt reception were initially experienced by 1 (20%) of the 5 participants, but these were promptly resolved by the research team. In addition, labor-intensive reporting of simultaneous substance use and documenting of constant nicotine use posed difficulties for this participant. Another participant noted increased awareness of substance-related thoughts owing to EMA prompts.

Discussion

Preliminary Findings

To our knowledge, this is the first study to evaluate the feasibility of using a mobile app–based EMA to prospectively capture substance use among the Native Hawaiian, Filipino, and Pacific Islander population. Despite challenges, this study provides evidence to support the feasibility and acceptability of using EMA methods for collecting data on substance use in this population.

Following our research protocol, we successfully recruited 5 participants for our study in the first month of recruitment. Our research protocol, which included 4 scheduled prompts per day, was designed to represent a lower to moderate participant burden [74,75]. Each participant consistently provided an average of 4 logs per day. We received no significant issues or complaints from the participants, and their logging activities have been continuous. This partially aligns with prior studies by Phillips et al [76], Turner et al [50], and Hanson et al [77], who found that it is feasible and acceptable to use EMA to evaluate substances (eg, alcohol and methamphetamine) with people who come from historically marginalized groups.

Meanwhile, 1 (20%) of the 5 participants showed hesitancy regarding privacy concerns when discussing certain types of substances, as reported in the study by Han et al [78] that substance use can still be associated with social stigma. This suggests that building and maintaining a trusting relationship with the participants throughout the study, and even afterward, is crucial.

Despite concerns raised by Adams et al [79] about the potential impact of busy schedules on response rates, no significant problems were encountered in this regard as long as participants initiated their study. However, instances were experienced in which eligible individuals needed to reschedule their meetings because of their demanding work schedules. To accommodate their availability, the research team maintained a flexible schedule to encourage these individuals to visit the laboratory at their convenience. Weekly check-ins were conducted by the research team with the participants to ensure effective participation and promptly address any issues that arose.

Although prior studies, such as those by Cao et al [80] and Rodrigues et al [81], have successfully used Fitbit devices to collect sleep data, one challenge encountered by the research team is the absence of those data (eg, SpO_2 level, HR variability, and breathing rate) that can only be collected while participants are asleep, despite the participants' claims that they wear the Fitbit devices during sleep. To address this issue, the research team recommended that participants activate the sensitive mode for sleep sensitivity in the Fitbit app settings and ensure that they wear the devices tightly or close enough to their wrists. However, this recommendation might negatively affect the

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participants' sleep quality, particularly for those who have self-reported sleeping problems.

This research protocol provides compensation to participants for reporting substance use events. However, this approach might lead to an increase in data noise, as observed when 1 (20%) participant provided 7 logs in a single day. The research team will diligently review these data to ensure their effectiveness and minimize potential noise.

None of the participants have reported participation exhaustion owing to the research protocol so far, despite such findings reported by Yang et al [75] and Semborski et al [82] in their studies. This may be attributed to the fact that many participants are still in their first or second weeks of the study. However, the research team observed that contacting participants >2 times per week could induce stress, particularly when technical issues persist without resolution. In response to these observations, the research team has currently limited their contact with each participant to a maximum of 2 times per week to mitigate participant exhaustion. Future studies may benefit from reducing contact frequency and providing clear and efficient instructions whenever such issues arise. Another issue related to participation fatigue or dropout is the extended waiting time for study entry. Despite the research team's efforts to maintain contact with individuals who registered as early as May 2023, some of them may no longer be available or interested after several months of waiting. Future studies should minimize the waiting period to prevent potential disengagement.

One (20%) of the 5 participants expressed concerns about the increased contemplation of substances when responding to EMA prompts. Similarly, Fridberg et al [74] noted a slight increase in self-reported alcohol consequences in their EMA study. One plausible explanation is that certain EMA protocols may induce stress [82], potentially triggering substance use [83]. This study is in its initial stages and cannot provide any conclusions. The research team will closely monitor this participant and conduct weekly check-ins to ensure that there are no adverse effects.

This study has several limitations. Given the small sample size, the preliminary findings do not have enough statistical power to provide any significant findings on participants' substance use and craving patterns or sociocultural factors that might affect those activities. The EMA prompts primarily collect quantitative data related to the scale, timing, or dates of substance use or cravings, excluding information on social and cultural factors that may trigger or influence substance cravings or use. For instance, we could not capture the presence of others during these moments using EMA prompts. Meanwhile, incorporating these questions into EMA prompts as self-reported data could have imposed cognitive demands on the participants, potentially impacting response rates and causing participation fatigue. To address this limitation, we plan to conduct in-depth semistructured interviews to explore the social and cultural factors.

One (20%) of the 5 participants highlighted the challenge of logging multiple substance use instances simultaneously and recommended the implementation of a more user-friendly feature in such situations. Currently, the research team is actively working to enhance this feature. In future studies, it is advisable to consider providing a more intuitive design when requiring participants to submit multiple logs in a more streamlined manner.

Our target population consisted of Native Hawaiian, Filipino, and Pacific Islander individuals; however, none of the team members belonged to this community, despite some team members having lived in Hawaii for >5 years. To address this limitation, the research team will work closely with the local partners, such as Hawaii Health and Harm Reduction Center and Hina Mauka, to ensure that key social and cultural factors are not overlooked.

Another limitation of our study is the exclusion of potentially eligible individuals who do not own a mobile phone or lack internet access. Future research endeavors could enhance inclusivity by considering the provision of mobile phones with a data plan for individuals who lack these resources.

Conclusions

An EMA using smartphone apps offers a broad scope of research perspectives. Its capacity to capture phenomena instantaneously within real-life contexts grants the EMA a promising vantage point for understanding methamphetamine use and cravings among the Native Hawaiian, Filipino, and Pacific Islander population and other racial groups in Hawaii who have experienced methamphetamine-related disparities from the 1980s. Given the dearth of research on this issue within the targeted, historically marginalized group, sharing and presenting a standardized and innovative protocol for conducting EMA studies on methamphetamine use is crucial, which is the primary objective of this study.

We anticipate that this study will yield valuable insights into the feasibility of using EMA methods in this particular population and the sociocultural factors that can affect precise data acquisition. Furthermore, it will enable the development of personalized AI models for predicting methamphetamine-related behaviors within this demographic group. To date, our preliminary findings indicate promising outcomes associated with the use of EMA methods for data collection.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AWS: Amazon Web Services
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
HR: heart rate
ML: machine learning
SpO_2: blood oxygen saturation
SSL: self-supervised learning

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Protocol

Digitally Diagnosing Multiple Developmental Delays Using Crowdsourcing Fused With Machine Learning: Protocol for a Human-in-the-Loop Machine Learning Study

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Abstract

Background: A considerable number of minors in the United States are diagnosed with developmental or psychiatric conditions, potentially influenced by underdiagnosis factors such as cost, distance, and clinician availability. Despite the potential of digital phenotyping tools with machine learning (ML) approaches to expedite diagnoses and enhance diagnostic services for pediatric psychiatric conditions, existing methods face limitations because they use a limited set of social features for prediction tasks and focus on a single binary prediction, resulting in uncertain accuracies.

Objective: This study aims to propose the development of a gamified web system for data collection, followed by a fusion of novel crowdsourcing algorithms with ML behavioral feature extraction approaches to simultaneously predict diagnoses of autism spectrum disorder and attention-deficit/hyperactivity disorder in a precise and specific manner.

Methods: The proposed pipeline will consist of (1) gamified web applications to curate videos of social interactions adaptively based on the needs of the diagnostic system, (2) behavioral feature extraction techniques consisting of automated ML methods and novel crowdsourcing algorithms, and (3) the development of ML models that classify several conditions simultaneously and that adaptively request additional information based on uncertainties about the data.

Results: A preliminary version of the web interface has been implemented, and a prior feature selection method has highlighted a core set of behavioral features that can be targeted through the proposed gamified approach.

Conclusions: The prospect for high reward stems from the possibility of creating the first artificial intelligence–powered tool that can identify complex social behaviors well enough to distinguish conditions with nuanced differentiators such as autism spectrum disorder and attention-deficit/hyperactivity disorder.

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KEYWORDS

machine learning; crowdsourcing; autism spectrum disorder; ASD; attention-deficit/hyperactivity disorder; ADHD; precision health

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Introduction

Background

Approximately 17% of minors in the United States aged 3 to 17 years have a diagnosis of ≥1 developmental or psychiatric conditions [1], with the true prevalence likely being higher because of underdiagnosis in rural areas and for minority populations [2]. Unfortunately, timely diagnostic services are inaccessible to a large portion of the United States and global population owing to cost, distance, and clinician availability. Digital phenotyping tools have the potential to shorten the time to diagnosis and bring diagnostic services to more people by enabling accessible evaluations. Although automated machine learning (ML) approaches for the detection of pediatric psychiatric conditions have garnered increased research attention in recent years, existing approaches use a limited set of social features for the prediction task and focus on a single binary prediction.

Many psychiatric conditions affecting adolescents contain overlapping etiologies and phenotypic characteristics. A major difficulty preventing the expansion of computational methods into the simultaneous prediction of multiple related conditions stems from heavy similarities between their phenotypes, creating barriers to achieving specificity and precision. Although some of the key overlapping and distinct features of these conditions are related to behaviors that can be automatically detected with ML methods, such as eye gaze patterns and facial emotion evocation, the majority are too complex for current ML techniques to classify precisely. For example, the degree to which a child enjoys participating in social games and interactions is one of the most salient behavioral features for autism spectrum disorder (ASD) diagnosis [3]. However, building an ML model for behavioral features is infeasible because of outliers and irrelevant, noisy features. These factors contribute to poor data generalization and increase the risk of overfitting. Furthermore, the constraints of existing benchmark data sets, characterized by a limited number of participants, pose challenges for deep learning (DL) models that thrive on substantial, diverse, and representative data to capture complex and nuanced features accurately [4]. By contrast, humans can naturally identify complex and nuanced behaviors by observing their peers. Crowdsourcing, or the use of distributed human workers toward a common goal, has the potential to bridge this gap by enabling rapid feature tagging of complex behaviors on demand. Although crowdsourcing has traditionally been used for public health studies and labeling ML training data, we plan to explore the incorporation of human labels into the feature extraction process. The intuition behind the proposed paradigm is that although nonprofessionals may be unable to directly identify psychiatric diagnoses from videos, many can tag behaviors that are relevant to a diagnosis.

We propose to develop a novel paradigm for accessible and scalable multicondition digital diagnostics of neuropsychiatric conditions by fusing traditional ML with novel human-in-the-loop crowdsourcing approaches. Although this approach (Figure 1) can be applied toward classification between any set of psychiatric conditions, we will focus on attention-deficit/hyperactivity disorder (ADHD) and ASD to maintain feasibility. The approach will comprise (1) developing gamified web applications to curate videos of social interactions adaptively based on needs of the diagnostic system, (2) innovative behavioral feature extraction techniques consisting of automated ML methods and novel crowdsourcing algorithms, and (3) ML models that classify several conditions simultaneously and that adaptively request additional information based on uncertainties about the data. We will collaborate with Dr Dennis Wall, who will provide domain expertise for pediatric developmental delays and methodological guidance for innovative biomedical data science solutions.

Figure 1. Overview of the proposed crowd-powered diagnostic system comprising adaptive gamified data curation, behavioral feature extraction by both crowd workers and computational workflows, and machine learning models for multicondition classification that also output individual symptom estimates and dynamically query participants based on crowd ratings. Each of these 3 major steps is independent yet can be combined to produce a synergistic improvement in remote and accessible diagnostics for pediatric psychiatry. ADHD: attention-deficit/hyperactivity disorder.

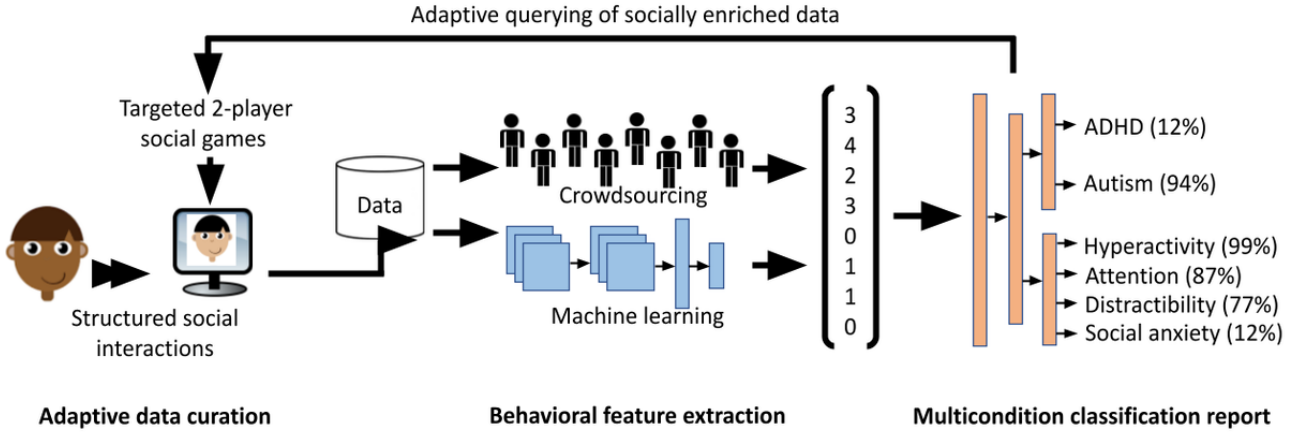

The proposed project involves the integration of multiple data modalities for its diagnostic tasks, including from ML and from crowd workers. In our prior work, we have worked with several sources of information such as facial emotion [5,6], body movements [7,8], audio streams [9], and crowd worker ratings [10,11], all of which were used toward the singular goal of digital ASD diagnostics. For this protocol, we hypothesize that the complex and heterogeneous nature of the conditions that

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we plan to study requires multimodal data analysis to achieve a clinically acceptable level of performance, and this protocol will involve testing this theory.

Related Work

Psychiatric conditions are widespread globally across demographic groups and geographical boundaries. The prevalence of ADHD is 2.5% in children and 5% in adults [3]. The prevalence of ASD is approximately 1% [3]. Approximately 50% to 70% of individuals diagnosed with ASD also have comorbid ADHD. Access to diagnostics, and therefore care, is limited for populations with low income or large geographic distances from clinicians. Although diagnostic modalities based on biomarkers are promising, they can be inaccessible to underserved populations. By contrast, a large and rapidly expanding portion of the global population has access to digital devices. As psychiatric conditions are fundamentally diagnosed based on behaviors, digital methods to measure behavior have the potential to bring diagnostic services to populations that have been traditionally neglected in health care.

A psychiatrist's diagnostic evaluation process involves identifying ≥1 condition from a large set of possibilities defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). However, current approaches to digital diagnostics tend to focus on binary predictions. A major bottleneck complicating the pursuit of multiclass psychiatric diagnostics is that behavioral conditions often have overlapping presentations (Table 1), severely complicating the use of purely automated methods.

Table 1. Overlap of a small subset of the core behavioral symptoms of ASD[a] and ADHD[b]. Overlap is determined according to the DSM-5[c] diagnostic criteria [3].

Behavioral symptom	ADHD	ASD
Difficulty with social skills	✓	✓
Concentration issues	✓	
Hyperfixation	✓	✓
Restrictive and repetitive behaviors		✓
High distractibility	✓	
Impulsivity	✓	
Hyperactivity	✓	

[a]ASD: autism spectrum disorder.

[b]ADHD: attention-deficit/hyperactivity disorder.

[c]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition.

In addition, each condition is heterogeneous, and all defining behavioral symptoms do not have to be present to warrant a diagnosis. Psychiatric conditions can either be comorbid (eg, ADHD and ASD) or not (eg, only ADHD or only ASD), creating a diagnosis space that scales combinatorially with each additional condition considered. For feasibility, we will only study 2 conditions to maintain a reasonably sized output space of 4.

The proposed research addresses a critical need in the field of pediatric neuropsychiatric diagnostics, focusing on the challenges posed by the prevalence of developmental and psychiatric conditions among minors in the United States. Current diagnostic practices face limitations in accessibility, particularly concerning cost, distance, and the availability of clinicians [10,12-14]. The *Background* section highlights the potential of digital phenotyping tools to overcome these challenges and expedite the diagnostic process through ML approaches. The field of digital phenotyping is vast and broad. A nonexhaustive list of National Institutes of Health–funded projects for developmental diagnostics includes the work by Guillermo Sapiro (NIH grant number R01MH120093) developing active closed-loop data collection for gaze and motor features for ASD as well as ADHD [15-22], work by James Rehg (NIH grant number R01MH114999) modeling nonverbal communication in atypical and typical development [23,24], work by Robert Schultz (NIH grant number R01MH118327) involving diagnostic computer vision analyses of motor movements displayed in videos of dyadic social interactions involving children with ASD [25], and work by Dennis Wall (NIH grant number R01LM013364) exploring the use of mobile games to acquire computer vision data for DL prediction of individual ASD-related behaviors [26-41].

Previous studies [4,12,42,43] have recognized the potential of ML techniques for detecting pediatric psychiatric conditions. However, a notable limitation of the existing approaches is their reliance on a limited set of social features for prediction tasks, often concentrating on a single binary prediction. For instance, in 2019, Carette et al [12] meticulously analyzed eye-tracking scanpath data using preprocessing procedures such as feature extraction via principal component analysis. The paper delineates comprehensive guidelines for the acquisition of the scanpath image data set. ML models were implemented, including support vector machine, logistic regression, random forest, and artificial neural network with diverse layers. The outcomes underscored the identification of a Childhood Autism Rating Scale score threshold of ≥36 as indicative of severe ASD. Notably, the single-layer artificial neural network model exhibited an improved area under the curve, outperforming support vector machine, which attained 77%. Despite the noteworthy findings, the study conscientiously recognized certain limitations, including a confined participant pool and shorter video scenarios, suggesting avenues for prospective

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investigations. This limitation raises concerns about the specificity and precision of these models, particularly when dealing with the overlapping etiologies and phenotypic characteristics inherent in many psychiatric conditions affecting adolescents [44].

The literature [14] underscores the complexity of overlapping psychiatric conditions, such as ADHD and ASD, and the challenges in achieving specificity and precision in their simultaneous prediction. Key behavioral features, such as eye gaze patterns and facial emotion evocation, present opportunities for automated ML methods, but the majority remain too complex for precise classification [10]. For example, a study [45] centered on analyzing eye-tracking image data using a clustering approach with 2 distinct algorithms, K-means and an autoencoder. The findings revealed that 33% of individuals were categorized into cluster 1, indicating the presence of ASD, whereas a higher prevalence of 85% was observed in cluster 2. However, the study lacks clarity on the specific feature extraction technique and parameter settings applied during the clustering process. Therefore, our study introduces a novel paradigm that integrates traditional ML with human-in-the-loop crowdsourcing approaches to address the limitation of feature annotation. The motivation behind this paradigm lies in the belief that although nonprofessionals may struggle to identify psychiatric diagnoses directly, they can effectively tag behaviors relevant to a diagnosis. This shift toward a crowdsourced, human-annotated feature space is a novel approach in the context of pediatric neuropsychiatric diagnostics.

In addition, ML models incorporating both human-annotated and automatically extracted features are hypothesized to outperform models using only 1 type of feature; there is a notable gap in the literature regarding the integration of human-annotated features through crowdsourcing for the specific purpose of enhancing diagnostic accuracy in pediatric psychiatry [4,42,46]. Mauro et al [13] introduced a model to extract sensory features from consumer feedback reviews, considering user preferences and compatibility information. The efficacy of their model was assessed across individuals considered autistic and neurotypical through integration into the recommendation algorithm. However, because the perception of places is inherently subjective, there exists a potential for bias in the feature values derived from explicitly crowdsourced data. Consequently, the authors recommended a comprehensive evaluation of the features through multimodal analysis to enhance the precision and accuracy of the proposed algorithm.

Our proposed research protocol fills a critical gap in the literature by combining automated ML methods with innovative crowdsourcing algorithms, aiming to create a diagnostic system with greater discriminative power than previously achievable in precision psychiatry.

Methods

Overview

In contrast to prior inspirational National Institutes of Health–funded efforts and others like them, we propose an approach to digital phenotyping that expands the possible feature vectors used to classify psychiatric conditions with complex and nuanced social features that only humans can identify using a novel *crowd-powered precision diagnostics* approach. The primary high-risk and high-reward differentiators from prior work are (1) the incorporation of a novel crowdsourcing pipeline into a precision diagnostic system to enable quantification of more complex social features, (2) the adaptive querying of the participant in question within a 2-player game-based system using active learning algorithms that exploit crowdsourced responses, and (3) the differential diagnosis of ASD and ADHD simultaneously. Differentiators (2) and (3) would not be possible without (1). The addition of targeted crowdsourcing into the diagnostic process creates several technical challenges that we will address, including automating the preservation of privacy of participants, efficiently and intelligently quantifying the behavioral feature–tagging ability of crowd workers, and creating algorithms for dynamically assigning workers to new data streams and tasks. Although prior projects have attained successful performances >90% using purely automated DL approaches to differentiate ASD from neurotypical peers [47], our preliminary data show that human-in-the-loop crowdsourced feature tagging of targeted behavioral features results in classification sensitivity, specificity, and accuracy >95%, even when privacy-preserving alternations are made to the video streams [42,48,49]. We hypothesize that incorporating both human observations, which are beyond the current and foreseeable abilities of ML, into the feature extraction process will provide enough social information for automated models to classify each condition using the same video data.

We hypothesize that diagnostic ML models that incorporate both human-annotated features acquired through crowdsourcing (to generate a complex feature space with respect to social human behavior) and automatically extracted features (to provide objectivity when possible) will outperform models that use only automatically extracted features or only human-provided features, as there will likely be nonlinear interactions between features. This complex feature space will allow the classification model to simultaneously distinguish 4 possible outcomes: only ASD, only ADHD, both ASD and ADHD, or neither condition. To support efficient and reliable feature tagging by workers, we will develop novel crowdsourcing algorithms for quantifying the behavioral tagging strengths and weaknesses of each worker. The algorithms will dynamically assign workers to tasks based on their tagging history. We will alter each video to provide privacy protection for the participants while still allowing reliable tagging. To facilitate the acquisition of sufficiently structured data, we will develop a broadly accessible gamified web platform for curating socially enriched video and audio clips in a targeted manner. We will use active learning algorithms to adaptively query for additional data in cases where the presence of a particular symptom is unclear from the current set of ML features and crowdsourced ratings. Each of these innovations (crowdsourcing algorithms, privacy-preserving video alterations, gamified social data capture systems, and active learning algorithms to dynamically query needed data), although useful for the field of precision psychiatry individually, will be combined to create a novel diagnostic system with greater discriminative power than previously possible.

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Achieving the precision required to distinguish between ASD, ADHD, both ASD and ADHD, or neither from videos of social interaction using ML at clinically acceptable levels requires a complex social feature space that is not necessarily impossible but highly infeasible with purely automated methods. In contrast, untrained human annotators can identify nuanced social features but are prone to error because of the subjective nature of the task. Combining features extracted by both nonexpert human raters and computational programs can enable precise diagnostics and quantification of behaviors by creating a rich diagnostic feature space. There are several challenges to accomplishing targeted crowdsourcing in a precision health context, which we will address, including privacy preservation, quantifying crowd worker capabilities, and developing algorithms for matchmaking crowd workers with incoming data streams. The rich social feature space provided by crowdsourcing enables improvements to the other aspects of the digital behavioral diagnostics pipeline, including the adaptive assignment of participants to data collection games using active learning crowdsourcing metrics. Although we will focus on ASD and ADHD in particular, the crowd-powered methods we will develop have the potential to benefit diagnostics for any condition primarily evaluated through behavioral observation.

Ethical Considerations

This study has been approved by the University of Hawaii Institutional Review Board (IRB; 2022-00909). We will only collect data from voluntary participants who sign an informed consent (parents) and assent (children) document during the intake session of the study. Participants whose videos will be shared for the 20 crowdsourcing tasks used to filter workers will be contacted by the study team to have a thorough discussion about the planned use of those videos. Workers who are qualified to rate the remaining videos for ≥1 question will be required to complete The Health Insurance Portability and Accountability Act training and The Collaborative Institutional Training Initiative training and will be required to encrypt their laptops using whole disk encryption. These workers will be added to the IRB protocol and will become official members of the study team after thorough training.

Although we will require participants to consent to sharing videos with crowd workers who have undergone thorough training, the clinical translation of this diagnostic system will require a more scalable approach that is sensitive to privacy concerns. We will experiment with privacy-preserving alterations to the curated videos to obfuscate identifiable information from the videos without degrading the feature-tagging performance of workers. Examples include pitch shifting the audio, which will allow workers to understand the content of the speech, and pixelating the video, which will obscure the participant's background and face but would still allow workers to observe body movement patterns. We will measure the extent to which each privacy-preserving mechanism degrades the answers to each question.

We will deidentify the participant data and anonymize any personally identifiable information. All the data will be immediately uploaded to our secure and encrypted server on Amazon Web Services (AWS) [50], which is Health Insurance Portability and Accountability Act–compliant. A fully anonymized version of the data set will be released to researchers only after signing a data use agreement, which will be approved by the University of Hawai'I Data Governance Office.

To ensure that the annotation task is manageable for crowd workers, each 15-minute video will be segmented into five 3-minute clips. During the profiling phase, crowd workers will be compensated US $0.50 per 3-minute video segment rated. Workers who are selected to continue rating videos in the primary portion of the study will be compensated US $0.05 per question answered per video segment, with the opportunity of a bonus of US $0.05 per question if the answer aligns with the clinician ratings for that question. These payment rates are consistent with practices in crowdsourcing research studies in the field of human-computer interaction, and our preliminary studies have shown that the retention rate for this level of compensation is >90% [10,42,49].

Gamified Data Curation

Description

We will develop novel gamified social experiences to curate video data containing diagnostically rich information. Each of these games will impose the structure required to extract salient behavioral features that are comparable across peers. Each game will involve 2 participants interacting on the web application through both the game itself and socially through live video and audio. During gameplay, each participant's camera and microphone will be turned on, and their video and audio will be displayed in a Zoom-style [51] feed to the other participant. The video and audio feeds will be recorded during each session, in addition to keyboard strokes and mouse movements.

Each game will correspond to a subset of targeted behaviors for data capture. The existing literature on "serious games" has documented the usefulness of certain games to capture behaviors related to psychiatric diagnostics, although these games are usually single player. An example is a Go/No-Go game, where the player presses the spacebar in response to a timed "go" prompt in the presence of auditory and visual distractions. This game has been shown to be a reliable estimate of attention, impulsivity, hyperactivity, and executive functioning when recording gaze behavior, response time, and correct reaction rate [52]. We will modify the game so that the "go" prompts are initiated by the social game partner rather than an automated computer, allowing for the capture of socially relevant features. The field of "serious games" for the assessment of psychiatric behaviors is vast, and therefore, we will base all games on previously published literature. However, many behavioral features that we will study will not be tied to a particular game but will rather be observable as a by-product of the social interactions between participants (eg, social anxiety).

One of 7 possible games will be administered each day. A complete list of games and the corresponding behaviors that each game is designed to measure is shown in Table 2.

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Table 2. List of previously validated data capture games that have successfully generated data relevant for distinguishing the targeted psychiatric conditions from neurotypical controls.

Game[a]	Targeted behaviors
Go/No-Go [52]	Concentration, impulsivity, hyperactivity, executive functioning, and reaction time
AULA Nesplora [52]	Process speed and motor activity
Plan-It Commander [52]	Planning and organization
Braingame Brian [52]	Working memory, cognition flexibility, and impulsivity
Charades [6]	Emotion evocation and recognition and restrictive and repetitive behaviors
Balloon Popping [53]	Visual motor coordination
Spot The Eyes and Face [53]	Eye contact and face gaze
Free-form conversation[b]	Social anxiety, difficulty with social skills, speech delays, and language narrative

[a]As the games themselves are not central to the innovation of this proposal, details of the gameplay can be found in corresponding references [6,52,53].
[b]Free-form conversation will naturally occur across all games.

The design of the games will be conducted in consultation with a team of practicing clinical psychiatrists at the University of Hawai‘i School of Medicine, including Dr Anthony Guerrero, who is the chair of the Department of Psychiatry and who specializes in digital technologies for pediatric and adolescent psychiatry, as well as Dr Gerald Busch, who is an assistant professor in the Department of Psychiatry and who has experience with digital health solutions for psychiatry.

A minimum of 15 minutes of gameplay will be required each day, although participants may elect to participate for longer. To facilitate consistent data capture across possible computer, microphone, and camera configurations, a pertinent step for enabling comparisons across participants, a calibration program will be developed that will require each participant to align the camera's zoom and their body position before each session. We will extensively test the calibration procedure before the study.

Participant Recruitment and Management

We plan to recruit a total of 400 study participants, comprising 100 individuals formally diagnosed with ADHD, another 100 diagnosed with ASD, a further 100 diagnosed with both ASD and ADHD, and 100 individuals evaluated and confirmed to not have any socially related psychiatric conditions. Our inclusion criteria are as follows: (1) adolescents aged between 14 and 18 (inclusive) years and (2) formally evaluated for ADHD and ASD by a licensed clinician with available documentation. The selection of the final 400 participants that comprise our core data set will be based on the personal information that participants are asked to disclose. Such metadata will be used to ensure a data set that is balanced with respect to race, ethnicity, and gender. The number of participants is based on testing the ability of our system to discriminate between groups of participants. As these groups are balanced, we set the prevalence for binary classification between each condition to 50%. Following a CI of 95%, an estimated theta of 95% [42,48,49], and a width of 15%, the sample size to compute the area under the receiver operating characteristic curve (AUROC) should be 37 [54]. Considering that we have 400 participants, with 100 participants per group, this enables us to follow a common 60:20:20 (train, validation and test ratio respectively) randomized split on the data. That is, we have a sample size (test set) of 40 participants to verify the system's ability to discriminate between the neurotypical participants and the participants who were diagnosed with either ASD, ADHD, or comorbid ASD and ADHD.

Although formal and well-established methods to perform power calculations for ML analyses have yet to be established, most digital diagnostics studies for conditions such as ASD include <100 participants per class in binary classification [47]. We aim to maintain a similar sample size per diagnostic category. The digital social experiences will be delivered to study participants for 15 minutes each day for a 3-week duration, with a single game out of the 7 possible delivered each day. At least 3 distinct 15-minute sessions will be collected per game for each participant, allowing for comparisons across days for analysis of within-peer consistency.

Given the remote delivery of the data collection, a critical challenge will be to ensure that all participants will have a social partner when logging into the study system. The participants will be asked to log in at a particular time each day to be scheduled in advance of the first day of the study. We will host 10 separate time slots and 3 makeup time slots every day of the study, and participants will be automatically matched with a partner during log-in.

Evaluation

We will evaluate the data curation system for (1) compliance of participants with respect to the study procedures during each session and (2) global participation rates. To measure compliance, we will run computer vision face detection algorithms in conjunction with skeletal pose estimation using MediaPipe [55] Python library to ensure that each participant's face, upper torso, and shoulders are fully visible and will calculate the percentage of valid frames across sessions per participant. To measure participation across sessions, we will record the total number of sessions with both participants and the mean session time. In addition to these quantitative analyses, we will run qualitative pilot user studies to understand participants' experiences about the data collection game process, including questions about the entertainment value provided by

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the games, the usability of the participant matching and scheduling system, and open-ended feedback.

Novel Crowd-Powered and Traditional ML-Based Feature Extraction

Description

We will create 2 pipelines for converting raw video and audio data into interpretable feature vectors that quantify social behavior relevant to ADHD and ASD diagnostics. For behaviors that can be feasibly quantified using computational methods, we will use existing toolkits. For highly complex and nuanced social behaviors that are beyond the scope of current ML tools but that are highly relevant to psychiatric classification, we will use a novel crowdsourcing pipeline to match crowd workers to labeling tasks.

We will perform automatic feature extraction for behaviors potentially related to diagnoses such as the percentage of total conversation time contributed by the participant, eye gaze patterns during the gameplay including the proportion of gaze directed toward the game versus the live video feed of the other participant, vocal prosody and intonation during conversation, natural language processing analysis of the content of the conversation after converting raw audio to text using speech-to-text programs, and breaks in task flow as measured by pauses in game-related keystrokes and mouse movements. The extracted information will be stored for each frame at a sampling rate of 5 frames per second. As depicted in Figure 2, each of these features will be concatenated into a temporal feature vector and used to train a time series DL model such as a long short-term memory recurrent neural network or an attention-based model (eg, transformers). There are existing Python libraries that enable the proposed automatic behavioral feature extraction such as OpenFace [56] and MediaPipe for eye gazing. For facial emotion recognition, we will use Amazon Rekognition [57], an AWS service that provides recognition of disgust, happiness, surprise, anger, confusion, calmness, and sadness in addition to other relevant facial features such as whether the eyes and mouth are open. In the audio domain, pitch will be extracted using the Convolutional Representation for Pitch Estimation library [58], and waveforms will be processed using the librosa library [59].

Figure 2. Feature extraction and quantification of behaviors relevant to neuropsychiatric diagnostics. LSTM: Long Short-Term Memory network.

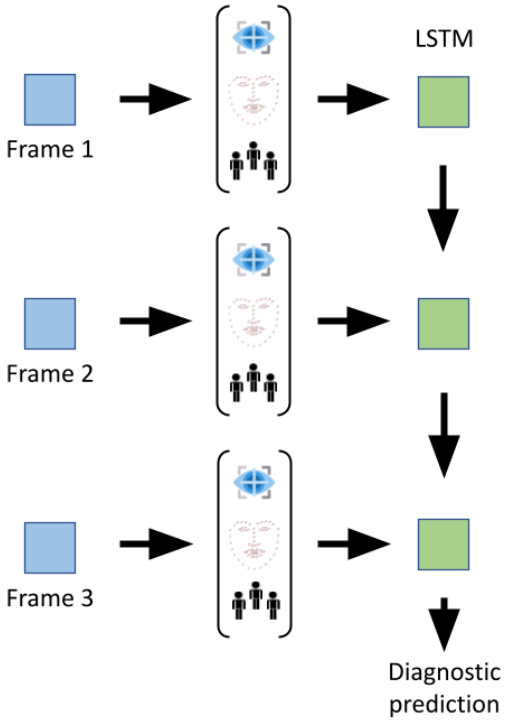

For complex social features beyond the scope of automated ML-powered computational processing, we will deploy a novel crowdsourcing framework consisting of a crowd worker profiling phase, followed by a study data tagging step. In the first phase, we will post 20 tasks on Amazon Mechanical Turk, each presenting a video acquired through pilot testing of the gamified social data collection platform, followed by a series of multiple-choice questions corresponding to items from the diagnostic criteria for ADHD and ASD, as defined by the DSM-5. Each task will correspond to a separate video, and there will be 4 videos per diagnostic category used to quantify worker abilities. Worker responses will be compared against the Clinical Global Impression gold standard ratings provided by our collaborators in the Department of Psychiatry at the University of Hawai‘i. Crowd workers who align with the ratings of clinical experts on at least 1 behavioral feature, where alignment is defined as <1 categorical ordinal deviation per 2 videos, will be recruited to label the final study data from 400 participants. Recruited workers will only label those features for which their alignment with clinicians was demonstrated during the profiling phase as shown in Figure 3.

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Figure 3. Crowd worker assignment to labeling tasks. Each crowd worker will only be asked to label those features for which they agreed with clinicians during a worker profiling step performed before the primary study.

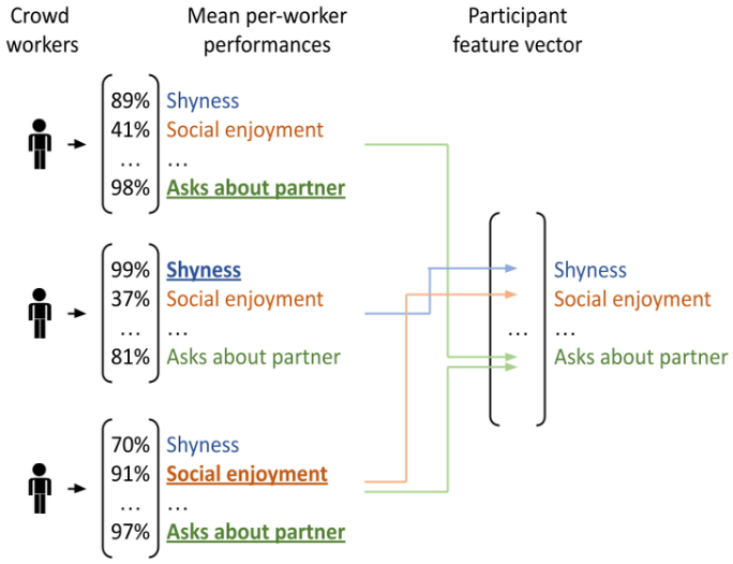

A valuable by-product of this process will be the generation of large behavioral multimedia data sets for ML of complex social features, enabling improved artificial intelligence modeling of human behavior more broadly. With explicit permission from study participants on a per-video basis, we will package and publish the collected data into novel computer vision, audio, and natural language processing data sets for ML. These labeled data sets will be released publicly, providing a stepping stone toward improved automated methods for quantifying complex human behavior.

Evaluation

To assess the effectiveness of the crowdsourcing pipeline, we will compare the performance of crowd workers before and after their recruitment. The preliminary data show that crowd workers who answer similarly to clinicians during filtering continue to perform in a similar manner on new, unseen videos. We will also measure crowdsourcing metrics such as latency to starting a task, interrater reliability, any decline in performance with increased ratings, and the completion rate for all assigned tasks. To evaluate the privacy-preserving mechanisms, we will randomly assign each worker to a single privacy condition per video, only asking them to rate the unaltered videos after the ratings for the privacy condition have been provided. We will measure the mean deviation from clinician answers per privacy condition for each question.

Multicondition Diagnostics With Adaptive Input Querying

Description

We will develop DL models for the multilabel classification of ADHD and ASD, which can emit four possible outcomes: (1) ADHD, (2) ASD, (3) ADHD and ASD, and (4) neither condition. The models will also output the behavioral characteristics that led to the final classification decision by producing the 95% CI of each behavior as derived from both crowd workers and automated computational models. This will involve synthesizing multiple sources of inputs and communicating the result to the end user in a manner that is understandable to the patient or the caregiver. The confidence scores will enable the model to adaptively request more data from the patient and to be specific about which types of data are needed.

To derive an interpretable quantification of each behavioral feature, we will collect clinical categorical ratings of each behavior by licensed psychiatrists at the University of Hawai‘i at Mānoa. We will compensate the psychiatrists for their service and will use the mean of the crowd worker responses as a baseline method for deriving the interpretable quantification of each behavior. Although this method could be sufficient, it is possible that crowd workers have varying levels of rating abilities depending on the qualities of the video and the qualities of the crowd workers themselves. Therefore, we will explore the use of the crowdsourced ratings themselves combined with crowdsourcing metrics derived from worker performance and the computationally generated behavioral features as collective inputs into an ML model for each behavior. Such metrics will include the time spent by each worker providing the annotations for the video, worker rating history for each question, and variability in the worker's answers across videos and within a particular video. It has been previously shown that these crowdsourcing metrics and similar metrics have predictive power in a crowd worker's annotation quality [11]. We will test whether the ML model is a better predictor than the crowdsourced ratings alone. The loss function for the ML model for individual behaviors will optimize with respect to the mean clinician rating per behavior.

To model the multilabel classification problem, we will create separate binary classifiers for ASD and ADHD. Each model will be optimized separately. In comparison with training distinct binary classifiers, a single model trained in a multitask learning setup is able to share parameters between the classification tasks. This helps the model focus on distinguishing features between conditions and has been found to reduce overfitting. We expect that the multitask setting will decrease the number

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of false-positive predictions by helping the model recognize features that overlap between conditions.

Using a sigmoid activation function for each independent classifier, the classification system will output a probability score for each diagnostic possibility as well as each of the behaviors defined by the DSM-5, which will be quantified by the system.

Using the output scores of the DL model, an active learning system will be developed that queries for additional data from the user in a targeted manner by suggesting the next game for the participant to play. For each participant, the algorithm will measure the confidence score of each behavioral symptom and produce a list of games for the user to play, sorted by the classifier's mean uncertainty of the behavioral symptoms each game is designed to curate data for. Classifier uncertainty will be measured by the entropy of each classifier's output vector. As neural networks are inherently uncalibrated, we will apply a method published by Kuleshov et al [60] based on isotonic regression to calibrate the probability estimates before measuring uncertainty.

Evaluation

The diagnostic ML model will be evaluated using balanced classification metrics including AUROC, area under the precision-recall curve, balanced accuracy, precision, recall (sensitivity), F_1-score, and specificity. Performance and CIs will be derived through Monte Carlo cross-validation, with each data split consisting of 300 participants in the training set, 50 participants in the validation set, and 50 participants in the test set. All splits will contain a balance with respect to the 5 diagnostic classes, age, gender, race, and ethnicity.

To evaluate the effectiveness of the active learning querying system, we will run post hoc simulations comparing the random selection of new data against targeted requests using active learning. We will train the classification system with 12 sessions of data, hold out the remaining 9 sessions, and plot the performance of each metric against the number of additional samples acquired using both active learning and random selection of data segments.

Results

Gamified Data Curation

A preliminary version of the web interface has been implemented (Figure 4). We are finalizing the features corresponding to video and metadata recording for downstream ML analysis. Over the course of this 5-year study, our objectives are to complete the development of the study's web system by the end of year 1, begin initial recruitment in year 2, and concurrently conduct human-in-the-loop ML analysis while continuing recruitment from years 3 to 5.

Figure 4. Preliminary interface for the study's central web platform. (A) Users who are not a part of the core user study where participant matchmaking occurs can select their game play partner. (B) One of the implemented games, Charades.

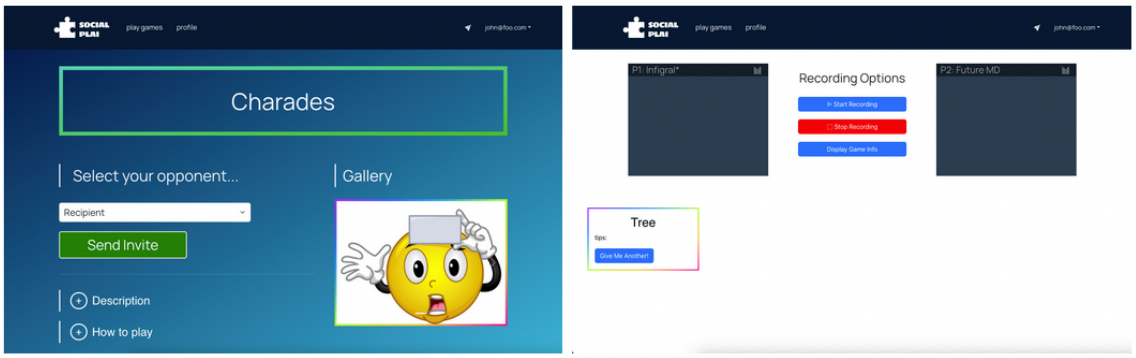

Novel Crowd-Powered and Traditional ML-Based Feature Extraction

We have conducted a series of preliminary studies testing the use of crowdsourcing for precision behavioral health, demonstrating that although there is a high degree of variability in crowd workers' innate ability to rate complex social behaviors in unstructured home videos [10], there exists a small fraction of crowd workers on platforms such as Amazon Mechanical Turk who consistently rate in alignment with licensed clinical experts [48,49]. In a study, we demonstrated that a group of 40 crowd workers filtered from an original pool of >1000 workers was able to rate behaviors that, when fed into a classifier trained on clinician records, achieved an AUROC of 0.9904 for one set of features and 0.9872 for another feature set [42]. Our experience of receiving approval from university IRBs and data privacy offices as well as obtaining consent from families to share their videos with crowd workers mitigates any risks related to this novel process.

After applying privacy-preserving modifications to the videos, such as pitch shifting the audio downward and using face detection to box out the child's face, the performance of the model remained >0.95 for both AUROC and area under the precision-recall curve [42]. Although these results show promise for predicting autism in a binary task, they are likely to decline in accuracy when expanding to include ADHD as a diagnosis too. These studies provide strong evidence to support the proposed worker matching procedure, which will enable the more nuanced feature space required for multicondition classification. The prior experience in developing automated

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pipelines for managing crowd workers will help streamline the development of the crowd management scripts.

The feasibility of the automatic feature extraction steps comes from the existing packaging of the required functionalities into Python libraries and the high documented performance of these tools. All the ML-powered feature extractors we have used are well documented.

Multicondition Diagnostics With Adaptive Input Querying

In 1 of our preliminary experiments involving 4-way ASD or ADHD classification (only ASD vs only ADHD vs both vs none) using publicly available survey data, a decision tree classifier achieved an F_1-score of 0.75 and Hamming loss of 0.23. The final data set consisted of 270,978 data points and 60 columns, with which we attempted multiple feature selection methods such as recursive feature elimination, decision tree feature importance scores, and logistic regression coefficients to quantify the strength of the relationship between the predictor variables and target variables. Across all 3 methods, the highlighted behavioral features were difficulty in making or keeping friends; difficulty in dressing or bathing; having behavioral problems; having difficulty concentrating, remembering, or making decisions; having anxiety; arguing too much; and sharing ideas or talking about things that really matter. On the basis of these observations, we believe that the games targeting behavioral and motor skills, mentioned in Table 2, can support the research findings and generate relevant data. We will modify the currently implemented games to specifically target these newly identified behavioral features.

The feasibility of DL models relies on the underlying data used to train them. DL has the capacity to learn any discriminative function, provided it has a large enough model and adequate computational power to train a large model. University of Hawai‘i at Mānoa has provided us with a dedicated Nvidia v100 graphics processing unit node and a dedicated Nvidia RTX5000 [61] for computationally intensive research. In addition, the Hawai‘i Data Science Institute has shared computing resources consisting of 346 nodes (8500 cores) with 63.19 terabyte of RAM, 120 graphics processing units, and >1 petabyte of storage. These resources are free to use for University of Hawai‘i laboratories. Collectively, these resources are more than sufficient to train DL models for the proposed data set size.

We have previously trained DL models for making a binary prediction of ASD (Table 3).

Table 3. Preliminary data supporting the use of multimedia data from social games to predict autism spectrum disorder.

Data modality	Prediction performance
Audio	AUROC[a]: 0.815 (0.077 or −0.077)
Facial emotion	Balanced accuracy: 71%
Eye gaze	Recall: 66.2%; precision: 63.5%

[a]AUROC: area under the receiver operating characteristic curve.

Although each of these models used a single data modality (audio, facial emotion expression, or eye gaze), their performances were on par with prior literature [47]. We hypothesize that incorporating additional modalities will not only allow for increased performance within a single class but will also enhance discriminative power across diagnostic categories.

Discussion

Principal Findings

There is a great need for improved, scalable, and accessible diagnostic assessments for neuropsychiatric conditions that require accurate and extensive evaluations. We propose to use a multimodal ML model to study heterogeneous psychiatric conditions through human-in-the-loop computing. Although DL models have been able to successfully classify participants with ASD from their neurotypical peers in prior work, the human-in-the-loop observations can help extract a more nuanced feature subset for the diagnosis of similar yet distinct conditions. We have deployed an initial set of games on the web interface targeting behavioral features, and we have extracted a subset of core behavioral features that aligns with the proposed games and can thus help us to effectively target our digital diagnostic. The crowd worker ratings appear to be of high quality based on our prior studies, aligning with the computationally extracted features and clinician's records, even after the videos are modified. Moreover, the reduced feature subset extracted using preliminary studies from multiclass classification of publicly available survey data has helped us identify the core behavioral features that we intend to target through our gamified approach.

This study aligns with multiple previous works [1,2,5-11,15-41] where the researchers worked with single-modality data to capture the phenotypic behaviors of ASD, ADHD or both. These studies were not only limited by the availability of social features but also by the small size and lack of diversity in the data set [1]. By contrast, our study encompasses several sources of information such as facial emotion, body movements, audio streams, and crowd worker ratings that will improve the predictive capability of the model for comorbid diagnosis and capture the overlapping features. Through this study, we aim to bridge the gap posed by diagnostic and therapeutic challenges in psychiatry using ML techniques. Such noninvasive studies can better use the complex social behaviors to characterize behaviors specific to ASD and ADHD.

The technical aspects of the project are highly feasible, with modest development requirements compared with modern real-time computer gaming systems. The web server will be developed using the Django Python framework [62] and hosted on an Elastic Compute Cloud (EC2) instance [63] on AWS, with extensive existing functionality and documentation existing

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for all technologies used. Extensive codes are available on the internet for implementing the video and audio chat features. A full-time developer, an engineering or computer science student, or a postdoctoral researcher can implement the entire system within the span of 4 person-months.

Limitations

Although our initial findings are optimistic, there are some limitations to the study. The primary challenge will be the recruitment and retention of 400 study participants, including the formal clinical validation of the diagnosis for each participant. Although this study can be successfully completed with fewer participants, smaller data sets can affect the model's learning capability, leading to overfitting, noisy outliers, or sample bias. To help manage this recruitment effort, we will hire a full-time clinical research coordinator to recruit and manage the participants. We will work with the clinical collaborators in the Department of Psychiatry to recruit in Hawai i's psychiatric clinics, where our collaborators and their colleagues practice. This will be supplemented with web-based recruitment using targeted advertisements on social media. We have discussed this recruitment plan and desired study size with our collaborators in the Department of Psychiatry, and we hold recurring monthly meetings to strategize about participant recruitment using both our existing access to several clinics in Hawai i and web-based targeted recruitment. In addition, our former mentor and collaborator, Dr Dennis Wall at Stanford University, has access to hundreds of families with adolescent children diagnosed with ASD as well as comorbid ADHD. He is the founder of Cognoa [53,64-69], an artificial intelligence–based digital diagnostic tool for studying early childhood development and pediatric behavior.

There might be technical challenges associated with web applications or user interfaces, which may occur at later stages of the study. The proposed data curation game platform may lack qualities that would garner repeated participant engagement over a 3-week period, such as poor user interface design, poor design of the automated notification system, or poor entertainment quality of the individual games. To mitigate this risk, we will run several iterative design sessions regarding proper implementation of the design process to maximize both user engagement and high-fidelity data collection. We will run several pilot studies to obtain both qualitative and quantitative measures of engagement before running the primary data collection study.

The other potential pitfalls are compliance and tardiness. We will run automated computer vision checks in real time to ensure participant compliance with camera calibration requirements. Another script will send automated text messages and email reminders to late participants, assigning them to makeup sessions. If these mitigation steps fail or if recruitment is unsuccessful and there are <100 participants with valid data per diagnostic category, the study can still be successful with as few as 20 participants per class, as ML studies with approximately 20 participants per diagnostic category have frequently been published in the field [47].

There are also limitations associated with crowdsourcing based on the expertise of the crowd workers or their temporal availability. Although this never occurred during preliminary data collection, a potential pitfall is that some questions may have no workers who consistently rate them in accordance with clinicians. If this occurs, then that question will be removed from any further components of the study (ie, removed as a feature for the diagnostic classifier).

In crowdsourcing, scaling the number of workers does not correlate with the time spent on recruitment. However, to ensure high-quality annotations, we do anticipate spending a considerable amount of time recruiting crowd workers. As mentioned previously, we plan a crowd worker profiling phase based on 20 tasks and data collected through pilot studies with our data-gathering platform. By periodically posing a gold-annotated question and providing a monetary bonus for correctly answering such questions, we incentivize workers to provide high-quality answers. On the basis of our prior studies, we expect that the level of compensation will lead to a worker retention rate of >90%. Furthermore, to account for the loss of workers, we will recruit 3 times more crowd workers than is minimally required for the study. With regard to the number of crowd workers required, we follow the study by Roitero et al [70]. As such, the recommended number of workers will be estimated based on a small amount of data collected during our pilot studies.

When verifying the automatically extracted computational features manually, it is possible that some features will be incorrect. Computational feature extraction approaches are not perfect and are not necessarily robust to unforeseen conditions (eg, dim lighting, obfuscation of certain body parts, and unfamiliar accents). If any feature is consistently unreliable across several participants, then we will remove that feature from the study. There are sufficient features available, so if some do not function as intended, the study can still proceed.

It is possible that the large number of features used to train the DL classification models will be overfitted to the training set, as a data set of 400 samples (of which approximately 300/400, 75% would be in the training set) is relatively small for ML and is unlikely to capture all the intricacies of social behavior that can be expressed with the feature space. If this happens, we will run feature selection and dimensionality reduction algorithms to reduce the number of features used in the model to a minimum viable set and to summarize the feature space in a low-dimensional manner, respectively. The feature selection will enable interrogations into which features are most useful in the differentiation of each condition.

Conclusions

Given the complex nature of neuropsychiatric conditions, ML models can greatly reduce time to diagnosis, for example, by identifying salient information in support of establishing a diagnosis through a low-cost and remote data collection approach. Multimodal data with human-in-the-loop crowdsourcing may improve not only digital diagnostics but also our understanding of the complexity of the conditions. The crowd workers' annotation can also provide data for other computer vision tasks, serving as a promising tool for genetic association, psychological, and kinematic studies.

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Acknowledgments

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Data Availability

The authors intend to create approved subsets of the data that can be shared with other researchers.

Conflicts of Interest

None declared.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
AUROC: area under the receiver operating characteristic curve
AWS: Amazon Web Services
DL: deep learning
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
IRB: institutional review board
ML: machine learning

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Protocol

Telehealth-Delivered Program and Accompanying Patients to Enhance the Clinical Condition of Patients Throughout a Liver Transplant: Protocol for a Mixed Methods Study

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Abstract

Background: Liver transplantation (LT) is indicated in patients with severe acute or chronic liver failure for which no other therapy is available. With the increasing number of LTs in recent years, liver centers worldwide must manage their patients according to their clinical situation and the expected waiting time for transplantation. The LT clinic at the Centre hospitalier de l'Université de Montréal (CHUM) is developing a new health care model across the entire continuum of pre-, peri-, and posttransplant care that features patient monitoring by an interdisciplinary team, including an accompanying patient; a digital platform to host a clinical plan; a learning program; and data collection from connected objects.

Objective: This study aims to (1) evaluate the outcomes following the implementation of a patient platform with connected devices and an accompanying patient, (2) identify implementation barriers and facilitators, (3) describe service outcomes in terms of health outcomes and the rates and nature of contact with the accompanying patient, (4) describe patient outcomes, and (5) assess the intervention's cost-effectiveness.

Methods: Six types of participants will be included in the study: (1) patients who received transplants and reached 1 year after transplantation before September 2023 (historical cohort or control group), (2) patients who will receive an LT between December 2023 and November 2024 (prospective cohort/intervention group), (3) relatives of those patients, (4) accompanying patients who have received an LT and are interested in supporting patients who will receive an LT, (5) health care professionals, and (6) decision makers. To describe the study sample and collect data to achieve all the objectives, a series of validated questionnaires,

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accompanying patient logbooks, transcripts of interviews and focus groups, and clinical indicators will be collected throughout the study.

Results: In total, 5 (steering, education, clinical-technological, nurse prescription, and accompanying patient) working committees have been established for the study. Recruitment of patients is expected to start in November 2023. All questionnaires and technological platforms have been prepared, and the clinicians, stakeholders, and accompanying patient personnel have been recruited.

Conclusions: The implementation of this model in the trajectory of LT recipients at the CHUM may allow for better monitoring and health of patients undergoing transplantation, ultimately reducing the average length of hospital stay and promoting better use of medical resources. In the event of positive results, this model could be transposed to all transplant units at the CHUM and across Quebec (potentially affecting 888 patients per year) but could also be applied more widely to the monitoring of patients with other chronic diseases. The lessons learned from this project will be shared with decision makers and will serve as a model for other initiatives involving accompanying patients, connected objects, or digital platforms.

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KEYWORDS

liver transplantation; accompanying patients; connected objects; health care model; digital platform

Introduction

Background

Liver transplantation (LT) is a surgical procedure to remove a diseased or injured liver that results in liver failure and replaces it with a healthy liver from a donor. LT is indicated in patients with severe acute or chronic liver failure for which no other therapy is available or with hepatocellular carcinoma. Acute liver failure has several causes, including viral (most commonly hepatitis B and C) and drug-induced hepatitis. Chronic liver failure can also have several causes, such as alcoholic liver disease, autoimmune liver disease, and fatty liver disease. LT offers an opportunity to improve not only the health-related quality of life but also the life span of patients living with chronic liver disease and its associated complications.

Liver failure is now the seventh leading cause of death worldwide, with 1.4 million deaths per year. In Europe, >5000 LTs are performed per year, with >140,000 LTs performed over the past 6 years [1] for a European population of 751 million. In the United States, 8906 LTs were performed in 2020 alone, with a total of 24,936 candidates listed for LTs that same year [2]. In Canada, liver failure is the 12th leading cause of death, particularly among the population aged between 25 and 64 years. Cumulative LT activity in Canada has reached 27,488 patients, including 498 transplants from living donors since 1998. In 2020, a total of 565 LTs were reported, with the transplantation rate increasing by 22% over the past 10 years [3]. However, the growing need for LTs also increases the number of candidates on the waiting list, which is greater than the number of viable livers. As a result, the waiting time for transplantations can vary from a few days to >1 year depending on the patient's condition [1].

With the growing number of LTs, liver centers worldwide must manage their patients according to their clinical situation and the expected waiting time for transplants. Moreover, the LT procedure and postoperative period adversely affect the patient's well-being. Therefore, patients should be carefully prepared both physically and mentally to undergo transplantation. Proper management of patients on the waiting list is essential to avoid death or dropout because of deterioration of their condition, as well as to ensure that patients are in the best possible physical, psychological, and social condition before the procedure. These factors are key to the success of the postoperative course [1]. Moreover, the organization of outpatient care is characterized by a certain number of dysfunctions, such as numerous medical consultations with several specialists, which require that patients travel several times to appointments. This is particularly the case with pretransplant assessments, for which patients may need to meet with numerous specialists and undergo several biological, clinical, and imaging tests. These numerous trips put a heavy burden on patients, often resulting in outdated examination results such that patients then have to retake them, unnecessary consultations, and a significant mobilization of caregivers.

However, implementing a model that will meet these requirements is costly and requires the availability of all qualified professionals involved in the LT process. Given the limited human resources in care services, follow-up tools such as mobile apps and web-based platforms may strengthen patient adherence and help empower patients who have undergone transplantation [4]. The mobilization of patients who have undergone transplantation or former patients to provide additional support may also improve patients' motivation and engagement in care [5]. Finally, involving professionals with a mission of health promotion may have an impact on the immediate and long-term health of patients with liver disease. Given this context, the University of Montréal Health Center (*Centre hospitalier de l'Université de Montréal*; CHUM) has decided to implement an innovative health care model to speed up pretransplant assessments, provide interdisciplinary support, and implement social and technological innovations that will enhance patient health.

Aims and Objectives

Drawing on implementation science, this mixed methods pilot study will evaluate the implementation of a new health care model to enhance the clinical condition of patients throughout

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their LT experience. In line with the outcome categories proposed for implementation research [6], this study's specific objectives are to (1) quantitatively evaluate the implementation outcomes of a patient platform through connected devices and accompaniment by a former patient (in terms of predefined benchmarks for acceptability, usability, response burden, feasibility [recruitment and retention], and fidelity), (2) identify implementation barriers and facilitators through semistructured interviews with stakeholders, (3) describe service outcomes in terms of health outcomes and the rates and nature of contact with the accompanying patient, (4) describe patient outcomes (based on daily self-reported health data, including symptoms, use of health services beyond the intervention, and patient satisfaction with teleconsultations if received), and (5) assess the cost-effectiveness of the intervention.

Intervention Implementation Strategy

Overview of the Strategy

This study draws on implementation sciences [7] that are intended to foster the adoption or implementation of an intervention. The selected strategies are presented based on the main corresponding implementation phase: preimplementation, implementation, and postimplementation phase. Central to our implementation strategy is our intention to involve patients and stakeholders through various engagement approaches. Our stakeholder engagement strategy is implemented by an interdisciplinary research team that includes not only researchers (MPP, ELR, CB, TP, CV, CR, and MJE), clinicians (CV, AB, GH, and CG), managers (NN and JP), and decision makers (KM and DO) but also patient coresearchers and former patients (FD, LL, and JTL) [8-11]. Our research and intervention development processes are based on a coconstruction methodology that respects the knowledge and responsibility of the stakeholders based on their values, expertise, and perspectives concerning a health condition and its associated care [12,13]. By involving all stakeholders in this project from the outset, we seek not only to detect and address the challenges associated with recruitment, accessibility, acceptability, and the comprehensibility of procedures and instruments [14] but also to enhance the relevance and meaningfulness of our research results [12].

At the CHUM, certain sectors of activity have been prioritized, including the LT clinic, to improve the patient pathway. The LT clinic constitutes a great target for work on a new model of outpatient care as the medical and nonmedical teams are highly motivated; the number of patients is manageable (60 patients undergoing transplants per year); and the clinic offers a platform where it is possible to integrate and coordinate several medical specialties, such as hepatology, nephrology, cardiology, endocrinology, and even psychiatry.

Overview of the Intervention

The proposed intervention is complex; it "comprises multiple interacting components, although additional dimensions of complexity include the difficulty of their implementation and the number of organizational levels they target" [15]. This new health care model is called Transplant'Action Connected in Liver Transplant (TAC) and includes five components implemented before, during, and after LT: (1) clinical team and technical support; (2) a kinesiology-based intervention plan; (3) a nutritional intervention plan; (4) peer support; and (5) the use of a digital platform, including an interface containing the intervention plans with support videos as well as the association of connected objects (COs; ie, a blood pressure monitor, scale, bracelet, and glucometer [if necessary]) to monitor patients' biological variables and physical activity.

Before Transplantation

In the regular care at the CHUM, patients who could potentially benefit from a transplant are assessed by the CHUM's *guichet rapide d'investigation en transplantation du foie* (rapid LT assessment service; GRIT-F), which provides a 1-week pretransplant assessment on an outpatient basis. GRIT-F usually includes a clinical team composed of hepatologists, a pretransplant nurse, and a cardiologist if necessary. Following this assessment, if the results are favorable, the patient is placed on the transplant waiting list. The patient is then monitored exclusively by the hepatologist every 3 months (or more often if the patient presents signs of deterioration). No systematic follow-up by a nurse or other health care professionals (HCPs) is provided during this period.

In the new TAC health care model, the GRIT-F will include additional professionals, such as a kinesiologist, nutritionist, psychologist, cardiologist (if needed), social worker, and accompanying patients. This team assesses not only the patient's clinical situation but also the patient's knowledge and understanding of the disease, living with the disease, the transplant, and drug treatments, as well as their digital literacy. If the patient is placed on the transplant list, the patient benefits from a 1-day individual meeting with the CHUM pretransplant team, consisting of the clinical team (hepatologist, nurse, nutritionist, kinesiologist, and accompanying patient) and the digital health specialist. During this day, an intervention plan is coconstructed with the patient that includes activities to be carried out as well as the fitness and nutritional goals to be achieved. To support them in implementing this intervention plan, the patient receives COs (ie, a blood pressure monitor, scale, bracelet to measure physical activity, and glucometer) as well as access to a digital platform that provides physical exercises and nutritional recommendations. This digital platform tracks the data collected by the COs and provides access to videos. A support plan is also implemented. It includes a follow-up by the transplant nurse every 4 weeks via teleconsultation, by the accompanying patient every month, and by the nutritionist and kinesiologist every month for the first 2 months and upon request thereafter. Technological support is also provided throughout this phase.

During Transplantation

In the regular care provided at the CHUM, the patient is followed by the medical team and the transplant floor nurse and is seen by the pharmacist for medication education. In addition, the services of a physiotherapist and a nutritionist are available on the transplant floor.

In the new TAC health care model, other professionals, such as psychologists, kinesiologists, and nutritionists, will intervene according to the patient's needs. However, the patient who undergoes transplantation continues to benefit from the support

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of an accompanying patient. Depending on their clinical condition, the patient can perform kinesiology exercises using a bicycle adapted to the bed. The use of COs during this phase is left to the patient's discretion.

After Transplantation

As part of the regular care at the CHUM, the patient is followed only by the hepatologist and posttransplant follow-up nurse in the months following the transplant.

As part of the new TAC health care model, upon returning home, the patient continues to receive weekly support via videoconference from the nurse and the accompanying patient during the first month and then monthly for 1 year, as well as in-person meetings with the clinical team. The patient resumes the use of COs at any time, and the nutritional plan is adapted as needs emerge. When allowed by the patient's general condition (eg, healing and muscular strength), a new physical exercise plan is proposed in the first 3 to 6 months after transplantation and carried out under the supervision of the kinesiologist and accompanying patient. An overview of the TAC health care model is presented in Figure 1.

Figure 1. Overall view of the intervention indicating key time points for data collection during (A) the pretransplant period and (B) the posttransplant period. CO: connected object; GRIT-F: guichet rapide d'investigation en transplantation du foie (rapid liver transplant assessment service); HCP: health care professional; LT: liver transplant.

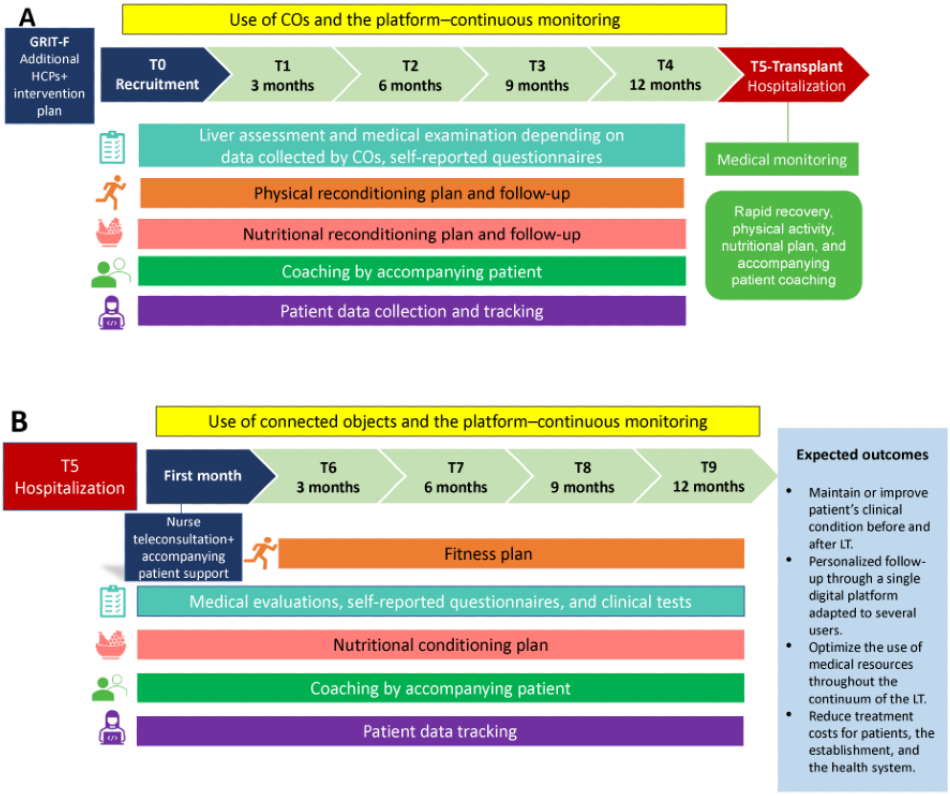

Strategies During the Implementation Phase

All the HCPs and accompanying patients will be trained in therapeutic education and motivational interviewing to support the patients throughout their treatment, as well as in the use of the digital platform and COs. The team's role is to provide recommendations on the use of the digital platform, the procedures to follow as part of their intervention plan, the procedures for remote monitoring using the COs, the patient's daily self-assessment, and information on the educational material to be provided to participants through the patient portal.

When patients receive their COs, they will be supported by the digital platform developers and by the CHUM telehealth coordination center. To centralize technical support, the CHUM telehealth coordinator will communicate with the digital platform development team (ML and ECN) to maintain, configure, and update the patient portal for the duration of the project. Regular meetings will be held to discuss the configuration of the digital platform to ensure that it integrates stakeholder recommendations as obtained from engaged HCPs, accompanying patients, and patients. RdP will also be available to provide technical assistance to patients via email throughout the study.

To ensure that the patients' needs are met, the accompanying patients and HCPs will be regularly consulted to obtain their feedback on the proposed procedures for remote monitoring and research material (eg, informed consent documents and all the data collection instruments, including the self-assessment). This will help ensure the relevance, comprehensibility, and comprehensiveness of the results.

To effect cyclical change, MPP is planning 4 prototype tests with engaged HCPs (ie, the clinical team), accompanying patients, and a sample of patients. For each test, the members will receive training on the digital platform; use it for 4 days; and then meet to discuss their experiences, report any problems, and make recommendations. Furthermore, a test is planned of

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the patient app portal involving 5 participants to adjust the intervention as required before the project begins with the patients. During that time, all HCPs, accompanying patients, and researchers will be trained on how to use the platform.

Once the platform is ready, patients will be registered to use it. Participants will be guided by a member of the research staff (CV or ME), who will confirm their identity and explain platform functionalities. The remote registration system will send a unique verification code to the user's smartphone with a link to the registration page, where the code will be entered. This is to ensure the security and privacy of patient information.

Strategy During the Postimplementation Phase

Our strategy is to re-examine the implementation phase by analyzing the participants' and stakeholders' views on implementation barriers and facilitators after implementation (based on qualitative interviews).

Methods

Study Design

A single-center pilot study will be conducted following the guidance provided by the CONSORT (Consolidated Standards of Reporting Trials) statement for pilot and feasibility studies [16,17]. It uses a mixed methods embedded design, with quantitative methods to measure the outcome and output and qualitative methods to extend the analysis of the implementation process [18].

Participants

To attain the study objectives, six types of participants will be included in the study: (1) patients who underwent transplantation 2 years before and received regular care (historical cohort or control group); (2) patients who will receive an LT during the next year under the new health care model (prospective cohort/intervention group); (3) relatives of the patients who will receive an LT; (4) accompanying patients who have already received an LT and are interested in supporting patients who will receive an LT; (5) HCPs, including proximity managers; and (6) decision makers.

Eligibility Criteria

Patient Population

All patients selected for an LT at the CHUM who are aged >18 years at the time of registration on the transplant waiting list and are fluent in French or English (written and spoken) will be considered for participation in the study. In addition, patients in the prospective cohort who will receive an LT will have to be able to use COs and remote monitoring platforms. The exclusion criterion for persons in the intervention group is not having a relative who can provide support in their use of the platform and the COs.

Other Population

Persons aged >18 years who are fluent in French or English (written and spoken) and linked to the study will be considered for participation.

Recruitment and Sample

Patient Population (Control Group)

This comprises patients *not exposed* to the new health care model. It consists of a historical cohort focused on the last 50 patients who underwent transplantation and reached 1 year after transplantation before September 2023. They will be identified through the hospital archive department.

Patient and Relative Population (Intervention Group)

This comprises patients (and their relatives) who will receive an LT from December 2023 to November 2024. Knowing that 60 patients receive an LT at the CHUM each year and that it is expected that 80% of these patients will be selected for the research project, we expect that 48 patients will be enrolled. This percentage is an estimate made by the clinical team based on their knowledge of the target population. During the week of the GRIT-F review, the research project will be presented to patients by the accompanying patient and the nurse. On the day that the patient is listed to receive an LT, the research assistant (CV or ME) will meet with the patient to present the project, give the informed consent form, answer their questions, and collect their consent or refusal to participate in the study. Patients who refuse to participate in the study will have the team's support without access to the digital platform and will not have any data collected in addition to what is routinely collected at the clinic.

Accompanying Patients and HCPs

This includes all the persons in these categories involved in patient care.

Decision Makers

This includes all persons involved in facilitating the implementation of the new health care model. It comprises the chairman and chief executive officer, the deputy chairman and chief executive officer, the director of medical affairs or their representative, the director of nursing or their representative, the director of multidisciplinary care or their representative, the director of the Information Technologies and Telecommunications Department or their representative, the director of the Technological Integration and Interoperability Operationalization Centers Department or their representative, the director of the Network Coordination Department or their representative, and the director of research or their representative.

Procedures

Table 1 presents all the study procedures and clinical and output indicators for patient data collection and evaluation to be used in the study. Table 2 details the data collection procedures to be used for accompanying patients, HCPs, and decision makers throughout the study.

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Table 1. Clinical and output indicators for patient data collection and evaluation.

Data source and description	Collection time
Clinical examinations	
Hepatic encephalopathy using the Stroop test	Every 3 months (during the medical visit)
Liver Frailty Index	Every 3 months (during the medical visit)
6MWT[a]	During the personal meeting day
Calf circumference	During the personal meeting day
Clavien-Dindo score (eg, presence of infectious complications, presence of wound dehiscence, and revision surgery) [1]	At the end of hospitalization
COs[b]	
Blood pressure	3 times a week
Weight	3 times a week
Capillary glucose (if needed)	3 times a week
Pulse	3 times a week
Number of steps and type of exercise	Continuously (ie, 3 times per day, 7 days per week)
Number of false alerts	Continuously
Number of interventions to solve problems related to COs	Continuously
Replacement of COs because of technological problems	Continuously
Medical records	
Number of medical visits (hepatologist, nephrologist, cardiologist, endocrinologist, psychiatrist, medical specialist in addiction, and dentist; via telephone or in person)	Continuously
Number of nonmedical visits (via telephone or in person)	Continuously
Number of emergency room visits	Continuously
Number of hospitalization days while waiting for the transplant and the reasons for these hospitalizations	Continuously
Number of days between registration on the transplant list and transplant	Continuously
Average length of stay (hospitalization days) for the transplant	At the end of hospitalization
Number of rehospitalizations in the first year after the transplant (average duration, location [eg, intensive care], and reasons for these hospitalizations)	Continuously
Surgical revision	Continuously

[a]6MWT: 6-Minute Walk Test.

[b]CO: connected object.

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Table 2. Data collection and procedures for accompanying patients, health care professionals, and decision makers throughout the study.

Data source	Description	Collection time
Accompanying patients		
Documents	• Logbook	Continuously
Questionnaires	• Compassion fatigue risk test [19]	At the beginning and end of the study
Focus group or interview	• Perception of the contribution of the new health care model to follow-up and user experience	At the beginning and end of the study
Health care professionals		
Questionnaires and focus group	• Workplace Ethical Climate Scale [20] • Ability to work with accompanying patients [21] • Contributions of this model of care to improving the patient journey and appropriate use of specialized medical resources+evaluation of technical difficulties and the user-friendliness of the data accessed from medical records	At the beginning and end of the study
Decision makers		
Interview	• Contributions of this model of care and its limits and impact on the service	At the beginning and end of the study

Study Data Collection and Metrics

Platform and Connected Device Implementation Questionnaires

To assess the implementation outcomes (for objective 1), a series of interviews will be conducted 1 and 6 months before the transplant and 6 and 12 months after the transplant. These interviews will include questions on acceptability, response burden, and usability.

To evaluate the effort required to complete the questionnaires and further evaluate acceptability, the perceived response burden measure [22] will be used. It consists of a single question on a 5-point response scale adapted from a survey question from the UK Office for National Statistics.

Usability (the extent to which users can achieve the specific goal of a product) and acceptability (how agreeable, pleasant, or satisfactory the intervention is to the stakeholders [6]) are considered important aspects of implementation outcomes [23]. Both aspects will be assessed using the System Usability Scale questionnaire [24], which consists of 10 items rated on a 5-point Likert scale that are then averaged to produce a total score from 1 to 5. The participants' scores for each question are converted to a new number, added together, and then multiplied by 2.5 to convert the original scores from a scale from 0 to 40 to a scale from 0 to 100. A System Usability Scale score of >68 will indicate that the technology is considered to have an important impact and be useful and easy to use.

Satisfaction with teleconsultations (for objective 4) will be evaluated using the Telemedicine Satisfaction Questionnaire [25], which will be sent to patients after each teleconsultation.

Clinical Questionnaires

To describe the study sample and collect the data needed to achieve the study objectives, a series of validated questionnaires will be completed by all patients. The questionnaires will cover patient characteristics, the assessment of the partnership relationship between patients and professionals (CADICEE) [26], quality of life (SF-6Dv2) [27], the ability to engage in one's own care (PAM) [28], the perception of one's ability to change one's lifestyle habits [29], monitoring of compliance with medication treatments [30], internet-based 24-hour recall (dietary assessment) [31], the Subjective Global Assessment [32], out-of-pocket costs by patients for health care (CoPaQ) [33], and medical visits and consultations. Table 3 presents a summary of the timing and frequency of data collection. The secure internet-based platform REDCap (Research Electronic Data Capture; Vanderbilt University), an application for building and managing web-based surveys and databases, will be used to administer the questionnaires, organize the data collection, and analyze the data.

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Table 3. Validated questionnaires for patient data collection and evaluation.

Domain and questionnaire	Dimensions	Number of items	Response scale	Time of measurement
Patient information				
Sociodemographic, medical, and capacity for use of COs[a] questionnaire	• Gender, age group, highest level of education, marital status, native language, ethnicity, and employment status • Medical background, smoking habits, other medical conditions, and chronic diseases (other than chronic liver disease) • Use of COs during a research study in the past	11 items	Varied	T0[b]
Emotional evaluation				
CADICEE questionnaire	• Evaluates the foundations of the partnership relationship between patients and health care professionals • Identifies potential gaps in the partnership	27 items	Varied	T0, T2[c], hospitalization, T7[d], and T9[e]
SF-6Dv2 Health Utility Survey	• Measures of health for QALY[f] calculations • Provides keen insights into patient healing by measuring 6 health domains: physical functioning, role limitations, social functioning, pain, mental health, and vitality	7 items	5-point Likert scale (1=not at all; 5=nearly all the time)	T0, T4[g], T6[h], and T9
Treatment monitoring and lifestyle habits				
PAM-13	• Ascertains the patient's self-reported knowledge, skills, and confidence in the self-management of their health	13 items	4-point Likert scale (1=strongly disagree; 4=strongly agree)	T0, T4, T6, and T9
Monitoring compliance with medication treatments	• Explores the intention or the need for help with current treatment plans	8 items	5-point Likert scale (1=strongly disagree; 5=strongly agree)	T0, T1[i], T2, T4, T6, T7, T8[j], and T9
Financial monitoring				
Out-of-pocket costs of health care for patients (CoPaQ)	• Collects net costs related to the patient's state of health that are not reimbursed by their insurers	33 items	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Clinical and health condition monitoring				
Online 24-hour recall	• Retrospective method that monitors and assesses an individual's food and drink consumption during the previous day	Electronic interface (images)	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
SGA[k]	• Diagnose malnutrition and identify those who would benefit from nutrition care • History of recent intake, weight change, gastrointestinal symptoms, and a clinical evaluation	Clinical assessment	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Medical visits and consultations	• Continuous monitoring of medical visits or consultations and the reasons for them	Continuous medical monitoring	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Hospital care				
Quality of care in hospitalization scale (ESQ-H)	• Self-reported questionnaire with 2 domains measuring patient satisfaction with the quality of medical and nursing care in hospitals • It contains 2 domains: quality of medical information and the relationship with staff and daily routine	18 items	5-point Likert scale (1=poor; 5=excellent)	Hospitalization

[a]CO: connected object.

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[b]T0: recruitment.
[c]T2: 6 months after recruitment.
[d]T7: 6 months after transplantation.
[e]T9: 12 months after transplantation.
[f]QALY: quality-adjusted life year.
[g]T4: 12 months after recruitment.
[h]T6: 3 months after transplantation.
[i]T1: 3 months after recruitment.
[j]T8: 9 months after transplantation.
[k]SGA: Subjective Global Assessment.

Clinical Indicators

Clinical indicators will be determined by the physician in charge of the patient or the team's kinesiologist. Among the clinical tests specific to this study, the physician will explore signs of hepatic encephalopathy (ie, deterioration of brain function that occurs in people with severe liver failure) using the Stroop test [34] to assess psychomotor speed and cognitive flexibility by recording the response time to interference between recognizing color fields and writing color names performed at different time points during the study (Table 3). Other clinical tests include the Liver Frailty Index [35], which consists of 3 tests representing 3 major components of the multidimensional construct of frailty in patients with cirrhosis: grip strength, chair stands (muscle weakness), and balance (altered neuromotor coordination). Moreover, the 6-Minute Walk Test (6MWT) [36], which assesses aerobic capacity and endurance, will be performed by the team's kinesiologist during the initial patient assessment (baseline) and every 3 months after the LT. The 6MWT measures the distance covered in 6 minutes (outcome) and will be used to identify changes in performance capacity. In conjunction with the 6MWT, the kinesiologist will also measure calf circumference [37], a representative anthropometric index used to screen for sarcopenia and in patient follow-up to adapt nutritional and exercise plans to meet each patient's needs throughout the posttransplant period. Other clinical indicators will be collected using COs: blood pressure, weight, pulse, number of steps/type of exercise, and capillary glucose (if needed).

In addition, to monitor the platform's reliability, we will look at the number of false alerts, the number of interventions required to solve problems related to COs, and the replacement of COs because of technological problems.

Output indicators will also be collected: number of medical visits (hepatologist, nephrologist, cardiologist, endocrinologist, psychiatrist, medical specialist in addiction, and dentist; via telephone, on the platform, or in person), number of nonmedical visits (via telephone, on the platform, or in person), number of emergency room visits, number of hospitalization days while waiting for the transplant and the reasons for these hospitalizations, number of days between registration on the transplant list and the transplant, number of hospitalization days during the transplant, surgical revisions, and number of hospitalization days after the transplant and the reasons for these hospitalizations.

Accompanying Patient Logbook

All accompanying patients participating in the study will document each of the meetings carried out with the patient in a logbook that will be available to all researchers and medical personnel in the project as well as in the REDCap application. In the logbook, the accompanying patient will provide information about the patient (last name and first name), the context of the meeting (health care facility, date of the meeting, start and end time of the meeting, person who requested the meeting, meeting number, and people present during the meeting), the stage of the patient's trajectory (pre-, peri-, or posttransplant stage), meeting method (in person or remotely and location of the meeting), the themes addressed (general aspects, organizational aspects, consequences on daily and family life, and clinical aspects), the accompanying patient's perceptions of the contribution to the patient and of the relationship with the patient, the difficulties encountered by the accompanying patient, unanswered questions, feedback to the clinical team and planned follow-ups, and any other comments deemed relevant by the accompanying patient. The accompanying patient's logbook can be found in Multimedia Appendix 1.

Coordinator Logbook

The coordinator logbook will capture qualitative and feasibility data that include entries on the following: (1) questions or challenges reported by the participants during consent and baseline educational meetings; (2) details about participant recruitment and fidelity throughout the intervention; (3) the recruitment rate (ie, the proportion of contacted eligible individuals who are included in the study); and (4) the retention rate, defined as the proportion of included participants who are retained over the full follow-up period. Fidelity, or the degree to which the intervention was implemented as intended, will be measured as the proportion of included patients who complete their daily self-assessments over the full follow-up period. The reasons for each of these activities will also be categorized and described based on the detailed information recorded in the coordinator logbook.

Interviews and Focus Groups

All qualitative interviews and focus groups will be conducted individually, preferably in person and, if not, via videoconference or phone. Each interview and focus group will be recorded and follow a semistructured guide with open-ended questions and specific prompts. Although adapted to each stakeholder group, the interview guide includes broad questions on the individual's experience of and thoughts on using the

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digital platform follow-up, with prompts on challenges and facilitators [38] as well as open questions to identify information and education needs during the study. The interview guides for each stakeholder group can be found in Multimedia Appendix 2.

With the agreement of patients, accompanying patients, HCPs, managers, and decision makers, all interviews and focus groups will be recorded and transcribed to ensure the reliability of the information collected. The recordings will be transcribed and uploaded into the QDA Miner software (Provalis Research) for further analysis and to identify expected and emerging themes.

Data Analysis

All statistical analyses will be conducted using the R software (R Foundation for Statistical Computing) [39]. For the accompanying patient and coordinator logbooks, descriptive statistics (medians, means, and SDs) will be calculated. Economic analysis will be conducted using the Stata software (StataCorp).

Concerning the various questionnaires, descriptive statistics (medians, means, and SDs), chi-square tests, and 2-tailed *t* tests will be calculated on the populations studied for the sociodemographic characteristics of the patients (eg, age, sex, and characteristics of the care pathway) as well as on all the data obtained at each measurement time (ie, at T0 [assessment to be on the transplant waiting list] and then at 3, 6, 9, and 12 months). Medians, means, and SDs will be calculated for all patients.

For individual nutritional and physical conditioning optimization plans, an analysis will be conducted of the gaps between what was proposed and what was achieved. Statistical analyses will also be used to compare the patient's ability to follow the plan before and after the LT. In addition, multivariate analyses will be conducted based on the intensity of the support provided by the accompanying patients.

For qualitative data, a thematic analysis will be conducted. Coding will be carried out independently by a research agent, students, and the researchers to (1) identify points of convergence and divergence in what is said by the different stakeholders, (2) codify the data using the QDA Miner software to systematize the analysis, (3) build emerging themes, and (4) highlight the convergences and divergences of the intervention.

The quantitative and qualitative data will be compared and analyzed to improve our understanding of the intervention [18]. The barriers and facilitators identified through semistructured interviews with the stakeholders (objective 2) will be used to interpret the findings on patient outcomes, the implementation, and the health services (objectives 1, 3, and 4).

Specific Analysis for Each Objective

Objective 1: To Quantitatively Evaluate the Implementation Outcomes of a Patient Platform With Connected Devices and Accompaniment by a Former Patient

Implementation outcomes will be summarized using descriptive statistics. Acceptability and usability will be evaluated using a linear mixed model for each corresponding outcome. The evaluation of perceived response burden and fidelity will be conducted using a generalized linear mixed model for each corresponding outcome, which is appropriate when the dependent variable is not continuous. For all these calculations, the dependent variable of each model will be the outcome, and the independent variables will be the different time points of data collection (Table 3), 3 sociodemographic variables that are reported to influence patient portal use (gender [man or woman], age [≤50 or ≥50 years], and ethnicity), clinical data from the Stroop test, and the presence or absence of relatives during the transplantation process. The goals of testing each model are to determine whether the outcome's mean score changes significantly over time and whether it differs significantly between the groups represented by the sociodemographic variables over time.

Thus, for acceptability and usability, if at each time point the outcome's mean score is greater than or equal to the predefined success threshold, then the target will be considered met. If it is below the threshold, we will use a unilateral *t* test to test the null hypothesis of threshold attainment as being slightly below this mark does not imply failure given the sample mean's variability. To evaluate threshold attainment during the evaluation of perceived response burden and fidelity, if the observed proportion is under the predefined success threshold, a unilateral *z* test will be conducted as it is appropriate for hypothesis testing with proportions. Finally, an evaluation of feasibility will be conducted by comparing the observed recruitment and retention rates with the predefined success thresholds at the end of the recruitment period and at the 1-year patient follow-up, respectively. If the observed rates are greater than or equal to the success threshold, the target will be considered met. If they are under the success threshold, we will use a unilateral *z* test to test the null hypothesis of threshold attainment.

Objective 2: To Identify Implementation Barriers and Facilitators Based on Semistructured Interviews With Stakeholders

To identify implementation facilitators and barriers and their proposed solutions, 2 analysts will conduct an analysis of the content extracted during the study. The source materials will include semistructured interview and focus group transcripts with the HCPs and the accompanying patients' logbook entries. The analysis will be conducted in three phases [40]: (1) the preparation phase, or the period during which the analysts become familiarized with the data set; (2) the organization phase, when the analysts systematically code the data using the QDA Miner software to identify implementation facilitators and barriers while remaining open to any possible emerging categories; and (3) the reporting phase, which consists of presenting and discussing the identified categories during monthly team meetings with the clinical and research teams to identify discrepancies either in coding or interpretation, ensuring data reliability.

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Objective 3: To Describe Service Outcomes in Terms of Health Outcomes and the Rates and Nature of Contact With the Accompanying Patient

A qualitative analysis will be conducted of the patients' health status, including visits to emergency rooms and continuous clinical monitoring as well as the reasons underlying participant contact with the team of HCPs (Table 1). This information will be monitored continuously and extracted from the medical records. Moreover, a content analysis will be conducted to assess the nature of contact with the accompanying patient based on the data collected in the accompanying patient logbooks. In addition, a content analysis will be conducted to assess expectations and experience with the health care model as well as the user experience with the digital platform and COs using data collected during interviews and from discussion groups (Multimedia Appendix 1).

Objective 4: To Describe Patient Outcomes Based on the Daily Self-Reported Health Data, Including Symptoms, Use of Health Services Beyond the Intervention, and Patient Satisfaction With Teleconsultations if Received

Descriptive statistics will be used to report patient outcomes collected from medical records (Table 1), daily health data self-reported through the use of COs, self-reported questionnaires completed throughout the study (Table 3), and patient satisfaction with teleconsultations and tools. For the analysis, each patient constitutes their own reference and comparison. Thus, δ calculations will be conducted, derived by comparing individual questionnaire results with outcomes from the same questionnaires at other time points throughout the study (ie, baseline vs time points before and after transplantation). For continuous outcomes, the mean, SD, minimum, and maximum values will be reported. For ordinal and nominal qualitative outcomes, absolute and relative frequencies (proportions) will be reported. Descriptive statistics will also be presented by gender and age group.

Objective 5: To Assess the Cost-Effectiveness of the Intervention

A cost minimization analysis will be used to meet this objective. The out-of-pocket costs for the patient and the caregiver will be measured using the cost for patient questionnaire, which was developed and validated in Quebec [41,42]. The costs for the health care institution will be measured using the PowerHealth software (PowerHealth Solutions) used at the CHUM, which combines financial data with data in patient clinical files. The costs for the health care system will include the costs borne by the institution, including physician remuneration. To identify these costs, a questionnaire on medical visits and consultations will be sent to the patient every 3 months so that the patient can indicate the number and nature of these events. The *Régie de l'assurance maladie du Québec* pricing manual will then be used to identify these costs.

Ethical Considerations

Approval and Consent

Ethics approval was obtained from the research ethics board at the Centre hospitalier de l'Université de Montréal (CHUM), Quebec, Canada (study ID: 20-5185). The research team and principal investigators at the hospital are responsible for recruitment and monitoring of participants. Any major modifications or protocol deviations are discussed with the other principal investigators during monthly meetings, and any major protocol modifications are reported and submitted to the ethics board for approval. Participants will be approached by the project medical team and then by the research team to inform them about the objectives, benefits, and risks of the research. If the participant is accepted for LT, the research team will meet with the patient and have them sign the consent form.

Safety and Anticipated Risks

There are no direct risks to participants in this study. Data security risks will be addressed through numerous measures, such as copying data to the CHUM Research Centre (CRCHUM) server and protecting them with a user code and password. Moreover, the study questionnaires, semistructured interviews, and accompanying patient logbook sessions may lead to distress related to the transplant procedure or follow-up, the economic details collected, or depression and anxiety explorations. Therefore, these research tasks carry a risk of emotional vulnerability. Individuals who experience psychological distress because of their involvement in the study will be instructed to inform a member of the study staff. Regular psychological assessments or support services will be provided by the team's psychologist throughout the study.

Confidentiality, Data Management, and Cybersecurity

All collected data and personal information will be deidentified (coded) and kept in computer format at the CRCHUM. No identification of individual participants in any images of the manuscripts or supplementary materials will be possible. When the study results are released, participants will not be identifiable. The project's principal investigator (MPP) and coinvestigators will have access to the data and study results. All computer data will be copied to the CRCHUM server and protected by a user code and password. Research data will be retained for 10 years after project closure. The person in charge will be the principal investigator of the study, MPP. To join the scientific community, peer-reviewed scientific publications will be recommended.

Compensation

No financial compensation is offered for participating in this study. However, patients will have access at no cost to all COs and follow-up consultations.

Results

Several study-related activities have already been carried out from July 2022 to October 2023 concerning the intervention implementation, research, and the platform promoter, in addition to funding. Some steps are ongoing.

Implementation Status

To complete the GRIT-F clinical team and strengthen the capacity to monitor patients at the pre-, peri-, and posttransplant stage, a nutritionist, a nurse, a kinesiologist, and a psychologist have been recruited. A total of 5 accompanying patients have

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been recruited and, along with the clinical team, trained on their roles and how to work together. A certain number of working committees have also been set up, including the following:

1. A steering committee comprising the physician responsible for the transplant clinic, the nursing comanager, the principal researcher, the 2 research assistants, and 3 accompanying patients. This committee meets every week to oversee the implementation of the project.
2. An education committee was also created in September 2023 to develop the tools needed to carry out the educational assessment, including identification of the patient's LT pathway, and the skills that patients and relatives can develop throughout the LT pathway. This committee also helps identify the resources that can be mobilized to support patients and their relatives and integrate these resources into the life course of the patients on the digital platform. This committee consists of not only the 5 accompanying patients but also all the members of the clinical team, the principal investigator, and representatives of the digital platform, as well as specialists in therapeutic education and health literacy. The committee meets every 15 days.
3. A clinical-technological committee ensures that the development of the platform is aligned with the clinical context and patient experience. This committee comprises the clinical team, accompanying patients, and digital platform representatives. It meets every 2 weeks.
4. A committee on prescriptions and nursing roles has also been set up to develop collective prescriptions to give nurses greater flexibility in their activities.
5. Finally, an accompanying patient community of practice has been formed, bringing together the 5 accompanying patients each week to discuss these practices and react to the research tools intended for them.

Research Status

In total, 2 research assistants and a PhD student have been recruited for ethics monitoring, development of the data collection plan and collection tools, recruitment of participants, and analysis of the data, as well as to ensure adherence to deadlines. This study will be conducted in a tertiary hospital. Written informed consent will be obtained from all participants before any study activities begin. Patient recruitment is expected to start in November 2023. All questionnaires; technological platforms; and clinicians, stakeholders, and accompanying patient personnel have been recruited for this study. The protocol was presented at the Canadian Association for Health Services and Policy Research conference in May 2023. In addition, the researchers will meet monthly to discuss the research plan, including the economic evaluation.

Platform Status

A contract has been signed between a digital platform developer and the CHUM, and 2 members of the company have been specifically designated to the project. Personalized training was offered by the company to all members of the clinical team, the accompanying patients, and the research team.

Funding Status

This study secured funding from the *Institut de la pertinence des actes médicaux* in June 2022.

Discussion

Expected Findings

Through this study, the CHUM LT clinic aims to explore the effects of a new health care model, called TAC, on the patient trajectory in LT. The project will be implemented in three phases: (1) a rapid investigation window model in pretransplant assessment will be developed with the introduction of COs and the mobilization of a kinesiologist, a nutritionist, a pharmacist, 2 nurses, a psychologist, a social worker, a computer technician, and accompanying patients; (2) the model will then be implemented throughout the care pathway, including after transplantation, through the integration of an digital platform that includes not only monitoring via COs but also access to educational material coconstructed with patients; and (3) data from the platform will be integrated into the electronic medical record and the CHUM computerized clinical file. Adjustments will also be made to the digital platform to ensure optimal follow-up with the COs as well as for access to personalized medication and nutritional and physical exercise treatment plans.

To our knowledge, this study will be the first to investigate and attempt a reorganization of the care pathway in LTs by optimizing trips to the hospital, reducing the time required for the patient to be registered on the transplant list, engaging an interdisciplinary team to cocreate strategies that encourage patient commitment to their own health promotion, mobilizing each health professional in a relevant manner, and establishing the use of COs to monitor health progression as well as the use of accompanying patients who have already undergone a transplant at the CHUM. Although many studies have brought to light the key roles played by patient monitoring throughout an intervention [43-45] and the inclusion of educational programs provided by HCPs to patients [46-48] in intervention effectiveness over time, this is the first study to integrate both components while also involving an interdisciplinary team to support and explore their application by combining them into a single health care model. The originality of this study lies in the fact that it integrates accompanying patients as full-fledged members of the clinical LT team to assess the potential effects at the clinical and organizational levels, as well as integrating them into the process of creating educational programs for the patients. This study introduces the use of multiple COs, which could have a major impact on patient plans by closely monitoring the patient's health status. This may lead to modifications in personalized nutritional and physical exercise treatment plans that will improve recovery rates after LTs. Moreover, the mixed methods nature of this study allows us to explore the variability between settings to delineate various clinical scenarios and document patients' economic, emotional, and personal realities during the transplant process.

If this new health care model is relevant, it might maintain or improve the clinical condition of patients before and after all types of transplantation through a more personalized and closely monitored follow-up, allowing for the creation of a single

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platform adapted to several users and cases. The model would also optimize the use of medical resources throughout the continuum of the LT process as well as reduce treatment costs for patients, the health care facility, and the health system.

Limitations and Challenges of This Research

This study, as complex and multidisciplinary research, is not without its limitations and challenges. Some of these challenges and solutions are, first, the management of a large interdisciplinary team and the standardization of peer support. To be able to overcome any difficulties related to the cohesion of the team, regular committee meetings will be held once a month to inform the HCPs, researchers, stakeholders, and accompanying patients about progress in the study; redirect guidelines; and discuss participant's cases to achieve a better cohesion among the members of the interdisciplinary team. Another limitation is the large number of questionnaires in addition to the introduction of COs (which increases the difficulty of training and use) as it may increase the burden on patients, which may lead to compliance issues. Some ways to reduce this workload are to select the questionnaires that are strictly necessary at each point during the study and use simpler versions of the questionnaires that require more time to complete. Participants will be informed beforehand of their consent to the tasks and the burden that this might carry. Moreover, the digital platform and CO provider will continuously monitor any difficulty using the COs, providing support and maintenance at all times, thus decreasing the burden on the patient.

Barriers to the generalization of research findings also need to be considered. This study is implemented by capturing data from deconditioned patients and factors specific to the liver failure context. However, if the results of the study are positive, our analysis of the implementation outcomes will shed light on the best conditions for implementing the model in other transplant care trajectories within the CHUM (ie, kidney and lung transplantations).

Finally, as this study will collect a large quantity of data from various medical and nonmedical sources, the data management platform REDCap will be used to apply, manage, and integrate all data collected.

Conclusions

By implementing this new health care model in the trajectory of LT recipients at the CHUM, it can be tested in an environment where the clinical team is motivated and united and where the number of patients is manageable. This new model has the potential to ensure that patients reach their transplantation in better health. This would ultimately reduce the average length of hospital stay and nursing unit care as well as promote better use of medical resources. In the event of positive results, this model could be transposed to all transplant units at the CHUM and across Quebec (potentially affecting 888 patients per year), but it could also be applied more widely to the monitoring of patients with chronic diseases. The lessons learned from this project will be shared with decision makers and serve as a model for other initiatives involving COs or digital platforms.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author (MPP) on reasonable request.

Authors' Contributions

In no order of contribution, MPP conceptualized the study. AB, CV, ELR, FD, NN, and JP were involved in planning and supervising the work. MPP, ELR, and MJE drafted the manuscript and designed the figure and tables. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Accompanying patient logbook.
[DOCX File , 1001 KB - resprot_v13i1e54440_app1.docx]

Multimedia Appendix 2
Qualitative interview guides for each of the stakeholder groups.
[DOCX File , 1844 KB - resprot_v13i1e54440_app2.docx]

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Abbreviations

6MWT: 6-Minute Walk Test
CHUM: Centre hospitalier de l'Université de Montréal (University of Montréal Health Center)
CO: connected object
CONSORT: Consolidated Standards of Reporting Trials
CRCHUM: Centre hospitalier de l'Université de Montréal Research Centre
GRIT-F: *guichet rapide d'investigation en transplantation du foie* (rapid liver transplant assessment service)
HCP: health care professional
LT: liver transplantation
REDCap: Research Electronic Data Capture
TAC: Transplant'Action Connected in Liver Transplant

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Protocol

Combating Fraudulent Participation in Urban American Indian and Alaska Native Virtual Health Research: Protocol for Increasing Data Integrity in Online Research (PRIOR)

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Abstract

Background: While the advantages of using the internet and social media for research recruitment are well documented, the evolving online environment also enhances motivations for misrepresentation to receive incentives or to "troll" research studies. Such fraudulent assaults can compromise data integrity, with substantial losses in project time; money; and especially for vulnerable populations, research trust. With the rapid advent of new technology and ever-evolving social media platforms, it has become easier for misrepresentation to occur within online data collection. This perpetuation can occur by bots or individuals with malintent, but careful planning can help aid in filtering out fraudulent data.

Objective: Using an example with urban American Indian and Alaska Native young women, this paper aims to describe PRIOR (Protocol for Increasing Data Integrity in Online Research), which is a 2-step integration protocol for combating fraudulent participation in online survey research.

Methods: From February 2019 to August 2020, we recruited participants for formative research preparatory to an online randomized control trial of a preconceptual health program. First, we described our initial protocol for preventing fraudulent participation, which proved to be unsuccessful. Then, we described modifications we made in May 2020 to improve the protocol performance and the creation of PRIOR. Changes included transferring data collection platforms, collecting embedded geospatial variables, enabling timing features within the screening survey, creating URL links for each method or platform of data collection, and manually confirming potentially eligible participants' identifying information.

Results: Before the implementation of PRIOR, the project experienced substantial fraudulent attempts at study enrollment, with less than 1% (n=6) of 1300 screened participants being identified as truly eligible. With the modified protocol, of the 461 individuals who completed a screening survey, 381 did not meet the eligibility criteria assessed on the survey. Of the 80 that did, 25 (31%) were identified as ineligible via PRIOR. A total of 55 (69%) were identified as eligible and verified in the protocol and were enrolled in the formative study.

Conclusions: Fraudulent surveys compromise study integrity, validity of the data, and trust among participant populations. They also deplete scarce research resources including respondent compensation and personnel time. Our approach of PRIOR to prevent online misrepresentation in data was successful. This paper reviews key elements regarding fraudulent data participation in online research and demonstrates why enhanced protocols to prevent fraudulent data collection are crucial for building trust with vulnerable populations.

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International Registered Report Identifier (IRRID): DERR1-10.2196/52281

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KEYWORDS

fraudulent survey participation; online survey research; American Indian and Alaska Native; data integrity; health research; research trust; online survey; case study; randomized control trial; RCT; social media; recruitment; young women; women; American Indian; Native Americans; Native American; fraudulent; data privacy

Introduction

Research related to health, health behavior, and risk and protective factors that influence health behavior has proliferated online since the late 20th and early 21st century. In an era dubbed "Web 1.0," content on the world wide web or internet was largely static [1], promoting material that was unidirectional on a website or landing page. Researchers interested in using the internet to recruit participants were at the vanguard of efforts that focused on documenting behaviors and risk and protective factors such as smoking [2], physical activity [3], sexual health [4], reproductive health [5], substance use [6], and mental health [7]. There are also multiple examples of efforts using the internet to recruit participants in intervention research to facilitate improvements in health behavior and factors that influence health behavior [8-11].

In the earliest examples of internet-based research recruitment, researchers noted the advantages of the medium reflected in the ability to increase recruitment efficiency, with the promise of enrolling larger samples in a shorter time frame [12]. Additionally, researchers noted that the internet offered opportunities to reach hidden, marginalized, or stigmatized groups [13], such as men who have sex with men at elevated risk for HIV [14] and substance users [15]. The rapid advent of a "Web 2.0" environment online [16], where users could engage with content on websites and generate their own content, was followed quickly by the earliest social media platforms, such as MySpace and Facebook, in the first decade of the 21st century [17], which allowed users to share content with each other. Efforts to use these platforms for recruitment ensued, with researchers subsequently citing similar enrollment fraud challenges with these new modalities, mirroring those experienced with Web 1.0 and Web 2.0 [12,18-21]. The ongoing pace of change in technology and the continual introduction of new platforms, such as Twitter, Snapchat, TikTok, Threads, and Reddit, have amplified recruitment and enrollment challenges [22,23]. Certainly, the opportunity for potential research participants to misrepresent themselves is not something necessarily unique to the internet and social media [24]; however, the quickly evolving online environment may offer new or enhanced motivations for misrepresentation to obtain an incentive or multiple incentives [25,26] or to deliberately mislead or "troll" researchers [27,28]. Such cases degrade the integrity of the study, erode data integrity, compromise scientific inquiry, and raise difficult ethical questions regarding confidence in results, which in turn may foster distrust and suspicion among truly eligible participants [29-31].

No doubt fostered by the surge in online research during the COVID-19 pandemic, several researchers have recently described methods for assessing fraudulent enrollment [32-35], primarily aimed at postdata collection analysis and algorithms for determining the likelihood of fraud and case exclusion. In this paper, we contribute to this emerging body of research by describing our strategies for detecting and addressing fraud prior to data collection. We present an example from the recruitment of urban American Indian and Alaska Native young women for the formative research phase of a preconceptual health study. Preventing fraudulent data in this context is particularly important. American Indian and Alaska Native communities are often suspicious of and resistant to engagement with research due to a long history of exploitative research practices [36-38]. Indeed, this research exploitation unfolded within the context of centuries of genocidal and assimilationist federal policies designed to destroy American Indian and Alaska Native peoples and their cultures. The resultant generational grief, exacerbated by unscrupulous research practices, has deepened the mistrust of research among both urban- and reservation-based American Indian and Alaska Native communities. This suspicion is a strong call to researchers to rebuild trust [37,39]. Ensuring data authenticity can play a crucial role in helping to bridge this trust between the researcher and the community.

One assimilationist policy, the Indian Relocation Act of 1956, was intended to move American Indian and Alaska Native individuals off reservation lands, out of sovereign Tribal nations, and into urban areas. The result was a concentration of American Indian and Alaska Native individuals in some major US cities, among them Chicago, Los Angeles, Minneapolis, Denver, Phoenix, and Seattle, with gradual spread into suburban and exurban developments in many metropolitan areas. American Indian and Alaska Native individuals living in urban areas—now over 70% of the American Indian and Alaska Native population [40]—do not typically live clustered in neighborhoods. In addition, they are not homogeneous but rather represent rich and diverse cultural backgrounds from their home communities. This dispersion and diversity renders traditional recruitment methodologies ineffective and costly, and thus urban American Indian and Alaska Native individuals have been largely ignored in prior research [41,42]. Yet health disparities are stark and persistent [43-46], with still a sparse research base to inform prevention and treatment [47].

Using the internet and social media for the recruitment of urban American Indian and Alaska Native individuals can provide the opportunity for a broad reach, especially with the growing use of virtual or online engagement via mobile phones [48]. However, using such methodologies could be particularly

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harmful to American Indian and Alaska Native populations because of the risk of fraudulent cases, as described above. This paper describes the development and integration of Protocol for Increasing Data Integrity in Online Research (PRIOR), which is our 2-step method for preventing fraudulent cases in the recruitment of urban American Indian and Alaska Native young women across multiple internet and social media platforms in our effort to build trust and foreground authentic American Indian and Alaska Native voices in research.

Methods

Study Design

We used social media posts and boosted ads plus email flyers to recruit participants nationally for the formative phase of a virtual randomized control trial (RCT), that is, a study design in which recruitment, data collection, and intervention implementation would be administered fully remote through technology. The RCT was designed to test the effectiveness of a culturally tailored mobile health app to prevent alcohol-exposed pregnancy risk among urban American Indian and Alaska Native young women (for details regarding the overall project, see Kaufman et al [49]). We recruited participants for this formative study from February 2019 to August 2020. Finally, the authorship team did not use any generative artificial intelligence in the development of this research protocol nor in the parent RCT study.

Ethical Considerations

The procedures associated with this study and the RCT, including ethical approval and oversight, have been approved by the Colorado Multiple Institutional Review Board (#18-0574). Additionally, a data safety monitoring board was created to review all protocols associated with the RCT, while also providing oversight on data collection and analyses and the interpretation of results [39]. Informed consent was obtained from all participants, and a US $50 Amazon gift card was issued as compensation for their time. All collected data within this protocol was analyzed for legitimacy and then deidentified for participation in the project. Details about the process are described below.

Participants

To meet eligibility criteria for this formative work, participants had to be female at birth; aged 16-20 years; self-identify as American Indian or Alaska Native; reside within the United States; not live on an American Indian and Alaska Native reservation or village; reside in a city with a population of 50,000 or more; and not be pregnant. Those living in Alaska were excluded since approval for research had not yet been obtained from the relevant research review board.

Procedures

We used online survey tools to create an eligibility screener. Recruitment ads containing a link to the screener were shared through comprehensive recruitment methods including in-person events and online through email listserves and on social media platforms such as Facebook and Instagram. When in-person events were halted due to the COVID-19 pandemic, all recruitment methods were moved to online platforms. All ads indicated eligible respondents would receive payment.

Fraud Prevention Integration to Procedures

The screener survey was initially programmed in REDCap (Research Electronic Data Capture; Vanderbilt University) [50], which is a secure web application for building and managing online surveys and databases. Understanding the potential for fraudulent responses, we followed common security guidance [18,51,52] and used reCAPTCHA, a test to distinguish humans from “bots,” or automated algorithms impersonating human engagement [53]. However, despite these security efforts, the screener links were inundated with over 500 fraudulent screener survey responses within 48 hours of launch. Fraudulent responses were quickly identifiable to the research team when the following were identified through analysis of the raw data: (1) continued incorrect responses to survey questions (eg, providing the first and last name as a response to “What is your first name?”); (2) multiple eligible repeated responses from the same town or city; and (3) evidence of trial-and-error responses to eventually achieve eligibility—for example, multiple records with the same contact information, but each record showing incrementally “correct” responses. Additionally, we noticed many of the fraudulent data responses originated from 1 specific recruitment link—Facebook. As soon as this fraudulent activity was detected, we disabled all original links to our screener survey and redistributed recruitment flyers with new links. Even though not all of the recruitment links contained fraudulent data responses, the research team made the difficult decision to redistribute all new links as a precautionary measure. Still, within 2 weeks, we received an additional 1300 fraudulent hits; the research team was only able to discern that 6 participants (0.46% of total responses) were deemed legitimate participants based on self-report. The links were again closed and this time, recruitment efforts were paused to allow time for the development of a more robust protocol to detect and prevent fraudulent attempts at study enrollment.

Development and Implementation of PRIOR

Subsequently, we developed a 2-step integration verification protocol known as PRIOR. The first step included the addition of four electronic protections to assist in limiting fraudulent hits to the screener as follows: (1) The screener survey was moved to Qualtrics [54] to take advantage of its robust security features, including the option to require a password for survey access or protect against bots using reCAPTCHA. (2) Embedded data points were created to assist in determining fraud. Embedded data points are information automatically collected via survey software from a participant’s device, such as IP address, latitude and longitude, duration (in seconds) of survey use, browser type, and browser version. (3) Timing features were enabled within the survey instrument. This allowed us to require participants to spend a certain amount of time on each screen prior to advancing to the next screen of questions, thus preventing “bots” or program codes from advancing through the survey. (4) Unique URL links were created for each method of recruitment such as each separate social media platform and email.

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The second step involved manual verification by phone with prospective participants deemed tentatively eligible based on their screener survey responses. Our phone verification process required tentatively eligible participants to speak by phone with a project team member who asked questions to verify the participant's eligibility by confirming specific identity information. In the following, we describe each of these steps and their elements in more detail.

Step 1: Actions to Electronically Detect Fraud

Qualtrics Security Features

The antifraudulent features unique to Qualtrics were key to the effectiveness of our new protocol. We first transferred the screener survey to Qualtrics to enable the "prevent ballot box stuffing" feature in addition to reCAPTCHA. The "ballot box stuffing" option in Qualtrics is unique and considered a critical element in mitigating fraud within research [18]. With this feature activated, Qualtrics places a unique browser cookie "marking" the participant's previous participation within the survey to prevent duplicate entries in the data [55], which in our case, would mitigate trial-and-error attempts to achieve eligibility, as well as multiple fraudulently eligible participants.

Geolocation and Embedded Data

Three individual embedded data points—IP address, latitude, and longitude—were used to assess geolocation, as recommended by Ballard et al [18] as a key tool in assisting with mitigating fraud in research. Globally, IP addresses are used to identify specific devices on specific networks, essentially being a unique form of identification in the online sphere [51]. IP addresses in combination with latitude and longitude comparisons create a single variable of geolocation, a critical step as IP addresses have documented inaccuracies as a stand-alone indicator for detecting duplicate responses [56]. This element of fraud prevention is imperfect in cases of legitimately eligible individuals residing in the same household, as devices connected to the same virtual private network will all have the same IP addresses [52]. However, geolocation works more efficiently in tandem with other key embedded data points such as the "Device Identifier" features housed within Qualtrics. This feature enables researchers to collect extra information about the device the participant used, if needed, and attach it to the individual participant's data [55]. After assessing geolocation, this feature allowed us to compare similarities in "suspicious" cases that appeared fraudulent. This information allowed for a deeper look into the specific circumstances under which the survey was conducted, such as browser-specific information, for example, Google Chrome or Firefox, and the version of the browser used by the participant; and the type of device being used, for example, Android or Apple.

Although these 2 types of variables, geolocation and embedded data points, are separate entities within Qualtrics, they were examined collectively to discern potential fraud. This collective integration occurred in several ways. First, we compared respondent-provided location to geolocation. If the locations differed, the response was flagged as "potentially fraudulent." Second, device identifiers were examined to determine if there were any cases with several identical responses across respondents with the same browser and browser version. If any of the cases had repeated similar responses, they were flagged as "potentially fraudulent." All other participants without any sign of potentially fraudulent data were categorized as tentatively eligible.

Embedding Timing on Survey Items

We also integrated timing elements into the screener survey. The presence of a "timing" question allows Qualtrics to track the time (in seconds) spent on each page to give the researcher a timestamp variable. This feature also prevents participants from "advancing" within the survey until a certain time has passed [55]. The decision to implement timing on questions within the survey was based on the aforementioned fraudulent data responses the research team received. That is, fraudulent responses were extremely rapid responses that only a bot could provide. To permit timing, we separated screener questions into 3 separate blocks (ie, mobile pages) meaning the eligibility questions did not appear all together but instead on different mobile pages. Doing so allowed the participants to only be able to advance to the next screen after at least 5 seconds had passed and autoadvancing after 60 seconds. The autoadvance feature was included to prevent individuals from memorizing questions and responses and from multiple attempts to respond "correctly."

Unique Recruitment URLs

Unique recruitment screener survey links were created for each separate method of recruitment. More specifically, we created a different link for each of the electronic recruiting methods, such as Facebook, Instagram, and other social media platforms, and we also created individual links for in-person recruitment flyers and for electronic postings via listserves or through email. Creating method-specific recruitment links allowed the research team to "close" a link if rounds of fraudulent responses were occurring without missing potential participants in other sources of recruitment. This was a critical lesson learned by the research team during the analysis of the fraudulent data, where approximately 87.1% of respondents indicated they heard about the study opportunity via Facebook. Had the protocol been in place prior to the onset of data collection, the research team could have isolated the issue to 1 recruitment source. This is critical in ensuring no potential participants are being denied the study opportunity on other platforms.

Step 2: Verification With Participants

Phone verification was a critical piece of our fraud prevention protocol. Participants deemed tentatively eligible or who had answered all eligibility questions correctly but were flagged as potentially fraudulent via the embedded data and geolocation were contacted by a member of the research team to ascertain eligibility through a series of questions designed to confirm true eligibility. Participants were required to provide a contact number in the screener survey. This number was used to contact participants who were then asked to confirm their birth date, city and state, email address, and how they heard about the study. If participants' responses affirmed the embedded data points and response they provided in the screener survey, they were enrolled in the study enrollment via an emailed consent form for e-signature; major discrepancies resulted in

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nonenrollment. For example, 1 "potentially fraudulent" participant, when asked about their residence by a research team member, was told about varying major urban cities by another individual in the background. This major discrepancy resulted in nonenrollment within the study. In contrast, 1 participant listed a major city as their place of residence, and when contacted by a member of the research team, they named a suburb outside of the city. This participant was not disqualified based on this minor discrepancy.

Results

We relaunched our recruitment campaign with the enhanced fraud protection protocol on May 11, 2020. After the implementation of this enhanced PRIOR protocol, we had 461 individuals total come through the combined screener surveys across all platforms (Figure 1)—433 total individuals for social media (Facebook, Instagram, and Twitter), and 28 individuals for email-based recruitment. A total of 80 participants were deemed tentatively eligible, and of these 80, a total of 55 (69%) participants met the inclusion criteria and were verified as unique, and 2 participants did not complete the survey, resulting in a final enrollment of 53 participants for the formative study. Of the remaining 25 (31%) participants that were not eligible, 6 participants were excluded because they did not live in a city meeting the population size criterion, and 4 participants attempted to re-enroll in the study after receiving their participant compensation, an action that was also flagged by our protocol. The remaining 15 participants were identified as fraudulent responses based on the protocol set in place.

Figure 1. Final participant enrollment after implementation of the PRIOR (Protocol for Increasing Data Integrity in Online Research) protocol.

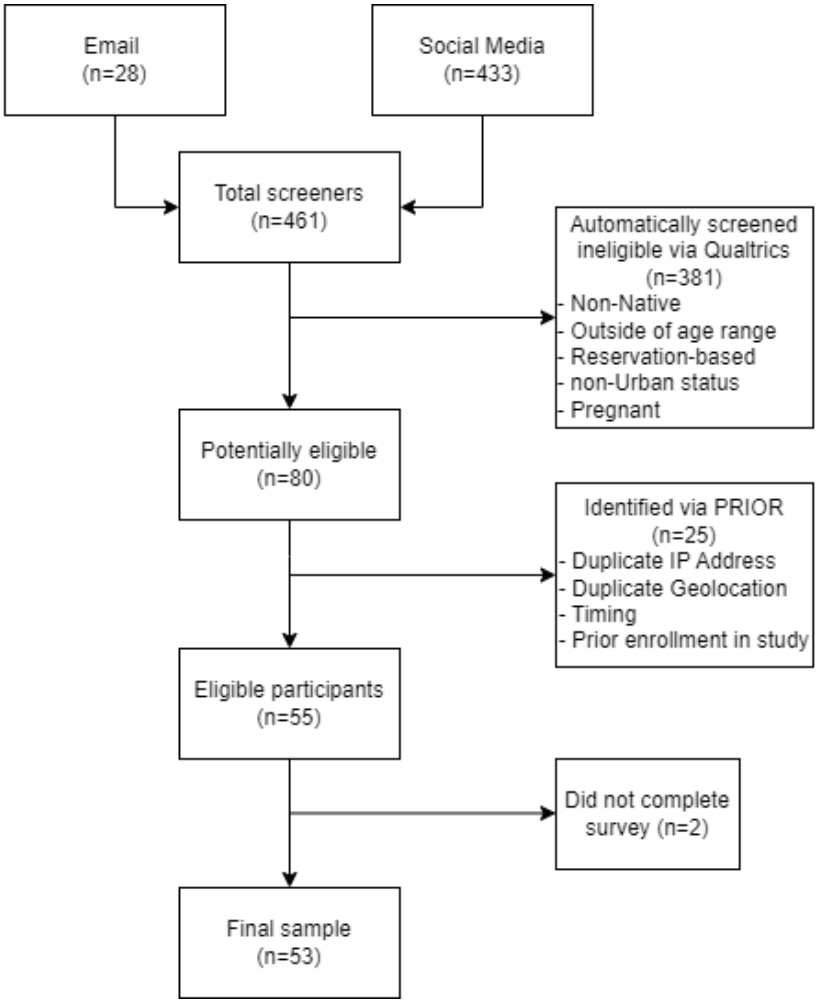

Before the implementation of PRIOR, fraudulent hits would begin with the first initial response well exceeding 5000 seconds (or about 83 min), which was far too long for a short set of screener questions, followed by several bouts of all eligible responses completed in less than 30 seconds. After the implementation of the enhanced fraud prevention protocol, the research team was able to determine that, on average, participants took 105.07 seconds to successfully complete the screener survey's 9 questions.

In the final sample (n=53), 4 participants were within the same geolocation—one set of siblings and one set of cousins residing in the same household. In these cases of family relations, only 2 individual responses had similar geolocation data points and device identifiers. In the follow-up phone call to the potential participants, we learned that 1 sibling informed the other of the research opportunity. Comparatively, in cases marked as fraudulent, there were more than 20 individual responses with differing geolocation data points, but device identifiers, such as browser version and operating systems, remained consistent among these individual responses. Finally, via the embedded

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data points, we identified some participants who did not successfully screen into the study and tried again with different responses to meet eligibility criteria. These 4 participants were excluded from the study and labeled as fraudulent.

Discussion

Principal Findings

As online data collection in diverse environments increases, so too increases the opportunities for—and experiences that researchers will have with—fraud, either perpetuated by bots or individuals with malintent. As we demonstrate in this work, the methods to detect and prevent fraudulent participation in online surveys that have been endorsed to date were insufficient and, thus, ineffective when attempting to recruit and enroll the sample for this study. The 2-step strategy described here contributes to a small but growing literature to address fraud in survey research [32,57] and reduce this threat to research integrity.

Our PRIOR protocol is comprised of many small points of information; however, these points, when reviewed together, created a full picture of the legitimacy of each participant and proved to be a powerful tool to determine and detect fraud. Changing data collection platforms, and using commonly recommended features of Qualtrics such as reCAPTCHA and "ballot box stuffing" prevention, was clearly impactful in the initial screening of potential participants. Of those who passed this initial stage, our added checks identified another 31% who were not eligible. Although this process is labor-intensive, it helped protect the integrity of the data. This is especially crucial for individuals working with marginalized populations, such as the American Indian and Alaska Native population, who have been subject to research harm in the past [58]. Further, during the phone verification, the research team heard from many participants that they appreciated the extra security measures in place and felt more comfortable enrolling in a virtual research project having talked with a study team member first. The research team hopes this critical step can aid in re-establishing trust between academia and American Indian and Alaska Native communities by making research teams more personable to the participants and actively showing that protections are in place for data collected in any phase of the study—from enrollment to participation in the study itself.

Having a robust security protocol in place helps researchers discern topics of relevance for communities and populations and adds credibility to the collected and analyzed data. Researchers who use this method can improve their reach and legitimacy for research with hidden or hard-to-reach populations and prevent fraudsters from disparaging the integrity of the overall data and receiving compensation inappropriately. Further, integrating a fraudulent data detection protocol into any research endeavor with American Indian and Alaska Native communities or other hard-to-reach populations helps build a foundation within the literature, which simultaneously ensures that data collection is ethical and reflects the authentic views of the community. Additionally, we caution researchers to limit how much information is relayed online to potential participants regarding respondent compensation, especially if research teams plan to use social media accounts to "boost" their recruitment links as ads. Doing so can attract a larger number of fraudulent respondents trying to access immediate funds via respondent compensation. While we note that such steps in a fraudulent data protocol, such as PRIOR, are time and labor-intensive, taking these steps will help to bridge the gap of research distrust and provide the community with accurate and authentic data.

Limitations

While there are many strengths found within this protocol, several potential limitations should be considered when using PRIOR. First, there are ethical concerns regarding the collection of both IP addresses and geolocation variables. Researchers must ensure that a plan is in place to delink these data points from participant responses to surveys or other data collection materials and to permanently destroy these variables after verification of identity has occurred. As an example, our research team immediately delinks all collected IP addresses from future participant responses and deletes all related variables. Additionally, the collected IP addresses are limited to only specific members of the research team and are kept in password-protected filing systems. Finally, the rigor involved in verifying authentic participants may pose too great a barrier for some eligible participants who may not complete the process. As noted, we found that most participants were pleased with the safeguards in place. While seemingly costly, the benefits include authentic participation, data integrity, and minimal losses in faulty respondent compensation.

Conclusions

Fraudulent surveys compromise the authenticity and integrity of the data, as well as deplete scarce research resources including respondent compensation and personnel time. It is crucial for researchers working with American Indian and Alaska Native communities or other populations that have experienced research harm to guard against online misrepresentations. Such protocols are critical to protecting the integrity of the data—that is, to ensure that data collected represent authentic voices of the population, in this case, urban American Indian and Alaska Native young women. Ensuring the integrity of the data in this way promotes trust between researchers and vulnerable or previously exploited communities and fosters the identification of authentic needs and priorities of the populations involved with the research. As new technologies, for example, machine learning or artificial intelligence, are used in virtual research methodologies, modification of, or new developments in, existing protective protocols will be essential. The PRIOR protocol described here advances an approach that may serve to prevent fraudulent survey participation in the short term and to foster new and expanded applications concurrent with new data collection technologies.

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Data Availability

Study data were provided by individuals residing in urban American Indian communities in the United States. We respect the rights of American Indian, Alaska Native, Native Hawaiian, and other Indigenous groups to protect research data that pertains to their communities. Questions about data access may be directed to the Centers for American Indian and Alaska Native Health Data Access Committee (DAC). Please contact Ms Sara Mumby, DAC Coordinator, Centers for American Indian and Alaska Native Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus at sara.mumby@cuanschutz.edu.

Conflicts of Interest

None declared.

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Abbreviations

PRIOR: Protocol for Increasing Data Integrity in Online Research
RCT: randomized control trial
REDCap: Research Electronic Data Capture

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Protocol

Recovery and Renewal of Co-Design Approaches in Health: Protocol for a Realist Synthesis

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Abstract

Background: The COVID-19 pandemic significantly transformed the landscape of work and collaboration, impacting design research methodologies and techniques. Co-design approaches have been both negatively and positively affected by the pandemic, prompting a need to investigate and understand the extent of these impacts, changes, and adaptations, specifically in the health sector. Despite the challenges that the pandemic imposed on conducting co-design and related projects, it also encouraged a re-evaluation of co-design practices, leading to innovative solutions and techniques. Designers and researchers have explored alternative ways to engage stakeholders and end users, leveraging digital workshops and participatory digital platforms. These adaptations have the potential to enhance inclusivity, allowing for a wider range of individuals to contribute their perspectives and insights through co-design and thus contribute to healthcare change.

Objective: This study aims to explore the impacts of the pandemic on co-design and related practices, focusing on co-design practices in healthcare that have been gained, adapted, or enhanced, with a specific focus on issues of equity, diversity, and inclusion.

Methods: The study uses a realist synthesis methodology to identify and analyze the effects of the pandemic on co-design approaches in health, drawing on a range of sources including first-person experiences, gray literature, and academic literature. A community of practice in co-design in health will be engaged to support this process.

Results: By examining the experiences and insights of professionals, practitioners, and communities who were actively involved in co-design and have navigated the challenges and opportunities of the pandemic, we can gain a deeper understanding of the strategies, tools, and techniques that have facilitated effective co-design during the pandemic, contributing to building resilience and capacity in co-design in health beyond the pandemic.

Conclusions: By involving community partners, community of practice (research), and design practitioners, we expect closer proximity to practice with capacity building occurring through the realist process, thus enabling rapid adoption and refinement of new techniques or insights that emerge. Ultimately, this research will contribute to the advancement of co-design methodologies and inform the future of co-design in health.

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KEYWORDS

participatory design; co-design; realist synthesis; equity, diversity, and inclusion; EDI; community of practice; online co-design; virtual platform; internet research ethics; health communication; health design; COVID-19; virtual health; digital health

Introduction

Background

Over the past decade, co-design as an approach for health system and service improvement has been rapidly adopted as a stakeholder-engaged process that promotes inclusivity and facilitates change. Co-design is a design approach that involves communities in collaboratively addressing health challenges while enhancing capacity [1]. In recent years, the adoption of co-design techniques in the health care sector has significantly increased, representing a crucial advancement toward integrating real-life experiences, incorporating unconventional knowledge, community-based decision-making, and shared responsibility, in the development and implementation of more equitable health care solutions [2-5]. Drawing on participatory and action research [6], co-design relies on the active involvement of all stakeholders, specifically including individuals with lived experience in conjunction with health care providers, and conventionally incorporates in-person activities. Unfortunately, the pandemic abruptly disrupted the opportunity for in-person engagement.

The COVID-19 pandemic significantly transformed the ways and landscape of work and collaboration, including having a profound impact on design and research methodologies. Despite the challenges that the pandemic imposed in conducting co-design projects in person, designers and researchers have explored and experimented with new ways to engage stakeholders and end users, leveraging digital workshops and participatory digital platforms. These adaptations have the potential to enhance inclusivity, allowing for a wider range of individuals to contribute their perspectives and insights. Rapid adjustments were made to participatory practices and techniques, but co-design, especially for marginalized and equity-seeking groups, experienced setbacks such as limitations, delays, and some loss of effectiveness [7]. Thus, co-design approaches have been both negatively and positively affected by the pandemic, prompting a need to investigate and understand the extent of these impacts, changes, and adaptations, specifically in the health sector.

The “Recovery and Renewal of Participation in Healthcare Change” project aims to enhance capacity and resilience in co-design within and for the health care sector. Its primary objective is to capture the experiences and adaptations that emerged in co-design projects during the pandemic. By examining the evolution of co-design practices, the project seeks to understand how these practices engaged or disengaged communities, and specifically marginalized communities, in health service research, delivery, and improvement throughout and beyond the pandemic. To ensure that the lessons learned during the pandemic are available to shape future co-design initiatives, this project also has a goal to establish a community of practice (CoP) in advanced co-design for health and social care. This community will serve as a platform for collaboration, learning, and knowledge sharing among stakeholders involved in co-design initiatives, highlighting, sharing, and codeveloping new guidance on techniques that can endure beyond the pandemic. This guidance will provide practical recommendations and strategies for implementing co-design methodologies in health care settings, ensuring their sustainability and ongoing impact.

The project’s budget also includes provisions for participant involvement, feedback reflection sessions, and representation of Black, Indigenous, and people of color and equity-seeking community members. The project aims to use case studies from different research teams and community partners, focusing on marginalized groups experiencing health or social status stigma. The engagement mechanisms will be flexible and inclusive to ensure diverse perspectives are included.

Project Objectives

The “Recovery and Renewal of Participation in Healthcare Change” project aims to enhance co-design capacity in health care by learning from pandemic co-design experiences. It examines how co-design practices affected communities, specifically marginalized communities in health research and delivery. It also establishes a health care co-design CoP for ongoing collaboration and knowledge sharing around co-design adaptations and emerging practices. The project’s main goal is to create practical guidance for effective co-design techniques in health care beyond the pandemic.

The pandemic has led to significant changes in co-design techniques, providing a unique opportunity to address fundamental concepts integral to participation and change [8], such as power relations, equity, and inclusion, including gender-related issues. To this end, this project aims to explore co-design practices that have been gained, adapted or enhanced, and adopted with specific emphasis on the engagement of marginalized, vulnerable, and equity-seeking groups. This will include a specific exploration of topics related to equity diversity and inclusion that intersect with principles of participation and co-design (refined as part of the realist approach) [9-13]

Research Questions

The project’s research questions are as follows, with a special focus on issues of equity, diversity, and inclusion (EDI): (1) how were co-design practices changed or adapted in what circumstances to give rise to successful or high-quality outcomes for participation? (2) What are the underlying mechanisms that explain how adapted co-design practices worked to enable participation in different contexts? (3) What generalized and context-specific recommendations emerge from these experiences to inform new approaches to postpandemic co-design practice particularly considering EDI?

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Methods

Study Design

The project uses a realist synthesis approach that engages the CoP as well as our community partners [14,15] together with a design research approach [16].

The project consists of three main phases: (1) planning and detailing the research plan and materials including activating the CoP through existing networks and venues; (2) data collection, analysis, and initial synthesis, CoP involvement in candidate guidelines and principles; and (3) translation of this work into resources, such as case study or demonstration project materials, and detailing of techniques for training and sharing.

A realist approach recognizes how "activities are brought about by the underlying mechanisms constituted by people's reasoning, and the resources they can summon in a particular context" [15]. This reflects the state of co-design research in health where research practice is emerging through the pandemic and community partners' experience of participation is highly contextual. While realist approaches will be able to give us an understanding of what works in different contexts for different people, designing will enable us to apply this understanding in new and better ways of working [16,17]. Design practice extends the project methodology from creating knowledge (realist synthesis) to applying knowledge and learning through that process (research through design by demonstration projects) through the CoP supported by this project, and capacity building in new co-design methods. Both realist and design approaches accept a plurality of sources of evidence and perspective, both are iterative, and both are participatory, aligning with the project's conceptual underpinning in participatory practice and constructivist epistemology, emphasizing the importance of involving multiple stakeholders and recognizing the cocreation of knowledge [15-17].

The study will use multiple sources of evidence, including academic and gray literature, blogs, expert opinions, and lived experiences of participants and community partner representatives. Within the frame of realist approaches, the focus is on the relevancy of the data and evidence using specific criteria generated in collaboration with a CoP rather than screening various types of data through traditional scientific credibility or validity standards, using specific criteria in collaboration with partners. The research direction will be informed by a CoP consisting of health researchers, design researchers, and co-design research contributors.

Ethical Considerations

The project was approved by the Ontario College of Arts and Design University Research Ethics Board (#102248) to involve human participants. Incentives were only offered to participants who requested them if meeting the EDI criteria.

Individuals signed a consent form to participate in workshops and interviews. All the data gathered throughout these research activities were deidentified for analysis. Membership of the CoP had to be self-initiated so no consent form was required, it is primarily a vehicle for knowledge mobilization and is not a data-gathering instrument.

CoP Overview

The project team will be closely involved in planning the research plan and materials for the recruitment process, data collection, analysis, synthesis, and translation of the findings into candidate guidelines. An online CoP will be established as a collaborative platform, inviting individuals to share personal knowledge, experiences, and best practices related to co-design for health. This platform will foster a participatory and inclusive environment for engagement.

We will assemble design researchers and practitioners from diverse geographies and equity-seeking groups who have shared adaptations in their practice. We aim to recruit from or through this developing CoP. The composition of the CoP will be purposely built as diverse and equitable, a deliberately diverse pool of collaborators, comprising co-design practitioners, co-design partners (from previous projects), co-design early adopters from other fields, and community members who were involved in co-design projects during the pandemic.

EDI considerations underpin the conceptual orientation of the project from the aim and objectives to our engagement with the CoP, community partners, and the theoretical orientation of participatory and co-design approaches whose intent is engagement in shared decision-making and change inclusive of underrepresented groups.

We will take a purposive sampling approach in our research methods to address EDI considerations in the structuring of the data collection. In this way, EDI considerations will be activated in part through the CoP. The research team is dedicated to respecting and valuing the contributions of all stakeholders, including co-design communities, community partners, researchers, designers, and patient representatives. They will ensure equity and inclusivity in participant selection and data analysis, obtain informed consent, and protect confidentiality and privacy. The study will adhere to human research ethics guidelines.

The realist methods will produce specific context, mechanism, and outcomes statements (CMOs), which will serve as design criteria in phase 3 of the project (design research and capacity building phase). The intent is to identify the underlying mechanisms that explain how adaptations to co-design work in different contexts, and to generate context-specific recommendations for how co-design can be implemented postpandemic or during pandemic conditions. To conduct a realist synthesis, the process will be started by formulating a theory of change, which outlines the key assumptions about how co-design was expected to be impacted by the pandemic, what contexts saw what changes and impacts, and what the outcomes were of these co-design experiences. Further, the team will systematically search for evidence to test the theory of change, using various sources such as published and unpublished studies, gray literature, and first-hand experiences of co-design. The collected evidence will be subjected to analysis using a realist approach, entailing the identification of patterns and trends in the data to develop and refine the theory of change [18,19].

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The realist synthesis process consists of the following key stages:

Stage 1: Formulating Research Questions

The study's foundation is built upon well-crafted research questions focused on understanding the impact of the pandemic on co-design with a focus on marginalized communities' involvement in health projects. These questions guided the investigation and framed this study's objectives.

Stage 2: EDI Framework

Drawing from existing research and insights provided by diverse teams involved in this study, an EDI framework will be carefully developed to support the application of the theory of change articulated in stage 1. This framework acts as a lens through which the research data will be analyzed, ensuring sensitivity to issues of EDI throughout this study.

Stage 3: Data Collection 1

Realist Review

A comprehensive realist review will be conducted to explore information about co-design during the pandemic, including adapting co-design techniques, challenges, limitations, and emerging practices. Additionally, we aim to address the initial study question of identifying effective mechanisms for remote and distanced co-design to ensure the engagement of the most impacted communities and marginalized populations in designing and implementing health solutions. The realist review process will commence with the collaborative creation of the initial reference set of articles by the project team. This will be achieved by using relevant keywords such as "co-design," "COVID-19," "remote," "distanced," "virtual," "hybrid," and exploring author reference lists in sources such as Google, Google Scholar, national or international design journals, and digital libraries like the Ontario College of Art and Design University library databases, which include CEL (University of Ljubljana School of Economics and Business), Academic OneFile (Gale), JSTOR (ITHAKA), and Literature Resource Center (Gale). To expand the scope of literature research, artificial intelligence literature search tools such as OK-maps (OkMap) and Litmaps (Litmap Ltd) will also be used. Additionally, gray literature searches will encompass social media platforms, including blogs, facilitated Instagram (Meta) and Twitter (X Corp) discussion posts, and threads related to co-design. Moreover, information from the co-design CoP, news, and co-design events such as workshops will be explored to further enrich the realist review process. This review will provide essential context and establish the groundwork for this study.

Workshops

Multiple online workshops will be organized, recruiting participants actively involved in or planning or managing co-design efforts within health projects during the pandemic. These workshops are designed to accommodate participants across 5 different time zones (EST, MST, PST, GMT, and Australian Eastern Daylight Time), ensuring inclusivity and widespread engagement. The primary objective of these workshops is to create a dynamic platform for knowledge exchange, enabling participants to share insights, experiences, and adaptations related to co-design during the pandemic. To facilitate seamless communication and collaboration, Zoom (Zoom Video Communications, Qumu Corporation) will be used as the virtual meeting platform, while Miro will serve as the collaborative virtual whiteboard. The workshop activities will be thoughtfully designed, drawing upon co-design and EDI principles identified from prior research [20-22]. By incorporating these principles, the workshops aim to foster an environment that encourages open dialogue and valuable exchange of ideas. Through these interactive sessions, participants will have the opportunity to explore the challenges, questions, successes, and failures encountered in co-design practices through the pandemic. The collective knowledge gained from these workshops will contribute to a deeper understanding of the adaptations and gains made in co-design during the pandemic. This will be used to develop initial CMOs' analyses that explain the achieved outcomes within different contexts and by various mechanisms [18].

Stage 4: Synthesis and Data Collection 2

Overview

The study will use an inductive coding approach, beginning with the EDI framework to support the interrogation of preliminary theories. A further round of analysis will be used to abstract demi-regularities in the data, which will be input to developing initial CMOs. To analyze the resources gathered for our research (realist review and workshops), we will use ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), a qualitative research tool designed for coding and analyzing various types of data such as published papers, transcripts, workshop data, blogs, and social media content.

Interviews, Webinars, and Online Survey

To address any potential data gaps identified during the research and gain more insights from relevant stakeholders, a series of interviews and webinars will be conducted. These interactions enrich this study by incorporating a wide range of diverse perspectives. The interviews will provide a valuable opportunity to delve deeper into specific aspects of the research, enabling us to gain deeper insights and gather nuanced information from key participants. Individually, the webinars will foster a collaborative environment where individuals who are involved in co-design practices with various backgrounds and expertise can actively engage in discussions and share their knowledge and experiences related to co-design for health. An online survey will be distributed to test, develop, and build consensus around identified contexts, mechanisms, and outcomes that led to adaptations or led to losses or failures of co-design in health through the pandemic. We are planning to conduct surveys in 2 formats: an initial short survey to assess the initial CMOs during our webinars, followed by a more comprehensive survey at a later stage to validate the final CMOs.

Stage 5: Evaluation and Validation Workshops and Survey

The findings of this study will be subjected to evaluation and validation workshops. This process ensures that the final CMOs are credible, and accurately reflect the impact of online

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co-design on marginalized communities' involvement and co-design techniques in health projects. We will also use surveys to validate our findings and achieve a consensus regarding the final CMOs. To do this, we will initially distribute concise surveys during CoP webinars to evaluate and test the Middle-range CMOs. Subsequently, we will use the Delphi survey technique which includes a series of iterative questionnaires. It will enable us to validate and establish a shared consensus regarding the final CMOs.

Stage 6: Demonstration Project Materials, Training, and Sharing

As an outcome of stages 1-5, this study will contribute valuable insights in the form of case studies, CoP dialogue, webinars, and training opportunities. This will include a refined EDI framework and guidelines to support and enhance resiliency [23] in co-design research and practice through capacity-building activities through the CoP.

Results

By following the realist synthesis process, the potential outcomes or results of this study will include a comprehensive understanding of how remote and distanced co-design and co-design adaptations can be leveraged effectively for designing and implementing health solutions with a focus on EDI.

The timeline for the project encompasses various stages, including realist review, data collection, data analysis, synthesis and evaluation, design and development of framework and guidelines, development of capacity-building materials, knowledge mobilization activities, and reporting over 3 years.

This project was initially funded in March 2022 and has hosted 7 webinars, 7 workshops, 1 winter school, and 15 interviews as of May 2024. The CoP has been active since October 2022 and has 169 members as of May 2024. Knowledge dissemination will involve journal publications, workshops, and talks across academic contexts to share key findings.

Discussion

Principal Findings

By examining the experiences and insights of professionals, practitioners, and communities who were actively involved in co-design, and having navigated the challenges and opportunities of the pandemic, we can gain a deeper understanding of the strategies, tools, and techniques that have facilitated effective co-design during the pandemic. The insights gathered can contribute to building resilience and capacity in co-design in health beyond the pandemic. Furthermore, the involvement of community partners, CoP, and design practitioners is expected to be closer to practice, thus allowing for capacity building, and potentially enabling rapid adoption and refinement of new techniques or insights that emerge.

Expected Findings

This project will explore and capture how co-design practices, adaptations, and experiences (including failures) emerged during the pandemic. It will also identify resilient practices, new practices that hold promise for enabling co-design in health, and ways in which equity and inclusion can be enhanced.

The potential results of this study will include an in-depth understanding of how co-design adaptations can be leveraged effectively to enhance co-design practices, for designing and implementing health solutions with a focus on EDI. Learnings from this work will then contribute to rapidly advancing co-design practices in health, with a specific focus on issues of EDI, while also providing new guidance on techniques that can enhance resilience while building capacity in co-design research and practices.

Strengths and Limitations

The project's key strengths lie in its application of an approach that combines realist synthesis and design approach. This approach empowers the project team to attain the essential knowledge needed for the development of comprehensive guidelines. The realist methodology enables the project team to explore and assess various studies and projects that have used co-design approaches and techniques through the pandemic to identify the fundamental mechanisms and contextual elements that play a key role in effective co-design [16]. Additionally, design approaches permit the project to surpass knowledge creation and use this knowledge to foster innovative and enhanced methods of operation. Moreover, active involvement and collaboration of the CoP and community partners in the project play a pivotal role in ensuring the achievement of the project's objectives.

Because the project explores emerging practices it may encounter some limitations, including that there might be limited existing research or data available for reference, the rapidly changing nature of the emerging practices makes it challenging to maintain up-to-date findings throughout the project duration.

Future Directions

We will use a range of various knowledge translation and sharing methods to disseminate our research findings. Our ongoing connection and collaboration with CoP members provide an opportunity to share, exchange, and disseminate our findings within the network and to broader audiences. Input from CoP members and other knowledge users will inform our dissemination strategies and guide the planning of future research initiatives. Additionally, the research team's strong connections to key journals in this space, such as JMIR, Design for Health, Health Expectations, and the International Journal of Integrated Care, highlight their ability to disseminate their contributions to a broad audience. Moreover, the outcomes of this project will make visible contributions to the evidence base through open-access publication venues, ensuring widespread accessibility for design researchers and health care improvement specialists.

Conclusions

The outcomes of this project will lead to the creation of a co-design framework and guidelines aimed at enhancing resiliency in co-design practices through an EDI lens. By focusing on EDI issues specifically in our examination of emerging techniques, we expect to contribute to the rapid

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development of inclusive co-design that may have positive impacts not only on equity-seeking groups but for all future participants. This framework is set to have an impact on communities in health service research, health service delivery, and health care improvement beyond the challenges posed by the pandemic.

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Data Availability

The data sets generated during this study are not publicly available due to ethical considerations. However, key findings that surged from the analysis of these data sets are available in the community of practice [24].

Authors' Contributions

To examine the impact of the pandemic, a group of researchers from the Health Design Studio at OCAD (Ontario College of Art & Design) University, the Design Health Research Innovation Lab at the University of Alberta, Emily Carr University Health Design Lab, SE Research Centre at SE Health, Lab4Living at Sheffield Hallam University, and CoLab at the University of Washington came together, supported by the Canadian New Frontiers in Research Fund program of Canada, supplemented by funding from JL's team. The Recovery and Renewal of Participation in Healthcare Change research team comprises a core group of 8 investigators and researchers—KS (principal investigator), GH (coprincipal investigator), CR (coapplicant), NB (coapplicant), PH (coapplicant), JL (collaborator), SW (collaborator), and MM (coinvestigator), supported by a dedicated team of research assistants (LAPG, Mariam Al-Bess, Lariena Kumar, Shraddha Kumbhar, Mehrnoush Zeidabadi), and Chieng Luphuyong (workshops facilitator).

Conflicts of Interest

None declared.

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Abbreviations

CMO: context, mechanism, and outcomes statement
CoP: community of practice
EDI: equity, diversity, and inclusion

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Protocol

Integrating Social Determinants of Health in Machine Learning–Driven Decision Support for Diabetes Case Management: Protocol for a Sequential Mixed Methods Study

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Abstract

Background: The use of both clinical factors and social determinants of health (SDoH) in referral decision-making for case management may improve optimal use of resources and reduce outcome disparities among patients with diabetes.

Objective: This study proposes the development of a data-driven decision-support system incorporating interactions between clinical factors and SDoH into an algorithm for prioritizing who receives case management services. The paper presents a design for prediction validation and preimplementation assessment that uses a mixed methods approach to guide the implementation of the system.

Methods: Our study setting is a large, tertiary care academic medical center in the Deep South of the United States, where SDoH contribute to disparities in diabetes-specific hospitalizations and emergency department (ED) visits. This project will develop an interpretable artificial intelligence model for a population with diabetes using SDoH and clinical data to identify which posthospitalization cases have a higher likelihood of subsequent ED use. The electronic health record data collected for the study include demographics, SDoH, comorbidities, hospitalization-related factors, laboratory test results, and medication use to predict posthospitalization ED visits. Subsequently, a mixed methods approach will be used to validate prediction outcomes and develop an implementation strategy from insights into patient outcomes from case managers, clinicians, and quality and patient safety experts.

Results: As of December 2023, we had abstracted data on 174,871 inpatient encounters between January 2018 and September 2023, involving 89,355 unique inpatients meeting inclusion criteria. Both clinical and SDoH data items were included for these patient encounters. In total, 85% of the inpatient visits (N=148,640) will be used for training (learning from the data) and the remaining 26,231 inpatient visits will be used for mixed-methods validation (testing).

Conclusions: By integrating a critical suite of SDoH with clinical data related to diabetes, the proposed data-driven risk stratification model can enable individualized risk estimation and inform health professionals (eg, case managers) about the risk

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of patients' upcoming ED use. The prediction outcome could potentially automate case management referrals, helping to better prioritize services. By taking a mixed methods approach, we aim to align the model with the hospital's specific quality and patient safety considerations for the quality of patient care and the optimization of case management resource allocation.

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KEYWORDS

diabetes; case management; case manager; social work; case mix; social determinants of health; clinical decision support; decision support; predictive analytics; disparities; health disparities; data warehouse; tertiary care; health care system; chronic disease management

Introduction

Diabetes is a major source of morbidity and mortality in the United States. According to the Center for Disease Control and Prevention, over 38 million people or 11.6% of the US population have diabetes [1-3]. Poorly managed diabetes leads to poor glycemic control and associated significant complications that require hospitalization. Furthermore, having diabetes can complicate recovery from other medical and surgical morbidities leading to a greater likelihood for longer hospitalization, repeat hospitalizations, and emergency department (ED) use [4-6]. Since 2010, hospitalizations associated with diabetes and related conditions have increased likely due to an increase in prevalence and deterioration in diabetes control [7,8].

There is convincing evidence that social determinants of health (SDoH), or the conditions where people are born, grow, live, work, and age are associated with the prevalence of diabetes as well as outcomes among those with a diagnosis [9-11]. SDoH frameworks suggest that there are multiple causal pathways that link SDoH to outcomes. Some frameworks appropriately acknowledge upstream regional determinants such as the political environment or government policy having impact on downstream determinants such as living conditions and health behavior which in turn impact health outcomes [12]. Another framework uses educational attainment as a starting point leading to various other determinants such as health literacy, work, income, social supports, and social standing, which in turn are related to health behaviors, access to nutrition, and health care, which are then linked to health outcomes [13].

Strategies for moderating the negative impacts of diabetes involve participation in lifestyle changes related to diet and exercise, the use of drugs, as well as screenings for acute and chronic complications [14]. The effectiveness of these strategies is impacted by SDoH as well as underlying other comorbidities. Therefore, health systems focused on reducing diabetes-related ED and inpatient use are working to incorporate the social context within programs aimed at helping patients with diabetes improve their health outcomes [11].

However, there are 3 important caveats to consider in applying an SDoH framework in attempting to explain inequalities in diabetes health outcomes. First, although descriptions and pictures of these frameworks imply that the relationship between SDoH factors and health are linear, in truth the interactions between these variables are complicated and difficult to isolate. Second, SDoH factors are both at the individual (eg, a person's wage) and societal level variables (eg, community infrastructure). Third, case managers and nurses must figure out how to assess patients' SDoH characteristics and health needs to properly identify patients who will most benefit from case management and then design a program specifically tailored to that patient's needs [15,16]. There are constraints in a health system's ability to provide comprehensive case management care [17,18] as exemplified at the University of Alabama at Birmingham Health System (UABHS), where the limited availability of registered nurse (RN) case managers for identifying and managing posthospitalization high-risk diabetes cases hinders effective case management. These 3 factors combined make it difficult to identify and address the individual and community level factors that might have a nuanced relationship on desired patient outcomes.

Decision support tools and predictive analytics hold promise for assisting health systems in identifying populations most at risk and developing targeted interventions. These tools can take a holistic approach [19-21], incorporating both health status and SDoH and address the nuanced relationships between these variables (eg, nonlinearity and interactions) and their combined effect on health outcomes. However, although predictive analytic and decision support systems can easily identify high-risk diabetes cases [22,23], many of these tools only relied on health system data overlooking the nuances of daily practice and operations and user perception, hindering the implementation of a developed tool. Stakeholders, including health care professionals, struggle to support implementation due to a lack of clear insights into the performance and clinical and operational relevance of these systems.

Our study responds to these significant research gaps and practical challenges by proposing the development of a Proactive Risk Assessment Decision Support (PRADS) model through a mixed-methods (qualitative and quantitative) approach. The quantitative component will use classification performance metrics and their visualization to identify and then validate a risk stratification model for predicting an ED visit post discharge among patients with diabetes. A focus group and survey will be done with nurse manager, case managers, clinicians, and care transition leaders at UABHS to qualitatively assess the model's fit with clinical and operational workflows and its potential impact on quality of care (motivated by [24,25]). Combined quantitative outcomes and qualitative feedback will be used to refine diabetes case management protocols, making

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them more effective and aligned with real-world health care delivery.

This new tool will be used to support UABHS' case managers in identifying and prioritizing patients with diabetes with a higher risk of subsequent ED use post hospitalization. The data-driven predictive model will amalgamate repositories of patient data that include both clinical and SDoH factors [26,27]. This predictive approach has the potential to automate case management referrals in a data-driven manner, helping to better prioritize services and use.

Methods

UABHS is a large public hospital with an academic mission and a level 1 trauma center. The health system has implemented a case management program using RN case managers with training in diabetes care to improve outcomes for those recently hospitalized with diabetes. With over 50,000 patients with diabetes receiving care in the health system, the case management referrals prioritize cases based on two highly exclusive, preset clinical rules at point of discharge: (1) hemoglobin A_{1c} (HbA_{1c}) > 10.5% or (2) blood glucose > 300 mg/dL and pH < 7.3. Our methodology aims to create an expanded set of data-driven referral criteria and validate the criteria through a mixed methods evaluation. Figure 1 depicts our study framework. The research will be conducted by a large multidisciplinary team, including experts from the 5 groups below:

Figure 1. Study framework.

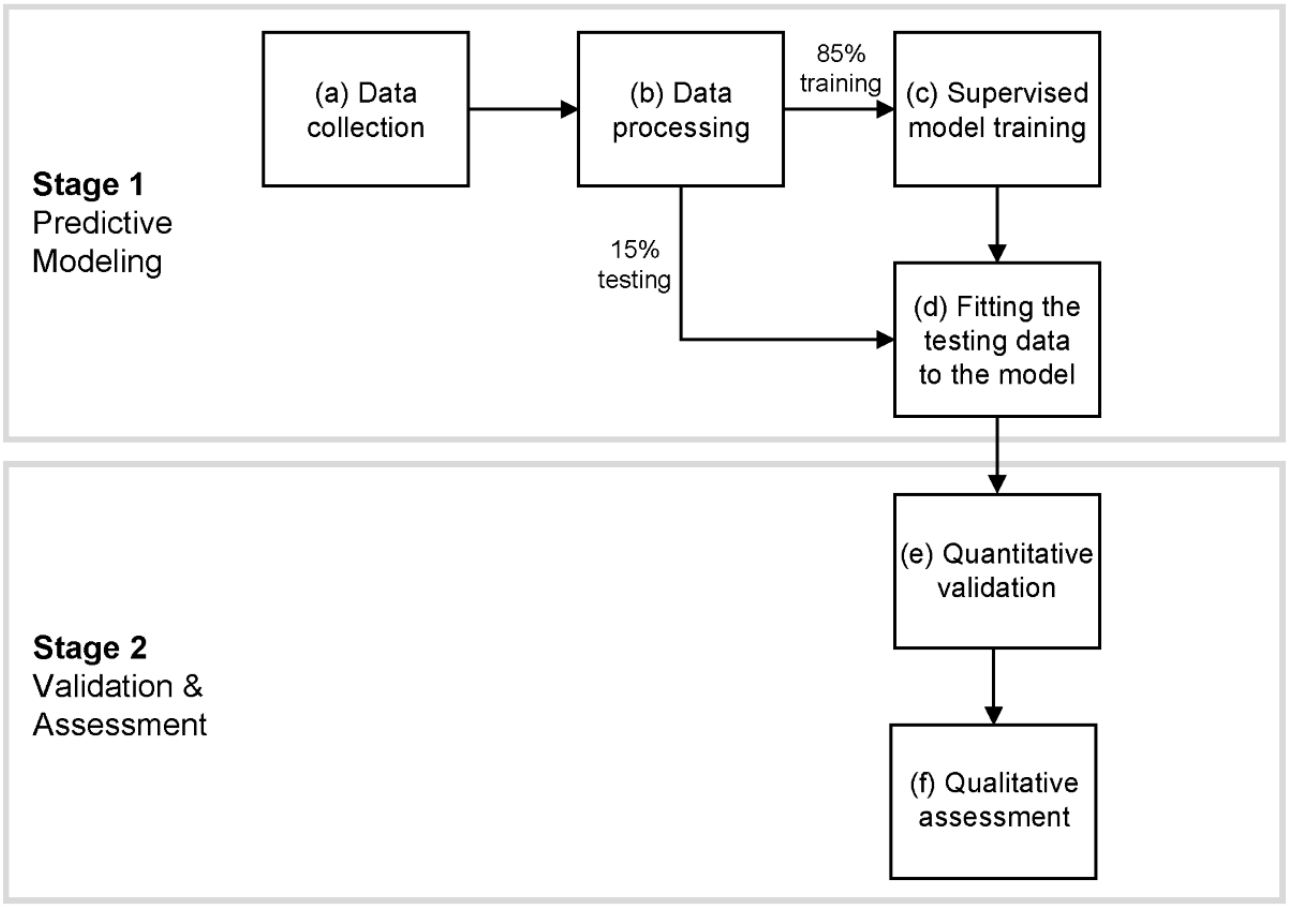

1. Case management providers, including directors of care transitions and diabetes case management RNs.
2. Primary care physicians from internal and family medicine.
3. Quality and patient safety experts, including the associate chief quality officer and quality outcome nurses.
4. Health data scientists and system analysts.
5. Large-scale electronic health record (EHR) experts, in this case the Director and staff for the University of Alabama at Birmingham (UAB) Enterprise Data Warehouse.

The large-scale EHR experts have already helped develop a process for standardizing data acquisition to use long term in the implementation of case management system changes. Our study framework requires several stages of data collection and analysis as shown in Figure 1 and described below.

Stage 1: Predictive Modeling

We will model the risk of a posthospitalization ED visit among inpatients with diabetic concerns admitted to UABHS between January 2018 and September 2023 using patient predictors and ED visit history, including health outcome post hospitalization. Patient predictors include both SDoH and clinical factors collected from the UABHS EHR repository. This approach aims to prioritize patients based on their likelihood of visiting the ED within a specific timeframe. Predictions will be

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retrospectively generated for the daily inpatient mix at UABHS, aligning with the current practices in case management.

Steps (a and b): Developing Measures for Analysis

Our initial study population includes those who were hospitalized with the following conditions (in Textbox 1) recorded as of October 2023.

Textbox 1. Laboratory test item and ICD-10 (International Statistical Classification of Diseases, Tenth Revision) codes included in the sample inclusion criteria.

- Hemoglobin A_{1c} level≥6.5% OR
- Diabetes mellitus due to underlying condition (E08) OR
- Drug or chemical induced diabetes mellitus (E09) OR
- Type 1 diabetes mellitus (E10) OR
- Type 2 diabetes mellitus (E11) OR
- Other specified diabetes mellitus (E13) OR
- Elevated blood glucose level (R73) OR
- Hypoglycemia (E16.2) OR
- Foot ulcer (L97.509) OR
- Wound infection (T14) OR
- Gastroparesis (K31.84)

The proposed criteria in Textbox 1 are more inclusive than the current restrictive case management referral criteria that are based exclusively on HbA_{1c}, blood glucose, and pH levels; yet, the sample size is not too expansive to perform large-scale machine learning modeling.

Figure 2 lists all the key diabetes-related clinical and socioeconomic factors collected from the UAB Enterprise Data Warehouse for the sample in this study. We choose to include variables that measure both individual levels of risk and societal or area-level measures of risk since SDoH frameworks suggest that both types of variables have some impact on the risk of poor health. Indeed, at our own institution we have recognized that individuals from certain communities are more likely to return to the ED compared to individuals at other communities. What is not clear from the literature is the relative impact of each type of variable on the specific risk of the individual. For example, there is some evidence that area level measures such as the Area Deprivation Index (ADI) may predict individual risk [28-30], and there is also evidence that such area level variables cannot predict individual risk [31]. Further, even if the area-level variables demonstrate less importance in predicting ED use, program planners must understand the context in which an individual lives. Area-level factors (including, the ADI and Social Vulnerability Index [SVI]) were collected from the Neighborhood Atlas and Agency for Toxic Substances and Disease Registry databases. The ADI and SVI were selected to reflect essential community-level barriers and resources that impact diabetes outcomes [32].

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Figure 2. Data items used to build the proactive risk assessment decision support model. ADI: Area Deprivation Index; ED: emergency department; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; ICD: International Classification of Diseases; PRAPARE: Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences; SVI: Social Vulnerability Index; uACR: urine albumin-creatinine ratio.

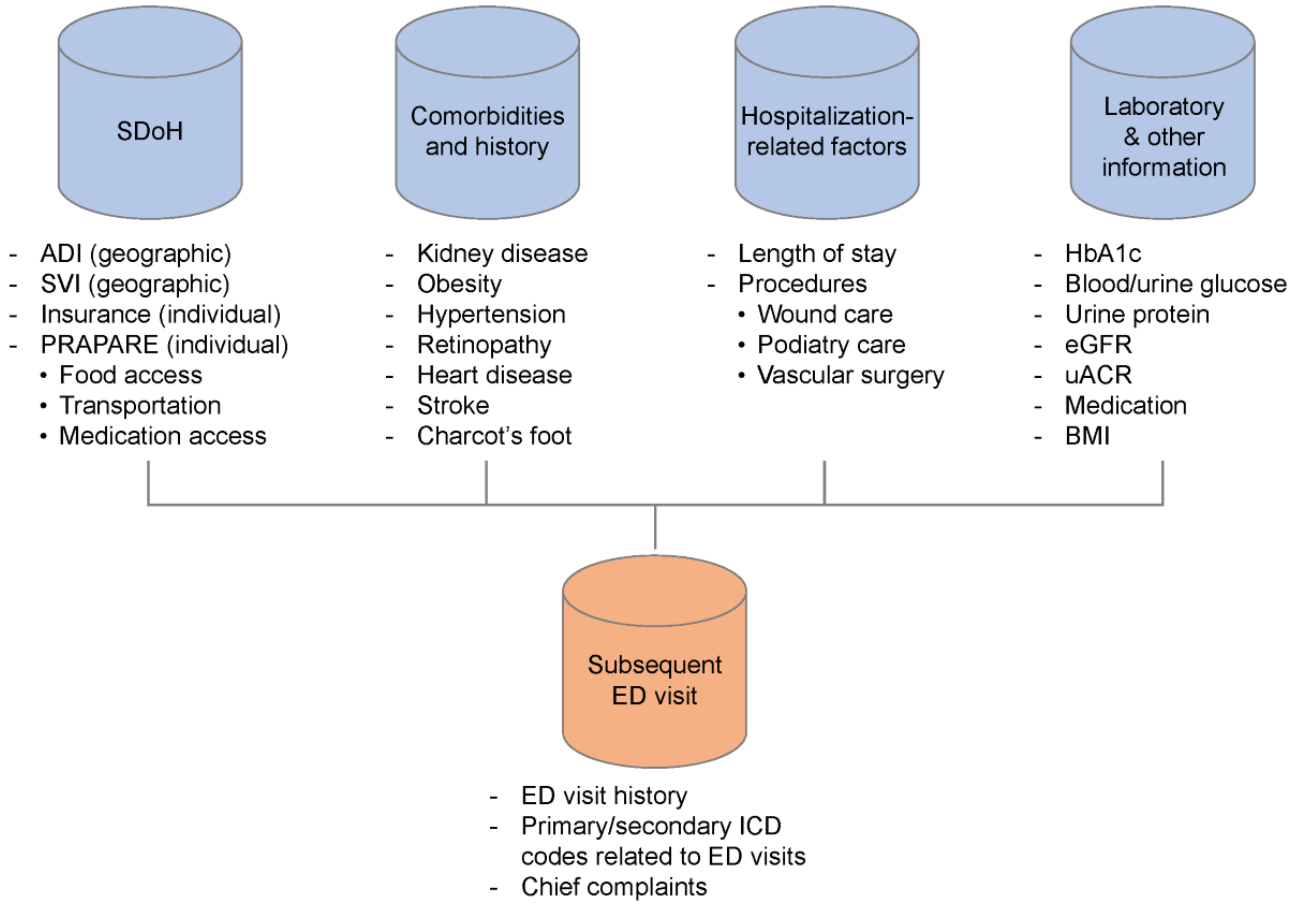

The importance of certain kinds of individual level factors (eg, race, insurance status, prior medical history, and comorbidities) has long been established as predictors of risk [33]. However, other kinds of socioeconomic data will help identify specific patient needs. The Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences (PRAPARE) [34] is a self-reported survey completed by patients during health care encounters, and include reports of access to housing and transportation, food security, and whether the patient is employed. The significance of these factors in the diabetes context has been discussed in the literature [35-37]. At UABHS, the PRAPARE survey has been implemented in the ED and inpatient settings as part of the health system's initiative, and our study will use PRAPARE data where available via the EHR repository for the study population. We will also incorporate individual-level variables included in administrative data and the medical record such as insurance status, use and visit history, age, gender, race, and ethnicity. To ensure the robustness of our findings, we will analyze and report on the missingness of the PRAPARE data items. This approach will help us assess potential biases in data collection and address their impact on the study results.

While area-level factors provide a broader view of SDoH for patients, individual-level SDoH factors also provide information of a patient's unique socioeconomic situation and together should be useful in predicting the most vulnerable and at-risk patients.

Our retrospective predictive modeling approach will use 85% of the data (148,640 inpatient visits) for training (learning from the data) and the rest of the data (26,231 inpatient visits) for validation (testing). Data elements will be cleaned and transformed based on expert clinicians' input (knowledge-driven) to create categorical and numerical variables for modeling. Categorical variables will be created from comorbidities, medications, and PRAPARE data, while ADI and SVI scales will be treated as numerical. Missing information on categorical variables will be coded as Not Measured. Our outcome variable, whether the individual returned to the ED post discharge for diabetic concerns, is a binary variable that will be taken from either the primary or secondary diagnosis at admission (see Textbox 1).

Step (c) Supervised Model Training

Given the availability of a wide range of EHR data elements at UABHS covering both predictors and the outcome variable, we choose to conduct supervised learning of patterns between the predictors and outcomes [38]. Our predictive model develops a scale of care urgency (eg, the Emergency Severity Index [39]) that identifies the likelihood that a patient may return to the ED within a specified timeframe post discharge, which can inform prioritization of patient cases in case management. We factor in a set of covariates X_i at the time that the patient (say, patient i) is hospitalized (T_i). These covariates include SDoH and the other 3 types of variables represented in Figure 2.

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In our modeling framework, defining t is an important task to ensure the practical applicability of prediction outcomes. The grouped bar graph in Figure 3 shows a preliminary analysis of the postdischarge diabetes-related ED visit frequency. The x-axis represents the frequency of ED visits from 1 month to 1 year post discharge. The y-axis shows the proportion of inpatients who returned to the ED with diabetic concerns specified in Textbox 1 as either the primary or secondary diagnosis. The result indicates that 5.7% visits to the ED occurred within a month of discharge and 10.6% within 3 months of discharge. Given the overall average of 42 daily hospitalizations with diabetes-related concerns, on average, 2.4 inpatients were likely to return to the ED within 1 month, and 4.5 were likely to return within 3 months. Discussions with the case management and clinical teams suggest that although a 1-month timeframe provided a more manageable number of cases for patient follow-ups, a 3-month period offered greater flexibility and aligned better with the projected capacity for posthospitalization case management. Therefore, we will examine whether a patient i will return to the ED post hospitalization between T_i and T_i + 3 months.

Figure 3. Diabetes-related posthospitalization emergency department (ED) visit frequency.

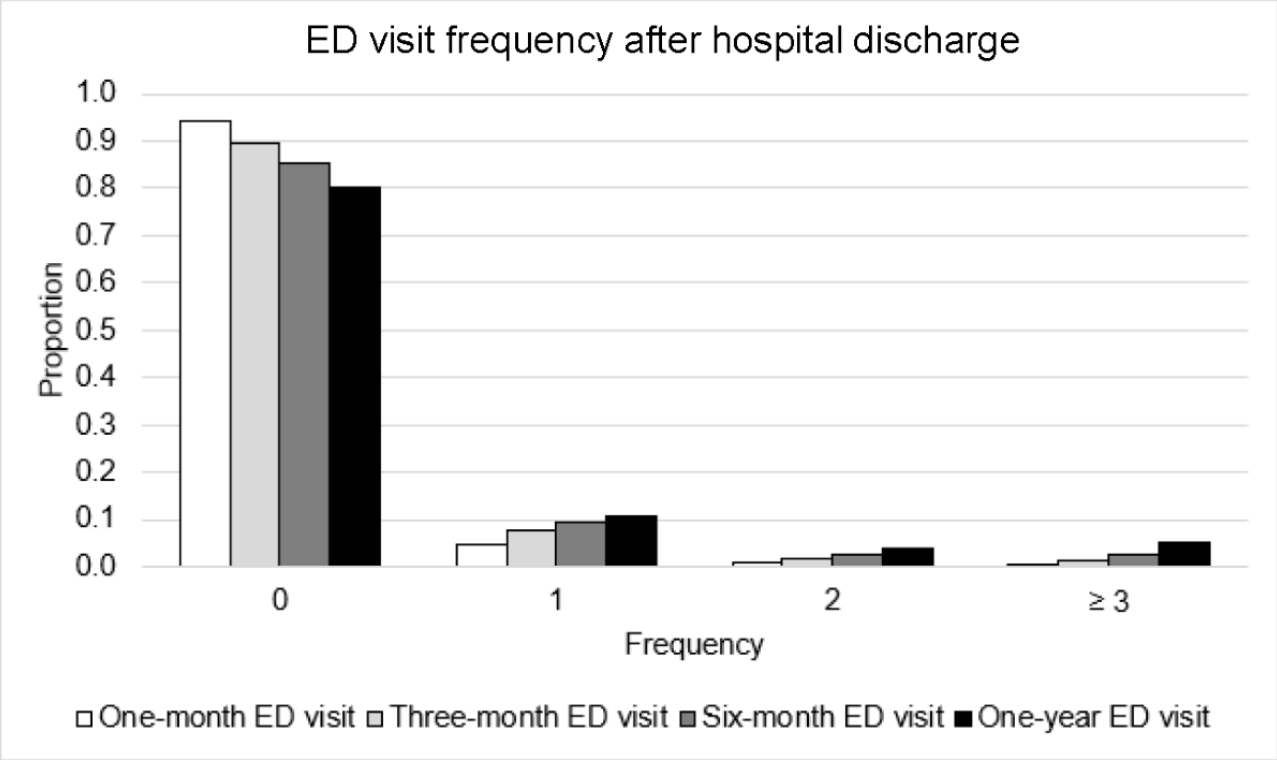

Using binomial classification structures, we will develop an Interpretable Artificial Intelligence (IAI) framework from the decision tree algorithm. The core algorithm will use a top-down search through the space of possible branches to create a tree-like decision structure [40]. Decision tree algorithms use a measure of information gained from choosing features that split the data best [40,41]. Decision trees can handle nonlinear relationships between predictors and outcome variables and interactions between predictors. Moreover, they generate inherently interpretable models, allowing for easy visualization and interpretation of the decision-making paths, which facilitate the understanding of how decisions are reached. These features make decision trees particularly suitable for meeting our study objectives, incorporating SDoH, and conducting mixed-methods validation. In our study, to be specific, we will apply the Classification and Regression Trees (CART) algorithm that uses the Gini impurity measure as a criterion for splitting [42]. Using the CART algorithm, the IAI model will be trained in a supervised manner (ie, learning from patterns between X_i and the outcome variable). After the model is trained, we will fit the testing data to the trained model to derive the prediction outcome.

Step (d) Fitting the Testing Data to the Model

A simplified example of trained decision trees is shown in Figure 4. The order of the variables partitioned (branches) and the threshold values that split the branches (in red) are determined in the training process, and the tree structure does not change during the testing step. Depending on the predicted likelihood of an ED admission assigned to a patient during testing, the visit will fall into one of the groups identified by the trained decision tree. For example, the simplified decision tree in Figure 4 shows 7 groups. Each of the groups (in Figure 4, that would be each of the 7 groups) is assigned an estimated probability of experiencing an ED visit as well as Yes/No indicators (for whether the probability leads to ED visit or not).

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Figure 4. A tree form example. HbA1c: hemoglobin A1c.

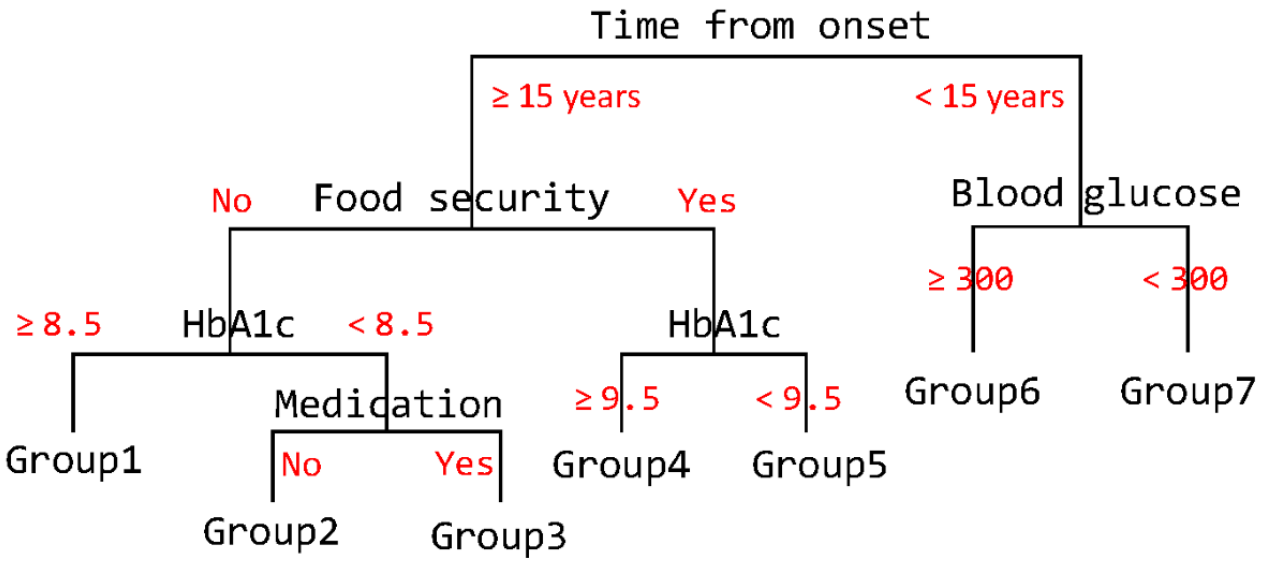

As represented in Figure 4, our IAI framework enables humans to comprehend the AI's decisions and facilitates discussion about the prediction outcomes and the variables involved between researchers and practitioners [43]. The prediction outcomes will be the basis for focus group follow-up during Stage 2 of the study.

Stage 2: Validation of the Model's Results

The results of our CART analysis will be validated by quantitative performance measures as well as qualitative data from case management, clinician, and quality and patient safety experts. A procedural diagram for our evaluation process is presented in Figure 5. The model development and validation are formative because the evaluation outcomes will be integrated in further development of the PRADS model.

Figure 5. Sequential mixed methods evaluation of the PRADS for Stage 2. 3P-MDM: three-phase modified Delphi method; AUC: are under the curve; PRADS: proactive risk assessment decision support.

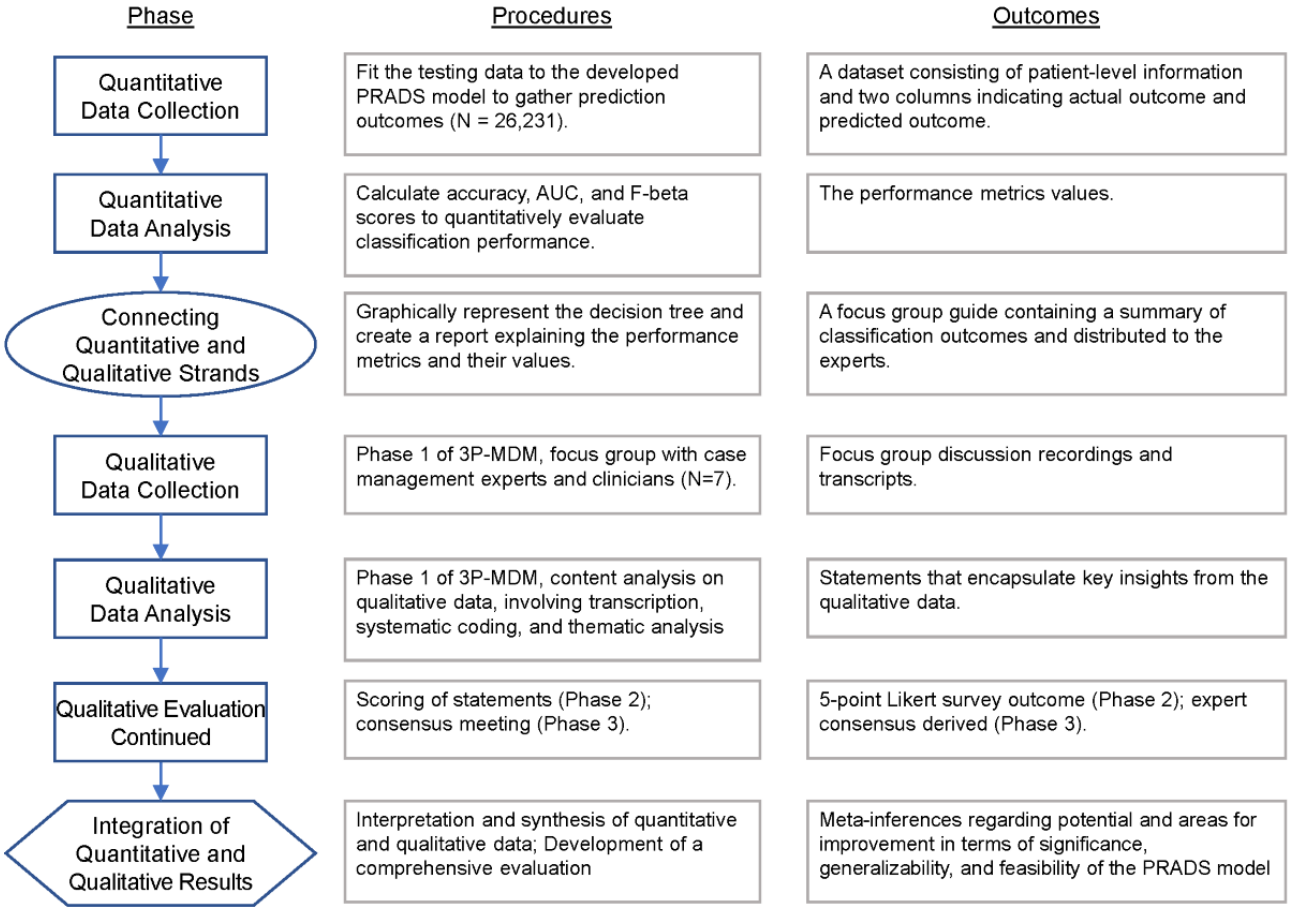

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Step (e) Quantitative Validation of Prediction

For quantitative validation of the PRADS model, predicted outcomes will be generated for the 15% testing data (N=26,231). We will take 3 steps to validate our predicted model. First, prediction accuracy, the most fundamental metric, will be evaluated. Prediction accuracy measures the proportion of true results (both true positives and true negatives) among the total number of cases examined [44]. Prediction accuracy can be misleading, particularly in imbalanced data sets where 1 class (eg, no ED visits within 3 months in our study) significantly outnumbers the other [45]. Second, we will estimate the area under the curve measure, which estimates the area under the receiver operating characteristic curve in a graphical plot illustrating the predictive ability of a binary classifier. Area under the curve is widely used as a measure of validity because it provides an aggregate measure of performance across all binary classification probability thresholds [46]. Lastly, we will estimate the F-beta score, which measures a model's accuracy both for precision and sensitivity. It can be more informative than prediction accuracy on imbalanced data sets because it considers the model's ability to identify positive results from the minority class, not just the majority class [47,48]. With beta > 1, the measure puts more emphasis on sensitivity than precision. In our scenario, sensitivity (ie, detection rate) and precision (ie, prediction reliability) deliver their unique implications; therefore, we will evaluate both F-1 and F-2 scores. It will be useful to examine these 3 metrics to provide a well-rounded understanding of the model's performance.

Step (f) Qualitative Assessment of Prediction

The qualitative assessment of the model's performance will be a crucial counterpart to our quantitative analysis, ensuring the clinical validity and practical use of our predictions for developing an implementation plan. We will use a 3-phase modified Delphi method (3P-MDM) [49], guided by the Consolidated Framework for Implementation Research (CFIR). The CFIR systemically evaluates factors that can impact the success of implementation in complex settings like health care and is applicable to the early stages prior to implementation [50,51]. Key figures from UAB Medicine Quality and Patient Safety, including the Associate Chief Quality Officer, the Director of Quality Outcomes, and the Quality Outcomes Coordinator, will develop key questions for the initial focus group, which will set the overall direction of our 3P-MDM approach. Details of the 3P-MDM are as follows.

Phase 1 of 3P-MDM: Initial Focus Group for Qualitative Feedback

1. Semistructured assessment focus group: The focus group will involve a semistructured discussion session, engaging a panel of experts from the UAB Medicine Department of Care Transition, including the Vice President of Care Transitions, the Senior Director of Care Transition, and an RN case managers, all of whom have extensive experience in case management. Additionally, Family & Community Medicine and Internal Medicine clinicians from UABHS will offer clinical insights from their respective fields. The combined perspectives of these professionals (N=7) will be critical for a comprehensive review of the model's predictive outcomes, ensuring that the decision-support tool is statistically robust, clinically relevant, and operationally feasible within UABHS. The focus group session will be asked to elaborate on how to implement the model's predictions based on the five major domains of CFIR:
   - Intervention characteristics: How do you perceive the strength and quality of the predictive models? Are there specific features that particularly stand out or need improvement to better serve socioeconomically vulnerable groups? Outer setting: What patient needs and resources are being addressed by these models? How does it align with the external policies and incentives in our health care system? Inner setting: How do the models fit into the existing workflow and systems? What is the level of readiness for implementing these models? Characteristics of individuals: From your perspective, how do the models affect your decision-making in patient care? What are the potential barriers and facilitators to using these models? Process of implementation: What strategies would you suggest for the successful implementation of these models in our practice? How can we ensure ongoing adaptations and sustainability?
   - Identification of key findings: The discussion will generate rich qualitative data that will be analyzed through content analysis, involving transcription, systematic coding, thematic analysis, and comprehensive reporting. This analysis will highlight key themes and patterns that can offer deep insights into the facilitators and barriers to implementation of the prediction model [52].

Phase 2 of 3P-MDM: Structured Evaluation and Ranking

1. Scoring of statements: the derived themes from Phase 1 will be presented back to the 7 experts, who will then score them on a 5-point Likert scale (1 being "strongly disagree" and 5 "strongly agree." This scale is specifically designed to quantify the importance and applicability of each finding.
2. Ranking of statements: statements will be ranked based on their assigned scores.

Phase 3 of 3P-MDM: Expert Consensus and Prioritization

1. Consensus meeting: an expert panel, consisting of 3 experts from case management and 2 primary care physicians, will conduct an anonymous poll to reach a consensus on the most critical findings for model adjustment and implementation. The poll will focus on which ranked findings should be prioritized in further model adjustment and for implementation.
2. Top insights for model adjustment: the identified top statements, as agreed upon by the expert panel, will inform the refinement of the predictive model and guide the implementation process.

This process underscores our commitment to developing a decision-support tool that is not just empirically sound but also pragmatically grounded and clinically endorsed. The qualitative

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development of an implementation plan, encompassing both the priority rankings and the rich discussions and comments from the focus groups, will provide a comprehensive understanding of the model's context and importance.

Ethical Considerations

The University of Alabama at Birmingham Office of the Institutional Review Board for Human Use (UAB Office of IRB) has waived ethics approval. Also, the UAB Office of IRB has waived informed consent to participate. The UAB Office of IRB determined this project is not subject to the Food and Drug Administration's regulations and is not human participants research. All methods will be carried out in accordance with relevant guidelines and regulations.

Results

As of December 2023, we have collected data on 174,871 inpatient encounters that occurred from January 2018 to September 2023. These encounters involve 89,355 unique inpatients who have met the criteria in Textbox 1. For this patient population and their respective inpatient encounters, we have fully collected the data items in Figure 2, and data collection was completed as of December 2023.

Discussion

The anticipated findings of this study would include the predictive capability of the decision tree model, interactions among clinical factors and SDoH, and qualitative assessment results. Our protocol is unique in 3 main aspects. First, the PRADS model will leverage SDoH information to improve diabetes risk stratification. Second, our model results will be interpretable to ensure the users understand how the model reached a recommendation. Third, our model validation and assessment for developing an implementation plan will take a mixed-methods approach, which will be guided by performance metrics (quantitative) and the CFIR (qualitative). Therefore, our protocol will ensure that our findings are grounded in the complex reality of health care delivery, where both numerical data and human insights are equally important. We expect to have the model that is not only statistically sound but also resonates with the needs and constraints of health care providers, ultimately enhancing patient outcomes.

The study has potential limitations. First, its findings, based on one institution, may not be broadly generalizable. Future research could consider comparing different diabetes case management settings, despite challenges due to differences in EHR systems across health care organizations. Second, while our study will include user's perspectives for model validation, it would still not demonstrate the effectiveness of our approach on patient outcome. This can be done by performing cost-effectiveness analysis on a potential intervention strategy [53], driven by the prediction system or by conducting a pilot implementation of the system to perform prospective data collection and analysis on patient outcome. While analysis on effectiveness is not within the scope of this protocol, future research should address these questions for the successful implementation of the system.

For the development and implementation of the PRADS model within the health system, a comprehensive approach encompassing training, education, system integration, and continuous feedback is critical [54,55]. In our future research, we plan to initiate this with a combination of practical workshops, where case managers engage with a simulated PRADS environment, and theoretical lectures to clarify the model's computational aspects, especially the use of SDoH data in assessing patient risk. These sessions will allow case managers to voice concerns and discuss practical applications. Simultaneously, we will focus on integrating PRADS into the existing decision-support framework, evaluating its compatibility with current case management strategies, IT infrastructure, and anticipated cost-benefit ratios, for agile development to create a comprehensive system blueprint [56].

As long-term consideration, central to our initiative is the establishment of a robust feedback loop that allows case managers to report discrepancies and contribute insights, keeping the model dynamic and responsive. This will be complemented by thorough documentation, encompassing the model's design, data processing, and methods of feedback integration, with a strong focus on data sensitivity and patient confidentiality. Ethical considerations will guide our approach, ensuring PRADS augments clinical judgment, and we will develop strategies for enhanced patient engagement in their care planning. Additionally, the PRADS model's deployment may be implications on health policy, particularly in the context of reimbursement models and value-based care. Continuous research and validation will compare PRADS with traditional risk stratification methods, using longitudinal studies to assess its long-term impact on patient outcomes and health care use.

In summary, the development of the PRADS model will be more than a technological advancement in diabetes care; it can serve as a catalyst for a holistic and nuanced understanding of patient management and a systematic incorporation of human insights into the model development and implementation process. Our model development protocol and the long-term strategy offer a blueprint for enhancing chronic disease management. The modeling and analysis results from this research protocol will be submitted to a medical informatics journal and be discussed in national and international academic conferences. The initial results will serve as preliminary data for follow-up studies, including multi-institutional model development, cost-effectiveness analysis, and prospective data collection and analysis on patient outcome. The research team will pursue extramural funds to fulfill the team's goal of optimizing chronic disease management and health care resource use.

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Acknowledgments

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Data Availability

The data sets generated and analyzed during the current study are not publicly available because the deidentified electronic health record data are obtained from the UAB Enterprise Data Warehouse and intended to be used for internal purpose only. Data are, however, available from the authors upon reasonable request and with permission of the UAB health system. Dr Seung-Yup (Joshua) Lee and the UAB Enterprise Data Warehouse should be contacted if someone wants to request the data from this study.

Authors' Contributions

SL designed the overall study framework and analytical methods and was the primary writer of the manuscript. LH contributed to establishing the research framework, identifying the issue of staffing shortage in diabetes case management, and forming the interdisciplinary research team. BO contributed to the manuscript and designing the analytical methods. SH contributed to the manuscript and investigated the current case manager's workflow. AG provided knowledge and experience of how electronic health records system can support diabetes case management practice and contributed to the manuscript. HB provided clinical guidelines in ambulatory or inpatient case management and defined key variables influencing decision-making in case management. AL contributed to identifying meaningful social determinants of health for this study and contributed to the manuscript. ED contributed to identifying key clinical variables and provided the outpatient clinic's perspective on diabetes case management. AP contributed to forming the quality and patient safety team for the focus group and reviewed the manuscript. AF contributed to defining and providing clarity on care quality evaluation metrics and contributed to the manuscript. AA provided knowledge of system implementation for designing analysis approaches and significantly contributed to the IRB submission and revision process. MW contributed to identifying the variables in the UAB (University of Alabama at Birmingham) Enterprise Data Warehouse database and standardizing the data acquisition process for this project. AH contributed to designing the structured qualitative validation approach and contributed to the manuscript, particularly discussion on social determinants of health. JBH served as the senior author of this manuscript, supporting SL in preparing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

3P-MDM: three-phase modified Delphi method
ADI: Area Deprivation Index
CART: Classification and Regression Trees
CFIR: Consolidated Framework for Implementation Research

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ED: emergency department
EHR: electronic health record
HbA1c: hemoglobin A1c
IAI: interpretable artificial intelligence
ICD-10: International Statistical Classification of Diseases, Tenth Revision
PRADS: proactive risk assessment decision support
PRAPARE: Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences
RN: registered nurse
SDoH: social determinants of health
UAB: University of Alabama at Birmingham
UABHS: University of Alabama at Birmingham Health System

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Protocol

Design of a Health Education Program to Manage Chronic Neck Pain: Protocol for a Development Study

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Abstract

Background: Chronic neck pain (CNP) needs attention to its physical, cognitive, and social dimensions.

Objective: We aimed to design a health education program (HEP) with a biopsychosocial approach for patients with CNP.

Methods: A literature search on CNP, health education, and biopsychosocial models was carried out. Seven physiotherapists with expertise in HEPs and chronic pain participated in three teams that evaluated the literature and prepared a synthesis document in relation to the three target topics. Experts compiled the information obtained and prepared a proposal for an HEP with a biopsychosocial approach aimed at patients with CNP. This proposal was tested in the physiotherapy units of primary care health centers belonging to the East Assistance Directorate of Madrid, and suggestions were included in the final program.

Results: The HEP for CNP with a biopsychosocial approach consists of 5 educational sessions lasting between 90 and 120 minutes, carried out every other day. Cognitive, emotional, and physical dimensions were addressed in all sessions, with particular attention to the psychosocial factors associated with people who have CNP.

Conclusions: The proposed HEP with a biopsychosocial approach emphasizes emotional management, especially stress, without neglecting the importance of physical and recreational exercises for the individual's return to social activities. The objective of this program was to achieve a clinically relevant reduction in perceived pain intensity and functional disability as well as an improvement in quality of life in the short and medium term.

Trial Registration: ClinicalTrials.gov NCT02703506; https://clinicaltrials.gov/study/NCT02703506

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KEYWORDS

neck pain; chronic pain; physiotherapy; health education; emotional expression; biopsychosocial model

Introduction

Neck pain is a frequent reason for medical consultation in primary care [1] and is often a reason for referral to physiotherapy units due to chronic pain [1,2]. It is associated with disability and work absenteeism; it has a 10.4%-21.3% prevalence in the general population. It is more common in women than in men [2,3]. The experience of pain is a significant burden, leading to a deterioration in quality of life that affects both physical and emotional well-being and has an impact on the person's work, social, and family environments. This results in a high cost for national health systems due to the increased use of health resources, along with important psychological repercussions for those affected, including the risk of associated pathologies, such as anxiety, depression, and sleep disorders. In general, these people report a negative impact on their social relationships: 22% lose their jobs, 4% change jobs, and 27%

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feel socially isolated and little understood by those around them regarding their condition. Despite the economic impact of the diagnosis and management of these processes, 48% of the individuals are dissatisfied with the long waiting times for treatment, 29% are dissatisfied with the type of treatment received, and a high percentage of health professionals would like to receive additional training to deal with these processes [2,4-6].

Neck pain represents the fourth cause of work incapacity. This musculoskeletal issue is second only to low back pain, with a prevalence of 10% in the population. Treatment techniques and modalities focus on reducing symptomatology through passive or pharmacological interventions [7]. The criteria for approaching these processes by physiotherapists vary according to their training and professional experience. Pain, generally considered as a symptom, is approached with mechanistic methods that tend to produce poor adherence to treatment and often unsatisfactory therapeutic results [8-10]. The National Institute for Health and Care Excellence does not recommend the use of drugs for the treatment of chronic pain, as they have not demonstrated medium- and long-term benefits [11]. It is necessary to seek new approaches based on scientific studies for the treatment of these processes, which guarantee their effectiveness and allow us to know the cost of treatment and the health benefits provided [10,12-17].

Scientific evidence points to the multifactorial nature of chronic pain and the need for educational-therapeutic strategies based on the biopsychosocial model [14,17-19]. The most recent studies show that psychosocial factors influence, favor, and increase the symptomatology and perpetuation of pain. Therefore, it is necessary to understand and manage these factors to provide comprehensive care for people with chronic pain [18,20-23]. Given the importance of physiotherapy in primary care in health promotion and prevention, it is essential to design and develop a strategy for the management of chronic pain. Advances in this field suggest an interdisciplinary intervention, although this is not always possible [24]. Therefore, a physiotherapy program is proposed, based on evidence to facilitate educational-therapeutic interventions [25]. Health education programs (HEPs) provide a valuable tool for physiotherapists to address these processes [26-28]. An HEP should integrate physical techniques that have been shown to be effective, such as therapeutic and recreational exercise; cognitive restructuring techniques; and training in the management of attention, maintained stress, and associated emotions [25-34].

The aim of this work is to design and develop an HEP that considers not only physical, cognitive, and behavioral factors but also other variables that have not been sufficiently taken into account so far, such as emotional factors, values, and beliefs of individuals with chronic neck pain (CNP).

Methods

Study Design

In the first phase, 6 primary care physiotherapists with more than 15 years of experience and an expert professor from the University of Alcala were divided into three groups and carried out an exhaustive bibliographic search. This search focused on 3 target topics: CNP, health education, and biopsychosocial model and emotional expression. The search followed a protocol based on the standards of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [35,36].

The inclusion criteria for the articles were as follows: (1) content focused on at least one of the three target topics; (2) published in the last 10 years; and (3) written in English or Spanish. All papers with their main topic not focused on any of the target topics were excluded.

Search Strategy

The search was carried out in the Medline databases through the PubMed platform, Cochrane Library, and Physiotherapy Evidence Database (PEDro). The following descriptors included in the Thesaurus were used: “Chronic neck pain,” “Biopsychosocial model,” “Emotional expression,” “Health education,” and “Physiotherapy” using AND/OR as Boolean operators. Studies relevant to the elaboration of the HEP were evaluated. Titles and abstracts were reviewed and a total of 81 articles were selected, of which 64 were excluded because they did not meet the preestablished inclusion criteria, and finally, 23 articles that followed the PRISMA standards were analyzed [12,19,22,24,26,29-31,37-51]. Based on these studies, the educational-therapeutic program was designed.

Data Analysis

In the second phase, the selected papers were analyzed by 3 expert physiotherapists and 3 professors. Afterward, 3 meetings were held to reach a consensus and select the information collected after testing its methodological quality and to propose an HEP for people with CNP.

The working procedure followed to develop this proposal adhered to the guidelines in the document “Basic methodological recommendations for developing an educational project,” as recommended by the Provincial Directorate of Madrid, which follows the methodology of the Commission for the Validation of Educational Projects of the Community of Madrid for the design of HEPs [35,36].

Once the proposal was developed, it was tested in 3 physiotherapy units. The suggestions for improvement that emerged from 16 patients and 2 physiotherapists were incorporated into the final document, which was evaluated and validated by the Comisión de Validación de Proyectos Educativos de la Comunidad de Madrid (COVAM—Validation Commission of Educational Projects of the Community of Madrid) and is available to all professionals in the library of the community of Madrid [37]. Once the program was developed, a research project was designed to measure its effectiveness.

Ethical Considerations

This project was approved by both the Clinical Research Ethics Committee of the Hospital Universitario Príncipe de Asturias and the Central Research Commission of Primary Care in Alcalá de Henares (Madrid) (approval number: OE 22/2015). This

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project was registered in the ClinicalTrials.gov registry (NCT0270350). The beneficiary population of the program included the following: individuals >18 years of age, diagnosed with CNP by their family physician, with physical and psychic capacity to enter the study, and having signed the informed consent. Our goal for the future is to assess the effectiveness of the HEP.

Results

Following the review of the literature and the consensus of the experts, the program was designed with the following general and specific objectives:

General Objectives of the Program

- Health: to improve the health of people with CNP and contribute to the improvement of the quality of life of these individuals.
- Educational: to enable people with CNP to understand the factors that modulate the perception of pain and to teach them methods and techniques to help them manage CNP.

Specific Objectives of the Program

- Cognitive: to know the basis of the neurophysiology of pain, to reconceptualize pain and its origin, to identify the factors that exacerbate pain, to analyze the affective factors that influence pain, to express emotions and feelings identified about pain, and to verbalize the characteristics of pain.
- Emotional: to identify emotions and express them, to share perceived positive and negative experiences, and to become aware of lifestyle changes needed due to having CNP.
- Skills: to perform techniques for managing attention to the body, thoughts, feelings, and emotions, allowing for a release of feelings that can improve health; and to develop skills and learn therapeutic exercises as well as relaxation and visualization techniques.

The HEP consisted of 5 group educational sessions of about 90-120 minutes divided into 2 weekly sessions on alternate days, allowing participants time to perform the tasks at home and be able to integrate them. Each session included an “observer’s guide” designed to collect feedback on areas of improvement. Each session addressed the physical, cognitive, and emotional dimensions of the participant and included the observer’s guidance. Follow-up assessments were conducted 3 and 6 months after the intervention [25].

The number of participants was limited to a maximum of 10. The HEP encompassed cognitive restructuring, therapeutic exercise, attention management, and emotion management. This HEP approach integrated physical techniques that were shown to be effective, such as therapeutic exercise and movement-based play activities. It also included cognitive restructuring techniques, attention management training, and strategies to manage stress and associated emotions through playful movement-based activities [25-34]. The program structure can be seen in Table 1.

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Table 1. Health education program (sessions, objectives, techniques, and duration).

Sessions (duration) and objectives	Techniques
Session 1 (120 minutes)	
• Presenting the program • Expressing the patient´s experience of pain • Understanding the factors involved in the perpetuation of pain	• Talk-colloquium • Brainstorming • Talk-colloquium
• Becoming aware of and connecting with the body	• Visualization technique
• Develop skills for cervical stretching practice	• Motor imagery techniques demonstration with training
• Reinforce knowledge, attitudes, and skills learned through work at home	• Task diary
Session 2 (90 minutes)	
• Clarify doubts and reinforce learning from the first session.	• Group discussion
• To understand the importance of dialogue with the body and its physical attitude	• Training
• To manage stress, thoughts, and emotions that influence the perpetuation of pain	• Demonstration with training (breathing and movement) • Relaxation and meditation
• Identify the importance of exercise • Initiate gradual exposure to exercise through play and recreational activities	• Talk-colloquium • Demonstration with training
• Reinforce knowledge, attitudes and skills learned through work at home	• Task diary
Session 3 (100 minutes)	
• Express and clarify doubts	• Talk-colloquium
• Acquire skills to identify thoughts, beliefs, and emotions associated with the perception of pain	• Belief restructuring
• Reinforce learned stretches and exercises • Playful activities through movement	• Demonstration with training • Motor imagery techniques (if required)
• Train positive self-communication at home	• Mirror technique
Session 4 (90 minutes)	
• Clarify doubts and express experiences	• Talk-colloquium
• To develop the ability to manage thoughts and emotions involved in physical pain	• Belief restructuring • Creative resolution technique • Anchors
• Reinforce the stress management techniques and the performance of exercises at home.	• Task diary
Session 5 (120 minutes)	
• Review and reinforce the tasks for the home and clarify doubts.	• Talk-colloquium
• Reinforce the ability to manage the emotional burden of the process being experienced	• Relaxation techniques
• Develop the ability to live in health	• Visualization technique
• Reinforce exercise skills • Playful activities through movement	• Training
• To reinforce the performance of exercises in the home	• Task diary

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Sessions (duration) and objectives	Techniques
• Express doubts and ideas about what have been learned	• Talk-colloquium
• Evaluate the intervention	• Questionnaires

Session 1

Session 1 was developed in a "large group" format with a maximum of 10 participants. It began with a brief presentation explaining the program, including its objectives and structure. The session aimed to help participants understand the causes of their pain, increase their awareness and connection with their bodies, and develop skills for practicing cervical stretching.

Learning was focused on acquiring skills to de-emotionalize the pain process (fear of movement and catastrophizing). Techniques were used to help the connection with the body and develop skills for practicing stretching and cervical exercises. Initially, motor imagery techniques were used until stretching could be initiated with real movements.

Finally, the participant was asked to practice and write down the tasks learned and review these tasks at home, and the program materials were handed out.

Session 2

Session 2 began with the clarification of doubts and reinforcement of the learning from session 1, with an emphasis on the importance of dialogue with one's own body. We worked on the ability to manage stress, thoughts, and emotions, teaching participants to consciously change their responses through body awareness and movement. It also highlighted the importance of gradual exposure to physical exercise and learning how to stretch and do basic cervical spine exercises. Playful aerobic activities were to promote social participation and attention management. It was explained how to do the exercises collected in the task diary at home.

Session 3

We began by dedicating a few minutes at the beginning of the session to clarify doubts about what was covered in previous sessions. This session delved into the identification of emotional impacts as possible causes of the perpetuation of neck pain, with special emphasis on social pain and interpersonal relationships.

It was also recommended that the participant took note of the moment when the pain appeared, the emotional situation prior to the onset, and the context surrounding the participant to analyze and explore the emotion-situation-pain relationship.

The session included a review and reinforcement of the stretching and cervical exercises learned in previous sessions, along with playful activities through body movement. For home practice, participants were instructed to continue with the same exercises as in session 2. Additionally, an exercise focused on training positive self-communication was introduced in this session.

Session 4

As in previous sessions, participants were invited to express their doubts and experiences about their neck pain.

Practices were done to acquire skills to learn to manage limiting thoughts and beliefs and include strategies to change them. The techniques learned to manage stress were reinforced, and playful activities were carried out through body movement and therapeutic exercise.

Practicing the techniques used to manage stress as well as stretching and cervical exercises were requested to be done at home.

Session 5

As in previous sessions, participants were invited to express their doubts and experiences about their neck pain.

The learning focused on the acquisition of skills to reduce the emotional burden of pain and improve health and well-being. Additionally, we reviewed and reinforced exercises to be performed daily at home, and the dates of their execution were noted down until the review or follow-up performed at 3 and 6 months, respectively, from the end of the HEP.

To ensure adherence to the HEP, participants were informed that a phone call would be made during the first 3-month follow-up and another one would be made during the second follow-up to clarify any doubts and encourage them to continue performing the tasks.

Discussion

The role of the physiotherapist includes facing important challenges due to new strategies that have emerged in response to the health needs of people. The HEP programs are a fundamental tool in primary care, to be used by these professionals who play a very important role in influencing and promoting behavior change related to the lifestyles of people with chronic pain. Their activities should not only provide assistance but also promote health and prevent issues. The primary areas of application are musculoskeletal (69%) and therapeutic physical activity (20.6%) [28,46].

Scientific literature includes interventions for chronic pain that use pain education as a tool by explaining the neurophysiology of pain. These interventions usually yield positive results in the short and medium term, reducing pain intensity and functional disability while improving the quality of life for individuals with chronic pain, compared to conventional physiotherapy interventions [48,52-55].

Other studies have shown that this type of educational strategy can also have a positive short- and medium-term effect on catastrophizing and physical performance [31,48-50,53]. In light of the current literature available, education in pain

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neurophysiology is considered a necessary but not sufficient pillar of an effective approach. For this reason, interventions have been developed that combine education in pain neurophysiology with therapeutic exercise and other forms of care.

Current scientific evidence points to the effectiveness of combining pain education with physiotherapy interventions based on therapeutic exercise in the short and medium term. This approach has been shown to improve functional disability and reduce fear avoidance [43,53,55-58].

Literature suggests that individuals should be considered as biopsychosocial beings; their beliefs; cognitive, emotional, and behavioral factors; as well as their social context play crucial roles in the manifestation, development, and perpetuation of pain [20,23,59]. Therefore, psychosocial factors must be taken into account in actively addressing these processes.

There are several studies that demonstrate the importance of considering these factors and the awareness of the individual's thoughts, feelings, and emotions in the face of pain to reduce symptomatology [12,20,23,26,28,46,48,50,53,57,59].

However, although physical therapists can often recognize the influence of these factors, few have developed the skills to successfully assess and manage them. It is essential that physical therapists acquire the knowledge, attitudes, and skills necessary to be able to perform an active and structured approach to physical therapy, focused on the person with chronic pain, and to be able to use scientifically based tools and techniques.

Some programs evaluate the effect of cognitive-behavioral therapy in the improvement of pain, disability, and quality of life of individuals with CNP. Changes were observed without clinical relevance in the long term. This might be due to the fact that although these psychosocial factors are mentioned, they are not specifically addressed in the interventions. Additionally, these interventions often do not take into account the impact of social pain on the perception of physical pain even though both types of pain activate common pathways and brain centers. Social pain, resulting from feelings of social exclusion or rejection in interpersonal conflicts, affects people's daily lives in general and can intensify the perception of pain in individuals with chronic pain [21]. If social pain is not taken into account and addressed in interventions, achieving clinically relevant results becomes more challenging. Furthermore, there is often a lack of direct approaches to sustained stress or the individual's internal emotional disturbances [38,60-64].

Patients with chronic pain are known to be subjected to high stress levels. The nervous system's response to stress interferes with perceived pain [6]. Therefore, individuals with chronic pain must learn to manage stress. The lack of inclusion of tools to address this may partly explain the absence of clinically relevant results in the management of chronic pain. Other interdisciplinary programs show the importance of approaching patient education from a biopsychosocial point of view. Moreover, in all of these programs, the active participation of the patient is considered essential [10,14,25,26,56]. To achieve the objectives, it is necessary for the individuals to take control of their process and become involved in its resolution with the appropriate support of health professionals.

Therefore, an HEP has been proposed that presents strategies with scientific evidence to address psychosocial factors [26,38,45,65-67], such as breathing and relaxation techniques, motor imagination, as well as play and recreational activities through body movement. This program also considers physical factors and promotes the return to normal activity and social participation for individuals with chronic pain, the importance of which is shown by systematic reviews that provide evidence of the benefits of exercise for CNP [39,68-70]. The fact that the program is conducted in small groups also allows the participants to get to know each other, share experiences, and establish social bonds and support. These interactions, both within and outside the program, can facilitate social participation and aid in their reincorporation into social life.

Regarding the number of program sessions and their duration, the literature consulted includes programs ranging from 1 or 2 sessions to some with 11 or more sessions. As for the duration of the sessions, the proposals range from 30 minutes to 4 hours [33,51,71].

Due to this variety in program structures and based on different guides for the elaboration of educational projects, along with the authors' extensive experience in the field of primary care, the educational proposal of this program is for 5 sessions of 2 hours each—a medium term among all those consulted [72-74]. This duration is considered sufficient to work on both physical and psychosocial factors, without delaying the process excessively, to achieve good adherence and minimize participant dropout. However, as future lines of action, we are considering increasing the number of sessions and their duration to allow for more gradual and in-depth interventions, both in addressing psychosocial factors and incorporating therapeutic exercises of greater intensity and strength, as indicated by current research in this field.

The review, revision, and possibility to raise doubts in each session help secure knowledge, reinforce new attitudes, support the changes that are taking place, and minimize possible and unlikely adverse effects. This approach has proven to be an effective and safe intervention.

We are working on extending the number of sessions and their duration with the aim of focusing deeply on psychosocial factors and incorporating more intense and strength-based therapeutic exercises, as indicated by current research in this field.

Currently, the approach to chronic pain, and in particular CNP, requires attention to the associated biological and psychosocial factors. The HEP program, with a biopsychosocial approach, emphasizes understanding one's own processes and questioning beliefs about pain through pain education, alongside managing emotions and stress through body movement. In addition, HEP emphasizes the use of therapeutic and recreational exercises for restoring function and promoting social participation in individuals with CNP, both in the medium and long term in individuals with CNP. More scientific research should be devoted to studies with methodologies that effectively define practical methods for individuals to learn how to manage their

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feelings and emotions as well as identify interventions that account for these factors. In the meantime, all health care professionals should be aware that “invisible psychological factors” play a role in chronic pain processes. These factors influence how individuals perceive and experience their pain and how they respond and behave to this condition, which affects the person as a whole.

Authors' Contributions

MPM and DPM conceptualized the study; GLP was in charge of the methodology; YPM did the investigation; IRC wrote the manuscript, reviewed, and edited it; TGI supervised the study. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CNP: chronic neck pain
COVAM: Comisión de Validación de Proyectos Educativos de la Comunidad de Madrid
HEP: health education program
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Establishing the Foundations of Emotional Intelligence in Care Companion Robots to Mitigate Agitation Among High-Risk Patients With Dementia: Protocol for an Empathetic Patient-Robot Interaction Study

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Abstract

Background: An estimated 6.7 million persons are living with dementia in the United States, a number expected to double by 2060. Persons experiencing moderate to severe dementia are 4 to 5 times more likely to fall than those without dementia, due to agitation and unsteady gait. Socially assistive robots fail to address the changing emotional states associated with agitation, and it is unclear how emotional states change, how they impact agitation and gait over time, and how social robots can best respond by showing empathy.

Objective: This study aims to design and validate a foundational model of emotional intelligence for empathetic patient-robot interaction that mitigates agitation among those at the highest risk: persons experiencing moderate to severe dementia.

Methods: A design science approach will be adopted to (1) collect and store granular, personal, and chronological data using Personicle (an open-source software platform developed to automatically collect data from phones and other devices), incorporating real-time visual, audio, and physiological sensing technologies in a simulation laboratory and at board and care facilities; (2) develop statistical models to understand and forecast the emotional state, agitation level, and gait pattern of persons experiencing moderate to severe dementia in real time using machine learning and artificial intelligence and Personicle; (3) design and test an empathy-focused conversation model, focused on storytelling; and (4) test and evaluate this model for a care companion robot (CCR) in the community.

Results: The study was funded in October 2023. For aim 1, architecture development for Personicle data collection began with a search for existing open-source data in January 2024. A community advisory board was formed and met in December 2023 to

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provide feedback on the use of CCRs and provide personal stories. Full institutional review board approval was received in March 2024 to place cameras and CCRs at the sites. In March 2024, atomic marker development was begun. For aim 2, after a review of open-source data on patients with dementia, the development of an emotional classifier was begun. Data labeling was started in April 2024 and completed in June 2024 with ongoing validation. Moreover, the team established a baseline multimodal model trained and validated on healthy-person data sets, using transformer architecture in a semisupervised manner, and later retrained on the labeled data set of patients experiencing moderate to severe dementia. In April 2024, empathy alignment of large language models was initiated using prompt engineering and reinforcement learning.

Conclusions: This innovative caregiving approach is designed to recognize the signs of agitation and, upon recognition, intervene with empathetic verbal communication. This proposal has the potential to have a significant impact on an emerging field of computational dementia science by reducing unnecessary agitation and falls of persons experiencing moderate to severe dementia, while reducing caregiver burden.

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KEYWORDS

persons with dementia; empathy-based care companion robot; agitation; fall risk; artificial intelligence; AI

Introduction

The Impact of Dementia Among Older Adults

The prevalence of Alzheimer disease and related dementias (hereinafter "dementia") has been increasing among older adults. In the United States, an estimated 6.7 million currently have dementia, and this number is expected to increase to 13.8 million by 2060 [1]. The majority of persons living with dementia experience neuropsychiatric symptoms of dementia [2] that are noncognitive, such as agitation, defined as inappropriate verbal, vocal, or motor activity [3]. Agitation is problematic because it can not only impact a person's morbidity and mortality but also impair motor functions during events of agitation and increase the risk of falling and sustaining severe injuries and subsequent hospitalization [4,5]. Falls are a major cause of morbidity and mortality among older adults. Indeed, persons experiencing moderate to severe dementia are 4 to 5 times more likely to fall than older people without cognitive impairments [4,6,7]. Despite close observation and monitoring by caregivers, the onset of agitation is often unpredictable [8]. In fact, research has shown that agitation in persons with dementia in long-term care settings is associated with higher medication use and an increased likelihood of experiencing falls, fractures, infections, and other neuropsychiatric symptoms compared to older adults without agitation (odds ratio 1.58 for falls, 95% CI 1.41-1.77; $P<.001$); thus, it is important to develop an approach to effective management of agitation symptoms in this population to prevent falls [5].

The Impact of Dementia on Caregivers

While much of the literature focuses on the fact that caring for persons experiencing moderate to severe dementia creates a heavy burden on caregivers, leading to caregiver burnout [9], only a few papers have highlighted ways in which caregivers of persons experiencing moderate to severe dementia can bring joy and happiness to their loved ones [10,11]. Furthermore, evidence has demonstrated that persons experiencing moderate to severe dementia can continue to express joy for minutes beyond remembering an event that was joyful [12]. However, more typically, the literature documents how informal caregivers (eg, spouses or adult children) for persons experiencing moderate to severe dementia experience chronic stress, depression, sleep disorders, poor health, low quality of life, and early mortality [13]. Family caregivers who live together with persons experiencing moderate to severe dementia show severe sleep disturbance compared to caregivers of persons with other health conditions, such as stroke or cancer [14]. Moreover, family caregivers of persons with dementia are twice as likely to experience depression as caregivers of persons without dementia [13,15]. Early mortality among spousal caregivers of persons with dementia is also not uncommon [16].

As a result, persons experiencing moderate to severe dementia are often removed from their homes due to worsening dementia and the heavy burden on caregivers [13,17]. Furthermore, despite evidence that person-centered intervention strategies may improve a person's state [18], such strategies are not widely adopted, and the factors impacting the success of such interventions are not fully understood [9,19]. Anecdotes and personal experiences shared by caregivers as well as recent literature suggest that the success of person-centered care may depend upon a caregiver's ability to relate to the patient and show empathy or the ability to imagine what they may be feeling or thinking [20]. However, the successful implementation of such care requires intense training, particularly when abusive behavior is present [9,19].

The Current Status of the Use of Socially Assistive Robots as a Health Care Approach

Socially assistive robots are innovative solutions to deliver quality care for patients with dementia and to reduce agitation via verbal and nonverbal communication [21-23]. Social robots are typically equipped with onboard sensing technologies, including cameras and motion sensors, to sense the patient's state and can support verbal and nonverbal communication with the person. Some robots come in the shape of an animal (ie, a dog) and have been shown to help persons with dementia build social relationships [22]. However, human-like robots (humanoids) that can demonstrate social patient-robot relationships can also have therapeutic effects, as measured in positive emotional responses [24]. Such social relationships are

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established through the presence of the social robot and sensorimotor interaction with the robot using haptics and vision (eg, touching and seeing the robot) and through the use of sound (eg, laughter). Currently, it is not clear whether and how robots might lower the risk of agitation through verbal communication. Furthermore, existing work on social robots fails to address 1 important issue: that agitation is associated with dynamically changing emotional disturbances [3].

Moreover, there is not sufficient research on how to design a care companion robot (CCR) that is equipped with such a conversational and empathetic intelligence that combines sound in the form of speech features with language-based interaction. Currently, there is a lack of understanding in how to best design emotionally aware robots that use empathetic conversations to trigger positive emotional change. Thus, research is needed that integrates both streams of research to close the gap on how emotional intelligence and empathetic conversations with caregiving robots can have therapeutic effects.

The specific research gaps we identified include three points: (1) The forms and the time-variant nature of emotions expressed by persons experiencing moderate to severe dementia are not sufficiently understood. (2) Existing technical solutions for emotion detection using data-driven machine learning (ML) algorithms, trained and fine-tuned on large amounts of data collected from healthy individuals and labeled, have not been sufficiently evaluated in the context of dementia, given the scarcity of emotional state data for patients experiencing moderate to severe dementia. While there is an active research community focused on detecting dementia based on language, speech signals, facial expression, and body movements, emotion detection for patients with dementia is not well studied. (3) Existing social robots lack the emotional intelligence to respond to person-specific emotional states through empathetic language-based communication, such as displaying understanding of a person's feelings and emotions through words and speech features (eg, using a warm tone). Existing conversational robots use standard implementations of large language models (LLMs) without considering the challenges of fine-tuning such language models for greater empathy. Research on empathy alignment in general, and in the particular context of health care and dementia care, is scarce and requires significant exploration. The few available efforts to align LLMs either use simple prompt engineering or rely on data sets from social media platforms that have been labeled without a deep consideration of the language-specific properties of empathy [25-27]; (4) finally, beyond the technical research gaps related to ML and artificial intelligence (AI) and LLMs, the correlation relationship between different forms of emotions with motor impairments expressed in agitation and subsequent falls is unclear. While new research papers continue to be published on the impact of socially assistive robots on persons experiencing moderate to severe dementia [24], the research is still in a nascent stage. We believe that our study will provide significant contributions by building on recent research and addressing the aforementioned points. Table 1 articulates a lack of emotional intelligence and empathy-based conversations by existing robots versus our proposed CCR, which overcomes these limitations.

Table 1. Comparison of existing social robots' limitations with the proposed care companion robot (CCR) improvements in emotional intelligence and empathy-based conversations.

Example	Limitations of existing social robot capabilities	Future capabilities of our social robot: the CCR
Paul, an 82-year-old resident with moderate to severe dementia, wakes up most mornings, forgetting how to use his walker as he gets out of bed.	He gets upset and angry trying to get out of bed. His social robot in the room, noticing a movement, approaches and starts talking using a standard dialogue flow with a normal voice pitch: "Hello Paul, how can I help you?" This makes Paul even more upset, worsening his emotional state. He becomes very angry and agitated, but the robot keeps asking: "How can I help you?" Paul's agitation escalates. He shouts at the robot: "You can't help me, stupid robot. I do not need your help." Paul tries to get up without the walker and almost falls. Luckily, the caregiver observing Paul comes into the room and prevents the fall by calming him down using soft language and talks about exciting events in Paul's past, about which he still has strong memories.	His CCR in the room senses a potential emotional shift ahead of time as Paul's facial expression, body movement, and utterances indicate that he is becoming angry. When Paul starts trying to get out of bed, the CCR starts talking to Paul using soft language: "Good morning, Paul! Shall we go to breakfast?" At this point, the CCR pauses to ensure that the comment was understood and then continues the conversation: "Let's use our walker this morning." The CCR now shows an image of the walker which is close by, before speaking again: "But before we go, let us talk about your colleague at Boeing that you worked with." Paul's response: "You mean Alfred? He was such a great guy." Paul continues his personal story, and the CCR responds, adding facts that Paul has forgotten. In the meantime, the caregiver, who had been informed about a potential onset of agitation, moves the walker closer to Paul so that he can get out of bed safely. Paul gets up. While walking to the breakfast room, the CCR and Paul are talking about Alfred. Paul has a happy start to his day.

The Proposed CCR

A CCR is an advanced technological solution designed to provide assistance, support, and companionship for older adults, while addressing specific challenges associated with aging and cognitive decline. Equipped with autonomous indoor navigation, human-safe movement capabilities, and robust open robotics framework middleware (Open Source Robotics Foundation, Inc), the robot seamlessly navigates indoor environments while ensuring safety and reliability. Its multimodal interaction capabilities enable intuitive communication with users through speech, touch, and physical gestures using head and neck

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movement, facilitated by an Android tablet interface. With a suite of environment-monitoring sensors and customization options, the robot can be used to detect anomalies and adapt to various use cases, including the early detection of behavior changes indicative of conditions such as dementia. Powered by an onboard NVIDIA Jetson Orin device, it processes sensor data and executes tasks with high performance and efficiency, making it a valuable companion and caregiver support tool for older adults.

While the theoretical mechanism for storytelling in soothing agitation is yet to be articulated, Rios Rincon et al [28] reported that storytelling has helped to support memory, reminiscence, identity, and self-confidence—potential mechanisms under which storytelling may reduce agitation. Furthermore, other authors found that quality of life, depression, and the quality of the carer-patient relationship improved after the intervention with storytelling [29], perhaps because storytelling helps to build therapeutic relationships, bonds, rapport, comfort, and trust between older adults and caregivers [30], possibly leading to reduced agitation and fall risk. By providing mental stimulation, such as by storytelling, cognitive functions (eg, attention, executive function, and memory) may be improved and agitation, depression, and anxiety may be reduced [31,32].

Objectives

This study describes the design and implementation of computational patient-robot interaction research designed to predict agitation and mitigate fall risk and tests the strategies in both a simulation laboratory with up to 50 undergraduate and graduate students and 12 persons experiencing moderate to severe dementia, who are residents of board and care facilities. The study aims to (1) collect and store new data sets used to train a CCR; (2) design new computational models focused on persons experiencing moderate to severe dementia; (3) develop new systems of empathy-based conversational models, using LLMs and theories of linguistics; and (4) pilot an empathy-focused intervention model for the CCR using a quasi-experimental intervention design and evaluate the conversational intervention longitudinally using mixed methods approaches.

Methods

Study Design

The proposed 2-year study builds on the expertise of a multidisciplinary research team (ie, nursing, computer sciences, ML, AI, engineering, linguistics, and medicine). We will use computational ML and AI methods to first collect noninvasive data and develop models that can forecast a person's emotional state, agitation level, and gait pattern in real time, using ML and AI and Personicle, a person-centric temporal activity or states database developed at the University of California Irvine (UCI) Institute for Future Health, and then test and evaluate the empathy-focused conversation model for the CCR in the community, using quasi-experimental and mixed methods approaches (Figure 1). We will use dynamic event analysis of conversations between the empathy-focused CCR and persons experiencing moderate to severe dementia to examine the impact of conversational events during a heightened emotional state on agitation level and gait pattern.

Figure 1. The design components of an empathy-focused conversation model to train a care companion robot (CCR) to assess the impact of conversational events on patients with moderate to severe dementia agitation.

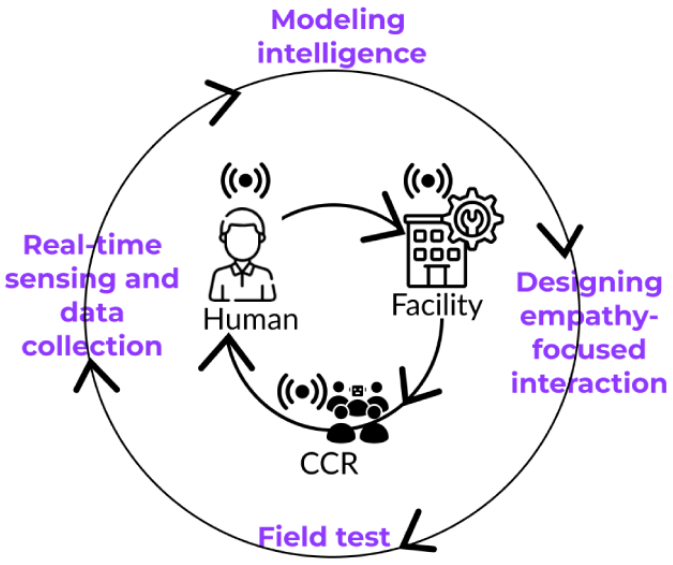

The aims of the study are as follows:

- Aim 1: collect and store granular Personicle data, using real-time visual, audio, and physiological sensing technologies in a simulation laboratory and at board and care facilities
- Aim 2: develop statistical models to understand and forecast the emotional state, agitation level, and gait pattern of a person experiencing moderate to severe dementia in real time using ML and AI and Personicle
- Aim 3: design and test an empathy-focused conversation model focused on storytelling
- Aim 4: test and evaluate the empathy-focused conversation model for the CCR in the community

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Before the onset of the study, a community advisory board (CAB) will be formed to ensure that community feedback will be integrated into the logistics of the study, ensuring privacy and safety, as well as the relevance of the empathy-focused conversational models delivered by the CCR. The team will meet 3 times in the first year of the study. The CAB is designed to help guide CCR observation and modeling and, over the 2-year study, provide ongoing evaluative feedback on usability and acceptability collected from family and professional caregivers. All members of the CAB will be compensated for their time.

Recruitment

Our study is being conducted at 4 board and care facilities in southern California, owned and operated by a certified family nurse practitioner. Each of the 4 facilities is licensed by the department of social services. Each board and care facility has an occupancy of 6 residents, who are cared for by a multidisciplinary team composed of nurse practitioners and medical assistants, with periodic visits by a physician and a music and exercise therapist. The residents are typically aged ≥65 years, and the majority typically experience moderate to severe Alzheimer disease; >50% also experience comorbidities, including hypertension and congestive heart failure, or have experienced a cerebrovascular accident. These conditions require 24-hour supervision and assistance due to safety concerns. The research staff work closely with the owner, who will ensure that all eligible residents (or their surrogates) receive a flyer about the study.

Sample and Setting for Human Participant Engagement for Specific Aims 1, 3, and 4

For aim 1 (observation of persons experiencing moderate to severe dementia and interviews with family and professional caregivers), aim 3 (simulation laboratory role-plays with undergraduate and graduate students), and aim 4 (testing and evaluation of the impact of CCR modeling), relevant details are provided in the following subsections.

Aim 1: Persons Experiencing Moderate to Severe Dementia

The sample will include persons experiencing moderate to severe dementia residing at 4 board and care facilities in southern California, where a total of up to 24 patients reside, with turnover approximately every 6 months; approximately 25% (6/24) stay for 2 to 5 years. Current demographics reveal an equal distribution of male and female residents, who are predominantly White. The mean age is 88.3 (SD 5.72) years, and at least 1 family caregiver is involved. Of the 19 residents, 16% (3/19) have mild dementia, 58% (11/19) moderate dementia, and 37% (7/19) severe dementia. Particularly with residents who experience agitation, the risk of falls is a reality that is very concerning. We estimate, at a minimum, that 32% (6/19) residents will meet the eligibility criteria and remain at the facility throughout the 2-year study, with new patients admitted every month.

The inclusion criteria are as follows: (1) admitted by a physician as a person experiencing moderate to severe dementia, (2) residing at 1 of the 4 board and care facilities, (3) aged ≥40 years, and (4) consent provided by a legally authorized representative. The exclusion criterion is as follows: severe medical conditions that would limit participation in the study, including terminal illness.

Aim 1 and Aim 4: Family Caregivers

The sample will include up to 14 family caregivers of persons experiencing moderate to severe dementia who will be asked about their interest in participating in informal interviews to discuss any experiences in dealing with agitation and the fall risk of their family member and the joyful times their family member experienced (aim 1). For aim 4, up to 6 family caregivers whose family member with dementia is enrolled in the 3-month intervention and who provide consent will be administered 2 structured instruments at baseline and 3-month follow-up. They will also participate in a formal interview about how the CCR functioned in mitigating agitation and fall risk. The inclusion criteria are as follows: aged ≥18 years, English speaking, and self-reported family member of the person experiencing moderate to severe dementia.

Aim 1 and Aim 4: Professional Caregivers

The sample will include up to 5 professional caregivers of persons experiencing moderate to severe dementia who work at the board and care facility and who will be asked about their interest in participating in informal interviews to discuss any experiences in dealing with agitation and the fall risk of the person experiencing moderate to severe dementia they care for at the board and care facility. They will also be asked to share experiences of what makes the person experiencing moderate to severe dementia joyful versus sad (aim 1). For aim 4, up to 5 professional caregivers who care for the persons experiencing moderate to severe dementia enrolled in the 3-month intervention and provide consent will be administered 2 structured instruments at baseline and 3-month follow-up. They will also participate in a formal interview about how the CCR functioned in mitigating agitation and fall risk. The inclusion criteria are as follows aged ≥18 years, English speaking, and working at the board and care facility.

Aim 3: Undergraduate and Graduate Student Volunteers

For aim 3, approximately 50 student volunteers will be consented to spend approximately 1 hour in the simulation laboratory and will be trained by our investigative team to role-play a person with dementia who is experiencing emotions such as agitation. To capture authentic emotions, students may also be provoked to display emotions as well. The inclusion criteria are as follows: aged ≥18 years, enrolled undergraduate or graduate student at UCI, and English speaking.

Ethical Considerations

Institutional Review Board Approval

Two institutional review board (IRB) requests have been submitted to the University of California Irvine (UCI) institutional review board. The first IRB request (non–human subject research), approved in December 2023 (UCI IRB #3795), related to accessing publicly available data sets containing multimodal and sensory input data for modeling emotion states, the degree of agitation and gait, as well as

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training the CCR for empathy-based conversational interventions for aims 2 and 3. The second IRB request (human subject research in the minimal-risk biomedical track) was approved in March 2024 for all aims (UCI IRB #4150). The IRB approval includes access to medical records and the observation of clinical care, and a partial waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization has been requested.

Informed Consent

Family Caregivers and Health Care Professionals

At the beginning of the study, a study team member will provide family and professional caregivers with comprehensive information about the study and obtain their consent.

Participants With Dementia

As the participants with dementia might be cognitively impaired, the informed consent procedure will use a validated decision-making assessment tool [33] tailored to the cognitive abilities of participants with moderate to severe dementia. This tool will assess each participant's capacity to comprehend the study objectives and procedure and determine their capability to provide informed consent regarding participation in the study. If the assessment indicates the participant's lack of decision-making capacity to provide informed consent independently, a surrogate decision maker who is a legally authorized representative or a family member will be identified. The study team will inform the decision maker about the study, provide comprehensive details, and obtain their consent on behalf of the participant.

In addition, despite requiring surrogate consent, efforts will be made to obtain assent from the participant whenever possible. The assent process involves presenting information about the study in a manner that aligns with the participants' cognitive abilities; seeking their agreement or disagreement (through words or nonverbal cues, including body language, facial expressions, gestures, or signs of agitation or discomfort when study-related discussions arise); and respecting their preferences to the best extent feasible.

However, because the study involves individuals with moderate to severe dementia, we anticipate fluctuations in decision-making capacity due to the natural progression of the disease. Consequently, participants' ability to provide or withdraw informed consent may vary throughout the study duration. Therefore, because regular assessments of decision-making capacity are essential, qualified professionals will continue to evaluate participants' ability to comprehend study information and make informed decisions. If, during the study, individuals demonstrate a diminished capacity to provide consent, the protocol outlines procedures for involving surrogate decision makers or legally authorized representatives to act in the participant's best interests. It is essential to mention that participation in the study is completely voluntary, and all participants can opt out at any time without consequences.

Privacy and Confidentiality

The participants' personal information and identifiers will be kept separate from the study data, and a code will be assigned to each participant. The deidentified data will be used for analysis and training purposes. After capturing audio and visual data of participants for whom they or their family members or legal guardians have provided consent, we will use the ARX data anonymization tool to anonymize sensitive personal data. All geographic locations, contexts, and environmental data will be abstracted to ensure that the collected data cannot be traced back to their original providers and will not be transmitted or stored in our cloud servers. In the cloud servers, the participants' data will be processed using automated tools. We will make all relevant deidentified data and findings available after publication and will honor intellectual property rights.

The single electronic file containing participant identifiable information will be password protected and stored on a laboratory computer in the principal investigator's locked laboratory, to which only the lead researcher, coresearchers, and study coordinators will have access. Research data will be stored electronically on a secure cloud-based data collection storage system maintained by the UCI Computer Science team led by a co-investigator.

As the audio recordings serve as primary training data for the CCR, it is crucial to preserve the integrity of identifiable audio recordings without transcription to preserve voice characteristics such as tone, intonation, and nuances in speech patterns, which are crucial for capturing the full complexity of human speech in developing ML algorithms. Therefore, the audio recordings will not be transcribed to prevent a loss or distortion of training data quality. However, deidentification procedures commence immediately after the audio recordings are obtained, ensuring minimal delay in protecting participant confidentiality.

The deidentification process for audio recordings involves several steps: (1) using specialized software such as Audacity or Adobe Audition designed for deidentification purposes; (2) using voice masking methods (including pitch shifting, time stretching, or applying filters to modify the frequency characteristics of the voice) within these tools to alter the pitch, tone, or timbre of the participants' voices to make them less recognizable; (3) conducting quality checks to ensure that all identifiable information has been effectively removed or altered; (4) using speech intelligibility metrics such as signal-to-noise ratio, mean opinion score, and perceptual evaluation of speech quality to objectively measure the clarity of the modified audio; and (5) finally storing the deidentified audio recordings securely in a protected database to prevent unauthorized access. Similarly, preserving identifiable video recordings without transcription is crucial for comprehensive emotion and agitation detection as well as gait analysis, especially in training the CCR. These recordings contain critical contextual cues, facial expressions, body language, and environmental elements, and deidentification risks the integrity of developing precise training models. Therefore, the video recordings will not be deidentified.

Compensation

For aims 1 and 4, interviews will take place with family and professional caregivers, and a compensation of US $20 will be provided per interview. We anticipate conducting interviews with 8 to 14 family and professional caregivers for aim 1 and with 6 to 12 family and professional caregivers for aim 4. In addition, we will compensate approximately 50 students who

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will take part in the simulation laboratory role-plays (aim 3) with US $10 each.

Research Description

Aim 1

For aim 1, we will collect and store granular Personicle data using real-time visual, audio, and physiological sensing technologies (including the CCR) to gain a deeper understanding of the emotional state, agitation level, and gait pattern of a person experiencing moderate to severe dementia over time.

Activity 1: Real-Time Data Collection and Sensing

The miles and outcomes involve creating (1) a database to store the hourly activities and behavioral states of a person experiencing moderate to severe dementia in real time and (2) a database to store their stories as episodic knowledge graphs.

Real-Time Sensing to Create Personicles

We will capture the behavioral states and patterns of a person experiencing moderate to severe dementia through real-time "lifelogging" using motion-sensing red-green-blue cameras with video capture and voice recording capacity (Microsoft Kinect), optical motion sensors (light detection and ranging [LIDAR] sensors), and remote photoplethysmography (rPPG) [34]. rPPG is a noninvasive optical technique used to estimate physiological parameters (eg, heart rate) remotely from a distance without the need for direct contact with the skin. The cameras and sensors will be installed in 2 bedrooms and the living room at 1 board and care facility at a time. We will begin observation of 2 patients at a time over at least a 2-month period, starting in month 2 and continuing until month 15, to capture the logs of 8 to 14 persons experiencing moderate to severe dementia. At least 6 to 8 persons experiencing moderate to severe dementia will remain for the full 2 years. In month 16, we will introduce the CCR and also use it as a real-time sensing device (using its onboard camera and LIDAR sensor). The CCR's vision system is equipped with a human identification system. It can recognize >1 patient and track them (the CCR is also capable of identifying the caregivers). This allows the CCR to log the gait pattern, activities, and agitation level of the person under observation. This system will be configured during the start-up or onboarding process.

These sensing technologies will capture lower-level atomic, person-centric data—the "logs"—with a timescale of 1 minute that can be enriched with higher-level, more meaningful behavioral states using the models developed in activity 2. Specifically, we will model the emotional state, agitation level, and gait pattern of a person experiencing moderate to severe dementia and design a multimodel taxonomy and activity and states ontology, extending the existing Personicle, a person-centric temporal activity and states database developed at the UCI Institute for Future Health. For the purpose of recognizing agitation, our initial approach involves constructing models that leverage audiovisual sensing technologies. These models are designed to accurately recognize and categorize standard agitated behaviors as outlined in the Cohen-Mansfield Agitation Inventory [35,36]. This inventory includes a range of specific activities, such as kicking, grabbing, pushing, throwing objects, and screaming. After successfully capturing and classifying these activities, the next phase will focus on using these models to evaluate and quantify agitation levels in individuals with moderate to severe dementia. We will store activities or states at the minute level. This ontology will be used in activity 2 to find the relationships among the hourly or daily states and activities and to create a robust temporal activity model.

The ultimate goal of the CCR system is to develop a dynamic model that accurately captures an individual's behavioral patterns. This model is intended to iteratively adapt and respond in a manner that positively influences and enhances these behaviors. In pursuit of this objective, a certain degree of tolerance for inaccuracy is considered acceptable, particularly in the precise identification of specific emotional states or the exact nature of agitated symptoms. This approach acknowledges that while exact details are beneficial, the primary focus is on the overall effectiveness of the model in improving behavioral outcomes.

Collecting Personal Stories

We will collect personal stories from our sample as input for activity 3. Our sensing devices will "lifelog" personal stories shared without probing when persons experiencing moderate to severe dementia converse with their caregivers at the board and care facilities. In addition, we will also elicit personal stories through informal interviews of the caregivers at least twice a week. By monitoring the behavioral state of persons experiencing moderate to severe dementia in their rooms, we can also categorize these events by emotion and agitation levels. Data will undergo manual review and labeling by our team of qualified clinical experts, performed offline for optimal focus. In addition, 2 to 3 interviews will be conducted with at least 1 family caregiver and the trained facility staff to collect information about their experiences about personal stories that have helped reduce agitation. We will also ask family members to share archival data (eg, videos of the persons experiencing moderate to severe dementia in the past as well as recordings of social and family events) that are representative of the past and positive or negative stories of the persons experiencing moderate to severe dementia. The unstructured natural language data will be translated into a knowledge graph to represent events or stories and additional attributes (eg, people and emotions) over time as an episodic relationship.

Aim 2

For aim 2, we will develop statistical models to understand and forecast the emotional state, agitation level, and gait pattern of a person experiencing moderate to severe dementia in real time using ML and AI.

Activity 2: Modeling Behavioral and Cognitive States

The miles and outcomes involve developing statistical models for modeling emotional states, agitation, and gait.

Modeling Emotional States

To model the emotional state of a person experiencing moderate to severe dementia, we will design multimodal ML and AI models using 4 types of data: natural language content, facial expression, body movements, and vocal features. We will focus

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on modeling emotions from each modality (eg, text as natural language content) and then integrate these models to create a comprehensive multimodal model. The goal is to evaluate the emotional content of a conversation at a particular point in time. In establishing these models, we consider both theoretical and technical aspects to ensure robustness. Specifically, in the case of the text modality, we will adapt existing theories (eg, the theory postulated by Parrott [37]) and ML and AI techniques (eg, pretrained models, such as Robustly Optimized Bidirectional Encoder Representations From Transformers Pretraining Approach [RoBERTa] [38], with fine-tuning) for inferring emotions from natural language to the context of dementia when modeling emotions using text extracted via speech-to-text techniques (for a comprehensive review, refer to the study by Zad et al [39]). This is especially pertinent to feature representation processes. In these processes, we will obtain word embeddings for emotions with the assumption that multiple emotional states can coexist simultaneously (for further information, refer to the study by MohammadiBaghmolaei and Ahmadi [40]). Our analysis will focus on 6 distinct emotional states: sadness, fear, joy, love, surprise, and anger. In the modeling process, we will pretrain our models on open-source data sets widely used for emotion recognition tasks in the natural language processing community (eg, the Interactive Emotional Dyadic Motion Capture Database [IEMOCAP] [41]) and then retrain them on data sets focused on conversation data from persons experiencing moderate to severe dementia, using both open-source data sets (eg, DementiaBank [42]) and our own (ie, the National Institute on Aging [43]).

Beyond the text modality, we will also train a deep learning model, using images and videos containing the facial expressions of a person experiencing moderate to severe dementia to infer emotions such as joy, sadness, or anger from their smiles, frowns, brow movements, and lip configuration. We will train our models using large image data sets such as Facial Expression Recognition 2013 [44], while also considering retraining them on data sets specific to patients with dementia [45,46]. In addition, videos and motion sensors will be used to infer emotions from a patient's body movements. Audio data will be used to infer emotions based on markers such as speech rhythm, voice intensity, and other spectral features (eg, mel-frequency cepstral coefficients). Empathy modeling, including the alignment of LLMs using prompt engineering and reinforcement learning techniques, will also be conducted, considering the relationship between emotion and empathy.

Our research aims to make scientific contributions to ML and AI for emotional intelligence and empathetic conversation of CCRs in two main ways: (1) designing a new multimodal model for empathy classification that enables CCRs to sense a patient's emotional state in real time; and (2) aligning LLMs for empathy using various techniques, such as prompt engineering, reinforcement learning, or a combination of both. For the first point, we plan to build a semisupervised ML model that uses a transformer architecture and pretrain it on healthy data sets. We will evaluate this baseline using dementia data sets carefully labeled by domain experts with respect to the emotional state of patients with dementia. We will then improve this baseline model by enhancing its self-supervision based on features identified from 4 modalities (ie, natural language content, facial expressions, body movements, and vocal features) in data collected from patients with dementia. We will examine different ML and AI models and evaluate their performance in both quantitative and qualitative ways.

Our major contribution will be the development of a semisupervised emotion classifier that integrates multiple data modalities, including text, speech features, facial images, and body movements. We will use established evaluation protocols and metrics, such as accuracy, precision, F_1-score, recall, and confusion matrices, to assess and compare various models to evaluate this baseline model. We will complement these evaluation protocols with a qualitative evaluation and inspection of our emotion classifier. Furthermore, we will also examine the model's run time, given the need for real-time evaluation of emotions.

For the second point, we will first evaluate existing open LLMs (eg, OpenLLaMA and NeuroLLaMa) using our own benchmarking data set and data sets published by others [27]. Building on this, we will then use prompt engineering methods to enhance the empathetic capabilities of the LLMs' conversations. To assess the performance of these fine-tuned LLMs, we will use well-established metrics and protocols in alignment research, including F_1-score, Bilingual Evaluation Understudy score, accuracy, precision, and recall. In addition to prompt engineering, we will leverage reinforcement learning to optimize the LLMs for empathy. Specifically, we plan to first use inverse reinforcement learning to develop a reward function for a highly empathetic caregiver.

Modeling the Degree of Agitation

We will develop an ML and AI model for the agitation exhibited by a person experiencing moderate to severe dementia that captures disturbances in verbal, vocal, or motor activity. Instead of relying on caregiver assessments, this model measures agitation in an objective way, using images, videos, and motion sensors, as well as collects nonintrusive physiological data using rPPG sensors (refer to the Real-Time Sensing to Create Personicles subsection). We first aim to extend recent novel research for modeling agitation via inertial body sensors to our setting of nonintrusive rPPG sensing [47]. We plan to enrich such models using image analysis following recent efforts to infer agitation via facial grimacing rather than body sensing [48]. We also aim to integrate vocal or verbal data to infer agitation states based on disturbances in verbal motor action. Using this multimodel ML and AI approach, we can enrich the Personicle of a person experiencing moderate to severe dementia by incorporating degrees and types of agitation (eg motoric functions). We will then build predictive models that allow us to predict both emotions and agitational states.

Modeling Gait

To facilitate continuous yet nonintrusive monitoring of gait and mobility, we will use a vision-based method to conduct comprehensive evaluations of crucial gait factors. Through the application of state-of-the-art computer vision techniques, the method will assess gait speed, step length, step width, knee flexion angle, and the Timed Up and Go test. The foundation

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of the vision-based method lies in its use of dependable and adaptable body pose estimation algorithms, which can be tailored to monitor and assess transitional activities. Thus, a more comprehensive comprehension of the gait patterns of the person experiencing moderate to severe dementia will be achieved, leading to a more precise identification of potential fall risks [49]. Integrating time-variant, person-level emotional, agitation, and mobility states will allow us to build models for understanding their causal relationships and prediction of high-risk events.

The system has been designed to operate in a normal home setting. Standard gait parameters such as gait speed, step length, step width, and cadence will be calculated using a combination of computer vision, statistical ML, and trigonometry. The Timed Up and Go test, which is a standard test, has been estimated from the aforementioned parameters using an ML model [50].

Aim 3

For aim 3, we will design an empathy-focused conversation model for successful human-robot intervention that considers the emotional state of a person experiencing moderate to severe dementia and associated events (using the outcomes of activity 1 and activity 2).

Activity 3: Designing Empathy-Focused CCR-Patient Interaction and Simulated Evaluation

The miles and outcomes involve developing natural language processing–based language models incorporating time-variant emotional states and events; an interface for empathy-based interaction (speech plus text display); and simulated validation of CCR usability as well as the impact of the conversational model on human emotional states, trust, and cognitive load.

In activity 3, we will focus on designing the empathy-focused intervention model for the CCR. The CCR is a social robot (standing 3 feet 9 inches tall and weighing 26 kg) that is primarily focused on acting as a companion for communication with the person experiencing moderate to severe dementia. In addition, it acts as a sensing device for activity 1. It is distinct from other social robots such as PARO, AIBO, or MINI, which are pets. The CCR is equipped with a 12-inch display and audio features to communicate with the person experiencing moderate to severe dementia via not only speech and sound (eg, music) but also text and visual content (eg, pictures and movies displayed). The software or hardware platform architecture of the CCR is modular and uses a widely adopted robot operating system. With state-of-the-art simultaneous localization and mapping (SLAM) and human-aware navigation capabilities, the CCR can expertly navigate complex environments while prioritizing the safety and well-being of humans.

Indeed, SLAM algorithms are used in many robotics applications in health care settings not only for research but also for day-to-day practice. Thus, the contribution to the field of SLAM research is not the priority of this research; instead, our focus lies on emotional intelligence and empathetic conversation. However, to ensure safety using SLAM, the team will advance existing SLAM models using vision for human recognition (in combination with other sensors such as those using LIDAR technology) to account for the dynamic environment in safety-critical conditions such as caregiving using visual SLAM, which integrates state-of-the-art research from fast-advancing computer vision research. Similar to the approach of Fang et al [51], we aim to improve the map construction of visual SLAM to allow for dynamic scene construction.

Design of an Emotionally Aware and Empathy-Based Conversational Model

To develop the CCR's emotional intelligence, we will leverage the results of the activity described in the Modeling Emotional States subsection to design an AI model for understanding and predicting the emotional state and agitation level of a person experiencing moderate to severe dementia, using real-time sensing via the sensing technologies in the room. Using this AI model, the CCR will interact with the person experiencing moderate to severe dementia when the likelihood of an emotional disturbance or agitation increases, using an emotionally aware and empathy-focused conversation model. To realize such a conversational model, we will extend an open LLM in a way that enables the CCR to engage in empathetic storytelling with the person experiencing moderate to severe dementia. To do so, we will design a rule-based prompt engineering model that changes the degree of empathy of the CCR's language. This empathy-prompting technique builds on recent research by Brunswicker et al [52] integrating AI with theories of empathy display in linguistics, reflecting the rules about how syntax and rhetoric in language display shape empathy in social conversations. In this research, the effect of AI-enabled empathy display in conversations with an artificial agent has been validated in randomized behavioral experiments with healthy participants exhibiting different degrees of emotional disturbances (eg, anger). We will advance these rule-based models in the context of patients with dementia to investigate the linguistic dimension of empathy for lowering the risk of agitation. Furthermore, we will integrate the LLM with an episodic knowledge graph that represents the personalized stories of the person experiencing moderate to severe dementia as connections of events, people, and activities [53]. This will enable the CCR to engage in personalized storytelling using empathetic language at the onset of an emotional arousal.

Design of the User Interface

Using the results of the activity described in the Design of an Emotionally Aware and Empathy-Based Conversational Model subsection, we will design a conversational interface that uses a dual-mode communication approach, incorporating both audio- and text-based interactions. This approach will allow the CCR to display empathy through its voice and on the display screen. Through these 2 ways, personal stories will be conveyed to the person experiencing moderate to severe dementia. Our design will focus on usability, aiming to reduce the cognitive load of the person experiencing moderate to severe dementia. To achieve this, we will draw upon established usability heuristics for interaction-enabled applications and revise our existing interface through an iterative and heuristic-based usability design process. This process will involve developing personas, which describe fictional or real individuals that represent end-user needs. These personas will support the product design of the audio and text interface.

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In evaluating the usability of this interface, we will base our tests on established literature, specifically focusing on 2 widely used methods in the practitioner community: the 10 general principles for user interface design postulated by Nielsen [54,55] and the heuristics for conversational agent design proposed by Langevin et al [56]. We specifically plan to use the criteria proposed by Langevin et al [56] with some modification as the basis for the design of our audio and speech interface. Evaluation heuristics can be broadly categorized into 3 main areas: design (eg, aesthetic and minimalist design), content (eg, designing content for dialogue), and security (eg, data privacy). We will iteratively evaluate and update the interface to ensure optimal usability and performance accordingly.

Simulated Validation

Before evaluating our new empathy-focused CCR at the board and care facilities with persons experiencing moderate to severe dementia, we will work in the simulation laboratory of the UCI Sue & Bill Gross School of Nursing [57]. First, we will use the laboratory for simulated, randomized experiments to examine whether and how our newly designed conversational model for the CCR responds to videos and audio recordings of the board and care facility residents experiencing moderate to severe dementia collected in the activity described in the Activity 1: Real-Time Data Collection and Sensing subsection and played on a large screen to perform out-of-sample validation experiments related to the persons experiencing moderate to severe dementia. We will evaluate the CCR's response time to approach the screen, its choice of a personal story, and its ability to align with the emotional state of the person experiencing moderate to severe dementia using both quantitative and qualitative techniques. Specifically, we will examine the content of the language, voice pitch, and the content logic of the stories. Afterward, we will perform exploratory evaluation studies as well as randomized controlled trials with healthy humans. We will carefully sample approximately 80 undergraduate and graduate students. Some will be provoked to be emotionally disturbed, using established scientific methods of emotion induction [58,59]. In the randomized controlled trials, we will use a simple 2×2 factorial treatment design (with CCR or without CCR and emotionally stable vs emotionally disturbed), with sessions lasting up to 1 hour. The goal is to evaluate usability, trustworthiness, helpfulness, cognitive load, and emotional states, as well as agitation levels before and after the interaction with the CCR (refer to the Activity 2: Modeling Behavioral and Cognitive States subsection) [58,59].

Aim 4

For aim 4, we will pilot an empathy-focused intervention model for the CCR using a quasi-experimental intervention design and evaluate the conversational intervention longitudinally using mixed methods approaches.

Activity 4: Pilot Implementation and Field Study

The miles and outcomes involve evaluating the impact of the CCR on the emotional state, agitation level, and gait pattern of 6 persons experiencing moderate to severe dementia and assessing the acceptability and usability of caregivers. We will use relational event analysis of empathy-focused conversations of patients and the CCR combined with pathway analysis of the persons experiencing moderate to severe dementia to examine dynamics over time.

Pilot Implementation

Starting in month 16, a total of 3 patients at a time will be interacting with 3 CCRs over a period of 3 months (1 introductory month for the patient and the CCR to become familiar with each other, while assessing for and mitigating agitation caused by the CCR as well as evaluating usability and acceptability periodically with family and professional staff every 2 weeks during a 2-month intervention period). Thereafter, an additional 3 persons experiencing moderate to severe dementia will be followed over the next 3 months, with observation ending in month 21 and final analysis and dissemination to follow. During the testing period, the CCR will be placed in the corner of the designated rooms; the family caregivers or staff will not need to program it in any way. At the onset of potential emotional disturbance, the CCR will move toward the person experiencing moderate to severe dementia, observe them closely, and start talking to them using empathy-focused conversations. The conversation will vary, depending on whether the person experiencing moderate to severe dementia expresses fear or anger. The CCR will use storytelling with the person experiencing moderate to severe dementia to prevent an onset of agitation when it detects relevant signals. If the CCR's empathy-based conversations to prevent agitation are not successful, the traditional de-escalation strategy will be applied, such as facility caregiver support and behavioral intervention (caregivers are always notified of any agitation events), as well as, if necessary, the use of medication indicated and previously prescribed for the individual person experiencing moderate to severe dementia.

Evaluation (Quantitative)

We will measure the emotional state, agitation level, and gait pattern of the person experiencing moderate to severe dementia [48-53,57-65] using the models developed earlier (refer to the Activity 2: Modeling Behavioral and Cognitive States subsection). This computational and nonintrusive granular measurement is very novel for dementia research and allows us to associate conversational events with the emotional state of a person experiencing moderate to severe dementia. We will then perform a quantitative cross-sectional event-level analysis (comparing similar event periods within and without CCR interactions) and an intervention analysis using a dynamic event-state model for a few case settings, allowing us to understand how interactions with the CCR affect the outcomes of persons experiencing moderate to severe dementia over time (eg, relational event modeling). We will also use longitudinal analysis to assess perceived stress and health among family caregivers, with assessments at baseline (beginning at month 1 of the 3-month intervention with the CCR) and after the intervention (end of month 3), using the Caregiver Self-Assessment Questionnaire [66]. For the facility caregivers, we will use the Maslach Burnout Inventory [67] to assess emotional exhaustion and depersonalization.

Evaluation (Qualitative)

We will also conduct interviews with both types of caregivers to assess acceptability and usability, with questions to assess

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why the CCR did or did not impact the emotional state, agitation level, and fall risk. Thematic analysis on transcribed data from the caregivers will be conducted by qualitative investigators (AN and JAL), along with trained research staff, using a rigorous process [68]. In vivo coding will be generated from the first and second cycle codes of the participants' responses [69]; these data will then be organized into a Microsoft Excel file.

The rigor of the iterative data analysis will be ensured by the trustworthiness of data (ie, credibility, confirmability, transferability, and dependability) [70]. Credibility will be ensured by delivering the sessions in safe and confidential areas to ensure open communication and audio recording and transcribing all conversations to ensure that the data are credible. Credibility will be further established by having 2 trained coders involved in the coding process, with a senior coder overseeing the entire process. Confirmability will be ensured through ongoing discussions of caring for the persons experiencing moderate to severe dementia with the caregivers and asking for feedback on previously collected data. Finally, dependability will be ensured by providing a detailed description of the methods used.

Data Management and Data Security

All study data will be entered and managed using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based application designed to support research data entry and storage. Data will be entered using electronic tablets with secure socket layer protocol and protected by a firewall service provided by the Office of Information Technology. Data encryption and network-based access and key management services will be used for data storage.

Results

CAB Formation

To provide cultural nuances for the development and training of the CCR, a CAB was formed in December 2023. The CAB is composed of 6 members, 3 (50%) of whom are family caregivers of patients with dementia residing at the board and care facilities, with the other 3 (50%) being directors of, or professional caregivers working at, these facilities. During the first of several meetings that will occur several times over the period of the grant, the members expressed gratitude for the work that has been planned and highlighted the importance of the work in mitigating fall risk among patients with dementia.

Activity 1: Real-Time Data Collection and Sensing

Architecture development for Personicle began in January 2024, using an existing open-source data set and foundations from the skeleton-based recognition module developed several years earlier [71]. To date, 16 actions (atomic, transition, and agitation markers) have been designed using client-server architecture. Accuracy to date is 99% on the test set and 96% on the validation set. Currently, we are developing a tracker with facial recognition capabilities for persons experiencing moderate to severe dementia and their caregivers.

Furthermore, to set the stage for capturing audio and visual images of the patients with dementia in their residential settings, camera stations were meticulously designed and customized according to the specific needs of the facilities we inspected. These internet-connected cameras are capable of detecting movement and start recording for 30 seconds when motion is sensed. In addition, a workstation computer was purchased in June 2024, and we will be using its graphics processing unit for training the models for aims 1 and 2; this workstation will also serve as substantial storage for all collected data. In addition, an automated and secure pipeline was developed, allowing the cameras to compress and transmit recorded videos, including point cloud images, and audio data to our high-performance workstation, where team members can securely access and analyze the data.

To test the functionality of our cameras, we conducted role-playing scenarios, simulating interactions between patients with dementia and caregivers, guided by dementia experts and facility observations. These simulations helped us identify potential issues, such as the high volume of the televisions in the rooms interfering with the detection of conversations between patients and caregivers, thereby limiting our ability to detect signs of agitation or emotional changes from audio cues. We addressed these issues by finding solutions to improve the accuracy of our recordings under such conditions. Through these activities, we created a simulated data set that mirrors real-life situations involving patients with dementia. This data set has been instrumental in training and testing our models to detect possible agitation or emotional changes, ensuring our system's reliability and effectiveness in real-world applications.

Activity 2: Modeling Behavioral and Cognitive States

First, as described in the Modeling Emotional States subsection, we initiated the development of ML and AI models by identifying open-source data sets and pretrained models relevant to our primary interests, such as emotion recognition and action recognition. These models serve as baselines for our project. This stage is particularly pertinent for problems related to classification or detection. Therefore, we focused on finding suitable open-source data sets and integrating them into our research objectives. The results of this stage are 2-fold: data set identification and construction and modeling.

Our initial objective was to establish an emotion classifier using various methods (eg, semisupervised method). To achieve this, we explored multiple data sets for emotion classification in the context of persons experiencing moderate to severe dementia and identified DementiaBank, which includes both text and audio files from 78 patients with dementia. As the data set was not labeled, 7 human labelers, 3 (43%) of whom are domain experts, were involved in the labeling process, during which we preprocessed the data set, including audio segmentation and utterance extraction from the text. During a training session, we built a guideline for labeling based on discussions with the labelers. Thereafter, the labelers labeled the data according to this guideline. The labeling activity has since been completed, and the labeled data are currently undergoing validation.

In parallel with the labeling activity, we established a baseline model for emotion classification using the IEMOCAP as well as the Multimodal EmotionLines Dataset (MELD) [72], open-source data sets widely used in emotion classification

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tasks. The IEMOCAP includes 151 dyadic dialogues, while the MELD consists of 1039 dyadic dialogues; both data sets contain text and audio data from healthy individuals. We obtained features from pretrained models, such as RoBERTa, for text and speech representation. Thereafter, multimodal modeling for emotion was implemented using transformers with self-attention and cross-attention layers, followed by emotion prediction. Through both quantitative and qualitative analyses of the results, we found that enhancing feature representations of each modality contributes to model performance.

Concurrently, a team from NaviGAIT and computer scientists from UCI are working on detecting agitation. We used the collected data and trained several models to detect different types of motions, such as sitting, standing, and so on, and annotate the video every 3 seconds. Currently, we are at the phase of training the model and improving its accuracy in detecting agitation. For audio, we are able to detect audio events using the Agitation Maker, which converts the audio into text and applies semantic scoring using a generative pretrained language model to obtain an agitation score. This work is under progress.

Activity 3: Design of the User Interface

In terms of aim 3, the design use subgroup began developing personas by April 2024 and to date has developed 10 personas characterizing persons experiencing moderate to severe dementia that will be useful for training the models. The personas include the backgrounds of real persons residing at board and care facilities, with first names and pictures replaced, and includes brief descriptions of the persons, interests, personality, sleep quality, health conditions and medications prescribed, conversational ability, and entertainment and communication devices used, as well as what makes them happy or upset. Finally, more recently, we added behaviors to watch for that often leads to agitation and caregiver instructions for dealing with these behaviors. A second document was also developed that outlines the typical daily activities of each person experiencing moderate to severe dementia.

Next Steps

Using client-server architecture, work is ongoing in predicting an action and activity every 3 seconds (refer to the Activity 1: Real-Time Data Collection and Sensing subsection). With multiple camera stations to be placed in position soon, the continued functionality of the cameras will be tested using role-playing. Furthermore, we will continue to advance the data set that mirrors real-life situations involving patients with dementia, which will be used to train and test our models to detect possible agitation or emotional changes, ensuring our system's reliability and effectiveness in real-world applications. Ongoing design-use personas and workplans will be created to add rich premodel training data.

Once an appropriate baseline model is identified, we will proceed to gather data. In scenarios where suitable data sets are unavailable, we will undertake the collection of in-house data, tailored to our specific requirements. In instances where an open-source data set is available but inadequately labeled, our team will perform a meticulous process of relabeling the data to ensure alignment with our research needs. Following data acquisition and preparation, we will embark on the training and fine-tuning of our model. This process leverages the baseline model and is informed by the unique characteristics of our collected or curated data set.

The next step involves retraining the baseline model on the labeled data of persons experiencing moderate to severe dementia (ie, DementiaBank), after training and fine-tuning the baseline model with healthy data sets (ie, the IEMOCAP and the MELD), followed by both quantitative and qualitative analyses. This process includes building and testing various architectures, such as enhancing modality representations (eg, text representation), to improve model performance. Considering the nature of the data for emotion recognition (eg, imbalance and data size), we will adopt and develop various ML techniques (eg, attention weight) to mitigate potential issues that can arise. In parallel, we will establish a baseline model for empathy recognition using LLM alignments, including prompt engineering and reinforcement learning, considering the close relationship between emotion and empathy. Both quantitative and qualitative analyses of the results of all interim processes will be conducted. After scrutinizing these results and gaining insights from the analyses, we will improve our baseline models to build a robust empathic conversational model for the CCR, with data to be collected.

The subsequent phase involves rigorous testing of the trained model in various stages to ascertain its efficacy and reliability. It is imperative to note that the transition from a trained model to its application in real-world settings involves additional steps. Given our use of Jetson devices for edge computing, we will convert the trained model into TensorRT format. This conversion is a critical step to facilitate the deployment of the model on edge devices. Such deployment enables real-time inference while also adhering to privacy considerations, a crucial aspect of our research protocol.

Finally, aim 4 will be the culmination of our evaluation, wherein the CCRs will be stationed at the residences of the persons experiencing moderate to severe dementia enrolled in our study. Our goal is to then test and evaluate the empathy-focused conversation model for the CCR with the enrolled residents and gather qualitative data from both family and professional caregivers.

Plan for Pretraining the Robot

We plan to develop a robust and efficient pretraining strategy for emotion detection in patients with dementia using publicly available data sets. We will first follow an unsupervised pretraining plan using speech feature extraction (eg, mel-frequency cepstral coefficients, pitch, and energy), visual feature extraction (eg, facial features related to emotion expressions, such as action units and facial landmarks), and physiological feature extraction (physiological signals such as heart rate and heart rate variability). The second step involves using supervised pretraining through fine-tuning the pretrained model on smaller, labeled data sets. Finally, we will further fine-tune the pretrained model on the final emotion detection task specific to patients with dementia.

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Our review of current literature indicated the availability of publicly accessible data sets, including the Dem@Care, DementiaBank, and UCI Alzheimer's Disease Research Center data set collections. The available data formats are text, voice, video, and sensor data (physiological signals). All data sets are in English, as the inclusion criteria were set and include healthy participants as well as participants experiencing dementia. The data sets were collected in controlled settings, such as research laboratories, or uncontrolled settings, such as home care or participants' homes.

To enhance the existing literature review seamlessly, we will delve deeper into data sets that provide a nuanced perspective on dementia-related research; for example, 1 data set that stands out is Dem@Care, which serves as a resource with its collection of video and audio recordings captured in both laboratory and home settings using the Microsoft Kinect red-green-blue-D device. This data set goes further by including information on sleep patterns and physiological aspects. Another example is the Technology Integrated Health Management data set, which may be promising for remote health care monitoring because it leverages sensor data such as motion and sleep mat recordings. What makes this data set particularly interesting is its inclusion of labels for agitation events over a 6-hour period, allowing for correlations with sleep and activity data. Another valuable resource may be the Prompt database from i2 labs, which adds diversity by featuring video, audio, and facial expressions of participants in a home-based setting. This database provides a resource for training classification models.

By contrast, there is the DEAP data set, which focuses more on classification but does not specifically revolve around patients with dementia. For the dimension, we came across 2 data sets: Mobile Device Voice Recordings at King's College London and the ADReSS Challenge. These data sets serve as voice banks for training audio-based models on individuals with dementia. However, both data sets require annotations to develop emotion-based audio models.

This careful choice of data sets, each with its own characteristics, not only expands the range of our exploration but also forms the basis for a thorough and detailed investigation into dementia across different methods and situations. As we progress, it will be important to consider the validity of such modeling and training using data sets from people without dementia or mild dementia and may not be fully applicable to persons with more advanced dementia. We will also consider cultural adaptation aspects in the CCRs, including customs, languages, and cultural social norms, in the designing phase. Engaging with communities to understand their values and preferences is key to ensuring that these robots are viewed as helpful companions rather than intrusive tools.

Discussion

Findings to Date

Worsening dementia places persons experiencing moderate to severe dementia at high risk for significant declines in cognition, emotion, and behavioral disturbances, including falls and serious injury due to unpredictable agitation. The findings of our study to date include for aim 1 and its activities, identifying, generating, and collecting public data sets for the training and testing of our models. We identified the key activities associated with persons experiencing moderate to severe dementia, including signs of agitation (such as standing up, pushing, and striking); we also located data sets for some of these activities and generated sample data sets with staff in our simulation laboratory and from the NaviGAIT team's internal recordings to train AI models to detect key activities and extract relevant events. This activity resulted in a list of motion and audio events that we found to be correlated with agitation, along with their respective data sets. Finally, we acquired a computer workstation and camera designed for custom data set creation in preparing for aim 4 and testing real-world situations, along with capturing new data in our simulation laboratory.

For aim 2, we established a baseline model with benchmark data sets (ie, the IEMOCAP and the MELD) for the emotion classification task before incorporating the labeled data of persons experiencing moderate to severe dementia (ie, DementiaBank; the data were labeled by our team). We extracted features from each modality (ie, text and audio) using pretrained models (eg, RoBERTa) and leveraged them for multimodal modeling using transformer-based architectures. Furthermore, our analyses indicate that text representation is more challenging than speech representation. This may be due to the fact that emotion is not heavily dependent on text. Specifically, emotion is often implicit and not always conveyed through emotion-specific words such as *mad*. As a result, text-based emotion recognition can be more complex, especially because contextual information plays a crucial role in detecting emotions within text. This discrepancy in modality representation merits further discussion.

Given our findings and analyses of the results, our next steps include the following. First, we will navigate and develop embedding techniques (eg, ontology-based approaches) to enhance feature representations, especially text representation. In parallel, we will apply our baseline model to the labeled data and conduct quantitative and qualitative analyses of the results to gain insights into the language of emotion expression of persons experiencing moderate to severe dementia. Another step includes finding ways to mitigate potential problems caused by highly skewed data (eg, multiple "neutral" labels in the labeled data) because data quality is of paramount importance to model performance. Our interim goal is to improve text and speech modeling further. Following these steps, we will focus on empathy modeling and LLM alignments, as well as incorporating more modalities (eg, from video). We expect that these interim processes will significantly contribute to achieve our overarching goal: developing a robust empathic conversational model for the CCR, with data to be collected, ultimately benefiting persons experiencing moderate to severe dementia.

Finally, as part of aim 3, we have begun to develop personas and workplans focused on real persons experiencing moderate to severe dementia to help in pretraining the models, which will then set the stage for aim 4.

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Comparison With Prior Work

This proposed study is innovative in many ways. It uses a caregiving approach, developed with advice from community stakeholders, which will be tested both in our state-of-the-art simulation laboratory and in the community. The CCR will be designed to forecast and recognize signs of agitation and other emotional behaviors and, upon recognition, intervene with empathetic verbal communication. The CCRs will be assessed for their ability to objectively observe, record, analyze, and appropriately respond to persons experiencing moderate to severe dementia, relieving human caregivers of some of the time-consuming and stressful work they currently perform. Robot caregivers can potentially reduce the escalation of agitation among persons with moderate to severe dementia, because robots, unlike human caregivers, will not be prone to displays of distressed emotions that can exacerbate the distress and behavioral disturbance of persons experiencing moderate to severe dementia.

By the end of our study, we hope to develop a comparable CCR with our partnering board and care facilities where the persons experiencing moderate to severe dementia reside. Currently, we are developing the notification system that will enable the CCR to alert professional staff at the facilities when their support is needed for a patient.

The critical aspects we will be focusing on relate to whether we can train the CCR to predict agitation and be able to use storytelling to calm the individual while a support person is notified. We will be analyzing the communication and behaviors of individuals with dementia within their environments. This technique can then be applied to broader contexts, ensuring that the care strategies are versatile enough to benefit a wider range of individuals in various care settings (from homes to communities).

Strengths and Limitations

The strengths of our study are significant. Our team has been collecting data from multiple sources, and the use of the Personicle data, gathered through real-time "lifelogging," will be a novel approach. In terms of our emotion recognition model, by leveraging diverse benchmark data sets such as the IEMOCAP and the MELD, our model benefits from exposure to varied conversational contexts, enhancing its generalizability. Moreover, the multimodal approach, which extracts and integrates features from text and speech, allows for a comprehensive analysis of emotional information. Furthermore, using transformer-based architectures, our model effectively processes both local and global emotional context, handling the short-term and long-term dependencies inherent in conversations. In addition, our model's performance benefits from the enhanced feature representation for each modality.

Despite these strengths, there are several prerequisites for the CCR to deliver on this vision. The first is the need for sufficient data to train and test the algorithmic models. There is a dearth of public data sets of persons experiencing moderate to severe dementia due in large part to the sensitive personal health information that would be revealed in an open format. Our team is overcoming these challenges by the combination of searching for and identifying new data sets; using the simulation laboratory to create data sets; and, for aim 4, testing the CCR at the board and care facilities with persons experiencing moderate to severe dementia.

Furthermore, building models for emotion classification comes with its own set of challenges. First, the data distribution of currently available benchmark data sets is highly skewed, with many "neutral" labels. Moreover, the diverse data sources of the benchmark data sets add to the complexity of the task. Specifically, the IEMOCAP includes dyadic conversations, while the MELD includes multiparty conversations. In addition, the IEMOCAP was created by actors in a laboratory setting, resulting in high-quality audio, whereas the MELD features conversations from the television show *Friends*. Consequently, model performance is sensitive to ambient factors, such as noise.

Conclusions

Family caregivers of patients with dementia often experience high levels of stress when dealing with a loved one's progressive dementia, often resulting in family disruption, with persons experiencing dementia being moved to community facilities. Moreover, even at these facilities, there is an inability of the professional staff to constantly observe and manage signs of agitation and fall risk. Our study has been making great progress in gathering existing data sets and collecting data via cameras and, subsequently, Internet of Things devices. These granular, personal, and chronological Personicle data will provide one of the first implementations of the framework envisioned by Jalali et al [73]. The development of novel models that receive input from persons experiencing moderate to severe dementia, algorithmically assess their emotional state and determine the appropriate intervention strategy, and deliver an empathetic conversational intervention is perhaps the most significant innovation in our proposal.

Dissemination Plan and Future Directions

While this study will be conducted in a facility, agitation is an issue experienced by persons with dementia who reside in many types of facilities as well as at home. Thus, regardless of setting, the critical aspects we will be focusing on are whether we can train the CCR to predict agitation and be able to use storytelling to calm the individual while a support person is notified. We will be analyzing the communication and behaviors of individuals with dementia within their environments. This technique can then be applied to broader contexts, ensuring that the care strategies are versatile enough to benefit a wider range of individuals in various care settings (from homes to communities).

Future research will focus on developing the baseline model by fine-tuning and enhancing feature representations. This includes assessing the model both quantitatively and qualitatively. Thereafter, we will retrain the model with the data from DementiaBank, which has been carefully labeled by our domain experts. We will explore and develop various model architectures (eg, semisupervised models) to analyze emotions in both healthy and dementia data sets and evaluate the model performance, after which features from another modality, video, will be incorporated into the model. This proposal thus has the

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potential to have a significant impact on an emerging field of computational dementia science and on society by reducing episodes of falls, injuries, and unnecessary hospitalizations of persons experiencing moderate to severe dementia, while helping to relieve caregiver burden.

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Data Availability

Data sharing is not applicable to this study because no data sets have been generated or analyzed yet for the preparation of this protocol manuscript.

Authors' Contributions

AN and SB co-wrote the grant proposal, assisted in conducting the research, and drafted the manuscript. ND supervised the methodology and reviewed the manuscript critically from a technical perspective. JAL reviewed the manuscript critically from the nursing perspective. DK, EK, CK, MA, AMR, MR, and SB played a key role in assisting in designing the study and revising the manuscript critically. HR, HL, RJ, FA, AA, BQ, and TYB contributed to software development. JL, LG, and JR reviewed the manuscript critically.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CAB: community advisory board
CCR: care companion robot
HIPAA: Health Insurance Portability and Accountability Act
IEMOCAP: Interactive Emotional Dyadic Motion Capture Database
LIDAR: light detection and ranging
LLM: large language model
MELD: Multimodal EmotionLines Dataset
ML: machine learning
REDCap: Research Electronic Data Capture
RoBERTa: Robustly Optimized Bidirectional Encoder Representations From Transformers Pretraining Approach
rPPG: remote photoplethysmography
SLAM: simultaneous localization and mapping
UCI: University of California Irvine

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Protocol

Effects of Combined Visual-Motor Response Training on Cognitive Function and Brain Plasticity Mechanisms in Various Populations: Protocol for a Single-Center, Open-Label, Controlled Clinical Trial

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Abstract

Background: Cognitive impairment is one of the major diseases facing the aging population. The progressive decline of cognitive function can lead to declining health or even the loss of life, work, and social ability. Exercise and behavioral stimulation can increase neurotransmitters in the brain and improve overall health and cognitive function. Reactivity training can mobilize neuromuscular function and induce changes in brain plasticity, which may effectively improve cognitive dysfunction and delay the occurrence and development of Alzheimer disease; however, the evidence supporting its effectiveness is still limited.

Objective: This study aims to explore the effectiveness and reliability of visual-motor reaction training in improving cognitive function, thereby promoting the application of novel nonpharmacological therapies.

Methods: This study is a single-center, open-label, controlled clinical trial. A total of 78 participants will be recruited for the study, including an equal number of athletes, ordinary healthy college students, and ordinary older adults in the community. Participants will receive 2 weeks of visual-motor response training. The primary outcome of this study is to assess differences in functional magnetic resonance imaging (fMRI) at 2 weeks. The secondary outcomes were the following: acousto-optic response time, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Mini Mental State Examination (MMSE), Activity of Daily Living (ADL) Scale, Subjective Cognitive Decline Questionnaire–9 (SCD-Q9), a 10-word memory test, and safety.

Results: The study was approved by the Shanghai Clinical Research Ethics Committee on January 2, 2024 (SECCR/2023-162-01). As of September 11, 2024, we have completed the recruitment of all 3 groups of volunteers. We expect to complete data collection and analysis by February 2025.

Conclusions: The purpose of this study is to compare improvements in brain perceptual motor functions and cognitive levels across different populations through response ability training and to explore the efficacy and safety of exercise-based nonpharmacological therapies in improving cognitive function. Other potential benefits include understanding the functional differences and perceptual characteristics of the brain's perceptual-motor system between athletes and the general population and exploring the adaptability of the brain in acquiring skills during competitive sports training. This could provide an evidence base for early sports talent development and broader youth development.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400079602; https://tinyurl.com/23fbbndw

International Registered Report Identifier (IRRID): DERR1-10.2196/56424

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KEYWORDS

visual-motor; response ability training; cognitive function; brain plasticity mechanism; study protocol

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Introduction

Population aging has become an increasingly serious global problem. In recent years, the global older population has increased rapidly. It is estimated that by around 2050, the number of people aged 60 and older will reach 2 billion, accounting for more than 21% of the world's population [1]. Older people have a high prevalence of cognitive impairment. China has the largest older population in the world, and cognitive impairment has a significant social impact on demographic imbalance [2]. Research shows that there are 15.07 million people with dementia aged 60 and older in China, including 9.83 million with Alzheimer disease, 3.92 million with vascular dementia, and 1.32 million with dementia [3]. With the accelerated aging of Chinese society, the increase of brain diseases, such as stroke, Parkinson disease, and Alzheimer disease, has increased cognitive dysfunction in the population; this seriously affects national health and greatly increases the economic and mental burden on patients, their family members, and society [4]. The demand for cognitive function training and cognitive impairment prevention in families and society is increasing daily, so the search for simple and easy-to-implement cognitive ability training methods is of great scientific significance and practical value.

Extensive studies on human beings have shown that exercise and response training are beneficial to overall health and cognitive function, especially in the aging population. In 1979, the United States Public Health Service detailed the role of exercise in health promotion, and for the first time, elevated national physical activity to the level of the national health plan, making exercise and health promotion a research hot spot. Exercise helps to improve the health of older people, enhances physical functioning, and reduces the incidence of chronic diseases and disabilities [5]. Studies have shown that exercise and behavioral stimulation can increase neurotransmitters in the brain, decrease levels of oxidative stress and inflammation, increase cerebral blood flow, and modulate the hypothalamic-pituitary-adrenal axis, which in turn alters the prefrontal cortex and the temporal lobe, increasing the volume of the hippocampal gyrus [6-8]. This change can promote neural activation in the cerebral cortex, enhance synaptic plasticity, and, it is hoped, improve cognitive ability and motor coordination [9].

In addition, response training is of great significance in ameliorating cognitive impairment and delaying the occurrence of dementia and Alzheimer disease [10]. People with different physical abilities may receive different results from reactivity training. Previous studies have found that the plasticity of the brain can change, particularly among professional athletes who have received extensive physical training [11-13]. In particular, volleyball players performed better in the implementation of control tasks and visual-spatial attention processing tasks. The action observation network plays an important role in these tasks, with the upper parietal lobe and auxiliary motor area being positively correlated with anticipatory capacity [14,15].

However, most forms of exercise are not suitable for the older population due to physical limitations. Therefore, the design and development of a combination of muscle and balance function training is an effective way to improve muscle coordination, prevent falls, and improve the cognitive state of older people. With advancements in technology, cognitive training equipment used in the community or by families is being widely used, which can better meet the issues of accessibility and portability of cognitive training. This study uses smart equipment to train the visual-motor response abilities of volleyball players, ordinary college students, and older people. We use functional magnetic resonance imaging (fMRI) to visualize the characteristic brain regions involved in perception of movement across different physical functions and explore the effects of cognitive training on cognitive function and the mechanisms of brain plasticity. The aims of this study are as follows: (1) to compare the functional advantages and characteristics of the brain perceptual-motor system in volleyball players and ordinary younger and older people; (2) to explore the influence of visual-motor response ability training on cognitive function in people with different physical functions; and (3) to preliminarily confirm the efficacy and safety of exercise-based nondrug therapy in improving cognitive function.

Methods

Study Design

This is a prospective, single-center, open-label, controlled clinical trial conducted between January 2022 and December 2025. This study will recruit professional volleyball players, ordinary college students, and older people without any professional sports training. In total, 78 participants will be recruited at the Shanghai University of Traditional Chinese Medicine, China, via the university website or posters, with 26 participants in each group. All participants will undergo baseline assessments, including acousto-optic response time tests and fMRI scans. This will be followed by 2 weeks of visual-motor response training. After 2 weeks, the outcomes of the intervention will be evaluated (Figure 1).

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Figure 1. Study flowchart. ADL: Activity of Daily Living; fMRI: functional magnetic resonance imaging; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; MMSE: Mini Mental State Examination; SCD-Q9: Subjective Cognitive Decline Questionnaire–9.

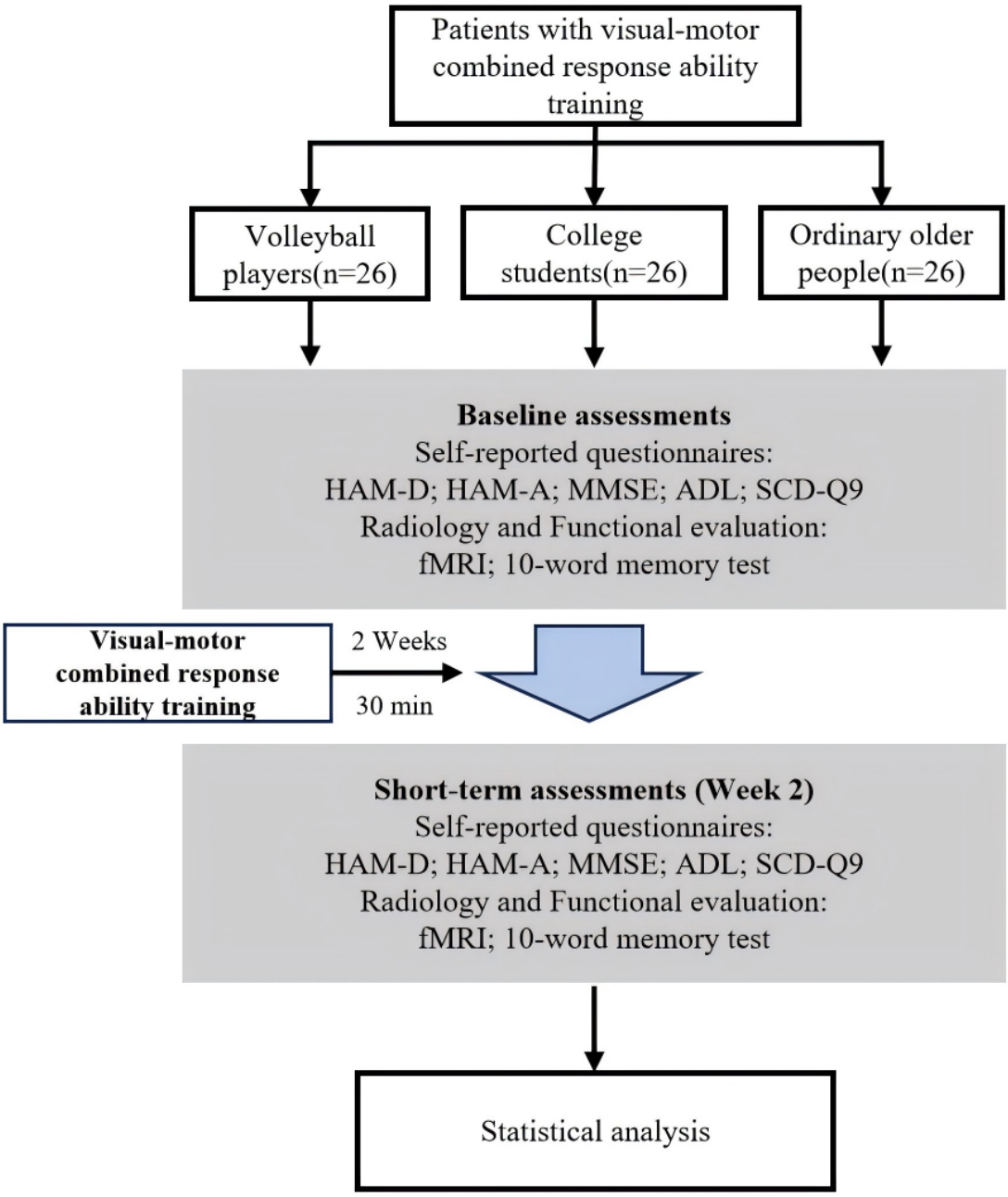

Participants

The participants in the athlete group will be recruited from the high-level volleyball team of Shanghai. The college students will be recruited from the Shanghai University of Traditional Chinese Medicine through posters on campus and advertisements in campus media. Participants in the older population group will be recruited from healthy older adults in the community; in-person outreach will be conducted in randomly selected neighborhoods in Shanghai to attract active participants. Within each group, an equally spaced sampling method will be used to determine the final participants in the study. Participants need to understand and agree to this study, voluntarily undergo preintervention assessment and 2 weeks of visual-motor combination response training, and sign an informed consent form.

Sample Size

Because of the exploratory nature of this study, it is impossible to estimate the total number of cases. Based on previous data, fMRI studies can be performed in groups of 12 participants with adequate statistical efficacy [16]. For the planned number of 20 participants in each group, if a 1-way ANOVA is used, it will be possible to detect a standardized mean-value effect (Cohen *d*) of 0.4, with a power of 80% and a significance level of 5% [17,18]. Assuming a loss to follow-up of 20%, the total sample size required for the study is 78 (n=26 in each group).

Inclusion Criteria

The fulfillment of the following conditions is a prerequisite for all participants: (1) meet the “Technical Grade Standard of Volleyball Players” issued by the General Administration of Sports of China and obtain a grade II title or higher; (2) vision

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or corrected vision of 1.0; (3) no history of mental illness, brain trauma, and other diseases that affect brain structure and function; (4) meet fMRI scanning conditions, such as not having metal implants in the body or claustrophobia; and (5) being right-handed. Volleyball players should be aged 18 to 23 years; college students should be aged 18 to 23 years and have no professional sports training; older adults should be aged 55 to 70 years, have no professional sports training, and have a physical condition that meets the basic research needs (including self-care and normal movement of limbs and joints).

Exclusion Criteria

Participants meeting any one of the following criteria will be excluded from this trial: (1) serious diseases of the heart and lung system; (2) diagnosis of mental illness, severe depression (suicidal tendency), or epilepsy; (3) metabolic systemic diseases, such as diabetes and uremia; (4) skeletal and muscle diseases, such as fractures, ligament injuries, severe arthritis, meniscus injuries, or spinal injuries; (5) hearing or visual impairment; and (6) use of drugs (eg, antiepileptic drugs, sedative drugs, and hypnotic drugs) that change the excitability of the cerebral cortex in the past 3 months.

Dropout Criteria

Dropout criteria for patients are as follows: (1) withdrawal from the study and (2) incomplete implementation of the treatment plan.

Suspension Criteria

If a patient develops other diseases or experiences serious adverse reactions during treatment, the trial will be discontinued by mutual decision of the participant and investigators.

Intervention

The implementation team of the intervention process includes a sports rehabilitation physician, a neurologist, a volleyball coach, a graduate student, and 2 undergraduate students. Before the formal intervention, the researchers were made familiar with the intervention equipment and intervention process through training. A between-group control design will be used with the same interventions. The 3 groups of participants will receive the same visual-motor response training for 30 minutes a day over 14 days. Response training will be completed with the help of gForceDual equipment and Neuro Rehab System (OYMotion). The participants download the Neuro Rehab System–based app and connect the gForceDual device to their mobile device through Bluetooth. During each training session, the gForceDual equipment will be secured to the transverse striation of the distal wrist of the participants' right upper limb, and its electrode will be attached to the ventral part of the palmar longus muscle, brachioradialis muscle, radial carpal flexor muscle, and ulnar carpal flexor muscle. The response sensitivity will be adjusted via the app, and the participants will be guided by visual information to carry out wrist dorsal extension and flexion. The speed adjustment function in the app will be set to divide the training speed into gears, with a total of 10 gears. The default setting is sixth gear during the intervention. If an older person cannot keep up with the response, the app will downshift through gears; conversely, if an athlete can adapt well to a high gear, the app will upshift the gear. The researchers will record electromyographic signals produced by dorsal extension and flexion of the wrist.

Outcome Measures

The aim of the study is to explore the functional characteristics of brain perceptions of movement and the cognitive changes in different groups after response ability training. The primary outcome is defined by differences in fMRI images of characteristic areas of the brain before and after the intervention. A Siemens Magnetom Verio 3.0T MRI system will be used for scanning before and after the intervention.

The secondary outcomes are as follows: acousto-optic response time, Hamilton Depression Rating Scale (HAM-D) [19], Hamilton Anxiety Rating Scale (HAM-A) [20], Mini Mental State Examination (MMSE) [21], Activity of Daily Living (ADL) Scale [22], Subjective Cognitive Decline Questionnaire–9 (SCD-Q9) [23], a 10-word memory test, and safety. At the beginning and the end of the intervention, all participants will be asked to fill in the test questionnaire with the assistance of the researchers. The EP 204 audio-visual reaction time measuring instrument (produced by the Science and Education Instrument Factory of East China Normal University) is used for acousto-optic response time. The instrument automatically presents auditory and visual (simultaneous 4-color light) stimuli. In each experiment, the number of light and sound stimuli is equal, and if the test is set to be repeated 20 times, then each stimulus will be presented 10 times in a random order. When the participant hears (or sees) the stimuli, they must lift their finger from the circular hole on the response keyboard. The instrument automatically records the time from the presentation of the stimulus to the time the participants lifts their finger from the circular hole on the response keyboard; this is defined as the reaction time for the sound (or light). During the experiment, if the participant does not put their finger back into the circular hole on the response keyboard, the instrument will automatically enter a waiting state until the participant puts their finger back and the next test can be performed. The 10-word memory test uses PowerPoint slides to have the participant read 10 words, presenting each word for 2 seconds. The participants will be then asked to recall the words out loud. The evaluator will check each correctly recalled word. A total of 3 reading and recall trials will be administered. The score will be the average number of words not correctly recalled over the 3 trials. HAM-D, HAM-A, MMSE, and SCD-Q9 are all scale-assessed and uniformly evaluated, and they will be used to assess a participant's psychological state. The ADL Scale will be used for participant baseline condition screening and assessment of the degree of improvement in mobility after treatment.

Adverse events are defined as any adverse experience that may be related to the trial treatment procedure that occurs during the course of the study. Any discomfort reported by the participants during the study will be carefully recorded.

Safety Measures

An excessively high gear or initial discomfort may cause dizziness, nausea, or fatigue in some participants during the audio-visual response training. During the training, research

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assistants will monitor the participants' status and provide medical assistance as needed. If a participant is unable to adapt to our training model, the training session will be promptly terminated, and follow-up medical counseling and assistance will be offered.

Statistical Analysis

All variables that can be measured directly will be analyzed descriptively by tabulating the empirical distributions. For continuous variables, mean (with SD), median, minimum, and maximum values will be documented. Classification variables will be recorded as incidence and percentage. Measurement data following a normal distribution will be analyzed with a 2-way repeated measures ANOVA. For intergroup factors, the participants will be divided into 3 groups, comprising athletes, young people, and older people. The intragroup factor will be evaluation time, which has 2 levels—before and after the intervention. The main effects and interactions among the 3 groups will be analyzed. For nonnormally distributed data, the Wilcoxon symbolic rank test will be used for intragroup analysis, and the Mann-Whitney *U* test will be used for intergroup comparison. The significance level of the statistical test is set at α=.05, and bilateral tests will be carried out. Differences in classification variables will be calculated using the χ^2 test. *P*<.05 will be considered statistically significant.

The differences in brain fMRI images will be analyzed by MATLAB (R2014a; MathWorks) and Statistical Parametric Mapping (version 12; UCL Queen Square Institute of Neurology) [24]. Based on the intergroup analysis of the resting-state amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) indices, we will perform a flexible-design ANOVA to characterize the individual samples at each time point. Analyses will include time main effects, grouping main effects, time × grouping interactions, and statistical parameter diagrams. The post hoc test mask will reflect differences in brain regions where *P*<.01 and voxel >10, as determined by the ANOVA results. The intergroup analysis of functional connections will be done using GRETNA (Neuroimaging Tools and Resources Collaboratory) [25]. The functional connection differences among the 3 groups will be analyzed with a 2-factor repeated measurement ANOVA, and the intragroup analysis will be conducted with a paired 2-tailed *t* test. A *P* value <.01 is considered to show statistical significance. BrainNet Viewer (Neuroimaging Tools and Resources Collaboratory) will be used to draw schematic maps of brain regions with significant differences.

Quality Control

All the researchers in this trial will receive a 5-day training course. Researchers involved in the treatment process will not be allowed to perform statistical analysis of the data. Data entry and statistical analysis will be the responsibility of professional researchers, and these participants will be unaware of the specific sources of data and the intervention process. The trial will establish an independent data monitoring committee, composed of 5 members, who will not participate in the operation of the trial and have no conflict of interest with the study. Members of the data monitoring committee will regularly review the research data to ensure the safety of participants and the reliability of the research data.

Ethical Considerations

The study will be conducted in accordance with the principles of the Helsinki Declaration and was approved by the review and ethics committee of the Shanghai Ethics Committee for Clinical Research on January 2, 2024 (ID: SECCR/2023-162-01). The study protocol has been registered on ClinicalTrials.gov and the Chinese Clinical Trial Registry (ID: ChiCTR2400079602). All participants will be aware of the potential risks and benefits of the study. All participants will provide informed consent and can opt out at any point during the study process. Use of participants' personal data will be prohibited for other purposes, and the data will be stored in specific cabinets. Treatment and medical advice will be provided at no cost to participants who experience accidental injuries in this study.

Dissemination of the Study Data

At the end of the study, a summary of the results will be provided to the participants. The results of the study will be published in peer-reviewed journals and presented at national and international conferences.

Availability of Data and Materials

The research data will be assigned a numeric code that can only be assessed by the specified researcher. The full dataset that can be used and analyzed at the end of the study can be accessed by contacting the corresponding author.

Results

As of September 11, 2024, we have completed the recruitment of all 3 groups of volunteers. We expect to complete data collection and analysis by February 2025.

Discussion

Principal Findings

This paper presents the protocol for a single-center, open-label, controlled clinical trial that will evaluate the effects of combined visual-motor response training on cognitive function to help patients recover and maintain quality of life. We aim to directly test the hypotheses that the perceptual-motor system of the brain of people with long-term exposure to combined visual-motor response ability training has a functional advantage compared to the general population and that combined visual-motor response ability training is effective in improving cognitive functioning in both the general population and the aging population. In addition, the trial will evaluate the effectiveness and safety of exercise-based nonpharmacological therapies when applied to improve cognitive function. This study highlights the importance of finding novel therapies for cognitively impaired populations. The implementation of exercise-based, nonpharmacological therapies is a potential option with profound implications for managing chronic diseases and improving health care in an aging society.

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Advanced cognitive functions, such as cognitive flexibility, working memory, and long-term memory, tend to decline with age after the age of 20 [26]. Cognitive aging is usually accompanied by atrophy in brain structures such as the caudate nucleus, cerebellar hemisphere, lateral prefrontal cortex, and hippocampal gyrus [27]. The results of several randomized controlled trials have shown that combined exercise and biofeedback-based training are effective in ameliorating cognitive impairment and improving physical functioning, memory, and executive function [28-31]. However, Griffen et al [32] confirmed through a randomized controlled trial that resistance exercise does not significantly improve cognitive function [32]. Other studies have had similar results, indicating that while exercise may improve overall cognitive functioning, it primarily enhances executive ability, with minimal impact on memory and social cognition [33,34]. Unlike the general population and the older population, improvements in cognitive functioning have long been demonstrated in athletes undergoing combined exercise and biofeedback training [35-37]. Therefore, differential findings prompted us to explore the effectiveness of visual-motor response training.

fMRI locates complex cognitive activities in the brain with high spatial resolution, providing a more accurate and objective view of brain information processing during exercise and identifying the brain regions involved in effective and reasonable information processing. ALFF is a relatively stable metric in fMRI sequences that responds to the low-frequency electrical activity of local neurons in the resting state [38]. ALFF and ReHo are used to identify neural networks throughout the brain [39]. Based on the assumption that a voxel is similar to its neighboring voxels over time, neural networks can be identified by evaluating and comparing the synchronization or similarity over time between each voxel in the region of interest and its neighboring voxels [39,40]. Unlike previous studies, we will not only use questionnaires and scales to assess the cognitive function of patients but also assess the changes in the functional structure of the brain by fMRI, which will make the evidence of the study more explicit. This exploratory study will attempt to open new horizons for subsequent trials. If the hypothesis is valid, combined visual-motor response ability training will replace exercise-only interventions as a new preventive measure and treatment method, which is significant for the current society with an aging population.

Strengths and Limitations

The study has some strengths. First, it used visual-motor response training rather than an exercise-only intervention, aiming to increase biofeedback and identify more effective measures for improving cognitive function. Second, we intervened with 3 groups with different training bases, physical functioning, and cognitive functioning to provide a broader perspective on the effectiveness of the intervention. In addition, this study simultaneously assessed changes in psychological status and functional brain imaging, providing a broader evidence base for the efficacy of the intervention. However, the study has some limitations. First, the study's intervention period is short, and it will not be known whether the intervention effect is significant over a 2-week period. The lack of randomized assignment in the study is also a limitation, as it can potentially affect the accuracy of the findings. Therefore, further studies with high evidence quality should be conducted in the future to better explore the efficacy of combined visual-motor response ability training.

Conclusions

This protocol outlines the design of a single-center, open-label, controlled clinical trial that evaluates the effects of a 2-week intervention with combined visual-motor response ability training on differences in characteristic brain regions in fMRI images, cognitive functioning, physical functioning, and social and psychological indicators. By examining the clinical effects of combined visual-motor response ability training, this study may provide an effective physical therapy for preventing cognitive decline, which is important for health care effectiveness.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The trial data will be publicly available for publication in international peer-reviewed journals, regardless of whether the results are positive or negative.

Conflicts of Interest

None declared.

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Abbreviations

ADL: Activity of Daily Living
ALFF: amplitude of low-frequency fluctuations
fMRI: functional magnetic resonance imaging
HAM-A: Hamilton Anxiety Rating Scale
HAM-D: Hamilton Depression Rating Scale
MMSE: Mini Mental State Examination
ReHO: regional homogeneity
SCD-Q9: Subjective Cognitive Decline Questionnaire–9

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Protocol

Combating Antimicrobial Resistance Through a Data-Driven Approach to Optimize Antibiotic Use and Improve Patient Outcomes: Protocol for a Mixed Methods Study

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Abstract

Background: It is projected that drug-resistant infections will lead to 10 million deaths annually by 2050 if left unabated. Despite this threat, surveillance data from resource-limited settings are scarce and often lack antimicrobial resistance (AMR)–related clinical outcomes and economic burden. We aim to build an AMR and antimicrobial use (AMU) data warehouse, describe the trends of resistance and antibiotic use, determine the economic burden of AMR in Uganda, and develop a machine learning algorithm to predict AMR-related clinical outcomes.

Objective: The overall objective of the study is to use data-driven approaches to optimize antibiotic use and combat antimicrobial-resistant infections in Uganda. We aim to (1) build a dynamic AMR and antimicrobial use and consumption (AMUC) data warehouse to support research in AMR and AMUC to inform AMR-related interventions and public health policy, (2) evaluate the trends in AMR and antibiotic use based on annual antibiotic and point prevalence survey data collected at 9 regional referral hospitals over a 5-year period, (3) develop a machine learning model to predict the clinical outcomes of patients with bacterial infectious syndromes due to drug-resistant pathogens, and (4) estimate the annual economic burden of AMR in Uganda using the cost-of-illness approach.

Methods: We will conduct a study involving data curation, machine learning–based modeling, and cost-of-illness analysis using AMR and AMU data abstracted from procurement, human resources, and clinical records of patients with bacterial infectious syndromes at 9 regional referral hospitals in Uganda collected between 2018 and 2026. We will use data curation procedures, FLAIR (Findable, Linkable, Accessible, Interactable and Repeatable) principles, and role-based access control to build a robust and dynamic AMR and AMU data warehouse. We will also apply machine learning algorithms to model AMR-related clinical outcomes, advanced statistical analysis to study AMR and AMU trends, and cost-of-illness analysis to determine the AMR-related economic burden.

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Results: The study received funding from the Wellcome Trust through the Centers for Antimicrobial Optimisation Network (CAMO-Net) in April 2023. As of October 28, 2024, we completed data warehouse development, which is now under testing; completed data curation of the historical Fleming Fund surveillance data (2020-2023); and collected retrospective AMR records for 599 patients that contained clinical outcomes and cost-of-illness economic burden data across 9 surveillance sites for objectives 3 and 4, respectively.

Conclusions: The data warehouse will promote access to rich and interlinked AMR and AMU data sets to answer AMR program and research questions using a wide evidence base. The AMR-related clinical outcomes model and cost data will facilitate improvement in the clinical management of AMR patients and guide resource allocation to support AMR surveillance and interventions.

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KEYWORDS

antimicrobial resistance; AMR database; AMR; machine learning; antimicrobial use; artificial intelligence; antimicrobial; data-driven; mixed-method; patient outcome; drug-resistant infections; drug resistant; surveillance data; economic; antibiotic

Introduction

Antimicrobial resistance (AMR) is among the greatest threats to global health and is predicted to become the leading cause of death by 2050 [1,2]. Mortality due to AMR will rise from 700,000 deaths to 10 million deaths annually if nothing is done to halt the current trends [3]. Indeed, in 2019, only 8 years from when these projections were made, 1.27 million deaths were attributed to AMR, higher than those due to HIV, malaria, and tuberculosis [2]. Moreover, 4.95 million deaths were associated with AMR [1]. If this trend continues unchecked, the world will confront a reality where many infectious diseases have “no cure and no vaccine” [4].

In addition, AMR has significant economic costs. The World Bank estimates that AMR could result in US $1 trillion in additional health care costs by 2050 and US $1 trillion to US $3.4 trillion gross domestic product losses per year by 2030 [5]. The impact of higher AMR is unlikely to be spread equally, with those more vulnerable likely to pay the highest price, as low-income countries suffer the biggest proportionate loss of population and economic output [4]. Low-income countries disproportionately bear the AMR burden [6]. For instance, the all-cause mortality in the review by the Antimicrobial Resistance Collaborators was highest in low-income countries: 27.3 per 100,000 in western sub-Saharan Africa (SSA) compared with 6.5 per 100,000 in Australasia [2].

Despite this worrying burden in sub-Saharan Africa, AMR data remain scant, and the systems to monitor and generate AMR data are underdeveloped. The region has a low Joint External Evaluation score of 53%, described as a voluntary, collaborative, multisectoral score to assess a country’s capacity to prevent, detect, and rapidly respond to public health risks whether occurring naturally or due to deliberate or accidental events [7]. Many of the countries in the region lack national action plans for AMR, alluding to AMR not being among their health priorities [8]. In contrast, some high-income economies of Europe and America had already instituted various regional and national AMR action plans as early as 2014 [9-12].

AMR is a natural phenomenon and tends to arise from enzymatic degradation, alterations in antimicrobial targets, or a change in membrane permeability to the antimicrobials, leading to a longer or no response to antimicrobial medicines [13,14].

Community-level drivers of AMR are diverse and enormous yet usually ignored in AMR control strategies. Among the antimicrobials, antibiotics are among the most abused due to their easier accessibility, lower cost, and relative safety compared with other antimicrobials [15]. Many people in the communities use nonprescription-based acquisition of antimicrobials from informal providers for both human and animal use [16]. Such providers are usually poorly trained, leading to wrong drug-pathogen matching, and are likely to be motivated by financial gains to offer suboptimal doses or stock substandard antimicrobials [17-19]. Drugs disposed of in this way find their way into the environment, interact with pathogens, and promote development of AMR in the environment [20]. There is also widespread use of antimicrobials in food-producing animals to treat and prevent disease or promote growth [21]. AMR drivers among European countries include human ambulatory consumption of antibiotics and per capita expenditure on health, accounting for 74% of AMR variation [19], accelerated by the misuse and overuse of antimicrobials; poor infection prevention and control; limited access to quality affordable medicines, vaccines, and diagnostics; lack of awareness; and poor enforcement of prescription regulations [1]. Overall, the drivers of AMR are similar across various World Health Organization (WHO) regions. Infections due to resistant microbes are more difficult to treat, spread more, and are of higher severity, resulting in increased morbidity, mortality, and cost of health care.

Antimicrobial misuse and overuse are the most critical drivers of AMR. For example, a review of Slovenia’s surveillance data showed that the prevalence of invasive *Streptococcus pneumoniae* resistant to penicillin decreased by 47.1% following a 32.8% decline in the area under the receiver operating curve (AUC) [22]. In the same study, high consumption of clarithromycin resulted in the selection and predominance of macrolide-resistant *Streptococcus pneumoniae*. Therefore, given the little global effort to develop new antimicrobials, the control of misuse and overuse presents the best chance to tackle AMR, more so in resource-limited settings.

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AMR is not without consequences to the individual and health systems; for example, the impact of methicillin-resistant *Staphylococcus aureus* on the management of hospital-associated infections with severe complications, prolonged hospital stays, mortality, and morbidity reduces the clinical and economic outcomes for patients [23-26].

Treatment of AMR infections necessitates the use of more expensive and potentially toxic medications, results in longer hospital stays, and ultimately increases the cost of treatment [1]. In addition, resistant infections pose a risk to specialized medical procedures—such as organ transplants, surgical operations, and cancer chemotherapy—denying many of these critically needed services [1].

Grudlewska-Buda et al [27] described the rise of AMR in major foodborne pathogens (*Campylobacter* spp., *Salmonella* spp., *Escherichia coli*, and *Listeria* monocytogenes) associated with the declining effectiveness of β-lactams, sulfonamides, tetracyclines, and fluoroquinolones and highlighting the risk of resistant zoonotic infections.

Although AMR is often framed as a "silent pandemic," recent figures demonstrate that this is not accurate, especially considering that its mortality and morbidity are gradually increasing with the drivers of high antibiotic use in animals and humans [28,29].

Furthermore, disability-adjusted life years (DALYs) are also increasing, indicating a reduction in life expectancy and quality of life [30]. Despite the importance of these parameters in characterizing the AMR burden, they are not routinely available, hindering comprehensive efforts to control the spread and effects of AMR.

The proposed project therefore aims to close 4 important gaps in AMR surveillance and interventions: (1) improve access to AMR and antimicrobial use and consumption (AMUC) data; (2) describe the AMR and antibiotic prescribing patterns, changes in the patterns over time, and associated factors; (3) determine the economic burden of excessive antibiotic use and the effect on hospital budgets; and (4) develop a machine learning model to predict the clinical outcomes of bacterial infectious syndromes caused by resistant pathogens. We hypothesize that this study will contribute to AMR and AMUC surveillance, identification of priority antibiotics to target for stewardship interventions, determining the cost implications, and identifying characteristics of individuals more likely to have poor clinical outcomes related to AMR so as to guide clinical decisions and health system planning in the allocation of scarce resources.

The overall objective of the study is to use data-driven approaches to optimize antibiotic use and combat antimicrobial-resistant infections in Uganda.

The specific study objectives are to (1) build a dynamic AMR and AMUC data warehouse to support research in AMR and AMUC to inform AMR-related interventions and public health policy, (2) evaluate the trends in AMR and antibiotic use based on annual antibiotic and point prevalence survey (PPS) data collected at 9 regional referral hospitals over a 5-year period, (3) develop a machine learning model to predict the clinical outcomes of patients with bacterial infectious syndromes due to drug-resistant pathogens, and (4) estimate the annual economic burden of AMR in Uganda using the cost-of-illness approach.

Methods

Study Design

The study will use different study designs for each of the 4 specific objectives.

For objective 1, we will conduct a data curation project aimed at building an AMR and AMUC data warehouse from prior and future AMUC surveys and routine AMR surveillance data from patients with bacterial infectious syndromes.

For objective 2, we will use a retrospective study using annual antibiotic surveys (AAS) and PPS data to determine the trends in antibiotic use and AMR using data accrued over a 5-year period.

For objective 3, we will conduct a modeling study in which a machine learning model will be developed to predict the clinical outcomes of patients with bacterial infectious syndromes due to resistant pathogens.

For objective 4, we will conduct a prevalence-based, cost-of-illness, descriptive study to assess the economic burden of AMR in Uganda by determining the average cost per AMR case.

Study Settings

This study will use data already accrued under the Fleming Fund project or abstracted from clinical and other records at the Fleming Fund project–supported surveillance sites during the study period. The Fleming Fund Country Grant project (2018-2026) is a health system strengthening project to improve AMR surveillance at 9 regional referral hospitals (RRHs) in Uganda. The surveillance sites include Arua RRH, Gulu RRH, Lira RRH, Soroti RRH, Mbale RRH, Jinja RRH, Masaka RRH, Mbarara RRH, and Kabale RRH. The RRHs are spread across the different regions of the country (Figure 1) and are the first level of specialized health care in Uganda with specialist health workers and services.

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Figure 1. Geospatial representation of the human health antimicrobial resistance surveillance sites in Uganda. RRH: Regional Referral Hospital.

Study Population

The study will use records of patients with bacterial infectious syndromes attending the surveillance sites for health care.

Inclusion Criteria

All medical records of patients with bacterial infectious syndromes attending the major hospital wards including the medical, surgical, pediatric, gynecology, and maternity wards and the outpatient department are eligible for the study. Further, records related to medicines and supplies procurement as well as human resources and utility bills will be targeted by the study for the cost-of-illness evaluation.

Exclusion Criteria

For the AMR data, records without antimicrobial susceptibility test (AST) results will be excluded from the study.

Study Procedures

Case Ascertainment

The patients with bacterial infectious syndromes will be identified from the diagnoses made by the attending clinicians and recorded in the patients' clinical records. The resistant infections are determined from the AST results of the cultured samples showing resistance to at least one antibiotic.

Data Sources

Data will be abstracted from the procurement and human resources records and the clinical records of patients with bacterial infectious syndromes attending Arua RRH, Gulu RRH, Lira RRH, Soroti RRH, Mbale RRH, Jinja RRH, Masaka RRH, Mbarara RRH, and Kabale RRH.

Data Elements Collected

The treatment-related variables collected include referral status, age, gender, occupation, ward, residence, prior antibiotic treatment, date of admission, date of sample collection, sample type, diagnosis, and AST results. ASTs were performed using the Kirby-Bauer disc diffusion method according to the updated Clinical Laboratory Standards Institute M100, 30th, 31st, 32nd, and 33rd editions [31-34]. The AMUC variables collected include ward, number of prescribed antibiotics, number of prescriptions, number of injectable antibiotic prescriptions, prescriptions by generic name, prescriptions according to

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guidelines, prescriptions with appropriate diagnosis, cultures requested, prescriptions based on AST, missed doses, patients with missed doses, referrals, days spent on the ward, and number of hospitalizations in the last 90 days.

The clinical parameters to be collected will include temperature, blood pressure, level of antibiotic resistance, antibiotic type, diagnosis, prior antibiotic exposure, site of infection, duration of symptoms, timing of effective antimicrobial treatment, and medical comorbidities, while the clinical outcomes will include duration of hospital stay, time to clinical improvement, time to negative cultures, mortality, medical complications, disability, and the cost of treatment.

The cost-of-illness variables will include direct medical costs (personnel, medical supplies, drugs, laboratory tests, and patient out-of-pocket costs), direct nonmedical costs (recurrent expenditures such as utility bills), capital expenditures (such as expenditures on hospital or health facility infrastructure), patient transportation, and patient upkeep while seeking medical care. Indirect costs will include productivity losses due to illness-related absenteeism, reduced work hours, disability, or premature mortality, as well as informal care provided by family members or friends.

Data Abstraction Procedure

AMR data are collected during the routine care of patients with bacterial infectious syndromes at the surveillance sites. The process includes the identification of patients requiring sampling, drawing of the sample using appropriate techniques, transportation of the sample to the laboratory, sample integrity assessment, sample processing, recording of results on paper and in electronic data systems, and reporting of results for clinical management of the patients. On the other hand, AMUC data are collected through quarterly PPS and AAS. During PPS, data are abstracted from the records of all patients on the wards for at least 24 hours; AAS data are abstracted from 100 systematically selected records of patients seen at a particular ward in the last year. During PPS and AAS, data are collected from 6 hospital units including the outpatient department and medical, surgical, gynecology, pediatric, and maternity wards. The clinical outcome and cost-of-illness data will also be abstracted from the clinical, procurement, and human resource records alongside the PPS data over 3 quarters. The clinical outcome data will be collected from the 5 hospital units including the medical, surgical, gynecology, pediatric, and maternity wards.

The laboratory request form, laboratory results register, WHONET, and African Laboratory Information System are used to collect the AMR data, while AMUC data are collected using the WHO PPS tool and a standardized Microsoft Excel tool based on the WHO/ International Network for Rational Use of Drugs drug use indicator for the AAS data. The PPS tool is built in Open Data Kit (ODK), an Android app with offline capabilities installed on mobile smart devices including mobile phones and tablet computers and used for collecting, managing, and using data. The abstraction tool was pretested to evaluate the validation rules in ODK and to ensure the completeness, reliability, and validity of the tools. The AAS data are collected annually over a period of 2 weeks for each facility, while the PPS data are collected quarterly over a period of 2 days for each facility. The clinical outcome and cost-of-illness data will be collected quarterly using data abstraction forms built in REDCap [35].

Hospital pharmacists who are supervised by the senior pharmacists and doctors abstract the data after being trained on the data collection tools and the approach for collecting antimicrobial use (AMU) data. The supervisors review each completed form immediately after collection, and the finalized form is submitted to the server, after which it cannot be edited further. Appropriate use is assessed using the current Uganda Clinical Guidelines.

Sample Size

Objective 1

All patients with bacterial infectious syndromes who access the surveillance sites for routine medical care are the primary source of the AMR data. The project has data on 12,366 patients over the last 4 years. We have also collected AMUC data on 13,500 patients over an 8-year period. We will also supplement these data with PPS data from 18,000 patients from AAS, giving a total of 31,500 patient records. As more data are gathered using the aforementioned data gathering techniques, the sample size will continue to increase for the periodic assessments.

Objective 2

The main outcome is the trends in the prevalence of antibiotic prescriptions. We used the following formula for sample size estimation for a proportion:

$$sample\ size = p(1-p)\times(z/e)^2\times n/[(1+(n-1))\times r]$$

where z is the z score corresponding to the desired confidence level (in this case z=1.96 for a 95% CI), p is the estimated prevalence of antibiotic use (using 74% as the prevalence determined by Kiggundu et al [36] in 13 hospitals in Uganda), e is the margin of error expressed as a proportion (assumed to be 0.03), n is the number of clusters (in this case, the 9 surveillance sites), and r is the estimated intracluster correlation coefficient. The prevalence was similar across our surveillance sites; therefore, we used r=0.9 [36]. The sample size for each round of survey was determined as $0.74\times(1-0.74)\times(1.96/0.03)^2\times9/((1+(9-1))\times0.9) = 903$.

Medical records of 100 patients from each of the major units including medical, surgical, pediatric, gynecology, and obstetrics/maternity wards and the outpatient department were selected for the AAS using systematic sampling. The nth patient was identified by dividing the total number of patients seen per year in each ward by 100 (the sample size). Therefore, 600 medical records were selected at each of the 9 surveillance sites during each survey, resulting in 27,000 (600×9×5) records in 5 years. On average, 20 to 30 records from each ward are included in the PPS, and 100 to 150 records from the 5 wards are considered for each of the 9 hospitals. Therefore 9000 (9×5×20×10) to 13,500 (9×5×30×10) records have been used for the last 10 PPS carried out to date. A total of at least 40,500 (27,000+13,500) records will provide the data for this evaluation. Therefore, the accrued data are sufficiently powered

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to estimate the prevalence and its trends over the evaluation period.

Objective 3

Generally, there is no fixed sample size for machine learning algorithms but the more data, the better the accuracy of the model at predicting the outcome. However, for prediction models, the rule of thumb for the sample size is to have at least 10 events for each predictor variable [37,38]. Therefore, the 18 variables that will be abstracted as outlined in the Data Elements Collected section would require at least 18×10=180 records. However, the study will utilize all available data from patients with bacterial infectious syndromes due to resistant and susceptible bacterial infections accrued through the quarterly data abstraction. We will use 70% of the data to train, while 30% of the data will be used to test the ability of the machine learning algorithm to predict the clinical outcomes of the patients with bacterial infectious syndromes.

Objective 4

Cost-of-illness or economic burden evaluations, unlike cost-effectiveness studies, are not typically based on a particular sample size [39]. The study will therefore utilize data from all patients with bacterial infectious syndromes due to resistance and those with susceptible bacterial infections and other related costs accrued through the quarterly data abstraction for this AMR economic burden evaluation.

Statistical Analysis

Objective 1

Expected Outcome

The expected outcome is a refined and dynamic AMR and AMUC data warehouse that is linkable to other databases to enable collaborative research and programming for decision-making, policy formulation, and quality improvement projects.

Building the Data Warehouse

Building the data warehouse will comprise all data curation steps including cleaning, merging, cataloging, and integration. The data variables will be aligned to national and international AMR and AMUC indicators for easy alignment to contemporary literature. The curated data will be uploaded to a secure repository, which will be continuously updated as more data are accrued. The data repository will be housed in the African Centers of Excellence in Bioinformatics and Data Intensive Science (ACE) High-Performance Scientific Computing (HPC) IT infrastructure at the Infectious Diseases Institute (IDI). The HPC has 40 nodes, of which only 20 nodes are currently in use. The other nodes will be connected once demand increases. Each node has 32GB of RAM and 16 cores. It also has 120TB of Synology storage supported by a 30KVA inverter system that provides extra uptime in the event of a power outage and a monitoring system that monitors HPC systems for power surges and internet outages. It has a voltage stabilizer and batteries that last for up to 2 hours to 3 hours. Access to the HPC system is via a password-protected user account that is associated with an active email address, and all first-time users of the HPC must undergo a mandatory training session. Access to the servers will be via a Secure Shell (SSH) protocol to respective login nodes with access to compute nodes via the job scheduler (Slurm). User data directories and shared data directories will be backed up to enable recovery in the event of data loss.

The warehouse will adhere to the FAIR principles: (1) findable: where the data are easy to find by humans and computer and machine metadata standards and tags based on a defined criteria; (2) accessible: found data will be accessible through appropriate authentication and authorization; (3) interoperable: the accessed data would be interactable with other data sets through different applications and workflows for analysis, storage, and processing; and (4) reusable: the data will be well-indexed so that it can be replicated or combined with other data sets to interrogate wide research, surveillance, and stewardship questions.

Access to the data warehouse will be managed by role-based access control for the warehouse developers, where system administrators will assign user roles and manage access for each role. For the researchers and program investigators, the process to access the data in the warehouse will include submitting a data request form and the concept for intended use. The data request form will specify the type of data and the specific variables required. A scientific committee will review the concept and will recommend whether access should be granted. Before the data are accessed, the researcher or investigator will sign a data use agreement defining the terms under which the data will be used.

Objective 2

The objective 2 outcome variables will be derived as indicated in Table 1.

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Table 1. Variables to assess objective 2 regarding antimicrobial use: measuring the impact on selected drug use indicators.

Indicator	Indicator definition		Disaggregation
	Numerator	Denominator	
Proportion of prescriptions with at least one antibiotic	Total number of antibiotic prescriptions	Total number of patients included in the sample	• Gender of the patients • Age of the patients
Proportion of prescriptions with an injectable antibiotic	Total number of antibiotic prescriptions with an injectable antibiotic	Total number of antibiotic prescriptions	• Gender of the patients • Age of the patients
Proportion of antibiotic prescriptions with a diagnosis that does not warrant an antibiotic	Number of antibiotic prescriptions with a diagnosis that does not warrant an antibiotic	Total number of antibiotic prescriptions	• Gender of the patients • Age of the patients
Proportion of antibiotic prescriptions for upper respiratory infections	Total number of antibiotic prescriptions for upper respiratory tract infections	Total number patients diagnosed with a URTI[a]	• Gender of the patients • Age of the patients
Proportion of antibiotic prescriptions[b] in accordance with current treatment guidelines	Total number of antibiotic prescriptions in accordance with UCG[c] 2016/2023 (antibiotic, dose, and frequency)	Total number of antibiotics prescriptions	• Antibiotics prescribed by WHO[d] AWaRe[e]
Proportion of antibiotic combinations with overlapping coverage	Total number of antibiotic combinations with overlapping coverage	Total number of antibiotic prescriptions	• Antibiotics prescribed by WHO AWaRe

[a]URTI: upper respiratory tract infection.

[b]Prescription involving at least one antibiotic.

[c]UCG: Uganda Clinical Guidelines.

[d]WHO: World Health Organization.

[e]AWaRe: Access, Watch, Reserve.

Trend analysis will be used to derive the slope coefficient for the trends in the proportion of each antibiotic and level of AMR over a 5-year period for the 9 RRHs. The trends will be disaggregated by age, gender, bacterial infectious syndromes, wards, and bacteria types, among others.

Objective 3

Expected Outcomes

The expected outcome is a machine learning model to predict the clinical outcomes (length of stay, mortality, time to clinical improvement, mortality, and disability) of patients with bacterial infectious syndromes due to resistant pathogens using clinical parameters and demographics. The model will be deployed as a web or mobile device app-based physician assistant that can be used as a point-of-care aid in the management of patients with AMR.

Building the Machine Learning Algorithm

The abstracted data will routinely be curated and standardized; the diagnosis will be reported per the International Classification of Diseases 11 [40]. Several classification machine learning algorithms including logistic regression, artificial neural networks, support vector machines, random forest, and AdaBoost will be trained, and their performance will be evaluated by computing their accuracy, F_1 score, precision, recall, and the AUC using a confusion matrix. The clinical outcomes of patients with bacterial-resistant infections will then be compared with those with susceptible infections using a chi-square test for categorical variables and nonparametric or parametric tests for the continuous data depending on the distribution of the data. The pipeline and derived algorithms will be stored on secure servers with access limited to only authorized personnel using the role-based access control model.

Objective 4

Expected Outcomes

The main outcome of this cost-of-illness analysis will be the cost per AMR case from societal and payer (government) perspectives.

Analysis of Outcome Variables

Data to parameterize the model will be obtained from the data warehouse and published gray literature. The activity-based (micro-costing) technique will be used to estimate the cost of diagnosis using the cost information in records related to the procurement of medicines, including antibiotics; AMR-related investigations; and clinical care of patients with AMR at the 9 surveillance sites.

The micro-costing technique decompounds each service (ie, diagnosis and treatment options) into the inputs and quantity required to provide it. The best price for each input will then be found and multiplied by the amount needed. The sum of all inputs provides a good estimate of the cost per intervention. Given that the analysis will be conducted from both the societal and payer (government) perspectives, direct medical costs, direct nonmedical costs, and indirect (productivity) costs will be included.

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Estimating the Direct Medical Costs of AMR

To estimate direct medical costs, we will use the available databases of AMR data at IDI and the Ministry of Health (MOH). These data will aid in estimating the resource use and costs of identified AMR cases. Data on health resource use—drugs, laboratory tests, and other supplies—will be obtained from the literature to estimate the type and quantity of resources, which will then be multiplied by the unit costs obtained from the available price catalogs (from either Uganda's Joint Medical Stores or Management Sciences for Health). Regarding personnel-related costs, we will use the opportunity cost of paid time for all health workers. Data on revised salaries will be obtained from the MOH or Ministry of Public Service to improve the precision of wage estimates.

All records related to the procurement of medicines including antibiotics, AMR-related investigations, and health care of patients with AMR at the 9 RRH surveillance sites over the 5-year period will be reviewed, and data will be abstracted. All the volumes and related costs of medicines procured, AMR-related investigations, and health care by the surveillance site over the evaluation period will be considered. All National Medical Stores invoices and delivery notes for each delivery cycle over the 5-year period will be reviewed, and data will be extracted for the volume of drugs delivered to the surveillance site, issued to the different units, and the unit cost of each medicine. In addition, information on clinical care including length of stay, investigations, and other medicines will be extracted. The parameters of interest will include volume and types of medicines and the cost of the medicines; types and cost of investigations; time of stay in the hospital; other costs of health care of patients with AMR, hospital medicines, investigations, and other sundries for clinical care; and total budget.

Estimating the Direct Nonmedical Costs of AMR

The overhead and recurrent costs related to outpatient and hospital treatment of AMR complications will be estimated from the available data in the MOH and IDI databases and the WHO-CHOICE (World Health Organization Choosing Interventions That are Cost-Effective) database for Uganda. All capital costs will be annualized using a discount rate of 3% with an assumed lifespan of 30 years for buildings, 5 years for computers, and 10 years for furniture to estimate the actual economic and opportunity costs. Other costs, such as transportation and upkeep for patients, will be obtained from the literature if unavailable at the MOH or IDI.

Estimating the Indirect Costs of AMR

Productivity losses for patients and their caregivers due to AMR-related morbidity and mortality will be estimated using the friction cost approach. The friction cost approach estimates the friction period—the time it takes an organization to replace an absent worker due to morbidity or mortality—and largely depends on the country's unemployment rate [41,42]. We will sum up the lost time spent in transit to hospitals or health facilities (for patients and caregivers), seeking care, convalescing, and being admitted to a hospital (for patients and caregivers). The time lost will be valued at Uganda's gross domestic product per capita as a proxy for wages, given the unavailability of these data in Uganda. The friction period accounts for absenteeism (actual absence from work) and presenteeism (available but not at the full productive level, thus affecting the workflow). Given Uganda's unemployment rate of 12% [43], we will benchmark the published and gray literature to estimate the friction period for Uganda and indirect costs associated with AMR [42]. All future costs will be discounted at an annual rate of 3%, as recommended by the second panel on cost-effectiveness in health and medicine [44].

The societal cost will be the summation of direct medical costs, direct nonmedical costs, and indirect costs, while the payer cost will only include direct medical and direct nonmedical costs. The total cost for antibiotics, essential medicines, and other AMR-related health care costs will be derived from the product of the volume of the items consumed, duration of the provision of services, and the unit cost of each.

The main study outcome will be the cost per AMR case from societal and payer (government) perspectives. This will be the sum product of the quantity of resources needed to treat 1 AMR case and its unitary costs. All costs will be converted to US dollars using the bank of Uganda official exchange rates, while costs from the literature will be inflated to the reporting calendar year using the local consumer price indices. Given the ever-present uncertainty surrounding parameter estimates, we will assign different distributions to each model parameter using the 95% CIs and standard errors if available and, if unavailable, using a ±50% range. Monte Carlo simulation will be used to generate 1000 iterations of the model results; these new estimates will provide the cost of an average case of AMR with a 95% credibility range around the estimated cost. We will also perform a 1-way sensitivity analysis—presented as a tornado diagram—to determine which variables greatly influence costs. All analyses will be programmed in Microsoft Excel and supported by R software (version 4.3.0).

Ethical Considerations

This study was approved by the IDI Research Ethic Committee (IDI-REC-2023-67:), which also granted a waiver of consent. The study was also approved by the Uganda National Council for Science and Technology (UNCST - HS3690ES). No participants' identification information will be used in the dissemination or publication of the study results.

Results

The study received funding from the Wellcome Trust through the Centers for Antimicrobial Optimisation Network (CAMO-Net) in April 2023. As of October 28, 2024, we completed data warehouse development, which is now under testing; completed data curation of the historical Fleming Fund surveillance data (2020-2023); and collected retrospective AMR records for 599 patients that contained clinical outcomes and cost-of-illness economic burden data across 9 surveillance sites for objectives 3 and 4, respectively.

Discussion

This study will create a data warehouse and analyze AMR and AMUC rates and trends using data science and traditional

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statistical approaches. We will also determine the associated societal costs in Uganda and develop a machine learning model to predict AMR-related clinical outcomes. The dearth of data on AMU and AMR trends, clinical outcomes related to AMU and AMR, and the economic burden of AMR on the health care system is a major hinderance to policy formulation, stewardship interventions, and resource allocation.

The proposed data warehouse will help organize the AMR and AMUC data, making it accessible and linkable to other databases to allow deeper data mining to answer research and program questions through individual and collaborative research. This will contribute to one of WHO's AMR surveillance plan pillars of generating knowledge through generation of quality data and evidence [45,46]. On the other hand, a concise description of AMR and AMU trends is critical to inform stewardship interventions to combat the escalating burden of AMR. Surveillance reports estimate that the AMR burden including mortality is disproportionately borne by SSA, but this has not been fully evaluated due to the scarcity of data in the region [47]. Further, optimization of AMU is important to address one of the biggest drivers of AMR in this setting—the overuse and misuse of antimicrobials [16,48,49]. By exploring AMU trends and the influencing factors, the study will inform strategies to address this problem.

Since the institution of the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015, Uganda, like many other countries in SSA, has developed its national action plan on AMR and started generating AMR and AMU surveillance data [50]. However, the AMR data generated lack information on certain aspects of the AMR burden including clinical outcomes (eg, disability and mortality) and the AMR economic burden [30]. Moreover, the few reports indicate that the DALYs for those who survive AMR are higher [51] and might equal to those of influenza, tuberculosis, and HIV combined [30]. This limits the optimization of clinical care for patients with AMR as well as national planning of AMR programs and guidance for resource allocation. This study will use machine learning algorithms and cost-of-illness estimation approaches to fill these critical gaps in the Uganda AMR surveillance data.

Our study's strength lies in its focus on critical gaps currently limiting AMR surveillance in SSA and its multipronged approach to address the gaps including data science and economic evaluation approaches. This will provide information based on a wide and robust evidence base to inform AMR clinical management and control policies. The study is limited by the lack of a qualitative assessment of the gaps, which would have provided a comprehensive overview of the drivers of AMR and better informed the policy formulation process. Further, the use of retrospective data will pose challenges regarding missing variables and the inability to control for confounders for the observed outcomes, while the economic evaluation will impute some variables from the literature that are not routinely collected, which may bias some of the conclusions.

In conclusion, the data warehouse will promote access to AMR and AMU data to answer AMR program and research questions using a wide evidence base. The AMR-related clinical outcomes and AMR economic burden data will facilitate improvement in clinical management of patients with AMR and guide resource allocation to support AMR surveillance and interventions.

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Data Availability

Data supporting this study are available from the IDI AMR Data Warehouse at [52]. Access to the data is subject to approval and a data sharing agreement due to legal or ethical reasons.

Conflicts of Interest

None declared.

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Abbreviations

AAS: annual antibiotic surveys
ACE: African Centers of Excellence in Bioinformatics and Data Intensive Science
AMR: antimicrobial resistance
AMU: antimicrobial use
AMUC: antimicrobial use and consumption
AST: antimicrobial susceptibility test
AUC: area under the receiver operating curve
CAMO-NET: Centers for Antimicrobial Optimisation Network
DALY: disability-adjusted life year
FCA: friction cost approach
GLASS: Global Antimicrobial Resistance and Use Surveillance System
HPC: High-Performance Scientific Computing
IDI: Infectious Diseases Institute
MOH: Ministry of Health
ODK: Open Data Kit
PPS: point prevalence survey
RRH: regional referral hospital
SSA: sub-Saharan Africa
SSH: Secure Shell
WHO: World Health Organization
WHO-CHOICE: WHO Choosing Interventions That are Cost-Effective

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Protocol

Using a Device-Free Wi-Fi Sensing System to Assess Daily Activities and Mobility in Low-Income Older Adults: Protocol for a Feasibility Study

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Abstract

Background: Older adults belonging to racial or ethnic minorities with low socioeconomic status are at an elevated risk of developing dementia, but resources for assessing functional decline and detecting cognitive impairment are limited. Cognitive impairment affects the ability to perform daily activities and mobility behaviors. Traditional assessment methods have drawbacks, so smart home technologies (SmHT) have emerged to offer objective, high-frequency, and remote monitoring. However, these technologies usually rely on motion sensors that cannot identify specific activity types. This group often lacks access to these technologies due to limited resources and technology experience. There is a need to develop new sensing technology that is discreet, affordable, and requires minimal user engagement to characterize and quantify various in-home activities. Furthermore, it is essential to explore the feasibility of developing machine learning (ML) algorithms for SmHT through collaborations between clinical researchers and engineers and involving minority, low-income older adults for novel sensor development.

Objective: This study aims to examine the feasibility of developing a novel channel state information–based device-free, low-cost Wi-Fi sensing system, and associated ML algorithms for localizing and recognizing different patterns of in-home activities and mobility in residents of low-income senior housing with and without mild cognitive impairment.

Methods: This feasibility study was conducted in collaboration with a wellness care group, which serves the healthy aging needs of low-income housing residents. Prior to this feasibility study, we conducted a pilot study to collect channel state information data from several activity scenarios (eg, sitting, walking, and preparing meals) using the proposed Wi-Fi sensing system continuously over a week in apartments of low-income housing residents. These activities were videotaped to generate ground truth annotations to test the accuracy of the ML algorithms derived from the proposed system. Using qualitative individual interviews, we explored the acceptability of the Wi-Fi sensing system and implementation barriers in the low-income housing setting. We use the same study protocol for the proposed feasibility study.

Results: The Wi-Fi sensing system deployment began in November 2022, with participant recruitment starting in July 2023. Preliminary results will be available in the summer of 2025. Preliminary results are focused on the feasibility of developing ML models for Wi-Fi sensing–based activity and mobility assessment, community-based recruitment and data collection, ground truth, and older adults' Wi-Fi sensing technology acceptance.

Conclusions: This feasibility study can make a contribution to SmHT science and ML capabilities for early detection of cognitive decline among socially vulnerable older adults. Currently, sensing devices are not readily available to this population due to cost and information barriers. Our sensing device has the potential to identify individuals at risk for cognitive decline by assessing their level of physical function by tracking their in-home activities and mobility behaviors, at a low cost.

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KEYWORDS

Wi-Fi sensing; dementia; mild cognitive impairment; older adults; health disparities; in-home activities; mobility; machine learning

Introduction

Background

Mild cognitive impairment (MCI) is underdetected in the community. About 15% of individuals with MCI progress toward Alzheimer disease (AD)/AD-related dementias (ADRD) after 2 years [1]. Older adults with health disparities, defined here as those with low socioeconomic status and racial minorities, are at increased risk of developing AD/ADRD due to poorly managed health conditions, structural racism, and barriers to health care access [2-4]. The United States federal poverty level definition of low income for a single-person household is US $15,060 in 2024. Resources to assess functional deterioration and detect the risk of progression to AD/ADRD are further limited in this population. Research suggests that functional decline begins years before clinical symptoms of AD/ADRD [5]. Therefore, innovative, accessible, and easy-to-use approaches are imperative to capture these functional changes early, intervene before symptoms arise, and provide quality care [6].

Older adults with MCI are at greater risk for physical function disability, such as limitations in activities of daily living (ADLs), instrumental activities of daily living (IADLs), and mobility behaviors [7-10]. For example, cognitive impairment affects the ability to perform and complete daily activities such as meal preparation and using electronic devices (eg, microwaves, computers, and telephones). Individuals with MCI are also more likely to be less mobile and engage in sedentary behaviors [8,11,12]. Limitations in daily activities threaten older adults' quality of life and well-being [13]. It is essential to monitor daily activities and mobility to capture early cognitive decline for a timely intervention. Failure to recognize early impairment in a timely manner is likely to lead to disability and adverse health outcomes such as falls, institutionalization, decreased quality of life, and mortality.

With the emergence of novel smart home technologies (SmHT) and advanced data analytics, it is possible to sense motion, presence, and other behavioral indicators continuously and with less intrusion into the daily lives of older adults. SmHT provides an objective assessment of activity and mobility that is not subject to the effects of recall bias or memory impairment [14-16]. Although these solutions have effectively identified digital health indicators, such as gait speed, variability over time [17], or sleep disturbance [18], these sensors cannot label specific activity types. The ability to identify and differentiate human activities will be improved when algorithms to disambiguate the data are fully available. Wearable sensors have been proposed to obtain objective, high-frequency, and remote monitoring [19-21]. The data collected from these sensors are fed into complex machine learning (ML) models (eg, long short-term memory and Gaussian Naive Bayes classifier) to recognize ADLs and identify anomalies [22-24]. However, these devices are not easy to use by those with MCI [25]. Moreover, these devices typically necessitate the use of a smartphone app for data syncing. However, it is worth noting that a significant portion of older adults facing health disparities may not possess smartphones, lack proficiency in using smartphone apps even if they own them, or have limited IT literacy [26,27].

Alternatively, Wi-Fi signal–based sensing solutions could mitigate this issue. We propose an ML-based data processing method for extracting discriminative activity features from Wi-Fi signals. Human activities incur changes in the signal received by a nearby Wi-Fi device [28], resulting in distinct patterns of wireless signals surrounding us. There are several advantages of using Wi-Fi signal–based sensing. First, it enables device-free wireless localization and activity recognition [29]. It is possible to sense the location and activity of an individual without equipping them with any wearable device. Second, this sensing technology allows for more accurate capturing of daily activities and mobility, even in situations with poor lighting or obstructed camera views, due to its capability to penetrate walls or furniture. Third, compared to the classic methods for tracking individuals and their activities (eg, global positioning system, inertial measurement unit, or video surveillance systems), this technology is lower-cost, less intrusive, and simpler to deploy [28,29]. Therefore, it holds promise for application in scalable methods for monitoring the types and levels of daily activities and mobility among older adults.

Wi-Fi sensing technology has been tested in the context of activity and gesture recognition, object sensing, and localization [30-34]. Using these Wi-Fi-sensing–based capabilities, researchers started to develop methods to apply Wi-Fi sensing to health care such as motion recognition and localization, fall detection, smoking behavior monitoring, and vital signs monitoring (eg, heart rates and breathing) [35]. Despite the potential of this technology as a low-cost in-home monitoring tool, this technology has primarily undergone deployment and assessment within controlled laboratory environments, often involving activities carried out by volunteers following specific prompts, and often within relatively brief timeframes [36]. To our knowledge, no study exists that tests its use for everyday functioning assessment in a natural setting with older adults over time. Review studies indicate that there is room for improvement in Wi-Fi health care sensing such as multisubject sensing, implementation of the setup, fine-grained motion sensing, and the need for massive datasets for training for deep learning model development [30,35]. Therefore, our goal is to develop and evaluate an innovative, affordable Wi-Fi sensing–based, nonintrusive system for tracking activity and mobility in a real-life setting involving older adult residents of

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low-income senior housing. This will be achieved through a week-long study in which each individual will engage in activities as per their daily routine. This research also shows the feasibility of using a collaborative transdisciplinary team approach to integrate engineering into behavioral science and ADRD research to provide tools to address MCI risk assessment challenges among older individuals with limited resources.

This proposed research aims to tackle unmet needs and address brain health challenges affecting older adults with health disparities. This research leverages our team's multidisciplinary skillsets related to sensor-based mobility assessment (nursing, JC [14,37]; nursing, IP-A [38,39]), Wi-Fi sensing signal processing and ML/artificial intelligence (engineering, EB [34,40,41]), technology acceptance (nursing, JC [42,43]), and health and wellness in older adult residents of low-income housing (nursing, PP [44,45]; nursing KF [45,46]). The use of a nurse-driven method to guide ML training for Wi-Fi sensing technology-based assessment could help address the gap that exists regarding transferring clinical knowledge from nursing to engineering in SmHT solution development [47]. This nurse-driven method will be useful for generating clinically relevant ground truth that is associated with real features of older adults' functional health. The outcomes of this study will offer valuable insights into the feasibility of implementing this innovative, cost-effective sensing solution to gather significant data on in-home activities and mobility.

Aims

This is a feasibility study to develop a novel channel state information (CSI)–based device-free, low-cost Wi-Fi sensing system and associated algorithms for localizing and recognizing different patterns of in-home activities and mobility in older adult residents of low-income housing with and without MCI. The proposed study aims to (1) test the feasibility of developing a novel CSI-based device-free Wi-Fi sensing system using ML classification to identify in-home daily activities and mobility, and (2) explore the acceptability of the Wi-Fi sensing system and implementation barriers in the low-income housing setting.

Methods

Study Design

This is a feasibility testing study to develop and implement a low-cost Wi-Fi sensing–based nonintrusive activity and mobility assessment system.

Ethical Considerations

Institutional review board approval has been granted on January 30, 2023 (Virginia Commonwealth University; HM#20024269). Potential participants are required to provide written informed consent to install the Wi-Fi sensing technology and other related devices in the home. Participants are informed that they have the ability to opt out of the study at any time. Except for the videotaping data of in-home activities used as ground truth, all other data will be anonymized. We provide a US $50 gift card at baseline and another US $50 at the end of the sensor-based monitoring period.

Preliminary Work

Our prior work with the Wi-Fi sensing system involved (1) experiments in a controlled setting, and (2) a pilot study in a natural setting.

First, the team conducted a series of preliminary experiments in a controlled setting. We asked a volunteer to engage in 10 distinct activities within an apartment (Table 1), with the floor plan shown below (Figure 1). The individual completed each of these activities once throughout the course and repeated this course 20 times. We used three Transmitter (TX)-Receiver (RX) pairs as marked in Figure 1. The devices were positioned to have each activity be performed close to the line-of-sight of at least one TX-RX pair so that good sensing accuracy could be achieved. For example, kitchen activities (Activity ID #1-3 in Figure 1) are best monitored by TX1-RX1 pair, while dining room and bathroom activities (#4-6) and living room activities (#7-10) can be best sensed by TX2-RX2 and TX3-RX3 pairs, respectively. We collected CSI data from each of these activities and developed simple deep learning models for detecting these activities through classification. We used data from the first 10 courses for training the ML model and the remaining 10-course data for testing the model.

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Table 1. Preliminary accuracy of ML[a] model for detecting 10 in-home activities.

Activity type and number	Preliminary accuracy (%)
Kitchen activities	93.8 (using TX1-RX1)[b]
#1: Washing dishes at the sink	96.7
#2: Cooking on stove top	00.4
#3: Opening and closing the refrigerator door	93.5
Dining room and bathroom activities	100 (using TX2-RX2)
#4: Writing in a notebook at the dining table	100
#5: Opening and closing closet door	100
#6: Washing hands in a bathroom	100
Living room activities	80.8 (using TX3-RX3)
#7: Walking up and down stairs	86.2
#8: Writing on the desk	67.5
#9: Sitting on the sofa	83.8
#10: Walking around	77.3

[a]ML: machine learning.

[b]TX: transmitter and RX: receiver.

Figure 1. The floor map of the environment used and the activities performed during preliminary experiments. TX: Transmitter; RX Receiver (see Table 1 to see labels for activities #1-10).

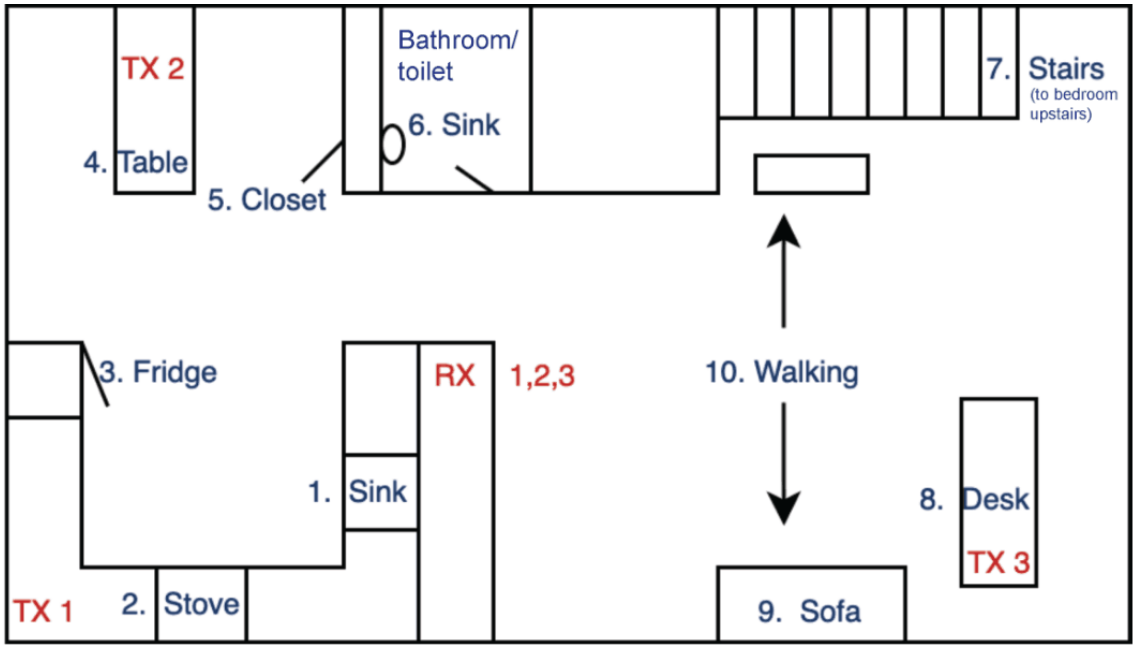

Table 1 shows the preliminary accuracy values of ML model–based in-home activity detection. Our results showed that the model identified the kitchen activities with 93.8% accuracy, dining room and bathroom activities with 100% accuracy, and living room activities with 80.8% accuracy. We found that the lower accuracy in identifying living room activities was mostly due to a confusion of classification between activity #8 and activity #9. These activities shared similarities, such as limited body movements, and their locations were relatively close to each other. It is anticipated that this confusion can be resolved by gathering more data from these activities and strategically placing additional TX-RX pairs closer to their locations. Even though the model was based on a limited set of data, these preliminary results show that the proposed system is promising.

In the second phase, we conducted a pilot study with two older adult residents of low-income housing. The sensing system was deployed for about 5-7 days in each residence and tracked in-home activities (eg, cooking, eating, and opening a refrigerator) and mobility behaviors (eg, entering the apartment and entering a bedroom). Figure 2 shows one participant's apartment floor plan with the Wi-Fi sensor setup.

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Figure 2. A participant's floor map of a one-bedroom apartment with the Wi-Fi sensor setup.

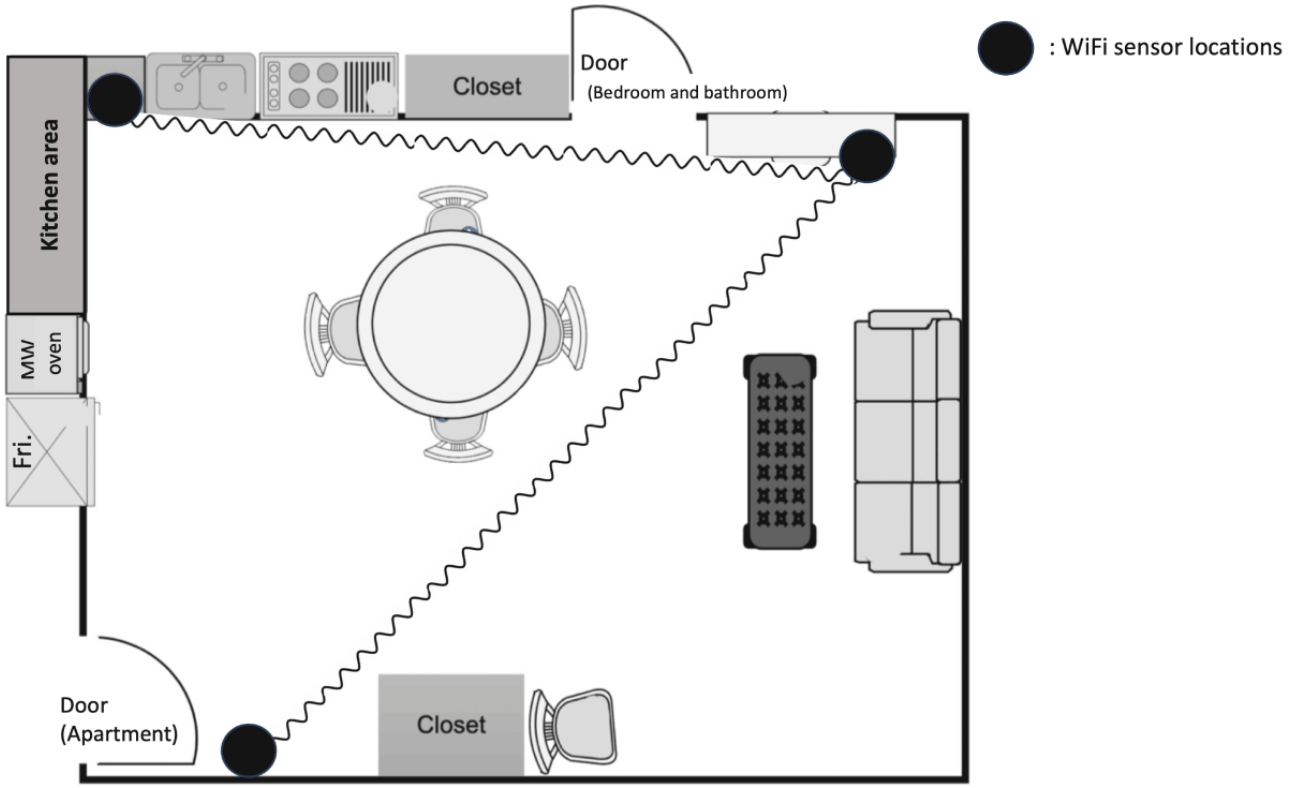

This pilot study demonstrated the successful deployment of the Wi-Fi sensing system in real-world environments of older adults, recruitment feasibility, and acceptance of the technology among the participants [48]. We developed an initial ML model to establish the accuracy of activity detection using preprocessed raw data and video-based ground truth. The model, based on the data from this participant, achieved 68.8% accuracy in recognizing six different activities, such as entering an apartment, entering a bedroom, opening a refrigerator, exiting an apartment, exiting a bedroom, and kitchen activities. Figure 3 shows the spectrogram images obtained from these activities.

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Figure 3. Spectrogram images obtained from six different activities of the first participant.

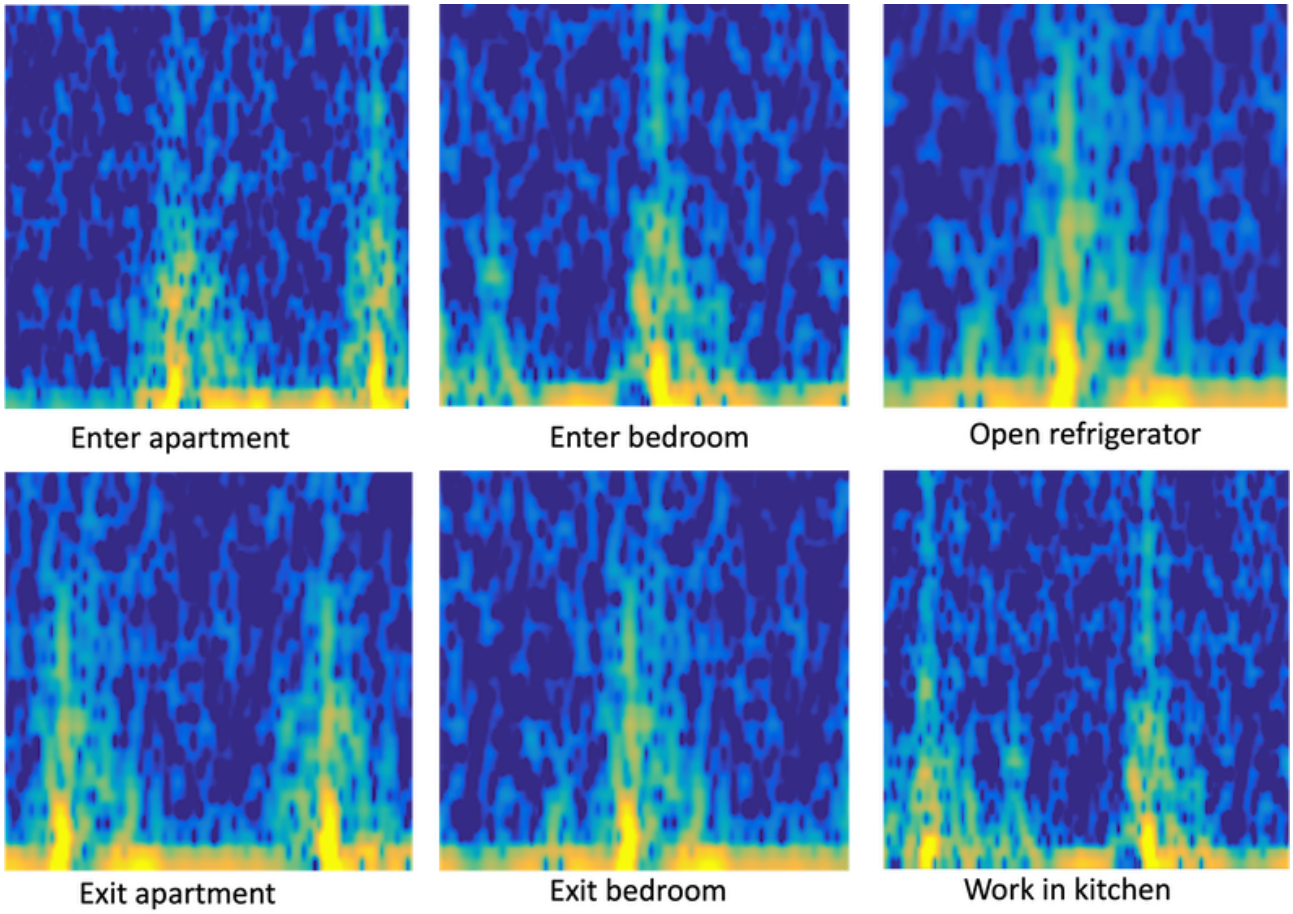

To ensure participant privacy throughout the pilot study, we implemented several measures. First, participants were instructed to wear clothing while in the monitored areas, such as the living room and kitchen, minimizing any potential for privacy breaches. Second, during the informed consent process, we ensured that participants would not bring any other visitors during the monitoring period. Additionally, during the annotation process of activities on video recordings, any footage depicting naked bodies was promptly identified and removed. These steps were taken proactively to maintain the privacy of our participants, particularly considering the sensitive nature of activities that may occur in areas, such as the bathroom and bedroom, which were deliberately excluded from sensor and camera deployment.

Participants and Recruitment

For this study, the sensing system will be installed over a week in the apartments of 10 older adults with MCI and 10 older adults without MCI. The age criterion for defining older adults varies, but adults 65 years and older are typically considered older adults by the US Census Bureau and Medicare. However, we decided to choose the sample with an age criterion older than 60 years to include a broader pool of individuals with varying levels of physical and cognitive function given that cognitive impairment can begin before age 60 [49]. Textbox 1 lists inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥60 years
- Living alone in low-income senior housing in the greater Richmond area, Virginia, that is subsidized by the US Department of Housing and Urban and other sectors
- Non–mild cognitive impairment (non-MCI) group, determined by the Montreal Cognitive Assessment (MoCA) score≥24; MCI group (n=10), determined by the MoCA score<24 and≥18

Exclusion criteria

- Severe visual or hearing impairment
- Severe motor disturbances (eg, wheelchair-bound and neurodegenerative diseases)
- Having a pet
- Inability to speak and understand English

The Mobile Health and Wellness Program (MHWP, previously known as the Richmond Health and Wellness Program) at Virginia Commonwealth University School of Nursing is the source of collaboration and research subjects for the proposed project [2]. MHWP is an interprofessional wellness care program for independent-living seniors at low-income housing facilities. MHWP coordinates with local services to provide health education and assessments at 5 low-income housing facilities in Richmond, Virginia, United States. We will recruit participants from these sites. Recruitment will be conducted via multiple mechanisms using institutional review board–approved materials, site information sessions, direct referrals from the MHWP staff, and study flyers.

Data Collection Procedures

Initial Contact and Screening Process

If interested, older adults will be encouraged to contact the study coordinator via telephone or in person. During the initial contact, the potential participants will be provided an overview of the study and screened to ensure they meet eligibility criteria. Further details about the study will be explained, and the study staff will answer any questions that participants have at that time. At all times, we will emphasize the voluntary nature of participation and the ability to withdraw without consequence.

Baseline Data Collection (Visit 1)

Following informed consent, we will administer questionnaires to assess participants' demographics, physical function, and psychosocial health. We will then ask the participants for a set of daily activities they usually perform in their living spaces such as where they sit (eg, couch and dining table), eat, lie down, prepare meals, use the computer or tablet (if any), and how much time they usually spend in each room and out of the home.

Wi-Fi Sensing System Installation (Visit 2)

Depending on the floor plan and the locations of the activities to be sensed, we will deploy the sensing system using as many TX-RX pair devices as needed to ensure each activity is in the line-of-sight of at least one TX-RX pair. Figure 4 shows how a typical Wi-Fi sensing system works. The sensing system will be left for a week at home to collect data for evaluating the system. To obtain ground truth values, we will place video cameras in several locations in the apartment (except the bathroom and bedroom to protect privacy) to monitor all tracked activities accurately. Once the evaluation period ends, we will use these recordings to label activities in the CSI data based on their timing.

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Figure 4. Overview of a typical Wi-Fi sensing system. CSI: channel state information.

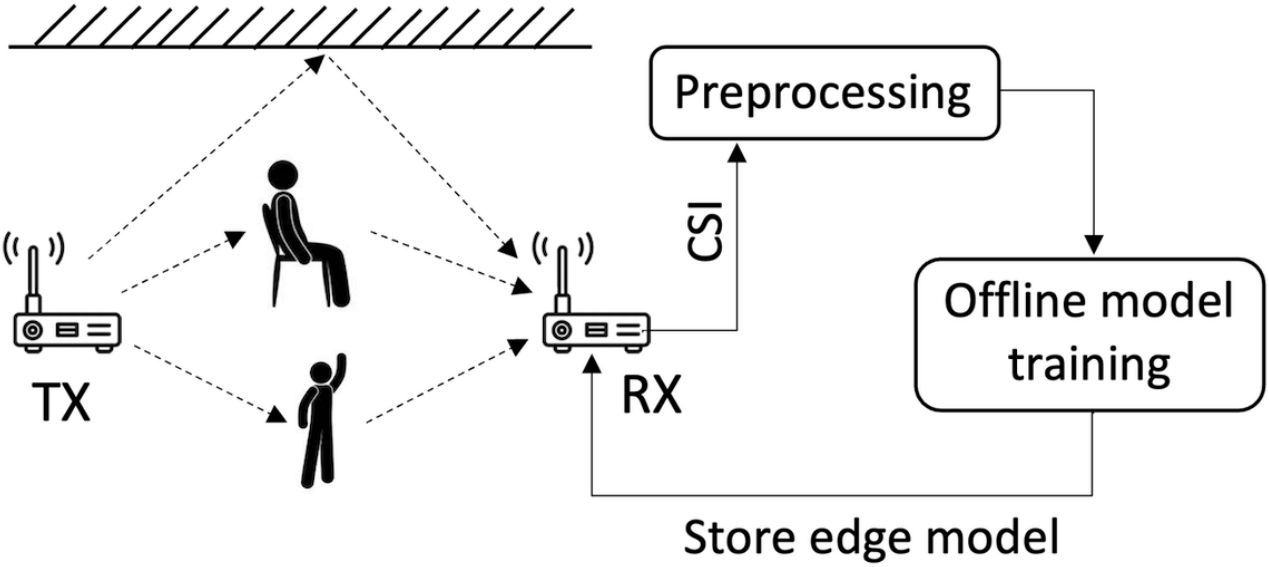

Sensor Removal and Exit Interviews (Visit 3)

Approximately one week after the sensor-based monitoring starts, the sensing system and video cameras will be removed. The collected data will be used to evaluate the system's accuracy by comparing the Wi-Fi sensing data with ground truth values. During this visit, we will conduct an individual qualitative interview to explore their perceptions and attitudes toward the sensing system. Specifically, informed by the Unified Theory of Acceptance and Use of Technology [50], we will assess perceived usefulness and behavioral intention to adopt a Wi-Fi sensing system [51]. The interviews will also provide feasibility outcomes, such as implementation barriers (eg, privacy and security concerns) and facilitators (eg, health monitoring needs, peer influence, and cultural values), and recommended changes for future system deployment. Textbox 2 shows semistructured qualitative interview questions we developed.

Textbox 2. Semistructured qualitative interview script.

- Please tell me two things you liked and two things you wondered (or "worried") about the sensor devices (cues: comfortable or uncomfortable, nervous, worried, and confused).
- Thinking back to the time when you heard about this study, what made you decide to participate in this study? Did you have any concerns about privacy, being monitored, or your information being breached and shared without your agreement?
- In general, what concerns did you have about the sensor devices? (cues: being monitored, inappropriate sharing of data, maintenance issues, etc)
  - Did you have any privacy concerns about the video cameras? If so, would you explain further?
  - (If the participant mentioned an abstract term, such as "privacy," "confidentiality"): Could you tell me specifically what types of things or examples you were thinking about when you said "privacy"?
- How often did you think about these devices? Do you think these devices have changed the way you carry out your daily activities? (cues: behaving differently, leaving out more frequently, doing more exercise, etc) If so, in what way? What activities have changed?
- How would the people around you react if you used these devices at home or if they saw them?
  - Why do you think they would react that way?
- Would you like to be able to turn the sensor system on and off depending on your preferences at any given time?
- This sensor system generates data about the timing, duration, and frequency of your daily activities and movement and shows how active you are in your home. For example, cooking, washing dishes, eating, sitting on the couch, sitting at the desk, walking, etc. Would this type of data have any usefulness for you?
- Would you like to see the data from the sensor system about your activity?
  - Would you be willing to share this data with your family? Would you explain why or why not?
  - How about friends and health care providers? Why and why not?
- Would you like to have this system if it were available in the future? Why or why not?
- We've already touched on privacy issues. Can you think of any other issues you ran into while you were living with these devices?
- Are there any other thoughts you would like to share about this technology or this research study?

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Data Processing and Analysis

Wi-Fi Sensing–Based ML Model Development

The collected CSI data and its labels will be used to develop an ML model. For the ML model, we will initially consider a lightweight dense neural network classifier architecture in order to fit the model in the low-memory ESP32 devices. However, for performance comparison, we will also consider developing more complex ML models (eg, convolutional neural networks, recurrent neural networks, and long short-term memory) with a different number of hidden layers. From the ML model, several Wi-Fi sensing–based metrics will be extracted such as the daily number and duration of each of the selected in-home activities and mobility behaviors.

Table 2 shows examples of activity features that will be captured by Wi-Fi sensing technology. These activities are categorized into IADL, ADL, or mobility. The majority of activities listed under the daily activities category in Table 2 relate to IADL. For instance, "Sitting in the dining table" may indicate engagement in "writing" or "technology device use" within the IADL context, or it may signify "eating" within the ADL context. Activities listed under the mobility behaviors category are specifically categorized as life-space mobility-related actions.

Table 2. Examples of anticipated activity and mobility features to extract and analyze from Wi-Fi sensing data.

Category and activity type	Definition
Daily activities	
Fridge time	The first moment the person touches the door to open it and actively performs fridge activity (eg, shuffling items around in the freezer)
Sink use	The start and end time of standing at the sink or faucet use time
Sitting in the dining area	The start and end time the body touches the dining chair and gets off the chair
Cooking	The start time and end time of stove use or microwave use
Phone use	The time the person starts using a phone or tablet (eg, text, app use, and phone call) and the time the person stops
Mobility behaviors	
Entering apartment	The time the person opens the front door and to the end time the person closes the door to get into the apartment
Exiting apartment	The time the person opens the front door and the time the person closes the door to exit
Entering a private area (eg, bedroom or bathroom)	The time the person passes a bedroom or bathroom door or threshold to enter a private area
Exiting a private area	The time the person passes a bedroom or bathroom door or threshold to exit from a private area
Sitting on sofa	The start and end time the body touches the sofa and gets off the sofa (sitting position, does not include the lying position)
Lying on sofa	The start time as the time the participant lies horizontally and end time as the time the participant returns to a sitting position
Other	
Second person	The time the person appears and disappears from space

Qualitative Interviews

Interview data will be analyzed using thematic analysis [51] and inductive coding method [52] to obtain insights into user perceptions, needs, barriers, and concerns that could influence the sensing system adoption and implementation in the future, especially in the low-income community setting. Audio files will be transcribed verbatim by a professional transcriptionist. Transcripts will be coded line-by-line by the analysis team (JC and IP-A). The team will conduct the initial analysis independently identifying significant statements from transcripts to develop codes. The codebook will then be developed collaboratively through regular meetings. Once the codebook is refined, the transcripts will be analyzed independently again by the coding team. The team will then meet to reach a consensus on the coding structure and develop related thematic categories. Data will be grouped and reviewed for trends, patterns, and ideas that provide insight into older adults' attitudes and perceptions of the sensor system. The analysis will be organized into an expanding list of themes arising from content, concepts, and descriptive categories. In order to ensure credibility, transferability, dependability, and confirmability, we will keep field notes, reflexive journaling, and audit trail and have team debriefings to discuss our reflections [53].

Table 3 shows specific methods for achieving each study aim.

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Table 3. Study aims and specific methods and their focus to achieve each aim.

Aim and method	Focus
Aim 1: to test the feasibility of developing a novel CSI[a]-based device-free Wi-Fi sensing system using ML[b] classification to identify in-home daily activities and mobility	
Ground truth data annotations ML model development	Evaluation of the accuracy of Wi-Fi sensing–based ML models in activity detection
Screening and enrollment log analysis	Recruitment feasibility
Aim 2: To explore the acceptability of the Wi-Fi sensing system and implementation barriers in the low-income housing setting	
Qualitative interviews	Wi-Fi sensing technology acceptance, privacy concerns, and factors leading to technology implementation

[a]CSI: channel state information.

[b]ML: machine learning.

Results

This project was funded in June 2023. Participant recruitment began in July 2023. We screened 10 individuals and obtained informed consent from 6 older adults. Four others either changed their minds before or during the consenting process. Among the 6 individuals who consented, 5 individuals were enrolled in the study and completed all the study activities. Recruitment and data collection is ongoing. We expect preliminary results to be available in the summer of 2025.

Discussion

Study Significance and Future Research

This study will investigate the feasibility, accuracy, and acceptability of the new sensing system in community-dwelling older adults with health disparities that can characterize and quantify daily activities in a real-world setting while also being discreet, affordable, and requiring minimal user engagement. Crucial to the successful implementation of the Wi-Fi sensing system to support older adults, a number of initial development stages are necessary. The proposed research fills the gap by experimenting with the system in the living environments of older adults and providing insights into the technology implementation in the community. This project has the potential to address unmet needs and brain health challenges among low-income older adults with chronic illnesses, disabilities, and social determinants of health.

Privacy Considerations for Community-Engaged Artificial Intelligence/ML Development Research

Given the historical distrust within the community, particularly among African American and low-income populations, toward academia, the health care system, and researchers, it is crucial to address privacy concerns transparently. In this study, we took deliberate steps to ensure privacy by refraining from installing sensors and video cameras in sensitive areas such as the bathroom and bedroom. This decision was made following consultations with the MHWP team to uphold privacy safeguards and facilitate the recruitment process. We aimed to respect the privacy and dignity of participants while still gathering valuable data on perceptions of novel sensing technology, acceptability, feasibility, and implementation facilitators and barriers within underrepresented communities.

ML Model Generalizability

There is a concern about the transferability of an ML model developed based on a small number of participants. There are solutions to generalize models that can provide an initial high accuracy with datasets from new people not used for training. This includes federated learning–based training of collected data from multiple individuals involved in training data collection. In our previous work [40], we shared results based on a federated learning approach and showed that we can obtain a subject-independent ML model. Moreover, with further training of this pretrained model using a few more datasets from new participants, we can customize it to this person and get much higher accuracy.

Our long-term goal is to implement this system in independent living facilities, including low-income housing, as a safety monitoring and home assessment tool for preventing further functional decline and coordinating value-based services for health and day-to-day management. This marks a crucial initial step toward early detection of MCI and the coordination of care efforts to delay the progression to AD/ADRD in older adults facing health disparities. If successful, we envision the potential application of the Wi-Fi sensing system across a broader spectrum. The system will ultimately improve the ability to assess functioning and capture early decline in community-dwelling older adults.

Limitations

This project is a pilot study that will be performed with a small sample of community-dwelling older adults. The demographics of the study sample are not representative of other groups of older adults. Another limitation of this study is that it uses video recordings as ground truth, which could raise privacy concerns among participants. Therefore, in the future, we will explore alternative methods for obtaining ground truth data beyond video-based approaches. This may involve using various types of sensors, such as contact sensors and force sensors, attached to objects within the environment. Additionally, Wi-Fi signals can potentially be sniffed from outside of the building by malicious actors to some degree. However, this will not release any information regarding the study participant's activities

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without knowing the ML model that is trained to recognize these activities from signals. Our goal is to observe a level of accuracy from the proposed device-free sensor system that is very close to the ground truth. In case of unexpected results, we will consider collecting more training data, optimizing the locations of TX and RX devices, applying additional filtering on Wi-Fi signals, and increasing the hidden layers of the ML model.

Conclusions

This pilot study is poised to make a valuable contribution to SmHT science and ML capabilities for early detection of cognitive decline particularly among socially vulnerable older adults, because sensing devices are not readily available to this population due to cost and information barriers. Our passive sensing device has the potential to identify individuals at risk for cognitive decline by assessing their level of physical function by tracking their in-home activities and mobility behaviors. The cost-effectiveness of the Wi-Fi sensing system will enhance its overall utility and adoption in underserved low-income communities. Our future plans involve (1) using the obtained results to evaluate the Wi-Fi sensing system across a wide range of populations and contexts, encompassing diverse socioeconomic groups, as well as individuals with varying degrees of AD/ADRD; (2) evaluating the impact of the Wi-Fi sensing system use on patient and caregiver outcomes, such as functional changes, care decision-making, and resource planning; and (3) determining the effective way of sharing the collected data with essential stakeholders (eg, older adults, family caregivers, health care providers, and social workers).

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Authors' Contributions

JC conceptualized the project, secured funding, administered and coordinated the project, secured a recruitment site and resources, and led the process of manuscript writing and revision. IP-A and EB conceptualized the project, secured funding, and participated in manuscript writing and revised the manuscript. EB developed a Wi-Fi sensing system, analyzed the Wi-Fi sensing data, and validated the system’s accuracy. PP and KF assisted the team in identifying recruitment sites and recruiting participants. All authors except for PP reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADL: activities of daily living
ADRD: Alzheimer disease–related dementia
CSI: channel state information
IADL: instrumental activities of daily living
MCI: mild cognitive impairment
MHWP: Mobile Health and Wellness Program
ML: machine learning
SmHT: smart home technology

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Protocol

Development of a Mobile App for Occupational Stress Screening Among Female Workers: Protocol for an Exploratory Sequential Design Study

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Abstract

Background: Occupational safety hazards include physical, chemical, ergonomic, biological, and psychological hazards. Technological innovation in screening for occupational stress, especially among female workers, is needed to improve their health and productivity.

Objective: This research is being conducted to obtain a prediction model of work stress through a questionnaire instrument that includes stressors and symptoms based on the transactional model, as well as measurement of work stress through a mobile app that can be used anywhere.

Methods: The research is conducted in 3 stages: qualitative research, quantitative research (cross-sectional), and mobile app development. Data were collected from companies located in Jakarta, Indonesia. The sample was chosen based on purposive sampling. For the quantitative research (n=430), logistic regression analysis was used.

Results: We are developing a work stress screening instrument for female workers, which includes stressors and symptoms based on the transactional model, in the form of a digital platform so that female workers can undertake the examination anywhere without interfering with working hours or home duties. This research was funded in January 2024 and qualitative data collection began in February 2024. Quantitative data were obtained in March 2024; the number of respondents in the qualitative stage was 6, and in the quantitative stage it was 430. The work stress screening app is in the development stage and will be launched at the same time as the data collection is performed so we can examine the respondents' perspectives on the use of the app.

Conclusions: This study analyzes the prediction of work stress to help female workers screen for work stress. Workers who are detected as experiencing work stress will be educated using an algorithm programmed in the app.

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KEYWORDS

mobile app; study protocol; occupational stress; female workers; stress; screening; worker; app; safety hazards; technological innovation; ergonomic; psychological hazards; mobile health; digital platform; algorithm

Introduction

The promotion of safety and preventative health is done through the creation and implementation of national policies, systems, and programs on occupational safety and health; a national system should implement appropriate measures to protect all workers, especially workers in high-risk sectors and vulnerable groups, such as informal-economy workers, migrant workers,

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and young workers or women. In designing national systems, the prevention recommendations should use a gender-sensitive approach to protect both women and men [1]. Stress is an external or internal stimulus that produces a compensatory biological response and can trigger or aggravate many diseases or pathological conditions [2]. Occupational stress has a significant adverse effect on workers' well-being, productivity, and performance and is becoming a major concern for both individual companies and the overall economy [3]. Female workers have special needs, and this has been the basis for the emergence of special regulations for them, such as the right to menstrual leave, the right to miscarriage leave, the right to maternity costs, the right to breastfeed after childbirth, and the right to special facilities [4]. Stress theory has evolved, but fundamentally, it can be categorized into three approaches: (1) the stimulus (stressor) stress model, (2) the response stress model, and (3) the transactional model [3,4]. The use of apps for occupational stress screening can help workers screen on the go, thereby reducing the impact on professional workload, increasing cost-effectiveness, and encouraging tactics for self-examination [5]. Progress in the field of occupational stress is based on attention to the issue of measuring occupational stress [6]. Past research has observed that multiple roles, lack of career advancement, discrimination, and stereotyping are factors that create stress among women, confirmed that women report higher levels of stress than men, and concluded that female entrepreneurs feel more stress than their male counterparts [7]. The inability to spend sufficient time for family and friends, child care, and children's education are considered highly stressful by both male and female entrepreneurs. It has been observed in Nigeria that obtaining annual leave or help from colleagues as coping strategies for organizational and personal stress are most widely used by female employees of commercial banks [8,9]. In some workplaces, women are still considered supplementary breadwinners for the family, so they are given lower wages than men, even when the workload and type of work are the same [9]. The annual cost of mental health problems is estimated to be more than €135 billion (US $145 billion) in the European Union (5% of gross domestic product), between US $150 billion and US $300 billion in the United States, and CAD $50 billion (US $35.9 billion) in Canada [10]. Occupational stress is a significant problem in occupational health, involving enormous costs for workers, employers, and governments. The European Agency for Occupational Safety and Health has recorded that more than US $550 million is lost each year in the United States because of workdays being missed due to stress. The Labor Force Survey also reported a US $11.3 million loss due to missed workdays among 487,000 employees in the United Kingdom in 2013 and 2014 [11].

This situation can be prevented by conducting mental health–related screening and comprehensive occupational stress screening among female workers. There is no existing occupational stress screening instrument specifically designed for female workers, even though they have a higher risk of experiencing occupational stress and mental health problems. The World Health Organization recommends strengthening mental health services by using mobile platforms so that the full spectrum of mental health needs can be met through a network of accessible, affordable, and high-quality community-based services and support [12]. Mobile health is the use of mobile devices to reinforce, sustain, and support public health interests, and it has become a widespread platform for the promotion and continuity of individual-led self-care, enhancing person-centered care and driving the advancement of health literacy to positively change people's views on screening or diagnosis [5].

Our research questions are as follows: What are the predictors of work stress for female workers? What is a valid and reliable occupational stress screening instrument for female workers? and What mobile app is best suited for occupational stress screening?

Out objective is to develop a mobile app–based occupational stress prediction model for female workers. Specifically, our objectives are to (1) identify predictors of work stress for female workers, (2) develop a valid and reliable work stress screening instrument for female workers, and (3) create a work stress screening mobile app.

Methods

Overview

The conceptual framework of this research is shown in Figure 1, which shows the phases of the research. The objectives of these phases were achieved using operational research, which was conducted sequentially in 3 stages (Figure 2). The participants involved in the qualitative research worked at various levels of health care. Participants were selected with various characteristics to enrich the findings. The workers involved were diverse, representing the sources of the participants. Data validation was conducted using theoretical triangulation [13]. This sampling design was expected to be representative of female workers in Jakarta, Indonesia. Female workers were involved in stages 1 and 2 in the hope that they could provide additional information about work stressors.

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Figure 1. Conceptual framework.

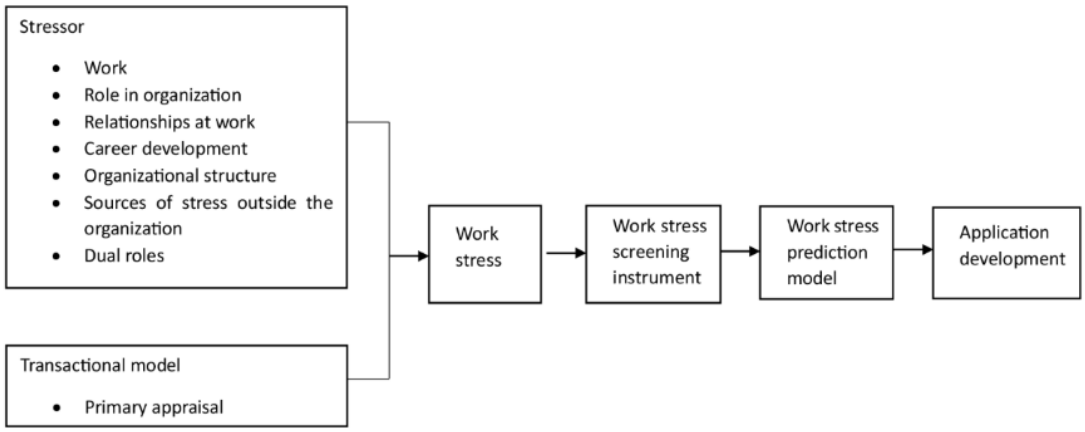

Figure 2. Research stages.

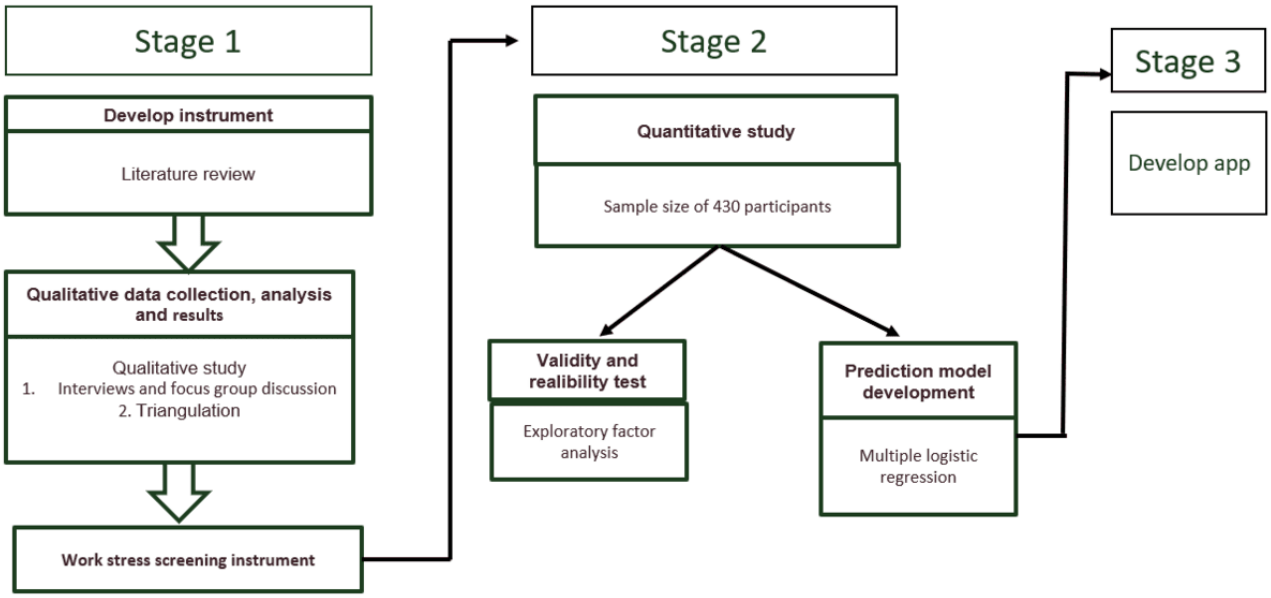

Operational Definition

Work stress assessment includes work (workload, work schedule, working conditions, work environment), roles in the organization (role conflict and ambiguity, role vagueness), relationships at work (relationships between colleagues or superiors), career development (job promotion, lack of job security), organizational structure (lack of participation in making decisions), sources of stress outside the organization (family problems, financial difficulties), having multiple roles (time-based conflict, strain-based conflict, behavior-based conflict), the transactional model (primary appraisal), and symptoms of work stress (physiological symptoms, psychological symptoms, behavioral symptoms).

The Qualitative Phase

For data collection, inductive (codes drawn from semistructured personal interviews) and deductive (codes drawn from the literature review) methods will be used. Semistructured personal interviews will be conducted with female workers. An interview guide will be used for the interviews. This guide will be developed in consultation with experts in qualitative research and occupational stress. Each interview will open by asking open-ended questions about work stress, the effects of work, and the role of female workers as wives or mothers in the household. Questions will be asked based on the answers to the first question and other questions also based on the interview guidelines; if needed, the researcher will use probing questions, such as “What do you mean by this?” “Can you give a more detailed explanation?” and “What do you feel about this topic?” In addition, at the end of each interview, the participant will be allowed to talk about any points that were missed. All interviews will be recorded and transcribed verbatim; during the interview, respondents’ nonverbal responses, such as tone, silences, emphasis, crying, and sighing, will also be documented [14].

The researcher interviewed an informant by visiting the workplace where the informant worked to seek approval and set the time and place of the interview.

Data Analysis

Processing of data obtained through the in-depth interviews was done through the following steps: (1) collecting data obtained from informants through interviews; (2) performing data transcription; (3) categorizing data to facilitate data grouping and data interpretation in the form of a matrix; (4) presenting

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a summary of data from in-depth interviews in the matrix; and (5) conducting data analysis using content analysis techniques, namely analyzing the primary data to identify the results and compare them with existing theories (this will be used to produce a collection of main items for the instrument).

Sample Size and Sampling Strategy

The research was conducted in the Daerah Khusus Ibukota (DKI) region in Jakarta from November 2023 to February 2024. The qualitative part of this research collected information from several related sources, including female workers, the DKI Jakarta Manpower and Transmigration Office, Badan Penyelenggara Jaminan Sosial (BPJS) Employment (a social security organizing agency), Apindo (the Indonesian Employers Association), trade unions and labor unions, and company stakeholders. The key participants were female workers.

Participants were selected who met the inclusion criteria of being older than 17 years; having a work history (divided into groups for 0-2 years or >2 years); having completed some form of education, either primary school, high school, or college; being unmarried or married; and either not having children or having children younger than 5 years.

The female workers in the sample were white collar workers, that is, those with job descriptions or tasks that are predominantly in an office, cubicle, or other administrative setting. This group of workers uses minimal physical exertion and rarely performs manual labor.

The Quantitative Phase

The focus of this phase is on assessing the psychometric properties of the female worker screening questionnaire, that is, its face, content, construct, divergent, and convergent validity, as well as its reliability [12,13]. The objectives of the quantitative research included assisting researchers in making decisions and obtaining results that could be used to make appropriate theoretical predictions and develop mathematical models; thus, this research not only uses theory or literature but also measurement as a very important aspect [15].

Validity and Reliability Test

The analysis at this stage included a factor analysis, which is used to validate new questionnaires created to measure abstract factors [13,14]. In this study, exploratory factor analysis was used to find the primary constructs or dimensions to improve the validation of the work stress screening instrument for female workers that had been developed and tested in the previous stage.

The first process we undertook was to examine the correlation between items; if there was a correlation between items of 0.6-0.7, it indicated that there was multicollinearity between the 2 items. If this was found, then one of the items had to be eliminated. The second process we undertook was to determine the adequacy of the sample size with the Kaiser-Meyer-Olkin (KMO) measure and the Bartlett test value. A sample is said to be adequate if the KMO measure value is >0.50 (0.50-0.70=moderate; 0.71-0.80=good; 0.81-0.90=very good; >0.90=superior). The Bartlett test significance value is expected to be <.05 if there is a meaningful correlation between assessment items. If the KMO and Bartlett tests meet the above requirements, then an interpretation of factor analysis can be performed [16]. The following process was used to determine the number of dimensions that could be formed from the assessment items. In other words, all items from the tested questions and statements could be grouped into factors or dimensions through having eigenvalues >1 or by using scree plots. The total variation in work stress scores that can be explained through the dimensions formed is expected to be ≥0.6 or 60%. After the number of dimensions was successfully determined, we determined the loading factor (ie, correlation between the assessment item and the dimension), which was 0.4 [5]. Finally, assessment items were included in the work stress screening instrument that had an interitem correlation of 0.3-0.9, a minimum correlation of 0.4 with each dimension, and a Cronbach α (internal consistency) of at least 0.6 for each dimension [17]. The work stress scores analyzed in relation to stressors, the transactional model, and symptoms comprised the final work stress screening instrument scores from the factor analysis.

Sample Size and Sampling Strategy

The variables to be examined quantitatively were elements of job stress, representing a type of primary data. Quantitative data collection was done using instruments that were developed for this study. The type of data collected was primary data. The data were distributed using Google Forms to female workers. The sample size was calculated based on the rule of thumb sample size for factor analysis, which is 20 subjects per variable [18].

The sample size was set at 390 with an anticipated dropout rate of 10%; thus, the final sample size for quantitative research was 429, rounded up to 430.

The sample was selected using purposive sampling because there were no data on types of businesses or their company names. Respondents were selected based on their employment by companies that had female workers and were willing to participate in the research. The inclusion criteria for the research locations were that they be the premises of companies that had more than 50% female workers and used mass production techniques. The inclusion criteria for research respondents were that they be physically and mentally healthy and aged at least 17 years. The exclusion criteria for research respondents were that they did not work at the workplace, were challenging to communicate with, or were sick or recovering from treatment. The female workers in the sample were all white collar workers.

Statistical Data Analysis

Univariate analysis aims to create a detailed picture for data from each variable. For categorical variables, data are presented in the form of percentage values. For numeric variables, data are presented in the form of means, medians, and modes. In addition, values for variation are also presented, namely SD, SE, and minimum and maximum values of the data.

We used a bivariate analysis to show differences in the proportion of work stress in female workers. The statistical test used was the χ^2 test. The basis of the χ^2 test is a comparison of the observed frequency with the expected frequency. The

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significance level used was 95%, with a significance value of 5%.

The criteria for relationships were based on the resulting *P* values (ie, probability) for the selected significance values, with the following criteria: if the *P* value was <.05, it was considered significant, and we considered there to be a difference in the proportion (ie, the null hypothesis was rejected), and if the *P* value was <.05, then we considered there to be no difference in the proportion (ie, the null hypothesis was not rejected).

This analysis aimed to determine the variables that most affected work stress in female workers. The test performed was multiple logistic regression. This analysis is a mathematical-model approach that aims to analyze the relationship between one or more independent variables with a dichotomous/binary categorical dependent variable.

In the first stage, bivariate selection is carried out to obtain variables that are included in multivariate modeling. In this bivariate selection stage, the independent variables that are eligible for selection are those that have a *P* value <.25, as seen in the omnibus test value. The next stage is multivariate selection, which is carried out in stages by removing the variables with the most significant *P* values; variables with *P*>.05 are removed. If the excluded variables result in a significant change in the odds ratios of the remaining variables (change >10%), then the variable is re-entered into the model.

In the next stage, an interaction test is conducted on variables that are suspected to have substantial interactions. If the interaction test results in a *P* value <.05, then the variable is included in the model.

Mobile App Development

The development of a work stress screening app for female workers is being conducted in stages, consisting of requirement planning, analysis, design, prototyping, and implementation, until there are no inputs or complaints based on system visualization. This prototyping method was chosen because it provides facilities for developers and users to interact with each other during the creation process so that developers can easily model the software to be created [19].

Planning Stage

At this stage, the IT team determines requirements to identify the needs of the app users and determine which needs can be implemented into the app. The method used is interviews with researchers regarding needs and expectations; these will be analyzed to determine the features of the app.

Analysis Stage

At this stage, 2 types of system requirements are collected and analyzed, namely functional requirements and nonfunctional requirements.

Design Stage

In this stage, we not only used unified modeling language (UML) to create use cases and activity diagrams, we also carried out a design process based on the design thinking method. Design thinking is generally defined as an analytical and creative process that involves a person experimenting, prototyping models, collecting feedback, and redesigning [20].

System Prototyping Stage

At this stage, the authors will create a prototype based on the results of the design stage that can perform interactions to be tested and presented to the researchers.

Implementation Stage

At this stage, the prototype will be implemented as an app with similar functions and features as the prototype. This will then be tested by researchers to determine whether it is appropriate and answers the problem or needs evaluation; improvement of the app will be undertaken.

Testing Stage

At this stage, the system that will be implemented will need to be tested to see whether it aligns with what is planned and expected. Testing will be done using the black box method and will be conducted among female workers. The testing of the system will aim to determine the extent to which the system can meet user needs and fulfill all requirements. Black box testing will be carried out based on app details such as app appearance, functions of the app, and the suitability of the function flow for the desired business process [21].

The app being developed will be called DINI Sehat Paripurna (Detection and Efforts to Normalize Immunity of Female Workers) and will be available for free download from the Android Play Store. It will be a work stress app (Figure 3) that will be tested by IT experts and female workers, who will assess the functionality and content of the system. The objective of this app will be to predict work stress in female workers and provide education. Female workers will answer the questionnaire in the app, and after completing all the questions, they will receive results indicating mild, moderate, or severe work stress (Figure 3).

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Figure 3. Mobile app for work stress prediction among female workers.

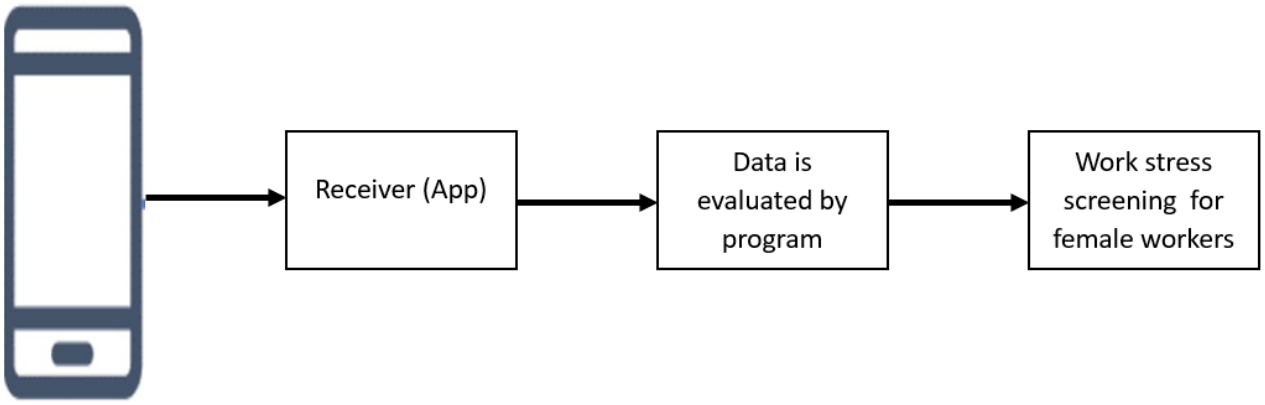

Ethical Considerations

Overview

The researchers will collect data from female workers using an online questionnaire. Data collection aimed to screen for work stress in female workers. There were no right or wrong answers in data collection, so respondents could provide answers according to their actual conditions. This method is useful to determine work stress in female workers based on the conditions identified, and allows efforts to be made to protect the workers' mental health.

Right to Resign and Compensation

Participation in this study was voluntary, and respondents had the right to withdraw at any time without adverse consequences to the respondents. Respondents who were willing to continue received a payment of IDR 25,000 (US $1.58).

Data Confidentiality

This study was performed according to research rules that included keeping the identities of the respondents confidential and using the data collected only for scientific activities. All respondents participated in filling out the questionnaire voluntarily.

Ethics Approval

At the time of publication, we were in the process of obtaining ethics approval from the Ethics Commission for Research and Community Health Services, Faculty of Public Health, University of Indonesia.

Results

This research was funded in January 2024 and qualitative data collection began in February 2024. Quantitative data were obtained in March 2024; the number of respondents in the qualitative stage was 6, and in the quantitative stage it was 430. The work stress screening app is in the development stage and will be launched at the same time as the data collection is performed so we can examine the respondents' perspectives on the use of the app.

Discussion

Overview

As an essential part of psychological-related research activities among workers, the assessment of occupational stress requires the use of appropriate instruments. The occupational stress questionnaire described here will be used to collect data on female workers' occupational stress and measure their level of occupational stress.

The questionnaire in this exploratory sequential study will be developed based on a definition of work stress that centers the perspective of female workers. Then, the psychometric properties of the questionnaire will be assessed. Given the lack of comprehensive work stress questionnaires for female workers, the development of a mobile app for work stress screening among female workers can be seen as an essential step in assessing and promoting the mental health of this population. The strengths of this study are the exploratory sequential design, the use of sampling among various stakeholders, and the relatively large sample size.

Limitations

A limitation of this study is the difficulty in obtaining data on companies that have female workers; the sample of workers was obtained only from companies that were willing to participate in this study. Furthermore, the analysis uses structural equation modeling to determine simultaneous linear relationships between work stress and variables that cannot be measured directly (ie, latent variables).

Conclusion

This research will screen for work stress among female workers with a method that can be used anywhere, based on a mobile app. This research will be useful for female workers, relevant stakeholders, policy makers, and academics.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

Apindo: Asosiasi Pengusaha Indonesia
BPJS: Badan Penyelenggara Jaminan Sosial
DKI: Daerah Khusus Ibukota
KMO: Kaiser-Meyer-Olkin

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UML: unified modeling language
WHO: World Health Organization

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Protocol

N-of-1 Trials of Antimicrobial Stewardship Interventions to Optimize Antibiotic Prescribing for Upper Respiratory Tract Infection in Emergency Departments: Protocol for a Quasi-Experimental Study

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Abstract

Background: Antimicrobial stewardship programs attempting to optimize antibiotic therapy and clinical outcomes mainly focus on inpatient and outpatient settings. The lack of antimicrobial stewardship program studies in the emergency department (ED) represents a gap in tackling the problem of antimicrobial resistance as EDs treat a substantial number of upper respiratory tract infection cases throughout the year.

Objective: We intend to implement two evidence-based interventions: (1) patient education and (2) providing physician feedback on their prescribing rates. We will incorporate evidence from a literature review and contextualizing the interventions based on findings from a local qualitative study.

Methods: Our study uses a quasi-experimental design to evaluate the effects of interventions over time in the EDs of 4 public hospitals in Singapore. We will include an initial control period of 18 months. In the next 6 months, we will randomize 2 EDs to receive 1 intervention (ie, patient education) and the other 2 EDs to receive the alternative intervention (ie, physician feedback). All EDs will receive the second intervention in the subsequent 6 months on top of the ongoing intervention. Data will be collected for another 6 months to assess the persistence of the intervention effects. The information leaflets will be handed to patients at the EDs before they consult with the physician, while feedback to individual physicians by senior doctors is in the form of electronic text messages. The feedback will contain the physicians' antibiotic prescribing rate compared with the departments' overall antibiotic prescribing rate and a bite-size message on good antibiotic prescribing practices.

Results: We will analyze the data using segmented regression with difference-in-difference estimation to account for concurrent cluster comparisons.

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Conclusions: Our proposed study assesses the effectiveness of evidence-based, context-specific interventions to optimize antibiotic prescribing in EDs. These interventions are aligned with Singapore's national effort to tackle antimicrobial resistance and can be scaled up if successful.

Trial Registration: ClinicalTrials.gov NCT05451863; https://clinicaltrials.gov/study/NCT05451836

International Registered Report Identifier (IRRID): DERR1-10.2196/50417

(JMIR Res Protoc 2024;13:e50417) doi:10.2196/50417

KEYWORDS

antibiotic resistance; emergency department; upper respiratory tract infection; N-of-1 trials; prescribing feedback; feedback; emergency; upper respiratory tract; respiratory; antibiotic; antimicrobial stewardship; antimicrobials; antibiotics; hospital; experimental study; antibiotic therapy; URTI; evidence-based intervention; evidence-based; patient education; prescribing rates; patient literacy; Singapore; regression analysis; regression

Introduction

Background

The discovery of antibiotics is among the most important public health achievements in the 20th century [1]. However, inappropriate antibiotic use has driven a rapid increase in antibiotic resistance, and with the drying up of the pipeline of new antibiotics, a postantibiotic era is imminent [2-4]. Hence, there is a need to reduce antibiotic use by changing physicians' antibiotic prescribing practices and reducing patient demand through antimicrobial stewardship programs (ASPs).

Despite the presence of ASPs in various settings, their effects are modest, as antibiotic prescribing practices have been difficult to change [5]. Systematic reviews of interventions to improve physicians' antibiotic prescribing practices have suggested that the traditional isolated forms of physician education (eg, didactic presentations or printed education materials alone) have only produced slight improvements in prescribing practices [6,7]. However, interventions such as educational outreach or training of local opinion leaders [8,9], as well as behavioral "nudges" in the form of public commitment devices [10] and peer comparison [11], were more effective in improving physician prescribing behaviors. In a systematic review evaluating information leaflets on common infections in general practice, 3 out of 4 studies on antibiotic use showed significant reductions in antibiotic prescriptions [12]. Another study using patient education in the form of an information leaflet regarding antibiotics for bronchitis showed a significant reduction (49% vs 63%) in antibiotic use compared with the control group [13].

Rationale for the Study

There is a need for more studies to assess the effectiveness of ASP in emergency departments (EDs) [14]. Antibiotics are often prescribed for upper respiratory tract infection (URTI) in the ED, although the routine use of antibiotics for URTI is not recommended [15,16]. A mixed methods study involving 8 EDs in 3 cities in the United States found that the fast-paced environment of the ED encouraged unnecessary antibiotic use [17]. In Singapore, URTIs also accounted for a substantial proportion of attendances at EDs and were associated with frequent ED attendance, as EDs were popular choices for primary care [18]. A previous study at an adult general hospital reported that 35% of adult patients presenting to the ED for URTI were prescribed antibiotics [19].

A physician's likelihood to prescribe antibiotics for a patient is complex and determined by many factors. The determinants of antibiotic prescribing may include the physician's worry about complications arising in the patient [20], busy clinical practice [17], insufficient physicians' knowledge [21], underestimation of the effect of inappropriate antibiotic prescribing leading to antimicrobial resistance (AMR) [22], and perception of the patient's expectations for an antibiotic [19]. Furthermore, decision fatigue can reduce the physician's ability to resist ordering inappropriate treatments and increase inappropriate antibiotic prescribing [23].

Given the multifactorial nature of inappropriate antibiotic prescribing, a single approach will unlikely work for all physicians [24]. Furthermore, different patient populations may warrant a variety of interventions. Hence, there is a need for interventions tailored to physicians and patients to promote the judicious use of antibiotics. We describe the protocol of a quasi-experimental study on 2 antibiotic stewardship interventions in the ED according to the SPIRIT (Standard Protocol Items: Recommendations for International Trials) checklist [25].

Hypothesis and Objectives

We hypothesize that (1) patient education via tailored information leaflets (addressing knowledge, perception, and belief gaps of the local patient population on antibiotic use for URTI) distributed while waiting for consultation with the physician can improve patient knowledge and change patients' expectations for antibiotics. The change in patients' expectations of antibiotics would reduce unnecessary antibiotic prescribing by physicians in response to patient demand in time-pressured EDs. (2) Surveillance of antibiotic prescribing rates and physician feedback enables physicians to reflect on their prescribing practices. Physician feedback by senior ED physicians, coupled with education on good antibiotic prescribing practices, serves as a reminder for physicians to improve their antibiotic prescribing practices.

Hence, we aim to evaluate the effectiveness of 2 tailored antimicrobial stewardship interventions in optimizing antibiotic prescribing for uncomplicated URTI cases in 4 adult EDs in Singapore. The two interventions are (1) patient information leaflets on appropriate antibiotic use and AMR. The ED triage nurses will provide pamphlets to patients suspected of URTI prior to their consultation with the physician. The pamphlets

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are available in Singapore's 4 official languages. (2) Feedback to physicians on their antibiotic prescribing rates. A senior ED doctor will send a personalized SMS text message to each physician who has seen at least 1 patient in the ED in the previous month at 2 monthly intervals. The feedback will contain the physicians' antibiotic prescribing rate compared with the departments' antibiotic prescribing rate and a bite-size message on good antibiotic prescribing practices.

Methods

Study Design

Our study uses a quasi-experimental design to evaluate the effects of interventions over time. The entire study period is from January 2021 to December 2023. All 4 EDs will be exposed to 2 interventions over 12 months, with the introduction of each intervention in a 6-month interval. The study will include an initial control period of 18 months, with none of the 4 hospitals exposed to any intervention. In the first 6 months, we will randomly assign 2 EDs to receive 1 intervention (ie, patient education), while the other 2 will receive the second intervention (ie, physician feedback). All EDs will subsequently receive the other intervention in the subsequent 6 months on top of the ongoing intervention. Data will be collected for another 6 months to assess the persistence of the intervention effects (Figure 1).

Figure 1. Quasi-experimental study of 2 tailored antimicrobial stewardship interventions in 4 emergency departments.

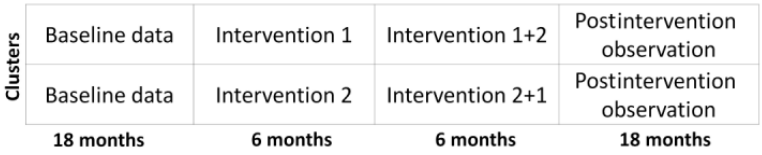

Study Population

The study population includes physicians working in the adult EDs of 4 public hospitals in Singapore.

Intervention

We will implement 2 interventions tailored to the context of EDs in Singapore. The interventions were selected based on a literature review of the effectiveness of ASP [12,26] and designed with input from ED physicians within our population via a qualitative study. We consulted senior ED physicians from our study sites to adjust the intervention to the local ED context and to facilitate buy-in prior to study implementation.

Patient Education

Patient information leaflets were designed to educate patients on appropriate antibiotic use and AMR. The design of the leaflets was based on the information from the United States Centers for Disease Control and Prevention patient educational materials [27] and tailored to the local ED context.

Patient leaflets (Multimedia Appendix 1) were made available at the EDs of the participating sites. ED triage nurses identified patients presenting to the ED with URTI symptoms and provided these patients with the leaflet prior to their consultation with the physician. The leaflets were made available in Singapore's 4 official languages—English, Chinese, Malay, and Tamil.

Feedback to Individual ED Physicians by Senior Doctors

A senior ED physician in the department will send the feedback messages to the ED physicians in the institution. The feedback message will contain the physicians' personal antibiotic prescribing rate and the department's average prescribing rate in the past month and will be administered at 2 monthly intervals. Bite-sized information on tips to reduce antibiotic prescribing for URTI, obtained from evidence-based sources and adjusted based on inputs from senior ED physicians of our study sites, will be sent together with the personalized message. The feedback will be delivered via Tiger Text, a messaging platform used by employees of Singapore's public health care institutions.

An example of the message is shown in Textbox 1.

Textbox 1. Example of a personalized physician feedback message.

Dear Dr X,

I would like to share with you the following feedback regarding antibiotic prescribing rates for URTI in TTSH ED.

Last month, 200 patients that visited TTSH ED were diagnosed with URTI (primary or secondary diagnosis) and discharged from the ED. Among these patients, 100 (50%) were prescribed with antibiotics.

You were the primary physician of 10 patients and 5 (50%) of them were prescribed with antibiotics.

I hope this feedback would be useful for your practice. Thank you for being our antibiotic guardian!

(Note: Common cold or non-specific upper respiratory tract infection (prominent symptoms include fever, cough, rhinorrhoea, nasal congestion, postnasal drip, sore throat, headache, and myalgia) are caused by at least 200 types of viruses. The receipt of antibiotics for common cold does not reduce the duration of symptoms.)

The medication and visit records of patients diagnosed with uncomplicated URTI will be extracted from the ED's electronic medical records over 36 months (18 months before and 18 months after the intervention). Patient particulars were

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deidentified prior to data processing in the R software (R Foundation for Statistical Computing). The medications given to these patients will be identified, and their primary physicians will be given feedback on the antibiotic prescribing rates for the patients they have seen.

Uncomplicated URTI includes but is not limited to acute nasopharyngitis and acute URTI of multiple or unspecified sites (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] 460 and 465); acute pharyngitis, tonsillitis, laryngitis, and tracheitis (ICD-9-CM 462, and 463, and 464); and acute or unspecified bronchitis and bronchiolitis (ICD-9-CM 466 and 490). The listed ICD-9-CM codes are for acute respiratory tract infection diagnoses for which antibiotics are not usually indicated [28].

Outcome Measure

The primary outcome measure of interest is physicians' monthly antibiotic prescribing rate. The antibiotic prescribing rate will be computed by dividing the number of patients prescribed antibiotics by the total number of patients with URTI seen by the physician in the month.

Sample Size

At the end of 12 months, all hospitals will be exposed to both interventions. Assuming 80 physicians per ED and an average of 1200 patients with URTI per ED over a 6-month period, a total of 640 physicians and 9600 patients will be exposed to the interventions in the 12-month intervention period.

Statistical Analysis

We will analyze the data using segmented regression models. Segmented regression models allow adjustments to confounding factor and slope changes at various time points but do not account for cluster differences. The inclusion of cluster differences will increase the robustness of the model [29]. The equation of the model is shown as follows:

$\beta 1$ measures the preintervention slope, $\beta_{2,4,6,8}$ measures the immediate change in mean outcome from the previous level, while $\beta_{3,5,7,9}$ measures the difference in slopes pre-post compared with the previous level. β_{11} measures the differences in groups or clusters at the preintervention level, $\beta_{12,14}$ measures the differences in groups or clusters on changes at the start of the intervention, while $\beta_{13,15}$ measures the differences in groups or clusters on changes in slope due to the intervention. Statistical software such as SPSS (IBM Corp), STATA (StataCorp), and R will be used for analysis.

Ethical Considerations

This study was approved by the National Healthcare Group Domain Specific Review Board in Singapore (2019/00174). Informed consent was waived by the review board as all individual-level data were extracted from the electronic medical records and deidentified by the respective institutions' independent trusted third parties. Data extraction does not interfere with the standard care the patients receive and does not pose more than minimal risk to the participants. No compensation is provided to the participants and the data team does not collect more data than required.

Results

The results are expected to be achieved by January 2024. The data analysis and manuscript are expected to be completed by the end of 2024. The results will be presented at scientific meetings and published in international peer-reviewed journals.

Discussion

Principal Findings

Our protocol describes the design and implementation of a context-based, 2-pronged approach to tackle the issue of antibiotic misuse and overuse in the ED setting. Many ASPs have had limited success due to the lack of vital personnel involvement (ie, senior physician), misalignment with the local context, and lack of physician involvement [30]. We plan to have senior physicians deliver the feedback messages to increase physicians' receptivity to the messages.

Hence, we designed the intervention with a rigorous review of evidence from the literature and considered the factors that contributed to the success of ASP. Our interventions were also tailored to the local ED context by considering the inputs of ED physicians via qualitative interviews and obtaining buy-in from senior physicians from the EDs.

Although randomized controlled trials are the most robust way of evaluating interventions, this approach is often not feasible in the health service setting in terms of blinding participants from interventions and preventing cross-contamination between the control and intervention groups. Quasi-experimental designs serve as a more practical option to evaluate health service interventions without compromising data robustness. Therefore, this study will provide an excellent opportunity for us to assess the effectiveness of a large-scale, context-based ASP in the ED.

With established processes already in place to store and distribute the pamphlets in the EDs involved in this study, we have received buy-in and will be able to re-engage the heads of departments of these EDs to continue our interventions or expand to other EDs in the long term if the intervention is shown to be effective.

Potential Limitations

The antibiotic prescribing feedback may not be accurate if the primary physician is not the prescribing physician. Furthermore, patients attending the ED may have multiple complaints and may receive antibiotics for conditions unrelated to URTI. Hence, the feedback message had to be adjusted to reflect an accurate interpretation of the data. There may also be a lack of continuity of feedback should junior physicians rotate out of the ED. The lack of feedback continuity may affect the statistical effectiveness of feedback intervention, although physicians who received the intervention may have positive spillover effects to other departments upon rotating out of the ED.

Some patients may also miss the pamphlets when the triage nurses are overburdened with a high patient load and forget to

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hand out the pamphlets to them. We have placed the pamphlets in the ED waiting areas for patients to pick up the pamphlets should they be interested in the topic. The ED nurses will help to perform periodic checks to replenish the pamphlets when the stock is low.

Conclusions

The lack of ASP in the ED represents a missed opportunity in a collective effort to tackle AMR nationally. Our protocol described a study that assesses the effectiveness of evidence-based, context-specific interventions to optimize antibiotic prescribing in EDs. These interventions are aligned with Singapore's national effort to tackle AMR and can be scaled up to other EDs if successful.

Acknowledgments

We would like to acknowledge Karthiga Natarajan for her assistance in the literature review. Generative artificial intelligence was not used to create any portion of this protocol.

Data Availability

Data sharing not applicable to this article as no data sets were generated or analyzed for this protocol.

Authors' Contributions

ZH and AC conceived the manuscript. HA and ZH drafted the manuscript and contributed equally to the work. HA, ZH, and AC reviewed and edited the manuscript. AC provided support and funding for the study. ZH administrated the study. All authors critically reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
English version of patient leaflet.
[PDF File (Adobe PDF File), 723 KB - resprot_v13i1e50417_app1.pdf]

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Abbreviations

AMR: antimicrobial resistance
ASP: antimicrobial stewardship program
ED: emergency department

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ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification
SPIRIT: Standard Protocol Items: Recommendations for International Trials
URTI: upper respiratory tract infection

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Proposal

Assessment of Patient Safety in a Low-Resource Health Care System: Proposal for a Multimethod Study

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Abstract

Background: The high prevalence of adverse events (AEs) globally in health care delivery has led to the establishment of many guidelines to enhance patient safety. However, patient safety is a relatively nascent concept in low- and middle-income countries (LMICs) where health systems are already overburdened and underresourced. This is why it is imperative to study the nuances of patient safety from a local perspective to advocate for the judicious use of scarce public health resources.

Objective: This study aims to assess the status of patient safety in a health care system within a low-resource setting, using a multipronged, multimethod approach of standardized methodologies adapted to the local setting.

Methods: We propose purposive sampling to include a representative mix of public and private, rural and urban, and tertiary and secondary care hospitals, preferably those ascribed to the same hospital quality standards. Six different approaches will be considered at these hospitals including (1) focus group discussions on the status quo of patient safety, (2) Hospital Survey on Patient Safety Culture, (3) Hospital Consumer Assessment of Healthcare Providers and Systems, (4) estimation of incidence of AEs identified by patients, (5) estimation of incidence of AEs via medical record review, and (6) assessment against the World Health Organization's Patient Safety Friendly Hospital Framework via thorough reviews of existing hospital protocols and in-person surveys of the facility.

Results: The abovementioned studies collectively are expected to yield significant quantifiable information on patient safety conditions in a wide range of hospitals operating within LMICs.

Conclusions: A multidimensional approach is imperative to holistically assess the patient safety situation, especially in LMICs. Our low-budget, non–resource-intensive research proposal can serve as a benchmark to conduct similar studies in other health care settings within LMICs.

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KEYWORDS

patient safety; health systems; quality assessment; safety culture; assessment; healthcare delivery; health system; hospital; low-middle-income countries; research methodology

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Introduction

Background

Adverse events (AEs) are instances of injury or harm to patients as a result of medical care and not their underlying medical condition [1]. They are ubiquitous, with some estimates saying that up to 1 in 10 hospitalizations involve medical errors [2]. Underreported and often overlooked, they take a heavy toll on health systems globally. In the United States alone, an estimated 250,000 deaths are attributed to AEs annually, making them the third leading cause of mortality in the country [3]. Moreover, anywhere from 25% to 80% of these errors—some of which lead to a loss of life or permanent disability—are entirely preventable [4,5]. Due to a myriad of factors including but not limited to, understaffing, resource availability and use, and lack of health literacy, health systems within low- and middle-income countries (LMICs) are estimated to experience far more AEs, with an incidence rate ranging between 2.5% and 18.4% [5].

Given these facts, it is understandable why the domain of patient safety and harm reduction gained traction around the world. Of note, the publication of the Institute of Medicine's report "To Err is Human" in 2000 served as a benchmark in establishing the relevance of this aspect of health care delivery [6]. Since then, it has become increasingly apparent that it is a complex issue requiring a multidimensional approach. This school of thought is also linked to the relatively recent emergence of the "systems thinking" concept. This concept emphasizes recognizing the importance of a systems approach in studying the causes of patient harm and advocates for designing an error-proof system. Such an environment is aimed at preventing human errors and focuses on mitigation rather than the elimination of human factors in health care provision [7]. Additionally, an open and transparent environment where a culture of patient safety is prevalent is also imperative in fostering safe health care systems, which ultimately reduce the chances of errors and AEs. This safety culture can be nurtured by upholding safety beliefs, values, and attitudes among the majority of the workforce [8].

Moreover, viewing patient safety through a systems lens is a low-resource exercise since it mainly requires a shift in cultural and systemic perspectives. By considering patient safety problems as a product of the interaction between human and system factors, clinicians can evaluate the factors contributing to patient safety issues without the need for expensive or time-consuming resources [7]. This is particularly important for LMICs where large groups of the population are catered to using precious scarce resources and more often than not, have fewer human resources available per capita. The low cost of these measures makes the establishment of a patient safety culture a near-ideal step in achieving the provision of safe health care delivery and maximizing the quality and impact of health care services [9]. The cost-effectiveness of patient safety culture and a systems approach is reflected in the idea that prevention of AEs is much less resource-intensive than treating the complications that arise from them and which impose a heavy burden on already strained health systems [1,10].

Knowledge Gap

Though sparse, the existing literature from LMICs suggests that there are considerable knowledge gaps in the patient safety domain despite a general awareness of its importance [11,12]. However, global awareness of patient safety has also resulted in a shift of focus toward improvement in the quality of care in LMICs [13,14]. The Global Patient Safety Collaborative is one such initiative established by the joint efforts of the World Health Organization (WHO) and the governments of the United Kingdom and Northern Ireland to scale up global efforts to prioritize patient safety and improve the safety of health systems at a country level [15].

Similarly, the WHO's Global Patient Safety Action Plan for 2021-2030 [16] outlines some key points in eliminating preventable harm in health care through their defined goals of completely eliminating avoidable harm and ensuring the delivery of safe clinical processes, building reliable health systems to protect patients' rights to safe and quality care, empowering both health care providers and patients by engaging in productive dialogue to influence patient safety policies, and ensuring effective information and knowledge sharing among health systems and partners to promote multidisciplinary involvement in patient safety. Therefore, to achieve a holistic understanding of the status of patient safety within a health care system, it is necessary to approach the problem simultaneously from multiple perspectives such as the health care provider's view of patient safety, the health care consumer's view of patient safety and AEs, the estimated incidence of AEs happening within a health care setting, and the infrastructure available to cater to these problems. To our knowledge, a unified framework that addresses all such facets of patient safety has not been used at scale, hence our proposal is unique in its approach.

As mentioned above, to establish a proper culture of safety, it is imperative to first assess the existing culture of safety within health systems [17]. The most commonly used tool for this assessment is the United States Agency for Healthcare Research and Quality's (AHRQ) Hospital Survey on Patient Safety Culture (HSOPSC), which has been implemented in many countries [18-21], translated into several different languages, and can be adapted to fit the local context of most countries [22]. Similarly, the AHRQ's Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) questionnaire is used globally to assess the patient perspective on health care provision and service delivery. Standards such as the Joint Commission International Accreditation and the WHO's Patient Safety Friendly Hospital Framework (PSFHF) serve as benchmarks against which health care settings can be measured on their quality indicators.

LMICs can greatly benefit from initiatives like the Global Patient Safety Collaborative and PSFHF and from using tools such as the HSOPSC and HCAHPS, to perform comprehensive risk assessments of their hospitals, deliver patient safety education and training, establish a culture of safety, and expand the capacity for patient safety within their hospitals [23]. The generalizability of these standardized, validated tools makes them easily adaptable to the local context and can help evaluate patient safety standards across varying health systems. However,

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there is a considerable dearth of research in this domain in LMICs and to our knowledge, a comprehensive study on patient safety has not been undertaken so far in Pakistan.

With this proposal, our goals are to evaluate, develop, and implement evidence-based patient safety assessment policies and recommend patient safety strategies and plans that can be replicated across low-resource settings. In order to achieve these goals we aim to perform a comprehensive assessment of the patient safety problem at a sample of hospitals in each province in the country. Additionally, we seek to analyze the results of these assessments to establish the status of patient safety problems in local hospitals, in order to recommend practical steps and policy guidelines for improvement.

Methods

Patient Safety Assessment Framework

To better comprehend the range of patient safety problems and their contributing factors at a variety of hospitals across the country, we propose a multifaceted, multimethod approach with the goal of developing a holistic understanding of patient safety issues within the local health care system. For this purpose, we have devised a conceptual framework for the holistic assessment of the patient safety status across variable health settings. Our framework for the assessment of patient safety (Figure 1) in a low-resource setting approaches the problem from a systems thinking lens. We aim to evaluate each hospital setting on its safety culture, the incidence of AEs, and existing infrastructural standards against a minimum, preset standard. After the study sites are identified and all necessary approvals are obtained, multiple methodologies will be used to analyze the patient safety situation at these sites within 3 interconnected domains: patient safety culture, AE detection, and patient safety infrastructure. We shall use 6 different approaches that can be variably used in either a multicenter study design or in individual health care settings.

Figure 1. Framework for patient safety assessment.

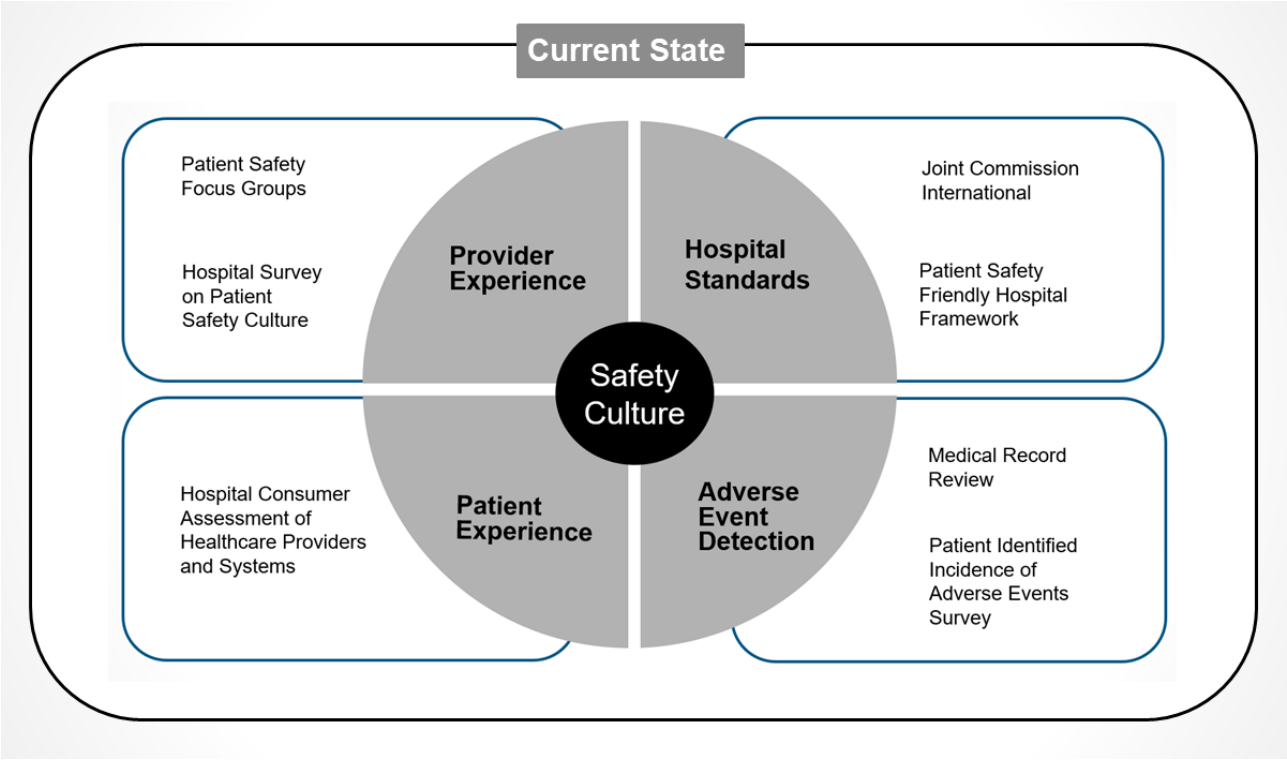

Study Site Selection

In our proposal, a cross-section of public and private hospitals providing varying levels of care to urban or rural populations will be considered for these assessments. Since there is not a single electronic health record network or a unique quality standard implemented across all hospitals in Pakistan, our aim would be to include hospitals participating in the World Health Organization's Patient Safety Friendly Hospital Initiative. The Patient Safety Friendly Hospital Initiative involves a basic, easily implemented framework for hospital quality standards developed by the WHO Regional Office for the Eastern Mediterranean and has been successfully piloted in 7 countries including Pakistan [24]. Attempts will be made to include 1 secondary or tertiary hospital from each province to accommodate for regional variations in a decentralized health system. Following this, key personnel will be identified from the selected centers and stakeholder meetings will be conducted to get the appropriate permissions from all relevant parties on board for subsequent hospital assessments.

Ethical Considerations

Prior to data collection, separate approvals will be obtained from the institutional research review board or an equivalent body of each participating institute. An overarching approval will also be obtained from the institution conducting the research. For study components requiring individual responses, an informed consent form in either English or a certified Urdu

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translation will be obtained per the respondent's preference. Each respondent will also be offered a blank copy of the consent form.

For study components requiring medical record access, a review of the participating health center's policy on data governance and sharing will be conducted before any medical records are requested for the study. Consent will be obtained from all relevant institutional authorities prior to medical record reviews. All identifying information will be coded to ensure strict patient confidentiality and anonymity. The collected data will be stored on secure servers with limited access provided only to authorized research personnel. All information generated will be used exclusively for research purposes in accordance with local regulations.

Safety Culture

Focus Group Discussions

To assess the existing infrastructure and culture of patient safety and quality improvement at the study sites, focus groups will be conducted with teams comprising each hospital's leadership, unit-level management, and frontline health care workers. Administrative staff, physicians, nurses, and technicians will be targeted for responses in representative proportions. During these discussions, in-depth interviews will be conducted to try to capture informal methods of health care delivery that might be in practice at each institute, to get an idea of the local understanding of patient safety, and to identify the problems associated with it. A qualitative analysis will be performed following these interviews to identify the relevant codes and themes pertaining to the patient safety situation in these hospitals. Textbox 1 shows a sample of the prompts that will be used for these interviews.

Textbox 1. Interview prompts for focus group discussions among health care providers on the status of patient safety.

Prompt:

- What is your understanding of quality and patient safety?
- What processes/activities/mechanism currently exist at your hospital for quality improvement and patient safety?
- Please share the last unexpected/adverse event that you have encountered/observed at your hospital
- What activities (if any) are planned for initiating/strengthening the existing quality and patient safety culture at the hospital?
- What are your suggestions to improve/strengthen patient safety at your hospital?

Evaluation of Existing Patient Safety Culture

To evaluate the existing safety culture in the participating hospitals, a survey will be conducted using the Agency for Healthcare Research and Quality's HSOPSC [25]. HSOPSC is a standardized, validated tool consisting of 42 items that assess patient safety culture across 12 basic dimensions (Textbox 2). For this survey, a minimum of 2 available personnel belonging to five categories—doctors, nurses, technicians, hospital management, and hospital aides—will be included via quota sampling from the participating hospitals, with a minimum of 10 personnel per hospital. Responses to most items in this survey will be based on a Likert scale, some of which will be dichotomized during analysis to be measured against the predefined composites listed in Textbox 2.

Textbox 2. Hospital Survey on Patient Safety Culture (HSOPSC) survey items and composite measures.

Item

- Teamwork
- Staffing and work pace
- Organizational learning—continuous improvement
- Response to error
- Supervisor, manager, or clinical leader support for patient safety
- Communication about error
- Communication openness
- Reporting patient safety events
- Hospital management support for patient safety
- Hands-off and information exchange
- Number of events reported
- Patient safety rating

Note: Survey items included in the HSOPSC are grouped by safety culture composite measures [25].

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Inpatient Hospital Experience Survey

To measure the quality of the inpatient hospital experience from the patients' perspective, a modified version of the AHRQ's Hospital Consumer Assessment of Healthcare Providers and Systems questionnaire will be used to conduct an interview-based survey. The HCAHPS is a widely used standardized survey used to measure patient satisfaction with in-hospital care [26]. The standard HCAHPS survey contains 29 questions split into 7 discrete categories, which measure the patient's experience during their hospital stay in specific areas of inpatient health care delivery. As a standard practice, it should be administered randomly to adult patients between 48 hours and 6 weeks after discharge from the hospital and a minimum of 300 patients should be surveyed per hospital, from 1 calendar year.

Our modified HCAHPS questionnaire adds one more category with additional questions on pain management, adapted from the Qatar Ministry of Public Health's Patient Experience Survey for Hospitals (Textbox 3). Using quota sampling for this survey, we aim to target a minimum of 20 patients being discharged from each participating hospital. Most responses in the HCAHPS are measured with a 4-point Likert scale, which during analysis, will be dichotomized into binary values to elicit the highest positive responses to the items—the so-called "top box percentages."

Textbox 3. Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey question categories.

Item:

- Nurse communication
- Doctor communication
- Hospital environment
- In-hospital care experience
- Pain management
- Discharge or transfer information
- Overall hospital rating
- Understanding your care transition upon discharge

Note: Survey categories are based on a standard HCAHPS survey form modified to include questions on pain management [26].

Adverse Event Detection

Patient–Reported Incidence of AE

To understand the patients' perspective of AEs during health care delivery, we propose a questionnaire-based survey to assess patient safety–related issues including patients' understanding and experiences of AEs, preventable harm, and local reporting. This survey is adapted from a tool implemented by Southwick et al [27] to suit the local health care setting. The original study design surveyed almost 700 patients in nearly a 4-year period through a web-based form.

To account for low digital literacy within LMICs we propose using quota sampling to screen patients within the outpatient departments at the study sites to survey those who have availed health care services. Participants will be requested to recall potential AEs experienced during health care delivery using the standardized questionnaire, and the responses will be recorded by a member of the investigating team. The results will be analyzed descriptively to determine the nature and severity of AEs, and their effects as perceived by patients who have received medical care. At least 50 respondents will be interviewed at each study site.

Medical Record–Based Incidence of AEs

To calculate the incidence of AEs during hospitalization, a review of medical records will be performed at each hospital. The sample size for this study will be calculated based on the annual inpatient volume at each hospital with a 5% significance, a precision of 3%, and an estimated 10% dropout rate due to unavailability or poor quality of medical records. A range of prevalence of 10%-18% will be assumed as representative of the population. A team of investigators will also perform a data quality check of the existing medical records against a standardized checklist prior to the review [28].

Following this, a retrospective chart review of the medical records will be conducted in a 2-step process. In the first step, all charts will be screened using a standardized AE screening form, "Review Form 1" (RF1) to identify any potential AEs. All AEs identified using RF1 will then be evaluated using "Review Form 2" (RF2) to establish the nature, causality, and the factors contributing to these AEs. Both review forms have been adapted from the WHO patient safety research tools for data-poor hospitals and contain extensive screening and investigative questions to assess and analyze "harmful incidents" or "adverse events" [29]. The incidence of AEs will be calculated using the following formula:

Additionally, a descriptive analysis will be performed on the types of AEs, their potential causes, and the likely systemic and human factors contributing to the event.

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Patient Safety Infrastructure Assessment Against the WHO's Patient Safety Friendly Hospital Framework

The PSFHF is based primarily on 5 domains and 22 standards [30], which together comprise 134 criteria that are prioritized into critical, core, and developmental categories (Table 1).

The 25 critical criteria are the basic minimum requirements that hospitals are encouraged to achieve in terms of quality improvement. To assess each hospital's standing against the PSFHF criteria, members of the investigating team will conduct in-person surveys of the facilities to observe the implementation of standards. They will also review standard operating procedures and existing hospital protocol documents, and check for the existence of an AE reporting system. Interviews with staff members and patients will also be conducted. All these observations will be recorded against the existing standard criteria set within the PSFHF and after a comprehensive review, a list of recommendations will be provided by the investigators in light of their findings.

Table 1. Attributes of the Patient Safety Friendly Hospital Network (PSFHF).

Domain	Standards, n	Critical criteria, n	Core criteria, n	Developmental criteria, n	Total criteria, n
Leadership and management	6	7	26	3	36
Patient and public involvement	7	2	22	7	31
Safe evidence–based clinical practice	4	14	24	2	40
Safe environment	2	1	20	1	22
Lifelong learning	3	1	2	2	5
Total	22	25	94	15	134

Project Execution

In order to conduct all the above study components in an organized and timely manner, the investigating team will comprise health care professionals recruited from the core team and regional partners, who will be trained in conducting each survey. All survey instruments will be developed and recorded in English, whereas the written consent forms for participant recruitment will be translated into the local language as well. The interviewers will be fluent in both languages. The proposed timeline of events for conducting each component of the assessment is given in Figure 2.

It should be noted that as part of a theoretical framework, this proposed timeline includes a timeframe for the completion of each part of this multimodal approach, carried out simultaneously by multiple teams at each site. However, the authors understand that various levels of care within various health care systems require different facets of evaluation. Thus, it is recommended that the approach within this framework be modified according to the local organizational and operational structures and the given limitations of the health care setting being assessed. Subsequently, the project timeline can vary depending on the number of assessments being conducted.

Figure 2. Proposed project timeline of events for a single study site.

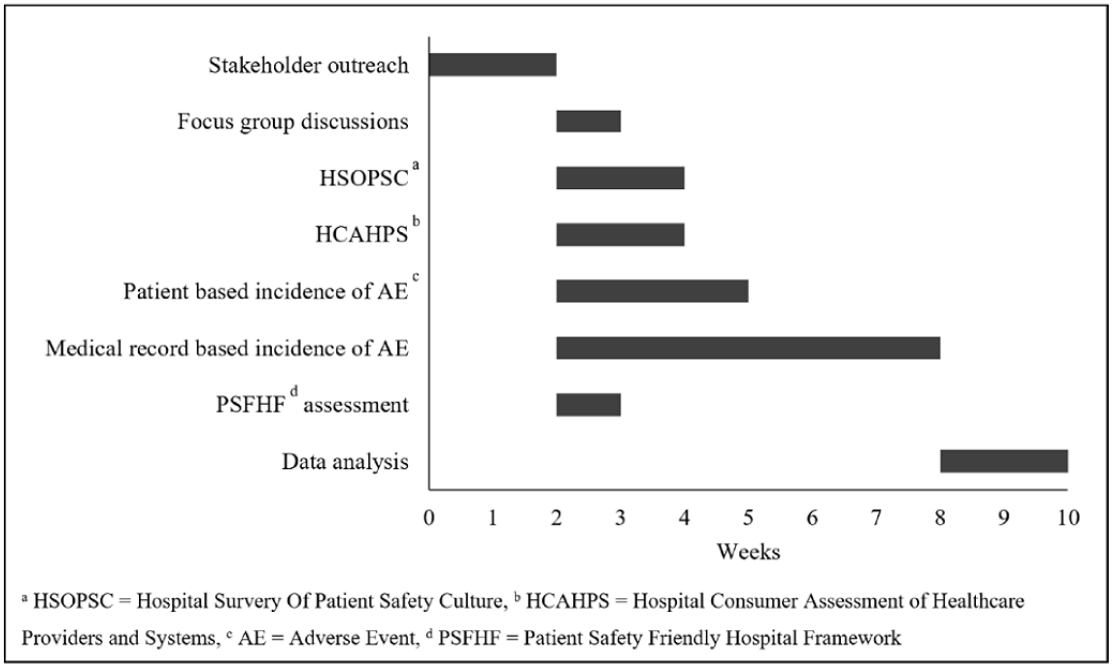

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Results

A thorough quantitative and qualitative analysis will be conducted which will be aimed for publication in the form of a technical report.

Discussion

Overview

Patient safety culture is an essential component of health care provision and can significantly impact patient outcomes. The beliefs, attitudes, and behaviors of health care providers can significantly affect their understanding of and commitment to ensuring patient safety [10]. Research has consistently shown that a positive patient safety culture leads to improved patient outcomes, increased staff satisfaction, and reduced health care costs [31]. Conversely, a lack of an open, transparent culture focused on patient safety can result in medical errors, AEs, and poor patient outcomes [17]. LMICs in particular fall behind in prioritizing patient safety due to a lack of practical policies and procedures, inadequate education and training, and lacking a culture of transparency and open communication to ensure the best possible patient outcomes [5]. These are largely attributed to the chronically depleted health resources in the region, however, establishing a culture of safety does not necessarily require high-cost interventions. Additionally, in order to establish a sustainable culture of safety, it is essential to first identify the gaps that lie within this system.

Studying the incidence and prevalence of AEs within a health system is an effective way to gauge the status of patient safety. Historically, this has been achieved using incident reporting systems and retrospective chart reviews to record error prevalence [32,33], health consumer and provider surveys [19,23,34], and by studying medical litigation cases [35]. There is a considerable amount of literature from high-income countries that highlights the incidence and impact of AEs in health care [2,27,36], however, the same is not true for LMICs [5]. Moreover, patient safety problems are multifactorial and therefore require a diverse yet intertwined approach to obtain a comprehensive understanding of the problems involved, such as system-based issues, which tend to be locally unique at the unit, hospital, or even regional level. For example, an inpatient hospital setup might have patient safety concerns due to culture issues, while the emergency room at the same hospital might have patient safety concerns due to inadequate resources for their volumes. Similarly, the same type of work area in variably resourced settings, such as the intensive care unit in a public versus a private hospital might have vastly different reasons for gaps in patient safety. Therefore, a comprehensive risk assessment of factors contributing to patient safety concerns is the first step in identifying these issues and subsequently addressing them.

Therefore, our proposed multimodal methodology for assessing patient safety issues in the Pakistani health care system is a pragmatic approach to the problem. With the participation of local and federal stakeholders, the application of our research proposal is easily achievable at a very low cost to the health system. Estimating the incidence of AEs from retrospective chart reviews and patient interviews, assessing the presence of a safety culture within hospitals by interviewing health care providers, learning from patient experiences within the hospital through surveys, and examining hospital compliance to quality improvement measures are all technically sound methods to ascertain the dynamics and challenges within patient safety culture.

Challenges and Solutions

However, even with a less resource-intensive approach such as ours, the local health system still poses many challenges. Implementation of patient safety protocols for quality health care provision in LMICs is limited, mainly due to the unavailability of resources and proper infrastructure. A significant number of health care facilities in Pakistan lack essential equipment, life-saving medications, and adequately trained staff to provide safe and effective care to patients [37]. Additionally, given the diversity in the local population in terms of language and regional lifestyle differences, health care providers can encounter cultural and linguistic barriers that hinder their ability to communicate effectively with patients, which can subsequently compromise patient safety.

Furthermore, the lack of access to continuing medical and nursing education and training opportunities results in poor understanding and implementation of patient safety protocols among health care providers. Additionally, a decentralized health care system paired with political instability and poor governance frequently results in inadequate funding [37] and a dearth of regulations for implementing patient safety protocols effectively. Consequently, health care providers in Pakistan continually navigate these multifaceted challenges while striving for the provision of safe, effective, and quality care for their patients [38].

We anticipate all these issues to surface during our research project as well. To begin with, a significant challenge in collaborative risk assessments in a decentralized health system is to have all the various stakeholders agree on a singular model. Additionally, the lack of a common understanding of the concept of patient safety risk assessment results in discrepancies in the identification and management of risks by the health care providers at different institutions. Moreover, limited channels of communication among the local health care systems also mean that effective collaboration and information sharing among health care providers is almost nonexistent.

Another significant challenge in our research will likely be the absence or inadequacy of medical records within the local hospitals. Poor medical records result in incomplete or incorrect information about medical histories, leading to inaccurate diagnoses, inappropriate treatment, and consequently, AEs. Predictably, poor medical records might limit our ability to track patient progress and treatment outcomes, which can hinder the identification and management of AEs in a retrospective analysis of medical errors and near-misses.

In order to mitigate these problems head-on, we shall aim to diligently communicate with all federal and provincial stakeholders, listen to their concerns, and with the help of our subject matter experts, express our research ideas, intentions,

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and expected outcomes as transparently as possible. Additionally, the investigating team will include regional partners who can provide valuable cultural and linguistic context to the data collection process. To streamline the project focus, we shall invite all the major stakeholders to a brainstorming session where their perceptions and practices regarding patient safety will be discussed and incorporated within the data analysis. To combat the problem of poor quality of medical records, all reviewed charts will undergo a quality assessment [28] before they are included in the data set and a wider margin for dropouts will be adjusted in the sample size calculation if needed. Finally, given the law-and-order situation in the country, all efforts will be made to ensure the physical security of the investigating team and the project data.

Our patient- and provider-centered approach to patient safety assessment incorporates the Global Patient Safety Action Plan goals [16] of empowering patients, encouraging health care workers to participate in fostering a culture of safety, sharing valuable information across health systems, promoting transparency in incidence event reporting and making health care delivery safer to produce better outcomes. Building on this knowledge of the patient safety status in Pakistan, we hope to inform and inspire policy making and strive to align local patient safety standards with global recommendations.

Strengths and Limitations

Our research proposal has many strengths. Given the proposed diversity of health care facilities in our study sample, and their varying capacities for health care provision, no single assessment tool can provide an exhaustive description of the patient safety situation in these hospitals. Hence, our diverse multimethod approach is not only unique within patient safety research in LMICs, but it will also provide a comprehensive assessment of the situation. The inclusion of patient safety and quality experts within the research group is also a unique feature for a survey of this magnitude. The relatively low cost of our proposed methodology and short execution time will encourage stakeholder interest in the project. Moreover, our final analysis is expected to provide a first-of-its-kind perspective on the patient safety situation, particularly within the public health care system.

Some of the limitations of our study include the significant disparity in the perception of health economics and literacy in the study population. This can result in a wide shift in the perception of quality indicators in health care between high and low-income countries. This requires adjusting the existing global standards in quality health care delivery against the local perception of it. Moreover, the reliance on retrospective chart reviews limits information availability, while patient interviews introduce the possibility of respondent recall bias in assessing the incidence of AEs. Additionally, some geographical areas of interest for our study might not be logistically or politically feasible for inclusion. There might also be concerns among the participating hospitals regarding data sharing with other institutions. However, all efforts will be made to ensure compliance with confidentiality standards.

Conclusions

Our multidimensional, multimethod research proposal to assess and analyze the patient safety situation on a large scale within the Pakistani health care system is a unique approach to broaching the domain of patient safety in the country. We are confident that our methodology will produce good quality data so that we can use our study results in writing situation analyses, offering policy recommendations, and hopefully, instigating some real change in prioritizing and implementing a safety culture in Pakistani hospitals. Moreover, our research proposal can be easily implemented in other LMICs with a few minor adjustments in the local context.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

AL, F Asif, and SS contributed to the conceptualization and design of the study. GH drafted the manuscript. AL, F Asif, FAA, F Ayub, SHS, NAP, MH, MMUS, SM, and TZ reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
AHRQ: Agency for Healthcare Research and Quality
HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems
HSOPSC: Hospital Survey on Patient Safety Culture
LMIC: low and middle–income country
PSFHF: Patient Safety Friendly Hospital Framework
RF1: review form 1
RF2: review form 2
WHO: World Health Organization

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Protocol

Assessment of the Feasibility of Objective Parameters as Primary End Points for Patients Affected by Knee Osteoarthritis: Protocol for a Pilot, Open Noncontrolled Trial (:SMILE:)

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Abstract

Background: Osteoarthritis (OA) is a disabling condition that affects more than one-third of people older than 65 years. Currently, 80% of these patients report movement limitations, 20% are unable to perform major activities of daily living, and approximately 11% require personal care. In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommended, as the first step in the pharmacological treatment of knee osteoarthritis, a background therapy with chronic symptomatic slow-acting osteoarthritic drugs such as glucosamine sulfate, chondroitin sulfate, and hyaluronic acid. The latter has been extensively evaluated in clinical trials as intra-articular and oral administration. Recent reviews have shown that studies on oral hyaluronic acid generally measure symptoms using only subjective parameters, such as visual analog scales or quality of life questionnaires. As a result, objective measures are lacking, and data validity is generally impaired.

Objective: The main goal of this pilot study with oral hyaluronic acid is to evaluate the feasibility of using objective tools as outcomes to evaluate improvements in knee mobility. We propose ultrasound and range of motion measurements with a goniometer that could objectively correlate changes in joint mobility with pain reduction, as assessed by the visual analog scale. The secondary objective is to collect data to estimate the time and budget for the main double-blind study randomized trial. These data may be quantitative (such as enrollment rate per month, number of screening failures, and new potential outcomes) and qualitative (such as site logistical issues, patient reluctance to enroll, and interpersonal difficulties for investigators).

Methods: This open-label pilot and feasibility study is conducted in an orthopedic clinic (Timisoara, Romania). The study includes male and female participants, aged 50-70 years, who have been diagnosed with symptomatic knee OA and have experienced mild joint discomfort for at least 6 months. Eight patients must be enrolled and treated with Syalox 300 Plus (River Pharma) for 8 weeks. It is a dietary supplement containing high-molecular-weight hyaluronic acid, which has already been marketed in several European countries. Assessments are made at the baseline and final visits.

Results: Recruitment and treatment of the 8 patients began on February 15, 2018, and was completed on May 25, 2018. Data analysis was planned to be completed by the end of 2018. The study was funded in February 2019. We expect the results to be published in a peer-reviewed clinical journal in the last quarter of 2024.

Conclusions: The data from this pilot study will be used to assess the feasibility of a future randomized clinical trial in OA. In particular, the planned outcomes (eg, ultrasound and range of motion), safety, and quantitative and qualitative data must be

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evaluated to estimate in advance the time and budget required for the future main study. Finally, the pilot study should provide preliminary information on the efficacy of the investigational product.

Trial Registration: ClinicalTrials.gov NCT03421054; https://clinicaltrials.gov/study/NCT03421054

International Registered Report Identifier (IRRID): RR1-10.2196/13642

(JMIR Res Protoc 2024;13:e13642) doi:10.2196/13642

KEYWORDS

pilot trial; feasibility study; knee osteoarthritis; hyaluronic acid; outcome assessment; osteoarthritis; ultrasonography; knee; pain

Introduction

Background

Osteoarthritis (OA) is a joint disease that causes inflammation and reparative bone response. It is a highly prevalent condition, affecting over 100 million people worldwide, and ranking among the top 5 most disabling conditions. More than 50% of the global population older than 65 years exhibit radiographic evidence of OA in at least 1 joint, indicating a high incidence of this disease. OA affects both sexes equally, although it seems to be more prevalent in men younger than 45 years and in women older than 45 years. Currently, 80% of individuals affected by OA experience movement limitations, and 20% are unable to perform important daily activities. Furthermore, 11% of the affected population requires personal care.

In OA, the articular cartilage undergoes repetitive inflammation due to focal loss or erosion, leading to joint space narrowing or subchondral sclerosis. OA can cause hypertrophy of osteoblastic activity or reparative bone response, which is known as osteophytosis. This can result in pain, immobility, and often disability. OA symptoms, such as joint pain, stiffness, and muscle weakness, are significant risk factors for mobility limitation and can negatively impact the quality of life (QoL) of affected individuals [1]. According to the literature, individuals with genetic predisposition, obesity, aging, or previous joint injury are more likely to develop OA at an earlier age. This disease is primarily caused by repetitive mechanical loads, age, and high levels of inactivity [2,3]. Physiologically, it is characterized by the loss of cartilage covering the joints, resulting in direct bone-to-bone contact [4]. The symptoms may vary greatly among individuals. While some patients may experience incapacitation due to the disease, others may be able to perform normal activities with little or no pain, despite the severity of the condition, as indicated by x-rays. Knee OA is commonly observed in individuals who engage in intense physical sports that require significant strain and loading on their joints, such as American football, soccer, rugby, and gymnastics. A prior injury is a major indication for future development of the disease. Obesity in the upper extremity is often associated with a major cause of knee OA, which results in heavy weight-bearing on the knee [5].

Rationale

In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommended using symptomatic slow-acting drugs for OA (SYSADOAs)—with the addition of paracetamol for short-term rescue analgesia when needed—as the initial pharmacological treatment for knee OA [6]. SYSADOAs exhibit excellent safety and tolerability. They consist of natural compounds that include repeating disaccharides, such as glucosamine sulfate, chondroitin sulfate, hyaluronic acid (HA), diacerein, and avocado-soybean unsaponifiable [7,8]. In recent years, extensive research has been conducted on HA, particularly its efficacy in treating mild to moderate knee OA through intra-articular (IA) administration. A meta-analysis of over 137 studies, including randomized clinical trials (RCTs), provided evidence of its effectiveness [9]. Following our experience in daily orthopedic clinical practice with the administration of both IA and oral HA, we have recently focused our research activities in OA on the use of oral high-molecular-weight HA (HMWHA). Although there is direct evidence that ingested HA reaches the knee joint in human-relevant preclinical mammalian models [10,11], it has not yet been determined whether HA is bioavailable in humans after oral administration. RCTs on oral HA administration are limited and inconsistent. Recent reviews have shown that while oral HA has been effective in relieving knee pain in various clinical trials without side effects, the heterogeneity of the efficacy end points strongly limits the generalization of these results [12]. Additionally, it has been observed that many of these trials used subjective parameters to measure pain, such as the visual analog scale (VAS), or specific scores for OA outcomes, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or the Knee Injury and Osteoarthritis Outcome Score (KOOS). In contrast, objective measurements, such as isokinetic dynamometry and ultrasonography, have been infrequently used and have shown several inconsistencies. With these considerations in mind, we conducted a thorough analysis of the existing medical literature [13] and decided to plan a double-blind RCT to test an oral formulation of HA in a calculated sample size of 80 patients with OA. The objective of the proposed study is to test the hypothesis that oral administration of HMWHA for at least 4 months would (1) reduce knee pain at the end of the study period, (2) demonstrate a statistically significant difference compared with a placebo-treated control group, and (3) demonstrate the aforementioned improvement by both subjective (eg, VAS and QoL) and objective measures (eg, ultrasonography). Unfortunately, conducting an RCT in a large patient population may pose a significant risk to our investigative team given our limited resources. Performing a pilot feasibility study before conducting the main RCT may be a reasonable solution. This 2-step procedure can help to prevent dangerous consequences when initiating the main trial. In fact, it can evaluate the feasibility of the monthly recruitment rate, estimate the time and budget required for the RCT, and avoid

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potential bias in the selection of end points and their measurements [14].

The research question, as shown in Figure 1 [12,13], is whether a pilot study using the same intervention (oral HMWHA) administered to 10% of the main study population for 8 weeks can assess the feasibility of a future RCT in patients with OA in terms of planned outcomes, time, and resources.

Figure 1. Mind map showing the rationale of the pilot study. ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; HA: hyaluronic acid; HMWHA: high-molecular-weight hyaluronic acid; IA: intra-articular; KOOS: Knee Injury and Osteoarthritis Outcome Score; OA: osteoarthritis; QoL: quality of life; RCT: randomized controlled trial; ROM: range of motion; SYSADOA: symptomatic slow-acting drug for OA; US: ultrasonography; VAS: visual analog scale.

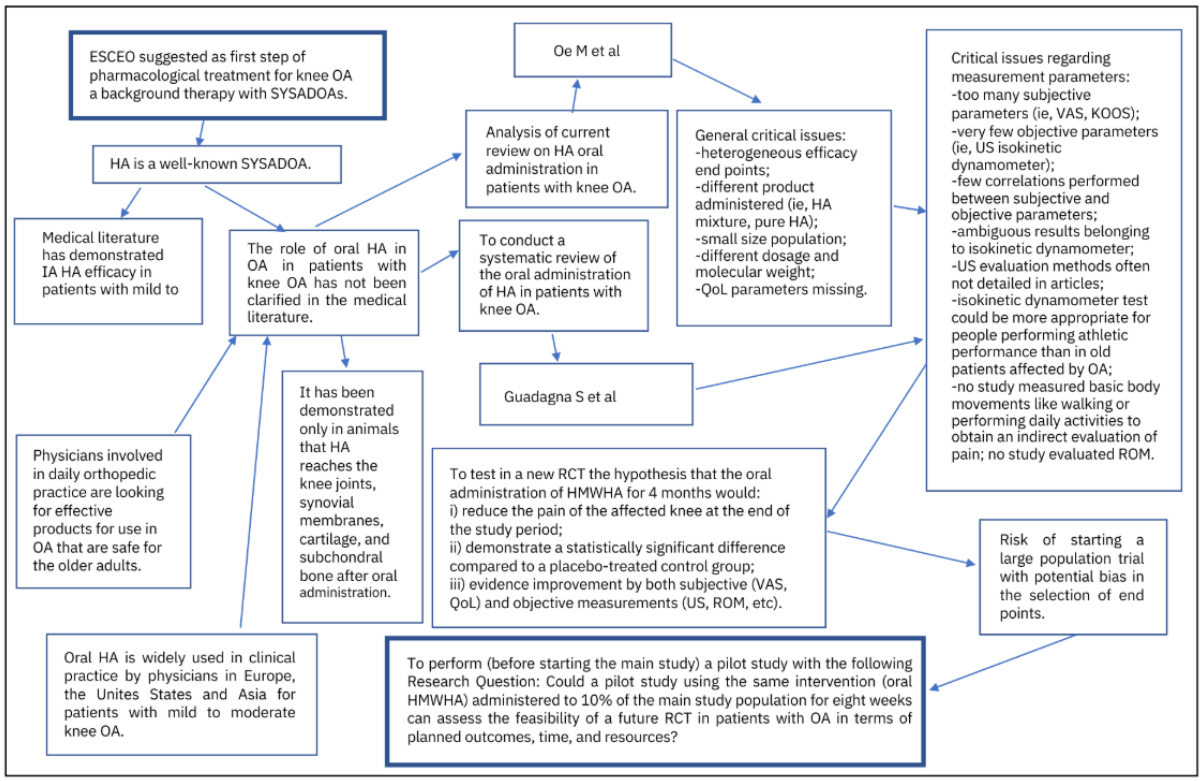

Methods

Overview

The study team is composed of 2 investigators from the University of Medicine and Pharmacy "Victor Babes" in Timisoara, Romania, in addition to the nurses and study coordinators from the participating site (Centrul Medical Medicali's, a private clinic specializing in orthopedics located in Timisoara, Romania). The Contract Research Organization (Opera CRO, a Tigermed company based in Romania) is selected directly by the team to handle logistics and study management, including document submission to the ethics committee (EC) and competent authority, project management, site monitoring, data management, and statistical analysis. The team choose the logo (Multimedia Appendix 1) and the study name :SMILE: (Syalox, Multicenter, Trial to Evaluate Knee OA) and prepare the protocol and all related documents, including the case report form (CRF), patient information leaflet, and informed consent form required for the feasibility pilot study. Before the project began, the study protocol was presented to River Pharma, a company based in Orio Litta, Italy, that manufactures a food supplement containing HA. The company provides the study team with the necessary products for both the pilot and main OA studies and partially funds the trials. The agreement between the parties stipulates that the sponsor will not be involved in the design, planning, collection, analysis, or interpretation of data in any future manuscript reporting the study results.

Study Design

This is an open-label, noncontrolled, single-center pilot feasibility study.

Ethical Considerations

The study protocol with the code OPRPH/0117/FS is approved by the local independent EC of Timisoara, Romania, the Comisiei Locale de Etica pentru cercetare stiintifica a Centrului Medicali, on December 12, 2017 (request # 012; Multimedia Appendix 2). Informed consent is obtained from each potentially eligible patient in accordance with the International Council for Harmonisation Good Clinical Practice (GCP) guidelines and the current version of the Declaration of Helsinki. Additionally, each included participant receives a patient information sheet that explains the trial's goal and procedure. This document, like the informed consent form, is written in plain Romanian language and is preapproved by the local EC. The information sheet describes the nature of the administered food supplement, its common use in orthopedic clinical practice, and its safety profile. The information sheet outlines the number of visits,

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types of procedures, assessments, and measurements to be performed during the trial. This provides potential participants with a clear understanding of the risks, inconveniences, and benefits that may arise from their involvement. The sheet should be updated as new important information becomes available that may affect a participant's willingness to participate or continue in the study. The investigators aim to inform potential participants that they are being invited to participate in a pilot feasibility study rather than a main study. Therefore, only future patients may benefit from the results of this study in terms of the efficacy of the product administered. In addition, the investigator should communicate the specific feasibility objectives of the study to the participants as well as the criteria for the pilot study to successfully lead to the main study. Participants are informed that their involvement in the trial is voluntary and that they may withdraw at any time while still receiving medical care. They are also informed that there is no compensation for their participation in the study and that the sponsor provides insurance coverage in the event of a trial-related injury. Potential participants are informed that their medical records would be reviewed by the sponsor, CRO personnel, and regulatory authorities in accordance with applicable laws and regulations, and that personal information would be collected and maintained in a confidential database. Written consent is obtained after the participants have been given sufficient time to review the information and ask questions. The procedure for obtaining informed consent requires that both the participant and investigator manually write and sign their names on 2 copies of the consent form after discussion. The investigator provides the participants with 1 copy of the signed informed consent form and 1 copy of the signed participant information sheet. The second copy of the original signed forms is kept in the on-site study file. The study adheres to the current General Data Protection Regulations (GDPR). Procedures for data collection and anonymization, as well as the explanation that data may be made available to other researchers in aggregate and anonymous forms, are detailed in a specific document (GDPR form) written in the local language and provided to the patient for approval and signature before the trial begins. The medical doctor in charge of the center is responsible for the treatment of patient data at the clinical site in accordance with the GDPR regulations.

This study protocol complies with the CONSORT (Consolidated Standards of Reporting Trials) statement for pilot and feasibility studies [15] and is registered at ClinicalTrials.gov under the identifier NCT03421054.

Inclusion Criteria

Patients who meet the following criteria are eligible for inclusion: (1) any sex and age between 50 and 70 years and (2) symptomatic OA of the knee with mild joint discomfort for at least 6 months before enrollment, following American College of Rheumatology (ACR) criteria with history and physical examination [16] (participants diagnosed with bilateral knee OA are asked to identify the most affected knee at baseline [BL], and this knee is evaluated throughout the study period); (3) available confirmatory radiographic diagnosis (performed within the previous 6 months) with Kellgren-Lawrence score 2 at the knee joint evaluated [17]; (4) participants experienced pain for at least 15 of the 30 days before study entry; (5) signed informed consent; and (6) demonstrated compliance with all study requirements.

Exclusion Criteria

Patients meeting any of the following criteria are excluded from the study: (1) any inflammatory arthritic condition (other than knee OA), fibromyalgia, multiple sclerosis, or autoimmune disorder; (2) oral corticosteroid treatment within 4 weeks before screening; (3) IA injections of HA or corticosteroids in the target joint within 3 months before screening; (4) participants who have taken anti-inflammatory or chondroprotective drugs (such as chondroitin sulfate, glucosamine, methylsulfonylmethane, HA, and diacerein) within 2 weeks before selection; (5) use of HA-containing nutritional supplements or cosmetics within the month before the study; (6) previous surgical treatment of the knee joint or require OA-related surgery (such as high tibial osteotomy or arthroplasty) or have complications that require hospitalization and surgical treatment; (7) significant injury to the target joint within the 6 months before screening; (8) participants who are following an energy-restricted diet for weight loss; (9) pregnant women, nursing mothers, or women of childbearing potential who are not using adequate methods of contraception; (10) participants with cardiovascular, hepatic, renal, respiratory, or hematologic disease, or any other medical or psychiatric condition that, in the opinion of the investigator, would impair participation or is likely to result in hospitalization during the course of the study; (11) participation in an interventional clinical trial within the past 30 days; and (12) presence of any clinically significant medical condition that, in the opinion of the investigator, precludes patient enrollment in the study.

Discontinuation Criteria

Patients may withdraw from the study at any time on their request. The investigator may withdraw a patient from the study at any time for health reasons. In both cases, the investigator must explain the reasons for withdrawal on the CRF and the participant is considered to have withdrawn. Additionally, the study may be terminated by the investigator or sponsor for any of the following reasons: (1) insufficient participant enrollment at the center, (2) persistent or serious noncompliance with the protocol, and (3) noncompliance with GCP or regulatory requirements. If the trial is prematurely terminated or suspended for any reason, patients will be promptly informed and the EC and regulatory authorities must be notified.

Recruitment

The study team at the involved site, including the principal investigator, are doctors trained in GCP with over 10 years of experience in orthopedics or rheumatology. To prevent selection bias, patients should be consecutively enrolled. Therefore, all patients with knee OA and visiting the center from February 2018 (start of enrollment) to April 2018 (planned end of enrollment) should be screened, asked for informed consent, and checked for inclusion and exclusion criteria. The data for each patient must be recorded in the CRF. In cases where patients are screened but not enrolled owing to exclusion criteria or participation in another interventional study, the decision to

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exclude the patient must be clearly reported on the CRF. Our goal is to recruit at least 8 patients with knee OA according to the ACR criteria (Figure 2) from a single site over a 2-month period. These participants must meet the inclusion criteria outlined in the pilot study protocol, which will also be used in the future main study.

Figure 2. Flowchart of the pilot study.

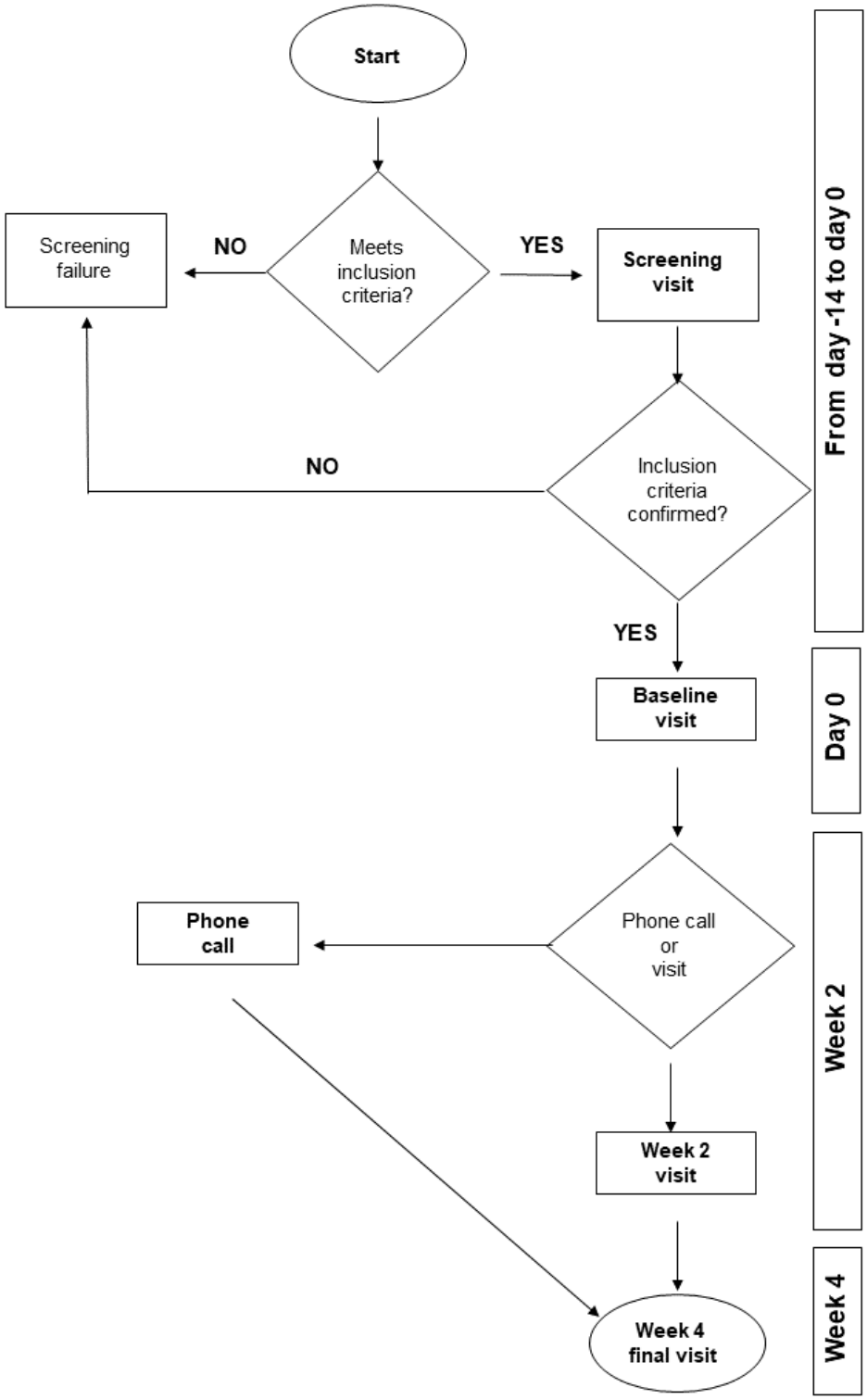

Intervention

All patients will receive Syalox 300 Plus (River Pharma), a food supplement containing HMWHA. Although this product has been available in European countries for several years and has been used in the clinical practice by hundreds of orthopedists, only a few clinical trials [18] have been conducted to test whether this type of product with oral HA could complement the treatment of patients affected by OA. In this study, the investigational product (IP) is administered as 1 tablet daily for 8 weeks, preferably before or during meals, with plenty of water. Following local legislation for food supplements, the product

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used is the same as that available in the market and must be administered as reported in the instruction for use. No changes in the dosage are planned during the study period. However, the investigator may decide to discontinue IP administration in case of adverse events (AEs) and serious AEs (SAEs) or to use other therapies at any time if he or she deems it necessary for the patient's health. The reason for discontinuing the administration must be documented in both the source documents and CRF. At BL, each patient is given an IP package for the entire duration of the study (60 tablets). Patients are instructed to return all IP packages to the investigator at the end of the study to ensure product accountability. The IP contains 2 ingredients: HMWHA and dry extract of Boswellia.

A medical literature analysis has shown that HMWHA has been effective in relieving knee pain in various clinical trials without side effects [12,13]. The amount of HMWHA in the IP used in this study, which is greater than 2.8 million Da, is comparable to or slightly higher than that of supplements already available on the market for viscosupplementation in OA [13] and used in clinical trials [19-21].

Among the boswellic acids obtained from the gum resin of Boswellia species, 11-keto-β-boswellic acid and 3-O-acetyl-11-keto-β-boswellic acid (AKBA) show strong evidence of downregulation of cytokine production and inhibition of inflammatory response enzymes [22]. A phase Ia study performed in the United States in 20 patients with invasive breast cancer [23] shows that oral administration of boswellia at a dose of 2400 mg daily for 5-56 days has a good safety profile, is well tolerated, and reduces breast tumor cell proliferation. A recent review [24] suggests that AKBA could be an effective and safe treatment option for patients with OA with a treatment duration of at least 4 weeks. There is a discrepancy between the amount of Boswellia extract and boswellic acid present in the tested IP (100 mg of dry extract and 10% AKBA, respectively) and the significantly higher levels found in products on the market in Europe and the United States (in particular, AKBA ranges from 17% to 66%) [25]. Furthermore, in the literature, improvement in OA symptoms has only been demonstrated in clinical trials using at least 20% AKBA [26,27].

Concomitant Care and Interventions

For ethical reasons, we decide to administer also rescue medications. This term [28] refers to drugs that can be administered to patients in a trial if the efficacy of IP is not satisfactory.

Two boxes of Paracetamol LPH 500 (40 tablets in total) are delivered at the BL and collected at the final visit (week 8). Each tablet contains 500 mg of paracetamol. If requested by the patient, an additional box of 20 tablets is delivered at week 4. In any case, a daily dosage of >3000 mg (6 tablets per day) is not allowed.

For the duration of the pilot study, participants are prohibited from consuming alcohol, abusing drugs, following an energy-restricted diet for weight loss, taking diuretics, or any medication listed in the exclusion criteria. Additionally, routine intake of antiresorptive drugs such as bisphosphonates or estrogen is not permitted.

There are no restrictions on treatments previously administered by the participants for clinical conditions unrelated to the study.

Objectives

The primary objective of this pilot study is to test the same outcomes that will be implemented in the future RCT. This next trial will have a calculated sample size of at least 80 patients and a study duration of 4 months. Therefore, the feasibility of using ultrasound and range of motion (ROM) to objectively measure the potential improvement in the tested joint mobility during the trial is evaluated. Additionally, we investigate whether there is a correlation between ROM or ultrasound improvement and subjective VAS scores.

This pilot study, even if it is a small-scale investigation, should also confirm the safety data belonging to the large use of oral HA in clinical practice.

Another objective is to collect data to assess the feasibility of the future main RCT in advance, estimating the time and budget required. The collected data can be both quantitative and qualitative.

Finally, this study should provide preliminary data on the efficacy of the tested product. However, these data will not be exhaustive, as the focus of the pilot study is on the reliability of the outcome and feasibility of measurement, rather than statistical significance [29].

Potential Risks

The potential risks to patients are related to the administration of oral HA, AKBA, and the rescue medicine (paracetamol). Although oral HA has no documented side effects, some users reported skin rashes and blurred vision after oral HA administration. These reports were anecdotal. In rare cases, HA (only if administered via IA) may cause allergic reactions [11].

In rare cases, AKBA may cause life-threatening allergic reactions, which can be identified by symptoms such as chest pain, breathing difficulties, hives, or swelling. Although AKBA is generally well tolerated, it may cause stomach discomfort, nausea, heartburn, fullness, or diarrhea [30].

Considering that the rescue medication paracetamol could be used only occasionally (high doses and prolonged treatment are not allowed in this study, and pre-existing renal and hepatic impairment are in the exclusion criteria), the potential risk should be low. In any case, the possible risks of this drug include hypersensitivity reactions (transient rash, paresthesia, and pruritus), thrombocytopenia (generally asymptomatic, rarely bleeding or bruising, black and soft stools, blood in urine and feces, and red spots on the skin), agranulocytosis (pharyngitis and fever, unexpected), dermatitis, hepatic impairment (conjunctival jaundice or skin current), renal colic with sudden onset of severe lumbar pain, and renal impairment (oligoanuria).

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Outcomes

Primary Outcomes

1. ROM: The improvement in active and passive knee flexion and extension, measured in degrees using a goniometer and assessed by the investigator, between the BL visit and the final visit.
2. Ultrasound: A qualified physician records improvements in ultrasound parameters including synovial fluid, articular cartilage damage, medial meniscus protrusion, lateral meniscus protrusion, medial osteophytes, lateral osteophytes, enthesopathies, and effusions.
3. VAS: The improvements in VAS (at rest) scores between the BL and final visit are measured in millimeters. A paper printed scale of 100 mm was used to measure pain intensity. Patients must draw a vertical line at the point considered to be the level of pain at a specific moment, that is, resting, moving, or pressing.
4. Safety: Investigators must collect and evaluate all AEs and SAEs according to the current local legislation. AEs and SAEs must be summarized based on the number of affected patients. This includes related AEs, including those that are possibly related to or not evaluable. The incidence, type, and severity of AEs or SAEs are presented in frequency tables using MedDRA (Medical Dictionary for Regulatory Activities) terms. Frequency is compared using the χ^2 test

Secondary Outcomes

Parameters necessary to estimate the time and budget required for the main study, which include the following:

1. Quantitative parameters, such as monthly recruitment rate, duration of enrollment and visits, choice of end points, and measurement.
2. Qualitative parameters, such as information on patient reluctance to enroll, difficulty understanding the consent form, logistic issues at the site, interpersonal relationships among staff, and patient-reported QoL measured by the KOOS questionnaire (paper printed version) and the Lequesne Algofunctional Index (which also includes physical activity questions).

At the end of the pilot trial, the following criteria are used to determine whether to proceed with the future main RCT: there must be evidence of improvement in both the subjective outcome (VAS at rest) and at least one of the objective outcomes (ROM and ultrasound) at the final visit. On the contrary, due to the small sample size, a statistically significant correlation (using the Pearson coefficient) between objective and subjective parameters is not required.

Exploratory Outcomes

In addition to the primary and secondary outcomes, we identify exploratory outcomes that could be implemented in the main trial:

1. Actigraphy: This specific tool measures physical activity levels using a triaxial accelerometer that collects 24/7 data points during the patient's daily activities. The investigator downloads and processes the data using specific software during routine visits at the center. The instrument is available in the market and has already been tested in OA clinical trials to objectively evaluate the composite measurement of pain and basic activities such as walking or performing daily tasks [31,32]. In this pilot study, an actigraph is worn around the knee to record data for 7 days.
2. Rescue medication: Measuring the use of rescue medication during a clinical trial can provide information on the robustness of the analgesic efficacy of the tested product. Rescue medication may also be used as a primary end point according to the US Food and Drug Administration guidelines [33].

This study also provides preliminary data on the efficacy of the tested product.

Framework of the Study

Before any study procedure, patients receive information about the nature, purpose, benefits, and risks of the trial. Participants are then asked to sign an informed consent form. After the screening assessment (from day –14 to day 0), patients undergo a BL visit (day 0) to assess the inclusion and exclusion criteria and check for routine orthopedic conditions (Figure 3). To confirm the diagnosis of knee OA, the investigator evaluates an x-ray test with anteroposterior and lateral views that are no earlier than 6 months old.

At BL (Table 1), the investigator also performs an ultrasound, ROM test, VAS, and the KOOS questionnaire. The actigraph must be placed above the affected knee 7 days before the visit and removed at BL. Safety is assessed by phone at week 4 ± 2 days, or an optional visit should be conducted to complete the questionnaires, scales, and scores.

The final visit is scheduled for week 8 ± 4 days to conduct an ultrasound, ROM assessment, VAS, and the KOOS questionnaire. Patients wearing the actigraph will also be asked to return to the site 7 days before the visit to place the device above the affected knee; it will be removed during the final visit.

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Figure 3. Flow diagram (CONSORT [Consolidated Standards of Reporting Trials]) of the pilot study.

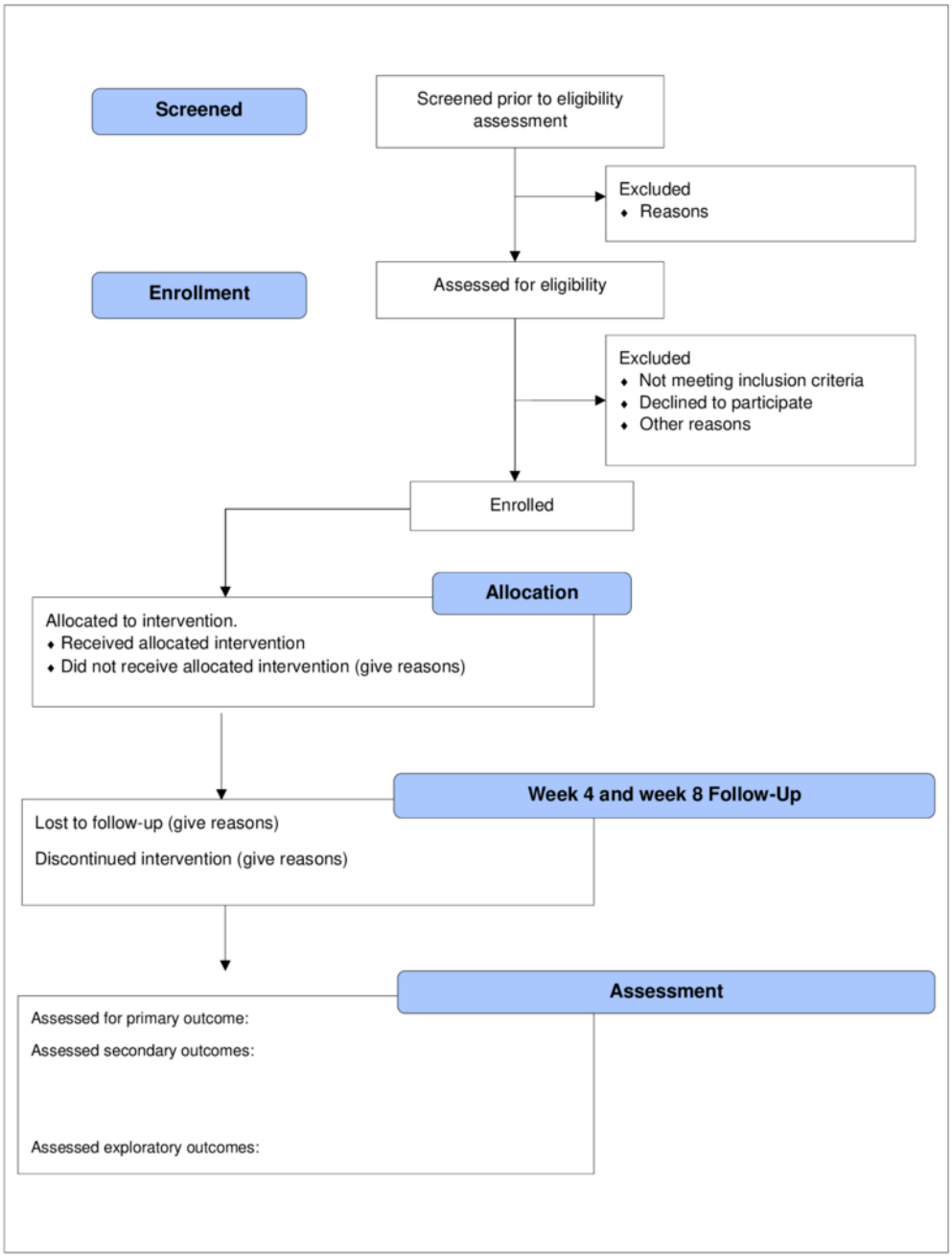

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Table 1. Schedule of observation points and assessments.

Assessments	Visit 1	Visit 2	Visit 3
Days	–14 to 0	28 (±2)	56 (±4)
Weeks	–2 to 0	4	8
Informed consent	✓		
Inclusion criteria	✓		
Exclusion criteria	✓	✓	✓
Demographics and medical history	✓		
Physical examination and vital signs	✓		
Orthopedic assessment	✓		✓
Concomitant treatments	✓	✓	✓
Actigraphy—sensor delivery (1 week before the visit; optional)	✓		✓
Actigraphy—sensor return (optional)	✓		✓
KOOS[a]	✓	✓[b]	✓
VAS[c]	✓	✓[b]	✓
ROM[d] by a goniometer	✓	✓[b]	✓
Ultrasonography	✓		✓
IP[e] delivery	✓		
IP return			✓
Rescue medication delivery	✓		
Rescue medication return			✓
Rescue medication accountability card delivery	✓		
Rescue medication accountability card return			✓
Adverse events	✓	✓[f]	✓

[a]KOOS: Knee Injury and Osteoarthritis Outcome Score.

[b]Tests and examinations not mandatory if the visit is performed via telephone call.

[c]VAS: visual analog scale.

[d]ROM: range of motion.

[e]IP: investigational product.

[f]Safety (adverse event or serious adverse event checking) is mandatory in any case.

Sample Size

For feasibility and pilot trials, it is important to justify the sample size; however, a formal calculation may not always be necessary [34] and is often not reported. In fact, a pilot study is not a hypothesis testing study, and often its main purpose is to test the feasibility of the proposed approach. This involves testing quantitative parameters, such as outcomes and resources, as well as qualitative factors, such as QoL and logistical issues at the site.

Although some papers suggest a sample size of 12-20 participants for pilot studies, it is generally reported that 10%-20% of the main sample size is a reasonable number for conducting such trials [35]. Given that the sample size of our main RCT will be 80 patients and the exploratory nature of this pilot study, investigators have agreed to enroll only 8 participants.

Statistical Analysis

Quantitative variables, such as demographics, are described using mean and SD if normally distributed and median and IQR if nonnormally distributed. Comparative analysis is performed using either the Student *t* test (2-tailed) or the Mann-Whitney *U* test, depending on the distribution of the variables. Factorial variance analysis can be used to evaluate interactions between quantitative variables and linear progression models to identify possible confounding bias with independent variables. Categorical variables are described using frequencies and percentages, and comparative analyses using the χ^2 test. The Spearman rank correlation, a nonparametric test, measures the degree of association between 2 variables. The Spearman rank correlation test is appropriate for analyzing correlations when variables are measured on at least an ordinal scale, as is the case in this study. This test does not make any assumptions about the distribution of the data. When analyzing the enrolled population, we use the Spearman rank correlation test to identify

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any strong positive correlations (at least 0.7) between the reduction in VAS (at rest) and ultrasound parameters, as well as between the reduction in VAS (at rest) and ROM improvement.

We evaluate the quality and completeness of the collected data before conducting any analysis. If a participant is missing information for 1 or more variables, even after the queries are resolved, the missing data are not replaced. Additionally, if a participant has violated the inclusion and exclusion criteria, the corresponding data are excluded from the analysis.

Results

Recruitment and treatment of the 8 patients began on February 15, 2018, and was completed on May 25, 2018. Data analysis was planned to be completed by the end of 2018, with full results expected to be published in the last quarter of 2024.

Discussion

"You Have to Walk Before You Can Run"

We wanted to perform an RCT to test oral HMWHA in patients with OA. We calculated the sample size (approximately 80 evaluable participants), defined the design (double-blind randomized vs placebo), and estimated the duration of treatment (at least 4 months). We have previously conducted and published a systematic review of existing RCTs on HA [13]. We were even trusted to have found a potential problem that caused the limited and equivocal results of the previous RCT with HA published in the medical literature. We abruptly halted our planning and, gazing into each other's eyes, reminded ourselves of the old adage: "You have to walk before you can run." It would be unrealistic to attempt to build and execute a future main RCT to test oral HMWHA in OA with only the limited resources of a team of investigators in Eastern Europe. The risk of misplanning trial management (ie, duration of enrollment, sites to be involved, visits, and examinations) and the possibility of bias in the selection of outcomes is too high. It is not feasible to consider such a significant risk in terms of finances, time, and resources without first testing the project, even on a small scale. To ensure the feasibility of the monthly recruitment rate, to estimate the time and budget requirements for the main study, and to avoid potential bias in the selection of end points and their measurement, it is necessary to perform a preliminary evaluation. For this reason, the present pilot feasibility study protocol was designed and developed. Three additional issues related to trials of oral HA in patients with OA can be discussed.

The first is a comment reported by the principal investigator in a letter to the editor [36]. In particular, he reported several additional critical issues regarding the parameters used to measure the end points. The use of VAS for pain measurement and specific scores for OA outcomes, such as KOOS, as well as scales tested only in the Japanese population, for example, Japanese Knee Osteoarthritis Measure and Japanese Orthopaedic Association scales [37,38], should be considered a subjective measure despite being standardized and validated. In 7 trials conducted in Japan, only the VAS and/or other types of scales were used to measure OA symptoms, and no objective tools, such as ultrasound or isokinetic dynamometers, were used. These instruments were used in only 4 of 10 studies performed in Europe and America. However, several studies have generated ambiguous results when using ultrasound [39-41] and isokinetic dynamometers [40-42]. In only 2 studies, ultrasound measurements showed a statistically significant difference from the control group [39,40]. Furthermore, it is hard to define a positive result when the only statistically proven difference from the control group is the isokinetic peak torque at 240° of the extensors [37]. In 2 trials [39,41], the methods used to apply and evaluate ultrasound examinations were not reported. In the third study [40], the only ultrasound data collected was the measurement of synovial effusion in the suprapatellar recess on the longitudinal axis in millimeters following the 2005 EULAR guidelines [43]. Isokinetic tests were conducted using the Biodex System (Biodex Medical Systems), which is considered the gold standard for such measurements. However, in the study protocol, it was not considered that an increased level of synovial fluid (4 mm in the suprapatellar recess) could be a common symptom in patients with knee OA. Therefore, in several cases in the abovementioned trials, excess synovial fluid could cause pain and interfere with the isokinetic assessment of muscle strength [40]. The reason for using this tool as the primary efficacy assessment in 3 trials was that a reduction in knee OA pain could indicate an increase in work, power, and peak torque of the leg muscles. This surrogate end point could be useful for testing HA on joint pain in athletes or young people. In contrast, the studies that tested isokinetic assessment had patients with a mean (SD) age of 56.1 (8.00) years [40], 42.38 (10.16) years [41], and 59.6 (8.3) years [42]. Even if there were a statistically significant difference in muscular strength in a similar population of older patients, it would not be considered clinically important because this parameter does not affect the patients' QoL.

None of the trial reviews objectively evaluated the composite measurement of pain and basic activities such as walking or performing daily tasks. Actigraphs, which are capable of recording these data, have been tested in clinical trials with patients with knee OA [32]. The cost of a single actigraph is approximately US $100, which is significantly less than that of the Biodex system. Additionally, actigraphs are user-friendly, and their data can be collected using a standard personal computer.

Second, ROM, another tool that can objectively measure the potential improvement in OA using a simple goniometer, paradoxically was not included as an outcome in these trials. ROM measurement remains widely used in orthopedics, and we believe that it can be easily correlated with specific scales such as VAS and KOOS to improve patient assessment. In this pilot study, because ROM is not the best way to assess disability in severe OA, we only included patients with a Kellgren-Lawrence score of 2.

The third topic is our willingness to include the daily average consumption of rescue medications as an exploratory outcome. In a similar OA population with a Kellgren-Lawrence score of 2 or 3 and treated with placebo for 24 weeks, the number of paracetamol 500 tablets used per day ranged from 0.34 [44] to 1.32 [33]. Effective medications should be the only option to

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reduce the need for rescue medications, so collecting and evaluating this objective parameter should be straightforward.

The criteria that we have identified for determining whether to proceed with the future RCT are improvement in both the subjective outcome (VAS at rest) and at least one of the objective outcomes at the final visit. We also believe that owing to the small sample size of this pilot study, a statistically significant correlation between objective and subjective parameters as a condition for starting the main future RCT is not required at this stage.

On the basis of the findings of this open-label pilot feasibility study, we will be able to design and conduct the future double-blind RCT to evaluate the efficacy of oral HA in knee OA. In clinical trials, investigators generally record these findings as the correlation between objective and subjective outcomes (ie, ROM and VAS, respectively). In daily medical practice, orthopedics uses the same findings (the link between the subjective symptoms reported by the patient and the objective signs of their visit) to demonstrate the patient's improvement. Therefore, correlating objective and subjective improvements in patients affected by knee OA could provide an additional measurement tool for medical doctors in their daily orthopedic practice.

Limitation of the Study

The main limitation of this study is the absence of a control group. In fact, to reduce costs and simplify the protocol, the placebo group was not included.

A second limitation is that the IP used does not contain HA alone, but a combination of HA and a very low amount of boswellic acid (10% AKBA). With such a low dose of AKBA, only 1 study [45] showed positive results for the treatment of OA. This study used a product that contains 14.4 mg of AKBA combined with a high dose of methylsulfonylmethane, a well-known SYSADOA. Therefore, it can be assumed that in the pilot study, the effect of HA should be more prevalent than that of AKBA.

Finally, the KOOS questionnaire is used in this pilot study, although the WOMAC is the most widely used test for evaluating hip and knee OA. The KOOS evaluates both the short- and long-term consequences of knee injuries. The KOOS is selected for this study as it is a free and open-access alternative to the expensive WOMAC index. The KOOS is an extension of the WOMAC.

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Data Availability

The data sets analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BA and DED conceptualized the study; BA and DFB were involved in the methodology for the trial; BA, DFB, and DED performed the formal analysis of the study; the investigations were performed by BA and SR; BA, DED, LB, and DFB wrote the original draft of the manuscript; DED, SR, and DFB performed the review and editing of the manuscript; BA and DED supervised the project; DFB, LB, and SG were responsible for the project administration. Finally, all authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

DFB and DED are employed at Opera Contract Research Organization (CRO), the CRO that managed the study. SG is a former employee at Opera CRO. LB is a former intern of TIGERMED Italy. The rest of the authors declare no conflicts of interest.

Multimedia Appendix 1
Logo of the pilot study.
[PPTX File , 1378 KB - resprot_v13i1e13642_app1.pptx]

Multimedia Appendix 2
Ethics Committee approval.
[PDF File (Adobe PDF File), 2189 KB - resprot_v13i1e13642_app2.pdf]

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Abbreviations

ACR: American College of Rheumatology
AE: adverse event
AKBA: 3-O-acetyl-11-keto-β-boswellic acid
BL: baseline
CRF: case report form
CRO: Contract Research Organization
EC: ethics committee
ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
GCP: Good Clinical Practice
GDPR: General Data Protection Regulations
HA: hyaluronic acid
HMWHA: high-molecular-weight hyaluronic acid
IA: intra-articular
IP: investigational product
KOOS: Knee Injury and Osteoarthritis Outcome Score
MedDRA: Medical Dictionary for Regulatory Activities
OA: osteoarthritis
QoL: quality of life
ROM: range of motion
SAE: serious adverse event
SYSADOA: symptomatic slow-acting drug for OA
VAS: visual analog scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

School Violence Exposure as an Adverse Childhood Experience: Protocol for a Nationwide Study of Secondary Public Schools

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Abstract

Background: Poor mental health and adverse childhood experiences (ACEs) predict extensive adverse outcomes in youth, including increases in long-term risk for chronic disease and injury, impaired emotional development, and poor academic outcomes. Exposure to school violence, specifically intentional gun violence, is an increasingly prevalent ACE. The anticipation of school shootings has led to the implementation of school safety and security interventions that may increase anxiety, depression, and other indicators of poor mental well-being among students and staff alike. Despite this, the association between exposure to existing school safety interventions and early adolescent student mental health outcomes, while accounting for one's history of ACEs, has not been previously investigated.

Objective: The study protocol described here aims to determine whether there is a significant difference in the prevalence of mental health outcomes, perceived school safety, and academic engagement between adolescent students (grades 6-12) at schools who have experienced a school shooting and those who have not; whether existing interventions to promote school safety and security are associated with poor mental health outcomes among students and school staff; and what the strength of the association between school safety interventions and mental health outcomes among students and teachers is in schools that have experienced a school shooting versus schools that have never experienced a school shooting.

Methods: This observational study will collect cross-sectional survey data from a nationwide sample of students, teachers, and principals at 12 secondary public schools across the United States. The participants come from 6 randomly selected exposure schools that have either experienced a recent (<2 years ago) intentional school shooting or have experienced an intentional school shooting less recently (>2 years ago). Data from these schools are being directly compared with 6 secondary schools that have never experienced a school shooting.

Results: Institutional review board approval for this research project was obtained and the study subsequently began its recruitment and data collection phase in January 2024. Data collection is currently ongoing and the expected completion date is January 2025. The analytic plan is designed to determine if the strength of the association between school safety interventions and mental health outcomes differs among students and school staff in schools with varying levels of school violence exposure. Analyses will be used to evaluate the role of ACEs on the relationships among exposure to an intentional school shooting, exposure to school safety strategies, and student outcomes (ie, mental health and well-being, perceptions of school safety, and educational outcomes).

Conclusions: The results from this study promise to generate meaningful and novel findings on the extent to which having a prior history of ACEs moderates the relationships among exposure to intentional school gun violence, school safety strategies, and student outcomes (ie, mental health and well-being, and perceptions of school safety).

Trial Registration: ClinicalTrials.gov NCT06153316; https://clinicaltrials.gov/study/NCT06153316

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International Registered Report Identifier (IRRID): DERR1-10.2196/56249

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KEYWORDS

adolescents; adverse childhood experiences; gun violence; health outcomes; injury prevention; school violence

Introduction

Background

Poor mental health and the prevalence of adverse childhood experiences (ACEs) have substantially increased among the youth in the United States over the past decade. This increase has been confirmed through independent national surveys, hospital admissions related to self-harm, and death by suicide, which has tripled for girls and doubled for boys aged 10-14 years [1-5]. Moreover, recent data from the Adolescent Behaviors and Experiences Survey conducted by the Centers for Disease Control and Prevention and others [6] have underscored that indicators of poor mental health among adolescent youth have persisted during the COVID-19 pandemic [7]. These increases have occurred concomitant with substantial increases in school shootings across the United States [8,9].

Exposure to gun violence over the past several years has catalyzed a national movement that has sought to increase school gun violence preparedness and safety. K-12 (the grades of kindergarten and 1st-12th grade) schools that have experienced intentional gun violence have implemented a number of policies specifying tactics designed to keep their schools safe and secure from future acts of violence. These have included arming teachers with firearms, using metal detectors, and implementing "zero tolerance" discipline policies [10-14]. Nearly all public schools that have not experienced intentional gun violence have responded to the anticipation of such incidents by implementing some form of school safety and security measures; as of 2019, 96% of all K-12 public schools in the United States reportedly conduct lockdown drills [15].

Although the pursuit of these efforts has value, research suggests that some of these interventions may not be beneficial and may decrease student perceptions of safety in their schools [10-12]. Additional research has drawn connections between perceived school safety and self-reported mental health symptoms among the youth [16]. However, little research has documented the burden of mental health problems on cohorts of students subsequent to actual as well as anticipated school gun violence. Understanding the nature and scope of this burden is critical for designing effective school safety interventions that attend to youth mental health needs while also accounting for prior histories of ACEs among students. In addition, there is scant research evaluating the mental health needs and perceptions of safety among school staff who have been present during a school shooting or who are also exposed to school safety interventions, or both.

Mental Health and Gun Violence

Poor mental health symptoms among youth predict extensive co-occurring adverse outcomes, including increases in long-term risk for chronic disease and injury, impaired child development, and poor academic outcomes [17-21]. This observed increase in prevalence of mental health problems followed the 2012 Sandy Hook Elementary School shooting, and perhaps not by coincidence—since January 2012, there have been hundreds of incidents of intentional gun violence on school grounds [8,9]. Thousands of children have been exposed to gun violence, specifically in school, during this same period [22]. Indeed, children are now often referred to as being a part of the "mass shooting generation," a cohort of youth growing up in the presence of gun violence [23].

The prominence of gun violence in communities across the United States is likely and, unsurprisingly, has a substantial impact on the mental well-being of adults, with over 40% of US adult residents expecting that they or an immediate family member could become a victim of gun violence [24-28]. In particular, school staff must now contend with gun violence or the possibility of gun violence in their schools. This burden also requires them to attend to the mental health needs of their students, and for some educators, reckoning with exposure to gun violence or the possibility of such exposure may take a significant emotional and physical toll. The National Education Association has referred to this phenomenon as "secondary traumatic stress" [29]; however, there is need for research that more clearly establishes the strength of the relationships among students and school staff who have either been exposed to gun violence or are contending with the anticipation of gun violence, and their mental health and well-being.

Adverse Childhood Experiences

The scientific literature conceptualizes ACEs as stressful or traumatic events that exert harmful impacts on the healthy development of children through adolescence and into adulthood [30]. Although historically research on ACEs has focused on child abuse and maltreatment, ACEs are now understood to include a wider range of traumatic events, including youth experiences with the juvenile justice system, household mental illness, family members who have been incarcerated, and childhood exposure to gun violence [17,18,30-33]. The cumulative and long-term influence of ACEs on multiple harmful and injurious behaviors has been well established [18]. Research has confirmed that ACEs increase a person's risk of poor mental health, illicit drug use, self-harm behaviors, and premature mortality [18,19]. The impact of the toxic stress typically associated with ACEs on a child's brain development is also well-documented [20]. More recently, research has established a clear relationship between an increased number of ACEs and poor academic outcomes in children [17]. Thus, it is quite possible that those students who have a higher number of ACEs may experience poorer mental health and educational outcomes following exposure to intentional school shootings and school safety strategies implemented in response to the anticipation of such violence, in comparison with their peers

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who have experienced very few or any ACEs. At the same time, there is an emerging body of research on positive childhood experiences (PCEs), which include feeling a sense of belonging, having meaningful and positive relationships, and that collectively may mitigate the impacts of ACEs on child outcomes [34]. This work will seek to understand and incorporate the role of PCEs on youth mental health, well-being, perceived safety, and learning.

Exposure to School Violence

Previous research has shown that exposure to different forms of violence are ACEs in and of themselves [32,33]. Similar to other ACEs, the impact of exposure to violence on children's short- and long-term health outcomes is significant. For example, research has demonstrated that children and adolescents who have recently witnessed violence are more likely to experience symptoms of trauma, including the onset of posttraumatic stress [15,35]. There are multiple studies confirming that exposure to violence during childhood is associated with poor chronic health outcomes and poor mental health, as well as a significant increase in the likelihood that young people who are exposed to violence will perpetrate violent crime themselves [33,36-38]. Moreover, there is a substantial body of research on school violence that has linked youth exposure to violence, specifically in school settings with multiple poor health and learning outcomes, such as decreased motivation to learn and lower classroom engagement [17,39]. Not surprisingly, exposure to violence also influences health outcomes during adulthood (including increasing one's likelihood for depression and other poor mental health outcomes, sleep quality, chronic disease, and substance use) [30,40-42]. The effect of exposure specifically to intentional school gun violence on youth and adult mental health outcomes and youth educational outcomes, however, has not been comprehensively documented.

Influence of School Climate

A robust set of research confirms that children who feel dissatisfied with, disconnected from, or unsafe within their school environment are more likely to experience poor health and learning outcomes [39,43-45]. If young people feel unsafe or threatened, their ability to focus and perform academically is drastically reduced [39]. Furthermore, perceptions of safety at school and prior exposure to violence have been, and continue to be, highly correlated with engagement in many risk behaviors [43-45]. Conversely, a nurturing school climate that fosters cohesion and student satisfaction with their academic learning has been shown to offset high-risk behaviors [45]. However, there has been an uptick in intentional school gun violence over the past few years [8,9]. In addition to likely influencing a school's social and emotional climate [46], exposure to such violence has substantial implications for a school's physical environment and has prompted schools, both those that have experienced intentional gun violence and those that have not, to increase school violence preparedness [10-15]. Such school safety tactics include target hardening efforts, zero-tolerance policies, presence of armed school resource officers and armed teachers, and emergency preparedness programs [10-14,47-49]. While there are a number of strategies available to schools, there is very limited empirical evidence as to their effectiveness. Of the evidence that exists, certain security efforts have been shown to be ineffective at deterring violence and may even have a criminalizing effect on a school's climate [10,12]. Given this collective body of work, it is reasonable to hypothesize that these school safety strategies may contribute to poor mental health and distress among students and staff. There is, however, very limited empirical work that has evaluated this relationship [29,50].

Purpose

Poor mental health symptoms and ACEs among the youth predict extensive co-occurring adverse outcomes, including increases in long-term risk for chronic disease and injury, impaired child development, and poor academic outcomes [17-20]. At the same time, the anticipation of school shootings has fueled school safety and security interventions that may inadvertently increase anxiety, depression, and other indicators of poor mental well-being among students and staff alike [29,50]. Despite this, the association between exposure to existing school safety interventions and student mental health outcomes, particularly beginning in early adolescence, is not clear. It is also unclear whether, how, and to what extent the strength of these associations might differ among students and staff members from those schools that have more recently experienced a school shooting, those that have experienced a school shooting less recently, and those that have never directly experienced a school shooting but are nonetheless indirectly aware of these tragic events via media and other networks. Finally, we do not know whether and to what extent having a prior history of ACEs moderates the relationships among exposure to school shootings, exposure to school safety strategies, and student outcomes (eg, perceptions of school safety and academic achievement). The role of PCEs is also unknown. This study therefore seeks to fill these critical research gaps by answering the following questions:

1. Is there a significant difference in the prevalence of mental health outcomes, perceived school safety, and academic engagement between early adolescent and adolescent students (grades 6-12) at public secondary schools that have experienced a school shooting and those that have not?
2. Are existing interventions to promote school safety and security associated with poor mental health outcomes among students and school staff members?
3. Does the strength of this association between school safety interventions and mental health outcomes differ among students and teachers who have experienced an intentional school shooting versus students and teachers who never experienced a school shooting? Furthermore, are these associations moderated by student ACE history?

Methods

Sampling Frame

Study Design

This is an observational study that will involve collecting cross-sectional survey data from a national sample of students, teachers, and principals from 12 secondary public schools across

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the United States. Our sample includes participants from 6 randomly selected exposure schools: secondary schools that have recently experienced an intentional school shooting (<2 years ago) and secondary schools that have experienced an intentional school shooting less recently (>2 years ago). Of the schools in our dataset that meet these criteria, we are randomly selecting schools to participate in our study from the group of eligible schools. If a school does not express interest in participating, we are replacing that school with another eligible school in our dataset. We are then matching our exposure schools to 6 randomly selected nonexposure schools: 6 secondary public schools that have never experienced a school shooting. We are matching the nonexposure schools to exposure schools on the following key variables: state, urban or nonurban status, and school level (ie, middle or high school).

Exposure School Selection

Our research team is identifying all possible intentional school shooting cases via a comprehensive review of multiple national school shooting databases, including the K-12 School Shooting database, the Everytown for Gun Safety database on gunfire on school grounds, and the Washington Post database on school shootings, to identify all schools that have experienced intentional gunfire on campus during school hours [51]. These data document all incidents in which a gun is fired or a bullet hits school property for any reason, regardless of the number of victims, time, or day of the week. Our research team is then coding this list of incidents to identify cases that meet the criteria for intentional school shooting at a secondary (ie, middle or high school level) public school—all cases of intentional gunfire on school property, occurring during school hours (including 1 hour before official school activities begin and 1 hour after all official school activities end), beginning January 1, 2015—to ensure we have enough schools in our sampling frame that meet our aforementioned criteria. We are excluding accidental discharges and attempted suicides where no other person was targeted or shot. We are also excluding any incidents taking place on a school bus and on school property that are noncontiguous with the school's primary campus. Furthermore, we are cross-referencing our list of incidents with other publicly available data sources [40] to ensure that no incidents meeting our criteria are missed. Two members of our research team are then independently coding this list of incidents to identify the cases that meet our proposed study's criteria for "intentional school shooting"; a third member of our study team is reviewing any potential discrepancies in coding efforts. The final list of exposure schools will then be divided into 2 based on recentness, that is, schools where the incident happened between January 1, 2015, and December 31, 2021, and schools where the incident happened between January 1, 2022, to December 31, 2023. In total, 3 schools will be randomly selected from each list. In case a school declines to participate, we will move to the next randomly selected school. Nonexposure schools will be matched to the final exposure schools. In case a school declines to participate, we will move to the next randomly selected school.

Recentness

To operationalize the "recentness" of a school shooting event, we considered the existing literature on posttraumatic stress. The evidence shows that the onset of posttraumatic stress disorder (PTSD) symptoms can vary drastically (eg, symptoms may appear within 3 months of the traumatic experience or be delayed by months or even years) [52-54]. A 2-year cutoff, therefore, allows us to assess the difference between a more immediate impact versus a longer-term impact on youth mental health outcomes. Similarly, we expect shifts in perceived school safety, school safety strategies, and the implementation of other related school initiatives and programs to vary considerably in the aftermath of a school shooting incident. The 2-year cutoff will allow us to compare schools in the midst of that "flux" to those schools that have had some time to adapt their practices and policies following exposure to such violence.

Nonexposure School Selection

To select the nonexposure schools, we are randomly selecting 6 schools from a database of all public secondary schools in the United States [55], matching for the aforementioned variables (ie, state, urban or nonurban, and school level).

Students

Within each participating school, all students between grades 6 to 12 are eligible for and invited to participate in this study. To encourage study participation, we are implementing reasonable incentives for participants, keeping the survey as brief as possible, communicating study expectations clearly and consistently, engaging thoughtfully with each school's leadership team during the recruitment process, and using other best practices [56,57]. Accounting for attrition and individuals choosing not to participate, we expect a 15% to 20% response rate (which is consistent with other research that has involved collecting survey data directly from students, teachers, and principals) [58,59], and therefore, anticipate sampling between 1000 to 1200 students across the 12 participating schools.

Teachers

Within each participating school, all teachers are eligible for and invited to participate in this study. Multiple efforts are being made to maximize participant recruitment and retention. We anticipate a minimum of 60 teachers and upward of 120 teachers (5-10 teachers per school, on average) to participate in this proposed study.

Principals

The current principal of each school is eligible and being invited to participate in this study.

Participant Recruitment

Recruitment Process

In mapping out the study's recruitment process, the project team has drawn on existing best practices to ensure the study's success. First, the project team defined a clear sampling frame for school recruitment to ensure that the 12 schools being recruited fall within the purview and meet the purpose of the study's aims. We are also providing reasonable and feasibly budgeted incentives for all participating schools (specifically, a US $250 gift certificate to Amazon) as a small way to appropriately recognize each school's time and commitment to this study effort. To ensure that this effort takes only minimal

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time away from the existing school day and does not detract from the various responsibilities of all participants, the project team has worked to ensure that each aspect of the data collection process is as brief and efficient as possible. All of these details are being conveyed to the potential participating schools during the recruitment process.

Principal and Teacher Recruitment

In line with best practices, the principal at each potential participating school within our sampling frame is being approached directly through a written letter (sent via email). After 2 weeks, and if there is no response, the co–principal investigators (co-PIs) of the study are following up through a telephone call. The co-PIs are then meeting with the principal via Zoom (Zoom Video Communications, Inc) at their convenience to engage with them and describe the processes and expectations of the study for the school's participation, as well as the corresponding risks and benefits, and provide opportunity for the principal to ask questions (with additional opportunity for further conversations, as needed). If the principal agrees to support the study effort, the co-PIs are working closely with each principal to then recruit the school's teachers and students for participation in the study. The project team's previous research experience conducting this kind of research suggests that this engagement approach is beneficial for participant recruitment and aims to ensure participant comfort and transparency with all aspects of the study protocol.

To maximize principal and teacher participation, the co-PIs are organizing an optional 30-minute recruitment meeting initially via Zoom at each school (to be scheduled, with the principal's support, during the school's professional development hours). During this time, the co-PIs are presenting an overview of the study's purpose and proposed methods, highlight any relevant risks and benefits (including provision of incentives), describing the informed consent process, and providing an opportunity for the principal and teachers to ask questions about the study itself.

It should be emphasized that participation in this study is relatively brief and will involve the completion of 1 web-based survey. The informed consent form will be included at the beginning of the survey. However, as noted above, part of the recruitment meeting will involve the co-PIs answering any questions about the study and its corresponding informed consent process.

Student Recruitment

Similarly, to maximize student participation, the co-PIs are organizing an optional 30-minute recruitment meeting via Zoom for the students and their parents at each school. During this time, the co-PIs will present an overview of the study's purpose and proposed methods, highlight any relevant risks and benefits (including provision of incentives), describe the informed consent process, and provide an opportunity for the students and parents to ask questions about the study itself. Again, during this time we are emphasizing that participation is relatively brief and will involve the completion of 1 web-based survey. The informed consent form is also being included at the beginning of the survey (and for students older than 12 years, this will also include an assent form). As noted earlier, part of the recruitment meeting will involve the co-PIs answering any questions about the study and its corresponding informed consent process.

Measures

Data Collection Overview

This study involves collecting cross-sectional survey data from students, teachers, and principals from 12 public secondary schools across the United States. Publicly available secondary data about each school will also be collected and used. All participants will complete the survey on the web.

Demographics

Data on sex, race, age, grade-level, and presence or not at the time of the school shooting incident for students in the exposure school will be provided by each student at the beginning of the survey. Self-report data on teacher and principal demographics (eg, their length of time working at the school) will also be collected at the beginning of the teacher and principal surveys, respectively.

Mental Health and Well-Being

Among the participating students in each school, self-report data on mental health and well-being will be assessed via a survey that comprises items from the following: (1) the Patient Health Questionnaire (PHQ)–A [60], a validated and widely used survey assessing mental health and symptoms of depression among the youth; (2) the Child and Adolescent Trauma Screen [61], which has been validated for use by young people aged 7 to 17 years; and (3) the World Health Organization Well-Being Index (WHO-5) [62], which has been validated for use by individuals 9 years and older. The PHQ-A and Child and Adolescent Trauma Screen items are multiple-choice with 4 response options, and the WHO-5 items are rated on a 6-point Likert scale [60-62].

Among the participating teachers in each school, self-report survey data on mental health and well-being will be assessed via items from the following: (1) the PHQ-9 [63], a validated scale assessing mental well-being and symptoms of depression among adults; (2) the Generalized Anxiety Disorder-7 scale [64], which has also been validated and assesses the most common anxiety disorders among adults; and (3) the WHO-5 [62]. The PHQ-9 and Generalized Anxiety Disorder-7 items are multiple-choice with 4 response options, and the WHO-5 items are rated on a 6-point Likert scale [62-64].

ACE and PCE Prevalence

Each student will provide self-report data on ACE and PCE prevalence. The ACE items were adapted in previous research [17] from a validated tool [19]. Building upon additional research that has argued that children experience a greater range of adversity than most ACE assessments currently capture [31,33], additional items will be included. The survey will, therefore, assess the following: bullying, residential instability, meeting of basic needs, divorced parents, family member with poor mental health, family member engaging in substance use, domestic violence, incarcerated parent, community violence, exposure to gun violence, and exposure to violence in school. Each item will be multiple-choice, with the following response options: "yes," "no," or "prefer not to answer," and these data

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will comprise an ACE prevalence score that denotes how many ACEs each student has experienced. PCE items were similarly adapted in previous research [34].

Perceptions of School Safety

The "Safe and Responsive Schools" Safe School Survey [65] is a validated tool designed to be administered to students and school staff. This instrument assesses six critical constructs, including perceptions of school climate, school safety, and belongingness. In line with previous research on school violence and in an effort to comprehensively assess perceptions of school safety, this tool seeks to capture both minor conflicts (eg, arguments among students) as well as more significant forms of disruption (eg, weapon possession on school grounds). Each student survey will include items from the Safe School Survey, which has a 5-point Likert scale response option [65]. Each teacher survey will include items from the Safe School Survey designed for school staff, which has a 5-point Likert scale response option [65]. Furthermore, each principal survey will also include items from the Safe School Survey designed for school staff [65].

Educational Outcomes

Among the participating students in each school, self-report survey data on academic engagement will be assessed via 4 items stemming from the Student Engagement Instrument [66,67]. The Student Engagement Instrument is a survey that assesses extrinsic motivation to learn, future goals and aspirations, class participation, teacher-student relationships, and perceived peer support for learning [66,67]. We will also include 1 multiple-choice item that has been adapted from the Centers for Disease Control and Prevention's Youth Risk Behavioral Surveillance System that asks students to describe their academic grades in schools over the past 12 months [68].

School Safety and Security

Data on school safety and security strategies for each participating school will be collected via 2 sources. First, principals from all participating schools will be surveyed on their knowledge of current school safety tactics and policies. Data on school safety and security indicators under the following seven categories will be assessed: (1) external target hardening efforts (eg, monitored school entry doors and signs indicating the school is a "Gun Free School Zone"); (2) internal target hardening efforts (eg, metal detectors and security cameras); (3) student or staff monitoring (eg, threat assessment team and zero-tolerance policies for weapons); (4) emergency procedures or drills (eg, written active shooter plan); (5) emergency notification technologies (eg, anonymous thread reporting systems and panic buttons); (6) medical support (eg, full or part-time school nurse on campus); and (7) school security staff (eg, law enforcement officers or police and teachers and other personnel armed with guns). Each multiple-choice item will include the following response options: "Yes, this policy/practice is active now at my school," "No, this policy/practice is not active at my school," or "Don't know/No answer." It should be noted that several of these survey items were adapted from the School Survey on Crime and Safety that is administered via the National Center for Education Statistics to a nationally representative sample of schools to assess whether individual schools are or are not implementing a range of school safety and security interventions [69]. First, for each school, a summative score will be generated that accounts for the number of policies or practices that each principal responded with "yes." Second, and especially if the principals do not necessarily have the time and capacity to review the safety details via a survey, we will review each school's current school safety plan, which is a comprehensive document developed by the school stakeholders that details preparation and response protocols to various school emergencies (ranging from bullying prevention efforts to fire safety drills and active shooter scenarios). A thorough review of each school's safety plan will allow our team to validate the data collected about current school safety strategies and also fill in any missing data. Should there be any discrepancy between the data provided by the principal and the protocols detailed in the school safety plan, the study team will defer to the data provided via the school safety plan.

Active Shooter Drills

Given the ubiquity specifically of active shooter drill implementation across secondary schools in the United States [15], we will identify each school's active safety drill protocol via the school's safety plan in our school recruitment effort for both exposure and nonexposure schools, and subsequently in our analyses. Specifically, we will identify whether our schools are currently implementing the Standard Response Protocol [70], which is the most widely implemented active shooter drill protocol in schools across the United States and involves high student-teacher preparedness and processing, versus other types of drill protocols [71] that may involve low student-teacher preparedness, a surprise element to the protocol, and more realistic portrayals of violence built into the drill. This will help us to identify and subsequently classify schools in our sample with two varying types of active shooter drill implementation.

Independent Covariates

Multiple independent covariates will also be collected via data sources like the National Center for Education Statistics and the US Census and adjusted for in conditional logistic regression models [72,73]. These covariates will include the length of time since the school experienced a shooting, demographics (eg, urbanicity, school level, and type of school), and school district characteristics. In addition, secondary data on education access, equity, and school discipline will be directly downloaded from the Civil Rights Data Collection website [74]. Using these recent data on each participating school, the study team will create a "school discipline" summative score that will comprise the following indicators (accounting for school population size and reflecting the number per academic year): attendance rate, number of in-school suspensions, out-of-school suspensions, students referred to law enforcement, students disciplined for harassment or bullying, and school-related arrests. Propensity score match and control statistical methods will be used to ensure rigor in association validity, controlling for these characteristics comprehensively.

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Data Collection Procedures

Students

Participating students in each school will complete 1 web-based survey administered on the web via Qualtrics (Qualtrics, LLC) [75], which is an web-based survey platform. This survey will take approximately 10 to 12 minutes to complete.

Teachers

Participating teachers will complete 1 on the web, also via Qualtrics, that will take approximately 10 to 12 minutes to complete.

Principals

Participating principals will complete one 10- to 12-minute survey, again via Qualtrics. As part of the principal survey, we will be asking them to provide a copy of their school's current school safety plan.

Ethical Considerations

Protection for Human Subjects

This study protocol (protocol #21-149) underwent a full board review and has been approved by the institutional review board (IRB) at Teachers College, Columbia University. Details on data confidentiality and privacy protections, informed consent descriptions, the study's inclusion criteria, and participant compensation are noted in the following sections.

Data Privacy and Confidentiality Protection

Survey data collected from students, teachers, and school staff will be confidential. All participants will be associated with a specific school. However, no identifying names or any other identifiers will be used at any point in the study. Each participant will be identified solely via an alphanumeric code during the data collection and organization process. This will be used solely for matching the survey data to the appropriate school for analyses. No information about any individual student or staff will ever be reported or shared. Furthermore, all survey data will be reported in aggregate.

Informed Consent Descriptions

As described in the participant recruitment section, all potential participants will engage in a thoughtful informed consent process. Parents and guardians of all students will have the opportunity to provide consent, if they choose, for their child to participate in this study. Similarly, the potential teacher and principal participants will also complete a consent form before participation. These consent forms, all also approved by the Teachers College, Columbia University IRB, review in clear language the purpose of the proposed study, what each participant will be asked to do if they agree to participate, any potential risks, discomforts, and benefits each participant might expect from taking part in the study, details about the study's confidentiality, how the results will be used, and the co-PIs' contact information should any questions arise during this process. For those students whose parents provide consent for them to participate, they then will have the opportunity to complete an assent form before participating in the study's survey. The assent form for the students similarly and clearly describes the purpose of the research, what the student can expect during the study itself, any consequences associated with participating in this study, how we will take care to protect their data privacy and confidentiality, the co-PIs' contact information should any questions arise, and also a statement underscoring that participation is completely voluntary and that the student does not have to participate.

Inclusion

The literature that has been synthesized for this study elucidates the critical role that members of minority groups, members of both sexes, and children all play in a study like this. Thus, members from all 3 groups are included.

Compensation

Each participating school will receive a US $250 gift card to Amazon for the school to put toward books or other school supplies. Following participation in the study, the study's co-PIs will send the electronic gift card directly to the participating school's principal.

Data Organization and Treatment

Survey Data Entry

All survey data collected in this study are being recorded initially in Excel (Microsoft Corp) for organization and management and then subsequently read into SPSS (version 29.0; IBM Corp) for analysis [76]. The study team maintains a codebook; variables will be recoded where needed and summative scores will be computed.

Document Review

Each school safety plan will be reviewed and coded independently by 2 members of our research team to determine if each of the school safety strategies and tactics of interest are being implemented. These data will also be recorded initially in Microsoft Excel for organization and management and then subsequently read into SPSS for analysis.

Missing Data

Consistent with previous research, we estimate the majority of survey items to have <10% missing data and no more than 19% missing survey data on any given item [58]. However, should higher levels of missing data occur, multiple imputation methods will be used [77].

Data Analysis Plan

The data collected from the students, teachers, and principals across all 12 participating schools will be analyzed and will fully respond to each of the research questions. Descriptive statistics will be calculated to summarize student and teacher participant characteristics within each school and also describe each school's safety and security strategies. Analyses of covariance will subsequently be used to identify potential significant differences in the prevalence of mental health and well-being, perceptions of school safety, educational outcomes, and ACEs among students in schools that have more recently experienced an intentional school shooting, schools that have experienced an intentional school shooting less recently, and

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schools that have never experienced a shooting, while controlling for key covariates.

ANOVA will also be used to identify potential significant differences in the prevalence of mental health and perceptions of school safety among teachers in schools that have more recently experienced an intentional school shooting, schools that have experienced an intentional school shooting less recently, and schools that have never experienced an intentional school shooting. We used G*Power (version 3.1; Heinrich Heine University Düsseldorf) to run power analyses in anticipation of our proposed analyses, assuming an α level of .05 and a power of 0.80. In the case of our proposed student analyses, a very small minimum effect size will need to be detected to meet our power requirements and given our anticipated minimum sample size (exposure schools: N=500-600, nonexposure schools: N=500-600). In the case of our teacher analyses, a medium effect size will need to be detected and given our anticipated minimum sample size (exposure schools: N=30-60, nonexposure schools: N=30-60). On the basis of the average enrollment across secondary public schools in the United States, we should be able to reach the minimum sample size from 12 schools.

Multiple regression analyses will then be used to determine if the strength of the association between school safety interventions and mental health outcomes differs among students and school staff in schools with varying levels of trauma exposure. Mediated moderation analyses will evaluate the role of ACEs on the relationships between exposure to an intentional school shooting, exposure to school safety strategies, and student outcomes (ie, mental health and well-being, perceptions of school safety, and educational outcomes) [78]. Again, power analyses revealed that for our student-level analyses and given an α level of .05 and a power of 0.80, a small effect size will need to be detected to meet our power and sample size requirements. In the case of our proposed teacher analyses, a medium effect size will need to be detected. It should be noted that these values reflect conservative estimates with regard to student and staff recruitment. Thus, we are confident that we will achieve reasonable power to fully answer all of our questions and achieve the specific aims of the study.

Results

IRB approval for this research project was obtained and the study subsequently began its recruitment and data collection phase in January 2024. Data collection is currently ongoing, and the expected completion date is January 2025. As of May 2024, we have recruited and administered the surveys at 3 secondary public schools. The full data analysis is expected to be completed by August 2025.

Discussion

Overview

Poor mental health symptoms and ACEs among the youth predict extensive co-occurring adverse outcomes, including increases in long-term risk for chronic disease and injury, impaired child development, and poor academic outcomes [17-20]. At the same time, the anticipation of intentional gun violence has fueled school safety and security interventions that may increase anxiety, depression, and other indicators of poor mental well-being among students and staff alike [29,50]. Despite this, the association between exposure to existing school safety interventions and student mental health outcomes is not clear. It is also unclear whether and how the strength of these associations might differ among students and staff from those schools that have more recently experienced gun violence, those that have experienced intentional gun violence less recently, and those that have never directly experienced intentional gun violence but are indirectly aware of these tragic events via media and other networks. Finally, we do not know whether and to what extent having a prior history of ACEs moderates the relationships among exposure to intentional gun violence at school, exposure to school safety strategies, and student outcomes.

There is no research that has documented the burden of mental health problems on cohorts of students subsequent to actual, as well as anticipated, school violence. Although the likelihood of an intentional school shooting occurring in a secondary school is relatively low in comparison with other forms of gun violence that occur in our communities [79], the anticipation of such violence in response to the violence experienced over the past decade has led schools to actively consider how best to keep their students and staff safe. Contributing to this movement is the fact that, although there are many schools that have never directly experienced a school shooting, students and staff nonetheless are indirectly aware of these tragic events via news coverage, social media, and other communication channels.

At the same time, there is a paucity of available evidence on the effectiveness of many school safety strategies and, importantly, their impact on student and school staff outcomes. Indeed, there are growing concerns that certain safety strategies (eg, active shooter drills) are potentially traumatic. Furthermore, exposing children, in particular, to such traumatic events may have significant implications for health and learning outcomes in both the short- and long-term. It is also unclear if exposure to a school shooting on student outcomes (ie, mental health and well-being, perceptions of school safety, and academic outcomes) might be more pronounced among students with a history of ACEs.

Potential Study Challenges, Limitations, and Strategies to Address Them

We acknowledge the potential challenges this study presents, and we have identified approaches to mitigate specific concerns that may arise in the implementation of the study. The primary challenge is that this study requires voluntary participation of 12 schools, their students, and staff. As noted earlier and to encourage participation, every effort is being made to minimize the time burden associated with participation in this study, prioritize confidentiality of data, and create an inclusive study environment by ensuring that all participants have regular opportunities to ask questions and express concerns throughout the study process. We will also be providing incentives to all participating schools to recognize their time spent on this study.

Other potential risks include emotional responses that may emerge during the data collection process. It is important to

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underscore that great care will be taken to ensure that the proposed data collection effort takes place in a manner that is comfortable and safe for all participants. It should be noted that our study will not be collecting data on self-harm or suicidality. In addition, the representativeness of our school sample may pose to be a limitation. Indeed, there is such variation in school size, urbanicity, variation by state, and budget, that the schools themselves may not be sufficiently representative of all possible schools meeting our criteria. However, as noted earlier, our sample has sufficient power and we have ensured representation to the best of our ability across geographic regions. Finally, there is the possibility of missing survey data; however, we will be using multiple data sources where possible and multiple imputation methods will be used to address the problem of missing data during the data analysis process.

Conclusions

Despite the potential challenges that we may encounter in conducting this study, we anticipate the results of this work will fill a significant gap in the literature on the impact of exposure to gun violence as an ACE. Ultimately, we believe the results of this study could hold the promise of not only contributing to understanding the relationship of exposure to gun violence to a range of youth, school, and health outcomes, but also providing schools with more data-driven evidence to more effectively inform their firearm violence prevention practices, the allocation of mental health resources, and other interventions, as they simultaneously consider how best to cultivate a positive school climate and attend to the mental health and well-being of their students and staff.

Acknowledgments

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Data Availability

The datasets generated during and analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ACE: adverse childhood experience
co-PI: co–principal investigator
IRB: institutional review board
PCE: positive childhood experience
PHQ: Patient Health Questionnaire
WHO-5: World Health Organization Well-Being Index

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Protocol

Feuerstein Instrumental Enrichment Program for People With Schizophrenia After the First Episode of Psychosis: Protocol for an Open-Label Intervention Study

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Abstract

Background: Schizophrenia is a disorder associated with neurocognitive deficits that adversely affect daily functioning and impose an economic burden. Cognitive rehabilitation interventions, particularly during the early phases of illness, have been shown to improve cognition, functionality, and quality of life. The Feuerstein Instrumental Enrichment (FIE) program, based on the Mediated Learning Experience and the Structural Cognitive Modifiability theory, has been applied in various disorders, but its applicability in schizophrenia has not yet been clarified.

Objective: This study aims to investigate the effects of the FIE program on the functionality of patients with first-episode schizophrenia.

Methods: In total, 17 patients will be recruited for an open-label intervention consisting of twice-weekly sessions for 10 weeks. The primary outcome measure will be changes in the Goal Achievement Scale score. Maze task performance from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery will serve as a secondary outcome measure. At the same time, changes in Positive and Negative Syndrome Scale scores and other MATRICS domains will be analyzed as exploratory outcomes. Assessments will be administered before and after the intervention, with a follow-up period of 6 months.

Results: This trial was preregistered in The Brazilian Registry of Clinical Trials (RBR-4gzhy4s). By February 2024, 11 participants were enrolled in the training. Recruitment is expected to be completed by May 2024. Data analysis will be conducted between May and September 2024. The results are expected to be published in January 2025.

Conclusions: This study may establish a protocol for the FIE program that uses mediation techniques for individuals in the early stages of schizophrenia. The results will add to the knowledge about strategies to promote cognitive skills and functional impairment in daily life.

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KEYWORDS

schizophrenia; Feuerstein Instrumental Enrichment program; cognitive intervention; functionality; first-episode psychosis; early stages; Feuerstein Instrumental Enrichment; FIE; psychotic disorder; psychotic disorders; neurocognitive deficits; economic

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burden; cognitive rehabilitation; functionality; quality of life; daily living; cognitive assessment; maze task; mental disorder; cognitive deficits; mental health; psychosis

Introduction

Background

Schizophrenia is a debilitating mental disorder characterized by hallucinations and disorganized thinking. It is influenced by genetic, neurological, and social factors that affect brain development and functioning [1]. Individuals often exhibit socialization difficulties and cognitive deficits [2] that are associated with low recovery rates [3-6].

Cognitive impairments, including deficits in executive functioning, processing speed, cognitive control, attention, working memory, and social cognition, are core features of schizophrenia [7-9]. Visual processing and perception impairments, including motion, color perception, and perceptual organization, are also observed and are associated with disorganization symptoms [10].

Cognitive deficits can be detected during the early stages of the illness, even up to a decade before the first episode of psychosis [2]. Despite initial improvement [11], the cognitive abilities of individuals experiencing their first episode of psychosis are similar to those of patients with chronic schizophrenia [12-14]. Furthermore, up to 90% of individuals diagnosed with schizophrenia may experience recurrence within 3 years [13]. The connection between clinical and cognitive insight, which in turn affects relapse rates, is well-established [15]. Specific cognitive skills, such as prospective memory, attention, and working memory, have been shown to impact both medication adherence [15] and overall functionality [16].

Cognitive remediation interventions in schizophrenia have been investigated and shown to improve neurocognition [17], although there is limited evidence of the generalization of trained abilities to daily life functioning [18]. On the other hand, studies have shown that cognitive remediation interventions that incorporate psychotherapy features, where therapists actively discuss behavioral and cognitive alternatives for the activities and personalize and contextualize the exercises to the real world, have the potential for higher generalization of cognitive gains to daily life [17,18].

The Feuerstein Instrumental Enrichment (FIE) program [19] is a paper-pencil set of tasks developed by Reuven Feuerstein based on 2 main principles that are, Mediated Learning Experience (MLE) and Structural Cognitive Modifiability (SCM) theory [20,21]. It has 14 tools or instruments, divided into 3 modules according to task complexity and progressive learning skills.

The FIE method is grounded in the foundational principle of altruism, with the intention of providing aid and support to individuals undergoing cognitive transformation. The mediator assumes the responsibility for making activities, tasks, and the environment comprehensible from an individual's perspective [22]. In the learning process, the mediator has a pivotal role in establishing purposeful intentions, providing guidance, and interpreting and personalizing stimuli to improve an individual's understanding of the world and themselves. This method fosters metacognition and the acquisition of personal knowledge [23,24].

The MLE is the basis for cognitive modification proposed by the SCM theory [24]. It emphasizes the possibility of developing new behaviors, skills, and cognitive abilities not previously presented in someone's individual functioning [22]. This repertoire is associated with neuroplasticity and, consequently, neurophysiological changes [22].

SCM theory proposes cognitive modification using MLE [24]. MLE facilitates the acquisition of new behaviors, skills, and cognitive abilities that were not previously present in an individual's functioning [22]. This acquisition is associated with neuroplasticity and subsequent neurophysiological changes [22]. The FIE program, a top-down paradigm, has been previously used for visual-perception organization training in patients with schizophrenia [25]. It has been associated with improvements in perceptual organization abilities and broader cognitive functions compared with computer-based bottom-up interventions such as CogPack (marker software GmbH).

Instrumental enrichment has been previously used for visual-perception organization training in patients with schizophrenia by Kurylo et al [25]. They compared 2 interventions, focused on perceptual organization, to a control intervention (a computer nonvisual-perceptual task, CogPack), of which one was a computer-based bottom-up intervention based on Gestalt principles, requesting the participant to group stimuli according to visual characteristics, like luminance, color, line orientation, and motion. The other was 2 of the 14 instruments from the FIE program, following a top-down paradigm: organization of dots and an analytic perception task. They found that both visual perception interventions were superior to the control task for the improvement of perceptual organization ability, generalizing gains to other visual cognitive tasks. Furthermore, FIE was also associated with improvements in broader cognitive functions compared with the other 2 interventions.

While FIE has the potential to improve cognitive flexibility and problem-solving through group mediation, its potential to generalize has not been explored. Therefore, this study aims to investigate the effects of peer-mediated FIE interventions on daily life functionality in patients with FES. The hypothesis is that FIE intervention will lead to improvements in daily life functionality in patients with FES.

Regardless of the cognitive visuo-perceptual improvement, FIE has great potential to improve cognitive flexibility and problem-solving through group mediation and has a high potential to generalize 2 features that were not explored by Kurylo et al [25]. In this study, we investigate the effects of peer FIE intervention on the functionality of patients with FES. Our main hypothesis is that FIE intervention improves daily life functionality in patients with FES.

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Aims and Objectives

This study aims to investigate the effects of the FIE intervention, delivered through a peer-mediator group format, on functionality in individuals with schizophrenia. Functionality will be evaluated based on individual goal achievement using the Goal Achievement Scale (GAS) [26,27]. Secondary outcomes will include changes in problem-solving and reasoning, measured through the maze task from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) score [28]. Exploratory analysis will also investigate changes in the Positive and Negative Syndrome Scale (PANSS) scores [29] and other MATRICS domains.

Methods

Research Design

The proposed research design is an open-label interventional pilot study that aims to investigate the effects of the FIE program on the functionality of patients with FES based on their personal goals. The study will measure outcomes at 3 time points that are baseline (t0), after the intervention (t1), and at the 6-month follow-up (t2).

Participants

Participants for this study will be recruited from the Early Intervention Group of the Federal University of São Paulo, as well as from other first-episode programs and public and private psychiatric offices in São Paulo. To be eligible, participants must be between 18 and 40 years old and have a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria [30], as confirmed by the Structured Clinical Interview for DSM-5-Research Version (SCID-5 RV) Axis I disorders [31], and received treatment for psychosis while being clinically stable, according to their psychiatrist. Participants must also have an estimated IQ of 70 or higher and be able to provide informed consent. Exclusion criteria include an inability to understand or communicate in Portuguese, any organic or neurological health condition that impacts cognition, substance abuse or dependence (except nicotine), and an estimated IQ lower than 70, indicating intellectual disability. A patient flowchart is shown in Figure 1.

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Figure 1. Study design and patient flowchart. (1) We applied the informed consent form, IQ assessment, and Structured Clinical Interview for DSM-5-Research Version. (2) Participants who are deemed ineligible or unwilling to participate or continue in this study will be removed from the study. (3) We conducted baseline assessments using Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), Positive and Negative Syndrome Scale, and Goal Achievement Scale. (4) We are awaiting a group of 2-3 eligible participants who have successfully completed the IQ and MATRICS assessments. (5) A 10-week training program with Feuerstein Instrumental Enrichment (FIE) will be conducted, with a frequency of 2 sessions per week. (6) A postintervention assessment will be conducted 1 week after the completion of the FIE program. (7) A follow-up assessment will be conducted 6 months after the completion of the FIE program. (8) The primary outcome of the study will be functionality, which will be measured using the Goal Attainment Scale scores. In addition, problem-solving and reasoning abilities will be assessed using the maze scores from the MATRICS assessment.

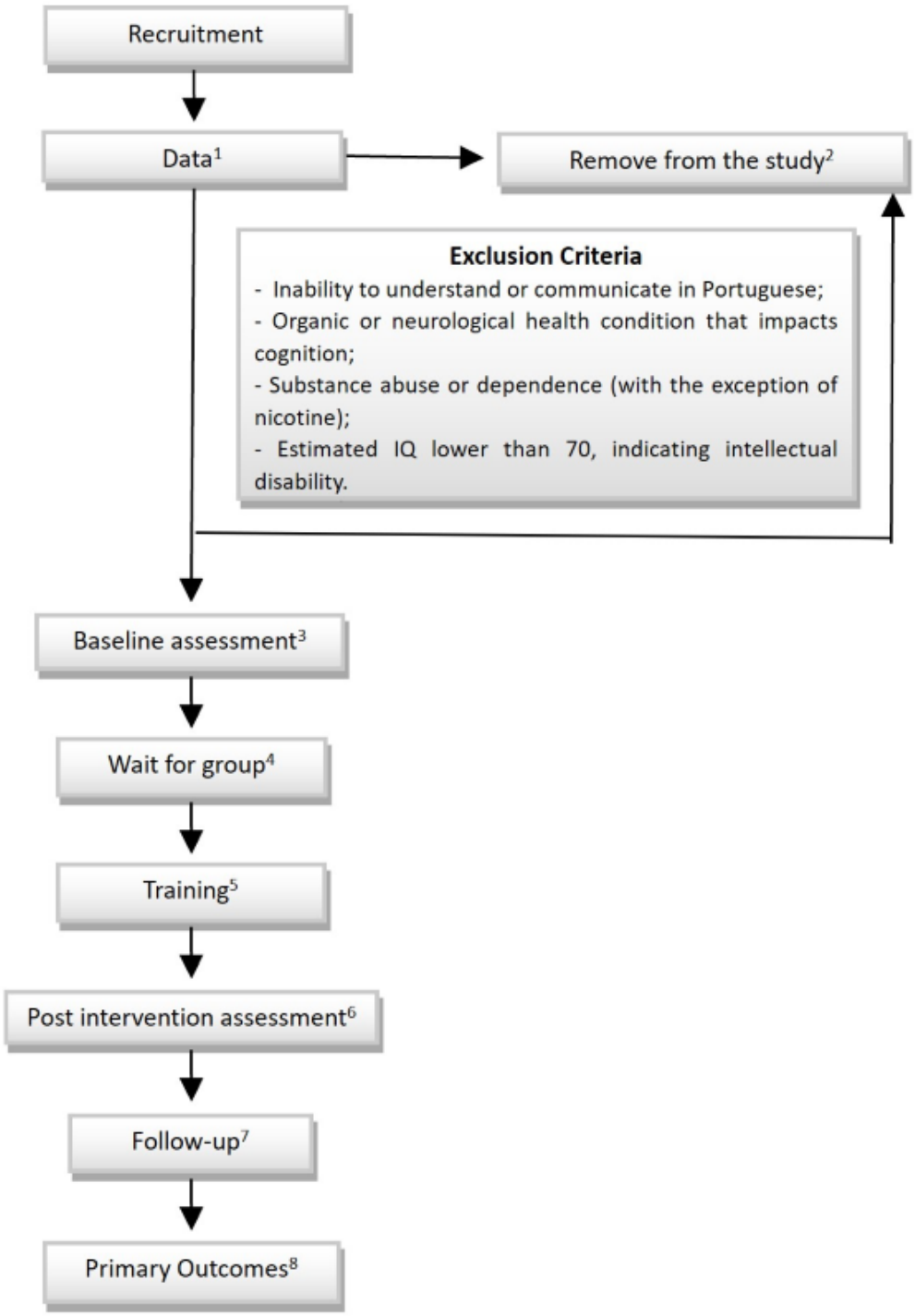

Intervention

The intervention will comprise 2 weekly sessions conducted over a period of 10 weeks. Patients will be enrolled in a pair or 3-person group and will always be accompanied by a mediator. Participation will be continuous and dependent on the patients' interest and fulfillment of the inclusion criteria. The intervention will use 3 tasks from the FIE program-standard instrument I, namely organization of dots, orientation in space I, and analytic perception [32].

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The organization of dots task involves identifying geometric images from a cloud of dots; the patient is required to draw lines to connect the dots and form the geometric image. To complete this task, it is necessary to project and create a virtual relationship between elements, focusing on the relevant aspects of the figure.

The orientation in space I task focuses on visuospatial flexibility and perception of the world, making the patient recognize and differentiate the position of objects on the paper sheet, exploring the patient's own references regarding left, right, front, and back to identify the position of objects in relation to others. This task promotes problem definition and solving strategies, hypothetical thinking, and the creation of conditionals (ie, If… then...) and comparison strategies with peers.

The analytic perception task practices the differentiation and integration of images. In this task, there is a model image, and there are several options for possible responses. The options are a set of shapes that need to be mentally grouped to form the model image, such as a jigsaw. The patient needs to analyze the options and choose the 1 that corresponds to the model. It explores the perceptual ability to focus on specificities, splitting the whole into parts, and the ability to see the whole picture, gathering parts into 1 element.

Each session will take 1-hour and involves 3 steps [20,32]:

1. Introduction: The mediator highlights the task's novelty and complexity, guiding patients toward the solution to the problem.
2. The task itself, where patients will work with the instrument and mediator, will observe their behavior, strategies, and reactions, mediating the process and acting as a bridge between the instrument and patients. The mediator will also provide feedback and correct answers and prevent frustration, among other things.
3. Conclusion: Patients will practice the transfer of knowledge acquired during the session to daily life, discussing the exercise's realization and the processes used during the intervention.

In this pilot study, one of the coauthors (MEDMAR) will be enrolled as a mediator, applying the intervention to all participants in all groups. Furthermore, 2 parallel groups can be run over time. The mediator graduated in the educational field and has been certified by the Feuerstein Institute since 2009. She has more than 10 years of experience as an FEI practitioner and is currently an authorized FEI trainer in Brazil.

Outcomes

The primary objective is to assess the impact of the intervention on functionality, as measured by the GAS [26,27,33], which evaluates the extent to which participants achieve their individual goals. The secondary objective is to evaluate problem-solving and reasoning skills using the maze score from the MATRICS assessment [28]. An exploratory analysis will also examine changes in PANSS scores and other domains of the MATRICS assessment. All assessments will be conducted at the end of the 10-week intervention period and during the 6-month follow-up period.

Clinical Assessments

To evaluate clinical symptomatology, the PANSS will be used [34]. PANSS is a widely used instrument consisting of 30 items and is used to measure the severity of clinical symptoms in patients with schizophrenia. The interviewee psychiatrist is rated on a scale of 1 to 7 by the interviewer psychiatrist.

Functionality Assessments

The GAS is a type of assessment that is centered on personal goals and is commonly used in physical rehabilitation (lifestyle, type of handicap, and aspirations) but is not often used in psychiatry [26,27]. GAS was first used in mental health settings in the 1960s and has also been applied for cognitive rehabilitation [33,35].

The patient and interviewer work together to define individual goals that are specific, measurable, attainable, realistic, and timely, using the "SMART" method. These goals are based on the patient's current lifestyle, daily routines, interests, and needs. If a patient expresses a desire for a long-term goal that cannot be achieved in a short time, the interviewer helps the patient break it down into smaller achievable goals that fit within a defined time frame. The GAS score is based on a defined goal and considers its weightage. Achievement of the defined goal is typically scored as 0, and if the achievement is better or worse than that defined, the score is either +1 or +2 or 1 or 2, respectively. The patient also rates the importance and difficulty of each goal on a 0-3 Likert scale. The final score is calculated by an algorithm that provides a baseline score, an achieved score, and the difference between the two [27].

Cognitive Assessments

The estimated IQ (for inclusion criteria) will be assessed using 2 subtests from the Brazilian version of the Wechsler Intelligence Scale [36], which are vocabulary and rational reasoning.

To assess cognitive changes, 9 tests from the Brazilian version of the MATRICS [28,37] will be used. The test evaluates 7 cognitive domains:

1. Speed of processing: Trail Making Test, Brief Assessment of Cognition in Schizophrenia Symbol Coding, and Category Fluency Animal Naming Test
2. Attention: Continuous Performance Test-Identical Pairs
3. Working memory: Spatial Span and Letter-Number Span Test
4. Verbal learning: Hopkins Verbal Learning Test-Revised
5. Visual learning: Brief Visuospatial Memory Test-Revised.
6. Reasoning and problem-solving: neuropsychological assessment battery maze.

The Mayer-Salovey-Caruso Emotional Intelligence Test Managing Emotions subtest was excluded due to its low-reliability coefficient in Brazilian versions [28].

Power and Sample Size

Sample calculation was performed using G*Power software (Heinrich-Heine-University), considering a post hoc analysis for 17 participants, effect size (Cohen d=0.5) [25], and estimated power (β=.62), where the GAS score means will be compared

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pre- and post-FIE intervention (described in the Intervention section) using a matched pairs Student *t* test.

Analysis

Data will be analyzed using IBM SPSS (version 21) or Jamovi software following the intention-to-treat approach. The last observation carried forward will be the procedure to impute the missing data. Sociodemographic and baseline information of the patients will be described to show the sample characteristics.

The study will use ANOVA or Kruskal-Wallis tests to analyze changes in numerical variables, including primary and secondary outcomes, as well as exploratory analyses, depending on the data distribution. Post hoc pairwise comparisons will be conducted using the Bonferroni adjustment for multiple comparisons in the Friedman test. The chi-square test will be used to analyze categorical data, such as sex. The effect size will be calculated using Cohen *d*, based on the mean and SD of the mean t1 for the GAS.

Ethical Considerations

To ensure that ethical standards were met, the study adhered to the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. The Ethics Committee of the Federal University of São Paulo approved the study (A00951289489), and it was preregistered in The Brazilian Registry of Clinical Trials (RBR-4gzhy4s). Participation will be voluntary and not remunerated, and the participants will only be enrolled after providing informed consent, which has been approved by the Ethics Committee. All patient data will be safeguarded by the research team to maintain participant anonymity and confidentiality.

Results

This trial has been preregistered in the Brazilian Registry of Clinical Trials (RBR-4gzhy4s). Recruitment started in February 2022, and by February 2024, 11 participants were enrolled in the training. Recruitment is expected to be completed by August 2024. Data analysis will be conducted between May and September 2024. The results are expected to be published in peer-reviewed journals and presented at mental health conferences after January 2025.

Discussion

Principal Findings

The FIE program is an ecological intervention that requires patients to apply strategies to solve tasks and generalize them to their daily lives. By promoting neuroplasticity, cognitive flexibility, self-awareness, and socialization, our study is designed to offer space for patients to engage in productive discussion and socialization through mediation, which may enhance patient insight into their own cognitive processes. The FIE program allows patients to build knowledge by sharing ideas with peers and mediators [21], which may improve engagement and self-esteem. In addition, cognitive abilities such as attention, visual perception, organization, and flexibility are required to perform these activities [25]. Under this intervention, we aim to challenge patients in a safe environment, creating opportunities for the generalization of real-life strategies.

The GAS assessment is a valuable tool not only for project staff to report changes in functionality but also for the patients themselves. By tracking the patient's progress toward their own goals, regardless of cognitive changes, they can become active participants in their own recovery process. This helps to increase motivation, engagement, and self-esteem and ultimately leads to better treatment outcomes. Our goal of evaluating functionality as a primary outcome was to focus on recovery from the patient's perspective, rather than data change, as an isolated construct.

The early years following the first episode of schizophrenia are crucial for recovery. Antipsychotic medications can improve positive symptoms, however, adherence to treatment may be highly influenced by psychological and behavioral interventions that aim to enhance insight and neuroplasticity. In addition to understanding the nature of the illness, it is important for individuals with schizophrenia to gain insight into their functional and cognitive deficits as part of the recovery process. This can help develop realistic goals and strategies to improve their overall functioning and quality of life. By recognizing and addressing these deficits, individuals with schizophrenia can play a more active role in their recovery and work toward achieving their full potential.

Professional capacitation in FIE requires intense training of the mediator, who needs to go through the experience of being mediated before becoming a mediator, using an immersive approach. Some of the FIE assumptions, such as intentionality or reciprocity and the mediation of transcendence, focus the interactions on the needs of the patient and on learning as a process that transcends the task itself. The mediator's intentionality involves ensuring the task and the information can be effectively understood by the patient, shaping the behavior and experience to a more holistic outcome [38]. Having a person with this profile as part of a multidisciplinary team can enrich the interaction of the professional group, expanding the perspective of how the team works with the patient and the patient himself translating the knowledge for daily life behavior for the group. After having a professional trained in FIE, it becomes an accessible and low-cost intervention.

Considering the topics described above, it is necessary to explore the effects of this intervention and disseminate the results to a broader community. Given the high prevalence of schizophrenia and its associated functional impairments, comprehensive interventions such as FIE may have positive impacts on the recovery process, which are essential public health priorities, particularly in low- and middle-income countries, where access to effective treatment is often limited. If this study shows a gain in functionality, the dissemination of this technique can increase access to evidence-based treatments, ultimately leading to improved outcomes for individuals with schizophrenia.

Limitations

The major limitation of this study is the absence of a control group, which was a decision made due to several issues recognized by the research team, including sample

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characteristics and the onset of the SARS-CoV-2 pandemic. The recruitment of patients after their first episode of schizophrenia within a 5-year time window posed a challenge, as many patients may have a long duration of untreated psychosis or have already had the disease for more than 5 years. In addition, some patients in remission may decline to participate in the intervention for personal reasons, such as a lack of insight into the disease or the side effects of medication, both of which can affect the willingness to participate in psychosocial interventions.

Other limitations are associated with the FIE technique. The mediator must be a specialist in the technique and trained by an authorized mentor or institution. Training a mediator in FIE is challenging not only because of its cost of nearly US $1000, equivalent to 72 hours of initial formation but also because of the need for a mediator's constant practice in order to develop the required skills that will enable him or her to work with the sample while maintaining the focus on the FIE proposition. Nowadays, this may represent a barrier to replicating the methodology in the general medical system. However, other behavioral techniques faced the same challenges when they were first applied. An example of this was the challenges faced by applied behavior analysis (ABA) applied to autism in the 60th/70th [39]. To be an ABA specialist, someone must be trained for approximately 2000 hours [40]. In addition, the gains achieved by the patients made it the first line of intervention for this population, leading to ABA popularization [39]. Therefore, difficulties in FIE capacitation and training may exist but should not discourage the investigation of its effects on schizophrenia.

Another possible issue is patient resistance to attending the intervention twice per week. We will provide a friendly and welcoming environment for intervention and rely on the possible gains as a key to maintaining adherence and reducing dropouts. Furthermore, none of the 11 participants enrolled by now dropped out of the study.

Conclusions

In conclusion, our project focuses on the investigation of the effects of the FIE program in patients with first-episode schizophrenia. Our results may show if this ecological approach, focused on generating insight and neuroplasticity, will impact functionality. If so, we expect to help patients become active participants in their own recovery process. Despite the limitations of this study, such as the absence of a control group and challenges associated with professional FIE training, investigating FIE intervention in first-episode schizophrenia is valuable because of the low cost of application and accessibility of this technique. Furthermore, we are exploring some gaps that still exist in the treatment of people with schizophrenia: (1) there is no effective intervention recognized as a first line to improve cognition and functionality in schizophrenia; (2) the current cognitive intervention programs in schizophrenia yield few or no effective generalizations to daily life; and (3) the importance of assessing functionality based on the patient's own goal, as we will do with the GAS, instead of relying only on scale scores. Our research can contribute to increasing the knowledge of nonpharmacological interventions for schizophrenia.

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Data Availability

Due to privacy restrictions, participants' previous consent did not include raw data, and therefore, these sets will not be deposited in publicly available repositories. Thus, in order to have access to any data besides those presented in the results session, a request must be submitted by email to the corresponding author, who will only grant access to those data if possible and according to the Ethics Committee of the Federal University of São Paulo approved considerations.

Authors' Contributions

AOF contributed to the whole design of the experiment and manuscript preparation. JSG contributed as part of the neuropsychological team and in manuscript preparation. RACBN contributed as part of the neuropsychological team. CLD contributed as part of the psychiatric team. MEDMAR contributed to the design of the Feuerstein Instrumental Enrichment part of the experiment. AG contributed by supervising the experiment and reviewing the paper. CN contributed by supervising the experiment and reviewing the paper.

Conflicts of Interest

AG has been a consultant or advisor to or has received honoraria from Cristalia, Lundbeck, Ache, Daiichi-Sankyo, Teva, and Janssen. CN has been a consultant or advisor to or has received honoraria from Ache, Daiichi-Sankyo, Teva, and Janssen. No other conflicts of interest were declared concerning the publication of this article. The other authors AOF, JSG, RACBN, CLD, and MEDMAR have no conflicts of interest to declare concerning the publication of this article.

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Abbreviations

ABA: applied behavior analysis
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FES: first-episode schizophrenia
FIE: Feuerstein Instrumental Enrichment
GAS: Goal Achievement Scale
MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia
MLE: mediated learning experience
PANSS: Positive and Negative Syndrome Scale
SCID-5 RV: Structured Clinical Interview for DSM-5-Research Version
SCM: Structural Cognitive Modifiability

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Protocol

Rethinking Health Systems Responsiveness in Low- and Middle-Income Countries: Validation Study

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Abstract

Background: Health systems responsiveness (HSR) is the ability of systems to respond to legitimate non-health expectations of the population. The concept of HSR by the World Health Organization (WHO) includes respect for dignity, individual autonomy, confidentiality, prompt attention to care, availability of basic amenities, choice of provider, access to social support networks, and clarity of communication. The WHO tool is applied globally to assess HSR in low, middle, and high-income countries.

Objective: We have revised the conceptual framework of HSR following a rigorous systematic review and made it specific for low- and middle-income countries (L&MICs). This study is designed to (1) run the Delphi technique to validate the upgraded conceptual framework of HSR, (2) modify and upgrade the WHO measurement tool for assessing HSR in the context of L&MICs, and (3) determine the validity of the upgraded HSR measurement tool by pilot testing it in Pakistan.

Methods: The Delphi technique will be run by inviting global public health experts to provide suggestions on the domains and subdomains of HSR specific to L&MICs. Cronbach α will be calculated to determine internal consistency among the participants. The upgraded HSR conceptual framework will serve as a beacon to modify the measurement tool by the research team, which will be reviewed by subject experts for refinement. The modified tool will be pilot-tested by administering it to 1128 participants from primary, secondary, and tertiary care hospitals in Rawalpindi district, Pakistan. Additionally, an "observation checklist" of HSR domains and subdomains will be completed to objectively measure the state of HSR across health care facilities. HSR assessment will be further strengthened by incorporating the perspective of hospital managers, service providers, and policy makers (ie, the supply side) as well as community leaders and representatives (ie, the demand side) through qualitative interviews.

Results: The study was started in January 2024 and will continue until February 2025. A multidimensional approach will yield significant quantifiable information on HSR from the demand and supply sides of L&MICs.

Conclusions: This study will provide a conceptual understanding of HSR and a corresponding measurement tool specific to L&MICs. It will contribute to global public health literature and provide a snapshot of HSR in Rawalpindi district, Pakistan, with concrete action points for policy makers.

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KEYWORDS

health system; healthcare system; health care; responsiveness; Pakistan; Low-and middle-income countries

Introduction

Responsiveness to legitimate non-health expectations of the population is listed as one of the three intrinsic goals of health systems by the World Health Organization (WHO), alongside improving health and providing financial risk protection [1]. Health systems responsiveness (HSR) relates to a "system's ability to respond to legitimate expectations of potential users

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about non-health enhancing aspects of care" [2]. The concept of HSR arose in the late 1990s [3] and was formalized in the landmark WHO report of 2000—"Health Systems: Improving Performance" [1]. Responsiveness is a social goal that emphasizes health systems should serve people, going beyond merely assessing people's satisfaction with the medical care they receive [3]. The World Health Report [1] defined HSR based on 7 domains, including respect for dignity, autonomy, confidentiality, prompt attention, quality of basic amenities, access to social support networks (particularly for inpatients), and choice of provider [1]. An additional domain of "clarity of communication" was subsequently added [2,4,5].

The significance of HSR has been repeatedly emphasized in the literature. The concept of responsiveness has its origin in Donabedian's framework of quality of care [6] and reflects the protection of human rights and dignity [4]. Improving HSR is essential to making progress toward achieving universal health coverage (Target 3.8 of Sustainable Development Goals) [7], which entails that everyone should receive good quality health services without incurring financial hardship [7]. HSR ensures a higher level of comfort for people [4] and is the most important predictor of client satisfaction rather than clinical competence [8-10]. It is suggested that aspects of HSR contribute to a patient's willingness to return to health care facilities and continue engaging in health care [11]. It is also suggested that improving HSR expands service coverage [6,12-14], decreases noncompliance with treatment regimens [15-17], and raises the chances of treatment success [18]. Evidence from Nigeria demonstrates that people's trust in the system improves the uptake of maternal health services among pregnant women [19,20]. From the perspective of policy makers, responsiveness can be improved with minimal investment in sophisticated technology, equipment, and human resources [21,22] compared to clinical aspects of health care. This has the dual impact of increasing client satisfaction and improving overall population health.

Although literature pertaining to HSR has been growing in the past 2 decades [23], conceptual clarity of its domains and subdomains has received little attention [19,24]. Ambiguity originates due to contextual variation, leading different researchers to address HSR in varied ways [25-30]. The terms "Health Systems' Responsiveness," "Health Service Responsiveness" and "Human Resource for Health (HRH) Responsiveness" have been used interchangeably and have generally referred to the user-service interface of patients and health care providers rather than addressing health systems responsiveness at a systemic level [19,24]. It is not evident what comprises a response, what the legitimate expectations of people are, at what level a response is anticipated (provider or systemic), and for whom the response is meant (patients, individuals, or the general public).

Varied understandings and interpretations of HSR have led to gaps in its scientific assessment as well as strategies to improve it. The most common measurement tool to assess HSR is the WHO tool utilized in the Multi-Country Survey study (2000-2001, across 61 countries) [31] and the World Health Survey (2002-2004, across 71 countries) [32]. It has been universally applied across high, middle, and low-income countries. The WHO HSR conceptual framework and measurement tool have received technical criticism from researchers around the globe. It is highlighted that the 8 domains of HSR skip important concepts, including but not limited to the quality of counseling, follow-up care, trust, coordination of the course of treatment, the quantity of information provided, and language barriers [33-35]. The most cited drawback of the WHO measurement tool is its universal application to countries of all income levels, with drastically varied social, cultural, and economic contexts. The health and non-health expectations of the populations of high-income countries as well as low- and middle-income countries (L&MICs) also differ, as these are embedded in the broader sociocultural macrosystem. It is stated that domains such as accountability of errors, ease of scheduling appointments, coverage during known provider absences, shared sense of urgency, and expression of empathy are critical for people in high-income countries, whereas these domains are not significant to people in L&MICs [36]. It is crucial to assess HSR in L&MICs, which generally have limited capital to invest in high-cost technology for improving clinical care. Investing in HSR is cost effective and can help countries make progress toward achieving universal health coverage as part of their commitment toward Sustainable Development Goals [7].

We designed this study to address the criticism and limitations of the WHO HSR conceptual framework and measurement tool. This study will revise and validate the concept of HSR (conceptual framework) as presented by the WHO 2000 report [1] and provide a comprehensive tool for its measurement, which is specific to the context of L&MICs. The specific objectives of the study are to (1) validate the upgraded conceptual framework of HSR (explained in the *Methods* section) by applying the Delphi process; (2) to revise the WHO measurement tool for assessing HSR; and (3) to validate the upgraded tool by pilot-testing it in primary, secondary, and tertiary care hospitals of Rawalpindi district, Pakistan.

Methods

Preliminary Work: Modification of the HSR Conceptual Framework and Measurement Tool

The WHO HSR framework was developed more than 2 decades ago through a literature review, examining surveys related to patient satisfaction and discussions with public health professionals and researchers involved in the health sector [5]. We have taken a similar approach to refine the HSR framework: a literature review followed by suggestions for modifications by global public health experts.

A systematic review was carried out by the research team in 2023 to revise and upgrade, (1) the WHO conceptual framework and (2) the measurement tool of HSR to suit the context of L&MICs. A search was carried out using the PubMed and Google Scholar databases, focusing on constructs related to "health systems" (Medical Subject Headings terms) and "responsiveness." The initial number of hits was 844 records, and 19 articles were included after screening [37-54]. These articles were specifically related to HSR in L&MICs and addressed the HSR conceptual framework and/or the measurement tool. The details of the systematic review and

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retrieval of literature are provided in Multimedia Appendix 1. Table 1 elaborates on the modified version of the HSR conceptual framework, based on the systematic review. We have added the following 4 new domains: building trust, guidance, financial sensitivity, and coordination and continuity of care. The existing domain of "prompt attention" has been changed to "access to care." Clarity of communication" has been modified to "attention and clarity of communication." The WHO measurement tool has been revised by the research team in concordance with the conceptual framework (Multimedia Appendix 2). Starting with the revised and upgraded HSR conceptual framework and measurement tool, we aim to validate both in the proposed study. The study will be conducted in concrete phases that align with each objective, as shown in Figure 1.

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Table 1. The revised conceptual framework of health systems responsiveness (HSR), based on systematic review.

Domains of HSR	Definition/concept	Elements of the domain
1. Respect for dignity	At the extreme, this means not sterilizing individuals with a genetic disorder or locking up people with communicable diseases, which would violate basic human rights. More generally, it means not humiliating or demeaning patients.	• Treatment with respect by health care staff. Patients should be welcomed at the health care unit, addressed respectfully at all times, and not shouted at or abused. • Privacy during examination and treatment. • Safeguarding of human rights (eg, freedom of movement for patients of leprosy or tuberculosis).
2. Respect for autonomy	This refers to freedom of patients to participate in choices about their own health. It includes helping choose what treatment to receive or not to receive.	• Right of an individual to information about their disease and alternative treatment options. • Right to be consulted about treatment. • *Informed consent in the context of testing and treatment.* • The right of patients of sound mind to refuse treatment.
3. Respect for confidentiality	It refers to the right to determine who has access to one's personal health-related information.	• Conducting consultations with the patients in a manner that protects their privacy. • Safeguarding the confidentiality of information provided by the patient and information relating to an individual's illness (except where such information needs to be given to another health care provider).
4. Quality of basic amenities	It refers to the quality of the environment in which health care is provided.	• Clean water, clean toilets, and clean linen. • Sufficient ventilation (fresh air). • Clean surroundings (regular procedures for cleaning and maintenance of hospital buildings and premises). • Healthy and edible food. • Adequate furniture and seating.
5. Access to social support networks during care	It refers to provision of social needs for people receiving health care. It only applies to people receiving inpatient care.	• Patients should be allowed visits by relatives and friends. • Provision of food and other consumables by relatives and friends, if not provided by the hospital. • Religious practices that do not interfere with hospital activities or offend others' sensibilities. • Access to newspapers, radio, and TV • *Support to the family of patients (caregivers)* [22]. • *Social financial networks*.
6. Choice of provider	It refers to the freedom to select which individual or organization can deliver one's care.	• Patients should be able to reach health services of choice without too much difficulty. • Within a health care unit, individuals should be able to choose their health care provider. • Individuals should be able to get a second opinion in cases of severe or chronic illness or surgery. • Individuals should be able to get general and specialist care as appropriate • *Choice of gender of the provider*[b] [31].
7. Prompt access to care[a]	Health care facilities should be geographically accessible–taking account of distance, transport, and terrain. People should also be promptly given care once in the health care setting.	• Patients should be entitled to rapid care in emergencies. • Patients should be entitled to care within reasonable time periods even in case of nonemergency health care problems. • Waiting times for consultation and treatment should be reasonable.
8. Attention and clarity of communication[c]	Whether proper attention was given to the patient by health care providers and if there was appropriate communication.	• Clarity in conveying information and evoking understanding. • *Providing time for patients to understand their symptoms and to ask questions (Enough time)* [31]. • *Insightful listening*[b] [32]. • *No interruptions during consultation (unnecessary calls, texting, chatting, or singing)*[b] [28]. • *Not using jargon*[b] [26]. • *Asking patients if they understood the explanation (quality of counseling)* [32].

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Domains of HSR	Definition/concept	Elements of the domain

9. *Building trust*[d] [26-28,35]	*The health care provider is advised to maximize the patient's benefit, not tomaximize their own benefit.*	• *Service oriented, not business-like behavior:*
		  • *Being asked to do tests from specified diagnostic centers.*
		  • *Visiting patients privately (by public sector physician)—moonlighting.*
		• *Not being involved in illegal activities:*
		  • *Bringing patients in own private clinics.*
		  • *Accepting gifts from pharmaceutical representatives—prescribing substandard medicine.*
		• *Mechanisms of accountability.*
		• *Earning trust of patients.*

10. *Guidance*[d] [22,26]	*General information on maintaining healthy lifestyle and specific guidance on the disease under consideration.*	• *Information and suggestions on healthy lifestyle in general (eg, smoking cessation, physical activity, and healthy diet).* • *Information and suggestions on disease prevention.* • *Facilitating follow-up.* • *Explaining access to medicines and diagnostic services* [37].
11. *Financial sensitivity*[d] [26,28]	*It refers to how mindful health care providers are to the financial burden put on patients due to illness.*	• *Trying to understand socioeconomic status of the patient.* • *Considering socioeconomic status of the patient in discussing management options.* • *Informing the cost of treatment/financial counseling.* • *Providing financial assistance if needed—referring to organizations or individuals that can provide financial assistance.*
12. Coordination and continuity of care[d] [26,31,32,35]	*It refers to the extent to which care progresses smoothly as the patient moves across different health care providers and sectors.*	• *Continuity of care (communication between providers).* • *Referral services.*

[a]Previously, this domain was "prompt attention" in the World Health Organization (WHO) framework of responsiveness.

[b]New additions to the original WHO domains of responsiveness.

[c]"Attention" has been added to "clarity of communication."

[d]Newly added domains. The italicized parts are new additions.

Figure 1. Phases of the study.

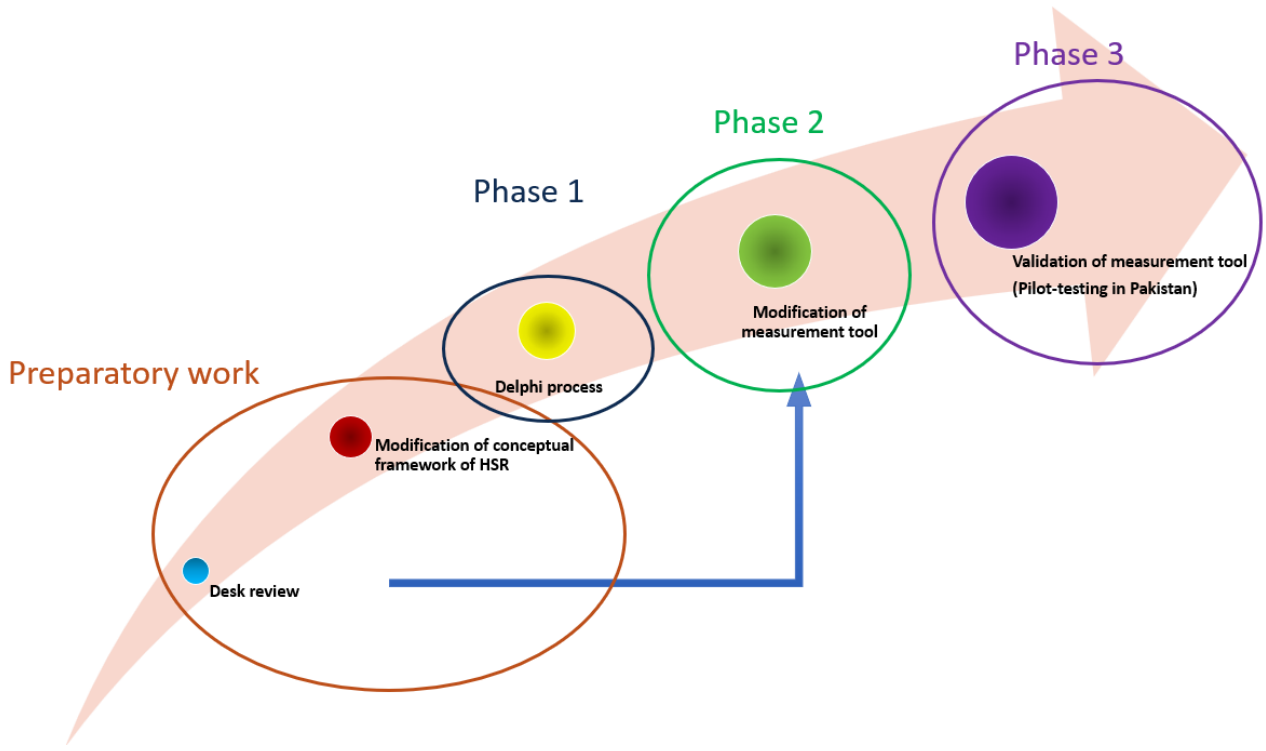

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Phase 1: the Delphi Technique

The revised conceptual framework (Table 1) will be run through the Delphi technique to validate its components (ie, domains and elements) and add robustness. All panel members included in the Delphi process will be experts in public health with a focus on health systems and/or HSR. We identified potential Delphi participants during literature review. Additional participants will be identified through a consultative process within the research team, supplemented by snowball sampling. They will be invited via email to participate in the study. Each participant will grade domains and elements of HSR according to "scientific strength" (face and content validity), "importance and relevance," and "feasibility of measurement." The grading will be recorded on a scale of 1 to 5, with 5 being the best and 1 being the worst score (1= strongly reject; 2= reject; 3= no opinion; 4= support; and 5= strongly support). They will also be requested to give percentage weight to each domain of HSR according to its importance. The domains and elements will be included in the conceptual framework if relevance and scientific strength are rated 4 or 5 by 70% or more of the experts and if feasibility is rated 4 or 5 by 50% or more of the experts [55].

Phase 2: Modification of the WHO Measurement Tool

The research team has already modified the WHO responsiveness assessment tool in concordance with the upgraded conceptual framework (Multimedia Appendix 2). However, these edits are not final. The research team will revisit the tool after the Delphi process and make necessary edits. The tool will then be run via (1) expert review and (2) prepiloting the questions. We will contact 3 to 5 subject experts for expert review and request a remote meeting to discuss the measurement tool. All changes in the tool will be discussed with experts for their opinion. They will be asked for the relevance, importance, scientific strength, and feasibility of each question and to suggest question eliminations, modifications, and/or additions. Furthermore, appropriate response options (ie, Likert scale, binary scale, or open-ended responses) and tool analysis will be discussed. We intend to establish the content validity of the tool through this process. After the expert review, the principal investigator of the study will administer the tool to 7 to 10 adults aged >18 years from Rawalpindi district, Pakistan. These would not be subject experts. This will help determine whether the general public understands and comprehends the questions, as intended. Any necessary edits will be made to the tool based on their feedback.

Phase 3: Pilot-Testing of the Measurement Tool and the HSR Assessment Methodology in Pakistan

The tool will be pilot-tested in Rawalpindi district, Pakistan. Pakistan has been chosen for testing based on the feasibility of the research team. The survey will be based on three components: (1) facility-based survey, (2) community survey, and (3) key-informant survey**,** according to the analytical framework of the study (Figure 2; adapted and modified from Mirzoev et al [19]). The framework involves assessing HSR from the perspective of supply (ie, hospital managers, service providers, and policy makers) and demand (ie, patients and community members) sides in the broader social, cultural, political, economic, and historical context. A mixed methods approach will be adapted according to the framework.

Figure 2. Analytical framework of the study (LHV: lady health visitor).

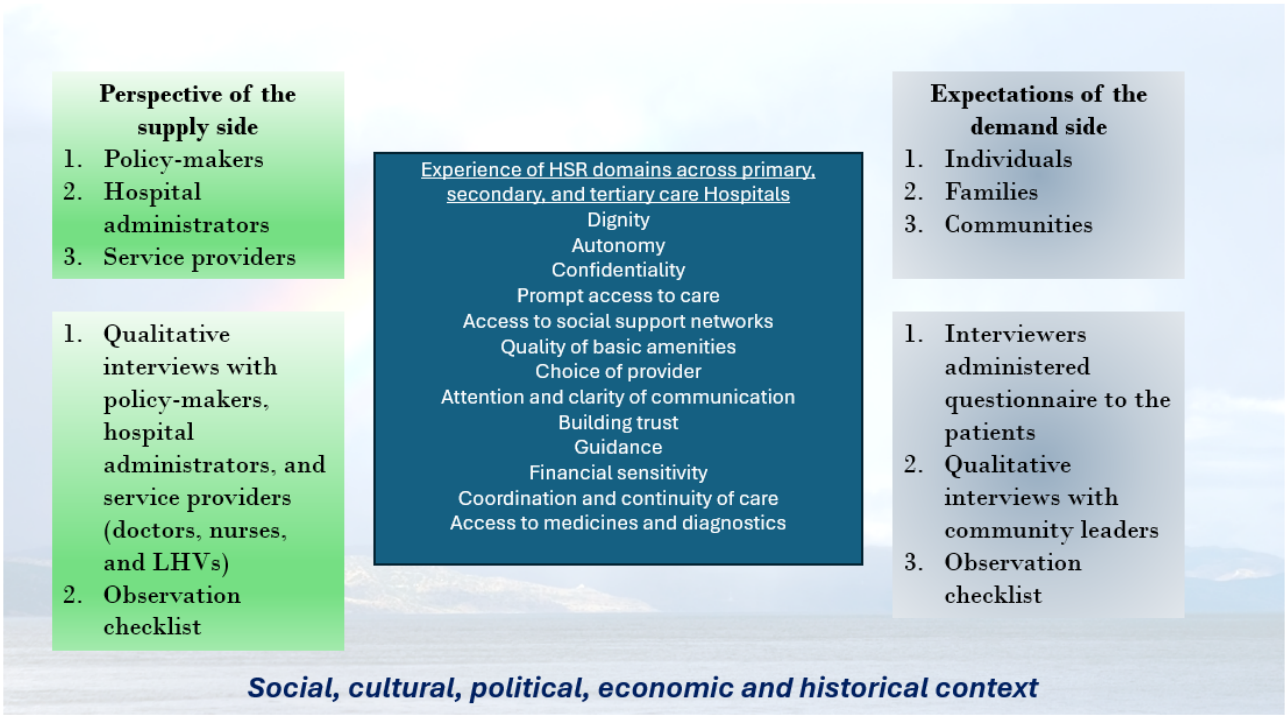

Facility-Based Survey

The facility-based survey will be a mixed methods study that will collect quantitative data from patients, qualitative data from hospital managers and service providers, and an observation checklist filled in by the research team. The semistructured interview guides and observation checklist are provided in Multimedia Appendix 3. The HSR measurement tool will be

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administered at the health care facilities. Participants will be sampled from three tiers of public health care facilities of Rawalpindi district, Pakistan. Data will be collected from 1128 participants spread across primary (basic health care units and rural health centers), secondary (Tehsil headquarters hospitals), and tertiary health care facilities. Figure 3 demonstrates the sample size distribution across the health care facilities of the Rawalpindi district. Multimedia Appendix 4 elaborates on sample size calculation and distribution as well as sampling strategy. The sample will be drawn from inpatients and outpatients across the departments of Medicine, Surgery, Gynecology/Obstetrics, and Pediatrics in secondary and tertiary care facilities according to probability proportionate to size sampling technique. Only outpatients will be included from primary care facilities. Purposive sampling will be done to recruit participants. Data will be collected from patients regarding their own or their child's experiences of HSR. Any person aged ≥18 years who receives treatment from the health care facility the same day for themselves or their children (aged <12 years), does not have a reported mental illness, was not unconscious in the past 24 hours, understands and speaks Urdu, and is willing to participate in the study will be recruited as outpatients. Inpatient participants must have been hospitalized for at least 1 night in the past week at the hospital under study. Data will be electronically recorded using KoBo ToolKit. The distribution of all variables will be assessed, and outliers will be identified and assessed individually, case by case. Cases with extreme outlier measures will be eliminated from the dataset. Any variable with more than 50% missing information will be considered defective and removed from the data set. For the rest of the variables, missing values will be imputed by the "hot deck" method. Basic descriptive statistics will be calculated. Principal component analysis will be applied to the domains of HSR to generate a composite score of HSR according to the weights given to each category. The detailed analysis of the measurement tool will be discussed and finalized with subject experts (phase 2).

Figure 3. Sampling distribution across primary, secondary, and tertiary care hospitals (BHU: basic health unit; RHC: rural health center).

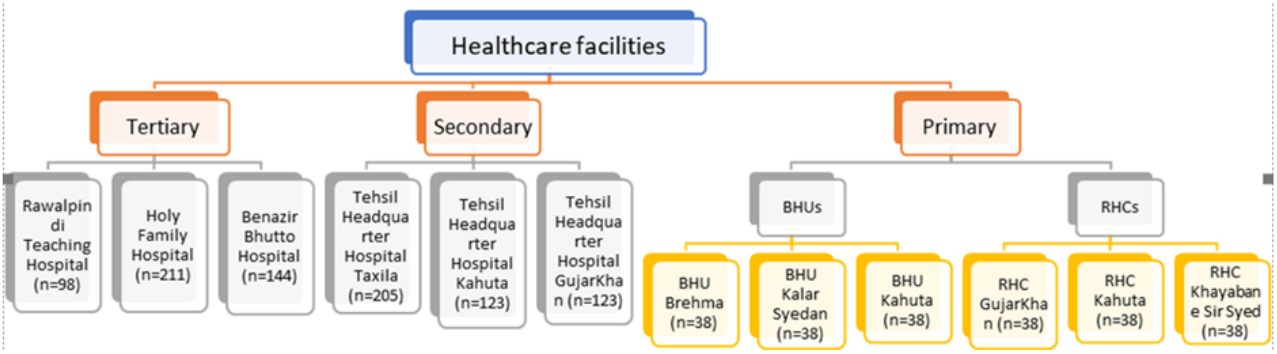

Hospital managers, general practitioners, specialists, nurses, and paramedic staff who have been working at the health care facility for the past year and are willing to participate in the study will be invited for qualitative interviews. A minimum of 3 interviews per secondary (n=9) and tertiary (n=9) health care facility and 1 within each primary health care facility (n=6) will be conducted (N=24). The research team will objectively determine the responsiveness of each health care facility using an observation checklist (total number of health care facilities =12) to minimize information bias (Multimedia Appendix 3).

Community-Based Survey

The research team will reach out to community representatives of Rawalpindi district to conduct in-person qualitative interviews and include their voices in the HSR assessment. They will be identified with the help of service providers, typically those working in primary health care facilities, through snowball sampling. A minimum of 15 community representatives will be included, and more will be added until the point of saturation is reached.

Key-Informant Survey

Key informant interviews will be carried out to include in-depth insights of policy makers in the study and understand the challenges, barriers, threats, opportunities, and possible solutions to improve HSR in Pakistan. We intend to apply the snowball sampling technique to interview 20 to 40 decision makers involved in the health sector in Pakistan. An effort will be made to include key people from the public and private sectors, academia, and WHO. As the country follows a devolved system, we also intend to capture representation from the federal government and the four provinces of Punjab, Sindh, KPK, and Balochistan.

All qualitative data will be transcribed and later analyzed using the directed content analysis technique [56], based on the conceptual framework of HSR. We will use Maxqda.v.24 for qualitative analysis. Codes, subthemes, and themes will be generated and organized in the broader umbrella of the HSR domains and elements. Word clouds and code matrices will be formed. Most qualitative information will be presented in narrative form, with verbatim excerpts supporting the quantitative information. Findings from all surveys will be triangulated and synthesized to generate meaningful information. Results will wholistically be displayed from the perspective of the demand and supply sides, according to the analytical framework of the study. The findings will help us formulate guiding principles and a strategic direction to improve HSR, culminating in potential action points for policy makers to help improve HSR and the overall health of the population.

Ethical Considerations

Written informed consent will be obtained via email from participants in the Delphi technique. Verbal consent will be obtained and audio-recorded from participants in qualitative

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interviews (policy makers, hospital managers, and service providers). Written informed consent will also be obtained from survey participants. The research team will explain the study and its potential risks and benefits to participants who are not able to read on their own. Thumbprints will be collected for informed consent from such participants. During the pretesting phase, we will assess whether monetary compensation is required for the survey participants. The ethical approval of the study has been obtained from the National Bioethics Committee Pakistan (4-87/NBCR-1048/23/1256), Institutional Research and Ethics Forum, Rawalpindi Medical University (725/IREF\RMU\2024), and the Institutional Review Board of the University of Texas (HSC-SPH-23-1089).

Results

Phases 1 and 2 of the study were completed from January to June 2024. Phase 3 of the study is currently in progress to collect data from primary, secondary, and tertiary health care facilities of Rawalpindi district, Pakistan. We will analyze the survey data by December 2024, followed by report writing and dissemination of results by March 2025.

A thorough quantitative and qualitative analysis will be conducted, which will be aimed at publication in the form of a technical report.

The findings of the study will be disseminated to the scientific community through publications and conference presentations. A dissemination workshop will be organized with the stakeholders of Pakistan to disseminate HSR findings specific to primary, secondary, and tertiary care hospitals of Rawalpindi district, Pakistan.

Discussion

Expected Outcomes

This study aims to develop a universal understanding of HSR alongside robust measurement methodology and tools in the context of L&MICs. We believe new domains and/or elements of HSR may be added to the current HSR framework, based on the Delphi process. The revised HSR framework will contribute to global literature and offer a blueprint for other countries to assess and improve HSR and the overall health of the population.

The bulk of prior work on HSR has used the WHO tool without modifications [18,22,25]. Previous efforts to improve the concept of HSR [19,23,26] have not systematically reviewed the current body of evidence or taken a stepwise approach to incorporate views and suggestions of global and L&MICs public health experts, nor have they included pilot-testing of the measurement tool. This study aims to pioneer a robust methodology for assessing HSR from both “demand” and “supply” sides using a mixed methods approach. We will also determine the importance of each HSR domain from the perspectives of global experts (through the Delphi process) and study participants (through a facility-based survey). Comparing the importance of HSR domains from these two diverse perspectives will help unfold a deeper understanding of HSR and identify the needs of people in L&MICs.

The findings from this study will be useful for policy makers to support evidence-informed decision-making. HSR measures the level of user satisfaction with health services and not the system’s response to health needs, which is included in health outcomes [57]. Investing in HSR is a cost-effective strategy for improving health systems utilization and access to services. It also helps early diagnosis and management of diseases and improves treatment compliance. “What cannot be measured cannot be improved,” as the famous quote by William Thomson says. This study will assess HSR from multiple angles and include the voice of the community and service providers. It will also highlight specific domains of HSR and action points for policy makers to improve HSR. The results of the study will translate into guidelines and recommendations for policy makers to improve HSR and enhance overall population health.

Strengths and Limitations

Although the greatest strength of this study is its contribution to the global literature, it is not without limitations. Gray literature was not included in the systematic review, and the study was confined to English language. Further bodies of knowledge exist in other languages and outside of traditional publishing channels, which could have led to useful insights for revising the conceptual framework of HSR in the context of L&MICs. The questionnaire will be administered in “Urdu,” which is the national language of Pakistan. There is a possibility that some participants speak other subnational languages and would be left out of the study. Another limitation is not including adolescents (13 to 18 years of age) in the facility-based quantitative survey. They were excluded for feasibility, as assent alongside consent would have been required. Additionally, we have no reason to hypothesize that HSR would differ for adolescents compared to children and adults. Beyond that, we foresee a positive picture of responsiveness being narrated by hospital managers and service providers (ie, supply side). We have tried to limit information bias in the results by introducing an observation checklist that will be completed by the research team. The tool will be tested in only 1 district of the Punjab province. The results would be generalizable to Punjab but would need to be interpreted cautiously for other provinces. Lastly, we intend to formulate a measurement tool applicable to all L&MICs. However, different countries have varied health systems, which are deeply rooted in diverse sociocultural contexts. Countries will always differ from one another, as there is no “average country.” Thus, we recommend other researchers to pilot-test the conceptual framework and measurement tool and tailor them to suit their specific context before using them widely.

Data Availability

The modified HSR conceptual framework and measurement tool for L&MICs will be published and freely available online.

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Authors' Contributions

MI and SS contributed to the conceptualization and design of the study. MI drafted the manuscript. CGZ, RM, CB, and SS reviewed and edited the manuscript. The study has been approved for funding by the Aga Khan University in Pakistan.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Systematic review.
[DOCX File , 91 KB - resprot_v13i1e59836_app1.docx]

Multimedia Appendix 2
Measurement tool.
[DOCX File , 41 KB - resprot_v13i1e59836_app2.docx]

Multimedia Appendix 3
Interview guides and observation checklist.
[DOCX File , 71 KB - resprot_v13i1e59836_app3.docx]

Multimedia Appendix 4
Sample size calculations.
[DOCX File , 47 KB - resprot_v13i1e59836_app4.docx]

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Abbreviations

HRH: Human Resource for Health
HSR: health systems responsiveness
L&MIC: low- and middle-income country
WHO: World Health Organization

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Protocol

Advancing Digital Education Technologies by Empowering Nurses With Point-of-Care Ultrasound: Protocol for a Mixed Methods Study

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Abstract

Background: Bedside ultrasonography, also known as point-of-care ultrasound (PoCUS), is a promising technological tool that enhances clinical assessment, enriching diagnostic capabilities and clinical reasoning. Its use in nursing spans various patient populations and health care settings, providing nurses with a valuable health assessment tool to improve care quality and patient safety. Despite its growing integration into clinical practice, PoCUS training has mainly focused on physicians, leaving a gap for trained nurses who demonstrate similar proficiency in conducting scans and interpreting images. Previous research highlights the value of digital tools in PoCUS training, showing their role in improving professionals' and students' knowledge, image interpretation skills, and clinical acumen.

Objective: This study aimed to (1) establish an assessment instrument gauging nurses' competency milestones in PoCUS and evaluate its content and appearance validity, (2) develop a series of 5 educational videos focused on PoCUS and assess their content and appearance validity, and (3) construct an online learning environment tailored to nurses' PoCUS training needs and evaluate its content and appearance validity.

Methods: We will conduct a methodological study of technological production guided by Rogers' diffusion of innovations theory. Subproject 1 will design and validate a comprehensive assessment tool for evaluating nurses' competency milestones in PoCUS use. For this purpose, a scoping review will be conducted. The review will be based on JBI Collaboration guidelines and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extended for Scoping Reviews (PRISMA-ScR) checklist. Subproject 2 involves an evaluation of content and appearance validity for a series of 5 educational videos on PoCUS, designed specifically for nurses about applying peripherally inserted central catheter lines, inserting nasogastric feeding tubes, assessing gastric residual volume, assessing pressure injuries and soft tissue conditions, and assessing muscle mass to monitor patient nutritional status. In subproject 3, a comprehensive online learning environment dedicated to PoCUS training for nurses will be developed and validated. The launch of an online learning environment represents a cornerstone of our dissemination strategy, scheduled to coincide with the inaugural Brazilian PoCUS symposium for nurses, an event organized by the project members. This platform will serve as a pivotal resource for continuous learning and professional development.

Results: Subproject 1 will start in the second half of 2024 and is expected to be completed by mid-2025. Subproject 2 is currently ongoing and is expected to be completed in early 2026. Subproject 3 is set to begin in early 2025 and is planned to be completed by 2026.

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Conclusions: Through these concerted efforts, the project aims to bridge the existing gap in PoCUS training for nurses, thereby fostering their proficiency and enhancing patient care outcomes.

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KEYWORDS

ultrasound; bedside ultrasound; patient safety; advanced practice nursing; digital technology in education; empowerment; nurses; Point-of-Care Ultrasound; PoCUS; quality care; decision-making; nursing assessment

Introduction

Background

Mitigating harm in health care settings is a fundamental duty and responsibility of nurses. The nursing process, with its structured stages, serves as a critical tool in minimizing patient risk by enabling nurses to systematically prioritize health needs and devise outcome-focused care plans [1]. Furthermore, the nursing process embodies the clinical methodology of the nursing profession, enhancing decision-making capabilities and fostering effective communication within the multidisciplinary health care team [2].

The initial phase of the nursing process involves a thorough and accurate data collection or nursing assessment [3,4]. This foundational step is crucial for establishing a comprehensive understanding of the patient's current health status, which in turn, guides the identification of nursing diagnoses and the determination of outcomes that are responsive to nursing interventions. In this context, nurses leverage technological advancements to bolster their assessments and decision-making processes.

Among these technologies, point-of-care ultrasound (PoCUS) stands out as a particularly promising tool. PoCUS enhances clinical assessments by providing immediate, real-time imaging support for clinical reasoning and diagnosis [5]. This cost-effective and reliable modality generates internal body images using sound waves, with the procedure involving the application of a transducer on the skin's surface. PoCUS has gained widespread adoption for bedside diagnostics and treatment guidance, offering rapid and efficient solutions [6,7].

Defined as both a portable bedside tool for immediate diagnostic or therapeutic use and a means for the instantaneous acquisition, interpretation, and clinical integration of ultrasound images by health care professionals, PoCUS has transcended its traditional medical confines. Research indicates its use and competency extend to nonmedical professionals [8-13], broadening its application across various clinical settings and care phases, from diagnostic screening to procedure guidance and monitoring [14-16].

The integration of PoCUS into clinical practice has been transformative, equating its diagnostic accuracy with that of conventional imaging methods like x-rays and computerized tomography scans. Its routine application not only reduces the reliance on more invasive tests and patient radiation exposure but also contributes to cost-effective patient care [17,18]. This has led to the proposition of ultrasound as the "fifth pillar" of physical examination, augmenting the traditional quartet of inspection, palpation, percussion, and auscultation [19].

In nursing, the application of PoCUS is diverse, spanning across patient populations [7] and health care levels, from primary [20] to critical [5,11] and emergency care [5,20]. Its use in bedside nursing facilitates the early detection of physiological dysfunctions, thereby enabling more timely and informed clinical decisions crucial for lifesaving interventions [16]. Furthermore, PoCUS complements the physical examination [7,9,13], aids clinical reasoning [5], supports nursing diagnoses, monitors sensitive outcome indicators, and guides invasive procedures [21,22].

In Brazil, the Federal Nursing Council has formally recognized the role of nurses in using bedside ultrasound through Technical Opinion 0052/2021/CTLN/DGEP/COFEn, with specific stipulations regarding its use and the requirement for specialized training. This regulatory endorsement underscores the evolving scope of nursing practice and the integration of advanced technologies like PoCUS in enhancing patient care and outcomes [4].

Despite the increasing recognition of PoCUS as an invaluable tool within nursing practices, a notable gap persists in the literature concerning specialized PoCUS training programs tailored specifically for nurses. While the deployment of PoCUS across various levels of health care underscores its versatility and critical role in enhancing patient care, the existing body of research predominantly focuses on its clinical applications and diagnostic capabilities, rather than on educational frameworks or curricula designed to equip nurses with the requisite skills and knowledge. This discrepancy highlights an educational void, where detailed, nurse-specific training methodologies; competency standards; and assessment criteria remain underexplored. Therefore, this lack of dedicated research into structured PoCUS training programs for nurses not only impedes the standardization of PoCUS proficiency among nurses but also limits the potential for its full integration into nursing care practices. Addressing this gap is essential for ensuring that nurses are adequately prepared to use PoCUS effectively, thereby maximizing its benefits for patient assessment, diagnosis, and management within the nursing scope of practice.

Primary Objectives

The primary objectives of this study were to (1) design and validate a comprehensive assessment instrument for evaluating nurses' competency milestones in PoCUS use, (2) develop and disseminate a series of structured educational videos tailored for nurses on the application of PoCUS, and (3) establish a

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comprehensive online learning environment dedicated to PoCUS training for nurses.

Secondary Objectives

This study also aimed to (1) conduct a comprehensive analysis of content and appearance validity for the PoCUS competency assessment tool tailored for nurses; (2) undertake a rigorous evaluation of content and appearance validity for a series of 5 educational videos on PoCUS designed specifically for nurses about applying peripherally inserted central catheter (PICC) lines, inserting nasogastric feeding tubes, assessing gastric residual volume, assessing pressure injuries and soft tissue conditions, and assessing muscle mass to monitor patient nutritional status; and (3) assess the content and appearance validity of the online learning environment dedicated to PoCUS training for nurses.

Methods

Subproject 1

To achieve the first general and specific objectives, subproject 1 was proposed.

Objective

The main objective of this subproject is to establish an assessment tool gauging nurses' competency milestones in PoCUS and evaluate its content and appearance validity.

This endeavor will undertake a thorough investigation into both the content and appearance validity of the proposed tool, ensuring that it precisely captures the competencies it purports to measure. By adopting a systematic methodology, the study aspires to forge a robust and credible framework for the evaluation of nurses' proficiency in using PoCUS, making a substantial contribution to the discipline. This endeavor is predicated on the premise that the assessment tool accurately mirrors the quintessential abilities and knowledge indispensable for efficacious clinical application.

In the context of this study, competence is delineated as the consistent and adept execution of a task, seamlessly integrating it into everyday clinical practice. Drawing on the scholarly work of Kumar et al [23], the competency domains identified for effective PoCUS use to encompass a spectrum include (1) the acquisition of foundational knowledge, (2) the practical application of this knowledge, (3) the demonstration of technical and procedural adeptness, (4) the seamless integration of these skills into clinical routines, and (5) the process of certification and recertification to ensure ongoing proficiency and adherence to evolving standards. This comprehensive approach underscores the multifaceted nature of competence in PoCUS, highlighting the importance of a well-rounded and continuous learning process. Through this study, we aim to establish an evaluative mechanism that not only assesses but also promotes the growth of these critical competencies among nurses, thereby enhancing the quality of patient care through the proficient use of PoCUS.

Study Design

To curate items for each domain of the proposed assessment tool, a comprehensive scoping review will be orchestrated. The scoping review will be conducted following the JBI Collaboration guidelines and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extended for Scoping Reviews (PRISMA-ScR) checklist [24,25].

Data Source

This review will leverage a wide array of databases to ensure a thorough exploration of the subject matter. These databases include but are not limited to Cochrane, CINAHL, Embase, PubMed, PsycINFO, Scopus, ERIC, and Scielo. In addition to these repositories, an extensive search of the gray literature will be conducted, encompassing resources such as Google Scholar, as well as repositories of theses and dissertations, to capture a broad spectrum of insights and evidence.

The scoping review will be characterized by its inclusivity, imposing no restrictions on the time frame or language of the studies considered. The inclusion criteria are designed to embrace primary research studies, including review articles, randomized controlled trials, cohort studies, and cross-sectional analyses, while excluding surveys, case reports, textbook chapters, conference proceedings, ongoing research, editorials, and comments. The process of determining relevant descriptors and keywords will be a collaborative effort with a librarian from the University of São Paulo who specializes in systematic reviews, ensuring a comprehensive and targeted search strategy.

Given the objective to acquire a holistic understanding of the field and pinpoint gaps in the existing body of research, the quality of the studies will not be appraised. This process will commence with 2 independent reviewers evaluating studies for inclusion based on their titles and abstracts, adhering to predefined eligibility criteria. In instances where titles and abstracts do not provide sufficient information for preliminary selection, full texts will be examined.

Reference Manager

The Rayyan Systems platform will further a double-blind selection process of articles, ensuring an unbiased and efficient review. Discrepancies in the selection process will be reconciled through discussion with a third reviewer.

For organization and analysis, selected articles will be managed using EndNote (version X9, Clarivate Analytics), which will assist in the removal of duplicates and promote the analytical process [26,27].

Data Extraction

The data extraction will encompass a diverse range of information, including but not limited to, the name of the instrument, authorship details, the country of development, language, publication year, constructs measured, target population, mode of instrument application, scale content and item number, response formats, and scoring methods (Multimedia Appendix 1). Furthermore, a detailed examination of the psychometric properties of each instrument will be conducted, with findings presented in tabular format. Additional data pertaining to the objectives, design, interventions, participants, sample sizes, and outcomes of the studies will also

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be extracted and systematically organized in tables, enhancing the clarity and accessibility of the evidence synthesized [28].

The review will be registered with PROSPERO (International Prospective Register of Systematic Reviews) in the second semester of 2024.

Drawing upon the comprehensive insights garnered from the scoping review, a designed assessment tool will be developed to evaluate nurses' competency milestones throughout their PoCUS training journey. This tool will be intricately aligned with the competency domains delineated by Kumar et al [23], ensuring a robust framework that encapsulates essential skills and knowledge. Following its development, the instrument will be subjected to a validation process, involving an evaluation by a professional proficient in Portuguese and a panel of nurses who boast significant experience in PoCUS-related care, education, and research. The Delphi technique [29], renowned for its structured communication process and consensus-building capabilities, will be used to expedite this evaluation, ensuring a comprehensive and iterative assessment.

Given the nascent stage of PoCUS use among Brazilian nurses and the limited pool of experts in this domain, the selection of experts will leverage the snowball sampling technique [30]. This method is particularly suited to the context, allowing for the identification and recruitment of key informants through the networks of initial participants, thereby ensuring a panel enriched with specialized knowledge and experience. Participants who do not return the completed assessment tools within a stipulated 30-day period will be considered nonresponsive and thus excluded from the study.

The recruitment of experts will be conducted through intentional nonprobabilistic sampling, emphasizing the deliberate selection of individuals based on their expertise and experience in PoCUS. Upon their voluntary agreement to partake in the research, evidenced by written consent, these experts will embark on a critical evaluation of the assessment tool. Their scrutiny will focus on the clarity of indicators, their theoretical relevance, and practical applicability, using a dichotomous scale of "agree" or "disagree" for each item. This systematic evaluation process is designed to ensure that each item on the assessment tool is clear, relevant, and practically applicable to the context of nursing practice.

To ascertain the content validity of the tool, the content validity ratio (CVR) for each indicator will be calculated. The CVR, a statistical measure of content validity, will serve as a quantitative gauge of the extent to which the items are deemed essential by the panel of experts [31]. The acceptance threshold for the CVR will be determined based on the number of experts participating in the assessment, adhering to established methodological standards. This validation process aims to establish an accepted assessment tool that accurately reflects the competencies necessary for effective PoCUS application by nurses, thereby contributing to the enhancement of training and practice in this evolving domain [31,32].

Subproject 2

To achieve the second general and specific objectives, subproject 2 was proposed.

Objective

The main objective of this subproject is to develop a series of 5 educational videos focused on PoCUS and assess their content and appearance validity.

Study Design

This methodological investigation uses a cross-sectional design, underpinned by the theoretical perspectives of Fleming et al [33]. It is set to unfold at the Ribeirão Preto College of Nursing, University of São Paulo, an institution renowned for its Nursing Practice Simulation Center, a state-of-the-art recording studio, and a dedicated multimedia team.

Given the emergent status of PoCUS expertise among Brazilian health care professionals, experts will be identified through a snowball sampling technique [30], ensuring a comprehensive representation of knowledge in this nascent field. Participants who fail to return their assessments within a 30-day window will be respectfully excluded from the study, emphasizing the importance of timely feedback. Recruitment will be intentional and nonprobabilistic, targeting individuals who demonstrate a profound understanding and experience in PoCUS. Those agreeing to partake in the study will be required to sign an informed consent form, marking their voluntary commitment to this scholarly endeavor.

The research is structured into distinct phases, each designed to ensure the elaboration and validation of high-quality educational content.

Phase I: Preproduction

This initial phase involves a narrative literature review focused on the procedural skills necessary for the ultrasound-guided insertion of PICC lines and nasogastric feeding tubes. In addition, it will explore the use of ultrasound in assessing gastric residual volume, pressure injuries and soft tissue conditions, and muscle mass, particularly in relation to patient nutritional status. This comprehensive review will span several databases including CINAHL, Embase, LILACS, PubMed, and Scopus, without constraints on publication date or language. Furthermore, textbooks and both national and international guidelines will be consulted to ensure a thorough understanding of the subject matter, including content about the physical principles of ultrasound.

Phase II: Production

Informed by the insights gathered in phase I, this phase involves the development of scripts and storyboards for the educational videos, adhering to the best practices as recommended by Fleming et al [33]. PoCUS experts, including physicians and nurses, will be invited to contribute to this creative process, ensuring the content's relevance and accuracy. Following previous studies [34-36], the Delphi technique [29] will be used to refine the scripts and storyboards, with participants providing their expertise through a structured, iterative consultation process.

To evaluate the content validity evidence of the scripts and storyboards for the educational videos, a tool, refined from Ferreira's [37] methodology, will be used (Multimedia Appendix 2). This comprehensive tool encompasses 6 pivotal categories,

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namely objectives, content, relevance, environment, verbal language, and inclusion of topics, ensuring a holistic assessment of the educational materials. Each category will be scrutinized using a nuanced 4-point Likert scale, where a rating of 4 signifies "strongly agree," 3 denotes "agree," 2 indicates "disagree," and 1 represents "strongly disagree." In addition, the tool thoughtfully includes a section for experts to articulate their detailed opinions and constructive suggestions on each evaluated item, fostering a rich, collaborative refinement process.

Upon the completion of this assessment by the panel of experts, a collaborative scheduling process will be initiated with the multimedia department of Ribeirão Preto College of Nursing, University of São Paulo, to plan the filming sessions. These sessions will take place in the Nursing Practice Simulation Center, ensuring a conducive environment for high-quality video production. The filming will necessitate the use of a portable ultrasound device, equipped with both linear and convex transducers, to accurately depict the procedures. In addition, simulators will be used to promote the realistic demonstration of the insertion of PICC lines and nasogastric tubes, guided by ultrasound technology. To further enhance the realism and educational value of the videos, volunteers will be recruited to portray patients, providing authentic scenarios for the nurses. These nurses will demonstrate the invasive procedures using simulators or clinical assessments using volunteers, showcasing practical applications of the skills being taught.

Phase III: Postproduction

This final phase focuses on the editing and polishing of the educational videos. The Ribeirão Preto College of Nursing, University of São Paulo, multimedia department will lend their expertise in video editing, using advanced software to enhance the educational content with graphic animations, text, images, and sound. Professional voice-over narration will be recorded to accompany the visuals, ensuring clarity and engagement. Upon completion, the videos will undergo a validation process, assessing both content and appearance validity with the help of PoCUS experts and audiovisual technicians.

Throughout this process, the project will leverage the Moodle system of the University of São Paulo [38] to enhance communication and collaboration among the experts. This online learning environment will host the scripts, storyboards, and validation tools, providing a centralized platform for the validation process. To evaluate the appearance of the educational materials, the study will implement the Instrument for Appearance Validity of Educational Technology in Health (IVATES) [39] (Multimedia Appendix 3). This tool comprises 12 targeted questions, each measured against a detailed 5-point Likert scale for nuanced feedback. The scale ranges from 1, indicating "completely disagree," to 5, representing "completely agree," allowing experts to precisely express their assessment of the educational content's effectiveness and aesthetic appeal.

To tailor this tool specifically for the unique demands of this study, thoughtful adaptations will be made. Notably, the original term "illustrations" will be substituted with "video segments" to better reflect the multimedia nature of the content being evaluated. Similarly, "figures" will be replaced with "images" to more accurately describe the visual elements used within the educational videos. In addition, a pivotal modification will be made to question 12, which will now focus on "assistance in teaching-learning procedures." This change shifts the emphasis from assessing attitudinal changes to evaluating the direct educational impact of the videos, aligning the instrument more closely with the study's objectives.

Data Analysis

Data characterizing PoCUS experts will be stored in the University of São Paulo Moodle platform for subsequent download into Microsoft Excel spreadsheets. They will then be transferred to the SPSS (version 26.0; IBM Corp). Descriptive statistics will be used for analysis, including measures of central tendency and dispersion for quantitative variables, and absolute and relative frequencies for categorical variables. Data normality will be checked using the Shapiro-Wilk test, with a distribution considered normal when $P>.05$.

During the evaluation stage of the video's content validity, the CVR will be calculated according to Ayre and Scally [31]. The CVR ranges from –1 to +1, with positive values indicating that more than half of the experts deemed the item essential. Ayre and Scally [31] proposed a table with minimum CVR values based on the number of experts, to determine an item's acceptability at a 5% significance level.

For the evaluation of the appearance of the videos, the appearance validity index (AVI) will be used, where the AVI for each item (AVI-I) will be calculated by dividing the number of experts who rate the item as 4 or 5 by the total number of participants. For the total AVI (AVI-T), the sum of the AVI-I values will be divided by the total number of items. An item with an AVI≥0.78 will be considered excellent; values between 0.60 and 0.77 will indicate the need for adjustments to improve the appearance of the educational health technology; an item with an AVI<0.60 will be classified as unsatisfactory, and the material will need to be revised starting from the key point of the item. The AVI-T should be ≥0.90 [39]. Data analysis will be conducted by a statistician from the Ribeirão Preto College of Nursing, University of São Paulo.

Subproject 3

Objective

The main objective of this subproject is to construct an online learning environment tailored to nurses' PoCUS training needs and evaluate its content and appearance validity.

Study Design

This cutting-edge methodological study in nursing education is grounded in the seminal work of Rogers' [40] diffusion of innovations theory. At the heart of this theory is the concept of innovation, defined as a novel idea, practice, knowledge, or object that is perceived as new by an individual or community and is integrated into their practices, leading to significant behavioral transformations. For such innovations to gain widespread acceptance and integration, they should be disseminated through effective communication channels that ensure easy accessibility. A prime example of this is the online learning environment, which transcends the traditional

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constraints of time and space, thereby promoting a seamless and impactful implementation of innovative educational strategies.

The process of adopting an innovation is delineated into five distinct stages [40]: (1) knowledge, the stage at which an individual gains awareness and understanding of the innovation; (2) persuasion, the stage where an individual develops a favorable attitude towards the innovation; (3) decision, the critical juncture at which an individual decides whether to embrace or reject the innovation; (4) implementation, the phase where the individual actively starts using the innovation, signifying a behavioral shift; and (5) confirmation, the final stage where the individual reaffirms their commitment to the innovation and fully integrates it into their practice. This study will delve into the initial 3 stages to uncover the dynamics of innovation adoption within the context of nursing education.

To further the development of the online learning environment, the instructional design will adhere to the comprehensive "ADDIE" model, which encompasses 5 pivotal phases: analyze, design, develop, implement, and evaluate [41].

Analysis Phase

Recognizing the nascent yet growing importance of ultrasound use in nursing, this phase will be addressed through subprojects 1 and 2, laying the groundwork for an informed instructional strategy.

Design Phase

The online learning environment will be crafted with learning objectives that span a broad spectrum of ultrasound applications in nursing. These objectives will include (1) mastering ultrasound-guided PICC line insertion, (2) learning ultrasound-guided nasogastric tube insertion techniques, (3) conducting qualitative and quantitative assessments of gastric residual volume to avert bronchopulmonary aspiration through PoCUS, (4) evaluating pressure injuries and soft tissue conditions using PoCUS, and (5) assessing muscle mass to monitor patient nutritional status with a focus on PoCUS.

Development Phase

The online learning environment will be structured into 5 comprehensive modules, each designed to address the learning objectives outlined. These modules will incorporate instructional videos that elucidate basic ultrasound principles and demonstrate procedural techniques essential for effective examinations, developed as part of subproject 2. To enrich the learning experience, the modules will also include recommended additional readings, anatomical landmark flashcards for quick recognition, educational quizzes to reinforce key concepts, pre- and post–self-assessment tests to gauge learning progress, and clinical case studies. These case studies are designed to foster clinical reasoning skills, with a strong emphasis on the nursing process and the integration of standardized nursing language systems, including NANDA International, Inc [42], Nursing Outcomes Classification (NOC) [43], and Nursing Interventions Classification (NIC) [44]. The modules will be created by experts in PoCUS and nursing education.

Implementation

During the implementation phase, the online learning environment will be evaluated through both content and appearance validity evidence analysis, ensuring its educational efficacy and user engagement. The content validity will be assessed by a panel of physicians and nurses, each boasting expertise in the relevant subject matter. This evaluation will be expedited through the use of the content validity index (CVI) [31,32], with experts being carefully selected through intentional nonprobabilistic sampling methods to ensure a comprehensive and informed review process. Similarly, the appearance validity will be scrutinized by professionals well-versed in the domain, using the IVATES tool [39] (Multimedia Appendix 3) to guarantee a thorough appraisal of the online learning environment's instructional design and content relevance.

In a strategic move to enhance the evaluation process, this project will incorporate the evaluation tool developed by Ferreira [37] (Multimedia Appendix 2), which categorizes the assessment criteria into 6 distinct domains: objectives, content, relevance, environment, verbal language, and inclusion of topics. Each category will be evaluated using a 4-point Likert scale, ranging from "strongly agree" to "strongly disagree," providing a nuanced framework for feedback. In addition, this tool thoughtfully allows experts to articulate their reasoning for any disagreements, further enriching the feedback with detailed insights and constructive suggestions for each evaluated item.

Evaluation Phase

Upon the completion of the content and appearance validity evidence analysis by the panel of experts, the online learning environment will transition to a pilot testing phase, engaging a select group of nurses to interact with and evaluate the system. Their experiences and perceptions will be captured through the System Usability Scale, Brazilian version [45] (Multimedia Appendix 4), an instrument comprising 10 items, scored on a scale from "strongly disagree" to "strongly agree." This scale not only aligns semantically, idiomatically, conceptually, and culturally with its original English counterpart but also demonstrates exceptional reliability and structural construct validity, ensuring a credible and comprehensive assessment of the online learning environment's usability.

Data Analysis

The content validity evidence for the online learning environment will be quantitatively assessed through the calculation of the CVI, with items receiving scores of 4 or 5 by experts deemed positively validated. The criteria for validity will follow established benchmarks, with a CVI≥0.78 indicating excellent validity, scores between 0.60 and 0.77 classified as good, and scores <0.59 considered poor [39,46].

To determine the overall usability score derived from the application of the System Usability Scale, Brazilian version [45], a calculation process will be used. For odd-numbered statements, the score assigned by the evaluator will be reduced by 1, whereas for even-numbered statements, it will be reduced by 5. The aggregated individual scores will then be multiplied by 2.5 to obtain the total scale value. This final score will speed a nuanced interpretation of the online learning environment's

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usability, ranging from the worst imaginable scenario to an ideal scenario, thus providing a comprehensive understanding of the user's perception and the system's overall performance. Data analysis will be conducted by a statistician from the Ribeirão Preto College of Nursing, University of São Paulo.

Ethical Considerations

The project was submitted for ethical review to the Research Ethics Committee of the Ribeirão Preto College of Nursing, University of São Paulo, in November 2023 (Institutional Review Board approval 78296623.2.0000.5393). This submission underscores our commitment to conducting the study in strict adherence to Resolution 466, dated December 12, 2012, issued by the National Council of Ethics in Research of the Ministry of Health. In addition, all participants will be furnished with an informed consent form (Multimedia Appendix 5).

It is important to note that participation in this study will not entail any financial burden on the participants, nor will it offer any direct monetary incentives. The anticipated risks associated with participation are deemed minimal, primarily concerning the potential inconvenience due to the time investment required for engaging with the research tools. To alleviate any potential discomfort, we will offer participants the flexibility to complete the tools at their own pace, in multiple sittings if preferred.

In the event of any unforeseen harm arising from participation in the study, we are fully prepared to uphold the participants' rights to compensation, in alignment with the prevailing legal standards of the country. This assurance is extended by both the research team and the sponsoring institution, highlighting our commitment to participant welfare.

Furthermore, we acknowledge the inherent risks associated with the digital environment, particularly the limitations of current technologies that may impede our ability to ensure absolute confidentiality and the potential risk of data breaches. Participants will, therefore, be advised to retain a copy of all electronic communications for their records. In an effort to mitigate these risks, upon the conclusion of the study, all collected data will be securely transferred to a password-protected computer, accessible solely to the project team members. Subsequently, all data stored on the online platform will be permanently erased.

While the direct involvement of specialists in this study may not yield immediate personal gains, it is anticipated to offer significant indirect and long-term professional benefits. The educational materials developed, including videos and the online learning environment, are expected to substantially enhance nurses' comprehension of the subject matter, thereby promoting future scholarly endeavors. Furthermore, the potential benefits of this study extend beyond the immediate academic community, promising to effectuate enduring improvements in nursing care for adult patients across all health care settings. This endeavor thus represents a commitment to ethical research conduct, participant protection, and the advancement of nursing education and patient care on a broader scale.

Results

Subproject 1 will start in the second half of 2024 and is expected to be completed by mid-2025. Subproject 2 is currently ongoing and is expected to be completed in early 2026. Subproject 3 is set to begin in early 2025 and is planned to be completed by 2026.

Discussion

Expected Findings

Previous studies have highlighted the importance of PoCUS in clinical settings, particularly in enhancing diagnostic accuracy [12,22,47,48] and patient outcomes [49-52]. However, there has been a lack of standardized tools to assess nurses' competency in using PoCUS. This study builds on the foundational work of researchers like Fleming et al [33], who have emphasized the need for structured educational materials and competency assessments. By incorporating a scoping review and expert consultations, this research addresses the gaps identified in previous studies and will offer a validated assessment tool [32,33].

The results will be showcased through presentations at undergraduate and master's thesis defenses, marking a significant contribution to the academic discourse. Furthermore, to ensure the findings are accessible to a diverse audience, they will be published in esteemed journals within the field. A deliberate focus will be placed on journals indexed in prestigious databases such as the ISI Web of Science and Scopus, with publications available in Portuguese, English, and Spanish.

The strengths of this study include its comprehensive methodology, which uses a scoping review following JBI Collaboration guidelines to ensure a thorough exploration of the subject matter. The involvement of PoCUS experts, including physicians and nurses, in the development of scripts and storyboards enhances the content's relevance and accuracy. In addition, the iterative validation process, which uses the Delphi technique for refining educational materials, ensures that the content is rigorously evaluated and validated by experts. However, there are limitations to consider. The study is conducted within a specific institutional context (Ribeirão Preto College of Nursing, University of São Paulo), which may limit the generalizability of the findings to other settings. The development and validation processes are resource-intensive, requiring significant time and expert involvement. Furthermore, the reliance on expert opinions in the Delphi technique may introduce bias, although this is mitigated through structured, iterative consultations [29].

Subproject 2 focuses on the creation and validation of 5 educational videos specifically designed for nurses. The expected results from this subproject include the development of high-quality, validated educational videos that can be integrated into nursing curricula. These videos aim to enhance nurses' practical skills and confidence in using PoCUS, ultimately improving patient care. The results will be showcased through presentations at undergraduate and master's thesis defenses and will be published in esteemed journals.

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Summarizing key findings and insights will be produced and disseminated through YouTube, complemented by strategic promotions through social media channels such as Facebook (Meta) and Instagram (Meta), as well as on the official websites of the participating universities. Recognizing the importance of linguistic diversity and inclusivity, one of the videos will be specially crafted in Spanish to cater to the Spanish-speaking audience. This initiative will be bolstered by the support from Sigma (Latin America and Caribbean Region), leveraging the unique position of a Chilean group member who is currently a master's student in the Fundamental Nursing Graduate Program at Ribeirão Preto College of Nursing, University of São Paulo.

Subproject 3 aims to construct and evaluate evidence of content and appearance validity for an online learning environment tailored to nurses' PoCUS training needs. This potent education resource is designed to foster clinical reasoning skills with a strong emphasis on the nursing process and the integration of standardized nursing language. The evaluation phase will involve pilot testing the online learning environment with a select group of nurses, capturing their experiences and perceptions through the System Usability Scale, Brazilian version. The results from this subproject will provide valuable insights into the usability and effectiveness of the online learning environment in enhancing PoCUS training for nurses.

Future research should focus on assessing the long-term impact of these educational videos and the online learning environment on nursing practice and patient outcomes. In addition, exploring the implementation of these educational resources in diverse health care settings will help evaluate their effectiveness and adaptability. Investigating the integration of advanced technologies, such as online reality and artificial intelligence, to enhance the educational experience is another promising area for future research.

To ensure the findings are accessible to a diverse audience, the results will be disseminated through multiple channels. Academic publications in esteemed journals indexed in prestigious databases such as ISI Web of Science and Scopus will be pursued. The results will also be presented at undergraduate and master's thesis defenses, as well as at national and international conferences. Workshops and training sessions will be organized for nurses and health care professionals to share the validated assessment tool, educational videos, and online learning environment. In addition, online platforms and social media will be used to reach a broader audience and facilitate knowledge sharing and collaboration. Key findings and insights will be disseminated through YouTube and promoted through social media channels such as Facebook and Instagram, as well as on the official websites of the participating universities.

Conclusions

The anticipated outcomes of this research underscore its potential to significantly enhance the competency of nurses in using PoCUS through the development and validation of a robust assessment tool. By addressing the current gaps in standardized competency evaluations, this study aims to elevate the quality of nursing education and clinical practice. The creation of high-quality educational videos and a tailored online learning environment is expected to provide nurses with practical, accessible, and engaging resources that foster both skill acquisition and confidence in PoCUS procedures. These educational interventions are poised to improve patient care outcomes by ensuring that nurses are well equipped to perform PoCUS with proficiency.

Furthermore, the dissemination of the findings through various academic and public channels will promote widespread adoption and integration of these resources into nursing curricula globally. The iterative validation process involving PoCUS experts ensures the relevance and accuracy of the educational content, while the use of advanced methodologies like the Delphi technique and structured scoping reviews guarantees a rigorous evaluation framework.

In conclusion, this research protocol not only aims to fill a critical void in PoCUS competency assessment but also aspires to set a new standard in nursing education. By leveraging innovative educational tools and methodologies, the study promises to contribute to the ongoing professional development of nurses and ultimately enhance patient care across diverse health care settings. The commitment to ethical research conduct and participant protection further strengthens the study's foundation, ensuring that the outcomes are both scientifically sound and socially responsible.

Acknowledgments

This research was supported by the Unified Scholarship Program of the Office of the Dean of Undergraduate Studies at the University of São Paulo, which provided scholarships to the undergraduate students involved in the project. In addition, we acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES) for providing a scholarship to the master's student associated with this research project.

We hereby declare that the research project was submitted to the São Paulo Research Foundation (FAPESP) for funding acquisition in March 2024.

In addition, we hereby declare that we used ChatGPT (OpenAI) [53] solely for the purpose of enhancing English writing proficiency.

Authors' Contributions

FG contributed to the conceptualization of ideas and the formulation or evolution of overarching research goals and aims. AMS performed the supervision (oversight and leadership responsibility) for the research activity planning and execution, including

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mentorship external to the core team. RMB contributed to the data curation and management activities to annotate (produce metadata), scrub data, and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse. VBS handled the project administration (management and coordination responsibility) for the research activity planning and execution. MGM and MSR contributed to writing—review and editing and the preparation, creation, and presentation of the published work by those from the original research group, specifically critical review, commentary, or revision (including pre- or postpublication stages). PRdP performed the investigation by conducting a research and investigation process, specifically performing the experiments or data and evidence collection. FGC contributed to the methodology (development or design of methodology) and creation of models. SANR performed the validation (verification), whether as a part of the activity or separately, of the overall replication or reproducibility of results, experiments, and other research outputs.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction tool.
[PDF File (Adobe PDF File), 35 KB - resprot_v13i1e58030_app1.pdf]

Multimedia Appendix 2
Validation of the educational video script tool.
[PDF File (Adobe PDF File), 81 KB - resprot_v13i1e58030_app2.pdf]

Multimedia Appendix 3
IVATES (Instrument for Appearance Validity of Educational Technology in Health) tool.
[PDF File (Adobe PDF File), 225 KB - resprot_v13i1e58030_app3.pdf]

Multimedia Appendix 4
System Usability Scale, Brazilian version.
[PDF File (Adobe PDF File), 108 KB - resprot_v13i1e58030_app4.pdf]

Multimedia Appendix 5
Informed consent forms.
[PDF File (Adobe PDF File), 153 KB - resprot_v13i1e58030_app5.pdf]

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Abbreviations

AVI: appearance validity index
AVI-I: appearance validity index for each item
AVI-T: total appearance validity index
CVI: content validity index
CVR: content validity ratio
IVATES: Instrument for Appearance Validity of Educational Technology in Health
NIC: Nursing Interventions Classification
NOC: Nursing Outcomes Classification
PICC: peripherally inserted central catheter
PoCUS: point-of-care ultrasound
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extended for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Differences in Messenger RNA Expression of Fibulin-1, Elastin, Matrix Metalloproteinase-1, Basic Fibroblast Growth Factor, and α-Smooth Muscle Actin Between the Ventral and Dorsal Tunica Dartos in Patients With Hypospadias and Chordee: Protocol for a Prospective Cohort Study

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Abstract

Background: Hypospadias is a common congenital anomaly characterized by the displacement of the urethral opening to the ventral side of the penis. Surgical correction is often necessary for functional and psychological reasons. The etiology involves genetic and environmental factors, and chordee, a downward curvature of the penis, is a common complication. Proteins such as fibulin-1, elastin, matrix metalloproteinase-1, basic fibroblast growth factor, and α-smooth muscle actin play roles in hypospadias development.

Objective: The study's aim is to investigate the differences in messenger RNA (mRNA) expression of fibulin-1, elastin, matrix metalloproteinase-1, basic fibroblast growth factor, and α-smooth muscle actin between the ventral and dorsal tunica dartos in patients with hypospadias and chordee.

Methods: This prospective cohort study aims to investigate differences in mRNA expression of the abovementioned proteins between the ventral and dorsal tunica dartos in patients with hypospadias and chordee. Ethics approval has been obtained, and consent from parents will be obtained before data collection. Eligible participants are aged 6-18 months, diagnosed with hypospadias and chordee, and planned for urethroplasty. Tissue samples will be collected from both aspects of the tunica dartos and analyzed using real-time quantitative reverse transcription–polymerase chain reaction. Data analysis will involve statistical tests and normalization of housekeeping genes.

Results: This study is at the protocol development stage. A pilot study regarding its feasibility has been ongoing as of August 2023. The study results are expected to be available by the end of 2024.

Conclusions: The study of mRNA expressions of various proteins in the tunica dartos of patients with hypospadias and chordee is expected to improve the understanding and expand the knowledge of the pathophysiology of hypospadias and chordee.

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KEYWORDS

chordee; gene expression; hypospadias; polymerase chain reaction; mRNA

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Introduction

Hypospadias is one of the most common congenital anomalies in male neonates. It is characterized by the urethral opening being misplaced on the ventral side of the penis instead of the tip. Its prevalence globally is around 1 in 200-300 male births [1]. It has significant psychological and functional impacts, requiring surgical correction to achieve normal appearance and function. Various surgical techniques exist, but controversies persist regarding the best approach for different types of hypospadias [2]. The etiology of hypospadias is believed to be multifactorial, involving genetic and environmental factors [3,4]. Chordee, a downward curvature of the penis, is commonly associated with hypospadias and results from tissue growth disturbances [5].

The proteins fibulin-1, elastin, matrix metalloproteinase-1 (MMP-1), basic fibroblast growth factor (bFGF or FGF-2), and α-smooth muscle actin (α-SMA) play roles in hypospadias development [4,6,7]. Fibulin-1 is related to extracellular matrix integrity, while elastin contributes to tissue extensibility. MMP-1 is involved in matrix remodeling, while bFGF affects differentiation. α-SMA is implicated in fibrosis. Messenger RNA (mRNA) expression of these proteins may shed light on their roles in hypospadias [2,4,8].

However, research on dartos tunic elasticity, genetic factors, and mRNA expression in hypospadias is limited. A better understanding of the genes influencing dartos tunic elasticity could provide insights into pathophysiology and chordee management. Therefore, this protocol is designed to investigate the differences in mRNA expression of fibulin-1, elastin, MMP-1, bFGF, and α-SMA between the ventral and dorsal tunica dartos in patients with hypospadias and chordee.

Methods

Study Design

This is an observational study using a prospective cohort, designed for the investigation of the differences in mRNA expression of fibulin-1, elastin, MMP-1, bFGF, and α-SMA between the ventral and dorsal tunica dartos in patients with hypospadias and chordee. The protocol is prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for reporting a protocol study [9].

Ethical Considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The approval for the protocol of this study was granted by the Medical Research Ethics Committee, Universitas Indonesia, in April 2022 (KET-413/UN2.F1/ETIK/PPM.00.02/2022). All participants provided written informed consent prior to their inclusion in the study, and the study protocol was reviewed and approved by the institutional review board to ensure ethical standards and participant safety.

Informed consent was obtained from all participants during the primary data collection phase. The original informed consent covered the possibility of secondary data analysis, and the institutional review board confirmed that no additional consent was required for this study's secondary analysis.

To ensure the privacy and confidentiality of participants, all study data were deidentified prior to analysis. Personal identifiers were removed, and the data were anonymized to protect the participants' identities. Appropriate measures were taken to maintain the confidentiality of the data throughout the study.

No additional compensation was provided for this analysis as it did not involve additional participant interaction.

There are no images included in the manuscript or supplementary material that could potentially identify individual participants. If such images are deemed necessary in future submissions, we will ensure that consent has been obtained from identifiable individuals, and relevant consent forms will be uploaded during resubmission.

Consent for the data collection and publication has been obtained from the parents of patients with hypospadias. The consent was sought after the parents and their children have already received an explanation from the main researcher.

The data taken for this study were stored and uploaded over the internet without any identifier.

Eligibility Criteria and Recruitment Procedures

The eligibility criteria for participants in this study are as follows:

- Inclusion criteria:
  1. Diagnosed as having hypospadias with chordee by a pediatric urologist
  2. Aged 6-18 months
  3. Planned to undergo urethroplasty
- Exclusion criteria:
  1. The amount of available tissue specimens is insufficient for further examination
  2. Patients with genital ambiguity characterized by clitoral hypertrophy
  3. The patient is experiencing an infection of the prepuce
  4. Patients with a history of previous chordectomy or urethroplasty surgery
  5. Patients with conditions that can experience dysregulation of extracellular matrix component proteins, namely malignancy and Marfan syndrome

Participants for this research will be enrolled through a consecutive recruitment method. Parents of eligible patients will receive information about the study's procedures and will be given the opportunity to decide whether they wish for their children to take part in the study during its duration.

Clinical Outcomes

The clinical outcomes measured in this study are as follows:

1. Expression of fibulin-1 mRNA
2. Expression of elastin mRNA
3. Expression of MMP-1 mRNA

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4. Expression of bFGF mRNA
5. Expression of α-SMA mRNA

The clinical outcomes will be measured from differences in mRNA expression from both the dorsal and ventral aspects of the tunica dartos excised during urethroplasty. A positive control gene for both dorsal and ventral tissues will also be measured in subsequent analyses. The expression levels of the 5 genes will be assessed relative to the housekeeping gene β-actin using fold change values.

Randomization and Blinding

This study is single blinded. The laboratory assistant does not know which aspect of the penis that the specimen belongs to.

Study Process and Data Collection

Specimen Collection

In this study, tissue samples from the dorsal and ventral sides of the tunica dartos will be obtained from patients with hypospadias and chordee. Ventral tunica dartos samples will be taken from each patient by the researcher as the performing operator, ensuring that the size and location of collection are standardized across all patients. The collected portions are shown in Figure 1.

Figure 1. Site of tissue sample collection from the dorsal and ventral sides of the tunica dartos from patients with hypospadias and chordee, from an observational study conducted in Arifin Achmad General Hospital Riau in 2023 (source: personal documentation of the researcher).

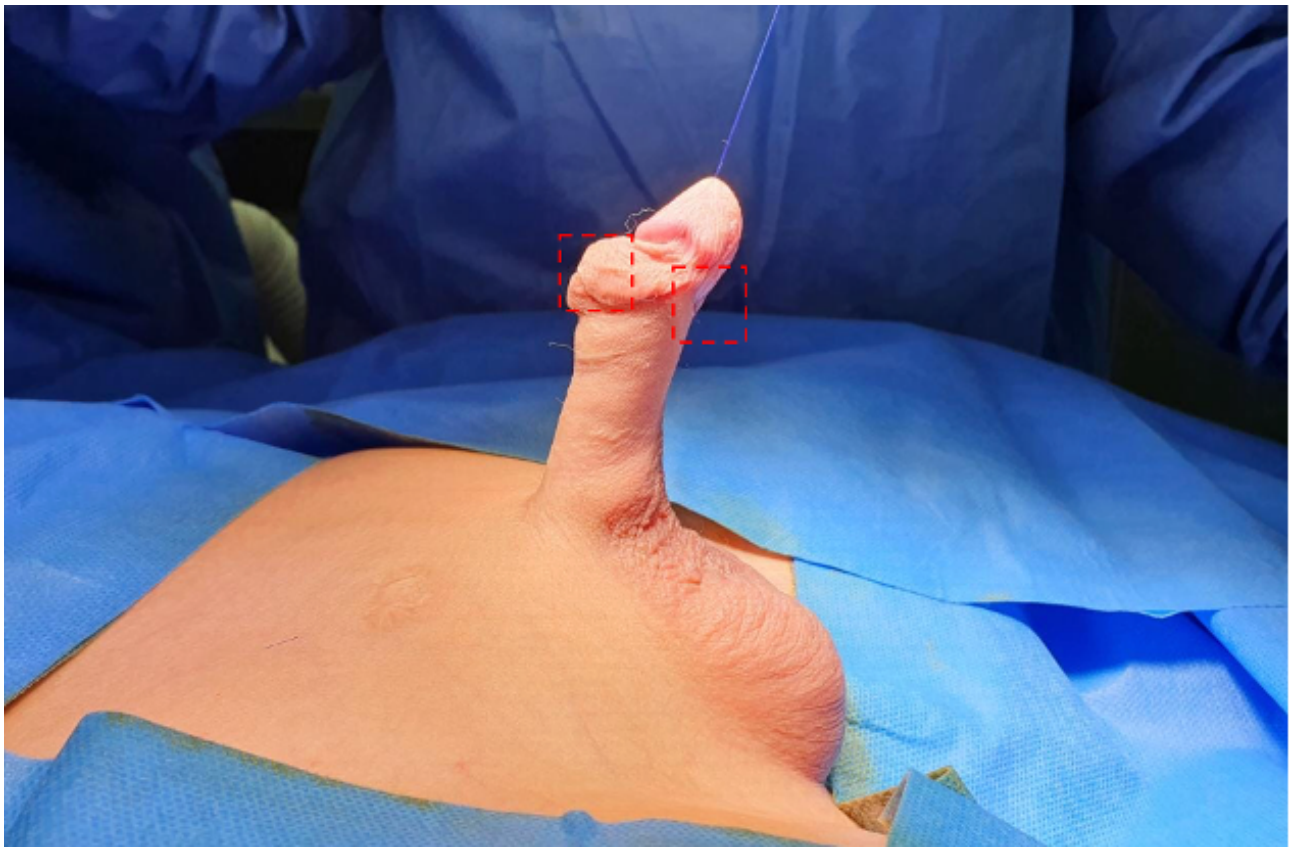

Total RNA Isolation

RNA will be isolated from all samples using the RNeasy Mini Kit (Qiagen) following the kit's manual instructions. Initially, β-mercaptoethanol and ethanol are added to Buffer RPE. Tissue samples are separated from RNAlater stabilization and then mixed with Buffer RLT. For tissue weighing 20-30 mg, 600 µL of Buffer RLT is added. Sample disruption and homogenization are performed using an ultrasonic disruptor tool for 20-40 seconds. The lysed samples are centrifuged at 17,000×g for 3 minutes, and the supernatant is collected for RNA extraction. Then, 70% ethanol, equal to 1× the lysate volume, is added and homogenized using a micropipette.

A total of 700 µL of the sample is transferred to a QIAamp spin column placed in a 2-mL collection tube and centrifuged at >8000×g for 1 minute. The supernatant is discarded, and the process is repeated by pairing a new 2-mL collection tube with the QIAamp spin column until all lysates, including precipitates, are processed. The supernatant and 2-mL collection tube are discarded. The QIAamp spin column is then transferred to a new 2-mL collection tube.

Buffer RW1 (700 µL) is added to the QIAamp spin column and centrifuged at >8000×g for 1 minute. The supernatant and 2-mL collection tube are discarded. This step is repeated with the addition of 500 µL of Buffer RPE. The QIAamp spin column is then combined with 500 µL of Buffer RPE and centrifuged at 17,000×g for 3 minutes, and the supernatant is transferred to a new 2-mL tube and centrifuged at 17,000×g for 1 minute. The QIAamp spin column is moved to a new 1.5-mL microcentrifuge tube, and 30-50 µL of RNase-free water is added directly to the QIAamp membrane, followed by centrifugation at >8000×g for 1 minute.

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Quantification of RNA and Circular DNA Synthesis

The quantification stage serves to determine the RNA concentration in each sample in order to dilute them to the same concentration, which is 0.2 ng/µL. RNA quantification from each sample and control will be performed using the Qubit dsDNA HS kit (Q32851; Thermo Fisher Scientific). All samples from the whole genome amplification stage are vortexed and diluted by mixing 5 µL of the sample with 45 µL of double-distilled water to achieve a 1:10 dilution. Samples, controls, and the Qubit standard solution are placed in 500-µL tubes containing Qubit dsDNA reagent with specific volumes.

All samples are then vortexed, spun down, and incubated at room temperature for 2 minutes. The RNA quantification results are then used for circular DNA synthesis using the cDNA Taqman MicroRNA Reverse Transcription Kit (4366596; Thermo Fisher Scientific). The composition of the reagents used can be seen in Hidayati et al [10]. The master mix, containing the samples, is then incubated in a thermal cycler.

Expression Quantification Using a Real-Time Quantitative Reverse Transcription–Polymerase Chain Reaction Machine

A real-time quantitative reverse transcription–polymerase chain reaction (qRT-PCR) machine will be used to perform the qRT-PCR amplification using the primary sequences in Table 1.

The machine monitors fluorescence levels after each PCR cycle to track the amount of amplified DNA in real time.

Table 1. Primary sequences of the genes used in the study.

Gene	Nucleotide code	Primary sequence (5'-3')
Fibulin-1	NM_006486.3	• F[a]: GATGGTGTCTCCTGTGAAGATG • R[b]: TGATGCATGTATGCCCGATAG
Elastin	NM_000501.4	• F: CTGCAAAGGCAGCCAAATAC • R: CACCAGGAACTAACCCAAACT
MMP-1[c]	NM_002421.4	• F: GCCTTCCAACTCTGGAGTAATG • R: GAATGGGAGAGTCCAAGAGAATG
bFGF[d]	NM_001361665.2	• F: TGAAACGAACTGGGCAGTATAA • R: TTGACCTGACTGTGGAAGAAC
αSMA[e]	NM_001613.4	• F: GACCCTGAAGTACCCGATAGA • R: CTCAGCAGTAGTAACGAAGGAATAG

[a]F: forward.

[b]R: reverse.

[c]MMP-1: matrix metalloproteinase-1.

[d]bFGF: basic fibroblast growth factor.

[e]α-SMA: α-smooth muscle actin.

Data Analysis

The amplification curve data will then be analyzed to determine the cycle threshold (Ct) value. The Ct values are then normalized to that of the housekeeping gene to calculate the relative gene expression using the ΔΔCt method.

Data Analysis

The data to be collected in this study include clinical characteristics such as age, height, weight, BMI, comorbidities, and delivery history, accompanied by mRNA expression from both the dorsal and ventral sides of the tunica dartos tissue.

All quantitative data obtained from this research will be analyzed using SPSS (version 25.0; IBM Corp) software. The normality of all numeric data will be tested using the Kolmogorov-Smirnov test. Numeric data will be presented as mean (SD) for normally distributed data and median (range) for nonnormally distributed data.

If the obtained data are normally distributed, an independent 2-tailed *t* test will be performed. Meanwhile, nonnormally distributed data will be tested using the Mann-Whitney *U* test to determine gene expression differences between research groups. The quantification of gene expression is expressed as fold change, compared to the housekeeping gene used in the study.

Results

This study is at the protocol development stage. A pilot study regarding its feasibility has been ongoing as of August 2023. The study results are expected to be available by the end of 2024.

Discussion

Hypospadias, characterized by the abnormal positioning of the urethral opening, is a prevalent condition that ranks as the second most frequent congenital anomaly in male neonates, following cryptorchidism. The condition is typified by the displacement of the urethral meatus to the ventral side of the penis, leading to curvature abnormalities in the penis and

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preputial skin. The quest for optimal restoration, both functionally and aesthetically, drives the need for hypospadias correction surgeries. The primary aim of these interventions is to achieve acceptability in both the appearance and function of the penis, while also addressing psychological concerns [1,2].

The realm of hypospadias surgery presents a diversity of approaches for penile reconstruction, yet controversies persist regarding the most suitable techniques for various types of hypospadias and the utilization or excision of tunica dartos in surgical procedures. Noteworthy among these techniques is the "tubularized incised plate" urethroplasty proposed by Snodgrass et al [11], utilizing tunica dartos excision to address chordee. Another technique, similar in approach but employing tunica dartos or tunica vaginalis as a second layer, was presented by Tavakkoli Tabassi and Mohammadi [12]. Diverging opinions among urologists surround the excision of all inelastic tissue (ventral tunica dartos), coupled with dorsal tunica dartos as a second layer. Intriguingly, prior studies failed to find disparities between the ventral and dorsal tunica dartos, attributing this to their concurrent formation and common origin [4,7,13].

The multifactorial etiology of hypospadias is underscored by its potential maternal and paternal inheritance, suggesting a likelihood of 57% to 77% heritability. Environmental factors, including exposure to chemicals, such as pesticides, diethylstilbestrol, vinclozolin, polychlorinated biphenyls, phthalates, and dioxins during pregnancy, have been implicated in hypospadias causation [3,4]. While the exact etiology of hypospadias remains elusive, histopathological findings in patients with hypospadias warrant further investigation into the disorder's etiological landscape [7].

Notable distinctions in collagen and elastin content are observed between normal and hypospadias-afflicted penises, affecting the stiffness and flexibility of the tunica dartos [7]. There are some proteins that play roles in the elasticity of a tissue. Elastic connective tissue is pivotal in various pathological tissue changes. Elastin, an essential component of the extracellular matrix, endows tissues with extensibility and elasticity. Low elastin concentrations are linked to impaired male urethral development, while elastin-rich concentrations in male fetus urethras elevate intrauterine pressure during the early stages of micturition [14]. Matrix metalloproteinases play a key role in embryological processes and wound healing. MMP-1, a collagenase enzyme, breaks down collagen types I, II, and III, influencing extracellular matrix repair. Decreased MMP-1 levels in hypospadias are linked to increased collagen production. Unbalanced collagen synthesis and degradation can lead to fibrotic tissue formation [15]. Fibroblast growth factors regulate fibroblast growth and differentiation. bFGF stimulates cell proliferation and differentiation, impacting the mesodermal, ectodermal, and endodermal areas. Abnormalities in the bFGF pathway contribute to urethral plate formation, potentially resulting in fibrotic tissue development. α-SMA, implicated in fibrogenesis, drives myofibroblast differentiation and extracellular matrix repair. In the context of hypospadias, α-SMA involvement points to fibrocontractive diseases such as chordee [16].

While this study may provide insights into the differences of the ventral and dorsal tunica dartos, we did not include samples of tunica dartos from healthy patients, which would limit the data analysis only to patients with chordee.

Understanding the differential mRNA expression of fibulin-1, elastin, MMP-1, bFGF, and α-SMA between the ventral and dorsal tunica dartos in patients with hypospadias and chordee presents an opportunity to explore the intricate molecular mechanisms underlying hypospadias development and its associated complications.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request

Conflicts of Interest

None declared.

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Abbreviations

α-SMA: α-smooth muscle actin
bFGF: basic fibroblast growth factor
Ct: cycle threshold
MMP-1: matrix metalloproteinase-1
mRNA: messenger RNA
qRT-PCR: real-time quantitative reverse transcription–polymerase chain reaction
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Real-Life Laboratory Setting for Clinical Practice, Education, and Research in Family Systems Care: Protocol for a Transformational Action Research Study

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Abstract

Background: Burdening health and illness issues such as physical or mental illnesses, accidents, disabilities, and life events such as birth or death influence the health and functioning of families and contribute to the complexity of care and health care costs. Considerable research has confirmed the benefits of a family systems–centered care approach for patients, family caregivers, families, and health care professionals. However, health care professionals face barriers in working with families, such as feeling unprepared. Family systems–centered therapeutic conversations support families' day-to-day coping, resilience, and health. A family systems care unit (FSCU) was recently established as a real-life laboratory at one of the Swiss Universities of Applied Sciences. In this unit, health care professionals offer therapeutic conversations to families and individual family members to support daily symptom management and functioning, soften suffering, and increase health and well-being. These conversations are observed in real time through a 1-way window by other health care professionals, students, and trainees and are recorded with video for research and education. Little is known about how therapeutic conversations contribute to meaningful changes in burdened families and the benefits of vicarious learning in a real-life laboratory setting for family systems care.

Objective: In this research program, we aim to deepen our understanding of how therapeutic conversations support families and individuals experiencing burdening health and illness issues and how the FSCU laboratory setting supports the learning of students, clinical trainees, and health care professionals.

Methods: Here we apply a transformational action research design, including parallel and subsequent substudies, to advance knowledge and practice in family systems care. Qualitative multiple-case study designs will be used to explore the benefits of therapeutic conversations by analyzing recordings of the therapeutic conversations. The learning processes of students, trainees, and professionals will be investigated with descriptive qualitative study designs based on single and focus group interviews. The data will be analyzed with established coding methods.

Results: Therapeutic conversations have been investigated in 3 single-case studies, each involving a sequence of 3 therapeutic conversation units. Data collection regarding the second research question is planned.

Conclusions: Preliminary results confirm the therapeutic conversations to support families' coping. This renders the FSCU a setting for ethically sensitive research. This program will not only support the health and well-being of families, but also contribute to relieving the financial and workforce burdens in the health and social care system.

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KEYWORDS

family systems care; family nursing; family health; family well-being; therapeutic conversation; real-life laboratory; transformational action research; case study research; qualitative research; vicarious learning

Introduction

Background

Family functioning and health influence each other [1]. Health-related burdens that affect family functioning and health may arise from physical or mental illnesses, accidents, disabilities, or meaningful life events such as the birth, divorce, or death of family members [2,3]. While supportive collaboration within families improves the behavior and outcomes of chronically ill minor and adult family members, overinvolvement and underinvolvement of families can be harmful [4]. Conversely, taking care of a family member increases the risks of physical and mental symptoms, chronic illnesses [5,6], and chronic sorrow [7] among family caregivers. Family caregivers are also at greater risk of unhealthy behaviors, such as excessive smoking and increased alcohol consumption [6].

Health-related burdens in families contribute to the complexity of care, increasing the demands on nurses and physicians [8,9] and adding to health care costs [10]. Nevertheless, according to literature reviews, health care professionals are optimistic about working with families. Nurses report that the various benefits for patients, families, and nurses outweigh the challenges of working with families [11]. In intensive care, health care professionals have a positive attitude regarding family-centered care and involving families in ward rounds, with physicians and allied health care professionals being more optimistic than nurses [12]. Barriers to working with families in health care are financial pressure, staffing shortage, feeling overburdened or unprepared despite education [2,11,13], lack of communication skills [14], limited intra- and interprofessional collaboration [13], and lack of reimbursement [14]. These factors contribute to the burden of families due to power imbalances between health care professionals and families, families experiencing inconsistent professional practices [13], unmet information needs [14,15], not being involved in discharge planning [11], or lack of care continuity [16].

Family systems care describes an interprofessional health care approach to support families with burdening health issues, recognizing the interactions among individuals, families, significant others, and the larger systems in which they are involved [2]. The term family is used for whom the individuals say it is for them [17], including individuals, their relatives, and significant others [2]. Family systems refer to the family as an entity, its broader social context, and the interactions between the two [2,17]. The literature has widely confirmed the health-related benefits of working with the family rather than the individual patient only for patients, family caregivers, family systems, and health care professionals [12,14,18-25].

One family systems care method is therapeutic conversations aiming to facilitate day-to-day coping and symptom management, relieve suffering, and sustain or regain health and resilience within families and individuals [26]. Therapeutic conversations improve family outcomes such as perceived support from professionals, family functioning, quality of life [27], decision-making, problem-solving, management of the patients' situations, and recognizing their strengths and needs [11]. Therapeutic conversations have mainly been evaluated in Scandinavian countries in the past years [27].

Therapeutic conversations are based on the Calgary family assessment and interventions model (CFAM/CFIM) [2] and the illness beliefs model (IBM) [3]. The CFAM provides a model to systematically explore a family's structure, development, functioning, strengths, and needs [2]. The CFIM describes the emotional-cognitive-behavioral responses of health care professionals intended to value the suffering of families and individual family members and reinforce their strengths and resilience [2]. Interventions also comprise recommendations for everyday life and symptom management based on scientific evidence and clinical reasoning [2].

The IBM describes the intersections of health and illness beliefs among individuals, families, and health care professionals, all influenced by broader cultural-societal beliefs [3]. Health and illness beliefs help people to find meaning in health and illness experiences [3]. In therapeutic conversations, both facilitating and constraining health and illness beliefs are explored [3]. Family systems care clinicians help families and individuals to strengthen facilitating beliefs, challenge constraining beliefs, and thus relieve suffering, support healing, and enhance resilience [3].

In Switzerland, family systems care has been taught at different nursing educational levels and established in various health care settings since the beginning of this century [28]. Family systems care has recently expanded to include interprofessional collaboration [29,30]. However, the Swiss Federal Office of Public Health has recognized the need for advancing and coordinating support for families experiencing burdening health and illness issues and establishing educational programs for health care professionals to improve collaboration with these families based on a national research program in 2020 [31]. According to this program, about 1 in 2 family caregivers confirmed a need to talk with health care professionals and a need for continuous, cooperative support [31].

In response to these needs for health care services for families and educational programs for professionals, the School of Health Sciences (SHS) of one Swiss University of Applied Sciences (UAS) launched a family systems care unit (FSCU) as a real-life laboratory. Real-life laboratories are user-centered, cocreative, real-life spaces that foster innovation testing, open innovation [32,33], research cocreation, and knowledge exchange [33]. In the FSCU, therapeutic conversations with families, education and training of health care students and professionals, as well as research in family systems care, are interconnected. The Family Nursing Unit of the University of Calgary [34] and the Center of Excellence in Family Nursing of the University of Montréal [35], both in Canada, and the Family Care Unit at

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Kalmar University in Sweden [36] were pioneering real-life laboratories for the development and advancement of theoretical knowledge on family systems care. The FSCU fits into the strategy of developing the SHS into a health university, combining interprofessional problem-based and practice-based learning with a contribution to local health care delivery [37].

Although considerable research has been done in family systems care in recent years, a need for further studies was identified in the literature. Regarding family systems care interventions, it is necessary to investigate which mechanisms bring about meaningful changes in families and individuals [20]. Concerning therapeutic conversations, research on positive outcomes, such as family competencies or strengths, is needed in addition to the prevention of adverse health outcomes [27]. Moreover, research on disseminating and implementing family systems care is required [38]. However, health care professionals need to be better prepared, given the barriers to working with families [2,11,13,14]. Finally, other real-life laboratories in health care have mainly been used to test [33] or implement [32] new services. In contrast, we are interested in the benefits of the FSCU real-life laboratory for a deeper understanding of the clinical work with families and individuals and the laboratory's added value for education and training.

Aims and Research Questions

Overall, this research program aims to deepen the understanding of the mechanisms of therapeutic conversations and the value of the FSCU laboratory setting for health care professionals and students. Based on this, we will advance the FSCU while contributing to the evidence of therapeutic conversations and the FSCU real-life laboratory as a learning environment.

We will investigate the following research questions: In what way do the therapeutic conversations support burdened families and individuals? In what way does the FSCU laboratory setting support the learning of students, clinical trainees, and health care professionals?

Methods

Overall Study Design

In this research program, we apply a transformational action research design as an overall study design [39].

Action research is used to understand practice, introduce innovation, facilitate change, and generate and test local theory [39]. This approach fits well with real-life laboratories' attributes [32,33]. Unlike previous scientists, Titchen [39] describes the action research process using the metaphor of a tree with the branches representing parallel, overlapping, and subsequent action research cycles relating to each other rather than a sequence of linear subsequent action research cycles. Each cycle consists of three phases: (1) planning, (2) acting and observing, and (3) reflecting and revising the processes under development [39]. The action research process of this research program will be broken into substudies, building on and complementing each other flexibly to remain adaptive to unexpected changes while working towards achieving the study aims [39]. The substudies are (1) planned, (2) performed, and (3) reflected on by the researchers and clinicians to decide on changes in the work of the FSCU and additional substudies needed.

Transformational action research is suitable for transforming the practice as the aim and means of the research program, as well as for the personal transformation of all those involved in the program by enabling human flourishing through the facilitation of personal growth and development [39].

Study Setting and Intervention

The study setting is the FSCU as part of the SHS of one Swiss UAS.

The therapeutic conversations based on the CFAM, the CFIM, and the IBM have been chosen as interventions because of their longstanding, international use in health care and their purpose of strengthening the families' resilience, everyday symptom management, and coping with health-related suffering, challenges, and needs [2,27]. The therapeutic conversations are moderated by a health care professional trained at the Master of Science level who specialized or specializes in family systems care. These health care professionals work in tandem (ie, a clinical expert and a trainee), one leading the therapeutic conversation and one available for reflection and mutual professional support. Since the data from the therapeutic conversations are used for research and education, the service is free of charge for the families.

Regarding education and training, the FSCU provides a clinical and research learning environment for health care students, postmaster trainees in family systems care, external partners, and the FSCU experts and researchers. The FSCU comprises 2 rooms with a 1-way window between them. It is equipped with an audio transmission system and video-recording technology. The therapeutic conversations take place in one of the 2 rooms. They are observed from the adjacent room through the 1-way window by the tandem partner, further clinical trainees and experts, health care students, researchers, or other guests such as health care professionals from external partner institutions. The therapeutic conversations are prepared, reflected on, and evaluated in presession and postsession discussions to ensure the quality of the therapeutic conversations and the reflection and learning processes of the present persons. In addition, post-master trainees conduct family conversations with live supervision from experts and peers. Furthermore, Master of Science and doctoral students accomplish their theses within this research program while advancing their clinical skills. Finally, selected video-recorded therapeutic conversations are used in classroom teaching of the UAS.

Populations

Overview

In this research program, we target two study populations: (1) families and individuals experiencing burdening health and illness issues and (2) students, trainees, and health care professionals.

Families or Individuals

We target families or individuals with any health conditions or life events of one or several family members that burden their

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functioning and health. As of July 2024, a total of 57 families of various age groups, family compositions, and life phases used the service of the FSCU. Examples were families with minors with a family member affected by a mental illness, such as anorexia in an adolescent or schizophrenia in a parent, or a physical illness, such as cancer, chronic pain, or fatigue in a parent. Other families were severely affected by COVID-19 due to the early death of a parent or post–COVID-19 condition in an adult sibling. Furthermore, families with a child with intellectual disability, couples who have experienced an acute myocardial infarction or are living with multiple sclerosis, and a family with an older family member in preparation for assisted suicide used the FSCU service. Often more than 1 family member is affected by a health condition that can be related to or independent of each other.

Study Design

We investigate therapeutic conversations using qualitative multiple-case study designs [40-42]. Case study research aims to reach a nuanced understanding of a case or multiple cases by finding patterns, insights, or concepts in the cases [41]. In multiple-case study designs, various single cases are compared and contrasted regarding similarities and differences [41]. Naturalistic, analytical generalizations, rather than statistical generalizations, can be derived from multiple-case studies to advance existing theoretical propositions, uncover new ones [41], learn from particular cases, and transfer and apply the learnings to populations of similar contexts [42].

In case-study research, cases are designated by defining the bounded systems constituting the casing [41,43]. In this research program, we define a case as a family, a unit of family members (ie, a couple or parents), or an individual participating in FSCU therapeutic conversations. The temporal boundaries of a case are defined as the period between the first contact of a family or individual with the FSCU and the end of the therapeutic conversations. The spatial boundaries are defined by the FSCU laboratory setting, exceptionally web-based, using a videoconference tool, or in a family's home. The boundaries by activity are therapeutic conversation units. One therapeutic conversation unit includes a presession, a therapeutic conversation, and a postsession.

Recruitment

We recruit families or individuals with 3 procedures (Textbox 1).

Textbox 1. Procedures for recruiting families or individuals.

- Families or individuals contact the family systems care unit (FSCU) as an advisory service via the Internet contact form, e-mail, or telephone.
- Other health care providers recommend the FSCU to families.
- We recruit families or individuals purposefully through health and social care organizations. We will ask these organizations to look for families interested in participating in a case study, initiate contact, and transfer the contact data to the clinical experts for further explanation and organization of an appointment.

Inclusion and Exclusion Criteria

We will include families or individuals in the study regardless of their financial situation, cultural background, age of family members, or gender diversity in families. We will include families, units of family members, or individuals meeting the following criteria (Textbox 2).

We will exclude families, units of family members, or individuals meeting the following criteria (Textbox 3).

Textbox 2. Inclusion criteria.

- If they are making use of the therapeutic conversations for the first time
- If they are taking part in one single or a sequence of therapeutic conversation appointments
- If these appointments are prepared and evaluated by a presession and postsession with the clinical team
- If the therapeutic conversations, the presessions and postsessions are recorded with sound or sound and video.

Textbox 3. Exclusion criteria.

- If they do not indicate a burden at all during the therapeutic conversations
- If they previously used the family systems care unit (FSCU) service and the therapeutic conversations were regarded as finished.

Sample Size and Sampling

Yin [41] recommended at least 4-6 cases in multiple-case study designs using a theoretical replication strategy if heterogeneous or even contradictory findings emerge from single cases. Theoretical replication means selecting new cases according to essential findings from previous ones [41]. Sandelowski [43] argues for small sample sizes representing a variety of characteristics of the target population and studying them intensively. Creswell and Poth [42] propose a maximum of 4-5 cases to identify themes across and between the single cases.

Since the families visiting the FSCU are heterogeneous in situations, health problems, and family compositions, we plan for a 2-step theoretical replication strategy [41]. Thus, we will group 3-6 cases into a first multiple-case study and add further

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multiple-case studies if needed to answer research question one, depending on whether the data will allow for analytical generalizations [41]. This proceeding is in line with the action research approach because it supports the application of action research cycles, including the reflection and adaptation of the FSCU practice, before starting a new action research cycle.

Data Collection

We apply data triangulation, which is typical in case-study research [41]. We collect qualitative data for each case from the therapeutic conversations, the team's presessions and postsessions, video or audio recordings, nonparticipatory observations through the 1-way window, and the clinical team's workbook notes.

For video and audio recordings, we simultaneously use the FSCU's permanently installed video and audio system and, as backup, additional recording tools offered within the secure authentication method of the UAS or other mobile camera systems, allowing safe data recording.

In terms of observations, we take nonstructured notes on observations regarding the aspects that were discussed in the presession based on the theoretical models of this study. Such aspects are a family's strengths and needs on the cognitive, emotional, and behavioral levels of family functioning [2], a family's health and illness beliefs [3], and moments indicating meaningful changes during the therapeutic conversation, such as emotional reactions of family members [2,3].

In the clinical team's workbook, the geno-ecogram of the closer and wider family's structure and relationships [2], important information, such as medical diagnoses of family members, and a synthesis of the presessions, the therapeutic conversations, and the postsessions based on a semistructured list of topics are summarized. With regard to the presessions, such topics are information about the family's concerns to be discussed, evidence-based information on relevant topics, for example, on medical diagnoses and treatments or health and social insurance issues, hypotheses regarding the family's strengths, health and illness beliefs, and needs, or red flags the clinician must be aware of, such as sensitive topics around a family's suffering. Topics of the therapeutic conversations to be noted are the family's concerns for the current conversation, the topics discussed, the feedback of the family regarding the conversation, and decisions on how to proceed. Regarding the postsession, moments of surprise, success, difficulty, and open questions for subsequent therapeutic conversations are summarized.

Data Analyses

Overview

All recordings are transcribed verbatim, either by students or external transcribers, as soon as participants are included in a substudy of this research program. We will use the transcripts and video recordings for the data analyses.

Following Yin [41] and Sandelowski [43], we will analyze the data in 3 steps, focusing on the case level (Textbox 4).

For inductive analyses, we will specify the methods for every substudy using interpretive description [44], content analysis, or thematic analysis [45]. These methods use coding methods to find, organize, and describe themes, patterns, and concepts meaningful for clinical practice in the data [44-46]. We will use various methods because of the real-life laboratory setting, which allows master of science and doctoral students working on case studies to consider suitable data analysis methods.

For deductive comparisons within a sequence of therapeutic conversation units and across cases, we will rely on the theoretical assumptions of the CFAM/CFIM [2] and the IBM [3]. Following these models, we will look for similarities and differences across the cases in the cognitive, emotional, and behavioral domains of the therapeutic conversations [2] and regarding facilitating and constraining health and illness beliefs of the families [3].

Following the theoretical replication strategy described by Yin [41], we will perform recruitment, data collection, and data analyses in an overlapping process. This process will enable us to include new cases based on the preliminary results and unanswered questions of the previous cases and thus reach analytical generalization [41]. We will use the software MAXQdA [47] to analyze qualitative data.

Textbox 4. Three steps to analyze data.

- We will analyze each therapeutic conversation unit for each case inductively and in-depth (first step of within-case analysis).
- We will inductively and deductively compare the sequence of therapeutic conversation units for each case (second step of within-case analysis).
- We will compare multiple cases for similarities and differences using an inductive-deductive approach (cross-case analysis).

Students, Trainees, and Health Care Professionals

We further target SHS students of different levels of education, such as bachelor of science, master of science, programs for advanced education, postmaster programs for advanced practitioners for trainees in family systems care, and doctoral students.

Finally, we target health care professionals, such as the FSCU's clinical experts or external guests.

Study Design

Descriptive qualitative research designs are used to investigate the learning experiences of students, trainees, and health care professionals [45,46,48]. These designs investigate research questions emerging from practice, such as educational practice, to provide useful insights for the practice in question [44-46].

Recruitment

Students, trainees, and health care professionals are recruited by direct contact with a researcher or one of the FSCU coheads.

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Inclusion and Exclusion Criteria

We include or exclude students, trainees, and health care professionals as per Textbox 5.

Textbox 5. Inclusion and exclusion criteria.

Inclusion criteria

- If they observe one or more therapeutic conversations through the 1-way window of the family systems care unit (FSCU) and participate in the presessions and postsessions, or
- If they take on an active role as a clinical team member in one or more therapeutic conversation units, or
- If they work with FSCU sound or video-recorded data of one or more therapeutic conversation units to complete their Master of Science or doctoral theses, or
- If they participate in classroom teaching based on video recorded material from the FSCU.

Exclusion criteria

- If they do not get in contact with real-life and/or video recorded data from one or more therapeutic conversation units.

Sample Size and Sampling

In terms of sample size, the number of participants varies from 8 to 50 in descriptive qualitative interview studies [49]. According to Malterud et al's [50] concept of information power, samples with ample information power need small sample sizes, and vice versa [50]. Thus, we estimate a medium sample size of 20 participants in a first action research cycle due to the narrow and specific research question on the one side (indicating high information power), the lack of existing theory, the low quality of dialogue expected due to the limited content to be discussed, and the focus of analysis across interview participants on the other side (indicating a larger sample size needed) [50]. If required, it is essential to adapt the sample size during the research process [50]. We will reflect on this during the action research process.

We choose a maximum variation sampling strategy typical in descriptive qualitative research [46] to gain information about participants with various backgrounds in terms of education level, health care practice experience, age, and gender, as well as having observed therapeutic conversations at the FSCU or worked with video material in classroom settings.

Data Collection

We will collect qualitative data from students, trainees, and health care professionals in single or focus group interviews based on semi-structured interview guides. These interviews will start with the question: "Can you tell me what it was like for you to participate in this therapeutic conversation at the FSCU/in this classroom teaching working with the video of a therapeutic conversation?" Depending on the interview proceeding, prompts will be used, such as: "Can you tell me more about this particular sequence of the conversation you mentioned?" Finally, more specific questions will be asked, such as: "How was it for you if the expert asked your considerations during the postsession?"

The interviews will take place in a quiet room at the SHS, exceptionally web-based, using a videoconference tool within about 4 weeks after observing a therapeutic conversation or the classroom teaching with video material of a therapeutic conversation. They will be recorded with audio or video.

Data Analyses

Students or external transcribers transcribe all recordings verbatim as soon as participants are included in a substudy of this research program.

The qualitative data will be analyzed inductively using interpretive description [44], content analysis, or thematic analysis [45], depending on the considerations of the researchers and students involved in the data analysis. We will use the software MAXQdA [47] to analyze qualitative data.

Ethical Considerations

Ethical Approval and Informed Consent

This research program does not fall under Swiss legislation regarding human research, as confirmed by the Cantonal Ethics Committee on the December 14, 2021 (waiver no. Req-2021-01424). Nevertheless, we will take measures to ensure good clinical practice guidelines and follow the Swiss legislation on data protection. First, we received ethical approval for this study protocol from the internal ethical commission of the UAS on the October 18, 2024 (EA-ZHAW 2024-027-G). Second, the researchers of this research program are trained in good clinical practice. Third, we ask all participants involved in the FSCU therapeutic conversation units and individual or focus group interviews to provide informed consent.

The informed consent form includes a range of levels of agreement, from agreeing to recordings to observation to providing the data for research and education. If someone does not agree to video recordings and observation, we offer an adapted solution, such as audio recording only, to ensure data collection for research.

Participation in this research program is voluntary. All participants can always withdraw from participation in the research program without giving reasons and without experiencing any disadvantages due to their withdrawal. Data used in ongoing substudies will then be used to finish this substudy. Subsequently, the data will be electronically sealed with a password known only to the 2 coheads of the FSCU.

All health care professionals, students, transcribers, and other persons with access to the clinical data of families and

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individuals or single or focus group interviews within their activities must sign a confidentiality agreement form.

Data Management

All personal data, video and audio recordings, transcripts, and professional documentation are stored securely. We store all electronic data on a restricted UAS server. All transcripts are anonymized. If AI-based tools for transcription or data analyses will be used, their alignment to Swiss data protection laws will be carefully checked.

Each family is given a number and an alias for internal communication. The 2 coheads of the FSCU have access to the key file, which connects personal data with the family number and alias. This password-secured key file is saved on a restricted UAS server.

The video and audio recordings are transferred by a clinical team member or one of the 2 coheads of the FSCU to the secure data storage via secure authentication methods within a maximum of 48 hours and then deleted on the source tool. The secure data storage is structured according to families. The clinical team has access to all family folders; researchers, trainees, and involved students have access only to the documents of the families with whom they work. Data material collected by students in connection with master theses is kept in a single secure restricted folder per master thesis, to which only students and the responsible research supervisors within the FSCU team have access.

Paper documents are saved in a locked cupboard in a locked room inside the FSCU as long as a family or individual is visiting or a substudy is proceeding. The rooms, including the video system's server room, are in a part of the SHS with an individual badge access system and a reception desk staffed on working days. When a series of therapeutic conversation units or one of the substudies is finished, the paper documents are stored in a locked research archive with restricted entrance regulations.

By Swiss Law, All Data Will Be Stored for 20 Years at the UAS

Risks and Benefits

The double nature of the FSCU, as a service for families and individuals and as a laboratory for research and education, bears 3 main risks for families and individuals. First, the families and individuals, being in a vulnerable situation due to their burdening health and illness issues and maybe even in urgent need of help, are asked to consent to the sharing of their experiences and thoughts with an additional "audience," immediately in the observation and later by allowing the use of the recordings for research and educational purposes. This may add to the pressure on those families or individuals. Second, they often live in the region of the SHS and may previously be known to professionals or students if their data are used in SHS classroom courses. Third, they are in a situation of dependency due to their need for help and lack of such services.

For these reasons, and beyond the affirmation of anonymity, it is crucial to assure confidentiality regarding sensitive and personal information by creating trusting relationships in addition to the informed consent process and written confidentiality agreements [51]. With these risks in mind, the clinical expert carefully explains the study information to the families and individuals, including the benefits for them, the FSCU's purposes in terms of research and education, and the UAS data protection and confidentiality measures, before asking them to sign the informed consent form. In classroom education, transcript excerpts will be anonymized and carefully chosen so as not to intrude on anyone's anonymity. In using video or sound recordings in education, one of the coheads will carefully select sequences of therapeutic conversations containing no personal features. This precaution applies over and above the consent of the family or individual to use their recordings for this purpose.

If families or individual family members deny recording and observing therapeutic conversations at all, ethical weighing is necessary. The benefits of therapeutic conversations are well known, making it ethically problematic to refuse burdened families or individuals. In such cases, individual solutions will be sought, such as helping to find another suitable professional service.

Considering the dependency of families, 2 measures are taken within the clinical routines. First, the visiting families and individuals are asked towards the end of every therapeutic conversation session how they perceive it, how they want to proceed, and whether they want to change anything in the next session. Second, red flags the clinical expert must be aware of are routinely discussed in the postsessions. Furthermore, therapeutic conversations are not part of the medical treatment of families and individuals, reducing the risk of dependency.

Regarding benefits, the FSCU provides a professional and sensitive data collection setting. The data of the families and individuals are collected in conversation situations where they receive emotional and practical support from the family systems care expert to lower their burdens. Furthermore, they are extended the opportunity for additional therapeutic conversations if desired.

In single and focus group interviews with students, trainees, and health care professionals, there is a risk of harm when participants are open to others and of dependency regarding education or working situation. Single and focus group interviews will be performed by experienced interviewers or by novice interviewers who have received training and will receive supervision. The interviewers will assure confidentiality orally and in writing as part of the study information. We judge that the benefits of sharing experiences and considerations outweigh this population's potential risks.

Data Quality Assurance

An experienced senior researcher leads the research program, which is staffed with 3 postdoctoral researchers. The FSCU was established and is comanaged by an experienced clinical family systems care expert in close contact with and relying on Canadian pioneers in this kind of work [34,35]. All researchers and clinicians are trained and experienced at the master of science or doctoral level in nursing, midwifery, or family medicine, and most of them also teach in higher education.

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We will assure data quality by adhering to guidelines for evaluating case studies and qualitative research as appropriate to the methods used in each substudy. Above all, we will engage in reflexive thinking [52] within the research and clinical team, and between researchers, clinical experts, trainees, and students.

Results

As of the July of 2024, a total of 3 single-case studies examined how therapeutic conversations supported families. Each investigated a sequence of 3 therapeutic conversation units. The manuscripts of these substudies are being prepared for publication. Data collection and analysis of further substudies are ongoing.

The data collection with regard to the second research question needs to be planned.

Discussion

Anticipated Findings

The results of our first single-case studies confirm the usability of the FSCU data and the case study approach to answer how therapeutic conversations support burdened families and individuals. The results confirm that therapeutic conversations support families in the way that they strengthen the families regarding coping with their longstanding, burdening, and complex situations, even if the challenges cannot be resolved. This is in line with a recent literature review, where 12 out of 14 studies approved therapeutic conversations to be effective for increasing perceived family support in various populations [27]. Previous qualitative studies showed that families developed new perspectives on their situations, felt facilitated in sharing their individual beliefs, and strengthened the family members' relations after participating in therapeutic conversations [27].

With this research program, we also intend to investigate the benefit of the FSCU as a real-life laboratory and learning environment for students, trainees, and health care professionals. Learning experiences among students, trainees, and professionals in the FSCU have anecdotally been told to improve traditional learning methods. In Canada, this setting initiated a learning process for nurses continuing in their clinical work [35]. Learning from each other's experiences is called vicarious learning [53], which is seen as a fundamental human skill and a complex task involving various cognitive processes and brain systems [54]. Vicarious learning occurs when valuing the experiences of others, feeling engaged in the situation, trying to understand it, and in discursive reflection [53]. To the best of our knowledge, evidence regarding the benefits of real-life laboratory settings for vicarious learning is scarce.

In qualitative research, there is always a risk of a hierarchical power imbalance due to the interviewees revealing themselves without receiving information regarding their health and illness issues [42,51]. They are then left alone with issues that may have arisen in the interview. This is particularly critical for families and individuals in vulnerable situations, even more so if families include their minor children or sick family members [51]. Using participatory methods can reduce power imbalances [51]. This research program addresses this by the clinical experts trained in working with participatory, non-hierarchical conversation methods. In addition, families and individuals determine the topics of the conversations and receive professional support regarding the day-to-day coping of their situations. They are also offered additional appointments in the FSCU if needed. This makes the FSCU a setting for ethically sensitive and justifiable research.

Furthermore, the FSCU, as a laboratory setting, reduces power imbalances among clinicians, researchers, and students and supports participatory collaboration and mutual learning. On the one hand, the clinical experts open the therapeutic conversation units to researchers and students by involving them as passive observers in the therapeutic conversations and as active contributors in the presessions and postsessions. On the other hand, clinical experts become coresearchers in action research, which has led to the term practitioner-researchers [39]. Accordingly, they receive an active role in contributing to the generation of scientific knowledge and, at the same time, in investigating their expertise, which often remains hidden in health care professions [39].

Limitations

The research program is prone to bias due to dependence between families or family members and clinicians, mentors and trainees, and researchers and students. Selection bias cannot be ruled out for the families and individuals attending the FSCU. Individuals with lower incomes may visit the FSCU since the service provided is free of charge. Due to the study designs, conclusions do not allow for statements regarding causality. However, case study and qualitative research approaches aim to gain deeper insights into the meaning individuals or groups assign to phenomena in their everyday lives [41,42]. Quantitative and mixed methods studies [40,55] are also planned in the future.

Conclusions

The FSCU data and the case-study approach show that therapeutic conversations support families and are beneficial for their coping. This research program aligns with the need for further research in family systems care, as recently identified in a comprehensive umbrella review [56]. In particular, there is a need to understand the mechanisms leading to meaningful changes in families [20] and further studies on the outcomes of therapeutic conversations [27]. We contribute to these gaps by applying a transformational action research program and non-hierarchical conversation methods. This makes the FSCU a setting for ethically sensitive and justifiable research. This research will help to alleviate family and individual suffering, promote their health and well-being, and thus, indirectly, relieve the financial and workforce burdens in the health and social care system.

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E Hu, AF, and BPB designed the research program. BPB and ES developed the concept of the FSCU. E Hu, E Ha, AF, and BPB drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved its final version. Open access funding was provided by ZHAW Zurich University of Applied Sciences.

Data Availability

The datasets generated or analyzed during this research program are not publicly available due to their high sensitivity and the vulnerability of the participating families. However, data on the learning experiences of students, trainees, and health care professionals are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare freedom of any conflict of interest. The last author runs a private company in this research field. However, the current research program is run by the UAS and has no financial connections to this company. No generative artificial intelligence tools have been used in this study.

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Abbreviations

CFAM: Calgary family assessment model
CFIM: Calgary family interventions model
FSCU: family systems care unit
IBM: illness beliefs model
SHS: School of Health Sciences
UAS: University of Applied Sciences

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Protocol

Tracking Implementation Outcomes of an Intensive Case Management Program for HIV: Protocol for a Mixed Methods Study

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Abstract

Background: Implementation science investigates the processes and factors that influence the successful adoption, implementation, and sustainability of interventions in many settings. Although conventional research places significant emphasis on the advancement and effectiveness of interventions, it is equally imperative to comprehend their performance in practical, real-life situations. Through outcome tracking, implementation science enables researchers to investigate complex implementation dynamics and go beyond efficacy, identifying the various aspects that contribute to the success of interventions.

Objective: This study aims to evaluate the implementation outcomes of TAIBU's intensive case management (ICM) model tailored for African, Caribbean, and Black communities living with HIV in the Greater Toronto Area. Specifically, it seeks to assess the fidelity, reach, and sustainability of the ICM program. Fidelity monitoring will ensure adherence to program protocols and consistency in service delivery, essential for achieving desired health outcomes. Reach assessment will examine the program's capacity to reach the target population, including demographic coverage and engagement levels among African, Caribbean, and Black individuals. Sustainability assessment will explore the determinants influencing the longevity and impact of the ICM program.

Methods: The study uses a mixed methods approach, where we will use probing questionnaires, interviews, and focus-group discussions to gather program performance and engagement data, in-depth insights, and perspectives from the implementation team responsible for delivering the ICM intervention. The collected fidelity and reach data through questionnaires will be analyzed using appropriate statistical techniques, such as descriptive statistics, to summarize the responses and identify patterns and trends within the data. Sustainability data collected through the interviews and focus groups will be analyzed and organized based on the Consolidated Framework for Implementation Research, which provides an organized way to identify and comprehend the determinants influencing implementation outcomes.

Results: The study commenced in January 2024, and initial data collection is expected to be completed by December 2024. As of September 2024, we have enrolled 5 participants.

Conclusions: This study will significantly contribute to improving the implementation of the ICM program. By conducting a study in an organizational or institutional setting, researchers can acquire valuable insights into the implementation process from those who are directly involved. The information gathered will inform strategies for improving implementation effectiveness; removing impediments; and enhancing the overall quality of the ICM program for African, Caribbean, and Black individuals living with HIV.

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KEYWORDS

implementation science; intensive case management; ICM; human immunodeficiency virus; HIV; tracking; outcome; fidelity; reach; sustainability; implementation outcomes; perspective; perception; Toronto; Canada; descriptive statistics; evidence-based intervention; effectiveness; barriers; facilitators; adoption

Introduction

The 90-90-90 targets were initiated in 2014 by the Joint United Nations Program on HIV and AIDS (UNAIDS) [1]. By 2020, the target was to have 90% of individuals living with HIV diagnosed, provide antiretroviral therapy to 90% of those who were diagnosed, and attain viral suppression for 90% of those who received treatment [1]. The Public Health Agency of Canada suggests that Ontario's progress in reaching the 90-90-90 targets has been facilitated by increased access to testing, treatment, and health services [2]. However, this overall provincial progress has not translated into similar success among African, Caribbean, and Black communities, which report high HIV prevalence rates, associated with overarching structural factors and barriers to accessing care, predisposing them to new HIV infections [3]. Over the past 10 years, African, Caribbean, and Black peoples have accounted for between 19% and 29% of first-time HIV and AIDS diagnoses in Ontario, while constituting less than 5% of the province's population [4]. African, Caribbean, and Black populations in Ontario have a higher disease burden, with recent data suggesting that African, Caribbean, and Black people are 12.5% more likely to be infected with HIV than people in the general population, are more likely to experience negative experiences of engagement in care, and are less likely to achieve viral suppression [5]. The uneven and inequitable success of 90-90-90 targets in Ontario suggests that the current evidence-based interventions (EBIs) to improve HIV services may not be culturally or racially effective, may not be translated adequately into practice, or may not be designed to have optimal impact on groups differently impacted by the social determinants of health.

Within the Greater Toronto Area, the TAIBU Community Health Centre has developed and implemented a racially and culturally informed intensive case management (ICM) program for African, Caribbean, and Black communities in the Greater Toronto Area living with HIV [6]. Generally, the ICM model involves promoting independence and quality of life through appropriate services and providing constant ongoing support as needed by the consumer [7]. ICM services can be provided for a wide range of social and health determinants, including mental health, housing challenges, and HIV management [8,9]. Although a standardized definition does not exist, ICM programs share common principles and functions derived from the concept of continuity of care [10]. In the case of TAIBU, the ICM program offers intensive HIV case management, patient navigation and linkage to community supports, access to other support services, peer-led support groups, and HIV education and awareness, along with support to develop personal and coping skills to better meet the unique needs of African, Caribbean, and Black clients [6].

Assessing the outcomes of implementing the TAIBU ICM program is critical to determine its effectiveness, particularly regarding the accessibility and availability of culturally tailored services for African, Caribbean, and Black communities.

To do this, implementation science can bridge the gap between research and practice, ensuring that EBIs are effectively integrated into real-world settings [11]. Central to the success of implementation efforts is the ability to track and evaluate outcomes systematically. Outcome tracking in implementation science enables researchers, practitioners, and policy makers to understand the effectiveness of interventions, identify barriers and facilitators to implementation, and refine strategies to improve the delivery and impact of evidence-based practices [12].

Implementation science outcome tracking is especially crucial for ICM programs. Outcome tracking facilitates the optimization and dissemination of effective ICM interventions by monitoring implementation fidelity, client-level outcomes, influencing factors, and sustainability and by contributing to the evidence base [13]. It equips practitioners, policy makers, and researchers to make informed decisions, enhance program outcomes, and improve the lives of individuals with complex needs. By examining implementation outcomes for African, Caribbean, and Black Canadian individuals with HIV, we can systematically measure key indicators, including accessibility and use of health care services, adherence to antiretroviral therapy, engagement in support programs, viral suppression rates, and overall quality of life [13].

The main goal of this study is to provide support in tracking implementation outcomes in relation to TAIBU's ICM model, with a specific focus on fidelity, reach, and sustainability.

The overall aim is to gather comprehensive data and insights to inform and improve the implementation of the ICM intervention. The objective is to understand the implementation team's perspectives, experiences, and perceptions regarding the ICM program and its impact on the target population.

Methods

Study Setting and Context

Tracking implementation outcomes within an organization is pivotal for the identification of potential barriers and facilitators to implementation; thus, the setting must be within the organizational or institutional context where the implementation occurs. In this case, the assessment will focus on the TAIBU Community Health Centre, particularly the ICM program that

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operates out of the center. The ICM program relies on a community-focused approach to HIV care and provides timely and individualized ICM and treatment for people of African, Caribbean, and Black descent who are newly diagnosed with HIV, at risk of HIV, or affected by HIV [6].

The assessment will involve engagement with staff members working in the program, such as the nurse practitioner, nurse, social worker, system navigator, and other relevant stakeholders responsible for implementing and delivering the ICM intervention. Within its context, the study emphasizes understanding the perspectives, experiences, and perceptions of the implementation and delivery team regarding the ICM intervention. The rationale for prioritizing these stakeholders lies in the opportunity to glean valuable insights into the implementation process directly from individuals actively engaged within the organizational or institutional framework. This information can inform strategies for improving implementation effectiveness, addressing barriers, and enhancing the overall quality of the ICM program for African, Caribbean, and Black individuals living with HIV.

Study Aims

The study included certain specific objectives: (1) identify the barriers, challenges, and facilitators encountered during the implementation process; (2) evaluate the fidelity of the implementation and adherence to established guidelines and protocols (the degree to which the program was implemented as it was prescribed in the original testing or as it was intended by its developers); (3) assess the program's reach to its intended audience or client base (a measure of the number, proportion, and representativeness of individuals who participated in or were exposed to the program); (4) examine the capacity, resources, and readiness of the implementation team to deliver the ICM intervention effectively; (5) explore the perceptions of the implementation team regarding the sustainability and long-term impact of the ICM program (the program continues to be delivered and individual behavior change is maintained); and (6) gather feedback and suggestions for improving and modifying the ICM intervention and implementation processes.

Study Design

The study design incorporates both questionnaires and semistructured interviews with the ICM implementation team. The questionnaires will be administered to investigate the fidelity and reach of the ICM program operating out of TAIBU. Furthermore, the study will incorporate semistructured interviews to gather in-depth insights and perspectives from the implementation team about the determinants of program sustainability. Data collected through the interviews (specifically the determinants) will be analyzed and organized based on the Consolidated Framework for Implementation Research (CFIR), which provides a structured approach to identify and understand the factors influencing implementation outcomes.

Participant Selection and Involvement

The participants in this study are the members of the implementation team responsible for delivering the ICM intervention for African, Caribbean, and Black Canadian individuals with HIV. As participants, they will respond to key questionnaires to share their knowledge, experiences, and perspectives related to the implementation. Their expertise in providing ICM services and their direct involvement in delivering the intervention makes them valuable sources of information.

As the ICM program team is small, we expect our sample size for the study to be small. We anticipate up to 10 participants in the study, given staff time, capacity, and availability. Through their participation, we will gather insights into their understanding of the ICM model, their attitudes toward the intervention, their challenges during implementation, and their perceptions of the barriers and facilitators that influence implementation success. The perspectives and experiences of the implementation team will provide valuable input for understanding the complexities of ICM implementation and informing strategies for improving the intervention's delivery, overcoming challenges, and ultimately enhancing the quality of care provided to African, Caribbean, and Black Canadian individuals living with HIV.

Data Collection

Overview

In total, 2 separate questionnaires will be administered to capture the fidelity and reach of the ICM program. The participants will complete the questionnaires quarterly, providing their responses to the quantitative criteria established on fidelity and reach. The completed questionnaires will be collected, securely stored, and entered into a Microsoft Excel spreadsheet for analysis. The data will be analyzed using appropriate statistical techniques, such as descriptive statistics, to summarize the responses and identify patterns and trends in the data. Using questionnaires as the data collection tool enables standardized data collection from the implementation team, providing quantitative insights into their perspectives on the implementation of ICM for African, Caribbean, and Black Canadian individuals living with HIV. In addition to the fidelity and reach questionnaires, participants will participate in semistructured interviews to solicit more in-depth and narrative accounts of the program's determinants associated with sustainability. The semistructured interviews will be conducted once a year, using an interview guide. Each of the 3 measured outcomes (fidelity, reach, and sustainability) will have its own set of questions, with fidelity being the most finely tuned, with an initial probing questionnaire that will eventually develop into a mature and finalized version.

Fidelity

Fidelity is a crucial outcome that we will closely monitor, as it ensures consistent program implementation across different settings. It can be defined as the degree to which the program was implemented as it was prescribed in the original testing or as it was intended by its developers [14]. Monitoring fidelity will identify areas that may require improvement and ensure that the program is delivered exactly as intended. Consistency in program delivery is vital to achieving the desired outcomes and minimizing variations that could compromise its effectiveness. For this program, fidelity will be measured using an open-ended questionnaire that relies on the premise of the

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program conductors understanding the concept of fidelity (Multimedia Appendix 1).

According to Singh and Saldana [15], to achieve the expected health outcomes, it is crucial that providers at EBI delivery sites possess a strong comprehension of the essential program components and the reasons they are needed for. This understanding ensures high-fidelity delivery of these components. Thus, the provided questionnaire will use components based on the criteria for ICM fidelity, resulting in a probing questionnaire intended to evaluate the facilitators' understanding of fidelity. This questionnaire will be administered only during the initial meeting with the program conductors so as to narrow down the questions that will be administered in later questionnaires. The purpose of the initial questionnaire is to probe the conductors' understanding of the ICM criteria for fidelity and subsequently create questions that examine that understanding.

Reach

The tracking of reach enables us to understand the extent to which the program is reaching its intended audience and identifies disparities in participation rates between different groups. Reach is defined as a measure of the number, proportion, and representativeness of individuals who participated in or were exposed to the program [14]. Such information is invaluable for assessing the program's impact on the target population and for identifying potential areas for improvement. Because reach is a program outcome that is difficult to evaluate without knowing the extent to which the program is successful in impacting its target population, a questionnaire will be distributed at the end of each quarter to gather quantitative data on the program's usage and demographics (Multimedia Appendix 2). The form will be sent automatically with the intention of gathering data to test the program's effectiveness in reaching its intended audience.

Sustainability and Determinants

We will also track the determinants of the program's sustainability, as this outcome is critical for its continuity, resource allocation, maximal impact, stakeholder engagement, and continual learning and improvement. For assessment purposes, sustainability is defined as the program continuing to be delivered and maintained over time [14]. Sustainability will be assessed through semistructured interviews with members of the ICM team, administered annually using an interview guide (Multimedia Appendix 3). The goal is to ensure that the program effectively mitigates the barriers, enhances the facilitators, and addresses the needs of the target population over the long term and makes a lasting positive difference. The Integrated Sustainability Framework will be used in creating the sustainability assessment to devise questions that consider all the relevant domains of ICM [16]. The assessment will be administered only once yearly, as the intention of understanding the determinants of sustainability is relevant only for later purposes when considering scalability. Thus, the 2 primary outcomes that will be tracked throughout the entire course of implementation are reach and fidelity, with the ultimate goal of creating a sustainable program.

Implementation Research Logic Model

The Implementation Research Logic Model (IRLM) serves as a helpful tool for assessing program sustainability by organizing determinants that influence sustainability outcomes. By delineating the relationships between determinants, implementation strategies, and mechanisms for implementation within the IRLM framework, researchers can effectively plan and execute strategies to enhance the effectiveness of interventions [17]. This structured approach facilitates a comprehensive understanding of how implementation strategies can be effectively implemented to ultimately improve sustainability outcomes in health care delivery systems. By using the IRLM, the study can effectively identify key determinants, implementation strategies, and mechanisms necessary for enhancing TAIBU's ICM program outcomes, thus informing specific strategies tailored to improve the overall effectiveness and sustainability of the program.

Successfully populating an IRLM with the corresponding determinants requires taking an initial approach that examines the existing literature and the subsequent expansion of such determinants through data collection (Multimedia Appendix 4). An iterative approach includes (1) reviewing the existing literature, (2) consulting with experts and stakeholders, (3) assessing organizational and contextual factors, (4) analyzing implementation data, (5) engaging with implementation experts and networks, and (6) iteratively refining the model.

Furthermore, the IRLM will be populated using the CFIR, a conceptual framework developed to guide the systematic assessment of multilevel implementation contexts to identify the factors that may influence intervention implementation and effectiveness across five domains: (1) innovation domain, (2) outer setting domain, (3) inner setting domain, (4) individuals' domain, and (5) implementation process domain.

The innovation domain encompasses determinants related to the innovation being implemented (eg, innovation design and cost). The outer setting domain explores external factors influencing the implementation setting (eg, partnerships and connections, and local conditions). The inner setting domain delineates the implementation setting of the innovation (eg, available resources and mission alignment). The individual's domain examines the roles and individual characteristics of people involved in or affecting the implementation (eg, opinion leaders and innovation deliverers). Finally, the implementation process domain focuses on the strategies and activities used during implementation (eg, assessing needs and tailoring strategies).

Considering these domains helps to identify potential barriers and facilitators, prioritize areas for intervention, and guide the selection and tailoring of implementation strategies. By considering a wide range of factors, the CFIR supports a comprehensive approach to implementation research and practice, ultimately aiming to enhance the uptake and sustainability of EBIs in real-world settings. This approach will be established through a 4-part questionnaire administered at the beginning of the implementation evaluation to identify the determinants that will fully populate the IRLM. The four-part questionnaire will include the following: (1) What are the

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barriers to the ICM? (2) What is your opinion on how to overcome the barriers? (3) What are the facilitators? (4) How can these enablers be strengthened?

Data Analyses

Our data analyses will follow a similar use of qualitative collection tools, including sorting, coding, and interpreting. The full methodology for each of the 3 outcomes is described below.

Fidelity

When analyzing fidelity, we follow a systematic approach to organize and interpret the responses obtained from questionnaires. First, we compile all the questionnaire responses and categorize them based on the corresponding questions, providing a clear overview of the data. Next, we read through the responses to identify the recurring themes or patterns that emerge. This involves looking for similarities and differences in the participants' understanding, implementation experiences, challenges faced, participant engagement strategies, monitoring approaches, and efforts to address the social determinants of health. To further organize and categorize the data, we assign codes or labels to each response that capture the main ideas or themes expressed. This process of coding helps us to summarize the findings effectively. We create a summary or summary table that presents the key findings for each question, highlighting the main themes, notable examples, challenges identified, strategies used, and areas for improvement suggested by the respondents. Finally, we present the results in a clear, concise manner using narrative descriptions and appropriate visual aids, such as charts and graphs. The aim is to ensure that the findings are easily understandable and to highlight the main points of interest. By following this process, we can thoroughly analyze fidelity and provide valuable insights for program implementation.

Reach

To assess the reach of the ICM program, several calculations are performed. First, the total enrollment is determined by summing the number of individuals who have enrolled or registered during the reporting period. Second, patient attendance is calculated by adding up the number of patients actively involved in the program in the reporting period. The next step involves identifying return patients by counting the number of individuals who participated in the program more than once during the reporting period. The dropout or discontinuation rate is then determined by counting individuals who discontinued their participation in the program during the reporting period. To gauge the program's reach, the reach percentage is calculated by dividing the total number of individuals reached by the program during the reporting period by the target population. The result is then multiplied by 100 to obtain the reach percentage. Furthermore, a reach comparison is conducted by comparing the reach achieved in the current reporting period with that of the previous reporting period. Once these calculations have been performed, the data are analyzed and interpreted to obtain insights into the reach of the ICM program. For instance, the enrollment and patient attendance numbers can be compared in order to evaluate the program's effectiveness in attracting and retaining participants. Similarly, analyzing the dropout or discontinuation rate can identify obstacles or challenges that may impact program engagement. In addition, the reach percentage and reach comparison offer valuable information about the program's outreach and its growth or decline over time.

Determinants and Sustainability

Several steps are taken to assess the sustainability of the ICM program. First, the responses provided by participants are transcribed and organized, ensuring that each response is linked to the corresponding question. These responses are compiled in a document or spreadsheet for analysis. Next, the responses are carefully reviewed to identify common themes and patterns across different questions. We note recurring ideas, perspectives, and observations related to policies, external partnerships, alignment with priorities, program champions, organizational leadership, and organizational infrastructure. To facilitate analysis, the data are then coded, assigning to each response a code or label that captures the main themes or concepts expressed. This process effectively categorizes and organizes the data.

Subsequently, a summary or summary table is created to present the main findings for each question, highlighting the key themes, examples, and insights provided by the participants. Patterns and connections within the responses are analyzed to better understand the identified sustainability factors. We explore relationships between policies, external partnerships, alignment with priorities, program champions, organizational leadership, and organizational infrastructure. The data are further analyzed to derive meaningful insights and interpretations. The implications of the findings for the ICM program's sustainability are considered by reflecting on the perceived influence of policies, the role of external partnerships and program champions, the support of organizational leadership, and the readiness of the organizational infrastructure for long-term sustainability. The analytical results are then presented in a clear, concise manner, with narrative descriptions or quotes from the participants used as evidence to support the findings. The presentation highlights the main points and provides a comprehensive understanding of the factors influencing the sustainability of the ICM program.

Ethical Considerations

The Non-Medical Research Ethics Board at the University of Western Ontario has approved this study (121549). Potential study participants will be informed about the study and will provide informed consent before their participation. They will also be informed of their right to withdraw from the study at any time. Questionnaire data, recorded interview files, and observations will be deidentified and securely stored in a designated folder on University of Western Ontario servers inaccessible to unauthorized individuals. Access to the data will be restricted solely to the principal investigator or individuals duly authorized by the principal investigator.

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Results

The study commenced in January 2024, and initial data collection is expected to be completed by December 2024. As of September 2024, we have enrolled 5 participants.

Discussion

Expected Findings

The expected outcomes of the assessment encompass gaining deeper insights into TAIBU's ICM program, especially regarding its implementation, efficacy, and sustainability. These insights will enable the identification of tailored implementation strategies aimed at enhancing the program's effectiveness in providing care to African, Caribbean, and Black communities within the Greater Toronto Area.

By assessing indicators of fidelity specific to this ICM program, such as caseloads, the use of integrated client-centered support system, and social determinants of health resources, the study seeks to determine whether the program adheres to its prescribed core functions, processes, and policies established during the planning stages. Similarly, examining indicators related to reach, such as levels of active participation and discontinuation rates, offers insights into program use among eligible individuals and the extent to which they maintain engagement. Any discrepancies in fidelity and reach indicators will prompt further investigation into underlying reasons. Through interviews, the study intends to contextualize assessment findings by exploring identified barriers or challenges, aiming to uncover factors influencing low scores in fidelity and reach. Anticipated outcomes of these interviews include identifying determinants and devising strategies to address them, along with mechanisms for implementing these strategies to enhance fidelity and reach outcomes.

The results of this assessment will offer empirical support for the efficacy of ICM programs tailored for African, Caribbean, and Black communities living with HIV—a crucial aspect given the significantly negative HIV-related outcomes experienced within these communities. The results from other studies assessing ICM programs have demonstrated promising outcomes, pointing to the effectiveness of the ICM model in promoting service uptake and engagement, access to social services including employment opportunities and housing, and cost-effectiveness by averting acute inpatient episodes. A systematic review of 40 trials involving 7524 individuals across multiple countries found that ICM interventions tailored to mental health (when compared with standard care) led to improved outcomes, including increased engagement with the service, enhanced general functioning, employment opportunities, reduced homelessness, and shorter hospital stays, especially for those with a history of extended hospitalizations [9]. Furthermore, the findings of an evaluation of ICM programs delivered in Youth Justice Service Centers at Queensland (Australia) identified maintained reductions in reoffending over time and significantly better performance than in alternative youth justice approaches, with approximately 50% greater reduction in reoffending compared with matched cohorts receiving other youth justice supports [18]. ICM has to be proven cost-effective by reducing the frequency and duration of acute inpatient episodes, which can offset its higher service cost when compared with standard services, particularly due to the high expenses associated with acute inpatient treatment [19].

This study demonstrates several strengths, notably its actionability of findings stemming from ongoing monitoring, allowing for the incorporation of emerging strategies throughout the project's duration. Second, engaging directly with program implementers and deliverers provides valuable firsthand insights into the implementation environment, enriching the understanding of the assessed program's dynamics. Furthermore, the use of multiple assessment tools, including interviews and questionnaires, ensures a comprehensive examination of the subject matter using both standardized, quantitative measures of outcomes and rich, qualitative narration. However, the study faces several limitations. First, the small sample size may restrict the impact of the interview findings, as the findings emerging may not encompass all possible factors influencing program sustainability. Second, the absence of an observational component limits the depth of understanding, relying solely on participant expression rather than observed actions. In addition, the lack of client satisfaction surveys or direct client engagement limits the ability to contextualize and corroborate the findings, potentially overlooking crucial perspectives from those directly impacted by the program.

Monitoring implementation outcomes generates evidence-based data to inform decision-making and resource allocation, which empowers stakeholders to make informed choices regarding the intervention's continuation, expansion, or modification based on objective measures of achievement related explicitly to the ICM project. Ultimately, tracking implementation outcomes is crucial to maintaining evidence-based practices; refining the program; and maximizing the intervention's potential impact on the intended population of African, Caribbean, and Black communities in Toronto.

Conclusion

This study will contribute significantly to improving the implementation of the ICM program. By conducting the study in an organizational or institutional setting, the researchers will acquire valuable insights into the implementation process from those directly involved. In total, 3 major outcomes will be measured: fidelity, reach, and sustainability. Measuring fidelity will identify areas that may require improvement and ensure that the program is delivered exactly as intended. Measuring reach will identify disparities in participation rates between groups. The information gathered will influence strategies for improving implementation effectiveness; removing impediments; and enhancing the overall quality of the ICM program for African, Caribbean, and Black Canadian individuals living with HIV.

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Acknowledgments

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Data Availability

All data generated or analyzed during this study will be included in the paper as a multimedia appendix.

Authors' Contributions

Study conception was performed by OE. Study design was contributed by KT and OE. Draft of the paper was contributed by MM and KT. Critical revision of the paper for important intellectual content was handled by MM, NM, LG, and OE. All authors read and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Fidelity questionnaire (responses captured as yes or no).
[DOCX File , 23 KB - resprot_v13i1e57452_app1.docx]

Multimedia Appendix 2
Reach questionnaire.
[DOCX File , 21 KB - resprot_v13i1e57452_app2.docx]

Multimedia Appendix 3
Interview guide to understand determinants to sustainability.
[DOCX File , 21 KB - resprot_v13i1e57452_app3.docx]

Multimedia Appendix 4
The Implementation Research Logic Model for intensive case management.
[DOCX File , 27 KB - resprot_v13i1e57452_app4.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
EBI: evidence-based intervention
ICM: intensive case management
IRLM: Implementation Research Logic Model
UNAIDS: Joint United Nations Program on HIV/AIDS

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Protocol

Health and Well-Being in the Context of Health-Promoting University Initiatives: Protocol for a Mixed Methods Needs Assessment Study at Qatar University

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Abstract

Background: Health-promoting universities are dedicated to fostering learning environments and organizational cultures that support the physical and mental well-being of students, faculty, and staff. As students constitute the largest group within the university community, any policy intervention targeting them is likely to have a significant impact on the university as a whole.

Objective: This study aims to assess the health status and needs of Qatar University (QU) students using a comprehensive and holistic definition of health, informed by the perspectives of students, faculty members, and key informants. The ultimate goal is to inform evidence-based policies and services designed to improve students' physical and mental well-being.

Methods: An explanatory sequential mixed-methods research design will be used to conduct a comprehensive assessment of students' health status and needs. This assessment will consist of a quantitative component (a web-based health survey) administered to a convenience sample of students, and a qualitative component, including focus groups with students and faculty members, as well as interviews with key informants. Priority health issues and their determinants, identified through the quantitative assessment, will inform and guide the qualitative assessment to provide a deeper understanding of the various contexts and factors shaping them. Descriptive analyses (eg, proportions or means with SDs), comparative analyses (eg, t tests or chi-square tests), and association analyses (eg, linear, logistic, or Poisson regression models) will be used to analyze the quantitative data. Thematic analysis will be used in the qualitative assessments. Additionally, an environmental scan will be conducted to assess relevant facilities, services, and programs at the QU campus and the QU Primary Healthcare Corporation Center, as well as to review

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university policies and regulations that may affect students' health and well-being. Together, the needs assessment and environmental scan will inform the design of multilevel interventions, including health education and promotion programs, health services orientation, and proposed policy changes.

Results: Between March and December 2022, 812 students completed the web-based health survey. Data have been extracted, cleaned, and harmonized. Analyses to assess the extent of selection bias and the calculation of weights to account for this in all subsequent analyses have been completed (by December 2023). Following the completion of all quantitative data analyses (expected by the end of 2024), focus groups, interviews, and the environmental scan will begin in January-December 2025.

Conclusions: This project will help identify and prioritize the health needs of QU students and their determinants, and inform relevant services and policies targeting these needs. By using comprehensive and context-appropriate methods, this project will contribute to QU's strategic efforts to become a Health-Promoting University.

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KEYWORDS

college students; needs assessment; qualitative; lifestyle behaviors; environmental scan

Introduction

University Students' Health and Well-Being

University students are primarily individuals transitioning from adolescence to young adulthood. This is a critical developmental period marked by milestones and challenges that significantly influence overall growth, as well as lifelong health and well-being [1-4].

Several studies indicate that university students are less likely to engage in health-promoting behaviors, such as regular physical activity, healthy eating, proper sleep hygiene, stress management, and mental health care [2,3,5-10]. For example, Aceijas et al [10] reported that approximately half of the students at a university in London (United Kingdom) exhibited health-damaging behaviors, including insufficient physical activity, an unbalanced diet, and excessive alcohol consumption, alongside concerning levels of mental well-being. A large study investigating the health status of local and international students at an Australian university found that the vast majority did not meet health recommendations for physical activity and nutrition. Additionally, 26.5% of local students and 14.0% of international students reported having a mental health condition [11].

According to social-ecological theory, students' health and well-being may be influenced by factors across multiple levels: intrapersonal (eg, age, gender, socioeconomic status, taste preferences), interpersonal (eg, peer pressure or support, lack of parental control), institutional (eg, campus built environment, schedules, policies), community (eg, student networks or events), and public policy (eg, state-regulated costs or support for tertiary education and housing) [12]. Specific challenges affecting students' lifestyles—and consequently their physical and mental well-being—during the transition from secondary school to university include peer pressure or support, changes in school facilities [2-4], the quality of food courts [9], use and access to sports facilities [13], adjustment to new schedules and academic demands [2,3,8,14], development of new social networks [2-4], and financial instability (eg, tuition fees and student debt) [9,15]. These interpersonal, institutional-, community-, and policy-level factors highlight the critical role universities play in health promotion.

Health-Promoting Universities

A Health-Promoting University is a system dedicated to enhancing and safeguarding the health and well-being of its community members through policies and practices that (1) foster social, cultural, economic, commercial, built, and natural environments that support and nurture the health, well-being, and sustainability of people and places; and (2) integrate health, well-being, and sustainability into the university's curricula, teaching, and learning [16-18]. Since their inception in England in the mid-1990s, Health-Promoting University initiatives have been established in most regions of the world [19]. The Okanagan Charter, an international Charter for Health-Promoting Universities and Colleges, calls on these to "transform the health and sustainability of our current and future societies, strengthen communities and contribute to the well-being of people, places and the planet" [20]. Health-Promoting University initiatives are system-based approaches grounded in a socioecological framework. This framework emphasizes the importance of comprehensively addressing personal and interpersonal factors, as well as contextual and environmental factors (eg, policies or built environments) that shape the health and well-being of university community members [12]. These members include students, staff, faculty, and others affected by university operations. As students represent the largest single group hosted by universities, any health-promoting initiatives targeting students are likely to have a broader impact on the university as a whole.

Following best practices, a Health-Promoting University initiative should begin with an assessment of community needs and assets [21]. In a needs assessment study, students at Newcastle University in the United Kingdom expressed a desire for access to sports facilities, safe walking areas, and healthy food options on campus to support a healthy lifestyle [22]. Similarly, a study exploring the health-related needs of medical students in the United Arab Emirates identified several on-campus health literacy initiatives as essential for fostering a healthier student population [23]. Consistent with these findings, a study examining factors influencing health-related behaviors among university students in Jordan concluded that programs promoting healthy behaviors are necessary and should

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be tailored to the sociodemographic characteristics of the student body [24].

Local Research and Gaps

In Qatar, most research conducted within the university context has focused on individual-level assessments of risk factors and their impact on health and well-being. Relevant to our study, these include studies examining the prevalence of overweight/obesity and unhealthy lifestyle habits [25], factors related to physical activity and sedentary behaviors [26,27], eating disorders [28], sleep quality and hygiene [29], tobacco use and cessation services [30-32], mental health [33-38], and health literacy (eg, inappropriate antibiotic use [39], screening programs [40], and COVID-19 vaccination [41]).

After reviewing the literature, we recognized the need to shift from an individual level to a more comprehensive assessment that includes the organizational, community, and policy levels. Such a holistic approach would provide the evidence needed to design and implement multilevel health promotion interventions, moving us closer to achieving a sustainable Healthy University. Aligned with this, a project was undertaken in 2019 to promote and update an existing policy prohibiting all forms of tobacco on campus, while also enhancing the availability of cessation support programs [42,43]. Additionally, contextual research was conducted to assess the educational needs and well-being of students during the COVID-19 pandemic [44-46].

In 2022, Qatar University (QU) was recognized as a Healthy University by the World Health Organization (WHO) following a thorough assessment of the Health-Promoting University indicators across its campus [16]. These indicators include, but are not limited to, initiatives promoting healthy lifestyles, mental health, reproductive health, communicable disease prevention, regular medical checkups and screening programs for students, the implementation and enforcement of national nutrition guidelines and the 100% tobacco-free policy, and the availability of qualified physical education professionals.

Objectives

This study aims to assess students' health and well-being, prioritize their needs and determinants, inform campus policies and services, and support QU's efforts to maintain its status as a Healthy University. This will be achieved through the mobilization of the QU community, beginning with a comprehensive needs assessment that includes individual-, organizational-, and policy-level evaluations. The assessment will be followed by a response to the identified needs and gaps through appropriate multilevel interventions. The intervention activities will align with the pillars of Health-Promoting Universities: health development, equity, sustainability, and solidarity [16]. These pillars encourage universities to promote the health of their communities by integrating health concepts into their processes and policies.

- Objective 1: To conduct needs assessments from the perspectives of students and key informants to:
  - Describe the health status and needs of QU students, specifically concerning physical and mental health, lifestyles (nutrition habits, physical activity, and smoking), oral health, health literacy, and health care utilization.
  - Examine the association between students' demographics (eg, gender, nationality, socioeconomic status) and various health status indicators and behaviors.
  - Identify priority health issues to address based on burden, impact, and unmet needs.
  - Assess the perceptions of the students, faculties, and key informants regarding the availability, utilization, and usefulness of various health services on the QU campus.
  - Identify priority areas for interventions that are informed by students' input and preferences, and are likely to have a meaningful impact.
- Objective 2: To conduct a campus environmental scan, including an assessment of the physical environment and an analysis of relevant policies.
- Objective 3: To plan and propose evidence-based intervention activities that align with the pillars of a Healthy University.

Methods

Study Setting

The study setting is QU, a public university located in the urban area of Doha, the capital of the State of Qatar. QU is the primary institution of higher education in the country, serving most of its college-aged population. During the 2021-22 academic year, a total of 24,988 unique students were registered (both full-time and part-time) across 10 colleges, 4 of which are part of the Health Sector (Health Sciences, Pharmacy, Medicine, and Dental Medicine). The majority of these students were at the undergraduate level (foundation or bachelor), comprising 22,699 out of 24,988 (90.84%). Most students were Qatari nationals (17,172/24,988, 68.72%) and female (18,222/24,988, 72.92%) [47].

Ethics Approval

All studies described below received approval from the QU Institutional Review Board (reference number QU-IRB 1649-EA/22).

Needs Assessments From Students' and Key Informants' Perspectives (Objective 1)

To achieve this objective, we adopted an explanatory sequential mixed methods study design. Specifically, quantitative data will be collected and analyzed first, followed by the gathering of qualitative data to gain an in-depth understanding of QU students' health status and needs. This design allows for the triangulation of data from both phases, thereby enhancing the validity, reliability, and objectivity of the study results [48]. The findings from the quantitative assessment will help identify priority health issues and their determinants in terms of burden, impact, and unmet needs. The qualitative assessment will then focus on these priority health issues to explore the different contexts and factors shaping them. Additionally, the findings from the quantitative assessment will inform and guide the

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development of interview guides for the focus groups (FGs) and individual interviews.

The *quantitative assessment* of students' sociodemographic characteristics, general health status (including mental health), lifestyle (physical activity, diet, and smoking), oral health, health literacy, and health care utilization will be based on data collected through a web-based survey (currently ongoing). The analyses will include both descriptive analyses (eg, the prevalence of risk factors) and associative or comparative analyses (eg, associations between sociodemographic factors and risk factors). In the *qualitative assessment* phase, we will adopt a constructivist interpretative framework, conducting FG discussions and semistructured interviews with students, faculty, and key informants. This approach will help gain a deeper understanding of their perspectives on services and policies that need to be implemented on campus to ensure the physical and mental health and well-being of students at QU [49].

Quantitative Assessment

A multidisciplinary team of faculty and students from the QU-Health cluster developed the QU Health Survey to conduct an initial assessment of the health status and needs of QU students. The survey consists of 6 sections: demographics, health status (including mental health), lifestyle (physical activity, diet, and smoking), oral health, health literacy, and health care utilization. It was developed using a compilation of validated questionnaires and tools (including some in Arabic), specifically the College Student Health Survey Questionnaire 2021 from Boynton Health, University of Minnesota [50,51]; the International Physical Activity Questionnaire—short form (IPAQ-SF) [52,53]; the 5-item Oral Health Impact Profile (OHIP-5) [54]; the 16-item European Health Literacy Questionnaire (HLS-EU-Q16) [55,56]; and the Youth Health Care measure—satisfaction, utilization, and needs (YHC-SUN) [57]. With the exception of the Boynton Health (college students) and the YHC-SUN (young adults in ambulatory care settings) questionnaires, the IPAQ-SF, OHIP-5, and HLS-EU-Q16 questionnaires were originally developed and validated in representative samples from the general population, rather than specifically among university students. However, all the questionnaires demonstrated adequate levels of reliability (ie, Cronbach α>0.7) during their development and validation phases, and they are widely used across various population segments, including university students [58-60]. Where necessary, the survey questions were translated into Arabic by a research group consisting of QU Public Health faculty members and graduate students. Both the English and Arabic versions underwent pilot testing for clarity and effectiveness with a group of 16 undergraduate students in a public health class. This process led to the rewording of some translated questions.

The health status section includes perceptions of physical and mental health, diagnoses, prescribed medications (including over-the-counter), current counseling received, stress levels, and recent vaccinations. The lifestyle section assesses physical activity (including vigorous- and moderate-intensity exercise, walking, and sitting), use of QU sports facilities, nutrition habits (such as daily consumption frequencies of main food items, breakfast habits, fast-food consumption, and binge eating), and smoking status. The oral health section evaluates self-assessed oral health issues, quality of life related to oral health, and oral health maintenance practices. The health literacy section measures the ease of finding, understanding, and using health information, while the health care utilization section addresses private health insurance, health care service usage, and satisfaction. The survey consists of 70 questions in total, with an estimated completion time of 60 minutes.

Study Sample Selection and Sample Size Calculation

After obtaining approval from the QU Institutional Review Board, various dissemination methods were used to reach eligible QU students, including advertisements and promotional videos (created by QU-Health students) shared on QU social media, announcements on course Blackboard pages, posters placed across the campus, and mass emails sent to students' email accounts. This approach resulted in a convenience sample for the study.

Eligibility criteria included students aged 18 years or older with active (part-time or full-time) registration during the Spring and/or Fall semesters of 2022. QU students meeting these criteria formed the target population for the survey (N=24,319).

An initial minimum sample size (n) of 385 students was determined to be necessary for estimating a single proportion of 50% (worst-case scenario), using the formula $n=[Z^2P(1–P)]/d^2$, where Z is the value from the standard normal distribution corresponding to the desired confidence level (ie, 1.96 for a 95% CI), P is the expected proportion, and d is the desired level of precision (ie, 0.05 or 5%) [61]. To facilitate not only the estimation of single proportions but also the comparison of proportions, means, and/or counts across various outcomes between sociodemographic groups (eg, men vs women, Qatari vs non-Qatari), we aimed to double this sample size. This was accomplished by keeping the dissemination methods active and the web-based survey open for participation throughout the entire calendar year of 2022.

Data Collection Procedures and Ethical Considerations

The survey was administered as an opt-in web-based questionnaire. Through various dissemination methods, students were provided with a web link to the survey (hosted on the Blue Survey platform; Explorance Inc.). Upon accessing the link, participants were directed to an introductory page outlining the purpose of the survey, information about the researchers and their contact details, eligibility criteria, and the consent form. The consent form emphasized the voluntary nature of the study, participants' anonymity, the confidentiality of the information collected, and their right to withdraw from the study at any point without consequences. It also highlighted the risks associated with participation. After consenting, participants were granted full access to the survey questions, which could be answered in either Arabic or English. No incentives were provided for participation. To ensure privacy, no identifying information (such as names, emails, or university ID numbers) was collected, and students' responses could not be tracked. All data were stored in password-protected folders on secure computers, accessible only to authorized researchers.

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Data Analyses

Overview

All quantitative data analyses were and will be conducted using Stata version 18 (StataCorp) statistical software.

Addressing Selection Bias

Data collected from opt-in web-based surveys, such as the one used in this project, are likely to suffer from self-selection bias, as they are limited to those who volunteered to participate [62]. The structure of this bias, a form of collider bias [63,64], is illustrated using a directed acyclic graph (DAG) [65] (Figure 1). We anticipated that factors such as sex/gender, nationality/ethnicity, age, and study field (health-related or not) could influence students' participation and their self-reported health outcomes or behaviors. Consequently, analyses of data from those who agreed to participate (depicted by the red box in the DAG) will inevitably introduce an artificial association between these characteristics, even if they are unrelated, or bias their correlation with outcomes if they are related in the population under study [66].

Figure 1. Directed acyclic graph illustrating the threat of selection bias in the present study sample; U, unmeasured or unknown factors.

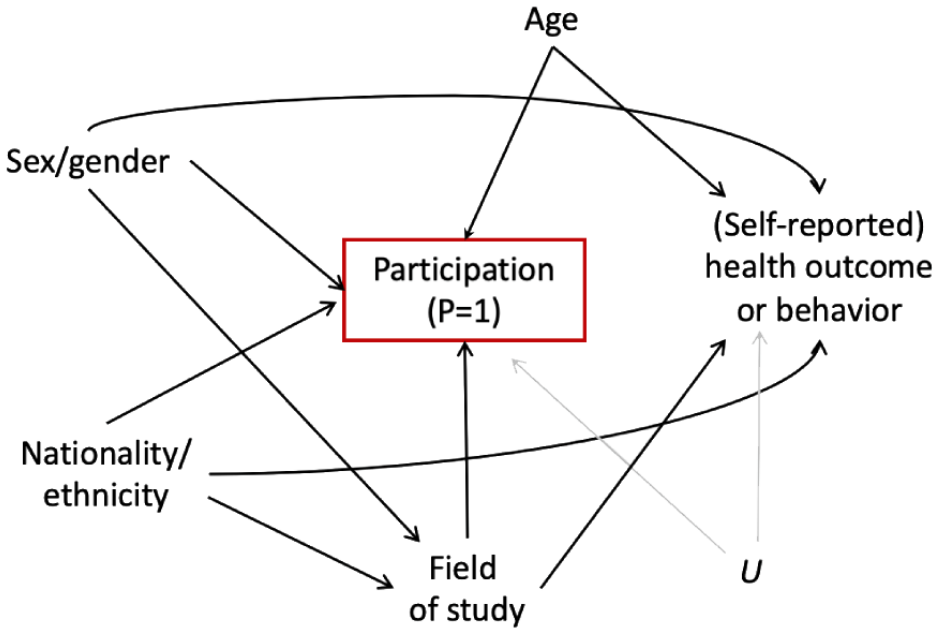

To mitigate selection bias and facilitate the generalization of the results from our study sample to the target population [62], we calculated the inverse probability of participation weights (IPPWs) for use in all subsequent analyses [67]. Briefly, the IPPWs were derived from a logistic model that predicted the probability of study participation (P=1), conditional on the following variables: gender (1=female vs 0=male), nationality (1=non-Qatari vs 0=Qatari), the field of study (1=health-related vs 0=all other), and academic level (1=postgraduate vs 0=undergraduate), with academic level serving as a proxy for age. All these variables were entered into the model simultaneously, along with all possible 2- and 3-way interactions between them. The inverse of the predicted probabilities, conditional on the predictors, was then used to assign sampling weights to each individual [68].

Descriptive and Association Analyses

Study variables will be described as proportions for categorical variables and as means with SDs (or medians with IQRs) for continuous variables, depending on their distribution (normal or skewed). Comparisons of variables based on students' sociodemographic characteristics (eg, gender, nationality) will be performed using chi-square or Fisher exact tests for categorical variables, *t* tests (unpaired) for normally distributed continuous variables, and Wilcoxon rank-sum tests for nonnormally distributed continuous variables. Depending on the type of outcome under analysis, linear, logistic, or Poisson regression models will be used to examine associations between exposures of interest (eg, sociodemographic characteristics) and study outcomes (eg, health behaviors or status). Results will be expressed as mean differences, odds ratios, risk differences, or relative risks, along with their respective 95% CIs. All analyses will adjust for selection bias using IPPWs, as previously described, and account for potential confounders. Relevant confounders for each association under study will be identified by constructing DAGs using DAGitty Software version 3.0 [69]. A DAG visually represents the assumed causal and often complex relationships between all relevant (measured and unmeasured) variables, helping to identify the minimum sufficient set of variables that must be adjusted for (eg, using multivariable regression methods) to control for confounding the estimates of associations between exposures and outcomes. DAGs are a modern and essential tool in epidemiology that, when comprehensively specified, help identify key confounding variables to consider. This ensures that sufficient adjustments are made to control for confounding, while also avoiding unnecessary (and often harmful) over-adjustments [65].

The reporting of all results will adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [70].

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Qualitative Assessment

FGs with students and faculty, along with semistructured interviews with other key informants, will be conducted to explore, in greater depth, perceptions of the services and policies that need to be considered on campus to ensure the physical and mental health and well-being of students at QU. This phase will allow the researchers to gain a detailed understanding of the issues that cannot be quantitatively measured within their natural context by engaging directly with students and other key informants [48]. This triangulation of data collection, in terms of both data source (varied participants) and data type (FGs and interviews), allows the phenomenon to be explored from multiple perspectives, thereby enhancing the credibility, dependability, and confirmability of the results [48,49,71].

Study Sample Selection and Sample Size

For the FGs, purposive sampling will be used to select students from all years of study. Flyers will be posted on campus and shared on QU's social media pages to recruit participants. To ensure a broad range of perspectives, 2-3 FGs will be conducted with students from the humanities, sciences, business, and engineering colleges, while another 2-3 FGs will be held with students from the QU-Health colleges. Similarly, a purposive sampling of faculty members with more than 3 years of working experience at QU will be recruited. Two FGs will be conducted with faculty members from the humanities, sciences, business, and engineering colleges, while another 2-3 FGs will be held with faculty members from the QU-Health colleges. Each FG will consist of 6-8 participants. The recruitment of students and faculty members will involve selecting participants from various colleges, genders, and nationalities/cultural backgrounds to ensure they reflect the diversity of the QU student and faculty population. FGs will be conducted with students and faculty members until theoretical saturation is reached, meaning no new themes emerge. Based on the literature and previous experience, it is anticipated that 6-8 FG sessions will be necessary to achieve saturation.

Data Collection Procedures and Ethical Considerations

The FG discussions will center on the perceptions of students and faculty members regarding the health needs and issues that students face, as well as the adaptations required within the university to support their health and well-being. Additionally, the sessions will emphasize the services and policies that should be considered to ensure the physical and mental health and well-being of students, from both the students' and faculty members' perspectives. The semistructured interviews will aim to gather in-depth data on the following topics: the major health needs and issues reported by students, the types of services provided to support students' health and well-being on the QU campus and at the QU Primary Health Care Corporation (PHCC) Center, the policies and regulations implemented to support students' health and well-being, and the resources and services required to better support students' health and well-being.

The development of the topic guide will be based on the findings from the qualitative assessment, literature review, and the expertise of the research team, ensuring a systematic approach to data collection. The topic guides will include key open-ended questions, along with probes to allow participants to comfortably express their views on issues related to both the physical and mental health and well-being of students at QU. Once finalized, the topic guides will undergo pilot testing for clarity and effectiveness with a group of students and faculty members from the QU Health.

FGs and interviews will be facilitated by 1 experienced researcher (GFA) who will guide the conversations and discussions within the scope of the topic, ensuring consistency and quality in data collection while minimizing biases. Another researcher (HK) will be present during the data collection sessions to take field notes, as necessary. The FGs and interviews will be conducted in either Arabic or English, depending on the participants' preferences, and will take place face-to-face on the QU campus or virtually via the Microsoft Teams platform. Data collection sessions will last approximately 45-60 minutes each and will be audio-recorded (with participants' consent before the session) and transcribed verbatim. Confidentiality and anonymity will be ensured by using alphanumeric codes and storing all research documents on password-protected laptops. No incentives will be provided for participation.

Data Analyses

The accuracy of the transcripts will be verified by the FG leader and the researchers' field notes (for the FGs) as well as by the interviewer (for the interviews). To enhance the trustworthiness of the study, the accuracy of the transcripts from both the FGs and the interviews will also be confirmed through consultation with participants. A copy of the transcript will be sent back to participants for member checking, allowing them to confirm whether the transcripts accurately represent their ideas.

Data will be analyzed using a thematic analysis approach, with codes assigned to common quotes and ideas expressed by participants. These codes will be compared and grouped into different categories of themes and subthemes, both inductively and deductively. Two researchers (GFA and BM) will be involved in the analysis process to ensure the credibility and dependability of the results, with any discrepancies resolved through consensus with a third researcher (HK). To perform the thematic data analysis, the computer-assisted coding software NVivo version 14.23.0 (Lumivero) will be used for data retrieval and to critically evaluate participants' quotes, assigning them to relevant codes and themes.

Measures of quality and trustworthiness in qualitative research, including credibility, dependability, reflexivity, transferability, and confirmability, will be ensured [72,73]. We will apply peer review to all processes, maintain a database of all research data and records, triangulate the data, and implement appropriate data analysis methods. To enhance the quality of reporting in the qualitative phase, we will adhere to the Standards for Reporting Qualitative Research [73].

Campus Environmental Scan (Objective 2)

The research team will develop checklists and tools for the environmental scan after reviewing the literature to adapt previous assessment tools and draw on relevant student input. They will collaborate with the QU Healthy University

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Committee members to ensure a comprehensive assessment is developed. QU-Health students (n=40, with 10 students from each college) and research assistants (n=4), supervised by the research team (n=20, faculty members from QU-Health) and QU Healthy University committee members (n=7), will scan the existing health services, programs, initiatives, and activities available on the QU campus and at the QU PHCC Center. They will map how these services align with the health-promoting university indicators. These services and initiatives include, but are not limited to, those promoting healthy lifestyles, health development, mental health, reproductive health, communicable disease prevention, and regular medical check-ups and screening programs for youth.

In addition, the team will review and analyze health policies and regulations available on the QU website. This will involve searching for, reviewing, and analyzing policies, regulations, guidelines, and violation forms related to promoting a healthy lifestyle on campus. Key areas of focus will include the implementation of a 100% tobacco-free policy, the national nutrition policy concerning the types of foods provided in educational facilities and cafeterias, and the availability of qualified and trained physical education instructors. To ensure a comprehensive search and assessment, the team will consult with the QU Healthy University committee members, who have prior experience in data collection from their involvement in submitting the Healthy University WHO award proposal.

Plan and Implement Evidence-Based Intervention Activities That Align With the Healthy University Pillars (Objective 3)

Together, the health needs assessments and the environmental scan will provide the evidence necessary to inform and plan effective multilevel interventions and activities tailored to the student's needs (Figure 2).

Figure 2. Integration plan of the data from the quantitative and qualitative assessments, and the environmental scan, to inform the design and plan of multilevel health promoting interventions.

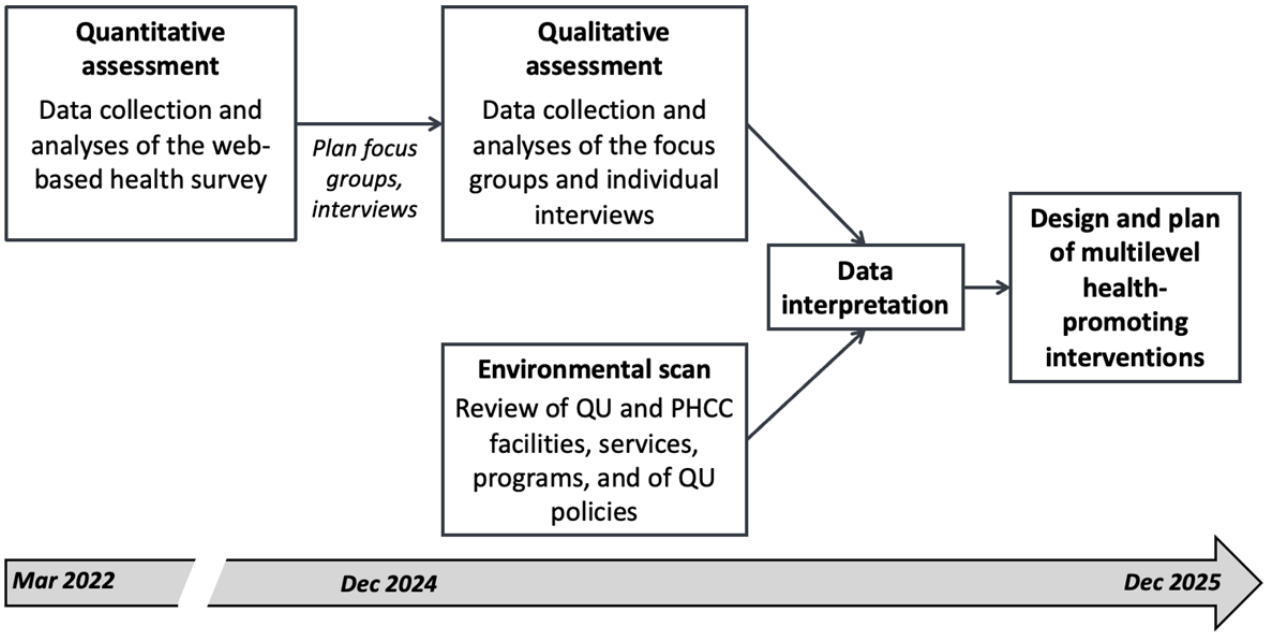

The research team members, students, faculty, and both internal and external stakeholders will collaborate to accomplish this objective. Specifically, we plan to achieve the following:

- Organize and deliver health education and promotion activities, initiatives, and programs on campus by organizing campaigns and seminars for students and faculty, both on campus and virtually, with invited international guest speakers from the Health-Promoting Universities network to share their experiences; implementing health and well-being initiatives at the Well-Being Space (a physical space created on campus to support students in practicing hobbies and coping strategies that positively affect their mental health); launching the Peer-helpers program at QU (an initiative between the student learning support and counseling centers to guide students in conducting support groups that empower peers with skills to boost their mental health); and integrating health and well-being modules into core curriculum courses.
- Reorient, where needed, the health services available on campus and at QU PHCC to target the health needs of QU students. This will be achieved by informing and coordinating with all stakeholders (including students, staff, faculty members, the QU PHCC manager, and relevant QU centers' directors) about the priority health topics identified in the needs assessments. These QU centers include the Career Development Center, the Student Learning Support Center, the Student Counselling Center, the Academic Advising Center, the Special Needs Center, the Facilities and General Services, the Health and Safety Section, and the Strategy and Development Office.
- Reform and/or issue new healthy policies and regulations on campus. This will be achieved by developing health policy recommendations in collaboration with the QU Healthy University Taskforce, which works on collecting data to sustain QU's Healthy University status.

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All findings and initiatives will be shared on QU Health Pulse, a health broadcast service provided by QU-Health to the QU community and beyond, as well as through email and on QU social media platforms.

Results

Thus far, we have completed the data collection for the quantitative assessment and conducted an initial analysis to assess the extent of potential selection bias. We have also estimated the IPPWs to mitigate this bias in all future data analyses.

Specifically, during the Spring and Fall semesters of 2022, a total of 904 students responded to the invitation to participate in the QU-health survey, with 842 agreeing to participate. Of these, 30 students were excluded due to failure to meet the eligibility criteria (ie, being younger than 18 years old despite providing consent; n=23) or not providing key demographic data required to generate the IPPWs (ie, age, college, academic level, nationality, and gender; n=7). Therefore, the final study sample for the quantitative assessment consists of 812 students (Figure 3).

Figure 3. Flowchart describing selection of participants into the quantitative assessment study. QU: Qatar University.

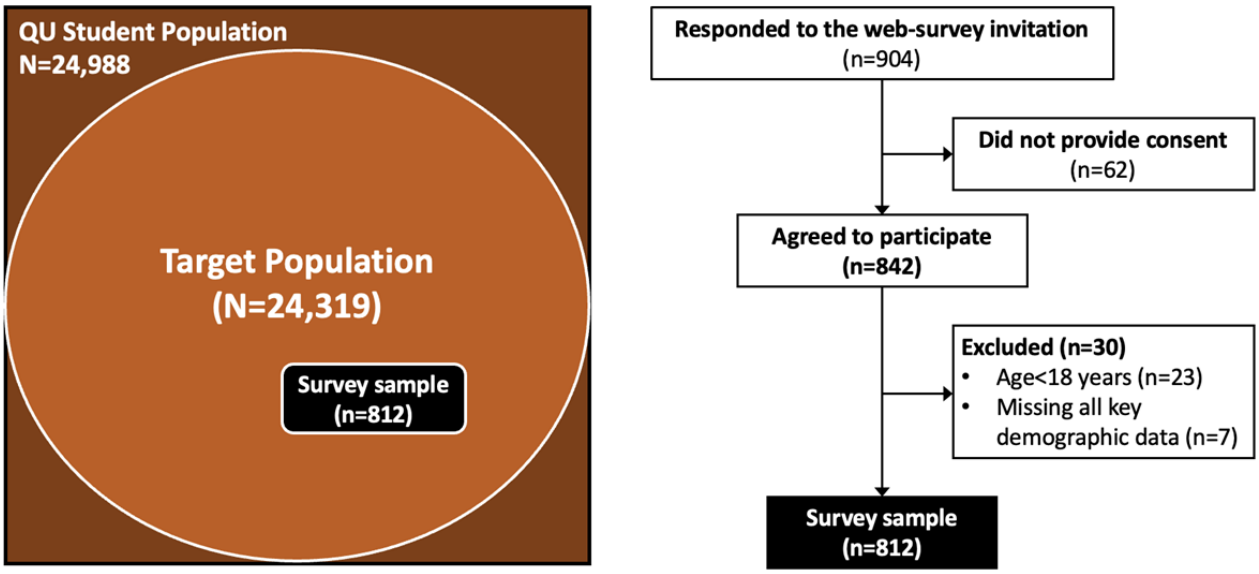

Comparisons of the general characteristics of the students included in the study sample and the QU-eligible student population (ie, the target population) revealed evidence of self-selection bias (Table 1). Specifically, students of Qatari nationality were underrepresented (393/812, 48.4%, participants in the study sample vs 16,698/24,319, 68.7%, students in the target population), as were men (125/812, 15.4%, in the study sample vs 6097/24,319, 25.1%, in the target population), particularly Qatari men. Representation across colleges and academic levels was also uneven, with an overrepresentation of students enrolled in QU-Health study fields (232/812, 28.6%, in the study sample vs 1560/24,319, 6.4%, in the target population). However, the academic level of enrollment (undergraduate vs postgraduate), used as a proxy for age, did not differ between the study sample and the target population.

The goal of the IPPW procedure was to make the study sample representative of the eligible population. Indeed, after weighting the data with the IPPWs we recovered the proportions observed in the target population (Table 1), and thus mitigated selection bias in as much as determined by these key variables. These weights will be used in all subsequent quantitative data analyses.

Following the completion of the quantitative data analyses, expected by the end of 2024, the subsequent stages of the project will commence. A detailed study timeline is provided in Table 2.

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Table 1. Summary statistics of all and the eligible QU[a] student population, and the study sample, before and after weighting with IPPW[b].

Variables	All QU students, AY[c] 2021-22 (N=24,988), n (%)	Eligible QU students (*target population*; N=24,319)[d], n (%)	Study sample (n=812)	
			Unweighted, n (%)	Weighted (with IPPW), %
Nationality				
Qatari	17,172 (68.72)	16,698 (68.66)	393 (48.40)	68.7
Non-Qatari	7816 (31.28)	7621 (31.34)	419 (51.60)	31.3
Gender				
Male	6277 (25.12)	6097 (25.07)	125 (15.39)	25.1
Female	18,711 (74.88)	18,222 (74.93)	687 (84.61)	74.9
Gender by nationality				
Male Qatari	3599 (14.40)	3484 (14.33)	22 (2.71)	14.3
Female Qatari	13,573 (54.32)	13,214 (54.34)	371 (45.69)	54.3
Male non-Qatari	2678 (10.72)	2613 (10.74)	103 (12.68)	10.8
Female non-Qatari	5138 (20.56)	5008 (20.59)	316 (38.92)	20.6
Academic level				
Undergraduate	22,699 (90.84)	22,030 (90.59)	739 (91.01)	90.6
Postgraduate[e]	2289 (9.16)	2289 (9.41)	73 (8.99)	9.4
College (field of study)				
QU-Health[f]	1602 (6.41)	1560 (6.41)	232 (28.57)	6.4
Health sciences	664 (2.66)	641 (2.64)	100 (12.32)	
Medicine	501 (2.00)	490 (2.01)	60 (7.39)	
Pharmacy	324 (1.30)	318 (1.31)	52 (6.40)	
Dental medicine	98 (0.39)	96 (0.39)	20 (2.46)	
QU-Health[g]	15 (0.06)	15 (0.06)	N/A[h]	N/A
All other	23,386 (93.59)	22,759 (93.59)	580 (71.43)	93.6
Arts and sciences	6914 (27.67)	6720 (27.63)	199 (24.51)	
Sharia and Islamic studies	1627 (6.51)	1591 (6.54)	62 (7.64)	
Business and economics	4587 (18.36)	4477 (18.41)	102 (12.56)	
Education	3156 (12.63)	3073 (12.64)	68 (8.37)	
Law	1975 (7.90)	1931 (7.94)	23 (2.83)	
Engineering	4372 (17.50)	4212 (17.32)	124 (15.27)	
Undefined[i]	755 (3.02)	755 (3.10)	2 (0.25)	

[a]QU: Qatar University.

[b]IPPW: inverse probability of participation weights.

[c]AY: academic year.

[d]Differs from the total QU population by excluding all those aged under 18 years.

[e]Enrolled in certificate, diploma, master, or PhD programs (or equivalent).

[f]Includes health sciences, pharmacy, medicine, and dental medicine.

[g]Registered at the umbrella college level (QU-Health) only.

[h]N/A: not applicable.

[i]These were all enrolled at the certificate level, available only at non–QU-Health colleges.

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Table 2. Timeline of the tasks in this study.

Task	Start date	End date
Development of study protocol and ethical approval	September 2021	February 2022
Health needs assessment		
Quantitative (health survey)		
Deployment to students	March 2022	December 2022
Data extraction and cleaning (database and codebook building)	January 2023	June 2023
Data harmonization and calculation of survey weights	September 2023	December 2023
Data analyses and reporting	January 2024	December 2024
Dissemination (reports, scientific publications, or presentations)	September 2024	December 2024
Qualitative (focus groups and interviews)		
Recruitment and conduit	January 2025	May 2025
Transcription and data analyses	May 2025	August 2025
Dissemination (reports, scientific publications, or presentations)	September 2025	December 2025
Campus environmental scan		
Review the literature for existing checklists and tools	September 2024	December 2024
Physical (built) environment assessment	January 2025	May 2025
Review and analyses of Qatar University policies and regulations (on website)	January 2025	May 2025
Dissemination (report or presentations)	June 2025	August 2025
Plan and propose evidence-based interventions based on findings from health needs assessment and campus environmental scan	September 2025	December 2025
Dissemination (writing final report, presentations, and meetings)	November 2025	December 2025

Discussion

Through this study, we aim to obtain empirical and comprehensive data on the health status and needs of QU students. The individual-level health and needs assessments, combined with assessments at the organizational, community, and policy levels, will provide the evidence needed to design and implement multilevel health promotion interventions tailored to the student's needs and likely to achieve more sustainable effects. While the project aims to inform relevant policies and services at QU, it is also expected to generate documented experiences and insights that may be applicable to other universities. Specifically, it will offer guidance on aligning institutional efforts with the WHO's Healthy University indicators by utilizing the Health-Promoting University socioecological framework [16].

This project will address the gap in local knowledge regarding systematic methods to design, implement, and evaluate context-specific interventions aimed at improving the health and well-being of students in the university setting. While several studies in the region have examined university students' health-related behaviors, along with their determinants and consequences, significant gaps remain that hinder the translation of these findings into impactful interventions. First, students' health-related behaviors have often been studied in isolation (eg, focusing on physical activity, dietary practices, tobacco use, or mental health [25,29,30,33,34,74,75]) without adopting a holistic approach that acknowledges the interconnected nature of these behaviors and their shared determinants. Second, these health behaviors are frequently analyzed without considering the structural context, including the policies, programs, and services that shape their trajectory and outcomes. Third, the voices of young people are often absent in the prioritization of issues affecting their well-being. This disconnect results in a gap between what policy makers and institutions consider significant and what students perceive as the most substantial contributors to their mental and physical health burdens [76,77].

This project addresses these gaps in several ways. First, it adopts a holistic approach to designing and evaluating multilevel interventions, incorporating the perspectives and preferences of end users. By using mixed methods, the project seeks to gain an in-depth understanding of the multiple layers of influence on health and well-being. In addition to surveys and interviews, the project will assess the environment from social, physical, and policy perspectives, identifying assets and opportunities for creating healthy environments, as well as areas for improvement. The findings from the needs assessment will guide the design of interventions, which will be cocreated and prioritized by university students—the primary end users. The interventions will be assessed for their effectiveness and impact, providing insights into how they can be enhanced to best suit the context and purpose for which they were designed. Thoughtful and tailored dissemination is also crucial to the success of this project. After studying the needs of the QU community and proposing customized interventions and improvements in policy and services, this project is expected to contribute to a broader body of scholarship on youth

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well-being. Dissemination will occur not only through scientific publications but also by presenting the findings to university leadership and service providers. Finally, a strength of this project is its alignment with national health objectives and initiatives, including Healthy Cities and Healthy Universities.

The main limitation of this study is that it is conducted at a single university in Qatar. However, given QU's size (the largest in the country), reach, and diversity of the student body, the findings are relevant to universities with similar demographic profiles and can provide a blueprint to be adapted to other contexts. Furthermore, although the quantitative assessment relies on a convenience sample of QU students, efforts have been made to overcome selection bias and ensure the generalizability of the findings to the entire QU student population. However, data obtained through self-reports or narratives may still be subject to recall bias or other measurement biases, such as social desirability in participants' responses. Additionally, the cross-sectional design of the survey limits the ability to infer causation between some of the assessed sociodemographic determinants and health status outcomes. Repeated assessments (eg, every other year, if feasible) could help mitigate, at least in part, this limitation.

The potential implications of this research include increased awareness of and prioritization of students' health needs, as well as more active involvement of their voices in the development of policies and services on campus, primary health care services, and other health education and promotion initiatives at QU. Communicating the study findings and proposed interventions to university leadership across various sectors will ensure that our research aligns with the university's broader strategies for maintaining Healthy University status. By monitoring the long-term impacts of these interventions, the university positions itself as a regional model for effectively integrating student health and wellness into policy frameworks and infrastructural developments. More broadly, the health promotion model established at the university contributes to the national health strategy, of which health promotion is a cornerstone. From addressing the risk factors of prevalent conditions (such as obesity and diabetes) to providing sustainable and culturally appropriate mental health services, this methodological approach could be replicated in community-based initiatives beyond the university. Indeed, this research plan will generate documented experience and insights that may serve as a model for other public institutions aiming to enhance their health promotion efforts.

In conclusion, this mixed methods study aims to identify and prioritize the health needs of QU students and their determinants, and to inform relevant services and policies targeting these needs. By using comprehensive and context-appropriate methods, this project will contribute to QU's strategic efforts to become a Health-Promoting University.

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Data Availability

The data sets generated and analyzed during this project will be available from the corresponding author upon reasonable request, after the completion of the primary analyses.

Authors' Contributions

All authors contributed to the conceptualization of the study and assisted in the drafting and editing of the paper. GFAJ led the conceptualization, methodology, investigation, project administration, writing—original draft, and writing—review and editing. DAH contributed to the conceptualization, methodology, investigation, and writing original draft. HAR contributed to the conceptualization, writing—original draft, and writing—review and editing. IF and MEAR contributed to writing—original draft, writing—review and editing, formal analyses, and data curation.

Conflicts of Interest

None declared.

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Abbreviations

DAG: directed acyclic graph
FG: focus group
HLS-EU-Q16: 16-item European Health Literacy Questionnaire
IPAQ-SF: International Physical Activity Questionnaire—short form
IPPW: inverse probability of participation weight
OHIP-5: 5-item Oral Health Impact Profile
PHCC: Primary Health Care Corporation
QU: Qatar University
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WHO: World Health Organization
YHC-SUN: Youth Health Care measure—satisfaction, utilization, and needs

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Protocol

Exploring Shared Implementation Leadership of Point of Care Nursing Leadership Teams on Inpatient Hospital Units: Protocol for a Collective Case Study

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Abstract

Background: Nursing leadership teams at the point of care (POC), consisting of both formal and informal leaders, are regularly called upon to support the implementation of evidence-based practices (EBPs) in hospital units. However, current conceptualizations of effective leadership for successful implementation typically focus on the behaviors of individual leaders in managerial roles. Little is known about how multiple nursing leaders in formal and informal roles share implementation leadership (IL), representing an important knowledge gap.

Objective: This study aims to explore shared IL among formal and informal nursing leaders in inpatient hospital units. The central research question is as follows: How is IL shared among members of POC nursing leadership teams on inpatient hospital units? The subquestions are as follows: (1) What IL behaviors are enacted and shared by formal and informal leaders? (2) What social processes enable shared IL by formal and informal leaders? and (3) What factors influence shared IL in nursing leadership teams?

Methods: We will use a collective case study approach to describe and generate an in-depth understanding of shared IL in nursing. We will select nursing leadership teams on 2 inpatient hospital units that have successfully implemented an EBP as instrumental cases. We will construct data through focus groups and individual interviews with key informants (leaders, unit staff, and senior nurse leaders), review of organizational documents, and researcher-generated field notes. We have developed a conceptual framework of shared IL to guide data analysis, which describes effective IL behaviors, formal and informal nursing leaders' roles at the POC, and social processes generating shared leadership and influencing contextual factors. We will use the Framework Method to systematically generate data matrices from deductive and inductive thematic analysis of each case. We will then generate assertions about shared IL following a cross-case analysis.

Results: The study protocol received research ethics approval (2022-8408) on February 24, 2022. Data collection began in June 2022, and we have recruited 2 inpatient hospital units and 25 participants. Data collection was completed in December 2023, and data analysis is ongoing. We anticipate findings to be published in a peer-reviewed journal by late 2024.

Conclusions: The anticipated results will shed light on how multiple and diverse members of the POC nursing leadership team enact and share IL. This study addresses calls to advance knowledge in promoting effective implementation of EBPs to ensure high-quality health care delivery by further developing the concept of shared IL in a nursing context. We will identify strategies to strengthen shared IL in nursing leadership teams at the POC, informing future intervention studies.

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KEYWORDS

case study; evidence-based practices; implementation leadership; inpatient hospital units; nursing leadership; point of care

Introduction

Overview

Leadership is a key factor in generating conducive contexts for the successful implementation of evidence-based practices (EBPs) in health care settings [1]. Developing effective point of care (POC) nursing leadership for implementation, or implementation leadership (IL), has the potential to create optimal climates for implementation and improve patient outcomes [2]. However, the current understanding of IL in nursing is limited and does not consider the diversity of formal and informal leadership roles that are involved in implementation [3]. In addition, formal and informal nurse leaders work within nursing leadership teams to lead implementation efforts, yet how nursing leaders share in this process has not yet been described. The exploration of IL in nursing is important since it is well known that successful implementation of EBPs in nursing continues to be elusive, contributing to persistent quality gaps in care delivery. Furthermore, within the existing culture of continuous and relentless change, failed implementation efforts may intensify nurses' experiences of physical and emotional sequelae of "change fatigue" including exhaustion, apathy, powerlessness, and burnout, which in turn threaten their engagement in further change initiatives [4].

This study will explore and deepen a relational view of IL, called shared IL, which resonates with the number and variety of nursing roles involved in implementation at the POC. Specifically, this study will describe the leadership behaviors of nurses in formal managerial and nonmanagerial leadership roles at the POC, including nurse managers (NMs), assistant nurse managers (ANMs), nursing professional development educators (NPDEs), and advanced practice nurses (APNs), as well as informal leaders such as champions in the change process who are often appointed to support local implementation efforts. In addition, this study will explore the social processes where shared IL emerges among the various leaders. Finally, the contextual factors that enable shared IL will be highlighted. A more holistic understanding of shared IL in nursing can support the development of effective leadership for implementation.

Background

IL is a nascent concept in implementation science literature that provides guidance on what POC leadership behaviors need to be developed and performed to support successful implementation [5]. IL describes strategic leadership behaviors based on transformational and effective leadership behavior theories whereby leaders are visibly committed, supportive of POC staff, and engaged at the granular level to prepare for and facilitate implementation [6,7]. These behaviors are posited to strengthen implementation climates, which consist of "employees' shared perceptions of the policies, practices, procedures and behaviors that are rewarded, supported and expected in order to facilitate effective EBP implementation and use" [8]. Recent evidence from a nonnursing longitudinal study in mental health clinics supports a link between the enactment of IL behaviors by POC clinical managers with higher levels of implementation climate and self-reported adoption of EBPs by clinicians, reinforcing the critical role of POC leaders in creating the conditions for implementation to succeed [9].

IL has been typically conceptualized as an approach that is manifested through the behaviors of individual leaders, in particular leaders who hold managerial positions at the POC [3]. Indeed, a growing body of research describes NMs as playing a vital role contributing to implementation success. In an updated systematic review, Gifford et al [10] found that NMs enacted change-, relational-, and task-oriented behaviors that included communicating organizational priorities for change, establishing partnerships with nursing and interprofessional colleagues, participating in planning for implementation, and providing resources. These behaviors indicated to staff that the use of the EBP in clinical practice was important and served to "inspire, encourage and provide tangible incentives to staff" to adopt EBPs [10]. Birken et al [11] similarly found that middle managers (including POC NMs) played multiple roles, which consisted of encouraging and enabling frontline staff to overcome obstacles, addressing concerns, coaching, and providing incentives to shape an implementation-conducive climate. These reviews suggest that NMs take on multidimensional leadership behaviors that consist of both enabling and enforcing roles to generate contexts supportive of implementation. In contrast, no studies were found on the role of ANMs in implementation despite their day-to-day involvement in the operations and care processes in a care setting.

Nonmanagerial nursing leaders at the POC also have responsibilities for engaging in processes that aim to optimize the health system, including research, leadership, and education [12]. However, in contrast to research on the role and behaviors enacted by NMs, no studies were found that explicitly explored the IL behaviors of these other types of nurse leaders. Rather, formal nonmanagerial leaders including NPDEs and APNs such as clinical nurse specialists and nurse practitioners, have typically been described in the literature as internal facilitators [13]. Facilitators use strategies that exert social influence to support behavior change including encouragement, role modeling, information sharing, peer-to-peer coaching, delivering formal and informal education, practice surveillance, demonstrating a commitment to the goal, and planning and goal setting among others [14-16]. Similarly, informal nurse leaders can take on champion roles in implementation, and like internal facilitators use a wide range of strategies that are congruent with their professional knowledge, skills, and practice expectations to support change [14]. While it appears that both leadership and facilitation are needed to support implementation,

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there is considerable overlap in these processes. In addition, it is unclear how the adoption of either facilitation or leadership roles and behaviors is influenced by the type of nursing leader position held, suggesting an important area for clarification and exploration.

Nursing leaders at the POC level may need better training to take on their leadership roles, and in particular to develop strategic IL behaviors to support implementation [17]. In a study by Lunden et al [18], nursing staff perceived weakness in the way their managers enabled implementation, particularly around providing resources, mitigating obstacles to implementation, and engaging in discussions about EBPs. When measuring IL-specific behaviors, Shuman et al [2] found NMs in acute care units only exhibited these behaviors moderately and suggested that interventions to strengthen IL were needed. However, it is unknown whether formal nonmanagerial nurse leaders also have similar performance gaps enacting IL. Some studies were found that described the development and feasibility testing of IL interventions as an implementation strategy and these were directed mainly at POC NMs to support the adoption of a clinical practice guideline [19,20]. A greater understanding of nursing leaders' behaviors and their interactions is needed to inform how these IL interventions could be adapted to address a team of diverse nursing leaders at the POC involved in implementation.

Nursing leadership to support implementation at the POC resonates with collective leadership models such as shared leadership, which moves away from a perspective of leadership that resides within an individual with formal authority and influencing power [21]. In contrast, shared leadership is a dynamic and collaborative relational process where influence is distributed among a number of networked individuals to achieve team or organizational goals [22,23]. A shared leadership model is viewed as a strength for teams completing complex tasks such as change and improvement in health care contexts and acts as a facilitator for organizations engaged in large-scale transformative change [24,25].

Research exploring the relational processes among nursing leaders that contributed to the successful implementation of EBPs is very limited. In a Canadian study evaluating the feasibility of an IL educational intervention, formal and informal leaders assigned greater value to generating collective versus individual action plans to implement a fall prevention guideline in residential facilities [19]. In another Canadian study, Fleiszer et al [26] described long-term and routine use of clinical practice guidelines in acute care units where the POC nurse leadership team worked cohesively and collaboratively to integrate implementation and sustainability strategies. However, these studies only alluded to the notion of shared leadership in implementation, as an attribute of effective leadership in nursing. In a study examining relational processes among NM and clinical leader dyads to implement urinary incontinence guidelines, van der Zijpp et al [27] concluded that implementation progressed when these leaders were "in sync." Further, this study pointed to the influence of the organizational culture on POC leaders, suggesting that leaders were reluctant to engage in their implementation role due to specific context factors including the challenges of managing competing priorities, hierarchical leadership structures, and the emphasis on top-down compliance to practice standards [27]. This indicates that more research is needed to explore factors influencing the enactment of IL by different formal and informal nurse leaders as a collective activity at the POC.

In summary, the conceptualization of IL is at odds with nursing leadership at the POC, where multiple leaders in distinct roles are called to lead the implementation of EBPs. Similarly, empirical work to date related to IL in nursing has focused predominately on the NM role, whereas how POC nursing leadership consisting of various formal and informal leaders is enacted to support the implementation of EBPs has been relatively unexplored. This represents an important knowledge gap in the field of implementation science and an area of conceptual evolution for IL. Moreover, how these various leaders work together to support implementation and what influences these processes has not been explicitly researched in depth.

Methods

Research Questions

The central research question is as follows: How is IL shared among members of the POC nursing leadership team in inpatient hospital units? The subquestions are as follows: (1) What IL behaviors are enacted and shared by POC formal and informal leaders? (2) What social processes enable shared IL by formal and informal POC leaders? and (3) What factors influence shared IL among the POC nursing leadership team?

Design

We will use a collective case study approach within the constructivist paradigm to answer the research questions [28]. Collective case study is an approach to inquiry where the researcher explores the particularities of multiple, contemporary, and real-life bounded systems (the cases) in order to generate an in-depth understanding of a social phenomenon [29]. In this study, the cases will include POC nursing leadership teams on 2 inpatient hospital units at a university health network where the implementation of an EBP was successful. In line with the research questions for this study, a case study answers "how" questions by disentangling complex relationships among various factors and processes, which emerge as a function of context both within and external to the case [29]. Case studies are also useful in exploring phenomena that have not been extensively researched, such as shared IL [30]. The emphasis on context distinguishes case studies from other qualitative approaches and promotes the use of multiple data sources and collection methods to develop a holistic understanding of the phenomenon [31]. The selection of multiple cases can generate a greater and more nuanced understanding of how effective shared IL is manifested in different environments, offering the potential to develop an explanatory framework of IL in POC nursing leadership teams [28].

Constructivist Paradigm

Applied widely across different disciplines, the methodological choices in the design of case studies can be approached from different ontological and epistemological orientations [32,33].

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Constructivism, based on a relativist ontology, ascribes to the belief that knowledge of the world is socially constructed [34]. A constructivist orientation to the case study assumes that understanding of a phenomenon such as shared IL in the social world occurs through the perspectives of individuals experiencing it, their shared meanings, and the interactive processes within a given context [35]. For this study, we understand leadership, as constructed through the interactions between grouped individuals, influenced by context and not merely assigned to formalized roles. The focus of this inquiry will be to explore these leaders' IL behaviors and the social processes that support shared IL from the perspectives and collective experiences of POC nurse leaders in inpatient hospital units. To meet the epistemic commitment to constructivism, the theorizations by Stake [34] characterizing case study as a holistic, empirical, interpretive, and empathic research approach will shape our methodological decisions, the role of the researcher in data coconstruction and interpretation, notions of data validation (eg, triangulation), and implications for knowledge generation.

Conceptual Framework

We developed a conceptual framework to guide the selection of key informants and frame the analytical and interpretive focus to explore shared IL among POC nursing leadership team members (Figure 1). A description of the terms can be found in Textbox 1.

This study will build on the dimensions of IL behaviors described in the Ottawa Model of Implementation Leadership, an empirically informed theoretical model in nursing developed over a decade of research [7]. The Ottawa Model of Implementation Leadership describes three meta-categories of leader behaviors to facilitate implementation and support the adoption of EBPs at the POC: (1) relations-oriented behaviors that include supporting, developing, recognizing, and empowering behaviors; (2) change-oriented behaviors that include advocating and envisioning change, encouraging innovation, and facilitating collective learning; and (3) task-oriented behaviors that involve planning, clarifying, monitoring, and problem-solving behaviors. This model is featured in the center of the conceptual framework to describe the specific IL behaviors that are enacted by the different leaders at the POC. Positioned around the IL behaviors are the formal and informal nursing leaders, to integrate the notion that IL behaviors are distributed among a diversity of leaders at the POC. The different leaders are linked to highlight their grouping as a leadership team and social processes where shared IL emerges. Social processes are the patterns of social interactions, that is, the actions and activities occurring over time, and are embedded in a dynamic context, that shapes how IL is shared and the activities across phases of an implementation project [36].

Figure 1. Conceptual framework of shared implementation leadership.

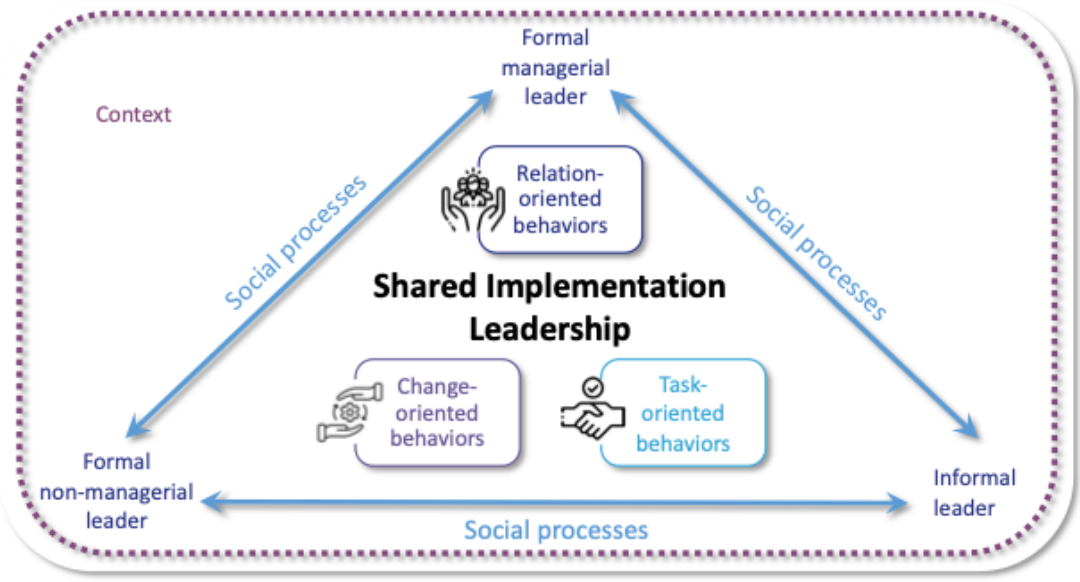

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Textbox 1. Description of terms (conceptual framework).

Implementation leadership

- Effective leadership behaviors facilitate the implementation and adoption of evidence-based practices at the point of care.
- Meta-categories of leadership behaviors described in the Ottawa Model of Implementation Leadership [7]:
  - Relation-oriented behaviors: Supporting, developing skills, and recognizing others and their contributions to increasing trust and cooperation.
  - Change-oriented behaviors: Integrating a vision, demonstrating commitment, building coalitions to support change, and creating a sense of need.
  - Task-oriented behaviors: Planning, clarifying roles, monitoring performance, and efficiently using resources.

Leaders

- Formal managerial: Individuals with appointed administrative and management roles with explicit and legitimate authority on the unit (eg, nurse manager and assistant nurse manager).
- Formal nonmanagerial: Individuals with formally recognized clinical leadership and professional development roles in the organization (eg, advanced practice nurses and nursing professional development educators).
- Informal: Individuals with a staff nursing position on the unit are viewed among peers and formal leadership groups as credible. Formalized in the role of nursing champion in the context of an implementation project.

Social processes

- Patterns of social interaction within the team (ie, the individual and collective actions and activities) over time where point of care leaders mutually influence each other for shared implementation leadership to emerge [36].

Context

- The structural, political, cultural, and historical environments of the inpatient unit and health care organization shape features of the social processes.

Sampling and Recruitment

Cases

Stake [34] defines a case as a "bounded system" from which much can be learned. With multiple cases, each case is unique and studied in detail, but it is the phenomenon expressed within each case and across cases that is of interest [28]. We will select 2 instrumental and bounded cases from a large bilingual teaching health network in Montreal, Canada to gain a broad appreciation of shared IL, the phenomenon of interest (or "quintain") in this study [28]. The case will be operationally defined as an inpatient unit in which the POC nursing leadership team has successfully implemented a specified EBP. Inpatient units are socially distinct microsystems that interact with external features, such as the larger organizational hospital context [37,38]. Therefore, inpatient units are considered individual cases, but embedded within the broader clinical and administrative organization and health care contexts. The cases will be bounded as follows: (1) spatially by the physical location, (2) purposefully, by the local clinical mission of the unit, where members of the POC nursing leadership team are assigned responsibility for and have supported the successful implementation of a specified EBP, and (3) temporally by the phases and timeline boundaries of the implementation project.

Case Selection

We will select individual cases based on their relevance to the quintain, the diversity of contexts, and access [28]. To identify potential cases, we will seek advisement from the senior leaders at the health network who are responsible for coordinating EBP project implementations and knowledgeable of implementation outcomes of potential cases. The first case (case A) will be purposively selected and based on predetermined criteria: (1) The successful implementation of the EBP project on the unit within the previous 6 months and senior NMs perception of a "strong" nursing leadership team on the unit, (2) the presence of diverse leaders at the POC, and (3) the availability of the nursing leadership team on the unit to participate in the study. In light of emerging findings as the study unfolds, we will use maximum variation sampling to identify the second case (case B) in consideration of different contextual elements influencing the case (eg, nursing leadership team factors such as composition and tenure, clinical mission, hospital site, and implementation project) [39].

Data Sources

A variety of data sources including key informants and documents will provide breadth and depth to understanding the quintain. We will purposively select key informants for their perspective of firsthand experiences in sharing IL including POC nursing leadership team members consisting of formal managerial and nonmanagerial leaders (ie, the NM, ANMs, NPDE, or APNs) who are assigned responsibility to the inpatient unit and were present during the implementation of the specified EBP; and informal leaders (ie, staff nurse who worked on the unit and were selected as a champion for the specific EBP implementation project). Through purposive and snowball sampling, we will also recruit key informants from the unit and organizational level, who interacted with or observed POC nurse leaders during the implementation, had a role in influencing the

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process of shared IL, or can offer a perspective on the contextual influences on shared IL (eg, interdisciplinary team members, staff nurses, and senior-level nursing administrators) [40]. Key informants are considered within the boundaries of the case if they are directly involved in the social processes where shared IL emerges. On the other hand, they will be considered external to the case if they are observers or influencers of the process. Participants will be identified iteratively as the study unfolds with the aim of sampling as many key informants as possible to acquire saturation and depth in understanding the quintain as manifested for each case [41]. Recruitment of POC nursing leadership team members will be completed first and facilitated by senior leaders in the health network. The total number of anticipated key informants recruited will range from 10 to 19 per case.

The documents collected for this study will provide background and historical information and will serve as a proxy for observations [42]. The content and information contained within documents may be useful in describing the quintain over time and can extend, clarify, support, or contradict the perspectives of the key informants. Documents may also provide insight into leadership roles in implementation-specific events, point to instances and processes of leadership being negotiated and distributed, and establish formal expectations for POC leadership in implementation [29]. These insights will inform ongoing data collection by including new interview questions and identifying other documents to gather [42]. Moreover, the documents themselves can be viewed as serving a specific function within the setting [43]. For example, documents created by the setting and using a particular form and structure can give insight into the context of unit and organizational values influencing the social processes among leaders. Examples of documentary sources for this study can include written organizational documents (eg, job descriptions, project charters, protocols, meeting notes, and annual reports), electronic material (eg, email messages and presentations), and physical objects (eg, “war rooms” or “quality boards”, bulletin/whiteboards, and unit layout schematics).

Data Generation

Interviews

We will conduct focus groups with the POC nursing leadership team first. As a pre-existing socially constructed group, participants will be able to draw on their shared experiences and individual group members’ recollections to construct a deeper understanding of the quintain [44]. Data collected from this facilitated discussion can highlight whether accounts and experiences are perceived similarly or differently across team members [45]. Due to the retrospective nature of the case, a facilitated discussion between team members may offer an approximation of their natural group interactions and provide insight into the nature of their relationships (eg, power differentials and conformity) and social processes (eg, reaching consensus and groupthink) [46]. As group interactions are largely nonverbal, observations of group dynamics, including forms of communication, patterns of discussion, group norms, and body language will be collected in the form of descriptive field notes [45-47].

We will conduct individual interviews with key informants for each case to acquire a breadth of perspectives to shape our understanding of shared IL and factors that influence the social processes of shared IL. Complementary to the focus group, individual interviews will yield granular accounts of the case, including greater depth into issues raised during the focus groups, perceptions of shared IL processes and influence, and to check assertions about the group dynamic [48]. Individual interviews with other key informants will clarify their interactions with members of the POC nursing leadership team, and their perceptions of how the POC nursing leadership team supported implementation and influencing factors. The principle of data saturation will guide the total number of interviews conducted for each case [41]. Minimally, 1 focus group interview (possibly over 2 sessions) and 1 individual interview with key informants (n=10-19) will be conducted per case. Additional interviews (focus group and individual) will likely be needed and will serve to validate the analysis (ie, member checking), discuss interview transcripts, clarify ideas, or explore emerging notions gleaned from other data [49].

For both focus group and individual interviews, we will offer face-to-face, in-person or digital interviews, at the convenience of the participants. Interviews will be audio-recorded to capture verbal content data. Prior to the interviews, all participants will complete a sociodemographic questionnaire (Multimedia Appendix 1), which will enable the reporting of details of the key informants in the case description. Interviews will be semistructured to foster an emic approach in line with the constructivist view. We developed an interview guide (Multimedia Appendix 2), with open-ended questions linked to key concepts in the conceptual framework, to explore topic areas aligned with the focus of inquiry while responding to emerging issues emanating from the participants’ experiences of the case [37]. The main questions in the interviews will relate to a description of the EBP project on the unit, the interviewee’s involvement in the EBP implementation, IL behaviors that were distributed or collectively enacted by POC nursing leaders throughout the implementation phases, activities that enabled the POC nursing leadership team to share IL, and the perception of factors related to the context that facilitated or constrained how POC leaders shared IL. In addition, the guide incorporates elements aimed at developing rapport with participants such as broad open-ended questions, with prompts and probes to encourage information sharing and to clarify points [47]. The interview guide concludes with ending questions to promote member checking by summarizing and clarifying what was discussed and asking participants to refer to other sources of information [30]. Throughout the course of inquiry, the interview guide may be adapted in light of emerging ideas and notions from other sources (eg, documents) [47]. Interview guides will be piloted for clarity and comprehension prior to the first interview.

We will identify documents in relation to each case by searching organizational papers and web-based databases, and by direct request of key informants. In addition, SAC will make unit site visits (brief 30-minute tours of the units guided by a leader on the unit to identify other relevant documents) and capture observations about the case through researcher-generated field

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notes. Identified documents will be scanned, digitally photographed, saved electronically in a secure study database, and logged. A document intake form will be used to log the characteristics of the document (eg, when, how, and from whom the documents were retrieved), the authenticity of the document, and key themes from the document that relate to the study questions (Multimedia Appendix 3 [40]).

We will generate several types of field notes throughout the course of data collection to accurately describe the research process and achieve an in-depth and credible interpretation of the findings [50,51]. Jottings of ideas, impressions, and brief details of observations will be noted sporadically on a paper notepad to serve as a memory jogger. A daily log of anticipated and actual data collection activities, activities that are being considered, and brief profiles of key informants will be kept electronically. Descriptive observational field notes will be written on separate electronic documents immediately following the case selection meetings, interviews, and unit site visits. Methodological field notes will capture reflections on the techniques and methods used, their perceived success, and adaptations in future data collection. Analytic memos will be used to develop ideas and interpretations of the data collected. Finally, a personal reflexive journal will be kept recording thoughts, feelings, and biases noticed throughout the research process.

Data Analysis

A 2-phase data analysis process will be conducted to ultimately deepen our understanding of the quintain: Within- and cross-case analysis [28]. A within-case analysis will generate an in-depth description of each case, the context and case-based themes, and will occur simultaneously with data collection so that emerging data can iteratively inform the selection of the second case, the pursuit of additional key informant perspectives, and direct lines of inquiry [29]. The Framework Method for the analysis of qualitative data will guide a structured, interconnected, and transparent flow of activities for an in-depth thematic analysis of the data and is aligned with the phases of case analysis described by Stake [34] (ie, case description, categorical aggregation, pattern recognition, and naturalistic generalization) [52]. Similarly, the Framework Method integrates inductive and deductive approaches to analysis, capitalizing on a balance of etic and emic constructions of the case. This approach generates matrix outputs where a large amount of diverse textual data (eg, interviews, documents, and field notes) are systematically reduced, summarized, and displayed facilitating a team approach to analysis [53,54].

The Framework Method moves through five stages: (1) familiarization with the data to form hunches about emerging issues or concepts that correspond with the conceptual framework for each case, (2) developing and iterative refinement of a thematic framework through deductive and inductive coding from a set of a priori codes and subcodes derived from the conceptual framework, (3) indexing the remaining data with the thematic framework, (4) charting of the indexed data into a matrix to allow for data from the entire case to be viewed, and (5) mapping of patterns among categories and interpretation of the data. This final step will be carried through a back-and-forth process between data categories, raw data, and analytic memos toward understanding the case and establishing relationships between case themes and the context.

The case reports generated from the within-case analyses will build toward a cross-case analysis, which aims to identify commonalities and differences of themes across the corpus of cases, and how these are influenced by the variations in contexts to make assertions about the quintain [28]. Assertions constructed about the shared IL may support or suggest modifications to the conceptual framework initially proposed for the study. An updated framework will inform the conceptual structure for the final cross-case report and will be examined against existing research and theory.

Ethical Considerations

The study protocol received research ethics approval (2022-8408) on February 24, 2022, and renewal on February 21, 2023. The study will undergo a research ethics review. There is minimal risk of harm to participants in this study. Potential participants will be informed about the study (eg, study purpose, nature of their involvement, potential risks, and benefits) and will be required to provide written consent prior to embarking on the study. The right to refuse to participate and withdraw at any time during the study without consequence will be explained. The anonymity of study participants will be ensured by identifying transcripts with a numerical code, with the code key kept separately; storage of data files in secured physical and electronic locations; and limited access to data files by the research team [30]. Due to the nature of case study research and its use of thick description to report on the uniqueness of the case, there is a risk of deductive disclosure especially as the POC leaders are known to all staff [55]. In addition, confidentiality will be impossible to maintain for group interviews. Therefore, additional safeguards will be put into place to ensure confidentiality and build rapport with participants. These include (1) a discussion with interviewees following data collection about the anticipated audiences for dissemination of the study results, (2) offering participants the opportunity to review interview transcripts, (3) consulting with participants on how to treat text that may be identifying in nature for the purposes of data analysis and dissemination, and (4) in group interview circumstances, reminding participants not to share any details of the discussion outside of the group context [55]. As interviews with participants will be held during work hours, compensation will not be provided.

Reflexivity and Rigor

SAC will conduct this study to partially fulfill the requirements toward a PhD in nursing degree. She will conduct this study as a trainee with the research institute in the setting and will be partially subsidized by the nursing directorate. SAC is a registered nurse and has worked in the study setting as a clinical nurse specialist and then as an advisor for EBP. As a function of these roles across different sites within the setting, SAC believes she has earned credibility and trust from colleagues, particularly nurses in leadership roles. SAC maintains a strong connection with senior leaders as well as with other colleagues. As a research trainee and recent previous employee with the setting, SAC believes to be positioned as an insider, due to the

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"lived familiarity" with the participants in the research and a priori knowledge of the setting and potentially of the cases as well [56]. As an insider, she collaborated with senior leaders in the conceptualization of the study, to strengthen the feasibility and alignment of the study plan with departmental expectations. SAC's insider status also raises questions about the implications of power with respect to data collection, disclosure of confidential knowledge and perspectives, and reporting that may negatively influence the site, participants, and herself [29]. In addition to the strategies mentioned above, SAC will strive to be transparent in interactions with the individuals in her role as a researcher and demonstrate openness to address any concerns in the field [29].

Integrated into the design of this study proposal are strategies that enhance the trustworthiness of a naturalistic inquiry and meet the criteria for a good case study report [34,35]. The strategies encompass researcher behaviors, inquiry, and reporting processes to promote confidence in the findings presented on shared IL (credibility criteria), that accepted research practices were followed in exploring shared IL (dependability criteria), that the findings are grounded in an emic perspective (confirmability criteria) and that there is sufficient contextual information presented in the reporting of this study on shared IL for readers to deliberate over the findings for applicability in other contexts (transferability) [57]. Table 1 details the compendium of strategies planned for each quality criterion.

Table 1. Methodological rigor criteria, definitions, and strategies.

Rigor criteria [58]	Definitions [57]	Strategies to enhance rigor	Criteria described by Stake [34] for a good case study report (adapted)
Credibility	The extent to which the reader has "confidence that [the researchers] have accurately recorded the phenomenon under scrutiny" [57]	• Adequate engagement in the field to generate data [40] • Triangulation to promote variation in views and ways of constructing data • Establishing rapport in interactions with key informants [57,59] • Member checking to validate the accuracy and interpretation of data [34] • Debriefing sessions with research team to discuss and challenge data construction • Transparency in data construction by engaging in reflective commentary [57]	• Data sources are well chosen and in sufficient numbers. • Observations and interpretations appear to be triangulated. • Sound assertions appear to be made, neither over- nor under-interpreting. • Individuals were not put at risk during the inquiry.
Transferability	The extent to which the reader has been provided sufficient contextual information by the researchers to apply the findings elsewhere	• Thick case description [57] • Maximum variation [40]	• Case adequately defined. • Reader is provided with some vicarious experience (sense of story). • Adequate attention paid to various contexts.
Dependability	The extent to which the reader can assess that the proper research practices have been followed	• In-depth methodological description [60]	• Final report is easy to read and edited well. • Research questions and themes developed in a serious and scholarly way.
Confirmability	The extent to which the reader can determine that the findings are based on an emic perspective, "rather than the characteristics and preferences of the researcher" [57]	• Researcher reflexivity [57] • Demonstration of an audit trail [44,57]	• Findings have a conceptual structure (ie, themes). • Quotations are used effectively. • Tables and figures are used effectively. • Sufficient raw data are presented. • The role of the researcher is apparent. • Empathy is shown. • Researcher's personal intentions are examined

Results

Data collection began in June 2022, and we have recruited 2 inpatient hospital units and 24 participants to date. We experienced several challenges locating and recruiting key informants (ie, no longer employed at the hospital) or delays in scheduling focus group interviews with nursing leadership teams and individual interviews with key informants due to high levels of workload during the COVID-19 pandemic. We amended the study protocol (approval received on July 18, 2022), with the research ethics board to be able to recruit employees no longer working at the hospital. We anticipate data collection to be completed by January 2024 and findings to be published in a peer-reviewed journal by late 2024.

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Discussion

Significance and Anticipated Contributions

Over, the next 10 years, Canada has committed to advancing the science of knowledge mobilization to generate more capable, effective, and humane health systems and to improve the health of individuals and populations [61]. The aims of this study address this priority by exploring more deeply how nursing leadership facilitates the successful implementation of EBPs to ensure high quality care delivery. Further, as nurses represent the largest regulated health professional group in health systems worldwide and are recognized as key drivers in care quality, the findings of this study will be an important contribution to this goal [62,63]. This study will answer calls for further research investigating how leadership as a complex contextual factor interacts with the implementation process and will add to the growing body of knowledge on POC leader roles in implementation [64]. By expanding the conceptual understanding of IL as behaviors enacted by a single managerial leader, we will be able to articulate in detail the specific contributions of formal and informal nurse leaders at the POC fostering implementation climates. This study will be the first one to hold a relational lens to IL, explore the social processes of an intradisciplinary team at the POC, and demystify the characteristics of effective leadership teams in facilitating evidence-based changes in nursing.

The knowledge generated from study findings can inform the development of tailored implementation strategies that seek to bolster nursing leadership at the POC, such as how to adapt interventions aimed at single POC managers for POC nursing leadership teams. Other nursing scholars in implementation are similarly exploring ways to "prepare context" that easily adapts to regular and ongoing implementation efforts and poses "fewer barriers to change" [65]. By equipping nurse leaders to engage staff and support consistent success in implementation efforts, we may lessen the cost of failed implementation efforts and generate healthier work environments for nurses [66]. Nursing leadership is distinguished from other health care professionals through its multiple and diverse leadership roles at the POC, yet little is known about their specific contributions in implementation, specifically ANMs. The findings may help to inform nursing administrators about what organizational supports are needed to strengthen effective IL at the POC and to facilitate the development of emerging nurse leaders. In addition, during the COVID-19 pandemic, NMs reported that their roles and responsibilities had expanded and sometimes changed altogether with little or no preparation and training [67]. NMs may be increasing their reliance on other POC leaders to distribute specific leadership tasks in order to support implementation and the quality of care in their units. This study is timely and can offer much-needed clarity for policymakers on the present-day contribution of formal and informal roles in nursing to the provision of quality care.

Limitations

One of the limitations of this study is the generalizability of the findings to other inpatient hospital units or health care settings, due to the idiosyncratic nature of the qualitative case study approach and exploration of 2 cases in 1 setting [29]. However, the in-depth focus on the particular and unique aspects of the cases will illuminate the complexity of leadership supporting implementation in nursing and the importance of context in shaping its manifestation [34]. There may be concerns about social desirability bias limiting what POC nursing leaders discuss and disclose during interviews, given the legitimate power relationships across leader types (ie, manager and subordinate relationship) and their ongoing working relationship [68]. Yet, it is the analysis of this social context (eg, group norms) that is of interest to this study. Increases in workload, shifted priorities due to the ongoing COVID-19 pandemic and the nursing workforce shortage in the wake of the acute pandemic phase presented challenges with recruitment and availability of POC nurse leaders, and other key informants in the health setting. We are offering digital interviews to improve the likelihood of participation by teams and individuals. POC nursing leaders may be accustomed to communicating with each other digitally because of the pandemic and therefore may approximate their interactions in the natural setting.

Conclusion

Implementation of EBPs drives and sustains high-quality nursing practice, where effective nursing leadership at the POC is integral to its success. This protocol for a collective case study aims to conceptualize IL through a shared leadership lens in nursing. The study findings will have broad implications for ongoing research in the fields of implementation science and nursing leadership; leadership practice by providing a model for leadership that enables successful implementation; developing leadership education competencies for current and emerging nursing leaders; and informing structural and cultural policy changes that support nursing leader roles in the health system.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study will not be publicly available due to the small sample size and risk of participant identification in this study, and in adherence to the requirements of confidentiality in line with the present ethics permission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sociodemographic questionnaire.
[DOCX File , 17 KB - resprot_v13i1e54681_app1.docx]

Multimedia Appendix 2
Semistructured interview guide.
[DOCX File , 19 KB - resprot_v13i1e54681_app2.docx]

Multimedia Appendix 3
Document intake form.
[DOCX File , 15 KB - resprot_v13i1e54681_app3.docx]

Multimedia Appendix 4
Peer-review report by the McGill University Doctoral Comprehensive Examination Committee.
[PDF File (Adobe PDF File), 231 KB - resprot_v13i1e54681_app4.pdf]

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Abbreviations

ANM: assistant nurse manager
APN: advanced practice nurse
EBP: evidence-based practice
IL: implementation leadership
NM: nurse manager
NPDE: nursing professional development educator
POC: point of care

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Protocol

Innovative Design and Development of Personalized Ankle-Foot Orthoses for Survivors of Stroke With Equinovarus Foot: Protocol for a Feasibility and Comparative Trial

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Abstract

Background: Ankle-foot orthoses (AFOs) are vital in gait rehabilitation for patients with stroke. However, many conventional AFO designs may not offer the required precision for optimized patient outcomes. With the advent of 3D scanning and printing technology, there is potential for more individualized AFO solutions, aiming to enhance the rehabilitative process.

Objective: This nonrandomized trial seeks to introduce and validate a novel system for AFO design tailored to patients with stroke. By leveraging the capabilities of 3D scanning and bespoke software solutions, the aim is to produce orthoses that might surpass conventional designs in terms of biomechanical effectiveness and patient satisfaction.

Methods: A distinctive 3D scanner, complemented by specialized software, will be developed to accurately capture the biomechanical data of leg movements during gait in patients with stroke. The acquired data will subsequently guide the creation of patient-specific AFO designs. These personalized orthoses will be provided to participants, and their efficacy will be compared with traditional AFO models. The qualitative dimensions of this experience will be evaluated using the Quebec User Evaluation of Satisfaction With Assistive Technology (QUEST) assessment tool. Feedback from health care professionals and the participants will be considered throughout the trial to ensure a rounded understanding of the system's implications.

Results: Spatial-temporal parameters will be statistically compared using paired *t* tests to determine significant differences between walking with the personalized orthosis, the existing orthosis, and barefoot conditions. Significant differences will be identified based on *P* values, with $P<.05$ indicating statistical significance. The Statistical Parametric Mapping method will be applied to graphically compare kinematic and kinetic data across the entire gait cycle. QUEST responses will undergo statistical analysis to evaluate patient satisfaction, with scores ranging from 1 (not satisfied) to 5 (very satisfied). Satisfaction scores will be presented as mean and SD values. Significant variations in satisfaction levels between the personalized and existing orthosis will be assessed using a Wilcoxon signed rank test. The anticipation is that the AFOs crafted through this innovative system will either match or outperform existing orthoses in use, with higher patient satisfaction rates.

Conclusions: Embracing the synergy of technology and biomechanics may hold the key to revolutionizing orthotic design, with the potential to set new standards in patient-centered orthotic solutions. However, as with all innovations, a balanced approach, considering both the technological possibilities and individual patient needs, will be paramount to achieving optimal outcomes.

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KEYWORDS

3D printing; 3D scanner; ankle foot orthosis; biomechanical analysis; equinovarus foot

Introduction

Overview

Stroke, often termed a cerebrovascular accident, poses a monumental global health issue and stands as the second leading cause of mortality worldwide [1]. In addition to the grave concern of mortality, survivors of stroke frequently grapple with substantial morbidity, most notably neurological impairments that substantially hamper their quality of life. Among these impairments, a prevalent issue is equinovarus foot, a symptom characterized by the foot being plantarflexed (downward) and inverted (turned inward), often resulting from muscle imbalances or neurological impairments [2,3]

In the management and rehabilitation of the equinovarus foot, ankle-foot orthoses (AFOs) serve as a foundational element, supporting and aligning the ankle and foot, suppressing spastic and overpowering muscles, and assisting weak or paralyzed muscles [4]. While these devices are indispensable in aiding patients to regain some semblance of normal gait, they come with their own sets of limitations. Broadly speaking, AFOs are categorized into 2 primary types: traditional off-the-shelf models and custom-crafted versions. Traditional AFOs, designed for a broad patient demographic, offer widespread accessibility but often miss the mark in addressing the unique biomechanical needs of each patient. This one-size-fits-all approach has drawn criticism for its rigidity and lack of individual customization [5]. Conversely, custom-made AFOs are meticulously tailored to fit a specific patient's anatomical structure. While they provide a more individualized fit, the process of creating these orthoses is time-consuming and very laborious. In addition, the process is also wasteful of materials, as plaster molds and other excess fabrication materials are discarded during the fabrication process [6]. This gap between age-old craftsmanship and cutting-edge precision sets the stage for technological intervention, aiming to meld the advantages of both approaches.

The concept of reverse engineering in orthotics involves capturing a patient's limb anatomy in great detail, translating this information into a digital model, and then crafting an orthotic device to perfectly align with the individual's biomechanical demands [7,8]. Using 3D scanning techniques allows for a highly accurate representation of human anatomy. This digital replica serves as a blueprint upon which orthotic devices can be meticulously designed, thereby ensuring that the device is tailored to an individual's unique biomechanical requirements. Nevertheless, the integration of 3D scanning technology into the orthotic field is fraught with challenges. Capturing a comprehensive scan, particularly of the plantar region of the foot, proves to be problematic. The quality of the scan is often compromised due to patient movements, exacerbated by the extended duration needed for the scanning process [9]. This prolonged duration can be uncomfortable for the patient, thereby leading to unintended movements and consequential errors in the scan data. Moreover, there are ongoing debates over the computational workload and adaptability of the resulting digital models. Such pitfalls, whether arising from anatomical complexities, patient movements, or technological limitations, could culminate in an improperly fitting orthotic device.

The science of photogrammetry, which involves making measurements based on photographs, offers a potential solution. Initially used for mapping and topographical studies [10], its application in the medical realm, particularly in orthotics and prosthetics, has only recently been explored. The capacity to transform photographs into intricate 3D models offers quicker scan times and could minimize errors induced by patient movements [11]. However, the full-scale integration of this promising technology into the orthopedic field is still in its infancy [12-16]. Ensuring that the resulting 3D models are an accurate reflection of patient anatomy and that the resultant devices are both functional and comfortable remains a challenge. Furthermore, orthopedics is a multidisciplinary field that includes physicians, physical therapists, and engineers. Consequently, any new technological adoption must be orchestrated carefully to ensure effective use across all these professions [17]. Armed with these technological advancements, the field of orthotics is poised for a transformative evolution—a shift toward a more patient-centric and technologically integrated paradigm. This fusion of traditional orthotic craftsmanship with cutting-edge computational tools heralds a new era in patient care, targeting both precision and broad accessibility.

Goal of This Study

This research protocol delineates our approach to developing a next-generation AFO system tailored to meet the specific needs of survivors of stroke. The primary objective is to harness advanced scanning tools and bespoke software for a holistic orthotic solution. By innovatively integrating technology and medical expertise, we envision a transformation in the rehabilitation journey, creating a more refined and effective recovery pathway for individuals with poststroke motor challenges. Our methodological framework will guide us from the initial stages of scanner and software development to a culminating phase of validation, where the proposed orthotic devices will undergo rigorous patient trials. Through this initiative, we aim to chart a progressive path in the realm of poststroke orthotic care.

Methods

Study Design

This nonrandomized feasibility study aims to harness advanced scanning technologies and innovative software for the design and refinement of orthotics tailored specifically to the unique anatomical and biomechanical needs of survivors of stroke presenting with equinovarus deformity. Following a noninferiority trial design for biomechanical outcomes and a superiority trial design for qualitative outcomes, our methodology focuses on the development of a novel AFO

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system. The goal is to ensure its biomechanical performance is at least as effective as off-the-shelf AFOs while also enhancing patient satisfaction. Feedback from patients and clinical observations will serve as the primary indicators of success.

Ethical Considerations

The approval for the protocol of this study was granted by the Health Ethics Committee of the Centro de Medicina de Reabilitação da Região Centro–Rovisco Pais (Tocha, Portugal) in August 2022.

Consent to Participate and Consent for Publication

Overview

A document was developed at the request of the health ethics committee for informed, clear, and voluntary consent for participation in research studies. The document outlines the research study's objective and assures that there will be no detriment to treatments and clinical follow-up should the patient choose to withdraw. It also guarantees the anonymity and confidentiality of all collected data, including photographs, results from the Quebec User Evaluation of Satisfaction With Assistive Technology (QUEST) [18], and biomechanical analysis data. The consent form must be signed by both the attending physician and the patient.

This protocol was prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for reporting a protocol study [19].

Eligibility Criteria and Recruitment Procedures

The inclusion criteria for this study have been defined with precision to select the most suitable candidates in alignment with the study objectives. We are targeting survivors of stroke, both male and female, aged between 18 and 75 years, who exhibit equinovarus foot secondary to hemiparesis, affecting either the left or right side. A prerequisite for potential participants is their current use of AFOs. Furthermore, the concurrent use of any assistive technologies such as tripods, crutches, or canes is deemed acceptable. Essential criteria include the capacity to provide informed consent and the ability to ambulate, either independently or with the support of the aforementioned devices. Conversely, candidates with concomitant neurological or orthopedic conditions that might confound the study outcomes, those with active dermatological conditions, or those with severe communication impairments potentially hindering consistent participation will be excluded.

The recruitment process will be at the Centro de Medicina de Reabilitação da Região Centro. Attending physicians will review patient profiles to identify individuals meeting the stipulated criteria. Those aligning with our research parameters will be briefed on the study's aims and subsequently provided with a detailed consent document. Upon granting written consent, these individuals will be enlisted as participants, ensuring a systematic and ethically rigorous approach to data acquisition and feedback.

Clinical Outcomes

In the pursuit of developing an optimized orthotic design system, an array of clinical metrics is implemented to gauge its efficiency, efficacy, and the comfort it bestows on both patients and health care professionals. Ensuring a comfortable experience for the patient during the photography process is paramount, given its pivotal role in orthotic design. This precision not only benefits the patient but also ensures that the system health care professionals navigate is intuitive.

Biomechanical assessments use the Qualisys Miqus M3 system, paired with Bertec force platforms. Patients will wear the Calibrated Anatomical System Technique lower body marker set, which consists of 36 reflective markers, as prescribed by Cappozzo et al [20]. Observations cover 3 walking conditions for each participant: unaided (where possible), with the current orthosis, and with the newly designed orthosis. This methodology provides an in-depth understanding of the orthosis's efficacy, drawing from 10 walking cycles for each leg, and analyzing both kinematics and kinetics.

The biomechanical data under scrutiny spans temporal-spatial parameters, which capture walking speed, gait cycle duration, step length, step time, time in stance, and time in swing. Kinematic parameters delve into pelvic movements such as anterior tilt, up obliquity, and internal rotation. Hip parameters include flexion, adduction, and internal rotation, while knee parameters assess flexion, varus, and internal rotation. Ankle and foot evaluations note dorsiflexion, inversion, pitch, and internal progression. Kinetic parameters are marked by the internal moments at the hip (extensor and valgus), knee (extensor and valgus), and ankle (plantarflexor and extensor), accompanied by the vertical ground reaction force.

The qualitative patient analysis will also incorporate the QUEST assessment. QUEST focuses on understanding the user's satisfaction with assistive technology. It evaluates a range of aspects, from device functionality to user confidence. This offers insights into patients' perceptions and benefits derived from the new orthosis in comparison to conventional models. Incorporating QUEST ensures the orthosis not only meets clinical requirements but also aligns with patient preferences and comfort levels.

Through these comprehensive evaluations, the study aims to offer an enriched perspective on the potential and effectiveness of the innovative orthotic system.

Data Analysis

The forthcoming data analysis is designed to provide an in-depth understanding of the impact of personalized orthoses on gait parameters in relation to both preexisting orthosis and barefoot walking. The sample size was estimated at a prespecified power of 90%, while the α value was set at <.05. The primary outcomes will be represented through spatial-temporal data tables and normalized gait graphs, spanning from 0% to 100% of the gait cycle for the left and right legs.

Spatial-temporal parameters will undergo statistical comparisons using paired *t* tests. This will discern any significant differences between walking with the personalized orthosis, the preexisting orthosis, and walking barefoot. Significant distinctions will be recognized based on *P* values, with a threshold set at 95% indicating statistical significance.

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Graphical comparisons of kinematic and kinetic data will use the Statistical Parametric Mapping (SPM) method. SPM is tailored for the analysis of 1D biomechanical data series, such as kinematic curves, yielding a nuanced understanding of differences across the entire gait cycle rather than mere isolated time points. The analysis will leverage the *SPM1D* script. By using SPM1D, it becomes feasible to pinpoint regions in the gait cycle where palpable differences between conditions (existing orthosis, personalized orthosis, and barefoot) arise. This rigorous method offers a continuous evaluation over the entire time or space continuum, safeguarding against missing subtle yet clinically pivotal variations.

Simultaneously, the QUEST responses will be statistically analyzed to evaluate patient satisfaction. Scores from the QUEST, which range from 1 (not satisfied) to 5 (very satisfied), will be presented as mean and SD values for each question. A 1-sample *t* test will be used to determine if the mean satisfaction scores significantly differ from a neutral value. Additionally, a Wilcoxon signed rank test may be used to determine differences in satisfaction levels between using the personalized orthosis and the preexisting orthosis. Any statistically significant variations in user satisfaction between the 2 orthoses will provide insight into the preferential use and comfort of the personalized design.

In essence, this multifaceted statistical approach aims to quantify not only the possible biomechanical advantages of personalized orthoses over standard ones but also the subjective satisfaction of users, ensuring a holistic assessment of the new system's efficacy.

Results

The methodology and approach of this research harbor specific expectations concerning its outcomes. We will use the Qualisys Track Manager from Qualisys to capture biomechanical data with unparalleled accuracy. Once gathered, the data will be processed and analyzed rigorously. With the integration of the Project Automation Framework from Qualisys and Visual 3D from C-Motion, the raw biomechanical data will be transformed into actionable insights that promise to inform and refine orthotic design.

One of the primary quantitative expectations is that the orthosis developed through the new system will either match or surpass the performance of the patient's current orthosis. This benchmark stems from the belief that the integration of state-of-the-art technology and personalized biomechanical data can achieve superior orthotic design. On the qualitative front, using the QUEST assessment, the expectation leans toward higher satisfaction rates with the new orthosis. Since the orthosis is tailored specifically to the patient's leg, it is anticipated that its unique design will resonate more with patients, ensuring better fit, comfort, and overall user experience. To ensure comprehensive results, feedback from health care professionals and participants will be actively sought throughout the trial phases. This blend of qualitative and quantitative data aims to present a holistic perspective on the impact of the new orthotic design, setting the stage for potential breakthroughs in patient-centered orthotic solutions. In summary, while this research protocol lays out the groundwork and anticipated outcomes, the subsequent study will seek to not just present numbers but to demonstrate the tangible and intangible benefits of a personalized orthotic approach.

Discussion

Over the years, the field of gait rehabilitation has witnessed significant advancements, with orthoses taking center stage in many innovative solutions. As such, they have played a pivotal role in enhancing gait and laying the foundation for more customized interventions [21,22]. In the chronicle of medical interventions, the present times showcase a blend of time-tested traditional methods coexisting with avant-garde technologies. It is within this dynamic backdrop that the new system emerges, positioning itself as a game changer in the realm of orthoses. With a design methodology that captures the transformative essence of technology, this system aims to usher in a new epoch where AFOs are no longer generic but are sculpted based on the detailed biomechanical nuances of individual patients [23].

A key component of this innovation lies in the use of 3D scanning and 3D printing techniques. Particularly, AFOs crafted through such state-of-the-art processes have been thrust under the academic microscope. In recent years, various studies have examined multiple outcomes with the use of these technologies for the fabrication of AFOs. Belokar et al [24] and Cha et al [25] conducted numerous mechanical tests to understand the strength and deformation of the AFO, while other studies focused on gait analysis [26-28], while others on a qualitative analysis of patient comfort [16,29]. The allure of these techniques is evident, offering unparalleled precision coupled with the prospect of personalization. However, as with all innovations, there is a spectrum of opinions. While numerous research endeavors highlight the undeniable advantages of 3D methodologies, others have voiced concerns—touching upon biomechanical compatibility, the robustness of materials used, and the overall comfort on prolonged usage studies [8].

While contrasting the biomechanics of barefoot walking with orthotic-assisted gait yields valuable insights, our central focus is on the differences between traditionally designed orthoses and those created using the novel system. Contemporary research reinforces the merits of tailored medical interventions, suggesting that custom orthoses can lead to enhanced foot function, pain relief, and overall improved mobility [30,31]. For patients, the benefits of this approach are substantial. Custom-made orthoses, derived from comprehensive biomechanical analyses, not only promise greater comfort but also accelerate gait rehabilitation and minimize complications arising from poorly fitted orthoses [6,7,25]. Such initiatives are in tune with the broader shift in health care toward patient-centered treatments, ensuring holistic and efficacious therapeutic outcomes [32].

Nonetheless, potential limitations exist. While the novel system promises tailored orthoses, individual patient responses, adaptation periods, and unique rehabilitation timelines could present challenges. The variability in individual reactions to orthoses, both in terms of comfort and therapeutic outcomes, remains a critical factor to consider.

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This proposed research protocol marks a pivotal juncture between technology and biomechanics in the health care landscape. It signals a shift in orthotic design, embracing recent advancements and a nuanced understanding of biomechanics. The endeavors are not merely about gait rehabilitation recovery but also about setting a new benchmark for precision and efficacy in patient care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e52365_app1.pdf]

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Abbreviations

AFO: ankle-foot orthosis
QUEST: Quebec User Evaluation of Satisfaction With Assistive Technology
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPM: Statistical Parametric Mapping

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Protocol

Experimentally Induced Reductions in Alcohol Consumption and Brain, Cognitive, and Clinical Outcomes in Older Persons With and Those Without HIV Infection (30-Day Challenge Study): Protocol for a Nonrandomized Clinical Trial

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Abstract

Background: Both alcohol consumption and HIV infection are associated with worse brain, cognitive, and clinical outcomes in older adults. However, the extent to which brain and cognitive dysfunction is reversible with reduction or cessation of drinking is unknown.

Objective: The 30-Day Challenge study was designed to determine whether reduction or cessation of drinking would be associated with improvements in cognition, reduction of systemic and brain inflammation, and improvement in HIV-related outcomes in adults with heavy drinking.

Methods: The study design was a mechanistic experimental trial, in which all participants received an alcohol reduction intervention followed by repeated assessments of behavioral and clinical outcomes. Persons were eligible if they were 45 years of age or older, had weekly alcohol consumption of 21 or more drinks (men) or 14 or more drinks (women), and were not at high risk of alcohol withdrawal. After a baseline assessment, participants received an intervention consisting of contingency management (money for nondrinking days) for at least 30 days followed by a brief motivational interview. After this, participants could either resume drinking or not. Study questionnaires, neurocognitive assessments, neuroimaging, and blood, urine, and stool samples were collected at baseline, 30 days, 90 days, and 1 year after enrollment.

Results: We enrolled 57 persons with heavy drinking who initiated the contingency management protocol (mean age 56 years, SD 4.6 years; 63%, n=36 male, 77%, n=44 Black, and 58%, n=33 people with HIV) of whom 50 completed 30-day follow-up

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and 43 the 90-day follow-up. The planned study procedures were interrupted and modified due to the COVID-19 pandemic of 2020-2021.

Conclusions: This was the first study seeking to assess changes in brain (neuroimaging) and cognition after alcohol intervention in nontreatment-seeking people with HIV together with people without HIV as controls. Study design strengths, limitations, and lessons for future study design considerations are discussed. Planned analyses are in progress, after which deidentified study data will be available for sharing.

Trial Registration: ClinicalTrials.gov NCT03353701; https://clinicaltrials.gov/study/NCT03353701

International Registered Report Identifier (IRRID): DERR1-10.2196/53684

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KEYWORDS

alcohol; contingency management; biosensor; HIV infection; cognitive function

Introduction

Alcohol misuse, or drinking in a manner that could cause harm to the user or those around them [1], is associated with poor HIV-related health outcomes (eg, lower rates of HIV viral suppression and suboptimal adherence to antiretroviral therapy) [2,3]. Alcohol consumption can contribute to a multitude of additional deleterious health effects, such as reductions in brain functioning, cognitive decline, liver disease, and systemic inflammation [4-8]. People with HIV tend to experience worse outcomes, including all-cause mortality, associated with alcohol misuse compared to persons without HIV [9]. Of additional concern is the combination of alcohol misuse and aging among people with HIV, as approximately 58% of people with HIV in the United States are at least 50 years of age [10]. Even mild cognitive impairments have detrimental functional effects and health outcomes that worsen as people with HIV age.

Several mechanisms have been proposed to explain how alcohol consumption could impact chronic disease outcomes. One of the most common is related to the gut-liver-brain axis (see Figure 1), and proposes that alcohol consumption can result in both alterations of the gut microbiota (dysbiosis) as well as microbial translocation, with resulting systemic inflammation that then impacts the liver and brain [11]. While several studies have shown chronic alcohol use to be associated with negative cognitive effects, if any current cognitive effects are due to current brain inflammation, then a reduction in drinking could result in a reduction in inflammation and improved cognition. However, the extent to which these cognitive effects are reversible versus permanent is not known. Since people with HIV also have increased rates of cognitive decline and chronic systemic inflammation, they may be especially vulnerable to the impact of alcohol and might benefit the most from alcohol reduction.

Figure 1. Conceptual model of the possible mechanisms by which alcohol could influence HIV-related health outcomes via the gut-brain axis.

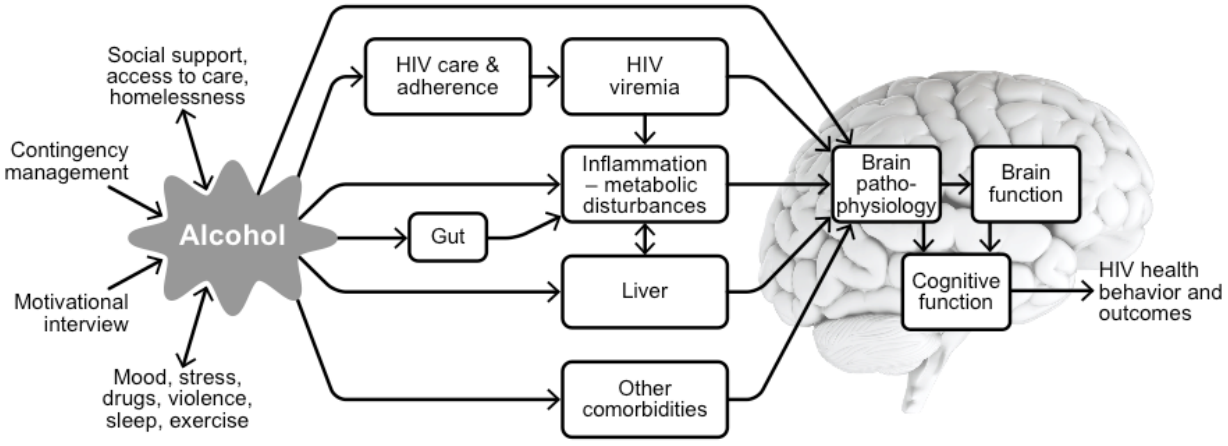

The true causal effect of alcohol consumption on these health outcomes can be difficult to tease out with observational studies. While it is not ethical to challenge persons to engage in ongoing heavy drinking to determine its adverse effects, removing alcohol consumption from heavy drinkers could help to identify whether certain health aspects are reversible when drinking is removed. Therefore, the research team designed a study to determine whether cessation of drinking or significant reduction would be associated with improved brain function, cognition, and HIV clinical outcomes. The study design would also examine whether these outcomes got worse again with any resumption of drinking and would examine potential biological mechanisms related to gut microbial dysbiosis, intestinal permeability, biomarkers of systemic inflammation, liver function, and brain pathology.

In order to experimentally reduce drinking, the research team proposed contingency management (CM), a well-established intervention for treating alcohol use disorder [12,13] that

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provides financial payments to encourage individuals to abstain from alcohol use [14]. In order to monitor daily drinking status, the research team used transdermal alcohol sensors, because these can continuously and noninvasively monitor alcohol use [15,16]. Specifically, the Secure Continuous Remote Alcohol Monitor Continuous Alcohol Monitoring (SCRAM CAM; Alcohol Monitoring Systems, Inc), a sensor locked onto the ankle, has effectively been used in CM trials [12,17-20]. The sensor data can be used to determine whether reinforcement should be provided and can be used as an objective evidence of reduction. Motivational interviewing (MI) is another intervention with a demonstrated ability to reduce alcohol consumption [21,22] and was proposed as a booster intervention to help maintain alcohol reduction after CM was removed. The purpose of this study was not to evaluate the effectiveness of either CM or MI as alcohol interventions (since these are already known to be effective), but rather to use the interventions as a method of experimental manipulation to produce maximal drinking reduction in the short term (30-90 days) and provide objective verification of that reduction in order to study the effects of these changes in drinking on the body.

The primary aims of the study were to determine whether CM-induced alcohol reduction would improve cognitive performance and brain function among people with HIV in as little as 30 days and up to 1 year. If the impact of alcohol on systemic and cerebral inflammation is temporary, then reducing or eliminating alcohol consumption could dramatically improve cognitive function and indices of brain health, even among people who have consumed alcohol for many years. We sought to focus the research on people with HIV, because the potential benefits from alcohol cessation may be even greater due to the interactive effects. A smaller group of persons without HIV was included as a control population. Secondary aims were (1) to determine the impact of alcohol reduction on HIV clinical status, markers of systemic inflammation, and liver fat and fibrosis; (2) to investigate factors associated with success in reducing or stopping drinking; (3) to identify mechanisms linking drinking changes to HIV-related behavior and clinical outcomes; and (4) to identify the optimal measures of individual alcohol consumption using biosensors, biomarkers, and self-report.

Methods

Study Design and Overview

This was a nonrandomized, single-arm clinical trial that used a pre-post comparison with extended follow-up. The majority of participants would be people with HIV but a subset of persons without HIV were also included as controls and to allow for subgroup comparisons. After confirming eligibility, all participants provided preintervention data and then received a CM intervention to stop or reduce drinking for 30 to 90 days, and a MI intervention 30 days after baseline. Detailed clinical and behavioral assessments were collected at baseline, 30 days, 90 days, and 12 months after enrollment. The first participant was enrolled in December 2017 and final participant data were collected in April 2022. The study procedures were modified after study initiation to include additional data related to the gut microbiome and to adapt to the COVID-19 pandemic in 2020-2022.

Ethical Considerations

Ethics approval was obtained from the institutional review boards at Florida International University (FIU; IRBSITE00000291), the University of Florida (UF; CED000000011), and the University of Miami (UM, 20170396). The study was registered at ClinicalTrials.gov (NCT03353701) in November 2017.

Recruitment and Informed Consent

Participants were recruited in the Miami Metropolitan region (Florida) from HIV clinics, community outreach, and a contract registry. Recruitment advertisements were placed on public transportation and in local HIV clinics. Potential participants were screened over the phone or in person and those initially eligible were invited to attend an enrollment visit to review procedures, obtain consent, and confirm eligibility.

Enrollment Visit

Potential participants were informed that one of the major goals of the study was to examine changes in the body after drinking reduction, and therefore they were asked to participate in a "30-Day Challenge," in which they would try to reduce or stop drinking for at least 30 days. After informed consent was obtained, participants completed a detailed assessment to determine whether they were eligible to continue with the study.

The inclusion criteria were age 45-75 years, 21 or more drinks per week for men or 14 or more drinks per week for women, confirmed HIV status (for those who reported being HIV positive), English speaking, willingness to participate in CM, and wear an alcohol biosensor for at least 30 days. Exclusion criteria included neurological disorders (eg, dementia, stroke, seizures, and traumatic brain injury); past opportunistic infection; major psychiatric disturbance (eg, severe major depression); unstable medical conditions (eg, cancer); magnetic resonance imaging (MRI) contraindications (eg, pregnancy, severe claustrophobia, metal implants, and physical impairment precluding motor response or lying still); inability to demonstrate an understanding of key aspects of the study; and currently participating in other alcohol research.

Additional assessments used to determine eligibility at this enrollment visit included the Montreal Cognitive Assessment (MoCA) [23], the Alcohol Withdrawal Symptom Checklist (AWSC) [24], and a 30-Day Drug and Alcohol Timeline Followback (TLFB) [25]. Participants with MoCA scores lower than 17 were discussed with the investigators and allowed to proceed if they could clearly discuss the study goals and purpose with the research assistants. Those with AWSC scores greater than 8 were excluded due to the high risk of alcohol withdrawal. The TLFB was used to determine the average number of drinks per week, and persons with less than 21 drinks per week (men) or 14 drinks per week (women) were also excluded from the clinical intervention at this point.

Pre-CM Test Week

At the enrollment visit, those who appeared to be eligible had the SCRAM CAM biosensor placed on their ankle. The monitor

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strap has a specialized clip that prevents removal without breaking the clip or cutting the ankle strap (and any removal sends an alert to SCRAM Systems and is viewable by the research team). The purpose of participants wearing the monitor for this week was to confirm that they did drink (for at least 3 days), they could go at least 24 hours without drinking and without withdrawal symptoms, they could tolerate wearing the SCRAM CAM, and they would communicate as expected with the research assistant. During this pre-CM phase, participants were instructed to drink as they normally would, except for at least 1 day of required abstinence (for persons who drink every day). Participants were given instructions about the monitor, including not submerging the device in water, avoiding using alcohol-based items, and not wearing socks under the monitor. A research assistant called the participant every other day to collect information on self-reported drinking and compared this information to that obtained by remote download from a cloud server from the SCRAM website. This ensured that for each participant, the monitor could accurately distinguish drinking from nondrinking days. During this pre-CM test week, participants received incentive payments for providing self-reports but no incentive for drinking behavior itself. During this pre-CM test week, some participants chose to withdraw, mostly due to not wanting to wear the ankle biosensor, and some were excluded because they did not drink enough or were not able to follow study procedures. All other people were scheduled to attend an in-person baseline assessment and to choose a specific date on which they would start the 30-Day Challenge.

Baseline Assessment

The baseline assessment included a study questionnaire, neurocognitive assessments, neuroimaging assessments, liver Fibroscan, and collection of blood, urine, and stool samples. The baseline questionnaire was completed either during the enrollment visit (before the test week) or at the baseline assessment. Participants were required to have a 0 breathalyzer reading in order to proceed with the baseline questionnaire. The primary domains of the measures and the administration schedule are in Table 1. The study questionnaire items are available from the research team upon request.

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Table 1. Summary of items assessed by study questionnaires for the 30-Day Challenge study at baseline and follow-up visits.

Domain (source)	Baseline	30 days	90 days	1 year
Sociodemographics				
Age, country of origin, race or ethnicity, sex at birth, gender, sexual orientation, education, and incarceration history	✓			
Marital status, homelessness, insurance, employment, income, and disability	✓			✓
Quality of life				
Quality of life (SF-12[a] Health Survey v1) [26]	✓	✓	✓	✓
Physical activity (Godin-Shephard Leisure-Time Physical Activity Questionnaire) [27]	✓	✓	✓	✓
HIV care and medical history				
HIV/AIDS status, ART[b] treatment adherence, and drinking impact on medication adherence	✓	✓	✓	✓
Year of first HIV positive test and HIV medications	✓			
Self-reported medical conditions and current medications	✓			
COVID-19 diagnosis history and vaccination status	✓			
Symptoms				
General symptoms (Veterans Aging Cohort Study Survey) [28]	✓	✓	✓	✓
Sleep quality-2 items (Pittsburgh Sleep Quality Assessment) [29]	✓	✓	✓	✓
Pain (Brief Pain Inventory Short Form) [30] and self-reported current and past pain treatments	✓	✓	✓	✓
Alcohol use for pain and effectiveness of alcohol use for pain	✓			
Mental health				
Anxiety (Generalized Anxiety Disorder-7) [31]	✓	✓	✓	✓
Depression (Patient Health Questionnaire-8) [32]	✓	✓	✓	✓
Posttraumatic stress disorder (PTSD; Primary Care PTSD Screen) [33]	✓	✓	✓	✓
Emotion regulation (difficulties in emotional regulation scale) [34]	✓		✓	
Childhood trauma 4 items (Childhood Traumatic Events Scale) [35]	✓			
Self-reported cognitive functioning (MOS[c] Mental Health) [36]	✓	✓	✓	✓
Substance use				
30-day alcohol and drug use timeline follow-back [25]	✓	✓	✓	✓
AUDIT-C[d] [37]	✓			✓
Alcohol use disorder assessment DSMV[e] Alcohol Assessment [38]	✓			✓
Drinking motives (Drinking Motive Questionnaire) [39]	✓			
Alcohol use of important persons (3 items), age of drinking onset, previous alcohol treatment, and expectancies about quitting drinking	✓			
Open-ended questions about expectancies and outcomes related to the 30-day challenge and any changes in drinking	✓	✓	✓	
Drug use frequency, including tobacco, readiness to quit smoking, injection drug use, noninjection drug use (Medical Monitoring Project survey) [40]	✓	✓	✓	✓
Lifetime alcohol use and alcohol drinking related to COVID-19 (adapted version of KMSK)[f,g,h] [41]	✓			
Sexual history				
Sexual behaviors (VACS[i] Patient Survey) [28] and substance use before sex	✓	✓	✓	✓
Sexual function and satisfaction—4 items (PROMIS[j] sexual function and satisfaction measures) [42]	✓	✓	✓	✓

[a]SF-12: Short Form Health Survey.

[b]ART: antiretroviral treatment.

[c]MOS: medical outcomes study.

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[d]AUDIT-C: Alcohol Use Disorders Identification Test for Consumption.

[e]DSMV: Diagnostic and Statistical Manual-V.

[f]KMSK: Kreek-McHugh-Schluger-Kellogg.

[g]Newly added to the study in revisions.

[h]Administered at other timepoints if baseline completed.

[i]VACS: Veterans Aging Cohort Study.

[j]PROMIS: Patient-Reported Outcomes Measurement Information System.

Neurocognitive Assessments

A comprehensive battery of neuropsychological measures was administered to all participants (Table 2). The National Institutes of Health (NIH) toolbox (cognition battery) was given to participants to obtain an estimate of their crystalized (2 assessments) and fluid intellect (5 assessments) [43]. Uncorrected summary scores were created for the NIH toolbox crystalized and fluid scores and further analyses of these index scores included demographic factors such as age, race, and education in the models. For follow-up cognitive assessments, we used different forms when available, because this helps reduce the magnitude of practice effects.

Due to reported participant fatigue in the early phases of the research, the initial battery was refined to be completed in 1 hour or less (we dropped the California Computerized Assessment Package [CALCAP], Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV], Brief Visuospatial Memory Test-Revised [BVMT-R]). Research assistants met with the team neuropsychologist regularly to ensure the best practices to maintain rapport and participant engagement. Reminders were given that the tests were purposefully created to be difficult, breaks were offered when somnolence was observed, and the research staff documented when people appeared to be providing limited effort. A summary of the specific neurocognitive tests and neuroimaging assessments obtained at their respective timepoints is included in Table 2.

For data analysis, the primary outcome for neurocognitive assessments is the change in performance on the 5 measures comprising the Fluid Cognition index from the NIH toolbox, which includes memory, attention, cognitive flexibility, processing speed, and executive functioning. Secondary outcomes of cognition will include changes in the other neuropsychological measures.

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Table 2. Battery of neurocognitive tests for participants in the 30-Day Challenge study[a].

Test name	Comments	Cognitive domain
NIH[b] toolbox—Fluid [43]	• Dimensional change card sort • Flanker inhibitory control and attention • Picture sequence memory • List sorting • Pattern comparison	• Executive function • Executive function and attention • Episodic memory • Working memory • Processing speed
NIH toolbox—Crystalized[c] [43]	• Picture vocab • Oral reading recognition	• Premorbid intellect
Montreal Cognitive Assessment[c] [23]	• N/A[d]	• General screen cognitive function
Trail Makings Test, Part A [44]	• Cognitive flexibility	• Graphomotor processing speed
Trail Makings Test, Part B [44]	• N/A	• Graphomotor processing speed and executive function
Stroop Test [45]	• Cognitive flexibility	• General processing speed and inhibitory function
Hopkins Verbal Learning Test-Revised (HVLT-R) [46]	• Included 3 learning trials, a delayed recall, and a recognition trial	• Verbal learning and memory
Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) [47]	• Symbol search • Digit span • Letter number sequencing	• Graphomotor processing speed • Auditory attention • Working memory
Adaptive Rate Continuous Performance Test (AR-CPT)[e] [48]	• N/A	• Maintained attention and inhibitory control
Controlled Oral Word Association Test [49]	• FAS or CFL[f]	• Language function, processing speed, and verbal fluency
Animal Fluency [50]	• N/A	• Semantic verbal fluency
Card Sorting Task[g] [51]	• N/A	• Novel problem-solving and set-shifting
Grooved Pegboard Test [52]	• N/A	• Fine motor dexterity

[a]Unless otherwise indicated, assessments were done at baseline, 30 days, 90 days, and 1 year after enrollment.

[b]NIH: National Institutes of Health.

[c]The Montreal Cognitive Assessment and the NIH Crystalized measures were only obtained at baseline.

[d]N/A: not applicable.

[e]Some participants did the California Computerized Assessment Package (CALCAP) at baseline and then switched to Adaptive Rate Continuous Performance Test at follow-ups (30 did the Adaptive Rate Continuous Performance Test at baseline).

[f]CFL: Measure of spontaneous production of words beginning with 3 letters (FAS or CFL).

[g]The Wisconsin Card Sorting Task was collected as part of the COVID-19 supplement and was completed by 20 participants.

Neuroimaging Assessments

Participants who had no contraindications underwent MRI neuroimaging at all 4 time points. Prior to the first MRI, participants were provided with instructions on the 2 functional MRI tasks. For example, they were administered the 2-back test, which required participants to view alphabets in English (ie, a stimulus) on a computer screen and indicate by clicking a button on a device held in their hand whether the currently displayed letter was the same or different from the letter that appeared 2 preceding times ago (ie, 2-back). The MRI protocol used for all 4 timepoints of this study is shown in Table 3. The total time to complete all the sequences in the MRI protocol was approximately 65 minutes.

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Table 3. Neuroimaging protocol used at all 4 timepoints for participants in the 30-Day Challenge study.

Sequence	Purpose	Measure	Anatomical coverage
T1[a] MRI[b]	To measure brain morphometric changes	Anatomical and tissue volumes and cortical thickness	Whole-brain
FLAIR[c] MRI	Identification of incidental brain pathologies	Pathology type and its volume	Whole-brain
MEGA-PRESS[d] Single-voxel MRS[e] [53]	Quantitation of changes in GABA[f] and other brain metabolites	Concentration of GABA, NAA[g], Cre[h], Cho[i], and m-Ins[j], and their ratios with Cre	Single voxel at the anterior midcingulate gyrus
2-back task-based fMRI[k]	Working memory	2-back alphabet letters	Whole-brain
Resting state fMRI	For assessment of changes in neural networks involved in the brain functional-segregation and functional-integration [54]	Functional connectivity measures for 5 major brain networks	Whole-brain
Diffusion tensor and kurtosis imaging [55]	To evaluate tissue microstructural changes	Diffusivities (axial, radial, and mean); fractional anisotropy (FA); free water fraction; kurtoses (axial, radial, and mean); kurtosis FA	Whole-brain
Whole-brain proton MR[l] spectroscopic imaging [56]	Quantitation of changes in NAA, Cre, Cho, and m-Ins metabolites	Concentration of NAA, Cre, Cho, and m-Ins, and their ratios with Cre	Whole-brain

[a]T1: spin-lattice relaxation time.

[b]MRI: magnetic resonance imaging.

[c]FLAIR: fluid attenuated inversion recovery.

[d]MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy.

[e]MRS: magnetic resonance spectroscopy.

[f]GABA: γ-aminobutyric acid.

[g]NAA: N-acetyl aspartate.

[h]Cre: total creatine.

[i]Cho: total choline.

[j]m-Ins: myo-inositol.

[k]fMRI: functional magnetic resonance imaging.

[l]MR: magnetic resonance.

The primary outcome from neuroimaging assessments is changes in brain inflammation from baseline to subsequent timepoints at the regional, tissue-type (ie, gray matter and white matter), and whole-brain levels. This outcome will be assessed from the quantitation of cerebral metabolite markers of neuroinflammation (ie, total choline and myo-inositol) and extracellular free water fraction (a measure determined from diffusion tensor imaging data). The above neuroinflammation markers will be quantified from the brain regions including the basal ganglia, thalamus, and frontal lobe that are primarily involved in HIV infection, alcohol use disorders, and their interaction [57-59]. Changes in brain function from functional magnetic resonance imaging and resting-state connectivity data will be measured for 5 major networks, that is, the default mode network, the dorsal attention network, the salience network, the limbic network, and the fronto-parietal control network.

Blood and Urine Testing

Blood samples were collected at each timepoint. Part of these were sent to a commercial laboratory for measurements of complete blood count with differential, comprehensive metabolic panel, hepatitis C antibody, HIV antibody (to confirm HIV status), HIV-1 RNA (only for people with HIV), and CD4 lymphocyte count (only for people with HIV). A dried blood spot was collected to measure phosphatidylethanol, an alcohol biomarker. We used these samples and performed measurements of cytokines, inflammatory biomarkers, adhesion molecules, and markers of intestinal permeability and microbial translocation. Additional blood samples are stored in a biorepository at the University of Louisville, where there is planned testing related to gut microbiome and gut-derived metabolites (metabolomics). Urine tests were performed at each timepoint for ethyl glucuronide (an alcohol biomarker), drug screen, and (after approximately 1 year) urine specific gravity. Urine-specific gravity was collected to ensure any potential changes in free water–based neuroinflammation (Table 4) were not solely due to brain rehydration after abstinence from alcohol.

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Table 4. Summary of additional laboratory and clinical assessments conducted during the 30-Day Challenge study[a].

Domain	Specific measures
Blood	• All participants: complete blood count, comprehensive metabolic panel, phosphatidylethanol (alcohol biomarker), hepatitis C antibody (once), HCV[b] viral load (tested in 2/5 who were HCV antibody positive). • HIV-related: HIV antibody (for those who self-reported HIV-negative). HIV viral load and CD4 lymphocyte count (for HIV-positive). • Cytokines and biomarkers of inflammation: TNF-RII[c], TNFα[d], IL-6[e], IL-10[f], IFN-γ[g] NFL[h], sCD163[i], VCAM-1, ICAM-1, sCD14, CRP[j], and LBP[k]. • COVID-19[l]: RBD[m] IgG[n] and nucleocapsid IgG (in those RBD ab positive).
Urine	• Drug screen (cocaine, methamphetamine, THC[o], MDMA[p], opioid, oxycodone, PCP[q], barbiturates, and benzodiazepines). • Specific gravity. • Urine ethyl glucuronide (at each visit and to confirm self-reported abstinence with positive alcohol biosensor).
Stool	• Gut microbiome: 16S rRNA[r] gene sequencing, relative abundance, Firmicutes/Bacteroidota ratio (F/B)
Fibroscan	• Controlled attenuation parameter (fatty liver), liver stiffness measurement (fibrosis and stiffness).

[a]Unless otherwise indicated, assessments were done at each timepoint.

[b]HCV: hepatitis C virus.

[c]TNF-RII: tumor necrosis factor receptor 2.

[d]TNFα: tumor necrosis factor α.

[e]IL-6: interleukin 6.

[f]IL-10: interleukin 10.

[g]IFNγ: interferon-γ.

[h]NFL: neurofilament light chain.

[i]sCD163: soluble CD163.

[j]CRP: C-reactive protein.

[k]LBP: lipopolysaccharide-binding protein.

[l]COVID-19 antibodies were tested on all blood samples obtained after March 1, 2020.

[m]RBD: receptor-binding domain.

[n]IgG: immunoglobulin G.

[o]THC: tetrahydrocannabinol.

[p]MDMA: methylenedioxymethamphetamine.

[q]PCP: phencyclidine.

[r]16S rRNA: 16S ribosomal RNA (or 16S ribosomal ribonucleic acid).

Stool Samples for Gut Microbiome Assessments (Metagenomic Analysis)

During the first year of the study, the research team received additional funding to add a collection of stool samples for gut microbiome assessment and to measure additional blood biomarkers related to systemic inflammation (U01AA026225). These assessments, together with a food frequency questionnaire [60], were added after 17 participants had been enrolled, but 11 provided this information at a follow-up visit. Stool samples were sent to the University of Louisville for 16S rRNA gene sequencing processing, taxonomic evaluation, and determination of longitudinal changes in bacterial composition and diversity.

A Fibroscan liver test was obtained on all participants (Fibroscan 502 Touch, EchoSens, Paris, and France with the XL probe). The 2 scores were calculated using an average of 10 assessments, fat or controlled attenuation parameter score and fibrosis or liver stiffness measurement.

Alcohol Interventions

Contingency Management

The CM period began after the completion of the baseline assessment. Initially, we sought to maintain abstinence for up to 90 days using CM payments based on reports from the ankle biosensor. After approximately 10 participants enrolled, we modified the protocol to include CM payments and ankle monitoring for only 30 days because the participants did not like to wear the SCRAM, and because the costs for both participant payments and SCRAM monitoring would exceed the awarded budget. The payment protocol followed recommended CM methods as well as prior research using the SCRAM [12,15] and incorporated information obtained from focus groups prior to initiating the study [61]. Participants would receive money for each day they were abstinent and additional bonus payments for completing 7 days of abstinence in a row. Abstinence was determined on a daily basis through ankle biosensor reports with payment amounts increasing for consecutive days. Specifically, on the first day of abstinence, a

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participant would receive US $5. For each consecutive day of abstinence thereafter (up to 7 in a row), the daily payout increased by US $1, meaning that after 7 days of abstinence, participants received a total of US $56 in daily payments plus a bonus of US $25 for maintaining abstinence for 7 consecutive days. Bonus payments increased by US $20 every 7 days up to a maximum weekly bonus of US $85. Participants received US $0 on any drinking day and the daily payment for abstinence restarted at US $5 after any drinking day. The maximum amount paid for maintaining abstinence throughout the CM period (30 days) was US $440. Participants were provided their payment as often as they wished but commonly chose to receive payments approximately once a week.

The alcohol biosensor provided data on transdermal alcohol concentration (TAC) assessed every 30 minutes. The specific TAC criteria used to differentiate a drinking day from a nondrinking day are based on several factors including peak TAC, absorption rate (rise rate), and fall rate (elimination rate). Different criteria can be used to minimize both false positives (for example, if alcohol is spilled on the device) and false negatives (for example, a participant may drink but not enough to reach a threshold level TAC). Our research team used the software (Transdermal Alcohol Sensor Data Macro [TASMAC] [62]) developed to identify drinking episodes on any given day (6 AM-6 AM), using more sensitive criteria than SCRAM Systems to detect drinking days (ie, peak TAC of at least 0.02 g/dL and either an absorption rate for the episode <0.05 g/dL per hour or an elimination rate for the episode <0.025 g/dL per hour [when peak <0.15 g/dL] and less than 0.035 g/dL per hour [when peak >0.15 g/dL]) [15]. If participants reported abstinence when alcohol was detected via the biosensor, the participants were given the opportunity to provide a negative in-person urine sample using dipstick ethyl glucuronide testing within 2 days of the SCRAM positive reading to maintain their CM payments.

Motivational Interview

During the 30-day visit, participants completed a single session of MI by videoconference using a computer within the clinical research setting. The MI was provided by a male, masters-level trained counselor at Brown University who had undergone over 20 hours of training in MI and had prior experience delivering MI. The MI session included a discussion of initial motivations for participating in the study, a review of the participant's drinking behavior prior to and during the 30-Day Challenge, a discussion of the perceived benefits of changing drinking, steps taken to reduce drinking successfully during CM, and creation of a change plan, which included discussion of future goals around drinking and brief problem-solving around meeting those goals. The MI assessments took approximately 30-45 minutes and were recorded and transcribed for further analysis. Every other week, a clinical supervisor with over 10 years of experience supervising MI counselors would listen to a session, if available, and provide feedback on MI counseling skills.

Follow-Up

Safety and Fidelity Monitoring

Several safety monitoring procedures were included in the protocol. A research assistant contacted participants on the first 3 days of CM to monitor for alcohol withdrawal symptoms. Research staff also collected self-reported data on drinking several times a week and helped with adjustments of the SCRAM monitor for comfort when needed. A study physician reviewed all laboratory results and participants were notified and referred to their physician for the occasional clinically significant laboratory finding. Potential adverse events were discussed with the research team and study principal investigators on a regular basis. During the first 3 years of the study, if research assistants noted anything that looked suspicious on neuroimaging, a radiologist was consulted, and participants were provided with information to discuss with their physician. For post–COVID-19 assessments, a clinical neuroradiologist reviewed every scan for clinically significant findings. No participants experienced serious alcohol withdrawal, and 1 participant was referred to their physician due to an abnormality found on brain MRI. To monitor fidelity to the research protocol, all research staff completed training and demonstrated the ability to do each of the study assessments. A senior research coordinator from our central coordinating team in Gainesville provided site monitoring in Miami 2-3 times per year.

Follow-Up Visits

Participants returned for in-person assessments at 30 days, 90 days, and 1 year. At each timepoint, updated alcohol consumption data were obtained, and the majority of the baseline measures were repeated (see Tables 2-4). The SCRAM monitor was removed at the 30-day visit for most participants (n=47), whereas 10 participants wore if for 90 days. Stool samples for gut microbiome assessments were obtained at baseline (n=40), 30 days (n=36), 90 days (n=36), and 1 year (n=23).

Procedures to Enhance Follow-Up

The study research staff communicated with participants regularly during the first 30 days (during the CM period) and scheduled follow-up visits in advance. Reminder calls were made to enhance adherence to follow-ups, which included additional participant incentives. The window period around each follow-up included at least 1 week before and 2 weeks after the scheduled appointment period.

Modifications After Study Initiation

Duration of CM

Prior to study initiation, the research team was encouraged by NIH peer grant reviewers and a scientific advisory board to extend the CM (and ankle biosensor monitoring) to 90 days, because it was not known whether any benefits of alcohol cessation or reduction would be fully achieved by 30 days or if a longer period would result in further improvements. A total of 10 of the initial participants chose to continue CM payments and ankle monitoring for 90 days, but many declined to continue monitoring and nearly every participant complained about some aspect of wearing the ankle biosensor. Also, extending the CM from 30 to 90 days added substantially to the cost of the study (participant payments and SCRAM monitoring fees), and with input from an external scientific advisory board, the research team modified the protocol to its original plan of CM payments only to 30 days.

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COVID-19–Related Modifications

All in-person research activities were halted for 3 months starting in March 2020, with limited in-person data collection beginning again in June 2020, and MRI studies resuming in July 2020. Study procedures were modified to include remote data collection, and 3 participants provided follow-up data remotely during this period. An NIH COVID-19 funding supplement supported the collection of qualitative data from a subset of participants, additional post–COVID-19 study assessments for interested participants, pilot-testing of remote neurocognitive assessments, and the testing of participant blood samples for COVID-19 antibodies. The research team ultimately decided that remote neurocognitive assessments could not be directly compared to the same assessments conducted face-to-face, and thus neurocognitive and neuroimaging data are missing from some participants at timepoints early during the COVID-19 pandemic in 2020.

Planned Data Analysis

Overview

For our primary exposure variable (change in alcohol consumption), the primary assessment will focus on the average self-reported number of drinks per week during the 4-weeks prior to each timepoint (baseline, 30 days, 90 days, and 1 year), and in changes in self-reported number of drinks per week. Secondary metrics of drinking at each time point will include the number of heavy drinking days (previous 30 days), and categorical definitions of drinking status based on current National Institute on Alcohol Abuse and Alcoholism (NIAAA)–recommended drinking amounts (heavy, mild or moderate drinking, and no drinking). We plan to validate the self-reported measures with other measures of alcohol consumption, especially the SCRAM TAC readings (only collected for 7 days preintervention through 30 days for most participants).

Cross-sectional analyses are planned to compare characteristics of persons at baseline (eg, people with HIV vs controls), and to determine the association of alcohol consumption and potential confounding variables with key outcomes including gut microbial dysbiosis, neurocognition, neuroinflammation, biomarkers of systemic inflammation, Fibroscan liver scores, and HIV-related outcomes.

Longitudinal analyses will assess the relationships between changes in drinking and changes in each of the main clinical outcomes. For each main outcome, we will consider potential confounding variables and whether those are fixed or changing over time. Baseline values will be controlled in the longitudinal analyses. Multiple testing will be adjusted by the false discovery rate approach [63]. Missing data that are considered to be missing at random will be handled by multiple imputation or EM algorithms. Missing data that are considered to be nonignorable missing or missing not at random will be handled with pattern-mixture models.

Sample Size

This study was originally approved to recruit 180 participants (140 people with HIV and 40 without HIV). However, the COVID-19 pandemic, availability of research staff and neuroimaging appointments, and reluctance of people to wear the ankle biosensor substantially impacted recruitment. Final enrollment numbers are detailed in Figure 2 and input from the scientific advisory board was obtained prior to cessation of enrollment and data collection.

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Figure 2. Flowchart of participants evaluated and enrolled in the 30-Day Challenge study. AWSC: Alcohol Withdrawal Symptom Checklist; CM: contingency management; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging.

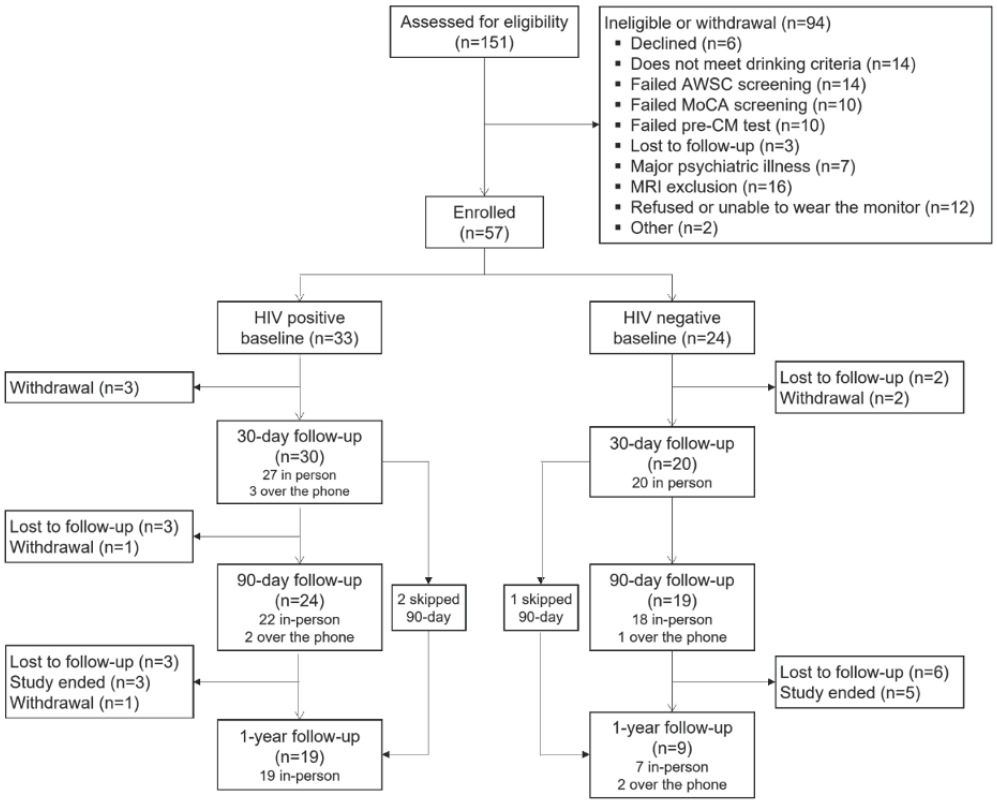

Results

Recruitment of participants began in December 2017 and ended in October 2021. Data collection was completed in April 2022. Baseline characteristics of 57 participants who initiated the 30-day challenge, including persons with and without HIV, are presented in Table 5. Of the 57 participants who initiated the 30-Day Challenge, 88% completed the 30-day follow-up, 75% completed the 90-day follow-up, and 49% completed the 1-year follow-up.

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Table 5. Participant baseline characteristics in the 30-Day Challenge study (N=57).

Characteristics	Total (N=57)	Persons with HIV (n=33)	Persons without HIV (n=24)
Gender, n (%)			
Man	36 (63)	19 (58)	17 (80)
Woman	20 (35)	13 (39)	7 (29)
Transgender	1 (2)	1 (3)	0
Age (years)			
Range	48-67	48-66	48-67
Mean (SD)	55.9 (4.6)	55.5 (4.3)	56.5 (5.1)
Race or ethnicity, n (%)			
Non-Hispanic, White	6 (10)	3 (9)	3 (12)
Non-Hispanic, Black	44 (77)	27 (82)	17 (71)
Hispanic	7 (12)	3 (9)	4 (17)
Marital status[a], n (%)			
No	47 (82)	25 (76)	22 (92)
Yes	10 (18)	8 (24)	2 (8)
Education, n (%)			
Less than high school	18 (32)	13 (39)	5 (21)
High school graduate or GED	19 (33)	6 (18)	13 (54)
More than high school	20 (35)	14 (42)	6 (25)
Homeless in the past 12 months, n (%)			
No	50 (88)	29 (88)	21 (88)
Yes	7 (12)	4 (12)	3 (12)
Employment, n (%)			
Not employed	11 (19)	6 (18)	6 (21)
Employed	13 (23)	4 (12)	9 (38)
Unable to work or disabled	33 (58)	23 (70)	10 (42)
Anxiety[b], n (%)			
None to minimal	29 (51)	15 (46)	14 (58)
Mild	17 (30)	11 (33)	6 (25)
Moderate	7 (12)	4 (12)	3 (12)
Severe	4 (7)	3 (9)	1 (4)
Depression[c], n (%)			
None or minimal	30 (53)	18 (55)	12 (50)
Mild	16 (29)	8 (24)	8 (33)
Moderate	5 (9)	4 (12)	1 (4)
Moderately severe or severe	6 (10)	3 (9)	3 (12)
Alcohol use disorder[d], n (%)			
No	5 (9)	4 (12)	1 (4)
Mild	6 (10)	3 (9)	3 (12)
Moderate	10 (18)	9 (27)	1 (4)
Severe	36 (63)	17 (51)	19 (79)

[a]Married or living with a long-term partner.

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[b]Measured by the Generalized anxiety disorder 7-item scale (GAD-7); scores of 5-9=mild, 10-14=moderate, and ≥15=severe.

[c]Measured by the Patient Health Questionnaire-8; scores of 0-4=none or minimal, 5-9=mild, 10-14=moderate, and ≥15=moderately severe or severe.

[d]Measured by diagnostic and statistical manual-V (DSMV) Alcohol Assessment; scores of 0-1=no, 2-3=mild, 4-5=moderate, and ≥6=severe.

Discussion

Previous research on the impact of alcohol on HIV infection has been primarily observational, making it hard to determine whether outcomes associated with alcohol consumption are caused by the alcohol itself. We designed an experimental research study to obtain stronger evidence on whether changes, and specifically, reductions in drinking would correlate with changes in other behavioral or biological processes in the body. The study is unique from other research studies that examined changes in drinking and changes in clinical outcomes. Previous studies examining neurocognitive changes have primarily enrolled persons who were initiating alcohol treatment or included persons without HIV. Other strengths of the study include the simultaneous collection of a range of biological and behavioral data from several time points, including alcohol consumption, cognitive assessments, neuroimaging, Fibroscan liver test, blood biomarkers, and longitudinal changes in gut microbial dysbiosis.

Challenges in the study included recruitment, the complexity of research activity involving several universities and institutional review boards, staff turnover (and delays in replacing staff), participant willingness to wear the ankle biosensor, coordination of study procedures across several settings, and locations for persons who are often without their own transportation. Also, the number of assessments collected at each timepoint led to the decision to collect data over 2 days rather than 1, which limited our ability to enroll more participants. Future research teams should consider the tension between the value of having additional assessments versus the cost savings and convenience of collecting research study data over a single day (rather than spread across 2 days).

The COVID-19 pandemic, starting in early 2020, had a major impact on the study procedures and enrollment. A second clinical research setting was prepared to begin recruitment and data collection in early 2020, but by the time most research activities could be resumed after the COVID-19 pandemic, the study procedures had begun to wind down.

Another limitation of the study is that persons at high risk of alcohol withdrawal were excluded. The research team developed a protocol to enroll drinkers at higher risk of alcohol withdrawal but ultimately decided the risks and complexity outweighed the benefits.

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VLR was affiliated with Southern HIV and Alcohol Research Consortium, University of Florida, Gainesville, FL, United States at the time of the study and is currently affiliated with Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, University Park, PA, United States

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the National Institutes of Health.
[PDF File (Adobe PDF File), 177 KB - resprot_v13i1e53684_app1.pdf]

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Abbreviations

AWSC: Alcohol Withdrawal Symptom Checklist
BVMT-R: Brief Visuospatial Memory Test-Revised
CALCAP: California Computerized Assessment Package
CM: contingency management
FIU: Florida International University
MI: motivational interviewing
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIH: National Institutes of Health
SCRAM CAM: Secure Continuous Remote Alcohol Monitor Continuous Alcohol Monitoring
TAC: transdermal alcohol concentration
TASMAC: Transdermal Alcohol Sensor Data Macro
TLFB: 30-Day Drug and Alcohol Timeline Followback
UF: University of Florida
UM: University of Miami
WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition

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Protocol

Personalized Management of Fatigue in Individuals With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Using a Smart Digital mHealth Solution: Protocol for a Participatory Design Approach

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Abstract

Background: Fatigue is the most common symptom in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID, impacting patients' quality of life; however, there is currently a lack of evidence-based context-aware tools for fatigue self-management in these populations.

Objective: This study aimed to (1) address fatigue in ME/CFS and long COVID through the development of digital mobile health solutions for self-management, (2) predict perceived fatigue severity using real-time data, and (3) assess the feasibility and potential benefits of personalized digital mobile health solutions.

Methods: The MyFatigue project adopts a patient-centered approach within the participatory health informatics domain. Patient representatives will be actively involved in decision-making processes. This study combines inductive and deductive research approaches, using qualitative studies to generate new knowledge and quantitative methods to test hypotheses regarding the relationship between factors like physical activity, sleep behaviors, and perceived fatigue in ME/CFS and long COVID. Co-design methods will be used to develop a personalized digital solution for fatigue self-management based on the generated knowledge. Finally, a pilot study will evaluate the feasibility, acceptance, and potential benefits of the digital health solution.

Results: The MyFatigue project opened to enrollment in November 2023. Initial results are expected to be published by the end of 2024.

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Conclusions: This study protocol holds the potential to expand understanding, create personalized self-management approaches, engage stakeholders, and ultimately improve the well-being of individuals with ME/CFS and long COVID.

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KEYWORDS

acceptability; myalgic encephalomyelitis/chronic fatigue syndrome; long COVID; mHealth; fatigue; physical activity; lifestyle health; personalized self-management; user-centered design

Introduction

Overview

Fatigue is recognized as one of the most common symptoms in individuals with chronic postviral conditions. It is defined as the early onset of tiredness after starting an activity, a feeling of exhaustion or difficulty in carrying out a physical (physical fatigue) or cognitive (cognitive fatigue) task, which is not recovered after a rest [1]. It is relevant to highlight several issues included in this definition. First, fatigue is a consequence of carrying out an activity, also referred to in the scientific literature as "postexertional malaise." Furthermore, patients experience two different types of fatigue—physical and cognitive. Finally, fatigue is essentially a subjective condition, encompassing feelings or difficulties. Thus, it is linked to perceived fatigue, which is defined as the subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [1]. Myalgic encephalomyelitis, also known as chronic fatigue syndrome (ME/CFS) and post–COVID-19 syndrome or postacute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID, are multisystem postviral conditions where chronic fatigue is present as the most common disabling symptom. ME/CFS is a complex, multisystem, and profoundly debilitating neuroimmune condition. Although individuals with ME/CFS experience several symptoms, fatigue is the most disabling one [1].

Some symptoms associated with the SARS-CoV-2 infection may persist for a significant period. Long COVID or PASC is an umbrella term for the wide range of health consequences that are present 4 or more weeks after SARS-CoV-2 infection. Most cases infected with SARS-CoV-2 are asymptomatic or have mild acute symptoms with low rates of hospitalization and death. However, some of them, including those with mild or asymptomatic infection, develop postacute manifestations following SARS-CoV-2 infection. There are many symptoms presented in PASC, such as sleep difficulties and anxiety or depression [2], with fatigue being the most frequently reported.

The extent of fatigue in patients' lives is huge, affecting their physical, cognitive, and socioeconomic conditions [3]. It affects several aspects of life, including physical and cognitive activity, decreasing adherence to treatments and recommendations, and affecting the ability to function or work. In addition, it is normally misunderstood by the social environment, causing isolation and frustration. Therefore, fatigue strongly affects patients' well-being and significantly reduces their quality of life.

The effective fatigue management of ME/CFS and long COVID would minimize the consequences of the disease, significantly impacting patients' and caregivers' quality of life. The clinical evolution of ME/CFS and long COVID is still unpredictable. Recommendations and strategies should consider the individual's physical and cognitive capabilities and other factors, such as daily perceived fatigue fluctuations, meteorological condition, level of physical activity, caffeine and alcohol consumption, sleep quality, mood, stress, and treatments. Many of those factors present a wide daily variability, and therefore, personalization must be driven by real-time data collected in a patient's real-life setting. An effective personalization strategy may help to increase compliance with management recommendations and strategies.

Digital health allows the implementation of interesting functionalities for the management of long-term conditions, such as tracking activities, remote monitoring of an individual's condition, real-time feedback, just-in-time recommendations, communication, educational content, and reminders. Digital health solutions have proven to be effective in the management of some chronic diseases, such as diabetes and cancer. Therefore, they may be effective as a self-management tool for individuals with ME/CFS or long COVID. Several recent studies have explored the effectiveness of internet-based cognitive behavioral therapies in fatigue management among individuals with ME/CFS [4,5]. Despite the potential benefits of digital health solutions for the self-management of ME/CFS and long COVID, there are no evidence-based, personalized, and context-aware solutions designed specifically for supporting patients with ME/CFS or long COVID in fatigue self-management.

Current Status

Despite the promising benefits of using digital health for the self-management of chronic diseases, there is a lack of studies exploring the specific needs and preferences of individuals with ME/CFS or long COVID haulers regarding digital fatigue self-management. Only 1 study examined how adolescents use the internet to cope with ME/CFS [6]. Moreover, there is a lack of evidence on how digital health may benefit fatigue self-management in this group of patients.

Remote monitoring in real-time is a relevant functionality to personalize fatigue self-management in ME/CFS and long COVID. Several studies that remotely monitor the health conditions of patients with ME/CFS in real-time using mobile health (mHealth) devices have been recently published. Worm-Smeitink et al [5] conducted an ecological momentary assessment (EMA) study aimed to explore the associations

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between cognitions, physical and cognitive activity, social behaviors and their effects, as well as fatigue in ME/CFS. King et al [7] used an accelerometer device to objectively measure the physical activity of patients with ME/CFS, intending to classify them into different categories. Palombo et al [8] used a commercial inertial measurement unit to develop a sensor-based method to measure an indicator of ME/CFS disease severity. Josev et al [9] used an actigraphy device to measure the sleep quality of the pediatric ME/CFS population. Russell et al [10] examined the relationship between subjective and actigraphy-defined sleep and next-day fatigue in ME/CFS. However, to our knowledge, there are no studies examining the impact of a combination of contextual factors, physical activity level, sleep quality, and mood on the fatigue severity in ME/CFS and long COVID. Moreover, there are no studies focused on analyzing the similarities and differences in fatigue between ME/CFS and long COVID. Analyzing these contextual data and their relationships with perceived fatigue severity using artificial intelligence (AI) models may enable the definition of successful data-driven personalization strategies for fatigue self-management in ME/CFS and long COVID, leading to an increase in patients' adoption and adherence.

Finally, AI models developed in ME/CFS and long COVID are focused on diagnosis, biomarkers, differentiating from other diseases, prevalence estimation, and association with anxiety or depression symptoms [11,12]. Therefore, there are no AI models to estimate fatigue severity based on contextual and behavioral factors in ME/CFS and long COVID.

Hypothesis

Although the use of digital solutions to self-manage fatigue among people with chronic conditions, such as multiple sclerosis, has been previously studied, the wide range of potential symptoms and their unpredictability and variability in ME/CFS and long COVID define a completely different scenario, posing new challenges to be solved. In addition, the similarities and differences between fatigue in ME/CFS and long COVID are still unknown, and there is a need for new research aimed at discovering them and translating them into actionable recommendations to manage fatigue in long COVID. Defining effective fatigue self-management in ME/CFS and long COVID is crucial to increasing patients' adherence to treatment, reducing mental health problems, and improving individual's well-being and quality of life. The MyFatigue project will progress beyond the state of the art on ME/CFS and long COVID fatigue self-management, providing new insights and actionable recommendations to fill in the gap.

We hypothesize that the use of a personalized and context-aware digital health solution supporting individuals with ME/CFS or long COVID in fatigue self-management increases their self-efficacy, reduces the risk of having mental health problems, and improves their quality of life. We also hypothesize that fatigue in ME/CFS and long COVID presents similar patterns regarding contextual factors.

The MyFatigue project will generate new knowledge on the relevance and relationships of factors impacting perceived fatigue severity in ME/CFS and long COVID, analyzing similarities and differences between both study populations. MyFatigue will also explore the specific needs and preferences of individuals with ME/CFS and long COVID haulers for digital health solutions, supporting fatigue self-management. Based on this knowledge, a personalized and context-aware solution supporting patients in their fatigue self-management will be co-designed, and its acceptance and potential benefits will be assessed.

Aims and Research Questions

The general aim of the MyFatigue project is to contribute to the understanding of fatigue in ME/CFS and long COVID, a modern medical challenge still unresolved, and to find opportunities for designing digital health solutions and supporting self-management to improve individuals' quality of life. The specific aims of this study are as follows:

1. To identify attitudes of patients with ME/CFS and long COVID haulers toward the use of digital health solutions, supporting them in fatigue self-management and their specific needs and preferences
2. To determine the current digital health solutions being used by individuals with ME/CFS and long COVID haulers in their self-management
3. To analyze the relevance of contextual factors and behaviors in the perceived fatigue severity, their daily fluctuations, and their relationships
4. To identify similarities and differences in fatigue symptoms between ME/CFS and long COVID
5. To define patient clusters based on fatigue patterns and to identify relevant factors impacting each cluster
6. To predict the perceived fatigue severity based on real-time data on contextual factors, behaviors, and individuals' conditions collected in real-life settings
7. To determine the feasibility, acceptance, and potential benefits of the use of a personalized and context-aware digital health solution for fatigue self-management in ME/CFS and long COVID

Participants and Methods

Ethical Considerations

Ethical approval will be sought before beginning the recruitment of participants. Written informed consent will be sought from all study participants before the initiation of participant-related study activities, such as the implementation and evaluation of the personalized digital mHealth-solution–based management intervention.

Participant Recruitment and Study Design

Health care institutions, such as Hospital Universitario Virgen del Rocío and Hospital Universitari Vall d'Hebron, are involved in the MyFatigue project. The proposed studies will be conducted in both institutions. Individuals with ME/CFS and long COVID haulers will be invited to participate in these studies. For all the proposed studies, a sample of individuals with ME/CFS and another sample of individuals with long COVID haulers will be recruited in each hospital for each study. In the proposed study, to reach specific aims 3 and 4, a supplementary sample of control healthy individuals, exhibiting

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similar sedentary behaviors to those with ME/CFS and long COVID, will be recruited in each site.

Eligibility Criteria

Potential participants should have been diagnosed with ME/CFS (based on the 1994 Fukuda case definition) or long COVID (based on the 2021 World Health Organization clinical case definition), be older than 18 years at the time of recruiting, have none to moderate physical disability, and have communication ability in Spanish. Several factors, such as age and gender, will be considered to ensure a rich sample for analysis. Project objectives, risks, benefits, and their rights as research participants will be explained to potential participants. An information sheet will be provided to the participants, and they will sign an informed consent, indicating that they will be able to withdraw from the study at any time**.**

The work plan and tasks for the MyFatigue project are presented in Figure 1.

Figure 1. MyFatigue work plan. EMA: ecological momentary assessment.

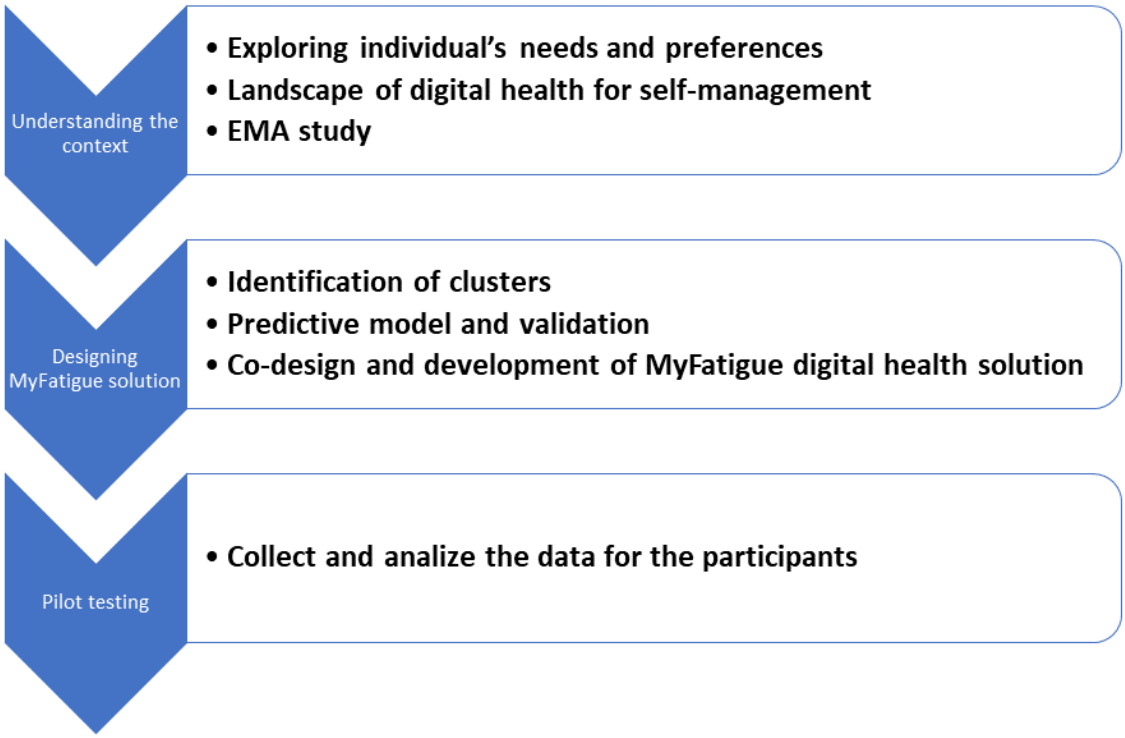

Understanding the Context

Exploring Individuals' Needs and Preferences

A mixed methods study design using qualitative and quantitative methods will be conducted to reach the first objective. Individual semistructured interviews will be carried out with each sample of participants. Once participants sign the informed consent, a face-to-face semistructured interview will be conducted, with a remote interview when an in-person meeting is not possible. An experienced interviewer will lead the interview following the script defined in the protocol. Initially, the defined questions will be inquired during the session. Interesting topics not initially included will be identified and added iteratively to be used during the following sessions. In the same way, irrelevant questions will be removed as the study progresses. All sessions will be recorded, digitally transcribed, and anonymized. Transcripts will be coded, and thematic analysis will be performed in an iterative process. Each participant's comment will be categorized as barriers or facilitators. Further refinement will take place by merging and removing redundant themes until consensus is reached.

Once data analysis ends, the findings will be discussed among all team members participating in the task. A deeper analysis of similarities and differences between findings found in ME/CFS and long COVID will be performed. We will also compare these findings with the findings in the study that is being conducted on multiple sclerosis. Once consensus is reached, we will validate the findings involving some of the participants in the interviews. We will apply a gender perspective in recruitment, data analysis, interpretation of findings, and validation of results.

Landscape of Digital Health for Self-Management

A patient survey will be designed by a group of experts involving health care professionals and computer engineers. The survey will aim to analyze the technological solutions that individuals with ME/CFS and long COVID haulers are currently using to self-manage their conditions, especially fatigue. The questionnaire will include sociodemographic variables, disease-related data, and respondents' general opinions on digital health solutions. It will also include questions about digital literacy and access, the advantages and disadvantages of using technology for fatigue management, perceived barriers in the use of these devices, personal data management, and general functionalities.

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Anonymized data will be collected, complying with the current regulations. Web-based questionnaires will be tested on a group of individuals with ME/CFS or long COVID and on professionals to optimize format and wording and to assess their usability before their large-scale administration. Discrepancies among reviewers' comments will be solved by consensus, and a final version of the questionnaire will be developed including the reviewers' suggestions. Participation will be voluntary and anonymous, and duplicate responses will be avoided. Data collected through the questionnaires will be analyzed, and descriptive statistics will be calculated using frequencies and cross-tabulations by key demographic and disease-related variables. Age and gender will be taken into consideration during the analysis. We expect the participation of at least 20 individuals per group (ME/CFS and long COVID).

EMA Study

The proposed quantitative study is based on EMA and continuous data collection using wearable devices (eg, Actigraphy GT3X). The research team has developed a mobile app that enables the remote monitoring of individuals' conditions through a questionnaire. The MyFatigue app will be developed to perform the EMA study. The app will allow participants to self-report fatigue severity during periods when they are not wearing the device required to distinguish low levels of activity from noncompliance, among other factors. The proposed study will begin with one-to-one introductory sessions during which the app and wearable device will be provided. They will be instructed about its use, and their demographic and relevant clinical data will be collected. Finally, participants will complete a set of standard questionnaires to define a baseline. The questionnaires to be filled include the Chalder Fatigue Questionnaire (CFQ), the Modified Fatigue Impact Scale (MFIS-5), the eHealth scale, the Satisfaction with Life Scale (SWLS), The Pittsburgh Sleep Quality Index (PSQI), and the Hospital Anxiety and Depression Scale (HADS). Participants will wear the device and self-report using the app for 14 consecutive days. They will be asked to carry out their regular daytime activities and to keep their usual sleep or wake schedules. The study will be conducted in 4 waves, collecting data in different seasons and avoiding insufficient data due to device failure or losses. We estimate that 120 individuals will participate in each wave. Participants will report the perceived fatigue severity using this app, by responding to a single-item questionnaire. At least, 3 self-reports per day (morning, afternoon, and evening) will be carried out, prompted by the app. Participants will be able to set reminders, postpone them, and silence them, if necessary. Moreover, they can carry out additional self-reports if they feel fatigued. Additionally, the app will collect data on potential factors like temperature, meteorological conditions, mental activity level, and mood.

Physical activity and sleep data will be continuously recorded using an actigraphy device worn on the dominant wrist. The device will be set to record in 1-minute epochs using zero crossing mode. Actigraphy data will be analyzed using a specific software, such as ActiLife. Raw data will be converted to counts, which will be analyzed to identify and calculate different physical activity variables. The intensity and absence of activity will be classified according to Fjeldstad et al [13] and based on the following cut-off points: sedentary (<1.5 metabolic equivalent of task [MET]: 0-199 counts per minute [CPs]); light (1.5-2.99 MET: 200-1952 CPs); moderate (3-5.99 MET: 1953-5724 CPs); hard (6.0-8.99 MET: 5725-9498 CPs); and very hard (>9.0 MET: > 9498 CPs). Other data, such as light conditions, environmental temperature, systolic blood pressure and diastolic blood pressure, heart rate, and heart rate variability could be collected if selected devices and budget allow it.

Descriptive statistics will be calculated, and Pearson correlation analysis will be performed among physical activity, sleep variables, and fatigue severity. Similarities and differences between ME/CFS and long COVID will be identified. Once the study period ends, a new in-person session will be conducted in which participants will return the device and fill out a questionnaire to identify any barriers they found in the use of the digital health solutions used in the EMA study. As a result of this task, a report on the statistical analysis findings will be delivered.

Designing the MyFatigue Digital mHealth Solution

Identification of Clusters

As a first step, we will identify and validate clusters in data collected based on patients who present similar fatigue patterns, considering the contextual data collected. The clusters will be identified using unsupervised learning algorithms and validated with 2 different methodologies. A validation based on a graphical representation will be conducted, and some groups of clusters could be discarded. The remaining groups of clusters will be validated and selected using the following process: first, the research team members with experience in AI will review them and assess their representativeness of the collected data; then, the groups that better represent the collected data and clusters that are easier to understand will be selected by consensus; next, a definition of persona (a representation of a group of patients) for each cluster will be developed; then, a validation through a participatory workshop involving health care professionals of the research team will be conducted.

Predictive Modelling and Validation

To estimate the relationships between perceived fatigue severity and the remaining variables included in the data set and to estimate the fatigue severity, an analysis will be performed using blocks based on the definition of temporal windows. We will develop 2 interpretable models for fatigue severity forecasting: one using decision tree algorithms and the other using autoregressive integrated moving averages. The models will be validated through cross-validation, and their performance will be compared.

Co-Design and Development of the MyFatigue Digital Health Solution

The proposed solution will be developed following user-centered design (UCD), using a co-design workshop that involves patients in the design process. This involvement will present challenges because of the combination of symptoms that patients may present. Cognitive fatigue could pose a great challenge because fatigue severity may increase rapidly when individuals engage in dialogues with multiple participants. We will define a

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workshop plan that controls the number of activities to be done, plans frequent breaks, and limits the number of participants in each session. Once the session ends, we will send a questionnaire to participants in which we will ask them to assess the barriers and advantages that they found during the session. Based on UCD, the collected data will be analyzed to identify relevant aspects and challenges in involving individuals with fatigue and other symptoms in the design process and steps to successfully address them. Following our research through a design method based on UCD, we will design and develop a prototype of the MyFatigue digital health solution. This prototype will be evaluated by experts to assess its usability, accessibility, and appropriateness for patients with ME/CFS and long COVID haulers.

Pilot Study

Through an initial in-person session, a member of the research team will provide the required device to participants and support them in the installation and configuration of the MyFatigue digital health solution. The researcher will also instruct participants on how they must process during their participation in the pilot study. A sheet summarizing those instructions and a tutorial on the MyFatigue digital health solution will be provided to participants. The pilot study will last 4 months. User logs for each participant will be saved in the MyFatigue database. After this period a new in-person session will be conducted in which a team member will ask participants to fill in an acceptance questionnaire and several standard questionnaires to assess the level of anxiety or depression, health-related quality of life, and the frequency or severity of fatigue. The acceptance questionnaire will be designed and validated by experts based on the Technology Acceptance Model. The collected data will be analyzed for each group of participants, paying special attention to relevant issues such as age and gender. Similarities and differences between both diseases will be explored.

Results

The MyFatigue project started in September 2022. Intensive administrative tasks alongside technological advancements have been underway, including the development of the web server and mobile app, as well as comprehensive literature review to identify and select appropriate questionnaires and hardware (eg, actigraphy devices) to be used for the project. The project is expected to be concluded in 2025, and initial findings would likely be published by the end of 2025.

Discussion

Expected Outcomes

The MyFatigue project aims to make a significant scientific and technical impact in the field of ME/CFS and long COVID. It seeks to advance the understanding of fatigue by investigating the influence of contextual and behavioral factors on its severity and identifying similarities and differences between ME/CFS and long COVID symptoms. Additionally, the project aims to develop intelligent personalized fatigue self-management methodologies using digital health and patient-reported outcomes, leading to the creation of new personalized management strategies for these conditions.

The project also emphasizes the social and economic impact it intends to generate based on the theory of change, which is a methodology or criterion for planning, participation, adaptive management, and evaluation for promoting social change. By involving people with ME/CFS and long COVID as well as health care professionals in participatory research activities, the project aims to promote mental health and well-being, aligning with the Sustainable Development Goal target 3.4. Through training activities and dissemination efforts, the project aims to increase empowerment and self-efficacy among people with these conditions, potentially reducing the risk of mental health problems.

The MyFatigue project expects to have a positive impact on the quality of life of patients with ME/CFS and long COVID. The project will track impact indicators, such as the number of individuals who experience increased empowerment and self-efficacy, the number of students completing the Massive Open Online Course training, and the number of people who reduce their risk of mental health problems by 20% after participating in the project's activities.

Conclusions

The result of the described study has the potential to advance knowledge, develop personalized management strategies, involve stakeholders, and contribute to improving the well-being of individuals with ME/CFS and long COVID.

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Data Availability

Data sharing is not applicable to this manuscript, as no data sets were generated or analyzed during the development of this protocol. Once data collection begins, all investigators will have access to anonymized patient-level data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Spanish Ministry of Science and Innovation (Spanish).
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e50157_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Spanish Ministry of Science and Innovation (English).
[PDF File (Adobe PDF File), 196 KB - resprot_v13i1e50157_app2.pdf]

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Abbreviations

AI: artificial intelligence
CFQ: Chalder Fatigue Questionnaire
CP: count per minute
EMA: ecological momentary assessment
HADS: Hospital Anxiety and Depression Scale
ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome
MET: metabolic equivalent of task
MFIS-5: Modified Fatigue Impact Scale
mHealth: mobile health
PASC: postacute sequelae of SARS-CoV-2
PSQI: Pittsburgh Sleep Quality Index
SWLS: Satisfaction with Life Scale
UCD: user-centered design

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Protocol

Development and Pilot-Testing of an Optimized Conversational Agent or "Chatbot" for Peruvian Adolescents Living With HIV to Facilitate Mental Health Screening, Education, Self-Help, and Linkage to Care: Protocol for a Mixed Methods, Community-Engaged Study

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Abstract

Background: Adolescents living with HIV are disproportionally affected by depression, which worsens antiretroviral therapy adherence, increases viral load, and doubles the risk of mortality. Because most adolescents living with HIV live in low- and middle-income countries, few receive depression treatment due to a lack of mental health services and specialists in low-resource settings. Chatbot technology, used increasingly in health service delivery, is a promising approach for delivering low-intensity depression care to adolescents living with HIV in resource-constrained settings.

Objective: The goal of this study is to develop and pilot-test for the feasibility and acceptability of a prototype, optimized conversational agent (chatbot) to provide mental health education, self-help skills, and care linkage for adolescents living with HIV.

Methods: Chatbot development comprises 3 phases conducted over 2 years. In the first phase (year 1), formative research will be conducted to understand the views, opinions, and preferences of up to 48 youths aged 10-19 years (6 focus groups of up to 8 adolescents living with HIV per group), their caregivers (5 in-depth interviews), and HIV program personnel (5 in-depth interviews) regarding depression among adolescents living with HIV. We will also investigate the perceived acceptability of a mental health chatbot, including barriers and facilitators to accessing and using a chatbot for depression care by adolescents living with HIV. In the second phase (year 1), we will iteratively program a chatbot using the SmartBot360 software with successive versions (0.1, 0.2, and 0.3), meeting regularly with a Youth Advisory Board comprised of adolescents living with HIV who will guide and inform the chatbot development and content to arrive at a prototype version (version 1.0) for pilot-testing. In the third phase (year 2), we will pilot-test the prototype chatbot among 50 adolescents living with HIV naïve to its development. Participants will interact with the chatbot for up to 2 weeks, and data will be collected on the acceptability of the chatbot-delivered depression education and self-help strategies, depression knowledge changes, and intention to seek care linkage.

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Results: The study was awarded in April 2022, received institutional review board approval in November 2022, received funding in December 2022, and commenced recruitment in March 2023. By the completion of study phases 1 and 2, we expect our chatbot to incorporate key needs and preferences gathered from focus groups and interviews to develop the chatbot. By the completion of study phase 3, we will have assessed the feasibility and acceptability of the prototype chatbot. Study phase 3 began in April 2024. Final results are expected by January 2025 and published thereafter.

Conclusions: The study will produce a prototype mental health chatbot developed with and for adolescents living with HIV that will be ready for efficacy testing in a subsequent, larger study.

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KEYWORDS

chatbot; digital assistant; depression; HIV; adolescents

Introduction

At the end of 2022, among the global population of children younger than 15 years of age, approximately 1.5 million were living with HIV, 130,000 new cases of HIV were reported, and 84,000 died from HIV-related causes [1]. AIDS remains the second leading cause of death among adolescents globally [2]. Lower adherence to antiretroviral therapy (ART) is the primary cause of AIDS mortality among people living with HIV across the life span; however, relative to children and adults, adolescents living with HIV are less likely to achieve viral suppression, a precursor to HIV treatment failure [3,4]. While many factors negatively affect ART adherence, depression disproportionately affects adolescents living with HIV compared to other age groups [5-7] and is associated with worse HIV treatment outcomes [8,9]. If left untreated, adolescents living with HIV and depression often face mounting problems, including poorer quality of life, more rapid progression of HIV, and premature death [10,11]. Moreover, depression complicates the transition from pediatric to adult HIV care in which adolescents living with HIV already face barriers to care retention, reduced ART adherence, lower CD4 lymphocyte counts, and lower viral suppression rates [3,8].

Despite the disproportionately negative impact of depression on adolescents living with HIV, a recent review of mental health interventions for adolescents with (or at risk of) HIV concluded that "surprisingly little" is known about treatments for this population [12]. Especially scarce are low-cost, evidence-based mental health treatments that could be easily scaled in resource-limited settings [13], including much of Latin America and the Caribbean, home to approximately 42,000 youths aged younger than 15 years living with HIV and where, in 2022, there were approximately 5300 new HIV infections and 3570 deaths among this population [14]. Emerging research has begun to demonstrate the benefit of treating comorbid depression and HIV [15,16], especially among adolescents [12]. Increasingly emphasized are integrated care models that simultaneously treat both HIV and depression to achieve better outcomes at the individual and programmatic levels for both morbidities [17-20]. The integration of mental health services into common priority health care platforms, including HIV, is part of a broader movement to increase access to mental health services for all people [21]. However, for young people, existing literature largely focuses on pathways to care for severe mental illnesses, leaving a gap in knowledge for other mental health conditions [22]. The scarcity of mental health resources is further exacerbated in low- and middle-income countries, where interventions are often reserved for only the most severe cases.

In Lima, Peru, we found evidence that depression care for adolescents living with HIV is an unmet health need unless symptoms are severe (eg, depression with psychosis and suicidal ideation) [23]. At the same time, we also observed in a small pilot study that the majority (92%) of adolescents living with HIV with depression did not have severe symptoms [24]. Adolescents living with HIV with mild to moderate depression do not receive support services (education, self-help strategies to develop coping skills and community bonding, and low-intensity care) as part of routine care that could help cushion the escalation to more severe depression and thereby sustain their commitment to HIV care. As a result, these young people may miss an early opportunity to attenuate depressive symptoms and their potential impact on adherence to ART, resulting in suboptimal individual and programmatic outcomes.

To address this gap, this project aims to use chatbot technology to provide education, self-help, and care linkage for adolescents living with HIV and depression. Chatbots—conversational agents that use text or voice in a human-like way to deliver information—allow users to receive information through multiple existing platforms such as SMS text messages, websites, WhatsApp, and Facebook Messenger without users needing special software and are ideal for low-resource environments. Furthermore, chatbots are already widely used in consumer environments due to their ability to quickly provide personalized information and increase the probability of purchase. In the health sector, the use of chatbots is less frequent but has been applied to providing mental health interventions [25,26] and, more recently, to link people with information and testing related to COVID-19 [27]. In Peru, during the COVID-19 pandemic, we observed that adolescents living with HIV had mobile devices and were able and amenable to receiving health information using technology [28]. In addition, the mental health team at Socios En Salud Sucursal Peru (the performance site for this study) developed and deployed mental health chatbots to screen for depression among adults during the first year of COVID-19, reaching >40,000 people in the country [29,30]. Building on our experience with adolescents living with HIV, mental health, and chatbot technology, we aim to create a novel

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chatbot dedicated to the unique mental health needs of adolescents living with HIV.

This project aims first to develop a chatbot, optimized to provide education, self-help skills, and care linkage for depression in adolescents living with HIV. Once a prototype chatbot is programmed, it will then be tested for feasibility and acceptability among adolescents living with HIV in Peru. We hypothesize that the chatbot will be feasible and acceptable to adolescents living with HIV to access depression education, self-help skills, and care linkage.

Methods

Study Overview

Using a mixed method, qualitative-quantitative design, we will develop (study phases 1 and 2) and pilot-test (study phase 3) a chatbot to deliver depression education, self-help skills, and care linkage for Peruvian adolescents living with HIV. All research instruments and the design of the chatbot will be done in collaboration with a Youth Advisory Board (YAB) comprised of adolescents living with HIV in Peru. Chatbot development will follow a human-centered approach, whereby feedback from the YAB (potential users of a future mental health chatbot) is solicited early and repeatedly during the development process to minimize design errors and maximize the fit of the chatbot to the preferences of the target population before pilot-testing. Figure 1 displays the study timeline and key milestones.

Figure 1. Study aims and process for the development and pilot-testing of an optimized conversational agent or "chatbot" for Peruvian adolescents living with HIV to facilitate mental health screening, education, self-help, and linkage to care. YAB: Youth Advisory Board.

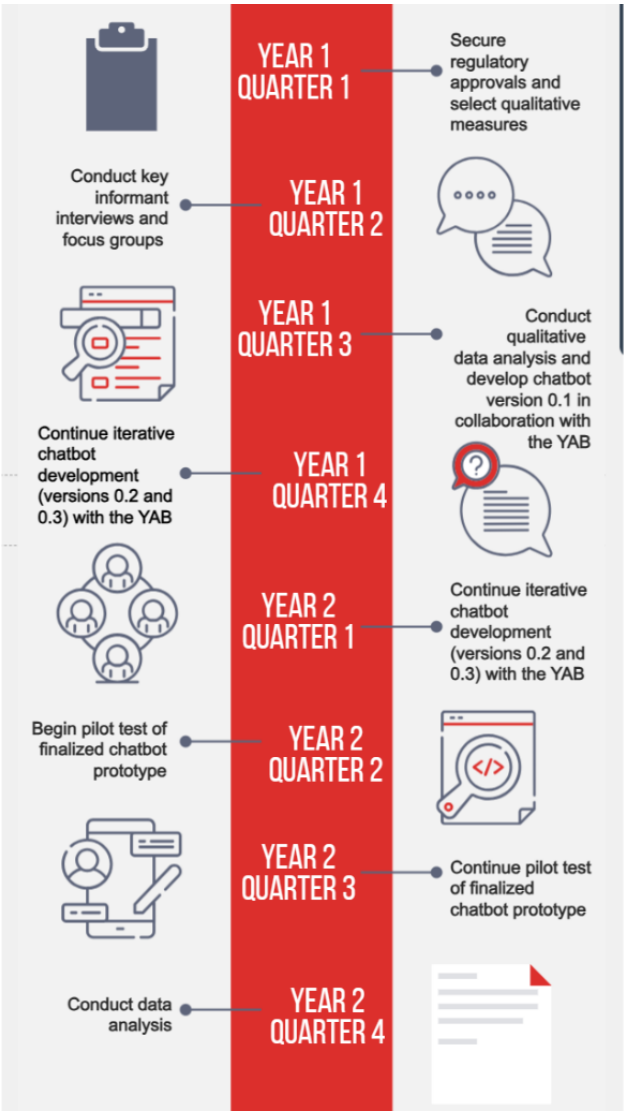

Study Population

Adolescent participants will be youths aged 10-19 years living with HIV in Lima, Peru. We will purposely recruit a diverse population of participants, including male and female participants, adolescents who acquired HIV at or near birth and adolescents who acquired HIV recently in life, pregnant adolescents, sexual and gender minorities (identifying as transgender, gay, or bisexual), and adolescents who have lost parents to HIV. Adult participants (caregivers and HIV care

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personnel) will be 18 years of age or older. Caregivers may be the adolescent's parents, family members, or other legal guardians providing care to an adolescent living with HIV. HIV care personnel will be persons currently working in the Peruvian National HIV care system with adolescents aged 10-19 years and living with HIV.

Youth Advisory Board

We will invite up to 10 adolescents aged 10-19 years living with HIV and residing in Lima, Peru to participate in the YAB. To ensure a heterogeneous group in terms of sex, sexual orientation, age, and HIV acquisition type, the adolescents will be recruited in collaboration with the infectious disease department of Peru's Instituto Nacional de Salud del Niño (National Institute of Children's Health), which cares for children and adolescents up to 18 years of age. Additionally, up to 2 adolescents between 18 and 19 years of age will be recruited through other national services of care for adults living with HIV. The YAB will review and provide feedback on all research documents (consents and instruments) and multiple versions of the chatbot while in the development phase (study phase 1).

Ethical Considerations

All study procedures have been approved by the Comité Institucional de Bioética de VÍA LIBRE, which is an institutional review board (IRB) of record for the performance site, Socios En Salud Sucursal, Peru. The IRB at the University of South Florida formally agreed to rely on VÍA LIBRE for the review, approval, and continuing oversight of the research project under an interagency IRB Authorization Agreement (University of South Florida IRB study # 005124). For study phases 1 and 2, the data are deidentified, and any participant names or other identifying information will be deleted from interview transcripts; only a study ID will be used for identification purposes. For phase 3, participant names and phone numbers will be stored on a password-protected computer only accessible to the study staff in Peru, and participants will be identified by a study ID for research purposes. All study participants (phases 1-3) and YAB members (for each meeting attended) will be compensated PEN 100 (approximately US $26.50) in vouchers redeemable at multiple local grocery stores. Transportation will be provided for in-person study visits.

Development of a Prototype Chatbot to Provide Depression Education, Self-Help, and Care Linkage

Phase 1: Formative Data Collection to Inform Chatbot Development

Overview

We will conduct up to 6 focus groups: 3 with adolescents aged 10-14 years living with HIV and 3 with adolescents aged 15-19 years living with HIV and residing in Lima, Peru. Additionally, up to 10 interviews will be conducted with key informants: 5 with caregivers of adolescents living with HIV and 5 with HIV care personnel. A semistructured interview guide for the focus groups and key informant interviews will be used to identify thoughts, views, and consequences of depression in adolescents living with HIV. Participants will also be asked about their perceived acceptability of the proposed mental health chatbot for adolescents living with HIV using open-ended questions derived from 7 core intervention acceptability constructs: affective attitude, ethics, burden, coherence of intervention, opportunity costs, perceived effectiveness, and self-efficacy [31]. Focus groups and key informant interviews will be audio recorded, transcribed verbatim, and analyzed using Dedoose qualitative data analysis software (version 9.2.007; SocioCultural Research Consultants, LLC).

Eligibility Inclusion Criteria

The inclusion criteria are adolescents who are older than 10 years and younger than 19 years of age, living with HIV, and aware of HIV diagnosis; caregivers who are 18 years and older and currently caring for an adolescent living with HIV; and HIV care personnel who are 18 years and older and currently working in the Peruvian National HIV care system with adolescents aged 10-19 years and living with HIV.

Eligibility Exclusion Criteria: Adolescents, Caregivers, and HIV Care Personnel

The exclusion criterion is any acute condition (emotional, physical, and social) that, by the decision of the investigator, could place the participant at significant risk due to participation in the study.

Data Analysis

Qualitative data will be analyzed using the framework analysis approach [32], beginning with a preliminary codebook derived from the focus group and key informant interview guides. As coding progresses, de novo codes will be added for emergent themes. After all transcripts are coded, reports that contain all text segments for each code will be compiled and analyzed for themes within each code. Emergent themes will be reported using illustrative quotes. The COREQ (Consolidated Criteria for Reporting Qualitative Data) checklist [33] will be completed to enhance data rigor and methodological transparency.

Phase 2: Chatbot Design and Programming With Iterative YAB Feedback

We will program the chatbot using the platform SmartBot360 [34]. The YAB will participate in ongoing or iterative testing of the chatbot over several months. First, we will develop an initial version of the chatbot with basic functionality (version 0.1) and convene the YAB to provide early feedback and suggestions, which will be incorporated into the chatbot design and programming yielding version 0.2; the process of YAB feedback solicitation and feedback incorporation will be repeated to arrive at version 0.3. During the YAB consultations, in addition to feedback on the chatbot functionality (eg, presentation, navigation, and menus), the YAB will guide the research team on content for up to 6 educational videos, or graphics and animations on depression and coping skills (30-90 seconds long) to be delivered by the chatbot. Once the YAB reviews and approves version 0.3, we will finalize the remaining programming suggestions to arrive at the pilot version of the chatbot, 1.0, for feasibility and acceptability testing.

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Assessing the Feasibility and Acceptability of the Chatbot Prototype

Phase 3: Pilot-Testing for Feasibility and Acceptability of Chatbot Prototype Version 1.0

We will recruit up to 50 adolescents living with HIV naïve to the development phase to test chatbot version 1.0 for feasibility and acceptability. Participants first will complete a survey to collect information on sociodemographics (age, sex, sexual and gender identity, and education level), HIV (HIV acquisition route, current viral load, and frequency of missed HIV care visits), knowledge and history of depression, and previous chatbot use (see Table 1 for all planned measures). Next, participants will interact with the chatbot and then complete a second questionnaire to assess their acquired knowledge about depression and measure the acceptability and feasibility of the chatbot. The acceptability and feasibility questionnaires will include 3 measures: the Acceptability of the Intervention Measure, the Intervention Appropriateness Measure, and the Feasibility of Intervention Measure [35]. Finally, participants will be offered the opportunity to use the chatbot on their own for 2 additional weeks and will receive a follow-up SMS text message to rate their experience. The number of adolescents living with HIV who use the chatbot on their own and the number of acceptances and refusals to use the chatbot will be recorded during these 2 weeks as further measures of acceptability.

Table 1. Planned pilot-testing survey measures, administration point, target, and rationale to assess the feasibility and acceptability of an optimized conversational agent or "chatbot" among 50 adolescents living with HIV in Peru to facilitate mental health screening, education, self-help, and linkage to care.

Administration point and measure or instrument	Target	Rationale
Before chatbot use		
Sociodemographic	Participant characteristics	Describe the study population including HIV or health information and previous chatbot use
Adolescent Depression Knowledge Questionnaire (ADKQ) [36]	Current understanding of depression	Measure baseline depression knowledge prior to interacting with the chatbot
Patient Health Questionnaire-9 adolescent version [37]	Current depressive symptoms	Measure baseline presence of depression symptoms
General Anxiety Disorder-7 questionnaire [38]	Current anxiety symptoms	Measure baseline presence of anxiety symptoms
The Self-Stigma of Seeking Help Scale [39]	Label avoidance	Aid in providing appropriate services based on stigma measure
Attitudes Towards Mental Health Treatment [40]	Feelings about getting mental health help	Aid in providing appropriate services based on attitudes toward treatment
Perceived Stress Scale [41]	Current stress levels	Aid in providing appropriate services based on stress levels
After chatbot use		
ADKQ [36]	Current understanding of depression	Measure change of depression knowledge after interacting with the chatbot
Acceptability of Intervention Measure [35]	Acceptability of the chatbot	Measures the perception of adolescents living with HIV that the chatbot is agreeable, palatable, or satisfactory
Intervention Appropriateness Measure [35]	Appropriateness of the chatbot	Measures the perceived fit, relevance, or compatibility of the chatbot to address depression among adolescents living with HIV
Feasibility of Intervention Measure [35]	Feasibility of the chatbot	Measures the extent to which the chatbot can be successfully used
Acceptability of mental health information delivered by the chatbot	Acceptability (or perceived acceptability) of mental health information delivered by chatbot and perceived continued use of chatbot	Measures the extent to which the user believes they would use the mental health information delivered by the chatbot and use the chatbot in the future and recommend to others
Chatbot feature satisfaction scale	Satisfaction with core chatbot features	Measures the extent to which chatbot features (eg, graphics, information, and self-help tools) are liked

Data Analysis

Data will be cleaned, and summary tables will be generated. Due to the small sample size, tests of association are not planned, and the main analysis is limited to descriptive statistics. For the Adolescent Depression Knowledge Questionnaire, which is applied before and again after interacting with the chatbot (during a single study visit), we will use matched paired 1-tailed *t* tests. Using G*Power (version 3.1; Heinrich Heine University Dusseldorf) [42,43], with a medium effect size, a sample size

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of 45 would be sufficient to detect effects if they are present using a matched pair 1-tailed *t* test.

Results

The study was awarded in April 2022, approved by IRB VÍA LIBRE in November 2022, received funding in December 2022, and commenced recruitment in March 2023. Study phases 1 and 2 are complete as of January 2024, and study phase 3 began in April 2024. Results on the feasibility and acceptability of the chatbot are expected by January 2025 and published thereafter.

Discussion

This study tests a pragmatic, inexpensive, adaptable, and highly scalable solution to increase access to a range of depression care services for adolescents living with HIV, beginning with education and self-help skills. Given the global shortage of mental health professionals to deliver depression care, especially in low- and middle-income countries where >90% of people with HIV live [44], we anticipate that our mental health chatbot holds the potential to go beyond depression identification and care referral; it could empower adolescents living with HIV by providing depression education and practical self-help coping skill. Moreover, the chatbot may be especially attractive to adolescents not wanting to immediately speak with another person due to the stigma surrounding both depression and HIV.

Our chatbot should meet adolescents living with HIV "where they are at," providing linkage to a mental health specialist as needed but also helping adolescents living with HIV learn healthy coping strategies. Moreover, future versions of our chatbot could be adapted to address other psychosocial issues, including HIV disclosure, sex, sexuality, dating and romantic relationships, stigma, body image, and other common psychosocial issues among adolescents, and could be easily adapted for delivery in multiple languages. As with all health problems, early intervention is associated with improved outcomes both at the individual and programmatic levels. At the individual level, adolescents living with HIV who learn how to recognize depression and enact healthy coping skills may be able to stave off the escalation of depression and associated disengagement with HIV care. At the programmatic level, enhanced mental health support for adolescents living with HIV could ultimately reduce missed clinic appointments, improve ART adherence (and consequently less need for inpatient care), and ultimately lead to better HIV outcomes for this vulnerable population.

Anticipated limitations of this study include the rapid formative and chatbot development period (12 months) with participants from 1 geographic location (Lima), which may not address experiences of depression by adolescents living in rural areas. Further, the small (convenience) sample of adolescents who will test the chatbot (phase 3) will preclude tests of association. Nonetheless, we expect that some participants (including youths, their caregivers, and HIV care professionals) will have previously lived in rural areas and could share insights from those experiences. Although the sample size precludes tests for association, the data collected using a battery of validated instruments from this pilot study should provide a clear indication of the acceptability and feasibility of the chatbot to facilitate mental health screening, education, self-help, and linkage to care among adolescents living with HIV and provide the groundwork for a future, appropriately powered study to determine the efficacy of the approach.

This study will contribute to a growing body of literature on the use of chatbots in the health services delivery sector and hold promise for addressing a mental health service gap among adolescents with HIV by providing education, self-help skills, and care linkage. If our chatbot is determined to be feasible and acceptable among adolescents in this study, future iterations could be expanded beyond depression (eg, anxiety, disordered eating and body image, and HIV and mental health stigma) and disseminated beyond the single geographic area in this study (ie, to rural areas and, potentially, other countries in Latin America).

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the study investigators (JTG and CC) on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Collaborative Initiative for Paediatric HIV Education and Research.
[PDF File (Adobe PDF File), 88 KB - resprot_v13i1e55559_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
COREQ: Consolidated Criteria for Reporting Qualitative Data
IRB: institutional review board
YAB: Youth Advisory Board

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Protocol

Reliability and Sensitivity of a Virtual Assessment Developed for Workplace Concussions: Protocol for a Method-Comparison Study

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Abstract

Background: Workplace mild traumatic brain injuries are frequently associated with persistent symptoms, leading to a reduction in productivity at work or even disability. People who sustain workplace injuries frequently need rehabilitation and support, and the challenges of delivering these services was heightened during the COVID-19 pandemic as injured workers had to be cared for remotely. Currently, clinicians are conducting both in-person and virtual (remote) concussion assessments; however, the measures that are being used to complete these assessments have undocumented psychometric properties.

Objective: This study will document the psychometric properties of the clinical measures that are being used remotely and their ability to produce similar results to in-person assessments. Specifically, through this method-comparison study, we aim to (1) evaluate the sensitivity of the measures included in a virtual assessment toolkit when compared to an in-person assessment and (2) determine the interrater and intrarater reliabilities of the measures included in a virtual assessment toolkit.

Methods: Patient participants (people living with acquired brain injuries) will attend two assessments (in person and virtual) at the Ottawa Hospital. The two assessments will be identical, consisting of the measures included in our previously developed virtual concussion assessment toolkit, which includes finger-to-nose testing, the Vestibular/Ocular Motor Screening tool, balance testing, cervical spine range of motion, saccades testing, and evaluation of effort. All virtual assessments will occur using the Microsoft Teams platform and will be audio/video-recorded. The clinician assessor and patient participant will complete a feedback form following completion of the assessments. A different clinician will also document the findings on observed videos of the virtual assessment shortly after completion of both in-person and virtual assessments and approximately 1 month later. Interrater reliability will be assessed by comparing the second clinician's observation with the first clinician's initial virtual assessment. Intrarater reliability will be evaluated by comparing the second clinician's observation with their own assessment approximately 1 month later. Sensitivity will be documented by comparing the findings (identification of abnormality) of the in-person assessment completed by the initial clinician assessor with those of the second clinician assessor on the observation of the recording of the virtual assessment.

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Results: As of May 2024, we have recruited 7 clinician assessors and completed study assessments with 39 patient participants. The study recruitment is expected to be completed by September 2024.

Conclusions: Currently, it is unknown if completing concussion assessments virtually produces similar results to the in-person assessment. This work will serve as a first step to determining the similarity of the virtual assessment to the matching in-person assessment and will provide information on the reliability of the virtual assessment.

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KEYWORDS

telehealth; virtual care; concussion; mTBI; mild traumatic brain injury; assessment; examination

Introduction

Background

A direct or indirect head impact leading to a concussion is a form of mild traumatic brain injury [1], which results in an alteration of brain functioning [2,3]. Most individuals who sustain a concussion experience rapid recovery within the first 2 weeks to 1 month following the injury. There are, however, instances where individuals continue to experience persistent symptoms after a concussion, with a reported occurrence of approximately 15%-20% [4]. These symptoms may persist beyond 1 year following the injury [3,5]. Factors such as premorbid characteristics (age, sex, concussion history), psychological factors, and injury-related factors (ie, severity of injury) are likely contributors to the persistence of the symptoms [6]. Postconcussion symptom presentation can vary widely, including cognitive deficits such as memory issues, vestibular deficits such as balance issues or dizziness, and ocular deficits such as blurred vision, among others [1,7-9]. There is a need for a multifactorial assessment approach due to the diversity in symptom presentation. Specifically, it is recommended to incorporate measures targeting each of the commonly experienced symptoms into a battery of tests [10].

There is evidence suggesting a growing documented incidence of concussion in the workplace context [11]. Kristman et al [12] reported that there are approximately 39-58 workplace concussions per 10,000 claims annually in Ontario, Canada [12]. Workplace concussions often lead to greater delays in return to work compared to injuries sustained outside of the workplace context [5,13]. It is estimated that roughly 60% to 90% of adults return to work within 6 months postconcussion injury, with the remainder continuing to be off work at this time point [5]. Compensation associated with a workplace injury may be a contributor to this delay in return to work [5,13].

Several factors can contribute to delays in return to work following concussion, including a lower level of education, more severe immediate symptoms post injury, and other injuries sustained [5]. In general, workplace concussions pose significant challenges. These include financial burdens that are felt by the health care system, employers, the Workplace Safety and Insurance Board (WSIB), and the workers themselves [14]. For the patient, lives are disrupted due to prolonged recovery times [13], resulting in the need for additional support from the WSIB for individuals presenting for specialized assessments.

The onset of the COVID-19 pandemic affected how specialized postconcussion assessments could be completed along with a need to switch to virtual care [15]. However, it is not known whether the measures being used by clinicians in virtual assessments are the same as those used for in-person assessments [16]. Additionally, the reliability of the virtual concussion assessments being conducted is unknown. Measures used in person that have shown strong psychometric properties may not produce the same or similar results when administered virtually [17]. Furthermore, the level of agreement between measures used in the in-person concussion assessment and those used in the virtual assessment has not yet been established. Currently, clinicians are continuing to complete both in-person and virtual concussion assessments; however, there is limited information on the measures used in the virtual assessment. It is important to gain an understanding of the properties of the clinical measures and their ability to produce similar results to the in-person assessment to inform the effectiveness of use in a virtual context [18].

The preparatory work for this study was initiated by developing a virtual assessment toolkit. Clinician surveys were used to identify relevant measures for assessing the physical domains of concussion [19]. A working group refined the measures feasible for virtual administration based on expert opinion. Focus groups then identified barriers and facilitators for virtual concussion assessments. The resulting virtual assessment toolkit was then used in a feasibility study to evaluate recruitment rates, procedure acceptability, and time to assess; the manuscript reporting these findings is currently being prepared for submission.

Objectives

The objectives of this method-comparison study are two-fold: (1) to evaluate the sensitivity of the virtual assessment against the gold standard of the in-person assessment and (2) to determine interrater and intrarater reliabilities of the measures in the virtual assessment. This study will further contribute to the development of a virtual toolkit of assessments across four physical domains along with the evaluation of effort, specifically designed for the WSIB context.

Methods

Design

This study will follow a prospective method-comparison study design [17].

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Participants

Patient Participants

Eligible participants will be adults 18 years or older who have sustained an acquired brain injury (concussion or other form) and are being assessed by a physician, physician assistant, and/or physiotherapist at the Ottawa Hospital. In addition to people with concussions, people living with acquired brain injuries, including moderate to severe traumatic brain injury or hypoxic brain injury, will be recruited. In this study, we are assessing the consistency of physical examination findings; people with other forms of acquired brain injury such as severe traumatic brain injury more frequently have signs of central nervous system deficits, whereas these assessments are often normal during a postconcussion examination [20,21]. This inclusion is thus intended to ensure recruitment of participants with a broad range of identifiable deficits on all components of the assessment. Those unable to complete the study assessments and unable to speak English or French will be excluded from the study. Participant information will be documented, including demographics, functional status, environmental aids used, socioeconomic and work status, injury information, and information related to technology experience.

Clinician Participants

Clinicians with expertise in conducting assessments for people with acquired brain injuries will be invited to participate in this project. Demographic information for participating clinicians will be documented, including age, years practicing with patients who have an acquired brain injury, professional background (physiotherapist, physician assistant, physiatrist, other), and self-reports of competency with in-person and virtual neurological assessments.

Sample Size

The target sample size of this method-comparison study is 60 patient participants. For the objective of assessing the sensitivity of the virtual assessment against the gold standard of in-person assessment, with a total of 60 participants, 50 (83%) of whom are expected to have an abnormal finding, and an estimated sensitivity ranging from 77% to 96%, the two-sided 95% CI around the estimated sensitivity will have a total width ranging from 8.7% to 25.3% (or margin of error 4.4%-12.7%). For the objective of assessing interrater agreement between two clinicians conducting a virtual assessment using the κ statistic, a sample size of 60 participants achieves 80% power to detect a true κ value of 0.89 using a one-sided test at the 5% significance level, assuming that 90% of participants are classified as abnormal; κ under the null hypothesis was specified as 0.5.

Recruitment and Consent

Patient Participants

Purposive sampling methods will be used to recruit individuals living with acquired brain injuries with impairments spanning all domains of interest. The participants will be recruited through the Ontario Workers Network and relevant rehabilitation clinics at the Ottawa Hospital. Electronic medical records will be screened to identify eligible patients, who will then be called or approached in person for consent.

Clinician Participants

Clinicians will be recruited from the Ontario Workers Network and relevant rehabilitation clinics at the Ottawa Hospital to participate as clinician assessors in the study. Consent will be obtained over the telephone or face to face.

Outcomes

The virtual toolkit of assessments will include the following outcome measures: the classification of abnormality (binary variable) on the finger-to-nose test, Vestibular/Ocular Motor Screening tool, balance testing, cervical spine range of motion, saccades testing, and evaluation of effort. The procedures outlined below provide details for these outcome measures, including the methods used for evaluating the sensitivity of the virtual assessment when compared to the in-person assessment and the interrater and intrarater reliabilities of the virtual assessment.

Procedures

Training

Training of the assessing clinicians on the outcome measures will occur prior to commencement of patient-participant recruitment. A previously developed training manual [22] will be used to complete the training. Training will be uniform with the goal of standardizing clinician completion of the assessments.

Assessments

Data collection will occur in Research Electronic Data Capture (REDCap), a secure electronic data capture application. An assessing clinician will conduct two assessments: one in person and one virtual. Both assessments will be identical consisting of all measures from the virtual assessment toolkit (see Table 1). Both assessments will be completed at the Ottawa Hospital. When possible, assessments will occur on the same day with a brief rest period in between [23,24]. The order of assessment completion (in person vs virtual) will be randomized and counter-balanced. A random-numbers table will be generated and imported into REDCap and the randomization will occur through REDCap. In addition to the assessments identified in Table 1, clinicians will document adverse events (if any) and will record findings from the assessments on a paper copy, which will be directly input into REDCap by a research team member.

For the virtual assessment, the patient participants will be located in a separate room from the assessing clinicians within the Ottawa Hospital. All patient participants will use the same computer and will be provided with technical support from a research team member as needed. The virtual assessments will be conducted in the clinical environment to standardize as many components of the assessment as possible, including computer screen, lighting, image size, and room setup. During the virtual assessment, several safety measures will be implemented: (1) a research team member will be present in the room throughout and (2) the patient participant will stand in front of a wall/bed/chair or with their back at a corner during the vestibular

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assessments in case of loss of balance. All the virtual assessments will occur through the Microsoft Teams platform. The study assessments will be audio/video-recorded using the record function on Microsoft Teams.

Where possible, both assessments will be completed on the same day. It is estimated that a portion (~5%) of participants may be unable to complete both the in-person and virtual assessments on the same day, either due to lack of time or inability to tolerate a second assessment as a result of symptom aggravation (eg, headaches, dizziness, nausea, sensitivity to noise and light). For these participants, the second assessment (virtual or in person) will be scheduled for completion within 1 week of the initial assessment.

Following completion of the assessments, the patient participants and clinician assessors will complete a feedback form. Participants will complete a feedback form (see Multimedia Appendix 1) related to completion of the virtual assessment, the environmental setup, and confidence in the assessment findings.

Table 1. Outline of measures included in the virtual assessment toolkit to be completed in both in-person and virtual assessments[a].

Domain	Measures	Documentation of findings by clinicians
Neurological examination	Coordination: finger-to-nose test	Abnormal (hesitation, tremor, over- or undershooting [25])/normal
Vestibular	VOMS[b]	Change in symptoms (≥2 point increase indicates abnormality [26]); average distance for 3 trials of near-point convergence in centimeters (≥5 cm convergence indicates abnormality [26])
Vestibular	Balance (feet together, single-leg stance, tandem stance) with eyes open and eyes closed for 20 seconds each	Abnormal (unable to complete 20-second balance [22])/normal
Oculomotor	Saccades	Abnormal (observe saccade initiation, range of motion and conjugacy, speed, accuracy, intrusions, or oscillations [27])/normal
Cervical	Range of motion (flexion, extension, right and left lateral flexion, right and left rotation)	Estimated angles for each recorded abnormality (determined by comparison to norms in people aged 20-59 years: flexion=50°-72°, extension=58°-77°, lateral flexion=37°-47°, rotation=67°-81° [28])
Effort	Rating scale	Full use of effort documented as yes or no (clinician discretion); rating scale documented from 0 (no effort) to 10 (maximum effort) (clinician discretion)

[a]For a complete presentation of the instructions used to administer the measures, see Johnston et al [22].

[b]VOMS: Vestibular/Ocular Motor Screening.

Observation and Rating of Audio-Video Recordings

A second clinician (rater B in Figure 1 [17]) will complete two ratings of the recording of the virtual assessment (in a randomized order for participants) at 1-month intervals. Clinicians will record findings from the assessments on paper or electronic copies, which will be input directly into REDCap by a research team member. See Figure 1 [17] for an outline of study assessment procedures.

Figure 1. Assessment procedures (adapted from Russell et al [17]).

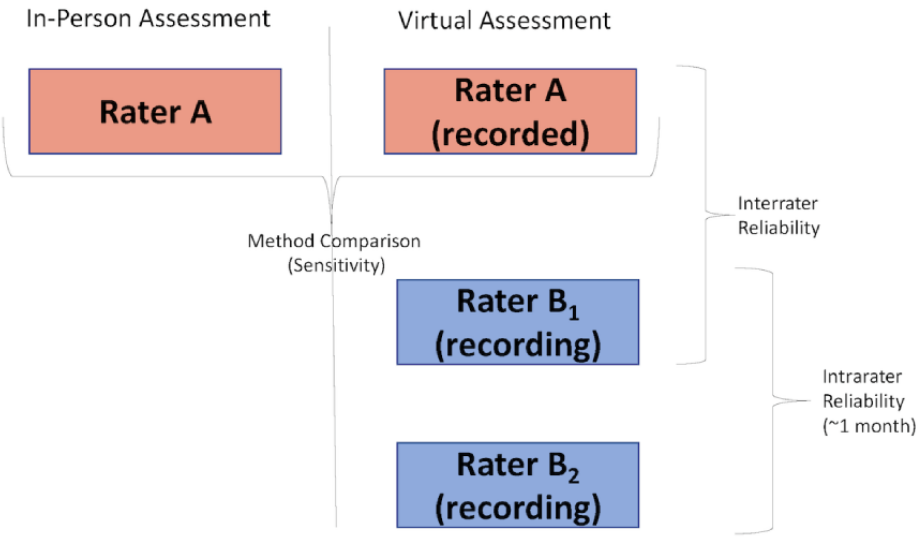

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Analysis

Assessments Overview

Patient and clinician participant characteristics will be descriptively analyzed. IBM SPSS (version 28) will be used to calculate the sensitivity of virtual assessments versus in-person assessments, along with the κ values (interrater and intrarater reliabilities) of the virtual assessments (see Figure 1 for comparisons).

Method-Comparison (Sensitivity) Analysis

The sensitivity of the virtual assessment compared to the gold-standard in-person assessment (rater A in person vs rater A virtual) will be determined, where the assessment of the uncertain classification of the measures used virtually will occur against the gold standard or "true" classification, which is the in-person assessment in this study. The findings of the initial clinician assessor (rater A) that completed the in-person and virtual assessments will be compared to determine the sensitivity of the measures administered virtually. In this case, sensitivity (true positives divided by the sum of true positives and false negatives multiplied by 100) refers to the ability of the virtual measure to identify a deficit or positive finding when the in-person measure identifies the deficit or positive finding. Values closer to 100% indicate greater sensitivity.

Reliability

To calculate the interrater reliability of the virtual assessment, the findings of rater A (virtual assessment) will be compared to the findings of rater B_1 (initial observation of the virtual assessment recording). To determine the intrarater reliability of the virtual assessment, the findings of rater B_1 (initial observation of the virtual assessment) will be compared to the findings of rater B_2 (second observation of the virtual assessment) approximately 1 month after the initial observation. Estimates of reliability will be calculated using the κ statistic (classification of abnormal vs normal) for all measures included in the toolkit.

Adverse Events

Adverse events, including the type and severity, will be summarized by assessment type (in person or virtual).

Ethical Considerations

Ethics approval was obtained from the Ottawa Health Sciences Network Research Ethics Board (20230311-01H), the Bruyère Research Ethics Board (M16-22-006), and the University of Ottawa Board of Ethics (H-06-23-9348). All potential risks and adverse consequences will be relayed to participants verbally and all participants will provide verbal consent over the telephone or informed consent in person prior to their scheduled appointment. A wet-ink signature will be obtained from all participants on the day of their scheduled assessment. Privacy and confidentiality will be maintained by using deidentified data. Patient participants will be provided with a CAD $30 (~US $22) gift card and parking voucher as a token of appreciation for their participation in the study.

Results

As of May 2024, we enrolled and completed both the in-person and virtual assessments for 39 patient participants. We have recruited 7 clinician assessors. Recruitment and testing are expected to be completed by September 2024.

Discussion

Projected Significance

This study will establish the reliability and sensitivity properties associated with 5 physical components of the virtual concussion assessment. There is an identified gap in current knowledge with limited research conducted on the reliability and comparability of virtual concussion assessments in comparison to in-person assessments. While virtual care has demonstrated to be a valuable approach to concussion assessment and management [29,30], there is a need for additional information regarding the psychometric properties of outcome measures. This information is essential for instilling confidence in the administration of these measures in a practical setting. Virtual approaches to care have been used for many years; however, the COVID-19 pandemic significantly increased their use in an effort to reduce hospital visits [15]. While the COVID-19 pandemic initiated this increased use of virtual care, some assessments are continuing to be offered virtually. Using measures with acceptable properties in a virtual context is important in practice to ensure accurate identification of problem areas on virtual assessments so that treatment interventions can be appropriately directed [31]. Despite measures showing adequate properties when administered in person, they may produce different results when administered in a virtual context [17,32], thereby providing a rationale to carry out this work. The aim of completing this method-comparison study is to obtain preliminary information on the virtual assessment in relation to the WSIB context.

Strengths and Limitations of the Methodological Approach

The strengths of this method-comparison approach include the use of commonly adopted technology and software for virtual brain injury assessments in a practical setting. Further, including a wide range of acquired brain injury severities in our sample ensures the inclusion of abnormalities spanning all relevant domains. This will make the findings not only applicable to current practice but also potentially generalizable to different types of acquired brain injury.

We plan to assess the virtual evaluation in a controlled hospital setting. Moving forward, it would be beneficial to evaluate the virtual assessment in environments that are less standardized such as patients' homes or community clinics where physician specialists are in a different location than the patient.

Finally, due to constraints in clinic scheduling, a methodological decision was made to have the same clinician (rater A) conduct both the in-person and virtual assessments with the participants. In attempts to address this concern, the order of study assessments (in person and virtual) will be randomized and counter-balanced.

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Conclusion

This method-comparison study is an important endeavor considering the limited exploration of virtual concussion assessments in the literature despite their increasing use in practice. This study aims to determine whether virtual and in-person assessments yield similar results in terms of the identification of abnormality in common physical domains of a concussion assessment. The study will also assess the interrater and intrarater reliabilities of the virtual assessment, contributing valuable insights to the field of concussion rehabilitation.

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Authors' Contributions

All authors have made substantial contributions to the work presented in this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Feedback forms.
[PDF File (Adobe PDF File), 180 KB - resprot_v13i1e57663_app1.pdf]

Multimedia Appendix 2
Peer-review reports from the Strategic Research - Workplace Safety and Insurance Board (WSIB) (Ontario, Canada).
[PDF File (Adobe PDF File), 164 KB - resprot_v13i1e57663_app2.pdf]

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Abbreviations

REDCap: Research Electronic Data Capture
WSIB: Workplace Safety and Insurance Board

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Protocol

Improving Antibiotic Use in Nursing Homes by Infection Prevention and Control and Antibiotic Stewardship (IMAGINE): Protocol for a Before-and-After Intervention and Implementation Study

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Abstract

Background: Despite the extensive use of antibiotics and the growing challenge of antimicrobial resistance, there has been a lack of substantial initiatives aimed at diminishing the prevalence of infections in nursing homes and enhancing the detection of urinary tract infections (UTIs).

Objective: This study aims to systematize and enhance efforts to prevent health care–associated infections, mainly UTIs and reduce antibiotic inappropriateness by implementing a multifaceted intervention targeting health care professionals in nursing homes.

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Methods: A before-and-after intervention study carried out in a minimum of 10 nursing homes in each of the 8 European participating countries (Denmark, Greece, Hungary, Lithuania, Poland, Slovakia, Slovenia, and Spain). A team of 4 professionals consisting of nurses, doctors, health care assistants, or health care helpers are actively involved in each nursing home. Over the initial 3-month period, professionals in each nursing home are registering information on UTIs as well as infection and prevention control measures by means of the Audit Project Odense method. The audit will be repeated after implementing a multifaceted intervention. The intervention will consist of feedback and discussion of the results from the first registration, training on the implementation of infection and prevention control techniques provided by experts, appropriateness of the diagnostic approach and antibiotic prescribing for UTIs, and provision of information materials on infection control and antimicrobial stewardship targeted to staff, residents, and relatives. We will compare the pre- and postintervention audit results using chi-square test for prescription appropriateness and Student *t* test for implemented hygiene elements.

Results: A total of 109 nursing homes have participated in the pilot study and the first registration audit. The results of the first audit registration are expected to be published in autumn of 2024. The final results will be published by the end of 2025.

Conclusions: This is a European Union–funded project aimed at contributing to the battle against antimicrobial resistance through improvement of the quality of management of common infections based on evidence-based interventions tailored to the nursing home setting and a diverse range of professionals. We expect the intervention to result in a significant increase in the number of hygiene activities implemented by health care providers and residents. Additionally, we anticipate a marked reduction in the number of inappropriately managed UTIs, as well as a substantial decrease in the overall incidence of infections following the intervention.

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KEYWORDS

antimicrobial stewardship; medical audit; hygiene; antibacterial agents; quality improvement; nursing homes; health personnel; drug resistance, microbial; frail elderly

Introduction

Life expectancy has been steadily increasing in the European Union. Population projections estimate that by 2050 the old-age dependency ratio, calculated as the number of individuals older than 65 years per 100 people of working age, will reach 50% [1]. The rise in the ageing population and the pressure on the health care provision systems across European countries has led to reductions in hospital beds and more patient care being provided in long-term care facilities [2]. In 2019, there were an estimated 2.9 million residents in such facilities, corresponding to approximately 0.7% of the total population in the European Union [3].

Residents in nursing homes are more prone to frequent and severe infections [4]. In general, infections are highly prevalent among older people, especially those living in nursing homes, as they are more vulnerable to urinary tract infections (UTIs), respiratory tract infections, and acute bacterial skin- and soft-tissue infections [5]. Although recent estimates are lacking, approximately 2 million infections occur in US nursing homes each year [6]. Residents in care homes are particularly susceptible to infections due to factors such as immunosenescence, multiple comorbidities, functional impairment, the use of indwelling devices such as catheters and feeding tubes, close living proximity, recent acute care admissions, and frequent contact with nursing staff and medical equipment [7-10]. Microorganisms can be found on residents, relatives, and friends, on surfaces in the facility, and even on the hands or gloves of health care professionals (HCP) and medical equipment. Without appropriate and adequate cleaning and disinfection methods, the germs may spread to other residents and the environment. In younger healthy individuals, the immune system fights off germs and prevents infection; however, the declining ability of the body and immune systems to resist germs makes older people more susceptible to infection and they can become infected more easily [11,12].

Antibiotic overprescribing for infectious diseases is high in nursing homes. In a recent project on the prevalence of antimicrobial agents in 3052 long-term care facilities in 24 European Union countries in 2016-2017, 4.9% of the residents had received at least 1 antimicrobial agent on the day of the survey [13]. This study also showed that for a 1% increase in the proportion of residents older than 85 years, the prevalence of antimicrobial use increased by 5%. In addition, approximately 30% of the antibiotics prescribed were given prophylactically, and most were given inappropriately, with a wide variation across European countries. Furthermore, the urinary tract was the most common body site for which antimicrobials are prescribed, with nearly 50% of the cases, and according to the authors, at least 60% of these antimicrobials prescribed for UTI were inappropriate, leading to a spread of multidrug-resistant uropathogens [13]. As a result, Watch and Reserve broad-spectrum antibiotics, as defined by the World Health Organization Access, Watch, Reserve classification [14], are commonly given to residents with these infections, perpetuating the problem of antimicrobial resistance (AMR), which is accompanied with higher morbidity, mortality, health, and intersectoral and societal costs [15].

In nursing homes, antibiotic prescribing decisions are known to be complex and influenced by many social and organizational factors [16-18]. Overdiagnosis of common infections largely explains antibiotic overuse for these infections. A review of 4 randomized controlled trials of interventions aimed at improving

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the diagnosis of UTIs in nursing home residents found that, despite being heterogeneous, the interventions used were to some extent successful, but there was no evidence that an intervention was feasible or sustainable following trial completion [19]. Several decision tools have been developed for the diagnosis of UTIs in nursing home residents to assist clinicians in identifying symptomatic UTI [20,21]. The overarching message is that there are no precise diagnostic rules for identifying UTI among elderly individuals in nursing homes. In general, there is agreement that nonspecific symptoms alone, such as changes in mental or functional status or changes in urine characteristics, including bad smell, color, or sediment, should not be used to diagnose UTI and that a diagnosis of UTI in nursing home residents should not be made on urinalysis or urine culture without UTI-specific symptoms.

Antibiotic-resistant bacteria have the potential to spread between individuals through direct or indirect contact. Therefore, the implementation of infection prevention and control (IPC) strategies plays a crucial role in reducing the risk of infection [22]. These strategies not only contribute to a decrease in the number of infections but also effectively and efficiently reduce antimicrobial consumption, thereby limiting opportunities for misuse [23]. It is essential to emphasize the significance of infection prevention, biosecurity measures, and control practices in managing all infectious microorganisms, as they minimize the reliance on antimicrobials and, consequently, hinder the development and spread of resistance [24]. Unfortunately, there is a general lack of IPC measures and antimicrobial stewardship (AMS) programs in nursing homes across Europe [13]. In addition, most countries exhibit weak interprofessional collaboration and inadequate integration of health and social care delivery, leading to increased mortality, as evidenced during the COVID-19 pandemic [25,26].

In summary, in the effort to urgently decelerate the development of AMR, there is a need for evidence-based nursing home-focused AMS policies and IPC strategies aimed at preventing and controlling the spread of infections, as well as promoting appropriate antibiotic use across health care settings. Our objective is to assess the impact of a multifaceted intervention aimed at nursing home HCPs on preventing common infections, particularly UTIs. Additionally, we aim to evaluate the effectiveness of this intervention in reducing the percentage of inappropriate antibiotic use for common infections. By targeting HCPs with comprehensive training and resources, we hope to improve infection control practices and promote more judicious use of antibiotics, ultimately enhancing the quality of care for nursing home residents.

Methods

Study Design

This is a before-and-after intervention study in HCPs working in nursing homes. We are using the Audit Project Odense methodology [27], as the strategy to implement the multifaceted actions suggested in point 4.2 of the European Union's AMR Guidelines for long-term care facilities states [23]: "establish a multi-faceted approach which includes elements such as education of nursing and medical staff, audits of antimicrobial use, feedback to the prescribers, and targeting identified areas of antimicrobial overuse and misuse." The improving antibiotic use in nursing homes by infection prevention and control and antibiotic stewardship (IMAGINE) project was initiated in January 2023 and is planned to finish in December 2025. The consortium includes 12 partners from 9 countries, as indicated in Table 1.

Table 1. Partners in IMAGINE[a].

Participant organization name	Abbreviation	Role
Institut Català de la Salut and Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol, Spain	ICS or IDIAP	Coordinator of the project. Spanish coordinator
The Capital Region of Denmark	CAP	Preparation of materials for intervention. Danish coordinator
Research Unit for General Practice Odense, Denmark	RUPO	Audit Project Odense methodology
Szeged Autumns Nursing Home, Hungary	SAN	Hungarian coordinator
University of Ljubliana, Slovenia	UOL	Slovenian coordinator
Medical University of Lodz, Poland	MUL	Polish coordinator
Slovak Medical University in Bratislava, Slovakia	SMU	Slovak coordinator
Ltd Mano Seimos Gydytojas (My Family Doctor)	FDC	Lithuanian coordinator
University of Crete, Greece	UOC	Greek coordinator
University of Las Palmas de Gran Canaria and Fundación Canaria Parque Científico Tecnológico	ULPGC or FCPCT	Analysis and evaluation of the results
Spanish Society for Family and Community Medicine	SEMFYC	Dissemination and training in communication skills
European Union of Geriatric Medicine Society	EUGMS	In charge of dissemination of results

[a]IMAGINE: improving antibiotic use in nursing homes by infection prevention and control and antibiotic stewardship.

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Aims

The primary objectives of this study (IMAGINE project) are aimed at increasing the IPC elements implemented by 50% and decreasing the incidence of inappropriate antibiotic consumption for UTIs by 40%, with a subsequent 20% reduction in the incidence of UTIs. Different secondary objectives are planned: (1) reduction in inappropriate use of urinary catheters in nursing home residents; (2) reduction in the percentage of inappropriate antibiotic use for the prophylaxis of UTIs; (3) reduction in the number of Watch and Reserve antibiotics from the World Health Organization Access, Watch, Reserve classification; (4) improvement in the satisfaction of nursing home HCPs, residents, and relatives; (5) reduction in the incidence of health care–associated infections treated with antibiotics others than UTI; and (6) reduction in the percentage of hospital admissions.

Setting

We are carrying out interventions in nursing homes in 8 European countries: Denmark, Greece, Hungary, Lithuania, Poland, Slovakia, Slovenia, and Spain. In each country, at least 10 nursing homes participate and a team of 4 HCPs in each nursing home are actively involved. Different types of professionals are involved in the health care of residents in the nursing homes: registered nurses, doctors that can be external or working in the facility part-time, health care assistants, or health care helpers. The participating nursing homes select the HCPs of their setting who actively take part in the study. These HCPs will, in turn, become trainers in their own nursing home after the intervention meetings.

Project Methodology

A point prevalence audit is scheduled to assess the outcomes of the multifaceted intervention [27]. The audit is conducted in 2 separate 3-month periods: one before the intervention and another after. The initial registration occurred from February 2024 to April 2024, prior to the intervention, while the second registration will take place from February 2025 to April 2025, after the intervention (Figure 1). Throughout the audit, HCPs record anonymized information on UTIs antibiotic prescriptions on a chart. Sometime during the audit registration, participants are asked to also register the IPC measures in place in the nursing homes. Between the first and second audits, participants will attend a multifaceted intervention aimed at improving the prevention and management of infections in nursing homes (November 2024). The intervention and the data collection sheets are specifically designed for the study, based on preliminary work conducted in 2023.

Figure 1. Audit Project Odense cycle in the IMAGINE (improving antibiotic use in nursing homes by infection prevention and control and antibiotic stewardship) project. IPC: infection prevention and control; PAR: participatory action research.

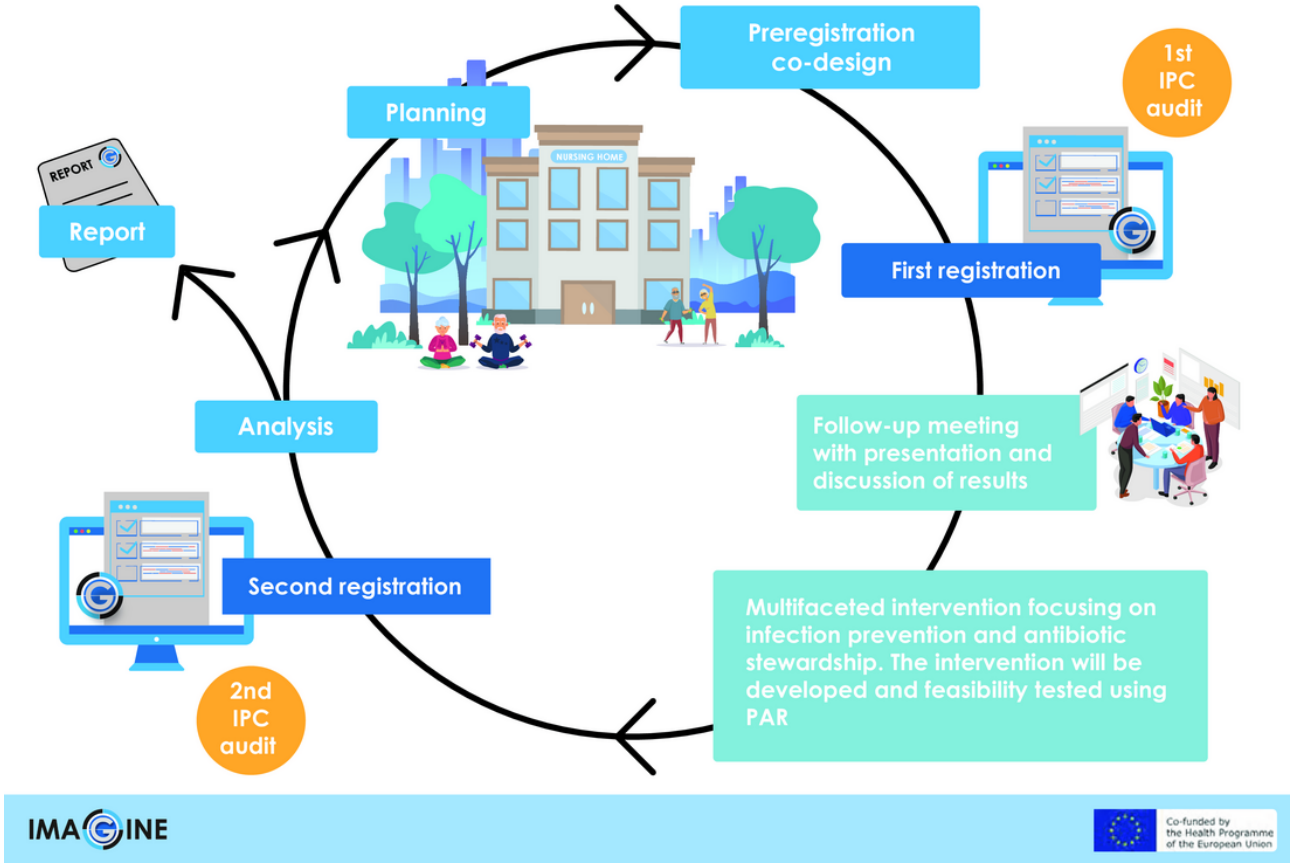

Preliminary Study: Context Analysis

A preliminary study was conducted to identify potential areas for improvement in nursing homes across the 8 participating countries. The study involved a context analysis, which included interviews with HCPs working in nursing homes. These interviews focused on IPC practices, as well as antibiotic

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management. The aim is to explore the factors that contribute to the spread of infections within the target organizations.

Qualitative analysis was used to incorporate the perspectives of various nursing home HCPs in the development of educational materials. These materials facilitate communication between HCPs, residents, and their relatives when discussing the necessity and appropriate use of antibiotics for common infections. The analysis also helps identify any gaps in information that need to be addressed during the multifaceted intervention. Local coordinators within the 8 target countries of the IMAGINE project have contacted nursing home HCPs, who serve as the panel of experts for prioritizing areas of improvement. Their expertise guides the project's focus on enhancing practices in nursing homes.

Data Collection

A specific registration chart has been developed considering the characteristics and the quality improvement areas identified during the preparatory study performed in 2023. During the audit period, the participants are using the Audit Project Odense registration chart developed to record all the antibiotic prescriptions made in the nursing home. At most, 10 main groups and a maximum of 45 variables are used to describe the topic being investigated [27]. The main groups are lined up in a logical way, for example, focus of infection, symptoms, indwelling urinary catheter, diagnostic tests, treatment, and referral or not. The variables are exhaustive (include all possibilities) and exclusive (no overlapping), and all are in the same logic plan. One line is filled in for each case. As a rule, only ticks are allowed (no writing). At least 1 tick per main group is needed. Figure 2 depicts the definitive template used by IMAGINE. A short instruction sheet (maximum 1 page) has been provided for all participants. The instruction sheet specifies the registration period, the inclusion and exclusion criteria for the cases and briefly explains the content of each main group. Information about where to return the completed charts was given. A local contact person from the national teams is available for questions from the participants [27]. A pilot test of the chart was performed between October 2023 and November 2023 with 3 to 5 nursing home HCPs per country to ensure that the content of the registration chart was easily understood and to confirm that enough cases are available.

Figure 2. Template used in the IMAGINE (improving antibiotic use in nursing homes by infection prevention and control and antibiotic stewardship) project for patients receiving antibiotics. Subject to subsequent changes that may arise during the pilot study.

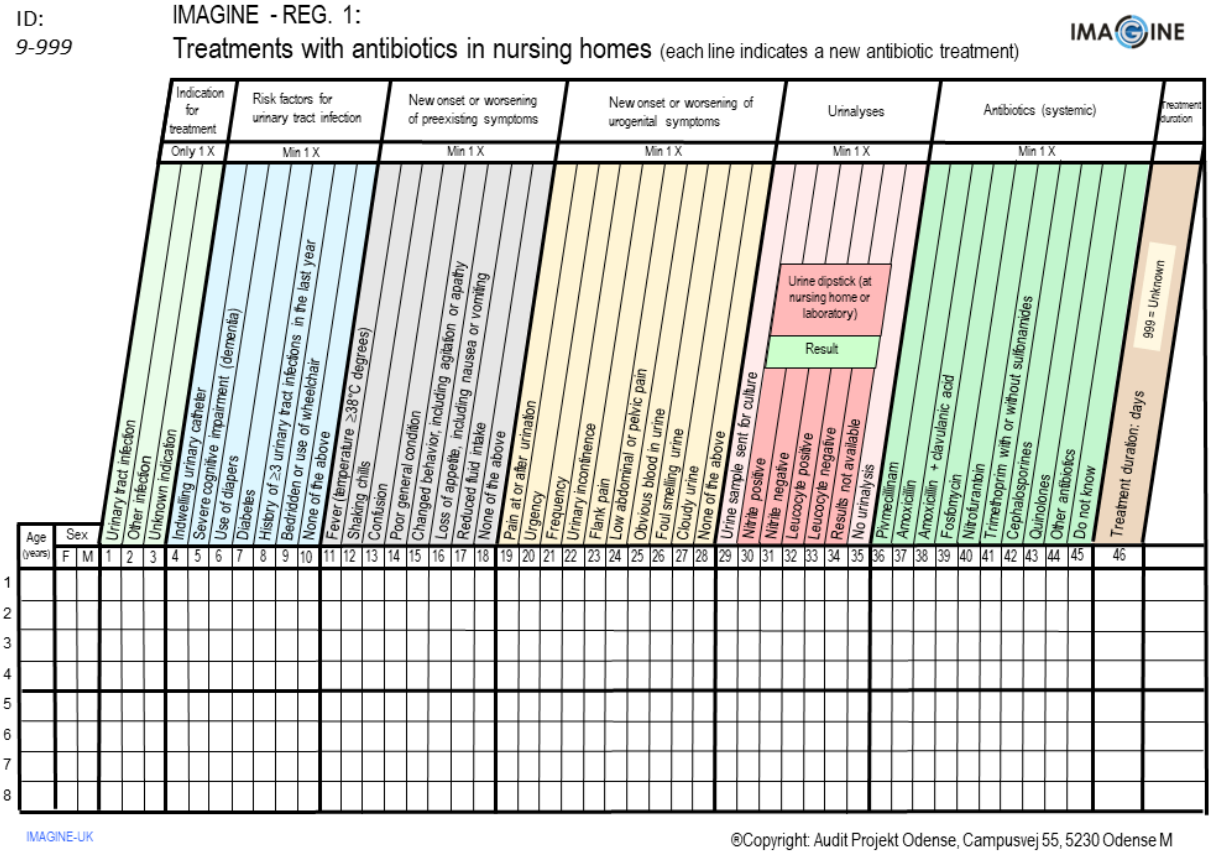

Multifaceted Intervention

Interventions that are expected to have the highest likelihood of success appear to align with the constructs of the normalization process theory, which explain the mechanisms of implementation [28]. These constructs include coherence (making sense of interventions), cognitive participation (engagement with the intervention), collective actions (enabling the intervention to take place), and reflexive monitoring (evaluating the costs and benefits). In the IMAGINE project, the multifaceted intervention aims to address all dimensions of the normalization process theory. It will achieve this by facilitating open discussions regarding variations in practice behaviors and by strengthening communication between HCPs,

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residents, and their families. Through these efforts, the intervention seeks to enhance the understanding and acceptance of the intervention among all stakeholders involved.

The multifaceted intervention will be composed by face-to-face and web-based activities, the latter in an asynchronous manner, enabling nursing home HCPs to engage in these activities at their own convenience. The main part of the training will be a 2-day intervention program consisting of (1) presentation of the first audit results and discussion with the rest of their colleagues in their respective countries, allowing self-reflection of their performance and discussing quality indicators associated with their practice; (2) AMR and IPC elements, with the participation of national experts; (3) discussion on AMS on how to improve the diagnosis of UTIs and the role of antibiotics for these infections; and (4) discussion of best practice case studies and practical issues.

The courses will be based on active discussion among participants, with the use of videos, leaflets, digital material, and role-playing, allowing fruitful discussion. This intervention will be recorded and adapted to a web-based environment. All material created for the intervention will be used to achieve three main objectives: (1) reinforcing the training of the HCPs, allowing them to revisit concepts whenever they need them; (2) training of the rest of the nursing home staff on IPC measures and AMS; and (3) after the end of the project, training of HCPs in other nursing homes in the country.

The intervention will be tailored to the nursing home setting. Achieving a significant behavioral change among multiple HCPs is essential for improving antibiotic prescribing in this population. To accomplish this, we will use the participatory action research methodology, which actively involves HCPs in the implementation of IPC and AMS interventions that are customized to their specific health care settings. This approach takes into account the local barriers and facilitators that may affect the successful implementation of these interventions [29]. The primary objective of the participatory action research is to generate practical knowledge that can be readily applied in local practice. By using this methodology, we aim to gain a better understanding of the complex decision-making process related to IPC practices and suspected health care–associated infections among frail elderly residents in nursing homes. It is important to consider the diverse elderly care settings across the various target countries, and participatory action research will help us navigate this heterogeneity [30].

National HCPs and stakeholders will participate to identify factors in the nursing home setting that contribute to increased risk of spread of infection and to determine national characteristics of nursing home management, diagnosis, and antibiotic prescription practices for nursing home residents and elderly patients with symptoms of infection. They will also work together to identify quality improvement areas related to hygiene, infection prevention, and inappropriate use of antibiotics; define priorities to be included when developing the educational material that will be used for facilitating communication between HCPs, residents, and relatives; and define an algorithm to be used for analyzing antibiotic inappropriateness in the different types of health care–associated infections.

Data Analysis Plan

The data collected in the specific registration charts have a primary function at the individual level of health professionals, that is, helping them to improve their practice by reconsidering their treatment choices considering clinical evidence, guidelines, and professional consensus [31]. The second function is to analyze the data to evaluate the effect of the intervention. In each audit, data are recorded for all antibiotics prescribed during the 3-month period. We aim to record a minimum of 50 cases in each of the nursing homes recruited (at least 100 nursing homes), yielding an approximate number of 5000 cases in each registration period.

We will apply the chi-square test to determine the frequencies and appropriateness of prescriptions before and after the intervention and Student *t* test for the number of hygiene elements implemented in the nursing homes to test the null hypothesis of no effect of the interventions. To measure the potential reduction in UTIs, we will assume that antibiotics are always prescribed for these infections and every antibiotic is associated with a new episode of UTI [32]. The number of hygiene elements implemented will be compared with a threshold that will be defined during the participatory action research analysis. The appropriateness of antibiotic prescriptions will be defined according to an algorithm based on symptoms and patient characteristics that will be developed at the start of the project. We will also estimate the effect of the interventions on inappropriate prescriptions for UTIs using multilevel logistic regression models with 2 levels: cases and HCP participants, to allow for the fact that patients belonging to the same HCP are not independent of each other [33]. Statistical significance will be considered with $P<.05$. The data will be analyzed using the current version of the Stata statistical program (version 18, StataCorp LLC).

Data Management

The collection of the audit data is performed on paper. The registration templates will be stored securely in in each participating nursing home and will be accessible only by study staff and authorized personnel. Charts will be transferred electronically to the Audit Project Odense service provider to be entered in a database [31]. Data from residents will be anonymously collected from the beginning and no identifiable or personal information will be gathered. Nursing homes will be identified by a code. Qualitative interviews will be audio recorded, transcribed, and translated, and any identifiable information will be deleted in the process. Translations will be transferred securely to the organization in charge of analyzing the results. Anonymized data from the survey will be stored for a minimum of 5 years after publication of the results. Anonymized project data will be shared for common analyses and presentation to the scientific community through publications and conferences.

Ethical Considerations

The study is conducted in accordance with the protocol, the Declaration of Helsinki, the principles of Good Clinical Practice,

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The General Data Protection Regulation (of the European Union) 2016/679 and the Human Research Act as well as other locally relevant regulations. Appropriate regulatory or ethical approval has been sought in each of the countries taking part in the study, and all study procedures started after gaining approval on the basis of the master protocol, translated where necessary to local language. In Spain, the coordinating country, the study protocol was approved by the Ethics Committee of Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol), Institute of Research in Primary Health Care (23/080-P).

Nursing homes have been contacted by local coordinators that have explained the study and handed over the information, giving the nursing home time to read it and ask any questions. Informed consent was obtained from all participants. HCPs are participating voluntarily in this quality improvement project. No personnel data are collected from either HCPs or patients. A nursing home can withdraw from the project at any time without giving any explanation. The information gathered from the residents' prescriptions are personally nonidentifiable data and we are collecting the minimum data set necessary for the study. Data are anonymized from the beginning, coded in the template with the code of the nursing home and a consecutive number for each antibiotic treatment. Individual patient consent is therefore not required.

Results

The local coordinators in each of the countries have already contacted all the nursing homes participating in the IMAGINE project, with a total of 109 nursing homes. All these nursing homes have already completed the first audit registration. The results of the first audit registrations will be available before the intervention takes place in November 2024. The overall results of the IMAGINE project will be available after summer 2025 and the results will be published by the end of 2025.

Discussion

We hypothesize that this 2-day multifaceted intervention for health care providers in nursing homes will significantly improve adherence to IPC practices and enhance understanding of when to suspect a UTI. This improved adherence is expected to result in a notable reduction in the rates of inappropriate antibiotic consumption for UTIs. We anticipate that these changes in practices and antibiotic usage will be followed by a subsequent reduction in the incidence of UTIs, as observed during the second registration audit. The overall aim is to enhance the quality of care and patient outcomes through better preventive measures and more judicious use of antibiotics in nursing homes.

The increasing concern about the emergence of AMR in nursing homes necessitates a cohesive and systematic approach to address challenges across very heterogenous settings and diverse health care delivery systems, already under pressure. Additional challenges result in a confluence of risks for colonization or infection with multidrug-resistant pathogens among residents, rendering nursing homes potential reservoirs for AMR [34]. Infections caused by antibiotic-resistant bacteria are associated with a greater need for medical visits; more hospital admissions; higher mortality; and higher economic, intersectoral, and societal costs [35,36]. A recent study tested a multifaceted AMS stewardship intervention in Poland, the Netherlands, Norway, and Sweden and found it effectively and safely reduced UTI antibiotic prescriptions among frail older adults [37]. This study demonstrates that educating care home staff about UTIs and improving their communication with HCPs significantly reduces inappropriate UTI antibiotic prescribing [38,39]. This high use of UTI antibiotics in care homes may be driven by a high prevalence of asymptomatic bacteriuria among residents, which can be as high as 50%, compared to just 4% in older people living independently [40,41]. This is despite no reported benefit from treating asymptomatic bacteriuria with antibiotics. Clinical uncertainty around symptoms such as confusion, falls, and agitation being attributed to UTIs also contributes to the high rate of antibiotic use [42].

Implementing hygiene strategies and reducing the unnecessary prescription of antibiotics has been shown to be the most effective measure to curb the problem of AMR [43,44]. The IMAGINE study aims to address gaps related with AMS and IPC elements through an intervention targeting HCPs to enhance their adherence to good clinical practices. Importantly, this study poses no risks to the HCPs or the residents whose treatment data will be collected. The intervention will use various techniques, including providing feedback to HCPs in nursing homes, conducting follow-up meetings, facilitating discussions on guidelines, offering training courses for HCPs with special focus on when a UTI should be suspected, and distributing informative and educational materials to residents and their relatives.

Furthermore, the IMAGINE study encompasses 8 European countries that exhibit diverse prevalence of antibiotic resistance, distinct cultural backgrounds, varying socioeconomic indices, and different health care systems. This broad scope increases the applicability of the study findings to a wide range of settings. If we find our intervention to be effective, we strongly believe this work has great potential for dissemination. The final results of this quality improvement project will be submitted for publication in a peer-reviewed journal and presented at international scientific conferences. Ultimately, these findings will inform public health interventions aimed at promoting appropriate antibiotic prescribing and implementing effective hygiene strategies in nursing homes.

The use of the Audit Project Odense method has certain limitations. The one notable weakness is the lack of external validity associated with the collected data. Since nursing home HCPs participate voluntarily, their prescribing habits may not accurately represent the average antibiotic use in all nursing homes within their country. Additionally, the nursing homes involved in the audits might exhibit a greater interest in quality improvement and potentially use more rational antibiotic practices compared to nonparticipating nursing homes [45]. Another aspect to consider is the potential influence of conducting an audit on providers' prescribing behaviors. The HCPs are aware of being observed, which can lead to what is known as the Hawthorne effect. It is important to note that this

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study is not a clinical trial and lacks a control group, which could be considered a limitation. However, the study will compare the same participants before and after the intervention. Participation in a quality improvement project can pose a barrier due to the required time commitment. While completing a registration takes less than 2 minutes, HCPs need to allocate time for educational courses and other planned activities associated with the intervention. Another weakness is the cross-sectional nature of the Audit Project Odense method. The variables included in the registration chart are aligned with the consultation process, and ideally, the decision to treat should follow the establishment of a diagnosis. However, in practice, diagnostic procedures and treatment decisions are often intertwined [46]. HCPs may determine whether to prescribe a medication concurrently or even prior to establishing a diagnosis. Consequently, clinicians may adjust the diagnosis to align with the treatment decision, potentially introducing a diagnostic misclassification bias. Nevertheless, this potential bias would impact the validity of the diagnosis both before and after the intervention, with minimal likelihood of influencing the intervention's effectiveness. Due to time constraints in the registration process and limitations on the maximum number of columns in the Audit Project Odense chart, only the typical signs and symptoms of UTIs are collected. This may result in certain limitations, as nonbiomedical factors that could serve as powerful predictors of antibiotic prescriptions are not considered in this study. This restricts the definition of antibiotic appropriateness in our study, as it is based on the collected items in the registration charts.

In conclusion, despite the widespread use of antibiotics and the increasing development of AMR, there have been limited efforts to reduce the occurrence of common infections in nursing homes and improve the diagnosis of UTIs. Moreover, there is a lack of initiatives focused on implementing measures related to hygiene and reducing the inappropriate use of antibiotics in this setting. This protocol has summarized the rationale and design of a before-and-after intervention study aimed at evaluating the impact of a multifaceted intervention on antimicrobial use for UTIs among residents in nursing homes, its appropriateness and the elements of hygiene implemented.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AGS, JNJ, JK, MPH, A Bjerrum, and C Llor conceived the study. C Llor drafted the manuscript. BGLV, FR, and LV were responsible for the statistical analyses. AGS, MPH, JNJ, AC, VSA, TM, BGLV, FR, LV, JL, MPH, JS, AK, C Lionis, MA, AA, and EP provided critical revisions. AGS, DM, JNJ, AC, VSA, TM, AMT, BGLV, FR, LV, JL, MPH, JS, JKO, AM, RB, A Balint, DP, NS, AK, MGC, HG, JG, RRJ, LJ, C Lionis, MA, AA, EP, GR, LA, MR, SB, A Bjerrum, RM, and C Llor read, commented, reviewed, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review Report from the European Commission (EU4 Health Programme).
[PDF File (Adobe PDF File), 234 KB - resprot_v13i1e60099_app1.pdf]

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Abbreviations

AMR: antimicrobial resistance
AMS: antimicrobial stewardship
HCP: health care professional
IDIAP Jordi Gol: Institut Universitari d'Investigació en Atenció Primària
IMAGINE: improving antibiotic use in nursing homes by infection prevention and control and antibiotic stewardship
IPC: infection prevention and control
UTI: urinary tract infection

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Protocol

Family Support Protocol for Adolescent Internalizing Disorders: Protocol for a Pre-Post Quantitative Treatment Development Study

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Abstract

Background: Internalizing disorders (IDs), primarily depression and anxiety, are highly prevalent among adolescents receiving community-based treatment for substance use disorders (SUDs). For such clients, interventions that do not holistically address both SUDs and IDs are less effective.

Objective: This pilot treatment development study aims to develop and test a modular treatment protocol for addressing cooccurring IDs among adolescents (aged 13 to 18 years) enrolled in routine care for substance use problems: Family Support Protocol for Adolescent Internalizing Disorders (Fam-AID). As an adjunctive protocol, Fam-AID will not require clinicians to markedly alter existing base practices for SUD. It will be anchored by 3 evidence-based foundations for treating cooccurring adolescent IDs: family engagement techniques, transdiagnostic individual cognitive behavioral therapy techniques, and family psychoeducation and safety planning.

Methods: This quasi-experimental study will proceed in 2 stages. The pilot stage will use rapid-cycle prototyping methods in collaboration with end-user stakeholders to draft protocol delivery and fidelity guidelines adapted from existing resources, solicit provider and client input on protocol content and delivery via cognitive interviewing, and pilot prototype components on 4 to 6 cases. The second stage will be an interrupted time series study for 60 comorbid SUD+ID cases across 2 sites serving diverse adolescents: 30 will receive treatment as usual (TAU); following clinician training in the protocol, 30 new cases will receive TAU enhanced by Fam-AID. For aim 1, the focus is on evaluating the acceptability of the Fam-AID protocol through therapist and client interviews as well as assessing fidelity benchmarks using therapist- and observer-reported protocol fidelity data. For aim 2, the plan is to compare the effects of TAU only cases versus TAU+Fam-AID cases on family treatment attendance and on adolescent ID and substance use symptoms, with measurements taken at baseline and at 3-month and 6-month follow-ups.

Results: Study recruitment will begin in April 2025.

Conclusions: We anticipate that Fam-AID will contain 5 treatment modules that can be delivered in any sequence to meet client needs: *family engagement* of primary supports in treatment planning and services; *relational reframing* of family constraints, resiliencies, and social capital connected to the adolescent's ID symptoms; *functional analysis* of the adolescent's ID symptoms and related behaviors; *cognitive behavioral therapy* to address the adolescent's ID symptoms and functional needs, featuring 3 core techniques (emotion acceptance, emotional exposure, and behavioral activation) to address negative affect and emotional dysregulation; and *family psychoeducation and safety planning* focused on education about comorbid SUD+ID and prevention of adolescent self-harm. If the abovementioned modules are found to be feasible and effective, Fam-AID will offer a set of pragmatic interventions to SUD clinicians for treating cooccurring IDs in adolescent clients.

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International Registered Report Identifier (IRRID): PRR1-10.2196/64332

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KEYWORDS

adolescent substance use; adolescent anxiety and depression; cooccurring disorders; adjunctive treatment; family-based interventions; usual care

Introduction

Anxiety and Depression Among Adolescents With Substance Use Disorders: Highly Prevalent and Disruptive

Anxiety (including trauma-related problems) and depression are highly prevalent among adolescents who misuse substances. National and community surveys report that adolescents with substance use disorders (SUDs) have comorbidity rates ranging between 17% and 30% for an anxiety disorder, major depressive disorder, or both [1]. Comorbidity is even higher in clinical samples. Adolescents enrolled in SUD treatment have cooccurrence rates ranging from 22% to 26% for anxiety disorders and 24% to 50% for depression disorders, along with an alarming range of 55% to 70% for clinically elevated symptoms of either disorder [2,3]. Anxiety and depression diagnoses themselves cooccur at such high rates in adolescents that prevailing clinical taxonomies place them within a single category of internalizing disorder (ID) whose core symptoms—anxious emotional states, depressed mood, somatization, and social withdrawal—are associated with overcontrolled behaviors and subjective distress. According to the tripartite model of comorbidity, the strong cooccurrence of anxiety and depression symptoms constitute a shared internalizing syndrome, *negative affectivity*, which is linked to other internalizing symptoms such as low positive affect and anxious arousal [4-6]. In this vein, developmental theories describe an internalizing pathway to SUD whereby childhood behavioral challenges marked by negative affectivity and social inhibition predispose adolescents to substance use (SU) problems [7,8].

Longitudinal outcome data suggest that adolescents with cooccurring SUD+ID are more difficult to treat effectively than those who do not have IDs. One systematic review [9] found that adolescents with comorbid SUD and depression showed higher attrition from treatment, and generally worse outcomes for both SU and depression, than those with a singular disorder. Another study [10] reported that baseline levels of elevated ID symptoms or diagnosis of an anxiety or depression disorder broadly predicted worse SU outcomes. Studies have also shown that maintenance of SUD treatment gains [11,12] and posttreatment recovery to adaptive levels of functioning [13] are harder to achieve for adolescents with IDs and related negative affect. It also appears that ID-related symptoms impact posttreatment SU behavior in multiple ways, foremost being that negative affect can induce adolescents to reinitiate use [14] or interfere with their motivation and capacity to use relapse prevention and health promotion skills learned during treatment [15].

Usual Care for Adolescent SUD: Sizable Gaps in Evidence-Based Treatment Planning for ID

A recent Substance Abuse and Mental Health Services Administration resource guide on adolescents with serious emotional disorders and cooccurring SU [16] asserts that integrated planning for adolescent SUD+ID is routinely inaccessible due to several factors, including broad service fragmentation and limited cross-training for both SU and mental health clinicians; moreover, few clinicians have specialized training in both disorders. Clinicians with specialty licenses to treat SUD are typically required to obtain only generic training in cooccurring disorders; they do not receive systematic training in IDs or certified training in evidence-based practices for ID [17]. Surveys of the adolescent SUD specialty workforce confirm this ID services gap [18,19]. One study [20] found that while only 10% of SUD clinicians reported using specific protocols to treat SUD+ID, 97% indicated they would use such a protocol, and moreover, they could dedicate 8 workday hours to train in it.

Integrated Treatment Models for Comorbid SUD+ID: Major Barriers to Implementation

One strategy to promote treatment planning and training for SUD+ID is to disseminate integrated treatment models that contain 2 components: one targeting SUD and the other targeting ID. However, because integrated models of this type require multidomain symptom targeting and intervention coordination, they are difficult to implement and evaluate [21]. To date, only a few integrated models for adolescent SUD+ID have been tested in randomized trials. Esposito-Smythers et al [22] demonstrated the effectiveness of a protocol that included cognitive behavioral therapy (CBT) for SUD, individual CBT for depression and suicidality, and family skills training. Rohde et al [23] varied treatment delivery sequence for adolescents with SUD and depression. This led to the finding that compared to a CBT-first model and a simultaneous family-and-CBT model, family therapy for SUD followed by CBT for depression was the most effective for combined SU and depression outcomes. Goldston et al [24] found that a protocol grounded in CBT and relapse prevention for SUD, depression, and suicidal behavior outperformed usual care. Two other manualized models [25-27] integrated family and individual CBT interventions for SUD and ID, including posttraumatic stress disorder; a handful of studies have examined brief interventions targeting both SU and ID in adolescents [28].

Unfortunately, none of the integrated models targeting adolescent SUD+ID has been scaled to widespread use. A first category of scalability barriers pertains to *characteristics of the behavioral health system*. Clinicians with specialty SUD licenses

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typically have little training or clinical support in addressing IDs. Factors related to clinician training, site licensing, and health care regulation contribute to this deficiency [16,29]. As a result, adolescent SUD clinicians are generally not familiar with evidence-based ID interventions and are not clinically prepared to deliver them [20,30]. This deficiency reflects a broader and longstanding service fragmentation problem in the United States: mental health and SU treatment systems are largely siloed from one another, failing to adequately address the needs of adolescents with cooccurring problems [31,32]. A second category of scalability barriers pertains to *characteristics of integrated models*. Previously described integrated SUD+ID models share basic structural features with the larger phylum of manualized behavioral models. Manualized models typically feature structured intervention sequencing and wholesale implementation of treatment components. In contrast, community clinicians favor piecemeal implementation and selective treatment planning, including the flexible use of techniques as adjunctive interventions for cases with complex diagnoses [33,34]. Manualized models also contain extensive quality procedures to facilitate therapist training, fidelity, and ongoing certification. Such procedures are difficult to sustain due to vicissitudes in regulatory practices, decrease in agency stamina to honor quality methods for extended periods, and demoralization when external experts manage quality control [35].

Promising Solution to Overcoming Implementation Barriers: Core Elements Strategy

Formidable implementation barriers negatively impact the proficiency of disseminating and training the SUD workforce to use integrated models for SUD+ID. Similarly, it will not be enough to more efficiently disseminate and train SUD clinicians in manualized models for adolescent depression, anxiety, or both, all the same barriers to widespread scalability loom. An alternative strategy to advance scalability of evidence-based treatments is to focus on core elements that are common across models for similar populations. The core elements strategy defines reduced sets of specific techniques that are common, active ingredients in multiple treatments for a given disorder [34,36]. This strategy offers implementation advantages in 2 key domains: *modularity and sustainability*. Regarding *modularity*: core elements, delivered as modular units or as a sequence of discrete interventions, can be more easily learned and retained by trainees and can be flexibly selected and coordinated to address diverse, comorbid, and emerging clinical problems [37,38]. Regarding *sustainability*, core elements promote clinician judgment, coupled with broad guidelines, to flexibly select interventions to fit client profiles [39]; provide strategies to select interventions for comorbid clients for whom no dedicated manuals exist [37,40]; and avail a few intervention modules to apply across numerous clients [34,36]. Core elements have proven feasible to scale in routine settings [37,41,42]; moreover, core elements can perform on equal footing with manualized treatments across an array of adolescent outcomes [41,43,44].

Core Elements for Targeting IDs Among Adolescents With SUD+ID: 3 Foundations

Overview

In line with the core elements strategy, this study is developing a core elements protocol designed to treat ID symptoms among adolescents with SUD in usual care. It combines several existing treatment techniques, most of which have empirical support for addressing treatment targets related to adolescent ID, into a single modular protocol: Family Support Protocol for Adolescent Internalizing Disorders (Fam-AID). As depicted in Figure 1, intervention selection is guided by 3 broad evidence-based principles for treating adolescent SUD+ID: Engage the Family System, Deliver Transdiagnostic Interventions for ID, Reinforce the Family Safety Net.

Figure 1. Protocol foundations for this study. CBT: cognitive behavioral therapy; ID: internalizing disorder; SUD: substance use disorder.

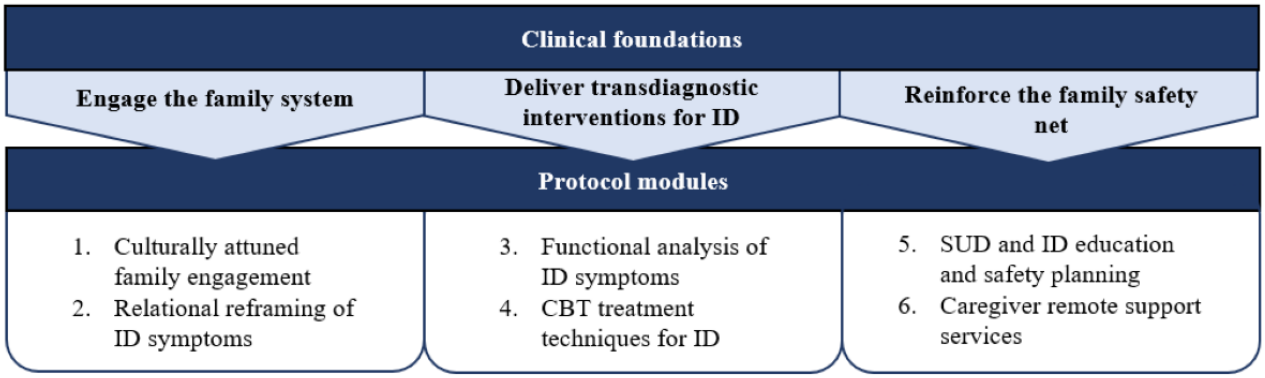

Engage the Family System

To enhance adolescent readiness to participate in behavioral treatment of any type, it is highly advantageous to engage parents and other family members actively [45]. Research-based family engagement interventions for an array of adolescent services include emphasizing the role of family involvement in services, anticipating how family resources and dynamics could impact participation, building alliances with multiple family members, and managing family interactions during initial clinical encounters [46]. Specific to adolescents, evidence-based interventions for engaging families include systemic family engagement [47-49], which focuses on recognizing incompatible agendas of family members and how this reduces the likelihood of any member attending, identifying who can act as a reliable family messenger and who has power to influence other members to attend, and providing rationale for treatment that

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accounts for concerns of key members. An engagement strategy unique to family-based treatment is relational reframing [50,51], which involves efforts to transform symptom- or person-focused perceptions of clinical problems into an understanding of those problems as having important, fundamentally relational aspects [52-55].

Deliver Transdiagnostic Interventions for ID

Adolescents with elevated ID levels often have underlying emotional vulnerabilities in 3 areas: negative emotional reactivity, in the form of more frequent experiences of intense negative emotions and less flexible reactions to these; affect intolerance, such that emotional experiences are perceived as difficult to endure; and emotional avoidance, wherein adolescent respond to affect intolerance with efforts to suppress, avoid, or otherwise control uncomfortable feelings [56,57]. Therefore, interventions for adolescent ID need to target high levels of negative affect, distress intolerance, and affect avoidance. An efficient approach for treating these overlapping vulnerabilities is to use transdiagnostic interventions, which treat similar behavior problems (eg, anxiety and depression) via interventions targeting higher-order precipitating processes (eg, emotion dysregulation) [58,59]. Transdiagnostic interventions have proven efficacious for adolescents with IDs in multiple baseline, open, and randomized trials [60-63], producing improvements in depression, anxiety, and emotion dysregulation symptoms [60,61,64]. Ideally, transdiagnostic interventions for ID symptoms among adolescents with comorbid SUD+ID should be guided by functional assessment of the adolescent's specific ID-related impairments [21], which facilitates treatment customization by narrowing the field of available techniques to those specifically indicated for the client [65-67]. Of the several transdiagnostic techniques available for adolescent ID, 3 appear most salient for addressing factors that also predispose SU among adolescents: *emotion acceptance*, which targets emotional regulation and distress tolerance and also enhances inhibitory learning during exposure [60,61,64,68]; *emotional exposure*, a primary driver of positive effects for adolescent anxiety [69]; and *behavioral activation*, a primary driver of positive effects for adolescent depression [70].

Reinforce the Family Safety Net

An essential component of comprehensive treatment planning for adolescents with SUD+ID is accounting for potential self-harm, suicidal ideation, and suicidal behavior, which often occur among adolescents with clinically elevated ID levels, especially when there is cooccurring SUD [71,72]. Adolescents and their families can be co-educated about potential self-injurious behaviors and invited to cocreate safety plans [73]. Although single-session adolescent-only safety contracts are not routinely effective, more intensive safety planning involving families can reduce self-harming behavior in adolescents [74]. Moreover, family members can be sources of recovery capital to help adolescents sustain reductions in SUD and ID symptoms.

Specific Aims of the Study

In year 1, this study will develop a Fam-AID implementation toolkit during a three-part *pilot stage* at 1 pilot site by (1) soliciting provider input on Fam-AID components; (2) creating video-based training and fidelity procedures, leveraging the research team's existing training and consultation resources in both core family-based interventions [75,76] and adolescent-focused transdiagnostic techniques [77] for adolescent behavior problems; and (3) piloting the toolkit with 4 to 6 clients. In years 2 to 3, this study will conduct an *interrupted time series* evaluation for 60 adolescent SUD+ID cases across 2 sites serving diverse clients: 30 cases will receive treatment as usual (TAU), and then following clinician training, 30 new cases will receive TAU enhanced by Fam-AID.

This protocol development study has 2 specific aims:

- Aim 1 (protocol feasibility): in the Fam-AID condition only, the study will evaluate (1) protocol acceptability via client and therapist qualitative interviews and (2) fidelity benchmarks via therapist- and observer-report fidelity measures of protocol coverage (Is each module delivered in at least 1 session?) and protocol dose (Is the average module extensiveness score greater than the mean of the fidelity measure?).
- Aim 2 (protocol outcomes): in comparing the TAU only condition versus the TAU+Fam-AID condition, the study will examine the protocol's impacts on (1) family member session attendance using clinic logs and (2) adolescent ID-related symptoms (emotion regulation, depression, and anxiety), SU, and family communication about SUD+ID at 3-month and 6-month follow-up. Overall, these pilot-scale protocol viability and impact findings, if promising, will set the stage for a randomized trial to examine the effects of Fam-AID on immediate and ultimate outcomes in a larger community sample.

Methods

Pilot Stage: 3-Phase Clinical Protocol Compilation Procedures

At *project initiation* (months 1 and 2), the study team will review three clinical protocols and companion training resources that were collectively produced by them: (1) archive of empirically distilled core family therapy treatment techniques for adolescent SUD [51], (2) adjunctive family-based protocols for targeting cooccurring attention-deficit/hyperactivity disorder among adolescents with primary SUD [78,79], and (3) the Unified Protocol for Adolescents for transdiagnostic CBT interventions to treat adolescent ID [60,77,80]. The team will converge these resources to create prototype components for the 5 Fam-AID modules. They will then launch the pilot stage, a 3-phase stakeholder-informed process to develop Fam-AID prototype components into a beta protocol. Pilot phase work will follow procedures of rapid-cycle prototyping that use mini-pilots to test early versions of protocols, combined with ongoing feedback from content experts and other stakeholders, to learn how to best design new strategies [81,82].

During *pilot phase 1* (study months 3 to 5), the study team will conduct in-depth interviews with clinic staff and families (adolescent and caregivers) at 1 pilot site, with 3 primary goals. First, they will interview both staff and families about existing

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barriers and potential facilitators to engaging caregivers in site services. Though evidence-based interventions exist for engaging families in adolescent services, and these will be systematically incorporated in Fam-AID module 1, such interventions are rarely used in routine care. To help prepare module 1 for this challenge, the team will apply their expertise in this area [83] to identify and investigate engagement barriers (logistic, attitudinal, and institutional) and generate pragmatic strategies to solve or ameliorate barriers and enhance both (a) family motivation and intention to participate and (b) site policies to facilitate family involvement. This information will feed forward into pilot phase 2 and phase 3 activities and ultimately into the design of the new protocol. Second, the team will confer with site administrators and staff to obtain feedback on proposed clinical and fidelity strategies for engaging the family system through culturally attuned engagement strategies and relational reframing of the adolescent's ID symptoms, delivering transdiagnostic interventions for adolescent ID using in-session functional analysis of ID symptoms followed by the selection of CBT techniques for ID, and reinforcing the family safety net via family-based psychoeducation about SUD+ID symptoms and long-term safety planning interventions related to adolescent self-harm. Third, they will interview 3 to 4 adolescents and families to canvass their knowledge, attitudes, social influences, and personal experiences related to SUD and ID services, with emphasis on perceived barriers and facilitators to integrated treatment planning for ID symptoms. The milestones for the completion of pilot phase 1 will be collaborative team-clinic consensus on initial drafts of enhanced family engagement strategies, overall protocol content, and training and implementation materials for the projected 5 Fam-AID modules.

During *pilot phase 2* (months 6 to 11), guided by phase 1 results, the team will finalize modifications to Fam-AID component prototypes. The team will subject prototype materials to cognitive interviewing [84] with staff and clients at the pilot site, during which respondents will be asked to think aloud when answering questions about components. Cognitive interviewing is used to refine procedures by assessing respondent comprehension, what is meant by a particular response, and whether additional content is needed to complete a process. This phase will also focus on usability testing of protocol and implementation materials to ensure they are user friendly and efficient in delivering specified interventions [85,86]. The milestones for pilot phase 2 completion will be rapid-cycle consensus on modifications to Fam-AID prototype components, resulting in a beta protocol that accounts for barriers and facilitators to delivery in routine care, which will then be vetted in pilot phase 3.

During *pilot phase 3* (months 12 to 14), the team will pilot the beta Fam-AID version by delivering components to 2 to 3 clients, successively adjusting component prototypes across clients and sessions, to tweak module design and troubleshoot clinical and technological features. They will then finalize component prototypes through culminating interviews with staff and clients to vet feasibility, utility, and resource requirements; this will help with empirical optimization of delivery parameters (dose, frequency, and sequencing benchmarks). The milestone for pilot phase 3 completion is rapid-cycle finalization of components constituting the Fam-AID modules.

Interrupted Time Series: Study Design

Following the completion of the pilot stage, the team will conduct an interrupted time series study featuring quasi-experimental pilot effectiveness research methods to evaluate the Fam-AID protocol and implementation toolkit [87]. Figure 2 depicts the basic design and timeline of the interrupted times series study. The quasi-experimental interrupted time series with nonequivalent groups, which tracks target data both before and after introducing a programmatic change to a group whose membership may vary over time, is appropriate for testing viability and impacts of new interventions delivered in field settings [88-90]. This design is functionally similar to a posttest-only design with a nonequivalent historical control group. Two partner clinic sites will be involved to reduce confounds from site-specific implementation effects and increase diversity in clients and therapists. Aim 1 methods will feature procedures designed for stage 1 treatment development [91,92] to establish proof-of-concept (acceptability and fidelity benchmarks) for the protocol and toolkit. Aim 2 methods will examine Fam-AID's impact on family member attendance in treatment and client outcomes (adolescent ID symptoms, adolescent SU, and parent-adolescent communication about SUD+ID).

Figure 2. Design and timeline of study activities for this study. TAU: treatment as usual.

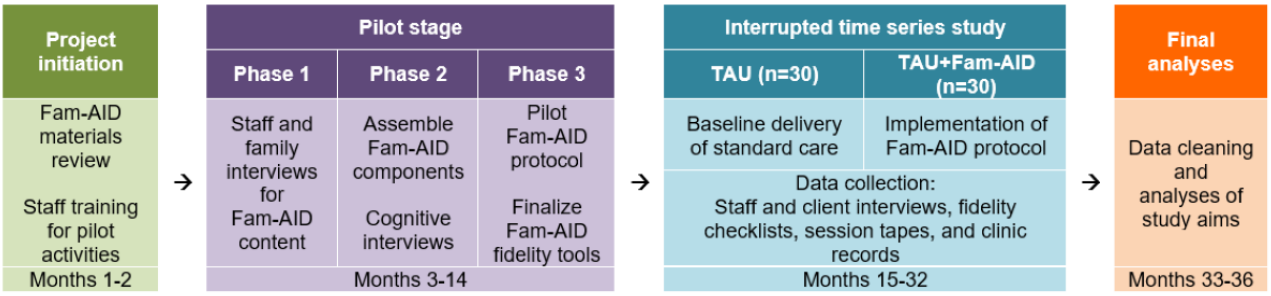

Study Sites and Participants

Both study sites are licensed to deliver SUD services to adolescents. Neither site currently supports an evidence-based treatment protocol that specifically targets IDs. Participant inclusion and exclusion criteria are shown in Textbox 1.

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Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- The adolescent is aged 13 to 18 years.
- The adolescent lives with a primary caregiver who can attend treatment sessions.
- The adolescent endorses ≥1 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* [93] symptom for substance use disorder and meets the American Society of Addiction Medicine criteria for outpatient substance use treatment.
- The adolescent meets the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* criteria, or has elevated symptoms and impairment, for an ID, with the following expected to be most common: current or recurrent major depressive episode, pervasive depressive disorder, social anxiety disorder, generalized anxiety disorder, panic disorder, and posttraumatic stress disorder.
- The adolescent completes intake and is enrolled as an active case at the study site.

Exclusion criteria

- The adolescent has an illness requiring hospitalization.
- The adolescent has current psychotic symptoms.
- The adolescent has severe substance use problems that require immediate relief (detox or residential placement).
- The adolescent has pervasive developmental disorder.

To match real-world care, no eligibility criteria or other study directives will pertain to medication status. Assessment data collected during previous studies in the same regions [79,94] provide the following adolescent demographic projections: average age approximately 16 years; male participants, 70% (42/60) and female participants, 30% (18/60); Black, 15% (9/60); Latinx, 40% (24/60); White non-Latinx, 40% (24/60); and other, 5% (3/60).

Study Condition: TAU Only

Previous research on TAU intervention delivery at both study sites using therapist self-report [95] and observational data from session recordings [96] indicates that site therapists routinely deliver relatively low-dose quantities of evidence-based SUD treatment techniques, favoring motivational interviewing and addiction counseling techniques, with even less delivery of CBT or family therapy techniques for SUD. Sites do not have existing protocols for treating IDs as either main referral problems or cooccurring conditions.

Study Condition: TAU+Fam-AID

Overview

Fam-AID will contain 5 modular components to be delivered in any order and to the extent indicated based on case status [37,43,97]. Modules can be individually or collectively completed in 1 session, staggered across sessions, and interspersed with other interventions. The time required to complete each module will vary based on client profile, practice habits of the provider, and case progress. Fam-AID will have standardized options for versatile delivery with individual adolescents alone whenever family members cannot be engaged in services; modules 3 and 4 can proceed intact, and module 5 can be adjusted for adolescent-only delivery. The study will be halted if it appears that Fam-AID delivery induces clinical harm. The following is a description of the projected module content, considering that the ultimate set of modules and their content will be determined over the course of the study:

Module 1: Culturally Attuned Family Engagement

To promote family engagement, clinicians collaborate with the family members by instilling hope and involving them in goals related to ID problems. They encourage the family members to attend sessions throughout care, present treatment as an opportunity to talk about new issues or old issues in new ways, connect with the family members by showing respect and validation, and use relevant self-disclosure to establish connections [98-100]. Family engagement is guided by the principles of cultural attunement [101], which include accentuating values and strengths minimized in dominant culture, remaining accountable for how interventions disrupt or reinforce existing inequities, and encouraging the family members to make conscious choices about how they frame their identities and respond to injustice.

Module 2: Relational Reframing of ID Symptoms

Clinicians use relational reframing techniques to shift the focus of treatment from exclusively fixing adolescents and their symptoms to improving the quality of adolescent-family relations. They assert that treatment should be grounded in acknowledging, understanding, and repairing relationship problems as a means of addressing adolescent ID problems and bolstering individual and family recovery paths. Basic approaches to delivering a relational reframe for adolescent IDs include identifying sequences of behaviors or emotions involving families that precede or directly cause identified problems; focusing on the impact that ID-related problems have on the thoughts, feelings, and behaviors of both adolescent and family; and supporting relational repair or improvement [52-55].

Module 3: Functional Analysis of ID Symptoms

Clinicians use functional analysis to uncover information about reinforcers of symptoms to render interventions that are personally relevant as well as help adolescents and families understand behavioral chains of antecedents and consequences that maintain problems. Functional analysis steps for adolescent ID include [102-104] articulating scenarios in which ID-related

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problems occur; examining circumstances that precede problems, ascertaining both internal and external antecedents; identifying short-term positive outcomes and long-term negative outcomes; and engaging clients in comparing positive versus negative consequences. Clinicians are careful to validate feelings that emerge, reflect appreciation for client sharing, and maintain a stance of curiosity about the perceived value of behaviors and an empathic position in exploring healthier alternatives.

Module 4: CBT Treatment Techniques for ID

Clinicians use data from the functional analysis of ID symptoms to choose from a selection of 3 transdiagnostic CBT techniques that have evidence for treating both depression and anxiety in teens [105,106]. In *emotional acceptance*, adolescents develop skills for noticing and accepting their emotions, including unpleasant and strong emotions [60,61,64,68], which help reduce anxiety sensitivity. They learn skills of present-moment and nonjudgmental awareness, which can increase affect tolerance [107]. In both *emotional exposure* and *behavioral activation*, adolescents are helped to approach situations, thoughts, and triggers that elicit strong emotions that have been previously avoided [60,61,64,102,104,108,109]. They try out various "opposite" actions to their typical emotional responses or behaviors (eg, volunteering to speak in class) to increase distress tolerance. Adolescents are encouraged to use new skills to fully engage in situations eliciting strong emotions and maintain clarity about the purpose of the opposite actions they select. All 3 techniques operate primarily on an approach versus avoidance clinical mechanism.

Module 5: SUD+ID Education and Safety Planning

Clinicians use family decision coaching [79,110,111] to converse with family members about three overlapping pathways of SUD and ID cooccurrence [10,112-114]: (1) self-medication: ID precedes the onset of SUD, and substances are valued for psychoactive properties that alleviate ID symptoms; (2) SU exposure: SUD precedes the onset of ID and creates developmental lag in the emergence of self-regulatory functions that precipitate ID and, if severe, impair neurocognitive functioning; (3) shared etiology: SUD and ID are mutually influencing axes of dysregulation that compromise healthy development. Family SUD+ID education transitions to family-based safety planning about both nonsuicidal self-injury and suicide ideation and attempts, guidelines for which focus on establishing physical and psychological safety, identifying strategies that can be used instead of self-harm, and identifying individuals to whom the adolescent can go for help [73,74,115,116].

Fam-AID Training and Fidelity Monitoring

Site clinicians will be trained for 6 hours. The session will feature video-based training [117,118] in Fam-AID modules and techniques. Thereafter, consultation at each site will include bimonthly live consultation with a protocol expert focused on equipoise between protocol fidelity and case tailoring, along with continuous feedback from therapist- and observer-report fidelity data, which is emailed directly to clinicians and used in live consultation to enable rapid adjustment in protocol delivery [119-121]. Two main fidelity benchmarks will be monitored for each case. These benchmarks include clinicians delivering interventions for every module in at least 1 treatment session (ie, coverage) and clinicians performing at or above the mean scale score for intervention extensiveness on the Fam-AID Fidelity Checklist (described in the Study Measures section) for at least 1 technique from each module (ie, dose), with both therapist- and observer-report checklist versions being tracked.

Study Procedures

All full-time therapists at both study sites who volunteer to participate will be consented. We project 4 therapists at each site (N=8) will participate. As in the authors' previous work [79], clinic staff will discuss the research opportunity with the families of all the adolescents during routine intake procedures. If consent is given, clinic staff will send the family's contact information to the study team through secure channels. The study team will contact interested caregivers by phone to complete (1) consent to phone screen, audio record sessions, complete outcome interviews and questionnaires, and grant access to clinic records and (2) an eligibility screener assessing IDs. IDs will be assessed using the Achenbach System of Empirically Based Assessment Child Behavior Checklist [122], a well-validated assessment method for screening for depression and anxiety problems in youth. IDs will also be assessed during the baseline research assessment using the Mini-International Neuropsychiatric Interview for Children and Adolescents [123,124], a structured diagnostic interview administered by lay interviewers; the interview yields Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision categories and has been used in diverse adolescent samples [79,125]. Client data on protocol viability (limited to Fam-AID cases only) and clinical outcomes will then be collected on all study clients (regardless of amount of treatment participation) at baseline, 3-month, and 6-month follow-up using REDCap (Research Electronic Data Capture; Vanderbilt University) cloud software, a widely used and secure Health Insurance Portability and Accountability Act (HIPAA)–compliant, web-based data collection platform.

Clinicians in both conditions will be asked to complete a self-report fidelity measure after every session with a study client. They will also be asked to audio record all sessions, a minimally intrusive procedure that is widely accepted by families and therapists in previous work [94]. Data will be collected using web-based links and uploaded to secure servers. As per the study team's numerous observational fidelity studies [126-130], 1 session will be randomly selected from the early phase of treatment (sessions 1 to 3) and 2 from the later phase (sessions from session 5) of each client for coding with an observational version of the Fam-AID Fidelity Checklist (described in the Study Measures section). Fidelity observational coders will be trained by the study team using gold standard procedures [126,131-133] and kept naive to the study condition.

Study Measures

Fam-AID Fidelity Checklist

This study will use an adapted version of the Inventory of Therapy Techniques (ITT [95,96]), a postsession therapist-report fidelity tool that requires 1 or 2 minutes to complete. ITT items

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are designed to measure the extensiveness (ie, thoroughness and frequency) with which a given treatment technique was used on a 3-point Likert-type scale: 0 (not at all), 1 (a little bit or moderately), or 2 (quite a bit or extensively). ITT items are derived from treatment protocols and their associated observational fidelity tools, for example, for family therapy [51] and for CBT [67], after being vetted for relevance by community clinicians in multiple treatment settings [134]. ITT has shown strong construct [50,134] and predictive [79,135] validity in studies with adolescents receiving family therapy and CBT in usual care. The Fam-AID Fidelity Checklist mimics the ITT structure, containing multiple items in each of the 5 Fam-AID modules: culturally attuned family engagement, relational reframing of ID symptoms, functional analysis of ID symptoms, CBT treatment techniques for ID, and SUD+ID education and safety planning. The Fam-AID Fidelity Checklist–Observer Version is an identical measure with instructions for observer coding.

Protocol Acceptability

Protocol acceptability interviews will be held with therapists and clients who participate in the Fam-AID protocol. Therapists will be interviewed in agency-based focus groups. Clients will be interviewed at the 6-month follow-up assessment point; adolescents and caregivers will be interviewed separately. Interview content will be adapted from existing treatment feasibility and acceptability interviews (refer to the study by Cho et al [136]) and include the following questions:

- What are the overall impressions of Fam-AID for use in routine practice (therapist; open-ended)?
- How effective and/or difficult it was to use Fam-AID for individual cases compared to usual practice? (therapist, Likert-type rating)
- Was it important for you (your caregiver) to be included in treatment? (client, open-ended)
- How much did emotion coping training help you (your child)? (client, Likert-type rating)

Adolescent and Family Outcomes

Clinical record data will be collected on the number of treatment sessions attended by family members, along with the data on adolescent attendance. Difficulties in Emotion Regulation Scale [137,138] is a 16-item measure of 6 aspects of emotion regulation: nonacceptance, engagement in goal-directed activities, impulsivity, emotional awareness, access to emotion regulation strategies, and emotional clarity. It uses a 5-point Likert scale and has shown acceptable test-retest reliability and internal consistency in adolescent populations [137-140]. The Revised Children's Anxiety and Depression Scale-Child and Parent version [141] is a 47-item measure of an adolescent's anxiety and depressive symptoms. The Revised Children's Anxiety and Depression Scale-Child version contains 6 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*–linked subscales: separation anxiety, social anxiety, generalized anxiety, obsessive-compulsive disorder, panic disorder, and major depressive disorder. A total anxiety subscale score sums 37 items from the 5 anxiety subscales; the major depressive disorder subscale score sums 10 items. The Revised Children's Anxiety and Depression Scale-Parent version is identical to the Revised Children's Anxiety and Depression Scale-Child version, but the wording of the items is from the parents' perspective. The Revised Children's Anxiety and Depression Scale-Child and Parent version have exhibited strong and acceptable internal consistency, respectively [142-144]. CRAFFT [145,146] is a widely used and well-validated adolescent-report tool that measures patient use of alcohol, cannabis, nicotine, illegal drugs, prescription medication, or anything else to get high in the past year and the past 3 months. It also asks about riding in a car driven by someone (including self) who was intoxicated. If SU is reported, the tool asks 5 additional questions: use to relax, use while alone, forget things you did while intoxicated, family or friends tell you to reduce use, and gotten into trouble while using. Parent-Teen SUD+ID Communication Frequency [147] is a 6-item adolescent and caregiver report of how often parents and teens talk to one another about key SUD-ID issues (eg, health risks of SU and ID and discipline regarding SU); response are scored on a 5-point scale, ranging from *never* to *very often* (refer to the studies by Sherman and Ehrenreich [77], Hogue et al [78], and Hogue et al [79]). Parent-Teen SUD+ID Communication Quality [148] is a 6-item adolescent and caregiver report on the quality of communication between parent and adolescent about SUD+ID issues (eg, my caregiver/child and I are interested in each other's opinions about SUD+ID, and if my caregiver/child and I talk about SUD+ID, I feel understood); responses are scored on a 5-point scale, ranging from *not at all* to *very much* (refer to the studies by Koning et al [147] and Carver et al [149]).

Plan of Analyses

Aim 1 acceptability analyses (Fam-AID condition only) will explore protocol acceptability and perceived effectiveness through formative qualitative interviews with staff and clients. Interviews will be recorded, transcribed, and then analyzed inductively [150] for data relevant to feasibility and acceptability. Two research staff members will separately code interviews for emerging concepts using thematic content analysis [151], an approach that applies inductive coding to identify themes within the data. Initial analysis will identify concepts through open coding [152]; inter-rater reliability checks will then be used to compare themes generated and resolve conflicts, and coding will continue to the point of saturation, that is, when no new concepts emerge.

Aim 1 fidelity benchmarks analyses (Fam-AID condition only) will examine both types of previously described fidelity metrics. Regarding coverage, descriptive statistics will capture frequencies related to (1) proportion of clients who received at least 1 intervention from each of the 5 modules and (2) interventions from which modules were most or least favored across clients. Chi-square analysis will be used to compare study conditions on the proportion of clients who received adequate coverage and conduct one-way analysis of variance to assess mean differences across modules in the Fam-AID condition to evaluate module preferences among therapists. Regarding dose, statistical equivalence testing [153] will be used to examine whether clinicians' average scores for intervention extensiveness on both observer- and therapist-report versions of the Fam-AID Fidelity Checklist are equivalent to a designated benchmark,

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which will be set (granting appropriate latitude for a pilot trial) for each module as mean 2.5 (SD 0.50). A CI approach will be adopted in which an equivalence interval is defined as the benchmark +10% and –10%. Next, a CI is defined by the following formula: $CI_{90\%}=M_R–M_T+/–z_\alpha(S_{MR–MT})$. In this equation MR represents the benchmark module mean, MT the average module score for study therapists, zα the critical one-tailed value from the z distribution for the chosen value of α, and SMR−MT the pooled SE. If the calculated CI falls within the equivalence interval, equivalence can be concluded. In addition, therapist variability in Fam-AID fidelity will be examined via statistical process control analyses (refer to the study by Hogue and Dauber [125]) in which individual therapist fidelity scores are plotted on a control chart to check for meaningful variation compared to control limits represented by the designated fidelity benchmark.

Aim 2a family attendance will involve between-condition comparison of treatment sessions attended by family members other than the adolescent. Linear mixed effects (LME) modeling will be used to examine the effect of condition on attendance counts. The model will include fixed effects for independent variables (ie, condition) and random effects to account for nesting at the therapist level, thereby providing unbiased parameter estimates [154,155]. Nesting at the client level will not need to be controlled in these analyses, as client summed totals will serve as a dependent measure: tallies of sessions attended by family members will be summed across the follow-up period. The LME models package [156] will be used; it provides full information maximum likelihood estimation and restricted maximum likelihood estimation, both of which produce unbiased parameter estimates based on the assumption that data are missing at random and outperform other missing data approaches even when missing at random is not met [157]. Effect sizes will be indexed by η_2 [158]. However, the nonlinear mixed effects model will be used if the assumption of continuous data is not tenable (eg, when attendance counts are not normally distributed).

Aim 2b adolescent and family outcomes analyses will involve similar LME models previously described. To test for change over time, each model will include fixed effects for time (months since baseline, coded as 0, 3, and 6) and random effects for (1) nesting of clients within therapists and (2) repeated measures within person across follow-up. Hypotheses will be tested by adding condition as a fixed effect and examining the condition-by-time interaction on each outcome in separate models. Acknowledging that outcomes may not demonstrate sharp trajectory change during the relatively brief 6-month follow-up window, the intercept will be set at the terminal assessment point by recoding time points (–6, –3, and 0); in doing so, the condition effect for the intercept will reflect a between-group difference at 6-month follow-up. LME modeling is recommended as an alternative to traditional modeling techniques for longitudinal designs with small samples [159].

Study Power

Aim 2 analyses will compare study conditions based on family attendance and client outcomes over time, with client (N=60) as the unit of analysis. Assuming α=.05, a total sample size of N=60 (with 30 clients per condition), 3 measurement occasions with a moderate intercorrelation (r=0.50), and a moderate effect size of Cohen d=0.60, the analysis yields a power of 0.80. A smaller effect size of Cohen d=0.50 yielded a power of 0.65, assuming α=.05. These estimates are in line with the impacts seen in the studies on adolescents with ID but not SUD [60,62] and in the studies on adolescents with SU problems treated in usual care [79,94].

Ethical Considerations

Ethics approval for this trial is pending from Solutions Institutional Review Board. Adolescents and caregivers will independently provide informed assent or consent before the initiation of the study activities (Multimedia Appendix 1). All study activities will be subjected to monitoring by the Data Safety and Monitoring Board of the same institution (Multimedia Appendix 2). Any modifications to the protocol that might impact the conduct of the study or its specified objectives and procedures will require a formal amendment to the protocol and approval by the Institutional Review Board and the Data and Safety and Monitoring Board before implementation. As reimbursement for interview completion, each participant receives a gift voucher (of their choice) worth US $110 via Tango Card: US $30 each for participation at baseline and US $40 each for participation during 3-month and 6-month follow-up. All assessment data will be automatically downloaded from the web-based data collection portal into a secure database maintained in a secure firewall- and password-protected location on a data network. All network data are backed up daily. Only project staff will have direct access to the data. All standard procedures for data management and security will be followed. For planned statistical analyses, database managers will extract data from the REDCap repository. All participant identifiers will be removed before the data are provided to statisticians for analysis.

Results

This study is being conducted over a 3-year period. Participant recruitment and data collection will begin in April 2025. We expect results from this study to be published in 2027.

Discussion

Overview

This pilot treatment development study will test feasibility (acceptability and fidelity) and short-term client outcomes (adolescent ID symptoms, adolescent SU, and family communication about SUD+ID) of a modular protocol for addressing cooccurring IDs among adolescents with SU in routine care. Fam-AID will contain 5 modules that can be delivered in any sequence to meet client needs: *family engagement* in treatment planning and services; *relational reframing* of family constraints, resiliencies, and social capital connected to the adolescent's ID symptoms; *functional analysis* of ID symptoms and related behaviors; *cognitive behavioral therapy* to address ID symptoms and functional needs; and *family psychoeducation and safety planning* focused on education about comorbid SUD+ID and prevention of adolescent

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self-harm. If shown feasible and effective, Fam-AID will offer a set of pragmatic interventions to SUD clinicians for treating cooccurring IDs in adolescent clients.

Importantly, Fam-AID is not intended to contain components that directly target SUD outcomes. This means that it is designed as an adjunctive intervention to complement and enhance the current SUD interventions, which are already being practiced by a given clinician or agency. The value of adjunctive protocols, such as Fam-AID, is to augment the overall effectiveness of care by addressing prominent cooccurring problems that, if untreated, derail treatment goals for a primary problem. The adjunctive nature of Fam-AID is a key asset for scalability; clinicians are not asked to exchange or markedly alter their base practices for SUD.

Fam-AID contains 5 modules, each consisting of core treatment techniques that have a strong evidence base. In keeping with the principles of modular intervention design [36,160,161], clinicians are invited to select and implement any Fam-AID module, in any order, based on client needs, with a default of delivering them sequentially. The 5 Fam-AID modules are intended to galvanize and reinforce the family support system and equip the adolescent to cope with and ameliorate ID problems. Notably, module 4 draws its menu of core CBT techniques to treat ID-related problems (emotional acceptance, emotional exposure, and behavioral activation) from an existing evidence-based transdiagnostic protocol, which treats the underlying negative affect and emotional dysregulation [77] associated with adolescent IDs. In these ways, Fam-AID is distinct from other adolescent SUD+ID options due to how it combines a core elements strategy, family-focused interventions, and individual CBT techniques, which might enhance the often modest long-term impact of interventions for ID symptoms in usual care [162].

Fam-AID contains 3 additional innovations intended to boost treatment effectiveness for this group identified as highly vulnerable and enhance the feasibility of implementing protocol modules in routine SUD care. First, in line with the core elements strategy, it is intended for use by invested clinicians of any clinical orientation and training background. To be sure, modules 1 and 2 contain techniques drawn from the family therapy approach, whereas modules 3 and 4 techniques derive from CBT. Nevertheless, Fam-AID modules are constructed as basic, step-by-step clinical practice guides that can be adopted and deployed by even entry-level clinicians. Second, it uses evidence-based family engagement techniques to systematically integrate caregivers in the treatment process. Families are not typically centralized in SUD services for adolescents [163] despite the compelling empirical rationale that family-based treatment is a first-line option for adolescent SUD [164], is well established for adolescent depression [165], and is a useful adjunct for adolescent anxiety [166]. Third, it contains a customization feature in which selected CBT techniques are integrated into treatment planning based on a functional ID assessment completed during sessions. In what amounts to a small-scale version of treatment tailoring [66,167], clients and therapists can collaboratively choose which of the 3 CBT techniques (emotional acceptance, emotional exposure, or behavioral activation) is best suited to address the adolescent's ID symptoms.

Study Design Limitations and Strengths

Due to the limited number of sites, clinicians, and clients in this study, results will not be generalizable to the broad network of adolescent SUD treatment clinics or SUD clinical workforce. Randomized designs, which provide control against unknown study confounds and allow for reasonable assumptions of causality related to manipulated variables even in small samples, are generally preferable to quasi-experimental interrupted time series designs. However, we decided against using a randomized design for many reasons. It would result in half as many therapists being trained in Fam-AID, which in a small-scale study exacerbates between-therapist variability in protocol fidelity that could dilute proposed effects and reduces therapist generalizability [87,168]. In addition, it introduces the potential for between-condition bleed from training procedures that could nullify protocol effects. In addition, to the degree that usual practices in the study sites (representing the TAU condition) already feature some type of ID-targeted interventions, the interrupted time series design is credibly stringent. This design was also vastly preferred by our partner clinics because it allows all staff to receive Fam-AID training. Importantly, this design can yield hypothesized viability and impact effects even if routine treatment services for SUD are basically inert at either or both study sites.

Reproducibility and Dissemination Plans

The Fam-AID protocol will be developed to maximize its reproducibility and scalability by featuring a clinically flexible, modular design strengthened by core element techniques. If the study aims are met, the foundation will be laid to test Fam-AID at R01-level scale. Study information and findings will be disseminated through publication of journal articles, presentations at relevant conferences, and reports to relevant stakeholders. If the Fam-AID protocol ultimately demonstrates feasibility and effectiveness, we will use existing state- and national-level clinician training and licensing platforms to ensure the protocol and its companion fidelity tools and procedures are made widely available to agencies and practitioners who serve youth with SUDs.

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AH). All statements in this report are solely those of the authors and do not necessarily represent the official views of the National Institutes of Health.

Data Availability

The data sets generated and analyzed during this study will be archived is the National Institute on Drug Abuse Data Archive.

Authors' Contributions

AH, MB, GMD, and JE-M authored the conceptualization and clinical content of the Fam-AID model. AH, NPP, AM, and MAS-G authored the study design, measures, and procedures. AH, CEH, and AJ-D authored the statistical approach, main study analyses, and study power.

Conflicts of Interest

JE-M receives royalties from the sales of the Unified Protocols for Transdiagnostic Treatment of Emotional Disorders in Children and Adolescents from the Oxford University Press, and additionally receives fees for consultation, training, and implementation support services for the intervention.

Multimedia Appendix 1
Sample consent form for this study.
[DOCX File , 49 KB - resprot_v13i1e64332_app1.docx]

Multimedia Appendix 2
Study committees and teams for this study.
[DOCX File , 28 KB - resprot_v13i1e64332_app2.docx]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist for this study.
[DOCX File , 76 KB - resprot_v13i1e64332_app3.docx]

Multimedia Appendix 4
Peer-review report from Interventions to Prevent and Treat Addictions Study Section (IPTA) - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 157 KB - resprot_v13i1e64332_app4.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
Fam-AID: Family Support Protocol for Adolescent Internalizing Disorders
HIPAA: Health Insurance Portability and Accountability Act
ID: internalizing disorder
ITT: Inventory of Therapy Techniques
LME: linear mixed effects
REDCap: Research Electronic Data Capture
SU: substance use
SUD: substance use disorder
TAU: treatment as usual

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Protocol

Design of a Tool Capable of Assessing Environmental Sociocultural Physical Factors Influencing Women's Decisions on When and Where to Toilet Within Real-World Settings: Protocol for the Build and Usability Testing of a Mobile App for Use by Community-Dwelling Women

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Abstract

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Background: Although surveys and apps are available for women to report urination and bladder symptoms, they do not include their decisions regarding toileting. Real-world factors can interfere with toileting decisions, which may then influence bladder health. This premise lacks data per want of a robust data collection tool.

Objective: The Prevention of Lower Urinary Tract Symptoms (PLUS) research consortium engaged a transdisciplinary team to build and test WhereIGo, a mobile data collection app for Android and iOS. The design goal was a comprehensive reporting system for capturing environmental, sociocultural, and physical factors that influence women's decisions for toileting. Aims include having (1) an innovative feature for reporting physiologic urge sensation when "thinking about my bladder" and shortly before "I just peed," (2) real-time reporting along with short look-back opportunities, and (3) ease of use anywhere.

Methods: The development team included a plain language specialist, a usability specialist, creative designers, programming experts, and PLUS scientific content experts. Both real-time and ecological momentary assessments were used to comprehensively capture influences on toileting decisions including perceived access to toileting, degree of busyness or stress or focus, beverage intake amount, urge degree, or a leakage event. The restriction on the maximal number of taps for any screen was six. PLUS consortium investigators did pilot-testing. Formal usability testing relied on the recruitment of community-dwelling women at four PLUS research sites. Women used the app for 2 consecutive days. Outcome measures were the system usability scale (SUS; 0-100 range) and the functional Mobile Application Rating Scale (1-5 range). These scales were embedded at the end of the app. The estimated a priori sample size needed, considering the SUS cut point score set at ≥74, was 40 women completing the study.

Results: Funding was provided by the National Institute of Diabetes and Digestive and Kidney Diseases since July 2015. The integrity of the build process was documented through multiple 5-minute videos presented to PLUS Consortium and through WhereIGo screenshots of the final product. Participants included 44 women, with 41 (93%) completing data collection. Participants ranged in age from 21 to 85 years, were predominantly non-Hispanic White (n=25, 57%), college-educated (n=25, 57%), and with incomes below US $75,000 (n=27, 62%). The SUS score was 78.0 (SE 1.7), which was higher than 75% of the 500 products tested by the SUS developers. The mean functional Mobile Application Rating Scale score was 4.4 (SE 0.08). The build and informal acceptability testing were completed in 2019, enrollment for formal usability testing completed by June 2020, and analysis was completed in 2022.

Conclusions: WhereIGo is a novel app with good usability for women to report toileting decisions, urination, and fluid intake. Future research using the app could test the influence of real-time factors on bladder health.

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KEYWORDS

mobile app; urinary bladder; woman's health; toileting; ecological momentary assessment; time factors; population studies; real-world environment; mobile phone

Introduction

Lower urinary tract symptoms (LUTS) are increasingly recognized as a public health concern. In community-based studies, 73% of women report at least one storage or voiding symptom, with LUTS expected to affect more than 43 million women in the United States over the next 30 years [1,2]. Despite this high prevalence, little is known about the prevention of LUTS in women.

The Prevention of Lower Urinary Tract Symptoms (PLUS) research consortium aims to identify influences ranging from individual biological to broad ecological factors (eg, environmental, sociocultural, and physical factors) that promote bladder health and prevent the onset of LUTS [3]. The PLUS definition of bladder health is "a complete state of physical, mental, and social well-being related to bladder function and not merely the absence of LUTS. Healthy bladder function permits daily activities, adapts to short-term physical or environmental stressors, and allows optimal well-being (eg, travel, exercise, social, occupational, or other activities" (page 978) [4].

Daily repeated decisions about toileting may affect the risk of developing LUTS, therefore, the PLUS Consortium has prioritized the study of toileting behaviors and their potential impact on bladder health. We aimed to minimize recall bias, favoring real-time reporting to the extent possible. A mobile phone app offered an ideal mode for this type of data collection.

The PLUS team hypothesized that a woman's location greatly influences toileting decisions and may also limit voiding in a specific environment. Thus, we named the proposed mobile app product "Where I Go" (abbreviated in the body text as WhereIGo). The intent was a user-friendly experience with an app that is self-explanatory, has visual appeal, and makes appropriate use of humor, while also providing ease in recording toileting decisions with no more than 6 taps at any reporting interaction done either in real-time or within a 3-4 hour recall period of the toileting event. We report here details of the conceptual development, construction, and usability testing of WhereIGo.

Methods

Overview

Multimedia Appendix 1 offers a road map to WhereIGo via a screen-based slide deck. This pictorial deck shows each screen

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of the app post–item development and post–complete build, just prior to the formal usability testing reported in this paper.

Developing Items for WhereIGo

In the early phase of development for the app, the PLUS research consortium brainstormed candidate items for inclusion in the app, followed by a survey to prioritize and then reduce items. Forefront in priority was the location of toileting events (where) and its situational influence on decisions women must make about when to toilet. This priority is consistent with the socioecological conceptual model used by the consortium [5].

The candidate items resulting from this process were organized in a large Excel (Microsoft Corporation) spreadsheet with rows that provided category headings in the cell above candidate items for the category beneath it. Example categories (in italics) and candidate items are *Onboarding activities* (eg, baseline information, pinning "home" location, and sleep time), *Captures* (time of pee, location of pee), *How strong was urge* (slider indicator), *Why went* (eg, no time to go later), *Barriers or delay reasons* (eg, work restrictions), *Bathroom quality* (eg, long wait), and *Ecological momentary assessment* (eg, beverage intake and urine leak tracker over last 3-4 hours). Additional columns showed the movement of items falling out over time as original candidate items conceptualized were reduced from 105 to 73 using an iterative process within the build team.

Constructing WhereIGo

Information demonstrating the item reduction process, transdisciplinary team build processes, and technical approaches to constructing the app are provided in Multimedia Appendices 2-6. Multimedia Appendix 2 is a 5-minute video that illustrates item candidate inclusion or exclusion tables and Multimedia Appendices 3-6 reveal the build team's processes.

In brief, WhereIGo was built at the University of Michigan's Center for Health Communications Research (UM invention registration OTT reference 2019-292) using Cordova (Apache) dual-platform software (simultaneous build for both iOS and Android). A guiding principle in the build was that any interaction asked for by the app would require no more than 6 clicks by the user.

The main variable of interest is a toileting event. Figure 1 portrays a brief overview of the screen visuals that guide women through WhereIGo. Each panel shows a key component within the app. Screen 1 highlights the logo and other design features. Screen 2 "thinking about my bladder" represents a real-time reporting option, which when tapped brings up a short survey on decisions made around that toileting event. Screen 3 "I just peed" similarly can be tapped in real time and offers reporting details.

Figure 1. Visual representation of selected key screenshots of WhereIGo, an app designed to collect data on toileting decisions made by community-dwelling women in real time wherever they are. Each of the 5 screens shown here leads to additional data collection screens under these lead messages: screen 1 logo, screens 2 and 3 real-time tap me components ("I'm thinking about my bladder" or "Now I peed"), screen 4 notification as heads-up for an upcoming look-back check-in (reflecting on the past 3-4 hours), screen 5 pin drop locator of common locations (home location pin required and opportunity to pin and name other locations as clarity of meaning for geocoding). Short look-back periods called "check-ins" were also offered with 3-5 push notifications per day that take the user to the menu. These prompts were to ascertain difficulty on the part of the participant in self-initiating reports on the main variable of interest—a toileting event. Screen 4 shows when the user's next check-in time will be as a form of anticipatory guidance using the push notification. Screen 5 shows the "pin-drop" feature used to identify a user's "home" location and optionally label other common locations such as "work." Screenshots of the entire WhereIGo app (its 72 "screen-pages" and an additional 15 exit survey items) are available in Multimedia Appendix 1.

WhereIGo does not constantly track location. Rather, it has a built-in feature of automatically capturing latitude and longitude coordinates only when triggered by a user interaction with the app. These coordinates allow for estimates of whether the user's location at the time of interaction was home or elsewhere.

WhereIGo captures toileting decisions under two real-time modes: "I'm thinking about my bladder" and "Now I peed." Tapping on either one of these real-time prompts triggers follow-up survey questions. When "I'm thinking about my bladder" is tapped, a slider scale for reporting the degree of urge appears. This urge-o-meter slider labeled "How strong is your urge to pee?" is anchored at either end as "No Urge" and "Strong," with a facial expression emoticon that changes to more concern as the marker slides toward the "Strong" end. Once the urge-o-meter has been slid, a screen follows: "When are you planning to pee?" with response categories "now" or "later." If "later" is chosen, a survey question appears: "Why

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aren't you going to pee now?" along with a previously determined list of responses or a chance to "Type your own reason." The entirety of this interaction requires only 4 taps but addresses the biological urge sensation variable and the socioecological factors for delaying voiding (eg, "No place to pee," "Long line for toilet"). The interaction is time and date stamped and geocoded by latitude and longitude.

When "I just peed" is tapped, a screen follows: "When did you pee?" with response categories "Now," "10," "20," or "30+ minutes ago." Then these response options appear, "Where did you pee?" response options including many preset options such as "Home," "Workplace," "Restaurant," "School," or a "New location" option. The urge-o-meter screen appears again to measure the urge at the time of toileting. Then the screen switches to "Why did you pee?" and "Check all that apply" with 5 preset response options and an opportunity to "Type your own reason." Finally, "If you had to wait before you peed, why did you wait?" with similar choices including an option to type your own reason. The entirety of this interaction requires only 6 taps (unless multiple options are selected).

In addition to the real-time modes, the app provides an opportunity to record missed events through "check-in" opportunities instigated by push notifications approximately every 3-4 waking hours. Times of check-ins are coded into the app and are individualized to the person's reported usual wake-up time and reported usual bedtime, divided evenly for push notifications across the awake time interval, but no more than 4 times per day and no less than 3. At the first morning check-in, the participant is asked to reflect on total sleep hours and to add any additional voids not recorded in real-time during the night.

Additionally, users are asked at check-in to report on items such as mindset (slider anchored by "Calm" and "Stressed" as the end points), beverage intake, "What strategies did you use in the last few hours to manage when you go pee?" and any urine leakage. At the end of each check-in, a cartoon joke appears as a fun reward.

Usability Testing Protocol

The research protocol for usability testing was fully approved by the external expert panel for the PLUS Consortium. Multimedia Appendix 7 provides the full protocol for usability testing. We purposely excluded the University of Michigan PLUS Research Center in formal usability study data collection to remove potential bias since this team did the build and iterative informal process of debugging checks. Refer to Multimedia Appendices 3-6 for additional details of work performed at the University of Michigan.

Ethical Considerations

The University of Michigan served as the oversight PLUS research center for building and testing WhereIGo. Institutional review board (IRB) approval (HUM00162517) was given on October 8, 2019. The additional 4 PLUS research centers, designated for recruitment and data collection activities, also gained approval per sites and IRB# as follows: Washington University in St. Louis (201912088), Loyola University Medical Center (LU212615), University of Pennsylvania (833718), and University of Alabama at Birmingham (300003879). Participants were asked to consent to 2 in-person study visits. The first study visit was described in the informed consent document as involving 40-60 minutes for filling out paper surveys including questions about the make and model of the participant's smartphone. Participants were primed about receiving a guide at visit 1 showing how to connect to the internet and download WhereIGo. Each participant was informed that visit 1 would involve opening the app, picking a nickname to use in it, responding to the app demographic questions survey within it, and dropping a map location pin for "home". Optionally, participants could drop up to 4 pins for places frequented routinely outside the home (eg, work, school, and gym). The general description for the consent of the 48-hour use of WhereIGo was described as being asked to (1) download a mobile phone app onto a personal smartphone, (2) self-initiate interactions with the app starting the next morning and for 48 hours following, (3) leave home at least once during the 48 hours' use, and (4) receive prompts by notifications 5 times a day (for responding to look-back questions about the prior 3-4 hours). The look-back questions consent descriptions included the opportunity to log missed pee events, any urine leakage, degree of felt stress or busyness, and volume or type of beverage intake. Participants were informed of additional prompted interaction with WhereIGo at the end of 48 hours of use to answer a survey that included 17 multiple-choice questions and 1 text response question about personal experience using the app. Consenting to the second study visit involved an agreement to open WhereIGo during the visit to make sure the final survey was completed, and answer 15-20 questions about having used the app and how it could be improved. Participants consented to (optionally) receive assistance in removing the app. Inconveniences of taking part in the study were made known including the potential for embarrassment and the risk for potential loss of confidentiality. The consent form provided information about the assignment of a unique identification number, storage in a password-protected file or locked research office, and contact information for research staff was provided for future questions. Participants were informed that only a single document linking the names and study code IDs would be maintained and would be password-protected or locked in an office accessible only to study members. Geolocation data would be kept private, specifically that the geocode data would be kept on a secure driver, again only accessible by key members of the research team. At no time would other parties, such as Apple or Google, have access to data on this secure app. Participants consented to compensation of US $25 for completion of the first in-person visit, US $75 for using WhereIGo over the next 2 days, and US $50 for the second in-person visit, totaling US $150 for completing the study.

Study Design

A cross-sectional study design was used with sampling from regions surrounding the 4 PLUS research centers listed above.

Sample and Recruitment

Recruitment strategies included the distribution of flyers, advertisements in local community centers, contacting participants from previous studies, social media, and

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word-of-mouth. The recruitment aim focused on adult women who were living in community settings.

For eligibility screening, inclusion criteria were (1) women 18 years and older; (2) fluent in written and spoken English; (3) able to stand and walk independently without human assistance (use of cane or walker allowed); (4) own a smartphone (Android or iOS) on which calls can be made; (5) have downloaded at least one app in the past 6 months; (6) willing to respond to WhereIGo prompts or texts and input data about toileting behaviors for a consecutive 48 hours, during which they will leave their home at least once, but not change time zones; and (7) agree to 2 in-person visits at the study site. Exclusion criteria were (1) having a physical or mental condition that would prevent completing written questionnaires and interactions with the app, (2) institutional living arrangements (ie, skilled nursing, long-term care, or rehabilitation center), (3) currently pregnant, (4) diagnosed with a neurogenic or congenital bladder condition, and (5) unable to use the toilet independently.

Procedures

Eligible women were sent study information and an IRB-approved consent form and were scheduled for an in-person visit. At this first visit, women were asked to download and install WhereIGo onto their smartphones. Women were requested to begin use of the app anytime they wished after download, and the formal data collection would start with a check-in notification they would receive the next morning, shortly after the "wake time" indicated individually at download. Starting with this "wake time," 48 consecutive hours of app use was expected. Participants received a final check-in notification that included a request to fill in usability surveys that were embedded within the app (approximately 20 questions).

Outcome Measures

The primary outcome measure was the system usability scale (SUS) [4]. SUS evaluates users' satisfaction based on ease of use. It is a validated self-administered questionnaire widely used in the evaluation of technology products [5], with a Cronbach α coefficient of 0.91. It consists of 10 items that are rated on a 5-point Likert scale ranging from strongly disagree (0) to strongly agree (4). Responses to each item are summed and multiplied by 2.5 to convert scores to a scale of 0 to 100 and then normalized to a percentile. SUS scores above 68 are considered above average [6]. A secondary outcome, the Mobile App Rating Scale, is a simple, objective, and reliable instrument with 5 subscales for classifying and assessing the quality of mobile health apps [7]. We used the function subscale (fMARS), which consists of 4 items assessing an app's performance, ease of use, navigation, and gestural design. Each item is rated using a 5-point Likert scale (1=inadequate, 2=poor, 3=acceptable, 4=good, and 5=excellent). An overall function score was calculated based on the mean score across items. This subscale has excellent internal consistency (Cronbach α=0.80) and moderate interrater reliability (interclass correlation coefficient=0.50) [7].

Statistical Analysis

We hypothesized cut point indicators for acceptability usability to include a SUS score above 74 [6] and a mean fMARS score of >3.5. Allowing for a 5% drop out, we estimated a minimal sample size of 40 participants to achieve sufficient precision for estimating the SUS score (ie, within one-third of the SE from the mean to the confidence limits). Per SUS developers, a SUS score of 74 has higher perceived usability than 70% of all products tested [6].

Results

Funding for the PLUS consortium was provided by the National Institute of Diabetes and Digestive and Kidney Diseases of the US National Institutes of Health. Funding began in July 2015 and continues through July 2025. Recruitment for this project began in September 2019 with completion of enrollment in June 2020.

A total of 44 community-dwelling women were enrolled. Participants were aged on average 44 (SD 18.2) years, and 39% (n=16) of participants identified as a racial minority, predominantly Black (Table 1). Within this sample, iOS phones were used by 75% (n=33) of participants, Android by 23% (n=10) of participants, and one phone type was missing.

A total of 41 (93%) women completed the SUS and fMARS usability surveys. The average score for the SUS was 78.0 (SE 1.7), statistically significantly higher than the minimal cut point of 74 established a priori as acceptable usability. The score for the fMARS was 4.4 (SE 0.08), also statistically significantly higher than the a priori established cut point of 3.5.

During the second visit, the overall feedback was very positive with no qualitative findings leading to additional changes in the app build. A single exception was a clear desire for feedback to be provided to the user about their bladder health habits, with many participants asking for this feature to be added in the future.

With these acceptable usability findings, the research team established timelines for the next steps. These are (1) 2023-2024 analyzing and publishing additional findings from these same women's data, which was collected across the full 48 hours of WhereIGo implementation, and (2) 2024-2025 launching, analyzing, and publishing the first population-based study to use WhereIGo per the PLUS consortium's ongoing National Institutes of Health-funded parent study called Rise for Health. Rise for Health is a study of women's bladder health conducted by research teams from 10 universities across the United States. The WhereIGo protocol published here will be an addition to that ongoing research, with WhereIGo data collection beginning midyear 2024.

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Table 1. Demographic information as collected within the WhereIGo app.

Characteristic	Community-dwelling women (N=44)
Age (years)	
Mean (SD)	44.3 (18.2)
Range	21-85
18-25, n (%)	8 (18)
26-45, n (%)	16 (36)
46-65, n (%)	15 (34)
≥65, n (%)	5 (11)
Race or ethnicity (check all that apply), n (%)	
American Indian or Alaska Native	1 (2)
Asian	4 (9)
Black or African American	12 (27)
Hispanic or Latino	8 (18)
Middle Eastern or North African	1 (2)
Native Hawaiian or other Pacific Islander	0 (0)
White	25 (57)
Other race or ethnicity or origin	1 (2)
Participant did not answer	3 (7)
Income (US $), n (%)	
<$25,000	9 (20)
$25,000-$49,999	9 (20)
$50,000-$99,999	15 (34)
>$100,000	9 (20)
Missing	2 (4)
Education, n (%)	
High school diploma, GED[a], or less	0 (0)
Some college	12 (27)
Associate or bachelor's degree	18 (41)
Master's degree	11 (25)
Professional or doctorate degree	3 (7)
Employment (check all that apply), n (%)	
Homemaker	5 (11)
Student	8 (18)
Not working or unable to work	8 (18)
Working one or more jobs	30 (68)
Language (check all that apply), n (%)	
English	43 (98)
Spanish	3 (7)
Other	2 (4)
Sought care for bladder from health care provider, n (%)	
Sought care	9 (20)
Did not seek care	34 (77)
Missing	1 (2)

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Characteristic	Community-dwelling women (N=44)
Number of toilets in home, n (%)	
1	12 (27)
2	23 (52)
3	9 (20)
Phone type, n (%)	
Apple	33 (75)
Android	10 (23)
Missing	1 (2)

[a]GED: General Educational Development.

Discussion

Principal Findings

In this report, we describe the development and usability results of a novel mobile app called WhereIGo, which collects real-time information on women's toileting decisions and behaviors. We tested the app in a variety of locations across the United States, showing well above-average user satisfaction across different geographic locations.

With this description of WhereIGo usability testing, we now embark on crucial validity testing. We are addressing certain minor limitations ("bugs") that arose from older phone models and from the Cordova dual-platform software, both of which are largely historical problems. The Cordova dual-platform software (novel at the time in incorporating Android and iOS in a single build) has ceded to newer dual-platform software with enhanced functionalities.

Limitations

Despite the participant's desire for feedback, currently, WhereIGo does not yet provide feedback data to the user but it remains a goal to incorporate in future versions. Of note, this was a highly educated sample of only English speakers. Future usability testing should include those with lower literacy. It is also acknowledged that all participants had resources to secure a cell phone for the app use, affecting the generalizability of results in future studies.

Conclusions

WhereIGo is a novel mobile app designed to collect data on women's choices of when and where to toilet. Women report above-average usability, good functionality, and high appeal. Our future goals are to further refine and enhance WhereIGo as informed by validity testing, participant feedback, and newer cutting-edge dual-platform software. Ultimately, the plan is to use WhereIGo in studies of lower urinary tract function to provide women with real-time reporting and to capture behaviors and influences on toileting decisions that may ultimately represent modifiable risk and protective factors for bladder health.

Acknowledgments

The authors wish to thank the WhereIGo build team at the Center for Health Communications Research, University of Michigan. Members of the build team William Newhouse (lead), Caroline Carter, Shelly Chang, Elizabeth Hershey, Ian Moore, Mike Novak, and Jay Semerad provided full technical support for WhereIGo, and together with scientific content expert JMM each created 5-minute video or videos that highlight components of the build process unique to their specialty (representative videos are provided in supplemental materials). The authors attest there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript. This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (NIH) by cooperative agreements (grants U24DK106786, U01 DK106853, U01 DK106858, U01 DK106898, U01 DK106893, U01 DK106827, U01 DK106908, U01 DK106892, and U01DK126045). Additional funding was from the National Institute on Aging, the NIH Office on Research in Women's Health, and the NIH Office of Behavioral and Social Science. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The members of *The Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium* are as follows:

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Data Availability

The data sets generated or analyzed during this study are not publicly available until the final archiving of Prevention of Lower Urinary Tract Symptoms Consortium data in a National Institutes of Health repository at the end of the grant. However, on reasonable request, the data can be made available from the corresponding author before that time.

Conflicts of Interest

HC is employed by and owns stocks in Pfizer. CSF receives UpToDate royalties, UroCure Consultation Fee, and a Medtronic Consultation Fee. LMR receives UpToDate royalties and reports association with the UroCure Quality and Safety Oversight Committee and the Renovia Clinical Advisory Board. ERM receives UpToDate author royalties.

Multimedia Appendix 1
Screenshots of the completed WhereIGo mobile app.
[PPTX File , 62703 KB - resprot_v13i1e54046_app1.pptx]

Multimedia Appendix 2
WhereIGo App candidate variables by author JMM. This 5-minute video features a spreadsheet compilation of candidate items for potential inclusion in a new data collection tool for influences on women's toileting decisions. The list, evolved out of a brainstorming session conducted by the National Institutes of Health Preventing Lower Urinary tract Symptoms (PLUS) research consortium, was foundational to the WhereIGo build process. The video includes initial candidate items that did or did not make it into the final version of the application.
[MP4 File (MP4 Video), 29017 KB - resprot_v13i1e54046_app2.mp4]

Multimedia Appendix 3
Part 1: creative design process of WhereIGo by artist and designer Ian Moore. This 5-minute video reveals the artist's process behind the many subtle and beautiful features in WhereIGo, including how careful imagery creation results in an inviting app.
[MP4 File (MP4 Video), 17682 KB - resprot_v13i1e54046_app3.mp4]

Multimedia Appendix 4
Part 2: user interaction design of WhereIGo by Ian Moore. This 5-minute video reveals more about how a designer builds code for the app to support choices on factors such as colors and movement (eg, "a sense of wiggling") for selected screen visuals.
[MP4 File (MP4 Video), 20386 KB - resprot_v13i1e54046_app4.mp4]

Multimedia Appendix 5
Role of behavioral science in building WhereIGo by plain language specialist Caroline Carter. This 5-minute video demonstrates how to achieve clear, concise, organized, and appropriate in-app text to maximize a satisfying experience for WhereIGo users.
[MP4 File (MP4 Video), 14063 KB - resprot_v13i1e54046_app5.mp4]

Multimedia Appendix 6
Behind the scenes tech team by Mike Nowak and Shelly Chang: This 5-minute video is presented as a conversation between two coding experts, who work behind the scenes, to actualize choice of platform for the build and the mechanics of coding that make the entire app viable. The two contributors role-play the use of WhereIGo, so viewers can see the app in action.
[MP4 File (MP4 Video), 21403 KB - resprot_v13i1e54046_app6.mp4]

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Multimedia Appendix 7
Protocol for WhereIGo formal usability testing, as used by the four PLUS consortium research sites who recruited community women to use WhereIGo for 2 days and provide usability feedback.
[DOCX File , 193 KB - resprot_v13i1e54046_app7.docx]

Multimedia Appendix 8
Peer-reviewer report from the National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) - Women's Bladder Health applications PLUS (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 114 KB - resprot_v13i1e54046_app8.pdf]

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Abbreviations

fMARS: functional Mobile Application Rating Scale
IRB: institutional review board
LUTS: lower urinary tract symptoms
PLUS: Prevention of Lower Urinary Tract Symptoms
SUS: system usability scale

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Protocol

Reward Learning as a Potential Mechanism for Improvement in Schizophrenia Spectrum Disorders Following Cognitive Remediation: Protocol for a Clinical, Nonrandomized, Pre-Post Pilot Study

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Abstract

Background: Cognitive impairment is common with schizophrenia spectrum disorders. Cognitive remediation (CR) is effective in improving global cognition, but not all individuals benefit from this type of intervention. A better understanding of the potential mechanism of action of CR is needed. One proposed mechanism is reward learning (RL), the cognitive processes responsible for adapting behavior following positive or negative feedback. It is proposed that the structure of CR enhances RL and motivation to engage in increasingly challenging tasks, and this is a potential mechanism by which CR improves cognitive functioning in schizophrenia.

Objective: Our primary objective is to examine reward processing in individuals with schizophrenia before and after completing CR and to compare this with a group of matched clinical controls. We will assess whether RL mediates the relationship between CR and improved cognitive function and reduced negative symptoms. Potential differences in social RL and nonsocial RL in individuals with schizophrenia will also be investigated and compared with a healthy matched control group.

Methods: We propose a clinical, nonrandomized, pre-post pilot study comparing the impact of CR on RL and neurocognitive outcomes. The study will use a combination of objective and subjective measures to assess neurocognitive, psychiatric symptoms, and neurophysiological domains. A total of 40 individuals with schizophrenia spectrum disorders (aged 18-35 years) will receive 12 weeks of CR therapy (n=20) or treatment as usual (n=20). Reward processing will be evaluated using a reinforcement learning task with 2 conditions (social reward vs nonsocial reward) at baseline and the 12-week follow-up. Functional magnetic resonance imaging responses will be measured during this task. To validate the reinforcement learning task, RL will also be assessed in 20 healthy controls, matched for age, sex, and premorbid functioning. Mixed-factorial ANOVAs will be conducted to evaluate treatment group differences. For the functional magnetic resonance imaging analysis, computational modeling will allow the estimation of learning parameters at each point in time, during each task condition, for each participant. We will use a variational Bayesian framework to measure how learning occurred during the experimental task and the subprocesses that underlie this learning. Second-level group analyses will examine how learning in patients differs from that observed in control participants and how CR alters learning efficiency and the underlying neural activity.

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Results: As of September 2023, this study has enrolled 15 participants in the CR group, 1 participant in the treatment-as-usual group, and 11 participants in the healthy control group. Recruitment is expected to be completed by September 2024. Data analysis is expected to be completed and published in early 2025.

Conclusions: The results of this study will contribute to the knowledge of CR and RL processes in severe mental illness and the understanding of the systems that impact negative symptoms and cognitive impairments within this population.

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(JMIR Res Protoc 2024;13:e52505) doi:10.2196/52505

KEYWORDS

cognitive remediation; fMRI; functional magnetic resonance imaging; negative symptoms; psychosocial functioning; reward learning

Introduction

Overview

Schizophrenia spectrum disorders (SSDs; eg, schizophrenia, schizoaffective disorder, and schizophreniform disorder) are defined by the presentation of a range of symptoms, including delusions, hallucinations, disorganized thoughts and behaviors, and negative symptoms (ie, reduced motivation and emotional expression) [1]. These disorders are linked to a variety of deficits in cognition, which extend to both neurocognition (eg, attention, memory, and planning) and social cognition (eg, difficulties perceiving and processing emotions) [2]. Both stand-alone and integrated programs have been used to treat these cognitive impairments. Cognitive remediation (CR) therapy has been widely used as an intervention for deficits in global cognition and functional difficulties in schizophrenia and has been shown to be particularly beneficial if rehabilitation is also incorporated into treatment [3,4]. Nevertheless, response to therapy is variable [5], and the impact individual characteristics have on the success of CR is still being investigated. The mechanisms by which CR is effective are yet to be clarified. A core component of CR is strategic learning principles, which ensure tasks are scaffolded based on previous successful achievements and the chances of successful task completion are optimized. There is, therefore, close reinforcement of learning.

One proposed mechanism for the effect of CR is reward learning (RL), which is potentially the pathway to improved cognition and motivational negative symptoms. In schizophrenia, there is impairment in reward anticipation [6,7] and representation [8], leading to poorer decision-making and goal-directed behavior, motivational deficits, and negative symptoms [8-11]. RL is a term used to identify the cognitive processes responsible for adapting behavior following positive or negative feedback. RL is a basic adaptive function of every living organism and provides the possibility to adapt and change in response to internal and environmental demands [12]. This process has been extensively studied in neuroscience and linked to the brain dopamine system. The dopamine hypothesis of schizophrenia is the single most influential theory in our understanding of the neurochemical basis of the disorder [13]. This theory suggests that fundamental dysregulation in this system is responsible for the illness's symptoms. Dysregulation in the dopamine system is also linked to RL abnormalities, which, in turn, are thought to influence cognitive and negative symptoms. A growing body of basic neuroscience literature has identified 2 complementary and interactive neural systems in the dopamine system responsible for predicting outcomes and learning from feedback [14]. The first of these systems, responsible for rapid learning, is mediated by the basal ganglia. This system, referred to as the "fast system," is believed to represent the predicted value of actions and rewards. These predictions bias actions and underlie learning based on positive and negative feedback. The second slower system is based primarily in the prefrontal cortex and allows for more detailed, conscious, and abstract representations of values and rewards. These representations of value are instrumental in allowing individuals to flexibly respond to reward value and adapt to novelty in the environment.

There is consistent evidence that people with SSDs are impaired at making rapid behavioral adjustments in response to feedback and that these impairments are associated with negative and cognitive symptoms [15-17]. Problems using the "fast system" are evident in situations requiring rapid change in responses to environmental changes when a situation previously rewarding begins to be associated with disadvantageous outcomes and oversensitivity to negative feedback and poor sensitivity to positive feedback. In contrast, several studies suggest that the gradual or procedural learning system seems intact in people with schizophrenia [18], but antipsychotic medication dosage, particularly for those with high levels of dopamine 2 receptor blockades, may exert a negative effect on this system.

Social environments are dynamic with constant rapid changes; hence, social situations require rapid behavioral adjustments in response to ever-changing social feedback. People with SSDs have impaired social functioning, and recent studies have shown that they also have impaired social reward processing [19,20]. Social approval induces rewarding feelings and is associated with increased activation in regions and networks associated with reward [21-23]. In those with SSDs, there is reduced activity in common reward brain regions during the experience of social reward [24], suggesting that they may have a reduced experience of the rewarding feeling of positive social attention. Positive social interactions have benefits for mental well-being and give life a sense of meaning [25]. Receiving praise and attention from others improves self-esteem [26] and increases motivation [27]. Although social reward has major impacts on functional outcomes, only recent efforts have explored social reward processing in SSDs. Further behavioral evidence suggests that RL difficulties are more pronounced in learning from positive, rather than negative, feedback [8]. This provides a further link between the effects of impaired RL and negative

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symptoms. Learning preferentially from negative outcomes is likely to lead to behavioral avoidance and social withdrawal, and have a negative impact on motivation. This hypothesis is supported by research suggesting that the magnitude of RL impairment, particularly for positive feedback, is associated with negative symptom severity [28].

Despite the significance of RL problems in people with SSDs, there is no therapy targeting this problem. One previous study explored the impact that a course of CR has on RL problems in people with schizophrenia [29]. The results of this study showed that CR could improve sensitivity to positive and negative feedback and that improvement in these parameters was moderated by the severity of negative symptoms. However, this study used a standard CR protocol and may not have achieved the maximum effect on RL problems. Furthermore, the nature of this study did not allow for investigating the retention of RL improvements and, more crucially, how these may impact cognitive and negative symptoms and, more broadly, recovery. RL difficulties in people with SSDs are associated with negative symptoms, and it is plausible that, by reducing RL difficulties, a reduction in negative symptoms could be observed. It is proposed that the structure of CR enhances rewards and motivation to engage in increasingly challenging tasks, and this is a potential mechanism by which CR can achieve functional outcomes in individuals with SSDs.

Aims and Hypotheses

Our primary aim is to investigate reward processing in individuals with SSDs before and after completing a course of CR and to compare this intervention group with a treatment-as-usual (TAU) group of individuals with SSDs. In addition, this study aims to investigate whether RL mediates changes in cognitive function and negative symptoms following CR. We will also examine potential differences in social RL compared with nonsocial RL in individuals with SSDs and the impact of CR on these potential differences in RL domains. Comparison with RL in a healthy adult control group will allow further differentiation of behavioral and neural impairments in SSDs.

Hypothesis 1A

At baseline, participants with SSDs will demonstrate deficits in RL when compared with healthy control volunteers. These differences in learning will be linked to aberrant activity in the dopamine system at a neural level in the prefrontal cortex and subcortical structures such as the basal ganglia, compared with healthy controls.

Hypothesis 1B

At baseline, participants with SSDs will demonstrate greater deficits in social RL when compared with nonsocial RL.

Hypothesis 2

Participants that complete CR will demonstrate improved RL, again reflecting improved neural activity within the prefrontal and basal ganglia regions, when compared with people with SSDs not receiving the intervention.

Hypothesis 3

Reward processing ability will mediate improved cognition following CR in participants receiving the intervention but not in the SSD control group.

Hypothesis 4

Reward processing will mediate improvements in negative symptoms following CR in participants receiving the intervention but not in the SSD control group.

Methods

Study Design

The study is a nonrandomized clinical pilot trial to investigate whether reward processing pathways are involved in the mechanism of action of cognitive remediation therapy (Computerized Interactive Remediation of Cognition-Training for Schizophrenia [CIRCuiTS]) [30,31]. We will recruit 3 participant groups: 20 participants with SSDs who will complete the CR program (the intervention group), 20 participants with SSDs who will receive TAU, and 20 matched healthy control participants. Figure 1 depicts a schematic of the study design.

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Figure 1. The reward learning as a potential mechanism for improvement in schizophrenia spectrum disorders following cognitive remediation pre-post pilot study design. BACS: Brief Assessment of Cognition in Schizophrenia; BIS/BAS: Behavioral Inhibition System and Behavioral Activation System; BPRS: Brief Psychiatric Rating Scale; CAINS: Clinical Assessment Interview for Negative Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; CRT: cognitive remediation therapy; fMRI: functional magnetic resonance imaging; LSP-16: Life Skills Profile; SCoRS: Schizophrenia Cognition Rating Scale; TOPF: Test of Premorbid Functioning.

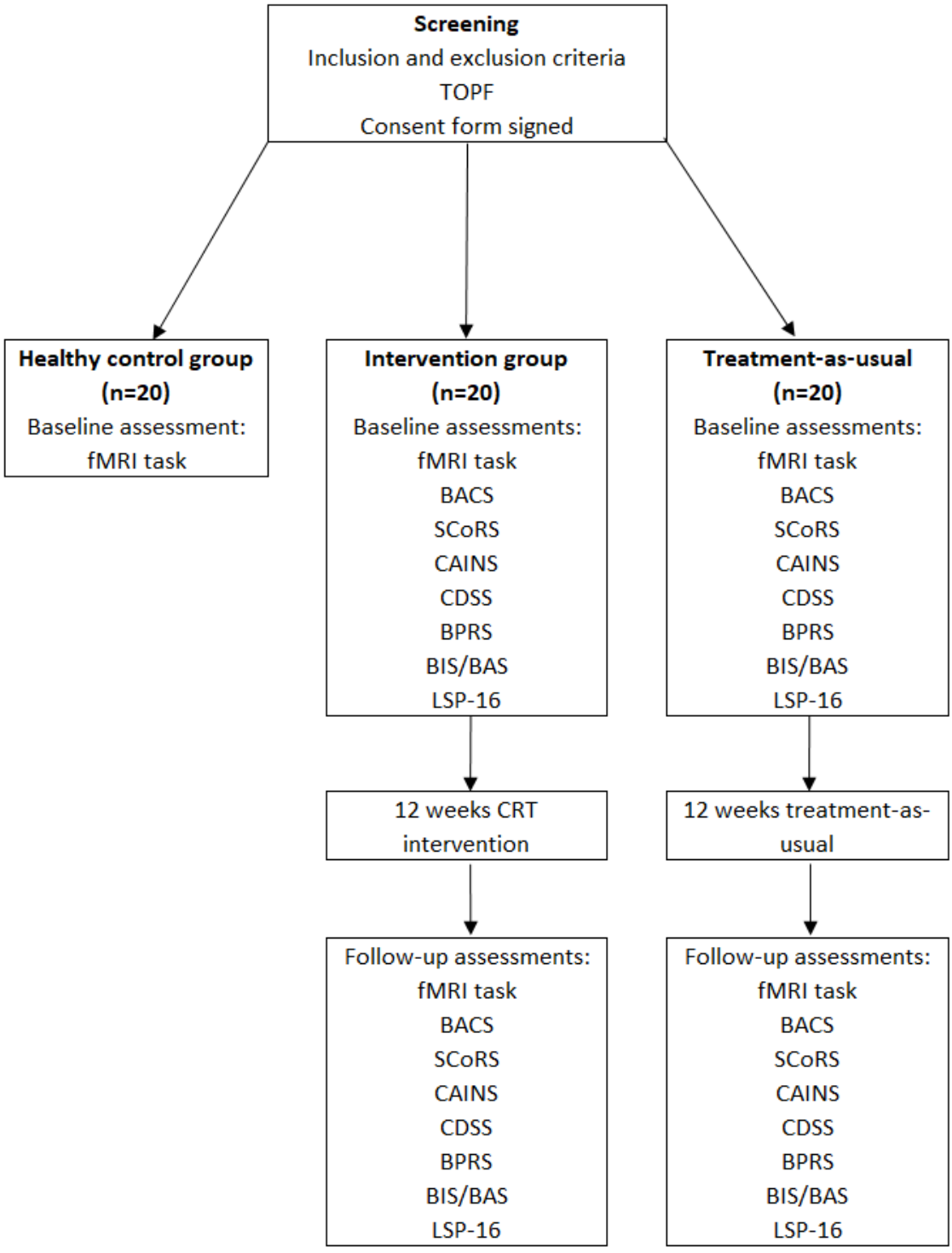

Participants

A total of 40 participants with a diagnosis of an SSD will be recruited from the Metro South Addiction and Mental Health Service community teams (Brisbane, Australia). Given that this is a pilot study, a power analysis was not conducted [32]. Instead, the sample size was informed by practical factors relating to the project, including the budget, the availability of CR facilitators, and the recruitment and attrition rates from our previous studies. This sample size is also consistent with other research in this area [33].

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The inclusion criteria for the intervention and TAU groups and the healthy control group, as well as the exclusion criteria for all groups, have been provided in Textbox 1.

Textbox 1. The inclusion and exclusion criteria.

Inclusion criteria for the intervention and treatment-as-usual (TAU) groups

- Patients of the Metro South Addiction and Mental Health Service
- Aged between 18 and 35 years
- Primary diagnosis of schizophrenia spectrum disorder (SSD)
- English literacy skills of at least grade 4 equivalence
- Absence of neurological disorders or acquired brain injury
- Estimated intelligence quotient >70 on the Test of Premorbid Functioning (TOPF)
- Agree to participate and have the capacity to consent to the study procedures

Inclusion criteria for the healthy control group

- Aged between 18 and 35 years
- No history of diagnosis of SSD
- English literacy skills of at least grade 4 equivalence
- Absence of neurological disorders or acquired brain injury
- Estimated intelligence quotient >70 on the TOPF
- Agree to participate and have the capacity to consent to the study procedures

Exclusion criteria for all groups

- Metallic object in their body (eg, cardiac pacemaker and cochlear implant)
- Pregnant or possibly pregnant (unprotected sex since last menstrual period)
- History of claustrophobia
- Permanent metal dental appliances
- Bodyweight ≥120kg

The researchers will obtain consent from all participants through a participation information and consent form. For participants with SSDs, half (n=20) will complete CR and form the intervention group. Those participants with SSDs (n=20) that are not interested in completing CR will form the patient TAU group and will complete the pre- and postmeasures only. Thus, group allocation will be based on an individual's preference to participate in CR. In addition, matched healthy controls (n=20) will be recruited from the Metro South Addiction and Mental Health community services in the Princess Alexandra Hospital district as well as from the general population. We do not anticipate that it will be difficult to collect these healthy controls, given our already established connections with other researchers and staff within this district. Therefore, we expect to be able to recruit this group through word of mouth and the snowball effect. These health controls will have no history of SSDs. This will provide a benchmark to compare the clinical groups. Hence, the total number of participants for the study is 60.

Intervention

CIRCuiTS is a therapist-supported CR web-based program that focuses on improving cognitive skills, particularly for individuals with psychosis [30,31]. Participants work through different cognitive tasks and exercises, many of which are based on real-life experiences (eg, creating a shopping list or cooking). Previous studies have shown CIRCuiTS leads to improvements in both cognition and functional recovery and is acceptable by participants [34]. Sessions typically last 1 hour, twice a week, for 12 weeks, and task practice is delivered through a computer. CIRCuiTS consists of 40 stages. A total of 20 sessions are considered adequate treatment exposure, and 20 minutes is the minimum time for a "session." In this study, participants in the CR group will have 1 face-to-face meeting with the therapist to orient themselves to the program. These participants will then complete the program either on the web or in person, in a group or individually. Only the intervention group will be able to complete these sessions.

All participants will continue their usual treatment under the supervision of their referring clinical team. This involves pharmacotherapy, monitoring, and case management. They can concurrently attend any psychosocial group that does not focus on improving neurocognition.

Outcomes

Screening Measures

During screening, participants will complete the Test of Premorbid Functioning (TOPF). The TOPF is a test of premorbid intelligence estimated from reading ability and will be used to screen for intellectual impairment [35,36]. It takes

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approximately 10 minutes to complete and is composed of a list of 70 words.

Demographic Information

At baseline, demographic and clinical information will be gathered, including sex, age, and date of birth. For the clinical groups, the case management team, primary and secondary diagnoses, mental health status, and list of current medications (name, dose, frequency, and route) will also be recorded.

A battery of validated assessment measures will also be delivered at baseline and follow-up for the clinical groups, as described in the subsequent sections.

Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS) assesses 5 domains of cognition, with 6 tests taking approximately 30 minutes [37,38]. The 6 tests include list learning (verbal memory), digit sequencing (working memory), token motor task (motor speed), verbal fluency (semantic fluency and letter fluency), Tower of London (reasoning and problem solving), and symbol coding (attention and processing speed). The BACS has high test-retest reliability, is sensitive to the unique cognitive deficits associated with SSDs, and is a routine measure of change in performance over time [37].

Schizophrenia Cognition Rating Scale

The Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item measure of cognitive difficulties in daily activities that is completed by the participant, an informant, and the interviewer at baseline and on completion of the CR program [39]. It has been found that global ratings of cognition are strongly correlated with cognitive performance, functional outcome, and functional capacity. The SCoRS has good interrater reliability [39].

Clinical Assessment Interview for Negative Symptoms

The Clinical Assessment Interview for Negative Symptoms (CAINS) is a measure of anhedonia, avolition, and emotional expression [40] with strong psychometric properties [41]. The CAINS has been found to have good convergent validity with the Brief Negative Symptom Scale [42]. It was developed to better align not only with the negative symptoms but also with constructs emerging from neurobiological research [43].

Calgary Depression Scale for Schizophrenia

The Calgary Depression Scale for Schizophrenia (CDSS) measures symptoms of depression in people with schizophrenia [44]. The scale has 8 structured questions with an additional observational item [45]. The scoring uses a 4-point Likert-type scale (0=absent, 1=mild, 2=moderate, and 3=severe), anchored by descriptors [44]. The summation of scores on all items provides a global score. The scale has good psychometric properties, identifying a major depressive episode at 82% specificity and 85% sensitivity for scores above 6.

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) is a semistructured assessment of 24 symptoms of schizophrenia. The 24-item anchored scale will be used. The anchored version has good psychometric properties [46]. Symptom severity is rated from 1 (not present) to 7 (extremely severe). High scores represent greater symptom severity. Based on a clinical interview, items 1-14 are based on the participants' self-report; observed behavior is also used to rate items 7, 12, and 13. Items 15-24 are rated based on the patient's observed behavior or speech during the interview.

Behavioral Inhibition System and Behavioral Activation System

The Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) is a 24-item self-report measure of behavioral inhibition and activation [46,47]. A total of 13 items reflect the activation system, divided into drive, pleasure-seeking, and sensitivity to reward, and 7 items reflect the inhibition system. There are 4 filler items. Responses are rated on a 4-point Likert-type scale with a range from 1 (very true) to 4 (very false). The BIS/BAS factor structure has been validated in a large Australian community sample [48].

Life Skills Profile

The Life Skills Profile (LSP-16) is a measure of activities of daily living over the previous 3 months with high test-retest and interrater reliability [49]. The 16-item version was specifically developed for use in Australian public mental health services [49-51]. The items are on a 4-point anchored scale. Higher scores indicate a greater disability. A total LSP score is calculated by adding all the individual scores.

Functional Magnetic Resonance Imaging

Participants will complete a computerized experimental learning task with 2 conditions: a social reward condition and a nonsocial reward condition (Figure 2). The task is a simple reinforcement learning design where participants must choose from a small number of potential responses and, over repeated trials, learn about the probable consequences. In our task, participants can choose a response from 3 buttons. Each choice is associated with a probabilistic outcome, generally with 1 winning choice, 1 losing choice, and 1 neutral choice. For example, the task might start with an 80% reward for choice A, a 40% loss for choice B, and no change for choice C. With repeated sampling, people learn to identify responses with the best outcomes and avoid irrelevant or losing responses.

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Figure 2. The experimental learning task with the nonsocial reward condition in the pre-post pilot study. Choice 4 represents the best outcome.

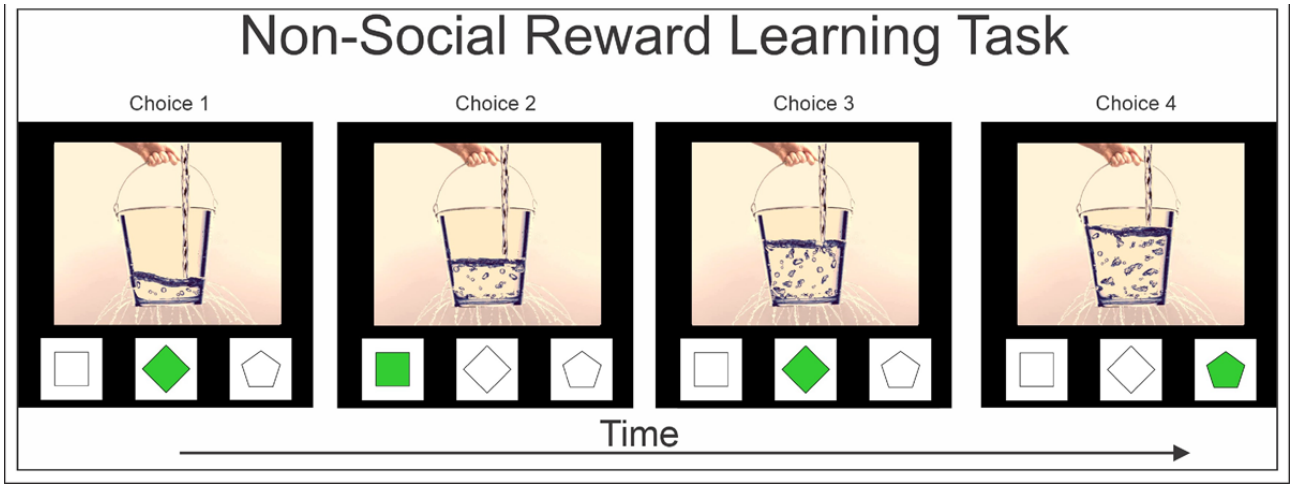

During the social learning task, participants view a picture of a neutral face, with rewarded button choices changing the facial expression toward a smile and losing choices changing toward a frowning expression. Alternatively, in the nonsocial learning task, participants view a picture of a bucket half full of water. Rewarded choices further fill the bucket, while losing choices drain the bucket. The task was developed by Dr Marcus Gray for this study and implemented in MATLAB (MathWorks) using the Cogent 2000 toolbox [52]. During the functional magnetic resonance imaging (fMRI) experiment, the task is seen by participants through a tilted mirror attached to the head coil on the magnetic resonance imaging scanner. Responses are made on a commercially available, magnetic resonance-compatible response box [53]. Participants are familiarized with the task and perform 2 blocks of each condition before brain scanning.

During the fMRI, structural and functional magnetic resonance imaging images will also be acquired by a 3T Siemens Magnetom TrioTim (Siemens Healthineers) system using a 12-channel head coil. The sequences acquired and their parameters are as follows: T1-weighted imaging, T2-weighted imaging, fMRI imaging, diffusion-weighted imaging, and susceptibility-weighted imaging.

- T1-weighted imaging: magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence. Time to acquire image=5:02; inversion 1=700 ms; inversion 2=2220 ms; repetition time=4000 ms; echo time=2.96 ms; voxel size=1 mm isotropic; field of vision=230 mm; and 192 slices with full brain coverage.
- T2-weighted imaging: fluid-attenuated inversion recovery sequence. Time to acquire image=2:44; repetition time=9000 ms; echo time=81 ms; inversion time=2500 ms; flip angle=150 degrees; voxel size = 0.72 × 0.72 × 5.2 mm; and 30 slices with full brain coverage.
- fMRI imaging: functional T2*-weighted blood-oxygen-level dependent images are acquired using a multiband, echo-planar sequence across the whole brain (repetition time=0.628 ms; echo time=30 ms; resolution=2.4 mm isotropic; field of view=192 mm; flip angle=52 degrees; and 54 slices with full brain coverage). During fMRI imaging, participants will complete a computerized experimental task. For each task condition, approximately 720 full brain images will be acquired, providing 1440 volumes acquitted in approximately 12 minutes.
- Diffusion-weighted imaging: A neurite orientation dispersion and density imaging sequence with 2 shells and 90 gradient directions (B1=1000 with 30 directions and B2=2500 with 60 directions) with 6 B0 measurements will be acquired in the anterior-posterior phase encoding direction, and an additional 6 B0 measurements will be acquired in the posterior-anterior phase encoding direction. Total acquisition time=7:24; repetition time=4100 ms; echo time=75 ms; voxel size=2mm isotropic; and 68 slices with full brain coverage.
- Susceptibility-weighted imaging: time to acquire image=2:56; repetition time=27 ms; echo time=20 ms; flip angle=15 degrees; voxel size = 0.89 × 0.89 × 2.5 mm; and 64 slices with full brain coverage.

Data Management

The Trial Management Group (TMG) consists of the principal investigator (FD) and associated investigators (GG and MG). All adverse events will be reviewed by the TMG and reported to the ethics committee. The process of recruitment and data management will be overseen by the TMG. The data will be securely entered and stored on the University of Queensland Data Manager repository. This trial may be subject to random auditing by the ethics committee. All protocol amendments will be reported to the ethics committee.

Statistical Analysis

Participants' medication dosages will be converted to olanzapine equivalents [54]. Outcome measures will be analyzed using the SPSS (version 27 or higher; IBM Corp) software package. A series of 2 (group: intervention and patient control) x 2 (time: baseline and postintervention) mixed factorial ANOVAs will be conducted to evaluate the treatment group differences for each of the outcome measures. If the normality assumption is violated, nonparametric analyses will be conducted.

For the fMRI analysis, standard preprocessing of the functionally weighted images will be carried out using the Statistical Parametric Mapping Version 12 [55]. The preprocessing steps follows: slice timing on the functional images, to correct for

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differences in slice acquisition times within each volume using the middle slice as reference; realignment (estimate and reslice) on the functional images, to correct for interscan movement within each run (defined as >3 mm translation and >2 degrees rotation); coregistration of the functional and structural images; segmentation of the structural image, with heavy regularization (0.1) recommended for MP2-RAGE sequence; normalization of the resliced images into a standardized, stereotaxic space (according to the Montreal Neurological Institute template); and smoothing of normalized images with a 8 mm full-width-at-half-maximum isotropic Gaussian kernel.

The general linear model approach for event-related designs will be conducted using the Statistical Parametric Mapping Version 8 [55]. For the first-level analysis, task-related changes in the blood-oxygen-level dependent signal will be estimated at each voxel for each participant. Head motion parameters will be included as a regressor to account for participant motion during the experiment. A 1/128 Hz high-pass filter will be used to remove slow signal drifts, and a canonical hemodynamic response function with no derivatives will be selected.

Computational modeling will allow the estimation of learning parameters at each point in time, during each task condition, for each participant. We will use a variational Bayesian framework to compute how the value of each button was estimated based on the behavioral choices made and feedback received. This allows us to measure how learning occurred during the experimental task and the subprocesses that must underlie this learning. Second-level group analyses will examine how learning in patients differs from that observed in control participants and how CR therapy alters learning efficiency and the underlying neural activity. We will correct for multiple comparisons; the voxel-level threshold will be set at P<.05 family-wise error corrected.

Ethical Considerations

This trial has been approved by the Metro South Health Human Research and Ethics Committee (HREC/2021/QMS/67093). All protocol modifications and serious adverse events will be reported to the ethics committee. The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participation will be based on voluntary, written, and informed consent. Participants with serious mental illness can be challenging to follow up with; thus, the researchers will make multiple attempts to contact each participant at baseline and postintervention. In cases of deterioration in mental state, the intervention will be discontinued, and the participant's treating team will be advised. Participants will be able to withdraw at any point in the study. All data used for analysis will be deidentified.

Results

This trial was registered in August 2018 and commenced recruiting in May 2022. As of September 2023, we have enrolled 11 healthy controls. We have also enrolled 16 individuals with SSDs, 15 into the CR group, and 1 into the TAU group. The projected completion of recruitment is September 2024. The projected final reporting date is September 2025. Results will be disseminated to mental health clinicians, researchers, and key stakeholders through peer-reviewed publications and presentations. In-kind funding is being provided by Metro South Addiction and Mental Health Services and the Translational Research Institute. This study received an Extraordinary Research Grant from the Princess Alexandra Hospital Research Foundation to assist with the purchase of fMRI scans in May 2023.

Discussion

Principal Findings

CR has demonstrated effectiveness in improving neurocognitive functioning in individuals with SSDs; however, the mechanisms that mediate this effect remain unclear. This study describes the unique protocol for a pre-post pilot study that aims to investigate RL as a potential mechanism for improvement following CR. In this study, we predict that at baseline, individuals with schizophrenia will exhibit deficits in RL when compared with healthy controls. Further, we predict that these deficits will be more pronounced in learning tasks that involve social versus nonsocial stimuli. This would support previous research highlighting impaired reward processing in SSDs [8], particularly in social processing [19,20]. Social reward has significant impacts on the functional outcomes of this population, and there are no current interventions that target this problem, emphasizing the importance of this area of research. Moreover, difficulty in responding to feedback has been associated with cognitive function and negative symptoms in SSDs [15-17]. Thus, we propose that by reducing RL problems, we may in turn see a reduction in negative symptoms and an improvement in cognition.

The primary focus of this study is to investigate whether RL is improved after CR in individuals with schizophrenia. Only 1 other study has specially looked at the impact of CR on reward processing in SSDs [29], and results from this research suggest CR may improve response to feedback, moderated by the severity of negative symptoms. We believe CR serves to strengthen the processes involved in rewards and motivation that are needed for participants to persevere with difficult cognitive tasks via reinforcement of learning. Learning more about the way in which CR works is important to be able to maximize the effects of the intervention. Currently, CR is undertaken for around 3 months, with 2-4 sessions per week. Understanding the mechanisms of effect may enable improvements in the programs that enable more efficient delivery of this effective intervention.

Limitations

The lack of blinding of researchers and the nonrandomized assignment of participants to conditions are limitations of the study design. Treatment allocation is based on individuals' preferences to minimize attrition. As the intervention group is self-selecting, arguably, these participants may be better functioning than the patient control group. However, we believe that this will not necessarily be the case. For instance, some higher-functioning participants might select to be in the control group due to time restraints (ie, because of full-time study or work) limiting their ability to complete the CR therapy sessions.

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Nevertheless, we aim to recruit comparable participants from the patient control group and intervention group by matching for age, sex, and premorbid function across groups. There will also be some flexibility in the delivery of CR (ie, on the web vs in person and individual vs group), depending on participants' access to the technology to run CR sessions and their preferences. This flexible mode of delivery was aimed at minimizing attrition, which has been an issue identified in the literature, in our work, and because of group therapy shutdowns during the COVID-19 pandemic [56,57].

Conclusions

It is hoped that the results of this study will contribute to the understanding of CR and RL in schizophrenia more generally. Greater knowledge of CR would seek to inform clinicians to develop more targeted interventions and, consequently, reduce negative symptoms and improve functional outcomes in individuals with SSDs. We hope to use this pilot to test the integrity of the protocol and plan for future funding, with the aim of progressing to a larger randomized controlled trial.

Data Availability

The data sets generated or analyzed during this study are not publicly available. Access to research data is restricted and governed by the Queensland Health Government.

Authors' Contributions

FD, MC, GG, MG, VGJ, VDM, and GR contributed to the design of the study. FD and VGJ drafted the original protocol. FD and MC conceptualized the original idea for the study. FD and VDM will run the cognitive remediation (CR) programs. VGJ and GR will conduct the cognitive assessments. MG and GR will support participants during functional magnetic resonance imaging (fMRI). No professional writers will be used. All researchers will have access to the final data set. No generative AI was used in any portion of the manuscript writing.

Conflicts of Interest

FD has received honorariums from Janssen and Lundbeck for the delivery of lectures at clinician education events.

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Abbreviations

BACS: Brief Assessment of Cognition in Schizophrenia
BIS/BAS: Behavioral Inhibition System and Behavioral Activation System
BPRS: Brief Psychiatric Rating Scale
CAINS: Clinical Assessment Interview for Negative Symptoms
CDSS: Calgary Depression Scale for Schizophrenia
CIRCuiTS: Computerized Interactive Remediation of Cognition-Training for Schizophrenia
CR: cognitive remediation
fMRI: functional magnetic resonance imaging
LSP-16: Life Skills Profile
MP2RAGE: magnetization prepared 2 rapid acquisition gradient echoes
RL: reward learning
ScoRS: Schizophrenia Cognition Rating Scale
SSD: schizophrenia spectrum disorder
TAU: treatment-as-usual
TMG: Trial Management Group
TOPF: Test of Premorbid Functioning

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Protocol

Education of Patients With Atrial Fibrillation and Evaluation of the Efficacy of a Mobile Virtual Patient Environment: Protocol for a Multicenter Pseudorandomized Controlled Trial

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Abstract

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a leading cause of mortality and morbidity. Patient knowledge about AF and its management is paramount but often limited. Patients need to be appropriately informed about treatment options, medicinal adherence, and potential consequences of nonadherence, while also understanding treatment goals and expectations from it. Mobile health apps have experienced an explosion both in their availability and acceptance as “soft interventions” for patient engagement and education; however, the prolific nature of such solutions revealed a gap in the evidence base regarding their efficacy and impact. Virtual patients (VPs), interactive computer simulations, have been used as learning activities in modern health care education. VPs demonstrably improved cognitive and behavioral skills; hence, they have been effectively implemented across undergraduate and postgraduate curricula. However, their application in patient education has been rather limited so far.

Objective: This work aims to implement and evaluate the efficacy of a mobile-deployed VP regimen for the education and engagement of patients with AF on crucial topics regarding their condition. A mobile VP app is being developed with the goal of each VP being a simple scenario with a set goal and very specific messages and will be subsequently attempted and evaluated.

Methods: A mobile VP player app is being developed so as to be used for the design of 3 educational scenarios for AF management. A pseudorandomized controlled trial for the efficacy of VPs is planned to be executed at 3 sites in Greece, Ukraine, and Kazakhstan for patients with AF. The Welch *t* test will be used to demonstrate the performance of patients’ evaluation of the VP experience.

Results: Our study is at the development stage. A preliminary study regarding the system’s development and feasibility was initiated in December 2022. The results of our study are expected to be available in 2024 or when the needed sample size is achieved.

Conclusions: This study aims to evaluate and demonstrate the first significant evidence for the value of VP resources in outreach and training endeavors for empowering and patients with AF and fostering healthy habits among them.

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KEYWORDS

atrial fibrillation; virtual patient; scenario based learning; technology enhanced learning; mHealth; mobile health; patient engagement; patient education; cardiac arrhythmia; mortality; mobile application; mobile app; health education; randomized control trial; cardiology; cardiac; heart; Greece; Ukraine; Kazakhstan; clinical decision support systems; CDSS; virtual patient scenario; myocardial infarction; arrhythmia; stroke

Introduction

Impact of Atrial Fibrillation and Non–Vitamin K Oral Anticoagulants and the Role of Integrated Management

Atrial fibrillation (AF) is the most frequent long-term cardiac arrhythmia in adults, presenting a considerable burden on patients, health care systems, societal health, and the global health economy [1]. Because AF is associated with significant morbidity and mortality, numerous research efforts and resources are being directed toward gaining more detailed information about the mechanisms underlying AF, its natural course, and effective treatments, and new evidence is being generated and published on a regular basis [2].

The current estimated prevalence of AF is between 2% and 4% [3], with a 2.3-fold increase projected due to the general population's increased longevity and the intensive search for AF [4]. AF is a well-known risk factor for thrombus development in the left atrium and eventual embolism on the left side. AF raises the risk of stroke by 5 folds, but the risk varies depending on the presence of stroke risk factors or modifiers [2]. Oral anticoagulants (OAC) are the cornerstone of AF treatment. Vitamin K antagonist (VKA) medication (mainly warfarin) lowers the risk of stroke and death by 64% and 26%, respectively, when compared to control or placebo [5]. Non–vitamin K oral OACs (NOACs) have outperformed VKAs in most therapeutic circumstances. NOAC medications do not have the practical constraints of VKAs, such as a small therapeutic window, interactions with food and other treatments, and the need to monitor coagulation levels. In 4 large randomized controlled trials (RCTs) with patients with AF, NOACs were compared to warfarin [6-9]. They were demonstrated to be at least noninferior to VKA therapy for the prevention of stroke or recurrent venous thromboembolism and were associated with a lower risk of bleeding. In a meta-analysis of these RCTs, NOACs were associated with a 19% significant reduction in the risk of stroke or systemic embolism, a 51% reduction in the risk of hemorrhagic stroke, and a similar reduction in the risk of ischemic stroke compared to VKAs. NOACs are also associated with a 10% reduction in all-cause mortality [10].

To provide optimal medical treatment to patients with AF, integrated management necessitates a patient-individualized care route. Treatment choices should be reviewed and a management plan agreed upon with health care experts in this patient-centered approach [11]. Treatment is liable to alter over time as new symptoms, risk factors, disease progression, and novel medicines emerge. To prevent stroke and improve symptoms, it is critical to consider optimizing resource usage. The initial stage in shared decision-making should be to investigate the patients' preferences [12]. The importance of stroke prevention and rhythm control among patients, as well as the corresponding risks of death, stroke, and significant bleeding, should be properly appraised for shared decision-making.

Patients’ awareness of AF and its management is sometimes restricted, especially when first diagnosed, because the majority of treatment decisions must be addressed and made. Furthermore, controlling patients' expectations of treatment goals, as well as ensuring that patients are correctly informed about treatment options, how to better adhere to therapy, and potential repercussions of nonadherence, are critical to increase adherence [2]. Thorough education of physicians on these approaches, as well as correct adherence and active engagement of the patient in the treatment process, are critical to the success of each treatment plan. Soft health interventions for education and empowerment of both clinicians and patients are critical in this environment.

Education and Other Soft Interventions Involving Mobile Health Apps in Cardiology

There has been an explosion of mobile health (mHealth) apps during the previous decade, with an estimated 3.7 billion downloads globally between 2013 and 2017 [13], many of which are intended for AF. A 2020 systematic review revealed around 11,152 articles related to mHealth apps for AF but only included 9 studies with real outcomes about mHealth therapies for AF in its results synthesis [14]. This indicates the prevalence of such solutions, as well as the dearth of data on their efficacy and impact. Only a few apps have been evaluated formally [15-17]. It should be emphasized that there are few apps that are specifically intended for patients. There are numerous informative apps that patients can use; however, a preferred option would be the development of a specific app for the treatment of a given ailment in order to help afflicted individuals in a more appropriate way [18].

Clinical decision support systems that digitize and provide evidence-based recommendations, therapeutic pathways, and algorithms to facilitate individualized, timely, and evidence-based treatment could be a valuable aid in the holistic management of AF. To improve patient-integrated AF management [19], the MobiGuide project [20] and numerous applications have been deployed. The European Society of Cardiology–Characterizing Atrial fibrillation by Translating its Causes into Health Modifiers in the Elderly Consortium partnership offers a smartphone or tablet app for patients with

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AF; however, it has yet to be tested prospectively [21]. Contradictory findings highlight the need for more properly designed trials, including evaluation of the intervention's influence on clinical outcomes [22].

As a result, the scope and impact of mHealth apps for AF, as well as the level of patient and health care professional (HCP) engagement and acceptability, are currently unknown. HCP engagement refers to information sharing between the patient and provider, shared responsibilities in decision-making processes, and support of patients' choices and acceptability to a degree to which an intervention is approved by most HCPs. Given both patients and HCPs may easily use these applications, it is critical to understand their scope and content and their acceptability among users, and to investigate the purpose and results of app adoption and usage.

Virtual Patients in Health Care Education

Virtual patients (VPs)—interactive computer-based clinical scenarios for the purpose of medical training, education, or assessment—have been increasingly used as learning activities in current health care education, particularly in teaching decision-making through scenarios [23]. Because VPs can enhance cognitive and behavioral skills, they have been successfully incorporated in undergraduate and postgraduate curricula [24]. With the rising use of VPs, there are opportunities for pedagogical synergies to allow trainees of diverse categories to practice in realistic and safe learning contexts [25]. The key characteristics of VP systems are that they enable repetitive and intentional practice by any student, regardless of time or physical location, and that mistakes are not fatal. These opportunities provided by VPs in current medical education, combined with positive evaluation results from various studies demonstrating that they may improve cognitive and behavioral skills better than traditional methods [24], have resulted in a widespread trend toward VP creation and use among academic institutions [26]. Furthermore, VPs enable the production and usage of more game-based educational content, which provides the student more exploratory flexibility and provides a different area for case-based content in current medical education.

The widespread adoption of these digital technologies, not only in medical student education but also in the health care community in general and in the patient community, has undoubtedly been limited thus far, but it has the potential to educate and psychologically support high-risk patients and vulnerable populations in these new and unprecedented circumstances. Because numerous academic institutions have the VP resources and expertise in their execution, such effective educational content might be simply repurposed in a more patient-centered format and be used more widely by the patient community as an educational aid.

Study Aim and Objectives

In this technological setting, we propose the development of a holistic approach to patient engagement and education based on the fundamentals of AF. The DEEP-RAFT (Doctors' Education, Empowerment of Patients, Regarding Atrial Fibrillation and Venous Thromboembolism) project would generate a suite of educational and informational interventions along an axis created by 2 poles: digital content cocreation and evidence-based educational impact. This effort will be based on a suite of digital teaching resources, in the form of VPs, co-designed by continuous and immediate involvement of health care specialists, health care policy influencers, and patients. This strategy seeks, first and foremost, to develop materials that are more patient-centered and address realistic problems relevant to the health care systems involved in the project. The focus of this effort is on the second topic, evidence-based educational impact, which attempts to demonstrate the educational efficacy and acceptance of the generated resources as they may be used in a diverse but targeted set of education and outreach activities.

In practice, a mobile app for natively deploying VPs on mobile devices is developed, along with a list of relevant VPs. In the following parts, we will provide these concrete and intangible tools and approaches to contextualize the protocol that is described below.

Methods

Study Design

This is a 2-arm, parallel-group pseudorandomized controlled trial that will be performed at 3 sites—Greece, Ukraine, and Kazakhstan—and will include the evaluation of the educational VP interventions. This will be conducted in 2 axes that correspond to the primary outcomes of the study. The first axis aims to determine the efficacy of the educational VP interventions, while the other will involve assessing the acceptance and opinions of the participants about the VP modality for education and information purposes. Correspondingly, the primary outcomes of the study include the efficacy and the acceptance of the VP interventions, and the secondary outcomes include the opinions of the participants about the VP modality for education and information purposes. The aims of the study are summarized in the following research question: are patients with AF better educated about their post–acute phase lifestyle changes and needs by using mobile virtual scenarios compared to conventional patient education methods?

A prepilot arm of the study will be initially conducted in Greece and will consist of hospitalized patients due to AF episodes, all of which should complete a short quiz. From among the patients who complete the quiz, half of the patients will be randomly allocated to the control (normal clinical information) cohort, while the other half will be informed with the help of VP vignettes.

After the prepilot arm, the pseudorandomized controlled trial will be conducted multicentrically. The same process, as in the prepilot arm, will be followed for recruiting the core sample, exploring the efficacy and impact of VPs in educating patients with AF. Since this trial will have been conducted during the COVID-19 pandemic, all national and international health and safety protocols will be followed.

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Inclusion and Exclusion Criteria and the Recruitment Process

The inclusion and exclusion criteria are outlined in Textbox 1. The dropout criterion is withdrawing consent during the study period.

In the Greek pilot where randomization of patient cohorts would occur, a simple coin toss algorithm will be used, implemented by Excel's (Microsoft Corp) RANDBETWEEN function. This will allocate patients between the VP education cohort and the control (normal clinical information) cohort. In the Ukraine pilot, a sampling of convenience will allocate most of the participants to the VP cohorts and fewer to the control (normal clinical information) cohort. In the Kazakhstan pilot, all accepted patients will be allocated to the VP intervention cohort. While this decision by the medical team of this center makes impossible the conduct of a distinct local evaluation of impact, we chose to include the sample in the multicentric data processing part of the study. It should be noted that evaluation results will be extracted on a per-site basis only in the Greece and Ukraine arms of the study. In the multisite comparison, the whole sample of intervention patients (including the totality of the Kazakh cohort) will be compared to the totality of the sample of control patients from Greece and Ukraine cohorts.

Patients who meet the requirements for that study will be informed about the study and will be asked if they would like to participate in it. They will then sign the consent form to take part in the study. Patients who may withdraw their consent during the study will be excluded from the analysis.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria:

- Patients with a history of paroxysmal, persistent, or permanent atrial fibrillation
- Access to an internet connection and adequate equipment
- Mastery of the country's first language
- Informed consent provided by the participant

Exclusion criteria:

- Organic or symptomatic mental disorders
- Alzheimer disease
- Mental and behavioral disorders due to alcohol abuse
- Mental and behavioral disorders due to drug abuse
- Refusal of patients to receive basic drug therapy

Intervention Cohorts

The full pilot arm of the study will be conducted multinationally in Greece, Ukraine, and Kazakhstan (Figure 1). In Greece, a pool of 700 patients will be reached by phone, and they will participate in the trial from their home. From among the patients contacted remotely, and from those who respond, those who would be eligible will be asked to complete the intervention. From among the patients who choose to complete the quiz, half of them will be randomly allocated to the control (normal clinical information) cohort, while the other half will be informed with the help of VP vignettes. In Ukraine, 160 patients will be reached and will be divided into the control and intervention groups. Finally, at the Kazakhstan center, 190 patients will be contacted.

Given that all recruitment and adherence criteria are followed, sufficient sample sizes for control and intervention groups will be ensured so as to use the Welch *t* test for analysis, which is robust to large sample size inequalities, in order to not exclude any useful data from the generalized multicenter VP cohort.

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Figure 1. The flowchart of the full pilot arm of the study. VP: virtual patient.

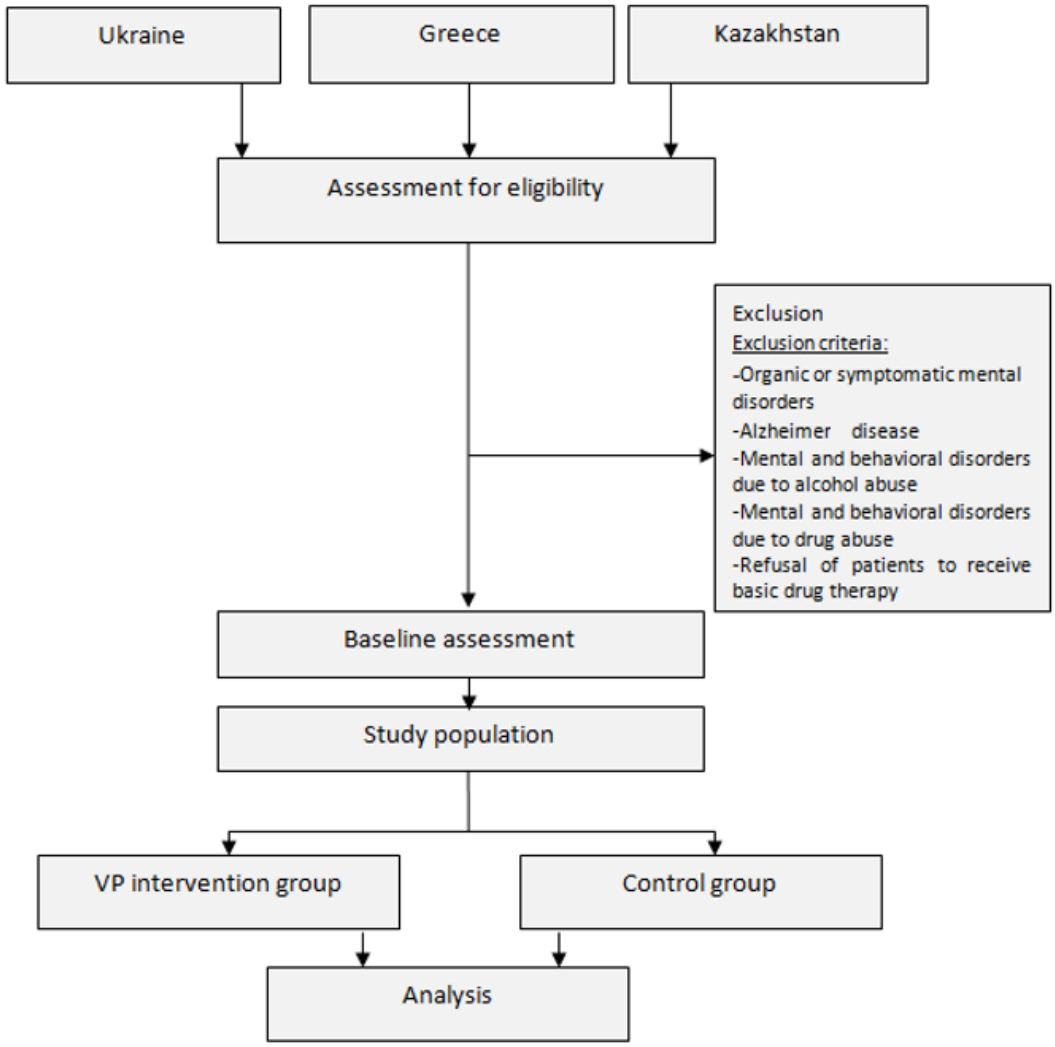

Blinding (Masking)

Participants and trial personnel will not be blinded after the point of assignment to interventions because of the nature of the interventions and outcomes assessed. Participants will know which group they will belong to because the group-specific intervention will follow immediately after randomization.

The Intervention

The 2 groups that will be compared are as follows.

The VP Cohort

In this cohort, doctors of the research team will contact patients and ask them to participate in the VP vignette case (see *The VPs* section for a detailed description of the virtual scenarios used in the intervention, and the *The Technical Architecture of the Mobile App* section for details of the mobile app that will be used for delivering the intervention). At the end of the case questions, further information will be provided.

The Control (Normal Clinical Information) Cohort

In this cohort, doctors of the research team will contact patients and provide the protocol—this will include dictated information for patients with AF.

The Technical Architecture of the Mobile App

A mobile VP player app has been created, which is capable of tracking the following user data: a detailed log of pathway detection and tracking, time spent in each node of the VPs or mobile VP, tracking of milestones, rate of successful completion of the VPs or mobile VP, and connection to learning outcomes. The player follows a flat development approach and should be available as a progressive web application. A progressive web application is a type of web-based application software that is built using standard web technologies such as HTML, CSS, and JavaScript. It is aimed to be compatible with any platform that supports a standards-compliant browser. The ability to work offline, receive push notifications, and access device hardware will enable the creation of user experiences similar to those found in native applications on desktop and mobile devices. Because a progressive web application is a subset of a web page or website known to be a web application, neither developers nor users should be required to install web applications through digital distribution systems such as the Apple App Store or Google Play.

Technically, communication between the backend and the front end player is accomplished through the use of the JSON application programming interface standard [27], which is an

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extremely efficient method of exchanging data over slow networks (eg, mobile phone networks).

The system's appearance and feel are based on Bootstrap, a free and open-source CSS framework for developing responsive, mobile-first front end web applications. It would be optimized for smartphone screens so as to provide a “mobile-first” user experience.

The VPs

Three scenarios will be explored by the participating medical teams. All will be focused on the patients, since these are the target group of the VPs. A tabulated outline of these scenarios is presented in Table 1. The first scenario should be dealing with a chronic case of AF, including guidance for good medication adherence, systematic medical appointments, and correct communication. The second scenario would be about detecting early onset and prevention of paroxysmic AF. The third scenario will deal with a case of AF that involves lifestyle-compounding factors to the disease (smoking, drinking, and unhealthy eating), as well as more heavy complications that are significantly more probable in such cases.

Table 1. Outline of suggested scenarios and educational objectives of virtual patients.

Scenario theme	Educational objectives (after encountering this educational virtual scenario vignette, the patient will be able to…)
Chronic case of AF[a]	• Identify correct medication adherence practices • Identify the correct frequency regimen of doctors’ appointments • Identify correct dietary restrictions
Early-onset and paroxysmic AF	• Identify initial onset of symptoms of AF • Identify timely medical consultation practices • Recognize the correct medicinal adherence procedure for the condition • Identify the correct exercise intensity to manage the condition
AF with lifestyle- compounding factors to the disease (smoking, drinking, and unhealthy eating)	• All educational objectives of “Chronic case of AF” • Identify risks of high-impact complications • Identify best practices for recovering from missed doses of medical treatment

[a]AF: atrial fibrillation.

Iterative brainstorming between the medical experts of all study centers will produce the detailed VP scenarios in the mobile digital platform (for details, refer to the previous section, *The Technical Architecture of the Mobile App*). After an internal review of these scenarios by the multinational expert panel, a selection would be made for the final case to be used. In that context, the team will choose to simply use 1 scenario in the multicenter multinational cohort trials. The most appropriate scenario would have the following characteristics: (1) it should be the most relevant—a significantly larger proportion of patients should be targeted; (2) it should be the most clinically impactful—it is important and useful for patients with AF to be aware of AF complications; and (3) it should be the most educationally important—both patients who fall within the parameters of the described case and those who do not would benefit from information and preventative knowledge of the impact of AF.

An acceptance rate of 75% by medical experts for each criterion for each scenario should be reached to be eligible for recruitment. Moreover, this patient education intervention will be based on techniques from the behavior change technique taxonomy—an international consensus for the reporting of behavior change interventions [28].

After this selection, a process of localization and adaptation to the specifics of each center (Greece, Ukraine, and Kazakhstan) would be conducted.

Evaluation Design

Evaluation Instruments

For educational efficacy, a multiple-choice questionnaire (MCQ) for knowledge retention will be used (Textbox 2). The choice of questions was based on the European Society of Cardiology’s *Guidelines for Management of Atrial Fibrillation* [29]. This instrument will be translated for all participating centers in Greece, Ukraine, and Kazakhstan. The translation and evaluation of the translation will be performed by teams of bilingual experts. The instrument in its original version will be provided to bilingual persons in alternating language order and will be assessed accordingly. Scoring each questionnaire follows a simple process of allocating a numerical score equal to the number of choices in the MCQ to weigh each response for randomly selecting the correct question. For example, a question that has 4 possible responses in the MCQ will be scored 4 points if answered correctly, while a question that has 5 possible answers will be scored with 5 points if correctly answered.

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Textbox 2. Questionnaire for knowledge retention on atrial fibrillation (the asterisk indicates the correct answer).

1. Atrial fibrillation:

- Is the most common cardiac arrhythmia
- More often concerns older people, but can occur in any age
- May be related with thyroid disorders
- All of the above*

2. The most common symptom of atrial fibrillation is:

- Chest pain
- Palpitations*
- Dizziness
- Blurry vision

3. How can atrial fibrillation be diagnosed?

- Following an electrocardiogram evaluated by a cardiologist*
- By describing symptoms of the arrhythmia to the doctor
- By checking the indication ‘’arrhythmia’’ of the blood pressure device
- All of the above

4. What is the most important complication a patient with atrial fibrillation not receiving treatment may suffer?

- Fainting spells
- Myocardial infarction
- Lethal arrhythmia
- Ischemic stroke*

5. Treatment with oral anticoagulants always mandates frequent blood tests:

- True
- False*

6. The patient with atrial fibrillation that visits a cardiologist:

- Probably does not need oral anticoagulation to prevent stroke
- Always needs treatment to cure the arrhythmia
- Cardiologist? There is no need to see a doctor
- Might have to be admitted to the hospital at the time of Atrial Fibrillation diagnosis *

7. When the patient with atrial fibrillation is being treated with an oral anticoagulant:

- It is better to receive the reduced dose so as to avoid bleeding
- This is always stopped at 3 months, since the danger for stroke is gradually reduced
- It is fine if he/she occasionally misses a dose
- He/she has to adherently receive the right dose of the drug, as prescribed by his/her treating physician*

8. The newer oral anticoagulants:

- Are at least as safe and effective as warfarin in preventing stroke
- Have to be taken every day on a fixed schedule, so as to be effective
- Do not have important interactions with other drugs or food, in contrast to warfarin
- All of the above*

9. Oral anticoagulants:

- Are not necessary, in case the patient already receives other blood thinning medication, such as aspirin

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- Are the most effective treatment in preventing stroke*
- Do not have any significant side effect
- All of the above

10. A patient that is under warfarin:

- Cannot switch to a newer oral anticoagulant if he/she has good anticoagulation control (international normalized ratio within the desired range)
- Can follow an unrestricted diet
- Can get advice from his doctor regarding treatment with a newer anticoagulant, so as there is no need for frequent blood tests*
- Always has good anticoagulation control (INR within the desired range) if he/she receives his medication in a fixed dose

Project Management

All project members will meet remotely every week to work through advances and challenges together and to provide methodological support to remain aligned with the protocol. Researchers will be hired and trained, regulate safety conditions, and oversee the data collection and analysis. The researchers will prepare the data collection tools and perform data collection, and ensure that the materials required are adequate and functional. The senior Greek PI (PDB) will coordinate the overall project.

Ethical Considerations

Ethics approval has been obtained from the Bioethics committee of the Medical School of the Aristotle University of Thessaloniki (178/19-3-2020). This study will be conducted in line with the tenets of the Declaration of Helsinki, and no participant will be randomized unless written informed consent is available for that participant. Participants can withdraw from the trial at any time and will be informed and assured of such right. This study follows the principles of data protection and management described in the European Union's General Data Protection Regulation.

Confidentiality

All personal and collected data will be treated as confidential at all stages of the study and will be stored separately. The electronic data will be saved with metadata in university network drives, which are protected by usernames and passwords. The participant ID list that links the study participants and research data will be disposed of after 15 years. Institutions hold the ownership of registry data.

Results

The trials will start in 2024 and are expected to end later that year or in early 2025 or when the needed sample size is achieved. The initial results are expected by March 2024.

To assess the results from the prepilot evaluation questionnaires, the Welch *t* test will be conducted. Of note, we decided to conduct the Welch *t* test because some of our sample sizes will be heavily unequal between intervention and control groups. The standard Student *t* test is robust to inhomogeneity of variance when sample sizes between cohorts are the same; however, this is not true for largely differing cohort sample sizes. The Welch *t* test does not assume homogeneity of variance and, hence, is robust to widely varying sample sizes [30,31].

Discussion

Expected Findings

The results of this study aim to demonstrate the efficacy of the VP educational modality in transferring knowledge in an impactful way so that it would be useful and retained by the learner. The rationale for this kind of expected efficacy may be attributed to various factors. The impact of information passed through narrative vehicles has been identified early on [32]. Additionally, the initiative that the learner has to guide the narrative through their choices facilitates engagement through 2 avenues: one avenue is the agency that the learner has over their narrative exploration, and the second one, dependent on the first but not identical, is the ability to direct the narrative toward educational needs that the learner may have. These factors are compounded by the immediacy and ease of access that the mobile delivery platform offers, which can create an engaging and user-friendly experience that may amplify the educational impact.

This work will focus on knowledge retention and efficacy and not on perceived changes in quality of life. The impact of AF itself in the quality of life of patients is well documented with a validated questionnaire that has been available since the last decade [33]. A cursory search with the keyword "AFEQT" revealed more than 550 references on Google Scholar, including several reviews (for characteristic examples, see Kotecha et al [34] and Parameswaran et al [35]).

On the other hand, there is a significant body of literature that has identified the perceived impact of impactful patient education in their risks for serious complications and quality of life. AF, when first diagnosed, is an overwhelming situation for the patient, and reliable information is one of the first requirements for alleviating the initial possible shock [36,37]. Furthermore, lack of knowledge leads patients with AF to have significantly skewed perceptions about the importance of their condition and the true risks that stem from this potentially life-threatening, possibly chronic, condition.

Multiple studies have demonstrated that patients do not identify the possibility of stroke as an acute complication of AF; a lot of them cannot even identify their arrhythmias as AF, and they

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do not recognize AF as life-threatening even though they receive verbal or printed information about their condition [38,39].

In that context, it is very important to constantly explore information and educational avenues that are impactful and engaging for patients who need reliable and immediately absorbable information. This study aims to demonstrate that in this very important aspect of knowledge retention, the approach of narrative virtual scenarios is one that could provide a distinct impact advantage over the conventional paper-based or verbal information to the patients.

Limitations

The study's core limitation lies with the knowledge retention questionnaire. This is not a validated instrument. While we were aware of a formal validated instrument (the Jessa Atrial fibrillation Knowledge Questionnaire [40]), the knowledge spectrum that it covers is far wider than what our VP vignette may cover. Given that verbal and printed conventional information covers all relevant material, while our VP may cover specific critical topics related to AF, using a wide instrument such as the Jessa Atrial fibrillation Knowledge Questionnaire would run the risk to evaluate knowledge retention gaps that the VP vignette cannot cover. While a counterargument can be made that we are thus narrowing the evaluation scope to the strong points of our VP resource, the concise focus of the VP vignette is itself an argument for implementing it as a more effective educational tool in personalized and focused endeavors for patient empowerment. As a follow through too, we aim to address the second weakness of our study, which is the lack of a qualitative exploration about the acceptance of patients regarding the electronic medium of mobile devices and the modality of VPs in comparison to other existing modalities such as video demonstration or even gamified virtual environments.

Even given these limitations, however, this study can provide evidence for the comparatively better efficacy of the VP modality in mobile media for impactful and effective information for and empowerment of patients with AF. This study would be the first evidence-based step to initiate this process toward better informing and subsequent empowerment of patients with regard to the management of their disease.

Conclusions

This project can generate new knowledge and relevant results for a deployed VP regimen for the education and engagement of patients with AF on crucial topics regarding their condition. A 3-center pseudorandomized controlled trial could add data to the evidence regarding the effects of interventions using VP resources in outreach and training endeavors for empowering patients with AF.

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Conflicts of Interest

GG received fees for lecture travels or research from Bayer, Boehringer Ingelheim, Pfizer, and LeoPharma. The other authors declare no conflicts of interest.

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Abbreviations

AF: atrial fibrillation
DEEP-RAFT: Doctors' Education, Empowerment of Patients, Regarding Atrial Fibrillation and Venous Thromboembolism
HCP: health care professional
MCQ: multiple-choice questionnaire
mHealth: mobile health
NOAC: non–vitamin K oral coagulant
OAC: oral anticoagulant
RCT: randomized controlled trial
VKA: vitamin K antagonist
VP: virtual patient

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Protocol

Web-Based Intervention to Act for Weight Loss in Adults With Type 2 Diabetes With Obesity (Chance2Act): Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: In adults with type 2 diabetes (T2D), weight loss can improve hemoglobin A_{1c}, blood pressure, and triglycerides, and reduce the frequency of medications needed. Unfortunately, a large proportion of these individuals are not ready to initiate weight efforts, making existing obesity management strategies less effective. Many digital health interventions aim at weight loss, but there is still limited evidence on their effectiveness in changing weight loss behavior, especially in adults with T2D.

Objective: This study aims to develop and validate "Chance2Act," a new web-based intervention, designed specifically to facilitate behavioral change in adults with T2D with obesity who are not ready to act toward weight loss. Then, the effectiveness of the newly developed intervention will be determined from a nonrandomized controlled trial.

Methods: A web-based intervention will be developed based on the Transtheoretical Model targeting adults with T2D with obesity who are not ready to change for weight loss. Phase 1 will involve the development and validation of the web-based health intervention module. In phase 2, a nonrandomized controlled trial will be conducted in 2 government health clinics selected by the investigator. This is an unblinded study with a parallel assignment (ie, intervention vs control [usual care] with an allocation ratio of 1:1). A total of 124 study participants will be recruited, of which 62 participants will receive the Chance2Act intervention in addition to the usual care. The primary outcome is the changes in an individual's readiness from a stage of not being ready to change (precontemplation, contemplation, or preparation stage) to being ready for weight loss (action stage). The secondary outcomes include changes in self-efficacy, decisional balance, family support for weight loss, BMI, waist circumference, and body fat composition.

Results: The phase 1 study will reveal the intervention's validity through the Content Validity Index and Face Validity Index, considering it valid if both indices exceed 0.83. The effectiveness of the intervention will be determined in phase 2, where the differences within and between groups will be analyzed in terms of the improvement of stages of change and all secondary outcomes as defined in the methodology. Data analysis for phase 2 will commence in 2024, with the anticipated publication of results in March 2024.

Conclusions: If proven effective, the result of the study may give valuable insights into the effective behavioral modification strategies for a web-based intervention targeting adults with T2D with obesity but not yet ready to change for weight loss. This intervention may be replicated or adopted in different settings, focusing on behavioral modification support that patients need. This study offers a deeper understanding of the application of behavior change techniques for a more holistic approach to obesity care in T2D.

Trial Registration: ClinicalTrials.gov NCT05736536; https://clinicaltrials.gov/study/NCT05736536

International Registered Report Identifier (IRRID): DERR1-10.2196/48313

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KEYWORDS

readiness to change; behavior change; diabetes; overweight; weight reduction; eHealth; obesity

Introduction

Obesity has become one of the leading global health concerns over the last century. Numerous studies have proved the complex relationship between obesity and type 2 diabetes (T2D). The majority of patients with T2D are either overweight or obese, thus increasing their long-term risks of developing cardiovascular diseases and diabetes complications [1]. The World Health Organization (WHO) has reported that around 2.8 million people die each year as a result of being overweight or obese [2]. In patients with T2D, weight loss can improve hemoglobin A_{1c}, blood pressure, triglycerides, and health-related quality of life, and reduce the frequency of medications required [3]. A significant reduction of body weight (>10%) can induce diabetes remission even among those with advanced disease and established diabetes complications [4,5].

In Malaysia, the prevalence of obesity among patients with T2D has been increasing each year, whereby 84% of the patients with T2D were recorded to be either overweight or obese in 2019 [6]. Unfortunately, studies have shown that a large proportion of them (59%-79%) are still not ready to act on losing weight [7,8]. Since they do not have the intention of losing weight, they would not be interested in practicing or acting upon the recommendations given by the primary care personnel and thus, are deprived of the benefit of losing weight.

Interventions in behavior modification have been proven as an important component in a successful weight control program, in addition to the dietary and physical activity components. A European guideline has shown that behavioral change can induce 5%-15% weight loss among overweight or obese individuals [9]. Theories on behavior change should be applied when developing any health intervention because it increases the likelihood of being more effective. Among the theories, the Transtheoretical Model (TTM) uniquely describes the behavior change process from not being ready (precontemplation, contemplation, and preparation) to the active stage (action and maintenance). Applying TTM may help researchers in understanding the behavioral issue and help to develop a tailored intervention based on the individualized readiness stage [10]. A systematic review has found that by implementing the stages of change of TTM, there were improvements in physical activity and dietary habits, specifically in terms of exercise duration and frequency, reduction in dietary fat intake, as well as increment in fruits and vegetable consumption [11]. Unfortunately, the current management of T2D does not identify those who are ready or not ready to make changes in their daily life [12]. Clearly, there is a need to help the large proportion of patients who are not ready to change to start taking action for weight loss.

Intervention in behavior modification should address the role of social environment on an individual's readiness to lose weight. Weight loss-related behaviors, specifically healthy diet and physical activity are embedded in the social context, particularly the family context. Therefore, addressing behavior modification embedded in daily family life might be a promising approach to boost family support, thereby facilitating progress. Family support can be received in the form of companionship, emotions, information sharing, and instrumental assistance to facilitate the weight loss journey [13]. Integration with the family support component can lead to a more maintainable behavioral change, a better improvement of diabetes outcomes, as well as help to improve the health of family members [14,15].

Over the decades, web-based health technologies are increasingly used as a delivery mode for health promotion and prevention. The web-based platform will provide a good opportunity to improve the management of patients with T2D with obesity. Implementing web-based health promotion and prevention can widen the opportunity to reach specific target groups, lower the cost of implementation, and improve the health of the population [16]. It may overcome problems such as time constraints, privacy concerns, and the negative perception of being obese. Furthermore, web-based intervention can be delivered within a social system so that all members, for example, of a family can simultaneously and collectively take part in the obesity intervention and share their plans, goals, and progress [17]. To increase the efficiency of the interventions, the intervention can be coupled with tailored feedback and counseling [18]. Unfortunately, there is limited knowledge in the literature on web-based health intervention that has been developed based on the TTM targeting adults with T2D with obesity and integrating the family support component.

The objective of this trial is to develop and validate "Chance2Act," an innovative web-based intervention grounded in the TTM, designed specifically to facilitate behavioral change in overweight or obese adults with T2D who are not ready to take action toward weight loss. Then, the effectiveness of the newly developed digital health intervention will be determined based on a nonrandomized controlled trial.

Methods

Overview

This study will be conducted in two phases, which are (1) phase 1: the development and validation of the Chance2Act intervention module and (2) phase 2: the nonrandomized controlled trial of the Chance2Act intervention.

Phase 1: Content Development and Validation

Phase 1 of the study concerns the development and validation of the health intervention module. To get the initial ideas, framework, and justification for the selection of topics, a literature review and document analysis will be done. The content selection will be based on the key findings from the review of previous studies, the available local and international guidelines, as well as published reports, and available statistical

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data. The search sources will involve web-based databases, websites and printed materials (guidelines, pamphlets, posters, factsheets, reports, etc) that incorporate behavior change theories and family support components.

In addition, experts in related fields from different sectors (government, private, and nongovernmental organizations) will be invited for informal interview sessions to share experiences and give input for the new intervention. Further exploration will be conducted through informal interviews with overweight or obese adults with T2D, focusing on the knowledge, awareness, and practice of unhealthy behaviors, challenges, and facilitators for weight loss.

The contents of the health education module will be arranged according to the Process of Change construct of TTM. Then, the contents of the module will be drafted including the texts and graphics, as well as the formatting and layout for the website which acts as the medium of delivery for the health intervention. The local language (Malay language) will be used for the communication. The website will be arranged with consideration of the appropriate sequence. An attractive illustration will be used to ensure participants' engagement and hence complete the entire package of the intervention module.

For the validation of the intervention module, 6 experts from relevant fields related to obesity and diabetes management will be selected to evaluate the newly developed health intervention module. The experts will consist of (1) an epidemiologist of noncommunicable diseases, (2) a health education expert, (3) a family medicine specialist, (4) a dietician, (5) a sports medicine specialist, and (6) a medical officer in-charge of the diabetes program in a health clinic. The Content Validity Index (CVI) will be analyzed to determine the relevance of the intervention content.

A face validation study will be conducted among overweight or obese adults with T2D and the public to determine the clarity, simplicity, and ambiguity of the intervention content. It will be quantified by using the Face Validity Index (FVI). After being proven to be valid to achieve the primary objective, the final version of Chance2Act Health Intervention will be ready to be used in phase 2: the nonrandomized controlled trial. Figure 1 illustrates the study flowchart for phase 1.

Figure 1. Study flowchart for phase 1.

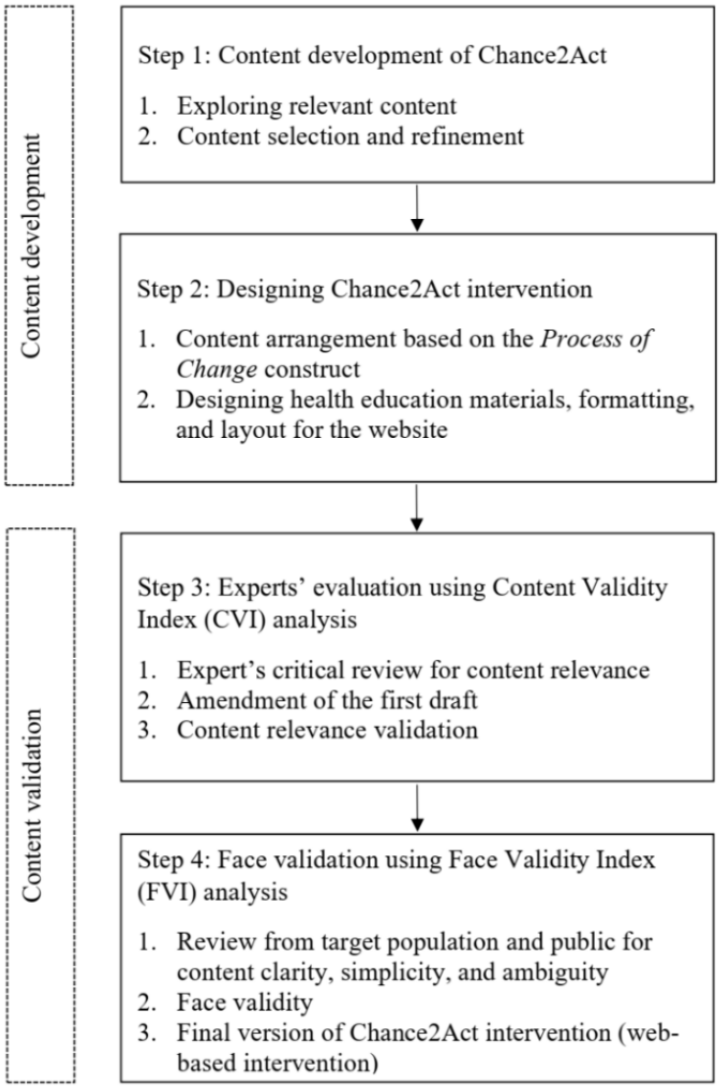

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Phase 2: Nonrandomized Controlled Trial

Study Setting

Phase 2 of the study will be conducted as a nonrandomized controlled trial, which is aimed to determine the effectiveness of the Chance2Act intervention. The study is expected to be conducted over 4 to 6 months, at 2 government health clinics in Pahang state, Malaysia. These 2 health clinics will be enrolled by the researcher and are expected to have similarities in terms of the sociodemographic background of the local community. The assignment into either the intervention or control group will be based on the health clinic where the participants are getting their treatment from. One health clinic will be assigned as the intervention arm whereas another clinic as the control arm. The study flowchart for phase 2 is summarized in Figure 2. This is an unblinded study with a parallel assignment (ie, intervention vs control [usual care] with an allocation ratio of 1:1). Blinding is not possible due to the nature of the intervention which is mainly health education.

To avoid contamination, the 2 health clinics will not be selected from neighboring localities. Access to the Chance2Act website will be restricted only to the registered participants and family members from the intervention arm. A username and password will be provided to log in to the website. The participants, family members, and the medical staff at the participating health clinics are not allowed to share any intervention material with a third party.

Figure 2. Study flowchart for phase 2. DBI: Decisional Balance Inventory; SEE: Self-efficacy for Exercise; SOC: Stages of Change; T2D: type 2 diabetes; WC: waist circumference; WEL-Q: Weight-efficacy Lifestyle Questionnaire.

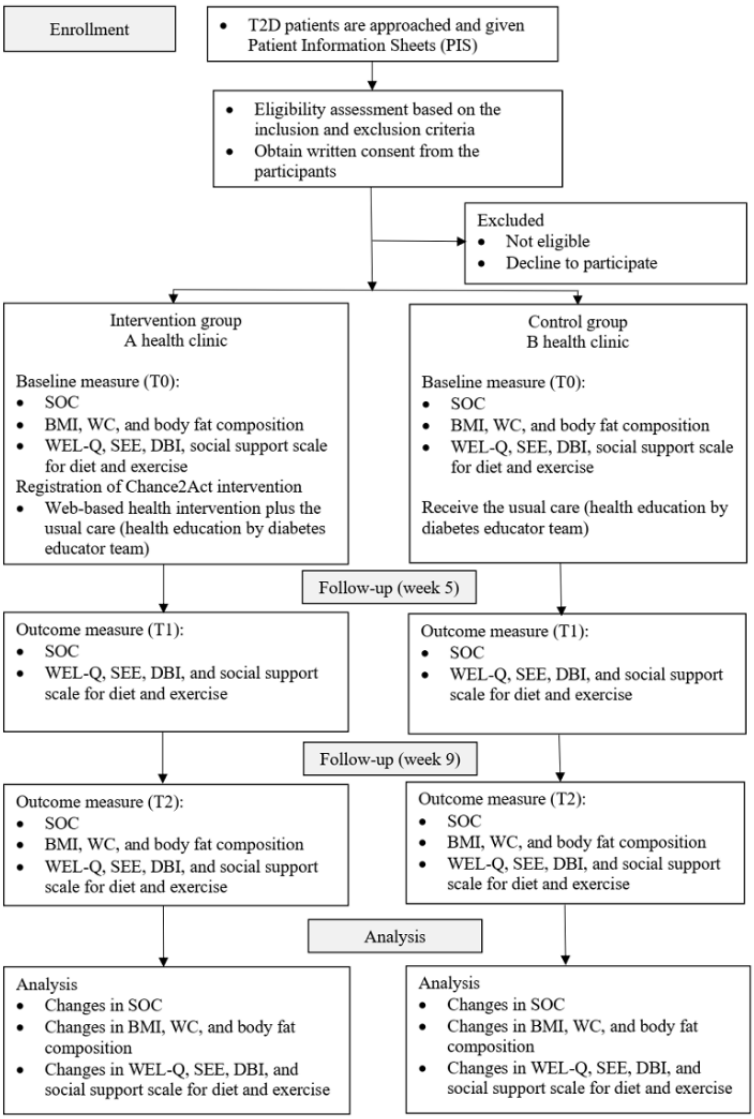

Study Population

The target population is patients with T2D aged 20-60 years old, with a BMI of more or equal to 23 kg/m^2, who are not ready to act for weight loss. Study participants will be selected via purposive sampling method to ensure homogeneity between the 2 arms.

Participants Recruitment

The patients with T2D, who come for a routine appointment at the selected health clinics during the recruitment period will be approached, given the Patient Information Sheet (PIS) about

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the study, and invited to participate. If they are willing to participate, they will be screened by the investigators to determine their eligibility based on the inclusion and exclusion criteria. Then, written informed consent will be obtained from those who are eligible. Participants from the intervention arm will be given a username and password to access the Chance2Act intervention, whereas participants from the control arm will continue the existing health education module in the health clinic.

Eligibility Criteria

The patients with T2D aged 20 to 65 years old who fulfill all the following inclusion criteria will be included (1) BMI of more or equal to 23kg/m^2; (2) in the precontemplation, contemplation, or preparation stage of change based on the s-weight questionnaire [19]; (3) able to understand, read, and write in the Malay language; (4) have access to any electronic device with internet service; (5) able to understand information and perform tasks in the digital environment, especially website; and (6) have at least 1 adult family member who is living in the same household.

Patients who fulfill any of the following criteria will be excluded (1) patients who are pregnant; (2) patients with advanced comorbidity and mental conditions that will affect participation and understanding of the study protocol, for example, vision problem, physically unfit to stand up and walk, advanced heart failure or cancer, and schizophrenia; and (3) patients who die or are transferred out to other health clinics during the study period.

Sample Size Calculation

The sample size was calculated using OpenEpi (version 3; Kelsey et al) open-source calculator for cross-sectional, cohort, and randomized control trials. To obtain 95% CI and 80% power of the study (α=.05), the minimum sample size required in each arm is 44 to achieve a 30% proportion difference postintervention [20]. Considering a 40% (n=21 participants) attrition rate, we aim for a total of 65 participants per arm.

Chance2Act Health Intervention

The Chance2Act digital health intervention is a web-based behavior modification program based on the 4 main constructs of the TTM. This model uses the stages of change to integrate the principles and processes of behavior change. The stages of change are influenced by the processes of change (activities people use to progress through stages), decisional balance (an individual's relative weighing of the pros and cons of changing), and self-efficacy (situation-specific confidence that people can cope with without relapsing to their former behavior) [21]. This intervention emphasizes the role of the immediate family members in creating a healthy social environment favoring weight loss. The main components of the intervention will be identified from an extensive review of published studies, health education materials, and gray literature that can boost the readiness to change for weight loss. This is the first version of the study protocol.

Delivery of the Chance2Act Intervention

The Chance2Act intervention will be delivered to the individual participants by the investigators. Participants will be given the Chance2Act website using their login account and password. Access to the website is free of charge. The intervention will comprise 4 main modules and will be delivered in sequence. Each module will take approximately 2 weeks to be completed. The sequence of the intervention was developed based on the Process of Change construct of the TTM [21].

The baseline measurements will be taken before the initiation of the intervention. Follow-up will be done by the investigator after the completion of the first 2 modules, approximately at week 5, and after the completion of the whole package of the intervention, at week 9. In addition, participants can seek help from the investigators to navigate through the functions of the Chance2Act website through the built-in messaging system.

The Chance2Act is a tailored intervention whereby the participants will receive personalized coaching about their weight-related behavioral problems to boost their motivation via the built-in messaging system. The principal investigator will actively monitor the progress of each participant and intervene according to the health education module. Information will be given through text on the website, sets of infographics, animations, and videos. Health quizzes will be conducted to assess the comprehensibility of the module. They will be given printed materials such as weight loss checklists and dietary and exercise weekly plan templates to assist their weight loss journey. Each participant will have at least 1 adult family member to join as part of the intervention modules. The family members will be guided on the ideal way to fully support the participants' efforts for weight loss. They will receive clear information on their role during the weight loss journey.

Participants are expected to finish each module in 2 weeks and give the required feedback and responses at the end of the module accordingly. Follow-up will be done by the investigators. Participants who did not comply with the follow-up requirements will be considered a loss to follow-up. Data analysis will be by the intention-to-treat (ITT). There is no specific concomitant care and intervention that are permitted or prohibited during the trial.

Data Collection

For both arms, the data for phase 2 will be obtained from a set case report form (CRF) which consists of demographic data, self-administered questionnaires, anthropometric measurements, and disease profiles. At week 0 (T0), once consented, anthropometric measurements will be taken by the investigator and clinical data will be obtained from the medical records.

Clear written and verbal instructions will be given on how to answer the questionnaires. Participants will be requested to circle which options suit them the most. Participants will be allowed to answer the questionnaires while waiting their turn for medical consultation. They will be encouraged to seek clarification from investigators at any time, should any queries arise.

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Before the initiation of the study, all investigators will be trained regarding the study procedures to minimize variability and bias during the data collection. The study procedures will comply with the Malaysian Guideline for Good Clinical Practice, fourth edition [22].

Study Instruments

For the anthropometric measurement, the height will be taken using a wall mounted stadiometer (SECA 206) and recorded to the nearest 0.1 cm. The body weight and body fat composition (total fat percentage and visceral fat percentage) will be measured using a body fat composition monitor (Omron HBF-222T) with an accuracy of 0.1 kg and 0.1%, respectively. Waist circumference will be measured to the nearest 0.2 cm using nonstretchable measuring tape midway between the lower margin of the 12th rib and the top of the iliac crest, just above the umbilicus in a horizontal plane.

The set of self-administered questionnaires will consist of (1) a Stages of Change (SOC) questionnaire using the S-weight; (2) a Weight-efficacy Lifestyle Questionnaire (WEL-Q); (3) Self-efficacy for Exercise (SEE); (4) a Decisional Balance Inventory (DBI) for weight loss; and (5) social support scale for diet and exercise. Verbal instruction will be given on how to complete the questionnaire. On average, participants will be expected to spend approximately 30 minutes to complete the questionnaires. Once they have finished, they will submit the questionnaires to the investigator to ensure the completeness of the responses given.

The S-weight questionnaire was initially developed in English and Spanish language simultaneously [19,23]. This questionnaire has been translated into Malay language and tested among the adolescent obese population [24]. It consists of a brief series of self-report questions assessing weight loss intentions and current activities. The S-weight has 5 mutually exclusive items each representing the 5 stages of change: precontemplation, contemplation, preparation, action, and maintenance. S-weight has been reported as an efficient tool to assess the readiness to change in weight management by a review [25].

A validated Malay version of WEL-Q will be used to assess dietary self-efficacy for weight loss. It is used to measure an individual's confidence to control eating in specific circumstances. It consists of 20 items representing 5 subscales which are negative emotions, availability, social pressure, physical discomfort, and positive activities. WEL-Q uses a Likert scale ranging from 0 (not confident) to 9 (very confident). The total score of each subscale is ranged between 0 and 36. The higher score shows better control to resist eating. WEL-Q has been tested among the Malaysian population with T2D. It is reported to have a good internal consistency reliability with Cronbach α of .893. Construct validity was measured by the item total correlation of r>0.700 and P<.01, and interitem correlation of r<0.005 and P<.01 [26].

The SEE was originally developed by Bandura and has been modified to suit the Malaysian population. It consists of 18 items measuring an individual's confidence to maintain routine exercises. A 5-point Likert scale is used ranging from 1 (cannot do) to 5 (certain can do). The Malay version of SEE has been tested among Malaysian patients with T2D with a composite reliability (CR) of 0.921 [27].

The DBI was developed in the English language by O'Connell and Velicer in 1988 [28]. It measures an individual's belief of the perceived pros and cons of weight loss. It consists of 20 Likert scale items, 10 items for pro (even-numbered items) and 10 items for cons (odd-numbered items). The scale ranges from 1 (not important at all) to 5 (very important). The total score range is 10 to 50. The Malay version of DBI shows good reliability. For the pro scale reliability was reported as Cronbach α=.902, intraclass correlation (ICC) (95% CI) is 0.88 (0.86-0.90). The con scale Cronbach α=.739 and ICC (95% CI) is 0.72 (0.70-0.78) [24].

The social support scale for diet and exercise was developed in the English language in 1987 [29]. In this study, the social support for diet and exercise will be measured separately and used specifically to measure the perceived social support received from the family members. The social support scale for diet consists of 10 items. Items 1-5 measure the encouragement, whereas items 6-10 measure discouragement received from the family members. The social support scale for exercise behavior consists of 12 items. The measurement uses a Likert scale ranging from 1 (never) to 5 (very often). A higher score implies that the participants have better social support received from their family members to lose weight. These questionnaires have been translated into Malay language and validated. This questionnaire has been proven valid and reliable. The social support for diet has internal consistency reliability of Cronbach α of .61-.91 and test-retest reliability, r of 0.55-0.86 [29]. The social support scale for exercise was reported to be reliable for the Malaysian population. It was reported to have a CR of 0.918, an average variance extracted of 0.560, and an ICC (based on test-retest) of 0.920 [30].

Study Outcome

Outcome measures are categorized into primary and secondary outcomes. These measures will be obtained from both the intervention and control arm at baseline, fifth week, and ninth week after the initiation of the intervention.

The primary outcome will be measured by the changes of the stages of change using the Malay version of the S-weight questionnaire. The secondary outcomes will be measured by (1) a change in dietary self-efficacy will be measured by the WEL-Q, (2) a change in exercise self-efficacy will be measured by the SEE, (3) a change in decisional balance for weight loss will be measured by the DBI, (4) change in family support for diet and exercise will be measured by the social support scale for diet and exercise, (5) change in BMI, (6) change in waist circumference, and (7) change in body fat percentage.

Control Group

The control group will continue to receive the usual care at the health clinic. The usual care includes the health talk and individual or group counseling sessions with the diabetes educators, physiotherapists, dieticians, or medical officers as scheduled by the health clinic. Participants from the control group will be offered to participate in the intervention after the completion of T2 data collection.

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Data Management and Statistical Analysis

For phase 1, the data will be entered in Microsoft Excel (Microsoft Office 365) and ready for analysis. The content validity will be assessed by the experts' ratings. The CVI will be assessed based on 2 indices, the Item-level Content Validity Index (I-CVI) and Scale-level Content Validity Index (S-CVI). The criteria that will be assessed are mainly content relevance. The I-CVI will reflect each item or intervention activity relevancy, whereas S-CVI will reflect the overall module relevancy. Then, the face validation will be determined based on the FVI. Similarly, the FVI will be assessed based on 2 indices, the Item-level Face Validity Index (I-FVI) and the Scale-level Face Validity Index (S-FVI). The criteria that will be evaluated are the module clarity, simplicity, and ambiguity. For both CVI and FVI, the results of at least 0.83 will be considered acceptable [31,32].

For phase 2, the data will be entered into IBM SPSS Statistics (version 27; IBM Corp). Each CRF will be given a unique identifier. Screening for missing, redundant data or wrong coding will be done. The investigator will try to contact the participants to complete the missing data via telephone. Then, any remaining missing data will be dealt with an appropriate missing data handling method. For redundant data, only 1 data will be selected. The wrongly coded data will be corrected accordingly based on the CRF. Then, the data will be ready for analysis.

For the descriptive statistics, the normality tests will be used to determine the distribution of the data. The normally distributed will be described by using mean and SD, whereas not normally distributed data will be described by using the median and IQR. The categorical data will be presented by using frequency and percentage.

To determine the homogeneity between the intervention and control group, an independent *t* test and chi-square test will be used to compare the demographic characteristics of the participants. The ITT analysis will be applied to measure the effectiveness of the Chance2Act intervention on the primary and secondary outcomes. The analysis models are within-group differences and between-group differences. The Generalized Estimating Equations (GEE) will be used as statistical analysis. A *P* value of less than .05 is considered statistically significant with 95% CI. Interim analysis will be conducted at T1 which is estimated at week 5. However, only certain outcome measures will be analyzed as predetermined in the phase 2 study flowchart.

Ethical Considerations

This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-01073-4YT IIR) and Universiti Teknologi MARA Research Ethics Committee (REC/07/2022PG/MR/157). The ethics committees will be informed in case of any changes to the study protocol. Before participants' enrollment, PIS will be given and explained to all the participants. Written informed consent will be obtained once patients understand the study well. The research assistants will be trained to conduct these procedures. The risk of privacy breaches is minimal. The website will only contain health education material. None of the personal information and medical information will be uploaded on the website. The data for the outcome measures will be stored by the investigator in a password-protected computer and cloud account provided by the Ministry of Health Malaysia (MyGovucUC 2.0 account). The data will be destroyed after 3 years postcompletion of the study. The permission to use the questionnaires has been obtained from the authors with proper citation.

Results

The objective of the phase 1 study is to develop and validate a new web-based intervention (Chance2Act) to facilitate behavioral change for weight loss among adults with T2D with obesity. To confirm the accomplishment of the study objectives, the data gathered from the expert panel's rating and the panel of raters will be analyzed using the CVI and the FVI. The phase 1 study was initiated in October 2022 and is expected to be completed within an 8-month period. Until May 2023, the analysis of the CVI data for the intervention has been finalized and is currently undergoing evaluation by the panel raters for FVI, marking the conclusion of phase 1.

After the validity of the intervention has been confirmed, the effectiveness of the intervention will be determined through a nonrandomized controlled trial. The data collection is expected to have started on June 2023 and to be completed within 4 to 6 months. The analysis will allow us to compare results between the intervention and the control arms, as well as changes within the arm itself in terms of the improvement of the stages of change for weight loss as per the TTM. We also hypothesize that the intervention can result in improvement in self-efficacy, decisional balance, and family support which ultimately may contribute to weight loss. Data analysis for phase 2 will commence in 2024, with anticipated publication of results as early as March 2024. This study was funded in July 2022.

Discussion

Principal Findings

This trial will determine the validity and effectiveness of Chance2Act, a newly developed web-based intervention in changing the behavior of adults with T2D with obesity to initiate weight loss efforts. The validity of the intervention is determined in phase 1 using the CVI and FVI. These tools are widely recognized as quantitative methods to evaluate the content validity of health intervention research [31,32]. In the context of developing interventions, CVI is essential to evaluate whether the elements of the intervention are relevant in relation to the initial objectives or the intended outcomes [33]. Likewise, face validity is crucial to ensure the target users' understanding of each item in the intervention. An intervention that appears relevant, clear, and comprehensible to the participants is more likely to be effective [34]. Integrating both CVI and FVI in the development phase ensures that the intervention is not only theoretically sound but also remains understandable and clear to the target audience.

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Then, the results of phase 2 will determine the effectiveness of the intervention in changing the behavior of adults with T2D with obesity toward weight loss. The analysis will focus on the differences of all outcome measures to demonstrate the effects of the intervention both within and across the different groups. If the hypothesis is confirmed, the findings of this study will provide valuable insights into effective strategies for web-based intervention aimed at behavior modification in the context of weight management for adults with T2D.

Strengths and Limitations

To our best knowledge, the Chance2Act intervention is the first web-based intervention that promotes behavior change, specifically designed for adults with T2D with obesity but not yet prepared to start losing weight. Developing an intervention for this population group is crucial, as a significant number (59%-79%) of them are not yet actively making weight loss efforts [7,8]. We hope that this intervention can contribute to better outcomes of obesity care in patients with T2D, thus, potentially leading to the metabolic benefits associated with weight loss.

In terms of the study design, the selection of a nonrandomized controlled trial method is acceptable due to the nature of the intervention given. Since the health interventions are delivered through a website, blinding of the study participants and researcher is not possible. The participants need to be aware of group assignments, thereby they will access the website and be involved in the intervention.

Another potential limitation that may arise during the study is that participants who do manifest interest are limited to patients with T2D with good digital literacy skills only. As a result, the findings of the study may not be applicable to a broader population, especially those with limited digital literacy. Digital literacy of the study participants may influence the conclusions concerning the uptake and attrition rate of the intervention.

Conclusions

To conclude, the potential findings from this study may bring significant implications of the effective strategies for a web-based intervention aimed at adults with T2D with obesity, who are not actively taking action for weight loss. If successful, the newly developed and validated intervention may be replicated or adapted in different settings, addressing the behavior change resistance for weight loss in adults with T2D with obesity. We hope that the Chance2Act intervention will benefit the target group in achieving better diabetes and metabolic control through effective weight loss. These findings may give valuable insights to inform future public health strategies toward a broader approach to obesity management in T2D, emphasizing the importance of behavioral modification in achieving maintainable weight reduction.

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Data Availability

The data sets generated or analyzed during this study are not publicly available in order to comply with the ethical board requirements and participants' confidentiality protection but are available from the corresponding author upon reasonable request, who will then seek necessary permissions from the Director General of Health Malaysia.

Authors' Contributions

NMS conceptualized and designed the study. MM acquired the funding for the study. MM and ANMR review the study critically and revised it for the important intellectual concept.

Conflicts of Interest

None declared.

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Abbreviations

CR: composite reliability
CRF: case report form
CVI: Content Validity Index
DBI: Decisional Balance Inventory
FVI: Face Validity Index
GEE: Generalized Estimating Equations
I-CVI: Item-level Content Validity Index
I-FVI: Item-level Face Validity Index
ICC: intraclass correlation
PIS: Patient Information Sheet
S-CVI: Scale-level Content Validity Index
S-FVI: Scale-level Face Validity Index
SEE: Self-efficacy for Exercise
SOC: Stages of Change
TTM: Transtheoretical Model
T2D: type 2 diabetes
UiTM: Universiti Teknologi MARA
WEL-Q: Weight-efficacy Lifestyle Questionnaire
WHO: World Health Organization

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Protocol

Compliance of Type 2 Diabetes Applications to International Guidelines: Protocol for a Quantitative App Assessment

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Abstract

Background: Diabetes is among the most common chronic conditions people live with across the world. While it can be managed to a substantial degree, it can result in significant complications. As such, easy access to accurate tools to aid diabetes management is useful in minimizing these complications. Mobile apps are highly accessible and widely used, but there is a gap in the literature examining their compliance with medical guidelines.

Objective: The aims of this study are to develop the Analysis of Diabetes Apps (ADA) checklist to evaluate apps' compliance to guidelines set by the International Diabetes Federation (IDF) on the treatment and management of type 2 diabetes; to assess type 2 diabetes apps in the Apple App Store and the Android Google Play Store, and their compliance with international guidelines using the ADA framework; and to compare the novel ADA checklist against both the Mobile App Rating Scale (MARS) tool kit and app ratings for each store.

Methods: We will develop a checklist based on the "IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care." Type 2 diabetes apps will be scraped from 6 countries' app stores using web scraping tools. These countries include Australia, Brazil, India, Nigeria, the United States, and the United Kingdom, which were selected based on the largest population of English-speaking people in each continent. The apps will be searched on the web-based scraper using the search terms "blood sugar," "diabetes," "glucose level," "insulin," "sugar level," and "type 2 diabetes." Apps will be excluded if they are paid or are not in English. The apps will be assessed using the ADA checklist to evaluate their compliance to the international diabetes guidelines. Once scored, the results will be analyzed with descriptive statistics. The most popular apps will be further analyzed using the MARS tool kit. The ADA checklist scores will then be compared to both the MARS tool kit score and app ratings for each store.

Results: The ADA checklist developed based on the IDF guidelines focuses on general information, risk factors, diagnosis, pharmacology, lifestyle modification, glycemic recommendations, and medications. The initial stress testing of the protocol resulted in 173 included apps. This will vary in the final search as the app stores are constantly changing.

Conclusions: The protocol presents the development of a checklist to investigate the compliance of type 2 diabetes apps with international guidelines. The checklist will hopefully form the basis of a scoring system for future research on compliance of mobile apps with international guidelines. High standardization of the ADA checklist will make it a robust tool for people with diabetes and their health care providers alike in assessing type 2 diabetes apps in the future.

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KEYWORDS

diabetes; mobile apps; Mobile Apps Rating Scale; mHealth; mobile health; diabetes application; application; chronic condition; monitoring; accuracy; safety; tool; assistance; treatment; management; type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition that is prevalent worldwide with its prevalence rising in low-, middle-, and high-income countries [1-5]. In the United Kingdom alone, around 4.7 million people were diagnosed with T2DM in 2019 representing about 7% of the population [6,7]. The Centers for Disease Control and Prevention (CDC) reported that 34.2 million people had T2DM in the United States in 2020 [2].

For individuals who are living with T2DM, there are significant risks of complications including cardiovascular and peripheral vascular damage. In the United Kingdom, T2DM causes 20% of strokes [8]. Individuals living with T2DM are 2.5 times more likely to have a myocardial infarction with 25% of patients arriving in a hospital for a stroke, myocardial infarction, or heart failure also having preexisting diabetes [6]. However, the complications also go beyond circulation, and there can be damage to the peripheral nerves as well. Foot ulcers are a common complication of T2DM. These can lead to foot amputations at much higher rates than those without T2DM. This significant change to a person's life can also increase their risk of death, with 40% of people who have had a major amputation dying within 5 years post surgery [6]. Other damages can be caused by the production of advanced glycosylated end products. Retinopathy is a common complication causing blindness. Nephropathy is also a common complication that can lead to kidney failure and death [6].

Diabetes treatment is multifaceted. There are multiple drug therapies as well as tertiary preventive measures that are required to minimize the complications of the disease [9]. Some of these measures including blood sugar monitoring and healthy nutrition are supported through mobile health (mHealth) apps [10]. The use of mHealth apps has shown benefits in the past for T2DM. In 1 paper, there was better control of glycemic indicators [11]. One study showed a reduction in hemoglobin A_{1c} in those who used diabetes apps regularly compared to a control population [12]. Previous research has shown better control of glycemic indicators for individuals who use mHealth applications for the management of their disease compared to those who use other methods [8,10,12-14]. However, more research is required to determine the quality of available apps including the accuracy of the information content.

In the past, mHealth apps for T2DM have been evaluated for their functionality, but not for the quality of the information provided in the apps. mHealth apps are often analyzed through the prism of app review criteria such as the Mobile App Rating Scale (MARS) [15]. In the MARS tool kit, apps are rated based on engagement, functionality, aesthetic information, and subjective opinion. Each of these categories is broken down further into questions whose answers range from inadequate to excellent. While this is good for the analysis of apps across many genres, it does not focus on the quality of specific recommendations on the management of T2DM from the guidelines.

Every country has its own specific guidelines for the management of T2DM. Each varies slightly in recommendations such as the diet preference or the pharmacology. The largest area of variation in guidelines between countries comes in the form of diet and exercise [9]. Each of the countries' guidelines suggests healthy eating, weight loss, as well as moderate exercise. Some countries go into more detailed suggestions for diets for instance in the United States, it is suggested that a weight loss diet of vegetarianism or low carbs is best, whereas in other countries, a Mediterranean diet is recommended. Recommended diets include DASH, Mediterranean, Nordic, or vegetarianism. The DASH diet is comprised of a meal plan with well-balanced meals with lower levels of fat, sugar and sodium in the diet [16]. Similarly, each country recommends at least 150 minutes of moderate exercise a week with variations in the type of recommended exercise. For instance, yoga is recommended in India's guidelines [17]. The differences in the national guidelines can lead to confusion for both users as well as app designers when apps are released in multiple countries [9].

In this review, we will analyze T2DM apps in a selection of countries with the highest population of English speakers in each continent, including Australia, Brazil, the United Kingdom, India, Nigeria, and the United States. As a result, this paper will evaluate the selected apps based on the recommendations of the International Diabetes Federation (IDF), which is a combination of hundreds of the world's national diabetes associations. As a result, the IDF's guidelines form a clear source of recommendations for the management of patients with T2DM across the world. Therefore, we aim to assess the content of selected apps for T2DM based on the IDF's diabetes guidelines [9].

In addition, the result of the content assessment will be compared to the users' rating and the result of another assessment of the same apps using MARS, which is a validated scale. The aim of this comparison is to examine concordance or otherwise between apps' compliance with guidelines, users' ratings, and assessment scores based on validated scales.

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Methods

Development of the Analysis of Diabetes Apps Checklist

The checklist (Multimedia Appendix 1) covers key areas of T2DM care. The checklist was developed based on the sections of the "IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care" [9]. The Analysis of Diabetes Apps (ADA) checklist focuses on general information, risk factors, diagnosis, pharmacologic treatment, lifestyle modification, glycemic recommendations, and medications. The first section focuses on health education. It asks if the app informs the users of the risk factors as listed in the IDF guidelines. The apps gain points depending on what is mentioned. The checklist is useful in that it provides a qualitative manner of ranking apps based on their information content. Information on diabetes diagnosis will also be assessed based on various diagnostic tests and laboratory values used by different systems. Glycemic targets will also be evaluated for accuracy as well as the different units used. Pharmacologic treatment is key for the management of T2DM and will also be evaluated. The final and largest section is the reduction of risk. This includes diet recommendations, exercise strategies, and other lifestyle modifications.

Sources and Search Terms

Both the Google Play Store as well as the Apple App Store will be searched, using a web scraping tool. Google Play Store and Apple Apps Store are the largest app stores on the market for the public. Both stores will be searched across 6 countries including Australia, Brazil, the United Kingdom, India, Nigeria, and the United States, which are countries that have the highest population of English speakers in their respective continents [18-22]. Although English is not the official language of Brazil, it has the highest population of English speakers in South America due to its large population. The inclusion of countries from all continents is intended to achieve a broad geographic coverage, which allows for increased generalizability of the study findings. Limiting the search to only 1 country per continent is aimed to reduce duplication as the same or similar apps are likely to be available across different countries, especially in the same continent.

The search terms to be used are blood sugar, diabetes, glucose level, insulin, sugar level, and type 2 diabetes. These terms were selected after a series of preliminary screenings. The search terms that yielded the most relevant apps were chosen. Each search term will be entered into a web scraping tool to collect apps.

Eligibility Criteria

This review will collect a list of apps that are related to T2DM so that they can be evaluated in terms of their compliance with the recommendations of the IDF. The inclusion criteria for the apps are that (1) the content of the apps is in English; (2) the apps are freely downloadable—that is, no payment is required for downloading or using the apps; (3) apps that focus on the aspects of self-management of T2DM such as diet, physical activity, blood sugar monitoring, and foot care; and (4) apps that are compatible with iOS and Android mobile platforms. Evidence from the literature suggests that T2DM is a condition that is prevalent among people with lower socioeconomic status [23]; hence, fees might limit the use of apps among people with T2DM.

Apps will be excluded based on the following criteria: (1) generic lifestyle apps that are not focused on T2DM; (2) apps requesting fees for download or use; (3) apps in languages other than English; and (4) apps with missing or incorrect information will also be removed as it will be difficult to locate and download them from the app stores. The expected data for each app on the scraping platform include the name of the app, the URL, the title, the star rating score, the last update, the publishing date, the genre, and the number of reviews.

App Selection

The top 30 apps from each keyword search result will be collated due to the limits of the scraping platform. Using the 6 identified search terms for each of the 6 countries will result in 36 different searches and a maximum of 1080 apps. The eligibility criteria relating to cost, language, and compatibility of the apps will be automatically applied using the filters on the scraping platform.

Once the app list is collated, the top 10 apps from each store on each search will be selected with a maximum number of 720 apps. The ranking of apps will be based on the search results with apps higher in the search result being higher on the list. The apps will not be ranked by star rating score or the number of downloads but by whichever method Apple and Google Play sort the apps as this is more representative of what a user would see when searching for a diabetes app [24]. After the compilation of the top apps, duplicates will be removed. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the proposed scraping method is presented in Figure 1. A similar app scraping methodology has been used in previous assessment studies [25,26].

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Figure 1. App selection flowchart.

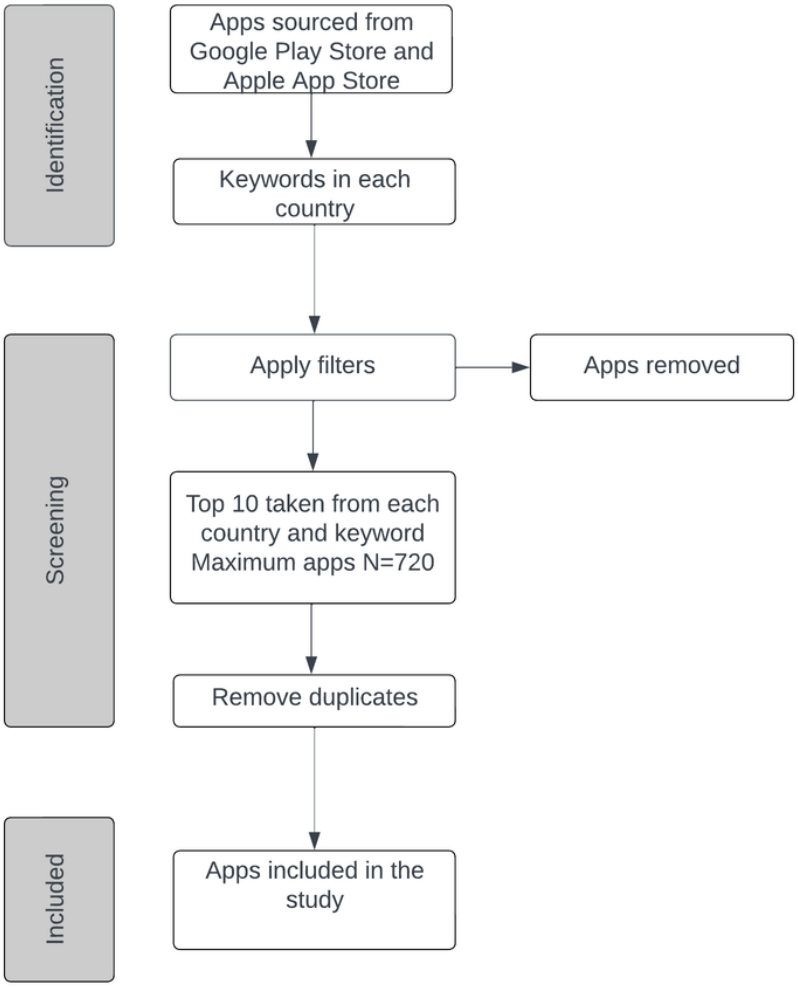

Apps Evaluation

The included apps will be evaluated within 6 months of first scraping using the novel ADA checklist (Multimedia Appendix 1) developed by the authors from IDF clinical practice recommendations for managing T2DM in primary care [9]. A total of 2 evaluators will independently assess each app based on the checklist. Disagreement will be resolved by discussion between the 2 evaluators [26].

The assessment data will be analyzed by descriptive statistics. As the data from the scoring system are ordinal, they will be compared via frequency distributions, median, and range. This will be used for each of the checklist items to determine whether there are associations or patterns that are visible.

Comparison With Other Rating Systems

Additionally, 12 of the apps will be evaluated using the MARS tool kit. The top app for each country under the keyword diabetes will be selected from both the Google Play Store and the Apple App Store. If there is duplication, the next app on the list will be selected. The results of the app assessment based on MARS will be compared to the results of the app assessment based on the ADA checklist to determine whether there are concordance or correlations. Further comparison will be done to ascertain whether there is a correlation with the star rating of the app stores. We would like to assess whether the score from the ADA checklist has a correlation with scores from MARS and the app stores' star rating. To test for correlation, Spearman rank correlation analysis will be used to compare the ADA checklist's total score to both the MARS total mean score and the app stores' star rating for the 12 selected apps.

Ethical Considerations

No ethics approval is required for this paper as it will not involve animal or human participants and all data to be collected are publicly available.

Results

The ADA checklist (Multimedia Appendix 1) developed based on the IDF guidelines focuses on general information, risk factors, diagnosis, pharmacologic treatment, lifestyle modification, glycemic recommendations, and medications. The initial stress testing of the protocol resulted in 173 included apps. This will vary in the final search as the app stores are constantly changing.

Discussion

Overview

This is the first time, to the best of our knowledge, that an mHealth app assessment checklist is being developed based on

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medical guidelines and tested on apps in the mobile app stores. The potential uses of this ADA checklist address a number of issues related to the quality of mHealth apps for T2DM. Primarily, it would provide patients with T2DM and their health care providers with a reliable tool by which they can assess whether diabetes apps provide information based on medical guidelines. The lifestyle changes required as part of diabetes care are extensive and the health consequences of failing to make these changes in a timely and appropriate manner can be severe. Due to the lack of filters in mobile app stores related to compliance with guidelines, it is of the utmost importance that if patients are reliant on apps such as those to be evaluated by this protocol, they are able to avoid those that would mislead them. This new checklist may be useful for further assessment of diabetes apps based on their compliance with medical guidelines. The ADA checklist will allow for more trust and transparency regarding diabetes apps that are currently used, as well as future applications.

Furthermore, it would be of interest to assess if users' star ratings in the app store correlate with app quality based on the novel ADA checklist, as most prospective users might have been relying on user ratings while choosing their apps. Users' star ratings, as a metric, are open to a number of biases that could potentially reduce its correlation to app quality [27,28]. For example, user reviews may be made on the basis of user interface, aesthetics, or the invasiveness and frequency of any advertisements the app displays [27,28]. Previous studies have compared users' star ratings with MARS, an analysis of whether app ratings correlate to compliance with IDF guidelines in this study will further assess the use of users' ratings. On the other hand, comparison with MARS could help to assess whether apps that do well on assessment with a generic mHealth app assessment tool also follow medical guidelines. Irrespective of the results of this comparison between the generic app assessment tool (MARS) and the guidelines-based ADA checklist, both are likely to become complimentary as they focus on different aspects of mHealth apps.

This novel methodology for assessing apps based on medical guidelines can be translated to apps for other conditions such as hypertension, hypercholesterolemia, and atrial fibrillation. While the aspects of the checklist will change between different conditions, the checklist could be used as a baseline framework in future studies, especially with other chronic conditions.

Limitations

The proposed methodology has a number of limitations. First, the app selection process is dependent on the order in which the apps are listed on the search results on both the Google Play Store and the Apple App Store. These algorithms are subject to change at any time without warning, and these changes would likewise be unbeknownst to users. For the purposes of this protocol, this unknown ordering process will influence which apps will be included or excluded in our evaluation, as only the first 30 apps from each set of search results will be included for evaluation, excluding duplicates. This may affect the reproducibility of the results, given the potential for the order of the app listings to change on search results without notification or warning. However, this approach was deemed to be the most objective and unbiased way to select the apps that would be evaluated as these are the apps that are seen first by the users. While analyzing apps based on the number of downloads may be useful, it skews the results of the search to older apps that may not be up to date on guidelines.

Another limitation of this protocol is that only free apps will be evaluated. This is a reasonable exclusion criterion for the purposes of this evaluation, as it would ultimately provide useful information for patients with diabetes in search of a medically accurate and useful app but who are not willing or able to pay for one. However, this also means that the results of this evaluation will not be generalizable across all diabetes apps; it may well be that many purchasable apps, or components of free apps that require in-app purchases, are better than those that would be included in this evaluation based on the criteria described above.

In addition, comparison with the apps' ratings may be problematic. The average score on a 5-star rating system may be skewed by the variability in the number of reviews given. Because we intend to evaluate many apps, there is bound to be a wide range in a number of reviews. As such, apps with few reviews are likely to have less reliable average ratings compared to those with high numbers of reviews. Additionally, this would not at all account for app developers who use methods to inflate their respective app store reviews. Controlling the number of reviews may be a helpful step in reducing the bias this could introduce, though no obvious or reliable method to reduce this bias exists.

Conclusions

There are hundreds of thousands of health-related apps in the app stores. Such apps have been assessed previously from different perspectives, including information quality, reliability, interface, and efficacy. However, there have been no tools to assess apps from a clinical guideline perspective. This methodology developed in this research will demonstrate how to assess the adherence of mHealth apps to clinical guidelines.

Acknowledgments

In this paper, there has been no use of machine learning, artificial intelligence, language models, and similar technology in any of the formation, writing, or analysis of this paper.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
ADA checklist to be used in protocol.
[PDF File (Adobe PDF File), 50 KB - resprot_v13i1e48781_app1.pdf]

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Abbreviations

ADA: Analysis of Diabetes Apps
CDC: Centers for Disease Control and Prevention
IDF: International Diabetes Federation
MARS: Mobile App Rating Scale
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
T2DM: type 2 diabetes mellitus

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Protocol

Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study

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Abstract

Background: For years, in Catalonia and in the rest of Spain, there has been a deficit and an unequal geographical distribution of health professionals specializing in pediatrics, especially in rural areas. Among the proposals to improve this situation is the promotion of the use of information and communication technologies (ICT) among users and professionals. Moreover, with the outbreak of COVID-19, the use of telehealth has become an essential tool, with an overall increase in non–face-to-face visits, including in primary care pediatrics. In this context, telemedicine, when used in primary care pediatrics, can be an effective means of improving families' access to medical care. Currently, in Catalonia, telemedicine involving patients and health professionals is used in pediatric primary care through telephone consultation and asynchronous teleconsultation (eConsulta). Video consultation is in practice not used, although it could have different applications.

Objective: The aim of this study is to evaluate the feasibility of a video consultation process with physical examination in acute pediatric pathology in rural areas among primary care professionals. In addition, the level of satisfaction with these remote consultations will be assessed from the perspective of both the users and the health care professionals.

Methods: We will conduct a prospective experimental study to analyze the possibility of using video consultation in pediatric acute care in primary care in central Catalonia (Spain). A minimum of 170 children aged between 0 and 14 years attending the primary care center (PCC) for acute illness for a period of 1 year will be included in the study. Initially, the telemetric visit, including a physical examination, will include a nurse at the patient and family's side and a pediatrician who will participate remotely. Subsequently, the pediatrician will visit the patient in person and the physical examination and diagnosis made during

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the remote visit will be compared with the physical examination and diagnosis of the face-to-face visit, which is considered the gold standard.

Results: Recruitment was planned to begin in the second half of 2023 and continue for at least 1 year. It is anticipated to be a good resource for a variety of acute pediatric conditions in primary care. The evaluation will focus on the feasibility of performing live remote visits and comparing their diagnostic accuracy with that of face-to-face visits.

Conclusions: We believe that this study could provide evidence on the feasibility and diagnostic accuracy of video consultation in pediatric acute primary care in a rural setting, as well as on satisfaction with video consultations among both users and professionals. If proven useful in addressing the acute needs of children in a variety of situations, it could become a digital health tool that improves the overall pediatric primary care service in rural areas, for both families and professionals.

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KEYWORDS

primary health care; pediatrics; remote consultation; telemedicine; rural health services; video consultation

Introduction

Over the last years, different demographic, social, and professional factors, such as the growth and depopulation of certain areas, changes in the pattern of use of services, and the lack of professionals with formal training, among others, have made it necessary to reshape pediatrics on a European scale [1]. Specifically in Catalonia (Spain), through the Strategic Plan for the Organization of Pediatric Care in Primary Care and the Health Plan of the Generalitat de Catalunya 2021-2025, several measures have been implemented, such as the development of pediatric territorial teams in some regions [2,3]. There are several difficulties in implementing these changes, particularly the lack of specialized professionals and their heterogeneous distribution, especially in rural areas.

In the human resources map for pediatric care in Catalonia, drawn up in 2018, there were 371 primary care teams with professionals specializing in pediatrics out of more than 400 primary care teams. It is believed that the situation has recently worsened. Of the total number of professionals, 28% worked in a coordinated and integrated manner according to the strategic plan. A survey conducted by the Catalan Society of Pediatrics in 2019 found that around 30% of pediatric positions in primary care were occupied by nonpediatric professionals, who do not need to be certified to provide pediatric care. In addition, the study found that 974 nurses were working in pediatric care without specific training. There are also clear differences in the coverage and availability of professionals between areas [4].

To improve this situation, the Catalan Society of Pediatrics proposes, in addition to increasing human resources and their distribution, the strengthening and optimization of information and communication technologies (ICTs) to facilitate the connection between users and professionals [4].

Likewise, with the emergence of COVID-19, digital health has become a tool commonly used in health care. The pandemic has revolutionized the care model of health systems worldwide and has redirected the system toward telemedicine, with a remarkable increase in remote visits, including in the pediatrics setting [5,6]. It has increased the use of tools such as telephone consultations and eConsulta, a type of asynchronous remote consultation integrated into the Catalan public health system [7-9]. Others, such as video consultation, have been more limited [10]. All of this has led to the question of whether digital tools can improve pediatric care, giving rise to the concept of telepediatrics.

Telepediatrics can be considered a subspecialty of telemedicine and can be defined as the use of ICT to provide health services to children at a distance [11]. In Catalonia, telepediatrics, in the form of telephone consultations and eConsulta, has become an integral part of health care, and in a trend similar to those in other countries, the COVID-19 pandemic has significantly altered the profile of pediatric primary care visit types. As a result, there is now a higher proportion of non–face-to-face visits than ever before [12]. A study indicates that, as of March 2020, in Catalonia, there was a drop of more than 80% in face-to-face pediatric visits compared to the previous year, along with 15 times more remote consultations. Subsequently, while the rate of face-to-face visits began to recover, it has not returned to pre–COVID-19 levels. More than 2 years after the pandemic, non–face-to-face visits continued to account for over 20% of the total [13].

Another type of virtual consultation in the Catalan health care system is the interconsultation, an asynchronous patient-free consultation between different health professionals, usually between primary care and specialized hospital care. It has been incorporated into daily clinical practice and validated by the Ethics Commission of the Barcelona College of Physicians [14]. The main types of this form of consultation are dermatological teleconsultation, teleaudiometry, the teleulcer program, and the tele-eyelid program [15]. Specifically, teledermatology has been established as a standard procedure to connect with the referral service in doubtful cases and before referring a patient face-to-face to specialized dermatologic care [16]. These types of services, moreover, have a positive environmental impact and show significant time savings for users [17].

In addition, at the Catalan Institute of Health (the main service provider of the Catalan health system), a pilot test is being carried out of the “digital briefcase,” which comprises a set of devices and accessories associated with a smartphone or tablet that allow for the provision of a basic level of health care; it aims to improve the capacity to resolve problems of primary care [18]. Some of the devices it incorporates are a blood

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pressure monitor with electrocardiographic rhythm, a portable complete electrocardiogram, a digital stethoscope, and a portable ultrasound scanner. It may incorporate other instruments that may be useful depending on the medical specialty.

Despite their potential to enhance communication by enabling visual contact, pediatric video consultations are not commonly used in the public health system [19]. This type of visit briefly emerged during the COVID-19 pandemic, but its current use is anecdotal [13]. It is well established that when video consultations are used by health care professionals, with one physically present alongside the patient, it improves the quality of the care process [20,21].

Video consultation has been applied in follow-up visits in pediatric hospital consultations for chronic illnesses such as diabetes, obesity, and mental health problems, as well as digestive, rheumatic, neurological, and even respiratory illnesses [22,23]. Also, in the hospital setting it has been used as a control after discharge and even to avoid days of hospitalization, with good results in terms of cost reduction and family satisfaction [24,25]. However, there are few studies on video consultation in pediatric primary care [26].

An additional possibility offered by video consultations, besides making a structured anamnesis, could be remotely carrying out physical examinations. This is especially important in cases of pediatric acute pathology, as children at these ages often have difficulties expressing their symptoms. Moreover, in pediatric cases, functional interdependence, that is, the functioning together of a child's organs, can commonly cause an underlying pathology to lead to unclear or ambiguous symptoms. [27]. In response, simple medical devices have been made available for the general population. They are sold in packs and include a digital camera, otoscope, and stethoscope. Good examples of these are the devices sold by the brands TytoCare, approved by the US Food and Drug Administration (FDA), and HIGO, developed by the University of Warsaw [28,29]. These devices are used by caregivers when the child is ill. Clinical data are recorded and sent to the practitioner via a remote application and the practitioner responds with the appropriate diagnosis and treatment. This reduces physical presence in emergency services. Currently, these devices are used in some countries, mainly by private mutual insurance companies [30]. There are also similar devices, such as those of the Firefly brand, aimed at health care professionals [31]. However, in Spain there is little evidence of the use of similar devices in clinical practice. One of the few examples is Kidscare, which offers a telemedicine service aimed at schools [32].

There are several practical reasons to use teleconsultation with physical examination for acute pediatric consultations in a rural context. One is that in rural areas with distant clinics where a pediatrician is not available every day, the pediatric nurse could manage visits with remote support from a pediatrician in another center. Currently, telephone support is already provided in these cases. If this were done through video consultation, the support would be more comprehensive. The second reason is that during vacations or when the pediatrician in charge is on leave, it could be possible in certain cases to see the patient remotely. Finally, a clear benefit would be observed out of hours when a patient needs to be evaluated by a pediatrician.

In this context, the general objective of this protocol is to evaluate a video consultation process with physical examination for acute pediatric pathology in rural areas among primary care professionals. Specifically, the aim is to assess 3 elements: the feasibility of the process, its diagnostic accuracy compared to face-to-face consultation at the same time (considered to be the gold standard), and user and professional satisfaction.

To achieve these specific objectives, the study will analyze the technical and human possibilities of pediatric video consultation, the most appropriate reasons for consultation, the diagnostic accuracy compared to concurrent face-to-face consultation, the difference in duration between the 2 types of visits, the acceptance and satisfaction of patients and professionals using validated questionnaires, and incidents that may occur during virtual visits.

Methods

Study Design

Trial Design

This will be a prospective experimental study of an acute pediatric care process using video consultation with a physical examination among health professionals.

Patients, Scope, and Period of Study

The study will involve children aged 0 to 14 years attending PCC Cardona for acute health problems. The acute pediatric conditions selected for video consultation in this research will be identical to those encountered in regular consultations, including any condition that requires a medical visit. Commonly observed symptoms include fever, cough, runny nose, sore throat, earache, abdominal pain, vomiting, diarrhea, skin lesions, and similar conditions.

The Cardona PCC is part of the health region of central Catalonia. Located in a rural area, Cardona covers a total area of 143 km^2 and serves an assigned population of nearly 5000 people. It comprises 5 family medicine and nursing teams, along with 1 pediatrics and pediatric nursing team, among other services.

Data collection will span at least 1 year to ensure the representation of all seasonal pathologies and was scheduled to commence in the second half of 2023. It is expected that by the end of 2024 all cases will have been collected and the data and conclusions can be analyzed. The results of the study will be published at the end of the project and will be presented in the form of a doctoral thesis.

Inclusion Criteria

The inclusion criteria will be patients aged 0 to 14 years who attend the Cardona PCC for acute conditions and who are authorized to participate by their legal representatives.

Exclusion Criteria

Exclusion criteria will be cases in which the legal representative does not allow participation, check-ups from the Healthy

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Childhood Programme, chronic illnesses and follow-up visits, consultations requiring immediate face-to-face medical assessment, and cases where there is a language barrier.

Sample Size Determination

The sample will be for convenience. Considering the main objective of the study (to analyze the diagnostic accuracy of telemedicine compared to concurrent face-to-face consultation), in order to estimate the required sample size, and given the absence of similar studies to predict this accuracy, it will be necessary to include 170 children. This sample size calculation is based on achieving a 95% confidence level, an 8% margin of error, and accounting for a replacement rate of 10%.

Data Collection, Sources of Information, and Intervention

Children aged 0 to 14 years presenting to PCC Cardona with acute conditions will be selected using nonprobability convenience sampling. The procedure will be integrated into the daily pediatric clinical practice to facilitate recruitment. The decision to invite the patient and their family to participate in the study will be based solely on the daily workload of the health care professional (to allow time for both virtual and face-to-face visits).

The patient and their legal representative will be informed verbally and in writing of the purpose of the study and will be given the opportunity to choose whether or not to participate. If they agree, they will be asked to sign the informed consent form.

First, the patient will go to an office with the pediatric nurse and will connect via video call (Microsoft 365 Teams) with their regular pediatrician, who will conduct the anamnesis. Then, the nurse, under the guidance of the pediatrician, will perform the physical examination with approved digital devices, which will include a Firefly digital camera, a video otoscope, and a Littmann CORE digital stethoscope [31,33]. The Firefly camera and video otoscope are FDA-approved and hold certifications for FC, CE, RoSH, and ISO for medical devices. The stethoscope is FDA-approved and complies with Health Insurance Portability and Accountability Act standards [31,33].

To conduct the physical examination, a translated and adapted version of the diagnostic questionnaire for pediatric telemedicine created by Bittmann [34] during the COVID-19 pandemic will be used. The physical examination will be systematic. First, anamnesis will be conducted and the reason for the visit will be recorded. Subsequently, there will be a clinical examination. The final step will be the initiation of treatment.

The case identification data, date and time, age, gender, accompanying person, reason for the visit, and medical history, as well as the results of a physical examination (general appearance, skin, throat, otoscopy, cardiorespiratory auscultation, and other data, if necessary), diagnostic orientation, and duration of the visit will be recorded on the data collection sheet.

To ensure the effectiveness of digital health consultations, both professionals conducting the visit have received training in performing physical examinations using the devices intended for video consultations. Additionally, an incident registration section has been included to identify issues of any type (technical or human).

Afterward, the same pediatrician will again examine the child in person and record the physical examination with the apparatus. The diagnostic orientation and duration of the visit, as well as the concordance between the telemedicine examination and the diagnosis, will be evaluated in comparison to the face-to-face visit (considered the gold standard). In addition, in each case we will record whether the virtual visit was viable (when the anamnesis and physical examination were completed and a diagnosis was reached) and whether there were any incidents.

Validated questionnaires on satisfaction will be given to both the family and health care professionals (nurse or pediatrician) [35,36].

Statistical Analysis

The aforementioned variables will be collected through Microsoft 365 Forms. For data analysis, R (version 4.0.3; R Foundation for Statistical Computing) will be used.

The accuracy of the video consultation diagnosis will be estimated by comparing it to the face-to-face diagnosis. The Pearson chi-square test will be used to analyze the relationship between pairs of categorical variables and the Student *t* test (2-tailed) or Mann-Whitney *U* test will be used to analyze the relationships between pairs of continuous variables. Categorical variables will be described as absolute frequencies and percentages, and continuous variables as mean and SD or median and IQR, depending on the distribution of each variable.

Ethical Considerations

The study protocol, which involves human subjects, was reviewed and approved by the University Institute for Research in Primary Health Care Jordi Gol i Gurina (Barcelona, Spain) ethics committee (22/236-P). Written informed consent will be requested from all parents or legal guardians participating in the study. The original data collection will be conducted with informed consent that includes provision for secondary analysis of the data. The ethics committee has confirmed that the secondary analysis is covered under the initial consent procedure and does not require additional consent forms. Participants in this study will not be compensated.

To protect participant privacy and confidentiality, all study data will be anonymized and deidentified prior to analysis. The video consultation, conducted through the Teams platform, will not be recorded, and no images, sound, or personal data of any patient will be captured. In cases where a photograph is required, for example for teledermatology services, just as in a face-to-face visit, explicit consent will be requested from the patient and their family. Regarding the sounds of cardiorespiratory auscultations that might be recorded for transmission between the nurse and the pediatrician, the audio will not contain any user-identifiable data and will be deleted from the corresponding application at the end of the visit.

In this regard, the fundamental principles of the physician-patient relationship in telemedicine are the same as

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in a face-to-face visit. While telemedicine has a distinct impact on the physician-patient relationship framework, adherence to good clinical practice, and ethical and deontological standards, the legal and professional regulations applicable to any medical act must be followed [20]. In the practice of telemedicine during this study, special attention will be given to aspects of identification, trust, prudence, confidentiality, clinical information and communication, informed consent, and clinical judgment, as well as record-keeping of medical history and during treatment, follow-up, and evaluation.

Results

Recruitment was scheduled to begin during the second half of 2023 and is expected to last 1 year and to include 170 patients. Preliminary results will be published by the end of 2024.

The visit via videoconference, with a physical examination of the patient performed by the pediatric nurse and the pediatrician attending remotely, is expected to be feasible and effective for most children with acute illnesses visiting primary care.

We believe that in other cases, such as when children are uncooperative or when the consultation is for specific reasons such as abdominal pain, video consultation may have limitations. In such cases, the reasons for this outcome will be recorded, and a face-to-face visit will always be conducted.

Discussion

Anticipated Findings

This study aims to provide evidence on the feasibility of, diagnostic accuracy of, and satisfaction with video consultation in the primary care pediatric acute care setting in a rural area. One of the traditional recommendations in telemedicine is not to use video consultations when the patient requires a physical examination, as is the case with acute pediatric pathology [21]. In this context, the purpose of this study is to test whether video consultation with a telemetric physical examination can be a viable and effective resource for acute pediatric conditions when there is on-site support from a health care professional. If video consultations are acceptable, they could partially alleviate the effects of the current shortage of pediatricians, particularly in rural areas.

Recommendations in telemedicine emphasize that non–face-to-face consultations should never be used as a way to enhance profitability during the workday or reduce the number of professionals [21]. In this study, these recommendations will not be breached; instead, there will be a redirection of the current approach used by pediatricians in conducting visits for acute conditions. This will ensure that children with acute conditions can be seen by a pediatrician without having to go to other urgent care centers or hospital emergency departments. Professionals must be aware that telemedicine cannot be a substitute for face-to-face examination of the patient when necessary. Therefore, telemedicine should be limited to cases where it is considered feasible. Setting limits on the use of telemedicine for patient care is a matter for the profession and professionals. Professionals must adhere to ethical and professional obligations with the same level of commitment as in face-to-face visits. Consequently, medical care must consistently maintain rigorous standards of both human and technical quality [20,21].

During the pandemic, the use of video consultation has provided an opportunity to understand its functionality and explore the potential it offers as a digital health tool in everyday medical practice. Regarding the potential benefits for pediatricians, just a few years ago it was difficult to imagine a virtual consultation that would involve examining a child, but the boost given to digital tools during the pandemic provides an opportunity to explore new modalities of care that can contribute to an optimization of resources while maintaining the quality of care and patient safety. In this context, it is important to train and raise awareness among professionals in order to determine when a visit can be carried out through a virtual consultation and when it is necessary to do it face to face [20,21]. Moreover, the study highlights the role of the pediatric nurse, who is physically present with the patient and family while the pediatrician guides the anamnesis and physical examination of the child from a distance. We believe involving pediatric nurses in this process will improve the quality of care and increase clinical safety [4].

It is also important to consider the views of health care professionals regarding telemedicine services. A recent study conducted in central Catalonia to evaluate the acceptance of telemedicine services found a positive reception, especially within the nursing community. Almost all participants agreed to continue using telemedicine in the future [37]. In relation to the benefits for health services, some articles have shown that telemedicine in general, and telepediatric health services for children living in rural areas in particular, can reduce the cost and travel time to access these services [38,39]. The use of teleconsultation can reduce the number of displacements, both for users and professionals, contributing to lower costs and time, increased efficiency, reduced pollution, and determining if there is overall greater satisfaction. On the scale of the public health system of Catalonia, studies have demonstrated that some of the digital tools that have been introduced, such as eConsulta, appear to be cost-effective. Others will need to be continually evaluated [40]. In turn, environmental benefits are gained by reducing the emission of atmospheric pollutants [41].

Video consultations can also be useful for health care providers. Health care organizations must develop practical strategies to consolidate the implementation of telemedicine and define new consultation structures to meet this new form of demand [20,21]. However, it should be noted that telemedicine in Spain does not have a specific legal regulation, as is the case in other countries in our context such as France, Sweden, Germany, or Switzerland. In the Spanish legal system and within the European framework, there are rules that are applicable and must be respected equally in both face-to-face and remote consultations [42,43]. Denmark and Israel, pioneers in the implementation of telemedicine, also have no specific legislation on the matter [44]. However, although the laws and regulations governing in-person medicine currently also apply to telemedicine, the development of specific laws and regulations will be essential.

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Telemedicine has advantages and limitations in the human, technological, and economic spheres, and these must be understood by all parties involved. Remote consultations performed by health care professionals are medical procedures, and as such they are subject to current legislation based on the General Data Protection Regulation and the doctor-patient confidentiality relationship. For this reason, the use of safe and appropriate technological tools is essential [20].

Limitations

This study has several limitations, primarily the risk of not achieving an accurate diagnosis through the virtual visit compared to the face-to-face visit. This could be due to technical or human causes (eg, if technological devices fail or if the child does not cooperate) or due to care-related factors related to, for example, abdominal pain, which requires careful palpation by an experienced professional to assess a possible acute abdomen. Other possible care demands not accessible at a distance may include eye and genital injuries, some wounds, and serious traumatic injuries. The fact that the video call is made between health care professionals, one of whom is always at the patient's side, will improve the quality of care and reduce the risk of incidents. The presence of an assistant is a well-defined aspect of telemedicine [45,46]. What sets assistants apart is that they are health workers, which means that their role goes beyond merely relaying information; they actively participate in the visit. This collaborative approach is crucial for successful video consultations, where teamwork is essential. In this study, the assistant will be a pediatric nurse who will explain and accompany the families during the remote visit with guidance from the pediatrician. This guidance will include conducting anamnesis and physical examination, as well as providing information, diagnosis, and treatment to both the patient and parents.

Second, there may also be a patient selection bias, since depending on the patient's characteristics (age, accompanying person, reason for consultation), some cases may not be selected if it is assumed that they are not suitable for virtual assistance. For this reason, an attempt will be made to carry out the study without the professionals knowing the characteristics of the patient or the reason for the consultation in advance.

Third, the fact that the same pediatrician performs both the telemetric and then the face-to-face visit may induce confirmation bias. Initially, the study was intended to be multicenter, with the participation of different professionals from different centers, but due to ethics and patient safety, as well as the lack of pediatricians, it was changed to a single-center intervention. Recording the physical examination and the diagnosis made during the virtual visit just prior to the face-to-face visit may mitigate this type of error.

Fourth, another possible limitation is nonacceptance by patients, family members, or the professionals themselves. There may be different reasons for this, including ethical, technological, and human reasons, as well as the risk of losing confidentiality. In this regard, detailed legislative regulation by the competent authorities of medical devices is very important. External validation of these devices must be essential to ensure efficacy and safety in real clinical practice and to be able to define the conditions under which they can be applied. Furthermore, providing adequate training to health care professionals and offering explanations to users is essential. As for the bioethical and patient safety aspects of virtual visits, currently, in Spain, they are comparable to those of face-to-face visits.

Last, other limitations may be the longer duration of virtual visits compared to face-to-face visits and the difficulty of conducting video consultations with families when there is a language barrier.

Conclusion

We believe that this study can have significant future applications and implications, such as providing faster care to families, reducing time and travel for both users and professionals, mitigating the low ratio of pediatricians per population in certain rural areas, reorganizing territorial pediatric care, highlighting the role of the pediatric nurse as a trained professional capable of assessing pediatric needs, and optimizing resources for health service providers.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the design and content of the study protocol. MC-R is responsible for the coordination of the study. MC-R, JV-A, FLS, AF-C, and QMC were responsible for the design and writing of the initial draft of the manuscript. MC-R, NS-B, and CF-C are responsible for data collection. JV-A, QMC, and AF-C are responsible for data processing and analysis. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

FDA: US Food and Drug Administration
ICT: information and communication technology
PCC: primary care center

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Protocol

Digital Phenotyping for Real-Time Monitoring of Nonsuicidal Self-Injury: Protocol for a Prospective Observational Study

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Abstract

Background: Nonsuicidal self-injury (NSSI) is a major global health concern. The limitations of traditional clinical and laboratory-based methodologies are recognized, and there is a pressing need to use novel approaches for the early detection and prevention of NSSI. Unfortunately, there is still a lack of basic knowledge of a descriptive nature on NSSI, including when, how, and why self-injury occurs in everyday life. Digital phenotyping offers the potential to predict and prevent NSSI by assessing objective and ecological measurements at multiple points in time.

Objective: This study aims to identify real-time predictors and explain an individual's dynamic course of NSSI.

Methods: This study will use a hybrid approach, combining elements of prospective observational research with non–face-to-face study methods. This study aims to recruit a cohort of 150 adults aged 20 to 29 years who have self-reported engaging in NSSI on 5 or more days within the past year. Participants will be enrolled in a longitudinal study conducted at 3-month intervals, spanning 3 long-term follow-up phases. The ecological momentary assessment (EMA) technique will be used via a smartphone app. Participants will be prompted to complete a self-injury and suicidality questionnaire and a mood appraisal questionnaire 3 times a day for a duration of 14 days. A wrist-worn wearable device will be used to collect heart rate, step count, and sleep patterns from participants. Dynamic structural equation modeling and machine learning approaches will be used.

Results: Participant recruitment and data collection started in October 2023. Data collection and analysis are expected to be completed by December 2024. The results will be published in a peer-reviewed journal and presented at scientific conferences.

Conclusions: The insights gained from this study will not only shed light on the underlying mechanisms of NSSI but also pave the way for the development of tailored and culturally sensitive treatment options that can effectively address this major mental health concern.

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KEYWORDS

nonsuicidal self-injury; NSSI; digital phenotyping; digital phenotype; wearable device; wearable; wearables; wrist worn; mood; emotion; emotions; heart rate; step; sleep; machine learning; multilevel modeling; ecological momentary assessment; EMA; self-injury; self-harm; psychiatry; psychiatric; mental health; predict; prediction; predictions; predictor; predictors; predictive

Introduction

Nonsuicidal self-injury (NSSI), defined as deliberate self-inflicted bodily harm without suicidal intent [1], is a major global mental health concern. A recent epidemiological study found that the estimated lifetime prevalence of NSSI in adults was 4.86%, with younger age being more associated with NSSI [2]. According to a meta-analysis, the pooled prevalence of NSSI in young adults was 13.4% [3], and epidemiological studies indicate that 1 in 5 young adults engage in NSSI at least once before the age of 25 years [4,5].

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Research has shown that NSSI is associated with academic and interpersonal difficulties [6,7], substance dependence [8], rehospitalization [9], and an increased risk for psychiatric disorders [10-14]. Remarkably, NSSI, despite its absence of initial suicidal intent, is a strong predictor of future suicidal thoughts and behaviors, independent of psychiatric disorders [15-18].

A recent scoping review [19] found that most mobile apps designed to intervene in NSSI were effective in reducing the frequency of urges to self-harm. Similarly, a systematic review found preliminary evidence that psychological interventions for self-harm are associated with reductions in self-injurious thoughts and behaviors, with positive treatment effects also found for suicidal ideation [20]. In addition, psychotherapeutic interventions for NSSI have shown efficacy in improving global functioning and reducing NSSI and depressive symptoms [21], with significant improvements in hopelessness and problem-solving [22]. Given the efficacy and effectiveness of interventions for NSSI, it is important to detect people with self-injury behavior early and provide NSSI-specific interventions.

Despite the pressing need for early detection and intervention for NSSI, it is a worrying reality that a majority of people with self-injury behavior do not seek medical care or help, including psychotherapy [2,23-25]. Furthermore, individuals engaging in self-injurious behaviors often face issues of stigma and social undesirability, making it essential to explore non–face-to-face diagnostic and intervention approaches [26-28]. Additionally, retrospective self-reported methods to assess self-injury may be limited by recall bias [29,30], failing to capture the transient nature of self-injurious thoughts, especially in adults, where the frequency and intensity of such thoughts can fluctuate even within a single day [31]. Recognizing that traditional clinical- or laboratory-based methodologies have limitations, there is a pressing need to detect and prevent NSSI at an early stage.

There is an urgent need for rigorous descriptive research, especially observational research to measure change over time and document various aspects of NSSI behavior [32]. Understanding NSSI requires a systematic and meticulous approach to longitudinal and real-time data collection to enable researchers to produce information of a descriptive nature on the occurrence of NSSI. Designating information on NSSI behavior as being of a “descriptive nature” refers to the detail and comprehensiveness of our understanding; for NSSI, this encompasses factors such as its frequency, duration, triggers, and consequences. However, there is still a lack of rigor in understanding when, how, and why self-injury occurs in everyday life [33]. This gap in knowledge largely persists because most NSSI research has relied on cross-sectional designs, which may not capture the dynamic nature of NSSI behavior over time. While there are some longitudinal studies, they often use long observation windows to identify developmental risk factors, providing insights into who is at higher risk of self-injury relative to others over extended periods (ie, at a between-person level) [34]. These methods focus on long-term trends rather than immediate occurrences of NSSI. In other words, these methods may not have the temporal precision to detect imminent risk of self-injury in daily life, occurring within minutes or hours.

Digital phenotyping, as an approach, offers the potential to predict and prevent NSSI in everyday life by assessing an objective and ecological source of measurements at multiple points [35,36]. By leveraging this technology, researchers can collect real-time data on an individual’s self-injury–related markers, such as mood, sleep condition, and physiological responses such as heart rate [37-39]. This comprehensive data set enables a deeper understanding of the complex factors contributing to NSSI behaviors, ultimately facilitating more accurate prediction, early detection, and intervention strategies.

Digital phenotyping techniques, using smartphone and wearable devices, encompass 2 types of data: active and passive. Active data, such as data obtained with ecological momentary assessment (EMA), involve self-reported questionnaires that requires conscious effort from users. Passive data, including heart rate and sleep condition, on the other hand, are collected automatically without any user input. Predicting a high risk of NSSI in daily life can prompt the delivery of early real-time interventions. Despite their potential, few studies have examined individuals’ dynamic NSSI patterns in daily life. This study aims to identify real-time predictors and explain an individual’s dynamic course of NSSI.

This study aims to use cutting-edge digital phenotyping techniques to identify young individuals at risk of NSSI and develop targeted interventions.

Methods

Study Design

This study will use a hybrid approach, combining elements of prospective observational research with non–face-to-face study methods. It will use a digital app to conduct continuous digital phenotype assessments of self-injury and suicide-related conditions, mood, physical activities (eg, walking), and sleep conditions. It will also use a wrist-worn wearable device (Apple Watch) to measure physiological state (eg, heart rate).

Ethical Considerations

The protocol for this study has been approved by the institutional review board of Kangwon National University (KWNUIRB-2023-02-008-001) to ensure compliance with ethical guidelines and research protocols. All participants will be given an informed consent form and will review its contents before making a decision to take part. The consent form will contain information about the purpose of the study, procedures, potential risks of participation, compensation, and privacy guarantees. Each participant will have 3 EMA periods spaced 3 months apart. If the EMA compliance rate is 90% or higher, the reward will be KRW ₩70,000 (equivalent to approximately US $53), if it is 70% or higher, KRW ₩50,000 (approximately US $38), and if it is 50% or higher, KRW ₩30,000 (approximately US $23); the reward will be given in the form of a gift certificate. All collected data will be anonymized and analyzed to ensure individuals cannot be identified. The data will be exclusively used for research purposes and will not serve any other function. Subsequently, data files will be transferred

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to an external hard drive and securely stored within the principal investigator's laboratory, secured under lock and key. Access to the data will be restricted to the principal investigator and authorized research staff, with the lab key held solely by the principal investigator.

Participants

This study aims to recruit a cohort of 150 adults aged 20 to 29 years who have self-reported engaging in NSSI on 5 or more days within the past year. Participants to be recruited will own a smartphone and provide signed informed consent. Exclusion criteria for participants are as follows: presenting suicidal ideation and plans at a level requiring immediate intervention, that is, if the participant reports (1) suicidal thoughts with actual intent to attempt suicide or (2) has attempted suicide or taken preparatory actions in the past month; current manifestation of psychotic or manic symptoms or substance use disorders; and currently receiving any other psychotherapy or counseling.

Procedure

Participants will be enrolled in a longitudinal study conducted at 3-month intervals spanning 3 long-term follow-up studies. The procedures shown in Textbox 1 and Figure 1 will be repeated for each study.

Textbox 1. Procedures for this longitudinal study conducted at 3-month intervals spanning 3 long-term follow-up studies.

Recruitment

Potential participants meeting the criteria will be identified through targeted outreach efforts and community engagement. They will be provided with study information and invited to participate.

Informed consent

Participants who express interest in joining the study will be provided with detailed information regarding the study objectives, procedures, potential risks and benefits, and their rights as participants. An electronic version of consent in which participants click "yes" or "no" will be obtained from each participant prior to their inclusion in the study.

Digital app enrollment

After providing consent, participants will be guided through the process of enrolling in the app, named Dear My Mind, specifically developed for this study. This app will facilitate the collection of digital phenotyping data and serve as the primary mode of communication between the researchers and participants.

Continuous digital phenotyping assessments

1. Participants will complete a preassessment. The preassessment questionnaire will consist of the following items: the Functional Assessment of Self-Mutilation (FASM) [40] for an in-depth assessment of self-injurious behavior, Columbia Suicide Severity Rating Scale (C-SSRS) [41] to assess suicidality, Patient Health Questionnaire 9-item scale (PHQ-9) [42] to measure depression, Generalized Anxiety Disorder 7-item scale (GAD-7) [43] to measure anxiety, Korean version of the Pittsburgh Sleep Quality Index (PSQI-K) [44] to assess sleep conditions, Primary Care PTSD Screen for DSM-5 (PC-PTSD) [45] to assess posttraumatic stress disorder symptoms, WHO-5 Well-Being Index [46] to measure well-being, Brief Resilience Scale (BRS) [47] to measure levels of resilience, Self-Harm Inventory (SHI) [48] to measure deliberate self-harm, and Personality Assessment Inventory–Borderline Features Scale (PAI-BOR) [49] for the assessment of borderline personality disorder tendencies.
2. Active data will be obtained using ecological momentary assessment. Participants will provide active data regarding their mood, sleep, and self-injury behavior patterns 3 times each day. Additionally, they will be asked to record their mood daily at night time.
3. Passive data will be obtained using a wearable device. All participants will wear a wrist-worn wearable device, specifically an Apple Watch, for 14 days to passively collect data. This will include data related to activity levels, heart rate, and other relevant measures.

Postassessment and debriefing

The same questionnaire used for the preassessment will be administered for the postassessment. As compensation, participants with an overall compliance rate of 50% or more will receive KRW ₩30,000 (approximately US $23), participants with an overall compliance rate of 70% or more will receive KRW ₩50,000 (approximately US $38), and participants with an overall compliance rate of 90% or more will receive KRW ₩70,000 (equivalent to approximately US $53). Compensation will be based on 56 measurements collected over the 14 days.

Figure 1. Study procedure. EMA: ecological momentary assessment.

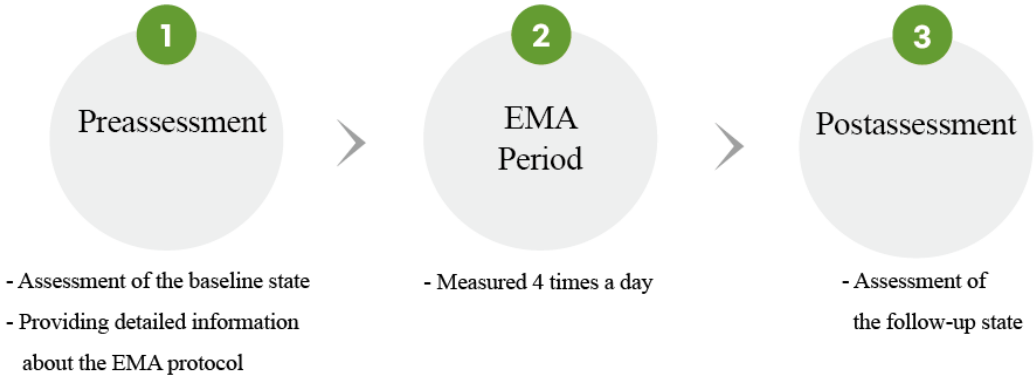

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Measures

Active Assessment

EMA will be conducted via a smartphone app called Dear My Mind (currently under development; Figure 2). The EMA aims to capture real-time data on participants' self-injury and suicidality, as well as mood appraisals. Participants will be prompted to complete the self-injury and suicidality questionnaire and the mood appraisal questionnaire 3 times a day for a duration of 14 days: at noon, in the evening, and at night (Table 1). Each morning, participants will be asked to answer a questionnaire regarding their sleep patterns from the previous night. This questionnaire will provide additional information about participants' sleep conditions to complement the objective sleep measures collected. Furthermore, participants will be asked to complete a mood diary each night (the Mood Diary section below presents detailed information).

Figure 2. Dear My Mind app (under development).

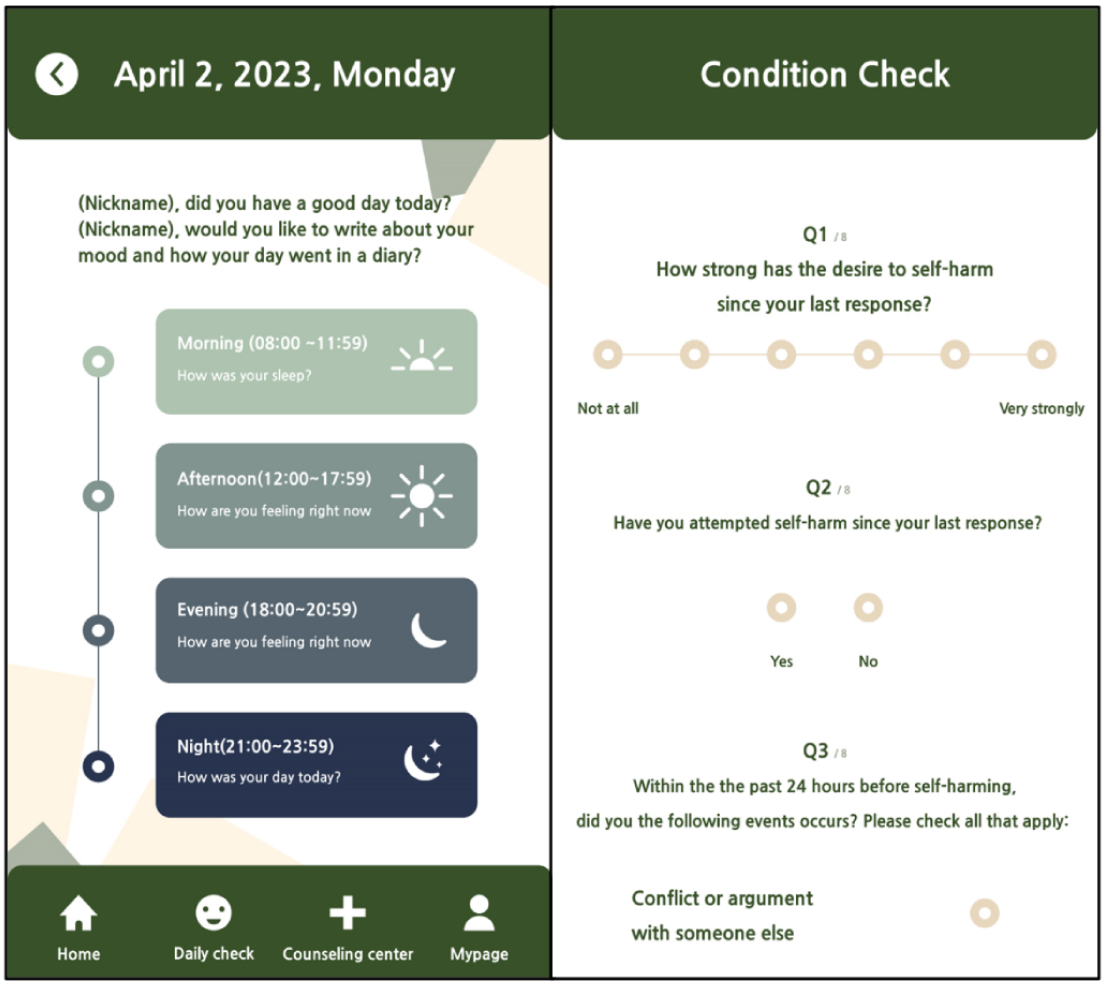

Table 1. Ecological momentary assessment schedule.

	Sleep condition check	Mood condition check	Self-injury and suicidality check	Mood diary
9 AM to 10 AM	✓			
Noon to 1 PM		✓	✓	
6 PM to 7 PM		✓	✓	
9 PM to midnight		✓	✓	✓

Self-Injury and Suicidality Questionnaire

The visual analog scale (VAS) is a rating of the participant's perceived level of "self-injurious & suicidal thoughts and urges." It is constructed on a horizontal line with "not at all" at one end and "very much" at the other (on a 7-point Likert scale). It can quantify a participant's self-injurious and suicidal thoughts and urges and is useful for capturing changes within individuals rather than differences between individuals. In addition, if the participant has attempted self-injury since the last response, a text box prompts the participant to indicate the method of the attempt. There are also additional questions about antecedent events, antecedent emotions that occurred within the 24 hours prior to the self-injury, and experiences immediately following the self-injury. If the participant indicates that they have attempted suicide since their last response, they will be classified

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as high risk and the monitoring researcher will contact them immediately to refer them to a local mental health clinic or counseling center for immediate help.

Mood Appraisal Questionnaire

Participants will be instructed to respond to the VAS 3 times a day about the emotions they are experiencing at that moment. The mood VAS will be constructed on a horizontal line with "not at all" at one end and "very much" at the other (on a 9-point Likert scale). Specifically, participants will be asked about their feelings of depression, sadness, anxiety, fear, loneliness, rejection/hurt, anger at self, anger at others, shame, and emptiness.

Mood Diary

Participants will be asked to engage in daily mood diary entries using a free-text box. Each night, participants will be prompted to write about an event they experienced during the day, how it affected their mood, and the strategies they used to resolve it. Participants receive clear instructions regarding the purpose and content of the mood diary entries. A free-text format provides participants the flexibility to express their thoughts and feelings in their own words, allowing for a more nuanced understanding of their mood dynamics. Additionally, we emphasize the importance of consistent and honest reporting to maximize the validity and reliability of the data collected. The purpose of the mood diary is to capture participants' subjective experiences and emotions, as well as their efforts to manage and overcome daily challenges. Participants will be encouraged to be as detailed and specific as possible when describing the event, their emotional response, and their coping strategies. This information will provide valuable insights into the contextual factors that influence participants' mood fluctuations and their adaptive responses. The daily nature of the mood diary entries allows for the examination of day-to-day variations in mood and the exploration of the relationship between specific events and emotional well-being. It provides a comprehensive picture of participants' subjective experiences and contributes to the overall understanding of their digital phenotypes.

Sleep Condition Questionnaire

To complement the objective sleep data obtained from the wearable device, participants will also be administered the sleep condition questionnaire to gather subjective sleep measures. This questionnaire includes items related to bedtime and wake time, actual sleep duration, and subjective sleep quality. Participants will be asked to respond to the sleep condition questionnaire once a day, specifically each morning, providing information about their sleep experience during the previous night. By capturing participants' subjective perceptions of their sleep, this questionnaire will help elucidate participants' personal experiences and perceptions of their sleep quality and add a valuable subjective component to the objective sleep data collected. Participants will be encouraged to provide accurate and detailed responses to provide a comprehensive understanding of their sleep patterns and experiences. By combining objective sleep data from the wearable device with participants' subjective reports, this study will gain a more comprehensive and holistic understanding of participants' sleep conditions.

Passive Assessment

The wearable device will be used to collect several types of passive data from participants. Previous studies have shown the psychometric validity of the wearable device in reliably collecting physiological data [50,51]. The types of passive data collected in this study are heart rate, heart rate variability, step count, and sleep patterns. More specifically, the wearable device's photoplethysmography sensor will collect data on an individual's heart rate and heart rate variability [51]. In addition, a combination of sensors, such as the accelerometer, gyroscope, altimeter, and GPS, will be used to count steps. Through a combination of the above sensors, we will also measure sleep patterns such as core sleep, deep sleep, and rapid eye movement (REM) sleep.

To ensure the protection of individual rights and privacy, passive data will only be accessed and used in accordance with Apple's officially authorized data access protocols. Each research participant will be assigned a unique identifier, and their information will be uploaded to the database in a deidentified format. This process safeguards the confidentially of participants' personal information. For the purpose of data collection, participants will be instructed to wear the wearable device on their wrist throughout the day, except during activities such as showering or charging. By leveraging the capabilities of the wearable device, this study aims to capture objective and continuous measurements of participants' physiological variables and activity. These passive data sources will provide valuable insights into participants' daily behaviors and help enhance the understanding of their digital phenotypes. Figure 3 shows an overview of the flow of digital phenotyping.

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Figure 3. Flow of digital phenotyping. DSEM: dynamic structural equation modeling; NSSI: nonsuicidal self-injury; RM: repeated measures.

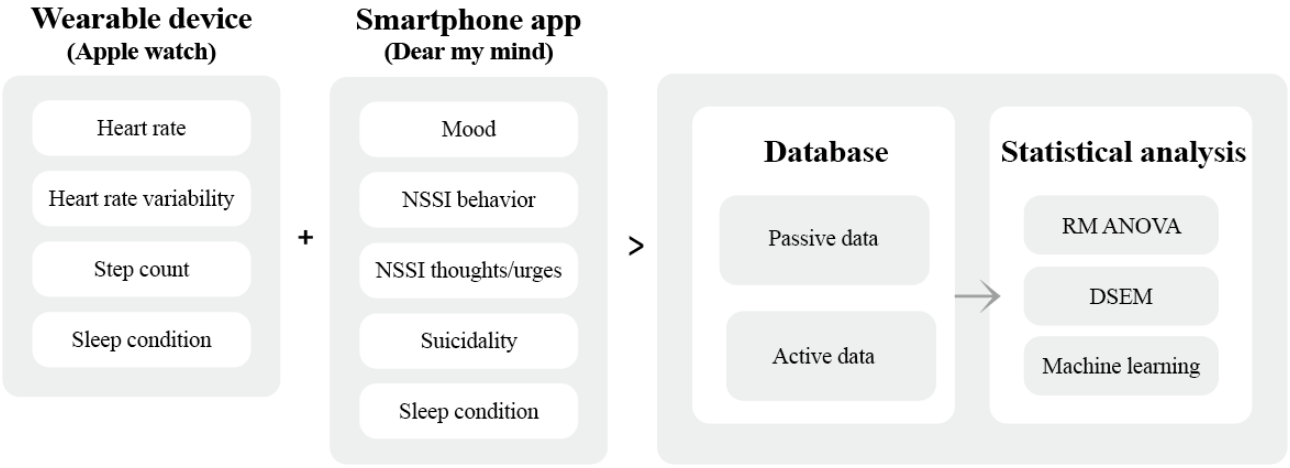

Analytic Plan

This study will use a variety of analytical methods based on the study hypotheses and the characteristics of the data. The analytic methods described below will be used.

Basic Data Analysis

Initially, basic data analysis techniques such as 2-tailed independent *t* tests, linear regression analysis, repeated measures ANOVA, or other appropriate methods will be used to analyze the data and identify any significant changes or associations.

Dynamic Structural Equation Modeling

To examine dynamic changes at the within-individual level, dynamic structural equation modeling (DSEM) will be used. This method allows for the investigation of time-varying relationships and the identification of individual-level patterns of change over time. Specifically, we will examine whether an individual's affective state, physiological state (heart rate, heart rate variability), and sleep state predict NSSI thoughts and behaviors from one observation window to the next. To address these 2-level structured data and to examine the temporal relationships between predictor variables and NSSI thoughts and behavior, multilevel vector autoregressive models were constructed within the framework of DSEM. This approach will enable us to investigate the extent to which time-varying variables at *t*–1 (eg, depressive affect) predict NSSI thoughts and NSSI behavior at *t*.

Machine Learning

To comprehensively analyze participants' digital phenotypes and predict NSSI thoughts and behaviors, sparse logistic regression will be used. Logistic regression predicts the probability of being categorized into 1 of 2 groups when the response variable is binary. This model has the useful property that the estimated coefficients are log odds ratios, but the results are difficult to interpret when the number of variables becomes large. To overcome this problem, sparse logistic regression using the least absolute shrinkage and selection operator (LASSO) can be considered. This model simultaneously conducts feature selection and estimation, allowing for interpretation with a few selected important predictors. To evaluate prediction performance, we will divide the data set into a 30% subset for model estimation and a 70% subset for model training. Additionally, we will perform 5-fold cross validation to avoid overfitting the model. In this process, the full data set will be divided into 5 subsets, with 4 subsets used for training and the remaining subset used as an independent validation set. To solve the problem of imbalance in the training data, the synthetic minority oversampling technique (SMOTE) will be used. SMOTE is an oversampling technique that takes samples from a small number of classes in the data and adds random values to generate new samples to add to the data. This algorithm helps to address the issue of the overfitting problem caused by random oversampling [52].

Other Measures

Measures including accuracy, precision, sensitivity, specificity, and area under the curve will be calculated to explore the prediction performance of sparse logistic regression.

The outcome variables to be entered into the model are NSSI thoughts and behaviors, which will be coded dichotomously (0: absent; 1: present). The predictor variables to be included in the model as interval averages are step count, heart rate, and heart rate variability. These variables will be binned according to the intervals at which the dependent variable, NSSI thoughts and behaviors, will be assessed. The mean value per bin will then be calculated and used as a predictor. For example, as active data collection occurs 4 times, at 9 AM, noon, 6 PM, and 9 PM, the numerous values in the passive data will be divided into 4 bins: 8:00 AM to 11:59 AM, noon to 5:59 PM, 6:00 PM to 8:59 PM, and 9:00 PM to 23:59 PM. For heart rate, values less than 30 or greater than 200 beats per minute (bpm) will be discarded. Heart rate will be calculated as the mean heart rate in bpm, and heart rate variability will be obtained via the SD of the normal-to-normal interval (SDNN), which is the SD of the NN interval and the square root of the variance. Subtracting the mean from each heart rate interval yields the SD of heart rate intervals. Regarding step count, the total step count, average, median, and SD for each period will be calculated. For sleep data, preprocessing will ensure only 1 value per day, representing 1 value per night. Sleep data preprocessing will include the average, median, and SD of core sleep, deep sleep, REM sleep, and total sleeping duration. The ratio of each sleep duration to the total sleep duration will also be calculated as a reference for sleep quality.

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Results

Participant recruitment and data collection started in October 2023. Data collection and analysis are expected to be completed by December 2024. The results will be published in a peer-reviewed journal and presented at scientific conferences.

Discussion

The objectives of this study are to identify the factors that can forecast NSSI thoughts and behaviors in real time within an individual's everyday experiences and to explore the dynamic course of NSSI. This study will be the first attempt in Korea to use digital phenotyping for predicting NSSI. In this project, we can quantify the digital phenotypes of NSSI in individuals by measuring daily mood, self-injury and suicidality, sleep state, and physiological data through the Dear My Mind app and a wearable device. By identifying specific digital phenotypes and analyzing within-individual variations over time, this study seeks to categorize NSSI groups that are relevant to Korean culture. Furthermore, the findings of this research are expected to improve the accuracy of NSSI assessment in psychotherapy. By incorporating digital phenotyping, clinicians will have access to objective and real-time data, enabling them to make more informed treatment decisions and personalized interventions based on individual needs. One approach to tailoring interventions is through the integration of digital phenotyping and intervention strategies [53]. For example, by leveraging multimodal digital signals, such as mobile sensing data, in combination with ground truth data like self-reported information using EMA, predictive models of NSSI risk can be developed. These models can be used to create personalized interventions that are specifically tailored to an individual's unique risk factors and patterns of NSSI behavior. By integrating real-time data collection and analysis, these interventions can provide timely and contextually relevant support to individuals at risk for NSSI, potentially enhancing their effectiveness.

One of the major limitations of this study is that it targets individuals who have engaged in NSSI 5 or more days in the past year, yet the brief 14-day monitoring period may not comprehensively capture NSSI behaviors. This can lead to an imbalance in the training data [54] and should be addressed by expanding the observation period and using appropriate methodologies. Despite this limitation, this research will ultimately serve as a crucial foundation for advancing our knowledge of NSSI in the Korean context. The insights gained from this study will not only shed light on the underlying mechanisms of NSSI but also pave the way for the development of tailored and culturally sensitive treatment options that can effectively address this major mental health concern.

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Data Availability

The data sets generated and analyzed during this study are not publicly available because this project is currently in progress, but they are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

bpm: beats per minute
DSEM: dynamic structural equation modeling
EMA: LASSO: least absolute shrinkage and selection operator
NSSI: nonsuicidal self-injury
REM: rapid eye movement
SMOTE: synthetic minority oversampling technique
VAS: visual analog scale

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Protocol

Adapting and Evaluating an AI-Based Chatbot Through Patient and Stakeholder Engagement to Provide Information for Different Health Conditions: Master Protocol for an Adaptive Platform Trial (the MARVIN Chatbots Study)

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Abstract

Background: Artificial intelligence (AI)–based chatbots could help address some of the challenges patients face in acquiring information essential to their self-health management, including unreliable sources and overburdened health care professionals. Research to ensure the proper design, implementation, and uptake of chatbots is imperative. Inclusive digital health research and responsible AI integration into health care require active and sustained patient and stakeholder engagement, yet corresponding activities and guidance are limited for this purpose.

Objective: In response, this manuscript presents a master protocol for the development, testing, and implementation of a chatbot family in partnership with stakeholders. This protocol aims to help efficiently translate an initial chatbot intervention (MARVIN) to multiple health domains and populations.

Methods: The MARVIN chatbots study has an adaptive platform trial design consisting of multiple parallel individual chatbot substudies with four common objectives: (1) co-construct a tailored AI chatbot for a specific health care setting, (2) assess its usability with a small sample of participants, (3) measure implementation outcomes (usability, acceptability, appropriateness,

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adoption, and fidelity) within a large sample, and (4) evaluate the impact of patient and stakeholder partnerships on chatbot development. For objective 1, a needs assessment will be conducted within the setting, involving four 2-hour focus groups with 5 participants each. Then, a co-construction design committee will be formed with patient partners, health care professionals, and researchers who will participate in 6 workshops for chatbot development, testing, and improvement. For objective 2, a total of 30 participants will interact with the prototype for 3 weeks and assess its usability through a survey and 3 focus groups. Positive usability outcomes will lead to the initiation of objective 3, whereby the public will be able to access the chatbot for a 12-month real-world implementation study using web-based questionnaires to measure usability, acceptability, and appropriateness for 150 participants and meta-use data to inform adoption and fidelity. After each objective, for objective 4, focus groups will be conducted with the design committee to better understand their perspectives on the engagement process.

Results: From July 2022 to October 2023, this master protocol led to four substudies conducted at the McGill University Health Centre or the Centre hospitalier de l'Université de Montréal (both in Montreal, Quebec, Canada): (1) MARVIN for HIV (large-scale implementation expected in mid-2024), (2) MARVIN-Pharma for community pharmacists providing HIV care (usability study planned for mid-2024), (3) MARVINA for breast cancer, and (4) MARVIN-CHAMP for pediatric infectious conditions (both in preparation, with development to begin in early 2024).

Conclusions: This master protocol offers an approach to chatbot development in partnership with patients and health care professionals that includes a comprehensive assessment of implementation outcomes. It also contributes to best practice recommendations for patient and stakeholder engagement in digital health research.

Trial Registration: ClinicalTrials.gov NCT05789901; https://classic.clinicaltrials.gov/ct2/show/NCT05789901

International Registered Report Identifier (IRRID): PRR1-10.2196/54668

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KEYWORDS

chatbot; master protocol; adaptive platform trial design; implementation science; telehealth; digital health; Canada; artificial intelligence; conversational agent; self-management; research ethics; patient and stakeholder engagement; co-construction; mobile phone

Introduction

Background

Self-management is key to patient health, and interventions to promote it are being increasingly implemented in the delivery of health care. Effective self-management involves multiple aspects, including problem-solving, decision-making, resource use, patient–health care professional partnership building, and taking action [1,2]. To improve self-management, patients often seek guidance from health care professionals, staff and volunteers from community organizations or peers, and a variety of internet resources [3,4]. However, the availability of these actors and resources can be inconsistent. Moreover, information encountered on the internet varies in quality [5-7]. From reliable but complex scientific articles to opinion blogs or outdated web pages, these sources do not always provide the clearest, most accurate, or most reassuring guidance. The importance of self-management has been further highlighted by the COVID-19 pandemic, which introduced additional barriers to accessing regular follow-up [8] and exposed individuals worldwide to an infodemic [9,10].

In addition to these challenges, frontline professionals are often confronted with complex questions from patients regarding treatment instructions, comorbidity management, side effects, and drug interactions. However, in the context of swiftly evolving knowledge and overwhelming workloads, health care professionals may not have sufficient expertise and time for certain questions [11,12]. Their responses may vary depending on their individual training, proficiency, and clinical experience. Rapidly obtaining accurate and clear health information and relaying it to patients can be a daunting challenge for professionals.

Safe and effective digital health interventions could help address the limitations of existing self-management or care support. A particularly promising avenue is the emergence of artificial intelligence (AI)–based chatbots—software applications that interact with users through simulated human text or voice conversations via smartphones or computers. Often harnessing AI to enable natural language interpretation and assist in decision-making, such tools possess the potential to revolutionize patient self-management and support [13]. They can be applied to diverse platforms to foster mutually beneficial outcomes for health systems and patients, including less time spent in hospitals, outpatient efficiency, and personalized treatment [9].

Successful implementation of an intervention (ie, positive implementation outcomes) is necessary to achieve desired changes in clinical or service outcomes [14]. Multiple studies have investigated the implementation of health-oriented chatbots, including in the areas of mental health support [15-17], problematic substance use treatment [18], cirrhosis patient education [19], and asthma self-management [20]. Nevertheless, such studies have typically focused on feasibility and usability in small-scale prototype implementations [21-23]. Digital health products are often dealt with through an "implement now, clinically validate later" ethos [24], as they encompass a large number of different technologies. Thus, there is no clear consensus on methods for assessing the clinical effectiveness of digital health interventions [24], and data on the impact of chatbot interventions on clinical outcomes are scarce [25]. Large

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user samples are necessary to gain more robust insights into chatbot implementation. In-depth studies including other valuable implementation (eg, fidelity, appropriateness, sustainability, and cost-effectiveness) and clinical (eg, safety, effectiveness, and efficacy) outcomes will also be critical for scaling up and long-term adoption of chatbot interventions.

Finally, very little engagement of stakeholders, including patients and health care professionals, has led to poor usability and low adoption of many digital health interventions [26]. In the context of chatbot development, a scoping review investigating patient engagement revealed limited involvement of patients and insufficient reporting of the relevant activities [27]. Among the 16 studies included, only 8 mentioned patient engagement, with just 3 offering adequate details on the methods and approach used. The authors also pointed out that future chatbot development would need to integrate multifaceted means of patient participation and document them thoroughly. Stakeholders should be engaged in defining research objectives and designing interventions tailored to their needs [28]. According to the patient-public partnership continuum proposed by the Montreal model [29], this inclusivity can be extended to "co-construction," where patients and stakeholders are involved throughout the process. Meanwhile, to answer the many questions raised by the use of intelligent machines and ensure that AI develops in harmony with democracy, the responsible integration of AI necessitates a co-construction process [30]. Engaging end users in discussions about the challenges posed by AI and drawing on their lived experiences can reveal key aspects of digital health research that might otherwise be overlooked [31], thus better paving the way for success.

Since 2020, led by YM, SA, and B Lebouché, an innovative chatbot named *Minimal AntiRetroViral INterference* (now named *MARVIN*) has been in development for people with HIV. Through a co-design approach involving patients and stakeholders, MARVIN aims to facilitate antiretroviral therapy self-management. The authors' team subsequently trialed the MARVIN chatbot among people with HIV and validated its usability and acceptability [32]. Given the initial success of MARVIN among people with HIV, we intend to build on this pilot study to increase MARVIN's areas of specialization and continue to develop our algorithms to improve MARVIN's intelligence, thereby expanding its reach and potential benefits to a broader audience.

Aim and Objectives

Grounded in patient and stakeholder engagement strategies and implementation science, this protocol aims to describe the methods and tools necessary to efficiently develop the innovative MARVIN chatbot interventions across multiple health domains and populations and assess their implementation for robust and widespread use. The study's primary objectives are to co-construct versions of MARVIN adapted for different health conditions and target populations (objective 1: development), assess their global usability (usability and acceptability) in a small participant sample context (objective 2: usability), and measure implementation outcomes (usability, acceptability, appropriateness, adoption, and fidelity) in the context of a large sample (objective 3: implementation) through a mixed methods approach in the respective setting of each chatbot. The secondary objective is to evaluate the impact of different stakeholder partnerships established for the aforementioned objectives on the development of the AI health care chatbots (objective 4: partnership evaluation).

Methods

Study Design

This multicenter study follows the CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials [33], CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) [34], and CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) [35] guidelines (Multimedia Appendices 1-3 [33]), as well as the Montréal Declaration for a Responsible Development of Artificial Intelligence [30] regarding the ethical conduct of research involving humans and AI.

The study is presented in the form of a master protocol, defined as a single overarching design developed to evaluate multiple hypotheses with the overall goal of increasing efficiency and establishing uniformity through the standardization of procedures in the development and evaluation of different interventions [36]. This master protocol will encompass multiple parallel individual chatbot projects sharing the MARVIN chatbot technology, subsequently referred to as "substudies." The chatbot of each substudy is considered as a distinct intervention as it will integrate specific features or content tailored to the corresponding health care setting (health condition and target population). The chatbots will be implemented in these different populations without control groups.

To accommodate this, we used an adaptive platform trial design, which combines features of both basket trials (designed to test a single intervention in different populations) and platform trials (designed to test multiple interventions in the context of a single disease) [37]. As defined by the US Food and Drug Administration, an adaptive platform design is appropriate for our trial as it allows for flexibility in managing multiple interventions adapted to different populations while enabling the early removal of ineffective interventions and introduction of new interventions based on interim data [38].

As shown in the example in Figure 1, substudy arms targeting different conditions can be initiated at different time points. The substudies are independent of each other, and their processes are illustrated in Figure 2. Objectives 1 to 3 will be completed in a sequential manner, whereas objective 4 will be assessed throughout the process. A decision will be made on whether to continue with the same chatbot intervention version in objective 3 (implementation) based on the results of objective 2 (usability). In addition, there is no initial fixed duration or sample size for each substudy.

This master protocol outlines the common elements of the individual chatbot substudies in terms of objectives and processes. Concurrently, each substudy will have its own subprotocol describing more specific standardized operational structures; additional inclusion and exclusion criteria;

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recruitment and selection methods; and data collection, analysis, and management. All subprotocols will be managed as appendices to this master protocol and will be subject to further review by the research ethics board (REB) when they are ready. In addition, certain criteria of the master protocol may be redefined by the research team based on progress in each substudy and submitted as amendments to the REB for review for subsequent application to all substudies.

Figure 1. Adaptive platform trial design without control group.

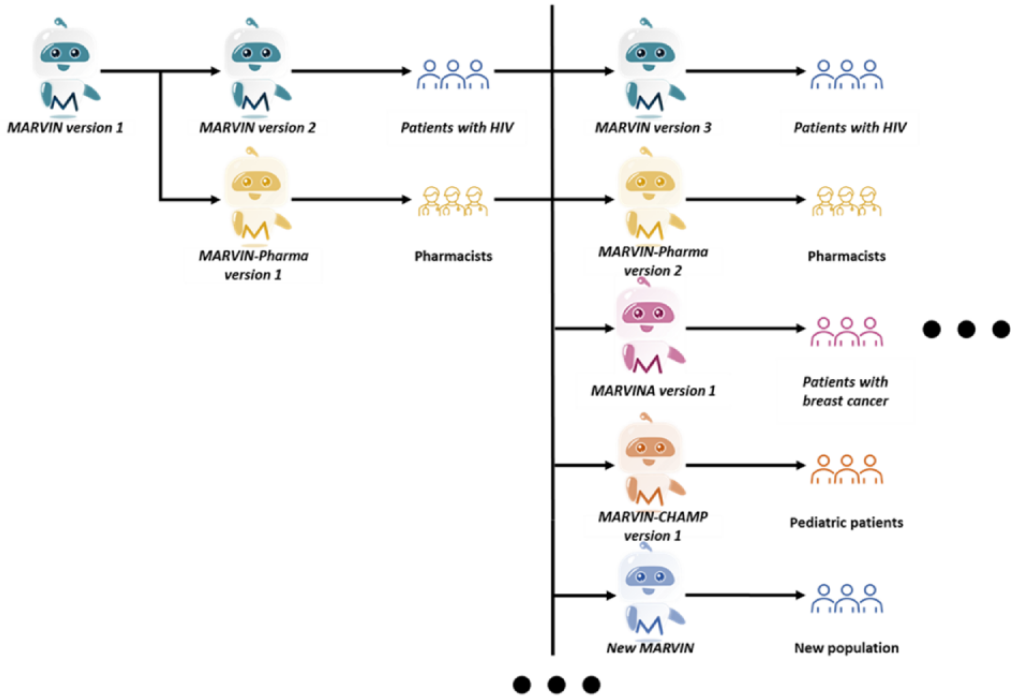

Figure 2. Study steps for each substudy.

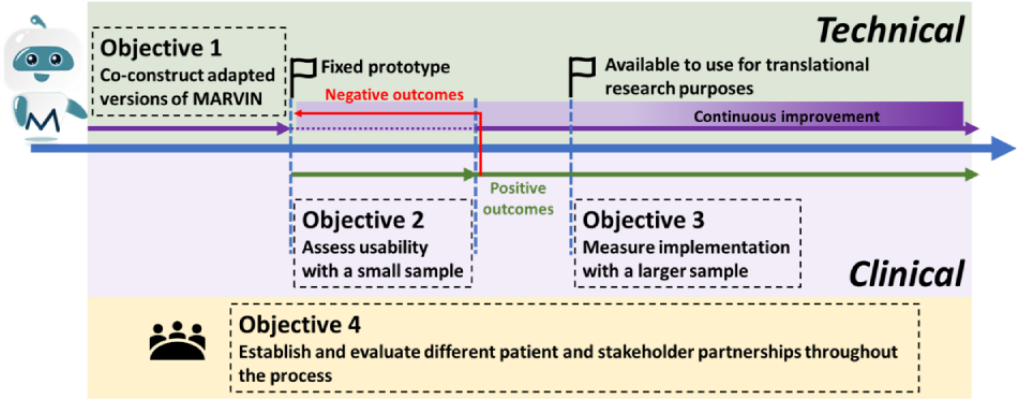

Ethical Considerations

This study received approval from the McGill University Health Centre (MUHC) REB on August 9, 2023 (approval MP-37-2023-9333); the Centre hospitalier de l'Université de Montréal REB (approval MEO-37-2024-11732) on October 13, 2023; and the Polytechnique Montréal REB (approval CER-2324-29-D) on October 10, 2023. It is also registered in the ClinicalTrials.gov database (NCT05789901).

Settings and Participants

This study will be conducted at the MUHC and the Centre hospitalier de l'Université de Montréal, both located in Montreal, Quebec, Canada. The study participants include patients and health care professionals, who will be the end users of the chatbots.

Eligibility Criteria

The primary inclusion criteria for participants are as follows: (1) age of ≥18 years; (2) fluency in English or French; (3) ability to understand the requirements of study participation and provide oral and written informed consent before and during the implementation of the study; (4) access to a smartphone, tablet, or computer in a private environment; and (5) access to an internet connection or data plan on their device. Specific to objectives 2 (usability) and 3 (implementation), additional inclusion criteria are (6) acceptance of using or creating a personal Facebook (Meta Platforms) account, (7) acceptance of using a Facebook Messenger-based chatbot, and (8) acceptance of Facebook's privacy and data security policies.

Participants may not take part if they (1) are affected by a cognitive deficit or medical instability that prevents them from

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participating in any aspect of the study and (2) self-report being insufficiently able to use the chatbot with the technical support provided. For objectives 2 (usability) and 3 (implementation), the patient partners involved in the co-construction design committee (defined in the following section) will not be able to participate in either phase.

Recruitment and Sample Size Justification

Objectives 1, 2, and 3 will use convenience sampling to recruit participants through different channels, including clinics, patient foundations, community-based organizations, and professional associations [39]. For example, patient participants will be introduced to the study by their health care service provider (eg, physician, nurse, or social and community worker) during their visits. Informational materials such as study flyers and a video (Multimedia Appendix 4) showcasing the MARVIN chatbot will be disseminated via email, newsletters, or a website.

Participants will be required to consent before engaging in each objective. For objectives 1 (development) and 2 (usability), interested individuals can reach out to the study coordinator. Detailed study procedures, eligibility checks, and consent collection will be facilitated by the study coordinator for those expressing interest. Verbal consent may be adopted for participants who continue from objective 1 to objective 2. This will be obtained remotely through teleconference with an impartial witness to ensure compliance with all aspects of free and informed consent. Following the co-construction approach [30], a co-construction design committee consisting of researchers, health care professionals, and volunteer patient partners will be formed starting from objective 1 to carry out the subsequent development. The sample size for objective 1 is 20 participants to ensure saturation for the needs assessment focus groups [40], whereas 30 participants will be recruited to complete the corresponding usability test for objective 2. This sample size is common for pilot studies and satisfies the minimum size recommended in the literature [41,42].

For objective 3 (implementation), an optimized version of the chatbot will be accessible from the web around the clock, 7 days a week, for translational research. As currently the MARVIN chatbots will be only released in Canada, recruitment will be exclusive to the Canadian population, and participants will engage in an electronic consent process through the MARVIN chatbots. Before using the chatbot, individuals will be required to review and accept MARVIN's privacy policy (Multimedia Appendix 5). Subsequently, they will be asked to review an electronic version of the information and consent form and then answer the following verification questions for eligibility criteria 1 to 3 via the chatbot: (1) *Are you at least 18 years old?* (2) *Are you comfortable using English or French while communicating with the chatbot?* (3) *Do you agree to participate in the study as described above?* The remaining criteria (4 to 8) will be met once users connect to the chatbot. Should participants agree to participate, their responses will be securely recorded in a separate encrypted database on the MARVIN cloud servers and synchronized to the electronic enrollment log. If users opt not to participate, no records will be kept. As a Facebook account will be a prerequisite for using the chatbot, no further measures will be taken to detect or prevent the possibility of multiple identities. The target sample size of 30 to 150 participants was obtained based on the usability, acceptability, and appropriateness outcomes, which are considered key outcomes for this objective. The analysis involves a 1-sided Student *t* test (1-tailed) evaluating whether the corresponding average attains a predetermined threshold. A power analysis for a 1-sample *t* test is then performed, with 80% power and a 5% significance level. Within the targeted sample size ($30 \leq n \leq 150$), small to moderate standardized effect sizes ($0.2 \leq \text{Cohen } d \leq 0.5$) are detectable in the total sample with the aforementioned statistical power.

Regarding objective 4 (partnership evaluation), upon completion of each objective, an email invitation will be sent to organize focus groups with stakeholders involved in the chatbot co-construction design committee.

The information and consent forms outline detailed study procedures, anticipated benefits, and potential risks. All template versions are available in Multimedia Appendix 6. Participants may withdraw from the study at any time after providing informed consent. This information will be recorded in the electronic enrollment log, and the related privacy management and protection measures will be detailed later. To protect the participants' personal data and identity, no identifying information will appear in any manuscript or report from this study.

Intervention: Status Quo of the MARVIN Chatbot

Overview

Running on Messenger 24/7 for free [43], MARVIN was created as a bilingual chatbot in both English and French trained to converse with people with HIV on the following self-management aspects: (1) guidance for antiretroviral therapy medication (with regard to time management, dosing, drug interactions, and medication reminders, among other things), (2) antiretroviral therapy management when traveling, and (3) common HIV-related knowledge (eg, symptoms, modes of transmission and prevention, and vaccination recommendations).

The team conducted the first pilot project (MUHC REB 2021-7191) in April 2021 with 28 people with HIV receiving treatment at the MUHC. The study results showed that MARVIN was tailored to patient requirements and was easy to use and approachable but that the chatbot's comprehension had limits [32]. For example, if a patient asked a question that was outside the range of topics in the question bank or was worded differently, the chatbot did not always understand it. Nonetheless, considering the development phase, participants reported being satisfied with MARVIN and mentioned that they intended to use it. Thus, by talking to the on-call chatbot, people with HIV could obtain the information they needed for self-management.

AI Algorithms and Strategies

MARVIN is currently being developed using the Rasa platform (Rasa Technologies Inc), an open-source machine learning framework for automating text- and voice-based virtual assistants [44]. As shown in Figure 3, MARVIN's architecture comprises 3 distinct modules: natural language understanding,

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dialogue management, and response selection. Together with a self-built knowledge database, these modules are used to process the message input and generate the message output.

The acceptable input data include natural language in text form as well as some auxiliary expressions commonly used for chatting (eg, emojis such as the thumbs up, smiley face, and sad face). The initial natural language understanding module allows MARVIN to semantically process the input messages through different algorithms such as text preprocessing, entity extraction, and intent classification. The current training data set encompasses a corpus of >3000 questions covering >30 topics. Figure 4 shows an example of text processing. The entity extraction mechanism enables the chatbot to obtain structured information (eg, date, time, and medication name) from the input messages, whereas intent classification helps MARVIN discern the purpose of the information received.

In particular, MARVIN adopts the *FallbackClassifier* algorithm as a fail-safe measure for unprocessable input forms such as images, videos, and sounds. It is also activated when the confidence level of the anticipated intent falls below an established threshold. If the input remains incomprehensible after 2 attempts, the chatbot responds in a uniform manner: "I'm sorry, I can't understand your question right now. Please contact a healthcare professional if you need to." As illustrated in Figure 5, this approach reduces the probability of the chatbot taking incorrect actions when confronted with ambiguity.

The machine learning–driven conversation management determines MARVIN's subsequent actions based on the input message and context in the conversation. A hybrid strategy of the *memoization policy* and *rule policy* was adopted [45]. The *memoization policy* remembers the decision trees from the training data and predicts the next action in conjunction with the derived intention: asking clarifying questions, providing tailored answers, and taking a fallback action. MARVIN can also remember and analyze a certain number of rounds of dialogue to support the prediction. Meanwhile, the *rule policy* handles pieces of conversation that should always follow the fixed behavior defined in the training data (eg, question: *What is ART?* answer: *It means AntiRetroviral Therapies*).

The final response selection module enables MARVIN to select messages predefined by the health care team as output messages. All the data required for processing by the first 3 modules are stored in the knowledge database—after each decision is made in the processing module, MARVIN communicates with the database to compare, extract, or save the data. All data are selected, edited, and validated by the medical team and then processed and added to the database by the development team. Data types include the previously mentioned antiretroviral therapy management–related information, decision trees for different problem scenarios, and predefined answers. An example of response selection from predefined answers in MARVIN is shown in Figure 6.

Figure 3. Operation process of MARVIN.

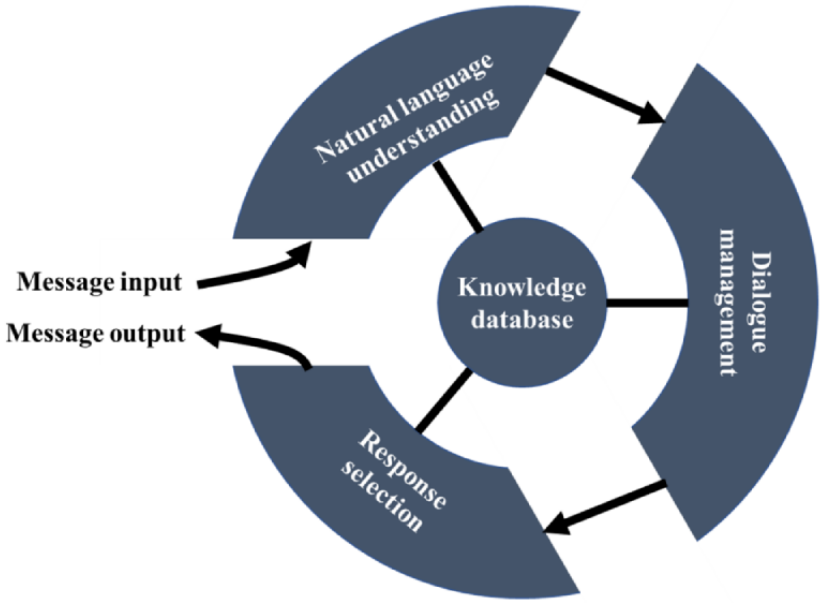

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Figure 4. Example of text processing in MARVIN.

Figure 5. Examples of MARVIN handling bad inputs: (A) fallback policy; (B) redirection after 2 failed attempts.

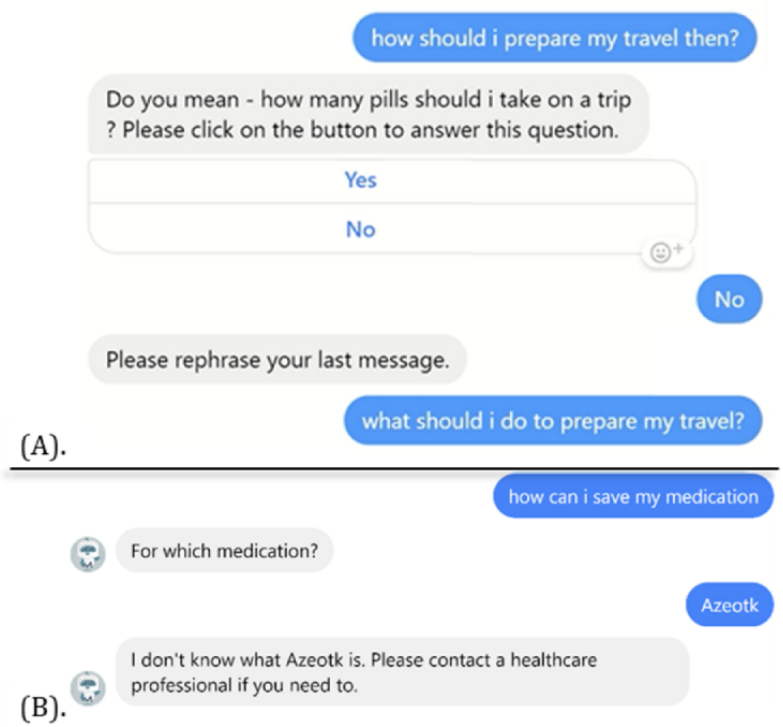

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Figure 6. Conversation example with MARVIN.

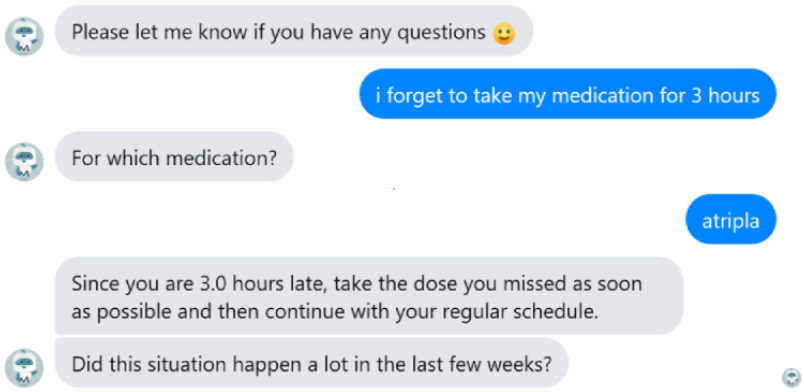

Content Development and Improvement Process

To train MARVIN to understand different types of questions and provide relevant and accurate answers, we assembled a multidisciplinary team of 2 clinicians (ML and B Lebouché), 2 pharmacists (B Lemire and RT), 4 patients, 2 engineers (YM and SA), and multiple developers. Each group's expertise played a crucial role in chatbot content development and continuous improvement: (1) health care professionals validated the medical accuracy of the answers and information given by the chatbot; (2) together with patient partners, they collaborated to identify common self-care challenges; (3) engineers then assisted in building decision models and preparing chatbot training data based on identified problems; and (4) finally, engineers and patients collaborated on testing and refining the chatbot based on feedback, completing the interdisciplinary cycle. This multidisciplinary team allowed us to ensure the accuracy and quality of the information provided as well as conduct holistic research and ongoing evaluation of the chatbot to promote its long-term usability.

The Interface

Messenger has 1.3 billion monthly active users worldwide exchanging 8 billion messages per day [46]. This indicates a robust familiarity with the Messenger interface among the population, simplifying their grasp of the platform's specifications and interaction capabilities, ultimately favoring the uptake of the MARVIN chatbots. In addition, the versatility of Messenger, compatible across smartphones, tablets, and desktops, reduces the potential risk of participant exclusion because of hardware limitations. Nevertheless, the privacy concerns brought up with Facebook in the past may make people hesitant, which could be one of the potential barriers to the implementation of Messenger for health purposes. Indeed, other user interface options such as a stand-alone mobile app, a web page, or other third-party applications (eg, Telegram or Instagram) are under consideration. As the study proceeds and evolves, relevant changes will be implemented as necessary.

Main Study Process

Overview

Multimedia Appendix 7 illustrates the entire study process.

Objective 1: Co-Construction of the MARVIN Chatbots

Overview

Objective 1 is intended to obtain a stabilized version adapted to the health care context for the subsequent objectives. Similar to the original MARVIN's development, it will follow 3 steps: user needs assessment, knowledge database creation, and continuous improvement of the prototype.

The expected duration of participant involvement in objective 1 is 4 months.

Step 1: Needs Assessment

Four 2-hour focus groups will be organized with 5 participants each led by a trained interviewer. Participants will first be shown a demonstration of the current MARVIN describing the interface, dialogue process, and other instructions for use. Semistructured focus groups will then be conducted to identify use scenarios, topics related to integration, and user expectations and preferences for chatbots.

The co-construction design committee will then be formed and meet every 2 weeks to participate in design tasks. The team may also contact them via email with specific questions.

Step 2: Knowledge Database Creation

A knowledge database will be built based on the results of the needs assessment, which is the core of each new chatbot. This database will include a bank of different questions, plausible answers, and necessary conversation templates. Among the most important components of this knowledge database is a corpus of qualified and trusted answers. The challenge is to generate medically accurate information that is easy to understand and sufficiently colloquial while maintaining professionalism. These data will be collected from different sources and validated by the co-construction design committee for adoption to ensure that the chatbot can respond with appropriate output [29,30]. A total of three 2-hour co-construction workshops will be conducted.

Step 3: Testing, Validation, and Continuous Improvement

The team of engineers will work closely with the co-construction design committee through development workshops to test the prototype's performance, especially its quality and safety. Participants will be invited to converse with the test prototype and complete an assessment. Such an approach will facilitate

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the continuous improvement of the prototype and the addition of new features (eg, user interface, questioning methods, and confidentiality measures) as necessary. Thus, each chatbot will evolve in real time during this step. A total of three 2-hour development workshops will be conducted.

It is important to note that, given the nature of software development engineering, steps 2 and 3 will be a continuous cyclic process. The research team will need to continually update the MARVIN chatbots based on feedback from the co-construction design committee on new requirements, improvement ideas, and technology updates.

Quantitative Data Collection and Analysis

During each development workshop, co-construction design committee members will perform a quick descriptive assessment of the tested prototype using the adapted Mobile App Rating Scale for health-related apps [47] (Multimedia Appendix 8).

The scale has 28 items (range 1-5) in 6 sections covering subjects including engagement, functionality, esthetics, information, subjective quality, and health-related quality. Item scores will be averaged to obtain a score for each section and an overall score. It has shown an excellent internal consistency (Cronbach α=.938) and interrater reliability (2-way mixed intraclass correlation coefficient=0.920, 95% CI 0.797-0.987) for the independent overall score ratings of 37 different digital health tools [47]. On the basis of developer recommendations, we will consider a successful prototype for testing to have an average score of at least 4 for the sections on information and health-related quality, as well as an overall average score of 4, as they are identified as key indicators of prototype safety.

Qualitative Data Collection and Analysis

Throughout the study, participants will have the option to take part in either English or French focus groups and workshops. All activities will be moderated by an experienced researcher with an assistant, digitally audio recorded, and manually transcribed verbatim for analysis while removing any nominal information provided to protect the participants' identity. NVivo R1 (QSR International) will be used for qualitative data management.

Participants will also receive transcripts of the sessions in which they participated to ensure the trustworthiness of these data. Therefore, they will have the opportunity to challenge information that is perceived as incorrect. This will also allow them to verify that no information that could potentially identify them was inadvertently retained [48].

A focus group guide will be developed for each substudy considering its specific setting. Focus groups will be analyzed using an inductive thematic analysis approach to gather user recommendations (ie, topics to be addressed, expected conversational style, and desired features). Qualitative workshop data will contribute to thematic analysis in pursuit of objective 4.

Objective 2: Usability Assessment

Overview

Although a usability study among people with HIV has already been conducted [32], usability will be evaluated for other individual chatbot substudies following the same methodology. During this stage, no updates will be made to the chatbots unless (1) the chatbots are not available because of force majeure (eg, host server failure or algorithm dependency update), in which case the team will implement updates to ensure the proper conduct of the study; (2) the results indicate suboptimal usability, in which case we will update the version and repeat the usability study; or (3) new medical information emerges that could benefit participants or prevent harm. Any such event will be documented in detail.

The expected duration of participation for objective 2 is 1 month. At enrollment, 30 participants will be required to complete an initial sociodemographic questionnaire. They will be given a training session and a user guide with instructions on how to access MARVIN via Messenger and the topics of questions they can ask MARVIN. Participants will be enrolled for a 3-week period of interacting with MARVIN by having at least 20 conversations, the topics of which will be specified in each subprotocol. Quantitative data will be collected using a usability survey once their 20 conversations are recorded.

Participants will be free to complete the tasks at any time during this 3-week period. If the chatbot does not receive a message from them within a week of their most recent conversation, it will proactively send a reminder. There will be no active third-party human involvement in the entire testing process between the chatbot and participant user except in the case of user-initiated requests (eg, to solve unexpected bugs).

In week 4, a total of 3 focus groups with 5 randomly selected participants each will be conducted to explore MARVIN's usability in greater depth and in the participants' own words. In total, 3 focus groups can capture at least 80% of the themes, which is sufficient saturation for a usability study [49].

Quantitative Data Collection and Analysis

The initial questionnaire for objective 2 will gather fundamental sociodemographic information (eg, year of birth, preferred language, gender, and ethnic group identity) and digital technology use (Multimedia Appendix 8).

Descriptive statistics will be used to depict the sociodemographic characteristics and digital technology use of the participants. Continuous variables will be reported using measures such as minimum, maximum, mean, and SD. In the case of ordinal and nominal qualitative variables, we will report both counts and proportions.

Global usability will be collected using 2 validated scales: the *shorter version of the Usability Metric for User Experience* (*UMUX-Lite*) [50] and the *Acceptability E-scale* (*AES*) [51] (Multimedia Appendix 8).

Usability is defined in part as "the extent to which a product can be used to be effective, efficient, and provide users' satisfaction within its defined goal" [52]. The UMUX-Lite is a

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2-item questionnaire answered on a 7-point Likert scale that is deemed appropriate for use in the evaluation of health technology [53]. The items ask whether the chatbot meets user needs and about perceived ease of use.

Acceptability is related to how agreeable, palatable, or satisfactory an intervention is perceived to be by stakeholders and is also considered part of global usability [14]. The AES contains 6 items rated on different 5-point Likert scales. It is a validated measure of the acceptability and usability of computer-based interventions for health care populations. Items evaluate, for example, how easy and enjoyable the innovation is to use, how helpful it is, and whether the amount of time to engage with it is acceptable.

As continuous outcomes, both usability and acceptability will be summarized using the minimum, maximum, mean, and SD. The sample mean of each global usability outcome will be compared with its recommended usability thresholds—68/100 for the UMUX-Lite score and 24/30 for the AES score—using a Student *t* test. It will test the null hypothesis that the average UMUX-Lite score is ≤68 and that the average AES score is ≤24. A significance level of 5% will be adopted.

Four central subconstructs of the Technology Acceptance Model (TAM) framework will also be assessed as secondary end points via validated instruments to complement the data: (1) perceived ease of use, (2) perceived usefulness, (3) attitude toward use, and (4) behavioral intention to use the chatbots.

Perceived ease of use will be measured using the Single Ease Question [54], which is answered on a 7-point Likert scale.

Drawing on instruments by Chau and Hu [55] and Davis [56], perceived usefulness will be measured on a 7-point Likert scale with 4 items slightly adapted for relevance to chatbots. The final score will be the average of these items.

Attitude toward using chatbots will be measured using the net promoter score (NPS) [57], which is used as a measure of user satisfaction. A single question will be asked on an 11-point Likert scale. To calculate the NPS, 3 groups are created: promoters (score of 9-10), passives (score of 7-8), and detractors (score of 0-6). Subtracting the percentage of detractors from that of promoters provides the NPS (range −100 to 100). Positive scores, and especially those of >50%, are judged positively.

Finally, behavioral intention to use the chatbots will be assessed using a validated 2-item questionnaire [58] rated on a 7-point Likert scale averaged to produce a final score.

Predicted positive associations between subconstructs within the TAM framework will be evaluated using simple linear regressions considering the slope coefficient. Their significance will be tested using a Student *t* test.

All statistical analyses will be conducted using the R software (R Foundation for Statistical Computing) [59].

Qualitative Data Collection and Analysis

Participants' experiences with MARVIN will be explored through a semistructured focus group on the main constructs of the TAM framework (ie, usefulness, ease of use, attitude, and behavioral intention to use), the analysis of which will help further explain the quantitative analysis. A focus group interview guide can be found in Multimedia Appendix 8.

A composite coding matrix based on the TAM and the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework will be favored for deductive content analysis [60]. The NASSS framework [61] was developed to support the implementation and scale-up of technological innovations in health care. It includes seven relevant domains: (1) the illness or condition, (2) the technology, (3) the value proposition, (4) the adopter system, (5) the organization, (6) the wider context, and (7) embedding and adaptation over time. Given that 5 to 7 are more focused on scaling up implementation, objective 2 will likely focus on the first 4 subdomains for analysis to illustrate associated barriers and facilitators of the early phases of implementation. All facilitators and barriers identified will be then subsequently matched to the subconstructs of the TAM, when possible, to understand their impact on global usability.

The content analysis involves 3 phases. In phase 1, preparation, the analyst will attempt to understand the entire data set through immersion in the data. In phase 2, organization, a composite coding matrix will be devised using the NASSS domains and the TAM subconstructs. The data will be coded and categorized using NVivo R1. Finally, in phase 3, reporting, the descriptive content of the categorization will be presented, addressing trustworthiness.

The saved transcripts of users' conversations with the chatbots may also be submitted for content analysis to describe and better understand the nature of chatbot-participant interactions, such as conversation topic trends.

Objective 3: Implementation Assessment

Overview

For this objective, we will further assess the implementation outcomes of the MARVIN chatbots after they are deployed to the general population via Messenger. During this stage, the chatbots will be regularly updated to introduce new features or content, and their impact on implementation will be assessed. If the outcomes are negative, the corresponding version of the chatbot will be submitted for continuous improvement and evaluation.

We anticipate that the participation period will be 12 months and could be adjusted according to the health care context. Participants will receive a link to the same sociodemographic questionnaire as before (ie, via REDCap [Research Electronic Data Capture; Vanderbilt University] or Google Forms) directly through the chatbot at entry into the study (Multimedia Appendix 8). They will then be able to send messages to MARVIN whenever they wish. If the chatbot does not receive a message from the participant within a month of its most recent conversation with them, it will proactively ask the participant the following: "It's been a month since our last conversation. How have you been?" The participant will be able to turn off this inquiry if they so wish.

Every 2 months, participants will receive a link to a questionnaire on implementation outcomes (Appendix 7). The

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chatbot will also ask 3 open-ended questions to collect information on the participant's overall experience and suggestions for continuous improvement of the chatbot.

Quantitative Data Collection and Analysis

The implementation outcome questionnaire will assess usability, acceptability, and appropriateness using validated instruments. Fidelity and adoption will be summarized using descriptive statistics on chatbot use metadata.

Usability and acceptability will be measured for objective 3 (implementation) as they will be for objective 2 (usability) using the UMUX-Lite and AES questionnaires as both measures are dynamic and vary with experience. Thus, usability and acceptability ratings may be different for each stage of implementation [14,62].

Appropriateness relates to the relevance or compatibility of the innovation to address a particular issue or problem [14]. The compatibility of an IT innovation is the extent to which it is considered consistent with users' values, needs, and past experiences [63]. The *Compatibility Subscale* is a validated tool that contains 3 items rated on a 7-point Likert scale (range 1-7) to assess how an IT innovation "fits" with the user's work style [64]. An adapted version will be administered to health care professional participants. A minimum average score of 5.5 is set as the threshold for adequate compatibility. For patient participants, the *Intervention Appropriateness Measure* will be used [65]. It contains 4 items scored on a 5-point scale to assess an innovation's suitability for a user. A mean score of at least 4 will indicate the appropriateness of the chatbot intervention for the patient population.

Fidelity is the degree to which the intervention is implemented as intended [14]. On the basis of the fidelity measures of digital health intervention implementation identified by Coorey et al [66], we will analyze the following metadata to comprehensively assess the chatbot fidelity: (1) intervention fidelity (the proportion of participants who continue to use the chatbot after a 1-month period), (2) frequency and duration (the monthly frequency with which participants use the chatbot and the average total duration of using the chatbot), (3) messages delivered (the total number of messages that participants interacted with in the chatbot over the course of the study period as well as the average number per participant), and (4) range of messages received (the frequency distribution of different conversational topics triggered by all participants).

Adoption, or uptake, is "the intention, initial decision, or action to try or employ an innovation or evidence-based practice" [14]. It will be measured using the proportion of monthly new users enrolled to all users in the study. The target will be 5% per month given that the median user growth rate for small-scale software services is 4.4% [67,68].

Statistically, a strategy similar to that of objective 2 will be adopted to describe the data. For usability, acceptability, and appropriateness, a Student *t* test will be used to test the null hypothesis that the average score is inferior or equal to the predetermined thresholds.

Qualitative Data Collection and Analysis

To better understand the implementation outcomes, participants will be invited to answer three open-ended questions: (1) What did you like most about using MARVIN? (2) What did you dislike about using MARVIN? (3) How would you improve MARVIN?

The content analysis of this material using the same coding matrix as in objective 2 will likely include the last 3 subdomains of the NASSS framework given the implementation stage at objective 3. This will help document and detail barriers to and facilitators of using the chatbots and their associated implementation outcomes as well as identify targets for continuous improvement.

As with objective 2 (usability), the saved transcripts of chatbot conversations may also be submitted for content analysis to characterize and better understand the nature of chatbot-participant interactions.

Objective 4: Evaluate the Impact of Different Stakeholder Partnerships

Overview

The reporting of patient and stakeholder engagement roles will follow the revised Guidance for Reporting Involvement of Patients and the Public [69].

Quantitative Data Collection and Analysis

Quantitative data on patient and stakeholder engagement activities, such as the number and length of actual workshops or focus groups conducted; the number of attendees; and the user requirements, design parameters, and improvement recommendations made by stakeholders during the workshops or focus groups, will be reported to illustrate the impact of patient and stakeholder engagement on the adaptation or development of the MARVIN chatbots.

Qualitative Data Collection and Analysis

Upon completion of each objective, focus groups will be conducted with stakeholders involved in the co-construction of the chatbots to identify the participants' perspectives on target users' involvement in research. A focus group guide will be developed for each substudy considering its specific setting. These data will be analyzed thematically along with workshop data from objective 1 to determine how potential end users (patient partners and health care professionals) were integrated into the research team, participated in the work, influenced decision-making, and contributed to chatbot adaptation or development.

Data Management, Confidentiality, and Security

Only data relevant to this study outlined in this protocol will be collected by the research team. A comprehensive overview of the study's data management strategy is presented in Table 1, including the collection of recruitment and study data. For objectives 1 (development), 2 (usability), and 4 (partnership evaluation), participants' basic sociodemographic data and contact information will be recorded. For objective 3 (implementation), only participants' Facebook account names will be gathered alongside their eligibility responses. Participants

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will be identified using alphanumeric codes. The link between these codes and the participants' identities will be kept by the research team within a password-protected digital file safeguarded by the MUHC firewall. Access to these records will be exclusive to the research team.

The scope of the study data will include information from the web-based research questionnaire, qualitative data, transcripts of participant conversations with MARVIN, and MARVIN-related metadata. Data required for distinct study objectives through questionnaires will be collected using an appropriate collection tool (eg, Google Forms or REDCap) and subsequently extracted into a password-protected Microsoft Excel (Microsoft Corp) spreadsheet for analysis. Qualitative data, once collected and transcribed, will be password protected and deidentified during analysis. All study data will only be accessible to the research team.

Regarding the technical cybersecurity aspects of the MARVIN chatbots, Figure 7 offers a visual representation of the data flow as participants engage with the chatbots. Throughout the study, participants will send messages to MARVIN chatbots via their personal devices. These messages will be relayed through Messenger's application programming interface to the Amazon Web Services (AWS) cloud server, where the research team deployed the MARVIN service. Response messages from MARVIN chatbots will then be sent back to participants' devices via the Messenger application programming interface. The entire communication process will be encrypted. The research team will be responsible for all of Facebook's MARVIN chatbot accounts and MARVIN servers deployed on the AWS cloud server. Records of chatbot conversations will be stored on an encrypted AWS cloud server. These data will be anonymized by the research team and used exclusively for future model training to enhance chatbot performance for research and quality assurance purposes.

Conversations on Messenger will also be logged and stored on Messenger's server, which is necessary for display on both the participant and chatbot interfaces. The data handling in this context adheres to Facebook's policies [70-72]. If a participant withdraws from the study, the collected study data will be removed as well if the participant so wishes. In particular, in accordance with Messenger's privacy policy, participants will be asked to delete the conversations with MARVIN from their personal accounts, and the research team will delete the conversations from MARVIN's account. Thus, Facebook will stop storing these data as they are no longer required to provide their services and Meta Platforms products.

Note that all platforms involved, including Messenger, Google Forms, and REDCap, comply with the General Data Protection Regulation implemented by the European Union. It is recognized as the highest standard available, especially in terms of AI applications, equivalent to or surpassing the Personal Information Protection and Electronic Documents Act in Canada [73], where MARVIN is deployed. Access to each platform's accounts will be exclusive to the research team and secured through 2-factor authentication.

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Table 1. Study data management strategy.

	Objective 1	Objective 2	Objective 3	Objective 4
Recruitment data				
Data type	• Basic sociodemographic data and contact information	• Basic sociodemographic data and contact information	• Facebook account name, answers to eligibility questions, and web-based consent records	• Basic sociodemographic data and contact information
Protection method	• Password-protected digital files	• Password-protected digital files	• Encrypted database on Amazon Web Services cloud server and synchronized to password-protected digital files	• Password-protected digital files
Storage location	• MUHC[a] internal storage	• MUHC internal storage	• Amazon Web Services and MUHC internal storage	• MUHC internal storage
Study data				
Data type	• Conversation histories	• Conversation histories • Study questionnaire data • Qualitative data	• Conversation histories • Study questionnaire data	• Qualitative data
Protection method	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account • 2-factor–authenticated Google Forms or REDCap[b] (Vanderbilt University) accounts and password-protected digital files • Password-protected digital files	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account • 2-factor–authenticated Google Forms or REDCap accounts and password-protected digital files	• Password-protected digital files
Storage location	• Amazon Web Services and Facebook	• Amazon Web Services and Facebook • Google Forms or REDCap and MUHC internal storage • MUHC internal storage	• Amazon Web Services and Facebook • Google Forms or REDCap and MUHC internal storage	• MUHC internal storage

[a]MUHC: McGill University Health Centre.

[b]REDCap: Research Electronic Data Capture.

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Figure 7. MARVIN chatbot—message data flow diagram. API: application programming interface; AWS: Amazon Web Services.

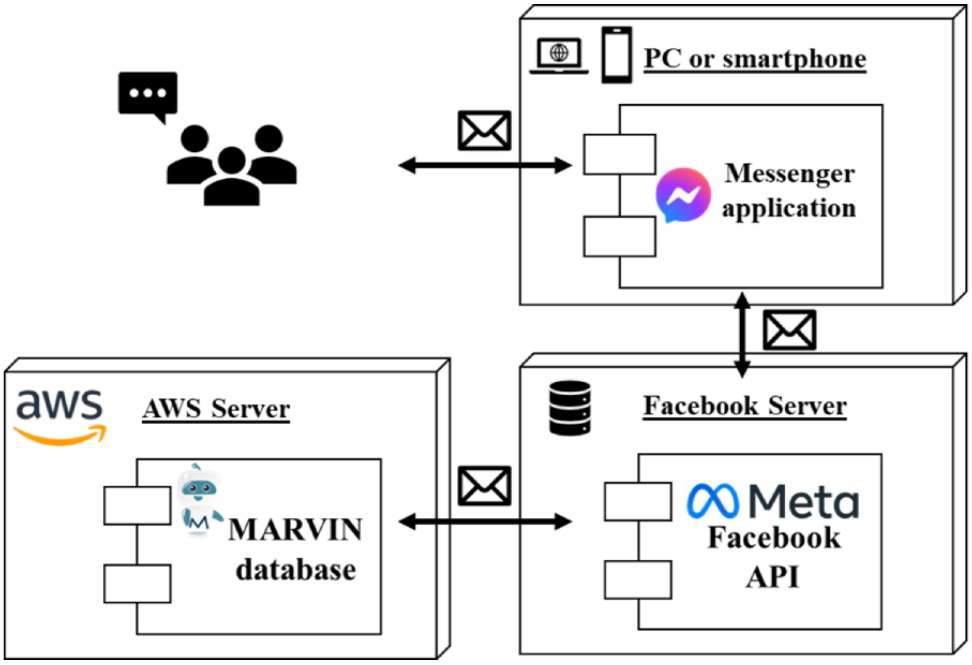

Governance Board

In view of the current ever shifting regulatory landscape surrounding health care AI applications, a governance board will be formed to help the research team obtain external perspectives; assess the ethical and technological issues that may arise from the MARVIN chatbots; and ensure prudent development, testing, and mitigation of associated risks. The board will also summarize best practices from the substudies to enhance future iterations.

Candidates for the governance board include expert patients as well as experts in the fields of AI, clinical science, ethics, legal affairs, and communications. Invitations will be sent by the research team via email. Annual assemblies will be held for reviewing study progress and exchanging insights. For specific inquiries, members of the governance board will remain reachable by the MARVIN research team via email summons.

Anticipated Risks and Benefits

Participants in this study will not be exposed to direct physical risk while partaking in focus groups or interviews, conversing with chatbots via messaging, or completing web-based surveys as they will not receive any pharmaceutical or invasive medical interventions. Furthermore, the preceding pilot study did not reveal any known risks of participation.

However, potential indirect risks are worth considering. In the case of web-based recruitment and verbal consent acquisition, there is a risk of confidentiality breach. This risk can be exacerbated if participants use a personal email address to communicate with the research team. In response, researchers will only use institutional email addresses for correspondence purposes. Participants will also be advised to protect their pertinent personal electronic data.

When using the web-based chatbot, participants will use their personal Facebook account and may share details of their participation in the study. Vulnerability to security breaches (eg, device loss, inadvertent device exposure, phishing, and malware) may arise concerning participants' Facebook accounts. To mitigate this risk, participants will be explicitly reminded during recruitment to secure relevant personal information. The MARVIN chatbots will similarly provide appropriate reminders in the electronic information and consent forms, such as "I recommend that you do not share study-related information with others unnecessarily."

The time required to complete the questionnaires and participate in interviews or focus groups may be inconvenient and distressing for certain individuals. Others may also be uncomfortable answering specific questions or interacting with the chatbot. In situations in which questions are deemed sensitive, private, or distressing, participants are not obliged to respond. The research team will always be available to discuss participant concerns and refer them to appropriate resources, including teleconsultation with a mental health professional or other support service.

It is possible that the MARVIN chatbots will have difficulty understanding messages from participants during the study. In such instances, the chatbot will indicate that it cannot understand, as described previously in Figure 5, and suggest seeking help from a health care professional. There is also a small chance that the chatbot will provide erroneous advice. As an example, the chatbot might inform a patient who missed a 2-hour dose to stop taking the medication completely and consult a health care professional immediately. To minimize this potential risk, participants will be informed of the limitations of the chatbots during the consent process. In addition, participants will be prompted to report any perceived inaccuracies and their consequences to the research team in a timely manner. Weekly revisions of user chat logs will be conducted by the research team to ensure timely human intervention in the event of errors. The governance board for this study will consistently monitor and discuss these reports.

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Finally, any other service-related risks (eg, chatbot or Facebook network service disruptions) will be communicated to each participant in a timely manner and properly documented by the study coordinator.

Participation in the study presents benefits, including early access to chatbot interventions with validated health care information. Participants will also be compensated appropriately upon completion of each study objective [74] in the form of a gift card or, exceptionally, a money transfer.

Results

From July 2022 to October 2023, four substudies were established in conjunction with the completion of this master protocol:

1. The first study is a continuation of the original MARVIN for HIV self-management. This project has secured funding from the Fonds de recherche du Québec – Santé Réseau SIDA/Maladies Infectieuses (AIDS and Infectious Disease Network). A subprotocol targeting objective 3 (implementation) is currently being prepared and scheduled for REB submission in early 2024. Recruitment is scheduled to begin in mid-2024, and the related data analysis will begin in early 2025.
2. The second study is MARVIN-Pharma, a project to promote community pharmacists' knowledge of HIV treatment, with its prototype to be completed by the end of 2023. A related manuscript based on a pharmacist needs assessment is in preparation. A subprotocol for objective 2 (usability) is being developed and is scheduled to be submitted for REB approval in early 2024, and recruitment is scheduled for mid-2024.
3. The third project is to develop the MARVINA chatbot for self-management of patients with breast cancer. This study is supported by funding from the MUHC Cedars Cancer Foundation. The subprotocol was approved by the MUHC REB on September 26, 2023 (approval MP-37-2024-9633). Recruitment for objective 1 (development) is expected to begin in early 2024.
4. The fourth study is to develop MARVIN-CHAMP, an accessible chatbot to assist in the management of pediatric patients with infectious conditions. A funding proposal for this project will be submitted to the Canadian Institutes of Health Research Spring 2024 Project Grant program. A subprotocol for objective 1 (development) is under development and scheduled to be submitted for REB approval in mid–October 2023. Recruitment for objective 1 (development) is expected to start in early 2024.

None of the funding sources had any role in the design of this study and will not be involved in the interpretation of the results or the decision to submit them for publication.

Discussion

Expected Findings

AI technologies have made phenomenal advances, but relevant clinical translation in key areas remains slow. To the best of our knowledge, this is the first known master protocol in digital health dedicated to implementing chatbot interventions across diverse health conditions and clinical settings. Before this, master protocols had been structured primarily for pharmaceutical intervention studies [75]. This master protocol shares key experimental components and operational processes while capitalizing on the similarities of the underlying IT infrastructures already in place. Coupled subsequently with thorough discussion and deliberation among intended users, developers, administrators, and regulators, the efficiency of creating and coordinating multiple studies of the same type has greatly improved. Although the upfront costs and planning time were significant, with this master protocol taking a year to complete from inception to REB approval, it will facilitate the generation of high-quality evidence essential for guiding medical practice. Through centralized management and shared governance, it also reduces development costs, enables broad decision-making, and allows patients to benefit earlier from advanced interventions.

The selected adaptive platform trial format, although designed initially for oncology and infectious disease drug development, has also been identified as being applicable to digital health interventions [76]. Its flexibility is a noteworthy advantage. Digital health interventions are now increasingly being applied to a wide range of conditions. The flexibility of the infrastructure facilitates the addition of substudies or necessary adjustments to each substudy, and health authorities, institutional review boards, and ethics committees will have a clear understanding of what changes are occurring across substudies [77]. Second, design features such as early termination of the trial or re-estimation of the sample size can avoid wasting resources, thus allowing for faster dissemination of research results to the communities that will benefit the most [38].

Patient and stakeholder contributions are integral to shaping this master protocol and associated materials. Their co-constructive engagement allows them to take a leading role in the ongoing digitization of health care and can help mitigate or even address the risks that chatbots face during implementation, such as those tied to trustworthiness, data privacy, and exacerbating inequalities in access to health care. Incorporating patient and stakeholder involvement strategies in developing master protocols, as suggested by Huml et al [78], can make them more successful for patients, providers, and sponsors. Patients and stakeholders will be invited to contribute on an ongoing basis to subsequent chatbot development, reporting of trial results, product marketing, and knowledge translation. Systematically documenting, investigating, and reporting this entire process will be beneficial in providing the scientific community with a clear and replicable model for responsible AI medical research.

Certain limitations need to be recognized. This master protocol focuses solely on the assessment of chatbot implementation outcomes, similar to master protocols typically prepared for pharmaceutical investigations that focus on "early exploratory development phases" [78]. Clinical and service-related outcomes are not included in this master protocol as there is no consensus on their assessment methods. Notably, <25% of AI-based digital health trials include patient-reported outcome measures as end points despite their widespread use in other health care trials

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[79]. Therefore, corresponding research efforts are necessary to develop relevant high-quality assessment metrics to foster the development and validation of user-centered chatbots. If the substudy decides to assess their clinical effectiveness, appropriate amendments will be made.

Large language model (LLM) technology is also not considered in this master protocol for the time being. The release of LLMs, represented by GPT-4, has been indeed impressive. Unfortunately, LLM-based chatbots exhibit limitations such as a lack of transparency, sharing of unverified health information, and poor interpretability [80]. These factors threaten the trustworthiness and security of chatbots, which are key to their successful implementation in health care. Although current state-of-the-art LLMs are, of course, embraced to help generate more diverse and personalized responses, trialing these models in clinical settings also remains a challenge owing to the lack of relevant regulatory compliance and the fact that the existing software-as-a-medical-device framework is not suited to such models [81]. Chatbots can be a safe tool to seek information if they are validated and approved by health care professionals and all personal data are properly secured through robust up-to-date privacy and security safeguards [82,83]. In line with this protocol, the team strongly believes in and adheres to a careful content validation and model fine-tuning strategy so as to maximize the accuracy, trustworthiness, and safety of the solutions being delivered for responsible AI innovation.

Finally, another limitation of the protocol is the use of convenience sampling, potentially introducing bias toward individuals more inclined to use digital health technologies. Furthermore, in the web-based direct recruitment process for objective 3 (implementation), all participants will be self-referred, which will make it challenging to assess whether the participants genuinely meet the inclusion criteria. In addition, the self-reported quantitative questionnaire may be susceptible to random participant responses. Outliers in the data will be checked, and appropriate statistical methods will be used to improve the quality of the final data.

Conclusions

Overall, the development and adaptation of the MARVIN chatbots, co-constructed with those directly involved, hold the promise of fostering patient self-management and enhancing health care efficiency. This study shall provide a comprehensive examination of the implementation outcomes of innovative chatbot interventions tailored for patients and health care professionals. Moreover, it will contribute to the formulation of best practice recommendations for the co-constructive engagement of patients and stakeholders in digital health research. If properly applied, this master protocol has the potential to be sustained for years or even decades and allow innovations to be rapidly translated to clinical practice. Advances in methodology combined with the surge in AI will provide deeper evidence to achieve the goal of patient-partnered personalized medicine and, ultimately, help deliver the right interventions for the right patient at the right time.

Acknowledgments

This study secured funding from the Fonds de recherche du Québec – Santé (FRQS) Réseau SIDA-Maladies Infectieuses (AIDS and Infectious Disease Network; project title: *Developing an AI chatbot-based triage solution to support people with HIV*; principal investigators [PIs]: YM, SA, and B Lebouché). This study is also supported by the Canadian Institutes of Health Research Strategy for Patient-Oriented Research Québec Support Unit–Methodological Developments (grant M006; PI: B Lebouché), the Partnerships to Improve HIV Outcomes and Treatments program from ViiV Healthcare (grant 2021-2186-PIHVOT; PI: RT), and the Cedars Cancer Foundation (project title: *Developing MARVINA, an Intelligent Conversational Agent for Breast Cancer Self-Management through Patient Stakeholder Engagement*; PIs: JA and B Lebouché). YM is supported by the Postgraduate Scholarships – Doctoral program; the Optimizing Power Skills in Interdisciplinary, Diverse, and Innovative Academic Networks (OPSIDIAN) program from the Natural Sciences and Engineering Research Council; and a doctoral research award from the Fonds de recherche du Québec – Nature et technologies in partnership with the Unité de soutien au système de santé apprenant Québec. MPP is supported by a Senior Career Award financed by the FRQS (322746 and 322747), the Centre de Recherche du Centre hospitalier de l'Université de Montréal, and the Québec Ministry of Health and Social Services. B Lebouché is supported by 2 career awards—a Senior Salary Award from the FRQS (311200) and the Lettre d'entente 250 from the Quebec Ministry of Health and Social Services for researchers in family medicine—and holds a Canadian Institutes for Health Research Strategy for Patient-Oriented Research Mentorship Chair in Innovative Clinical Trials in HIV. EO is funded as a clinical research scholar–junior 1 (2023-2027) by the FRQS (331771), awarded in partnership with the Unité de soutien au système de santé apprenant Québec. MHZ is supported by a Junior 1 Career Award from the FRQS (309777). The funding sources had no role in the design of this study and were not involved in the interpretation of the results or the decision to submit them for publication. The authors acknowledge the technical support provided by students and interns from Polytechnique Montreal for the development of the MARVIN chatbots and Lévis Thériault for referring the students. The authors also acknowledge Imane Frih, Maria Nait El Haj, and Gavin Tu for the creation of the clinical content. The names of the members of the MARVIN chatbots Patient Expert Committee cannot be provided as they are patients and their names must remain confidential. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

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Data Availability

The data sets generated and analyzed for this study are available from the corresponding author (B Lebouché) upon reasonable request.

Authors' Contributions

In no order of contribution, YM, MPP, JP, NA, SV, KE, and B Lebouché helped conceptualize the study and data collection tools. YM and SA on the software side and ML, B Lemire, RT, B Lebouché, and the MARVIN chatbots Patient Expert Committee on the clinical side collaborated to develop the MARVIN chatbots. YM, JP, and B Lebouché wrote the manuscript. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

B Lebouché has received research support, consulting fees, and speaker fees from ViiV Healthcare, Merck, and Gilead. The authors are developers of the MARVIN chatbot intervention.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials checklist.
[PDF File (Adobe PDF File), 93 KB - resprot_v13i1e54668_app1.pdf]

Multimedia Appendix 2
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) V 1.6.1 checklist.
[PDF File (Adobe PDF File), 1162 KB - resprot_v13i1e54668_app2.pdf]

Multimedia Appendix 3
CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) checklist.
[PDF File (Adobe PDF File), 161 KB - resprot_v13i1e54668_app3.pdf]

Multimedia Appendix 4
Demonstration video—the MARVIN chatbots study.
[MP4 File (MP4 Video), 117965 KB - resprot_v13i1e54668_app4.mp4]

Multimedia Appendix 5
Privacy policy—the MARVIN chatbots study.
[PDF File (Adobe PDF File), 180 KB - resprot_v13i1e54668_app5.pdf]

Multimedia Appendix 6
Information and consent form.
[PDF File (Adobe PDF File), 549 KB - resprot_v13i1e54668_app6.pdf]

Multimedia Appendix 7
Summary of study procedures for participants.
[PDF File (Adobe PDF File), 129 KB - resprot_v13i1e54668_app7.pdf]

Multimedia Appendix 8
Study questionnaires and semistructured interview guide for the usability study.
[PDF File (Adobe PDF File), 227 KB - resprot_v13i1e54668_app8.pdf]

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Abbreviations

AES: Acceptability E-scale
AI: artificial intelligence
AWS: Amazon Web Services
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-AI: Consolidated Standards of Reporting Trials–Artificial Intelligence
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
LLM: large language model
MUHC: McGill University Health Centre
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NPS: net promoter score
REB: research ethics board
REDCap: Research Electronic Data Capture
TAM: Technology Acceptance Model
UMUX-Lite: shorter version of the Usability Metric for User Experience

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Protocol

Development of an App for Symptom Management in Women With Breast Cancer Receiving Maintenance Aromatase Inhibitors: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer often experience a reduced quality of life after primary treatment. The disease and treatment trajectory consists of surgery followed by chemotherapy or radiation therapy. Upon this, maintenance hormone therapy with an aromatase inhibitor can result in several physical and psychosocial symptoms. Optimal symptom control during maintenance therapy is central to maintaining the patient's quality of life.

Objective: This study aims to (1) develop an electronic symptom management tool for patients with postmenopausal early breast cancer receiving maintenance aromatase inhibitors with an endocrine aspect and (2) assess the feasibility, acceptability, and usability of the pilot version of the Bone@BC app. Furthermore, longitudinally, symptom prevalence and quality of life for patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer will be explored.

Methods: This study follows a multistage research plan. In stage 1, a systematic literature review to establish an overview of aromatase inhibitor–related symptoms reported by postmenopausal women with nonmetastatic estrogen receptor–positive breast cancer will be completed. In stage 2, a comprehensive overview of symptoms related to aromatase inhibitors (letrozole, exemestane, and anastrozole) will be performed (eg, by reviewing medical leaflets and guidelines). In stage 3, an electronic app with a user-friendly Patient Concern Inventory list to comprise symptoms and concerns will be developed. Last, in stage 4, a convergent mixed methods feasibility study of the pilot version of the Bone@BC app will be conducted. A total of 45 patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer will use the app daily for symptom identification and respond to 6 serial patient-reported outcome measurements for 12 weeks. Finally, semistructured interviews will be performed. The primary outcome includes consent rate, attrition rate, retention rates, technical issues, and adherence, assessed using preestablished criteria on feasibility and a mixed methods approach for exploring acceptability. A patient advisory board consisting of 5 women with breast cancer is recruited to include their perspectives and experiences in the planning, organization, implementation, and dissemination of the research throughout the project.

Results: At the time of submitting this paper (January 2024), a total of 23 patients have been included in the stage 2 medical audit over the recruitment period of 3 months (November 2022 to February 2023), and 19 patients have been enrolled in stage 2, the semistructured patient interviews.

Conclusions: This protocol describes a study investigating the feasibility, acceptability, and usability of the symptom management tool Bone@BC developed for patients with breast cancer with an endocrine aspect.

Trial Registration: ClinicalTrails.gov NCT05367830; https://clinicaltrials.gov/ct2/show/NCT05367830

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International Registered Report Identifier (IRRID): DERR1-10.2196/49549

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KEYWORDS

acceptability; aromatase inhibitors; breast cancer; cancer; chemotherapy; disease; feasibility; inhibitor; management; mHealth; postmenopausal; psychosocial; QoL; quality of life; radiation therapy; symptom management; symptom; tool; treatment; usability; user-friendliness

Introduction

Breast Cancer

Patients with postmenopausal nonmetastatic estrogen receptor–positive (ER+) breast cancer (BC) in maintenance therapy with an aromatase inhibitor (AI) deal with numerous long-term cancer- and treatment-related side effects (eg, affected bone health). These side effects lead to impaired health-related quality of life (HRQoL) even years after ending primary treatment and during maintenance hormone therapy [1-3].

The Transition

The transition from being closely monitored by specialists to fewer follow-up visits is difficult for the survivors of BC [4]. These difficulties are explained by reduced interaction with and less psychological support from health care professionals (HCPs) [5-8], as well as, in light of the less frequent consultations, the fact that their surroundings begin to consider the survivors of BC to be cured and healthy [9]. Still, patients during this trajectory stage must be capable of reacting sufficiently to the experienced side effects and potential symptoms [9]. Hence, understanding where and how information and support can be sought for these women is crucial [10] to optimize their self-efficacy and self-management [11].

Patient-Reported Outcomes and Mobile Health

Patient-reported outcomes (PROs) are an important element in the person-centered care of patients with cancer [12,13]. Numerous applications have been developed to collect electronic patient-reported outcomes (ePROs) [14-16]. Mobile health (mHealth) apps have the potential to increase patients' self-efficacy, strengthen empowerment, and offer value to patients in their daily lives [17,18]. The growing field of mHealth has been applied to numerous areas, including health promotion, behavior change support, and self-management of cancer diseases. mHealth is a subset of digital health, or eHealth, which also includes health information, telemedicine, and personalized medicine [19]. mHealth can be quickly scaled to reach thousands of people and potentially increase access to health care. mHealth is well-suited to symptom management, as it can provide timely dissemination of health information, encourage patients to acquire information during their communication with clinicians, and guide self-management.

Hypothesis

We hypothesize that patients with postmenopausal nonmetastatic ER+ BC often experience reduced HRQoL after primary treatment due to treatment-related symptoms. Furthermore, transitioning from being closely monitored by HCPs to fewer follow-up visits can indeed be challenging for some patients. The close monitoring provided by HCPs can provide a sense of security and reassurance, and reducing the frequency of visits may therefore lead to feelings of uncertainty or anxiety. To help patients navigate this transition more smoothly, we will develop a symptom management tool in the form of a pilot version of the Bone@BC app. The pilot version of the Bone@BC app has the potential to significantly support patients in several ways, leading to an improved HRQoL and enhanced communication with HCPs. The app can include features that enable patients to monitor their symptoms regularly so that they will be able to act on them if necessary. It is important to note that the effectiveness of the Bone@BC app will depend on its design, functionality, and user experience. Conducting user testing and gathering feedback during the pilot phase will help identify areas for improvement and ensure that the app meets the specific needs of the target group of patients.

Methods

Study Design

This study follows a multistage feasibility design [20,21] comprising 4 stages (Figure 1 [21]).

As recommended in *Guidelines for Reporting Non-Randomized Pilot and Feasibility Studies* by Lancaster and Thabane [22], the reporting of the study protocol adheres to the CONSORT (Consolidated Standards of Reporting Trials) extension to pilot and feasibility trials.

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Figure 1. A multistage feasibility study. Convergent refers to the quantitative and qualitative data set being collected concurrently. Merge mean data will be analyzed separately and then merged according to allowing the research purpose from multiple perspectives. Metainferences refer to quantitative and qualitative results combined in a conclusion. ER: estrogen receptor; HRQoL: health-related quality of life.

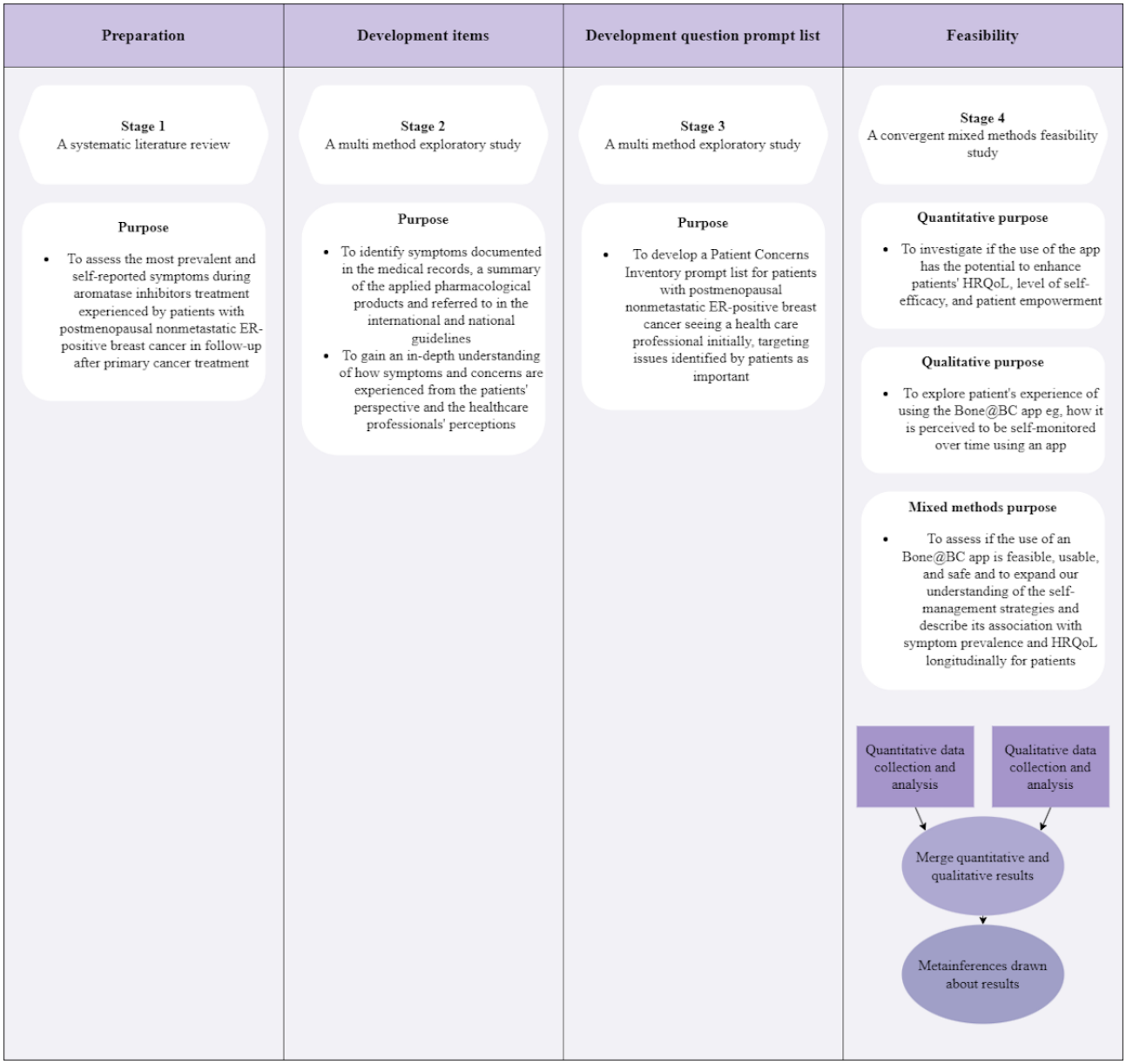

Study Setting

This study will be carried out as a single-center study at the endocrinology outpatient clinic at the Copenhagen University Hospital, Rigshospitalet, in Denmark.

Recruitment

The patients will be recruited from the endocrinology outpatient clinic by clinicians at routine consultations. The semistructured interviews will be performed by the principal investigator (TLJ) not being involved in the treatment and care of these patients. Patients will be screened for inclusion criteria during routine appointments. The informed consent can be withdrawn at any time. A screening log will be kept collecting reasons for nonresponses.

Eligibility

The predetermined eligibility criteria are women aged between 50 and 70 years with a diagnosis of postmenopausal nonmetastatic ER+ BC; in maintenance therapy with an AI (letrozole, anastrozole, or exemestane); who are able to understand, read, and speak Danish; have access to a smartphone that can display the app (eg, iOS, iPADOS, or Android); and provide informed consent. Patients will be considered ineligible if they are unable to provide informed consent due to cognitive or linguistic inability, have a physiological or cognitive impairment that would prevent or inhibit the participation in using the app and answering the ePROs, have a previous malignancy, or are in maintenance therapy with tamoxifen.

Patient and Public Involvement

Because patient involvement is essential for this study, to ensure patient-centeredness [23], a patient advisory board consisting of 5 women diagnosed with BC was recruited through an

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advertisement on the Danish Breast Cancer Organization's website. The primary objective of the patient advisory board is to enhance the researcher's communication and cooperation with patients, thereby ensuring the integration of their perspectives, requirements, experiences, and expectations throughout the various stages of research, including planning, organization, implementation, and dissemination [24,25].

Intervention Description

The Proof-of-Concept Version of the Bone@BC App

Originally, a proof of concept of the Bone@BC app was developed (2015-2018) by a team of clinicians with specialist experience from the Healthy Living After Breast Cancer research group. The proof-of-concept app was published in 2 languages, Danish and English. The proof-of-concept version provides (1) advice on treatment elements (eg, blood samples and prevention); (2) daily questions about daily living; and (3) private notes. However, the proof-of-concept version of the app did not follow a systematic selection of symptoms to include, and no patients were involved in the design or content of the app (Figure 2).

Figure 2. Overview of the proof-of-concept version of the Bone@BC app.

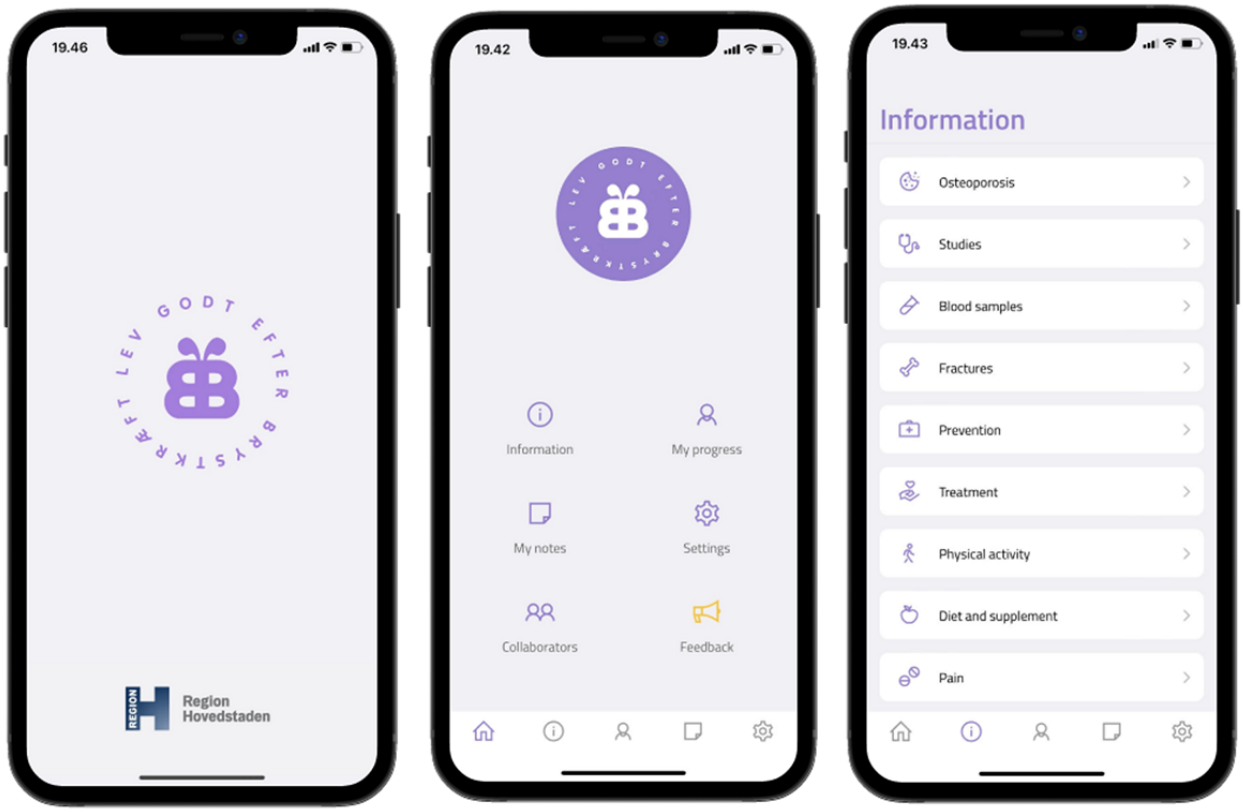

The Pilot Version of the Bone@BC App

The proof-of-concept version of the app yielded several noteworthy patient feedback examples, which are as follows:

- Patients expressed the desire for an app that goes beyond educational purposes and provides support in their daily lives. Specifically, they highlighted the importance of having a tool that helps them remember changes in their symptoms.
- Patients emphasized the need for visual information, such as trends indicating their quality of life based on daily responses to HRQoL assessments.
- Patients expressed the expectation that the app should assist them in identifying relevant topics to discuss with HCPs.
- Some patients did not find the notes module in the app useful.
- Additionally, certain features such as blood samples, daily habits, and dual-energy x-ray absorptiometry scan were deemed unhelpful by patients.

This study seeks to develop a pilot version of the Bone@BC app based on the above feedback from the patients who used the proof-of-concept version of the Bone@BC app. The pilot version of the Bone@BC app will increase patient friendliness by implementing functionalities developed systematically in collaboration with patients and clinicians to solve patients' specific needs using this symptom management tool (Table 1).

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Table 1. Overview of components in the proof-of-concept version versus the pilot version.

Components	Proof-of-concept version	Pilot version
Information on treatment-related osteoporosis, blood samples, and physical activity (both text and video) with health care professionals	✓	✓
Training instructions videos		✓
My progress	✓	
My results (eg, blood samples)	✓	
My medication (eg, breast cancer medication)	✓	
Body measures (height and weight)	✓	
Daily habits	✓	
Activity from your mobile phone health tracker		✓
My notes	✓	
Feedback	✓	✓
Patient Concerns Inventory prompt list		✓
Reminder module		✓
Reminder list based on the previous Patient Concerns Inventory prompt list		✓
Intelligent progress of the health-related quality of life measurements		✓
Trends for the health-related quality of life measurements (tendencies algorithm)		✓
Simplified user interface		✓
Danish version	✓	✓
English version	✓	✓

Definition of Symptoms

Our study will use the definition of symptoms from the National Institutes of Health and the National Cancer Institute: "A physical or mental problem that a person experiences that may indicate a disease or condition. Symptoms cannot be seen and do not show up on medical tests. Some examples of symptoms are headache, fatigue, nausea, and pain" [26].

Development of the Pilot Version of the Bone@BC App

To develop the pilot app version, this multistage study consists of 4 stages (Figure 1) where the Bone@BC app will be further developed and then tested in a feasibility study.

Stage 1

A systematic review will be undertaken to appraise the current literature and provide an overview of AI-related symptoms reported by postmenopausal women with nonmetastatic ER+ BC. The systematic literature review will be reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols) 2015 statement [27]. A comprehensive search will be undertaken on the following databases: PubMed, MEDLINE, CINAHL, Embase, Cochrane, Web of Science, PsycINFO, and Scopus. The Mixed Methods Appraisal Tool version 2018 [28] will be used for assessing the included studies' methodological quality.

Stage 2

Stage 2 will be an explorative multimethod stage relying on patient involvement. Moreover, symptoms and concerns identified by the European Organization for Research and Treatment of Cancer (EORTC) Library Item [29] will be selected to be included in the Bone@BC app.

Multimethod data collection will be carried out to explore the symptoms reported by the patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy with AI (letrozole, anastrozole, and exemestane; Figure 3).

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Figure 3. Study assessments in stage 2. EORTC: European Organization for Research and Treatment of Cancer.

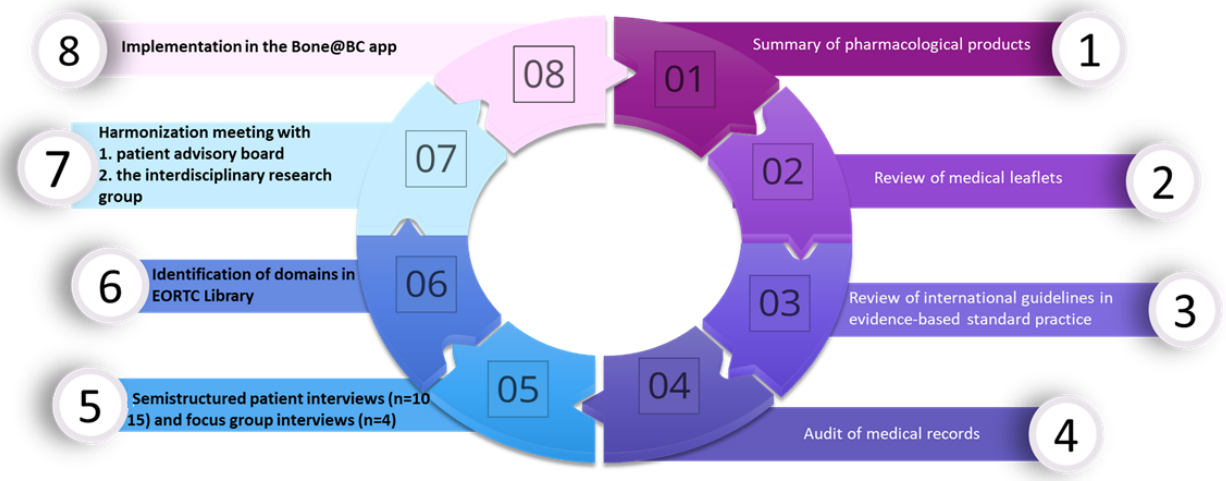

1. A summary of pharmacological products at the European Medicines Agency [30] and the Food and Drug Administration [31].
2. Review of medical leaflets at the website Medicine.dk [32].
3. Reviews of international and national guidelines for the standard clinical practice: oncological (American Society of Clinical Oncology [33], European Society for Medical Oncology [34], and Danish Breast Cancer Group [35]) and endocrinological (Endocrine Society [36], European Society of Endocrinology [37], and Danish Endocrinological Society [38]).
4. Medical record audit from patients with postmenopausal nonmetastatic ER+ BC. The inclusion period will be from November 14, 2022, to February 14, 2023. All patients attending routine consultations will be invited to participate. The principal investigator will perform the reviews and exclude patients who do not meet the predetermined inclusion criteria.
5. Semistructured face-to-face patient interviews on symptom experience (n=15-20).
6. The quantitative and qualitative results from steps 1 to 5 will, together with the systematic literature review, provide a comprehensive overview of the symptoms, side effects, and concerns that patients with postmenopausal early BC are dealing with. These symptoms and concerns will be organized into domains for HRQoL measurements to identify related and validated items in the EORTC Library that can be implemented in the pilot version of the Bone@BC app daily questions [29].
7. Finally, a harmonization meeting will be organized, initially involving the patient advisory board, followed by the interdisciplinary research group (the authors). The purpose of this meeting will be to facilitate discussion, collaboration, and consensus among participants regarding the selection of specific items from the EORTC Library [39].

Stage 3: Multimethod Exploratory Study

In this stage, an electronic Patient Concerns Inventory list (PCI) will be adapted from the English version of the PCI developed by Kanatas et al [40] for patients with BC. The adapted PCI will be modified to fit the app. A PCI is a structured list of frequently asked questions and concerns. It is designed to support and encourage patients to acquire information during their communication with HCPs. The development of the electronic PCI relies on the following steps: (1) translation and linguistic validation according to the Professional Society for Health Economics and Outcomes Research [41]; (2) focus group interview with the patient advisory board; (3) development of a minimum variable product (MVP) app only to test the electronic PCI list; (4) the patient advisory board testing the MVP app and evaluating it in a focus group interview; (5) pilot-test patients (n=15) using the MVP app will be interviewed by semistructured face-to-face interviews; and (6) harmonization meeting in the multidisciplinary research team.

The identified items from the EORTC Library [39] and the PCI will be implemented in the pilot version of the Bone@BC app.

Stage 4

Stage 4 is a convergent, nonrandomized, single-arm mixed methods feasibility study [21] (Figure 4 [20,21,42-49]) investigating the feasibility of the pilot version of the Bone@BC app.

The purpose of this stage will be to explore the patients' perspectives on feasibility, acceptability, and usability while being offered the pilot version of the Bone@BC app, which will be provided to them as a tool for symptom identification over a period of 12 weeks. Moreover, the consent rate, attrition rate, adherence rate, and retention rate will be explored. Furthermore, the potential changes in self-efficacy, HRQoL, and patient empowerment over time will be measured. The findings from the quantitative data (PRO questionnaires and data in the Bone@BC app) and the qualitative data (patient interviews) will be compared and merged. The intent is to obtain a more comprehensive understanding of the feasibility, usability, barriers, and subgroup of patients who may benefit from using the app.

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Figure 4. Stage 4: convergent mixed methods feasibility study. Convergent mean that the quantitative and qualitative data sets are collected concurrently, analyzed separately, and then merged accordingly to achieve the research purpose from multiple perspectives. After analysis of each data set, inferences will be drawn. At the end of the study, the metainferences will be drawn and included in the larger interpretation being made in the study's discussion section. Consecutive sampling refers to every participant who meets the criteria of inclusion and is selected until the required sample size is attained [50]. Purposeful sampling refers to the researcher intentionally recruiting participants who have experienced the central phenomenon being explored in the study. Matomo refers to an open-source digital analytics platform (Matomo). EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30; HADSA: Hospital Anxiety and Depression Scale; heiQ: Health Education Impact Questionnaire; HRQoL: health-related quality of life; PROM: patient-reported outcome measure; SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale; SGPALS: Saltin-Grimby Physical Activity Level Scale; SUS-DK: System Usability Scale–Danish version.

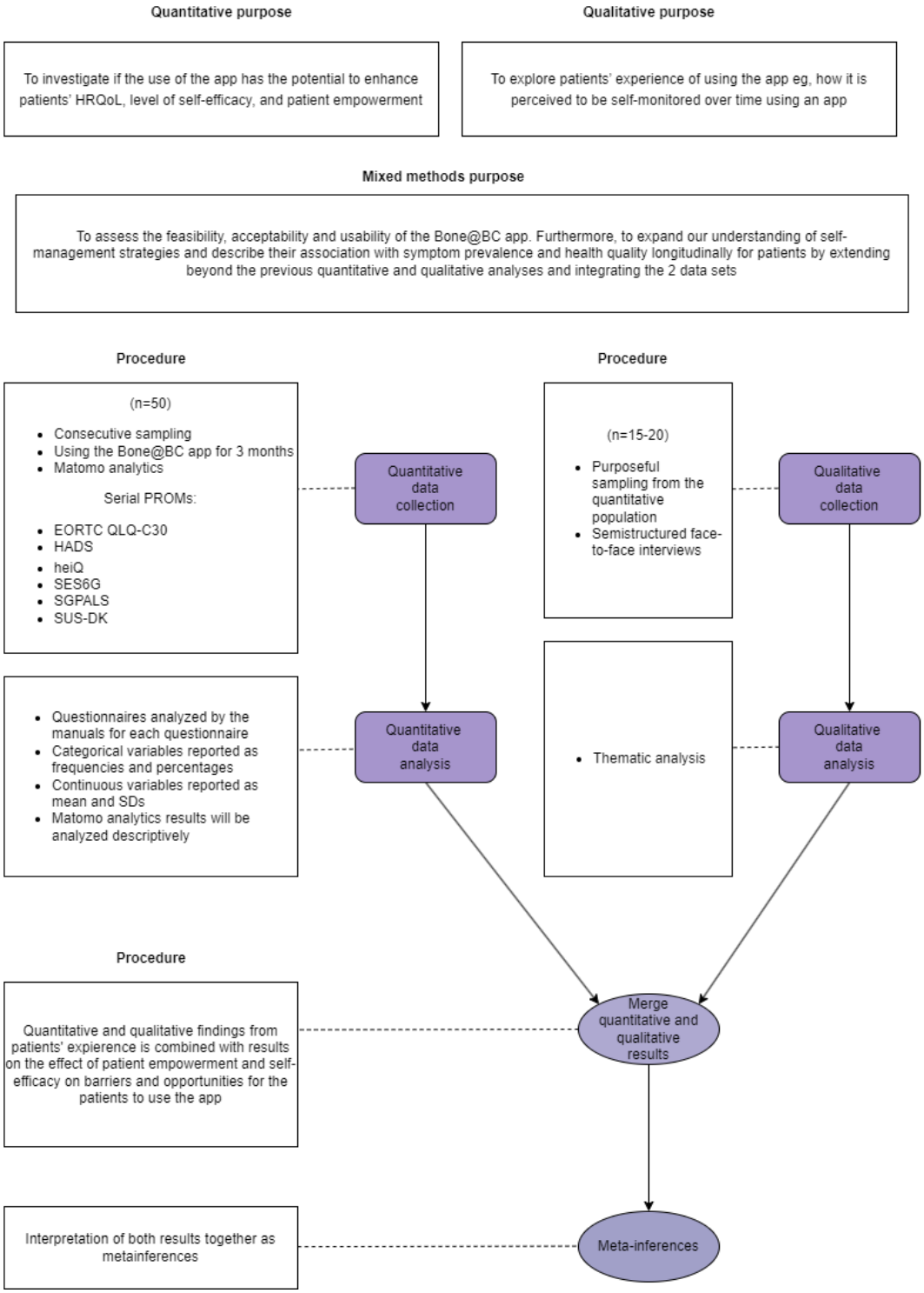

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Measures

Feasibility

The feasibility of the study will be assessed by the rate of recruitment and retention over the study duration (12 weeks). The feasibility parameters include adherence rate, acceptability, response rate, representativeness, recruitment rate, technical difficulties, and satisfaction [51].

Acceptability

The acceptability of the pilot version of the Bone@BC app will also be explored by semistructured interviews with a subgroup of the 40-50 invited participants in the study.

Usability

The satisfaction survey will be the System Usability Scale–Danish version (SUS-DK) [42] and will be explored in semistructured patient interviews after the intervention. The System Usability Scale is a 10-item questionnaire with 5 responses ranging from “strongly disagree” to “strongly agree” [42]. The final question allows respondents to provide further comments in an open-ended format. The criteria for being satisfied will be a system usability score of ≥68% [42].

App Use

The open-source web analytic platform Matomo Analytics [43] will be used to investigate user statistics and traffic in the app. In-app user analytics will be collected to track user behavior such as the number of app sessions, length of app sessions, frequency of use, date the app was first opened, the number of pages, time spent on the pages, and bounce rate.

Health-Related Outcomes

Health-related outcomes will be collected at baseline upon registration for the pilot version of the Bone@BC app and then at 3 different time points (Table 2).

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Table 2. Study assessments and time points stage 4.

Data Collection (n=50)	Baseline	Week											
		1	2	3	4 (~1 mo)	5	6	7	8 (~2 mo)	9	10	11	12 (~3 mo)
Data for the research database REDCap[a]													
Informed consent	✓												
Demographic data[b]	✓												
EORTC QLQ-C30[c]	✓				✓								✓
SES6G[d]	✓				✓				✓				✓
heiQ[e]	✓												✓
HADS[f]	✓												✓
SGPALS[g]	✓				✓				✓				✓
SUS-DK[h]													✓
Open-source web analytic platform Matomo Analytics 3.0[i]	✓				✓				✓				✓
PRO[j] data through the app													
Electronic patient-reported PRO questionnaires on symptoms Bone@BC (everyday)[k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Semistructured interviews													✓

[a]REDCap: Research Electronic Data Capture.

[b]Demographic data (eg, marital status, family status, educational level, and occupation).

[c]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30.

[d]SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale.

[e]heiQ: Health Education Impact Questionnaire.

[f]HADS: Hospital Anxiety and Depression Scale.

[g]SGPALS: Saltin-Grimby Physical Activity Level Scale.

[h]SUS-DK: System Usability Scale–Danish version.

[i]Open-source web analytic platform Matomo Analytics.

[j]PRO: patient-reported outcome.

[k]Patient-reported outcomes from the app on the questions provided daily on health-related quality of life, late side-effects, symptoms and concerns perspectives, and level of physical activity in the Bone@BC app and question prompt list. Items developed in stage 3 and implemented from the European Organization for Research and Treatment of Quality of Life Item Library in the domains of late side-effects and symptoms management.

The health-related ePROs being assessed before and after the study will be the HRQoL by the 30-item EORTC Quality of Life C30 (QLQ-C30) [44]. The HRQoL domains are divided into multi-item subscales: functional (physical, role, cognitive, emotional, and social), symptom (fatigue, pain, nausea/vomiting, and dyspnea), financial adversity, and global health status [44]. The EORTC-QLQ-C30 has proven to be reliable and valid in a range of patient populations and a variety of treatment settings [52].

Self-efficacy will be measured by the Self-Efficacy for Managing Chronic Disease 6-Item Scale (SES6G) [45]. SES6G is a self-administered questionnaire with 6 items on the patient's perceived self-efficacy on a 10-point Likert scale ranging from "not at all confident" to "totally confident" [45]. Ritter and Lorig [53] conducted 2 new studies and reviewed 8 independent studies to investigate the psychometric properties of the scale. Cronbach α was a minimum of .88 across all studies; minimal floor and ceiling effects were observed; the measure was sensitive to change; and moderate and significant correlations provide convergent validity evidence when measured against selected health indicators [53].

Physical activity will be measured by the Saltin-Grimby Physical Activity Level Scale (SGPALS) [46]. SGPALS is a 4-level scale. The questionnaire measures the level of physical activity as 3 months before the patients were diagnosed with BC and how the level of physical activity is today [46]. The SGPALS is found to be reliable, with a high level of validity and consistency [54].

Anxiety and depressive symptoms will be measured by the Hospital Anxiety and Depression Scale (HADS) [47]. HADS is a validated screening tool and includes 14 questions

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addressing anxiety and depressive symptoms with 7 items each in the previous 7 days [47]. In an updated literature review, the HADS was found to be reliable with a Cronbach α between .70 and .90 [55].

Patient empowerment will be measured by the Health Education Impact Questionnaire (heiQ) [48]. heiQ is an outcome and evaluation measure for patient education and self-management interventions for people with chronic conditions. heiQ is a validated screening tool and includes 42 questions with the following 4 options for the answer: "strongly disagree," "disagree, agree," or "completely agree" [48]. The heiQ is a valid, reliable measure of key dimensions of generic health-related empowerment [56].

Statistical Analysis

Preestablished Criteria

Feasibility will be explored by looking at the success threshold, attrition rate, and adherence. The success threshold of ≥60% will be defined as the proportion of informed patients giving consent. The attrition rate will be calculated as the proportion of participants withdrawing from the intervention, leaving no data on outcomes available. The retention rate of ≥85% will be the number of individuals who remained in the study and responded to the daily PRO in 12 weeks. The retention rate and success threshold are based on a recent systematic review of internet-based supportive care for patients with lung disease [57]. Patient adherence will be the proportion of patients completing self-reports for each time point adjusted for withdrawals. The adherence rate is the proportion of patients replying to ≥80% of the daily PRO questions. Adherence to daily completion will be analyzed according to, for example, material status and educational level using the Fisher exact test.

Acceptability will be assessed based on the following predetermined criteria: (1) system usability score ≥68% [42]; (2) patients' experience identified in follow-up interviews; and (3) HRQoL must be at least at the same level before and after the intervention as measured by the EORTC QLQ-C30 [44].

Quantitative Data

The quantitative data will be exported to R software (version 4.1.2; R Foundation for Statistical Computing) [58]. All questionnaires will be scored according to the specific manuals. The analysis of the obtained data will be based on CIs and will focus on exploring the longitudinal changes over time. The daily self-report of symptoms will be analyzed using multiple linear regression after the variables have been checked by diagnostic plots to see if they meet the following 5 main assumptions: (1) linearity, (2) homoskedasticity, (3) independence of errors, (4) normality, and (5) independence of independent variables. Descriptive statistics will be performed to describe the sociographic and clinical characteristics. The categorical variables will be reported as frequencies and percentages. Continuous variables will be tested for normality before we decide to report them as mean and SD or median and IQR. In addition, an open-source digital analysis platform (Matomo) [43] will be used to track traffic and user behavior on the app.

Qualitative Data

The qualitative data will be collected through individual interviews. All interviews will be recorded and transcribed verbatim. The transcripts will be handled systematically in NVivo (QSR International Pty Ltd) [59] to create an audit trail and facilitate transparency [60]. The observational data and interviews will be analyzed based on the 6 steps of thematic analysis outlined by Braun and Clarke [61,62]. Using inductive coding, transcripts will be interpreted, and themes will be generated. Furthermore, researcher triangulation will strengthen the credibility of the results [60].

Power

For the semistructured patient interviews, the sample size will be guided by the notion of information power, according to Malterud et al [50]. Being a feasibility study with predetermined criteria for success, a formal sample size calculation is not necessary [63]. However, sample sizes of 40-50 participants have been recommended for feasibility studies [64]. Thus, 40-50 participants will be recruited for the intervention.

Ethical Considerations

The research will be carried out following the Declaration of Helsinki [65], the General Data Protection Regulation [66], and the Human Research Ethics Committee Denmark [67]. Ethical approval has been obtained from the ethical committee of the Capital Region of Denmark (jr nr 210777457). Data are reviewed and registered in the Capital Region of Denmark (Pactius jr nr P-2022-162). All participants will be required to fill out an informed consent after verbal and written information about the study have been given. A screening logbook will be performed.

The systematic literature review is registered in PROSPERO (ID: DR42021281012). The Bone@BC app is data-reviewed and registered in the Capital Region of Denmark (jr nr 6203, local jr nr RH-2018-38, Pactius jr nr P-2020-520). The Bone@BC app has been approved for the integration of the entered app data with region security requirements and is an official Region Capital of Denmark app. The app uses MITID log-in (national electronic personal ID) and a disclaimer of responsibility. The Bone@BC app is approved by the Danish Breast Cancer Patients Society and the unified Danish eHealth Portal [68]. Licenses are obtained for included patient-reported questionnaires that require a license.

Results

The enrollment for the stage 2 medical audit of patients started in November 2022, and lasted until February 2023; a total of 23 patients have been included. The enrollment for the stage 2 semistructured patient interview is ongoing, and a total of 19 patients have now been enrolled.

The scientific findings derived from the study, regardless of being positive, negative, or inconclusive, will be documented in original manuscripts and submitted for publication in peer-reviewed international journals specializing in the relevant field (with authorship defined by the International Committee of Medical Journal Editors criteria) [69]. The results will

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furthermore be disseminated at relevant scientific conferences and professional meetings as oral presentations, as well as in poster forms. The Vancouver recommendations [69] will be followed in all publications based on the study.

Discussion

Principal Findings

This study is, to our knowledge, the first to develop an ePRO platform specific to PRO for patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy with AIs with an endocrinology aspect. Furthermore, to our knowledge, there are no previous studies regarding the development of an electronic app with a user-friendly PCI prompt list. The BELIEVE@BC study will contribute knowledge about how the use of an app for women with BC can be a helpful symptom management tool in their everyday lives. The BELIEVE@BC study will also contribute knowledge about whether the use of an app can be an important communication tool during consultations with HCPs. The use of ePROs offers HCPs an improved understanding of patients' symptoms during the intervals between their hospital visits.

Comparison With Previous Work

Overview

Due to improvements in diagnostics and treatments, the 5-year survival rate for patients with BC is 90% after the initial diagnosis [70]. During treatments, patients typically have consultations weekly and then gradually reduce to annual visits [71]. During this transition from hospital-based care to health self-management, the patients with BC are encouraged to exercise because of accumulating evidence for the efficacy of exercise training in cancer survivorship [6,71] and, in the majority of cases, adherence to endocrine treatments to reduce the risk of BC recurrence [9]. There is accumulating evidence that many patients with BC (and other patients with cancer) find this transition physically and mentally difficult due to reduced interaction with psychological support from HCP [5-8]. Additionally, ongoing late side effects, for example, pain, fatigue, and loss of appetite [9], and less support from surroundings, given that their surroundings consider them to be healthy [9], are important factors. The late side effects may develop months or even years afterward, and the patients with BC are therefore, in their everyday lives, troubled with being alone with their burdens. A systematic review [72] included 42 studies of self-management education for patients with cancer. Hereof, 16 studies concerning BC suggest that self-management interventions may reduce symptoms of fatigue, pain, depression, anxiety, and emotional distress and increase HRQoL [72].

By equipping patients with the necessary skills, confidence, and knowledge to self-manage their health, they gain increased autonomy and control over their well-being. This empowerment fosters healthy behaviors and encourages proactive measures to prevent long-term illnesses. In many cases, individuals are capable of managing minor illnesses on their own, leading to a decreased reliance on professional assistance. This enables HCPs to allocate their resources and attention toward providing care for patients at higher risk, particularly those with coexisting medical conditions or comorbidities. Around 1 in 5 visits to the general practitioners are made for social needs such as isolation, management, low mood, and anxiety [73]. A systematic review from 2019 [18] found that mHealth apps with interventions focusing on BC survivorship showed a positive effect. By promoting weight loss, improving HRQoL, and decreasing stress. They find that future research is needed to explore the impact of mHealth apps on patients with BC undergoing maintenance therapy [18]. The knowledge of the use of mobile apps for monitoring patients with BC during maintenance therapy is still limited.

Timeline

The study will be conducted over a duration of 3 years, encompassing well-defined stages. The planning of the study appears to be realistic and feasible within the specified timeline. Stage 4 is deemed feasible, and the deliverables are realistic given that the Bone@BC app has already been implemented in a proof-of-concept version.

Limitations

One of the limitations of this study is that the EORTC Library was chosen for selecting the ePROs in the app. Despite an overlap of primary treatment symptoms from chemotherapy and maintenance therapy with AI, more specific ePROs measurements could have been included in the app. Furthermore, it is important to note that the app primarily addresses symptoms associated with maintenance therapy. However, it may be worth considering the development of a future app that encompasses symptoms related to both primary and maintenance therapies.

Conclusions

Carefully developed with the involvement of patients and systematically validated, the Bone@BC app may have the potential to be a tool for optimal symptom management for patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy. This protocol outlines the BELIEVE@BC study, which seeks to enhance the care and comprehension of the needs and symptom burden experienced by patients with postmenopausal early BC during maintenance therapy. The patient-friendly version of the Bone@BC app may help to increase patients' self-efficacy. Increased self-efficacy can lead to improved confidence and engagement in their health care decisions and actions.

Acknowledgments

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jr. nr. 06-2019). The study is a part of the Healthy Living After Breast Cancer Research Program, the Models of Cancer Care Research Program, and the PRO-Oncology Research Program.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

TLJ, PS, HP, and KP were involved in conceptualization. TLJ contributed to the visualization and writing and preparing the original draft. KP, PS, HP, and GM were responsible for supervision. PS and TLJ were involved in project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: aromatase inhibitor
BC: breast cancer
CONSORT: Consolidated Standards of Reporting Trials
EORTC: European Organization for Research and Treatment of Cancer
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30
ePRO: electronic patient-reported outcome
ER+: estrogen receptor–positive
HADS: Hospital Anxiety and Depression Scale
HCP: health care professional
heiQ: Health Education Impact Questionnaire
HRQoL: health-related quality of life
mHealth: mobile health
MVP: minimum variable product
PCI: Patient Concerns Inventory list
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols
PRO: patient-reported outcome
SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale
SGPALS: Saltin-Grimby Physical Activity Level Scale
SUS-DK: System Usability Scale–Danish version

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Protocol

A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e60298

Abstract

Background: Low back pain (LBP) was the fifth most common reason for an emergency department (ED) visit in 2020-2021 in Australia, with >145,000 presentations. A total of one-third of these patients were subsequently admitted to the hospital. The admitted patient care accounts for half of the total health care expenditure on LBP in Australia.

Objective: The primary aim of the Back@Home study is to assess the effectiveness of a virtual hospital model of care to reduce the length of admission in people presenting to ED with musculoskeletal LBP. A secondary aim is to evaluate the acceptability and feasibility of the virtual hospital and our implementation strategy. We will also investigate rates of traditional hospital admission from the ED, representations and readmissions to the traditional hospital, demonstrate noninferiority of patient-reported outcomes, and assess cost-effectiveness of the new model.

Methods: This is a hybrid effectiveness-implementation type-I study. To evaluate effectiveness, we plan to conduct an interrupted time-series study at 3 metropolitan hospitals in Sydney, New South Wales, Australia. Eligible patients will include those aged 16 years or older with a primary diagnosis of musculoskeletal LBP presenting to the ED. The implementation strategy includes clinician education using multimedia resources, staff champions, and an "audit and feedback" process. The implementation of "Back@Home" will be evaluated over 12 months and compared to a 48-month preimplementation period using monthly time-series trends in the average length of hospital stay as the primary outcome. We will construct a plot of the observed and expected lines of trend based on the preimplementation period. Linear segmented regression will identify changes in the level and slope of fitted lines, indicating immediate effects of the intervention, as well as effects over time. The data will be fully anonymized, with informed consent collected for patient-reported outcomes.

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Results: As of December 6, 2023, a total of 108 patients have been cared for through Back@Home. A total of 6 patients have completed semistructured interviews regarding their experience of virtual hospital care for nonserious back pain. All outcomes will be evaluated at 6 months (August 2023) and 12 months post implementation (February 2024).

Conclusions: This study will serve to inform ongoing care delivery and implementation strategies of a novel model of care. If found to be effective, it may be adopted by other health districts, adapting the model to their unique local contexts.

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KEYWORDS

length of stay; back pain; musculoskeletal pain; telemedicine; hospital-based home care; mobile phone; home care; virtual care; remote care; virtual hospital; pain; telehealth; eHealth; musculoskeletal; implementation; model of care; back; cost; economic; readmission; hospital stay

Introduction

Background

Low back pain (LBP) was the fifth most common reason for an emergency department (ED) visit in 2020-2021 in Australia, with more than 145,000 presentations [1]. One-third of these patients were subsequently admitted to hospital. The current annual admission rates for spinal conditions are high in Australia, at 465 per 100,000 population, compared to 219 in the United Kingdom, 197 in the Netherlands, and 142 in Canada [2]. Admission rates following LBP presentations to ED are higher in Australia [3,4] than have been reported in the United States [5]. The potential contributors to high admission rates are differences in case mix [6], patient expectations of hospital admission when experiencing high levels of distress [7], and lack of alternative pathways for prompt pain management. These hospitalizations pose a significant burden on the health care system. In Australia, for example, admitted patient care of LBP lasts an average of 9 days and costs Aus $15,000 (US $10,000) per admission [8].

Most patients admitted to the hospital with a primary LBP diagnosis do not have a serious underlying condition and there is evidence that admissions carry the risk of harm. Our recent medical record review of 1982 admissions found that 57% of inpatients with provisionally diagnosed musculoskeletal LBP in ED were discharged with this same diagnosis [9]. Bed rest, as typically occurs with traditional hospital admission, is not recommended in LBP guidelines [10] as it can delay recovery. A recent study showed that 23% of LBP admissions had opioid-related complications and other serious events such as falls in hospital (4%) and hospital-acquired infections (1.4%) [11]. These patients could be diverted to more cost-effective and safer alternate clinical pathways.

Virtual hospitals have been proposed as a potential clinical pathway for people with LBP [12], to facilitate early discharge. Interviews with people admitted for acute LBP have identified that returning home as soon as possible is a key patient priority; however, patients fear a lack of support if discharged home [13]. There is also evidence from other conditions that virtual hospitals are cost-effective. Systematic reviews of “early supported discharge” have been shown to safely reduce the length of the hospital stay in adults with a range of medical conditions [14]. A recent US trial of virtual hospital admission for mixed acute medical conditions showed 38% lower costs for virtual hospital patients compared to traditional admissions, and reduced use of laboratory tests, imaging, and consultations [15]. The virtual hospital cohort had higher levels of patient satisfaction and lower rates of adverse events [15].

We currently lack alternatives to traditional hospital admission for patients with musculoskeletal LBP who present to Australian EDs and require acute clinical care. A virtual hospital has been implemented in Sydney Local Health District, Australia for COVID-19–positive patients and other patient cohorts [16], caring for over 16,000 patients to date [17]. In the virtual hospital, clinicians use technologies for remote patient monitoring and management [12]. Monitoring via daily clinician contact is designed to reduce representation to the ED while providing clinical support and pain management until the patient is able to link in with and attend outpatient services. Given the higher rates of potentially serious pathology in this cohort (compared to primary care), it is also a form of safety netting, allowing prompt escalation if required. Physical activity monitoring is designed to substitute regular reminders to mobilize as would be delivered on a traditional ward and encourage patients to slowly upgrade physical activity. A virtual hospital service, however, is yet to be formally evaluated in patients with musculoskeletal LBP.

Alongside the diagnostic challenge of LBP, is the difficulty of discharging patients home when safe mobility is not yet achieved. Some patients may still require short-term traditional hospital admission to allow for effective analgesia to facilitate mobility. Hence, in this study, we will evaluate the effectiveness of an early-supported discharge virtual hospital model of care, with traditional hospital length of stay as the primary outcome.

Aims

The main aims of the Back@Home study are to assess the effectiveness of a virtual hospital model of care for LBP on health service outcomes (eg, length of admission), patient-reported outcomes (eg, satisfaction with care), and costs. The secondary aims are to evaluate the acceptability and appropriateness of the virtual hospital model of care for LBP, as well as the feasibility and fidelity of our multifaceted implementation strategy.

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Methods

Study Design

This is a hybrid effectiveness-implementation type-I study [18]. This study design will allow us to assess the effectiveness of a new virtual hospital model of care for LBP on health services outcomes while assessing the feasibility and acceptability of the new model and our multifaceted implementation strategy, as described by Curran et al [18]. We have used the guidance for conducting implementation trials by Pearson et al [19] and Proctor et al [20] to design this study.

Setting

This study will be conducted at 3 public hospitals in Sydney, New South Wales, Australia. The hospitals have a combined 169,000 ED attendances per year, with 650,000 total "bed days" available annually, averaging 1530 inpatients per day [21].

Population

To identify the study population, Systematized Nomenclature of Medicine Clinical Terms-Australian (SNOMED-CT-AU) diagnosis codes will be used to select patients in the ED aged 16 years and older with a primary discharge diagnosis related to musculoskeletal LBP. Those with an ED diagnosis code of a "serious" LBP condition (eg, vertebral fracture, spinal abscess, and cauda equina syndrome) will be excluded. We will then use inpatient discharge diagnosis codes (*International Classification of Diseases, Tenth Revision, Australian Modification* [*ICD-10 AM*]) to classify the LBP admissions as "serious" or "musculoskeletal" (ie, nonspecific LBP and lumbosacral radicular pain). Only data from admissions where inpatient discharge diagnosis codes are musculoskeletal LBP admissions will be evaluated.

Patients who presented to the ED with a primary diagnosis related to musculoskeletal LBP and were discharged without admission into a short stay or inpatient unit will be included in the data analysis to determine rates of hospital admission.

Intervention

Patients with LBP requiring admission in ED short stay or inpatient units will be assessed by senior ED staff. Eligible patients will be referred to the "Back@Home" virtual LBP service by the ED medical officer, in consultation with local rheumatology or general medicine admitting teams. The eligibility criteria for the virtual hospital are people aged 16 years and older diagnosed with musculoskeletal LBP, with or without radicular pain, requiring a higher level of clinical support above standard discharge home (see Figure 1).

Figure 1. Virtual low back pain service workflows. ED: Emergency Department; LBP: low back pain.

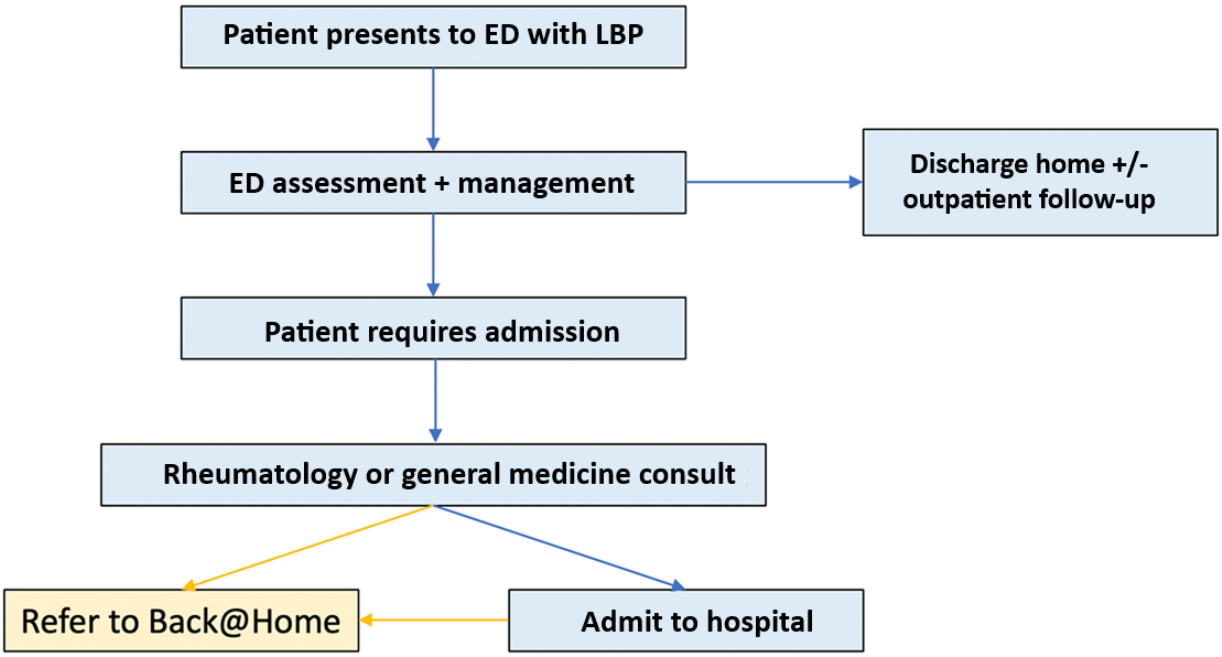

Back@Home, a service run by Royal Prince Alfred Hospital (RPA) Virtual Hospital, will provide virtual "Hospital in the Home" care, including home visits, video calls, and remote monitoring. Eligible patients already admitted to the inpatient ward will also be referred to "Back@Home" to facilitate earlier discharge. Patients will be remotely monitored from home, and have 24/7 access to hospital-based clinicians through a "virtual" care center. An escalation pathway will be available if a patient's condition deteriorates at home, and traditional admission, expedited imaging, or intervention is deemed necessary.

Medical care will be provided by virtual hospital physicians and nurses, with consultations from rheumatology specialists provided as required. All patients will be virtually assessed and treated by a physiotherapist, with additional assessments provided by occupational therapists, psychologists, and social workers as required.

Videoconferencing calls will be used to collect clinical observations and provide care. If required, patients will receive home visits from a physiotherapist [17]. The need for home visits will be decided by the multidisciplinary team (physician, nurse, and physiotherapist) during daily clinical reviews, in

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response to patient needs. If a patient appears to not be coping well at home and is at risk of ED representation, a home visit will be scheduled.

Remote monitoring of physical activity, such as step count, will be enabled via an activity tracker. The wearable device used (Garmin Vivovit 4) is a validated method of recording sleep cycles and sedentary and active time in community settings [22,23]. Patients will be able to report activity measures to their virtual physiotherapist during daily video calls, assisting in goal setting and behavioral health coaching.

Care will be provided through a variety of technologies as appropriate. SMS, telephone calls, videoconferencing calls (Zoom; Zoom Video Communications), patient information sheets emailed directly to patients, as well as access to the "Physitrack" smartphone app for the provision of health information content and exercise programs.

Traditionally admitted patients will receive usual clinical care, with a referral for physiotherapy mobility assessment if required, as per standard ward protocols. They will be eligible for referral to Back@Home to facilitate early supported discharge, if appropriate.

Implementation Strategy

The implementation strategy will last for 3 months at each site. The "Knowledge to Action Framework" [24] (see Figure 2) was used to guide a research program to develop and evaluate the implementation of Back@Home. The framework structure includes identifying a clinical problem, and then developing evidence-based potential solutions while adapting these to the local context, evaluating the solution, and monitoring outcomes.

Figure 2. Knowledge to action framework. ED: Emergency Department; LBP: low back pain.

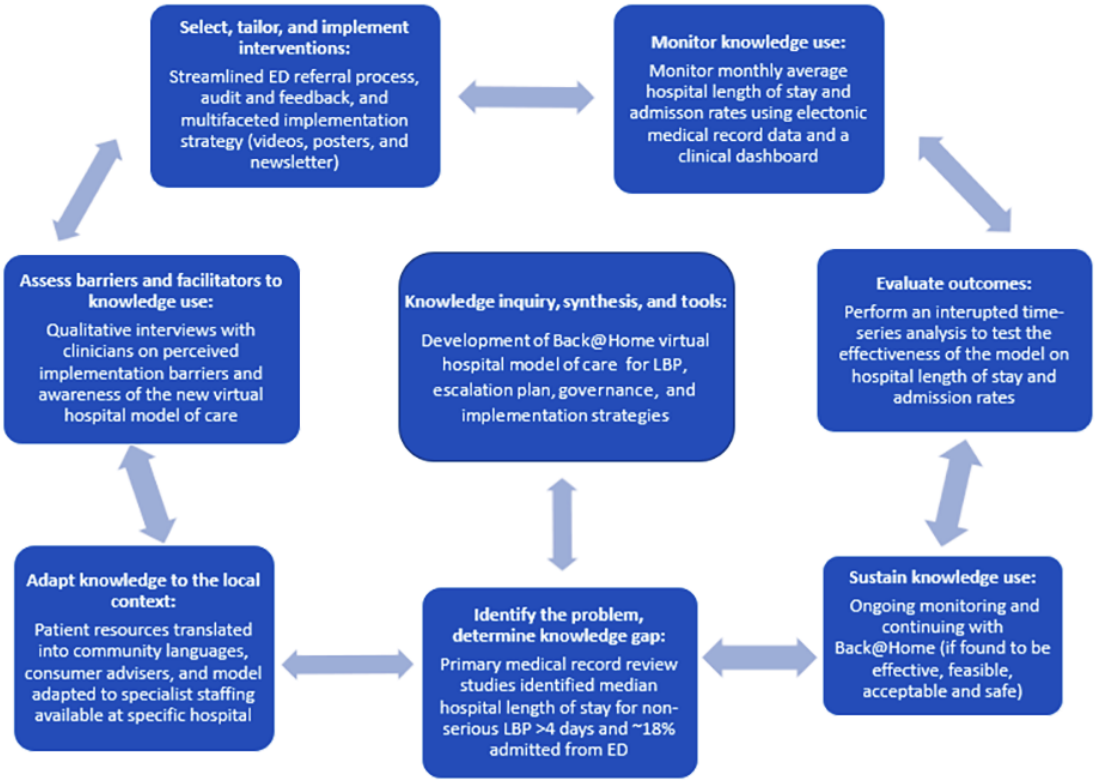

Semistructured interviews with hospital clinicians regarding perceived barriers and facilitators to implementation have informed the current design of the model of care [7]. Based on clinicians' input, the Back@Home model of care will incorporate the loan of internet-enabled devices, health care interpreters, and written resources translated into community languages to facilitate more equitable access to care for marginalized groups. Feedback was provided by the Director of Aboriginal Health and the Aboriginal Cultural Support Team. Consultation on the model was also provided by ED medical officers, rheumatology, general medicine, and allied health departments, as well as nurse practitioners and social workers.

We will explore additional local barriers to implementation, design, and implement strategies to address these barriers, and monitor clinical practice and clinician behavior change. The evaluation will determine the effectiveness of the model of care, and if found effective, we will develop strategies to maintain health care system changes (see Figure 1).

To increase the uptake of the Back@Home model of care, we plan to use several implementation strategies that have been previously shown to be effective in changing professional behavior. First, staff training will be delivered by Back@Home investigators (MJT, ER, MM, and OH) at scheduled staff education sessions attended by physiotherapists, nurses, registrars, trainees, and consultants in ED and general medicine. Sessions will last 15 minutes and be delivered before implementation and at 1 and 3 months post implementation. Training will describe the process of referral to virtual care, deliver updates on implementation progress, and provide a forum to raise concerns or questions. Second, key local opinion leaders [25], in the form of "staff champions" will be provided with training. These staff will remind all clinical staff about

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Back@Home as an option for patients with musculoskeletal LBP requiring admission and will be identified by wearing a badge with the Back@Home logo. The ED primary care physiotherapist will play a key role in championing the Back@Home model of care. Third, a summary card containing admission criteria and contact details for the virtual hospital will be provided to relevant staff, which can be attached to staff lanyards for easy access (if permitted). This printed material will be used to reinforce the content of educational sessions [26,27]. Fourth, a monthly email update will be sent to ED, general medicine, and rheumatology staff regarding the length of hospital stay and rates of admission to traditional hospitals. Audit and feedback strategies have been shown to be effective in influencing health professionals' behavior [28], and in supporting back pain model of care implementation strategies [29].

Evaluation

Health Service Outcomes

The health service outcomes include (1) monthly mean length of hospital stay (ED short stay units and inpatient units) in those admitted as a traditional inpatient following an ED presentation for musculoskeletal LBP (primary outcome; Table 1); (2) monthly proportion of ED musculoskeletal LBP presentations that result in traditional hospital admissions (ED short stay or inpatient units); (3) monthly proportion of admitted patients representing to traditional hospital, including representations to the ED within 48 hours since discharge and readmissions to an inpatient unit within 28 days; and (4) mean and total hospital health care costs per month, for patients admitted to traditional and virtual hospitals.

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Table 1. Evaluation plan.

Outcome dimension	Outcome	Outcome definition	Data source	Data collection and analysis period
Service	(1) Length of hospital stay; (2) inpatient admission; (3) rerepresentations; and (4) readmissions to inpatient units	(1) Monthly mean length of hospital stay (ED[a] short stay units and inpatient units) in those admitted as traditional inpatients following an ED presentation for musculoskeletal LBP[b]; (2) monthly proportion of ED musculoskeletal LBP presentations that result in traditional hospital admissions (ED short stay or inpatient units); (3) monthly proportion of admitted patients representing to a traditional hospital, including representations to the ED within 48 hours since discharge; and (4) monthly proportion of admitted patients who are readmissions to an inpatient unit within 28 days.	1-4: eMR[c]	Baseline: 2016 January to 2023 February; T1[d]: 2023 August; T2[e]: 2024 February
Implementation	(1) Acceptability; (2) appropriateness; (3) feasibility; and (4) fidelity	(1-3) acceptability, appropriateness, and feasibility of the Back@Home "Model of Care" and implementation strategies (posters, staff training, videos, and newsletter); and (4) fidelity of the delivery of implementation strategies as planned.	(1-3) Semistructured interviews with clinicians and patients; (4) logbook of implementation delivery	T1: 2023 August
Patient	(1) Pain intensity; (2) physical function; (3) satisfaction with care; and (4) adverse events	(1) Numeric rating pain scale (0-10); (2) PROMIS[f] Physical Function-6a; (3) global satisfaction with care for traditional and virtual admissions (0-10 points) and patient-reported experience measures as routinely collected by the virtual hospital (26-item survey); and (4) proportion of patients experiencing any AE[g]; frequency of AEs for virtual admissions	(1-3) Patient survey; (4) eMR	Collected at 2 and 4 weeks post ED presentation or during admission (adverse events), analyzed at T1 and T2
Process	(1) Diagnostic tests ordered; (2) pain medicines used; (3) video and phone calls; (4) home visits received; (5) Physitrack app use; and (6) Physitrack and activity tracker usefulness	(1) Proportion of virtually admitted patients receiving diagnostic tests; (2) proportion of virtually admitted patients prescribed specific medicines; (3) number and frequency of video consultations with virtual hospital clinical staff; (4) number and frequency of clinician home visits; (5) usage rates of the Physitrack app by patients (log-ins, viewing, and marked completion of exercise program); and (6) patient-reported experience measures questions 7 and 9 (5-point scale).	(1-4) eMR; (5) Physitrack app; and (6) Patient-Reported Experience Measure survey	Collected during virtual admission, analyzed at T1 and T2
Health economic	Hospital admission costs	Cost of delivering virtual care compared to inpatient care for nonserious low back pain.	eMR and finance reporting systems	Collected during admission and analyzed at T1 and T2

[a]ED: Emergency Department.

[b]LBP: low back pain.

[c]eMR: electronic medical record.

[d]T1: 6 months post implementation.

[e]T2: 12 months post implementation.

[f]PROMIS: Patient-Reported Outcomes Measurement Information System.

[g]AE: adverse event.

Implementation Outcomes

Implementation outcomes discussed in clinician and patient interviews will include (1) acceptability, appropriateness, and feasibility of the model of care to clinicians and the health service evaluated at 6 months using semistructured interviews [30] and (2) fidelity to planned implementation at 6 months using a logbook of implementation.

Patient-Reported Outcomes

Patient-reported outcomes will be collected at 2 and 4 weeks following hospital admission from patients admitted to traditional and virtual hospitals. Outcomes include average pain intensity in the past week (Numeric Rating Scale, range 0-10), Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form—Physical Function 6b (range 6-30), and global rating of satisfaction with care (range 0-10).

Process Measures (Virtual Hospital Admissions Only)

First, the proportion of virtually admitted patients receiving diagnostic tests, by type: laboratory tests; lumbar imaging tests: plain radiography (x-ray), computerized tomography scan, magnetic resonance imaging; and per month.

Second, the proportion of virtually admitted patients prescribed specific medicines, per month. Pain medicines will be classified according to the Anatomical Therapeutic Chemical (ATC) classification systems. The drug dosage regimens will also be collected for the following groups of medicines: simple

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analgesics (ie, paracetamol); nonsteroidal anti-inflammatory drugs; weak opioids (eg, tramadol and codeine); strong opioids (eg, oxycodone and morphine); muscle relaxants; benzodiazepines; antiepileptics; antidepressants; and corticosteroids.

Third, the usage rates of the Physitrack app by patients (log-ins, viewing, and marked completion of exercise program). Fourth, the number and frequency of video consultations with virtual hospital clinical staff. Fifth, the number and frequency of face-to-face consultations (home visits) with staff. Sixth, the number and frequency of escalations of care (patient transferred to hospital), and adverse events. Seventh, the patient-reported experience measures as routinely collected by the virtual hospital, with additional questions relevant to Back@Home patients (26-item survey).

Data Collection

Health Service Outcomes

We will extract primary and secondary health care use data from electronic medical records. Data extracted will include patient demographics (eg, age, gender, and postcode), ED presentation and inpatient admission or discharge date, length of ED and admission stay, discharge primary and secondary Systematized Nomenclature of Medicine (SNOMED)/*ICD-10* codes, diagnostic tests used (eg, laboratory tests and imaging), pain medicines received, specialist and allied health consultations, and health care costs. Hospital-acquired complications or adverse events will be identified via Classification of Hospital Acquired Diagnoses (CHADx) codes present in *ICD-10 AM* data [30]. Patient medical record number, encounter or visit identifier will be replaced by study ID as part of the data extraction process, resulting in deidentified data.

Implementation Outcomes

Semistructured interviews will be conducted with key clinical staff and hospital managers at the implementation site, as well as those involved in delivering virtual care. Purposeful sampling will aim for input from physiotherapists, nurses, ED medical officers, and rheumatologists. Patients who have experienced Back@Home virtual care will also be asked to participate (approved by Sydney Local Health District X21-0094 and 2021/ETH00591).

The fidelity of training-related implementation delivery will be assessed via a logbook of staff training, noting the number of sessions delivered, session delivery mode, and number of attendees.

Patient-Reported Outcomes

Patients with musculoskeletal LBP as the primary reason for admission (to traditional or virtual hospitals) will be eligible to complete the patient-reported outcome survey. Before implementation, we will use electronic medical records to identify a cohort that would have likely been eligible for virtual admission if it were available. This will include traditionally admitted patients with a Waterlow Mobility Score of 0-3 (not bed-bound) on admission, with a diagnosis of musculoskeletal LBP. All virtually admitted patients with LBP will be eligible. Automated text message invitations will be sent to eligible patients (via REDCap [Research Electronic Data Capture; Vanderbilt University] and Twilio) containing a link to an web-based survey, at 2 and 4 weeks following the ED presentation. One reminder message will be sent to nonresponders, and patients who do not respond to the text message will be followed up with a telephone call and offered the opportunity to ask any questions regarding participation or complete the survey by telephone. This process will be used to maximize the response rate of the surveys and has been proven to be feasible [31].

Statistical Analysis Plan

Health Service Outcomes

Time-series trends during a retrospective 48-month period before the implementation of the new model of care will be compared with trends during a 12-month postimplementation period. Preliminary analysis will be conducted at 6 months post implementation. We will display the length of admissions as monthly averages and construct a plot of the observed and expected lines of the trend based on the preimplementation period. Linear segmented regression will identify changes in the level and slope of fitted lines. The standard interrupted time series model that will be used is

In this equation, Y_t is the outcome variable (eg, length of admission) measured at each equally spaced time point t (monthly). β_0 represents the intercept or starting level of the outcome variable and β_1, the slope or trajectory of the outcome variable until the introduction of the intervention. T_t represents the month of the initial ED presentation with T_0 representing the first month (2017 January). β_2 represents the change in the level of the outcome that occurs in the period immediately following the introduction of the intervention (compared with what would have happened in the absence of the intervention). β_3 represents the difference between preintervention and postintervention slopes of the outcome. Thus, we look for significant differences in β_2 to indicate an immediate treatment effect, and in β_3 to indicate a treatment effect over time.

Data will be analyzed using SAS software (version 9.4; SAS Institute). Descriptive statistics will be used for patient demographics and clinical characteristics. Categorical variables will be described with frequencies (%) and continuous variables will be described with means and SDs.

To account for fluctuations in preimplementation hospital admissions due to COVID-19 pandemic–related restrictions, a time series analysis will account for these time periods. Restricted periods will be considered as February 1 to June 30, 2020; June 1 to December 1, 2021; and January 1 to May 1, 2022.

Patient-Reported Outcomes

Patient-reported secondary outcomes will include pain, physical function, and satisfaction with care at 2 and 4 weeks following admission. Group sample sizes of 100 eligible patients admitted to traditional hospital wards and 100 patients admitted to RPA

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Virtual Hospital, will be required to achieve 80% power to detect a noninferiority 1-point difference in patient-reported outcomes for satisfaction with care (0-10 continuous scale) between groups using a 1-sided, 2-sample equal-variance *t* test. The margin of noninferiority will be –1. The actual difference between the means will be assumed to be 0. The significance level (α) of the test will be set at .025. The data will be drawn from populations with an SD of 2.5 in both groups.

Ethical Considerations

This investigation will be conducted in full compliance with the Declaration of Helsinki. Ethics approval has been granted by the Ethics Review Committee of Royal Prince Alfred Hospital (protocol X21-0278 and 2021/ETH10967). A waiver of consent has been approved for routinely collected data sourced from electronic medical records. Study data will be fully deidentified, to protect patient, clinician privacy, and confidentiality. Informed consent will be collected for all patient-reported outcomes. No compensation will be offered for participation.

Patient and Public Involvement

The virtual hospital model of care was developed with the assistance of semistructured interviews with clinicians from several disciplines across 3 metropolitan hospitals. Clinicians from the departments of physiotherapy, rheumatology, and emergency medicine participated in a co-design process with researchers and administrators at RPA Virtual Hospital at Sydney Local Health District.

Economic Evaluation Plan

An economic evaluation will be undertaken from the health system perspective. Costs associated with implementing Back@Home virtual care and patients' health service use will be measured, using a combination of electronic medical records and financial trial records. Intervention-related costs include the development of training materials and salaried time of staff attending training workshops, changes in workload for staff delivering virtual care and costs related to information technology support and maintenance of the virtual network. Health service costs will be measured using Independent Health and Aged Care Pricing Authority national weighted activity units for admitted inpatient hospital and ED presentations; prescription and over-the-counter medications using the Pharmaceutical Benefits Scheme and pharmacy prices. All costs will be reported in Australian dollars. Where necessary, costs will be converted to 2023 prices using the health consumer price index published by the Australian Bureau of Statistics. Costs and effects will be discounted where appropriate.

We plan to conduct a cost-effectiveness analysis alongside this time series analysis with data from the intervention site. Similar to the time series model for health service outcomes, a generalized linear model with a gamma distribution and logarithmic link function will be used for the segmented regression analysis of health care costs. An incremental cost-effectiveness ratio will be calculated for the health services outcomes: length of stay and hospital admissions. This will be presented as incremental costs per bed day avoided and incremental cost per hospital admission avoided. Nonparametric bootstrapping with 5000 replications will be used to estimate the 95% CIs around the incremental cost and effect pairs for both health services outcomes. These will be presented on an incremental cost-effectiveness plane. We also plan to explore the cost-effectiveness using the patient outcomes from this study. If the patient outcomes analysis shows noninferiority as hypothesized, we will perform a cost-minimization analysis by comparing the cost between the control and intervention phases.

Results

We will collect data from January 1, 2017, to September 30, 2024, and a 60-month period within this time frame will be used in the analysis, determined by the implementation schedule for the new model of care. Back@Home participant data will be collected from February 2023, following roll out of the service. For primary and secondary health service outcomes, we expect to collect data from approximately 12,500 patients with musculoskeletal LBP attending the 3 study EDs over a 5-year period, via the electronic medical record system. Interim process evaluation and implementation outcomes are expected to be published in early 2024, and the final study results are expected to be published in 2025. As of December 6, 2023, a total of 108 patients have been cared for through Back@Home. A total of 6 patients have completed semistructured interviews regarding their experience of virtual hospital care for nonserious back pain. All outcomes will be evaluated at 6 months (2023 August) and 12 months post implementation (2024 February).

Discussion

This study will investigate the implementation of a novel model of care for nonserious back pain, delivered through a virtual hospital. Process evaluation will be used to inform further iterations of the service, guided by the Knowledge To Action framework [24]. We anticipate that the feasibility of implementing Back@Home will be demonstrated, along with the acceptability of the model of care to clinicians and patients and cost-effectiveness. Additionally, we hypothesize that patient-reported outcomes (pain and satisfaction with care) will be noninferior to traditional hospital admission. Interpretation of the patient-reported outcomes may be limited by response rate and strategies have been planned to optimize the response rate.

The interrupted time-series design has been commonly used to evaluate the impact of new patient pathways on admission rates, length of stay, and ED representation [32-34] for a variety of health conditions. We hypothesize that following the introduction of Back@Home, hospital length of stay, and admission rates for LBP will be reduced, compared to preimplementation measures. If proven to be safe, acceptable, effective, and cost-effective, virtual care for nonserious back pain could be expanded to other health districts in New South Wales, and potentially other states. Implementation in other jurisdictions would depend on staffing and technological resources to deliver virtual care.

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The Back@Home Investigators are: Alla Melman, Danielle M Coombs, Qiang Li, Laurent Billot, Bethan Richards, Eileen Rogan, Ananthila Anandacoomarasamy, Owen Hutchings, Min Jiat Teng, Kirsten McCaffery, Mona Marabani, Miranda Shaw, Cassandra Dearing, Ian Harris, Rachelle Buchbinder, Chris Needs, James Edwards, Narcyz Ghinea, Michael Dinh, Dane Chalkley, Rachael Dodd, Chris G Maher, Gustavo C Machado.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AM, CGM, and GCM conceived the research evaluation. AM drafted the protocol with guidance from GCM, DMC, and CGM. MJT, DMC, OH, MM, and ER are involved in developing and implementing the model of care. QL and LB contributed to the statistical analysis plan. All authors revised and reviewed the final protocol paper.

Conflicts of Interest

MJT is a physiotherapist at RPA Virtual Hospital.

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Abbreviations

ATC: Anatomical Therapeutic Chemical

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CHADx: Classification of Hospital Acquired Diagnoses
ED: emergency department
ICD-10 AM: International Classification of Diseases, Tenth Revision, Australian Modification
LBP: low back pain
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
RPA: Royal Prince Alfred Hospital
SNOMED: Systematized Nomenclature of Medicine
SNOMED-CT-AU: Systematized Nomenclature of Medicine Clinical Terms-Australian

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Protocol

Investigating Digital Patient-Reported Outcome Measures in Patient-Centered Diabetes Specialist Outpatient Care (DigiDiaS): Protocol for a Multimethod Prospective Observational Study

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Abstract

Background: Living with type 1 diabetes is challenging, and to support self-management, repeated consultations in specialist outpatient care are often required. The emergence of new digital solutions has revolutionized how health care services can be patient centered, providing unprecedented opportunities for flexible, high-quality care. However, there is a lack of studies exploring how the use of digital patient-reported outcome measures (PROMs) for flexible specialist care affects diabetes self-management. To provide new knowledge on the relevance of using PROMs in standard care, we have designed a multimethod prospective study.

Objective: The overall aim of this protocol is to describe our prospective multimethod observational study designed to investigate digital PROMs in a routine specialist outpatient setting for flexible patient-centered diabetes care (DigiDiaS).

Methods: This protocol outlines the design of a multimethod prospective observational cohort study that includes data from electronic health records, self-reported questionnaires, clinical consultation field observations, and individual in-depth interviews with patients and diabetes health care personnel. All patients with type 1 diabetes at a designated outpatient clinic were invited to participate and use the digital PROM implemented in clinical care. Both users and nonusers of the digital PROM were eligible for the prospective study, allowing for a comparison of the two groups. Data were collected at baseline and after 12 months, including self-management as the primary outcome assessed using the Patient Activation Measure, along with the secondary outcomes of digital health literacy, quality of life, health economy, and clinical variables such as glycated hemoglobin.

Results: The digital solution was implemented for routine clinical care in the department in November 2021, and data collection for the prospective study started in October 2022. As of September 6, 2023, 84.6% (186/220) of patients among those in the digital PROM and 15.5% (34/220) of patients among the nonusers have consented to participate. We expect the study to have enough participants by the autumn of 2023. With 1 year of follow-up, the results are expected by spring 2025.

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Conclusions: In conclusion, a multimethod prospective observational cohort study can offer valuable insights into the relevance, effectiveness, and acceptability of digital tools using PROMs in diabetes specialist care. Such knowledge is crucial for achieving broad and successful implementation and use of these tools in a large diabetes outpatient clinic.

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KEYWORDS

patient-reported outcome measures; PROMs; diabetes mellitus; DM; type 1; patient acceptance of health care; telemedicine; mobile apps; mobile phone

Introduction

Background

Living with type 1 diabetes can impact one's daily life [1]. Self-management is required to reduce late complications, but it can be exhausting and stressful [2], and the burden of living with type 1 diabetes often impacts a person's mental health [3,4]. However, there is a significant variation in the needs and concerns of people with type 1 diabetes and varying perceptions of the diabetes burden. To improve patient-centered diabetes care, targeting unique needs and perspectives in both clinical care and research is necessary [5].

A recent systematic review has provided evidence for the effect of an integrated care model in diabetes care on essential patient outcomes [6], which is in line with clinical recommendations [7]. Thus, the increased involvement of patients is warranted. One way of increasing the involvement and bringing the voice of the patients forward is through "patient-reported outcomes" (PROs), that is, patients' responses to outcomes relevant to their condition [8]. Therefore, PRO measures (PROMs) are the measures used to assess PROs systematically.

PROMs in diabetes care can improve patient-centered care by collecting information directly from patients to obtain a complete picture of the patient's health status. Health care providers could better understand their patients' needs and concerns and tailor care to meet these individual needs [8,9]. However, it has been challenging to select the tools for PRO measurement to ensure that they are valid and responsive to changes in patient health status [10]. In addition, the clinical value of the PROMs has not been established, and the adaptation of standardized PROMs used in research might not be straightforward because the measures are usually lengthy and time-consuming to answer for the patient and to interpret for the clinician. The use of PROMs in previous research has varied widely in terms of using one or several PROMs, using disease-specific or generic PROMs, and determining at what times or under which conditions the measures are used [11]. The use of PROMs in diabetes care has become increasingly multidimensional, focusing on a range of patient outcomes and highlighting the need for a broader multidisciplinary and shared effort in clinical practice [12].

Digital development has affected the use of digital PROMs in the last decades, offering easier and more timely access to patient reports and an easier and more timely way of evaluating patient reports for health care personnel [13,14]. Digital PROMs have been successfully implemented in various services [15], including diabetes [16,17]. Despite the many benefits of digital PROMs, the reasons for the lack of use among patients remain, including a lack of motivation, technical barriers, emotional distress, and a reduced ability to participate in a digital PROM [18].

To ensure the patients' participation in digital PROMs as intended by the health services, research on the patients' perspectives is essential to providing a more complete understanding of health care needs and preferences. Patients' acceptance of digital support is crucial and can affect their engagement and adherence [19]. Furthermore, patient perception, acceptability, and engagement in designing and implementing digital health intervention evaluations remain crucial [20]. By understanding and addressing the concerns and barriers to digital solutions faced by patients who may be uncomfortable or unable to engage in digital support, we can promote more equitable access to health care services. Similarly, measuring technology acceptability after use—rather than predicted use—might provide valuable insights into users' perceptions and experiences of technology, helping to identify areas for improvement [21].

An increasing number of patients are in need of care, with limited resources and staff to ensure their needs, which holds true in diabetes care [22]. Thus, implementing digital PROMs to support self-management in line with patient-centered care might alleviate the burden on both patients and services [23]. However, further research is needed to fully understand the interactions in these new services among the patient, the clinicians, and the digital solution to understand the effects and implications on the users.

Aims

The overall aim of this protocol is to describe our prospective multimethod observational study designed to investigate digital PROMs in a routine specialist outpatient setting for flexible patient-centered diabetes care. Specifically, the DigiDiaS will (1) quantitatively investigate and describe the characteristics of patients with type 1 diabetes participating in a digital PROM in comparison with patients in traditional follow-up and evaluate the effect of participating in digital PROMs on clinical outcomes, self-management, diabetes distress, quality of life, and health care utilization and (2) qualitatively, through observations and qualitative interviews, assess patients' acceptability of consultations prepared and supported by digital and flexible services using PROMs.

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Methods

Study Design

This protocol describes a prospective, multimethod observational cohort study to investigate the relevance and effects of digital and flexible services using PROMs. The PROM in the planned trial is based on DiabetesFlex, which was developed and implemented in Danish health care services for type 1 diabetes [16,17,24], and it has been adapted to a Norwegian digital context in preparation for this study [25]. Consenting participants will be enrolled for 12 months, with assessments at baseline (T0) and 12 months (T1), with additional data from electronic health records, field observations of clinical video, or in-person consultations, along with individual in-depth interviews with the patients and diabetes health care personnel (Figure 1). Field observations and in-depth interviews among the patients participating in the digital PROMs will be conducted at any given time for those not participating in the survey and after completing T1 for those consenting to the survey study to avoid contamination of the survey and interview data.

This study is a collaboration between Akershus University Hospital and Oslo Metropolitan University—OsloMet and will be conducted at the Endocrinological Outpatient Clinic at Akershus University Hospital.

This protocol is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance [26]. The reporting of the proposed study and participation in digital tools and PROMs in clinical practice will be guided by better reporting of interventions: template for intervention description and replication (TIDieR) [27] and the PRO reporting guide [28].

Figure 1. Study flow.

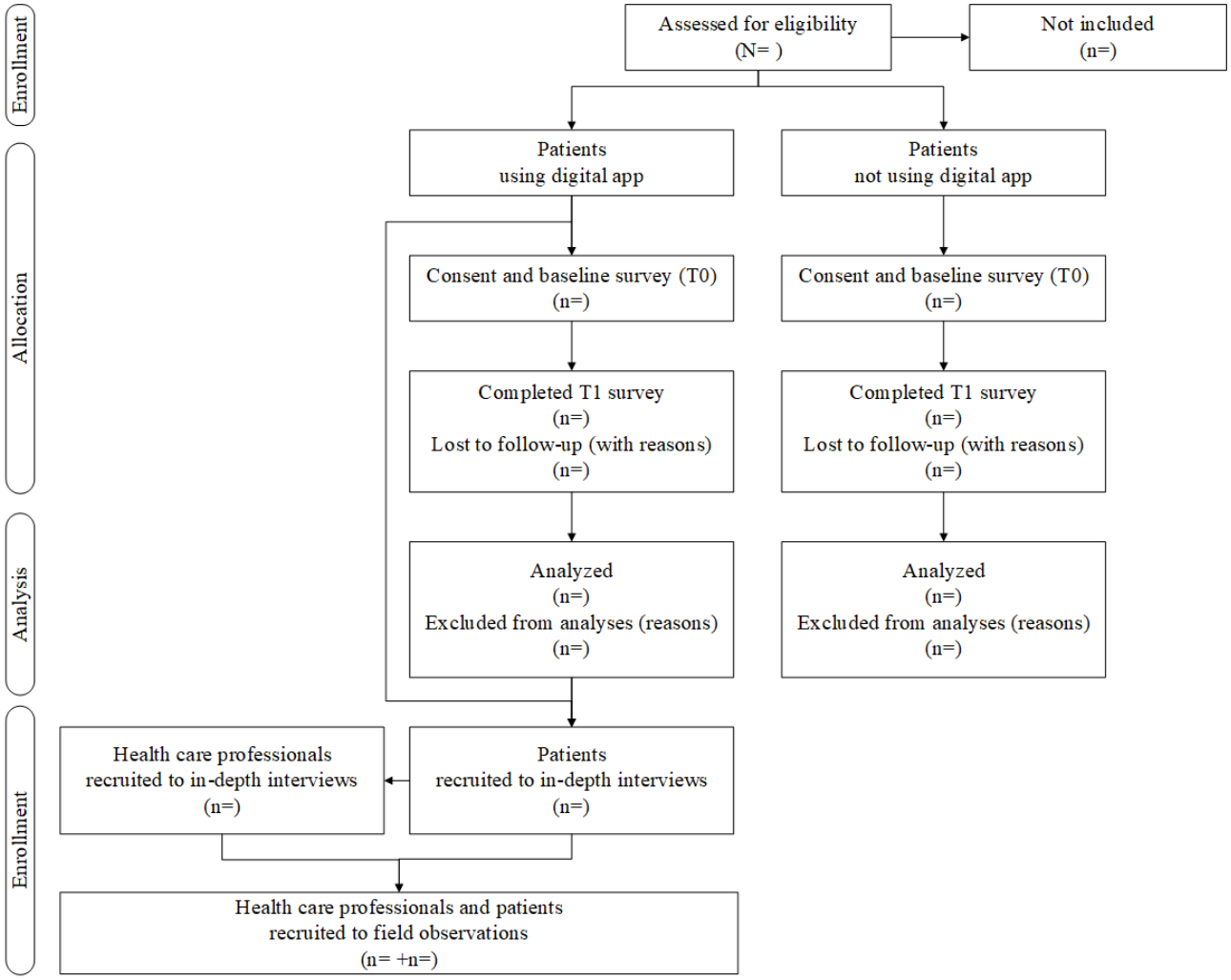

Overview of the Implemented Service

A Digital and Flexible Service

All patients at the clinic will be offered to engage with digital and flexible services in addition to standard care. If they are interested, the digital service will be available through a mobile app on their private smartphone and will contain functions for self-monitoring, chat, video consultations, and PROMs before or between consultations. The digital PROMs implemented in this study have been described in detail elsewhere [25]. Standard care at the outpatient clinic includes a once-a-year consultation with an endocrinologist, a diabetes specialist nurse, or both. In the given situations, patients have ≥1 added consultation a year [29]. The clinic offers video-based and physical face-to-face consultations based on the patient's preferences and needs for care through solutions approved by the hospital.

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Digital Platform: Dignio Connected Care

Although the study does not focus on evaluating the functionality of a specific digital solution, the clinical implementation of elements from DiabetesFlex will be carried out through the digital platform Dignio Connected Care [30]. The MyDignio and DignioPrevent interfaces are presented in Multimedia Appendices 1 and 2. The patient app MyDignio allows patients to store health data and communicate with health care personnel at the clinic through self-monitoring, answering PROM questionnaires sent between consultations, communicating through a message system (chat), or engaging in video consultations with their health care personnel [31]. The health care personnel software DignioPrevent offers a flexible way of reviewing patent-reported data, using the traffic light principle to guide and prioritize which patients need attention. Dignio Connected Care allows patients to reflect on self-care and needs, take preventive actions, and prepare for consultations, both for patients to give responses of their prioritizing of needs and for the health care personnel to obtain an overview of the complexity, personalize the care, and offer the right level of expertise at the right time [25,32]. The platform facilitates a more informed dialogue between patients and health care personnel based on experience and knowledge [33]. It has also been suggested to make specialist health care more fluid and accessible to patients [34].

Information and Training

The patients will receive information regarding the digital service in consultation, regardless of this research project. If they consent to engage in the digital service, more detailed information on the MyDignio app will be provided by the diabetes specialist nurse. An invitation to download MyDignio will be sent to the patient's smartphone in consultation, and if they wish and have their national ID with them, they can download MyDignio immediately. The patient interface is easy and intuitive, and extensive training should not be required for most patients.

As the patient interface, the health care personnel site DignioPrevent has been developed to be simple and intuitive. The diabetes specialist nurses have been trained in using the Dignio Connected Care personnel interface DignioPrevent, by personnel from the information and communications technology unit at the university hospital, in addition to a close collaboration with personnel from Dignio Connected Care. Similarly, diabetes health care personnel will receive training in the video consultation systems used in the clinic.

Participants

Patient Participants

Patients with type 1 diabetes at the Endocrinological Outpatient Clinic at Akershus University Hospital who meet the inclusion criteria are eligible for enrollment. The inclusion criteria include age ≥18 years, a type 1 diabetes diagnosis, and the ability to read Norwegian. Both users and nonusers of the MyDignio platform are eligible. The exclusion criteria are type 2 diabetes, gestational diabetes, or any cognitive impairment inflicting their ability to participate in the research project. Patients with type 1 diabetes are not eligible if they are pregnant at the time of recruitment, and they will be excluded from follow-up if they become pregnant during the 12 months because of an expected change in response caused by the pregnancy and not digital care. They will still be able to participate in the flexible digital care model.

Health Care Personnel Participants

In the outpatient clinic, health secretaries, diabetes specialist nurses, and physicians will be involved in the digital platform. The health secretaries send the PROM in the app to the patients along with their scheduled appointments. If the patients wish to change their scheduled appointment, the health secretaries can arrange this, but they do not handle any medical questions, assessments of PRO responses, or other messages in the system. The diabetes specialist nurses are responsible for all questions from the patients and PRO responses, including the need for a consultation, new tasks in the system, and any need for information. The physicians handle the PRO response for the yearly control in the system and otherwise consult and guide the diabetes specialist nurses if needed. Except for the yearly physician consultation, the diabetes specialist nurses are responsible for all consultations with patients with type 1 diabetes at the clinic. Thus, both diabetes specialist nurses and physicians are eligible for participation in field observations of their consultations with patients in the digital service and for in-depth interviews.

Procedures

Eligible patients will be identified and given brief information at the outpatient clinic by health care professional staff. If the patients are interested, they will be contacted by a researcher (IS or MAM). If they consent to participate after receiving oral and written information, their written consent will be secured either through Nettskjema digital consent or through a paper-based consent form. Immediately after their consent, the patients can choose whether they will fill out the baseline questionnaire digitally through Nettskjema, paper-based in the mail at home with a free return envelope, or through a telephone interview with a researcher (IS or MAM). For consenting participants not responding to or returning the baseline questionnaire or the 1-year follow-up, an automatic email reminder will be sent, followed by a phone call reminder and a SMS text message reminder if they still do not reply. The digital consents and the digital questionnaire data will be securely stored in the Service for Sensitive Data at the University in Oslo. Paper-based consent forms and questionnaires will be securely locked in a safe for storage, and the paper-based questionnaires will be manually entered into SPSS (IBM Corp). Data from the patients' medical records will be extracted by a researcher (IS), and 10% of the extractions will be controlled by a second researcher (MAM) to ensure valid and reliable data extraction.

Health care personnel will be recruited for 2 purposes: in-depth interviews and observations of consultations with patients engaged in the digital PROM. The personnel will be recruited from the department, and written informed consent will be secured using the same procedures as those for the patients.

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Study Outcomes

Overview

The primary outcome in this study is the change in self-management, as measured through the Patient Activation Measure (PAM) questionnaire after 1 year, which will then be compared between the users and the nonusers of the digital PROM. The secondary outcomes include glycated hemoglobin (HbA_{1c}), quality of life, health literacy, acceptability, health economics, and the use of health service resources. Quantitative data will be collected through patients' self-reports and the extraction of clinical variables from patients' medical records. In addition, data on the patients' use of MyDignio will be extracted, including how many clinical PROMs they completed during the study period. Self-reported and clinical variables will be collected among all consenting participants, regardless of their participation in the digital solution. The standardized self-reported outcome measures are presented in Table 1.

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Table 1. Standardized self-reported outcome measures.

Domain and questionnaire and item, scale, and interpretation	Time point	
	T0	T1
Self-management		
PAM-13[a]		
• 13 items • 4-point Likert scale ranging from “strongly disagree” to “strongly agree” and “nonapplicable” • Higher scores indicate higher patient activation • A total of 4 activation levels in progressing difficulty: (1) belief that their role is important (0-47; items 1-2); (2) confidence and knowledge to act (47.1-55.1; items 3-8); (3) taking action (55.2-72.4; items 9-11); (4) staying on course under stress (72.5-100; items 12-13) • Domains: Knowledge, beliefs, confidence, and skills related to self-managing health and improving outcomes	✓	✓
Diabetes distress		
PAID[b]		
• 20 items • 5-point Likert scale ranging from 0 (“not a problem”) to 4 (“serious problem”) • The sum score multiplied by 1.25 gives a total score ranging from 0 to 100. • A higher score reflects greater emotional distress. A score of ≥40 indicates severe emotional distress.	✓	✓
Quality of life		
WHO-5[c]		
• 5 items (statements) • 6-point Likert scale ranging from 0 (“at no time”) to 5 (“all of the time”) • Total raw score ranging from 0 to 25 is multiplied by 4 (total score), where 0 represents worst imaginable well-being and 100 represents best imaginable well-being.	✓	✓
EQ-5D-5L		
• 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression • Each dimension has 5 levels, from “no problems” (level 1) to “extreme problems” (level 5)	✓	✓
Digital health literacy		
HLS19-DHC-NO[d]		
• 10 items • 4-point Likert scale from 1 (“very hard”) to 4 (“very easy”) with added “I don’t know” • Higher scores reflect higher digital health literacy.		✓
HLS-Q12[e]		
• 12 items • 4-point Likert scale from 1 (“very hard”) to 4 (“very easy”) with added “I don’t know” • Higher scores reflect higher digital health literacy.		✓
Patient acceptability		
SUTAQ[f]		
• 22 items • 6-point Likert scale ranging from 1 to 6, reflecting more or less agreement with the statements. • High values reflect a high degree of agreement, except for 2 categories: *privacy and discomfort and care personnel concerns.*		✓
Perceived benefit		
• Enhanced care—beliefs about how health technology enhances care from health care personnel • Increased accessibility—beliefs on how health technology increases access to care		✓
Privacy and discomfort		
• Concerns about the impact of the kit on the person and the safety of the information monitored		✓

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Domain and questionnaire and item, scale, and interpretation	Time point	
	T0	T1
Care personnel concerns		
• Beliefs about personnel skills and continuity of care		✓
Kit as substitution		
• Beliefs about health technology as an alternative to standard care		✓
Satisfaction		
• Beliefs of acceptance and satisfaction with health technology used in health care services		✓

[a]PAM: Patient Activation Measure.

[b]PAID: Problem Areas in Diabetes.

[c]WHO-5: World Health Organization-5.

[d]HLS19-DHC-NO: Health Literacy Survey-19 Digital Health Care in Norwegian.

[e]HLS-Q12: Health Literacy Survey Questionnaire-12 item.

[f]SUTAQ: Service User Technology Acceptability Questionnaire.

Self-Management

To evaluate self-management, we propose the PAM short version (PAM-13) for assessing self-management through patient activation in 4 domains: knowledge, beliefs, confidence, and skills for managing one's health [35]. The PAM-13 is suitable for the evaluation of health programs, which will enable patients to take responsibility for their own health; it contains 13 items, with scoring ranging from strongly disagree to strongly agree. The total PAM score can be divided into 4 levels: level 1 ("not believing activation is important") and level 2 ("a lack of knowledge and confidence to take action") indicate lower patient activations and level 3 ("beginning to take action") and level 4 "taking action" indicate higher patient activation. The PAM-13 was developed by Hibbard et al [35,36] for working with people with and without chronic conditions, and the initial validation showed strong psychometric properties. The PAM has previously been used among people with diabetes, albeit mostly type 2 diabetes [37], and has been translated into Norwegian and validated in a previous study [38].

Diabetes Distress

To evaluate diabetes distress, the Problem Areas in Diabetes-20 scale is used. This is an emotional distress scale for measuring diabetes-related concepts, such as depression, social support, health beliefs, and coping style; the scale aims to identify high risk for negative effects on self-management and emotional burnout because of diabetes [39]. The Problem Areas in Diabetes-20 contains 20 items, with a 4-point Likert scale ranging from no problem to a serious problem. It has been translated into Norwegian and validated in a previous study [40].

Quality of Life

Quality of life will be assessed using the 5-item World Health Organization Well-Being Index, which is a measure of current mental well-being and overall quality of life over the individual's past 2 weeks [41]. It contains 5 statements, with responses on a 6-point Likert scale that ranges from "no time" to "all of the time." The questionnaire has been validated and applied across various study fields [41] and is available and widely used in Norwegian.

To assess quality of life with added relevance to the health economic analyses, the EQ-5D-5L, including the EQ visual analogue scale, will be used. EQ-5D includes questions about mobility, self-care, usual activities, pain, discomfort, anxiety, and depression on a 4-level scale that ranges from "no problem" to "unable to/extreme problems." The EQ-5D visual analogue scale allows patients to rate their own overall current health. EQ-5D is a standardized generic instrument that is suitable for use in economic evaluations in health care. It was previously translated to Norwegian with population norms established [42], and it is widely applied on a global scale [43,44].

Digital and Health Literacy

Digital health literacy will be evaluated using the generic Health Literacy Survey-19 Digital Health Care in Norwegian (HLS19-DHC-NO). It measures the skills in using electronic tools to follow-up on one's own health and disease, as well as the competence to use digital home-based follow-up. This scale contains 10 items that are scored on a 4-point Likert scale from very hard to very easy, in addition to an "I don't know" category. It has recently been translated and applied to a Norwegian population survey [45] and is currently under validation.

The 12-Item Short-Form Health Literacy Survey Questionnaire is a generic measure of the ability to make informed health choices through 4 domains: access, understand, appraise, and apply health information. This scale contains 12 items, which are scored on a 4-point Likert scale that ranges from "very hard" to "very easy," in addition to an "I don't know" category. The 12-Item Short-Form Health Literacy Survey Questionnaire has been validated among the general Norwegian population [46].

Patient Acceptability of Digital Care

To assess the patients' satisfaction and acceptability with participating in digital care, we will use the Service User Technology Acceptability Questionnaire, which has 22 items

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[21]. The Service User Technology Acceptability Questionnaire measures the acceptance of mobile health technology and can also be used to identify the characteristics of participants with low acceptance of technology. The responses are given on a 6-point Likert scale, ranging from strongly agree to strongly disagree. It has been translated into Norwegian and validated in a previous study [47].

Sociodemographic and Clinical Variables

Sociodemographic variables will be extracted from the patient records, whereas clinical variables will comprise self-reported data and data extracted from the patients' medical records (Table 2).

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Table 2. Sociodemographic and clinical variables.

Variables, scale, and interpretation	Time point	
	T0	T1
Sociodemographic variables		
Age		
• Years	✓	
Sex		
• Female or male	✓	
Education		
• Not completed primary school (10 years) • Primary upper secondary school • Vocational school • College or university (≤4 years) • College or university (>4 years) • Unknown	✓	
Employment status		
• Employed 100% • Student • Unemployed (disability benefits or retired or other) • Part-time employment (≤25%, 26%-50%, 51%-75%, 76%-99%)	✓	✓
Cohabitation status		
• Living alone yes or no	✓	
Ethnicity		
• European • Asian • African • Unknown	✓	
Tobacco habits		
• Current user • Previous user	✓	✓
Clinical variables		
Diabetes duration		
• Years	✓	
HbA_{1c} [a]		
• Mmol/mol	✓	✓
Time in the range		
• The last 14 days • Time below range <3.9 mmol/L • Time in range of 3.9-10 mmol/L • Time above range >10 mmol/L	✓	✓
Diabetes complications		
• Number of diabetes late complications; • Albuminuria, treated with dialysis, transplanted kidney, retinopathy, neuropathy, stroke, arterial vascular surgery, amputation, and diabetic foot ulcers	✓	
Equipment		
• Pump, CGM[b] sensor, pump and pen	✓	✓

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Variables, scale, and interpretation	Time point	
	T0	T1
DKA[c]		
• Never • Once • Several times • Unknown	✓	✓
Hypoglycemia in need of help		
• Never • Once • Several times • Unknown	✓	✓
Symptomatic hypoglycemia		
• Number of incidents, 0-90 past 30 days	✓	✓
Height		
• cm	✓	
Weight		
• kg	✓	✓
Lipid status		
• LDL[d]-cholesterol, mmol/L	✓	✓
Blood pressure		
• Systolic and diastolic mm Hg	✓	✓
Comorbidity		
CCI[e]		
• Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, chronic kidney disease, solid tumor, leukemia, lymphoma, and AIDS	✓	

[a]HbA_{1c}: glycated hemoglobin.

[b]CGM: continuous glucose monitoring system.

[c]DKA: diabetic ketoacidosis.

[d]LDL: low-density lipoprotein.

[e]CCI: Charlson Comorbidity Index.

Utilization of Health Care Resources

Data regarding the utilization of health care resources will be collected, including the type of health care services provided, frequency of utilization, participation, and any engagement in digital services. The variables are presented in Table 3.

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Table 3. Utilization of digital solutions and health care resources.

Variables, scale, and interpretation	Time point	
	T0	T1
Health care use		
Consultation type		
• Physical, video, or telephone		✓
Attendance		
• Number of on-attendance and number of late cancelations		✓
Health care profession		
• Number of consultations with a physician, a nurse, and a nutritionist		✓
GP[a] visits		
• Number of GP consultations		✓
Absence from work		
• Days of absence		✓
Patient involvement		
Patient involvement and shared decision-making		
• 6 items reflecting decision-making, communication, and interaction • 5-point Likert scale from 1, “absolutely not” to 5, “to a very high degree,” with an added “I don’t know” • Higher scores reflect a higher feeling of involvement	✓	✓
Digital user data		
Participation in the digital outpatient care		
• Yes or no, including start date	✓	✓
PROMs[b] completed		
• Type of measures and frequency, number		✓
Messaging services		
• Frequency of use and number		✓
Use of other mobile health apps		
• 2 items reflecting use and frequency • Including open-ended responses	✓	✓

[a]GP: general practitioner.

[b]PROM: patient-reported outcome measure.

The items reflecting patient involvement [48] and patient role [49] have been previously adapted from their original form and used in the DiabetesFlex study [16,17]. For this project, the items adapted in the DiabetesFlex study have been translated from Danish by the project team into Norwegian and then back-translated by a bilingual Danish researcher not affiliated with the project. The translation was then reviewed by ALJ, AT, and IS, and small adjustments were made before a translation consensus was reached.

Health Economy

To estimate the cost-effectiveness of the digital care model, we will conduct a cost-utility analysis based on decision-analytic modeling [50,51]. Those using the digital PROMs will be compared with those continuing with the standard follow-up. Health benefits will be measured using the EQ-5D-5L at baseline and at 12 months. Data for health care resource use will be collected using survey data on general practitioner visits, visits to nurses and other health care professionals, and absences from planned consultations and hospital admissions (Table 3). The time used for training will be based on experiences from implementing the digital care model. Microsimulations will be used to estimate the cost of traveling and other patient expenses. The unit costs will be based on the Norwegian reimbursement systems, the marked prices, and the literature. The results will be reported as incremental cost-effectiveness ratios with

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credibility intervals and cost-effectiveness acceptability curves. We use probabilistic sensitivity analysis to estimate the uncertainty caused by parameter uncertainty and use deterministic sensitivity analysis to assess the effect of changes in resource use, unit cost, and assumptions [52].

Qualitative Outcomes

The qualitative outcomes of this proposed project include in-depth interviews with patients with diabetes and diabetes health care personnel and observations of consultations between diabetes health care personnel and patients participating in the digital care model. The semistructured in-depth interviews will aim to explore patients' acceptability of digital communication and how patients and diabetes health care personnel utilize the technology. The same patients will be observed and interviewed after obtaining their written informed consent. The interview guide for patients and health care professionals can be found in Multimedia Appendices 3 and 4, respectively.

Sample Size

The proposed study will evaluate the relevance and effects of digital services in practice without participants being randomly drawn to a control group and, therefore, excluded from the possibility of using technological solutions in clinical follow-up. Therefore, we can assume that there is a difference between patients who choose to engage in digital care and those who choose traditional health care services. It is impossible to foresee or decide how many patients will participate through the digital PROM, but we expect more patients in the group of users of the digital service. To statistically identify the similarities and differences between the groups, we consider a 10% alteration in PAM-13 to be clinically significant, such as a change of ≥4 points. To identify a clinically relevant change to this extent, a minimum of 32 participants is required in each group. To account for potential dropouts, we will continue the recruitment of participants until we have included the required number of at least 35 participants in the control group. Consenting patients will be compared based on their chosen group, that is, engaged or not engaged in digital care. If they choose to continue with standard care at the clinic, they will contribute data for comparison purposes after providing their consent. Recruitment will continue for an estimated year, or until nearly all patients in the clinic have been offered the digital solution.

We will use purposive sampling for the qualitative interviews and the observations [53] when recruiting patients and health care personnel for the qualitative study. Approximately 25 patients participating in the digital care model are regarded as sufficient. Patient participants will be included based on purposeful sampling to gain variations in age, gender, and HbA_{1c} levels. Thus, the number of patients included will depend on the findings of a constant comparative analysis. The sample size for diabetes health care personnel depends on the consenting number of health care personnel from the outpatient clinic under study.

Analysis

Statistical Analysis

The baseline (T0) and follow-up (T1) variables will be descriptively presented, whereas continuous variables will be analyzed using the median and range if the data are skewed and the mean and SD for normally distributed data. Categorical data will be presented as counts and percentages. The mean change will be estimated by subtracting the baseline scores from the follow-up scores. Any differences in mean changes in short- and long-term variables will be modeled using an ANOVA. To adjust for possible confounders, logistic regression models will include age, gender, and education. We will assess the number of patients tested for eligibility, declined to participate, lost to follow-up, and included in the analysis.

Qualitative Analysis

In the qualitative analysis, we will use interpretive description as a methodology [53-55]. Interpretive description aims to generate a practical understanding of the importance of applied disciplines within their context [53]. The interpretive description analysis will be performed in parallel with the data collection. All data from the transcribed interviews and field notes from the participant observation will be included in the analysis. Interpretive description analysis is an inductive, open, and exploratory approach that includes a constant comparative analysis. Hence, it builds from specific data toward a broader generalization. This analysis will lead to the identification of final themes describing patients' acceptability of digital communication and how patients and diabetes health care personnel use the technology [53]. The NVivo software is used for data management, coding, and analysis [56]. The initial coding phase will be broad-based inductive coding into categories, followed by fine-tuned coding and interpretation of the data.

User Involvement

In this study, health care personnel will participate alongside patients and stakeholders to adapt the DiabetesFlex to a Norwegian context, resulting in a set of PROM items that may be highly relevant to the patients. On the basis of their answers, health care personnel can triage their patients to offer suitable treatment when needed through a traffic light model. User involvement regarding the project's development has been described elsewhere [25]. In addition, a reference group for the project will be established, containing individuals with type 1 diabetes, diabetes specialist nurses, endocrinologists, management, and researchers.

Ethical Considerations

The Data Protection Office approved the study at Akershus University Hospital (2022_125). Patients at the outpatient clinic will be screened for eligibility for the study by health professionals, and all patients meeting the inclusion criteria will be offered the digital PROM. Therefore, a randomized controlled trial is impossible, and the proposed study has no control group. However, those declining to engage in digital tools will act as a comparative group in the analysis. All participants will provide their written informed consent before the study starts. All data will be securely stored in Services for Sensitive Data. Data

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shared in the MyDignio app will be encrypted and stored according to legislation on the privacy and secure storage of sensitive health information. The Data Protection Office performed a comprehensive risk assessment analysis of the technology upon initiation, and the research team completed a risk assessment analysis of the risks related to the conduct of the research before the start of the study. SIKT—the Norwegian Agency for Shared Services in Education and Research—will be notified per the Norwegian protocol to assess project data protection and information security.

To ensure data safety, patients must use their national ID to identify themselves, either through BankID or MinID, both to provide their digital consent and self-report on the digital questionnaires of the research evaluation and to log in when using MyDignio.

Results

The study received funding in March and October 2022 from Oslo Metropolitan University–OsloMet internal funding. The digital solution was implemented in clinical care at the department in November 2021, and the first participant was enrolled in the research project with a completed T0 on October 27, 2022. As of September 6, 2023, a total of 220 patients have been enrolled in the project, of which 84.5% (n=186) are digital users and 15.5% (n=34) are nonusers in the comparative group. The data collection is projected to end during 2024.

Discussion

Overview

We anticipate that this study will generate knowledge on the relevance and effects of participation in digital PROMs for communication and self-management and about the characteristics of users compared with nonusers of the digital PROM. Evaluating the use of digital follow-up might facilitate the need for further development of the tools based on actual clinical use. Finally, investigating the communication between patients and their health care personnel will increase the understanding of how technology impacts consultation.

Significance of the Study

Although diabetes care has faced considerable improvements in medical equipment facilitation and glycemic control, there is a need for more patient-centered and flexible care using recent developments in digital PROMs in routine care [11,12]. To do so, the possibilities of flexible digital care using PROMs in clinical care must be investigated. The study described in this protocol aims to provide knowledge regarding the characteristics of patients with type 1 diabetes engaged in a digital PROM, their effect on participating in digital PROMs, the patients' acceptability of consultations prepared and supported by digital and flexible services using PROs, and how these services affect health care personnel.

Although previous research from Norway provides valuable insights into the use of PROMs in clinical diabetes consultations through the DiaPROM study, their findings highlight the need for further investigation into implementation challenges and patient acceptability [57]. In the Danish DiabetesFlex study, PROMs in the diabetes outpatient clinic had a positive impact on patients' management of their diabetes and their responsibility for care plans. Compared with standard care, using PROM in flexible visits improved diabetes-related well-being and decreased face-to-face visits while maintaining safe diabetes management [16,24]. Using a PROM, patients were encouraged to reflect on their diabetes management; this led to a more tailored and individualized treatment approach and made the consultations more flexible, allowing for a broader dialogue between patients and health care providers [24]. Similarly, diabetes care support is crucial when living with diabetes [58]. Using PROMs in diabetes specialist care can improve communication, enhance patient engagement in their care, and improve patient outcomes. Nonetheless, it remains necessary to explore the acceptability of the use of digital PROMs to prevent inequality in health for patients who do not engage in digital health care and, as such, do not receive the intended care [18], while also identifying the barriers preventing these patients from accessing care and exploring alternative ways of delivering health care services and support. This study will investigate the effects and acceptability of a digital PROM, emphasize the potential benefits and barriers by further exploring the impact of using a PROM in a diabetes outpatient clinic, and, as such, add knowledge to existing evidence.

Limitations

In evaluating the implementation of digital tools and PROMs, a randomized controlled trial could be considered the gold standard to minimize confounding variables and provide stronger evidence. In this case, to design a control group, we would have to withhold the tools from patients in the clinic, which could be considered unfair clinical practice in the clinic. We could have chosen to have a control group at another hospital. However, practices in endocrinology outpatient clinics are changing, making it difficult to find a hospital department administering the usual care. Therefore, this study has been planned as an observational quasi-experimental design, with its limitations being potential confounding variables and bias. This is a novel study, and we plan to include numerous participants with a long follow-up period. We will minimize bias and confounding by including patients engaged in digital PROMs and patients choosing traditional care, controlling for known confounders, and using appropriate statistical methods to analyze data in collaboration with a statistician.

A potential limitation, according to the qualitative part of the study, is related to the conduct of the observations of consultations with patients and being interviewed about their practice, with a potential risk for reactivity of social desirability bias. Diabetes health care personnel might modify their behavior while being observed to conform to expectations about performance. Similarly, they could provide responses in the interviews that they believe are socially acceptable, rather than giving honest and accurate answers. It will be important for the researchers to establish trust and ensure that the responses are kept confidential and not used to evaluate performance.

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Conclusions

There is a need for elaborate knowledge on patient participation in digital tools using PROMs in diabetes specialist care. A multimethod prospective observational cohort study can provide valuable insights into the effectiveness and acceptability of PROM digital tools, aiming for a broad measurement of their full-scale implementation in a large diabetes outpatient clinic.

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Authors' Contributions

AT, TS, NMW, ALJ, LR, and HH substantially contributed to the development of this study protocol. AT drafted the manuscript in collaboration and through discussions with HH on the adaptation and tailoring of the intervention. TS, NMW, IS, MAM, PJ, LR, and ALJ commented on and revised versions of the draft, and all authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshot of the MyDignio interface.
[DOCX File , 95 KB - resprot_v13i1e52766_app1.docx]

Multimedia Appendix 2
Screenshot of the DignioPrevent interface.
[DOCX File , 54 KB - resprot_v13i1e52766_app2.docx]

Multimedia Appendix 3
Interview guide—patients.
[DOCX File , 34 KB - resprot_v13i1e52766_app3.docx]

Multimedia Appendix 4
Interview guide—health care professionals.
[DOCX File , 30 KB - resprot_v13i1e52766_app4.docx]

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Abbreviations

HbA_{1c}: glycated hemoglobin
HLS19-DHC-NO: Health Literacy Survey-19 Digital Health Care in Norwegian
PAM: Patient Activation Measure
PRO: patient-reported outcome
PROM: patient-reported outcome measure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effectiveness of Chinese Herbal Medicine as a Complementary Treatment for Neutropenia Prevention and Immunity Modulation During Chemotherapy in Patients With Breast Cancer: Protocol for a Real-World Pragmatic Clinical Trial

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Abstract

Background: In recent years, advancements in cancer treatment have enabled cancer cell inhibition, leading to improved patient outcomes. However, the side effects of chemotherapy, especially leukopenia, impact patients' ability to tolerate their treatments and affect their quality of life. Traditional Chinese medicine is thought to provide complementary cancer treatment to improve the quality of life and prolong survival time among patients with cancer.

Objective: This study aims to evaluate the effectiveness of Chinese herbal medicine (CHM) as a complementary treatment for neutropenia prevention and immunity modulation during chemotherapy in patients with breast cancer.

Methods: We will conduct a real-world pragmatic clinical trial to evaluate the effectiveness of CHM as a supplementary therapy to prevent neutropenia in patients with breast cancer undergoing chemotherapy. Patients will be classified into CHM or non-CHM groups based on whether they received CHM during chemotherapy. Using generalized estimating equations or repeated measures ANOVA, we will assess differences in white blood cell counts, absolute neutrophil counts, immune cells, and programmed cell death protein 1 (PD-1) expression levels between the 2 groups.

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Results: This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A). The enrollment process began in September 2021 and will stop in December 2024. A total of 140 patients will be recruited. Data cleaning and analysis are expected to finish in the middle of 2025.

Conclusions: Traditional Chinese medicine is the most commonly used complementary medicine, and it has been reported to significantly alleviate chemotherapy-related side effects. This study's findings may contribute to developing effective interventions targeting chemotherapy-related neutropenia among patients with breast cancer in clinical practice.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2023000054; https://tinyurl.com/yc353hes

International Registered Report Identifier (IRRID): DERR1-10.2196/55662

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KEYWORDS

complementary treatment for cancer; neutropenia; real-world study; bedside to bench study; immune cell profile; programmed cell death protein 1; PD-1; breast cancer; breast; cancer; oncology; Chinese medicine; herb; herbs; herbal; complementary; immunity; immunology; immunomodulation; immunological; neutrophil; chemotherapy; blood cell; blood cells

Introduction

Chemotherapy-induced neutropenia (CIN) is a common complication and represents the most severe hematological toxicity associated with cancer chemotherapy. This condition has several complications, including severe infections, aggressive hospital management, life-threatening morbidity, and mortality [1]. Briefly, CIN is generally characterized by a decreased absolute neutrophil count (ANC) of <2000 cells/mm^3 in the peripheral blood and is classified into 4 grades according to the National Cancer Institute Common Toxicity Criteria. The classifications of CIN severity are as follows: (1) grade 1 with an ANC of 1500-2000 cells/mm^3, (2) grade 2 with an ANC of 1000-1500 cells/mm^3, (3) grade 3 with an ANC of 500-1000 cells/mm^3, and (4) grade 4 with an ANC <500 cells/mm^3. The current standard treatment for CIN is the use of granulocyte colony-stimulating factor (G-CSF) to attenuate white blood cell (WBC) count and ANC [2]. The use of prophylactic G-CSF also improves patients' quality of life (QoL) [3].

Breast cancer, particularly triple-negative breast cancer (TNBC), encompasses a heterogeneous group of cancer cells, and its treatment remains challenging. In patients with neoadjuvant chemotherapy (NAC)–treated TNBC with residual disease, higher stromal tumor–infiltrating lymphocytes (sTILs) in the resected tumor conferred an improved prognosis [4]. Moreover, higher pre-NAC sTILs and elevated pre-NAC expression of cytotoxic T-cell markers and cytokines are associated with better pathological complete response and overall survival rates [5]. sTILs, with a published cutoff of 30%, are the most widely studied marker of antitumor immunity. Besides, these sTILs could be used to predict improved response to NAC and better prognosis in the context of residual disease of patients lacking pathologic complete response. However, the mechanisms underlying the immunomodulatory effects of chemotherapy on sTILs and the influence of chemotherapy on the tumor-immune microenvironment are poorly understood.

NAC alters both tumor-infiltrating and peripheral immune cells in patients with breast cancer. The reduced levels of signal transducer and activator of transcription 1 (STAT1), activator protein-1 transcription factor subunit (Jun), and nuclear factor kappa B (NF-κB) in B cells, cytotoxic T cells, and natural killer (NK) cells, respectively, from the pretreatment stage to the mid- and posttreatment stages indicated that NAC could inhibit the activation, proliferation, and differentiation of these cells. Moreover, B cell signatures detected using single-cell RNA sequencing are significantly associated with improved survival in patients with breast cancer [6]. However, a significant decrease in the fraction of B cells and C-X-C chemokine receptor type 4, which are involved in maintaining B cell population and function, was reported during and after NAC in peripheral blood mononuclear cells (PBMCs). A previous study also demonstrated that decreased neutrophil levels correlated with a poor response to NAC [7]. High levels of systemic cluster of differentiation 8 (CD8+) cytotoxic T cells are associated with improved survival in patients with metastatic breast cancer [8]. Furthermore, the expression of cytotoxic genes in PBMCs, as opposed to tumor-immune microenvironment, may be invasive biomarkers of persistent micrometastatic disease, ultimately leading to recurrence [9]. Accordingly, lower neutrophil density in patients with breast cancer is associated with metastasis or poor prognosis.

In addition, the percentages of CD3+CD4+CD25+CD127-FoxP3+ regulatory T cells, intermediate monocytes (CD14++CD16+), and HLA-DR-CD11b+CD33+CD15+ myeloid-derived suppressor cells were reported to be significantly higher in the PBMCs of patients with breast cancer. After a single round of NAC, the intensity of CD56 expression in NK cells was significantly increased, as was the percentage of activating receptors NKp44, NKp30, and 2B4 and inhibitory receptors leukocyte-associated immunoglobulin-like receptor (LAIR) and NKG2A. The activity, rather than the proportion of NK cells, is affected [10].

In addition to conventional therapy, an increasing number of patients with breast cancer are seeking Chinese herbal medicine (CHM), as indicated by web-based surveys exploring the perspectives of patients with breast cancer concerning complementary and alternative medicine. CHM has been reported as one of the most common complementary treatments for patients with breast cancer, associated with a possible reduction in the risk of complications, including alopecia [11], neuropathy [12], and fatigue [13], as well as with an

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improvement in the overall QoL [14]. Moreover, the results based on claims data suggest that using CHM in combination with conventional therapy may improve the overall survival rate by 45% [15]. However, whether CHM as a complementary therapy can alleviate myelosuppression and neutropenia remains controversial. Previous studies have demonstrated that *shenqi fuzheng* injection [16] and *xihuang* pill or capsule [17] could regulate immunity and reduce tumor markers. Nevertheless, other placebo-controlled randomized controlled trials have stated that using CHM as a complementary therapy did not prevent myelosuppression in patients with breast cancer treated with adjuvant chemotherapy [18].

Understanding how NAC reshapes antitumor immunity, both in the tumor and peripheral compartments, is essential; however, the immunomodulatory effects of NAC are still unclear. The Chinese herbs frequently used in cancer treatment, including *huang qi*, *dang gui*, *huang qin*, *bai zhu*, and *nuzhenzi* (Table 1), could regulate immunity, but how they affect immune cell profiles is mainly unknown. Given that some CHM has been suggested to have immune regulatory effects, we hypothesized that CHM, as a supplementary therapy during chemotherapy, could lower the risk of neutropenia in patients with breast cancer. Accordingly, we are conducting a real-world pragmatic clinical trial to evaluate the effectiveness of CHM as a complementary treatment for neutropenia prevention and immune modulation during chemotherapy in patients with breast cancer.

Table 1. Candidate Chinese herbal medicines in this study.

Pharmaceutical Latin	Chinese name	Applications or effects	Possible side effects
Astragalus membranaceus	*Huang qi*	Enhance immune system, heart function, and blood sugar control	Rash, itching, runny nose, nausea, and diarrhea
Angelica sinensis	*Dang gui*	Heart diseases, menopausal and menstrual symptoms, high blood pressure, and inflammation	Fatigue, allergic reactions, and should not be prescribed to pregnant women and children
Scutellaria baicalensis Georgi	*Huang qin*	Diarrhea, insomnia, dysentery, high blood pressure, hemorrhaging, respiratory infections, and inflammation	Gastric discomfort, nausea and vomiting, and diuresis
Atractylodes macrocephala	*Bai zhu*	Antiulcer, enhance immunity, and antioxidant	Decrease blood pressure and hypoglycemia
Fructus ligustri lucidi	*Nuzhenzi*	Optic neuritis, leukopenia, chronic hepatitis, hyperlipidemia, coronary heart disease, and hypertension	Dizziness and diarrhea

Methods

Participant Recruitment

Participants are being recruited from the Hualien Tzu Chi Hospital. Recruitment began on September 12, 2021, and is expected to continue until December 2024. We expect to complete the study in the middle of 2024.

Ethical Considerations

This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A), and informed consent will be collected from all study participants. The information of patients will be deidentified, and each visit will be compensated for US $16. This study was registered on the International Traditional Medicine Clinical Trial Registry website (ITMCTR2023000054).

Sample Size Estimation

The sample size calculation was based on the mean and SD of the amount of CD4+ between control and treatment groups based on the published literature [19]. By setting the effect size as 0.5, the sample size of each group was estimated as 64 to achieve a power of 0.80 at a significance level of .05 using G*Power software (version 3.1; Heinrich-Heine-Universität Düsseldorf). After accounting for an anticipated dropout rate of 10%, the final sample size was determined to be 70 in each group.

Inclusion Criteria

Patients aged 20 years and older, with a histologically confirmed diagnosis of breast cancer before the initiation of chemotherapy, are considered eligible for this study.

Exclusion Criteria

Patients who will not be able to complete the chemotherapy and follow-up procedures based on oncologists' experience before grouping, those who receive other medication, and those with an Eastern Cooperative Oncology Group score of 3-4 will be excluded from the study.

Study Design

This study is a real-world pragmatic clinical trial conducted at the Hualien Tzu Chi Hospital in Taiwan. Patients with breast cancer scheduled to receive chemotherapy for their cancer treatment will be recruited as per the flowchart shown in Figure 1. Patients willing to receive CHM during chemotherapy are allocated to the CHM group, whereas those in the non-CHM group will not receive CHM.

To evaluate the effectiveness of CHM, the number of WBCs, the ANC, and the use of G-CSF in patients will be measured. The following questionnaires in Taiwanese will be used: (1) the Brief Fatigue Inventory—Taiwanese Version, (2) the World Health Organization Quality of Life-BREF, (3) the National Cancer Institute-Common Terminology Criteria for Adverse Events & Patient Reported Outcomes, and (4) the body

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constitution questionnaire. In addition, blood samples will be collected and analyzed for immune profiles and programmed cell death protein 1 (PD-1) expression. Generally, visit 1 represents the first collection of questionnaires and blood samples before the first chemotherapy session. Following the chemotherapy regimen, the first 4 rounds of chemotherapy will be performed every 3 weeks with 3 visits (visits 2-4). Subsequently, 12 rounds of chemotherapy will be performed once per week with another 4 visits (visits 5-8, 3 weeks per visit). Patients will be followed up within 1 month of undergoing chemotherapy. Patients in the CHM group will receive complementary CHM treatment after the first chemotherapy session.

The clinical data will be extracted from the medical history system. The questionnaires will be coded and transformed into numerical values (eg, 5=very satisfied or none, 4=satisfied or light, 3=no change or intermediate, 2=unsatisfied or severe, and 1=very unsatisfied or none) to facilitate statistical analysis. Immune profiles will be analyzed using flow cytometry. The data monitoring committee, clinical trial center of Hualien Tzu Chi Hospital, is independent from the funder and competing interests. The SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) 2013 checklist is provided in Multimedia Appendix 1 [20].

Figure 1. Flowchart of the study design from enrollment to analysis. CHM: Chinese herbal medicine.

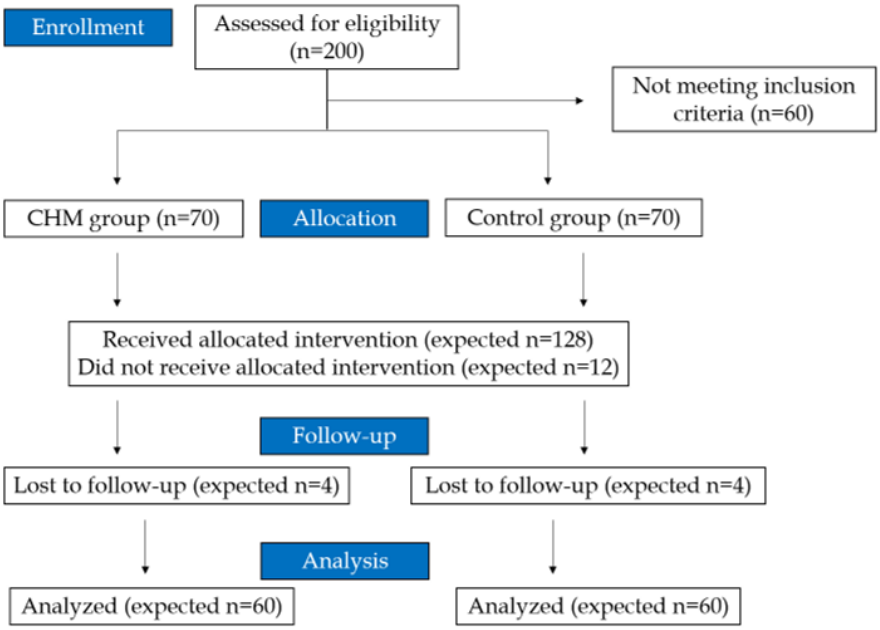

Chemotherapy and CHM Administration Protocol

Upon the diagnosis of breast cancer in a patient, a clinical nurse manages the case. The questionnaire and blood collection before chemotherapy are represented by visit 1 (red arrow in Figure 2). The first 4 rounds of chemotherapy will be performed every 3 weeks, and visits 2-4 will be located in the second, third, and fifth rounds, respectively, 1 day before chemotherapy treatment.

The following 12 rounds of chemotherapy will be performed every week, and visits 5-8 will be located in the first, fourth, seventh, and tenth rounds, respectively, 1 day before chemotherapy treatment. The patients will be followed up within 1 month after chemotherapy (Figure 2 and Table 2). Patients receiving CHM 3 times per day started the first round of chemotherapy.

Figure 2. Chemotherapy, Chinese herbal medicine intervention, and data collection procedures. The questionnaire and blood collection before chemotherapy represent V1 (red arrow). The first 4 rounds of chemotherapy will be performed every 3 weeks (V2 to V4), 1 day before chemotherapy treatment. The subsequent 12 rounds of chemotherapy will be performed every week (V5 to V8), 1 day before chemotherapy treatment. The patients will be followed up (FU) after chemotherapy within 1 month. V: visit.

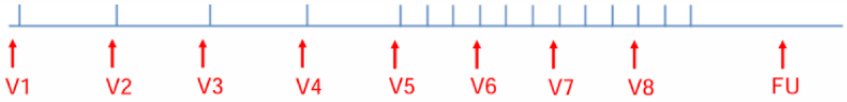

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Table 2. Recommended content for the schedule according to the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) 2013 guidelines.

Time point	Enrollment	Allocation	Treatment								Follow-up
	Week 1	Week 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Enrollment											
Eligibility screen	✓										
Informed consent	✓										
Allocation		✓									
Intervention											
Control group			✓	✓	✓	✓	✓	✓	✓	✓	
CHM[a] group			✓	✓	✓	✓	✓	✓	✓	✓	
Assessment											
ANC[b] or WBC[c]			✓	✓	✓	✓	✓	✓	✓	✓	
Frequency of G-CSF[d] injection			✓	✓	✓	✓	✓	✓	✓	✓	
Questionnaire			✓	✓	✓	✓	✓	✓	✓	✓	
Immune cell profile			✓	✓	✓	✓	✓	✓	✓	✓	
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓	

[a]CHM: Chinese herbal medicine.

[b]ANC: absolute neutrophil count.

[c]WBC: white blood cell.

[d]G-CSF: granulocyte colony-stimulating factor.

Primary Outcome

The primary outcome used in this study is the number of immune cells, including CD4+ and CD8+ T cells (under CD45+ and CD3+ population), CD56+ NK cells (under CD45+ population), CD19+ B cells (under CD45+ population), CD14+ monocytes (under CD45+ population), and CD11c dendritic cells (under CD45+ population), as well as PD-1 expression levels in these cells. For NK cells, the expression of NKG2D will be also confirmed. The analytic panels used are listed in Table 3.

Table 3. Antibodies used for flow cytometry analysis[a].

Cells or conjugate	FITC[b]	PE[c]	APC[d]	APC-Cy7[e]	PE-Cy7[f]
T cells	CD45[g]	CD4	CD8	CD3	PD-1[h]
B and NK[i] cells	CD45	NKG2D	CD56	CD19	PD-1
Monocytes or DCs[j]	CD45	CD14	CD11c	—[k]	PD-1

[a]CD45 (304006), CD4 (317410), CD8 (301014), CD3 (344818), and CD19 (302218) were purchased from Biolegend. PD-1 (25-9969-42), CD56 (17-0567-42), NKG2D (12-5878-42), CD14 (12-0149-42), and CD11c (17-0114-82) were purchased from eBioscience.

[b]FITC: fluorescein isothiocyanate.

[c]PE: phycoerythrin.

[d]APC: allophycocyanin.

[e]APC-Cy7: allophycocyanin-cyanine 7.

[f]PE-Cy7: phycoerythrin-cyanine 7.

[g]CD: cluster of differentiation.

[h]PD-1: programmed cell death protein 1.

[i]NK: natural killer.

[j]DC: dendritic cell.

[k]Not available.

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Secondary Outcome

Secondary outcomes include the number of WBCs, the ANC, evaluation of the Brief Fatigue Inventory—Taiwanese Version, World Health Organization Quality of Life-BREF, National Cancer Institute-Common Terminology Criteria for Adverse Events & Patient Reported Outcomes, body constitution questionnaire, and frequency of G-CSF inoculation.

Safety Assessments

All adverse events (AEs) will be recorded throughout the study. In cases where AEs are caused by chemotherapy or CHM intervention, prompt measures will be taken to address those AEs. If needed, participants will be withdrawn from the study. Continuous monitoring of the participant's blood, liver, and kidney functions, body weight, and vital signs will be performed throughout the study. The possible side effects associated with CHM are listed in Table 1.

Flow Cytometry Analysis

Peripheral blood (10 mL) will be collected in ethylenediaminetetraacetic acid–coated tubes and processed within 24 hours of collection. Whole blood (100 µL) will be mixed directly with the fluorescence-conjugated antibodies, including CD45, CD3, CD4, CD8, CD19, CD56, NKG2D, CD14, CD11c, and PD-1 (Table 3), protected from the light, and incubated for 20 minutes at 4 ˚C. Blood cells will be washed twice with 2 mL staining buffer (phosphate buffered saline+2% fetal bovine serum), centrifuged at 300×g for 5 minutes at room temperature, and further incubated with Red Blood Cell Lysis Buffer (Thermo Fisher Scientific) for lysing the erythrocytes for 10 minutes at room temperature. This step may repeat until the red blood cell is completely lyzed. The cells will be further fixed in 2% paraformaldehyde for 10 minutes at room temperature. Subsequently, the cells will be subjected to 2 additional washes with 2 mL staining buffer and centrifuged 300×g for 5 minutes at room temperature. Then, the cells will be preserved at 4 ˚C and analyzed using flow cytometry (Lyric, BD) within 3 days.

Statistical Analysis

All statistical analyses will be performed using the SPSS software (version 13.0; IBM Corp) or SAS software (version 9.4; SAS Institute Inc). Continuous variables will be reported as mean and SD, whereas categorical variables will be reported as frequencies and percentages. The Shapiro-Wilk test will be used to analyze the normality of baseline characteristics and outcome variables. The Mann-Whitney *U* test will be used to compare nonnormally distributed continuous data, and the 2-tailed *t* test will be used to compare normally distributed continuous data. The chi-square test will be used to compare categorical data between the groups. Both primary and secondary outcomes involve repeated measurement data. The Friedman test and repeated measures ANOVA will be used to compare the differences between every visit in each group in nonparametric and parametric data, respectively. In addition, we will use generalized estimating equations or repeated measures ANOVA to compare the differences between the 2 groups. We will evaluate the risks of each clinical characteristic by the multivariate logistic regression analysis and adjust the age and other factors or characteristics that may have bias in the analysis. We set $P<.05$ as a significant difference. All data will be recorded in a case report form.

Results

This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A). The enrollment process began in September 2021 and will stop in December 2024. A total of 140 patients will be recruited. Data cleaning and analysis are expected to finish in the middle of 2025.

Discussion

Advantages and Disadvantages of Selected CHM

Traditional Chinese medicine is the most commonly used drug in Taiwan and shows significant potential in alleviating side effects related to anticancer treatments, such as chemotherapy. Even with sourcing from traditional Chinese medicine pharmaceutical factories in Taiwan certified under the Good Manufacturing Practices guidelines, our rigorous approach involves continuous toxicity monitoring throughout the study to minimize AEs.

Astragalus polysaccharide (APs), a bioactive extract of *Astragalus membranaceus*, has many biological activities, including anti-inflammatory, antioxidant, and immunoregulatory properties [21,22]. APs may modulate immunity by activating the toll-like receptor 4 (TLR4)–mediated myeloid differentiation primary response 88 (MyD88)–dependent signaling pathway [22] and induce apoptosis in human hepatocellular carcinoma cells by decreasing the expression of Notch1 [23]. Furthermore, APs inhibit TNBC cell invasion and proliferation and induce apoptosis through the PIK3CG/AKT/BCL2 pathway [24]. APs could activate macrophages to release nitric oxide and tumor necrosis factor alpha, directly blocking breast cancer cell growth [25]. *A membranaceus* extract has also been reported to inhibit breast cancer cell proliferation via the PI3K/AKT/mTOR signaling pathway [26].

Polysaccharides of *Angelica sinensis (Oliv) Diels* promote apoptosis in breast cancer cells via cyclic adenosine monophosphate response–binding protein (CREB)–regulated caspase-3 activation [27]. In a population-based case-control study in Taiwan, the use of *A sinensis* showed a significant protective effect on breast cancer (adjusted odds ratio 0.95, 95% CI 0.93-0.98) [28].

Baicalin, a flavonoid compound isolated from the roots of *Scutellaria lateriflora*Georgi, enhanced the chemosensitivity of breast cancer cells to doxorubicin via the upregulation of oxidative stress–mediated mitochondria-dependent apoptosis [29] and inhibited the metastasis and epithelial-to-mesenchymal transition of highly aggressive breast cancer cells by targeting β-catenin signaling [30].

Atractylenolide-I, a major bioactive component from *Atractylodes macrocephala*, suppressed tumorigenesis of breast cancer by inhibiting TLR4-mediated NF-κB signaling pathway [31] and sensitized TNBC cells to paclitaxel by blocking connective tissue growth factor expression [32].

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Fructus ligustri lucidi could enhance chemosensitivity and induce apoptosis via Tbx3 suppression in human colorectal carcinoma cells [33]. Besides, it has been reported to induce apoptosis in glioma cells in vitro and in vivo through the regulation of the AKT/mTOR pathway [34]. In addition, it induces senescence and apoptosis in hepatocellular carcinoma cells by upregulating p21 [35].

While these CHMs have mostly exhibited antitumor effects, their effects on immune cells have not been fully elucidated. Hence, we aimed to investigate the effects of these CHMs as a complementary treatment on neutropenia, a common chemotherapy side effect known to damage qi and aggravate its depletion. Notably, these CHMs not only regulate qi but also modulate immune cells and their functions. Thus, this study may provide additional insights into therapeutic strategies for breast cancer, including immunotherapy.

Strengths and Limitations

The strength of this study lies in its pragmatic trial design conducted in a clinical setting. Compared with randomized controlled trials, this study design has higher generalizability and provides evidence of its effectiveness in daily practice. This study has some limitations that may have affected the results. First, the internal validity was compromised. A pragmatic clinical trial design could achieve greater generalizability of the effectiveness of CHM as a complementary treatment. To improve internal validity, the statistician analyzing the data was blinded to the group assignment and adjusted for all confounding variables during data analysis. Second, there was a lack of important clinical characteristics, such as dietary and exercise habits. Although dietary intake and moderate-intensity aerobic exercise are crucial for patients with cancer during chemotherapy [36], we could not control daily diet and exercise intensity in this real-world clinical trial. In our clinical setting, oncology nurses educate all participants about the importance of healthy dietary intake and exercise habits during chemotherapy. Third, due to financial considerations, the observation time was not long enough to detect the change in the lymphocyte levels after completing chemotherapy, and further long-term and large-scale studies are needed to evaluate the variation in the number of WBCs and the ANC during the recovery phase after chemotherapy.

Conclusions

In conclusion, we have proposed an open-label, single-center, pragmatic clinical trial and a real-world study to evaluate the effectiveness and safety of CHMs for treating CIN in patients with breast cancer. Using this study platform, we will analyze the effects of CHM on the regulation of QoL by evaluating the complications of chemotherapy and immune cell profiles. The findings of this study may contribute to developing an effective intervention for chemotherapy-related neutropenia in patients with breast cancer in clinical practice.

Acknowledgments

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Authors' Contributions

HSS, SCC, TFW, CYP, and CCL conceptualized and designed the study. KHW, HSS, and SCC were involved in data analysis. KHW and HSS drafted the paper. HSS, CWL, SCC, TFW, WHH, and YFW were involved in the selection and enrollment of participants. All authors finally approved the paper. CCL was responsible for the integrity of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v13i1e55662_app1.pdf]

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Abbreviations

AE: adverse event
ANC: absolute neutrophil count
AP: Astragalus polysaccharide
CD8: cluster of differentiation 8
CHM: Chinese herbal medicine
CIN: chemotherapy-induced neutropenia
CREB: cyclic adenosine monophosphate response–binding protein
G-CSF: granulocyte colony-stimulating factor
LAIR: leukocyte-associated immunoglobulin-like receptor
MyD88: myeloid differentiation primary response 88
NAC: neoadjuvant chemotherapy
NF-κB: nuclear factor kappa B
NK: natural killer
PBMC: peripheral blood mononuclear cell

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PD-1: programmed cell death protein 1
QoL: quality of life
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
STAT1: signal transducer and activator of transcription 1
sTIL: stromal tumor–infiltrating lymphocyte
TLR4: toll-like receptor 4
TNBC: triple-negative breast cancer
WBC: white blood cell

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Protocol

Navigating Social Cognitive Impairments in Schizophrenia Spectrum Disorders: Protocol for a Pilot Pre-Post Quasi-Experimental Study for Remote Avatar-Assisted Cognitive Remediation Therapy

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Abstract

Background: Social cognitive impairments are prevalent in schizophrenia spectrum disorder (SSD) and have detrimental effects on functioning. Cognitive remediation (CR) has shown its efficacy in improving social cognitive impairments, although the transfer of these skills to daily life and the personalization of these interventions remain challenging. RC2S (*Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie*; Cognitive remediation of social cognition in Schizophrenia) is a French CR that combines the learning of strategies and practice using paper-and-pencil exercises and digital relational simulations. This French program was designed as an in-person intervention.

Objective: This project aims to culturally adapt the RC2S program, in French-Canadian and North American English and to assess the feasibility, acceptability, safety, and implementation of a remote version in people with SSD. An exploratory objective is to assess the preliminary effect of remote RC2S on goal attainment, social cognition, and psychosocial outcomes.

Methods: We will use a pre-post quasi-experimental design. First, the translation and cultural adaptation in North American English and French-Canadian of RC2S is presented. Then, 20 participants aged ≥18 years with a diagnosis of SSD, presenting with a subjective or an objective impairment in social cognition, will be included to receive RC2S. In addition, 5 therapists will be included as research participants to assess their perspective on RC2S. Participants with SSD will undergo a baseline remote assessment of their social cognition, clinical symptoms, and functioning. They will then start remote RC2S for 24 biweekly individual 1-hour sessions with a therapist. Following the case formulation and goal setting, participants will complete personalized paper-and-pencil exercises to develop strategies and integrative digital relational simulations, during which they will help an avatar navigate through a variety of social contexts and relationships. The last 2 sessions are dedicated to the transfer to daily life. All participants will complete in-session questionnaires assessing therapeutic alliance, motivation, acceptability, feasibility, and implementation. Following RC2S, the participants with SSD will repeat the same assessment as the baseline. Descriptive statistics will be used to summarize the data about acceptability, feasibility, safety, and implementation. To assess the preliminary effect of RC2S, an intention-to-treat approach will be used with linear mixed models for repeated measures with fixed effects of time.

Results: So far, 45% (9/20) of participants with SSD (mean age 37.9, SD 9.3 years) have completed the project. They received a mean of 20.5 out of 24 (SD 3.5) sessions of RC2S. A total of 5 therapists also completed the project.

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Conclusions: Improving social cognitive impairments is an important target in SSD to promote functional recovery. Using digital technologies to address these impairments and deliver the intervention is a promising approach to increase the ecological validity of CR and access to the intervention.

Trial Registration: ClinicalTrials.gov NCT05017532; https://classic.clinicaltrials.gov/ct2/show/NCT05017532

International Registered Report Identifier (IRRID): DERR1-10.2196/54251

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KEYWORDS

social cognition; schizophrenia spectrum disorder; psychosis; cognitive remediation therapy; social cognitive training; digital relational simulation; cultural adaptation; feasibility; acceptability; mobile phone

Introduction

Background

Social cognitive impairments are among the most important barriers to functional recovery in people with schizophrenia spectrum disorder (SSD) [1,2]. Significant relationships have been highlighted between social cognition and personal recovery [3] as well as between different areas of functioning, including social functioning, productive activities, and instrumental activities of daily living [1,2]. Thus, social cognitive impairments are a relevant treatment target to support recovery in people with SSD.

Social cognition refers to the mental processes underlying social interactions, including the abilities involved in perceiving and interpreting social information to guide social interactions [4,5]. The experts of the Social Cognition Psychometric Evaluation initiative have selected the most relevant social cognitive domains in schizophrenia, including emotion processing (ie, perceiving and using emotions), social perception (ie, decoding and interpreting social cues in others, including social context processing and social knowledge), theory of mind (ie, the ability to represent the mental states of others including the inference of intentions, dispositions, or beliefs), and attributional style and bias (ie, the way in which individuals explain the causes or make sense of social events or interactions) [6]. Social cognitive impairments are highly prevalent in people with SSD [7,8] and have been observed in all phases of the illness [7,9,10]. A recent meta-analysis assessing the performance in each of the 4 main domains of social cognition in people with SSD, compared with healthy controls, revealed decreased performance in emotion processing (medium to large effect size), social perception (large effect size), theory of mind (large effect size), and attributional bias (small to medium effect size) [8].

Cognitive remediation (CR) therapy is an evidence-based intervention that has shown benefits for social cognitive impairments in people with SSD [11,12]. CR has been defined by a consortium of experts as a "behavioral training intervention targeting cognitive deficits (attention, memory, executive function, social cognition, or metacognition), using scientific principles of learning, with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning" (Cognitive Remediation Experts Working Group, 2010 [13]). CR for social cognition falls under the umbrella term of social cognitive training that includes targeted programs to train specific domains of social cognition (eg, [14,15]), broad-based interventions targeting multiple domains (eg, [16-18]), and interventions combining the training of neurocognition (eg, attention) and social cognition (eg, [19,20]) [21,22]. These programs include strategy learning as well as the practice of these strategies through various social stimuli, such as pictures, videos, or role-playing.

Several meta-analyses have assessed the effect of social cognitive training [12,21,22], revealing their effectiveness in most social cognitive domains. In 2020, Nijman et al [22] published a network meta-analysis comparing targeted and broad-based interventions with or without training in neurocognition, active control interventions, and treatment as usual. The results suggest that broad-based interventions targeting multiple domains and focusing solely on social cognition (ie, without the training of neurocognitive functions) yielded the most consistent effect on most social cognitive domains, including emotion recognition (medium effect size), social perception (large effect size), and theory of mind (medium effect size), in addition to benefits on social functioning. No significant effect was observed for attributional bias. In 2022, Yeo et al [12] also performed a network meta-analysis with supplementary references and included only social cognitive training with or without minimal training in neurocognition. The results suggest medium effect sizes for social perception and theory of mind, and a medium to large effect size for emotion recognition. No significant effect was observed for attributional bias, in addition to a small and nonsignificant effect on functioning.

Altogether, these results suggest a significant effect of social cognitive training on most social cognitive domains in people with SSD, while also highlighting that the effect on functioning remains limited and influenced by the methodology of the studies. The results of a recent systematic review [23] focusing on the methodological quality and intervention modalities of social cognitive interventions for people with SSD have concluded the need to improve skill transfer during social cognitive training to everyday functioning. This review also highlights the importance of investigating the service user's perspective and personal goals in treatment to address their needs and priorities.

Thus, the results of these recent systematic reviews and meta-analyses suggest the potential benefit of using a social cognitive training program with a broad-based approach (ie,

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targeting multiple domains of social cognition), tailored to the person's needs, and focusing on transferring skills to functioning. Previous social cognitive training programs present with several strengths and have shown their efficacy to improve different domains of social cognition, particularly lower-level domains such as emotion recognition and social perception. However, as proposed by Peyroux and Franck [24], most programs currently use relatively basic deductive reasoning and associations and focus on only one domain of social cognition at a time, which is not representative of everyday social interactions that involve multiple domains of social cognition simultaneously. Using a program that emulates complex and multimodal real-life interactions, in addition to learning strategies to improve each domain of social cognition, might generalize learning to higher-order processes such as theory of mind or attributional bias. Furthermore, group interventions might not always be appropriate; an individualized and personalized approach using ecological digital relational simulations could help people with SSD practice these new skills in a safe environment with a therapist.

The program *Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie* (RC2S; Cognitive remediation of social cognition in Schizophrenia) is a French personalized social cognitive training targeting the 4 main domains of social cognition in SSD [6]. This program uses a practice and strategy learning approach to target the person's specific social cognitive deficits while also building on social cognitive domains that are preserved or less affected. RC2S includes paper-and-pencil sessions dedicated to learning strategies to improve the different social cognitive domains as well as integrative computerized ecological sessions to further practice these skills by interacting with an avatar in different social contexts and relationships through digital relational simulations [25]. A total of 2 case studies and a randomized controlled trial (manuscript in preparation) conducted in France with people with SSD have provided preliminary evidence of the acceptability, feasibility, and efficacy of RC2S with the report of significant improvements in social cognitive and functional impairments [24,26]. Although these preliminary results are encouraging, social stimuli and social behaviors can be interpreted differently and are influenced by the culture of the geographic regions in which they are assessed [8,27]. Thus, it is necessary to adapt social cognitive training programs to the language, expressions, and context of the culture in which they are used and to assess their effects in these different settings. This is particularly true for social cognitive training programs using digital relational simulations that include both verbal and nonverbal cues.

In addition, there is also a need to develop social cognitive interventions that are accessible to many people with SSD. The COVID-19 pandemic has highlighted the important vulnerability of health care delivery for people with SSD and the need to adapt evidence-based interventions such as CR to increase access to mental health care services. Remote interventions have rapidly developed in recent years, and these interventions address important factors that are known to limit access to psychiatric care for people with SSD, such as territorial disparities in the provision of health care services, geographic distance, or symptoms such as avolition or social withdrawal. Furthermore, for people with SSD within their process of recovery, it can also be a challenge to combine work, school, or other engagements with multiple visits to the clinic to receive CR. Delivering care remotely could also decrease the stigma and the self-stigma associated with visiting a hospital or a clinic to receive mental health care.

Objectives

This project aims to culturally adapt (ie, language, expression, and geographic context) the French program RC2S in North American English and French-Canadian. As RC2S was initially developed as an in-person intervention, we also aim to assess the feasibility, acceptability, safety, and implementation of the remote French-Canadian and North American English versions of RC2S in people with SSD. An additional exploratory objective is to assess the preliminary effect of remote RC2S on goal attainment, social cognition, and other psychosocial variables (eg, functioning and positive and negative symptoms). The data from this preliminary study will provide information for a future efficacy study of remote RC2S (randomized controlled trial).

Methods

Ethical Considerations

This project was approved by the Ethics Committee of the Montreal West Island Integrated University Health and Social Services Centre (#2022-333, IUSMD-21-34) on August 17, 2021.

Cultural Adaptation of RC2S

From August 2021 to December 2021, our team adapted and translated the RC2S program into North American English and French-Canadian. For the North American English version, the translation was performed by a professional agency and further revised by the bilingual members of our team. For the French-Canadian version, all scenarios were revised to adapt expressions and turns of phrase. The names of places and characters were also revised in both versions to culturally adapt to the scenarios. All audio files were then recorded by professional actors, and the realization was performed using the studio SFX based in Quebec City, Quebec, Canada. Our team then applied North American English and French-Canadian audio files to the computerized scenarios and videos in collaboration with the company Happy Neuron.

Study Design

This study is a pre-post quasi-experimental design. Quantitative measures will be used to assess the preliminary effect of RC2S on primary and secondary outcomes. To assess the feasibility, acceptability, and implementation of RC2S, homemade questionnaires including both quantitative variables and open-ended questions will be used.

Recruitment

A total of 2 categories of participants will be recruited for this study: participants with SSD and participants delivering the intervention (therapists).

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Participants With SSD

We aim at recruiting 20 participants with SSD. For these participants, the inclusion criteria will be as follows: (1) a diagnosis of schizophrenia or a related psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; (2) being followed and treated by a clinician at the Douglas Mental Health University Hospital; (3) being aged ≥18 years; (4) having either a self-report or an objective impairment (≤1 SD) in at least 1 social cognition domain (ie, emotion recognition, theory of mind, attributional bias, or social perception); (5) being considered symptomatically stable and capable of using the web-based platforms, as judged by their primary clinicians (ie, psychiatrist, case manager, or psychologist); (6) having access to the internet and to a private space (a room where the participant can be alone); and (7) being able to nominate an emergency contact as the study is conducted remotely. For this group, the exclusion criteria will be as follows: (1) evidence of an organic cause for cognitive difficulties (eg, neurological disease and history of brain trauma), (2) history of intellectual disability or autism spectrum disorder, (3) being hospitalized at the time of recruitment, and (4) inability to speak or read French or English.

Participants with SSD will be recruited through convenience sampling at the Douglas Mental Health University Institute. Participants will be recruited from (1) direct reference of the treating psychologist at the Centre d'Intervention Psychologique Personnalisé pour la Psychose (Ci3P; a clinic dedicated to psychological treatments for psychotic disorders), (2) directly from the individual's case manager following a clinic visit by the research coordinator to explain the research project, or (3) from our list of participants who were recruited in previous studies and gave their consent to be recontacted for future studies. A research assistant will call the participant to explain the research project, including the inclusion criteria, the assessment and treatment procedures, and the consent form. During this first contact, the research assistant will also assess access to the digital technology required for this project (eg, a smartphone, a tablet, or a computer).

Therapists

We aim at recruiting 5 therapists who will be included if they have a master's or doctoral degree in psychology, neuropsychology, or any relevant field or relevant clinical experience. They will be excluded if they are unable to speak or read French or English. The therapists will be recruited among the professionals offering services at the Douglas Mental Health Institute as well as research assistants in the Comprehensive Research into Schizophrenia and Other Psychopathologies laboratory. Participation in the project will be optional for those offering RC2S. Once they agree to act as therapists for this intervention and complete their training, they will be offered to participate in the research project. If they are interested, a research assistant will contact them by phone or a secure videoconferencing platform to complete a short screening and present the consent form. If they agree to participate, a short sociodemographic questionnaire will be administered. If they refuse to participate, the therapists will still be allowed to offer the intervention.

Procedure

Participants With SSD

The assessments will be conducted remotely via a secure videoconference platform by a trained research assistant physically present at the Douglas Research Center. A baseline will first be conducted during which the participants will read and sign the consent form and will be invited to ask any questions they may have. If they choose to participate, they will be invited to complete the remote assessment, which will last for approximately 2 hours. To continue with the intervention, the participant will have to present with a self-reported or an objective impairment in at least one of the main domains of social cognition, which will be determined by the baseline assessment. If a participant does not present with such a complaint or an impairment, financial compensation for the assessment will be provided, and it will be possible for the participant to be contacted for other psychosocial and cognitive interventions offered at the Ci3P.

For participants presenting with at least 1 social cognitive complaint or impairment following the baseline assessment, the intervention with RC2S will begin for 12 weeks. The intervention will be conducted remotely by trained therapists using a secure videoconference platform. In-session questionnaires will be administered to participants to assess their motivation toward treatment, their perception of the therapeutic alliance, their acceptability of the program, and its implementation. A posttest assessment will be conducted directly after 12 weeks of treatment.

Therapist

The therapists will be contacted by phone or videoconference to administer a short screening questionnaire and to present the informed consent form. If they are eligible and interested in participating, a short sociodemographic questionnaire will be administered. In addition, the in-session questionnaires will be completed at the same time as the participants with SSD. These questionnaires will assess their perception of the therapeutic alliance, the program, and the motivation of their client toward treatment.

Measures

For participants with SSD, the primary outcomes will consist of (1) therapy goal attainment (ie, assessing if the participants have not reached, reached partially, or reached completely their initial CR goals in daily life) and (2) the 4 main domains of social cognition (emotion recognition, social knowledge, theory of mind, and attributional bias) in addition to the functional impact of social cognitive impairments. The secondary outcomes will include measures of symptoms (positive and negative symptoms, depression, and social anxiety), functioning, recovery, and cognitive biases. In addition, complementary outcomes pertaining to different aspects of RC2S (eg, program interface, cultural adaptation, and ease of use) and remote delivery will be assessed through in-session questionnaires. These will include motivation toward the treatment, perception of therapeutic alliance, suicide risk, engagement toward treatment, feeling of immersion in the digital relational simulations, and aspects related to implementation (eg, attitudes

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toward the intervention such as its usefulness, the probability of using it, and the perception about one's ability to use the intervention).

For therapists, in-session questionnaires will be administered to assess their perception of their client's motivation toward treatment, therapeutic alliance, and their perspective and satisfaction toward RC2S. The details regarding the different measures and time of administration for both categories of participants are presented in Table 1.

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Table 1. List of measures included in the study.

Name of the measure and domain assessed	Time point
Participants receiving RC2S[a]	
Primary outcomes	
Goal Attainment Scale [28]	
Therapy goals attainment	Sessions 1 and 24
Penn Emotion Recognition Task [29]	
Emotion recognition	Baseline, posttest
Social knowledge test [30]	
Social knowledge	Baseline, posttest
Combined Stories Test [30]	
Theory of mind	Baseline, posttest
Internal, Personal and Situational Attributions Questionnaire [31]	
Attributional style	Baseline, posttest
Secondary outcomes	
Davos Assessment of Cognitive Biases Scale [32]	
Cognitive biases	Baseline, posttest
6-item Positive and Negative Syndrome Scale [33]	
Positive and negative symptoms	Baseline, posttest
Social Interaction Anxiety Scale [34]	
Social anxiety	Baseline, posttest
Patient Health Questionnaire [35]	
Depressive symptoms	Baseline, posttest
First Episode Social Functioning Scale [36]	
Functioning	Baseline, posttest
Questionnaire about the process of recovery [37]	
Recovery	Baseline, posttest
Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale [38]	
Functional impacts of social cognitive impairments	Sessions 1 and 24
Other outcomes	
Ask Suicide-Screening Questionnaire [39]	
Suicide risk	Session 1
MUSIC Model of Motivation Inventory, Cognitive Training version [40]	
Motivation toward RC2S	Sessions 5, 11, and 23
Working Alliance Inventory-Short form [41]	
Therapeutic alliance in RC2S	Sessions 5, 11, and 23
e-Therapy Attitudes and Process Questionnaire [42]	
Engagement in e-interventions	Session 24
RC2S+ Acceptability, Usability, Safety, Impact, and Satisfaction Questionnaire	
Implementation of RC2S	Session 24
Igroup Presence Questionnaire [43]	
Feeling of immersion in RC2S	Session 24
Therapists	
MUSIC Model of Motivation Inventory, Cognitive Training version for clinicians [40]	

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Name of the measure and domain assessed	Time point
Perceived client's motivation toward RC2S	Sessions 5, 11, and 23
Working Alliance Inventory-Short form—therapist [41]	
Therapeutic alliance	Sessions 5, 11, and 23
Questionnaire on therapists' perspective	
Perspective and satisfaction of the therapist regarding RC2S	Session 24

[a]RC2S: Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie.

In addition to measures administered with both categories of participants, objective indicators of feasibility will be collected, including the safety of the study (comprising whether there are any adverse events reported), the number of participants who have completed therapy (at least 50% of the treatment completed), reasons for dropping out, duration of sessions, and the number of missed sessions and reasons.

Intervention: RC2S

RC2S is an individualized computerized CR composed of 24 biweekly individual sessions of 1 hour with a therapist. The intervention is divided into 3 parts, as presented in Figure 1 and described in the subsequent section. RC2S provides a standardized approach regarding the material, duration, frequency, delivery of intervention, and CR principles and strategies, while also offering a personalized approach as a function of the person's profile.

Figure 1. Description of RC2S (Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie) sessions.

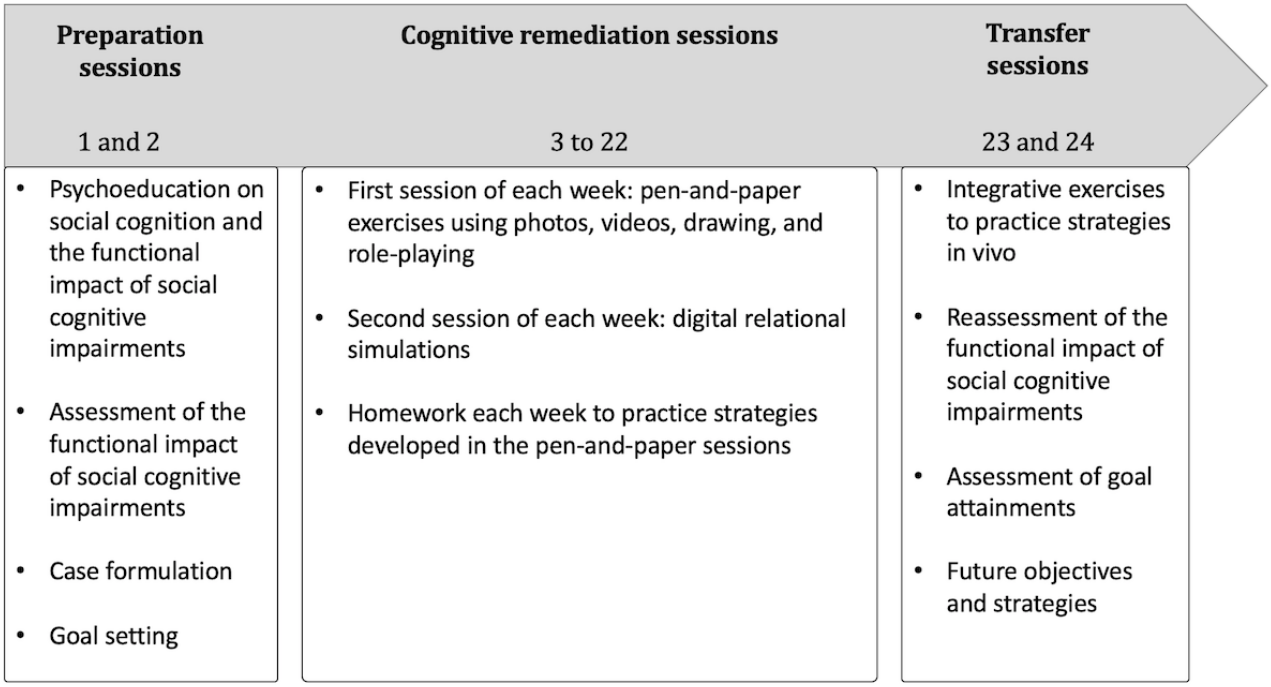

During the first 2 sessions of therapy, a case formulation is elaborated to identify the strengths, weaknesses, and CR goals. Psychoeducation about social cognition and the impact of social cognitive impairments on functioning is presented. To complement the objective assessment of social cognition performed at baseline, the functional impacts of social cognitive impairments are assessed with the Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale (ERF-CS; *Scale for the assessment of functional impacts of social cognitive deficits*) [38]. This semistructured interview explores the presence and impact of various social cognitive impairments in daily life. The interview also assesses how much the participant is bothered by these impairments. The results from the ERF-CS provide a detailed perspective on how social cognitive impairments disrupt the participant's life. Furthermore, given the psychometric limitations of most available social cognitive tasks, particularly regarding the ecological aspect of these tasks, the ERF-CS provides in-depth and concrete information to build a case formulation and support the client while creating treatment objectives. In this project, treatment objectives will be developed with the Goal Attainment Scale (GAS) [28], a flexible scale that allows the elaboration of personalized objectives before starting treatment, with a reassessment at the end of therapy. The GAS is rated on a scale from −2 to +2. A score of 0 indicates that the participant has reached their initial goal. Scores of +1 or +2 are obtained if the participant has exceeded or greatly exceeded their initial goal. Scores of −1 and −2 are obtained if the participant did not completely reach their objective. When the objectives are set, an operational definition is established for each level of rating.

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Weeks 2 to 11 of RC2S are dedicated to CR. During the first session of each week, stimuli such as photography, videos, and role-plays are used to teach strategies for social cognitive impairments, first for basic (eg, emotion recognition) and then for complex (eg, theory of mind) social cognitive processes. The number of paper-and-pencil sessions dedicated to each social cognitive domain, the exercises used to work on these domains, and the intensity of difficulty used are tailored based on the participant's objective and subjective social cognitive impairments, as well as the treatment objectives. Evidence-based strategies used in CR are applied in RC2S (eg, repeated practice, scaffolding, verbalization, errorless learning, and information reduction).

During the second session of each week, digital relational simulations are used. During each simulation, the participant assists a character named Tom in different social scenarios presenting various types of relationships and interactions (eg, Tom is having an altercation with his boss or Tom initiates a conversation with an acquaintance). Depending on each participant's individual difficulties, the order of presentation of the different scenarios is adapted to respect an increase in difficulty each week. For each scenario, the participant must read a short vignette introducing the simulation and answer the different questions on the *wheel of questions* (Figure 2A). The participant gathers information through the wheel of questions, including who will be involved in the simulation, where and when it is happening, what will be happening in the situation, why, and how. This initial analysis allows the participant to differentiate between what is a known fact in the situation and what is unknown, thus supporting the interpretations and choices that they will make during the simulation. Once the wheel has been completed, the participant begins the digital relational simulation. Each scenario is based on an algorithm of various propositions of behavioral patterns, and the scenario evolves based on the answer of the participant at each interaction. To assist Tom in navigating the different social scenes, the participant can choose among 3 types of behavior (ie, passive, aggressive, or assertive) based on social skills training and self-affirmation programs [24] (refer to Figure 2B for an example). The simulations are multimodal and integrative sessions that allow working on several social cognitive domains simultaneously including analyzing social context (social perception), emotions through verbal and nonverbal cues (emotion recognition), and understanding the mental states of Tom and his interlocutor (theory of mind) as well as their reactions (attributional style). For each interaction, the participant is encouraged to use the strategies learned during the paper-and-pencil sessions to perceive and interpret the different social cues and to verbalize these strategies. After the simulation, the participants' choices are decomposed to focus on specific social cues. It is also possible to run the simulation again to experience another behavioral approach to the scene; this allows the participant to experience how different social approaches can lead to different outcomes for both Tom and his interlocutor.

Figure 2. Digital relational simulations in RC2S (Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie): (A) The wheel of questions presented before each simulation; (B) An example of a digital relational simulation with an avatar.

In addition to the 2 therapy sessions, each week, the participant is also assigned a home activity related to the objectives of CR to practice strategies learned in sessions and to support bridging in everyday life.

Week 12 (sessions 23 and 24) is dedicated not only to the transfer of acquired skills to daily life via role-play or activities in the community but also to a final assessment of the progress that was made. These last 2 sessions are thus also dedicated to assessing the current situation of the participants regarding their perception of the functional impacts of social cognitive impairments and their objectives. During these sessions, the ERF-CS will be administered again to assess the progression regarding the functional impacts of social cognitive impairments from the beginning of the therapy. Furthermore, goal attainment will be assessed again with the GAS to determine if the participant reached their goals partially or completely. This will also allow a discussion on how the participant can continue working on goals that are partially reached and set new goals to work on in the future.

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Statistical Analysis

Power

On the basis of previous psychosocial intervention studies with a similar population at our recruitment site, we expect an attrition rate of 20% for the participants with SSD [44,45]. Thus, for a targeted sample of 20 participants, the inclusion of a maximum of 4 additional participants should be expected, leading to 24 participants with SSD. This sample size will allow us to determine potential barriers for remote RC2S, improve the protocol and the adapted versions, determine the preliminary effects of the treatment, and obtain sufficient data to compute effect sizes for statistical power analyses in a future efficacy study. Although no stratification for gender and language will be applied, we aim, as much as possible, to recruit 10 English speakers and 10 French speakers, and we aim to have a proportion of men and women that is consistent with what is observed clinically.

As for the therapists, we aim to recruit 5 participants to obtain a variety of perspectives.

Data Analysis

To assess the acceptability, feasibility, safety, and implementation of remote North American English and French-Canadian versions of RC2S, descriptive statistics will be used to summarize the objective indicators and the quantitative answers from the questionnaires (eg, number of missed sessions). Open-ended questions in the RC2S+ Acceptability, Usability, Safety, Impact, and Satisfaction Questionnaire and the Questionnaire on therapists' perspective will be classified into categories associated with the implementation of remote psychosocial interventions [46,47]. These analyses will notably determine if the participants with SSD and the therapists perceive the remote administration of the culturally adapted versions of RC2S as feasible and acceptable. We will assess the engagement of participants (eg, motivation, number of sessions completed, and number of completers), the perception of the usefulness of the intervention by both participants with SSD and therapists, and the overall satisfaction with the intervention and the delivery mode. This information is necessary to determine if the remote administration of the culturally adapted versions of RC2S is feasible and acceptable before planning an efficacy trial. These results will also provide information to determine if some modifications to the protocol are necessary.

For the objective regarding the preliminary effect of RC2S on primary and secondary outcomes, we will use an intention-to-treat approach, including the data of all participants who entered the study. Effect sizes will be calculated by subtracting scores at baseline from posttest scores and dividing them by the SD of baseline scores for both primary and secondary outcomes. Linear mixed models for repeated measures will be used to assess the effect of RC2S on both primary and secondary outcomes, with fixed effects of time. Gender, language, and the severity of social cognitive impairments will be used as covariates. Although *P* values will be calculated, we will be mostly interested in the effect sizes to guide power analyses for a future efficacy trial.

For other outcomes, including the in-session questionnaires, descriptive statistics will be used to summarize the data for both groups of participants. Motivation toward treatment and perception of therapeutic alliance will be correlated with primary and secondary outcomes, as well as with the objective indicators of feasibility and acceptability.

Results

Recruitment and data collection for the project started in January 2022, and the study is expected to be completed by August 2024. To date, 9 participants with SSD (3/9, 33% women and 6/9, 67% men) have completed the project (mean age 37.9, SD 9.3 years; mean years of education 12.6, SD 1.9 years). All participants completed the baseline and posttest assessments. They received a mean of 20.5 of 24 (SD 3.5) sessions of therapy, with a mean of 1.3 (SD 1.8) missed sessions. The reasons for missing sessions were related to the participant's health status (eg, being too tired or sick), schedule conflicts (eg, work or a medical appointment), or forgetting about the scheduled session.

We also recruited 5 women therapists who were doctoral-level students in psychology and neuropsychology (4/5, 80%) or a licensed neuropsychologist (1/5, 20%).

Discussion

Overview

This study will first provide necessary information regarding the translation and adaptation of RC2S in North American English and French-Canadian. Participants with SSD, therapists, and the members of the research team will be able to test the program to identify any typo or error that might be present in these initial versions of the program. This will be important to correct any issues for a future efficacy trial.

This project will also provide initial information regarding the feasibility and acceptability of remote administration of these new versions of RC2S. Thus, this study will provide the first insights into the positive impacts and challenges of delivering this intervention remotely, which has never been done before. We hope that we will be able to address most of these challenges in a future efficacy trial. Furthermore, the results from this project will provide information regarding the implementation of RC2S in clinical settings. This information is central to documentation in any intervention study, given the significant research-to-practice gap [48] limiting the implementation of interventions developed in the context of research in clinical settings.

Finally, this study will provide preliminary information regarding the effect of the intervention on different outcomes. This type of pilot study is essential to gathering data to guide a future efficacy trial. Among other advantages, the results of this study will provide the data to calculate the effect sizes necessary to determine the required sample size in a future randomized controlled trial assessing the efficacy of RC2S.

Dissemination of Results

The ClinicalTrials.gov page for this project will be updated with the results. We also plan on presenting the results of this project

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at local and international conferences and submitting them to a scientific journal in the fields of SSD and cognition. We also plan to disseminate these results to clinical teams and people with SSD through conferences to help recognize the presence and impacts of social cognitive impairments and the type of intervention that exists to support these difficulties. We also hope that this project will provide initial insight into the implementation of this intervention to facilitate its inclusion in clinical care.

Limitations

The first limitation of this study is the absence of a control group. We chose this quasi-experimental design because the main objective of this study is to adapt RC2S in North American English and French-Canadian and to assess the acceptability, feasibility, safety, and implementation of administering this intervention remotely. Although an exploratory objective is to assess the preliminary effect on different outcomes, we do not aim to establish the efficacy of this intervention. Even though we believe that a control group is not necessary to achieve these objectives, we recognize that the absence of a control group can limit our interpretations regarding the preliminary effects of the intervention.

The second limitation is the potential imbalance between gender and language among the participants. Our final sample might have an unequal proportion of women and men, as well as English- and French-speaking participants. On the basis of our previous studies with the same population and the same site of recruitment, we believe it will be possible to have a good representation of both genders and languages, with a ratio of 60% to 40% of people receiving their services in French or English at the Ci3P clinic and a ratio of 50% to 50% of women and men interested in participating in psychosocial interventions at the clinic. These variables will also be considered in our statistical analyses.

Conclusions

This is the first study to assess the acceptability, feasibility, safety, implementation, and preliminary effects of the new and remote North American English and French-Canadian versions of RC2S. Improving social cognitive impairment is an important target for SSD to promote functional recovery. Using digital technology to address these symptoms but also to deliver the interventions is a promising approach to increasing the ecological validity of CR and increasing access to the intervention.

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Data Availability

The data sets analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

ET was responsible, in collaboration with others, for the design of the study, the adaptation and translation of the program, for offering therapy to the participants, as well as the training and supervision of the therapists, and for writing this manuscript. She will also be responsible for the statistical analyses and for leading the future publications associated with this project.
ML was responsible, in collaboration with ET, for the design of the study and the writing of the manuscript. He will also be involved in the future publications associated with this project.
EP and NF both created the original French version of RC2S. They agreed to collaborate on the adaptation of their program in North American English and French-Canadian languages. EP trained ET to deliver the intervention and train therapists for the project. EP and NF were both available to answer any questions regarding the program and its delivery, and they revised the current manuscript. They will be involved in the future publications associated with this project.
HC helped with the revision of the manuscript and performed the formatting and linguistic revision. She also helped as a research assistant with the translation and adaptation of the North American English version and the assessment of the participants.

Conflicts of Interest

This project is carried out in collaboration with the company Happy Neuron, which owns the rights to the RC2S program. The RC2S program was originally developed in the French language, in France. This research project involves French-Canadian adaptation as well as North American English translation of the program, which has been conducted in collaboration with the company. However, no raw data from this project are shared with the company, and the company is not involved in the planning or administration of this project. The research team will receive profits from the sale of the French-Canadian and North American English licenses to reimburse the costs of translating and adapting the 2 licenses. Once this reimbursement is made, the research team will not receive any profits associated with the sales. Through this collaboration, the research team has free access to the RC2S license. This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund awarded

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Abbreviations

Ci3P: Centre d'Intervention Psychologique Personnalisé pour la Psychose
CR: cognitive remediation
ERF-CS: Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale
GAS: Goal Attainment Scale
RC2S: Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie
SSD: schizophrenia spectrum disorder

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Protocol

Implementing and Evaluating a National Integrated Digital Registry and Clinical Decision Support System in Early Intervention in Psychosis Services (Early Psychosis Informatics Into Care): Co-Designed Protocol

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Abstract

Background: Early intervention in psychosis (EIP) services are nationally mandated in England to provide multidisciplinary care to people experiencing first-episode psychosis, which disproportionately affects deprived and ethnic minority youth. Quality of service provision varies by region, and people from historically underserved populations have unequal access. In other disease areas, including stroke and dementia, national digital registries coupled with clinical decision support systems (CDSSs) have revolutionized the delivery of equitable, evidence-based interventions to transform patient outcomes and reduce population-level disparities in care. Given psychosis is ranked the third most burdensome mental health condition by the World Health Organization, it is essential that we achieve the same parity of health improvements.

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Objective: This paper reports the protocol for the program development phase of this study, in which we aimed to co-design and produce an evidence-based, stakeholder-informed framework for the building, implementation, piloting, and evaluation of a national integrated digital registry and CDSS for psychosis, known as EPICare (Early Psychosis Informatics into Care).

Methods: We conducted 3 concurrent work packages, with reciprocal knowledge exchange between each. In work package 1, using a participatory co-design framework, key stakeholders (clinicians, academics, policy makers, and patient and public contributors) engaged in 4 workshops to review, refine, and identify a core set of essential and desirable measures and features of the EPICare registry and CDSS. Using a modified Delphi approach, we then developed a consensus of data priorities. In work package 2, we collaborated with National Health Service (NHS) informatics teams to identify relevant data currently captured in electronic health records, understand data retrieval methods, and design the software architecture and data model to inform future implementation. In work package 3, observations of stakeholder workshops and individual interviews with representative stakeholders (n=10) were subject to interpretative qualitative analysis, guided by normalization process theory, to identify factors likely to influence the adoption and implementation of EPICare into routine practice.

Results: Stage 1 of the EPICare study took place between December 2021 and September 2022. The next steps include stage 2 building, piloting, implementation, and evaluation of EPICare in 5 demonstrator NHS Trusts serving underserved and diverse populations with substantial need for EIP care in England. If successful, this will be followed by stage 3, in which we will seek NHS adoption of EPICare for rollout to all EIP services in England.

Conclusions: By establishing a multistakeholder network and engaging them in an iterative co-design process, we have identified essential and desirable elements of the EPICare registry and CDSS; proactively identified and minimized potential challenges and barriers to uptake and implementation; and addressed key questions related to informatics architecture, infrastructure, governance, and integration in diverse NHS Trusts, enabling us to proceed with the building, piloting, implementation, and evaluation of EPICare.

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KEYWORDS

Early Intervention in Psychosis; digital registry; clinical decision support system; participatory co-design; participatory; co-design; registry; psychosis; mental health; psychiatry; decision support; study protocol

Introduction

Background

Psychotic disorders, including schizophrenia, are among the most disabling illnesses worldwide and are often accompanied by enormous personal, family, societal, and caregiver burden [1]. Rates of psychosis are unequally distributed throughout the population, with the highest rates found in historically underserved communities, younger populations, and those from minority ethnic backgrounds [2-5]. For example, within the United Kingdom, people from Black ethnic backgrounds (African, Caribbean, and British) are between 3 and 5 times more likely to experience a first episode of psychosis than White British individuals, and there is evidence that the rates are also approximately twice as high for people from Pakistan, Bangladesh, and mixed ethnic backgrounds in England [2,6]. Further, the need for treatment delivered by early intervention in psychosis (EIP) services in England has been identified as highest in several historically underserved regions of England, and in related major conurbations, such as Birmingham, Greater Manchester, Bradford, and parts of inner-city London [6]. This need for EIP care is closely aligned to populations exposed to greater structural disadvantage including multiple deprivation and social fragmentation [6].

EIP is an internationally adopted model of care based largely on social inclusion, service user and caregiver engagement, and relapse prevention. In England, EIP services are nationally commissioned to provide evidence-based, multidisciplinary care according to eight National Institute for Health and Care Excellence (NICE)–based national standards for people experiencing first-episode psychosis: (1) maximum waiting time of 14 days from initial referral to commencement of treatment; (2) offer of cognitive behavioral therapy for psychosis; (3) take-up of family interventions; (4) offer of clozapine after poor response to at least 2 other antipsychotic medications; (5) take-up of supported employment and education programs; (6) annual physical health assessments; (7) offer of interventions relevant to physical health (for example, smoking cessation, exercise, or substance use programs); and (8) take-up or referral to caregiver-focused education and support programs [7]. Each care standard is evidence-based, often from randomized controlled trials. Each standard has demonstrated improvement in patient outcomes, including remission of symptoms, readmission, recovery, premature mortality, and important social and vocational outcomes [8,9]. Importantly, EIP care is cost-effective relative to other forms of care and management for people with psychosis, and EIP services are highly valued by service users [10,11].

Despite evidence-based standardized targets, only 30%-40% of people experiencing psychotic disorders make a full recovery [12], with evidence of large variation in care [13-16]. Longer-term outcomes are equally poor, with increased rates of physical illnesses [17] and life expectancy reduced by around 15 years compared with people who do not go on to develop severe mental illness [18]. This suggests that much work is needed to understand which elements of EIP services are

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working, for whom, and whether they lead to better long-term outcomes [16].

Variation in outcomes may be related to regional or individual disparities in the care offered and received during EIP, particularly in historically underserved communities where the need is greatest, but where there may be insufficient resources to offer standardized care tailored to the needs of local populations. For example, recent data indicate that people with psychosis from Black African and Caribbean backgrounds were 15%-30% less likely to receive the equivalent level of cognitive behavioral therapy for their condition compared to White British people [19]. Cross-sectional survey data from England and Wales has highlighted further inequalities in care, with Black service users being around 44% less likely to be offered clozapine [19], the only existing medication for treatment-resistant schizophrenia [13]. There is also evidence for disparities in outcomes post-EIP, with deprivation related to higher rates of relapse and the need for continuing care in secondary mental health services [20]. Black and Asian racial minoritized groups are also more likely to continue in secondary mental health care 2 years following EIP discharge [21].

Despite this, data currently being routinely collected via a patient's electronic health record does not provide accessible, longitudinal, and nationally representative data to determine the magnitude, causes, or consequences of inequitable access to EIP care in England. Relatedly, routine data collected by EIP services in England does not include measures of symptomatic recovery, usually the primary outcome for understanding what treatments work for whom, thus preventing us from developing a national understanding of the clinical effectiveness of treatments in the real world. In turn, neither does it provide a mechanism for immediately improving clinical practice by feeding back real-time actionable insights that would allow treatments to be targeted and tailored to individual patient needs. For example, while all EIP providers send data on broad levels of service use into National Health Service (NHS) Digital's Mental Health Services Data Set, the data set is less suited to ascertain accurate estimates of the incidence of psychotic disorders in England, because current methods of data collection do not differentiate between people engaging in EIP treatment for their first-ever episode of psychosis and those who may have existing psychosis, but are engaging in treatment in a new EIP service for the first time. Further, Mental Health Services Data Set data do not record whether those engaging with EIP treatment later fulfill diagnostic criteria for psychotic disorder. The Mental Health Services Data Set also does not allow us to understand what treatments are delivered to whom and when, nor their impact on patient recovery and other downstream outcomes. Furthermore, the pioneering National Clinical Audit of Psychosis [22], which has assessed service fidelity annually since 2017, is a retrospective, cross-sectional manual audit of up to 100 patients with first-episode psychosis in each EIP team in England [22]. Although plans exist to revise the data collection methodology, the current practice reduces data quality, delays service improvement, and diverts finite EIP resources away from frontline care. There are also no plans for the audit to provide real-time feedback of data to clinical teams. These issues could be eliminated by the provision of a prospectively collected national digital psychosis registry, able to supply actionable insights in real time to patients, clinical teams, service managers, and policy makers via an embedded clinical decision support system (CDSS).

We propose to revolutionize the use of electronic health record data to improve national, local, and individual clinical decision-making and promote better patient and public health outcomes for people experiencing first-episode psychosis, by carefully developing and demonstrating the effectiveness of a prospectively collected digital registry and CDSS in England, capable of being implemented nationally. This would provide standardized information to understand the treated burden of psychosis in the NHS; ensure equitable, responsive, local resource allocation; support reliable, quick, and efficient identification and targeting of any local, regional, or group-based disparities in access to care; improve patient pathways through care and downstream outcomes, including recovery; and finally, enhance understanding of the relationship between interventions provided and outcomes, as well as the relationship between clinical and social characteristics and outcomes.

The potential for further record linkage to other health and social domains also offers the prospect of integrating prospectively collected data from other routine sources including primary care, the Office for National Statistics mortality, the Office for National Statistics Census, the National Pupil Database, and Hospital Episode Statistics. This would provide a deeply phenotyped, longitudinal database for clinical and policy decision-making. It would also support gold-standard research in clinical psychiatry, experimental medicine, and observational epidemiology, to identify, understand, and address the causes and consequences of disparities in health and patient treatment, as well as improve downstream outcomes for people experiencing psychosis.

Digital registries have been deployed successfully in the United Kingdom for other disease areas such as stroke, cancer, cystic fibrosis, and dementia [23-28]. For example, in the United Kingdom, a national stroke registry has transformed patient care and outcomes, with early recognition of different patterns of stroke presentation, focused treatment on previously untreated risk factors, and targeted interventions for improving cognitive impairment [27]. In cancer care, tailored interventions based on risk profiles have extended the lives of thousands of people [28]. Yet there are no contemporary examples of digital registries for any secondary care-treated mental health condition listed in the Health Research Classification System mental health category, nor within the international literature, and no specific CDSS for any mental health condition. Integration of a patient-centered digital registry and CDSS for psychosis could be equally transformative and give parity of esteem to one of the most common and disabling sets of mental health disorders—psychosis—where there is already a well-developed national infrastructure of EIP services.

To achieve this paradigmatic change in mental health care, our aim is to develop, evaluate, and establish a national psychosis registry and CDSS, known as EPICare (Early Psychosis Informatics into Care) in 3 stages. Stage 1—establish a multidisciplinary and multisector stakeholder network to

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co-design, derisk, and define the framework and protocols required to build and implement EPICare as a successful national registry and CDSS. Stage 2—build, pilot, implement, and evaluate the ability of the EPICare platform to improve patient care, enhance service delivery, reduce disparities in care, and demonstrate cost-effectiveness in 5 demonstrator NHS Trusts, serving underserved and diverse populations with substantial need for EIP care in England. Stage 3—subject to successful implementation and evaluation, seek NHS adoption of EPICare for rollout to all EIP services in England.

Aims and Objectives

In this paper, we report the protocol for the program development phase of our activity (stage 1), in which we aimed to co-design and produce a framework and protocols for onward building, implementation, piloting, and evaluation of a national integrated, patient-centered digital registry and CDSS for psychosis.

To meet this aim, we specifically addressed the following objectives: (1) establish a network with strong patient and public involvement and engagement (PPIE) and other essential stakeholders to identify essential and desirable elements and minimize unforeseen challenges (work package 1), (2) address key questions on informatics architecture, infrastructure, governance, and integration plans to facilitate onward development and testing of EPICare in diverse NHS Trusts (work package 2), and (3) identify implementation factors from the outset to ensure they are considered in designing, implementing, and maintaining the future deployment of EPICare in a measurable way (work package 3).

Methods

Study Design

We conducted 3 concurrent work packages over 12 months, with reciprocal knowledge exchange between work packages, coordinated via fortnightly program management group meetings. Figure 1 provides a schematic of work packages. The program management group contained a lived experience facilitator, lived experience member, clinicians working in early psychosis, and academic members from epidemiology, NHS health informatics, data, and implementation science.

Figure 1. EPICare program development phase study design. CDSS: clinical decision support system; EPICare: Early Psychosis Informatics into Care; PPIE: patient and public involvement and engagement.

Work Package 1: Stakeholder Co-Design of the EPICare Registry and CDSS

A participatory co-design framework previously established for informatics in mental health [29] was used to engage a diverse network of stakeholders, including clinicians, academics, policy makers, and PPIE members, in a series of 4 co-design workshops. Due to the COVID-19 pandemic, the workshops were convened online. While this enhanced the scope for collaboration between centers in the study, there were also potential drawbacks of this approach, which included PPIE members needing to have access to and know-how of technology. Second, hosting face-to-face meetings on neutral ground in an approachable format may have helped to remove traditional power structures. The workshops were in a facilitator-led, semistructured format, including presentations, whole-group discussions, and themed breakout activities (card-sort tasks and small group discussion) with both mixed (random allocation) and streamed group (by broad stakeholder type) sessions on a per-task basis. Essential materials were circulated to stakeholders in advance of each meeting. We also convened additional online preparatory sessions for PPIE

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stakeholders, led by our PPIE coordinator, to aid understanding and participation in the main workshops. Registry and CDSS goals were examined by stakeholders, who reviewed, refined, and identified a core set of essential and desirable measures that should be collected in the integrated EPICare registry and CDSS, across 4 domains: sociodemographic measures, treatment measures, patient-reported outcome measures, and clinician-reported outcome measures.

To facilitate this process, stakeholders were provided with a list of data already recorded in electronic health records in EIP services, in addition to information on data relevant to the 8 nationally mandated NICE standards for EIP care [30] and key outcome measures (Health of the Nation Outcomes Scales [HoNOS] on functioning; quality of life and treatment satisfaction [DIALOG]; and patient-reported recovery [QPR]). This was supplemented with a minimal set of other initial measures recognized as potentially relevant by the program management group based on expert knowledge, prior to the first workshop. Examples included symptom ratings, duration of untreated psychosis, and genotyping, among others. In workshops 1 and 2, stakeholders were asked to review, refine, prioritize, and suggest additions or subtractions from this list, with other data that may not currently be routinely collected, but considered by stakeholders to be essential or desirable. The group also explored what barriers to implementation and uptake may be encountered in EPICare (eg, data security and ownership, time for completion, and digitizing of routine data currently collected on paper). Similarly, in workshop 3, stakeholders identified the essential and desirable features of a CDSS to provide timely actionable insights for patients and clinicians, including potential clinician prompts to complete health assessments aligned to NICE standards for EIP care.

After these 3 initial workshops, we synthesized all information gathered via a modified Delphi approach involving all stakeholders and members of the research team, to develop a consensus of data priorities (what, when, and by whom). We shared this with the members of work package 2 to understand technical and governance barriers to implementation to further refine our framework to identify a set of “must have” and “could have” data elements. Finally, in workshop 4, we presented our proposed framework to stakeholders, sought further feedback, and outlined our plans for stage 2 of EPICare development. From our initial stakeholder network, we sought to retain a representative group of stakeholders for our stage 2 activity, who will continue to guide the pilot, testing, and evaluation throughout the project.

Work Package 2: Informatics Architecture, Infrastructure, and Integration—Framework, Protocol, and Tool Kit

Work package 2 aimed to reduce technical and governance challenges in the future full build of EPICare by addressing key questions and unknowns. Based on prior experience and knowledge, the area of biggest technical risk for EPICare is the retrieval of data from electronic health records and the standardization of this into a common data model, while ensuring compliance with information governance and ethical standards. Previous work by the group involved auditing all EIP services that are part of the National Institute for Health Research (NIHR) Mental Health Translational Research Collaboration in Early Psychosis (MHTRC-Early Psychosis), to inform understanding of the existing infrastructure, capacity, capabilities, and limitations around designing and developing the EPICare platform for potential national implementation. This initial scoping work has highlighted several different electronic health records in use as well as different ways of capturing and storing relevant data in each of the trusts.

To build on this knowledge, health informatics specialists within the research team contacted and liaised with 5 NHS Trusts, including Greater Manchester Mental Health NHS Foundation Trust, Birmingham Women’s and Children’s NHS Foundation Trust, Cambridgeshire and Peterborough NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, and Camden and Islington NHS Foundation Trust. Information technology team leads and proposed demonstrator sites were identified, gathering information to further understand what electronic health record system is used by each trust; what relevant data are currently captured in the electronic health record (key foci: 8 NICE standards for first-episode psychosis treatment); how that data can be retrieved, such as via application programming interface or through regular exports; how the data can, and should be secured during retrieval, complying to the highest information governance standards; and the data formats used for each type of data.

Once this information was captured from all trusts, it was then used alongside the information gathered from the stakeholders in work package 1 to develop and document key requirements for the EPICare system; software architecture for the registry and CDSS; data model design including standardization of data items into a common format; security threat model including planned treatments for identified threats; proposed infrastructure to include an appropriate hosting solution, such as a secure cloud environment; and an integration plan for retrieval of data from each trust’s electronic health record.

This was drafted into an overall framework document and set of technical infrastructure and information governance protocols and tool kits to inform the future build, pilot, implementation, and evaluation of the EPICare platform. With all of this in place, the technical and governance challenges for the main program grant for applied research application should be significantly reduced.

Work Package 3: Implementation Evaluation Framework

Working in parallel and in collaboration with the members of work packages 1 and 2, the purpose of this work package was to establish the preliminary implementation framework for the subsequent testing and rollout of EPICare. Founded on the idea that implementation research should be integrated throughout all stages of innovation development rather than at “end-stage,” this involved understanding the distinct and interconnected implementation issues within the stages of problem definition; iterative evidence-building, intervention conceptualization, development, and testing; and subsequent rollout, experimentation, and embedding in different service settings. With particular reference to EPICare, this involved

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understanding how the earlier stages of stakeholder engagement contributed to intervention development and, at the same time, how stakeholders perceived challenges to future adoption and use. With regards to PPIE stakeholders (work package 1), this involved understanding views about (1) current challenges in EIP care; (2) how clinical registries and CDSS might influence care and service improvement; (3) expectations about how interventions might be used in standard practice; and (4) participants' experiences of the co-design process. We also studied the early stage activities of the health informatics team (work package 2) to understand the explicit and tacit design assumptions; the contingencies presented by current technological parameters; the influence of prevailing governance arrangements; and importantly, to understand and evidence the interaction between the relative influence of multiple stakeholders in the co-design process. This evidence will be brought together with existing implementation science frameworks, such as normalization process theory (NPT) [31], in conjunction with complementary insights drawn from science and technology studies [32,33].

NPT helps understand how service innovations are implemented, embedded, and normalized within organizations, to the point where new practices are no longer regarded as new. It is different from other implementation models because it focuses on the specific "work" undertaken by social actors to implement innovations into everyday practice while taking into consideration the interplay between actions, contexts, and objects. NPT has 4 linked constructs, "coherence," or the work of making sense of an innovation; "cognitive participation," or the work involved when engaging with an innovation; "collective action," or the combined work of integrating new practices into existing skills, relationships, and contexts; and "reflexive monitoring," or the work of continually appraising and adapting to the introduction of new practices. It has been widely used to explain the factors that shape the implementation of complex interventions [31].

Field researchers directly observed all 4 stakeholder co-design workshops and considered the influence of multiple social, cultural, and organizational factors on the co-design process. They also observed a selection of key design meetings held between the technologists, NHS Trust partners, and other stakeholder groups to map and describe the iterative development of EPICare. Each researcher recorded their observations following an agreed semistructured guide which were then aggregated for analysis.

To clarify the observational data, qualitative semistructured interviews guided by the constructs from NPT were then conducted with all stakeholder groups to understand the factors likely to influence the subsequent implementation of EPICare. An initial set of questions and topics derived from the study objectives were used to systematically code interview transcripts and develop themes. This was piloted on 4 transcripts by 2 researchers, before agreeing to a revised set of codes, followed by further coding of remaining transcripts. Interviews focused on the different cognitive-cultural perspectives of each stakeholder group, their experiences of participating in the co-design process, and their perceptions about their influence on the co-design, together with their recommendations for subsequent development and testing.

Study Participants

Participants were recruited between November and December 2021. We recruited 40 participants across all stakeholder workshops (work package 1). This included at least 10 people with lived experience of psychosis, and ideally, lived experience of early intervention, to form the PPIE stakeholder group. PPIE members were recruited from the Birmingham University Youth Advisory Group, Cambridgeshire and Peterborough Foundation Trust, Bristol Lived Experience Advisory Panel, and PPIE networks at University College London, including those associated with the NIHR Mental Health Policy Research Unit. As an acknowledgment of the time and effort involved in taking part in the study, PPIE participants were reimbursed in line with the Involve payment policy [34], which equates to £25 (US $33.19 at the time of the study) per hour of participation.

The remaining 30 participants were recruited from the breadth of multidisciplinary care in EIP services (psychiatrists, psychologists, occupational therapists, social workers, and nurses), in addition to stakeholders from the charitable sector, NHS England, policy makers, and other academics, for facilitated group meetings. The clinical collaborators were recruited from NHS Trusts serving diverse and underserved areas with a combined population of approximately 3.4 million people (corresponding to 9.1% of the English population eligible for EIP services): Birmingham Women's and Children's Trust, Manchester Health and Care NHS Foundation Trust, Camden and Islington NHS Foundation Trust, Avon and Wiltshire Mental Health Partnership Trust, and Cambridgeshire and Peterborough Foundation Trust. Attendance at the stakeholder group meetings was taken as consent for this process and no individual written consent was required from stakeholders (including PPIE).

All stakeholders were also invited to participate in individual qualitative interviews in work package 3 to ensure that we selected a representative subset of each stakeholder group from our work package 1 stakeholder meetings. Written informed consent was obtained and interviewees were given a unique participant identification number, which was used throughout the transcription of interviews to ensure anonymity.

Given the online group format of the stakeholder workshops, individual participants attending these workshops were identifiable to each other and to the authors. However, the identities of participants who consented to an individual qualitative interview were known only to the interviewer, and as noted above, interviewees were assigned a unique participant identification number to ensure their anonymity during the transcription of their interviews.

Ethical Considerations

The EPICare study was reviewed and granted full ethical approval by the Health Research Authority on November 8, 2021 (306234). Attendance at the stakeholder group meetings in work package 1 was taken as consent for this process and no individual written consent was required from stakeholders, including PPIE contributors. Written informed consent was

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obtained from all stakeholders who participated in individual qualitative interviews as part of work package 3.

Given the online group format of the stakeholder workshops, participants attending these workshops were identifiable to each other and to the authors. However, the identities of participants who consented to an individual qualitative interview were known only to the interviewer, and interviewees were assigned a unique participant identification number to preserve the anonymity of their interview transcripts. PPIE contributors were reimbursed £25 (US $33.19 at the time of the study) per hour for their participation in the study, in line with the Involve payment policy [34].

Results

Work Package 1: Stakeholder Co-Design of the EPICare Registry and CDSS

In work package 1, we established a network with representation from PPIE and other essential stakeholder groups (clinicians, academics, and policy makers) and engaged stakeholders in a series of 4 workshops, using a modified Delphi approach to identify essential and desirable elements of the EPICare registry and CDSS and to develop a consensus of data priorities. The 4 co-design workshops took place in December 2021, February 2022, May 2022, and September 2022, respectively.

Work Package 2: Informatics Architecture, Infrastructure, and Integration—Framework, Protocol, and Tool Kit

Work package 2 occurred in parallel with work packages 1 and 3, between December 2021 and September 2022. In this work package, we collaborated with NHS informatics teams to address key questions about informatics architecture, infrastructure, governance, and integration plans to facilitate onward development and testing of EPICare in diverse NHS Trusts.

Work Package 3: Implementation Evaluation Framework

Work package 3 also took place between December 2021 and September 2022. In this work package, we conducted individual qualitative interviews with representative stakeholders and took notes during observation of the stakeholder workshops to identify implementation factors from the outset and ensure they are considered in designing, implementing, and maintaining the future deployment of EPICare in a measurable way. All interviews were recorded and transcribed. For quality control, transcript summaries were shared with participants and feedback was elicited as to their veracity. Observation notes of the stakeholder workshops and transcripts of the individual interviews were subject to interpretative qualitative analysis, guided by the NPT implementation science framework. Preliminary data analysis of observation notes involved producing short descriptive summaries of field observations, for the purpose of summarizing and sharing data with the study team. NVivo software (Lumivero) was used to organize the qualitative observational and transcribed interview data. An iterative coding process was followed with data being subject to systematic close reading and coding. Through sharing and deliberating preliminary codes and interpretations with the wider study team and through the processes of constant comparison, secondary inductive, and interpretative themes were developed. At this stage, the constructs of NPT were used to further analyze and explain the study findings. Through discussion and disputation with PPIE, clinicians, and the project team, inferences were made about how the implementation science framework should be further refined.

Stage 1 of the EPICare study is now complete and we are currently preparing a paper detailing our findings from work package 3 activities (ie, field observations of the stakeholder workshops and qualitative interviews). Data collected and decisions made in the stage 1 program development phase of the project will directly inform the stage 2 building, piloting, implementation, and evaluation of the EPICare platform and CDSS in 5 demonstrator NHS Trusts serving underserved and diverse populations with substantial need for EIP care in England. If successful, this will be followed by stage 3, in which we will seek NHS adoption of EPICare for rollout to all EIP services in England.

Discussion

In this program development phase (stage 1), we co-designed a framework and protocols for the onward building, implementation, piloting, and evaluation of the EPICare registry and CDSS. We achieved this by adopting a participatory design with input from diverse relevant stakeholders, including lived experience experts and clinical, academic, technologist, and organizational stakeholders. By engaging multiple stakeholders in an iterative co-design process, using qualitative methods to capture and synthesize rich data representing a variety of perspectives, we have met our work package 1 objectives of establishing a network with representation from PPIE and other essential stakeholder groups to collaboratively identify essential and desirable elements of the EPICare platform and CDSS. In addition, we have addressed key questions related to informatics architecture, infrastructure, governance, and integration in diverse NHS Trusts (in line with our work package 2 objectives), and in doing so, have identified and minimized potential challenges and barriers to uptake and implementation (thereby meeting our work package 3 objectives).

We are now ready to build, implement, and evaluate a national patient-centered digital registry and CDSS for psychosis (EPICare) to improve national, local, and individual clinical decision-making and promote improved outcomes for people experiencing first-episode psychosis. While similar efforts to leverage routinely collected data in EIP services are currently underway in other parts of the world; for instance, in Canada [35] and Australia [36]; the EPICare registry and CDSS potentially represent a paradigmatic shift, as they would be the first national patient-centered digital registry and integrated CDSS for psychosis, one of the most common and disabling mental health disorders disproportionately affecting deprived and disadvantaged youth. By combining routine, standardized, prospective data collection via a national digital registry with real-time actionable insights delivered to patients, clinical teams, service managers, and policy makers via an embedded CDSS,

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the overall aim of EPICare is to improve patient care, enhance service delivery, reduce disparities in care, and further our understanding of the relationship between the interventions offered to, and received by, young people receiving EIP care and outcomes. Insights provided by the EPICare registry will also enable more equitable, responsive resource allocation and more rapid, reliable identification of local, regional, or group-based disparities in access to care and treatment outcomes and will support clinical and policy decision-making and research on various aspects of early psychosis. The registry may also improve access to much-needed stratified trials (eg, for clozapine and neurostimulation) and facilitate the development of novel treatments.

While we have achieved all of the objectives set out for the first phase of this study, it is worth noting that adoption and integration of all the desirable elements identified by stakeholders may not be feasible or pragmatic for the initial build of the EPICare platform and CDSS. This will be tested in our next stage, as noted above.

A national psychosis digital registry—leveraging routine data to provide real-time actionable insights—will be vital to improving real-world outcomes, identifying and preventing inequalities in care, and ensuring that individuals receive the most appropriate treatments at the right time to promote recovery and maximize life chances.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

RU and JBK are joint project leads and hold joint senior authorship. SLG drafted the paper with further input from RU and JBK. SJ, GKM, MAP, NC, JW, JA, RJD, MM, SMA, TW, JBK, YL, TB, and SAS also contributed to the study as well as provided comments on the paper. All authors approved the final version.

Conflicts of Interest

GKM has received consultancy fees from ieso. RU reports speaker fees from Sunovion, Springer Healthcare, Otsuka, and Vitaris outside the submitted work and holds unpaid officership with the British Association for Pharmacology—Honorary General Secretary 2021-2024 and is deputy editor of the British Journal of Psychiatry. JA is funded by the NIHR Manchester Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

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Abbreviations

CDSS: clinical decision support system
EIP: early intervention in psychosis
EPICare: Early Psychosis Informatics into Care
HoNOS: Health of the Nation Outcomes Scales
MHTRC-Early Psychosis: Mental Health Translational Research Collaboration in Early Psychosis
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
NPT: normalization process theory
PPIE: patient and public involvement and engagement
QPR: The Questionnaire about the Process of Recovery

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Protocol

Examining Parent Mood, Feeding Context, and Feeding Goals as Predictors of Feeding Practices Used by Parents of Preschool Children With Avid Eating Behavior: Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: An avid eating behavior profile is characterized by a greater interest in food and a tendency to overeat in response to negative emotions. Parents use specific strategies to manage feeding interactions with children with avid eating behavior. While momentary and contextual factors, such as parental mood, have been found to influence parental feeding practices, there is a lack of research examining parents' daily experiences of feeding children with avid eating behavior. Examining this is important because parental feeding practices are key levers in tailored interventions to support children's healthy eating behavior.

Objective: We aim to describe the ecological momentary assessment methods and procedures used in the APPETItE (Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively) project, which aims to examine how variation in parental mood, feeding goals, and the context of eating occasions affect the parental feeding practices used to manage feeding interactions with children with an avid eating behavior profile.

Methods: Participants are primary caregivers from the APPETItE cohort who have a preschool-age child (aged 3-5 years) with an avid eating behavior profile. Caregivers complete a 10-day ecological momentary assessment period using signal- and event-contingent surveys to examine (1) mood and stress, (2) parental feeding goals, and (3) contextual factors as predictors of parental feeding practices.

Results: Recruitment and data collection began in October 2023 and is expected to be completed by spring 2024. The data have a 3-level structure: repeated measurements (level 1) nested within days (level 2) nested within an individual (level 3). Thus, lag-dependent models will be conducted to test the main hypotheses.

Conclusions: The findings from this study will provide an understanding of caregivers' daily experiences of feeding preschool children with avid eating behavior, who are at greater risk for the development of obesity. Understanding the predictors of feeding practices at the moment they occur, and across various contexts, will inform the development of tailored resources to support caregivers in managing children's avid eating behavior.

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KEYWORDS

ecological momentary assessment; avid eating; children's eating behavior; parental feeding practices; feeding behaviour; parent; children; eating behaviour; obesity; environmental factors; observational study; feeding; United Kingdom

Introduction

Individuals differ in their susceptibility to obesity due to complex interactions between genetic and environmental factors that contribute to the development of eating behavior [1]. One population who are at greater risk of developing obesity is children with more avid appetites. Avid eating behavior is characterized by higher enjoyment of food, greater responsiveness to food cues, a tendency to overeat in response to negative emotions, faster eating, less sensitivity to satiety cues, and lower levels of food fussiness [2,3]. We have established that around 1 in 5 children aged 3-5 years in the United Kingdom show an avid eating behavior profile [3]. The findings from prospective research have shown that avid eating behaviors are positively associated with children's adiposity [4]. Thus, children with avid eating behavior may be at greater risk of developing obesity. Given the immediate and long-term negative health consequences associated with childhood obesity [5], it is vital to identify strategies across time and contexts to support the development of healthy eating behavior for children with avid eating behavior profiles.

One powerful and modifiable influence on the development of children's eating behavior is the feeding practices used by parents or caregivers which directly influence what, when, and how much food children consume [6,7]. We have demonstrated that parents of children aged 3-5 years with an avid eating behavior profile use more restriction of food and greater use of food for emotion regulation than those children without avid eating behavior [3]. However, this analysis, like much research examining parental feeding practices, has relied on static, self-report measures that do not capture the intraindividual variability in parent feeding behavior across time and context. Further, 1 methodology that has been used more recently to capture variations in factors that influence feeding behavior is ecological momentary assessment (EMA). Research using EMA has extended our understanding of parent-child feeding interactions, demonstrating that parental feeding practices differ across time and contexts (eg, the type of eating occasion) [8,9]. This suggests that the use of specific parental feeding practices is situation-dependent and highlights the complexity of parent-child feeding relationships. While the use of momentary parental feeding practices remains to be examined in children with avid eating behavior, findings from qualitative research suggest that parental feeding practices used to manage children's avid eating behavior also vary by context, such as the type and location of the eating occasion [2]. For example, parents of children with an avid eating behavior profile reported greater use of controlling feeding practices at snack times, compared to mealtimes. Therefore, since feeding practices to manage children's avid eating behavior appear situation-dependent, research using momentary observation (eg, EMA) is needed to examine the effect of contextual factors on feeding interactions with children with avid eating behavior.

Other key influences on parental feeding practices include parental mood and stress [10]. EMA research has demonstrated that fluctuations in parental mood and stress throughout the day influence the subsequent use of parental feeding practices. For example, higher maternal stress and depressed mood earlier in the day have been found to predict feeding practices (eg, greater pressure to eat), and the type of food served in the evening (eg, fewer homemade meals) [11-13]. Furthermore, qualitative research has shown that parents use specific feeding strategies to manage challenging feeding interactions with children with avid eating behavior [2]. For example, parents described using indulgent feeding strategies, such as emotional feeding and food as a reward, when parenting energy is low. Given this, it is possible that momentary changes in parental mood and stress could influence the use of subsequent feeding practices with children with avid eating behavior. This remains to be examined but is critical for the development of effective support targeting feeding practices of parents of children with avid eating behavior. If mood and stress are key predictors of the use of less adaptive strategies, our intervention must provide support tailored for the management of those experiences.

Parental feeding goals have also been shown to influence feeding interactions [14]. Parental feeding goals may predict feeding practices, for example, parents may use greater restriction of less healthy foods when their feeding goal is health-related. Previous research has specifically focused on mealtime feeding goals [14], however, it is also important to investigate parental feeding goals during snack times, to determine whether feeding goals vary by time and context. Examining this is particularly important because parents of children with avid eating behavior have described their children as frequently requesting snacks [2]. Additionally, it is possible that parental mood throughout the day could influence subsequent feeding goals. For example, parents might aim to avoid stress and conflict at an evening meal after experiencing high stress throughout the day. However, whether fluctuations in parental mood throughout the day influence subsequent feeding goals remains to be examined.

In summary, EMA research has extended our understanding of parent-child feeding interactions, demonstrating that parental feeding practices are situation-dependent and are influenced by momentary factors, such as context and parental mood [8,11-13]. Feeding children with avid eating behavior is challenging [2], however, there is a lack of research examining parents' daily experiences. Thus, examining feeding interactions as they occur in real time and contexts using EMA will provide insight into the parents' experiences of feeding their child with avid eating behavior. Hence, this protocol aims to provide a detailed overview of the EMA methods and procedures used in the APPETItE (Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively) project. This study aims to

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examine how variation in parental mood, feeding goals, and the context of eating occasions affects the parental feeding practices used to manage feeding interactions with children with an avid eating behavior profile.

Methods

Study Design and Participants

This observational study is part of a larger program of research (APPETItE project) which examines feeding and eating in preschool children with avid eating behavior, to inform future intervention design and efficacy. The APPETItE project has identified an avid eating behavior profile in preschool children using latent profile analysis [3]. Primary caregivers (N=200) of a child aged 3-5 years who was identified as having an avid eating behavior profile in this initial study [3] are invited to participate in this EMA study. Given the novelty of this research, a reliable power calculation could not be conducted. Thus, based on previous research [11] we aimed to invite 200 parents to participate to account for attrition and to provide sufficient data to examine within- and between-subject effects. Eligibility criteria include English-speaking primary caregivers from the United Kingdom who are responsible for feeding their child for more than half the time when their child is at home. Caregivers whose child is autistic, has severe learning disabilities, or a chronic illness that directly influences their dietary requirements and eating habits are not eligible to participate.

Ethical Considerations

Ethical approval was provided by the Aston University Health and Life Sciences Research Ethics Committee (HLS21003). All participants are asked to provide informed consent.

Recruitment

Eligible primary caregivers are invited to participate by email. After registering their interest to participate, caregivers receive an email including details of how to download the mobile app, and how to complete the baseline questionnaire. Following completion of the baseline questionnaire, caregivers receive an email including details about how to complete the survey period, along with an information video and leaflet. If caregivers experience any technical difficulties, have any questions, or want to go through this study's procedures, they can contact the research team by email or arrange a video call.

Data Collection Procedures

Overview

Caregivers complete a baseline questionnaire, 10 days of EMA, and an end-of-study questionnaire. Participation in this study is remote; surveys are administered through a mobile smartphone app, which is downloaded directly to caregivers' personal smartphones. Caregivers who do not own a smartphone can request one from the research team to use for this study's period. This study, including a list of all the items used, was preregistered on the Open Science Framework [15].

Baseline Questionnaire

The baseline questionnaire gathers information about caregivers' food security and general mood (anxiety, depression, stress, and well-being). Caregivers are also asked to provide their home postcode as a measure of Index of Multiple Deprivation. The Index of Multiple Deprivation decile scores are calculated by ranking residential areas in England into 10 equal groups, with scores ranging from 1 (indicating the most deprived 10% of residential areas) to 10 (indicating the least deprived 20%-30% of residential areas) [16]. Caregivers' food security is measured using the Short Form of the Household Food Security Scale [17]. Responses are summed and categorized as 0-1 = high or marginal food security, 2-4 = low food security, and 5-6 = very low food security.

Additionally, caregivers are asked to complete 3 questionnaires to assess their general mood. The Hospital Anxiety and Depression Scale [18] measures caregivers' anxiety (7 items, eg, "I feel tense or wound up") and depression (7 items, eg, "I still enjoy the things I used to enjoy"). Responses are on a 4-point Likert scale from 0 (eg, "not at all") to 3 (eg, "most of the time"). The Hospital Anxiety and Depression Scale has been found to have good reliability and validity [19]. The Perceived Stress Scale [20] measures caregivers' baseline stress across 10 items (eg, "in the last month, how often have you felt nervous and stressed?"), with scores from 0 ("never") to 4 ("very often"). The Perceived Stress Scale is a valid and reliable measure [21]. Finally, the World Health Organization Well-Being Index [22] assesses caregivers' well-being across 5 items (eg, "I have felt calm and relaxed"), with scores from 0 ("at no time") to 5 ("all of the time"). The World Health Organization Well-Being Index has been found to have good reliability and validity [22].

Caregivers also provide information about how much time they usually spend with their child on a weekday and weekend, upcoming periods where their typical eating routine is altered (eg, holidays and feasting or fasting for religious reasons), or periods where they are not with their child (eg, shared custody). This information is gathered so that the EMA period can be adjusted to suit participants (eg, delaying the start date of the EMA period).

Ten-Day EMA Period

Overview

Caregivers complete 10 days of EMA surveys. While 7 complete days are required for this study, caregivers are asked to complete 10 consecutive days of EMA to allow flexibility for some incomplete days (eg, a sensitization period) [23]. The EMA period examines parents' mood, feeding goals, feeding practices, and contextual factors using three sampling schemes: (1) signal-contingent surveys (morning and mood surveys), (2) event-contingent surveys (food surveys), and (3) end-of-day surveys (Table 1). Surveys take less than 5 minutes for caregivers to complete.

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Table 1. Primary variables and covariates assessed during the 10-day EMA[a] period.

Survey (delivery) and variables	Example item
Mood survey (notification)	
Feeding goals[b]	To give my child food that is nutritious
Mood	I feel annoyed
Stress	I feel tense
Context	Who am I with?
Food survey (self-initiated)	
Feeding practices	Did you have to make sure your child did not eat too much food?
Feeding goals	I didn't want to give in to my child, even if this caused an argument
Context	Where did your child ask for food?
End-of-day survey (notification)	
Mood	How stressful was your day?
Feeding practices	Today, how often did you have to limit your child's eating of snack foods?
Children's eating behavior	How satisfied are you with how your child ate today?

[a]EMA: ecological momentary assessment.

[b]Examined at the morning survey only.

Signal-Contingent Surveys

Each day, caregivers are sent four signal-contingent surveys at semirandom times within one of four 120-minute blocks: 7 AM to 9 AM (morning survey); 10 AM to noon; 1 PM to 3 PM; and 4 PM to 6 PM. Each block is separated by 60 minutes, to avoid overlap between surveys. To accommodate different routines, the notification window for morning surveys can be adjusted between 5 AM and 9 AM. When a survey is ready to complete, caregivers receive a notification on their phone. A reminder notification is sent 15 minutes after the initial notification, if the survey has not been completed, to ensure that responses are momentary [24]. From the first notification, caregivers have 60 minutes to complete notification surveys before the link expires.

Signal-contingent surveys examine caregivers' mood (positive and negative affect), stress, and the context in which the survey is completed. Items measuring positive and negative affect are adapted from the Positive and Negative Affect Schedule [25] and have been used extensively in EMA research [26]. Items measuring parents' stress are adapted from the Perceived Stress Scale [20] for use in EMA research [23,27]. All responses are made on a 5-point Likert scale from 1 ("not at all") to 5 ("extremely"). Surveys also examine the context in which caregivers complete the survey, using questions adapted from the PsyMate (Department of Psychiatry and Psychology at Maastricht University) standard assessment protocol [28]. To determine whether feeding goals vary throughout the day, morning surveys examine parental feeding goals. Questions are adapted from the Family Mealtime Goals Questionnaire [14] to assess caregivers' health-related goals and stress and conflict avoidance goals. Feeding goals are not examined in other mood surveys.

Event-Contingent Surveys

Event-contingent (food) surveys are self-initiated by caregivers each time their child asks for or consumes food when their caregiver is present. For example, eating occasions when children are at preschool will not be reported. Caregivers have previously reported that children with avid eating behavior frequently ask for food [2], thus, caregivers are asked to report each time their child requests food, even if their child is not given food (eg, not allowing children a snack before dinner). Food surveys involve (1) "food consumed" surveys and (2) "food request" surveys. While the same broad domains are assessed, questions are adapted to suit the type of feeding situation. For example, "food consumed" surveys ask caregivers about their goals for the eating occasion ("what was your aim for this meal or snack time?"), whereas "food request" surveys ask caregivers about their goal for saying no ("what was your aim for saying no to your child when they asked for food?"). Caregivers are directed to complete a "food consumed" survey if they report that their child has eaten or to complete a "food request survey" if they report their child asked them for food but has not eaten.

Food surveys examine parental feeding practices across several domains: structure-related, autonomy support, coercive control, and indulgent feeding practices. Indulgent feeding practices are only measured in "food consumed" surveys because questions relate to occasions where children consume food. Questions are adapted from the Real-Time Parent Feeding Practices measurement tool [29]. Food surveys also examine parental feeding goals, including health-related goals, and stress and conflict avoidance goals. Questions are adapted from The Family Mealtime Goals Questionnaire [14] to suit the EMA format. For example, responses were changed from a 5-point Likert scale to "yes" or "no." A "not applicable" option was also included for questions about parental feeding practices. When assessing parents' main feeding goal, the "other" response option

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can be selected for parents to specify their own feeding goal. Questions examining the context of eating occasions and requests for food are adapted from the EMA component of the Family Matters study [23].

Completing event-based surveys relies on self-initiation by caregivers, thus, there may be occasions when caregivers forget to report children's food requests or consumption. To ensure these feeding interactions are captured, each EMA survey ends with the option to report an occasion where children have asked for, or consumed food, that caregivers have not previously reported, as done in other EMA research [23,30].

End-of-Day Surveys

Each day, caregivers are asked to complete an end-of-day survey to provide a summary of how their day has been. Caregivers receive a semirandom notification between 8 PM and 10 PM when the end-of-day survey is ready to complete. Caregivers can adjust the survey window between 7 PM and midnight, to suit their evening routines. A reminder notification is administered 15 minutes after the first notification if caregivers have not yet completed the survey. End-of-day surveys are available for 60 minutes after the initial notification, before expiring.

End-of-day surveys include general questions about parental mood and feeding practices, the amount of time parents spent with their child, children's eating behavior, and a feasibility question [23]. Questions also assess the number of meals and snacks children consumed and requested throughout the day, to help determine parents' compliance with completing food surveys.

Feasibility and Usability

After the 10-day EMA period, caregivers complete a short questionnaire to assess the feasibility and usability of completing the EMA period. Questions are adapted from the PsyMate standardized protocol [31]. Examining the feasibility and usability of completing EMA research is important in this sample since feeding interactions with children with avid eating behavior can be challenging [2].

Incentives

Caregivers receive a £100 (approximately US $126) shopping voucher if at least 8 days of surveys are complete. Based on previous research [29], the criteria for 1 complete day of EMA includes the completion of 2 signal-initiated (random) surveys and 1 event (food) survey. This accommodates for a variation in routines (eg, families where the child consumes most of their food in childcare settings), but also provides sufficient data to analyze within-day effects. All caregivers who complete 10 days of EMA are entered into a prize draw to win an additional £100 (approximately US $126) shopping voucher. If participants withdraw prematurely from this study, their time is reimbursed on a pro rata basis of £10 (approximately US $12.60) per complete day. The digital shopping vouchers are emailed to participants after taking part.

Pilot Study

Study procedures were piloted with 25 primary caregivers of children aged 3-6 years with high food approach tendencies, to determine the feasibility and usability of this study's processes. All caregivers provided feedback about their participation in this study which informed researchers of the adjustments needed (eg, increasing the time surveys are available) and technical difficulties.

Results

Overview

Recruitment and collection of data began in October 2023. At the time of this paper's submission, data collection is ongoing and is anticipated until spring 2024. This study hypothesizes that parental mood, feeding goals, and the context of eating occasions (eg, meal setting) will predict the feeding practices that parents use to manage children's avid eating behavior. Specifically, analyses will test the following hypotheses: (1) higher momentary stress, negative affect, and goals of reducing mealtime chaos will predict use of coercive and instrumental feeding practices at the subsequent eating occasion; (2) parental feeding goals will change throughout the day in response to parental mood, feeding goals, and mealtime context; (3) momentary mood and context will be associated with parental feeding goals; (4) parents will be more likely to report coercive and instrumental feeding practices when in public and when they report the atmosphere as tense or stressful; and (5) parental low mood, high stress, increased requests for food will predict changes in feeding goals.

Statistical Analysis Plan

SPSS (IBM Corp) will be used for data cleaning and descriptive analyses, and R (R Foundation for Statistical Computing) will be used for main analyses. Skewness and kurtosis will be evaluated before data analysis, with relevant transformations administered if data violate the assumptions of the model. The data have a 3-level structure: repeated measurements (level 1) nested within days (level 2) and nested within an individual (level 3). Thus, lag-dependent models will be used to test our main hypotheses. More details of the analytic plan are on the Open Science Framework [15].

Discussion

Principal Findings

This will be the first study to examine how fluctuations in parental mood, feeding goals, and the context of eating occasions affect the parental feeding practices used with children with avid eating behavior. Determining momentary and contextual factors that influence parental feeding behavior is essential for better understanding caregivers' daily feeding experiences. This is particularly important for caregivers of children with avid eating behavior since eating occasions have been reported as frequent and challenging [2].

However, experiencing frequent and challenging feeding occasions could negatively impact caregivers' engagement with EMA. For example, caregivers would need to complete many food surveys, making this study more burdensome. In addition, time constraints have been reported to impact feeding decisions [32]; thus, caregivers of preschool children who are time-poor

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may struggle to engage with the EMA period. Hence, this study will provide an important understanding of the feasibility of conducting EMA research with a diverse sample of caregivers of preschool children with challenging eating behavior.

Strengths and Limitations

This use study uses a novel methodology to gather a large amount of data about parental behavior across multiple time points and contexts. This novel approach will further our understanding of parental feeding practices, which has been predominantly based on static self-report measures, by capturing the intraindividual variability in feeding behavior across time and context. However, this study has several limitations. First, the use of a mobile app in this study relies on participants having good technological literacy, which may exclude participants from underrepresented communities. To improve the accessibility of this study, researchers from the APPETItE team can be contacted by email, web-based video chat, or phone to discuss and troubleshoot issues. Second, the limited number of items used in this study may not fully reflect parents' experiences. However, given the large number of surveys, each survey must be short enough to reduce participant burden, while gathering sufficient information about parent behavior. Finally, the 10-day survey period may be particularly intensive for parents of preschool children with avid eating behavior given the expected frequent requests for food. This could potentially result in high attrition and data loss, and limit the findings to parents with the resources to complete multiple surveys. Given this, and the novelty of EMA research in this area, it is important to examine the feasibility of using this methodology with parents who may be experiencing feeding challenges with their child.

Conclusion

Overall, this novel study will provide momentary evidence about caregivers' daily experiences of feeding preschool children with avid eating behavior. The findings will contribute to the APPETItE project which aims to produce tailored guidelines to help parents nurture the development of children's healthy eating behavior, particularly for children who are at greater risk for the development of obesity.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors were involved in the conceptualization and methodology of this study, and the writing (review and editing) of this paper. KE was responsible for writing the original draft. JB, HC, CF, MH, CL, and EH worked on the funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

APPETItE: Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively
EMA: ecological momentary assessment

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Protocol

Evaluation of the Gonadotoxicity of Cancer Therapies to Improve Counseling of Patients About Fertility and Fertility Preservation Measures: Protocol for a Retrospective Systematic Data Analysis and a Prospective Cohort Study

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Abstract

Background: Cytotoxic treatments such as chemo- and radiotherapy and immune therapies are required in cancer diseases. These therapies have the potential to cure patients but may also have an impact on gonadal function and, therefore, on fertility. Consequently, fertility preservation treatments such as freezing of gametes and gonadal tissue might be required. However, as detailed data about the necessity to perform fertility preservation treatment are very limited, this study was designed to fill this data gap.

Objective: Primary objective of this study is to analyze the impact of cancer therapies and chemotherapies on the ovarian reserve and sperm quality. Secondary objectives are to analyze the (1) impact of cancer therapies and chemotherapies on other fertility parameters and (2) probability of undergoing fertility preservation treatments in relation to specific cancer diseases and treatment protocols and the probability to use the frozen gametes and gonadal tissue to achieve pregnancies.

Methods: First, previously published studies on the gonadotoxicity of chemo- and radiotherapies among patients with cancer will be systematically analyzed. Second, a prospective cohort study set up by approximately 70 centers in Germany, Switzerland, and Austria will collect the following data: ovarian function by analyzing anti-Müllerian hormone (AMH) concentrations and testicular function by analyzing sperm parameters and total testosterone immediately before and around 1 year after gonadotoxic therapies (short-term fertility). A follow-up of these fertility parameters, including history of conceptions, will be performed 5 and 10 years after gonadotoxic therapies (long-term fertility). Additionally, the proportion of patients undergoing fertility-preserving procedures, their satisfaction with these procedures, and the amount of gametes and gonadal tissue and the children achieved by using the frozen material will be analyzed. Third, the data will be merged to create the internet-based data platform FertiTOX. The platform will be structured in accordance with the *ICD* (*International Classification of Diseases*) classification of cancer diseases and will be easily be accessible using a specific App.

Results: Several funding bodies have funded this study. Ten systematic reviews are in progress and the first one has been accepted for publication. All Swiss and many German and Austrian ethics committees have provided their approval for the

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prospective cohort study. The study registry has been set up, and a study website has been created. In total, 50 infertility centers have already been prepared for data collection, which started on December 1, 2023.

Conclusions: The study can be expected to bridge the data gap regarding the gonadotoxicity of cancer therapies to better counsel patients about their infertility risk and their need to undergo fertility preservation procedures. Initial data are expected to be uploaded on the FertiTOX platform in 2026.

Trial Registration: ClinicalTrials.gov NCT05885048; https://clinicaltrials.gov/study/NCT05885048

International Registered Report Identifier (IRRID): DERR1-10.2196/51145

(JMIR Res Protoc 2024;13:e51145) doi:10.2196/51145

KEYWORDS

fertility; fertility preservation; cancer; gonadotoxicity; FertiPROTEKT; FertiTOX; data analysis; cohort study; internet; platform; internet-based; data

Introduction

Background

After reaching milestones in fertility preservation such as freezing of sperm and testicular tissue—and more recently, the first birth after transplantation of cryopreserved ovarian tissue [1], the introduction of luteal-phase random-start gonadotropin stimulation [2], and vitrification of oocytes [3]—fertility preservation treatments have been introduced in most countries, and fertility preservation has been accepted and defined as an important element to be considered before cancer treatments (Figure 1).

Medically, this has been evidenced by several national and international guidelines stating that fertility preservation counseling is required before administering gonadotoxic therapies [4-11], and this has been politically been shown as many countries have introduced reimbursement or coverage of fertility preservation treatments.

However, data about the gonadotoxicity of the numerous cancer treatment regimens are mostly very limited. Additionally, a recent study in mice has revealed that immune therapies such as checkpoint inhibitors have substantial impact on the ovarian reserve [12], but human data are not yet available.

Accordingly, indications for or against fertility-preserving therapies are not well defined with either the risk of overtreating patients or imposing unnecessary medical risks and burdens to the patients and, therefore, unnecessarily postponing the gonadotoxic therapies. However, the risk of undertreating patients with respective therapies imposes the risk of infertility, which can have a substantial impact on their quality of life after the onset of cancer [13].

Meanwhile, effective methods are available to reliably quantify the gonadotoxicity of cancer therapies. In women, ovarian function can be evaluated by analyzing anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) concentrations, and in men, testicular function is evaluated by analyzing sperm counts and total testosterone, FSH, and LH concentrations.

Figure 1. Algorithm for indicating fertility preserving therapies in women and men.

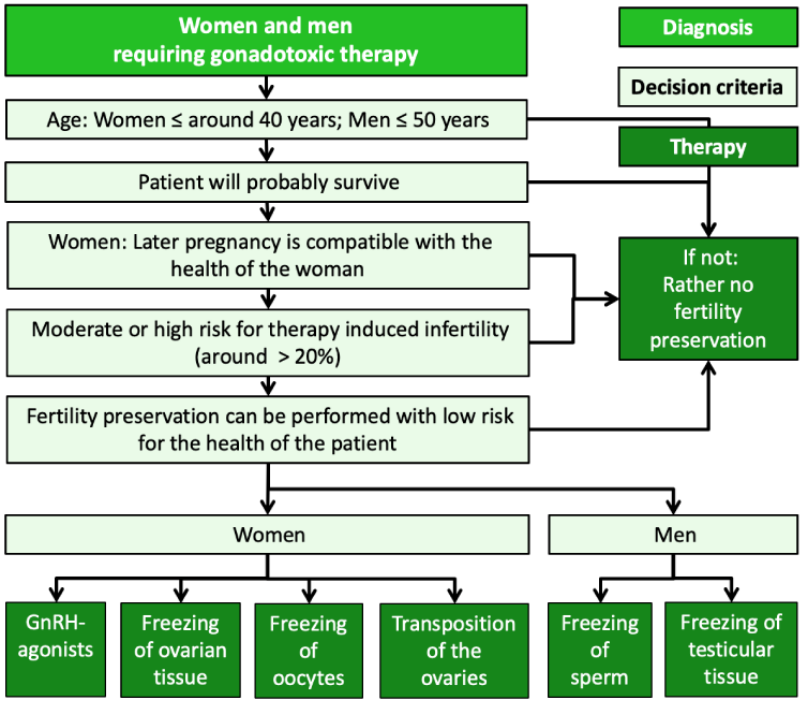

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Even though these functional parameters exist, prospective and systematic short- and long-term data regarding the impact of specific cancer therapies on fertility based on these parameters are limited. It can be assumed that this is due to a lack of effective fertility preservation network structures in most countries. However, in Switzerland, Germany, and Austria, network structures that permit a systematic and continuous large-scale data analysis have been established.

Data should be made available as an easily accessible internet-based platform that is merged with already published data on the gonadotoxicity of cancer therapies and other relevant data such as the 5-year survival rates of the cancer diseases. The data platform will support physicians and other experts as well as patients in counseling about fertility risks imposed by cancer treatments and the necessity to undergo fertility-preserving measures.

We, therefore, designed a study to collect data on the gonadotoxicity of cancer therapies by systematically analyzing already published data and by setting up an international multicenter prospective cohort study to collect data on the gonadotoxicity of chemotherapies, radiotherapies, and immune therapies among men and women and to upload summarized data on an internet-based data platform.

Objectives

The primary objective is to determine whether cancer therapies and specific chemotherapy protocols reduce AMH concentrations in women and sperm quality in men.

Secondary objectives are to analyze the impact of cancer therapies and chemotherapies on other fertility parameters such as the probability of undergoing fertility-preserving treatments in relation to the type of cancer disease and specific treatment protocols, the number of children, the future wish to have children, and age. Further objectives are to assess satisfaction with the decision to have undergone fertility-preserving procedures, the proportion of women and men who use their frozen gametes to achieve a pregnancy, the effect of different gonadotoxic therapies on long-term fertility, and the quality of life after the administration of cancer therapies.

Methods

Study Design

The study consists of 2 parts: first, a series of systematic reviews; second, an international multicenter prospective exploratory observational cohort study of fertility-related parameters with a long-term follow-up of the fertility of patients with cancer in university and nonuniversity public hospitals and private infertility centers in Germany, Switzerland, and Austria. All data will be uploaded on an internet-based data platform.

First Part: Retrospective Systematic Data Analysis

A series of systematic reviews will be performed in Switzerland, one of which will be performed in Germany. The reviews encompass diseases for which a sufficient number of studies has been published to perform a systematic review and which are relevant regarding fertility and fertility-preserving issues. The following reviews were initiated in 2023 and 2024 or are expected to be published in 2024 and 2025. They are registered in PROSPERO:

- A systematic review of the gonadotoxicity of Osteoscarcoma and Ewing´s sarcoma chemotherapies in postpubertal females and males: CRD42023331654, accepted for publication (*Journal of Adolescent and Young Adult Oncology*).
- Effects of chemotherapy and radiation in male genital organ tumors on ovarian and testicular function and fertility: CRD42023384057, submitted for publication in 2024.
- Effects of chemotherapy and radiation in mesothelial and soft tissue cancer on ovarian and testicular function and fertility: CRD42023385402, to be submitted for publication in 2024.
- Effects of chemotherapy, radiation and immunotherapy in breast cancer on ovarian and testicular function and fertility: CRD42023384042, to be submitted for publication in 2024.
- Effects of bone marrow transplantation in hematological cancers on ovarian and testicular function and fertility: CRD42023486928, to be submitted for publication in 2024.
- Effects of chemotherapy and radiation in eye, brain and central nervous system cancer on ovarian and testicular function and fertility: CRD42023385408, to be submitted for publication in 2024.
- Effects of chemotherapy and radiation in Hodgkin lymphoma on ovarian and testicular function and fertility: CRD42023384052, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in Non-Hodgkin lymphoma on ovarian and testicular function and fertility: CRD42024511940, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in colorectal cancer on ovarian and testicular function and fertility: CRD42024511944, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in leukemia on ovarian and testicular function and fertility: CRD42024511946, to be submitted for publication in 2025.

Second Part: Prospective Cohort Study

The cohort study will collect data on the ovarian reserve and sperm from patients undergoing gonadotoxic therapies. Data collection was initiated on December 1, 2023, and will be continued at least for 5 years to analyze short-term fertility. Long-term fertility data will be collected until at least 2036. An initial version of the FertiTOX internet-based platform is expected to be set up in 2026. The trial is registered in ClinicalTrials.gov (NCT05885048).

Inclusion Criteria

Each center that counsels patients with cancer about fertility issues and can also provide fertility-associated parameters may participate. A prerequisite requirement is that each center has received ethical approval for the study. Even though the study is intended to mainly include FertiPROTEKT network centers [14] and FERTISAVE [15] networks in Germany, Switzerland, and Austria, any other center worldwide can participate if the inclusion criteria are fulfilled.

Women and men aged 14-50 years (18-50 years in Germany due to national regulations) undergoing cancer therapies using

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chemotherapy, radiotherapy, or immune therapy (Figure 1) will be included.

Recruitment and Informed Consent Procedure

Patients are recruited by reproductive physicians who are associated with the participating infertility centers. Approximately 70 centers (44 in Germany, 21 in Switzerland, and 6 in Austria) will participate in the study and will collect data (see Multimedia Appendix 1).

Patients who need gonadotoxic therapies will be counseled before the onset of the respective therapies. During counseling, patients are screened for their eligibility to be included in the study.

Furthermore, patients will be provided counseling forms to provide informed consent before the onset of gonadotoxic therapy to collect specific basic data and data on gonadal function from patients with cancer. Data will also be collected 12-15 months and 5 and 10 years after the end of gonadotoxic therapy.

The study participants will be informed that they will be contacted by the fertility center or a defined coworker of the study by telephone, email, or post to collect the respective data after the administration of gonadotoxic therapy.

Study Registry

Data will be collected using the REDCap (Research Electronic Data Capture) software, a secure web application for building databases [16]. The REDCap registry has been set up and optimized by the study consortium with the support of the Clinical Trials Unit in Bern, REDCap technicians, and statisticians. The contents of the study registry (consultation before and 12-15 months after the end of the gonadotoxic therapy) are shown in the paper version of the registry (Multimedia Appendices 2-5). The participating centers will add the data to the registry without adding any definite identifiers such as name and date of birth. The participating centers can only see their patients. Patients can be traced with an individual code that is safeguarded by the centers. Only very few authorized persons will be provided access to all data in order to assess the data quality and to remind the centers to invite the patients for follow-up consultations.

End Points

The primary end points are the AMH concentration in women and sperm count before and after gonadotoxic treatments. End points will be assessed before and 12-15 months after the end of the gonadotoxic treatments (patients with melanoma receiving adjuvant checkpoint inhibitor treatment will be evaluated every 3 months).

Secondary end points are FSH, LH, and E2 concentrations in women and total testosterone, FSH, and LH concentrations, total sperm count, and sperm motility in men. Further secondary outcome parameters are the number of patients who freeze gametes and gonadal tissue and satisfaction with the decision to have undergone fertility-preserving measures.

Long-term end points to be determined 5 and 10 years after the end of the gonadotoxic therapy are the abovementioned hormone and sperm parameters as well as the number of patients who become pregnant after gonadotoxic therapies spontaneously or after the use of frozen gametes and gonadal tissue.

Sample Size Calculation

A power calculation was performed to determine whether the expected number of patients is sufficient to detect an effect of cancer treatment on fertility with a reasonable power.

The calculation was performed for the primary outcome (ie, sperm count for men and AMH concentration for women) for men and women separately. Calculations were performed within each cancer entity and for each specific treatment protocol separately with a paired *t* test using Stata (release 17.0; StataCorp).

We set the effect size so that a relative risk of 50% was not missed. For the sperm count, where the mean value in healthy men is 64 million (SD 47 million) [17], this would correspond to an effect size of 0.67. For AMH concentration in women, where means and SDs can be assumed to be equal [18], it would correspond to an effect size of 0.5. The intraindividual correlation was set to 0.5 [17,18]. To account for multiple testing (analysis will be performed with 43 treatment groups for men and women separately), the Šidák correction was used, and the significance level was adjusted to 0.0006 (2-sided).

Table 1 shows that a sufficient power of >80% will be reached for most treatments. If the number of cases was twice as high and the intrapatient correlation coefficient was 0.7, a power of >80% would be reached for all treatment levels. As the study is expected to be extended, a sufficient number of patients can be expected in order to reach this goal.

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Table 1. Expected number of cases and resulting power reached per specific treatment (treatment protocols) in the most common *ICD (International Classification of Diseases)* cancer groups [19].

ICD cancer group	Cases, n[a]	Specific treatments (treatment protocols), n	Effect size (females/ males)[b]	Power (females/ males)[b], %/%
Breast	2000	6	0.5/—[c]	100/—
Hodgkin lymphoma	1000	2	0.5/0.68	100/100
Bone and articular cartilage	400	3	0.5/0.68	98.6/100
Female genital organs	350	3	0.5/—	96.5/—
Male genital organs	2000	4	—/0.68	—/100
Digestive organs	200	7	0.5/0.68	14.3/41.4
Mesothelial and soft tissue	200	3	0.5/0.68	67.2/96.7
Eye, brain, and central nervous system	300	2	0.5/0.68	99.5/100
Non-Hodgkin lymphoma	300	8	0.5/0.68	26.2/64.4
Leukemia	200	5	0.5/0.68	30.6/70.8

[a]The estimation of the number of cases is based on the number of patients previously counseled and documented in the FertiPROTEKT and FERTISAVE registries.

[b]Power is calculated for each treatment protocol for men and women separately. The number of patients per protocol is calculated as the number of cases divided by the number of treatment protocols. The sex ratio is assumed to be 1:1, except for cancer of the breast and genital organs.

[c]Not available.

Data Analysis

The impact of cancer therapies and chemotherapies on the primary outcomes will be assessed for each *ICD* cancer group [19] and for each specific treatment regimen separately by comparing values measured before and after the gonadotoxic therapy using paired *t* tests. *P* values will be adjusted for multiple testing using the false discovery rate controlling procedure.

Consequences on other fertility parameters measured before and 12-15 months after the end of gonadotoxic therapy (ie, AMH, FSH, LH, and E2 concentrations in women and total testosterone, FSH, and LH concentrations and total sperm count, sperm concentration and motility in men) will be assessed using the same methodology, but without false discovery rate adjustment. Long-term consequences will be investigated later by comparing values measured before and 5 and 10 years after the gonadotoxic therapy. However, due to the long period until the final analysis, statistics might be adapted in relation to future development of cancer and fertility-preserving therapies.

As age was identified to potentially modify the effect of gonadotoxic therapy on female fertility, we will additionally conduct stratified analyses and document the impact of gonadotoxic therapy in the different female age groups.

Finally, the effects of different cancers, treatment protocols, age, and the presence of the patients' children before cancer therapy on primary and secondary fertility outcomes will be analyzed using linear mixed effect models.

The frequency of patients undergoing fertility-preserving treatments, namely freezing of ovarian tissue, oocytes and embryos, testicular tissue, and sperm will be calculated for each *ICD* cancer group and for each specific treatment protocol separately and additionally presented with the associated 95% Wilson CI. Potential effects of the patients' characteristics on the abovementioned binary outcomes will be analyzed using logistic regression analysis.

Consortium of Experts Involved in the Study

The study is supervised by several experts in Germany, Switzerland, and Austria (Figure 2). Each country provides the logistics, manpower, and experts to collect and control data collection and analysis. Interpretation of data will be supported by oncologists. Data are added to a REDCap study registry, which is provided by the Clinical Trial Unit in Bern, Switzerland, which is also responsible for statistical analysis. The data platform will be programmed by an IT company, and data presentation will be optimized by the involved experts and by the patients' representatives. The data platform, called "FertiTOX," will be part of the network "FertiPROTEKT."

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Figure 2. The consortium of experts who control the project.

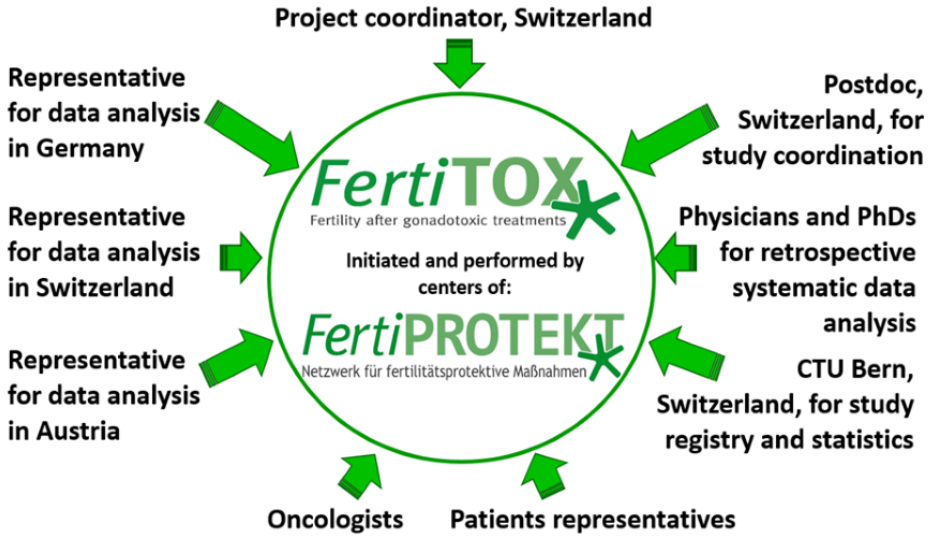

The FertiTOX Platform

The FertiTOX platform is an internet-based information platform that will be accessible to everybody and will be structured on the basis of the *ICD* cancer disease groups (Figure 3). The brand name FertiTOX has been registered and the domains will be used. A study website [20] has been set up.

Data of women and men will be presented on the FertiTOX platform in 3 hierarchies:

- First hierarchy: presentation of data regarding incidences and 5-year survival according to the *ICD*-classified cancer disease.
- Second hierarchy: presentation of already published data regarding gonadotoxicity and fertility preservation issues regarding specific *ICD*-classified diseases.
- Third hierarchy: presentation of prospective short-term and long-term data on the ovarian reserve and sperm quality before and after gonadotoxic therapies in accordance with *ICD*-classified diseases.

Once the internet-based platform is successfully established, a platform-specific app will be developed to allow easy retrieval of data.

Figure 3. The internet-based platform FertiTOX that will be used to distribute the data. *ICD: International Classification of Diseases.*

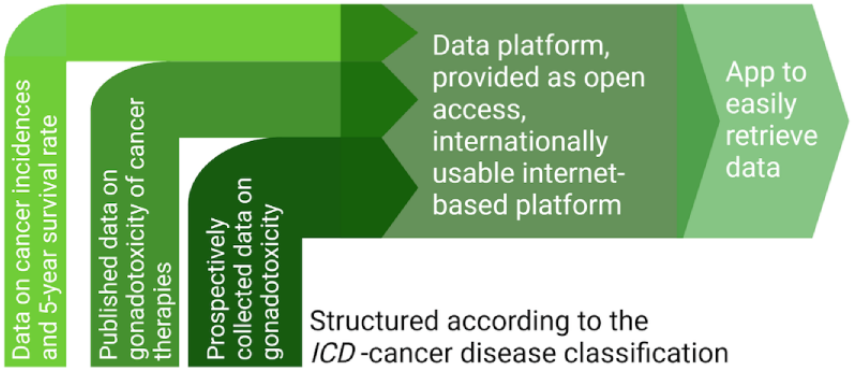

Dissemination

Data about the progress of the study will be disseminated through a study website [20]. The findings will be propagated through journal articles, conference presentations, and the FertiTOX platform.

Ethical Considerations

Ethical approval has been granted by the relevant ethics committees. In Switzerland, all 7 cantonal ethical committees have provided consent for all 21 participating centers. In Germany, the ethics committee in Heidelberg and in Austria, the committee in Innsbruck were chosen as the national leading ethical committees. Based on the ethical votes approved by these 2 committees, all other participating centers in Germany and Austria submitted an ethics application to their ethical committee.

Written consent was obtained from the participants. The participants have been informed about the processing of data and their rights. The participants also provided written consent for anonymized data to be transferred to other registries for further analysis if the other registries have the same high security standards as the REDCap registry. The data are collected in a REDCap study registry that complies with several data security and confidentiality conditions. Specific identifiers are not added to the registry; only the year of birth is added. The data are stored in Bern, Switzerland.

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The participating centers can only access the patient's data that they have added to the registry. The patients can be identified with an individual code generated by the REDCap system, which is locked in a safe place by the investigator of the participating center. Traceability of the data is ensured by these identification codes. Patients provide permission to be followed up. Patients are only contacted by the center or by authorized personnel employed by the principal investigator or the national representatives of the study. Statistical analysis will be based on anonymized data.

No compensation will be offered to the patients (potential users of the internet-based platform) for participating in the study.

Results

As of February 18, 2024, the following has been accomplished.

The first systematic review analyzing the impact of cancer therapies on bone tumors has been accepted for publication (in the *Journal of Adolescent and Young Adult Oncology*). Nine more systematic reviews have been initiated, encompassing the impact of cancer therapies on fertility in testicular cancer; soft tissue cancer; breast cancer; eye, brain, or central nervous system cancer; Hodgkin lymphoma; non-Hodgkin lymphoma; rectal or sigmoid cancer; leukemia; and on bone marrow transplantation.

The prospective cohort study has been prepared. All Swiss ethics committees and the leading ethics committees in Germany and in Austria have provided their approval. In total, 70 infertility centers (Multimedia Appendix 1) have started to be prepared for data collection. The study registry has been set up and activated, and a study website [20] has been created.

Funding for the study has been obtained from several funding bodies, which were not involved in the study's conceptualization, analysis, and data dissemination.

Recruitment of the patients started on December 1, 2023, and initial data are expected to be uploaded on the FertiTOX platform in 2026.

Discussion

Anticipated Findings

The first systematic reviews we have already carried out have revealed that data on the impact of gonadotoxic therapies on fertility are quite comprehensive in some diseases such as breast and testicular cancers and Hodgkin lymphoma. For these diseases, a meta-analysis will also be carried out to analyze the overall effect of oncological therapies on fertility. Furthermore, for these diseases, the gonadotoxic effect of specific chemotherapy protocols on fertility will also be assessed. For the other diseases, data are very poor, and outcome parameters will probably need to be limited to a rather vague outcome parameter defined as "suspected infertility." Long-term fertility data based on the ovarian reserve and sperm parameters and on spontaneous conceptions and conceptions using cryopreserved gametes or gonadal tissues are very poor or nonexistent in all kinds of cancers.

This finding supports the necessity to perform the large prospective cohort studies, as described in this paper. This cohort study has already successfully been set up and data collection was initiated on December 1, 2023.

Robust data on the gonadotoxicity of different treatment regimens, mainly in cancer therapies, is the last major deficit in fertility preservation. All other requirements have been established in many countries, such as fertility preservation procedures and specialized centers to counsel patients and to perform these procedures. Furthermore, many oncologists have been sensitized to address the fertility risk of cancer therapies and the possibility to perform fertility preservation procedures.

However, comprehensive data about the specific gonadotoxicity of different treatment regimens required to counsel patients and to decide if fertility preservation measures should be recommended or not are still missing.

Previous studies have addressed fertility issues in patients with cancer and the impact of cancer therapies on fertility, but these studies are mostly based on spontaneous pregnancies following cancer therapies or are based on data such as the onset of puberty, cycle regularity, and low sperm counts. Studies based on pre- and postchemotherapy levels of AMH and sperm counts are very limited and are mainly limited to female patients with breast cancer [21-24].

To bridge this data gap, we designed a study to analyze published data and data that will be collected in at least 3 countries by centers belonging to the FertiPROTEKT network. The data will be analyzed und disseminated via the FertiFOX web-based platform to provide patients, researchers, and clinicians access to the analysis, which will be graphically illustrated. By including patients' representatives in the data analysis, we will ensure that the data are presented in a manner that is also understandable to patients. The data will not only be presented as a single curve presenting the means and showing odds ratios and CIs, which presents the average impact of therapies on gonadal function, but also show individual variations by presenting a set of curves.

The study has been designed to follow up on patients for at least 10 years. Such a long follow-up will enable us to evaluate how many patients have undergone fertility-preserving procedures but unfortunately did not survive. Furthermore, we will be able to estimate how many patients conceived spontaneously or by using the frozen gametes and gonadal tissue. Such an analysis is essential to evaluate the long-term efficacy of fertility preservation counseling and treatment. We are aware that some patients might be lost to follow-up. However, as the number of included patients is expected to be very high, it can be assumed that the amount of data will still be sufficiently high.

Limitations

A limitation of this study is that data are mainly collected in Germany, Switzerland, and Austria. Accordingly, data will not be available for other treatment regimens performed elsewhere. However, as other countries are also invited to participate in this study, this limitation could possibly be reduced. Another limitation is that children will not be evaluated primarily because the study is based on AMH values and sperm parameters, which

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can hardly be interpreted in (AMH concentration) or cannot be collected from (sperm parameters) children.

The last limiting factor is that new therapies are evolving very fast and that new combination therapies combining conventional chemotherapy agents and immune therapies will be developed, which will increase the complexity of our data analysis. However, it is expected that this limitation can at least in part be compensated by the prospective design of the study, which will include a higher number of new therapies. Furthermore, the impact of checkpoint inhibitors, which have been shown to be gonadotoxic in female mice, will be analyzed separately in women with melanoma undergoing adjuvant therapy with checkpoint inhibitors. These results can be used to better estimate the gonadotoxicity of combination therapies involving checkpoint inhibitors.

Conclusions

In conclusion, the study can be expected to bridge the data gap regarding the gonadotoxicity of several therapies and gonadotoxic treatment regimens to better counsel patients regarding their infertility risk and their need to undergo fertility-preserving procedures.

Acknowledgments

We would like to thank all the participating centers for their support in preparing this study and collecting the data. This study is funded by several funding bodies such as the Swiss Cancer League (grant KLS-5650-08-2022: CHF 349.000,-) and pharmaceutical companies such as IBSA Institut Biochimique SA, Theramex Switzerland GmbH, and Ferring AG, Switzerland. These pharmaceutical companies are not involved in any issues regarding the study's conceptualization, the analysis, and the dissemination of data. A grant application has been submitted to the German Cancer Aid "Deutsche Krebshilfe."

Data Availability

Participants have provided written consent that the data can also be analyzed by others if sufficient data safety can be confirmed. Accordingly, data can be considered by the study consortium to be transferred to others if sufficient data safety has been proven.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Centers participating the prospective cohort study (in alphabetical order).
[DOCX File , 23 KB - resprot_v13i1e51145_app1.docx]

Multimedia Appendix 2
REDCap registry: Documentation in females before gonadotoxic therapy.
[PDF File (Adobe PDF File), 1440 KB - resprot_v13i1e51145_app2.pdf]

Multimedia Appendix 3
REDCap registry: Documentation in males before gonadotoxic therapy.
[PDF File (Adobe PDF File), 1362 KB - resprot_v13i1e51145_app3.pdf]

Multimedia Appendix 4
REDCap registry: Documentation in females 12-15 months after the end of gonadotoxic therapy.
[PDF File (Adobe PDF File), 1499 KB - resprot_v13i1e51145_app4.pdf]

Multimedia Appendix 5
REDCap registry: Documentation in males 12-15 months after the end of gonadotoxic therapy.
[PDF File (Adobe PDF File), 1485 KB - resprot_v13i1e51145_app5.pdf]

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Abbreviations

AMH: anti-Müllerian hormone
E2: estradiol
FSH: follicle-stimulating hormone
***ICD*:** *International Classification of Diseases*
LH: luteinizing hormone
REDCap: Research Electronic Data Capture

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Protocol

Using a Rapid Learning Health System for Stratified Care in Emerging Adult Mental Health Services: Protocol for the Implementation of Patient-Reported Outcome Measures

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Abstract

Background: Mental illness among emerging adults is often difficult to ameliorate due to fluctuating symptoms and heterogeneity. Recently, innovative approaches have been developed to improve mental health care for emerging adults, including (1) implementing patient-reported outcome measures (PROMs) to assess illness severity and inform stratified care to assign emerging adults to a treatment modality commensurate with their level of impairment and (2) implementing a rapid learning health system in which data are continuously collected and analyzed to generate new insights, which are then translated to clinical practice, including collaboration among clients, health care providers, and researchers to co-design and coevaluate assessment and treatment strategies.

Objective: The aim of the study is to determine the feasibility and acceptability of implementing a rapid learning health system to enable a measurement-based, stratified care treatment strategy for emerging adults.

Methods: This study takes place at a specialty clinic serving emerging adults (age 16-24 years) in Calgary, Canada, and involves extensive collaboration among researchers, providers, and youth. The study design includes six phases: (1) developing a transdiagnostic platform for PROMs, (2) designing an initial stratified care model, (3) combining the implementation of PROMs with stratified care, (4) evaluating outcomes and disseminating results, (5) modification of stratified care based on data derived from PROMs, and (6) spread and scale to new sites. Qualitative and quantitative feedback will be collected from health care providers and youth throughout the implementation process. These data will be analyzed at regular intervals and used to modify the way future services are delivered. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework is used to organize and evaluate implementation according to 3 key objectives: improving treatment selection, reducing average wait time and treatment duration, and increasing the value of services.

Results: This project was funded through a program grant running from 2021 to 2026. Ethics approval for this study was received in February 2023. Presently, we have developed a system of PROMs and organized clinical services into strata of care. We will soon begin using PROMs to assign clients to a stratum of care and using feedback from youth and clinicians to understand how to improve experiences and outcomes.

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Conclusions: This study has key implications for researchers and clinicians looking to understand how to customize emerging adult mental health services to improve the quality of care and satisfaction with care. This study has significant implications for mental health care systems as part of a movement toward value-based health care.

International Registered Report Identifier (IRRID): PRR1-10.2196/51667

(JMIR Res Protoc 2024;13:e51667) doi:10.2196/51667

KEYWORDS

learning health system; stratified care; patient-reported outcome measures; mental health; emerging adults; protocol papers; pragmatic clinical trials; e-mental health; RE-AIM; Reach, Effectiveness, Adoption, Implementation, and Maintenance; implementation science; adult; health system; stratified care; treatment; implementation; acceptability; measurement-based care

Introduction

Background

Most mental disorders emerge before the age of 25 years, resulting in a considerable burden of disease across the life span [1,2]. Emerging adulthood (age 16-24 years) represents a unique stage in life [3], characterized by low mental health service use and high treatment attrition rates [4,5]. Emerging adults are also burdened by perceptions of stigma and embarrassment surrounding help-seeking behaviors, which is further worsened by the lack of mental health literacy in this population [6,7].

Transdiagnostic Stratification of Mental Illness

Symptoms of mental illness in emerging adults are often evolving and do not always fit neatly into diagnostic categories created for older adults [8]. Rapid changes in symptoms make it difficult to conduct accurate diagnostic assessments and select appropriate treatments, especially when there are significant delays between first contact with a health care provider and the beginning of treatment [9].

Adopting a transdiagnostic approach to mental illness in young adults may improve assessment and treatment [10-12]. Transdiagnostic assessments focus on identifying the severity of mental illness and symptom domains, which cut across conventional diagnoses rather than diagnosing a discrete disorder [8,11]. Likewise, transdiagnostic treatments use shared principles of evidence-based therapies to help clients manage a range of symptoms [13].

Another emerging method to improve youth mental health treatment is through an approach whereby standardized patient-reported outcome measures (PROMs) of mental health are used to monitor treatment progress. A growing body of literature is showing how adopting PROMs in mental health care settings improves clinical outcomes, improves communication between patients and providers, and reduces treatment attrition, although the evidence supporting integrating PROMs into clinical decision-making is stronger among older adults relative to young people [14-18]. To date, mental health providers have been slow to embrace the routine use of PROMs even though many acknowledge the potential benefits [19].

Pairing the implementation of PROMs with a transdiagnostic approach facilitates the use of "stratified care." Stratified and stepped care represent 2 different models of care with differing approaches to selecting the most appropriate interventions for patients. With "stepped care," all patients begin with lower-intensity treatments and change to higher-intensity treatments if they do not respond [20]. In contrast, stratified care patients with more severe illness (and associated functional impairment) will receive appropriately more intensive treatment from the outset [20,21]. Recent randomized clinical trials of depression and anxiety indicate that the stratified care approach resulted in better clinical outcomes than stepped care or standard care [22,23].

Rapid Learning Health Systems

The implementation of a stratified care model in clinical settings is complicated by the fact that it is difficult for individual clinics to understand how to assign clients to strata and how to select which services should be available in each stratum. One potential way to implement stratified care in a routine clinical setting is through the adoption of a rapid learning health system (RLHS). The RLHS was first proposed by Etheredge [24] and involves the use of health records to determine the best treatment options in a personalized care environment based on the specific needs of each presenting patient. By comparing a patient's health records to individuals in similar medical situations, health practitioners unlock new capabilities to compare treatment effectiveness, adopt best practices, assess results, and provide feedback from their unique case [25]. Furthermore, as evidence is formulated through information supplied by typical health care patients rather than clinical trial participants selected based on highly specific criteria, the RLHS may not face issues of generalizability that are typically associated with randomized clinical trials [24]. As such, this lends credence to the use of the RLHS in biomedical practice, where clients are heterogenous, time and resource constraints are common, and treatment planning needs to evolve dynamically to fit the situation.

An RLHS has been shown to improve the quality, efficiency, and cost-effectiveness of health care delivery across a range of patients, medical conditions, and settings [26]. For example, in cancer care, Abernethy et al [27] showed that an RLHS provided detailed data on the patient's experience and rapid analysis of feedback to support subsequent care and allowed for continuous monitoring of outcomes to support patient safety, quality of care, and rapport with health practitioners. Although the RLHS has primarily been used in physical health care [26], there has been recent interest in using RLHS methods to treat mental disorders. Several commentaries have been published providing advice on implementing an RLHS in mental health, behavioral health, and substance use [28-30]. Likewise, several recent protocol papers describe ongoing work using an RLHS to

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improve treatments for epilepsy [31], autism [32], and early intervention for psychosis [33].

An RLHS is an inherently collaborative process that involves coproduction and joint evaluation of new models of care by patients, family members, providers, researchers, and decision makers [29]. Thus, the RLHS may also be beneficial for bridging the gap between research and practice [25]. To facilitate the uptake and use of an RLHS, implementation science methods can be used to guide and document the process [30,31,33].

Using Implementation Science to Promote New Models of Care

One of the most widely used implementation science frameworks is the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) model [34]. RE-AIM evolved from a need to evaluate health care interventions when conducted under complex situations typically found in a health care setting. Outcomes for each dimension provide researchers and policy makers insight as to the use of an intervention for a certain population and setting. *Reach* is defined by the number, or proportion, of willing participants undergoing the intervention. *Effectiveness* examines the impact of the intervention on individual outcomes. *Adoption* refers to the proportion of organizations that agree to take part in the intervention. *Implementation* is the extent to which a program is adapted, modified, or used as intended within an organization. Finally, *Maintenance* considers the sustainability of the intervention at an individual and organizational level.

Several studies have used the RE-AIM framework to describe and enhance the implementation of PROMs in mental health care. For example, Mascayano et al [35] paired RE-AIM with measurement-based care to evaluate the implementation of early intervention for psychosis program and identified key areas for improvement such as lack of access in rural areas, lack of qualified staff, and an unsustainable funding model. Several teams have also used RE-AIM to facilitate the uptake of PROMs in primary care clinics to screen adolescent and adult patients for potential mental health issues [36,37]. Finally, a protocol paper by Ferrari et al [33] described using RE-AIM to evaluate the impacts of an RLHS designed to improve early intervention for psychosis.

This protocol will use the RE-AIM framework to evaluate the implementation of standardized PROMs delivered using a digital platform and an RLHS as a way to allocate clients to stratified care in an effort to improve mental health outcomes in a specialty clinic for young adults (age 16-24 years). True to the goals of an RLHS, this project entails a collaboration among youth, family members, health care providers, and researchers to co-design a patient-centered system of care that collects data in real time to identify how to continuously improve both processes and outcomes.

Methods

Clinical Setting

This study will take place in a clinic that provides specialized mental health services within a large publicly funded provincial health care organization (Alberta Health Services) to emerging adults in Calgary, Alberta, Canada. Emerging adults (age 16-24 years) referred to the clinic are accepted based on whether they require level 3 care (High Intensity Community Based Services) on the Level of Care Utilization System developed by the American Association of Community Psychiatrists [38]. The clinic requires a referral, which may come from a health care provider or self-referral through telephone helplines. The clinic primarily provides psychotherapy (although psychiatric assessment and medication are also available) so clients need to be motivated to engage in treatment and demonstrate sufficient cognitive capacity to benefit from psychotherapy.

Ethical Considerations

This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB21-0616). Potential participants will be recruited through referral by staff within the clinic. Participants will sign a consent form, which includes study information, procedures, length, potential risks and benefits, confidentiality measures, and information about choosing not to participate or withdrawing from the study with no penalty and no impact on the standard of medical care they receive. Participants receive an electronic gift card as an incentive for participating in this study (CAD $40 [approximately US $30] for completing each assessment). Participant data collected in this study are stored on the Research Electronic Data Capture (REDCap; Vanderbilt University) platform and backed up on the University of Calgary's secure data storage servers. Data are also stored within the Innowell (Innowell Pty Ltd) platform, which is legally an Alberta Health Services–held repository of patient data that uses encryption to protect data. Data access is limited to clinicians, individual participants, and the research team.

Key Objectives

The objectives of the study are as follows:

1. Improve treatment selection: Through the use of stratified care, the clinic is seeking to provide the right intensity of service the first time, resulting in better alignment between client needs and services offered.
2. Reduce average wait time (prior to service) and treatment duration (once in service): If the clinic can increase the precision of services by providing higher-intensity services for higher-need clients and lower-intensity services for lower-need clients, the increased efficiency has the potential to reduce wait times and treatment duration.
3. Increase the value of services: The clinic also seeks to understand the value of services provided to increase cost-effectiveness. By tracking client outcomes associated with each treatment, the clinic can identify which services provide the greatest return on investment.
4. Understand barriers and facilitators to implementing standardized PROMs delivered using a digital platform and to stratified care: Knowledge gained about the barriers and facilitators will rapidly be applied to improve organizational, clinical, and youth-related factors to improve care in the clinic.

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Study Design and Phases

Overview

The study phases and their relation to an RLHS model are outlined in Figure 1.

Figure 1. Phases in the development and evaluation of a rapid learning health system using PROMs and stratified care. PROM: patient-reported outcome measure.

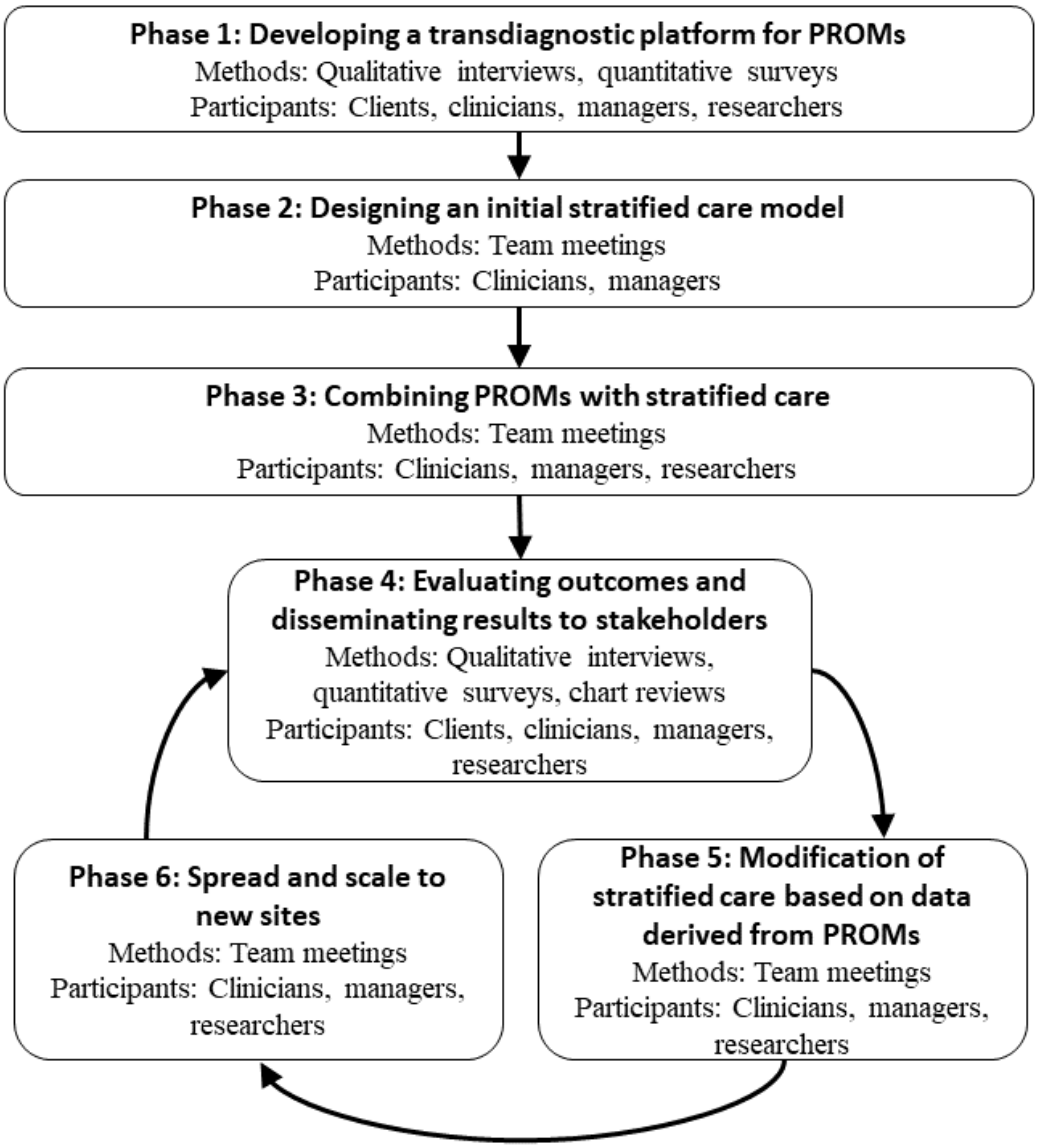

Phase 1: Developing a Transdiagnostic Platform for PROMs

We set out to select a platform of PROMs, delivered digitally, that would be useful for clinicians in categorizing the severity of mental illness and would be brief and respond to patient-oriented concerns. The goal was to identify a platform that would allow for the simple sharing of information among the relevant stakeholders (clients, clinicians, and researchers) while being compliant with local privacy laws for the storage and distribution of health information. Perhaps most critically, the platform needed to have high acceptability for youth so that they would be willing to complete the instruments.

We decided to implement Innowell [39], which uses freely available, validated instruments that are part of a curated set of instruments that are embedded in a proprietary web-based platform that was primarily developed by Australian academics with support from the Australian government [39-41]. Raw scores on instruments are converted into categories with clinical interpretations (Figure 2). For example, responses to the Overall Anxiety Severity and Impairment Scale [42] are automatically categorized as “minimal,” “mild,” “moderate,” or “high.” The Innowell platform also allows clients to access resources to work on a specific domain (eg, depressed mood), either by referring them to external resources (typically websites, mobile apps, or phone lines) or allowing them to flag to their provider that they want to address a specific domain.

Clients will complete the Innowell instruments at a minimum of baseline, 6 months, and 12 months (Table 1). If a client is discharged or transferred before 12 months, we will ask them to complete one final assessment at discharge or transfer. Clients can also repeat 1 or more Innowell instruments at any time to gauge treatment progress. All fixed time points except baseline also include a custom instrument to provide feedback on the

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Innowell system, which includes measures of satisfaction, clinical use, and ease of use. To minimize attrition between time points, we will include the following in the protocol: (1) research coordinator following up with patients to complete measures and sending up to 3 email or text reminders, (2) sharing results with patients including visual graphs so they can see their progress, and (3) providing a small honorarium (in the form of a gift card) for completing measures.

Several additional measures will be collected using the REDCap platform since Innowell does not allow for instrument customization. After each therapy session, clients will be sent an SMS text message (via REDCap) asking them to complete 2 brief 4-item instruments: the Outcome Rating Scale, which measures overall well-being, and the Session Rating Scale, which measures satisfaction with a therapy session [43,44]. At baseline, 6 months, and 12 months, clinicians will be sent an email asking them to provide feedback on the use of PROMs in the Innowell platform and stratified care using the measures listed in Table 2.

Figure 2. Dashboard for Innowell software used in patient-reported outcome measures among emerging adults to assess disease severity.

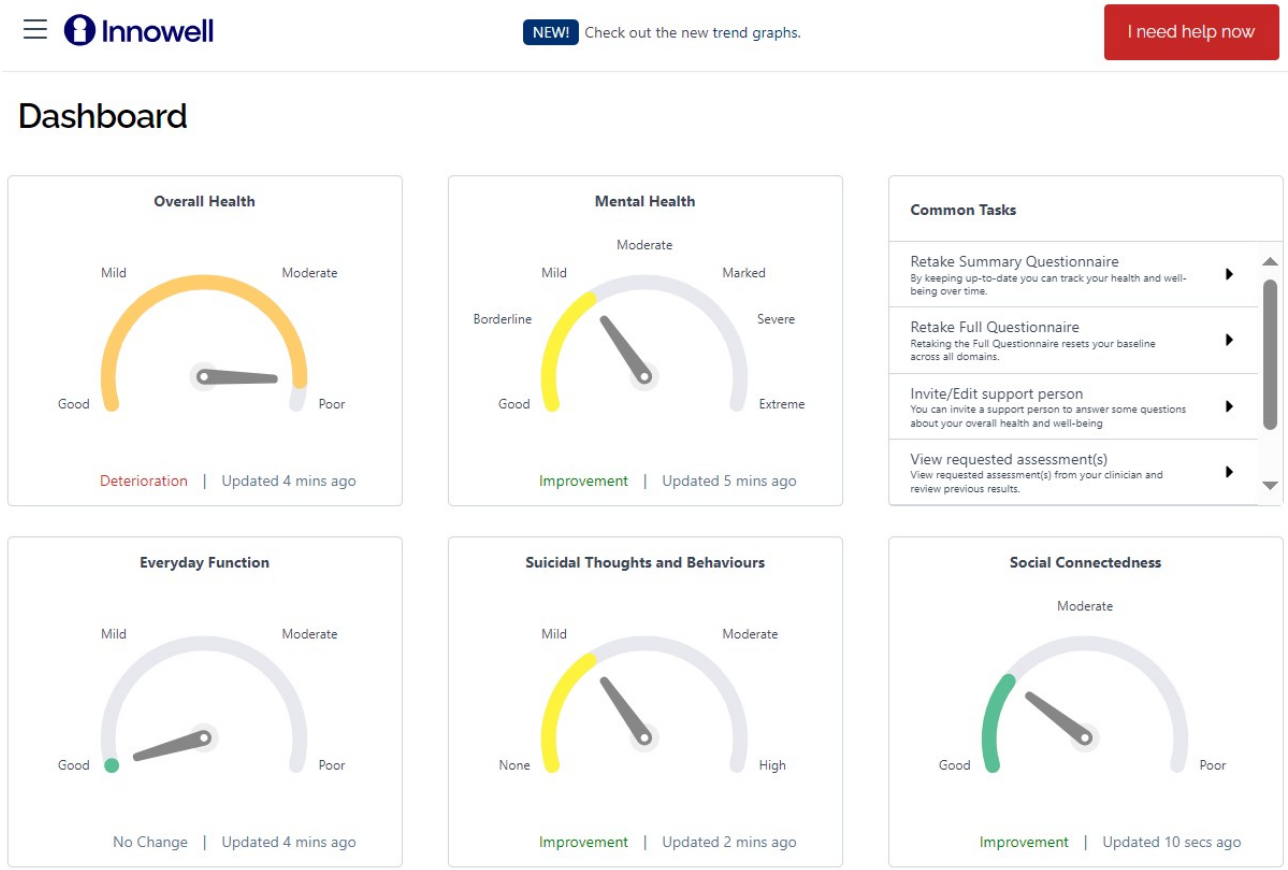

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Table 1. Standardized measures collected from clients. All instruments are administered at baseline, 6 months, and 12 months using the Innowell platform, except for the Outcome Rating Scale and Session Rating Scale, which are collected after each treatment session using the Research Electronic Data Capture (REDCap) platform.

Instruments	Domains
Kessler Psychological Distress Scale	Psychological distress
Overall Anxiety Severity and Impairment Scale	Anxiety
Quick Inventory of Depressive Symptomology	Depressed mood
Prodromal Questionnaire	Psychosis-like experiences
Altman Self-Rating Mania Scale	Mania-like experiences
Primary Care PTSD[a] Screen for DSM-5[b]	Posttraumatic stress
Eating Disorder Examination	Eating behaviors and body image
Suicidal Ideation Attributes Scale; Columbia Suicide Severity Rating Scale	Suicidal thoughts and behaviors
Brief Non-Suicidal Self-Injury Assessment Tool	Self-harm
Alcohol, Smoking and Substance Involvement Screening Test; AUDIT[c] Alcohol Consumption Questions	Alcohol, tobacco, and cannabis use
OECD[d] Youth not in Education or Employment; WHO[e] Disability Assessment Schedule; Work and Social Adjustment Scale	Social and occupational function
Schuster's Social Support Scale	Social connectedness
Pittsburgh Sleep Quality Index; Munich Chronotype Questionnaire	Sleep-wake cycle
Child and Youth Resilience Measure—Revised	Resilience
Multigroup Ethnic Identity Measure	Cultural connectedness
Spiritual Health and Life-Orientation Measure	Spirituality
Inventory of Complicated Grief	Grief and loss
Height, weight, and waist circumference; International Physical Activity Questionnaire	Physical health
Outcome Rating Scale	Overall well-being
Session Rating Scale	Treatment session satisfaction

[a]PTSD: posttraumatic stress disorder.

[b]DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

[c]AUDIT: Alcohol Use Disorders Identification Test.

[d]OECD: Organization for Economic Co-operation and Development.

[e]WHO: World Health Organization.

Table 2. Standardized measures collected from clinicians to assess feasibility and satisfaction with the use of patient-reported outcome measures. All instruments are administered at baseline, 6 months, and 12 months using the Research Electronic Data Capture (REDCap) platform.

Instruments	Domains
Attitudes Toward Standardized Assessment Scale	Opinion on psychometric instruments
Evidence-Based Practice Attitudes Scale	Opinion on using evidence-based interventions
Monitoring and Feedback Attitudes Scale	Opinion on routine progress monitoring
Brief Individual Readiness for Change Scale	Capacity to implement change in clinical practice
Implementation Leadership Scale	Capacity to implement evidence-based practice
Factors Associated with Referrals and Holding	Stratified care decision-making

Phase 2: Designing an Initial Stratified Care Model

Prior to the implementation of an RLHS, standard care at the study clinic was to have clients work with their assigned clinician to select appropriate treatments from among the available options at the clinic. Coincident with the implementation of an RLHS, the clinic made an operational decision to move to a stratified care model, whereby new clients would be appropriately matched to different intensities of care. The optimal timing for PROMs was identified within the clinical workflow: specifically, after a client had received their orientation to the clinic, but before they were assigned to a primary clinician. Managers and clinicians at the study site engaged in multiple rounds of discussion, feedback, and

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revisions to organize both existing and new services into different strata of care. The initial model includes 3 strata of care (low, medium, and high, which are known in the clinic as "yellow," "blue," and "purple," respectively). Some services are only available to clients in each stratum, while other services are available to all clients regardless of stratum (Figure 3).

Figure 3. Clinical and research flow diagram showing progression from emerging adult patient intake into clinical strata using PROMs. PROM: patient-reported outcome measure.

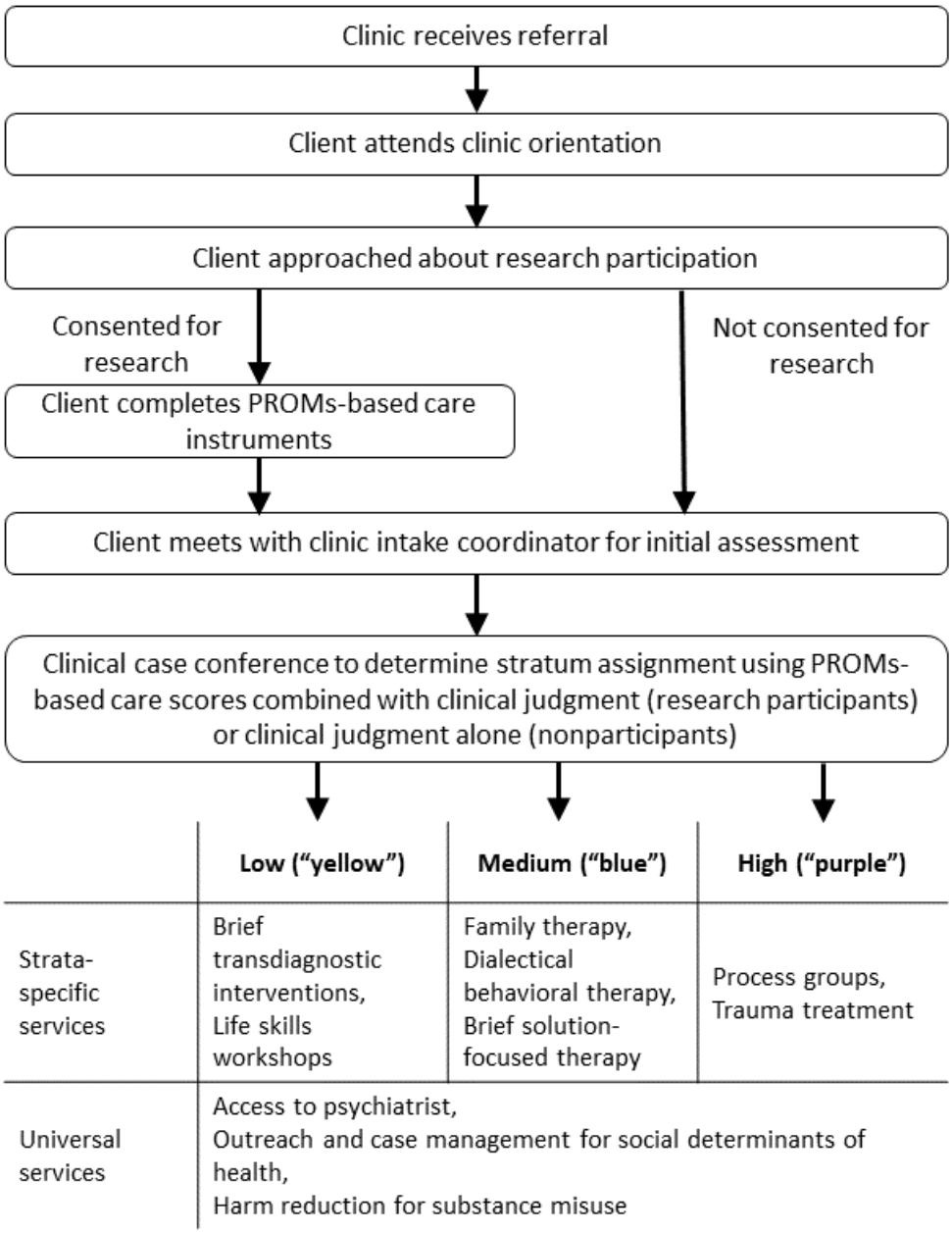

Phase 3: Combining Implementation of PROMs With Stratified Care

After selecting and implementing a digital platform for the delivery of PROMs and a stratified care model, the next phase was to identify how to use the platform to guide stratification within the study clinic. This involves engaging in rapid learning cycles as the Innowell system was created with a population-wide focus, but the study site serves a much narrower population of emerging adults with moderate to severe mental health concerns. Further, given the clinic-specific stratified care model implemented, further learning cycles were required to determine how to use the results from the selected platform to assign a stratum of care. To accomplish this, at the study site, new clients who consent are onboarded to the Innowell platform and asked to complete all 20 domains available on the platform. In the last 9 months, we introduced the Innowell platform and successfully onboarded 56 clients. Uptake has increased during this time, and at the time of writing, we were onboarding an average of 9 emerging adults per month. Managers and clinicians participate in weekly case conferences where individual clients' results, referral information, and case history are presented and discussed. Consensus-based decision-making is used to determine the initial client stratum. A researcher will be present during each case conference to capture notes regarding the decision-making process including the key

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findings used to determine stratum and level of agreement among team members.

As per the stratified model of care, clients will meet with their clinician every 3 months to review treatment progress including current results from readministering all 20 domains. Treatment reviews will be used to determine if clients should be moved to a different stratum of care, transferred to another program, or discharged from the health system. After each clinical stratification treatment review, clients will complete a custom form to provide their feedback on the treatment review and clinical stratification process. We will also conduct a detailed chart review to understand the impact of implementing standardized PROMs and stratified care on the services clients use at the study clinic as well as their use of wider health system resources. This chart review will also include clients who did not consent to research if a waiver of consent can be obtained.

Phase 4: Evaluating Outcomes and Disseminating Results to Stakeholders

An exploratory mixed methods approach will be used to evaluate implementation outcomes. Initially, feedback from qualitative interviews will be prioritized since qualitative interviews yield rich data and allow flexibility to probe deeply on specific issues. The first 20 clients to use the digital platform to inform their stratification of care will be approached for qualitative interviews. We will ask clients about their satisfaction with the PROMs and stratified care systems, what factors they felt influenced the stratification decision, the extent to which they agreed with the stratification decision, as well as probe for barriers and facilitators to the use of PROMs and stratified care.

Once 100 clients have been enrolled in the study for at least 3 months (meaning they have received their initial clinical stratification and at least one treatment review), we will begin to use quantitative data to evaluate outcomes of the stratified care process. Based on current rates of onboarding described earlier, we estimate that we will reach this target sample size in approximately 1 year. We will examine the stratum a client is assigned to and map the trajectory of symptoms and satisfaction with clinical services (see instruments in Table 3). Statistical regression models will be developed to describe symptom change over time and determine whether symptom trajectory (eg, slope of regression model) is modified by stratum of care when controlling for other variables (eg, demographics and social determinants of health).

Clients and their clinicians will have access to the data provided by the client to inform future treatment decisions. The research team will present their interim analysis of the results to the clinical team at team meetings at least once every 3 months. One year after recruitment begins, the research team will conduct focus groups and interviews with clinicians and managers at the study site to understand their satisfaction with PROMs and stratified care, barriers and facilitators to the use of PROMs and stratified care, and the factors that influence their decisions about clinical stratification.

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Table 3. Data collection using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework.

RE-AIM category and data source	Items
Reach (individual)	
Clients	The proportion of clients who participate in a research study, complete quantitative surveys, take part in qualitative interviews, and use extra support resources in Innowell platform
Clinicians	The proportion of clinicians who complete training on using PROMs[a], participate in a research study, complete quantitative surveys, and take part in qualitative interviews
Managers	The proportion of managers who complete training on using PROMs, participate in a research study, and take part in qualitative interviews
Effectiveness (individual)	
Admin data (health region)	The proportion of clients who (for psychiatric reasons) visit urgent care center, who visit emergency department, and who are hospitalized
Admin data (clinic)	Change over time in the proportion of clients assigned to each stratum of care, the proportion of clients who drop out of treatment, length of waitlist, time spent in the program, cost of services used, number of sessions used, type of services accessed, and number and timing of strata changes
Clients	Change over time in answers to quantitative surveys, reasons for dropping out of research or treatment, confidence managing mental health services, satisfaction with mental health services and care coordination, satisfaction with the use of PROMs and stratified care, individual barriers and facilitators to the use of PROMs and stratified care, and agreement with clinician and data derived from PROMs regarding stratified of care assignment
Clinicians	Change over time in answers to quantitative surveys, satisfaction with the use of PROMs and stratified care, individual barriers and facilitators to the use of PROMs and stratified care, and agreement with client and data derived from PROMs regarding stratum of care assignment
Managers	Change over time in satisfaction with the use of PROMs and stratified care and individual barriers and facilitators to the use of PROMs and stratified care
Adoption (organizational)	
Clinics, clients, clinicians, managers	The proportion of clinics that adopt PROMs and stratified care and stakeholders within clinics (clients, clinicians, and managers) who take part in the implementation of PROMs and stratified care
Implementation (organizational)	
Clinics, clients, clinicians, managers	Organizational barriers and facilitators to the implementation of PROMs and stratified care and changes to the use of PROMs and stratified care relative to the intended use
Maintenance (individual and organizational)	
Clinicians, managers, executive leaders	Commitment to continuing using PROMs and stratified care beyond the study period and spread and scale of PROMs and stratified care

[a]PROM: patient-reported outcome measure.

Phase 5: Modification of Stratified Care Based on Data Derived From PROMs

Initially, the clinical team will make rapid changes to both the services offered within each stratum of care and the way dashboards displaying data from PROMs are interpreted and used to match clients into a stratum of care. This pilot phase will be used to ensure managers and clinicians can use early learnings to make effective and efficient changes. Once the management and clinical team report that early learnings have plateaued, planned for 3 months into implementation, the team will use the researcher's summary analysis of case notes from each case conference to create a decision tree to assign patients to appropriate clinical interventions using the stratified care model developed by the clinical team. As an added step before acting upon the decision tree, every 3 months the research and clinical team will meet to examine the data that have been generated and try to understand how they can adapt the decision tree to increase the precision of using data derived from PROMs to assign a client to a stratum of care. The clinical services available in each stratum will also be re-evaluated.

Phase 6: Spread and Scale to New Sites

Initially, this research will be conducted at a single clinic to maximize feasibility and allow for careful evaluation of the use of the stratified care model and its integration with the digital PROM platform.

Data Analysis

We will use the RE-AIM framework to design and organize the data collection system (Table 3). The *Reach* dimension captures individual outcomes and includes the proportion of stakeholders who take part in the research, complete quantitative and qualitative assessments, and use the additional care options, apps, and e-tools on the Innowell platform. The *Effectiveness* domain also examines individual outcomes and measures changes over time in key outcomes related to mental health

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(among youth clients), satisfaction with PROMs and stratified care (among clients and clinicians), as well as the use of health care resources (from administrative data). *Adoption* and *Implementation* measure organizational outcomes and so will be more important in later phases of the research when examining how many clinics adopt PROMs and stratified care as well as what are the barriers and facilitators to adoption. *Maintenance* has the longest timescale among RE-AIM dimensions, and it will be used to measure the sustainability of implementation of PROMs and stratified care over time at an organizational and individual level.

This study will begin at the same time as the clinic is implementing stratified care for all clients. For clients who consent to research, PROM results will be used to help inform stratified care, whereas nonresearch participants will be stratified based on clinical judgment alone. The impact of stratified care and implementing PROMs will be inferred from longitudinal changes in client and clinic data, although we cannot control for the impact of other variables changing over time. We will seek a waiver of consent to compare research participants to nonresearch participants, which will provide more direct insights into the impact of using PROMs to inform a stratified care model of mental health service delivery. Analysis will be guided by the three key objectives.

1. Improving treatment selection: We will examine changes over time in symptoms for clients at the study clinic. To the extent that implementation of PROMs is leading to continuous improvements in treatment selection as part of an RLHS, we would expect that participants enrolled at the beginning of the study will show slower improvements in their mental health relative to clients enrolled later in the study (as measured by instruments in Table 1). Additionally, if a waiver of consent can be obtained to compare research participants to nonresearch participants, we expect that research participants will show greater improvements in mental health than nonresearch participants when controlling for clinic intake date.
2. Reducing average wait time (prior to service) and treatment duration (once in service): We will examine clinic administrative data to understand whether the implementation of PROMs and stratified care leads to reductions in wait time and treatment duration. If we can obtain a waiver of consent, we will examine whether research participants (completing PROMs using the Innowell platform) spend less time in treatment than those who opt out of research (and do not complete PROMs using the Innowell platform).
3. Increasing the value of services: Clinic administrative data will be used to understand the cost of providing care to each client. When combined with data derived from PROMs, this will provide information about the degree of symptom improvement associated with each type of service. If we can obtain a waiver of consent, we will be able to determine whether the average cost of providing care to a client changes when informed by PROMs. The clinic also seeks to understand the value of services provided to increase cost-effectiveness. By tracking client outcomes associated with each treatment, we can identify which services provide the greatest return on investment.

Results

This project is funded by the Alberta Children's Hospital Foundation as one part of a program grant (the "Framework for Research in Emerging Adults") that is funded from 2021 to 2026. Ethics approval for this study was received in February 2023. Presently, we have developed a system of PROMs and organized clinical services into strata of care. We will soon begin using PROMs to assign clients to a stratum of care and using feedback from youth and clinicians to understand how to improve experiences and outcomes.

Discussion

Principal Findings

This protocol paper describes how we will evaluate the implementation of an RLHS to improve service delivery within a stratified model of care. The study clinic is looking for ways to target the right service to the right client at the right time, in line with current movements toward a precision mental health care system [20]. However, standard care at the study clinic has historically been similar to mental health care in most areas of the world, in that, treatment progress is not systematically tracked using objective measures for most clients [19]. Thus, even if the clinic implemented stratified care as a means to tailor services to client needs, the clinic would have no way of knowing if the stratified care model resulted in improved outcomes. Therefore, the clinic needed to develop a platform for PROMs to monitor outcomes to understand the impact of their new stratified care model. Using PROMs to inform stratified care is challenging since there are no existing guidelines to help clinicians understand how scores on different standardized measures translate into treatment recommendations. Therefore, the clinic will need to use an RLHS framework to guide the use of PROMs in informing stratified care decision-making. Initially, stratification using data derived from PROMs (in combination with clinical judgment) may not be superior to stratification using clinical judgment alone. However, as data are collected on how stratification and treatment selection impact the trajectory of a client's symptoms, the goal is to iteratively improve the ability to stratify clients and select the best treatment plan.

This project has broad implications for mental health care systems as part of a movement toward value-based health care, which is grounded in the notion that compensation for health care services should be based on the amount of benefit to patients rather than the expense incurred by providers and the system [45]. By tracking the relationship between health services and health outcomes, organizations that pay for health care (eg, governments and insurance companies) can obtain an enhanced understanding of which services provide the greatest value for patients at the lowest financial cost [45]. Implementing value-based health care requires a digital platform, patient-centered outcome measurements, tools to support clinical decision-making, and the means to allow for continuous improvement based on data fed into the digital platform [45,46].

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An RLHS, such as the one we are implementing and evaluating, leverages these same key components [47] and therefore represents a potentially important first step toward achieving the goal of a value-based health care system [48].

This research will provide practical guidance to help other research and clinical teams collaborate to implement an RLHS as part of the transition toward value-based health care. The engagement of multiple stakeholders early in the design process allowed us to identify the key outcomes that are fundamental toward creating a value-based health care system. Testing out multiple strategies should allow us to identify a system that patients and providers would be willing to use consistently enough to understand which services are having the biggest impact on patient outcomes. Once additional data are generated, we will be able to report on strategies that clinicians use to identify the treatment that is predicted to provide the most value to patients. However, this research protocol focuses on the systematic evaluation of individual outcomes, which is only one component of a value-based mental health care system. At a population level, value-based mental health care also requires additional system-level quality measures including evaluation of structure (eg, number and availability of mental health specialists) and process (eg, number of sessions of psychotherapy) [48].

Potential Challenges and Limitations

A major uncertainty is the extent to which clinicians will be willing to embrace the use of standardized PROMs to inform decisions about stratified care. Most mental health providers do not use standardized measures and instead rely on their own clinical judgment to determine the best course of care [19]. It will take some time before enough data are collected to allow for past client outcome data to meaningfully inform decisions about future client stratification. The status quo exerts a powerful effect on organizations, and it is common for new mental health initiatives to be abandoned after a few years, especially if there are problems with staff turnover or funding [49,50]. To mitigate these issues, our team spent 3 years building collaborative relationships among researchers, clinic management, and staff through working together on smaller projects, such as a feasibility study of brief transdiagnostic psychotherapy [12]. We are also embedding qualitative and quantitative measures of clinician satisfaction and decision-making throughout the process to identify how we can support clinicians to implement standardized PROMs and stratified care. Another limitation of this protocol is that the decision tree will have limited generalizability to clinics with different patient populations and referral criteria. In the future, we plan to include additional sites to evaluate the approach in other clinical settings serving emerging adults with mental health concerns. Finally, there is the potential bias toward those who contribute the most data [51]. Specifically, emerging adults who consent to completing PROMs and participating in research may not fully represent all patients referred to the clinic. We will evaluate this potential source of bias by analyzing differences between clients who consent to research and those who do based on demographic and clinical variables (eg, diagnoses) available in administrative data.

Conclusions

This project aims to implement and evaluate an RLHS and enable a data-driven, stratified care approach to improving emerging adult mental health services. The RE-AIM framework is being used to organize and evaluate the implementation according to the key objectives (Figure 4). The goal of this work is to move away from a “one size fits all” approach to youth mental health services and toward one that customizes the modality and intensity of treatment based on client symptoms and preferences. Now that the initial system has been designed, the immediate next steps are to collect and analyze the outcome data to make iterative improvements in stratification. This study will provide valuable insights for clinicians and researchers who are seeking to use mental health data to improve the allocation and delivery of health care resources in real-world settings.

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Figure 4. Relationship among RE-AIM framework, research methods, and key objectives. RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

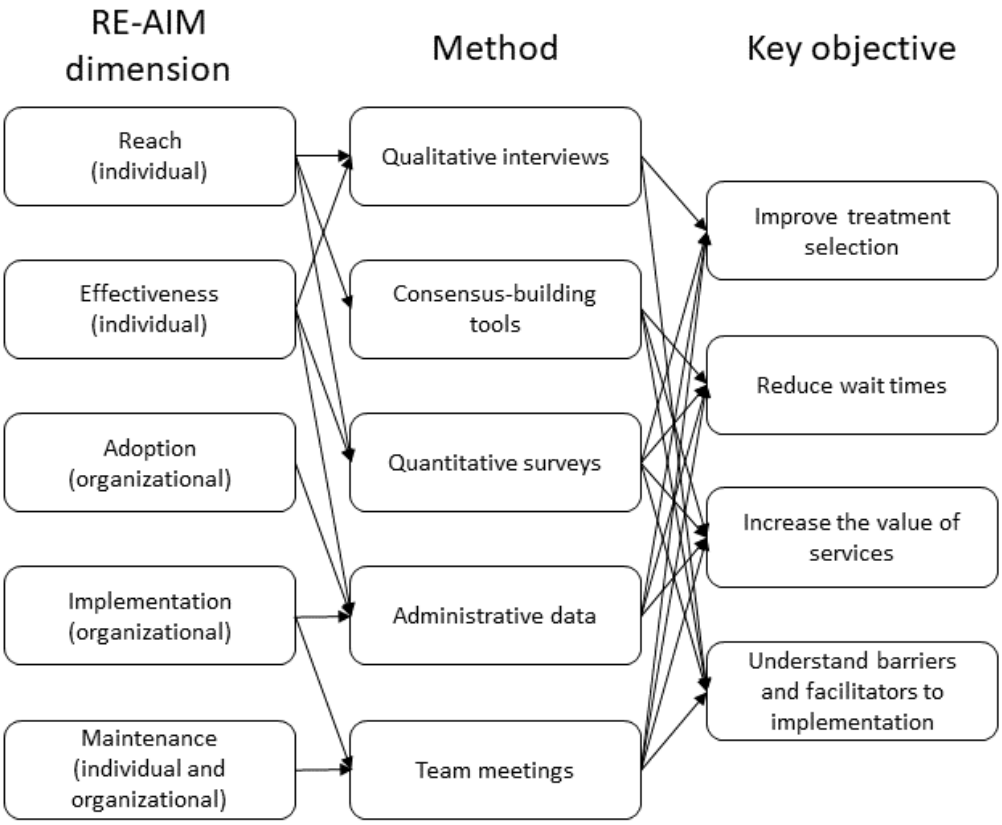

Acknowledgments

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Data Availability

The data sets generated during this study are not publicly available because they contain potentially identifiable health care data but are available from the corresponding author on reasonable request.

Conflicts of Interest

IH is the codirector of health and policy at the Brain and Mind Centre at the University of Sydney. The Brain and Mind Centre operates early intervention youth services at Camperdown under contract to headspace. IH is the chief scientific advisor to, and a 5% equity shareholder in, Innowell Pty Ltd. Innowell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the Aus $30 million (US $21.63 million) Australian government–funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and to lead the transformation of mental health services internationally through the use of innovative technologies. PDA receives support from the Alberta Innovates Translational Health Chair in Child and Youth Mental Health. HML is a section editor at JMIR Aging, but this does not afford HML preferential treatment in the peer review or publication process. The other authors have no financial relationships or other ties to disclose.

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Abbreviations

PROM: patient-reported outcome measure
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
RLHS: rapid learning health system

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Protocol

Remote Evaluation of Sleep and Circadian Rhythms in Older Adults With Mild Cognitive Impairment and Dementia: Protocol for a Feasibility and Acceptability Mixed Methods Study

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Abstract

Background: Sleep disturbances are a potentially modifiable risk factor for neurodegenerative dementia secondary to Alzheimer disease (AD) and Lewy body disease (LBD). Therefore, we need to identify the best methods to study sleep in this population.

Objective: This study will assess the feasibility and acceptability of various wearable devices, smart devices, and remote study tasks in sleep and cognition research for people with AD and LBD.

Methods: We will deliver a feasibility and acceptability study alongside a prospective observational cohort study assessing sleep and cognition longitudinally in the home environment. Adults aged older than 50 years who were diagnosed with mild to moderate dementia or mild cognitive impairment (MCI) due to probable AD or LBD and age-matched controls will be eligible. Exclusion criteria include lack of capacity to consent to research, other causes of MCI or dementia, and clinically significant sleep disorders. Participants will complete a cognitive assessment and questionnaires with a researcher and receive training and instructions for at-home study tasks across 8 weeks. At-home study tasks include remote sleep assessments using wearable devices (electroencephalography headband and actigraphy watch), app-based sleep diaries, online cognitive assessments, and saliva samples for melatonin- and cortisol-derived circadian markers. Feasibility outcomes will be assessed relating to recruitment and retention, data completeness, data quality, and support required. Feedback on acceptability and usability will be collected throughout the study period and end-of-study interviews will be analyzed using thematic analysis.

Results: Recruitment started in February 2022. Data collection is ongoing, with final data expected in February 2024 and data analysis and publication of findings scheduled for the summer of 2024.

Conclusions: This study will allow us to assess if remote testing using smart devices and wearable technology is a viable alternative to traditional sleep measurements, such as polysomnography and questionnaires, in older adults with and without MCI or dementia due to AD or LBD. Understanding participant experience and the barriers and facilitators to technology use for

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research purposes and remote research in this population will assist with the development of, recruitment to, and retention within future research projects studying sleep and cognition outside of the clinic or laboratory.

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KEYWORDS

feasibility; sleep; mild cognitive impairment; dementia; Lewy body disease; Alzheimer disease; Parkinson; wearable devices; research; mobile phone; electroencephalography; accelerometery; mobile applications; application; app; cognitive; cognitive impairment; sleeping; sleep disturbance; risk factor; Alzheimer; wearable; wearables; acceptability; smart device

Introduction

Background

Dementia is the leading cause of death in the United Kingdom [1]. While the search continues for disease-modifying therapies, key research priorities include preventing, identifying, and reducing dementia risk and improving symptom burden and quality of life for patients with dementia and those who care for them [2]. With increasing evidence to support poor sleep as an important risk factor for dementia [3-5], sleep may offer an untapped opportunity in both reducing dementia incidence and improving quality of life for those with or at risk of developing dementia.

Sleep and Dementia

Sleep is essential for optimal brain function and health [3]. Disrupted sleep and circadian rhythms are considered among the most debilitating symptoms in dementia, and increasing evidence suggests that sleep disturbances are a consequence of and contribute toward neurodegeneration underlying dementia including Alzheimer disease (AD) and Lewy body disease (LBD) [3,6].

Changes to sleep such as shorter total sleep time, more nocturnal awakenings, less time spent in deep slow-wave and rapid eye movement (REM) sleep, and a slight shift to earlier circadian rhythms are commonly observed as we age [7,8]. Most of these changes appear to stabilize around the seventh decade of life in healthy older adults [9]. In AD, sleep and circadian disturbances are more robust and severe than the changes seen in normal aging [10,11]. Some people with AD also experience a phenomenon known as “sundowning” (worsening of neuropsychiatric symptoms in the late afternoon or evening), which is thought to be in part caused by disturbances in circadian rhythms [12,13]. LBD is more typically associated with worse subjective sleep quality, REM sleep behavior disorder, sleep-related movement disorders such as restless legs syndrome, and higher levels of daytime sleepiness [5] compared to other dementias.

Sleep as a Modifiable Risk Factor for Dementia

Individuals with sleep disorders (such as insomnia), sleep-disordered breathing, sleep-related movement disorders, circadian rhythm disorders, and poor quality or insufficient sleep are more likely to develop dementia later in life [14].

Mechanistically, chronic sleep deprivation and fragmentation are associated with various neurodegenerative processes including neuroinflammation [15], amyloid deposition [16,17], autophagy [15], tau phosphorylation [18], and hippocampal atrophy [19,20]. Sleep and circadian disturbances can precede cognitive and functional impairment, appearing in cognitively unimpaired older adults with AD biomarkers such as decreased cerebrospinal fluid amyloid-beta 42 and in mild cognitive impairment (MCI), and correlate with severity of cognitive impairment in AD [21-23]. Sleep disturbances also appear early in the disease course for LBD, particularly REM sleep behavior disorder [24,25]. Profiling sleep may offer noninvasive biomarkers for earlier diagnosis and staging, as well as targets for intervention to improve prognosis.

Improving Quality of Life and Symptom Burden for People With Dementia

Sleep disturbances impact daily functioning, socialization, emotional well-being, and cognitive function in patients [26] and have a profound impact on caregivers [27]. Identifying targets for sleep interventions, whether tailored to an individual’s sleep profile or general advice given alongside dementia diagnosis or care, could help improve the quality of life for both persons with dementia and their caregivers. A single night of sleep deprivation disrupts cognitive performance [28], increases AD-related pathology such as amyloid burden [29], and reduces waste clearance in the brain [30], and improving sleep through treating sleep-disordered breathing has been associated with improvements in both neuropsychological assessments and blood biomarkers relating to AD in people with MCI [31]. Therefore, improving sleep could also benefit those with already established dementia and MCI, in addition to reducing incidence.

Further research is warranted to identify the most important sleep metrics and different sleep profiles in older adults with and without cognitive impairment to help identify targets for intervention [32].

Measuring Sleep in Individuals With, or at Risk of, Dementia

Technological advancements in “wearables” (such as smartwatches and electroencephalography (EEG) headsets), “nearables” (such as a mattress or room sensors), and smartphones offer the unprecedented ability for tracking sleep at home for both consumers and researchers—to varying degrees of accuracy and accessibility [33,34]. The use of wearable technology is not new to sleep medicine or research; the current gold standard for sleep medicine is polysomnography (PSG) conducted under laboratory conditions, and wrist-worn actigraphy has been used for decades alongside paper-based sleep diaries to monitor rest and activity patterns typically over days or a couple of weeks [35]. However, most studies to date

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assessing sleep in individuals with MCI and early dementia have used questionnaires, with fewer studies adopting objective sleep technologies that could complement them such as actigraphy and EEG [32,36].

Alongside technological advancements, improved digital literacy and accessibility in older adults in recent years offer great promise for sleep research. A 2020 survey identified that 94.6% of 55-64 year olds, 85.5% of 65-74 year olds, and 54% of those aged 75 years and older had used the internet in the last 3 months [37]. Leveraging technology and remote assessments offers several potential benefits above PSG under laboratory conditions. PSG is often used across 1 or 2 nights, potentially leaving results vulnerable to the well-established "first-night effect," which describes how sleep is quantitatively and qualitatively different during the first compared to subsequent night recordings. This has been observed to affect REM and non-REM sleep, awakenings, total sleep time, and subjective sleep quality [38]. PSG also limits mobility during the night. Conducting research in the home setting is more likely to capture naturalistic sleep as participants can largely continue their usual sleep-wake routines. Remote assessments enable longitudinal assessment, which may uncover natural night-to-night sleep variations. Newer sleep technologies enable the collection of both objective (via wearables and nearables) and subjective (via smartphone apps) sleep data that are considered the best practice to accurately capture sleep quality in older adults [39]. Subjective and objective sleep data may produce complementary or conflicting results [22] and allow multiple aspects of sleep (architecture vs experience) to be captured, enabling comprehensive profiling of sleep. Circadian and infradian rhythms may also be more accurately captured over a longer assessment period than is practical in a laboratory or outpatient setting, using actigraphy and repeated saliva samples that participants complete themselves. Finally, since participants do not need to attend sleep clinics, remote and technology-supported research may improve accessibility to research studies for those with less access to transport, reduce participant and study partner burden, and be more affordable, allowing for larger sample sizes.

However, before large-scale clinical trials and observational studies invest in and adopt technology- and home-based sleep measurements for dementia research, it is important to determine whether research conducted in this way is feasible and acceptable to older adults with and without cognitive impairment or dementia. People living with MCI and dementia experience changes in their communication or thinking, which may influence their experience of remote research, or they may have difficulty remembering to complete or understanding tasks without in-person support from a researcher; however, remote research may offer significant benefits including overcoming logistical issues typically faced in research and thus increase participation while reducing study burden [40]. The few studies that have addressed the feasibility of home-based sleep research and wearable technologies have often collected basic short-term feasibility data across only a few nights [41,42] and have typically required participants to be supported by a caregiver or care home staff [43,44]. Research is needed to see if community-dwelling participants with MCI and early dementia tolerate remote sleep and memory testing across an extended period of weeks or months (as would be expected in a clinical trial setting) and if they themselves can complete the study tasks. Caregivers or partners can provide important contributions to sleep and dementia research [45,46] but they often report poor quality sleep and high burden [47,48], and requiring a study partner may be a barrier to enrollment in research [49]. Independent (or minimally supported) involvement in research in milder stages of cognitive impairment may also positively acknowledge someone's cognitive ability to engage in autonomous decision-making regarding their health [50].

Improving how we measure sleep and cognition in this population can deepen our understanding of the link between sleep and brain health, advice around sleep we give to patients, and improve monitoring in future interventional studies.

Objectives

We will test the feasibility and acceptability of remote, in-home sleep and cognitive testing in a cohort of older adults with MCI or mild to moderate dementia due to AD or LBD and older adults without cognitive impairment. We hypothesize that using technology (wearable devices and smart devices) and remote study tasks will be well-tolerated by all study participants. Firstly, we will apply mixed methods to evaluate the feasibility and acceptability of remote study tasks based on the recruitment and retention of study participants, participant adherence to remote study tasks, data quality and completeness, and qualitative feedback on study tasks from participants. Secondly, we will explore whether sociodemographic or clinical variables explain any of the variability in feasibility and acceptability outcomes (whether someone is supported with tasks at home, cognitive impairment at baseline, and psychological variables at baseline such as apathy and anxiety). Thirdly, we will compare agreement on core sleep outcome measures (such as total sleep time, sleep efficiency, nocturnal awakenings, and sleep quality) across different measures. Finally, we will explore key themes in feedback from participants to identify strengths, limitations, and guidance for future sleep and remote-based research.

It is envisaged that these outcomes will be used to inform future research methodologies for both observational and interventional sleep research in older adults with and without dementia.

Methods

Study Design

This is a mixed methods study assessing the feasibility and acceptability of a novel combination of remote technology-supported sleep and cognitive assessments in older adults with and without cognitive impairment and dementia. The feasibility study is embedded within a prospective, longitudinal, and observational cohort study called the Remote Evaluation of Sleep to Enhance Understanding of Early Dementia (RESTED) study. Participants will complete baseline assessments and undergo remote sleep and cognitive assessments for a main study period of 8 weeks and a follow-up cognitive assessment at 6 months. Feasibility and acceptability will be assessed through the analysis of quantitative and qualitative

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data collected throughout the study and during the end-of-study interviews. Qualitative data will help to contextualize and enhance quantitative outcomes to deliver a more comprehensive analysis of the feasibility and acceptability [51].

Setting

The study will be conducted at the Bristol Brain Centre, Southmead Hospital, within the North Bristol NHS (National Health Service) Trust and is sponsored by the University of Bristol. Baseline and follow-up assessments will be conducted at Southmead Hospital, remotely via phone or video call, or at the participant's home. Participants will be asked to complete study activities from home, with visits from a researcher where needed, to deliver or collect study materials or provide support with study activities. Participants will be asked to complete a follow-up cognitive assessment at 6 months.

Participants and Sample Size

Participants will be eligible if they are 50 years of age and older at consent, have full capacity to consent and are willing to adhere to study procedures, have Wi-Fi at home, and meet the criteria to fall into 1 of the 3 study arms: AD group, LBD group, and the control group.

For the AD group, participants will require a clinical diagnosis of MCI due to probable AD or mild AD dementia obtained from medical records. This may include participants with mixed dementia where AD is considered a significant component of clinical presentation.

For the LBD group, participants will require a clinical diagnosis of established or prodromal Parkinson disease dementia, dementia with Lewy bodies, MCI due to Parkinson disease, or MCI due to LBD obtained from medical records. This may include participants with mixed dementia where LBD is considered a significant component to clinical presentation.

For the control group, participants will confirm that they have no known cognitive impairment or neurodegenerative condition. Efforts will be made to match the AD and LBD cohorts on age and sex.

For all groups, participants with a clinically significant untreated sleep disorder predating or unrelated to a dementia diagnosis (such as narcolepsy or untreated sleep apnea), a severe medical or psychiatric comorbidity that may substantially impact sleep (such as refractory epilepsy), or a diagnosis of dementia other than AD or LBD will be excluded from the study.

Study participants will be recruited from cognitive and movement disorders clinics at the North Bristol NHS Trust, volunteer databases, and Join Dementia Research. The study is expected to be open to recruitment between February 2022 and June 2023 with a recruitment target of 75 participants (n=25 in each group). Prospective participants will be introduced to the study via a telephone call from the research team or during a meeting with their clinical team and provided with a digital or paper copy of the participant information sheet. Those who are interested in taking part will be invited to a screening visit for further discussion and, if agreeable, to provide consent. The participants will be asked if they would like to attend with a friend or relative, but we will not recruit formal study partners.

Following consent, participants will undergo a Montreal Cognitive Assessment (MoCA). Those scoring <11/30 will be withdrawn from the study as this would indicate more advanced cognitive impairment, unless in the opinion of the principal investigator that there is a mitigating factor impacting performance on the MoCA (such as prominent speech disorder), in which case they will be eligible to continue in the study.

Outcome Measures

Brief Overview of the RESTED Study

Participants in the RESTED study will be asked to undergo screening and baseline assessments, including the MoCA, medical and clinical observations, questionnaires on sleep (Pittsburgh Sleep Quality Index [52], including responses from a cohabitant if available at the assessment, Epworth Sleepiness Scale [53], STOP (Snoring Tiredness Observed Pressure)-Bang Questionnaire [54], REM Sleep Behavior Disorder Single-Question Screen [55], Ultra-Short Version of the Munich ChronoType Questionnaire [56]), anxiety (Generalized Anxiety Disorder—7-item scale [57]), depression (Patient Health Questionnaire depression scale—8 [58]), and apathy (Apathy Evaluation Scale [59]). Participants will be asked to undergo blood biomarker testing for potential biomarkers of AD (amyloid beta 40 and 42, phosphorylated tau 181), neuroinflammation (glial fibrillary acidic protein), and neurodegeneration (neurofilament light chain) and overnight pulse oximetry using the Nonin 3150 WristOx$_2$ to screen for obstructive sleep apnea (OSA), except where a diagnosis of OSA has already been given or assessment has been completed within 6 months of recruitment to the study. The main study period will involve 8 weeks of remote study tasks, such as sleep diaries (Consensus Sleep Diary—Main [60] with a bespoke additional question on comparison of the previous night to typical sleep), wrist-based actigraphy (Axivity AX3), and regular online cognitive tests (choice reaction time, digit span, and self-ordered search via Cognitron). Throughout the main study period, participants are supported by researchers via MyDignio, a patient-facing mobile platform designed specifically for delivering remote health care, using task reminders and checklists. During 1 of the 8 weeks, participants will undergo an "intensive week" consisting of daily browser-based cognitive testing, wearing a Dreem 2 EEG headband during sleep, saliva samples for dim light melatonin onset (evening) and cortisol awakening response analyses (morning), and verbal memory recall and recognition tasks via a video link with a researcher. Participants will also be asked to provide feedback on their experiences throughout the study. A subsample of participants will be invited to take part in an end-of-study interview. Finally, participants will be invited to a 6-month follow-up MoCA.

Feasibility Outcomes

The feasibility and acceptability outcomes will be predominantly based on data relating to recruitment and retention, the remote study tasks (Table 1), and participant feedback. The core outcomes of the study are outlined in Figure 1.

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Table 1. Summary of data collection methods and frequency of remote home-based study tasks for the Remote Evaluation of Sleep to Enhance Understanding of Early Dementia study.

Remote study task	Method of data collection	Frequency of data collection	Duration of data collection
Sleep diary	App-based, via MyDignio	Daily	8 weeks
Actigraphy	Wrist-based actigraphy	Continuous	8 weeks
Remote browser-based cognitive tasks	Participants' own device, via Cognitron website	Twice per week, then daily during intensive week	8 weeks
Recall and recognition tasks with a researcher	Videoconferencing software	Four brief tasks to complete across 4 separate days (<5 minutes each)	1 week (intensive week only)
Overnight electroencephalography (EEG)	Dreem EEG headband	Every night	1 week (intensive week only)
Saliva samples for cortisol awakening response	Saliva swabs	Three swabs (0, 30, and 60 minutes after awakening)	1 morning (intensive week only)
Saliva samples for dim light melatonin assay	Passive drool samples	Seven samples hourly starting from 5 hours before usual bedtime	1 evening (intensive week only)
Overnight pulse oximetry for sleep apnea screening	Pulse oximeter	Overnight	2 nights

Figure 1. Conceptual map of feasibility and acceptability outcomes for the remote evaluation of sleep to enhance understanding of early dementia study. The core outcomes will be recruitment and retention, data quality, resources required, and participant experience.

Recruitment and Retention Rates

Recruitment and retention to the study will be described and presented in a flowchart following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Figure 2). Key recruitment and retention outcomes will include the proportion of eligible patients who consent to take part in the study and the proportion of patients who withdraw from the study after consent. Reasons for ineligibility and nonparticipation at each stage (prescreening, screening, main study period, and follow-up), as well as barriers and facilitators to recruitment, will be summarized. Sample characteristics will be presented in tables.

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Figure 2. A template flowchart of participant flow through the RESTED study, based on STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. This flowchart will document participant recruitment and retention at each stage of the study. MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; RESTED: Remote Evaluation of Sleep to Enhance Understanding of Early Dementia.

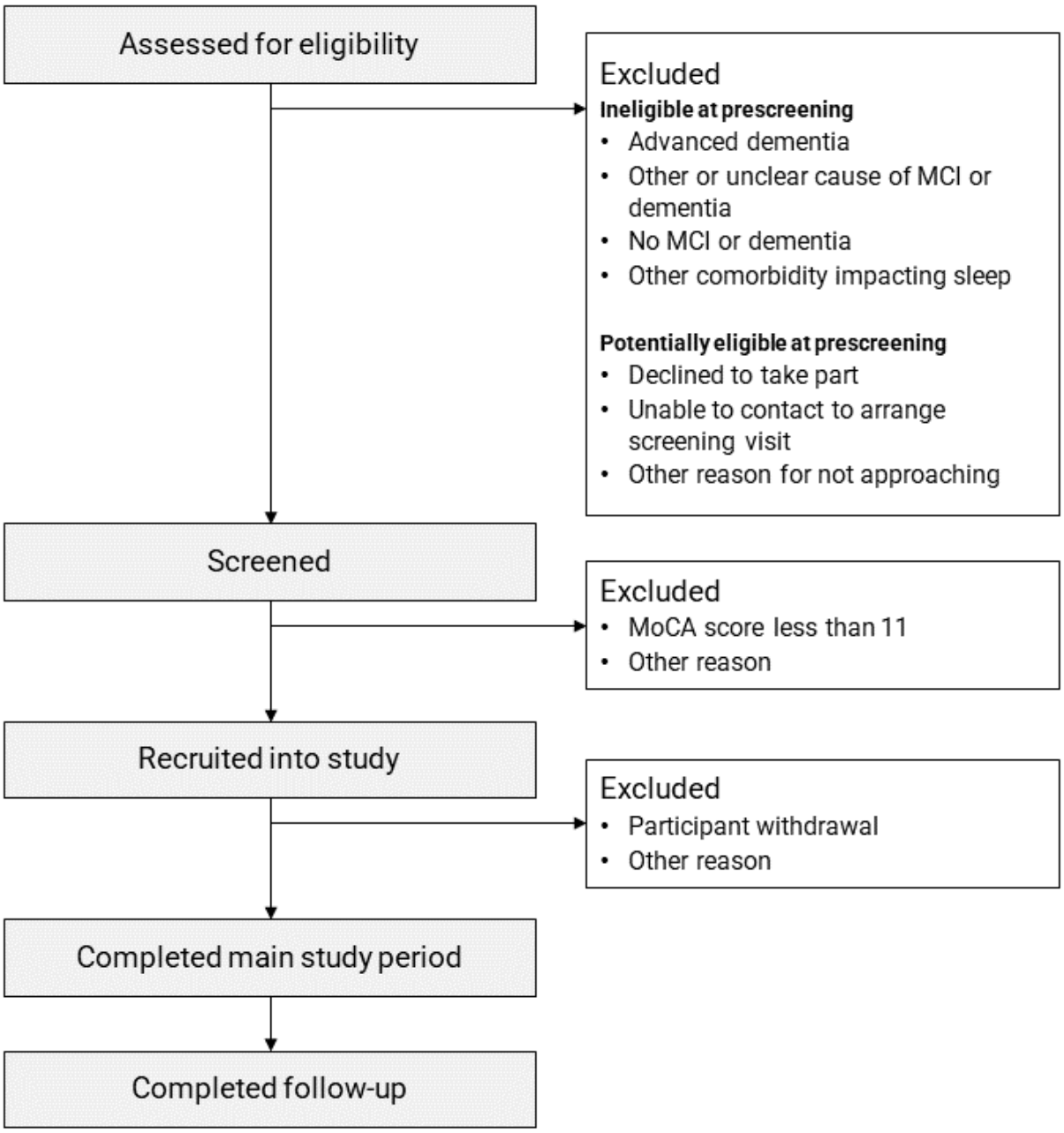

Data Quality, Participant Adherence, and Data Completeness

The participants will be provided written and verbal guidance and reminders on how and when to complete each of the study tasks. Descriptive statistics on adherence and data completeness for each remote study task will be summarized (eg, the number of nights the EEG headband was worn and the number of completed sleep diaries). Reasons for incompleteness (eg, participant nonadherence and technical problems) and methods used to encourage or improve data completion (eg, reminders to complete tasks) will be described.

We will also assess the extent to which data appear to be valid and of sufficient quality for analysis of core sleep metrics (eg, for EEG data, this will include individual EEG channels and overall record quality metrics).

Where multiple sleep metrics are measured on a single night (eg, total sleep time via actigraphy, sleep diary, and EEG), an agreement between different measurement tools will be calculated (eg, Bland-Altman plot comparing sleep diary-adjusted actigraphy to EEG).

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Resources

We will assess the amount of support and resources (eg, in-person visits, email, app-based, and telephone support) required from the research team to complete remote study tasks. Though the study will not require a study partner, we will also record whether participants perceive that they have access to support from outside of the study team (eg, family member, caregiver, or friend), whether this support is used, and what support is provided (eg, technical support and reminders).

Barriers, Facilitators, and Participant Feedback

We will review participant feedback expressed before, during, and at the end-of-study interviews to identify barriers and facilitators in (1) participating in remote sleep and cognitive research in general and (2) study-specific remote tasks.

The end-of-study interviews were designed and guided by the Capability Opportunity Motivation-Behavior (COM-B) system model of behavior, which suggests that capability, opportunity, and motivation interact with behavior in a system [61]. The interviews will probe the capacity to engage in the study activities (capability), habits and decision-making around study involvement (motivation), external factors that influenced behavior, and completion of the study tasks (opportunity). Interview transcripts will be coded and organized into themes using NVivo (version 20; Lumivero; or newer) software. We will use an inductive approach to thematic analysis and aim to identify semantic and latent themes [62,63].

Where appropriate and scientifically sound, we will incorporate feedback on acceptability and feasibility to improve the study design. Changes to the study design due to feasibility or acceptability or based on feedback from prospective or enrolled participants will be documented.

Subgroup Analyses

We will compare acceptability and feasibility outcomes between study arms (AD, LBD, or controls) and conduct exploratory analyses to determine whether subjective sleep quality support from a relative or friend or baseline apathy and anxiety predict overall adherence to study tasks.

Ethical Considerations

This study has been approved by the Health Research Authority (Yorkshire and the Humber—Bradford Leeds Research Ethics Committee, reference 21/YH/0177) and carries minimal risk to participants. The study will be conducted in accordance with Good Clinical Practice and the Helsinki Declaration to protect the rights and welfare of all participants. All data will be kept securely and handled in accordance with the General Data Protection Regulation (EU 2016/679). Capacity to consent to the research study will be assessed and participants will be required to provide full written informed consent prior to participation in any study activities. The participants will be reminded of their right to withdraw at any point, without providing a reason, and without this affecting their health care. Participants will be offered cash reimbursement for travel or postage expenses incurred during the study. The participants will be assigned a study ID at consent to allow pseudonymization of participant data, with personal information stored separately and securely from deidentified data. The final paper and any data shared will contain no information that allows for the identification of individual participants.

Results will be presented at scientific meetings and conferences and published in peer-reviewed journals. Summaries will be provided to participants where they have indicated consent to be contacted about results from the study.

Results

The study opened to recruitment in February 2022. Participant recruitment is scheduled to be completed in 2023. Data collection is anticipated to continue until February 2024, with analysis beginning in 2023 and continuing into 2024.

Results will be reported in line with guidance from the STROBE checklist [64] and the CONSORT 2010 extension [65] for pilot and feasibility trials [66].

Discussion

Principal Findings

Sleep is a fundamental component of health, and sleep disturbances are commonly observed in people living with MCI and dementia. Insufficient or poor sleep may represent both a risk factor and a symptom of these conditions, but more work is needed to confirm the relationship between sleep and MCI or dementia. Improvements to the way we measure sleep, such as measuring sleep in someone's natural home environment and using technologies to supplement data collected from sleep questionnaires may help us to better understand the sleep profile in these conditions compared to normal aging, identify targets for intervention, and monitor disease progression [32,67]. However, we first need to understand whether it is possible to collect good-quality sleep and cognitive data from people living with MCI and dementia in their own homes. Accordingly, this paper proposes a study to investigate the feasibility and acceptability of remote sleep and memory data collection using study tasks designed to be completed at home by people living with MCI or dementia. The study aims to assess whether people with MCI or dementia are willing to engage in sleep studies using technology and home-based study tasks, describe participant experience, and evaluate the study tasks based on retrieving complete and analyzable data. The findings from this study will guide future research design in sleep and memory.

Limitations

The eligibility criteria for the study require participants to have an internet connection and be willing to use technology for the duration of the study. Understanding the feasibility and acceptability of technology-supported remote research is the purpose of the study; however, this inherently may introduce bias into the study. For example, it is possible this may mean those who are unfamiliar or uncomfortable with technology may not take part, or those who are particularly interested in technology may find the study more acceptable or feasible. If recruitment, retention rates, or feedback from patients who would otherwise be eligible but were unable or unwilling to take part because of limited access to or ability to use the

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internet or a smart device, we may offer an adapted version of the study and will record whether this influences recruitment rate and other relevant outcomes.

Subjective measures used in the study may be prone to recall bias and may be difficult for individuals with cognitive impairment to answer accurately. While participants themselves will need to provide answers to questions during the study, they can be supported by a family member, friend, or caregiver where needed and requested by the participant. Subjective measures will also be complemented by objective measures which are not prone to recall bias.

The longitudinal and remote nature of the study may result in a greater proportion of missing data compared to sleep research studies conducted in a laboratory setting. As a study enrolling persons with MCI and dementia, it is also expected that participants may have difficulty remembering to complete study tasks. Reasonable efforts will be taken to encourage adherence and data completion throughout the study period, particularly in the intensive week (eg, schedules and digital reminders via SMS text messaging or email). Automated scheduled reminders and task lists will be supplemented with ad hoc contacts from the research team directly (eg, contacting to ascertain reasons behind consecutive days of missing data).

Conclusions

Technological advancements and improved digital literacy offer the opportunity to research sleep longitudinally and in the home environment. However, further research is needed to understand whether these developments may benefit MCI and dementia study design. This protocol outlines a mixed methods study that examines the feasibility and acceptability of remote sleep and cognitive testing in a cohort of older adults specifically those with MCI or dementia due to probable AD or LBD. Outputs from the study will inform the approach to studying sleep in people with MCI or dementia in this population, contributing toward global efforts to identify and better understand potentially modifiable risk factors in these conditions.

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Data Availability

Data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

VGG contributed to the study authorship, protocol authorship, study management, study design, participant recruitment, participant consent, and data collection. JB and HDM contributed to the protocol authorship, study design, sub principal investigators, participant recruitment, participant consent, data collection, and study review. EC contributed to the project conception, study design, principal investigator, and study review. BB contributed to the study design, data collection, and study review. HL contributed to the participant recruitment, participant consent, and data collection. NT contributed to the data analysis methodology. AJ, WT, and AH performed the cognitive task formulation. AW, GMR, and RG contributed to the study design.

Conflicts of Interest

AH is owner and director of Future Cognition Ltd and H2 Cognitive Designs, which provide custom cognitive assessment software and digital research and healthcare services. WT is employed by H2 Cognitive Designs LTD, owners and developers of the Cognitron software

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Abbreviations

AD: Alzheimer disease
COM-B: Capability Opportunity Motivation-Behavior
CONSORT: Consolidated Standards of Reporting Trials
EEG: electroencephalography
LBD: Lewy body disease
MCI: mild cognitive impairment
MoCA: Montreal Cognitive Assessment
NHS: National Health Service
OSA: obstructive sleep apnea
PSG: polysomnography
REM: rapid eye movement
RESTED: Remote Evaluation of Sleep to Enhance Understanding of Early Dementia
STOP: Snoring Tiredness Observed Pressure
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Benchmarking Mental Health Status Using Passive Sensor Data: Protocol for a Prospective Observational Study

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Abstract

Background: Computational psychiatry has the potential to advance the diagnosis, mechanistic understanding, and treatment of mental health conditions. Promising results from clinical samples have led to calls to extend these methods to mental health risk assessment in the general public; however, data typically used with clinical samples are neither available nor scalable for research in the general population. Digital phenotyping addresses this by capitalizing on the multimodal and widely available data created by sensors embedded in personal digital devices (eg, smartphones) and is a promising approach to extending computational psychiatry methods to improve mental health risk assessment in the general population.

Objective: Building on recommendations from existing computational psychiatry and digital phenotyping work, we aim to create the first computational psychiatry data set that is tailored to studying mental health risk in the general population; includes multimodal, sensor-based behavioral features; and is designed to be widely shared across academia, industry, and government using gold standard methods for privacy, confidentiality, and data integrity.

Methods: We are using a stratified, random sampling design with 2 crossed factors (difficulties with emotion regulation and perceived life stress) to recruit a sample of 400 community-dwelling adults balanced across high- and low-risk for episodic mental health conditions. Participants first complete self-report questionnaires assessing current and lifetime psychiatric and medical diagnoses and treatment, and current psychosocial functioning. Participants then complete a 7-day in situ data collection phase that includes providing daily audio recordings, passive sensor data collected from smartphones, self-reports of daily mood and significant events, and a verbal description of the significant daily events during a nightly phone call. Participants complete the same baseline questionnaires 6 and 12 months after this phase. Self-report questionnaires will be scored using standard methods. Raw audio and passive sensor data will be processed to create a suite of daily summary features (eg, time spent at home).

Results: Data collection began in June 2022 and is expected to conclude by July 2024. To date, 310 participants have consented to the study; 149 have completed the baseline questionnaire and 7-day intensive data collection phase; and 61 and 31 have completed the 6- and 12-month follow-up questionnaires, respectively. Once completed, the proposed data set will be made available to academic researchers, industry, and the government using a stepped approach to maximize data privacy.

Conclusions: This data set is designed as a complementary approach to current computational psychiatry and digital phenotyping research, with the goal of advancing mental health risk assessment within the general population. This data set aims to support the field's move away from siloed research laboratories collecting proprietary data and toward interdisciplinary collaborations that incorporate clinical, technical, and quantitative expertise at all stages of the research process.

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KEYWORDS

audio data; computational psychiatry; data repository; digital phenotyping; machine learning; passive sensor data

Introduction

Background

Modern mental health care is the product of a tremendous volume of basic and applied research. Until recently, the majority of this research has relied on methods and practices (eg, randomized controlled trials [1]) that require large amounts of human labor to recruit participants (eg, through in-person recruitment at clinics or calls to members of research registries) and collect the necessary data (eg, through clinical interviews, performance-based tasks, or manual extraction from eHealth records). These methods and practices also tend to generate siloed data sets that are difficult to share beyond the original study team (see [2] for a review). Though existing research using these methods and practices has produced very valuable findings and greatly improved treatment options for individuals coping with mental health challenges, the pace of development is slow [3], and recent estimates suggest that only 40% to 50% of Americans who need mental health care receive treatment [4]. Novel approaches to mental health research are needed to address these challenges, and recent advances in computational analysis and digital technology have the potential to do just that (see [5-7] for reviews).

Computational psychiatry is an approach that includes both theory- and data-driven applications of mathematical modeling with the goal of advancing the diagnosis, mechanistic understanding, and treatment of mental health conditions [8-10]. For example, on the theory-driven side, reinforcement-learning models applied to functional magnetic resonance imaging data have helped predict posttreatment outcomes (ie, abstinence vs relapse) in patients with alcohol dependence [11], and Bayesian models of cognitive task performance have improved our understanding of how the ability to flexibly update previous beliefs differs between diagnoses (see [12] for a review). Similarly, data-driven studies using machine learning models with high-dimensional data (eg, electroencephalogram and magnetic resonance imaging data) have been able to accurately distinguish patients with schizophrenia from controls [13,14] and have also identified multivariate "biomarkers" that have helped improve pharmacological treatment-response prediction in patients with depression [15-17].

Enthusiasm about this body of work has led to numerous calls to extend these methods to mental health risk assessment in the general public [18-20]. However, one of the largest barriers to doing so is that many of the data sources used in computational psychiatry research with clinical samples (eg, brain imagery data and standardized task performance data) are not available for community-dwelling individuals in the general population. As a result, researchers are increasingly leveraging the near ubiquity of personal digital devices (PDDs) [21] (eg, smartphones and smartwatches) as a more scalable and accessible means of collecting high-dimensional behavioral, contextual, and even physiological data streams from individuals [22,23]. Research of this type represents a subset of the broader computational psychiatry field commonly referred to as digital phenotyping.

Digital phenotyping refers to using quantitative methods with PDD data—particularly passive sensor data (eg, GPS, accelerometry, call and text logs, and app usage)—to identify behavioral phenotypes or "digital biomarkers" relevant to mental health [24-26]. Thus far, digital phenotyping research has primarily focused on using computational methods such as machine learning models for detecting, monitoring, and predicting changes in symptom severity as well as predicting or improving treatment response in clinical samples (for reviews, see [27-29]). For example, machine learning algorithms applied to passive sensor data have been able to successfully identify depressive and manic episodes in individuals with bipolar disorder [30,31] and predict psychotic relapses in patients with schizophrenia [32]. Furthermore, digital biomarkers derived from PDD data have demonstrated reasonable accuracy for predicting treatment response to transcranial magnetic stimulation in patients with depression [33]. Finally, a growing body of research demonstrates that passive sensor data from PDDs can also be used to identify common risk factors for mental health conditions (eg, stress, depressed mood, and anxiety) in clinical [34] and student samples [35].

This nascent body of research provides an empirical and methodological foundation for extending digital phenotyping to identify markers of mental health risk in the general population. While, to the best of our knowledge, no studies have done this using a prospective study design with community-dwelling adults, existing computational psychiatry and digital phenotyping research, along with guidance from leading advocates in these fields, provides a strong set of recommendations for generating a data set that is well-suited to this objective. These recommendations include: (1) using a transdiagnostic and dynamic understanding of mental health to guide study design and data collection [20,36]; (2) incorporating the data requirements of cutting-edge computational methods into data collection methods [37,38]; and (3) using careful consent procedures and data curation methods to ensure that data can be safely and ethically shared with researchers across academia, industry, and government so as to harness the expertise of diverse professionals working toward improving mental health [39].

Objectives

On the National Institute of Mental Health Data Archive [40], there currently exists a small number of shareable computational psychiatry data sets that include longitudinal PDD data from community-dwelling participants [41,42], while other such data sets are in the process of being created [43,44]. Nevertheless, all of these data sets comprise participants who either meet specific diagnostic criteria (eg, trauma exposure [42], diagnosis with a serious mental illness [43], and binge drinking [44]) or developmental characteristics (eg, school-attending adolescents) and are best suited for identifying digital biomarkers of mental health risk in clearly defined subsamples of the population.

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Therefore, as a complement to this existing work, we aim to create the first computational psychiatry data set that is tailored to studying mental health risk in the adult general population, includes PDD sensor-based behavioral features, and is designed to be widely shared across academia, industry, and government using gold standard guidelines for privacy, confidentiality, and data integrity.

To maximize the relevance and use of this data set for researchers from a wide array of disciplines, we will use the guidelines listed above to ensure our proposed data set is optimized for both mental health and computational considerations. On the mental health side, our proposed data set will be informed by state-of-the-art etiological and phenomenological models of mental health and mental health disorders. On the computational side, our proposed methods are designed to generate a high-dimensional, multimodal, and multirate feature set with maximum variability across levels of measurement and analysis, a balanced classification design, and minimal missing data [22,38]. These considerations will therefore support the primary objective of this project, which is to create a data set that, through its design and accessibility, has the potential to advance mental health risk assessment in the general population using digital phenotyping methods. Although we do not have specific hypotheses or analytic plans guiding the creation of this data set, we believe that in combination with computational methods, the data we collect could be used to investigate research questions such as the following: can PDD sensor-based features predict the likelihood of a future mental health event (eg, receiving a psychiatric diagnosis or treatment) at rates significantly above chance? and does incorporating information about preexisting vulnerability factors (eg, difficulties with emotion regulation and past mental health conditions) improve the accuracy of these predictions?

Methods

Participants

We are recruiting 400 individuals at varying levels of risk for a lifetime incidence of experiencing an episodic mental health disorder (eg, depression, anxiety, and adjustment disorder). To achieve this goal, we are using a stratified, random sampling design with 2 crossed factors: (1) difficulties with emotion regulation [45], a transdiagnostic risk factor for a wide range of mental health conditions [46], and (2) perceived overall life stress during the past 30 days [47]. These 2 factors are assessed during screening, and eligible individuals will be included in the sample such that 40% to 60% of participants report higher than average difficulties regulating strong emotions and 40% to 60% report currently experiencing significant life stress. This sampling design and the choice of these 2 factors were guided by the diathesis-stress model of psychopathology, which suggests that many episodic (ie, non-neurodevelopmental [48]) psychological disorders are the result of an interaction between preexisting vulnerabilities—in this case, difficulties with emotion regulation—and stress due to life experiences [49]. Participants must also meet the following eligibility criteria: be 18 years of age or older, currently living in Utah, have a smartphone with an active cellular data plan and an Apple or Android operating system, be able to speak and read English fluently, and receive their health care through either the University of Utah Health (UHealth) or Intermountain Health Care (IMHC) systems.

Individuals who report suicidal ideation in the past 3 months or any history of a suicide attempt, active mania, or psychosis (ie, severe mental health problems potentially requiring hospitalization during their participation) during screening are ineligible to participate. Initially, individuals who reported current symptoms of a substance use disorder (eg, daily binge drinking) and were not engaged in substance use treatment were also ineligible for participation; however, we received additional funding after beginning the study that allowed us to increase the study staffing so that we could remove this exclusion criterion. This change to the exclusion criteria occurred approximately 6 months into recruitment, after 180 participants—almost half of our target sample size of 400—had provided consent. Finally, individuals with a history of conviction for a violent crime; a history of child abuse or neglect perpetration substantiated by child protective services; and, for individuals in committed relationships, recent physical intimate partner violence are also excluded for potential ethical reasons. Specifically, licensed mental health providers and physicians are legally required to report instances of each of these final criteria to authorities in most states in the United States, and this duty is not waived by a certificate of confidentiality. The presence of these events would therefore render the data set unshareable for most purposes.

Procedures

Participants are recruited using web-based advertising through the University of Utah websites, social media websites, and listserves, as well as paper fliers posted throughout the Salt Lake City area. Interested participants complete a web-based screening survey to determine eligibility. Eligible participants are then forwarded to an electronic consent form, and consenting participants complete another web-based battery of questionnaires to assess current and lifetime psychiatric and medical diagnosis and treatment, current psychological symptoms and social functioning, and demographic variables. Participants who complete this baseline battery are compensated US $25 and are scheduled for a videoconference call during which study staff instructs them on how to use the study equipment (ie, audio recorder) that is mailed to them.

Following this call, participants begin a continuous 7-day period of intensive data collection that includes wearing the audio recorder during waking hours, providing raw sensor data collected through a smartphone app (Beiwe [50]), completing a brief survey to assess mood and important events at the end of each day, and responding to a brief phone call from study staff every evening. During this phone call, study staff assess compliance with study procedures, ask participants to describe the most positive and negative events from that day, and inquire whether there is any period of the recording from that day that they wish to delete. Providing participants the opportunity to review the contents of their recordings is necessary to meet ethical standards for long-term, ambulatory data collection [51]. After returning the audio recorder, participants are compensated

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US $10 and US $4.28 for every day that they provided raw sensor (PDD) data and audio recording, respectively.

Participants also complete web-based questionnaires 6 and 12 months after the 7-day intensive data collection phase to reassess current psychological symptoms and social functioning, as well as psychiatric and medical diagnosis and treatment during the intervening time; they are compensated US $20 for the completion of each of these questionnaires. See Figure 1 for the complete procedure flow diagram. All of these procedures are described in more depth below.

Figure 1. Procedures flowchart. DERS: Difficulties with Emotion Regulation Scale; PSS-4: Perceived Stress Scale-4.

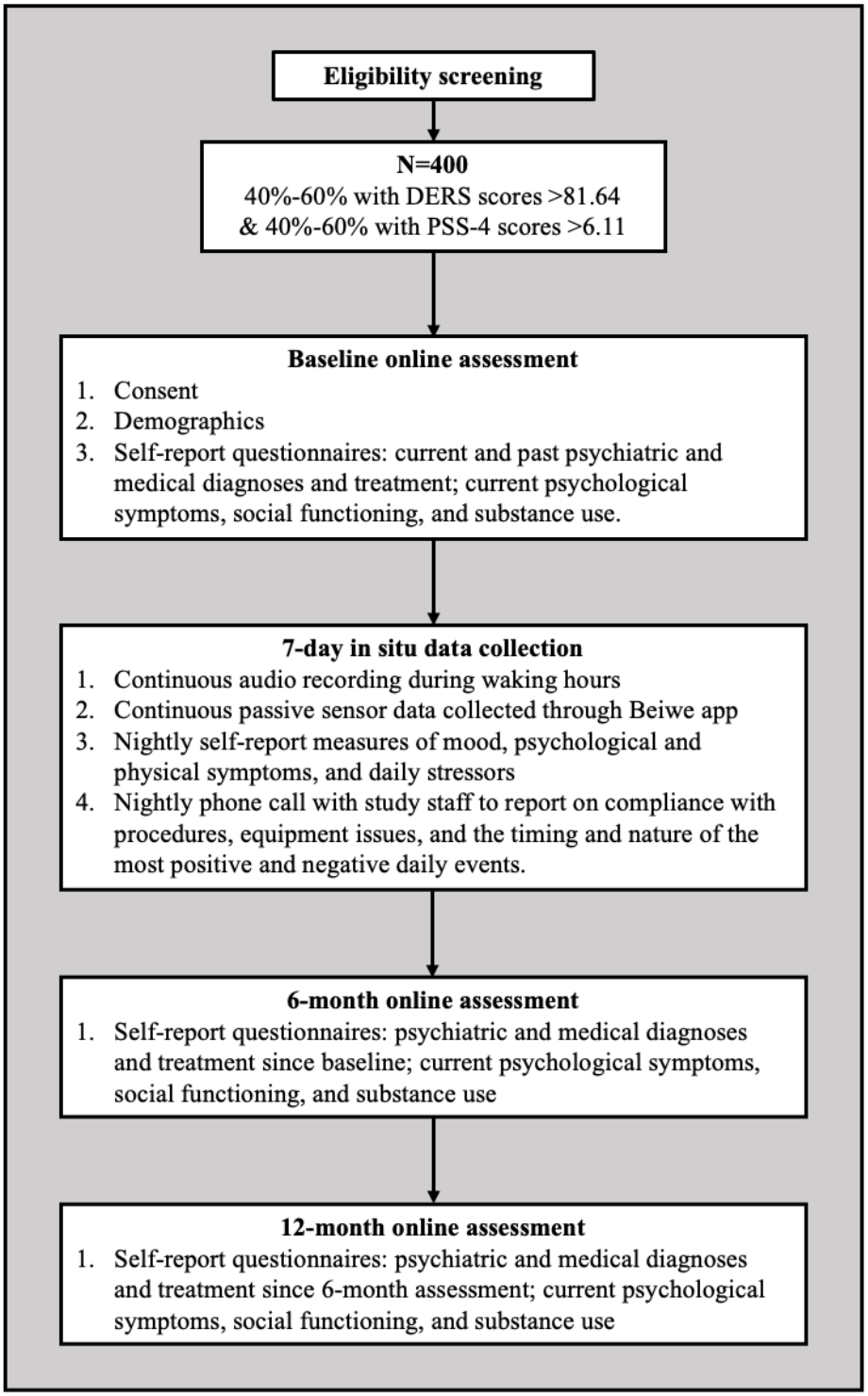

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Data Privacy and Confidentiality

To maximize data privacy and security, data from all sources are encoded and can only be matched using a key maintained in a password-protected file only accessible to approved study personnel. Study data collected from the Beiwe app are encrypted in transit and at rest, and no identifiable data are stored on participants' devices. For complete details on all the security features of the Beiwe research platform, see [52]. Audio files are saved to a microSD card and returned with the recorders through registered mail. All digital data, both in raw and processed formats, are stored in a Health Insurance Portability and Accountability Act (HIPAA)–compliant protected environment maintained by the University of Utah Center for High-Performance Computing.

Data Sources

Self-Report Questionnaires

Participants are given the option to skip any self-report questionnaire item. See [53] for full versions of all publicly available standardized measures as well as any nonstandardized questionnaires included in this study (ie, demographics questionnaire, clinical history questionnaire, and daily events questionnaire).

Difficulties With Emotion Regulation Scale

The Difficulties with Emotion Regulation Scale (DERS) [45] is a well validated and widely used measure of subjective emotion regulation ability [54]. A total of 36 items are responded to on a 5-point Likert scale (from 1="almost never [0%-10%]" to 5="almost always [91%-100%]"; range of scores 36-180), such that higher total scores indicate greater difficulty regulating in the context of strong emotions. Overall, 6 subscale scores can also be generated, capturing individuals' lack of emotional awareness, lack of emotional clarity, nonacceptance of emotions, limited access to emotional regulation strategies, and difficulties engaging in goal-directed behavior or inhibiting impulsive responses in the context of strong emotions. The DERS is administered as part of the screening survey and is only presented to individuals who have already met all other inclusion and exclusion criteria. The mean total DERS score from a community sample [55] is used to classify participants as having high (ie, total score >81.64) versus low (ie, total score ≤81.64) difficulties with emotion regulation for enrollment purposes.

Perceived Stress Scale-4

The Perceived Stress Scale-4 (PSS-4) [47] is a 4-item short form of the widely used Perceived Stress Scale, which measures individuals' subjective level of life stress during the previous month. The PSS-4 displays acceptable psychometric properties in nonclinical populations [47,56] and is used to assess how unpredictable and overwhelming individuals currently find their lives. Items are responded to on a 5-point scale anchored by 0 (never) and 4 (very often), and higher total scores indicate greater perceived stress (range of scores 0-16). The PSS-4 is only presented to eligible participants as part of the screening survey. The mean total score from a validation sample of community participants [56] is used to identify participants experiencing high (ie, total score >6.11) versus low (ie, total score ≤6.11) life stress for enrollment purposes.

Demographics Questionnaire

As part of the baseline battery, participants are asked to report on a number of demographic factors, including age, biological sex, gender, sexuality, relationship status, race, ethnicity, spoken languages, religion, education history, and current employment and income.

Clinical History Questionnaire

Participants are asked to provide information about their current and past physical and mental health, including smoking status; history of a major medical event (eg, cancer, diabetes, or stroke); current and past psychiatric diagnoses; current and past use of psychiatric medication; or other mental health treatment, including when and what service or medication was used. This questionnaire was created for this study and is included in the baseline battery as well as the 6- and 12-month follow-up questionnaires as a way of assessing any significant physical or mental health changes during the study period.

Depression, Anxiety, and Stress Scale-21

The Depression, Anxiety, and Stress Scale-21 (DASS-21) [57] is a 21-item questionnaire designed to measure depression, anxiety, and tension or stress during the past week. It is a short form of the widely used and well-validated original DASS-42 [58]. Individuals respond to items on a 4-point Likert scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time), and 3 subscale scores are produced corresponding with the 3 negative emotional states. The DASS-21 is administered at baseline as well as at the 6- and 12-month time points.

Tobacco, Alcohol, Prescription Medications, and Other Substance Tool

The Tobacco, Alcohol, Prescription Medications, and Other Substance (TAPS) [59] tool is a 2-part measure of substance use. In the first part, individuals respond to 4 items assessing how frequently (ranging from "never" to "daily or almost daily") they have used tobacco, alcohol, illicit drugs, or prescription drugs for nonmedical reasons in the past year. Any individual who screens positive in part 1 (ie, responds with anything other than "never") then completes part 2, which consists of a brief assessment of use-related behaviors during the past 3 months. Scores from part 2 can be used to generate 3 levels of risk for each substance endorsed (ie, no use in the past 3 months, problem use, and higher risk). The TAPS tool has demonstrated adequate psychometric properties as a screening measure for high-risk substance use behaviors in adult primary care patients [59]. We are including a measure of substance use in our data set because this is a well-established, transdiagnostic behavioral marker of risk, and in combination with our affective marker of risk (ie, difficulty regulating emotions), it will improve the precision of risk estimation [60]. This measure is administered at baseline as well as at the 6- and 12-month time points.

Life Functioning Questionnaire

The Life Functioning Questionnaire (LFQ) [61] is a 2-part questionnaire designed to assess individuals' subjective difficulty functioning in 4 domains of life (leisure time with friends, leisure time with family, duties at work or school, and

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duties at home) during the past month. In part 1 of the LFQ, individuals indicate the degree of problems (from 1 [no problems] to 4 [severe problems]) they have experienced within each domain in terms of the amount of time spent on related activities, amount of conflict experienced, level of enjoyment, and self-assessed performance (for work and home duties only). For duties in the work or school domain, individuals are also asked to indicate the number of days they were absent as well as the factors that contributed to their absence (eg, mental or physical health symptoms and interpersonal difficulties). Part 2 asks additional questions about individuals' work situation during the previous month, previous full-time work, and reasons for leaving, as well as their living and financial status in the past 6 months. The LFQ was originally designed to assess functional capacity in psychiatric patients and has demonstrated adequate psychometric properties with adult inpatients seeking treatment for mood disorders [61]. In this study, the LFQ is administered at baseline and at the 6- and 12-month time points.

Brief Symptom Inventory-18

The Brief Symptom Inventory-18 (BSI-18) [62] is an 18-item measure that assesses the level of distress a person has experienced in the past day due to various psychological (eg, feelings of worthlessness) and physical (eg, pains in the heart or chest) symptoms. Questions are responded to on a 5-point scale from 0 (not at all) to 4 (extremely) and can be summed to produce 3 subscale scores (depression, anxiety, and somatization) as well as a global severity index that measures overall psychological distress. The BSI-18 has been validated and normed with community samples and is acceptable to use repeatedly as a measure of symptom change [63]. The BSI-18 is administered nightly during the 7-day intensive data collection phase of this study.

Daily Positive and Negative Mood Questionnaire

Aspects of participants' daily mood are assessed using a version of the Positive and Negative Affect Schedule [64] described by Smyth et al [65]. Participants rate their current level of 4 positive and 5 negative mood adjectives on a 7-point scale anchored by 0 (not at all) and 6 (extremely). Items are summed to produce positive and negative mood subscales that demonstrated acceptable psychometric properties in a previous sample of community participants [65]. This measure is administered nightly during the 7-day intensive data collection phase of this study.

Daily Events Questionnaire

The Daily Events Questionnaire asks individuals to select from a list of common daily stressors (eg, a lot of work at school or work or a financial problem) and people (eg, a friend or spouse) to assess if any troublesome events happened to them since they woke up that morning, as well as if they experienced any tension or arguments with anyone. Individuals can select as many options as apply and have the option to describe any "other" event or relationship not listed. For each selected event, individuals are then asked to indicate approximately when this event occurred and how distressed they felt during the event, from 1 (not at all) to 10 (very much). Similarly, for each person that a participant indicates they had an argument with, they are asked to provide approximately when the argument began and ended, as well as how distressed they felt and how satisfied they felt with the outcome of the event (using the same 10-point response scale). This measure has been used previously to successfully identify the approximate timing of various distressing events throughout the day [66]. In this study, it is administered nightly during the 7-day intensive data collection phase of this study.

Daily Call With Study Staff

Study staff calls participants each evening near the end of the day (ie, between 6 PM and 8 PM) to inquire about compliance with study procedures, problems with study equipment, and the nature and timing of participants' most positive and negative events of the day. A transcript of the semistructured interview questions used during these phone calls is available on our Open Science Foundation site [53].

Audio Data

In situ audio is continuously recorded while participants are awake at 24-bit/48 kHz using omnidirectional Lavalier microphones connected to miniature field recorders. Recordings are segmented into smaller, 15-minute-long files to optimize data transfer and increase data processing efficiency.

We have carefully considered legal and ethical issues in proposing these in situ recordings. Audio recordings are governed by wiretapping laws, which vary from state to state. Utah is a single-party consent state, meaning that as long as a study participant consents to be recorded, other individuals captured on those recordings do not need to additionally consent. However, the ethical principles of beneficence, nonmaleficence, autonomy, and justice require that other individuals who may be recorded need to be aware of that possibility and given the opportunity to not be recorded. For these reasons, participants are instructed to wear a badge that states that they are participating in a study that records audio during daily life and will be allowed to pause the recording whenever an individual they come into contact with requests that they do so, or the participant wishes or is required to do so by policy or law [51]. We have used these methods in previous work, and they typically generate 10 to 14 hours of audio per day.

Passive Sensor Data

Raw smartphone sensor data are collected using Beiwe, a cross-platform digital phenotyping app created by Onnela and colleagues [25,50]. The Beiwe platform collects raw data generated by smartphone sensors, including, but not limited to, GPS and accelerometry, Wi-Fi connectivity, Bluetooth device scans, phone and screen status, and phone call and SMS text message event logs linked to onboard device contacts. The specific data collected for a participant is determined by the sensors on their smartphone and the policies of the smartphone manufacturer [52].

Medical Records

The state of Utah maintains the Utah Population Database (UPDB) and All Payer Claims Database, which are standardized (ie, use the Systemized Nomenclature of Medicine–Clinical Terms), digital archives of medical encounters in the UHealth

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and IMHC systems, and insurance claims filed in the state, respectively. These databases are generated for research purposes and will be used to verify and augment participant reports. These databases represent a highly unique and valuable opportunity because it is well documented that retrospective reports of psychiatric history incorrectly fail to identify ~25% to 40% of true positives relative to medical records [67]. Relevant records from these databases will be linked to other participant data. UPDB policy dictates that these records will not be shareable, and individuals or entities wishing to access them will have to seek permission directly from the database administrators.

Planned Data Processing

Raw item responses as well as relevant total and subscale scores from the self-report questionnaires will be created using standard scoring protocols and included for all self-report measures in the final data set. In addition to raw DERS scores, age- and gender-adjusted *t*-scores computed using the methods in [55] will be included in the final data set. Annotations of participants' most positive and negative daily events will also be available in the data set. To create these, study staff will use the information provided by participants during the daily phone calls to annotate details about their most positive and negative event for each day, including the beginning and end time of the event, and the type (eg, interaction with another person or financial problem) and nature of the event (eg, positive vs negative). Study staff will additionally annotate speaker IDs (eg, participant and female 1), emotional expressions, and communication behaviors (eg, arguing or cooperating) using information from the corresponding recorded audio.

Audio recordings will be processed to generate gold-standard acoustic feature sets used in behavioral signal processing [68] and affective computing [69] research using the openSMILE toolkit [70]. These methods produce 88 acoustic variables that represent frequency-, energy-, and spectral-related aspects of speech and ambient noise. Acoustic variables will be generated over the smallest window of time possible for each variable and downsampled to produce a summary score for each acoustic variable for each 1 second of the recording.

Raw PDD sensor data will be processed using Forest [71], a freely available library for analyzing Beiwe data developed by the creators of Beiwe. Similar to the acoustic variables described above, Forest produces summary variables for each sensor type that quantify a wide range of behavioral and contextual information. For example, outputs of GPS data include time spent at home, total distance traveled, physical circadian rhythm, and the type (eg, shop, restaurant, and place of worship) and duration of locations visited. The location type is generated using information from the open-source platform OpenStreetMap [72] and is particularly valuable for the current data set as it will allow for the creation of a library of geographically referenced place tags that index risky (eg, amenity=bar; amenity=tobacco retailer) and protective (eg, amenity=library; amenity=gym) locations and will increase the potential information value of the database by providing additional context for the passive sensor data streams collected. Another example of the summary features available from Forest includes outputs of call and text logs, the total number of calls received, the total number of unique callers, and the total duration of calls received. Additional details about all summary variables are available on the Forest GitHub page [71]. Summary variables will be generated for each day and included in our final data set.

Ethical Considerations

All study procedures were approved by the University of Utah Institutional Review Board (00149365). Eligible participants are given the opportunity to review all study procedures, including planned data-sharing processes, and are provided with contact information for the study's principal investigator to answer any additional questions before signing the consent form on the internet. Several measures are in place to protect the privacy and confidentiality of participants' data (see *Data Privacy and Confidentiality* and *Results* sections for additional details). These include using a secure and password-protected database for storing all study data, only sharing deidentified and nonsensitive data publicly, and requiring a more stringent data use agreement and relevant ethics approval to be provided by individuals requesting access to identifiable data sources (eg, raw audio data). All participants are offered US $165 as compensation for completing all study procedures.

Results

Data collection for this project began in June 2022 and is expected to conclude by July 2024. To date, 310 participants have consented to the study; 149 have completed the baseline questionnaire and 7-day intensive data collection phase; and 61 (ie, 85% of eligible participants) and 31 (ie, 91% of eligible participants) have completed the 6- and 12-month follow-up questionnaires, respectively.

Once completed, the proposed data set will be made available consistent with the findable, accessible, interoperable, and reusable guidelines for data management and stewardship [73]. We will publish a description of the data set in a general science outlet with a broad readership to increase awareness of it among a broad audience. We will also index the data set on recommended data banks, such as the Open Science Foundation and Science Data Bank [74] to increase its findability.

We will use a stepped approach to making the data set accessible to academic researchers, industry, and government. Deidentified, nonsensitive data (eg, raw item and scale scores from self-report measures, summary features from acoustic and passive sensor data, and annotations of daily events) will be publicly available for download directly from data repositories after completion of a brief data use agreement but without contact with the study team. Identifiable and other sensitive data (eg, raw audio recordings and raw passive sensor data) will only be made available for download from a University of Utah server after researchers have provided evidence of the necessary approvals from their institutional review board or comparable entity, completed a more stringent data use agreement, and have communicated with a member of the study team. Data will be made available to academic and government researchers at no cost and licensed to commercial entities.

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Discussion

Contributions

Computational psychiatry and digital phenotyping have the potential to make significant contributions to mental health research and treatment development. Digital phenotyping studies have already demonstrated that by applying machine learning techniques to PDD data, it may be possible to predict upcoming mental health events (eg, manic episodes and hospitalization) in clinical samples [32] and detect mental health risk factors (eg, increasing stress and depressed mood) in students [35]. These findings are paving the way for a future where digital markers of increased risk could be used to trigger just-in-time interventions that connect individuals with their mental health care team when they need support most and before their symptoms worsen [75]. Similarly, ongoing computational psychiatry work aims to improve mental health treatment by using machine learning to identify the precise cognitive and neurobiological mechanisms underlying psychiatric disorders and their symptoms [76]. These findings may then be used to gain a better understanding of which treatments work best for which patients at what time.

Whereas much of this existing work focuses on predicting and treating mental health symptoms in individuals who meet certain diagnostic criteria or have received treatment for a psychiatric diagnosis, we are proposing a data set that is designed to advance the field's ability to identify community-dwelling members of the adult general population at risk for a future mental health event. This is a complementary approach to current computational psychiatry and digital phenotyping research and has the potential to improve mental health risk assessment within the general population. The proposed data set possesses several strengths that make it well suited for this goal. First, in response to numerous calls for more theory-driven digital phenotyping studies [20], both the sample we are recruiting and the data we are collecting are guided by a well-established, transdiagnostic model of psychopathology development—the diathesis-stress model [49]. Second, instead of focusing on stable individual differences or 1-time measures of risk, the proposed data set will include multimodal data collected across multiple time scales and levels of analysis. By including digital traces of behavior that can be linked to both time and context, the proposed data set will therefore allow for the identification of features that better capture the dynamic nature of mental health risk [36,37]. Third, by using the Beiwe platform to collect raw PDD data, future analyses will not be limited by inconsistencies in the algorithms used to derive summary statistics or features from different devices [22]. Similarly, including raw PDD data in this data set means that not only is it designed to support current computational techniques, but it will continue to be relevant for future quantitative developments. Finally, the shareable nature of this data set will encourage interdisciplinary collaboration and ideally maximize the rate, rigor, and accuracy of the predictive machine learning models that are developed from it.

Limitations

Although the proposed data set possesses many strengths, there are also some limitations to acknowledge. First, the types of digital data included in this data set are limited to what is available through the Beiwe platform [52]. Although it is possible that other passive data streams (eg, app usage log) may carry digital traces of participants' behaviors that are informative for mental health prediction, our decision to use only what is available from Beiwe was guided by the desire to prioritize participant privacy and the shareability of the data set, which are 2 features supported by the design and maintenance of Beiwe. Second, some of the data sources captured by Beiwe are not consistent across Apple and Android devices due to variability in the sensors installed on different devices and the policies of different smartphone manufacturers (eg, call and SMS text message logs are only available on Android devices [52]). This may limit some of the analyses that can be performed and features that can be developed if certain data sources are only available from a small subset of the total sample. Third, our decision to exclude participants with suicidal thoughts and behaviors or other persistent and severe mental health conditions (ie, active mania or psychosis) means that the predictive models arising from this data set will not be optimized for identifying an increase in risk for the mental health events associated with these conditions (eg, inpatient hospitalization). However, such events are less likely in the general population and are not the primary outcome of interest for the proposed data set.

Conclusions

Computational psychiatry and digital phenotyping have been lauded as pillars of the next great revolution in mental health care [7,8,39]. The past 2 decades have seen a dramatic increase in the number of mental health studies using these methodologies with PDD data. Furthermore, rapid developments in digital technology and quantitative analysis suggest that the potential benefits of PDD data and computational techniques for mental health research and treatment development are only going to continue to expand. In order to achieve these benefits, it will be important for the field to move away from siloed research laboratories collecting proprietary data and toward interdisciplinary collaborations that use clinical, technical, and quantitative expertise to produce widely applicable and shareable data sets.

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REK conceptualized and designed the study, led data collection, and drafted the manuscript. AB, OE, and EB assisted with data collection and provided feedback and edits for the manuscript. FRL provided clinical oversight for the study and feedback and edits for the manuscript. BRWB conceptualized and designed the study and provided feedback and edits on the manuscript.

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Data Availability

Upon completion of this study, the data sets generated and analyzed during this study will be available in a widely accessible data repository.

Conflicts of Interest

None declared.

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Abbreviations

BSI-18: Brief Symptom Inventory-18
DASS-21: Depression, Anxiety, and Stress Scale-21
DERS: Difficulties with Emotion Regulation Scale
HIPAA: Health Insurance Portability and Accountability Act
IMHC: Intermountain Health Care
LFQ: Life Functioning Questionnaire
PDD: personal digital device
PSS-4: Perceived Stress Scale-4
TAPS: Tobacco, Alcohol, Prescription medications, and Other Substance
UHealth: University of Utah Health
UPDB: Utah Population Database

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Protocol

A Global Health Survey of People Who Vape but Never Smoked: Protocol for the VERITAS (Vaping Effects: Real-World International Surveillance) Study

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Abstract

Background: There is only limited information about the health effects of regular vaping. Research on the health status of people who used to smoke faces the challenge that previous smoking may have caused unknown health effects. Only studies of people who vape but have never smoked combustible cigarettes can enable the detection of harms attributable to vaping. Large prospective studies of well-characterized electronic cigarette users with and without a history of combustible cigarette smoking are warranted to establish the long-term effects of regular vaping on respiratory health.

Objective: We will conduct a global cross-sectional survey of individuals from 6 world regions. Respiratory symptoms will be assessed using a validated questionnaire—the Respiratory Symptom Experience Scale (RSES). Current vapers who are nonusers of other tobacco or nicotine products will be compared with matched controls who are nonusers of vapes and other tobacco or nicotine products.

Methods: This will be a multicountry, cross-sectional internet-based survey of 750 adults aged ≥18 years who satisfy the criteria for inclusion in either a cohort of people who exclusively vape and who are nonusers of other tobacco or nicotine products (“vapers cohort”; target N=500) or a cohort of nonvapers who are also nonusers of other tobacco or nicotine products (“controls cohort”; target N=250). The primary end point of the study is the RSES score. RSES scores of people in the “vapers cohort” will be compared with those of people in the “controls cohort.” Additionally, the study will collect data to characterize patterns of vaping product use among the vapers cohort. Data collection will include information about the age initiation of using vape products,

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reasons for starting and continuing the use of vape products, specific types of products used, flavors and nicotine strengths of recently used products, as well as the frequency and intensity of product use in the past 30 days.

Results: Participant recruitment started in April 2023, and enrollment was completed by November 2023 with 748 participants. Results will be reported in 2024.

Conclusions: This will be the first study providing key insights into respiratory health effects associated with using electronic cigarettes in people who vape with no established use of combustible cigarettes or other tobacco or nicotine products.

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KEYWORDS

electronic cigarette; health effects; respiratory symptoms; survey; real-world use study; e-cigarette; e-cigarettes; smoke; smoker; smokers; smoking; vape; vaping; respiratory; pulmonary; cross-sectional; questionnaire; questionnaires; survey; surveys

Introduction

Electronic cigarettes (ECs) are battery-powered electronic devices that vaporize a water-soluble nicotine solution for inhalation. They do not create smoke or use combustion to operate. These consumer products have been rapidly gaining ground on combustible cigarettes (CCs) among smokers because of their potential for harm reduction from cigarette smoke and smoking cessation [1-3], their competitive price [4,5], and because of allowing people who smoke to continue having a "smoking experience without smoking" [6-8].

Considerable controversy persists surrounding the use of these products, particularly concerning potential misuse by nonsmoking youths and their potential negative impact on respiratory health [9-11]. Many studies examining nicotine vaping face challenges in data analysis due to participants having a history of CC smoking. This history might contribute to some of the adverse effects reported in prior studies, as highlighted in recent papers [12-14].

Under normal operational conditions (without overheating or dry burning coils), ECs present a significant reduction in exposure to harmful constituents compared to CCs [15-17]. No discernible negative health effects solely attributed to EC use (commonly known as "vaping") have been conclusively established [18-20]. Analytical chemistry and toxicology studies of vaporized chemicals suggest no imminent health risks, although concerns persist about potential long-term respiratory implications [21-23]. Hence, further investigation into the prolonged health impact of persistent vaping is warranted.

The respiratory system is the most likely site for any potentially harmful effects of constituents in EC aerosol emissions. Only a few clinical studies have investigated the impact of regular vaping. No deterioration in lung function, airway responses, and respiratory symptoms were observed in a 1-year prospective randomized controlled trial of "healthy" people who smoked and were invited to quit or reduce their cigarette consumption by switching to ECs [24,25]. Specifically, FEF25-75% (a sensitive measure of obstruction in the more peripheral airways) [24], nitric oxide (a noninvasive biomarker of airway inflammation in airway disease as well as in studies of environmental and occupational exposure) [25], and carbon monoxide (an exposure unique to smoking, among tobacco product uses, causing airway inflammation and cardiovascular disease) in the exhaled breath returned to normal limits [25]. Similar results were observed for those who continued to use ECs versus those who quit using them. In addition, restoration of lung defense has been shown in smokers who had switched to exclusive use of ECs; they exhibited mucociliary clearance efficiency similar to that of a never-smoker and a former smoker [26]. Overall, these preliminary studies do not appear to suggest negative respiratory health outcomes in people who smoke and have switched to ECs.

Researching individuals who switch from CC smoking to ECs and then quit presents challenges in understanding their health outcomes. Studying the health of former smokers is complicated due to unknown health effects caused by previous smoking. Precise information about their smoking history—duration, quantity, and puffing behavior—alongside a large sample size is necessary to accurately control for these effects. Recent work by Sargent et al [13] underscores the importance of appropriately accounting for smoking history. They used data from the PATH (Population Assessment of Tobacco and Health) study and, by adjusting for the cumulative amount of CCs smoked (pack-years), demonstrated how using more refined analytical approaches revealed a previously significant association as nonsignificant. This highlights the substantial residual confounding present when using basic binary measures instead of more comprehensive assessments.

Therefore, only studies of people who vape but have never smoked CCs or have only a limited smoking history (ie, those who have smoked fewer than 100 CCs in their lifetime) can enable the detection of harms attributable to EC use. Without studies of people who use ECs with no established smoking history, it will be impossible to distinguish the harms of vaping from neither vaping nor smoking. Concluding that vaping poses less risk than smoking is easy [11,15-20,27-29]. Quantifying the absolute health risks of vaping independent of smoking requires cleaner data.

In a small study of daily EC users who had never smoked, no noticeable changes in blood pressure, heart rate, lung function, respiratory symptoms, exhaled breath nitric oxide, exhaled carbon monoxide, and high-resolution computed tomography of the lungs from baseline were observed over an average 3.5-year observation period [30]. Daily exposure to EC aerosol emissions caused no significant changes in any of the health outcomes investigated, including measures of lung function and

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lung inflammation. Moreover, no significant structural abnormalities were identified in the high-resolution computed tomography of the lungs, and no respiratory symptoms were consistently reported. Some of the strengths of this study included prospective rather than retrospective data collection from study participants; the detailed vaping history and precise characterization of the study participants; as well as the use of a panel of different clinical, functional, and inflammatory measures during the study.

Large prospective studies of well-characterized EC users with and without a history of CC smoking are warranted to establish the long-term effects of regular vaping on respiratory health. We will conduct a global cross-sectional survey of individuals from 6 world regions. Respiratory symptoms reported by a cohort of individuals who vape with no established history of CC smoking or other tobacco or nicotine product use will be compared against those reported by a cohort of matched controls with no established history of vaping, smoking, or use of any other tobacco products.

The primary aim of this study is to test the hypothesis that chronic exposure to EC aerosols does not cause an increase in respiratory symptoms among people who vape with no established cigarette smoking or other tobacco and nicotine product use history. The secondary aims are to determine the feasibility of assembling a large cohort of individuals who vape with no other established tobacco or nicotine product use history to evaluate such effects for future studies and to characterize patterns of vaping product use behavior among this unique cohort.

Methods

An overview of the study is illustrated in Figure 1.

Figure 1. Study design. The infographic illustrates the different stages of the study.

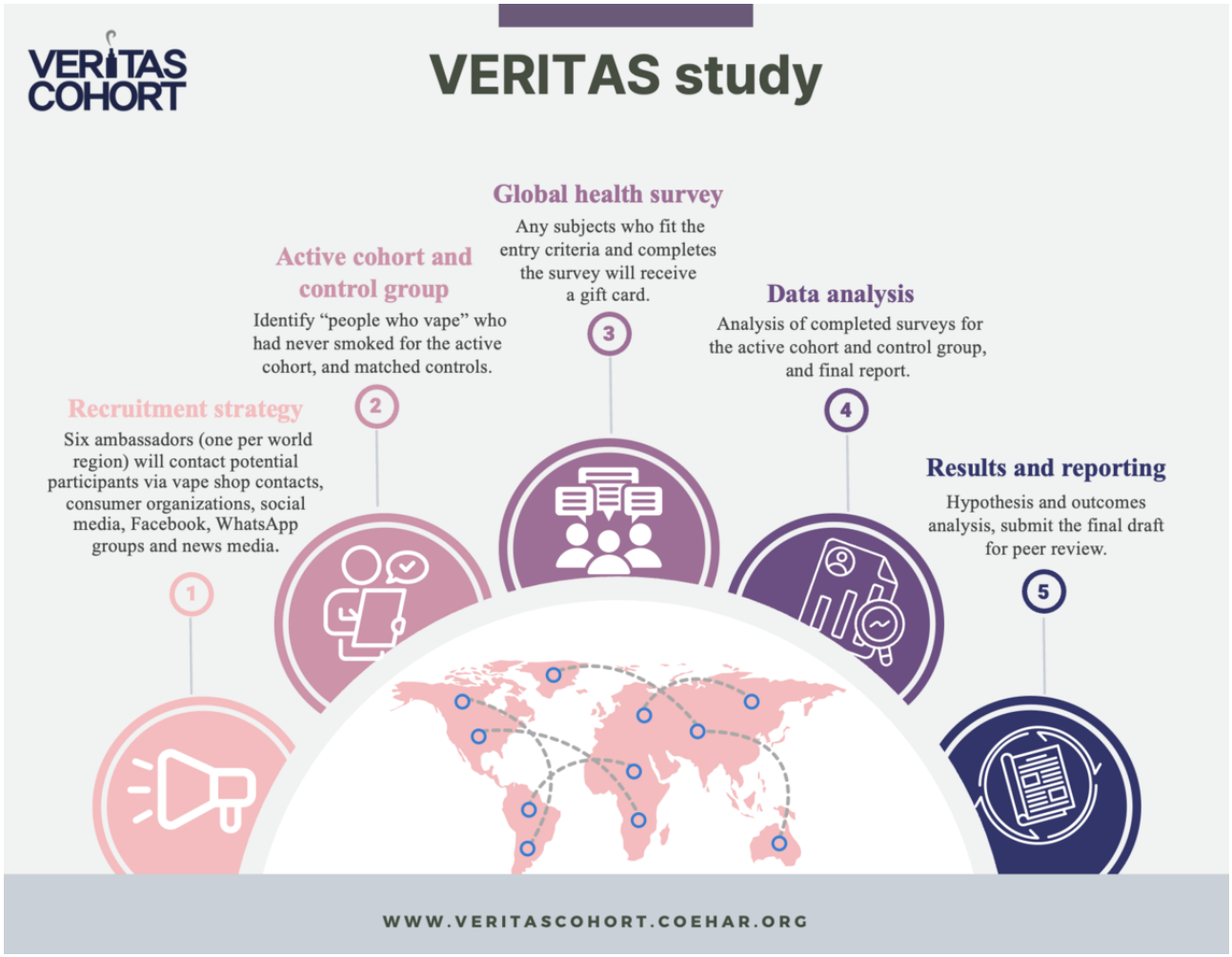

Study Design

This will be a multicountry, cross-sectional, internet-based survey study. Individuals expressing an interest in participating in the study will be directed toward a website [31] with further information and will be screened using a brief questionnaire to assess their eligibility (Multimedia Appendix 1). All screening information gathered for contacts who are not potential recruits (ie, screen failures) will be discarded. Before conducting the survey, potential participants will be rescreened via telephone or email to confirm eligibility, to make sure they have an adequate understanding of the study, and to determine what language is required for the survey. Participants in the cohort will then be subjected to a web-based or mobile-based survey [32] using standard secure web-based survey tools, with central data collection. After completing the survey, participants will receive an email explaining how to redeem an Amazon or

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Take-A-Lot gift card code for an equivalent value of US $30, as appreciation for participating in the study.

Ethics Approval

The study protocol has been reviewed and approved by the Ethic Review Board of Dipartimento di Scienze della Formazione Sezione di Psicologia at the University of Catania on November 25, 2020 (Ref 104/20).

Population

This study plans to recruit approximately 750 individuals globally, who satisfy the criteria for inclusion in either a cohort of "people who vape and who are nonusers of other tobacco or nicotine products" ("vapers cohort"; target N=500) or a cohort of "nonvapers who are also nonusers of other tobacco or nicotine products ("controls cohort"; target N=250), as defined in the following sections.

Recruitment

Carefully selected recruiters, the VERITAS (Vaping Effects: Real-World International Surveillance) ambassadors (AB, JJCL, AM, KY, and MS), will make sure to identify and screen individuals for the VERITAS Cohort Study. The VERITAS ambassadors will pursue recruitment through social media channels, WhatsApp groups, Google email groups, posters in vape shops and universities, recommendations from other participants, and recommendations from local vape shop owners in each of the 6 geopolitical world regions (ie, Africa and Middle East, North America, Latin and South America, Asia-Pacific, Western Europe, and Eastern Europe). Ambassadors will instruct vape shop owners to ask their regular clients about their smoking history and EC use patterns to identify potential participants. The reference or control group will comprise adults who never used any tobacco or nicotine products. Control group participants will be recruited primarily among vaping individuals' circles of friends and acquaintances. They will be matched for age and sex to the extent possible. In the event of shortfalls from this recruiting pathway, the Veritas Ambassadors will recruit further controls.

VERITAS ambassadors will be acting as the main point of contact for study participants and will be coordinated by a project leader (JZG). A document detailing the ambassadors' roles can be found on the VERITAS Cohort website [33].

Eligibility Criteria

Eligibility to participate in this study will be assessed by a self-complete screener questionnaire administered immediately after participants provide informed consent to participate.

Inclusion Criteria

Eligibility for participation in the study is determined by the following criteria. All individuals who wish to participate must be aged ≥18 years and provide informed consent to participate in the study.

The vapers cohort should meet the following inclusion criteria:

1. Use at least 1 of 3 types of EC or vape—disposables, rechargeable with replaceable prefilled pods or cartridges, or rechargeable and refillable with e-liquid.
2. Have never smoked a CC *or* have smoked a CC *but* have not smoked more than 100 CCs in their lifetime [34] *and* have not smoked a CC in the past 3 months.
3. Has never used, *or* has never used more than once a week, any of 9 other tobacco or nicotine products listed below:
   - Traditional cigars
   - Cigarillos or filtered cigars
   - Smoked tobacco in a hookah
   - Smoked tobacco in a pipe
   - Smokeless tobacco (including dip, spit, moist snuff, pouches, and chewing tobacco)
   - Snus pouches
   - Dissolvable tobacco
   - Heated tobacco products (eg, iQOS, Glo, and Pulze)
   - Tobacco-free nicotine pouches

The controls cohort should meet the following inclusion criteria:

1. Have never used, or have never used more than once a week, any of the 3 types of EC or vaping products listed above.
2. Same as the vapers cohort's inclusion criterion 2.
3. Same as the vapers cohort's inclusion criterion 3.

Exclusion Criteria

Individuals who do not satisfy the criteria for inclusion in either the vapers cohort or the controls cohort will be excluded.

Study Procedures

All study procedures, from recruitment and obtaining consent to eligibility checks, questionnaires, data collection, and participant compensation, will be carried out exclusively online. The VERITAS web-based survey software (custom-based) will serve as the primary platform for data collection and displaying the Informed Consent Form. This software is intended not only to optimize the presentation of materials for study participants but also to facilitate data submission across various devices, such as laptops, smartphones, and tablets, while being compatible with all web browsers, including Chrome, Safari, Firefox, and Internet Explorer. By adopting this approach, study participants will have the freedom to engage in the research at their convenience, within the privacy of their choosing, and using their preferred device. As a result, participants will be empowered to take part in the study on their terms, in a comfortable setting, and at a time that suits them best.

Web-Based Survey Questionnaires

After prescreening by the ambassadors, eligible individuals who consent to participate will be directed to the study website [32], where they will be subject to a 2-step verification process. When participants reach the survey platform, they will click "Don't have an account? Register"; participants will register their email addresses. Following registration, participants will receive a "Welcome email" and a link to re-enter the survey platform, where they will be asked for their phone number to receive a confirmation code via SMS. After confirming their email addresses, they will start filling out the survey, which will consist of sociodemographic data, medical history, as well as tobacco and nicotine product use behavior. Details about the VERITAS survey document can be shared upon specific request

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to the corresponding author. The information collected via the web-based questionnaire will help to characterize or describe the unique cohort. Individuals will then be included in the vapers cohort or the controls cohort or they will be excluded based on their responses to questions about their past and current use of cigarettes, EC or vapes, and other tobacco and nicotine-containing products.

Individuals in the vapers cohort will then be asked questions about their historical and current patterns of use of 3 types of vaping products (ie, disposable vaping products, rechargeable prefilled pod vaping products, and rechargeable refillable vaping products). For each vaping product category, data will be collected on 12 outcomes, as applicable: (1) age of first use; (2) age of initiation, when started to vape more than once a week; (3) the number of product units used in their lifetime; (4) the number of product use days in the past 30 days; (5) length of time (eg, years or months) of vaping more than once a week; (6) nicotine content of products used; (7) flavor categories vaped more than once a week; (8) number of flavors vaped more than once a week; (9) name of favorite flavor used in the past 30 days; (10) number of product units used in the past 30 days; (11) reasons for initiating product use (free-text response); and (12) reasons for current product use (free-text response). The VERITAS survey document can be shared upon specific request to the corresponding author.

All participants will then complete the Respiratory Symptom Experience Scale (RSES), a validated scale that asks participants to rate the frequency with which they experienced 5 respiratory symptoms in the past 30 days [35]. The 5 symptoms rated are as follows: (1) morning cough with phlegm or mucous, (2) coughing frequently throughout the day, (3) shortness of breath that makes it difficult to do normal daily activities, (4) becoming easily winded during normal daily activities, and (5) wheezing or whistling in the chest at times when not exercising or doing other physically strenuous daily activities. Rating for each symptom is made on a 5-point scale, where 1=Never (0 out of the last 30 days); 2=Rarely (1-5 days); 3=Occasionally (6-15 days); 4=Most days (16-29 days); 5=Every day (all 30 out of the last 30 days). A mean RSES score will be calculated by averaging the 5-item scores. The RSES can be found in the Multimedia Appendix 1.

Lastly, questions will assess participants' sex, country of residence, employment status, highest educational attainment, height, and weight.

If necessary, surveys will be translated into the local language by the ambassador for countries where not all participants are fluent in English. Data will be collected on whether the participant completed the survey in English, Spanish (translation available on the platform), or their local language (in case it is determined that some questions of interest had some important difference in nuance when translated).

Study End Points

The primary end point of the study is the RSES score [35]. The objective of the study is to compare the RSES scores between people who vape with no established CC smoking history (ie, the "vapers cohort") and people who have never vaped nor smoked (ie, the "controls cohort").

Additionally, the study will collect data to carefully characterize people who vape with no established CC smoking history in the "vapers cohort." Data collection will include information about the age of initiation of using vaping products, reasons for starting and continuing use of vaping products, specific types of products used, flavors and nicotine strengths of recently used vaping products, as well as the frequency and intensity of product use in the past 30 days.

Statistical Analyses and Reporting

The primary objective of the study is to retrospectively estimate the effect of current, regular use of vaping products on respiratory symptom experience in the past 30 days, measured in this study by the mean score (0 to 5) on the 5-item RSES [35]. Details of sample size calculation and power analysis to detect differences in respiratory symptoms (ie, the RSES scores) between the "vapers cohort" and the "controls cohort" are included in Multimedia Appendix 1. In brief, with 75 participants per group, a study should be adequately powered to detect a difference of 0.57, the proposed minimal important difference, with a power of 98%. However, to detect a more conservative difference of 0.40, a study with 75 individuals per group would still have a power of 89%. The target study population will consist of approximately 500 exposed individuals and 250 matched controls–approximately 83 people who vape per each of the 6 world regions. If the initial recruitment falls short of the goal, or in the case of substantial early loss to follow-up, rolling enrollment will be considered to make up the deficit.

Data analysis of the RSES scores will be both descriptive and inferential in nature. The RSES scores and the demographic characteristics of the vapers cohort and the controls cohort will be descriptively summarized. We will test the null hypothesis that the RSES scores will not significantly differ between the vapers cohort and the controls cohort when adjusted for demographic differences. This hypothesis will be tested through a one-way between-subjects Analysis of Covariance in which the mean RSES score will be entered as the dependent variable, "Cohort" will be entered as the between-subjects independent variable, and 4 demographic variables—age, sex, education, and employment status—will be entered as covariates. Inferential and descriptive statistics will be reported for the Cohort variable adjusted for the effects of the covariates. *P* values <.05 will be considered statistically significant.

The secondary objective of this study is to characterize the use of different vaping products by the vapers cohort. Data analysis of this objective will be purely descriptive in nature. Descriptive summary statistics will be reported for all questionnaire measures of vapers' use of vaping products within each of the 3 product categories—disposable vapes, rechargeable prefilled pod vapes, and rechargeable refillable vapes. Data on the following variables will be descriptively summarized for the subsets of participants within the vapers cohort who are current users of each product category, as follows: number of current users, age of first use, age of first regular use, number of products used in a lifetime, number of product use days in the

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past 30 days, time of regular product use, the nicotine concentration of products used typically, type of e-liquid flavors used in the past 30 days, number of e-liquid flavors used regularly in the past 30 days, and number of products used in the past 30 days.

Descriptive summary statistics for continuous variables will include the number of participants in the population of interest (N), the number of participants in the population of interest with nonmissing data on the variable or measure (n), as well as appropriate measures of central tendency (eg, mean and median) and dispersion (eg, SD, SE, range, and IQR) for the observed data. Descriptive statistics reported for categorical variables or measures will include the total number of participants in each subject group who provided nonmissing responses, the proportion of each subject group who selected each categorical response option, and when appropriate, 95% CIs around the proportion of participants who selected each categorical response option.

Additional data analyses may be conducted where data on variables or measures are filtered or stratified by other independent variables of interest. If undertaken, the reporting of descriptive summary statistics for each variable or measure filtered and stratified by additional independent variables of interest will closely resemble the reporting of the planned analyses described above. All data analyses will be conducted using the IBM SPSS (version 27 or higher; IBM Corp) statistical software. Data tables not presented in primary reports or in the manuscript will be presented in supplementary files.

Results

Participant recruitment started in April 2023, and enrollment was completed by November 2023 with 748 participants. Results will be reported in 2024.

Discussion

Research into the respiratory health effects of regular vaping is limited [11,36,37]. Previous research investigating the health status of individuals who used to smoke faces challenges due to unknown health effects caused by prior smoking. Consequently, studies involving individuals who solely vape with no established smoking history are essential to identify potential harms attributed to vaping. A small prospective study of daily EC users who never smoked CCs demonstrated no significant alterations in lung function, inflammation, or structural abnormalities observed in lung scans [30]. Moreover, consistent respiratory symptoms were not reported in this study [30]. However, large longitudinal studies focusing on well-characterized EC users, with and without a history of CC smoking, are necessary to establish the long-term effects of regular vaping on respiratory health.

This proposed study aims to be the first investigation exploring the association between respiratory health effects and the use of ECs in a large group of individuals who exclusively vape, with no established CC smoking history. Additionally, the research will delve into potential confounding factors that could influence any association identified between vaping and respiratory symptoms.

Several noteworthy features distinguish this study. First, by enlisting participants globally, it intends to capture diverse experiences and behaviors related to EC use across different countries and regions. Second, the study's focus on respiratory symptoms and in-depth characterization of vaping product use in a real-world context enhances its generalizability. Third, the study sample has been adequately powered to detect minimum clinically important differences in respiratory symptoms between exclusive vapers and those who neither vape nor smoke. Finally, the study implements a stringent 2-step verification process to deter potential abuse by unauthorized users attempting to exploit the possibility of receiving a gift card and uses manual analysis to identify and verify legitimate participants.

Although this study promises important insights into respiratory symptoms and vaping behaviors among a culturally diverse group of adults who exclusively vape, it should be considered within the context of several limitations. First, its cross-sectional design limits the ability to draw conclusions about the causal relationship between vaping and respiratory symptoms. Longitudinal studies will be crucial to discern the prospective effects of vaping behavior on respiratory health. Second, the study's reliance on nonprobability sampling methods may introduce a self-selection bias, impacting the generalizability of the findings to the broader population of exclusive vapers. However, given the rarity of this population subgroup, these methods were deemed the most practical approach to gathering a sufficient sample. Third, relying on a single respiratory health assessment (ie, RSES) based on self-report might introduce biases and inaccuracies. Participants might hesitate to disclose certain information or be influenced by social desirability bias, potentially affecting the data quality. Lastly, variations in survey interpretation due to linguistic, cultural, or regulatory differences across countries could lead to diverse responses, impacting the consistency and accuracy of the data collected for the research question.

The results obtained from the VERITAS study may offer crucial insights into the impact of vaping on health outcomes, providing a foundation for implementing essential public health measures. These findings can be effectively used within public health sectors and policies to address health concerns related to vaping, establishing necessary preventive measures to safeguard vulnerable populations. Moreover, the study methodology stands as a valuable reference for forthcoming research. Building such unique cohorts could serve as a pivotal resource for future studies, enabling the thorough examination of safety concerns and the quantification of potential risks or harm associated with vaping.

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Acknowledgments

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The contents, selection, and presentation of facts, as well as any opinions expressed herein, are the sole responsibility of the authors and under no circumstances shall be regarded as reflecting the positions of the funders.

Conflicts of Interest

JZG is the President of the Asociación de Usuarios de Vaporizadores y Métodos de Reducción de Daños por Tabaquismo de Costa Rica (ASOVAPE Costa Rica), a consumer organization in favor of harm reduction; president of Asociación de Reducción de Daños del Tabaquismo Iberoamérica (ARDT Iberoamérica), an alliance of consumer organizations in Latin America, Spain, and Portugal in favor of harm reduction; director of social media and audiovisual producer of the International Network of Nicotine Consumer Organisations (INNCO), a global coalition of consumer organizations in favor of harm reduction; and a recipient of a scholarship from Knowledge-Action-Change.
TP serves as the director for Confidosoft Ltd, a company specializing in creating tailored software and crafting sophisticated solutions for various research projects. In addition to offering application development services, the company has secured funding for software development and maintains a collaboration agreement with ECLAT Srl.
CS is the owner of Seo Ergo Web, a company that specializes in web design, web security, and digital system administration.
CR acts as codirector of Russell Burnett Research and Consultancy Ltd, which has received research funding or consultancy fees from Cheerain HK Ltd, McKinney Regulatory Science Advisors LLC, Los Angeles Clinical Trials LLC, Health Diplomats, Centre for Substance Use Research Ltd, whatIF? Consulting Ltd, British American Tobacco, Rogue Holdings LLC, Japan Tobacco International, NJOY LLC, SkyX Group Inc, and ECLAT Srl to conduct or consult on perception and behavioral research of noncombustible tobacco and nicotine products.
JJCL is the president of Mexico y el Mundo Vapeando ONG, recipient of a scholarship from Knowledge-Action-Change (a program funded with an unrestricted grant from the Foundation for a Smoke-Free World, Inc. (FSFW), a US nonprofit 501 (c) (3) private foundation).
MS is the cofounder of the Smoke Free Baltic and Smoke Free Latvia non-profit organizations, recipient of a scholarship from Knowledge Action Centre (a program funded with an unrestricted grant from the Foundation for a Smoke-Free World, Inc. (FSFW), a US nonprofit 501 (c) (3) private foundation).
RP is a full-tenured professor of Internal Medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from U-BIOPRED and AIR-PROM; Integral Rheumatology & Immunology Specialists Network (IRIS); Foundation for a Smoke-Free World; Pfizer; GlaxoSmithKline; CV Therapeutics; NeuroSearch A/S; Sandoz, Merk Sharp & Dohme; Boehringer Ingelheim; Novartis; Arbi Group Srl; Duska Therapeutics; Forest Laboratories; Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU); and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell Universita' e della Ricerca (MUR)—PNRR EU Community. He is the founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbook royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO), and he is chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).
KY is the cofounder of the Consumer Advocacy movement Vaping Saved My Life, a consultant for the Vapour Products Association of South Africa, a member of the Advisory Board for the World Vapers Alliance, and a recipient of the Tobacco Harm Reduction Scholarship Programme from Knowledge Action Change. Knowledge Action Change receives funding from the Foundation for a Smoke-Free World.
Other authors declare no conflicts of interest.

Multimedia Appendix 1
Cohort study questionnaire.
[DOCX File , 237 KB - resprot_v13i1e54236_app1.docx]

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Abbreviations

CC: combustible cigarette
EC: electronic cigarette
PATH: Population Assessment of Tobacco and Health
RSES: Respiratory Symptom Experience Scale
VERITAS: Vaping Effects: Real-World International Surveillance

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Protocol

Design of a Remote Multiparametric Tool to Assess Mental Well-Being and Distress in Young People (mHealth Methods in Mental Health Research Project): Protocol for an Observational Study

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Abstract

Background: Mental health conditions have become a substantial cause of disability worldwide, resulting in economic burden and strain on the public health system. Incorporating cognitive and physiological biomarkers using noninvasive sensors combined with self-reported questionnaires can provide a more accurate characterization of the individual's well-being. Biomarkers such as heart rate variability or those extracted from the electrodermal activity signal are commonly considered as indices of autonomic nervous system functioning, providing objective indicators of stress response. A model combining a set of these biomarkers can constitute a comprehensive tool to remotely assess mental well-being and distress.

Objective: This study aims to design and validate a remote multiparametric tool, including physiological and cognitive variables, to objectively assess mental well-being and distress.

Methods: This ongoing observational study pursues to enroll 60 young participants (aged 18-34 years) in 3 groups, including participants with high mental well-being, participants with mild to moderate psychological distress, and participants diagnosed with depression or anxiety disorder. The inclusion and exclusion criteria are being evaluated through a web-based questionnaire, and for those with a mental health condition, the criteria are identified by psychologists. The assessment consists of collecting mental health self-reported measures and physiological data during a baseline state, the Stroop Color and Word Test as a stress-inducing stage, and a final recovery period. Several variables related to heart rate variability, pulse arrival time, breathing, electrodermal activity, and peripheral temperature are collected using medical and wearable devices. A second assessment is

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carried out after 1 month. The assessment tool will be developed using self-reported questionnaires assessing well-being (short version of Warwick-Edinburgh Mental Well-being Scale), anxiety (Generalized Anxiety Disorder-7), and depression (Patient Health Questionnaire-9) as the reference. We will perform correlation and principal component analysis to reduce the number of variables, followed by the calculation of multiple regression models. Test-retest reliability, known-group validity, and predictive validity will be assessed.

Results: Participant recruitment is being carried out on a university campus and in mental health services. Recruitment commenced in October 2022 and is expected to be completed by June 2024. As of July 2023, we have recruited 41 participants. Most participants correspond to the group with mild to moderate psychological distress (n=20, 49%), followed by the high mental well-being group (n=13, 32%) and those diagnosed with a mental health condition (n=8, 20%). Data preprocessing is currently ongoing, and publication of the first results is expected by September 2024.

Conclusions: This study will establish an initial framework for a comprehensive mental health assessment tool, taking measurements from sophisticated devices, with the goal of progressing toward a remotely accessible and objectively measured approach that maintains an acceptable level of accuracy in clinical practice and epidemiological studies.

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KEYWORDS

mental health; mental well-being; mobile health; mHealth; remote monitoring; physiological variables; experimental protocol; depression; anxiety

Introduction

Background

Mental health conditions are one of the leading causes of disability worldwide and are estimated to reduce life expectancy by 10 years [1]. For instance, depressive disorders were considered the eighth cause of disability in Spain in 2000, rising to fifth in 2019 [2]. Depression, anxiety, and stress-related disorders impose a major economic impact and burden on the public health system. To date, the prevalence of depression in the Spanish population is close to 5%, and the annual cost is estimated at €6145 (US $6648) million [3].

Young people and university students are populations of particular interest. Approximately 75% of mental health conditions have an early onset before the age of 24 years, and several risk factors (including genetic, early life adversity, family, community, and environmental factors) are involved in the development and course of these conditions [4]. Moreover, the recent COVID-19 pandemic has aggravated this situation [5]. Several systematic reviews and meta-analyses have indicated a high prevalence of mental health conditions among young people, with a pooled prevalence for depression of 31% to 33.6%, anxiety of 28% to 39%, sleep problems of 40%, and suicidal ideation of 12.3% [6-8], in line with the results of longitudinal studies suggesting a possible worsening of mental health in this population in recent years [9]. There is a need for early identification and prevention of mental health conditions, which includes the design and implementation of mental health promotion activities that lead to an increase in emotional well-being [10].

In recent decades, interest in mental health research has been steadily increasing, recognizing it a crucial aspect of overall health, rather than simply the absence of related conditions [11]. According to the World Health Organization [12], mental health is characterized by individuals' ability to effectively manage typical stressful situations, develop their potential and skills, and contribute productively to both themselves and the community. This comprises an adequate stress response and recovery as well as maintaining cognitive abilities such as attentional level and proper time of response. Stress reactivity is this capacity to respond to a stressor. It is a disposition that underlies individual differences in response to stressors and is assumed to be a vulnerability factor for the development of mental health conditions [13]. In this context, monitoring physiological response during a stress-inducing task could yield different reactivity patterns, offering valuable insights to differentiate between mental well-being and distress.

In clinical practice, self-reported questionnaires are commonly used to assess the severity of mental health symptoms, quality of life, and mental well-being. Nevertheless, several studies have reported limitations of these tests related to memory biases and distortions in retrospective recall [14,15]. To expand such assessments, including physiological biomarkers information will improve the characterization of endophenotypes (research domain criteria) [16]. Owing to technological advances, small sensors can measure physiological data for behavioral health, interventions, and outcomes (digital phenotyping) [17,18]. Given the significance of stress reactions as complex phenomena encompassing psychological, cognitive, and physiological reactions involving the autonomic nervous system (ANS) and the neuroendocrine system, which, in turn, can affect other bodily systems, exploring these dynamics could enhance our comprehension of mental distress. Hence, physiological data monitoring including a stress-eliciting task may have an important role in early detection and intervention in mental health care. Heart rate variability (HRV), pulse arrival time (PAT), breathing parameters, electrodermal activity (EDA), and skin temperature (ST) are physiological variables broadly used to study the stress response and gather information about ANS functioning [19-24].

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To progress in this field, the use of wearables in mental health research shows promise, offering increased accuracy in data collection and reduced participant burden. Wearable devices allow researchers to passively monitor individuals in real time and gather data outside of traditional laboratory settings, that is, along with everyday life situations, providing a more holistic understanding of mental health status [25,26]. Currently, many studies on stress detection are conducted in controlled environments because accuracy decreases when conducted in real-time environments [27]. In addition, different instruments to measure perceived stress are used, which hinders the comparability of results [28], or a small number of signals are usually collected [29-31]. However, previous studies have shown optimistic results for further advancement in the field for the objective assessment of mental health status and stress. A study analyzing data from 510 participants wearing a Fitbit device during a 2-year follow-up [32] showed a correlation between decreased resting heart rate variation during the day and the severity of depression, whereas the mean heart rate at night was higher in participants with more severe depressive symptoms. In line with these results, a decreased autonomic reactivity measured through dynamic changes in photoplethysmography (PPG) waveform morphology was associated with a higher degree of depression in the study by Kontaxis et al [33]. Sano et al [30] conducted an observational study among university students using wearable sensors that collected EDA and ST, and using psychometric questionnaires as reference, they found an accuracy of 78% and 87% to classify into high or low stress groups and high or low mental health groups, respectively. Similarly, Sano et al [34] found an accuracy of 90% in classifying stress and mental health groups. From a literature review [27], it was observed that heart rate and EDA are the most regularly used sensory signals, offering the most promising results and high accuracy for detecting stress.

Effective prevention interventions require strategies to identify early risk groups according to risk factors through the development of predictive models. In addition, from a mental health promotion perspective, effectively assessing mental well-being would help identify the right time to intervene, evaluate the efficacy of the therapy applied, empower the citizens, offer stress-reducing programs, and prevent negative consequences. Here, we present the development and evaluation of a novel multiparametric tool to improve mental health assessments and to facilitate the evaluation of risk and protective factors as well as the effectiveness of promotion and prevention interventions.

Objectives

This study aims to design and validate a remote multiparametric tool, including several physiological and cognitive variables, to objectively assess mental well-being as well as mental distress (ie, symptoms of depression and anxiety) among young people for epidemiologic and clinical studies.

The specific objectives of this study are (1) to develop an assessment tool for mental well-being and distress based on the most relevant physiological and cognitive variables; (2) to validate the assessment tool using self-reported measures and evaluate the tool reliability and accuracy; and (3) to develop and establish a protocol to automate the measurement process, ensuring that it can be reproduced in large populations.

Methods

Study Design and Setting

This is a multicenter observational study of the mHealth Methods in Mental Health Research (M&M) project, currently ongoing, being conducted by the Autonomous University of Barcelona (UAB) and Parc de Salut Mar (PSMAR).

Three different mental health states will be studied: (1) high mental well-being, (2) presenting mild to moderate psychological distress, and (3) depressive or anxiety disorder (diagnosed by a mental health professional). For the high mental well-being and the mild to moderate psychological distress groups, a web-based mental health questionnaire is being distributed among UAB students for screening and analyzed to determine the participant's eligibility. Participants who meet the selection criteria are consecutively included. For the mental health condition group, the patients are being referred from the Institute of Neuropsychiatry and Addictions-PSMAR, the Hospital Sant Joan de Déu, and the Psychology and Speech Therapy Service of the UAB. The assessments are planned at 2 time points and are being conducted at the site of recruitment (UAB, Institute of Neuropsychiatry and Addictions-PSMAR, or Hospital Sant Joan de Déu). The second assessment takes place after 1 month of the first assessment.

Participants and Eligibility Criteria

The 3 abovementioned participant groups are being recruited according to the inclusion and exclusion criteria described in detail in Table 1. To ensure a homogeneous sample in terms of age, participants aged between 18 and 34 years are being recruited in all 3 groups.

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Table 1. Inclusion and exclusion criteria for the 3 groups of the participants being recruited in the multicenter observational study (mHealth Methods in Mental Health Research project).

Groups	Inclusion criteria	Exclusion criteria	Site of recruitment
High mental well-being	• No history of emotional distress for at least a year • PHQ-4[a] score: <3 and SWEMWBS[b] score: ≥30	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan	University campus (UAB[c])
Mild to moderate psychological distress	• Recent history of mental health issues • PHQ-4 score: 3-8 or SWEMWBS score: 20-29	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan	University campus (UAB)
Mental health condition	• Diagnosed with current depression or anxiety by a mental health professional	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan • The symptomatology has an organic origin or is owing to the physiological effects of a substance • Presence of acute suicidal ideation • Being medicated	Mental health services (INAD-PSMAR[d] or HSJD[e])

[a]PHQ-4: Patient Health Questionnaire-4.

[b]SWEMWBS: short version of Warwick-Edinburgh Mental Well-being Scale.

[c]UAB: Autonomous University of Barcelona.

[d]INAD-PSMAR: Institute of Neuropsychiatry and Addictions-Parc de Salut Mar.

[e]HSJD: Hospital Sant Joan de Déu.

For the high mental well-being and mild to moderate psychological distress groups, inclusion criteria are assessed for eligibility through a web-based questionnaire that contains questions about mental health history (eg, "Have you ever experienced any mental health issue?"). The Patient Health Questionnaire (PHQ; PHQ-4) [35] is used to screen for anxiety and depression symptoms, and the short version of Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [36,37] is used to evaluate mental well-being. The cutoff points to be considered as high mental well-being are based on data from a representative sample of young adults of Catalonia from the Catalonia Health Survey conducted in 2016 [38], in which a median score of 30 points in SWEMWBS was found. Individuals with SWEMWBS well-being score ≥30 and PHQ-4 <3 points are classified in the high well-being group. Individuals with SWEMWBS score between 20 and 29 points or a PHQ-4 score between 3 and 8 are classified into the mild to moderate psychological distress group.

Recruitment

The primary recruitment pathway for nonpatients is the dissemination of the study through institutional mail or social media and the placement of posters in public areas of UAB. The information includes a link or QR code to answer a web-based questionnaire. To facilitate the recruitment of the mild to moderate psychological distress group, the Psychology and Speech Therapy Service of the UAB is collaborating by inviting students who attended the service to participate in this study. In both cases, once the responsible researcher confirms the eligibility criteria, the participant is contacted to schedule the first assessment.

For the mental health condition group, the patients who meet the criteria are identified at the consultation with the psychologist or psychiatrist, who briefly informs them about the study and suggests participation. The research assistant contacts the interested patients by phone and makes an appointment for the first assessment. Written informed consent is provided by all participants before starting the first assessment interview.

Study Procedure

All participants who agree to participate are asked to abstain from tobacco, alcohol, caffeine, or any other beverage or stimulating substance for 2 hours before the study. Figure 1 shows the complete schematic of the experimental procedure.

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Figure 1. The study experimental procedure outline for the first and second (conducted after 1 month) assessments includes recruitment, obtaining informed consent, and data collection. A research assistant performs the same procedure for both assessments in this observational study (mHealth Methods in Mental Health Research [M&M] project).

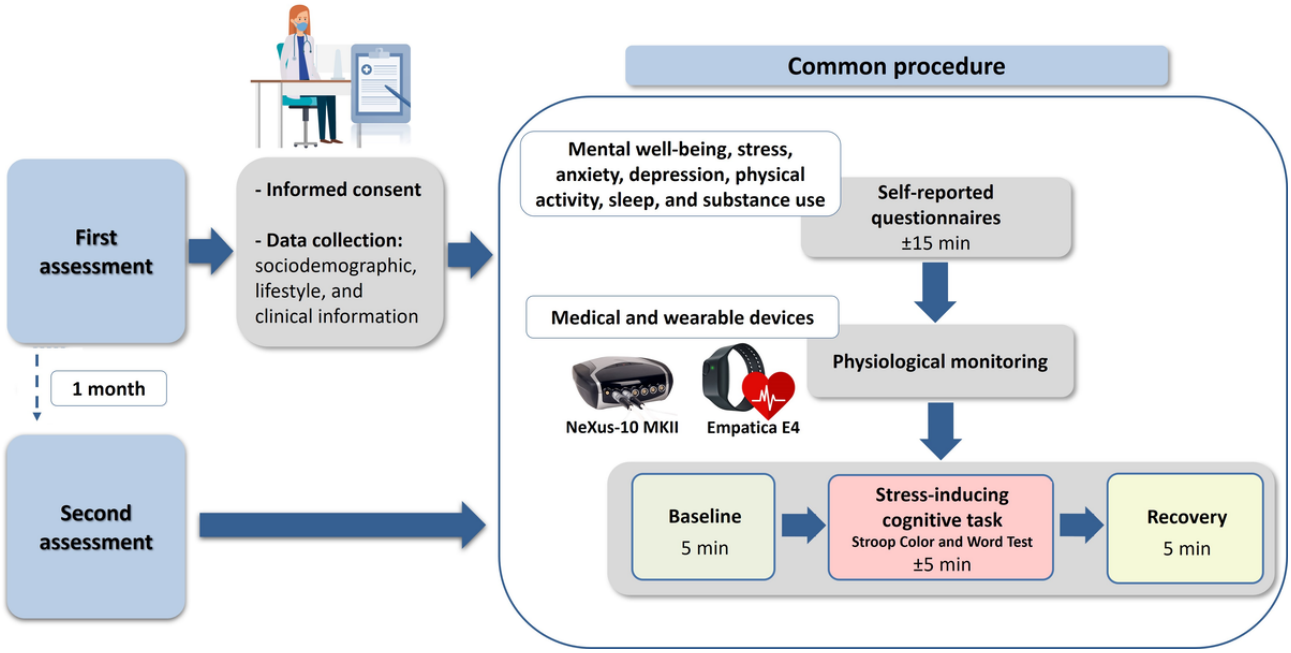

At the first assessment, the participants are fully informed about the study procedure and are requested to sign the informed consent form. This visit includes an ad hoc interview conducted by a qualified examiner to collect individuals' sociodemographic, modifiable lifestyle factors, health-related variables, and clinical data through the management software Qualtrics (Silver Lake). Subsequently, a psychological assessment is carried out. The participants respond to 7 self-reported questionnaires using the same software. These questionnaires aim to estimate the current mental well-being, stress perception, symptoms of anxiety and depression, physical activity, sleep quality, and substance use. All these measures are described in the *Study Variables* section.

The physiological assessment consists of recording different stress-related physiological signals using (1) the medical-graded device NeXus-10 MKII (Mind Media BV) and (2) the wearable E4 Empatica wristband (Empatica Inc). PPG, EDA, and ST will be the physiological signals recorded simultaneously by both devices. The electrocardiogram (ECG) and respiration can only be measured using a medical-graded device. This device is used to obtain a more accurate measure for preliminary analysis and, thereafter, validate the predictive model with the wearable device.

The wristband is placed on the nondominant wrist and the PPG (middle finger), EDA (middle phalanges of the second and fourth digits), and ST (fingertip of the fifth finger) sensors are placed on the nondominant hand to avoid excessive movement artifacts. An adjustable elastic band is placed over the abdomen to measure the respiration signal. For lead 1 of the ECG signal, electrodes are positioned below the right collarbone and below the left rib cage, whereas for lead 2, electrodes are positioned on the fifth intercostal space along the midaxillary line on the left side and symmetrically on the right side. The reference electrode is placed on the left collarbone.

This part of the procedure lasts approximately 15 minutes and is divided into three different stages: (1) baseline (green block in Figure 1): participant in a resting state, sitting comfortably with eyes open; (2) cognitive task (red block in Figure 1): corresponds to the stress-inducing stage, when the individual is submitted to a cognitive task, the Stroop Test [39]; and (3) recovery (yellow block in Figure 1): when the individual's physiological responses are expected to return to the baseline levels. All physiological signals and variables of interest will be detailed in the *Physiological Variables* section.

A second assessment is then scheduled 1 month apart and includes the same psychological and physiological assessments. This follow-up session is intended to allow test-retest reliability and account for random errors that could occur in a single session.

Study Variables

Outcome Measures

The following outcome measures are used:

1. Depression: It is evaluated using the PHQ-9 [40,41]. It is a Likert-type scale used to screen the severity of depressive symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. All 9 items are rated from 0 (not at all) to 3 (nearly every day). Total scores can range from 0 to 27, with higher scores indicating more severe depression. Furthermore, 5, 10, 15, and 20 represent the cutoff points for mild, moderate, moderately severe, and severe depression, respectively [42].
2. Anxiety: The Generalized Anxiety Disorder-7 [43,44] is an instrument for screening the presence of symptoms of anxiety as listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. It is a 1-dimensional scale with scores for all 7 items ranging from 0 (not at all) to 3 (nearly every day). The total score was categorized

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into 4 severity groups according to the original authors: minimal (0-4), mild (5-9), moderate (10-14), and severe (>15).

3. Mental well-being: The SWEMWBS [36,37] is an instrument used to assess mental well-being. This unidimensional scale comprises 7 items ranging from 1 (none of the time) to 5 (all of the time). The higher the total score, the greater the perception of well-being.

Covariates

Sociodemographic variables include age, gender, nationality, marital status, living status, educational level, and occupation.

Current physical and mental health conditions, previous mental health treatments, medication, and suicidal thoughts and behaviors are evaluated through items in the ad hoc interview. Perceived stress is evaluated using the 10-item Perceived Stress Scale [45,46]. It is a 5-point Likert scale with questions about the frequency of feelings and thoughts during the last month, with each item ranging from 0 (never) to 4 (very often). Higher scores indicate higher levels of perceived stress. To assess substance use problems, the CAGE-Adapted to Include Drugs [47] scale is used. It is an adaptation of the original CAGE questionnaire [48] for conjointly screening for alcohol and drug problems based on lifetime. The scale contains 4 yes or no questions, and a higher score indicates substance use problems.

Modifiable lifestyle variables are assessed using an ad hoc interview, including coffee consumption, cigarette smoking, alcohol and drug consumption, and BMI. Physical activity is measured using the short form of the International Physical Activity Questionnaire [49,50]. This questionnaire comprises 7 open-ended questions about individuals' 7-day recall of physical activity. According to the total energy expenditure in metabolic equivalent of task (ie, 1 metabolic equivalent of task is the energy cost of sitting quietly) in minutes per week, the physical activity level is determined as low or inactive, moderate, or high.

Sleep is evaluated using the Medical Outcomes Study Sleep Scale [51,52]. This questionnaire contains 12 items about a 4-week recall, divided into 8 subscales (sleep adequacy, optimal sleep, quantity of sleep, awakening shortness of breath or with headache, snoring, sleep disturbance, somnolence, and global index of sleep interference). In general, higher scores indicate greater sleep problems. The quantity of sleep score is the patient-reported number of hours of sleep per night, and optimal sleep is scored as 1 (7 or 8 h of sleep per night) or 0 (any different response).

The comfort level is evaluated by asking participants if they are currently experiencing higher stress than usual and identifying its potential causes.

Stress-Inducing Cognitive Task

The Spanish version of the standard Stroop Color and Word Test (SCWT) is applied (originally [53] and Spanish version [39]) as a cognitive stress-inducing task. This test is extensively used to assess cognitive inhibition and processing speed. Furthermore, it has also been shown to be a reliable method to induce mental stress in experimental settings [54]. The individuals are required to read the 3-color cards as fast as possible in a fixed time of 45 seconds each. The stimuli presented on the first 2 cards are congruent, that is, read names of colors or name different colors. In contrast, the last card represents the incongruent stimuli, that is, name the color of the ink instead of reading the color.

Three direct scores are derived by tallying the correct responses for each condition: (1) *W* (word) represents the number of colors read on the first card (where colors are written in black ink), (2) *C* (color) represents the number of elements identified on the card of colors (where name colors are represented with strings of XXXXs), and (3) *CW* (color word) represents the number of items correctly identified on the third card (where colors are printed in an ink that does not correspond to the color name, requiring participants to say the colors of the ink). Two other scores will be calculated from these: (1) predicted *CW* (*PCW*): ($W \times C / W + C$) and (2) interference: ($CW - PCW$). A higher score indicates a greater ability to inhibit interference.

Direct scores are then converted to *T* scores, with a preset mean of 50 and SD of 10, so that they can be more easily compared in similar age ranges (in this study, young adults aged between 18 and 44 years). The limits considered normal are between 35 and 65 *T* points in any of the scores (for details, refer the study by Golden [39]).

Physiological Variables

Overview

We are following a methodology already used and validated as stress assessment for healthy students and principal caregivers [20,55]; the electrophysiological raw signals recorded with NeXus-10 MKII (ie, ECG, PPG, EDA, respiration, and ST) are analyzed using BioSigBrowser [56] in MATLAB software (The MathWorks Inc); and several groups of variables are extracted, as described in Table 2. A literature review was conducted to select the most relevant variables for assessing stress response and mental health. A summary of the findings can be found in Multimedia Appendix 1 [19-24,57-65].

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Table 2. Description of the variables that will be extracted from raw electrophysiological signals monitored with the medical device NeXus-10 MKII.

Group of variables	Electrophysiological signal	Physiological variables	Description
HRV[a] or PRV[b]	ECG[c] or PPG[d]	HR[e,f] (bpm)[g]	Mean HR
HRV or PRV	ECG or PPG	IBI[f] (ms)[h]	Mean IBI
HRV or PRV	ECG or PPG	pNN50[f] (%)	Percentage of adjacent normal beats intervals differing from each other by >50 ms
HRV or PRV	ECG or PPG	SDNN[f] (ms)	SD of normal beats intervals
HRV or PRV	ECG or PPG	RMSSD[f] (ms)	Root mean square of successive differences between normal beats
HRV or PRV	ECG or PPG	SDSD[f] (ms)	SD of differences between adjacent R-R peaks intervals
HRV or PRV	ECG or PPG	VLF[i] (s^{-2})	Absolute power of the VLF band (0.003-0.04 Hz)
HRV or PRV	ECG or PPG	LF[f,j] (s^{-2})	Absolute power of the LF band (0.04-0.15 Hz)
HRV or PRV	ECG or PPG	HF[f] (s^{-2})[k]	Absolute power of the HF band (0.15-0.4 Hz)
HRV or PRV	ECG or PPG	LF/HF ratio[f]	Ratio of LF to HF power
HRV or PRV	ECG or PPG	HFn[f] (nu)	Relative power of the HF band normalized
PAT[l]	ECG and PPG	PAT (ms)	Mean PAT, the time between the beat detected by ECG and the pulse by PPG
PAT	ECG and PPG	stdPAT (ms)	SD of PAT
Breathing	Respiration	RR[m] (Hz)	Mean RR
Breathing	Respiration	Pk (%)	Peak of respiratory power spectra
EDA[n]	EDA	Tonic[f] (µS)	Average value of the tonic component, that is, slowly changing skin conductance level, also known as SCL[o]
EDA	EDA	Phasic[f] (µS)	Average value of the phasic component, that is, fast-changing responses typically associated with short-term events, also known as SCR[p]
EDA	EDA	aucPhasic[f] (µS·s)	Area under the curve of the phasic component, which is related to SCR
EDA	EDA	EDASymp[f] (µS)	Electrodermal response in the power spectrum (0.045-0.25 Hz)
Peripheral temperature	ST[q]	TFinger[f] (°C)	Mean finger temperature
Peripheral temperature	ST	TGradient[f] (°C)	Mean gradient of finger temperature
Peripheral temperature	ST	TPower[f] ($°C^2$)	Mean power of finger temperature

[a]HRV: heart rate variability.
[b]PRV: pulse rate variability.
[c]ECG: electrocardiogram.
[d]PPG: photoplethysmography.
[e]HR: heart rate.
[f]These will also be extracted from the recordings of the Empatica E4 wearable device.
[g]bpm: beats per minute.
[h]IBI: interbeat interval.
[i]VLF: very low frequency
[j]LF: low frequency.
[k]HF: high frequency.
[l]PAT: pulse arrival time.
[m]RR: respiratory rate.
[n]EDA: electrodermal activity.
[o]SCL: skin conductance level.

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[p]SCR: skin conductance response.

[q]ST: skin temperature.

The raw signals recorded with the Empatica E4 wearable device (ie, EDA, PPG, and ST) will be also analyzed in MATLAB (The MathWorks Inc) using a similar procedure, given the different format files. The variables intended to be explored in this case are indicated in the footnotes in Table 2. Furthermore, the stress reactivity, that is, the difference between the stress-inducing cognitive task stage and the baseline stage (stress−baseline), and the stress recovery, that is, the difference between the stress and the posterior recovery stage (stress−recovery), will also be computed for each variable to determine the most relevant set of variables to be considered to design the final model.

Physiological Data Processing

For processing the ECG signal, beat detection is performed through a discrete wavelet transform [66]. Afterward, the existence of ectopic beats or false QRS detections will be verified and corrected using the algorithm reported by Mateo and Laguna [67] before the computation of the interbeat interval series. Segments of up to 3 interpolated or corrected beats are accepted and assumed to be normal. Following this, the HRV parameters are calculated by a time-domain analysis and a frequency-domain analysis by Fourier transform of the heart rate signal.

PPG signal is preprocessed using a low-pass finite impulse response (FIR) filter with a cutoff frequency of 35 Hz (order 50) and then a high-pass FIR filter with a cutoff frequency of 0.3 Hz (order 5000). PPG artifacts are suppressed using a Hjorth parameter–based PPG artifact detector described by Gil et al [68]. Pulses are detected from the PPG signal on those time slots without artifacts using an algorithm based on the study by Lázaro et al [69]. The same ECG parameters are also extracted in PPG, in this case, referred to as pulse rate variability. Subsequently, the mean time difference between the R peak in the ECG signal and the point of 50% increase, corresponding to the pulse detected on the finger by the PPG signal, is considered as the PAT, and its SD (SD of PAT) is also calculated.

The respiration wave is filtered with an FIR passband filter with cutoff frequencies of 0.03 and 0.9 Hz. The respiratory rate is estimated as the frequency to which the maximum peak of the power density spectrum corresponds, estimated using a fast Fourier transform [70]. When the peak is >65%, then respiratory rate is considered valid.

The EDA signal is visually inspected to remove motion artifacts and linearly interpolated. First, a time-domain analysis is performed using a convex optimization model, called cvxEDA [57], to calculate the tonic and phasic components. The second procedure is a frequency-domain analysis, proposed to assess sympathetic tone through a parameter named EDASymp, described in the study by Posada-Quintero et al [71].

Finally, for the ST signal, a visual inspection is carried out to look for possible large artifacts. These segments are discarded before proceeding with the calculation of the parameters.

Statistical Analysis Plan

An initial descriptive analysis will be conducted for all study variables, for the overall sample and stratified by study group. The quantitative variables will be summarized, assuming normal distribution (Shapiro-Wilk normality test), using the mean and SD. The qualitative variables will be summarized using the relative and absolute frequencies. Physiological variables that present a skewed distribution will be logarithmically transformed.

A parametric test (Pearson correlation) or nonparametric test (Spearman correlation) will be, accordingly, applied as a descriptive measure of the association between quantitative variables.

To develop a useful tool for assessing mental distress and well-being, the initial step of the statistical analysis plan will involve variables reduction using two methods: (1) a correlation analysis to prioritize the most relevant variables for the prediction of the primary outcome measures and (2) a principal component analysis to find the directions of maximum variance in the data and reduce collinearity. Subsequently, the generated components that account for at least 85% (51/60) of the sample's variability will be included. From these components, 2 separate analyses will be conducted. First, a generalized linear model will be fitted to predict the values of each primary outcome measure. Second, a model will be developed to differentiate the 3 groups identified in the study, each representing a different level of mental health. The models will be fitted using standardized variables and performing k-fold cross-validation to quantify the model's performance using R^2 for the linear regression model and area under the curve for the classification models. Known-group validity will be assessed by comparing the mean scores of the tool among the preestablished groups at baseline: diagnosed with current depression or anxiety, symptoms of mental distress, and high mental well-being. The predefined hypothesis that higher model scores are predicted for individuals with higher well-being will be evaluated using the Jonckheere-Terpstra test, and Cohen effect sizes will be computed for each category as compared with the lowest category (mental health condition), considering small (0.2), moderate (0.5), and large (0.8) effect sizes [72].

The model test-retest reliability will be assessed with a 2-way random effect intraclass correlation coefficient (ICC), taking repeated evaluations of the same *unchanged* individuals, to assess the extent to which measures remain stable. A *change* will be considered a clinically relevant change in the outcome scores, ie, ≥4 points for the Generalized Anxiety Disorder-7, ≥5 points for PHQ-9, or ≥3 points for SWEMWBS) [73-75].

The significance level will be set at α=.05. Statistical analysis will be performed using SAS (version 9.4; SAS Institute).

Sample Size

As a proof-of-concept study, we plan to include 20 individuals per group (a total of 60 individuals×2 evaluations). For the assessment of known-groups validity of the developed tool,

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with this sample size of 20 individuals per group, and a type I error rate α=.05 on a 1-sided *t* test, we will have power of 0.80 to detect a difference between 2 groups corresponding to an effect size of 0.8. For a moderate effect size of 0.5, the power will decrease to 0.47 [17].

Concerning the assessment of test-retest reliability of the tool, assuming a 15% (9/60) loss in follow-up or nonstable participants from baseline participants, an ICC of 0.6 under the null hypothesis, and a type I error rate of α=.05, a sample size of 51 participants with 2 observations per participant achieves a power of 0.90 to detect a hypothetical ICC value of 0.8 under the alternative hypothesis [17].

Ethical Considerations

This study protocol was approved by the research ethics committees of both institutions (2021/10163 for PSMAR and 5912 for UAB). This study is in line with the principles established by national and international regulations, including the Declaration of Helsinki and the Code of Ethics. Ethics approval has been obtained in Barcelona from the independent PSMAR Clinical Research Ethics Committee and the Research Ethics Committee of the UAB. Informed consent is requested from all participants before their inclusion in the study. Participants are explained that they can withdraw from the study at any time without giving a reason and that they can request to delete all the data collected from them.

All personal data will be handled following Regulation (European Union) 2016/679 of the European Parliament and the Council on the protection of natural persons concerning the processing of personal data and on the free movement of such data and the National Organic Law 3/2018, of December 5, on Personal Data Protection and the Guarantee of Digital Rights. Physiological and psychometric data will be pseudoanonymized to guarantee privacy in data analysis and will be stored in a research database following the General Data Protection Regulation of the European Union.

Participants receive a €10 (US $11) gift card for enrolling in the study, and participants receive another gift card of the same value if they complete the second assessment.

Results

The project was granted in February 2022 and the approval from ethical committees was obtained between April and May 2022. Participant recruitment started in October 2022 and is expected to continue through June 2024. Different recruitment strategies are implemented, including advertising campaigns and invitation letters at the university and recruitment of patients by psychologists.

As of July 2023, a total of 41 participants completed the first and second assessments. The sample corresponds mainly to the group with mild to moderate psychological distress (n=20, 49%), followed by the group with high mental well-being (n=13, 32%) and, finally, those diagnosed with an anxiety disorder (n=8, 20%). At this point, preprocessing and quality checks of the data are ongoing, and the statistical analysis will subsequently begin. The first results are expected to be published in September 2024.

Discussion

Overview

There is a growing interest in remotely assessing mental health through changes in the ANS functioning and its association with mental health and well-being [26]. There is significant evidence to support the notion that changes in the ANS can be inferred from changes in physiological variables, such as HRV, EDA response, and peripheral temperature [58,76,77]. However, there is a challenge in designing a robust predictive model that allows this assessment to be easy and objective to be systematically used in epidemiology and clinical settings. To fill this gap, it is important to carefully measure electrophysiological signals considering the updated standards of measurement (eg, [78]), following a structure of 3-time point experimental design: considering a basal condition, during a stress-inducing task to investigate the stress reactivity, and a recovery stage. This study is applying a similar methodology used in previous research that reached good reliability in its predictive models [20,79]. However, in this novel approach, individuals with a clinically diagnosed mental health condition are being enrolled, which may allow for a better distinction between different profiles of mental health through the stress reactivity pattern and cognitive performance.

The SCWT is a well-known neuropsychological test reported as a reliable moderate mental stressor, provoking significant physiological changes such as reduced HRV and increased EDA and blood pressure [59,80,81]. Furthermore, it is a useful tool for evaluating cognitive processes and has the advantage of not generating a significant learning effect [82]. Cognitive inhibition is compromised in multiple mental health conditions; for example, individuals with anxiety disorders tend to have longer reaction times and higher error rates on the SCWT, particularly in the incongruent condition, which suggests difficulties with selective attention and response inhibition [83]. Thus, although the impaired performance of the task may be indicative of an underlying neurological disorder, a good result performance may add another layer of confidence in evaluating mental well-being.

There is a lot of research committed to investigating biomarkers and stress reactivity in patients diagnosed with depression and anxiety disorders [15,84]. The evidence supports differences in physiological behavior in patients with depression and anxiety compared with healthy individuals. Considering this, the decision to include 3 groups with different mental health states will facilitate the detection of patterns that could discriminate them more accurately. The age range selected is justified by the typical early age of onset of mental health conditions and the need for assertive responses to prevent a poor prognosis. Moreover, the recruitment is planned to be carried out in part at a university, considering that university students have been reported as a susceptible population with a higher risk to manifest mental health symptoms [85], which enables us to recruit the mild to moderate psychological distress group effortlessly. To minimize interindividual variation in

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physiological measures and the influence of external factors, we propose 2 different sessions with the same participants, which will also increase the statistical power [78].

Mobile health (mHealth), which includes physical devices, sensors, software, and other technologies, has been proposed to improve clinical care as it enables data collection, symptom monitoring, and provision of interventions [29]. In this sense, it could be a valuable resource to reach both regular patients and those who do not receive adequate care [12]. Specifically, the use of wearables provides a new and unobtrusive way to monitor physiological biomarkers and gather continuous information about individuals' daily lives and clinical symptoms for both clinical and research purposes. These devices with multiple embedded sensors can be useful in following up patients and remotely assessing their mental well-being through robust models that combine a set of relevant biomarkers [31].

Nevertheless, to ensure that autonomous nervous system biomarkers are effectively used for objectively measuring mental well-being in health services, it is necessary to undertake substantial work in identifying the most useful biomarkers and comprehending the possible obstacles and enablers of widespread adoption. To advance in this direction, this study intends to carry out a preliminary model validation by enrolling a preselected sample with different states of mental well-being in a laboratory-controlled condition; subsequently, we plan to explore its application in larger populations and in a real-life context.

To summarize, our study aims to design a comprehensive multiparametric model combining physiological and cognitive variables to assess the mental well-being among young people. The self-reported questionnaires currently used in clinical settings will be used as a reference to select the best model fit. This novel approach proposes shifting the paradigm to assessing mental well-being rather than measuring the severity of symptoms or a mental health condition. We believe that this change may allow health professionals to properly recommend prevention strategies and increase the possibility of intervening before the diagnosis of a mental health condition. To effectively develop a model that can be easily calculated by a wearable device, we first take a measurement of a standard medical device to ensure the best quality of physiological signal and then establish the final predictive tool.

Conclusions

This study represents the primary phase in developing a comprehensive mental well-being assessment tool. Our goal is to progress toward remote measurements with acceptable accuracy, using sophisticated devices as a benchmark for comparison. Developing a robust predictive model will facilitate objective assessment that can be systematically used in epidemiological and clinical settings. Further research is required to explore the full potential of this technology in mental health research and clinical practice.

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Data Availability

The data sets generated during this study will be deposited in the Open Science Framework public repository.

Authors' Contributions

TCR, EGP, and J Aguiló drafted the first version of this manuscript. LB, J Alonso, and GV provided critical revision of further drafts of the manuscript. J Alonso, J Aguiló, TCR, EGP, HGM, GV, and FA made substantial contributions to the conception and design of the study protocol. RB and PM contributed to the scientific knowledge of the project. VPS and ASB contributed to patients' referral. TCR, EGP, and VSA were involved with the clinical interviews and psychophysiological assessments. J Alonso and J Aguiló are the principal investigator and coinvestigator of the study, respectively. All authors reviewed the latest version of the paper draft, provided comments, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of the literature review of the physiological variables assessed in the M&M mHealth Methods in Mental Health Research (M&M) Project

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[DOCX File , 23 KB - resprot_v13i1e51298_app1.docx]

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Abbreviations

ANS: autonomic nervous system
ECG: electrocardiogram
EDA: electrodermal activity
FIR: finite impulse response
HRV: heart rate variability
ICC: intraclass correlation coefficient
M&M: mHealth Methods in Mental Health Research
mHealth: mobile health

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PAT: pulse arrival time
PHQ: Patient Health Questionnaire
PPG: photoplethysmography
PSMAR: Parc de Salut Mar
SCWT: Stroop Color and Word Test
ST: skin temperature
SWEMWBS: short version of Warwick-Edinburgh Mental Well-being Scale
UAB: Autonomous University of Barcelona

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Protocol

National Tunisian Study of Cardiac Implantable Electronic Devices: Design and Protocol for a Nationwide Multicenter Prospective Observational Study

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Abstract

Background: In Tunisia, the number of cardiac implantable electronic devices (CIEDs) is increasing, owing to the increase in patient life expectancy and expanding indications. Despite their life-saving potential and a significant reduction in population morbidity and mortality, their increased numbers have been associated with the development of multiple early and late complications related to vascular access, pockets, leads, or patient characteristics.

Objective: The study aims to identify the rate, type, and predictors of complications occurring within the first year after CIED implantation. It also aims to describe the demographic and epidemiological characteristics of a nationwide sample of patients with CIED in Tunisia. Additionally, the study will evaluate the extent to which Tunisian electrophysiologists follow international guidelines for cardiac pacing and sudden cardiac death prevention.

Methods: The Tunisian National Study of Cardiac Implantable Electronic Devices (NATURE-CIED) is a national, multicenter, prospectively monitored study that includes consecutive patients who underwent primary CIED implantation, generator replacement, and upgrade procedure. Patients were enrolled between January 18, 2021, and February 18, 2022, at all Tunisian public and private CIED implantation centers that agreed to participate in the study. All enrolled patients entered a 1-year follow-up period, with 4 consecutive visits at 1, 3, 6, and 12 months after CIED implantation. The collected data are recorded electronically on the clinical suite platform (DACIMA Clinical Suite).

Results: The study started on January 18, 2021, and concluded on February 18, 2023. In total, 27 cardiologists actively participated in data collection. Over this period, 1500 patients were enrolled in the study consecutively. The mean age of the patients was 70.1 (SD 15.2) years, with a sex ratio of 1:15. Nine hundred (60%) patients were from the public sector, while 600 (40%) patients were from the private sector. A total of 1298 (86.3%) patients received a conventional pacemaker and 75 (5%) patients received a biventricular pacemaker (CRT-P). Implantable cardioverter defibrillators were implanted in 127 (8.5%) patients. Of these patients, 45 (3%) underwent CRT-D implantation.

Conclusions: This study will establish the most extensive contemporary longitudinal cohort of patients undergoing CIED implantation in Tunisia, presenting a significant opportunity for real-world clinical epidemiology. It will address a crucial gap in the management of patients during the perioperative phase and follow-up, enabling the identification of individuals at particularly high risk of complications for optimal care.

Trial Registration: ClinicalTrials.gov NCT05361759; https://classic.clinicaltrials.gov/ct2/show/NCT05361759

International Registered Report Identifier (IRRID): RR1-10.2196/47525

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KEYWORDS

Tunisia; study; pacemaker; implantable cardioverter defibrillator; cardiac resynchronization therapy; design; complication

Introduction

Background

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PMs), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy devices with or without defibrillators (CRT-Ds or CRT-Ps), are standard therapy for bradyarrhythmia, tachyarrhythmia, and systolic heart failure [1,2]. Their use has increased over the last decade [3,4]. However, CIED implantation comes with a considerable burden of complications, leading to elevated patient morbidity, health care costs, and mortality [5-8]. The most recent consensus on device implantation and replacement by the European Heart Rhythm Association [9] has been significantly influenced by the invaluable contributions of various international registries. One of the most prominent among them is the “Replace” registry [10], which has played a pivotal role in advancing our understanding of this crucial aspect of cardiac care.

A comprehensive understanding of post-CIED implantation complications and their predictive factors is essential for patient management when considering CIED implantation. Therefore, a survey of patients undergoing CIED implantation in Tunisia is crucial to identify specific CIED complications due to the demographic and epidemiological specificities of the patients, as well as the conditions of the local health care system.

Study Aims

This study aims to assess the incidence, characteristics, and predictors of complications arising in the initial 12 months following the implantation of CIEDs, describe the demographic and epidemiological profiles of a national cohort of consecutive patients with CIED, and provide insights into the level of compliance exhibited by Tunisian electrophysiologists with international guidelines pertaining to cardiac pacing and the prevention of sudden cardiac death.

Methods

Study Design and Patients’ Enrollment

NATURE-CIED (National Study of Cardiac Implantable Electronic Devices) is a nationwide, multicenter, prospective observational study with a 1-year follow-up period. The study’s steering committee extended invitations to all electrophysiologists, interventional cardiologists, and

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cardiovascular surgeons with experience in CIED implantation, regardless of whether they are practicing in the Tunisian public or private sectors, to participate in the study.

Patients' enrollment occurred between January 18, 2021, and February 18, 2022, at all Tunisian public and private CIED implantation centers that agreed to participate in the study. Eligibility screening was conducted during hospitalization.

The study population consisted of consecutive patients undergoing primary CIED (conventional PMs, ICDs, and cardiac resynchronization: CRT-P–CRT-D) implantation, generator replacement, and upgrade procedure. To be enrolled, eligible patients have to provide written informed consent. All enrolled patients entered a 1-year follow-up period with 4 consecutive visits at 1, 3, 6, and 12 months after the CIED implantation. Exclusion criteria are nonconsenting patients and those operated exclusively for lead dysfunction.

Data Sources

A steering board with 2 main investigators pre-established a specific case report form (CRF) for each type of CIED. Baseline data included patient demographics, ethnic specificity, medical history, cardiovascular history, cardiovascular risk factors, the CIED implantation indication, vital signs, laboratory measurements, electrocardiographic and echocardiographic findings, details of medical management, and results of eventual invasive and noninvasive investigations prior to CIED implantation (echocardiography, Holter monitoring, treadmill exercise stress test, and electrophysiological study).

The form also includes data regarding the technical aspects of the CIED implantation procedure and the occurrence of any periprocedural complications. Finally, the form specifies data on the clinical follow-up and device electrical testing parameters, as well as the eventual major incident events and CIED complications during the follow-up period. Investigators (electrophysiologists and interventional cardiologists) who agreed to participate in the study were asked to complete the pre-established form (CRF) for each type of implanted device at the enrollment visit and each scheduled visit.

Collected data were electronically recorded on a clinical suite platform (DACIMA software), which complies with international standards including US FDA 21 CRF part 11 (Food and Drug Administration 21 Code of Federal Regulations Part 11), US HIPAA (Health Insurance Portability and Accountability Act) and ICH (International Conference on Harmonisation), and Medical Dictionary for Regulatory Activities. The main investigators and the DACIMA consulting team periodically validated recorded data. The clinical suite platform generates alerts and requests in case of inconsistencies and missing data. Throughout the planned duration of the study, the steering board supervises the inclusion of patients, checks the data sources, and prepares the study's statistical analysis plan.

Timeline

Patient enrollment and data collection began on January 18, 2021, and continued until February 18, 2022. Follow-up continued until all patients had 1-year data. The end of the study was therefore scheduled for February 18, 2023 (Figure 1).

Figure 1. The Timeline of the Nature CIED study.

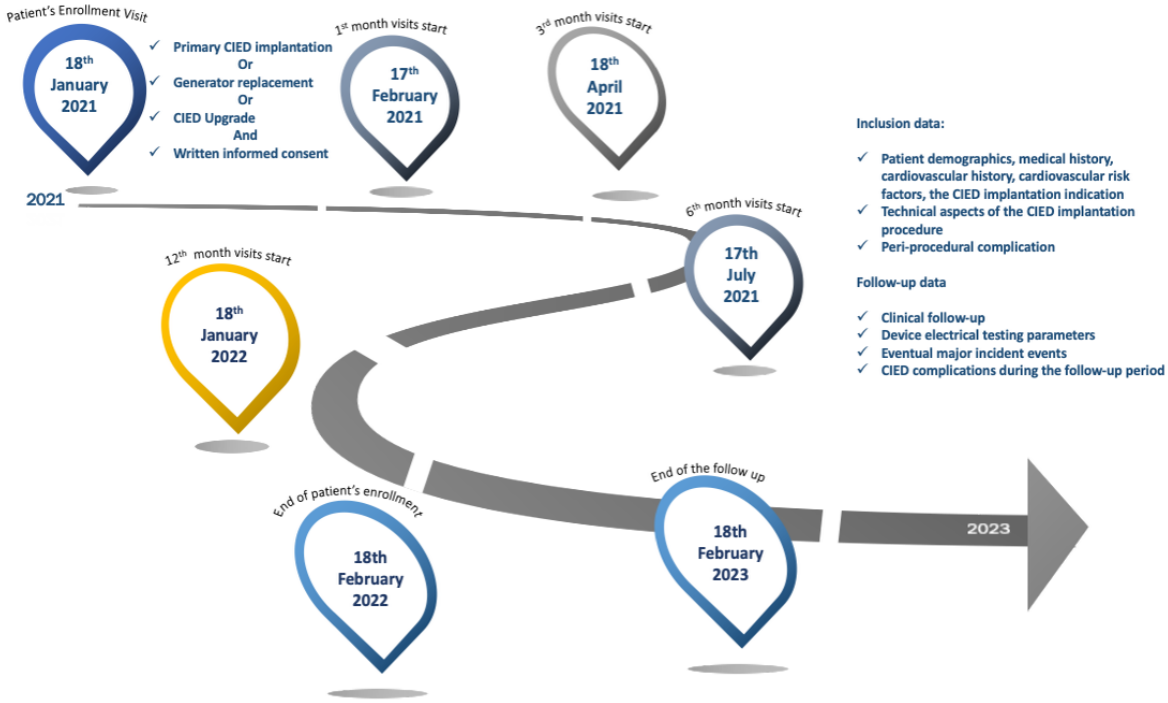

If patients missed a scheduled follow-up visit, they or their relatives were contacted by phone to assess any adverse event and to reschedule a follow-up appointment.

Outcomes

The main objective of this observational study is to assess the incidence, characteristics, and predictors of major and minor

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complications arising in the initial 12 months following the implantation of CIEDs.

The complications were characterized as major when life-threatening or requiring surgical reintervention for correction, and minor when suitable for treatment on an outpatient basis, involving device reprogramming, or requiring exclusive clinical observation [11]. Major complications include implantation failure, lead-related reinterventions, tamponade or myocardial perforation, pneumothorax requiring drainage, hematoma requiring evacuation, wound or pocket infection, systemic infections or endocarditis, Twiddler syndrome, and procedure-related deaths. Minor complications include pacing threshold increase, phrenic nerve stimulation, heart failure or left ventricular ejection fraction decrease, pericardial effusion, and conservatively treated hematoma and pneumothorax.

Ethical Considerations

The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki and the ICH Good Clinical Practices. Ethics approval was obtained from the human research ethics committees at Abderrahmen Mami Hospital in Tunis (04/2021). Written informed consent was obtained from all the patients who participated in the study. The protocol of NATURE-CIED was approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-CIED study was submitted to ClinicalTrials.gov (NCT05361759).

Statistical Analysis

The DACIMA Clinical Suite platform enables the collection of web-based data and their extraction in SAS (SAS Institute) or SPSS (IBM Corp) format. The statistical analysis is exploratory, involving the calculation of 95% CI. The data will be described for the whole analyzed population. Continuous variables will be described by mean and SD or median and IQR. Categorical variables will be described by the size and frequency of every modality. Mean comparison will be performed by analysis of variance or by nonparametric tests if the hypothesis of normality is rejected.

The normality of continuous variables will be verified with the Shapiro-Wilk test. The statistical tests are bilateral with a 95% CI. A chi-square test will be performed for categorical variables. Yates correction or the Fisher exact test will be used if the conditions of validity for the chi-square test are not met.

A multivariate analysis will be performed with each complication as a dependent factor. The independent variables will be age, gender, ethnic specificity, BMI, CIED type, procedure type, procedure priority, implantation center (private and public), and CIED implanting operator whether he is an electrophysiologist or not (interventional cardiologist or cardiac surgeon).

Univariate logistic regression will be carried out with a 10% output threshold. The final model will be performed with the parameters selected by the backward stepwise method of Wald. The selected variables in the final model will be tested at the 5% threshold. The interaction between selected parameters is tested at the 10% threshold. The intermediate analyses will be carried out after formulating the statistical analysis plan.

Expected Implications

NATURE-CIED is the first national and North African study that will (1) provide validated data on short- and medium-term complications and their predictors, which will allow us to individualize high-risk patients for optimal care, (2) identify the epidemiologic and demographic characteristics of Tunisian patients undergoing CIED implantation, and (3) clarify the contemporary CIED indications in Tunisia and their compliance with international guidelines.

Results

In total, 27 investigators, comprising 14 from the public sector and 13 from the private sector, volunteered to take part in the study. It is worth noting that some of the investigators were involved in both the public and private sectors. A total of 1500 consecutive patients were enrolled for a 12-month follow-up period following CIED implantation. Sixty percent (n=900) of the patients were from the public sector, while 40% (n=600) were from the private sector. The patients' mean age was 70.1 (SD 15.2) years, with a sex ratio of 1:15. A total of 1298 (86.3%) patients received a conventional PM and 75 (5%) patients received a biventricular pacemaker (CRT-P). ICDs were implanted in 127 (8.5%) patients. Of these patients, 45 (3%) underwent CRT-D implantation. The detailed analyses of this study are currently under investigation and will be published elsewhere in the near future.

Discussion

Summary

To the best of our knowledge, NATURE-CIED is the first National study of CIEDs in North Africa to provide the combination of large numbers of patients and devices and diverse implanting physicians. Twenty-seven cardiologists (electrophysiologists and interventional cardiologists) enrolled 1500 patients who underwent CIED implantation.

According to the second report from the Pan African Society of Cardiology working group on cardiac arrhythmias and pacing [12], Tunisia had the highest implant rates, with 164.3 PMs per million inhabitants and 2.16 PM implantation practitioners per million inhabitants in 2018, which makes it rank in the second position after Mauritius [12].

However, there is still a gap concerning patients' demographics, CIED indications, and conformity to recent European Society of Cardiology guidelines [2] and CIED-related complications [12-14].

Both patient-related and procedure-related predictors of complications may identify patients with a particularly high risk of complications [15]. Previously reported incidences of complications after CIED implantation varied widely because of differences in the definitions of complications and length of follow-up [15-18]. Several previous studies in the 2000s reported that complication rates for PM were 4%-10% [13,17-19] and 3%-10% for ICDs and CTRDs [6,20]; however, an analysis of

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US Medicare states that data in 2014 showed much lower complication rates [21].

In 2010, the "Replace" registry, comprising data from a substantial cohort of 1744 patients who underwent device replacement procedures, yielded pivotal insights into predictive factors for complications [10]. This comprehensive analysis has, in turn, informed the development of practical and evidence-based procedural recommendations. By identifying the key determinants of complications, the registry has empowered health care professionals to more effectively anticipate and mitigate risks, ultimately leading to improved patient outcomes.

Therefore, the NATURE CIED study aims to offer detailed and comprehensive data on the predictors of CIED complications during the perioperative and 1-year follow-up period, which are derived from real-world data in Tunisia. The information generated by this study will prove valuable in the development of a national peri-implantation management protocol and the assessment of overall health care costs [11,12,14,22].

Study Limitations

This study presents some limitations that must be considered in the interpretation of the results. This study is voluntary for both investigators and patients, and there is no routine audit to monitor the proportion of enrolled patients by participating electrophysiologists or cardiologists. This currently limits our ability to examine exact implant rates and to examine equity of access to PM therapy across the country. Some patients were lost to follow-up.

We identified all complications documented in patients during hospitalization and follow-up. We believe that this approach is the most accurate and comprehensive way to detect complications. In addition, this study was not designed to assess the effects of each investigator's experience level and the volume of procedures performed individually. Therefore, the electrophysiologists' or interventional cardiologists' positions on their learning curve may influence the rate of complications mainly in teaching hospitals.

Conclusions

NATURE-CIED study will fill an important gap in the management of patients undergoing CIED implantation both perioperatively and during follow-up and will identify patients at particularly high risk of complications for optimal management.

In Tunisia, this study will yield the largest contemporary longitudinal cohort of patients undergoing CIED implantation and will provide real-world data regarding heart rhythm diseases' epidemiology and management with insights into the degree of adherence to international guidelines.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CIED: cardiac implantable electronic device
CRF: case report form
CRT-D: cardiac resynchronization therapy defibrillator
CRT-P: cardiac resynchronization therapy pacemaker

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HIPAA: Health Insurance Portability and Accountability Act
ICD: implantable cardioverter defibrillator
ICH: International Conference on Harmonisation
NATURE-CIED: National Study of Cardiac Implantable Electronic Devices
PM: pacemaker

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Protocol

Preference-Based Implementation of Video Consultations in Urban and Rural Regions in Outpatient Care in Germany: Protocol for a Mixed Methods Study

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Abstract

Background: Particularly in rural regions, factors such as lower physician density and long travel distances complicate adequate outpatient care. However, urban regions can also be affected by deficits in care, for example, long waiting times. One model of care intending to improve the situation is the implementation of video consultations. The study protocol presents the methodology of the research project titled “Preference-based implementation of the video consultation in urban and rural regions” funded by the German Federal Joint Committee (funding number 01VSF20011).

Objective: This study aims to identify existing barriers to the use of video consultation and the preferences of insured individuals and physicians as well as psychotherapists in order to optimize its design and thus increase acceptance and use of video consultations in urban and rural regions.

Methods: Built on a mixed methods approach, this study first assesses the status quo of video consultation use through claims data analysis and carries out a systematic literature review on barriers and promoting factors for the use of video consultations. Based on this preliminary work, focus groups are conducted in order to prepare surveys with insureds as well as physicians and psychotherapists in the second study phase. The central element of the survey is the implementation of discrete choice experiments to elicit relevant preferences of (potential) user groups and service providers. The summarized findings are discussed in a stakeholder workshop and translated into health policy recommendations.

Results: The methodological approach used in this study is the focus of this paper. The study is still ongoing and will continue until March 2024. The first study phase has already been completed, in which preliminary work has been done on potential applications and hurdles for the use of video consultations. Currently, the survey is being conducted and analyses are being prepared.

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Conclusions: This study is intended to develop a targeted strategy for health policy makers based on actual preferences and perceived obstacles to the use of video consultations. The results of this study will contribute to further user-oriented development of the implementation of video consultations in German statutory health insurance. Furthermore, the iterative and mixed methods approach used in this study protocol is also suitable for a variety of other research projects.

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KEYWORDS

study protocol; video consultation; preference elicitation; discrete choice experiment; implementation; telemedicine; teleconsultation; e-consultation; outpatient; rural area; remote; preferences; strategy

Introduction

Particularly in rural regions, factors such as lower physician density and long travel distances complicate adequate outpatient care [1]. However, urban regions can also be affected by deficits in care, for example, due to long waiting times [2]. One model of care that could improve the situation is the implementation of video consultations in outpatient care, meaning online contact in real time with video transmission between physician or psychotherapist and patient. In addition to questioning about symptoms and medical history (anamnesis), signs of illness can be examined, and—possibly—a diagnosis can be made. Particularly in the case of long journeys, for follow-up appointments (for example after minor surgeries), or for the provision of repeated prescriptions, video consultations can be a useful tool and the insured individual does not have to visit the doctor’s office for every appointment. In the field of psychotherapy, therapeutic or certain diagnostic sessions can also take place in the form of video consultations [3].

Several studies provide preliminary clinical evidence of the benefits of telemedicine in certain patient populations, such as the chronically ill or patients living in nursing homes. A project in a predominantly rural region in Germany demonstrated the effectiveness of video consultations for nursing home residents. In particular, routine appointments, such as follow-up treatments, could be carried out efficiently remotely. Advantages for all parties involved were demonstrated through improved access to general practitioners (GPs) and specialists, a reduction in hospital admissions, and the elimination of stressful journeys and time-consuming home visits [4]. For people with mental disorders such as depression, telemedicine has proven to be a promising tool to enhance quality of life and access to treatment [5-7]. In addition, high patient satisfaction rates with video consultations could be shown in the field of orthopedics [8,9].

Since the health care system in Germany is predominately based on a social insurance system, in which 88.3% of the German population is insured [10], the project focuses on the statutory health insurance (SHI) system. In the German SHI, since April 2017, video consultations could initially only be provided by a few specialist groups and only for selected indications and follow-up appointments. In the second quarter of 2019, these restrictions were mostly abolished and the assessment of the appropriateness of a diagnosis or treatment via video consultation was placed in the decision-making responsibility of the physician [3,11]. During the COVID-19 pandemic, there were numerous (primarily temporary) adjustments in the regulations for their provision. Video consultations are part of the SHI benefits catalog. The remuneration of video consultations in outpatient medical care in the German SHI system is not fee-for-service based, but predominantly part of age-differentiated quarterly flat rates, which cover the entire medical care of a patient (not just video consultations) by the attending physician during this period. In addition, there are supplementary payments that compensate for the additional technical effort and the digital authentication of an unknown patient in video consultations [3].

However, since 2017 and up to the beginning of the COVID-19 pandemic, video consultations have hardly played a role in outpatient medical care in Germany [11]. Many physicians feared an estrangement of the physician-patient relationship and that as a consequence this would result in the physician's inability to meet the patients' needs. In addition, some assume that the reduced sensory perception on the screen and the lack of a holistic perspective could lead more easily to treatment errors or misdiagnoses. Concerns are also expressed about data protection and data security [12]. A study by Noweski et al [13] also showed that personal contact with the doctor is given high priority by the insured individual and that the insured individual only accepts digital doctor-patient consultations as an alternative in part or under specific conditions.

Thus, the central prerequisite for the creation of acceptance—related to the willingness to offer video consultations, but also to the willingness to make use of them—is the consideration of the preferences and perceived barriers of those involved. For this reason, this study addresses the question of how video consultations should be designed to improve situations of outpatient medical care while taking into account the preferences of the insured individual and physicians as well as psychotherapists. Weinhold and Gurtner [14] showed that patient satisfaction in primary care in rural regions depends on different factors than in urban regions. In order to be able to develop targeted strategies, a comparative preference assessment between rural and urban regions is carried out.

This study aims to address the following research questions:

- How often and for which treatment occasions are video consultations used in outpatient medical care in the SHI system in Germany? What are the characteristics of the user groups in rural and urban areas (use of video consultations in standard care)?

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- What findings can be drawn from national and international studies on the implementation of video consultation with regard to best practices so far?
- Under what conditions (expectations of form and content, inhibiting and promoting factors) do insured individuals accept the digitalization of their medical consultations?
- Which application options do physicians and psychotherapists prefer?
- How do the preferences differ among GPs, psychotherapists, and other specialist groups?
- How do the preferences of insured individuals and the physicians as well as psychotherapists differ between urban and rural regions?
- Which kind of implementation of video consultations should be pursued in rural and urban regions?
- Where are the hurdles that need to be overcome?
- Is there a need for regulatory adaptations?

So far, there are no research results on the use of video consultations that consider users (patients) and providers (physicians/psychotherapists) on the one hand and compare preferences between urban and rural regions on the other hand. To elicit these preferences, this study uses the particularly suitable method of discrete choice experiments (DCE), which, in contrast to other instruments of preference elicitation, allow for an intuitive decision-making process by evaluating alternatives as a bundle of their characteristics. A DCE also offers the advantage of a realistic assessment situation, which avoids the problem of compositional methods, which is that respondents tend to rate all attributes as very important [15].

Methods

Study Design

In order to develop a strategy for the preference-based implementation of video consultations in rural and urban regions, this study uses a mixed methods approach with a particular focus on DCE. The following Figure 1 shows the course of the study. The duration of the study is 3 years, beginning in April 2021 and continuing prospectively until March 2024.

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Figure 1. Study design and course of the study from April 2021 to March 2024. SHIF: statutory health insurance fund.

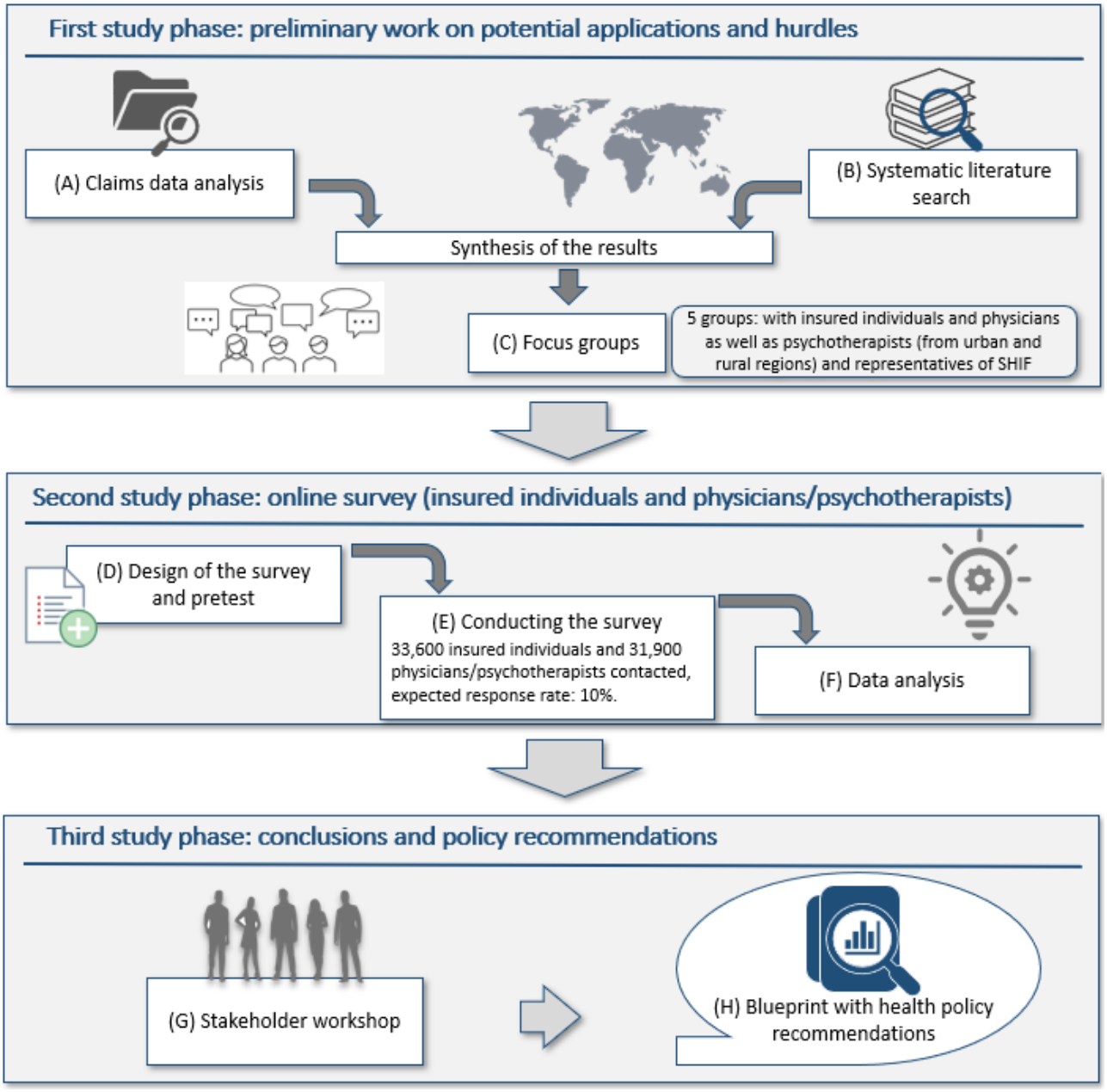

In the first study phase, the status quo of the use of video consultations is examined by a claims data analysis (A). At the same time, a systematic literature review (B) on possible barriers and promoting factors on the use and provision of video consultation is conducted. Then, preliminary findings are discussed in focus groups (C) in order to prepare the following surveys with DCE. In the second phase of the study, surveys including DCE are designed (D), conducted (E), and analyzed (F) to elicit preferences for the design of video consultation of insured individuals on the one hand and physicians as well as psychotherapists on the other hand, comparing rural and urban regions. In the third study phase, all results are combined and discussed in a stakeholder workshop (G) and policy recommendations (H) are developed.

Claims Data Analysis (A)

In work package A, claims data are analyzed focusing on patterns of the use of video consultations as well as the characteristics of their user groups in rural and urban regions (status quo).

To depict both, the perspective of insured and service providers, claims data from 3 statutory health insurance funds (SHIF) and 4 regional associations of statutory health insurance physicians (ASHIP) are used from the period April 2017 to the end of 2020.

Data for insured individuals and physicians, as well as psychotherapists in 4 German regions (“Westfalen-Lippe,” “Mecklenburg-Vorpommern,” “Schleswig-Holstein,” and “Berlin”), are analyzed. These regions are chosen because they include both rural and urban districts. The classification as a rural or urban district is carried out using the interactive web app “INKAR: Indicators and Maps of Spatial and Urban Development” offered by the Federal Institute for Research on Building, Urban Affairs, and Spatial Development. Among other things, the settlement structure of the district is considered

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as a combination of the population density and the settlement area share [16].

After a preliminary analysis of the data by the SHIF and ASHIP according to a consented evaluation concept, only aggregated data are sent to the University of Duisburg-Essen for further analysis. There, the data are combined and further evaluated according to the research question.

Aggregated data of approximately 6 million insured living in 1 of the 4 selected regions are analyzed. In addition to data on the use of video consultation, patient data on sociodemographic characteristics and diagnostic records are included. To depict the perspective of service providers, data from 31,900 physicians and psychotherapists are analyzed. Information on specialist groups (eg, GPs, psychotherapists, and other specialist groups) and sociodemographic characteristics of users compared with nonusers are collected. Furthermore, the influence of the place of residence or practice location on the use of video consultation is examined.

Descriptive analyses, differentiated according to subgroups (insured: age group, gender, employment situation, and type of region; physicians/psychotherapists: specialist group, age group, gender, type of operation and employment, and type of region) are conducted. Since the data are not provided at the individual level, the analysis of the aggregated data is performed using Excel (version 16.0; Microsoft Corp).

Systematic Literature Review (B)

A systematic literature review including national and international studies on the application settings of video consultation as well as possible hurdles in their implementation is conducted in parallel with the claims data analysis. Best practice models and, if applicable, existing empirical results (especially with regard to the acceptance of users) are to be analyzed. The systematic review is conducted in accordance with PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) guidelines [17]. Literature research is performed in PubMed and Embase. The search strategy is developed using the PICO scheme [18]. Relevant search, MeSH (Medical Subject Headings) or Emtree, terms are assigned to each category and linked with Boolean operators. The search is limited to publications from 2011 onward and to articles written in English and German. The study selection is divided into the steps of title, abstract, and full-text screening. To ensure an objective approach, literature screening, as well as extraction, is carried out by 2 researchers independently of each other. Studies are included according to the following criteria: the study deals with the implementation of video consultation in the form of video-based consultation via web in real time between the patient and the medical or psychotherapeutic service provider in outpatient care, and the study focuses on useful fields of application and promoting/inhibiting factors. Since a very high heterogeneity of the results is assumed, a qualitative information synthesis of the results of the included studies on possible implementation factors, encouraging features, and barriers is performed using the program MAXQDA (VERBI).

Focus Groups (C)

At the end of the first phase, 5 focus group discussions with relevant stakeholders on potential applications of video consultation and barriers to its use are conducted. The interim results of the claims data analysis and the systematic literature review are reviewed in order to achieve a well-grounded basis for the development of the interview guidelines for the focus groups.

Due to the uncertainties associated with the coronavirus pandemic regarding the possibility of face-to-face meetings, all focus groups are conducted online. In 2015, Abrams et al [19] demonstrated that focus groups in an audio-visual format can achieve a similar richness of data as physical face-to-face focus groups, distinguishing them from purely written text-based forms.

Relevant stakeholders include representatives of insured individuals, physicians as well as psychotherapists, and the SHIF perspective. In order to adequately take into account the differences between urban and rural areas, for each region type 2 focus groups are conducted for both the perspective of insured individuals and that of the service providers in order to include content relevant to urban and rural regions.

The recruitment of physicians and psychotherapists is carried out by the participating ASHIP, and interested insured persons are recruited by a cooperating self-help association. Participants of the payer perspective are recruited by the participating SHIF themselves. The composition of the focus groups with insured individuals should take into account characteristics such as age group, gender, presence of a chronic disease, and video consultation users/nonusers. For the focus groups with physicians and psychotherapists, relevant characteristics are age group, gender, and specialist group. The focus groups are led by a team of moderators, as described by Krueger and Casey [20], and take approximately 60 minutes per stakeholder group. The basis for the focus groups are semistructured interview guides that are derived from the content-related preliminary work of the systematic literature research. The course of the focus groups is video-recorded and transcribed afterward. On this basis, a qualitative content analysis according to Mayring [21] is carried out using the software for qualitative data analysis MAXQDA (VERBI).

Design of the Surveys Including Discrete Choice Experiments (D-F)

Preferences play an increasingly important role in health care decision-making [22]. However, the complexity of health-related decisions poses a challenge due to the multitude of alternatives available. In such circumstances, the DCE method has been widely used for preference elicitation in health care [23]. DCEs are based on Random Utility Theory, a theory of human preference behavior that assumes respondents behave in a manner that maximizes their utility. Therefore, econometric models based on Random Utility Theory can be used to analyze data from DCE surveys. It is assumed that services or goods can be valued on the basis of the characteristics (called attributes) that determine them [24]. DCEs usually consist of a number of choice sets that represent hypothetical options as

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alternatives. Each choice set is composed of a set of attributes and each attribute is described by values (called levels). By asking respondents to choose between the choice alternatives, preferences are determined. The respondents' choices are then used to derive the importance of the attributes and levels in terms of overall utility [25]. DCEs support the design of health programs and the prediction of demand and acceptability [23].

Based on the preliminary work, namely literature searches and focus groups, the survey and the DCEs are constructed. The DCEs are designed to elicit preferences for the design of video consultations of insured persons as well as physicians and psychotherapists. Relevant attributes and their levels are therefore determined in the first study phase. Following, choice alternatives are modeled using SAS (version 9.4; SAS Institute Inc).

The choice set (which covers multiple choice alternatives) should take into account design recommendations by Huber and Zwerina [26]. Generally, choice sets should not contain any stimuli for which 1 option is clearly advantageous and therefore does not require weighing. According to The Professional Society for Health Economics and Outcomes Research—ISPOR—recommendation on conjoint analyses, the maximum number of pairwise comparisons (tasks) that each respondent should answer should be between 8 and 16 [27]. In order to limit the number of stimuli per respondent, it is possible to use optimal designs in which, based on certain quality criteria, an appropriate subset (fractional design) is selected from the set of theoretically possible stimuli (full-factorial design) and thus a minimum number of pairwise comparisons is required [28]. Additionally, if the number of calculated tasks exceeds ISPOR recommendations, the questionnaire could be split into 2 or more blocks as response efficiency could decrease otherwise [27].

The DCE is embedded in a survey which is structured into three sections: (1) possible barriers and promoting factors for the use of video consultations, (2) preference survey using DCE, and (3) sociodemographic information. Additionally, for the insured individuals, health-related information is requested and for the physicians or psychotherapists, information on the medical profession are asked in the third section.

Prior to the distribution of the questionnaires, they are subjected to a pretest and revised accordingly. The methods of think-aloud and probing are used to determine comprehensibility, manageability, completeness, and the time required for completion [29].

To determine the sample size, the rule of thumb according to Reed and Orme [30] is applied. Under the further assumptions of generating multiple questionnaire versions with different blocks, an estimated 10% response rate, and in order to enable differentiated statements about subgroups, around 33,000 insured persons have to be contacted. Applying the previously described rule of thumb, possible blocking, 10% response rate, and possible subgroup analysis for the survey of physicians and psychotherapists 31,900 individuals are contacted. The final sample size depends on the results of claims data analysis and systematic literature review in order to form relevant subgroups.

The surveys are carried out with randomly selected insured persons—under the application of defined inclusion and exclusion criteria—by the participating SHIF and with all physicians as well as psychotherapists of the ASHIP who are allowed to provide video consultations in principle.

Inclusion criteria for the survey of insured individuals contain (1) insurance by 1 of the 3 participating SHIF, (2) 18 years or older, and (3) place of residence in 1 of the 4 selected regions as done in claims data analysis (A). Insured persons under legal guardianship, with a high need for nursing care ("Pflegegrad 4" and higher), nursing home residents, patients in palliative care, patients diagnosed with dementia, and insured persons whose data may not be used for research are excluded.

The participating SHIF and ASHIP contact their insured and members by means of a short letter, which includes further information on the study, the survey itself for paper-participation as well as an invitation to participate web-based via QR code.

The survey starts in November 2022 and ends at the end of March 2023. If necessary, a reminder is used to increase the response rate.

The survey is analyzed in terms of possible barriers and preferences. Econometric analysis follows the ISPOR guidance for DCEs [31]. Descriptive procedures as well as logistic regression analyses are carried out. The target variable of the DCE is the subjects' choice decision for 1 of 2 stimuli. Depending on the model, the attributes or their characteristics as well as sociodemographic and health-related characteristics of the test persons are included as explanatory variables. A mixed logit model is estimated. A hierarchical Bayesian model is used for the main analysis.

Workshop With Stakeholders (G) and Health Policy Recommendations (H)

Finally, a stakeholder workshop (G) is performed to combine all findings of prior sections and summarize results. Participants include 1 representative each from the participating associations of SHI-accredited physicians, the participating SHIF and the participating cooperation partners of the self-help associations, patient representatives, the German Association of Medical Specialists, and the Professional Association of German Internists. Participants are asked to sign a declaration of consent. The workshop is held in person with an estimated duration of 6 hours and is led by a team of moderators from the University of Duisburg-Essen.

Finally, the results of the workshop are implemented in a blueprint with health policy recommendations (H).

Ethical Considerations

The study received ethical approval from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen on September 27, 2022 (reference: 21-10283-BO). For the purpose of claims data analysis, the University of Duisburg-Essen only has access to aggregated data. There is no possibility of participant identification. The data collected in the focus groups is considered pseudonymized, with only statements needed in connection with the project being stored. The list of participants is deleted after the focus groups have been conducted and the

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audio recordings are deleted after transcription. For the participation in focus groups participants are compensated with 50 Euro (US $49.98) for insured individuals and 120 Euro (US $119.952) for physicians as well as psychotherapists. To take part in the surveys or the workshop, participants are asked to sign a declaration of consent.

Results

As the study runs until March 2024, the methodological approach used in this study is the focus of this paper. The claims data analysis (A) demonstrates that video consultation has had almost no relevance in outpatient care in the German health care system from 2017 to 2019. This changes significantly with the beginning of the COVID-19 pandemic. Displaying the initial situation gives insights into areas of application and user groups which are published separately. Furthermore, the analysis is a necessary basis for further work.

The systematic research (B) on possible applications of video consultation and possible hurdles as well as promoting factors also aims to identify possible attributes and their levels for the DCE. Challenging aspects of the video consultation have been identified. In-depth descriptions of hurdles and promoting factors on the use of video consultation are published separately.

Focus groups (C) complement the systematic literature research to discuss the relevance of the attributes identified, as well as the levels and their scaling, which supported developing additions or modifications if necessary. They have been conducted with insured persons as well as with physicians and psychotherapists from rural and urban regions. This was supplemented by a focus group with representatives of SHIF.

The conception of the surveys (D) to collect preferences for the design of video consultations by insured individuals as well as by physicians and psychotherapists has been completed. Extensive pretests have been conducted. In addition, the questionnaires have been implemented on the web-based survey platform Question Pro for the additional option of digital participation, so that the recruitment of survey participants could begin in the fourth quarter of 2022 and was completed in March 2023 (E). The data are analyzed since April 2023 (E).

Discussion

Video consultation is a promising tool in medical and psychotherapeutic care, as shown by its increasing use with the onset of the COVID-19 pandemic in claims data analysis (A) and more generally in light of advancing digitalization [32]. The study is directly designed for practical use to further develop the potential of video consultation in Germany. To the authors' knowledge, a comprehensive approach to analyzing the use and provision of video consultations from the providers' perspective on the one hand and the perspective of insured individuals on the other hand in 1 study has not been conducted to date in Germany. The results of this study will specifically address the conditions (expectations of form and content, inhibiting and promoting factors) under which the insured individual accepts the digitalization of their medical consultations and which application possibilities of video consultation are accepted by medical and psychotherapeutic service providers (differentiated by specialist groups). This is accomplished by taking into account possible barriers and considering the differences between rural and urban regions in order to be able to apply the defined recommendations in a targeted manner. Recommendations for legal and sublegal adjustments are then derived from this.

However, as this study addresses the German SHI, the legal framework might differ elsewhere; thus, our results may not be completely applicable to other countries. The subject of this study is video consultation and does not include telephone care or other types of telemedicine, which limits the perspective of this research.

Regardless of the topic addressed by this study (video consultations in outpatient medical care in Germany), the iterative and mixed methods approach used in this study protocol is also suitable for a variety of other research projects. The use of a systematic literature review as a first step to examine settings for video consultation and possible barriers ensures a systematic inclusion of the current state of the art while also taking into account the quality of the literature. The explorative elicitation of initial information on the basis of qualitative methods (in this case focus groups, which can also be supplemented or replaced by expert interviews) in the first study phase as a solid basis for the second study phase, in which the exploratively collected theses are to be examined quantitatively, is suitable for a wide range of inquiries in health services research. Furthermore, as urban and rural settings are explored, the study in general contributes to a better understanding of urban and rural differences in preferences in the provision of digital care. This can help policy makers in finding suitable solutions for both the rural and the urban population.

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Data Availability

The data sets generated or analyzed during this study are not publicly available due to data protection reasons.

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Authors' Contributions

All authors contributed to the study organization and conception of the surveys. LK and TH were the major contributors to writing this manuscript. All authors contributed to the manuscript in different stages and also read and approved the final version.

Conflicts of Interest

None declared

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Abbreviations

ASHIP: associations of statutory health insurance physicians
DCE: discrete choice experiment
GP: general practitioner
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting for Systematic Reviews and Meta-Analyses
SHI: statutory health insurance
SHIF: statutory health insurance fund

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Protocol

Participation in Advance Care Planning Among Medically At-Risk Rural Veterans: Protocol for a Personalized Engagement Model

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Abstract

Background: Many of the challenges in advanced care planning (ACP) conversations are linked to the waxing and waning progress of serious illnesses. Conversations with patients about future medical care decisions by a surrogate decision maker have historically been left until late in the patient's disease trajectory. These conversations often happen at a time when the patient is already very ill. The challenge in effective early ACP and serious illness conversations is to create a situation where patients appreciate the link between current and future medical care. Setting the stage to make these conversations more accessible includes using telehealth to have conversations at the patient's place of choice. The personalization used includes addressing the current medical and social needs of the patient and ensuring that expressed needs are addressed as much as possible. Engaging patients in these conversations allows the documentation of patient preferences in the electronic health record (EHR), providing guidelines for future medical care.

Objective: The objective of our telehealth serious illness care conversations program was to successfully recruit patients who lacked up-to-date documentation of ACP in their EHR. Once these patients were identified, we engaged in meaningful, structured conversations to address the veterans' current needs and concerns. We developed a recruitment protocol that increased the uptake of rural veterans' participation in serious illness care conversations and subsequent EHR documentation.

Methods: The recruitment protocol outlined herein used administrative data to determine those patients who have not completed or updated formal ACP documentation in the EHR and who are at above-average risk for death in the next 3-5 years. The key features of the telehealth serious illness care conversations recruitment protocol involve tailoring the recruitment approach to address current patient concerns while emphasizing future medical decision-making.

Results: As of September 2022, 196 veterans had completed this intervention. The recruitment method ensures that the timing of the intervention is patient driven, allowing for veterans to engage in ACP at a time and place convenient for them and their identified support persons.

Conclusions: The recruitment protocol has been successful in actively involving patients in ACP conversations, leading to an uptick in completed formal documentation of ACP preferences within the EHR for this specific population. This documentation is then available to the medical team to guide future medical care.

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KEYWORDS

advance care planning; chronic disease; end-of-life care; health care decision; medical decision-making; recruiting; shared medical decision-making

Introduction

Overview

Advance care planning (ACP) involves dialogues between patients and their health care providers regarding the patient's values and health care preferences [1-3]. These discussions provide a foundation for health care providers and surrogate decision makers to make informed decisions in situations where the individual is unable to do so. Veterans Health Administration (VHA) offers ACP as a named health care benefit for enrolled veterans [4]. Advance directives (ADs) are documents outlining instructions for future medical care and go into effect only if an individual is not capable of making medical decisions or communicating their wishes [3]. Not all ACP sessions result in the completion of an AD, nor is completing an AD always the goal of specific ACP discussions [1,2]. This project focuses on increasing ACP participation and documentation among VHA enrolled veterans.

ACP is a key factor in end-of-life care, yet it is an underused intervention [5]. Among US veterans, it is estimated that 7.1 million of the 9.6 million veterans who are enrolled in VHA do not have ACP preferences documented in their medical records [1,6,7]. Work on AD discussions by Matthieu and colleagues [1] shows only 5.2% of all VHA beneficiaries had a documented ACP discussion in 2020.

Research suggests older adults may not be informed about the ACP process and may assume that physicians initiate conversations about advanced illness or end-of-life care [5,8]. Additionally, some older adults might lack adequate health literacy to understand the contents of end-of-life care conversations or the risks related to treatments they may receive throughout the illness trajectory [9-12]. Communication about end-of-life preferences may also be difficult if the health care provider or the patient is reluctant to initiate discussion or the provider lacks sufficient time to engage in the conversation [1,9,13,14]. Yet there are benefits to ACP, such as reducing uncertainty when a patient is unable to communicate their wishes, receiving care that is more congruent with personal preferences, and including care that is more consistent with the spiritual cultural needs of patients and their families [14-17]. Additionally, for specific high-risk populations, the presence of an advanced care plan before hospital admission has been shown to decrease intensive care unit length of stay [8,18,19].

VHA supports multiple approaches to facilitate ACP conversations between patients, surrogate decision makers, and providers, including, but not limited to, the serious illness care conversation (SICC), the goals of care conversations, and the Life-Sustaining Treatment Decisions Initiative [4,20]. The National Center for Ethics in Health Care is at the forefront of making ACP information available to veterans and the Veterans Administration's (VA) clinical and nonclinical workforce. National Center for Ethics in Health Care has been central to providing guidelines and training to support ACP practices within VHA. Enterprise-wide initiatives, such as advance care planning through group visits, are additional offerings at various VA sites that are successfully increasing access to ACP [1,21]. VHA has been promoting life-sustaining treatment (LST) as the AD of choice for VHA; however, the limitation of LSTs to VA health systems restricts the transferability of the veteran's wishes to community-based hospitals and providers. LSTs are ADs that are only valid in VA health facilities and are not widely accepted outside of VHA. Despite known benefits and resources for providers and veterans for engaging in ACP, documentation of ACP discussions in veterans' electronic health records (EHRs) remains low [1].

Challenges of ACP in a Rural Veteran Population

Rural veterans living with serious illness, compared to their urban peers, have increased barriers to ACP within VHA and community health care systems [15,22,23]. Serious illness has been defined as a "health condition that carries a high risk of mortality and either negatively impacts a person's daily function or quality of life or excessively strains their caregivers" [24]. Veterans who rely on VHA for care are often sicker, tend to live in rural areas, and face significant travel challenges regarding broad geographic distance and seasonal weather impacting travel safety [22,23]. While the VA Mission Act of 2018 has increased access to medical care for rural veterans [25], formalizing ACP processes still lags for rural veterans [1,26]. Access to medical care is a concern for many rural veterans, and with fewer care options, there are fewer opportunities to talk about serious illness and advance care planning [15,27]. Urban-dwelling veterans often face similar challenges, so any improvements to access through these interventions have the potential to benefit all veterans.

Many rural veterans use both VA and community-based health care [28,29], indicating a need for ACP that is translatable to both VA and community-obtained health care. As such, this intervention seeks to promote ACP and offers support to veterans wishing to complete whichever formal AD documentation format is best suited for their unique health care needs. For veterans, whose primary care location is VA, LST offers a nuanced format for documenting future care decisions. For those, whose primary site of care is outside VA, the state-based AD, such as the durable power of attorney form, should be filled out.

SICC acknowledge that the disease is unlikely to resolve, and managing symptoms and medical crises is an ongoing challenge for patients and their support team [2-4,30]. While SICCs are widely applicable, they are an underutilized structure for conversations between a provider and a patient who is focusing on living with a serious illness [9,31]. The telehealth serious illness care conversation (tSICC) adapts many of the tenets of SICC for a telehealth intervention while utilizing VA clinical standards designed for ACP [32]. These frameworks have been adjusted to suit conversations with veterans in their homes who are not expected to be in a current medical crisis [4,32]. The

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provider talks with the patient about their values and priorities for health care, as well as how those might change in the context of advancing illness with or without an acute medical crisis. The goal is more than simply discussing resuscitation status; but rather, it is to develop a personalized plan for medical care as the patient's illness progresses. While SICC acts as an entry into the ACP process, these types of conversations often happen too late in a person's medical trajectory [16,31]. Early engagement allows for relational decision-making for veterans and their families [33], accommodating the more complex information about the variable clinical trajectory of older and more seriously ill veterans.

Personalized approaches have been shown to promote engagement in the ACP process [5,34]. Our project tailored the recruitment strategies for rural veterans, recognizing they have more barriers to receiving end-of-life health care, including limited access to hospice and palliative care services [15]. This manuscript outlines a recruitment protocol for rural, seriously ill veterans into a quality improvement (QI) project at a veteran healthcare system in the Midwestern United States.

To optimize integration of veteran-specific values, this QI project used community-based participatory research (CBPR) practices [35-37]. According to National Institutes of Health, CBPR involves researchers and community members to combine "knowledge with action to improve health outcomes and eliminate health disparities" [38]. To accomplish our goal of developing a veteran-centric approach to engaging in ACP, we established a team that included veterans and veterans' proxy decision makers (through a Veteran Engagement Panel [VEP]), an advocacy expert, social workers, licensed VA medical providers, and veteran service officers. The VEP was convened specifically to provide guidance for the pilot, accompanying the project from institutional review board (IRB) approval through the development of the intervention and analysis of preliminary results. The VEP was integral to the development of veteran-facing materials, including flyers and other recruitment materials, as well as the development of metrics reflecting veteran priorities. Panel members shared their insights on how to personalize all aspects of the study to support the goal of making the process relatable to the veteran population.

A Telehealth-Based, Multimodal, and Veteran-Centric Intervention

Improving access and decreasing barriers were driving forces in our QI project: develop and disseminate a veteran-centric clinical protocol for ACP through tSICC. Telehealth visits expand access for patients who face barriers to receiving medical care [39-41]. However, technology issues limit the use of telehealth as an equitable or appropriate care mechanism [39]. While VHA has been using telehealth for many years, rural veterans' limited access to high-quality broadband service can be a barrier to telehealth services [42,43]. Evidence has suggested veterans with a serious illness were satisfied with telehealth encounters, as these types of appointments improved their access to care and diminished the need for travel [39].

Information About the tSICC Pilot

Our project targets at-risk veterans with no ADs or out-of-date AD documentation in veterans' EHRs. Our team obtained funding through VHA Office of Rural Health for a QI project within VHA; we are a rural-serving Midwest VA medical center. We present here a systematic description of a stakeholder informed, multimodal recruitment strategy for a clinical intervention for ACP.

Setting for the Development of the Engagement Strategy

Our QI project sought to determine the appropriate timing and setting for a tSICC within a veteran's clinical trajectory. We had a driving slogan: "the right care, for the right veteran, at the right time." The steps chosen for recruitment were consistent with local IRB guidelines, local and national VA practices, and were influenced by veteran feedback [32]. To our knowledge, there is no specific literature outlining the development of a veteran-centric recruitment model for telehealth-based ACP.

Objective

This manuscript describes a recruitment protocol for engaging veterans who have not been reached through existing opportunities to participate in a tSICC and ACP within VHA.

Methods

Study Context

This paper reports on the methodology of an initial pilot study that is part of a larger clinical work-flow QI project to increase veteran engagement in and documentation of ACP within VHA. Our team is developing a telehealth-based approach to an existing clinical intervention, the SICC, with a focus on allowing the veteran and their chosen support persons to participate in ACP on their own timeline and in a setting that is convenient and comfortable for them. This is especially important for rural veterans who may face a significant travel burden to access care at VHA. Veterans and their families often accommodate this burden by cramming many of their medical appointments into one day. However, reducing the travel burden can lead to a busy, medically-focused schedule and increased fatigue. The lack of time during clinical visits is a barrier for interventions like SICC that promote ACP [31,39,44]. By removing this clinical intervention from an already taxing day and creating a space for this important conversation to occur outside of stressful clinical visit days, we hypothesized that veterans would be better able to participate in ACP. Consequently, as this discussion is documented in the EHR and veterans are guided on how to have future ACP conversations, there is a prospect for increased efficacy in future discussions of ACP among veteran participants and their VHA medical providers and social workers.

Engaging participants in research or QI studies can be difficult, especially if participants are seriously ill or the study is focused on a sensitive issue such as ACP. Further study of clinical interventions can help identify better strategies for recruitment and participation in research focused on ACP and palliative care [44,45]. Studies have shown that using multiple strategies in the recruiting phase may help increase participation related to

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ACP [46-48]. Chau and colleagues [46] demonstrated that mailing information along with making phone calls to participants is an effective method for increasing their willingness to engage in the ACP process. For this QI project, an assortment of methods were used to recruit participants to the ACP process.

Study Design

The tSICC intervention was implemented in a medium-sized VA health care system in a Midwestern city in the central United States with a regional metropolitan population of 171,000. VHA EHR system was used for population-based identification of medically at-risk veterans. The pilot cohort was recruited from July 2021 to October 2021 using a project-developed risk metric that identifies and categorizes by risk level those who might experience a serious health episode in the next 5 years. Veterans were identified as not having an AD or other VHA-based ACP documentation in their EHR within the last 2 years. Veterans were receiving care through VHA but may also be supplementing it with community-based care. The recruitment goal was for 200 veterans to participate in the intervention.

While the intervention was planned as a telehealth intervention, recruitment was initially done during a clinical appointment starting in April 2021. The project team quickly identified that in-clinic recruitment was difficult due to existing workflows that did not easily integrate the recruitment process. This experience is noted in the literature, with previous works [33,40] showing that having ACP conversations as part of the clinical workflow is challenging and does not engage populations that may have significant comorbidities and more pressing medical concerns. In October 2021, the study team transitioned to an entirely remote, multimodal recruitment process.

Applying CBPR principles to further enhance veteran-centricity, veteran participants were invited to take part in a concise survey of their experience in both the recruitment process and the intervention. Evaluation questions from the CollaboRATE survey, based on core elements of shared decision-making [49], were used in a postintervention call to assess if participants felt informed about the purpose of the intervention and if they felt they were part of the decision-making process [50]. The collaboRATE questions have been delivered through multiple modalities (eg, paper, digital tablet, and social media) [50,51], which makes this short survey a viable option for individualized projects such as our QI pilot. Feedback from these questions was an important element in adapting the pilot study to veteran-identified concerns and wishes.

Study Protocol

The required steps of local IRB and VA offices at the time of this intervention development were mail notification before placing up to 3 unsolicited phone calls and leaving up to 1 unsolicited voicemail. The parameter aligns with evidence that 3 phone calls promote engagement and minimize fatigue [34]. In addition to institutional guidelines, the recruitment strategy was shaped by our work with the VEP, which identified 3 concepts that became guideposts for the recruitment strategy: personalization, continuity of information, and the benefit of participating in ACP now. See Figure 1 below for an overview of the major steps in our pilot project. Figure 2 offers a more detailed view of our process.

Figure 1. Overview of the quality improvement recruitment process. ACP: advanced care planning.

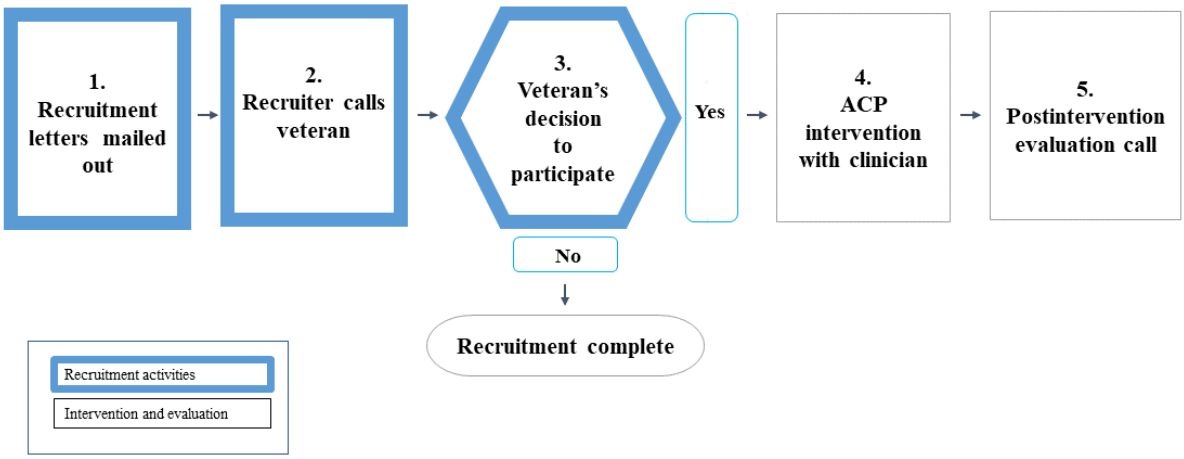

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Figure 2. A detailed view of the personalized recruiting process. ACP: advanced care planning; IRB: institutional review board; tSICC: telehealth serious illness care conversations.

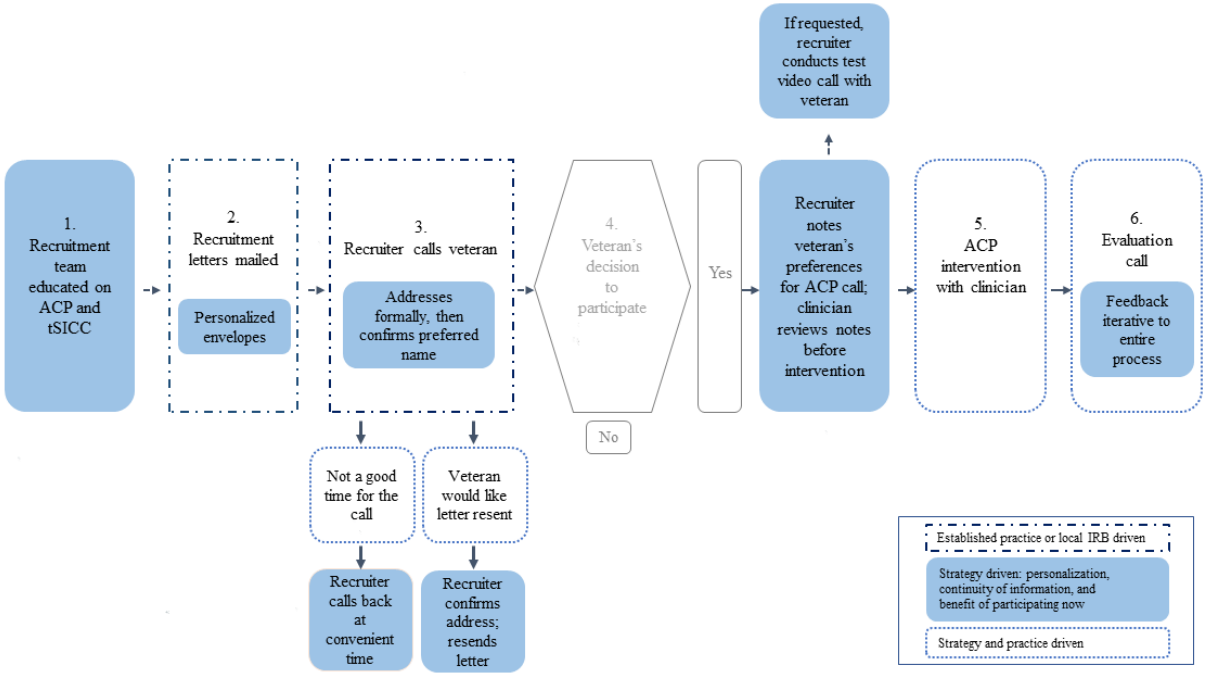

To personalize the mailing phase of recruitment, special attention was given to the items being sent to the veteran. Large manilla envelopes were hand-addressed in blue ink to appear unique among other pieces of mail and later be referenced by color and size during recruitment phone calls.

Several strategies were available during phone recruitment to personalize the experience for the veteran. The recruiter, trained on the components of ACP, reviewed the veteran's medical record before the call to ensure familiarity with the veteran's preferred name and correct address, identify any recent major medical events, and obtain the name of the veteran's emergency contact or next of kin (inviting the veteran to include them in the tSICC if they wished). During the call, attention was paid to the veteran's health literacy and comfort with technology. The recruiter estimated the veteran's understanding of the project and if the veteran might need technical assistance (ie, in preparing for video chat) to participate in the telehealth intervention. When needed, further explanation was provided, or plans were made to provide technical assistance before the intervention.

Continuity of information can be challenging in any large health care system, and veterans may feel that information is not shared among members of the health care team. This was reported as a negative experience by the VEP and indicated decreased confidence in both competency and compassion from their care team. To address that concern, the recruitment team used a formal hand-off to ensure that concerns and topics raised by the veteran during the recruitment call were passed on to the next team member. During recruitment, veterans were informed that they would have an opportunity to talk with a VA medical provider about their general concerns related to ACP. Concerns shared during the recruitment phone call would be relayed to the provider and could be discussed further during the telehealth visit.

The final concept proffered by the VEP regarded the benefit of this ACP intervention and said that every interaction with the veteran should be of potential benefit. Early in the disease process, veterans are active decision makers, and tSICCs are grounded in patient autonomy. The tSICC protocol offers ACP at the veteran's convenience rather than during a busy clinic schedule or a time of medical crisis, creating time and space for veterans to ask for help with medical decision-making. In line with the project's objective to enhance veteran comprehension of ACP and the support available from VA, veterans were informed that the health care provider involved in this intervention could assist them in translating their values, goals, and wishes into future treatment decisions, all of which would be recorded in their VA EHR. This included how completing an AD can be a significant step in gaining agency in their future medical decision-making.

How the Principle of Tailoring Follows Through Subsequent Steps

Veterans successfully recruited for the project participated in the tSICC intervention and a postintervention follow-up call. During the intervention, the VA provider was sure to ask about topics important to the veteran and their family that may have been identified during the recruiting phone call. The VA provider then documented the ACP conversation in the veteran's EHR. As needed, appropriate referrals were made to VA providers, and relevant resources were shared with the veteran.

Following the intervention, veterans were invited to participate in the evaluation of the recruitment and intervention protocols. To assess the appropriateness, timeliness, and usefulness of the intervention, there was a 3-item questionnaire as well as a query of their opinion about the intervention and any suggestions they may have for improving the process. An iterative process was used to incorporate input from veterans that shaped continued recruitment procedures. The concluding phone call also provided

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a chance to address any inquiries regarding ACP or the tSICC and to ensure the completion of any previous tasks.

Analysis of Project-Generated Engagement Data

Data collection on recruitment focused on monitoring the number of attempts, the results of these attempts, and veteran-reported satisfaction with the recruitment process. The structure of the phone call outcomes gave insight into the challenges of reaching veterans at home (Textbox 1).

Textbox 1. The possible outcomes for telephone recruiting.

Outcomes of phone calls

- Message left
- Did not leave message
- Telephone problem
- Wrong number or disconnected
- Deceased
- Call back requested
- Declined
- Asked for more information
- Resend letter
- Agreed to participate
- Refused to participate

If the recruiter got a message "No longer in service," "Busy signal," or "Unable to leave a message," it was not logged as first contact; those were simple telephone problems or technical issues. Some cellular services provide a message if the call cannot be completed as dialed. If the issue was telephone company-related and not customer-related, it was not considered a contact.

Ethical Considerations

This project was determined as quality improvement nonhuman participants research by the University of Iowa IRB for January 2020 (#201911479), March 2020 (#202002148), and April 2021 (#202102175). We did not require a waiver or informed consent as this intervention was nonhuman subject research. All study data for this QI project has been deidentified, and no personal information has been reported in this paper. There was no compensation since this project was nonhuman subject research.

Results

This project seeks to understand how VHA can deliver ACP that supports "the right care, for the right veteran, at the right time." Here we report the results of the feedback received from veterans in the development of the recruitment process and its integration into our ongoing recruitment for this multiyear project. VEP and intervention participants provided the insight that 3 concepts should be at the forefront of our approach: personalization, continuity of information, and a benefit to the veteran now.

Personalization occurred at all levels of the recruitment protocol. Our team aimed to have mailed materials "stand out" against mail that could otherwise be perceived as junk by using larger envelopes and hand-addressing them. We also customized recruitment discussions (and subsequent intervention discussions) to align with the veteran's ACP experiences to date. Further, project team members recognized and addressed the individual needs of the veteran as identified in the EHR and from previous interactions with the project team. By not repeating already shared information, veterans, and staff saved time. This allowed conversations to move to solutions for veterans' concerns and building next steps for planning more efficiently.

Immediate benefits to veterans from the intervention included: provider documentation of veterans' values and personal health goals to be used as guidance to future proxy decision makers; updating incorrect or incomplete next-of-kin information stored in the EHR; and assistance in the completion of AD to be entered into the EHR. Further, increasing a veteran's understanding of ACP and how VHA can help the veteran with future medical decision-making was a vital component of the clinical intervention and, as such, was integrated into every contact, starting at recruitment. To facilitate this, our recruiter was knowledgeable of ACP principles and the tSICC intervention and had the necessary resources to explain the project and the background verbally in electronic and paper form.

The impact of the recruitment strategy was that of the 343 veterans successfully reached during recruitment by phone, 199 agreed to participate, and 196 completed the intervention. From this group, 146 completed the post call evaluation. Veteran satisfaction with the intervention is reported in Table 1. Notably, 50% (98/196) of veterans who completed the intervention then requested to have AD forms mailed to them for completion. When asked whether the timing of the tSICC was appropriate and timely for them, 66.4% (97/146) of respondents agreed it was.

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Table 1. Veterans' satisfaction with a telehealth Serious Illness Care Conversation intervention (N=146).

Veteran agreement with elements of satisfaction	Value, n (%)
Provider understood patient's values	
Rural[a]	86 (76.1)
Urban[a]	23 (65.7)
Total	109 (74.7)
Provider includes what matters most	
Rural[a]	83 (73.4)
Urban[a]	22 (66.7)
Total	105 (71.9)
Appropriate timing of conversation	
Rural[a]	75 (66.3)
Urban[a]	22 (66.7)
Total	97 (66.4)

[a]Rural-Urban Commuting Area Codes guidelines were used to determine rural or urban status [52].

The intervention and related data collection for the ongoing QI project are expected to be completed in the fiscal year 2024. The results of that data are forthcoming.

Discussion

The results of this QI project support the hypothesis that veterans are more likely to engage in ACP if the conversation is timely, not perceived as burdensome, and addresses veterans' current medical and related concerns [5,14,41]. The recruitment method outlined herein offers personalized strategies to engage veterans in ACP outside of a clinical setting that were informed and evaluated by veterans.

The QI team adapted VA trainings on advance care and serious illness conversations to be used in a short, home telehealth setting and focused on identifying a process to engage veterans in a way that fits their unique needs. The digital divide was identified as a significant barrier for rural veterans [42-44]. Our findings are consistent with previous results, which show that offering lower tech communication options as well as support for connectivity in the form of personalized assistance lowered systemic barriers to access [43,46].

Data reported in the literature and gathered from our dedicated VEP underscores the importance of the veteran's perception that their unique needs and perspectives are important to the ACP process [39]. This both serves to build rapport and to tailor subsequent information offered in the course of the intervention about ACP. Particular focus was on how engaging in ACP now can help inform their current medical decision-making as well as the benefit of formal documentation of ACP within the veteran's EHR [9,14].

A notable limitation of this study is that while we documented increases in ACP behaviors across the sample, we did not capture uniform, preintervention data that may have provided insight into the unique barriers and facilitators that influence an individual's engagement in ACP. Another limitation is the study's small size, at 1 Midwest VA medical center. This important limitation will require further study before any generalization, ideally as a multisite pilot.

The recruitment strategies used over the course of this QI project support veterans in accessing and understanding ACP by addressing both common and unique barriers to engaging in ACP. Furthermore, this project demonstrates that telehealth is a viable mechanism to provide meaningful and satisfactory recruitment of veterans into the ACP process. Overall, we show that personalization in recruitment allows veterans to see that their needs are being met by VHA services. Demonstrating sensitivity to current veteran needs can increase access to the delivery of ACP. This approach is clinically feasible as a telehealth intervention. We demonstrate that a telehealth protocol with personalization and continuity of communication increases the engagement of veterans in clinical interventions about sensitive issues such as ACP and SICC. Engaging veterans in these conversations and documenting the results in the EHR is the first important step in ensuring veteran-centric care in times of medical crisis.

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Conflicts of Interest

None declared.

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Abbreviations

ACP: advanced care planning
AD: advance directive
CBPR: community-based participatory research
EHR: electronic health record
IRB: institutional review board
LST: life-sustaining treatment
QI: quality improvement
SICC: serious illness care conversations
tSICC: telehealth serious illness care conversations
VA: Veterans Administration
VEP: Veteran Engagement Panel
VHA: Veterans Health Administration

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Protocol

Fostering Digital Life Skills Through Social Media With Adolescents in 6 German States: Protocol for an Accessibility Study According to the RE-AIM Framework

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Abstract

Background: Social media is essential in the lives of adolescents, with 97% of US teenagers engaging daily. While it facilitates communication, learning, and identity development, it also poses risks like harmful content exposure and psychological distress, particularly for adolescents in their critical developmental stage. Teaching digital life skills innovatively counters these risks, adapting traditional competencies such as decision-making, problem-solving, creative and critical thinking, communication, interpersonal skills, self-awareness, empathy, and emotional and stress management to digital challenges.

Objective: This study evaluates the accessibility of the "leduin" program, a novel intervention designed to impart digital life skills through Instagram. The program aims to leverage social media's educational potential, focusing on effective strategies to engage adolescents. Emphasizing accessibility is crucial, as it determines the program's overall impact.

Methods: The leduin program, developed through intervention mapping, applies behavior change techniques via social media for 9th and 10th graders. It is a 14-week spaced learning curriculum with daily sessions <5 minutes. Emphasizing the "reach" aspect of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) model, the recruitment targets diverse educational settings across 6 German states, aiming for inclusivity. Recruitment will involve schools, youth centers, and therapeutic facilities. The study seeks at least 128 participants, a calculated minimum to detect medium-sized effects in the quasi-experimental design and explore varying engagement levels and program responses. Data collection includes preintervention, postintervention, and 6-month follow-up surveys, using multilevel regression, latent growth models, and qualitative analysis to extensively assess reach and gain first insights on effectiveness, acceptance, implementation, and maintenance. The study aims to reveal key factors influencing program participation and interaction; a detailed analysis of engagement patterns will reveal the effectiveness of the recruitment strategies and barriers to participation. Additionally, initial indications of the program's impact on life skills, social media–related skills, health status, risk behaviors, and academic performance will be analyzed.

Results: Recruitment was planned from May 2023 until the beginning of the leduin program in October 2023. As of March 2024, we have recruited 283 participants.

Conclusions: The leduin program stands as an innovative and essential initiative in adolescent health promotion, harnessing the power of social media to teach important digital life skills. This study highlights the critical role of accessibility in the success of social media interventions. Effective adolescent engagement strategies are imperative, as they dictate the overall impact of such interventions. The insights gained from this study will be instrumental in shaping future programs, laying groundwork for a subsequent, more comprehensive cluster-randomized controlled trial. The study's design acknowledges the limitations of the current quasi-experimental approach, including the anticipated sample size and the absence of a control group, and aims to provide a foundational understanding for future research in this field.

Trial Registration: Deutsches Register Klinischer Studien DRKS00032308; https://drks.de/search/de/trial/DRKS00032308

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KEYWORDS

adolescents; social media; prevention; life skills; RE-AIM-framework; mixed-methods; digital life; accessibility; innovative; utilization; teaching skill; empower; digital skill; life skill; German; digitalized; adolescent; adolescent health; study protocol; validity; innovation; leduin-program

Introduction

Background

Social media, a staple in the lives of 97% of US teenagers [1], facilitates communication, learning, and identity development for adolescents [2-5]. However, the functions and the lack of censorship on these platforms can lead to risks such as addiction, psychological distress, and exposure to harmful content [6-8]. Given the ongoing developmental stage of adolescents [9], they frequently lack the essential social-emotional and cognitive skills required for functional and constructive engagement with social media [10]. These challenges underscore the importance of building social media literacy, a crucial skill that enables adolescents to navigate digital content critically and responsibly [11]. Enhancing media literacy involves teaching adolescents to understand and manage the psychological impacts of digital interactions, including the development of self-regulation and critical thinking skills [12-14].

The widespread use of social media also offers a unique opportunity for preventive health interventions. As a cost-effective platform with a broad reach [3,15-17], social media can play a pivotal role in promoting mental and physical health [18-22]. Its accessibility makes it particularly valuable for reaching socially disadvantaged adolescents, who may engage more frequently with digital platforms, often in dysfunctional ways [23-26]. Thus, social media emerges as a critical tool in enhancing equity in health promotion.

While recognizing the potential of social media in adolescent health promotion, the limited evidence base highlights the need for careful consideration of practical, methodological, and ethical implications [22,27-30]. Current studies focus on engaging content and tailored interventions for diverse needs [20,29,31,32] but often lack a comprehensive, evidence-based approach that integrates psychological mechanisms and behavioral change techniques [30]. This gap extends to the challenge of effectively recruiting adolescents, especially for programs addressing sensitive health issues [33,34]. Recruitment complexities arise from stigma and the need to align with adolescents' varied interests and obtain parental consent [35-37]. Addressing these challenges necessitates multifaceted strategies: empathetic engagement; using diverse channels; and clearly communicating the benefits while ensuring trust, confidentiality, and cultural sensitivity [38,39]. These methods emphasize the need for a supportive and safe environment, messages that resonate with adolescents, and the involvement of the broader community in the recruitment process for prevention programs.

Digital Life Skills in the Age of Social Media

Modern prevention strategies must encompass the growing convergence of analog and digital life, acknowledging the diverse challenges in both realms. In this context, promoting life skills emerges as a valuable and effective approach, contributing significantly to overall well-being, academic success, and the reduction of risk behaviors and chronic diseases [40-44].

Life skills, as defined by the World Health Organization [45], include decision-making, problem-solving, creative and critical thinking, communication and interpersonal skills, self-awareness, empathy, and managing emotions and stress. Traditional programs, despite their benefits, face challenges such as high costs and limited accessibility [46,47]. The digital era offers new avenues through e-learning and apps to effectively impart these skills while addressing issues such as substance abuse [48-53] but also necessitates developing digital skills to tackle digital challenges [11,12,54].

Development of a Digital Life Skills Program (Leduin)

Overview

Consequently, we have developed the "leduin" program, using the social media platform Instagram to teach digital life skills in a low-threshold and interactive manner, seamlessly integrated into everyday life. In doing so, we followed the intervention mapping methodology [55], which directs the conceptualization, development, and implementation of health promotion programs. The leduin program is a digital intervention specifically designed to empower adolescents in the 9th and 10th grades with crucial digital life skills to navigate challenges presented by social media and everyday life. The following steps were undertaken to develop the leduin program (E Zimmermann and S Tomczyk, unpublished data, 2024).

Logic Model Development

The development of the leduin program began with a comprehensive logic model, addressing the complexities of adolescent life in the context of social media. This model focuses on developing digital life skills that enhance health, reduce risk behaviors, and improve school performance, particularly targeting 9th and 10th graders. This timing is strategic as life skills are especially beneficial and more effectively imparted during such transitional periods in a student's life [56]. The model was informed by focus groups with 67 adolescents aged 14 to 17 years and heterogeneous educational backgrounds.

Psychological Mechanisms Identification

The second step involved identifying psychological mechanisms vital for behavioral change and digital life skills development.

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The leduin program integrates (1) personal variables such as attitudes and self-efficacy, based on social cognitive theory and the theory of planned behavior [57-59]; (2) environmental factors including social norms and support [60,61]; and (3) information processing mechanisms to optimize message impact [62]. Additionally, it focuses on (4) activating resources to support the development of digital life skills [63].

Developing Methodological Framework and Intervention Design

For the third step, we crafted a methodological framework using the behavior change taxonomy [64], tailored to social media context. Influenced by research on social media [65], behavior change techniques in health programs [66], and user preferences [67], we chose Instagram for its interactivity and popularity [3,68]. The program integrates behavior change techniques within Instagram, encompassing (1) content sharing through posts and stories for information dissemination, (2) interactive features such as quizzes for behavioral regulation, (3) material and social incentives to enhance engagement, and (4) social processes such as polling and commenting to encourage participation. These components collectively support habit formation, problem-solving, and identity development related to behavior change (see Table 1 for detailed mechanisms and associated features), with the selection process also being guided by adolescent focus group feedback.

Table 1. Mechanisms, exemplary behavior change techniques, and associated exemplary social media features within the social media–based life skills program (leduin).

Mechanism	Exemplary behavior change techniques	Exemplary social media features
Content sharing	• Information about (1) health consequences (5.1) • Information about (2) social and environmental consequences (5.3) • Information about (3) emotional consequences (5.6) • Pros and cons (9.2) • Salience of consequences (5.2) • Instruction on how to perform the behavior (4.1) • Verbal persuasion about capability (15.1) • Credible source (9.1)	• Content sharing methods: posts, tweets, and stories using text, image, and video
Behavioral regulation	• Self-monitoring of behavior (2.3) • Self-monitoring of outcomes of behavior (2.4) • Discrepancy between current behavior and goal (1.6)	• Interactive elements like quizzes, sliders (similar to Likert-scale), templates, and question stickers
Incentives	• Material incentive (behavior; 10.1) • Social reward (10.4)	• Raffles and prizes • Likes, comments, and direct messages
Social processes	• Social comparison (6.2) • Social support (unspecified; 3.1) • Restructuring the social environment (12.2)	• Sliders, polls, and direct messages • Direct messages, likes, and group chats • Community and account recommendations
Processes initiated	• Habit formation (8.3) • Problem-solving (1.2) • Goal setting (behavior; 1.1) • Identity associated with changed behavior (4.1)	• Push notifications

Program and Module Structuring

In the fourth step of the intervention mapping approach, the leduin program's structure and modules were developed. It resulted in a 14-week program that encompasses modules on individual, social, and health skills, detailed in Textbox 1. Each module introduces, specifies, applies concepts to risk situations and relates them to everyday life, aligning with World Health Organization life skills education guidelines [69]. Modules cover areas such as emotional and stress management, communication skills, and digital safety. Content is delivered through Instagram stories and feeds using short videos, images, quizzes, and surveys to foster active learning. Additionally, the program incorporates weekly self-care and stress management activities and interactive challenges with prizes to boost engagement. An accompanying analog workbook with journaling activities complements the digital content. This dual approach ensures comprehensive life skills training, emphasizing concise, daily content to promote spaced learning [70], contrasting with traditional massed learning methods.

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Textbox 1. Contents of the 14 modules of the 14-week social media–based life skills program (leduin) divided into individual, social, and health skills.

Individual skills (modules 1-4):

- Strengths, goals, emotions, and stress

Social skills (modules 5-8):

- Communication, needs, boundaries, identity, and peer pressure

Health skills (modules 9-12):

- Risks, addictions, digital violence, and information

Cross-module:

- Self-care, stress reduction, problem-solving, and self-reflection
- Modules 0 and 13 contain introduction and conclusion

Pilot Study of the Leduin Program

In a pilot study, we assessed the feasibility, acceptance, and engagement of the leduin program, implementing it with 101 students of 9th and 10th-grade in high schools and secondary schools in North Rhine-Westphalia and Lower Saxony, Germany, from November 2022 to February 2023 (E Zimmermann and S Tomczyk, unpublished data, 2024). A total of 13 interviews with participating adolescents aged 14 to 17 years and 6 interviews with their teachers were conducted to evaluate acceptance and initial effectiveness. These qualitative findings indicate that the social media–based prevention program was successfully conducted, well-received by participants, and executed with high commitment. Participants reported positive subjective learning outcomes in social media use, self-care, and stress reduction and perceived the leduin program as personally beneficial and enriching. Although the program yielded favorable results, its accessibility presented a substantial hurdle in the recruitment phase. We conducted informational sessions in schools and a youth center to educate adolescents about the program, enabling them to make informed choices about participating in their leisure time. However, the participation rates varied significantly among schools, with certain classes showing high engagement, while others had minimal involvement. This variation underscores the importance of developing effective strategies to engage adolescents in social media–based prevention programs. Consequently, in the fifth step of the intervention mapping approach as the subject of this study, our focus is to examine and enhance accessibility to guarantee effective program execution.

Methods

Overview

The objectives of the accessibility study for the leduin program, grounded in the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [71], primarily focus on evaluating the first dimension of the framework—"reach"—to identify effective strategies for engaging adolescents in digital life skills interventions on social media. This includes reaching a diverse demographic of 9th and 10th graders, encouraging participation, and ensuring sustained engagement. While also considering the remaining RE-AIM aspects—effectiveness, adoption, implementation, and maintenance—the study mainly seeks to understand the characteristics and engagement levels of participating adolescents and to identify what drives active or low engagement. This understanding is critical for refining recruitment strategies and enhancing the impact of social media–based health interventions for youth.

Reach

The focal point of our study is to encompass a broad and representative demographic of 9th- and 10th-grade adolescents. To achieve this, we are targeting a diverse population from various school types, including grammar schools, comprehensive schools, secondary schools, and independent schools. Moreover, recognizing the importance of reaching adolescents undergoing high stress, recruitment efforts are also extended to youth centers and therapeutic facilities. We will explore the characteristics of adolescents who have consented to participate. Based on insights from the pilot study, we anticipate varying levels of engagement among the participants: some may actively engage with the program's social media content, while others may have minimal to no interaction although initially interested. This variance allows for a quasi-experimental design, using engagement levels (ranging from none to high) as the basis for group assignment. Such a design is capable of highlighting differences between these engagement groups, and we will explore the predictors that are associated with active engagement or no or low engagement. We will also conduct a qualitative process evaluation to explore the facilitators and barriers encountered during recruitment. This will involve the recruitment team documenting feedback about the program and information event, as well as the reasons participants choose to join or decline participation. This documentation will be captured both in written form and verbally.

Effectiveness

The program's effectiveness will be evaluated by its impact on life skills, social media–related skills, health status, risk behaviors, and school performance. Using the quasi-experimental design, we aim to test the hypothesis that enhancing digital life skills through the intervention leads to improved social media skills and reduced risk behaviors. To detect medium-sized effects, a power analysis indicates the need

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for 128 adolescent participants (power=0.8, α=.05), aligning with existing evidence of medium effect sizes in digital interventions (d=0.30 to 0.76) [72]. This evaluation will provide crucial data for potential effectiveness, shaping the direction of future trials.

Adoption

The study will evaluate the proportion of schools, youth centers, and therapists willing to participate, providing insights into broader program acceptance and feasibility.

Implementation

We will examine the effectiveness of data collection and participant engagement on Instagram, which is critical for understanding how the program can be successfully implemented in a larger trial.

Maintenance

A 6-month follow-up will gauge the long-term impact of the intervention on intended outcomes and evaluate interaction and retention rates. These data are crucial for understanding the sustainability of the program's effects.

The operationalization of these dimensions is summarized in Table 2. The trial will be conducted in a single-group design.

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Table 2. Overview of the questionnaires used with a single-group design to assess primary and secondary outcomes in preintervention, postintervention, and 6-month follow-up surveys.

Outcome and construct	Questionnaire	Reliability
Primary outcomes		
Life skills		
Decision-making or goal setting	Subscale "goal setting" of the Life Skills Ability Scale (LSAS) [73]	α=.89
Problem-solving	Subscale "problem solving" of the Life Skills Ability Scale (LSAS) [73]	α=.85
Creative and critical thinking	Self-generated items to test knowledge based on the developed program content	—[a]
Communication	Subscale "communication" of the Life Skills Ability Scale (LSAS) [73]	α=.78
Interpersonal skills and empathy		
—	Questionnaire on resources in childhood and adolescence (FRKJ 8-16) [74]	α=.68-.89
—	Subscale "Social skills" of the Life Skills Ability Scale (LSAS) [73]	α=.82
Self-confidence and self-efficacy	Questionnaire on resources in childhood and adolescence (FRKJ 8-16) [74]	α=.68-.89
Dealing with emotions	Emotion regulation questionnaire [75]	α=.74-.76
Dealing with stress		α=.69-.88
—	Stress- and Coping-Inventory (SCI)	—
—	Subscales "Physical symptoms" + "Coping strategies" [76]	—
Social media–related skills		
Cyberbullying	European Cyberbullying Intervention Project Questionnaire (ECIPQ) [77]	α=.96
Media-based empathy		α=.80
—	Media-Based Empathy (MBE)	—
—	Subscale "Cognitive Media Empathy with Real Persons" [78]	—
Social media use		
—	Social media use time	—
—	Social media disorder scale-short form [79]	α=.81
—	Bergen social media addiction scale [80]	r_{tt}=.82
Smartphone use	Smartphone addiction scale [81]	α=.85
Secondary outcomes		
Risk behavior		
Substance use		
—	Alcohol Use Disorder Identification Test (AUDIT) [82]	α=.80
—	Cigarettes and cannabis - questions from the HBSC study [83]	—
Health status		
Subjective state of health	Subjective state of health [84,85]	—
Well-being	World Health Organization-5 well-being-index [86]	α=.92
Life satisfaction		
—	German version of the Satisfaction with Life Scale (SWLS) [87,88]	α=.87
—	Short scale for the assessment of general life satisfaction (L-1) [89]	r_{tt}=.67
Mental health: anxiety and depression	Hopkins Symptom Checklist-25 (HSCL-25) [90]	α=.94
School performance	School grades (German, English, and Math), grade point average, and change	—
Covariants		
General		
Acceptance and feasibility of the program		—

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Outcome and construct	Questionnaire	Reliability
—	Self-generated items based on the Training Evaluation Inventory (TEI) [91]	—
—	Net-Promoter-Score	—
Sociodemographic variables		
—	Gender, age, migration background, socioeconomic status: family affluence scale [92,93]	r_{tt}=.90
—	Subjective Socioeconomic Status scale (SSS-Scale) [94]	α=.70

[a]Not applicable.

Recruitment

This accessibility study will recruit participants via schools, youth centers, and therapeutic facilities across Germany. Adolescents from various school types (grammar, secondary, comprehensive, and independent) and socioeconomic backgrounds are targeted. Recruitment spans several federal states (Berlin, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Saxony, Lower Saxony, and Thuringia), chosen for representativeness and synchronized holidays, encompassing both rural and urban areas. State school participation requires ethical approval and ministry or school board consent. Schools, youth centers, and therapeutic facilities are randomly selected within these states.

Recruitment will begin once approvals are obtained, with invitations issued in waves based on response rates. Teachers, youth workers, and therapists initially agreed to participate (Multimedia Appendix 1). Adolescents are then recruited through digital information events, which aim to build motivation to participate through highlighting the relevance of the programs' content for their life stage (Multimedia Appendix 2). In addition to research findings on that, key adolescent concerns were identified in the pilot study. The use of Instagram minimizes participation effort and the recruitment in schools fosters group dynamics. Further, the program incentivizes engagement with rewards and ensures anonymity and confidentiality, creating a safe space for discussing sensible and at the same time interesting topics. Finally, together with their parents, adolescents agree to participate in the study.

To join the study, participants need an Instagram account, must be proficient in German, and must be aged 14-17 years. The recruitment goal includes 2 classes from grammar schools, 3 classes from secondary schools, and 1 class from an independent school per state, plus 20 adolescents from youth centers and therapeutic institutions in each state, accommodating additional participants if interested.

As we are taking an innovative approach, it is not clear how complete the recruitment will be. The sample size depends on adolescents who voluntarily want to participate. Since adolescents work on the program in their free time, it can be assumed that fewer will participate than in compulsory programs conducted in school. Recruitment will start in May 2023 and end as soon as the target criteria are met or the program starts in September.

Data Collection

In this study, both qualitative and quantitative data are gathered to explore the RE-AIM framework's dimensions, involving (1) documentation by the recruitment team and (2) personal-level outcomes via questionnaires. Figure 1 illustrates the study design with the recruitment phase and points of assessment.

To assess RE-AIM's aspects of reach, acceptance, and implementation, data will be collected on the number of schools, youth centers, and therapeutic facilities contacted per state; their response rates; information events held; and consents after the event. The recruitment team will also document institutions' responses.

Personal level characteristics outcomes, measuring reach, effectiveness, and maintenance, are gathered through web-based questionnaires in a preintervention, postintervention, and follow-up design. Participants and institutions receive unique codes for tracking. The institutional link aims for support through teachers or youth workers and therapists and thus comprehensive data collection by conducting the entire study, including data collection, within 1 school year. Schools optionally receive supplementary teaching materials for the leduin program content.

The following constructs are collected by means of questionnaires: primary outcomes (life skills [decision-making or goal setting, problem-solving, creative and critical thinking, communication, interpersonal skills and empathy, self-confidence and self-efficacy, managing emotions, and managing stress], and social media–related skills [media-based empathy, cyberbullying, smartphone, and addictive or disordered social media use]); secondary outcomes (health status [well-being, subjective health and mental health, and life satisfaction], risk behavior [substance use], and school performance); and covariants (acceptance and feasibility of the program and sociodemographic variables). Table 2 lists the survey instruments used to measure the constructs just described, including reliability.

For the web-based data collection of the participants' personal data, we use the SoSci Survey platform with which we have an order data processing agreement for the leduin study that has been reviewed by the data protection officer of the University of Greifswald. This ensures the technical and organizational measures required for data security. The provider SoSci Survey works with SSL encryption (HTTPS) of the data when filling out the questionnaire and when retrieving the collected data. A secure SSL configuration (Qualys SSL Labs) secures the transmission of the data. The servers of the University of

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Greifswald are used to store the data. The data are secured by daily backup and are usually stored for 90 days (3 months).

The initial data collection in the pilot study proved successful due to teacher involvement. However, transferring responsibility for the subsequent data collection to the adolescents led to significant gaps in the data. To address this in the accessibility study, we will prioritize early emphasis on the importance of data collection and ensure consistent supervision of the adolescents to mitigate missing data issues.

Figure 1. Flowchart illustrating recruitment process, single-group design (1 intervention group), and points of assessment (preintervention, postintervention, and 6-month follow-up surveys). M-V: Mecklenburg-Western Pomerania; NRW: North Rhine-Westphalia.

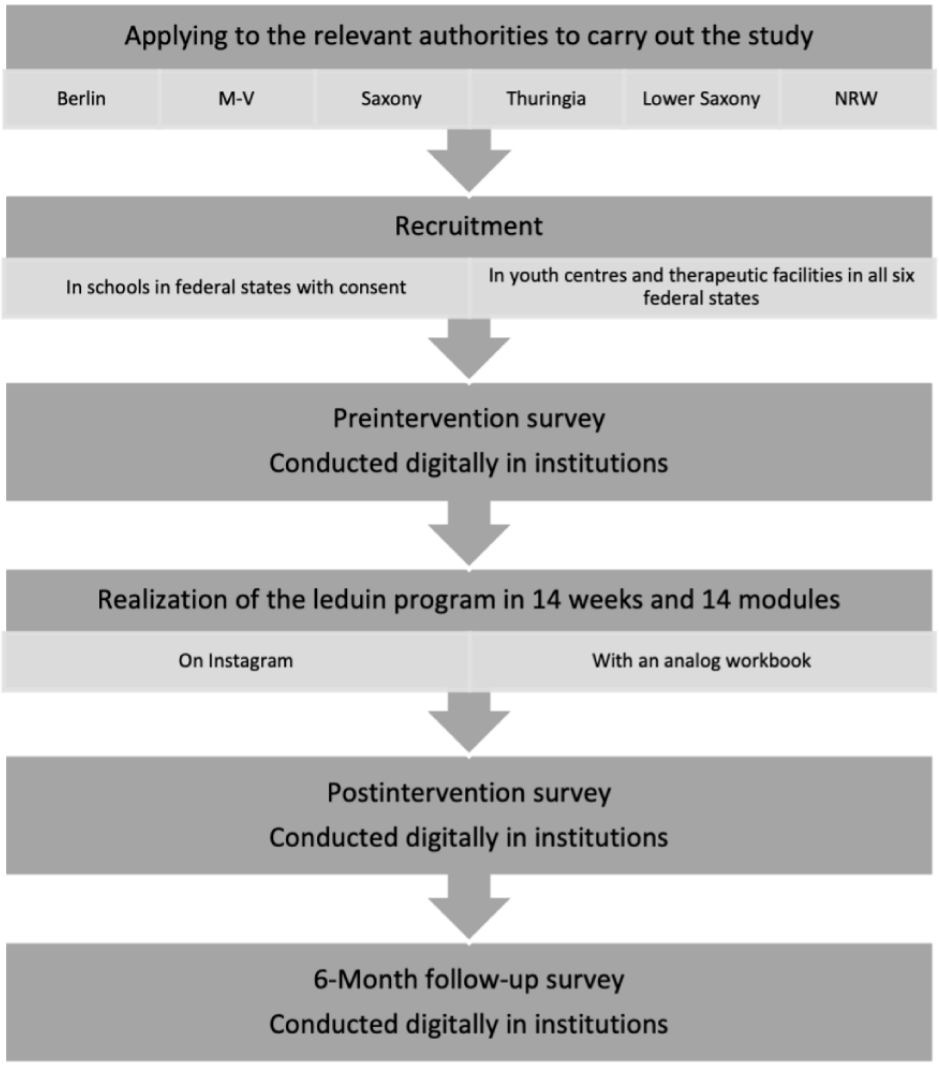

Data Management

Participation in the study is voluntary, with participants receiving detailed information about the procedure and providing informed consent according to the Declaration of Helsinki. This consent can be withdrawn anytime without justification or repercussions. Pseudonymized data can be deleted until fully anonymized, a detail made clear in the study information.

The data are stored on password-protected servers at the University of Greifswald, secured by daily backups. Access is restricted to authorized scientific personnel for qualitative and quantitative analysis. Project management and data processing staff at the university ensure data plausibility, completeness, and accuracy. After collection, data are quickly anonymized.

Data management adheres to the German Psychological Society's recommendations, focusing on quality assurance, knowledge optimization, and maximizing cost-benefit ratios. Cleaned, anonymized primary data, along with associated syntax commands, will be openly accessible in line with open science principles, a fact communicated to participants in the study information.

Data Analysis

Statistical Methods

Quantitative analyses will vary according to the different dimensions of the RE-AIM framework [71]. The software R Studio (Posit) and SPSS (IBM Corp) will be used [95]. Multilevel logistic regressions will be conducted to evaluate the dimensions of reach, acceptance, and implementation. Here, the extent to which the following variables influence institutions' initial interest in the program, individuals' initial willingness to participate in the program, completeness of data, and individual engagement within the program is examined: socioeconomic status, gender, age, mode of recruitment (school,

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youth center, and therapeutic facility), school type, performance, well-being, life satisfaction, and mental health. The initial interest of institutions in the program is operationalized by the proportion of institutions (schools, youth centers, and therapeutic institutions) that participated in an information session. The initial willingness of individuals to participate in the program is assessed by the percentage of students who decide to participate in the program after an information session. The completeness of data is examined by the percentage of data in the preintervention, postintervention, and follow-up surveys, and individual engagement is measured by the participants' self-assessment.

For quantitative analyses of the dimensions of reach, effectiveness, and sustainability, mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, and follow-up) will be carried out. The multilevel structure will be assumed if the actual design effect resulting from the intraclass correlation is >2 [96]. The influence of covariants such as gender, age, and socioeconomic status will be controlled. In addition, the individual courses in the outcome variables, as described before, will be examined by using latent growth models across the 3 time points. Logistic regressions will be conducted to investigate the impact of the program on participants' addictive or disordered social media use by comparing pre- and postintervention data.

Qualitative analyses of the recruitment process will be executed by conducting a qualitative content analysis [97] using the software MAXQDA (VERBI Software). This should provide information on the barriers to participation in the program and also identify the facilitators.

Table 3 summarizes the different dimensions of the RE-AIM framework, their operationalization, and corresponding statistical methods.

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Table 3. Dimensions of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework, operationalization, and statistical methods to evaluate a social media–based life skills program (leduin).

Dimension	Operationalization	Statistical method

Reach	• Dependent variables
	  • Initial interest
	  • Institutional level: number of institutions (schools, youth centers, and therapeutic facilities) contacted per federal state and positive responses
	  • Individual level: proportion of adolescents who agree to participate
	  • Qualitative process information of facilitators and carriers
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
		• Multilevel logistic regressions
		• Qualitative content analysis

Effectiveness	• Primary outcomes: Life skills and social media–related skills • Secondary outcomes: mental health, well-being, risk behavior, school performance	• Mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, and follow-up) • Latent growth models • Logistic regressions

Acceptance	• Dependent variables
	  • Willingness to participate:
	  • Number of information events
	  • Number of consents
	  • Individual engagement
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
	  • Qualitative process information of facilitators and carriers
		• Multilevel logistic regressions
		• Qualitative content analysis

Implementation	• Dependent variables
	  • Completeness of data collection in the different institutions
	  • Participation of adolescents in the program on Instagram (active and passive)
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
		• Multilevel logistic regressions

Maintenance	• Primary outcomes: life skills and social media–related skills • Secondary outcomes: mental health, well-being, risk behavior, school performance • Participation of adolescents in the program on Instagram (active and passive)	• Mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, follow-up) • Latent growth models • Logistic regressions

Monitoring

Since the leduin study is not a clinical study, it is not expected that the participants will experience any harm. Therefore, the use of a data monitoring committee is waived. However, communication within the program will be monitored by an internal monitoring team in accordance with netiquette [98]. Violations of netiquette will be commented on and discussed within the program, and if necessary, the authors will be excluded from the program if there is no improvement. If harm is unexpectedly caused to a participant during the program, the program will be interrupted if there are indications that the harm may have been caused by the program. After review, the program will either be revised or continued.

Ethical Considerations

The leduin study has been positively assessed by the ethics committee of the Greifswald University Medical School (BB

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190/22). Approval for the study has also been sought from the relevant education authorities and ministries for state schools in Germany. The data protection regulations have been developed with the data protection officer of the University of Greifswald and a register of processing activities is available. If important protocol modifications are made, this will be communicated to the responsible ethics committee, the school authorities and ministries, the data protection officer, and the study participants.

Participating adolescents and their parents consent to their participation in the study. Consent is given on the basis of the study information and information events.

Dissemination Policy

Trial results will be communicated to participants, schools, prevention professionals, and authorities via publication and in edited form in a brochure and on the project website, further through publications, conference contributions at academic conferences, and practitioners' congresses (eg, Digitallabor and Medienschule).

Results

Recruitment for the study was planned from May 2023 until the beginning of the leduin program in October 2023. As of March 2024, a total of 283 participants agreed to participate in the study.

Discussion

Overview

Social media offers effective ways of reaching a broad audience and can be used to address risk behavior and skill development [3,15,22]. To this aim, life skills can be a holistic approach. Despite the prevalence of digital training, few are evidence-based and access to the target audience remains challenging [27,29,30,33]. Moreover, existing life skills training often fails to address digital challenges. Further, the potential of using existing social media to reach adolescents has not been exploited. Our program is designed to improve digital life skills using Instagram, a platform that aligns with adolescents' habits and offers interactive features suitable for e-learning. The program addresses both the benefits and the risks associated with social media use. Our upcoming study aims to assess the accessibility of this innovative approach, leveraging existing social media to develop digital life skills, with future plans to evaluate its effectiveness.

In a pilot study, the leduin program was tested with 101 students in 9th and 10th grade across schools in North Rhine-Westphalia and Lower Saxony, Germany (E Zimmermann and S Tomczyk, unpublished data, 2024). The study, conducted from November 2022 to February 2023, involved interviews with 14- to 17-year-old participants and their teachers to evaluate the program's acceptance and initial effectiveness. Results showed positive reception and commitment, with participants reporting beneficial learning outcomes in social media use, self-care, and stress reduction. However, our pilot study highlighted substantial challenges in reaching the target group. While some classes were very interested in participating, others showed minimal involvement. This disparity suggests that simply making the program available is not sufficient. Effective strategies are needed to actively engage adolescents, ensuring they are both aware of and interested in participating. The leduin program is crafted to subtly enhance life skills through everyday activities with minimal effort over an extended period with spaced learning, aligning with effective learning and skill acquisition theories [69,70]. While social media proves effective in health interventions [22,30], participation depends on the individual's choice. Accordingly, adolescents might not fully appreciate the personal benefits of such engagement in their developmental stage [9]. To address this, we aim to reach adolescents through institutions already engaged in preventative work. However, since the intervention occurs during leisure time, even with its low barriers, consistent participation cannot be assured. Additionally, there is a possibility of waning intrinsic motivation over time.

The objectives of the accessibility study focus on identifying effective methods to engage adolescents in a digital life skills program on social media. It aims to encourage participation and sustain engagement to improve digital life skills. The study uses the RE-AIM model to guide its design, primarily focusing on the dimension "reach". Accordingly, key aspects include reaching a representative adolescent sample, examining the characteristics of consenting participants, and analyzing the variance in engagement levels. We thus aim to assess the accessibility of a social media intervention amidst heightened stress levels in schools and among adolescents post–COVID-19 pandemic, as indicated by our pilot study. Despite the critical need for prevention work, overall accessibility may be significantly constrained due to resource limitations, independent of the program's specifics.

The study further aims to identify relevant aspects of the other dimensions of the RE-AIM framework (effectiveness, acceptance, implementation, and maintenance) and thus examines the program's effects on life skills and social media–related skills, along with health, risk behavior, and school performance. It assesses program acceptance among schools, youth centers, and therapeutic facilities; the effectiveness of data collection, participant interaction, and retention rates on Instagram; and the long-term impact of the intervention. While this approach may yield valuable information, further studies must follow to fully evaluate the aspects of the comprehensive RE-AIM model.

Limitations

The limitations of the described approach include potential sampling bias, as engagement levels and the willingness of schools and youth centers to participate may not represent the broader adolescent population. Schools and youth centers facing significant challenges could be unable to participate in the study due to capacity constraints. This stress could be related to having a particularly burdened student body, affecting representativeness. Moreover, while directly recruiting adolescents for a social media intervention via social media platforms might initially appear to be an effective strategy, it presents substantial challenges in the context of a scientific

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study. The primary issue lies in the difficulty of reliably verifying adolescents' identities and securing parental consent in an online environment. Additionally, while data collection itself is not intended to be conducted through social media, motivating adolescents to consistently participate in data collection becomes challenging without a supervised setting. This lack of direct oversight and engagement can significantly impact the reliability and consistency of data collection. Therefore, this approach is considered unfeasible for maintaining the rigorous standards required for scientific research.

The quasi-experimental design, while useful, might not fully account for confounding variables influencing engagement and outcomes. We are launching the leduin program with a digital information event, aiming for cost-effectiveness and wide reach among adolescents from diverse regions. This event serves to arouse interest. However, it is essential to thoroughly explain the scientific study's framework accompanying the program for informed consent. While this detailed explanation may dampen interest, it is a necessary step to ensure ethical compliance and informed participation. Consequently, we will only be able to examine the characteristics of adolescents who initially agreed to participate in the study and take part in the follow-up survey. This will limit representativeness. Since we are also dependent on the voluntary participation of the participants, dropouts are to be expected, both in the program itself and in the surveys.

Additionally, relying on social media platforms, Instagram could limit reach to adolescents not actively using or engaging with this platform. The follow-up period of 6 months, although significant, may not be sufficient to fully assess the long-term sustainability of the intervention's effects. Further, our sample size for evaluating the effectiveness of the intervention is calibrated for detecting medium-sized effects, which, while possible, are not guaranteed.

Conclusions

Our aim is to deepen our understanding in this field by identifying effective access strategies for social media interventions. Accessibility is crucial, acting as the "eye of the needle" for such interventions. Even the most effective programs cannot achieve their intended impact if they fail to reach and be accepted by the target group. By successfully navigating this pivotal aspect, we can ensure that our interventions are both accessible and effective, maximizing their potential benefits. We recognize the dual role of social media in interventions. On the one hand, these platforms offer valuable tools for reaching and engaging our target audience. On the other, it is imperative to acknowledge and address the inherent risks associated with social media use. Neglecting these risks could lead to unintended negative consequences, following a "dark-logic-model" where interventions might inadvertently cause harm. Thus, our focus is not only on leveraging social media for positive outcomes but also on mitigating its potential adverse effects to ensure a safe and effective intervention environment.

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Authors' Contributions

EZ was involved in conceptualization, as well as writing the original draft and reviewing and editing. ST contributed to the conceptualization and participated in reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study information and declaration of consent for the leduin study for caregivers.
[PDF File (Adobe PDF File), 252 KB - resprot_v13i1e51085_app1.pdf]

Multimedia Appendix 2
Study information and declaration of consent for the leduin study for adolescents.
[PDF File (Adobe PDF File), 251 KB - resprot_v13i1e51085_app2.pdf]

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Abbreviations

RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

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Protocol

Toward Telemonitoring in Immune-Mediated Inflammatory Diseases: Protocol for a Mixed Attention Model Study

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Abstract

Background: Rheumatic and musculoskeletal diseases (RMDs) are chronic diseases that may alternate between asymptomatic periods and flares. These conditions require complex treatments and close monitoring by rheumatologists to mitigate their effects and improve the patient's quality of life. Often, delays in outpatient consultations or the patient's difficulties in keeping appointments make such close follow-up challenging. For this reason, it is very important to have open communication between patients and health professionals. In this context, implementing telemonitoring in the field of rheumatology has great potential, as it can facilitate the close monitoring of patients with RMDs. The use of these tools helps patients self-manage certain aspects of their disease. This could result in fewer visits to emergency departments and consultations, as well as enable better therapeutic compliance and identification of issues that would otherwise go unnoticed.

Objective: The main objective of this study is to evaluate the implementation of a hybrid care model called the mixed attention model (MAM) in clinical practice and determine whether its implementation improves clinical outcomes compared to conventional follow-up.

Methods: This is a multicenter prospective observational study involving 360 patients with rheumatoid arthritis (RA) and spondylarthritis (SpA) from 5 Spanish hospitals. The patients will be followed up by the MAM protocol, which is a care model that incorporates a digital tool consisting of a mobile app that patients can use at home and professionals can review asynchronously to detect incidents and follow patients' clinical evolution between face-to-face visits. Another group of patients, whose follow-up will be conducted in accordance with a traditional face-to-face care model, will be assessed as the control group. Sociodemographic characteristics, treatments, laboratory parameters, assessment of tender and swollen joints, visual analog scale for pain, and electronic patient-reported outcome (ePRO) reports will be collected for all participants. In the MAM group, these items will be self-assessed via both the mobile app and during face-to-face visits with the rheumatologist, who will do the same for patients

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included in the traditional care model. The patients will be able to report any incidence related to their disease or treatment through the mobile app.

Results: Participant recruitment began in March 2024 and will continue until December 2024. The follow-up period will be extended by 12 months for all patients. Data collection and analysis are scheduled for completion in December 2025.

Conclusions: This paper aims to provide a detailed description of the development and implementation of a digital solution, specifically an MAM. The goal is to achieve significant economic and psychosocial impact within our health care system by enhancing control over RMDs.

Trial Registration: ClinicalTrials.gov NCT06273306; https://clinicaltrials.gov/ct2/show/NCT06273306

International Registered Report Identifier (IRRID): PRR1-10.2196/55829

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KEYWORDS

digital health; mHealth, telemonitoring, rheumatic musculoskeletal diseases; digital resources, mixed attention model; rheumatic disease; musculoskeletal diseases; chronic diseases; pain; inflammation; antirheumatic drugs; telemonitoring; rheumatology; hybrid care model; care model; MAM; implementation; clinical outcome

Introduction

Background

Rheumatic and musculoskeletal diseases (RMDs) are a heterogeneous group of chronic diseases that mainly affect the joints, bones, muscles, tendons, and ligaments, but they can also affect other organs and systems. The growing significance of these diseases stems from their prevalence and their profound impact on the patient's quality of life. Some examples of RMD are rheumatoid arthritis (RA), with a global prevalence estimated at 0.46% (95% CI 0.39-0.54), and spondyloarthritis (SpA), with a prevalence between 0.2% and 1.6% [1,2].

These diseases are characterized by symptoms including pain or inflammation that may flare up, requiring professional evaluation and treatment modifications. Because these flares may negatively impact a patient's quality of life, it is essential to identify them and act as early as possible. For this reason, closely monitoring the disease and its treatment is important. Sometimes, this follow-up can be hampered by the enormous burden of care and consultation time limitations typical of outpatient settings, as well as by the patients' difficulty in keeping appointments due, in many cases, to work-related reasons or displacements [3]. In addition, the complexity of the treatments administered can lead to doubts regarding dosage and potential contraindications or adverse effects [4-7]. For all these reasons, it is important to maintain open communication channels between patients and professionals to keep everyone informed of incidents in the evolution of the disease and treatment. Telemedicine and digital health thus present a novel opportunity for the clinical management of chronic patients. In this context, implementing telemonitoring in the field of rheumatology has great potential, as it can enable the close monitoring of patients with RMDs [8].

Telemedicine has seen widespread implementation in recent years, not only in rheumatology (as we want to highlight in this protocol) but also in other areas of health care (eg, emergency departments, intensive care units, pharmacies, primary care, etc) [9]. This approach to patient care is endorsed by the World Health Organization (WHO) [10], as increasing scientific evidence shows that it can be a very important channel in patient-physician communication, improving clinical care and aiding in therapeutic decision-making. In fact, it has gained more strength following the COVID pandemic, a time when face-to-face visits to hospitals or health centers were restricted, especially for patients who were more susceptible due to their clinical history [11,12]. Moreover, recently published literature on telemedicine in the context of rheumatology care suggests that telemedicine may be an effective mode of care delivery for diagnosing and managing rheumatic diseases. However, despite these promising results, more studies are still needed to evaluate the effectiveness of this new approach [13,14].

Telemedicine does not necessarily substitute the traditional care model but rather complements it. Both telemedicine and traditional care have their own advantages, and the most effective approach often involves integrating these models to provide comprehensive and patient-centered health care. Telemedicine can complement traditional care by offering additional options for delivering health care services. It provides a means for remote consultations, monitoring, and follow-up care, especially in situations where physical presence is not mandatory. However, for some cases, traditional care models with in-person consultations, diagnostic tests, and procedures may be more appropriate. Therefore, adopting hybrid models that combine in-person and telemedicine services may optimize the strengths of both models and provide a more flexible and adaptive health care system [15,16].

Considering the increasing relevance of telemedicine and the need to continue to provide further evidence, the objectives of this study are outlined in the following section.

Objectives

The main objective is to evaluate the implementation of a conceptual framework for a hybrid care model called the mixed attention model (MAM) for use in clinical practice.

The secondary objectives are as follows: (1) to identify features associated with adherence to follow-up through the MAM; (2) to evaluate the technological acceptance of the digital solutions included in the MAM; (3) to assess the agreement between patient-reported join assessments and clinician-based join assessments; (4) to evaluate whether the implementation of the

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MAM improves clinical outcomes compared to conventional follow-up; and (5) to assess patients´ health literacy using a digital interface.

Methods

Study Context

Using this framework, we conducted a previous pilot study (Digireuma study) [17] on the needs of patients with RMDs to develop a treatment strategy combining face-to-face visits with telematics follow-up through a mobile health (mHealth) tool. This tool allowed for the monitoring of disease activity, functionality, and overall patient health using electronic patient-reported outcomes (ePROs). Moreover, patients could also report incidents such as flares between their outpatient visits. This pilot study essentially sought to identify unmet needs in the follow-up and treatment of patients with RMDs and redefine the functionalities and features of future versions of this digital tool. During a 3-month follow-up period, patients had the opportunity to complete disease-specific ePROs at a prespecified frequency, as well as flare-ups and medication changes at any time. The number of interactions and alerts was assessed. The usability of the mobile solution was measured using the Net Promoter Score (NPS). Following the MAM development, there were 46 patients, 22 with RA (48%) and 24 (52%) with SpA). There were a total of 4019 interactions in the RA group and 3160 in the SpA group. A total of 15 patients generated a total of 26 alerts, of which the majority were managed remotely. In terms of patient satisfaction, 65% of respondents were considered to have approved the mobile solution, resulting in an NPS of 57 and an overall rating of 4.3 out of 5 stars, so we conclude that the use of the digital health solution is feasible in clinical practice to monitor ePROs for RA and SpA. Therefore, these results highlighted the next steps in implementing this telemonitoring method in a multicenter setting.

Accordingly, with the results and feedback obtained from previous experience, we detail the design of a clinical study wherein we will evaluate a new version of our digital health solution for monitoring and treating patients with RA and SpA.

MAM Explanation

All patients with RMDs treated with biological or targeted disease-modifying antirheumatic drugs (b/ts-DMARDs) are followed up in the immune-mediated disease (IMID) unit. This is a structured care unit comprising a multidisciplinary team of rheumatologists and specialized nurses. All care actions are protocolized, and face-to-face IMID unit visits of patients with RMDS under b/ts-DMARDs are recorded in a database. Based on the objectives described, a theoretical protocol was drawn up on how to implement a mixed model combining face-to-face visits with telematic follow-up. The MAM protocol [17] is a care model that incorporates a digital mobile app that patients can use at home and professionals can review asynchronously to detect incidents and monitor clinical evolution between face-to-face visits (Figure 1 depicts a flowchart escribing the participant inclusion in the study and subsequent steps). This protocol considers the role of each of the professionals in the unit, how face-to-face and telematic follow-up is carried out, and how to act according to the response to prescribed treatment.

Figure 1. Flowchart describing the inclusion in the study and the different steps according to the timetable established for the face-to-face and digital visits. ePRO: electronic patient-reported outcome; IC: informed consent; RA: rheumatoid arthritis; SpA: spondyloarthritis.

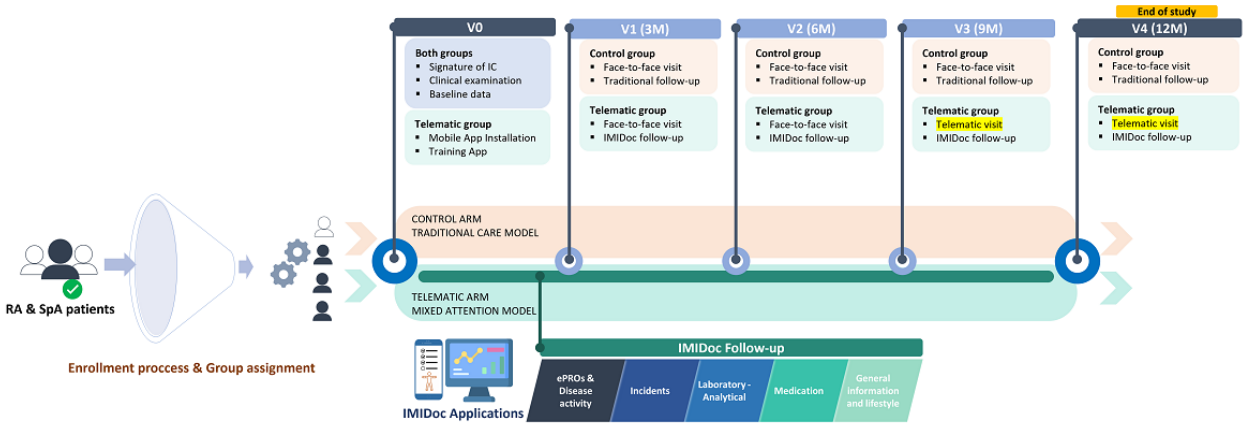

Development of the Digital Health Solution

A survey of health professionals and patients was carried out with the aim of identifying their needs and preferences regarding digital health as applied to rheumatology. Questions queried patients' familiarity with telemonitoring tools and mobile apps, the ease with which they could contact their rheumatologists, and their preferences and suggestions about the features that a digital solution should include. As for the professionals, they responded to a survey on the use of telemonitoring tools in clinical practice, training in the subject, and restrictions that hinder a wider implementation of telemedicine.

Combining this information and following a team-based approach, the IMIDoc digital health tool was then designed and developed (Figure 2 shows the digital solution outline). Throughout the process, clinical, technical, and biomedical researchers and patient teams participated in a collaborative and interdisciplinary manner. IMIDoc is based on the MAM.

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Figure 2. Digital health solution outline. ePRO: electronic patient-reported outcome; RMD: rheumatic and musculoskeletal disease.

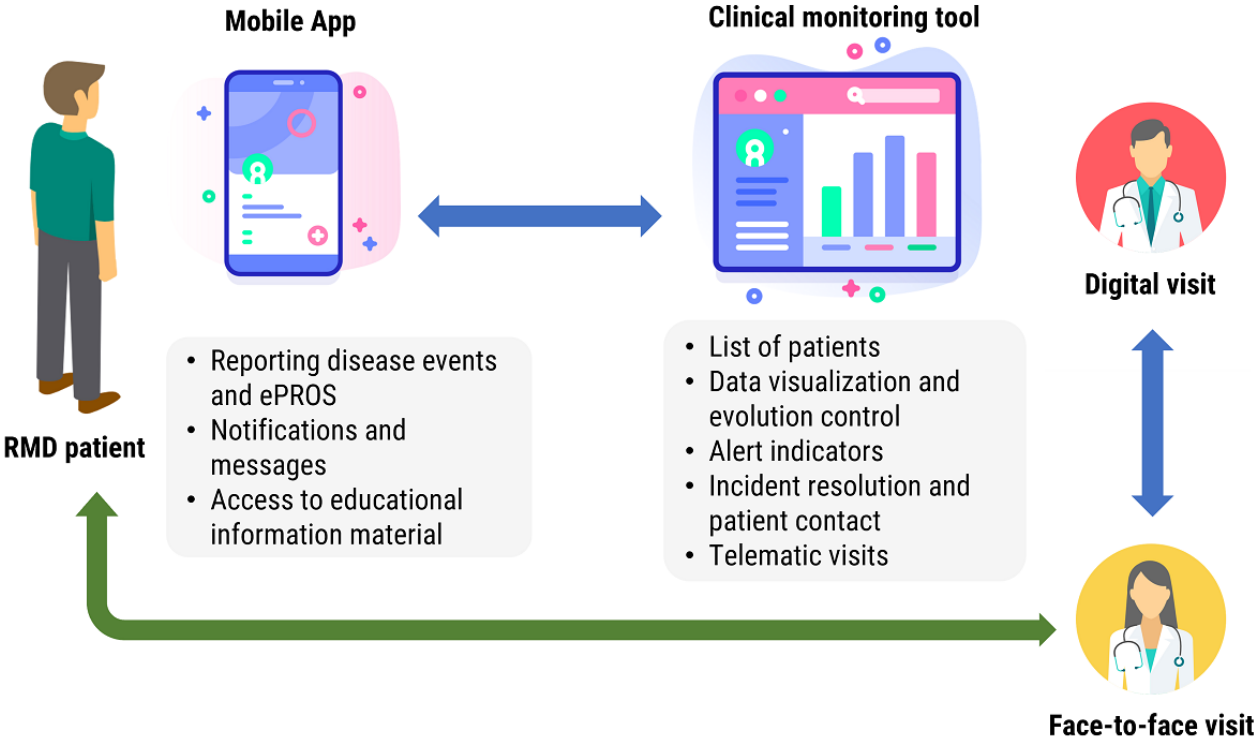

The IMIDoc technical platform consists of a mobile app for patients with RA and SpA, a web tool for clinicians, and the back-end infrastructure for data processing and storage. The IMIDoc platform has its own infrastructure to function independently of the hospital information system. Its back-end implementation is deployed in the cloud with a service-based technology approach that provides support to the IMIDoc mobile app and clinical tool.

The IMIDoc mobile app has been developed for both Android and iOS platforms and will be available through Google Play and the Apple Store, respectively. This implementation ensures that the app is easily accessible to a wide population of patients and accommodates various smart device preferences. On the other hand, the clinical tool is a web-based application accessible via a link in any standard web browser.

Patients with RA and SpA can record disease-related events and incidents, as well as ePROs, and they can receive messages from rheumatologists and automatic notifications regarding pending tasks and educational content. Likewise, rheumatologists can access the information recorded by patients through a web application. This enables clinicians to monitor and track the disease and contact patients to address any issues remotely.

Study Design

Overview

This is a multicenter prospective observational study involving 360 patients with RA and SpA from 5 Spanish Hospitals: Hospital Universitario La Paz (HULP), Hospital Universitario Vall d´Hebron (HUVH), Hospital Universitario Bellvitge (HUB), Hospital Universitario Infanta Leonor (HUIL), and Hospital Universitario Ramón y Cajal (HURyC).

Participants

A total of 360 patients will be enrolled in the clinical study, comprising the group receiving MAM intervention and the control group, following the traditional care model matched by age and sex (Table 1). The inclusion criteria for patients in the MAM group are as follows: (1) adult patients >18 years; (2) patients with RA or SpA under treatment with b/tsDMARDs followed in the complex therapy unit (CTU); and (3) patients with an available smartphone. The exclusion criterion includes patients with conditions that hinder or prevent the use of a mobile app (eg, blindness, developmental delay, dementia, and digital illiteracy).

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Table 1. Patients at each hospital treated with the MAM[a] or a traditional care model.

Hospital	Patients in the MAM (n=280), n		Patients in the traditional care model (n=80), n	
	RA[b]	SpA[c]	RA	SpA
HULP[d]	40	40	10	10
HURyC[e]	30	30	10	10
HUVH[f]	30	30	10	10
HUIL[g]	20	20	5	5
HUB[h]	20	20	5	5

[a]MAM: mixed attention model.

[b]RA: rheumatoid arthritis.

[c]SpA: spondylarthritis.

[d]HULP: Hospital Universitario La Paz.

[e]HURyC: Hospital Universitario Ramón y Cajal.

[f]HUVH: Hospital Universitario Vall.

[g]HUIL: Hospital Universitario Infanta Leonor.

[h]HUB: Hospital Universitario Bellvitge.

All patients from outpatient consultations treated with b/tsDMARDs for at least 6 months will be invited to participate in the study. Those who have been invited but have declined will be registered, and then if they accept, will be enrolled in the study. The control group will be formed by patients with the same treatments and similar sociodemographic and clinical characteristics.

Due to the exploratory nature of the trial and the fact that the objectives will be measured with different end points, no formal sample size calculation was performed. Based on previous studies in rheumatology comparing clinical parameters using telemonitoring versus conventional monitoring, the number of patients included varied in a wide range (from 44 to 294 patients) [18-20]. The primary end point considered in our study in terms of a 20% reduction in face-to-face visits has not been previously studied, and there is no data in the literature to support the inclusion of a specific number of patients. Therefore, using a crude calculation, we estimated a sample size of 300 patients to be sufficient, considering an infinite population, a confidence level of 95%, a precision of 3%, and an assumption of 15% loss to follow-up. Furthermore, other important aspects to consider in telemonitoring projects with digital health tools are usability and feasibility. Recent studies, similar in objectives to the one proposed here, have included between 40 and 120 patients to evaluate the usability and feasibility of telemedicine applications and systems in RMDs [21]. As for the usability evaluation of the clinical tool discussed in this paper, the study is designed as a multicenter initiative, anticipating the participation of at least 10 health care professionals or digital clinicians. Considering the factors mentioned earlier and the expertise of these users within the field, we contend that this participant count is sufficient for the intended evaluation.

Data Collection and Statistical Analysis

Data Sources

The application of MAM, via the use of IMIDoc incorporates 2 primary sources of information.

First, demographic, laboratory, clinical, and treatment characteristics will be extracted from electronic clinical records during the initial visit.

Second, ePROs recorded by patients participating in the IMIDoc users' arm through the application, as well as those documented by health care personnel during telematic and face-to-face visits through the web application, will be stored in the system's database in a pseudoanonymized and encrypted format.

Access to this data will be restricted exclusively to members of the research team. Data security will be supervised by the data protection officer. All actions performed on the platform will be traceable to the authorized personnel with access to the platform. User authentication tied to role-based security protocols will allow for the effective management of varying access privileges among members of the research team.

Data Collection and Schedule for Digital and Face-to-Face Visits

Overview

To facilitate understanding, variables are divided into general variables, face-to-face variables, and digital variables (Table 2). General variables correspond to background information captured during baseline visits. Face-to-face variables are captured during in-person visits and are registered in the electronic health record.

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Table 2. Variables reported in both face-to-face and digital visits.

Dimensions and variables	AR[a]	SpA[b]	Frequency
ePROs[c] and disease activity			
PGA[d], VAS[e], TJC[f], SJC[g]	✓	✓	Every 15 days
Enthesis		✓	Every 15 days
DAS28[h], HAQ[i]	✓		Monthly
ASAS-HI[j], ASDAS[k], BASDAI[l]		✓	Monthly
Incidents			
Flares, infections, medication problems, and others	✓	✓	By occurrence
Laboratory and analytical variables			
CRP[m] and ESR[n]	✓	✓	Monthly
Medication			
Medication list and reminders	✓	✓	On demand
CQR[o]	✓	✓	Monthly
General information about the disease and lifestyle	✓	✓	Every 7 days

[a]RA: rheumatoid arthritis.
[b]SpA: spondylarthritis.
[c]ePRO: electronic patient-reported outcome.
[d]PGA: Patient Global Assessment.
[e]VAS: visual analog scale.
[f]TJC: tender joint count.
[g]SJC: swollen joint count.
[h]DAS28: Disease Activity Score 28.
[i]HAQ: Health Assessment Questionnaire.
[j]ASAS-HI: Assessment of Spondyloarthritis International Society Health Index.
[k]ASDAS: Ankylosing Spondylitis Disease Activity Score.
[l]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[m]CRP: C-reactive protein.
[n]ESR: erythrocyte sedimentation rate.
[o]CQR: Compliance Questionnaire for Rheumatology.

General Variables

General variables are those that correspond to clinical records documenting background or baseline information. The following will be collected during baseline visits: demographic variables (sex, age, and BMI); smoking habit; date of diagnosis; serological status for RA, such as rheumatoid factor (RF) anticitrullinated peptide antibodies (ACPA), and histocompatibility antigen (HLA)-B27 for SpA; and treatment information, including start date of current b/tsDMARDs and concomitant therapies such as prednisone, conventional disease-modifying antirheumatic drugs (csDMARDs), and previous treatments.

Face-to-Face Variables

Clinical activity and functional capacity will be evaluated according to specific indexes and questionnaires compiled in clinical practice.

For patients with RA, these include the tender joint count (TJC) and swollen joint count (SJC), Disease Activity Score 28 (DAS28), Simplified Disease Activity Score (SDAI), and Health Assessment Questionnaire (HAQ).

For patients with SpA, these include TJC and SJC, Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Assessment of Spondyloarthritis International Society Health Index (ASAS-HI).

Results from laboratory parameters, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are routinely determined in routine clinical practice at each patient visit.

Digital Variables and ePROS

For RA patients, the variables include self-assessed tender joint count (sTJC), self-assessed swollen joint count (sSJC), and SDAI. DAS28 will be calculated and managed as patient-derived DAS28 (PtDAS28) and HAQ. Finally, in patients with SpA, the variables include sTJC, sSJC, BASDAI, BASFI, and ASAS-HI.

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Health care resource utilization will be documented, including the number of outpatient consultations, emergency visits, drug switches, and nursing and consultant calls. Questions for assessing patient status and treatment tolerance will be recorded. These will include questions such as, “Are you feeling well with the current treatment regimen?” “Have you had symptoms similar to previous outbreaks of your disease?” “If yes, how many outbreaks have you had during the last month?” “Have you experienced any symptoms that you attribute to tolerance problems with the current treatment?” “If yes, please indicate which symptom and to which treatment you attribute it.” “Have you had any recent fever or infections?” “Have you engaged in any physical activity equivalent to walking for 30 min at least 3 times during the past week?”

To assess the usability of the IMIDoc, questionnaires will collect information regarding willingness, such as the NPS, which evaluates how participants recommend the IMIDo, and follow-up with other patients using the MAM. The System Usability Scale (SUS), consisting of a 10-item questionnaire answered on a scale from 1 to 5 (strongly disagree to strongly agree), will also be used to assess the IMIDoc.

All patients who sign the informed consent form for this project will be invited to participate in a mixed clinical follow-up combining traditional face-to-face visits and home monitoring. The patients will be provided with access to a mobile app that can be downloaded free of charge and that was specially designed in consultation with and under supervision by rheumatologists. The patients will have access to complete questionnaires addressing disease activity, disability, and other domains such as ePROs (Figures 1 and 2). Face-to-face visits will be scheduled at baseline and 6 and 12 months, both for patients included in MAM and for those under the traditional care model.

Support Resources for Patients

Explanatory material will be provided at the scheduled routine medical visit for all patients included. This explanatory material includes the information required to download the digital solution, the content, and recommendations regarding the frequency with which patients should fill out the questionnaires. Once the patient agrees to be part of the MAM, they will receive a phone call from the digitally partnered clinician to ensure understanding of all the material, clarify doubts, and resolve any issues.

Clinical activity, functional capacity, and overall health will be evaluated according to specific indexes and questionnaires included in IMIDoc, with a predefined frequency for each instrument (alternate assessments of pooled instruments every 15 days, implying a weekly assessment). Reminders with predefined frequencies for each variable will be sent to guarantee their fulfillment.

A messaging and alert system will be available whereby patients can notify their physician of any incidents.

Additionally, the IMIDoc educational material will be provided to patients in a short text format containing information of interest regarding their disease, the different treatments available, and explanatory videos recorded by collaborating rheumatologists.

Workshops and Tasks for Collaborators

The established collaboration between HULP, HUVH, HUB, HUIL, and HRyC will also act as a facilitator for the development of this study. In fact, web-based meetings have already been held between researchers from all centers to evaluate the resources and the viability of implementing this project. Prior to starting patient recruitment, a web-based meeting will be held with the entire research team to discuss the best way to identify patients and carefully review the methodology that will be followed in the participating centers. Thus, all the information provided to patients will be shared and agreed upon by the centers. Moreover, reminders will be sent to the people responsible for and involved in each project task. In this regard, the clinician in charge of the telematic (digital clinicians) and clinical (onsite clinicians) for each center will be assigned. The incidents recorded in the tool will be periodically reviewed on a web interface by a physician whose clinical work is partly dedicated to this purpose (digital clinician). This professional or another professional from the CTU or biologic clinic (onsite clinician) will contact the patient by telephone to resolve the reported incident. The incident may be resolved completely remotely, or a face-to-face visit may be arranged to address the problem.

Assessment of Primary and Secondary End Points:

The primary end point will be an at least 20% reduction in face-to-face visits compared to visits carried out in the previous year. This reduction in face-to-face visits will be driven by the number of incidents that can be resolved telematically, the number of total interactions, and the number of ePROS that patients complete during the follow-up period that allows us to assess adherence and telematic monitoring.

The secondary end points will be assessed by tracking the number of accesses and time per access to the digital solution per patient to assess adherence. Agreements between the patients' self-assessment and clinician assessment will be assessed to compare face-to-face visits at 6-month intervals with the closest assessment in the digital solution. We will also measure the proportion of patients in remission or low disease activity according to the activity index every 6 months. Usability and satisfaction perceived by patients will be assessed by the SUS NPS.

Data Analysis

A descriptive analysis of the demographic and clinical variables will be performed. The results will be expressed as the mean and SD or median and IQR for continuous variables and absolute numbers and relative frequencies for categorical variables. The frequency data will be compared using a chi-square or Fisher exact test depending on the distribution of the variables. Comparisons for unpaired continuous data will be assessed using a Mann-Whitney U test or *t* test depending on the variable distribution. Comparisons of paired continuous data will be conducted using the paired *t* test or Wilcoxon test, depending on data distribution. $P<.05$ will be considered statistically significant. Univariate analysis will be carried out using the

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most relevant demographic and clinical variables (ie, age, sex, concomitant methotrexate, baseline activity score measured by DAS28 or BASDAI, disease duration, and smoking habit). In the multivariate analysis, only the variables with a $P<0.1$ in the univariate analysis will be included. Interactions and collinearity will be evaluated. The last phase of the study will consist of exploring the construction of a predictive model from the follow-up data using the MAM. For this purpose, artificial intelligence tools and techniques such as machine learning will be utilized. R-Cran (version 3.5.1; R Project for Statistical Computing))software will be used for the statistical analysis.

Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki and the General Data Protection Regulation (GDPR) of the European Union. The protocol has been approved by the local Ethics Committees of HULP (PI-4519), HUB, HUIL, HRyC, and HUVH. This protocol was submitted to a public call for applications and obtained funding for the development of a solution and implementation of the MAM in clinical practice. Informed consent will be obtained from all participants prior to study onset. This study will have a protected and anonymized database, wherein data will be stored at baseline and throughout follow-up. All patient data will be collected and handled confidentially in a protected database located on an encrypted server owned by the digital health company in compliance with the European GDPR of May 25, 2018.

Results

Recruitment began in March 2024 through initial contacts with patients at the IMID unit, and it will continue until December 2024. The follow-up period will be extended for 12 months for all patients. Data collection and analysis are scheduled for completion in December 2025. The main contribution of this protocol paper is a detailed description of the development of a digital solution to improve and implement an MAM in the field of RMDs.

Discussion

We have designed a clinical study to evaluate the MAM in clinical practice using the IMIDoc digital health tool. We developed this tool in collaboration with clinicians, biomedical engineers, and patients using a participatory or team-based approach. We believe that close collaboration between health care professionals and patients is essential for developing mHealth solutions tailored to patients' needs.

Digital health solutions or tools based on the use of mHealth technologies can empower patients by supporting self-management skills and providing information on health status and symptom management [8,17,22]. The application of health information technologies and wearable monitoring is widespread in other fields of medicine, such as brain health, HIV, and cancer [23-25]. In addition, mHealth supports the follow-up of symptoms that rheumatologists might miss during time-limited visits, thereby helping reduce the mismatch between issues important to patients versus those important to clinicians [26]. Piga et al [27] published a systematic review of tools for remote monitoring and treatment that included studies of patients with rheumatoid arthritis, systemic sclerosis, fibromyalgia, and osteoarthritis. Their study showed that feasibility and patient satisfaction rates were high or very high depending on the type of intervention and that the efficacy of these interventions was at least similar to that of standard care. Thus, it was shown that telemedicine could assist both rheumatologists in monitoring treatment and patients in participating in their treatment. However, according to the same study, the tools developed were generally unidirectional, serving either the clinician in disease assessment and treatment monitoring or the patient as an educational or disease support tool.

In this context, 2 systematic reviews have shown that there is scant evidence concerning instruments and their use for following up patients with RA [28,29]. Although several projects, such as My Joint Pain or RAHelp [30-32], have shown that telemedicine can provide a new opportunity for managing patients with chronic illness, further research is still needed, as implementation in clinical practice remains very limited [18]. Some new tools have recently been designed ranging from rheumatology referral support [33] to symptom capture [34]; however, the evidence on app use in IMIDs lags far behind that of other fields in terms of treatment adherence [35] or disease symptom improvement [36].

Both the development and implementation of mHealth technologies present several challenges and risks. In this regard, our project meets relevant Sustainable Development Goals adopted by the United Nations. First, our project addresses the goal of “good health and well-being” in the interest of promoting better patient care. Since this project focuses on chronic inflammatory diseases, good disease control can empower patients to reduce their functional disability, resulting in less impact on the quality of life. All this is only possible with a personalized follow-up approach, enabling clinicians to anticipate disease damage. The ability to access more detailed information on patient evolution and adherence problems or adverse effects can ameliorate the repercussions of erroneous therapeutic decisions [37,38].

Overall, this project aims to have both an economic and psychosocial impact on our health care system. On the one hand, the use of these tools can help educate patients about their disease, providing instructions on self-management for certain disease aspects. This can result in fewer visits to the emergency department, fewer consultations, and better therapeutic compliance. On the other hand, the availability of ever-greater amounts of data will make it possible to identify challenges or issues that would otherwise go unnoticed, thus avoiding incorrect strategies. New disease management strategies aimed at more appropriate resource use, based on clinical practice data, are needed.

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Acknowledgments

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Authors' Contributions

MNN and JMIC wrote the first version of the manuscript and share the first authorship. MNN, CPR, JMIC, and DB contributed to the design and conceptualization of the manuscript. All the authors have participated in the preparation of this article, reviewed it, and made extensive comments and valuable contributions.

Conflicts of Interest

MNN reports grants from UCB Pharma, Lilly, Galapagos, and Janssen outside the submitted work. DBN reports grants from Lilly, Janssen, UCB Pharma, MSD, Galapagos, and Novartis. ECA reports grants from Menarini, Grünenthal, Asac Pharma, MSD, Lilly, Pfizer, Roche, Astra-Zeneca, and Galapagos. HB reports grants from Lilly, Abbvie, Galapagos, Bristol Myers Squibb (BMS), Nordic Pharma, and UCB Pharma. LBA reports grants from Novartis, Lilly, Janssen, MSD, Theramex, and Abbvie. VNC reports grants from Abbvie, Lilly, Fresenius Kabi, Janssen, MSD, Novartis, Pfizer, and UCB Pharma. IMH reports grants from Roche, Novartis, UCB, and Gedeon Richter outside the submitted work. CP-R reports grants from AbbVie, Pfizer, Novartis, Lilly, and Roche outside the submitted work. AB reports grants from AbbVie, Amgen, Pfizer, Galapagos, Novartis, Gilead, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB, and Roche outside the submitted work. The rest of the authors have no conflicts of interest to declare.

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Abbreviations

ACPA: anticitrullinated peptide antibodies
ASAS: Assessment of Spondyloarthritis International Society
ASAS-HI: Assessment of Spondyloarthritis International Society Health Index
ASDAS: Ankylosing Spondylitis Disease Activity Score
b/ts-DMARD: biologic or targeted synthetic disease-modifying antirheumatic drug
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
CRP: C-reactive protein
csDMARD: conventional disease-modifying antirheumatic drug
CTU: complex therapy unit
DAS28: Disease Activity Score 28
ePRO: electronic patient-reported outcome
ESR: erythrocyte sedimentation rate
GDPR: General Data Protection Regulation
HAQ: Health Assessment Questionnaire
HLA: histocompatibility antigen
HUB: Hospital Universitario Bellvitge
HUIL: Hospital Universitario Infanta Leonor
HULP: Hospital Universitario La Paz
HURyC: Hospital Universitario Ramón y Cajal
HUVH: Hospital Universitario Vall d´Hebron
IMID: immune-mediated disease
MAM: mixed attention model
mHealth: mobile health
NPS: Net Promoter Score
PtDAS28: patient-derived Disease Activity Score 28
RA: rheumatoid arthritis
RF: rheumatoid factor
RMD: rheumatic and musculoskeletal disease
SDAI: Simplified Disease Activity Index
SJC: swollen joint count
SpA: spondylarthritis
sSJC: self-assessed swollen joint count
sTJC: self-assessed tender joint count
SUS: System Usability Scale
TJC: tender joint count

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Protocol

Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study

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Abstract

Background: Healthy lifestyle interventions have a positive impact on multiple disease trajectories, including cancer-related outcomes. Specifically, appropriate habitual physical activity, adequate sleep, and a regular wholesome diet are of paramount importance for the wellness and supportive care of survivors of cancer. Mobile health (mHealth) apps have the potential to support novel tailored lifestyle interventions.

Objective: This observational pilot study aims to assess the feasibility of mHealth multidimensional longitudinal monitoring in survivors of cancer. The primary objective is to test the compliance (user engagement) with the monitoring solution. Secondary objectives include recording clinically relevant subjective and objective measures collected through the digital solution.

Methods: This is a monocentric pilot study taking place in Bangor, Wales, United Kingdom. We plan to enroll up to 100 adult survivors of cancer not receiving toxic anticancer treatment, who will provide self-reported behavioral data recorded via a dedicated app and validated questionnaires and objective data automatically collected by a paired smartwatch over 16 weeks. The participants will continue with their normal routine surveillance care for their cancer. The primary end point is feasibility (eg, mHealth

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monitoring acceptability). Composite secondary end points include clinically relevant patient-reported outcome measures (eg, the Edmonton Symptom Assessment System score) and objective physiological measures (eg, step counts). This trial received a favorable ethical review in May 2023 (Integrated Research Application System 301068).

Results: This study is part of an array of pilots within a European Union funded project, entitled "GATEKEEPER," conducted at different sites across Europe and covering various chronic diseases. Study accrual is anticipated to commence in January 2024 and continue until June 2024. It is hypothesized that mHealth monitoring will be feasible in survivors of cancer; specifically, at least 50% (50/100) of the participants will engage with the app at least once a week in 8 of the 16 study weeks.

Conclusions: In a population with potentially complex clinical needs, this pilot study will test the feasibility of multidimensional remote monitoring of patient-reported outcomes and physiological parameters. Satisfactory compliance with the use of the app and smartwatch, whether confirmed or infirmed through this study, will be propaedeutic to the development of innovative mHealth interventions in survivors of cancer.

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KEYWORDS

cancer; survivorship; artificial intelligence; remote monitoring; mobile health; mHealth; digital health; circadian; actigraphy; mobile phone

Introduction

Background

Cancer survivorship begins with the diagnosis and continues throughout the whole life span of the person [1]. Owing to repeated advances in anticancer and supportive treatments, survivors of cancer represent an ever-growing population [2]. Indeed, accelerated by the recent COVID-19 pandemic, alternative models of care for survivors of cancer are being proposed to meet the growing demands, driven by patient-specific issues and local health care resource constraints [3]. Survivors of cancer could be still receiving anticancer treatment, or they may have already completed treatment, albeit only temporarily. In the former case, acute toxicities from anticancer treatment might be the most relevant and bothersome, whereas in the latter case, delayed and long-lasting toxicities and a plethora of physical, emotional, social, practical, and informational issues become the most critical unmet care needs for their well-being [4].

Healthy lifestyle interventions have a positive impact on cancer-related outcomes, such as overall survival, tolerance to treatment, and health-related quality of life (HRQoL), as well as other metabolic and degenerative diseases [5]. Specifically, appropriate habitual physical activity, adequate sleep, and a regular wholesome diet are of paramount importance for the wellness of survivors of cancer [1] and are considered fundamental pillars of supportive care in survivors of cancer [6]. Thus, the promotion of interventions for healthier habitual nutritional, sleep, and physical activity behaviors is broadly recommended [7]. Nevertheless, there are motivational, practical, and informational barriers to the wide adoption of modifiable healthy lifestyle behaviors in survivors of cancer [8-10].

As a class of ubiquitous technologies, mobile health (mHealth) apps have the potential to support lifestyle interventions. The combination of wearables and smartphone sensors allows scalable and practically implementable study of human behavior and physiology [11]. Automatic collection of personal health data can be complemented by self-reported assessments delivered through mHealth apps, allowing real-time monitoring of patient-reported outcomes. Such a combination of mHealth data with electronic medical records and electronic health records also opens the possibility of a new breed of artificial intelligence (AI) apps, with the potential to facilitate early detection of new conditions, identify worsening of symptoms, and provide novel delivery methods for lifestyle interventions.

Objectives

The European Union's (EU's) Horizon 2020 GATEKEEPER (GK) project is a flagship innovation action aimed at implementing this vision and delivering the future EU data and AI infrastructure for health care solutions [12]. GK has several goals, ranging from the technical software architecture and cross-countries' and cross-organizations' information security and data policy to the evaluation of data-driven services and AI-based interventions. GK's key innovation is combining health medical records with medical sensors and non–medical data from mHealth apps, wearables, and smart devices. The intuition is that apps and devices would bring critical contextual and behavioral information that, combined with medical data and knowledge, would lead to a breakthrough in AI for health care. For instance, ongoing investigations within the GK project involve the development of risk prediction algorithms for mental health and cognitive impairment and digital coaching to mitigate loneliness-related risks [13]. These breakthroughs are the result of this new approach and the data sets collected as part of the project.

In this regard, GK includes a multicentric large-scale pilot across 8 EU and 3 Asian countries for a total of 11 Reference Pilot Sites. The large-scale pilot aims to develop and test a novel approach to the evaluation of digital innovation in health care. The proposed approach can be described as an integrative analysis of cost-benefits, combining the local evaluation of the wide range of approaches and solutions at the reference sites with 10 main health care themes [13]. Pilots within the GK project evaluate, monitor, or treat the most prevalent, chronic, noncommunicable conditions according to the World Health

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Organization, including cardiovascular, metabolic, and respiratory diseases, whereas this pilot study focuses on cancer [14].

Specifically, the proposed study is 1 of the 3 UK Reference Pilot Sites and falls under the Reference Use Cases on *co-morbidity and polymedication*. In preparation for the proposed study, a new mHealth solution for survivors of cancer was co-designed. This solution was initially tested in a small-scale study focused on the use of a wearable mHealth app before further expansion within the context of GK [13].

In the proposed study, behavioral data (nutritional intake, physical activity, and sleep) will be obtained through self-reporting (recorded via an app) and automatic collection (by a wearable smartwatch). The data will then be used for remote monitoring of cancer symptoms, automatic assessments of biometric data, and integration with health medical records. Thus, the aim of this study is to assess the feasibility of mHealth monitoring in survivors of cancer. It is hypothesized that mHealth monitoring will be feasible in survivors of cancer; specifically, at least 50% (50/100) of the participants will engage with the GK app at least once a week in 8 of the 16 study weeks.

Methods

Ethical Considerations

The study protocol has been approved by the National Health Services (NHS) Research Ethics Committee (Integrated Research Application System ID: 301068; Research Ethics Committee reference: 22//SC/0323) and therefore by the Health Research Authority and Health and Care Research Wales.

Informed consent describes both the primary and secondary uses of data. Concerning secondary uses, participants are informed about the full anonymization of their data with the aim of creating a resource for the study of predictors of symptom worsening, cancer relapse, and hospitalization events. The informed consent form is provided both in English and Welsh.

The study approval included a comprehensive data protection impact assessment and a data management plan concerning data flow, processing, and sharing. In summary, participants will be given a study code and an anonymous user account for the use of the wearable device and study app. The study will only use biometric data generated through commercially available systems—Samsung Health (SH) app and Samsung Galaxy Watch. The mHealth solution decouples and anonymizes data from their data vault on patients' phones before transfer and processing. Only the hospital staff will have access to the identity or personal information of patients, and no other researchers involved will be able to access the registry of patient identifiers.

Participants will be gifted with the wearable device (smartwatch) and replacement Android phone (provided to iOS users). Furthermore, a form of compensation is the training in the use of these widely available technologies as well as the opportunity to learn more about how digital coaching and digital health technologies make use of personal data. Finally, the study will provide participants with the opportunity to reflect on the role of self-management and potential support available to them.

Study Setting

This study is the result of a co-design approach involving the Betsi Cadwaldr University Health Board Cancer Services; specialists on nutrition, sleep, and physical activity; technology providers; AI researchers; experts on clinical research and evaluation; acute medicine physicians; and patients with cancer. Over a period of 2 years, weekly meetings between main investigators and technical partners, focus groups with patients with cancer, and a cocreation group involving all stakeholders generated a patient-facing app, a clinician facing dashboard, AI algorithms, communication and training materials, and specialist outcome assessments, which led to an mHealth solution that could be pragmatically implemented alongside current routine care for survivors of cancer, as provided by the public health care system, NHS Wales.

The study design is also the result of learning from other GK Reference Pilot Sites. In this regard, we propose a feasibility design with a duration of 16 weeks, which will be conducted at a single institution, the Oncology Service of Ysbyty Gwynedd Hospital, Bangor, Wales, United Kingdom.

Eligibility Criteria

To be enrolled in the study, all participants must meet all the following requirements: (1) diagnosis of any solid malignancy, at any stage; (2) completion of treatment (including surgery, radiotherapy, and any type of systemic anticancer treatment); (3) clinical, biochemical, and radiological confirmation of controlled disease (no evidence of residual disease or nonprogressive disease); (4) scheduled for either a therapeutic break (from systemic anticancer treatment) or having completed the planned multimodal treatment; (5) scheduled for active surveillance plan within the oncology service; (6) male or female patients aged at least 18 years; and (7) scored World Health Organization performance status 0 to 2 [15].

Patients will be excluded from participating in the study if they meet any of the following criteria: (1) not possessing a SIM card, (2) no internet access through Wi-Fi or unwilling to use mobile data allowance on a daily basis, (3) inability to understand and follow the instructions autonomously, (4) uncontrolled severe comorbidities (eg, cardiovascular, metabolic, neurological, and respiratory), (5) lack of capacity, (6) inability to understand English, (7) still undergoing systemic anticancer treatment (apart from bone-targeted agents, hormonal treatment against breast or prostate cancers, or maintenance monoclonal antibody monotherapy), (8) poor general condition (performance status>2), and (9) inability to sign informed consent.

We decided to focus on survivors of cancer who were not receiving anticancer treatment to minimize the potential impact of treatment-induced fatigue or anorexia. On the basis of previous discussion with patients with cancer, it was felt that this population was the most suitable to test our mHealth solution in the first place, which can be adapted in future studies to the needs of patients on active disease-modifying treatment.

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Digital Health Care Technology

SH App and Samsung Galaxy Watch

The SH app, coupled with Samsung Galaxy Watch, can track a number of parameters, including (1) food and water intake (including calorie tracking), (2) sleep patterns, (3) blood oxygen saturation levels, (4) body composition, (5) body weight, (6) calorie intake, (7) heart rate, (8) blood pressure, and (9) habitual physical activity (step counts and minutes of moderate and physical activity completed per day).

The SH app uses biometrics obtained by the connected wearable device, the smartphone itself, and self-reporting to record variables such as accelerometry, heart rate, time, distance traveled, and speed. Data are then used for activity tracking by matching the signature characteristics of a wide range of exercises (such as walking, hiking, or swimming) to calculate step counts, the number of minutes of moderate and vigorous physical activity completed, and the number of calories expended. The SH app supports tracking of food intake during the day. For instance, users can record meals and snacks as well as fluid and caffeine intake. Macronutrients (proteins, carbohydrates, and fats) and micronutrients (vitamins and minerals) can be calculated. The SH app also implements sleep analysis, sleep duration tracking, and sleep stages to provide insights about the quantity and quality of sleep.

GK App

The GK app is an mHealth solution that will be installed on a personal smartphone and paired with the SH app. Patients will use it to periodically fill self-assessment questionnaires and view data visualization analytics.

Web Portals and Tablets

To complement the data collected by the SH app, Samsung Galaxy watch, and GK app, the patients will fill in questionnaires. These questionnaires will be completed by patients using a tablet, and paper forms will be provided in cases where a tablet is not available. The questionnaires will cover data describing HRQoL, symptoms, sleep, and patient feedback on care. Patients will also use an web-based survey platform (Qualtrics) to fill in questionnaires about habitual physical activity, any structured exercise completed, and patient activation.

Recruitment Program

Participants will be identified from oncology services at Ysbyty Gwynedd Hospital, Betsi Cadwaladr University Health Board, by reviewing the outpatient clinic lists of each participating oncologist, advanced nurse practitioner, and clinical pharmacist on a daily basis. For potentially eligible patients, the appropriateness of proposing participation in this trial will be decided by the lead oncologist. At the end of the clinical consultation, if deemed appropriate, the clinician will introduce the study and provide the information leaflet, and a date in the future will be set for the volunteer to meet a member of the clinical research team to answer all the possible queries and to confirm sign-up for participation. If and when a participant agrees to proceed with the study, they will be asked to sign the consent form and will receive the smartwatch (and a smartphone, if required). The clinical research team member will help with the setup of the apps and smartwatch pairing and will provide a technical overview of both as well as the troubleshooting and contact information. Baseline questionnaires will be completed on a dedicated tablet or paper as per the recommended procedures with a standard approach to collect these patient-generated data with the supervision of the clinical research nurse or officer [16]. The same approach will be used to collect end-of-study questionnaires data. The expected recruitment period is January 2024 to June 2024, with the maximum duration of data collection for each participant set to up to 16 weeks. We anticipate being able to recruit about 5 patients per week over a 24-week period to reach our target.

Contingency Plans for Potential Recruitment Risks

For this monocentric pilot, we have built on previous experience within the oncology department with digital monitoring studies [17-19], and the estimated recruitment has been discussed at length between clinicians and research team members. A risk assessment analysis has been performed, and no transfer, avoidance, or prevention of the risk of poor recruitment has been identified. To mitigate the risk of lower than expected acceptance from the patients, we have trained the involved clinician to present the study to their patients, who were potentially eligible for participation, rather than simply referring them to the research team for study explanation. To mitigate the risk of poor engagement from the clinicians themselves, we have already involved them since the beginning of the study, and we have planned meetings between the delivery research team and clinicians after multidisciplinary team meetings to remind them of the study objectives and inclusion criteria. We have also printed a leaflet containing the main study features for each relevant outpatient clinic. Finally, we decided to accept the risk of slow recruitment as, within the GK project, we have no further studies pending upon the results of this study.

Study Procedures

Following the provision of written informed consent, the following measures will be obtained and recorded in the case report form (CRFs) at baseline and at the end of the study (16 weeks):

- Height (only measured at study entry)
- Body mass
- BMI
- Waist circumference
- Hip circumference
- Medical history
- Concurrent conditions
- Concomitant medications
- WHO performance status [15]
- Cancer type and stage
- Harms—adverse events.

We will record and report “unexpected” serious adverse events resulting in death, life-threatening complications, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital abnormality or birth defect, and other “important medical events” that are considered serious if they jeopardize the participant or require

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an intervention to prevent 1 of the abovementioned consequences.

The following adverse events are considered to be "expected": anxiety related to the monitoring of symptoms, diet, and exercise; distress related to the regular use of digital well-being technology; cutaneous allergic reactions to the smartwatch; and visual strain with the light-emitting smartphone screen.

The study uses the following questionnaires:

- EQ-5D-5L: Participants' HRQoL will be measured using the EQ-5D-5L questionnaire [20]. EQ-5D-5L is a widely used tool for assessing the domains of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression as well as recording patients' self-rated health on a visual analog scale.
- Multidimensional Fatigue Inventory Short Form: Multidimensional Fatigue Inventory Short Form [21] will be used to assess fatigue. This is a validated short form of the more in-depth Multidimensional Fatigue Inventory questionnaire [22] and uses 10 simple questions to assess physical, emotional, and cognitive fatigue [21].
- Satisfaction, Alertness, Timing, Efficiency and Duration (SATED): The SATED questionnaire [23] will be used to assess subjective sleep. SATED is a simple questionnaire to determine the degree of sleep fulfillment and to measure the dimensions of sleep health based on 5 simple questions [24]. It has been used in >150 peer-reviewed papers and studies.
- Patient Assessment of Chronic Illness Care: Patient Assessment of Chronic Illness Care questionnaire [25] will be used to assess experience with care. It is recommended for research and quality improvement and has been successfully deployed in digital oncology studies [26].
- Edmonton Symptom Assessment System (ESAS; digital form completed daily through the GK app): The global symptom burden will be assessed through ESAS [27]. ESAS has a recall time of 24 hours and is adapted to daily completion [28]. Daily total symptom distress scores (ESAS physical score+emotional score+well-being) [29] will be computed, and their temporal trajectories will be compared using general linear and random mixed effects models for longitudinal data [30].
- Global Physical Activity Questionnaire: Habitual physical activity will be assessed using the Global Physical Activity Questionnaire short form [31] and four unvalidated questions: (1) minutes of moderate physical activity completed per week, (2) minutes of vigorous physical activity completed per week, (3) number of sessions of strength training completed per week, and (4) number of sessions of balance training completed per week.
- Patient Activation Measure–13: Patient activation, an individual's knowledge, skills, and confidence integral to managing their own health and health care, will be assessed using the Patient Activation Measure–13 [32].

Table 1 lists the timeline and type of data collected throughout the study period.

Participants will then be presented with the mHealth solution: the GK app on a personal smartphone and a smartwatch paired with the SH app. The participant will be trained to use the apps and watch. The GK app features a set of interactive questionnaires to collect the baseline and periodic self-assessment data. Furthermore, the GK app provides timely reminders about the need to complete the self-assessments and data visualization analytics. Finally, the GK app collects and anonymizes data from the smartwatch and SH app for daily data collection on a dedicated remote server. The smartwatch adopted can be configured and used in different ways; each patient will be able to set up complementary apps offering extra functionalities such as the stress level analysis and to identify the preferred patterns of use. Overall, the data generated by the smartwatch will be collected and aggregated on a daily basis, including heart rate, sleep and physical activity patterns, and calories and food intake. The sampling of data will be dependent on the user settings and contingencies, such as charging at night or battery level. Throughout the 16-week study period, the smartwatch will continuously and unobtrusively record habitual physical activity, sleep patterns, energy expenditure, step counts, and oxygen saturation through its biosensors (Figure 1). For example, the amount of moderate and vigorous physical activity completed per week will be obtained automatically through the study using heart rate data recorded by the wearable smartwatch. Specifically, the maximal heart rate will first be predicted using the following formula: maximal heart rate = 207 − (0.7 × age) [33].

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Table 1. Data collected at each time point of the study.

	Baseline: day 0	Day 1-14	Daily from baseline	Thrice weekly (alternate days)	Weekly	End of the study (4 months +7 or −7 days)
Eligibility	✓					
Informed consent	✓					
Demographics	✓					
Height, weight, BMI, and waist circumference	✓[a]					✓
WHO[b] performance status	✓					
Medical history or concomitant conditions and medications	✓					✓
Cancer type and stage	✓					
ED-5D-5L	✓[a]					✓
MFI[c]-10	✓[a]					✓
SATED[d]	✓[a]					✓
PACIC[e]	✓[a]					✓
PAM 13[f]	✓[a]					
Issue of smartwatch and Android device if required	✓[a]					
Food diary				✓		
Weight					✓	
Physical activity appointment including cardiorespiratory fitness and muscular strength		✓				
GPAQ[g]		✓				✓
Habitual physical activity assessment		✓				
Minutes of activity done by patient including strength and balance					✓	
Borg's CR100 rating of perceived exertion scale					✓	
ESAS[h]			✓			✓
Continuous smartwatch data collection	✓[i]	✓	✓			
Usability questionnaire						✓
Adverse event assessment	✓[i]	✓	✓	✓	✓	✓
Collection of UKONS[j]	✓[i]	✓	✓	✓	✓	✓

[a]Conducted in person at baseline assessment visit.

[b]WHO: World Health Organization.

[c]MFI-10: Multidimensional Fatigue Inventory Short Form.

[d]SATED: Satisfaction, Alertness, Timing, Efficiency and Duration.

[e]PACIC: Patient Assessment of Chronic Illness Care.

[f]PAM-13: Patient Activation Measure–13.

[g]GPAQ: Global Physical Activity Questionnaire.

[h]ESAS: Edmonton Symptom Assessment System.

[i]To be collected from informed consent onward.

[j]UKONS: United Kingdom Oncology Nursing Society.

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Figure 1. Study schematic of the trial design (longitudinal and observational) with features of the patient-generated data collected through the smartwatch (objective and mostly continuous) and app (subjective and repeated measures or snapshots).

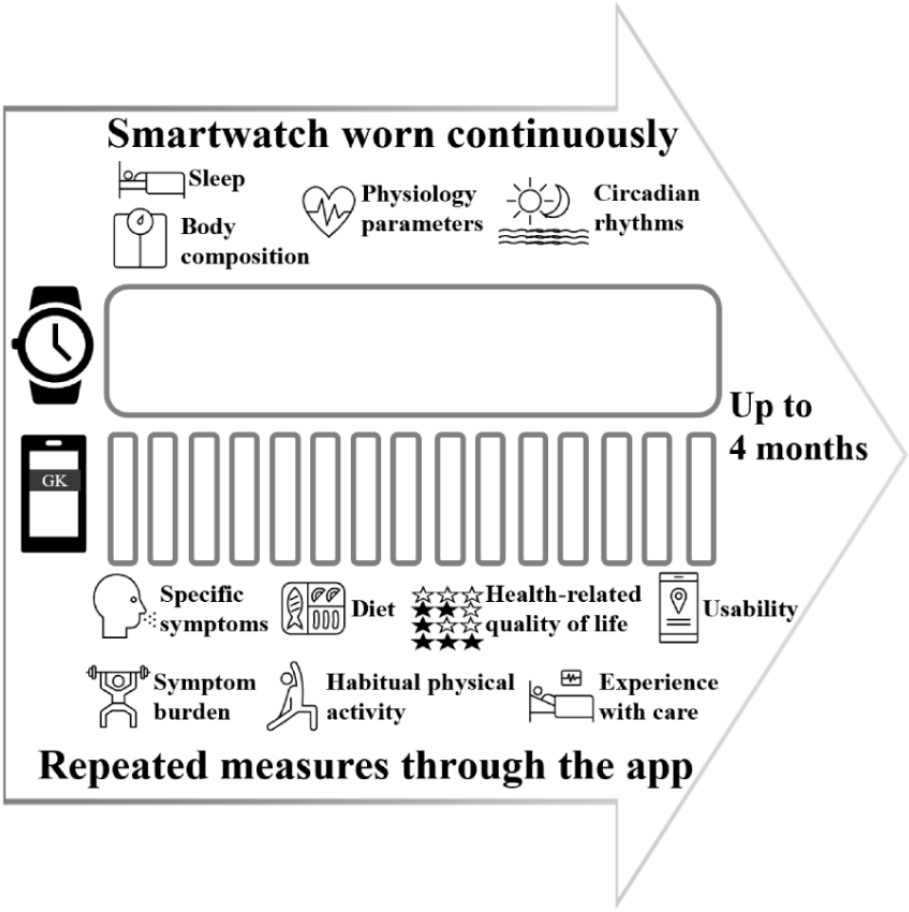

If a patient obtains a higher than predicted maximal heart rate during exercise, the actual maximal heart rate will replace the predicted maximal heart rate. The resting heart rate will then be recorded automatically by the watch. Heart rate zones will then be used to identify habitual physical activity intensity: very light (<30% heart rate reserve [HRR]), light (30%-39% HRR), moderate (40%-59% HRR), vigorous (60%-89% HRR), and near maximal to maximal (≥90% HRR) [34].

Energy expenditure during structured exercise will be estimated from the power output calculated from the mode of exercise, distance completed, and floors climbed. Other measurements such as body fat percentage, oxygen saturation, and blood pressure will be obtained using the standard features available within the smartwatch and smartphone.

The smartwatch will also prompt the participant to complete the ESAS questionnaire on a daily basis and to self-report the amount of habitual physical activity using the 4 abovementioned unvalidated questions on a weekly basis.

The SH app uses the Samsung Galaxy Watch to monitor sleep patterns, track sleep movements, and generate a sleep score. Additionally, the SH app provides daily goals and coaching programs based on sleep data to help improve sleep habits. Sleep analysis uses Samsung proprietary algorithms currently available through the public release of the SH app.

The SH app also allows the self-logging of the type and timing of meals and snacks. It is possible to set a daily target for caloric intake. After inputting details of the food type and quantity from a menu of common meals, the SH app provides a real-time view of the current calorie count for the day and a summary of the nutritional intake to determine if one is within the recommended levels. Moreover, it provides access to an overall dietary report over the span of a week.

Contact From the Research Team

To ensure compliance with the trial, a telephone call by a member of the research team to all participants will be arranged at week 1 and then, if required, every 4 weeks until the end of the trial data collection period. The nature of these calls is to resolve any problems or concerns. The frequency of calls will be arranged and adapted by the research team members on an individual basis according to each participant's needs and wishes. On the basis of prior experience with digital monitoring in patients with cancer [19], we believe that offering a regular opportunity to speak to someone who can help reassures participants, reduces anxiety, and in turn facilitates more accurate and consistent data collection.

Concomitant Care Permitted During the Trial

During the study period, each participant will receive the indicated surveillance and routine care in accordance with their needs and clinical condition. Thus, any form of intervention for the underlying cancer or any intercurrent issue will be allowed (and recorded). Similarly, any type of diagnostic investigation, workup, or health care provider encounter will be permitted.

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To maximize participants' safety, multiple measures have been put into place.

We will provide technical support and contact information for any inquiries, along with an escalation plan for clinical needs. This support includes online assistance, drop-in clinics, and remote technical support during office hours. Patients will be directed for any medical concerns to contact the Acute Oncology Hotline: 24/7 availability of the Acute Oncology Hotline support, to which participants have been accustomed during the on-treatment period in Alaw (oncology department in Ysbyty Gwynedd, Bangor, United Kingdom). The occurrence of any unplanned health care encounter (with general practitioner, district nurse, practitioner nurse, specialist nurse, dietician, physiotherapist, psychologist, occupational therapist, clinical pharmacist, or any hospital specialist) will be recorded with a weekly question through the GK app. Finally, members of the research team will be given access to a web-based portal, where they can log in and access patient data. Although data will not be checked with regard to patient clinical condition (the portal is designed to check only if data have been collected or not), for safety reasons, if when checking for data availability, the research team will notice any symptom with a severity score of ≥7 (on a 10-point scale) or any other potentially serious medical issue, the lead clinician or the consultant oncologist of the week (available 24/7) will be informed, and they will decide accordingly whether it is sensible to contact the participant to inquire about their complaint and select the most appropriate action.

Primary Outcome

The main outcome of this trial is to assess the feasibility of mHealth monitoring in survivors of cancer not receiving toxic anticancer treatment. A priori criteria based on a traffic light system will be used to determine whether mHealth monitoring is unfeasible and future trials should be halted (red), whether changes to the study design or mHealth intervention are required before future trials are initiated (amber), or whether mHealth monitoring is considered feasible, and progress to future trials can occur without modification of the study design or intervention (green) [35]. The traffic light system will be applied at the end of the 16-week study period following collection of the last follow-up assessment from the last participant (on an intention-to-treat basis) to the following feasibility outcomes: eligibility (no set criteria but number of patients screened and eligible will be recorded); recruitment rate (green: n =>75, amber: n =≥50, and red: n=<50); acceptability of randomization and assessment procedure (no set criteria but the characteristics [and the proportion by group] of participants withdrawing post randomization will be captured); mHealth acceptability (green: ≥50/100, ≥50% of participants engage with the app at least once a week on at least 12 weeks out of the 16-week study, amber: ≥50/100, ≥50% of participants engage with the app at least once a week on at least 8 weeks out of the 16-week study, and red: <50/100, <50% of participants engage with the GK app at least once a week on at least 8 weeks out of the 16-week study); attrition rate (green: 20/100, <20% dropout rate, amber: ≤40/100, ≤40% dropout rate, and red: <40/100, >40% dropout rate); and missing data (green: <20/100, <20% of data missing, amber: ≤40/100, ≤40% of data missing, and red: >40/100, >40% of data missing). Engagement with the GK app is defined as logging on and completing at least 1 of the scheduled measures (ESAS, food intake, or habitual physical activity).

Secondary Outcomes

All other measures (as described in the *Study Procedures* section and in Figure 2) are secondary outcomes. They will be obtained to explore the direction and effect size of any changes as a groundwork for the development of future trials with meaningful end points, if appropriate. HRQoL will be further used in cost-effectiveness analyses. Within GK, cost-effectiveness is being conducted with the Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP) tool [36] to support evidence-based decision-making processes for all institutions and users in the health care sector. The main objective of the MAFEIP tool is to estimate the outcomes of a large variety of social and technological innovations by providing an early assessment of the likelihood that interventions will achieve their anticipated impact. In addition, MAFEIP also helps identify the drivers of a technology's effectiveness or efficiency to guide further design, development, or evaluation. To conduct the cost-effectiveness assessment, all costs will be included in a comprehensive impact assessment (eg, hospitalizations, emergency department admissions, and procedures). The costs for treatment as usual will be collected from historical evidence to complement the comparison.

The patterns over 24 hours of accelerometry and heart rate measurements collected *continuously* (epochs defined through user settings ranging from hourly to continuously during workouts) through the smartwatch will be analyzed to retrieve relevant circadian (ie, of approximately 1 day) physiology parameters through cosinor, nonparametric, and hidden Markov model methods [37-40]. The circadian biorhythms parameters that will be retrieved integrate the endogenous body clock [41], physical activity, and sleep cycles [42]. Circadian rest-activity rhythm has shown relevance in oncology with regard to the well-being and overall survival of patients with cancer [43-45].

At 2 and 4 months, participants will also be asked to complete a usability questionnaire to obtain a System Usability Score [46] and a Net Promoter Score [47]. In addition, patients will be invited to attend a participant focus group. The focus group question guide will include two aspects: (1) experience of using the app and smartwatch during the previous 16 weeks and (2) a beta version of a future iteration of the app will be presented to the patients, and potential acceptability of the new features of this beta version will be explored.

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Figure 2. Summary of the pilot primary and secondary outcomes, which are categorized as subjective (from questionnaires) and objective (measured or from the smartwatch).

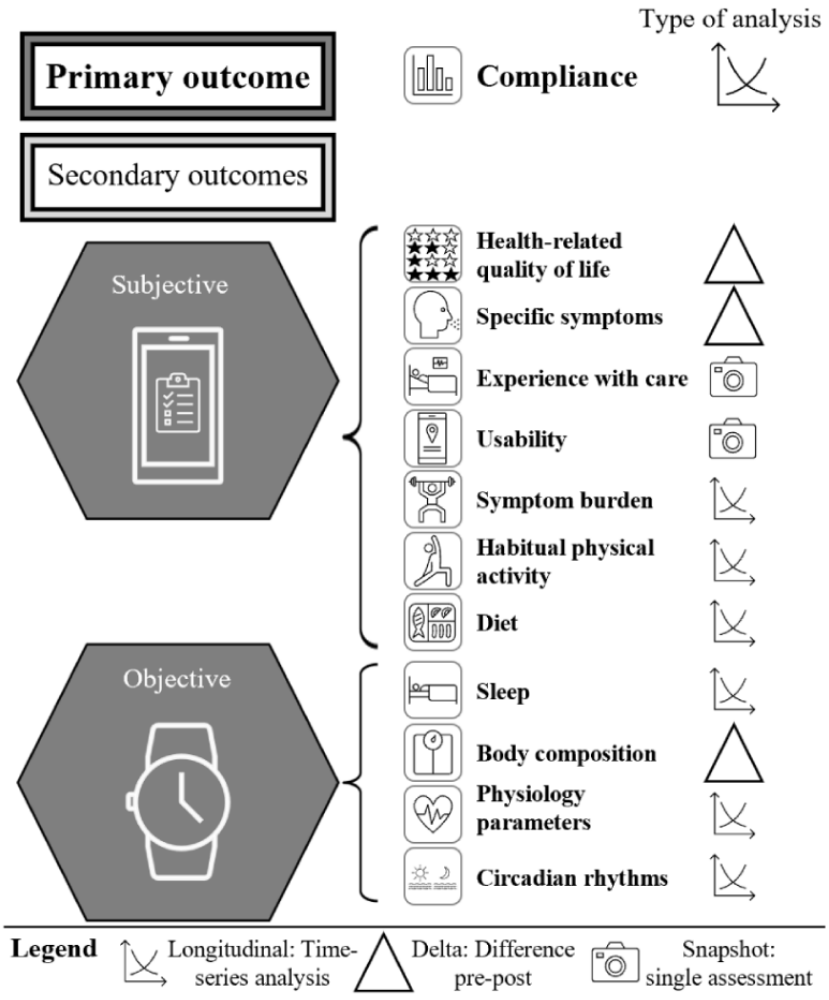

Exploratory Outcomes

The exploratory end points include the assessment of the precision (sensitivity and specificity) of AI-generated prediction of events based on the longitudinal patient-generated data sets. Specifically, events of interest will be severe symptoms requiring a call to the Acute Oncology Service (ranked amber and red on the United Kingdom Oncology Nursing Society triage tool [48]) or relapse (recurrence or progression) of cancer. Machine learning techniques applied to longitudinal datasets will be used, based on our previous experience [49].

Data Management

Data in this study are multidimensional and will be collected via a range of sources including paper-based CRFs, paper-based and electronic questionnaires (completed via the GK app), and biometric data obtained from the smartwatches. All anonymized data collected by the NHS research team via paper-based methods will be transferred into a secure digital database, in a locked room, and on a password-protected desktop computer, whose access will be logged and monitored and limited to the research team members involved in the study.

Raw accelerations and heart rate data collected through the smartwatch will be periodically and seamlessly downloaded and sent to the GK app onto the paired smartphone. Afterward, once a day, these data will be automatically and securely uploaded onto the GK repository server through the internet in an anonymized fashion, where they will be kept for further time-series analyses, as previously described.

Confidentiality and Data Protection Considerations

The sponsor (Betsi Cadwaladr University Health Board) has undertaken a full data protection impact assessment. To protect the confidentiality of participant data, paper-based CRFs and questionnaires will be linked to the participant via a trial identification number and stored in a separate location in the Investigator Site File containing the original consent forms. All paper-based documents will be stored in a locked cabinet in a restricted access office area. Participants will not be required to provide any personal information (such as name and date of birth) to register or use the GK app; instead, they will use the provided study account. The GK app will pull and anonymize data from the SH app, excluding contact details and other information that could be used to reidentify participants. The key linking the participant with the data set will only be held by the NHS research team and never be shared with other organizations.

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Trial Management and Risk Assessment

The sponsor has undertaken a risk assessment in line with the sponsor's standard operating procedures, and the overall trial has been assessed as moderate risk, principally in relation to the multidimensional monitoring. The trial conduct and progress will be monitored by a trial management group including independent experts and patients to provide advice and support. A trial risk-adapted monitoring plan has been developed to check the research procedures; evaluate overall safety; and assess protocol compliance, data accuracy, and completeness.

Statistical Considerations

The study's primary outcome is feasibility, which, by design, is assessed by multiple outcomes (as described above). Arguably, the most important of these is patient engagement with the mHealth solution, and we have defined the solution as feasible if at least 50% (50/100) of the participants engage with the app at least once a week in 8 of the 16 study weeks. If we recruit 100 eligible participants, we will be able to estimate an engagement rate of 50% (n=50) with a 95% CI of +10% or −10%, whereby the width of the CI (in percentage) was calculated as follows:

$$1.96\times\sqrt{(p\times(1-p)/n)} \quad \textbf{(1)}$$

where p is the percentage (50%) and n is the intended sample size (100). For this feasibility study, we considered this CI appropriate for estimating drop-off rates in future studies. Finally, we considered this sample size suitable for the preplanned exploratory subgroup analyses.

The main analysis of the primary outcome (compliance) will be performed on an intention-to-treat basis. Similarly, the secondary outcomes will be evaluated on an intention-to-treat basis. However, for the secondary outcomes, preplanned subgroup and sensitivity analyses will also be conducted. They will include (1) subgroups with at least 75% (75/100) of available patient-generated data (from the app and the smartwatch combined) to exclude unengaged participants and focus on the most committed participants, (2) subgroups defined by the performance status and presence or absence of evidence of neoplastic disease, and (3) subgroups defined by sex and median age. For the primary outcome, no form of inference will be performed on the missing data, as they provide the main outcome of the study. For secondary analyses, neither mean imputation nor the last observation carried forward will be used [50]. However, based on the proportion of missing data, exploratory analyses including low-rank approximation–based imputation [51] could be performed to ensure that the observed effect sizes remain of the same order of magnitude with this approach as well.

Results

As of January 8, 2024, we are performing the last preparatory steps before enrollment, such as finalizing letters for GPs and internal communication to the oncology department staff about the study, its finalities, and referral criteria.

We anticipate enrolling the 100th patient by the end of June 2024. Thus, the last patient's last visit is expected in late November 2024. We foresee an additional month to complete the data collection and solve the pending queries. Data analyses will then be performed once all data have been collected, and the database will be frozen. Primary and secondary outcomes will be prioritized over the exploratory and sensitivity analyses. The overall evaluation of the study will be presented as part of the results of the GK large-scale pilot to the EU Commission and via the project web portal.

The main outcomes will be submitted for publication to an appropriate peer-reviewed scientific journal and, if opportune, to a scientific meeting in the domains of oncology, digital health, behavioral medicine, and sport and exercise science. Additional reports of specific findings elaborated more in depth will be considered for submission for scientific publication or presentation, according to the pertinence of the results obtained and their clinical and scientific relevance.

Discussion

Study Goals and Expected Findings

This study aims to determine the feasibility of self-monitoring of symptoms, biometrics, and behavior using an mHealth solution. If feasible, the efficacy of the mHealth solution will be addressed in subsequent studies. Ultimately, this study has two synergic objectives: (1) The first concerns the improvement of the quality of life and expectancy of independent active life. (2) The second concerns the cost-benefit to health care systems facing an increasing number of older adults and an increase in life expectancy, which is not compensated by a comparable increase in budget and staff. Regarding the first concern, in the case of patients with chronic conditions, this expectation should be considered in the context of the detrimental effects of long-term treatments and stress and anxiety related to the monitoring period. Regarding the second concern, the ultimate goal of the mHealth solution is to lower the likelihood of hospitalization, the worsening of patients' conditions, and the resulting complexity of life-long treatments. In this regard, the mHealth solution we propose to evaluate here for acceptance and compliance aims to ultimately lower the risks of worsening and adverse events via a combination of (1) early prediction leading to early intervention, and (2) prevention through behavioral intervention focused on the wide-spread adoption of good healthy lifestyle practices.

Technology is a key enabler in achieving these synergistic objectives. On the one hand, devices and apps lower the cost of monitoring while improving the variety, granularity, and frequency of data. For instance, apps exploit patients' hardware, freeing up time during appointments to be used to discuss patients' well-being. In the context of cancer survivorship and unmet care needs, the use of digital tools to try to overcome some of the barriers to the adoption of a healthy diet, sleep, and exercise behaviors is particularly relevant from the clinical, scientific, and health economics standpoints.

Thus, this observational pilot study has been tailored to provide feasibility evidence in view of future interventional studies aimed at specifically addressing some of the unmet needs of survivors of cancer. The personalized promotion of healthy

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habits, including diet, sleep, and physical activity, as pillars of supportive care in survivors of cancer combined with the monitoring of signs and symptoms is expected to improve (or at least sustain) HRQoL. Moreover, given its relatively inexpensive implementation and the potential for benefits, we expect such an intervention to be cost-effective.

With this objective in mind, we have selected multiple secondary end points, all relevant for gaining insight into (1) the effect size of the clinical impact of the mHealth solution on symptom burden, HRQoL, and perceived care; (2) the temporal patterns of physical activity, diet, and sleep in survivors of cancer; and (3) the usability of such digital solutions. In our opinion, collecting these dense, multidimensional, longitudinal patient-generated data is paramount for the development of new forms of tailored behavioral interventions. Indeed, initial evidence in oncology is being produced, testing integrative behavioral approaches to improve cancer-associated and treatment-induced symptoms [5,52-58].

Along with these observational outcomes, patient safety remains paramount in our pilot and in all future interventions [59,60]. Therefore, besides the patient-prompted 24/7 acute oncology helpline, we have also put in place a safety net by which the clinical research team will have access to the web-based dashboard summarizing all the ESAS scores and the smartwatch objective data, with the possibility of escalation to the leading oncologist in case of severe symptoms or profoundly abnormal vital data. Moreover, as part of the exploratory analyses, we plan to use AI to investigate whether adverse events (unplanned health care provider encounter, emergency admission, or severe symptoms) could be reliably predicted between 3 and 5 days in advance from the temporal patterns of the collected objective and subjective patient-generated data [61-64]. Finally, we plan to use the same AI-enabled predictive approach to explore the accuracy of predicting cancer relapse at least 3 weeks before formal clinical suspicion. However, we expect relatively few such events during the study period.

Strengths and Limitations

The main limitations of this study include the choice of a very heterogeneous population of survivors of cancer, at very different stages of the clinical trajectory of their disease, as well as marked diversity in terms of prognosis. This was a deliberate choice for our first pilot, influenced by recruitment time constraints exacerbated by the disruption in research delivery caused by the COVID-19 pandemic. Associated with this is the monocentric nature of the study, a limitation in terms of potential generalizability but a compelled choice for an initial testing of the digital solution in a pilot feasibility trial.

We also acknowledge that the behavioral medicine approach deployed in this study has been derived mainly from published evidence [65,66] and minimally from in-house expertise. Thus, we have consciously selected to simplify our behavioral change approach, for example, avoiding ecological momentary assessments [67] or interpersonal social rhythm interventions [68].

We also accept that technology faces some barriers to adoption. From digital literacy to internet access, a large segment of the older adult population does not have or does not wish to use digital technology. Although this is likely a temporary challenge, characteristic of a demographic transition, it provides the need or opportunity to design noninvasive solutions that blend within our activities and habits. In the case of patients with chronic conditions, this type of design can be seen as part of the effort in mitigating the long-term effects of having to manage their conditions and treatments on their mental health and well-being.

Despite these limitations, we believe that this pilot study is both timely and relevant. Digital monitoring in oncology is becoming increasingly widespread and often integrates both patient-reported outcomes and data from a wearable biosensor [69-73]. We focus here on survivors of cancer after treatment, a population in which gaps in research have been identified [73]. Integrating in the future, an interventional approach of tailored coaching for behavioral change alongside the longitudinal multidimensional digital telemonitoring, we trust this pilot can provide unique and novel insight into the clinical relevance of predictive, preventive, personalized and participatory (P4) medicine in survivors of cancer [74]. Thus, we anticipate that if feasibility is demonstrated with this pilot study, we will test a novel form of AI-enabled digital behavioral intervention in a future dedicated randomized study. Such a future intervention could include (1) an initial dietary, sleep, and physical activity consultation; (2) behavioral monitoring recorded via a smartphone app and wearable smartwatch; (3) monitoring of symptoms and health medical records; (4) integration of data to allow delivery of AI-generated, personalized digital coaching on nutritional and physical activity behaviors; and (5) development of risk prediction algorithms to allow early identification and management of cancer-related symptoms, hospitalization events, and cancer relapse.

Conclusions

As part of the GK large-scale pilot, this study (its design, anonymized data, results, and technologies) will be made available to other selected health care organizations. These organizations, such as regional health care agencies and hospitals, will assess and evaluate the proposed approach with the aim of transferring the lessons learned from the study and, ideally, readapting and adopting this approach to their context, resources, and constraints. These activities are part of a specific *twinning* work strand that is open to both GK Reference Pilot Sites and third-party health care organizations interested in practices exchange and in being early adopters of new AI solutions.

This study is one of the many being developed within the scope of the GK project, all of which share the underlying aim of improving the quality of life of the aging population and people living with chronic conditions. However, this is 1 of the only 2 GK studies focused on cancer, with a study in Cyprus focusing on palliative care for the end of life [13]. As such, this is the only pilot in the GK large-scale pilot that addresses the challenges of long-term monitoring of cancer symptoms. Although its uniqueness is limited only to the GK projects, this study provides essential input to understand how a fairly common technological setting (a mobile app and wearable) can be adapted to this scenario and be potentially used at scale for

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lifelong monitoring of survivors of cancer. This type of study generates an unprecedented quantity of multidimensional and longitudinal datapoints. It provides an opportunity but also a new set of risks. Indeed, part of the GK project activities concern the legal, policy, and practical arrangements necessary to move, share, combine, and reuse patient data. This is a significant challenge that can be addressed through this type of study, which is also aimed at identifying hidden barriers. Furthermore, this new setting presents both a challenge and an opportunity to redefine the relationship between patients and caregivers. It raises questions about the optimal use of data to promote dialogue and enhance understanding of the recovery journey after discharge, such as from a cancer support service.

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Data Availability

The data sets generated and analyzed during this study will be made available in the Open Research Online repository of the Open University.

Authors' Contributions

PFI, JHM, WS, LL, LP, and AA contributed to the conception of the study. PFI, JHM, WS, IN, CA, RE, SR, and AA contributed to the design. PFI, JHM, WS, LL, RG, IN, CA, FF, JdB, and AA drafted the paper as the first authors. PFI and AA were responsible for funding acquisition and CPS helped in funding support. All authors performed contributed to critical review.
All coauthors gave their final approval for submission and agreed to be accountable for all aspects of this study.

Conflicts of Interest

CA and RA are employed by Health Innovation, Samsung, Communications House, United Kingdom, and as part of their paid employment, they have helped develop the digital health solution used in this study. No patent applications (pending or actual), including individual applications or those belonging to the institution to which the authors are affiliated, have been submitted regarding the digital health solution. All other authors declare no other conflicts of interest.

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Abbreviations

AI: artificial intelligence
CRF: case report form
ESAS: Edmonton Symptom Assessment System
EU: European Union
GK: GATEKEEPER
HRQoL: health-related quality of life
HRR: heart rate reserve
MAFEIP: Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing
mHealth: mobile health
NHS: National Health Services
SATED: Satisfaction, Alertness, Timing, Efficiency and Duration
SH: Samsung Health

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Protocol

KIJANI App to Promote Physical Activity in Children and Adolescents: Protocol for a Mixed Method Evaluation

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Abstract

Background: The prevalence of physical inactivity among children and adolescents is alarmingly high despite the well-documented and comprehensive benefits of regular physical activity (PA). Therefore, PA promotion should start early in childhood and adolescence. Although reducing recreational screen time in children and adolescents is an urgent concern, digital approaches have the potential to make activity promotion attractive and age appropriate for the target group. KIJANI is a mobile app approach to promote PA in children and adolescents via gamification and augmented reality.

Objective: This study protocol aims to describe the KIJANI intervention in detail, as well as the evaluation approach.

Methods: KIJANI is based on the concept that virtual coins can be earned through PA, for example, in the form of a collected step count. With these coins, in turn, blocks can be bought, which can be used to create virtual buildings and integrate them into the player's real-world environment via augmented reality. PA of users is detected via accelerometers integrated into the smartphones. KIJANI can be played at predefined play locations that were comprehensively identified as safe, child-friendly, and attractive for PA by the target group in a partner project. The evaluation process will be divided into 2 different stages. The phase-I evaluation will be a mixed methods approach with one-on-one semistructured interviews and questionnaires to evaluate the user experience and receive feedback from the target group. After the implementation of results and feedback from the target group, the phase-II evaluation will proceed in the form of a 2-arm randomized controlled trial, in which the effectiveness of KIJANI will be assessed via objectively measured PA as well as questionnaires.

Results: The study received ethical approval from the ethical board of the Technical University of Munich. Participants for the phase-I evaluation are currently being recruited.

Conclusions: The study will help to determine the efficacy, applicability, and user experience of a gamified activity promotion application in children and adolescents. Overall, digital health approaches provide easy and wide reachability at low cost and are age appropriate and attractive for the target group of adolescents. Strategies have to be developed to apply digital health approaches in the best possible way for activity promotion.

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KEYWORDS

physical activity; health promotion; digital health; gamification; childhood; adolescence; adolescents; adolescent; children; augmented reality; KIJANI intervention; KIJANI; intervention; user experience

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Introduction

Physical inactivity has emerged as a worldwide pandemic, constituting the fourth leading cause of mortality worldwide [1]. A study involving 1.6 million healthy adolescents aged 11 to 17 years revealed that a staggering 81% of healthy youth are not sufficiently physically active [2]. The situation has been further exacerbated by the emergence of the COVID-19 pandemic and its associated restrictions that have further increased physical inactivity among adolescents. According to current analyses, activity levels among healthy youth decreased by 20% during the COVID-19 pandemic [3]. The prevalence of physical inactivity among children and adolescents is alarmingly high despite the well-documented and comprehensive benefits of regular physical activity (PA) including improvements in physical fitness, cardiometabolic health, bone health, cognitive performance, and mental health, among other benefits [4].

Adolescence marks a critical transitional phase during which health habits such as an active lifestyle and future health behaviors are established and manifest [5]. This implies the presence of a tracking effect of PA, whereby the more active a person is during childhood and adolescence, the more likely they are to remain active in adulthood [6,7]. Therefore, PA promotion starting from childhood and adolescence is of immense importance.

Although reducing recreational screen time in children and adolescents is an urgent concern and is strongly recommended by the World Health Organization, the potential of digital technology to make prevention and health promotion attractive and age appropriate for adolescents needs to be recognized [4]. Adolescents are power users of technology, and digital approaches allow them to reach adolescents in their personal environment. To promote PA in the particularly important phase of adolescence, we have developed a digital intervention approach called “KIJANI” that provides new opportunities for promoting and supporting PA. Specifically by targeting children and adolescents, the interdisciplinary project aims to motivate the target group through an app with a game-based concept and augmented reality to engage in PA, especially outdoors [8]. Various studies have demonstrated that gamification in health applications positively influences the behavior of the target audience [8-10] and enables children and adolescents to achieve recommended activity goals in a playful context [11]. Based on a review exploring the potential of augmented reality games for children and adolescents, the fusion of virtual and real-world elements offers promising opportunities to enhance PA and social interaction [12]. Augmented reality integrated into exergames has shown particular appeal among children [13], possibly due to their innate inclination toward play, making children an ideal target audience for gamified activity promotion [9].

This paper describes the KIJANI intervention in detail as well as the study protocol for its evaluation.

Methods

KIJANI Intervention

The name KIJANI is Swahili and translates to “green.” It stands as a German abbreviation for “Children & Youth: active, nature-conscious, innovative!” KIJANI is a smartphone app explicitly developed for children and adolescents to increase PA through a gamified approach. The basic game concept is that virtual coins can be “earned” through PA, for example, in the form of a collected step count. These coins can in turn be used to “buy” blocks, which can be used to create virtual buildings and integrate them into the player’s real-world environment via augmented reality, see Figure 1. Using challenge-achievement-reward loops as provided via the coin reward system in KIJANI was shown to increase the desire to play in previous research [14]. PA of users is detected via accelerometers integrated into smartphones and is linked to the KIJANI app on a technical basis.

Earning coins is based on a fitness challenge in the app, for example, consisting of 10,000 steps per day. The achievement of the main goal as well as intermediate goals are rewarded with coins. The main goal of 10,000 steps is rewarded with 50 coins, and intermediate goals, for example, 5000 steps, are rewarded with 20 coins. The blocks differ in price, for example, grass and brick cost 2 coins, water and bookshelf cost 5 coins, and the most expensive is glass and gold with 10 coins. Some blocks such as dirt and stone are free and unlimited to ensure enjoyment for the users. A progress bar in the app shows the individual progress over the course of the day, encouraging participants to reach the daily goal.

KIJANI is designed to be played both alone and with friends in a group. To play together with friends, requests must be sent and confirmed. Then KIJANI can be played together in a group and buildings can be created together. Players can individually specify who can visit, build, and administrate buildings, which ensures that no uninvited players can participate and therefore is another safety issue in KIJANI. In addition, the individual activity behavior can be compared with friends in a ranking list, which is another incentive for PA, see Figure 2. The ranking is also available for nonfriends, as there is a setting to show all players.

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Figure 1. An overview of screens in the KIJANI app: KIJANI home screen (left), KIJANI shop to buy blocks (middle), and KIJANI game in augmented reality (right).

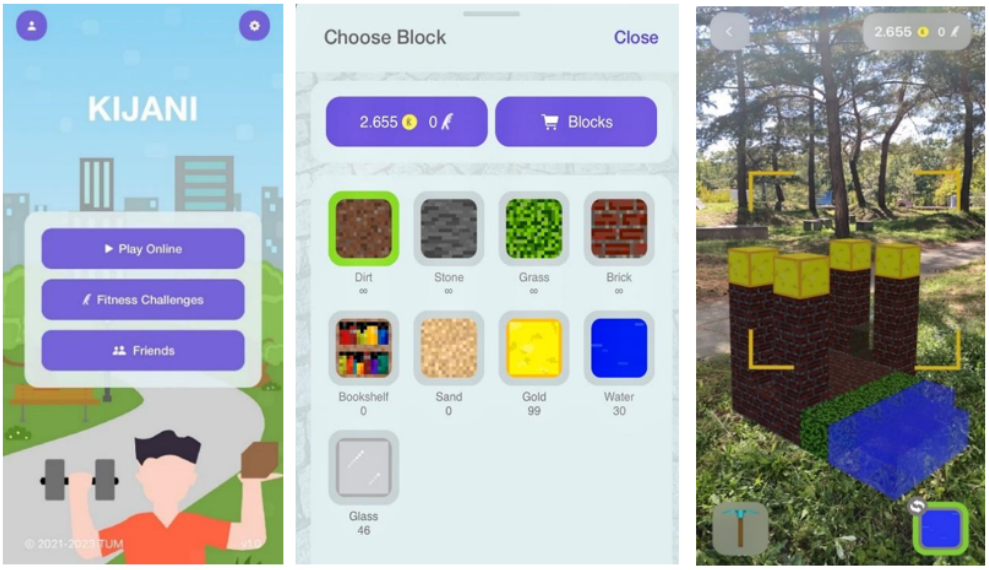

Figure 2. The features of the KIJANI app to connect with friends: friends ranking (left) and friends list (right).

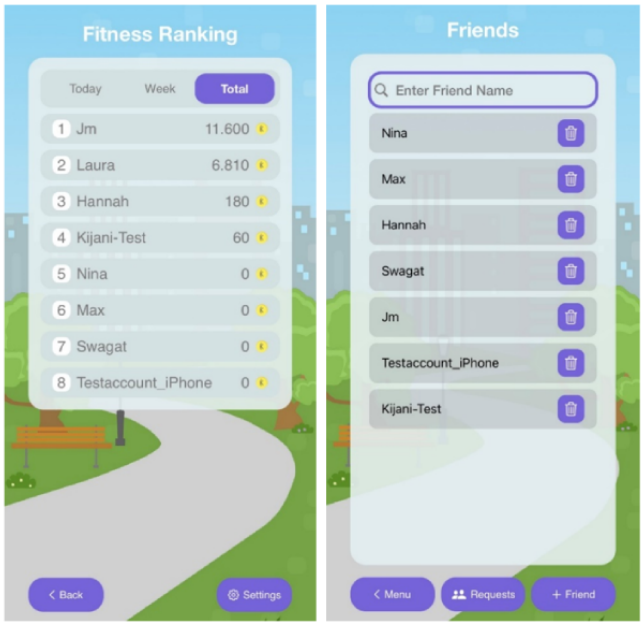

KIJANI was developed in cooperation with the research project "WALKI-MUC – Evaluation of physical activity opportunities and walkability perceived by children and youth in Munich," conducted by the Associate Professorship of Didactics in Sport and Health at the Technical University of Munich. In WALKI-MUC, children and adolescents aged 6 to 17 years (n=93) identified walkable places in Munich (places within walking distance from their homes) that they considered supportive of PA. The participants provided qualitative descriptions of these PA-friendly places through participatory methods such as photovoice, walking interviews, and mapping exercises while researchers tracked the walked routes and GPS locations. Focus group discussions and the one-on-one sharing of the individual significance of these places in interviews provided insights into factors contributing to safety and attractiveness (eg, accessibility and presence of people) at the locations, as perceived by the children and adolescents. The descriptions and locations of these identified PA-friendly places of WALKI-MUC are incorporated into the KIJANI app. KIJANI can only be played in these comprehensively defined, child-friendly locations, ensuring that KIJANI can only be used in a safe and appealing environment for the target group. There is a location search feature implemented in the KIJANI app to find the play locations in the close environment. In addition, the route to the locations is displayed on the map (see Figure 3). This not only encourages users to be active but also supports a healthy lifestyle as extra steps can be accumulated.

At these play locations, a server is created in which KIJANI is played. Multiple servers can be created at 1 play location so that different buildings with different friends can be created at 1 play location. If players want to play in groups, friends have to be invited to the server to ensure that the players are in a safe play environment where no one else can intrude.

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Figure 3. The WALKI-MUC map with play locations (left) and the navigation to play locations (right).

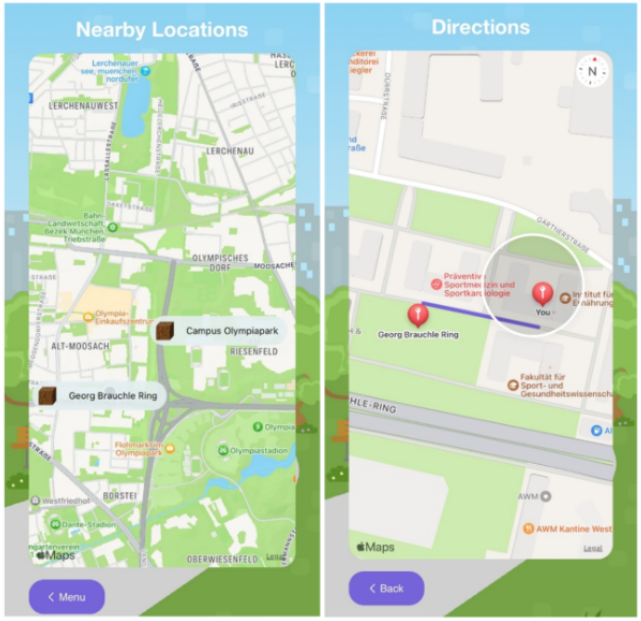

Evaluation Design

It is planned to evaluate the KIJANI app in a 2-phase approach as displayed in Figure 4. The phase-I evaluation will be a mixed methods design, in which the target group evaluates the user experience of the KIJANI app. The phase-II evaluation will be a 2-arm randomized controlled trial (RCT), in which the intervention group (IG) will use the KIJANI app, while the control group (CG) will not use the KIJANI app. Within this second evaluation stage, the effectiveness of KIJANI will be assessed via objectively assessed PA as well as standardized questionnaires.

Figure 4. The evaluation procedure with the phase-I and phase-II evaluations and feedback loop.

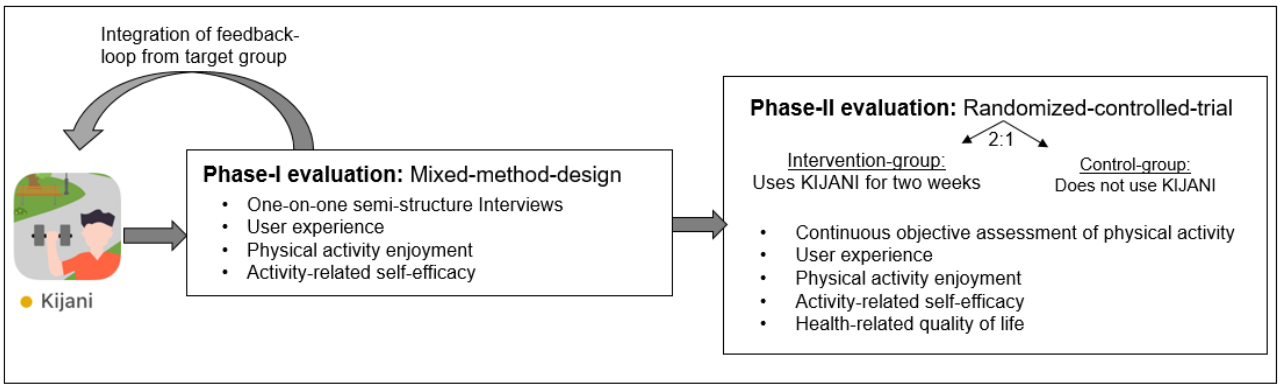

Ethical Considerations

The study protocol has already been approved by the ethical board of the Technical University of Munich (project 2023-185-S-NP). All children and their guardians will provide written informed consent.

For the described evaluation study of KIJANI, a development version of the app is used and distributed through TestFlight. Participants are required to log into the app using pseudonyms to safeguard their data privacy. Throughout app use, step count and GPS location are shared and digitally stored in a firebase. Personal data is processed in accordance with the provisions of the current data protection laws pursuant to Art. 12 (1) BayDSG. Prior to the official release of KIJANI, all necessary international regulations will be considered.

Participants and Enrollment

Children and adolescents at the age of 10-16 years will be included in this study. Children with walking impairments and cognitive impairments that hinder their ability to understand the task will be excluded from the study.

Phase-I Evaluation

Overview

The primary outcome of the phase-I evaluation is the individual evaluation and feedback on KIJANI by the target population. Study participants will use the KIJANI app for 25 minutes in a group of 3 participants at a KIJANI play location under the supervision of the researcher. For this evaluation design, participants will have enough coins available as the main focus is on the user experience with KIJANI. Researchers ensure that all participants of a group have sufficient time and experience

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with the app allowing them to give informed feedback at a later stage. Afterward, the app will be evaluated qualitatively with each participant in one-on-one semistructured interviews as well as quantitatively with standardized questionnaires on user experience, PA enjoyment, as well as activity-related self-efficacy.

Qualitative Evaluation

In one-on-one semistructured interviews, participants will report on their opinions and experiences with KIJANI. For this purpose, a previously generated interview guide, including mainly open - ended questions, will be used. The interview guide includes warm-up questions to establish a good relationship with the participants and to inquire about their attitudes toward smartphone use, digital games, as well as PA. The main part of the interview is related to the participants' opinions on the KIJANI app, including questions about what participants liked and what they would improve in the app. At the end of the interview, participants will have another opportunity to express further comments and ideas. All interviews will be conducted in person, audio recorded, and then transcribed verbatim. Interviewers will not be familiar with the participants prior to study initiation. The interviews will be evaluated by the respective interviewer. For evaluation purposes, categories will be generated guided by a systematic reduction process during data analysis. Text sequences will be classified into suitable categories, and thereby codes will be generated inductively. Possible uncertainties concerning the coding scheme will be discussed by the researchers and homogeneously adjusted. Data collection will proceed until data saturation has been achieved. Data will be considered saturated when recurring codes are observed across various interviews, accompanied by a decreased emergence of new codes during analysis (inductive thematic saturation). The qualitative evaluation process is displayed in Figure 5.

Figure 5. The procedure of the qualitative evaluation process of KIJANI.

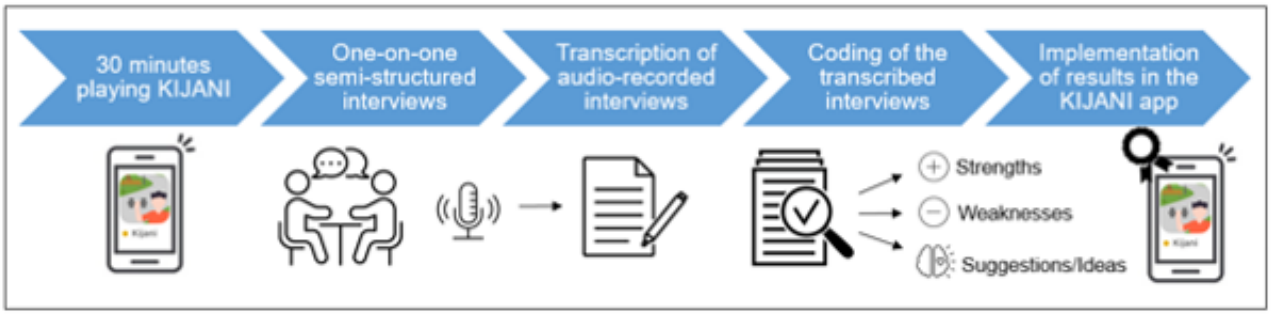

User Experience

In addition, the user experience with the KIJANI app is evaluated with a user experience questionnaire [15]. User experience thereby summarizes different aspects that are important for the subjective evaluation of a product: usability aspects, joy of use, as well as aesthetic design. The user experience questionnaire consists of 26 bipolar terms (pairs of opposites, eg, annoying and enjoyable), which are evaluated over 7 levels. The items consist of the following 6 domains: effectiveness, transparency, predictability, stimulation, originality, and attractiveness. The questionnaire shows high reliability and construct validity [16].

PA Enjoyment

PA enjoyment is evaluated using the short version of the PA Enjoyment Scale (PACES-S). The PACES-S is a measurement tool commonly used in intervention research to measure enjoyment of PA, as it is closely associated with adherence and compliance to PA guidelines [17]. The German version of the PACES is reliable and valid for use in children and adolescents [18]. The short version of the questionnaire consists of 4 items with 5 scales (eg, PA brings me joy). It shows comparable measurement properties to the long version of the PACES and is therefore used in this study [19].

Activity-Related Self-Efficacy

Perceived self-efficacy in the context of PA is measured using the German version of the PA Self-Efficacy Scale. The scale consists of 8 items, each of which is answered on a 5-point Likert scale ranging from 1 ("do not agree at all") to 5 ("fully agree"). The self-efficacy scale for PA measures activity-related self-efficacy with 6 items and activity-related social support from family and friends via the remaining 2 items. The reliability and validity of the German version were shown in a study with 454 schoolchildren [20].

Phase-II Evaluation

Overview

After the implementation of the results of the first evaluation phase, the second evaluation in the form of an RCT will be conducted. The IG will use the KIJANI app in their everyday life over a period of 2 weeks, while the CG sticks to their normal everyday life without using the KIJANI app. Randomization will be 2:1 into IG and CG, with the randomization process clustered by age and gender to ensure equal distribution in the groups. The phase-II evaluation sample size was calculated with G*power (2-sided α of 0.05, power 0.9). A sample of 62 participants is planned for this study. Of these, 41 participants will be assigned to the IG and 21 participants will be assigned to the CG. After completion of the study, the CG will also have the opportunity to use the KIJANI app.

The primary outcome of the phase-II evaluation is the everyday PA of the children and adolescents. PA is objectively recorded in the form of daily step count via accelerometers integrated into the smartphone over the entire study period in IG and CG.

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Through the KIJANI intervention, we hope to increase the PA of children and adolescents by 10%.

Secondary end points are health-related quality of life, activity-related self-efficacy, PA enjoyment, as well as the user experience with the app. The last 3 will be investigated as described above in the phase-I evaluation. Secondary end points will be assessed before and after the intervention period.

Health-Related Quality of Life

Health-related quality of life is self-assessed by the Kinder Lebensqualitätsfragebogen (KINDL) questionnaire. The KINDL is a generic instrument for assessing health-related quality of life in children and adolescents. For study participants younger than 14 years, the KINDL child version is used, and for study participants 14 years and older, the KINDL adolescent version is used. The KINDL is a short, methodologically tested, and flexible measurement instrument consisting of 24 questions on the 6 domains of body/physis, feelings/psychology, self-assessment, family, friends, and school [21].

Statistical Methods

The data analysis will involve both descriptive and analytical analyses. Initially, descriptive analysis will focus on the sociodemographic characteristics of the study population. Normal distribution of the data will be tested with the Shapiro-Wilk test. In terms of dropouts, intention-to-treat analysis will be performed using multiple imputations, to be able to calculate with a complete data set. To capture the longitudinal development of the activity level throughout the study period, a linear mixed model will be used to compare the change of the PA behavior over time between IG and CG. To investigate differences between the groups in activity-related self-efficacy, health-related quality of life, and PA enjoyment, these will be compared with 2-tailed *t* test or Mann-Whitney *U* test as appropriate depending on the distribution of the data. All analyses will be performed with RStudio (version 4.1.2; RStudio Team), with the level of significance set to 2-sided *P* values <.05 for all tests. RStudio was used for its tailored integration with the R programming language, providing an efficient and organized environment for reproducible data analysis, visualization, and documentation in our scientific study.

Results

Once the phase-I evaluation is completed, the outcomes will be discussed with the app development team and adjustments will be incorporated in KIJANI through this feedback loop. Data collection for the phase-I evaluation started in August 2023 and recruitment is currently still ongoing.

Discussion

Principal Findings

KIJANI is a mobile game explicitly developed for PA promotion in children and adolescents with a special focus on creativity as well as PA in the outdoor setting. The objective of the KIJANI intervention is to increase everyday PA in adolescents through a digital intervention approach using gamification and augmented reality. This study protocol describes the KIJANI intervention in detail, as well as the evaluation approach.

Even though activity promotion is highly indicated in adolescents, this young target group is difficult to reach, and adherence to intervention approaches, especially over the long term, is mostly rather low [22].

Several previous studies have assessed the effectiveness of mobile health approaches to increase PA in healthy adolescents. A systematic review on the effects of mobile health to increase PA concluded that mobile devices and apps may be an effective strategy for promoting PA in adolescents as they have high technology use. However, overall, there is only a small number of studies; a lack of RCTs; and a high risk of bias in this research sector, mostly including self-reported measures with the risk for recall as well as report bias [23]. Another systematic review on the quality and features of apps to improve PA, sedentary behavior, and diet also reported that generally, very few apps are available that specifically target children and adolescents and app quality was only moderate [24]. Overall, there is a need for high-quality app-based activity promotion approaches especially in children and adolescents.

Some previous studies have assessed the effects of digital gamification approaches on activity promotion. A meta-analysis revealed that the popular mobile augmented reality game “Pokémon Go” was associated with a significant increase in the users’ daily step count. In the game, participants are required to travel to different locations to capture virtual characters. Even though the game was not primarily designed to promote PA, it has reached masses of users and has shown to have the potential to influence their health behavior at least in the short term [25]. Long-term results are rare, but it seems that the novelty effect tends to wear off with time, and after 3 months, 80% of players stopped using the app [26].

Direito et al [27] assessed the effect of 2 smartphone apps, 1 immersive and 1 nonimmersive app, on cardiorespiratory fitness and PA levels in healthy young people. Both apps consisted of 8-week training programs, whereby in the immersive app the training program was embedded with a story where the user has to collect supplies and protect a town from zombies. After 8 weeks, they were not able to report any intervention effect compared with a CG in both apps. Adherence to app use was a major concern during their investigation [27].

Garde et al [28] evaluated another smartphone app called “MobileKids Monster Manor,” in which behavioral psychology, positive peer pressure, and rewards are used with a monster character theme to increase PA in healthy adolescents. In a school-based environment, this intervention increased PA over a short-term period [28].

Limitations

Several limitations should be considered when discussing this study protocol. In the phase-I evaluation, one-on-one interviews carry the risk of social desirability bias, where participants may provide responses perceived as socially acceptable rather than expressing their true opinions or behaviors. The phase-II evaluation carries the risk of the Hawthorn effect, which implies the awareness of being observed and studied that impacts

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people's behavior. Based on this effect, PA levels might be higher than normal throughout the measurement period of 2 weeks.

Conclusions

Overall, digital health approaches provide easy and wide reachability at low cost and are age appropriate and attractive for the target group of adolescents. Strategies have to be developed to apply digital health approaches in the best possible way for activity promotion. The study will help to determine the efficacy, applicability, and user experience of a gamified activity promotion application in children and adolescents.

Acknowledgments

This study was funded by an unrestricted grant from the Bavarian State Ministry for Health and Care (StMGP) as part of the initiative "Gesund.Leben.Bayern."

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JM, BB, DAS, and LW were all involved in the development of the study protocol. LW prepared the initial draft of the manuscript. FS, LMR, and SJ developed the KIJANI app. ROF and JM gave important input for revising and improving the quality of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CG: control group
IG: intervention group
KINDL: Kinder Lebensqualitätsfragebogen
PA: physical activity
PACES: Physical Activity Enjoyment Scale
PACES-S: short version of the Physical Activity Enjoyment Scale
RCT: randomized controlled trial

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Protocol

A Factorial Randomized Controlled Trial to Optimize User Engagement With a Chatbot-Led Parenting Intervention: Protocol for the ParentText Optimisation Trial

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Abstract

Background: Violence against children (VAC) is a serious public health concern with long-lasting adverse effects. Evidence-based parenting programs are one effective means to prevent VAC; however, these interventions are not scalable in their typical in-person group format, especially in low- and middle-income countries where the need is greatest. While digital delivery, including via chatbots, offers a scalable and cost-effective means to scale up parenting programs within these settings, it is crucial to understand the key pillars of user engagement to ensure their effective implementation.

Objective: This study aims to investigate the most effective and cost-effective combination of external components to optimize user engagement with ParentText, an open-source chatbot-led parenting intervention to prevent VAC in Mpumalanga, South Africa.

Methods: This study will use a mixed methods design incorporating a 2 × 2 factorial cluster-randomized controlled trial and qualitative interviews. Parents of adolescent girls (32 clusters, 120 participants [60 parents and 60 girls aged 10 to 17 years] per cluster; N=3840 total participants) will be recruited from the Ehlanzeni and Nkangala districts of Mpumalanga. Clusters will be randomly assigned to receive 1 of the 4 engagement packages that include ParentText alone or combined with in-person sessions and a facilitated WhatsApp support group. Quantitative data collected will include pretest-posttest parent- and adolescent-reported surveys, facilitator-reported implementation data, and digitally tracked engagement data. Qualitative data will be collected from parents and facilitators through in-person or over-the-phone individual semistructured interviews and used to expand the interpretation and understanding of the quantitative findings.

Results: Recruitment and data collection started in August 2023 and were finalized in November 2023. The total number of participants enrolled in the study is 1009, with 744 caregivers having completed onboarding to the chatbot-led intervention. Female participants represent 92.96% (938/1009) of the sample population, whereas male participants represent 7.03% (71/1009). The average participant age is 43 (SD 9) years.

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Conclusions: The ParentText Optimisation Trial is the first study to rigorously test engagement with a chatbot-led parenting intervention in a low- or middle-income country. The results of this study will inform the final selection of external delivery components to support engagement with ParentText in preparation for further evaluation in a randomized controlled trial in 2024.

Trial Registration: Open Science Framework (OSF); https://doi.org/10.17605/OSF.IO/WFXNE

International Registered Report Identifier (IRRID): DERR1-10.2196/52145

(JMIR Res Protoc 2024;13:e52145) doi:10.2196/52145

KEYWORDS

parenting intervention; chatbot-led public health intervention; engagement; implementation science; mobile phone

Introduction

Background and Rationale

The detrimental consequences of physical and emotional violence against children (VAC) have been associated with multiple lifelong health disorders [1-3]. VAC negatively affects children's physical (ie, atypical structural development of the brain and altered functioning of the endocrine system) and cognitive (ie, harsh corporal punishment in children increases the risk of alcohol and substance abuse in adulthood and affects cognitive processes such as reasoning and attention) development [1,4]. Children exposed to violence also have an increased risk of experiencing and perpetrating domestic violence in adulthood [5]. VAC has also been associated with inequalities in academic achievements for boys and girls, with children exposed to physical and sexual violence being 13% less likely to complete high school [6].

While VAC is a global public health concern, rates are higher in low- and middle-income countries (LMICs) such as South Africa [7]. In a study with 3515 South African children, the prevalence of lifetime physical and emotional abuse was 56% and 35%, respectively [8,9]. Child sexual abuse is also widespread in the country, with a nationally representative cross-sectional survey reporting that 14.6% of girls and 10% of boys had experienced this form of abuse [10]. The economic costs of VAC in South Africa are significant. In the fiscal year 2015-2016, an estimated 4.3% of the country's gross domestic product was lost to VAC [11]. In addition, the expenditure on childcare and protection attributable to VAC was estimated to be 1.6 billion South African rands (US $124 million) [11].

Inequitable gender norms, such as societal acceptance of male aggression toward women and children, further impede adolescent girls' healthy development and education in South Africa [12]. In addition, adolescent girls are a recognized vulnerable group and susceptible to increased risk of sexually transmitted infections, including HIV, and violence, risks that stem from sexist social principles (ie, adolescent girls tend to be sexualized because of their physical development changes) and structural constraints (eg, poverty, socioeconomic inequality, and high levels of alcohol abuse and crime within communities) [12,13]. In 2018, approximately 16% of adolescent girls aged 15 to 17 years reported that they had experienced sexual abuse perpetrated mainly by a known male adult [10]. In addition, 21% of girls aged 15 to 21 years indicated that their first sexual experience was either coerced or forced [14].

While legislative development efforts have been made to address VAC in South Africa, entrenched social norms condoning physical and emotional abuse toward children are hard to change [15]. Research has demonstrated that a healthy growing environment positively affects children's early brain development, providing the foundations for developing long-term cognitive abilities such as language and reading [4]. Previous research has linked parental engagement in early childhood with better language development and literacy outcomes in children [16,17]. Open access, evidence-based parenting interventions such as the Parenting for Lifelong Health (PLH) suite of programs offer a prime opportunity to address such norms both within the family and at the broader societal level and create a safer environment for children. These interventions, typically delivered as in-person, group-based programs, have been effectively implemented worldwide to increase responsive and positive parenting [18]. However, in low-resource settings, factors such as employment, transportation, and childcare costs represent a significant financial and accessibility barrier to in-person parenting programs for many participants [19-21].

Prospects for Implementing Chatbot-Led Public Health Interventions

In recent years, digital interventions have been used as a delivery mechanism to address the structural barriers to accessing in-person parenting programs [22,23]. For example, PLH has recently developed digital adaptations of their in-person programs in response to restrictions placed on in-person parenting programs during the COVID-19 pandemic and challenges reported by implementing partners in delivering programs at scale in low-resource settings in sub-Saharan Africa. One such PLH adaptation is ParentText, an internet-based self-guided chatbot sent via instant messaging platforms such as WhatsApp and Telegram [24]. Text-based chatbots delivered through instant messaging platforms are being widely explored in the digitalization of public health programs, including parenting interventions. The Oxford Dictionary defines a chatbot as "a computer programme that can hold a conversation with a person, usually over the internet" [25]. They are also referred to as conversational software applications designed to interact in humanlike in-text or text-to-speech conversations with human users [26]. There is evidence suggesting that chatbots have been successfully applied to support health promotion interventions focused on improving mental well-being [27], reducing alcohol consumption [28], and supporting weight loss [29,30].

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In 2022, according to World Bank estimates, 70% of South Africa's population had internet access, and there were 162 mobile phone subscriptions per 100 people [31]. This level of digital coverage makes internet-based interventions such as chatbots a promising delivery channel for parenting programs in the country. Several chatbot-led public health interventions have already been successfully implemented in South Africa. MomConnect, a chatbot that provides pre- and postnatal health information to pregnant women and new mothers to improve their health and that of their babies, has been operating in the country since 2014. By 2016, the chatbot, an initiative of the South African National Department of Health, had reached over half a million users [32]. In 2020, HealthConnect was launched to provide COVID-19–related health information to the general population, and it was estimated that the platform had reached tens of millions of users [33]. Another successful chatbot-led intervention is ChattyCuz, a gamified interactive chatbot targeted at young women to support them in maintaining healthy dating relationships and preventing intimate partner violence (IPV). In a randomized controlled trial with 19,643 young women, researchers reported 59% retention in the intervention [34]. Participants reported improved gender beliefs and reduced rates of IPV because of their interaction with ChattyCuz [34].

Despite the promise of chatbot interventions, the engagement rate of users enrolled in digital parenting interventions and public health interventions more broadly remains low [35-37]. Several factors that affect human-chatbot interaction, such as user trust, satisfaction, and external structures (eg, difficult access to smartphones and the internet and low levels of digital literacy), may undermine their effective implementation [38]. To date, research has primarily focused on investigating the effectiveness of chatbot-led public health interventions on changing behavior and health outcomes [38,39]. However, few digital public health interventions have investigated the factors underlying participant engagement [38,39]. Engagement can be conceptualized as "the extent (e.g., duration of interaction, frequency of contact and depth or variety of content used) of usage" and as "a subjective experience characterised by attention, interest and affect" [40]. Previous research has suggested 4 distinguishable attributes inherent to engagement: point of engagement (ie, initiation stage), period of sustained engagement (ie, maintenance stage), disengagement (ie, period of interruption), and re-engagement [41]. Even though understanding how each of these stages occurs is of extreme relevance to designing the most optimal digital health interventions, this study will focus on the second stage. The rationale behind this decision stems from previous research reporting higher dropout rates after 2 weeks of enrollment in digital health interventions [29,42,43]. In addition, there is a paucity of research focused on investigating how users remain engaged with parenting chatbots [44].

High engagement rates are presented in the literature as an average open-app ratio of 17.71 and 12.14 times over a 2-week period [29,42]. Another complication is that high rates of participant dropout challenge this research, and the determinants of attrition are uncertain as previous studies have lacked statistical power to analyze engagement [27,38]. Another critical factor in user dropout in human-chatbot interaction is the interaction breakdown due to the chatbot's inability to understand users' input, which may arouse negative emotional responses in users [45-47].

Cultural determinants are another potential factor affecting user enrollment and engagement with digital public health interventions. Cultural determinants of health refer to factors related to perceptions, relationships, and cultural identity that interact with society and influence an individual's good health and well-being [48]. Once identified, efforts can be made to promote positive cultural aspects supporting user engagement with chatbot-led public health interventions. In a Kenyan study, intent to use mobile health (mHealth) was associated with the degree to which individuals perceived that their peers had a favorable opinion about their use of mHealth [49]. In Pakistan, participants' perceptions of how easy it was to use an mHealth intervention and their positive attitude toward digital health interventions were associated with their intent to use them [50]. This finding highlights the need for increased user participation in the design process of digitally supported interventions [51] and competent cross-cultural delivery of digital parenting programs. There is also a need to strengthen the evidence base to optimize chatbot-led parenting interventions in LMICs. Such research should (1) assess the financial and implementation constraints to institutionalize them across stakeholders efficiently, (2) develop a culturally sensitive approach in their implementation to ensure effectiveness in terms of the acceptability and satisfaction of users, and (3) evaluate their effectual impact in increasing positive parenting behavior and reducing VAC.

Objectives

Overview

The ParentText Optimisation Trial aims to optimize user engagement through a chatbot-led parenting intervention delivered to parents (ie, any adult responsible for the care and well-being of a child regardless of biological relationship) and their adolescent girls aged 10 to 17 years in South Africa. It will test the relative effectiveness and cost-effectiveness of two intervention components designed to support user engagement with the ParentText chatbot: (1) remotely facilitated WhatsApp support groups delivered to participating parents and (2) in-person sessions delivered to parents and their adolescent girls. In addition, this study will investigate the effectiveness of selected intervention component levels on adolescent and parent behavioral, mental health, and educational outcomes.

Primary Objectives

The primary objectives are as follows:

1. To examine the effectiveness and cost-effectiveness of selected component levels on the primary engagement outcome of the total number of modules completed in ParentText.
2. To examine the effectiveness and cost-effectiveness of selected component levels on secondary engagement outcomes in terms of the percentage of modules and goals completed, the rate of self-reported completion of home practice activities based on the self-reported intention to

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do home practice activities, and the total number of overall interactions of participants with the chatbot.

Secondary Objectives

The secondary objectives are as follows:

1. To examine the effectiveness and cost-effectiveness of intervention component levels on parent and adolescent behavioral, mental health, and educational outcomes assessed at baseline and 6 weeks after the baseline.
2. To identify the cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) that significantly contribute to improved behavioral intentions of parents to engage with ParentText.
3. To identify how behavioral intention significantly contributes to improved primary and secondary engagement outcomes.
4. To identify participants' baseline characteristics and cultural determinants that predict primary and secondary engagement outcomes of parents with ParentText.
5. To explore the role of baseline characteristics as potential moderators of the effectiveness of the intervention components on primary and secondary engagement outcomes.
6. To identify participants' characteristics that moderate the effect of behavioral intention on primary and secondary engagement outcomes.
7. To explore the role of baseline characteristics as potential moderators of the effectiveness and cost-effectiveness of intervention components on parent and adolescent behavioral, mental health, and educational outcomes assessed at baseline and 6 weeks after the baseline.
8. To qualitatively explore parents' perceptions of challenges in engaging with ParentText and their perception of the most feasible and acceptable components and component levels for its implementation in South Africa.
9. To identify the incremental cost of adding each of the component levels in the ParentText implementation package.
10. To select the most effective and cost-effective combination of components and component levels to be tested further in a randomized controlled trial in 2024.

Trial Design

Overview

This study design was derived from the multiphase optimization strategy framework developed by Collins [52], which consists of 3 stages: preparation, optimization, and evaluation. In the multiphase optimization strategy, intervention optimization is the process of evaluating and identifying from a set of intervention components the combination with the most effective and scalable design that can be obtained subject to existing constraints such as limited financial and human resources [49]. The preparation phase of this study took place between October 2022 and February 2023. It comprised a formative evaluation with stakeholders from government and nongovernmental organizations (NGOs) in South Africa. The findings of this phase informed the selection of the intervention components for inclusion in this trial.

The ParentText Optimisation Trial will be conducted from August 21, 2023, to November 10, 2023, in Mpumalanga, South Africa. It will use a 2 × 2 cluster-randomized experimental design to investigate the effectiveness and cost-effectiveness of two components delivered externally from the ParentText chatbot: (1) in-person sessions with parents and adolescent girls (1 or 4 sessions) and (2) facilitated WhatsApp support groups with parents (yes or no). All caregivers and adolescent girls will be onboarded to ParentText in the in-person session (the first session for those assigned to receive 4 in-person sessions). The 2 × 2 factorial trial will include four experimental conditions (Table 1):

1. Condition 1: ParentText chatbot and 1 in-person session (onboarding to ParentText) with parents and adolescent girls
2. Condition 2: ParentText chatbot, 1 in-person session (onboarding to ParentText) with parents and adolescent girls, and facilitated WhatsApp groups for parents
3. Condition 3: ParentText chatbot and 4 in-person sessions (with the first session focused on onboarding to ParentText) with parents and adolescent girls
4. Condition 4: ParentText chatbot, 4 in-person sessions (with the first session focused on onboarding to ParentText) with parents and adolescent girls, and facilitated WhatsApp groups for parents

The study will randomly assign 32 clusters split equally (n=8 clusters) across the 4 different treatment conditions. A total of 1920 parents and their adolescent girls aged 10 to 17 years (approximately 60 parents and 60 adolescent girls per cluster) will be recruited to participate in the study. Each cluster will be randomly assigned a dedicated community-based facilitator to deliver the in-person and WhatsApp support group sessions. The study will adopt a between-cluster assignment to prevent contamination across experimental conditions.

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Table 1. Experimental conditions for a 2 × 2 factorial trial (n=32 clusters, n=60 parent-adolescent dyads, and N=3840 participants).

Condition	Clusters[a] (n=32), n (%)	ParentText (always on)[b]	In person (1 session vs 4 sessions)[c]	WhatsApp groups (yes vs no)[d]
1	8 (25)	On	1	No
2	8 (25)	On	1	Yes
3	8 (25)	On	4	No
4	8 (25)	On	4	Yes

[a]*Cluster* refers to parent and adolescent groups linked to a designated facilitator.

[b]*Always on* refers to the provision of the chatbot without any external support.

[c]Parents and adolescent girls will receive either 1 or 4 in-person sessions.

[d]Parents will either receive (yes) or not receive (no) facilitated WhatsApp groups.

Primary Hypotheses

The primary hypotheses are as follows:

1. Facilitated WhatsApp support groups (yes or no): we hypothesize that parents receiving the ParentText delivery package combined with web-based support via WhatsApp groups will have higher engagement rates than those receiving the ParentText delivery package without facilitated support via WhatsApp groups.
2. In-person sessions (1 or 4 sessions): we hypothesize that parents receiving the ParentText delivery package combined with 4 in-person sessions will have higher engagement rates than those receiving the ParentText delivery package with 1 in-person session.
3. Incremental cost-effectiveness: we hypothesize that, while the inclusion of facilitated WhatsApp groups will be more cost-effective than not including facilitated WhatsApp groups based on the incremental cost advantage, the higher dosage of in-person sessions will not be a cost-effective component.

Secondary Hypotheses

The secondary hypotheses are as follows:

1. Behavior outcomes: we hypothesize that the most intensive combination of component levels will have the greatest effect on parent and adolescent behavioral, mental health, and education outcomes.
2. Cultural determinants: we hypothesize that cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) will be associated with more favorable intentions to engage with ParentText.
3. Behavioral intention: we hypothesize that more favorable intentions to engage with ParentText will lead to higher primary and secondary engagement rates.

The positive directionality of the effects of the 2 intervention components on engagement outcomes will be preferred in this study due to evidence of the positive impact of engagement boosters in parenting interventions [53,54]. No hypotheses will be made a priori for potential moderators of effectiveness or cost-effectiveness.

Methods

Study Setting

The ParentText Optimisation Trial is nested within a larger project implemented by mothers2mothers (m2m), a South African NGO, as part of their Children and Adolescents Are My Priority (CHAMP) program funded by the US Agency for International Development and the President's Emergency Plan for AIDS Relief. The study will be conducted across 2 districts in Mpumalanga Province—Ehlanzeni (mostly rural zones) and Nkangala (rural and periurban zones)—where CHAMP was implementing the orphaned and vulnerable children program or Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) family-strengthening interventions to approximately 28,500 adolescent women and girls (aged between 10 and 17 years) and their caregivers in 2023. The primary home languages spoken by participants include English, isiZulu, and siSwati. The CHAMP program delivers a portfolio of age-specific, needs-based interventions aimed at reducing HIV and AIDS incidence among orphaned and vulnerable children, adolescents, and their families in communities across the province. A key component of CHAMP includes evidence-based interventions to decrease family violence and improve health and social outcomes for orphaned and vulnerable children and adolescents, such as the PLH program.

Eligibility Criteria

Participants recruited for this trial will be parents, adolescent girls, and implementing facilitators.

Eligible clusters are communities with at least 60 households with a resident adolescent girl aged between 10 and 17 years and assigned to an m2m CHAMP implementer. Each implementer will be responsible for 60 households.

Eligible parents are those (1) aged ≥18 years and who are English, isiZulu, or siSwati speakers; (2) currently caring for an adolescent girl aged between 10 and 17 years; (3) living in the same household with the adolescent girl for a minimum of 4 nights a month over the previous 3 months; (4) having access to a mobile phone compatible with WhatsApp; (5) willing to enroll in the ParentText chatbot and receive messages via WhatsApp; and (6) who provide written informed consent to participate in the full study.

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Eligible adolescents are (1) female teenagers aged between 10 and 17 years who (2) have a parent enrolled in the trial and (3) have provided written informed assent to enroll in the full study.

Eligible facilitators are (1) m2m CHAMP implementers in Mpumalanga aged ≥18 years who (2) have completed a workshop training for program delivery before the trial; (3) have a mobile phone compatible with WhatsApp and access to the internet or a data bundle; (4) speak English, isiZulu, or siSwati; and (5) have provided written informed consent to participate in the trial.

Parents with a severe learning disability or those exhibiting acute mental health disorders will be excluded due to their limited capacity to provide informed consent. Parents whose child refuses to participate in the study will not be excluded to prevent threats to internal validity. Children who have healthier relationships with their parents could be more interested in participating in the study; thus, this could lead to selection bias.

Informed Consent

Trained m2m program facilitators will collect informed consent from adults and informed assent from adolescents before the baseline at local schools in communities where the study is taking place (Multimedia Appendices 1 and 2). Informed consent and assent forms will include clear descriptions of the intervention, study objectives, use and protection measures for participant data, and participant rights to refuse to respond to survey questions or withdraw at any point from the study. Adolescents' participation will be conditional on their parents providing consent. Adults and adolescents who agree to participate in the intervention will be invited to sign a paper-based informed consent form to indicate their consent. Participants will also receive a hard copy of information sheets, which include contact details of the local research team and ethics board.

Additional Consent Provisions for Collection and Use of Participant Data

Parents and adolescents will be required to have provided informed consent to participate in the CHAMP project before recruitment to the study.

Interventions

Intervention Description

The core parenting intervention component will be ParentText, a chatbot that delivers personalized and gamified scheduled and on-demand messages through text, audio, and visual media based on development stages for parents of children aged 0 to 23 months, 2 to 9 years, and 10 to 17 years. Previous research has reported the acceptability and feasibility of ParentText in LMICs. A qualitative formative research study in Jamaica reported an average participant (ie, parents) engagement length of 14 days throughout the 37 days of the intervention [43]. The version of the program targeting those aged 10 to 17 years will be used in this study in alignment with the age group of adolescent girls targeted by the CHAMP program. ParentText was originally developed by the UK-based charities PLH and Innovations in Development, Education, and the Mathematical Sciences (IDEMS) International in collaboration with the United Nations Children's Fund (UNICEF); the Universities of Oxford and Cape Town; and Clowns Without Borders South Africa (CWBSA), one of the local partners, to ensure linguistic, cultural, and contextual relevance. The main program content was derived from the PLH for Parents and Teens program, a 14-session in-person intervention developed and tested in a cluster-randomized controlled trial in South Africa [55]. Additional content was included to support adolescent mental health (UNICEF's Helping Adolescents Thrive program [56]), adolescent educational outcomes (the LEGO Foundation's learning through play resources [57]), and gender-based violence prevention (No Means No Worldwide). All content was translated into isiZulu and siSwati and reviewed by parenting experts who were fluent in the 2 languages.

ParentText messages are grouped into nine positive parenting goals: (1) *improve my relationship with my teen*; (2) *understand teen development*; (3) *support my teen's education*; (4) *create structure for my teen*; (5) *improve my family's finances*; (6) *care for my teen's well-being*; (7) *manage my teen's behavior*; (8) *keep my teen safe*; and (9) *have a healthy relationship with my partner*, the latter only delivered to parents who have indicated that they are in a partnered relationship. Each goal is supported by learning modules (37 in total) designed to build parent interpersonal skills through comics, videos, and text illustrating key parenting tips. ParentText also includes internal components to support user engagement, such as gamification (eg, earning badges toward goals), personalization (eg, male and female videos), and activities (eg, quizzes). Participants can select the order of goals based on their preferences after completion of the first goal (*improve my relationship with my teen*).

The goal *improve my relationship with my teen* "improve my relationship with my teen" (Table 2) will provide content on how to spend one-on-one time with the teenager and techniques to praise the adolescent and talk about feelings. For the goal "understand teen development," parents will complete modules related to understanding teenage mental, social, and physical changes. The goal "support my teen's education" will deliver content related to creating a fun and positive environment to support the teenager's academic learning process. Parents will learn skills to create a routine for teenagers and establish rules for the goal "creating a structure for my teen." The goal "improve my family's finances" will equip parents with budgeting skills through lessons related to savings and expenses. The goal "show kindness to your teen" will deliver content related to identifying and managing stress signs and techniques for supporting adolescents. For the goal "keep my teen safe," parents will receive content related to building skills to manage teenagers' misbehavior and help keep their adolescents safe in the community and relationships. Finally, parents who report being in a relationship will receive additional content on how to be supportive, solve conflicts in a relationship, and share responsibilities. The number of assigned modules will vary based on the age of the child and the number of goals but will be up to a total of 37, or 32 for nonpartnered parents.

Participants will be enrolled in the intervention for 6 weeks. Participants who enroll in the hybrid format of the program will also participate in 6 weekly WhatsApp live support sessions and 3 biweekly sessions of the in-person program subject to the

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study components available to their cluster. Parents will participate in the intervention by interacting with ParentText and completing each of the 37 modules and 9 goals sequentially. All goals and modules will be available to parents from the moment they enroll in the parenting chatbot. The goal "Have a Healthy Relationship with my Partner" will only be available for parents who reported being in a relationship. The order in which parents choose to access the goals will not be relevant because the goals were not developed to be interdependent. Adolescents will not interact with the chatbot but will experience the program through voluntary participation in the home practice activities of their parents.

The implementation will follow a group-based format that includes 3 joint parent-and-teenager sessions on (1) emotional check-in and mindfulness-based exercises to reduce stress, (2) feedback activity on participants' experience with ParentText, (3) core lesson supported by illustrations, (4) collaborative discussion problem-solving, and (5) practice of skills at home. Participants will be trained on skills such as family budgeting, widening circles of support, and keeping safe in the community and in relationships. WhatsApp live chat group sessions will only include text messages. The session will include (1) a welcome and check-in message sent by the m2m facilitator, (2) sharing success (parents will be encouraged to share a positive experience when trying one of the ParentText skills with their teenagers), (3) fun activity that parents will be encouraged to replicate after with their teenagers (eg, a dance move), (4) sharing challenges (challenges faced by parents when trying a new skill with their child), and (5) collaborative discussion problem-solving.

Table 2. Intervention modules—ParentText content.

Goal	Number of modules	Justification
Improve my relationship with my teenager	3	A stronger parent-child relationship is associated with lower levels of conflict and violence in families [58].
Understand teenager development	3	Parents who understand the development of an adolescent's sexual and reproductive health are better equipped to create a safe and supportive environment for them. Parental monitoring, communication, and support are vital in sexual violence and VAC[a] prevention [59].
Support my teenager's education	5	Research suggests that parents who are involved in their adolescents' education help provide a positive school environment by promoting the love for learning [60].
Create structure for my teenager	4	Rulemaking can decrease disputes between parents and their children. When parents set rules, they can protect their children from harmful acts or behaviors that may result in abuse by other adults [61].
Manage my teenager's behavior	4	Managing adolescents' behavior prevents later involvement in risky behavior, such as substance use, violence, later delinquency, and conduct problems [62].
Care for my teenager's well-being	4	Listening actively helps adolescents feel heard, understood, less alone, and calmer. In contrast, if parents do not listen to and support their adolescents properly, this can leave them feeling defensive, frustrated, alone, or hurt [63].
Keep my teenager safe	4	Adolescents are at a higher risk of becoming victims of crime than any other age group [64].
Have a healthy relationship with my partner	5	Fatherhood programs that encourage fathers to be more engaged in caregiving and parenting show hopeful findings in terms of reducing VAC and IPV[b] [65].
Improve my family's finances	4	According to the family stress model, financial problems increase parents' stress and depression, which in turn increases harsh parenting practices and child maltreatment [66].

[a]VAC: violence against children.

[b]IPV: intimate partner violence.

Tested Intervention Components

Intervention Component 1: In-Person Sessions

This trial will examine whether varying frequency of in-person human support significantly affects user engagement with the chatbot. In-person parenting programs come with the costs of training facilitators and commonly present limited community resources and infrastructure for their delivery [21]. Of the variants of human support selected for this trial, the in-person component requires a greater allocation of resources. Nevertheless, there is great value in understanding how much of the in-person component is necessary to bolster engagement in chatbot-led public health interventions. Proponents of remote support tools argue that including social networking as a tool to support participants is associated with greater engagement rates [67,68]. In supported digital interventions, participants receive technical and clinical troubleshooting assistance to bolster engagement [69]. Previous studies have reported that the frequency with which participants interacted with a counselor or clinician coach predicted their adherence to digital health interventions [67,70].

This study will compare the differential effects of delivering either 1 or 4 in-person group-based sessions to parents and their adolescents (maximum of 60 families per group). Each session will be delivered by an m2m CHAMP lead facilitator and a cofacilitator and last approximately 2 hours.

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Intervention Component 2: Facilitated WhatsApp Support Groups

This study will also test the impact of facilitated WhatsApp support groups on user engagement in the ParentText chatbot intervention. Self-guided interventions present greater scope for scalability due to the low allocation of financial and human resources required. However, low engagement rates risk their sustainability over time. Although including engagement boosters is a common practice in parenting programs to increase parent engagement [53,54], their effectiveness in increasing engagement has been challenged in previous studies. Day and Sanders [71] found that parents benefited from phone support when completing the Triple P Online self-guided parenting program. Parents in the practitioner-supported condition engaged more with the program, completing more modules and reporting greater program satisfaction [71]. However, Epstein et al [72] found that providing opportunities for parents to interact via Facebook groups while participating in a self-directed family intervention did not increase engagement or improve parenting practices.

In this study, 6 one-hour WhatsApp support groups will be delivered to participating parents (maximum of 60 participants) by a trained m2m CHAMP facilitator. The facilitator will lead and monitor discussions and respond to any questions parents raise about technical troubleshooting and the content of the chatbot. At the end of the fifth WhatsApp group session, participants will be asked to select 2 peer leaders who will assume the responsibility of moderating the group after the sixth session.

As shown in Figure 1, the study components will contribute to increased engagement rates (eg, the number of modules and home practice activities completed within the parenting chatbot) among participants. Higher engagement rates will lead to more positive parenting practices and parent-teenager relationships, resulting in improved mental health and education outcomes for teenagers. Engagement with the chatbot will also contribute to improved intimate partner relationships and lead to positive mental health outcomes for parents. The sustainment of proximal outcomes will lead to a healthier environment within the household and contribute to reduced VAC and improved child learning outcomes.

Figure 1. ParentText Optimisation Trial conceptual model.

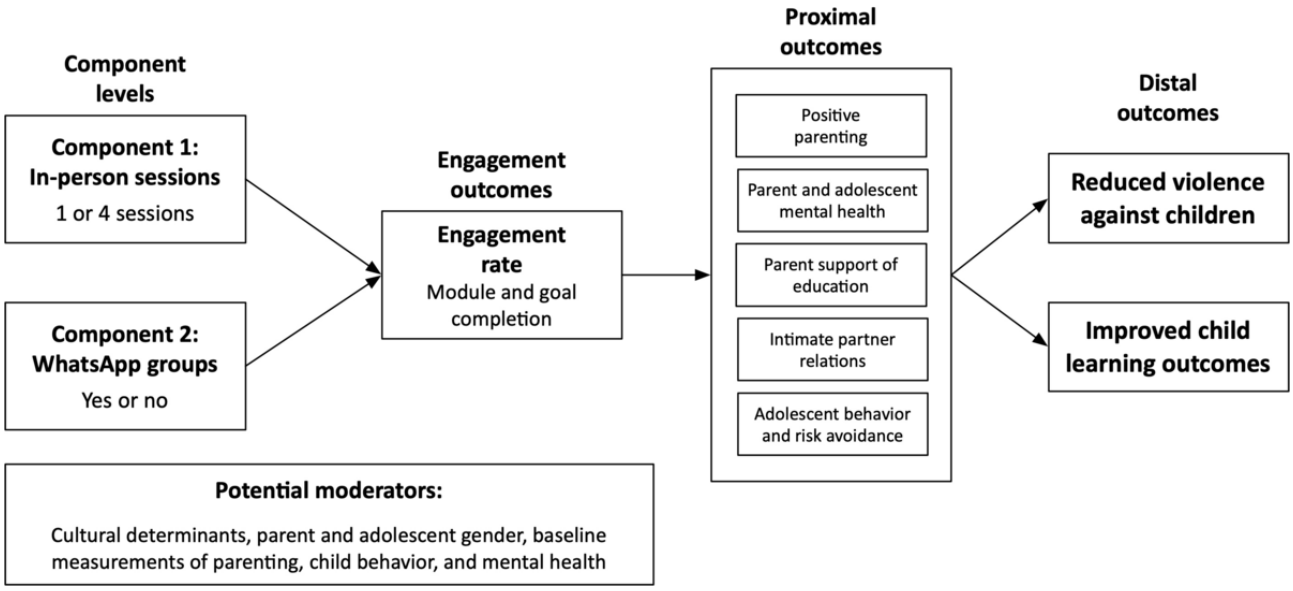

Training of Facilitators

m2m staff will be trained as program facilitators by certified trainers from CWBSA, a South African NGO with vast expertise in leading PLH program training. Training will occur over 2 days lasting a total of 12 hours. In total, 4 separate intervention manuals were developed to create a standardized delivery of the sessions based on condition allocation (ParentText+onboarding; ParentText+onboarding+WhatsApp support group; ParentText+onboarding+WhatsApp support group+3 in-person sessions; ParentText+onboarding+3 in-person sessions).

Criteria for Discontinuing or Modifying Allocated Interventions

Adult and adolescent participants will have the right to decline any assessment or participation at any time during the study. Participants can opt out of receiving ParentText messages at any point by typing "EXIT" or simply by not responding to the messages. The decision to withdraw from the study will not affect a participant's entitlement to other services or result in any penalty. Data collected through paper-based surveys and in-built assessments will be retained unless participants request otherwise.

Strategies to Improve Adherence to the Intervention

Internet bundles (50 ZAR [approximately US $2.60] per person) will also be provided to support engagement with ParentText regardless of intervention condition allocation. Additional data bundles will also be provided to those allocated to participate in WhatsApp support groups.

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Relevant Concomitant Care Permitted or Prohibited During the Trial

Participants will not be prevented from receiving other care or services during the trial period.

Provisions for Posttrial Care

Safeguarding procedures will be used to mitigate risks to participants. There is a possibility of participants disclosing violent practices toward their children, their partners, or themselves. The informed consent form indicates that some information regarding harmful behaviors will be disclosed without the participant's consent if they pose a danger or harm to themselves or their family members. Participants at risk will be referred to local child welfare, health organizations, and other social services. Building on UNICEF's safeguarding guidelines, ParentText has been designed to recognize high-risk keywords such as "trouble," "SOS," "ill," "anxiety," and "fire" in free-text fields. Participants can also type "HELP" to receive troubleshooting messages. The chatbot will respond to participants' disclosure of dangerous situations automatically in an empathetic and empowering manner. It will also provide referral contacts localized in Mpumalanga to offer support to participants who are in danger of being harmed. All supporting services available for participants were identified by m2m and implementing teams following a meticulous mapping of local governmental and nongovernmental support systems. Finally, if respondents or their families are determined to have experienced significant harm because of participating in the study (ie, severe abuse, suicidality, IPV, or other potential psychological or physical injuries), we will cease further activities until these issues can be addressed adequately.

Outcomes

Primary and secondary engagement outcomes will be collected through the course of the program implementation from August 21, 2023, to September 8, 2023.

Primary Outcomes: Engagement

The primary outcome related to user engagement is defined as the overall number of modules completed within the ParentText chatbot.

Secondary Outcomes

Engagement Outcomes

Secondary engagement outcomes will include the percentage of modules and goals completed. We will also examine the rate of self-reported completion of home practice activities based on the self-reported intention to do home practice activities. In total, 3 home practice activities will involve actual interaction with the chatbot, which will allow for testing whether users lie about completing home activities when prompted. Additional engagement outcomes will include the number of days users interact with the chatbot, number of triggered safeguarding messages, number of active and passive dropout from the chatbot, number of times users use the menu and option functions, number of times users access learning through play activities and type of activity (ie, calm, active, quick, or group), type of media selected for engagement (ie, text, audio, or video), and goal selected by users after completion of the first goal. For participants in all clusters, we will compute sum scores for each engagement outcome measure for the complete study period. High engagement rates will be defined as values standing at the highest quartile of the averaged engagement score, medium engagement rates will be defined as values at the second or third quartile, and low engagement rates will be defined as values at the lowest quartile.

Adult and Child Behavior Outcomes

Data collection of parent- and adolescent-reported mental health and behavior outcomes will occur at 2 time points: baseline and postintervention. Outcome measurements will be standardized to capture the occurrence of practices and behaviors over the "past month (last 30 days)."

1. *Child maltreatment (adult and adolescent report)* will be assessed using a subset of items from the physical abuse (2 items) and emotional abuse (2 items) subscales of the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool–Trial Version [73].
2. *Positive parenting (adult and adolescent report)* will be assessed using a subset of items from the positive involvement (3 items), positive parenting (3 items), and parental supervision (3 items) subscales of the Alabama Parenting Questionnaire [74].
3. *Parent support of education (adult and adolescent report)* will be measured using 4 items assessing how often the parent engages the adolescent in behaviors that support learning [75].
4. *Mental health distress (adult and adolescent report)* will be measured using the 4-item Patient Health Questionnaire, which screens for anxiety and depression symptoms [76].
5. *Parenting stress (adult report only)* will be measured using the parental stressors subscale (6 items) of the Parental Stress Scale [77].
6. *Economic strengthening (adult report only)* will be measured using 1 item from the Financial Self-Efficacy Scale [78].
7. *Parent-child communication (adult report only)* will be measured using items adapted from the Parent-Child Communication Scale used in the Fast Track intervention study [79].
8. *Learning through play (adult report only)* will be assessed using a subset of items from the Alabama Parenting Questionnaire, the Parent-Child Communication Scale, and the items on parent support of education [74,75,80]. The selected scales will overarch the learning through play characteristics evidenced in the literature [57,81]. Parents will report the frequency of parent-child engagement [78].
9. *Intimate partner relationships (adult report only)* will be investigated by assessing gender-equitable behavior. Gender-equitable behavior will be measured using items adapted from the core questionnaire in the World Health Organization multicountry study on domestic violence [82] and from questionnaires used in previous violence prevention studies [83,84].
10. *Risk avoidance (adolescent report only)* will be assessed using 4 locally derived items on risk.
11. *Adolescent involvement in decision-making (adolescent report only)* will be assessed to investigate to what extent

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adolescents' voices are heard within families regarding decisions affecting their lives. A total of 3 items adapted from questionnaires used in previous research on parent-child engagement in decision-making will be used to assess adolescent involvement in decisions related to their education, daily activities, and money expenditure in the household [85].

12. *Attitude toward punishment (adult and adolescent report)* will be assessed using a single item from the UNICEF Multiple Indicator Cluster Surveys 5 child discipline module [86].

ParentText also includes 1-item questions on parenting stress, parent-teenager interaction and communication, parental monitoring, teenage behavior, and intimate partner relationships that are embedded within the chatbot. These will be assessed both before and 1 week after the completion of each ParentText goal (total: 9 items).

Cultural Determinants of Engagement Outcomes

This study will investigate the cultural determinants associated with user engagement with ParentText through a parent-reported survey administered immediately after the in-person onboarding session. We will use the technology acceptance model 1 scale (16 items) to assess the following constructs: perceptions (ie, knowledge, attitudes, values, and beliefs affecting parents' motivation for engaging with ParentText), enablers (ie, structural factors within society motivating parents' engagement with ParentText, such as access to the internet), and nurturers (ie, the extent to which parents' beliefs and attitudes are influenced and nurtured by their family, friends, and peers) [87]. Hedonic motivation (the perceived enjoyment of using the technology), habit (the extent to which an individual believes the use of a technology to be automatic), price value, and social influence were also included as additional variables to the technology acceptance model 1 due to their potential influence on the relationship between intention to use and engagement [88,89].

Moderators and Covariates

Sociodemographic characteristics (adult and adolescent report) such as age, gender, literacy, disability, and family structure will be assessed at baseline to describe the sample population and investigate whether the intervention and components have differential effects across these subgroups.

Study assessments are summarized in Table 3.

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Table 3. Summary of study measures.

	Measurement instrument	Study period			
		Baseline	Onboarding	Intervention	Posttest
Primary engagement outcome					
Number of modules completed	—[a]			✓	
Secondary engagement outcomes				✓	
Percentage of goals and modules completed	—			✓	
Rate of self–home practice activity completion	—			✓	
Total number of interactions	—			✓	
Number of days of interaction	—			✓	
Behavior outcomes					
Child maltreatment	ISPCAN[b] Child Abuse Screening Tool–Trial Version (4 items)	✓			✓
Positive parenting	Alabama Parenting Questionnaire (9 items)	✓			✓
Parent support of education	4 items	✓			✓
Mental health distress	Patient Health Questionnaire (4 items)	✓			✓
Parenting stress	Parental Stress Scale (6 items)	✓			✓
Economic strengthening	Financial Self-Efficacy Scale (1 item)	✓			✓
Parent-child communication	Parent-Child Communication Scale (5 items)	✓			✓
Intimate partner relationships	WHO[c] multi-country study on domestic violence (4 items)	✓			✓
Risk avoidance	6 items	✓			✓
Adolescent involvement in decision-making	3 items	✓			✓
Attitude toward punishment	Multiple Indicator Cluster Surveys (1 item)	✓			✓
Moderators and covariates					
Cultural determinants of engagement	Technology acceptance model 1 (16 items)		✓		
Sociodemographic characteristics and family structure	For example, age, gender, literacy, and disability	✓			
Cost outcomes					
Intervention costs	Staff time and expenditures related to the preparation and delivery of specific intervention components		✓	✓	✓
Qualitative interviews and focus groups	—				✓

[a]The outcome indicated was not collected at the referred time point.

[b]ISPCAN: International Society for the Prevention of Child Abuse and Neglect.

[c]WHO: World Health Organization.

Qualitative Assessment

Qualitative interviews with parents will investigate their overall experiences with the chatbot-led intervention, including the enrollment and interaction process. Questions will probe participants' perceptions regarding the acceptability, usefulness, and cultural relevance of the chatbot, WhatsApp groups, and in-person sessions. Interviews will also explore the perceived impact of the intervention on parenting and family relationships.

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Participant Timeline

The participant timeline is summarized in Figure 2. Sampling will be purposive and integrated into m2m CHAMP's current recruitment strategy for the DREAMS project component. Recruitment will proceed until 60 parent-adolescent dyads per cluster are enrolled. Adult and adolescent participants will then be invited to an in-person session that will include (1) informed consent, (2) baseline assessment, (3) onboarding session, and (4) intention to use and cultural determinant survey (August 21, 2023, to September 8, 2023). Parents who complete the baseline assessment will receive a WhatsApp link to connect with ParentText and receive guidance on how to interact with the chatbot. The onboarding session will also include end-to-end testing to ensure that the chatbot functions correctly. Participants will be invited to interact with the chatbot for 5 minutes simulating a real-world interaction. They will then be asked to complete a paper-based assessment to collect their behavioral intention to use ParentText and cultural determinants. Depending on their assignment condition, parents will also be invited to join a facilitated WhatsApp support group or attend additional in-person sessions with their adolescent girls. The ParentText messages will be sent daily to parents via WhatsApp regardless of assignment condition. Data collectors will conduct posttest assessments approximately 6 weeks after the baseline (October 8-27, 2023). Follow-up assessments beyond the postintervention end point will not be conducted.

Figure 2. Study flow diagram.

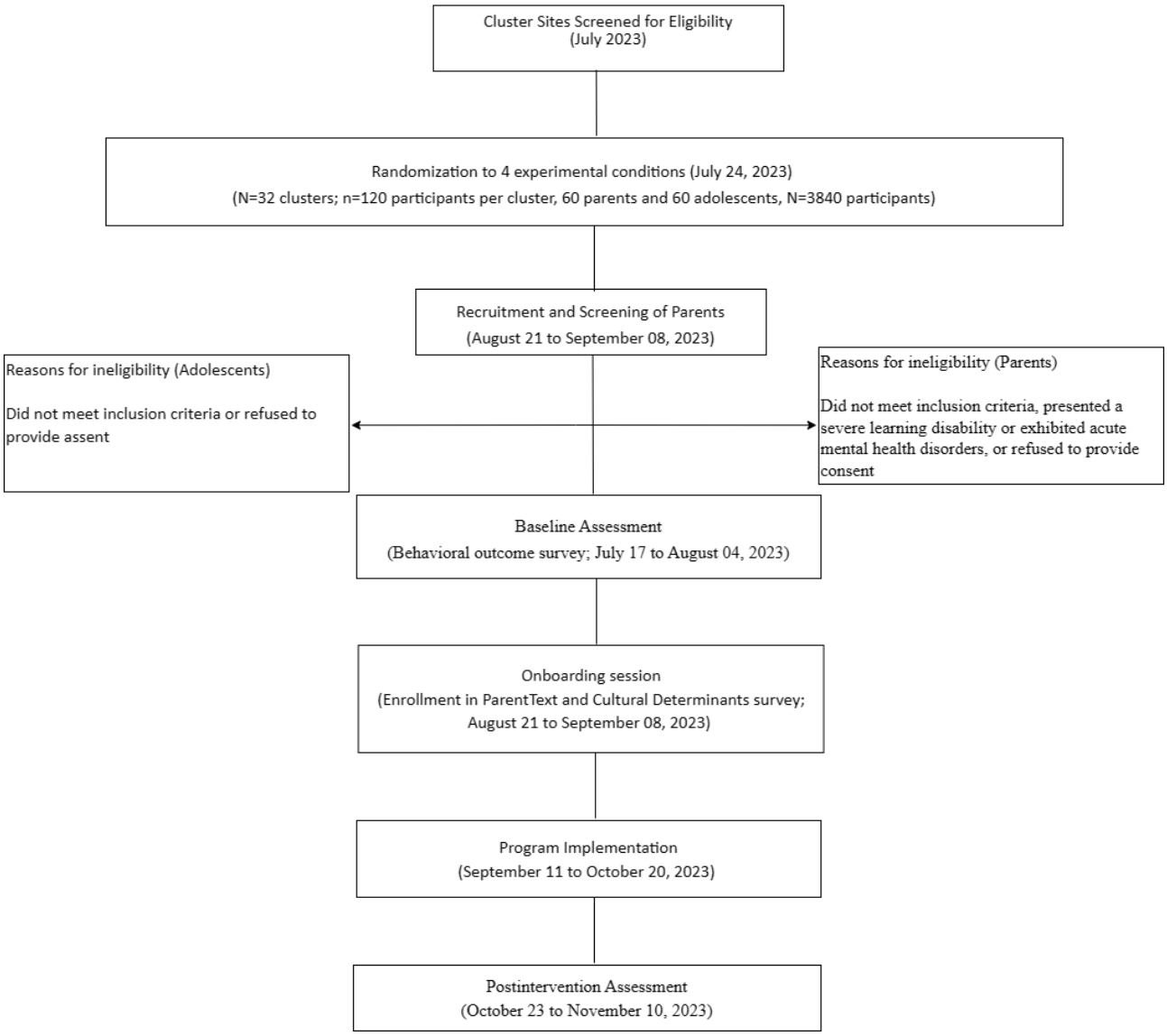

Sample Size

The study has a fixed sample size by design with 32 clusters of equal size and equal treatment allocation across intervention arms. Sensitivity power analysis was conducted to estimate the minimum detectable effect size of the selected components on engagement and on behavior outcomes. Assuming a 2-sided test at the 10% level of significance varying the power (0.9 and 0.8) and the intracluster coefficient (0.02, 0.05, and 0.10), the minimum detectable effect ranges between a mean difference of 0.168 and 0.298 (80% power) and between a mean difference of 0.197 and 0.351 (90% power).

Recruitment

Recruitment of participants will be based on purposive sampling relying entirely on 32 m2m CHAMP implementers and previous

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enrollment in the CHAMP program. CHAMP implementers will screen parents and their children to verify their eligibility for the trial. If required, recruitment will include peer-to-peer referrals in the community through respondent-driven sampling. Recruitment will proceed until 60 parent-adolescent dyads per cluster are enrolled. Participants will then be invited for a baseline assessment with trained data collectors where they will provide full written consent and complete the baseline assessment.

Assignment of Interventions: Allocation

Sequence Generation

This study will adopt a cluster randomization procedure with allocation stratified by district using a parallel design. Cluster randomization will be stratified by facilitators and occur before the baseline assessments (12 clusters from Nkangala and 20 from Ehlanzeni). Random allocation will be conducted by the off-site research team in the United Kingdom using the Excel (Microsoft Corp) function "=Rand()." The in-country research team will assign clusters to 1 of the 4 experimental conditions (32 total clusters, 120 participants per cluster; 60 parents and 60 adolescent girls; N=3840 total participants). Using a 2 × 2 factorial design, this trial will randomly assign clusters so that parents receive the following engagement packages:

1. Engagement package 1: ParentText plus onboarding session for parents and adolescents led by an m2m facilitator
2. Engagement package 2: ParentText plus onboarding session for parents and adolescents and 6 moderated WhatsApp group sessions for parents only led by an m2m facilitator
3. Engagement package 3: ParentText plus onboarding session plus 3 in-person sessions for parents and adolescents and 6 moderated WhatsApp group sessions for parents only led by an m2m facilitator
4. Engagement package 4: ParentText plus onboarding session and 3 in-person sessions for parents and adolescents led by an m2m facilitator

Concealment Mechanism

Participants within a specific cluster and treatment condition will not be aware of the allocation of other clusters due to the geographical distance between clusters and lack of communication across groups.

Implementation

Participants will be recruited in blocks of 32 clusters linked by m2m. Households will be randomly selected from the assigned communities, and recruitment will proceed until 60 households are recruited in each block of 32 clusters.

Assignment of Interventions: Blinding

Who Will Be Blinded

Due to the nature of the intervention, CHAMP facilitators, research assistants, and participants will be aware of condition allocation (based on cluster assignment). The range of conditions and allocation status of other enrolled clusters will be concealed from participants to reduce the risk of contamination. Trial statisticians conducting analyses on postintervention effects will be blinded to the assignment condition of clusters.

Procedure for Unblinding if Needed

This is not applicable for this study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

This study will include quantitative and qualitative procedures for data collection. Data collected will consist of pretest-posttest parent and adolescent behavior questionnaires, parent cultural determinants of engagement, digitally tracked engagement data, and facilitator process data. All data will be collected using paper-and-pen forms. Individual semistructured interviews will be conducted to further explore participants' engagement with ParentText and observed behavior outcomes.

Quantitative Data Collection

Baseline and Postintervention Surveys

Parent and adolescent behavior outcome surveys will be administered at baseline and the postintervention time point. Data collection will occur at the household level or at a meeting venue at the designated DREAMS schools. Data collectors will be 32 CHAMP implementers fluent in written English, isiZulu, or siSwati trained in ParentText delivery and study procedures such as interview techniques, research ethics, safety protocol, data management and security, informed consent, and adverse event report procedures. CWBSA and local researchers will conduct training and supervision of data collection. All measures, interview guides, workshop modules, and ParentText content will be translated from English into isiZulu and siSwati. Considering potential low literacy levels among some participants, data collection staff will read out the survey questions and response options, and participants will follow along. Facilitators will capture all data collected via Open Data Kit–based surveys (Get ODK Inc).

Cultural Determinants of Engagement Surveys

Cultural determinant outcome surveys will be collected at the ParentText onboarding session.

Chatbot Engagement Data

ParentText engagement data will be tracked digitally by the software developers, IDEMS International.

Engagement on Human Support Components

Facilitators will record in-person attendance and WhatsApp group discussion participation of parents enrolled in the cluster to which they were assigned.

Cost Data

Financial and economic costs associated with the resource inputs required to deliver the intervention and the intervention components will be considered in this study. Financial costs are defined as actual expenditures incurred on resource inputs, and economic costs are defined as the market value of all donated and subsidized resource inputs. Intervention costs include facilitator costs such as those associated with their training to deliver ParentText (captured as their time spent attending training sessions) and with preparing and delivering specific intervention components. Physical space used to deliver in-person sessions, as well as expenditures related to travel and

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supplies (such as internet data and cell phones), will be audited and valued. Local researchers and coordinators will collect resource use data *inreal time* (ie, alongside the full study trial) via the completion of weekly Open Data Kit–based surveys. Costs related to the development of ParentText and content adaptation and translation will be included as a capital start-up cost. Because the cost analyses will be conducted from the provider perspective, costs incurred by participants (travel expenditure and opportunity costs) will be excluded. While the implementing organization's program monitoring and evaluation costs will be included in cost estimates, broader research activity costs will be excluded.

Qualitative Data Collection

A subsample of parents will be purposively selected and invited via phone for in-person or over-the-phone individual semistructured interviews. Purposive selection will be based on gender and those with low, medium, and high levels of engagement (approximately 5 male and 5 female parents from different age groups). Engagement levels will be operationalized based on quartiles (ie, low engagement=lowest quartile; medium engagement=second and third quartile; high engagement=highest quartile). The subsample size will depend on the heterogeneity and availability of participants. To ensure that the interviews are standardized, interviewers will follow an interview guide developed by the research team. The interviews will be conducted by a trained qualitative researcher with the support of an interpreter. In addition, focus group discussions will be conducted with the implementing partner, m2m, to understand the challenges and opportunities during implementation.

Plans to Promote Participant Retention and Complete Follow-Up

To promote retention in the chatbot, participants will receive badges for each module completed, a trophy for each goal, and a certificate of completion at the end of the program. Participants attending the in-person sessions will be provided with refreshments at each session and receive a certificate of acknowledgment at the end of the fourth session.

Data Management

This study will implement the following data management measures to ensure confidentiality, security, and safety. Per the US Agency for International Development implementation guidance, raw baseline and postintervention data collected will be captured to the Community-Based Intervention Monitoring System database, a South African community-based intervention monitoring system. Zoë-Life, a global training and consulting firm, will assist m2m with the deidentification of the data before they are transferred to the University of Oxford central server via an application programming interface. A Community-Based Intervention Monitoring System or system-generated ID will be assigned to uniquely identify each participant. ParentText engagement data will be automatically stored through end-to-end encryption to an IDEMS International server. During the data merging process, participants will be assigned a unique study code. The data on the University of Oxford central server will be managed by the University of Oxford Global Parenting Initiative data management team with technical support from the University of Oxford Department of Social Policy and Intervention IT team. Hard copies (eg, paper-and-pen questionnaires and participant attendance records of WhatsApp group and in-person sessions) will be stored in locked fireproof storage spaces and be permanently destroyed after being uploaded to a secure web-based data repository managed by the University of Oxford. Consent forms will be retained for at least 3 years after the study is published in compliance with the funders' requirements.

Confidentiality

Anonymized baseline and postintervention data sets will be stored in a password-protected server at the University of Oxford. Access will be controlled and only granted to members of the study team or partnered institutions that aided in the research project. Audio recordings of interviews and focus group discussions will be transcribed verbatim and stored in password-protected devices and will then be securely uploaded and backed up at the University of Oxford server. Once uploaded to the server, audio files will be deleted from the recording devices. After anonymizing and verifying the transcripts, audio recordings will be permanently deleted from data repositories. All Excel and Word (Microsoft Corp) files will be named following a standardized protocol, including the download date, to ease version control. Deidentified interview transcripts and data sets will only be shared by the Global Parenting Initiative data manager by granting access to specific files through the OneDrive for Business at the University of Oxford. Deidentified data sets will be stored securely for perpetuity and use per UK Data Archive guidance [90]. Raw baseline and postintervention data collected will be owned by the m2m South Africa office. Participants' data will be stored by m2m in compliance with the South African Protection of Personal Information Act. IDEMS International will own the raw data collected through ParentText.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial or Future Use

This is not applicable for this study as no biological specimens for genetic or molecular analysis will be collected.

Data Analysis

Statistical Methods for Primary and Secondary Outcomes

This study will examine the main effects of each component level on user engagement and behavior outcomes**.**

Engagement Outcomes

Baseline differences between groups will be described using proportions, means, and SDs. The main effect of each intervention component and interaction effects between components on primary and secondary engagement outcomes will be estimated using multilevel models (including mixed models if outcomes are continuous, Poisson models if outcomes are counts or count distributed, and logistic models if outcomes are binary). Separate models will be tested using effect coding [91,92]. Each model will specify 3 levels to account for the longitudinal and clustered nature of the data—repeated measures are nested within individuals, which are, in turn, nested within

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clusters. Level 1 will include a term for categorical time (pre- and posttest time points) and for the interaction between time and intervention status, level 2 will include terms for individual sociodemographics such as age (parent and adolescent) and gender (parent) and other individual-level covariates centered at the sample mean, and level 3 will include terms for the intervention components and the stratifying factor. Robust SEs will also be estimated to adjust for clustering. This study will report the direction and magnitude of β, incidence risk ratios, and odds ratios at a significance level of $P<.10$ with 90% CIs. Two-tailed tests will be conducted across all analyses.

Behavioral, Mental Health, and Educational Outcomes

The main effect of each intervention component and interaction effects between components on behavioral, mental health, and educational secondary outcomes will be estimated using the same multilevel models and specifying the same levels and structures as with the engagement outcomes. Within-group analyses will also be conducted to examine pretest-posttest differences across the sample accounting for clustering in analyses.

Analysis of Qualitative Data

Qualitative data will be analyzed using NVivo (QSR International) and Word through framework analysis [93]. Qualitative data analysis will be performed simultaneously with quantitative analysis to assess whether qualitative themes generalize to the entire population and expand the understanding of quantitative results. The analysis will include 5 stages: familiarization, identification of themes, indexing, charting and summarization, and interpretation and mapping. Researchers will begin by familiarizing themselves with the transcripts and identifying emerging themes. A code will then be assigned to each theme and subtheme at the indexing stage. After themes are indexed, they will be charted and summarized. Finally, interpretation and mapping will be used to understand the findings more deeply.

Cost-Effectiveness Analysis

This study will evaluate the efficiency and affordability that results from the expansion or contraction of the ParentText delivery package from the provider's perspective. Program implementation costs and outcome data will be recorded and analyzed in Excel. The total costs of the intervention (setup and operating costs) for each intervention component and the average cost per participant enrolled (unit cost) will be estimated. The trial's primary outcome relates to levels of user engagement (ie, the overall number of modules completed by participants), and this will be used to understand the cost-effectiveness of the intervention components that will maximize user engagement with ParentText. The estimated cost-to-engagement ratio for each of the intervention components will be calculated and compared to assess the incremental cost-effectiveness of each component. All costs will be adjusted to 2023 US dollars using the Consumer Price Index.

Analytical Strategy for Selecting the Most Optimal Intervention Package

We will use the decision-making framework presented by Collins [52] to select the most effective, cost-effective, and feasible components and component levels for inclusion in the optimized intervention before testing in a randomized controlled trial. As shown in Figure 3, the most optimal intervention package will be the one presenting higher effectiveness while considering resource and feasibility constraints. First, the main effects of each component on primary engagement outcomes will be identified and averaged across the other intervention components. Second, intervention components will be divided into a screened-in and screened-out set based on their positive effectiveness on participants' engagement with ParentText. Intervention components with negative or no effect will be included in the screened-out set, and the lower level of that component will not be considered further. Third, intervention components in the screened-in set (ie, those showing positive effects and cost-effectiveness) will be considered for further evaluation. Results from qualitative interviews and focus group discussions conducted with the implementing partner will be used to further understand the feasibility, acceptability, effectiveness, and cost-effectiveness of the retained component levels and draw conclusions to develop the final optimized ParentText delivery package.

The posterior expected value approach will be included in the decision-making process to increase the robustness of our results. In previous research, the posterior expected value approach has modestly outperformed the component screening approach in accuracy, sensitivity, and specificity [94]. Estimates of the posterior expected value for each intervention component will be obtained using Markov chain Monte Carlo methods. We will prefer intervention components with higher Markov chain Monte Carlo posterior distribution of mean outcomes.

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Figure 3. Analytical strategy for selecting the most optimal intervention package for evaluation in a subsequent randomized controlled trial.

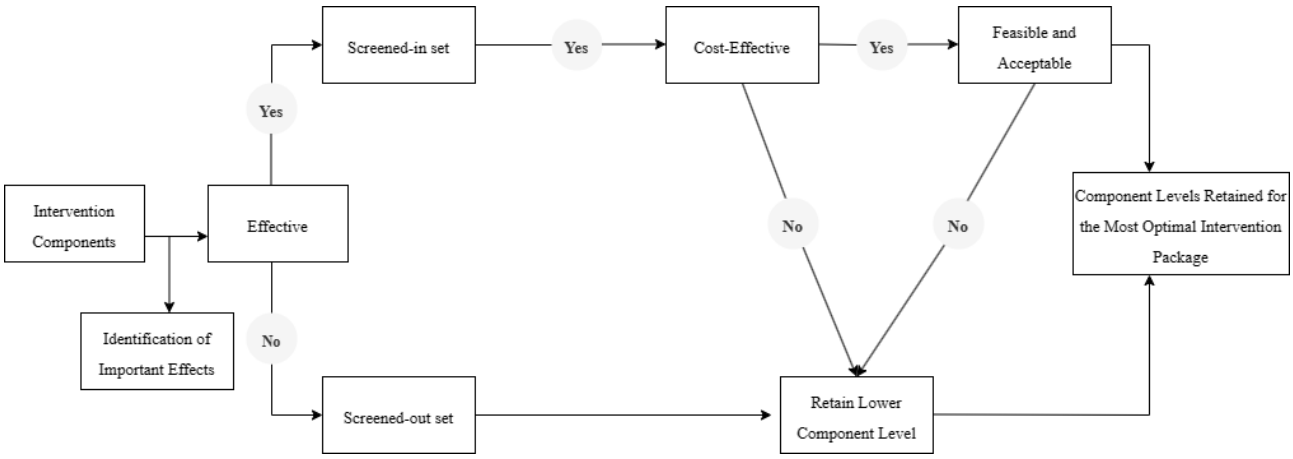

Interim Analyses

No interim analyses will be conducted.

Methods for Additional Analyses

Exploratory analysis will examine the effect of cultural determinants on parents' behavioral intention to use ParentText. Pearson correlations will be used to determine the relationship between cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) and behavioral intention toward ParentText use. Multiple regression analysis will be used to investigate the strength of the association between cultural determinants and behavioral intention and between behavioral intention and primary and secondary engagement outcomes. Predictive models will be used to investigate how behavioral intention predicts parents' primary and secondary engagement outcomes.

Moderation Analyses

In addition, the study will use regression analysis and multilevel regression models to investigate the following: (1) which adult baseline characteristics moderate the effect of the intervention components on primary and secondary engagement outcomes and (2) which adult baseline characteristics moderate the effect of the intervention components on parent and adolescent behavioral, mental health, and educational outcomes.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Quantitative data analysis will be conducted on an intention-to-treat basis. Missingness will be inspected before analysis and addressed via multiple imputation techniques. Multiple imputation by chained equations will be favored to estimate item-level missing data when response patterns allow for estimation. Multiple imputation by chained equations allows more complex models involving moderations and multiple levels of mixed modeling to be accounted for.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

This research protocol and all components of this research, including but not limited to publications, fully anonymized data sets, data analysis plans, and code, will be available to the public at the Open Science Framework on an access-upon-request basis.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

A Trial Steering Committee (TSC) has been assembled and includes international experts with vast experience in experimental and implementation research and VAC prevention. The TSC will meet twice a year and at key study implementation time points (eg, after final data analyses) to ensure that the study is being conducted with rigor and respond to any arising issues associated with participant safety and study conduct.

Composition of the Data Monitoring Committee and its Role and Reporting Structure

The research team, including the principal investigators, research assistants and coordinators, and data managers, will monitor the full life cycle of data management, such as baseline and posttest collection, curation, storage, and analysis. Data quality checks will be conducted by creating a survey monitoring checklist to track errors (eg, wrong name in participant ID list, duplicated data entries, noneligible participants, and survey answers submitted incorrectly).

Adverse Event Reporting and Harms

Safeguarding strategies for each stage of this trial were created based on the universal principles of research ethics, respect, beneficence, and justice. The local research team will be trained on the safety protocol developed for this study. The local partner, m2m, also has a child safeguarding policy complying with the South African child welfare and protection legislation [95]. The policy includes guidelines for reporting suspected child abuse and exploitation. All m2m employers, partners, and other representatives have a duty to respond immediately (within 24 hours) to any allegations of child abuse and exploitation. They are trained to minimize risks and prevent harm to children.

Participants will be informed that ParentText is an entirely self-guided chatbot. However, building on UNICEF's safeguarding guidelines, ParentText has been designed to recognize high-risk keywords such as "trouble," "SOS," "ill," "anxiety," and "fire" in free-text fields. The chatbot will respond to participants' disclosure of dangerous situations automatically

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in an empathetic and empowering manner. It will also provide referral contacts localized in Mpumalanga to offer support to participants who are subject to being harmed. There is a possibility of participants' disclosure of violent practices toward their children, their partners, or themselves. The informed consent form indicates that some information regarding harmful behaviors will be disclosed without the participant's consent if they pose a danger or harm to themselves or their family members. Weekly supervision meetings with all qualitative project staff members will discuss issues that arise concerning harm to research participants and children. Finally, if we determine that respondents or their families have experienced significant harm because of participating in the study (ie, severe abuse, suicidality, IPV, or other potential psychological or physical injuries), we will cease further activities until these issues can be addressed adequately.

Frequency and Plans for Auditing Trial Conduct

Given that the intervention is being led by an external partner, trial conduct audits will be mainly processed by m2m. Deem it necessary, before any necessary actions or modifications affecting the implementation course of this intervention, m2m will communicate and seek advice from the TSC.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethics Committees)

Any significant modifications to this protocol version 1.0 (August 7, 2023), including changes to objectives; design; recruitment; and data collection, storage, and analysis, will require a formal amendment. Modifications will be submitted for consideration and approval to the TSC and approved by the respective institutional research ethics committees. Minor administrative modifications not affecting the methodology described in this manuscript will be documented and reported to the TSC and ethics committees.

Ethical Considerations

Ethics approval for this study was granted by the University of Cape Town Centre for Social Science Research Ethics Committee (reference: CSSR 2023/05), the University of Oxford Social Sciences and Humanities Interdivisional Research Ethics Committee (reference: R88177/RE001), and the Mpumalanga Department of Health and Department of Social Development (reference: R69569/RE003). Before the baseline assessments, participants will be asked to provide written informed consent by trained assessors under the supervision of the local research team. Participants assigned to facilitated WhatsApp groups will receive data bundles of 50 ZAR (approximately US $2.60) per person and a certificate of completion at the end of the sixth session. Study retention will be promoted by providing each parent and adolescent with 60 ZAR (approximately US $3.21) per person at each assessment point. Participants will be informed of any potential risks related to their participation in the trial and have the ability withdraw from the study without affecting any entitlement to other services or result in any penalty system. Deidentification of the data will be conducted before analysis and storage.

Results

Overview

The results of this study will be disseminated through publications in peer-reviewed journals, webinars, and conferences in South Africa and worldwide. Authorship of publications emerging from this study will adopt the recommended guidelines of the International Committee of Medical Journal Editors [96]. Brief reports containing relevant information and recommendations will also be created for stakeholders within NGOs, public health, and social care services in South Africa. Researchers will also provide verbal reports to local participants through local community meetings to help disseminate findings. Participant-identifiable details will be omitted in all research dissemination processes. The dissemination approach will provide the opportunity for early-career researchers and South African partners involved in this study to publish and present findings.

Trial Status

Recruitment for the ParentText Optimisation Trial will begin on August 21, 2023, and is anticipated to continue until September 8, 2023. Baseline data collection will start on August 21, 2023, and is expected to be completed by September 8, 2023. This is the protocol version [1] of August 22, 2023.

Discussion

Expected Findings

Chatbot-led public health interventions offer a promising opportunity to scale up parenting programs in LMICs. However, it is crucial to understand the key pillars of user engagement to ensure their effective implementation. The ParentText Optimisation Trial is the first study to rigorously test engagement with a chatbot-led parenting intervention in an LMIC. This study brings a novel perspective to the research field of digital health interventions as it investigates the impact of engagement boosters associated with human support and the role of cultural determinants of health in designing a chatbot-led public health intervention. Moreover, the results that emerge from this trial will provide recommendations to enhance the development and delivery of interventions tailored for populations in LMICs. The identification of a context requiring lower resources and presenting higher acceptability and feasibility will enable the scale-up of digital public health interventions and support governments in improving populations' health and addressing health inequalities.

Acknowledgments

The authors are grateful to mothers2mothers South Africa for the superb support provided by their Children and Adolescents Are My Priority program team led by Clever Mubuyayi, Dlalisile Lekhuleni, and Boitumelo Buthelezi in preparation for data collection

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and intervention delivery. Similarly, the authors extend their appreciation for their partners Zoë-Life South Africa, Dewald Heath, Nokuthula Heath, and Nompumelelo Mathonsi for facilitating the data management process in this study. They would also like to thank their Trial Steering Committee for their ongoing guidance. Finally, they thank their funders for making this study possible. This study is part of the Global Parenting Initiative, which is funded by the LEGO Foundation, Oak Foundation, World Childhood Foundation (16191), The Human Safety Net, and the UK Research and Innovation Global Challenges Research Fund (ES/S008101/1). Funding for the implementation of the ParentText Optimisation Trial was provided by the United States Agency for International Development (72067418CA00026). The sponsor and funders did not influence any stage of the study design and will not be involved in any stage of the study execution, data analysis, and dissemination of the results.

Data Availability

No data sets or analysis were generated during the development of this manuscript as the research trial is still in the initial stage and no data have been collected at this point.

Authors' Contributions

JML and HG are the principal investigators of the study. MGA led the conceptualization and writing of this protocol. All authors contributed to the conceptualization, development, and writing of this manuscript. MGA, JML, FG, PZ, FC, GJMT, IV, and SV provided critical input in the selection of the quantitative measures in this study. HG led the development of the qualitative measures. SV, GJMT, and JML proposed power simulation and contributed to the proposed research design and statistical analysis. PZ, DS, CF, and LM developed the content for the chatbot. KB and ND contributed to the development of the cultural adaptation of the intervention. All authors provided critical feedback on the manuscript and approved the final version. Authorship in this study will follow the International Committee of Medical Journal Editors guidelines.

Conflicts of Interest

ParentText, the primary intervention in this study, was developed and implemented by members of the research team. JML is the chief executive officer of the Parenting for Lifelong Health (PLH) charity. The intellectual property of the intervention is licensed by the PLH charity under a Creative Commons Attribution 4.0 International license (CC BY 4.0). MGA, JML, FG, FC, IV, SV, HS, PZ, LM, and GJMT currently work on other studies by PLH, and the University of Oxford receives research grants to support this work. The investigators will not benefit from any financial gains from implementing and disseminating this intervention. ND and KB work for Clowns Without Borders South Africa, a South African–based nonprofit organization responsible for providing capacity training and technical support on the delivery of PLH programs in Africa.

Multimedia Appendix 1
Qualitative information sheet and consent forms for interviews.
[DOCX File , 359 KB - resprot_v13i1e52145_app1.docx]

Multimedia Appendix 2
Quantitative information sheets and consent for participation in surveys.
[DOCX File , 89 KB - resprot_v13i1e52145_app2.docx]

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Abbreviations

CHAMP: Children and Adolescents Are My Priority
CWBSA: Clowns Without Borders South Africa
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe
IDEMS: Innovations in Development, Education, and the Mathematical Sciences
IPV: intimate partner violence
LMIC: low- and middle-income country
m2m: mothers2mothers
mHealth: mobile health
NGO: nongovernmental organization
PLH: Parenting for Lifelong Health
TSC: Trial Steering Committee
UNICEF: United Nations Children's Fund
VAC: violence against children

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Protocol

Digital Interventions to Understand and Mitigate Stress Response: Protocol for Process and Content Evaluation of a Cohort Study

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Abstract

Background: Staffing and resource shortages, especially during the COVID-19 pandemic, have increased stress levels among health care workers. Many health care workers have reported feeling unable to maintain the quality of care expected within their profession, which, at times, may lead to moral distress and moral injury. Currently, interventions for moral distress and moral injury are limited.

Objective: This study has the following aims: (1) to characterize and reduce stress and moral distress related to decision-making in morally complex situations using a virtual reality (VR) scenario and a didactic intervention; (2) to identify features contributing to mental health outcomes using wearable, physiological, and self-reported questionnaire data; and (3) to create a personal digital phenotype profile that characterizes stress and moral distress at the individual level.

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Methods: This will be a single cohort, pre- and posttest study of 100 nursing professionals in Ontario, Canada. Participants will undergo a VR simulation that requires them to make morally complex decisions related to patient care, which will be administered before and after an educational video on techniques to mitigate distress. During the VR session, participants will complete questionnaires measuring their distress and moral distress, and physiological data (electrocardiogram, electrodermal activity, plethysmography, and respiration) will be collected to assess their stress response. In a subsequent 12-week follow-up period, participants will complete regular assessments measuring clinical outcomes, including distress, moral distress, anxiety, depression, and loneliness. A wearable device will also be used to collect continuous data for 2 weeks before, throughout, and for 12 weeks after the VR session. A pre-post comparison will be conducted to analyze the effects of the VR intervention, and machine learning will be used to create a personal digital phenotype profile for each participant using the physiological, wearable, and self-reported data. Finally, thematic analysis of post-VR debriefing sessions and exit interviews will examine reoccurring codes and overarching themes expressed across participants' experiences.

Results: The study was funded in 2022 and received research ethics board approval in April 2023. The study is ongoing.

Conclusions: It is expected that the VR scenario will elicit stress and moral distress. Additionally, the didactic intervention is anticipated to improve understanding of and decrease feelings of stress and moral distress. Models of digital phenotypes developed and integrated with wearables could allow for the prediction of risk and the assessment of treatment responses in individuals experiencing moral distress in real-time and naturalistic contexts. This paradigm could also be used in other populations prone to moral distress and injury, such as military and public safety personnel.

Trial Registration: ClinicalTrials.gov NCT05923398; https://clinicaltrials.gov/study/NCT05923398

International Registered Report Identifier (IRRID): DERR1-10.2196/54180

(JMIR Res Protoc 2024;13:e54180) doi:10.2196/54180

KEYWORDS

web-based platform; stress; distress; moral distress; wearable; oura ring; virtual reality; VR; COVID-19; nursing; digital health implementation

Introduction

Background

Work-related stress is a major issue encountered by health care workers (HCWs), as they face a variety of stressors due to the nature of their work, which often involves high-pressure situations and contact with pain and death [1]. The COVID-19 pandemic caused numerous difficulties for many individuals, with HCWs bearing unprecedented professional and personal demands due to challenges such as resource and staffing shortages. Nurses were affected most significantly, reporting the highest levels of burnout, emotional exhaustion, and psychological distress among all HCWs [2]. As COVID-19 cases decreased, levels of emotional exhaustion and psychological distress also decreased but continued to remain higher than the levels reported before the pandemic [2]. Prolonged elevated levels of stress can lead to anxiety, depression, and chronic diseases such as hypertension [3]. Work-related stress can also lead to burnout, a major contributor to nursing shortages faced by health care systems across the globe [4]. In a recent survey, 62% of Canadian nurses said they were considering leaving nursing altogether, citing stressors such as increased workload, staffing shortages, and frequent overtime [5]. Importantly, excessive stress can also impact the quality of care; increased stress is associated with increased medical errors [6] and decreased caring behaviors [7].

Continued unrelenting personal and work-related challenges have, at times, resulted in individuals compromising their beliefs and values to make difficult decisions, which may have life-or-death consequences [8-12]. Clinicians have reported acting in ways that are contrary to their moral values, integrity, and professional commitments, particularly during the initial phases of the COVID-19 pandemic [13,14]. Moral suffering can ensue when a clinician's moral foundation has been threatened or violated because of witnessing, participating in, or precipitating decisions or actions that degrade their integrity [15].

Moral suffering encompasses the related but distinct concepts of moral distress and moral injury. Moral distress was first described within the nursing context by Jameton [16] as "...when one knows the right thing to do, but institutional constraints make it nearly impossible to pursue the right course of action." For example, commonly cited sources of moral distress in nursing include inadequate staffing, inadequate pain relief for patients, and prolongation of life support when they believe it is not in the best interest of the patient [17]. First defined within the military and veteran context, moral injury was said to be the maladaptive biopsychosocial and spiritual outcome of a betrayal of moral character, typically by an individual holding authority [18]. Since this original definition was suggested, literature within the military context has expanded the definition to include maladaptive outcomes following perpetration, witnessing, and being the victim of acts that violate one's moral values [19]. Importantly, moral suffering is thought to exist on a continuum, with moral injury representing a more extreme outcome; repeated instances of moral distress can ultimately lead to moral injury, which is characterized by impaired function and longer-term psychological harm [20]. Also of relevance is the concept of potentially morally injurious events, which have been described in nursing as situations in which professionals find it impossible to carry out the usual standards of care [21].

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Limited information exists on treating and preventing moral injury and moral distress, especially in a health care context. While moral injury may have overlapping symptoms with posttraumatic stress disorder (PTSD), treatments used for PTSD have generally been found to be less effective for the treatment of moral injury [22]. Effective treatments for moral injury are likely required to tap into integrity that is degraded, as strengthening an individual's moral compass has been shown to be an effective way to promote healing [23]. Additionally, psychoeducation on ethics [24] and moral distress [25], support seeking [20], and engagement in critical self-reflection [26] have been suggested as potential interventions for moral distress.

Given that it is infeasible and unethical to subject HCWs to real-life events that evoke moral suffering, virtual reality (VR) represents a promising tool for studying this topic. Exposure to VR scenarios is more ethical, as it is unlikely to cause severe distress but has nonetheless been shown to elicit real psychophysiological responses [27,28]. Moreover, VR allows for the creation of customizable environments and real-time data capture of physiological responses in a controlled setting. VR has previously shown success in the assessment and treatment of a variety of mental health disorders, including anxiety-related disorders, schizophrenia, substance use disorders, and eating disorders [28]. In the assessment of mental health disorders, VR can be used to present potentially triggering scenarios during which physiological measurements are made. For example, several studies have used VR to simulate combat situations while measuring markers of stress in those with PTSD [29-31]. Moreover, the ability of VR to simulate reality in a low-stakes environment renders it useful for exposure therapy. Indeed, a meta-analysis of studies that used VR exposure therapy (VRET) found that VRET was effective in treating a variety of anxiety and related disorders, including PTSD, and did not differ in effectiveness from in vivo exposure therapy [32]. Given the similarities previously outlined between moral injury and PTSD, and the variety of anxiety-related conditions that have been shown to be responsive to VRET, VR may be a promising tool for the treatment of stress and moral suffering.

In phase 1 of this project, we examined the feasibility of using our digital suite (VR and app-based monitoring of participants' physical activity and subjective states) in 15 HCWs to understand stress and moral distress. This work was published as a protocol paper [33], a machine learning model used to predict moral distress [34], and a summary of our results [35]. Based on the feasibility demonstrated in phase 1, we are completing phase 2 with several key changes. First, the study will be conducted with a larger sample of 100 nursing professionals to evaluate the preliminary efficacy of our digital suite in mitigating and understanding both stress in general and moral distress in particular. Additionally, using feedback from phase 1, we developed a new VR simulation and educational video, as described by Sivanathan et al [36]. We aimed to create a more immersive environment to increase perspective-taking and heighten moral awareness, closing the dissonance in moral judgment between hypothetical scenarios and real-life situations. Also new in this study, we will use a wearable device [37] to longitudinally monitor participants' physiological states. Combining this with longitudinal monitoring of participants' subjective states with a web-based platform, we will use a novel machine learning approach [38] to predict stress and moral distress on an individual level. Furthermore, based on poor engagement in phase 1 [35], we have created a new strategy for encouraging participant compliance. Both phases 1 and 2 of the study are funded by the Canadian Department of National Defence.

Objectives

In the current trial, nursing professionals (registered nurses and registered practical nurses) in the province of Ontario will be recruited. During the experimental visit, participants will use our digital intervention suite, composed of (1) a VR moral decision-making simulation and educational video, to examine the acute effects of the simulated moral dilemmas. For at least 2 weeks before and 12 weeks after the intervention, participants will complete questionnaires through (2) a web-based platform and (3) use a wearable device to longitudinally monitor the effects of the VR session.

In conducting this trial, we have the following aims: aim 1—we will use a VR simulation to characterize and reduce stress and moral distress related to difficult decision-making in complex moral situations faced by nursing professionals; aim 2—we will use a web-based platform to measure stress, moral distress, and other mental health symptoms, as well as a commercial wearable device to collect physiological data (this will be done to understand and examine the contribution of active, ie, subjective experiences as reported through self-report assessments, and passive, ie, physiological measurements collected without conscious participant input, data in predicting stress and moral distress); aim 3—we will create a personal digital phenotype profile (pDPP) based on the physiological data (ie, electrocardiogram, electrodermal activity (EDA), plethysmography, and respiration) collected during exposure to a hypothetical moral dilemma in a virtual environment, as well as the wearable and web-based data, to help understand its impact on stress and moral distress at the individual level.

Methods

Participants

A total of 100 nursing professionals from Ontario will be recruited to determine the preliminary efficacy of our digital intervention suite. Eligible participants must (1) be a registered practical nurse or a registered nurse currently employed at an Ontario health care institution and (2) be an owner of a smartphone. Exclusion criteria include (1) history of seizures except febrile seizures (as seizures are listed as an unlikely but possible symptom of using the VR headset [39]); (2) use of electronic medical devices (due to the risk of interference with physiological data collection); (3) score of ≥15 on the 7-item Generalized Anxiety Disorder-7 (GAD-7) [40] scale, an indication of severe anxiety; and (4) score of ≥20 on the 9-item Patient Health Questionnaire (PHQ-9) [41], an indication of severe depression.

Participants will be recruited through (1) social media advertisements, (2) flyers posted at St. Michael's Hospital, and (3) email notices sent through various listservs (eg, the Canadian

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Nursing Informatics Association and the Nursing Research Interest Group). Interested participants will contact the study coordinator, who will send potential participants an informed consent form, a demographic form, and the PHQ-9 and GAD-7 scales. The coordinator will also confirm the individuals' employment and lack of seizure history and electronic medical devices. If the eligibility criteria (as defined above) are met and the participant consents, they will be scheduled for a baseline visit at the interventional psychiatry program.

Trial Design

The trial will take place at St. Michael's Hospital, Unity Health Toronto, Ontario, and will be composed of 3 main phases: baseline, VR simulation, and follow-up, which are visualized in Figure 1. The baseline period will last for a minimum of 2 weeks, during which participants will use the wearable every day and complete scales on a commercial web-based data collection platform, according to the schedule outlined in Figure 1. Following this, participants will engage in a VR simulation that requires complex moral decision-making. The simulation will be followed by an educational video on stress response, and then participants will repeat the simulation to provide them with the opportunity to apply the stress management strategies from the video. At the conclusion of the VR session, participants will engage in a semistructured debrief interview. Physiological signals will be collected through the entirety of the VR session and the debrief. The wearable and web-based platform will continue to be used by participants in the follow-up period, which will take place approximately 12 weeks following the VR session. As described in "Engagement Strategy" section, research team members will be actively involved during this follow-up period to encourage compliance and assess engagement. A semistructured exit interview will take place at the conclusion of participation.

Figure 1. Phase 2 study schema. Brief MIOS: (clinical version) MIOS-4; GAD-2/7: Generalized Anxiety Disorder-2/7 item scale; IPQ: Igroup Presence Questionnaire; MIOS-4: Moral Injury Outcomes Scale; PHQ-2/9: Patient Health Questionnaire-2/9 item scale; SUDS: Subjective Units of Distress Scale; UCLA-3: UCLA 3-item loneliness scale; UEQ: User Experience Questionnaire; VR1: Virtual Reality Simulation Run 1; VR2: Virtual Reality Simulation Run 2; VRSQ: Virtual Reality Sickness Questionnaire Scale.

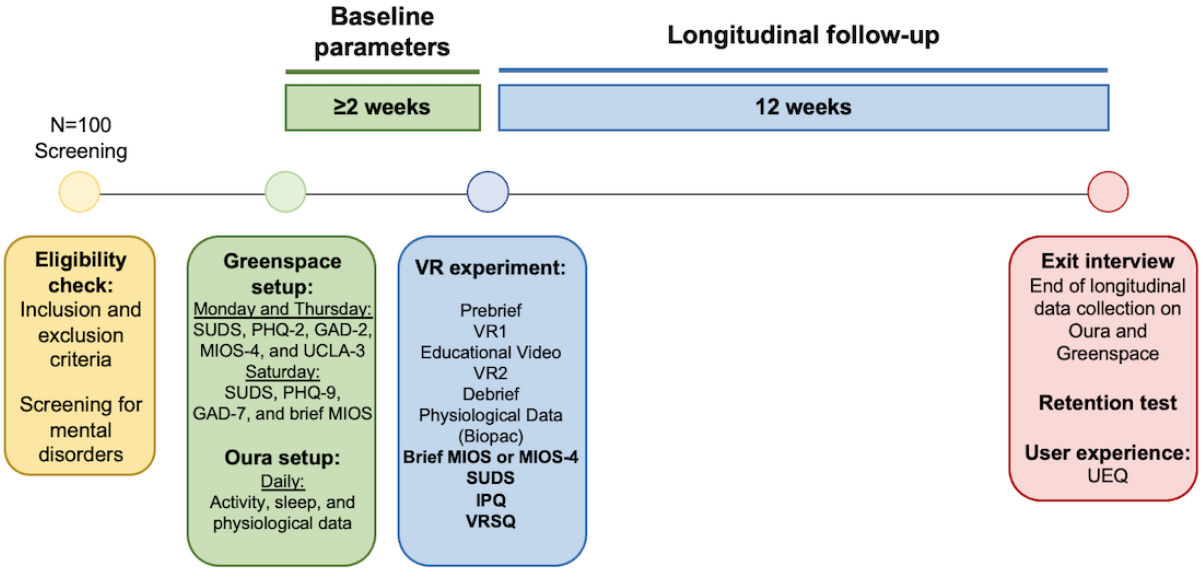

Data Storage

Eligible participants who are screened will be assigned a unique 7-digit ID. All identifiable information will be handled in one password-encrypted master linking file on the Unity Health Toronto server. The master linking file will contain identifiable information corresponding to the assigned participant's unique ID. Deidentified information will be stored on 2 password-protected (through advanced encryption standard encryption) external hard drives located in a locked office at a Unity Health Toronto research site. Participant information will be deidentified on the wearable app and the web-based platform through the use of a unique ID and dummy emails. Data from each of these sources will be downloaded in a weekly data pull, and data from VR sessions will be transferred daily onto the external hard drives.

VR Session

Design of VR Simulation

Details on the development of the simulation are described elsewhere [36]. Briefly, the content of the VR simulation was developed by a panel of subject-matter experts using a modified Delphi methodology [42]. The script was then created in an iterative manner, with versions reviewed and adjustments made on a regular basis until a final version was approved.

The VR simulation places a novice nurse (the research participant) in a high-stakes scenario within a general ward unit. Faced with a code-blue situation, the participant must make a critical decision between attending to one of 2 patients: one experiencing ventricular fibrillation and the other in cardiac arrest. Compounding the urgency, the general ward unit is devoid of additional medical staff and lacks emergency crash carts. On the second run-through of the VR simulation,

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participants are automatically directed to care for the same patient they chose during their initial experience. The design, software, and hardware are identical to phase 1 (reported in the protocol paper [33]).

At several points during the VR simulation, participants will be asked to respond to the situation by selecting a response from a list of options (Figure 2). Participants will be instructed before the VR simulation to select the responses that best represent their internal feelings, even if they are not reflective of what they would say in a professional setting. The research team will record all responses.

Participants will view the educational video (Multimedia Appendix 1) following the first simulation. The video was designed using a similar iterative feedback method and provides psychoeducation on stress and moral distress, as well as strategies to mitigate their effects. Specifically, we will teach unburdening techniques [43], self-compassion [44], and grounding tools (ie, diaphragmatic breathing [45]).

Figure 2. User interface displaying an example of a participant response.

VR Data Collection

A visual overview of the data collection process during the VR simulation is shown in Figure 3.

A total of 4 scales and one short-form scale will be used to collect self-reported data during the session. The Moral Injury Outcome Scale (MIOS) [46] is used to assess an individual's reaction to a potentially morally injurious event and is indexed to the most morally distressing experience of their life that currently distresses them. While the VR simulation is intended to simulate moral distress, the MIOS is designed to assess moral injury and, as such, is used as a proxy of our intended measure. This study will use the clinical version of the brief MIOS (Multimedia Appendix 2), which consists of 14 questions that assess an individual's thoughts and feelings in response to a distressing event and eight items that assess how the event has impacted their daily life. The scale was adapted for nursing professionals by the research team in collaboration with the creator of the scale. Additionally, we will use a shortened version, termed the MIOS-4 (Multimedia Appendix 2), which contains the 4 items from the MIOS with the largest variance. The purpose of the MIOS during the VR session is 2-fold: first, it is used to characterize preexisting moral injury symptoms in participants. Second, the content of the scale is leveraged to assess acute reactions to the simulated moral dilemma.

The Subjective Units of Distress Scale (SUDS) [47] measures the level of distress an individual is experiencing at the moment. Individuals rate their current level of anxiety or discomfort on a scale of 0 to 100, in intervals of 10. The purpose of administering this scale is to obtain a general measure of acute distress elicited by exposure to a moral dilemma.

The Igroup Presence Questionnaire Scale [48] measures an individual's sense of presence and reality during the VR session. This scale is used to assess the VR quality and user experience.

The Virtual Reality Sickness Questionnaire [49] assesses common side effects after VR exposure. This scale will be used to assess the safety and tolerability of the VR simulation.

Physiological data will be collected throughout the duration of the VR session, from the beginning of baseline until the end of the debriefing. Data collection will be done using a Biopac MP160 (Biopac Systems Inc) system, as described in phase 1 [33]. The following 4 physiological signals will be collected as indicators of stress: EDA, electrocardiogram, respiratory impedance (RI), and photoplethysmography. EDA is a measure of the change in conductivity of the skin, which occurs due to changes in the activity of sweat glands. Since sweat gland

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activity is mediated by activation of the sympathetic nervous system, EDA provides a measure of sympathetic activity and, thus, arousal [50]. An electrocardiogram measures the electrical activity of the heart. Relevant features extracted from the electrocardiogram signal will include heart rate, which increases with arousal, and heart rate variability (HRV), a signal that reflects the activity of the autonomic nervous system and can be used as an indicator of stress [51]. RI, which is defined as the mechanical load of ventilation, will be used to measure the respiratory rate, which also increases with arousal [52]. Lastly, photoplethysmography uses infrared light to measure changes in blood volume. Similar to HRV, peripheral blood flow is mediated by the autonomic nervous system and, thus, is an indicator of acute mental stress [53]. Representative tracings of these signals are shown in Figure 4.

Figure 3. Design of the virtual reality (VR) experimental session. All scales during the VR session will be completed in the immersive virtual environment. Brief MIOS: (clinical version) MIOS-4; IPQ: Igroup Presence Questionnaire; MIOS-4: Moral Injury Outcomes Scale; SUDS: Subjective Units of Distress Scale; VR1: Virtual Reality Simulation Run 1; VR2: Virtual Reality Simulation Run 2; VRSQ: Virtual Reality Sickness Questionnaire Scale.

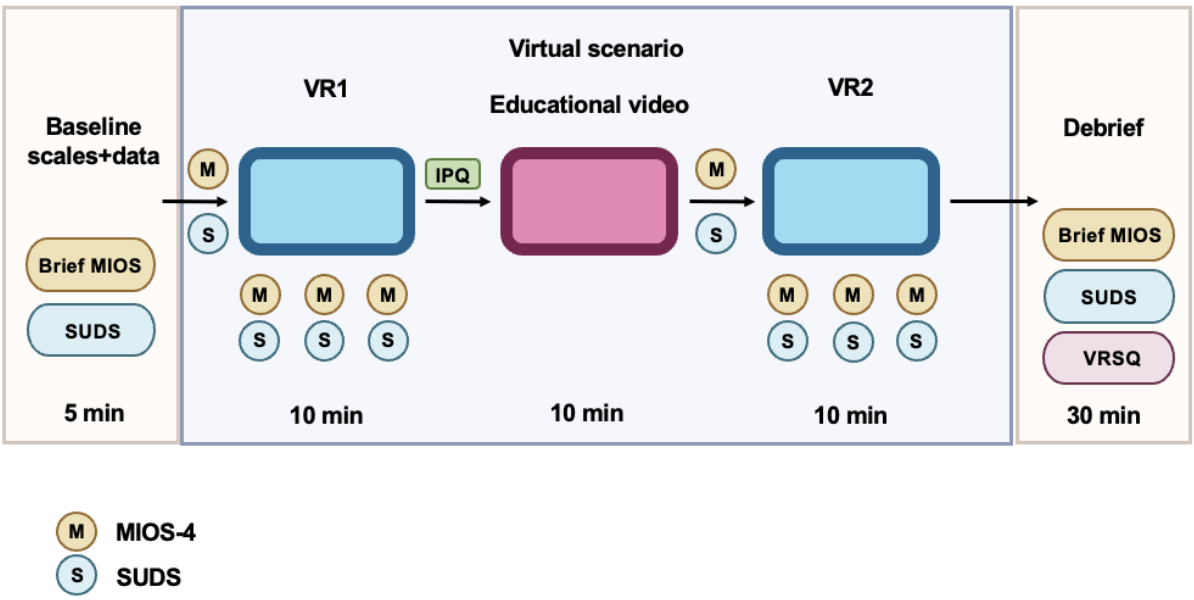

Figure 4. Physiological data collected during the virtual reality (VR) session and debrief. The image shows representative tracings of (from top to bottom): respiratory impedance (RI), photoplethysmography, electrocardiogram, and electrodermal activity (EDA) signals.

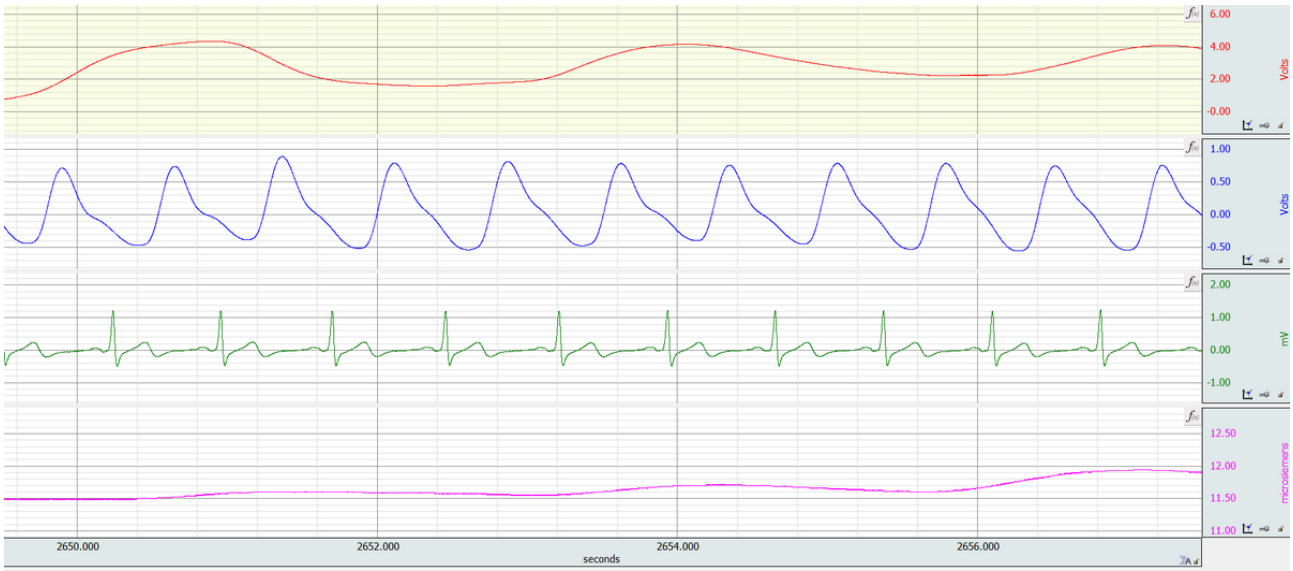

Wearable

Passive data will be collected using an Oura Ring (Oura Health Oy), a commercially available wearable device [37]. The ring can be worn on the finger with minimal interference to collect a variety of physiological signals, including heart rate, workout heart rate, respiratory rate, HRV, daily activity, activity score, body temperature (delta), blood oxygen saturation, recovery score, sleep efficiency, and sleep score. The device will be worn for a minimum of 2 weeks before the VR session to ensure appropriate baseline data collection and will be worn continuously for 12 weeks post-VR. Participants will be asked

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to open the app daily to allow their data to be uploaded, and they can use the app to monitor their personal data.

Web-Based Platform

We will use the web-based platform developed by Greenspace Mental Health (Greenspace) to collect active data during the trial [54]. This platform facilitates the continuous measurement of mental health symptoms and well-being through the regular administration of standardized assessments. Participants will complete these assessments for the duration of their enrollment in the trial, including the baseline period leading up to the VR session and the 12-week follow-up thereafter.

Additional Scales

In addition to the brief MIOS or MIOS-4 and the SUDS, the scales in the following sections will be included on the web-based platform.

GAD Scale

The GAD Scale [40] is a measure that assesses the level of anxiety a person has experienced over the last 2 weeks. The scale consists of 7 items, with each item scoring on a Likert scale of 0 to 3. The total score ranges from 0 to 21, with higher scores indicating greater anxiety. The GAD-2 only includes items 1 and 2 of the GAD-7 and has a total score that ranges from 0 to 6.

PHQ Scale

The PHQ [41] is a self-report questionnaire assessing symptoms of depression over the last 2 weeks. The PHQ-9 scale consists of 9 items, with each item scoring on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27, with higher scores indicating more severe symptoms of depression. The PHQ-2 includes only the first 2 items of the PHQ-9 and has a total score range of 0 to 6.

UCLA 3-item Loneliness Scale

The UCLA 3-item Loneliness Scale (UCLA-3) [55] is a self-report questionnaire assessing subjective feelings of loneliness and social isolation. This scale consists of three items, with each item scoring from 1 (hardly ever) to 3 (often). The total score ranges from 3 to 9, with higher scores indicating more severe symptoms of loneliness.

Scales will be administered 3 times per week, according to the schedule shown in Table 1.

Table 1. Scale administration schedule.

Day	Scale
Monday	• SUDS[a] • GAD-2[b] • PHQ-2[c] • MIOS-4[d] • UCLA-3[e]
Thursday	• SUDS • GAD-2 • PHQ-2 • MIOS-4 • UCLA-3
Saturday	• SUDS • GAD-7[f] • PHQ-9[g] • Brief MIOS[h]

[a]SUDS: Subjective Units of Distress Scale.

[b]GAD-2: Generalized Anxiety Disorder-2.

[c]PHQ-2: Patient Health Questionnaire-2.

[d]MIOS-4: Moral Injury Outcome Scale-4.

[e]UCLA-3: UCLA 3-item Loneliness Scale.

[f]GAD-7: Generalized Anxiety Disorder-7.

[g]PHQ-9: Patient Health Questionnaire-9.

[h]Brief MIOS: Brief Moral Injury Outcome Scale.

Engagement Strategy

We will use several new strategies to maximize participant engagement. First, we will send daily SMS text messages reminding participants to use their wearable and to open the wearable app. The text messages will also include a reminder on Mondays, Thursdays, and Saturdays to complete the questionnaires. Second, we will send emails reminding participants on Mondays, Thursdays, and Saturdays to complete the questionnaires. Third, we will actively monitor which participants are missing data and contact those who are on a weekly basis. Different actions will be taken depending on the amount of missing data, which are outlined in Table 2.

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Lastly, we will establish a compensation system to further encourage compliance. For every 2-week period following their VR session, participants will be compensated CAD $30 (US $21.93) if they did not go a single day without any missing active or passive data. Participants will be given this honorarium upon completing the study. Participants will also be given CAD $80 (US $58.48) for completing the screening visit, CAD $80 for the VR visit, and CAD $30 for the exit interview (see Exit Interview section).

Table 2. Engagement action according to the amount of missing questionnaire and wearable data received.

Severity level	Amount of missing data	Engagement action
Minor	Missing at least one day of questionnaires or one day of wearable data in a week.	Call participant and ask them to contact the research team if they are having technical difficulties.
Medium	Missing one or 2 days of questionnaires, 2 weeks in a row; 2 questionnaires in one week; or wearable data 3 days a week, 2 weeks in a row.	Call and text participants, ask them to contact the research team regarding their missing data regardless of whether there are no technical difficulties. Repeat contact daily until response is established.
Major	Missing questionnaire 3 days in a week; wearable 4 days or more in a week; or at least 3 days of wearable data in addition to one day of questionnaires per week.	Call and text participants, ask them to contact the research team regarding their missing data regardless of whether there are no technical difficulties. Repeat contact daily until response is established.

Debrief

The debrief, which will take place immediately after the VR session, will be composed of a semistructured interview, open-ended feedback, and 3 Likert-rated statements (an interview guide is included in Multimedia Appendix 3). The semistructured interview will ask participants to reflect on and explore emotions elicited by the VR simulation and will test participants' retention of the material from the educational video. Open-ended feedback and Likert-rated statements will explore participants' impressions of the VR simulation and how it could be improved and made more realistic.

Exit Interview

At the end of the 12-week follow-up period, participants will complete a semistructured exit interview regarding their experience in the study, including perceptions of the utility and relevance of the educational video and barriers to the use of digital platforms (an interview guide is included in Multimedia Appendix 4). Included in this interview will be a retention test on the concepts and strategies discussed in the educational video. After the interview, the participant will complete the User Experience Questionnaire for the wearable and web-based platform. The User Experience Questionnaire is a widely used questionnaire for measuring impressions of the user experience of interactive products [56,57].

Quantitative Data Analysis

Sample Size

This project aims to demonstrate the preliminary utility of multimodal digital platforms to understand and mitigate general stress and moral distress. Sample size calculations were estimated based on the results of a post hoc analysis of a pilot study [33].

We calculated sample sizes for a 2-tailed paired *t* test to compare the means of the prescore and postscore of MIOS using the POWER procedure in SAS (version 9.4; SAS Institute). Parameters for the sample size calculation were estimated from a pilot study, as the SD of each score was 9.86 and the correlation of pre- and postscores was 0.75. A sample size of 55 pairs (55 patients) was estimated with a 2-sided α of 5% and a power of 90%. We set the effect size (mean difference between prescore and postscore) to detect at 3.13. Therefore, assuming a conservative dropout rate of 30%, the proposed sample size of 100 patients will still provide 70 pairs, which is sufficient to achieve >90% power based on the parameter assumptions.

Statistical Analysis

R (R Core Team) and SAS will be used to conduct statistical analysis. General participant characteristics and demographics will be listed in a baseline characteristics table. Continuous variables will be presented with the mean and SD when normally distributed, or with the median and IQR for skewed data. Dichotomous and categorical variables will be presented with frequency and percentage.

For the brief MIOS and other scales from the VR session (eg, MIOS-4 and SUDS), the prescore, postscore, and their differences will be summarized using descriptive statistics such as mean (SD) and median (IQR). For each scale, the prescore and the postscore will be compared using 2-tailed paired *t* tests. Similar analyses will be performed for the scales in the web-based platform (eg, GAD-7, GAD-2, PHQ-9, PHQ-2, and UCLA-3). The normality of all scale data will be assessed using a Shapiro-Wilk test to validate the use of the 2-tailed paired *t* test, which assumes normality. If the normality test indicates a significant deviation from a normal distribution, the Wilcoxon signed rank test, a nonparametric test for paired data, will be used. Results will be considered significant with a P value ≤ 0.05.

Personal Digital Phenotype Profile

With the active and passive data collected throughout this study, we will perform digital phenotyping as outlined in aim 3 to further understand and quantify the experience of stress and moral distress in a naturalistic setting (details on the methodology are described by Nguyen et al [34]). Digital phenotyping is defined as the "moment-by-moment quantification of the individual-level human phenotype in situ using data from smartphones and other personal digital devices" [58]. This approach can be used to effectively represent longitudinal data and may present an opportunity for tailored monitoring of treatment response and relapse prediction in individuals with mental disorders [59]. Additionally, digital

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phenotyping allows for the monitoring of patients in natural contexts and in real time [59].

Once the digital phenotype profile (DPP) representation has been created, we additionally enhance this definition by proposing the term personal DPP (pDPP) as a personalized version of the DPP, where we collect longitudinal data to design digital biomarkers to monitor the changes in physical and behavioral health of an individual participant. The pDPP will be used to provide insight into a person's affective state using an individual's physiological data, even without any active data.

The process of digital phenotyping involves building a machine learning model using the active and passive data collected from each participant. An individual model is built for each person by incorporating their physiological data together with their self-reported affective states collected from questionnaires. In the long run, such models could allow for insights into nurses' mental well-being in a nonintrusive way that can improve mental health care and responses to stress.

Our goal is to perform a systematic investigation of the DPP with an emphasis on robustness for long-term utility. We envision the DPP to be represented as a multidimensional vector composed of passive and active data, where each profile is unique to one another. To do so, we propose a statistics, information theory, and data-driven (SID) pipeline to develop the foundation of the DPP as described by Nguyen et al [38]. The proposed novel SID pipeline is shown in Figure 5.

Figure 5. A block diagram representation of the proposed statistics, information theory, and data-driven (SID) pipeline (adapted from Nguyen et al [38], with permission from the Institute of Electrical and Electronics Engineers [IEEE]). DPP: digital phenotype profile.

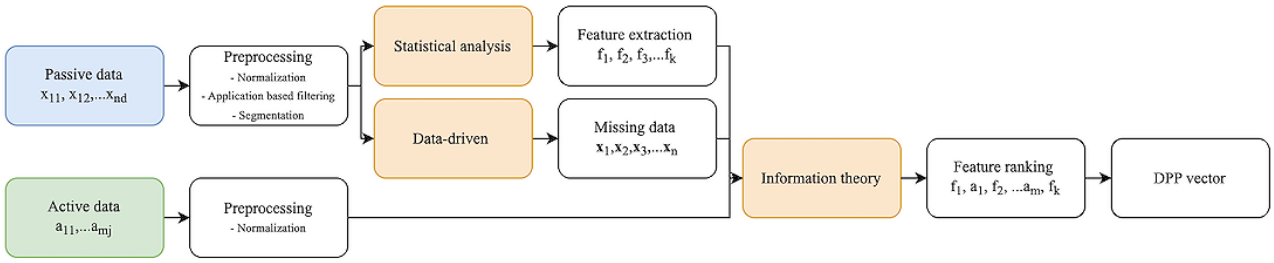

The DPP will be created through the use of the SID and will be a representation for each individual user. Once the DPP is created, we will enhance the analysis by proposing the pDPP, where we develop individual models for each participant by incorporating their physiological data together with their self-reported affective states collected from questionnaires. The pDPP will be used for long-term utility, where we monitor the changes in physical and behavioral health of an individual participant.

MATLAB (Cleve Moler) and Python (Python Software Foundation) language will be used for signal processing and machine learning. The physiological signals will be collected in raw format during the VR intervention and will be further sent to preprocessing, feature extraction, and machine learning techniques for data analysis. Preprocessing techniques involve filtering and cleaning the signal. Techniques such as low-pass, high-pass, and notch filters will be used to remove noise, and the resulting filtered signal will be submitted to the extraction of relevant features. Feature extraction will involve extracting attributes of the signal to be better represented. Both handcrafted features and deep learning features will be extracted. Techniques for feature extraction include handcrafted features and automatic deep learning features. Handcrafted features will involve statistical values extracted from the signal, whereas automatic deep learning features will be extracted through deep learning models. Since deep learning models will be used, the features may be abstract and better represent the data in a higher dimension. Lastly, machine learning techniques will be used for the final data analytics. Trends, classifications, and relationships will be determined using different machine learning techniques. Implementations of preprocessing, feature extraction, and machine learning will be conducted in MATLAB and Python.

Preprocessing, feature extraction, and machine learning techniques will be applied to the data collected during the VR intervention to identify data patterns and develop prediction models for stress and moral distress. Similarly, active data from the web-based platform and passive data from the wearable device will be analyzed using data-driven techniques to monitor participants' activity and mental well-being in naturalistic environments and develop prediction models for stress and moral distress.

Qualitative Analysis

Audio recordings from the post-VR debrief and exit interviews will be transcribed using a 3-stage approach. First, each audio file will be transcribed (audio to text) using an automated pipeline. Each transcript will then be reviewed for accuracy and adapted to simple transcription conventions that preserve conversational prosody and deidentify personally identifying information [60].

Thematic analysis will be used to extract recurring codes and overarching themes elicited during the post-VR debrief session and exit interview [61,62]. In particular, the post-VR debrief analysis will focus on themes arising from the emotional experiences elicited by the VR simulation, decisions made in the VR simulation, and feedback on how participants thought the scenario could be improved. The exit interview analyses will focus on themes emerging from participants' recollection and impressions of the VR simulation, the perceived usefulness of the techniques presented in the educational video, and experiences with the wearable and web-based platform.

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Ethical Considerations

This study was approved by the St. Michael's Hospital Research Ethics Board (22-279) in April 2023 before any participants were recruited.

Results

This project was funded by Innovation for Defence Excellence and Security: Competitive Projects, Department of Defence, Canada in January 2022. The first participant was enrolled in May 2023. As of September 2023, all 100 participants had completed screening, and 99 had completed their VR session (1 dropout). The data collection was completed in December 2023.

Discussion

Potential Benefits

Participants may benefit from psychoeducation related to stress, moral distress, and techniques to address those experiences. Participants may also experience some degree of relief from moral distress throughout this study from the educational video, and the opportunity to better understand their mental and physical health through self-monitoring built into the web-based and wearable platforms. Further, participation in this study can benefit nursing professionals as a whole, contributing to the understanding and prevention of stress and moral distress in health care professions.

Potential Risks

There are no serious risks associated with participation in this study. Participants may experience side effects associated with VR, such as nausea and dizziness, in which case the experiment will be paused. These symptoms are typically transient in nature and are expected to pass within hours after VR exposure. Participants will be asked about the occurrence of such symptoms during their VR session through the Virtual Reality Sickness Questionnaire scale. There is always a risk of data leaks when using digital platforms. However, data shared with third parties (ie, Greenspace and Oura) will be shared under a dummy email. As such, third-party platforms will have no identifiable information about participants. Data stored at St Michael's Hospital, Unity Health Toronto will be stored on encrypted and password-protected drives. It is possible that exposure to a simulated distressing event may provoke negative feelings in participants, which warrants professional assistance. The study psychiatrist will be on call should such a situation arise. Finally, all adverse events will be recorded in an adverse event log maintained by study staff.

Limitations

There are several limitations to this study. One drawback is the potentially limited ability of the VR simulation to mimic a real-life moral dilemma, which would lead to a less ecologically valid understanding of moral distress. Previous research using VR simulations has demonstrated the elicitation of genuine subjective experiences, including fear, anxiety, and paranoia, as well as objective psychophysiological responses such as changes in heart rate and skin conductance [27,28]. However, the VR simulation in phase 1 of this study induced limited changes in MIOS and Perceived Stress Scale scores [63], albeit in a small sample. Another limitation is the lack of a control group. Given that all 100 participants will be subjected to the VR simulation twice with the educational video played in between, we will not be able to discern whether changes in responses between the first and second instances of the VR simulation are caused by the educational video itself or other factors such as simulation repetition. That being said, evaluation of the efficacy of the educational video in reducing acute symptoms of stress is not the primary aim of this study.

Future Directions

The proposed project could allow for the development of evidence-based methods for the prevention and treatment of stress, moral distress, and moral injury. This will allow for a conceptual integration of perspectives from ethics, nursing, philosophy, psychology, mental health, and social science through concept mapping and examination under a rigorous data analytical framework of biostatistics and machine learning.

There is a promising potential for digital platforms to aid in the real-time identification of factors that mediate the potential for long-term psychological trauma and impairment associated with ethical conflicts. However, this will require significant modifications to the application of existing digital technologies and seamless integration across modalities. Integration with wearables and examination in virtual environments represent the next wave of digital innovation to understand patterns of physiological response and the development of machine learning training models, which would assist in predicting and responding to risks associated with moral distress.

This project is built upon the original proof-of-concept study, where a process and content evaluation of the technology platform, VR environment, and remote interventions will be undertaken by each participant over approximately 3 months. This will set the stage for more definitive studies to develop the potential of these technologies to predict and prevent moral distress. This project has the potential to develop innovative paradigms, which can be further examined in other occupational contexts prone to moral distress or injury (eg, military populations).

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Conflicts of Interest

JM, AR, HP, VKT, GHL, MI, BCD, LB, DMC, BN, AT, HJ, WL, AN, AA, BK, BL, RJ, AD, GS, and SK declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. VB is supported by an Academic Scholar Award from the Department of Psychiatry, University of Toronto, and has received research support from the Canadian Institutes of Health Research, Brain & Behavior Foundation, Ministry of Health Innovation Funds, Royal College of Physicians and Surgeons of Canada, Department of Defence (Canada), New Frontiers Research Fund, American Foundation for Suicide Prevention, University of Toronto Connaught Funds, University of Toronto EMH Seed Fund, and investigator-initiated trials from Roche Canada, Eisai Canada, Novartis, Associated Medical Services Inc Healthcare, and the National Research Council of Canada.

Multimedia Appendix 1
Educational video on stress and moral distress.
[MP4 File (MP4 Video), 190396 KB - resprot_v13i1e54180_app1.mp4]

Multimedia Appendix 2
Moral Injury Outcome Scale (MIOS) versions used in this study.
[DOCX File , 14 KB - resprot_v13i1e54180_app2.docx]

Multimedia Appendix 3
Post-VR debrief interview guide.
[DOCX File , 14 KB - resprot_v13i1e54180_app3.docx]

Multimedia Appendix 4
Exit interview guide.
[DOCX File , 12 KB - resprot_v13i1e54180_app4.docx]

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Abbreviations

DPP: digital phenotype profile
EDA: electrodermal activity
GAD-7: Generalized Anxiety Disorder-7
HCW: health care worker
HRV: heart rate variability
MIOS: Moral Injury Outcome Scale
pDPP: personal digital phenotype profile
PHQ-9: Patient Health Questionnaire-9
PTSD: posttraumatic stress disorder
SID: statistics, information theory, and data-driven
SUDS: Subjective Units of Distress Scale
UCLA-3: UCLA 3-item Loneliness Scale
VR: virtual reality
VRET: VR exposure therapy

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Protocol

Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study

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Abstract

Background: Physical capacity and physical activity are important aspects of physical functioning and quality of life in people with a chronic disease such as Parkinson disease (PD) or chronic obstructive pulmonary disease (COPD). Both physical capacity and physical activity are currently measured in the clinic using standardized questionnaires and tests, such as the 6-minute walk test (6MWT) and the Timed Up and Go test (TUG). However, relying only on in-clinic tests is suboptimal since they offer limited information on how a person functions in daily life and how functioning fluctuates throughout the day. Wearable sensor technology may offer a solution that enables us to better understand true physical functioning in daily life.

Objective: We aim to study whether device-assisted versions of 6MWT and TUG, such that the tests can be performed independently at home using a smartwatch, is a valid and reliable way to measure the performance compared to a supervised, in-clinic test.

Methods: This is a decentralized, prospective, observational study including 100 people with PD and 100 with COPD. The inclusion criteria are broad: age ≥18 years, able to walk independently, and no co-occurrence of PD and COPD. Participants are followed for 15 weeks with 4 in-clinic visits, once every 5 weeks. Outcomes include several walking tests, cognitive tests, and disease-specific questionnaires accompanied by data collection using wearable devices (the Verily Study Watch and Modus StepWatch). Additionally, during the last 10 weeks of this study, participants will follow an aerobic exercise training program aiming to increase physical capacity, creating the opportunity to study the responsiveness of the remote 6MWT.

Results: In total, 89 people with PD and 65 people with COPD were included in this study. Data analysis will start in April 2024.

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Conclusions: The results of this study will provide information on the measurement properties of the device-assisted 6MWT and TUG in the clinic and at home. When reliable and valid, this can contribute to a better understanding of a person's physical capacity in real life, which makes it possible to personalize treatment options.

Trial Registration: ClinicalTrials.gov NCT05756075; https://clinicaltrials.gov/study/NCT05756075

International Registered Report Identifier (IRRID): DERR1-10.2196/55452

(JMIR Res Protoc 2024;13:e55452) doi:10.2196/55452

KEYWORDS

Parkinson disease; COPD; chronic obstructive pulmonary disease; physical activity; physical capacity; wearable devices; walking; exercise; locomotion; home-based; wearable; wearables; wearable sensor; dementia; smartwatch; StepWatch; treatment

Introduction

Physical functioning is an important aspect of daily living. It represents a broad concept defined as one's ability to carry out activities that require physical actions, ranging from activities of daily living to more complex activities that require a combination of skills within a social context. It is also known to be a powerful factor in the prevention and treatment of several health conditions in older adults [1-5]. Physical functioning is an independent predictor of functional independence, disability, morbidity, and mortality in healthy older people [4,5]. It is also relevant in a wide spectrum of people with chronic diseases [6-9], which makes it an important aspect to measure. Physical functioning requires multiple factors, including physical capacity and physical activity [1]. Physical capacity can be defined as what a person can do in a standardized environment, where physical activity is what a person truly does in daily life [10,11]. Today, physical capacity is measured in clinical settings using advanced tests like maximal oxygen uptake or walking tests such as the 6-minute walk test (6MWT) [1]. Validated questionnaires are generally used to obtain self-reported levels of physical activity in real-life situations [12,13].

Relying only on in-clinic standardized tests is suboptimal for several reasons. First, in-clinic tests give limited information on how a person is functioning in daily life. For example, people with Parkinson disease (PD) experience the so-called *kinesia paradoxa* in which they function unexpectedly well under stressful circumstances, which a clinic visit is for most [14]. Other symptoms such as tremors are typically worse during in-clinic assessments [15]. This problem is compounded by the fact that many people with PD take extra medication before their consultation hoping to make a good impression. Some even practice the clinical tests while sitting in the waiting room. Second, episodic visits are not well suited to detect the complex and evolving fluctuations in daily functioning [6,9,16]. Moreover, the brief in-clinic evaluations cannot reliably capture the common and disabling fluctuations in response to Parkinson medication [17]. Finally, measuring physical activity with a questionnaire is highly unreliable because of its retrospective and subjective nature [13].

With the advent of innovative technologies such as smartwatches, both aspects of physical functioning have become measurable in a person's free-living environment [18-22]. Wearable technology may thus offer an attractive solution to overcome the aforementioned limitations of in-clinic testing [23]. This would be especially helpful for the evaluation of people with chronic conditions like PD or chronic obstructive pulmonary disease (COPD) because the symptoms of both diseases fluctuate within a single day per medication intake or environmental factors [17,24]. Deploying wearable sensors enables monitoring of daily physical functioning over a prolonged period, without relying on the person's in-clinic performance or memory. Remote assessments of physical activity may also lower the barrier for people to check their performance regularly, and also lower the burden to do so for caregivers and researchers [25]. Wearable technology can also better evaluate the effectiveness of treatments, thus enabling a more personalized treatment. Today, measuring physical activity at home using wearable devices has become mainstream and is feasible [12,26,27]. More recently, also measuring physical capacity using wearables has been shown to be feasible but the clinimetric properties have been investigated to a very limited extent as yet [8,28-31].

Here, we propose a protocol to study a wrist-worn device that can measure physical activity and physical capacity passively and remotely while performing assessments at home. The measurement properties of this device regarding physical activity are good but have been obtained in a healthy population [32,33]. We will extend these results and focus on the measurement properties of measuring physical capacity using the 6MWT in people with PD and COPD.

Our primary aim is to study the measurement properties of a device-assisted 6MWT performed at home compared to in-clinic assessments. Our secondary aim is to study the clinimetric properties of the device-assisted Timed Up and Go test (TUG) at home compared to in-clinic assessments.

Methods

Study Design

This is a decentralized, prospective, observational study with a 15-week follow-up involving participants with PD and COPD (Figure 1). This study will be coordinated by the Radboudumc and will be executed in 25 physiotherapy practices throughout the Netherlands. The physiotherapists will perform the in-clinic assessments. Participants will visit their local physiotherapy practice 4 times, once every 5 weeks, for in-clinic assessments of walking capacity, cognitive functioning, daily functioning, and specific disease symptoms. Data collection during each visit will take approximately 2 hours. During the in-clinic assessments, participants will wear 2 different wearable sensor

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devices; the Verily Study Watch on 1 wrist and the Modus StepWatch on the ankle. Participants will be instructed to wear the devices on the same side throughout this study. Moreover, during the course of this study, participants will wear the Verily Study Watch at home for 23 hours a day. Additionally, participants will perform 2 walk tests at home every week. Between visit 2 and visit 4, participants will participate in supervised, in-clinic, high-intensity exercise training according to the current physiotherapy guidelines [34,35]. During this training period, participants will wear the Modus StepWatch at home for 2 weeks. This will provide data to validate real-life walking measures from this study's watch against the StepWatch. Throughout this study, a dedicated helpdesk will proactively assist participants, address problems and questions, and solve issues regarding this study and the devices. The Accuracy of Digital Assessment of Performance Trial (ADAPT) study is registered at ClinicalTrials.gov (NCT05756075).

Figure 1. Study overview. 6MWT: 6-minute walk test; 10MWT: 10-meter walk test; TUG: Timed Up and Go test.

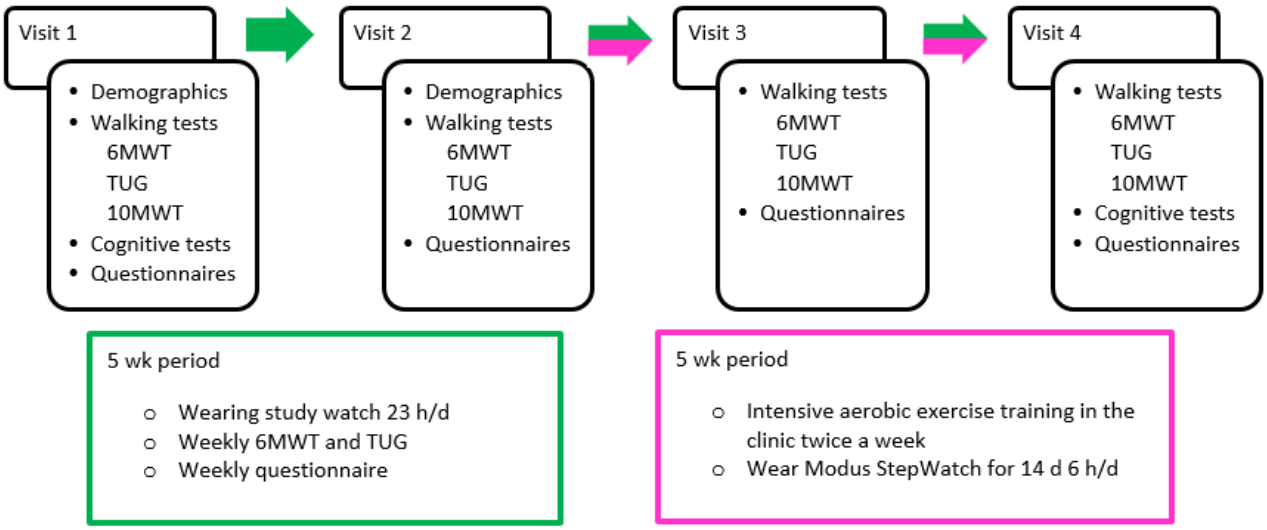

Study Population

We aim to enroll 200 participants, 100 with PD and 100 with COPD between December 2021 and July 2023. Participants are eligible for this study if they meet the following inclusion criteria:

PD or COPD diagnosed by a neurologist or pulmonologist, respectively; aged 18 years or older; able to read and understand Dutch; willing, competent, and able to comply with all aspects of the protocol, including follow-up schedule; willing and able to complete patient-reported outcomes via the internet; able to walk without the use of an assistive device; Hoehn and Yahr stage 1 or 2 (PD-specific); and COPD with perceived limited exercise capacity, irrespective of airway obstruction severity (COPD-specific).

Potential participants will be excluded if they have a high fall risk (for PD) or cardiovascular risk profile (for COPD) impacting the safety of performing the walk tests at home without supervision, as judged by the general practitioner. Patients with other comorbidities are explicitly not excluded from participation. Other exclusion criteria include a co-occurrence of PD and COPD, the inability to make an arm swing at all or if a patient is in a situation that prevents arm swing completely (eg, use of rollator), pregnancy, cognitive impairment as judged by the physiotherapist, participating in another investigational study, participating in a supervised high-intensity aerobic exercise program, or nickel allergy as components of the Verily Study Watch contain trace amounts of this metal.

Recruitment and Enrollment

In each physiotherapy practice, 2 physiotherapists will participate, 1 specializing in COPD and 1 specializing in PD affiliated with the Dutch nationwide ParkinsonNet infrastructure [36]. The physiotherapists will be trained extensively and certified in performing all assessments of this study's protocol to facilitate standardization between the participating practices. Up-to-date standard operating procedures will be shared with every practice as a reference and will be reviewed by the Radboudumc research team regularly. Further, the Radboudumc research team will guide and coach the physiotherapists to support adherence to this study's protocol.

Physiotherapists will identify potentially eligible patients who are already known in their practice because of a former treatment episode or patients newly referred by the general practitioner or medical specialist and provide them with the information letter. If a patient shows interest in this study, a researcher from the Radboudumc will contact them providing additional information, address any questions, and check eligibility. When willing and eligible to participate, participants will be directed to Verily's proprietary web-based system "Baseline Platform" where they are invited to create an account and digitally sign the screening consent form. Once the account is created, the physiotherapist will contact the participant's treating physician to confirm the diagnosis and will ask about potential contraindications to participation in this study (ie, history of falling or cardiovascular risk). If the treating physician expresses no objections, the first appointment will be scheduled.

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At the first visit, the physiotherapist will check eligibility again whereafter this study's informed consent form will be signed on paper by both the participant and physiotherapist, who will perform the assessments. A copy will be provided to the participant. Participants who withdraw their participation during this study will be excluded from follow-up, but the data obtained will be kept in the central database and will be used for data analysis.

Devices

Verily Study Watch

Throughout this study, participants with PD will wear the Verily Study Watch on the wrist of the least affected side while participants with COPD will wear the watch on the wrist of the nondominant side.

Participants will be asked to wear the Verily Study Watch preferably for 24 hours a day, except during daily charging and during wet activities (eg, showering or swimming). During the baseline visit, the physiotherapist will clarify the importance of the wear time with the participant and will explain and demonstrate the use of the Verily Study Watch. A paper-based manual plus an instructional video will be available for participants with instructions for the Verily Study Watch.

The Verily Study Watch is exclusively for investigational use in clinical trials only. It is a multi-sensor wearable device to extend data collection for clinical studies beyond trial sites and into the free-living environment. The watch contains an accelerometer, gyroscope, and a photoplethysmography. The device is not CE (Conformité Européenne) marked or cleared in the United States. The device enables the collection of physiological and environmental data about movement and activity, pulse rate, and skin impedance. Data from the Verily Study Watch will be encrypted and sent securely to the Verily Cloud using a USB synching and charging cradle and wireless connectivity bridge (Verily Study Hub; Figure 2). The Verily Study Watch has been deployed in several studies, including the Baseline Health Study [37], the Parkinson Progression Markers Initiative [38] in the United States, and the Personalized Parkinson Project [39] in the Netherlands.

Figure 2. The Verily Study Watch, along with syncing and charging cradle and Verily Study Hub.

Modus StepWatch

The Modus StepWatch will be placed on the ankle on the corresponding side of the Verily Study Watch during the 4 in-clinic visits. Between visit 2 and visit 4, participants will wear the Modus StepWatch at home for 14 consecutive days for at least 6 hours a day. Participants will be able to choose these 14 consecutive days themselves. To gain insight into the exact wearing times, the participants will create a log where they write down the exact times of wearing the Modus StepWatch.

This device is an ankle-worn wearable medical device (CE class 1 and marked medical in Europe) which will be used as a reference device for measuring participants' ambulation. The onboard 2D accelerometer collects motion data. The collected data can be transferred to the corresponding StepWatch app installed on an iPad. From there, data will be transferred to this study's database. The validity of this device has been obtained in people with PD [40] and COPD [41] as well as in healthy people [42-44].

Assessments

Demographics

During the first visit, demographics, medical history, and medication intake will be registered. Cognitive functions will be assessed during the first and last visit. During each visit, several additional questionnaires on disease symptoms and quality of life will be completed (see Tables 1 and 2 for an overview).

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Table 1. Overview of assessments performed by physiotherapist and questionnaires in the Accuracy of Digital Assessment of Performance Trial (ADAPT) study[a].

Assessments	Visit 1	Visit 2[b]	Visit 3[b]	Visit 4[b]
Motor functioning				
MDS-UPDRS-III/IV[c] (PD[d] only)	✓	✓	✓	✓
H&Y scale[e] (PD only)	✓	✓	✓	✓
TUG[f]	✓	✓	✓	✓
6MWT[g] (2×); pre- or post-Borg score fatigue and dyspnea	✓	✓	✓	✓
10MWT[h] (Single context [3×], dual context [3×]	✓	✓	✓	✓
Cognitive functioning and quality of life				
MoCA[i] (with alternative version during follow-up)	✓			✓
MDS-UPDRS-I (PD only)	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓
Demographics and lifestyle				
Medical history	✓	✓		
Medication	✓			
Arm Hair Index	✓			
Skin tone (Fitzpatrick Scale)	✓			
Autonomic function				
Blood pressure (before 6MWT)	✓	✓	✓	✓
Heart rate (before 6MWT, 0 min after 6MWT, 1 min after 6MWT, 2 min after 6MWT)	✓	✓	✓	✓
SpO2[j] (before 6MWT, 0 min after 6MWT, 1 min after 6MWT, 2 min after 6MWT)	✓	✓	✓	✓

[a]Study Watch sensor data will be recorded during all in-clinic activities, including all walking tests. With the timestamps recorded on the Study Watch for the onset and offset of tasks via the Study Watch graphical user interface, a sensor-based 6-minute walk test will be estimated and compared to the site coordinator's recorded actual 6-minute walk test.

[b]Every fifth week.

[c]MDS-UPDRS-I/II/III/IV: Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (I) nonmotor aspects of experiences of daily living, (II) motor experiences of the daily living section, (III) motor examination section, and (IV) motor complications section.

[d]PD: Parkinson disease.

[e]H&Y scale: Hoehn and Yahr scale.

[f]TUG: Timed Up and Go test.

[g]6MWT: 6-minute walk test.

[h]10MWT: 10-meter walk test.

[i]MoCA: Montreal Cognitive Assessment.

[j]SpO2: oxygen saturation.

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Table 2. Devices and at-home assessments.

Methods	Assessments	Time collected
Verily Study Watch	• Photoplethysmography • Heart rate • IMU[a] including a 3-axis accelerometer and 3-axis gyroscope • Step count • Skin impedance	Continuous data collection, up to 24 h/d
Modus StepWatch	• Step count	All visits[b]
Self-reported patient questionnaires[c]	• ESS[d] • MDS-UPDRS-II[e] (Parkinson disease only) • HADS[f] • PDQ-39[g] (Parkinson disease only) • LAPAQ[h] • CCQ[i] (chronic obstructive pulmonary disease only)	After each visit
At home assessments (walking tests with Verily Study Watch)	• Timed Up and Go test • 6-minute walk test with pre- and post-Borg score	Weekly
Self-reported questionnaires	• FACITF-4[j]	Weekly

[a]IMU: inertial measurement unit.

[b]Wearing at home for 14 consecutive days between visit 2 and visit 4.

[c]Within 2 weeks after each in-clinic visit.

[d]ESS: Epworth Sleepiness Scale.

[e]MDS-UPDRS-II: Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (II) motor experiences of the daily living section.

[f]HADS: Hospital Anxiety and Depression Scale.

[g]PDQ-39: 39-item Parkinson's Disease Questionnaire.

[h]LAPAQ: Longitudinal Aging Study Amsterdam Physical Activity Questionnaire.

[i]CCQ: Clinical Chronic Obstructive Pulmonary Disease Questionnaire.

[j]FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy.

In-Clinic Measurements

The in-clinic assessments will consist of 3 different walking tests. The first test is the 6MWT which will be performed twice according to the most recent guidelines over a straight course of 10 meters [45]. The participants will be instructed to walk at a comfortable speed that they can sustain for 6 minutes. The physiotherapist measures the walked meters during the 6MWT. Second, the TUG will be performed and will be executed twice [46]. Participants will sit in a chair, stand up, walk for 3 meters at a comfortable speed, turn, walk back, and sit down in the chair again. The physiotherapist will measure the time it takes to complete this task. The third walking test is the 10-meter walk test (10MWT) [47]. This test will be performed 6 times; 3 times without cognitive tasks (single context 10MWT) and 3 times with cognitive tasks (dual context 10MWT). During all 6 times, participants will walk over a straight 10-meter course at a comfortable speed with alternating contexts. The physiotherapist will measure the time it takes to walk between the 2nd and 8th meters of the walkway. During the dual context 10MWT, participants will perform a small cognitive task during walking, for example counting backwards from 100 with steps of 7.

Home Measurements

Participants will wear the Verily Study Watch for 24 hours a day throughout the whole study. The device collects passively recorded data while participants wear it. Additionally, participants will be asked to complete the virtual walk test (VWT) independently at home. The TUG and 6MWT with pre- and post-Borg scores will be performed once a week with the guidance of the graphical user interface on the Verily Study Watch. The Verily Study Watch will provide a notification to the participant on the chosen preset day and time to remind them to perform the VWT. The watch will record the start and end of the 6MWT and TUG from button presses on the watch by the participant. Participants with PD will be asked to perform the walk tests 30 minutes to an hour after medication intake and give a tag on the Verily Study Watch, while participants with COPD can choose a standardized time unrelated to medication intake. The VWT can be postponed to the next day at the same time if desirable.

Participants will choose a course to perform the 6MWT inside their homes where they can walk straight for as many meters as possible. Throughout this study, participants will use the same course every time they perform the VWT. A map will be sent to the Radboudumc research team containing an overview

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of the course taken. After each visit, participants will complete a set of validated questionnaires at home, including about quality of life, physical activity, fatigue, sleep, anxiety, and depression in a diagnosis-specific questionnaire [48-55]. These questionnaires will be completed digitally within 2 weeks after each visit. The questionnaire about fatigue will be completed every week.

Intervention

Between visit 2 and visit 4 participants will participate in high-intensity aerobic exercise training according to current physiotherapy guidelines [34,35]. With this intervention, we aim to increase the physical capacity of our participants and, more specifically, the participants' walking capacity to measure the sensitivity to detect changes of the device-assisted 6MWT.

The participants will follow a training session twice a week under the supervision of their physiotherapist. These sessions can be individual sessions or group sessions together with other study participants. Alongside these training sessions, participants will be asked to train independently at home once a week by going outside for a walk. The supervised training sessions will consist of a mix between general physical capacity training and localized muscle function training with a focus on the lower extremities. If needed, the session can be completed with components that are important for the participant, for example, balance training. The physiotherapists will keep a log of each supervised session including the so-called FITT factors: frequency, intensity, timing, and type of training.

Statistical Analyses

The primary aim is to study the measurement properties of the device-assisted 6MWT to assess its ability to obtain physical capacity at home. Our secondary aim is to study these measurement properties of the device-assisted TUG.

The data from the device-assisted 6MWT will be derived from three different situations: (1) during the in-clinic walk tests, (2) during the VWT at home administered via application of the watch, and (3) during free-living where the data are passively recorded.

For our primary aim, we first obtain the measurement agreement between the in-clinic 6-minute walk test distance (6MWD) derived from the Verily Study Watch and the measurements by the physiotherapist. This will be assessed using the intraclass correlation coefficient (ICC) and will be obtained for every study visit. Further, the measurement agreement between the 6MWD of the last virtual 6MWT before the in-clinic assessments and the measurements by the physiotherapist in-clinic will be assessed with the ICC. A Bland-Altman plot will be provided as well. The measurement agreement will be considered "good" when the ICC is at least 0.70 [56].

Second, the test-retest reliability of the 6MWT taken at different visits will be assessed by reporting the ICC. Here, we will use the 6MWD derived from the Verily Study Watch of the 2 in-clinic 6MWTs performed during all 4 visits. The test-retest reliability of the weekly 6MWT at home will also be obtained using the ICC. A Bland-Altman plot will be provided to assess the test-retest reliability too.

Third, we will characterize the performance of the device-assisted 6MWT in capturing changes over time with the physiotherapy intervention. For this comparison, we will use the 6MWD derived from the device-assisted 6MWT during visit 2 and visit 4.

For our secondary aim is the measurement agreement between the in-clinic TUG obtained with the Verily Study Watch and the measurements by the physiotherapist. We will assess this for every study visit using the ICC. Further, the measurement agreement between the last virtual TUG before the in-clinic assessments and the measurements by the physiotherapist will be assessed with the ICC. A Bland-Altman plot will be provided as well.

The TUG derived from the Verily Study Watch of the 2 in-clinic TUGs will be used to obtain the test-retest reliability during all 4 visits. The test-retest reliability of the weekly TUG at home will also be obtained using the ICC. A Bland-Altman plot will be provided too.

Finally, we will characterize the performance of the sensitivity of the device-assisted TUG in capturing changes over time after the physiotherapy intervention. For this comparison, we will use the TUG time derived from the device-assisted TUG during visit 2 and visit 4.

As an exploratory aim, the passively recorded data will be used to relate clinical assessments and free-living–based metrics to patient-reported outcomes.

Sample Size Consideration

No formal sample size calculation was performed. Prior research states that a sample size of at least 50 participants is recommended for validity studies wherein correlation coefficients are estimated [57]. However, larger sample sizes are preferred especially in populations with chronic conditions. Given the fact that we use the ICC as the end point of our primary aim and potential loss of data due to dropouts or device failure, 100 participants with PD and 100 participants with COPD will provide a reasonable sample size for the characterization of performance.

Ethical Considerations

This study is being conducted in conformance with the Good Clinical Practice ICH E6 guideline. Further, this study is conducted in compliance with the Ethical principles for medical research involving human subjects as defined in the Declaration of Helsinki (2007-2008), the Dutch Personal Data Protection Act, and the ISO 14155:2020 (Medical devices). The Medisch Ethische Toetsing Comissie Arnhem Nijmegen approved this study's protocol and communication materials (2021-13165; NL78292.091.21). Written informed consent is obtained before any study procedure is performed. Participants who are not able to give written consent will be excluded from participation.

Results

In total, 89 people with PD and 65 people with COPD were included in this study. Data analysis will start in April 2024, with the first results of the analysis expected in the fourth quarter of 2024.

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Discussion

The purpose of the ADAPT study is to evaluate the measurement properties of a device-assisted 6MWT and a device-assisted TUG for assessing physical capacity in the daily lives of people with PD and COPD.

Currently, the 6MWT is used to measure physical capacity but it is performed in clinical settings, where the circumstances are always optimized. That makes it hard to obtain a representative view of a person's physical capacity in their own environment. Wearable technology may offer a solution that enables us to better understand true physical functioning in daily life and its fluctuations throughout the day when deployed at home [23]. Therefore, it is relevant to investigate the measurement properties of a home-based 6MWT when using a wearable device.

This study will lead to unique insights for several reasons. First, the collected data using both regular assessments and continuous data collection using wearable sensors will give us important insights into daily life functioning. Another unique element is the broad inclusion criteria, that allow us to collect data from "real-life" patients and to obtain a more representative view of the true population. Besides that, the repeated measurements in the clinic but also at home and the passively recorded data provide insight into a patient's functioning in daily life. Those include fluctuations regarding medication intake and several other environmental or personal factors, like heart rate and quality of sleep.

The design of this study is complex, which creates potential challenges. This includes the complex logistic distribution of study materials and this study's coordination throughout the country. Using 2 different devices that both have different ways regarding preparation and setup before data collection can take place is also challenging, for both participants and physiotherapists. We have addressed this issue by extensively training the physiotherapists and creating videos about the devices for participants. In case of emergencies or questions, we are easily reachable by email and phone for both physiotherapists and participants.

Another challenge will be the inclusion of participants since we only approach patients who are under treatment within the trained physiotherapists' clinics. Should the inclusion of participants stagnate, we will use our own network to approach participants and see if they are willing to travel to an affiliated practice near their homes. However, even with these solutions, we are aware that participants may feel insecure or not skilled enough about using the devices and decide not to participate or even stop participation. This is compounded by the fact that the vast majority of both people with PD and people with COPD are older.

We also expect a challenge in the analysis of the 6MWT measurements at home. Every participant chooses their own course indoors, which leads to an enormous variety in course shapes, course lengths, and number of turns. Not every participant can walk straight for 10 meters indoors, leading to a shorter course compared to the in-clinic measurements. The study from Fell et al [58] showed that a shorter pathway reduces the 6MWD compared to the traditional 30-meter pathway. We chose to use the 10-meter course to ensure comparability with the 6MWT performed at home. It is more likely that participants can walk for 10 meters straight in their homes than to walk for 30 meters. To gain insight into the courses of our participants, they will create a map of their homes in which they draw their 6MWT course and add the distances of several components of their course.

Additionally, there might be a potential influence of disease severity in the PD cohort when determining the 6MWD from the Verily Study Watch. It is known that people with PD have a significantly reduced step length compared to healthy controls [59]. When analyzing the data, the step length of the participants needs to be defined. The equations used in healthy populations to estimate a person's step length based on body height and age might not be appropriate here. A sensitivity analysis will be performed during the data analysis to check if participants with higher disease severity (ie, a higher Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale part III score) will have a worse correlation between the 6MWD from the Verily Study Watch compared to the measurements of the physiotherapists.

This study design also serves as an important feasibility test for remote VWTs. In recent years, the 6MWT and TUG have been studied at home in people with cardiovascular, pulmonary, and neurological diseases [25,60-62]. Different approaches were used to measure the distance walked and time to complete both tests, for example with wearable sensors [19,63], smartphone apps [25,64-66], and more traditional tools like a rope and a stopwatch [67,68]. Based on their results, administering physical capacity tests at home seems to be a promising tool for clinical management or research. However, these tests should be uncomplicated to perform safely and require little space. An example of a home-based test can be the Parkinson's Disease Virtual Motor Exam which has been deployed to remotely measure the severity of tremor, bradykinesia, and gait impairment [39]. The data from this latter study suggest that people with PD engage with the Parkinson's Disease Virtual Motor Exam and can complete remote active assessments of motor function and yield data of sufficient quality [15]. Since we use the same smartwatch and user interface but with different tests, we expect that the quality of the data is sufficient for our purposes.

With the results of this study, we will gain insight into the measurement properties of the device-assisted 6MWT and TUG in the clinic and at home. When reliable and valid, we will be able to digitally assess a person's physical capacity performed in their own familiar environment and capture daily life functioning. This can contribute to better information that makes it possible to personalize treatment options.

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Authors' Contributions

All authors read and approved the final paper. DdG, AvH, NMdV, JJPS, TvdZ, BB, SS, NK, PB, RK, and WJM Jr contributed to this study's conception and design, data collection, analysis planning, and paper preparation.

Conflicts of Interest

DdG, TvdZ, and JJPS report no conflict of interest. NMdV reports grants from The Netherlands Organisation for Health Research and Development (ZonMw) and The Michael J. Fox Foundation. BB currently serves as editor in chief for the Journal of Parkinson's Disease; serves on the editorial board of Practical Neurology and Digital Biomarkers; has received honoraria from serving on the scientific advisory board for AbbVie, Biogen, and Union Chimique Belge (UCB); has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare, and Bial; and has received research support from the Netherlands Organization for Scientific Research, The Michael J. Fox Foundation, UCB, AbbVie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, the Gatsby Foundation, and the Parkinson Vereniging. SS, NK, PB, WJM Jr, and RK report employment at Verily Life Sciences and equity ownership in Verily Life Sciences.

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Abbreviations

6MWD: 6-minute walk test distance
6MWT: 6-minute walk test
10MWT: 10-meter walk test
ADAPT: Accuracy of Digital Assessment of Performance Trial
CE: Conformité Européenne
COPD: chronic obstructive pulmonary disease
FITT: frequency, intensity, timing, and type of training
ICC: intraclass correlation coefficient
PD: Parkinson disease
TUG: Timed Up and Go test
VWT: virtual walk test

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Protocol

Effectiveness of Virtual Reality in Reducing Perceived Pain and Anxiety Among Patients Within a Hospital System: Protocol for a Mixed Methods Study

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Abstract

Background: Within hospital systems, diverse subsets of patients are subject to minimally invasive procedures that provide therapeutic relief and necessary health data that are often perceived as anxiogenic or painful. These feelings are particularly relevant to patients experiencing procedures where they are conscious and not sedated or placed under general anesthesia that renders them incapacitated. Pharmacologic pain management and topical anesthetic creams are used to manage these feelings; however, distraction-based methods can provide nonpharmacologic means to modify the painful experience and discomfort often associated with these procedures. Recent studies support distraction as a useful method for reducing anxiety and pain and as a result, improving patient experience. Virtual reality (VR) is an emerging technology that provides an immersive user experience and can operate through a distraction-based method to reduce the negative or painful experience often related to procedures where the patient is conscious. Given the possible short-term and long-term outcomes of poorly managed pain and enduring among patients, health care professionals are challenged to improve patient well-being during medically essential procedures.

Objective: The purpose of this pilot project is to assess the efficacy of using VR as a distraction-based intervention for anxiety or pain management compared to other nonpharmacologic interventions in a variety of hospital settings, specifically in patients undergoing lumbar puncture procedures and bone marrow biopsies at the oncology ward, patients receiving nerve block for a broken bone at an anesthesia or surgical center, patients undergoing a cleaning at a dental clinic, patients conscious during an ablation procedure at a cardiology clinic, and patients awake during a kidney biopsy at a nephrology clinic. This will provide the framework for additional studies in other health care settings.

Methods: In a single visit, patients eligible for the study will complete brief preprocedural and postprocedural questionnaires about their perceived fear, anxiety, and pain levels. During the procedure, research assistants will place a VR headset on the patient and the patient will undergo a VR experience to distract from any pain felt from the procedure. Participants' vitals, including blood pressure, heart rate, and rate of respiration, will also be recorded before, during, and after the procedure.

Results: The study is already underway, and results support a decrease in perceived pain by 1.00 and a decrease in perceived anxiety by 0.3 compared to the control group (on a 10-point Likert scale). Among the VR intervention group, the average rating for comfort was 4.35 out of 5.

Conclusions: This study will provide greater insight into how patients' perception of anxiety and pain could potentially be altered. Furthermore, metrics related to the operational efficiency of providing a VR intervention compared to a control will provide insight into the feasibility and integration of such technologies in routine practice.

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KEYWORDS

virtual reality; digital health; feasibility; acceptability; pain; anxiety; hospital; hospitalization; in-patient; observational study; pharmacologic pain management; pain management; topical anesthetic creams; topical cream

Introduction

Overview

Standard pain management protocols in adult medical settings, such as a hospital or clinic, typically rely on the use of pharmacotherapies such as acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids to alleviate acute pain. Although these forms of treatment can be effective, there are growing concerns surrounding the use of opioids and the potential health risks associated with the use of pharmacotherapies under certain conditions. As a result, there is a growing demand to support limiting the use of pharmacotherapy for acute pain in favor of nonpharmacologic options. However, there are few alternative options for providing pain management in adults who often receive inadequate pain control. There is a need to find effective and acceptable alternate forms of pain management and anxiety reduction in a hospital or clinic setting. Virtual reality (VR) could potentially be this alternate form of pain management due to its ability to distract.

Distraction-based therapy techniques are used by hospital staff to help patient cope with injuries, hospitalization, or illness and they differ based on each patient's needs and preferences. Some common techniques used by specialists include controlled breathing, guided imagery, and relaxation and passive techniques like auditory distraction and television. Studies for each of these different techniques over the years found positive, but mostly mixed results [1]. There is no conclusive study suggesting that 1 technique supersedes others since each patient has different preferences, medical situations, behavioral needs, and developmental needs. Among the adult population, distraction proves beneficial in reducing perceived pain [2]. Distraction became particularly useful for handling illness and procedure-associated pain among adolescents and children with cancer [3,4].

As an emerging technology, VR provides an immersive user experience that shows promise as a tool that can reduce perceived pain and anxiety related to acute pain in an emergency room or other clinical settings through a distraction-based therapy method. Some studies have already used VR technology as a beneficial distractor for pain given its inherent immersive properties [5,6]. With recent advancements, VR technology is being used in numerous settings, but limited research has been done thus far in adult populations.

VR may manage different types of painful experiences, including dressing changes, needle procedures, burns, and postsurgical and chronic pain [7-9]. A study using immersive VR with an adult population suggests that VR can significantly reduce the use of opioids during painful procedures [10].

Successful VR interventions include several factors—the ability to capture attention, enjoyment, immersion, novelty, interactivity, and goal-directedness [11]. Based on the properties of VR, motion sickness and nausea sometimes occur [12]. Therefore, it is necessary to ensure it is safe to use in adults, especially in patients with cancer, by indicating any linked adverse events [13].

There is evidence to support the use of VR as a distraction tool during acute pain events and minor surgeries or procedures. Until recently, the use of VR required a PC, phone, wires, or additional items creating a barrier to adoption in a hospital or clinic setting. The Oculus Quest 2 (Reality Labs) stand-alone headset's hardware is base priced at US $250, making it an affordable alternative that can potentially provide a nonpharmacologic treatment for acute pain management and anxiety reduction. This study will be using the Oculus Quest 2 as a distraction method because the Quest devices are among the first stand-alone devices commercially available.

The purpose of this pilot study is to evaluate the effectiveness of using nonpharmacological VR distraction methods for specific procedures to reduce perceived anxiety and pain in various medical settings. The information gained will help to design future studies needed to ensure the capability and the reliability of the devices for additional study sites in the future.

Specific Aims

Overview

Specific aims are used to demonstrate the efficacy of the proposed VR intervention in hospital patient populations.

Specific Aim 1

Specific aim 1 examines the effect of VR on pain perception before and after a conscious medical procedure in the hospital or outpatient setting.

Specific Aim 2

Specific aim 2 examines the effect of VR on perceived anxiety before and after a conscious medical procedure in the hospital or outpatient setting.

Specific Aim 3

Specific aim 3 assesses the efficacy of VR as a distraction-based therapy for a conscious medical or dental procedure in the hospital or outpatient setting.

Methods

Participants

This research study will use a mixed methods research design to compare the efficacy of using VR as the sole distraction method and the standard of care using other nonpharmacological distraction methods. There will be no alternation to the analgesics or opioids provided to patients during any of their respective medical procedures. Trained research assistants who are familiar with the study protocol for recruitment and eligibility to participate in this research will recruit patients in coordination with medical staff at the respective clinical sites.

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The sample population will consist of 250 adults between the ages of 18 and 99 years. The sites this study will operate in include the University of Florida (UF) Health oncology, dental, cardiology, nephrology, and anesthesiology clinics.

Criteria to participate in this study vary between clinical sites based on the conscious medical procedure this study is approved to enroll patients in. Across all sites, this study will only enroll adult (older than 18 years of age) participants. In the oncology ward, adult participants must receive a prescription for a bone marrow biopsy by hospital staff to meet the minimum eligibility requirements. Adult participants from the UF Health Dental clinic coming in for a cleaning will be eligible. Similarly, at the UF Health Cardiology clinic, adult patients undergoing cardiac ablations will be recruited. At the UF Health Nephrology clinic, adult patients undergoing renal biopsies will be recruited. At the UF Health Anesthesiology clinic, adult patients with a broken bone (hand, arm, and leg) receiving an epidural will be recruited.

The study will exclude patients matching the criteria of nausea or vomiting upon admission; require urgent procedures or are otherwise deemed unstable by hospital staff; and have a condition that prevents the use of VR technology such as epilepsy, or a facial or scalp wound. These same exclusion criteria apply to patients enrolled at all UF Health medical or dental clinics.

The VR content displayed to all participants in the experimental group is game developed through an engineering team affiliated with the University of Florida. The VR game requires the user to slightly shift their head to collect tokens and capture images of wildlife going through a nature trail. Current distraction-based methods that are standard in the clinics this study operates in include music.

Participants will be randomly assigned into 1 of the 2 groups. The groups are group 1, participants who received VR as the only distraction method during their medical procedure (n=25 per site; n=125 total), and group 2: participants who received no VR but standard distraction methods during their procedure (n=25 per site; n=125 total). The sites that will be enrolling participants include oncology, dental, cardiology, nephrology, and anesthesiology.

Recruitment

After identifying eligible participants for this study, trained research assistants will approach and recruit them. If these eligible participants are interested, a trained study member will review and obtain consent directly from the participant. A standardized informed consent script will be adhered to ensure consistency in the consenting process. Participants will receive a copy of the informed consent document.

Procedure

Research assistants will identify and determine the eligibility of patients admitted in the UF Health Division of Hematology and Oncology wards, UF Dental, UF Cardiology, UF Nephrology, and UF Anesthesiology clinic working in coordination with medical staff. Consent will be obtained directly from the participant.

Before the procedure, medical staff will measure the blood pressure, heart rate, and rate of respiration for participants in both the VR intervention and control groups. These measures are a part of the "standard of care" at all medical or dental clinics in the UF Health system.

All participants, regardless of group, will be asked to complete a procedural anxiety question and to rate their pain using the Verbal Numerical Rating Scale (VNRS) before the procedure. Additionally, patients will be asked to complete the clinically validated Surgical Fear Questionnaire (SFQ) prior to the procedure. Patients will also be asked if they have a history of motion sickness and if they are familiar with VR. A research assistant will assist the patient or participants with putting the VR headset on and turning on a program.

We will begin timing the total length of the procedure as soon as a distraction method begins, that is, the start of a distraction method or when a VR program is turned on, before the procedure. Then, the hospital staff will perform the procedure. During the procedure, vitals (heart rate, respiration rate, and O_2 stat) will be recorded from a pulse oximeter. Blood pressure will be collected if possible or otherwise recorded via the medical record.

After the procedure is complete, a research assistant will assist patients with removing and shutting off the VR headset and clearing any other distraction method. Timing will stop once the procedure is complete. At the end of the medical procedure, medical staff will remeasure blood pressure, heart rate, and rate of respiration for participants in both groups as part of the standard of care.

Participants, in both groups, will be asked to complete the procedural anxiety question and VNRS post their procedure. Any participant who used VR will be asked to answer questions related to their VR experience via the Likert scale listed in the secondary measures. These questions relate to the perceived effectiveness of the VR intervention and their willingness to use VR in a medical setting in the future. At the end of the study visit, participants will be thanked for their time and participation.

Following the study visit, research assistants will retrieve demographic information (age, sex, race, and ethnicity) on the participants from their electronic medical record. Research assistants will also retrieve the participant's pre- and postprocedure vitals (blood pressure, heart rate, and rate of respiration) from the participant's electronic medical record. Data from the site of the procedure will also be collected by research assistants through a retrospective review of the participant's medical records. This information will be recorded on the preprocedure survey which will be uploaded along with the postprocedure survey digitally to a secured, university-affiliated Dropbox file. Study staff will also sanitize the VR equipment according to the guidelines developed to prevent contamination and the spread of infection.

Outcome Measures

Overview

The following listed measures will be collected for all participants in both groups. All data will be stored via a secured,

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university-affiliated Dropbox account approved by the institutional review board (IRB), a Health Insurance Portability and Accountability Act (HIPAA) compliant, and university-supported application used for data capture and storage.

Primary Measures

Pain

The participant will use the VNRS and SFQ to self-report measurement of pain felt before and after the procedure.

Verbal Numerical Rating Scale

The VRNS is 1 of the most commonly used validated methods for assessing pain in adult populations [14]. Study staff will ask patients in both groups to rate their pain on a scale of 1 to 10 before the procedure, to establish a baseline pain level, and after the procedure.

Time

The time it takes to perform the respective procedures with a nonpharmacologic distraction method is measured. Timing will begin at the beginning of the procedure once the intervention has been set up. Timing will end once the procedure ends.

Secondary Measures

Anxiety

We will ask the participant a question about their anxiety before and after the procedure using a single anxiety question on a Likert scale.

Surgical Fear Questionnaire

The SFQ is a validated 8-question survey that assesses preoperation anxiety and fear [15]. Study staff will ask patients in both groups to rate their fear levels associated with specific questions on a scale from 1 to 10.

Procedural Anxiety Question

A 2007 study found that a single question with a Likert scale can quickly and accurately measure anxiety in situations where a full anxiety questionnaire or scale cannot feasibly be used [16]. Study staff will ask patients in both groups about their anxiety level using the question “How worried or anxious are you about the medical procedure?” and the response choices are (1) not anxious or worried at all, (2) slightly anxious or worried, (3) somewhat worried or anxious, (4) very worried or anxious, and (5) extremely worried or anxious.

VR Experience

Participants will be asked to rate their VR experience using a 5-point Likert scale on the following statements after being asked the question, “How worried or anxious are you about using VR during this medical procedure?” and the response choices are (1) not anxious or worried at all, (2) slightly anxious or worried, (3) somewhat worried or anxious, (4) very worried or anxious, and (5) extremely worried or anxious. A few open-ended questions regarding their VR experience are “What did you like about using the VR headset?” “What did you not like about using the VR headset?” and “What do you think could be improved about using VR during the procedure?”

Demographics and Vitals

Pre- and postprocedure vitals (blood pressure, heart rate, and rate of respiration) and demographic information (age, sex, race, and ethnicity) will be retrieved from the participant’s medical record and stored using the secured, IRB-approved Dropbox.

Statistical Analyses

Data from the VNRS and procedural anxiety question will be analyzed using paired *t* tests to compare differences between the intervention and control groups. The average time of the suturing procedure will also be compared between groups.

Average ratings for both Likert scales relating to patient experience using VR and hospital staff evaluation of VR use during the procedure will be analyzed for any trends.

Ethical Considerations

This study, which includes human participant research, was approved by the IRB of the Florida Department of Health (IRB201900850). The informed consent forms, used in this study, provide subjects with a description of the study, its qualitative and quantitative measures, potential risks and discomforts, and explicitly ask the patient to voluntarily agree to participate and allow their data to be collected. Study data are deidentified as all participants are assigned a numerical code. This code follows the format of OC001. Anonymity of all study subjects is ensured. No compensation of any sort is offered to human participants. This is stated in the informed consent form. No identification of individual participants is present in any images of this study or in any supplemental material.

Results

Our preliminary operations at the oncology site have shown promising results. Anxiety measures indicated a parallel decrease between the control and VR intervention group from preprocedure levels to postprocedure levels with a slightly greater decrease of 0.3 points in reported anxiety in the VR intervention group. Pain measurement comparisons between the control and VR intervention groups indicated a greater difference of decrease in perceived pain among the VR intervention group. The preprocedural pain score for the control group was 2.4 out of 10 and postprocedural pain score was 2.67 out of 10, indicating a 0.27 increase in perceived pain after the procedure was completed. In contrast, the preprocedural pain score for the VR intervention group was 2.95 out of 10 and the postprocedural self-reported pain score was 1.95 out of 10, representing a 1.00 decrease in perceived pain.

Most participants reported enjoyment, comfort, and ease of use when VR was in use. Among the VR intervention group, the average rating for comfort was 4.35 out of 5. A total of 10 respondents mentioned clarity as an area for improvement regarding the visibility of the VR content. Notably, there was an 8.75-minute faster completion of the medical procedure among the VR intervention group (n=125) compared to the control group (n=125).

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Discussion

A total of 50 participants underwent a bone marrow biopsy or lumbar puncture and were randomly assigned to experimental or control groups with 25 VR interventions and 25 control participants included in the analyses. With respect to preliminary findings of clinical effectiveness, results indicated encouraging data trends among the participants in the oncology site with a reported decrease in anxiety and pain and no significant variations in vital sign measurements in the VR intervention group compared to the control group receiving a medical procedure. Thus, the pilot study indicated improvements in the VR group for pain, anxiety, and stress along with quantitative metrics of blood pressure, pulse, and respiratory rate when compared to the control group. Across the entire study period, these differences met the criteria of clinical noninferiority for quality of life. Participants reported feelings of relaxation and enjoyment and reported being highly likely to use the interventions again.

Measurements of feasibility for VR focused on the usability and comfort of the technology, as well as its impact on the length of time for the medical procedure to be completed. Results revealed that the use of VR as a distraction-based relaxation tool in an adult hospital setting is feasible. Participants enjoyed using VR and the majority reported comfort and ease of use when VR was used. Issues related to the clarity of viewing the VR can be addressed through better practices fitting the Oculus Quest 2 headset on the patient. Results also indicated a faster completion of the medical procedure among patients in the VR intervention group. Therefore, the faster completion of the procedure can occur without compromising the quality of care and provides valuable clinical application for VR in the hospital setting as it improves the efficiency of providers while performing routine procedures.

Limitations to the study include the fact that the study was not designed to measure the impact of potential moderators on the outcomes, and the data cannot provide reliable information about the potential impact of age, gender, and pain tolerance of participants enrolled in the study. Additionally, the randomization could not control the use of additional pain medication prior to a medical procedure that was self-prescribed by the patient prior to being approached regarding participation in the study. Furthermore, the study did not factor in medications that the patients are on or the full past medical history of participants to consider the impact of those factors on how the participant's vital signs report.

Overall, this study indicates that the use of an Oculus Quest 2 Headset with the VR program for both distraction and relaxation is acceptable, feasible, and with preliminary measures, effective for adult patients undergoing a variety of medical procedures by reducing anxiety and pain and reducing procedure time in a hospital setting.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

TW serves as a site PI for the following sponsors: Takada, Sanofi, Sobi, Genentech, Regeneron, and Amag. All other authors have no conflicts to declare.

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
SFQ: Surgical Fear Questionnaire
UF: University of Florida
VNRS: Verbal Numerical Rating Scale
VR: virtual reality

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Protocol

A Mindfulness-Based App Intervention for Pregnant Women: Protocol for a Pilot Feasibility Study

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Abstract

Background: Pregnancy is a complex time characterized by major transformations in a woman, which impact her physical, mental, and social well-being. How a woman adapts to these changes can affect her quality of life and psychological well-being. The literature indicates that pregnant women commonly experience psychological symptoms, with anxiety, stress, and depression being among the most frequent. Hence, promoting a healthy lifestyle focused on women's psychological well-being is crucial. Recently developed digital solutions have assumed a crucial role in supporting psychological well-being in physiologically pregnant women. Therefore, the need becomes evident for the development and implementation of digital solutions, such as a virtual coach implemented in a smartphone, as a support for the psychological well-being of pregnant women who do not present psychological and psychiatric disorders.

Objective: This study aims to assess the feasibility, acceptability, and utility of a mindfulness-based mobile app. The primary objective is to explore the feasibility of using a virtual coach, Maia, developed within the TreC Mamma app to promote women's psychological well-being during pregnancy through a psychoeducational module based on mindfulness. Finally, through the delivery of this module, the level of psychological well-being will be explored as a secondary objective.

Methods: This is a proof-of-concept study in which a small sample (N=50) is sufficient to achieve the intended purposes. Recruitment will occur within the group of pregnant women belonging to the pregnancy care services of the Trento Azienda Provinciale per i Servizi Sanitari di Trento. The convenience sampling method will be used. Maia will interact with the participating women for 8 weeks, starting from weeks 24 and 26 of pregnancy. Specifically, there will be 2 sessions per week, which the woman can choose, to allow more flexibility toward her needs.

Results: The psychoeducational pathway is expected to lead to significant results in terms of usability and engagement in women's interactions with Maia. Furthermore, it is anticipated that there will be improvements in psychological well-being and overall quality of life. The analysis of the data collected in this study will be mainly descriptive, orientated toward assessing the achievement of the study objectives.

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Conclusions: Literature has shown that women preferred web-based support during the perinatal period, suggesting that implementing digital interventions can overcome barriers to social stigma and asking for help. Maia can be a valuable resource for regular psychoeducational support for women during pregnancy.

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KEYWORDS

mindfulness; promoting well-being; pregnancy; eHealth; mobile health; mHealth; mobile apps; development; usability; user-centered design; mindfulness based; intervention; pregnant women; pregnant; feasibility study; well-being; women; quality of life; psychological symptoms; digital solution; virtual coach; smartphone; mobile phone

Introduction

Overview

The transition to motherhood represents a profound shift in a woman's life, necessitating a reorganization of her identity, skills, attitudes, and values [1]. Pregnancy is characterized by major transformations. Pregnancy brings about substantial changes that impact a woman's physical, mental, and social well-being. How a woman adapts to these changes can affect her quality of life (QoL) and psychological well-being. The literature indicates that pregnant women commonly experience psychological symptoms, with anxiety, stress, and depression being among the most frequent. Specifically, between 12.2% and 39% of pregnant women are reported to experience symptoms of anxiety and psychosocial stress [2], the latter defined as "an imbalance that a pregnant woman perceives when she is unable to cope with the demands of the new condition, which manifests itself behaviourally and psychologically" [3]. These findings were also confirmed by the study conducted by Woods et al [4], which revealed that 6% of women reported high levels of stress symptoms, 78% exhibited low to medium stress symptoms, and 16% reported no stress symptoms. Other studies have investigated perinatal depression in pregnant women, which has been recognized as a prevalent clinical condition [5]. Specifically, the study [5] found an incidence of depressive symptoms reaching 14.5% during pregnancy and 49% during the first year after delivery. Therefore, both pregnancy and the transition to motherhood are commonly seen as vulnerable periods marked by escalating worries and fears about managing the changes ahead, including caring for the baby or children yet to be born [6]. Therefore, it is crucial that pregnancy is experienced positively by women, thereby fostering the development—spontaneous or voluntary—of a positive level of cognitive motivation [7]. Indeed, promoting a healthy lifestyle focused on the woman's psychological well-being is central to her mental health and future relationship with the child or children.

To date, psychoeducational interventions promoting women's psychological well-being during pregnancy are scarce. They tend to focus on the effect of such interventions on specific subgroups of pregnant women with psychiatric symptoms (eg, perinatal depression disorder). Using digital tools to promote psychological well-being can be optimal for pregnant women, who can benefit from the intervention by accessing them anywhere and at any time. In addition, digital interventions are designed to be flexible to the mother's needs and reduce the barriers related to social stigma and help-seeking behaviors [8,9]. Therefore, promoting tailored and easily accessible digital interventions aimed at addressing the specific needs of mothers during the transitional period is crucial for fostering positive relationships with their children. In this regard, a growing body of evidence reports promising results concerning the effectiveness of evidence-based mindfulness interventions delivered via web for promoting the psychological well-being of pregnant women [10,11]. Studies have also found that the psychological state of the pregnant woman appears to be closely related to the course of the pregnancy and the psychological and cognitive development of the child. Indeed, the literature reports a positive association among anxiety, stress symptoms, the likelihood of preterm delivery, and the variability in fetal heart rate [12]. Therefore, mindfulness interventions provide an active approach to managing stress levels, anxiety symptoms, and depression, aiming to reduce them. Thus, developing skills related to this practice enables women to mindfully deal with many potentially critical situations, including the moment of childbirth.

In conclusion, the psychoeducational interventions heralded through the use of digital solutions reported so far are shown to be a viable solution with the potential to promote psychological well-being, support the psychological adaptation of women in physiological pregnancy, and prevent the development of clinically relevant symptoms.

Local Background

The autonomous province of Trento (PAT) is committed to promoting community welfare by providing a comprehensive initiative supporting and empowering parents at the provincial level. This includes a wide range of preventive, protective, and curative interventions spanning from early pregnancy to the first thousand days of a child's life. These interventions are designed to have significant short-, medium-, and long-term health impacts for the newborn in both childhood and adulthood as well as for parents, the community, and future generations. In these initiatives, the integration of digital health tools is a crucial component within the framework of a pervasive digital health approach [13].

The overall strategy to support pregnant women begins with the active provision of the Birth Pathway initiative. The Birth Pathway encompasses all services aimed at promoting the health of women, infants or newborns, and families, providing appropriate care throughout pregnancy, childbirth, and

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postpartum, including support during breastfeeding, the postpartum period, and parenting.

Because of these comprehensive efforts at the provincial level, in 2022, the PAT and the provincial health services institution (Azienda Provinciale per i Servizi Sanitari—Azienda Provinciale per i Servizi Sanitari di Trento; APSS) achieved the United Nations International Children's Emergency Fund—Baby Friendly Initiatives accreditation for all birthing facilities and the community. This accreditation reflects the long-lasting commitment to the continuous improvement of care standards and outcomes. The PAT is also designated as Friends of Children, a status which the Trento birthing facility had already attained in 2015.

This research project has been developed in full harmonization with the overall principles of the PAT initiatives mentioned in the previous paragraphs and considering the broader provincial context in terms of organizational assets and service delivery. In particular, the project is promoted in the context of the First Thousand Days Module scenario of the Digital health care and artificial intelligence—tools for bringing the health service closer to citizens and for the development of the provincial system project, described and approved in deliberation number 2475 of the PAT on December 22, 2022. This strategy scenario is geared toward enhancing well-being and promoting healthy lifestyles during normal pregnancies, while also incorporating digital health principles and tools into organizational assets.

Goal of the Study and Research Questions

This study is positioned within the design and development cycle of the Obesity-Related Behavioral Intervention Trials model (specifically the Refine phase) [14]. It involves delivering mindfulness-based materials in text, audio, and video formats by a virtual coach (ie, a digital assistant, hereafter identified as Maia) implemented within the TreC Mamma app.

This intervention is positioned within the framework of behavior change interventions [15], which aim to enable women to acquire adaptive strategies for their psychological well-being. It is emphasized that the term intervention in this context is used to identify an app (in this case, the virtual coach) that will periodically offer, in a predefined (ie, rule based), structured, and ordered manner, informational materials in audio, text, and video formats, which will be structured and reviewed by psychological professionals.

The end user reads and manages this material independently; therefore, the virtual coach will be used as a simple information transmission tool. In addition, the software (app and virtual coach) is used to administer questionnaires and collect, store, and transmit data in this project. This intervention has been developed and implemented for research purposes, with the final goal of validating a digital health intervention targeting women's psychological well-being during pregnancy through a module of mindfulness practices.

Primary Objectives

The primary objectives of this proof-of-concept study are (1) to exploratively investigate user experience (UX) and user engagement (UE), that is, women's experience and engagement with the TreC Mamma app and the virtual coach dedicated to the mindfulness intervention (Maia); and (2) to assess the women's UE with Maia and the TreC-Mamma app through semistructured interviews and investigate their feelings and overall experience during the psychoeducational intervention.

Secondary Objective

The secondary objective is to assess the level of pre-post psychological well-being through administering self-report questionnaires at the beginning and the end of the intervention.

Maia Intervention

The virtual coach, Maia, is structured to deliver a module featuring psychoeducational content based on mindfulness to promote the QoL and psychological well-being perceived by pregnant women. The module is self-administered and available on both Android and iOS devices. All the contents of the dialogues have been developed by a group of researchers from the Digital Health Research of the Bruno Kessler Foundation (Fondazione Bruno Kessler–Trento; FBK) of Trento and psychologists from the Istituto Pavoniano Artigianelli with specific skills in mindfulness protocols and communication. Subsequently, materials have been revised by a psychologist from the psychology operating unit of the APSS of Trento. The dialogues, videos, and audio tracks were developed based on an educational rather than an emergency management approach.

Technological Tools

The technological component of the study is based on TreC Mamma. This platform allows citizens of the PAT to access, manage, and share information regarding their health and well-being [16]. TreC stands for *cartella clinica del cittadino* and is a reliable and well-tested platform designed to be a "system of systems" rather than a simple data hub. The central pillar of the TreC Mamma platform is the role of the citizen or patient as the manager of their own health-related data as in the case of a personal health record. TreC Mamma is designed with a flexible architecture, which enables the collection and management of heterogeneous data and allows the development and use of further subsystems to provide additional and specific functions.

This research project uses an additional module of the TreC Mamma platform, called TreC Mamma, a technological platform for supporting pregnant women who are residents in the PAT and are enrolled to APSS's services. TreC Mamma can be downloaded for free by all pregnant women in the provincial health service. Authentication should be carried out via the *sistema pubblico di identità digitale* (ie, the public digital identity system) or *carta di identità elettronica* (ie, electronic identity card), which are secure national identification system services.

Mindfulness Practices Module

The mindfulness practice intervention lasts 8 weeks, with 2 sessions of approximately 10 minutes each per week. Figure 1 shows a graphical representation of the conversational protocol delivered to women and its chronological structure.

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Figure 1. Graphical representation of the conversational protocol delivered to the participants and its chronological structure. DASS-2: Depression Anxiety Stress Scales–21; ERQ: Emotion Regulation Questionnaire; FFMQ: Five Facet Mindfulness Questionnaire; IES-R: Impact Event Scale–Revised; MARS: Mobile Application Rating Scale; PANAS-SF: Positive and Negative Affect Schedule–Short Form; SF-12v1: Short Form–12 Health Survey Version; UES-SF: User Engagement Scale–Short Form; UX: user experience.

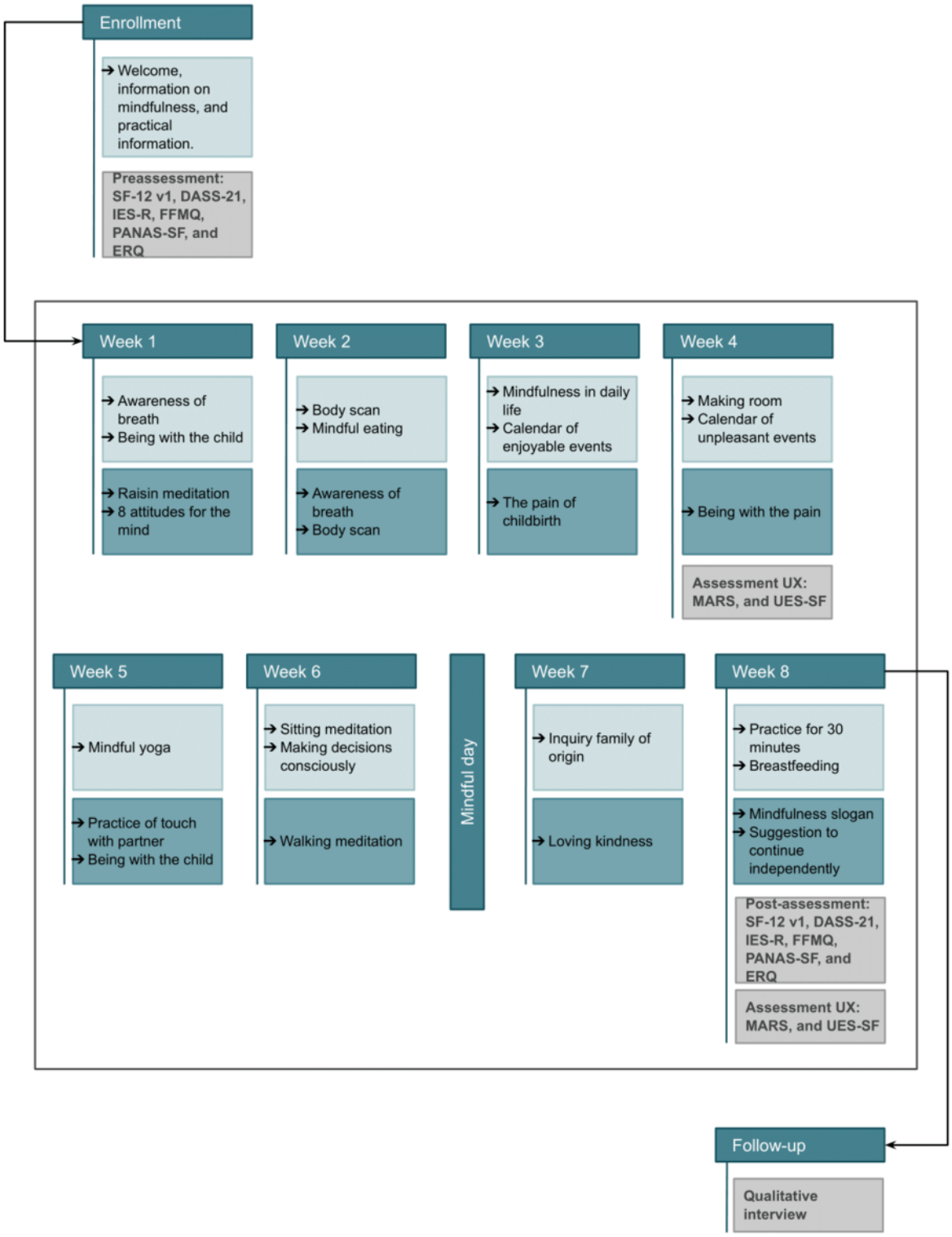

This module aims to enable women to acquire healthy coping strategies with specific reference to mindfulness practices to promote psychological well-being during and after pregnancy. Pregnant women can learn mindfulness techniques to manage the typical anxiety and stress experienced during pregnancy, cope with pain and fear during childbirth, and enhance couple cooperation and parental sensitivity.

The module was developed in line with the mindfulness-based childbirth and parenting approach [17], adapting it to a psychoeducational intervention delivered via a virtual coach. The contents are presented through a gradual pathway that will enable the woman to be mindful of herself and the present moment, to accept and normalize internal states, to cope with stress, and to perceive an improvement in her psychological

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well-being. Specifically, formal practices (eg, "body scan") and informal practices (eg, audio tracks on "eating a meal with mindfulness"), readings, or videos related to important topics about mindfulness practice will be proposed. Furthermore, the woman will be asked to carry out tasks independently. If she wishes, she can ask for support from her partner or a trusted person for some practices, but it is not mandatory.

Methods

Design and Study Plan

Maia is designed to interact with pregnant women 8 weeks from the 24th and 26th week of pregnancy. Precisely, 2 sessions per week are planned. The woman can choose the day and time that best suits her needs to interact with Maia.

At the beginning of the psychoeducational pathway, Maia will administer 6 self-report questionnaires, described in the Data Collection section, to establish a baseline.

After the data collection phase, the psychoeducational module will be administered, and its contents will be presented in different formats (ie, text, images, audio tracks, and video tracks).

An additional round of administering questionnaires is expected at the end of the psychoeducational intervention to assess potential changes in terms of the psychological well-being and QoL perceived by the women. Two questionnaires will be administered to assess usability. Reminders will be scheduled to fill out the questionnaires 24, 48, and 72 hours after the first request to ensure the collection of all the necessary data. However, at present, there are no reminders for session completion.

Two months after giving birth, women who have given their consent will be invited to a semistructured interview to investigate their experience of using Maia and the TreC Mamma app and to collect a more in-depth understanding of their experiences during the psychoeducational process. The 2-month postpartum period was chosen for both organizational convenience and methodological considerations. The expert group identified this timeframe to find a balance between scientific appropriateness and practical arrangements of the interviews, avoiding a prolonged span after the end of the intervention while ensuring that interviews with the patients do not occur too closely to the childbirth weeks. The underlying assumption is that the period immediately following childbirth (ie, the first 2 months) may be a logistically and emotionally complex time for the family, with a particular focus on the mother's availability and experience.

Participant Recruitment and Withdrawal

The study's target population includes all pregnant women residents in the PAT.

The inclusion criteria to participate in the study are as follows: (1) be pregnant; (2) be in a gestational state between the 24th and 26th week; (3) be aged ≥18 years; (4) have a smartphone with internet access, be able to download the app, and be able to use it; (5) be a resident of the PAT; and (6) know and understand the Italian language.

The exclusion criteria are as follows: (1) patients unable to provide informed consent, which is a prerequisite for participation in the study; (2) inadequate understanding of the Italian language; (3) substance addiction or in recovery for <1 year; (4) suicidal tendencies; (5) psychosis; (6) posttraumatic stress disorder; (7) depression or other psychiatric diagnoses; (8) social phobia; (9) women undergoing medically assisted procreation; and (10) positive obstetric history for late intrauterine fetal death and stillbirth, polyabortion, therapeutic abortion, or sudden infant death syndrome.

Recruited women who meet the inclusion criteria and give their consent to participate in the study will be enrolled in the research. All women who decide to take part in the study will be asked to sign an informed consent form at the time of enrollment after a careful explanation of the project; its aims; how the data will be collected, managed, and processed; the level of involvement required; and the duration of the research as well as any confidentiality issues. The woman will also be informed of the possibility of quitting the study at any time she wishes without any explanation and that this option would not impact the quality of care or interfere with her course of treatment.

The participant must provide informed consent freely, voluntarily, and in writing.

Participants will also receive a privacy policy statement regarding the data processing of their personal data during the research. They should provide their explicit consent to the data processing.

Copies of the study's informed consent form and privacy consent form will be provided to the participant. This information will also be available in a dedicated section of the app.

A flowchart of the research project procedure in sown in the Figure 2.

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Figure 2. Flowchart of the research project procedure.

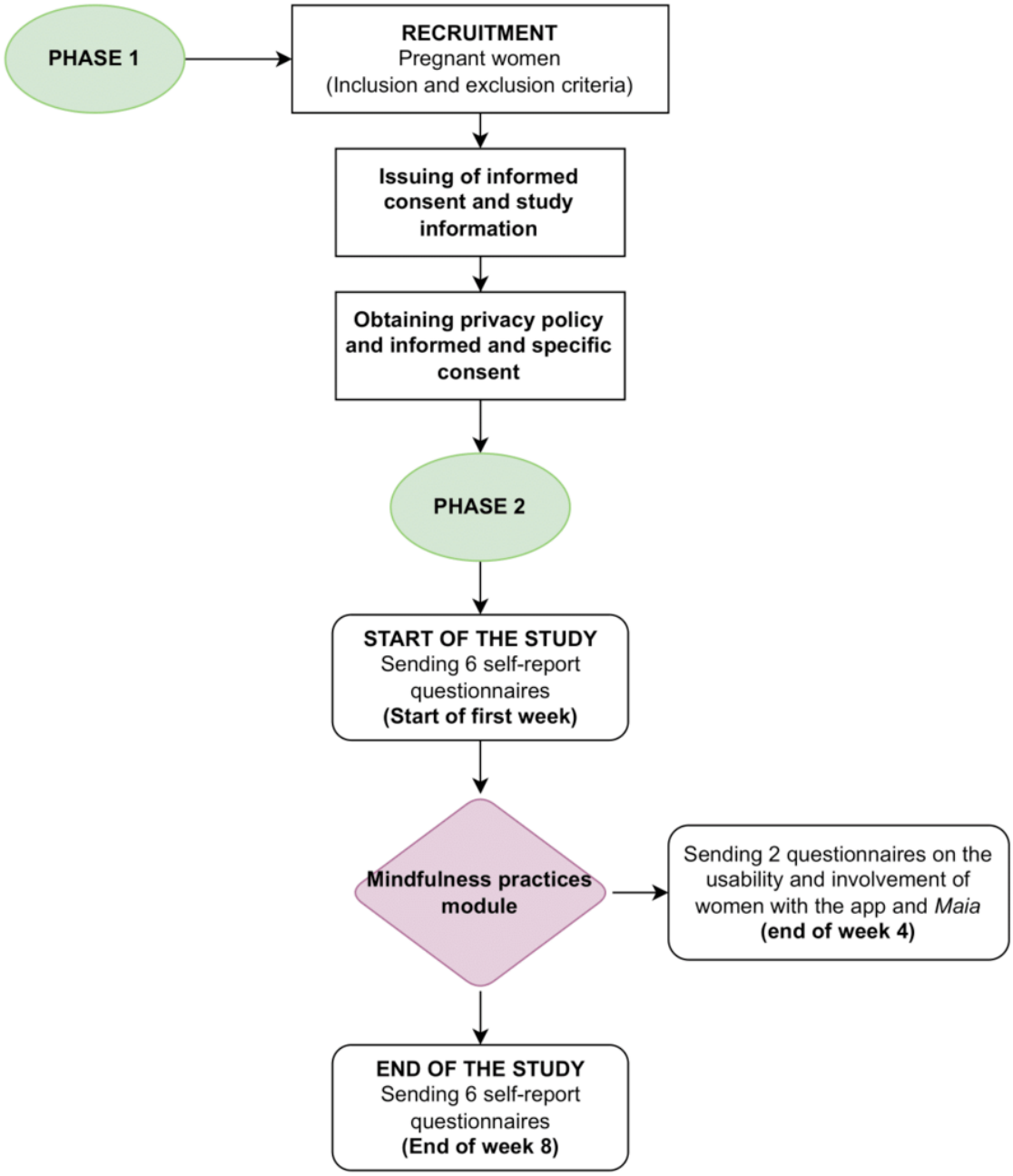

Sample Size

This research project is designed as a proof-of-concept study, where a small sample is sufficient to achieve the intended aims. It was calculated that if nonparametric statistics are conducted (assuming the distribution is not normal), the sample should consist of 24 pregnant women with Bonferroni correction (Cronbach α=.025). The sample size and power for nonparametric tests (Kruskal-Wallis test and Wilcoxon post hoc test) c according to Noether [18]. If parametric statistics are conducted (assuming the normal distribution), the sample must instead consist of 41 pregnant women with Bonferroni correction (α=.025). Thus, with a power level set at 0.80, a significance level of .025, and factoring in a 20% potential dropout rate, we estimated that recruiting 50 women would be necessary to conduct the study.

Role of Health Care Personnel

Pregnant women attending the pregnancy care services of the APSS will be recruited between the 24th and 26th week of gestation. To identify women potentially eligible to participate in the study and collect informed consents and initial sociodemographic data, the involvement of some midwives or doctors belonging to the hospital and territorial service of the APSS is planned.

Study Outcomes

Primary Outcome

The primary outcomes are UX and UE. They will be assessed using 2 questionnaires, namely, the Mobile Application Rating Scale (MARS) [19] and the User Engagement Scale–Short Form (UES-SF) [20], which will be administered at different time

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slots throughout the study, in particular, at the end of week 4 and at the end of the study (ie, week 8).

The end points that will be measured are as follows: a score of the individual items of the questionnaires (MARS and UES-SF); the average score of the questionnaires; and the difference between the average score values of the individual questionnaires at different survey times.

The evaluation of the experience of using the app and the virtual coach (Maia) and the use of the intervention itself will also be assessed through semistructured interviews, conducted 2 months after childbirth. In this case, qualitative data will be collected to enrich the information related to the primary outcome.

Secondary Outcome

The variable expressing the "psychological well-being" outcome will be assessed by administering self-report questionnaires at the beginning (ie, week 1) and end (ie, week 8) of the psychoeducational course (refer to Table 1 for a detailed overview of the questionnaire adopted). The end points that will be measured are as follows: a score of the individual items of the questionnaires; the average score of the questionnaires; and the difference between the average score values of the individual questionnaires in the 2 survey times.

Table 1. Summary of the questionnaires administered and their timing.

At the beginning of the study (week 1)	At the end of week 4	At the end of the study (week 8)	Follow-up (2 months after birth)
SF-12 v1[a]	N/A[b]	SF-12 v1	Qualitative interview
DASS-21[c]	N/A	DASS-21	N/A
IES-R[d]	N/A	IES-R	N/A
FFMQ[e]	N/A	FFMQ	N/A
PANAS-SF[f]	N/A	PANAS-SF	N/A
ERQ[g]	N/A	ERQ	N/A
N/A	MARS[h]	MARS	N/A
N/A	UES-SF[i]	UES-SF	N/A

[a]SF-12 v1: Short Form–12 Health Survey Version 1.

[b]N/A: not applicable.

[c]DASS−21: Depression Anxiety Stress Scales–21.

[d]IES-R: Impact Event Scale–Revised.

[e]FFMQ: Five Facet Mindfulness Questionnaire.

[f]PANAS-SF: Positive and Negative Affect Schedule–Short Form.

[g]ERQ: Emotion Regulation Questionnaire.

[h]MARS: Mobile Application Rating Scale.

[i]UES-SF: User Engagement Scale–Short Form.

The mindfulness-based childbirth and parenting protocol is aimed at creating a connection between expectant mothers and their bodies and fetuses. The literature highlights the growing interest in mindfulness-based interventions [21] due to their consistent effects, including reduced depressive [22], anxiety [23], and stress symptoms [24] as well as enhanced emotional regulation [25] and sleep quality [26].

Therefore, we intend to incorporate variables such as maternal stress levels, frequency of mindfulness practice, and gestational age as predictors. Particularly, we will explore stress and anxiety (Impact Event Scale–Revised and Short Form–12 Health Survey, Version 1), depression (Depression Anxiety Stress Scales–21), emotion regulation (Positive and Negative Affect Schedule–Short-Form and Emotion Regulation Questionnaire), and mindfulness level (Five Facet Mindfulness Questionnaire).

These confounding variables are pivotal as they could impact both the independent variables and outcomes, ensuring a comprehensive understanding of the association between mindfulness and maternal health outcomes. By addressing these factors, we aim to deliver a more robust analysis of the efficacy of mindfulness interventions during pregnancy.

Data Collection

The midwives will collect the sociodemographic data at the time of enrollment using a prestructured form. A unique alphanumeric code will be used to link the different pieces of information with the project's participants. The sociodemographic data collection form and the data collected during the study will be kept separately. In addition, data will be pseudonymized to ensure confidentiality.

The parameters requested from the women will be (1) age, (2) week of pregnancy, (3) weight and height, (4) socioeconomic level, (5) educational level, (6) occupation, (7) marital status, (8) number of pregnancies, and (9) current or previous experience of psychological support (to investigate and describe the prevalence of women who have requested support to care for their psychological well-being).

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The participants will also be asked if they would like to participate in a qualitative interview 2 months after delivery. In case of positive feedback, their telephone number will be collected to facilitate future contact and follow-up interviews.

To properly assess participants' experience during the psychoeducational pathway, some questionnaires were adopted and delivered at the beginning, during, and at the end of the interaction with Maia (Table 1).

Specifically, 8 questionnaires will be administered at the beginning and the end of the psychoeducational intervention. Two questionnaires will be delivered during the psychoeducational pathway to assess the usability and engagement of the woman with the app and Maia. Specifically, the usability questionnaires will be administered at the end of week 4 and week 8 (ie, the end of the study).

A detailed description of each instrument that will be administered is presented in the following paragraphs.

Short Form–12 Health Survey Version 1 [27] is a self-report questionnaire characterized by 12 items assessed on different scales (Likert and dichotomous). The questionnaire investigates the QoL in 8 health dimensions to assess physical and mental health. Domains related to physical health include (1) general health, (2) physical functioning, (3) physical role, and (4) body pain. The mental health scales include (1) vitality, (2) social functioning, (3) emotional role, and (4) mental health. The questionnaire was translated and culturally adapted into various European languages and countries, including Italy, as part of the International Quality of Life Assessment project.

The Depression Anxiety Stress Scales–21 [28] is a self-report questionnaire consisting of 21 items based on a 4-point Likert scale, ranging from 0 (it never happened to me) to 3 (it almost always happened to me). This questionnaire is characterized by 3 scales investigating symptoms of anxiety, depression, and stress, including a total distress scale. Higher scores correspond to a higher level of distress. This scale was translated into Italian and validated in an Italian context [28]. The total scale found very good internal reliability (α=.90).

The Impact Event Scale–Revised [29] is a self-report questionnaire consisting of 22 items rated on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely). This questionnaire assesses the impact of events that may be perceived as stressful through three scales: (1) intrusion, (2) avoidance, and (3) hyperarousal. This questionnaire will be administered in this research project to consider the investigated data net of the participant's pregnancy situation, eliminating potential external stressors (eg, COVID-19). The questionnaire was translated and validated in an Italian context [29]. The 3 scales show good internal reliability: α=.78 for intrusion; α=.72 for avoidance; and α=.83 for hyperarousal.

The Five Facet Mindfulness Questionnaire [30] is a self-report questionnaire consisting of 39 items rated on a 5-point Likert scale, ranging from 1 (never or very rarely true) to 4 (very often or always true). The questionnaire assesses the tendency to be attentive in daily life using five scales: (1) observe, (2) describe, (3) act with awareness, (4) do not judge, and (5) do not react. Higher scores indicate greater awareness. The questionnaire was translated and validated in an Italian context [31]. The Cronbach α values were .74 for observation, .92 for description, .85 for acting with awareness, .91 for nonjudgment, .79 for nonreactivity, and .84 for total score, indicating good reliability.

The Positive and Negative Affect Schedule–Short Form [32] is one of the most widely used instruments to assess positive and negative affective states. It measures 2 distinct and independent dimensions: positive affection (PA) and negative affection (NA). The questionnaire consists of 20 adjectives, 10 for the PA subscale and 10 for the NA subscale. The PA subscale reflects the degree to which a person feels enthusiastic, active, and determined; the NA subscale refers to general unpleasant states, such as anger, guilt, and fear. The participant is asked to rate how they generally feel in the manner described by the adjective, responding on a 5-point Likert scale (1=not at all to 5=very much). The instrument has excellent psychometric properties: the internal consistency coefficient of the PA subscale ranges from 0.86 to 0.90 and that of the NA subscale ranges from 0.84 to 0.87. Furthermore, the test has good convergent and divergent validity. The 2 subscales show a low correlation (−0.12 to −0.23), and this characteristic aligns with the theory that the 2 factors, PA and NA, are independent. The questionnaire has been translated into many languages; the Italian version was validated by Terracciano et al [33] on a sample of 600 participants and replicated the psychometric characteristics of the original study.

The Emotion Regulation Questionnaire [34] is a 10-item scale designed to measure the tendency to use 2 emotional regulation strategies, that is, cognitive reappraisal and expressive suppression. Respondents answer each item on a 7-point Likert-type scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Balzarotti et al [35] translated and validated the questionnaire in Italian, showing good psychometric characteristics. In this study, Cronbach α was .81 for cognitive reappraisal and .84 for expressive suppression.

The MARS [36] is characterized by 23 items rated on a 5-point Likert scale, ranging from 1 (poor) to 5 (excellent), which assesses the quality of the app and its functionalities (eg, virtual coach) on 4 dimensions of objective quality: engagement (5 items), functionality (4 items), esthetics (3 items), and information (7 items), as well as a final scale assessing subjective quality (4 items). The average of the scores of the individual items will be calculated to obtain an average quality score for each dimension investigated; subsequently, the average of the scores of the 4 objective quality dimensions will be calculated to obtain a total MARS score. The questionnaire also includes an "application-specific" section (6 items) to assess the potential impact of a particular app on the users' knowledge, intentions, and so on. The total and subscale scores of the MARS have very high Cronbach α coefficients (.90 and .80-.89, respectively). The scale has been validated in an Italian context [36]. For this study, only the subscales "information," "subjective quality of the app," and "app-specific" will be considered for 17 items.

The UES-SF [37] is a short self-report questionnaire to assess UE with a digital solution. This measure includes 12 items based on a 5-point Likert scale, ranging from 1 (strongly disagree) to

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5 (strongly agree). The questionnaire consists of four factors: (1) focused attention, which indicates the feeling of being immersed in the interaction; (2) perceived usability, which is the negative effect experienced due to the interaction and the effort expended; (3) esthetic attractiveness, which represents the graphical and visual appeal to a digital solution; and (4) the reinforcement factor (ie, reward). The reinforcement factor is a single factor that includes duration, which evaluates the overall success of the interaction; novelty, which examines the general interest related to the interaction with a digital solution; and, finally, the perceived engagement factor, which evaluates the overall enjoyment of the interaction. This questionnaire had not been translated into Italian and was therefore translated through the back translation procedure. The 4 scales show good internal reliability: ω=0.82 for focused attention, ω=0.86 for perceived usability, ω=0.84 for esthetic attraction, and ω=0.81 for reinforcement.

Qualitative Interview

The interviews will be conducted by a psychologist from FBK. Interviews are structured with ad hoc items to purposively capture specific characteristics of the study and participants' experiences. During the qualitative interview, the participants will also be asked if someone supported them during the course, whether it was helpful, and how easy it was to involve another person in some of the exercises. This will allow them to reason, in terms of experience, about whether to involve their partner or a trusted person in a more structured way in the intervention itself. Interviews will be conducted 2 months after the birth; will last approximately 20 minutes; and, subject to the woman's consent, will be audio recorded to allow subsequent analysis.

The platform adopted for the intervention allows for the recording of activity logs, enabling proper mapping of the participants' actions and experiences. This covers a range of logs, assessing whether the participant is properly exposed to the intervention protocol while recording use patterns (eg, session execution time, number of accesses, and use patterns of different features). Any missed sessions or interruptions will be considered as variables. These data will be correlated with acceptability scores during the analysis phase. In case a participant does not complete the activities and misses filling in specific questionnaires (leading to missing data), specific pieces of information on their experiences and platform use will be collected during the scheduled postintervention interview sessions.

Privacy and Data Protection

Concerning data protection, a privacy policy will be formulated pursuant to articles 13 and 14 of the regulation EU 2016/679 of the General Data Protection Regulation, explaining the purposes and legal grounds of the data processing, how the personal data will be collected, the data collection categories, and how data will be managed, including the data retention period, the obligations of the data controllers, and the rights of the participants. The data controllers are APSS and FBK. Personal data are processed for specific research purposes within the scope of public interest tasks of the data controllers. Informed, voluntary, and explicit consent regarding the processing of particular categories of personal data (ie, data concerning health and data on self-reported behavioral habits in the area of lifestyle health) will be collected. Moreover, a specific consent will be asked on the possibility to contact the participant via telephone to carry out the interviews for the research.

All data collected will be kept confidential, managed by authorized persons, and data necessary for evaluating the study objectives will be pseudoanonymized before processing. Therefore, data are pseudonymized and not anonymized.

Copies of the information on the study and the privacy policy will be issued to the participants and made available permanently in a dedicated section of the app.

The study manager undertakes the responsibility to produce a report on the research and to ensure that the data are reported responsibly and consistently. Personal data will neither be disclosed nor disseminated, except in anonymized or aggregated form for publishing purposes. The publication of data resulting from this study will take place independently of the results obtained. The transmission or dissemination of the data, by means of scientific publications or presentations at congresses, conferences, and seminars, will take place exclusively in anonymous form using only aggregated data that prevent any identification of the participants, even indirectly. This sharing is expected to happen within 1 year after the conclusion of the study.

As the participants use the TreC Mamma app, they will be able to give their consent to be contacted for other research initiatives, including initiatives aimed at the continuous improvement of the platform and the acceptability and usability of the app, the collection of data in aggregated form for epidemiological purposes, and promoting specific projects in the social health care field. For all research activities, as the consent should be specific, dedicated information will be provided, and an ad hoc explicit consent will be requested. Using an eHealth mobile app as a "technological intermediary" to enroll users in medical research projects creates an "alliance with the citizens" of the PAT for the proactive use of personal data in scientific studies.

Data Analysis

Preliminary data analysis is scheduled for early June 2024, while the final results will be available at the end of the study (second half of 2024). The publication of the results will take place within 1 year after the conclusion of the study.

Quantitative Analysis

Statistical data processing will be conducted using the software R (version 4.0.0; R Foundation for Statistical Computing), SPSS Statistics (IBM Corp), and Stata17 (StataCorp LLC).

Categorical variables will be summarized by absolute and percentage frequency distributions and quantitative variables of appropriate centrality and variability indexes.

Descriptive analyses will be calculated both for psychological variables (QoL, anxiety, stress, depression, distress, the impact of external events, mindfulness, positive and negative affect, and emotional regulation) and usability (UX) and user

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involvement (UE) variables. These analyses will be performed on the variables analyzed at the beginning, during, and at the end of the interaction with Maia.

The relationships between variables will be analyzed mainly through ad hoc statistical tests, such as the chi-square test, Fisher exact test, 2-tailed *t* test for paired data or Wilcoxon nonparametric tests, and the sign test (based on an assessment of compliance with assumptions), to understand the differences between the beginning and the end of the course in the same study sample with respect to the variables under investigation.

Furthermore, univariate logistic models or multinomial regression models will be presented. Finally, to consider possible confounding factors, multiple regression models will be proposed, where the effects of the explanatory variables on the outcome variables will be adjusted for possible confounders.

For each analysis, statistical significance will be set at a *P* value of ≤.05.

Qualitative Analysis

With regard to the analysis of the semistructured interviews, a text mining approach [38] will be used to extract the answers that appear repeatedly from the interviews that will be conducted with respect to the women's experience of interacting with Maia and with respect to how they felt during the psychoeducational process.

Ethical Considerations

This study was approved by the ethics committee of the APSS (15742; September 14, 2023). At the time of enrollment, all women who freely decide to take part in the study will be asked to sign an informed consent form after receiving a careful explanation of the study, its aims, the level of involvement required, and the duration of the research, as well as all ethical issues concerning confidentiality (the explanation of the study will be carried out partly by the midwives, but a video recorded by the research team with an explanation of the study, its purpose, and the woman's level of involvement in simple and understandable words will also be available). The participants will be informed of the study's results through the app.

Results

The psychoeducational course delivered through a virtual coach, Maia, integrated within the TreC Mamma app, is expected to have significant results regarding women's satisfaction and involvement with the innovative digital solution.

Moreover, an increase in the levels of psychological well-being, QoL of the pregnant woman, emotional regulation, and positive affect is expected at the end the intervention compared to the beginning.

Discussion

Conclusions

This study aims to investigate and evaluate women's experience and engagement with the TreC Mamma app and the virtual coach dedicated to the mindfulness intervention (Maia) and also to assess the level of psychological well-being before and after the intervention.

We expect to collect relevant feedback and suggestions from the participants to possibly improve the structure of the intervention, making it more engaging and improving the interaction. Furthermore, we expect to find differences in terms of improved pre-post psychological well-being, although we are aware that this change may not be related to the intervention itself and that the evaluation of effectiveness will be carried out through a randomized clinical trial at a later stage.

All results will be reported and adequately discussed, including through a comparison with the relevant literature.

Limitations

This study has several limitations that need to be considered and addressed in future research implementations. First, it is important to consider that this study does not aim to evaluate the effectiveness of the intervention, which is why a control group is not planned. It will be crucial to involve a control group to evaluate the actual effectiveness in a randomized clinical trial study. In addition, this study involves a number of pregnant women from the PAT in Italy. It would be interesting to be able to extend the study to women from other Italian regions as well.

On the one hand, it is important to emphasize that Maia might be a valuable technological support in providing regular psychoeducational services to women during pregnancy.

On the other hand, literature has shown that women during the perinatal period indicated a preference for the support provided on the web, suggesting that the implementation of digital interventions can overcome barriers to social stigma and seeking help. Finally, it is crucial to remember that this technological support (Maia and TreC Mamma) is not a substitute for clinical and medical pathways and life medical support; instead, it is an additional element in promoting psychological well-being and healthy lifestyles during pregnancy.

Should the results of this study be positive, we expect that, after evaluation of effectiveness, the intervention could be made available as a tool to support the psychological well-being of pregnant women.

Data Availability

The data sets generated during and analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

APSS: Azienda Provinciale per i Servizi Sanitari di Trento
FBK: Fondazione Bruno Kessler–Trento
MARS: Mobile Application Rating Scale
NA: negative affection
PA: positive affection
PAT: autonomous province of Trento
QoL: quality of life
UE: user engagement
UES-SF: User Engagement Scale–Short Form
UX: user experience

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Protocol

The Google Health Digital Well-Being Study: Protocol for a Digital Device Use and Well-Being Study

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Abstract

Background: The impact of digital device use on health and well-being is a pressing question. However, the scientific literature on this topic, to date, is marred by small and unrepresentative samples, poor measurement of core constructs, and a limited ability to address the psychological and behavioral mechanisms that may underlie the relationships between device use and well-being. Recent authoritative reviews have made urgent calls for future research projects to address these limitations. The critical role of research is to identify which patterns of use are associated with benefits versus risks and who is more vulnerable to harmful versus beneficial outcomes, so that we can pursue evidence-based product design, education, and regulation aimed at maximizing benefits and minimizing the risks of smartphones and other digital devices.

Objective: The objective of this study is to provide normative data on objective patterns of smartphone use. We aim to (1) identify how patterns of smartphone use impact well-being and identify groups of individuals who show similar patterns of covariation between smartphone use and well-being measures across time; (2) examine sociodemographic and personality or mental health predictors and which patterns of smartphone use and well-being are associated with pre-post changes in mental health and functioning; (3) discover which nondevice behavior patterns mediate the association between device use and well-being; (4) identify and explore recruitment strategies to increase and improve the representation of traditionally underrepresented populations; and (5) provide a real-world baseline of observed stress, mood, insomnia, physical activity, and sleep across a representative population.

Methods: This is a prospective, nonrandomized study to investigate the patterns and relationships among digital device use, sensor-based measures (including both behavioral and physiological signals), and self-reported measures of mental health and well-being. The study duration is 4 weeks per participant and includes passive sensing based on smartphone sensors, and optionally a wearable (Fitbit), for the complete study period. The smartphone device will provide activity, location, phone unlocks and app usage, and battery status information.

Results: At the time of submission, the study infrastructure and app have been designed and built, the institutional review board of the University of Oregon has approved the study protocol, and data collection is underway. Data from 4182 enrolled and consented participants have been collected as of March 27, 2023. We have made many efforts to sample a study population that matches the general population, and the demographic breakdown we have been able to achieve, to date, is not a perfect match.

Conclusions: The impact of digital devices on mental health and well-being raises important questions. The Digital Well-Being Study is designed to help answer questions about the association between patterns of smartphone use and well-being.

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KEYWORDS

digital; health; well-being; mobile; google health; digital health; well-being; mhealth; digital device; smartphone

Introduction

The impact of digital device use on health and well-being is a pressing question to which individuals, families, schools, policy makers, legislators, and digital designers are all demanding answers [1]. However, the scientific literature on this topic to date is marred by small and unrepresentative samples, poor measurement of core constructs (eg, device use and smartphone addiction), and a limited ability to address the psychological and behavioral mechanisms that may underlie the relationships between device use and well-being [2-5]. A number of authoritative reviews have made urgent calls for future research projects to address these limitations [6-9]. The critical role of the research is to identify which patterns of use are associated with benefits versus risks and who is more vulnerable to harmful versus beneficial outcomes, so that we can pursue evidence-based product design, education, and regulation aimed at maximizing benefits and minimizing the risks of smartphones and other digital devices.

Leveraging objective data from smartphones and wearables is needed to advance scientific research in this area. Physiological and behavioral biomarkers that can be measured by smartphones and wearables present a valuable way of identifying those at risk and measuring risk factors. Promising prior research has found that longitudinal smartphone and wearable data can be used to predict and, perhaps more importantly, complement existing clinical measures [7,10,11]. Indeed, the variables that can be captured by these devices can help us understand some of the most important determinants of health. For example, behavioral risk factors such as poor mental health, sleep, and physical activity are the greatest predictor of preventable illness and death [12], and nearly 8% of the US gross domestic product is lost to mental disorders each year [13]. However, mental and behavioral health conditions are complex and multifaceted phenomena, and measurement is nontrivial. Illness can manifest in a wide range of symptoms [14] that impact both physiological states and behavior. While there are examples of impressive longitudinal studies [7,15], the scientific literature on these topics is still dominated by studies with small and often unrepresentative samples, poor measurement of core constructs (eg, device use), self-reported measures of behavior that may not correlate with objectively measured end points, and a limited ability to address the psychological and behavioral mechanisms that may underlie the relationships between device use and well-being. For example, some studies focus solely on college students [15] or medical interns [7]. A number of recent authoritative reviews have made urgent calls for future research projects to address these limitations [7-9,16].

To address this gap in the literature, we have designed a large-scale intensive longitudinal study (the Digital Well-Being [DWB] study) to analyze the relationships among smartphone use, physiological and behavioral data from wearables and smartphones, and self-reported measures of mental health and well-being. We will recruit up to 14,000 participants who opt-in to complete intake and outtake surveys and daily ecological assessments and enable sensing of features from their smartphone. In addition, at least 50% (n=7000) of the participants will wear a smartwatch (Fitbit). Each individual's participation in the study will be for 28 days.

The aims of the DWB study are manifold. We aim to (1) provide normative data on objective patterns of smartphone use and describe how these patterns of use vary with age, gender, geography, and functioning or mental health; (2) identify how patterns of smartphone use impact well-being and who is most vulnerable to harmful effects related to smartphone use; (3) identify groups of individuals who show similar patterns of covariation between smartphone use and well-being measures across time; (4) examine sociodemographic and personality or mental health predictors; (5) examine which patterns of smartphone use and well-being are associated with pre-post changes in mental health and functioning and compare the predictive capacity of these objective measures to relevant self-report measures (eg, smartphone addiction measures); (6) discover which nondevice behavior patterns (eg, sleep, physical activity, geographic movement, and social interactions) mediate the association between device use and well-being; (7) identify and explore recruitment strategies to increase and improve the representation of traditionally underrepresented populations; and (8) provide a real-world baseline of observed stress, mood, insomnia, physical activity, and sleep across a representative population.

Next, the methods used in our data collection protocol and preliminary statistics on the demographic profile of the first cohort of participants will be described.

Methods

Study Design

The DWB study is a prospective, nonrandomized study to investigate the patterns and relationships between digital device use patterns, including sensor data from phones and wearables reflecting both behavioral and physiological processes and self-reported measures of mental health and well-being. The study is 4 weeks long with passive sensing from a smartphone, and optionally a wearable (Fitbit), for the complete study period (Figure 1).

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Figure 1. The design of the 4-week intensive digital sensing study. Participants will complete baseline and poststudy assessments, and the first and last weeks of the study involves daily intensive ecological momentary assessments. Mobile sensing consisting of measurements from a smartphone, and optionally a wrist-worn wearable, will be conducted throughout the study. EMA: ecological momentary assessment.

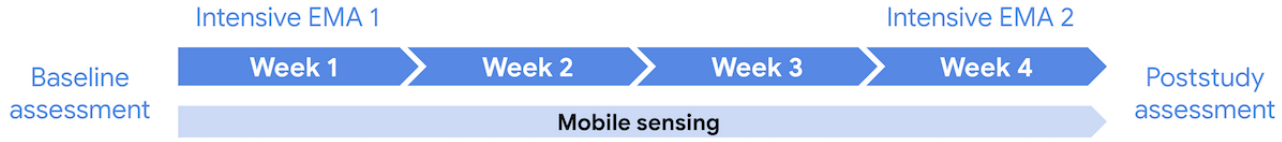

Recruitment

Overview

A key goal of the study is to explore methods to collect a representative study sample that reflects the relative proportions of various demographic subgroups and their intersectionalities in adults of the US population. For example, according to the US Census Bureau [17], 51% of the population is female and 44% of adults are between 20 and 44 years of age. Among those who reported a single race, about 13% are African American, 6% are Asian, and 74% are White. A February 2021 Gallup poll [18] reported that 5.6% of US adults identified themselves as lesbian, gay, bisexual, or transgender; 86.7% said that they were heterosexual or straight; and 7.6% refused to answer. In the past, some subgroups have been traditionally underrepresented in health studies (eg, female individuals; African American individuals; and those with a lesbian, gay, bisexual, transgender, queer, intersex, and asexual orientation) [19], and recent reviews have emphasized the importance of setting explicit recruitment goals in overcoming these biases [19,20]. As such, a key aim of the study is to learn more about how to increase the participation of traditionally underrepresented groups in digital health studies.

To explore methods to overcome recruitment barriers of traditionally underrepresented subgroups and make sure the study sample reflects sufficient diversity, we will pursue a two-prong approach: (1) a primary-augmented 2-wave metered recruitment schema and (2) multistakeholder engagement. Metered recruitment schema refers to the potential delay of eligible study participants in consent and enrollment (baseline characterization and initiation into the monitoring portion of the study). The pace of enrollment will be adapted based on study and clinical bandwidths and the distributions of demographic characteristics, with metering instituted by invitation to consent. The research team plans to begin the metered recruitment strategy once the study has achieved or has nearly achieved the enrollment of 10,000 participants. Depending on the distribution of key demographic variables, once consent and appropriate permissions are obtained, enrollment and initiation of monitoring will commence. To help reduce the effect of seasonality and other external factors on the data collected in this study, we are careful to design the strategy to recruit participants in a balanced manner across time and outside of periods containing major seasonal holidays.

Wave 1 (Open Enrollment With Enriched Recruitment)

During the initial several weeks that the study is open, we anticipate enrollment of up to approximately 1000 new participants per week (but will not limit to this pace). Enrollment will increase as infrastructure allows. An increase in consecutive enrollment of up to 10,000 new participants who are eligible for study participation will be invited to begin the enrollment process. The study will monitor the progress in recruiting traditionally underrepresented groups. Recruitment efforts will focus on enriched representations, with recruitment via email, social media, and Fitbit in-app notifications. Posts will be made on social media platforms, leveraging the reach and audience of the University of Oregon and Google accounts. In-app notifications will be made in the Fitbit app, and these notifications ensure high visibility of the study. At the conclusion of wave 1, the study investigators will assess study participation rates and revise the enrollment targets for wave 2.

Wave 2 (Augmented Enrollment)

Upon the completion of wave 1, wave-2 efforts will discontinue the enrollment of sufficiently represented groups and focus entirely on increasing the participation of underrepresented groups, as defined by race and ethnicity (eg, African American, Asian, Latina or Latino, Native Americans or Indigenous, and White populations), biological sex at birth (female and male), age (18-40 and over 40 years), sexual orientation or gender identity (heterosexual and lesbian, gay, bisexual, transgender, queer, intersex, and asexual), and whether participants are Fitbit users. Multistakeholder engagement refers to the study's collaboration with major stakeholders such as active groups or key opinion leaders of underrepresented groups of interest to codevelop adaptive recruitment goals and strategies.

The study will aim to recruit a study sample that reflects enriched participation of traditionally underrepresented groups in the United States. The wave-2 targeted recruitment strategy will include 5 demographic factors in addition to the ownership of Fitbit devices. If wave-1 enrollment is not sufficiently at parity with population representation, wave-2 efforts will target up to an additional 4000 participants to demographically balance the aggregate sample (potential total n≤14,000).

Ethical Considerations

If they choose to enroll, participants will be directed to a consent form administered via an in-app onboarding flow that describes the data that are collected and how they are used to advance the goals of the study. Each prospective study participant must pass the eligibility survey before proceeding to an assurance of understanding flow, where they are given a summary of the summary and key points of the consent. They are then quizzed on this content before they can proceed. There are multiple points to ensure comprehension of the study and consent. Prospective study participants agree to an e-consent, which provides short explanations for the data they are sharing and how they are used and a long form consent, which is a full institutional review board–approved consent form detailing the data use and rights. In addition, at the top of the form is a

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textbox including basic details of the study designed to make sure participants receive the most critical details, regardless of how.

The consent form will be associated with a unique participant ID that is stored securely. The purpose of this ID is to be able to link the consent form to the data collected in order to confirm that data were collected with consent if needed. As mobile sensing is nonintrusive, participants may easily forget they are participating in the study; therefore, the participants will receive daily notifications reminding them that they are enrolled in the study.

Participants will be informed that if they choose to withdraw, and they will have the option to remove or retain all or part of their data. In addition, even if they do not withdraw from the study, they may choose at any time to have any portion of their data omitted, giving the dates and times between which they want their data to be removed.

Each consent form will be read and signed electronically, since this study is entirely on the web. Participants will indicate their consent to participate in this study by inputting their name and email to indicate that they have read and understood the informed consent document. Participants will be given the option to contact the research staff if they have any concerns regarding the consent. Participants will be emailed a copy of the consent form to their email address.

Finally, the study design includes an assurance of understanding quiz made up of 8 short questions about the study procedures. This includes questions on risks, benefits, data collection, data access and security, and privacy measures. Participants could only enroll in the study if they answered all 8 questions correctly.

Passive data collection begins only after participants have completed all onboarding surveys. To initiate passive data collection, participants must complete a comprehensive permission granting process in which they grant access to each data type in turn (eg, GPS signal and activity signal). The data will be collected in a manner that inherently restricts the granularity and detail of participant information. For example, data on app usage will be bundled by hourly bucket and by category of app rather than collecting individual app names and timestamps. As another example, location information is collected semantically (eg, “home,” “work,” or “other location”) rather than precisely (eg, GPS coordinates). That is, investigators do not know where participants geographically are; instead, they only possess information regarding whether participants spent time at certain semantic locations of interest.

Data will be encrypted from the point of collection to the point of delivery in the secure database and transmitted in this fashion. Even if these data were intercepted by a nefarious actor, they would be protected by Secure Hash Algorithms 256 encryption and would only be accessible to systems that have the private decryption key (only the research team).

Data will be deidentified. Although this study is outside the bounds of HIPAA (Health Insurance Portability and Accountability Act; neither party is a covered entity or a business associate of a covered entity), the research team has removed all of the 18 HIPAA identifiers (name, email, address, etc) from the study data. The data will be stored in a secure, access-restricted, and password-protected database that is audited extensively at monthly, quarterly, semiannual, and annual intervals by security, privacy, and compliance teams and processes. Access to this database is restricted strictly to members of the research team who all completed Collaborative Institutional Training Initiative training.

There are two main types of data collected in the study: (1) study data, which include all active and passive investigational data (surveys, smartphone data, and wearable data) and (2) consent responses, which contain the participant consent forms. These 2 data sets are kept entirely separate. Consent forms must be retained for liability and legal purposes. Access to these forms is restricted to members of the research team who do not have access to the study data.

The institutional review board of the University of Oregon has approved the study protocol (STUDY00000162). In addition, this study went through several rounds of ethical reviews within Google, including sign-off from the responsible artificial intelligence team; the health ethics team; and the privacy, security, and legal teams. Further, an external advisory panel was assembled with mental health experts from outside of Google to solicit their input and feedback on the study design.

We leverage a raffle design for incentives and compensation. Participants who complete the required elements of the study will be eligible to enter the raffle to receive a US $50 gift card. Specifically, the conditions for eligibility were to (1) consent and enable sensor collection at study start, (2) complete the prestudy assessments, (3) complete a minimum cumulative of 7 days (1 week) of daily status assessments, and (4) complete the poststudy assessments. We will segment the raffles in batches of 1000 participants to avoid delaying delivery of the incentive until the completion of the study (which could be quite some time after the first several thousand participants complete the participant duration of 4 weeks). Up to 1610 participants may receive this incentive over the course of the study, with an 11.5% win ratio.

Data Collection

Digital Measures

The study includes digital measurement from both smartphones and wearable physiological devices. After enrolling in the study, participants will be asked to grant permissions to their devices. Figure 2 shows screenshots of the phone app to illustrate the design.

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Figure 2. Screenshots of the Android phone app that will be used in the Digital Well-Being study. The app facilitates enrollment and consent, baseline and poststudy surveys, EMAs, and logging of the smartphone measures. Participants can optionally link their Fitbit account. EMA: ecological momentary assessment.

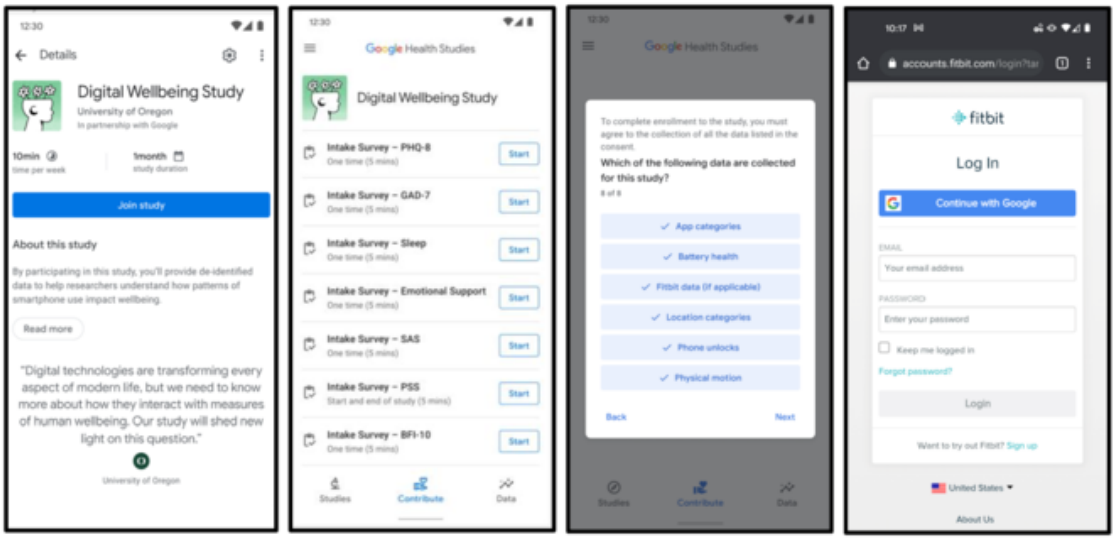

Mobile Data

Patterns of device use will be measured objectively via the study mobile app. The measurements will include:

- Screen on time and app usage: the amount of screen time derived from smartphone app usage data such as time of day and day of week computed per app type—app usage will be quantified for categories of apps rather than individual apps and app categories will be determined by those listed on the Google Play Store.
- Mobility and semantic location information: various measures of geographic mobility will be discerned from GPS data such as daily count of travel or stop events per person per day; duration of each travel or stop event (minutes); and proportion of day spent at home, work, or some other location (labeled "other").
- Human activity recognition from smartphone accelerometer: various movement patterns of human activities of interest such as stationary, walking, running, biking, and driving will be derived from data generated by smartphone accelerometers without being limited by phone location or orientation.
- Battery and charging status: smartphone battery status and plug-in or unplug events.

Wearable Data

We will collect the following data from participants who sign up with Fitbit devices. As access to devices can vary, participation is allowed with any generation of Fitbit devices. Different Fitbit devices have different sensors and algorithmic capabilities, and therefore not all the measures described below will be available for all participants. Minute-level features include accelerometer-based measures of steps and photoplethysmography-based heart rate measurements. Day-level features include accelerometer-based measures of activity (eg, total steps, number of floors climbed, and number of active zone minutes), sleep stages, duration and quality, minutely heart rate, daily resting heart rate, respiration rate during sleep, heart rate variability during sleep, skin temperature during sleep, blood oxygen saturation during sleep, and tonic electrodermal activity.

Survey Instruments

Participants will complete a battery of self-report questionnaires at the beginning (baseline) and end of the study (poststudy) as follows: (baseline only) demographics questionnaire and Big Five Inventory [21,22], Patient Health Questionnaire [21,23], Generalized Anxiety Disorder Scale [24], Patient-Reported Outcomes Measurement Information System Sleep Disturbance and Sleep-Related Impairment short form [25,26], Patient-Reported Outcomes Measurement Information System Emotional Support Short Form 4a [27,28], Shortened Smartphone Addiction Scale [29], and Perceived Stress Scale [27].

Ecological Momentary Assessments

The first and last week of the study will include intensive ecological momentary assessments (EMAs). During these weeks, 3 times per day, participants will be sent 6 identical survey questions per day for 7 days, on a quasirandomized schedule. The first 5 questions will be "How X do you feel right now?" where X will be replaced with a specific affect descriptor from happy, calm, anxious, sad, stressed, and participants will be asked to rate each item. The final question is "Over the last few hours, who have you spent the most time with?" and participants will choose from alone, friends, family, spouse or partner, coworkers, and costudents. Finally, every day for the entire duration of the study, participants will be asked "In general, how have you been feeling over the last day?" once each morning.

Analysis Plan

The first phase of the hypothesis-driven data analysis will be to process the raw data signals to derive interpretable features to test explicit hypotheses. The study will test a range of specific hypotheses and it would be beyond the scope of this paper to list them all. However, we present an exemplar here to

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demonstrate how such hypotheses could be tested. For example, 1 hypothesis that has been proposed in the research literature is that a key mechanism by which device use may affect mental health and well-being is by disrupting healthy sleep behaviors [30]. Specifically, it has been found that device use during the prebedtime period may delay sleep onset either by displacing sleep by device use or by increasing psychological arousal prior to lights out, thereby increasing sleep onset latency. In this study, estimates of device use (in the prebedtime period) will be combined with sleep features, including bedtime and rise time, time in bed, and total sleep time. Specifically, we will test whether the hypothesized mechanisms of change (ie, sleep) mediate the relationship between device use patterns and measures of the change (slope) in measures of mental health and well-being across the study period. Mediating effects will be tested using the strategies outlined by Hayes and Preacher [31], which are standard in behavioral research trials. Using linear structural equation models, support for mediation will be determined if measures of changes in measures of mental health and well-being become nonsignificant or are significantly reduced after controlling for the hypothesized mediating variable. We will assess the joint significance of the indirect pathways (ie, the joint significance of the pathways from the predictor to the mediating variable and from the mediating variable to psychiatric outcomes) using the bias-corrected bootstrap test and will also use the bootstrapping technique to test multiple simultaneous mediators [31].

The intensive longitudinal data on these features and self-reports of well-being will be subjected to data reduction techniques such as dynamic factor analysis, which are a set of techniques for estimating common trends in multivariate time series [32]. Dynamic factor analysis is a dimension reduction technique that aims to model a multivariate observed time series in terms of a finite number of common trends, with the aim of detecting the smallest number of trends that can summarize the data without losing information. The principle is the same as in other dimension reduction techniques, such as principal component analysis and factor analysis, except that the axes are restricted to be latent smoothing functions over time. The dynamic factor analysis will initially use data from the entire 4-week data collection period to examine the patterns of association between daily patterns of device use and daily variations in well-being and then will go on to examine the data from the two 1-week burst of intensive EMA to examine within-day covariation between patterns of device use and well-being. Variables that do not load on to 1 of the identified factors, but that are of strong interest as putative risk factors based on theory or previous empirical research, will be investigated in the statistical analyses as univariate predictors.

The second phase of the statistical analyses will consist of a number of analyses to be conducted to address the aims outlined above. A range of analytic techniques will be used, including ANOVA, specialized multilevel regression techniques that have been used in previous studies of intensive longitudinal data [33], and mixed Markov models [34]. These models are appropriate for testing the hypotheses with our aims, whereby changes in well-being across time can be considered an observed state switch and analyzed using observed Markov models (also referred to as manifest or simple Markov models or Markov chains [34-36]). These methods can also be used to investigate the temporal relationship between the intensive longitudinal data streams and the optimal time lag between these measurements and state switches (ie, the time lag between a predictor and the onset of a change in well-being status), which can be investigated by using higher order models, where the current state is modeled as depending on multiple preceding states [37].

We also plan to investigate the use of neural models to create machine-learned representations in our analysis. The intensive longitudinal nature of the data collection will enable large-parameter models to be trained using unsupervised and supervised machine learning techniques. Learning with self-supervision has recently attracted increasing interest as simple pretext tasks can be used to create versatile compressed representations of data. The main advantage of these embeddings is that they provide an initialization for downstream tasks. This is a more label-efficient mechanism to train supervised models. The benefits of unsupervised or self-supervised learning techniques studying human behavior are still relatively underexplored. However, the high dimensionality and the scale of the data described in this protocol lend themselves to this type of analysis. We plan to empirically test whether leveraging these methods has a positive impact on downstream predictive performance.

Given that participants are not required to complete all surveys, missing data will be handled via established imputation or multiple imputation techniques; however, we also plan to test machine learning–based imputation using autoencoders (eg, masked autoencoders). We expect that some partial data may be unusable, with the wearable devices adherence in intensive longitudinal studies is a known issue.

Results

At the time of submission, the study infrastructure and app have been designed and built, the institutional review board of the University of Oregon has approved the study protocol, and data collection is underway. Data from 4182 enrolled participants have been collected as of March 27, 2023.

Table 1 shows the distribution of participants enrolled in the DWB study at the time of writing. We have been able to achieve a demographic split relatively similar to the 2021 US Census data [17] in terms of race, biological sex, age, and sexual orientation.

Figure 3 shows the geographic distribution of the participants based on home state. This map illustrated the geographic representation enabled by performing a study with our mobile platform and ubiquitous wearable and smartphone sensing.

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Table 1. Comparison between our study sample and the demographic breakdown of the US adult population. Statistics as of March 27, 2023.

Factor (level)	2021 US census [17], %	Digital Well-Being study, %
Ethnicity		
Hispanic or Latino	20	8
Not Hispanic or Latino	80	92
Race		
Asian	7	3
Black	14	6
Native American or Alaskan Native	1	1
White	76	82
Some other race	5	8
Biological sex		
Male	48	32
Female	48	65
I prefer something else	N/A[a]	3
Age (years)		
18-40	55	54
40+	45	46
Orientation		
Heterosexual	88	78
LGBTQIA+[b]	8	20
I prefer something else	2	2
I do not know	2	N/A

[a]N/A: not available.

[b]LGBTQIA: lesbian, gay, bisexual, transgender, queer, intersex, and asexual.

Figure 3. The distribution of participants by home state (in percentage). (Left) Digital Well-Being study home state density and (Right) US 2021 Census population density.

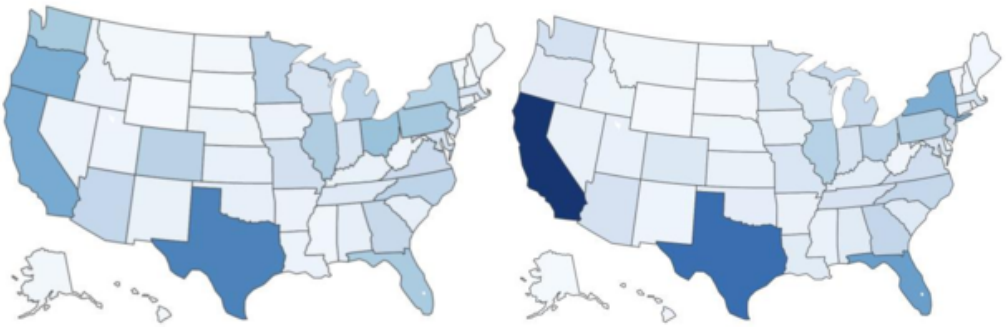

Discussion

Principal Findings

There is a pressing need for more research into the role that digital device use plays in mental health and well-being and how these devices may be used to better monitor symptoms and complement existing clinical measures. The DWB study is an intensive longitudinal study designed to collect representative data across a large and representative population in the United States to help answer questions about the interaction between digital device use and mental health. At the time of writing, data collection is underway, with over 4000 participants enrolled.

A study of the general population means we cannot draw the same conclusions as a study of a more specific, narrow group. Unlike studies of medical interns or undergraduate students [15,38,39], where there may be some common stressors (eg, start of an internship or an examination period) that might impact all participants within a similar time frame, this study represents a much more diverse population.

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Although we have made many efforts to sample a study population that matches the general population, the demographic breakdown we are able to achieve will likely not be a perfect match. This is evidenced by our study sample to date and is in part due to the desire to recruit participants with Fitbit wearable devices, a customer population that does not match the general population. It is not possible to provide participants with these devices, we therefore rely on people enrolling who have access to a Fitbit; as a result, it may be difficult to reach enough people from every demographic. Nevertheless, our initial study sample shows a promising picture that we will come close to achieving the goals.

Given the scale and nature of the study, we had to balance privacy and adherence considerations with the desire to collect highly descriptive digital data. The choice of digital probes is a product of this process. We wanted to understand sleep, mobility, physical activity, and social connectedness and, therefore, selected the digital signals informed by the desire to understand these behavioral processes. We recognize that more detailed logging (eg, app-level names) would be helpful, but these would also contain significantly more privacy sensitive data.

The Google Health DWB study will provide a valuable source of in situ behavioral and physiological observations paired with self-reported data for studying. The objective of this study is to provide normative data on objective patterns of smartphone use. To identify how patterns of smartphone use impact well-being, groups of individuals who show similar patterns of covariation between smartphone use and well-being measures across time were identified. We will examine sociodemographic and personality or mental health predictors and which patterns of smartphone use and well-being are associated with pre-post changes in mental health and functioning. These data should allow us to discover which nondevice behavior patterns (eg, sleep, physical activity, geographic movement, and social interactions) mediate the association between device use and well-being and identify and explore recruitment strategies to increase and improve the representation of traditionally underrepresented populations.

Conclusions

A large in situ study could provide valuable insight into the role of digital device use on mental health and well-being. Through the DWB study, we intend to answer critical questions based on a large population analysis. We plan to combine measurements from wearable devices, smartphones, surveys, and EMAs. By leveraging ubiquitously available devices, we aim to sample a more representative snapshot of the US population than has previously been reported.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available.

Authors' Contributions

JH, AB, and NBA conceived the research question and initiated the project. NBA, JH, and AB designed the research and wrote the protocol. DM wrote the first draft of the manuscript. All authors revised the manuscript. NBA and JH provided senior supervision of the project.

Conflicts of Interest

DM, AB, AJ, FC, and JH are employees of Google LLC. NBA holds an equity interest in, and receives salary from, Ksana Health Inc. No Ksana Health products were used in this research study.

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Abbreviations

DWB: Digital Well-Being
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act

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Protocol

Grocery Delivery to Support Individuals With Type 2 Diabetes: Protocol for a Pilot Quality Improvement Program

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Abstract

Background: People with low income are disproportionately affected by type 2 diabetes (T2D), and 17.6% of US adults with T2D experience food insecurity and low diet quality. Low-carbohydrate eating plans can improve glycemic control, promote weight loss, and are associated with improved cardiometabolic health and all-cause mortality. Little is known about supporting low-carbohydrate eating for people with T2D, although food-as-medicine interventions paired with nutrition education offer a promising solution.

Objective: This program aims to support the initiation of dietary changes by using grocery delivery and low-carbohydrate education to increase the quality of low-carbohydrate nutrition among people with T2D and food insecurity.

Methods: This program was a nonrandomized pilot conducted at 21 primary care practices in Michigan. Adults with T2D and food insecurity or low income were eligible to enroll. Patients were referred by primary care clinic staff. All participants received the 3-month program, which included monthly US $80 credits for healthy foods, free grocery delivery from Shipt, and low-carbohydrate nutrition education. Food credits were restricted to the purchase of healthy foods. Education materials, developed in collaboration with providers and patients, included print, digital, interactive web, and video formats. At enrollment, participants completed a survey including demographics, diabetes health, diet and physical activity, and diabetes management and knowledge. After the 3-month program, participants completed a survey with repeat assessments of diabetes health, diet and physical activity, and diabetes management and knowledge. Perspectives on participant experience and perceived program impact, food purchasing behaviors, and use of educational materials were also collected. Diabetes health information was supplemented with data from participant medical records. We plan to perform mixed methods analysis to assess program feasibility, acceptability, and impact. Primary quality improvement (QI) measures are the number of patients referred and enrolled, use of US $80 food credits, analysis of food purchasing behavior, participant experience with the program, and program costs. Secondary QI measures include changes in hemoglobin A_{1c}, weight, medications, self-efficacy, diabetes and carbohydrate knowledge, and activity between baseline and follow-up.

Results: This program started in October 2022. Data collection is expected to be concluded in June 2024. A total of 151 patients were referred to the program, and 83 (55%) were enrolled. The average age was 57 (SD 13; range 18-86) years, 72% (57/79) were female, 90% (70/78) were White, and 96% (74/77) were of non-Hispanic ethnicity. All participants successfully ordered grocery delivery during the program.

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Conclusions: This pilot QI program aimed to improve diet quality among people with T2D and food insecurity by using grocery delivery and low-carbohydrate nutrition education. Our findings may help inform the implementation of future QI programs and research studies on food-as-medicine interventions that include grocery delivery and education for people with T2D.

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KEYWORDS

T2D; type 2 diabetes; food insecurity; low carbohydrate; quality improvement; healthy eating; grocery; delivery program; diabetes; T2DM; type 2 diabetes mellitus; low-income; US; United States; adults; adult; low diet quality; carbohydrate; carbohydrates; glycemic control; nutrition education

Introduction

Over 12% of adults in Michigan have diagnosed type 1 or 2 diabetes, representing almost 1 million people. An additional 34.7% of adults, or 2.7 million people, have prediabetes [1]. Populations with low income are disproportionately affected by type 2 diabetes (T2D) [2]. Costs of diabetes related to complications including cardiovascular disease and kidney failure exceed US $7 billion dollars, making diabetes the most expensive chronic condition in the United States [3,4]. Medical nutrition therapy reduces cardiovascular complications of T2D, and low-carbohydrate diets (LCDs) are noted by the *American Diabetes Association Consensus Report on Nutrition Therapy* to improve glycemic control, promote weight loss, and improve lipid profiles. In addition, LCDs can reduce the need for hyperglycemic medications and promote diabetes remission, while LCDs emphasizing healthy plant-based foods are associated with decreased mortality [5-7].

Nearly 1 in 5 US adults with T2D experience food insecurity and low diet quality [8]. Drivers include low income, high cost of food, poor access to neighborhood grocery stores, lack of transportation, and lack of knowledge or time to prepare healthy foods. Food insecurity is associated with poorer diet quality, diabetes self-management skills, glycemic control, micro- and macrovascular complications, and increased health care use [9]. Evidence-based interventions to target food insecurity and low diet quality include food-as-medicine programs such as medically tailored meals, food pantry and produce prescriptions, diabetes self-management education, and participation in the federally funded Supplemental Nutrition Assistance Program (SNAP) and SNAP for Women, Infants, and Children (WIC) [9].

Adults with T2D are more inclined than the general population in Michigan to make changes in their diet and lifestyle [10]. This creates a window of opportunity to intervene and support behavior change that can positively impact their health and quality of life. Grocery delivery is a convenient and accessible intervention that addresses logistical barriers to obtaining healthy foods [11]. In 1 randomized controlled trial of patients with T2D, online grocery delivery with prefilled carts was associated with improved nutritional quality purchases when paired with healthy recipes [12]. Less is known about the implementation of online grocery delivery paired with healthy LCD education at scale in quality improvement (QI) initiatives for T2D. The purpose of this pilot QI program is to support the initiation of dietary changes by using grocery delivery and low-carbohydrate education to increase the presence of healthy, low-carbohydrate foods in the home.

Methods

Program Overview and Design

This pilot QI program, the Healthy Eating JUMPSTART (HEJ), was nonrandomized, and all participants received the program. The program consists of 2 main components, low-carbohydrate dietary education and grocery delivery of healthy foods. Participants were adults with T2D, and outcomes were measured by surveys, grocery purchasing data, and medical record (MR) review. The objective of this study is to assess the feasibility and acceptability of this program. The protocol follows the SQUIRE (Standards for Quality Improvement Reporting Excellence) checklist [13].

Program Setting

The program was conducted at 21 primary care practices across Michigan belonging to physician organizations participating in the Michigan Collaborative for Type 2 Diabetes (MCT2D), a statewide Collaborative Quality Initiative focused on improving care for T2D in primary and specialty care practices across the state of Michigan. The team of researchers and staff involved in implementing this program included family and internal medicine physicians (LO, TC, and DG), a project manager (MW), a dietitian (RH), and 2 human-centered designers (NK and LY).

Population and Eligibility Criteria

Program eligibility criteria were (1) aged ≥18 years; (2) diagnosis of T2D; (3) residence in a Shipt delivery zone; and (4) one of the following criteria for low income: Medicaid insurance status, positive screen for food insecurity, or self-reported earning <150% of federal poverty level based on household earnings and the number of people in the household. We planned to recruit a maximum of 150 individuals meeting program eligibility criteria.

Exclusion criteria were (1) type 1 diabetes; (2) active pregnancy or breastfeeding status; and (3) prescription for a sodium-glucose cotransporter-2 inhibitor (SGLT2i), as concomitant use of an SGLT2i and carbohydrate restriction can increase the risk of euglycemic ketoacidosis [6].

Recruitment and Screening

Staff (case managers, social workers, dietitians, etc) at the participating primary care practices identified patients likely to

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meet program eligibility criteria. The physician or advanced practice provider for each potentially eligible patient then completed a signed attestation form, either paper or web based, confirming that the patient had a diagnosis of T2D, was interested in nutrition education, was not prescribed an SGLT2i medication, was willing to work with their primary care team to adjust insulin and sulfonylurea medication dosing as applicable, was not currently pregnant or breastfeeding, and agreed to be contacted by the program team. A program team member then reached out to the patient via email, phone call, or text to follow up on the referral and provide options to be screened for the program via a web-based form or phone call with program staff.

During screening, the home address was confirmed to verify the availability of Shipt delivery or pickup in their area. Financial status was assessed in a stepwise fashion using first a validated 2-question food insecurity screener, then Medicaid enrollment status, and lastly household income [14]. Team members then contacted patients via phone to review the program, confirm eligibility, answer patients' questions or concerns, confirm contact information, and affirm their agreement to participate.

Intervention

Overview

The 3-month program consisted of healthy food delivery via Shipt and education to guide participants through adopting a lower carbohydrate eating plan. The timeline of the participant's involvement in the program, including assessments, are outlined in Figure 1.

Figure 1. Timeline of participant enrollment from referral through completed data collection. MR: medical record.

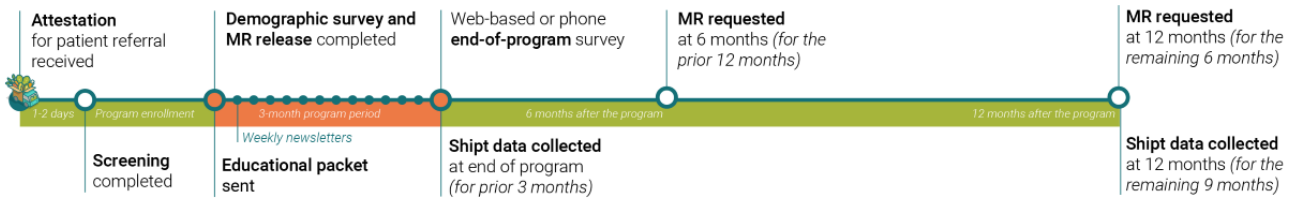

Grocery Delivery

The grocery delivery portion of the program provided free access to a grocery delivery subscription for 12 months plus 3 months of credits to purchase healthy foods that promote a low-carbohydrate eating plan to treat T2D. The program was delivered through the Shipt food delivery website [15]. Participants were provided with a US $80 Healthy Choice Allowance deposited on their Shipt account each month during the 3-month program period to be used to select from a limited menu of "healthy choice" food items. The Healthy Choice Allowance is an online credit that allows a customer to purchase from a restricted category of food, medicine, or other household items on the Shipt Marketplace. This amount of credit was chosen because (1) related healthy food pilots have noted changes in food purchasing behaviors with stipends around US $60 to US $100 per month [16,17]; (2) it is in line with current healthy food credits offered by insurance companies, which range from US $10 to US $300+ per month [18-21]; and (3) it allows for participants to place 2 delivery orders per month without a delivery fee (free on orders over US $35).

Participants could purchase a variety of healthy food options with their US $80 credit, including fruits, vegetables, proteins, dairy, healthy snacks, canned goods, and other staple foods (Textbox 1). Participants could not use the US $80 credit on items such as desserts, chips, pop, and candy but could purchase these items for delivery using their own funds. Healthy foods were not meant to supplant regular meals. Rather, they were intended to increase the prevalence of healthy, low-carbohydrate foods in the home.

Textbox 1. Examples of recommended healthy foods for program participants.

Vegetables

- Kale, spinach, asparagus, mushrooms, tomato, cucumber, cauliflower, broccoli, peppers, green beans, and cabbage

Fruits

- Raspberries, blackberries, strawberries, plums, clementines, blueberries, peaches, and avocados

Proteins

- Chicken, eggs, pork, turkey, fish, tofu, and tempeh

Other

- Cheese, plain yogurt, sour cream, cottage cheese, nuts, and sunflower seeds

Participants had 2 options for placing food delivery orders depending on their preference: (1) participants could order independently using the Shipt website or (2) practice personnel could help participants place orders from the clinic. Program staff were available to support ordering as needed and provided an overview of using Shipt and the Healthy Choice Allowance to all participants during the onboarding process.

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Low-Carbohydrate Education

Educational materials were developed by a registered dietitian (RH), physicians with expertise in low-carbohydrate eating plans for T2D who care for patients with diabetes (LO and DHG), and human-centered designers (LY and NK). Low-carbohydrate eating in the education intervention was defined as 50 to 130 g of total carbohydrates per day. Participants received a set of educational materials to teach them how to initiate and adhere to an LCD plan. These materials are available online and include education about the benefits of an LCD, meal planning strategies with a 7-day sample meal plan, grocery lists, nutrition label reading, and additional resources [22]. The resources were designed to introduce participants to the concept of low carbohydrate incrementally, starting with understanding the basics, then developing personalized low-carbohydrate goals, building meals, and tracking. Emphasis was placed on choosing high-quality sources of macronutrients and building balanced meals. A stepwise process for meal planning was described as consisting of diversity in nonstarchy vegetables, quality protein sources, healthy fats, and complex carbohydrates. Examples of food sources, recommendations for serving size, carbohydrate counting, and mindfulness tips were further conveyed in educational materials. Additional consideration was given to developing materials that would be accessible for individuals with low income including the creation of guides to eating low carbohydrates on a budget, categorization of recipes by price, developing recipes requiring limited appliances (eg, microwave friendly options), and highlighting weekly sales. Scientific evidence guiding the LCD plan was based on recommendations from the low-carbohydrate Diabetes Prevention Program diet program and aligned with the principles of the Healthy Low Carb Diet Score.

Participant educational resources were evaluated and revised in four stages: (1) automated assessment of Flesch-Kincaid Grade Level, (2) review by designers and clinical lead author, (3) live review by MCT2D affiliated health care providers, and (4) review by patients on the MCT2D Patient Advisory Board. With each iterative assessment, the team made revisions to improve the accessibility of the reading level, identify plain language words or phrases, provide accessible definitions, and reduce the number of words. Program materials were then adapted to be delivered in a variety of modalities including print, digital PDF, interactive web pages, and videos. At enrollment, all participants were mailed a packet containing a welcome booklet, which included resources on low-carbohydrate meal planning, a 3-month program calendar, and milestone stickers. They were then provided the link to the HEJ website and began receiving a weekly email newsletter designed to help introduce LCDs including low-carbohydrate recipes and blog posts. Because the team delivered new recipes and information via weekly newsletters, Shipt promotional sales and data regarding participant allergies and cultural or religious food preferences were incorporated into these weekly materials.

Participant Retention

To maintain communication and engagement with participants throughout the program, the program team communicated with participants based on their preferred method. Phone calls, text messages, emails, and physical mailers were all used to share program information and to prompt participants to complete surveys. Email and text messaging were the default options. Phone calls were used only for individuals who selected it as their preferred form of communication or for individuals who were not responsive to other modes of communication. Participants were also contacted to notify them of unspent credits as they neared the end of each program month.

Data Collection

Overview

Participants were enrolled in the program on a rolling basis between October 2022 and May 2023. Each participant's enrollment started immediately after their screening and baseline survey and continued through a 3-month program period. The full program evaluation period continued through 12 months after enrollment. Participants completed an end-of-program survey either via phone, mail, or web-based form at the end of month 3. Data from Shipt were obtained in batches monthly during the program and at the conclusion of the evaluation period. MR data were requested from clinics in batches at month 6 and month 12 of the evaluation period.

Information Sources

All participants were asked to complete a set of baseline and end-of-program surveys during the program. Additional details on the assessments used are described below and listed in Table 1.

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Table 1. Sources of pilot program data and timing of measurements for enrolled participants.

Measure	Data source	Measurement timing
Sociodemographic information		
• Age, race, ethnicity, gender identity, and highest level of education • Food insecurity • SNAP[a] and WIC[b] receipt • Home food environment • Primary food sources	Demographic survey	Baseline
Diabetes health information		
• Height and weight	Demographic survey and medical record review	Throughout the evaluation period
• HbA_{1c}[c] • T2D[d] diagnosis date • Medications	Demographic survey and medical record review	Baseline and end of program
Diet and physical activity		
• Physical activity	PAVS[e] [23]	Baseline and end of program
• Diet quality	ASA24[f] [24]	Baseline and end of program
• Self-efficacy for healthy eating	WEL-SF[g] [25]	Baseline and end of program
Diabetes management and knowledge		
• Diabetes and carbohydrate confidence	Likert question	Baseline and end of program
• Sources of diabetes and nutrition information	Open-ended survey	Baseline
• Challenges and benefits to low carbohydrate diet	Open-ended survey	Baseline and end of program
• Diabetes and nutrition label knowledge	Selected questions from the Michigan Diabetes Research and Training Center's Revised Diabetes Knowledge Test [26] and the AdultCarbQuiz [27]	Baseline and end of program
Perceived program impact		
• Program helpfulness and perceived impact	Likert and open-ended survey	End of program
• Diet changes and perceived impact	Open-ended survey	End of program
• Likelihood to continue eating lower carb	Likert and open-ended survey	End of program
Program use data		
• Food purchasing [15]	Type, quantity, and cost of foods purchased	Throughout the evaluation period
• Website and newsletter analytics	Number of hits, unique users, and duration of use	Throughout the evaluation period

[a]SNAP: Supplemental Nutrition Assistance Program.

[b]WIC: Women, Infants, and Children.

[c]HBA_{1c}: hemoglobin A_{1c}.

[d]T2D: type 2 diabetes.

[e]PAVS: Physical Activity Vital Sign.

[f]ASA24: Automated Self-Administered Dietary Assessment Tool.

[g]WEL-SF: weight efficacy lifestyle short form.

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Sociodemographic Information

All sociodemographic information was collected upon enrollment, at baseline, via a secure web-based Qualtrics (Qualtrics International Inc) survey completed by participants, by printed and mailed survey, or via phone by the program team. This included age, self-reported race and ethnicity and gender identity, zip code, and highest level of education. Participants were additionally asked where they typically purchase food and groceries and whether any household members use SNAP and WIC. A modified version of the home food environment assessment, which measures the availability of the 13 major food categories in the home, was used to assess baseline food purchase patterns in the home [28]. Individual and household members' food allergies and cultural or religious food preferences were additionally collected.

Diabetes Health Information

At baseline, participants reported their date of diagnosis of T2D and most recent HbA_{1c} (hemoglobin A_{1c}) as well as a current list of medications and doses for the treatment of glycemia and other medications for diabetes such as statin medications. HbA_{1c} and medication changes were additionally self-reported by participants at the end of the program. Self-reported height and weight were also collected at baseline.

Diabetes health information was additionally collected through MR review. Participants signed an MR release form at enrollment via the University of Michigan's online SignNow system or via a physical mailed copy permitting the release of MRs spanning 6 months before enrollment through 1 year after enrollment. MRs were then requested, in batches, from each participant's diabetes care sites at 6 months and 12 months after enrollment. Study team members abstracted diabetes-relevant laboratory results (HbA_{1c}, blood glucose levels, complete blood count, urine studies, liver or renal studies, and lipid results), vital signs (weight, height, blood pressure, and pulse), and medications prescribed during the entire 18-month period.

Diet and Physical Activity

Baseline and end-of-program physical activity and diet quality were assessed using the 2-question validated Physical Activity Vital Sign and the Automated Self-Administered Dietary Assessment Tool, respectively [29,30]. Self-efficacy for healthy eating was collected using the 8-question validated Weight Efficacy Lifestyle Short Form both at baseline and end of the program as well [25,31].

Diabetes Management and Knowledge

Participants completed a Likert scale regarding their confidence in diabetes management as well as a variety of different questions about their current sources of information about following a diabetes-friendly diet, whether they had worked with a nutritionist or dietitian, as well as their hopes for how the program would benefit them and what they anticipated may be challenging about following a low carbohydrate eating plan. Additional questions on diabetes and carbohydrate knowledge were also selected from the Michigan Diabetes Research and Training Center's Revised Diabetes Knowledge Test and the AdultCarbQuiz [26,27].

Perceived Program Impact

Participants completed a web-based or phone-based survey at the end of the 3-month program. Participant's experience with grocery delivery and LCDs, the impact of delivery on their diet, and the perceived impact on their T2D management and overall health were assessed. Experiences with educational materials were assessed iteratively and through multiple channels, using (1) a voluntary web-based survey 1 month into participation and (2) voluntary web-based or phone surveys with participants at the end of the program. Survey methods elicited both opinions of educational materials and understanding of which materials they used. These triangulated sources of feedback allowed the program to improve the content and delivery of supplemental educational materials iteratively. Descriptions reported in this paper reflect the final iteration of the program.

Program Use Data

With participant consent, obtained through the same methods as the MR release above, Shipt provided access to details on groceries purchased during the 3-month program period as well as the 1-year follow-up period in which participants retained free account access as part of the program. Data include the type, quantities, and costs of foods ordered by participants during the evaluation period.

Quantitative evaluation of program materials was conducted through the use of website and email marketing platform analytics. Analytics collected include link clicks from the emailed newsletters, detailed usage of each portion of the website, and unique users accessing information. Bounce rates were also assessed to evaluate sustained engagement with various pages of the website.

Governance

This program was conducted as a collaboration between 3 Collaborative Quality Initiatives with overlapping missions related to healthy eating and lifestyle for Michiganders with T2D and low income: Healthy Behavior Optimization for Michigan, Michigan Social Health Interventions to Eliminate Disparities, and the MCT2D.

Ethical Considerations

This QI program was deemed to be exempt from Institutional Review Board review by the University of Michigan Medical School Institutional Review Board. All participants verbally affirmed their interest in the program before enrolling. Participants were prompted to separately sign medical and Shipt record releases for data collection. No incentives were included for participating.

Participant data were collected via secure university-approved iterations of Qualtrics or REDCap (Research Electronic Data Capture; Vanderbilt University), phone calls, and printed surveys [32,33]. Nutrition survey data were collected via the National Cancer Institute–sponsored Automated Self-Administered Dietary Assessment Tool and did not contain any participant identifiers during collection. All data are stored in the Michigan Medicine SharePoint build, which is approved for personal health information storage and is only accessible by members of the program team [34]. Program IDs were assigned to all

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participants to allow for the deidentification of data for analysis to protect participant privacy.

Primary QI Measures

The primary aim of this pilot QI program was to deliver a low-carbohydrate grocery delivery and educational program to people with T2D and low income or food insecurity. Therefore, the primary outcome measures were planned to evaluate the feasibility and acceptability of this program by participants with the following quantitative measures:

- Number of patients referred by each participating clinic for enrollment
- Number of patients enrolled in the program
- Use of the US $80 monthly credit
- Food choices and food ordering behavior with the US $80 credit and additional foods purchased by the participants during the 3-month program period, specifically assessing low carbohydrate food item purchase
- Participants reported experience with the program including the use of grocery delivery and educational materials
- Program costs include the cost of grocery delivery, food credits, and educational materials

Secondary QI Measures

The secondary aims of this pilot QI program were to preliminarily assess the impact of the grocery delivery and educational program on a variety of diabetes control metrics. Clinical measures (weight and HbA_{1c}) will be evaluated at follow-up time points (3 months, 6 months, etc) up to 12 months after enrollment, as available. The secondary QI measures are as follows:

- Percent change in HbA_{1c} between baseline and follow-up
- Percent change in weight between baseline and follow-up
- Percent of patients with diabetes control at baseline, defined as HbA_{1c}<8, compared with follow-up time points
- Changes in diabetes medication between baseline and follow-up
- Changes in self-reported Weight Efficacy Lifestyle Short Form measured between baseline and 3-month follow-up
- Changes in diabetes and carbohydrate knowledge between baseline and 3-month follow-up
- Changes in Physical Activity Vital Sign results between baseline and 3-month follow-up

Sample Size

Our sample size was determined based on participant flow, budgetary constraints, and published guidelines for designing feasibility pilot studies [35]. The sample was selected to provide sufficient data regarding the pilot program to understand methods and procedures to inform the potential dissemination of the program in a larger setting. Specifically, we planned to understand whether we could feasibly identify patients with T2D and low-income or food insecurity from primary care practices, enroll and retain them in the program, and deliver the program effectively to help participants participate in low-carbohydrate eating.

Data Analysis

A mixed methods approach was used for data analysis. For quantitative results, we performed descriptive statistical analysis for baseline survey response data, including demographic characteristics and self-efficacy. For all continuous outcomes, we calculated median change and IQRs from baseline to 6 months and 12 months. Summary statistics will be calculated for all program experience data collected at the end-of-program survey. We will compare baseline and follow-up data points from closed-ended responses related to self-efficacy and diabetes knowledge (multiple choice, scales, dichotomous, and categorical) using standard quantitative techniques including χ^2 tests for categorical data and 2-tailed *t* tests for continuous data (α=.05 for significance). These same methods will be applied to clinical metrics being assessed as secondary measures.

Brief text responses to open-ended questions from the end-of-program survey will be analyzed using standard qualitative techniques including content and thematic analysis [36-39]. Further, 2 investigators will review all responses, create memos of major concepts present, and iteratively develop a codebook. Responses will be coded, and major themes and conclusions determined by consensus conference. The themes identified from these responses will describe participants' satisfaction or dissatisfaction with delivery, the perceived impact of food delivery on their health and diet, and other challenges or barriers to healthy behaviors managing T2D. These quantitative and qualitative data will then be merged to provide context and will be used in dissemination to tell the participants' perspectives.

Results

During the enrollment period (October 2022 through May 2023), a total of 151 patients were referred to the program from the 21 participating practices, and we enrolled 83 (55%) participants (Figure 2). The 3-month program period has been completed for all enrolled participants as of September 2023. Data collection will conclude in May 2024 and results are expected to be published in 2025.

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Figure 2. CONSORT diagram for patients referred to the program between October 2022 to May 2023. CONSORT: Consolidated Standards of Reporting Trials; SGLT2i: sodium-glucose cotransporter-2 inhibitor; T2D: type 2 diabetes.

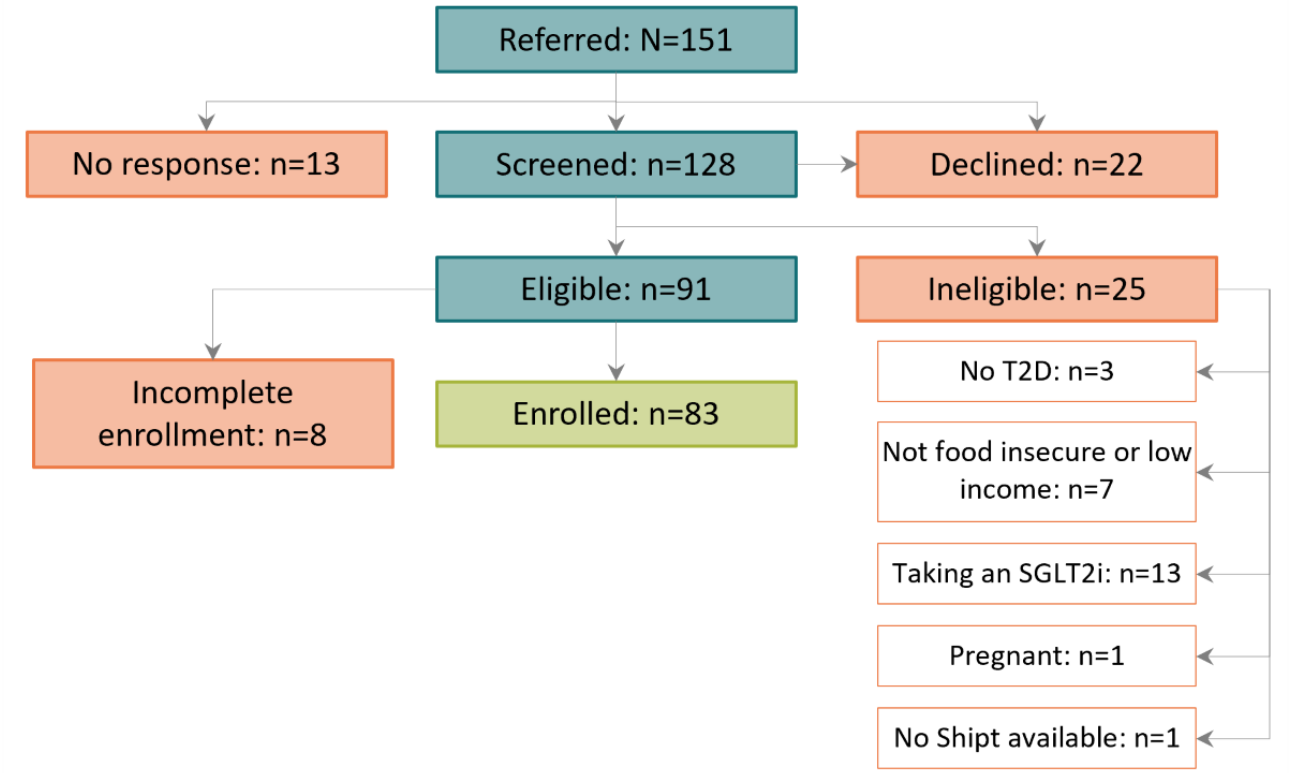

Enrolled participants were on average aged 57 (SD 13) years, with a range from 18 to 86 years (Table 2). They were predominantly female-identifying (57/79, 72%), White (70/78, 90%), and non-Hispanic (74/77, 96%). Participants most commonly had completed a high school education or less (35/79, 46%) or some college or technical school (25/79, 33%). During enrollment, 81% (67/83) of participants screened positive for food insecurity, while 14% (12/83) qualified based on Medicaid enrollment and 5% (4/83) based on income level. All participants were successfully able to order groceries during the program period and an example of the foods ordered with the US $80 monthly credit can be seen below in Table 3.

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Table 2. Demographic characteristics for program participants enrolled between October 2022 to May 2023.

Characteristics	Values[a]
Age (years), mean (SD)	56.6 (13.5)
Gender (n=79), n (%)	
Female	57 (72)
Male	22 (28)
Race (n=78), n (%)	
Black	4 (5)
Mixed race	1 (1)
Native American	1 (1)
Other	2 (3)
White	70 (90)
Hispanic (n=77), n (%)	
Yes	3 (4)
No	74 (96)
Education level (n=79), n (%)	
High school graduate or less	35 (46)
Some college or technical school	25 (33)
Associate's or technical degree	8 (11)
Bachelor's degree or higher	11 (14)
Eligibility criteria met (n=83), n (%)	
Food insecurity screen positive	67 (81)
Medicaid eligibility or enrollment	12 (14)
<150% of FPL[b]	4 (5)

[a]Not all questions were answered by all participants, resulting in different N values for different characteristics.
[b]FPL: federal poverty level.

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Table 3. Example monthly purchasing for a program participant.

Product name	Product price (US $)	Product quantity	Product total (US $)
Boneless and skinless tilapia fillets	6.39	1	6.39
Broccoli and cheese sauce	2.39	1	2.39
Cut okra	2.09	1	2.09
Frozen fruit bars variety pack, no sugar added	5.29	1	5.29
Grade A eggs large	3.99	1	3.99
Lemons	0.79	3	2.37
Mozzarella cheese and beef salami sticks combo pack	5.79	1	5.79
Pork sausage patties	4.09	1	4.09
Purified bottled drinking water	3.49	1	3.49
Purified drinking water	1.49	1	1.49
Roasted red potato in garlic sauce	3.29	1	3.29
Seasoned black beans	1.59	4	6.36
Seasoned Southern-style blackeye peas	1.79	1	1.79
Seasoned Southern-style collard greens	3.09	1	3.09
Tail-on medium peeled and deveined cooked shrimps	10.49	1	10.49
Wild-caught boneless and skinless Pacific cod fillets	6.99	1	6.99
Zespri sun gold kiwi	5.79	2	11.58

Discussion

Principal Findings

This protocol describes a pilot QI program to evaluate whether the implementation of the HEJ, a grocery delivery and healthy LCD education program, is feasible and acceptable for patients with T2D in primary care practices. Preliminary feasibility data demonstrate that primary care practices were able to refer appropriate patients with food insecurity and T2D to the HEJ and that 55% (83/151) of referred patients were able to enroll in the program. All enrolled participants successfully placed grocery orders and engaged with the program further providing evidence to support the feasibility of this program. The final end-of-program data analysis will focus on program evaluation, including participant knowledge and skill acquisition, and diabetes-specific outcomes to inform larger-scale implementation of similar programs.

Medical nutrition therapy and adherence to LCDs are evidence-based interventions associated with numerous benefits in T2D. We anticipate a positive change in the diets of program participants by making low-carbohydrate foods more accessible and convenient through the use of grocery delivery and healthy food credits. Long-term findings can help inform on whether anticipated dietary changes result in sustained change. Our results may also provide insight into the implementation of similar programs in the primary care setting to address food insecurity as a social determinant of health with the goal to improve T2D care and reduce complications and cardiovascular mortality.

The strengths of this pilot QI program include the simplicity of program design, ease of implementation in primary care clinics, and its relatively low cost. This program was additionally developed in the context of recent changes to allow SNAP food benefits to be used when shopping online. Its results may therefore help inform the implementation of larger-scale programs using online shopping and grocery delivery to reduce barriers to healthy eating for people with food insecurity and other associated social determinants of health [40]. The use of human-centered design to incorporate participant and provider feedback throughout the development of educational materials and program structure helped the team engage with individuals across the state. Further qualitative experience data from clinic staff and participants will provide richer detail into barriers and facilitators of the success of the program.

Limitations

Limitations of this program include the inherent limitation to Shipt delivery zones, which does not fully encompass all patients with T2D in Michigan. Detailed evaluation of clinical impact as well as isolating the impact of the educational materials, the healthy food credits, and the grocery delivery components are not feasible in this iteration of the program as it was pragmatically implemented as a QI program. Changes in sociodemographic information and sources of diabetes information may impact participant outcomes but were not re-evaluated beyond baseline measurement. Our pilot participants were also overwhelmingly White and female, and further research should focus on understanding food insecurity among a more diverse population to ensure that larger-scale programs to improve health equity in T2D care reach communities most in need. Lastly, Shipt purchasing behaviors may not reflect the overall food purchased in the home as participants were also expected to obtain food from other sources.

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Conclusions

This pilot QI program aims to improve diet quality among people with T2D and food insecurity by using grocery delivery and low-carbohydrate nutrition education. Future research should more critically evaluate the impact on clinical outcomes and implementation costs in more rigorous randomized clinical trials. Our findings may help inform the implementation of future QI programs and research studies on food-as-medicine interventions that include grocery delivery and education.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon request.

Authors' Contributions

LO contributed to the program design and drafted this paper. MW contributed to the program design and coordination and drafted this paper. RH, NK, and LY all contributed to the program design and coordination. DHG contributed to the program design. TC conceived of this study and contributed to the program design. All authors read and approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

HbA_{1c}: hemoglobin A_{1c}
HEJ: Healthy Eating JUMPSTART
LCD: low-carbohydrate diet
MCT2D: Michigan Collaborative for Type 2 Diabetes
MR: medical record
QI: quality improvement
REDCap: Research Electronic Data Capture
SGLT2i: sodium-glucose cotransporter-2 inhibitor
SNAP: Supplemental Nutrition Assistance Program
SQUIRE: Standards for Quality Improvement Reporting Excellence
T2D: type 2 diabetes
WIC: Women, Infants, and Children

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Protocol

Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO) in Metropolitan France: Protocol of a Mixed Methods Study and Intervention

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Abstract

Background: While the scientific community widely recognizes the benefits of physical activity (PA) in oncology supportive care, cancer survivors who have undergone chemo- or radio-immunotherapy treatments struggle to meet PA recommendations. This underscores the importance of identifying factors influencing active lifestyle adoption and maintenance and proposing a multilevel model (micro-, meso-, and macrolevel) to better understand facilitators and barriers. Currently, no socioecological model explains an active lifestyle in the posttreatment phase of breast, colorectal, prostate, and lung cancers.

Objective: The objective is to identify factors influencing an active lifestyle in cancer survivorship and assess the feasibility of an individualized program targeting an active lifestyle. The objectives will be addressed in 3 stages. Stage 1 aims to elucidate factors associated with the active lifestyle of cancer survivors. Stage 2 involves developing an explanatory model based on previously identified factors to create a tailored health education program for an active lifestyle after oncology treatments. Stage 3 aims to evaluate the feasibility and potential effects of this personalized health education program after its national implementation.

Methods: First, the exploration of factors influencing PA (stage 1) will be based on a mixed methods approach, using an explanatory sequential design and multilevel analysis. The quantitative phase involves completing a questionnaire from a socioecological perspective. Subsequently, a subset of respondents will engage in semistructured interviews to aid in interpreting the quantitative results. This phase aims to construct a model of the factors influencing an active lifestyle and develop an individualized 12-week program based on our earlier findings (stage 2). In stage 3, we will implement our multicenter, multimodal program for 150 physically inactive and sedentary cancer survivors across metropolitan France. Program feasibility will be evaluated. Measured PA level by connected device and multidimensional variables such as declared PA and sedentary behaviors, PA readiness, motivation, PA preferences, PA knowledge and skills, and barriers and facilitators will be assessed before and during the program and 52 weeks afterward.

Results: The institutional review board approved the mixed methods study (phase 1) in April 2020, and the intervention (phase 3) was approved in March 2022. Recruitment and data collection commenced in April 2022, with intervention implementation concluded in May 2023. Data collection and full analysis are expected to be finalized by July 2024.

Conclusions: The Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO) study seeks to enhance our understanding, within our socioecological model, of factors influencing an active lifestyle among cancer survivors and to assess whether a tailored intervention based on this model can support an active lifestyle.

Trial Registration: ClinicalTrials.gov NCT05354882; https://www.clinicaltrials.gov/study/NCT05354882

International Registered Report Identifier (IRRID): DERR1-10.2196/52274

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KEYWORDS

socioecological model; mixed methods; cancer survivorship; physical activity; sedentary behavior; individualized health education program; feasibility

Introduction

Background

The beneficial effects of physical activity (PA) in oncology have been widely demonstrated by the scientific community [1]. This nonpharmacological intervention [2] is now recognized as supportive care in oncology in France [3], given its efficacy in improving quality of life [4], reducing cancer-related fatigue [5], and decreasing the relative risk of cancer recurrence [6]. A high level of PA (ie, 600 to 900 metabolic equivalents of task [METs] as h/week) postdiagnosis appeared to be relatively protective against cancer-specific mortality in breast, colorectal, and prostate cancers, as well as all-cause mortality in breast, colorectal, lung, and prostate cancers [7].

Despite the documented benefits of PA and the risks associated with sedentary behavior (SB), defined as any waking behavior in a sitting or lying position, many adult cancer survivors who have completed chemo-radio-immunotherapy treatments remain insufficiently active and may even engage in SB [8]. While advancements in cancer management have led to a 20% increase in patient survival [9], adverse effects persist long after treatment completion, with a gradual decline observed over 10 to 15 years [10]. The posttreatment period, where the end of treatments marks a break within the "clinical pathway," is particularly crucial to understand. Health promotion is often overlooked during follow-up medical checkups [11]. Furthermore, individuals who have completed treatment must readjust their daily routines to balance returning to work with family responsibilities while rebuilding their sense of self [12]. Consequently, cancer survivors embark on the "care pathway," wherein they grapple with managing their health behaviors [13], including an active lifestyle. For instance, upon returning to work, individuals frequently report feeling more tired, making it challenging to strike the right balance between rest and PA [14].

Previous Work

Studies delineate personal factors (eg, self-efficacy, PA history, and motivation) and environmental factors (eg, equipment accessibility and health care system) implicated in adherence to PA during and after cancer treatment [15,16]. French researchers have proposed a conceptual framework for physio-psychological mechanisms—3H (hypodynamia, hypokinesia, or hypoxia) syndrome—[17], while others aim to propose a psychosocial model [18]. Socioecological approaches to health education interventions in PA [19] offer a framework for identifying the intricate interrelations between cancer survivors and their environment. While acknowledging the importance of individual factors in behavioral change, such as stage of change, processes of change, decisional balance, self-efficacy, and knowledge, socioecological approaches also encompass influences at organizational, environmental, and policy levels. These approaches constitute one of the main pillars of promoting health-enhancing PA [20]. Thus, there is a need to enhance our understanding of active lifestyle in oncology, as highlighted in the French National Cancer Institute report on PA in 2017 [4] and other international reports [21]. To our knowledge, there is no study examining factors influencing PA and SB among breast, prostate, colorectal, or lung cancer survivors, using the transtheoretical model (TTM) [22] as a framework and structuring collected data within a socioecological model [19].

Exploration and intervention targeting factors associated with an active lifestyle—clinical, psychological, cognitive, behavioral, social, or even linked to the clinical pathway and the geographical environment—can provide insights into the complex behaviors of PA and SB, as well as potential influences on them.

Aims

The 3 phases of the Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO) study are described in Figure 1.

Figure 1. Design of the Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO) Study.

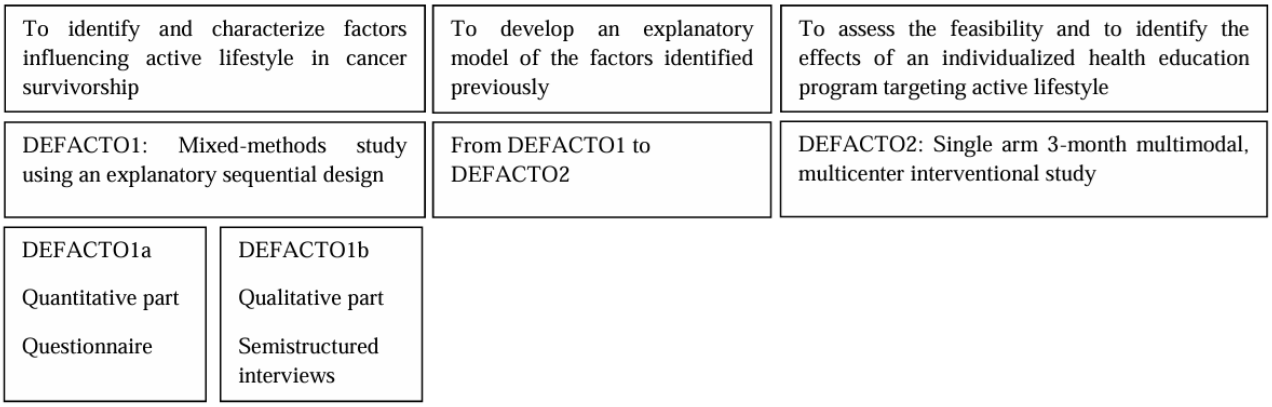

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The first phase seeks to identify and characterize the factors that positively and negatively influence PA and SB among breast, colorectal, prostate, and lung cancer survivors, ranging from 3 weeks to 20 years after chemo- or radio-immunotherapy treatment. This phase of the study (DEFACTO1) will use a mixed methods approach. Participants' "lifestyle profiles" will be delineated based on their PA and SB levels: (1) high PA and low SB, (2) high PA and high SB, (3) low to moderate PA and low SB, and (4) low to moderate PA and high SB [23,24].

The second phase aims to develop an explanatory model [19] for categorizing the previously identified factors.

The third phase is dedicated to assessing the feasibility and potential effects of a multimodal, individually tailored health education program designed in accordance with the model. The program will be specifically tailored for physically inactive and sedentary cancer survivors. A verification of the preestablished model will also be conducted.

Methods

Phase 1: Exploratory Study Using a Mixed Methods Approach

The mixed methods approach of DEFACTO1 adheres to the Good Reporting of A Mixed Methods Study recommendations [25]. The sampling, collection, and analysis of quantitative and qualitative data, as well as the integration of phases [26], are outlined below.

An explanatory sequential design is used, beginning with a quantitative phase, followed by a qualitative research phase. Given the multifaceted nature of an active lifestyle, the use of mixed methods allows for a comprehensive exploration of this complex topic [27]. Quantitative data obtained from a self-reported questionnaire are used to develop a semistructured interview guide. Additionally, qualitative data derived from semistructured interviews aids in interpreting and understanding the quantitative data [28].

Quantitative Phase (DEFACTO1a)

The aim is to identify factors influencing an active lifestyle among cancer survivors. A questionnaire titled "DEFACTO questionnaire" was developed between September 2019 and January 2020 from validated questionnaires on factors influencing PA practice, ranging from the microlevel to the macrolevel [29].

Recruitment

Overview

The French UNICANCER group on supportive care, the French League Against Cancer, and patient associations are invited to participate in quantitative data collection by distributing the questionnaire to cancer survivors (digital or paper survey). To ensure the most representative sample and avoid solely including cancer survivors from hospitals, and associations, information is shared on social networks (eg, Facebook [Meta], LinkedIn [Microsoft Corporation], and X [formerly known as Twitter]). Information and consent forms are provided to participants in both digital and paper formats.

Inclusion Criteria

Participants in the quantitative study must be aged 18 years or older; diagnosed with breast, prostate, colorectal, or lung cancer (stage 1 to 3 cancer, primary, second and relapse included); have completed chemo- or radio-immunotherapy treatment within the past 3 weeks and up to 20 years; be able to read, comprehend, and respond to a questionnaire in French; and have signed the informed consent form for the study.

Exclusion Criteria

Participants are excluded if diagnosed with metastatic cancer; residing outside mainland France to maintain focus on the French context; having an absolute medical contraindication to PA, as this is a known barrier to engagement for these cancer survivors and cannot be intentionally changed through lifestyle interventions; being pregnant or breastfeeding; being under guardianship, curatorship, or deprived of liberty.

Considering the median age at diagnosis for all cancer types combined in France, projected to be 68 years for women and 70 years for men [30], we aimed to target the broadest possible population during the initial phase of the study. The study encompasses cancer survivors ranging from 3 weeks to 20 years posttreatment, recognizing this time frame as the period during which late effects of treatments may still be experienced [31]. The 3-week threshold corresponds to the point at which cancer survivors realizes that the end of treatments does not indicate a return to life as it was before diagnosis [32]. The study focuses on the 4 most common French cancers—breast, prostate, colorectal, and lung—for which the benefits of PA are well established [4,30].

Data Collection and Assessments

The self-administered DEFACTO questionnaire [29] was developed by integrating validated questionnaires and various other validated scales. Estimated PA level through different domains (ie, occupational PA, leisure-time PA, and transport-related PA) and estimated SB are collected by the self-reported Global Physical Activity Questionnaire (GPAQ) [33]. Data collected through the GPAQ are the PA level (in MET-min/week), the time spent in moderate to high intensity PA in minutes per week (min/week), and the time spent in SB in minutes per day (min/day). Variables from the TTM—stages of change, processes of change, decisional balance, and self-efficacy—are collected with the following validated questionnaires: Stages of Change of Exercise Behavior Scale [34,35], exercise processes of change [36], decisional balance for exercise [37], and Exercise Confidence Survey [38]. Types of PA motivation are collected through the Echelle de Motivation envers l'Activité Physique en contexte de Santé (EMAPS), a motivation scale toward health-oriented PA [39].

A subcategory of health literacy level is collected using a single question concerning the need for help to understand health information [40]. The idea is not to assess health literacy levels but to identify cancer survivors with special needs according to this single question. Quality of life is assessed by the Short-Form 12 [41]. Stereotypes related to the benefits of exercise are explored through specific items extracted from the Cancer Beliefs and Exercise Scale (items 5, 15, 20, and 30)

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[42]. PA barriers already identified in the general population are collected with the "Barriers to Being Active Quiz" [43]. This 21-item tool examines 7 areas: (1) lack of time, (2) social influences, (3) lack of energy, (4) lack of willingness, (5) fear of getting hurt, (6) lack of skill sets, and (7) lack of resources. A total score of 6 or above in any area indicates that this is an important barrier to PA for the respondent. The Barriers to Being Active Quiz also gathers data concerning body image, pleasure felt during PA practice, the individual's environment (eg, home space walkability, sport facilities, and equipment), and the availability of the entourage, all of which are variables identified within the theoretical framework as influencing PA participation [44,45]. It also explores the PA participation of social and family environments in 3 items (eg, opportunities to practice PA with a close circle, other commitments relating to family life, and other people's perception of oneself).

Other Assessments

Finally, PA experiences, sociodemographics, anthropometrics, clinical data, and tobacco use are also collected. Cancer survivors complete the whole DEFACTO questionnaire once. All variables are gathered from it.

PA Experience

Respondents are asked a series of open-ended and closed-ended questions to ascertain whether they have benefited from an adapted physical activity (APA) during their cancer treatment. This includes inquiries into the modalities of the program (eg, type of supervision, location, and frequency of meetings) and the satisfaction level, rated from 0 (not satisfied at all) to 10 (very satisfied).

Sociodemographic Data

Sociodemographic data include age (in years); sex (male or female); education level (>college, college, high school, or <high school); economic category (<EUR 600, EUR 600-EUR1200, EUR 1200-EUR 2000, EUR 2000-EUR 3000, and >EUR 3000 per month [A currency exchange rate of EUR 1=US $1.08 is applicable]); professional category (without employment, in sick leave, student, retired, or worker); household type (alone, single-parent family, couple without children, couple with children, or other configuration); accommodation (flat or house) and area of residence (urban or rural); and subscription to health insurance (yes or no).

Anthropometric Data

Weight (kg) and height (cm) are declared by the respondent. BMI (in kg/m²) is calculated, and cancer survivors are classified into normal weight (18.5 kg/m² and 24.9 kg/m²), overweight (25 kg/m² and 29.9 kg/m²), and obesity (>30 kg/m²) categories [46].

Clinical Data

Clinical data related to cancer and comorbidities are assessed using items of the French survey of cancer survivors 2 years after diagnosis Vie après le CANcer à 2 ans du diagnostic (VICAN2) [8]: date of diagnosis (month and year), cancer location, stage, treatments received, time-lapse since the end of treatments (month and year), the presence or not of a second cancer—new primary cancer or recurrence—and the presence of other pathologies and disabilities.

Tobacco Use

Tobacco use and consumption are assessed through a closed-ended question. Actual smokers are invited to complete the 2 items of the Fagerström questionnaire related to tobacco dependence level [47].

Data Analysis

Descriptive and correlation analyses will be conducted using SAS software (version 9.4; SAS Institute Inc) and SAS STAT software (version 15.3; SAS Institute Inc). Cancer survivors reaching or not a high PA level (≥3000 MET-min/week) [48] and having or not a high SB (≥5 h/day) [23,24] will be categorized into four lifestyle profiles [23] as follows: (1) high PA and low SB (≥3000 MET-min/week and sitting <5 h/day), (2) high PA and high SB (≥3000 MET-min/week and sitting ≥5 h/day), (3) low to moderate PA and low SB (<3000 MET-min/week and sitting <5 h/day), and (4) low to moderate PA and high SB (<3000 MET-min/week and sitting ≥5 h/day).

Descriptive analysis and multivariate logistic regression will analyze the association between the lifestyle profiles of cancer survivors and factors identified through the DEFACTO questionnaire. Descriptive and correlation analyses will use SAS (version 9.4) and the SAS STAT package (version 15.3), presenting descriptive data as frequencies, percentages, and mean (SD) for continuous variables. The Kruskal-Wallis test will compare the distributions of processes of change and PA barriers among lifestyle profiles. The final multiple ordinal logistic regression model will be defined through stepwise selection, examining associations between lifestyle profiles and various parameters from the DEFACTO questionnaire. The ordinal logistic regression will use cumulative probability. Results from the multiple ordinal logistic regression will be reported as odds ratios and 95% CIs, with significance levels set at $P<.05$.

Qualitative Phase (DEFACTO1b)

An interview grid will be developed based on significant results from the DEFACTO1a study.

Recruitment

Quantitative study respondents who agreed were contacted for the qualitative study. Cancer survivors are selected according to their lifestyle profile.

Data Collection

Semistructured interviews are carried out by telephone due to the health context related to COVID-19. After patient approval, interviews are recorded and transcribed. According to the mixed methods' design, interviews' topics correspond to the significant results of the multivariate logistic regression from the quantitative study.

Data Analysis

Transcripts of the interviews will be qualitatively analyzed using the Nvivo software (version 1.5.1; QSR International). After the coding of data and the exploration of major themes and topics of the interviews, data interpretation shall be based on

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the interview grid. Qualitative data will complete quantitative data according to the mixed methods research design.

Phase 2: Ecological Model of PA and SB Based on DEFACTO1

The Booth model provides a global vision of factors influencing the initiation and maintenance of an active lifestyle [19]. Other socioecological models of PA determinants in the overall population have also emerged [49-51], highlighting microscopic or individual factors (eg, psychological factors and beliefs), mesoscopic factors (eg, family, housing, and security), and macroscopic factors (eg, societal, political, and legislative influences) [19]. Compared to other socioecological models, the Booth model appears to be the most adaptable, with its design featuring nested circles that effectively capture the complexity of health behaviors across various environments. Additionally, the model facilitates an understanding of the connections between these environments. To our knowledge, this model has not been previously used to elucidate factors associated with an active lifestyle among cancer survivors in a French context.

The socioecological model will be completed with barriers and facilitators to active lifestyle identified during the DEFACTO1 study and significantly associated with lifestyle profiles of cancer survivors.

Phase 3: Health Education Program (DEFACTO2)

Study Design

The DEFACTO2 intervention is a single-arm 3-month health education program, aligning with the typical duration of interventions in this field [52,53] and the anticipated time needed to establish habits during behavior changes [54]. This multimodal, multicenter intervention is neither randomized nor controlled. Its purpose is to assess the feasibility of implementing an individualized program; further research is required to evaluate the effectiveness of DEFACTO2 in relation to variations in PA and SB.

Inclusion Criteria

Eligible participants are aged between 18 and 75 years old to avoid geriatric oncology [55] and to ensure population homogeneity in the feasibility study. They must be survivors of primary nonmetastatic breast, lung, prostate or colorectal cancer (stage 1 to 3, including primary, second cancer, and relapse), have completed chemo-radio-immunotherapy treatments within the past 3 weeks to 20 years, have no contraindications for individual discovery session of APA, be willing to commit to the DEFACTO2 3-month program and 12-month follow-up, be physically inactive and sedentary (ie, <150 min/week of moderate PA or <75 min/week of vigorous PA, with an average of 5 h/day or more of SB), be proficient in reading, understanding and speaking French, be capable of using the connected device (Garmin Vivosmart 4 [Garmin International Inc]) and performing basic operations (eg, pressing a button and charging the battery), possesses a smartphone or a computer to download the Garmin Connect app (Garmin International Inc), be able to walk unassisted (to prevent bias in connected device data), reside in France, and have signed the consent form.

DEFACTO2 targets physically inactive and sedentary cancer survivors, aiming to increase their PA to meet established guidelines [21,56]. A total of 145 participants are required to detect a change of 75 minutes of moderate-intensity PA per week between before and after the 3-month intervention, with an output of 90% and a 5% risk (2-sided). This calculation is based on a moderate intensity PA variation of 75 min/week according to the study of Lynch et al [57], an average moderate-intensity PA of 50.6 (SD 48.2) min/week in a subset of physically inactive cancer survivors from the DEFACTO1 study (not yet published), and a common SD of 140, considering the SD of moderate PA averages observed before and after the intervention in Lynch et al [57]'s study.

Recruitment

Information is disseminated among League Against Cancer committees, with calls for participation in the health education program sent through email. The 15 participating committees inform cancer survivors who meet the inclusion criteria, after which interested individuals contact the principal investigator through email or phone to schedule an appointment. Furthermore, calls for participation are distributed nationally to hospitals, patient associations, and social networks to maximize outreach to cancer survivors. Ultimately, we anticipated recruiting 10 volunteers per committee, each providing a certificate confirming no contraindication to PA and signing the consent form.

Intervention Design

The primary end point of the interventional phase of the DEFACTO2 study is the feasibility of a health education program aiming to increase moderate intensity PA by 75 min/week in physically inactive and sedentary cancer survivors. All participants undergo a 3-month program comprising an APA discovery session, group educational sessions, and 7 or 8 motivational interviews by telephone. The intervention duration follows the guidelines for exercise programs [56].

The APA individual discovery session will be supervised by a qualified APA professional trained in the DEFACTO approach with expertise in tailoring APA sessions. Participants will select an activity from a list of several APAs. The content of educational group sessions will be predefined by the research team, reflecting findings from the DEFACTO1 exploratory study. Only APA discovery sessions and educational sessions will be conducted in-person at the French League Against Cancer departmental committee sites.

A motivational interview is a kind of support strategy used here in a research context [58]. The motivational interview series begins with discussions on participants' expectations and reasons for participation. Then, the content of motivational interviews is tailored based on participant's responses to the DEFACTO questionnaire at inclusion (T_0), focusing particularly on stage of change, processes of change [59], self-efficacy, motivation types, barriers, and facilitator data. Motivational interviews aim to provide practical support for implementing an active lifestyle, addressing individual needs such as balancing PA with work,

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managing family life, and discovering local PA options or programs, as well as financial support. As motivational interviews progress, an individualized education tool is developed to help participants visualize their barriers and facilitators within a socioecological model. The number of motivational interviews is determined based on the average of interventions in similar fields [60].

Participants are followed up 12 months after the intervention, as shown in Figure 2.

All participants receive a Garmin Vivosmart 4 connected device to monitor PA and will retain the watch upon completion of the study.

Figure 2. Flowchart for study design of Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO2).

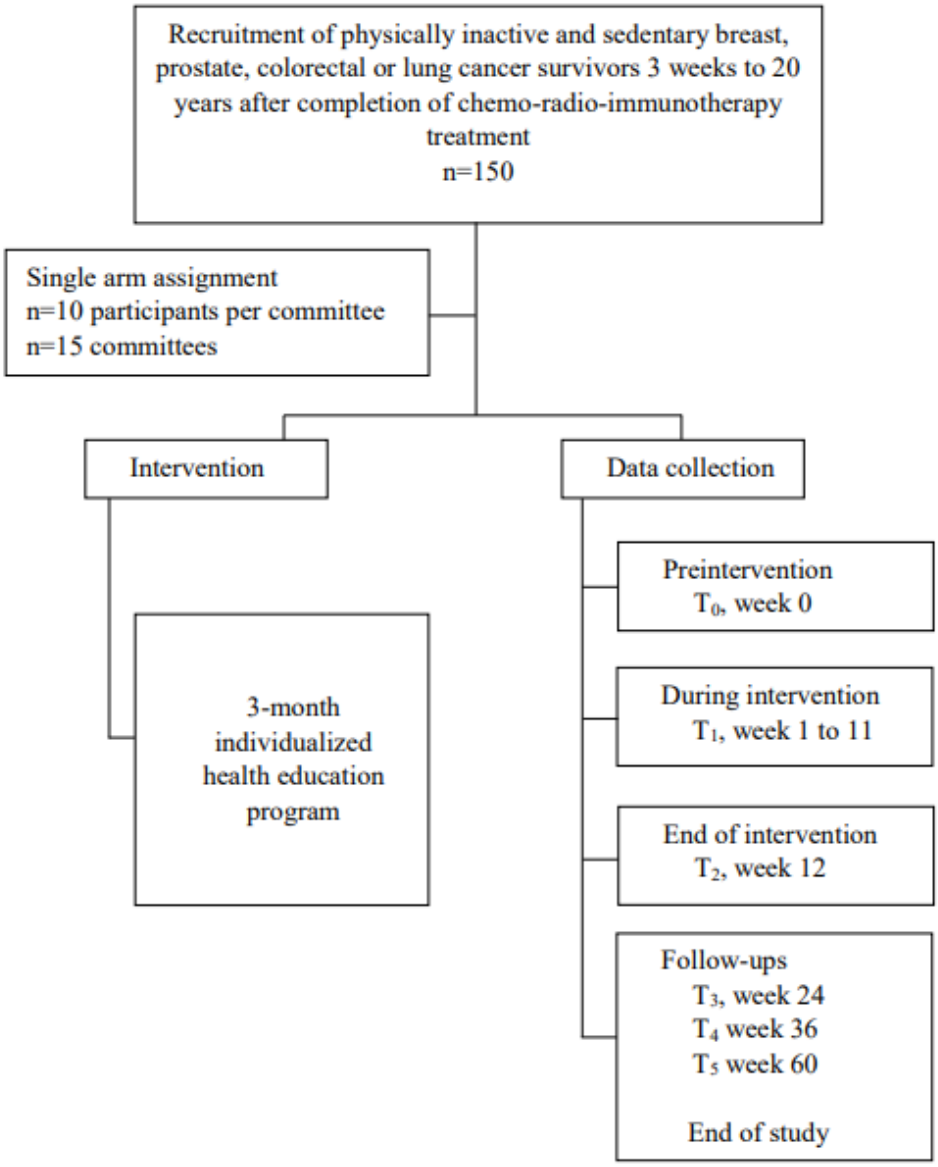

Data Collection and Assessments

Overview

A total of 6 data collection periods are taking place (Table 1): before the intervention (T_0), continuously during the 12-week intervention (T_1), at the end of the 12-week intervention (T_2), 3 months after the intervention for the first follow-up (T_3), and at the 6- and 12-month follow-ups (T_4 and T_5, respectively). From T_2 to T_5, no specific instructions about PA or SB will be provided.

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Table 1. Participant assessment and program evaluation Determinants and Factors of Physical Activity After Oncology Treatments (DEFACTO2).

Data collection period	Participant assessment and program evaluation
Participant assessments	
T_0: 1 week before intervention	• PA[a] barriers and facilitators, preferences, self-efficacy, motivation types, knowledge about PA and its link with cancer, subjective PA level and time spent in sedentary behaviors, quality of life (DEFACTO questionnaire) • Objective PA level (Vivosmart 4)
T_1: 12 weeks during DEFACTO intervention	• Objective PA level (Vivomsart 4) • Punctual and informal feedbacks on experience in the program • Adherence to PA recommendations
T_2: End of the 12th week of intervention	• PA barriers and facilitators, preferences, self-efficacy, motivation types, knowledge about PA and its link with cancer, subjective PA level and time spent in sedentary behaviors, quality of life (DEFACTO questionnaire) • Objective PA level (Vivosmart 4)
T_3: 3-month postintervention follow-up	• Objective PA level (Vivosmart 4)
T_4: 6-month postintervention follow-up	• Objective PA level (Vivosmart 4)
T_5:12-month postintervention follow-up	• Objective PA level (Vivosmart 4)
Program evaluation	
T_0: 1 week before intervention	N/A[b]
T_1: 12 weeks during DEFACTO intervention	• Adherence to the program • Adverse events declared by the participant
T_2: End of the 12th week of intervention	• Satisfaction and experience of participants regarding the individualized program, perception of the intervention's usefulness • Satisfaction of adapted physical activity professionals regarding the educational tools • Fidelity of the intervention
T_3: 3-month postintervention follow-up	N/A
T_4: 6-month postintervention follow-up	N/A
T_5:12-month postintervention follow-up	N/A

[a]PA: physical activity.

[b]Not applicable.

DEFACTO Questionnaire

Participants will complete the questionnaire at T_0 to develop the individualized education tool and tailor the intervention based on TTM processes of change, and PA barriers and facilitators. The questionnaire is completed again at T_2 to identify modifications made during the intervention.

PA Preferences

Participants' PA preferences will be collected at T_0 through a brief interview for program individualization.

PA Level

Objective PA level will be measured using the Vivosmart 4 connected watch by Garmin. Variables required for each Garmin Connect account include sex, age (in years), weight (in kg), and height (in cm). These elements are required to calculate variables associated with PA measurement (explained in the Data Analysis section).

Average daily steps, distance traveled (km/day), floors climbed (number of floors climbed per day), heart rate (bpm), and cumulative duration of PA of moderate and vigorous intensities (min/week) will be collected over a 7-day period at T_0, T_2, T_3, T_4, and T_5. Data will be continuously collected from T_0 to T_1, covering a 12-week period [48].

Subjective PA level will be assessed using the GPAQ self-questionnaire [33] at T_0 and T_2.

Adherence

Adherence to the program will correspond to the number of sessions done regarding the planned sessions.

Program Evaluation

Satisfaction and Experience

At T_2, overall satisfaction will be assessed, along with participants' opinions on the individualized health education program. Open-ended questions will allow participants to

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express any aspects that may have been omitted and that would need to be incorporated into future interventions. Throughout the 3-month program, punctual and informal feedback will be collected, as well as potential adverse events reported by the participants.

Satisfaction of Qualified APA Professional

An interview will be conducted with all 15 professionals involved in the program at T_2 to gather collective feedback on the overall program. The use and practicality of the communication medium used in educational group sessions will be specifically examined.

The feasibility of DEFACTO2 is evaluated based on criteria such as the recruitment process, and the capacity to target the intended participants, the appropriateness of procedures and measures in line with study objectives, and the study population. The acceptability and fidelity of the intervention are evaluated by including both open and closed questions in the DEFACTO questionnaire at T_2. Subsequently, the resources and skills of the research team to implement the intervention are assessed, along with the potential effects of the program on an active lifestyle [61].

Data Analysis

Data analysis will use SAS software, summarizing the demographic and baseline characteristics of participants at T_0. Continuous variables will be presented as means (SDs), while categorical variables will be reported as frequencies and percentages. Descriptive statistics will detail each component of the DEFACTO questionnaire.

For the primary outcome, both objective PA levels measured by Vivosmart 4 and subjective data will be considered. Usable data from continuous assessment, that is, when the connected watch is worn for at least 10 h/day and 4 days in a week, will be described through means (SDs). Following verification of data normality, comparative analysis will be conducted using 1-tailed student *t* test between objective PA levels at T_0 and T_2 to evaluate the primary outcome and between T_2, T_3, T_4, and T_5 to analyze PA maintenance after the 3-month program. The relationship between PA levels measured by Vivosmart 4 and estimated by the self-questionnaire (GPAQ) will be analyzed at T_0 and T_2.

A comparison will be conducted between T_0 and T_2 to assess the evolution of processes of change, self-efficacy, knowledge about PA and its link with cancer, motivation types, barriers, and facilitators to PA, declared PA and SB levels, and quality of life.

Ethical Considerations

The Committee for the Protection of Persons (CPP) approved the DEFACTO1 mixed-methods study on April 3, 2020 (CPP South Mediterranean II, 2019-A03183-54). The DEFACTO2 intervention was approved on March 7, 2022 (CPP North West III, 2021-A01570-41) and registered on ClinicalTrials.gov on May 2, 2022 (NCT05354882). Free and informed consent was collected before any act related to research.

Results

DEFACTO1a recruitment and data collection took place between April 2020 and January 2021. A total of 175 cancer survivors completed the DEFACTO questionnaire. From June 2021 to August 2021, semistructured interviews have been carried out with 18 participants. DEFACTO2 began in April 2022. The implementation of the intervention was concluded in May 2023, and data collection and full data analysis are expected to be completed by July 2024.

Discussion

Overview

DEFACTO uses a mixed methods approach with an explanatory sequential design and multilevel analysis. This approach aligns with implementation strategy recommendations and is informed by previous research on needs, barriers, and facilitators [62]. Our tailored and multimodal intervention, grounded in a socioecological model, aims to support physically inactive and sedentary cancer survivors in adopting and sustaining an active lifestyle. We anticipate this approach to be customizable, feasible, and applicable, fostering lasting behavior change with a broader impact on cancer survivors' lifestyles. Future plans include implementing this program across the 97 departmental committees of the Metropolitan French League Against Cancer. This study will contribute to current research in the field of supportive care in cancer and in public health. This study addresses several gaps in current scientific studies, such as considering patients' preferences (eg, type of PA proposed) and demographic and socioeconomic factors that remain underexplored and should be investigated more thoroughly [4,21]. The French context is particular in the field of active lifestyle promotion in the oncology care pathway, as it is not implemented in every country. For example, French physicians can prescribe exercise, and a new French decree allows cancer survivors to benefit from fitness and motivation assessment, including motivation interviews for PA (decree No. 2020-1665 of December 22, 2020, relating to the global care pathway after oncology care). Our program could complement current advances in the health care system, promoting an active lifestyle that can be incorporated into people's daily lives.

Expected Results

The implementation of an individualized active lifestyle program like DEFACTO2 may be influenced by various elements. These elements can either support or impede the program's success. By examining these elements, we can pinpoint the circumstances conducive to implementing such interventions across different settings. This research protocol seeks to offer support based on a model for cancer survivors encountering challenges in embracing an active lifestyle through an individualized approach. This approach integrates an individual behavior change model with a broader examination of environmental influences on behavior. Additionally, it aims to equip professionals with practical tools to provide effective support to promote an active lifestyle among cancer survivors.

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Strengths and Limitations

This study has certain limitations. First, the GPAQ in the DEFACTO questionnaire gathers subjective PA and SB data, potentially leading to inaccuracies [63]. To address this, accelerometer-based PA measurements will be used in the third phase of the study.

Wearing a connected watch produces a motivating effect for PA, particularly linked to the "awareness" process of experiential change, with direct feedback from exercise [64], and associated with learning to self-measure [65]. The connected watch will serve as both an assessment tool and part of the support provided, as all participants will use it and frequently refer to it.

The DEFACTO questionnaire is not validated but uses validated questionnaires widely used in care pathways.

The committees of the French League Against Cancer have varying ongoing or upcoming projects, motivations, facilities, resources, organizations, and local policies. Ensuring feasibility across different League Against Cancer committees involves standardizing the proposed APA, communication methods, and participant instructions. A toolkit package and one-on-one training are mandatory for professionals involved in DEFACTO2 intervention study.

Conclusions

The findings of this study will have significant implications for the feasibility of implementing tailored interventions promoting PA across the French metropolitan territory. Additionally, they will influence the implementation of PA initiatives in oncology care pathways worldwide. In addition to improving the active lifestyle among cancer survivors, such interventions have the potential to provide support to individuals facing difficulties after completing their oncology care pathway, such as better management of priorities and health behaviors.

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Data Availability

The data that will be generated during the study will be available from the corresponding author on request.

Authors' Contributions

AA and AMF developed and wrote the study protocol; RG provided the mixed methods; and he also provided feedback on the protocol and this manuscript. All authors (AA, AMF, and RG) have written, read, and approved the submission of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APA: adapted physical activity
CPP: Committee for the Protection of Persons
DEFACTO: Determinants and Factors of Physical Activity After Oncology Treatments
EMAPS: Echelle de Motivation envers l'Activité Physique en contexte de Santé
GPAQ: Global Physical Activity Questionnaire
MET: metabolic equivalent of task
PA: physical activity
SB: sedentary behavior
TTM: transtheoretical model
VICAN2: Vie après le CANcer à 2 ans du diagnostic

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Protocol

Assessing and Optimizing Large Language Models on Spondyloarthritis Multi-Choice Question Answering: Protocol for Enhancement and Assessment

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Abstract

Background: Spondyloarthritis (SpA), a chronic inflammatory disorder, predominantly impacts the sacroiliac joints and spine, significantly escalating the risk of disability. SpA's complexity, as evidenced by its diverse clinical presentations and symptoms that often mimic other diseases, presents substantial challenges in its accurate diagnosis and differentiation. This complexity becomes even more pronounced in nonspecialist health care environments due to limited resources, resulting in delayed referrals, increased misdiagnosis rates, and exacerbated disability outcomes for patients with SpA. The emergence of large language models (LLMs) in medical diagnostics introduces a revolutionary potential to overcome these diagnostic hurdles. Despite recent advancements in artificial intelligence and LLMs demonstrating effectiveness in diagnosing and treating various diseases, their application in SpA remains underdeveloped. Currently, there is a notable absence of SpA-specific LLMs and an established benchmark for assessing the performance of such models in this particular field.

Objective: Our objective is to develop a foundational medical model, creating a comprehensive evaluation benchmark tailored to the essential medical knowledge of SpA and its unique diagnostic and treatment protocols. The model, post-pretraining, will be subject to further enhancement through supervised fine-tuning. It is projected to significantly aid physicians in SpA diagnosis and treatment, especially in settings with limited access to specialized care. Furthermore, this initiative is poised to promote early and accurate SpA detection at the primary care level, thereby diminishing the risks associated with delayed or incorrect diagnoses.

Methods: A rigorous benchmark, comprising 222 meticulously formulated multiple-choice questions on SpA, will be established and developed. These questions will be extensively revised to ensure their suitability for accurately evaluating LLMs' performance in real-world diagnostic and therapeutic scenarios. Our methodology involves selecting and refining top foundational models using public data sets. The best-performing model in our benchmark will undergo further training. Subsequently, more than 80,000 real-world inpatient and outpatient cases from hospitals will enhance LLM training, incorporating techniques such as supervised fine-tuning and low-rank adaptation. We will rigorously assess the models' generated responses for accuracy and evaluate their reasoning processes using the metrics of fluency, relevance, completeness, and medical proficiency.

Results: Development of the model is progressing, with significant enhancements anticipated by early 2024. The benchmark, along with the results of evaluations, is expected to be released in the second quarter of 2024.

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Conclusions: Our trained model aims to capitalize on the capabilities of LLMs in analyzing complex clinical data, thereby enabling precise detection, diagnosis, and treatment of SpA. This innovation is anticipated to play a vital role in diminishing the disabilities arising from delayed or incorrect SpA diagnoses. By promoting this model across diverse health care settings, we anticipate a significant improvement in SpA management, culminating in enhanced patient outcomes and a reduced overall burden of the disease.

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KEYWORDS

spondyloarthritis; benchmark; large language model; artificial intelligence; AI; AI chatbot; AI-assistant diagnosis

Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease that comprises a collection of diseases rather than a singular specific disease. It is commonly classified into several subtypes, including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis, juvenile chronic arthritis, and undifferentiated SpA. Among these subtypes, ankylosing spondylitis is the most prevalent, characterized by radiologically positive axial SpA [1].

These subtypes of SpA often have many similar clinical, radiological, and serologic features, and primarily affect the axial skeleton and sacroiliac joints, resulting in a decline in spinal function and a significant impairment of daily life due to persistent back pain and arthritic complications. Early and comprehensive management of the disease is crucial to alleviate the symptoms, improve the quality of life, and reduce the risk of severe complications [2]. As of 2019, there are more than 200 million individuals afflicted with rheumatic diseases in China. Yet, there is a pronounced disparity between the number of these patients and the rheumatology and immunology specialists available to treat them. The shortage of dedicated professionals is compounded by the absence of specialized departments in many hospitals; fewer than one-third of tertiary hospitals nationwide have independent rheumatology and immunology departments. This disparity is even more acute in remote clinics with limited resources, where the deployment of trained, validated diagnostic assistive models could be instrumental in facilitating early diagnosis and appropriate treatment recommendations, thus diminishing the broader impact of the disease. Currently, the integration of large language models (LLMs) within rheumatology, specifically tailored to SpA, remains unexplored.

Foundation models [3], once refined with domain-specific data sets, exhibit remarkable capabilities in specialized fields. These models adeptly execute diverse tasks, including sentiment analysis, image captioning, and command execution. The health care sector has seen a notable increase in chatbot usage, where they provide advanced, personalized treatment guidance. Enhanced with comprehensive medical data sets, foundation models proficiently interpret and articulate intricate medical terminologies while offering reliable question-answer services. LLMs, such as generative pretrained transformers, are recognized as foundational models and are increasingly being used in medical settings, owing to their exceptional ability to process and generate natural language.

In the realm of medicine, LLMs exhibit significant potential across clinical, educational, and research domains. They play a crucial role in enhancing clinical diagnostics and treatments, advancing physician training, and fostering robust clinical research within health care organizations [4]. Purpose-built LLMs such as foresight, effectively predict outcomes using electronic health records [5]. Novel architectures, such as the hybrid value-aware transformer, enhance the performance of LLMs by integrating longitudinal and multimodal clinical data [6]. Additionally, LLMs excel in tasks that extend beyond expert domains or are guided by user prompts [7-9], thereby, significantly reducing physicians' administrative load, as seen in the preparation of discharge summaries. However, challenges including accuracy, outdated training data, the potential for producing plausible but incorrect information, lack of transparency, and ethical issues persist. Despite these challenges, the development of LLMs continues, focusing on enhancing their efficacy and safety in health care applications.

In the health care sector, particularly within rheumatology, there exists a potential for advanced models, such as ChatGPT (OpenAI), to produce incorrect outputs or disseminate medically unsound information, masquerading as authoritative advice [10]. This risk is exacerbated in conditions like SpA—a disease prone to diagnostic challenges and frequent misidentification—where a lack of comprehensive evaluation by LLMs prevails. Evaluation methodologies often resort to subjective measures. Kung et al [11] introduced the accuracy, concordance, and insight metrics, while Uz and Umay [10] developed the reliability and usefulness scores for appraising ChatGPT's responses. Gilson et al [12] assessed ChatGPT's response quality via logical reasoning and the relevance of internal and external information.

The following benchmarks collectively underscore the diverse methodologies and applications within medical artificial intelligence (AI), ranging from language understanding to clinical decision-making. The Comprehensive Medical Benchmark in Chinese (CMB) [13] and the Chinese Biomedical Language Understanding Evaluation Benchmark (CBLUE) [14] are notable for their focus on linguistic and cultural nuances in the medical context. CMB evaluates LLMs like ChatGPT and GPT-4 (OpenAI) within the framework of traditional Chinese medicine, reflecting the importance of cultural context in medical AI. Similarly, CBLUE assesses pretrained Chinese models for biomedical language understanding, emphasizing the need for language-specific AI tools in health care. Chen et al's [15] work on a benchmark for automatic medical

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consultation systems represents a leap toward practical AI applications in health care. By proposing frameworks for doctor-patient dialog understanding and task-oriented interaction, this research paves the way for AI to enhance patient engagement and clinical workflows. MedEval [16] stands out for its comprehensive approach, encompassing a multilevel, multitask, and multidomain medical benchmark. This benchmark integrates data from various health care systems, covering an extensive range of medical tasks and scenarios, thereby demonstrating the versatility required in medical AI applications. Recent additions to this array of benchmarks include an explainable and reliable medical report generation benchmark based on fundus fluorescein angiography images and reports [17], which focuses on reliability and explains the ability of medical report generation, a critical aspect in clinical documentation and patient care.

In response to the absence of a standardized benchmark within rheumatology, Madrid-García et al [18] have made a significant contribution by creating a data set comprising 145 rheumatology-related questions, meticulously extracted from the Spanish Médico Interno Residente exams conducted between the academic years 2009-2010 and 2022-2023. This data set is thoughtfully categorized into “Case” and “Factual” types, including 14 questions that are specifically related to SpA. In these benchmarks, there are few questions related to SpA, and the variety is also limited, which hinders the accurate and objective assessment of LLMs’ accuracy in addressing the queries related to SpA. In collaboration with clinical experts, we are in the process of developing a benchmark data set consisting of 222 multiple-choice questions on SpA. This initiative aims to challenge models to demonstrate a profound understanding of medical knowledge and advanced reasoning skills. The questions span various degrees of difficulty and formats, encompassing both medical concepts and case-based scenarios. Assessments bifurcate into answer-only and chain-of-thought (CoT) approaches. We prioritize model accuracy while also using fluency, relevance, completeness, and proficiency in medicine from the CMB benchmark’s metric to gauge the quality of the model’s response.

We aim to rigorously assess the foundation models by refining them with publicly accessible medical databases and a bespoke data set comprising authentic medical cases, culminating in the development of our proprietary model, RobotGPT (Dataa Robotics Inc). Our goal is to augment their adeptness in fielding SpA-centric inquiries. Forthcoming experiments, as outlined in the Methods section, will benchmark the efficacy of various LLMs against our novel spondyloarthritis multi-choice question answering (SpAMCQA) data set. Furthermore, we aspire to juxtapose our model’s explanatory capabilities with its peers by using fluency, relevance, completeness, and proficiency in medicine as our evaluative metric.

Methods

Benchmark

Overview

The development of a robust benchmark is crucial for the advancement of LLMs in the medical domain, particularly in specialized domains not adequately addressed in the existing literature. The section “Setting” of our protocol unveils a thoroughly developed benchmark dedicated to SpA, addressing a significant gap in available data sets and enabling a comprehensive evaluation of LLMs in this specialized field. The section “Evaluation Framework” outlines the evaluation framework for these questions, highlighting the data set’s reliability and value in precisely evaluating the diagnostic and therapeutic reasoning abilities of LLMs.

Setting

Current medical benchmark data sets encompass an extensive array of medical subjects, but there is a notable deficiency regarding SpA. To address this shortfall, our team has developed an innovative bilingual (English and Chinese) benchmark data set comprising multiple-choice questions specifically about SpA, designed to objectively measure the precision of LLMs.

Knowledgeable clinicians from the Department of Rheumatology and Immunology at Chinese People’s Liberation Army (PLA) General Hospital gathered insights on SpA from essential medical literature [19-21]. Capitalizing on their profound clinical experience and informed by established question banks, they created 222 multiple-choice questions. These questions were meticulously refined through multiple rounds of expert review, guaranteeing their lucidity and precision. Spanning various levels of complexity, they simulate genuine diagnostic and therapeutic situations, thus offering a comprehensive measure to appraise the capability of LLMs.

The benchmark data set consists of 194 single-answer and 28 multiple-answer questions, categorized into 106 questions focused on medical knowledge and 116 questions on case analysis. The experts categorized them by types (concept definition, logical inference, and case analysis), dimensions (etiology, clinical manifestations, diagnosis, treatment, and multidimensional), themes (exclusively SpA and SpA alongside other diseases), and complexities (elementary, intermediate, and advanced), according to their professional judgment. These classifications are thoroughly itemized in Table 1.

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Table 1. Comprehensive overview of the benchmark data set tailored for SpA[a] in the evaluation of LLMs[b].

Question categories	Single-choice questions (n=194), n	Multiple-choice questions (n=28), n	Total (N=222), n
Type			
Concept definition	49	13	62
Logical inference	33	11	44
Case analysis	112	4	116
Dimensions			
Etiology	16	0	16
Clinical manifestations	26	7	33
Investigation	14	7	21
Diagnosis and differential diagnosis	114	7	121
Treatment	12	4	16
Multidimensional	12	3	15
Theme			
Exclusively SpA	75	21	96
SpA alongside other diseases	119	7	126
Complexities			
Elementary	93	5	98
Intermediate	70	13	83
Advanced	31	10	41

[a]SPA: spondyloarthritis.

[b]LLM: large language model.

Evaluation Framework

Overview

Figure 1 presents the SpAMCQA experimental setup. Our evaluation outlines 2 strategies—answer-only and CoT. CoT prompting and guiding LLMs through sequential reasoning, has improved problem-solving across tasks. By using CoT, we investigated LLMs' performance in both answer-only and CoT contexts [22]. Responses to multiple-choice questions were quantitatively evaluated using objective criteria while rating each response across 4 aspects—fluency, relevance, completeness, and medical proficiency—using a grading scale from 1 to 5. This 2-fold methodology ensures an exhaustive evaluation of LLMs, gauging both accuracy and analytical depth.

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Figure 1. Evaluation framework for assessing LLMs in SpA diagnosis and treatment. LLM: large language model; SpA: spondyloarthritis.

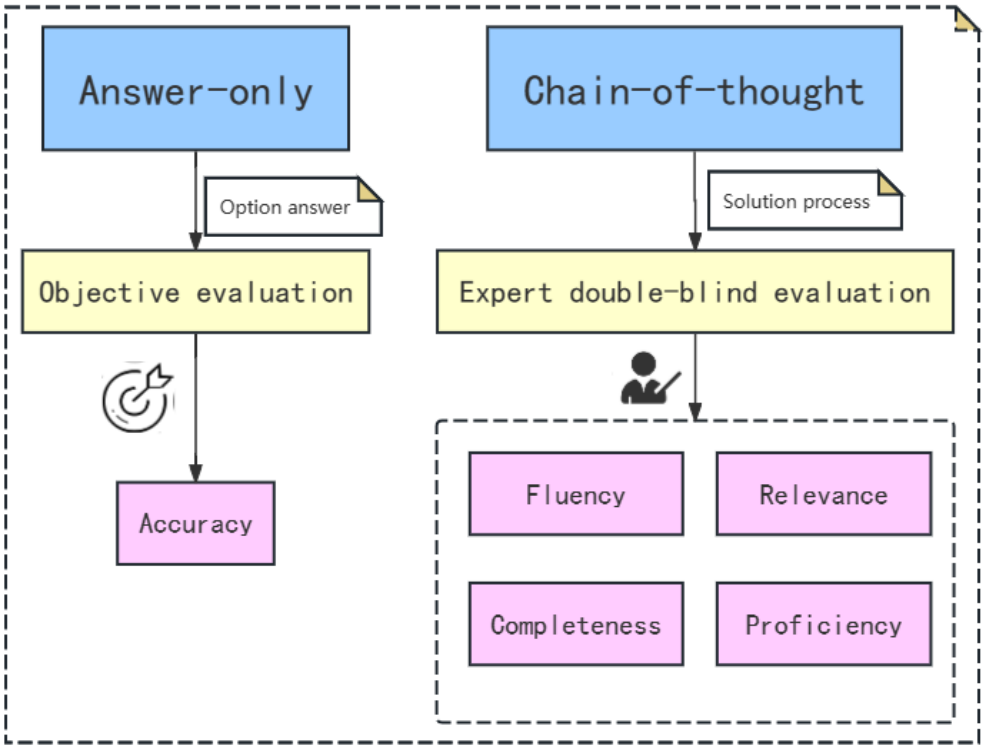

Objective Evaluation

Figure 2 illustrates the input prompts tailored for the answer-only evaluation. Examples illustrating comprehension tasks in answer-only scenarios are presented in both English and Chinese versions. The completed responses from LLMs are highlighted in red, whereas the inputted prompts are shown in black text. In this setup, the models must discern the correct answer without auxiliary cues. For single-choice queries, scoring depends solely on the correct selection. Multiple-choice question scoring adopts principles from the Chinese Medical Examinations (CMExam), where each question is worth 1 point, divided equally among the correct answers. Correct selections earn their share of points, while incorrect ones deduct an equivalent amount, down to 0. For example, in a question with 5 answer choices, 2 of which are correct, selecting 2 correct and 1 incorrect option yields a 0.5 score; omitting 1 correct option also results in a score of 0.5.

Figure 2. Answer-only evaluation setting for LLM assessment in SpA diagnosis (Chinese and English versions). It showcases the format and structure of multiple-choice questions designed specifically for this study, highlighting how models are required to select the correct answer without additional contextual cues or reasoning paths. LLM: large language model; SpA: spondyloarthritis.

Answer-only scenario (Chinese version)
以下是与医学相关的单选或多选题。请仅提供正确答案，无需解释或分析。问题及其相应选项如下：强直性脊柱炎的特点不包括（）
A.多数为老年发病
B.主要累及骶髂关节和脊柱
C.呈炎性病变
D.最终可导致脊柱强直
答案：A

Answer-only scenario (English version)
Below are medical-related single or multiple-choice questions. Please provide only the correct answer(s), no explanations or analyses needed. The questions and their respective options are as follows: Which of the following is not a characteristic of ankylosing spondylitis?
A. Most cases occur in the elderly.
B. It primarily affects the sacroiliac joints and the spine.
C. It manifests as an inflammatory lesion.
D. It can ultimately lead to spinal ankylosis.
Answer: A

Expert Evaluation on CoT

Merely providing an answer does not fully assess a model's competence in processing medical queries, as it might rely on guesswork. In clinical practice, an expert critically evaluates the question and each answer choice. Accordingly, we require the model to present its selection with a corresponding CoT rationale, as depicted in Figures 3 and 4. Examples illustrating comprehension tasks in CoT scenarios are presented in both Chinese and English versions. The completed responses from LLMs are highlighted in red, while the inputted prompts are shown in black text. To evaluate the quality of the rationale, we conducted a double-blind study with 2 medical experts rating each response across 4 aspects.

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Figure 3. CoT evaluation setting for LLM assessment in SpA diagnosis (Chinese). Unlike the “Answer-Only” setting, the CoT approach requires the models not only to select the correct answer but also to provide a reasoned explanation for their choice, mimicking a clinician’s thought process in diagnosing SpA. CoT: chain-of-thought; LLM: large language model; SpA: spondyloarthritis.

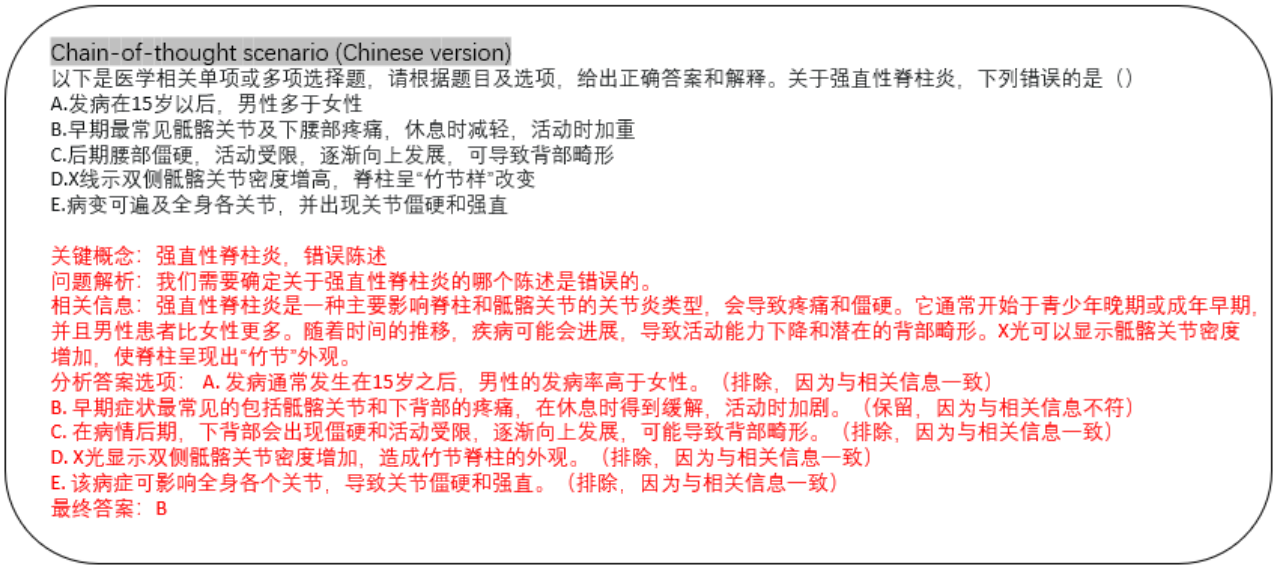

Figure 4. CoT evaluation setting for LLM assessment in SpA diagnosis (English). Unlike the “Answer-Only” setting, the CoT approach requires the models not only to select the correct answer but also to provide a reasoned explanation for their choice, mimicking a clinician’s thought process in diagnosing SpA. CoT: chain-of-thought; LLM: large language model; SpA: spondyloarthritis.

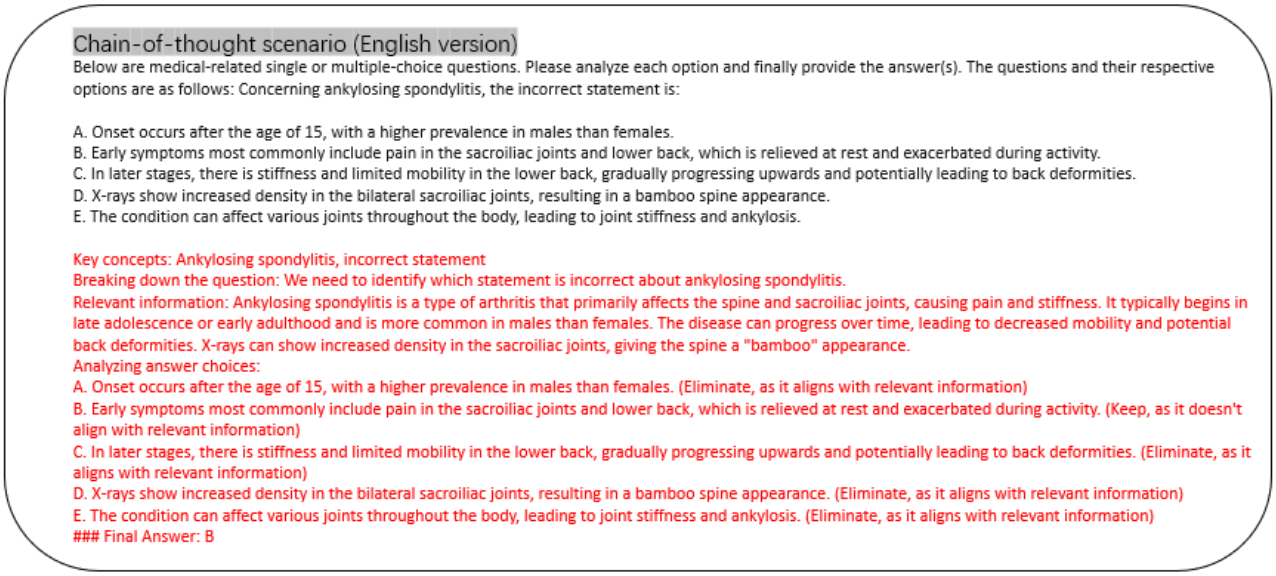

Modeling

Trial Design

The “Modeling” section delineates our approach to constructing and enhancing a specialized LLM for the medical field. It involves curating a comprehensive medical data set, selecting a cutting-edge foundation model, and applying rigorous fine-tuning methods to elevate performance. Initially, the data sets, both public and proprietary, which inform the model’s training will be described. Subsequently, a leading foundation model will be identified through empirical testing. Finally, our fine-tuning strategy, tailored to our medical benchmark, aims to improve the model’s precision and use in medical diagnostics and therapy.

Ethical Considerations

All experimental protocols were approved by the Ethics Review Committee of Chinese PLA General Hospital (S2022-255-01). This study adhered strictly to the hospital’s data management and usage protocols, applying deidentification procedures to patient-specific information such as names, national identification numbers, and medical record IDs within the extracted medical records to protect patient privacy. Additionally, researchers involved in this study signed confidentiality agreements, and the development of the model training and application systems was conducted entirely within the hospital’s internal network, effectively eliminating the risk of information breaches. However, the initial training of generic data was performed by technicians on external networks, using data sets that are publicly available. Throughout the research

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process, we diligently followed applicable laws, regulations, and standards to ensure that our research activities and data usage conformed to ethical principles and legal requirements.

Data Sets

The Huatuo-26M [23] data set, comprising 26 million medical question and answer (Q&A) pairs, is categorized into 4 distinct segments—medical descriptions generated by automated tools, as well as both simulated and authentic single-turn and multi-turn medical dialogs. It is versatile, aiding in training Q&A data sets, serving as a base for retrieval-augmented generation, and enhancing pretrained language models.

In the future, a collection of 100,000 multiple-choice questions will be compiled from diverse sources such as CMB, CMExam [24], MedQA [25], and MLEC-QA [26], with each source contributing 25,000 questions. Among these, only the CMExam data set includes explanations. For SpA and related rheumatic diseases, we generated explanations via ChatGPT, which were then validated by medical professionals. Additionally, SpA-focused questions from professional medical examinations will be incorporated into the training corpus, carefully avoiding duplication with the benchmark data set.

To refine the LLMs' proficiency in multiple-choice question responses, we extracted Q&A pairs from academic publications and medical texts, thus expanding the model's feature repertoire and enhancing its domain-specific knowledge. These Q&As, infused with rich contextual and semantic detail, are instrumental in advancing the model's predictive precision.

Drawing on a data set encompassing more than 80,000 medical cases from the Chinese PLA General Hospital, we assembled a substantial corpus of more than 390,000 consultations. Table 2 presents the initial demographic distribution of patients by age and gender. We adhered to stringent privacy compliance protocols in refining the data into categories of symptoms, diagnoses, and treatment plans. The hospital's medical records were meticulously prepared for model training by deduplicating data, correcting formatting inconsistencies, and anonymizing personal information to uphold patient confidentiality and meet privacy standards. To enhance the data set's diversity, it was imperative to incorporate cases diagnosed with ankylosing spondylitis and those presenting similar symptoms, such as SpA, psoriatic arthritis, reactive arthritis, sacroiliac joint infection, hypophosphatemic rickets, lumbar disk herniation, and rheumatoid arthritis. These cases were stringently validated by medical experts to ensure their relevance to the diseases of interest. When the data set for a specific disease type exceeds 200 instances, we cap it at 200; if it contains fewer than 200, all instances are included in the training set. The training set was carefully curated to include approximately 1400 verified medical records, covering 8 distinct disease categories. The internal hospital record–based training corpus was formatted as single-choice diagnostic queries. Each query comprised patient demographics, clinical history, physical examination outcomes, and auxiliary test results, followed by a set of 4 options—1 correct answer and 3 distractors.

Table 2. Demographic distribution of patients with SpA[a] in the study population[b].

Age range at first diagnosis (years)	Males, n	Females, n
0-10	140	59
10-20	7263	1631
20-30	21,303	7140
30-40	16,389	7602
40-50	7837	4887
50-60	3301	2918
60-70	1129	995
70-80	283	240
80-90	84	66
90-100	10	2

[a]SpA: spondyloarthritis.

[b]The table details the demographic characteristics of patients at their initial consultation for SpA treatment, categorized by age and gender, within the study cohort.

Selection of the Foundation Model

From the C-Eval leaderboard [27], we selected a series of the latest open-source models—Baichuan-13B (Baichuan Inc), ChatGLM2-6B (Beijing Zhipu Huazhang Technology Co, Ltd), Llama2-7B (GenAI, Meta), Qwen-7B (Aliyun). Concurrently, we use a pretrained model RobotGPT, an LLM that integrates ideas from influential papers such as InstructGPT, LLaMA, and Bloom. This model was built on approximately 200 TB of raw, unfiltered data and underwent fine-tuning with about 3 TB of high-quality, meticulously curated data. The data set supporting RobotGPT is diverse and comprehensive, including data from various sources—25% from Common Crawl, 16% from the multilingual Open Super-large Crawled Aggregated Corpus (OSCAR) database, and 14% from books. Additionally, 8% of the data set comprises Chinese novels, enriching its linguistic diversity. The model also integrates a substantial amount of programming-related data, with 12% from GitHub Code and

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13% from CodeContests Code. The remaining 12% of the data set consists of various multilingual sources, further enhancing the model's robustness and versatility in processing different languages and contexts. RobotGPT is available in 13B and 34B versions.

We fine-tuned 6 state-of-the-art open-source models with different parameter versions on the public data set (in the section "Data Sets")—ChatGLM2-6B-32K, Baichuan-13B-Chat, Llama2-7B-Chat, Qwen-7B-Chat, Qwen-14B-Chat, and Openbuddy-70B. After evaluating these fine-tuned models with 122 test questions sourced from public data, we found that Qwen-7B outperformed Qwen-14B, while the largest model, Openbuddy-70B, did not achieve significant results compared with the others. Therefore, only ChatGLM2-6B-32K, Baichuan-13B-Chat, Llama2-7B-Chat, and Qwen-7B-Chat were selected for further fine-tuning with EMR data.

Fine-Tuning

Supervised fine-tuning facilitates the enhancement of model performance on specific data sets by leveraging pretrained knowledge combined with minor task-specific adjustments. This is particularly critical in the medical field, where the acquisition and review of specialized textual data often incur high costs and are challenging to amass in large quantities. Supervised fine-tuning allows for superior model performance with fewer specialized data sets. Although this method can improve performance for specific tasks, it poses a risk of overfitting, especially when the training data are exceedingly limited. To address this, we constructed Q&A pairs and extracted examination questions and answers from publicly available data sets, and balanced data samples across various diseases within a private medical record data set to supervise the model fine-tuning with multiple-choice questions. We then applied low-rank adaptation (LoRA) [28] fine-tuning technique, freezing the pretrained model's weight parameters while incorporating additional network layers without altering the original model parameters, training only the parameters of these new layers. Given the relatively small number of added parameters, this approach significantly reduces the cost of fine-tuning while achieving results comparable to the comprehensive model fine-tuning. This technique enables the model to use the general knowledge acquired during the pretraining phase and learn features useful for addressing the questions related to the diagnosis and treatment of SpA.

LoRA involves integrating trainable rank decomposition matrices into transformer layers while preserving the pretrained weights. A significant advantage of LoRA is its ability to drastically reduce the number of trainable parameters by a factor of 10,000, and to decrease graphic processing unit memory usage by 3-fold. Figure 5 shows the neural network model implementing LoRA for advanced fine-tuning. The model's architecture features an input embedding module, a self-attention mechanism with query (Q), key (K), value (V) elements, a Softmax layer, and a causal mask. Additionally, it includes a multilayer perceptron, specialized components like Swish gated linear unit and root mean square layer normalization, and concludes with a linear and Softmax layer for generating predictions. This strategic enhancement will be applied to a Q&A data set, sourced from the extensive medical consultation records at Chinese PLA General Hospital.

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Figure 5. Neural network architecture with LoRA for LLMs in SpA diagnostics. LLM: large language models; LoRA: low-rank adaptation; SpA, spondyloarthritis.

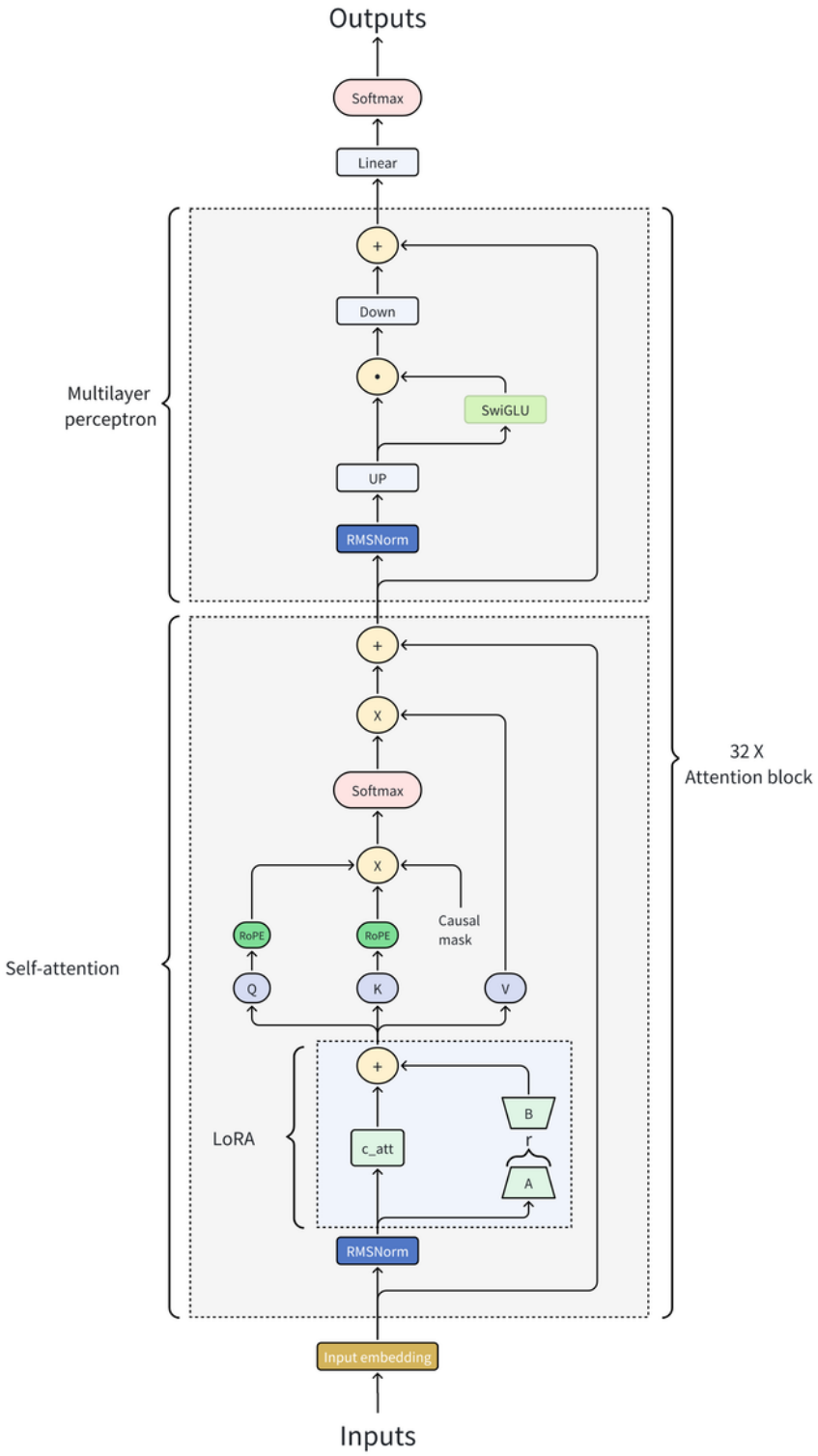

Results

At the time of paper submission, our advanced medical model, RobotGPT-30B, ranks first on the CMB leaderboard. The extraction of internal medical record data from the hospital has been completed, and the selection of the base model has been finalized. Model development is underway, with further development planned for early 2024. The benchmark will be released in May 2024. The outcomes of both objective and subjective evaluations are scheduled to be published in June 2024. This project was funded in December 2021 and concluded in November 2024.

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Discussion

Limitations

In the domain of health care, LLMs may encounter inherent limitations when addressing the nuances of specific medical fields. This is particularly evident in scenarios involving rare diseases or unique treatment protocols, where these models may fail to deliver accurate diagnostics. A notable challenge for these models, especially when parsing complex medical literature and data, is the propensity for "hallucinations"—the generation of seemingly plausible but unfounded or erroneous assertions in the absence of sufficient evidence. This issue is of paramount importance in clinical settings, where it could significantly impact the quality of diagnoses and treatments.

Continuous Enhancement and Future Work

As the corpus of medical knowledge continues to expand and clinical practices advance, the diagnostic and treatment guidelines for SpA are subject to frequent updates. In response, we have established a systematic framework for the periodic review and enhancement of our LLMs to maintain their efficacy and accuracy within clinical applications. We envisage conducting a comprehensive evaluation of the model biannually to ascertain the necessity for updates, although this interval may be adjusted in the light of significant breakthroughs in the medical field or the release of new guidelines. Upon identifying the need for an update, our team will initiate the collection of pertinent new data, including recent research publications, clinical trial outcomes, and updated treatment guidelines. These data will be scrutinized by clinical experts before technical personnel proceed with the fine-tuning of the existing model using the validated data set, making requisite adjustments and optimizations to ensure our model accurately reflects the latest knowledge and guidelines. We believe that through continuous updates and enhancements, our language model will become an indispensable tool for clinicians in the diagnosis and treatment of SpA.

To ensure a thorough assessment, we plan to broaden the benchmark data set to include a wide array of questions. Our long-term objective is to expand the benchmark data set to cover a comprehensive range of major disease categories. The preliminary results of our model are promising, and we foresee further enhancements through improvements in data quality, volume, and model architecture. For optimal performance, we advise future studies to include a broader range of real clinical data and to incorporate demographic factors such as gender and age for more nuanced model insights. Although our current focus is on SpA, our methodology is designed to be adaptable to other diseases. We are also exploring the potential of expanding our research into the multimodal domain, including medical image analyses such as x-ray and magnetic resonance imaging. This integrated approach, combining textual and visual data, aims to transform patient diagnosis and treatment, with a view toward potential application in medical robotics. These robots, equipped with computer vision, will be able to interpret medical images and, complemented by insights from the language model, offer preliminary diagnoses. With the ongoing enhancement of capabilities in LLM technologies, medical models specialized for vertical domains are anticipated to soon integrate with the health care information systems such as hospital information systems and laboratory information systems. This synergy is expected to significantly improve the diagnostic and therapeutic efficiency of health care facilities, heralding a paradigmatic shift in medical diagnostics. For instance, by leveraging LLMs to directly access patients' laboratory tests, imaging data, and historical medical records, it is possible to recommend treatment plans to the attending physicians. This approach has the potential to significantly enhance diagnostic and therapeutic efficiency while conserving health care resources.

Conclusions

Our main findings are expected to reveal that the RobotGPT model, after fine-tuning, will exhibit promising capabilities in navigating the intricate landscape of SpA diagnosis and treatment recommendations, particularly in resource-limited settings where specialized care is scarce. Simultaneously, our benchmark and evaluation methods will be well-equipped to measure the capabilities of LLMs in diagnosing and treating SpA issues.

Our approach builds upon the foundational work in LLMs, extending their application to a niche yet critically important area of medicine. Upon fine-tuning with domain-specific public and proprietary data sets, the capacity of LLMs to address SpA inquiries is anticipated to enhance significantly. Concurrently, our model will be evaluated against state-of-the-art counterparts through both objective accuracy and subjective assessments, with the expectation that our model will achieve commendable performance. While benchmarks like CMB [13], CBLUE [14], and MedEval [16] have been instrumental in advancing LLMs in general medical contexts, the novelty of our approach lies in the development of a tailored benchmark for SpA, addressing the gap in existing LLM applications within rheumatology. This benchmark not only facilitates the accurate assessment of the model's performance but also ensures its relevance to real-world clinical scenarios.

Through continuous updates and enhancements, our language model will become an indispensable tool for clinicians in the diagnosis and treatment of SpA. Simultaneously, the development of this benchmark for LLMs in the context of SpA establishes a new precedent in rheumatology research. It serves not only to evaluate the accuracy of AI-driven diagnostics in this specific disease area but also acts as a prototype for comparable advancements in other rheumatological conditions.

Acknowledgments

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Data Availability

The data sets from the public data sets analyzed in this study are available in the CMB [13], Huatuo-26M [23], CMExam [24], MedQA [25], and MLEC-QA [26]. Additionally, the data sets from the private data sets trained and generated during this study are not publicly available due to protect patient privacy but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CBLUE: Chinese Biomedical Language Understanding Evaluation Benchmark
CMB: Comprehensive Medical Benchmark
CMExam: Chinese Medical Examinations
CoT: chain-of-thought
LLM: large language model
LoRA: low-rank adaptation
OSCAR: Open Super-large Crawled Aggregated Corpus
PLA: People's Liberation Army
Q&A: question and answer
SpA: spondyloarthritis
SpAMCQA: spondyloarthritis multi-choice question answering

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Protocol

Investigating the Efficacy of a Community Support Network Rehabilitation Intervention for Improving Resiliency, Quality of Life, and Neurocognitive Function in Survivors of Intimate Partner Violence–Caused Brain Injury: Protocol for a Feasibility Study

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Abstract

Background: Globally, approximately 1 in 3 women experience intimate partner violence (IPV) in their lifetime. Brain injury (BI) is a common, yet often unrecognized, consequence of IPV. BIs caused by IPV tend to be mild, occur repetitively over the course of months or years, are remote in time, and result in chronic symptoms. Similar to BI from other causes, therapeutic treatment for women with IPV-caused BI (IPV-BI) is crucial to help resolve any physical or cognitive impairments, enhance the quality of life (QoL), and minimize longer-term neurodegeneration.

Objective: This study aims to investigate the feasibility and efficacy of a community support network (CSN) rehabilitation intervention regarding its impact on resiliency, QoL, and neurocognitive function.

Methods: In this pre- and postexperimental design, women (aged 18 to 50 years) who are survivors of IPV and IPV-BI will be recruited from various community organizations serving survivors of IPV. Exclusion criteria will include current pregnancy and any diagnosed neurological disorder known to affect cerebrovascular, neurocognitive, or sensorimotor function. A CSN rehabilitation intervention that includes aerobic exercise, cognitive training, mindfulness meditation, and counseling will be administered. A trauma-informed approach will be integrated into the design and implementation of the program. Furthermore, the program will include a participant navigator who will provide trauma- and violence-informed advocacy and systems navigation support to participants, in addition to facilitating a monthly peer support group. The intervention will be provided for 2.5 hours a day and 2 days a week for 3 months. Participants will complete psychological assessments and provide clinic-demographic information in the first assessment. In the second (before intervention), third (after intervention), and fourth (at follow-up) sessions, they will complete tests of resiliency, QoL, and neurocognition. The estimated sample size is 100. The objective of this study will be accomplished by quantitatively measuring resiliency, QoL, and neurocognition before and immediately after the intervention. A follow-up assessment will occur 3 months after the completion of the intervention to evaluate the maintenance of any improvements in function. One-way ANOVAs will be used to evaluate the intervention outcome across the testing times. Relationships among various variables will be explored using regression analysis.

Results: We anticipate that the CSN rehabilitation intervention will be effective in improving resiliency, QoL, and neurocognitive function in women who have experienced IPV-BI. Furthermore, we anticipate that this intervention will be feasible in terms of study recruitment, adherence, and retention.

Conclusions: The CSN rehabilitation intervention will have a positive impact on resiliency, QoL, and neurocognitive functions in survivors of IPV-BI. Subsequently, a comparative study will be conducted by recruiting a control group receiving usual care.

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(JMIR Res Protoc 2024;13:e54605) doi:10.2196/54605

KEYWORDS

brain injury; cognitive functions; community support network; intimate partner violence; quality of life; rehabilitation

Introduction

Background

Intimate partner violence (IPV) is remarkably prevalent (for women, lifetime prevalence has been reported as high as 1 in 3, and 12-month prevalence has been reported as high as 1 in 10) [1], leading to a variety of negative physical and mental health outcomes, including posttraumatic stress disorder (PTSD), anxiety, and depression [2]. Brain injury (BI) resulting from violent blows to the head, face, and neck or episodes of strangulation is increasingly recognized as part of the IPV experience [3-5]. The prevalence of IPV-caused BI (IPV-BI) is estimated at >70% [6,7]. Furthermore, strangulation is a common mechanism of injury in IPV [8] and often indicates an increase in the severity of BI. As such, nonfatal strangulation (NFS) is an important risk factor for negative health outcomes in people who experience IPV [9]. NFS is commonly a repetitive rather than an isolated event, and is used to exert control by inducing feelings of pain and helplessness [10]. NFS can lead to BI by one or more of the following mechanisms: (1) *anoxic or hypoxic* BI due to compression of the trachea; (2) *ischemic* BI due to occlusion of arterial blood flow; (3) *hypoxic-ischemic* BI due to the combined compression of the trachea and the carotid arteries or due to the triggering of carotid sinus reflex leading to dysrhythmia or cardiac arrest, which subsequently could cause BI; and (4) *pressure-related BI* due to the occlusion of the jugular veins leading to venous congestion, increased intracranial pressure, blocking of the removal of metabolic byproducts, and pinpoint hemorrhage [7,11,12].

Survivors of IPV-BI demonstrate cognitive impairments (eg, deficits in memory, attention, reasoning, planning, and executive functioning) [13], psychological or emotional disturbances (eg, depression, anxiety, fatigue, and PTSD) [5,13], and sensorimotor problems (eg, paralysis or paresis of facial or extremity muscles, numbness, loss of sensation, muscle spasms, facial droop, and unilateral weakness) [14], which ultimately impacts the quality of life (QoL). Therefore, therapeutic treatment for survivors of IPV-BI is crucial, and any physical or cognitive impairment in these survivors requires therapeutic interventions similar to those for BIs from other injury mechanisms (eg, sport-related concussion and car accidents). Effective therapeutic interventions would not only improve the QoL of survivors of IPV-BI but also have the potential to prevent longer-term neurodegeneration if early detection is possible and timely treatment is provided [15].

In the case of BI from other causes, individuals often access rehabilitative resources through the health care system [16]. Given the goals of care outlined by the Canadian Medical Association, resources are positioned to assess and treat both short- and long-term effects of BI, with the overarching goal of complete recovery. Rehabilitation is individualized and may include a range of services spanning emergency care to physical or occupational therapy [17]; however, differential access is common. Women who have experienced IPV-BI are chronically underserved [4,7,18]. This is in part due to the failed recognition of IPV and an inability to link IPV and BI within the more comprehension health care system. The complexities surrounding IPV, such as safety, stigma, and child custody concerns, discourage survivors from accessing primary health care. If survivors do access primary health care, they may not feel comfortable or see marked benefit in disclosing the cause of their injuries [19]. Disclosure of IPV in health care settings is further influenced by negative health care provider attitudes, survivors' perception of safety, and concerns about the consequences of disclosing. Importantly, help-seeking behaviors are intersectional and may also be influenced by race, ethnicity, gender identity, or sexual orientation [20]. As a result of these factors, evidence-based therapeutic interventions to improve the QoL of survivors of IPV-BI are still lacking. Therefore, in collaboration with ABI Wellness, our team has developed a rehabilitation program termed the "community support network" (CSN) rehabilitation intervention specific to IPV-BI. Traditionally, health care and community supports that offer services for those who have experienced IPV typically do not take IPV-BI into account. Recent Canadian research by Nicol et al [21] found that 75% of the women's shelter workers in a national sample reported they did not screen for BI following IPV [21]. The challenge in assessing IPV-BI is further complicated by the increased risk of psychopathological comorbidities such as PTSD, depression, anxiety, and substance use that can mask or exacerbate BI symptoms. Cumulatively, the need for a rehabilitation intervention spanning primary health care to independent activities of daily living is evident. Therefore, by definition, the support provided to survivors must be multifaceted, multidisciplinary, integrated, trauma- and violence-informed, and culturally safe.

Following BI, the recovery trajectory is strongly affected by the severity of the injury. In mild cases, 80% of individuals with a concussion or mild BI make a complete recovery. However, a portion of individuals experience persistent symptoms, cognitive impairments (eg, deficits in executive function and working memory, reduced processing speed and attention, difficulty in focusing, and difficulty with word recall), and reduced QoL for months to years after the injury. We propose that this gap in recovery is related to higher-order cognitive functions and, by targeting these core functions through rehabilitation and regaining function through the CSN rehabilitation intervention, individuals can return to a complete and meaningful life after the injury.

With all this in mind, this study protocol aims to evaluate a community-based, neurorehabilitative intervention to improve outcomes for survivors of IPV and IPV-BI.

Objectives

The *primary objectives* of this study protocol are as follows:

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1. To measure the efficacy of the CSN rehabilitative intervention in terms of its impact on resiliency, QoL, and neurocognitive functions
2. To evaluate the feasibility of the CSN rehabilitative intervention in terms of study recruitment, adherence, and retention

The *secondary objectives* of this study protocol are as follows:

1. To characterize neurocognitive function in women who have experienced IPV-BI
2. To characterize mental health consequences in women who have experienced IPV-BI

Methods

Design

This study will follow a pre- and postexperimental study design. Subsequently, a comparative study will be conducted by recruiting a control group receiving usual care.

Participant Inclusion and Exclusion Criteria

Self-identified women (aged 18 to 50 years) who are survivors of IPV (disclosed) and IPV-BI (Brain Injury Severity Assessment [BISA] score ≥1) [5] will be eligible for recruitment to this study. Although IPV is not exclusive to women, this protocol study will only examine women. This approach was selected for two primary reasons: (1) the prevalence of reported IPV is higher in women compared to men [1] and (2) the infrastructure currently available for women who experience IPV is adequate to support recruitment into the intervention. The realities of recruiting self-identified women for a study of this nature are both impactful, from a survivor standpoint, and achievable, from a CSN approach.

Exclusion criteria will include current pregnancy; any diagnosed neurological disorder known to affect cerebrovascular, neurocognitive, or sensorimotor function (eg, stroke, Parkinson disease, Alzheimer disease, cerebral palsy, multiple sclerosis, migraine, or seizures); and taking medication that might alter blood pressure. Participants will be tested in the early follicular phase or, if they are on combined hormonal contraception, at the end of the week they have stopped this contraception.

Recruitment

Recruitment will occur through partnerships with the Nanaimo Brain Injury Society (Nanaimo, British Columbia), the Central Okanagan Elizabeth Fry Society (Kelowna, British Columbia), William and Associates Counselling Services (Kelowna, British Columbia), and Connect Counselling and Therapy (Kelowna, British Columbia). Potential participants will be made aware of the project through promotional media and by direct staff referral within partner organizations. Potential participants will be screened by the research coordinator for eligibility using the adapted HELPS BI assessment tool [22].

Ethical Considerations

The study has been reviewed and approved (H20-02412) by the behavioral ethics board at the University of British Columbia, Okanagan.

Participants who agree to take part in the study will be asked to provide informed consent and will be reminded that they can withdraw from the study at any time.

The identity of participants will be kept secure by storing consent forms and any other documents that could be used to determine the participants in a locked filing cabinet in the office of the senior author (PvD). Data will be deidentified and anonymized using codes so that participant information will remain confidential.

Participants will be compensated a total of CAD $550 (US $405.45) across the different components of the project for contributing their time and effort.

CSN Rehabilitation Intervention

The CSN intervention is an evidence-based, multipillar, interdisciplinary rehabilitation program grounded in the ABI Wellness Brain Enhance And Recovery System (BEARS) program platform, with additional components incorporated to support the unique needs of survivors of IPV-BI.

The BEARS Program

Overview

The BEARS program [23] is a highly structured, noninvasive multidisciplinary rehabilitation program focused on improving cognitive capacity across a wide range of higher-order cognitive functions, resulting in a generalized improvement of cognitive ability and QoL. The BEARS program is designed based on the principles of neuroplasticity. In addition to the 10 general principles of neuroplasticity [24], the BEARS program includes the following five key components that promote neuroplastic changes: (1) *attention* (focused attention on the demands of a specific task), (2) effortful processing (task that is challenging enough that it requires effort to accomplish but not so difficult as to be discouraging), (3) *novelty/complexity* (task involving new learning with an appropriate level of complexity), (4) *differentiated stimulation* (specific tasks targeting a cognitive function), and (5) *sustained engagement* (sufficient time spent working on a particular cognitive task). The BEARS platform consists of 4 pillars (Textbox 1) that have been shown to improve function following BI from various causes [25-29].

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Textbox 1. Pillars of the Brain Enhance And Recovery System (BEARS) platform.

Pillars

- Aerobic exercise
  - The BEARS aerobic exercise pillar aims to take advantage of the neuroplastic benefit of aerobic exercise to complement and accelerate the changes occurring as a result of cognitive training [25,29]. The aerobic exercise can include, but not be limited to, running, jogging, walking, rope jumping, swimming, stationary or recumbent bicycling, Zumba or dancing, using a treadmill or rowing machine, or elliptical exercises. The key factor for aerobic exercise is the release of neurochemicals that promote neuroplasticity and cognitive recovery. For this to be accomplished, it is critical that a specific exercise intensity is reached and maintained. The modality of the exercise is not important as long as the intensity level is met and maintained for a sufficient amount of time. A participant should be working at approximately 70% to 80% of their maximum heart rate for 30 minutes, or a minimum intensity of 12 on the Borg scale must be reached and maintained for a minimum of 30 minutes. At times, when participants are not able to exercise at this intensity or for the complete duration, the facilitator will work with the participants on improving their fitness level, aiming to enhance their intensity as high as possible. The aerobic exercise pillar will be monitored and recorded using an app embedded in the BEARS program. Facilitators will ensure that clients have been allowed to participate in physical activity by their physician or that the aerobic exercise is completed under the supervision of a certified professional (eg, physiotherapists and occupational therapists). ABI Wellness acknowledges that not all clients will be able to participate in the physical activity pillar; however, all possible accommodations will be made to allow for participation.
- Cognitive rehabilitation
  - The cognitive rehabilitation pillar is focused on recovering and rebuilding higher-order cognitive functions, such as working memory, attention, and executive functions [23]. The cognitive training program used as part of the BEARS program is the Brainex program, which is a multiexercise program that specifically targets multiple brain regions and functions. The cognitive exercise being implemented is the Brainex symbol relations task, which is a computer-based cognitive exercise consisting of a sustained visual-spatial processing or relational reasoning task of progressively increasing difficulty. It requires participants to use relational reasoning on an analog clock to conceptually and automatically process relationships that increase in complexity. The participant enters the value, and feedback is presented. Once a criterion of 90% accuracy is attained over a series of consecutive responses, the complexity of the task increases. This cognitive exercise is not language dependent, so it is accessible to participants with different language backgrounds. Individually tailored goals will be set or adjusted for improving accuracy, increasing the number of correct responses per day, improving the number of sets completed per day, and lowering the time per set while maintaining accuracy. The best approach for optimal recovery adopted in this program is to focus on capacity-building rehabilitation and help individuals regain as much cognitive function as possible before using compensatory strategies to supplement and support continuing areas of impairment. Furthermore, the symbol relations assessment is incorporated within the program to measure the cognitive capacity of participants. A pilot intervention showed cognitive improvement in participants who had sustained a BI [26].
- Mindfulness meditation
  - Regular mindfulness meditation has been shown to have a myriad of benefits to both the body and the mind. In particular, following BI, mindfulness can help with increasing self-awareness, and breathing techniques are very beneficial for helping to lower stress when feeling overwhelmed or frustrated [27]. Mindfulness meditation requires the client to participate in a guided meditation block that focuses on educating the client on various types of meditation and to develop their own familiarity and skill with meditation to begin practicing on their own. The critical factors for the mindfulness meditation exercise are regulation of attention, self-awareness, and engagement. The mindfulness meditation activity is monitored and tracked using the embedded app.
- Integrated health
  - The BEARS program was developed to improve the quality of life (QoL) of individuals recovering from BI. The integrated health pillar is focused on bringing the behavioral, social, and emotional aspects of recovery and function together to complete the holistic and integrated recovery of the client. The integrated health pillar is composed of the (1) Traumatic BI (TBI)-QoL measurement system; (2) specific, measurable, attainable/achievable, realistic, and time-based (SMART) goal setting; and (3) transition planning. Using the TBI-QoL measurement system, the facilitator and the support team will be able to identify areas of concern that should be monitored or addressed during the program. The TBI-QoL measurement system is fully embedded into the BEARS program and is included as part of the intake process as well as the subsequent progress assessments. Data will be collected on each client throughout their time in the program. This allows for a deep level of understanding of the client's initial level of function and the progress made throughout the program. A key factor of this program is effortful processing, meaning the more effort a client puts into the activities, the greater the improvement to be expected. In addition, QoL will be measured regularly to track progress in the domains of physical, emotional, cognitive, and social health. The TBI-QoL measurement system is accessible through the facilitator tracking system and the client portal. SMART goal setting allows the facilitator to help the client take small, manageable steps toward their various goals during their time in the program and teach them how to set goals for success. By working with the client with SMART goal setting, the facilitator will be providing the client with the necessary skills required to succeed upon completion of the program. In addition, transition planning is a critical component of all successful rehabilitation programs as this prepares the client for reintegration into the community and their future success.

Three Critical Factors of the BEARS Program

The 3 critical factors of the BEARS program are as follows:

1. *Setting goals:* The BEARS program creates standard goals for each pillar and exercise that act as reference points for ideal daily engagement. At times, when the standard goal may not accurately reflect an individual client's ability or there may be limitations that prevent a client from reaching the standard goal, personal goals may be used to more accurately reflect the client's engagement in the program.

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2. *BEARS tracking system:* The BEARS program will be delivered through web-based applications available on Android tablets. The BEARS Facilitator app has been developed to fully integrate the 4-pillar approach and allow effortless client tracking and real-time data analysis for the facilitator. The app can be used for *organization, progress and engagement tracking, goal setting, program modification, and exercise settings*. The client portal will be used by clients to access the computer-based exercises. All client work done in the client portal will be automatically recorded, and data will be presented on the app. All administration functions of the BEARS program will be done through the BEARS tracking system.
3. *Client engagement:* Engagement is key in the BEARS program, and therefore, if a client is not fully engaged in a portion of the program, it is vital that the facilitator steps in and makes the necessary adjustments. At all times, the client's progress, engagement, and goals will be monitored and adjusted based on their performance. The app will record and display client progress and engagement for every exercise within the program. It will provide an overview of weekly progress (against the benchmark expectations) and daily engagement goal (regarding the personal goal) graphs.

Additional Components

The purpose of integrating additional components into the BEARS program was to develop an IPV-BI–specific rehabilitation intervention for improving survivors' cognitive function, brain health, and QoL. The additional components are described in Textbox 2.

Textbox 2. The additional components into the community support network (CSN) rehabilitation intervention.

Components

- Trauma-informed approach or practice
  - It is essential to integrate a trauma-informed approach (TIA) into the design and implementation of programs for survivors of intimate partner violence (IPV). Therefore, the BEARS program will be adapted for the community support network to be trauma informed. Integration of TIA addresses traumatic experiences with the goal of reducing symptoms, minimizing barriers to accessing health care, optimizing therapeutic outcomes, and working with survivors of IPV toward recovery. The four key elements of TIA (4Rs) are to (1) realize the trauma, (2) recognize signs of trauma, (3) respond through trauma principles, and (4) resist retraumatization. These are applied through six principles: (1) safety; (2) trustworthiness and transparency; (3) peer support; (4) collaboration and mutuality; (5) empowerment, voice, and choice; and (6) cultural, historical, and gender issues [30]. All staff who participate in and deliver the intervention will undertake specific and intentional orientation to TIA and language, particularly as they pertain to IPV. Furthermore, TIA will be achieved through the inclusion of a participant navigator who has lived experience with brain injury (BI) and career expertise working in the gender-based violence sector supporting survivors of IPV.
- Counseling
  - The CSN will integrate a counseling component because survivors of IPV-caused BI often struggle with mental health issues. A great benefit has been observed with the inclusion of counseling into the rehabilitation program [31]. Therefore, targeted counseling of 60 minutes biweekly will be provided by clinical counselors who are trained in handling survivors of IPV and have extensive experience working with survivors of IPV.
- Inclusion of a navigator
  - Because women who have experienced IPV are often dealing with a host of extra challenges, it is important that they have someone to connect with in addition to the BI experts delivering the rehabilitation program itself. The participant navigator will provide trauma- and violence-informed advocacy and program or systems navigation support to the participants as well as referrals to other community agencies or services as needed. The participant navigator will connect and support by phone or video call. Furthermore, the navigator will guide participants to maintain an activity logbook for 3 months after the completion of the intervention.
- Peer support
  - The participant navigator will facilitate a monthly peer support group discussion, which will include personal development presentations from a variety of subject matter experts on topics, including navigating life after BI, healthy nutrition and lifestyle, art therapy, and the power of laughter in improving mental wellness.

Measures

Demographics

Demographic information, including age, education level, race or ethnicity, socioeconomic status, gender, and sexual orientation will be obtained via self-report to accurately characterize participants.

BISA Interview

The BISA is a semistructured interview tool containing a series of questions regarding loss of consciousness and alterations in consciousness (eg, dizziness, memory loss, feeling stunned or disoriented, or seeing stars or spots) following potential BI due to IPV and provides a BI load summary score with a range of 0 to 8 (Table 1) composed of frequency, recency, and severity subscores [5,32]. The frequency score provides an estimate of the number of previous BIs, the recency score probes the time since the most recent event resulting in a BI and the time of the

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interview, and the severity score indicates whether a moderate-to-severe BI was ever sustained. The BISA tool has been useful in capturing the effects of IPV-BI on resting-state brain activation [32], white matter diffusions [13], brain morphology [33], cognitive-motor function [34], and BI symptoms [35]. Thus, the literature suggests that it will be appropriate to assess for previous BI and to assess a reliable subjective measure to allow strong inferences about BI and function.

Table 1. Scoring Brain Injury Severity Assessment (BISA) interview. Frequency (scale range 0-4), recency (scale range 0-3), and severity (scale range 0-1) are 3 subscales of the BISA tool. The BISA tool provides a summary score ranging from 0 to 8.

Subscales and score	Description
Frequency	
0	There have been no previously reported brain injuries
1	There have been 1 to 5 previously reported brain injuries
2	There have been 6 to 10 previously reported brain injuries
3	There have been 11 to 15 previously reported brain injuries
4	There have been ≥16 previously reported brain injuries
Recency	
0	The event occurred >52 weeks ago
1	The event occurred between 27 and 52 weeks ago
2	The event occurred between 14 and 26 weeks ago
3	The event occurred within the past 13 weeks
Severity	
0	The presence of exclusively mild brain injuries
1	At least 1 episode involving loss of consciousness for >30 minutes or a period of posttraumatic amnesia for >24 hours had occurred (indicating moderate-to-severe brain injury)

Mental Health Screening Tools

Each participant will undergo a mental health screen that includes clinical evaluations of abuse history, anxiety, depression, PTSD, substance use, and childhood trauma. These instruments listed in Textbox 3 will be explained and administered to each participant by the research coordinator.

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Textbox 3. Mental health screening tools.

Tools

- *Adverse Childhood Experience Questionnaire:* This is a 10-item questionnaire designed for administration to people aged ≥18 years. Questions cover family dysfunction; physical, sexual, and emotional abuse and neglect by parents or caregivers; peer violence; witnessing community violence; and exposure to collective violence [36]. It is a reliable [37] and valid [38] tool for the measurement of childhood trauma and negative health outcomes in adulthood. This was effectively used in exploring whether individuals exposed to physical and sexual abuse in childhood or domestic violence–prone environments are more likely to be involved in intimate partner violence (IPV) later in their life [39].
- *Conflict Tactics Scale-2 (CTS-2):* The CTS-2 (an updated version of the CTS tool) is a self-report 39-item survey measuring both the extent to which partners in a dating, cohabiting, or marital relationship engage in psychological and physical attacks on each other and their use of reasoning or negotiation to deal with conflicts [40]. Scoring for the CTS-2 involves assigning numerical values to responses and calculating subscale sores. Each question on the CTS-2 asks the participant to report the frequency of a specific behavior in the past year, with responses including 0=this has never happened, 1=once in the past year, 2=twice in the past year, 3=three to 5 times in the past year, 4=six to 10 times in the past year, 5=eleven to 20 times in the past year, 6=>20 times in the past year, and 7=not in the past year but it did happen before. To calculate a subscale score, the scores for each item in that subscale are added together. The CTS-2 has been shown to be valid and demonstrates reliable stability across its subscales: psychological aggression (r=0.69), physical assault (r=0.76), injury (r=0.70), and negotiation (r=0.60). However, the reliability coefficient for sexual coercion is noticeably weaker (r=0.30) [41].
- *Posttraumatic stress disorder (PTSD) checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (PCL-5):* The PCL-5 is a 20-item self-report measure that assesses the presence and severity of PTSD symptoms [42]. Items on the PCL-5 correspond with DSM-5 criteria for PTSD. The PCL-5 can be used to quantify and monitor symptoms over time, to screen individuals for PTSD, and to assist in making a provisional or temporary diagnosis of PTSD. The PCL-5 is composed of 20 items, each from 0 (not at all) to 4 (extremely). The total score for PCL-5 is calculated by adding together the scores for each of the 20 items. Each item is scored between 0 and 4, so the total score will range from 0 to 80. A cut-off score of 33 is often used, suggesting a high likelihood of PTSD [43]. The PCL-5 exhibits robust reliability, with impressive internal consistency (Cronbach α=0.94) and notable test-retest reliability (r=0.82) [42] and validity [44]. Furthermore, there was a strong relationship between current PTSD symptoms and meeting criteria for all 4 DSM-5 PTSD symptom clusters in women with IPV-caused brain injury [45].
- *Generalized Anxiety Disorder Scale (GAD-7):* The GAD-7 is a 7-item self-report inventory used for measuring the severity of anxiety [46]. The questions ask about common symptoms of anxiety the participant had during the past 2 weeks, such as worrying, being restless, being easily annoyed, and fearing. Each question is rated on a scale of 0 to 3, with higher scores indicating higher levels of anxiety. The total score ranges from 0 to 21. The GAD-7 is a quick and reliable tool for identifying the presence and severity of generalized anxiety disorder symptoms [46].
- *Patient Health Questionnaire-9 (PHQ-9):* The PHQ-9 is a 9-item self-report measure used to assess the levels of depression. The questions ask about common symptoms of depression the participant had during the past 2 weeks, such as feeling hopeless, having little energy, and difficulty concentrating [47]. Response options range from 0 (not at all) to 3 (nearly every day). The total score for the PHQ-9 ranges from 0 to 27, with higher scores indicating greater severity of depressive symptoms [48]. The validity and reliability of the PHQ-9 have been established in various studies [48]. The PHQ-9 questionnaire has been used to evaluate depression symptoms in individuals who have experienced IPV [49].
- *Alcohol Use Disorders Identification Test (AUDIT):* The AUDIT is a 10-item screening tool developed by the World Health Organization [50] to assess alcohol consumption, drinking behaviors, and alcohol-related problems. Each item in this tool is evaluated on a 0 to 4 scale, and the total score can range from 0 to 40 [51]. It is a valid and reliable tool for measuring alcohol-related problems [52].
- *Somatic Symptom Severity Scale (PHQ-15):* The PHQ-15 is a 15-item questionnaire that assesses somatic symptoms of pain across different body systems [53,54]. The tool uses a rating scale ranging from 0 (not at all) to 2 (nearly every day), and total scores range from 0 to 30, with higher scores indicating more severe somatic symptoms [54,55]. The PHQ-15 is a reliable tool with a test-retest reliability of r=0.60 [56]. It has also been used to show that survivors of IPV have greater levels of somatic symptoms [57].
- *International Trauma Questionnaire (ITQ):* The ITQ is an 18-item questionnaire that assesses PTSD and complex PTSD [58]. The reliability of the ITQ has been well established, as evidenced by several publications [59,60]. Furthermore, it has been used in studies to assess the relationship between complex PTSD and the severity of IPV psychological perpetration [61,62].
- *Brief Irritability Test (BITe):* The BITe is a 5-item questionnaire assessing common feelings of irritability [63]. The BITe consists of questions regarding how the individual has felt in the past couple of weeks, and they rate their experience on a scale from 1 (not at all) to 6 (always). The score ranges from 5 to 30, with higher scores indicating higher levels of irritability.
- *Level 2-Substance Use-Adult:* This questionnaire is a 10-item screening tool developed by the US National Institute on Drug Abuse to assess substance use [64]. The participant rates each item on a 5-point scale, from 0=never to 4=nearly every day. Scores on the individual items are interpreted independently because each item inquires about the use of a distinct substance. The rating of multiple items at scores >0 indicates greater severity and complexity of substance use.

Outcome Measures

The following outcome measures, which will be administered by a trained member of the research team, will be used to assess resiliency, QoL, and neurocognitive function:

1. *Resiliency:* Resiliency will be characterized using the Connor-Davidson Resilience Scale [65]. This 25-item questionnaire measures responses to 5 factors associated with resilience on a 5-point Likert scale ranging from 0 (not true at all) to 4 (true nearly all the time). The scale has been shown to have good psychometric properties, with high internal consistency and test-retest reliability [65].
2. *QoL:* QoL will be measured using a modified version of the Medical Outcomes Study short form-36 [66]. This 36-item questionnaire consists of 8-scaled scores covering several aspects of QoL and general health. Each scale is

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scored separately and transformed onto a scale that ranges from 0 to 100 for ease of comparison, with lower scores indicating a lower QoL.

3. *Neurocognition:* Neurocognitive function will be assessed using the Creyos (formerly known as Cambridge Brain Sciences) tool [67], which consists of 12 different tasks that assess aspects of cognition, including reasoning, memory, attention, and verbal ability. The tasks include digit span, double trouble, feature match, grammatical reasoning, monkey ladder, odd one out, paired associates, polygons, rotations, spatial planning, spatial span, and token search. The tasks have been validated in studies of patients, in brain imaging studies of healthy volunteers, and in several large-scale public studies [67-69]. The Creyos tool maintains a global normative database of >75,000 participants that allows for detailed comparisons of individuals to specific populations. The tests have been shown to be valid and reliable, and a meaningful change can be calculated using the normative database [67]. Notably, all tasks, which users report to be fun and engaging, will be administered through web application or in person using a desktop or laptop and require no expert technical support to administer. Task results will be stored securely in the cloud and can be easily downloaded for offline analyses [65,69].

In addition to the tasks included in the Creyos tool, a task-switching paradigm will be used to probe executive functions [70]. A simplified version of the task that is run on an Android tablet will be used to capture executive dysfunction in this study. This simplified version has been implemented in a study (unpublished) examining head impacts and concussions in ice hockey players.

Furthermore, we will have access to the following measures collected throughout the intervention, which are incorporated within the BEARS program [23]:

1. *Traumatic BI-QoL (TBI-QoL) measurement system:* The TBI-QoL measurement system is a recently developed QoL measure specifically designed for people who have experienced TBI. It consists of a 20-item questionnaire covering the domains of physical health, emotional health, cognitive health, and social participation [71]. The findings of this tool would be helpful in corroborating the findings of the study short form-36.
2. *Brainex cognitive assessment:* This is a series of tests of neurocognitive function, including assessments of symbolic thinking. The findings of this tool will be helpful in strengthening the findings of the Creyos assessment.
3. *Functional performance indicators:* The functional performance indicators are independently derived by ABI Wellness and act as additional composite scores that are purely indicative and aim to reflect the ability of the individual to function in everyday life. The scores are created from various TBI-QoL subdomains, which were chosen to best reflect these functional performance measures.
4. *ABI Wellness overall engagement:* The overall engagement assessment is done to provide an overview of the weekly and cumulative engagement across the different activities of the ABI Wellness 4-pillar program. The engagement is measured against the personal goal of each activity set by the facilitator.

Feasibility Measures

Study recruitment, adherence, and retention will be used to assess feasibility. Recruitment will be measured as the proportion of individuals enrolled compared to those who were approached and eligible but did not enroll. The proportion of weekly sessions attended by the participants will be calculated to assess adherence. Retention will be evaluated by the proportion of participants with complete data sets on primary outcome measures at pre and postintervention time points. Withdrawing will be calculated at the postintervention time point as the proportion of the participants who will withdraw from the intervention [72]. In addition, we will be collecting qualitative feedback and anecdotal information on how participants like the program, what they think about the program overall, and which component of the intervention was most or least enjoyed.

Procedure

Overview

The intervention program and assessments will be in person or remotely operated (on a university-licensed Zoom app), or a hybrid combination of in person and remote operation based on participants' preference, their location, and context such as public health orders. After the research coordinator explains what is involved in the study, if a client is willing and eligible to participate, informed consent will be obtained. All participants will undergo 4 testing sessions: the first and second sessions will occur before enrollment in the intervention, and the third and fourth sessions will occur within 1 week and 3 months of the end of the intervention, respectively. In the first session (lasting approximately 2.5 hours), participants will complete a mental health screening battery. In the second, third, and fourth sessions (lasting approximately 1.5 hours), they will complete tests of resiliency, QoL, and neurocognition. If, as a result of the assessments, a clinically significant abnormal finding is obtained, the participant will be directed to seek medical advice from a health care provider. Various steps of the study and the roles of the study team are outlined in Figure 1.

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Figure 1. Steps to participation, enrollment, and assessment with the program team. Right side of the figure provides various steps of the study, and the left side shows roles of the study team at various stages. CSN: community support network, PAR-Q: Physical Activity Readiness Questionnaire.

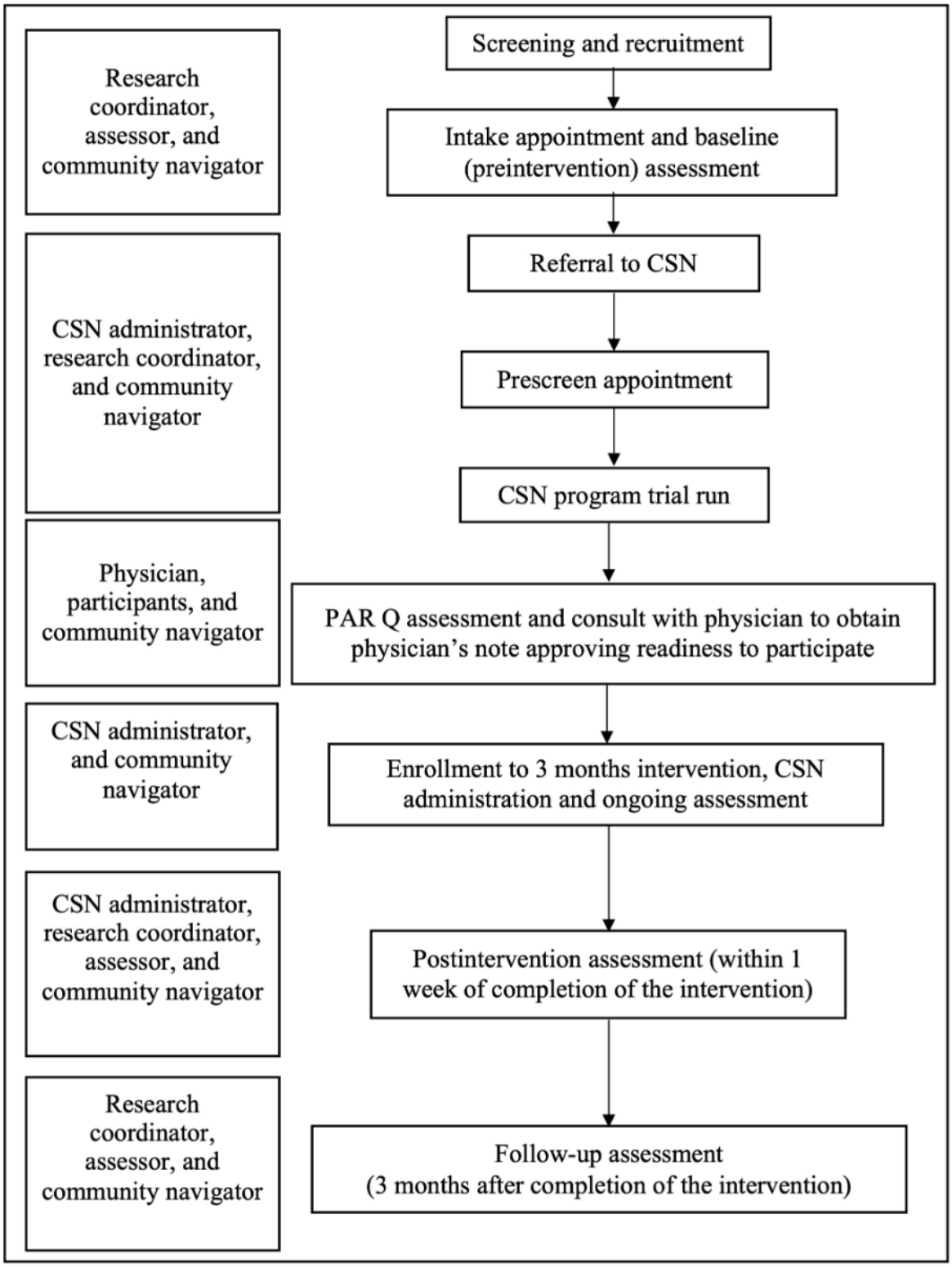

Structure of the CSN Intervention

The dose and sequence of the CSN rehabilitation intervention is outlined in Table 2.

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Table 2. An example of a 2 days per week schedule of the community support network rehabilitation intervention. The table provides the administration sequence and duration of aerobic exercise, cognitive training, and mindfulness meditation with an additional note on monthly peer group support discussion and biweekly counseling sessions.

Time	Duration[a] (total duration/day: 2.5 hours)	Activities
9:30 to 10 AM	30 minutes	Aerobic exercise
10 to 10:10 AM	10 minutes	Break
10:10 to 10:50 AM	40 minutes	Cognitive training, block 1
10:50 to 11:10 AM	20 minutes	Mindfulness meditation
11:10 to 11:50 AM	40 minutes	Cognitive training, block 2
11:50 AM to noon	10 minutes	Wrap up

[a]Participants must commit to attending the program on a part-time basis for 3 months. The program is adaptable, with an example 2 days per week version outlined in this table.

The following activities will be provided to the participants in addition to the activities mentioned in Table 2:

- There will be a peer group support group session for approximately 60 minutes once a month.
- The program includes counseling of approximately 60 minutes twice a week.
- There will be a participant navigator who provides trauma- and violence-informed advocacy and program or systems navigation support to participants and referrals to other community agencies or services as needed.

Program Team

All members of the program team will receive foundational training in IPV and trauma-informed practice. The CSN facilitators will take formal training on the BEARS program from ABI Wellness and will be certified for its administration. The research coordinator will receive formal training in the administration of the various assessment tools. The team will meet every other week, or more frequently as needed, to track the program and participant progress and address questions or issues that arise.

Sample Size Estimation

To generate and design a study with adequate power, we estimated the required sample size based on previous data from our laboratory in both healthy participants and those with IPV-BI [34,35]. Power calculations are based on the desired end point to detect a change in each of the assessments across testing times. Therefore, assuming our published SDs for these measures and considering the potential for increased variability in this study population, a total sample size of 100 participants would provide a >90% probability that the study will detect a significant change score at a 2-sided 5% significance level.

Statistical Analysis

The objective of this project is to evaluate the efficacy of a CSN intervention for women who have experienced IPV-BI. This will be accomplished by quantitatively measuring resiliency, QoL, and neurocognition before and immediately after the intervention. A follow-up assessment will occur 3 months after the completion of the intervention to evaluate the maintenance of any gains in function. The mean (or median) for each assessment will be compared across testing times using 1-way ANOVAs. Relationships between BISA scores and the change scores for each assessment will be evaluated using regression analysis. Furthermore, the outcome of the intervention will be compared among various subgroups based on the findings of various mental health screening tools (eg, participants with PTSD vs participants without PTSD), substance use, and adverse childhood experience (eg, participants with adverse childhood experience vs participants without such experience). Various demographics and mental health screening assessments will be used to control for nonspecific effects of IPV. In addition, we will have opportunities to better characterize IPV-BI based on the BI load from the BISA tool, findings of various mental health screening tools, and cognitive findings using the Creyos assessment and task-switching paradigm. The α value will be set a priori at $P<.05$. All data will be analyzed using SPSS (IBM Corp).

Potential Risks, Safety, and Security

We will take appropriate precautions to minimize potential risks associated with the proposed study. The participants are not expected to encounter any substantial physical or mental risks as a result of this study. The BISA and other psychosocial assessments will be conducted by a trained research coordinator who has substantial career experience directly supporting survivors of IPV, previously at a women's shelter and currently at a community agency as a victim support worker. She is well-versed in trauma- and violence-informed practice and will take all the necessary steps to protect participant safety and well-being. In addition, the assessments will be conducted at the community agency with which the participants are already familiar and where trauma support services are in place and readily available should they be required. We will also develop a series of participant safety protocols that outline how the research coordinator will identify suicidal ideation and risk factors for suicide, participant safety, and child safety and what actions she will take if required. All participants will be undergoing clinical counseling as part of the study and may have received professional support resulting from their trauma and abuse. Nonetheless, completing the testing involved in this study may trigger painful memories and create a triggering state. If the participant expresses any concerns during the data collection that suggest the need for immediate attention, they will be counseled by the research coordinator or participant navigator, both of whom will have strong professional backgrounds supporting survivors of gender-based violence.

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The assessment and intervention administration will be based on the trauma-informed approach (TIA). Research team members will be trained to follow TIA. All interviews and mental health screening instruments will be completed with each participant privately. The mental health screening process will be conducted by the research coordinator who will have to complete specific training and practice with all instruments and interview schedules.

Results

This study is in the testing phase. As of October 2023, we enrolled 6 participants. We anticipate that the CSN rehabilitation intervention will be effective in improving resiliency, QoL, and neurocognitive function in women who have experienced IPV-BI. Furthermore, we also anticipate that this intervention will be feasible in terms of study recruitment, adherence, and retention. This study will also be able to characterize, more generally, neurocognitive and psychopathological consequences in women who have experienced IPV-BI. We will report the results in follow-up papers.

Discussion

Principal Findings

To the best of our knowledge, this will be the first study to systematically investigate the efficacy of an evidence-based, multipillar, interdisciplinary rehabilitation program in improving resiliency, QoL, and neurocognitive functions in women who have experienced IPV-BI. All components of the CSN program are evidence based and have shown a positive impact on QoL in people with TBI and those with various other forms of BIs [26-29,31]. This intervention also aims to take advantage of the neuroplastic benefits of its various components [24,25,29]. In addition, this intervention will be administered based on TIA that addresses traumatic experiences with the goal of reducing symptoms and optimizing therapeutic outcomes [30]. Therefore, we anticipate improvement in resiliency, QoL, and neurocognitive functions with the CSN intervention in women who have experienced IPV-BI. Moreover, we expect that the CSN intervention will be feasible in terms of recruitment, adherence, and retention because it has been successfully implemented to address physical and cognitive impairments in individuals with BI from various causes. Furthermore, the CSN is IPV-BI specific in that it is structured with the addition of TIA, counseling, a participant navigator, and peer support.

This efficacy and feasibility study will help to address the current gap in the intervention study aimed at improving resiliency, QoL, and neurocognitive functions in women who have experienced IPV-BI. Successful implementation will help to support future full-scale comparative studies and randomized controlled trials.

Limitations

The proposed study will not be without limitations. The lack of a comparative control group will be a limitation. Having a comparable control group to an IPV-BI intervention group is a substantial challenge. Furthermore, an IPV-BI–specific gold standard rehabilitation intervention is not available, which makes a comparative study with a control group even more challenging. However, the addition of an appropriate control group would obviously strengthen the outcome of the CSN intervention; therefore, it is a recommendation for future studies. Having limited recruitment sites within a specific geographical region could limit the pool of participants and the generalizability of the findings of this study.

Conclusions

This will be the first intervention study of its kind to examine the impact of a rehabilitation intervention on resiliency, QoL, and neurocognitive function in women who have experienced IPV-BI. If this intervention is successfully implemented and its effectiveness is demonstrated, the findings will not only benefit individual participants and their families but could also have far-reaching implications for policy makers, service seekers, and service providers.

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Data Availability

The data sets generated or analyzed during this study are not publicly available due to the sensitivity of the data but are available from the corresponding author on reasonable request.

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Authors' Contributions

SPA, PvD, and KM conceptualized the study, structured the methodology and intervention and contributed in writing and editing the manuscript. SPA, additionally drafted the paper as the first author. TNS, SNZT, and SP contributed in writing, reviewing, and editing the manuscript.

Conflicts of Interest

KM and PvD are in a personal relationship. SP was employed by ABI Wellness during the development of this project and writing of this manuscript.

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Abbreviations

BEARS: Brain Enhance And Recovery System
BI: brain injury
BISA: Brain Injury Severity Assessment
CSN: community support network
IPV: intimate partner violence
IPV-BI: intimate partner violence–caused brain injury
NFS: nonfatal strangulation
PTSD: posttraumatic stress disorder
QoL: quality of life
TBI: traumatic brain injury
TIA: trauma-informed approach

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Protocol

Daily Time-Use Patterns and Quality of Life in Parents: Protocol for a Pilot Quasi-Experimental, Nonrandomized Controlled Trial Using Ecological Momentary Assessment

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Abstract

Background: The gender gap in time use and its impact on health and well-being are still prevalent. Women work longer hours than men when considering both paid and unpaid (eg, childcare and chores) work, and this gender disparity is particularly visible among parents. Less is known about factors that could potentially mediate or moderate this relationship (eg, work-family conflict and gender role beliefs). Ecological momentary assessment (EMA) allows for the documentation of changes in momentary internal states, such as time use, stress, or mood. It has shown particular validity to measure shorter-term activities (eg, unpaid work) and is thus useful to address gender differences.

Objective: The feasibility of the daily EMA surveys in a parent sample will be examined. The associations between time use, well-being, and stress will be examined, along with potential moderating and mediating factors such as gender, gender role beliefs, and work-family conflict. Finally, the act of monitoring one's own time use, well-being, and stress will be examined in relation to, for example, the quality of life.

Methods: We conducted a quasi-experimental, nonrandomized controlled trial with 3 data collection methods, namely, online questionnaires, EMA surveys, and qualitative interviews. The intervention group (n=64) will participate in the online questionnaires and EMA surveys, and a subsample of the intervention group (n=6-17) will also be invited to participate in qualitative interviews. Over a period of 1 week, participants in the intervention group will answer daily EMA surveys (4 times per day). In contrast, the control group (n=17) will only participate in the online questionnaires at baseline and after 1 week. The following constructs were surveyed: sociodemographic background (eg, age, gender, and household composition; baseline questionnaire); mediators and moderators (eg, gender role beliefs and work-family conflict; baseline and follow-up questionnaires); well-being, quality of life, and trait mindfulness (baseline and follow-up questionnaires); momentary activity and well-being, as well as state mindfulness (EMA); and feasibility (baseline and follow-up questionnaires as well as interviews). We anticipate that participants will regard the daily EMA as feasible. Particular daily time-use patterns (eg, high paid and unpaid workload) are expected to be related to lower well-being, higher stress, and health-related quality of life. These associations are expected to be moderated and mediated by factors such as gender, gender role beliefs, work-family conflict, and social support. Participants in the intervention group are expected to show higher values of mindfulness, well-being, health-related quality of life, and lower stress.

Results: Patient recruitment started in November 2023 and ended in mid April 2024. Data analysis commenced in mid April 2024.

Conclusions: This study aims to provide valuable insights into the feasibility of using EMAs and the potential benefits of activity tracking in various aspects of daily life.

Trial Registration: Open Science Framework 8qj3d; https://osf.io/8qj3d

International Registered Report Identifier (IRRID): PRR1-10.2196/54728

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KEYWORDS

time-use; well-being; parents; ecological momentary assessment; feasibility; health-related quality of life; ambulatory assessment; work-family conflict; gender roles; mixed-methods; sex differences; stress

Introduction

Overview

Despite aspirations for gender equality, the "gender gap" continues to be evident in many areas of daily life, including everyday time use and the associated consequences for health and well-being. During the COVID-19 pandemic, this divergence was particularly evident as many women (eg, due to school closures and working from home) felt increased pressures from 2 sides, namely work and family [1]. Overall, time use is an important determinant of health and quality of life. For example, long work hours [2,3], physical and inactive lifestyles [4,5], and informal caregiving for family members [6] are associated with poorer quality of life.

Women, like men, now spend most of their day doing paid work; however, women also do most of the housework, childcare, and unpaid care work [7]. According to Coltrane [8], women's share of housework is double that of men's. The largest gender differences are seen among those with children of preschool age [9]. As a result, when paid work and this so-called unpaid work are summed, women (mean 6:44-9:13 hours) work significantly longer hours than men (mean 6:36-8:07 hours) [10]. In terms of leisure time, fathers report more free time than mothers, which is made up of longer uninterrupted periods of rest and is also less often followed by childcare [11]. Gender differences in time use and the impact on health and well-being have been well established in previous research [6,7,10,12,13]. Less is known about how gender and other factors could potentially mediate or moderate the relationship between time use and health and well-being.

Theoretical Frameworks

There are several theoretical models that explain how people use their time and how this affects their quality of life. One of these theories is the conservation of resources theory [14], which states that people use their time in a way that preserves or enhances their resources (eg, energy, money, or social support). Instead, the time availability theory [15] states that time budgets are dependent on the availability of time and demands in a particular role, while the relative resources theory [16] assumes that time budgets are set depending on the relative power someone has in a relationship or organization. In addition, the work-family conflict model [17] states that time budgets are divided between work and family based on conflicts and demands. The gender perspective—which is often used to complement these theories—is concerned with how gender roles influence time use. For example, the theories of "doing gender" [18] or "gender performativity" [19] highlight how gender roles are constructed through actions and behaviors.

Survey Methods of Time Use

Generally, diaries are the most common method to measure time use [20,21]. In some cases, self-reports are combined with objective physiological measurements; for example, sleep and wake times are recorded by a motion sensor and well-being is recorded in a diary throughout the day [22]. Ambulatory assessment, such as ecological momentary assessment (EMA), is the measurement of, for example, the mood, symptoms, and activities of individuals in real time and in their natural environment. An advantage of EMA is that it can be used in any situation (eg, on a person's own smartphone) and allows for the documentation of changes in momentary internal states, such as stress, tension, or mood [23]. Time-use research using EMA has primarily examined individual activities (eg, physical activity [24,25]), yet this methodology has rarely been used to study time-use patterns of different daily activities [26,27].

This is a key research gap because time-use survey techniques differ in that standard survey questionnaires more accurately and reliably measure longer-lasting activities such as paid work, whereas EMA through smartphones is more reliable for shorter-term and less frequent activities (eg, errands and housework) [27]. This means that research questions concerning gender differences in time-use patterns (especially with regard to unpaid activities such as housework and childcare) can be measured more precisely with EMA. Nevertheless, this has rarely been implemented in previous research.

Moreover, introducing EMA to daily activities might focus one's attention on the present moment, thus increasing state mindfulness. Being present and bringing attention to the present moment is a key component of mindfulness [28,29]. Mindfulness is positively associated with higher levels of life satisfaction, optimism [30], and empathy [31]. It is also negatively associated with, for example, neuroticism [31,32] or difficulties in emotion regulation [33]. Hence, it is likely that regular reflection of and recording of the current activity and associated affect as a momentary and passing state depicts a form of mindfulness exercise [34]. As an exploratory hypothesis, the association between trait, state mindfulness, and daily activities will be examined.

Research Questions

The planned study will address the relationship between time-use patterns, quality of life, and mindfulness, as well as momentary well-being and stress, with parents as the target group. The theoretical models and factors describing this relationship often neglect the type, duration, and sequence of activities; therefore, they will be complemented using the EMA method.

The EMA method has been used in the target group of parents only to measure specific activities (eg, activities with their own children like supervision and playing together) [35], whereas

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the measurement of global, daily time use combined with well-being has been used in this context only using student samples [26,27]. Thus, the feasibility of using the EMA methodology with a sample of parents will be examined.

Further, it will be investigated whether the monitoring of daily time use coupled with well-being and stress leads to a change in quality of life and mindfulness. In order to exclude the possibility that these daily mindfulness exercises alone can lead to a change in these constructs, a control group—that does not complete the daily surveys but only the baseline and follow-up questionnaires—will be included.

In summary, the following research questions are examined:

1. How do parents assess the feasibility of the study design?
2. To what extent do mothers' and fathers' time use influence well-being and feelings of stress, and vice versa? Does social support represent a mediator for the above association? Do gender, gender role beliefs, and work-family conflict represent moderators of the abovementioned associations?
3. To what extent does monitoring one's own time use, well-being, and stress perception influence (1) the quality of life and (2) mindfulness?

Methods

Study Design

As this is a pilot study, a quasi-experimental, nonrandomized controlled trial with 3 data collection methods (ie, an online questionnaire [baseline and follow-up], an EMA survey, and interviews) was chosen. The intervention group will participate in the online questionnaires and EMA surveys, while the control group will only participate in the online questionnaires. A subsample of the intervention group will be invited to participate in interviews. The added benefit of recruiting a control group is to investigate whether daily monitoring of time use, well-being, and stress levels has an impact on overall quality of life and mindfulness.

Participant Characteristics

Sample Description

The sample consists of fathers or mothers of at least 1 biological or adopted child who is younger than 18 years of age and living in the household. Participants are included irrespective of sexual orientation and relationship status. A completed informed consent form is also a requirement for inclusion in the study.

The following exclusion criteria will be applied: if participants (1) are younger than 18 years of age, (2) have one or more children with a chronic illness or disability, (3) have one or more foster child or children, and (4) do not own an Android smartphone (intervention group only). Due to technical reasons, only Android users can be included in the intervention group, and since families with a child with a chronic illness differ considerably in their daily routine from families without [36], we decided to exclude them.

Sample Size

The minimum sample size for the intervention group was calculated using G*Power (version 3.1.9.6; Erdfelder, Faul, and Buchner; ANOVA, repeated measures, within group, effect size [well-being]=0.25, α=.05, power=0.80, and correlation among repeated measures=0.5), and the target sample size is 64 participants.

For the control group, the target sample size is 17 participants. The sample size was also calculated using G*Power (ANOVA, repeated measures, within-between group, effect size [mindfulness]=0.25, α=.05, power=0.80, and correlation among repeated measures=0.5).

Regarding the number of participants for the interviews, the determination of the number of cases is based on the theoretical concept of data saturation [37]. This means that the sample size should be chosen according to how many interviews are necessary to provide significant new insights into the subject of the study [38,39]. Recommendations on the number of interviews to conduct until data saturation is reached vary from 5 to 60 interviews [37]. Because data saturation in homogeneous samples can be achieved with 6 to 17 cases [37,40], the target subsample size for interviews for this study is 6-17 participants.

Incentives

Intervention Group

Participants will be offered an incentive of €35 (US $37.91) for participating in the questionnaires and daily EMA surveys, with an additional €15 (US $16.25) if they complete at least 80% of the daily surveys (ie, €50 [US $54.15] in total). If participants in the intervention group also take part in an interview, they will be offered an additional €10 (US $10.83).

Control Group

Participants taking part in the control group, that is, the baseline and final questionnaire, will be offered an incentive of €20 (US $21.66).

Procedure and Measures

Participant Recruitment and Inclusion (T0)

Recruitment will take place through the snowballing method, in which the study will be advertised by means of leaflets through, for example, contacts with parents, parent groups, and relevant organizations (eg, family service centers and counseling centers). An overview of the data collection procedure can be found in Figure 1. An overview of the measures used in the questionnaires and during the EMA surveys can be found in Table 1. See the preregistration for the full questionnaires and interview guides [41].

The study will be advertised through leaflets. These contain a link (eg, by means of a QR code) to a short questionnaire, in which the contact information of the interested parties is collected. This questionnaire is carried out on an online survey platform (eg, SoSci Survey).

Afterward, an appointment is made by phone or email to introduce the study. This takes place digitally (eg, by telephone or video call). First, participants are informed about the study

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procedure and design. The inclusion and exclusion criteria are checked, and if excluded, they are informed of the reasons for their nonparticipation. If participants do not own an Android smartphone but fulfill all other inclusion criteria, they will be invited to the control group instead. If participants meet the inclusion criteria, they will be asked to download the movisensXS app (movisens GmbH; the survey tool of the EMA part of the study) on their personal smartphone and receive an introduction to its use. During the conversation, they will be given the opportunity to ask questions about the background and the study process. Participants are then sent an email with the link, where they provide written, informed consent. Only then can they access the links to begin the study.

Figure 1. Overview of data collection. EMA: ecological momentary assessment.

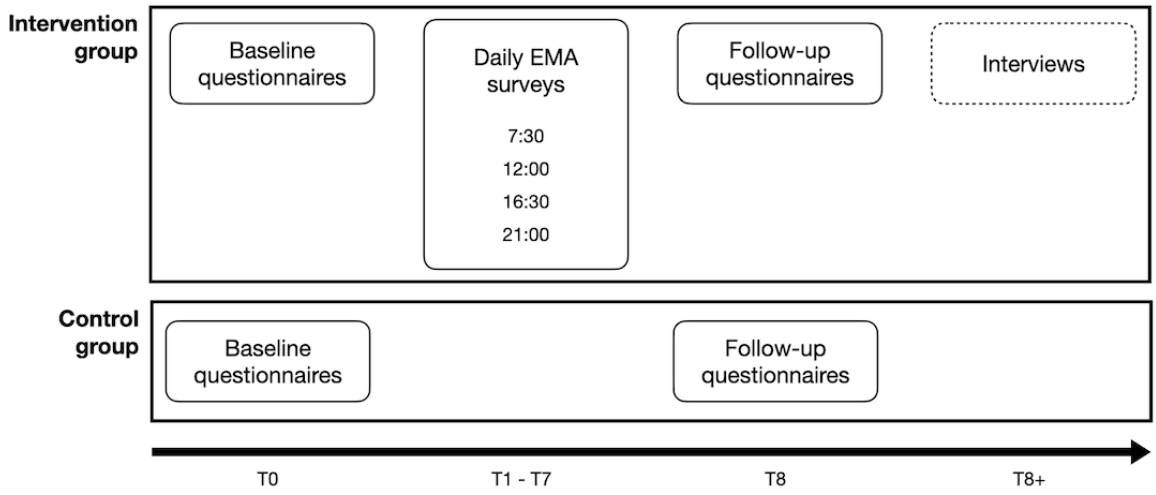

Table 1. Overview of the measures for the questionnaires and ecological momentary assessment (EMA) surveys.

Survey time point or variable and questionnaires	T0	T1-T7	T1-T7 end-of-day questions	T8
Questionnaires				
Expected feasibility[a]	✓			
Sociodemographic background[a]	✓			
Gender role beliefs[a]	✓			
Work-family conflict[a]	✓			
Social support[a]	✓			
Quality of life, well-being, and stress[a]	✓			✓
Trait mindfulness[a]	✓			✓
Feasibility[b]				✓
EMA surveys				
Current well-being and stress[b]		✓		
Time use (current and since last survey)[b]		✓		
Type of day[b]			✓	
Daily social support[b]			✓	
State mindfulness[b]			✓	

[a]Relate to both the intervention and control groups.

[b]Relate only to the intervention group.

Baseline Questionnaires (T0)

The baseline questionnaires will also be conducted on an online survey platform (eg, SoSciSurvey). Participants then complete the baseline questionnaires (T0); both the control and intervention groups will participate in the baseline questionnaire survey.

Participants will be asked, through open-ended questions, about the expected feasibility of the EMA surveys as well as their

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sociodemographic background (eg, age, gender, education and employment status, household income and size, partnership status, and number and age of children). In addition, gender role beliefs are surveyed using the Scale of Gender Role Attitudes [42], and work-family conflict is surveyed using the Work and Family Conflict Scale [43]. Further, social support is measured with the brief form of the Perceived Social Support Questionnaire (F-SozU K-6) [44], quality of life is measured with the World Health Organization-Quality of Life-8 (WHO-QoL-8) [45], affective well-being is measured with 3 items to assess positive affect (happy, relaxed, and satisfied) and 2 items to assess negative affect (nervous, downhearted, and worried) [46], and stress is measured with the global measure of perceived stress [47]. Finally, trait mindfulness is assessed with the Five Facet Mindfulness Questionnaires (FFMQ-D) [48].

EMA (T1-T7)

Overview

The intervention group will begin the EMA surveys after the baseline questionnaire. The EMA part of the study will be conducted through the movisensXS platform, which specializes in ambulatory assessment software. For graphic examples of the user interface, refer to movisensXS [49].

Over a 7-day period, participants will be surveyed 4 times per day (T1-T7). The survey times are 7:30 AM, 12 PM, 4:30 PM, and 9 PM, plus a tolerance period of 30 minutes; any later and the survey time point is considered not completed. Participants will receive push notifications at each survey time point and will be asked to complete the appropriate measurement instruments. The daytime surveys take approximately 5 minutes to complete, while the evening survey takes approximately 8 minutes.

Since 1 of the main objectives of the pilot study is to test the feasibility of the EMA design in a parent sample, an initial evaluation of feasibility (research question 1) will be conducted with the data from the first participants (n≤16). For this, the questions addressing feasibility, that is, the open-ended questions in the follow-up questionnaires and the interviews, will be examined. Subsequently, the study design (eg, survey times, item order, and item wording) will be adjusted if necessary. Therefore, a larger number of participants will be recruited for piloting.

EMA Questions

In the EMA surveys, participants are asked about their current well-being, feelings of stress, and current activities, as well as activities since the last survey at each of the 4 daily survey time points.

Well-being and stress perception are asked comparably to the baseline questionnaire, only with reference to the current state. Affective well-being is assessed with 4 items [46], cognitive well-being is assessed with the life satisfaction item of the WHO-QoL-8 [45], and stress perception is assessed with the global measure of perceived stress [47].

Participants can select the following categories, according to Tomczyk et al [6], to determine activities: (1) work; (2) housework, errands, and repairs; (3) childcare and organizing; (4) unpaid care work; (5) study and education; (6) leisure, physical activity, and hobbies; and (7) self-care. Multiple selections of activities at 1 point are possible. Participants first report the current activity as well as when they have been doing this activity. Then they are asked to recreate the sequence since the last survey point, that is, “we are interested in what you did between the last survey and now,” “what did you do afterwards,” and “for how long?”

In the last survey of the day, in addition to the questions mentioned above, so-called “end of day” questions are asked. The type of day (eg, ordinary working day or vacation day) is asked using the item from the Harmonised European Time Use Surveys [50]. The received and desired social support of significant others [51] is surveyed. Finally, the 3 dimensions of state mindfulness—present-moment attention, acting with awareness, and nonjudgmental acceptance—are measured using the Multidimensional State Mindfulness Questionnaire [52].

Follow-Up Questionnaire (T8)

One week later, both the intervention group and the control group will receive an email with the link to the follow-up questionnaire. This will take place on the same online survey platform (eg, SoSciSurvey).

At follow-up, social support (F-SozU K-6) [44], quality of life (WHO-QoL-8) [45], affective well-being [46], stress [47], and trait mindfulness (FFMQ-D) [48] will be measured again. The intervention group will be further asked questions about the feasibility of the EMA survey. For this, previous studies were used as a reference (eg, [26,53,54]). Example items include “Did using the EMA survey make them more aware of their thoughts, feelings, and behaviors?” (inspired by Businelle et al [53]) or “In my opinion, the questions were understandable” (inspired by Spook et al [55]).

Interviews (T8+)

Finally, a subsample of the intervention group will be invited for an interview (eg, by telephone or video call) lasting 20-30 minutes. The interview guide was developed using previous qualitative research focusing on usability and feasibility evaluations [56,57] and adapted to the present procedure (eg, feasibility of specific time points).

The interviews will address the feasibility of the EMA survey method and study design in more detail. The structure and content of the interviews are as follows:

1. General assessment of the study design
2. Time expenditure and integration into everyday life
3. Contents of the EMA surveys
4. Effects of the study
5. General and conclusion

Analyses

Various between-person factors (eg, age, gender, family composition, and work situation) act as descriptive measures of the sample.

The quantitative material of the questionnaire survey will be analyzed using descriptive analyses to answer the first research

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question (feasibility of the design). On the other hand, for the evaluation of the open-ended questions in the baseline survey and the interview material, the content analytic approach of Kuckartz [58] is applied. The analysis and coding of the texts or transcripts will be done independently by 2 people. The text sequences or sense units are coded, and categories are derived from these contents or assigned to existing categories. The resulting category systems enable structured processing of the contents.

To answer the second research question (relationship between time use and well-being and stress), variance-analytic and regressive models with repeated measures and multilevel design will be used to analyze within-person change in baseline and follow-up questionnaires as well as to model the sequence of time use, well-being, and stress within the 7-day measurement. In addition, moderator and mediator variables will be considered (eg, gender role beliefs, social support, and work-family conflict).

To answer the third question (influence of monitoring of own time use, well-being, and stress perception on quality of life and mindfulness), within- and between-person models will be used to look at potential differences in the intervention and control groups.

Ethical Considerations

The pilot study was approved by the Ethics Committee of the University Medicine Greifswald in July 2022 (BB 113/23) and will be conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, its later amendments, or comparable ethical standards. This study has been preregistered on the Open Science Framework in November 2023 [59]. Informed, verbal as well as written consent is obtained from each participant; they are informed about how their data will be used and stored, as well as about their pseudonymized participation, and their ability to withdraw from the project at any time without any repercussions will be made clear to them. Ethical guidelines and General Data Protection Regulation will be followed concerning data usage and storage.

Expected Outcomes

We anticipate that participants will regard the daily EMA as feasible. Particular daily time-use patterns (eg, high paid and unpaid workload) are expected to be related to lower well-being, higher stress, and health-related quality of life. These associations are expected to be moderated and mediated by factors such as gender, gender role beliefs, work-family conflict, and social support. Participants in the intervention group are expected to show higher values of mindfulness, well-being, and health-related quality of life and lower stress. Furthermore, we will report on dropout rates and reasons for dropout.

Results

Patient recruitment started in November 2023 and ended in mid April 2024. Data analysis commenced in mid April 2024.

Discussion

This study aims to provide valuable insights into the feasibility of using the EMA method with a sample of parents. A strength of the study design is the mixed methods approach, which combines online questionnaires, EMA surveys, and qualitative interviews. In the online surveys and qualitative interviews, we survey parents' acceptance, challenges, barriers, facilitators, and feasibility of implementing EMAs in their everyday routine. This provides quantifiable feedback regarding the feasibility of the study design and is enriched by a subgroup of participants' being able to speak in greater detail and with their own words. Studies with student samples suggest that daily diary methods more accurately and reliably measure longer-lasting activities such as paid work, whereas EMA through smartphones is more reliable for shorter-term and less frequent activities (eg, errands and housework) [27]. We examine how feasible the EMA method is in a sample (ie, parents) that is highly stressed, faces a large burden, and is notably strapped for time. Based on our findings, we will be able to make recommendations for the effective use of EMAs in parent samples.

The study is designed to provide insights into the associations between time use, well-being, and stress, as well as potential moderating and mediating factors such as gender role beliefs and work-family conflict. By using sequence analysis, we can determine which activities have a significant impact on stress and well-being. This information can then be used to recommend daily practices from a prevention perspective. Additionally, we recognize the relevance of gender issues and aim to explore gender and gender role-based differences in daily activities and how these relate to cognitive and affective states. Furthermore, we explore the effect of activity tracking on mindfulness and whether daily tracking can assist in guiding attention and promoting mindfulness or, conversely, increase perceived stress, particularly in individuals who are already stressed.

However, it is important to acknowledge the limitations of this study. It is a pilot study, and therefore, any associations found between variables should be interpreted with caution. Future research could explore dyadic effects between partners and also examine partner relationships. A further focus could be on specific target groups, such as individuals with high stress levels (eg, parents of children with a disability or chronic illness), who may particularly benefit from time management training interventions or planning interventions.

Overall, this study aims to contribute valuable insights into the feasibility of using EMAs and the potential benefits of activity tracking in various aspects of daily life. The implications of this study may contribute to the design of future mobile apps that track and use daily activities for purposes such as improving well-being, activity planning, or time management.

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Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

EMA: ecological momentary assessment
FFMQ-D: Five Facet Mindfulness Questionnaires
F-SozU K-6: Perceived Social Support Questionnaire
WHO-QoL-8: World Health Organization-Quality of Life-8

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Protocol

Evaluation of Ambient Sensor Systems for the Early Detection of Heart Failure Decompensation in Older Patients Living at Home Alone: Protocol for a Prospective Cohort Study

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Abstract

Background: The results of telemedicine intervention studies in patients with heart failure (HF) to reduce rehospitalization rate and mortality by early detection of HF decompensation are encouraging. However, the benefits are lower than expected. A possible reason for this could be the fact that vital signs, including blood pressure, heart rate, heart rhythm, and weight changes, may not be ideal indicators of the early stages of HF decompensation but are more sensitive for acute events triggered by ischemic episodes or rhythm disturbances. Preliminary results indicate a potential role of ambient sensor–derived digital biomarkers in this setting.

Objective: The aim of this study is to identify changes in ambient sensor system–derived digital biomarkers with a high potential for early detection of HF decompensation.

Methods: This is a prospective interventional cohort study. A total of 24 consecutive patients with HF aged 70 years and older, living alone, and hospitalized for HF decompensation will be included. Physical activity in the apartment and toilet visits are quantified using a commercially available, passive, infrared motion sensing system (DomoHealth SA). Heart rate, respiration rate, and toss-and-turns in bed are recorded by using a commercially available Emfit QS device (Emfit Ltd), which is a contact-free piezoelectric sensor placed under the participant's mattress. Sensor data are visualized on a dedicated dashboard for easy monitoring by health professionals. Digital biomarkers are evaluated for predefined signs of HF decompensation, including particularly decreased physical activity; time spent in bed; increasing numbers of toilet visits at night; and increasing heart rate, respiration rate, and motion in bed at night. When predefined changes in digital biomarkers occur, patients will be called in for clinical evaluation, and N-terminal pro b-type natriuretic peptide measurement (an increase of >30% considered as significant) will be performed. The sensitivity and specificity of the different biomarkers and their combinations for the detection of HF decompensation will be calculated.

Results: The study is in the data collection phase. Study recruitment started in February 2024. Data analysis is scheduled to start after all data are collected. As of manuscript submission, 5 patients have been recruited. Results are expected to be published by the end of 2025.

Conclusions: The results of this study will add to the current knowledge about opportunities for telemedicine to monitor older patients with HF living at home alone by evaluating the potential of ambient sensor systems for this purpose. Timely recognition of HF decompensation could enable proactive management, potentially reducing health care costs associated with preventable emergency presentations or hospitalizations.

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Trial Registration: ClinicalTrials.gov NCT06126848; https://clinicaltrials.gov/study/NCT06126848
International Registered Report Identifier (IRRID): PRR1-10.2196/55953

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KEYWORDS

heart failure; home telemonitoring; digital health; biomarker; ambient sensor system

Introduction

The results of telemedicine intervention studies in patients with heart failure (HF) to reduce rehospitalization rate and mortality by early recognition of HF decompensation are encouraging [1-7]. However, benefits have been found to be lower than expected. Therefore, according to the European Cardiology Guidelines, home telemonitoring (HTM) of patients with HF is a class IIb indication, while in the American Guidelines, there is no recommendation for HTM [8,9]. One reason that previous studies with HTM have failed to show greater benefits may be that vital signs, including blood pressure, heart rate, heart rhythm by rhythm strips, and weight changes, may not be ideal indicators of the early stages of HF decompensation but may be more sensitive for acute events such as ischemic episodes or rhythm disturbances.

Recently, early detection of impending HF hospitalization through continuous wearable monitoring analytics has been described [10]. However, wearables are difficult to use in some patient populations, as good compliance is essential. This can be particularly challenging for older adults or individuals with limited digital literacy or cognitive impairment, as devices need to be recharged daily and have rather small screens and complex user interfaces [11].

Ambient sensor systems (ASSs) are increasingly used to monitor older people in their apartments not only for safety but more recently for monitoring physiological factors such as physical activity and detection of health problems such as frailty, cognitive impairment, depression, social isolation, sleep, pulmonary emboli, heart rhythm disturbances, and COVID-19–related health deteriorations [12-17]. Preliminary data indicate that an ASS in the home of older patients with HF living alone has the potential to indicate early stages of decompensated acute HF [18].

The aim of this prospective interventional cohort study is to evaluate the sensitivity and specificity of a set of ASS-derived digital biomarkers with the highest potential for early detection of HF decompensation, allowing timely intervention to prevent serious health deterioration and rehospitalization.

Methods

Study Design and Participants

This is a prospective, interventional cohort study. In total, 24 consecutive patients living alone at their homes and with hospitalization for HF decompensation at the 2 Solothurner Spitäler AG secondary care hospitals in Olten and Solothurn (Switzerland) will be included.

The study inclusion criteria are current hospitalization for HF decompensation, aged 70 years and older, left ventricular ejection fraction (LVEF) <50%, treatment with diuretics, New York Heart Association classification II or III, living alone, willingness to participate with informed consent, and agreement for follow-up appointments in the hospital at 3 and 6 months.

Exclusion criteria include major depression (Patient Health Questionnaire-9 score>9) or being on hemodialysis. In addition, patients with a left ventricular assist device or those who had undergone coronary revascularization or cardiac resynchronization therapy implantation within 28 days before the index event of HF decompensation or have been scheduled for such interventions are excluded from the study.

Ethical Considerations

The study will be conducted based on the principles expressed in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use—Good Clinical Practice, and the Human Research Act after protocol approval by the regional ethics committee (Ethikkommission Nordwestschweiz; Swissethics BASEC ID 2023-02138). Patients will provide written informed consent. Participants can withdraw from the study at any time during the study process. Data that were collected until withdrawal will still be analyzed. Data will be collected by specially trained research staff and entered into a password-protected data environment. Each patient will be attributed a study-specific patient identifier (PID). For statistical analysis, these data sets will be merged using the PID as an identifier. At the end of the data acquisition, including follow-up, patient data will be coded using the PID, and the database will be locked. Coding using the PID will be done at the earliest time point after the completion of follow-up data collection. Data generation, transmission, storage, and analysis of health-related personal data within this study will follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art 5. Health-related personal data captured during this study is strictly confidential, and disclosure to third parties is prohibited. Participants will be compensated for costs resulting from travel expenses due to follow-up visits in the hospital. For study participation, no costs incur for participants or health insurance companies.

Baseline Assessment

The following baseline parameters will be evaluated at hospital entry: age, gender, BMI, medical history, diagnosis (ischemic or nonischemic origin of cardiomyopathy), current medication, as well as N-terminal pro b-type natriuretic peptide (NT-proBNP) and 2D echocardiography after decongestion. LVEF will be calculated according to current guidelines [19].

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A 6-minute walking test and isometric hand strength test (handgrip test) will be performed before hospital discharge.

Ambient Sensor System

Physical activity in the apartment and bathroom visits are quantified using a commercially available passive infrared (PIR) motion sensing system and visualized on a dashboard (DomoHealth SA). The system includes PIR motion sensor units for each room that is used in the home and 2 magnetic door sensors for entry-door and fridge-door openings that communicate wirelessly with a base unit (Figure 1). Motion activation is measured with a resolution of 1 second. The absence of motion is notified when no motion is recorded for 30 seconds. All sensors communicate with the base unit through an encrypted radiofrequency protocol. The base unit collects the data and sends them to the cloud in real time using the Global System for Mobile Communications network. The participants' kitchen, living room, entrance, bedroom, and bathroom will be equipped with 1 PIR sensor based on the room size of the patients' apartment. Motion signals are collected room by room and combined as the total activity in the apartment. Normalized daily PIR sensor activity refers to the time the PIR sensors are registering activity at home, normalized by the total time spent at home for a given day. It is thus corrected for the influence of time spent out of home. A bathroom visit is identified as such if, in a 30-minute window, at least 1 sensor firing in the bathroom is recorded. Nighttime is defined as the period from 9:30 PM to 8 AM (local time) based on the daily activity habits of the patients. Heart rate, heart rate variability, respiration rate, and presence are recorded in bed with the commercially available Emfit QS device (Emfit Ltd), a contact-free piezoelectric sensor placed under participants' mattresses. These sensors use thin quasi-piezoelectric films that measure even light pressure differences produced by the beating heart. The Emfit QS sensor will be fixed under the participants' mattress, in proximity to the chest. The device requires no further manual intervention. Data will be transmitted to the cloud in real time through local Wi-Fi and, subsequently, the Global System for Mobile Communications network. The device extracts a variety of vital signs, including heart rate, respiration rate, heart rate variability, movements in bed, sleep duration, and sleep onset delay. Recent results suggest that this sensor can accurately measure heart rate and respiration rate [20]. The reliability and potential of the use of ASS-derived digital biomarkers as indicators for health conditions and diseases have been shown in several publications by members of our research group [12-18,21-25].

Sensor data are then visualized on a dedicated dashboard (entry door openings, activity in different rooms, fridge openings, bathroom visits, and bed presence), and the DomoCare (DomoHealth SA) app (heart rate, respiration rate, sleep quality, and preventive warnings) can be used by the investigator team to easily monitor the health and behavior of a system user. Sensor-derived digital biomarkers are summarized in Table 1.

Figure 1. Graphical representation of the ambient sensor system used in this study: (1) alarm button, (2) door sensor, (3) Emfit QS bed sensor, (4) passive infrared motion sensor in each room (including bathroom), and (5) interphone.

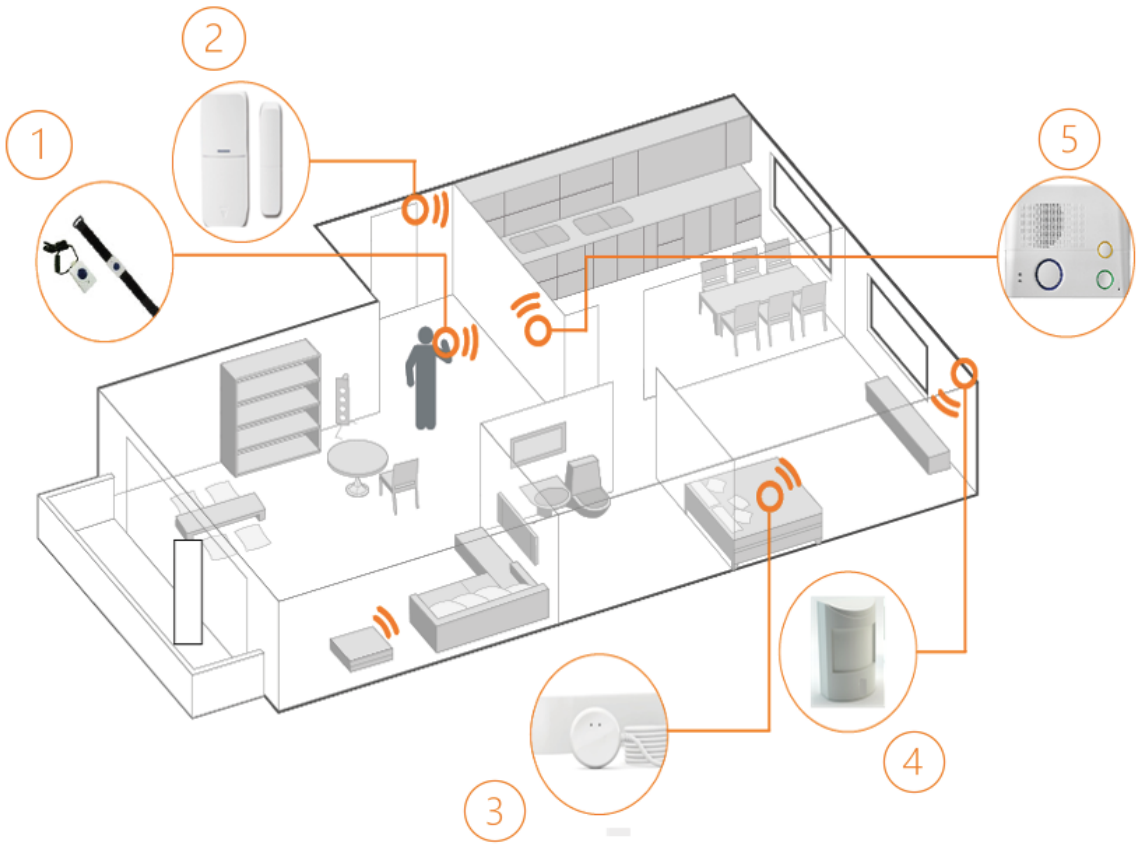

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Table 1. Ambient sensor–derived digital biomarkers.

Biomarker	Sensor
Disease-specific digital biomarker	
Number of toilet visits at night	PIR[a] motion sensor+Emfit QS bed sensor
Average heart rate in bed	Emfit QS bed sensor
Average respiration rate in bed	Emfit QS bed sensor
Unspecific digital biomarker	
Daily activity	PIR motion sensor
Number of toss and turns in bed	Emfit QS bed sensor
Time spent in bed	Emfit QS bed sensor
Number of refrigerator openings	Contact sensor

[a]PIR: passive infrared.

Outcome Assessment

Ambient Sensor–Derived Digital Biomarkers

Based on previous experience from the use of the system in older patients with HF, the changes (based on a 1-week moving average) of the measured parameters (presented in Table 2) over 3 weeks will be used as potential indicators of HF deterioration.

Table 2. Potential indicators of heart failure deterioration.

Indicators	Values
PIR[a] motion sensor–derived daily activity	–1000 units or –30%
Time spent in bed	+20%
PIR motion sensor–derived number of toilet visits at night	+30%
Emfit QS bed sensor–derived number toss and turns at night	+30%
Emfit QS bed sensor–derived average heart rate (night)	+3 bpm with β-blocker or +6 bpm without β-blocker
Emfit QS bed sensor–derived average respiration rate increase (night)	≥5 per minute

[a]PIR: passive infrared.

Indicators for Significant Health Deterioration

If the dashboard reports relevant changes, as described before, in at least 1 specific and 2 unspecific digital measures or 2 specific measures, the patient will be contacted and called in for a visit by the investigator team to check for changes from the last visit. We will use an NT-proBNP increase of >30% compared to the measurement after recompensation at hospital discharge as confirmation for health deterioration. This will be called successful event detection for the ASS or the respective digital biomarker [26].

Primary Outcome

The primary outcome of the study will be the sensitivity and specificity of different ambient sensor–derived digital biomarkers to recognize HF decompensation (defined as an NT-proBNP increase of ≥30%).

Secondary Outcome

The secondary outcomes include outcome data such as the total number of rehospitalizations for HF decompensation, the total number of HF decompensations requiring medical intervention, and cardiovascular and all-cause death over the follow-up period (Table 3). We will also evaluate the quality of life measured through the Kansas City Cardiomyopathy Questionnaire, as well as functional status (6-minute walking test and handgrip strength test) and changes in NT-proBNP values at follow-up visits after 3 and 6 months.

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Table 3. Timeline of follow-up data.

Outcome	Baseline	3 months	6 months
LVEF[a]	✓		
NT-proBNP[b]	✓	✓	✓
6MWT[c]	✓	✓	✓
Handgrip test	✓	✓	✓
KCCQ[d]	✓	✓	✓

[a]LVEF: left ventricular ejection fraction.

[b]NT-proBNP: N-terminal pro b-type natriuretic peptide.

[c]6MWT: 6-minute walking test.

[d]KCCQ: Kansas City Cardiomyopathy Questionnaire.

Statistical Analysis

There are no previous data to be used for a regular power calculation. The selected number of 24 study patients is based on experience from a previous study including a similar patient population with hospitalization for HF decompensation. This study showed that approximately 30% of HF decompensation with rehospitalization without HTM intervention is to be expected within 6 months after hospital discharge in this patient population [27].

We will count the true-positive and false-positive indicators for a significant event (>30% increase of NT-proBNP) for the calculation of the sensitivity and specificity of the respective digital biomarkers.

The completion of the study will be achieved if the number of 24 patients has been reached or if an interim analysis of the first 10 patients shows sensitivity or specificity of the digital biomarkers for impending HF decompensation of ≤60% at the 3-month evaluation. A timeline of the study procedure is provided in Figure 2.

Figure 2. Timeline of the study procedure. HF: heart failure.

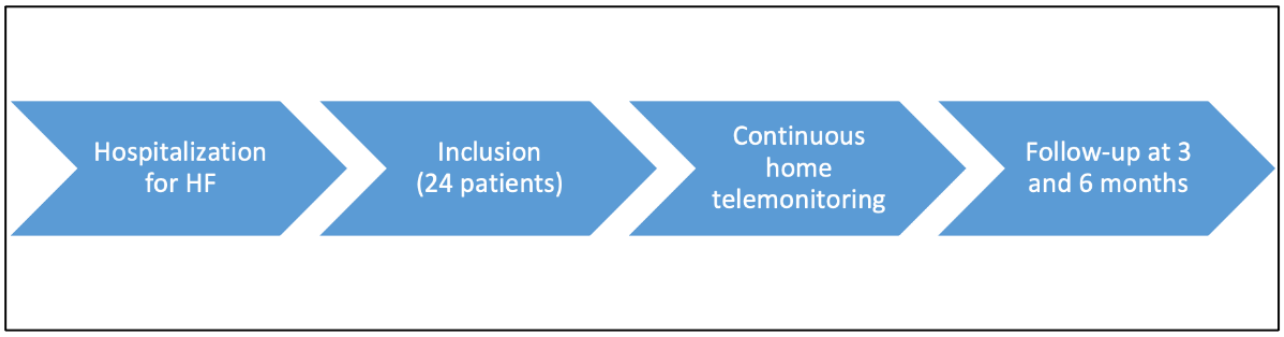

Results

The study is in the data collection phase. Study recruitment started in February 2024. Data analysis is scheduled to start after all the data are collected. As of manuscript submission, 5 patients have been recruited. Results are expected to be published by the end of 2025.

Discussion

What Does the Study Offer?

The use of telemedicine with home monitoring of patients with HF has been well studied under various circumstances [1-7,28-30]. In Germany, telemedical surveillance of patients with HF is even covered by health insurance. Especially in patients with chronic disease, where a regular follow-up is beneficial, telemedicine seems to be a favorable way of patient management due to the possibility to detect health deterioration in the early stages. In terms of chronic HF, the worsening of HF symptoms or ultimately HF decompensation could be intercepted by regular telemedical follow-up visits with the possibility of making early adjustments to the therapy and through that potentially preventing hospital admissions. Remote patient management includes observation and determination of disease seriousness by patient feedback and, for example, the collection of data on vital parameters (eg, heart rate, blood pressure, blood oxygen saturation, and bodyweight) and activity status. However, the commonly used approach to telemedicine in patients with HF includes self-measurements of blood pressure, heart rate, single-lead electrocardiogram, and body weight, which carries a significant risk of noncompliance.

This is to our knowledge the first prospective study investigating ASS-derived digital biomarkers in patients with HF. Contact-free ASS has the advantage that they can be unrestrictedly used even in a patient population with moderate to severe cognitive impairment as they bypass user-dependent sources of error [21]. Clinical signs of HF decompensation include shortness of breath, rhythm disturbances, fatigue and weakness, reduced ability to exercise, edema, and nycturia. Most of these can be detected by ASS, and associated signals

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or a combination of them may be used as digital biomarkers for HF decompensation.

Preliminary data have been promising in the detection of significant health deterioration using unobtrusive ASS. This study offers insights into the effectiveness of the system to detect HF decompensation in the context of an older patient population with HF who are particularly at risk for frequent HF decompensations and rehospitalizations.

Limitations

A prospective cohort is most accurate for discovering predictive biomarkers. However, this study has several limitations. First, these markers or combinations must be validated internally and externally. Second, the 2-center nature of this study may imply selection bias. A third limitation of the study, concerning primarily the use of ASS, is that its operating area is limited to patients who live alone. Patients who live in multiperson households may display different behaviors within the residential environment. This complicates the generalizability of the investigated digital biomarker thresholds to other HF populations. The small sample size is based on the "proof-of-concept" design of this study.

Conclusions

This study aims to provide a new set of ASS-derived digital biomarkers for early recognition of HF decompensation in an older population with HF with reduced LVEF. Accurate prediction of impending HF decompensation will allow for proactive management of patients with HF, with the possibility to reduce HF-related worsening of health conditions and thus reduce health care costs associated with preventable emergency department presentations or even hospitalizations. If the "proof-of-concept" is positive, the concept of using ASS-derived biomarkers for early detection of signs of HF decompensation should be further investigated in larger prospective studies.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

PB works for domo.health, one of the manufacturers of sensor systems used in the study.

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Abbreviations

ASS: ambient sensor system
HF: heart failure
HTM: home telemonitoring
LVEF: left ventricular ejection fraction
NT-proBNP: N-terminal pro b-type natriuretic peptide
PID: patient identifier
PIR: passive infrared

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Protocol

Social Media Promotion of Health Tests With Potential for Overdiagnosis or Overuse: Protocol for a Content Analysis

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Abstract

Background: In recent years, social media have emerged as important spaces for commercial marketing of health tests, which can be used for the screening and diagnosis of otherwise generally healthy people. However, little is known about how health tests are promoted on social media, whether the information provided is accurate and balanced, and if there is transparency around conflicts of interest.

Objective: This study aims to understand and quantify how social media is being used to discuss or promote health tests with the potential for overdiagnosis or overuse to generally healthy people.

Methods: Content analysis of social media posts on the anti-Mullerian hormone test, whole-body magnetic resonance imaging scan, multicancer early detection, testosterone test, and gut microbe test from influential international social media accounts on Instagram and TikTok. The 5 tests have been identified as having the following criteria: (1) there are evidence-based concerns about overdiagnosis or overuse, (2) there is evidence or concerns that the results of tests do not lead to improved health outcomes for generally healthy people and may cause harm or waste, and (3) the tests are being promoted on social media to generally healthy people. English language text-only posts, images, infographics, articles, recorded videos including reels, and audio-only posts are included. Posts from accounts with <1000 followers as well as stories, live videos, and non-English posts are excluded. Using keywords related to the test, the top posts were searched and screened until there were 100 eligible posts from each platform for each test (total of 1000 posts). Data from the caption, video, and on-screen text are being summarized and extracted into a Microsoft Excel (Microsoft Corporation) spreadsheet and included in the analysis. The analysis will take a combined inductive approach when generating key themes and a deductive approach using a prespecified framework. Quantitative data will be analyzed in Stata SE (version 18.0; Stata Corp).

Results: Data on Instagram and TikTok have been searched and screened. Analysis has now commenced. The findings will be disseminated via publications in peer-reviewed international medical journals and will also be presented at national and international conferences in late 2024 and 2025.

Conclusions: This study will contribute to the limited evidence base on the nature of the relationship between social media and the problems of overdiagnosis and overuse of health care services. This understanding is essential to develop strategies to mitigate potential harm and plan solutions, with the aim of helping to protect members of the public from being marketed low-value tests, becoming patients unnecessarily, and taking resources away from genuine needs within the health system.

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KEYWORDS

social media; influencers; tests; overdiagnosis; overuse; evidence-based medicine; promotion

Introduction

The idea that early detection of health conditions or diseases is always better, as it offers the best chance of being cured, has been around for decades, and continues to grow in popularity [1]. However, evidence demonstrates that lay people often overestimate the benefits and underestimate the harms of tests [2], and there is increasing evidence that inappropriate testing can harm healthy people, and the quest for early detection can lead to overdiagnosis [3-9]. Overdiagnosis is now widely recognized and occurs when generally healthy people are diagnosed or labeled with a disease that would never cause them harm [10,11]. This can occur as a result of undergoing screening tests (eg, cancer screening [12]) and can lead to the overuse of further tests and overtreatment. More recently, there have been concerns that direct-to-consumer (DTC) tests can lead to overdiagnosis of generally healthy people and overuse [13,14]. The harmful consequences of overdiagnosis can include physical harm from unnecessary tests and treatments, psychological harm from being labeled with a condition or disease that would not cause harm, and receiving invasive treatments that also carry financial consequences [11]. It can also lead to an unsustainable burden on the health care system. A review of relevant literature has identified potential drivers of overdiagnosis across 5 domains: culture, the health system, industry, professionals, and patients and the public [15]. The review found many causes, including common beliefs that "more is better," systemic financial incentives to deliver more tests and treatments, technological changes enabling increasingly sensitive tests, and patient expectations that clinicians will "do something" [15]. While the use of more sensitive tests, the promotion of tests, and advertising and traditional media were identified as drivers of overdiagnosis, there are as yet few data on how social media may drive overdiagnosis or overuse.

In recent years, social media have emerged as an important space for commercial marketing of health products [16], including various early detection tests [17], which can be used for the screening and diagnosis of otherwise healthy people. Companies themselves are very active on social media, promoting their products through traditional advertisements that appear in users' news feeds. Companies are also partnering with social media influencers [18]—individuals who amass large followings on social media and exert significant influence over their audience through engaging content [19]. While platforms themselves claim to regulate health information and misinformation, the current regulations around what can be promoted on social media are minimal [13]. Influencers may share health information to their audiences, even though they may not necessarily be qualified to give health information. The social media promotion of health products can often be based on personal anecdotes and opinions or, at worst, on pseudoscience or conspiracy theories. For example, studies now have identified the impact that influential social media has on health misinformation across various conditions [20-23], including most recently widespread COVID-19 misinformation [24,25] that has negatively affected people's health behaviors [26,27]. However, little is known about how health tests are promoted on social media, whether the information provided is accurate and balanced, and if there is transparency around conflicts of interest.

This study therefore aims to quantify and understand how social media are being used to discuss or promote health tests with the potential for overdiagnosis or overuse to generally healthy people. The study will explore how the benefits and harms including overdiagnosis and overuse of the tests are discussed, whether evidence is being used in the promotion of tests, what is the overall tone, transparency around potential conflicts of interest, and what themes are being used in the discussion or promotion of tests.

Methods

Study Design

This study uses content analysis of information on tests from influential social media platforms, Instagram and TikTok. Content analysis [28] is a widely used qualitative research technique, which also uses quantitative methods to analyze written content, enabling themes, meanings, and concepts to be quantified and evaluated through coding. The study will be reported according to the Standards for Reporting Qualitative Research reporting guideline [29].

Inclusion and Exclusion Criteria

The inclusion criterion includes English-language social media posts on 5 specific tests from influential international social media accounts. The 5 tests have been identified as meeting the following criteria: (1) there are evidence-based concerns about overdiagnosis or overuse, (2) there is evidence or concerns that the results of tests do not lead to improved health outcomes for generally healthy people and may cause harm or waste, and (3) the tests are being promoted on social media to generally healthy people. The authors also have interest and expertise in several of the identified tests [14,30,31].

Influential accounts are defined for the study as an individual or company account with >1000 followers that discusses the specific test in question and categorized as nano (1000-10,000 followers), micro (10,000-100,000 followers), macro (100,000-1 million followers), and mega (1 million+ followers) [32] based on number of followers. Text-only posts, images, infographics, articles, recorded videos including reels, and audio-only posts will be included. Posts from accounts with <1000 followers as well as stories, live videos, and non-English posts are excluded.

Data Collection

The tests include the anti-Mullerian hormone (AMH) test, whole-body magnetic resonance imaging (MRI) scan,

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multicancer early detection (MCED) test, testosterone test, and gut microbiome test. These tests are intended for individuals of varying sociodemographic characteristics including sex and age and included a range of costs.

We chose to focus on the platforms Instagram and TikTok as they are 2 of the most fastest-growing platforms across all age demographics relevant for the promotion of the 5 identified tests. These platforms are predominantly for short-form content (eg, infographics, reels, and TikToks), which has become more popular than longer-form content (eg, long videos, long posts, and blogs) in recent years. Shorter content is likely to be more impactful as it is more accessible and receives more engagement [33]. Furthermore, these platforms have the recent documented instances of influential celebrities promoting tests with significant evidence-based concerns about overdiagnosis (eg, Kim Kardashian and the whole-body MRI on Instagram [17]).

We created new Instagram and TikTok accounts and searched the 2 platforms using keywords related to each of the tests. Keywords for each test were included based on pilot testing. We searched and screened the top posts (as defined by the platform) until we had 100 eligible posts in each platform for each test. We included and assessed posts based on the platform they have been posted on (ie, if a post was created on TikTok but posted on Instagram, then we will include it in the eligible Instagram posts), and any duplicate posts across the keywords and platforms were removed. This method was first piloted with 1 test (AMH test). Searching and screening were conducted on the 2 platforms by 1 researcher (BN) using the newly created accounts. Eligibility of posts was confirmed by a second researcher (JZ). The eligible posts were saved in the account and returned to by the researchers to summarize, extract, and analyze the data.

Summarized data on publicly available demographics (eg, date of the post), credentials of influencers or credibility of influential pages (eg, expertise—a medical doctor or not), paid partnership or disclosure (present or absence of the information), amount of followers (micro, macro, midtier, and mega), and engagement metrics (eg, views, likes, and comments) were collected.

Included Tests

AMH Test for Fertility

As the average age of mothers at first birth is increasing in high-income countries [34], there has been growing attention around the AMH test, often termed the “egg timer test.” AMH test is a blood test that is used to estimate ovarian reserve; in other words, the number of eggs in a woman’s ovaries [35,36]. While AMH testing has been shown to be useful in the context of a fertility treatment [37], there is no evidence to support the AMH test as a reliable measure of fertility for women in the general population as it cannot reliably predict the likelihood of pregnancy, timing to pregnancy, or specific age of menopause for individuals [38-40]. As a result of this evidence, the American College of Obstetricians and Gynecologists strongly discourages AMH testing in women not undergoing in vitro fertilization [41]. Yet, despite clear evidence of its lack of benefit, recent data suggest that some women are taking the test as they believe it can inform their chance of conceiving [42]. Furthermore, recent content analyses of both fertility clinics’ [30] and companies’ [31] websites found that these tests are being widely marketed to the general population on the web and that many of the websites are making false and misleading claims to women about what the AMH test can tell them. Together this raises concerns about the widespread overuse of the AMH test [42].

Whole-Body MRI Scan for the Detection of a Range of Diseases in Their Earliest Stages (eg, Cancers)

Whole-body MRIs use strong magnetic fields and radio waves to scan and generate detailed images of the entire body. Whole-body MRI scanning has been available for more than a decade and is largely used for screening those with a high genetic risk of cancer [43]. This procedure now typically takes an hour, and despite the claimed usefulness of whole-body MRI for cancer detection in high-risk individuals, its promotion to generally healthy people in the general population is raising concerns about overdiagnosis [44,45]. There is currently no evidence that these highly sensitive tests provide net benefit for people at average risk of disease [46,47]. Alongside the potential for overdiagnosis across a number of conditions and potentially unnecessary invasive treatments, the associated anxiety and cost (ranging between approximately US $2000-US $4000) of whole-body MRIs are important to consider. Whole-body MRIs are not recommended by major international medical professional societies for people without symptoms.

MCED Tests

MCED tests are a type of “liquid biopsy” that aims to detect cancers early before symptoms develop. They use genomic profiling to detect cancer DNA cells circulating in the blood [48]. In 2016, the Food and Drug Administration (FDA) first approved liquid biopsies for the detection of gene mutations in circulating tumor DNA, designed for clinicians to monitor patients with cancer [49]. At present, the MCED test has not been fully approved by the FDA, yet, it has granted “breakthrough device designation” to at least 3 MCED tests. Companies are currently offering the tests to consumers and clinicians as laboratory-developed tests. While clinical and community interest continues to grow, with MCED tests being discussed as the “holy grail” for cancer detection [50], it is still unclear whether the benefits outweigh the harms. Although MCED tests have been shown in early small-scale studies to increase cancer detection and are designed to have high specificity, that is, reduce false-positive results [51-54], there are valid concerns surrounding overdiagnosis [55]. There are clinical trials [56,57] underway internationally to assess the performance and use of the tests. However, data from these trials could take over a decade, and to date, no evidence exists to robustly inform decisions about effectiveness, including reduction in late-stage cancer incidence and overall mortality. Furthermore, like the whole-body MRI scan, the cost of these tests is expensive (currently approximately US $1000), raising additional health inequity issues for population screening.

Testosterone Test for Low Testosterone

As men age, testosterone levels naturally begin to decline. While testosterone deficiency can be a serious medical condition in

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some men and requires treatment for many men, low testosterone or "low T" is a prime example of disease mongering [58,59]. Since early 2000, there has been an increase in testosterone testing and prescribing [60-62]. "Low T" awareness campaigns targeting middle-aged men in high-income countries with messages about checking testosterone levels if they had low libido, were experiencing mood changes, or had gained weight have in part driven this increase in testing and prescribing [63,64]. More recently, testing has been promoted among men in the fitness industry as a way to go on testosterone therapy and help build muscle. Testing for testosterone levels typically requires a blood sample to be taken in the morning by a medical professional; however, DTC tests that usually involve collecting a blood sample now exist, and results can be provided within days. While there is variability in guidelines of what is considered low testosterone, there is currently no evidence that testosterone testing provides clinical benefit for asymptomatic healthy men [65]. Furthermore, as testosterone levels vary, a single measurement is unreliable, and without a clear context of the person being tested, in the case of DTC testosterone testing, it runs the risk of both false-positive and false-negative results. It is also important to note that the long-term safety in relation to adverse cardiovascular events and mortality of testosterone therapy has not yet been established, with an FDA-mandated study ongoing [66].

Gut Microbiome Test

The gut microbiome test measures the microorganisms in a person's gastrointestinal tract. A sample of stool is taken and sent to a laboratory and analyzed for, in some cases, hundreds of different types of bacteria, viruses, and fungi. Although the microbiome test has not been rigorously tested for accuracy or safety, with the FDA having yet to approve home microbiome tests, a growing number of companies are offering this "wellness" test with the promise of identification of diseases and disorders (and precursors to diseases and disorders) such as bowel diseases or disorders, depression, diabetes, and cancer. These tests also provide personalized reports that suggest dietary adjustments. Experts have noted that while the test looks promising, the evidence behind the claims of what the test can do is still in its infancy—with promises being made that are greater than what the current science can offer [67]. At this time, the tests can only really satisfy a person's curiosity rather than add any value to clinical decision-making [68], which in turn can lead to overdiagnosis and overtreatment of those taking the test [69].

Data Analysis

Data from the caption, audio or video, and on-screen text (if applicable) will be summarized and extracted into a Microsoft Excel (Microsoft Corporation) spreadsheet and included in the analysis. The analysis will take both an inductive approach when generating key themes arising from the posts and a deductive approach using a prespecified framework in line with our aims to examine (1) benefits, (2) harms including overdiagnosis and overuse, (3) evidence, (4) overall tone, and (5) financial disclosures. Independent extraction and review of the data was undertaken by 1 researcher (RM) to develop an initial list of recurring themes. The coding tool was then informed by analysis of other coding tools used in similar previous work on media reporting of new tests [70,71]. Two researchers then independently applied this coding tool to 20% (n=40 per test) of posts to evaluate the reliability of the coding tool. The level of agreement between the 2 coders across the codes (eg, benefits, harms, evidence, tone, and disclosures), and by test, will be assessed using Cohen κ and be interpreted as <0.00=poor, 0.00-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, and ≥0.81=almost perfect [72]. The agreement will be considered acceptable if κ>0.6 for a sample of at least 20% (n=40) of posts per test. In some cases, the level of agreement might appear low using the κ statistic due to the high prevalence of a particular value for a variable. This is known as the κ paradox [73-76]. Therefore, we will also consider the level of agreement acceptable if κ is ≤0.6, but crude agreement is ≥85%. If κ is ≤0.6, and crude agreement is <85%, data will be recoded (using n=40, 20% blocks for each test) until an acceptable level of agreement is met. Once agreement is acceptable, 1 researcher with experience in public health and overdiagnosis will code the remaining posts.

Differences in outcomes by test and by platform, followers, and length of posts (across all 1000 posts) will be reported. Logistic regression analyses will be used to investigate whether posts by medical doctors, posts with evidence, and posts with clear financial disclosures are more or less likely to be balanced in their discussion or promotion of test in terms of benefits, harms, and overall tone. Our hypothesis is that posts by medical doctors and posts with evidence are more likely to be balanced, and posts with clear financial disclosures are less likely to be balanced. Quantitative data will be analyzed in Microsoft Excel and Stata SE (version 18.0; Stata Corp).

Ethical Considerations

The data collected and analyzed in this study is unequivocally public. Data will be largely reported in aggregate form, however, in cases where specific excerpts (eg, quotes) are reported as examples, as is typical with the content analysis method [28], these will be short (eg, a few lines) and nonidentifiable (eg, no personal or professional information or reference will be given). A waiver of consent from The University of Sydney Human Research Ethics Committee has been granted (2023/913).

Results

Progress to Date

Data on each of the 5 tests have been searched and screened on Instagram and TikTok. Analysis is currently being conducted.

Dissemination

The findings will be disseminated via publications in peer-review international medical journals and presentations at national and international conferences in late 2024 and 2025.

Discussion

Anticipated Findings

It is anticipated that this study will reveal fresh insights into how balanced the information and promotion of tests with the

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potential for overdiagnosis or overuse is on social media. This study will therefore contribute to the limited evidence base on the nature of the relationship between social media and the problems of overdiagnosis and overuse of health care services. Analyzing how these 5 popular tests are currently being promoted on 2 influential social media platforms will provide a snapshot of the wider issue.

It is now acknowledged that the public and patients alike are turning to social media for health information [77]. Therefore, the concerns driving this analysis are not that these tests exist, are being promoted on social media, or are used by those with serious symptoms, but that the tests may be being promoted to generally healthy individuals without good evidence of benefit, explicit information about their harms, and potentially relevant information on conflicts of interest [15]. Future research using similar methods can also be conducted to investigate the promotion of drugs, treatments, and disease definitions and the potential ways to reduce the volume of misleading marketing, to further add to the much-needed evidence base, as social media continues to disseminate health information and market health products.

This study has both strengths and limitations. This is the first study to analyze the promotion of tests on social media that have concerns relating to overdiagnosis or overuse. The study will only include and analyze posts on Instagram and TikTok. However, as stated in the Methods section, these were chosen as they are 2 of the most widely used and fastest-growing platforms across relevant age groups in which the tests relate to, are predominantly used for shorter more impactful content [33], and have been recently used to promote these tests by influential celebrities [17]. Posts on these platforms have been screened systematically using the methods described earlier, and the top 100 eligible posts mentioning the tests were included. Comments and replies will not be analyzed nor will posts from influencers with <1000 followers, which may have provided additional information to the analysis although it is not anticipated that this will impact the overall findings. Finally, the posts will be screened and returned to for analysis. In that time, the content may be removed, or the number of followers may have changed. Again, it is not anticipated that this will impact the overall findings.

Conclusions

Understanding whether there is a problem in how tests with potential for overdiagnosis or overuse are discussed and promoted on social media, and the extent of the promotion, is essential to develop strategies to mitigate potential harm and plan solutions. This information will also potentially help to protect members of the public from being marketed low-value tests and becoming patients unnecessarily. It will also help to minimize overuse, which takes resources from genuine need, threatening the sustainability of health systems.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

BN and JZ conceptualized the study and screened the data. All authors were involved in the design. BN, TC, EGG, RM, and JZ were involved in the acquisition of the data. All authors were involved in the drafting, critical revision, and approval of the final paper.

Conflicts of Interest

BN and EGG are members of the International Scientific Committee of Preventing Overdiagnosis.

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Abbreviations

AMH: anti-Mullerian hormone
DTC: direct-to-consumer

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FDA: Food and Drug Administration
MCED: multicancer early detection
MRI: magnetic resonance imaging

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Protocol

Feasibility of Web-Based Single-Session Empowered Relief in Patients With Chronic Pain Taking Methadone or Buprenorphine: Protocol for a Single-Arm Trial

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Abstract

Background: Chronic pain affects tens of millions of US adults and continues to rise in prevalence. Nonpharmacologic behavioral pain treatments are greatly needed and yet are often inaccessible, particularly in settings where medication prescribing is prioritized.

Objective: This study aims to test the feasibility of a live-instructor, web-based 1-session pain relief skills class in an underserved and potentially at-risk population: people with chronic pain prescribed methadone or buprenorphine either solely for pain or for comorbid opioid use disorder (OUD).

Methods: This is a national, prospective, single-arm, uncontrolled feasibility trial. The trial is untethered from medical care; to enhance participants' willingness to join the study, no medical records or drug-monitoring records are accessed. At least 45 participants will be recruited from outpatient pain clinics and from an existing research database of individuals who have chronic pain and are taking methadone or buprenorphine. Patient-reported measures will be collected at 6 time points (baseline, immediately post treatment, 2 weeks, and months 1-3) via a web-based platform, paper, or phone formats to include individuals with limited internet or computer access and low literacy skills. At baseline, participants complete demographic questions and 13 study measures (Treatment Expectations, Body Pain Map, Medication Use, Pain Catastrophizing Scale [PCS], Patient-Reported Outcomes Measurement Information System [PROMIS] Measures, and Opioid Craving Scale). Immediately post treatment, a treatment satisfaction and acceptability measure is administered on a 0 (very dissatisfied) to 10 (completely satisfied) scale, with 3 of these items being the primary outcome (perceived usefulness, participant satisfaction, and likelihood of using the skills). At each remaining time point, the participants complete all study measures minus treatment expectations and satisfaction. Participants who do not have current OUD will be assessed for historical OUD, with presence of OUD (yes or no), and history of OUD (yes or no) reported separately. Feasibility threshold is set as an overall group treatment satisfaction rating of 8 of 10. In-depth qualitative interviews will be conducted with about 10 participants to obtain additional data on patient perceptions, satisfactions, needs, and wants. To assess preliminary efficacy, we will examine changes in pain catastrophizing, pain intensity, pain bothersomeness, sleep disturbance, pain interference, depression, anxiety, physical function, global impression of change, and opioid craving at 1 month post treatment.

Results: This project opened to enrollment in September 2021 and completed the recruitment in October 2023. The data collection was completed in February 2024. Results are expected to be published in late 2024.

Conclusions: Results from this trial will inform the feasibility and preliminary efficacy of Empowered Relief in this population and will inform the design of a future randomized controlled trial testing web-based Empowered Relief in chronic pain and comorbid OUD.

Trial Registration: ClinicalTrials.gov NCT05057988; https://clinicaltrials.gov/study/NCT05057988

International Registered Report Identifier (IRRID): DERR1-10.2196/53784

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KEYWORDS

chronic pain; opioid use disorder; methadone; buprenorphine; behavioral medicine; telehealth; psychology

Introduction

Background

Chronic pain, a condition defined by persistent pain lasting longer than 3 months [1], affects upward of 50 million US adults [2] and is rising in prevalence every year [3]. One-third of individuals with chronic pain report experiencing severe pain [4], about one-third have pain in multiple locations [5], and more than a third have activity-limiting pain [6], indicating a significant toll on life [4]. Indeed, for millions of adults, chronic pain results in reduced productivity, poor quality of life, difficulties with interpersonal relationships, and disability [7,8]. These disturbances are costly to both the individual and the nation, resulting in the loss of billions of dollars each year in health care expenditures and lost productivity [3].

Historically, opioids were often prescribed to treat chronic pain, though prescribing trends have decreased sharply since 2016. For instance, the US national trend analysis of 2014 data revealed that the majority of people taking prescription opioids (79.4%) at that time were taking them long-term [9], a period defined as 90 days or longer. The risk for overdose, misuse, and development of opioid use disorder (OUD) became a growing concern following the declaration of the opioid epidemic as a national public health emergency in 2017 [10]. From 2019 to 2022, the total number of opioid prescriptions decreased by 14.2% (153.6 million in 2019 to 131.8 million in 2022) [11]. Yet, overdose deaths involving prescription opioids remained high, with 8.5 million individuals in the United States reporting opioid misuse in 2022 [12]. While some patients gain durable analgesic benefits from prescription opioids for chronic pain [13], there remains a clear need to provide patients access to the lowest risk pain treatment options.

Nonpharmacologic treatment options have gained substantial clinical attention to optimize pain care at lowest risk. Psychological treatment for chronic pain encompasses a wide variety of interventions focusing on the ability to self-manage pain, pain-related worry, and distress [14]. Multisession cognitive behavioral therapy (CBT), the gold standard psychological therapy for chronic pain [15], has been shown to be effective in reducing pain intensity, pain interference [16], and improving quality of life [17]. Other multisession therapies, such as 8-session acceptance and commitment therapy and 8-session mindfulness-oriented recovery enhancement (MORE), offer slight strategic variations from 8-session CBT and are similarly applied in the management of chronic pain. These pain psychology treatments have shown equivalent effects on pain-related outcomes measures [18] and compatible treatment satisfaction ratings [19,20]. Although MORE was not designed for chronic pain and comorbid OUD, MORE has notably shown effectiveness in reducing opioid craving [21,22]. However, the availability of psychological treatments for chronic pain is limited by a lack of clinicians trained in pain management, time and cost required, and health insurance barriers [3,23]. Furthermore, patients taking medication for OUD (MOUD), including either buprenorphine or methadone, are of specific interest because of their risk for unmanaged pain-triggering relapse. Indeed, patients taking MOUD often have difficulty accessing nonpharmacological treatments and many report unmanaged pain as the primary reason for opioid relapse [24].

Empowered Relief (ER) is a single-session group-based pain relief skills intervention that was developed to reduce treatment burden and increase accessibility to effective low-risk pain care. Results from a randomized controlled 3-arm clinical trial conducted in 263 patients with chronic low back pain revealed that ER was comparable with 8 sessions of CBT [25] in improving pain catastrophizing, pain intensity, pain interference, pain bothersomeness, sleep disturbance, anxiety, depression, and fatigue at 3 months post treatment, with benefits being clinically meaningful. A second randomized controlled trial tested a live-instructor, web-based ER compared with usual care in 105 patients with mixed etiology chronic pain. Results revealed that at 3 months post treatment, ER was superior and significantly reduced pain catastrophizing, pain intensity, pain bothersomeness, anxiety, and sleep disturbance [26]. Digital versions of ER have been used in 2 randomized controlled surgical studies with results showing that it was associated with reduced opioid use after breast cancer surgery [27] and reduced pain up to 3 months after orthopedic trauma surgery [28]. While the collective ER trials are promising, the intervention has not yet been tested as a web-based treatment for people who may have a history of OUD or current OUD, or for people taking medications commonly prescribed for these circumstances. This study is designed to examine whether web-based ER is a plausible and accessible pain treatment option for patients with any chronic pain condition who are receiving methadone or buprenorphine (commonly prescribed medications) for OUD in various clinics in the United States.

Objectives

This study aims to conduct a single-arm uncontrolled trial to assess the feasibility and preliminary efficacy of a web-based single-session pain education class to participants with chronic pain conditions who are taking methadone or buprenorphine in the United States. We have 3 primary hypotheses. First, we hypothesize that patients with chronic pain who take methadone or buprenorphine will report overall acceptable satisfaction with the brief web-based intervention. Second, we hypothesize that web-based ER will reduce pain metrics (catastrophizing, pain intensity, and pain bothersomeness) as well as sleep disturbance and opioid craving at 1 month post treatment (primary end point) and 3 months post treatment (secondary end point).

Methods

Overview and Setting

We are conducting a single-arm, uncontrolled feasibility clinical trial for patients with chronic pain conditions taking methadone or buprenorphine anywhere in the United States (Figures 1 and 2). All study procedures are performed over the phone or internet

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(ie, Zoom) and no in-person visits are required. All enrolled participants will attend a web-based ER session. Participants will be assessed for 3 months following the class via web-based surveys. Participants will be surveyed during an initial phone screening; immediately after treatment; 2 weeks; and 1, 2, and 3 months after the class. For clinical outcomes, the primary end point is 1 month (short-term outcomes) and the secondary end point is 3 months (delayed outcomes) post treatment. The primary aim of the study is to report the feasibility of web-based ER using a quantitative treatment satisfaction survey administered immediately post treatment (all participants) and an in-depth qualitative interview with about 10 participants to enhance understanding of patient preferences. The secondary aim is to examine the preliminary efficacy of web-based ER. The secondary outcomes are pain catastrophizing, pain intensity, pain bothersomeness, and sleep disturbance at 1 month and 3 months post treatment. The tertiary outcomes include pain interference, mood, physical function, global impression of change, and cravings at 1 month and 3 months post treatment.

Figure 1. Study design flowchart.

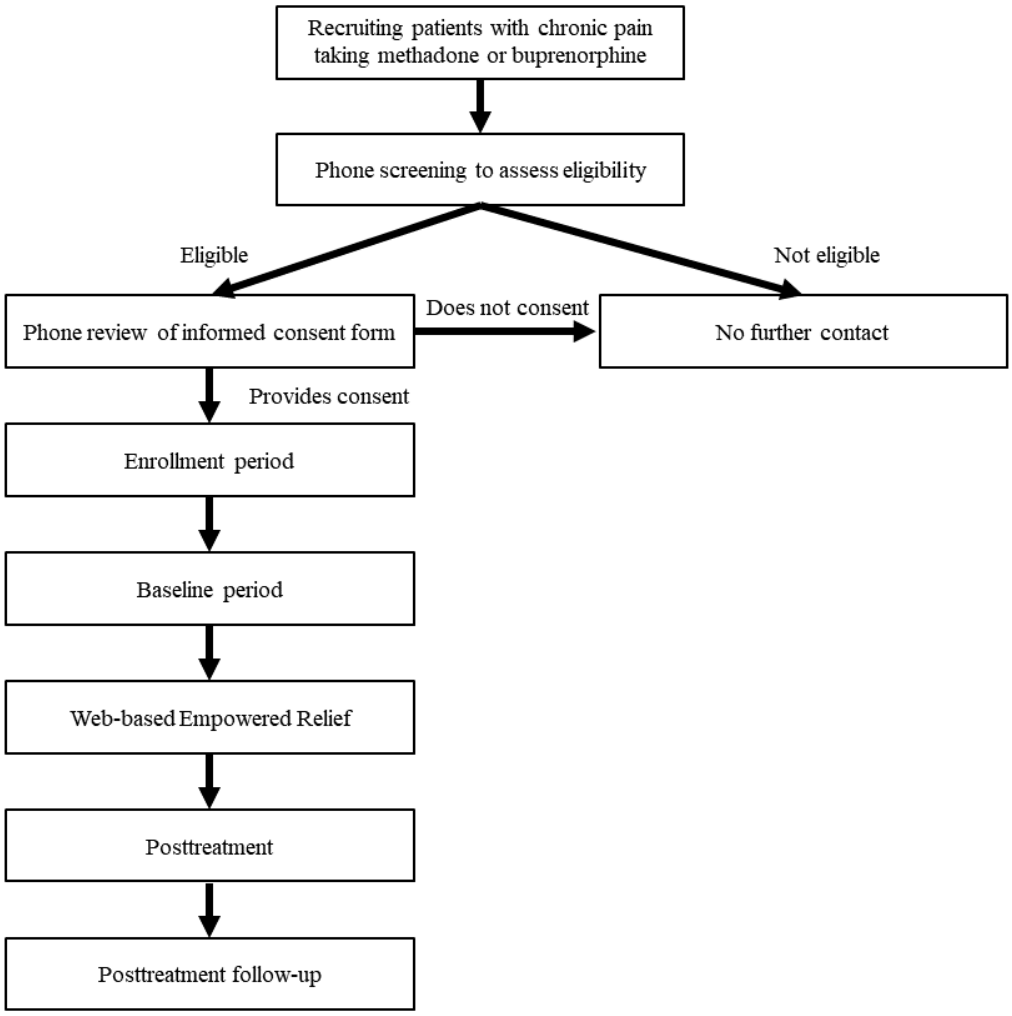

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Figure 2. Timeline of enrollment, assessments, and intervention. Note: measures are highlighted in yellow. OUD: opioid use disorder.

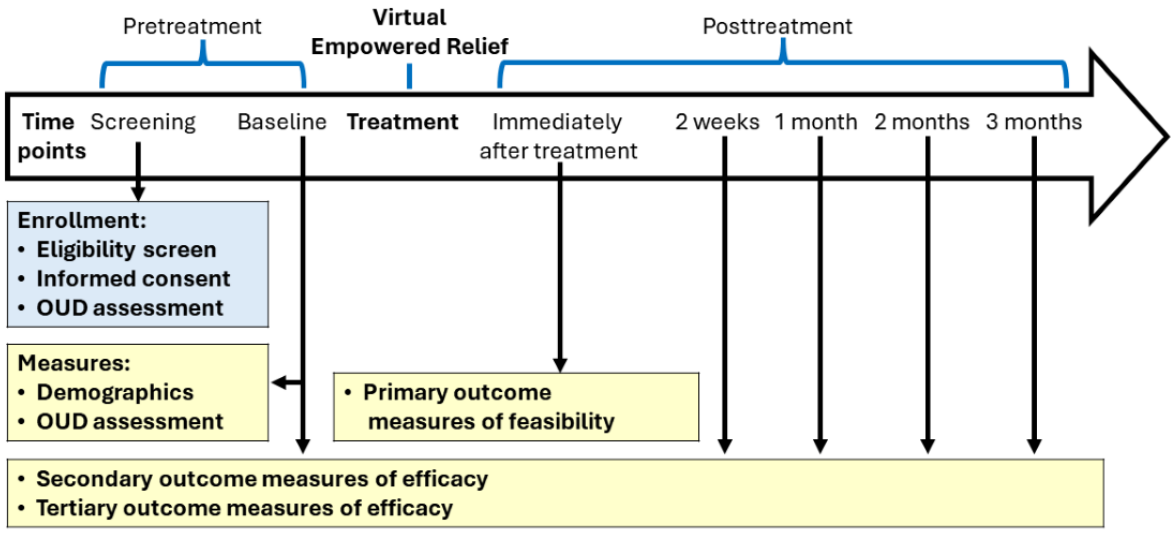

Ethical Considerations

The protocol for this trial has been approved by Stanford institutional review board (IRB; 60855). This research adheres to the Helsinki Declaration's ethical standards for research involving human subjects. Informed consent will be obtained from all participants prior to study enrollment. Participants are also notified that they can revoke their consent at any time for any reason without any repercussions. Data access will be exclusively limited to the research team members. After data collection is complete and the results have been published, deidentified data will be preserved. Consequently, any future requests for data access will be limited to this deidentified information, implemented after request approval and conducted in accordance with all IRB regulations. Participants will be compensated up to US $145 in the form of Amazon gift cards ranging from US $10 to US $45 each for successful completion of study surveys with prorated compensation possible. Participants who agreed to participate in the 30-minute qualitative interview will be compensated with an additional US $20 Amazon gift card.

Data Collection

Data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Stanford University [29,30]. REDCap is a secure, HIPAA (Health Insurance Portability and Accountability Act) compliant, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources. All study measures will be completed using a web-based survey platform unless a participant requests paper-based or telephonic format. All web-based surveys will be completed directly by the participants and sent by email through a secure, participant-specific link.

Study Sample and Recruitment

Participants will be recruited nationally through pain and addiction clinics by patient referral from physicians and clinic staff briefed on the treatment research opportunity. This study invites patients with any chronic pain conditions who are also taking methadone or buprenorphine; we will recruit at least 45 participants completing study measures at the primary end point. Interested individuals will be scheduled to complete a brief phone screening interview with study staff to assess eligibility. Individuals who meet the eligibility criteria will be contacted by phone to complete informed consent and study enrollment. Enrolled participants will complete an assessment of OUD symptoms at this time.

Inclusion and Exclusion Criteria

Eligibility criteria include ongoing body pain for more than half of the days for ≥3 months, taking either methadone or buprenorphine, 18 years of age or older, having access to a device with video call capabilities, and verbal English fluency (written English fluency is not required because participants may choose 1 of 3 survey options: web-based, paper, or research coordinator–assisted phone surveys). Furthermore, internet or computer access is not required if referring clinics can accommodate the Zoom (Zoom Technologies Inc) ER group meeting for 2 hours. Individuals who are pregnant or have previously received ER will be excluded for this feasibility study to minimize the incompletion of research tasks during the 3-month study period and maintain the homogeneity of the sample.

One-Session ER Intervention

ER was developed in 2013 at the Stanford University Division of Pain Medicine with clinician certification workshops initiating at Stanford University in 2019 [29,31]. ER provides an accessible, low-risk ntervention for pain management. The didactic 2-hour class may be delivered to large groups of patients. A certified instructor uses a structured PowerPoint slide deck and instructor manual to deliver content that includes pain neuroscience education, experiential and interactive exercises, 3 core pain management skills, and a guided binaural

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relaxation audio application that participants download onto their smartphone or other device. Instructors assist participants with the creation of a personalized plan that uses the skills presented in the course and can be implemented outside of the class. ER has been shown as multidimensional benefits to participants with chronic pain conditions with both short-term and long-term effects.

For this study, the ER class will be offered once monthly to small groups that consist of 5-20 participants each. The class is hosted through the Zoom platform. To ensure participant confidentiality, participants' cameras are off and they are asked to display only first names. Furthermore, the classes are not recorded. Participants can receive the study materials via email or mail and can receive the guided binaural relaxation audio file by direct app download or by email.

Safety Monitoring and Adverse Experiences

Prior research has documented no ER study–related adverse events [25,26]. For this study, participants are asked to report any adverse events or new problems they have experienced since their last survey at each survey time point. The adverse event forms are reviewed by the study staff and a determination is made regarding event severity and whether the event is related to the study or not. Any reported adverse event cases will be discussed in team meetings and reported to the IRB annually. All serious adverse event cases will be evaluated by the study staff and principal investigator (DY) within 24 hours of acknowledgment of the incident and immediately reported to the Stanford IRB.

Study Measures

Measures

We collect clinical and demographic information listed in Table 1. The 11 *DSM-5* OUD [32] symptoms are assessed to evaluate both present and lifetime OUD status. Diagnostic criteria for OUD are met when 2 or more symptoms are endorsed. The 6-item Stanford Expectation of Treatment Scale [33] is administered to assess positive and negative expectation of upcoming treatment on an 11-point Likert scale (α=.86). We will calculate the means of negative and positive treatment expectations, which will be compared with previous in-person ER class (mean values 2.29 with SD of 1.34 for negative expectation and 3.71 with SD of 1.30 for the positive expectation [25]). The Body Map [34], a whole body topography with 36 anterior and 38 posterior segments, is administered to assess pain locations (1-week test-retest reliability=0.93). The 13-item Pain Catastrophizing Scale (PCS) [35] is administered to assess the levels of pain catastrophizing (α=.87) on a 5-point scale from 0 (not at all) to 4 (all the time). The PCS measures a multifaceted construct with 3 subscales: rumination, magnification, and helplessness about pain. The PCS total score ranges from 0 to 52, with higher scores indicating higher levels of pain catastrophizing. Pain bothersomeness [36,37] is assessed with a single item on a scale of 0 (not at all bothersome) to 10 (extremely bothersome) in the past 7 days. This single-item measure of pain bothersomeness has shown to be predictive of poor functional outcomes in the future [38] and be sensitive to intervention-related changes [25]. The Patient-Reported Outcomes Measurement Information System (PROMIS)–Pain Intensity item [39] is used to assess average pain in the past 7 days on a 0-10 scale. In addition, short-form versions of the PROMIS [40] measures of pain interference, physical function, fatigue, sleep disturbance, depression, anxiety, and social isolation are administered to assess the previously observed outcomes of in-person ER intervention [25]. The PROMIS measures are reported on a T-score metric (mean 50T, SD 10), with higher scores indicating more symptoms or greater function of the domain measured. The Patient Global Impression of Change [41,42] is a 6-item measure to assess perceived progress after the ER intervention. The Patient Global Impression of Change is rated on a 1 (very much worse) to 7 (very much improved) scale. Next, the level of craving for opioid medication is assessed with a single item ("how much do you crave opioid medication now?") rated on a scale of 0 (not at all) to 10 (extremely) as others have demonstrated opioid-craving reductions in patients with chronic pain and OUD following receipt of pain management programs [43-45]. Feasibility is assessed using 3 items (perceived usefulness, participant satisfaction, and likelihood of using the skills) from a treatment satisfaction and acceptability measure that includes 11 questions (Table 2) about the class content and format (eg, overall satisfaction, understandability, relevancy, worry related to the web-based class, and length of the class) [46] on a 0-10 scale. Finally, participants are asked to report any adverse events and major life events during the study period in a text format.

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Table 1. Study measures and time point of administration.

Measure	Description	Enrollment	Baseline	Posttreatment	Follow-up[a] (~3 months)
DSM-5[b] OUD[c] [32]	Assessing opioid use disorder symptoms in lifetime and the past 12 months (11 items)	✓	✓		
Demographics	Gender, age, ethnicity, race, education, employment, marital status, household income, housing status, and self-reported medical diagnoses		✓		
Medication use	Self-reported name, start date, dose, and frequency of current medications		✓		✓
Stanford Expectation of Treatment Scale [33]	Expectations and concerns about the treatment on a 7-point scale (6 items)		✓		
Body Map [34]	A body diagram to indicate location of pain		✓		✓
Pain Catastrophizing Scale [35]	Thoughts and emotions when experiencing pain on a scale ranging from 0 to 4 (13 items)		✓		✓
Pain Bothersomeness [36,38]	Assessing how "bothersome" the pain is on a 0-10 scale (1 item)		✓		✓
PROMIS[d] Measures [39,40]	Pain intensity, pain interference, physical function, fatigue, sleep disturbance, depression, anxiety, and social isolation		✓		✓
Opioid Craving Scale [47]	Assessing the strength of opioid cravings on a 0-10 scale (1 item)		✓		✓
Patient Global Impression of Change [41]	Perceived changes in social, recreational, and occupational activities following the intervention measured on a 7-point scale (6 items)		✓		✓
Class Satisfaction and Acceptability [26]	Experience with ER[e] class including overall satisfaction, relevancy and usefulness of material, and ease of using Zoom platform (11 items)			✓	
Treatment Change and Adverse Events	Any major life events, new injuries/illnesses, and changes in lifestyle and treatment				✓

[a]Two weeks and 1, 2, and 3 months after treatment.

[b]DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)

[c]OUD: Opioid Use Disorder.

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

[e]ER: Empowered Relief.

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Table 2. Eleven-item class satisfaction and acceptability measure[a].

Questions	Scale
1. Was the content easy to understand?	• 0 (not understandable at all) to 10 (completely understandable)
2. How relevant was the class to you?	• 0 (not relevant at all) to 10 (completely relevant)
3. *How useful was the information presented in the class?*	• 0 (completed useless) to 10 (very useful)
4. *Please rate your overall satisfaction with the class.*	• 0 (very dissatisfied) to 10 (completely satisfied)
5. *How likely are you to use the skills and information you learned?*	• 0 (not at all likely) to 10 (highly likely)
6. Rate your likelihood to recommend this class to another person who has chronic pain.	• 0 (would not recommend) to 10 (absolutely would recommend)
Please indicate how much you agree with the following statements: 7. It was easy for me to operate Zoom as a platform for attending the class. 8. While attending the Zoom class, I worried about privacy. 9. I felt comfortable engaging with the Zoom instructor and class participants. 10. I felt connected to the instructor.	• 0 (strongly disagree) to 10 (strongly agree)
11. Would you prefer to have a single class (2 hours) or two classes (1 hour each)?	• Prefer single class (2 hours) • Prefer two classes (1 hour each) • Other (if other, explain)

[a]Text in italics indicates primary outcomes.

Baseline (Pretreatment) Assessment

Following enrollment, participants will be asked to provide demographic information and complete all baseline study measures during a 2-week window prior to attending the web-based ER intervention. The *DSM-5* OUD symptoms are assessed by a trained study staff at enrollment and with a self-report survey at baseline that assesses current and lifetime history of OUD.

Posttreatment

Immediately following receipt of ER, participants complete the treatment satisfaction survey. Participants complete surveys at the following 4 posttreatment time points: 2 weeks, 1 month (primary end point), 2 months, and 3 months (secondary end point). Posttreatment surveys will assess the benefits of the ER class over time.

Primary Outcome Measures of Feasibility

Feasibility will be evaluated in qualitative and quantitative methods (treatment satisfaction survey). Of the 11 feasibility questions, the 3 primary outcomes are overall treatment satisfaction [26], perceived usefulness, and likelihood of using the skills learned. We will also conduct about 10 qualitative interviews with open-ended questions (Textbox 1) to understand participants' perception of the study and to request feedback on study design including the use of Zoom platform, recruitment method, survey burden, and compensation.

Textbox 1. Ten-item qualitative interview.

1. Please tell us about the content of the class. Were any parts of the class difficult to understand?
2. Did any parts of the class make you feel uncomfortable?
3. Is there anything we can do differently for the next participants?
4. Did you have any issues attending the Zoom class?
5. Did you have any concerns about our recruitment methods? As a reminder, we posted a flyer, we asked your health care provider at the clinic to introduce our study, and we reached out to you for the phone screening.
6. Do you have any suggestions about how we can better advertise our pain study to people who may benefit from our study?
7. Did you have any difficulties in completing the web-based survey, via phone, or on a paper? (If yes) Tell us your difficulties in completing the web-based survey, via phone, or on a paper.
8. Can we do anything differently to help people complete the survey?
9. What do you think about the study compensation?
10. Did you have any concerns while you participated in this study?

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Secondary Outcome Measures of Efficacy

The secondary outcome measures are pain catastrophizing [35], pain intensity [39], pain bothersomeness [38], and sleep disturbance [40] as reported by the patient at the 1-month posttreatment time frame. We will also evaluate the long-term outcomes at 2 and 3 months post treatment.

Tertiary Outcome Measures of Efficacy

Other outcome measures include pain interference [48], physical function [40], fatigue [40,49], depression [40], anxiety [40], social isolation [40], the global impression of change [41,42,50], and the opioid-craving levels [47]. These outcomes will all be assessed at the 1-, 2-, and 3-month posttreatment time points.

Statistical Analyses

Sample Size Calculation

In a previous single-arm ER pilot study involving mixed etiology chronic pain, a sample size of 57 participants was needed to detect a significant time effect on pain catastrophizing scores at 1 month post treatment (Cohen d=1.15, large effect) [46]. In addition, when conducting a repeated-measures ANOVA with a prior in-person randomized controlled trial (RCT) ER class data only [25], a sample size of 52 was needed to detect a significant time effect. The analysis also revealed moderate to large effects in reducing pain catastrophizing (Cohen d=0.91), pain rating (Cohen d=0.45), pain bothersomeness (Cohen d=0.84), and sleep disturbance scores (Cohen d=0.47) at 1 month post treatment. To calculate sample sizes for this study, power analysis was conducted using the G*Power 3.1.9.7. Specifically, we calculated sample sizes needed to detect a moderate effect (f=0.25) for a 1-way repeated-measures ANOVA, with α level of .05, 3 data points, and 0.50 correlation coefficient among repeated measures. The result indicated that the sample sizes of 36, 43, and 59 would yield the power of 90%, 95%, and 99%, respectively. Originally, 20% attrition rate was noted in the in-person ER class [25] and this pilot study initially estimated high attrition rate (ie, 50%). However, the observed attrition rate of this ongoing pilot study has been 25%, so we will recruit at least 45 participants to detect at least moderate effect sizes with a power of 90% and α level of .05.

Primary Outcome Analysis to Determine Feasibility

To determine the feasibility of a future RCT, we will evaluate the following criteria.

1. At least 75% of enrolled participants will attend the web-based ER class [27].
2. Demographic data (sex, age, race or ethnicity, education, income) will be compared between those who drop out and complete the study at the primary end point.
3. The mean scores of the 3 primary feasibility outcome measures will meet or exceed an 80% threshold of acceptability (8 or higher on a 0-10 scale) [28].
4. The qualitative interview data will be analyzed to evaluate perceived feasibility and to identify areas for improvement in the study design for a future, large-scale RCT [51].

Secondary and Tertiary Outcome Analysis to Examine the Preliminary Efficacy

To test the secondary and tertiary hypotheses, repeated-measures ANOVAs will be conducted to examine whether the secondary and tertiary outcomes will be significantly changed over time. False discovery rate adjustments will be used to control for type 1 error for the multiple comparisons. If the ANOVA results reveal significant change in the outcomes over time, post hoc analyses will be conducted to examine whether the secondary and tertiary outcomes will be improved by 1 month (primary end point) or 3 months (secondary end point) after the web-based ER class.

Results

An IRB approved all the study procedures on August 31, 2021. This project opened to enrollment in September 2021. Recruitment began in May 2022 and ended in October 2023. The end date for data collection was February 2024. Findings will be published upon completion of the study. The results are expected to be published by the end of 2024.

Discussion

We anticipate that the internet-delivered ER will be a feasible treatment for patients with chronic pain taking methadone or buprenorphine. In addition, our findings will support the primary and secondary hypotheses. Specifically, the internet-delivered ER will be a satisfactory and potentially efficacious treatment in this patient population as evidenced by the mean rating of the treatment satisfaction of ≥8 of 10 and significant improvement in pain-related outcomes, sleep disturbance, and opioid craving at 1 month (primary end point) and 3 months later (secondary end point).

Through this trial, we will determine whether the web-based 1-session ER intervention is feasible and effective for individuals with chronic pain who are taking methadone or buprenorphine. Qualitative data will yield richer information on participant perceptions of the intervention, the group-based and web-based format, and study procedures. Combined, quantitative and qualitative data will determine whether a fully powered RCT is warranted and whether refinements are needed. If study results suggest that the web-based ER has acceptable feasibility and shows preliminary efficacy, our next step would be to conduct a larger RCT. If this study reveals that the web-based ER does not significantly improve any of the primary and secondary outcomes, we will refine the protocol based on participants' feedback and consider next steps in this line of research (but not a next-step national RCT). Recognizing that a web-based intervention or clinical study would benefit from being fully embedded into the clinical environment, this study is a first step in that direction. Theoretically, on the one hand, this study benefits from being untethered to medical care in that participants may feel safer disclosing sensitive information about opioid use, craving, or substance use. On the other hand, the study is disadvantaged by being disconnected from clinics in that there is no in-house staff to promote the study or deliver the study treatment; rather, the study relies on colleague

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clinicians sharing information with their patients about an outside and unaffiliated study.

The single-session, 2-hour web-based ER is a low-burden, easily accessible, and scalable pain management intervention compared with traditional treatments involving 8-12 sessions [52,53]. A prior RCT conducted in people with chronic low back pain demonstrated that it was noninferior to 8 weeks of CBT (16 hours) for reducing pain catastrophizing, pain intensity, pain interference, sleep disturbance, and pain bothersomeness, and other outcomes at 3 months post treatment [25]. A web-based ER was also shown to have clinically meaningful efficacy in reducing a range of symptoms at 3 months post treatment for people with mixed etiology chronic pain [26]. Building on these studies, we have designed this web-based ER national study to reach people with chronic pain who are receiving medications that are often prescribed for pain and OUD (current or historical) and who likely have poor access to pain psychology treatment.

To facilitate the study of web-based treatments for this underserved patient population, we provide a detailed research protocol, with a goal of sharing this resource widely with clinicians and researchers who work with this patient group. Limitations of this study include the single-arm design, reliance on self-report data, an enrollment criterion for medications commonly used to treat pain and OUD, and reliance on clinician colleague referrals. Despite these limitations, this study may yield important information. If the single-session web-based ER intervention is shown to be feasible and have preliminary efficacy, a future rigorously designed multisite or national RCT would be warranted, one that includes longer-term follow-up and objective measures alongside the participant self-report data (eg, medical records data). This line of research may provide a viable and accessible pain care option for people living with any type of chronic pain and past or current OUD. Future research may also explore whether the intervention favorably impacts MOUD adherence and relapse prevention.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available upon study team approval of written requests with analytic plan included in the request.

Authors' Contributions

MRK was a major contributor to the writing of this manuscript. BDD developed the study intervention, Empowered Relief. In close collaboration with BDD, DSY developed the study design and the questionnaire for this project. DSY oversaw the implementation of the study, which included recruitment, data management, data quality, and data privacy. Both BDD and DSY critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Empowered Relief was created by BDD and Stanford University is the copyright and trademark owner of the intervention. BDD receives no personal revenue from Empowered Relief. Stanford University receives fees from Empowered Relief CME clinician training and certification workshops. BDD holds NIH research grants and PCORI research awards to study Empowered Relief. BDD is chief science advisor at AppliedVR and receives compensation for this role. BDD receives royalties for 4 books she has authored. BDD serves on the NIH Interagency Pain Research Coordinating Committee (scientific member), the medical advisory board of the Facial Pain Association, the board of directors of the Institute for Brain Potential. She formerly served on the Centers for Disease Control and Prevention Opioid Prescribing Guidelines Workgroup (scientific member) and the board of directors of the American Academy of Pain Medicine.

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Abbreviations

CBT: cognitive behavioral therapy
ER: Empowered Relief
HIPPA: Health Insurance Portability and Accountability Act
IRB: institutional review board
MORE: mindfulness-oriented recovery enhancement
MOUD: medication for opioid use disorder
OUD: opioid use disorder
PCS: Pain Catastrophizing Scale
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Technology-Assisted Mental Health Intervention Delivered by Frontline Workers at Community Doorsteps for Reducing Anxiety and Depression in Rural Pakistan: Protocol for the mPareshan Mixed Methods Implementation Trial

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Abstract

Background: There is a dearth of specialized mental health workforce in low- and middle-income countries. Use of mobile technology by frontline community health workers (CHWs) is gaining momentum in Pakistan and needs to be explored as an alternate strategy to improve mental well-being.

Objective: The aim of this study is to assess the feasibility, acceptability, and usefulness of an app-based counseling intervention delivered by government lady health workers (LHWs) to reduce anxiety and depression in rural Pakistan.

Methods: Project mPareshan is a single-arm, pre- and posttest implementation research trial in Badin District, Sindh, using mixed methods of data collection executed in 3 phases (preintervention, intervention, and postintervention). In the preintervention phase, formative qualitative assessments through focus group discussions and in-depth interviews assess the acceptability and appropriateness of intervention through perceptions of all concerned stakeholders using a specific interview guide. A REDCap (Research Electronic Data Capture)-based baseline survey using Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 Scale (GAD-7) determines the point prevalence of depression and anxiety among consenting men and women older than 18 years. Individuals with mild and moderate anxiety and depression are identified as screen positives (SPs) and are eligible for mPareshan app–based intervention. Mental health literacy of health workers is improved through customized training adapting the World Health Organization's Mental Health Gap Action Programme guide 2.0. The intervention (mPareshan app) consists of tracking, counseling, and referral segments. The tracking segment facilitates participant consent and enrollment while the referral segment is used by LHWs to transfer severe cases to the next level of specialist care. Through the counseling segment, identified SPs are engaged during LHWs' routine home visits in 6 face-to-face 20-minute counseling sessions over 6 months. Each session imparts psychoeducation through audiovisual aids, breathing exercises, and coping skills to reduce stress. Clinical and implementation outcomes include change in mean anxiety and depression scores and identification of facilitators and barriers in intervention uptake and rollout.

Results: At the time of this submission (April 2024), we are analyzing the results of 366 individuals who participated in the baseline prevalence survey, the change in knowledge and skills of 72 health workers who took the mPareshan training, change in anxiety and depression scores of 98 SPs recruited for app-based counseling intervention, and perceptions of stakeholders pre- and postintervention gathered through 8 focus group discussions and 18 in-depth interviews.

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Conclusions: This trial will assess the feasibility of early home-based mental health screening, counseling, and prompt referrals by frontline health workers to reduce anxiety and depression in the community. The study findings will set the stage for integrating mental health into primary health care.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12622000989741; https://tinyurl.com/5n844c8z

International Registered Report Identifier (IRRID): DERR1-10.2196/54272

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KEYWORDS

anxiety; depression; feasibility; mental health; health workers; mPareshan app; implementation research

Introduction

Background

Mental disorders account for 14% of the global burden of disease [1]. Globally, 322 million (4.4%) and 264 million (3.6%) people endure depression and anxiety, respectively [2]. The data from World Mental Health Surveys concluded that people with mental disorders sought treatment in a very small proportion, particularly in low- and-middle income countries (LMICs) [3]. Barriers to accessing mental health care facilities in LMICs include the cost of mental health care, poor distribution of available resources, and the distance to reach a mental health facility [4,5].

Pakistan has a sizable burden of psychiatric morbidity, particularly depression and anxiety. It is an LMIC with a population of 220 million, with almost 60% residing in rural areas [6,7]. Pakistan has the highest depression rates in contrast to other transitional countries which can be attributed to several factors such as poverty, political turmoil, gender inequality, and natural disasters, to mention a few [1,5,7,8]. The COVID-19 pandemic has worsened the mental health crisis with a rise in depression, anxiety, and stress [9]. The number of deaths by suicide has also increased since the pandemic [10].

Community health workers (CHWs) are the first contact for individuals seeking health care in transitional countries [11]. A well-structured CHW program has already been established in Pakistan, known as the Lady Health Worker Programme (LHW-P) [12]. Lady health workers (LHWs) and lady health supervisors (LHSs) will be collectively referred to as CHWs or health workers in this protocol. The LHW-P covers 85% of the rural population in Pakistan through 115,000 LHWs. They act as “focal points of care” for their assigned catchment areas [13]. LHWs are required to have a minimum of 8 years of education and receive 15 months of training. They maintain health records and track basic health indicators [14]. An LHW typically serves between 100 and 150 houses (1000 people) per month [15] and provides health promotion and disease prevention counseling and monitoring for vaccinations, family planning, and maternal and child health care along with appropriate referrals to specialists where needed [16]. Each LHW is supervised by an LHS. LHSs have higher educational and competency levels as compared to LHWs and are tasked with coordination, monitoring, and supervision of the LHWs at the level of union council (smallest administrative unit of the district). Typically, each LHS oversees 20-25 LHWs and provides them with the required supervision and mentorship. LHSs report to their District Health Officer or District Coordinator [14].

In Pakistan, LHWs can be used to deliver mental health care by acting as the first responders to screen, counsel, and make suitable referrals. Mental health interventions offered by LHWs can provide cost-effective health promotion preventive options for communities with limited resources [17]. The stigma associated with seeking mental ill-health can be reduced if LHWs are tasked to provide mental health care at community doorsteps. Previously, engaging CHWs has been shown to improve health outcomes for heavily stigmatized disorders such as schizophrenia [18].

The role of mobile and wireless technologies has an immense capacity to promote and strengthen health care through CHWs. These innovations use the ubiquity of mobile phones to enhance the functionality of health systems [19]. Mobile penetration being greater than 90% in LMICs has strengthened the viability of mobile health (mHealth) programs, especially in remote areas [20].

Besides being cost-effective, mobile technology has better potential for extensive population-based outreach given its higher penetration and accessibility [21,22]. App-based interventions offer early detection of symptoms, decrease barriers associated with traditional in-person interventions, and offer efficient use of time by minimizing delays in initiating contact with the health care system and self-pacing. It no longer remains limited by proximity to available psychotherapists [23-25].

The promising role of mHealth in screening symptoms of depression and anxiety and halting progression toward severity has been highlighted in previous work [26]. The usefulness of mobile apps for making mental health referrals was highlighted by a quasi-experimental study from India in 2020, in which CHWs were trained to screen the community participants (CPs) through a mobile app for depression and anxiety using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 Scale (GAD-7) and make referrals with the help of psychiatrists. The study reported a significant reduction in the depression and anxiety scores of 900 participants and this task-sharing was found useful for increasing access to mental health care in rural areas [26].

Like other transitional countries, Pakistan has also given less consideration to mental health at the policy level [27]. Hence, instead of initiating a parallel mental health system, the most convincing strategy would be the horizontal integration of

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mental health services within the current primary health system [28]. This would require the integration of the primary health care workforce into the agenda of the governments, nongovernmental organizations, and global mental health stakeholders [29].

The general objective of this study is to assess the feasibility, acceptability, and usefulness of a digital app-based mental health intervention (mPareshan) delivered by LHWs at community doorsteps to screen or track symptoms of anxiety and depression, offer supportive counseling to halt disease progression, and provide appropriate referrals to the next level of care.

Aims and Objectives

The aims and objectives of this study are to (1) assess the feasibility, acceptability, and usefulness of a digital app-based intervention (mPareshan) delivered by LHWs to adult men and women in Badin District, Sindh, Pakistan; (2) examine the effect of mPareshan intervention on-screen positive (SPs) participants' mean anxiety and depression scores; and (3) observe the effect of a contextually adapted Mental Health Gap Action Programme (mhGAP) training on mental health literacy (knowledge) and skills of LHWs and LHSs working in Badin District.

Methods

Study Procedure Outline

Project mPareshan is a prospective, single-district, pre- and posttest implementation research trial, using mixed methods (qualitative and quantitative) of data collection. All phases of the trial are described in detail in the following sections. In the preintervention phase, formative qualitative assessments are conducted with relevant stakeholders (CPs, LHWs, LHSs, and policy makers) to determine the acceptability and appropriateness of delivering mental health counseling via a mobile app. Following this, in a baseline prevalence survey, residents of Badin District are screened by trained data collectors for symptoms of anxiety and depression using standardized psychometric scales of GAD-7 and PHQ-9, respectively. Individuals having symptoms of mild and moderate anxiety or depression are then identified as SPs. Before commencing the intervention, LHWs and LHSs are trained so that their mental health literacy, communication, and counseling skills improve. The training content is contextually adapted from the World Health Organization (WHO) mhGAP guide 2.0 (designed for nonspecialist settings) [30]. A pre- and posttraining assessment of health workers assesses improvement in their knowledge and skills. Next, the mPareshan app is developed based on stakeholder feedback acquired during the formative qualitative inquiry. The app segments and intervention contents are described below. In the intervention phase, SPs receive 1 home-based counseling session per month by LHWs over a period of 6 months. After the intervention phase, a quantitative end line assessment of the SPs is done to assess change in anxiety and depression scores. Postintervention qualitative assessments of key stakeholders determine barriers and facilitators in intervention uptake and rollout. A schematic diagram of the study procedures and expected outcomes is presented in Table 1. This study has been prospectively registered by the Australian New Zealand Clinical Trial Registry (ACTRN12622000989741). Written informed consent is taken from all participants at each stage of the study.

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Table 1. Summary of mPareshan implementation research methods: phase-wise data collection procedures and expected outcomes in Badin District, Sindh, Pakistan (2022-2023).

Research questions	Phase 1: preintervention			Phase 2: intervention	Phase 3: postintervention		Expected outcome
	Qualitative data	Quantitative data		Intervention roll-out[a]	Qualitative data	Quantitative data	
	FGDs[b] and IDIs[c]	HH[d] survey, PHQ-9[e], and GAD-7[f]	mh-GAP[g]-based training	Regular feedback received through mPareshan app	FGDs and IDIs	End line survey, PHQ-9, and GAD-7	
What is the point prevalence of anxiety and depression among a sample of rural households?		✓					Establishing prevalence of mild, moderate, and severe symptoms of anxiety and depression in Badin District.
Is it feasible to implement an mHealth[h]-based mental health intervention through LHWs[i] at community doorsteps?	✓				✓		Acceptability of LHW or LHS[j] for using mPareshan app in managing anxiety and depression. Perceived barriers and facilitators in using the mPareshan app.
Is there a change in CHW knowledge and skills in assessing, diagnosing, and managing anxiety and depression because of mPareshan mhGAP-based training?			✓				Capacity building of LHS and LHWs through mPareshan training.
Is there any change in anxiety and depression scores of SPs[k] because of mPareshan intervention?		✓				✓	Change in anxiety and depression scores of SPs. Operability, usefulness, and task-technology fitness of mPareshan app to the end users.

[a]Intervention described in the last figure.

[b]FGD: focus group discussion.

[c]IDI: in-depth interview.

[d]HH: household.

[e]PHQ-9: Patient Health Questionnaire-9.

[f]GAD-7: Generalized Anxiety Disorder-7 Scale.

[g]mhGAP: Mental Health Gap Action Programme.

[h]mHealth: mobile health.

[i]LHW: lady health worker.

[j]LHS: lady health supervisor.

[k]SP: screen positive.

Study Site

Participants for the intervention are recruited from Badin, which is a coastal district in Pakistan's southern province of Sindh with a population of 1.8 million. There are 5 Talukas (administrative units) and 49 union councils. Badin has an average literacy rate (ability to read and write) of 24% with an approximate household (HH) size of 6 persons [31]. The district has one of the highest suicide rates in the province with a poor mental health care infrastructure [32]. Badin has a functional national LHW-P with 1100 LHWs working under the supervision of 36 LHSs.

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Phase 1: Preintervention

Formative Qualitative Assessments

The study framework for the qualitative assessment was guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) components of the RE-AIM framework [33]. The framework provides a thorough implementation research structure and focuses on several outcomes like acceptability, appropriateness, adoption, feasibility, and so forth [34].

Qualitative assessments (focus group discussions [FGDs] and in-depth interviews [IDIs]) in the initial formative phase are conducted in separate groups with various stakeholders comprising LHSs, LHWs, CPs, and policy makers. The purpose is to assess stakeholder perceptions regarding the acceptability, appropriateness, and feasibility of executing the digital intervention. Permanently employed LHWs and LHSs who regularly perform HH visits and report to their program supervisors are randomly selected for the interviews. CPs are influential people of the community (religious scholars and teachers) capable of providing their viewpoints. Policy makers who are key decision makers at the Provincial Department of Health and the Provincial Program Implementation Unit of LHW-P, Badin are selected for IDIs. Thus, information and feedback obtained before rolling out the intervention are helpful in designing the various features of the mPareshan app (the main intervention).

A semistructured guide helps to carry out the FGDs and IDIs. The guide has a preset list of open-ended questions, organized in a logical pattern with relevant probes (Multimedia Appendix 1). The probes explore the acceptability and appropriateness of involving LHWs in this technology-driven intervention. This guide is translated into the local language, Sindhi, and then translated back into English. Qualitative interviews last about 30-45 minutes, or until the point of saturation. All participants provided written consent before starting the interview.

Baseline Quantitative Assessments

HH Survey

A baseline survey was conducted in 5 Talukas of Badin District, Sindh to identify individuals having symptoms of anxiety and depression. Trained field staff visit HH for data collection. Data collectors are provided training on administering the GAD-7, PHQ-9, and entering data electronically using REDCap (Research Electronic Data Capture; Vanderbilt University) on a tablet. Data are also collected on basic sociodemographic variables.

The GAD-7 scale is used to screen symptoms of anxiety disorders. This scale has 7 items, and each item is rated on a sliding scale of 0-3 based on the frequency of occurrence of the symptoms. The maximum possible score is 21 and the minimum score is 0. Scores of 5, 10, and 15 are taken as the cutoff points for mild, moderate, and severe anxiety, respectively. GAD-7 has 89% sensitivity and 82% specificity for detecting generalized anxiety disorder at a cutoff score of 10 [35].

The PHQ-9 screens for symptoms of depression. There are 9 items rated on a scale of 0 to 3. The maximum possible score is 27 and the minimum score is 0. Scores 5, 10, 15, and 20 represent cutoff points for mild, moderate, moderately severe, and severe depression, respectively. PHQ-9 has 88% sensitivity and 88% specificity for detecting major depression at a cutoff score of 10 [36].

Participants with mild or moderate symptoms of anxiety and depression on the GAD-7 and PHQ-9 are identified as SPs and invited to take part in the mPareshan app–based counseling sessions.

Assessment of CHW's Mental Health Literacy

Before commencing the mental health intervention, a manual is designed to train LHSs and LHWs in the identification of symptoms of anxiety and depression, counseling techniques, and making appropriate referrals [37]. The brief outline of this modular training curriculum is given in Figure 1. The curriculum content is an adaptation of WHO Mental Health Gap Action Program-Intervention Guide V2.0 (mhGAP-IG 2.0) [30]. A pre- and posttraining knowledge and skills assessment of the health workers is also carried out to determine change in their mental health literacy and awareness.

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Figure 1. Outline of mPareshan training curriculum to improve the mental health literacy of health workers.

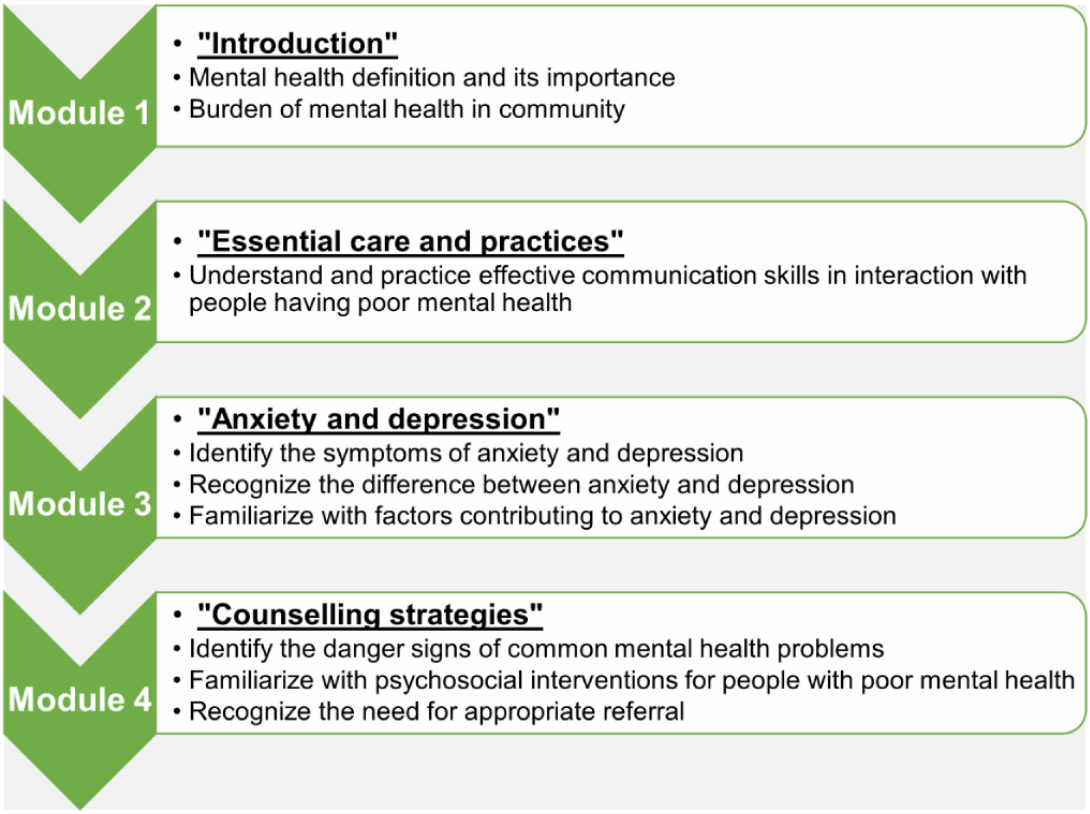

Phase 2: Intervention Rollout

Eligibility Criteria for Participant Enrollment in Intervention

Residents who are 18 years of age and older, who are SP for "mild" or "moderate" symptoms of anxiety or depression as determined by the GAD-7 and PHQ-9, are recruited for the mPareshan intervention. Individuals receiving therapy or pharmacological treatment for mental health issues and exhibiting severe anxiety or depression with danger signs (self-harm, harm to others, and suicidal ideation) are not included in the study.

Main Intervention: mPareshan Digital App

The mPareshan app has been designed based on feedback received from stakeholders in the formative phase. The app has 3 segments—tracking, counseling, and referral. The tracking segment records information on participant recruitment or retention and consent, and has interfaces for LHS, LHW, and study coordinator to access and record their feedback. Based on a 2-week recall, the referral segment identifies danger signs related to suicidal ideation, self-harm, and harm to others and then suggests appropriate referrals to the nearest mental health facility accordingly. In the absence of danger signs, the LHW is guided to the counseling segment of the app to deliver counseling to the SPs. This segment of the app has features of psychoeducation delivered through audio and video clips, breathing exercises, and imparts skills to cope with stress. The counseling segment has different content for each of the 6 sessions, which last around 20 minutes. An outline of the content covered in the 6 sessions is provided in Figure 2.

Prior to the commencement of the 20-minute counseling session, the LHW requests the SP to be seated in a comfortable, preferably less crowded place in the home. At the end of each session, the participant is instructed to practice breathing exercises as homework until the next session. The LHW ensures that the participant feels comfortable and consents to receiving the counseling. If the SP feels uncomfortable at any point in time, the session is discontinued.

Completion of counseling segment redirects the LHW to the section on feedback where she checks all activities that are performed in the session and records her written comments. Once submitted to the server by the LHW, the session gets locked and is passed on to her LHS for review. The LHS logs in from her portal to review all the feedback provided by the LHW and submits it to the study coordinator for a final check. The subsequent session gets unlocked for the LHW after 15 days of completion of the previous session.

These sessions coincide with LHWs' scheduled monthly HH visits in their catchment area. The health workers assigned to the HH of SPs are trained to use configured Samsung Galaxy Tab A7 (4G; Samsung Electronics) on which the mPareshan app is downloaded. The training facilitators demonstrate how health workers are to operate tracking, referral, counseling, and feedback segments of the mobile app.

A summary of the app layout and project workflow (implementation steps) is presented in Figures 3 and 4, respectively.

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Figure 2. mPareshan app: the content of counseling sessions delivered by lady health workers to those who screened positive for anxiety and depression.

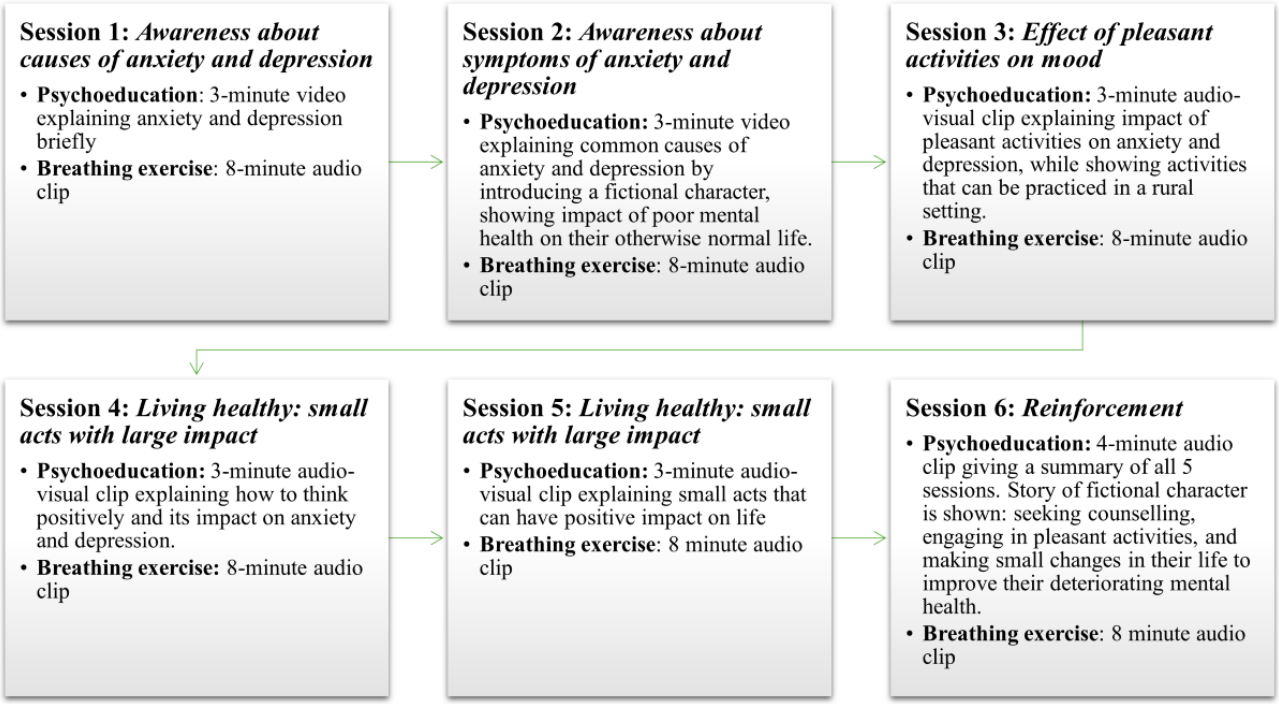

Figure 3. Overview of mPareshan app segments. LHS: lady health supervisor; LHW: lady health worker; SC: study coordinator.

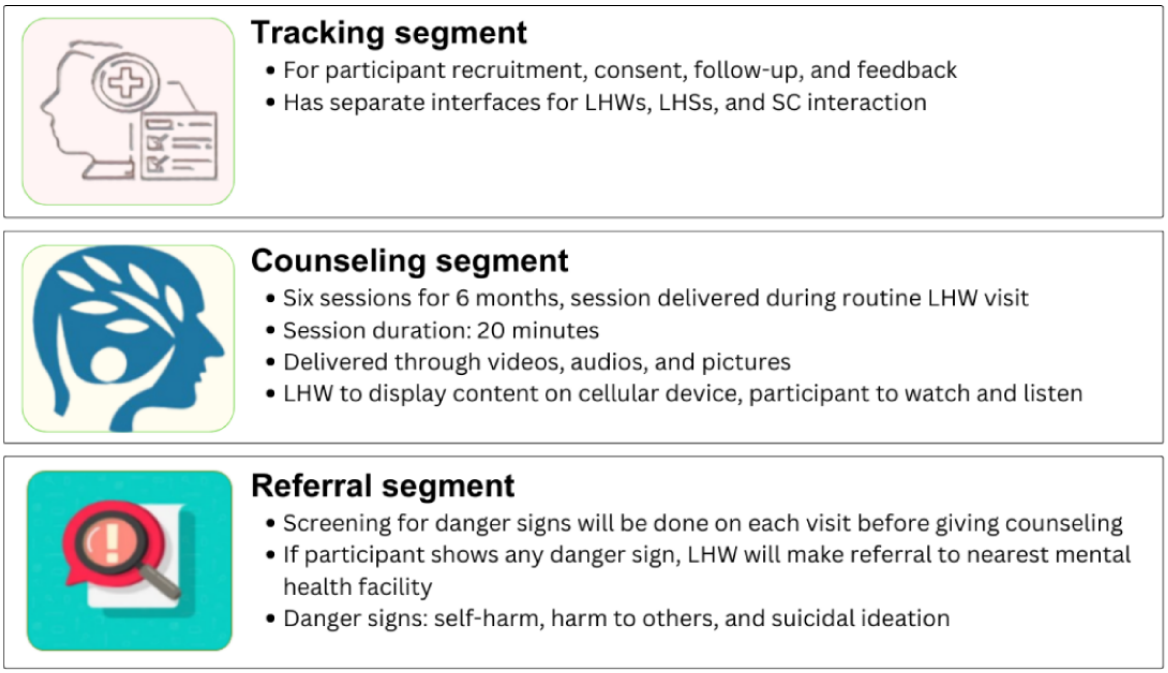

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Figure 4. mPareshan intervention workflow steps for implementation roll out. LHS: lady health supervisor; LHW: lady health worker; SC: study coordinator.

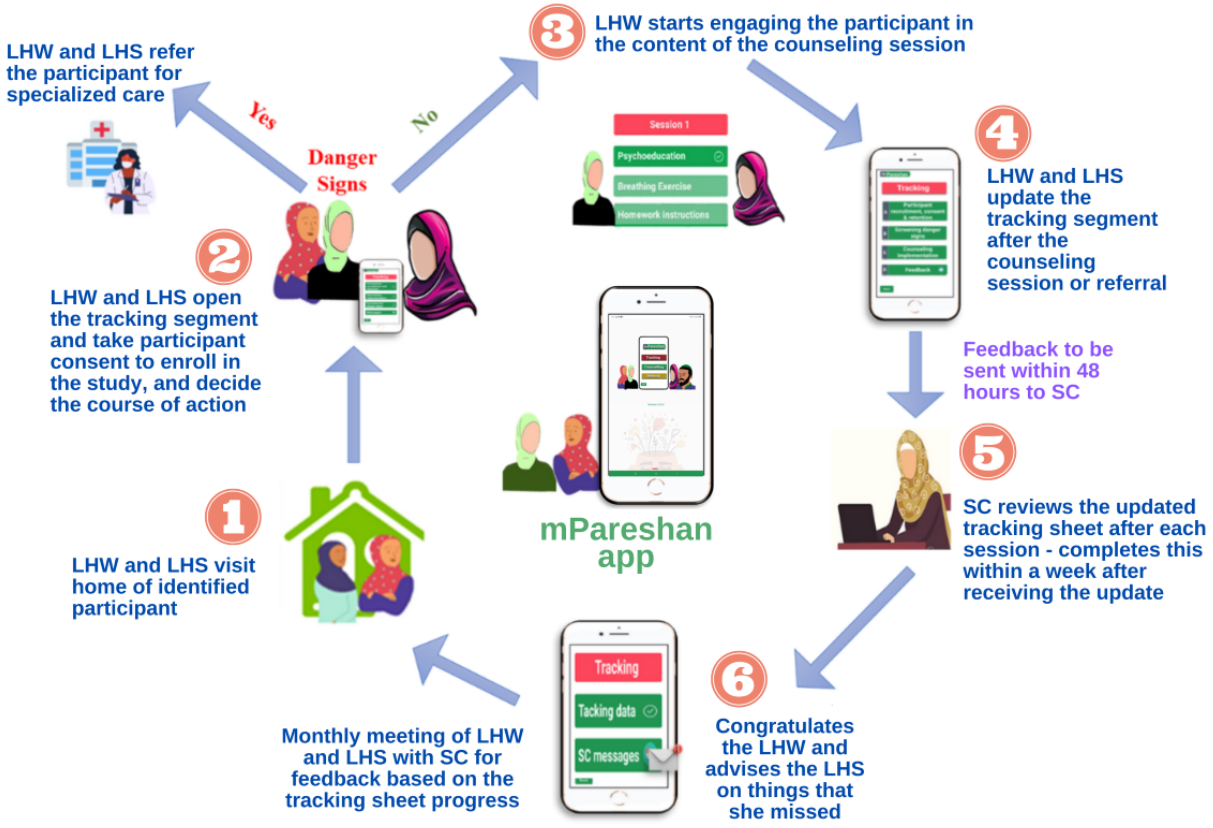

Phase 3: Postintervention

End Line Quantitative Assessment

After the conclusion of the sixth mental health counseling session, an end line HH survey is conducted by trained data collectors using the same PHQ-9 and GAD-7 psychometric tools. This determines the change in mean symptomatic scores of anxiety and depression among intervention recipients (SPs), indicating intervention effectiveness (clinical outcome).

End Line Qualitative Assessment

In the postintervention phase, qualitative assessments (FGDs and IDIs) are done to ascertain the feasibility of intervention uptake and understand facilitators and barriers in implementation rollout. Key stakeholders for FGDs include those randomly selected LHSs and LHWs who took part in the delivery of the intervention. Moreover, for IDIs, CPs in the postintervention qualitative phase also include those individuals who receive the digital counseling intervention, namely, the SPs. All participants provided written informed consent prior to their interviews.

Sample Size Calculations

For the baseline screening survey, the sample size is calculated using OpenEpi (version 3.01; Emory University) [38]. Assuming a 30% prevalence of depression and anxiety symptoms among adults, at a 5% level of significance and 80% power, 323 people are required to assess point prevalence of depression and anxiety [39]. Catering to 10% refusals, the final sample size is 366 individuals.

For the change in mental health literacy of CHWs, a total of 72 LHSs and LHWs are required to detect a mean difference of 1.5 (SD 3.9) in pre- and posttraining knowledge and skills scores, assuming 5% significance level and 80% study power [40].

For receiving mPareshan app-based intervention, the sample size for recruitment of SPs is calculated using Medcalculator (version 19.8; MedCalc Software). Assuming a mean difference between pre- and postintervention of PHQ-9 scores of 1.5 (SD 5.6; mean score at baseline=11.61 and postintervention=10.1), the minimum sample size required at a 5% level of significance and 80% power is 112. Considering a 10% attrition rate, with some oversampling, the expected sample size is 123 for recruiting participants for the mPareshan intervention and demonstrating a reduction in symptoms [41].

Data Analysis

Baseline and end line data collected from respondents is being exported from REDCap to SPSS (version 21; IBM Corp). Frequency and proportion will be used to report categorical variables. Depending on the distribution of anxiety or depression scores of SPs and knowledge or skills scores of health workers, paired *t* tests or McNemar's chi-square tests will be used to evaluate the change in outcomes. The mean difference with 95% CIs will be reported. A *P* value of <.05 will be considered statistically significant.

All interviews will be transcribed in English. Using NVivo (Lumivero), content analysis will be conducted on all IDI and FGD transcripts, and codes will be organized into either

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emergent or predetermined categories by the researchers. Commonalities and differences across the data will be identified and clustered around thematic sections. Verbatim quotes will be added to complement the themes. RE-AIM framework will be used to describe the feasibility outcomes [33].

Ethical Considerations

This study protocol has been approved by the Ethical Review Committee of Aga Khan University (ERC# 2021-6570-20015). mPareshan is an implementation research feasibility trial and is not a clinical or drug trial. No adverse events are, therefore, anticipated. Any participants exhibiting (the a priori–defined) danger signs will be immediately referred during participant recruitment or counseling phases. Written, informed consent is obtained from each participant in their local language at each phase of the study. Data are anonymized and participant confidentiality is maintained. No compensation is offered to SPs for participation in the counseling sessions.

Results

Data were collected in 2022-2023. At the time of this submission (April 2024), we are analyzing the results of 366 individuals who participated in the baseline prevalence survey, the change in knowledge and skills of 72 health workers who took the mPareshan training, change in anxiety and depression scores of 98 SPs recruited for app-based counseling intervention, and stakeholder perceptions gathered from 8 FGDs and 18 IDIs as part of qualitative assessments. Final data cleaning and data analysis are ongoing and the results will be disseminated through peer-reviewed publications in 2024.

Discussion

Project mPareshan will assess the feasibility of using frontline workers in early home-based screening of anxiety and depression, providing app-based mental health counseling and prompt referrals. The community will ultimately benefit as the mental well-being of the population improves by a projected decrease in mean symptomatic scores of anxiety and depression. The contextually adapted mhGAP training for health workers will also lead to an improvement in their mental health literacy thus building the capacity of the primary health care workforce in mental health service delivery.

Previous studies using mHealth modalities have used cellular devices for the purpose of making referrals and record-keeping [26]. Despite the high reported suicide rate, there is a lack of awareness about mental health and the availability of specialized mental health services is suboptimal in Badin District. The novel approach being tested in this trial is expected to improve the mental health of rural populations where access to health care is limited and difficult. Results from this study will be important in initiating a policy dialogue for horizontal integration of basic mental health counseling initiatives in the current primary health system of low-resource settings.

Implementation challenges in this trial in the field included partial disruption and delay in intervention execution attributed to natural disasters, for example, floods in 2022. Furthermore, fluctuations in internet connectivity partially compromised the delivery of the app-based counseling sessions initially. The current substantial workload of LHWs makes it difficult to add mental health counseling as part of their routine package of service delivery. Moreover, considering the small sample size of participants enrolled for receiving the intervention, the generalizability of study findings may be an issue.

Based on the anticipated results of this pilot project, mental health can be introduced as part of the LHW curriculum and service delivery package. This will set the stage for integrating mental health into primary health care.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request. It is to be noted that additional data pertaining to measurement of loneliness was also collected on the University of California, Los Angeles (UCLA) Loneliness Scale (LS-10) at the time of baseline and end-line household survey and will be reported separately.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Guide for focus group discussions and in-depth interviews used for qualitative assessments to assess feasibility and uptake of intervention.
[DOCX File , 20 KB - resprot_v13i1e54272_app1.docx]

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Abbreviations

CHW: community health worker
CP: community participant
FGD: focus group discussion
GAD-7: Generalized Anxiety Disorder-7 Scale
HH: household
IDI: in-depth interview
LHS: lady health supervisor
LHW: lady health worker
LHW-P: Lady Health Worker Programme
LMIC: low- and-middle income country

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mHealth: mobile health
mhGAP: Mental Health Gap Action Programme
mhGAP-IG 2.0: Mental Health Gap Action Program-Intervention Guide V2.0
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
SP: screen positive
WHO: World Health Organization

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Protocol

Factors Affecting Specialty Training Preference Among UK Medical Students (FAST): Protocol for a National Cross-Sectional Survey

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Abstract

Background: The UK medical education system faces a complex landscape of specialty training choices and heightened competition. The Factors Affecting Specialty Training Preference Among UK Medical Students (FAST) study addresses the need to understand the factors influencing UK medical students' specialty choices, against a backdrop of increasing challenges in health care workforce planning.

Objective: The primary objectives of the FAST study are to explore UK medical students' preferred specialties and the factors that influence these choices. Secondary objectives are to evaluate students' confidence in securing their chosen specialty, to understand how demographic and academic backgrounds affect their decisions, and to examine how specialty preferences and confidence levels vary across different UK medical schools.

Methods: A cross-sectional survey design will be used to collect data from UK medical students. The survey, comprising 17 questions, uses Likert scales, multiple-choice formats, and free-text entry to capture nuanced insights into specialty choice factors. The methodology, adapted from the Ascertaining the Career Intentions of UK Medical Students (AIMS) study, incorporates adjustments based on literature review, clinical staff feedback, and pilot group insights. This approach ensures comprehensive and nondirective questioning. Data analysis will include descriptive statistics to establish basic patterns, ANOVA for group comparisons, logistic regression for outcome modeling, and discrete choice models for specialty preference analysis.

Results: The study was launched nationally on December 4, 2023. Data collection is anticipated to end on March 1, 2024, with data analysis beginning thereafter. The results are expected to be available later in 2024.

Conclusions: The FAST study represents an important step in understanding the factors influencing UK medical students' career pathways. By integrating diverse student perspectives across year groups and medical schools, this study seeks to provide critical insights into the dynamics of specialty, or residency, selection. The findings are anticipated to inform both policy and educational strategies, aiming to align training opportunities with the evolving needs and aspirations of the future medical workforce. Ultimately, the insights gained may guide initiatives to balance specialty distribution, improve career guidance, and improve overall student satisfaction within the National Health Service, contributing to a more stable and effective health care system.

International Registered Report Identifier (IRRID): DERR1-10.2196/55155

(JMIR Res Protoc 2024;13:e55155) doi:10.2196/55155

KEYWORDS

medical students; NHS; specialty preferences; workforce planning; medical education; National Health Service

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Introduction

In the United Kingdom, medical students typically undergo 5 years of undergraduate medical education, which may be extended if obtaining an additional degree during medical school, commonly known as an intercalated degree. Additionally, for those with previous degrees and pursuing a graduate-entry medical course, it generally spans 4 years. Following medical school, graduates enter the National Health Service's (NHS) 2-year foundation program, exposing them to a variety of medical specialties. As specialty training commences immediately after the completion of the foundation program, those not intending to take a career break must apply to specialty training (also known as residency training) in the United Kingdom at the beginning of their second year of their career (Foundation Year 2). This underscores the early career decision-making required of medical graduates [1].

Postgraduate medical training in the United Kingdom follows 2 main pathways: "run-through" and "uncoupled" program. "Run-through" programs allow trainees to secure training posts from the outset and, subject to satisfactory progress, continue for the full duration of the program unencumbered by further application processes. Examples of run-through specialties include general practice, pediatrics, and ophthalmology. By contrast, "uncoupled" programs require trainees first to secure a training post at "core" level, in the broad specialty such as anesthetics, surgery, or internal medicine, and then again to enter "higher specialty training," such as in cardiology or vascular surgery [2]. Notably, in the UK health care system, salary progression for doctors, whether in training or at the consultant level, is uniform across specialties. The primary factors that could influence the professional experience within the NHS are not solely the chosen specialty but include wildly variable aspects such as the duration of working hours, the intensity of the clinical environment, and the specific nature of clinical settings.

Since 2007, recruitment for much of specialty training in the United Kingdom has been centralized, using competitive national processes in which applicants are ranked according to various criteria [3]. Competition for specialty training in the United Kingdom is at an all-time high, having surged in recent years. In 2016, there were 20,044 applications for 10,671 posts aggregated across all specialties, conferring a ratio of 1.88 applications per post. By 2023, this ratio had risen to 3.37, with applications increasing by 249% while training places only grew by 183%. Some specialties, already renowned for being competitive have seen marked increases in their competition ratios. In neurosurgery, for example, the ratio climbed from 6.50 in 2016 to 12.75 in 2023. Meanwhile, even in specialties where the demand for services is exceedingly high—and rising—competition has intensified, with the ratio rising from 1.28 to 2.67 over the same period in general practice for instance [4]. Competition for residency training in the United Kingdom is set to worsen yet further, as the government announces plans to double medical school places by 2031/32 [5-8].

Medical students' decisions may be influenced by their demographic backgrounds [9-13], experiences at medical school [14-16], and perceptions of the chosen specialty's lifestyle, including work-life balance [17-19], financial incentives, and prestige [20]. External guidance from mentors [21] or family [22] and internal drivers, such as personal health experiences or the desire to serve particular patient demographics, also contribute to this complex decision-making process [22]. Although there have been international studies exploring which specialties resident doctors or medical students intend on pursuing and factors affecting these decisions [14,23-27], UK studies focused on why individuals are attracted to pursuing one specialty, and studies exploring which factors attract them to one specific specialty [28-44], there is currently a lack of broad, high-powered studies investigating the choice of specialty among UK medical students of all year groups and the factors influencing this preference.

Recently, we conducted the largest UK medical student study—the (Ascertaining the Career Intentions of UK Medical Students (AIMS) study—which investigated medical students career intentions and demonstrated that a noteworthy 35% of medical students intend to leave the NHS within 2 years of graduation [45,46]. Among our findings, we identified that a majority of medical students were dissatisfied with several aspects of residency training in the United Kingdom, including the cost of training, the rotational aspect of training, the ease of entry into a specialty training program, and the length and standard of training. This highlights the need to better understand medical students' views, concerns, and expectations of specialty training in the United Kingdom.

We previously explored the role of medical schools in mitigating the current trends of medical students intending to leave the NHS. This work emphasized the importance of understanding and developing strategies within medical education to retain future doctors in the UK health care system. It also raised critical questions about the influence of medical school experiences, mentorship, and curricular design on career decisions [7,47].

The Factors Affecting Specialty Training Preference Among UK Medical Students (FAST) study seeks to understand the factors influencing specialty training choices among UK medical students. By examining these determinants across all student year groups, the study seeks to inform policy and educational strategies to better align training opportunities with the expectations and needs of the future medical workforce.

Methods

Study Objectives

Primary Objectives

The primary objectives of this study are (1) to examine the preference of UK medical students regarding their choice of specialty training and (2) to investigate the factors that influence UK medical students' choice of specialty training.

Secondary Objectives

The secondary objectives of this study are (1) to assess the confidence levels among UK medical students regarding their ability to pursue their chosen specialty within the UK health care system; (2) to analyze the impact of demographic variables

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on students' choice of specialty and their certainty and confidence in these choices; (3) to explore the association between academic variables and students' specialty choice, as well as their certainty and confidence in these decisions; and (4) to identify and compare the variability in specialty choice trends and confidence levels across different UK medical schools.

Study Design

FAST is a national, multicenter, cross-sectional study of UK medical students, following a similar methodology to the AIMS study [45]. Participants' responses will be recorded via a web-based survey platform. The survey contains 17 questions. Questions are structured using a combination of Likert scale matrices, multiple-choice options, and free-text entry to broaden the capture of sentiment nuance and improve precision in the data. Data collection will take place from December 4, 2023, aiming to be completed on March 1, 2024. A full project timeline can be found in Table 1. This timeline will be approached with a level of flexibility to account for any national or center-specific challenges with data collection.

The survey consists of 3 sections. Section 1, to be completed by all participants, seeks background and demographic information. Consent is also obtained in this section. Section 2 gathers information on the certainty and choice of specialty as well as knowledge and guidance received regarding the pursuit of their chosen specialty. Section 3 invites participants to rate the importance of various factors influencing their specialty choice and provides an optional free-text entry for additional factors. The full questionnaire can be found in Multimedia Appendix 1.

To identify gaps in knowledge and inform the aim of the project, a review of the existing literature was conducted, including similar questionnaires and qualitative studies on students' and doctors' perspectives. Feedback from senior clinical staff was also obtained and used to revise questions based on the comments received. These steps were taken to ensure as nondirective and comprehensive a survey as possible, while remaining unencumbering so as to maximize the number of responses for statistical power. Further, an informal pilot group was convened, consisting of medical students from different stages of training. These students responded to the survey, and shared their experiences and perspectives on factors that influence their specialty training choices during a series of discussions. These informal discussions aimed to identify both positive and negative factors that could influence these decisions. The resultant feedback was critical in refining the survey's contents to enhance participants' experience.

The survey will be hosted on the Qualtrics survey platform (Provo, Utah, US), a General Data Protection Regulation–compliant web-based survey platform which supports both mobile and desktop devices. The survey will be distributed through multiple channels, including university mailing lists, student society social media pages, conferences, and personal and medical school social media platforms (such as Facebook, Instagram, LinkedIn, and X, formerly known as Twitter). To maximize distribution across the United Kingdom, a national network of approximately 200 FAST Collaborative members was recruited, representing all medical schools in the United Kingdom. Each member will be asked to liaise with their medical school dean to distribute the survey through official channels and advertise it at regular intervals over the collection period from December 2023 to March 2024.

Table 1. Project timeline.

Dates	Activity
October 1, 2023, to October 31, 2023	Conceptualization and planning phase
November 1, 2023, to December 3, 2023	Recruitment and training of factors affecting specialty training collaborative network across UK medical schools
December 4, 2023, to February 29, 2024	Data collection period
March 1, 2024, to August 1, 2024	Data analysis and manuscript preparation

Study Population

All current students in all years at UK medical schools recognized by the General Medical Council and the Medical Schools Council are eligible to participate in the study. A list of eligible medical schools and approved programs can be found in Multimedia Appendix 2. At the time of writing, certain new schools, although approved by the General Medical Council, were yet to admit their first cohort of students, so they were excluded from this study.

Data Collection

The survey will be disseminated largely through recruited medical student collaborators recruited prior to the study launch. These collaborators will ensure that their medical school is formally engaged at an early stage of this study and will be primarily responsible for disseminating this questionnaire among students at their medical school.

Ethical Considerations

This study adheres to UK NHS Health Research Authority guidance, with NHS Research Ethics Committees' review exemption applied. Participants will provide explicit consent prior to voluntarily completing the survey and are free to withdraw at any time by contacting the study team. All data analyzed are anonymous.

To obtain informed consent, a participant information sheet (Multimedia Appendix 3) will be made available to all participants. This information sheet will explain the rationale and purpose of the study, emphasizing its voluntary nature and the anonymity and confidentiality of participation. It will be

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made clear on the study materials and on the first page of the questionnaire that submitting responses provides consent for data usage. Additionally, the first question of the survey will obtain consent, and it will be mandatory to complete the survey. Consent can be withdrawn at any time, during or after completing the questionnaire by contacting the study lead. Email addresses will only be collected and stored for participants who provide explicit consent to this in the final question of the survey. Email addresses will be kept separate from the responses to survey questions, ensuring anonymity.

The anonymous responses will be collected and stored on the secure web-based server Qualtrics. Survey data will be extracted from Qualtrics and stored in a password-protected Microsoft Excel (Microsoft Corporation) file accessible only to the central study team. University of Cambridge standards for data handling will be followed for all data management and record keeping.

Participants will not receive compensation for completing the questionnaire. However, participants who provide their contact information will be entered into a prize draw, with one randomly selected individual receiving a cash prize of £250 (equivalent to US $316.42) at the end of data collection.

Data Analysis

The forthcoming analysis of the FAST study data aims to construct a robust statistical representation of the factors influencing specialty training decisions among medical students. The initial step will involve descriptive statistics to establish a foundational understanding of the data set. This will include the calculation of frequencies, means, medians, and modes for the survey responses to provide a comprehensive picture of central tendencies and dispersion within the responses.

For the comparison of means among continuous variables across multiple groups, ANOVA will be used. This analysis will support discerning whether there are statistically significant differences in attitudes toward specialty training between different subgroups within the population, such as students from different academic years. In addition to these methods, logistic regression analysis will be performed to model the probability of certain outcomes, such as the likelihood of choosing a specific specialty based on a range of influencing factors. This will allow us to estimate odds ratios and understand the strength and direction of associations between multiple predictors and specialty choices. Moreover, discrete choice models will be used to analyze the choices made by medical students among a set of specialties. This method will provide insight into the relative preferences and the trade-offs that students make when considering various specialty attributes. Where appropriate, multivariate methods will be applied to simultaneously account for multiple influencing factors at once. This comprehensive approach will provide deeper insights into the complex interplay of variables affecting specialty decisions. Data analysis will be performed using Microsoft Excel (v16.71) and RStudio (version 4.2.1; Posit PBC).

Participants were given the opportunity to provide additional insights into factors influencing their specialty training decisions through free-text entries. These qualitative responses will undergo a thematic analysis to identify recurring themes. This qualitative approach will complement the quantitative analysis, providing nuanced insights into the factors influencing specialty training decisions beyond those captured by the survey questionnaire. By incorporating participants' own perspectives and experiences, the thematic analysis will enrich the understanding of the complex interplay of variables shaping medical students' career aspirations.

The study will adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies [48].

Results

Following study completion, it is intended that results will be presented at local, regional, national, and international conferences. In addition, the results will be disseminated via publication in a peer-reviewed medical journal. All collaborators will be given PubMed-citable collaborative coauthorship under the institutional name: *the FAST Collaborative*. We will have a hybrid authorship list of named authors and the institutional collaborative.

Following study completion, medical school collaborators will be able to request their institution-specific data and the analysis performed on said data from the FAST steering committee. These data will be anonymized. The fully anonymized data set will be made publicly available.

Data collection is currently underway, with the study being launched nationally on December 4, 2023. Data collection will close on March 1, 2024, and data analysis will commence. The results are expected to be available later in the year.

Discussion

The FAST study anticipates significant variability in specialty preferences among medical students, influenced by the wide array of factors being explored in this investigation. Personal interests, prior experiences, and perceptions of the lifestyle conferred by pursuing different specialties are anticipated to be highly influential. We hypothesize that demographic factors, including gender, ethnicity, socioeconomic background, and geographical location, will also play a significant role in shaping specialty preferences. In addition, medical school experiences, such as teaching quality and clinical exposure, are expected to strongly influence students' decisions regarding specialty training. The role of mentorship is predicted to impact specialty choice in a similar fashion. Other factors, including personal health experiences may also influence some students, while awareness of specialty training opportunities and current health care trends could shape students' perceptions of certain specialties. Furthermore, we predict that knowledge of specialty pathways, application processes, and portfolio quality will increase as students progress through medical school, thus, leading to more informed decisions relating to specialization.

Although this study is centered on the UK health care system, the insights derived will have broader implications. The challenges and decision-making processes—and their associated challenges—faced by UK medical students are not unique to

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the NHS and often reflect wider global trends in medical education. For instance, factors influencing specialty choice, such as work-life balance and financial considerations, have been highlighted as also significant among medics in other health care systems [49-65]. This study's findings can, therefore, offer valuable perspectives to international audiences, serving as a reference point for similar research conducted in other countries. Moreover, the detailed exploration of the UK system may help other nations identify and address similar challenges within their own medical education frameworks.

The FAST study is poised to provide a comprehensive examination of the factors influencing UK medical students' preferred medical specialties. The strategic focus on a broad spectrum of elements, from work-life balance to mentorship, will yield critical insights valuable for educational institutions and policy makers in understanding the determinants of specialty selection. Furthermore, by incorporating a wide-ranging demographic profile, this study aims to discern patterns and potential inequities in the specialty choice process, affording a detailed perspective on how students' different backgrounds might steer career trajectories within the medical field. Additionally, the study's inclusive approach, encompassing students from all year groups and UK medical schools, will help to create a robust and diverse data set: one which offers a more accurate cross-section of the current student body and enhances the generalizability of the findings.

It is important to note the potential limitations of the FAST study. As with many cross-sectional studies, the FAST study's main limitation is its snapshot view, which precludes tracking changes in students' preferences and influencing factors over time. There is also the potential for selection bias, where students with certainty regarding their specialty training choices or strong opinions about factors influencing their decision-making may be more inclined to participate. Therefore, this could unintentionally exclude some students who are in the process of making these decisions. To address this, the study's distribution strategy is extensive, involving a variety of channels and touchpoints to encourage a balanced response rate across the student population. The survey was also explicitly designed to be inclusive of those whose future specialty is uncertain. Recruitment and engagement challenges could also pose a risk to achieving a truly representative sample. Acknowledging this, extensive efforts are being made to secure a comprehensive and representative collaborator network to support student outreach. Finally, the survey design could restrict the depth of insights obtainable from predefined responses. However, the iterative process used during the extensive preparatory phase involving peer review and expert consultation, along with the provision for free-text responses, will ensure a rich and nuanced collection of data pertinent to specialty training choices.

The FAST study endeavors not only to inform but also stimulate strategic improvements in the way medical education is structured and how future doctors are supported with making decisions about their career. Insights gained could drive initiatives aimed at increasing the appeal of less popular specialties, improving mentorship programs, and refining the career guidance offered to medical students. These actions could potentially mitigate the specialty imbalances and contribute to a more even distribution of medical professionals across the health care system and increase retention rates of medical graduates in the NHS by providing a stronger sense of identity through specialty interest [7].

By capturing the preferences and perceptions of the future workforce, the FAST study will support the broader objective of establishing a regular, comprehensive survey of UK medical students, akin to a workforce census. This initiative could aid the government and educational authorities in their workforce planning strategies, ultimately fostering a more satisfied, fulfilled, and well-distributed medical workforce.

Acknowledgments

This work was supported by Queens' College, University of Cambridge. The institution had no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

Data Availability

The data sets generated and analyzed during this study will be made publicly available once the study is completed.

Authors' Contributions

TF was responsible for conceptualization and drafting the manuscript. TF and AMC were responsible for designing the survey. All authors were responsible for editing and revising the manuscript. TF was responsible for supervision. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Copy of the Factors Affecting Specialty Training Preference Among UK Medical Students (FAST) questionnaire.
[PDF File (Adobe PDF File), 160 KB - resprot_v13i1e55155_app1.pdf]

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Multimedia Appendix 2
List of eligible medical schools and General Medical Council–approved programs.
[DOCX File , 14 KB - resprot_v13i1e55155_app2.docx]

Multimedia Appendix 3
Participant information sheet for the Factors Affecting Specialty Training Preference Among UK Medical Students (FAST) study.
[PDF File (Adobe PDF File), 64 KB - resprot_v13i1e55155_app3.pdf]

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Abbreviations

AIMS: Ascertaining the Career Intentions of UK Medical Students
FAST: Factors Affecting Specialty Training Preference Among UK Medical Students
NHS: National Health Service
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Measuring Relationship Influences on Romantic Couples' Cancer-Related Behaviors During the COVID-19 Pandemic: Protocol for a Longitudinal Online Study of Dyads and Cancer Survivors

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Abstract

Background: Research has established the effects of romantic relationships on individuals' morbidity and mortality. However, the interplay between relationship functioning, affective processes, and health behaviors has been relatively understudied. During the COVID-19 pandemic, relational processes may influence novel health behaviors such as social distancing and masking.

Objective: We describe the design, recruitment, and methods of the relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic study. This study was developed to understand how relational and affective processes influence romantic partners' engagement in cancer prevention behaviors as well as health behaviors introduced or exacerbated by the COVID-19 pandemic.

Methods: The relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic study used online survey methods to recruit and enroll 2 cohorts of individuals involved in cohabiting romantic relationships, including 1 cohort of dyads (n=223) and 1 cohort of cancer survivors (n=443). Survey assessments were completed over 2 time points that were 5.57 (SD 3.14) weeks apart on average. Health behaviors assessed included COVID-19 vaccination and social distancing, physical activity, diet, sleep, alcohol use, and smoking behavior. We also examined relationship factors, psychological distress, and household chaos.

Results: Data collection occurred between October 2021 and August 2022. During that time, a total of 926 participants were enrolled, of which about two-thirds were from the United Kingdom (n=622, 67.8%) and one-third were from the United States (n=296, 32.2%); about two-thirds were married (n=608, 66.2%) and one-third were members of unmarried couples (n=294, 32%). In cohorts 1 and 2, the mean age was about 34 and 50, respectively. Out of 478 participants in cohort 1, 19 (4%) identified as Hispanic or Latino/a, 79 (17%) as non-Hispanic Asian, 40 (9%) as non-Hispanic Black or African American, and 306 (64%) as non-Hispanic White; 62 (13%) participants identified their sexual orientation as bisexual or pansexual, 359 (75.1%) as heterosexual or straight, and 53 (11%) as gay or lesbian. In cohort 2, out of 440 participants, 13 (3%) identified as Hispanic or Latino/a, 8 (2%) as non-Hispanic Asian, 5 (1%) as non-Hispanic Black or African American, and 398 (90.5%) as non-Hispanic White; 41 (9%) participants identified their sexual orientation as bisexual or pansexual, 384 (87.3%) as heterosexual or straight, and 13 (3%) as gay or lesbian. The overall enrollment rate for individuals was 66.14% and the overall completion rate was 80.08%.

Conclusions: We discuss best practices for collecting online survey data for studies examining relationships and health, challenges related to the COVID-19 pandemic, recruitment of underrepresented populations, and enrollment of dyads. Recommendations

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include conducting pilot studies, allowing for extra time in the data collection timeline for marginalized or underserved populations, surplus screening to account for expected attrition within dyads, as well as planning dyad-specific data quality checks.

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KEYWORDS

cancer prevention; COVID-19; risk perceptions; dyads; romantic relationships; cancer; oncology; survivor; survivors; dyad; spouse; spousal; partner; health behavior; health behaviors; cohabiting; cohabit; study design; recruit; recruitment; methodology; methods; enrol; enrolment; enroll; enrollment

Introduction

Research has shown that romantic relationships can impact individuals' morbidity and mortality outcomes; however, there is a need to understand how partners in romantic relationships influence one another's health outcomes, including through their health behaviors [1]. In the context of cancer prevention and control, most of the research has focused on the role of romantic partners at the stages of diagnosis, treatment, and survivorship (eg, as caregivers), rather than the role of partners at the stages of prevention and detection [2,3]. Romantic relationships often involve mutual and enduring influence over time, shared decision-making regarding cancer-relevant health behaviors (eg, diet), and shared social and living environments. Therefore, focusing cancer prevention efforts on individuals rather than on romantic dyads, when feasible, may represent a missed opportunity for positive impact. As such, there is a need to understand how relational processes in romantic relationships influence cancer prevention. In this study, we describe the protocol of the relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic (R2C2) study, which aimed to (1) examine ways in which romantic partners influence each other across a wide range of cancer prevention behaviors and COVID-19–related behaviors, (2) examine ways in which the COVID-19 pandemic has influenced both cancer control and romantic relationships, and (3) recruit participants from historically underrepresented and medically underserved backgrounds.

The COVID-19 pandemic has disrupted many stages along the cancer control continuum including the health behaviors individuals engage in, their ability to receive treatment, survivorship care, and even the grieving process [4-8]. In addition, the pandemic has disrupted social relationships [9,10], an important social factor contributing to cancer prevention and control, both in terms of changing the ways in which people interact and by introducing new stressors and opportunities for conflict [11]. The COVID-19 pandemic affords the opportunity to examine not only disruptions across the cancer prevention and control continuum and disruptions to individuals' romantic relationships but also to study ways in which romantic partners influence each other's health. Thus, we sought to examine ways in which cancer prevention and control have been disrupted during the pandemic, how romantic relationship functioning has been disrupted, and how romantic partners influence each other's COVID-19–related behaviors, such as social distancing, masking, and vaccination.

The COVID-19 pandemic has also widened gender, sexual orientation, and racial or ethnic disparities in health and well-being [12-15]; yet, very little is known about how close relationships during the pandemic might influence the health behaviors of these populations. Specifically, dyadic health research often fails to include people with racialized identities as well as people who identify with lesbian, gay, bisexual or pansexual orientations (LGB), and who can be characterized as underrepresented populations in the literature. In addition, cancer survivors have been particularly vulnerable to COVID-19 during the pandemic [16]. The greater risk of health consequences for cancer survivors due to the COVID-19 pandemic, combined with evidence gaps in the existing survivorship literature [17], demonstrates a critical need to better understand the mechanisms of health behavior and risk perceptions during survivorship. Thus, a multilevel analysis of health behaviors, including measuring the role of relationships is needed to fill these evidence gaps. Close relationships during the pandemic may impact health behaviors differently across the cancer control continuum and intersect by identity. Therefore, we aimed to recruit cancer survivors and underrepresented populations.

Dyadic research, in which both members of a dyad (eg, a romantic couple) are assessed on the same or similar measures, is an important methodology that allows for a better understanding of how individuals in a relationship influence one another's health. Dyadic methods can estimate the degree of correspondence (ie, similarity) in health behaviors and behavioral correlates between 2 members of a dyad. These analyses also provide insights into how individuals' behaviors are influenced by their partners in a way that cannot be accomplished by models that assume participants are independent of one another.

Research designs that investigate the intricate interplay of environmental factors, health behavior patterns, and shared risk perceptions within dyadic relationships, particularly romantic partnerships, are valuable for a better understanding of individuals' health. Numerous studies have shown that close relationship partners, and the quality of those relationships, have significant impacts on mortality, morbidity, and their underlying determinants [18-20]. Furthermore, recent research focusing on romantic relationships during the COVID-19 pandemic has highlighted the profound impact of mental health indicators related to COVID-19, such as psychological stress and depressive symptoms, on the functioning of these relationships [11,21]. In addition, changes in certain health behaviors during the pandemic, such as increased alcohol use, have been

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associated with heightened COVID-19–related relationship conflict [22].

Understanding the specific dynamics of health-related behaviors and perceptions within romantic partnerships, especially given the unique challenges posed by events like the COVID-19 pandemic, is crucial. The pandemic introduced stressors and changes that influence relationship processes, which in turn may influence how couples engage in health or health-risk behaviors. Investigating these dynamics can provide insights into how environmental factors, health behaviors, and shared risk perceptions influence the health and well-being of both individuals and their relationships.

Recognizing the largely untapped potential, as well as the gaps and shortcomings in the existing literature such as homogenous (ie, White and heterosexual) samples and frequent use of cross-sectional approaches, led to the conceptualization of this study examining the complex interplay of multilevel factors in this context, including relationship variables, risk perceptions, cancer-related behaviors, and COVID-19–related factors, as well as structural and environmental factors that may play a role.

To address evidence gaps in the literature and to assess how the ongoing COVID-19 pandemic may influence dyadic processes relevant to health, we designed a dual-cohort repeated-measures online survey study for the development and testing of comprehensive models that identify dyadic influences on cancer risk and prevention behaviors. The first cohort in R2C2 consisted of cohabitating, romantic dyads while the second cohort consisted of individual cancer survivors who cohabitated with a romantic partner. R2C2 included the measurement of multiple relationship variables as well as multiple health-related outcomes and moderators as a reflection of a more complex health behavior theoretical framework (discussed in the "Study Development" section; Figure 1). Surveys were developed with the intention to include analysis of the effects of individual differences, emotion coregulation, health behaviors, COVID-19 and cancer-related risk perceptions, and contextual or environmental factors.

Figure 1. A conceptual framework for the relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic (R2C2) study of cancer survivors and romantic dyads.

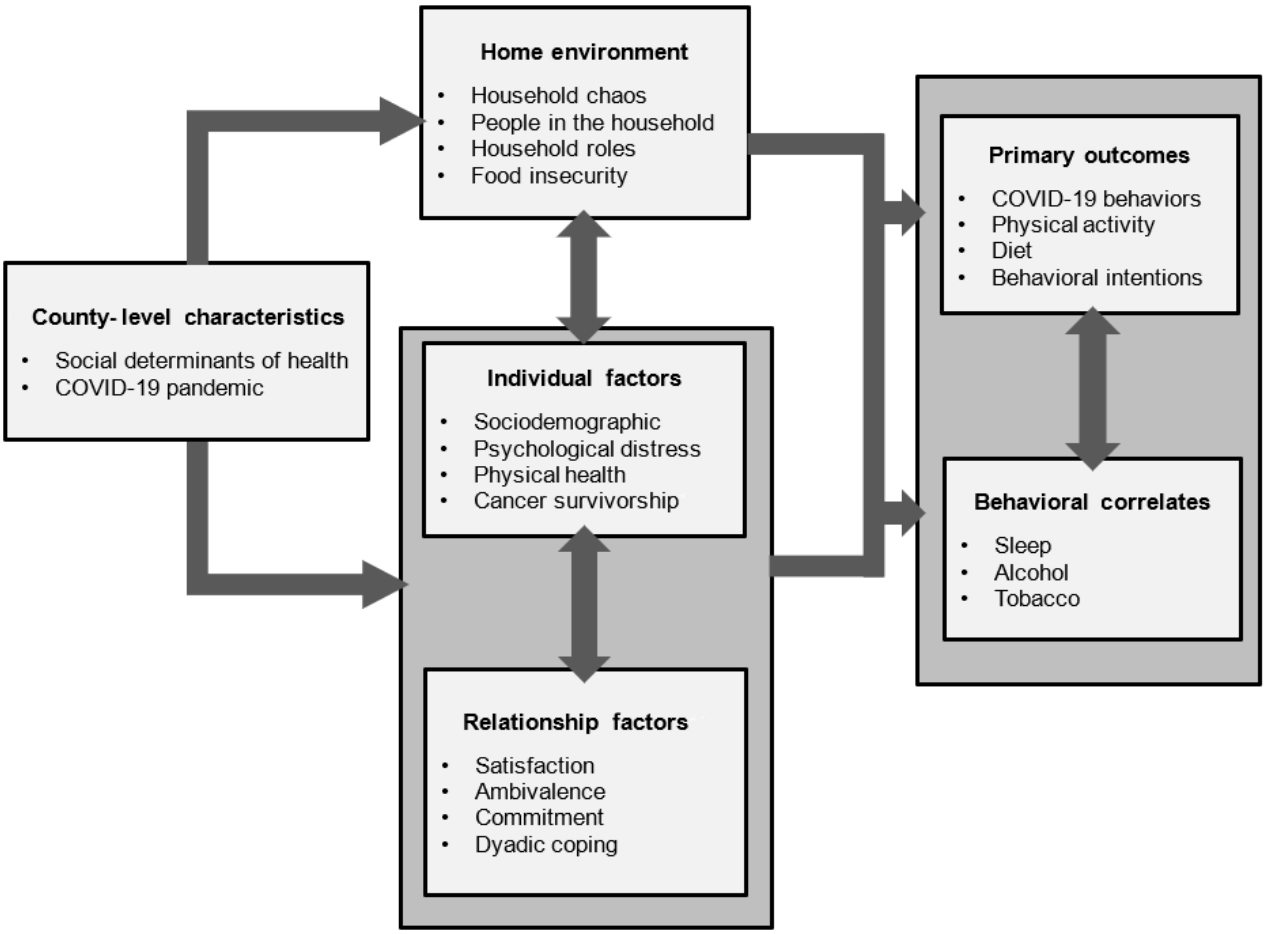

The purpose of this methods report is to describe methodologies and approaches that are seldom described in detail but will be valuable for progressing future research on dyadic relationships and health. There is limited detailed research on best practices for recruiting specific samples, such as romantic dyads and cancer survivors, through online panels. Furthermore, dyadic research is complex and challenging (eg, deciding on whether to prioritize dyadic completion as a recruitment strategy). Thus, this report aims to (1) detail the methodological decisions, tools, and processes that were used during the R2C2 study, (2) report recruitment, enrollment, and response data, and (3) reflect on best practices and limitations to guide future study design.

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Methods

Study Development

We engaged in a multipronged approach to develop the study in a way that would address the abovementioned gaps in cancer prevention research among dyads. First, we identified that other federally sponsored surveys did not already focus on multiple preventive health behaviors among romantic couples. Second, we conducted a series of literature searches in which we scanned published literature on specific cancer prevention behaviors to (1) identify the scope of previous dyadic research that included outcomes of diet, physical activity, sleep, tobacco use, and alcohol use and (2) examine measures and methods used in previous studies of romantic relationships and social support. Third, we conducted a portfolio analysis to determine National Cancer Institute (NCI)–funded grants that involved dyads. We identified the types of dyads sampled, the purpose and specific aims, outcomes, and the constructs and measures used in these studies. Fourth, we engaged in a survey development process in which we asked experts to identify and refine our survey measures. We identified NCI experts on relationships and health and held retreats with them to identify key areas and additional external experts (some of whom were identified during the literature searches) who could provide feedback on our conceptual framework (Figure 1), constructs, and measures. This process was iterative, such that we sent the conceptual framework to experts for feedback, collated that feedback to refine the areas, had NCI fellows conduct reviews to identify relevant items in published work and existing surveys, and sent a long-form survey to the experts for comment and reductions or additions. We also solicited feedback on dyadic research gaps from the general scientific community and the public through the NCI Behavioral Research Program website before selecting the items included in the survey.

These efforts helped refine the methods and content of the study. For example, through this feedback, we added an assessment of stressful life events commonly experienced among adults to examine how these events influence individuals' and dyads' cancer risk behaviors. We also collected data at more than one time point to meaningfully study social exchange and support processes within couples. Our conversations with other researchers also confirmed the importance of recruiting dyads that included individuals who have been underrepresented in the literature (ie, individuals with racialized identities and individuals who identify with LGB sexual orientations). We maintained a focus on these recommendations when deciding how to incorporate pandemic-related influences into the survey.

Recruitment and Enrollment

We recruited 2 cohorts of participants using Prolific, a UK-based online platform for research participant pool recruitment and paid participation [23]. Prolific has protocols intended to fairly compensate participants and deliver high-quality data to researchers. At the time of our study recruitment, Prolific had a pool of approximately 122,110 total available users, all of whom were 18 years or older. We used their standard sample recruitment method and prescreening tool to launch our studies. The prescreening tool allows the recruitment of selected groups of participants based on an extensive set of screening questions carried out by Prolific for each user. Screening criteria can be very specific to meet the needs of a study; for example, researchers can select participants who report a diagnosis of a specific chronic illness, like cancer. Multiple types of screening criteria can be applied, and researchers can preview an estimate of the available user pool for their specific criteria when they create a new study. This estimate is based on the number of potential participants who meet the selected criteria and who have been active on Prolific in the past 90 days.

Eligibility criteria used for both cohorts of adults (cohort 1 of romantic partners and cohort 2 of cancer survivors) were selected using the prescreening tool and included: (1) fluent in English, (2) living with a spouse or partner, and (3) living in the United States or the United Kingdom. In addition, cohort 1 required both partners to affirm using Prolific's prescreening tool that they have a romantic partner who also has a Prolific account, and cohort 2 required individuals to report having had cancer using Prolific's prescreening tool (cohort-specific considerations are further discussed in this paper). At the time of initiation of data collection, according to Prolific, the resulting number of participants eligible for the studies was 6141 for cohort 1 and 731 for cohort 2. Figure 2 contains details regarding study recruitment.

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Figure 2. Relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic (R2C2) study flow diagram.

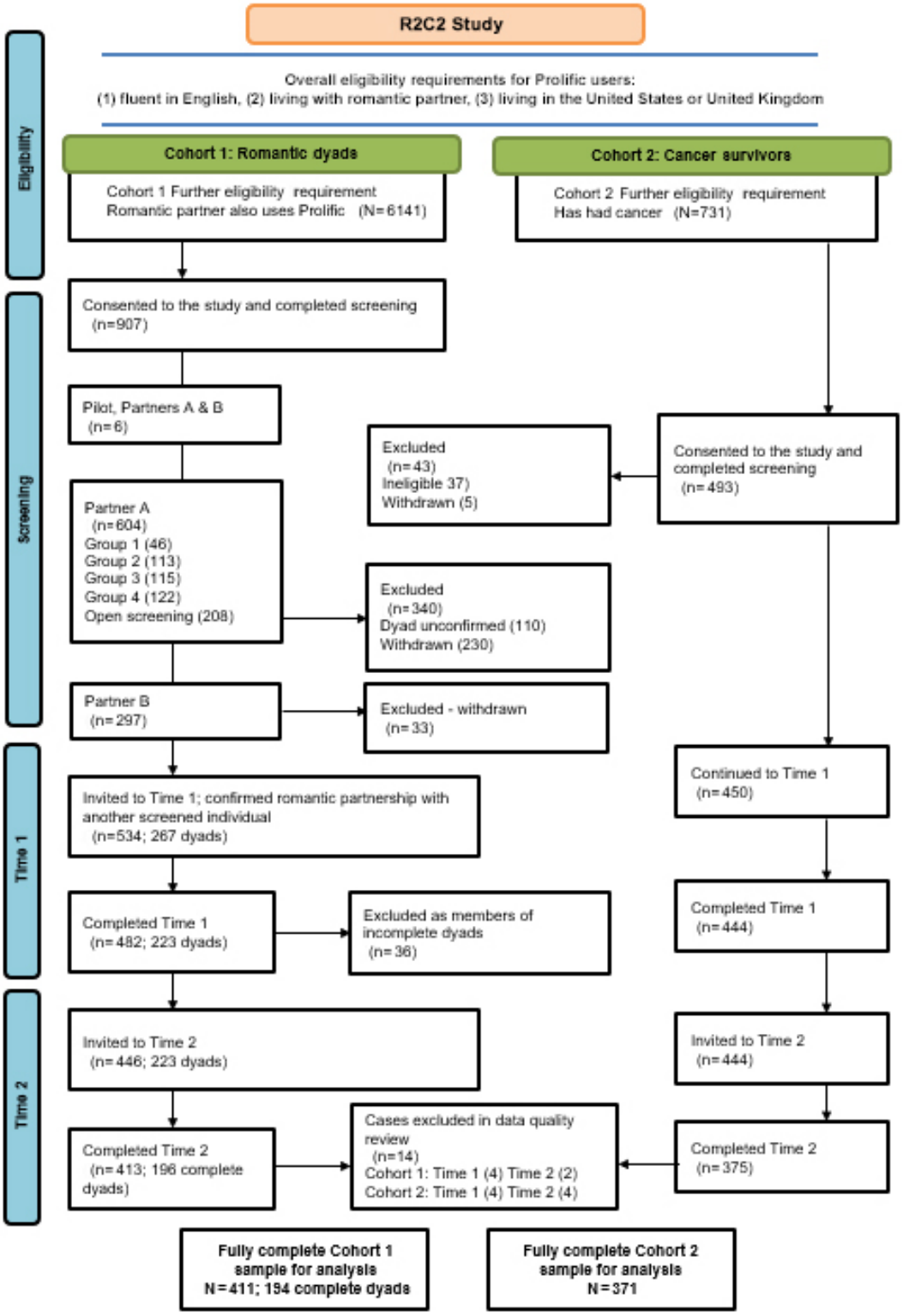

Stratification

Prolific is typically found to have a more diverse participant pool and higher quality data compared with other online recruitment platforms such as Amazon Mechanical Turk [23,24]. However, to ensure adequate recruitment of individuals from underrepresented populations, we implemented a stratification approach for our study. While we initially intended to use this stratification approach for both cohorts, the small number of eligible cancer survivors from diverse backgrounds necessitated opening recruitment to the entire pool of cancer survivors to achieve adequate statistical power. Therefore, the following stratification method was only used throughout the entire study for cohort 1. For cohort 2, the stratification method was implemented toward the end of data collection to attempt to better balance race or ethnicity in the sample.

Prolific offers a built-in recruitment process to balance across sex but balancing across other demographic groups requires

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researchers to create multiple copies or versions of their study to select the specified prescreening criteria for each. For cohort 1, we created 4 versions of the study (all linked to the same single Qualtrics survey) to meet recruitment goals for the individuals, identifying as (1) people with both a racialized identity and an LGB sexual orientation (group 1), (2) people with a racialized identity and heterosexual orientation (group 2), people who identified as White and an LGB sexual orientation (group 3), and (3) people who identified as White and heterosexual (group 4). Specifically, Prolific-defined categories for "ethnicity (simplified)" and "sexual orientation" were used so that individuals who selected the Black, Asian, mixed, and other response options represented people with underrepresented racialized identities and individuals who selected the homosexual, bisexual, asexual, and other response options represented people with underrepresented sexual orientations, respectively. Partner A's Prolific screening information was used to assign dyads to a stratification group.

Finally, to confirm that eligibility criteria data provided to Prolific by users remained accurate at the time of enrollment (eg, still living with a romantic partner) we conducted a brief validation of prescreening data by readministering screening questions used by Prolific before administering "time 1" surveys to each cohort. Enrollment in study screening was ongoing for several months of the iterative data collection process. Every 48 hours, Prolific sends email invitations to a random proportion of users who are eligible for studies that have not reached their maximum number of submissions [25].

Data Collection

Cohort 1 data collection ran from October 13, 2021, to June 10, 2022, and cohort 2 from December 20, 2021, to August 31, 2022. Surveys were administered online using Qualtrics. Questionnaires and items used in each of the surveys were similar across the 2 cohorts and the 2 time points, and summaries of these measures (constructs and example items) can be found in Multimedia Appendix 1.

Demographic characteristics were only assessed at time 1. Prolific and Qualtrics have integration features available to ensure continuity between participants' completing studies on Qualtrics and receiving completion credit on Prolific. We used these integration features to automatically record participants' Prolific IDs in the embedded Qualtrics data, as well as provided a completion code to participants at the end of their Qualtrics survey to enable their receipt of credit on the Prolific platform. For further information about this process, we recommend visiting Prolific's research help center [25]. After building our survey in Qualtrics by inserting our Institutional Review Board–approved questionnaires, we estimated the time for time 1 and time 2 completion to be about 20-30 minutes. Our study team then piloted the survey to confirm the formatting was displaying as intended and the completion time estimates were correct. Accordingly, we set the Prolific time effort as 30 minutes. The screening assessment for cohort 2 was built-in to the beginning of the time 1 survey, and access to the survey was contingent on this screening.

Before launching the surveys, another phase of pilot testing was done. After study team members piloted the surveys to confirm format and timing, 6 Prolific users who met the criteria for cohort 1 (ie, 3 dyads) were invited as pilot participants. These participants helped us test the process of screening, tracking, matching, inviting, and compensating eligible dyads in Prolific and Qualtrics. In addition, 5 of these participants took part and provided proof of concept for the study setup. Because changes were not made to the study following these pilot tests, the 5 pilot participants were included in the final data set for cohort 1.

Each participant who successfully completed time 1 was compensated for their participation within 2 weeks. After completing time 1, invitations to complete time 2 for additional compensation were sent to eligible individuals after 4 weeks, which was done by pasting each time 1 participant's Prolific ID into a "custom-allow list" for each of the cohort's respective time 2 surveys on Prolific.

Considerations for Cohort 1

Prolific enables dyadic data collection from romantic couples [25]. The key feature used to achieve this is the prescreening question, "Do you have a romantic partner who has a Prolific account and are you willing to participate in studies as a couple?" It is required to create 2 versions of a study to recruit cohabitating couples on Prolific due to a mechanism that blocks duplicate IP addresses from participating in the same study. Therefore, our screening process entailed administering 4 versions for Partner A (discussed in "Stratification" section), and 1 additional survey for Partner B. The label of Partner A was assigned to the first user in a dyad who completed our screening process. In addition to confirming eligibility criteria during screening, we also asked Partner A to provide the Prolific ID of their romantic partner so that we could add them to the allowed list for the Partner B version of the study. Finally, demographic information from Partner A was used to assign dyads to stratification groups. Once we obtained screening information for Partner A, a unique Dyad ID was assigned.

Once Partner B completed the screening and confirmed the Prolific ID of their romantic partner, we invited each partner to enroll in the respective A and B copies of the time 1 survey. These survey copies were identical, with the same Qualtrics link, and existed as a workaround to the IP address blocking mechanism. For time 2, invitations to complete the survey were only sent to dyads 4 weeks after both partners had completed time 1 (ie, 4 weeks after the second partner completed time 1. Both partners' time 1 completion was a requirement for time 2 eligibility). In addition, to minimize excessive time elapsing between the time points, we sent reminder messages through private messages after about 8 weeks to the participants for whom their partner had already completed time 1.

Considerations for Cohort 2

The unique aspect of the data collection process for cohort 2, the cancer survivor cohort, required screening individuals for any history of cancer. The Prolific prescreening question used for this was, "Do you have–or have you had–any condition, injury, or chronic illness?" and the response required for eligibility was "Cancers." In the time 1 survey, we asked participants to indicate their specific cancer type from a list we

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provided. In cases where a cancer type was not listed, we accepted this information through secure Prolific messages from participants. All other data collection processes followed according to the description in the section, "Data Collection." Cohort 2 was not dyadic; we only required participants to report cohabitating with their romantic partner.

We were unable to target cohort 2 using the stratified enrollment strategy we used for cohort 1 due to the small sample size of cancer survivors participating on Prolific. After recruiting cohort 2 for 8 months, we examined the race or ethnicity of the sample and decided to try to focus recruitment on participants who were from underrepresented racialized backgrounds. This resulted in the recruitment of 7 more participants to the cancer survivor cohort.

Ethical Considerations

After a human subject ethics review, the study was classified as exempt by the National Institutes of Health Office of Institutional Review Board Operations (#000535), under the exemption for "uses educational tests, surveys, interviews, or observations of public behavior". Each participant provided informed consent online (with the choice to instead opt out) before beginning the study. Per Prolific rules, participants were not asked to provide any personally identifying information. The research team has access to participants' Prolific ID, but this ID can only be linked to their participants' personally identifying information by Prolific. Prolific staff members do not have access to any of the study data, which were collected using Qualtrics. As such, no individual or entity is able to connect participants' personally identifying information with their study data. Compensation was set on Prolific as US $3.50 for time 1 and US $5 for time 2. The increased incentive was intended to reduce attrition and incentivize participation at follow-up [26]. In addition, to properly screen each member of the dyads in cohort 1, US $0.25 was awarded for the separate screening process.

Data Quality and Analysis

A power analysis to determine the number of participants to enroll for cohort 1 was calculated using the online tool, Power Analysis for the Actor-Partner Interdependence Model (APIMPowerR) [27] using the following assumptions: α=.05, 85% power, moderate effect size for actor pathways (Cohen d=0.50), small effect size for partner pathways (Cohen d=0.30), r=0.25 correlation of actor with partner variables, and r=0.25 correlation of errors. These analyses indicated 201 dyads (n=402 participants) would yield adequate power to detect partner pathways (and 74 dyads, or n=148 participants, would yield adequate power to detect actor pathways). For cohort 2, using G*Power [28], we conducted power analyses for multiple linear regressions using assumptions such as α=.05, 85% power, small-medium effect size (f^2=0.05), and up to 10 predictors. This analysis indicated that 372 participants would yield adequate power to detect an R^2 deviation from 0. The power analysis for each cohort helped inform the minimum number of participants to recruit.

We implemented several measures to promote high-quality final data across both cohorts. In building the study surveys in Qualtrics, we included CAPTCHA (Completely Automated Public Turing test to tell Computers and Humans Apart) technology that detects bot-like responses. When the data became available, we checked for abnormally fast response rates, reviewed responses to our attention check item (Multimedia Appendix 1), and reviewed couple concordance on expected responses in cohort 1 (eg, county of residence). To identify fast responses to the surveys, we set a parameter of 2 SDs under the mean completion time, identifying no responses to remove on this basis. Among the few participants who had failed the attention check item, we reviewed their other responses to identify strings of low-quality data (eg, straight-lining), removing no respondents on this basis; rather, we added a flag variable to the data set to alert analysts of failed attention checks. We contacted Prolific to verify that flagged users were in good standing, and with their recommendation, we removed 2 cases from the cohort 1 data sets that we flagged for suspicious discordance in their data. Another individual was removed from cohort 1 time 1 after a review of their survey responses indicating they were not based in the United States or the United Kingdom. Furthermore, 1 more case was removed for being a duplicate. For cohort 2, 1 case was removed from time 1 for being a duplicate, and 1 case was removed from time 2 for having incomplete data. Finally, a check for participants who may have entered both cohorts (despite attempts to exclude based on previous participation—ongoing studies were not able to be factored into these exclusions) revealed 3 cases that were removed from each time point in cohort 2 (Figure 1).

Enrollment is defined in our study in the following way: enrolled users at each time point refer to the number who met all the criteria (and were therefore paid for their participation), that are (1) were found to be eligible through our screening process, (2) completed the survey on Qualtrics, (3) did not withdraw their participation on Prolific, and (4) did not time out on Prolific after the 87 minutes allowed (calculated by Prolific based on estimated completion time of 30 minutes).

Results

Enrollment

The overall enrollment rate for the R2C2 study was 66.14%, with 926 individuals enrolled in time 1 after screening 1400. The overall completion rate for those who completed both time points out of those who were invited to time 1 was 80.08%. Enrollment data for each cohort and time point are reported below and in Figure 1.

Cohort 1 Enrollment

Screened Participants

We screened 907 individuals; that is, 907 individuals consented to the study and completed the screener (and were compensated). This number includes pilot participants. This number does not include participants who returned their screener or who timed out of the screener (ie, who did not complete the screener).

Invited Participants

Of the 907 individuals who completed the screener, we obtained 267 dyads (534 individuals). That is, of the 907 individuals who

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completed the screener, 534 (58.9%) individuals confirmed their romantic partnership with another screened individual, resulting in 267 dyads being invited to take the time 1 survey. Individuals were only sent the time 1 survey if they were confirmed to be in a relationship with another person who completed the screener.

Time 1 Enrollment

Of the 267 dyads (534 individuals) who were sent the time 1 survey, 482 (90.3%) individuals and 223 (83.5%) dyads had fully completed time 1 surveys. Individuals were only sent the time 2 survey if they and their partner both completed the time 1 survey.

Time 2 Enrollment

Of the 446 individuals (making up the 223 dyads) who were sent the time 2 survey, 413 (92.6%) individuals and 196 (87.9%) dyads completed the time 2 survey.

Dyadic Enrollment Rate

In sum, screening 907 individuals resulted in complete dyadic data for 196 dyads (392, 43.2% individuals). In other words, 43.2% of the screened individuals confirmed they were in a dyad, we sent them and their partner the time 1 survey and they both completed it, and we sent them and their partner the time 2 survey 4 weeks later and they both completed it. Of the eligible dyads who were invited to the time 1 survey, 73.4% (196/267) fully completed the study.

Sample Characteristics

Sample characteristics were calculated based on the number of participants who completed the time 1 survey, after exclusions (discussed in the “Data Quality and Analysis” section; n=478). The mean age of participants was 34.31 (SD 9.28) years. Out of the total, 78% (373/478) were based in the United Kingdom and 22% (105/478) in the United States. The average length of participants’ romantic relationships was 10.05 (SD 7.59) years. Other characteristics, including gender, race, ethnicity, sexual orientation, history of COVID-19 infection, education, and relationship type appear in Table 1.

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Table 1. Sample characteristics.

Characteristics	Cohort 1 (N=478)	Cohort 2 (N=440)
Country of residence, n (%)		
United States	105 (22)	191 (43.4)
United Kingdom	373 (78)	249 (56.6)
Gender, n (%)		
Men	215 (45)	128 (29.1)
Women	259 (54.2)	310 (70.5)
Nonbinary or gender-queer	4 (<1)	2 (<1)
Age (years), mean (SD)	34.31 (9.28)	50.25 (13.85)
Race or ethnicity, n (%)		
Hispanic or Latino/a	19 (4)	13 (3)
Non-Hispanic American Indian or Alaska Native	0 (0)	1 (<1)
Non-Hispanic Asian	79 (17)	8 (2)
Non-Hispanic Black or African American	40 (8)	5 (1)
Non-Hispanic Middle Eastern or North African	2 (<1)	2 (<1)
Non-Hispanic multiple races selected	23 (5)	13 (3)
Non-Hispanic other[a]	8 (2)	0 (0)
Non-Hispanic White	306 (64)	398 (90.5)
Not reported	1 (<1)	0 (0)
Sexual orientation, n (%)		
Bisexual or pansexual	62 (13)	41 (9)
Heterosexual or straight	359 (75.1)	384 (87.3)
Homosexual, gay, or lesbian	53 (11)	13 (3)
Something else	4 (<1)	2 (<1)
History of COVID-19 infection, n (%)		
Yes	106 (22.2)	93 (21)
No	367 (76.8)	346 (78.6)
I don’t know	5 (1)	1 (<1)
Cancer type[b], n (%)		
Breast	1 (<1)	138 (31.4)
Cervical	0 (0)	37 (8)
Colorectal	0 (0)	24 (5)
Endometrial	2 (<1)	19 (4)
Head and neck	0 (0)	39 (9)
Hematologic	3 (<1)	60 (14)
Lung	0 (0)	6 (1)
Melanoma	1 (<1)	26 (6)
Ovarian	0 (0)	20 (5)
Prostate	1 (<1)	29 (7)
Renal	0 (0)	12 (3)
Other[c]	1 (<1)	74 (17)
No current or past cancers	469 (98.1)	0 (0)

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Characteristics	Cohort 1 (N=478)	Cohort 2 (N=440)
Relationship type, n (%)		
Married	271 (54.1)	337 (76.6)
Divorced	3 (<1)	10 (2)
Widowed	0 (0)	3 (<1)
Separated	2 (<1)	3 (<1)
Never married	25 (5)	17 (4)
A member of an unmarried couple	200 (39.9)	94 (21)
Education, n (%)		
Less than a high-school degree	11 (2.3)	15 (3)
A high-school degree or GED[d]	67 (14)	60 (14)
Some college but not a college degree	108 (22.6)	122 (27.7)
A 4-year college degree or higher	292 (61.1)	243 (55.2)

[a]Non-Hispanic Other: participants who did not select Hispanic for ethnicity, selected "Some other race," and did not select anything else listed in the response options for race. For cohort 1, most individuals who selected this either chose not to specify or identified with a country or region of origin (eg, "N/A," "Caribbean," "Moroccan," and "Polish").

[b]Values and percentages may sum >cohort N as they are "check all that apply" items.

[c]Other: for cohort 1, nonmelanoma skin cancer (n=1); for cohort 2, nonmelanoma skin cancer (n=36), bladder (n=9), bone (n=9), liver (n=3), oral (n=1), pancreatic (n=1), pharyngeal (n=1), and another cancer not listed (n=14).

[d]GED: General Educational Diploma.

Cohort 2 Enrollment

Screened Participants

We screened 493 individuals; that is, 493 individuals consented to the study and completed the screener. Of the 493 individuals who completed the screener, 450 (91.3%) individuals were confirmed as eligible and were immediately directed to continue to time 1 if they wished.

Time 1 Enrollment

Of the 450 individuals who were administered the time 1 survey, 444 (98.7%) individuals completed it.

Time 2 Enrollment

Of the 444 individuals who were sent the time 2 survey, 375 (84.5%) individuals completed it.

Sample Characteristics

Sample characteristics were calculated based on the number of participants who completed the time 1 survey, after exclusions (n=440). The mean age of participants was 50.25 (SD 13.85) years. In total, 57% (249/440) were based in the United Kingdom and 43% (191/440) in the United States. The average length of participants' romantic relationships was 21.86 (SD 14.37) years. Complete sample characteristics appear in Table 1.

Discussion

Principal Findings

As research across multiple disciplines has increasingly used online techniques [29], the importance of ensuring high enrollment rates, minimizing attrition, and maintaining high data quality for online studies with specific recruitment criteria and complex methods remains important. The experience of conducting the R2C2 study, which included a dyadic cohort and a cohort of cancer survivors who were surveyed across 2 waves online, can be used to inform recommendations for researchers aiming to conduct surveys using similar methodologies in online recruitment and data collection platforms. We have discussed several lessons learned from the R2C2 study and provided concrete recommendations for researchers who study romantic relationships or cancer survivorship throughout the "Discussion" section.

Challenges and Successes During Recruitment and Enrollment

We had several objectives with respect to recruitment. First, we aimed to recruit and retain a sample of 201 dyads for cohort 1, and second, to maximize diversity in cohort 1 with respect to sexual orientation, race, and ethnicity. Third, we aimed to recruit a sample size of 372 individuals to cohort 2, and fourth, to maximize sample diversity in cohort 2 with respect to racial or ethnic background.

Despite having a relatively long data collection period of 9 months, increasing incentives for survey completion, and screening and recruiting additional individuals, we fell short of our goal of 201 dyads with complete data (final n=194 dyads with complete, quality-checked data). Our initial assumptions, using Prolific's prescreening tool, were that 20% of individuals screened would be ineligible for participation. However, about half of the participants or their partners did not meet the inclusion criteria, or individuals' partners did not complete the screening survey to complete the dyad. We, therefore, recommend that the researchers screen about twice as many individuals than they need to achieve a dyadic recruitment goal

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on Prolific. Among those who passed screening, dyadic completion of the full study was relatively high (196/267, 73.4%). Finding eligible participants to pass the screening was in reality the more challenging hurdle because it involved both the dyad members completing the screening, including questions for which the responses could have changed between the Prolific prescreening and our screening process (eg, partner no longer uses Prolific). For cohort 2, with only 1 participant to screen and cancer survivorship being a fixed screening response, over-recruitment of the same magnitude was not necessary.

Our second aim was to maximize the cohort 1 sample diversity with respect to sexual orientation, race, and ethnicity. We consider our efforts partially successful. Approximately 24.9% (119/478) of the cohort 1 sample identified with an underrepresented sexual orientation, about 31.8% (152/478) of the sample identified with an underrepresented racial group, and about 4% (19/478) of the sample identified as Hispanic or Latino. From these data, we can conclude that we oversampled underrepresented groups from the available pool on Prolific. However, the proportion of our sample identifying as Hispanic or Latino falls short of the US population estimates (about 19%; [30]). Therefore, in future studies aiming to obtain a sample of more representatives of the US population, we would recommend more targeted recruitment efforts to oversample participants who identify with Hispanic or Latino ethnicity. In addition, researchers aiming to use stratification methods for online panels as a recruitment strategy should consider exclusively opening the survey to targeted recruitment populations at the start, to get a sense of the sampling patterns and efforts required. We also suggest that researchers contact their recruitment platform before implementing stratification efforts to estimate the length of time it might take to reach sampling goals, and to plan for a longer data collection period compared with a nonstratified sampling study.

Although efforts were successful in recruiting a dyadic sample inclusive of those with sexual orientations not well-represented in previous research, it is important to note the limitations associated with Prolific's sexual orientation prescreening criterion. Specifically, Prolific's sexual orientation question includes limited response options (ie, "heterosexual," "homosexual," "bisexual," "asexual," and "other") which may fail to capture the full range of diverse sexualities present among Prolific's participant pool at the time of data collection, and the exclusive use of the term "homosexual" may be deemed offensive by some who prefer to identify as gay or lesbian, potentially leading to inaccurate responses or discomfort for the participants.

Our third aim was to recruit a sample of 372 cancer survivors. This goal was achieved; 444 participants completed the time 1 survey, and 375 participants completed the time 2 survey. When we began the study, a total of 731 cancer survivors were eligible; this indicated a high rate of engagement or interest in participation, and low attrition among the cancer survivor cohort. Data collection for cohort 2 took approximately 9 months. Given that the available pool of cancer survivors was small (n=731), it was not feasible to conduct a dyadic study in which 1 partner was a cancer survivor or to prioritize stratified recruitment to maximize sample diversity with respect to race, ethnicity, or sexual orientation. Near the end of data collection for cohort 2, we closed the main survey open to all individuals who met our inclusion criteria and opened a separate survey that was only open to individuals who identified as one of the following ethnicities: African, Black or African American, Caribbean, East Asian, Latino or Hispanic, Middle Eastern, Mixed, Native American or Alaskan Native, South Asian, Other, White or Sephardic Jew, Black or British, White Mexican, Romani or Traveller, or South East Asian (variable "ethnicity"). The survey was open for approximately 4 weeks and 7 participants completed the study. Given that we were nearing the end of our planned data collection period, we decided to close this survey and end data collection at that time. Our recommendation to researchers aiming to recruit underrepresented populations on Prolific is to be mindful of the inclusion criteria they use and how it may further restrict their sample size. In addition, patience is key.

Challenges and Successes During Study Design and Data Collection

We would like to acknowledge that we had an overall positive experience using Prolific as our recruitment platform. Prolific has a very responsive support team that was able to address questions and issues that arose, from data collection to data cleaning. However, there were some challenges associated with using Prolific with our study design and we learned a few lessons while using the platform that may be useful to other researchers. First, researchers should be aware that Prolific prevents individuals in the same household (according to IP address) from taking the same survey. We realized this when piloting our survey with a small number of dyads for cohort 1 (which we recommend researchers do to minimize data collection errors at a larger scale). This is intentional—the goal is to prevent individuals from taking the same survey twice [25]. However, this feature of Prolific means that researchers must send the members of a dyad 2 separate invitations to enable them to complete the study. We set up 2 studies in Prolific, one for Partner A and one for Partner B, and manually sent separate study invitations to participants by adding them to custom-allow lists. This meant that we had to identify Partner A and Partner B in each dyad, keep them straight throughout data collection, and take the time to manually send surveys to participants using the custom-allow lists. Although this can be done in batches (by setting up surveys so that they are accessible by invitation only), this is time consuming compared with the typical online survey. This poses a limitation to researchers who aim to send surveys to individuals immediately when they become eligible for the study.

It was found that one strength of using Prolific and other online platforms in behavioral research, especially in a COVID-19 pandemic or postpandemic world, is that we can achieve better reach. This was especially crucial for our recruitment of cancer survivors, as this population may have been even more challenging to reach if we had required an in-person component of our study, given their increased health risks during the pandemic. Most recruitment platforms also provide the ability to send participants study reminders—we recommend investigating if this is done automatically and otherwise deciding a priori intervals to send reminders manually. Online survey

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methods and platforms have become more critical tools than ever before.

Related to the COVID-19 pandemic, there were several challenges with respect to our study design and data collection. The primary challenge was the need to be responsive to pandemic-related changes in the items that we included in our surveys. For instance, as variants evolved and vaccines became more widely available, there were changes in individuals' risky behaviors (and what was considered risky), their perceptions, etc. This is something that will need to be addressed in all the analyses that use the data from this work. In addition, there were changes in vaccine availability and recommendations across the data collection period (eg, vaccine recommendations for children). Furthermore, there were pandemic-related differences between the United States and the United Kingdom that need to be accounted for, such as governments' responses to the pandemic and cultural perceptions of the pandemic.

There were also several challenges in collecting dyadic, repeated measures data online. First, managing data collection for dyads is quite complex and requires frequent team meetings for the purpose of decision-making (eg, whether to use data from partial dyads or whether to allow individual partners to continue the study if their partner is not responding). Second, we identified that there is a need to verify that participants are (1) in cohabiting relationships with the other participant they identified on Prolific and (2) are not completing the study for their partner. In other words, there is a need to verify that 2 people are in a dyad but that both members of the dyad completed their respective surveys independently of one another. We recommend that researchers include questions for which the responses should differ for partners (and questions for which the responses should be the same). For instance, partners should generally indicate similar time frames for the start of their relationship and cohabitation, as well as residing in the same county if cohabitating; partners should generally report different specific heights and weights. We also recommend examining the times that participants start and complete their surveys compared with their partners and paying close attention to dyads who complete their surveys at close times. To protect participants' privacy, we chose to disable the collection of IP address data in Qualtrics, however, this data could potentially be useful for data quality checks, as well. We recommend contacting a recruitment platform directly with questions about data quality. Prolific does have protocols to retain users who provide high-quality data [23].

Conclusion

With this protocol paper, we aimed to describe the decisions and methodological approaches that were used in the R2C2 study to inform best practices for future online research on dyadic relationships and health. Online data collection methods can enable research teams to obtain cross-sectional or repeated-measures data from participants and their romantic partners; however, obtaining data from underrepresented populations such as cancer survivors and medically underserved populations was a challenge. We encountered several important considerations for designing dyadic health research in particular that have not been previously described in detail. We recommend conducting pilot studies to test the infrastructure of the data collection process—screening at least 2 times the number of individuals that complete data is needed in order to account for the attrition that occurs with this panel-based design, as well as planning dyad-specific data quality checks. For recruiting large samples of underrepresented populations, we recommend allowing for extra time in the data collection timeline and working with the online panel to create realistic expectations for recruitment goals. Relationships are significant to all aspects of life including health, and with valuable tools and sound methods, online research in this area can make worthwhile contributions to further our understanding of this complex association.

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Authors' Contributions

RF, AMA, TAC, and LD contributed to the conceptualization of the study, visualization, supervision, and project administration. JB, CH, and AMA contributed to writing-original draft, and LG, RF, LD, and TAC to editing and writing-review. JB, CH, and AMA contributed to methodology, investigation, and data curation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measured constructs and example items.
[DOCX File , 25 KB - resprot_v13i1e48516_app1.docx]

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Abbreviations

APIMPowerR: Power Analysis for Actor-Partner Interdependence Model
CAPTCHA: Completely Automated Public Turing test to tell Computers and Humans Apart
LGB: lesbian, gay, bisexual, or pansexual
NCI: National Cancer Institute
R2C2 study: relationships, risk perceptions, and cancer-related behaviors during the COVID-19 pandemic study

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Protocol

Effectiveness of a Virtual Reality Open-Air Bath Program in Reducing Loneliness and Improving Brain Function for Dementia Prevention in Older Adults: Protocol for a Prospective Randomized Crossover Study

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Abstract

Background: Older adults often face loneliness due to chronic illness or loss of close ones, a situation worsened by the COVID-19 pandemic. Increased loneliness heightens the risk of diseases, especially dementia, necessitating urgent action.

Objective: This study aims to assess the impact of a virtual reality (VR)–based open-air bath program on depression and loneliness in older individuals with subjective cognitive decline/mild cognitive impairment attending the Dementia Medical Center in Kyoto, Japan. We further aim to evaluate the feasibility of the program (participant recruitment and adherence) and to measure program enjoyment and satisfaction.

Methods: The study design is a crossover trial with a 1:1 ratio, wherein 12 participants will be randomly assigned to groups 1 and 2, with group 2 serving as a waitlist control and group 1 receiving the VR program from the onset for 6 months; the VR program will be conducted 6 times (monthly). Program completion for group 1 will be followed by an observation period from months 7 to 12. Group 2 will participate in the VR program from months 7 to 12, with an observation period from months 1 to 6. Cognitive tests, psychiatric assessments, and the University of California, Los Angeles Loneliness Scale will be conducted before the study, at 6 months, and at 12 months. Results will be analyzed using repeated-measures ANOVA. Head magnetic resonance imaging and single-photon emission computed tomography scans will be performed before and after the VR program to evaluate changes and effects on brain regions.

Results: Recruitment began in September 2023 and data collection is expected to be completed by March 2025. Complete study results will be published by September 2025.

Conclusions: This study examines the preliminary effects of VR on loneliness in older adults with predementia through open-air bath simulations. VR experiences could benefit this population, particularly those with limited outdoor activities. Quantifying VR's impact will aid in determining the size for a larger clinical trial. Qualitative results will inform participation mechanisms and guide the implementation and design of future trials.

Trial Registration: University hospital Medical Information Network UMIN000052667; https://tinyurl.com/3yaccay5

International Registered Report Identifier (IRRID): DERR1-10.2196/57101

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KEYWORDS

loneliness; virtual reality; VR; Alzheimer disease; predementia; intervention; subjective cognitive decline; mild cognitive impairment; dementia; older adult; geriatric; depression; cognitive impairments

Introduction

Background

In recent years, we have experienced social isolation on an unprecedented scale, partly due to the spread of infectious diseases. The Japanese government has addressed the issue of isolation and loneliness by establishing a Minister of State for Isolation and Loneliness in 2021. This health issue is attracting global attention, with the World Health Organization also emphasizing the importance of measures to combat loneliness [1]. Feeling lonely and socially isolated can seriously impact physical and mental health. A review distinguished between loneliness and isolation, noting that loneliness is subjective and psychological, while isolation is objective and social. However, social isolation does not necessarily imply loneliness, and loneliness is a stronger predictor of mental and physical health status than social isolation [2]. Loneliness is an independent risk factor for depression, even after accounting for covariates such as demographic characteristics, marital status, social isolation, and psychosocial risk factors [3]. The health burden of loneliness is extensive, including increased mortality from hypertension and cardiovascular disease, heightened risk of diabetes and immune system dysfunction, and increased risk of suicide [4-6]. In a recent meta-analysis, loneliness was identified as a risk factor for coronary heart disease and stroke [7]. The odds ratio of increased mortality due to loneliness is approximately 1.5, which is comparable to smoking and heavy drinking and exceeds the effects of other risk factors such as obesity and physical inactivity [8]. Lonely individuals often have poor mental health, which is reported to increase the risk of dementia as well as depression and other mental illnesses.

Impact of Loneliness on Dementia

Older adults who are lonely are 1.64 times more likely to develop dementia than those who are not [9]. Furthermore, loneliness can exacerbate the behavioral and psychological symptoms of dementia [10]. As one ages, the likelihood of experiencing loneliness increases, with 30%-40% of older adults reporting feelings of loneliness [11]. The growing global population of people with dementia and the increasing costs of medical and nursing care are placing a significant burden on younger generations [12,13]. Therefore, preventing loneliness and isolation among older adults is a pressing worldwide issue. Although the exact mechanism by which loneliness increases the risk of dementia is not fully understood, it has been linked to amyloid load and tau pathology, as well as decreased gray matter volume in the thalamus and parahippocampal gyrus, potentially accelerating the pathology of Alzheimer disease due to the increased strain on the brain [14-16].

Interventions to Reduce Loneliness

Reducing social isolation and loneliness can help prevent dementia [17]. Reviews of interventions for social isolation and loneliness have shown that participation in meaningful and satisfying group activities is effective in reducing loneliness [18]. However, opportunities for such activities are declining due to restrictions on outings and social distancing considerations during infectious disease outbreaks [19]. Even when infectious diseases are at an all-time low, many older adults find it challenging to go outside due to underlying medical conditions. Group activities using virtual reality (VR) can be enjoyed by these individuals as they can participate from the comfort of their own homes or facilities. The immersive experience provided by the headset can increase motivation to participate compared to mere video images.

VR Program to Reduce Dementia Risk

Subjective cognitive decline (SCD) and mild cognitive impairment (MCI) are known as a preliminary stage or risk factor for dementia [20,21]. Intervening with VR programs for people with these conditions may reduce their sense of isolation and decrease the risk of dementia. Moreover, such interventions may not only improve mental functions, such as creating enjoyment in the lives of older adults and increasing their motivation to live, but may also help prevent physical diseases such as cardiovascular diseases and diabetes. Although various studies have been conducted to test methods of reducing loneliness among older adults [22], there are no studies examining the effects of interventions on cognitive function, mental status, and the risk of dementia, and there is no precedent for VR-based initiatives. Furthermore, although VR for rehabilitation and training of cognitive functions in patients with MCI has been developed and shown to be useful for improving general cognitive functions, especially executive functions [23,24], there is no precedent for a program aimed specifically at improving loneliness.

Therefore, we hypothesize that meaningful activities using VR programs could reduce social isolation and loneliness among older people, thereby reducing the risk of dementia. This study has two objectives. The first is to examine the effects of a VR-based open-air bath experience program on depression and loneliness among older adults with SCD and MCI attending our Medical Center for Dementia Diseases. The second objective is to examine feasibility indicators such as recruitment and adherence status, program enjoyment, and satisfaction. In this study, participants will be randomly assigned to 2 groups: a VR group (group 1) and a waitlist control group (group 2). The design of the study is a crossover, superiority trial with an allocation ratio of 1:1.

Methods

Study Design

This is an intervention and prospective study with minor invasiveness using VR and the protocol is developed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [25] (Multimedia Appendix 1). Two groups of 6 people each, totaling 12 participants, will be recruited from a group of older adults who visited the Medical

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Center for Dementia Diseases at Kyoto Prefectural University of Medicine and were diagnosed with SCD or MCI. This number meets the minimum recommendations of a feasibility study considering the sample size for a large clinical trial [26]. Participants will visit the outpatient clinic once a month for a total of 12 times for standard outpatient care, including examination, evaluation, and prescribing. Although this is the standard frequency of visits at our center, monthly visits are expected to improve adherence to this protocol and prevent dropout.

During this 12-month period, changes in pharmacotherapy will be minimized but made when necessary. During the period of the VR program, participants will receive the VR program in addition to outpatient care. In the observation period, they will chat with the same members for the same amount of time in addition to outpatient care.

The allocation method will be simple randomization with a 1:1 ratio to either group 1 or group 2 based on computer-generated random numbers. Due to the nature of the intervention, double-blinding is challenging. Therefore, to minimize measurement bias, only the data collectors and analysts will be blinded. An investigator not involved in the study will perform the allocation and only the facilitator will be informed of each group's allocation. Group 1 will participate in the VR program once a month from the start to 6 months, with an observation period from 7 to 12 months. Group 2 will participate in the VR program monthly from 7 to 12 months, with an observation period from 1 to 6 months from the start. Participation in the VR program is planned to involve 6 sessions in total (once a month).

The loneliness scale, stress index, various cognitive function tests, and psychiatric symptom evaluation will be conducted before, at 6 months, and 12 months after participation to observe changes due to participation in the VR program. The detailed study procedure is depicted in Figure 1. These evaluations will be performed by a psychiatrist or psychologist skilled in geriatric psychiatry. No statistical analysis will be performed for adverse events or impressions. This study has been registered in the University Hospital Medical Information Network (UMIN) (UMIN000052667).

Figure 1. Schedule and assessment timeline for the virtual reality (VR)–based open-air bath experience program. ADL: activities of daily living; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography; UCLA: University of California, Los Angeles.

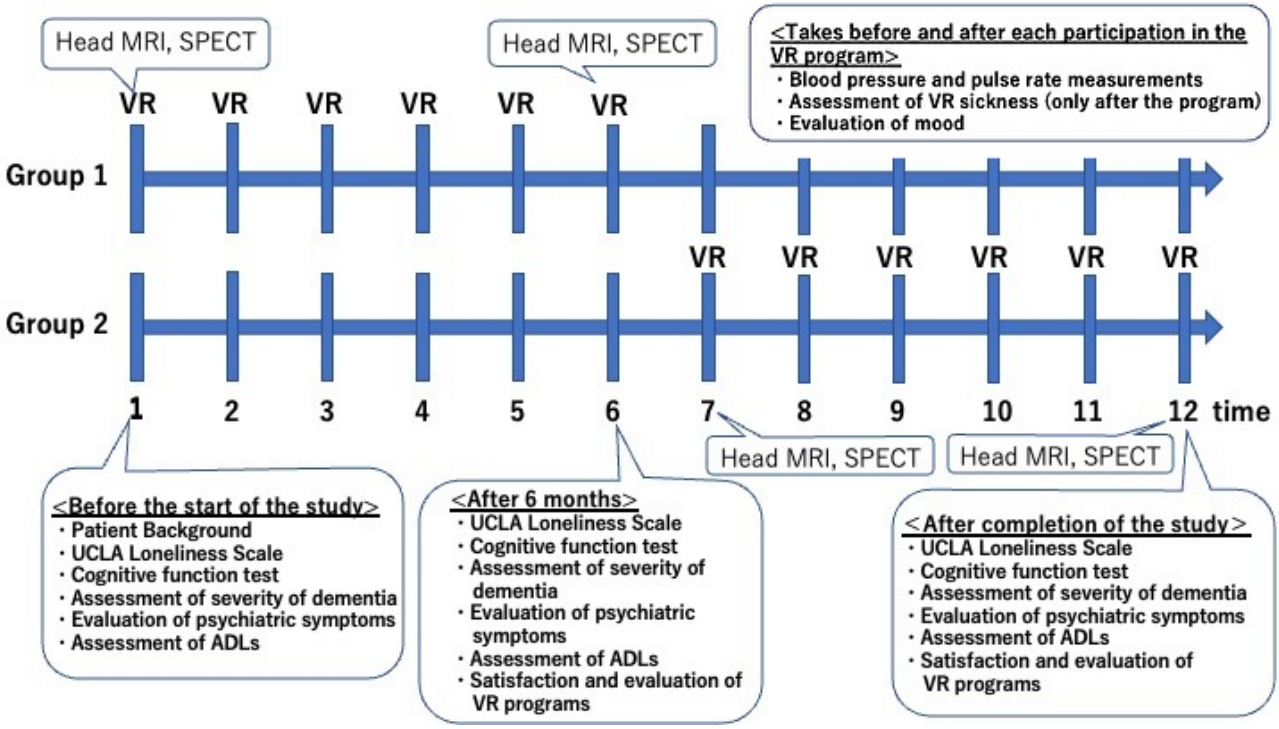

Ethical Considerations

The protocol and informed consent were approved by the Ethical Review Board of Kyoto Prefectural University of Medicine on October 31, 2023 (ERB-C-2978). Study participants will be informed in writing and consent will also be obtained in writing (Multimedia Appendix 2). Consent can be revoked at any time without any disadvantage to the participant, in which case the data will be discarded except for those necessary for medical treatment. Any important modifications to the protocol will be promptly submitted to the institutional review board or UMIN for approval, and research participants will be informed by telephone to obtain their consent to continue participation in the study. Although the VR may cause VR sickness, this is considered a minor invasion and the collection of information is not invasive. The examination items consist of items used in routine medical care and are not invasive beyond routine clinical practice. Therefore, no compensation will be provided because no health hazard is expected for the research participants as a result of this study.

Data, anonymized and managed by assigned numbers, will be entered into an Excel table and stored securely. Access to the intermediate and final datasets will be limited to the principal investigator JN and coinvestigators AI, TM, CN, and NH. The data manager, who is not involved in this study, will oversee

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data handling. Adverse events or unexpected intervention effects will be documented and reported to the principal investigator. The research team will collectively decide on the continuation or discontinuation of the intervention upon receiving such reports. The principal investigator will make the final decision on study termination.

Eligibility for Participation

Participants will be older adults aged ≥60 years diagnosed with SCD or MCI who visited the Medical Center for Dementia Diseases at Kyoto Prefectural University of Medicine Hospital between November 1, 2023, and March 31, 2025, and who can provide written consent to participate in the study. The Petersen criteria for MCI diagnosis [27] and the definition of SCD proposed by Jessen et al [28] (ie, a condition of ongoing subjective cognitive problems without dementia or MCI) will be used. Participants complaining of SCD but judged by expert psychiatrists to have normal cognitive function based on neuropsychological tests such as the Mini Mental State Examination (MMSE) [29], Alzheimer's Disease Assessment Scale (ADAS) [30], Rivermead Behavioral Memory Test [31], and Clock Drawing Test [32] and brain imaging tests will be diagnosed as having SCD. The purpose of the study along with the benefits and disadvantages will be explained in writing, and only those who agree to participate will be included. Patients with a history of mental illness, head injury, or drug or alcohol abuse; those with significant visual or hearing impairment; and those unable to use both hands will be excluded.

Procedure

The primary endpoint will be the score on the loneliness scale. The secondary endpoints include cognitive function tests (MMSE and ADAS); assessment of depression (Geriatric Depression Scale [GDS] [33]), dementia severity (Clinical Dementia Rating [CDR] [34]), and activities of daily living (ADLs; Instrumental Activities of Daily Living [IADL] and Physical Self-Maintenance Scale [PSMS] [35]); and the Mild Behavioral Impairment Checklist (MBI-C) [36,37]. All of the above assessments will be taken the day of consent. Patient background (age, gender, educational history, dominant hand, medical history, and presence of a roommate) will also be obtained via an interview conducted the same day.

Loneliness will be assessed using the revised University of California, Los Angeles (UCLA) Loneliness Scale [38,39]. This 20-item scale has scores ranging from 20 to 80, with higher scores indicating more severe loneliness. If a participant has already obtained a score on this scale in the past 3 months, that information from their medical record or other sources may be used. If fatigue or other complaints occur during these tests and all test items cannot be obtained on the same day, the schedule will be adjusted and the remaining test items will be performed within 1 month from the original test date.

The cognitive function and clinical rating scale assessments will be conducted by a data collection staff member through questionnaires and interviews at the psychiatric outpatient department of the hospital on weekdays between 9 AM and 5 PM. This staff member will be the psychologist who is usually in charge of cognitive function tests and interviews at the Medical Center for Dementia Diseases and is familiar with the methods used. The results will be explained to the patient if desired.

Immediately before and after implementation of the VR program, blood pressure and pulse rate measurements will be taken along with evaluation of mood state. Immediately after the program, an evaluation of VR sickness will be conducted. All participants will be evaluated for the loneliness scale, cognitive function test, psychiatric symptoms, dementia severity, and ADLs at the time group 1 completes the program (after 6 months) and when group 2 completes the program (after 12 months). Head magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) will be performed at the beginning and end of the VR program. Satisfaction and evaluation of this program will be assessed at the end of the VR program.

If VR sickness occurs more than expected, we will consider changing the program specifications. Furthermore, if a participant requests discontinuation or is unable to continue participation for some reason, the intervention will be stopped only for that patient. Participants who discontinue or withdraw from the intervention will have the reasons for discontinuation or withdrawal confirmed and recorded, and data collected up to that point will be used if approved. To prevent dropouts, the program will be scheduled every 4 weeks on Monday afternoons, and the schedule will be distributed to participants and their families in advance.

Program Content

This 6-month program offers participants a 20-minute virtual open-air hot spring experience once a month. In this program, participants virtually visit hot spring resorts around the world through VR while enjoying a footbath with a bucket and bath salts, mimicking a real hot spring resort experience. The program features actual hot spring scenery and environmental sounds, with no actual people appearing in the program. The open-air bath simulation occurs in an outpatient consultation room and involves a facilitator and an attendant. Participants use an Oculus Quest 2 headset and immerse their feet in 40 °C water in a footbath bucket. During the 20-minute session, participants and the facilitator are encouraged to converse naturally, although no specific script is provided. The VR sessions are conducted in a medical examination room with appropriate infection prevention measures in place, including temperature checks, proper ventilation, mask-wearing, hand sanitization, and maintaining a distance of at least 1 meter. When the VR program is not in session, patients will engage in a 20-minute conversation with the facilitator and attendant once a month in addition to their regular medical examination.

Analysis

As a preliminary study, this research focuses on estimating outcomes rather than determining validity. The findings will inform the sample size and design for larger studies. Statistical analysis will include descriptive statistics (mean, SD), effect sizes, and 95% CIs. Baseline characteristics such as age, gender, diagnosis, and cohabitation status will be compared for each group. The revised UCLA Loneliness Scale will serve as the

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primary endpoint, with assessments conducted at baseline, 6 months, and at the end of the study. Comparisons between the groups will be made using 2-way repeated-measures ANOVA. Secondary endpoints, including MMSE, ADAS, GDS, MBI-C, CDR, and PSMS scores, will undergo a similar analysis. Changes in brain volume and cerebral blood flow, as observed in head MRI images and SPECT scans, will be compared using a paired *t* test before and after the intervention with Statistical Parametric Mapping software. Multiple regression analysis will be used to explore the relationship between changes in loneliness scale scores and preintervention brain images to identify brain regions predicting improvements in loneliness. Additionally, changes in mood state and vital signs before and after the program will be compared using paired *t* tests. The degree of VR sickness and satisfaction with the program will be described in a report.

Participant discontinuation or dropout cases will be excluded from the analysis, but their numbers will be clearly noted. Missing values will be deleted or imputed using appropriate methods.

Results

This study was approved by the Ethics Review Committee of Kyoto Prefectural University of Medicine on October 31, 2023. The study was initiated on November 1, 2023, and the first participants were enrolled on December 18, 2023. Recruitment of the last participant is scheduled for March 31, 2025, and the study is projected to be complete by September 2025.

Discussion

This study aims to explore the preliminary effects of a VR-based open-air bath experience program on loneliness in older adults at the predementia stage. Given the tendency of this population to limit outdoor activities due to infectious disease outbreaks and other factors, a VR-simulated outdoor bath experience could be highly beneficial and may help alleviate depressive symptoms and feelings of loneliness. The study will quantify the effects of the VR program on these factors and provide data that could inform the sample size for a larger-scale clinical trial. Additionally, the qualitative results will enhance our understanding of the behavioral mechanisms that promote participation and continued use, thereby informing the design and implementation procedures for future trials.

Loneliness in older adults is often the result of a combination of health and environmental factors. Health-related factors include chronic illness and communication difficulties [40] as well as cognitive decline impairing the ability to recall recent conversations or appointments [41]. Environmental factors contributing to loneliness include a lack of friends, moving to a nursing home, the bereavement of a loved one, and excessive time spent alone, all of which increase feelings of isolation from others [42,43]. Lonely people are at high risk for reduced life satisfaction, depression, low self-esteem, negative emotions, and impaired functioning in ADL, all of which can impair health and well-being [44,45].

Various interventions have been implemented to promote social connectedness and reduce loneliness in older adults. These include group activities such as cognitive enhancement workgroups and participation in adult day centers, one-on-one interventions such as befriending and animal-assisted therapy, internet access training, and service provision such as transportation and medical care [46-48]. Studies focusing on reducing loneliness have identified effective interventions such as those increasing social contact opportunities, enhancing social support, focusing on social skills, and addressing maladaptive social cognitions through methods including cognitive behavioral therapy [18,49]. However, these programs often have limitations such as difficulty with equipment-handling techniques and infectious diseases, along with challenges for older individuals who struggle to leave their homes. The VR program used in this study offers the advantage of easy participation by simply wearing a head-mounted display. The VR program can be used from any location with a network environment, including homes and facilities.

Notably, there have been no previous studies examining changes in cognitive function, brain blood flow, and brain structure as a result of interventions aimed at reducing loneliness. However, this study has certain limitations, including its small sample size. The findings will need validation in a larger clinical trial. Additionally, the requirement for participants to see the screen of a VR headset may not be suitable for those with visual impairments.

In conclusion, should the results indicate a benefit to the mental health of older adults in the predementia stage, this study may pave the way for innovative and scalable methods to enhance both the mental and physical health of this population group.

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Authors' Contributions

AI, TM, MS, and JN conceptualized the study. AI is responsible for data curation. AI and TM are responsible for funding acquisition. CN and NH will contribute to the investigation. AI, TM, and MS designed the methodology. AI, TM, and JN are the project administrators. MS and JN are responsible for resources and software. TM and JN are the study supervisors. AI and TM wrote the original draft of the manuscript with review and editing contributed by CN, NH, MS, and JN.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 30 KB - resprot_v13i1e57101_app1.docx]

Multimedia Appendix 2
Consent form.
[PDF File (Adobe PDF File), 50 KB - resprot_v13i1e57101_app2.pdf]

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Abbreviations

ADAS: Alzheimer's Disease Assessment Scale
ADL: activity of daily living
CDR: Clinical Dementia Rating
GDS: Geriatric Depression Scale
IADL: Instrumental Activities of Daily Living
MBI-C: Mild Behavioral Impairment Checklist
MCI: mild cognitive impairment
MMSE: Mini Mental State Examination
MRI: magnetic resonance imaging
PSMS: Physical Self-Maintenance Scale
SCD: subjective cognitive decline
SPECT: single-photon emission computed tomography
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UCLA: University of California, Los Angeles
UMIN: University Hospital Medical Information Network
VR: virtual reality

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Protocol

Evaluating the Population-Based Usage and Benefit of Digitally Collected Patient-Reported Outcomes and Experiences in Patients With Chronic Diseases: The PROMchronic Study Protocol

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Abstract

Background: Chronic diseases are associated with a high disease burden. Under- and overprovision of care as well as quality variation between health care providers persists, while current quality indicators rarely capture the patients' perspective. Capturing patient-reported outcome measures (PROMs) as well as patient-reported experience measures (PREMs) is becoming more and more important to identify gaps in care provision, prioritize services most valuable to patients, and aid patients' self-management.

Objective: This study aims to measure the potential benefits and effectiveness of using electronic patient-reported outcome measures (ePROMs) and electronic patient-reported experience measures in a structured and population-based manner to enhance health care for chronic disease patients in Germany.

Methods: This prospective cohort study aims to evaluate the potential benefits of PROM usage in patients with chronic diseases. We evaluate whether (1) digitally collected PROMs and PREMs can be used for health system performance assessment by generating a representative response of chronically diseased individuals with asthma, chronic obstructive pulmonary disease, diabetes, and coronary artery disease across Germany, and (2) based on the PROMs and PREMs, low-value care can be identified. As patient-reported outcomes (PROs) are rarely presented back to patients, (3) this study also examines patients' reactions to their PROM scores in the form of digital PRO feedback. For these purposes, randomly selected patients from a nationwide German insurer are digitally surveyed with generic and disease-specific PROMs and PREMs, as well as additional questions on their health-related behavior, 4 times over 1 year. Individual PRO feedback is presented back to patients longitudinally and compared to a peer group after each survey period. Patient-reported data is linked with health insurance data. Response rates, changes in health and experience outcomes over time, self-reported changes in health behavior, and health care system usage will be analyzed.

Results: The PROMchronic study explores the usage of PROMs in patients with chronic diseases. Data collection began in October 2023, after the initial invitation letter. All the 200,000 potential patients have been invited to participate in the study. Data have not yet been analyzed. Publication of the interim results is planned for the autumn of 2024, and the results are planned to be published in 2025.

Conclusions: We aim to fill the research gap on the population-based usage of PROMs and PREMs in patients with chronic diseases and add to the current understanding of PROM data-sharing with patients. The study's results can thereby inform whether a health care system-wide approach to collecting PROMs and PREMs can be used to identify low-value care, assess quality variation within and across chronic conditions, and determine whether PRO feedback is helpful and associated with any changes in patients' health behaviors.

Trial Registration: German Clinical Trials Register DRKS00031656; https://drks.de/search/en/trial/DRKS00031656

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International Registered Report Identifier (IRRID): DERR1-10.2196/56487

(JMIR Res Protoc 2024;13:e56487) doi:10.2196/56487

KEYWORDS

health care policy; PROM; PREM; PRO feedback; health behavior; chronic disease; asthma; COPD; diabetes; coronary artery disease; value-based health care; quality of care; artery disease; chronic; self-management; effectiveness; Germany; cohort study; pulmonary disease; utilization

Introduction

Background and Rationale

Globally, 1 in 3 persons and up to 60% in industrialized countries are living with at least 1 chronic disease [1-3]. Furthermore, this share is continuously increasing across the globe due to demographic change and consumption patterns [3,4]. Chronic diseases, including conditions such as diabetes, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD), are long-lasting conditions that can significantly impact a patient's quality of life and are a key driver of escalating health costs in both developed and developing economies [5]. Diagnosing and treating chronic conditions comes with substantial uncertainties for patients, families, and caregivers [6]. The high complexity of chronic care, for instance, raises uncertainty regarding whether patients with chronic diseases will respond to a selected treatment in the way a priori expected and, in the event they do, whether it is the most efficient one [7].

Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) have been used for over 20 years, but have become increasingly widespread and accepted only in recent years [8], as reflected by their increasing usage in oncology [9-11] and orthopedics [12-14]. The use of PROMs in monitoring interventions has, for instance, shown benefits in terms of increased survival rates, lower hospitalizations, improved health-related quality of life in oncology and reduced fatigue, and improved health-related quality of life in orthopedics [15,16]. PROMs are questionnaires that allow valuable insights into the patient's perspective of living with a (chronic) disease as they reflect the patient's own perception of their health status [17,18]. PREMs are questionnaires used to gather information from patients about their personal experiences and perceptions of the care and services they have received [19]. With electronic PROMs (ePROMs) and electronic PREMs (ePREMs) being reported and used more frequently in the last few years [20,21], usage for population health purposes appears more in reach but has rarely been examined [22].

PROMs and PREMs might have care improvement potential in the field of chronic diseases due to their information value for patient empowerment, including self-management and shared decision-making, which could influence treatment adherence and lifestyle choices [23]. However, PROMs and PREMs have rarely been used in routine chronic care due to the unspecified timeline and the complexity of implementation [24]. Due to the high relevance of this topic, the OECD (Organisation for Economic Co-operation and Development) PaRIS (Patient-Reported Indicator Surveys) initiative focuses on collecting and analyzing PROMs in patients with chronic diseases across 18 countries, starting their trial phase in 2023. The initiative does not cover Germany [25]. The present study, "PROMchronic," aims to fill the research gap by evaluating the usage of ePROMs and ePREMs in the German chronic disease population for 4 selected chronic disease profiles.

Furthermore, providing patients with information on their health status based on PROMs in reference to a comparable peer group is rarely done [26,27]. Yet, specific information about patients' health status is crucial because it can help patients better understand their health conditions and enable decision-making and overall patient empowerment. When patients are well-informed about their health, they are more likely to adhere to treatment plans and achieve better health outcomes [28]. Patients can use this information together with their health care providers to set realistic goals for their treatment, monitor their progress, and identify areas where additional support is needed.

Objectives

Our study aims to evaluate the potential benefits of the structured and population-based use of ePROMs and ePREMs to improve care for chronically ill patients in Germany. First, we evaluated whether and how representative the response to the digitally collected questionnaires is and thereby investigate PROMs as a tool for health system performance assessment (HSPA). Second, we assessed if low-value care elements can be identified in today's care for chronically ill patients across Germany. Third, we analyzed patients' understanding of and reactions to individualized patient-reported outcome (PRO) feedback. To achieve these objectives, this study aims to answer 3 overarching research questions and their subquestions (Textbox 1).

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Textbox 1. Overarching research questions and their sub-questions.

Can electronic patient-reported outcome measures (ePROMs) and electronic patient-reported experience measures (ePREMs) be used in patients with chronic diseases for quality measurement at the health system level (eg, for health system performance assessment [HSPA])?

- How representative are response rates in patients with chronic diseases via digital surveys in terms of gender, age, and diagnoses?
- How do response rates and willingness to respond multiple times vary over time by age, gender, indication, city or state, health system use (frequent versus infrequent users), web- or app-based surveys, and Disease Management Program (DMP) participation?

To what extent can value-of-care variation be identified from ePROMs and ePREMs surveys?

- What is the share of suspected low-value care and suspected high-value care in Germany, per indication and in subgroups?
- How do ePROM and ePREM results and health indicators of health insurance data differ according to age, gender, indication, city or state, health care system usage (changes in frequency of outpatient practitioner attendance, prescriptions, hospitalizations, etc), and DMP participation?
- Can ePROMs and ePREMs function as an early warning signal for deteriorating chronic conditions or adverse events such as hospital admission?

What are the benefits or drawbacks of patient-reported outcome (PRO) feedback (outcome reports) sent to patients?

- Are the PRO outcome reports understandable to patients?
- Can PRO feedback function as a positive nudge (be associated with positive behavioral changes, eg, healthier or more active lifestyle, more active participation in medical treatment, actively approaching treating physicians in the office setting)?
- Are there any negative emotional reactions when receiving PRO feedback that shows values worse than those of a comparable group?

Methods

Trial Design

This is an observational prospective cohort study covering the 4 chronic diseases: asthma, COPD, diabetes types 1 and 2, and coronary artery disease (CAD). As shown in Figure 1, the first point of contact will be a letter from the insurer to insured patients selected for their chronic disease. A patient can then sign up digitally for the study via a QR code or web-based link. For each of the different diseases, a distinct patient pathway is automatically assigned, with a registration process followed by some background questions and the respective generic and disease-specific PROMs and PREMs. The study covers a timeframe of 1 year, split into 4 time intervals with further information and reoccurring questionnaires. The time intervals are split into smaller tasks to facilitate the answering process for participants. The first interval includes self-registration and a baseline assessment of health behavior. A few weeks after responding to the first set of questions (Figures 1A and 1B), patients will receive a report with their individual PROM scores compared to a peer group and will be surveyed on the comprehensibility of the PRO report (Figure 1C). From the second interval onwards, patients will also receive their individual PRO results longitudinally. Lastly, following the individual PRO feedback report, participants will be surveyed regarding their health behavior (Figure 1D). After 1 year, the primary data collection process is finished, and patient-reported data will be merged with health insurance data. Further explanations of subgroup definitions can be found in the Statistical Analysis Plan (Multimedia Appendix 1).

Figure 1. Study design: patient pathways including timeline and tasks. PREM: patient-reported experience measure; PRO: patient-reported outcome; PROM: patient-reported outcome measure.

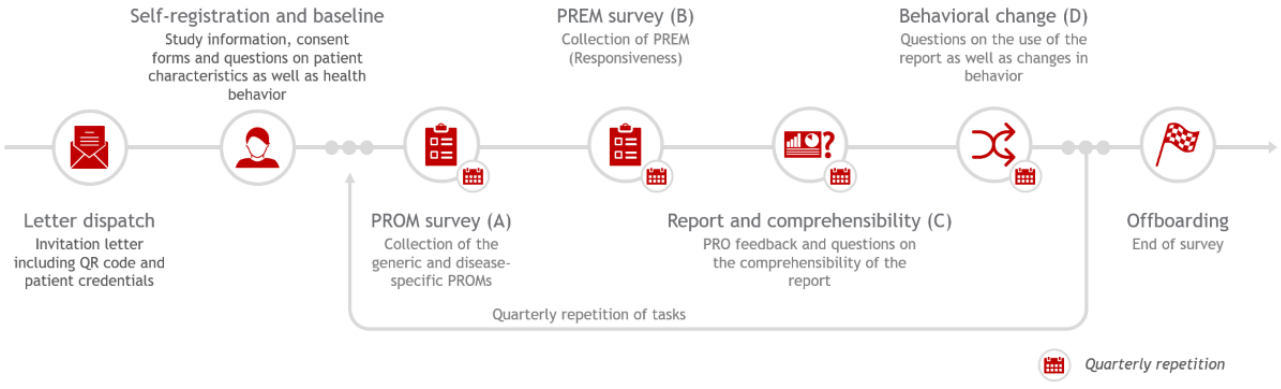

Study Setting

This study will recruit patients all over Germany who are insured by one of the largest statutory health insurers in Germany (BARMER). The BARMER represents more than 10% of the German population. After the identification of individuals based on their chronic disease profile, validated PROM sets are used digitally to regularly survey patients with asthma, COPD, diabetes, or CAD on their health outcomes as well as their experience with the health care system.

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Eligibility Criteria

Patients are eligible for participation in the study if they are above the age of 18 years and have at least 2 outpatient consultations in 2021 documenting a confirmed chronic disease diagnosis of 1 of the 4 focus diseases. Additionally, for type 1 diabetes patients, at least 1 insulin prescription must be documented in 2021. To contact patients and enable the linkage of health insurance data, patients must be insured by BARMER health insurance all year in 2021. Patients enrolled in a Disease Management Program (DMP) as well as patients not enrolled in any DMP are eligible. However, enrolment in more than 2 DMPs is not permitted to avoid multiple invitation letters and cross-over groups.

Participant Timeline

Eligible participants will be participating in the study for a maximum of 4 quarters, starting with the first access to the digital questionnaires, followed by quarterly digital surveys split into several tasks (compare Figure 1). To start the survey, participants register with their study pseudonyms received in their enrollment letter and then share basic demographics. Each survey period contains 4 tasks to be completed by participants, defined as sets of questions that each will take 5-10 minutes to complete. The participants will receive individual reports on their patient-specific and peer group outcomes (PRO feedback) and will be asked about the comprehensibility of the report. Following the report, the participants receive a set of questions regarding their health-related behavior.

Sample Size

The initial enrollment letter is sent to 200,000 insured patients, 50,000 for each of the selected chronic conditions. Diabetes type 1 and type 2 are considered jointly, as there is no differentiation in the selected PROMs. Patients with all chronic diseases are allocated to groups based on their participation in DMP (DMP or non-DMP group). Prior experiences suggest that around 30% of patients react to invitations to participate in research by their insurer [29-31]. Two-thirds of initial participants are expected to allow follow-up contacts and processing of their health insurance data, and around 40% of these patients will continue participating in all the follow-up surveys after receiving reminders for each task. Therefore, after accounting for nonparticipants and participants with no complete survey data, we expect a complete data set for 16,000 participants. However, the first research question will investigate response rates, as there is no evidence on this population yet.

BARMER Health Insurance will send out enrollment letters based on a random selection of BARMER-insured patients following the defined eligibility criteria. Matching of DMP- and non-DMP participants will be done according to the steps provided in Textbox 2.

The output is a data set containing matched pairs per indication. The first 25,000 matching pairs for each chronic condition will be selected. Diabetes type 1 and type 2 are considered jointly, with patients having diabetes type 1 selected first (approximately 6600 matched pairs are expected), followed by supplementing the remaining required matched pairs with patients having diabetes type 2.

Textbox 2. Matching of Disease Management Platform (DMP) and non-DMP participants.

Stratification by:

- Gender (male or female).
- 10-year age groups (first group: 18 to younger than 30 years and last group: 90 years and older).
- Number of outpatient cases with indication diagnoses within the year 2021 (outpatient cases in less than 4 quarters, outpatient cases in all 4 quarters but less than or equal to 6 cases, outpatient cases in all 4 quarters with more than 6 cases).
- Matching DMP and non-DMP patients by strata and a generated random numbering within the strata (1:1 matching).
- Consecutive selection of randomly sorted matched pairs if both matched individuals are insured all year long.

Recruitment

An initial enrollment letter including the study explanation, a QR code, and a link as an invitation to participate in the study will be sent to insured patients in October 2023 (Multimedia Appendix 2). The enrollment survey and, thereby, the recruitment period will be open for 2 months.

Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and was approved by the Charité's Ethic Committee, Berlin (EA2/035/23). All potentially eligible participants will be approached to offer their informed consent to participate in the study as well as to allow linkage of their insurance data for further analysis. This protocol is version 1, dated January 10, 2024. Any changes in the study design will be communicated to all project partners.

Informed consent must be provided digitally before patients can participate in the study. By signing the informed consent, patients allow contact for follow-up surveys via email and to process their survey data for academic research purposes. Additionally, patients are asked to sign a second consent form for processing and linking their insurance data to their survey data. The second consent form is optional and is not a prerequisite to participating in the study. Patients will be free to withdraw from either one of the consents without stating a reason until the anonymization of the data. Through the anonymization of the primary and secondary data before the provision of data sets to research institutions in the project, patient identification will not be possible. If the patients withdraw their consent for participation, all their data will be deleted. Consent forms can be found in Multimedia Appendix 3. Participants are not reimbursed for their participation.

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Intervention

Explanation for the Choice of Comparators

This prospective observation cohort study does not involve any specific therapeutic treatment. To analyze and report insights on sub-cohorts of the study population, splits for age, gender, indication, PRO feedback, and usage of the health care system (eg, DMP) are formed.

Intervention Description

In addition to filling out the survey questions (considered here as intervention 1), all participants will receive PRO feedback (considered here as intervention 2—see Multimedia Appendix 4). The PRO feedback will be a pdf report sent via email, which graphically (line charts) shows the patients' individual generic and disease-specific health status in comparison to a patient-specific peer group. In addition to the visual feedback, the results will shortly be explained on the same page. The description will cover whether patient-individual PRO scores are better or worse compared to the peer group, and if worse, the patients' health status might be still good and can be discussed with the patients' physician. Additional details on the scores and sub-scores are shared with the patients on the subsequent pages of the report. Peer groups are classified according to their disease, gender, and age group (18-45 years, 45-65 years, 65-75 years, and 75 years and above). The report refers to a patient's routine care physician as the main contact to discuss the results or if there are questions.

Criteria for Discontinuing or Modifying Allocated Interventions

Participants may withdraw from the study at any time. Following discontinuation, all participants' individual study data will be deleted, and surveys and reminders will not be sent anymore.

Strategies to Improve Adherence to Interventions

To enhance adherence, the sign-up process for the digital solution was minimized. In addition, email reminders will be sent to patients. Moreover, the PRO feedback includes multiple elements (graphics, bolded text, and descriptions), as this was shown to improve patient understanding [27,32].

Outcomes

The primary end point (research question 1) of the study is sufficient study participation to determine the representativeness of the results. As expected, study participation will vary depending on gender, age, and diagnosis, but this can be compensated for by weighting the study participants according to structural information on the target population.

Within our study, data on health care usage is available for both participants and the whole target population. Weighted measures of health care usage from participants will be compared with measures of health care usage of the complete target population and will be assumed to be formally representative if the weighted measures from participants fall within the 95% CI of the same measures based on data from the complete target population.

Secondary end points are the end points to answer research questions 2 and 3 (Textbox 3; Figure 2).

Figure 2 represents how PROMs and PREMs can be combined into one value of care indicator, for example, if PREMs and PROMs are both average or above (up to 1 SD), care is suspected to be high-value, whereas if PROMs and PREMs are below 1 SD of the average, care is suspected to be low-value. Since for each disease group, a disease-specific PROM will be used next to a generic PROM, the assessment of low- and high-value care across diseases will be conducted by using the generic PROMs. Moreover, the disease-specific PROMs will be used to create low- and high-value care categorizations on a detailed level within a disease group. Adding cost data as a third dimension to the value of care framework (as described in the Statistical Analysis Plan, Multimedia Appendix 1) then enables a clear distinction between patients considered to have received low-value care and patients who received high-value care. A more detailed description of the outcomes can be found in the Statistical Analysis Plan (Multimedia Appendix 1).

Textbox 3. Research questions 2 and 3.

Research question 2:

- Share of low-value care using the VBHC framework introduced in Figure 2 and specified in further detail in the Statistical Analysis Plan (Multimedia Appendix 1)
- Share of high-value care, specified in Figure 2
- Outcome and patient experience variation across subgroups
- Adverse events such as hospital admission due to a chronic disease profile

Research question 3:

- Comprehensibility and usability of patient-reported outcome (PRO) feedback
- Impact of PRO feedback on health care behavior

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Figure 2. Assessment of value-based health care—outcome dimensions of suspected high-value and low-value care. PREM: patient-reported experience measure; PROM: patient-reported outcome measure.

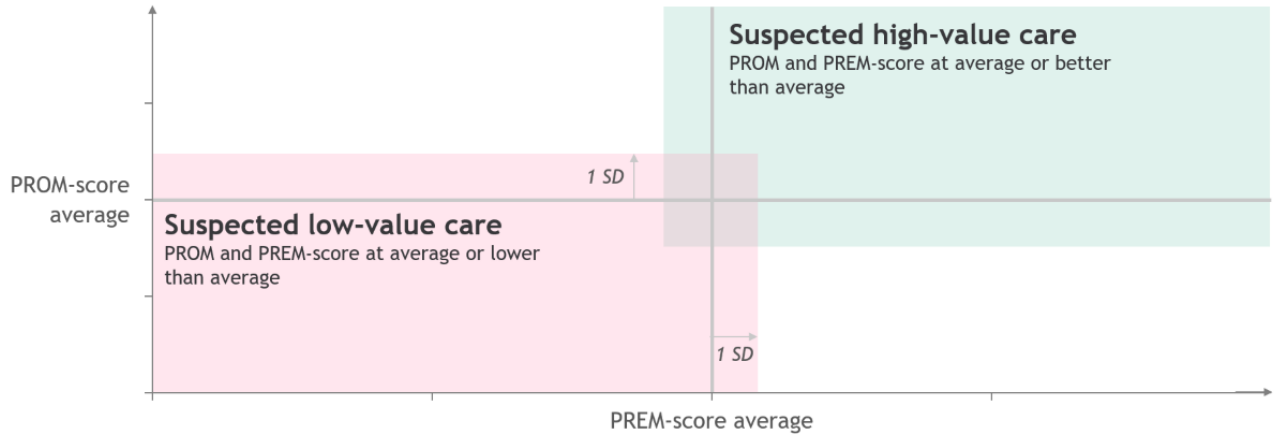

Assignment of Interventions: Allocation

Sequence Generation

The sequence generation data are provided in Textbox 4.

The output is a data set containing matched pairs per indication. The first 25,000 matching pairs for each chronic condition will be selected. Diabetes type 1 and type 2 are considered jointly, with patients having diabetes type 1 selected first (approximately 6600 matched pairs are expected), followed by supplementing the remaining required matched pairs with patients having diabetes type 2.

Textbox 4. Sequence generation.

- The BARMER health gender (male and female)
- 10-year age groups (first group: 18 to younger than 30 years, last group: 90 years and older)
    - Number of outpatient cases with indication diagnoses within the year 2021 (outpatient cases in less than 4 quarters, outpatient cases in all 4 quarters but less than or equal to 6 cases, outpatient cases in all 4 quarters with more than 6 cases)
- Matching Disease Management Program (DMP) and non-DMP patients by strata and a generated random numbering within the strata (1:1 matching).
- Consecutive selection of randomly sorted matched pairs if both matched individuals are insured all year long

Implementation

The random selection of patients will be performed by BARMER Health Insurance according to the selection process description provided by the independent evaluating aQua institute.

Data Collection and Management: Plans for Assessment and Collection of Outcomes

There are 2 main data sources used in this study. First, primary data will be collected from the participants' surveys. Second, secondary data from the cooperating health insurer, BARMER, will be used. The primary data collection is conducted via digital surveys, which include different questionnaire categories, namely PROMs, PREMs, comprehensibility of the PRO feedback, and questions on patients' health behavior. Additionally, an anchor question using the Global Rating of Change scale [33] with 5 answer options is included to assess changes in health status.

An overview of all selected survey items, including the selected validated PROMs, can be found in Figure 3 and is described in more detail in the following paragraphs.

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Figure 3. Survey items in the PROMchronic trial. AIRQ: Asthma Impairment and Risk Questionnaire; CCQ: Clinical COPD Questionnaire; COPD: chronic obstructive pulmonary disease; PAID-5: Problem Areas in Diabetes Scale–5; PREM: patient-reported experience measure; PRO: patient-reported outcome; PROM: patient-reported outcome measure; RDS: Rose Dyspnea Scale; SAQ-7: Seattle Angina Questionnaire-7.

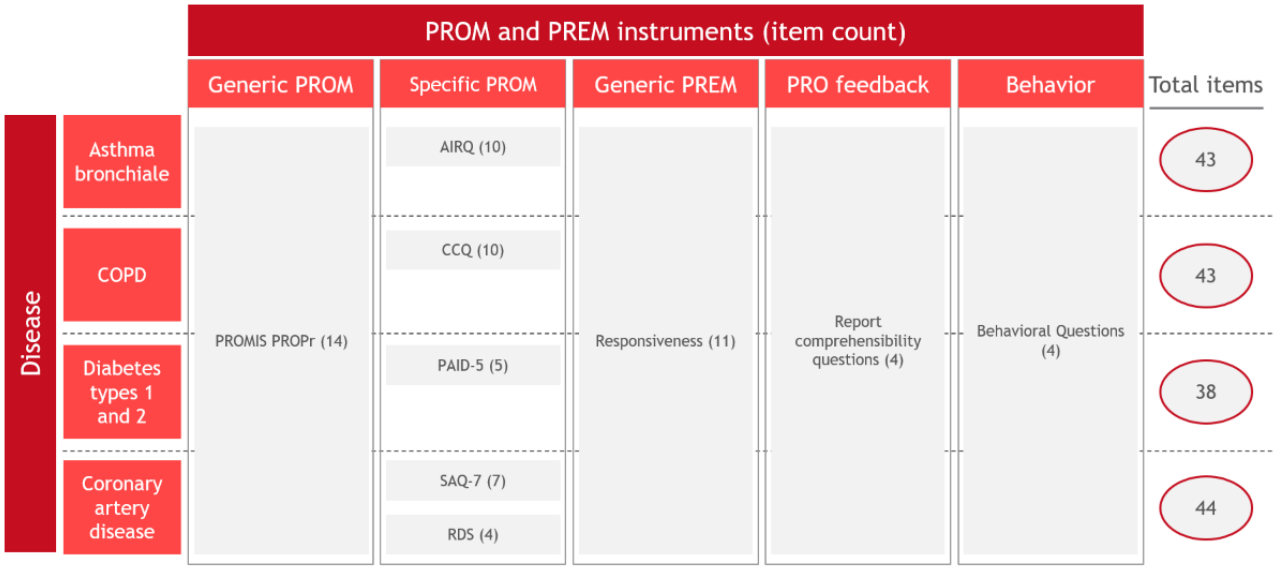

PROMs

Overview

Various PROMs exist that can be classified into generic, treatment-specific, and disease-specific instruments. Generic PROMs assess health outcomes broadly and enable comparison across diseases, whereas treatment- or disease-specific PROMs are tailored to a specific treatment or disease and are more suitable for comparisons inside patient groups receiving the same treatment or a population with similar diseases [17]. The selection of the PROMs is in line with the selection criteria reported in the literature [34-37] as well as project-specific criteria. The criteria that were used for the selection of PROs are listed in Textbox 5.

Textbox 5. Criteria used for the selection of patient-reported outcomes (PROs).

Short

- The questionnaire must be brief to not burden participants and increase response rates [38]. The overall item count across one survey period was restricted to 60 items and a maximum of 15 minutes to complete.

Language

- The patient-reported outcome measures (PROMs) must be available in German.

Validation

- The sets must be validated, at least in the German language, and ideally also for digital applications.

Licensing fees

- Licensing fee for surveys for academic use does not exceed US $5000 per set.

Scoring

- Scoring information must be available to enable PRO feedback based on overall scores.

Health dimensions

- The combined set of PROMs must cover all overarching health dimensions of physical, mental, and social health and reflect a mix of generic and disease-specific PROMs to enable informative intra- and inter-group comparisons.

OECD comparison

If possible, given the above-mentioned selection criteria, similar PROMs as the OECD (Organisation for Economic Co-operation and Development) PaRIS (Patient-Reported Indicator Surveys) initiative were selected to facilitate the comparability of results.

As a result, all participants will receive the PROMIS (patient-reported outcomes measurement information system) Preference Score (PROPr) [39] as well as disease-specific PROMs based on their chronic disease (Textbox 6).

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Textbox 6. Disease-specific patient-reported outcome measures (PROMs).

- Asthma: Asthma Impairment and Risk Questionnaire (AIRQ) [40]
- COPD: Clinical COPD Questionnaire (CCQ) [41]
- Diabetes: Problem Areas in Diabetes (PAID-5) [42]
- CAD: Seattle Angina Questionnaire-7 (SAQ-7) [43], and Rose Dyspnea Scale (RDS) [44]

PREMs

PREMs are used to collect information about the experiences of patients with health care services. PREMs ask patients about aspects of care such as communication, coordination, and access to care [19,45]. The responses can provide valuable insights into how health care services are perceived by patients and how they can be improved. There are a variety of different PREMs survey available, each with its own strengths and weaknesses and focus areas. Similar to the selection of the PROMs, the selection of PREMs followed criteria of time required to complete, validity, language, licensing fees, and HSPA relevance. Consequently, participants will receive the 11-item "responsiveness" component of the IPHA questionnaire with modified observation periods, as it is validated in chronic disease patients in Germany, is available in the German language, and is relatively short (11 items) [46].

Questions on PRO Feedback

The study examines a patient's perception and reaction to individual PRO feedback. First, patients will be asked if they have opened the pdf report. In addition, the comprehensibility and usefulness of the report will be investigated by asking 1 question each. A final question is asked about a possible change in mood after seeing the results in the pdf report. The set of questions can also be found in Textbox 7.

Textbox 7. List of questions on reactions to patient-reported outcome (PRO) feedback.

Review of report

- Have you looked at your health report?

Comprehensibility

- Is the information in the health report understandable to you?

Usefulness

- Is the information in the health report helpful for you?

Change in mood

- How do you feel based on the information in your health report?

Health Behavior

Health behavior is significantly associated with health outcomes like mortality or the occurrence of chronic diseases [47]. Regarding chronic diseases, there are 5 essential health behaviors related to health outcomes, which include physical activity, diet, smoking, alcohol consumption, and sleep [48]. Participants' perceptions of health behavior are assessed by 1 question on each of these 5 health behavior dimensions. Thereafter, their intention to change health behavior in the coming months and triggers for change are assessed. Additionally, participants receive a question regarding whether the results were discussed with their treating physicians.

Health Insurance Data

For those participants who have given consent, health insurance claims data will be linked to the participants' primary data after the completion of the final survey period. Claims data will contain health care resource consumption (residence, comorbidities, inpatient hospital stays, outpatient consultations, complications, rehabilitation, drugs, physiotherapy, medical remedies and aids, and care services) and additional data points further specified in the Statistical Analysis Plan (Multimedia Appendix 1).

Plans to Promote Participant Retention and Complete Follow-Up

Complete survey data is important to calculate PROM scores [49]. Participants can access digital dashboards showing open tasks (questionnaires) and the remaining time to complete them. To increase data completeness, the participants will be reminded by email to fill in their follow-up questionnaires 1, 3, and 10 days after the initial dispatch of surveys.

Data Management

The collection, storage, and processing of personal data in this project are carried out in accordance with the General Data Protection Regulation in Germany, the specific data protection provisions of the Social Code, and all other national data protection regulations. During the study, all electronically recorded primary data, as well as participation and consent forms, will be stored on the server of Oncare GmbH and deleted after the end of the evaluation period. The Oncare team will manage patient information through the myoncare app and study website, always respecting data security and confidentiality.

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All reading and processing processes are logged in the database. All data will be collected and transferred completely pseudonymized.

Pseudonyms are created by the health insurer BARMER following the universally unique ID standard and are only re-identifiable by BARMER health insurance. Consequently, the pseudonym is added to the health insurance data to match primary patient data to insurance claims data. All identification information will be erased prior to data transfer to the research institutes Technical University Berlin and aQua Institute. Pseudonymized data will be kept for the period of data analysis of 2 years by the Technical University Berlin and aQua Institute and stored for an additional 10 years at study centers to ensure further evaluation of the study's outcome. This follows the recommendations for good practice in secondary data analysis [50].

Confidentiality

A unique study pseudonym is assigned to each participant by the health insurer. The pseudonym list with patient names will only be accessible to the health insurer, and they will not receive any primary data. During the primary data collection, no data that would allow re-identification will be collected. Minimum contact data is collected to ensure follow-up surveys can be completed and reminders can be sent to the participants. Linkage of health insurance data will be conducted via study pseudonyms. The project adheres to all data protection laws.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

The statistical analyses are reported in the separate Statistical Analysis Plan (Multimedia Appendix 1) but generally include descriptive statistics, parametric and nonparametric methods, as well as time series analyses for the primary and secondary end points.

Methods for Additional Analyses (eg, Subgroup Analyses)

Participants with the respective chronic diseases are grouped into specific subgroups based on the research questions. For all participant groups, additional control data from overall insured patients will be accessible on an aggregated level. Therefore, the study population is segmented into different subgroups (Figure 4 and Textbox 8).

Figure 4. Definition of study population and patient groups based on response status for statistical analysis.

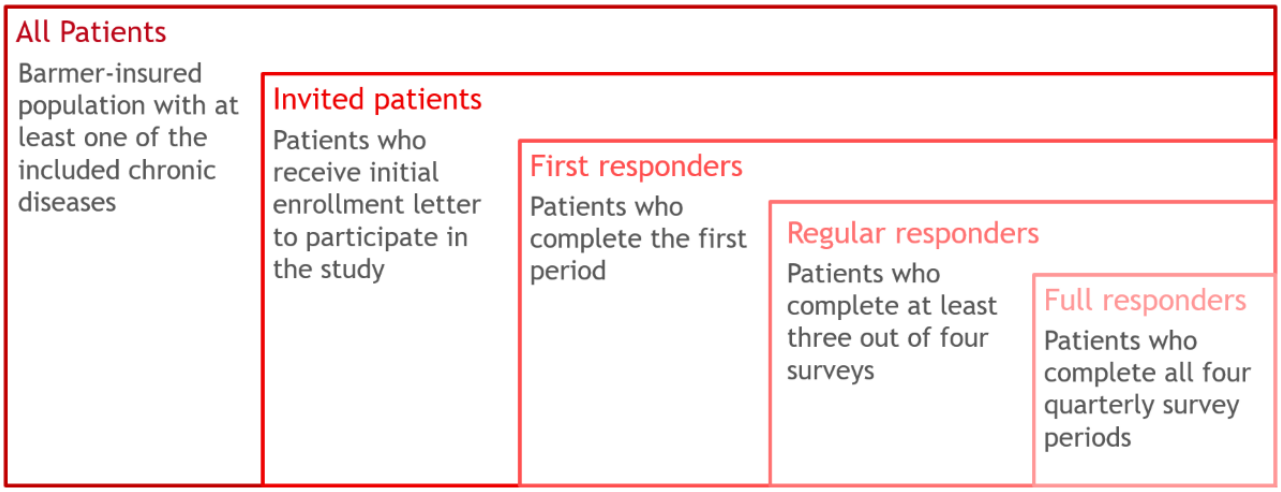

Textbox 8. Subgroups of study population.

- All patients: a full BARMER-insured population with at least one of the chronic diseases included in the study, with data available only at an aggregated level
- Invited patients (from “All patients”): Patients who receive the initial invitation letter
- First responders (from “Invited patients”): Patients who complete the first survey period, including consent to use their health insurance data
- Regular responders (from “First responders”): Patients who complete at least 3 out of 4 survey periods
- Full responders (from “Regular responders”): Patients who complete all 4 quarterly survey periods

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

The study is set up as a prospective observational cohort study, inviting patients to complete different surveys over a 1-year time frame. Nonadherence, defined as nonparticipation or dropout in this study, is one of the main research questions and will not be handled specifically for research question 1. Complete PROM data are important to calculate scores. In cases of missing data, we will adhere to PROM-specific guidelines to handle missing data (eg, imputation or calculating scores based on remaining values).

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Results

Composition of the Coordinating Center and Trial Steering Committee

The study is monitored by the German research center "Deutsches Zentrum für Luft- und Raumfahrt" (German Aerospace Center). Quarterly status reports are provided by the project team. Status reports include an overview of the achievement levels of the milestones defined prior to the start of the study.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

The management of the study is overseen by a project team from Technical University Berlin. The project team is composed of researchers responsible for the study's design, representatives from the participating BARMER health insurance, the technical service provider Oncare, and the evaluating aQua Institute. Regular updates on the study's status are provided to the sponsor.

Adverse Event Reporting and Harms

Adverse events are not expected as the medical treatment of patients with chronic care is not affected. The effects of the PRO feedback intervention are one of the primary end points, and the results will be monitored and published.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethical Committees)

Any substantial amendments to the protocol will be submitted to the ethics committee (see below) and all relevant regulatory institutions. Additionally, any amendments to the study design, timeline, or budget need to be communicated to the study sponsor, and approval by the coordination center must be obtained.

Dissemination Plans

The results of this study will be disseminated via publications in peer-reviewed journals and presentations at relevant conferences. Moreover, the funding institution (Innovation Fund of the Federal Joint Committee) will receive an evaluation report that includes the findings of the study as well as interim reports on the study's milestones. All results will be aggregated, with no opportunity to reconnect on an individual patient level.

Discussion

Principal Findings

The study aims to fill the gap in the literature on large-scale usage of ePROMs and ePREMs in patients with chronic diseases. First, the study protocol details how the representativity of the responses to ePROMs and ePREMs will be assessed over time in different subgroups. This foundational groundwork will help with future targeted efforts and the mitigation of representativity issues. Second, the study protocol identifies how PROMs and PREMs will be used to uncover potential low-value care for patients with chronic diseases. The results can thus inform future investigations on activities for low-value care reduction. Third, it introduces how individual PRO feedback can be shared with patients with chronic diseases and provides insights into the usability and usefulness of PRO feedback. The results of the evaluation can thereby aid the understanding of this specific PRO feedback mechanism.

ePROM collection will increasingly be the standard for capturing patients' perspectives on treatment outcomes as well as their own health status. It was previously shown that the administrative burden for patients and health care providers can be significantly reduced through the collection of ePROMs compared with phone- or paper-based collection, while response rates and the completeness of data collection remain high [51]. The results of this study will fill the research gap in terms of the representativity of the patient population through ePROM and ePREM collection, for which no previous evidence exists. While this study uses ePROM to measure care quality variation, most of that research was focused on oncological studies [52]. This study aims to fill the research gap on measuring care quality through ePROM and ePREM usage in patients with chronic diseases. Other studies have shown, that working with PROMs can improve care by significantly reducing low-value behavior [53,54]. Additionally, the use of ePROMs and ePREMs can enable (almost) real-time, individual PRO feedback [55-57]. Providing PRO feedback is one way to enhance the use of PROMs in clinical practice and shared decision-making [58]. Previous studies indicate that patients who reviewed shared information on their PRO outcomes are more engaged and actively participate in their health care, but they have not investigated direct-to-patient feedback in patients with chronic diseases [59,60].

There are some limitations to the study that need to be considered. One limitation is the potential for nonresponse bias, as patients who choose to participate in the study may differ from those who do not. However, given the access route via large-scale, randomized health insurance paper-based outreach, we hope some participants who would not take part in studies in a clinical study will be accessed. Moreover, it is one of the study's aims to detect the representativeness of the responders. Given that the letter and questionnaire will be in German, we anticipate that non-German speakers will be excluded from the study, which unfortunately could not be addressed via the digital solution, the adjustment to letters, and the low availability of validated PROMs in other languages often spoken besides German in Germany (eg, Russian or Turkish). Moreover, respondents to the study might do systematically better in terms of their PROMs and PREMs results, which cannot be assessed if there are no other systematic differences between the responder and nonresponder population [61]. This could also be the case if the monitoring itself improves health outcomes, as suggested in the current literature [62,63].

The broader implications of this study are insights generated for (1) ePROM and ePREM usage among patients with chronic diseases globally and specifically in Germany, as well as (2) cross-country learnings. (1) The expected benefits of PREM and PREM usage among patients with chronic diseases were previously stated by experts, while a lack of evidence in the treatment of chronic diseases exists [22]. This study will examine if and to what extent digitally collected PROMs and

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PREMs as well as automatically generated PRO feedback could strengthen patient empowerment, informed shared decision-making, and behavior changes in patients with chronic diseases. (2) Given that the OECD PaRIS study will assess PROMs and PREMs across many countries besides Germany, the results of this study can enable Germany to be part of this research community and to benchmark its health care system against those of other OECD countries. Long-term benchmarking results across countries and within Germany can have implications for health care spending based on patients' needs and care reorganization while raising awareness of care value.

Trial Status

This protocol is version 1, dated October 5, 2023. Patient recruitment will begin with BARMER's letter dispatch around October 11, 2023. The collection of survey data will be finished by September 30, 2024. The study is expected to run until June 30, 2025.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

For transparency purposes, CP is contracted full-time with Stryker Corporation, a medical technology company that also produces knee and hip implants. JN is partially employed at Boston Consulting Group GmbH, a global consulting company. All others declare that they have no relevant competing interests.

Multimedia Appendix 1
Statistical Analysis Plan.
[DOCX File , 498 KB - resprot_v13i1e56487_app1.docx]

Multimedia Appendix 2
Invitation letter for participation in the study.
[DOCX File , 1981 KB - resprot_v13i1e56487_app2.docx]

Multimedia Appendix 3
Study Information and Consent Form.
[DOCX File , 101 KB - resprot_v13i1e56487_app3.docx]

Multimedia Appendix 4
Patient-reported outcome feedback.
[PDF File (Adobe PDF File), 3490 KB - resprot_v13i1e56487_app4.pdf]

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Abbreviations

CAD: coronary artery disease
COPD: chronic obstructive pulmonary disease
DMP: Disease Management Program
ePREM: electronic patient-reported experience measure
ePROM: electronic patient-reported outcome measure
HSPA: health system performance assessment
OECD: Organisation for Economic Co-operation and Development
PaRIS: Patient-Reported Indicator Surveys
PREM: patient-reported experience measures
PRO: patient-reported outcome

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PROM: patient-reported outcome measures
PROPr: PROMIS (patient-reported outcomes measurement information system) Preference Score

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Protocol

Development of Automated Triggers in Ambulatory Settings in Brazil: Protocol for a Machine Learning–Based Design Thinking Study

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Abstract

Background: The use of technologies has had a significant impact on patient safety and the quality of care and has increased globally. In the literature, it has been reported that people die annually due to adverse events (AEs), and various methods exist for investigating and measuring AEs. However, some methods have a limited scope, data extraction, and the need for data standardization. In Brazil, there are few studies on the application of trigger tools, and this study is the first to create automated triggers in ambulatory care.

Objective: This study aims to develop a machine learning (ML)–based automated trigger for outpatient health care settings in Brazil.

Methods: A mixed methods research will be conducted within a design thinking framework and the principles will be applied in creating the automated triggers, following the stages of (1) empathize and define the problem, involving observations and inquiries to comprehend both the user and the challenge at hand; (2) ideation, where various solutions to the problem are generated; (3) prototyping, involving the construction of a minimal representation of the best solutions; (4) testing, where user feedback is obtained to refine the solution; and (5) implementation, where the refined solution is tested, changes are assessed, and scaling is considered. Furthermore, ML methods will be adopted to develop automated triggers, tailored to the local context in collaboration with an expert in the field.

Results: This protocol describes a research study in its preliminary stages, prior to any data gathering and analysis. The study was approved by the members of the organizations within the institution in January 2024 and by the ethics board of the University of São Paulo and the institution where the study will take place. in May 2024. As of June 2024, stage 1 commenced with data gathering for qualitative research. A separate paper focused on explaining the method of ML will be considered after the outcomes of stages 1 and 2 in this study.

Conclusions: After the development of automated triggers in the outpatient setting, it will be possible to prevent and identify potential risks of AEs more promptly, providing valuable information. This technological innovation not only promotes advances in clinical practice but also contributes to the dissemination of techniques and knowledge related to patient safety. Additionally, health care professionals can adopt evidence-based preventive measures, reducing costs associated with AEs and hospital readmissions, enhancing productivity in outpatient care, and contributing to the safety, quality, and effectiveness of care provided.

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Additionally, in the future, if the outcome is successful, there is the potential to apply it in all units, as planned by the institutional organization.

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KEYWORDS

machine learning; ambulatory care; patient safety; medical records systems; computerized; patient safety; technology; quality of care; automated triggers; limitation; predict; potential risk; outpatient; ambulatory patient; walk-in; adverse events; evidence-based; preventive; low-income countries; middle-income countries; data; scarcity; standardization; quality intervention

Introduction

Overview

In low- and middle-income countries, the burden of poor-quality health care has not been adequately quantified due to data scarcity, lack of standardization, and insufficient research on quality interventions. Moreover, recent estimates suggest that in these countries, between 5.7 and 8.4 million people die annually due to adverse events (AEs), where an incident resulted in harm to a patient [1]. Among the common AEs that can lead to preventable harm to patients are medication errors, unsafe surgical procedures, health care–associated infections, diagnostic errors, patient falls, pressure injury, patient misidentification, unsafe blood transfusions, and venous thromboembolism [1,2]. Annually, the indirect costs of harm from unsafe health care practices amount to trillions of US dollars worldwide, with 4 out of every 100 patients in low-to-middle-income countries losing their lives due to substandard [3]. According to the World Health Organization (WHO), the financial and economic costs of safety lapses in the health care sector will be even greater and will remain a challenge for modern health care delivery in all countries. This is attributed to patient safety incidents resulting in fatalities, disabilities, and distress for both patients and their families, along with health care workers involved in serious patient incidents [2]. This situation reinforces the hypothesis that AEs are a significant yet neglected public health issue. Furthermore, during the 72nd World Health Assembly held in May 2019, the WHO recognized patient safety as a global health priority and an essential component for achieving universal health coverage across all countries. The WHO, in collaboration with Member States, adopted resolution WHA72.6 “Global Action on Patient Safety,” with the objective of transforming the movement into a social action where patients start demanding safer health care. This marks a strategic moment as this action has been globally acknowledged as a powerful policy tool that will shape the global patient safety agenda in the coming years and reduce the costs related to AEs at all levels of health systems [1].

There are several methods available for investigating and measuring AEs, such as voluntary reporting, retrospective review of medical records involving the analysis of past patient records, prospective analysis of the patient charts of inpatients which includes capturing real-time data, direct observation, interviews with patients and health care professionals, and analysis of indicators, reports, and complaints of poor practices [4]. Among these methods, one of the most used inpatient safety research is voluntary reporting, which relies on health care providers reporting AEs that they encounter during patient care [5,6]. Another frequently used methodology in research is manual and retrospective medical record review [5,7-10]. This method is considered the “gold standard” for estimating the occurrence of AEs in hospitalized patients due to its ability to capture detailed information and this involves trained reviewers examining patient charts to identify potential AEs, followed by physician review to determine if an AE indeed occurred [11].

In the year 2003, the Institute for Healthcare Improvement (IHI) developed the Global Trigger Tool for Measuring Adverse Events [8]. This approach involves external reviewers who gather information through triggers, which are clues or indicators recorded in archived medical records that signal the potential occurrence of an AE associated with patient care [7,8]. In 2001, the IHI proposed triggers focused on tracking AEs in the outpatient setting [8], known as the Outpatient Adverse Event Trigger Tool [12]. It is important to note that the first step of the patient safety research cycle proposed by the WHO involves measuring the magnitude of AEs [1].

Despite the advantages of trigger tools in AE tracking, the methodology presents disadvantages including variation in detected AEs [6,13], limited scope [7,10], resource-intensive usage [14-16], lack of specificity [16,17], delay in tool application [7,10,15,16], dependency on complete and legible documentation [7,18], reliance on human judgment [15,16], limited data extraction [15], need for data standardization [16], and limited sensitivity [7,10,18]. For these reasons, researchers have proposed the use of automated triggers to overcome the limitations of the manual method. In investigations conducted in the United States [14] and Switzerland [16,18], researchers used automated triggers to track AEs.

In another study, machine learning (ML) was used to assess risk factors associated with severe AEs, after tracking patient harm in a cancer hospital in Chongqing, China [19]. The findings indicated that automated triggers and ML successfully identified risk factors for severe AEs induced by antineoplastic drugs in patients with cancer. The ML model incorporated variables such as age, cancer type, number of prescribed medications, and other factors. The study’s outcomes were considered promising, as the developed model demonstrated the ability to predict severe AEs induced by antineoplastic drugs in patients with cancer. The researchers concluded that the use of automated triggers and ML is a promising approach to identifying risk factors for severe events, in contrast to the manual and retrospective method which aims to track events that have already occurred. Consequently, automated triggers

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represent a proactive approach, while triggers developed by the IHI are reactive.

Theoretical and Methodological Framework

Using Design Thinking Framework

Design thinking is defined as a human-centered approach to solving complex problems and finding innovative solutions [20]. Its objective is to creatively address adversities, focusing on the needs of the users [20]. The method has been used in the health care field with the purposes of enhancing the patient's experience, developing solutions for clinical complications, creating business models in health, and improving service efficiency [20]. Previous research results have demonstrated that the use of design thinking in health care can lead to bold and people-centered solutions, as well as improvements in the efficiency of services provided to patients [20].

The method consists of the phases of (1) empathize and define the problem, which involves observations and questioning to understand both the user and the challenge at hand; (2) ideation, where various solutions to the problem are generated; (3) prototyping, which involves building a minimal representation of the best solutions; (4) testing, where user feedback is obtained to refine the solution; and (5) implementation, where the refined solution is tested, the change is evaluated, and scaling is considered. This phase may lead to new discoveries and the continuation of the process [20].

Recent research conducted in the health care field [21-24] with the purpose of applying design thinking in clinical research [25,26], patient safety, and quality of care [27], as well as in the education of health care professions [21-24], demonstrated that the method has contributed to the development of simple yet efficient solutions for managing problems. For example, it has been effective in reducing the outbreak of the COVID-19 pandemic [24], improving health research reporting [26], enhancing clinical researchers' understanding of issues in dementia care [25], refining patient safety and overall quality of care in the operating room [27], proposing ethical implications for organ transplantation [21], and fine-tuning curricula and educational programs for health care professions [22].

ML in the Health Care Field

In recent years, there has been an increased interest in ML in the health care field, driven in part by the availability of large data sets and the development of powerful computing resources. ML, a branch of artificial intelligence (AI) and computer science, focuses on using data and algorithms to mimic the way humans learn, gradually improving its accuracy. The method is being applied to a wide range of fields, including health and finance [28,29]. With the rise of AI and the growing influx of digital data in health care, new tools have emerged that can enhance patient care and alleviate the labor-intensive nature of nursing work [28,29]. It is anticipated that in the next decade, health care delivery will be revolutionized by the integration of digital health technologies and AI [29].

Recent research using ML in the health care field, such as the development of an early warning system for sepsis [30], the assessment of mortality risk in older adults [31], the prediction of hospital admissions in emergency departments [32], and the forecast of AEs after percutaneous coronary intervention [33], has concluded that these techniques are effective in predicting such events and can provide increased accuracy in outcomes.

Goals and Research Question

This protocol describes a methodology designed using design thinking frameworks to develop ML-based automated triggers for outpatient health care settings in Brazil and overcome the limitations of manual methods. Additionally, the specific objectives are (1) to apply the principles of design thinking in the creation of automated triggers; (2) to gain insights into risk factors for AEs and limitations in early detection of health care–related harm from the perspectives of health care professionals, patients, and family or caregivers; (3) to create automated triggers through ML; and (4) to evaluate the implementation of this solution in the real world. Considering the foregoing, the question arises if it is possible to develop automated triggers through ML to predict early risks of avoidable harm related to outpatient health care.

Methods

Study Design and Setting

Mixed methods research will be conducted within a design thinking framework. The study will take place at the outpatient unit of a prominent tertiary-level teaching hospital in the Metropolitan Region of Ribeirão Preto, located in the state of São Paulo, Brazil. The institution provides services across various medical specialties, offering exclusive services to the Unified Health System. Within the outpatient building is the institution's largest surgical center, as well as the Central Laboratory Division—the first public laboratory in Brazil certified by the American College of Pathologists. The unit also has jointly a pharmaceutics unit, responsible for dispensing prescribed medications and regularly producing various categories of pharmaceuticals.

Participants

Study Inclusion and Exclusion Criteria

In this study, exclusively included will be adult patients aged 18 years or older, fluent in Brazilian Portuguese, along with their family members or caregivers and members of the multiprofessional health care team (physicians, nurses, nursing technicians or assistants, pharmacists, nutritionists, physiotherapists, psychologists, and speech therapists) with a work experience in the outpatient unit exceeding 1 year. Residents and health care professionals on vacation or leave during the data collection period will be excluded. Regarding patients' electronic medical health records (EMHRs), those originating from pregnant individuals and psychiatric patients will be excluded. Additionally, patients' EMHRs with insufficient and incomplete information will be excluded.

Sample Size

The sample size will be divided into 2 stages. For the interview, a sample size of 20 participants will be considered, including patients, family members or caregivers, and members of the

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multidisciplinary health care team, taking into account the concept of data saturation [34,35]. Finally, for predictive analysis in ML for patients' EMHRs, the sample size will depend on the number of variables identified and included for triggers that need to be considered [36].

Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and in compliance with the standards and guidelines established by the National Research Ethics Commission, as specified in the regulations and recommendations of Resolution 466/12 of the National Health Council [37], which regulates research involving human participants.

This project also involves documentary research as the incident or AE reports that occurred with ambulatory patients will be analyzed. It will not be possible to obtain informed consent from individuals whose data are contained in these restricted-access documents, as they do not attend the owning institution. In this case, the researcher will sign the Commitment Term for Data Use and Handling, which will be handled only after approval by the Research Ethics Committee and the owning institution.

The study was approved by the members of the organization within the institutions (146.00010241/2023-15) and it has been approved by the College of Nursing, Ribeirão Preto, University of São Paulo (Brazilian Ethics Board 6.811.085) and by the ethics board of the institution where the study will take place (Brazilian ethics board 6.851.281), enabling the commencement of data gathering in the ambulatory care unit.

Participants will be informed about the study's objectives and, upon agreeing to participate voluntarily, they will be asked to sign the informed consent form. There will be 3 informed consent processes—2 separate informed consent for stages 1 and 2 (1 for patients, family members or caregivers, and another for participants who are members of the multidisciplinary health care team). The third informed consent will be considered for stage 4 participants in this study.

Participants will not receive direct benefits or compensatory benefits, but the results of this study may generate indirect benefits. The results will be useful for developing automated triggers in the outpatient setting. As mentioned in stage 1, under step 4, participants' identification will be encrypted, to guarantee privacy and will not be disclosed when publishing the study results. All data obtained will be used for scientific purposes only.

Procedures for Data Collection and Data Analysis

Overview

This phase will be divided into 5 stages based on design thinking, as presented in Figure 1 [20].

Figure 1. Stages of design thinking (adapted from Altman M et al [20], which is published under Creative Commons Attribution 4.0 International License [38].

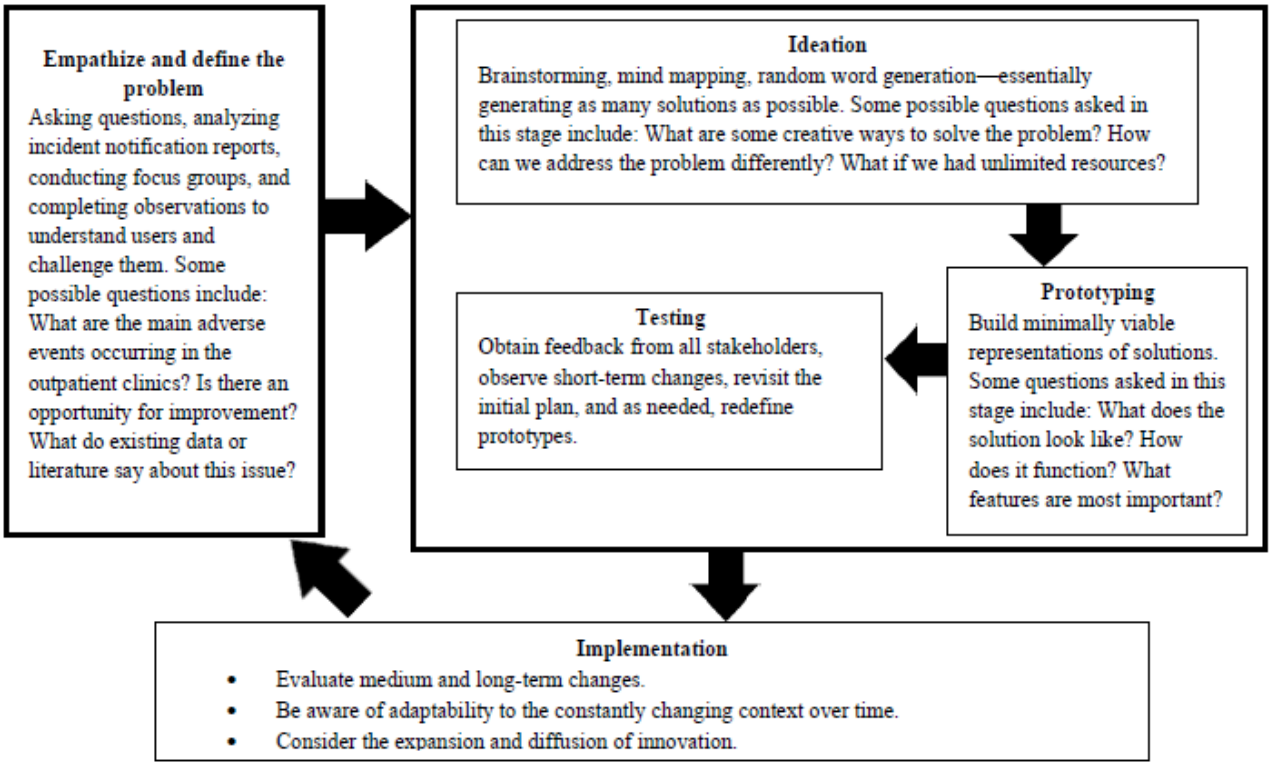

Empathize and Define the Problem: Stage 1

Overview

In this stage, qualitative research will be conducted. The researcher will meet with stakeholders to collect data on their perceptions of a specific problem and conduct on-site observations to understand users and challenges at hand. In addition, the institution's incident notification reports will be analyzed to map the most frequent types, severity according to the WHO classification [39], and prevalence.

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To access incident or AE reports from the institution and conduct interviews, the researcher will contact the unit manager and the institution's risk management representative to present the research project and clarify its objectives. After obtaining proper authorization from the unit manager and the institution's risk management, the risk management manager will proceed to provide tabulated data, which includes the variable of interest. These variables include the patient's registration number, patient characterization information, type of event, severity or degree of resulting damage or harm, consequences of the damage or harm, and the occurrence location, specifically within which medical specialty. Also, during these visits, with the purpose of analyzing AE notification reports and mapping the patient's journey from admission to discharge. Furthermore, "extreme patients" will be identified, those with multiple admissions in a short period. Additionally, the EMHR will be examined to characterize patients who have experienced AEs, defined as incidents resulting in patient harm due to health care [1], such as medication errors and readmissions within 30 days.

Subsequently, authorization will be requested to access patients, family members or caregivers, and health care professionals working in the unit, who will be invited to participate voluntarily and in writing. The researcher will schedule interviews within the unit, in a reserved location agreed upon with the manager, so as not to interfere with the institution's care routine. In this case, semistructured interviews will also be conducted, recorded in audio and later transcribed [40] to understand the experiences of patients, family members or caregivers, and health care professionals regarding AEs related to care provided in the outpatient setting.

An interview protocol with 4 to 5 questions will be considered [40]. Then, participants will be asked to elaborate on their ideas or what they said in detail [40]. The interviews will be fully transcribed and later analyzed with the assistance of the ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH) [41]. Data will be analyzed following the process [40] that involves the following steps.

Step 1

Organize and prepare data for analysis—involves transcribing interviews or classifying and organizing data into different types, depending on the sources of information.

Step 2

Read all data—the first step is to get a general idea of the information and reflect or begin to record general thoughts about the data at this stage.

Step 3

Start detailed analysis with a coding process—involves taking collected text data, segmenting sentences (or paragraphs) into categories, and labeling these categories with a term, often a term based on the participant's actual language.

Step 4

Use the coding process, as well as categories or themes for analysis—involves a detailed representation of information about people, places, or events in an environment. Then use coding to generate a small number of themes or categories, which should show multiple participant perspectives and be supported by diverse quotations and specific evidence.

Step 5

Move forward in how the description and themes will be represented—the most popular approach is to use a narrative text to convey the results of the analysis, which can be a discussion mentioning a timeline of events, a detailed discussion of various themes (with subthemes, specific illustrations, multiple perspectives from individuals, and quotes), or a discussion with interconnected themes. Visuals, figures, or tables are also used as supplements to discussions.

Step 6

Make an interpretation or meaning of the data—capturing the essence of the idea and lessons can be the researcher's personal interpretation, inserted into the understanding that the researcher brings to the study from their own culture, history, and experiences. It can also be a meaning derived from comparing results with information obtained from literature or theories. Thus, the results confirm past information or deviate from it. It can also suggest new questions that need to be asked—questions raised by the data and analyses that the researcher had not previously anticipated in the study. Based on the themes identified from the qualitative data analysis, the researcher will identify the most common AEs in outpatient care and their likely causes. In this stage, the Consolidated Criteria for Reporting Qualitative Research (COREQ) guideline [42] will be adopted.

Ideation: Stage 2

In this phase, the probable causes of the most common and severe AEs in outpatient care will be explored from the perspective of health care professionals and users or patients, and family members or caregivers. To achieve this, the methodology of root cause analysis will be used, using an Ishikawa diagram, also known as a cause and effect or fishbone diagram. This tool enables the systematic categorization and identification of the root causes of a problem. Through this diagram, it becomes possible to visualize and analyze the various variables that may be contributing to the issue at hand, facilitating the identification of its primary causes [43]. It is noteworthy that the patient's journey in the service will also be mapped, and subsequently, a process flowchart will be developed.

Based on the results from stages 1 and 2, as many solutions as possible will be generated to address the challenge of developing automated triggers capable of predicting potential risks of harm to ambulatory patients.

Prototyping: Stage 3

In this phase, a patient-centered approach will be applied to create automated triggers capable of identifying risks of avoidable harm. To achieve this, ML techniques will be adopted as illustrated in Figure 2. Moreover, a separate paper focused on explaining the method of ML in detail will be applied after the outcomes of stages 1 and 2, as well as the access gained to patients' EMHRs in this research project.

The ML models are mathematical models whose parameters are adjusted based on the examples presented during the training

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phase [28]. Before training, the data must undergo preprocessing to standardize and eliminate any inconsistencies. Removing duplicate entries, correcting missing values, converting categorical data into numbers, and filtering relevant attributes are examples of data preprocessing techniques. At this stage, the subsets of samples to be used for model training and evaluation must also be defined. To avoid bias in learning, samples will be randomly selected.

From the preprocessed data, a classification model will be trained to indicate the risk of an AE (output variable) based on specific triggers (input variables). The model selection will be based on the data distribution, which should be interpreted by an expert in the field. Gradient boosting–based models [44-46] and logistic regression [44,45,47] are examples of modern ML algorithms well-suited for classification tasks involving tabular data. Finally, the trained model will be used to identify or "predict" the most likely outcomes of new data not present in the training data set [28].

Quantitative evaluation metrics such as calibration, discrimination, sensitivity, and specificity will be used to quantitatively assess the model's performance from the evaluation subset [36]. It is emphasized that the entire process involving ML techniques will involve collaboration with an expert in the field of AI. Additionally, the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline [48] will be followed with the aim of reporting an AI-related intervention, also considering the Guidelines for Developing and Reporting Machine Learning Predictive Models [49].

Figure 2. Application scheme of machine learning algorithms.

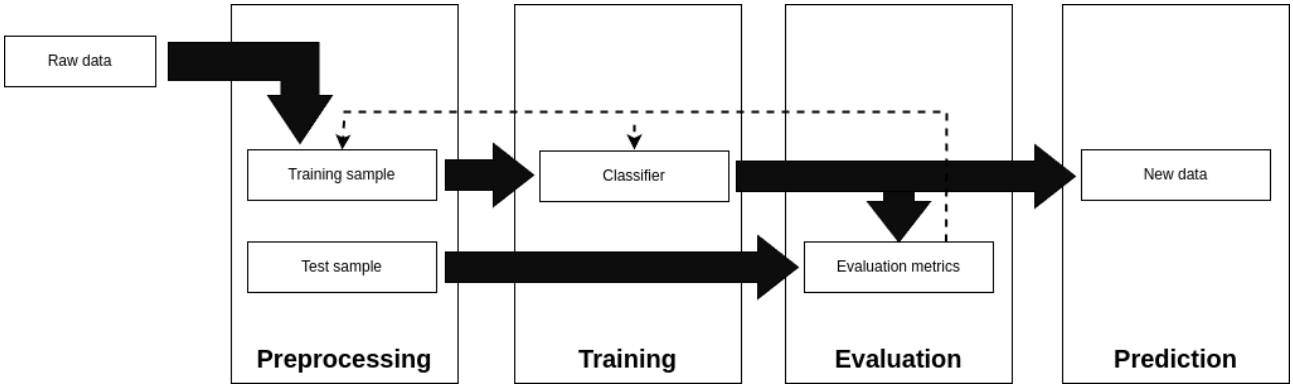

Testing: Stage 4

In this stage, the prototype is tested with health care professionals as participants to obtain feedback and identify areas for improvement. For this purpose, the think aloud method will be used [50]. Initially, participants will receive a brief explanation of the technique and the tasks they should perform. While participants perform the tasks, they must verbally report everything they are thinking and doing, from the moment they start the task until they complete it.

The researcher will take careful notes on the observations made by participants in a field diary. After completing the task using the think aloud technique, the researcher will analyze the observations and identify patterns of behavior and common problems encountered by participants during the interaction with the user interface. Finally, the researcher will prepare a report describing the observations made, including the identified problems and possible solutions to these problems.

Implementation: Stage 5

In this final phase, the algorithms developed through the ML technique, in collaboration with an expert in the field of ML, will be tested on a sample of patient records treated in outpatient care and evaluated for possible adjustments and changes. Additionally, this stage may result in new discoveries and the continuation of the process. In Figure 3, the operationalization of the study is illustrated, including data collection and data analysis.

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Figure 3. Operationalization of the study, including data collection and data analysis. COREQ: Consolidated Criteria for Reporting Qualitative Research; TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis.

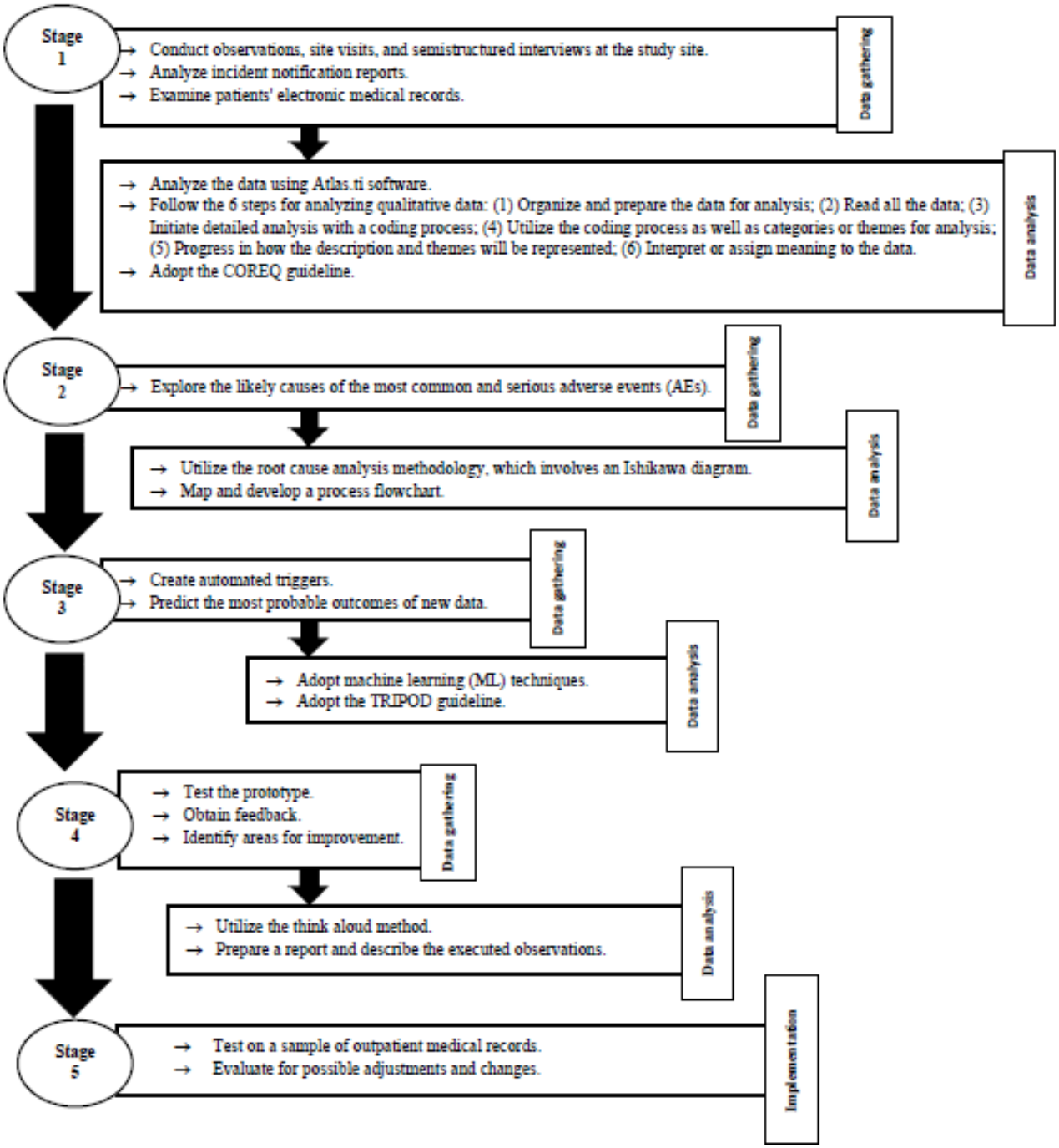

Results

This protocol describes a research study in its preliminary stages, prior to any data gathering and analysis. The research is currently in its initial phases, with the institution's organization showing support for the project. As mentioned previously, the study was approved by the members of the organization within the institutions in January 2024 and in May 2024, it was approved by the ethics board of the University of São Paulo and the institution where the study will take place.

After approval by the ethics board, stage 1, commenced with data gathering for qualitative research in June 2024. The researcher conducted a brief meeting with the unit manager and the risk management manager. Site observation began and as of June 17, 2024, semistructured interviews were initiated and ended on June 28, 2024, with 25 participants having participated in individual interview, taking into account the concept of data saturation. Data analysis has begun, considering the first step, which involves organizing and preparing data for analysis, including transcribing interviews. If the data information is not enough, follow-up questions will be added for the individual participants. Moreover, tabulated data of notification reports will be collected from August 12 to 31.

Additionally, funding for this study was granted by the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e

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Tecnológico) under process 141042/2024-9 as of May 2024. The study was granted funding in the Doctoral Sandwich Program Abroad (Programa de Doutorado Sanduíche no Exterior), process (88881.982930/2024-01), which aims to support research projects in higher education and research institutions outside Brazil, starting from November 2024 until April 2025 in Finland.

The abstract of this study was selected for presentation during the 35th International Nursing Research Congress from July 2024 to August 2024 in Singapore, organized by Sigma Global Nursing Excellence.

As this is the early stage of the research project and stage 3, which involves prototyping based on the framework of design thinking, will entail the creation of automated triggers using the method of ML, it can only present some possible models that will be used. The possible models will depend on the outcomes of stages 1 and 2 of design thinking, as well as the access gained to patients' EMHRs. Moreover, it will depend on the number of variables identified and included for triggers that need to be considered. A separate paper focused on explaining the method of ML can be considered after the outcomes of stages 1 and 2 in this research project.

Discussion

Principal Findings

In this paper, we present the research protocol in its preliminary stages, prior to any data gathering and analysis. This study is the first to create automated trigger tools in ambulatory settings in Brazil, presenting a valuable contribution to the health field while also adapting the design thinking framework. This framework is still underexplored in Brazilian research, especially in the context of patient safety. It is crucial to highlight the real-world application, specifically the effective implementation in the local realities.

Comparison to Prior Work

In Brazil, despite a few published studies on the application of the trigger tool, most have focused on hospital settings [51,52], and more recently, on dental care [53]. However, according to the 2018 report from the Organization for Economic Cooperation and Development [54], about half of the global burden of AEs originated in primary health care, and 4 in 10 patients experience safety incidents, often resulting in hospitalizations and increased care needs. Moreover, the most common AEs in primary health care are related to medication use, largely caused by polypharmacy.

Given this context, in 2001, IHI proposed triggers for tracking AEs in the outpatient setting [12], known as the Outpatient Adverse Event Trigger Tool [55]. The tool comprises 11 triggers that provide clues or hints regarding the existence of an AEs in the patient's medical record, including (1) new cancer diagnosis, (2) placement in a nursing home, (3) hospital admission and discharge, (4) 2 or more outpatient visits in a year, (5) surgical procedure, (6) emergency department visit, (7) use of more than 5 medications, (8) change of physician, (9) complaint letter, (10) more than 3 nursing calls in a week, and (11) abnormal laboratory value. These triggers were tested in American outpatient clinics but are certainly not the only possible triggers, although they represent an important starting point. According to IHI [8], each institution should choose to add, remove, or modify the triggers currently on the list to meet local realities. However, this study will develop automated triggers, in contrast to the manual and retrospective methods.

Strengths and Limitations

This study has the potential to positively impact the quality of care provided and simultaneously make a valuable contribution to the international scientific community. Thus, the best practices for outpatient care encompass principles of care continuity beyond hospital walls. In line with these observations, the importance and urgency of identifying events related to unsafe care in the outpatient context are emphasized to guide improvement and safety strategies for patients in these health care settings [56]. Furthermore, decisions can be made to minimize the burden of preventable harm, both economically and socially [57], as well as to promote a safety culture and establish high-reliability organizations.

This study will be conducted in an ambulatory setting with participants who are adults aged 18 years or older. It will exclude EMHR from pregnant individuals and psychiatric patients, which are anticipated limitations of this study.

Future Directions

For this study protocol, a separate paper focused on explaining the ML methods can be considered after the outcomes of stages 1 and 2 in this study. In the future, it will be used in every unit and will adjust the triggers based on each unit of the hospital. As mentioned, this is the first study to create automated triggers in Brazil. Therefore, there is a potential high demand for contributions nationally, and our study will also benefit other lines of research both nationally and internationally.

Conclusions

After the development of automated triggers in the outpatient setting, it will be possible to prevent and identify potential risks of AEs more promptly, providing valuable information. This technological innovation not only promotes advances in clinical practice but also contributes to the dissemination of techniques and knowledge related to patient safety. Additionally, health care professionals can adopt evidence-based preventive measures, reducing costs associated with AEs and hospital readmissions, enhancing productivity in outpatient care, and contributing to the safety, quality, and effectiveness of care provided. Additionally, in the future, if the outcome is successful, there is the potential to apply it in all units, as planned by the institutional organization.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CNH (claire.nierher@usp.br) and FREG (fregimenes@eerp.usp.br) are co-corresponding authors for this study.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
AI: artificial intelligence
COREQ: Consolidated Criteria for Reporting Qualitative Research
EMHR: electronic medical health record
IHI: Institute for Healthcare Improvement
ML: machine learning
TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
WHO: World Health Organization

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Protocol

Ameliorating Racial Disparities in HIV Prevention via a Nurse-Led, AI-Enhanced Program for Pre-Exposure Prophylaxis Utilization Among Black Cisgender Women: Protocol for a Mixed Methods Study

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Abstract

Background: HIV pre-exposure prophylaxis (PrEP) is a critical biomedical strategy to prevent HIV transmission among cisgender women. Despite its proven effectiveness, Black cisgender women remain significantly underrepresented throughout the PrEP care continuum, facing barriers such as limited access to care, medical mistrust, and intersectional racial or HIV stigma. Addressing these disparities is vital to improving HIV prevention outcomes within this community. On the other hand, nurse practitioners (NPs) play a pivotal role in PrEP utilization but are underrepresented due to a lack of awareness, a lack of human resources, and insufficient support. Equipped with the rapid evolution of artificial intelligence (AI) and advanced large language models, chatbots effectively facilitate health care communication and linkage to care in various domains, including HIV prevention and PrEP care.

Objective: Our study harnesses NPs' holistic care capabilities and the power of AI through natural language processing algorithms, providing targeted, patient-centered facilitation for PrEP care. Our overarching goal is to create a nurse-led, stakeholder-inclusive, and AI-powered program to facilitate PrEP utilization among Black cisgender women, ultimately enhancing HIV prevention efforts in this vulnerable group in 3 phases. This project aims to mitigate health disparities and advance innovative, technology-based solutions.

Methods: The study uses a mixed methods design involving semistructured interviews with key stakeholders, including 50 PrEP-eligible Black women, 10 NPs, and a community advisory board representing various socioeconomic backgrounds. The AI-powered chatbot is developed using HumanX technology and SmartBot360's Health Insurance Portability and Accountability Act–compliant framework to ensure data privacy and security. The study spans 18 months and consists of 3 phases: exploration, development, and evaluation.

Results: As of May 2024, the institutional review board protocol for phase 1 has been approved. We plan to start recruitment for Black cisgender women and NPs in September 2024, with the aim to collect information to understand their preferences regarding chatbot development. While institutional review board approval for phases 2 and 3 is still in progress, we have made significant strides in networking for participant recruitment. We plan to conduct data collection soon, and further updates on the recruitment and data collection progress will be provided as the study advances.

Conclusions: The AI-powered chatbot offers a novel approach to improving PrEP care utilization among Black cisgender women, with opportunities to reduce barriers to care and facilitate a stigma-free environment. However, challenges remain regarding health equity and the digital divide, emphasizing the need for culturally competent design and robust data privacy

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protocols. The implications of this study extend beyond PrEP care, presenting a scalable model that can address broader health disparities.

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KEYWORDS

artificial intelligence; PrEP care; PrEP; pre-exposure prophylaxis; nurse-led; AI; HIV prevention; HIV; prevention; AIDS; nurse; Black cisgender women; Black; cisgender; women; HIV pre-exposure prophylaxis; prophylaxis; biomedical; effectiveness; medical mistrust; Black women; nurse practitioners; chatbot; socioeconomic; HumanX technology; health care interventions

Introduction

HIV pre-exposure prophylaxis (PrEP) is a safe and proven biomedical strategy to prevent HIV transmission among cisgender women [1-3]. However, Black cisgender women remain underrepresented throughout the PrEP care continuum compared to their White counterparts [4,5]. Our preliminary studies reveal that multilevel barriers, such as a lack of PrEP awareness and knowledge, low perceived risk, limited access to care, medical mistrust, and intersectional racial or HIV stigma, often hinder PrEP utilization [6-8]. Conversely, the "PrEP care cascade" model describes the progressive stages of PrEP care [9]. It suggests that the engagement of providers and patients is critical to optimal PrEP care implementation. Research has demonstrated that nurse practitioners (NPs) are well suited to lead PrEP care initiatives [8,10]. Our recent meta-analysis showed that NPs reported a 40% higher likelihood than physicians to prescribe PrEP and provide PrEP care to patients with indications [8].

Furthermore, evidence shows that an NP-based PrEP care model may successfully engage and retain patients in PrEP care [10]. NPs' holistic care approach integrates patients' psychological and social factors with biological components, increases patients' satisfaction in health care, and is a strong predictor of retaining and adhering to treatment and prevention care plans [7,8,10]. Therefore, involving NPs is critical when developing programs to facilitate PrEP utilization. Despite these benefits, interventions promoting PrEP utilization involving NPs are scarce [8,10]. Our preliminary studies showed that a lack of awareness, insufficient clinical support, and a lack of workforce all contributed to NPs' under-representativeness in PrEP care [7,8].

Despite digital technology-assisted HIV prevention programs being effective and well received among Black cisgender women [11,12], they are severely underrepresented in relevant research [13-15]. Equipped with the rapid evolution of artificial intelligence (AI) and advanced large language models, chatbots effectively facilitated health care communication and linkage to care in various domains [13,16,17]. In the HIV-related field, chatbots can provide personalized health information, remind patients to take their medications, schedule appointments, and offer psychological support. They can also assist in triaging patients, identifying high-risk patients, and providing tailored interventions to improve PrEP adherence and retention in care [14,15]. Chatbots can provide round-the-clock access to PrEP information, dispel myths, and reduce stigma by offering anonymous support, which is crucial in overcoming barriers such as medical mistrust and low perceived risk [14,15,18-20]. While our preliminary studies show high acceptability for chatbot technology among Black cisgender women, its full potential in addressing PrEP disparities in this population remains untapped [15,17,20,21]. By integrating chatbot technology into PrEP care models, especially those led by NPs, we can enhance PrEP awareness, improve patient engagement, and ultimately increase PrEP utilization among Black cisgender women.

Therefore, our study harnesses NPs' holistic care capabilities and the power of AI through natural language processing algorithms, providing targeted, patient-centered facilitation to PrEP care. Our overarching goal is to create a nurse-led, stakeholder-inclusive, and AI-powered program to facilitate PrEP utilization among Black cisgender women, ultimately enhancing HIV prevention efforts in this vulnerable group [8,10,22,23]. This objective will be achieved through the following 3 phases. Phase 1 aims to understand the preferences and needs of Black cisgender women and NPs for the development of a culturally responsive, AI-powered chatbot designed to facilitate PrEP care. Phase 2 aims to develop and refine a tailored, culturally appropriate, theory-guided, and AI-powered chatbot platform using a participatory design approach. Phase 3 aims to evaluate the developed chatbot's acceptability, feasibility, and effectiveness in facilitating linkage to PrEP among Black cisgender women. This project aims to mitigate health disparities and advance innovative, technology-based solutions.

Methods

Study Populations and Inclusion Criteria

Using our well-established research infrastructure, we will recruit key stakeholders nationwide who may contribute to understanding AI-powered chatbots in the HIV care and prevention continuum using semistructured in-depth interviews. These key stakeholders include PrEP-eligible Black cisgender women (n=50: n=10, 20% in phase 1; n=20, 40% in phase 2; and n=20, 40% in phase 3) and NPs who provide HIV treatment and prevention services to patients (n=10). We will use semistructured interviews to elicit information regarding these stakeholders' opinions on chatbot development and evaluation. Black cisgender women who participate in phase 1 will not be invited to phases 2 and 3 to avoid the issue of information contamination. A community advisory board (CAB) with volunteer members (n=10) representing key stakeholders will be established to ensure our research reflects the priorities of

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the study population. These members will be selected to represent different characteristics (eg, socioeconomic status and geolocations) in the targeted community. Leaders from local community organizations and general community members will also be invited to strengthen the acceptability and quality of the proposed research. Once the CAB members are recruited, they will remain throughout the study.

For *PrEP-eligibleBlack cisgender women*, we will recruit 50 Black cisgender women who are eligible for HIV prevention services. The inclusion criteria include (1) aged 18 years or older, (2) self-identifying as Black or African American, (3) self-reported as female, (4) not tested as HIV positive (either HIV negative or unknown status), (5) eligible for HIV prevention (engaging in unprotected sex, having multiple sexual partners, or history of sharing needles with others), (6) willing to provide consent for participation, (7) fluent in English, and (8) able to engage in either in-person or web-based interviews. For *HIV care providers*, we will recruit 10 NPs who provide HIV prevention or treatment to patients. Eligible health providers need to (1) be aged 18 years or older, (2) work as a nurse or NP, (3) have ever provided HIV prevention or treatment in the past 12 months, (4) be willing to provide consent for participation, (5) be fluent in English, and (6) be able to engage in either in-person or web-based interviews. For *CAB members*, we will invite 10 members representing different characteristics (eg, socioeconomic status and geolocations) in the targeted community. Eligible CAB members need to be (1) aged 18 years or older, (2) interested in HIV prevention and treatment topics, (3) fluent in English, (4) willing to provide consent for participation, and (5) able to engage in either in-person or web-based meetings.

Recruitment Strategy

Participants will be recruited via multiple routes. For *HIV nurses or NPs*, an institutional review board (IRB)–approved recruitment message and flyers will be distributed via local newsletters or the listserve among members of the Association of Nurses in AIDS Care or the National Black Nurses Association using the IRB-approved recruitment email script message for nurses. We will recruit *CAB members* via email listserves and flyers for recruitment. For *PrEP-eligibleBlack cisgender women*, we will distribute the recruitment information via the regional ResearchMatch portal to recruit willing volunteers. Anyone interested in this study can use the survey link or scan the QR code for eligibility screening. They can also contact the research team members via email or phone, and the research team will direct them to the screening procedures. Other interested participants will be recruited using "snowball" chain referral sampling, where we ask Black cisgender women, nurses, or potential CAB members to identify others within their networks who might be interested in the study. Participants can either complete the brief screening over the phone or be emailed a link to complete the screening via REDCap (Research Electronic Data Capture; Vanderbilt University). A referrer will be compensated a small amount (ie, US $5) for each peer they successfully refer, with a cap on referral payments at 3 successful enrollments from participants. When potential participants contact us, the study team members will explain the study and obtain verbal consent to proceed with phone screening using the script, or they can access the REDCap link directly from the study flyer by scanning the QR code.

Description of the Chatbot

Overview

Our project leverages the cutting-edge HumanX chatbot technology developed by KLaunch [24], which is designed to integrate conversational AI within businesses and research. This platform, combined with Smartbot360's secure chatbot technology, offers a seamless, safe, and highly personalized communication experience aimed at facilitating PrEP utilization among Black cisgender women at risk of HIV infection. The integrated system ensures HIPAA (Health Insurance Portability and Accountability Act) compliance, safeguarding protected health information (PHI) through technical, physical, and administrative measures.

Security and Compliance

The HumanX and Smartbot360 platforms prioritize protecting patient information, ensuring that all data, including PHI, are encrypted in transit and at rest. Robust access controls and authentication measures prevent unauthorized access, and regular security assessments address evolving threats and vulnerabilities. Comprehensive risk assessments tailored to the health care context help identify potential risks to PHI and implement mitigating strategies to ensure ongoing HIPAA compliance. Our dynamic compliance strategy adapts to regulatory changes and incorporates best practices in data protection, with all personnel trained on HIPAA requirements.

Third-Party Assessments

Independent auditors thoroughly evaluate the SmartBot360 and HumanX technologies to ensure they meet or exceed HIPAA compliance standards. These third-party assessments validate our security measures, risk management practices, and compliance with health care regulations, offering our stakeholders an additional layer of assurance.

Study Phases

In this proposed study, our primary objectives will be achieved through the following 3 phases within the 18-month timeframe by recruiting 50 Black cisgender women and 10 NPs.

Phase 1: Exploration (Months 1-3)

Phase 1 of the proposed study aims to understand preferences for the development of a nurse-led, stakeholder-inclusive, and AI-powered program to facilitate PrEP utilization among Black cisgender women, ultimately enhancing HIV prevention efforts in this group. Research indicates that adopting the participatory design [23,25-27] is feasible by actively engaging stakeholders within target communities, consequently providing a solid foundation for the newly developed tools. Thus, our project will use a stakeholder-inclusive and participatory design approach [25-27] to collect critical stakeholders' opinions and feedback. Our design will also incorporate culture-oriented content expressly for Black cisgender women by consulting a CAB, PrEP-eligible women, and NPs who provide HIV prevention and treatment services. Using in-depth interviews with Black cisgender women and NPs, we will gather their opinions

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regarding the chatbot. By the end of phase 1 of this study, we expect an enhanced understanding of factors affecting PrEP utilization among Black cisgender women and preferences regarding the chatbot prototype in the later phases.

Primary Outcomes and Assessment for Phase 1

We will use a stakeholder-inclusive and participatory design approach to evaluate two primary outcomes: (1) stakeholder preferences for the chatbot development will be assessed through in-depth interviews with Black cisgender women and NPs—we will gather opinions on features, content, and cultural appropriateness; and (2) factors influencing PrEP utilization among Black cisgender women will be assessed through thematic analysis of interview transcripts.

Phase 2: Development (Months 4-8)

We will develop and refine a tailored and culturally appropriate, theory-guided, and AI-powered chatbot platform using participatory design to ensure cultural appropriateness for the target population. The basic structure of chatbot scripts (eg, PrEP facts and HIV risks) will be extracted from the Centers for Disease Control and Preventions (CDC) and other health departments [23,25,26] and validated studies [20,27]. We will develop features (ie, complexity and aesthetics) and workflow (ie, frequency of the interaction) of the platform that best meets end-users needs [28-31]. Once the initial platform is developed, its features will be tested within 2 small groups of eligible Black cisgender women who did not participate in phase-1 interviews. We will use the think-aloud strategy in the refinement process. The first 10 eligible Black cisgender women will interact with the chatbot. We will use their feedback to improve the chatbot and launch it with another 10 Black cisgender women. After collecting input from the second group, we will further enhance the chatbot. A total of 20 Black cisgender women will be recruited in phase 2. Before launching the chatbot, we will provide a training session to the NPs to guide them in providing psychological and clinical support to women during their interactions with the chatbot, particularly when women have unaddressed needs.

Primary Outcomes and Assessment for Phase 2

We will develop and refine a tailored, culturally appropriate, theory-guided, and AI-powered chatbot platform using participatory design to ensure cultural appropriateness for the target population with two primary outcomes: (1) chatbot development—the initial development of the chatbot platform, including scripts and features, will be based on CDC guidelines and validated studies; and (2) user feedback—the usability and functionality of the chatbot will be assessed through think-aloud sessions with 2 small groups of Black cisgender women (10 in each group) who will interact with the chatbot and provide feedback.

Phase 3: Evaluation (Months 9-18)

We aim to evaluate and improve the developed chatbot in phase 3. We will assess the chatbot's acceptability and feasibility in facilitating linkage to PrEP among another 20 eligible Black cisgender women. Using the longitudinal mixed methods, we will determine the feasibility (Feasibility Scale for assessment) [32], acceptability (Evidence-Based Practice Attitude Scale) [33], and user experiences (Usability Metric for User Experience Scale) [34] of the chatbot at baseline (eg, chatbot initiation), 3 months, and 6 months using both surveys and in-depth interviews. By triangulating the collected quantitative and qualitative data, we will enhance the chatbot to better address the needs of the target population in a real-world setting. We will also conduct a focus group among the 10 NPs who deliver the holistic approach to explore their feedback on the effectiveness of the chatbot platform. We will continuously improve the chatbot throughout the study period with the collected information.

Primary Outcomes and Assessment for Phase 3

We will evaluate and improve the developed chatbot using four leading indicators: (1) the acceptability of the chatbot will be measured using the Evidence-Based Practice Attitude Scale [29] at baseline, 3 months, and 6 months; (2) the feasibility of the chatbot will be assessed using the Feasibility Scale [30] for assessment; (3) user experience will be evaluated using the Usability Metric for User Experience Scale [31]; and (4) effectiveness in facilitating linkage to PrEP will be assessed through surveys and in-depth interviews with another 20 eligible Black cisgender women.

This proposed study will conduct all research activities on the web or at university locations. Based on our well-established research infrastructure, we will recruit 50 eligible Black cisgender women (n=10, 20% in phase 1; n=20, 40% in phase 2; and n=20, 40% in phase 3) and 10 NPs. Study information will be distributed through community events, health clinics, professional organizations, and social media. If a participant drops out from any phase, a replacement will be recruited to maintain the sample size. To ensure the feasibility of recruitment, we will use our extensive network of community partners and leverage our previous success in similar recruitment efforts.

Additionally, recruitment progress will be regularly monitored, and strategies will be adjusted to meet the target sample size within the study timeline. During the chatbot development and refinement, monthly meetings with CAB members will be held for feedback. A project start-up meeting, including training sessions for team members, will be conducted before data collection. Our interdisciplinary team is uniquely equipped to carry out this innovative project.

Data Analytical Plan

Quantitative data include demographic information, socioeconomic characteristics, and implementation and usability outcomes. Due to the limited sample size (n=20), we will perform descriptive analyses to present participants' characteristics (eg, demographics, sexual behaviors, and HIV risks) and user experiences (eg, feasibility and acceptability) to observe potential similarities and differences in particular characteristics' implementation and use outcomes (eg, age group). *Qualitative data* (ie, opinions regarding the chatbot development and experience) will be transcribed and loaded into qualitative analytical software for analysis. This will follow the 5-step framework analysis approach, which includes familiarization (describing potential themes), thematic

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framework (generating a nascent code or subcode list), indexing (producing a final consensus code list), charting (organizing critical thematic constructs into hierarchical themes), and mapping and interpretation (summarizing and interpreting) [32]. Participants' verbal utterances collected by think-aloud sessions will be transcribed and analyzed by propositional analysis (an analysis to create a basic semantic model of the text to comprehend an individual's thoughts and critical ideas for a given product) [33]. *Usability data* gathered by the dashboard will be used to describe user activities and profiles, such as log-in time, bounce rate, retention rate, and conversation channels. *Conversation data* will be downloaded from the dashboard and explored using the systematic thematic analysis strategies (familiarization, code assignment, pattern identification, and defining and reporting themes) [34-36]. Specifically for data collected from the NPs, we will analyze both quantitative and qualitative responses. Quantitative data will include NPs' demographic information, professional background, and their engagement with PrEP care. We will use descriptive statistics to summarize these data and examine correlations between NP characteristics and their effectiveness in promoting PrEP utilization. Qualitative feedback from NPs on the chatbot's functionality, its integration into their workflow, and its impact on patient engagement will be transcribed and analyzed using the same 5-step framework analysis approach mentioned earlier. This analysis will help us identify specific barriers and facilitators NPs face in utilizing the chatbot for PrEP care and how the chatbot can be optimized to support their efforts. By combining these methods, we aim to provide a comprehensive understanding of the chatbot's usability, effectiveness, and potential areas for improvement, particularly in facilitating PrEP utilization among Black cisgender women and supporting NPs in their role.

Ethical Considerations

Upon submitting this manuscript, we obtained IRB approval for the research activities of recruiting participants to gather their preferences of chatbot features (University of Rochester Research Subjects Review Board: STUDY00009105).

All participants will provide informed consent before participating in the study. The consent process will be conducted on the web via REDCap, a secure web-based platform designed for research data collection and management. An information sheet detailing the study's purpose, procedures, risks, and benefits will be provided to participants prior to study participation. Consent will be documented through an electronic consent form that participants will complete before any study activities begin.

Data collected during the study will be anonymized and deidentified to protect participants' privacy. All data will be stored securely on the university's servers, and access will be restricted to authorized study team members only. Measures such as encryption, secure servers, and compliance with HIPAA regulations will be implemented to safeguard participant information. Audio recordings of interviews will be transcribed and deidentified before analysis, and all identifiers will be deleted once transcription is complete.

Participants will be compensated for their time and contributions to the study. Black cisgender women participating in the in-depth interviews will receive US $30 each, while CAB members will receive US $20 for each meeting, for a total of 3 times throughout the study. Additionally, a small incentive of US $5 will be provided for each successful referral made through snowball sampling, with a cap on referral payments at 3 successful enrollments. Compensation will be provided irrespective of the completion status of the interviews or activities to ensure fairness.

Results

As of August 8, 2024, our project is in the initial stages of implementation. The IRB protocol for phase 1 was approved in May 2024. We plan to start recruitment for Black cisgender women and NPs in September 2024, with the aim to collect information to understand their preferences regarding chatbot development. We are currently working on attaining IRB approval for phases 2 and 3. To date, we have made significant progress in networking for participant recruitment, and we have established connections with individuals and colleagues who have expressed interest in assisting with the recruitment process, leveraging our established network and infrastructure. This step is instrumental in ensuring a robust and diverse participant base, aligning with our study's objective to engage Black cisgender women in PrEP care. We plan to collect data soon, and further updates on the progress of recruitment and data collection will be provided as the study advances.

Discussion

Expected Findings

Our proposed study harnesses AI technology and nursing skills through an AI-powered chatbot designed to facilitate PrEP care utilization among Black cisgender women. This culturally responsive, nurse-led, and AI-powered chatbot encapsulates biomedical, psychological, and sociocultural factors affecting PrEP utilization, making it a holistic tool for HIV prevention. Our model is scalable both geographically and technologically, making it capable of addressing health disparities beyond the immediate context of this study. As AI improves with increased data and user engagement, we anticipate the AI chatbot will significantly improve PrEP awareness, adherence, and retention among Black cisgender women by providing personalized, accessible, and stigma-free support.

Comparison to Prior Work

Implementing AI-powered chatbots in health care has shown promise in various domains, including mental health support, chronic disease management, and patient education [13-15]. Previous studies have demonstrated that digital technology-assisted health care can improve patient engagement and outcomes [13-15]. However, few studies have specifically focused on using AI chatbots to address HIV prevention among Black cisgender women [11,12]. Our study builds on existing research by integrating cultural competence and stakeholder feedback into the chatbot design, making it uniquely tailored to the needs of this population. Our approach offers a novel

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solution by combining AI technology with nursing expertise, bridging the gap between digital health innovations and culturally sensitive care.

Limitations and Strengths of the Protocol

Implementing AI-powered chatbots presents several challenges and strengths [24,37,38]. Expected limitations include the following. First, technology accessibility: PrEP-eligible individuals without consistent access to technology or who are less comfortable with digital tools may face unintended exclusion, potentially reinforcing existing health care disparities. Second, data privacy: ethical considerations regarding data privacy and security are critical, as chatbots gather sensitive health information. Ensuring HIPAA compliance, robust encryption, and clear communication about data use is essential to maintain users' trust. Third, generalizability: while our study focuses on Black cisgender women, the findings may not be generalizable to other populations without further adaptation and testing. On the other hand, there are several strengths identified in the proposed study. First, cultural competence: our chatbot is designed to meet the unique needs of Black cisgender women by incorporating their cultural contexts and addressing their specific concerns, enhancing its relevance and effectiveness. Second, scalability: the model is scalable both geographically and technologically, making it capable of addressing health disparities beyond the immediate context of this study. Third, holistic approach: the integration of biomedical, psychological, and sociocultural factors provides a comprehensive approach to HIV prevention, potentially leading to better health outcomes.

Conclusion

As the AI component evolves with more data and user interaction, we foresee opportunities for further technological advancements, enhancing the efficacy of our model. Upon completing this pilot, we aim to roll out this innovative program to other marginalized populations to expand its reach and impact using a subsequent large-scale hybrid type I study design. By doing so, we aim to contribute tangible, scalable solutions to the pressing challenge of racial disparities in HIV prevention. This vision aligns seamlessly with the funding foundation's key priorities, including challenging conventional strategies, demonstrating potential as a best-in-class intervention, narrowing gaps in health equity, and showcasing the potential for scalability. We are deeply committed to realizing this vision and driving forward the fight against racial disparities in HIV prevention and beyond.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CAB: community advisory board
CDC: Centers for Disease Control and Prevention
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
NP: nurse practitioners
PHI: protected health information
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture

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Protocol

Acceptability, Perceptions, and Experiences Regarding Electronic Patient-Reported Outcomes After Laparoscopic Cholecystectomy: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Patient-reported outcomes (PROs) can be defined as any report of a patient's health taken directly from the patient. Routine collection of PRO data has been shown to offer potential benefits to patient-doctor communication. Electronic forms of PRO measures (PROMs) could be more beneficial in comparison to traditional PROMs in obtaining PROs from patients. However, it is currently unclear whether the routine collection of electronic PRO data could result in better outcomes for patients undergoing laparoscopic cholecystectomy (LC).

Objective: This study aims to explore the perspectives of patients and surgeons on the use of electronic PROMs. Based on prior research, technical skill and experience level of the surgeon, long-term quality of life, patient involvement in decision-making, communication skills of the surgeon, cleanliness of the ward environment, and standards of nursing care are identified to be the most important factors for the patients.

Methods: This is a mixed methods prospective study that will collect both quantitative (survey) and qualitative (interview) data. The study has two components. The first involves the distribution of an electronic presurvey to patients who received elective LC within 48 hours of their surgery (n=80). This survey will explore the perspective of patients regarding the procedure, hospital experience, long-term outcomes, and the perceived value of using PROMs. These patients will then be followed up after 1 year and given another survey. The second component involves the distribution of the same survey and the completion of structured interviews with general surgeons (n=10). The survey will ascertain what PROs from the participants are most useful for the surgeons and the interviews will focus on how the surgeons view routine PRO collection. A convenience sampling approach will be used. Surveys will be distributed through Qualtrics and interviews will be completed on Microsoft Teams.

Results: Data collection began on February 14, 2023. As of February 12, 2024, 71 of 80 recruited patients have been given the presurvey. The follow-up with the patients and the general surgeon components of the study have not begun. The expected completion date of this study is in April 2025.

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Conclusions: Overall, this study will investigate the potential of electronic PRO collection to offer value for patients and general surgeons. This approach will ensure that patient care is investigated in a multifaceted way, offering patient-centric guidance to surgeons in their approach to care.

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KEYWORDS

patient-reported outcomes; digital technology; hepatobiliary surgery; surgery; laparoscopic cholecystectomy; electronic patient; general surgeon; mixed methods; prospective study; quantitative; qualitative; Qualtrics; interview; Microsoft Teams; data collection; patient care; patient-centric; patient-doctor communication; eHealth

Introduction

Patient-Reported Outcomes

Patient-reported outcomes (PROs) can be defined as any report of a patient's health outcome taken directly from the patient [1]. PROs are normally investigated through the use of standardized patient-reported outcome measures (PROMs), which are typically self-completed questionnaires that measure patient quality of life, symptom burden, functional status, health-related quality of life, and personal care experience [2,3]. The investigation of PROs allows for the generation of a health care system that is truly patient-centered [4]. Patient-centered health care has already proven to improve health status and the efficiency at which care is delivered [5]. Thus, it would be beneficial to understand the measures that could be taken to improve PROs after the completion of surgical procedures such as laparoscopic cystectomy (LC). PROs are particularly relevant to LCs since patients undergo this operation to relieve their pain; thus, measuring PROs after the procedure is crucial [6].

A systematic review demonstrated that most studies evaluating the effects of LC did not use an electronic method of measuring PROs, despite advances in technology [7]. Another systematic review concluded that there is limited literature regarding the use of electronic PRO systems in surgery, and the authors proposed that future research should explore the challenges associated with using such systems [8]. A more recent systematic review found that the integration of electronic PROM systems through the use of mobile apps has the potential to improve patient outcomes and the efficiency of hospital resources [9].

Han et al [6] demonstrated that LC results improved PROs regarding pain, quality of life, and the relief of gastrointestinal symptoms. Several factors significantly influence PROs after LC. For instance, a 2019 study in Singapore found that the technical skill and experience level of the surgeon, long-term quality of life, patient involvement in decision-making, communication skills of the surgeon, cleanliness of the ward environment, and standards of nursing care were crucial factors that influence PROs [10]. Conversely, factors such as hospitalization leave duration, length of hospital stay, the opinion of the patient's family about the hospital, and scar cosmesis were factors with relatively less importance on PROs [10].

Patient-Reported Experiences

Patient-reported experience measures (PREMs) are tools used to report on a patient's process of care (eg, communication and timeliness of care) rather than on the outcomes specifically [2,11]. PREMs are a useful predictor for overall patient satisfaction [12]. As a result, PREMs will also be used in this study to evaluate the hospital experience of the patient.

Routine Collection of PROs in Other Specialties

The implementation of routine PRO collection has been shown to be beneficial and feasible in various health care fields such as oncology, cardiology, and integrative medicine [13-16]. However, the integration of routine electronic PRO collection in oncology is currently limited due to inadequate information technology infrastructures, time, and difficulty in using electronic devices [17]. In the field of ophthalmology, one pilot study indicated that ophthalmologists recognized the powerful potential benefits of electronic PROs for patient-doctor communication [18]. Furthermore, an observational study [19] investigated whether passive collection of behavioral data could be associated with PROs using patients' smartphone sensors and activity data, demonstrating that patients with lower activity levels tended to have poorer PRO scores. While the passive monitoring of PROs is beyond the scope of this project, this previous work highlights the immense potential benefits that routine PRO monitoring could have for LC and other general patients.

In the field of surgery, systematic reviews have indicated that routine PRO collection has benefits in relation to colorectal and orthopedic surgical specialties [20,21]. One quality improvement study also indicated that routine PRO collection was a critical factor in improving thoracic surgery care [22]. Although the logistical implication of routine collection remains the most challenging factor, the advancement of technology could assist in solving this issue. Thus, electronic PROMs could be useful for patients undergoing LC, which will be explored in this study.

Routine Collection of PROs

The evidence that PROs can be useful as a feedback tool in surgery to improve patient outcomes is currently limited. One study indicated that there is currently only weak evidence that PROs provide any benefit to patient outcomes when used as a feedback tool [23]. Furthermore, more qualitative research is needed to investigate the practical issues that could arise with routine PRO collection [23,24]. However, another systematic review exploring routine PRO monitoring during cancer care

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demonstrated significantly improved health-related quality of life among patients [25]. These conflicts demonstrate a lack of clear consensus regarding the routine collection of PROs. Thus, this study will investigate the perspective of surgeons on PRO collection. These data could elucidate the type of feedback that is most relevant for surgeons to improve care. In addition, qualitative interviews will be conducted with the surgeons to obtain insight into the potential benefits and barriers of routine PRO collection.

The use of routine PRO collection specifically in relation to LC is currently very limited. One feasibility study investigating the use of electronic PROMs indicated that the collection of such measures could be a convenient process for patients that would be beneficial in evaluating quality-of-life trends for physicians [26]. Authors have also proposed the need for future research with more robust methodologies such as randomized controlled trials exploring this area. Using electronic PROMs has been indicated to help resolve the logistical and cost issues associated with PROM collection [13,26].

Study Objectives

This study aims to explore the perspectives of patients and surgeons on the use of electronic PROMs. These perspectives will be investigated through the distribution of surveys to both groups and via the completion of interviews with the general surgeons.

The specific objectives of the study include (1) understanding the acceptability and perceived value of electronic PROs from the perspective of both patients undergoing LC and general surgeons and (2) determining the feasibility of following up with patients regarding their PROs using email correspondence.

Methods

Study Design and Overview

This is a mixed methods prospective study that will collect both qualitative and quantitative data. The study will involve two components. The first is the distribution of a survey to patients who have completed an elective LC. The second smaller component is the distribution of the same survey to consultant surgeons in addition to the completion of structured qualitative interviews with the same surgeons. This is an observational study and will have no influence on the care of patients.

Component 1: Patient Survey

Patient Participants

The subjects will include all patients who completed elective LCs from Cork University Hospital and Mercy University Hospital, both in Cork, Ireland. Patients undergoing LC were chosen for this study owing to the high number of LCs completed in these hospitals. This makes the study more feasible and realistic to complete.

Inclusion Criteria

Patients must be >18 years old and have completed an elective LC. Patients must have the capacity to access the Qualtrics survey through their smartphone and have completed the LC within 48 hours of distribution of the first survey. For the sake of feasibility, any indication for the elective LC will be eligible for recruitment in this study to ensure an adequate sample size.

Exclusion Criteria

Patients who cannot read, are pregnant, have a mental disability, have dementia, or do not speak English will be excluded. Additionally, patients who are sedated, ventilated, or intubated will be excluded as they will not be capable of offering informed consent.

Sample Size

This study will aim to recruit 80 patients. This sample size was chosen for the sake of feasibility. Due to time constraints, with 10 months of allocated time for data collection and 2 participating hospitals collaborating on the project, it would not be feasible to collect more data.

Power calculation was considered for determining the sample size. However, power calculation requires an estimation of the proportion of the event of interest [27]. For this study, it would be unrealistic to estimate the number of elective LCs that are completed in Ireland, as these data are not readily available. Consequently, it was decided to estimate the sample size primarily based on feasibility rather than power.

Recruitment of Patient Participants

Participants will be recruited using a nonprobability convenience sampling approach. The patients undergoing elective LCs will be viewed from the daily theater list and through communication with the operating surgical team. Participating patients will be identified as eligible by surgeons from Cork University Hospital who are collaborating in this study. The participant information sheet and consent form will be integrated into the beginning of the Qualtrics survey.

After completion of the presurvey, the participants will be sent a link for the postsurvey 12 months later through email. The recruitment and data collection flow for patients is presented in Multimedia Appendix 1.

Patient Participant Survey

The survey will be based on the PROM questionnaire, which measures the effect of different factors on the PROs [10]. The following factors will be measured using the PROM survey: (1) age, sex, education level, marital status, employment status, ethnicity, smoking, and exercise frequency; (2) procedure perception; (3) hospital experience perception (PREMs); and (4) perception of longer-term consequences.

In addition, the acceptability and perceived value of the PROMs will be assessed with a survey from Stover et al [28].

The presurvey will be administered electronically by email using Qualtrics to patients who have completed an elective LC within the past 48 hours. These patients will then be followed up after 1 year and the survey will be administered again (Multimedia Appendix 2).

Other Data Collection Tools Considered

Other PRO surveys such as the Gastrointestinal Quality of Life Index survey and visual analog pain scores were also considered [29,30]. However, we ultimately determined to not use these

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tools in this study, as they only measure the PROs directly rather than determining what PROs and experiences patients find most important to them. Including a combination of these surveys could have been optimal, but it would have resulted in an overly long survey and potentially poor participant completion rates.

Component 2: Surgeon Survey and Interview

Surgeon Population

Ten general surgeons will be recruited from Cork University Hospital and Mercy University Hospital. This sample size was chosen based on the feasibility within these hospital settings.

Inclusion Criteria

Only general surgeons will be included, as they represent the group that would be most knowledgeable about LC, which is the surgery that the study is based around. The surgeons must have been registrars, specialist registrars, or consultants for at least 1 year in a general surgery team. They must be currently employed within Cork University Hospital or Mercy University Hospital.

Exclusion Criteria

The surgeons involved in the creation of this study will be excluded from participation.

Recruitment of Surgeon Participants

The participants will be recruited using a nonprobability consecutive sampling approach. They will be briefed on the study using an information sheet and given a consent form for the interview.

Interview

All the surgeon participants (n=10) will also be interviewed using an interview guide adapted from the PROFILE trial [24]. The interviews will take place online using Microsoft Teams. The interviews will explore the following factors: (1) background of PRO use by the surgeon, (2) attitude of the general surgeon toward PRO use, (3) perception of the surgeons regarding the impact that PROs can have on clinical practice, and (4) perception of the surgeons regarding practical issues regarding PRO collection (Multimedia Appendix 3 and Multimedia Appendix 4).

Surgeon Survey

A modified version of the PROM questionnaire will be distributed to general surgeons (n=10). The general surgeons will be asked to complete the survey only once. The survey will be given to the surgeons with the goal of ascertaining what feedback from patients is most important for them to improve their quality of care. The modified survey will only measure the following factors: (1) procedure perception, (2) hospital perception, and (3) perception of longer-term consequences (see Multimedia Appendix 5).

Data Analysis

SPSS v28.0.1.1 (IBM Corp) will be used to complete the data analysis for the patient surveys. The 4-point Likert-scale questions will be tallied into two categories of either “more important” or “less important.” Mean scores will be used to determine the most important and least important factors. Univariate analysis with χ^2 tests will then be used to determine if any demographic relations exist between what PROs participants find to be more or less important. Additionally, the Wilcoxon ranked sign test and 2-tailed ANOVA will be used to compare the differences between the patients’ answers in their first and second survey responses.

Data from the survey for the surgeons will also be analyzed with SPSS. Mean scores will be tabulated for the general surgeons’ responses to the survey. For the general surgeons’ interviews, the results will be transcribed verbatim and analyzed with thematic synthesis [24]. The qualitative data will explain the overall view that surgeons have regarding PRO collection and the quantitative data will be analyzed in conjunction to illustrate the specific PROs that the surgeons view as important. The patient and surgeon data will also be integrated by comparing the views that both stakeholders have as indicated in the PROM surveys.

Ethical Considerations

This study has been approved by the Clinical Research and Ethics Committee of the Cork Teaching Hospitals (ECM 01/2023 PUB). The study poses a low risk to patients and does not interfere with any of the treatments that the patients will receive. Data will be stored in line with University College Cork standards and requirements.

A standardized consent form and patient information leaflet will be given to the patients, and they will be briefed on the project through information presented on the survey before they begin answering questions. Patients’ involvement will be fully voluntary and they will be given the option to withdraw from participation at any time. The researchers’ contact information will also be given to the patients so that they have any questions answered that might come up throughout the study. Only the email addresses of the patients will be collected, as patients’ identifiers so that the patients can be followed up with. The data will be pseudonymized as a result. Data will be kept on University College Cork servers for 10 years, excluding the email addresses, which will be used for following up with patients and will be immediately deleted after study completion. Patients will not be compensated for participating in this study.

Outputs and Dissemination

The study results will be disseminated through international peer-reviewed research journals and local conference presentations.

Results

Data collection began on February 14, 2023. As of February 12, 2024, 71 of 80 patients have been given the presurvey. The follow-up will begin once 80 patients have completed the presurvey. This is expected to be completed in March 2024 and the follow-up is expected to conclude in March 2025. General surgeons will then complete their surveys and interviews in March and April 2025. The overall expected completion date of the study is in April 2025.

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Discussion

Study Significance and Strengths

This study will convey the perspective of participants regarding which PROs are most important for them after LCs. Based on prior research, we expect the technical skill and experience level of the surgeon, long-term quality of life, patient involvement in decision-making, communication skills of the surgeon, cleanliness of the ward environment, and standards of nursing care to be the most important factors for the patients [10]. Furthermore, this study will indicate the acceptability and perceived value of participants regarding electronic PRO surveys, which is a topic that is relatively more limited in the literature in the context of LCs. The study has well-defined inclusion and exclusion criteria, with all patients being given the survey less than 48 hours after their surgery and only elective cases being included. This will help make the sample more homogenous, as patients undergoing emergency surgery might have different perspectives on what is important for them in comparison to those having elective surgery [11].

Furthermore, the long-term follow-up of 1 year will assist in better understanding the views of patients undergoing LC. The distribution of the survey to postoperative patients will ensure that the patients already had the experience of having an LC and can reflect upon it when answering the survey. This perspective would not be achievable with patients in a preoperative setting. The use of a 50-item survey also ensures that several PROs and factors will be analyzed, thereby offering a broad view of patients' perspectives on PROs. Moreover, the integration of the perspectives of surgeons regarding the study may help elucidate improved procedures when following up with patients.

Limitations

As a result of this being a feasibility study, there are several associated limitations. Primarily, the small sample size of 80 participants will limit the generalizability of the study. Moreover, the use of convenience sampling also limits the external validity and generalizability of the results. It has been shown that convenience sampling has greater validity when the sample is more homogenous with respect to the participants' sociodemographic characteristics [31]. However, making the sample completely homogenous in this study would result in an inadequate sample size. Thus, this bias will be mitigated through statistical analyses exploring differences in the factors that are deemed important according to the participants' demographic characteristics. Another significant bias associated with using convenience sampling is that the participants accepting to partake in the study could be more likely to find perceived value in completing the electronic survey in comparison to those who declined to participate. These biases will be mitigated through the use of rigid inclusion and exclusion criteria, ensuring that the sample is as homogenous as possible.

Another limitation is the use of a 4-point Likert scale. Likert scales ideally have between 4 and 7 options, although 4-point scales might commit participants to give answers they may not wish to give [32].

Although only including patients undergoing elective surgery will aid in further defining the inclusion and exclusion criteria, this restriction will also limit the generalizability of this study, as patients undergoing emergency LC will not be represented.

In addition, recruiting patients within 48 hours of their LC means that their postoperative condition could influence their answers. The survey also contains mild medical jargon (eg, "bile leak") that might be confusing for participants.

There is no electronic literacy scale for the participants involved. Incorporation of such a scale would have improved the interpretation of the results by demonstrating whether the ability to use technology impacts the participants' views on electronic surveys.

The lack of direct comparison with paper surveys is another potential limitation, as this prevents a comprehensive interpretation of the benefits of electronic surveys over paper surveys. Although this study addresses the difficulty that patients might have in using electronic devices, it does not address other major barriers to electronic PROs, such as inadequate information technology infrastructure and the time needed to complete the survey [17].

The survey from Stover et al [28] may also be biased toward favorable responses. The reason for this is that the study aimed to maintain a neutral response option, while also having only 4 options to be consistent with the other survey questions. For this reason, there is only one "negative" option.

Finally, the follow-up will also be very challenging due to the small sample size. A prior study exploring email-based PRO systems following hand surgery indicated that this approach may be effective [33], although only 28% of participants completed the follow-up PRO survey 1 year after their enrollment in the study. Despite the lack of valid generalizability of the email follow-up data in this study, the results will convey the feasibility of using email to distribute PRO surveys and help guide future studies with more robust samples.

Conclusions

Overall, this study will investigate the potential of electronic PRO collection to offer value for patients and general surgeons. This approach will ensure that patient care is investigated in a multifaceted way, offering patient-centric guidance to surgeons in their approach to care. The results will illustrate any differing views that surgeons and patients may have in relation to what is important for the patient's care, allowing for further exploration of these differences. This study will thus guide future research to further analyze any potential uses of PROs and the value that electronic systems can provide for PRO collection.

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Authors' Contributions

KC is the lead author, JOD is the principal investigator, and KPF is the corresponding author. KC, JOD, and KPF developed the main concept of the study and played an active role in all aspects of the study design. MC, AOS, and MYK contributed to the conceptualization, methodology, investigation, supervision, project administration, and writing of the paper. SB, LS, PH, OD, and YYT all contributed to the investigation and writing of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of all data collection points for the patient participants.
[DOC File , 47 KB - resprot_v13i1e57344_app1.doc]

Multimedia Appendix 2
Survey for patient participants.
[DOCX File , 19 KB - resprot_v13i1e57344_app2.docx]

Multimedia Appendix 3
Interview consent sheet for general surgeons.
[DOCX File , 1286 KB - resprot_v13i1e57344_app3.docx]

Multimedia Appendix 4
Procedure for interviews with general surgeons.
[DOCX File , 15 KB - resprot_v13i1e57344_app4.docx]

Multimedia Appendix 5
Survey for general surgeons.
[DOCX File , 19 KB - resprot_v13i1e57344_app5.docx]

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Abbreviations

LC: laparoscopic cholecystectomy
PREM: patient-reported experience measure
PRO: patient-reported outcome
PROM: patient-reported outcome measure

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Protocol

Exploring New Models for Implementing Sustainable Integrated Health Access for People in Vulnerable Positions: Protocol for a Mixed Methods Multiple Case Study

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Abstract

Background: Health care is a strongly universal right across European welfare states; however, social inequalities in health persist. This literature argues that health care organization is an important but overlooked determinant of social inequalities in health, as health systems buffer or amplify structural and individual health determinants. The Client-Centered Coordination Platform (3CP) model offers integrated health access to people with severe mental illness, through core groups of professionals from across health and social services.

Objective: This study focuses on vulnerable people with severe mental health problems and aims to analyze how the model can give people with severe mental illness more integrated access to health and social care. This can form a stepping-stone for the upscaling of the 3CP model.

Methods: We conduct a 5-year multiple case study of 3 municipalities in Denmark, where 3CP is being implemented. In a 1-year pilot study, we expect to gather quantitative registry data from the municipalities and the Central Denmark Region to explore the characteristics of people included in 3CP. We will also collect qualitative data, including 21 hours of observations; 36 interviews with users, professionals, and managers; and 3 focus groups across the 3 municipalities. In a subsequent, 4-year qualitative study, we aim to conduct 120 hours of observations, 120 interviews, and 24 focus groups. In parallel with the qualitative study, we will facilitate a cocreation process to develop tools for sustaining integrated health access.

Results: As of January 2024, we have completed the individual interviews with users of 3CP and professionals and the focus groups. Individual interviews of managers will be conducted during the 1st quarter of 2024. The quantitative data are being collected.

Conclusions: Inequality is one of the greatest challenges that European societies face. Understanding new and innovative approaches to integrated care may provide valuable solutions to the challenges posed. Especially understanding and designing health and social care systems that meet the needs and abilities of those users requiring them most, is vitally important to tackle inequality.

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KEYWORDS

health care organization; social inequality in health; vulnerable people; integrated health access; healthcare access; accessibility; healthcare; Europe; social inequalities; health inequalities; mental illness; inequality; Denmark

Introduction

Background

Health care is a strongly universal right across European welfare states: citizens have access to health care based on need rather than income. However, social inequalities in health persist. In Denmark, the risk of dying before the age of 65 years is almost 4 times higher for people who leave school after 9 years compared with those who continue with their education [1]. Social inequalities in health can be defined as systematic, avoidable, and unfair differences in health outcomes between social groups in a population [2].

The social inequalities in health are especially high among people in vulnerable situations, who experience many avoidable health and social care problems and a high risk of early death [3,4]. People in vulnerable situations are individuals who lack personal, material, and social resources to tackle the challenges of getting the right health and social care when in need [5]. They are a highly heterogeneous group and include people experiencing homelessness, people with disabilities, people with limited social support, and those with complex health conditions. Their life situations are highly complex and potentially volatile, and people in vulnerable situations typically have persistent contact with a wide range of different health and social care services [5-7]. Paradoxically, however, the chance to reach and obtain appropriate care in situations of perceived need remains poor [3,8].

Many countries struggle with increasing fragmentation of health and social care services including the Nordic countries [9]. Studies document the continued negative consequences of fragmentation for people in vulnerable situations, and it becomes evident that fragmented services affect this group particularly strongly [10].

Providing better access to health and social care for people in vulnerable situations should involve easy and flexible opportunities to reach and obtain an appropriate range of services [11]. Approaches to strengthen access to care have typically fallen into 2 camps, focusing on either an individual level (eg, empowerment, health literacy, social capital, trust, and expectations) or an organizational level to make services more accessible (eg, changes to service information, opening hours, location of services, outreach services, and appointment procedures) [6,9]. However, the reach of the second type of approach is often limited [12,13]. As Smithman et al [5] conclude, health care organizations must adapt their accessibility to vulnerable populations' abilities, which requires innovations, tailored to reach and meet people in vulnerable situations' specific needs (similarly Richard et al [6] and Hardin et al [12]). This calls for a new approach of integrated access that combines the individual level and organizational level approaches and adopts an intersectoral perspective across the health and social care system.

This is precisely the aim of the novel Client-Centered Coordination Platform (3CP) model that has been implemented in 3 municipalities of the Central Regional Psychiatry in Denmark. This model is inspired by Flexible Assertive Community Treatment (FACT) but emerged from the bottom-up and has a distinct intersectoral focus. The 3CP model combines an individual, needs-based approach with an intersectoral, integrated service organization. The 3CP requires specialized competence and organizational coordination which is costly, and 3CP is therefore targeted and limited to people who, in addition to severe mental illness, often have a limited level of social functioning, reflecting, for example, unstable housing, substance abuse, and financial problems [14]. The 3CP model includes an individually tailored core group of professionals from the regional specialist mental health services and the community-based services provided by municipalities. This multidisciplinary and cross-sectoral integration distinguishes 3CP from other, existing integrated care or case management models. The cross-sectoral implementation of 3CP in the Central Denmark Region, however, proved to be complex. In this study, we, therefore, investigate a cross-sectoral implementation of the 3CP model between the 3 municipalities and the specialist mental health services in the region.

There is not yet scientific evidence for the effectiveness of FACT in Denmark (which inspired the 3CP model). However, studies conducted elsewhere show positive results. Some main findings of FACT suggest increased remissions [15,16], fewer hospital admissions and inpatient bed use [17], better psychosocial functioning and more use of outpatient [18-20] care, increased compliance with treatment, decrease in unmet needs and improved quality of life [15], better working environments for professionals, and an increase in quality of care [21]. Many studies, however, often pertain to implementation, evaluation, or clinical issues and we need more knowledge on how vulnerable people with severe mental illness experience integrated access to care under this novel model; what specific organizational practices best support and sustain the integrated access to health and social care; and the distribution of health and social care costs in primary and secondary care. To answer these questions, this study adopts a theoretical perspective from the sociology of organizations.

Objectives

The overall aim of this study is to analyze how 3CP can give people with severe mental illness more integrated access to health and social care. This can form a stepping-stone for the upscaling of the 3CP model to FACT.

More specifically, our aims are to (1) map out the characteristics of the people with severe mental illnesses participating in 3CP and their use of services; (2) explore how vulnerable people with severe mental illnesses perceive and engage in ongoing processes of integrated health and social care access, as well as treatment under the 3CP model; (3) analyze the organizational mechanisms of implementing and sustaining innovative practices

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for integrated health and social care access and ongoing treatment under the 3CP model; and (4) support people with severe mental illness, professionals, managers, and policy makers in sustaining practices for integrated care pathways and ongoing treatment.

Methods

Overview

The investigation of complex and multilevel processes and systems requires a range of data. We conducted a 5-year multiple case study in Silkeborg, Skive, and Viborg municipalities in Denmark, where 3CP is implemented. This allows for comparisons across different local contexts and underlying organizational structures. The study includes three parts: (1) a 1-year explorative study of how 3CP can give vulnerable people more integrated access to care; (2) a 4-year qualitative study of how to sustain user engagement in and organizational practices of integrated health access and ongoing treatment under 3CP; and, in parallel, (3) a 4-year cocreation process to develop tools for sustaining integrated health access, through bridge-building committees (Figure 1).

Figure 1. Overview of the study.

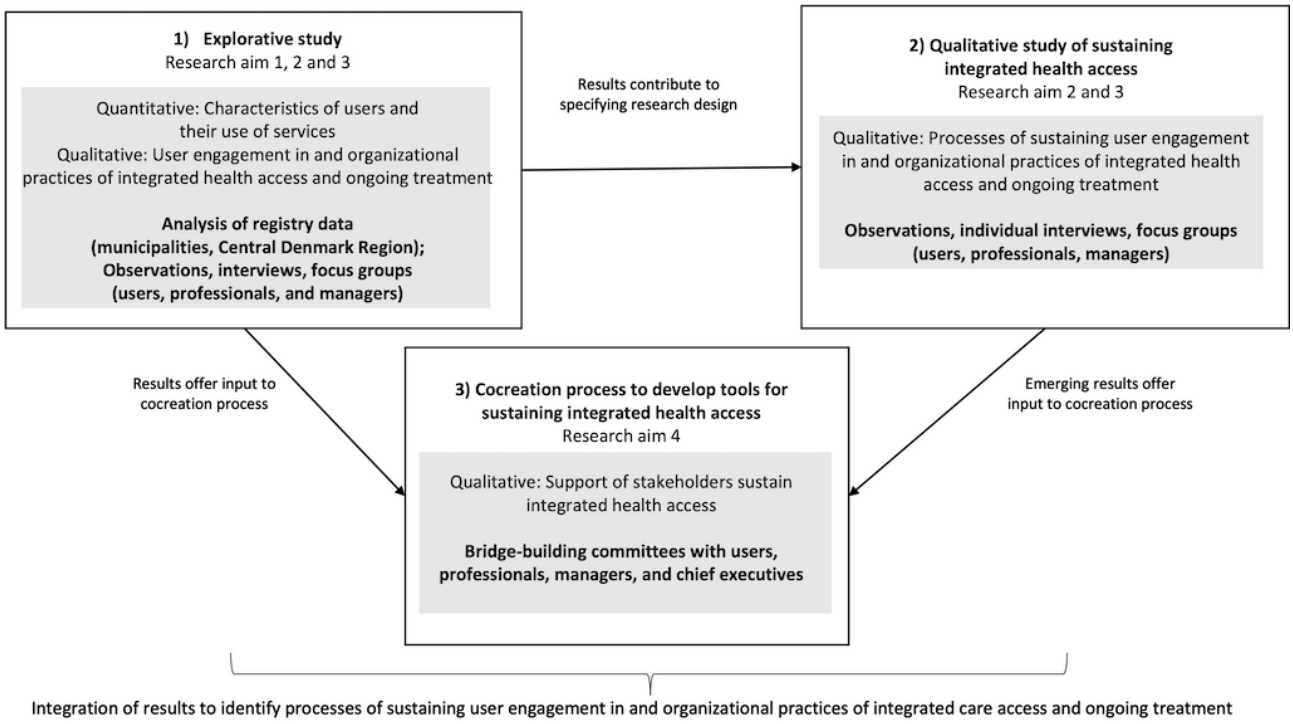

Theoretical Foundation

In many countries, mental health services are provided in a broad and complex structure between the health care and social care system. This coexists with the competing organizational and individual interests and pressures from, for example, regulators, decision makers, professionals, and the public. Navigating these structures may be challenging for people in vulnerable situations and there is, therefore, a need for organizations to meet the specific needs of individuals. This study uses the theory of inhabited institutionalism [22,23] as this allows examining both organizational structures and social interactions. The focus is on-the-ground activities of people doing things together against the background of how rules, norms, and culture operate in society [22,23]. This is because, these rules, norms, and cultures of health and social care organizations (institutions) shape and are shaped by the interactions of users, professionals, and managers. This approach is therefore ideally suited to understand the interplay between the institutions underpinning health and social care organizations, the processes of service delivery, and how this interplay shapes the unequal pathways of services for people [22,23].

Ethical Considerations

This research will be carried out in accordance with the Helsinki Declaration. Ethical approval was waived by The Central Denmark Region Committees on Health Research Ethics (number 1-10-72-124-22). Participants gave signed informed consent for study activities.

The study involves people with severe mental illness, health and social care professionals, and managers. Health and social care professionals will assist in selecting people with severe mental illness to ensure that those involved have sufficient personal resources to participate. As the professionals possess a high degree of integrity toward the 3CP users and have gained their trust, professionals are highly suitable to select those who are able to participate in this research. The life course of the people with severe mental illness, who are included in 3CP core groups, varies (eg, from maintaining a stable daily life to having relapses). Therefore, the inclusion of participants will occur in a continuous dialogue between researchers, health and social care professionals, and managers. Data collection, handling, and analyses will further be done in accordance with national and European Union regulations, and participants will remain entirely anonymous. To ensure privacy, we do not use their

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names, initials, or other identifiers during the research process. All participants are given a number that identifies them. Participants in the study are also volunteers, receive information to make an informed decision about participation, and can withdraw at any time. Finally, a supervision team will be established as in-depth ethnographic encounters with people in vulnerable positions can pose distinct ethical challenges, that require self-reflection about the researcher's position, biases, and relationship building [24,25]. This team of researchers, professionals, and users will discuss these issues as part of regular meetings.

Research Setting

The 3CP model in this study distinguishes itself from the FACT approach in the following ways: there is less coordination across health and social care services, this occurs in a core group rather than a team with a shared caseload and joint management, meetings take place once a week instead of daily, and there are fewer professional groups involved and less flexibility in terms of scaling up or scaling down treatment.

The implemented model builds on a collaboration between mental health services in the Central Denmark Region, the municipalities of Skive, Silkeborg, and Viborg, and the Certification Centre for ACT and Flexible (F)ACT in the Netherlands. The research team consists of the Danish Center for Social Science Research, Aarhus University, and managers from the municipalities and the Central Denmark Region. This coproduction provides a unique platform for understanding the mechanisms and structures that are needed to be successful in implementing and sustaining models of integrated care access. It further safeguards the users of health and social care services, as the professionals act as advocates for this group.

Danish Health and Social Care Setting

In Denmark, the responsibility for health and social care is shared among the national, regional, and municipal administrative levels. Each of the administrative levels has considerable autonomy in relation to the management, structure, and composition of services. Therefore, the contexts for the implementation and sustainment of the 3CP model can vary to some extent. The 3 included municipalities vary somewhat in size but possess a comparable population composition. At the same time, there are differences in the internal organizational structure and collaborative culture that may impact the implementation and sustainment of 3CP. For example, in each of the 3 municipalities, different departments are responsible for introducing 3CP and the extent of collaboration with the regional mental health services varies (Table 1). Great political and administrative autonomy is another reason why municipalities may implement and sustain 3CP differently.

Table 1. Local context of Client-Centered Coordination Platform core groups in Skive, Silkeborg, and Viborg.

Composition of core group	Organizational setting
Skive	Municipality: Centre for Mental Health and Substance Abuse
Region: 3 nurses and 1 middle manager	
Municipality: 9 outreach support workers and 1 social worker	
Silkeborg	Region or municipality: Integrated Mental Health Centre
Region: 5 nurses, 2 doctors, 2 secretaries and 2 middle managers	
Municipality: 4 outreach support workers, 3 substance abuse counselors, 2 secretaries, 3 middle managers, and 1 development officer	
Viborg	Municipality: Centre for Substance Abuse, Centre for Welfare Services
Region: 8 nurses and 1 middle manager	
Municipality: 4 outreach support workers and 1 middle manager	

3CP Model in Skive, Silkeborg, and Viborg

In Skive, Silkeborg, and Viborg municipalities, the 3CP core groups are organized differently, reflecting variations in resources (personnel and economic), values, and existing collaborations with the region (Table 1). In Skive and Viborg, the core group consists of housing support professionals from the municipality, a municipal manager (only in Skive), and specialist mental health professionals from the region. In contrast, in Silkeborg, professionals from the municipal center for substance abuse play a prominent role together with professionals from the specialist teams for attention-deficit/hyperactivity disorder and substance abuse in the region (Table 1).

However, the tasks of the three 3CP core groups are similar: following disease and symptom development, providing guidance and practical help in everyday life, working with rehabilitation, and supporting the person's recovery. Those users included in 3CP teams experience severe mental illness and have chaotic life circumstances (eg, abuse, homelessness). The 3CP core groups thus provide long-term follow-up services for people living in their local community. The core groups offer services at two levels of treatment intensity: (1) regular individual follow-up in the core group and (2) intensive treatment and follow-up, where the user has contact with several group members, and where the core group discusses the user every week and plans what services are delivered by whom.

The core groups have shared caseloads and meet once a week to discuss those users who receive intensive treatment and

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follow-up support. Most users manage with regular individual follow-up, but if there is a risk of, for example, psychotic relapse, alcohol or drug relapse, or increased need for hospitalization, the core group intensifies its effort. The core group can provide this intensified effort in both the short and the longer term and during crises. When the crisis is over, professionals go back to normal individual follow-up.

Data Collection (Parts 1 and 2)

Overview

All participants are chosen based on being part of a 3CP core group in 1 of the 3 municipalities. The users are together with the professionals from the core groups selected for individual interviews. This will be a dialogue between the researchers, health and social care professionals, and managers in the interdisciplinary core groups, to understand the users' capabilities to participate. Second, the health and social care professionals, who are involved with the users, will also be invited to participate in individual interviews and focus group discussions. This will help provide an understanding of the 3CP users' care pathways from their perspective and the perspective of the professionals surrounding them. The first 2 parts of the study involve various data collection methods, which are described below.

Explorative Study

In the 1-year explorative study, the collection of quantitative and qualitative data occurs in parallel (convergent mixed methods) to maximize synergies in the analysis of the data (Figure 1) [26]. This will offer a powerful platform for methodological triangulation [26,27]. Data consist of registry data and ethnographic material (eg, observations, focus groups, and interviews; Table 2). The explorative study focuses on mapping out the characteristics of people with severe mental illness included in 3CP core groups. On this basis, the study explores the experience and engagement of these people, and the health and social care professionals around them (eg, nurses, social workers, and substance abuse counselors). This study seeks to gain new knowledge about how people with severe mental illness navigate multiple encounters with health and social service providers, and their opportunities to reach and obtain appropriate access to services. It further focuses on the organizational practices across different local contexts that underpin processes of integrated access to care.

The quantitative study will present the demographic and socioeconomic profile of the people included in 3CP core groups, such as level of education, patterns of disease, labor market participation, and occurrence of homelessness. This study is based on registry data from the participating municipalities, the Central Denmark Region, and the national registries (eg, information on diagnosis, contacts with the health and social care services, and receipt of transfer payments; see Table 2). Data are collected in collaboration with the municipalities and the region, and data will cover a period of 5 years (2018-2022) and include 51 individuals included in 3CP core groups between 2020 and 2022. The characteristics of the individuals will be reported as simple yearly means. The qualitative data will include a total of 7 hours of observations of core group meetings or interactions between users and health and social care professionals, 12 interviews with users and professionals, and 1 focus group in each municipality (Table 2).

Table 2. Overview of planned data collection in Silkeborg, Skive, and Viborg municipalities.

Study	Characteristics
Explorative study (1 year)	
Observations in each municipality	3 core group meetings and 2 professional or user interactions
Individual interviews in each municipality	5 users of 3CP[a], 5 professionals, and 2 managers
Focus groups in each municipality	3-4 professionals
In all municipalities	21 hours of observations, 36 interviews, and 3 focus groups
Registry data	
Silkeborg municipality	19 users of 3CP
Skive municipality	16 users of 3CP
Viborg municipality	16 users of 3CP
All municipalities	51 users of 3CP
Qualitative study (4 years)	
Observations in each municipality per year	3 core group meetings and 4 professional or user interactions
Individual interviews in each municipality per year	2 users of 3CP, 4 professionals, 2 managers, and 2 chief executives
Focus groups in each municipality per year	3 professionals and 3 managers or chief executives
In all municipalities per year	120 hours of observation, 120 interviews, and 24 focus groups

[a]3CP: Client-Centered Coordination Platform.

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Qualitative Study of Sustaining Integrated Health Access

This 4-year qualitative study aims to understand how to sustain user engagement in and organizational practices of integrated health access and ongoing treatment under 3CP in the longer term. Like in the explorative study, we will focus on both: how vulnerable people with severe mental illnesses perceive and engage in ongoing processes of integrated health and social care access as well as treatment; and how organizational practices by professionals, managers, and chief executives can sustain these innovative practices. In each municipality, we expect to gather the following material each year, over a period of 4 years: 10 hours of observations of core group meetings or interactions between users and health and social care professionals, 10 interviews with users, professionals, managers, and chief executives, and 2 focus groups with professionals and managers or chief executives, respectively. The interviews and focus groups will also be informed by the data collected in the explorative study (Figure 1).

Cocreation Process to Develop Tools for Sustaining Integrated Care Access (Part 3)

To support the sustainment of integrated access to health and social care, this third part of the study consists of a cocreation process with local stakeholders. We will initiate and conduct bridge-building committees involving users of 3CP and the relevant professionals, managers, and politicians. Initially, a planning team with representatives from all 3 municipalities and the region will meet to discuss implementation. This is part of the cocreation process and will occur once a year and involve users, professionals, and managers. Subsequently, the planning team will meet once a year to share experiences of the bridgebuilding committee meetings (Table 3).

In each municipality, we aim to organize 5 bridgebuilding committee meetings of 2 hours each (over a period of 4 years). Each meeting will include 10 participants from across the municipality and the region; 2 users (who are able to participate), 4 professionals, 2 managers, and 2 politicians (Table 2).

The first meeting is a kick-off meeting, where the participants will assist in tailoring the structure and function of the meetings as part of a cocreation process. Next, there is a pilot meeting, before moving on to the regular committee meetings (Table 3). The final meeting focuses on sustainment to secure the long-term involvement of users, the adaptation of the 3CP model, and the continuous flexibility in care pathways. At all the committee meetings, the researchers involved in this study will develop questions and topics to facilitate discussion.

Table 3. Overview of bridge-building committees.

Years and its quarters	Committee meetings		
	Silkeborg	Skive	Viborg
Year 1			
1	Planning team meeting	Planning team meeting	Planning team meeting
2	#1 Cocreation workshop (kick-off)	#1 Cocreation workshop (kick-off)	#1 Cocreation workshop (kick-off)
3	__[a]	—	—
4	#2 Pilot	#2 Pilot	#2 Pilot
Year 2			
1	Planning team meeting	Planning team meeting	Planning team meeting
2	#3	#3	#3
3	—	—	—
4	—	—	—
Year 3			
1	Planning team meeting	Planning team meeting	Planning team meeting
2	#4	#4	#4
3	—	—	—
4	—	—	—
Year 4			
1	Planning team meeting	Planning team meeting	Planning team meeting
2	#5 Sustainment workshop	#5 Sustainment workshop	#5 Sustainment workshop
3	—	—	—
4	—	—	—

[a]Not applicable.

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Collecting Data With People in Vulnerable Positions

Ethnographic methods are characterized by flexibility and studies that are less fixed in terms of their specific form and extent of empirical material [28,29]. This is a highly suitable approach, as the users in our study are all vulnerable, as well as heterogeneous; they possess very different resources for participating in research. Their experiences with health and social care services may also change over time [29]. Likewise, the interactions between service users and service providers are "in the making" as our study progresses [28]. Even the organizational practices of 3CP are intended to be "flexible," so that they can be adjusted to the needs of the user. We thus expect to combine various methods of data collection and do so in a flexible manner; this includes qualitative semistructured interviews, observations, photovoice [27,30], and informal conversations (see interview guide in Multimedia Appendix 1). Interviews will allow us to gain knowledge about the experiences of being part of a 3CP core group, as well as views of the organization of the services under the 3CP model. In relation to users, we will combine this with photo-voice to help us inquire into their underlying understandings of health and social care services. This method particularly provides a way of engaging people with intellectual disabilities, as their thoughts may be illustrated in a picture rather than expressed in wording [27,30]. We will provide the 3CP users with a disposable camera, where they can take pictures that they find relevant to their involvement in treatment. These pictures will be used in the interviews, to facilitate the discussion around their experiences with accessing health and social care services under the 3CP model. Observations and informal conversations will further give us more in-depth knowledge about their concrete experiences navigating the system as users and professionals, respectively.

Results

As of January 2024, we have completed the individual interviews with users of 3CP and professionals and the focus groups (Table 2). We will, during February or March 2024, proceed with the individual interviews of managers in each of the 3 municipalities.

We are further in the process of collecting the quantitative data (Table 2).

Discussion

Principal Findings

Fragmented health and social care services affect people in vulnerable positions particularly strongly [4] and therefore organizations must adapt their accessibility to the needs and abilities of vulnerable populations. This study aims to analyze, if and how the 3CP model can give people in vulnerable positions more integrated access to care, drawing on an in-depth analysis of the interplay between individual needs and care-seeking practices, organizational practices, and underlying structures and mechanisms.

We anticipate that this study will contribute to existing knowledge in 3 respects. First, it will provide in-depth knowledge about pathways of health and social care seeking and the related barriers and facilitators, particularly under the 3CP model. Second, this knowledge can contribute to better understanding and addressing unequal access to health and social care. The causes of inequality in health are often assigned to "social determinants" (education, income, and gender) although these are correlations rather than causations; being a poor, low-educated man does not determine one's health or access to health, even if more low educated men have poor health. The relationships between social factors and health are not simple and instead, this requires a more careful exploration of the "causes of the causes" [31]; that is, what are the specific links between social factors on the one hand and health on the other? Third, this study will contribute to existing knowledge on the relations between individual care practices and organizations' practices of service delivery; in short, how organizations can facilitate and hamper access, especially across different sectors. This will contribute to addressing the lack of knowledge about the interplay between human interactions on the one hand and organizational structures on the other [32].

One limitation of our study is the uncertainty in collecting data with a group of highly vulnerable people. We therefore need to be flexible and adapt our strategies as we are in the field. Further, using the 3CP teams provides us with valuable knowledge on integrated health access, however, this is one context to be explored. Other models or settings might provide other insights.

Dissemination of Results

To disseminate the results, we will reach out to stakeholders by presenting results on a regular basis at relevant workshops, conferences, and in (professional) journals. We will also deliver presentations at practitioner conferences on mental health care and substance abuse counselors such as those organized by the umbrella organization of Danish regions. The research team will publish the results of the study in at least 3 articles in international, peer-reviewed journals.

Implications

The results of this study will strengthen integrated health access for vulnerable people. More specifically, the study will (1) identify strategies to help people in vulnerable positions with severe mental health problems to improve their experience of access across different sectors of the health and social care system; (2) develop a catalog of strategies for good practice for professionals and decision makers in municipalities, hospitals, and general practice to strengthen integrated access to care for people in vulnerable positions who experience severe mental health problems; and (3) offer a stepping stone for upscaling the 3CP model across other regions or municipalities and to other vulnerable groups, based on detailed knowledge about the specific contexts and mechanisms fostering integrated access to care.

Conclusions

Inequality is one of the greatest challenges European societies face and there are many opportunities for future research within this field. However, understanding new and innovative approaches to integrated care may provide valuable solutions

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to the challenges posed. Especially, understanding and designing health and social care systems that meet the needs and abilities of those users requiring them most is vitally important to tackle inequality.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 18 KB - resprot_v13i1e56197_app1.docx]

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Abbreviations

3CP: Client-Centered Coordination Platform
FACT: Flexible Assertive Community Treatment

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Protocol

Evaluating the Implementation of Integrated Proactive Supportive Care Pathways in Oncology: Master Protocol for a Cohort Study

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Abstract

Background: Supportive care (SC) refers to the prevention and management of complications of cancer and its treatment. While it has long been recognized as an important cancer care delivery component, a high proportion of patients face unaddressed SC needs, calling for innovative approaches to deliver SC.

Objective: The objective of this master protocol is to evaluate the implementation of different integrated proactive SC pathways across the cancer care continuum in our institution (Gustave Roussy, Villejuif, France). Pathways studied in this master protocol may occur shortly after diagnosis to prevent treatment-related burden; during treatment to monitor the onset of toxicities and provide timely symptom management; and after treatment to improve rehabilitation, self-management skills, and social reintegration.

Methods: This study is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework. The primary objective is to evaluate the impact of SC pathways on patients' distress and unmet needs after 12 weeks, measured by the National Comprehensive Cancer Network's Distress Thermometer and Problem List. Secondary objectives will focus on the pathways (macrolevel) and each SC intervention (microlevel), evaluating their reach (administrative data review of the absolute number and proportion of clinical and sociodemographic characteristics of patients included in the pathways); short-term and long-term efficacy through their impact on quality of life (EQ-5D-5L and the 30-item European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire) and symptom burden (MD Anderson Symptom Inventory, Hospital Anxiety and Depression Scale, Insomnia Severity Index, and 22-item European Organization for Research and Treatment of Cancer Sexual Health Questionnaire); adoption by patients and providers (administrative data review of SC referrals and attendance or use of SC strategies); barriers to and leverage for implementation (surveys and focus groups with patients, providers, and the hospital organization); and maintenance (cost-consequence analysis). Pilot evaluations with a minimum of 70 patients per pathway will be performed to generate mean Distress Thermometer scores and SDs informing the calculation of formal sample size needed for efficacy evaluation (cohorts will be enriched accordingly).

Results: The study was approved by the ethics committee, and as of February 2024, a total of 12 patients were enrolled.

Conclusions: This study will contribute toward innovative models of SC delivery and will inform the implementation of integrated SC pathways of care.

Trial Registration: ClinicalTrials.gov NCT06479057; https://clinicaltrials.gov/study/NCT06479057

International Registered Report Identifier (IRRID): PRR1-10.2196/52841

(JMIR Res Protoc 2024;13:e52841) doi:10.2196/52841

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KEYWORDS

care delivery; pathway of care; oncology; supportive care; quality of life; cohort study

Introduction

Background

Due to the rapid evolution of modern anticancer treatment, cancer is often considered a chronic disease. Novel treatments deliver longer survival but frequently with a range of acute toxicities and long-term side effects, which negatively impact the quality of life and necessitate ongoing health service use [1].

Supportive care (SC) is defined as the prevention and management of adverse effects of cancer and its treatment [2,3]. This includes management of physical and psychological symptoms and side effects across the continuum of cancer experience, from diagnosis through anticancer treatment to posttreatment care [2,3]. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to SC. Financial and social issues that may be associated with risk of toxicities or access to SC should also be considered [2,4-6].

While SC has long been recognized as an important component of cancer care delivery, published evidence suggests an ongoing, high burden of unaddressed needs across all SC domains for many patients, at all phases of cancer experience [7,8]. A systematic review of 57 studies quantifying patients' unmet SC needs across different tumor types and phases of the cancer continuum reported that, although highly variable, these could reach 93% for unmet informational needs, 89% for unmet physical needs, 89% for unmet psychosocial needs, 63% for unmet sexuality needs, and 51% for unmet spiritual needs, with many of these unmet needs experienced concurrently [9]. In addition, while unmet needs appeared to be highest and most varied during treatment, a greater number of individuals were likely to express unmet needs after the end of treatment compared to any other time [9]. More specifically, long-term physical and behavioral symptoms (fatigue, neuropathy, weight management, emotional distress, insomnia, and cognition decline), intimacy-related concerns, financial and work-related concerns, and provider-communication and information needs have been highly cited as common unmet needs across the cancer care continuum [10].

A recent study aimed to identify and synthesize patient's views about areas where they need support through cancer care [8]. Quantitative and qualitative studies were included, and the authors presented 3 lines of work for managing chronic illness ("illness-work," "everyday-life work", and "biographical work"), including a group of key common patient needs. For "illness-work," the key needs identified were understanding their illness and treatment options, knowing what to expect, communication with health care professionals, and staying well. With regard to "everyday-life work", patients wanted to maintain a sense of normalcy and look after their loved ones. For "biographical work," patients commonly struggled with the emotional impact of illness and a lack of control over their lives. Spiritual, sexual, and financial problems were less universal. For some types of support, demographic factors influenced the level of need reported.

Importantly, there is evidence demonstrating that unmet SC needs are associated with inferior quality of life, increased symptom burden, and worse clinical outcomes such as emergency visits and hospitalizations [11-13].

Although a large body of evidence exists on interventions addressing SC needs in patients with cancer [14], implementation of effective interventions in clinical practice has been suboptimal [7,15]. The delivery of SC requires a multidisciplinary approach, involving the screening, assessment, management, treatment of side effects, symptoms, and needs of patients with cancer, carriers, and family [2]. A recent framework highlighted the importance of perceiving SC as a way of understanding, planning, delivering, and evaluating integrated cancer care, where each component of cancer care and treatment occur within a SC framework, instead of considering it as a subspecialty, discipline, or series of interventions [16]. Ideally, SC needs to be delivered in all health care settings at all steps of the cancer pathway from diagnosis to survivorship and end of life [2]. Most commonly, SC is primarily delivered in everyday practice by treating oncologists who during their routine oncological consultation may detect SC needs and refer patients to multiple multidisciplinary strategies such as palliative care, social work, rehabilitation, psycho-oncology, and integrative medicine. However, this approach can lead to heterogeneous access and fragmented care [16]. An integrated SC delivery model has been proposed to overcome these challenges [17]. In this model, longitudinal specialist SC is provided by an interdisciplinary SC team, with timely involvement of other teams (eg, cancer pain service and rehabilitation) when the need arises [17]. For patients who have completed curative treatments and are on surveillance, the survivorship care team may be the main SC service [18]. Key features of this model include universal referral, systematic SC needs screening, tailored specialist involvement and evidence-based symptom management strategies, streamlined care, and collaborative teamwork [17]. In addition, several modifiable risk factors for toxicity and quality of life deterioration have been identified across the cancer care continuum [19-23]. Therefore, an integrated preventive strategy that anticipates tailored SC services to patients at higher risk of toxicity or quality of life deterioration has been suggested [22] and requires further evaluation of its implementation and impact on patient-reported outcomes.

Objectives

At our institution (Gustave Roussy, Villejuif, France), several SC resources were co-designed and deployed in clinical practice (Figure 1 and Textbox 1), including integrated SC pathways of care and specific SC referrals. In Gustave Roussy, the integrated SC pathways include a formal SC needs assessment and tailored SC referrals and resources according to patient's needs. These pathways are offered to patients across the entire cancer care continuum: shortly after diagnosis to prevent treatment-related

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burden; during treatment to monitor and manage treatment-related toxicities; and after treatment to accelerate rehabilitation, social integration, and self-management. This study will evaluate the implementation of integrated and proactive SC pathways in oncology.

Figure 1. Examples of core supportive care components of supportive care pathways across the cancer care continuum. ePRO-CTCAE: electronic patient-reported outcomes version of the common terminology criteria for adverse events.

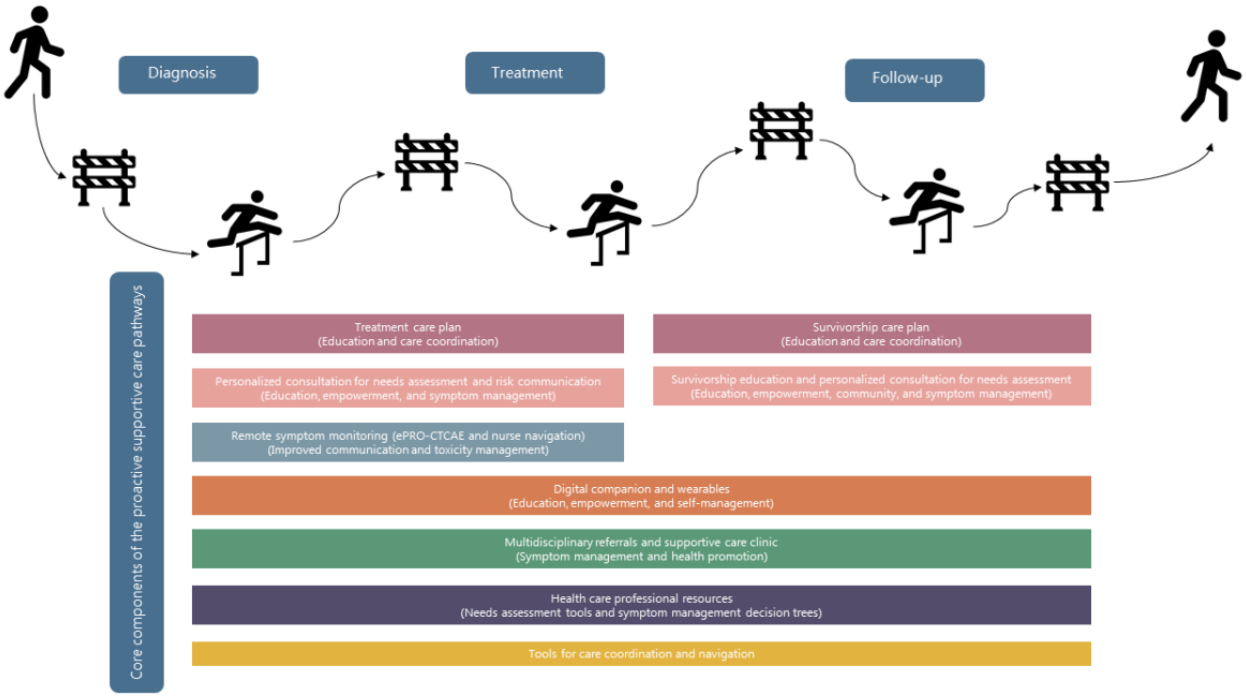

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Textbox 1. Current supportive care interventions and referrals available at Gustave Roussy.

Integrated supportive care pathways

- Shortly after diagnosis
  - Supportive care pathway for preventing treatment-related burden after breast cancer (eg, cancer-related fatigue and cluster of behavioral symptoms)
  - Supportive care pathway to prevent treatment-related burden for patients considered vulnerable with brain, head and neck, thoracic, and neuroendocrine tumors
- During treatment
  - Remote symptom monitoring pathway with weekly electronic patient-reported outcomes (ePROs) and nurse navigation (for patients during active systemic treatment with chemotherapy, immunotherapy, or targeted agents)
  - Immunotoxicity management pathway
- After treatment
  - Proactive survivorship care pathway (breast cancer and others)

Supportive care interventions available at the institution

- Digital health tools
  - Remote monitoring (ePRO system) for patients receiving active treatment (chemotherapy, target agents, and radiotherapy)
  - Mobile app delivering education and self-management advice (articles, videos, and podcasts)
  - Internet-delivered self-care programs of evidence-based validated supportive care strategies (physical activity, mindfulness, yoga, and cognitive behavioral therapy)
  - ePRO data collection web system for research studies
- In-person multidisciplinary supportive care resources at the supportive care clinic
  - Adapted physical activity program
  - Mindfulness program
  - Acupuncture consultations
  - Hypnosis consultations
  - Sophrology program
  - Art-therapy program
  - Socioesthetician follow-up
  - Return-to-work educational seminars
  - Diet and nutrition educational seminars
  - Survivorship educational seminars
  - Individualized risk of toxicity assessment
- Community-based survivorship resources
  - Nutrition follow-up
  - Adaptive physical activity
  - Psychological support
- In-person multidisciplinary supportive care resources at the hospital
  - Nutritionist follow-up
  - Palliative care follow-up
  - Addiction treatment programs (tobacco and alcohol)
  - Social services follow-up
  - Organ specialists for toxicity management of cancer therapies (cardiologist, pneumologist, endocrinologist, neurologist, rheumatologist, etc)

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- Day hospital for acute toxicity management
- Rehabilitation hospital
- Psychologist or psychiatrist follow-up
- Pain evaluation and management at pain clinic
- Sexologist follow-up
- Speech therapy
- Ostomy nurses
- Supportive care nurses
- Thrombosis evaluation team
- Bone metastases evaluation team

Methods

Study Design and Interventions

The study design is a master protocol [24] for a prospective cohort study focused on evaluating the implementation of integrated proactive pathways of SC at Gustave Roussy. This master protocol study is conducted with a collection of substudies for each SC intervention that share key design components and operational aspects. Data collection will allow the evaluation at a macro level (integrated SC pathway, including SC needs assessment and tailored multidisciplinary referrals) and at a micro level (separated for each SC intervention).

The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [25] was used to guide the definition of study objectives and the data collection plan. As a framework, RE-AIM has both individual-level and staff- or setting-level dimensions, including Reach and Effectiveness (individual-level), Adoption and Implementation (staff and setting levels), and Maintenance (both individual and staff or setting levels) [26].

Patients will be clinically monitored from the date of their screening visit until the date of the last visit, loss to follow-up, withdrawal of consent, disease progression, death, or end of study, whichever occurs first. There are no treatments prescribed to the patients other than those prescribed in routine practice.

Patients will be prospectively entered in the study after checking for eligibility criteria and signature of the informed consent form. Data will be collected at baseline, 4 weeks, 12 weeks, and 24 weeks. For patients participating in the immunotoxicity management pathway, data will also be collected at 1 month. Study participants will be asked to complete the study web-based questionnaires using the WeShare platform's electronic patient-reported outcomes module [27,28]. Identifying data (personal data) are recovered at the time of the creation of the WeShare account and will be separated from the study data. The investigation plan is detailed in Table 1. In-paper questionnaires will also be available if preferable by the patient.

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Table 1. Investigation schedule.

	Electronic case report form creation	Baseline visit	Follow-up month 1[a] week 4 (–2 weeks to +2 weeks)	Follow-up month 3 week 12 (–2 weeks to +2 weeks)	Follow-up month 6 week 24 (–2 weeks to +2 weeks)
Prescreening informed consent	✓				
Screening informed consent		✓			
Eligibility criteria		✓			
Clinical data[b]		✓	✓	✓	✓
Supportive care resources proposed[c]		✓			
Attendance and adoption data to supportive care resources proposed[d]				✓	✓
Out of schedule use of hospital services (emergency visits, extra consultations, and hospitalization)				✓	
Resilience mobile app use data[e]		✓	✓	✓	✓
Electronic patient-reported outcomes[f]					
Sociodemographic questionnaire		✓			
National Comprehensive Cancer Network's Distress Thermometer and Problem List		✓	✓	✓	✓
5-level EQ-5D version		✓	✓	✓	✓
MD Anderson Symptom Inventory		✓	✓	✓	✓
Patient Assessment of Chronic Illness Care				✓	
Health Literacy Questionnaire		✓			
Gustave Roussy vulnerability questionnaire[g]		✓			
30-item European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire[h]		✓		✓	✓
Hospital Anxiety and Depression Scale[i]		✓		✓	✓
Insomnia Severity Index [j]		✓		✓	✓
22-item European Organization for the Research and Treatment of Cancer Sexual Health Questionnaire[k]		✓		✓	✓
Experience and satisfaction questionnaires[l]				✓	
Qualitative research					
Focus groups[m]				✓	

[a]For patients included in the immune toxicity management pathway.

[b]Complete clinical data including type of cancer; stage; prior and ongoing oncological treatments; comorbidities; disease status; description and grading of treatment-related toxicities and its relationship with treatment; treatment discontinuation and reintroduction; supportive care strategies proposed and attendance log to supportive care strategies; and use of hospital services, including emergency visits, extra consultations, and hospitalizations. Oncological scores used for supportive care management included: Geriatric score G8, thrombosis score, nausea, and vomiting score.

[c]For the complete list of supportive care resources, refer to Textbox 1.

[d]Including attendance data in all in-person supportive care interventions.

[e]Resilience [29] is a mobile app used in routine care at Gustave Roussy for remote symptom monitoring, patient empowerment, and education. Data on mobile app use, including symptoms reported, alerts generated, and content used, will be evaluated.

[f]Specific questionnaires can be added if pertinent to a new pathway.

[g]Sent only for patients participating in the pathway to prevent treatment-related burden (brain, head and neck, thoracic, and neuroendocrine tumors).

[h]Sent only for patients in the pathway for preventing treatment-related burden after breast cancer.

[i]Sent only for patients in the pathway for preventing treatment-related burden after breast cancer or patients referred to supportive care services for emotional distress and anxiety (mindfulness meditation programs, cognitive behavioral therapy, and psychological consultation).

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[j]Sent only for patients referred for supportive care strategies for insomnia (cognitive behavioral therapy and mindfulness meditation programs).

[k]Sent only for patients with sexual concerns referred for sexologist consultation.

[l]The experience questionnaire will be specific for each supportive care intervention.

[m]Focus groups with participants of each supportive care intervention.

Eligibility Criteria

Patients are eligible if they have histological confirmation of cancer of any type and stage, are aged ≥18 years, and provided written informed consent. For the primary end point, all patients included in SC pathways (ie, who received a formal SC needs assessment and tailored multidisciplinary referrals) will be invited to participate. As for the secondary end points, any patient participating in SC interventions may be invited to participate. As for health care providers, those who assist the patients included in the SC pathways, care managers, and coordinators involved are eligible. If a patient withdraws consent for the study, no further study-specific evaluations will be performed, and no additional data will be collected.

Integrated SC Pathways

At Gustave Roussy, integrated pathways of SC were co-designed with patients, providers (including nurses, oncologists, radiotherapists, surgeons, and SC specialists), sociologists, care managers, technology experts, and implementation scientists. These pathways aim to provide a formal SC needs assessment and tailored multidisciplinary care referral across the entire cancer care continuum, leveraging mechanisms that ensure the inclusion of patients considered vulnerable. During the co-design phase, each pathway carefully considered the available scientific evidence and the needs of patients and providers according to tumor type and disease stage. Shortly after the moment of diagnosis, the objective of the integrated SC pathways is to anticipate and prevent treatment-related burden. An autoevaluation of patient's symptoms and SC needs alongside a health care provider's assessment are conducted to implement a personalized SC plan. This pathway is being implemented for patients with brain, head and neck, thoracic, and endocrine tumors and will be adapted and expanded to other tumor types, including breast cancer (long-term fatigue after breast cancer prevention of cancer-related fatigue and cluster of long-term behavioral symptoms pathway). During treatment, the goal is to continuously monitor and manage the toxicity of systemic therapies at an earlier stage, reduce symptom burden, and avoid recourse to emergency care. A total of 2 pathways are implemented: a remote patient monitoring pathway using electronic weekly patient-reported outcomes (electronic patient-reported outcomes version of the common terminology criteria for adverse events) with nurse navigation [19] and an immunotoxicity management pathway with a multidisciplinary expert team providing mobile evaluation for hospitalized and ambulatory patients and follow-up consultations. Both the remote patient monitoring pathway and the immunotoxicity management pathway are agnostic (any cancer type and stage). After treatment, the objective is to mitigate long-term treatment-related toxicities, accelerate rehabilitation, give support during long adjuvant treatments, promote healthier behaviors, and facilitate social reintegration. This pathway is implemented for breast cancer [20] and encompasses a personalized survivorship care consultation for needs assessment and SC referrals, the delivery of a survivorship care plan document, invitation to attend face-to-face survivorship educational group seminars, access to a mobile app delivering personalized education and self-management advice, and decision aids for physicians focused on SC needs. This pathway will be adapted and expanded to other tumor types in our institution.

A pathway implementation committee oversees the co-design and deployment process of the SC pathways, including the need for staff training or specific recruitments before the pathway is implemented in routine care. If staff replacements are needed, proper training is provided to new team members.

Study Objectives

Primary Objective

The primary objective of this study is to evaluate the impact of an integrated proactive SC pathway in patients' distress and unmet needs at 12 weeks' follow-up in difference phases of the cancer continuum (at diagnosis, during treatment, and survivorship phase). Distress and unmet needs will be measured by the National Comprehensive Cancer Network (NCCN) Distress Thermometer and Problem List, respectively [30,31]. For patients participating in the immunotoxicity management pathway, the impact of the pathway will be evaluated at 4-week follow-up.

Secondary Objectives

The study's secondary objectives are to (1) evaluate the *Reach* of the pathway through the absolute number, proportion, and representativeness of patients who participated in the SC needs assessment and in each SC intervention; (2) evaluate the microlevel *Efficacy* of the pathway and each SC intervention through the impact of the pathway and each SC intervention on patients' quality of life, symptom burden, and distress; (3) evaluate the *Adoption* of the pathway through the absolute number, proportion, and representativeness of physicians and patients engaged with the pathway and each SC intervention; (4) evaluate barriers and leverages for pathway *Implementation* through collection of patient, health care provider, and organization experience; and (5) plan for *Maintenance* of the pathway through a cost-consequences analysis, with analysis of health resources and costs related to hospital services and efficacy outcomes (quality-adjusted life years [QALYs]) over a 6-month follow-up.

Study Assessments

The NCCN's Distress Thermometer and Problem List [30] will be used to measure patients' distress and unmet needs at baseline and after 12 weeks and 24 weeks. In addition, we will evaluate at 12 weeks the Reach as the absolute number, proportion, and representativeness of patients: offered to participate in a SC pathway, who accepted the participation in a SC pathway, and for whom each type of SC strategy was indicated.

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At baseline, a socioeconomic questionnaire and a health literacy questionnaire [32] will be completed. Quality of life will be evaluated at baseline, 12 weeks, and 24 weeks with the EQ-5D-5L [33] in the overall cohort and the 30-item European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire [34] for patients with breast cancer participating in fatigue prevention pathway. Symptom burden will be evaluated at baseline, week 12, and week 24 with the MD Anderson Symptom Inventory [35] in the overall cohort and relevant questionnaires for specific patient cohorts, such as the Hospital Anxiety and Depression Scale [36] for patients in the frailty prevention pathway (breast cancer) and patients referred to SC services for emotional distress and anxiety, the Insomnia Severity Index [37] for patients referred for SC strategies for insomnia, and the 22-item European Organization for Research and Treatment of Cancer Sexual Health Questionnaire [38] for patients with sexual concerns referred for sexologist consultation. In addition, patients with brain, lung, head and neck, and neuroendocrine tumors participating in the pathway to prevent treatment-related burden will also complete a vulnerability questionnaire at baseline.

Adoption at week 12 and week 24 will include metrics focused on (1) physicians: absolute number, proportion, and representativeness of physicians referring patients to the SC pathways and (2) patients: absolute number, proportion, and of patients that fully adopted each SC intervention (eg, in the after cancer pathway: attendance to consultations, seminaries, classes, completion of a SC program, and use data). To evaluate implementation, we will look at patient, provider, and organizational experience (levers and obstacles to proper implementation) within the proactive SC pathways at week 12 of follow-up. A patient experience questionnaire, the Patient Assessment of Chronic Illness Care [39], will be applied at week 12. In addition, an ad hoc patient satisfaction questionnaire (5-point Likert scale) will also be collected at 12 weeks after pathway delivery. This questionnaire includes core common questions for all pathways (overall satisfaction, perceived usefulness of the needs assessment and supportive are services proposed, clarity of the recommendations, and ability to comply with the SC plan recommended) and specific satisfaction and perceived usefulness questions for SC services used in each pathway; a free text field for comments is also included. All these quantitative analyses will be enriched with preplanned qualitative analysis with focus groups with patients, providers, and implementation team to assess experience, satisfaction, and contextual factors that influence implementation [40]. Maintenance of the pathway will be performed through a cost-consequences analysis. Hospital costs from the perspective of the French national health insurance will be assessed during the study period. This will be calculated by administrative data review of internal allocated resources for pathway delivery and estimated costs of use of hospital services (unplanned hospitalization, consultations, and emergency visits recorded in the electronic medical records). QALYs will be measured using utility values derived from the EQ-5D-5L. QALYs will be computed combining survival time by utility values.

Assessments at week 4 will be conducted exclusively with patients participating in the immunotoxicity management pathway (Table 1).

Statistical Considerations

The NCCN's Distress Thermometer scores are based on mean and SD values at baseline and have been used in heterogeneous populations [31,41]. To estimate the expected effect of the integrated and proactive SC pathway on Distress Thermometer scores, a pilot evaluation will be conducted to calculate the formal sample size needed for efficacy evaluation. According to the sample size requirements for pilot studies proposed by Teare et al [42], pilot evaluations with a minimum of 70 patients will be performed to generate NCCN's Distress Thermometers mean scores and SDs before and after going through a SC pathway (70 patients for each SC pathway).

The primary analysis will compare patient distress scores by the NCCN's Distress Thermometer measured before and after the intervention (baseline and week 12) using the Wilcoxon signed rank test.

For secondary analyses, the scores and subscores of the patient-reported outcome measurements (EQ-5D-5L, MD Anderson Symptom Inventory, Hospital Anxiety and Depression Scale, Insomnia Severity Index, 30-item European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, and the 22-item European Organization for Research and Treatment of Cancer Sexual Health Questionnaire) and patient-reported experience measurement (NCCN Distress Thermometer) questionnaires and scales will be calculated using mixed models to take into account the repeated measures and the initial value before intervention.

All patients receiving SC interventions and referrals as well as health care providers and care coordination professionals performing activities related to the SC clinical pathways (nurses, oncologists, gynecologists, surgeons, radiation oncologists, and members from the multidisciplinary SC team) may be included in the study. For the primary end point, any patient who received a needs assessment in the context of an integrated supportive pathway will be included. For the secondary end points, any patient participating in SC activities will be included.

For the cost-consequence analysis, costs from the perspective of the French national health insurance will be assessed during the study period. This will be calculated by administrative data review of internal allocated resources for pathway delivery and estimated costs of use of hospital services (unplanned hospitalization, consultations, and emergency visits recorded in the electronic medical records). Utility values will be assessed using the EQ-5D-5L. QALYs will be computed combining survival time by utility values. Long-term efficacy will be evaluated with the same efficacy outcomes at 6-month follow-up.

All analyses will be performed using SAS (version 9.4; SAS Institute) and R (version 4.0.3). Statistical significance will be defined with a $P<.05$.

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Data Collection, Management, and Auditing

The Biostatistics and Epidemiology unit at Gustave Roussy implemented an electronic case report form (eCRF) to allow secure online-direct data collection using REDCap. Each user has personal identifiers (user ID and password), and data access is strictly limited according to profiles: (1) hospital clinical research assistant (CRA), allowing data entry on the eCRF; (2) data manager, allowing the first data monitoring, perform consistency checks, and edit requests for clarification addressed to the investigator or hospital CRA; and (3) investigator profile, enabled to sign and validate the data electronically. Electronic learning is mandatory to access the eCRF. The password is configured when the profile is activated and must be changed every 6 months. For each patient included, the eCRF has to be completed by hospital CRA and signed by a study investigator. An audit trail within the system tracks all the changes made to the data. Data sources of the study include the eCRF, data from the WeShare platform, and data from the technology providers of remote care interventions (Resilience Care). SC referrals and attendance will be captured in the eCRF of the study. Attendance to each of the SC strategies will be retrieved from the electronic medical records or from a specific attendance-log database in the case of integrative therapies. Usability data from technology-enabled SC interventions will also be retrieved and transferred by Resilience Care. Patient-reported outcomes data will be collected and hosted by the WeShare platform and transferred to the investigator at the end of the study. Both patient-reported outcomes data and usability data from Resilience Care are interoperable with Redcap. Data collected will be managed in the Biostatistics and Epidemiology unit at Gustave Roussy. Standard institutional practices will be followed to maintain the confidentiality and security of data collected in this study. A copy of the consent form and documentation of consent will be stored in a locked cabinet or an encrypted, password-protected computer drive. All protected health information collected from the study eCRF will be encrypted and password protected. If any questionnaire is filled out on paper, this will be stored in a locked cabinet in a secured office in Gustave Roussy. Data will be stored until data analysis is complete, and then the data will be transferred to a centralized repository. Access to the repository will be limited to the principal investigator, coinvestigators, and associates from the original study team. Future studies requesting the use of the data must either be related to the original research study or will require separate institutional review board approval. To guarantee the authenticity and the credibility of the data in conformity with good clinical practices, auditing and quality assurance systems include (1) study management in accordance with standardized procedures at Gustave Roussy and (2) quality control performed by the CRA. Particularly, it is the responsibility of the CRA to (1) check that the investigator's file is correctly and regularly updated; (2) verify the signatures and validity of consent forms, fulfillment of eligibility criteria, validity of evaluation criteria, and adverse events; and (3) assure that reporting requirements are met. Regular meetings, held at least monthly, with the investigator team and study coordinator ensure a thorough review of study procedures, provide periodic updates on study progress (including patient enrollment numbers vs expected numbers), and address any procedural issues.

Equity, Diversity, and Inclusion

To ensure equity, diversity, and inclusion, social determinants of health and health-related social risks are screened at pathway entry. In addition, SC services targeting actionable unfavorable social determinants of health, such as social services and financial counseling, referrals to smoking and alcohol cessation programs, and nutritional counseling, are part of the actions delivered in the context of the pathways. In addition, plain language standards are applied to educational materials used to communicate pathway activities toward patients. An objective guidance on equity, diversity, and inclusion is publicly available for researchers and providers involved in this study via the WeShare platform [28], and a cultural competency training is being developed and will be recommended for all providers involved in pathway activities (screening and care delivery). Social determinants of health and demographics are collected during the study and will allow to monitor the participation of populations that have been historically excluded in SC interventions.

Patient Involvement in the Study

The SC pathways implemented in this study are co-designed with patient representatives upfront before deployment. Particularly, the study team meets with patient representatives at four key moments to foster cocreation: (1) at conceptualization to identify patient's SC needs, (2) during development of pathway components giving input and ideas of components to prioritize and how to model them, (3) just before implementation, and (4) after implementation. In addition, a patient representative is a member of the operational team (JA). The study protocol was also discussed in detail and approved by patient representatives. Across the study, qualitative and quantitative assessments of patient experience are planned. These data will serve to continuously improve pathway components and delivery to meet the needs of the patients.

Ethical Considerations

This study received regulatory approval by the institutional review board of Gustave Roussy and by the French national review board on September 4, 2023 (ID-RCB 2023-A01225-40). All participants (patients, providers, and managers) will provide informed and signed consent before taking part in the data collection process. Information that could potentially identify participants will be securely stored in a password-protected, locked database. Whenever possible, data will be deidentified through codification. Participants will not receive any monetary compensation for taking part in the study.

Results

As of February 2024, the evaluation of the SC pathway to prevent treatment-related burden for patients considered vulnerable with brain, head and neck,

thoracic, and neuroendocrine tumors has started, and 12 patients were enrolled in the study. The evaluation of the SC pathway for preventing treatment-related burden after breast cancer and the proactive survivorship care pathway (breast cancer) is expected to start in April 2024. Data will be analyzed once at least 70 patients have completed the study evaluations for one

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of the pathways. Results of this study will be sent for publication in peer-reviewed journals and will also be presented to the multidisciplinary implementation team so that SC pathways can be refined accordingly to better serve the needs of patients and providers. The clinical trial is registered at ClinicalTrials.gov (NCT06479057).

Discussion

Principal Findings

The proposed study will evaluate the implementation of distinct integrated proactive pathways of SC that are offered to patients treated at Gustave Roussy. Our study has several strengths. It is a master protocol for a prospective study on patients diagnosed with any type of cancer, across different moments of the cancer care continuum, using the RE-AIM framework to guide its evaluation. Quantitative analyses will use a variety of data, including validated patient-reported outcomes measures; experience and satisfaction surveys; and administrative, sociodemographic, health literacy, and clinical data. Furthermore, these will be enriched with preplanned qualitative assessments (focus groups) with several stakeholders. This study design will allow for analysis of patterns of unmet needs that are currently difficult to generalize. In addition, it may serve as an umbrella protocol for ancillary prospective studies focusing on each SC intervention. It is expected to lead to a higher level of coordination than the one achieved by independently conducted studies.

Despite the existing literature on interventions addressing SC needs in patients with cancer, their implementation has been suboptimal due to inconsistency of empirical evidence for interventions and the difficulties experienced by policy makers and health service providers in finding and assessing the evidence for interventions [15,43]. Typical obstacles include low level of awareness among oncologist on SC services, lack of a comprehensive multidisciplinary SC team, fragmented and unclear communication and referral processes for SC interventions, nonstandardized delivery of needs assessment and tailored referrals, uneven access to SC services among patients considered vulnerable and minority groups, incorporation of nonevidence-based practices, reimbursement and care valorization issues, and lack of integration with community-based resources [7].

Conclusions and Impact

This study will provide evidence on the implementation process of integrated, proactive SC pathways and will also inform future care delivery strategies to improve the reach and adoption of SC in oncology centers. It may serve as a model for other cancer centers trying to implement such integrated pathways. The analysis of quantitative and qualitative data collected from the patient, providers, and the health care organization for this study will be used to improve the design and delivery of SC pathways so that they meet the needs of patients and are feasible to be implemented according to a provider point of view. In addition, it will provide a detailed description of patients' unmet SC needs across the cancer care continuum in multiple cancer types.

This study will also add evidence on using technology to facilitate the delivery and evaluation of SC pathways. More specifically, for care, electronic patient-reported outcomes are integrated with medical records and used for needs assessment to screen patient vulnerability status being used to perform tailored SC referrals since diagnosis. Technology is also used for remote patient monitoring where electronic patient-reported outcomes are transmitted in real time to nurse navigators during active treatment phase with chemotherapy and targeted therapies. Several digitally enabled SC strategies are also implemented, such as physical activity, meditation, yoga, and cognitive behavioral therapies. Finally, for research purposes, technology is used to collect patient-generated data and clinical data for outcomes assessment.

This study has the potential to impact policy and global SC practices in oncology through several mechanisms. First, it can serve as a model to other cancer centers to build and implement coordinated and integrated SC pathways. It will report in detail the infrastructure required in cancer centers to deliver integrated SC. It will also introduce innovative methods to facilitate implementation, such as using technology to screen patients' needs, monitor symptoms, deliver specific SC interventions, and partner with community-based SC infrastructures. Furthermore, the proactive supportive care pathway approach is innovative as it allows to anticipate SC needs in a tentative manner to prevent treatment-related burden instead of using the standard reactive supportive care pathway approach currently used in most institutions. Finally, the presentation of this study in medical conferences and the publication of its results both in peer-reviewed journals and in lay media channels will also contribute to raise awareness among cancer care providers and policy makers to stimulate care and research initiatives of innovative models of SC delivery to improve patients' quality of life, addressing the physical and psychosocial needs of patients while improving the organization of health services.

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Data Availability

The data sets generated during and/or analyzed during this study will be available in the WeShare Data repository [28].

Conflicts of Interest

MAF declares receiving research funding from Resilience (for the institution) and Gilead (for the institution) and speaker honoraria from Novartis (for the institution). ADM declares expert testimony activities for Kephren, Techspert (personal; not related to this manuscript). FS declares receiving honoraria from Leo Phar, Viatris, Pharmanovia, Amgen, Gilead Sciences, BMS GmbH & Co. KG, and GlaxoSmithKline. IV-L declares receiving speaker honoraria from Amgen, AstraZeneca, Pfizer and Edimark, Novartis, Sandoz (institutional); a writing engagement from Pfizer and Edimark (institutional); research funding from Resilience Care (institutional); and travel support from Novartis. All other authors have no other conflicts to declare.

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Abbreviations

CRA: clinical research assistant
eCRF: electronic case report form
NCCN: National Comprehensive Cancer Network
QALY: quality-adjusted life years
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SC: supportive care

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Protocol

Evaluation of the Continuing Education Training “Beratende für Digitale Gesundheitsversorgung” (“Consultant for Digital Healthcare”): Protocol for an Effectiveness Study

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Abstract

Background: The digital transformation in health care requires training nursing and health professionals in the digitally competent use of digital assistive technologies (DAT). The continuing education training “Beratende für digitale Gesundheitsversorgung” (“Consultant for Digital Healthcare”) was developed to fill this gap. The effectiveness of the training program will be assessed in this study.

Objective: The primary objective is to record and measure the participants’ learning success. We will assess whether the previously defined teaching intentions, learning objectives, competencies, and participants’ expectations have been achieved and whether a transfer of learning occurred. The secondary objective is participant satisfaction and feasibility of the training. The tertiary objective is the successful transfer of DAT by participants in their institutions.

Methods: Approximately 65 nursing and health care professionals will participate in the pilot phase of the further training and evaluation process, which is planned in a mixed methods design in a nonsequential manner. The different methods will be combined in the interpretation of the results to achieve a synaptic view of the training program. We plan to conduct pre-post surveys in the form of participant self-assessments about dealing with DAT and content-related knowledge levels. Exploratory individual interviews will also be conducted to build theory, to examine whether and to what extent competence (cognition) has increased, and whether dealing (affect) with DAT has changed. Furthermore, an interim evaluation within the framework of the Teaching Analysis Poll (TAP) will occur. The knowledge thereby gained will be used to revise and adapt the modules for future courses. To assess the transfer success, the participants create a practical project, which is carried out within the training framework, observed by the lecturers, and subsequently evaluated and adapted.

Results: We expect that the learning objectives for the continuing education training will be met. The attendees are expected to increase their level of digital competence in different skills areas: (1) theoretical knowledge, (2) hands-on skills for planning the application and practical use of DAT, (3) reflective skills and applying ethical and legal considerations in their use, (4) applying all that in a structured process of technology implementation within their practical sphere of work.

Conclusions: The aim of this study and appropriate further training program are to educate nursing and health care professionals in the use of DAT, thereby empowering them for a structured change process toward digitally aided care. This focus gives rise to the following research questions: First, how should further training programs be developed, and which focus is appropriate for addressee-appropriate learning goals, course structure, and general curriculum? Second, how should a training program with this specific content and area be evaluated? Third, what are the conditions to offer a continued program?

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KEYWORDS

digitization; digital-assistive technologies; nursing and health care professionals; further training program; digital competence; digital healthcare; digital health; effectiveness study; training program; nursing; nursings; health professional; health professionals; transfer of learning; satisfaction; mixed-method; self-assessment; Teaching Analysis Poll; technology; technologies; innovation; exploratory; intervention

Introduction

The use of existing and development of new and innovative digital assistive technologies (DAT) offer great potential to meet both current and future challenges in care. DAT is a collective term for systems that are intended to support people in their diverse tasks with the aim of promoting independence and self-sufficiency, expanding one's own abilities, and promoting well-being [1,2]. In addition, it aims to improve quality of life when used in a planned, problem-oriented manner [3,4]. Furthermore, DAT is discussed as a useful support mechanism for caregivers by enabling them to be additional resources for health care provision. When used correctly, DAT creates relief opportunities and strengthens the willingness of family members to provide care [5,6]. In the sense of “on-site” assistance, DAT can thus increase the radius of action of people in their environment. The Organisation for Economic Co-operation and Development's aging-in-place approach is authoritative in this regard [7]. Consequently, health professionals can also benefit from the acquisition of transformative competencies and the participatory acquisition of health-related technical knowledge.

The targeted and user-centered use of digital technologies in the health care sector can lead to improved care and offers countless potential opportunities. Health and care professionals can be supported and relieved in their daily work, and the recipient of health services can experience an increase in the quality of the service thanks to a technically supported offering, thereby improving their own quality of life [8,9].

Of course, there are also ethical, social, and practical challenges concerning the use and implementation of digital technologies in the health care sector that need to be addressed. These are, for example, questions of acceptance, data protection, the corresponding integration into existing work processes, and how they are financed [10-16].

Since digitization in nursing care facilities has been comparatively underdeveloped to date, the sector is about to undergo a profound change [17-19]. Preparing the players involved for this and enabling them to actively shape the transformation and contribute their professional expertise to the development, design, and implementation of new technologies are necessary educational tasks for the success of this process. The necessary competencies should be learned in practical, daily-use scenarios in order for the technologies and new processes to be confidently integrated into nursing practice [20,21].

In order to systematically and broadly familiarize health care and nursing staff with the topic, it is necessary to anchor the teaching of digital competencies in education, training, and continuing education [22]. The need and willingness to learn the practical use of DAT are strong among nursing trainees [23]. Nevertheless, these requirements have so far been insufficiently implemented in the framework curricula of the federal states and in the design of targeted continuing education programs in Germany [23,24].

Comparable continuing education offerings, such as the “Online Campus Pflege” or “Pflege 4.0,” mostly focus on simply teaching digital skills and involve a relatively low number of hours, especially the face-to-face sessions [25-28]. In contrast to these offerings, the continuing education training “Consultant for Digital Healthcare” is characterized by a high level of application orientation, emphasizes ethical and reflective skills transfer, and, finally, is accompanied by and focuses on a practical project in which the implementation of digital technologies is supported in practice. In addition to imparting theoretical knowledge and practical application skills, the training aims to have a direct influence on digital transformation and to demonstrate and accompany the successful theory-practice transfer with the resulting projects.

This research project would like to close the gap and pursue the research question of how digital competencies should be taught in an addressee-appropriate manner in the form of continuing education in order to enable professionals to become sovereign designers and multipliers of the digital transformation in health care and health care delivery. Therefore, the training program “Consultant for Digital Healthcare” shall be evaluated.

Methods

Study Design

The study is planned as an exploratory intervention feasibility study with a follow-up survey. Through a mixed methods approach, the qualitative and quantitative survey methods used are combined in a nonsequential design [29,30]. This means that the results of the individual parts should enable a better overall understanding of the research questions raised [30].

The aim of the study is to evaluate whether the continuing education program for “Consultants for Digital Healthcare” empowers nursing and health care professionals to shape the digital transformation, specifically by serving as multipliers for transformation projects in various health care facilities. This is intended to promote the sustainable implementation of digital systems in practice. To achieve this, multipliers require diverse competencies, including not only technical expertise but also skills in guiding, advising, and training colleagues. The multiplier can be broadly considered a change agent. For this reason, digital competence is understood here as a cross-sectional skill that should enable a diverse, multidimensional approach to aspects of digital transformation.

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To be able to evaluate the structure, learning objectives, and didactic methods of further education scientifically, they can be examined using a mixed methods design. For this purpose, previously offered events were systematically reviewed through literature research and compared with existing theory (Project Format) on the development of digital competencies [12,17,31,32]. This comparison revealed that corresponding continuing education programs, which understand the conveyance of digital competency as a cross-sectional skill and thus aim for sustainable, connectable development, are underrepresented. Against this background, a blended learning concept was developed based on theoretical and evidence-based considerations that promote learning and practical transfer through action-guided instruction and aim to address the preceding research desideratum. The hypothesis underlying this is that the use and conveyance of specific assessment tools and action guides and the practical design of training situations promote learning transfer.

The level of outcomes reflects the learning and success monitoring of the further education program. We examine whether participants can build digital competencies in handling digital and assistive technologies and transfer them into practice. The structure primarily reflects the macrodidactic framework. This aims to assess whether the resources available and used for the learning situations were appropriate and effective. The process describes the course of the pilot phase and serves to monitor the success of implementation and feasibility of the project.

The evaluation of learning success will be conducted quantitatively through a self-assessment questionnaire and item questions on participants' knowledge content. The questions relate to the 2 dimensions of cognition and affect in dealing with digital and assistive technologies, with cognition being the primary dimension reflected. It is assumed that these dimensions function similarly to attitudinal characteristics. The questionnaire was developed along various areas of action-oriented competence development in health care, such as areas of professional, social-communicative, ethical-reflective, and general methodological competence. [33]. By promoting self-efficacy, either through the building of knowledge content or the reduction of barriers to deal with DAT, transfer into practice as well as acceptance in use can be promoted. For the qualitative assessment of the training by the participants, guided interviews are used. The questions were developed using the SPSS (collect, check, subsume, and sort) method [34]. These will be evaluated using qualitative content analysis, according to the method described by Kuckartz and Radiker [35]. Deductively derived categories from theory will be examined using a coding system and checked for fit. Furthermore, the coding allows for the formation of inductive categories to identify further codes, which is intended to promote theory building and examination in the field of digital competencies.

Another tool consists of standardized questionnaires to evaluate specific training situations. These assess various dimensions of the teaching situation, including spatial setup, lecturer skills, and atmosphere.

Additionally, through a practical project conducted by the participants and the associated observation by the lecturers in terms of open observation, the behavioral dimension of the participants dealing with DAT becomes visible and is documented by the lecturers using observation sheets. Further education thus provides the opportunity to assess not only acquired competencies in closed training settings but also directly with the participants and to finally reflect on them.

We planned 3 measurement points for the study. The first measurement point (t1) occurs before direct participation. Here, self-assessment questionnaires and the participants' knowledge of dealing with DAT are recorded. The second measurement point occurs at the halfway mark of the respective conducted modules (t2). At this point, the first revision of the modules is made using the Teaching Analysis Poll (TAP). The third measurement point occurs after the completion of the continuing education (t3). Here, the self-assessment questionnaires or knowledge levels for dealing with DAT are recorded again. Furthermore, at this point, the qualitative individual interviews are conducted. Since participants are not subject to strict scheduling due to the modular structure, there are no scheduled dates but individual measurement points for the participants.

The target group is nursing and health professionals, and the prerequisite for further training is basic vocational training in those professions. With this target group in mind, the training is designed according to the Deutscher Qualifikationsrahmen (German qualification framework) with a requirement level of level 4 [36]. In addition, there are no specific requirements for participation in the training.

The participants in the study were informed about the various survey instruments and gave their consent. The data are stored on an access-restricted cloud and evaluated and analyzed in an anonymized form, complying with the General Data Protection Regulation (GDPR).

Description of the Intervention: Continuous Education to Become a "Consultant for Digital Healthcare" ("Beratende für Digitale Gesundheitsversorgung")

In order to enable health care professionals to deal confidently with digital technologies and help shape the digital transformation, the training to become a "Consultant for Digital Healthcare" ("Beratende für digitale Gesundheitsversorgung") was funded by the Saxony-Anhalt Ministry of Labor, Social Affairs, Health and Equality. The novel training is currently in the pilot and development phase under the direction of the AG Versorgungsforschung | Pflege im Krankenhaus and the Dorothea Erxleben Learning Center of the Medical Faculty of Martin Luther University Halle-Wittenberg. The addressees of the training are health and nursing professionals primarily from the federal state of Saxony-Anhalt. For the pilot phase, approximately 65 participants are registered and went through a modularized curriculum with a workload of 200 teaching units and 5 days of classroom training over a period of 9 months.

On the one hand, the further training is characterized by a strong application orientation that, in addition to theoretical introductions to technical, legal, and financial aspects of digitization, focuses in particular on practical familiarization

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and experience with new technologies and the promotion of facility-related digitization projects, thus advancing theory-practice transfer and the training of competent multipliers. On the other hand, a special focus is placed on the training of ethical-reflective competencies in order to learn to ethically assess the integration of digital assistance systems into the care process and possible consequences of increasing digitization.

The designed self-study and preparation phase initiates learning content prior to the days of attendance and familiarizes the participants with the first set of content. In the follow-up phase, extensive tasks are designed to ensure sustainable results and learning transfer.

The training is divided into 3 modules (Table 1).

The learning goals listed in Textbox 1 are set to be achieved with the further training program. They were selected based on existing overviews of the necessary acquisition of skills in the area of digital health care [25].

Table 1. Overview of the 3 modules in the "Beratende für Digitale Gesundheitsversorgung" training program.

Module	Components
Module I: Fundamentals of digital transformation and its relevance for the nursing professions	• Raising awareness and introducing digital health care • ePA[a], DiPA[b], DiGA[c],and more • Ethical and legal aspects as a prerequisite for digital transformation
Module II: Digital transformation in a value-oriented and professional manner in professional practice	• Supply process integration and scenario-based reflection on digital assistive technologies • Evidence-based digital transformation—fundamentals of evidence-based work in the context of digital transformation • Practical application based on the SEQI[d] process, including practical support
Module III: Promoting personal development	• Basics of project management, moderation methods, creative methods • Project work on digital transformation at the facility

[a]ePA: electronic health record.

[b]DiPA: digital nursing applications.

[c]DiGA: digital health applications.

[d]SEQI: Sensitization, Evaluative Introduction, Qualification, Implementation.

Textbox 1. Select learning goals of the continuing education training program.

- Learners acquire basic knowledge of the digital transformation of health care.
- The learners are sensitized to the need to acquire skills for digital transformation in the context of health care and know its importance for cross-sector care.
- Learners develop a reflective attitude toward digital and assistive technologies.
- The learners know the background and objectives of digital health applications.
- Learners assess the relevance of digital health applications in relation to the professional context.
- Learners can identify, analyze, reflect on, and solve ethical problems by getting to know various ethical theories and models and using practical case studies to demonstrate how to systematically work on and think through an ethical problem.
- Learners know the meaning of ethics in the context of their profession by becoming familiar with the codes, guidelines, and profession-specific guidelines that express this connection.
- Learners can evaluate individual digital assistive technologies (DAT) ethically by getting to know models for the ethical evaluation of DAT.
- Learners can transfer theoretical knowledge into their professional practice by learning the practical use of various technologies and being able to discuss and reflect based on scenarios.
- Learners can critically reflect on the opportunities and risks of using DAT as an additional resource for nursing process planning by testing this with the help of case vignettes.

Study Population

All participants in the continuing education program for "digital health care consultants" were eligible for inclusion in the study. The target group for participation is fundamentally trained nursing and health care professionals. Since the training is funded by the state of Saxony-Anhalt, participation is also primarily offered to professionals from Saxony-Anhalt. Due to the high demand also from outside Saxony-Anhalt, a quota system was for applicants from other federal states as long as there were free places available.

The inclusion criteria were health professionals (nurse practitioner, health care nurse, nursing specialist, pediatric nurse practitioner, health and pediatric nurse practitioner, geriatric nurse, surgical technologist assistant, anesthesia technician assistant, emergency paramedic, midwife and maternity nurse,

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physiotherapist, occupational therapist) who are at least 18 years old and have sufficient knowledge of written and spoken German.

The exclusion criteria are a lack of knowledge of the German language and inability to consent.

Quantitative Study

The "Reflection sheet for recording the competencies of a nurse" questionnaire was designed to record the digital competencies of nursing and health care professionals. Using it, the participants' self-assessments rate their professional, social-communicative, ethical-reflective, and methodological competencies on a 5-level Likert scale. This takes place as a pre-post comparison, by recording once at the beginning of the training (t1) and once after completion of the training (t3). The questionnaire was completed online and made available via Ilias 1 month before the start of the training. Participants are encouraged to complete the questionnaire as fully as possible. The questionnaire for self-assessment records the subjective feeling of competence by the participants in the areas with corresponding questions for self-assessment (Table 2).

Furthermore, the knowledge levels of the participants were recorded before the start of the modules in order to make possible learning gains visible. This also took place in the sense of a pre-post comparison using single-choice, multiple-choice, open, and closed questions.

Table 2. Reflection sheet to record the competencies of the nursing staff in the pre-post assessment.

Category	Items for self-reflection
1. Expertise	• Knowledge of DAT[a] and their classification options • Knowledge of the possible uses of DAT • Technically correct preparation, implementation, and follow-up of the DAT • Recognizing the client's individual care needs • Knowledge of how to use DAT • Knowledge of SEQI[b] as a structured implementation model • Applying SEQI as a structured implementation model • Knowledge of the legal basis of DAT
2. Social-communicative competence	• Knowledge of psychological, pedagogical, sociological, and communicative basics within project work • Client-appropriate communication and empathy • Recognizing and responding to nonverbal signals • Carrying out advice, guidance, and training • Knowledge of different models of (joint) decision-making • Ability to cooperate and work in a team
3. Ethical-reflexive competence	• Knowledge of ethical theories and models • Knowledge of the importance of ethics in the context of nursing • Identification of an ethical problem • Analyzing an ethical problem • Justifying your own actions ethically • Ethical assessment of individual DAT • Knowledge of models for the ethical assessment of DAT • Application of models for the ethical assessment of DAT • Reflected deployment or reflected deployment planning of DAT
4. Methodological competence	• Knowledge of scientific research • Conducting scientific research • Organization and coordination of work processes • Presentation techniques • Selection and use of assessment instruments

[a]DAT: digital assistive technologies.

[b]SEQI: Sensitization, Evaluative Introduction, Qualification, Implementation.

Qualitative Study

One series of interviews was planned to qualitatively assess the learning success of the participants and evaluate the overall design of the further training. A total of approximately 10 interviews were planned. The selection of inquiries took place according to the principle of convenience sampling; the achievement of statistical representativeness is not envisaged [37].

By means of the interview guide, the survey was carried out with the clear aim of retrieving specific knowledge necessary to answer the precise and theoretically embedded research question. Accordingly, the interviews conducted after the completion of the training dealt with the following questions or main topics: (1) learning success of the participants (different competencies), (2) participant satisfaction with the course and contents of the training, (3) transfer success as applied in the project work in the facilities.

Thus, the quantitative assessments of the participants in the training are supplemented and explained by the interviews. The methodological recourse to expert interviews for data collection

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results from the fact that conducting expert interviews already presupposes a good knowledge of the field of investigation, which is guaranteed by the target group. In the expert interviews, the focus was on narrative elements relating to the ideas of a meaningful training concept. The guidelines were developed iteratively using the SPSS method according to [38]. The methodical preparation was developed in the sense of the mechanism-exploring research paradigm of qualitative content analysis according to [39].

Teaching Analysis Poll (TAP)

TAP is a method for the interim evaluation of teaching units, in which a group discussion takes place with the participants in the absence of the teacher. The evaluation is moderated by uninvolved staff members. The participants first discuss the following 3 questions in small groups: (1) What do you learn most from in this event? (2) What makes your learning difficult? (3) What suggestions for improvement do you have for points perceived as obstructive?

The answers from the groups were discussed in plenary, unclear answers were clarified, and the results were checked for their majority ability. A summary of the majority-acceptable results was sent to the teachers in a feedback meeting, which should take place promptly after the TAP. Ideas are jointly developed on how to implement the participants' suggestions for modifying the content. Subsequently, the teacher discusses with the participants how the training can be modified, if necessary, during the training event and who can contribute to this and how. The goal is to provide feedback for teachers and stimulate reflection and exchange about teaching and learning in the professional development event.

Open Questions in the Questionnaire Survey

The qualitative part of the quantitative preliminary survey included 2 open-ended questions: (1) What are your expectations for continuing education? (2) What difficulties might arise with regard to continuing education?

Ethical Considerations

Ethics approval was given for the survey by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg (processing number: 2023-143 21 06 23).

Results

Data were collected at the beginning of, in the course of, and at the end of the training program. The program ran from September 2023 until July 2024. The funding of the project started in September 2022. In the course of this period, there were several data points. This study will evaluate the learning outcome of the training program. A change in digital competences in the pre-post comparison is expected. To further investigate the reasons for the expected change, 10 expert interviews were conducted to generate structured feedback from the participants. We expect that the learning objectives of the training will be met. The attendees are expected to increase their level of digital competence in different skills areas: (1) concerning their theoretical knowledge, (2) concerning their hands-on skills planning for the application and practical use of DAT, (3) their reflective skills and applying ethical and legal considerations in their use, (4) applying all that in a structured process of technology implementation within their practical sphere of work. At the time of publication, data analysis and evaluation were underway, and we plan to publish the results in spring 2025.

Discussion

This pilot study will evaluate a new training program for nurses and allied health services workers to become a “Consultant for Digital Healthcare.” The aim of this study and the appropriate continuing education training program is to educate nursing and health care professionals on the use of DAT. As a result, it is expected that the digital skills of the participants will increase in accordance with the survey instrument used. In addition, the structure and content of the further training will be analyzed and evaluated in a differentiated manner so that targeted adjustments can be made for further runs. This focus gives rise to the following research questions: First, how do continuous education training programs need to be developed, and which focus is appropriate for addressee-appropriate learning goals, course structure, and the general curriculum. Second, which digital competences do the individuals in question require? Third, how should a training program with this specific content and area be evaluated? Fourth, what are the conditions for continued program offering?

In particular, it is expected that the participants will have acquired new knowledge and can apply it in practice. This application focus will be promoted in particular through the project work. The social form of group work and informal exchange between participants is also expected to be crucial for learning success. The special orientation of the continuing education training, with a high level of application relevance, will play a decisive role in preparing the participants for the dynamic and project-related digital transformation of health care [20,21].

This builds on previous research work that initially aimed to assess the needs for digital skills in nursing. A structured training process for the introduction of digital technologies in the facilities was then piloted and evaluated [21]. Ultimately, this preparatory work will be made accessible to a large number of skilled workers in a wide area through further training and converted into a continuing educational program.

The special feature of the training is that it addresses a heterogeneous target group, with many different professional groups from health care, extending from the operational level to the management level. In addition, the aim is to cover as wide a range of technologies as possible in order to provide not only an overview but also a selection of possible technologies for participants’ own practical project.

This study assessing continuing education has some limitations. On the one hand, only methods of subjective self-assessment by the participants are used, which is subject to bias and misjudgment. This point needs to be carefully considered during the evaluation of the results. Furthermore, the pilot phase of the

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further training program is rather short, which is a necessary prerequisite for further development and a first evaluation of the results and effects of the training on the development of digital competences of the participants. As for the projects within the context of the training program, they are accompanied by the study content and team but need to be developed and implemented with further stakeholders and companies in the real world as a so-called living-lab environment. This implies levels of complexity that cannot be fully controlled by the training program but can still be guided and prepared. The sample size of 65 participants is rather small, but for a first pilot phase, it is enough for the first evaluation and interference regarding appropriate training methods for allied health care workers.

Looking at the results in a broader context, it is important to note that there is still a long way to go to achieve targeted digitally supported health care, for which targeted training and further education are keystones and promoted by the program outlined. General standards for the training should be outlined and accepted on a political level. Furthermore, new technologies must also be developed explicitly for nursing care, with the explicit participation of specialists to address the specific needs of the sector.

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Conflicts of Interest

None declared.

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Abbreviations

DAT: digital assistive technologies
GDPR: General Data Protection Regulation
SPSS: collect, check, subsume, and sort
TAP: Teaching Analysis Poll

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Protocol

Smartphone App for Prehospital ECG Transmission in ST-Elevation Myocardial Infarction Activation: Protocol for a Mixed Methods Study

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Abstract

Background: Timely diagnosis and treatment for ST-elevation myocardial infarction (STEMI) requires a coordinated response from multiple providers. Rapid intervention is key to reducing mortality and morbidity. Activation of the cardiac catheterization laboratory may occur through verbal communication and may also involve the secure sharing of electrocardiographic images between frontline health care providers and interventional cardiologists. To improve this response, we developed a quick, easy-to-use, privacy-compliant smartphone app, that is SMART AMI-ACS (Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction Acute Coronary Syndromes), for real-time verbal communication and sharing of electrocardiographic images among health care providers in Ontario, Canada. The app further provides information about diagnosis, management, and risk calculators for patients presenting with acute coronary syndrome.

Objective: This study aims to integrate the app into workflow processes to improve communication for STEMI activation, resulting in decreased treatment times, improved patient outcomes, and reduced unnecessary catheterization laboratory activation and transfer.

Methods: Implementation of the app will be guided by the Reach, Effectiveness, Acceptability, Implementation, and Maintenance (RE-AIM) framework to measure impact. The study will use quantitative registry data already being collected through the SMART AMI project (STEMI registry), the use of the SMART AMI app, and quantitative and qualitative survey data from physicians. Survey questions will be based on the Consolidated Framework for Implementation Research. Descriptive quantitative analysis and thematic qualitative analysis of survey results will be conducted. Continuous variables will be described using either mean and SD or median and IQR values at pre- and postintervention periods by the study sites. Categorical variables, such as false activation, will be described as frequencies (percentages). For each outcome, an interrupted time series regression model will be fitted to evaluate the impact of the app.

Results: The primary outcomes of this study include the usability, acceptability, and functionality of the app for physicians. This will be measured using electronic surveys to identify barriers and facilitators to app use. Other key outcomes will measure

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the implementation of the app by reviewing the timing-of-care intervals, false "avoidable" catheterization laboratory activation rates, and uptake and use of the app by physicians. Prospective evaluation will be conducted between April 1, 2022, and March 31, 2023. However, for the timing- and accuracy-of-care outcomes, registry data will be compared from January 1, 2019, to March 31, 2023. Data analysis is expected to be completed in Fall 2024, with the completion of a paper for publication anticipated by the end of 2024.

Conclusions: Smartphone technology is well integrated into clinical practice and widely accessible. The proposed solution being tested is secure and leverages the accessibility of smartphones. Emergency medicine physicians can use this app to quickly, securely, and accurately transmit information ensuring faster and more appropriate decision-making for STEMI activation.

Trial Registration: ClinicalTrials.gov NCT05290389; https://clinicaltrials.gov/study/NCT05290389

International Registered Report Identifier (IRRID): DERR1-10.2196/55506

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KEYWORDS

ST-elevation myocardial infarction; m-health; cardiac systems of care; knowledge mobilization; digital health; smartphone technology; technology; STEMI; Canada; implementation; mobile phone

Introduction

ST-segment elevation myocardial infarction (STEMI) requires efficient communication and collaboration to ensure timely care. Clinical practice guidelines recommend patients who present to a percutaneous coronary intervention (PCI)–capable center should receive PCI within 90 minutes, and those presenting to a non–PCI-capable center should receive PCI within 120 minutes [1]. Those receiving care beyond these time thresholds have an increased risk of mortality, reinfarction, congestive heart failure, and rehospitalization compared with those who receive care within these time thresholds [2-4]. However, achieving timely care can be challenging, especially for patients in rural and remote areas with limited resources.

Despite guideline recommendations, patients fail to receive timely care [5]. There are over 7000 STEMI cases in Ontario every year [5], the majority of which present to non–PCI-capable centers [6]. The Ontario Ministry of Health has set a target that more than 75% of patients should receive care within the time thresholds mentioned above. However, only 49% of patients presenting to a PCI-capable hospital and 44% of patients presenting to a non–PCI-capable center received care within these thresholds [5]. This may be due to several factors, including local geography, weather constraints, delay in diagnosis, delay in transfer, or delay in management by the STEMI team [7]. The COVID-19 pandemic also had a significant impact on the delivery of STEMI care. Prepandemic (2019), 42% of patients presenting to a PCI-capable center in Ontario received care within 90 minutes. This reduced to 28% during the pandemic (2020). Similarly, those presenting to non–PCI-capable centers noted a decline from 47% of patients receiving care within 120 minutes down to 37% during the pandemic [8]. This highlights an important and ongoing need.

The current process for STEMI activation in the Hamilton, Ontario, Canada, health care region typically relies on the emergency medicine (EM) physician making a diagnosis of STEMI and contacting the interventional cardiologist (IC) on call. The suspected STEMI case is reviewed by telephone, which is coordinated through a STEMI hotline. A 12-lead electrocardiography (ECG) is essential in the diagnosis of a STEMI, and, as per the 2021 American Heart Association policy statement, should be communicated with the IC before activating the STEMI team and accepting the patient for transfer [9]. The approved process for ECG transmission is by a fax machine and, while secure, this method has its challenges. For example, it requires both the referring EM physician and the IC to have easy access to a functioning fax machine. This is not always the case, especially for the IC, who is often away from the hospital while on call. Where the ECG cannot be transmitted to the IC, the risk of inappropriate transfer to the catheterization laboratory can occur, potentially leading to false or "avoidable" activation, where the team is activated when the patient does not, in fact, have a STEMI or evidence of significant coronary artery disease [10]. That may lead to inefficient use of scarce resources, downstream delays for other patients, and unnecessary risk of procedure for the patient transferred [11].

An alternative to fax transmission is texting a photo of the ECG from the EM physician to the IC, using a mobile phone. However, standard texting software is not privacy-compliant and may lead to a breach of personal health information. Some providers have explored the use of a secure smartphone app as a strategy to transfer ECG data while overcoming privacy concerns. There are limited data showing the effectiveness and acceptability of this technology. For example, a retrospective, before-and-after trial using an app for communication at a center in the United States was also able to demonstrate a 22% improvement in the timing of care [12]. Similarly, a study performed in China demonstrated a reduction in the time to activate the STEMI team, the timing of intervention, and an increase in the proportion of patients meeting the guideline-recommended timing for care [13]. Furthermore, in New York, ECG images from a sample of STEMI cases were managed through an app, leading to decreased treatment times [14,15]. While these studies are important to demonstrate the feasibility of the use of an app, they were small and were performed in health care system contexts very different from what exists across Canada. Furthermore, the apps used may not conform to Canadian-specific privacy requirements for smartphone technology. As such, it is less likely that these apps would be approved for use in our local setting.

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Recognizing the need for improved communication with the challenges described, a team of local clinicians created a fast, secure, easy-to-use, and privacy-compliant smartphone app, that is, SMART AMI-ACS (Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction Acute Coronary Syndromes), which allows real-time ECG review, thus allowing rapid decision-making. The app is designed to be used for all cases where a STEMI is suspected by EM physicians following a diagnostic ECG. CorHealth Ontario, a provincial organization that oversees the quality of cardiac care across Ontario, recently released recommendations supporting the need for enhanced communication for STEMI activation during the COVID-19 pandemic [16]. Initial data from one hospital group in our region (Niagara Health), on the acceptability and user experience among EM and IC physicians, shows promise [17], but is insufficient to promote the technology as an evidence-based innovation for care. By expanding the use of the app and conducting this implementation research study, we hope to further close the knowledge gap on a potentially useful method for optimizing the timeliness of care in our region [18-20].

The SMART AMI-ACS app research study will enable the assessment of the app's implementation and impact across 14 hospitals and urgent care centers, with a population of 1.4 million people [21]. We will work in collaboration with the Centre for Evidence-Based Implementation (CEBI) at Hamilton Health Sciences (HHS) to conduct pre- and postimplementation surveys that assess the barriers and facilitators to implementing the app, and the acceptability and sustainability of continued app use. The findings of this project will be shared with our knowledge user group with the goal of scaling our experience to implement the app across the remaining STEMI systems in Ontario and beyond. We will also explore opportunities to expand the use of the app to the prehospital ambulance services in this region. The overall aim of this mixed methods evaluation is to assess the feasibility and effectiveness of integrating a smartphone app in the treatment of suspected STEMI.

Methods

Overview

We propose a multicenter, mixed methods observational study focused on EM physicians who care for patients presenting to our 14 regional partner hospitals (a list of participating hospitals can be found in Multimedia Appendix 1) with suspected STEMI. The study will use a pre-post design to evaluate the implementation and use of a clinical intervention, the SMART AMI-ACS app. This evaluation will be supported by a quantitative assessment of STEMI registry data that are already collected through the SMART AMI project at HHS, data based on app uptake and use, and quantitative and qualitative data from participating physicians' completion of the pre- and postimplementation surveys. No new patient data will need to be collected for the purpose of this study. Objectives and outcomes for this study will be guided by the use of the Reach, Effectiveness, Acceptability, Implementation, Maintenance (RE-AIM) framework, an evaluation framework for the implementation and assessment of health interventions [22].

Clinical Intervention

All local EM and IC physicians will be invited to use the app to communicate, transmit the ECG images, and activate the STEMI team, regardless of participation in this research study. We plan to use the app as the primary means of STEMI activation in our health region. The app enables transmission of up to 3 ECG images, which can be reviewed immediately by the IC (screenshots of the app can be found in Multimedia Appendix 2). The app further provides information about diagnosis, management, and risk calculators for patients presenting with acute coronary syndrome [1]. Full security testing, including penetration testing, has been completed as part of an initial pilot study [17].

Study Population and Recruitment

The study will take place at the HHS general site (HGH), a larger quaternary-care cardiac center, and the 13 referring emergency departments. EM physicians working at partner emergency departments included in this study will receive email invitations to join the research study. Participation will involve providing feedback about the use of the app between 6 and 8 months after app implementation. All EM physicians working at one of the referring centers will be eligible to participate.

For evaluation of the impact of the app on timing and appropriateness of care, we will access data on a consecutive sample of patients experiencing STEMI referred from the partner emergency departments to HGH during the period of study entered into the regional STEMI database, between January 1, 2019, and March 31, 2023.

Sample Size

We estimate that approximately 184 EM physicians are working at the referral centers in our region. As this is primarily a descriptive study examining the barriers and facilitators to the implementation of the app, we have not performed a formal sample size calculation. Based on our experience in an initial pilot study in Niagara Health, we are confident that a sufficient number of EM physicians will participate by downloading the app and providing feedback about the use of the app through a survey.

There are approximately 800 patients with STEMI per year, transferred and treated in the HGH cardiac catheterization lab. As we will be running this study over the course of 1 year, we expect to review aggregate patient-level data on approximately 800 patients with STEMI in the STEMI database. We anticipate that this is a sufficient number for regression modeling using an interrupted time series (ITS) approach.

Analysis

Quantitative and qualitative analysis of survey results will be conducted by the research team, and adjustments will be made to the app and its implementation based on the feedback received. Survey results will be reviewed to generate themes around barriers and facilitators to app use, as well as user satisfaction, usability, and feasibility for wider distribution using Microsoft Excel and NVivo 12 (Lumivero).

Descriptive and inferential statistics will be used for quantitative data derived from the STEMI registry and physician surveys.

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Continuous variables will be described using either mean with SD or median and IQR (25th and 75th percentiles) at pre- and postintervention periods by the study sites. Categorical variables, such as false or "avoidable" activation, will be described as frequencies (percentages). Unadjusted comparisons of the outcomes between pre- and post-app implementation periods will be performed using *t* tests (means), Mann-Whitney *U* tests (medians), or chi-square or Fisher exact tests (if expected cell counts are less than 5 for categorical variables). For each outcome, an ITS regression model will be fitted to evaluate the impact of the app besides any underlying trend, after adjusting for potential confounders, patient demographics, and clinical characteristics, as well as variables such as days of the week, times of day, and seasons. For a continuous outcome, an ITS regression model of the following form will be fitted: $Y_i = \beta_0 + \beta_1 T_i + \beta_2 X_i + \beta_3 T_i X_i + \beta_4 \text{Confounder}_{1i} + \ldots + \beta_p \text{Confounder}_{pi} + \varepsilon_i$, where, for the i^{th} patient, Y_i is the continuous outcome, T_i is the time elapsed since the study started, X_i is a dummy variable representing pre (X_i=0) and post (X_i=1) app periods, and ε_i is the random error that follows a normal distribution. Here, β_1 is the adjusted average change per unit time in the outcome in pre-app period (pre-app trend/slope), β_2 is the adjusted average level change in the outcome following the app, and β_3 is the slope change following the app. For a categorical outcome (yes or no), a log-binomial regression model will be fitted. All the variables considered for the linear model will also be considered for this model. A *P* value .05 will be considered statistically significant. Statistical analyses will be performed using Stata 13.1 (StataCorp) and SAS 9.4 (SAS Institute) software.

Ethical Considerations

This study is approved by the Hamilton Integrated Research Ethics Board (#13643). Consent will be implied if the EM physician decides to submit information to the IC through the app. Participating EM physicians can withdraw by not using the app to transmit ECGs and instead reverting to the current practice of communication with the IC. EM physicians will be required to read information about the app's privacy and required to click "Accept" before app use.

Consent to provide feedback will be obtained from physicians using a question at the beginning of the surveys. Participants will be notified that they can withdraw by exiting the survey without submitting it. As survey responses will be anonymous, physicians will not be able to withdraw their data after survey submission. The intervention (use of the app) represents a process change and is noninvasive with minimal risk. Individual patient consent will not be required, as patient data reviewed for this project are already being collected as standard practice through the STEMI registry to improve quality-of-care metrics.

Objectives and Outcomes

The RE-AIM framework will be used to guide our evaluation of the app [22].

Objective 1

Reach means ensuring the broad availability of the app to all emergency departments and physicians in the region with 80% (240/300) of EM physicians signing up for the app. First, the number of full-time EM physicians who have downloaded the app is divided by the total number of full-time EM physicians in the sample (data from the Amazon Web Services Portal). Second, the number of EM physicians who have used the app to transmit and discuss at least 1 case (data from the Amazon Web Services Portal).

Objective 2

Effectiveness means assessment of any changes in evidence-based quality-of-care metrics for STEMI care, which includes (1) time from diagnosis to ambulance departure, (2) number of false positive activations, and (3) door-to-balloon time. First, timing-of-care intervals (including door-to-balloon time) for every STEMI activation. These data are already routinely collected by the STEMI registry for CorHealth auditing; therefore, there are no new data to collect. These include, but are not limited to, parameters, that are (1) EM registration to time of first ECG (reported on the ECG), (2) time of first ECG to time of EM physician assessment (reported on the patient chart), (3) time from EM physician assessment to call to the STEMI hotline (documented on the operator record), (4) time of the first call to the STEMI hotline to the time at which the IC made the decision to activate the STEMI team (documented on the operator record), (5) the time of STEMI team activation to the time for transfer to the cardiac catheterization lab at HGH (time stamp on the paramedic transport records), and (6) the time of arrival HGH to the first intervention (time stamp on the cardiac catheterization lab records).

Second, false positive activation, which is, cases where the patient with a presumed STEMI is transferred for PCI but found to have minimal to no coronary artery disease on angiography. These numbers will be divided by the total number of STEMI cases to determine false activation rates. These outcomes will be measured using data collected as part of the STEMI registry and SMART AMI program. This will be subdivided into (1) the number of cases where the patient was noted to have ST-elevation or ECG criteria for STEMI, and (2) the number of cases where the patient was not noted to have ST-elevation or ECG criteria for STEMI.

Objective 3

Acceptability means the assessment of the functionality of the app in real-life applications. Pre- and postimplementation surveys will assess the acceptability and usability of the app and feedback on the app following use. Questions will be based on selected domains of the Consolidated Framework for Implementation Research [23].

Objective 4

Implementation means encouraging routine use of the app across the region. The goal was to have 80% (240/300) of eligible STEMI activations use the app (excluding those cases presenting directly from emergency medical services or the emergency department of the HGH) to measure sustainability. These outcomes will be measured using data collected as part of the STEMI registry and SMART AMI program, which are (1) number of STEMIs activated through the app divided by the

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total number of STEMI activations and (2) number of STEMI activations that did not occur through the app.

Objective 5

Maintenance means sustainability of the adoption and metrics over a 1-year period after implementation. Some factors of maintenance include (1) measuring patient-level outcomes monthly to evaluate the sustainability of effect. This will be measured using data collected as part of the STEMI registry and SMART AMI program, and (2) obtaining physician survey data from 6 to 8 months postintervention. This will be collected through a feedback survey hosted on REDCap (Research Electronic Data Capture; Vanderbilt University).

Data Collection and Management

As stated above, patient data will be acquired from the regional STEMI registry as part of the SMART AMI program. Patient data from the SMART AMI program are collected and deidentified by a research assistant at HHS, a community of hospitals in the Southwestern region of Ontario, from which the participating hospitals in this study reside. These deidentified patient data are shared with CorHealth, a provincial oversight body, for measuring quality and stored in an encrypted and password-protected server at HHS. A study coordinator (and postgraduate clinical fellow) will periodically audit a proportion of cases and ECGs to ensure accuracy in transcription. No protected health information will be entered into the app, as ECGs are recognized by the receiving IC according to the name of the sending physician and the time stamp.

Participating EM physicians will be invited to provide feedback about their experience with the app through a survey administered using the REDCap application [24]. Invitations will be sent by email from local physician chiefs or by research project staff approximately 6 to 8 months after implementation of the app. Participants will have 4 weeks to complete the survey, with email reminders sent as required. Survey data will be anonymous but will be associated with a specific hospital site. Survey questions will be based in part on selected domains of the Consolidated Framework for Implementation Research [23], with the goal of identifying additional barriers and facilitators to uptake and any improvements to the app's content and implementation process. Use of the app will be tracked using Google Data Analytics for Firebase.

From a technical standpoint, the app is available on the Apple App Store and Google Play Store. It has undergone multiple user-interface expert assessments and optimization, as well as privacy testing. The app is encrypted and secure as assessed by Niagara Health and an external third-party penetration test (CyberHunter Solutions, Inc). The app is small (15-20 MB) and fast without failures in transmissions over the 12 months of the pilot study. A team of expert information technology consultants is available to onboard new physicians or solve any potential technical issues that arise with the app, and updates can be made immediately. For health care providers, the app is accessible, quick, easy to use, reliable, and secure. Data are not stored on the physician's smartphone. However, the IC app can access the secure cloud server to access the ECGs, thus enabling real-time decision-making.

Data are encrypted and transmitted to a secure server, which stays within Ontario, Canada. The app has strict password requirements. As the IC app can access personal health information, it automatically logs out the user if the app is idle for more than 15 minutes. Data are also automatically deleted from the server every 7 days, and the data are no longer available beyond this time frame unless downloaded by the clinical and research team. This is done to reduce the risk and severity of a privacy breach.

Results

Funding for this study began in April 2021. Preimplementation survey data were collected in the Fall of 2021 and app implementation data collection began in April 2022 and was completed in March 2023. By the end of March 2023, 84% (253/300) of physicians had downloaded the app. The analysis is anticipated to be completed by Fall 2024.

Discussion

Principal Findings

The delivery of timely and appropriate care is crucial for patients with STEMI, as blocked coronary arteries need immediate intervention to restore blood flow [1]. The app being evaluated in this study is designed to help with the communication and ECG transmission between EM and IC physicians so that patients can be transferred for care quicker than current practices allow. In addition, the app offers up-to-date educational resources that allow physicians to follow current standards of care regarding the optimal choice and delivery of STEMI reperfusion strategies [1].

The 1-year implementation study period will allow for user testing and feedback on the app, which will be gathered through qualitative assessment and used for app improvement in future iterations. Furthermore, results and evaluation of effectiveness may inform the expansion of the app intervention to local ambulance services and other health regions in the province.

Dissemination Plans

Research findings will be shared with our knowledge user partners: CorHealth Ontario, Regional Emergency Services Steering Committee, and Regional Partner hospitals and emergency medical services paramedics. In addition, the findings will be shared through typical academic channels, such as conference presentations, regional rounds, and peer-reviewed journal publications. We will also leverage social media networks in cardiology and EM. Finally, we plan to distribute findings through department communication networks at each of the partner hospitals. The regional STEMI program (SMART AMI) has developed a strong network of collaboration with the 13 referring hospitals within our health region over the past 10 years that includes the development of a mechanism for feedback of STEMI quality-of-care outcomes to partner hospitals and referring clinicians. We will partner with local program leads to roll in the smartphone app as part of the STEMI care process.

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Limitations

There are several limitations that are important to highlight. First, in order to use the app, access to a reliable internet connection is needed; however, we do not expect this to be a challenge in EM departments where users can connect to their hospital Wi-Fi. This may be a greater challenge in the future when implemented among paramedics in the community, especially in rural and remote communities. The user's smartphone operating system must also be kept up to date, which is often done automatically. If not done and there are issues in downloading or using the app, our team will provide support to address the issue. Users will need to be capable of using mobile phone technology to capture ECG image photos. Although we expect all users to know how to use the camera on their smartphone, there may be a variety in their skills of acquiring high-quality ECG images to enable accurate diagnosis. To understand this, we will be conducting a structured analysis of the ECG quality and whether it is sufficient to make a diagnosis. For security reasons, users of the IC version of the app are logged out after 15 minutes of inactivity; therefore, password recollection may be a challenge. To address this, a biometric authentication feature was added to enable immediate login based on the user's facial recognition. The data on timing and accuracy of care are retrospective and may be prone to errors or missing data. However, a full-time staff is assigned to collect this information and ensure accuracy based on detailed chart reviews for each case. As such, missing data are expected to be rare in this study. To minimize bias in the feedback survey results, all eligible physician participants will be invited to complete the survey, and participants will be made aware that the results will be anonymous.

Conclusions

Smartphone technology is well integrated into clinical practice and widely accessible. The proposed solution being tested is secure and leverages the accessibility of smartphones. EM physicians can use this app to quickly, securely, and accurately transmit information ensuring faster and more appropriate decision-making for transfers.

Acknowledgments

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Authors' Contributions

HM, MKN, JDS, and MM contributed to the design of the study, with input from RS, SJ, MT, MW, and GR. KJC and KM will manage the ethics application, implementation, and evaluation of the app. QI will lead the statistical analysis. All authors contributed to writing the manuscript and approved the final version.

Conflicts of Interest

HM is an inventor of the smartphone application used in this study. There is no specific financial conflict of interest to declare as the tool is being used in research and not commercialized. The other authors declare no conflict of interest.

Multimedia Appendix 1
List of participating hospitals.
[DOCX File , 14 KB - resprot_v13i1e55506_app1.docx]

Multimedia Appendix 2
Screenshots of SMART AMI-ACS (Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction Acute Coronary Syndromes) app.
[DOCX File , 332 KB - resprot_v13i1e55506_app2.docx]

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Abbreviations

CEBI: Centre for Evidence-Based Implementation
ECG: electrocardiography
EM: emergency medicine
Fax: facsimile
HGH: Hamilton Health Sciences General Site
HHS: Hamilton Health Sciences
IC: interventional cardiologist
ITS: interrupted time series
PCI: percutaneous coronary intervention
RE-AIM: Reach, Effectiveness, Acceptability, Implementation, Maintenance
REDCap: Research Electronic Data Capture
SMART AMI-ACS: Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction Acute Coronary Syndromes
STEMI: ST-elevation myocardial infarction

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Protocol

Prevention of Recurrent Spontaneous Preterm Delivery Using Probiotics (Clostridium butyricum, Enterococcus faecium, and Bacillus subtilis; PPP Trial): Protocol for a Prospective, Single-Arm, Nonblinded, Multicenter Trial

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Abstract

Background: The rate of recurrent spontaneous preterm delivery (sPTD) ranges between 27% and 34% and is 22.3% in Japan. Although it currently remains unclear whether probiotics prevent sPTD, retrospective studies recently reported a reduction in the rate of recurrent sPTD with the administration of probiotics including *Clostridium* spp., which induce regulatory T cells that play an important role in maintaining pregnancy.

Objective: The objective of this trial is to evaluate the preventative effects of available oral probiotics, including *Clostridium butyricum*, on recurrent sPTD.

Methods: This is a prospective, single-arm, nonblinded, multicenter trial in Japan. The sample size required for this trial is 345 pregnant women with a history of sPTD, considering a clinically significant reduction in the relative risk of 30% (risk ratio=0.7). The primary endpoint is the rate of recurrent sPTD at <37 weeks of gestation. The secondary endpoints are the rate of sPTD at <34 weeks of gestation, the rate of recurrent sPTD at <28 weeks of gestation, the ratio of intestinal *Clostridium* spp. (detected by next-generation sequencing), and bacterial vaginosis (using the Nugent score).

Results: The trial procedures were approved by the Clinical Research Review Board of Toyama University Hospital (SCR2020008) on March 31, 2021. The trial was registered on the Japan Registry of Clinical Trial website on April 28, 2021. Recruitment began on May 1, 2021, and the trial is estimated to finish on March 31, 2025.

Conclusions: The findings will clarify the rate of recurrent sPTD following probiotic administration including *Clostridium butyricum*. Outcomes from this trial will inform clinical practice and guide future randomized controlled trials.

Trial Registration: Japan Registry of Clinical Trials jRCTs041210014; https://jrct.niph.go.jp/latest-detail/jRCTs041210014

International Registered Report Identifier (IRRID): DERR1-10.2196/59928

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(JMIR Res Protoc 2024;13:e59928) doi:10.2196/59928

KEYWORDS

clostridium; multicenter open label trial; preterm delivery; probiotics; recurrent spontaneous preterm delivery; prospective single-arm; spontaneous preterm delivery; infection; oral probiotics; pregnant women; pregnant; pregnancy; neonates; preterm births; systematic review; meta-analysis

Introduction

According to a systemic analysis, 13.4 million (12.3-15.2 million) live neonates were estimated to be delivered as preterm births (<37 weeks) in 2020 (9.9% [9.1%-11.2%] of all births) worldwide [1]. In addition, the number of neonate (aged 0 days to 27 days) deaths due to preterm birth complications is estimated at 938,000 [2]. Preterm neonates are at an increased risk of mortality and morbidity, such as sepsis, periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), cerebral palsy, seizures, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), feeding difficulties, and visual or hearing disorders [3]. Between 30% and 35% of preterm births are indicated, 65% to 70% are spontaneous preterm deliveries (sPTD) [4], and the rate of recurrent sPTD ranges between 27% and 34% [5]. In Japan, the rate of recurrent sPTD was recently reported to be 22.3%, based on real-world data from 2014 to 2016 [6].

sPTD is caused by multiple pathological processes [4,5,7], with intra-amniotic inflammation or infection being the main cause [7-9]. As the clinical characteristics of sPTD, severe intra-amniotic inflammation and infection were more frequent in the earlier weeks of gestation [8-10]. Since preterm labor, the preterm premature rupture of membranes, and cervical insufficiency develop due to the collapse of the intrauterine environment, such as by inflammation or infection, it is difficult to avoid sPTD after the appearance of clinical symptoms. Therefore, precautions are needed to prevent sPTD in pregnant women at a high risk of sPTD starting in the first trimester or before pregnancy.

In 2013, alliums (garlic, onion, leek, and spring onion) and dried fruits (raisins, apricots, prunes, figs, and dates) were reported to be associated with a decreased risk of sPTD [11]. In another prospective cohort study reported in 2019, intake of fermented food, such as miso soup, yogurt, and soybeans, before pregnancy significantly reduced the risk of early sPTD at <34 weeks [12]. According to a large-scale, epidemiological, observational, cohort study conducted in Norway, the consumption of probiotic milk during early pregnancy was correlated with a lower risk of preterm delivery (adjusted odds ratio 0.79, 95% CI 0.64-0.97; *P*=.03) [13]. As one of the pathological characteristics in the intestinal flora of pregnant women with sPTD, the abundance of *Clostridium* spp. was significantly lower than in pregnant women who delivered at term [14]. These findings of large-scale epidemiological studies and the specificity of the intestinal flora strongly suggest the potential of prebiotics or probiotics to improve the intestinal microbiota and prevent sPTD.

On the other hand, clinical studies using probiotics have not been sufficiently powered to prevent sPTD [15]. The findings of a systematic review and meta-analysis showed that the consumption of probiotics or prebiotics during pregnancy did not affect the risk of sPTD [16,17]. However, the types of probiotics or prebiotics used in each trial varied. Moreover, the initiation of their administration was not constant, or the characteristics of pregnant women at risk of sPTD differed. Therefore, findings on the efficacy of probiotics to prevent sPTD have been inconsistent.

Clostridium spp. induce the production of regulatory T (Treg) cells [18], which are essential for the maintenance of pregnancy [19-22]. Since the abundance of *Clostridium* spp. is significantly reduced in sPTD cases [14], the number of Treg cells produced may be insufficient to maintain pregnancy. Therefore, probiotics including *Clostridium* spp. have the potential to prevent sPTD in women at risk of sPTD. In 2 retrospective cohort studies, probiotics including *Clostridium* spp. reduced the recurrence of sPTD. One study showed that the rate of preterm delivery at <32 weeks of gestation was significantly reduced in pregnant women at a high risk of sPTD [23], while the other demonstrated that the rate of recurrent sPTD was significantly reduced (9.8% vs 30.1%, *P*=.002) by probiotics including *Clostridium* spp [24].

Based on this clinical and pathological background, we are planning a phase 3, prospective, single-arm trial to confirm the preventative effects of probiotics, including *Clostridium butyricum*, on sPTD in pregnant women with a history of sPTD. This trial will evaluate the rate of recurrent sPTD based on that reported in a perinatal registration database from the Japan Obstetrics and Gynecology Society for the perinatal center (22.3%) [6], which covers approximately 25% of deliveries in Japan.

Methods

Trial Design

The Prevention of Recurrent Spontaneous Preterm Delivery by Probiotics (PPP) trial is designed as a prospective, single-arm, nonblinded, multicenter clinical trial to confirm the prevention of sPTD by oral probiotics in pregnant women with a history of sPTD. In Japan, 31 hospitals are participating, and the trial is scheduled to run from April 1, 2021, to March 31, 2025 (registration period was from June 1, 2021, to March 31, 2024.) The design of the trial is summarized in Figure 1. This trial will be performed according to the ethical principles originating from the Declaration of Helsinki and the Clinical Trial Act.

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Figure 1. A summary of the design of the Prevention of Recurrent Spontaneous Preterm Delivery by Probiotics (PPP) trial. After informed consent, the oral administration of probiotics, including *Clostridium butyricum* (10 mg/tablet), *Enterococcus faecium* (2 mg/tablet), and *Bacillus subtilis* (10 mg/tablet), is initiated at 10-14 weeks. BFS: Bristol Stool Form Scale; CRP: C-reactive protein; CSS: constipation scoring system; NGS: next-generation sequencing; WBC: white blood cell count.

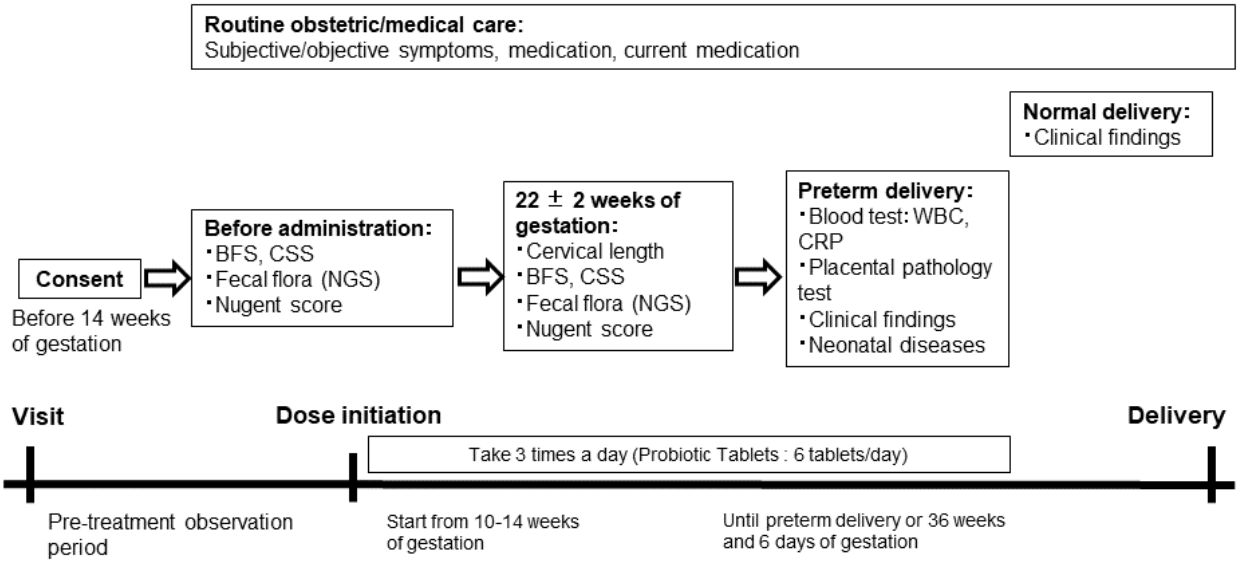

Study Participants

Recruitment Setting

We will recruit pregnant women who meet all the inclusion criteria and do not have any of the listed exclusion criteria. In Japan, most women visit an obstetrical clinic between 5 weeks and 8 weeks of gestation. After confirming the eligibility criteria, we will register pregnant women. In this trial, a history of sPTD is defined as preterm delivery by labor pains, clinical chorioamnionitis, intrauterine infection, or histological chorioamnionitis diagnosed after preterm delivery, with or without obstetrical complications. Informed consent will be obtained from pregnant women prior to their registration. Pregnant women can review the details of this trial on the Japan Registry of Clinical Trial.

Inclusion Criteria

The inclusion criteria were women who had been pregnant <15 weeks, with a history of sPTD, aged 18 years to 43 years at consent, and who provided written informed consent.

Exclusion Criteria

The exclusion criteria included pregnant women with a history of indicated preterm birth, such as abruptio placentae, gestational diabetes mellitus, pregnancy-induced hypertension, eclampsia, HELLP (Hemolysis, Elevated Liver Enzymes, and Low Platelets) syndrome, pulmonary embolism, cerebral hemorrhage, pulmonary edema, acute fatty liver of pregnancy, placenta previa, fetal growth restriction (≤–2.0 SD), oligohydramnios, polyhydramnios, fetal diseases with chromosomal abnormalities, fetuses with multiple malformations, fetal edema, fetal dysfunction, and pregnant women with histories of sPTD for a multiple pregnancy. In addition, pregnant women with a multiple pregnancy (singleton cases after multifetal pregnancy reduction or another fetal death are also excluded), a severe physical disability, with a history of serious hypersensitivity or anaphylactic reactions caused by probiotics (including lactomin, *C. butyricum*, and amylolytic bacillus), using a medical drug or supplement including *Clostridium* spp. within 2 weeks before enrollment, with a history of cervical conization, with uterine malformation, with cervical polyps and massive genital bleeding before 10 weeks of gestation, with subchorionic hematoma and massive genital bleeding at the time of obtaining informed consent, who regularly use steroids, with diabetes mellitus, with autoimmune disease, diagnosed or treated for malignant disease at the time of informed consent (cases in which malignant disease has been completely cured may be included), with fetal morphological abnormalities at the time of informed consent, currently participating in other clinical trials or those who previously participated in a clinical trial and for whom at least 1 month has not passed since the last dose of the study drug was taken, or classified as inapplicable for this trial by the investigators are excluded.

Study Procedures

The trial schedule is shown in Figure 2. All registered pregnant women will receive oral probiotics. The probiotics used are already available drugs including *C. butyricum* (10 mg/tablet), *Enterococcus faecium* (2 mg/tablet), and *Bacillus subtilis* (10 mg/tablet), because the probiotics containing *C. butyricum* alone are not commercially available in Japan. Probiotics are started from 10 weeks to 14 weeks and stopped at 36 weeks 6 days of gestation, late miscarriage, or sPTD. The maximum duration of administration is 188 days.

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Figure 2. The schedule of the Prevention of Recurrent Spontaneous Preterm Delivery by Probiotics (PPP) trial. CSS: constipation scoring system; NGS: next-generation sequencing; sPTD: spontaneous preterm delivery.

	Before administration	Administration of medicine			Delivery	4 weeks in case of sPTD	Discontinued
		Start	22 ± 2 weeks	Ended (36 weeks and 6 days)			
Range	~ 14 weeks	10 ~ 14 weeks	21 ~ 24 weeks				
Informed consent	●						
Background of patient	●						
Registration	●						
CSS, Bristol test	●		●				
Intestinal flora (NGS)	●		●				
Bacterial baginosis (Nugent score)	●		●				
Cervical length			●				
Neonatal information					●	●	
Medication diary		←	—	→			
Obstetrical disease(s)		←	—	→			
Adverse event(s)		←	—	→			
Record of reason(s)							●

Before the initiation of probiotics, stool (for the NGS) and vaginal secretion (for the Nugent score) samples will be collected, and the Bristol Stool Form Scale (BFS; Figure 3) and the constipation scoring system (CSS: Table 1) are rated. The BFS expresses the characteristics of stool as numbers: the lower the number, the less water the stool contains and the harder it is, whereas the higher the number, the more watery and soft it is. Stool is classified into 7 levels from Type 1 to Type 7, with Type 3 to Type 5 being considered the normal range of stool, and Type 4 stool being ideal. The BFS is evaluated before and during treatment. The CSS results in a subjective score of 30 points resulting from 7 items being rated on a scale from 0 to 4 and 1 item rated on a scale from 0 to 2; the items include the number of bowel movements per week, residual bowel movements, frequency of abdominal pain, and time required for bowel movements [25]. In this trial, the CSS is a modified CSS consisting of 26 points, excluding the “duration of constipation,” and is evaluated before and during treatment. At 22 ± 2 weeks of gestation, these samples will be collected again, the questionnaire will be completed for evaluations during probiotic administration, and cervical lengths will be measured.

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Figure 3. The Bristol Stool Form Scale.

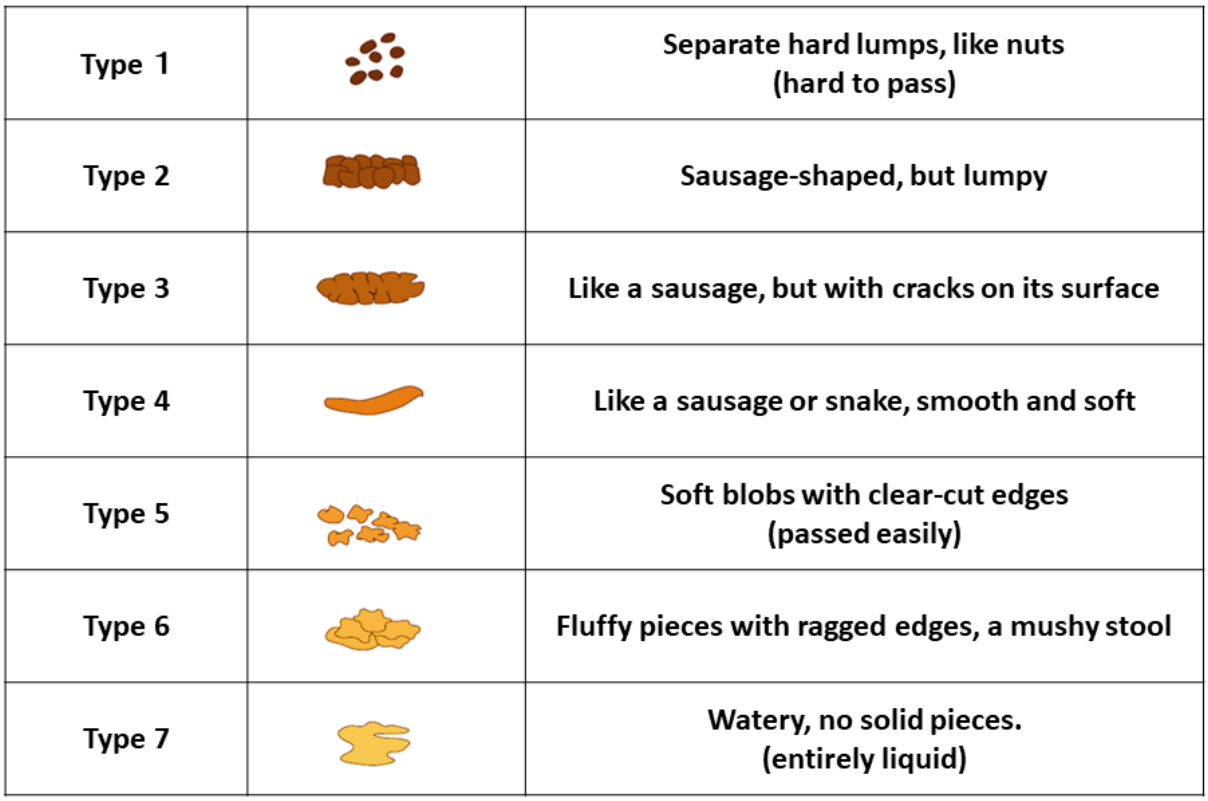

Table 1. The Constipation Scoring System (total of 30 points possible).

Items evaluated	Points				
	0	1	2	3	4
Frequency of bowel movements	1-2 times per 1-2 days	2 times per week	Once per week	Less than once per week	Less than once per month
Painful evacuation effort	Never	Rarely	Sometimes	Usually	Always
Feeling of an incomplete evacuation	Never	Rarely	Sometimes	Usually	Always
Abdominal pain	Never	Rarely	Sometimes	Usually	Always
Time spent on the toilet to defecate (minutes)	<5	5-9	10-19	20-29	≥30
Type of assistance	No assistance	Stimulative laxatives	Digital assistance or enema	—[a]	—
Unsuccessful attempts to evacuate per 24 hours	0	1-3	4-6	7-9	≥10
Duration of constipation (years)	<1	1-5	6-10	11-20	≥21

[a]Not applicable.

In this trial, any treatment to prevent late miscarriage or sPTD, such as progesterone (17-alpha-hydroxyprogesterone caproate, which is used at a dosage of 125 mg and covered by the national health insurance system in Japan but is not used to prevent sPTD in the first trimester), cerclage, tocolysis, and antibiotics, could be used because there is no evidence to support their prevention of sPTD. The previously reported rate of recurrent sPTD of 22.3% in Japan [6] is presumed to be the result of these treatments.

Endpoints

The primary endpoint is the rate of recurrent sPTD at <37 weeks of gestation. The secondary endpoints are the rate of sPTD at <34 weeks of gestation, the rate of recurrent sPTD at <28 weeks of gestation, the proportion of stillbirth, constipation (using the BFS and CSS), the ratio of intestinal *Clostridium* spp. (as measured using next-generation sequencing [NGS]), and bacterial vaginosis (using the Nugent score). In cases of sPTD, histological chorioamnionitis, or funisitis, neonatal prognosis (gestational weeks at delivery, birth weight, hospitalization in

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the neonatal intensive care unit [NICU], neonatal death, respiratory distress syndrome, PVL, BPD, IVH, and NEC) will be evaluated.

In this trial, to analyze the composition of the microbiota (using NGS), a stool collection brush and storage tube (Fujifilm WAKO Pure Chemicals) containing DMSO-EDTA salt solution buffer [26] was prepared, and 2 tubes were delivered to each participant. Pretreatment feces were collected in the tubes by each participant and stored under cool conditions. Posttreatment (22±2 weeks of gestation) feces were also collected. These tubes were compiled at ReLife Inc at a temperature <4°C, then transported to the Kyoto Institute of Nutrition and Pathology for analyses of the microbiota composition.

Fecal DNA was extracted using a commercial kit (QuickGene DNA tissue kit, KURABO) as described elsewhere [27]. The procedure for metagenomic 16S rRNA sequencing using Miseq (Illumina) was the same as that previously described [28]. The processing of sequencing data, including quality filtering, chimera checks, operational taxonomic unit definitions, and taxonomy assignments, was performed using QIIME1.9.1, USEARCH, and UCHIME in the same manner as previously described [28]. Alpha-diversity metrics (the Chao1 or Shannon index) were calculated using QIIME1.9.1 software. To calculate the distances between samples, beta-diversity was estimated using the UniFrac metric and visualized using a principal coordinate analysis.

Adverse Event Reporting and Harms

As for safety evaluations, all adverse events will be reported and evaluated. Adverse events refer to any unfavorable change in clinical symptoms, laboratory data, or disease temporally associated with probiotics used in this trial, regardless of whether it is considered to be related to the trial product. However, unfavorable clinical symptoms such as constipation, which could be considered due to maternal physiological changes, are not treated as an adverse event. When an adverse event occurs, patients will receive appropriate treatment, and the cost will be supported by the national health insurance. All serious adverse events that could be assumed to be caused by probiotics used in this trial must be reported and investigated to the Clinical Research Review Board of Toyama University Hospital. In addition, the information will be shared with all investigators.

Data Analysis

Sample Size Calculation

Based on the previously reported rate of recurrent sPTD at <37 weeks of gestation of 22.3% in Japan [6], we considered a clinically significant reduction in the relative risk to be 30% (risk ratio=0.7). Assuming the effect of the probiotics corresponds to a risk ratio of 0.7 (with the rates under the null hypothesis being 0.223 and under the alternative hypothesis being 0.156) and using a 1-sided test with a significance level of .025 and a power of 80%, the required sample size was calculated to be 298 participants. We considered a withdrawal rate of 10% based on the incidence of miscarriage at <22 weeks of gestation [29] and a dropout rate of 5% and, thus, set the required sample size to 345 participants.

Statistical Analysis

The efficacy analysis set consists of all patients enrolled in this trial except for patients who will not be treated with the protocol treatment, whose data will not be collected after the protocol treatment starts, who are designated to be ineligible after enrollment, or in whom pregnancy was terminated before 21 weeks of gestation for any reason.

The safety analysis set consists of patients who will be treated with the protocol treatment at least once. Frequencies and percentages are calculated for discrete variables, and summary statistics (mean, standard deviation, minimum, median, or maximum) are calculated for continuous variables. As the primary analysis, we will conduct a binomial test on the rate of recurrent sPTD at <37 weeks of gestation.

Data Management

After registration, the maternal characteristics (the number of pregnant histories, the number and gestational weeks of previous miscarriage or sPTD, date of birth, age, height, weight, BMI, smoking, uterine myoma, allergy, medical history, diseases, internal medicine) will be recorded. BFS and CSS will be calculated before probiotic initiation and again at 22±2 weeks of gestation, at which time cervical length will also be recorded.

In cases of term delivery, information, such as neonatal body weight, sex, and Apgar scores, will be recorded. On the other hand, in cases of preterm delivery, more information will be recorded for the 4 weeks after delivery, including histological chorioamnionitis, funisitis, and neonatal prognosis (hospitalization in the NICU, neonatal death, respiratory distress syndrome, PVL, BPD, IVH, and NEC). All trial data are housed within a Research Electronic Data Capture (REDCap) system in Toyama University Hospital. The local principal investigator in each hospital will input the trial data online. Data management will be performed every 6 months by the data center in Toyama University Hospital.

Monitoring

This trial is monitored to ensure the safety of pregnant women, that the protocol is being followed, and that data are being accurately collected. The monitor is not involved in this trial and is approved by the investigator.

Ethical Considerations

The protocol for this trial was approved by the Clinical Research Review Board of Toyama University Hospital (SCR2020008) on March 31, 2021. This trial was registered in the Japan Registry of Clinical Trials on April 28, 2021. All participants will be required to sign and date an informed consent form. Each participant will be given a unique ID for the PPP trial and will be registered in the RedCap system without personal information such as their name. Participants will receive probiotic tablets at no cost but will not receive any monetary compensation.

Results

Recruitment began on May 1, 2021. This trial is ongoing, and 345 pregnant women with a history of sPTD have been

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registered to date. Data collection is expected to be completed by October 2024, and the trial will finish on approximately March 31, 2025.

Discussion

The reasons behind the effectiveness of probiotics or prebiotics for preventing sPTD have not been verified by meta-analysis [15-17]; potential reasons include differences between the characteristics of pregnant women at risk of sPTD, the types of probiotics or prebiotics, and initiation of their administration. In addition, the main probiotic used in previous research was *Lactobacillus* spp. This trial will examine the effects of probiotics, including *Clostridium* spp., which induce the production of Treg cells that play an important role in maintaining pregnancy [18-22]. There are a few reports that probiotics, including *Clostridium* spp., improved clinical symptoms in inflammatory bowel disease [30,31]. However, there is no report showing changes in intestinal flora or Treg cells. The proliferation of Treg cells in this study cannot be shown as direct evidence at present, and all theories remain a matter of speculation.

We are carrying out a prospective, single-arm, nonblinded, multicenter clinical trial to confirm the efficacy of oral probiotics including *C. butyricum*, *E. faecium*, and *B. subtilis* for the prevention of sPTD starting in the first trimester in pregnant women with a history of sPTD. *E. faecium* and *B. subtilis* can coexist symbiotically, and they increase their metabolic products and themselves [32]. In addition, *B. subtilis* and *C. butyricum* can coexist symbiotically, and they increase their metabolic products and themselves [33]. Therefore, these 3 bacteria, namely *E. faecium*, *B. subtilis*, and *C. butyricum*, might coexist symbiotically. Furthermore, proliferation of *C. butyricum* might further lead to the proliferation of *Clostridium* spp. in the human intestine [34,35]. Hence, the presence of these 3 types of bacteria is predicted to increase the proliferation of *Clostridium* spp. in the intestine.

The rate of sPTD in each country is different depending on region, ethnicity, income, and the level of medical care. Although the rate of sPTD in Japan tends to be low [1] and the recurrence of sPTD is also low [6], it is important in this single-arm trial to investigate the rate of recurrent sPTD (22.3%) using reliable data [6]. Antimicrobial agents could affect the prolongation of pregnancy. Therefore, we would like to consider excluding cases in which antibiotics were used for a long time (1 week or more). However, most cases who receive antibiotics for a long time have sPTD. Therefore, we did not exclude study participants. In addition, the use of antibiotics in the first trimester would be rare.

The first limitation of the PPP trial is that it has not been proven whether intestinal *Clostridium spp*. directly induce the proliferation of Treg cells. This trial focuses on the rate of recurrent sPTD. Second, this is a single-arm trial with no placebo group. This clinical trial involves pregnant women and requires the administration of oral medicine for a long time, approximately 6 months. Although a randomized controlled trial (RCT) is considered the gold standard for evaluating the efficacy of probiotics, pregnant women and children are considered a high-risk group for RCTs. In such trials, real-world data could be used and analyzed for comparison [36]. If the results of this single-arm trial show a significant reduction in the rate of recurrent sPTD, an RCT may be performed in the near feature. Probiotics are not expensive, and their use is already widespread. Therefore, the use of probiotics to prevent recurrent sPTD may be easily used in many countries. In lower-income countries with a high rate of sPTD, probiotics could contribute to the prevention of recurrent sPTD.

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This trial is sponsored by TOA Biopharma Co Ltd. The funds needed for the Prevention of Recurrent Spontaneous Preterm Delivery by Probiotics (PPP) trial will be paid every year when its schedule proceeds as planned. Oral probiotics, including *Clostridium butyricum* (10 mg/tablet), *Enterococcus faecium* (2 mg/tablet), and *Bacillus subtilis* (10 mg/tablet), will be provided free of charge. The authors declare that they have no competing interests. TOA Biopharma Co Ltd will not be involved in the collection, analysis, or interpretation of data.

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Data Availability

The data set used and analyzed in this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

SY, KO, AN, and SS developed the original concept for the trial, and SY, TK, KK, SI, TT, DC, KO, AN**,** and SS designed the study. SY is the principal investigator of the trial. SI is a biostatistician and responsible for statistical planning and analyses. TK, KK, TT, and DC provided advice about the outcome measures for the protocol. SY wrote the manuscript, and the other authors revised and commented on the subsequent draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BFS: Bristol Stool Form Scale

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BPD: bronchopulmonary dysplasia
CSS: constipation scoring system
HELLP: Hemolysis, Elevated Liver Enzymes, and Low Platelets
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
NGS: next-generation sequencing
NICU: neonatal intensive care unit
PPP: Prevention of Recurrent Spontaneous Preterm Delivery by Probiotics
PVL: periventricular leukomalacia
RCT: randomized controlled trial
RDS: respiratory distress syndrome
REDCap: Research Electronic Data Capture
sPTD: spontaneous preterm delivery
Treg: regulatory T

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Protocol

Overdose Detection Among High-Risk Opioid Users Via a Wearable Chest Sensor in a Supervised Injecting Facility: Protocol for an Observational Study

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Abstract

Background: Opioid overdose is a global health crisis, affecting over 27 million individuals worldwide, with more than 100,000 drug overdose deaths in the United States in 2022-2023. This protocol outlines the development of the PneumoWave chest biosensor, a wearable device being designed to detect respiratory depression in real time through chest motion measurement, intending to enhance early intervention and thereby reduce fatalities.

Objective: The study aims to (1) differentiate opioid-induced respiratory depression (OIRD) from nonfatal opioid use patterns to develop and refine an overdose detection algorithm and (2) examine participants' acceptability of the chest biosensor.

Methods: The study adopts an observational design over a 6-month period. The biosensor, a small device, will be worn by consenting participants during injecting events to capture chest motion data. Safe injecting facilities (SIF) in Melbourne, Victoria (site 1), and Sydney, New South Wales (site 2), which are legally sanctioned spaces where individuals can use preobtained illicit drugs under medical supervision. Each site is anticipated to recruit up to 100 participants who inject opioids and attend the SIF. Participants will wear the biosensor during supervised injecting events at both sites. The biosensor will attempt to capture data on an anticipated 40 adverse drug events. The biosensor's ability to detect OIRD will be compared to the staff-identified events that use standard protocols for managing overdoses. Measurements will include (1) chest wall movement measured by the biosensor, securely streamed to a cloud, and analyzed to refine an overdose detection algorithm and (2) acute events or potential overdose identified by site staff. Acceptability will be measured by a feedback questionnaire as many times as the participant is willing to throughout the study.

Results: As of April 2024, a total of 47 participants have been enrolled and data from 1145 injecting events have already been collected, including 10 overdose events. This consists of 17 females and 30 males with an average age of 45 years. Data analysis is ongoing.

Conclusions: This protocol establishes a foundation for advancing wearable technology in opioid overdose prevention within SIFs. The study will provide chest wall movement data and associated overdose data that will be used to train an algorithm that

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allows the biosensor to detect an overdose. The study will contribute crucial insights into OIRD, emphasizing the biosensor's potential step forward in real-time intervention strategies.

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KEYWORDS

wearable sensor; overdose; opioid-related deaths; injecting opioid use; medically supervised injection center; opioid induced respiratory depression; mobile phone; opioid overdose; drug overdose; Australia; United States; chest biosensor; biosensor; wearable device; respiratory depression; algorithm; detection algorithm; observational design; illicit drugs; safe injecting facilities; naloxone; wearable

Introduction

Worldwide, more than 27 million people have an opioid use disorder and more than 150,000 people die each year from opioid overdose [1,2]. In the United States, in 2022-2023, there are estimated to be more than 100,000 drug overdose deaths [3]. Naloxone is an opioid antagonist and an antidote to opioid overdose. Effective interventions, such as take-home naloxone are available [4,5] but coverage is incomplete and they are not suited to many overdose situations, such as when people may be alone or the onset of their overdose goes unnoticed [6-8]. In such situations, intervention requires detection of the overdose to signal the need for a response.

Recently, technological developments in wireless "wearable" devices have enabled real-world, real-time measurement of physiological functioning and these devices have grown hugely in popularity [9-11]. Devices in relation to overdose could capture a wide range of different parameters but it is important that these are sensitive, accurate, and reliable. Opioids affect the control of breathing and can cause fatal overdoses, usually by respiratory failure. Respiratory depression, referring to the characteristic effect of opioid drugs, is slowed and shallow breathing (or reduced chest movement) which can sometimes lead to changes in levels of blood gasses and a suppression of the usual responses to these changes. This can lead to hypoxia, respiratory failure, and death. However, currently available wearable devices lack the ability to analyze and interpret respiratory depression data in real time and with sufficient accuracy to achieve medical device regulatory clearance. They are also not practical or economically viable for individual use in the community [12]. A chest sensor that reliably detects the overdose breathing signature, in real time, could alert family or friends to help or could directly alert emergency service. This could save lives when fully developed and used in the community.

The PneumoWave chest biosensor is a small device (Figure 1; 40 mm in diameter and 14 mm in height) that sticks onto the chest using a small plastic patch (an [electrocardiographic] ECG sticker). The device measures chest motion, and consequently will be able to detect changes in chest movement. However, to be relevant to the detection of overdoses in the community, research is required on people at high risk of opioid-induced respiratory depression (OIRD) to capture chest motion during an injecting event, where the absence or presence of overdose can be externally verified. This will then be used to develop and refine sensitive and specific OIRD detection algorithms that can interpret chest movement data in real time on a smartphone or tablet without the need for live clinician analysis and interpretation.

Figure 1. Image of PneumoWave chest sensor and location of placement on the body.

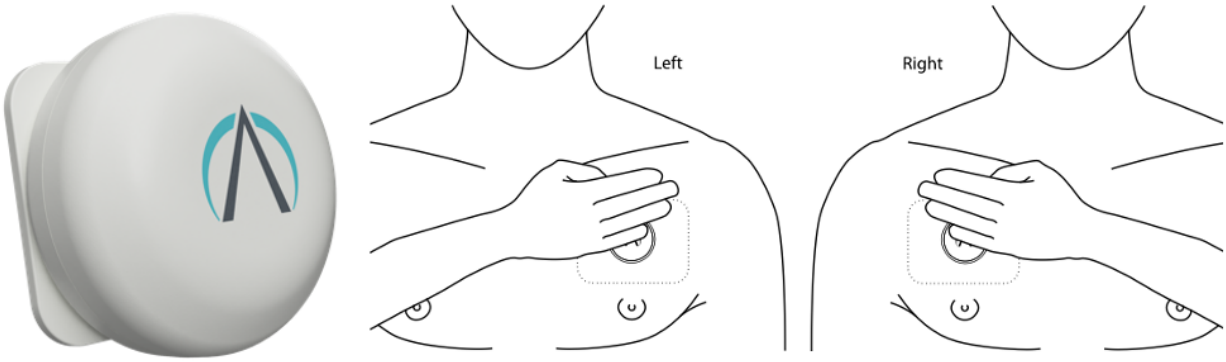

Those who inject opioids die at a much higher rate than other drug-using groups [13]. A safe injecting facility (SIF), also known as a medically supervised injecting center or room, drug consumption room, safe consumption room, or overdose prevention center, is a legally sanctioned space where people can bring their own preobtained illegal or illicit drugs, and either inject or inhale them using sterile equipment under the supervision of nurses or other medical professionals. The main objective of a SIF is to improve survival and increase social integration [14]. However, overdoses, while at a lower rate than the general using population, still occur at SIFs [15]. This also provides an important opportunity for study [16].

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In this study, as participants wear the biosensor while they are injecting their opioids, the objectives of the study are (1) to capture chest motion data using the PneumoWave biosensor, and staff-measured outcomes as the clinical reference (including clinical identification of an acute event), during instances of opioid injection and potential opioid overdose by attendees at a SIF, to develop and refine the overdose detection algorithm and (2) to examine acceptability to SIF attendees of the chest biosensor.

Methods

Ethical Considerations

This paper is based on version 1.1, April 5, 2023, of the study protocol. Ethics was approved by the Alfred Hospital Ethics Committee (92786). This study adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Multimedia Appendix 1).

In order to obtain informed consent, the site research personnel will explain the study methodology to the potential participant, the individual will be given time to read the participant information sheet and consider participation, and if they agree to participate, informed consent will be obtained. Study explanation can occur before or after using the SIF, depending on the preference of the client and aligning with the capacity to consent. Study enrollment and first recording injecting events can, therefore, occur on different days.

Data will be recorded pseudo-anonymously (ie, pseudonyms will be used; no personally identifiable information will be stored alongside chest motion data) and streamed to a secure cloud. Participants who consent to take part will be assigned a numerical study ID number that will be linked to subsequent visits that they make to the Medically Supervised Injecting Centre (MSIC) or Medically Supervised Injecting Room (MSIR). All electronic data will be anonymous and stored on secure, password-protected devices or servers, accessible only by approved study personnel. All paper-based consent forms containing participant names will be kept on site at the MSIC or MSIR following completion and will not be removed from the site.

To reimburse participants for their time and inconvenience, participants will be reimbursed Aus $50 (US $33.20) following initial screening and study enrollment. Participants will then receive a weekly reimbursement of Aus $20 (US $13.30) on the basis they have attended the MSIC or MSIR to inject opioids (either alone or in combination with other drugs) while wearing the biosensor device at least once during the week.

Objectives

The objectives of the study are (1) to capture chest motion data using the PneumoWave biosensor, and staff-measured outcomes as the clinical reference (including clinical identification of an acute event), during instances of opioid injection and potential opioid overdose by attendees at a SIF, to develop and refine the overdose detection algorithm and (2) to examine acceptability to SIF attendees of the chest biosensor.

Study Design

This is an observational pilot study. Over 6 months, this study aims to capture approximately 40 overdose events that occur for consenting participants who are wearing the chest sensor during visits to inject at the SIF. Participants who consent to take part will be assigned an anonymous, numerical study ID number that will be linked to subsequent visits that they make to the SIF.

Chest motion data will be collected on the device securely and pseudo-anonymously (ie, pseudonyms will be used; no personally identifiable information will be stored alongside chest motion data) and streamed to a secure cloud. A SIF is designed to respond to a broad spectrum of adverse drug reactions, recognizing that not all incidents may escalate to an opioid overdose (thus any event that is attended to and requires prompting by staff is termed an “acute event”). The data collected here will be used to test and further develop chest wall movement “signatures” to accurately detect an “acute” drug event or potential overdose, as diagnosed by the current clinical observations in the SIFs. Wearing the device will not alter the services participants receive at the SIF and the sites will manage each acute event as per their standard protocols.

PneumoWave Biosensor and Data Collection Platform

The study will use the PneumoWave biosensor and data collection platform, which includes a wearable biosensor that attaches to the press-stud on a supplied and approved ECG electrode. The biosensor can be placed in a number of locations on the chest and diaphragm area and automatically connects to a Data Hub via Bluetooth (Figure 1). In this study, the Hub will be a router-type device or a mobile computing platform (app running on a tablet or phone).

Once consented to and enrolled in the study, participants will be asked to wear the biosensor each time they attend their relevant SIF to take opioids, an unlimited number of times. There will be no predefined number of visits that each participant should adhere to, though reimbursement will be predicated on attendance to the SIF and wearing of the biosensor at least weekly. We will now highlight the inclusion and exclusion criteria applicable to the study.

Eligibility Criteria

Inclusion Criteria

Participants will be recruited from the SIFs via advertisement and direct approach by site personnel and must meet the criteria that are (1) be an adult (18 years of age or older), (2) current injecting opioid user (note: participant may be using other substances as well), (3) regular client of the SIF (minimum of 4 visits in the past month), and (4) willingness to wear biosensor device while injecting at the facility.

Exclusion Criteria

The exclusion criteria are (1) inability to provide informed consent, (2) younger than 18 years of age, (3) not currently injecting opioids, (4) skin sensitivity to ECG electrodes, (5) broken skin over the chest area, (6) implanted pacemaker device in situ, and (7) in the clinical opinion of the investigator would not be suitable to participate.

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Sample Size

Participants will be recruited via purposive selection—SIF staff will identify individuals who frequently attend the SIF and inject opioids—and via site advertisements, with individuals approaching site research personnel about potential participation.

During a study period of 6 months, we estimate that approximately 100 participants will be recruited at each participating SIF to meet the desired targets of approximately 2000 opioid injecting visits (a total of 4000 visits), leading to approximately 40 recorded acute or overdose events. This is based on an estimated overdose event rate (the proportion of injections that result in an overdose event) to be 1.2%, from previous data from the medically supervised injecting center in Sydney, New South Wales, Australia [15,17]). An estimated 1200 opioid injecting visits occur per month per site, with an estimated 70 unique individuals attending for opioid injecting per month, per site.

Outcome Measures

Overview

We will initially separate outcome measures into categories of primary outcome measures (chest motion measures and acceptability) and SIF-determined measures. The latter will then be separated into intervention measures and acute event measures.

Primary Outcome Measures

Capture of chest motion of participants includes chest wall measurements via PneumoWave biosensor of people before and after injection of opioids in a SIF, compared by (1) those experiencing hypoxia and meeting defined criteria for an acute or opioid overdose (SIF-determined outcome measure or acute event) and (2) those not experiencing symptoms of hypoxia or acute or opioid overdose (ie, safe injecting event).

SIF-Determined Outcome Measures

The data that will be collected for each opioid injecting event in the SIF are (1) participant study ID, (2) time or date of client presentation to SIF, (3) substances reported by the participant as intended for injecting (confirmation that opioids are being injected), (4) time of opioid use, and (5) any apnea and prompts to breathe.

The outcome data that will be recorded for any intervention by SIF clinical staff (including acute event response) are (1) precise timing of the first clinical indication of acute event, (2) unique ID number of clinician initially assessing the event to be an opioid overdose, and (3) opioid overdose criteria being met (based on-site specific training materials or opioid overdose reference criteria). These are based on the measures that are described next.

The outcome measures that will be collected for each acute event (including prompts), as applicable are (1) response to audio, physical, and painful stimuli; (2) level of consciousness—timepoints as per standard of care, recorded (using Alert Verbal Pain Unresponsive [AVPU] scale—see Multimedia Appendix 2) at intervals indicated by clinical concern; (3) respiratory rate recorded at least every 5 minutes (though in practice, likely more often) after first clinical indication of opioid overdose; (4) heart rate—timepoints as per standard of care; (5) oxygen saturation via pulse oximetry were measured—timepoints as per standard of care, recorded at intervals indicated by clinical concern; (6) administration of oxygen; (7) administration of manual resuscitation or ventilate (bag-valve-mask ventilation); (8) administration of airway adjunct (nasopharyngeal or oropharyngeal airway); (9) administration of naloxone (yes or no); (10) cardiopulmonary resuscitation; and (11) ambulance called.

Acceptability

Acceptability measures incorporate participant feedback or satisfaction survey (see Multimedia Appendix 3). During study participation, each participant will be asked at least once if they wish to provide feedback on their experience of attaching or wearing the biosensor during injecting drug use. Participants may complete the feedback questionnaire more than once to record fluctuating levels of acceptability. For any feedback provided, the site will collate responses and provide them as an anonymized table listing (see Multimedia Appendix 3). There will also be a subset of participants who will be interviewed and surveyed in more depth.

Participant Timeline and Study Visits

The process of the investigation is more clearly understood through an examination of the schedule of events (visits 1 and then subsequent visits).

Baseline Procedures

Overview

After the participant has consented, completion of participant's basic, baseline (eg, demographics and drug use characteristics) questionnaire will be conducted using a stand-alone data collection tool using an electronic tablet. Each participant's height and weight will be recorded at the site at baseline and changes in their height and weight will be recorded every 4 weeks.

The following schedule of events will be followed for visit 1 and then visit 2 (until withdrawal or final self-injecting event).

Visit 1 Procedures (Performed by Site Research Personnel)

Initially, research personnel will confirm the injection of opioids (either alone or in combination with other drugs) and then provide instructions on the use and wearing of the biosensor (Table 1). The biosensor will then be issued to the participant and the biosensor number will be recorded with the participant ID number. The researcher will verify that the biosensor has been correctly attached to the chest wall and provide further guidance to the participant, as required.

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Table 1. Visit 1 (baseline and first study–specific self-injecting visit).

	Enrollment or baseline	Prior to injecting event	Acute or overdose event[a]	Postinjecting event	Early withdrawal[b]
Informed consent[c]	✓				
Eligibility criteria	✓				
Complete baseline questionnaire	✓				
Instructions (use of biosensor)		✓			
Issue chest sensor		✓			
Attach to chest wall		✓			
Record of event[d]			✓		
Adverse events		✓	✓	✓	✓
Return of biosensor				✓	
Early withdrawal form					✓

[a]If a self-injecting event occurred without the need for intervention the event should be recorded to reference the time of the device was attached and returned and that no interventions were required.

[b]If participant withdraws after providing consent and prior to any use of the sensor.

[c]Consent and eligibility review, performed at a time most suitable to site personnel and participant during their visit (Multimedia Appendix 4).

[d]Event start time, event stop time, assessment of event, and event outcome, if an applicable acute event occurs.

Research personnel will record basic information (day or time and drug reported for injection) for each participant's SIF attendance. Site research personnel will record the time of self-injecting by monitoring participants from a distance and estimating the time of drug injection (this may include multiple injections within a single episode). If this is not possible to record, the site personnel will document that it could not be collected. Site research personnel will also record event interventions for an acute or overdose event (as applicable), including start time, end time, event assessment or level of intervention, clinicians' unique ID, and overdose criteria. A record of "no acute event" will also be maintained if the self-injecting visit occurred without any requirement for site personnel intervention. Any adverse events will also be recorded and, if necessary, an early withdrawal form will be completed if the participant did not progress to use the biosensor at visit 1 and declined further participation.

Visit 2 to Withdrawal or Final Self-Injecting Visit (Performed by Site Research Personnel)

At visit 2 and subsequent visits until withdrawal or final self-injecting visit, research personnel will verify that the informed consent remains valid for the participant to continue on the study (Table 2). They will also confirm the injection of opioids (either alone or in combination with other drugs) and provide a reminder instruction on the use and wear of the biosensor. They will then issue the biosensor to the participant and record the biosensor number used with the participant ID. They will verify that the biosensor has been attached to the chest wall correctly and provide further guidance to the participant as required.

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Table 2. Visit 2 to final self-injecting visit.

	Prior to injecting event	Acute or overdose[a,b] event	Postinjecting event	Withdrawal[c]
Verify informed consent remains valid	✓			
Instructions (use of sensor; as required)	✓			
Issue chest biosensor	✓			
Attach to chest wall	✓			
Record of event[d]		✓		
Adverse events		✓	✓	✓
Return of biosensor			✓	
User experience survey (during enrollment period, prior to withdrawal, or final self-injecting visit				
Withdrawal form[c]				✓

[a]If a self-injecting event occurred without any need for intervention the event should be recorded to reference the time the device was attached and returned and that no interventions were required.

[b]If a self-injecting event occurred without the need for intervention the event should be recorded to reference the time of the device was attached and returned and that no interventions were required.

[c]For all withdrawals from visit 2 onwards.

[d]Event start time, event stop time, assessment of event, and event outcome, if an applicable acute event occurs.

Site research personnel will record basic information (day or time and drug reported for injection) for each participant's SIF attendance and will record the time of self-injecting by monitoring the participant from a distance and estimating the time of drug injection (may include multiple injections within a single episode). If this is not possible to record, the site personnel will document that it could not be collected. Site research personnel will also record event interventions for an acute or overdose event (as applicable) including start time, end time, event assessment or level of intervention, clinicians' unique ID, and overdose criteria. A record of "no acute event" will also be maintained if the self-injecting visit occurred without any requirement for site personnel intervention. Any adverse events will also be recorded and, if necessary, a withdrawal form will be completed if the participant did not progress to use the biosensor and declined further participation.

Example Study Schedule

The number of visits and injection events per participant will differ. The following range of frequency of attendees at the SIF may be anticipated—frequent attendee: 2 visits per day, mid-level attendee: 5 visits per week, and low-level attendee: 1 visit per week [15,17].

Data Management

All data will be captured using a dedicated web-based data system accessible only to site research personnel. Following completion of any given data form, data will be uploaded to a secure, password-protected server managed by the sponsor and located in Canada. It will be the Contract Research Organization's (CRO) responsibility to manage data security. Following project completion, the CRO will lock the data system from further changes and securely transfer data to PneumoWave, where data will be securely stored. Site-specific data sets will also be provided to the SIF. All data will be anonymous, using only study IDs.

PneumoWave Managed Biosensor Data

As soon as the biosensor chest placement has been carried out, chest movement data will commence being captured. Data from the biosensor will be uploaded securely and automatically to a Data Hub stored in a small container, located within the SIF (Figure 2).

The data storage platform (supplied by Galen Data) complies with HIPAA (Health Insurance Portability and Accountability Act) requirements as set forth in the Galen Cloud HIPAA Compliance Matrix (004-0020), General Data Protection Regulation (GDPR) requirements as set forth in the Galen Cloud GDPR Compliance Matrix (004-0021), and California Consumer Privacy Act (CCPA) requirements. Additionally, Galen Cloud deployed on Amazon Web Services (AWS) is Health Information Trust Alliance (HITRUST) certified.

PneumoWave will review both chest movement data stored within the Galen Cloud and study data, including baseline questionnaire, injecting event, acute event, and satisfaction questionnaire data.

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Figure 2. Data management flow. CCPA: California Consumer Privacy Act; CRA: Clinical Research Associate; EDC: Electronic Data Capture; GDPR: General Data Protection Regulation; HIPAA: Health Insurance Portability and Accountability Act; HITRUST: Health Information Trust Alliance; OD: overdose.

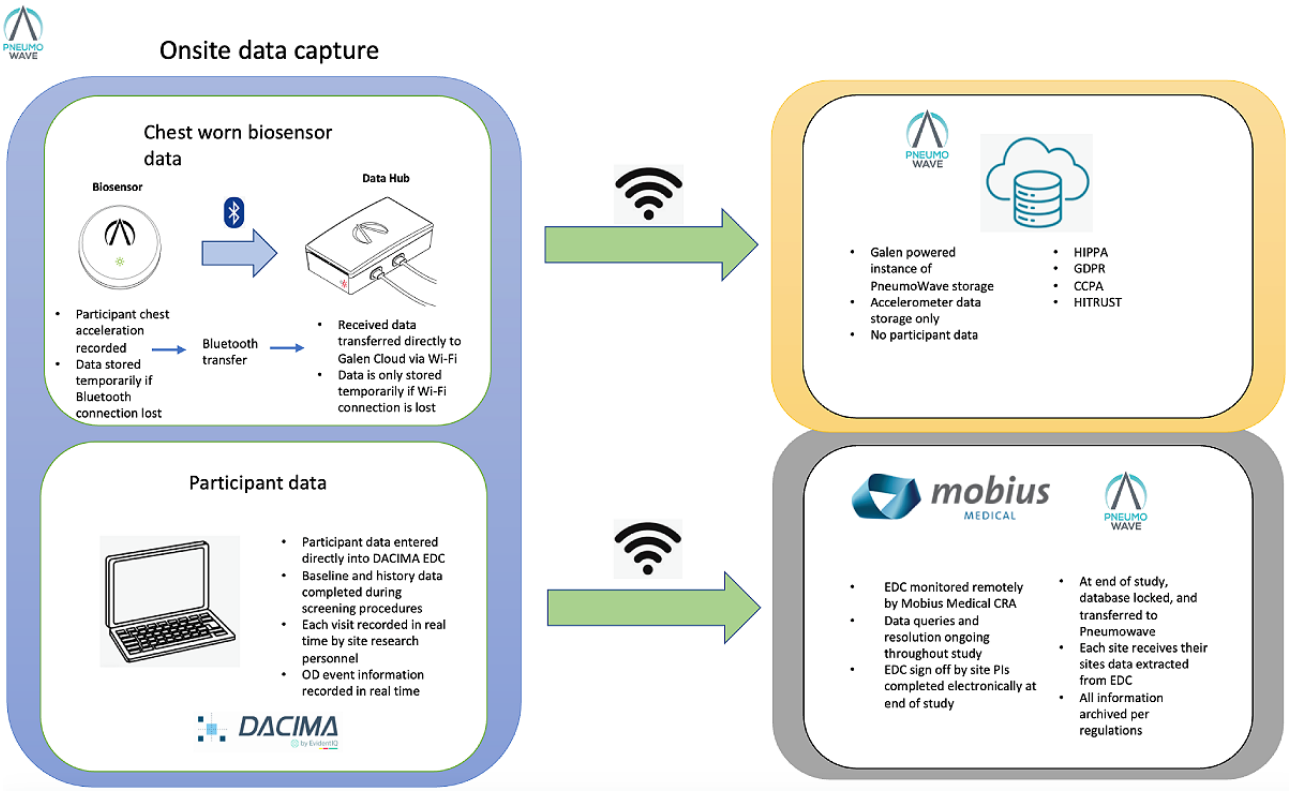

Early Withdrawal

Participants may request to withdraw from the study at any stage for any reason without prejudice. Participants will need to complete an early withdrawal form. Participants may also request deletion of all study data collected about them up until the point of their withdrawal.

Study Procedure Risks and Benefits

It is understood there may be the occasional loss of a biosensor with the key issue being the potential for a participant to leave the facility prior to removal of the biosensor. While site personnel will aim to minimize this risk, it does remain a factor for device accountability or traceability records. The safety risk relating to a biosensor being taken off-site is assessed to be minimal. Anticipated risks are expected to be very minimal and with a low chance of occurrence. This is a noninterventional, observational study with retrospective analysis of the biosensor data and no protocol-specified procedures impacting the standard of care. Even so, potential study risks include data breaches. However, all electronic data will be anonymous and stored on secure, password-protected devices or servers, and accessible only by approved study personnel. Numerical study IDs will be used in place of participant names. All paper-based consent forms containing participant names will be kept on-site at the SIF following completion and will not be removed from the site. ECG electrodes used in the study are designed to be worn for up to 3 days continuously. The average duration of wear is expected to be less than 1 hour; however, there is a low risk of mild skin irritation.

Given the preliminary, small-scale nature of this research, it is not anticipated that there will be any direct benefits to participants. This work aims to advance the development of future devices that may identify and intervene during opioid overdose; however, such devices may not eventuate for a number of years. The absence of immediate benefit will be outlined to participants during the consent process.

Safety

The capture of safety events will be solely related to adverse device effects (ADE) and will only be captured for an event relating to the use or wearing of the device. All ADEs and serious ADEs will be recorded by site research personnel and will be assessed for severity (mild, moderate, or severe) by the study team.

All ADEs and serious ADEs will be recorded from the time a participant is enrolled until the participant's last study visit as per the time periods outlined. Participants who have enrolled but then withdrawn prior to wearing the biosensor for the first time will not have adverse events captured. Only unanticipated effects will be captured as reportable ADEs.

Analyses

Statistical Analysis

For the SIF-determined outcome measures (eg, demographic data) and satisfaction survey, descriptive statistics will be reported using means and SD for continuous data. Absolute numbers and percentages will be reported for categorical data. Any statistical software can be used.

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Biosensor Analyses

Reference Event

Staff-identified events are any event that has required an intervention by staff in the facility. Interventions can range from a simple audio stimulus, up to and including requesting an ambulance to attend. These events include those where overdose may not have occurred, but the response will have been managed in the same way according to the site's standard operating procedures. These incidences will be recorded as an "acute event." Where an overdose has been clearly identified using the tools mentioned previously, these incidences will be identified as "overdose event." The analysis will incorporate both types of "reference" events.

Algorithm Under Test

The PneumoWave Hub receives and transmits biosensor data to a cloud storage facility. The stored data are then processed in the cloud using experimental algorithms for the presence of reduced chest movement events in adults.

The performance of the algorithm under test will be compared to the reference events at the SIF in terms of the AUT's sensitivity and false alarm rate. If the target numbers for sample size, injecting visits, and acute events are not reached, the analysis will still be possible and feasible.

Results

Funding was granted in July 2023 and dates for data collection are August 2023 to February 2024. As of April 2024, we have enrolled 47 participants, consisting of 17 females and 30 males with an average age of 45 years. Heroin was the preferred drug for most participants (40/47) and then methadone or an opioid agonist treatment (6/47), with the largest proportion injecting 2 to 5 times daily (BD-5D—n=23), and then once daily (14/47). The majority had experienced an overdose in the past (29/47). Among all the participants, a total of 1145 injecting events were recorded while participants wore the sensor, with 10 overdose events being observed. Data analysis of the outcome measures is ongoing.

Discussion

There has been a recent surge of interest in mobile health and wearable devices to treat opioid use disorders [18,19] and specifically to detect and respond to opioid overdoses. However, there is limited research on detecting true overdose (which requires intervention) and the effectiveness of these devices to detect overdose in the community has not yet been adequately evaluated. A chest sensor that reliably detects the overdose breathing signature could alert the emergency services and save lives when fully developed and used in the community.

This observational study aims to capture chest motion data while participants wear a small chest-worn biosensor within medically supervised injecting centers in Australia. The data collected here will be used to test and develop respiratory "signatures" to accurately detect an acute or potential opioid overdose. Testing will allow for the differentiation of patterns that occur following opioid use but do not result in an overdose.

It is anticipated that this study will capture chest motion data from the sensor while participants inject opioids and it is likely that some instances of potential overdose will also be captured by the sensor. It is uncertain how much chest motion data will be corroborated with staff-measured outcomes. It is anticipated that the sensor will be considered positively overall among participants.

The findings of this study will be compared to a previous study of this chest sensor among participants who wear the sensor at home and are on opioid agonist treatment (paper in preparation), as well as other studies on wearable devices that have been examined acceptability and feasibility of varied technologies to combat the overdose crisis [20-25]. The potential effectiveness and acceptability of these studies are varied. Generally, there is limited but expanding research in this area with studies focused on products or technologies that are relatively new or in early development [12]. There is no published work on a remote chest sensor that can reliably detect chest wall movement in the context of an opioid overdose.

The strengths of this study are that it examines the effectiveness of the chest sensor among people who are injecting opioids in a relatively controlled but real drug-using environment. Research within an SIF is a unique opportunity to address external validity as participants will be those who the sensor is eventually intended for.

However, the study is likely to be limited in a few different ways. First, it is likely that participants will be polydrug users and it may not be possible to examine the effect of opioids alone. Additionally, the number of prompt or acute events is likely to be lower than in other drug-using environments as participants will be users who are using in a safe setting that is aimed at reducing harms and mortality around injecting drug use. This may mean the target number of acute events will be negatively impacted. Other potential limitations could include the physical movement of individuals while using the device interfering with the data capture, or data quality. The more the participants, the better the quality of data will be.

Future development of this work will involve conducting a randomized clinical investigation of a medical device to determine its effectiveness in detecting OIRD. It will also be important to test the device in people's personal environments, for example, in their homes.

Acknowledgments

The study is funded by PneumoWave (who are developing a chest sensor for the detection of opioid-induced respiratory depression and will submit relevant parts of these findings for further approvals of the device). PneumoWave will have the ultimate decision

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on the submission of the final report to regulatory authorities with close discussions with King's College London and academic colleagues in other institutions. PneumoWave is the sponsor of the study.

Authors' Contributions

This study design was conceived and proposed by JS, BT, and WL and all authors contributed to the write-up of the protocol.

Conflicts of Interest

BT is supported by National Institute for Health & Care Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley National Health Service (NHS) Foundation Trust, King's College London and part funded by the Maudsley Charity. JS is a clinician and academic who has worked with local, national and international government and nongovernment agencies to develop and test new approaches to tackling addiction and related problems including risk of death from drug overdose. Through his employer (King's College London), he has worked with pharma and tech companies (including MundiPharma, Camurus, Accord, Catalent, Pneumowave and CMI in the past 3 years) and his employer (King's College London) has received project grant support and/or honoraria and/or consultancy payments and also device and app supply in order to develop or study potentially improved formulations and devices. JS's research is supported by the National Institute for Health & Care Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. WL, PD, DOK, MJ, MB, NC, BH, CC, and OM declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.
[PDF File (Adobe PDF File), 74 KB - resprot_v13i1e57367_app1.pdf]

Multimedia Appendix 2
AVPU (Alert Verbal Pain Unresponsive) scale.
[PDF File (Adobe PDF File), 226 KB - resprot_v13i1e57367_app2.pdf]

Multimedia Appendix 3
Participant satisfaction survey.
[PDF File (Adobe PDF File), 145 KB - resprot_v13i1e57367_app3.pdf]

Multimedia Appendix 4
Consent form.
[PDF File (Adobe PDF File), 67 KB - resprot_v13i1e57367_app4.pdf]

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Abbreviations

ADE: adverse device effect
AVPU: Alert Verbal Pain Unresponsive
AWS: Amazon Web Services
CCPA: California Consumer Privacy Act
CRO: Contract Research Organization
ECG: electrocardiography
GDPR: General Data Protection Regulation
HIPAA: Health Insurance Portability and Accountability Act
HITRUST: Health Information Trust Alliance
MSIC: Medically Supervised Injecting Centre
MSIR: Medically Supervised Injecting Room
OIRD: opioid-induced respiratory depression
SIF: safe injecting facility

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SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Psychological Health and Wellness and the Impact of a Supportive Text Messaging Program (Wellness4MDs) Among Physicians and Medical Learners in Canada: Protocol for a Longitudinal Study

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Abstract

Background: Burnout, anxiety, and depression continue to affect physicians, postgraduate medical trainees, and medical students globally and in Canada particularly after the COVID-19 pandemic.

Objective: The primary goal of this project is to design, implement, monitor, and evaluate a daily supportive SMS text messaging program (Wellness4MDs, Global Psychological e-Health Foundation). The program aims to reduce the prevalence and severity of burnout, anxiety, and depression symptoms among physicians, postgraduate medical trainees, and medical students in Canada.

Methods: This longitudinal study represents a multistakeholder, mixed methods, multiyear implementation science project. Project evaluation will be conducted through a quantitative prospective longitudinal approach using a paired sample comparison, a naturalistic cross-sectional controlled design, and satisfaction surveys. Prevalence estimates for psychological problems would be based on baseline data from self-completed validated rating scales. Additional data will be collected at designated time points for paired comparison. Outcome measures will be assessed using standardized rating scales, including the Maslach Burnout Inventory for burnout symptoms, the 9-item Patient Health Questionnaire for depression symptoms, the 7-item Generalized Anxiety Disorder scale for anxiety symptoms, and the World Health Organization–Five Well-Being Index.

Results: The project launched in the last quarter of 2023, and program evaluation results will become available within 36 months. The Wellness4MDs program is expected to reduce the prevalence and severity of psychological problems among physicians in Canada and achieve high subscriber satisfaction.

Conclusions: The results from the Wellness4MDs project evaluation will provide key information regarding the effectiveness of daily supportive SMS text messages and links to mental health resources on these mental health parameters in Canadian physicians, postgraduate trainees, and medical students. Information will be useful for informing policy and decision-making concerning psychological interventions for physicians in Canada.

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KEYWORDS

wellness; doctors; Canada; depression; burnout; anxiety; supportive text messages; eHealth

Introduction

Burnout, anxiety, and depression continue to be a problem among physicians globally and in Canada. The recent Canadian Medical Association National Physician Health Survey shows that the well-being of physicians across Canada has significantly decreased [1]. The survey demonstrates that many physicians report poorer mental health than before the COVID-19 pandemic, with 53% of respondents nationally reporting symptoms of burnout, including emotional exhaustion [1]. According to the Medscape National Physician Burnout and Suicide Report, the burnout rate among physicians was reported to be as high as 42% in 2020, compared with 39% in 2013 [2,3]. Similarly, high rates were reported for residents with scores between 41% and 74% across different specialties [4]. Furthermore, 27% of residents stated that they rarely or never had time to lead a satisfying social life; of these, 68% reported having failed relationships for this reason [5,6].

During the COVID-19 pandemic, these figures increased further with about 60% of physicians in Canada reporting that their mental health worsened after the pandemic [7]. Similarly, 35% of a sample of emergency residents demonstrated symptoms of posttraumatic stress disorder acutely during the COVID-19 pandemic crisis [8].

The impact of burnout on the physician workforce is substantial, including a higher likelihood for medical errors, lower quality of care, higher costs, and overall worse outcomes along with reduced patient satisfaction [9-12]. Physicians reporting burnout symptoms work for fewer hours and leave clinical medicine at a higher rate than those not affected, and the resultant decreased productivity may exacerbate physician shortfall [13-15]. In addition, physicians with high levels of distress and burnout are more prone to self-perceived or reportedly commit medical errors [4,16,17]. Furthermore, the risk of depression, stress, alcohol use, and suicidality were increasingly reported among postgraduate trainees who have experienced more working hours, burnout, and less sleep time [4,17,18]. On the other hand, physicians who have high empathy and more positive attitudes tend to demonstrate positive attributes with better clinical outcome profiles in terms of developing better doctor-patient relationships associated with a high patient satisfaction and moral reasoning with clinical competence [19-21]. A recent study investigated the strength and significance of the associations of health workforce with multiple health outcomes and COVID-19 excess deaths across countries, using the latest World Health Organization dataset [22]. The study reported that a higher aggregate density of health human resources, particularly physicians, was significantly associated with healthy life expectancy at birth [22].

Addressing stress and burnout among physicians, postgraduate trainees, and medical students is a priority, given that decreasing rates of medical professionals usually seek psychological help or support. In a study among university hospital physicians in Europe, it was reported that overall, more than 3 in 4 distressed physicians had never sought professional help for depression or burnout [23]. In another study that evaluated the help-seeking behaviors of medical students with burnout and compared their stigma perceptions with those of the general US population and age-matched individuals, it was reported that only a third of respondents with burnout (154/454, 33.9%) sought help for an emotional or mental health problem in the last 12 months [24]. Furthermore, medical students with burnout were more likely than those without burnout to agree or strongly agree with 8 of 10 perceived stigma items [24]. It is well-recognized that the stigma and potential professional reputational damage associated with seeking help for mental health problems often deter many physicians, residents, and medical students from seeking psychological support when they are stressed, burnt out, or dealing with anxiety or depression.

Thus, there was a need for an evidence-based, technology-enabled, cost-effective, and geographic location–independent mental health service to address the psychological problems faced by physicians, postgraduate trainees, and medical students. Previous research examining supportive SMS text messages has demonstrated positive outcomes, in terms of improved clinical symptoms and high user satisfaction [25-27]. In a rigorous evaluation of Text4Mood, an SMS text messaging service launched in Fort McMurray, Alberta to address unmet psychological treatment gaps, it was reported that supportive SMS text messages helped the majority of the subscribers feel more hopeful about managing issues (82%), in charge of managing their depression and anxiety (77%), and connected to a support system (75%). Furthermore, a majority reported that the intervention improved their overall mental well-being (83%) [26]. Similar findings were observed in other contextual studies, such as Text4Baby and quit4baby; the 2 programs that have sought to assist women by providing supportive and informative SMS text messaging during pregnancy [28,29]. Participants in such services indicated that receiving these messages gave them a sense of reassurance and made mothers feel supported, particularly in disadvantaged communities [30]. Similarly, texting services, such as Text4Support, have effectively reduced the risk of harm to self and other harm symptoms after 6 months of intervention in a randomized controlled trial [31] and reduced distress, anxiety, and depression symptoms in clinical samples [32]. In addition, the Text4PTSI program has achieved fidelity and significantly reduced psychological distress among public safety personnel post intervention [33,34]. Furthermore, during the COVID-19 pandemic, people needed to feel connected to a health support system. Text4Hope service was provided to support the mental health of the general public in Alberta; the service reported a significant reduction in stress, anxiety, depression symptoms, and suicidal ideation during the pandemic [35-38]. Another related service, the Text4Hope-Addiction program was introduced to people living with substance use disorders [39]. The service reported significant improvement in standardized measures for craving, anxiety, and depression in subscribers. SMS text message–based population-level messaging programs

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have reported user satisfaction rates of well over 80%, and most subscribers have reported feeling connected to support systems and improving their ability to manage anxiety, depression, and general life issues, suggesting an improvement in mental health literacy [26,27,40-42].

In this study, we propose the Wellness4MDs (Global Psychological e-Health Foundation) initiative, a text-based proposed program that will deliver daily supportive and informative SMS text messages with or without embedded web links for mental health support or literacy resources to the physicians in Canada for 6 months. The Wellness4MDs program SMS text messages are based on cognitive behavioral therapy (CBT) principles and developed by psychiatrists, mental health therapists, clinical psychologists, and users of mental health services. Wellness4MDs program may help provide a first-line intervention that addresses the help-seeking barrier of stigma that fits with the busy lifestyle of physicians, postgraduate trainees, and medical students.

The goal of this project is to support the mental health of physicians, postgraduate trainees, and medical students in Canada using a daily supportive SMS text message. We aim, first, to evaluate the prevalence and correlates of burnout and probable mental health symptoms and, second, to determine if daily supportive SMS text messages can help reduce the prevalence and severity of these symptoms and improve well-being among subscribers in Canada. We will also assess the experience and satisfaction of the Wellness4MDs program subscribers with the daily supportive SMS text messaging program.

Methods

Study Design

This is a quantitative longitudinal study with data collected from subscribers of the Wellness4MDs program using a web-based survey at the onset of the program and at designated follow-up timepoints. The surveys will include questions related to sociodemographic characteristics, roles, years of training, specialty, work, and clinical information. The Wellness4MDs program will deliver daily supportive and informative SMS text messages with or without embedded web links for mental health support or literacy resources to subscriber cell phones for 6 months. Participation in the surveys would be voluntary, and nonparticipation in any of the surveys will not impact program participation or service delivery. The Wellness4MDs is a national collaborative project that will leverage stakeholder partnerships to disseminate the program to physicians, postgraduate trainees, and medical students. Potential collaborating organizations include the Royal College of Physicians and Surgeons of Canada, faculties of medicine across Canada, provincial medical associations, provincial health authorities, and provincial medical licensing colleges. Initially, promotional material will be provided and give an overview of the Wellness4MDs program and information about how physicians, postgraduate medical trainees, and medical students can subscribe and unsubscribe to the program. Collaborating organizations will be requested to share information about the Wellness4MDs program with physicians, postgraduate medical trainees, and medical students on their databases and social medical handles, including Facebook, LinkedIn, Instagram, and Twitter (rebranded as X). Thus, the Wellness4MDs recruitment plan will mirror the successful recruitment plan of similar programs in Alberta, including the Text4Hope program that was launched in response to COVID-19 in March 2020 [36,37,43] as a collaborative initiative between the University of Alberta, Alberta Health Services, and six health foundations. Text4Hope was the subject of a wide-exposure communications campaign (television, radio, internet, and print media), including the local provincial mental health foundation, Alberta Health Services, and a media release by the provincial chief medical officer [44].

Study Setting and Participants

The bilingual Wellness4MDs program will enroll physicians, postgraduate trainees, and medical students in all provinces and territories in Canada. In 2021, the total number of physicians in Canada was 108,040, according to the annual census [45]. According to the Canadian Medical Association, the total number of residents in all postgraduate programs in 2018-2019 was 16,508, and the total enrollment in undergraduate medical schools in Canada in 2017-2018 was 11,737 [46].

Program Timelines

The Wellness4MDs initiative will be a 3-year project, with timelines as detailed in Table 1.

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Table 1. Wellness4MDs project Gantt chart.

Milestones	Year 1				Year 2				Year 3			
	Q1[a]	Q2[b]	Q3[c]	Q4[d]	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Milestone 1: recruitment of a project staff and creation of the bank of supportive SMS text messages												
1.1 A project coordinator and evaluation specialist would be recruited to support project coordination, implementation, monitoring, and evaluation	✓											
1.2 Review and adaptation of the bank of supportive SMS text messages and creation of new messages for the Wellness4MDs program by an expert group	✓											
Milestone 2: launch of the Wellness4MDs program, advertisement, and delivery of service												
2.1 Recruitment		✓	✓	✓	✓	✓	✓	✓	✓	✓		
2.2 Provision of the service		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Milestone 3: evaluation of the service, including clinical assessment and satisfaction of the participants, and stakeholders' feedbacks												
3.1 Baseline survey (excluding satisfaction survey)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.2 Follow-up survey (including satisfaction survey)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.3 Key informant interviews and Focus group workshops						✓				✓		
Milestone 4: data compilation, analysis, and preparation of reports, publications, and presentations for multi-scale dissemination												
4.1 Data compilation				✓	✓	✓	✓	✓	✓	✓	✓	✓
4.2 Data analysis				✓	✓	✓	✓	✓	✓	✓	✓	✓
4.3 Preparation of reports, publications, and presentations				✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Q1: first quarter.

[b]Q2: second quarter.

[c]Q3: third quarter.

[d]Q4: fourth quarter.

Wellness4MDs Program

The Wellness4MDs program is modeled on the highly successful Text4Hope and Wellness4Teachers initiatives in Canada [35,47]. The program is powered by the ResilienceNHope software, a web-based application that delivers the suite of supportive SMS text and email messaging programs, including Text4Mood, Text4Hope, Wellness4Teachers, Text4PTSI, Text4Wellness, and MoreGoodDays [48]. Canadian physicians, postgraduate trainees, and medical students will be able to subscribe to the Wellness4MDs program by texting "WellMD" to a designated phone number. Individuals can unsubscribe to the program by simply texting "stop" to the program phone number. The Wellness4MDs program will deliver daily supportive and informative SMS text messages (some with embedded web links for mental health support or literacy resources) to subscriber cell phones for 6 months. The Wellness4MDs program SMS text messages are based on CBT principles and were developed by psychiatrists, mental health therapists, clinical psychologists, and users of mental health services. About a third of the SMS text messages will have embedded web links that include additional physician health and wellness resources from reputable sources.

Examples of SMS Text Messages

The following are example SMS text messages that will be sent.

1. "Perfectionism can cause anxiety. Remember a perfect work environment does not exist. Try deliberately being imperfect and see what happens. Do your anxious thoughts come true? Remember that there are many possibilities in life. Try not to limit yourself from enjoying all that is possible." In addition, an embedded web link has been provided [49].
2. "We each have different signature strengths. It's not about competing with others but learning our unique strengths. Strengths come in many varieties, such as humor, curiosity, persistence, kindness, love, forgiveness, cooperativeness, and optimism. Share your strength with others. Help a struggling colleague."
3. "Problems are almost never solved in one step. See if you can break the problem into steps. Take the first step today by starting with a manageable situation. Get the support of a friend, family, colleagues, or supervisor." In addition, an embedded web link has been provided [50].

Hypothesis

We hypothesize that the Wellness4MDs program will achieve (1) at least a 20% reduction in mean scores for burnout, anxiety, and depressive symptoms on validated scales and a 20% increase in self-reported well-being at 6 weeks, 3 months, and 6 months after receiving the service, and (2) at least 80% of subscribers will express satisfaction with the program and perceive the daily

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supportive SMS text messages as contributing to their overall mental well-being.

Sample Size Calculation

With a projection that the effect size for the reduction in mean 7-item Generalized Anxiety Disorder (GAD-7) scale and 9-item Patient Health Questionnaire (PHQ-9) scores at 6 months from baseline would be 0.1, a population variance of 1 for each scale mean score, a 2-sided significance level α=.05, and a power of 90% (β=.1), using a web-based script [51], we estimated that the sample size needed to assess the effects of the daily supportive SMS text messages on the outcome variables would be 1053.

Data Collection and Outcome Measures

The project will run for 3 consecutive years. Quantitative data will be collected from subscribers of the Wellness4MDs program using a web-based survey at the onset of the program (baseline), 6 weeks, 3 months (midpoint), and 6 months (end of service) as illustrated in Table 2. The surveys will include demographic questions such as sex and gender, as well as information about their role (physicians, postgraduate trainees, or medical students), their years of training or practice, and their specialty of retaining or practice if they are residents or physicians, in addition to the clinical outcome measures.

Primary outcome measures include changes in the mean scores on the PHQ-9 [51], the GAD-7 [52], the Maslach Burnout Inventory (MBI) [53], and the World Health Organization-Five Well-Being Index (WHO-5) [54] for subscribers from baseline to 6 weeks, 3 months, and 6 months.

The PHQ-9 is a self-administered scale designed to measure likely depression. It is an effective tool for patients and a validated tool for screening of depressive symptoms among the general population [55]. Symptoms experienced by patients during the 2 weeks before answering questionnaires are considered. Scores range from never (0), several days (1), more than half of days (2), to 3 (nearly every day), with every item ranging from 0 to 27 [51,56]. The tool's reliability and validity have shown good psychometric properties with accepted sensitivity using 10 or above as a cutoff score and high internal consistency (Cronbach α=0.79) [55,57].

The GAD-7 scale is a self-administered valid tool designed to measure likely anxiety [58,59]. The 7 self-reported items are used to assess the severity of generalized anxiety disorder (GAD) symptoms over the past 2 weeks. Ratings are based on a 4-point Likert scale: not at all sure (0), several days (1), over half the days (2), and nearly every day (3). The scores ranged from 0 to 21, with higher scores indicative of more severe symptoms. A sensitivity of 89% and a specificity of 82% for a cutoff score of 10 [59] are considered. The GAD-7 also showed good test-retest reliability (intraclass correlation 0.83), as well as excellent internal consistency (Cronbach α=0.92) [58,60].

The WHO-5 is a self-reported measure of subjective well-being that is highly useful in clinical practice and in research studies to assess well-being over time or to compare well-being between groups [61]. The scale includes 5 positively worded items with a 6-point Likert scale used to assess participant's feelings in the last 2 weeks, ranging from 0 (not present) to 5 (constantly present). The raw scores are transformed into a score from 0 (worst thinkable well-being) to 100 (best thinkable well-being) [62]. Having a score <50 indicates poor emotional well-being and requires further evaluation. The WHO-5 demonstrated satisfactory internal consistency reliability and concurrent validity with other scales [61,62].

Table 2. Client-oriented outcome measures and feedbacks and experiences of clients and stakeholders.

Construct	Tool (scale)	T_0[a]	T_1[b]	T_2[c]	T_3[d]
Likely MDD[e]	PHQ-9[f]	✓	✓	✓	✓
Likely GAD[g]	GAD-7[h]	✓	✓	✓	✓
Burnout	Maslach Burnout Inventory	✓	✓	✓	✓
Mental well-being	WHO-5[i]	✓	✓	✓	✓
Satisfaction with the service	Standardized satisfaction survey		✓	✓	✓
Experience and feedback	Focus groups and key informant interviews				✓

[a]T_0: baseline timepoint.

[b]T_1: 6-week timepoint.

[c]T_2: 3-month timepoint.

[d]T_3: 6-month timepoint.

[e]MDD: major depressive disorder.

[f]PHQ-9: 9-item Patient Health Questionnaire.

[g]GAD: generalized anxiety disorder.

[h]GAD-7: 7-item Generalized Anxiety Disorder.

[i]WHO-5: World Health Organization-Five Well-Being Index.

The MBI, a short questionnaire-based tool, is designed to measure the symptoms and severity of burnout. In total, 3 main domains are examined, that are depersonalization, emotional exhaustion, and professional fulfillment index. The professional fulfillment index includes 2 domains, that are work exhaustion and interpersonal disengagement (Burnout scale) and the

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professional fulfillment scale. The reliability of MBI is supported by several studies, where Cronbach α ratings of 0.90 for emotional exhaustion, 0.76 for depersonalization, and 0.76 for personal accomplishment [63].

Secondary outcome measures include changes in prevalence in subscribers of burnout, likely GAD and likely major depressive disorder (MDD), from baseline to 6 weeks, 3 months, and 6 months measured using the GAD-7, the PHQ-9, and the MBI. Other secondary outcome measures include subscriber satisfaction.

Statistical Analysis

Quantitative data will be analyzed with descriptive statistics, paired *t* test, and chi-square tests using SPSS Statistics for Windows (Version 25; IBM Corp) [64]. Descriptive data will be presented as numbers and percentages. Paired *t* test will be used to assess the differences in the mean scores of each of the outcome scales for the baseline and the follow-up time points. In addition, the chi-square test will be used to compare the prevalence of burnout, likely GAD and likely MDD, from baseline to the follow-up time points.

Ethical Considerations

This study has been approved by the human ethics review boards of the University of Alberta (Pro00129541). Informed consent will be implied if subscribers access the study information leaflet, complete the survey questions, and submit responses. Study data will be anonymized and deidentified using encrypted files that will be accessible only to the principal investigator and the research coordinator. No identification of individual participants in any images of the paper or supplementary material. No compensation will be used. No incentives will be provided to the study participants.

Results

The project was launched in the fourth quarter of 2023, and program evaluation results will become available by January 2027. Aligned with similar previous initiatives, the Wellness4MDs program is expected to reduce the prevalence and severity of psychological problems among physicians in Canada and achieve high subscriber satisfaction.

Discussion

Principal Findings

The Wellness4MDs project represents an innovative initiative that aligns with 2 main strategic directions, namely, highest quality and proactive and innovative approach. In terms of highest quality, the evidence in favor of the potential effectiveness of the Wellness4MDs program to alleviate stress, burnout, anxiety, and depression among physicians, postgraduate medical trainees, and medical students is derived from meta-analyses of randomized controlled trials and evaluations of related population-level interventions [26,31,32,36-38,40,65-67]. For example, in 2 randomized controlled trials, when CBT-based daily supportive SMS text messages were delivered to patients with MDD either as part of inpatient postdischarge community follow-up care or as part of outpatient clinic care, there was a 50% and 25% greater reduction in mean depression symptoms scores measured on the Beck's Depression Inventory Scale compared with the control group, respectively [68,69]. Similarly, in an evaluation of the Text4Hope program launched in Alberta during the COVID-19 pandemic, subscribers who had received daily supportive SMS text messages for just 6 weeks had a significantly lower prevalence of moderate to high stress, likely generalized anxiety disorder, likely MDD, suicidal ideation, and disturbed sleep compared with new subscribers during the same time frame [37]. The Wellness4MDs program therefore has the potential to offer physicians an intervention that is of the highest quality with respect to the evidence of effectiveness. The approach to using daily supportive and informative SMS text messages to promote physician wellness would be innovative as it will be the first of its kind globally. In addition to addressing issues of stress, burnout, anxiety, and depression among physicians, residents, and medical students, the embedded web links in some of the messages to be preprogrammed into the Wellness4MDs program are expected to improve the mental health literacy of subscribers and provide information on complimentary mental health resources and approaches that would also be proactive and innovative.

The goal of this project is to provide mental health support and information about available resources to physicians, postgraduate medical trainees, and medical students in Canada through a daily supportive SMS text message program. Similar to the impressive uptake by teachers in Canada of the Wellness4Teachers program (close to 2000 teachers subscribed within 3 months) [47], we anticipate high subscriptions to the Wellness4MDs program from physicians, postgraduate medical trainees, and medical students across Canada. Furthermore, similar to outcomes achieved from the Text4Hope program launched for the general public during the COVID-19 pandemic, we anticipate that the Wellness4MDs program will reduce stress, burnout, anxiety, and depression among physicians, postgraduate medical trainees, and medical students. The expected long-term outcomes could include lower rates of absenteeism due to stress and burnout, reduced physician turnover, reduced medical errors in clinical practice, better safety profile of patients and patient satisfaction, and fewer patient complaints. Thus, we anticipate the benefits of the Wellness4MDs program will lead to better health profiles for physicians, postgraduate medical trainees, and medical students, and the health care system will ultimately benefit through cost savings from the avoidance of expenses that directly relate to or stem from these activities.

Limitations of the Study

This study has a number of limitations. First, the self-reported scales to be used for assessment of the psychological problem, although validated, are not diagnostic. In addition, it is highly probable that the physicians, postgraduate medical trainees, and medical students who are impacted by burnout, stress, or anxiety may be more likely to subscribe to the Wellness4MDs program and so be overrepresented in this study, and thus impact the generalizability of the prevalence estimated for psychological problems. Finally, the duration of the intervention is limited for 6 months; thus, the long-term outcomes after cessation of the service will not be established. These limitations

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notwithstanding, this study is the first to provide e–mental health support for stress, burnout, anxiety, and depression among physicians, postgraduate medical trainees, and medical students in Canada. This study is a pioneer in assessing if daily supportive SMS text messages delivered through the Wellness4MDs program can reduce the prevalence and severity of stress, burnout, anxiety, and depression, and improve well-being among physicians, postgraduate medical trainees, and medical students. The findings would therefore be of interest to policy makers, especially those working in the health care sector.

Conclusion

The Wellness4MDs program is an innovative first-line population-level, cost-effective, and easily scalable e–mental health program that is expected to reduce psychological problems in physicians, postgraduate medical trainees, and medical students in Canada. The successful implementation of Wellness4MDs and positive outcomes will provide the imperative and overarching guidance on the design, implementation, and evaluation of similar e–mental health interventions tailored for the health workforce globally, including nurses and allied health professionals.

Acknowledgments

Wellness4MDs program would be promoted through collaborating organizations in each province, including but not limited to the Alberta Health Services, Nova Scotia Health Authority, College of Physicians and Surgeons of Nova Scotia, Dalhousie University, and the University of Alberta.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization was performed by VIOA. Methodology was performed by VIOA, RS, BA, RD, GOD, MKA, SS, and NLY. Resources were contributed by VIOA. Writing of the original draft was done by RS and VIOA. Reviewing and editing were performed by RS, BA, RD, GOD, MKA, SS, NLY, and VIOA. Project administration and funding acquisition were handled by VIOA. All authors have read and agreed to the published version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
GAD: generalized anxiety disorder
GAD-7: 7-item Generalized Anxiety Disorder
MBI: Maslach Burnout Inventory
MDD: major depressive disorder
PHQ-9: 9-item Patient Health Questionnaire
WHO-5: World Health Organization–Five Well-Being Index

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Protocol

A Digital Intervention for Capturing the Real-Time Health Data Needed for Epilepsy Seizure Forecasting: Protocol for a Formative Co-Design and Usability Study (The ATMOSPHERE Study)

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Abstract

Background: Epilepsy is a chronic neurological disorder affecting individuals globally, marked by recurrent and apparently unpredictable seizures that pose significant challenges, including increased mortality, injuries, and diminished quality of life. Despite advancements in treatments, a significant proportion of people with epilepsy continue to experience uncontrolled seizures. The apparent unpredictability of these events has been identified as a major concern for people with epilepsy, highlighting the need for innovative seizure forecasting technologies.

Objective: The ATMOSPHERE study aimed to develop and evaluate a digital intervention, using wearable technology and data science, that provides real-time, individualized seizure forecasting for individuals living with epilepsy. This paper reports the protocol for one of the workstreams focusing on the design and testing of a prototype to capture real-time input data needed for predictive modeling. The first aim was to collaboratively design the prototype (work completed). The second aim is to conduct an "in-the-wild" study to assess usability and refine the prototype (planned research).

Methods: This study uses a person-based approach to design and test the usability of a prototype for real-time seizure precipitant data capture. Phase 1 (work completed) involved co-design with individuals living with epilepsy and health care professionals. Sessions explored users' requirements for the prototype, followed by iterative design of low-fidelity, static prototypes. Phase 2 (planned research) will be an "in-the-wild" usability study involving the deployment of a mid-fidelity, functional prototype for 4 weeks, with the collection of mixed methods usability data to assess the prototype's real-world application, feasibility, acceptability, and engagement. This phase involves primary participants (adults diagnosed with epilepsy) and, optionally, their nominated significant other. The usability study will run in 3 rounds of deployment and data collection, aiming to recruit 5 participants per round, with prototype refinement between rounds.

Results: The phase-1 co-design study engaged 22 individuals, resulting in the development of a mid-fidelity, functional prototype based on identified requirements, including the tracking of evidence-based and personalized seizure precipitants. The upcoming

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phase-2 usability study is expected to provide insights into the prototype's real-world usability, identify areas for improvement, and refine the technology for future development. The estimated completion date of phase 2 is the last quarter of 2024.

Conclusions: The ATMOSPHERE study aims to make a significant step forward in epilepsy management, focusing on the development of a user-centered, noninvasive wearable device for seizure forecasting. Through a collaborative design process and comprehensive usability testing, this research aims to address the critical need for predictive seizure forecasting technologies, offering a promising approach to improving the lives of individuals with epilepsy. By leveraging predictive analytics and personalized machine learning models, this technology seeks to offer a novel approach to managing epilepsy, potentially improving clinical outcomes, including quality of life, through increased predictability and seizure management.

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KEYWORDS

epilepsy; seizure forecasting; data science; artificial intelligence; machine learning; wearable technology; mobile phone

Introduction

Background of the Study

Epilepsy, a chronic neurological disorder, is characterized by recurrent and unpredictable seizures, affecting individuals across all age demographics [1]. As a leading cause of chronic morbidity globally, epilepsy presents significant challenges, including a heightened risk of premature death, injuries, and diminished quality of life [2]. With a prevalence rate of 5-10 cases per 1000 people [1], the disorder imposes a considerable burden on individuals and health care systems alike. The financial impact is also notable, with the UK National Health Service spending approximately £1.5 billion (US $2 billion) annually on care that ranges from primary treatment and management to addressing seizure-related injuries and mental health issues [3,4]. The disability-adjusted life-years rates in the United Kingdom, estimated at 92,400 per 100,000 population [5], highlight the extensive health loss attributed to epilepsy. Sudden unexpected death in epilepsy remains a critical concern, with an incidence rate of approximately 1 in 1000 people with epilepsy annually, emphasizing the need for ongoing research and innovative management strategies [6,7]. Accurate forecasting of seizures could allow people with epilepsy to take additional safety precautions at times of increased risk.

Rationale for the Study

Despite advancements in treatment—such as resective surgery, neurostimulation devices, new antiseizure medication, many with novel modes of action, not to mention the increasing availability of treatment across the world, with several antiseizure medications on the World Health Organization's list of essential medicines—approximately one-third of the population (more than 50 million people) living with epilepsy globally still experience uncontrolled and apparently unpredictable seizures [8]. A large community survey (n=1056) [5] and the UK Epilepsy Priority Setting Partnership [9] ranked the unpredictability of seizures as one of the most impactful aspects of the condition and a research priority, underscoring an urgent need for solutions that can offer predictability and management of seizure risk. Seizure forecasting technologies emerge as a promising avenue in this regard, potentially enabling individuals to take pre-emptive measures during high-risk periods, therefore mitigating the risk of injury and premature death, and alleviating the psychological burden associated with the unpredictability of seizures [10].

One potential avenue for seizure forecasting is leveraging technologies that directly monitor brain activity, combining this with data analytics to explore seizure risk modeling. Video–electroencephalography (EEG) is the gold standard for monitoring brain biosignals to detect seizure activity. However, this is not well-suited to explore as an out-of-clinic seizure forecasting solution, as it is not feasible for long-term use in real-world scenarios [11]. Ultra–long-term electroencephalography monitoring (UNEEG) represents a significant advancement in the field [12]. UNEEG's technology, involving surgical implantation, offers continuous EEG data capture in the user's real-world context. People with epilepsy who have trialed the technology have found the continual monitoring valuable, both in terms of internalizing their locus of control and providing information to inform treatment changes. However, UNEEG is a minimally invasive method with intrinsic risks and costs of surgery, making it inaccessible to a wider range of users [12,13]. Noninvasive scalp EEG represents a more accessible solution that is designed for use outside of clinical settings. Yet, the adoption of this technology is hampered by limitations such as the stigma of visible devices, practicality, acceptance among users [13], and the technical and practical challenges of long-term outpatient monitoring [14].

An alternative seizure forecasting approach is to explore predictive analytics based on seizure precipitants that can be captured through noninvasive, nonmedical grade wearable devices (WDs), such as smartwatches. This presents a high-potential solution, as ubiquitous wearable technologies can be easily integrated into the end user's everyday life, to continuously capture real-time data over the long term. Noninvasive WDs that can be used outside of clinical settings have been successfully used for epilepsy management in the form of the Empatica E4 wristband [11]. This device has shown promise in detecting epileptic seizures by monitoring physiological parameters such as heart rate and acceleration. However, the Empatica E4 focuses primarily on seizure detection rather than forecasting [11].

Exploration of seizure forecasting based on seizure precipitant data remains in its infancy. Emerging research has explored seizure cyclicity for forecasting models. However, these

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approaches on their own have limited accuracy for seizure forecasting [15-17]. There is potential to build upon and improve these models by including a greater range of seizure precipitants. This is a promising approach, given the existing evidence on the range of external and physiological variables that play a precipitating role in seizure propagation. Measurable biomarkers, such as emotional stress, infections, menstrual cycles, sleep deprivation, and alcohol use, have all been identified as seizure precipitants. The relationship between precipitants and seizure propensity could be quantified using mathematical models [13,17], with these models informing algorithms to analyze person-specific data and facilitating personalized seizure forecasts.

Ubiquitous technologies with multimodal sensors, combined with ecological momentary assessment (EMA; repeated sampling of an individual's cognitions, emotions, symptoms, and behaviors) could enable the real-time capture of the broad spectrum of known seizure precipitants. These real-time data, combined with predictive analytics, offer a feasible and accessible solution for seizure forecasting. To our knowledge, there is a pressing need to address the research gap in developing and evaluating technology for real-time seizure precipitant data collection, essential for supporting seizure forecasting interventions.

Person-Based Approach

A technology to collect real-time seizure precipitant data relies on people with epilepsy actively engaging with the technology. As such, it is essential that a user-centered design approach is taken. The person-based approach [18] integrates methods from user-centered design and qualitative research to design and evaluate complex digital health technologies. This approach can lead to solutions that are more acceptable, feasible, meaningful, and optimally engaging to the people who will use them. The person-based approach advocates undertaking iterative design cycles with users through both formal qualitative research and patient and public involvement. Previous research [16,19] underscores the necessity of using person-based approach for the future design of epilepsy-related technologies, emphasizing iterative design cycles and user involvement to create solutions that are not only technologically effective but also deeply aligned with the needs and experiences of those living with epilepsy. Therefore, this study used the person-based approach, recognizing its critical role in developing effective, user-centered epilepsy management technologies.

The ATMOSPHERE study, funded by the Engineering and Physical Sciences Research Council (EPSRC) and in collaboration with the N-CODE network [20], represents an effort to leverage technology for the benefit of individuals with epilepsy. The ATMOSPHERE project is an early-stage, proof-of-concept research initiative seeking to develop and evaluate a noninvasive, wearable, epileptic seizure forecasting technological solution. This innovative approach aims to tackle the apparently unpredictable nature of seizures by collecting real-time data on various seizure precipitants, such as sleep quality, heart rate, menstrual cycle, medication adherence, and stress levels, from adults living with epilepsy.

The ATMOSPHERE Project

The entire project is organized into several work packages, each targeting a specific aspect of seizure forecasting technology development, such as (1) work package 1—synthesizing the evidence based on seizure precipitants or triggers, (2) work package 2—designing and testing the usability of a mid-fidelity functional prototype to capture real-time precipitant data from individuals living with epilepsy, (3) work package 3—developing predictive models for seizure risk forecasting, and (4) work package 4—identifying user requirements for the end user app interface including presenting seizure forecasting output. Developing a high-fidelity functional prototype is based on the outcome of the usability study in work package 2.

This protocol paper specifically addresses workstream 2 of the ATMOSPHERE study, reporting the results from the completed co-design study and outlining the protocol for the upcoming usability study.

Aims of Work Package 2

This multiphase research workstream aims to design, develop, and test prototypes for collecting real-time data on seizure and seizure precipitants.

Objectives

The first objective is to collaboratively design a mid-fidelity functional prototype capable of collecting real-time seizure and seizure precipitant data from people with epilepsy. The second objective is to conduct "in-the-wild" usability testing of this prototype to evaluate its feasibility and user acceptance and engagement. This step is critical to assessing the data capture prototype's real-world application and identifying areas for improvement based on user feedback. The third objective is to use insights gained from usability testing to refine and enhance the prototype, and focus on improving its functionality, ease of use, and overall effectiveness in collecting high-quality data for seizure forecasting.

Methods

Study Design

Drawing on the person-based approach [21], we undertook iterative patient and public involvement to co-design the data collection prototype (phase 1). We are now preparing to conduct a mixed methods "in-the-wild" usability study in phase 2 to further investigate the prototype's usability and implement refinements (Figure 1).

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Figure 1. Overview of study phases, with the study design based on the person-based approach.

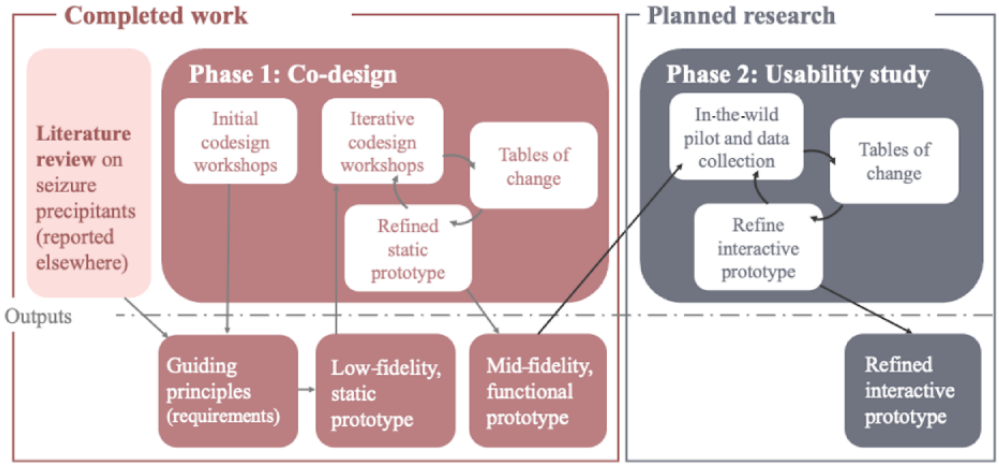

Phase 1: Co-Design—Completed Work

Co-Design Contributors

Lived Experience Contributors

We disseminated an advertisement for the co-design sessions through Epilepsy Action (a UK epilepsy charity) and the SHAPE Network (the Epilepsy Research Institute; United Kingdom's patient and public involvement and engagement service group). The advertisement invited individuals with lived experience of epilepsy to take part in the co-design workshops and provided a link to an expression of interest form capturing consent for the research team to contact the individual. We invited individuals completing the expression of interest form to complete a form capturing clinical and demographic characteristics; these data were pseudonymized and used to understand the diversity of the group.

Health Care Professional Contributors

We used our existing professional networks to invite health care professionals with experience in providing care for epilepsy, both in primary and secondary care services.

Co-Design Sessions

Lived Experience Contributor Sessions

The co-design involved iterative workshops, based on workshop plans and lasted 60-90 minutes. Early sessions explored the acceptability of collecting evidence-based precipitant data, views on the content of EMA items, the acceptability of different wearables for data collection, and the wider sociotechnical space within which the technology would be used. From these early sessions, a guiding principles document [21] was developed to identify the users' needs, context, and required components for the data-collection technology (presented in *Phase 1: Co-Design—Completed Work* in the *Results* section). Based on the guiding principles, we developed a low-fidelity prototype in Microsoft PowerPoint. In subsequent user consultation sessions, we iteratively refined the prototype by gathering feedback, completing a table of changes document (a summary of required changes) [21], and implementing required changes.

Health Professional Contributor Sessions

We conducted one-to-one discussions through video calls using a semistructured topic guide lasting 30-60 minutes. Discussions explored the health professionals' views on design considerations from the perspectives of people with epilepsy, design considerations from the clinician's perspective (eg, how data might fit into the clinical workflow), and an investigation into the potential harms or unintended consequences. From these discussions, a guiding principles document was developed that informed prototype design.

Prototype

At the end of the co-design process and in preparation for the usability study, a functional mid-fidelity prototype was developed (discussed in detail in the *Results* section; Figure 2).

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Figure 2. An overview of the mid-fidelity, interactive prototype for the primary participant. API: application programming interface.

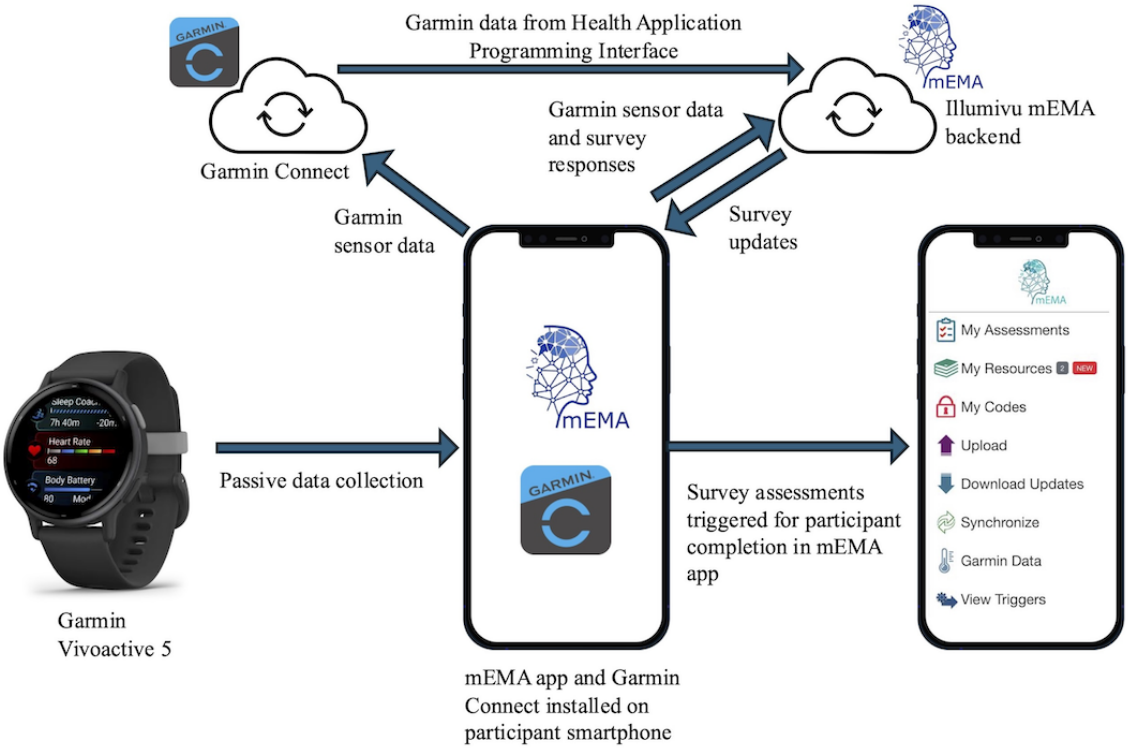

Phase 2: Usability Testing—Protocol for Planned Research

Participants

Primary Participants

The primary participants in this study will be adults diagnosed with epilepsy. We will disseminate an advertisement through Epilepsy Action, the SHAPE Network, and Caafi Health (an organization with expertise in engaging underserved communities, for example, those from ethnic minority groups) [22]. The inclusion and exclusion criteria for participation in the study are detailed in Textbox 1. These criteria were established to ensure that participants will be representative of the broader population of individuals with epilepsy, while also considering safety and ethical considerations pertinent to conducting research within this group.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Primary participant (participant with epilepsy diagnosis)
  - Adult (older than 18 years)
  - Have a diagnosis of epilepsy
  - Likely to have a seizure within the 4-week testing period (based on self-report)
  - Are fluent in English (to be able to engage with the technology and qualitative interview)
  - Can provide consent
  - Can wear a wrist wearable device (smartwatch)
  - Able to input data into a smartphone app
  - Own a smartphone that can download apps from either the Apple Store (iPhone) or the Google Play Store (Android phones; individuals were not required to own a smartwatch as this was supplied as part of the study)
- Nominated participants (a significant other identified by the primary participant)
  - Nominated by a person meeting the criteria above
  - Adult (older than 18 years)
  - Fluent in English (to be able to engage with the technology and qualitative interview).
  - Able to consent to the study
  - Own a smartphone which can download apps from the Google Play Store or the Apple Store
  - Be able to input data into a smartphone app

Exclusion criteria

- Primary participant (participant with epilepsy diagnosis)
  - Those who have a major cardiac condition
  - Those with a diagnosis of a major psychiatric condition (defined as needing secondary care mental health services support)

Nominated Participants

The primary participants (adults living with epilepsy) will be invited to nominate a significant other, such as a carer, friend, or family member, to also participate in the study. This will be optional. The inclusion and exclusion criteria for nominated participants are detailed in Textbox 1.

Recruitment and Consent Process

Primary Participants (Individuals Living With Epilepsy)

Potential participants will be given a participant information sheet and invited to contact the research team to express interest in the study. Those expressing interest will be asked to complete a sampling form, providing demographic and clinical information; this will be used to undertake purposeful sampling, aiming to recruit a diverse sample in terms of age, gender, ethnicity, and the type of epilepsy. Individuals sampled for the study will initially be contacted by an epilepsy clinician who will screen for eligibility. Eligible participants will then be contacted by a member of our research team for a recruitment consultation. Following the recruitment and screening consultation, informed consent will be obtained from individuals wishing to participate. This consent process will be conducted in accordance with ethical guidelines to ensure that participants are fully informed and willing to participate in the study voluntarily.

Nominated Participants

On entering the study, the primary participants will be invited to nominate a significant other (eg, family member, friend, and carer) and provide consent for us to contact this individual. We will contact these nominated individuals, provide them with a participant information sheet, undertake a recruitment consultation, and obtain fully informed consent from those wishing to take part.

Sampling and Sample Size

To achieve a comprehensive understanding of the usability and effectiveness of the intervention, we aim to recruit approximately 15 primary participants (with additional nominated participants). Recruitment will be organized into 3 rounds, with each round consisting of 5 participants. The sample size of 5 primary participants per round was based on the usability testing literature, where a sample size of 3-5 participants has been found to detect the majority of usability problems [23]. This phased approach will allow for iterative refinements to the intervention and study procedures based on feedback from each round of participants, enhancing the robustness and relevance of our findings.

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Study Procedures

Participant Procedure 1: Customization Survey and Onboarding

The prototype is a smartwatch and smartphone app for the primary participant and a smartphone app only for the nominated participant (full description of the prototype is given in the *Methods* section). Participants will be sent a questionnaire (using Microsoft Forms) to gather their requirements for customization (description of customization options is given in the *Methods* section), and the prototype will then be adapted to their requirements. Participants will be sent the prototype, along with details for downloading the smartphone app, and we will undertake an onboarding meeting to orientate participants to the technology.

Participant Procedure 2: Deployment of Data Collection Prototype

Participants will be invited to use the technology for 4 weeks. The 4-week study period was intentionally chosen to encompass a complete menstrual cycle, enabling comprehensive capture of physiological data parameters across the full cycle. If the research team notices that the user has not worn the device or manually entered the data, the participant will be sent an email offering a technical support meeting.

Participant Procedure 3: Qualitative Interview

At the end of the 4-week usability period, the participants will be invited to a qualitative interview with a member of the research team (video call or face-to-face, depending on participant preference and feasibility of travel for the research team). This qualitative interview will use a semistructured topic guide, will be designed to last up to 60 minutes, and will be audio recorded by Microsoft Teams. We will explore various fields, such as section 1, an open-ended exploration of the participant's views and experiences of the technology, including an exploration of the technology within the sociotechnical space; section 2, exploration of the technology features, for example, cotracking and passive data collection; section 3, exploration of the specific items and wording of the EMA; and section 4, exploration of views to improve the technology (also gathered throughout sections 1-3)

Upon completion of the study, participants will receive financial compensation and can opt to receive a visual summary of the data collected.

Outcome Measures to Investigate Feasibility, Acceptability, and Engagement

The outcome measures being used to determine feasibility, acceptability, and engagement are reported in Table 1.

Table 1. Outcome measures for feasibility, acceptability, and engagement.

Outcome measure	Data points	Analysis
Quantitative outcome measures		

Smartwatch wear time	Assessed using the presence of the heart rate data	• Descriptive statistics[a] on
		  • Proportion of days the device was worn for
		  • Number of hours during the day the device was worn for

EMA[b] response rate	Assessed for each EMA item	• Descriptive statistics on response rate for each EMA item
Qualitative outcome measure		
Users' perspectives	Qualitative interview data	• Thematic analysis [24] on pseudonymized transcripts to identify issues related to acceptability, feasibility, and engagement • Tables of change to identify requirements to optimize the prototype

[a]Descriptive statistics: measures of central tendency (mean and median) and dispersion (SD and IQR) to provide a comprehensive overview of the wear time, response rate, and missing data.

[b]EMA: ecological momentary assessment.

Prototype Refinement

After each usability round, we will analyze qualitative interview data to produce a table of changes document, identifying requirements to optimize the prototype [21]. If feasible, these changes will be implemented before the next round of deployment (Figure 1).

Ethical Considerations

Phase 1 involved a co-design with patient and public involvement contributors, which does not necessitate formal ethical approval [25]. However, we adhered to the General Data Protection Regulation (GDPR) guidelines [26]. To protect patient and public involvement contributor privacy, we used pseudonymization for sampling forms, and we secured consent to report aggregated data. During co-design sessions, no direct quotes were captured; instead, we created summaries in the form of guiding principles and tables of changes. We offered patient and public involvement contributors the equivalent of £20 per hour (US $26) in shopping vouchers.

For phase 2, ethical approval was obtained from the University of Bristol, Faculty of Engineering Research Ethics Committee on March 10, 2022 (reference 10152). In alignment with our commitment to data privacy and protection, we carried out a data protection impact assessment [27]. This assessment (ensures compliance with the GDPR within the European Union [26]), aims to evaluate and minimize potential risks to the rights and freedoms associated with personal data. The information compliance manager and data protection officer from the

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University of Bristol approved the data protection impact assessment on January 29, 2024.

Results

Phase 1: Co-Design—Completed Work

Overview

We involved 12 individuals with lived experience of epilepsy, undertaking 21 consultations across the iterative design process. We involved 10 clinicians, with each individual contributing once. The demographic and clinical demographics are presented in Table 2. Table 3 presents the guiding principles derived from the co-design sessions. The first row is based on existing evidence, the subsequent rows are based on the co-design.

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Table 2. Summary of numbers, demographic, and clinical characteristics of patient and public involvement contributors.

Characteristics	n (%)
Individuals with lived experience (n=12)	
Gender	
Women	8 (67)
Men	4 (33)
Geographical region	
South East England	7 (58)
South West England	3 (25)
West Midlands	1 (8)
East Midlands	1 (8)
Ethnicity	
White British	10 (83)
Not reported	2 (17)
Age (years)	
More than 65	1 (8)
55-64	2 (17)
45-54	2 (17)
35-44	4 (33)
25-34	1 (8)
Not reported	2 (17)
Levels of deprivation[a]	
10% and 20% most deprived	0 (0)
30% and 40% most deprived	4 (33)
50% most deprived	1 (8)
50% least deprived	3 (25)
30% and 40% least deprived	4 (33)
10% and 20% least deprived	0 (0)
Seizure types[b]**, n**	
Tonic clonic	5
Focal impaired awareness	4
Absence	3
Complex partial	2
Focal aware	2
Tonic	1
Atonic	1
Myoclonic	1
Drop seizures	1
Not reported	3
Health professionals (n=10)	
Professional background	
General practitioner	3 (30)
Epilepsy nurse specialist	3 (30)

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Characteristics	n (%)
Learning disability nurse or psychiatrist	2 (20)
Junior doctor	2 (20)

[a]Estimated using contributors' postcodes against the 2019 English Indices of Deprivation data.
[b]Some contributors identified as having multiple characteristics within the domain.

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Table 3. Guiding principles for data collection technology.

User characteristics	Key feature(s)[a]
Individuals with epilepsy	
• Individuals with epilepsy are likely to have precipitants to seizures, as documented in the evidence.	• Features to enable tracking of a range of evidence-based precipitants: emotional states, stress, fatigue, sleep disturbance, phase of menstrual cycle, seizure cycles, medication usage, and fever or illness.

• In addition to evidence-based precipitants, individuals experience:
  • A wide range of other seizure precipitants (eg, cognitive overwhelm and certain foods).
  • Auras and prodromal symptoms (eg, speech, emotional, and behavioral changes).
	• Features to offer customized tracking of personal seizure precipitants and prodromal symptoms, including subjective experiences.

• Precipitants and prodromal symptoms can be personal (ie, specific to that individual), subjective (ie, hard to capture with objective, sensing data), and sometimes the individual can lack insight in these variables (see cotracking below).	
• SUDEP[b] is a major concern for users, and users would like SUDEP risk assessments. Some users already complete regular SUDEP risk assessments (including on mobile apps).	• There are existing apps for SUDEP risk assessment [28]. Consideration should be given to how the apps could work together.
• With assurances around privacy and security, individuals are positive about providing data that may improve forecasting performance. • Most users are positive about active, manual tracking, viewing this as necessary for subjective data points (eg, mood and fatigue). Many users already actively track seizures and precipitants (eg, through paper diaries and spreadsheets). Some users described tracking as giving a sense of control and empowerment. • However, active tracking can be a burden and challenging due to memory impairment and reduced insight. There may be strong individual differences (see "individual differences" below) in the desire or ability to actively track.	• Features to maximize trust, identity, privacy, and security in the collection, processing, and storage of data. • Features to passively track precipitants, prioritizing passive where possible. • Features to enable manual tracking of trigger data, as an option for those willing and able.
• Epilepsy management often involves carers, families or friends, and individuals with epilepsy would like the technology to reflect this. • Some individuals with epilepsy are fully reliant on carers to track precipitants. Some manage independently but still have periods when they need support from their significant other(s) to track precipitants (eg, during periods of epilepsy-related amnesia or reduced consciousness, due to cognitive impairment and due to deceased personal insight). • Individuals still want a sense of independence and control over the tracking process.	• Features to enable optional cotracking; whereby significant others (family, friends, or carers) can also track data on the primary user's health states. This feature must preserve independence, giving the user control over who tracks, what they track, and control over stopping cotracking.
• Different seizure types present different types of risks to individuals and require different self-management approaches.	• Feature for individuals to track different seizure types, to enable forecasting to differentiate between seizure types.

• There are individual differences in the user group. Some that need particular attention are:
  • The variability in the motivation for actively tracking data.
  • Vulnerable and digitally excluded groups need careful consideration. This may include older adults (with a higher prevalence of certain types of epilepsy, for example, poststroke seizure), those with an intellectual disability (who have higher prevalence of epilepsy and treatment-resistant seizures), and those who are socially disadvantaged (eg, lower level of education, drug users, prisoner population, and homeless populations).
	• Simplicity and accessibility are essential. The technology should draw upon HCI[c] principles to achieve inclusive design [29].

Clinicians (secondary care)	

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User characteristics	Key feature(s)[a]

• Out-of-clinic data are critical for diagnosis and treatment planning. However, out-of-clinic data are often limited or can be inaccurate.
• Fuller and accurate data that would be useful for diagnosis and management include:
  • seizure data: type, frequency, and duration
  • postictal symptoms
  • medication adherence
  • medication side effects
  • the individual precipitants
	• Features to enable tracking of data useful for clinical management.

[a]Key feature(s): a feature is a component of an application from the end user's perspective.

[b]SUDEP: sudden unexpected death in epilepsy.

[c]HCI: human-computer interaction.

Prototypes and Tables of Change

Based on the guiding principles, a low-fidelity prototype was initially developed, and a table of changes was used to capture user requirements for further refinement. Based on the final tables of change, a mid-fidelity and functional prototype was developed (presented in Figure 2 and Table 4). The mid-fidelity functional prototype and study materials (customization questionnaire and onboarding process) were tested with 3 patient and public involvement contributors (all people with epilepsy) before the implementation of the main usability study.

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Table 4. Data collection protocol from primary participants.

Data point	Data collection schedule
Garmin (passive data)	
Sleep score	• Daily summary
Heart rate	• Continuous
Respiration rate	• Continuous
Pulse oximetry blood oxygen saturation	• Continuous
Stress score	• Continuous
Accelerometer	• Continuous
Ambient light	• Continuous
Step count	• Continuous
Smartphone App (EMA[a])	
Seizure event (type, timing, duration, and severity)	• Notification[b]: twice daily • User-initiated[c]
Prodromal symptoms	• Notification: once daily
Postictal symptoms	• Notification: once, if seizure event reported
Epilepsy medication usage (routine and emergency)	• Notification: once daily notification • User-initiated
Emotional states and emotional intensity	• Notification: twice daily • User-initiated • Contingent[d]: if elevated stress detected on Garmin (capped at 3 notifications daily)
Sleep duration and quality	• Notification: once daily
Acute illness or infection	• Notification: once daily
Customizable precipitant question	• Notification: once daily
Alcohol intake	• Notification: once daily
Menstrual cycle	• One-off series of questions

[a]EMA: ecological momentary assessment.

[b]Notification: smartphone notification pushed to user as a prompt for them to complete the EMA item.

[c]User-initiated: users able to open the app and complete the EMA item any time.

[d]Contingent: a push notification prompting EMA completing sent, based on data from the Garmin device.

Primary Participant

Data collection will take place through the mEMA (Illumivu) app installed on participants' smartphones, connected to a Garmin VivoActive 5 smartwatch worn by participants as outlined in Figure 2. Quantitative data captured passively through the Garmin wearable (Table 4) will be streamed to the mEMA app and relayed to an encrypted database hosted by Illumivu. Simultaneously, Garmin sensor data will be relayed to Garmin Connect and processed through Garmin's algorithms to generate compound measures (based on a combination of variables), such as stress level and sleep score, which will be streamed to Illumivu's backend by Garmin's Health application programming interface (Figure 2). The use of Garmin's API enables access to the raw data from the smartwatch. These data are transmitted by Bluetooth directly from the WD to the mEMA app on the phone. From there, raw data are sent up to the Illumivu servers to be integrated with incoming EMA data.

The EMA surveys that participants will receive in the mEMA app have been developed for participants to record data on

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seizures (type, timing, duration, and severity), prodromal symptoms, postictal symptoms, and seizure precipitants (triggers). There will be three modes for EMA completion: (1) daily notifications to the participant at a set time to prompt EMA survey completion; (2) contingent notifications, based on Garmin data (eg, elevated stress levels) to prompt survey completion; and (3) user-initiated data entry, where the users can access the app and enter the data on an ad hoc basis. Completed surveys will be uploaded to the secure mEMA backend where they can be accessed by permissioned members of the core research team.

Customizable Components

There are some elements that can be customized by the participants. First, EMA notification timings—EMA notifications will be sent between 8 AM and 8 PM. Users can indicate times within this window during which they do not wish to receive notifications. Second, optional survey items—users can opt-in to receive questions on the menstrual cycle and EMA items on alcohol usage. Third, personalized EMA item—users will be asked if they would like to track an individual, personal seizure precipitant, and if feasible, we will create a personalized EMA item to capture these data.

Nominated Participant for Cotracking (Optional)

During the customization process, the primary participant will select which EMA items they consent for the nominated participant to receive (options being medication usage, emotional states and intensity, sleep duration and quality, alcohol intake, seizure events, prodromal symptoms, and postictal symptoms). The nominated participant will use the mEMA app installed on their smartphone and will receive notifications as prompts to complete the EMA survey.

Phase 2: Usability Testing—Planned Research

This phase focuses on usability and the refinement of the prototype. Data collection for phase 2 started in May 2024, and the findings are expected to be available in August 2024.

Discussion

Principal Findings

This paper reports (1) the co-design process of a novel technology designed to collect real-time data needed for seizure forecasting and (2) the protocol for the usability testing of the prototype. Our co-design identified guiding principles for the prototype, including:

1. The implementation of tracking features for both evidence-based and custom seizure triggers, sudden unexpected death in epilepsy risk data, and data to support clinical management. These features are designed to maximize user trust, identity protection, privacy, and security in the handling of data.
2. Where feasible and appropriate, passive tracking methods should be used, with the option for users to log data actively or manually on potential seizure precipitants.
3. The introduction of cotracking features, giving users the freedom and capability to invite significant others (such as caregivers, friends, or family members) to participate in tracking precipitants of seizure onset.
4. The accommodation of diverse user needs and preferences, ensuring the design is inclusive and considers individual differences.

Strengths and Limitations

This project emphasized the co-design of the prototype, ensuring that the technology aligns with the preferences and requirements of its target community. We engaged with clinicians from a range of relevant clinical specialties. We also engaged with a diverse group of individuals living with epilepsy, varying in aspects such as gender, age, seizure type, and socioeconomic background (determined by indices of deprivation). Individuals living with epilepsy are a diverse group, and we acknowledge that it will be important to continue to gather more views on the technology beyond the 15 individuals involved in the phase-1 co-design. A notable limitation of phase 1 is the lack of ethnic diversity among contributors and absence of individuals from the very lowest indices of deprivation. To find a remedy, in phase 2, we are working with a specialized organization to actively engage and involve ethnic minority groups and those from more deprived areas. This approach aims to make the development more inclusive and the technology more representative of the community it serves.

The second phase of our study is designed to evaluate the usability of our technology in a naturalistic setting (in the wild). The prototype undergoing testing is currently focused exclusively on the capabilities related to data collection. Consequently, it does not yet incorporate the advanced features, such as predictive analytics, for determining seizure risk scores and the provision of seizure forecasting outputs to end users. These more sophisticated functionalities are currently under development within separate workstreams. It is hypothesized that the availability of seizure forecasting output would serve as the primary motivation for individuals to continuously use the technology over an extended period. Therefore, the current limitation of the prototype, in its inability to replicate this aspect of real-world application and motivation, is acknowledged. To offset this limitation, we have endeavored to introduce an alternative form of motivation for participants by offering summaries of their data (data visualizations of seizure and precipitant data) at the conclusion of the study period.

The data collection protocol, including the type and frequency of prompts, was co-designed with individuals with lived experience. Subsequently, the prototype was tested with 3 patient and public involvement contributors who did not raise concerns about the frequency of prompts. Instead, users welcomed the reminders, especially those experiencing the well-documented memory impairments associated with epilepsy [30]. However, there is a possibility that the frequency of prompts could be burdensome when the technology is used in the wild over an extended period. During qualitative interviews, we will explicitly explore participants' views on the data collection protocol, and we will refine the protocol, where necessary, based on this feedback.

The prototype developed for this phase is characterized as a mid-fidelity and functional prototype, which permits the testing

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of its core functionalities, such as passive data collection and EMA. Despite its capabilities, this prototype is not without its limitations, including a user experience interface that may not meet high standards and the necessity for some manual operations. However, the adoption of an agile methodology for this phase offers significant advantages. This approach allows for rapid learning and adjustments based on real-world, in-the-wild use, aligning with the principles of technological probing. While acknowledging its current constraints, this phase is pivotal in facilitating immediate, invaluable insights into the usability and potential impact of the technology in everyday contexts, guiding subsequent developments and enhancements.

This phase of the study did not include individuals with intellectual disabilities, an important population given their increased risk of epilepsy [31]. Recognizing the necessity of designing interventions that cater specifically to their needs, it is evident that this group requires a thorough investigation into their specialized design requirements (beyond the scope of this study). Such an exploration should be a priority for future research to ensure the development of more inclusive and effective solutions. Furthermore, the study focuses on adults, and a separate investigation for pediatric epilepsies is needed.

Overall, this work will inform the development of a high-fidelity functional prototype. The assessments of that prototype will be conducted through user experience walkthroughs and qualitative interviews to identify usability and accessibility challenges. The results from these upcoming assessments will be reported in a separate paper for work package 4.

Conclusions

The co-design presented here identified user requirements for technology to capture the real-time data needed for seizure forecasting. Requirements include the ability to collect data passively where possible (with options for manual data input); collect custom, personal seizure precipitant data (in addition to evidence-based precipitant data); enable cotracking, where family or carers can input data; and consider inclusive design (due to variation in user characteristics and needs). The planned research in phase 2 will test the usability test of a mid-fidelity and functional prototype developed to meet these requirements. This co-design and usability testing contributes to a broader research aim; to develop seizure forecasting technology, leveraging real-time data on seizure precipitants, and using predictive analytics.

This technology could significantly improve the quality of life for individuals with epilepsy. By providing insights into the likelihood of seizure occurrence, such technology could offer a new level of independence and safety, reduce the economic and health care burdens associated with epilepsy, and facilitate a more personalized and efficient use of health care resources for epilepsy management. This technology development will be explored through proof-of-concept research of developing a noninvasive, WD specifically designed for seizure forecasting, integrating machine learning models for personalized predictive analytics, and using smartphone apps for real-time feedback to end users.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study. Phase 1 was co-designed through patient and public involvement; therefore, no research data are available. Phase 2 is planned research; therefore, no research data are available.

Authors' Contributions

EEVQ drafted the initial paper and is involved in data collection and analysis for phase 2. SD was involved in setting up the prototype for phase 2 and is involved in data collection and analysis for phase 2. MTD was involved in the co-design sessions and outputs for phase 1. LS and RC conceptualized the study and were involved in the co-design sessions for phase 1. PT conceptualized the study and offered supervision from a clinical perspective. LJ, PK, YQ, AKK conceptualized the study. AB conceptualized the study, designed the methodology of both phases, supervised the phase-1 co-design sessions and outputs, supervised prototype development, is supervising the data collection and analysis for phase 2, and supervised the paper write-up. All authors reviewed and contributed to the paper.

Conflicts of Interest

RC is a data scientist at Neuronostics. Neuronostics develops technologies for the diagnosis, treatment, and monitoring of neurological conditions, including epilepsy. The other authors declare no conflicts of interest.

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Abbreviations

EEG: electroencephalography
EMA: ecological momentary assessment
EPSRC: Engineering and Physical Sciences Research Council
GDPR: General Data Protection Regulation
UNEEG: ultra–long-term electroencephalography monitoring
WD: wearable device

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Protocol

Patterns of Use and Withdrawal Syndrome in Dual Cannabis and Tobacco Users (DuCATA_GAM-CAT): Protocol for a Mixed Methods Study

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Abstract

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Background: Approximately 1 in 6 cannabis users develop a cannabis use disorder (CUD) and the odds increase to 1 in 2 for daily users.

Objective: The Dual use of Cannabis and Tobacco Monitoreing through a Gamified Web app (DuCATA_GAM-CaT) project aims to identify cannabis-tobacco patterns of use and withdrawal symptoms among individuals with CUD who are attending substance abuse programs.

Methods: The project uses a mixed methods approach consisting of 3 studies. First, a participatory qualitative study involves focus groups comprising individuals with CUD, clinicians, project researchers, and an expert gamification company to co-design a gamified web app. Second, a longitudinal prospective study to follow up individuals over 6 weeks with CUD attending substance abuse programs . Participants report their cannabis-tobacco usage patterns, type and frequency of tobacco use, nicotine dependence, withdrawal symptoms, psychoemotional factors, and motivation to quit both substances. Predictive analysis techniques are used to analyze clinical, demographic, psychological, and environmental data to predict the probability of achieving abstinence. Third, homogeneous focus groups to explore participants' experiences during their CUD treatment.

Results: By June 2024, the project had completed the first study, defining eligible cannabis user profiles, developed the initial web app prototype, and initiated recruitment across 10 centers, with 74 participants enrolled, aiming to reach 150 participants in total.

Conclusions: All participants are required to provide informed consent, and their information is kept confidential and anonymized following confidentiality rules. The research team is committed to disseminating the results obtained to professional and patient groups, as well as informing public health agents, to positively influence political and social decision makers and design programmers. Additionally, we aim to prioritize the publication of the results in high-impact journals specialized in drug abuse, public health, and health care services research.

Trial Registration: ClinicalTrials.gov NCT05512091; https://clinicaltrials.gov/study/NCT05512091

International Registered Report Identifier (IRRID): DERR1-10.2196/58335

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KEYWORDS

cannabis; tobacco; substance abuse; withdrawal symptoms; mobile phone; protocol; addiction; pattern use; withdrawal syndrome; mixed method; participatory; qualitative study; focus groups; cannabis use disorder; clinicians; researchers; predictive analysis

Introduction

Cannabis and Tobacco Use

Cannabis has emerged as the most widely used illegal drug globally [1]. In Spain, it also holds the status of the most commonly used illegal drug. According to the latest survey conducted in Spain in 2019, 37.5% of adults aged 15-64 years have experimented with cannabis at some point in their lives, with 10.5% reporting usage in the last month (men: 11.4% and women: 4.7%) [2]. Furthermore, approximately 1 in 6 cannabis users develop a cannabis use disorder (CUD) and the odds are increasing to 1 in 2 among daily users [2].

In Western countries, cannabis use is commonly intertwined with tobacco**,** resulting in a significant prevalence of combined usage that continues to rise [3]. For instance, in the United States, the daily use of both substances remained stable over the years from 2005 to 2014, with a usage percentage of 6%. This proportion is higher than that of individuals who consume only cannabis without tobacco, which is around 2% [4]. However, it is important to note that dual cannabis and tobacco use, or co-use, can manifest in various patterns such as (1) concurrent use, where both substances are consumed simultaneously in the form of joints, which is the most prevalent form of cannabis use in Europe [3,5,6]; (2) sequential concurrent use, involving the use of cannabis followed by tobacco or vice versa; (3) asynchronous concurrent use, characterized by cannabis and tobacco usage within the past month but not necessarily during the same instance of consumption; and (4) exclusive cannabis use, where tobacco is not involved [4].

Moreover, dual cannabis-tobacco use entails a nuanced description of dependence diagnosis for both substances collectively and individually, alongside the emergence of withdrawal symptoms, particularly when cannabis consumption is reduced or halted [7-9]. Cannabis withdrawal symptoms typically manifest within 2 to 4 days after a reduction or cessation of consumption, peak during the first week, and may persist for up to 4 weeks [10]. The cannabis withdrawal syndrome is recognized and included in the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [11]. It is characterized by symptoms such as irritability, anger or aggression, nervousness or anxiety, sleep difficulties (eg, insomnia and disturbing dreams), decreased appetite or weight loss, restlessness, depressed mood, and at least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness or tremors, sweating, fever, chills, or headache. The symptoms can be assessed using the "Cannabis Withdrawal Checklist" scale. While this scale has been validated [12] and used primarily in English-speaking populations [13-16], its applicability elsewhere warrants consideration.

A meta-analysis has estimated that 47% of cannabis users experience withdrawal syndrome upon cessation, with its occurrence often linked to tobacco use [9]. Additionally, the severity of the cannabis withdrawal syndrome inversely affects the likelihood of successful cessation, with more severe symptoms correlating with lower rates of quitting [9]. Given

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that cannabis withdrawal syndrome frequently contributes to relapse [17], resulting in modest rates of abstinence maintenance, it is noteworthy that only 30% of individuals who undergo treatment manage to sustain abstinence during the initial month [18]. Various factors contribute to relapse, including the use of other psychoactive substances [19], psychological variables (emotions, social pressure, etc), perceptions of social norms, self-efficacy [20], and sociodemographic variables (sex, age, ethnicity, etc) [16].

Cannabis and Tobacco Dependence Withdrawal Syndromes

The limited number of studies conducted on individuals undergoing treatment for CUD who also use tobacco fail to provide sufficient insight into the interaction between the consumption patterns of both substances. Consequently, there exists a potential misclassification of withdrawal syndromes between cannabis and tobacco [10,21]. As a result, the influence of cannabis and tobacco dependence, along with their respective withdrawal syndromes, on cannabis use remains unclear, particularly in conjunction with other cognitive and environmental factors previously associated with substance use and cessation. Drawing from the social science literature and conceptual models that aid in understanding individual behaviors, we propose using the Attitudes, Social Influences, and Efficacy (ASE) model [20] to decipher the factors affecting cessation and maintenance processes. Therefore, we integrate this model [20] with individual attributes (such as sex, age, and socioeconomic status) and addiction characteristics (smoking pattern, dependence, etc) to unravel this intricate phenomenon (see Figure 1).

Figure 1. Logic model of the study. ASE: Attitudes, Social Influences, and Efficacy. de Vries H, Backbier E. Self-efficacy as an important determinant of quitting among pregnant women who smoke: the phi-pattern. Prev Med. 1994;23(2):167-174. [doi: 10.1006/pmed.1994.1023] [Medline: 8047522].

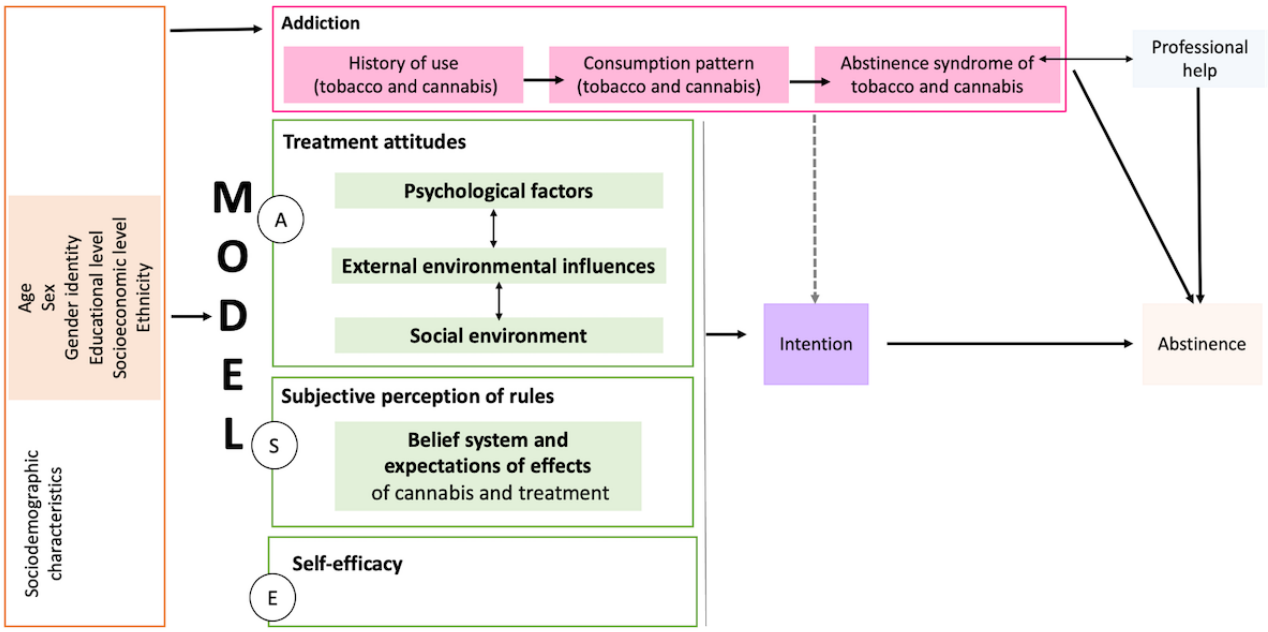

The lack of a detailed characterization of the influence of tobacco and cannabis use is partly due to the absence of techniques enabling real-time assessment, such as Ecological Momentary Assessment (EMA) [22]. While these powerful tools have been used to characterize and predict patterns among individuals with alcohol use disorder [23,24], they have yet to be used among cannabis users. Consequently, the combination of these tools could facilitate the characterization of the prevalence and patterns of dual cannabis-tobacco consumption, including a detailed description of the severity and types of symptoms experienced by users during cannabis withdrawal syndrome.

Consequently, due to limited knowledge regarding (1) how tobacco impacts cannabis withdrawal syndrome and (2) the effect of dual consumption on dropout probabilities during CUD treatment, we propose the Dual users of Cannabis and Tobacco (DuCATA) study. This mixed methods project encompasses 3 studies (qualitative, quantitative, and mixed methods) with a clinical and epidemiological focus, enabling the characterization and monitoring of consumption and withdrawal syndromes of cannabis and tobacco among individuals initiating treatment for CUD. The monitoring of dual cannabis-tobacco use and withdrawal symptoms will be conducted via a prospective follow-up of participants using a gamified web app [25] based on the EMA model [22,26] facilitating real-time collection of participants' consumption and symptoms based on their daily experiences. Gamification, through the incorporation of gaming elements, encourages active user participation in data reporting, thereby enhancing adherence to the registry and improving data quality [25].

This knowledge bears significant implications for clinical practice and public health, as it will provide precise insights into the characteristics of dual cannabis-tobacco users, a profile increasingly prevalent in programs. Moreover, it will enable us

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to use and validate an instrument developed in April 2023 for monitoring cannabis withdrawal symptoms among the Spanish population and investigating nicotine dependence. Ultimately, we are confident that comprehending and describing the dual use of cannabis-tobacco will equip future studies with a tool to accurately assess this complex phenomenon and facilitate the design of tailored interventions.

Study Objectives

Overview

The research aims of the "Characterization of the pattern of consumption and withdrawal syndrome of dual use of cannabis and/or tobacco in people with CUD who start cessation treatment: DuCATA study" can be described, indicating the studies in which each objective falls.

Objective 1 (First Study)

Determinate the treatment preferences of individuals with CUD, based on age (18-34 years and 35 years or older) and sex, for the design of a gamified web app.

Objective 2 (Second Study)

Examine the consumption patterns of cannabis and tobacco products among individuals seeking help to reduce and quit their cannabis use. This includes considering structural determinants of inequality (age, sex, social class or educational level, and territory) and clinical history (use of other substances, psychiatric comorbidity, etc), and identifying different typologies of cannabis-tobacco users, such as concurrent use, sequential use, asynchronous use, and exclusive cannabis use.

Objective 3 (Second Study)

Analyze changes in tobacco use during the cannabis treatment process based on the identified typologies of cannabis-tobacco users and the level of clinical care they receive (with or without assistance for quitting tobacco).

Objective 4 (Second Study)

Validate the "Cannabis Withdrawal Checklist" scale in the Spanish population and explore the relationship between the intensity and duration of craving and abstinence.

Objective 5 (Second Study)

Describe and predict the likelihood of cannabis and tobacco abstinence based on consumption patterns (eg, type of consumption), psychological factors (trait and state), and contextual factors (eg, environment, social influences, and activities) while considering structural determinants of inequality.

Objective 6 (Third Study)

Investigate the clinical experiences of individuals undergoing treatment for CUD, taking into account their typologies, age, and sex.

In conclusion, the "DuCATA study" aims to achieve 6 objectives across different studies. These objectives involve understanding treatment preferences for CUD through a gamified web app, examining the patterns of cannabis and tobacco use among individuals seeking help, validating assessment scales, and exploring clinical experiences.

Methods

Project Design

The project adopts a sequential mixed methods research design encompassing 3 studies. The first study, a qualitative participatory action study aimed at addressing objective 1 by exploring key elements pertinent to the co-design of the gamified web app. The second study is a prospective longitudinal (cohort) study targeting objectives 2 to 5 to quantitatively examine implementation and effectiveness outcomes. The third is a qualitative phenomenological study addressing objective 6 to delve into participants' experiences within the project. This integrated approach enables a comprehensive investigation into the patterns of consumption and withdrawal syndrome associated with dual cannabis and tobacco use among individuals undergoing cessation treatment for CUD, synthesizing qualitative insights with quantitative findings to provide a holistic understanding of the research objectives.

Ethical Considerations

The study protocol has been reviewed and approved by the Hospital Universitari de Bellvitge Ethics Committee (PR328/19) and registered on ClinicalTrials.gov (NCT05512091) [27]. The research complies with institutional guidelines and adheres to Law 3/2018 of Personal Data Protection and the General Data Protection Regulation 2016/679 of the European Union. All participants have provided or will provide informed consent before participating in the study. They have been or will be informed of their right to drop out at any time without any negative consequences. For any secondary analyses using existing data, the original consent includes permission for secondary analysis without the need for additional consent. The confidentiality of all information has been or will be ensured, and the research team has adhered to or will adhere strictly to confidentiality rules. Data will be anonymized to protect participant privacy. If data cannot be anonymized, protective measures will be in place to safeguard participant information. Participants do not receive monetary compensation for their participation. Instead, they are thanked and acknowledged for their valuable contribution to the research.

First Study: Development of a Gamified Web App

Objective

The objective is to develop a gamified web app co-designed by the research team and potential users.

Method

This study uses a participatory action approach, using focus groups to explore the perspective of potential users and ensure high usability and adherence. Participants include 10 cannabis-tobacco users or former users selected from 3 substance abuse programs (SAP) in Barcelona province, based on purposive sampling and inclusion criteria of 18 years of age or older, undergoing treatment for cannabis use, and owning a smartphone. The focus groups consist of 5 participants, homogeneously grouped by sex and age profiles, with sessions

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lasting 60 to 90 minutes. Both focus groups and participatory activities are conducted, engaging participants in-person discussions and interactive activities while recording conversations for analysis. Each group is led and coordinated by 3 individuals, including an expert in qualitative research, a web app developer, and a project investigator member.

Recruitment

Purposive sampling is used to recruit participants meeting the inclusion criteria. The eligibility criteria are determined by the clinicians of the SAP centers that collaborate in the study.

Data Collection Technique

Focus groups and participatory activities, were used, consisting of 2 pilot sessions (where a homemade board game was used to explore participants' gaming preferences), and 3 participatory sessions (including 2 exploratory sessions with clinicians and former cannabis users to profile this population, and a third session of in-depth interviews to explore into participants' personal experiences overcoming cannabis use). These sessions were conducted to gather pertinent information for web app design. Each session involved discussions among participants to explore various themes, such as users' experiences with gamified web apps, expectations and preferences regarding app features, preferred game types, and personal experiences related to cannabis use.

Data Analysis

Transcriptions of focus group discussions and participatory activities serve as primary data for analysis, involving familiarization, coding, theme development, data interpretation, and validation. The thematic categorical content analysis will be conducted using ATLAS.ti (ATLAS.ti Scientific Software Development GmbH). Based on these findings, a web app prototype is developed.

Design of the Web App

With input from participating groups, an external company experienced in gamified web app design, along with patients and researchers, designs the web app prototype. The prototype incorporates variables of interest in an engaging manner. The same participants involved in co-design will pilot the web app.

Second Study: Monitoring Patterns of Cannabis and Tobacco Use Among a Cohort of Cannabis Users Searching for Treatment

Objective

The aim is to monitor patterns of use of cannabis and tobacco, withdrawal symptoms, abstinence, and other indicators among cannabis users.

Method

This study uses a prospective longitudinal follow-up approach. The inception cohort consists of cannabis users attending SAP centers in the province of Barcelona during 2023 to initiate treatment for their disorder.

Eligibility for Centers and Clinicians

All SAP coordinators in the province of Barcelona (48 centers) are contacted. We plan to recruit 10 to 14 centers, each recruiting 8 to 12 participants on average.

Recruitment

Clinicians recruit individuals who have commenced reducing or quitting cannabis use attending in SAP. Participants are invited to self-manage and self-report their cannabis-tobacco use and symptomatology through a gamified web app and an external software that sends questionnaires regularly (every 6 days) to monitor other behavioral and contextual aspects. Before launching the study, the recruitment protocol is piloted in 3 SAP centers to make necessary adjustments for ease of recruitment by clinicians and increased acceptability among eligible participants.

Cohort Members

The cohort members are cannabis users beginning treatment for CUD at SAP centers in Catalonia.

Inclusion Criteria

Participants must be older than 18 years of age, daily cannabis users regardless of tobacco consumption pattern or type, in treatment for cannabis use or another substance in an SAP, followed by collaborating clinicians, own a smartphone or computer with an internet connection, commit to daily participation in the web app for 6 weeks, have and use WhatsApp (Meta Platforms) and email, and provide informed consent.

Exclusion Criteria

Individuals unable to guarantee 6 weeks of follow-up, those without access to a device for 6 weeks, inability to read and understand Spanish, and moderate or severe cognitive limitations and severe psychopathology, which will be assessed by clinicians during consultation at the time of participant invitation.

Sample Size

According to a recent meta-analysis, the probability of cannabis cessation in this patient population treated using diverse therapeutic approaches is relative risks (RR)=1.48 (28). Given its heterogeneity, we will use a more conservative estimate (RR=1.20). Thus, with an alpha risk of 0.05, a beta risk of 0.20 in a bilateral contrast, and accounting for 20% losses to follow-up, 282 participants will be required. Approximately 2000 people start treatment for cannabis use each year in Catalonia [28], making it feasible to recruit 282 participants within a 1-year period.

Instruments

Gamified Web App

A gamified web app was developed in the first study to prospectively follow-up participants and monitor cannabis and tobacco use, as well as identify withdrawal symptoms (see Table 1). The game of the gamified web app was named DuCATA: Your heroic journey deserves to be told (the original name is "DuCATA: Tu viaje heroico merece ser contado").

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Table 1. Variables included in the web app to monitor tobacco and cannabis use.

Frequency	Variable	Description
Every 72 hours	Tobacco use in the last 48 hours	• Have you used tobacco in the last 48 hours, with or without cannabis?
Every 72 hours	Cannabis use in the last 48 hours	• Have you used cannabis in the last 48 hours?
Every 72 hours	Number of joints	• How many joints have you consumed in the last 48 hours?
Every 72 hours	Cannabis reduction	• Compared to 2 days ago, have you reduced your cannabis use?
Every 72 hours	Cannabis withdrawal checklist	• Have you experienced any of these symptoms in the last 48? • Shakiness or tremulousness • Depressed mood • Decreased appetite • Nausea • Irritability • Sleep difficulty • Sweating • Craving to smoke marijuana • Restlessness • Nervousness or anxiety • Increased aggression • Headaches • Stomach pains • Strange dreams • Increased anger

Monitoring Software

The monitoring software was designed to record participants' recruitment, obtain their baseline information, and periodically send additional questionnaires to assess participant behavior, contextual factors, and so forth (see Table 2). This software was created to carry out the study, and we have named it DuCATA software.

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Table 2. Baseline and follow-up variables regarding sociodemographic characteristics, tobacco, cannabis use, attitudes, social norms, and motivation to quit of the participants (variables included in the monitoring software).

Variables	Temporality				
	Baseline before acceptance	Baseline after acceptance	6 days software	18 days software	Final software
Dependent variables					
Cannabis addiction	✓	✓	✓		✓
Cannabis use pattern	✓	✓	✓		
Dependency severity		✓	✓		
Cannabis type and way of use		✓		✓	
Cannabis withdrawal symptoms		✓	✓		
Addiction to tobacco	✓	✓			✓
Tobacco use pattern		✓	✓		
Nicotine dependence		✓	✓		
Alcohol addiction		✓	✓		
Attitudes		✓			
Psychoemotional factors		✓		✓	
Social environment		✓		✓	
Subjective perception of norms		✓		✓	
Beliefs and expectations of consumption and treatment					✓
Self-efficacy		✓	✓		
Level of approach in smoking or cannabis received		✓			✓
Motivation			✓		
Cannabis dropout					
Tobacco dropout			✓		
Independent variables					
Recruiting center	✓				
Sociodemographic variables		✓			
Basic mental and physical health measures		✓		✓	
Family environment or place of residence		✓			

Primary Quantitative Effectiveness Outcomes of the Web App in Monitoring Behavioral Changes

End Points

The end points are (1) variables reported every 3 days during 6 weeks within the web app and (2) variables collected in the external software at baseline and every 6 days.

Cannabis Use

Cannabis use is determined based on the (1) consumption of cannabis in the last 48 hours (yes or no), reduction of cannabis in the last 48 hours (yes or no), and cannabis abstinence or reduction requiring a cannabis withdrawal test and (2) cannabis product used (hashish, marijuana, etc), mode of administration (smoking, snorting, ingestion, etc), frequency of cannabis use in the last month and week, type of use (alone, accompanied, and both), and reasons for use (addiction, recreational, social, sleeping, etc).

Tobacco Use

Tobacco use is determined based on (1) tobacco consumption in the last 48 hours (yes or no) and (2) pattern of tobacco use—type of tobacco products (manufactured cigarettes, roll-your-own, electronic cigarettes, heated tobacco, or similar), frequency of use (daily and occasional), number of units

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(cigarettes, etc), and nicotine dependence measured using the Heavy Smoking Index (0 to 6), classified as low (0-2), moderate (3-4), and high (5-6) [29,30].

Abstinence From Cannabis, Tobacco, and Both

If abstinent of both substances we will ask for a CO measurement test (performed by their clinician and introduced in the software; yes or no).

Cannabis-Tobacco Users' Classification

Cannabis-tobacco users will be classified as concurrent use, sequential concurrent use, asynchronous concurrent use, and exclusive cannabis use.

ASE Model variables

The ASE model variables are attitudes, subjective norms, and self-efficacy.

Attitudes

Motivation to quit was measured on a Likert scale, psychological factors (states of change or readiness to quit cannabis and tobacco and psychological distress) [31]. Psychological distress was measured by using the General Health Questionnaire (GHQ-12) [32].

Self-Perceived Health Status

The self-perceived health status will be assessed based on "How would you say your general health is?" (excellent, very good, good, fair, fair, or poor).

Self-Efficacy

Self-efficacy is defined as the individual's confidence to quit cannabis and tobacco [33]. This will be assessed by asking participants, "To what extent do you feel capable of quitting cannabis consumption?" using a Likert scale ranging from 0 to 10 (0= very low to 10= very high).

Independent Variables

Sociodemographic variables are (baseline) sex, age, education level, employment status, and occupation. Mental and physical health measures are mental illness presence and comorbidities. Centers are where care is received. The family environment is cohabitation, socioeconomic level, and so forth.

Implementation Outcomes

To test the acceptability, appropriateness, and feasibility besides using the qualitative methodology explained, we will quantitatively measure these dimensions among all the participants enrolled in the cohort. We will use the scale developed by Weiner et al [34] that consists of 12 items scored from 1 (completely disagree) to 5 (completely agree). This evaluation will be conducted at the end of the follow-up period (6 weeks), and we will collect this information using a customized questionnaire administered via phone call or text message. Additionally, we will assess other implementation outcomes at the end of study 2 by gathering data on (1) acceptability—the number of individuals who accept or decline to participate in the study; (2) fidelity or adherence—the duration of participants' usage of the web app, time devoted to playing, number of completed sessions, and so forth; and (3) satisfaction—participants' opinions about the proposed web app. These variables will be measured using the metadata of the web app (encrypted).

Recruitment Procedure

Clinicians verify participant eligibility using a checklist of inclusion and exclusion criteria. They provide oral and written information to potential participants through a leaflet containing study details and information about the study sponsors. Potential participants are informed about the study objectives, procedures, potential risks, benefits, confidentiality measures, and their right to withdraw at any time. This process ensures that only eligible participants who meet the criteria are enrolled in the study.

Additionally, clinicians show a short video explaining the purpose of the research and soliciting participants' collaboration (available on YouTube [35]). If participants agree to participate, they sign the informed consent and then complete a questionnaire with brief personal information (telephone number, email, name, and national identity document). Subsequently, participants register on the web app and engage with the game daily.

Statistical Methods

For independent variables, a descriptive analysis will be conducted, including frequencies, percentages, and their 95% CIs. To assess effectiveness measures such as changes in cannabis-tobacco use, withdrawal syndrome, and treatment adherence, frequencies and percentages will be described for baseline and main assessment end points according to the four patterns of cannabis use and they are (1) concurrent, (2) sequential concurrent, (3) asynchronous concurrent, and (4) exclusive cannabis. Incidence rates of abstinence and symptomatology will be calculated for the same assessment end points across the 4 patterns. The RR of quitting or reducing cannabis and tobacco, as well as quit attempts for both substances (95% CI), adjusted for independent variables, and initial consumption pattern, will be calculated using Cox or Poisson robust regression models. Predictive analysis techniques including logistic regression and random forest will be used to model the probability of events occurring based on other factors. Time series analysis will be used to observe consumption trends during the follow-up, and survival analysis of recurring events will be conducted to observe abstinence or reduction processes among participants.

For all analyses, SPSS (IBM Corp) for Windows version 21, Python (version 3; Python Software Foundation), R (version 4.0.3; R Core Team), and scikit-learn will be used. The level of significance will be set at 5% (P<.05).

Third Study: Assessment of the Acceptability of the Web App

Objective

The objective is to evaluate the acceptability of the web app and investigate participant and clinician experiences during study 2, focusing on implementation outcomes.

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Method

The methodology used is a qualitative phenomenology study using participatory groups.

Sample

Participants will be selected from study 2 cohort members based on their web app usage experience. A total of 4 groups comprising 5-7 participants each are anticipated.

Recruitment

Purposive sampling will be used, targeting individuals meeting the inclusion criteria and having engaged with the web app. Homogeneity criteria will be applied to ensure diversity across fidelity levels and gender—group 1: high fidelity male users; group 2: low fidelity male users; group 3: high fidelity female users; and group 4: low fidelity female users.

Main Themes

The main themes are exploration of barriers and opportunities encountered during web app usage, assessment of the use of web app monitoring for cannabis or tobacco use and mood, and identification of preferred and disliked features of the web app.

Data Collection Technique

Focus groups are expected to last between 60 and 90 minutes. Conversations will be recorded to facilitate transcription and analysis while ensuring confidentiality. Each group will be facilitated by 2 individuals, including an expert in qualitative research and a project investigator.

Data Analysis

Transcribed data will undergo analysis involving familiarization, coding, theme development, interpretation, and validation; the thematic categorical content analysis will be conducted using ATLAS.ti. Insights garnered will inform the refinement of a web app prototype.

Results

By June 2024, significant progress had been achieved in the Dual use of Cannabis and Tobacco Monitored through a Gamified Web app (DuCATA_GAM-CaT) project.

First Study: Development of a Gamified Web App

Study 1, focusing on qualitative investigation through participatory focus groups, was completed, providing valuable insights into the profile of cannabis users eligible for the project.

Additionally, an initial prototype of the gamified web app has been developed, representing a critical advancement in addressing cannabis-tobacco withdrawal symptoms among individuals with CUD attending SAP.

Second Study: Monitoring Patterns of Cannabis and Tobacco Use Among a Cohort of Cannabis Users Searching for Treatment

Recruitment efforts have commenced across 10 centers, with 74 participants enrolled to date. We anticipate reaching our target enrollment of 150 participants shortly (see Figure 2). This longitudinal prospective study will track participants' cannabis-tobacco usage patterns, types and frequencies of tobacco use, nicotine dependence levels, withdrawal symptoms, psychoemotional factors, and motivation to quit both substances over a 6-week period.

Figure 2. Study timeline.

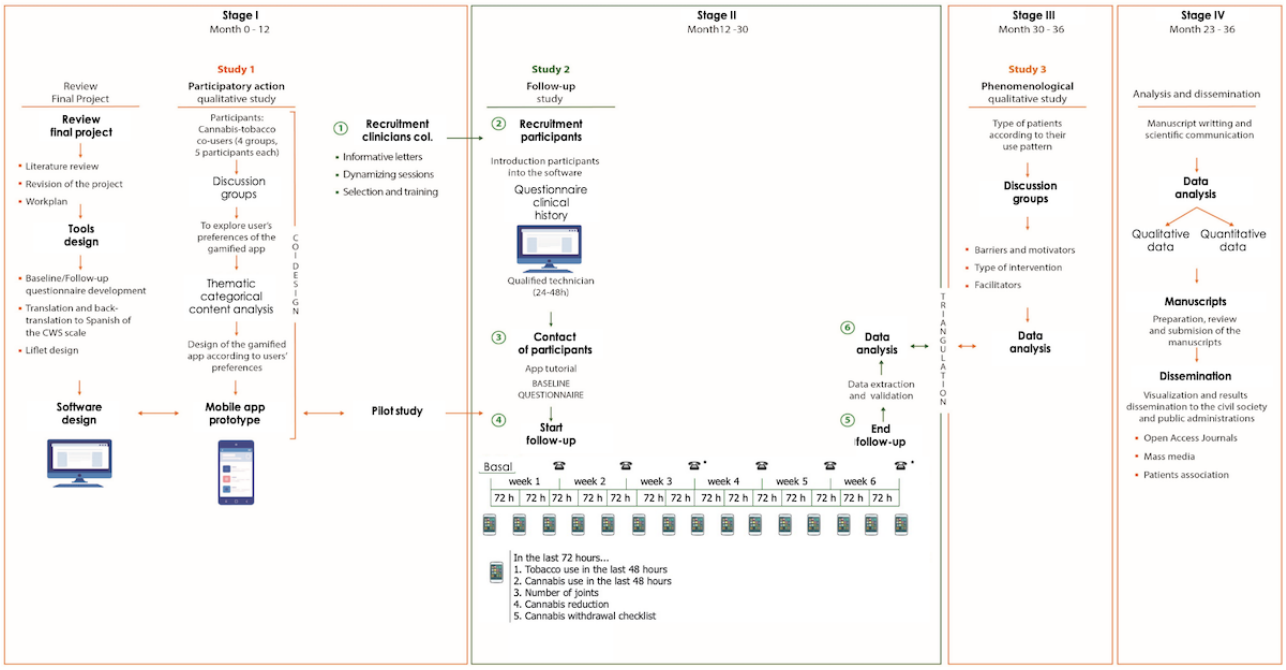

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Third Study: Assessment of the Acceptability of the Web App

Once study 2 is finished, we will start this qualitative study, which is scheduled for January 2025.

Discussion

Principal Findings

To address the objective of the study, we aimed to characterize the patterns of cannabis and tobacco use among individuals initiating cannabis treatment at SAP centers, while also monitoring cannabis withdrawal syndrome in both tobacco users and nonusers. Our primary objectives include acquiring knowledge and establishing the groundwork for a clinical intervention program theory.

Main Findings

Our study will provide insights into the diverse patterns of cannabis and tobacco use among participants entering treatment at SAP centers. We will identify their symptomatology if cannabis withdrawal syndrome appears, whether in combination with tobacco use or alone, which will help us determine the overlap of the symptoms.

Additionally, the mixed methods design of our study will allow for the triangulation of results from various perspectives, facilitating a comprehensive understanding of the phenomena under investigation.

Comparison to Prior Work

We will compare our results with the scarce literature on the topic. We will not only be able to understand the complexity of use and withdrawal symptoms but also explore the use of a gamified app for monitoring several variables of interest.

Strengths and Limitations

A key strength of our study lies in its methodological rigor, combining qualitative exploration with quantitative measurement. However, the study is limited by its observational nature and the potential for self-report biases in substance use reporting.

Future Directions

Moving forward, these findings can inform the development of targeted intervention strategies aimed at cannabis cessation, whether used exclusively or in combination with tobacco. Future studies could further explore specific intervention protocols and assess their efficacy in diverse clinical settings.

Conclusions

In conclusion, our study contributes valuable insights into the complex interplay between cannabis and tobacco use behaviors and withdrawal symptoms. These findings lay a foundation for future research and intervention efforts aimed at addressing CUD within substance abuse treatment programs.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JS contributed to the conceptualization, methodology, investigation, formal analysis, writing the original draft, and supervision. AF performed the conceptualization, methodology, and investigation. MEM performed the investigation, project administration, and writing—review and editing. MF contributed to the investigation and writing—review and editing. MB contributed to the investigation and writing—review and editing. YC contributed to the formal analysis and writing—review and editing. MP performed the investigation and writing—review and editing. NR did the investigation and writing—review and editing. PR contributed to the investigation and writing—review and editing. EMG did the investigation and writing—review and editing. CC performed the conceptualization, methodology, investigation, writing—review and editing, and supervision. JC performed the investigation, writing—review and editing, and supervision. JMS contributed to the investigation and writing—review and editing. SM did the investigation and writing—review and editing. PB performed the investigation and writing—review and editing. MA performed the investigation and writing—review and editing. AR did the investigation and writing—review and editing. JB performed the investigation and writing—review and editing. JV contributed to the software, investigation, and writing—review and editing. XRT performed the investigation and writing—review and editing. JG performed the investigation and writing—review and editing. EF contributed to the conceptualization, methodology, and investigation. CM contributed to the conceptualization, methodology, investigation, data curation, writing the original draft, supervision, and funding acquisition.

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Conflicts of Interest

None declared.

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Abbreviations

ASE: Attitudes, Social Influences, and Efficacy
CUD: cannabis use disorder
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DuCATA: Dual users of Cannabis and Tobacco
DuCATA_GAM-CaT: Dual use of Cannabis and Tobacco Monitored through a Gamified Web app
EMA: Ecological Momentary Assessment
GHQ-12: General Health Questionnaire
RR: relative risks
SAP: substance abuse programs

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Protocol

Implementation of a Virtual Reality Intervention in Outpatient Physiotherapy for Chronic Pain: Protocol for a Pilot Implementation Study

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Abstract

Background: Chronic pain is a global health issue that causes physical, psychological, and social disabilities for patients, as well as high costs for societies. Virtual reality (VR) is a new treatment that provides an opportunity to narrow the gap between clinical practice and recommended care in the use of patient education and behavioral interventions in the outpatient physiotherapy setting. However, there is currently no implementation strategy to integrate VR treatments into this setting.

Objective: This protocol outlines a pilot implementation study that aims to (1) identify barriers and facilitators for implementing a VR intervention in outpatient physiotherapy care for people with chronic pain and (2) develop and pilot test an implementation strategy in 5 practices in Germany.

Methods: The study consists of 4 phases. The first phase involves adapting the treatment protocol of the VR intervention to the local context of outpatient physiotherapy practices in Germany. The second phase includes the collection of barriers and facilitators through semistructured interviews from physiotherapists and the development of a theory-driven implementation strategy based on the Theoretical Domains framework and the Behavior Change Wheel. This strategy will be applied in the third phase, which will also include a 6-month span of using VR interventions in practices, along with a process evaluation. The fourth phase consists of semistructured interviews to evaluate the developed implementation strategy.

Results: The recruitment process and phase 1, including the adaptation of the treatment protocol, have already been completed. We recruited 5 physiotherapy practices in Lower Saxony, Germany, where the VR intervention will be implemented. The collection of barriers and facilitators through semistructured interviews is scheduled to begin in February 2024.

Conclusions: This pilot implementation study aims to develop a theory-driven implementation strategy for integrating a VR intervention into outpatient physiotherapy care for people with chronic pain. The identified barriers and facilitators, along with the implementation strategy, will serve as a starting point for future randomized controlled implementation studies in different settings to refine the implementation process and integrate VR interventions into the outpatient care of people with chronic pain.

Trial Registration: German Clinical Trials Register DRKS00030862; https://tinyurl.com/3zf7uujx

International Registered Report Identifier (IRRID): DERR1-10.2196/58089

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KEYWORDS

chronic pain; implementation; virtual reality; VR; physiotherapy; virtual reality intervention; pain; outpatient; chronic pain conditions; evidence-based

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Introduction

Chronic pain defined as persistent or recurrent pain lasting longer than 3 months [1] is a major global health problem. Chronic pain conditions (back pain, musculoskeletal disorders, and neck pain) are 3 of the leading causes for years lost to disability in the last decades [2,3]. Prevalence rates in industrial nations such as the United States (20.5%) [4], Germany (28.3%) [5], the United Kingdom (34%) [6] and Chile (48.1%) [7] are high, but also among low- and middle-income countries which prevalence rates ranging from 13% to 49.4% [8]. Chronic pain often results in physical disability, psychological distress, and reduced quality of life [3,9], and is associated with higher rates of divorce and suicide, and affects relationships and self-esteem [10,11]. For societies, chronic pain is an enormous financial burden on the health care system. The financial cost of chronic pain in the United States is estimated to be between US $560 billion and US $635 billion in 2010, including medical costs and lost productivity [12]. In Germany chronic pain costs at least €53.9 billion (US $59.4 billion) annually [13]. Although evidence-based treatments and guidelines for the management of chronic pain are available [14-16], they are only partially used [17,18]. In Germany, for example, only 38% of physiotherapists in a survey reported that they work according to guidelines in chronic pain management [19]. Perceived barriers to the use of guidelines in clinical practice include lack of time, lack of research skills, limited access to guidelines, and inapplicability of guideline recommendations to individual patients [19,20].

Implementation studies offer an opportunity to improve this situation and overcome these barriers by developing and testing targeted implementation strategies for evidence-based interventions [21]. Currently, frameworks, models and theories for the development of implementation interventions and strategies are not yet used as standard in the implementation of virtual reality (VR) interventions, although this is recommended. [22]. One model to guide the process of implementation is the knowledge to action (KTA) cycle [23]. The KTA cycle is a process model, which is increasingly used since its introduction in 2006 [24-27]. The KTA was developed from a concept analysis of 31 planned action theories to make sense of the complex implementation process. It provides a comprehensive view by integrating concepts of knowledge creation and application. At each stage of the action cycle, other frameworks or theories can be applied [23].

One such framework to determine barriers and facilitators is the Theoretical Domains framework (TDF) [28,29]. The TDF was created to enhance health care researchers' access to psychological theory by providing a systematic and simplified approach to behavior change theories. Consisting of 14 theoretical domains derived from 33 theories and 128 constructs, this framework serves as a valuable tool for examining the barriers and facilitators that influence professional behavior change. Once the barriers and facilitators in a setting have been identified, they can be mapped to the domains. The behavior change wheel (BCW) [30] can then be used to develop implementation interventions with specific functions and behavior change techniques to influence the targeted behavior. The BCW is a comprehensive framework that incorporates behavioral theory to effectively capture and address the mechanisms of action within interventions. Developed through expert consensus and a rigorous validation process, the wheel is organized into 3 levels. Its central element is the capability, opportunity, and motivation model of behavior change (COM-B model), which includes aspects of capability (both physical and psychological), opportunity (both social and physical), and motivation (both automatic and reflective). It is proposed that people need these 3 factors to increase the likelihood of performing the behavior in question [30].

A new evidence-based intervention for people with chronic pain is VR [31]. It is used in physiotherapy in many specialties such as neurology and orthopedics to manage pain [32]. VR treatments include VR games, mindfulness-based interventions, practical exercises, and visual illusions for people with chronic pain [33]. For example, 1 part of an intervention is a relaxation exercise in which deep breathing is used to make a virtual tree blossom. Another is a virtual journey through the body to explain chronic pain to the patient. A meta-analysis showed large effects of VR interventions on pain (standardized mean difference [SMD] 1.6, 95% CI 0.83-2.36) and body functioning (SMD 1.4, 95% CI 0.13-2.67) in people with chronic pain [33]. However, it is unknown how often VR treatments are used in the care of people with chronic pain. A recent review about the barriers and facilitators in the implementation of VR intervention for people with chronic pain shows various barriers. The main barriers were the inappropriate choice of VR devices and VR interventions in relation to the patients, and that patients did not have the required skills to use VR and no tutorials or instructions were available [34]. Though, there are also some facilitators to the implementation of VR interventions for people with chronic pain, such as positive beliefs about consequences from the patient's perspective [34]. However, little is known regarding barriers and facilitators from a health professional perspective. The next step in the implementation of VR interventions into health care is the development of an initial implementation strategy, supported by implementation frameworks focusing on behavior change of all stakeholders [35]. Therefore, the aim of this study is (1) to identify barriers and facilitators from the perspective of health care professionals and (2) to develop and test a strategy for the implementation of VR interventions in outpatient physiotherapy practices.

Methods

Overview

The 4 phases (Figure 1) of the pilot implementation study are derived from the KTA cycle [23] and the entire implementation process is accompanied by a formative evaluation [36], which makes it possible to collect data at several points throughout all phases and influence the implementation at the same time. The implementation takes place in 5 outpatient physiotherapy practices in Germany. In the first phase (adapt knowledge to local context), the treatment protocol of the VR intervention is adapted to the context of outpatient physiotherapy practices. The second phase (assess barriers to knowledge use) consists of collection of specific barriers and facilitators to the

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implementation of the VR intervention from a health care professional perspective. Participating therapists first receive training in the use of the VR devices and the VR intervention, and then semistructured interviews are conducted with them. This will be the basis for the development of an implementation strategy with tailored implementation interventions in phase 3 (select, tailor, implement interventions, and monitor knowledge use). After the implementation strategy has been carried out, the physiotherapists will use the VR intervention in the practice with an accompanying process evaluation. Finally, the entire process and implementation strategy will be evaluated and adapted in phase 4 (evaluate outcomes).

Figure 1. The four phases of the pilot implementation study for the development and evaluation of an implementation strategy. VR: Virtual reality.

VR Intervention

The VR intervention (Reducept, the Netherlands) is a psychological VR intervention for the treatment of chronic pain. Reducept aims to teach patients that pain can be influenced and managed by changing the way they think about their pain. In the game, the user travels through the body in a spaceship (Figure 2). Along the way, the user learns about the mechanisms of pain. Reducept is based on the “explain pain” guidelines [37], which state that understanding pain and influencing the cognitive, emotional, and behavioral processes associated with it enables patients to reduce their pain experience. In addition to pain education, the user plays several serious games that stimulate the visual, auditory, and proprioceptive systems to control chronic pain through distraction and relaxation. The VR intervention uses techniques from cognitive behavioral therapy, acceptance and commitment therapy, mindfulness, and hypnotherapy [38]. The game is divided into 5 modules that build on each other and last from 5 to 10 minutes. A workbook with in-depth content on the VR modules accompanies the therapy. The planned therapy sequence consists of 6 therapy sessions of 10 to 20 minutes each.

Figure 2. Screenshot from the nerve level of Reducept.

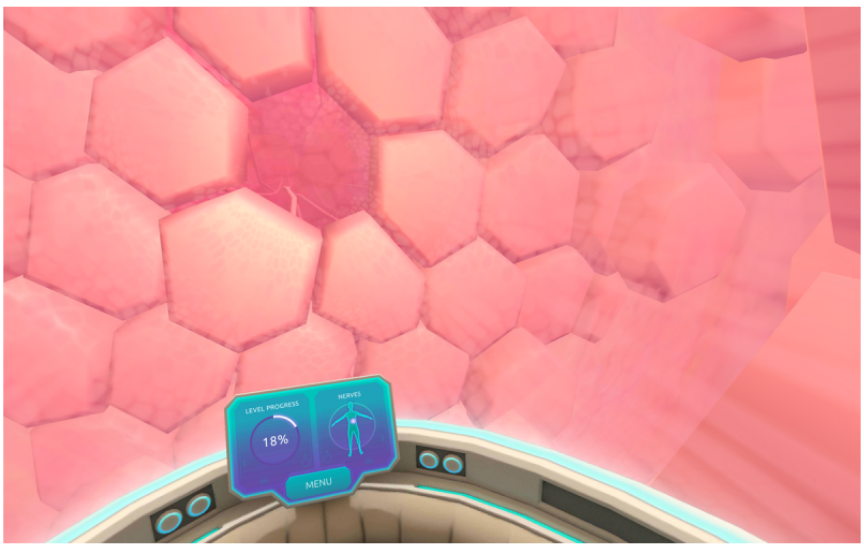

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Data Analysis

Qualitative content analysis according to Kuckartz [39] will be used throughout the study to analyze qualitative data. Qualitative content analysis is a systematic and structured way of analyzing qualitative data. First, main categories are identified deductively or inductively, then text segments are systematically assigned to these categories. From these text segments, subcategories are inductively derived. This method helps to identify themes, patterns, and correlations in the data, thus providing deeper insights into the phenomenon under study. In addition, Kuckartz content analysis provides a transparent approach that increases the validity and reliability of research findings. MAX Qualitative Data Analysis (MAXQDA Plus 2022, version 22.0.1, VERBI software) will be used for the qualitative analysis.

The data related to the patients' health outcomes are evaluated for normal distribution and sphericity, and then analyzed using repeated measures ANOVA in SPSS (version 28.0.1.0, IBM Corp).

Phase 1

The first phase of the implementation process consists of adapting the treatment protocol of the VR intervention to the context of outpatient physiotherapy practices in Germany.

In total, 5 outpatient physiotherapy practices in Lower Saxony (Germany) will participate in the study and implement the VR intervention. At least 5 physiotherapists must work in the practices to be eligible to participate in the study. Practice managers or owners and 2 researchers will participate in guided focus groups to adapt the original treatment protocol of the VR intervention. Focus groups are a good method to investigate what participants think and why they think it [40]. In addition, the group setting can stimulate new ideas that may be hidden in individual discussions [41]. Another goal is to establish collaboration and networking among participants. The focus group guideline will be developed using the implementation outcomes of acceptability, appropriateness, adoption and feasibility [42]. The guideline will be pretested and adapted, if necessary.

The focus group will take place at the University of Applied Science and Arts in Hildesheim/Holzminden/Göttingen (Germany) and will last approximately 2 hours. One researcher will moderate the focus group, while a second researcher will take care of technical aspects, keep time, and take notes on important aspects or special incidents.

At the beginning of the focus group, the moderator gives an introduction explaining the process and goals of the overall study and the focus group, followed by a presentation of the original VR treatment protocol. During the focus group, a table is displayed with the content and duration of the 6 VR treatment sessions originally planned in the treatment protocol. The main part of the focus group addresses the 4 outcomes of acceptability, appropriateness, adoption, and feasibility in relation to the treatment protocol. By discussing these aspects, it will be possible to adapt the treatment protocol to the context of outpatient physiotherapy practices. The final section is an open-ended question and answer session where participants can speak and discuss freely about the treatment protocol and possible adaptations. At the end of the focus group, participants will complete an online demographic survey. The audio of the focus group is recorded with an audio recorder for the entire duration.

In this phase, the qualitative content analysis according to Kuckartz and Rädiker [39] will focus on possible adjustments to the original treatment protocol in relation to the setting. After the analysis, the VR treatment protocol will be adapted in consultation with the practice owners to develop a treatment protocol for implementation.

Phase 2

The second phase is derived from the "assess barriers to knowledge use" step of the KTA cycle [23]. A total of 2 physiotherapists from each practice will participate in the study. They must have completed their physiotherapy training and be employed in the practice. Participants will receive training in the use of the VR intervention, including the use of VR devices (Pico 4 [ByteDance]), as the first part of the implementation strategy. In addition, participants will receive information on how the VR intervention should be applied to people with chronic pain. This information will also be made available on demand on an online platform. After the VR training, the acceptance, appropriateness, and feasibility of the VR intervention from the therapists' perspective will be assessed through an online survey using the German versions of the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and the Feasibility of Intervention Measure questionnaires [43,44]. Then they receive the VR devices to test the intervention at home. Approximately 2 weeks later, an optional online meeting will be offered to therapists to answer any remaining questions about the VR intervention or the use of the VR devices. The barriers identified in the focus group and in the online survey after the VR training will be used to define the behaviors that need to be changed or implemented when the VR intervention is used in practices. From these behaviors, the study team will select 1 or 2 core behaviors to change that appear promising to support implementation of the VR intervention. The selection of the target behaviors will be based on the potential impact on the implementation of the VR intervention, the potential multiplier effect in practices, and the feasibility of measuring behavior change. These target behaviors are specified by the question: who needs to do what differently, when, where, how, and with whom [45]?

Approximately 1 week after the online meeting, semistructured interviews will be conducted with the participating physiotherapists to identify and specify barriers and facilitators to the implementation of the VR intervention. An interview guideline will be developed to understand the factors that may influence the implementation of VR interventions in practices. It will be based on the previously defined target behaviors and the domains of the TDF [28,29]. Before being used, the interview guide is pilot tested with 2 physiotherapists to test its comprehensibility.

The interviews are expected to last approximately 45 to 60 minutes and will be conducted online through Zoom (Zoom Video Communications). Participants will receive written

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informed consent before participation in the study. Interviews will be audio-recorded and transcribed verbatim. Data collection and storage will be pseudonymized. The data of the focus group and the semistructured interviews will be analyzed at the end of this phase using qualitative content analysis according to Kuckartz [39]. The TDF domains will be used as deductive codes to which the data will be assigned, to gather barriers and facilitators from the focus group and the semistructured interviews.

Phase 3

Based on the qualitative and quantitative assessed barriers and facilitators in phase 1 and 2 and the barriers and facilitators found in a scoping review [34], an implementation strategy, consisting of various implementation interventions, will be developed. The identified domains of the TDF are mapped to the COM-B model of the BCW [46]. This helps to determine what underlying factors need to be changed in order for the therapist's behavior to change. Based on these factors, the functions of the implementation interventions and the recommended behavior change techniques can be specified and preliminary implementation interventions (eg, training, modeling, and environmental restructuring) can be developed [46]. Affordability, practicality, effectiveness and cost-effectiveness, acceptability, side effects or safety, and equity will be used to select the most appropriate and effective implementation interventions for the implementation strategy [46]. In our study, we will not include policy categories such as regulation, fiscal and legislation, as recommended by the BCW framework. This exclusion is due to the limited timeframe and scope of our project, which does not extend to policy-level changes.

The developed implementation strategy will be discussed with the stakeholders from the participating practices, to specify the execution of the implementation interventions. The strategy will then be executed in all 5 practices and process evaluated through an online questionnaire. The strategy will be reported according to the standards of Proctor et al [47].

Patients are eligible if they are aged 18 years or older, self-report that they have a chronic pain condition, and are able to understand and speak the German language fluently. Patients will be excluded if they have a current or previous diagnosis of epilepsy, dementia, migraine, or other neurological conditions that may prevent the use of VR or lead to adverse effects such as hypersensitivity to flashing lights or severe hearing impairment. Pain intensity, disability due to pain, fear of movement, pain catastrophizing, quality of life, and pain-related self-efficacy will be assessed using the German versions of the Numeric Pain Rating Scale [48,49], Pain Disability Index [50], Tampa Scale for Kinesiophobia [51], Pain Catastrophizing Scale [52], EQ-5D-5L (quality of life) [53], and a questionnaire assessing pain-related self-efficacy [54] before and after the VR intervention.

Physiotherapists will complete an online questionnaire to document each session of the VR intervention. The questionnaire consists of questions about the fidelity of treatment delivery based on the fidelity protocol in the study by Toomey et al [55] (eg, did the therapist adhere to the treatment protocol or which components of the treatment were delivered) and whether there were any adverse events during that session. The therapists will use the VR intervention in their practices for 6 months. Before participation in the study, written informed consent will be obtained from participants. The collected process evaluation data will be analyzed descriptively using SPSS.

Phase 4

The final phase will be an evaluation of the overall implementation process and an analysis of the health-related outcomes of the patients.

The evaluation of the implementation process will be done through semistructured interviews with 3 patients, 3 therapists, and 3 practice owners. Patients must have received the full treatment duration to be eligible for the interviews, therapists are included if they have treated at least 5 patients with Reducept, and 3 participants are selected from the practice owners of the participating practices. Before the interviews, all participants will complete the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and the Feasibility of Intervention Measure questionnaires. The data from the questionnaires, noticeable aspects from the process evaluation in phase 3 and the implementation outcomes adoption, acceptability, appropriateness, feasibility, fidelity, and implementation costs [42] will be used to develop an interview guide. The interviews will determine the perceived effectiveness of the implementation strategy was, how the VR intervention was used in the practices, how patients perceived the use of the VR intervention and give indications how the implementation strategy can be adapted for future projects. Before use, the interview guide is pilot-tested with people from the same background who are not part of the study to ensure comprehensibility.

The interviews will be conducted online through Zoom and are expected to last approximately 60 minutes. Written informed consent will be obtained from participants before participation in the study. Interviews will be audio-recorded and transcribed verbatim. Data collection and storage will be pseudonymized. Data will be analyzed using Kuckartz's qualitative content analysis [39].

This data will be used to adapt the implementation strategy and to create recommendations for the implementation of VR interventions for people with chronic pain in outpatient physiotherapy practices.

Ethical Considerations

Ethical approval for the study has been obtained from the ethics committee of the University of Applied Science and Art in Hildesheim/Holzminden/Göttingen (Germany) (April 3, 2023). The principles of the Declaration of Helsinki [56] will be strictly followed in this research project. Eligible participants will be informed of the objectives and procedures of the study. Before inclusion, written informed consent will be obtained from all patients. Participation will be voluntary, and participants will be free to withdraw from the study at any time. The reporting of this protocol follows the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement: extension to randomized

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pilot and feasibility trials [57]. The study is registered in the German Clinical Trials Register (DRKS00030862).

Results

The recruitment process and phase 1 with the adaption of the treatment protocol are already conducted. In total, 5 physiotherapy practices were identified in which the VR intervention is to be implemented. A focus group with 4 practice owners was held in November 2023. Due to personal appointments, 1 owner had to cancel the focus group at short notice and was subsequently interviewed by a semistructured interview about the treatment protocol. The data was then analyzed by qualitative content analysis and used to adapt the treatment protocol.

Discussion

Principal Findings

The described pilot implementation study will provide insight into the implementation of VR interventions for people with chronic pain managed in outpatient physiotherapy practices. The developed implementation interventions and implementation strategy can be foundation for future implementation projects. Especially the insights into the perspective of health care professionals will play an important role in the further implementation of VR interventions for people with chronic pain, as they play an important role in the implementation of digital interventions [58]. The implementation of VR interventions can lead to better outpatient care for people with chronic pain, as VR can help reduce pain, positively influence disability, and reduce fear of movement [59-61].

Previous research suggests that technology adoption in health care is still lacking due to technically challenged staff, resistance to change, high costs and low acceptance [34,62,63]. In the implementation of VR in the organizational structures and VR technology itself have been barriers to the implementation of VR interventions in various health care settings [35,64,65]. Regarding the use of VR in physiotherapy, VR itself seems to be the main barrier due to technical issues, lack of guidelines for VR interventions, and patient-related factors [32]. In contrast, staff and health care professionals can act as facilitators by reducing anxiety about new technologies and changing attitudes toward VR [32,35,65]. There is also a general interest in the use of VR in rehabilitation among health care professionals [35]. The development and application of systematic implementation strategies can help to promote the use of new technologies and VR. By identifying the barriers and facilitators in each setting, it will be possible to target implementation interventions to change the behavior of health care professionals, patients, and practice owners. The implementation study described here can develop an initial implementation strategy for the implementation of VR interventions for the outpatient physiotherapy treatment of people with chronic pain. This strategy can be a first step to increase the acceptance and use of VR interventions in the field of chronic pain, leading to better patient care. The next step in implementing VR interventions in physiotherapy practices should be to evaluate the effectiveness of the implementation strategy in a controlled trial.

Limitations

This study has some limitations that should be noted. First, the lack of a control condition (eg, cluster randomization with other physiotherapy practices) makes it difficult to accurately assess the effectiveness of the implementation strategy. Second, the small sample size of only 5 practices limits the generalizability of the implementation strategy. In addition, involving all stakeholders in each phase of the study may allow for more comprehensive input into the development of implementation interventions.

Conclusions

The findings of this pilot implementation study will contribute to the body of knowledge regarding the development process and effectiveness of an implementation strategy for VR interventions for the treatment of people with chronic pain in outpatient physiotherapy practice. The objective is to develop an initial implementation strategy that can be used in future implementations of VR, with adaptation if necessary. The successful implementation of VR interventions in the outpatient treatment of people with chronic pain will lead to increased guideline adherence among physiotherapists and therefore to better care.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AE, CK, and AS were responsible for the conception of the research project and the drafting of the manuscript. All authors contributed to the preparation of this manuscript and read and approved the final version for publication.

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Conflicts of Interest

None declared.

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Abbreviations

BCW: behavior change wheel
COM-B: capability, opportunity, and motivation model of behavior change

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KTA: knowledge to action
SMD: standardized mean difference
TDF: Theoretical Domains framework
VR: virtual reality

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Protocol

Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis With Ambulatory Cognitive Tests: Protocol for the Longitudinal Observational CogDetect-MS Study

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Abstract

Background: Cognitive dysfunction is a common problem in multiple sclerosis (MS). Progress toward understanding and treating cognitive dysfunction is thwarted by the limitations of traditional cognitive tests, which demonstrate poor sensitivity and ecological validity. Ambulatory methods of assessing cognitive function in the lived environment may improve the detection of subtle changes in cognitive function and the identification of predictors of cognitive changes and downstream effects of cognitive change on other functional domains.

Objective: This paper describes the study design and protocol for the Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis (CogDetect-MS) study, a 2-year longitudinal observational study designed to examine short- and long-term changes in cognition, predictors of cognitive change, and effects of cognitive change on social and physical function in MS.

Methods: Participants—ambulatory adults with medically documented MS—are assessed over the course of 2 years on an annual basis (3 assessments: T1, T2, and T3). A comprehensive survey battery, in-laboratory cognitive and physical performance tests, and 14 days of ambulatory data collection are completed at each annual assessment. The 14-day ambulatory data collection includes continuous wrist-worn accelerometry (to measure daytime activity and sleep); ecological momentary assessments (real-time self-report) of somatic symptoms, mood, and contextual factors; and 2 brief, validated cognitive tests, administered by smartphone app 4 times per day. Our aim was to recruit 250 participants. To ensure standard test protocol administration, all examiners passed a rigorous examiner certification process. Planned analyses include (1) nonparametric 2-tailed *t* tests to compare in-person to ambulatory cognitive test scores; (2) mixed effects models to examine cognitive changes over time; (3) mixed effects multilevel models to evaluate whether ambulatory measures of physical activity, sleep, fatigue, pain, mood, and stress predict changes in objective or subjective measures of cognitive functioning; and (4) mixed effects multilevel models to examine whether ambulatory measures of cognitive functioning predict social and physical functioning over short (within-day) and long (over years) time frames.

Results: The study was funded in August 2021 and approved by the University of Michigan Medical Institutional Review Board on January 27, 2022. A total of 274 adults with MS (first participant enrolled on May 12, 2022) have been recruited and provided T1 data. Follow-up data collection will continue through March 2026.

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Conclusions: Results from the CogDetect-MS study will shed new light on the temporal dynamics of cognitive function, somatic and mood symptoms, sleep, physical activity, and physical and social function. These insights have the potential to improve our understanding of changes in cognitive function in MS and enable us to generate new interventions to maintain or improve cognitive function in those with MS.

Trial Registration: ClinicalTrials.gov NCT05252195; https://clinicaltrials.gov/study/NCT05252195

International Registered Report Identifier (IRRID): DERR1-10.2196/59876

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KEYWORDS

ambulatory assessment; longitudinal data collection; ecological momentary assessment; cognitive function; cognitive assessment; multiple sclerosis; physical activity; neuropsychology; physical function; observational study; wrist-worn accelerometry; social function; smartphone app; mobile phone

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disease of the brain and spinal cord that affects approximately 1 million people in the United States [1]. It is the leading cause of nontraumatic disability in young adults [2]. Cognitive dysfunction is one of the most common problems in MS; up to 70% of people with MS report some type of cognitive dysfunction [3], including deficits in processing speed [4], episodic memory, visual memory, verbal fluency [5], working memory [6], and executive functioning [7]. Cognitive dysfunction in MS exerts a dire impact on many aspects of health-related quality of life, including employment, independent living, social participation, and physical functioning [8-10], and has been linked to poor treatment adherence [11]. Unfortunately, progress in developing preventative, compensatory, and restorative interventions for cognition in MS is stymied by major gaps in our knowledge of the natural history of cognitive decline and of the characteristics and mechanisms of cognitive dysfunction where it matters most—in the everyday lives of people with MS [12].

Our knowledge of the nature and impact of cognitive functioning in MS is restricted by measurement limitations and insufficient attention to potential contributors to and consequences of changes in cognition. Measurement of cognitive function is limited by reliance on cross-sectional data and the use of standard neuropsychological testing protocols. These assessment protocols are insensitive to subtle cognitive changes and demonstrate practice effects, temporal bias, and poor ecological validity [13-15]. A crucial limitation is that the "snapshot" of cognitive function, typical of cross-sectional neuropsychology studies, fails to capture day-to-day and within-day variability in an individual's cognitive function [16,17]. Understanding such short-term variability in cognitive function in MS is important for 3 key reasons: first, within-person fluctuations in cognitive performance may be an independent indicator of poor cognitive functioning [18,19] and vulnerability to future cognitive decline [20,21]. Second, identifying time-varying modifiable factors that precede and predict changes in cognitive dysfunction can provide crucial clues about potentially productive targets for intervention, particularly real-time interventions that can have immediate effects. Finally, studying within-person covariation between cognitive function and other functional domains, such as social and physical function, can provide convincing evidence as to the contribution of cognitive dysfunction to important person-centered outcomes.

To address measurement limitations of gold-standard neuropsychological testing, this study leverages technology-assisted ambulatory assessment techniques to provide a unique and multidimensional window into cognitive dysfunction in the everyday lives of people with MS. Multiple complementary ambulatory assessment strategies are used. A customized smartphone app is used to administer a battery of objective ambulatory cognitive tests that are designed specifically for serial administration in the lived environment, as well as ecological momentary assessments (real-time assessment) of self-reported symptoms and functioning as a person goes about daily life, an approach that is not as subject to recall bias or memory decay [22]. The smartphone app is paired with accelerometer technology, which provides objective, continuous, and unobtrusive measures of physical activity during day and night (ie, sleep). Ambulatory assessments are administered in a "measurement burst design," incorporating bursts of intensive repeated assessment in people with MS over 2 weeks, with bursts repeated longitudinally, at baseline and 1- and 2-year follow-up. The burst design provides 2 main benefits: improved detection of subtle long-term changes in cognitive functioning and the ability to examine fine-grained temporal associations between fluctuations in daily experiences (eg, pain, fatigue, and stress) and cognitive function [23].

Using these innovative assessment methods, we aim to explore foundational questions that have yet to be examined in MS, such as the degree and prognostic utility of within-person lability in cognitive function. We will determine if ambulatory assessments are sensitive to subtle declines in cognitive functioning. We will also explore the impact of modifiable factors, such as sleep, physical activity, mood, and somatic symptoms on cognitive function. Finally, we will explore whether variability in cognitive functioning predicts short- and long-term changes in other patient-centered functional domains, social participation, and physical functioning. In pursuit of these primary objectives, the study is designed to test three hypotheses: (1) ambulatory measures of subjective and objective cognitive function will be more sensitive to longitudinal changes (over 2 years) in cognitive functioning compared to conventional clinic-based assessments; (2) ambulatory measures of modifiable factors—physical activity, sleep, fatigue, pain, mood, and stress—predict short-term (same-day) and long-term (at 1- and

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2-year follow-up) changes in cognitive functioning; and (3) ambulatory measures of cognitive functioning will predict social and physical functioning over short- (same-day) and long-term (at 1- and 2-year follow-up) time frames.

Methods

Study Design

The Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis (CogDetect-MS) study applies an observational design that combines microlongitudinal (ie, frequent, repeated "burst" measures across 14 consecutive days) and longitudinal (ie, 1- and 2-year follow-up) data collection methods in a sample with MS. Participant recruitment and data collection are conducted across 3 sites: the University of Michigan (UM; lead site and data coordinating center) in Ann Arbor, Michigan; Wayne State University (WSU) in Detroit, Michigan; and the University of Washington (UW) in Seattle, Washington. Ambulatory data are managed by researchers at the Pennsylvania State University, who return scored and combined ambulatory datasets to UM.

Ethical Considerations

This multisite study has received a single institutional review board (IRB) approval from the medical IRB at UM (HUM00199732; participating site approvals: UM: HUM00213744, WSU: SITE00000462, and UW: SITE00000461). Initial IRB approval was obtained on January 27, 2022. All volunteers provided written informed consent. Participants are compensated US $600 for the full completion of the study (US $200 for each visit—T1, T2, and T3). For those who do not complete the full study, the compensation schedule is as follows: US $50 per laboratory visit and US $150 per home monitoring period (for <14 days of data, compensation is graded with US $4 per day for days 1-5, US $10 per day for days 6-10, and US $20 per day for days 11-14).

Study Sample and Recruitment

The aim was to recruit 250 participants, with the expectation that 210 would also provide data at the final (2-year) follow-up. Participants were recruited through existing participant registries; electronic health record queries; institution-specific, participant-recruitment websites; clinic- and community-based recruitment; posting of flyers; and outreach to local partners, such as the local chapters of the National MS Society. Inclusion criteria (assessed by self-report) were (1) 18 years of age or older, (2) able to fluently converse and read in English, (3) MS diagnosis (confirmed via medical record review; all relapsing and progressive subtypes included), and (4) able to ambulate either independently or with the use of a cane or walker (or similar device) for at least 50% of the time at baseline; participants who lose ability to ambulate over the course of the study are retained, as this criteria only applies to initial enrollment. Exclusion criteria were (1) MS relapse within the past 30 days (may become eligible after 30 days; criteria used at T1, T2, and T3) and (2) inability to use study data collection tools (ie, ActiGraph wGT3X-BT [ActiGraph], smartphone app; volunteers "pass" this final exclusion criterion by independently completing a trial of the ambulatory assessment battery during the laboratory visit).

Participant Screening, Enrollment, and Data Collection Procedures

Volunteers underwent an initial prescreening by telephone to determine general inclusion or exclusion criteria and were fully screened at the T1 laboratory visit to establish study eligibility. MS diagnosis was either preconfirmed through medical record review or initially gathered by self-report and later confirmed through record review. Written informed consent procedures were either conducted remotely (via Zoom [Zoom Video Communications] or telephone, and a signature obtained via e-consent in REDCap [Research Electronic Data Capture; Vanderbilt University]) prior to the T1 laboratory visit or in person at the laboratory visit.

Participation in this study involves assessments at baseline (T1), 1-year follow-up (T2), and 2-year follow-up (T3). Each assessment period includes a ~2.5-hour laboratory visit immediately followed by a 14-day ambulatory monitoring period (measurement "burst"). At each laboratory visit, certified examiners administer cognitive and physical function test batteries and demonstrate the use of a study-specific smartphone (programmed with a data collection app) and an ActiGraph wGT3X-BT accelerometer for the collection of ambulatory data. A battery of web-based self-report surveys is also completed at each time point, either prior to (within 30 days of laboratory visit) or during the laboratory visit.

During each ambulatory monitoring period, participants continuously wear an ActiGraph wGT3X-BT to passively collect physical activity data. At 4 intervals throughout the day (wake, midday, and bedtime), participants complete a set of brief, valid, and reliable cognitive tests assessing processing speed and working memory [13] along with a battery of ecological momentary assessment (EMA; real-time self-report) measures of somatic symptoms, mood, functioning, behaviors, and context on the smartphone app. The wake-up and bedtime assessments are initiated by the participant when waking up (ie, waking and not necessarily getting out of bed) and going to bed (ie, "lights out" and not necessarily when getting into bed). The other 2 assessments are prompted by an audible alert on a quasi-random schedule determined by their usual waking time. At the end of each home monitoring period, participants return the ActiGraph wGT3X-BT and smartphone in a prepaid mailer to the laboratory for data download.

Data Collection Platforms and Technology

Survey data are collected via a secure, study-specific REDCap website. REDCap is an open-source, secure, HIPAA (Health Insurance Portability and Accountability Act)–compliant, web-based platform designed to support data capture for research studies. It has been designed specifically to protect patient privacy and confidentiality while assisting investigators in clinical research. REDCap provides an interface for data entry and validation, auditing features for tracking data manipulation, the ability to import data from external sources, calculated data fields, branching logic, and the capability to export data to many statistical packages. System-level and app-level security include

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Secure Sockets Layer encryption of internet traffic (https pages), hosting in a secure data center with nightly backup, fine-grained control over user rights, detailed audit trails, record locking, and deidentification features for data export. REDCap was initially developed by Vanderbilt University but now has collaborative support from a wide consortium of many domestic and international partners.

Self-report EMAs and ambulatory cognitive tests are administered via a customized app (Figure 1; Wear-IT, developed by the Real Time Science Lab, Pennsylvania State University) installed on a Motorola g^8 Power mobile phone with a 6.4″ display (1080×2300 pixels). The phone is loaned to participants for use during the study; it is not associated with any phone number and is used with an inactive SIM card for keeping accurate time on the phone; thus, there are no signals sent or received via the phone. Phones are loaned to study participants to ensure device consistency across participants and across time periods and because ambulatory cognitive assessment apps on personal phones have not been validated at the time the study launched. Response times are recorded in milliseconds. Data are stored onboard the smartphone until it is returned to the laboratory for data download.

Figure 1. (A) The Wear-IT app landing page, (B) morning survey landing page, (C) self-reported wake-up time, (D) an item from the perceived cognitive function scale, (E) an item from the depressed mood scale, and (F) the survey of substance consumption.

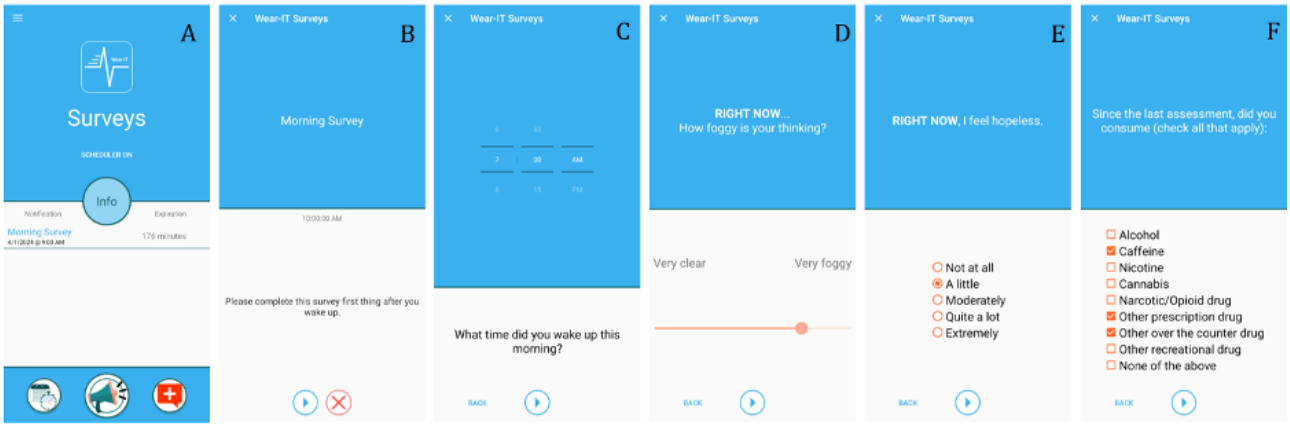

The ActiGraph wGT3X-BT triaxial accelerometer (Figure 2) is used to measure physical activity. It is mounted on a fabric band on the nondominant wrist. In cases of hemiparesis, the accelerometer is placed on the nonparetic side. It is lightweight (19 g) and compact (3.3×4.6×1.5 cm) and measures movement using a capacitive accelerometer that digitizes a voltage detected from movement at a sampling rate of 30 Hz. The samples are summed over a 60-second epoch period and output as activity counts. Higher activity counts relate to more physical activity. We use a wrist-worn placement, as this placement has been used extensively in physical activity studies and to validate the ActiGraph in MS [24-35].

Smartphone app data (EMA and cognitive tests) are combined, and time synced with accelerometer date by the Wear-IT team.

Figure 2. The ActiGraph wGT3X-BT triaxial accelerometer.

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CogDetect-MS Study Measures: Laboratory Visit Measures

Self-Report Measures

The self-report survey battery includes surveys of demographics, clinical characteristics, and medical history (eg, medications and therapies) and a selection of valid and reliable self-report measures (Table 1 and Multimedia Appendix 1).

Table 1. Validated self-report surveys administered in the Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis (CogDetect-MS) study.

Domain	Measures
Sleep	• PROMIS[a] Sleep Disturbance Short Form 8b [36] • STOP-Bang [37]
Fatigue	• PROMIS Fatigue Short Form 8 V1.0 [38] • Michigan Fatigability Index Short Forms
Pain	• PROMIS Pain Intensity 3a [36] • PROMIS Pain Interference 8a [39-41] • painDETECT [42] • American College of Rheumatology Fibromyalgia Diagnostic Criteria [43,44]
Depressed mood	• PROMIS Depression 8b [45]
Stress	• Perceived Stress Scale [46]
Social functioning	• Neuro-QoL Ability to Participate in Social Roles and Activities Short Form 8 [47,48]
Cognitive function	• PROMIS Cognitive Abilities Short Form 8 [49] • Compensatory Cognitive Strategies Scale [50]
Physical functioning	• Neuro-QoL Upper Extremity Function-8 [47] • Neuro-QoL Lower Extremity Function-8 [47] • Patient Determined Disease Steps [51]
Falls	• 1-Month Falls History • Falls Efficacy Scale [52] • Fear of Falling Avoidance Behavior Questionnaire [53] • Concern and Fear of Falling Evaluation [54,55]
Substance use	• Tobacco, Alcohol, Prescription Medications, and Other Substances Tool [56-58]
Comorbidities	• Comorbidity Questionnaire [59]
Personality[b]	• Ten-Item Personality Inventory [60]
Demographic and clinical variables	• Demographic and clinical characteristics survey • Pet ownership survey [61]

[a]PROMIS: Patient Reported Outcomes Measurement Information System.

[b]Evaluated at T1 visit only.

Performance-Based Laboratory Measures

Motor Function

We administer the full lower-extremity and upper-extremity National Institutes of Health Toolbox (NIHTB) motor test battery [62,63] via the NIHTB iPad App. In addition to the NIHTB motor measures, we also administer a 4-Meter Backward Walking Test to calculate backward walking speed [54,64,65]. Table 2 provides a full list of motor tests, and Multimedia Appendix 2 provides further details.

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Table 2. Cognitive and physical performance tests administered in the Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis (CogDetect-MS) study.

Domain	Measures

Cognitive function	• Symbol Digit Modalities Test (oral administration) [66]
	• Paced Auditory Serial Addition Test-3 seconds [67][a]
	• Rey Auditory Verbal Learning Test [68][a]
	• ReacStick Test [69]
	• NIH[b] Toolbox Cognitive Battery [62,70]:
	  • Dimensional Change Card Sort Test
	  • Flanker Inhibitory Control and Attention Test
	  • List Sorting Working Memory Test
	  • Oral Reading Recognition Test
	  • Oral Symbol Digit Test
	  • Pattern Comparison Processing Speed Test
	  • Picture Sequence Test[a]
	  • Picture Vocabulary Test

Physical function	• 4-Meter Backward Walking Test [64]
	• NIH Toolbox Motor Battery [62,63]
	  • 2-Minute Walk Endurance Test
	  • 4-Meter Walk Gait Speed Test
	  • 9-Hole Pegboard Dexterity Test
	  • Grip Strength Test
	  • Standing Balance Test

[a]Alternate test forms used across T1, T2, and T3.

[b]NIH: National Institutes of Health.

Cognitive Function

We administer the NIHTB cognitive test battery plus the supplemental NIHTB Oral Symbol Digit Test [62,70] via the NIHTB iPad App. We also administer the Symbol Digit Modalities Test (oral administration) [66], the Paced Auditory Serial Addition Test (3 seconds) [67], the Rey Auditory Verbal Learning Test [68], and the ReacStick Test [69]. See Table 2 for a full list of laboratory-based cognitive tests and Multimedia Appendix 2 for further details.

Ambulatory Measures

A set of EMA items and scales (administered via a smartphone app, 4× per day except where noted) are administered. Some measures were adapted for daily administration from existing validated recall measures. See Table 3 for a full list of items and Multimedia Appendix 3 for further details.

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Table 3. Ambulatory data collected in the Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis (CogDetect-MS) study.

Data type and measure	Schedule
Ecological momentary assessment (via smartphone app)	
Perceived cognitive function (3 items)	4× per day
Pain intensity (1 item)	4× per day
Fatigue intensity (2 items)	4× per day
Perceived stress (1 item)	4× per day
Depressed mood (3 items)	4× per day
Location during cognitive tests (1 item)	4× per day
Distractions during tests (4 items with branching logic)	4× per day
Substance use (1 item)	4× per day
Activity pacing (3 items)	3× per day[a]
Sleep quality (2 items)	Morning
Overnight falls (4 items with branching logic)	Morning
Social participation (6 items)	Evening
Physical function (2 items)	Evening
Daytime falls (4 items with branching logic)	Evening
Cognitive function (via smartphone app)	
Symbol Search Test	4× per day
Dot Memory Test	4× per day
Physical activity (via ActiGraph accelerometer)	
Daytime physical activity and nighttime sleep activity	Continuous for 24 hours

[a]All time points except morning.

Two brief, valid, and reliable cognitive tests [13] are administered via the smartphone app. Response time speed is recorded in milliseconds for all tests. The Symbol Search Test (Figure 3) is a test of processing speed. Participants see a 2x2 grid of 4 symbol pairs at the top of the screen and are presented with 2 symbol pairs at the bottom of the screen. Stimuli are presented until a response is provided. Participants decide, as quickly as possible, which symbol pair at the bottom matches one of the symbol pairs at the top and select the matching pair by touching their selection at the bottom. In total, 24 trials are administered for each session. Reaction time and errors are recorded for sessions where effort is deemed adequate (accuracy >70%).

Figure 3. (A) Symbol Search landing page, (B and C) test instructions, and examples of (D) a “nonlure trial” (where neither symbol in the incorrect pair on the bottom appears in the pairs above) and (E) a “lure trial” (where one of the symbols in the incorrect pair on the bottom appears in a pair above).

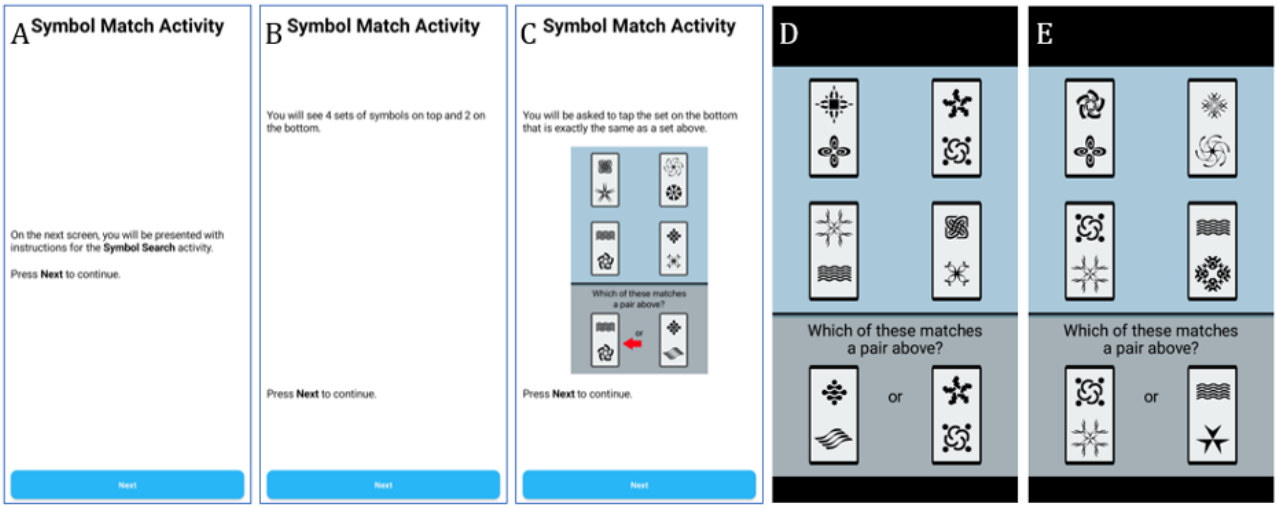

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The Dot Memory Test (Figure 4) is a test of working memory. Each trial consists of 3 phases: encoding, distraction, and retrieval. During the encoding phase, the participant is asked to remember the location of 3 red dots appearing on a 5×5 square grid. After a 3-second study period, the grid is removed, and the distraction phase begins, during which the participant is required to locate and touch the F's in an array of E's. After performing the distraction task, an empty 5×5 square grid is presented, and the participant must place the red dots (by touching the empty squares) in the correct locations. Participants press "Done" when they are finished. Speed and Euclidean distance (a score of the collective distance of the 3 dots from their correct locations) are recorded. In total, 4 trials are administered for each session.

Figure 4. (A) Dot Memory Test landing page, (B) instructions, (C) E's and F's distraction phase, and (D) response page.

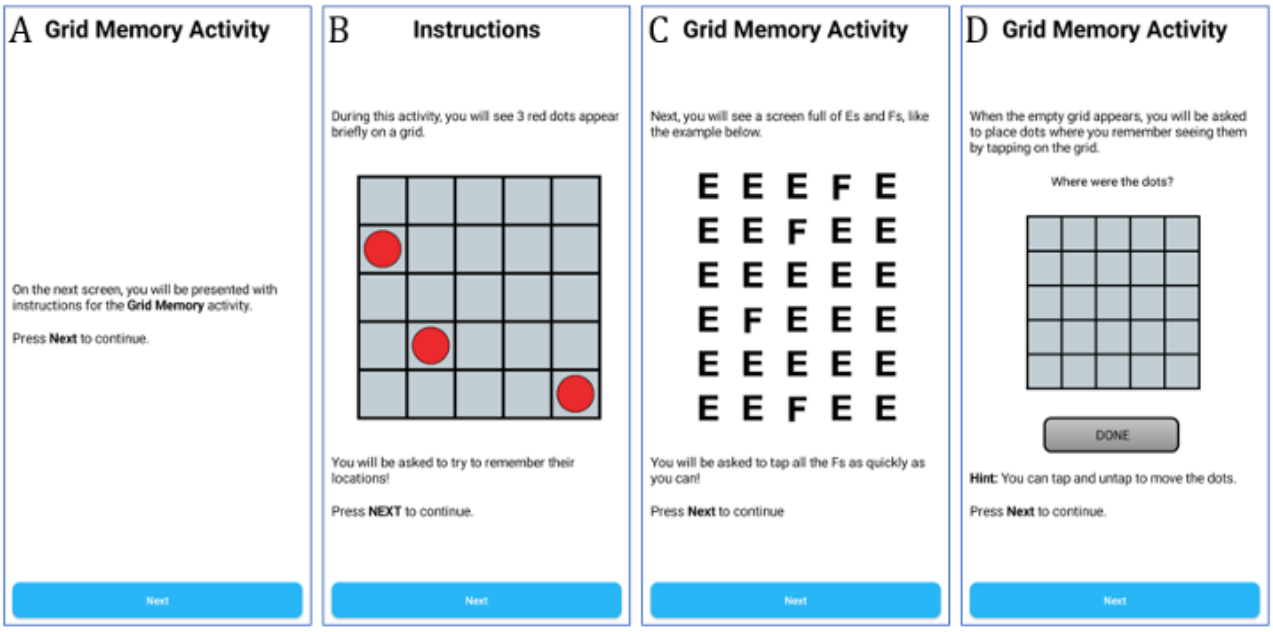

The ActiGraph produces variables representing different facets of day and nighttime physical activity. Our main measurements for daytime (awake) activity are activity counts, steps, physical activity intensity, and sedentary bouts across the 14-day home monitoring period, providing daily and typical activity levels. Our main measures for nighttime activity will be sleep latency, total sleep time, wake after sleep onset, and sleep efficiency.

Examiner Certification Process

To ensure standard test protocol administration across study sites and time, a rigorous examiner certification process was established. To achieve initial certification to administer tests, research staff were required to read the study protocol and manual of procedures, read the NIHTB Administration Manual, watch all training videos, and pass quizzes at the end of each training video. Training videos were from the NIH Toolbox eLearning Course or were custom-made by the study investigators, who had expertise in motor testing (NEF) or neuropsychological test administration (ALK, DME, and KNA). The videos provide detailed instructions on general best practices for test administration and how to administer each non-NIHTB test. After these initial training activities, research staff practiced the full laboratory-visit protocol with at least 5 nonparticipants (eg, fellow laboratory staff), video recording the final testing session. This video along with all accompanying case report forms and test materials were evaluated by 2 investigators—one with expertise in administering motor tests and one with expertise in administering neuropsychological tests. Together, the evaluators decided whether the examiner passed or failed the certification. Failure is defined as 2 or more minor errors or 1 or more major errors. A major error is defined as any error that indicates a lack of understanding of the proper standardized administration of any test or any scoring error that is large enough to change the interpretation of the data. Errors are reviewed with the examiner and their site principal investigator (ALK, NEF, or KNA). If the assessment is failed, the examiner practices at least 1 more time and submits a new certification video for review; this process can continue until the examiner passes certification. After initial certification, the examiner can begin testing study participants and is required to video record the first testing session with a person with MS; this video is also reviewed for consistency with study protocol, and feedback shared with the examiner. To ensure continued adherence to testing protocol, examiners record the laboratory visit for every 10th session, and this recording is reviewed by investigators as with the earlier certification videos. Consent for video recording is included in the study consent form.

Data Monitoring

The principal investigators (ALK and NEF) and lead research coordinator (KP) from the data coordinating center (UM) conduct in-person data audits at each site on an annual basis. Data related to adverse events, protocol deviations, study personnel training, screening procedures, participant withdrawal or termination, and enrollment procedures and documentation were audited for all participants enrolled at the site; data related to eligibility screening and documentation, study visit tracking, participant contact information, compensation record of human participants, and data collection were audited for a random subsample of all participants enrolled at the site. Audit reports,

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detailing findings, and required responses to the audit were produced and delivered to the site principal investigator (ALK, NEF, or KNA) and lead site research coordinator.

Multisite Coordination

To ensure multisite coordination and fidelity of procedures, the full study team, including all examiners and investigators at all study sites, met weekly to discuss study-related questions and troubleshoot any issues that had arisen during the prior week for the first 18 months of the study. As fewer questions arose, and study teams were immersed in recruitment and testing, meetings were shifted to every other week (months 18-36). After month 36, meetings were shifted to once per month. UM keeps a record of all meeting agendas and meeting minutes, and any clarifications to the study manual of procedures are recorded by the UM team and updated in a shared folder that includes all study-related documents.

UM serves as the data coordinating center for the study. Data from all sites are fully accessible to the investigators and staff at UM, who conduct monthly data checks to assess for data completeness and quality. Data double entry of case report forms from each study site and data cleaning, scoring, and merging to produce final, analyzable datasets are completed by UM staff and investigators.

Sample Size Analyses

We conducted analyses to determine the sample size needed to address all study aims. The goal of the first study aim is to determine whether the ambulatory tests are able to detect cognitive decline from baseline (T1) to 1-year (T2) or 2-year follow-up (T3) for individuals where clinic-based tests do not detect decline. The proportion of participants who show no decline or improvement, absolute but subtle decline (change <1/2 SD), meaningful decline (change between 1/2 SD-1 SD) [71], or clinically significant decline (≥1 SD decline) [71,72] will be calculated for both ambulatory and clinic-based neurocognitive tests. For each cognitive domain, a binary variable will be created for each participant indicating whether the ambulatory and clinic-based cognitive measures are consistent with each other (eg, agree) about the degree of change or laboratory-based or ambulatory measures indicate a larger degree of decline. We will test whether the proportion of cases where ambulatory measures indicated a larger degree of decline (relative to clinic-based tests) is statistically different from 0; sample size analyses for this test indicate that a sample of 199 will have 95% power (with critical α=.01) to detect significance, where ambulatory cognitive tests show a greater level of decline compared to clinic-based tests in as few as 1.5% (n=3) of cases. This suggests that our expected final sample size of 210 has the power to detect even modest differences in analyses comparing proportions of the sample that show a decline on ambulatory cognitive tests but not on clinic-based tests.

Effects sizes from a prior study of perceived cognitive functioning in daily life in MS [73-75] informed sample size estimation for the second and third aims, which examines factors that predict later cognitive decline or that are predicted by cognitive changes. We calculated the sample size needed to test the aims in a linear regression framework [76], which is a relatively conservative estimate, given that the repeated measures design imparts greater measurement reliability and therefore greater power [77]. We based our estimates on models that included up to 6 covariates (see list of covariates below) and 6 predictor variables of interest (eg, sleep quality, physical activity, pain, fatigue, mood, and stress) in predicting any given cognitive variable. The sample size for these models was expected to provide a conservative estimate for power required for the third aim (which had fewer predictors in each model). Critical α (P) value was set at .01. Our analyses indicated that a sample size of 214 will have 95% power (critical t=2.34, 1-sided significance test) to detect an association between cognitive functioning, and the variable expected to show the weakest association with cognition: mood (effect size f^2=0.075).

Data Analysis

Overview

Primary data analyses will account for covariates that have been shown to be associated with cognitive change in MS—age, sex, disease duration, MS subtype (relapsing vs progressive subtypes combined), disease severity, personality variables, and cognitive reserve (education level plus scores on vocabulary test). After primary analyses are completed, analyses will be repeated stratifying by sex, age group, baseline cognitive impairment, and MS subtype. We have intentionally included participants with both existing cognitive impairment and no known cognitive impairment at enrollment. This will allow us to also conduct sensitivity analyses to explore whether people who show evidence of cognitive impairment at baseline show a more rapid decline on either laboratory or ambulatory cognitive assessments as has been identified in prior research [78,79].

Specific Aim 1: Are Ambulatory Measures of Subjective and Objective Cognitive Function More Sensitive to Longitudinal Changes in Cognitive Function Compared With Conventional Clinic-Based Assessments?

Nonparametric tests (Wilcoxon signed rank test, 2-tailed) will be used to compare cognitive test scores (ambulatory vs clinic-based measures) for each participant at each time point. We will test whether the proportion of cases where the ambulatory test indicates a greater degree of cognitive decline compared to the clinic-based cognitive tests is statistically different from 0. Additional sensitivity tests of the paired differences in proportions of 4 categories (no decline, absolute but subtle decline, meaningful decline, or clinically significant decline) for each cognitive domain between ambulatory and clinic-based neurocognitive tests at both 1- and 2-year follow-up will be conducted [80]. Mixed effects models will be used to examine changes over time for each cognitive measure, with the expectation that the ambulatory measures will show larger time effects at both 1- and 2-year follow-up.

Specific Aim 2: Do Modifiable Factors Predict Short- and Long-Term Changes in Ambulatory Measures of Cognitive Functioning?

Short Term

Mixed effects multilevel models (MLMs) for momentary (within-day) associations, one for each ambulatory cognitive

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variable (perceived cognitive function and cognitive test scores), will be constructed. In each case, predictor variables of interest will be physical activity (accelerometer data), sleep (accelerometer data and EMA-sleep quality), and EMA measures of fatigue, pain, mood, and stress from the previous within-day time point (all moment-to-moment analyses will be conducted within-day). Similarly, MLMs for day-level associations, one for each cognitive variable, will be constructed; only day-level analyses will explore the association between sleep and cognition. Given the lack of data on the temporal effects of these variables on cognitive functioning, exploratory analyses of lagged effects (1- and 2-day lag) will also be examined.

Long Term

Ambulatory measures of predictor and outcome variables will be aggregated within a time period for baseline and 1- and 2-year follow-up periods. Laboratory-based measures of cognitive functioning will also be examined. MLMs will be used to test whether ambulatory measures of physical activity, sleep, fatigue, pain, mood, and stress predict changes in objective or subjective measures of cognitive functioning (ambulatory and laboratory-based measures) 1 or 2 years later. The change will be modeled within an analysis of covariance framework, where T2/T3 values for an outcome of interest are modeled controlling for T1 values of the said outcome. In contrast to specific aim 1, where the primary interest is on comparing the performance of the ambulatory tests to standard clinic-based cognitive tests, the primary interest of specific aim 2 is in understanding what factors contribute to variation or changes in cognitive function and in identifying probable targets for cognitive rehabilitation regardless of the measure used to identify such associations; therefore, no direct comparisons between measurement types will be made.

Specific Aim 3: Do Ambulatory Measures of Cognitive Functioning Predict Social and Physical Functioning Over Short-Term and Long-Term Time Frames?

Short Term

In the momentary data, MLMs will be constructed to predict same-day social participation and physical functioning (upper- or lower-extremity functioning, balance, and falls or missteps) from the ambulatory cognitive variables. Analyses for falls or near falls will be conducted using a special case of MLM for categorical outcomes. Exploratory analyses of lagged effects (1- and 2-day lag) will also be examined.

Long Term

In terms of distal prediction of social and physical function from ambulatory cognition, we will conduct MLMs with the cognitive variables (averaged across each time period) predicting social and physical functioning at 1- and 2-year follow-up. The change will be modeled within an analysis of covariance framework, where T2/T3 values for an outcome of interest are modeled controlling for T1 values of the said outcome. These MLMs exploring long-term associations between cognitive changes and changes in social and physical functioning will be repeated in a set of secondary analyses with standard clinic-based cognitive test scores as predictor variables. Prediction of long-term changes in social and physical functioning from ambulatory cognitive measures will be compared to the ability of laboratory-based measures to predict these same changes. Ambulatory measures of cognition are of primary interest for specific aim 3, given that their microlongitudinal burst design allows for examination of short- and long-term associations, and are assumed to be more reliable and therefore more likely to demonstrate robust associations with the other functional outcomes.

Results

This research received funding on August 1, 2021, from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (R01HD102337-01A1). Enrollment and T1 data collection occurred between May 12, 2022, and February 29, 2024. The study recruited 301 individuals with MS (UM: n=107, WSU: n=102, and UW: n=92); of these, 274 (UM: n=101, WSU: n=88, and UW: n=85) participated in T1 data collection. Longitudinal data collection will continue through March 2026. Data analysis has not yet started as of the time of this submission.

Discussion

Principal Findings

The anticipated findings of this study are 3-fold. First, we anticipate that ambulatory cognitive tests will be more sensitive to subtle cognitive changes in people with MS over 1-2 years. Second, we expect to identify modifiable factors (eg, mood, sleep, and physical activity) that precede and predict later cognitive decline on a short- and long-term scale. This information could help to prevent future decline or mitigate current cognitive dysfunction. Third, we hypothesize that cognitive changes will predict changes in social and physical function on a short- and long-term scale; such information will help to delineate the full impact of cognitive change in MS.

The collection of intensive longitudinal data in a large, heterogenous sample will allow for an in-depth characterization of individuals with MS and provide multiple avenues for future research. Data from this study are expected to inform comprehensive models of cognitive change in MS as well as provide insights on potential targets for intervention development to help people with MS optimize cognitive function.

Strengths and Limitations

One limitation of this study is that the inclusion criteria require participants to be able to ambulate. The rationale for this criterion is that we would like to collect meaningful accelerometer data in order to explore the associations between physical activity and cognitive function. However, this criterion limits the generalizability of the findings to those with more significant mobility limitations.

This study has a number of notable strengths. Technology-enabled assessment of day-to-day cognitive function in the lived environment has the potential to greatly improve the sensitivity and ecological validity of cognitive assessment

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in people with MS. The advancement of measurement sensitivity is critical, as cognitive changes can be subtle and compound slowly over time; however, despite the small magnitude of these changes, individuals with MS often report distress over noticeable changes in their cognition that are not detected on standard laboratory-based cognitive tests. Another advantage is the intensive within-person design that allows for the exploration of dynamic associations between potentially modifiable predictors of cognitive dysfunction while accounting for "third variables" such as a person's disease severity, age, and sex. AnΩΩΩhone. This allows for exploring different trajectories of change over time.

Future Directions

Future work that capitalizes on the findings of this study and advances in assessment methods can also be used to improve treatment decision-making, including the timing and type of treatment approach. We will use these findings to design and test trials of behavioral, medical, and combination therapies to prevent cognitive decline and improve cognitive functioning in people with MS. Additionally, our innovative assessment methods may also be used to improve the measurement of outcomes in clinical trials of both pharmacological and nonpharmacological interventions, enriching understanding of the effects of such interventions. To our knowledge, there are few studies that track cognitive and other functional domains in MS beyond 2 years; thus, long-term outcomes will yield a rich dataset for understanding longitudinal function in persons with MS.

Acknowledgments

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Data Availability

The datasets generated during this study are not publicly available at the time of this publication due to ongoing data collection but will be available at the conclusion of the study on a secure web-accessible data repository. The availability of data sharing will be publicized in publications and presentations.

Authors' Contributions

ALK designed the study, obtained grant funding, oversaw the conduct of the study, contributed to the original draft, made revisions during the review and proofing phases, and served as the corresponding author. DME, KNA, and NEF designed the study, obtained grant funding, oversaw the conduct of the study, contributed to the original draft, and made revisions during the review phase. KP supervised study staff at the University of Michigan, oversaw multisite coordination including data management, contributed to the original manuscript draft, and helped to revise the manuscript during the review phase. KG conducted study visits and collected data, managed and cleaned study data, contributed to the original manuscript, and helped to revise the manuscript during the review phase. All authors reviewed and approved of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed description of CogDetect-MS self-report measures. CogDetect-MS: Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis.
[DOCX File , 28 KB - resprot_v13i1e59876_app1.docx]

Multimedia Appendix 2
Detailed description of CogDetect-MS performance-based measures. CogDetect-MS: Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis.
[DOCX File , 26 KB - resprot_v13i1e59876_app2.docx]

Multimedia Appendix 3
Detailed description of CogDetect-MS ambulatory self-report measures. CogDetect-MS: Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis.
[DOCX File , 24 KB - resprot_v13i1e59876_app3.docx]

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Abbreviations

CogDetect-MS: Optimizing Detection and Prediction of Cognitive Function in Multiple Sclerosis
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
MLM: multilevel model
MS: multiple sclerosis
NIHTB: National Institutes of Health Toolbox
REDCap: Research Electronic Data Capture
UM: University of Michigan
UW: University of Washington
WSU: Wayne State University

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Protocol

Identifying Gravity-Related Artifacts on Ballistocardiography Signals by Comparing Weightlessness and Normal Gravity Recordings (ARTIFACTS): Protocol for an Observational Study

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Abstract

Background: Modern ballistocardiography (BCG) and seismocardiography (SCG) use acceleration sensors to measure oscillating recoil movements of the body caused by the heartbeat and blood flow, which are transmitted to the body surface. Acceleration artifacts occur through intrinsic sensor roll, pitch, and yaw movements, assessed by the angular velocities of the respective sensor, during measurements that bias the signal interpretation.

Objective: This observational study aims to generate hypotheses on the detection and elimination of acceleration artifacts due to the intrinsic rotation of accelerometers and their differentiation from heart-induced sensor accelerations.

Methods: Multimodal data from 4 healthy participants (3 male and 1 female) using BCG-SCG and an electrocardiogram will be collected and serve as a basis for signal characterization, model modulation, and location vector derivation under parabolic flight conditions from µ*g* to 1.8*g*. The data will be obtained during a parabolic flight campaign (3 times 30 parabolas) between September 24 and July 25 (depending on the flight schedule). To detect the described acceleration artifacts, accelerometers and gyroscopes (6-degree-of-freedom sensors) will be used for measuring acceleration and angular velocities attributed to intrinsic sensor rotation. Changes in acceleration and angular velocities will be explored by conducting descriptive data analysis of resting participants sitting upright in varying gravitational states.

Results: A multimodal data set will serve as a basis for research into a noninvasive and gentle method of BCG-SCG with the aid of low-noise and synchronous 3D gyroscopes and 3D acceleration sensors. Hypotheses will be generated related to detecting and eliminating acceleration artifacts due to the intrinsic rotation of accelerometers and gyroscopes (6-degree-of-freedom sensors) and their differentiation from heart-induced sensor accelerations. Data will be collected entirely and exclusively during the parabolic flights, taking place between September 2024 and July 2025. Thus, as of June 2024, no data have been collected yet. The data will be analyzed until December 2025. The results are expected to be published by June 2026.

Conclusions: The study will contribute to understanding artificial acceleration bias to signal readings. It will be a first approach for a detection and elimination method.

Trial Registration: Deutsches Register Klinische Studien DRKS00034402; https://drks.de/search/en/trial/DRKS00034402

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KEYWORDS

ballistocardiography; seismocardiography; acceleration; artifact; weightlessness; gravity; observational study; heartbeat; blood flow; intrinsic sensor; hypotheses; assessment; heart-induced; sensor; gyroscopes; cardiovascular; diagnostic

Introduction

Complex methods of cardiovascular diagnostics are increasingly being integrated from the clinical setting into everyday life. Wearable smart sensor technology necessitates real-life measurements to make the results usable for individualized and tailored care [1]. Ballistocardiography (BCG) and seismocardiography (SCG) are generally suitable for cardiovascular diagnostics (heart rhythm, functionality, and vascular status) and the extraction of parameters such as blood pressure or respiration at a relatively low cost and with a low-risk potential. They can thus provide support for diagnosing and monitoring potential heart abnormalities [2-12]. BCG and SCG are noninvasive methods for measuring oscillating recoil movements of the whole body (in the case of BCG) or the chest (in the case of SCG), caused by ballistic forces generated by the blood flow (in the case of BCG) or mechanical actions of the heart (in the case of SCG) [13]. The accelerations of these movements can be derived from digital 3D acceleration sensors (accelerometers) on the body surface [14,15]. These sensors are commonly positioned over the apex of the heart or the sternum and measured across all axes. Even though BCG-SCG has been known for several decades and despite numerous research projects, there is still a fundamental uncertainty in characterizing the SCG-BCG signals, making interpretation extremely difficult. Earth gravity (g=1) can influence the translational 3D acceleration measurement of SCG signals because of the rotatory movement of the sensor on the body surface. The heart beat does not only cause 3D translatoric (x, y, z) but also rotatory movements (angular velocity: x=yaw, y=pitch, and z=roll) [16]. Hence, both translatoric movements and angular velocities are in the same frequency domain of the regular SCG signal. As a result, the actual translatoric acceleration caused by the heart is affected by additional “artifacts” due to the change in orientation of the acceleration axis relative to the earth’s gravity. This can lead to BCG-SCG–like acceleration artifacts on the axes and thus to constructive or destructive interference with the actual BCG-SCG signal. These can lead to deformation and, thus, misinterpretations of the signal. Considering these artifacts, the interpretation of SCG signals is biased, so there is a strong need to obtain a clear SCG signal description so that the correlation of the SCG signal with the physiological parameters of the heart can be successful in the long term.

To characterize the BCG-SCG signals and their features as precisely as possible, clearly defined and compensated position vectors of the acceleration on the reference system “heart” are necessary. The signals can be compared with reference methods, which helps characterize BCG-SCG signals. This study aims to answer the overall question of what form the BCG-SCG signal takes when the acceleration artifacts created by the intrinsic rotation of synchronous accelerometers, measuring acceleration, and gyroscopes, measuring angular velocities (6-degree-of-freedom [6-DOF] sensors), in relation to earth’s gravity are filtered out. In this context, the question arises of what related artifacts look like and whether it is possible to eliminate them from the signal. Thus, ARTIFACTS is an observational study to generate hypotheses on detecting and eliminating such artifacts and differentiating them from heart-induced body acceleration. Against this background, ARTIFACTS aims to detect these artifacts by performing examinations in different gravitational states. This includes describing the artifacts (eg, by determining how strongly they influence the BCG-SCG signal), differentiating them from heart-induced sensor accelerations, and, following this, eliminating them from the signals. For this purpose, data on individual acceleration patterns of cardiac physiology under different gravitational influences will be collected. These data will then be descriptively analyzed concerning intra- and interindividual differences, serving as a basis for signal characterization, model modulation, and location vector derivation. One focus of the analysis will be to describe aspects related to the formation and the effects of the artifacts. Data from reference methods will be collected to help characterize the signals. Exploratively, artificial patterns will be identified and described using individually collected data and actual conditions. The data will serve as a basis for developing models for defined and compensated acceleration position vectors.

Methods

Overview

The study aims to collect intra- and interindividual multiaxial movement (angular velocity, measured using gyroscopes, and acceleration, measured using synchronous, using synchronous accelerometers [6-DOF sensors]) and electrocardiogram (ECG) data at different gravitational states (µg to hypergravity) under physiological real-life conditions in parabolic flights. The data will be used to describe acceleration artifacts caused by the sensors’ physical rolling, yawing, and pitching movements on the body surface. ARTIFACTS is designed as an open, prospective, noninterventional, noninvasive, nonrandomized, descriptive study. The procedure, including the experiment, will be identical for all participants. For this reason, blinding is not appropriate. The study will last 10 months (September 2024 to July 2025). The data collection will take approximately 3 weeks.

Study Objectives

The primary end point comprises the description of acceleration artifacts (morphology and expression), differences in accelerations or angular velocities, and the identification of variables that affect acceleration sensors due to gravitational acceleration. The evaluation of signal filtering and peak detection algorithms are the secondary end points of this study. Of particular interest are differences in motion trajectory resulting from SCG-BCG data to describe and quantify the influence of artifact formation, more specifically dedicated consideration of the differences in accelerations and angular velocities in 6 spatial dimensions on 2 different body locations in µg, 1g, max 1.8g, and transitions.

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Hypothesis

During the phases of hyper-*g* conditions (*g*=1.8*g*), the acceleration changes caused by rotation (artifacts) are more dominant. In the phase of 0*g* (no gravitational influence), the impact of artifacts should not be present. Figure 1 depicts an example of this artifact formation for a rotation of the sensor around x-axis.

Figure 1. Schematic representation of the artifact formation as a basis for the derivation of the hypothesis (example for x-rotation). Due to the change in the axis position relative to the gravitational acceleration, there is a change in acceleration along this axis (here z-axis and y-axix). At g=0 the impact of gravity is ruled out and no change in acceleration due to rotation is expected (no artifacts). At hyper-g (g=1.8g) the effects of the artifacts can increase. SCG: Seismocardiography.

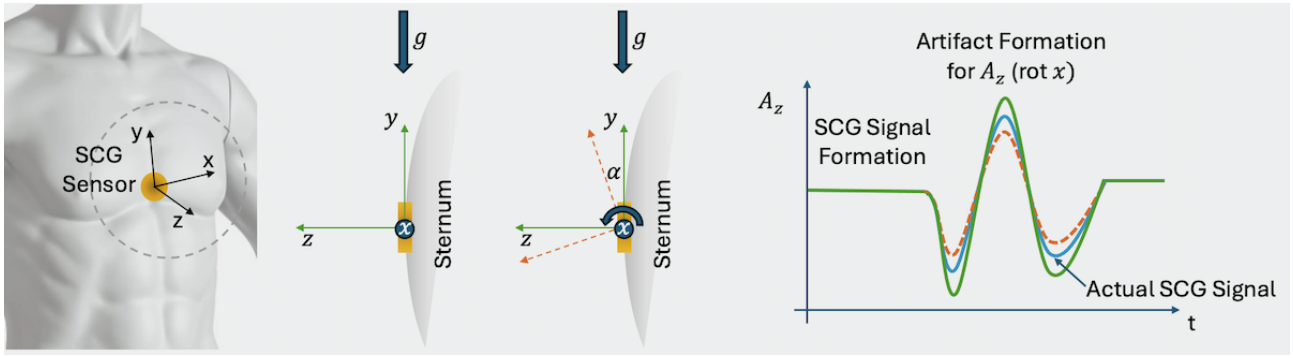

Participants

In ARTIFACTS, 4 healthy adult persons (male and female; 18-65 years old, fit for duty) without structural heart disease and in stable sinus rhythm will be included. Participants who are unwilling or unable to participate; who have an addiction, heart or cardiovascular disease, mental illness or panic disorders, allergy or intolerance to electrode gel or wound dressings, emphysema, and multimorbidity (ie, co-occurrence of at least 2 chronic conditions); or who are breastfeeding or pregnant will be excluded from the study. Recruitment takes place via personal contact. All study participants are members of the scientific group. Recruitment is done on a strictly voluntary basis. The project's explorative and hypothesis-generating approach justifies the number of cases. The project is a data collection of heart-healthy individuals in the form of an observational study to generate hypotheses on detecting and eliminating acceleration artifacts due to the self-rotation of the 6-DOF sensors and their differentiation from heart-induced body acceleration. Four participants (3 male and 1 female) are sufficient for (1) evaluating the feasibility of the measuring or recording method, (2) obtaining data for postanalysis, (3) determining variation in individual biophysical vibrations related to the cardiovascular system, and (4) having sufficient backup personnel for dropouts, for example, due to sudden illness. The participants are a convenience sample of the study personnel. There are no financial expenses for the participants in this study.

Study Procedure

The German Space Agency, Germany, initiated and organized the campaign. The study participants will be prepared for the measurements in Bordeaux, Mérignac, at the NoveSpace center. The measurements are carried out in an aircraft designed explicitly for parabolic flights as part of the parabolic flights over the Atlantic. All data will be collected in France. The total duration of a single measurement series is approximately 3.5 hours. One measurement point is planned per study participant.

The study participants will be informed in advance about the study, and their consent to participate will be obtained. A physician will obtain informed consent outside of a possible dependency relationship. After the candidates have consented to participate in the study, the information required to validate the inclusion and exclusion criteria is requested and checked. A flight physician will check the physical condition of the participants. Age, weight, height, and BMI are inquired and recorded. While still on the ground, the study participants will be outfitted with three 6-DOF sensor patches and ECG electrodes, and both types of sensors will be taped to their bodies (Figure 2). Data acquired via the patches and the ECG will be clock-synchronous. For the ECG, the Einthoven II lead will be used. For the SCG-BCG measurements, sternal and lower back positions will be used. The study participants will be transferred to the Airbus A310 Zero G and seated (Figure 1). During the experiment, participants will stay seated for the duration of the parabolic flights. The participants are asked to avoid any physical activity during the measurements. There is a one-time role change from the participant to the investigator. Participation in this study lasts a maximum of 6 days, including preparation and 1 flight day during the parabolic flight campaign. On the flight day, the participation will consist of 2 hours for preflight activities, 3.5 hours for the parabolic flight, and approximately 30 minutes for postflight follow-up after landing.

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Figure 2. Setup, accelerometric angular velocity and ECG readings of a resting participant fixed to a seat (right) during parabolic flights. An operator manages preparation and execution of the experiments (person on the left, fixed to a sting position). Roles change during each flight. A reference accelerometer-gyroscope is fixed to the ground of the aircraft for reference. 6-DOF: 6-degree-of-freedom; ECG: electrocardiogram; HW: hardware.

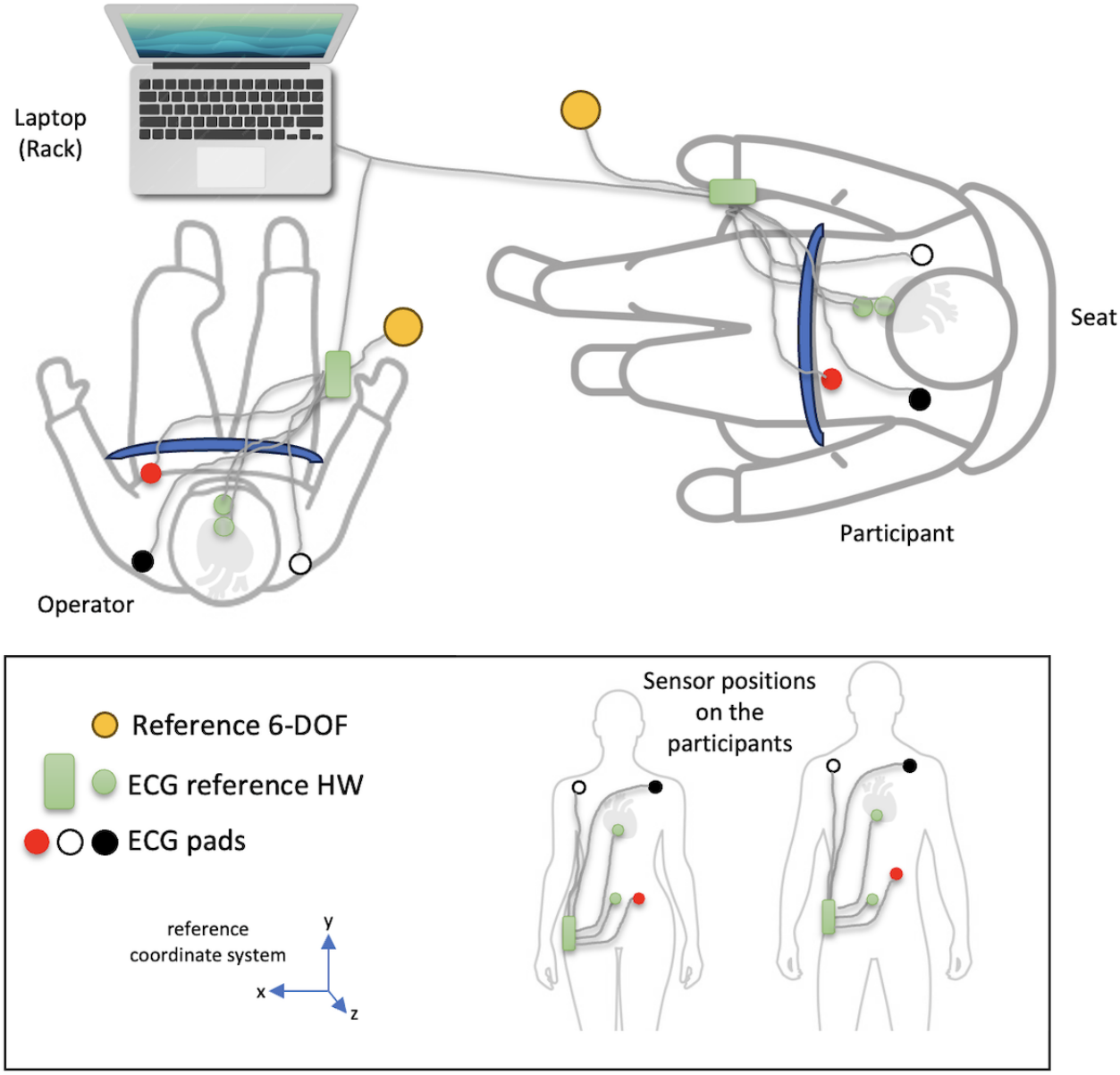

Schedule

Three parabolic flights with 30 parabolas (+1 test parabola excluded from measurements) are planned. One parabolic flight is planned per day (see Figure 2). The participant and operator are fitted with the SCG and BCG sensor patches (sternum and lower back) and the 1-channel ECG on the ground. After entering the aircraft, the operator and test participants check the available equipment and its functionality. The positions of the reference sensors are approved. The participant is strapped to the seat during the flight and for the experiment preparation. The operator then tests connectivity and checks data recording (including the reference sensor). When all readings are satisfactory, and no adjustments are required, the operator straps himself into a sitting position. The operator starts the logging of data, and the experiment starts. After 20 parabolas, the operator and test participant switch positions and roles. After the last parabola, the logging is stopped, the data are stored and backed up, and the operator and the test participant are released from their positions. Back on the ground, the sensors and the ECG are removed, and the equipment is prepared for the next flight.

A schematic schedule of how the 4 test participants will be used on the 3 flight days is shown in Figure 3 and Table 1. The key operator (here, participant 1) will start with the operator's role to rectify technical problems at an early stage and obtain as much data as possible from the participant. After 20 parabolas, the role is changed, as mentioned before. The first parabola of the day is not counted and serves as the first test of the sequence. This results in the total data after 3 days of flight (the amount of data is based on the parabola cycles), as shown in Table 1.

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Figure 3. Schematic schedule for all 3 flight days and all 4 participants with 30 parabolas per flight day. A cycle comprises a parabola (P) and a rest phase (R). The role change between the operator and participant occurs after 20 parabola cycles during the resting phase.

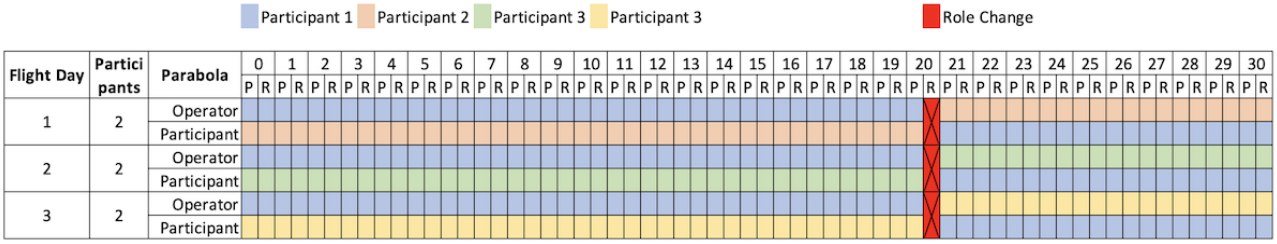

Table 1. Number of measurements (parabolas) for each participant and in each role.

Role	Flight day						Sum	
	1		2		3			
	Participant	Operator	Participant	Operator	Participant	Operator	Participant	Operator
Participant 1	10	20	10	20	10	20	30	60
Participant 2	20	10	—[a]	—	—	—	20	10
Participant 3	—	—	20	10	—	—	20	10
Participant 4	—	—	—	—	20	10	20	10

[a]Not applicable.

Measurements

Aside from sociodemographic data (sex and age), linear accelerations, and angular velocity (6-DOF SCG-BCG signals), the heart rate (ECG) and the gravity level will be recorded. The acceleration will be detected in the form of SCG-BCG signals.

Equipment

For the measurements, a fused sensor system consisting of commercially available 3D accelerometers and 3D gyroscopes used for determining the micromovements, and an ECG, serving as a reference system, is employed. This device can simultaneously record 3 times 6-DOF SCG-BCG signals along with an ECG (all with clock synchronization), while still maintaining high precision. This system is required to investigate artifact formation precisely. To ensure high-precision and low-noise measurement, the principle of differential sensing [17] is used to make SCG-BCG data measurable with ultralow noise and also to record data for the reference coordinate system on the aircraft floor. It is crucial for the experiment that all data are recorded synchronously and with as little jitter as possible. A field-programmable gate array, whose parallel structures are very well suited for this purpose, is used for this. The basic implementation of the ECG reference hardware is based on a previous prototype [18] (see Figure 4).

Figure 4. The basic structure of the measurement system is illustrated on the block diagram (left) and BCG/SCG/ECG reference hardware (right). 6-DOF: 6-degree-of-freedom; BCG: ballistocardiography; ECG: electrocardiogram; HW: hardware; LP FPGA: low power field-programmable gate array; SCG: seismocardiography.

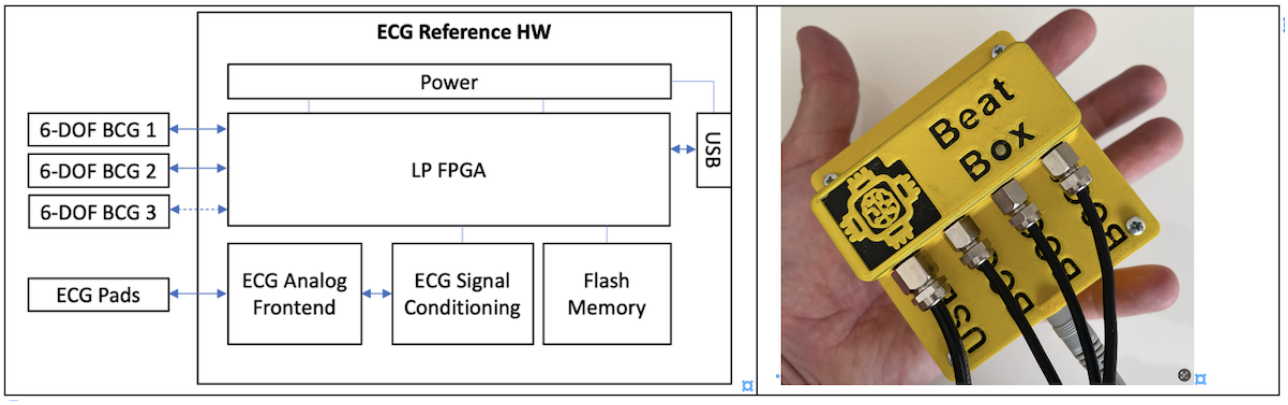

Ethical Considerations

The risk of damage to health through participation in the study is negligible and is offset by the positive benefit of the knowledge gained. There is no direct benefit for the study participants. The data collected are of great interest to the general public, for example, for further scientific studies of health monitoring systems and possible technology transfer. There is no therapeutic intervention. The principal risk associated with parabolic flights is the risk of an aeronautical accident. This risk has been assessed by the technical experts of the European Aviation Safety Agency, who concluded that

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these flights provide an acceptable level of safety. The study-related examinations are all painless and noninvasive. There is minimal risk in conducting the study due to very rare allergic reactions to the electrode gel or wound dressing. The risk of damage to the participants' health through participation in the study is negligible (allergic reactions to electrode gel, symptomatic motion sickness, and pressure effects in the middle ear are all rare occurrences). The positive benefit of the knowledge gained offsets these risks. Participation in the study has no consequences for further clinical treatment. The main undesirable effect may be travel sickness (nausea and vomiting) due to the succession of variations in gravity levels. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the observation period, until a satisfactory explanation for the adverse event is found or the investigator considers it medically justifiable to terminate follow-up. In case of motion sickness, the experiment is stopped, and the participant returns to a seat under the supervision of the onboard doctor. Once the aircraft has taken off, it is impossible to get off the plane, and the participant will thus have to endure the remaining flight. Neither interactions with concomitant medical treatments nor serious adverse events, including serious health hazards and severe effects of the measurement devices or reportable adverse events, are expected.

Freedom of publication is guaranteed. All project members will be informed before the study findings are used and published. All publications based on the data obtained will be coauthored by both parties in accordance with the DFG (German Research Foundation) criteria.

The study's objectivity can be guaranteed through critical consideration and the comprehensive and targeted division of the implementation, analysis, support, and monitoring by unbiased study staff, as well as compliance with the premise of the 2-eye principle and universal study transparency.

As stated, the participants are part of the study personnel. The study participants do not receive any separate remuneration.

ARTIFACTS was approved by the Ethics Committee of the Ärztekammer Westfalen-Lippe and WWU Münster, Germany, on May 13, 2024 (2024-081-f-S; Chairman: Prof Dr WE Berdel).

Informed Consent

Participants' informed consent is mandatory for study participation. Volunteers will receive an electronic version of the experiment information file several weeks before the parabolic flight campaign. This document will detail the experiment's purpose, methods, and duration. By the day before the flight, volunteers will be given a paper version of the experiment information file, meet the research team, tour the aircraft, and become acquainted with the procedures and devices used in the experiment. Potential risks and constraints will be explained, and volunteers will have the opportunity to ask questions. They will have at least 2 hours to review the information before signing the informed consent form. After this, an enrollment visit will occur, and volunteers will be further familiarized with the procedures.

Safety

Only tried and tested measurement system components are used to prevent any risk of impairment or injury to the study participants. Furthermore, all measurements concerning the study participants will be done by trained personnel. The technology, which is used directly on the study participants' bodies, works exclusively with low voltage that is harmless to health. The devices are fully insulated. The measurement can be terminated at any time by the study personnel or participants. The health risk of participating in studies is negligible. In the event of study-related damage, all participants in a flight are covered by insurance.

Data Collection

All data, including electronically stored data and hard copies, will be pseudonymized for the purposes of the research. Data collection and documentation are primarily carried out electronically on an encrypted and password-protected research laptop. The data records are then transferred to the secure server infrastructure (research area) at Bielefeld University and Hamburg University of Technology (TUHH). An authorization and role concept regulates access to the research data. The password-protected pseudonymization list is stored separately on an encrypted data carrier and physically stored in a suitable, lockable cabinet. Only the study management has access to this list and the data. The data are analyzed anonymously. Information related to data security and protection can be found in the corresponding section in the provided information material. Data protection is taken into account in accordance with the applicable laws. The European Union General Data Protection Regulation (EU-GDPR) is relevant for the European area. The legal basis for the collection, storage, processing, and transfer is the informed written consent of the study participants. Retention and deletion periods are based on the GDPR; the same applies to the data participants' rights to information. The data collected during this study will be stored for at least 10 years after the completion or discontinuation of the study following DFG regulations. Research data management is implemented to handle research data, taking into account the guidelines for handling research data at TUHH and the research data policy of Bielefeld University. The existing infrastructure of both universities is used to ensure long-term storage within the permitted time limits. All data used as a basis for publications will be made available anonymously together with the publication.

Analysis

Primarily, no inferential statistics are planned. In the early research stage, the focus is on descriptive questions. The description is carried out by determining minima and maxima, mean value, SD and variance, median and IQR, correlations, interrater stability, and signal-to-noise ratio. In the event of a termination of data collection due to external circumstances such as air sickness, all data recorded up to that point are analyzed. Multiple imputation compensates for missing values.

Statistical analyses will be carried out using R software (version 4.4.1 or later, open source; R Project for Statistical Computing) and Python (version 3.12.4 or later, open source; Python

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Software Foundation). The research team will carry out the data analysis.

Results

ARTIFACTS is an experiment within the AuRelia project. AuRelia has been funded since August 2023 by the German Federal Ministry of Economics and Climate, funding code FKZ:50RP2350. Additional institutional resources are used.

The data will be collected entirely and exclusively during the parabolic flights, which will take place between September 2024 and July 2025. As of June 2024, no data sets have been collected yet. Data analysis will take place until December 2025. The publication of results is planned for June 2026.

A total of 4 participants have been recruited (3 male and 1 female). The study's primary end point involves characterizing acceleration artifacts, including their morphology and expression, analyzing variations in acceleration, and identifying factors influencing acceleration sensors under gravitational acceleration. The secondary end points encompass the assessment of signal filtering and peak detection algorithms. A multimodal data set will be available that serves as the foundation for research into a noninvasive and gentle method of BCG-SCG using 6-DOF sensors (3D gyroscopes and 3D accelerometers). This research explores hypotheses regarding the formation, detection, and mitigation of acceleration artifacts arising from the intrinsic rotation of BCG-SCG sensors and their differentiation from heart-induced sensor accelerations. The collection of the multimodal basic data set provides the necessary basis for research into a noninvasive and gentle method of BCG-SCG with the aid of low-noise and synchronous 6-DOF sensors. This research contributes fundamental findings for unambiguous characterization based on compensated location vectors. It also helps develop methods for integrating signal characterization on resource-limited sensors and translational models for mapping between BCG-SCG and reference methods.

Discussion

Prior Work

To our knowledge, prior work on BCG-SCG signals has not considered acceleration bias caused by gravitational influences on the self-rotation of acceleration sensors. However, we found several studies in our literature that address the participant of motion artifacts in BCG and potential countermeasures [19-21]. Also, we identified 2 publications considering BCG measurements under parabolic flight conditions, which address highly artifact-biased data sets but without explaining the kind or source for the artifacts [22,23].

Anticipated Findings

This study will have shown that artifacts in BCG-SCG signals caused by the roll, pitch, and yaw movements of accelerometers in relation to the earth's gravity can be detected and eliminated from BCG-SCG signals, and these signals can thus be characterized more precisely. In the context of the use of multimodal measurement systems in this study, uncertainties in using these are expected to become apparent. However, this demonstration is not the aim of the study. Thus, the study provides insights into the uncertainty of multimodal measurement systems.

Interpretations and Implications

Our study will provide a basis for using more clearly characterized BCG-SCG signals in future studies and applications. In future studies in which BCG-SCG signals are to be evaluated, more reliable evaluations can thus be made. The precise signal characterization will also be of clinical relevance in the future. According to [24], monitoring by SCG and associated applications is still only possible to a very limited extent due to artifacts in the signal. Through a good characterization of BCG-SCG signals, BCG-SCG could be used more reliably than before for the diagnosis of diseases such as heart disease and the monitoring of heart health. Based on the findings of this study, clinical applications for diagnostics using BCG-SCG can be further developed.

Strengths and Limitations

A strength of this study is that investigating artifacts in BCG-SCG signals using different gravity states is a pragmatic approach to improving signal characterization. A small sample is sufficient to obtain fundamental findings. Matching BCG-SCG signals with reference methods such as ECG is fundamental for subsequent studies on how ECG and BCG-SCG can complement each other. Although it is assumed that the scope of the study is sufficient to characterize the BCG-SCG signals as planned, even longer sensory measurements in different gravitational states could possibly further improve signal characterization. In this study, the accelerations caused by the movement of the accelerometers in relation to the earth's gravity are distinguished. Generally, valid statements about heart-induced sensor accelerations cannot be made because of the small and diverse sample size. However, because this is not the aim of this study, it is not a limitation in the strict sense.

Future Directions

Future studies can test how well the findings from this study regarding the detection and removal of artifacts can be transferred to BCG-SCG signals recorded over more extended periods under normal terrestrial gravity conditions. In addition, various test conditions can be used to investigate how precisely the artifacts can be detected and how they can be removed from the signal, even when the respective sensor is in different positions due to various everyday body postures (such as lying down or bending over). In addition to the artifacts examined in this study, artifacts may arise from other sources (eg, internal body movements caused by speech or external movements such as passing vehicles). Artifacts coming from different sources are not always easy to distinguish. As a result, it is not always possible to identify which source leads to strong artifacts. Knowing this may help determine under which circumstances BCG-SCG signals can be best characterized and thus should be recorded, which could be investigated in future studies.

Conclusions

ARTIFACTS is fundamental research, the findings of which will contribute to precise signal characterization based on

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compensated position vectors. It also provides insights into the uncertainties of multimodal measurement systems and develops methods for integrating characterization on resource-limited sensors and translational models for mapping between BCG-SCG and reference methods, namely, echocardiography, phonocardiography, and electrocardiography. Taken together, a portfolio of methods will be available as a scientific basis for further research to enable cost-effective wearables with a wide range of applications for outpatient diagnostics and monitoring in prevention, health promotion, and diagnostics.

Acknowledgments

The study protocol considered the "Standard Protocol for Items: Recommendations for Interventional Trials" (SPIRIT) as described in the SPIRIT-Outcomes 2022 Checklist [25]. The authors acknowledge support for the publication costs by the Open Access Publication Fund of the University of Bielefeld and the German Research Foundation (DFG).

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request. The full data sets are, however, not publicly available due to restrictions as they contain information that could compromise the privacy of research participants.

Conflicts of Interest

None declared.

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Abbreviations

BCG: ballistocardiography
DFG: German Research Foundation
6-DOF: 6 degrees of freedom
ECG: electrocardiogram
GDPR: General Data Protection Regulation
SCG: seismocardiography
TUHH: Hamburg University of Technology

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Protocol

Development and Evaluation of the Telehealth in Motor Neuron Disease System: The TIME Study Protocol

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Abstract

Background: For more responsive care provision for motor neuron disease and caregivers, a digital system called Telehealth in MND-Care (TiM-C) was created. TiM-C sends regular symptom questionnaires to users; their responses are sent to health care professionals (HCPs). To enable people with motor neuron disease to participate in research studies more easily, a parallel platform was developed from TiM-C, called Telehealth in MND-Research (TiM-R). TiM-R can advertise studies, collect data, and make them available to MND researchers.

Objective: This study has 4 work packages (WPs) to facilitate service approval, codevelop the TiM systems, and evaluate the service. Each WP aims to understand (1) what helps and hinders the approval of the TiM-C system as a National Health Service; (2) what aspects of MND care and research are currently unmet and can be addressed through the TiM-C and TiM-R systems; (3) how TiM-C influences MND care, from the perspective of people with motor neuron disease, their caregivers, and HCPs; and (4) the costs and benefits associated with TiM-C.

Methods: WP1 will use semistructured interviews with 10-15 people involved in the approval of TiM-C to understand the barriers and facilitators to governance processes. WP2 will use individual and group interviews with 25-35 users (people with motor neuron disease, caregivers, HCPs, MND researchers, and industry) of TiM-C and TiM-R to understand the current unmet needs of these user groups and how TiM services can be developed to meet these needs. WP3 will use a process evaluation involving 5 elements; local context, engagement, user experiences, service impact, and mechanisms of action. A range of methods, including audits, analysis of routine data, questionnaires, interviews, and observations will be used with people with motor neuron disease, caregivers, and HCPs, both those using the system and those who declined the service when invited. WP4 will use data collected through the process evaluation and known costs to conduct a cost-consequence and budget impact analysis to explore the cost-benefit of the TiM-C service. Most data collected will be qualitative, with thematic and framework analysis used to develop themes from transcripts and observations. Descriptive statistics or *t* tests and chi-square tests will be used to describe and analyze quantitative data.

Results: This study has received ethical approval and has begun recruitment in 1 site. Further, 13 specialist MND centers will adopt TiM-C and the TIME study, beginning in July 2024. The study will conclude in November 2026 and a final report will be produced 3 months after the completion date.

Conclusions: This study will facilitate the implementation and development of TiM-C and TiM-R and fully evaluate the TiM-C service, enabling informed decision-making among health care providers regarding continued involvement and contribute to the wider literature relating to how technology-enabled care services can affect clinical care.

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KEYWORDS

motor neuron disease; amyotrophic lateral sclerosis; telehealth; digital health; process evaluation; implementation; co-production; digital technology; mhealth; eHealth; virtual medicine

Introduction

Motor neuron disease (MND) is an incurable disease, that causes progressive weakness of muscles involving the limbs, speech, and swallowing, leading to progressive disability and eventual respiratory failure. In the United Kingdom, there are approximately 5000 people with MND at any one time [1]. The average life expectancy following diagnosis is 2 to 3 years but the course of MND can vary from only a few months to over 10 years. The distress and burden of the disease affects people with MND, their family, and caregivers and the relenting progression of disability causes social, emotional, and financial strain [2,3].

In the United Kingdom, multidisciplinary teams (MDTs) deliver specialist MND care through MND Care Centers or care networks across the country. Expert health care professionals (HCPs) monitor symptoms and offer interventions such as Riluzole, which can improve survival by approximately 2 to 3 months [4], gastrostomy feeding to promote good nutrition [4], or treatment of respiratory failure with noninvasive ventilation, which improves both quality of life and life-expectancy [5]. Attendance at specialist MND clinics has been reported to improve survival independent of these other interventions [6,7]. Traditionally, clinics are held at regular fixed intervals, approximately 3 months apart.

Despite the potential benefits of MDT care, this model is not always sufficiently responsive to the needs of patients because these can change rapidly, and therefore, can require people with MND and their families to undertake progressively more difficult journeys to the clinic at a time predicted by the clinician at their last meeting. Given the burden associated with traveling to the clinic, it is important that visits occur when they are most needed. Conversely, some people with MND whose needs may not change considerably over time, may not benefit from a clinic appointment every 3 months.

To supplement traditional care for people with MND and their caregivers, and provide greater information on symptoms for the MDT, the Telehealth in MND-Care on MyPathway system (herein referred to as TiM-C) was codeveloped with people with MND, caregivers, and HCPs. TiM-C is software that enables people with MND and their caregivers to report their progress and symptoms to the hospital MDT from their homes using an app or via the online website [8] (TiM-C). Users are regularly asked to complete a variety of symptom questionnaires (eg, appetite, weight, functional rating, breathing, and mental health), answers to which are securely sent to the clinical portal. An initial evaluation in one center found TiM-C to be easy to use, even for those with significant disabilities, acceptable, and low in burden, taking approximately 5 minutes per week to complete. Around 85% of people with MND would recommend TiM-C to others and 95% would use TiM-C if they could not travel to the clinic. HCPs also found it accurate and easy to use [9,10]. However, additional research is needed to understand how best to implement TiM-C in MND centers, further user needs, the impact of the service, and the costs of the system. TiM-C is currently being adopted as a clinical service within 14 MND specialist centers across the United Kingdom.

In addition to supporting clinical care, this type of remote monitoring is a useful method for research data collection [11,12]. Therefore, a second system called Telehealth in MND-Research (TiM-R; Figure 1) is being adapted from TiM-C to decrease the burden of MND research and enable people with MND to participate in studies regardless of where they live. However, it is important to codevelop technological systems to best meet the needs of end users [12,13] and research is required to ensure TiM-R is feasible and acceptable for people with MND, caregivers, HCPs, and MND researchers before this is launched in Summer 2024.

The aim of this study is to create an approval strategy alongside information governance experts, further develop TiM-C and TiM-R alongside end users, and understand the effects on clinical practice and cost of the TiM-C clinical service. The following research questions will be answered:

1. From the perspective of individuals involved in the approval of National Health Service (NHS) services, what are the barriers and facilitators of approving TiM-C at scale?
2. What are the unmet needs of people with MND, their caregivers, HCPs, MND researchers, and industry?
3. How can TiM-C and TiM-R be developed to support end user needs?
4. Does the use of the TiM-C service result in better MDT care for people with MND and their caregivers?
5. What are the costs associated with the TiM-C service and how do they affect health care expenditure?

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Figure 1. Overview of how TiM-R links patients to research. MND: motor neuron disease; NHS: National Health Service; TiM-R: telehealth in MND-research.

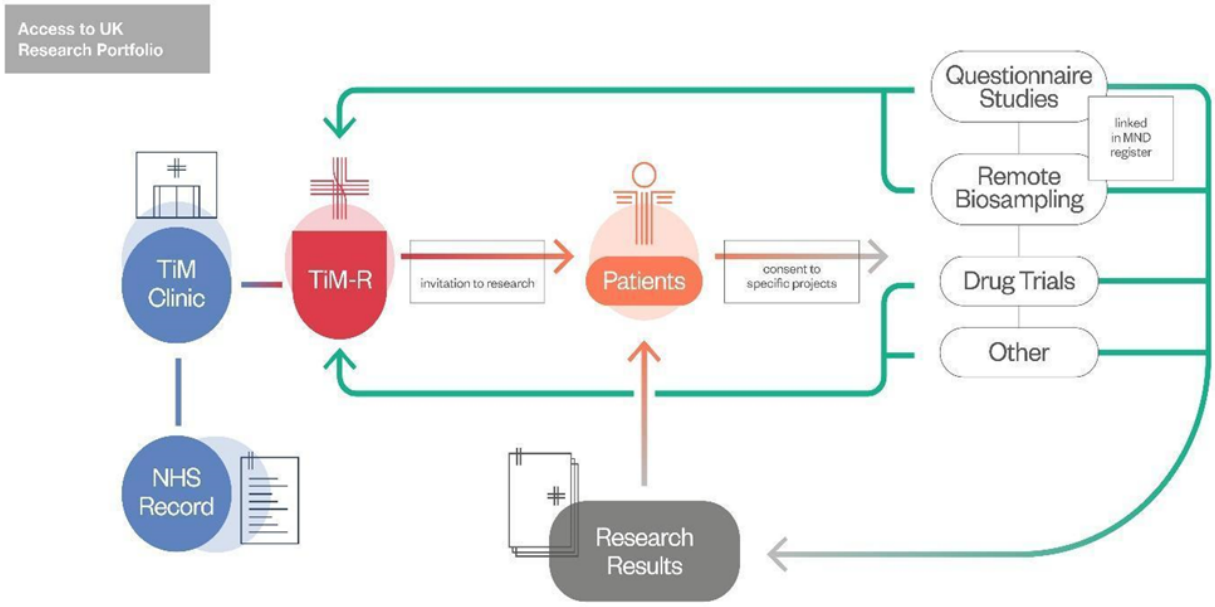

Methods

Design

The design of this project was based upon multiple frameworks and guidelines, which have helped develop a logic model, consider outcomes, and data collection methods. These include the MRC framework for the development and evaluation of complex interventions [14], National Institute for Health and Care Excellence Evidence Standards Framework [15], Person-based approach to intervention development [13], and Non-adoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) [16]. A total of 14 sites will collect data, however, some work packages (WPs) will only use a subset of sites (eg, WP1 only collects data from 5). The project has 4, interconnected WPs, which answer the research questions above:

1. Governance approval strategy development (research question 1)
2. TiM-C and TiM-R codevelopment (research questions 2 and 3)
3. TiM-C process evaluation (research question 4)
4. TiM-C economic evaluation (research question 5)

Through the NASSS framework and the collection of other data in the 2nd and 3rd work packages (described below), we will collect information that can be used to identify barriers that affect TiM-C and TiM-R implementation and use. Throughout the study, using an implementation science lens, we will address identified barriers to facilitate the uptake of the TiM system, using methods suggested by Cane et al [17]. We will document any adaptations made to our governance approval strategy or the TiM intervention.

To reduce the number of under-served groups within this project, the research team will aim to involve a diverse range of participants throughout the entirety of this study and overcome known barriers to participation [18]. This will include remote research activities to reduce the need to travel, support for caregivers to enable participation, and continual data monitoring to ensure representative inclusion of different ages and genders.

Each of the 14 sites involved in this study will be given permission to mildly modify research activities to enable people with different abilities or circumstances, who meet the eligibility criteria, to participate in any and all parts of the study they want to. For example, modifying consent or data collection procedures to enable the participation of people with MND and caregivers who are physically unable to complete documents, or questions being shared ahead of an interview to allow participants who have difficulty communicating time to prepare recorded answers.

Development of a Governance Approval Strategy (WP1)

This WP will use qualitative research to understand and assess the barriers and facilitators of successful technology approval. The research question in this work package will be addressed using a qualitative approach because there is a dearth of information available on which aspects help and hinder technology governance approval in MND care within the NHS [19]. Therefore, the semistructured interviews with individuals involved in the approval process of the TiM-C system within NHS organizations will provide rich data on this issue [20].

Convenience sampling will be used to recruit 10-15 individuals involved in the approval process of TiM-C (eg, governance, ICT, and data security staff) within 5 NHS organizations (out of the 14 using TiM-C). Semistructured interviews will be conducted using video-conferencing software (in line with participant preferences and permissions) or telephone. The interviews will last approximately 30-60 minutes in duration and be conducted by members of the research team.

The interviews will begin with general, open-ended questions relating to the participant's experience within their work role, and how they were involved in the approval process of TiM-C. Specific questions will explore what aspects of the approval process went smoothly and what factors they believe contributed

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to this. Further questions will relate to aspects of the approval process that hindered progress and how these may be overcome in the future. The interview schedule is informed by the NASSS framework, combined with the Complexity Assessment Toolkit (NASSS-CAT) [16] to help identify areas of complexity within NHS organizations.

Interviews will be audio-recorded and transcribed verbatim for analysis. All identifiable information will be removed during transcription with a pseudonym replacing the participant's name. The research team will conduct a framework analysis using NVivo [21]. The analysis will focus on semantic (as opposed to latent) meanings within the transcripts. The information gained from this WP will be used to inform a toolkit that provides suggestions for future health care interventions aiming to become clinically adopted services within the NHS. This toolkit will be freely available and provide suggestions gained from the governance experts interviewed to decrease the current lengthy process of service adoption.

TiM-C and TiM-R Development (WP2)

This work package will use a qualitative research design, with semistructured interviews with users of TiM-C and prospective users of TiM-R, including people with MND, caregivers, HCPs, MND researchers, and industry representatives. A qualitative design is most appropriate in order to continue the person-based approach to TiM development [13], and to ensure the intervention remains relevant, acceptable, and feasible, it is important to explore the views of the people who will be interacting with it [22,23]. We will use the information collected throughout this WP to make further refinements to the TiM-C and TiM-R interventions and ensure they meet the needs of end users.

A mixture of individual and group interviews will be used to collect the data, based on participant preference. Purposive sampling will recruit approximately 25-35 participants for this WP (approximately 5-to-7 per user group) across 5 sites. In line with the INCLUDE study [18], methods will be used to recruit those who do not usually engage in research and include a range of demographics (eg, age, gender, and ethnicity), clinical characteristics (eg, duration and severity of MND), and levels of experience with technology to support access to health care and research. We will not set specific numbers we will recruit for each of these categories, but will continually assess our inclusivity throughout recruitment to ensure we are not excluding any group. Interviews will be conducted either face-to-face or using videoconferencing software. The interviews will last approximately 30-60 minutes in duration and be conducted by members of the research team.

All interviews will begin with simple introductory questions to ask the participants about their experience with MND (either having, supporting, or researching MND). Group interviews will also begin with introductions between the various group participants. After the introduction, specific questions will depend on which user group the participant belongs to.

For people with MND and caregivers, questions will relate to what needs they have that are currently not being met and how TiM-C may be developed to meet these needs. Further questions will relate to how they feel about engaging in remote research (eg, consenting, data collection, and building trust through TiM), and any specific developments they believe TiM-R should include.

For HCPs, questions will be asked about how they use TiM-C, elicit unmet needs within their services, what aspects are required to provide good quality care, and how TiM-C could be further developed to help provide these. Questions will also be included relating to the TiM-R development and how this will interact with TiM-C.

For MND researchers and industry, questions will focus on the current difficulties with conducting research within MND, what is required to deliver good-quality research studies, and how TiM-R can incorporate those functions to facilitate the conduct of remote research and large-scale clinical trials.

Interviews will be audio-recorded and transcribed verbatim for analysis. All identifiable information will be removed during transcription with a pseudonym replacing the participant's name. Participants will have the option to choose their own pseudonyms. The research team will conduct a framework analysis using NVivo [21]. The analysis will focus on semantic (as opposed to latent) meanings within the transcripts. Findings from the analysis will be provided to an intervention development team, consisting of multiple different stakeholders, and used to further develop the TiM-C and TiM-R systems. After developments have been implemented, the intervention development team will then decide whether to conduct an additional round of interviews, using the same methodology described above. These interviews may use the same individuals who participated in the first round.

TiM-C Process Evaluation (WP3)

This WP will use a mixed methods design to conduct an in-depth process evaluation to explore implementation, mechanisms of action, and context [24], and investigate the impact the TiM-C system has on MND specialist center's services. Purposive sampling will be used to recruit people with MND, their caregivers, and HCPs using TiM-C to participate in semistructured interviews, case studies, and quantitative surveys (Multimedia Appendix 1 presents an overview of when these activities will be conducted).

A process evaluation will be conducted because it is not feasible to evaluate a complex digital intervention such as TiM-C via a randomized controlled trial [10,24]. There are 5 components in this process evaluation, "local context," "engagement," "user experiences," "service impact," and "mechanisms of action", each with its own section below and in Multimedia Appendix 1. Data collected on these components will enable an assessment of context, implementation, and mechanisms of action [24]. A triangulation protocol adapted from Farmer et al [25] will be employed to separately conduct and analyze each component before triangulating the findings.

Description of Service and Local Context

To collect information regarding how the local context may affect the delivery and outcomes of the TiM-C service, sites will complete a survey after they begin using the system. This

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survey will include questions relating to what HCPs are included in the local MDT, who reviews the TiM system and how often, how issues are escalated or referred to other HCPs, and what complexities exist within the organization (informed by the complexity assessment tool of the NASSS).

Additionally, most MND MDT services conduct biannual audits. Where available, the last 2 audits will be collected to provide an overview of the level to which each site meets National Institute for Health and Care Excellence guidelines.

Engagement

Manually and automatically collected data at every site will be analyzed in accordance with an adapted version of the taxonomy of adherence Vrijens et al [26]. This will provide information relating to the uptake, initiation and discontinuation, persistence, nonpersistence, and activity of the TiM-C service.

Local HCPs will keep a record of the number of people with MND who have been invited to TiM-C and the reasons for people not creating an account if these are offered at the time of face-to-face invitation. The TiM-C system automatically collects the number of people with MND who create an account. The TiM-C system also automatically collects the number of caregivers who are invited and the number who create an account. Combining this data will provide information on uptake (the proportion of people with MND and caregivers who create an account when invited) at each site, in addition to reasons for nonuptake that can be used to develop the invitation process.

If available at the MND center, demographics and routinely collected data will be analyzed to investigate whether there are any statistically significant differences between those who do and do not create TiM-C accounts. Relevant data may include, age, gender, partial postcode (to explore the effects of deprivation), and outcomes relevant to MND such as functional rating, date of onset, site of onset, and date of diagnosis. Statistical analyses will include *t* tests and chi-square tests for parametric and nonparametric data, respectively.

The TiM-C system automatically collects anonymized data relating to the date and time people with MND and caregivers complete a questionnaire. This data will be analyzed to calculate initiation and discontinuation (the date of first and last questionnaire completion, respectively), persistence (the time from first to last questionnaire completion), nonpersistence (the time following persistence during which no questionnaires are completed), and activity (the percentage of questionnaires completed during persistence). Similar to the above, if data is available, statistical analyses will be conducted to investigate whether any aspect of engagement can be predicted by individuals' demographics or disease-relevant data.

TiM-C also automatically collects the number of times an HCP logs into the system and sends feedback or resources to people with MND and caregivers. These data will be aggregated to calculate how often the TiM-C system is reviewed and used to send information to people with MND and caregivers.

People With MND, Their Caregivers, and HCP (User) Experiences

All TiM-C users will be invited to complete a short questionnaire to assess the acceptability and feasibility of the system, 1 month and 12 months after they create their TiM-C accounts. Questions will be based on the Theoretical Framework of Acceptability [27].

Additionally, 10 semistructured interviews will be conducted with people with MND, their caregivers, and HCPs at 2 time points (60 in total) from up to 5 centers, to facilitate understanding of the experiences, perceived impacts on knowledge, and access to care, and potential unintended consequences of the TiM-C system. Interviews will be conducted after users have had their TiM-C accounts for 3 months and 12 months.

Interviews will use videoconferencing software (in line with participant preferences and permissions) or telephone. All interviews will begin with general, open-ended questions relating to the participant's understanding of MND and their perception of the care they receive, or the participant's role and experience with MND care. For people with MND and their caregivers, specific questions will then relate to their experiences of the TiM-C service and how this has affected their care. For HCPs, specific questions will relate to their understanding of MND in general and of the people with MND and caregivers using TiM-C. Further questions will be asked about how HCP's use the TiM-C system and their perception of how it affects the care that they deliver.

The interviews will last approximately 30-60 minutes in duration and be conducted by members of the research team. Interviews will be audio-recorded and transcribed verbatim for analysis. All identifiable information will be removed during transcription with a pseudonym replacing the participant's name. Participants will have the option to choose their own pseudonyms. An inductive reflexive thematic analysis [28] will be conducted by the research team using NVivo. The analysis will focus on semantic (as opposed to latent) meanings within the transcripts.

Service Impact of TiM-C Upon MDT Care and the MND Service

To explore how TiM-C has affected the structure of each organization's MDT care, the same survey completed to describe the service and local context (see "TiM-C process evaluation" section above) will be completed yearly after the first. Additionally, any audit on the MND MDT services conducted within the duration of this study will also be collected.

Semistructured interviews will be conducted with HCPs using the TiM-C system to explore their beliefs about their connectedness with users, timeliness of care, and the quality of care that they deliver. These questions will be asked at the same time as those described in 4.3.3 above, to reduce the burden the research has on participants.

To explore whether the TiM-C system has improved the experience of MND care for people with MND and their caregivers, participants will complete a patient-reported experience measure (PREM) 1 month and 12 months after they

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have been invited to create TiM-C accounts. Participants who have created an account will be allocated to the "user" group and those who do not create accounts will be allocated to the "non-user" group. The PREMs will be compared between these 2 groups across both data collection points. The PREM is adapted from the Client Satisfaction Scale [29].

TiM-C Mechanisms of Action

In-depth case studies will be used to explore how HCPs use the data from TiM-C during clinical appointments and MDT meetings, which will enable an investigation into TiM-C's mechanisms of action. Yin [30] suggests that 5 case studies are appropriate for complex interactions and 3 for literal replications. Therefore, a collective case study approach will be adopted using 5 MND centers. Within each case study, data will be collected relating to how TiM-C is used during 3 clinical appointments and 3 MDT meetings.

A combination of data collection techniques will be used, including focused ethnography, consisting of observations and field notes within clinical appointments and MDT meetings, alongside short questionnaires, and related document analysis. Information from the other elements of this process evaluation will also be incorporated into the case studies (eg, engagement data).

Members of the research team will conduct direct, nonparticipant observations of 3 clinical appointments and 3 MDT meetings. The same researcher will take field notes and potentially ask follow-up questions after the appointment or MDT meeting has finished. The researcher will either attend such activities physically or join virtual meetings. Appointments and MDT meetings will be audio-recorded and transcribed verbatim for analysis. Framework analysis will be used to analyze the transcripts and field notes.

A short, bespoke questionnaire was created to explore how HCPs perceived the use of the TiM-C data during MDT meetings. The questionnaire includes items on the trustworthiness of TiM-C data and whether and how the HCP acts on the data. All HCPs attending the MDT will be asked to complete this questionnaire after the meeting or appointment has finished.

Local HCPs and researchers will collect other documents relating to the use of TiM-C for the people with MND discussed at the clinical appointments or MDTs (eg, TiM-C messaging data, clinical notes, and emails) and securely transfer them to the central research team for analysis. Only data relating to TiM-C will be used. This information is necessary to identify how TiM-C data is used to support people with MND and caregivers outside of meetings. Farmer et al [25] triangulation protocol will be used to analyze the data set, due to the large amount of data involved, collected from multiple sources. Each case study will be analyzed separately before similarities and differences are considered in cross-case comparisons.

TiM-C Economic Evaluation (WP4)

This WP includes a health economic analysis of the TiM-C system, as it is implemented in MND specialist centers and networks across the United Kingdom. A cost-consequence analysis [31] will form the primary economic evaluation because TiM-C is a complex digital intervention with multiple possible effects, including both health and nonhealth outcomes, which makes the creation of a single measure difficult. A budget impact analysis [32] will also be conducted, to help future health care commissioners understand how the implementation of TiM-C may affect expenditure under different circumstances.

The cost-consequence analysis will only focus on costs for intervention delivery, as TiM-C is not designed to replace any part of usual care (ie, TiM-C will incur costs in addition to usual care, rather than accrue cost-savings). Per patient and caregiver costs incurred from the need for a HCP to regularly review user scores, will be calculated by asking HCPs to estimate how long it takes to review the account of a single user. This will be combined with unit costs of health, accessed from the Personal Social Services Research Unit. These will be combined with the central cost of TiM-C per MND service, which is already known, in addition to HCP time to receive the necessary training. Outcomes will be taken from the process evaluation and presented alongside the per-user cost of TiM-C to aid comparison.

A budget impact analysis will be conducted using the costs calculated as part of the cost-consequence analysis described above. Engagement data from the process evaluation will then be used to describe the cost of TiM-C for the MND center (in terms of HCP time and system cost) under different review protocols. For example, TiM-C does not dictate how often HCPs should review the system. The more often TiM-C is reviewed and the higher the user engagement from people with MND and caregivers, the more HCP time will be needed and the higher the associated costs. This analysis will display these different circumstances to aid health care commissioners in understanding the affordability of the TiM-C service.

Participants

Participant numbers are provided within each WP and each section of the process evaluation. Where numbers are not provided, we will recruit everyone who meets the below eligible criteria (Textbox 1; eg, The PREM described in the section "Service impact of TiM-C upon MDT care" and the MND service will be sent to every individual with MND at each site). To be as inclusive as possible, there are no exclusion criteria.

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Textbox 1. Eligibility criteria for each participant group.

Patient inclusion criteria:

- Aged 18 years or older
- Diagnosis of clinically definite, lab supported, clinically probable, or possible motor neuron disease (MND) by the El-Escorial criteria and additionally the Progressive Muscular Atrophy variant where appropriate investigation has excluded mimics of MND
- Capacity to give informed consent
- Has been invited to create a TiM-Care (TiM-C) account at least 1 month ago
- Can understand written/verbal English

Caregiver inclusion criteria:

- Aged 18 years or older
- Capacity to give informed consent
- Has been invited to create a TiM-C account at least 1 month ago
- Can understand written/verbal English

Health care professional inclusion criteria:

- Health care professionals (HCPs) who provide support to people with MND, including medics, specialist nurses, dietitians, speech and language therapists, physiotherapists, occupational therapists, health care assistants, etc.
- Part of an MDT that has used the TiM-C system for at least 1 month
- Can understand written/verbal English

MND research inclusion criteria:

- Aged 18 years or older
- Any researcher who has previously or is currently conducting research with people with MND, their caregivers, or HCPs.
- Can understand written/verbal English

Industry staff inclusion criteria:

- Aged 18 years or older
- Currently or recently (within last year) used by an industry organization that has conducted clinical research involving people with MND. This includes clinical trials, questionnaire-based studies, qualitative research, or telehealth research.
- Can understand written/verbal English

Consent

All potential participants to each WP will be provided with written information about the nature and objectives of the study in the form of a Participant Information Sheet and given a minimum of 24 hours to decide whether to take part. However, a participant can consent immediately if they wish. Potential participants will also be given the opportunity to discuss the research with the relevant researcher and ask questions either in person or via contact details supplied in the Participant Information Sheet. Potential participants will be reminded that their participation is entirely voluntary and that they have the right to withdraw at any point (without it affecting the service provision for people with MND). Formal written consent will be obtained for all research participants, the process for which will be adapted for those participants unable to physically provide this. Consent may be taken remotely by verbally recording the participant, only if necessary. The consent procedure will be completed by the researcher/interviewer prior to any interview or observation. They will explain the study and make sure each person fully understands what they are agreeing to.

For the quantitative elements of the study, participants can immediately complete any questionnaires they have consented to. For the qualitative elements of the study, the local teams will pass on their contact details to the central research team. The research team will then contact the potential participants to provide them with more information about the study. Where relevant, the next step will be for the researcher to organize a mutually convenient time and place for the interview. Participants will not be offered payment for taking part in this study. Should interviews be conducted face-to-face, reasonable travel expenses will be reimbursed for participants.

Within the MDT observations, there is the possibility that some HCPs consent to be observed, whereas other HCPs do not provide this consent. In such a situation, the observation will still continue and be recorded. However, all instances where a nonconsenting HCP speaks will be removed from the transcript and any identifiable information about nonconsenting HCPs,

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such as names or job titles, will be removed. Nonconsenting HCPs will not be asked to complete a questionnaire.

Nonexplicit Consent

Within the engagement section of the TiM-C process evaluation, this study proposes to analyze data on people with MND and their caregivers, which has been collected as part of running the MND clinical service. This data will only be used to investigate engagement with TiM-C and facilitate the exploration of reasons for the engagement and nonengagement with the TiM-C service.

As this data is collected as part of the standard running of the MND service, explicit consent will not be sought from people with MND and their caregivers before this data is analyzed. All individuals who have opted out via the national data opt-out service will have their data removed from this analysis. The legal basis for the use of this data is to improve or benefit health and care by monitoring the use of this novel intervention to investigate how effective it is.

Ethical Considerations

This study was approved by the Health Research Authority and NHS Research Ethics Committee (reference number: 22/NI/0192). Informed consent is (or waiver thereof) and the process used to obtain this, is fully described in the section above. All data are anonymized, with participants being given a number (quantitative) or pseudonym (qualitative). Participants were given the choice of their own pseudonyms. No compensation or remuneration was provided as an incentive for any WP described within this protocol. However, reimbursement for reasonable expenses incurred (eg, travel to interviews) was provided to participants.

Results

The study received ethical approval in January 2023 (22/NI/0192) and is currently being set up in MND specialist centers in the United Kingdom. Thirteen MND researchers and industry representatives have been recruited to the TiM-C and TiM-R development (WP2). Framework analysis has identified the current unmet needs of these participant groups and the functionality that can be implemented into TiM-R. This work will be presented at the MND Association 2024 symposium and published shortly.

Discussion

Principal Findings

This study will collect data relating to NHS clinical approvals, TiM-C and TiM-R development, and evaluate the TiM-C service. The project will open approximately 14 sites to recruit to all WPs. The study is due to be completed in November 2026, and the final report will be produced within 3 months of the study closing. However, we will also separately disseminate the results for each WP. We anticipate that the data from WP1 will enable the development of a toolkit to aid the approval process of future health care interventions in the NHS, which will be disseminated through a publication and publicly available website. This responds to our group's collaboration with multiple industry partners who describe significant delays in governance approval processes. Findings from WP2 will primarily inform the refinement of TiM-C and TiM-R, but could also be useful for future researchers who wish to develop innovative digital services for people with long-term conditions. We will publish this through 2 academic publications.

WP3 and WP4 will collect data relating to the current provision of MND services and the effect of TiM-C on this provision. We anticipate that this will enable greater conclusions to be drawn relating to the benefits and consequences of the TiM-C service, whilst also enabling the testing of our program theory and logic model. As per the MRC's guidelines for complex intervention development [14], we will explore whether to further explore implementation and effectiveness depending on the results of the process evaluation. Alongside stakeholders, we will publish this work academically but also work with wider groups (eg, NHS decision makers, policy groups, and charities) to increase the impact of this work.

Limitations

A limitation of this study is the exclusion of a randomized controlled trial design, which is widely considered to provide one of the highest levels of evidence for or against an intervention. The decision to focus primarily on a process evaluation was taken due to the guidance provided by the MRC [14], which acknowledges that randomized controlled trials are not suitable in all situations, and a previous feasibility study indicating that such a design would not be feasible [10]. Nevertheless, a future study could reexamine the feasibility of conducting a randomized controlled trial and, if possible, implement this design to provide the best quality evidence relating to the effectiveness of TiM-C.

Conclusions

This study will collect and publish information to support the efficient approvals of remote monitoring systems in the NHS (WP1), further coproduce the TiM-C and TiM-R services (WP2), and fully evaluate the TiM-C service (WP3 and 4). This work will enable health care decision makers to make an informed decision regarding whether to continue using the TiM services within their specialist centers and to support research.

Acknowledgments

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participants for their involvement in this study. The NIHR Academy is the funder of this project via the Research Professorship scheme. No generative AI was used in the writing of any portion of this manuscript.

Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization and funding acquisition were performed by CM, EH, and EC. Methodology was performed by CM, EH, EC, and LK. Data collection and analysis were completed by LK, YA, and AG. Writing of original draft preparation was performed by LK, AG, and YA, with review and editing of the manuscript being completed by CM, EH, EC, AG, LK, and YA. Project administration was completed by LK, AG, and YA. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
A visualization of when each activity will be conducted. All timings are ±1 month.
[DOCX File , 15 KB - resprot_v13i1e57685_app1.docx]

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Abbreviations

CAT: Complexity Assessment Toolkit
HCP: health care professional
MDT: multidisciplinary team
MND: motor neuron disease
NASSS: Non-adoption, Abandonment, Scale-up, Spread, and Sustainability framework
NHS: National Health Service

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PREM: patient-reported experience measure
TiM: telehealth in motor neuron disease
TiM-C: TiM-Care
TiM-R: TiM-Research
WP: work package

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Protocol

Clinical Data Flow in Botswana Clinics: Protocol for a Mixed-Methods Assessment

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Abstract

Background: Botswana has made significant investments in its health care information infrastructure, including vertical programs for child health and nutrition, HIV care, and tuberculosis. However, effectively integrating the more than 18 systems in place for data collection and reporting has proved to be challenging. The Botswana Health Data Collaborative Roadmap Strategy (2020-24) states that “there exists parallel reporting systems and data is not integrated into the mainstream reports at the national level,” seconded by the Botswana National eLearning strategy (2020), which states that “there is inadequate information flow at all levels, proliferation of systems, reporting tools are not synthesized; hence too many systems are not communicating.”

Objective: The objectives of this study are to (1) create a visual representation of how data are processed and the inputs and outputs through each health care system level; (2) understand how frontline workers perceive health care data sharing across existing platforms and the impact of data on health care service delivery.

Methods: The setting included a varied range of 30 health care facilities across Botswana, aiming to capture insights from multiple perspectives into data flow and system integration challenges. The study design combined qualitative and quantitative methodologies, informed by the rapid assessment process and the technology assessment model for resource limited settings. The study used a participatory research approach to ensure comprehensive stakeholder engagement from its inception. Survey instruments were designed to capture the intricacies of data processing, sharing, and integration among health care workers. A purposive sampling strategy was used to ensure a wide representation of participants across different health care roles and settings. Data collection used both digital surveys and in-depth interviews. Preliminary themes for analysis include perceptions of the value of health care data and experiences in data collection and sharing. Ethical approvals were comprehensively obtained, reflecting the commitment to uphold research integrity and participant welfare throughout the study.

Results: The study recruited almost 44 health care facilities, spanning a variety of health care facilities. Of the 44 recruited facilities, 27 responded to the surveys and participated in the interviews. A total of 75% (112/150) of health care professionals participating came from clinics, 20% (30/150) from hospitals, and 5% (8/150) from health posts and mobile clinics. As of October 10, 2023, the study had collected over 200 quantitative surveys and conducted 90 semistructured interviews.

Conclusions: This study has so far shown enthusiastic engagement from the health care community, underscoring the relevance and necessity of this study’s objectives. We believe the methodology, centered around extensive community engagement, is pivotal in capturing a nuanced understanding of the health care data ecosystem. The focus will now shift to the analysis phase of the study, with the aim of developing comprehensive recommendations for improving data flow within Botswana's health care system.

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KEYWORDS

global health; health information systems; electronic health care records; EHRs; interoperability; data flow; access to information; health information interoperability; pediatric; pediatrics; infant; infants; clinical data; mixed method; Botswana; health care information; child health; tuberculosis; HIV; eLearning; survey; health informatics; communication

Introduction

Background

Over 2500 years ago, Hippocrates argued it was important to keep a record of a patient's conditions and symptoms [1,2]. While we have developed new ways of record keeping, accurate and timely record keeping remains as important, if not more so, given the interconnectedness of communities. The World Health Organization has further emphasized the importance of electronic health records (EHRs) toward the achievement of Universal Health Coverage and health-related sustainable development goals [3]. In the United States and other high-income countries, EHRs capture 90% or more of these data. However, in low- and middle-income countries, the percentage is much smaller but steadily increasing. Despite the documented benefits of EHRs, a number of concerns have been raised. The aim of this study is to assess the flow of clinical data through various systems (EHRs and electronic medical records) by understanding and describing the flow of clinical data. In addition, the study explores the perceptions of health care workers regarding health care data collection, sharing, and use across Botswana's health care facilities.

Data Generators

Data are often collected using multiple separate systems and reported in aggregate at a system or national level, with varying benefits seen by frontline clinicians [4]. This is more than simply an aggravation. Ensuring that frontline clinicians have proper access to data could improve clinical outcomes on a wide range of issues, from the correct treatment of pediatric malaria [5] to decreasing medication errors in tuberculosis treatment and even reducing patient wait times in clinics [6].

From a systems perspective, lack of access to data, concerns about data validity and accuracy, perceived uselessness of data collection, and an inability to transfer information are continually ranked among the leading barriers to effectively implementing EHRs by clinical staff, administrators, medical directors, and information technology personnel [7,8]. A study conducted in South Africa [9] emphasized that data routinely collected at health care facilities and submitted to district offices are commonly unreliable. The study investigators further asserted that "data validation was limited" and "little analysis of data occurred" at the participating facilities sampled in their study, leading to a gloomy picture overall. However, even if analysis tools were improved, with multiple systems in use, they would only be applicable to a small subset of all the data collected. Another study on the Prevention of Mother to Child Transmission of HIV (PMTCT) in South Africa [10] adds that there are major gaps in both completeness and accuracy in the collection and reporting of data that track service delivery.

Given these concerns, it is crucial to understand the views of those inputting and generating these data. As one study found, "data quality issues are not a result of the type of record, but the attitude of the person inputting the data" [11].

Interoperability

What is desired is to integrate organizational information systems, devices, and applications to access, exchange, and cooperatively use data across organizations. This would provide a platform where systems with different infrastructures could share data and services and, hence, have the same expectations for the contents, context, and meaning of the data. To advance health information system interactions, there must be interoperability ("the ability of two or more systems or components to exchange information and to use the information that has been exchanged" [12]). Improved interoperability would result in a decrease in missing data as systems fill in each other's gaps and alleviate some of the clerical burden inherent in using multiple systems. Consequently, there would be improved health data quality [13]. Interoperability is often guided by an interoperability framework, offering an agreed approach for multiple organizations to achieve interoperability toward the joint delivery of services.

Botswana supports noninteroperable diverse health information systems [14] and currently has more than 18 systems in place for data collection and reporting. A 2019 UNICEF report on Botswana highlights these points [15], making note of the different data tracking systems that "are not necessarily coordinated or reliable across health facility levels and systems." For example, UNICEF highlights Botswana's strong HIV early infant diagnosis program but notes the long turnaround times for results and lack of HIV-exposed infants' final infection status. The report further states, "Key PMTCT variables have poor quality data thought to be associated with lack of understanding of the required data and lack of uniformity in recording and reporting" [15]. One of the key recommendations of this report was to "look for opportunities to simplify, harmonize, reduce redundancy and roll out the most reliable systems to all districts and health facilities."

In response, the Botswana Ministry of Health (MOH) released the Botswana Health Data Collaborative Roadmap Strategy (2020-24) [16], which states that "there exists parallel reporting systems and data is not integrated into the mainstream reports at the national level", seconded by the Botswana National eLearning strategy (2020) [17], which states that "there is inadequate information flow at all levels, proliferation of

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systems, reporting tools are not synthesized; hence too many systems are not communicating."

Objectives

This study was driven by 2 primary goals to align with the MOH's objectives of enhancing data collection, data sharing, reporting, and usage: to create a visual representation of data flow within the health care ecosystem of Botswana, and gain insights into how frontline workers perceive the collection, use, and sharing of data with the health care sector.

A data flow diagram would encompass the entire data journey, starting with data generation by the frontline clinician and tracking it through various stages, including data transfers, reporting, administrative processes, laboratory operations, government involvement, and, where applicable, returning it to the frontline workers who generated it. By visualizing this data flow, the study intends to offer insights into how data inform operations at different levels and highlight the exchange of information among people, processes, and system components. Describing and understanding this flow, along with relevant system protocols and boundaries, is crucial for improving decision-making and strategic planning within an organization. Poor data flow could lead to incompatible and inconsistent data systems, resulting in information silos. Conversely, if data linkages are properly established, there is potential to enhance data access and sharing, ultimately leading to valuable insights that exceed the sum of isolated data sources.

Understanding the perceptions of frontline health care workers is essential, particularly in the context of potential system integration and workflow changes. Frontline workers' attitudes toward data collection directly impact how it is used as well as its quality [11]. This goal aims to assess how health care data are currently accessed, transferred, used, and reported by workers, as well as whether they recognize value in these processes.

Methods

Setting and Community Engagement

This study commenced to engage health care facilities across the country, with an attempt to engage facilities as widely as possible in each district. The purpose of the sensitizations was to introduce the study, secure buy-in, and increase the participation of health care workers at each site.

The approach to engaging health care facilities involved direct contact with their leadership. The study team reached out through phone calls and formal email invitations, followed by virtual and onsite sensitization meetings and workshops. Over 70 emails were sent out to health care facilities to arrange their involvement in the study, and close to 100 phone calls were made to engage facilities' leadership to coordinate participants' involvement in the study. These sessions played a crucial role in gaining the facilities' buy-in and motivating their health care workers to participate. To encourage maximum participation and inclusivity, we embraced an open community research approach. Our target population consisted of health care professionals who were directly involved in data collection, data sharing, and data-driven decision-making or used information and communications technology systems for health care tasks. Healthcare workers' daily experience in data-related tasks made them invaluable contributors to this study. The study team emphasized clinicians' role as collaborators in the project, underlining the significance of their input in shaping the research instruments. This approach resulted in the refinement of questions in the REDCap (Research Electronic Data Capture; Vanderbilt University) survey instruments and the inclusion of new ones, ultimately leading to more insightful responses.

Study Design

This study adopts a mixed methods approach to assess the flow of clinical data across Botswana's health care facilities. The design of the study encompassed both qualitative and quantitative methods to gain a comprehensive understanding of how health care data are collected, shared, and used in the selected facilities. The surveys were informed by the rapid assessment process [18-20] model and the technology acceptance model for resource-limited settings [21,22], ensuring they were both comprehensive and contextually relevant.

Survey Instruments

Our data collection instruments were developed to align with the study's objectives and to ensure that we could capture a comprehensive view of the health care data flow in Botswana's health care system. During the development, we discovered a notable gap in the existing literature. Previous assessments of e-health readiness and maturity have used various frameworks [23-26] that assess dimensions such as core need readiness, technological readiness, and learning readiness. The MEASURE Evaluation [27] framework emerged as the only assessment we found that documents the flow of clinical data from the patient to the clinician, to the labs or government, and ultimately back to the clinician and patient. Visual representations were essential for enhancing our comprehension, given their widespread use across various health care specialties and industries [28,29].

This resulted in a 2-pronged survey approach. The first was a self-led quantitative digital survey used to broadly understand how clinicians collect data and share it. This method focused on the demographics of the participants, the electronic systems used, data collection mechanisms, frequency of reporting, and usage of the collected health care data.

The qualitative component of this study involved a semistructured interview method, allowing the participants to offer detailed perceptions on the use of technology and data management practices within health care settings in Botswana. These interviews, conducted by research assistants, were informed by the study's objectives and relevant literature, focusing on health care workers' perspectives on collecting and managing health care data and service delivery. Participants, including administrators, nurses, and doctors with various roles in the health care sector, were encouraged to provide in-depth insights into both manual and digital data collection methods, along with their views on data sharing and usage in Botswana. The aim was to elicit comprehensive information and opinions regarding the flow of clinical data, focusing on key features and critical questions outlined in Figure 1.

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Figure 1. Key features and questions.

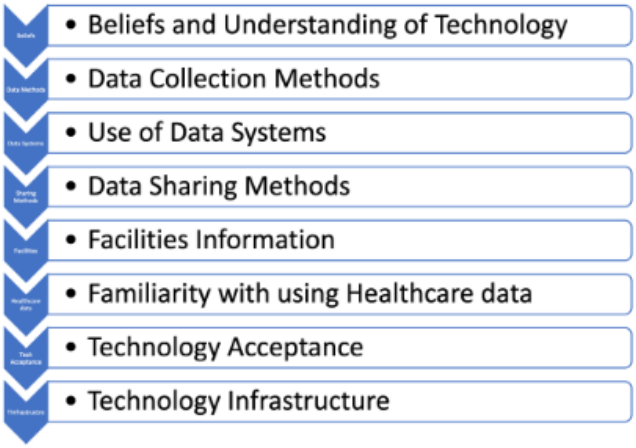

Sampling

Purposive sampling was used to select participants who interacted with health care data representing various levels of the health care system, including general nurses, monitoring and evaluation officers, health care administrators, frontline clinicians, and IT professionals. All participants were invited to participate in the 2 surveys of this study.

Selection Criteria and Representation

We strategically chose health care facilities located at 3 locations in Botswana: Gaborone, Maun, and Selebi Phikwe. Each of these facilities and their surrounding areas represent a distinct region of the country. This choice allowed us to capture diverse perspectives, reflecting the varied health care environments within the country. Ethical approval at the facility level was a paramount prerequisite before the study commenced, with key contacts typically residing within the institutional review board (IRB) chairmanship.

Data Collection

The REDCap system, together with interviews, was used to collect data from study participants. The surveys were distributed electronically to a representative sample of health care workers across different health care facilities in Botswana. A comprehensive list was compiled for all of the large public health care facilities in the country, leading to invitations being extended to over 30 health care facilities, encompassing both comprehensive public hospitals and clinics. Out of these, 23 sites expressed interest in the study and actively participated in it, with full engagement in sensitization and data collection workshops. About 15 sensitization sessions were held to inform and engage health care facility leadership and health workers about the study's objectives, methods, and potential impacts and obtain feedback. Of the 15, 4 were held in-person, while 11 were held virtually via Microsoft Teams led by the study team research assistants at the University of Botswana.

A total of 157 responses were collected from the first survey, while the second survey had 227 responses.

Data Analysis

Data from the quantitative survey will be analyzed using descriptive statistical methods to examine trends, correlations, and associations related to health care data sharing and usage at hospitals and clinics.

We plan to use thematic analysis to analyze the qualitative results of the study, mainly to identify recurring themes, patterns, and insights from the qualitative data provided by the study participants. The analysis will begin by focusing on themes such as perceptions of the value of health care data, experiences of data collection and sharing, and the adoption and familiarity of different technological solutions.

Findings from both qualitative and quantitative data collection will be integrated to provide a comprehensive understanding of the flow of clinical data across the sampled facilities. Data integration will involve comparing and contrasting qualitative themes with quantitative survey results to validate and complement the findings.

For analysis purposes, tools including Jupyter notebooks and NVivo software will be used to pre-process the data and develop code for analyzing the data coming from the participating health care workers.

Ethical Considerations

Before starting this study, we ensured we had all appropriate permissions from the IRBs at the University of Botswana (protocol or reference number UBR/RES/IRB/BIO/258), the Human Research Development Committee in Botswana, the University of Pennsylvania (protocol number 849993), and the Children's Hospital of Philadelphia (protocol number 22-019994), in addition to letters of support from the MOH and the local institutions with which we were working. Additionally, ethical approval was obtained at the health facility level through IRB approval and review. Prior to participating, all responders agreed and signed an informed consent. All identifiable data were stored securely in an encrypted cloud server, requiring password access, with regular security auditing.

Adapting to COVID-19 Restrictions

Acknowledging the constraints imposed by the COVID-19 pandemic, this study was adapted to ensure safety without compromising engagement. Most sensitization sessions and all interviews were conducted remotely, using video conferencing tools to maintain interactive and personal communication channels.

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Results

This study recruited close to 44 health care facilities, including district hospitals, public referral hospitals, primary health care clinics, mobile health clinics, and health posts. Out of the 44 facilities recruited, 27 responded to our surveys and interviews. About 75% of the health care professionals who participated in the study came from clinics, 20% from hospitals, and 5% from health posts and mobile clinics. Our results indicate that 2 essential factors are crucial to participation in our assessment. First, sensitization meetings are followed by stakeholder engagement workshops with participants. Second, establishing an open and collaborative environment and treating participants as experts and key stakeholders in the project will ensure their inputs and suggestions are valued and incorporated into the study.

The steps taken in order to perform our study so far have broader value. These steps should be adopted by most research studies in the health care sector and are especially important in environments where it may be difficult to get buy-in regarding participation.

During this process, local health care centers commented that they required further data science education. To this end, we created a free data science workshop to teach basic skills to those working in the health care sector. As part of this workshop, we invited the participants to help us collect further data about Botswana's data health care infrastructure as part of phase 2 of our project to try and broaden and deepen our understanding.

The data collection process commenced in June 2022 and was projected to end in December 2023. Data were collected virtually using REDCap forms, and interviews were conducted via Zoom and Microsoft Teams and then transcribed into the REDCap system. Out of the 30 facilities enrolled in the study, as of October 24, 2023, we have collected 200 records for the initial survey and captured 90 records for the semistructured interviews.

Discussion

This research project aims to systematically map the data flow within Botswana's health care infrastructure and to delve into health care workers' perspectives on data sharing practices. Using a series of sensitization meetings, the study effectively engaged the community, making them aware of the project and eliciting feedback for the project itself. The enthusiastic engagement from the health care community underscored the relevance and necessity of the study's objectives. The use of virtual tools (such as REDCap forms) for data collection demonstrates adaptability to modern technologies, which can enhance efficiency in remote data collection, especially in the context of global events such as the COVID-19 pandemic. As of October 24, 2023, over 200 records were collected for the initial survey and 90 records were captured for the semistructured interviews from 30 facilities around the country.

Given the response and enthusiasm to the study, it would seem to suggest both that the health care community appreciates why this project is important and that engaging the community early and fostering collaboration and transparency encourage more active participation. This approach was instrumental in building trust and a sense of ownership among participants, qualities that are often overlooked yet critical for the success of such endeavors. The preliminary results do seem to indicate that the study was successful in engaging a wide range of health care professionals involved in the day-to-day management and utilization of health care data. The insights derived will help identify bottlenecks in data flow and opportunities for enhancing interoperability among the myriad of health care information systems currently in use.

The study highlights the significance of engaging stakeholders in the health care sector, including health care professionals from various types of facilities. Sensitization meetings and workshops were found to be crucial in encouraging participation and ensuring the insights and perspectives of participants were valued. This emphasizes the importance of collaboration and inclusive decision-making processes in health care research. The finding that stakeholder engagement and participation are critical for the success of health care research aligns with previously published works. A growing body of literature in global health has emphasized the importance of involving stakeholders, including health care professionals, in all stages of research to enhance relevance, ownership, sustainability, and uphold ethical standards [30-33]. Although no studies specifically evaluating participatory research in global health informatics were found, this study would seem to suggest that these principles observed in a broader global health context appear to be applicable.

There are a number of limitations that should be taken into account. A wide range of health care professionals, but with this kind of study, a larger cross section of the health care workers would improve the generalizability of the findings. In addition, the study relied on self-reported data, which may introduce response bias. Interviews conducted and recorded by research assistants could have inconsistencies due to variations in data capturing or missing nuanced information from participants. Future research could benefit from a larger sample size, more varied health care facilities, audio recording and later transcribing all of the interviews, and direct observation at health care facilities.

As we move forward, the focus will shift toward a more in-depth analysis of the data collected, with the aim of developing comprehensive recommendations for improving data flow within Botswana's health care system. The anticipated second manuscript will detail these findings and recommendations, providing more concrete guidance for Botswana's continued digitization of its health care system. By documenting and sharing the methodology and initial steps of our study, this research aims to provide a blueprint for similar research endeavors, emphasizing the importance of community engagement and methodological rigor. This approach will not only inform health care policy but also contribute to more effective and integrated health care practices.

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Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available as Botswana law requires institutional review board approval to access all health care–related research data

Authors' Contributions

GF was involved in conceptualization, data curation, formal analysis, funding acquisition, methodology, and writing original draft. AM was involved in conceptualization, funding acquisition, methodology, writing original draft, project administration, and supervision. BM was involved in data curation, methodology, investigation, project administration, and writing original draft. KN was involved in conceptualization, funding acquisition, methodology supervision, and writing original draft.

Conflicts of Interest

GF is the chief technological officer of MayJuun.

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Abbreviations

EHRs: electronic health records
IRB: institutional review board
MOH: Ministry of Health
PMTCT: Prevention of Mother to Child Transmission of HIV
REDCap: Research Electronic Data Capture

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Protocol

A Combined Telemedicine and Ambulatory Wound Care Team Intervention for Improving Cross-Sector Outpatient Chronic Wound Management: Protocol for the Mixed Methods TELE-AMBUS Research Project

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Abstract

Background: There is a growing prevalence of nonhealing wounds and chronic diseases in society, and there is an associated need for wound management solutions that include the use of telemedicine. A broad spectrum of factors influences the planning and execution of interventions within telemedicine in chronic wound management, spanning organizations, technologies, and individuals, including professionals and patients. The Telemedicine and Ambulatory Wound Care Team (TELE-AMBUS) project applies a whole-system research approach to account for this spectrum of factors.

Objective: The primary objective of this study was to explore and analyze the implementation and consequences of an outpatient wound management model, comprising 2 interconnected quality improvement interventions (ie, telemedicine and ambulatory wound care team) aimed at older and vulnerable patients with chronic wounds, across the specialist and primary health care sectors. Embedded in this objective is the aim to improve the competence levels of health care providers and, consequently, the service quality of outpatient wound management across specialist and primary health care services.

Methods: This project examines the implementation and consequences of an outpatient wound management model through a combined process and economic evaluation research strategy. A sociotechnical system theory approach and multiple work package design support the examination. The project uses observations, conversations, interviews, and economic assessments to gather rich, in-depth insights and understanding on why and how the new wound management model contributes to a change or not compared with the traditional treatment model.

Results: The project has been funded from 2021 to 2025. Baseline interviews have been conducted since April 2022 and concluded in January 2024. Fieldwork, including nonparticipant observations, semistructured interviews, and informal conversations,

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has been conducted since November 2022 and is expected to conclude in March 2025. In parallel and as part of the cost-effectiveness analyses, time usage data on the outpatient and regular clinical models are being gathered during the fieldwork.

Conclusions: We applied a whole-system approach in multiple ways, that is, to design or inform our fieldwork and to explore, evaluate, and translate project findings into practice across services. To our knowledge, this approach has not been undertaken in telemedicine in chronic wound management literature and associated human factors and ergonomics research. Thus, our approach can produce both original and novel research and theoretical results internationally.

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KEYWORDS

chronic wound management; specialist health care sector; primary health care sector; ambulatory wound care team; telemedicine; process evaluation; economic evaluation; observations; interviews; whole system framework

Introduction

Background

The prevalence of nonhealing wounds (ie, not healing within 6 weeks) and chronic diseases in society is growing, which impacts both patients' quality of life and the costs of health care delivery [1-3]. Furthermore, society is facing an increasingly overburdened and financially strained health care system due to global pandemics, multifront conflicts and wars, economic decline, and so forth. To alleviate the overall burden on the health care system, the Norwegian National Health and Hospital Plan 2020-2023 focuses on integrated health care services that are closer to patients' homes. The plan emphasizes the creation of outreach hospitals that will provide more health care in patients' homes; collaborate better with municipal health and care services, both in person and online; and work more closely with other hospitals [4]. Aligning with this plan, the Norwegian Digital Strategy for the Public Sector 2019-2025 highlights that public services shall be perceived as seamless and integrated by the users [5]. Reflecting the concern for chronic states in society and associated political measures, as manifested in national health planning, this article presents the protocol for the research project "TELE-AMBUS – Exploring and redesigning a cross-sector outpatient chronic wound management model comprising telemedicine and ambulatory wound care interventions." The Telemedicine and Ambulatory Wound Care Team (TELE-AMBUS) project was initiated based on (1) a strong desire of our project partner, the Wound Diagnostic Centre (WDC) in Stavanger, to test an outpatient chronic wound management model, combined with (2) identified knowledge needs within the domain of telemedicine in chronic wound management interventions.

Regarding current domain knowledge, our systematic literature review revealed a need for broader or more comprehensive empirical exploration into quality improvement and integration of telemedicine and chronic wound management [6]. These explorations should expand on and extend beyond the currently identified intervention barriers and opportunities. Specifically, barriers of telemedicine in chronic wound management include delays in installing the telemedicine software and workforce shortages, which, over time, leads to a steep decline in individuals using telemedicine [7]; limitations set by the organization and technology in terms of management focus, resources, economy, consultation time, wound training, and the need for updated equipment [8,9]; and qualities of the individual or professional such as the patient's confidence in the competence and professional skills of health professional [10]. On the flip side, opportunities generated by telemedicine in chronic wound management include the telemedicine technology's potential for improving wound evaluation accuracy by means of tools and software developments [11-14]; the potential that gathering individual health care professionals with a shared focus on the patient can enhance clinical outcomes across the wound spectrum, clinical care settings, and geographical locations [15]; and the health-related quality of life dimension that professional, patient, and next-of-kin express satisfaction with telemedicine as a treatment method [14,16]. Shedding light on both quality of life and monetary cost reduction opportunities, Dardari et al [17] found that "...telemedical intervention with an expert nurse could lead to a length of hospitalization and direct costs that are two times lower compared to conventional follow-up."

Concerning the specific outpatient model explored in the TELE-AMBUS project, wound specialist nurses at the WDC expressed a years-long desire to explore an outpatient model where a team of specialist nurses, in consultation with the relevant hospital physician, provides ambulatory wound care diagnosis and treatment to vulnerable patients with chronic, nonhealing wounds that have various mobility challenges and reside in the municipalities. The mobility challenges include the patient being older or frail, having advanced or complex wounds, and experiencing travel stress and appointment difficulties. The underlying rationales for testing the model are that (1) patients may be evaluated by nursing and physician specialists before their conditions deteriorate; (2) vulnerable patients' quality of life may improve as the pain and discomfort caused by wounds is reduced; (3) primary care (municipal) health care professionals may learn from the specialist ambulatory wound care team (AWCT) and be provided with a more direct line of communication with the hospital specialists through telemedicine, thus improving general wound care for patients; and (4) the AWCT provides early interventions aided by the telemedicine solution that may reduce costs at the hospital and primary care facilities.

Illustrated by the contextual backdrop of national plans and strategies, the current knowledge status, and the outpatient wound management model, intervention barriers and opportunities have as much to do with the organizations and

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the individuals involved as with the technology. Thus, research conducted on interventions within telemedicine in chronic wound management needs to consider a broad spectrum of factors that can influence the planning and execution of interventions with factors spanning organizations, technologies, and individuals, including professionals and patients. This spectrum of factors or conditions has been accounted for in the TELE-AMBUS project's whole system research approach (described in the *Methods* section). Our approach resonates with Kahn's [18] suggestion:

> *Researchers should explore the crucial issue of context, studying not only whether telemedicine [and by extension, the overall outpatient model in this project] works but also how, when, and where it works best, to provide a roadmap for more effective implementation.*

Key Definitions

Telemedicine, as a central concept in the outpatient model of the TELE-AMBUS project, can be clarified as the use of electronic information and communication technology to exchange health care information between health care practitioners across sites and distances, which can improve health care delivery and outcomes including patients' health status [19]. The telemedicine solution selected for the TELE-AMBUS project involves the primary care nurses using a secure cell phone to send wound pictures to the specialist AWCT, who reviews and logs the pictures (through the patient's journal) and responds to the primary care nurses with suggestions and recommendations. This is not a dedicated telemedicine solution that is currently unavailable in Norway. Telemedicine is part of eHealth, which is understood as health care services provided electronically through the internet.

The specialist AWCT is a team of specialized wound nurses who travel to the patient's home, examine and treat the patient, and educate the present municipal health personnel on the wound treatment procedure applied to the patient.

Primary and Secondary Project Objectives

Targeting the knowledge needs identified above, as well as the WDC's desire to test an outpatient chronic wound management model, the TELE-AMBUS research project has the primary objective: to explore and analyze the implementation and consequences of an outpatient model comprised of 2 interconnected quality improvement interventions (ie, telemedicine and AWCT) aimed at older and vulnerable patients with chronic wounds across the specialist and primary health care sectors. Embedded in this objective is the aim to improve the competence levels of health care providers and, consequently, service quality of outpatient wound management (diagnosis and treatment) across specialist and primary health care services.

In addition, four secondary objectives support and extend the primary objective, grounded in qualitative and quantitative approaches: (1) to systematically review and synthesize existing knowledge on interventions within telemedicine in chronic wound management, including barriers and opportunities and associated measures or elevation efforts across the specialist and primary health care sectors (described in the *Introduction* section and in Høyland et al [6]); (2) from a sociotechnical system (STS) theory approach focused on the Systems Engineering Initiative for Patient Safety (SEIPS) model, to explore and analyze the outpatient model or interventions and cross-sector work system (discussed in the *Methods* section); (3) from a health economic perspective, to assess the cost-effectiveness of implementing an outpatient model across the specialist and primary health care sectors; and (4) to transform project findings into managerial and employee strategies and practices across specialist and primary health care. Each secondary objective constitutes an individual work package (WP) in the TELE-AMBUS project.

Methods

Setting and Participant Recruitment

The WDC, responsible for organizing and running the new outpatient wound intervention, is located at the Department of Dermatology, Stavanger University Hospital, Norway. Stavanger University Hospital employs more than 7600 individuals and provides health care services to 18 municipalities with a population of about 350,000. The WDC is unique in a Norwegian context, as specialists from different professions and disciplines (wound specialist nurses, a vascular surgeon, and a dermatologist) gather to examine patients in one location comprehensively and assemble coherent treatment plans. The WDC operates each Tuesday with cross-disciplinary wound assessment and treatment. Each week, the WDC has an average of 2 patients with diabetic wounds, 1-2 patients with arterial wounds, 3 patients with venous wounds, 2 patients with immunological wounds, and 1 patient with a pressure wound, totaling 10 patients. The size of the ulcerations varies from the size of a pin to most of the leg. Healing varies according to wound size; the patient's condition (physical and mental); activity levels and self-insight; the competency levels of municipal health personnel, including wound follow-up; and more.

There are other interdisciplinary wound centers comparable to the WDC in Norway in terms of being interdisciplinary and outpatient-focused and sharing publicly financed health care systems and institutions. Within the Nordic countries, there are the Copenhagen Wound Healing Centre at Bispebjerg University Hospital (Denmark), the University Center of Wound Healing in Odense (Denmark), and the Wound Center (Haavakeskus) at Helsinki University Hospital (Finland). Extending further, the former Welsh Wound Innovation Centre in the United Kingdom is focused on outpatient chronic wound healing and innovation.

The project manager from the Norwegian Research Centre, in dialogue with the WDC, conducted the initial municipal partner recruitment process as well as subsequent calls for additions or adjustments of included subunits (home care services and nursing homes), with the latter process being facilitated by the project manager's contact with appointed coordinators in each municipality. The WDC's main criterion for selecting municipalities was practical proximity to the hospital running the outpatient intervention, specifically, about 1-hour driving

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distance. In addition to a regional university hospital in Norway, a total of 6 municipalities, varying in size, chose to participate in the research project. Of these, 5 of the municipalities included home care services and nursing homes, while 1 municipality limited inclusion to nursing homes and only 1 of 5 home care services zones. Regarding recruitment of patient cases for the intervention, the AWCT at the WDC receives and processes ongoing patient referrals from units in the municipalities. Specifically, the wound specialist nurses or AWCT receive patient referrals from general practitioners in the municipalities. The AWCT assesses whether the referred patient is a suitable candidate for the intervention, with the selection criteria being hard-to-heal wounds and the patient having a multimorbid condition. The exclusion criteria are immunological and diabetic wounds. Both the WDC and municipalities self-organize the internal recruitment of study participants for research activities in the TELE-AMBUS project.

To gain empirical insights into the process of implementing and operating the outpatient intervention, combining AWCT and telemedicine implementation and operation, individuals involved with the intervention will be asked to participate in research activities, including observations (ie, being observed by the researchers), semistructured interviews, and informal conversations. Combining observations with asking questions, including clarification questions, constitutes a contextual design approach [20]. To account for both service ends of the intervention, invited participants will include the AWCT, which was comprised of 2 wound specialist nurses and the nursing staff in the municipalities (from home care services and nursing homes). In addition, key informants associated with the outpatient intervention will be invited to participate in semistructured interviews, including health care managers, information technology personnel, and other stakeholders at different levels of the hospital system. Table 1 provides an overview of the participants involved in the project's intervention and research activities.

Table 1. Categories and types of participants involved in the intervention and research activities in the Telemedicine and Ambulatory Wound Care Team (TELE-AMBUS) project, including regional, national, and international partners.

Project participant category	Project participant type	Specific roles
Regional partner: university hospital	Wound specialist nurses, a dermatologist, a vascular surgeon, a general surgeon, information technology–personnel, higher- and mid-level managers, including the local project coordinator and economy department	Operated the new wound management model; participated in observations, conversations, and interviews; participated in regular scientific advisory meetings
Regional partners: 6 municipalities	Medical and nonmedical trained nursing staff at home care services and nursing homes; higher- and mid-level managers at the municipal level, including local project coordinator and economy department	Participated in observations, conversations, and interviews; one municipal partner participated in regular internal meetings at the university hospital
National partner: Norwegian Centre for E-health Research	Senior advisor	Participated in regular scientific advisory meetings, partner-specific meetings, and dissemination activities
International partners: WWIC[a] and the University of Wisconsin-Madison	WWIC: chief operating officer, clinical research director, professor in chronic wounds; University of Wisconsin-Madison: professor in system theories	Participated in regular scientific advisory meetings, partner-specific meetings, and dissemination activities

[a]WWIC: Welsh Wound Innovation Centre.

To summarize, the inclusion criteria applied by the TELE-AMBUS project were (1) municipalities with practical proximity to the hospital running the outpatient intervention, (2) vulnerable patients with chronic, nonhealing wounds who have various mobility challenges and reside in the municipalities (discussed in the *Introduction* section), and (3) all health care professionals and levels involved in the AWCT intervention (Table 1). In addition, the study applied the following exclusion criterion: patients with diabetic foot ulcers who belong to another hospital department and are not involved in the outpatient intervention.

Given that we study a hospital-initiated intervention where patient visits (cases) are generated by referrals from the involved municipalities, no sample size limitation was defined. However, we have recently crossed the threshold of 30 patient visits or cases, which includes 30 observations (by 1-2 participating researchers) and associated on-site and later follow-up interviews with municipal health personnel and the AWCT. Our impressions of the newer patient visits are beginning to converge with impressions from previous visits, suggesting the effect of data saturation. However, due to the ongoing nature of this intervention and our desire to pursue "challenging" cases (where things go less according to plan), of which we have fewer, we expect that further patient visits will be conducted until the first quarter of 2025 and perhaps beyond (depending on perceived data saturation), likely ending with around a total of approximately 40 patient visits or cases.

Research Approach

Overview

Improvement interventions, defined broadly as purposeful efforts to secure positive change, have become an increasingly important focus of activity within health care, including wound management [21-23]. The larger intervention studied in the TELE-AMBUS project is the outpatient wound management model itself, which can be considered an improvement intervention in its initial form improvement rather than research directed [21] due to the wound specialist nurses' ownership and desire to explore the model in the context of older and vulnerable patients. It is also a complex coordinated care intervention,

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comprising multiple interacting and intertwined components (telemedicine and AWCT) across different levels and organizations, in this case, involving primary and specialist health care services, and in the case of primary health care, numerous municipalities with specific characteristics [15]. Therefore, the most appropriate design is process evaluation because it can "assess fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes" [24]. Supportive of this design, we identified a need for broader or more comprehensive empirical explorations into quality improvement and integration of telemedicine in chronic wound management to capture the complexity of organization, technology, and individual interplay across sectors (discussed in the *Introduction* section).

The Process Evaluation

For the TELE-AMBUS project, we use a qualitative longitudinal study design, following and analyzing the intervention as it unfolds in practice. We apply the process evaluation framework by Moore et al [25], with descriptions of the intervention, implementation, mechanisms, and outcomes in relation to the context, and where we use several data collection and analysis methods. The qualitative research approach comprises situated methods and data collection that are carried out for a long period of time (for this project, the systematic literature review, nonparticipant observations, semistructured interviews, and informal conversations are situated and carried out in an outpatient wound management setting for a long period of time); a view that the social world is multifaceted and thus requires a certain degree of interpretation (outpatient chronic wound care occurs in a complex setting of multiple disciplines and technologies, types of patients, and so forth across sectors); and an inherent exploratory nature suited to the study and conceptualization of new or emerging phenomena, such as this project's tandem exploration of telemedicine and AWCT [26-31].

Findings of our systematic literature review on the topics of telemedicine and ambulatory wound care management interventions [6] shape a basic mental orientation for the fieldwork, including the observational protocol and associated observations of the AWCT and nursing staff during patient consultations. This mental orientation also assists in identifying the broader and more specific questions to raise during informal conversations and in-depth semistructured interviews with managers and employees across specialist and primary health care case organizations. Seminars and digital meetings with project partners conducted throughout the project period, where partner insights and experiences (including from specialists in wound management, innovation, eHealth, health economy, and system perspectives) and empirical findings are presented, serve to adjust and "sharpen our field lens" in terms of observational and interview focus (such as, what barriers or outcomes to explore further) for the continuing fieldwork. Furthermore, the lens sharpening effect is also reversed, whereby we as researchers apply our whole system perspective in partner meetings and dialogue as well as during the intervention (through observations, interviews, and conversations), thus challenging the partners to adopt a broader understanding of systems, organizations, and change.

The Economic Evaluation

Regarding the quantitative approach applied in the project, we aim to conduct a health economic evaluation of the outpatient model (intervention) compared with the regular clinical wound management model. An economic evaluation will measure 2 parameters, costs and outcomes or effects, and compare the 2 approaches. Intended to inform decision-making, the idea behind an economic evaluation is not necessarily to identify which of the 2 improvement interventions is the "better" one; rather, if the cheapest option is the most effective, it will be the most cost-effective or dominant option, or if the cheapest option is not the most effective, incremental cost-effectiveness ratio will be measured [32]. There are several methods for the economic evaluation of health care programs. In the context of this project, it is relevant to focus on the intervention. Since the new model or intervention will also have consequences for resource allocation, considerations of both cost and benefits (here, health improvement) are necessary and fundamental to quality improvement evaluation (eg, the Institute for Healthcare Improvement, United States). There are alternative perspectives on the economic evaluation of health care programs as well. In this project, we are concerned with a health care sector perspective, that is, focusing on consequences for primary and specialist health care and the patient. Potentially, the intervention may lead to both short-term and longer-term health improvements. Short-term improvements may follow from earlier referrals to specialist health care, thereby resulting in less severe admissions to the hospital, shorter length of stay, less pain and discomfort for the patients, and potentially quicker recovery. In the longer term, increasing competence and awareness in primary health care services can potentially reduce the number of severe cases admitted to the hospital. Specific measures and outcomes of health improvements are in the short-term analyses related to positive changes in the number of hospital admissions due to a reduction in serious and complicated cases compared with the regular wound model. In the longer term, health improvements are related to positive changes in the number of admitted wound patients, regardless of whether they are complicated or not, compared with the regular wound model. Costs may change, too, for both primary and specialist health care services, and the relative distribution of costs between services may change. The regular wound model too often seems to result in severe and complicated admissions to the hospital, a situation that increases costs both at primary care and specialist care levels. However, one consequence of a suboptimal level of competence and capacity at the primary health care level is that some of the treatment costs are passed on to specialist health care. Hospitals are compensated for at least part of these costs through the remuneration system (diagnosis-related groups–based), but that is not a relevant issue from a societal or health care sector perspective.

The economic evaluation will be based on case data collected during the intervention period. The data include reported time usage by nurses and physicians, allowing cost calculations to be made in Norwegian Krone. The intervention's costs, including equipment costs, are compared with treatment as usual costs collected from participating municipalities. Based on relevant *International Classification of Diseases, Tenth Revision*

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(*ICD-10*) codes, register data from the Norwegian Patient Register are used to estimate nationwide costs associated with wound treatment. To the extent the intervention contributes to reducing the use of hospital care and hospital resources for the treatment, we can estimate net benefits and model the potential aggregate net benefits nationwide of the intervention.

Summarized, the TELE-AMBUS project applies a combined process and economic evaluation research strategy with associated qualitative and quantitative endpoints that can affect the primary and specialist health care systems within and across. The end points include improvements in cost-effectiveness (economic evaluation) and competence and service quality (process evaluation) of the new outpatient model versus the regular clinical wound management model.

STS Approach

Reflecting the knowledge limitations identified in the *Introduction* section, our conceptual and analytical whole system approach selected for this project is based on system theories. STS theory concerns interactions between and joint design of the technological subsystem, the personnel subsystem, and relevant external surroundings, being mutually interdependent and where any alterations or changes in one part of a system (eg, technology such as telemedicine) will impact other parts of the system [33]. Embedded in the STS tradition is the human factors and ergonomics (HFE) discipline focusing on systems where humans interact with the environment "to jointly improve performance and well-being by designing the integrative whole better, and by integrating the human into the system better" [34]. The core characteristics of the HFE discipline are, therefore, (1) the system approach, (2) the design-driven approach, and (3) the focus on outcomes related to both system performance and well-being [34]. Perspectives and models from the HFE discipline are recommended in the *World Health Organization's Global Patient Safety Action Plan* [35], specifically, the second strategic objective to "build high-reliability systems and health organizations that protect patients daily from harm," that is, the emphasis is on designing safe and sustainable health care systems for the future.

Anchored within the STS tradition is the SEIPS framework, illustrated in Figure 1, which applies a whole system perspective on health care [36]. The framework details elements within a work system (person, technology and tools, task, environment, and organization) that interact and are mutually interdependent. The design of the work system affects different processes (eg, clinical treatment and patient follow-up) that influence different outcomes related to the patient, employee, and organizational outcomes [36]. A core aspect of the SEIPS framework, in relation to the TELE-AMBUS project, lies in its ability to inform implementation, change management, and overall design of complex systems, thereby contributing towards prevention and avoidance of undesired outcomes across system performance and well-being in a health care context, specifically in terms of patient outcomes (mortality, complications, quality of life, and medical errors), organizational outcomes (efficiency and treatment time), and employee outcomes (well-being aspects such as job satisfaction and motivation) [37]. The feedback loops in the framework suggest that knowledge or insights into the dynamics of the model, including outcomes, can be applied to adjust and redesign the work system [37].

Figure 1. The Systems Engineering Initiative for Patient Safety (SEIPS) framework of work system, processes, and outcomes.

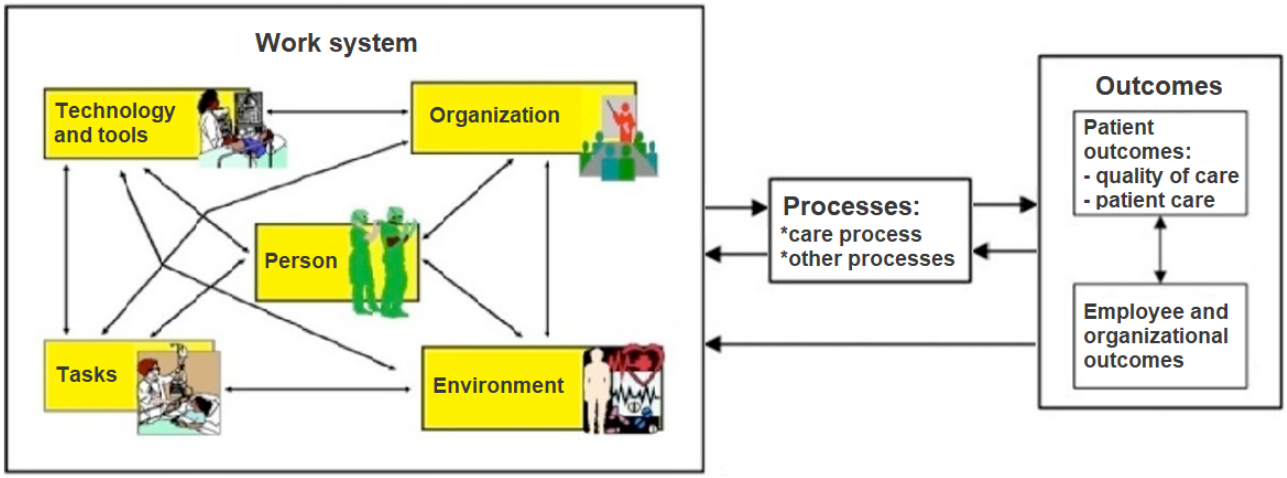

The outpatient model relates to the SEIPS framework (Figure 1) as follows: The specialist AWCT and primary care nurses constitute the center of the work system (person aspects), enabled or constrained by other aspects of the work system spanning both specialist and primary health care. For example, technology aspects of the work system include the telemedicine solution (used by both specialist and primary health care) and the patient journal system, that is, Distributed Information and Patient Data System (used by the specialist health care), while organizational aspects include staffing and competency levels and priority given or time allocated to outpatient wound management in everyday practices. Thus, the outpatient model and work system understanding take on an interorganizational and interprofessional form, encompassing persons involved, the technology used, the specifics of the organization, and so forth across services. This cross-sector work system influences the outpatient wound care process (middle part of SEIPS) in terms of enabling or constraining the work tasks of the wound specialist nurses (eg, evaluation of the patient's wound, bedside teaching of primary care nurses in wound care procedure and how to use telemedicine) and the primary care nurses (eg, follow-up of wound development including the transference of

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pictures through the telemedicine solution). Finally, the quality of the outpatient wound care process produces organizational and individual outcomes (the right part of SEIPS) that are desirable to a larger or lesser degree. For the TELE-AMBUS project, these outcomes concern (1) the costs and benefits of the regular clinical versus outpatient treatment models and (2) changes in health care provider competence and quality across specialist and primary health care services. The latter outcome is tied to the project's degree of success or not in transforming empirical findings into managerial and employee strategies and practices across services.

While studies using the SEIPS framework have become substantial in recent years, there is a lack of SEIPS-based intervention studies, in particular (1) studies that jointly consider physical, cognitive, and organizational HFE issues and (2) studies that apply a broad approach to outcomes linking design with patient outcomes [37]. Furthermore, the involvement of end users (patients and providers) is emphasized from a participatory perspective [37]. Finally, reviews show that with a few exceptions, there is a lack of studies analyzing health care with an HFE perspective within the Scandinavian context [37-39]. The operationalized SEIPS framework enables us to explore and analyze implementation and design aspects of the outpatient model, comprised of interconnected telemedicine and AWCT interventions embedded within existing organizations and practices across the specialist health care services, the primary health care services, and, not least, the specific context of the chronic wound patient.

The model can analytically appear daunting due to its dynamic nature, that is, in the presentation of mutually interacting work system relationships, but when purposefully operationalized, it enables the researcher to capture the intricacy of the human-technological–organizational complexity under study. In our operationalization, we applied the 5 work system dimensions of the SEIPS model, that are internal environment, external environment, individual and team, organization, and technology and tools, not only to create a mental orientation for our fieldwork (in terms of what to look for during the patient visits) but also as coding guidance when processing data in the computer-assisted qualitative data analysis software QSR NVivo (Lumivero) and Dedoose (SocioCultural Research Consultants).

Ethical Considerations

The TELE-AMBUS project does not apply a clinical trial design and approach; the project seeks to improve the quality and holistic integration of wound diagnosis and treatment across primary and specialist health care services. This is achieved by exploring and analyzing cross-sector implementation and consequences of a new outpatient chronic wound management model comprising an ambulatory wound team and telemedicine components. In other words, the project's purpose is to study and improve current health services across sectors, and not to procure knowledge on the patient's health and disease.

Specifically, 1-2 researchers observe the ambulatory wound team's consultation and interaction with municipal nursing staff and the patient. Written observational notes focus exclusively on service quality aspects, that is, no personal or sensitive information will be taken down including from patients, and no audio or visual recording will be involved during the observations. The only audio-recorded data will be semistructured interviews, involving the health care personnel, management, and information and communications technology personnel from specialist health care. While it should be noted that audio recordings could potentially contain background information that enables identification of a person, all background and other possible person-identifiable information are deleted during transcription.

Written information and consent forms about project purpose and participation, secure data processing and storage, a field for providing written consent, and so forth corresponding to the Norwegian Centre for Research Data templates, are sent to and gathered from all project participants including primary and specialist health care personnel and managers as well as patients. While no personal or sensitive information is collected from any participants including patients, informed consent is secured from each patient in advance of the ambulatory wound team's consultation visit to allow for the researchers' presence and observations of health care personnel during the visits. Beginning in January 2023 and in advance of the patient visits and fieldwork, the hospital partner involved in this project also sent out an informal information letter to all 6 participating municipalities. This letter describes in detail the practical aspects of the research project, including how the ambulatory wound team will operate across sectors and the researchers' specific roles and involvement.

Based on the above premises, the TELE-AMBUS research project was accepted by the Regional Committee for Medical Research Ethics Western Norway (application ID 375986) and approved by the Norwegian Centre for Research Data (reference 236558). The project has also been agreed upon by the internal data protection representative at Stavanger University Hospital (protocol 2847-2847).

Data Collection and Analysis

As part of this project's qualitative longitudinal study design (discussed in the *Research Approach* section), empirical field data are gathered through observations, semistructured interviews, and informal conversations across the specialist and primary health care services. The resulting data are analyzed through QSR NVivo and Dedoose, which enables systematization and transparency in both the analysis and dissemination of results, improving the reliability and trustworthiness of the study [27,40]. As we apply these approaches to the TELE-AMBUS project, we seek to map emergent patterns and connections in the data material related to (1) the implementation and consequences of the outpatient wound management model and (2) associated improvements in health care provider competence and overall service quality across specialist and primary health care services (discussed in the *Primary and Secondary Project Objectives* section).

As part of economic evaluation (refer to the *Research Approach* section) and based on data gathered through the qualitative empirical fieldwork (as described above), costs associated with a generic pathway in the regular clinical wound model are calculated as costs at the primary health care level (eg, staff hours, wages, medical equipment, and so forth) and costs at the

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specialist health care level (eg, staff hours, wages, length of inpatient stay, and so forth). We do the same costing exercise for the new outpatient model comprising telemedicine and the AWCT. We conduct one-way and deterministic sensitivity analyses as well as probabilistic sensitivity analyses (if feasible) for the quantitative cost-benefit analyses. The analyses feed into the overall objective of mapping emergent patterns and connections in the data material related to the implementation and consequences of the outpatient wound management model and associated improvements in provider competence and service quality.

Results

The project has been funded from 2021 to 2025. A series of baseline qualitative focus group interviews and semistructured interviews with project participants or stakeholders at the hospital and in the 6 municipalities have been conducted since April 2022 and concluded in January 2024. Starting November 2022, the AWCT has conducted outpatient visits and follow-up telemedicine consultations, with the latter part lasting until the wound has healed or the patient's death (typically, patients are older adults with multimorbid conditions). The patient's wound condition is evaluated during the initial visit and subsequent follow-up telemedicine consultations. The outpatient visits are expected to end in mid-2025. Fieldwork, including observations, semistructured interviews, and informal conversations, has been undertaken with project participants and stakeholders at the hospital and in the 6 municipalities since November 2022 and is expected to conclude in March 2025. The baseline interviews and subsequent fieldwork cover WP 2 and WP3 in the TELE-AMBUS project, focused on exploring the intervention from an STS perspective as well as documenting health economic costs and effects of implementing the intervention, respectively (Table S1 in Multimedia Appendix 1). The results of WP2 and WP3 feed into WP4 on transforming project findings into cross-sectoral managerial and employee strategies and practices. Initial empirical results from the baseline interviews were presented at the 14th Organizational Design and Management Conference [41]. In addition, 1 peer-reviewed publication has been published in the International Wound Journal [6], as part of WP1 targeting a cross-sector synthesis of existing knowledge on telemedicine and chronic wound management interventions (Table S1 in Multimedia Appendix 1).

Note that the Gantt chart provided in Table S1 in Multimedia Appendix 1 also elaborates on the roles and tasks of the project participants, such as designated researcher groups and advisory boards spanning the years and quarters of the project's time span.

Discussion

Principal Findings

In terms of the TELE-AMBUS project status, findings of systematic reviews conducted in WP1 indicate that there is a pressing need for more comprehensive empirical explorations into quality improvement and integration of telemedicine in chronic wound management, including using system frameworks that can capture cross-sector system perspectives and associated implications. We specifically suggest that the design and execution of telemedicine improvement interventions and associated research projects should be conducted in close cooperation with managers and practitioners knowledgeable about barriers and opportunities that can influence the implementation of important interventions within chronic wound management [6]. The baseline results from WP2 and WP3, to be finalized this year, and the larger fieldwork data collection and analysis processes, to conclude in March 2025, are expected to reveal insights into organizational, environmental, technological, individual (personnel), and cost-effect considerations that are critical to account for in the design or redesign of telemedicine and outpatient model interventions across the primary and specialist health care sectors.

We apply the sociotechnical SEIPS framework in multiple and creative ways, that is, to design and inform our fieldwork and explore, evaluate, and redesign the outpatient wound management model and work systems across the primary and specialist health care sectors. Thus, SEIPS becomes a pedagogic tool to translate and implement project findings into practice across services. To our knowledge, such an approach has not been undertaken in telemedicine in chronic wound management literature or associated HFE research. Specifically, existing cross-sector quality improvement studies focus on identifying telemedicine-related barriers, benefits, acceptance levels, and outcome variables rather than on transforming findings into cross-sectoral managerial and employee strategies and practices and redesigning (work) systems across the primary and specialist health care sectors and services [6,42]. Thus, our approach can produce both original and novel research and theoretical results internationally. The project's tandem exploration of the 2 quality improvement interventions within telemedicine in chronic wound management (combining telemedicine and AWCT to bring specialist and primary health care sectors closer) has, to our knowledge, not been undertaken in a Norwegian context and thus can produce novel national results within the field of telemedicine and chronic wound management.

Strengths and Limitations

As is the case for any research project using a qualitative design approach, extrapolation and generalizability of the resulting findings can be problematic and, thus a limitation [43,44]. However, a qualitative approach offers unique, in-depth insight into the richness and complexity of the phenomenon under study. Applied to the TELE-AMBUS project, we use process and economic evaluations to capture why and how the studied intervention (outpatient model) contributed to change or not, including the associated mechanisms and outcomes at individual and organizational levels. Our primary research interest lies in knowing how the intervention works in practice across the involved organizations and influencing work system factors, hence allowing for redesigning or adjusting per the identified barriers. Thus, we address calls for whole system approaches within telemedicine in chronic wound management research and STS research (discussed in the *Introduction* and *Research Approach* sections, respectively).

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Conclusions

As noted in our systematic review [6], telemedicine interventions in chronic wound management must adopt a longitudinal and broader system perspective across primary and specialist health care services that accounts for clinical applications, team approaches, and wound management and implementation strategies. The system perspective must also consider the quality of life, the existing care system, and cost aspects. These research needs are reflected in the new wound management model explored in the TELE-AMBUS project. This includes not only insights the project produces by means of identifying sociotechnical barriers and facilitators and cost-effectiveness aspects associated with the outpatient model, in the latter case or analyses compared with a regular treatment model, but also by "thinking system redesign" including everyday health care management and professional strategies and practices across the primary and specialist health care sectors. This way of connecting system theory and empirical findings to actual practice (transformation) represents a key element and novelty of the TELE-AMBUS project with a potential impact spanning research and practice fields from HFE to eHealth and chronic wound management.

Acknowledgments

The Telemedicine and Ambulatory Wound Care Team (TELE-AMBUS) research project was funded from 2021 to 2025 by the Research Council of Norway, project 326574.

Data Availability

The economic datasets generated and analyzed during this study will be limitedly accessible in the Norwegian Centre for Research Data repository once the embargo is lifted on January 1, 2027.

Authors' Contributions

Sindre AH conceptualized, administrated, and drafted the research project and conducted the empirical investigation and formal data analysis. KAH, OØ, KI, EK, and RG-S contributed to conceptualizing the project, empirical investigation, and formal data analysis. Synnøve AH and HRW contributed to conceptualizing the project and the empirical investigation. As scientific advisory board members and project partners, PC, MF, SB, MG, SEH, and ER provided input on the project conceptualization, empirical investigation, and formal analysis. Sindre AH drafted the manuscript, while all other authors reviewed, edited, read, and approved the final manuscript.

Conflicts of Interest

Sindre AH and Synnøve AH are spouses, with separate organizational affiliations and roles. Sindre AH (Norwegian Research Centre) and colleagues research the innovation explored in this project while Synnøve AH (Stavanger University Hospital) together with HRW (Stavanger University Hospital) run the innovation.

Multimedia Appendix 1
Telemedicine and Ambulatory Wound Care Team (TELE-AMBUS) Gantt chart from 2021 to 2025, detailing main tasks and participants across work packages and years.
[DOCX File , 20 KB - resprot_v13i1e55502_app1.docx]

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Abbreviations

AWCT: ambulatory wound care team
HFE: human factors and ergonomics
ICD-10: International Classification of Diseases, Tenth Revision
STS: sociotechnical system
SEIPS: Systems Engineering Initiative for Patient Safety
TELE-AMBUS: Telemedicine and Ambulatory Wound Care Team
WDC: Wound Diagnostic Centre
WP: work package

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Protocol

Development and Implementation of an Online Patient Education Program for Children and Adolescents With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Their Parents, Siblings, and School Personnel: Protocol for the Prospective BAYNET FOR ME/CFS Study

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Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) presents significant challenges for affected children and adolescents, their social environment, and treating physicians, due to its profound impact on quality of life and the lack of causal therapeutic approaches. One crucial aspect of care that has been missing for these patients is comprehensive education for both them and their social circles.

Objective: This study protocol aims to outline the goals, study design, execution, and evaluation of the subproject within the BAYNET FOR ME/CFS project. The focus is on developing online education programs for children and adolescents with ME/CFS, as well as for their parents, siblings, and school staff. These programs are designed to improve independent disease management, increase knowledge, and promote interaction with other affected individuals.

Methods: In phase I, the group-based online education programs were developed by a multidisciplinary team based on the ModuS concept created by the Competence Network for Patient Education (KomPaS). These programs were then piloted and finalized. Phase II involved recruiting participants and implementing the finalized programs. Given the restricted physical and cognitive capacities of the affected individuals, the patient education programs were exclusively designed in a digital format to facilitate participation. In phase III, the programs will be evaluated for acceptance, completeness, and participant satisfaction.

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The qualitative assessment will focus on individual expectations and benefits derived from the training. Phase IV will further assess the programs in terms of improvements in disease knowledge, health-related quality of life, life satisfaction, and family burden.

Results: The programs were developed, piloted, and finalized during phase I, which ran from December 2022 to May 2023. The pilot phase, from March to May 2023, led to adaptations in the program concept. In total, 8 patients and their parents, 5 siblings, and 59 school staff participated in the piloting. Adjustments were made to the format, content, duration, and schedule to better meet the needs of the affected individuals and their social circles. In phase II, participant recruitment for the patient education program took place from January to July 2023. The study successfully recruited 24 young patients with ME/CFS and their parents, along with 8 siblings and 51 school staff. Two program blocks for patients and parents and 2-3 blocks for siblings and school staff commenced in May 2023 and were completed within the same year. Phase III began after phase II and involves the evaluation of the programs, with the process expected to conclude by the end of 2024. Phase IV, planned for 2025-2026, will involve the rollout of the program to 150 children and their caretakers. This phase will focus on evaluating disease knowledge, health-related quality of life, life satisfaction, and family burden, as well as include longitudinal assessments.

Conclusions: The data aim to support the development of a comprehensive, interprofessional care model for children and adolescents with ME/CFS.

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KEYWORDS

patient education; ME/CFS; children; adolescents; ModuS; parents; teachers; siblings; training

Introduction

Background

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe chronic illness that causes significant life changes for those affected as well as their social environment [1,2]. It is estimated that approximately 300,000 people in Germany suffer from ME/CFS, including up to 90,000 children and adolescents [3]. An increase in cases has been observed during the COVID-19 pandemic [4]. Given these numbers, ME/CFS is not considered a rare disorder [5]. Despite ongoing research, the underlying pathophysiology of ME/CFS remains only partially understood [6]. Infections are often identified as the most common triggers [7]. The primary symptoms include profound fatigue that does not improve with rest and can lead to limitations in all areas of school, leisure, and social activities [8]. Another diagnostic criterion is postexertional malaise (PEM), characterized by a decrease in functional level or exacerbation of symptoms after minimal physical, cognitive, or emotional effort, often described as a “crash.” This often occurs with a time delay after exertion and can last from hours to months [8,9]. Additionally, various forms of muscle pain, joint pain, and headaches are reported, along with sleep disturbances and orthostatic intolerances, which can manifest as postural orthostatic tachycardia syndrome [6,8,10,11]. The disease significantly reduces health-related quality of life (HRQoL) [12]. This reduction is attributed not only to the symptoms themselves but also to their impact on school or occupational participation, often resulting in reduced attendance or complete absence from school. Consequently, social isolation frequently occurs [13].

To address knowledge deficits and empower individuals with ME/CFS to engage in self-management and disease control, experts from the European Network on ME/CFS (EUROMENE), which defines diagnostic standards for adults, recommend patient education as part of the therapeutic measures [14]. Patient education programs have become an integral part of therapy options for children and adolescents with various chronic diseases. The objective of these programs is to promote self-management among individuals and within their social environment. Several studies have demonstrated that patient education programs lead to increased self-efficacy, disease competence, and satisfaction [15,16], as well as improved HRQoL and a reduction in disease-specific burden [17]. Additionally, disease-specific symptoms decreased, and the risk of relapses or exacerbations was reduced [18,19]. One established and validated concept is the standardized modular training program, ModuS, developed by the Competence Network for Patient Education (KomPaS) with support from the Federal Ministry of Health [20]. ModuS is available for some less common and rare chronic illnesses for individuals [18,20], as well as for siblings [21] and parents. The training concept consists of 4 generic modules and 3 disease-specific components [20]. The generic modules address psychosocial topics relevant to all children and adolescents with chronic diseases. By contrast, the disease-specific modules provide detailed information about the etiology, course, and therapeutic measures for the respective condition. The structure of the ModuS training allows it to be adapted to various chronic diseases [20]. Additionally, these programs can be customized to meet the needs of other groups, such as parents, teachers, and siblings [20,21].

Study Goal

Currently, there is no standardized education program for children and adolescents with ME/CFS and their surroundings. Given the importance of learning and implementing self-directed strategies in the treatment of ME/CFS—such as “pacing,” managing energy throughout the day, maintaining good sleep hygiene, and using relaxation techniques—training programs are a crucial aspect of care for these patients. The goal of these strategies is to avoid PEM and enhance HRQoL [14].

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Additionally, understanding the disease is crucial for the comprehensive care of the immediate environment, including family members and school personnel. Therefore, the objective of this project was to develop, implement, and evaluate modular group education programs for children and adolescents with ME/CFS, as well as for their parents, siblings, and teachers.

Nearly all children and adolescents with ME/CFS experience substantial limitations in their (school) activities and social interactions [6]. As a result, in-person group training sessions are not feasible for this patient group. Consequently, this project developed training sessions based on the ModuS concept for digital implementation. Short online sessions provide these individuals with the opportunity to participate, even if leaving the house or bed is not possible. This approach allows them to receive education and connect with others who are affected. Eliminating the need for travel to and from the program venue is an additional advantage for this group. As parents are limited in their time resources due to caring for affected children and adolescents, handling the bureaucratic aspects associated with the illness, and siblings also have time constraints, online formats offer a viable option for participating in education programs. In the professional realm, online continuing education has become increasingly available and valued, particularly during the COVID-19 pandemic [22]. For school staff, online training is beneficial due to its accessibility and time efficiency.

The study design presented describes the development, implementation, and planned evaluation of an online training model for individuals with ME/CFS up to the age of 20 years, as well as their parents, siblings, and school staff. This model is part of a new interprofessional care approach.

Methods

Study Design

This is a prospective study without a control group and will be evaluated using both qualitative and quantitative analyses. The objective of this study is to conceptualize, implement, and evaluate online education programs based on ModuS for adolescents with ME/CFS, their parents, siblings, and school staff. In phase I, the online programs were developed by a multidisciplinary team, piloted, and revised. Phase II involved the implementation of the finalized programs. In phase III, the programs will be evaluated with the primary objective of investigating participant acceptance. This will be assessed by measuring attendance frequency and responses to the question "Would you recommend the program to others?" in the online education programs. Additional objectives include investigating participants' satisfaction with the programs and their assessment of the program's completeness. This will be evaluated using quantitative questionnaires. Further, interviews with the individual groups participating in the programs will qualitatively analyze themes of individual expectations and benefits. In phase IV, disease knowledge gain, changes in HRQoL, and overall satisfaction will be investigated within a larger cohort.

Development of the Training Program (Phase I)

Patient Training

In phase I of the education program development, the needs of individuals with ME/CFS were identified (Figure 1). This was achieved through consultations with ME/CFS experts and a literature review on the etiology, symptoms, and both pharmaceutical and conservative treatment options for ME/CFS in children and adolescents. The review was conducted using relevant databases such as PubMed, MEDLINE, and Cochrane Libraries. Additionally, input was gathered from patient organizations, which provided insights into the most common issues and challenges faced by affected individuals. Relevant topics were discussed within an interprofessional team, including members with ME/CFS from patient organizations, experienced physicians, psychologists, physiotherapists, and occupational therapists. Based on these discussions, the content deemed relevant to the affected individuals was selected.

Figure 1. Process of developing the patient education program for affected children and adolescents. ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

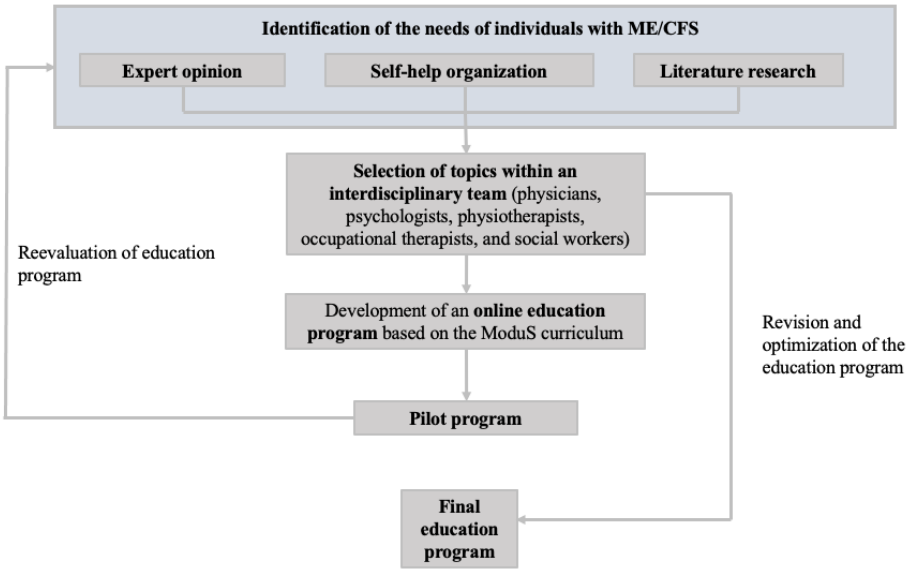

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The foundational structure of the training was based on the modules of the ModuS concept [20], with each training unit having a maximum duration of 45 minutes. This was complemented by customizable pre- and postprogram materials, considering the reduced endurance of patients with ME/CFS. The concept was pilot-tested in an initial program block from March to May 2023. Following this, the concept was reevaluated in collaboration with participants, experts, and patient organizations. Based on the feedback received, the education program was revised by the team, focusing on aspects such as flow, time allocation, and training materials. The final version of the education program was then developed.

Parent, Sibling, and School Staff Training

In addition to the online education program for affected children and adolescents, a slightly modified program concept was developed for parent training. The development process for this program was identical to that of the adolescent and young adult training, including collaboration with the interdisciplinary team and patient organizations. An education program specifically designed for minor siblings of affected individuals was also developed. This program was conceptualized in consultation with individuals affected by the condition and experienced health care providers. Another target audience for the online education program includes teachers and school staff. Given their significant role in the adolescents' environment, it is crucial to inform schools about the condition and work together to determine how to support affected individuals in the educational setting, enabling them to continue participating in education and school life. The development process for this program was identical to that used for the training program for siblings.

After being piloted from March to May 2023, the programs were reevaluated, revised, and optimized.

Recruitment and Implementation (Phase II)

Recruitment

Our specialized tertiary care center for young people with ME/CFS recruited participants up to the age of 20 years for online educational training after confirming the diagnosis during a short inpatient stay. Parents were recruited through the selected participants. Siblings and school personnel were informed about the training opportunities via patient organizations, a website, and the affected individuals themselves.

Implementation

Each training session was conducted by 2 professionals, with at least one having completed the patient trainer certification at the basic competence level according to KomPaS. This certification includes knowledge and skills in patient education as well as didactic tools. A maximum of 14 participants was allowed per training block.

Evaluation (Phases III and IV)

Instruments

The selected measurement instruments include validated scores as well as self-developed questionnaires. Epidemiological data collected are gender, age, and type of school. Educational attainments are also queried from parents and school staff.

The evaluation forms for the different training sessions were developed based on the patient training assessment forms by Meng et al [23] and adapted to the program. These forms include items for assessing the content of the entire education program, as well as specific sessions, the format of the program, group dynamics, and practical usefulness in daily life. They investigate the satisfaction and completeness of the education programs. Response options are provided on a scale of 1=very good to 6=not poor, similar to a grading system. Additionally, 2 open-ended questions are included.

For assessing the perceived burden of the disease and HRQoL, patients complete a questionnaire with selected International Classification of Functioning, Disability and Health (ICF) items [24], the 36-item Short Form Health Survey (SF-36) [24,25], and the Bell score [26]. Parents complete the SF-36 and Bell score. Siblings complete the Large Analysis and Review of European Housing and Health Status (LARES) [27] and the Sibling Perception Questionnaire (SPQ) [28].

The selected ICF items cover domains such as learning, communication, mobility, self-care, household tasks, interpersonal relationships, school/work, and leisure, according to the ICF [24]. These items were selected through consensus among the interdisciplinary team, ensuring a comprehensive representation of important aspects for the participants.

The SF-36 covers 8 areas: physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, mental health, vitality, and social functioning [25].

The SPQ includes questions about interpersonal and intrapersonal difficulties, as well as open communication with other caregivers about the disease. Responses are provided on a 4-point Likert scale (0=never to 4=always).

The LARES questionnaire is a screening tool for detecting distress in healthy siblings. It covers topics such as sibling relationships, social integration, family burden, school competence, and knowledge about the illness [27]. Response options are provided on a 4-point Likert scale (0=never/not at all to 4=always/very strongly).

For phase IV, the questionnaires will be adapted and shortened for the rollout.

Procedure

The evaluation will involve a quantitative analysis of the questionnaires and a qualitative analysis of the interviews (Figure 2).

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Figure 2. Overview of the evaluation of the study. ICF: International Classification of Functioning, Disability and Health; LARES: Large Analysis and Review of European Housing and Health Status; ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; SF-36: 36-item Short Form Health Survey; SPQ: Sibling Perception Questionnaire.

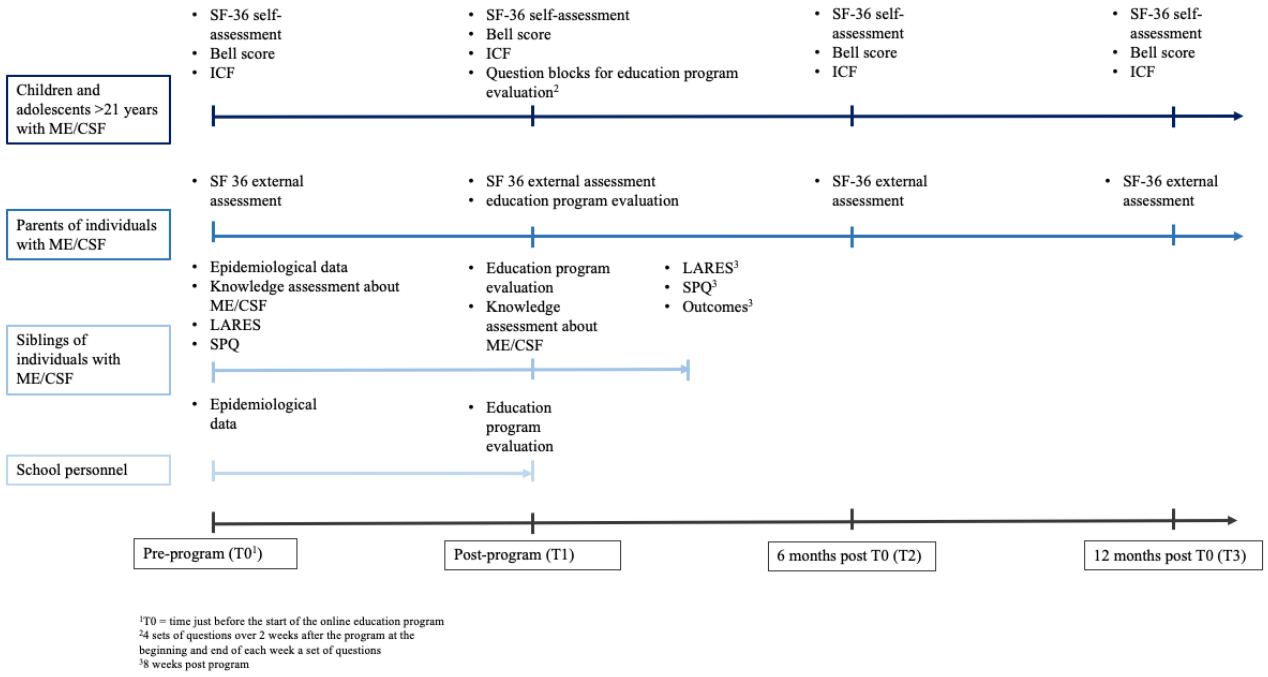

During recruitment, participants were invited to consent to receiving quantitative questionnaires. Participants with ME/CFS who agreed were surveyed at baseline, before the start of the online education program (T0). They were assessed regarding their participation, HRQoL, and perceived burden using selected ICF participation goals, the SF-36 questionnaire, and the Bell score. This baseline assessment aimed to evaluate the feasibility of the instruments for phase IV. The same questionnaires are administered immediately after the training (T1) and again at 6 and 12 months after the training (T2 and T3). Given the participants' low energy levels, a total of 4 questionnaire blocks containing 10 questions each will be sent over 2 weeks, starting at the end of the training (T1). Responses will be recorded and submitted using a mobile device and will be qualitatively analyzed after transcription. Parents will complete the SF-36 questionnaire at baseline (T0) and immediately after the training (T1) for external assessment. Additionally, at T1, participants will receive questionnaires related to training evaluation. School staff will be surveyed at baseline (T0) for epidemiological data and will receive a training evaluation questionnaire immediately after the training (T1). Siblings will be surveyed at baseline (T0) for their epidemiological data and knowledge about the ME/CFS condition. Their daily burden due to their sibling's chronic disease will also be assessed using the LARES and SPQ questionnaires. Following the training (T1), questionnaires are sent to evaluate the training and assess participants' knowledge about the condition. Additionally, 8 weeks after completing the training, the LARES and SPQ questionnaires are administered, along with an assessment of the training's impact on participants' satisfaction.

For further qualitative investigation of the training program, semistructured interview guides were developed for school personnel, siblings, and parents by a multidisciplinary team. These interviews will be conducted after the completion of the programs. The guides aim to capture the impact of the education program on participants, as well as their individual expectations and perceived benefits.

In phase IV, the rollout of the program is planned for 150 children and their caregivers. The evaluation will focus on disease knowledge, HRQoL, life satisfaction, family burden, and longitudinal assessment at the following time points: T-1 (registration), T0 (before the start), T1 (after completion), T2 (6 months after completion), and T3 (12 months after completion).

Data Processing

The data platform REDCap (Research Electronic Data Capture; Vanderbilt University) is used for sending out questionnaires and storing data. A separate database was created for each survey, containing the corresponding questionnaires. If training participants agreed to participate and provided their email addresses, their information was entered into the databases. Questionnaires are sent as links in emails at the designated time points. Each study participant is assigned an ID, which is linked to their corresponding email address in a separate document. This document is stored in a manner that allows only study staff with access to trace back the identity. Linking will only occur for combining the SF-36 self-assessment and external assessment by the participants and their parents. All other questionnaires will be stored and analyzed anonymously. In cases of missing or incomplete questionnaire responses, participants will receive reminder emails after 1 week. Audio files containing responses to questionnaire sections can be uploaded and stored using the clinic's internal data exchange program, "fex." Transcription backups will be stored exclusively

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on the clinic's secure server. The analysis will be conducted using pseudonymized data only.

Statistical Analysis

The study follows an exploratory approach. The goal is to obtain responses from 30 participants for the quantitative surveys, which is projected to provide sufficient statistical power to assess acceptability. This will be measured by the variable "Would you recommend the program to others?" on a scale from 1 to 6, with responses dichotomized as follows: 1-2=high acceptance and 3-6=low acceptance. Based on the EduKids study, which involved staff training on diabetes [29], a comparable proportion of 87% with high acceptance is assumed. A sample size of 30 participants is deemed sufficient to estimate the proportion of individuals with high acceptance of the training at 87%, with a precision of 12% (half the width of the 95% CI according to the Wilson score). The quantitative questionnaire data will be analyzed using SPSS software (version 29.0.1.1; IBM Corp.). Questionnaires from different training programs will be analyzed separately.

Epidemiological data of participants, as well as their satisfaction, perceived usefulness, completeness of the modules, knowledge gain, and acceptance (in terms of attendance rates) across different training programs, will be represented through descriptive analyses, including means and SDs. For categorical variables, such as gender and severity of disease, results will be presented using both relative and absolute frequencies. The perceived burden of the disease will be assessed through various specific questionnaires (SF-36, Bell, LARES, and SPQ) and analyzed using descriptive statistics. Changes in these variables before and after the programs will be analyzed using statistical tests for dependent samples, such as the paired 2-tailed *t* test.

A significance level of $P \leq 0.05$ will be assumed for all procedures.

Qualitative Analysis

In the qualitative analysis of interviews, an exploratory analysis will focus on themes related to individual benefits and satisfaction. Achieving saturation is not a specific target.

Interviews with parents, siblings, and school staff will be conducted using semistructured interview guides. The questions will be developed through collaboration between interdisciplinary teams and external researchers with expertise in qualitative analysis, through multiple discussion rounds. As a result of the dispersed geographical distribution of participants, all interviews will be conducted online and recorded. The recordings will be pseudonymized and transcribed verbatim. The analysis will be carried out using MAXQDA software (VERBI Software). Category creation will involve both deductive approaches, based on themes outlined in the interview guide, and inductive approaches, derived from the data. The qualitative content analysis method by Kuckartz [30] will be used as a guideline. After an initial analysis of the material, all transcripts will be independently analyzed again by a second person, with categories formed using the same process. The analyses and categories from both iterations will be discussed within the team, and the material will be reanalyzed based on the revised categories. The analyses were regularly discussed and debated within an interdisciplinary team consisting of physicians, psychologists, physiotherapists, social workers, and occupational therapists. Upon reaching a consensus, a category handbook will be created, and the results will be presented using hierarchical code-subcode models and word clouds.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the University Hospital of the Technical University of Munich approved the BAYNET FOR ME/CFS study (approval number 2023-1-S-KH). Additionally, the Ethics Committee of Julius-Maximilians-University approved the conduct of the training evaluation on August 11, 2023 (approval number 71/23). Written informed consent will be obtained from participants or, for children under 18 years, from a parent or legal guardian after recruitment. Participation is voluntary, and there will be no consequences for not participating or completing the study. The confidentiality and privacy of participants' information will be protected by deidentifying the data and using a secure, encrypted, and password-protected database for storage.

Results

Piloting

All programs were pilot-tested in an initial phase from March to May 2023, as part of phase I. Participants were recruited through a patient organization and advertisements on the institute's website. In total, 8 patients and their parents, 5 siblings, and 59 school staff took part in the piloting. Participants who participated in the pilot testing were not eligible to participate in the finalized online education programs.

Finalized Online Education Programs

In total, 4 programs were developed for young individuals with ME/CFS, their parents, siblings, and school staff. In the final version of the online education program for young individuals with ME/CFS, the generic modules on introduction and disease management were placed at the beginning and end of the program, following the ModuS curriculum (Table 1). As a result of the limited endurance of patients, the content was condensed and shortened. Each unit included brief practical sequences alongside theoretical input and group discussions. Theoretical content was regularly reviewed with the affected individuals, individual barriers were identified, and collaborative solutions were developed within the group. Presentations for each program unit were created in consultation with patient organizations and included a comic story. Before the education program sessions, participants can familiarize themselves with the topics through these comics or short videos/podcasts, along with small preparatory tasks. For the postsession phase, each unit's content is summarized in an age-appropriate comic, which will be provided to participants for reflection and as a reminder.

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Table 1. Overview of units of the online ME/CFS[a] education program for children and adolescents with ME/CFS based on the ModuS curriculum[b].

ModuS modules[c]	Description of modules	Program units	Content	Methods/materials	Profession of trainer
0 + I + II[b,d]	Introduction and motivating education about the illness, treatment, and prognosis	1. Introduction	Introduction, team presentation, group formation, disease education, symptoms, and introduction to pacing diary	Training materials, group discussions, and surveys	Physician
III + IV[e]	Skills and motivation for low-symptom intervals and skills for regulating and avoiding acute crises: emergency management	2-3. Breathing and relaxation exercises and strategies	Reflection on previously known relaxation strategies, importance and benefits of relaxation techniques, and teaching of relaxation and breathing exercises (diaphragmatic breathing, body scan, progressive muscle relaxation, guided imagery)	Training materials, breathing exercises, and surveys	Physiotherapist
II + IV[e]	Motivating education about the illness, treatment, and prognosis and skills for regulating and avoiding acute crises: emergency management	4-5. PEM[f]/crash	Reflection on individual stressors, definition of PEM, strategies for managing PEM, and exercise for applying pacing to prevent PEM	Training materials, group discussions, and surveys	Occupational therapist
III + IV[e]	Skills and motivation for low-symptom intervals and skills for regulating and avoiding acute crises: emergency management	6-7. Pacing	Definition of pacing, pacing rules, energy-saving techniques, and development of individual pacing strategies	Training materials, surveys, and group discussions	Occupational therapist
III + IV[e]	Skills and motivation for low-symptom intervals and skills for regulating and avoiding acute crises: emergency management	8-9. Additional therapies	Current medication treatment options, main pillars of ME/CFS therapy, treatment options for sleep disorders, circulatory issues, pain, and brain fog	Training materials, surveys, and group discussions	Physician
V[d]	Disease management within the family system	10-11. Disease management	Current emotional energy drains, teaching emotion regulation strategies, and practice for recognizing one's own emotional capacity	Training materials, surveys, individual work, and group discussions	Psychologist
VI[d]	Conclusion	12. Open discussion	Formulating personal goals for the future, feedback opportunities, and conclusion	Surveys and group discussions	Physician

[a]ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

[b]The unit includes topics from both cross-disease and disease-specific modules.

[c]All modules are conducted by 2 trainers, with the lead professional for each session indicated in the table. Either a physician or a psychologist participates in every session to ensure the continuity of the program.

[d]Generic modules.

[e]Diagnosis-specific modules.

[f]PEM: postexertional malaise.

All online program units for the affected individuals were conducted in the early afternoon and were scheduled for 45 minutes. Participants had the option to end the session early if they felt exhausted. During the project, 2 training blocks, each consisting of 12 sessions, were conducted, involving a total of 24 participants. Each training unit was led by 2 trainers with at least one certified as a ModuS patient trainer. The objective was to empower the affected individuals to become "experts" in managing their own condition.

For the parents' online education program, in addition to information about ME/CFS, care strategies, and therapy, social, legal, and educational topics were included. The units were tailored to the needs of parents (Table 2). The focus was on current treatment approaches, particularly pacing, as well as relaxation and breathing techniques, which are central to ME/CFS therapy. Parents were given the opportunity to address emotionally distressing experiences related to ME/CFS. The parental program consisted of 4 evening sessions, each conducted online and lasting 1.5 hours. Similar to the program for affected patients, it was designed to support and inform parents in managing their child's condition.

In addition to providing information about the disease, the siblings' program focused on the experiences of siblings and offered them an opportunity to share their thoughts. The program was based on the ModuS sibling workshop but was condensed to fit an online format within 1 afternoon. For school staff, an online education program was developed to provide information about ME/CFS and its symptoms, as well as strategies for supporting affected individuals within the educational setting.

Both the sibling and school staff training sessions consisted of 90-minute online meetings held in the evening via a conventional online platform.

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Table 2. Overview of modules of the online ME/CFS[a] education program for parents of children and adolescents with ME/CFS based on the ModuS curriculum[b].

ModuS module	Module description	Program units	Content	Methods/materials	Profession of trainer
0 +I + II + V[b,c]	Introduction and motivational education on illness, treatment, prognosis, and disease management within the family system	1. Disease pathogenesis and coping	Introduction, team introduction and training structure, explanation of ME/CFS pathophysiology and symptoms, and presentation of the 5-phase model of illness coping and coping strategies	Training materials, small group activities, and surveys	Physicians and psychologists
III + IV[d]	Skills and motivation for low-symptom intervals and skills for regulating and avoiding acute crises: emergency management	2. Breathing and relaxation exercises and strategies and pacing	Importance and benefits of relaxation techniques as well as teaching relaxation and breathing exercises (diaphragmatic breathing, body scan, muscle relaxation, and guided imagery)	Training materials, breathing exercises, and survey	Physiotherapists and occupational therapists
II + IV + V[b,c]	Motivational education about the illness and skills for regulating and avoiding acute crises: emergency management and disease management within the family system	3. Therapy options and management of disease	Presentation of conservative treatment measures for the most common symptoms of ME/CFS, reflection on individual family challenges, effects of chronic stress, guidance for dealing with stress and promoting emotional stability, and reflection on challenges and strategies for dealing with the social environment	Training materials, surveys, and group work	Physicians and psychologists
III + IV[d]	Skills and motivation for low-symptom intervals and skills for regulating and avoiding acute crises: emergency management	4. Social legal aspects and school	Information on social legal entitlements and presentation of various educational participation options	Training materials	Social workers

[a]ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome.

[b]The unit includes topics from both cross-diseases and disease-specific modules.

[c]Generic modules.

[d]Diagnosis-specific modules.

Implementation of the Education Programs

The goal of recruiting 30 patients was not achieved, as some patients had previously participated in in-hospital training and declined to join the online program. Recruitment of siblings was also unexpectedly low despite advertising through various channels. Between January 2024 and June 2024, the study successfully recruited 24 young patients with ME/CFS and their parents, along with 8 siblings and 51 school staff. The participants agreed to take part in both the programs and their evaluation. The online education programs, which included 2 program blocks for patients and parents and 2-3 blocks for siblings and school staff, commenced in May 2023 and concluded by the end of October 2023. All participants were surveyed at baseline (T0) before the programs began, and ongoing evaluations will continue through the end of 2024. Data analysis will begin after the completion of the programs and is anticipated to be finalized by the end of 2024.

During recruitment, participants had the option to agree to interviews. From those who consented, 3 participants attending school and 3 participants not attending school were selected for interviews after completing the program, along with parents who agreed to participate in interviews. Additionally, for siblings and school staff, 6 individuals who consented to interviews were randomly selected after the program concluded.

In phase IV, the rollout of the program is planned for 2025-2026, targeting 150 children and their caretakers. This phase will focus on investigating disease knowledge, HRQoL, life satisfaction, family burden, and conducting a longitudinal evaluation.

Discussion

Overview

Currently, there are only a few specific and regionally limited health care options available for children and adolescents with ME/CFS. Educational programs for both patients and their social environment represent a crucial step toward providing comprehensive care for these individuals. This study aims to design, implement, and evaluate an online education program for children and adolescents with ME/CFS, as well as for their social environment, including parents, siblings, and school personnel. The training programs are developed based on the ModuS training concept [20] and aim to empower participants in the self-management of ME/CFS. They provide a comprehensive understanding of the disease and promote exchange among those affected.

Primary Findings

In contrast to typical standardized education concepts, the ME/CFS education programs for all target groups were designed as online offerings. For patients, these online sessions allowed

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participation even when leaving the house or bed is not possible. By offering the training program online, adolescents could receive disease-specific education and connect with other affected individuals. Additionally, the program sessions could be attended from various positions, such as lying down, which minimizes physical exertion. Participants could also shorten their involvement if their energy levels declined during the session. The elimination of the need to commute further alleviated the burden on this group. Most electronic devices, such as PCs, laptops, and mobile phones, equipped with cameras, enabled virtual introductions and direct interactions among participants. Hence, the core advantage of this patient education program—interaction and networking—remained intact in the digital format.

For parents, who are often constrained by the care of affected children and the bureaucratic demands associated with the disease, the online format provides a practical solution. It eliminates the need for time-consuming travel and offers flexibility, allowing them to participate from various locations. Similarly, for siblings, the online format reduces barriers to participation, enabling them to connect easily and participate without needing parental support for mobility.

In the professional realm, online events have become increasingly common, particularly due to the COVID-19 pandemic, and are now widely offered and appreciated [22]. Consequently, the education program for school staff was also designed as online sessions to maximize reach, leveraging the accessibility and time efficiency of this format.

The design of the education programs accounted for the individual needs of each participant beyond the digital format. Given that ME/CFS is often associated with significant fatigue and reduced concentration spans [14], the education program units for patients were kept brief and included minimally taxing practical exercises. Therefore, each unit was limited to 45 minutes. To mitigate the risk of PEM associated with ME/CFS [6], participants were encouraged to assess their energy levels at the start, midway, and end of each session. A short break was provided midway to prevent overexertion. Participants were also informed that they could leave the session early if they reported low energy levels. Trainers did not exclude any participants due to low energy, as managing one's own resources was a central learning objective of the training.

Given the time limitations of each unit, preparatory and follow-up materials, including podcasts, were developed for each training session. This approach allows participants to review these materials at their convenience, according to their energy levels. To enhance comprehension for children and adolescents, materials were presented visually as comics, avoiding lengthy text passages. Videos and podcasts were incorporated to support multisensory learning and facilitate information absorption.

The ModuS curriculum was initially developed for managing rare or chronic diseases [20]. Its positive impact on disease management and HRQoL has been consistently demonstrated in various studies [16,31].

The modular structure of the ModuS concept, which provides predefined topics with a high degree of flexibility, allows for the customization of content to meet the specific needs of individuals with ME/CFS and their social environment. Efforts were made to select content that is most relevant to patients with ME/CFS, their parents, siblings, and school staff.

Consistent with the ModuS concept, the training for patients extended beyond medically relevant subjects to encompass psychosocial themes that are common across chronic diseases [20].

The training sessions for parents were designed to cover essential aspects such as navigating their child's illness, communicating it in a child-friendly manner, and accessing specialized medical support [6]. Given that the disease imposes various burdens on parents [32,33], which can significantly affect daily family life, the training aimed to address these challenges comprehensively. Therefore, the program not only addressed the origins and treatment of the disease but also dedicated an entire session to disease management. Recognizing that parents of patients with ME/CFS often lack information about social and legal aspects [32], these topics were incorporated into the program through collaboration with social pedagogues. This approach aimed to provide a comprehensive understanding of the various dimensions of managing ME/CFS and its impact on families.

The content for the sibling training was selected based on the unique challenges faced by siblings of children with chronic illnesses. These illnesses can place burdens on siblings as well [34], potentially leading to feelings of shame, jealousy, and anxiety [6]. Additionally, there may be a redistribution of resources, such as time spent with parents, increased family stress, and social challenges [

35]. This training primarily focuses on providing a child-friendly explanation of the illness. Additionally, it aims to foster understanding of the disease and empathy for the affected family member. The sibling training emphasizes facilitating interaction among affected siblings and creating a platform for them to express their needs, questions, uncertainties, and fears.

Limitations

This study has several limitations. First, the number of participants is limited, and their participation in both the program and the evaluation is voluntary. This may result in a disproportionate representation of less severely affected patients, who might be more capable of taking part in the program and evaluation, potentially biasing the responses. Additionally, this could lead to higher acceptance rates compared with more severely affected patients, who may be less able to participate due to the severity of their condition. However, we plan to address this by conducting interviews and qualitative analyses that include patients with varying degrees of disease burden, incorporating these results into the overall assessment. Second, patients were recruited from only 1 center, which may disproportionately represent individuals from a specific region. Nevertheless, this is the only center in Germany for young patients with ME/CFS, ensuring accurate diagnosis and adherence to the inclusion criteria. Lastly, the evaluation of the

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program is conducted immediately after its completion, so no conclusions can be drawn about the long-term effects of the programs in phases I-III.

Conclusions

This study protocol outlines the study design, goals, conceptualization, and implementation of newly developed online training programs for individuals up to the age of 20 years with ME/CFS, as well as their parents, siblings, and school staff. The primary aim of the training is to enhance disease knowledge and empower affected individuals to manage their own condition. Individuals with ME/CFS often face significant limitations in social participation due to restricted mobility. Online training programs not only support affected individuals in managing their disease but also foster social participation through interactions with others who are similarly affected.

However, the impact of the disease extends to the social environment, including parents, siblings, and school personnel. There is a notable knowledge gap in these groups, which the training programs, as part of an interprofessional care model, aim to address. The newly established interdisciplinary training program, based on the ModuS principle for ME/CFS, can make a valuable contribution to raising awareness about the condition and expanding regional coverage, thereby significantly enhancing the care of children and adolescents with ME/CFS.

Following a positive evaluation, plans are underway to establish train-the-trainer programs to facilitate the widespread implementation of ME/CFS training as part of a standardized care model for affected children and adolescents. The high demand for the pilot training programs underscores the need for such initiatives, not only among affected individuals but also among parents, school staff, and siblings. In the future, multiple training blocks are planned to be offered throughout the year, contributing to comprehensive care. These programs will be adjusted and improved based on the initial evaluations.

Acknowledgments

This study was funded by the Bavarian State Ministry of Science and Art as part of the BAYNET FOR ME/CFS project (Bavarian Network for Research on ME/CFS). JS, UB, and BV conceptualized and designed the study. We have applied for further funding to conduct phase IV.

Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

UB acquired funding and coordinated the BAYNET FOR ME/CFS project. JS coordinated the education program. UB, BV, CW, CZ, DBRH, ME, M Saramandic, NPSS, RJ, SA, SE, SS, JS, UB, JE, M Schottdorf, NS, NLR, VD, LS, JT, and KD developed the online education programs. Trainings were led by JS, JE, M Schottdorf, NPSS, NLR, VD, LS, KD, and JT. JE, Mara S, JS, NS, NLR, VD, LS, JT, and KD conducted the pilot tests. All authors contributed to the subsequent revisions of the education programs. FK drafted the manuscript. All authors have read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EUROMENE: European Network on ME/CFS
HRQoL: health-related quality of life
ICF: International Classification of Functioning, Disability and Health
KomPaS: Competence Network for Patient Education
LARES: Large Analysis and Review of European Housing and Health Status
ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome
PEM: postexertional malaise
REDCap: Research Electronic Data Capture
SF-36: 36-item Short Form Health Survey
SPQ: Sibling Perception Questionnaire

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Protocol

mHealth Apps in German Outpatient Mental Health Care: Protocol for a Mixed Methods Approach

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Abstract

Background: Mental disorders are complex diseases that affect 28% (about 17.8 million people) of the adult population in Germany annually. Since 2020, certain mobile health (mHealth) apps, so-called digital health applications (DiGA), are reimbursable in the German statutory health insurance system. A total of 27 of the 56 currently available DiGA are approved for the treatment of mental and behavioral diseases. An indicator of existing problems hindering the use of DiGA is the rather hesitant prescribing behavior.

Objective: This project aims to develop health policy recommendations for the optimal integration of DiGA into outpatient psychotherapeutic care. The project is funded by the Innovation Fund of the Joint Federal Committee (grant 01VSF22029). The current status quo of the use of DiGA will be analyzed. Furthermore, concepts for the integration of mHealth apps, as well as their transfer into the care process will be investigated. In addition, barriers will be identified, and existing expectations of different perspectives captured.

Methods: The project will be based on a mixed methods approach. A scoping review and a qualitative analysis of focus groups and expert interviews will be carried out. Additionally, an analysis of claims data of the statutory health insurance will be conducted. This will be followed by a written survey of insured persons and health care providers. Finally, health policy recommendations will be derived in cooperation with stakeholders.

Results: The scoping reviews and qualitative analyses have been completed, and the quantitative surveys are currently being carried out. The target number of responses in the survey of insured persons has already been achieved. Furthermore, the analysis claims data of the statutory health insurance is currently being conducted.

Conclusions: There is a need for research on how DiGA can be optimally integrated into the care process of patients with mental disorders as evidence regarding the topic is limited and prescribing behavior low. Although the potential of DiGA in mental health care has not yet fully unfolded, Germany serves as a model for other countries regarding reimbursable mHealth apps. This project aims to explore the potentials of DiGA and to describe the organizational, institutional, and procedural steps necessary for them to best support mental health care.

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KEYWORDS

mental health care; mHealth; digital health applications; Digitale Gesundheitsanwendungen; mental disorders; health care research; applications; app; mental health; outpatient; digital health; adults; Germany; mobile health apps; treatment

Introduction

Background

Every year, approximately 28% of the adult population in Germany (approximately 17.8 million people) is affected by a mental disorder. Their prevalence has increased in the recent years [1]. Among these complex conditions, the most common include anxiety disorders, mood disorders, and disorders relating to substance misuse [2]. For patients and their relatives, mental illnesses cause significant personal and health-related burdens [3]. Further, mental disorders can lead to major challenges for society, such as prolonged sick leave. For example, Germany's largest statutory health insurance (SHI) company—Techniker Krankenkasse (TK)—found that 20% of all absences at work could be attributed to mental disorders in 2020, which is the highest level since records began [4].

In Germany, a multifaceted support and health care system is in place for people having from mental disorders. The treatment costs are predominantly borne by SHI. Depending on the illness and its burdens, easily accessible psychosocial interventions, psychotherapeutic treatments and other types of therapy are available to patients [5]. However, when it comes to the psychotherapeutic treatment itself, issues relating to access and interface problems can arise. Insured persons wanting to access outpatient psychotherapy often have to contact various psychotherapists before finding long-term therapy provisions. This requires skills such as health literacy and self-management. These skills can help individuals to make the necessary efforts. Since not all potential patients have these competencies, some groups are disadvantaged, and therefore, at risk of disease progression up to a chronic level [6].

Mobile health (mHealth) apps represent one possibility for reducing problems associated with access and improving the health care provision currently available [7]. In this paper, smartphone apps, as well as browser applications, are meant by this term. They provide an easily accessible option for improving access to treatment, especially in the case of disorders that are often accompanied by stigmatization and shame, such as mental disorders. Moreover, mHealth apps can be used to support outpatient treatment and be integrated into relevant processes [8].

Since the Digital Act (Digitale-Versorgungs-Gesetz) in 2019, health care providers in Germany have been able to prescribe reimbursable digital health applications (Digitale Gesundheitsanwendungen or DiGA in German) also known as "apps on prescription." In September 2020, the first DiGA was approved for inclusion in the official DiGA directory of the Federal Institute for Drugs and Medical Devices [9]. DiGA are a digital-technology-based medical device (Medical Device Regulation—Class I, IIa or IIb) [10]. In principle, a DiGA may be either a native app or a desktop or browser application. DiGA can also include other hardware such as virtual reality glasses. These apps support the detection, monitoring, treatment, and alleviation of medical conditions but are not permitted for use as primary prevention [10]. For mHealth apps for mental disorders to be reimbursed by the SHI in Germany, they must undergo an assessment process and prove a positive impact on health care. This positive impact may be either a medical benefit or a patient-relevant structural or procedural improvement [10]. The so-called "Fast Track Process" is an initial admission procedure for inclusion within the DiGA directory, which allows them to be reimbursed by the SHI [10]. This process requires potential DiGA to prove their positive health care impact through comparative studies. As a minimum standard, retrospective studies are required. However, in most cases, randomized controlled trials are carried out in order to fulfill this evidence requirement [10].

mHealth apps in general, and DiGA specifically, enable new approaches to and methods of treatment, in which the patients become independent actors with regard to the management of their illnesses. These apps have the potential to enhance the insured person's ability to self-manage and reflect on their illness, for example, by symptom recording and awareness exercises [11]. In addition to allowing patients to proactively influence their treatment, data, and information collected by mHealth apps and DiGA can also be used to optimize existing treatment processes and reduce liaison issues between different health care sectors potentially enhancing the quality of care provided [12].

However, the use of DiGA is still relatively infrequent in Germany. One projection has revealed that only 374,377 DiGA codes had been generated by September 2023 [13]. Further, the potential of DiGA is restricted by a high user dropout rate. Studies observing people with chronic illnesses have estimated dropout rates of up to 43% [14]. Barriers to fully using the potential of mHealth apps include poor user-friendliness, patient fears concerning insufficient contact with a health care provider, and apps' limited ability to be adapted to patients' individual needs [14].

Project Objective

The objective of the project "Realizing the Potential of Digital Health Applications (DiGA) in Outpatient Mental Health Care (DiGAPsy)" is to develop public health policy recommendations—in terms of a blueprint—for optimizing the incorporation of DiGA within mental health care. The project is funded by the Innovation Fund of the German Federal Joint Committee (grant 01VSF22029). One focus of the project will be to combine the use of DiGA with traditional components of outpatient (mental) health care. This will include looking at the potential of DiGA as a stand-alone treatment—for example, for mild mental disorders—as well as the potential of bridging waiting times and the possibility of integrating DiGA within the psychotherapeutic and psychiatric treatment process itself. The project will also examine how and in which situations DiGA can be used. Different options for the integration of mHealth apps such as a substitute or a supplement to traditional forms

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of care will be analyzed. Ensuring an optimized incorporation of DiGA within health care provision is essential. To achieve this, it is necessary to mitigate existing provision deficits and to prevent problems relating to unsuitable use of DiGA, as well as liaison issues. This research aims to promote both the purposeful deployment of DiGA and a patient-centered approach to the incorporation of DiGA within health care provision to improve the quality of care.

Research Questions

This project will address the following research questions:

- What approaches to the incorporation of mHealth apps within mental health care exist nationally and internationally? What are the potential areas for application in terms of outpatient mental health care?
- What are the current barriers preventing DiGA from being implemented and used by health care providers (the term "health care providers" refers to both physicians and psychotherapists) and patients both in Germany and internationally?
- How are DiGA currently used for the treatment of patients with mental disorders? (Status quo)
    - Can key areas of application be identified? Who is prescribing DiGA, what indications are DiGA prescribed for, under which circumstances are they prescribed, and for what type of patients?
    - What is the perspective of patients and health care providers on the integration of DiGA within the treatment process?
        - Within which diagnostic and therapeutic treatments are DiGA used and how often (number of follow-up prescriptions)? (Prescription patterns)
        - For what purpose, at which stage of the illness, and for how long are DiGA used by patients? (Use patterns) Can specific patient journeys be identified?
        - Under what circumstances do patients use DiGA without a prescription from their health care provider?
- What are health care providers' and patients' preferences when it comes to the design, areas of application, and organizational structures of DiGA and what expectations do both groups have in terms of the integration of these apps within mental health care? What barriers prevent a more extensive incorporation of DiGA within mental health care and at which points of the care provision process do these barriers arise?
- What recommendations can be derived based on the results both for integrating DiGA within mental health care and for ensuring good coordination between the DiGA and the various health care providers?
    - Which adjustments are necessary in different care settings to sustainably and economically realize the innovative potentials of DiGA for patients with mental disorders?
    - How can these viable recommendations be institutionally and procedurally implemented? (Implementation)

Recommendations derived from answering these questions will outline the organizational, institutional, and procedural steps necessary to ensure that DiGA provide optimized support for the treatment of patients with mental disorders. These recommendations will determine how these apps can be used in a manner that maximizes their potential effectiveness.

Methods

Overview

A mixed methods approach will be used based on three different complementary and consecutive project stages. The mixture of research methods enables to integrate all relevant perspectives on the research topic into the project. Relevant approaches to the integration of mHealth apps within mental health care will be identified and the transferability to the German health care system examined. In addition, current treatment practice, as well as the barriers preventing more extensive incorporation of DiGA, will also be assessed. Based on this information, recommendations for optimizing the incorporation of DiGA within mental health care will subsequently be derived with the ultimate objective of improving the quality of care. Figure 1 illustrates the study design.

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Figure 1. Project overview—DiGAPsy.

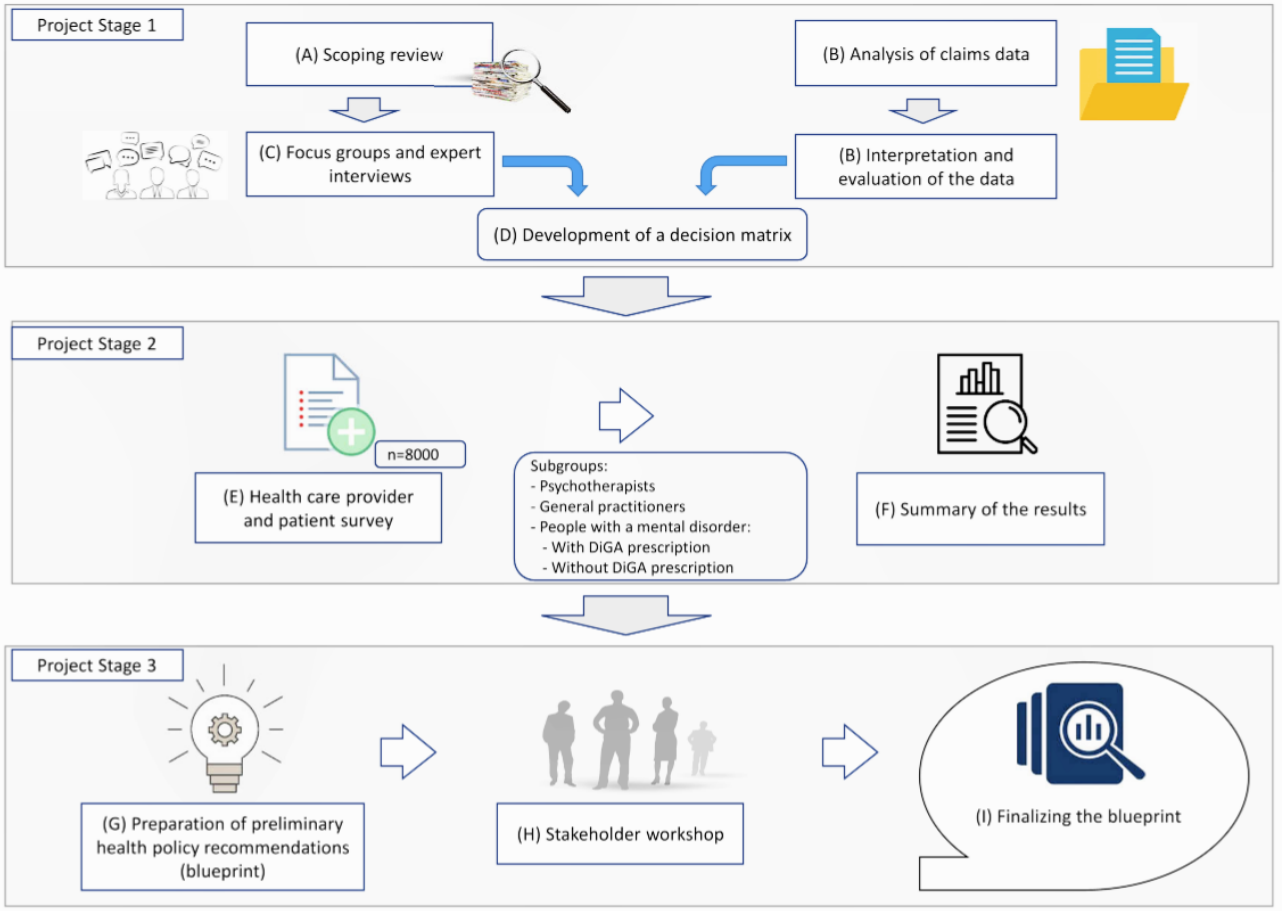

Project Stage 1

Overview

Project stage 1 will examine research questions 1 to 3 and is divided into four modules. The results from project stage 1 will function as a base for the analytical steps to be carried out in project stages 2 and 3.

Module A: Scoping Review

The first module aims to identify national and international evidence regarding (1) approaches to the integration of DiGA and DiGA-equivalent mHealth apps within mental health care and (2) the barriers that hinder the optimized incorporation of these apps within outpatient care provision. The objective is to identify best practice models and the relevant parameters for the implementation of DiGA.

Therefore, a scoping review will be carried out [15] and for compilation and reporting purposes, the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist will be used [16]. Title and abstract screening, as well as the full-text screening, will be carried out by two researchers (FP and SSolar) independently of each other.

The identified approaches to the incorporation of DiGA within mental health care will be used as a base for the subsequent development of a decision matrix. The results of the scoping review will be published in a subject-related journal.

Module B: Analyzing Claims Data of the SHI

This module aims to analyze the prescription and use patterns, as well as the current incorporation of DiGA treatment pathways. Data for the analysis are based on SHI claims data of the TK. The TK is the largest German SHI in terms of number of insured persons, providing insurance to 11.2 million people [17].

The analysis will include data of adult insured persons of 18 years or older who received an ICD-10-GM (German Modification of the International Statistical Classification of Diseases and Related Health Problems) F-diagnosis (mental and behavioral disorders) and a DiGA in the category of mental disorders during the index period. A matching analysis is carried out to compare patient journeys. For this purpose, a control group consisting of people older than 18 years who have received an *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) F-diagnosis and no DiGA is included.

The index period will be from Q4 2020 to Q1 2022. The observation period for the included persons will cover a total of 2 years: 12 months prior to the DiGA and 12 months subsequent to this. Figure 2 illustrates the planned procedure.

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Figure 2. Routine data collection - DiGAPsy.

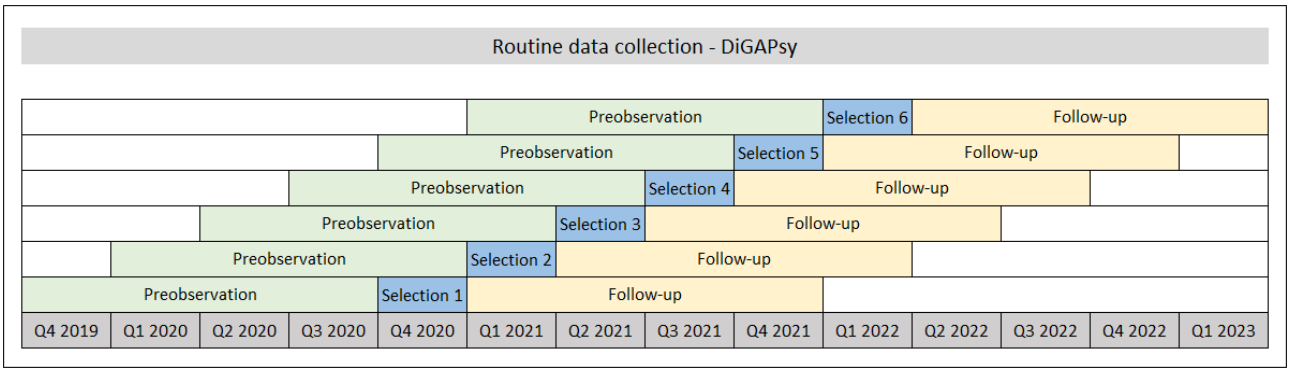

A descriptive and multivariate analysis of current key areas of application, prescription, and use patterns, as well as patient journeys, will be carried out, taking into consideration aspects such as patient characteristics and use of other health care options. Furthermore, the patient journeys and patient characteristics will be compared to those of non-DiGA users identified by a matching approach.

Univariate and bivariate analyses will be carried out. Depending on the variable, frequencies, mean or median values will be compared, alongside statistical significance testing. Subgroup analyses will also be performed, for example, based on different diagnosis indications.

Module C: Focus Groups and Expert Interviews

The objective of this module is to answer research questions 1 (approaches, best practice, potential areas of application) and 2 (barriers), factoring in results from the scoping review (module A).

To consider the perspective of psychotherapists and physicians, as well as of patients (DiGA-using and non–DiGA-using), 8 focus groups of approximately 6 persons will be carried out. Additionally, 12 semistructured interviews will be conducted to incorporate other relevant perspectives, such as those of medical associations, SHI companies, and DiGA developers. To motivate individuals to participate, financial incentives will be provided. A declaration of informed consent has to be signed by participants to ensure voluntary participation and confidentiality.

Following Krueger and Casey [18], the focus groups and interviews will be guided by a team of moderators. These will be based on semistructured interview guides, which will allow the integration of findings from the literature review (module A) and provide flexibility to explore any additional aspects that have not yet been specifically identified. The guides will be adapted to the specific target groups, whilst also attempting to ensure results demonstrate a certain level of comparability.

The focus groups and interviews will primarily take place via a videoconferencing system. There will be a video recording, which will be transcribed afterward. A qualitative content analysis will then be carried out following Mayring and Kuckartz using the software MAXQDA (VERBI GmbH) [19,20].

Module D: Development of a Decision Matrix

The objective of this module is to systematically summarize the project results from module A (scoping review) and module C (focus groups and interviews).

Module D will result in the establishment of a 2D decision matrix for preparing the policy recommendations. Furthermore, the matrix will enable best practice models to be examined in the context of existing barriers both of which will have been identified in modules A and C. Subsequently, the results from the claims data analysis will be incorporated into the decision matrix (module B).

Project Stage 2

Overview

Project stage 2 will implement modules E and F to address research questions 2 to 4 (barriers, status quo, and expectations). The results from project stage 1, particularly the decision matrix from module D, will be used for drafting the survey.

Module E: Patient and Health Care Provider Survey

Overview

This module will involve collecting primary data using a survey questionnaire. The target groups for this survey will be patients insured by TK who have mental disorders (group A) and health care providers (group B). Both surveys will be carried out anonymously. Respondents will be informed about the study and the voluntariness of participation. For the written surveys, samples of at least 201 respondents will be necessary to determine statistically significant mean differences with a power of 90% and α value of .05 for a moderate effect size for the four groups (groups A1, A2, B1, and B2). Accordingly, 2000 people per group will be contacted.

Patient Survey (Group A)

Two patient groups will be analyzed. DiGA users will be surveyed to collect information relating to the use and incorporation of DiGA within health care provision from the perspective of the patient. Additionally, nonusers will be included to analyze potential barriers. Both groups will be recruited by the TK according to the inclusion and exclusion criteria:

- Group A1: adults who will have received reimbursement for at least one DiGA for an *ICD-10* F-diagnosis in Q1 2023.

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- Group A2: adults with a relevant *ICD-10* F-diagnosis who will have not received a DiGA reimbursement in 2022 or 2023.

Further inclusion and exclusion criteria will be defined by the consortium based on the results already obtained by the project.

The insured persons will each receive a questionnaire adapted to the specifics of their respective group (group A1 or A2). Participation will be possible by filling out the questionnaire manually or digitally.

Health Care Provider Survey (Group B)

To achieve a comprehensive overview both of health care provision and potential barriers, 2 groups of certified health care providers authorized by the SHI will be recruited:

- Group B1: psychotherapists and psychiatrists
- Group B2: general practitioners

For this, a random sample of groups B1 and B2 that meet the requirements will be selected by an agency. The exact inclusion and exclusion criteria will be defined by the consortium based on the results already obtained by the project. The survey questionnaires will be adapted according to the specifics of the two different groups.

Questionnaire Development

The questionnaires will be developed based on the results of project stage 1, module D. For this, current guidance and recommendations will be taken into account [5,21]. Sociodemographic and socioeconomic factors will be surveyed to identify any differences between patient groups or health care providers.

Interpretation

The survey will be designed to provide results on how DiGA are incorporated within mental health care, the impact of DiGA use on the quality of health care provision, difficulties that patients and health care providers encounter regarding the incorporation of DiGA within patients' specific treatment, as well as respondents' expectations. In addition, the survey will record how DiGA impact mental health care–related liaison issues between different health care sectors.

Module F: Summary of the Results

Upon completion of the second project stage, results will be summarized. This will involve integrating the results from the survey and the finalized claims data analysis into the decision matrix from project stage 1, module D. The barriers identified during the scoping review, focus groups, and interviews will be reviewed and verified for the German perspective using the results of the surveys. The combined results from the extended decision matrix will then be discussed with and approved by the project consortium. The results will be included in a scientific paper and be used as a basis for project stage 3.

Project Stage 3

Overview

Project stage 3 consists of 3 consecutive modules and pursues the objective of answering research question 5 (health policy recommendations). It aims to derive a comprehensive strategy based on the matrix of module F to improve the integration of DiGA in outpatient mental health care.

Module G: Preparation of Preliminary Health Policy Recommendations (Blueprint)

The objective of module G is to develop actionable health policy recommendations for optimizing the incorporation of DiGA within mental health care. This will involve establishing recommendations relating to legislation or sublegislative regulations.

Module H: Stakeholder Workshop

The consistency and applicability of the conclusions reached in module G will be examined during a critical discussion, bringing together the perspectives of a variety of different stakeholders, such as Medical Associations, the Association of SHI Physicians, the Federal Institute for Drugs and Medical Devices, and SHI companies. In terms of an expert workshop, a maximum of 20 relevant stakeholders will discuss the conclusions of the blueprint (module G) to find consent or argue about substantiate dissent.

Module I: Finalizing the Blueprint

The blueprint will be adapted and finalized in accordance with the results of the workshop, producing a coherent and practically applicable overall strategy to better incorporate DiGA into outpatient mental health care, which can be implemented within the SHI system.

Ethical Considerations

The study received ethical approval from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen on April 2, 2024 (reference: 23-11209-BO). For the purpose of the claims data analysis (module B), pseudonymized data will be used, assuring that there is no possibility of participant identification. Data protection and safety are ensured by a data protection concept, which is approved by the Federal Social Security Office. The approval allows to analyze the SHI claims data without additional informed consent. The data collected in the focus groups and interviews (module C) is considered pseudonymized because, after the transcription, all personal data will be removed. Before participation, participants will need to sign informed consent which allows the transcripts to be stored and analyzed. The list of participants will be deleted after conducting the focus groups. The audio recordings will be deleted after transcription. Participants in the survey (module E) will be informed that their participation is voluntary and anonymous and that they agree to participate by submitting the survey. To take part in the workshop (module H), participants will need to sign an informed consent. Participants will receive financial incentives for participating in the focus groups, interviews, and workshops.

Results

This project will examine the incorporation of DiGA within mental health care. It aims to improve the current integration and use of DiGA. It will also identify the requirements for a successful implementation of DiGA in the health care system.

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This will be done by analyzing empirical data from a variety of sources and including the perspectives of health care providers and (potential) patients. This way, targeted, realistic, and empirically based health policy recommendations for legislators and self-governing bodies will be developed. These recommendations shall support the development of an appropriate and economical use of DiGA in mental health care. Concepts for the integration of mHealth apps for mental disorders will be derived and potential areas of application in the care process will be defined. The project will examine the status quo of how DiGA are used in outpatient psychotherapeutic care (key areas of application, prescription patterns, use patterns, and patient journeys). Further, conclusions will be drawn concerning barriers that prevent a more extensive implementation of DiGA. The circumstances under which health care providers recommend the use of DiGA and other facilitating factors will be analyzed. Expectations regarding format, content, and usability will also be part of the study. Further, the conditions under which patients are most likely to accept the use of these apps as part of their psychotherapeutic treatment will be analyzed. These recommendations for the deployment of DiGA within mental health care will be presented in a blueprint and thus be available to a professional readership (eg, health care providers and other relevant stakeholder groups). The knowledge obtained through this research project has the potential to contribute to the improvement and adaptation of health care based on patient's needs. As of November 2024, the scoping review and qualitative analyses have been completed, and the quantitative surveys are currently being carried out. The target number of responses in the survey of insured persons has already been achieved. Furthermore, the analysis of claims data for the SHI is currently being conducted.

Discussion

Principal Findings

The aim of the project "DiGAPsy" is to optimize the integration of DiGA in mental health care. At the end of the project, health policy recommendations for an optimal integration of DiGA in outpatient mental health care will be developed. A mixed methods approach will be used, combining both qualitative and quantitative methods.

The use of DiGA, reimbursed by the SHI, has been possible since the end of 2020. Therefore, there is a limited amount of evidence regarding the topic. Germany was the first country to introduce reimbursable mHealth apps in the health care system and thus serves as a role model for other countries considering the implementation of DiGA-similar concepts. The innovative character of DiGA limits the extent to which international studies can be found. Existing international studies such as surveys on preferences for mHealth apps have only analyzed individual aspects of the issue, such as existing problems and barriers related to the use of DiGA in general [22]. Another aspect was analyzed in a study by Smail-Crevier et al [23], where they showed that gender differences in opinions exist. Their study showed that women were more likely than men to use mHealth apps and seek health information digitally. Men preferred programs with a high degree of gamification.

This study aims to optimize the integration of DiGA into outpatient mental health care and fill research gaps. mHealth apps for mental disorders—including DiGA—are burdened by limiting factors and a range of barriers hindering their optimal integration, which reduces their usefulness in health care [24,25]. As a result, mHealth apps and DiGA tend to fall short of expectations and fail to fully unfold their potential. This is particularly problematic in the German scope, as the financial situation of the German health care system is worsening and there is a shortage of skilled workers. Innovative approaches are needed to improve the efficiency of the health care system. The project presented here provides concrete, actionable recommendations for a holistic and patient-centered use of DiGA, which help to overcome existing obstacles. This will help to improve the quality and efficiency of the health care system.

Limitations

Limitations include that this study focuses on mHealth apps that are reimbursable by the German statutory health care system (DiGA). The framework of financing and eligibility for reimbursement of certified mHealth apps may be different in other countries. Thus, the results of this study may not be completely applicable to them. As there are different legal frameworks, there may be also other requirements for reimbursable certified mHealth apps. For example, other countries might have a different perspective on data protection requirements. This could lead to the addition of blended care features, which are currently not considered in the concept of DiGA. Another limitation is that the level of DiGA integration within mental health care is still relatively low. Low prescription numbers demonstrate hesitancy when it comes to prescribing DiGA across all indications. Similarly, despite half of approved DiGA being for mental disorders, the highest prescription rates of DiGA can be found for obesity, back pain, and tinnitus [13].

Conclusions

The results of this study do not only aim to improve the implementation of DiGA in outpatient mental health care in Germany but may be also of international interest. Even if different legal frameworks may limit the direct application of the study results in other countries, they provide a starting point for the design of blueprints to facilitate the integration of similar apps. Thus, the knowledge and research results can help implement similar systems within their health care structures. This helps to avoid mistakes and accelerate implementation. France and Austria, for instance, consider rolling out mHealth apps using a similar strategy [26].

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Authors' Contributions

All authors were involved in the conception of the study and the study design. KH, CA, and AB were the major contributors to writing and reviewing this manuscript. All authors contributed to the manuscript in different stages and also read and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

DiGA: Digitale Gesundheitsanwendungen
***ICD-10*:** *International Statistical Classification of Diseases, Tenth Revision*
ICD-10-GM: German Modification of the International Statistical Classification of Diseases and Related Health Problems
mHealth: mobile health
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
SHI: statutory health insurance
TK: Techniker Krankenkasse

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Protocol

A Gender-Informed Smoking Cessation App for Women: Protocol for an Acceptability and Feasibility Study

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Abstract

Background: Tobacco smoking remains the leading preventable cause of death and disease among women. Quitting smoking offers numerous health benefits; however, women tend to have less success than men when attempting to quit. This discrepancy is partly due to sex- and gender-related factors, including the lower effectiveness of smoking cessation medication and the presence of unique motives for smoking and barriers to quitting among women. Despite the gendered nature of smoking, most smoking cessation apps are gender-neutral and fail to address women's specific needs.

Objective: This study aims to test the acceptability and feasibility of a smartphone app that delivers gender-informed content to support women in quitting smoking.

Methods: We co-developed a smoking cessation app specifically tailored for women, named My Change Plan-Women (MCP-W). This app builds upon our previous gender-neutral app, MCP, by retaining its content grounded in behavioral change techniques aimed at supporting tobacco reduction and cessation. This includes goal setting for quitting, identifying triggers to smoking, creating coping strategies, tracking cigarettes and cravings, and assessing financial savings from quitting smoking. The MCP-W app contains additional gender-informed content that acknowledges barriers to quitting, such as coping with stress, having smokers in one's social circle, and managing unpleasant emotions. This content is delivered through testimonials and animated videos. This study is a prospective, single-group, mixed methods investigation in which 30 women smokers will trial the app for a period of 28 days. Once participants provide informed consent, they will complete a baseline survey and download the app on their smartphones. After 28 days, participants will complete follow-up surveys. Acceptability will be assessed using the Theoretical

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Framework of Acceptability, which evaluates whether participants perceive the app as helpful in changing their smoking. The app will be deemed acceptable if the majority of participants rate it as such, and feasible if the majority of the participants use it for at least 7 days. Furthermore, after the 28-day trial period, participants will complete a semistructured interview regarding their experience with the app and suggestions for improvement.

Results: Development of the MCP-W app was completed in September 2023. Participant recruitment for testing of the app commenced in February 2024 and was completed in July 2024. We will analyze the data upon completion of data collection from all 30 participants. We expect to share the results of this acceptability trial in the middle of 2025.

Conclusions: Offering smoking cessation support tailored specifically to address the unique needs of women through a smartphone app represents a novel approach. This study will test whether women who smoke perceive this approach to be acceptable and feasible in their journey toward smoking cessation.

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KEYWORDS

smoking cessation; mHealth; co-development; feasibility; smoking; mobile app; cigarette smoking; tobacco cessation; gender-informed design; app design; women's health; behavior change; health behavior change; mobile phone

Introduction

Cigarette smoking is the leading cause of morbidity and mortality among women in Western countries through cancer, heart, and lung diseases [1]. The risk for developing smoking-related diseases is higher among women than men, mainly due to their body size and other biological factors [2]. Both men and women share a similar interest in quitting and attempt to quit at similar rates; however, women are 30% less likely than men to quit successfully [3]. This discrepancy can be partly explained by the influence of sex and gender on smoking behavior. Research suggests male brains exhibit a greater pleasurable response to nicotine than female brains [4]. Whereas smoking behavior is propelled by the pleasurable response to nicotine (ie, addiction) among men, it may be propelled by other motives among women, such as external social cues [5]. This partly explains why nicotine replacement therapy is less effective in women compared with men [6]. Women rely on smoking for stress relief to a greater degree than men [7]. Consequently, women in adverse social and economic circumstances, who depend on smoking for stress reduction, encounter particular difficulties in quitting [8]. Furthermore, many women lack support for quitting from their partners, friends, and others in their environment [7]. This hampers women's efforts in both initiating abstinence and maintaining it [3,9]. Despite the presence of sex- and gender-related influences on smoking, most smoking treatment guidelines are sex- and gender-neutral and do not call for a differentiated approach for women smokers that is based on advances in sex and gender science. Inadvertently, this may perpetuate existing gender disparities in quit outcomes [3,9].

Recently, greater attention has been given to sociocultural contexts that are conducive to smoking initiation and its maintenance and their interaction with the psychopharmacological effects of nicotine [10]. The sociopharmacology theory provides an explanation for the disparity in cessation outcomes between men and women. The theory posits that adverse social circumstances (eg intimate partner violence, lone parenting) make nicotine particularly rewarding and that stress related to these adverse social circumstances then becomes a conditioned cue for cigarette smoking. Since women face more life stressors than men due to societal inequalities, they are less likely to succeed in quitting. It has been suggested that offering behavioral interventions that offset sociocontextual factors in combination with cessation pharmacotherapy could improve quit outcomes for women [11].

Mobile health technologies, such as smartphone apps, can effectively deliver interventions to aid smokers in quitting [12]. They provide an opportunity to expand on existing gender-neutral approaches by addressing sociocontextual factors that influence smoking behavior among women. Apps have a number of advantages compared to traditional in-person interventions, including having a wide reach, being available at all times, and reducing treatment time and travel needs. Also, apps are easily customizable and allow for tailoring of content to meet the needs of specific populations. Indeed, a previous review identified 33 unique smoking cessation smartphone apps with about half targeting specific groups, such as people with mental illness, youth, and pregnant women [13]. Yet, only one app was tailored for nonpregnant women [14]. Armin et al [14] developed a gender-specific app to target multiple unhealthy behaviors among women, including smoking, physical inactivity, and low-quality diet. The app delivered guided imagery to women to reduce their concerns regarding postcessation weight gain and negative body image, which is reported by some women as a barrier for quitting [15]. While fear of postcessation weight gain is a known barrier to cessation among women, there is a need to address the influences of additional sociocontextual barriers in smoking cessation apps for women.

To address this need, we developed a gender-informed evidence-based smoking cessation app with input from patient partners and a multidisciplinary team of clinicians and researchers [15-18]. The app is grounded in the principles of both gender and sociopharmacology theories [10,19]. This theory-based approach allows for an appreciation of the social determinants of smoking behavior in women and appropriate mitigation strategies. This newly developed My Change Plan-Women (MCP-W) app provides women with psychoeducation on the sociocontextual factors that influence

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smoking behavior, offers strategies to overcome gender-specific barriers to quitting, and provides encouragement through testimonials from women who have quit. In addition, MCP-W contains gender-neutral content such as tracking cigarette use, a diary of urges and cravings, cost savings associated with reduction or cessation, and motivation reinforcement through app notifications. The aim of this mixed methods study is to investigate the acceptability and feasibility of the MCP-W app among women smokers.

Methods

Development of MCP-W

Our team has previously developed an evidence-based app for smoking cessation to support the efforts of smokers who enroll in the publicly funded Smoking Treatment for Ontario Patients (STOP) program [20]. The app, My Change Plan (MCP) [21], contains gender-neutral content grounded in behavioral change techniques for supporting tobacco reduction and cessation [22]. This includes the development of a personalized change plan, which allows users to set goals, identify triggers to smoking, create coping strategies, seek support systems, track their cigarettes and cravings, and assess financial savings from reducing or quitting smoking. The app also contains evidence-based content on the different smoking cessation medications, local support for smoking cessations (ie, smokers' helpline), and general content on how to improve other aspects of health when trying to quit including recommendations for physical activity, nutrition, low-risk alcohol consumption, stress reduction, and sleep hygiene.

Between July 2022 and August 2023, we developed a women-specific version of the MCP app, MCP- W. The MCP-W app was developed in collaboration with patient partners (ie, women with lived experience of smoking) and subject matter experts in tobacco addiction, sex, and gender science, implementation science, public health, app development, and human-computer interactions. We chose to co-design the app with patient partners to ensure the app is relevant to our target population in accordance with the best evidence of co-design principles [23]. We invited 5 patient partner women who were treated in the STOP program for smoking cessation in the past, to co-develop the content of the app.

Gender-Informed Content in MCP-W

We co-developed gender-informed content consistent with the best available evidence regarding women-centered care [17,18]. The content is anchored within gender and sociopharmacology theories [10,19]. As such, the content refrains from using harmful gender norms to promote cessation, such as promoting quitting by emphasizing the ill effects of smoking on women's appearance, rather than on women's general health. Also, the content refrains from coercion to quit through shaming or blaming women for their smoking or inability to quit. Instead, it respects the autonomy of women to make changes when they are ready, accepting harm-reduction goals such as a gradual reduction rather than a complete quit. One way to achieve this is by placing an emphasis on preparations for quitting (eg, tracking the number of daily cigarettes (Figure 1-3), delaying the first cigarette of the day). Also, the content encourages the acceptance that quitting is a journey and that for some, it may take months or even years to achieve. Consistent with the sociopharmacology and gender theories, the content provides examples of how adverse social circumstances (eg, intimate partner violence, lone parenting) make nicotine particularly rewarding and that stress related to these adverse social circumstances then becomes a conditioned cue for cigarette smoking [10]. It then provides suggestions from other women on how to overcome these challenges such as identifying available supports in one's environment, using smoking cessation medications, and finding alternative healthy behaviors for coping with stress.

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Figure 1. Home page of the My Change Plan-Women app.

Figure 2. Logging cigarettes in the My Change Plan-Women app.

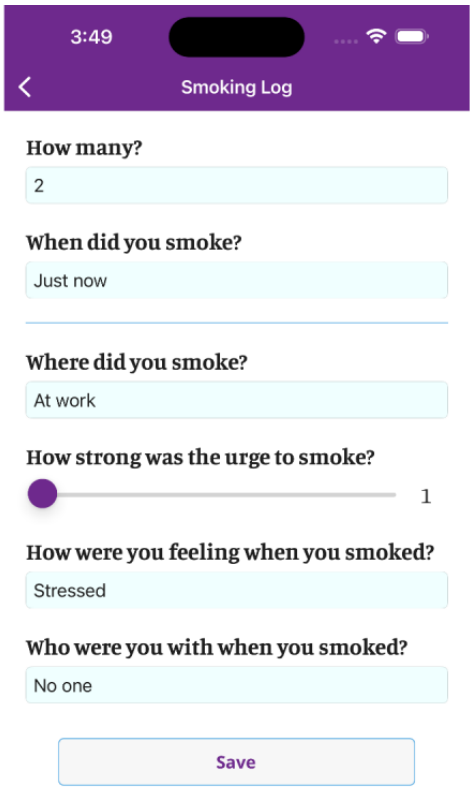

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Figure 3. "My progress" page in the My Change Plan-Women app.

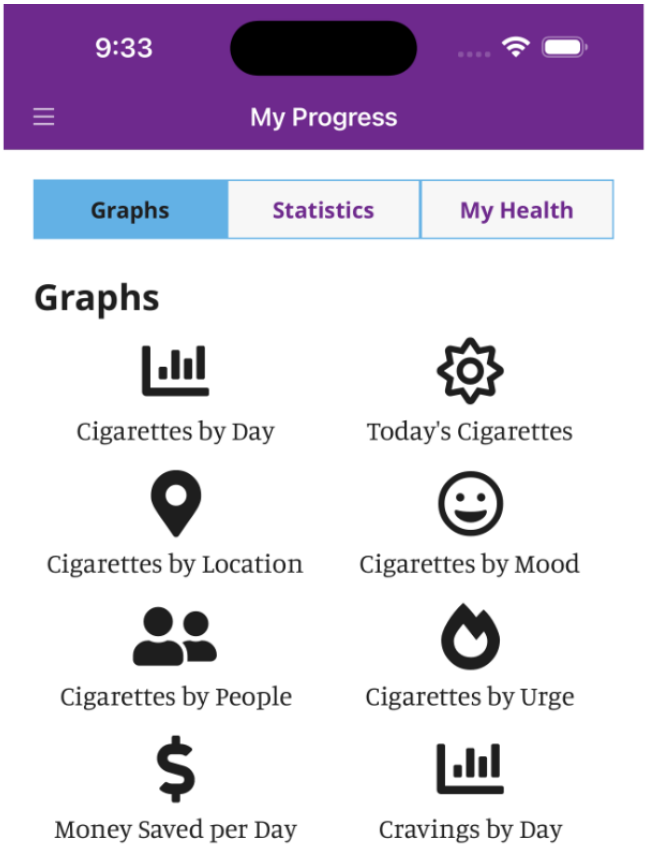

We included the newly developed content in the app's library under a tab titled "Women Talk about their Quit Journey" (Figure 4-6). This tab includes written information in the form of testimonials that bring forward the voices of other women offering strategies for quitting and encouragement. Also, it includes 4 animation videos that summarize key concepts regarding women-specific barriers to quitting and how to overcome them in a user-friendly manner. The app includes the following four videos, for which full transcripts are included in Multimedia Appendix 1:

1. A woman's monologue: a woman talks about her life-long relationship with cigarettes, from initiation, through maintenance and the decision to quit, highlighting gender-specific motives for smoking and barriers to quitting.
2. Smoking and Stress: a dialogue between a woman and her physician regarding the link between smoking and stress.
3. Women's dialogue: a group of 3 women talks about their experiences of smoking, their challenges in quitting, and what helped them overcome the challenges.
4. Initiating change to my smoking: a woman describes her first steps in the smoking cessation journey.

Figure 4. "My library" in the My Change Plan-Women app.

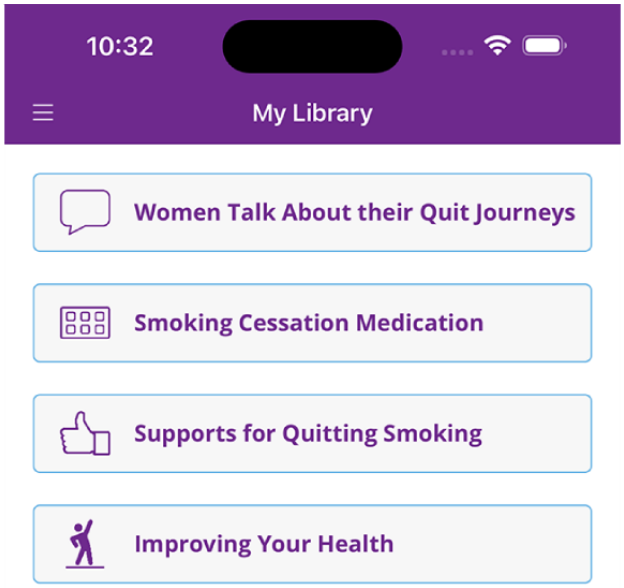

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Figure 5. Animation videos in the My Change Plan-Women app.

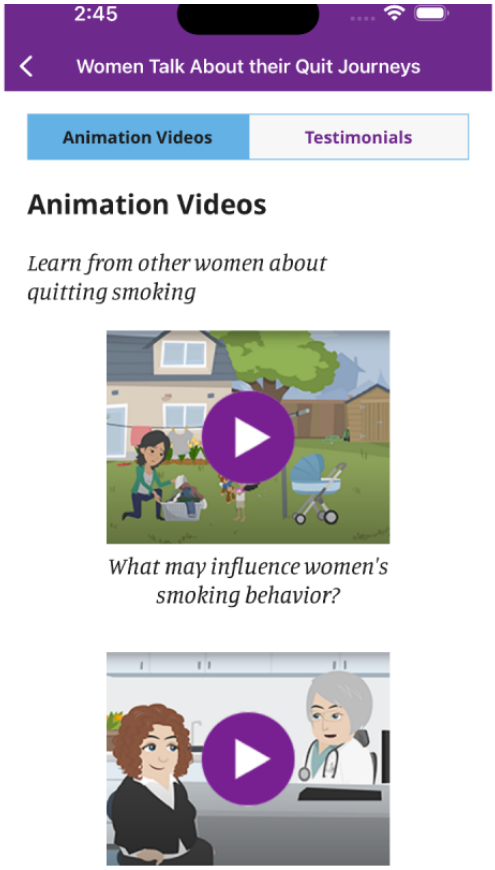

Figure 6. Testimonials in the My Change Plan-Women app.

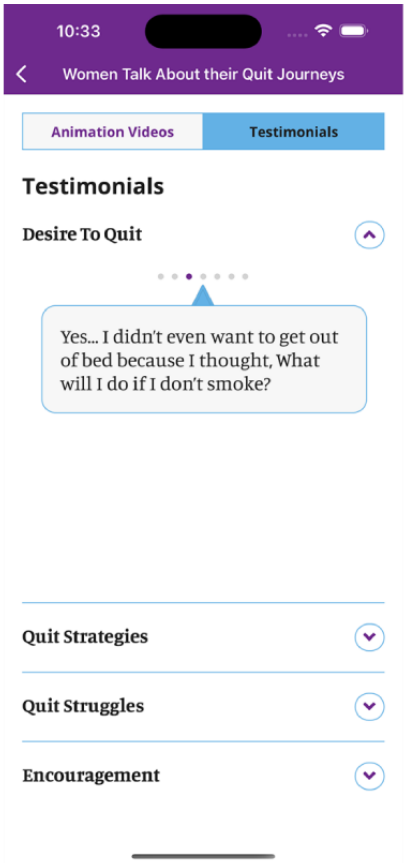

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Study Design, Setting, and Participants

This study is a prospective, single-group, mixed methods investigation to test the acceptability and feasibility of delivering a gender-specific smoking cessation intervention through a smartphone app. The study is being conducted in the INTREPID lab at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario. We aim to recruit 30 women who smoke to test the MCP-W app.

Recruitment and Procedure

We will promote the study among primary care providers who deliver the STOP smoking cessation program in Ontario, and who will be asked to refer interested patients. We will place recruitment flyers in our hospital (CAMH) bulletin boards, so interested women will be able to self-refer. In addition, we will reach out to previous STOP program participants who have expressed interest in participating in research studies. Interested patients will be screened against eligibility criteria. Those deemed eligible will be offered to enroll in the study after providing written informed consent.

Participants will be granted access to use the MCP-W app on their personal smartphone devices for a trial period of 28 days and provided a short demonstration of the app and its features. We have both Android and Apple versions of the app. During the trial period, participants will be asked to complete surveys at 2 time points: baseline, and at the end of the trial period (Multimedia Appendices 2-4). Once the 28-day trial period concludes, a research analyst will reach out to the participants and schedule a semistructured interview (Multimedia Appendix 5). During the interview, participants can provide additional feedback regarding their experience with the app and offer suggestions for improvement. The total duration of participant involvement in the study will span between 5 and 8 weeks. All interactions with the participants will be conducted remotely using the secure videoconferencing software, Webex, or via telephone. Quantitative and qualitative data analyses will be done within 3 months after the 28-day trial period concludes. Inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria

Inclusion criteria

- Self-identify as a woman
- Ages of 25-65 years
- Smoke at least 5 tobacco cigarettes per day
- Own a smartphone and have continuous internet access
- Have experience with using smartphone apps (ie, Facebook, Weather, News)

Exclusion criteria

- Does not feel comfortable using smartphone apps
- Severe general health or mental health conditions that interfere with study compliance
- Pregnancy, breastfeeding, or trying to become pregnant in the next 3 months

Outcome Measures

Primary Outcome

The primary outcome of this study is the acceptability of the intervention. To define acceptability, we will use the Theoretical Framework of Acceptability (TFA) [24], which assesses the extent to which the app is perceived to have achieved its intended purpose. Participants will rate their perception of the app's effectiveness using a 5-point Likert scale (Multimedia Appendix 3), ranging from “strongly disagree” to “strongly agree,” in response to the statement: “Using the app is likely to help me make changes to my smoking habits.” Acceptability will be assessed using the surveys disseminated to participants at baseline and at the end of the 28-day trial period. To assess the extent to which participants engage with the app, our second primary outcome is feasibility, as evidenced by the number of days participants actively used (ie, logged into) the app during the 28-day trial period.

Secondary Outcome

The secondary outcome is the participants’ motivation to change their smoking behavior. Motivation to change will be assessed through 3 validated questions that rate reasons, taking steps, and ability to change one’s smoking [25]; the questions ask for ratings for the following statements: (1) it is important for me to change my smoking habits (reduce or quit), (2) I am trying to change my smoking habits (reduce or quit), and (3) I could change my smoking habits (reduce or quit). Each item will be rated on a Likert scale ranging from 1 to 5, with the following categories under the numbers: definitely not (1), probably not (2), maybe (3), probably (4), and definitely (5).

Tertiary Outcome

The tertiary outcome will be participants’ smoking habits as evidenced by the number of daily cigarettes [26] (Multimedia Appendix 3). We will measure any changes to participant smoking habits from baseline to end of trial. In addition, participants will report on the number of deliberate quit attempts (24-hour smoke-free period) in the preceding week both at baseline and at end of trial.

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Exploratory Outcomes

Following the 28-day trial period, at the final survey we will assess participant perceptions on the usability of the app using the System Usability Scale [27] (Multimedia Appendix 4). This scale is a validated questionnaire to assess participants' experiences regarding the ease of use of a new website or app platform.

Demographic Variables

Demographic information will be collected from participants using a baseline survey at the start of the 28-day trial period (Multimedia Appendix 2). Demographic information collected on the survey will include age, gender identity, education level, marital status, household income, general health, and medical comorbidities.

Data Analysis Plan

Sample Size Calculation

This is a single-arm study testing the acceptability and feasibility rather than the effectiveness of the MCP-W app in supporting change in smoking behaviors. The literature suggests a sample size of 30 participants for feasibility and usability studies [28].

Primary Outcomes

The primary outcome is the acceptability and feasibility of the MCP-W app.

We will measure acceptability by calculating the proportion of participants responding "agree" or "strongly agree" to the statement, "using the app is likely to help me make changes to my smoking habits." We will deem the MCP-W app as acceptable if this proportion is equal or greater than 50% (15/30); needs further work if it is 26% (8/30) - 49% (14/30); and to be unacceptable if this proportion is 25% (7/30) or lower. As the small sample makes multiple imputations impractical, we will impute nonresponse values at the final follow-up to "do not agree," on grounds that low study engagement is likely to indicate lower acceptability of the intervention.

For feasibility, we will calculate the proportion of participants who used the app on at least 7 days out of the 28-day trial period. We will use the same thresholds (50%+; 26%-49%; and 0%-25%) for interpreting this outcome. As these data are based on Google Analytics, they will be available for all participants; no missing data should occur. We are able to access Google Analytics data through Google Firebase. Firebase is a set of backend cloud computing services and application development platforms provided by Google. We will assign unique login IDs for each participant. Every time a participant opens the app and uses their unique ID to login, the data is recorded. This will allow us to observe how many days the app was used by each research participant. We do not expect to have any missing data on feasibility measures as they are automatically collected on the backend of the app (ie, the app opened vs not opened).

To understand the precision of our estimates, we will calculate the exact binomial 95% CI. However, our decisions will rest on the point estimates only.

Secondary and Tertiary Outcomes

The secondary outcome will assess participant' motivation to change their smoking behavior. The tertiary outcome will be changed in the participant's smoking behavior. We will report all secondary and tertiary outcomes descriptively at all-time points at which data are collected. We will also calculate the proportions showing increased motivation, substantial reductions (≥50%) in cigarettes per day, and an increased number of quit attempts. Although this study is not powered to detect significant differences, we will calculate CI and perform statistical tests to gain insight into the precision of results. We will use McNemar tests for binary outcomes; exact Wilcoxon signed-rank tests for paired ordinal data; and linear, Poisson, or negative binomial regression for cigarettes per day, depending on the observed distribution.

If unanticipated issues necessitate any deviation from these approaches, we will describe the analysis originally intended, the analysis actually used, and detail the reasons for differences.

We will use Stata (version 16; StataCorp LLC) to conduct the data analyses.

Qualitative Analysis

To analyze the data from the semistructured interviews, we will employ a deductive (top-down) approach. The coding process will be guided by the 7 constructs of the TFA [24] to assess the user experience with the app: affective attitude, burden, perceived effectiveness, opportunity costs, intervention coherence, self-efficacy, and ethicality. Analyzing the qualitative data using this method will allow for a rich description of how participants perceived the acceptability of the women-informed app. Researchers with appropriate training will thoroughly review the data and assign relevant excerpts to the respective codes. Through these analyses, we anticipate that our codes will closely align with the initial codebook we established. Researchers will meet regularly during the coding process and any disagreements will be resolved through consensus.

Ethical Considerations

The study was reviewed and approved by the institutional Research Ethics Board of CAMH in Toronto, Ontario (protocol 122-2023). Participants will receive CAD $30 (US $21.59) in compensation at the time of baseline survey completion, and an additional CAD $30 (US $21.59) following the completion of the posttrial interview.

Results

We secured funding for the study in July 2022 and completed the development of the MCP-W app in September 2023. Participant recruitment for testing of the app commenced in February 2024 and is expected to be completed by December 2024. We will analyze the data upon completion of data collection from all 30 participants. We expect to share the results of this acceptability trial in the middle of 2025.

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Discussion

Principal Findings

This study will examine whether women who smoke find the MCP-W app acceptable and feasible for their smoking cessation needs. We will also explore whether using the app is associated with changes in the motivation of women to quit or reduce smoking, the number of cigarettes smoked per day, and the number of smoke-free days in the last 7 days. We will be able to expand our understanding of the quantitative findings using rich qualitative data captured in the exit interviews.

Novelty of the Study

Smartphone apps are increasingly used to improve health behaviors among the general public. However, they are seldom customized based on the gender of the user. This may pose a disadvantage for health behaviors that are directly influenced by the individual's gender, such as in the case of tobacco smoking. Recently, a number of studies attempted to tailor smoking cessation apps according to gender, including an app to support women in making a change to multiple health behaviors [29], and an app to support women who are pregnant [30]. This study adds to the scholarly work in this domain by developing a smoking cessation app with gender-specific content and assessing its acceptability and feasibility.

Strengths and Limitations

This study is a novel attempt to deliver a gender-informed intervention for smoking cessation anchored within gender theory. Given the wide reach of smartphone apps and the relative ease of customizing content to specific population groups, it has the potential to improve women's health. Since the app was codeveloped with patient partners, it's expected to be both relevant and acceptable to women who smoke. The development of MCP-W leveraged existing assets, such as MCP, the gender-neutral smoking cessation app. This not only reduces development costs but also provides a conceptual model for tailoring content to other groups facing disparities in smoking quit rates.

This study will provide us with information on the acceptability and feasibility of the gender-informed app but due to a small sample size, it is underpowered to study the app's effectiveness in supporting smoking cessation. Furthermore, the majority of participants recruited for testing the app are individuals seeking treatment for smoking, which could potentially limit the generalizability of the app's acceptability among women with lower interest in quitting.

Future Directions

The findings from this study and the feedback provided by research participants will inform the development of additional gender-specific digital tools including a gender-specific smoking cessation conversational agent (ie, a chatbot). In addition, adding a gamification component to the current MCP-W app may increase its acceptability and be an avenue for future research [29,30].

Knowledge Dissemination Plan

We plan to publish the results in a scientific publication and present the results at scientific conferences, namely, those of the North American Primary Care Research Group, and the Society for the Research of Nicotine and Tobacco. Also, we plan to share the results with the Gender, Evidence, and Health Network, which promotes gender equity in scientific research.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available due to privacy limitations set forth by our institution. The corresponding author will consider sharing data provided the researchers obtain approval from their institutional review board for their suggested data analysis plan.

Authors' Contributions

OM conceived the study with the support of PS. OM and RP were involved in gaining ethical approval. OM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicting interests with respect to this manuscript; however, some authors have general disclosures to report. OCM receives research support from the Department of Family and Community Medicine at the University of Toronto and the INTREPID lab at the Centre for Addiction and Mental Health. NM reports receipt of funding from the Canadian Institutes of Health Research, the Canadian Cancer Society, and the Discovery Fund of the Centre for Addiction and Mental Health. PS reports receipt of funding from the Canadian Institutes of Health Research, Canadian Cancer Society, Pfizer Inc, Pfizer Canada, and the Ontario Lung Association. PS also reports that through an open tender process, Johnson & Johnson, Novartis, and Pfizer Inc are vendors of record for having provided smoking cessation pharmacotherapy for research studies for free or at

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discounted rates. PS is the vice-chair, research, and is the Giblon Professor in Family Medicine Research, a university named professorship at the University of Toronto.

Multimedia Appendix 1
Video scripts.
[DOCX File , 29 KB - resprot_v13i1e60677_app1.docx]

Multimedia Appendix 2
Baseline demographic survey instrument.
[DOCX File , 20 KB - resprot_v13i1e60677_app2.docx]

Multimedia Appendix 3
Surveys for baseline and follow up.
[DOCX File , 16 KB - resprot_v13i1e60677_app3.docx]

Multimedia Appendix 4
System Usability Scale survey instrument for the follow up survey.
[DOCX File , 17 KB - resprot_v13i1e60677_app4.docx]

Multimedia Appendix 5
Interview guide.
[DOCX File , 19 KB - resprot_v13i1e60677_app5.docx]

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Abbreviations

CAMH: Centre for Addiction and Mental Health
MCP: My Change Plan
MCP-W: My Change Plan-Women
STOP: Smoking Treatment for Ontario Patients
TFA: Theoretical Framework of Acceptability

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Protocol

A Digital Mental Health Solution to Improve Social, Emotional, and Learning Skills for Youth: Protocol for an Efficacy and Usability Study

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Abstract

Background: The COVID-19 pandemic has exposed a devastating youth mental health crisis in the United States, characterized by an all-time high prevalence of youth mental illness. This crisis is exacerbated by limited access to mental health services and the reduction of mental health support in schools. Mobile health platforms offer a promising avenue for delivering tailored and on-demand mental health care.

Objective: To address the lack of youth mental health services, we created the Science Technology Engineering Math and Social and Emotional Learning (STEMSEL) study. Our aim was to investigate the efficacy of a digital mental health intervention, Neolth, in enhancing social and emotional well-being, reducing academic stress, and increasing mental health literacy and life skills among adolescents.

Methods: The STEMSEL study will involve the implementation and evaluation of Neolth across 4 distinct phases. In phase 1, a comprehensive needs assessment will be conducted across 3 diverse schools, each using a range of teaching methods, including in-person, digital, and hybrid modalities. Following this, in phase 2, school administrators and teachers undergo intensive training sessions on Neolth's functionalities and intervention processes as well as understand barriers and facilitators of implementing a digital mental health program at their respective schools. Phase 3 involves recruiting middle and high school students aged 11-18 years from the participating schools, with parental consent and student assent obtained, to access Neolth. Students will then be prompted to complete an intake questionnaire, enabling the customization of available modules to address their specific needs. Finally, phase 4 will include a year-long pre- and posttest pilot study to rigorously evaluate the usability and effectiveness of Neolth in addressing the mental health concerns of students across the selected schools.

Results: Phase 1 was successfully completed in August 2022, revealing significant deficits in mental health resources within the participating schools. The needs assessment identified critical gaps in available mental health support services. We are currently recruiting a diverse group of middle and high school students to participate in the study. The study's completion is scheduled for 2024, with data expected to provide insights into the real-world use of Neolth among the adolescent population. It is designed to deliver findings regarding the intervention's efficacy in addressing the mental health needs of students.

Conclusions: The STEMSEL study plays a crucial role in assessing the feasibility and adoption of digital mental health interventions within the school-aged youth population in the United States. The findings generated from this study have the potential to dismantle obstacles to accessing mental health assistance and broaden the availability of care through evidence-based strategies.

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KEYWORDS

mental health; digital health; mHealth; usability; pilot study; United States; mental health crisis; Science Technology Engineering Math and Social and Emotional Learning; STEMSEL; efficacy; well-being; barriers; facilitators; resources; youth; adolescents; teenagers; students; feasibility; adoption; evidence-based; intervention; anxiety; depression; Neolth; digital app

Introduction

Background and Rationale

The burgeoning crisis of youth mental health underscores an urgent need for effective interventions, as barriers to accessing mental health care persist among this vulnerable demographic group. The school years represent a critical period in a young person's life, marked by profound physical, emotional, and social changes, thus heightening their susceptibility to mental health issues [1]. The COVID-19 pandemic has intensified concerns about the rise in youth mental health challenges. The Centers for Disease Control and Prevention's "Youth Risk Behavior Surveillance Data Summary & Trends Report: 2013-2023" declared the pandemic-related decline in adolescent mental health a national emergency. It reports nearly all indicators of poor mental health and suicidal thoughts and behaviors worsened from 2013 to 2023. Specifically, there were increases in the percentage of students who experienced persistent feelings of sadness or hopelessness, seriously considered attempting suicide, made a suicide plan, and attempted suicide. Around 32% of US teenagers are diagnosed with anxiety, and 12% with depression. More than 4 in 10 (42%) students reported feeling persistently sad or hopeless, signifying a significant prevalence of emotional distress among adolescents. Furthermore, nearly one-third (29%) of high school students reported experiencing poor mental health, reflecting a concerning trend that demands immediate attention and intervention. Additionally, more than 1 in 5 (22%) high school students seriously contemplated attempting suicide, highlighting the pervasive nature of suicidal ideation among this demographic. Even more alarming is the fact that 1 in 10 (10%) high school students reported attempting suicide, underscoring the urgent need for comprehensive strategies to address the mental well-being of our youth. These Centers for Disease Control and Prevention statistics paint a grim picture of the mental health landscape among youth and underscore the critical need for comprehensive mental health services. They serve as a sobering reminder of the vital role that public health interventions and initiatives must play in addressing the youth mental health crisis.

To confront this growing concern, innovative and evidence-based approaches are imperative, with a particular focus on enhancing access to mental health care, reducing stigma, and promoting social and emotional learning (SEL) within educational settings. However, barriers such as limited accessibility, affordability, and scalability of mental health services hinder access, particularly among resource-limited communities, exacerbating the youth mental health crisis [2]. Furthermore, stigma about mental illness is a formidable obstacle that discourages adolescents from seeking mental health support [3]. Stigma about mental health can lead to discrimination and isolation, exacerbating the challenges faced by young individuals. These multifaceted barriers highlight the urgent need to address these access disparities and reduce the stigma associated with mental health. To achieve this, innovative, creative, and adaptable solutions must be developed to increase access to and methods for promoting SEL, especially in a post–COVID-19 world. These solutions should not only target the various barriers often faced by adolescents but also align with their preferred methods of support. Safeguarding their well-being, nurturing socioemotional development, and ensuring access to mental health care are pivotal imperatives for their health and overall resilience.

The ever-evolving mobile health (mHealth) technology ecosystem and the widespread adoption of mobile devices present a unique opportunity to tackle the aforementioned challenges hindering youth access to quality mental health care. With nearly 6.4 billion smartphone mobile network subscriptions in 2022, and projections to reach 7.7 billion by 2028 [4], mHealth stands as a powerful platform for delivering on-demand mental health support and interventions to adolescents. Digital mental health services have demonstrated potential in engaging youth and have the advantage of circumventing the barriers that have long plagued traditional mental health care, including cost, availability, access, and personalized treatment [5]. In response, we created the Science Technology Engineering Math and Social and Emotional Learning (STEMSEL) study, aiming to explore the psychological, stress-related, emotional, and behavioral changes experienced by middle and high school students while evaluating whether a digital mental health solution, Neolth, can enhance social and emotional well-being, reduce academic stress, and increase mental health literacy and life skills among adolescents. The STEMSEL study holds the promise of leveraging digital and mobile mental health solutions to break down access barriers and reduce stigma, enabling young individuals to access quality mental health care anytime and anywhere.

Theoretical Framework

The STEMSEL study draws upon the theoretical underpinnings of SEL and the transformative potential of digital technology in youth mental health care. SEL emphasizes vital life skills to navigate emotional and societal challenges, serving as protective factors for mental health. The study leverages digital tools to enhance access and effectiveness, aligning with policy priorities. Additionally, it builds upon the moderated online social therapy (MOST) framework, designed for young adults to address the unique needs of school-aged youth in stress, emotional well-being, mental health, and SEL. This theoretical foundation

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guides STEMSEL in bridging gaps in mental health care and promoting resilience among youth.

Goal of SEL

The goal of SEL is to equip individuals, especially young students, with a set of crucial life skills that go beyond academic knowledge. SEL focuses on nurturing emotional intelligence, self-awareness, interpersonal skills, and resilience, among other essential attributes. By fostering these competencies, SEL aims to empower individuals to navigate the complex landscape of emotions, relationships, and societal interactions effectively. Importantly, these skills can serve as powerful protective factors against mental health issues. When students are equipped with strong SEL skills, they are better equipped to manage stress, cope with challenges, build healthy relationships, and maintain a positive sense of self. These competencies not only bolster their emotional well-being but also create a supportive environment that reduces the risk of mental health problems. Thus, the goal of SEL is not just academic success but also the promotion of mental health and overall well-being among students.

Value of Digital Technology

The use of digital technology, particularly mHealth, holds significant promise in improving access, engagement, and treatment effectiveness in youth mental health care [6]. Extensive research spanning nearly 3 decades has demonstrated that internet-delivered treatments can greatly enhance accessibility and produce outcomes in engagement and effectiveness that are on par with traditional face-to-face psychological therapy [7,8]. Mental health system evaluations have called for the integration of digital interventions into service delivery, marking it as a national and international policy priority. For example, the mental health system in Australia enabled by digital technology enhanced accessibility and continuity of care [9].

However, challenges persist in user uptake, engagement, and adherence to digital interventions, particularly among young people, where rates of engagement in digital services for youth are lower compared to adults [10]. Additionally, there has been a historical global failure to effectively integrate digital interventions into real-world mental health services. To address these challenges and fully harness the potential of digital technology in youth mental health care, innovative solutions, accompanied by well-structured implementation and integration plans, are urgently needed [7,11-15].

The MOST framework, originally designed as a digital mental health platform for individuals aged 12-25 years, played a pivotal role in shaping the STEMSEL project. MOST provided the foundational framework for STEMSEL, offering a versatile structure for integrating digital interventions into established face-to-face youth mental health services. Stemming from MOST's components, including evidence-based psychotherapeutic content, remote clinician and peer support, vocational guidance, and a peer-led digital community, STEMSEL adopted a flexible approach to address the diverse needs of youth navigating the complexities of adolescence.

The aims of the STEMSEL study are to evaluate the effectiveness of the Neolth digital mental health intervention in improving adolescents' social and emotional well-being, reducing academic stress, and increasing mental health literacy and life skills. Specifically, the study seeks to assess the feasibility, usability, and real-world impact of integrating such digital interventions in diverse school settings, with the broader goal of addressing barriers to youth mental health care access, reducing stigma, and providing scalable solutions for resource-limited populations.

Methods

Study Design Overview

STEMSEL is a pre- and postdesign study that aims to increase SEL skills among Florida students in grades 6-12 using Neolth throughout the 2022-2024 academic years. As stated previously, Neolth is a mobile app that provides tier 1 resources for emotional awareness, coping skills, health education, and stigma reduction.

The study was designed to address the critical challenges in youth mental health care, leveraging the potential of digital and mobile mental health solutions. In the context of a rapidly evolving technological landscape, marked by the widespread adoption of mobile devices, the STEMSEL study seeks to harness the transformative power of mHealth interventions to enhance the accessibility, effectiveness, and acceptability of mental health support for school-aged youth.

The study is driven by four primary objectives (1) to assess whether Neolth effectively increases social and emotional wellness among students in grades 6-12, (2) to evaluate Neolth's potential to decrease stress within an academic setting, (3) to examine whether Neolth contributes to improving mental health literacy and life skills among students, and (4) to investigate the rate of engagement and use of Neolth among students. These objectives encompass a comprehensive assessment of psychological, stress-related, emotional, behavioral, and sleep-related changes associated with the experiences of middle and high school students. Additionally, the study will investigate the usability and acceptance of digital mental health solutions, aiming to provide valuable insights into the transformative potential of such interventions in the context of youth mental health care.

Study Procedures

Timeline

The STEMSEL study involves the implementation and evaluation of Neolth across 4 distinct phases. Phase 1 entailed conducting a comprehensive needs assessment across 3 participating schools, each with its own teaching methods and styles, ranging from in-person to hybrid models. This phase aimed to understand the specific mental health support requirements and challenges unique to each school setting. Subsequently, phase 2 focuses on administering a comprehensive training program to school administrators and teachers to familiarize them with Neolth's functionalities, features, and intervention processes. The objective will be to

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equip educators with the necessary skills to effectively use the platform for supporting students' mental health needs within their respective school environments. During phase 3, middle and high school students aged 11-18 years are recruited from the participating schools, with consent obtained from parents or legal guardians for students younger than 18 years of age, and assent secured from all participating students. During this phase, students gain access to the Neolth app, where they complete an intake questionnaire to customize available modules addressing their immediate needs. The final phase will involve the implementation of a pre- and posttest pilot study conducted over a 10-month period to assess the usability and effectiveness of Neolth in addressing the mental health needs of students within the STEMSEL study framework.

Participants

Participants in the STEMSEL initiative are recruited from 3 participating Florida schools. To be eligible for participation, individuals must meet specific inclusion criteria. First, participants must be aged 11 years or older. Second, they must be currently enrolled in 1 of the 3 participating schools. Third, they need to demonstrate English language proficiency to engage effectively with the intervention. Finally, parental consent is required for participation.

Conversely, certain exclusion criteria have been established to ensure the suitability of the sample. Individuals diagnosed with psychosis or those younger than 11 years of age are excluded from participation. Additionally, individuals who do not speak or understand English and those not enrolled in the participating institutions for the specified academic year are ineligible. Furthermore, individuals with a history of seizure, vertigo, significant vision or hearing impairment, significant motion sickness, epilepsy, or sensitivity to flashing light or motion, as well as those with injuries to the eyes, face, neck, or arms that would make the use of the app uncomfortable are also excluded from participation. These criteria are implemented to maintain consistency and ensure the eligibility of the sample size, which is targeted to exceed 60 participants.

Study Setting

Students will primarily engage in the research study through the Neolth mobile or web app. This app operates on mobile devices, tablets, or any desktop and serves as the primary platform for their participation. Guidance and encouragement to use this app will be provided by their teachers, who will play a pivotal role in facilitating their involvement. Students will be actively encouraged to use the Neolth app both within the school environment (1 time per week) and in their home settings, fostering comprehensive engagement in the study.

Recruitment Plan

Prior to the recruitment of students, written confirmation was obtained from 3 Florida schools agreeing to participate in the implementation of the digital health solution. Designated school personnel notified all parents and guardians of students regarding the opportunity to engage with Neolth, the digital mental health solution platform. Parents and guardians receive informational materials, including a pamphlet and recruitment documentation, to facilitate the granting of consent for their child's participation in this research initiative. Subsequently, students interested in partaking in the intervention, upon expressing their intent through opt-out forms provided by school personnel, undergo an eligibility screening process facilitated through a REDCap (Research Electronic Data Capture) link provided by study staff. Those meeting the established eligibility criteria are contacted by a dedicated research team member via telephone or Zoom (Zoom Video Communications) to seek their informed assent and proceed with enrollment in the foundational phase of the study (Figure 1).

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Figure 1. Recruitment process and school partnership methodology.

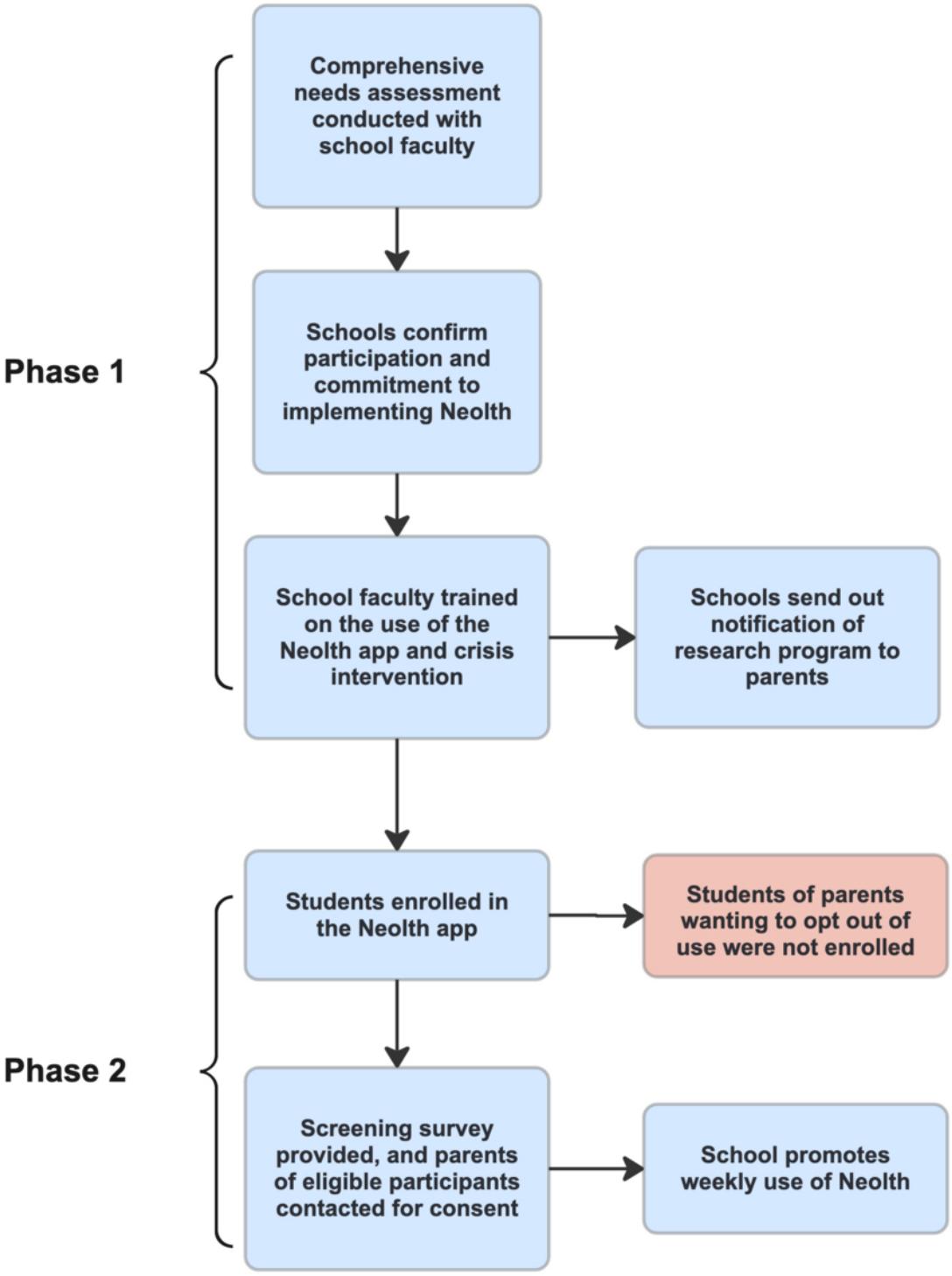

Ethical Considerations

The STEMSEL study adheres to stringent ethical standards to ensure the protection and privacy of all participants. This study has received ethical approval from the institutional review board at the University of Miami (UM) Miller School of Medicine (approval 20220661). The research will be conducted in accordance with the principles of the Declaration of Helsinki, ensuring the protection of participants' rights, safety, and well-being. Written commitment letters have been obtained from the leadership of each participating school, including principals and other relevant administrators, affirming their support for the study. All procedures will be carried out with strict adherence to ethical standards, including obtaining informed consent from participants and ensuring data confidentiality. All participating schools, students, and parents or guardians were provided with detailed information about the study, including its objectives, procedures, and potential risks

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and benefits. Informed consent will be obtained from all participants and, for minors, from their parents or legal guardians. Each participant and their guardian will be provided with comprehensive information about the study, including its objectives, procedures, potential risks, and anticipated benefits. The consent process will ensure that participants understand their rights, including the right to withdraw from the study at any time without penalty. Data will be collected and stored securely to maintain confidentiality, with only authorized personnel having access to identifiable information. Youth and their caregivers participate in an unrecorded Zoom call with a study staff member. At the start of the Zoom call, the study staff member obtains verbal consent to send consent and assent documents via email using REDCap for an e-signature. Study staff verbally reviews approved consent and assent documents. Translation is provided for non–English-speaking parents or guardians. Caregivers and their youth sign upon agreement. The caregiver is sent a copy of the signed documents. All caregivers are asked to provide written informed consent, and all youth are asked to provide written assent digitally via email using REDCap. Caregivers and youth are provided relevant study information at the time of consent and given as much time as needed to decide on whether to participate. Written informed consent is first obtained from the caregivers or guardians of participating youth, and written assent is then obtained from youth. Caregivers and children are given a blank copy of the consent or assent form to review prior to deciding. A second copy of the consent or assent form is given to the caregiver or child after signing. Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, the reported trial data are accurate, complete, and verifiable, and the conduct of the trial is in compliance with the currently approved protocol or amendments, with good clinical practices, and with applicable regulatory requirements. At UM, the data manager will manage study data under the principal investigator's (AAS) supervision. The data manager will create computerized data collection forms to ensure the integrity and accuracy of data entry. They will help to minimize the problem of missing data by resolving omissions and errors as they arise. There will be no transfer of data from UM to Neolth. UM staff will have access to participants' use data. Safety monitoring will include careful assessment and reporting of adverse events to the appropriate institutional review board and privacy boards. Medical monitoring will include a regular assessment of the number and type of serious adverse events. These measures ensure that the study is conducted with the utmost respect for participant confidentiality, privacy, and ethical standards.

Data Collection

Baseline and Follow-Up

Participants will obtain access to the app through trained faculty on the respective campus in order to complete the preliminary baseline survey. During the preliminary baseline survey, participants will fill out a questionnaire battery that consists of standard psychological measures. Demographic information, including age, year of schooling, gender, and ethnicity will be collected. Each participant will be invited to complete the same survey a month following the completion of the intervention (at the 12-month mark) and will be monitored until 1 year later.

Measures

Overview

The study instruments are presented in Table 1.

Table 1. Study instruments.

Instruments	Baseline	6 Months	12 Months
Demographic survey	✓		
Perceived Stress Scale-10	✓	✓	✓
Pediatric Social Relations-Interaction With Peers-Short Form	✓	✓	✓
Patient-Reported Outcomes Measurement Information System Pediatric Family Relationships 4a Short Form	✓	✓	✓
Patient-Reported Outcomes Measurement Information System Pediatric Global Health 7+2	✓	✓	✓
National Institutes of Health Toolbox Emotional Support Short Form 8-17	✓	✓	✓

Perceived Stress Scale-10

The Perceived Stress Scale (PSS-10) is a 10-item questionnaire developed by Cohen et al [16], used to gauge stress levels in individuals aged 12 years and older. It examines the degree to which situations are perceived as stressful in terms of how unpredictable, uncontrollable, and overloaded respondents find their lives. Scores range from 0 to 40, with higher scores representing higher levels of stress. Average scores are calculated by adding up the scores and dividing by the number of items, providing a useful indicator for evaluating the overall level of agreement on the Likert scale (where 0=never, 1=almost never, 2=sometimes, 3=fairly often, and 4=very Often).

Pediatric Social Relations-Interaction With Peers-Short Form

The Pediatric Social Relations-Interaction With Peers-Short Form is an 8-item scale that monitors social relationships and peer interactions in children with neurological conditions enduring lifelong functional limitations. Each question is scored numerically based on the individual's response (1=never, 2=almost never, 3=sometimes, 4=often, and 5=almost always), higher scores indicate better peer interactions. Scoring involves totaling the raw scores manually, followed by conversion to a *t* score.

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Patient-Reported Outcomes Measurement Information System Pediatric Family Relationships 4a Short Form

The Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Family Relationships 4a Short Form is a 4-item tool that assesses the determinants, outcomes, and protective impacts of children's subjective family relationship experiences. Each question receives a numerical score based on the individual's response (1=never, 2=rarely, 3=sometimes, 4=often, and 5=always), with higher scores indicating stronger family relationships. Scoring involves totaling the raw scores manually, followed by conversion to a *t* score.

PROMIS Pediatric Global Health 7+2

PROMIS Pediatric Global Health 7+2 is a 9-item scale that examines a child's overall perception of his or her physical, mental, and social health. This scale comprises a global health score alongside 1 fatigue and 1 pain interference item, scored separately. While these 2 items are administered, they do not contribute to the global health score; instead, they provide initial estimates for pain interference and fatigue. To calculate the total raw global sum score, add the response scores of the 7 items. Refer to the raw sum to *t* score tables for the appropriate scale. For the extra 2 items in Pediatric 7+2, no sum is needed.

National Institutes of Health Toolbox Emotional Support Short Form 8-17

The National Institutes of Health Toolbox Emotional Support Short Form 8-17 is a self-report measure that gauges emotional support through a 7-item form for ages 8-17 years. Each item uses a 5-point scale (where 1=never, 2=rarely, 3=sometimes, 4=usually, and 5=always). The surveys are scored using item response theory methods. An item response theory–derived θ and an uncorrected standard score (*t* score) are generated for each participant. Increased scores signify greater levels of emotional support.

Neolth

Neolth, a digital mental health app, provides preventative mental health support and education to teenagers ages 11 years and older. Neolth was devised specifically for youth as the target audience and is characteristically unique with the inclusion of school staff in the implementation of the program. Neolth's technology creates an individualized mental health education plan for each student in order to be able to provide personalized mental health content. Their existing digital program provides stress and mental health support to teens via the self-guided platform by delivering guided activities, a practice calendar, and activity reminders. Through the program, they have readily available access to resources for relaxation, emotional awareness, health education, and stigma reduction. Over a period of 5 logins, Neolth's evidence-based self-help process reduced teen stress [17]. In 3 weeks, Neolth reduced help-seeking stigma, acting as a stepping stone to clinical care for teens who need it [18].

Neolth is a digital app developed to serve as a resource for adolescents and young adults to support their mental health during this developmental period. It is primarily a preventive (tier 1) tool designed to support users manage mild to moderate levels of emotional distress. Additionally, Neolth offers an artificial intelligence (AI) system that flags users who exhibit signs of depression or self-harm. This feature serves as a supplementary safety measure for educational institutions, helping counselors by providing continuous monitoring of every student on a 24/7 basis. It is available for use as a mobile app, tablet, or desktop asset. The content and user interface of Neolth are based on current theories of stress and coping with the goal of maximizing accessibility and relevance while avoiding the pitfalls of a one-size-fits-all approach. Alignment with governmental support for school-based programs like SEL and the need for early identification of suicidality and distress, both optional features available to academic customers, are other priorities in the design and implementation of Neolth.

Neolth stands out as a unique digital mental health solution in several keyways. First, Neolth prioritizes school-centric accessibility, provides free access to 400 educational institutions across the United States, and ensures its widespread availability in academic settings. Second, Neolth places a strong emphasis on individualized mental health plans, as students create accounts and undergo initial assessments, forming the basis for crafting a personalized individualized mental health education plan tailored to the youth's specific stressors and coping styles. Third, Neolth actively engages users, enabling them to shape their mental health goals and interaction preferences and fostering higher engagement and personal investment in their well-being. Fourth, the app offers tailored engagement through user-specific calendars filled with guided activities and strategic reminders via email and push notifications. Fifth, Neolth uniquely integrates students into its development, from design aesthetics free of clinical jargon to content generated by student interns and ambassadors under the guidance of mental health professionals. Finally, Neolth distinguishes itself with diverse and relevant content, addressing a wide range of mental health topics through concise videos and informative blogs, ensuring that students' daily mental health concerns find practical solutions. Dynamic updates, including expert interviews, user-generated content, and monthly livestream sessions determined through user voting, underline Neolth's commitment to fostering a supportive mental health community within educational settings.

Neolth Features

Neolth offers a range of features specifically designed to address the diverse mental health needs of adolescents with precision and empathy. Recognizing that a one-size-fits-all approach is inadequate, Neolth provides personalized content recommendations that cater to individual needs rather than relying on generic anxiety or depression modules. This customization ensures that the app supports a spectrum of needs from clinical to wellness-oriented. Neolth also includes personalized crisis resources that cover a wide array of issues beyond suicide, such as domestic violence and substance use, preventing users from having to navigate extensive lists or websites for help. The community section is a valuable resource offering educational content from trusted professionals, thereby eliminating the need for adolescents to verify web-based information independently. This section also provides a private platform for learning about mental health and understanding

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others' experiences. Complementing this, the Student Stories feature fosters an emotional connection by allowing users to relate to and feel supported through the experiences shared by their peers, reinforcing the sense of community and alleviating feelings of isolation.

Neolth offers a comprehensive range of features designed to support and enhance mental health and well-being. The platform includes over 100 guided practices across several categories, such as mindfulness, breathing exercises, guided imagery, creative art, meditation, journaling, and cognitive behavioral therapy. These practices address diverse needs with topics including "beat self-doubt," "explore emotions," "mood booster," "rapid relaxation," "strengthen relationships," and "wipe out worry." In addition to its extensive library of guided practices, Neolth offers several unique features to support users' mental health journeys. Student Stories provide over 50 podcast and vlog-style narratives where students openly discuss their mental health experiences, fostering a sense of connection and reducing stigma. The Expert Advice Stories feature includes more than 100 interviews with health care professionals on topics such as academic stress; loneliness; health among lesbian, gay, bisexual, transgender, queer, and others; and healthy relationships with alcohol; thus offering users valuable insights and advice. To support users in monitoring their progress, Neolth includes tools for setting personalized goals, scheduling activities, tracking stress levels, and logging practice minutes, with monthly progress reports available to assess improvement. Additionally, Neolth enables users to confidentially share their progress with a therapist or doctor if desired. The platform's integration with Apple HealthKit further enhances tracking by incorporating data on time spent engaging in mental health activities.

Teachers will be given access to Neolth's educator platform, giving them the ability to curate lesson plans using Neolth's content geared toward their students' needs. Teachers can incorporate Neolth into their classroom routines in a way that suits their needs, allowing them to explore practical ways of implementing digital mental health tools in school settings. Teachers will also introduce Neolth's mobile app to students 11+, facilitating student sign up. By using both the educator platform and student mobile app, teachers will facilitate lesson plans within the classroom and allow students to complete self-guided activities on their own time.

Neolth Surveys

Intake data are collected via a brief in-app survey that is presented at the time of use initiation. The survey includes questions about stress and coping, mental and physical health diagnoses, behaviors and psychoemotional symptoms, and basic demographics. Based on intake survey responses, users are presented with initial content that is tailored to their needs. As users progress through the app, additional recommended practices will become available (Figures 2 and 3).

After beginning Neolth, users will be prompted to complete weekly and monthly check-ins within the app to report on their symptoms over time. Both weekly and monthly check-ins include the Short-Form PSS-4 [19]. On the PSS-4, respondents will be asked to report on the frequency of experiencing stressful situations, rated on a 5-point Likert scale ranging from 0 to 4 (where 0=never, 1=almost never, 2=sometimes, 3=fairly often, and 4=very often). Higher total scores indicate greater perceived stress. The PSS-4 assessments will be optional, meaning users can continue using Neolth whether they complete the periodic assessments or not. Neolth compiles users' self-assessment data recorded at check-ins within their profile, allowing users to visually track their own symptoms over time.

Figure 2. Neolth's dashboard for schools.

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Figure 3. Neolth's mobile app for students. (Explicit consent was obtained from the individuals in the image for their inclusion in the publication.).

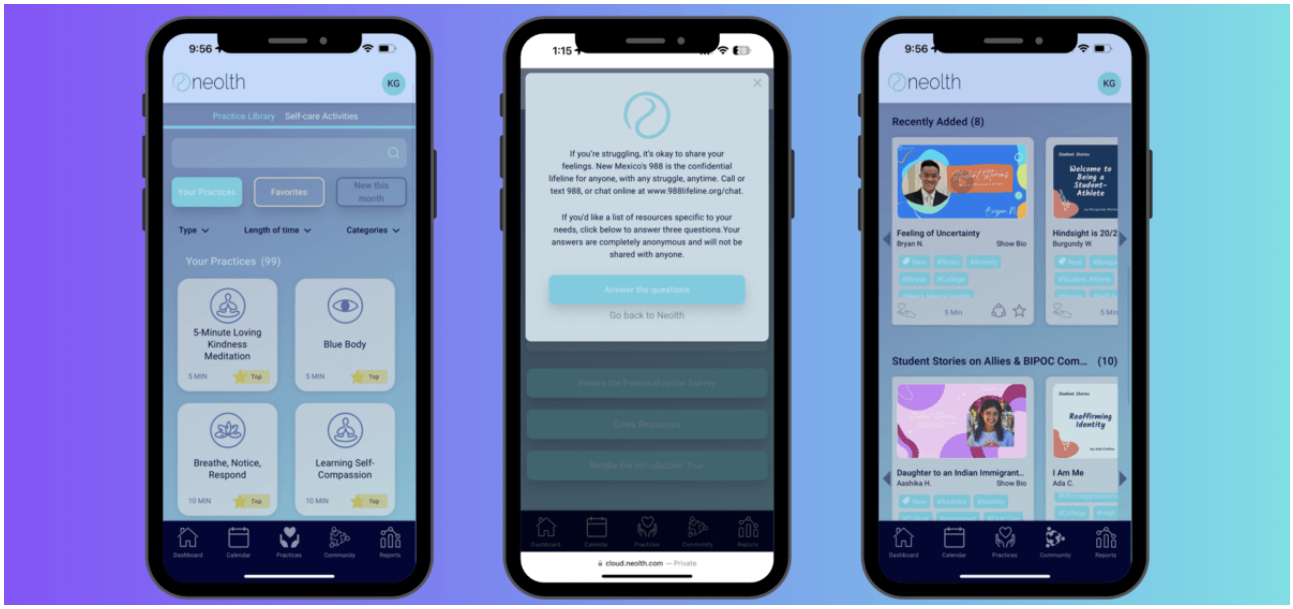

App Engagement

Engagement with the app will be measured using objective session-level use data, which was provided by Neolth. Retention rates, including 30, 60, 90, and >90-day retention, were provided, as well as the average number of Neolth logins per student and the average minutes per Neolth login.

The PSS-4 is a psychological instrument used to measure the perception of stress levels. We aim to assess the impact of using the platform on users' stress levels. The analysis of the PSS data will involve calculating mean scores and SDs to understand the average perceived stress level of Neolth users. Pre- and postuse measurements may also be compared to evaluate changes in stress levels.

The User Experience Questionnaire (UEQ) is a standardized tool designed to measure the user experience of digital products or services. It comprises various dimensions, such as attractiveness, efficiency, and dependability. By administering the UEQ to Neolth users, we aim to assess the overall experience of using the platform. The analysis will involve calculating mean scores and SDs for each dimension of the UEQ.

Statistical Analyses

The statistical analyses for the STEMSEL study will be conducted using the SPSS software (version 22.0; IBM Corp). Initially, paired-sample 2-tailed *t* tests will be used to compare the mean changes in the primary outcome measures, which include students' social and emotional well-being, anxiety, depression, and perceived stress levels, between the baseline assessment and the 12-month follow-up (Figure 4). These outcome measures will be assessed using validated instruments to ensure the reliability and validity of the results.

Subsequently, a linear regression analysis will be conducted to investigate the relationship between participants' engagement with the Neolth platform, specifically in the context of the well-being function of the app (recorded in minutes), and changes in their mental health status. This analysis will explore whether increased engagement with the digital mental health solution predicts improvements in mental health, including reductions in anxiety, depression, and perceived stress scores. Change scores for these mental health indicators will be calculated by subtracting follow-up scores from baseline scores, with positive values indicating improvements in mental health. To account for potential confounding factors, demographic variables, such as age and gender, will be included as control variables in the regression analysis. Additionally, ethnicity, treated as multicategorical variable, will be assessed using 1-way ANOVA with the primary outcome measures. Bonferroni post hoc tests will be conducted to follow up on any significant effects, allowing for a comprehensive examination of the data. Prior to conducting the statistical analyses, relevant assumptions, including the normal distribution of outcome measures, independence, normal distribution of residuals, linearity, and homoscedasticity, will be rigorously assessed to ensure the appropriateness of the chosen statistical methods. These robust analytical techniques will provide a thorough evaluation of the STEMSEL study's outcomes, shedding light on the impact of the digital mental health intervention on students' mental well-being and academic performance.

Demographic information will inform our study regarding gender, age, and ethnicity background. We will calculate the mean, median, and mode to gain insight into the central tendency of the data. We will note the distribution of the data and if there is outlier information that is pertinent to the data. For the primary objective of this study, to assess whether Neolth increases social and emotional wellness in students in grades 6-12, we will perform a general linear model (GLM) approach. The GLM is a statistical approach used to analyze the relationships between the dependent and independent variables. By applying the GLM, we will be able to assess whether Neolth had a significant impact on social and emotional intelligence over time among middle and high school students.

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Figure 4. Timeline.

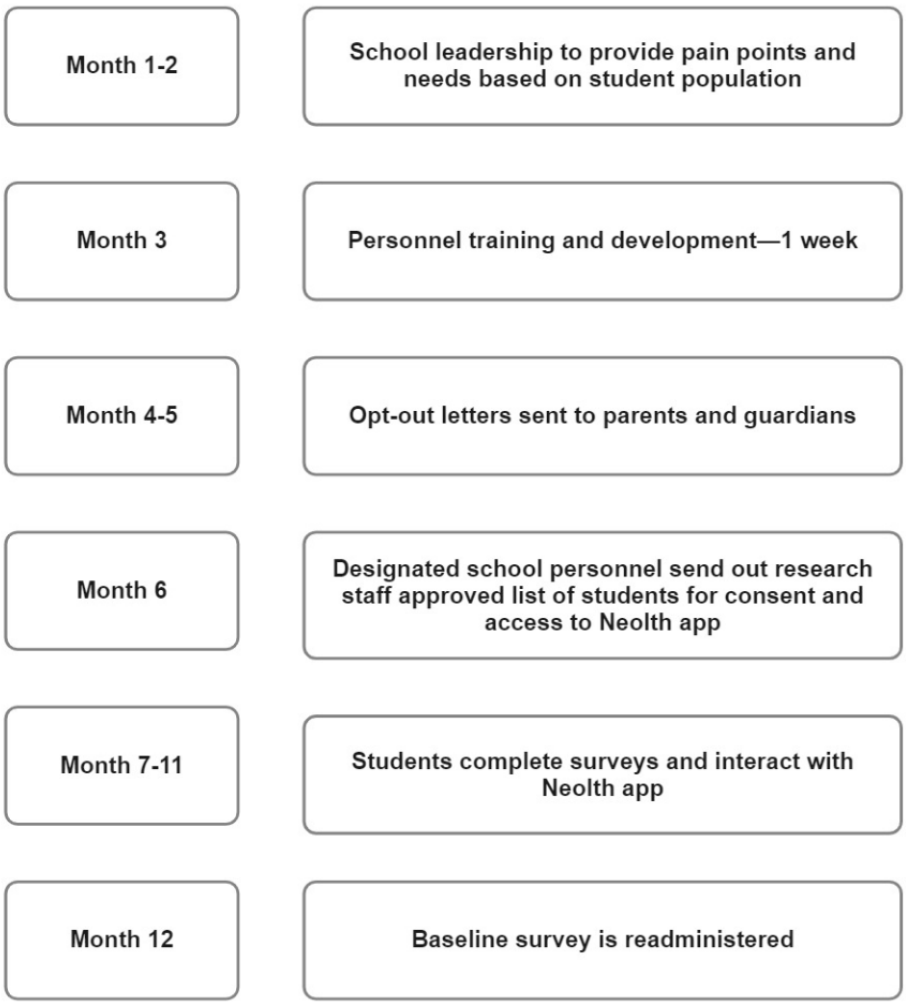

Crisis Escalation

As a tier 1 mental health program, Neolth offers psychoeducation, stigma reduction, and skill-building for students. However, Neolth also includes health tracking and alert features that seamlessly integrate into tier 2 and 3 supports for clinical and crisis care. Neolth's data scientists developed an AI system that screens students on the app, flagging those who exhibit signs of depression or self-harm. This feature serves as a supplementary safety measure for educational institutions, considering that counselors are unable to provide continuous monitoring of every student on a 24/7 basis. Any data that are flagged by Neolth will be reviewed by study clinicians. If it is determined escalation is needed, school staff will be notified per their established crisis protocol so they can check in with the student. The time period from app identification to clinician review and school notification should be approximately 30 minutes, meaning school staff can intervene immediately (Figure 5).

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Figure 5. Crisis response protocol. AI: artificial intelligence; STEMSEL: Science Technology Engineering Math and Social and Emotional Learning.

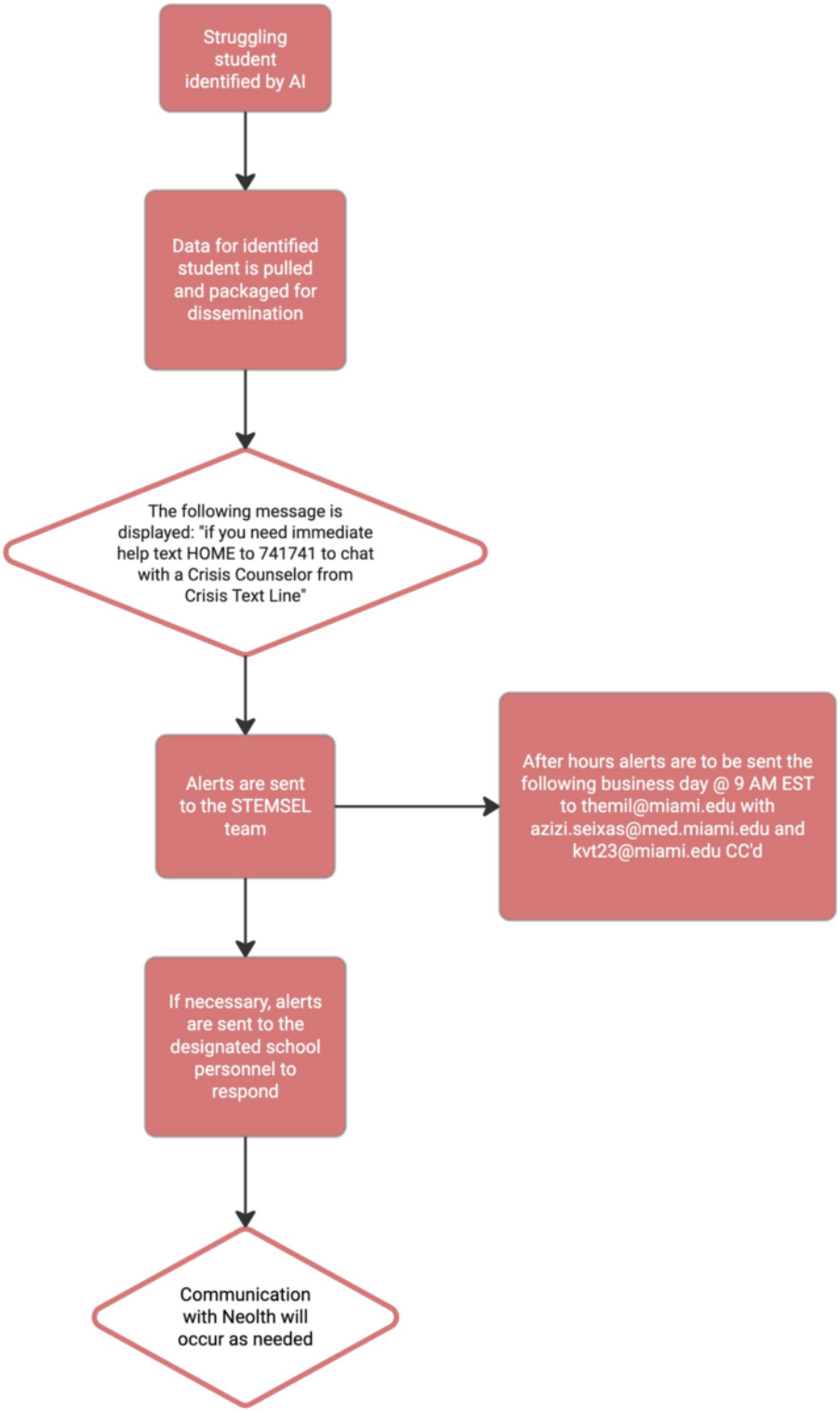

Results

Phase 1 Results

Phase 1 of the STEMSEL project was dedicated to conducting a comprehensive needs assessment across the participating schools, shedding light on the barriers and facilitators for implementing the program. One prominent finding was the stark limitations in available mental health resources within the school environment. Many of the schools lacked dedicated mental health professionals, resulting in a significant shortage of support services for students grappling with emotional and psychological challenges. Additionally, more rural schools faced a shortage of community-based mental health professionals available for students to access long-term care. This resource deficit emerged as a notable barrier to providing adequate mental health care within the school setting.

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Despite the resource constraints, the needs assessment revealed that many teachers and school staff exhibited a keen awareness of the mental health issues their students faced. This heightened awareness was perceived as a potential facilitator for the successful implementation of the STEMSEL program. It suggested that teachers and staff could play a pivotal role in identifying and supporting students in need of mental health interventions. Their awareness, coupled with a genuine concern for their students' well-being, hinted at a positive synergy that could drive the program's success. The needs assessment also highlighted that teachers and school staff exhibited a strong willingness to actively participate in the program's training sessions. This enthusiastic response signified a high level of commitment and engagement in addressing the mental health needs of the students they served. It underscored the potential for collaborative efforts between educators and mental health professionals to create a supportive and nurturing environment for school-aged youth.

We are recruiting middle and high school students aged 11-18 years from the participating schools. The recruitment process highlights the project's ability to engage and involve a wide range of students, recognizing that mental health challenges cut across various demographics. We are also obtaining consent from parents and legal guardians for students younger than 18 years of age, alongside securing the assent of all participating students. This phase reveals strong support from parents and legal guardians who willingly grant consent for their children's participation. This parental support emphasizes the importance placed on addressing the mental health and well-being of the younger generation, adding a layer of validation to the STEMSEL project's objectives.

Implementation Lessons Learned

The initial phase of the STEMSEL project was successfully completed in August 2022 and provided valuable insights into the challenges and opportunities of program implementation. These early findings yielded several critical lessons, including the urgent need for additional mental health resources within schools to effectively support students. The project also highlighted the importance of harnessing the awareness and willingness of teachers and staff to engage in mental health initiatives. Furthermore, it underscored the significance of securing parental support and student engagement as pivotal elements for successful program implementation. These findings and lessons learned serve as the foundation for the next phases of the STEMSEL project, guiding its efforts to improve the social and emotional well-being of school-aged youth while addressing the complexities of youth mental health care in educational settings.

Phase 2 Results

Data collection and enrollment commenced in October 2022 and is currently ongoing. Phase 2 is anticipated to conclude by the end of 2024. Data cleaning, analysis, and reporting of results are anticipated to be completed by early 2025. To date, educators at one STEMSEL site have reported positive outcomes with Neolth's AI feature, which assesses each student's needs and creates a personalized learning journey. Nonverbal students used Neolth's art practices to communicate their emotions, while college-bound students benefited from Neolth's Life Skills videos, which helped them develop communication and organization skills. The use of AI to personalize content has proven effective in addressing students' unique mental health needs. At another study site, Neolth played a critical role in supporting a student with attendance difficulties that raised concerns about potential expulsion. Neolth's AI algorithm identified signs of bullying and depression, prompting the school administration to address the bullying issue. The school also facilitated a connection between the student and a therapist, providing essential support. As a result of these interventions, the student is now on a path toward graduation, with noticeable improvements in their overall mental well-being and classroom engagement. This case demonstrates how Neolth's AI-powered platform can make a significant and tailored impact on individual students, addressing their unique challenges within the educational setting.

Discussion

Principal Findings

The discussion on mental health in our current society has become more prevalent and has furthered the acceptance of discourse on mental health. Youth populations, however, do not have adequate resources in regard to their mental health. Digital health resources are part of a new trend for access health care. mHealth has garnered attention because of its application being either a smartphone or tablet. mHealth interventions can be used as a more effective supplement regarding mental health for the youth population compared to traditional mental health methods. In total, 89% of teens have smartphones and spend, on average, over 7 hours per day on them [20,21]. While 90% of teens have favorable opinions of mHealth apps, less than 50% feel comfortable seeking counseling from a mental health provider [18,22]. Delivering mental health support through a mobile app enables mental health professionals to reach teens who are otherwise falling through the cracks. This is especially relevant for teens of color, who are less likely to use counseling even though their risk for depression and suicide is greater [23].

The partnership with Neolth sheds light for the need of an mHealth intervention for youth-age children within the school system that is aligned with students' generational care preferences. By providing technology-enabled support to all students, schools can normalize mental health at a young age, empowering teens with critical self-help knowledge and the courage to use clinical services when needed.

Despite these devices having a diverse selection of mental health apps, the effectiveness is still being questioned by researchers. Common themes that have created reservations about mHealth apps are privacy and confidentiality in regard to third parties having access to individuals' data, accessibility, and equal access across all socioeconomic levels, clinical validation, and the need for ethical-legal guidance [24]. The corroboration of mHealth apps use and decreasing mental health issues in the youth population is limited. Researchers are particularly focused on the efficacy of mHealth apps because those apps are not necessarily designed with the youth population in mind. The current mHealth apps for youth are being critiqued because they

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are not supported by evidence-based research to back their findings and they also may not be backing evidence-based treatment guidelines for certain mental health issues in the youth population [25].

Digital mental health apps like Neolth offer significant value in addressing youth mental health issues by tackling several critical challenges. They play a pivotal role in reducing stigma by providing a private and accessible platform for mental health support, enabling users to seek help without fear of judgment. The app's on-demand nature ensures that adolescents can access mental health resources anytime and anywhere, overcoming barriers related to geographical and scheduling constraints. By offering personalized content and treatment plans tailored to individual needs, Neolth addresses the variability in mental health challenges and preferences among youth. This personalization enhances engagement and effectiveness, as the app caters to specific issues such as anxiety, depression, and stress. To further advance this field, future research should explore how digital mental health tools can be integrated with traditional services to create a more holistic support system. Additionally, studying the long-term impacts of these apps on various demographics will provide insights into their sustained effectiveness. Enhancing user engagement and adherence through innovative features and continuous feedback mechanisms will also be essential for maximizing the benefits of digital mental health interventions.

Limitations

This study lays out a thorough plan for implementing the Neolth intervention in 3 selected Florida schools, with a focus on its accessibility, scalability, and feasibility. Despite these strengths, several limitations must be acknowledged. The study's restriction to 3 schools in Florida limits the generalizability of the findings. This geographic limitation means that the results may not be applicable to schools in other regions with varying demographic, socioeconomic, and educational contexts. Regional educational policies and practices unique to Florida, such as specific state mandates and funding priorities, could also influence the outcomes in ways that may not be relevant to other states. Additionally, differences in educational settings within Florida, such as urban, suburban, and rural schools, could lead to varying results not captured by the limited sample of 3 schools. Future research would benefit from involving a broader range of schools across different regions to enhance the generalizability of the findings.

The digital nature of Neolth presents potential challenges, including technical issues with the app and varying levels of digital literacy and engagement with the app outside of school hours. While Neolth's innovative approach offers new opportunities, the intervention may not be ideal for all students, particularly those facing a digital divide or with limited access to technology. Teachers may also struggle to integrate the intervention effectively due to time constraints and competing responsibilities. Furthermore, Neolth primarily caters to English-speaking students, which may exclude non-English speakers or those with limited English proficiency. Despite these limitations, the study's strengths lie in its potential to reach a broader audience compared to traditional mental health methods. Future studies should address these limitations by exploring diverse educational settings, overcoming digital access barriers, and ensuring inclusivity for all students to fully evaluate the efficacy and scalability of digital mental health interventions.

Conclusions

The STEMSEL project highlights the advantages of using digital solutions to address the complex mental health and SEL needs of school-aged youth. Implementing digital interventions allows for flexible, on-demand access to resources tailored to individual needs, making it easier to reach students where they are. Engaging multiple stakeholders, including teachers, parents, students, and counselors, is crucial for overcoming the multifaceted barriers to mental health support. Schools provide a structured environment where these interventions can be seamlessly integrated into daily routines. The phased implementation and training of school staff are essential for ensuring the program's success, as they equip educators with the skills and knowledge necessary to effectively support and sustain the intervention. This comprehensive approach aims to bridge existing resource gaps and empower educators to play a pivotal role in enhancing student well-being.

Future research should concentrate on the longitudinal effects of digital mental health interventions, particularly in understanding their long-term impact on student well-being and academic outcomes. Emphasizing the role of the decentralized trial framework, future studies need to explore how this approach can enhance the accessibility, engagement, and effectiveness of mental health tools across diverse educational settings. Evaluating how these interventions sustain their benefits over time and across different contexts will be crucial for informing future strategies and ensuring the broad applicability and success of digital mental health solutions. Finally, future studies should incorporate comprehensive training for educators and students on using digital solutions prior to deploying the app, as this will enhance digital literacy and reduce the risk of confounding variables that could affect the study's findings.

Conflicts of Interest

KBG is a co-founder of Neolth. All other authors declare no conflicts of interest.

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Abbreviations

AI: artificial intelligence
GLM: general linear model
mHealth: mobile health
MOST: moderated online social therapy
PROMIS: Patient-Reported Outcomes Measurement Information System
PSS: Perceived Stress Scale
REDCap: Research Electronic Data Capture
SEL: social and emotional learning
STEMSEL: Science Technology Engineering Math and Social and Emotional Learning
UEQ: User Experience Questionnaire
UM: University of Miami

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Protocol

Virtual Reality–Applied Home-Visit Rehabilitation for Patients With Chronic Pain: Protocol for Single-Arm Pre-Post Comparison Study

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Abstract

Background: Pain inhibits rehabilitation. In rehabilitation at medical institutions, the usefulness of virtual reality (VR) has been reported in many cases to alleviate pain. In recent years, the demand for home rehabilitation has increased. Unlike in medical situations, the patients targeted for in-home rehabilitation often have chronic pain due to physical and psychosocial factors, and the environment is not specialized for rehabilitation. However, VR might be effective for in-home rehabilitation settings.

Objective: This study aims to evaluate the feasibility of applying VR to home-visit rehabilitation for homebound patients with chronic pain.

Methods: This study will test the feasibility of VR applied to home-visit rehabilitation for patients with chronic pain. A single-arm pre-post comparison will be conducted to evaluate its feasibility. Screening will be conducted on patients who have given consent to participate in the study, and those who have pain that persists or recurs for more than 3 months and receive home-visit rehabilitation will be enrolled in the study. Baseline measurements will be conducted on study participants before the start of the VR intervention. VR-applied home-visit rehabilitation will be conducted once a week for a total of 10 VR interventions. The primary endpoint is the change in pain from the baseline to the tenth intervention. Pain is a subjective symptom of the study participants and will be subjectively assessed by the Numerical Rating Scale of 11 levels from 0 to 10. Pain as the primary endpoint will be measured at 3-time points per rehabilitation session: before, during, and after the rehabilitation so that changes between time points can be evaluated. Secondary endpoints are heart rate variability, range of motion of the area in the musculoskeletal system where the pain occurs, motivation for rehabilitation, catastrophic thoughts of pain, mood state, quality of life, and interviews. Assessments will be conducted at the baseline, first, fifth, and tenth interventions. After completing the clinical study (10 VR interventions), patients will continue their regular home-visit rehabilitation as usual.

Results: Recruitment of participants began on February 22, 2022, and data collection is ongoing as of November 2024. The research results will be published in international peer-reviewed journals and through presentations at national and international conferences.

Conclusions: This study will contribute to the development of novel rehabilitation-based solutions for homebound patients who have had difficulty obtaining adequate relief from chronic pain. Future studies will consider conducting randomized controlled trials as clinical trials to validate the efficacy of VR during home-visit rehabilitation for patients with chronic pain.

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KEYWORDS

chronic pain; homebound patient; home-visit rehabilitation; virtual reality; protocol; feasibility study; VR; pain; recurrent pain; home visit; rehabilitation; home rehabilitation; in-home; effective; screening; VR intervention; feasibility; alleviate pain

Introduction

Chronic pain is defined as pain that persists or recurs for longer than 3 months [1]. It is multifactorial with biological, psychological, and social factors and affects an estimated 20% of people worldwide [2]. Rehabilitation has been shown to be effective in improving not only functional disabilities but also chronic pain [3-5]. However, the increase in exercise-induced pain and the fear of exercise due to pain are challenges that hinder effective rehabilitation [6]. Furthermore, as indicated by the fear-avoidance model of pain [7], the experience of chronic pain caused by physical disabilities and exercise-induced pain associated with rehabilitation can increase anxiety and fear in patients. This leads patients to avoid physical activity, including rehabilitation, and the resulting inactivity and depression lead to a vicious cycle that exacerbates chronic pain.

Many homebound patients have chronic pain and functional disabilities [8]. These patients are often anxious and depressed due to restricted social participation [9]. Homebound patients have psychosocial factors, making it difficult to establish a treatment for chronic pain. As many homebound patients are unable to visit medical institutions, home rehabilitation is important. Unlike medical institutions, patients' homes are not optimal environments for engaging in effective rehabilitation programs. As a result, patients find it difficult to engage in rehabilitation and are more likely to lose their motivation [10]. Maintaining motivation is more difficult when the home rehabilitation session is prolonged [11]. Home rehabilitation for patients with chronic pain requires an approach that not only relieves pain but also considers psychosocial factors, such as depression, anxiety, and low motivation.

Other chronic pain management measures include pharmacotherapy [12,13], interventional therapy [14], and psychotherapy [15]. However, the use of analgesics can lead to dependence, and, in older people with many underlying medical conditions, there is a risk of multiple drug use leading to adverse symptoms [16]. Furthermore, interventional treatment, which requires regular hospital visits and inpatient care, is burdensome for patients at home. Psychotherapy may also be difficult to manage adequately due to human and time constraints on visits by professional staff [17]. Therefore, there is a need for chronic pain management measures that are nonpharmacological and can be easily implemented at home.

Virtual reality (VR) is a 3D computer-generated simulated environment, which attempts to replicate real-world or imaginary environments and interactions [18]. In recent years, VR has been used in a variety of applications in the medical field, including to alleviate pain and facilitate rehabilitation. Immersion in a simulated virtual environment that produces powerful psychological effects, including relaxation, has been shown to be effective in relieving various types of pain, from acute to chronic [19,20]. VR brings a sense of presence that can be very overpowering and diminish a person's ability to respond to noxious stimuli and attend to nociceptive neural signals, resulting in less perceived pain [21]. This mechanism is described as a distraction, and any strategy used to modulate pain in VR typically builds on a level of distraction [19]. A rehabilitation program with VR can help patients maintain a positive attitude toward rehabilitation and promote recovery of physical functions [22]. For in-home rehabilitation, a focus on motivation and medical costs for homebound patients has been reported to improve training effectiveness due to motivation [23,24]. However, there is currently insufficient clinical evidence regarding the effects of VR for chronic pain in home-visit rehabilitation. This study aims to evaluate the feasibility of applying VR to home rehabilitation for homebound patients with chronic pain. Alleviation of chronic pain using VR will help facilitate rehabilitation; thereby, rehabilitation will be more effective in improving chronic pain.

Methods

Overview

A single-arm pre-post comparison will be conducted to evaluate the feasibility. This study protocol has been developed using the findings from our case report on the VR applied to home-visit rehabilitation for hemiplegic shoulder pain in a patient with stroke [25]. In this case, VR was newly applied to a part of the home-visit rehabilitation that the patient had been working on. The VR-applied home-visit rehabilitation was carried out on a weekly basis, and during the intervention period, which was close to a month, the results suggested the chronic pain was continuously relieved compared with before the use of VR.

Recruitment Process

The study participants will be recruited from several institutions. Screening will be conducted on patients who give consent to participate in the study, and those who meet the criteria will be enrolled as research participants.

Researchers contact the representative of the home health care agency providing the home rehabilitation service, explain the research outline, and establish a cooperative framework. Each representative picks up patients who meet the criteria. Researchers visit the patients, assess them for compliance with the criteria, and obtain explanations and consent. As the study period coincides with the COVID-19 pandemic, researchers should explain to patients and take the following actions: standard infection control measures should be taken during the researchers' visit; research equipment should be controlled and disinfected by the researchers; and the possibility of COVID-19 infection in relevant personnel should be considered. If there is a possibility that the person concerned may be infected with COVID-19, the visit should be canceled or postponed.

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Inclusion Criteria

Patients who meet all of the criteria will be enrolled in the study and the criteria are to (1) have pain that persists or recurs for more than 3 months, (2) receive home-visit rehabilitation, (3) have adequate visual and auditory functions to use the VR equipment, (4) have adequate cognitive and perceptual functions to answer questions measuring subjective symptoms, (5) be at least 20 years of age at the time of consent, and (6) give their free and voluntary written consent to participate in the study, after being fully informed. As the study participants are patients with chronic pain in home care and may have different physical and cognitive ability levels, the following points should be noted; no sensory or cognitive impairment has been diagnosed by the family doctor; the patient is able to see and hear the content with the opportunity to trial the VR before the study begins; and there is a good level of understanding of the research description.

Exclusion Criteria

Patients who meet any of the criteria will be excluded from the study and the criteria are to (1) have a history of adverse events due to the use of VR devices and (2) are deemed inappropriate for the study by the principal investigator.

Sample Size

The sample size of 40 cases was not set by statistical detection. It was established based on the median number of cases in reports of studies using immersive VR for pain relief [26-29]. In this study, the targeted number of cases was set based on the assumption that due to the many older patients in the trial, there would be a dropout rate of approximately 15% during the intervention. This dropout rate was based on previous studies that used VR-based rehabilitation interventions [22,30].

Information on Virtual Reality Devices and Contents

The intervention in this study is VR-applied home-visit rehabilitation. VR will be used during the rehabilitation procedures that the study participants usually engage in.

The VR device used in this study will be Meta Quest 2 (Meta Platforms Inc), which is one of the most widely used VR devices by the general public (Figure 1). Meta Quest is a headset-type VR viewing device, which is worn by fixing on the head a device covering the field of vision. It enables viewing of images in 360 degrees in all directions, in accordance with the frontal orientation of the face, and listening to environmental sounds that accompany the images. The researcher manages the VR device and brings the device to the patient's home. If the patient has difficulty setting up and fitting the VR device themselves, the researcher will fit or assist them.

Figure 1. The virtual reality device which is used in this study (Meta quest2).

The VR content viewed with Meta Quest 2 will be selected by researchers from natural landscapes available on YouTube VR [31]. This is because one of the VR contents that has the psychological effect of promoting pain relief is landscape

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[32,33]. In addition, to prevent adverse symptoms associated with the use of VR, the contents that do not change the viewpoint frequently and violently should be selected [34]. In addition, as the participants used VR during their usual rehabilitation, there is no need to perform online operations during VR viewing to avoid affecting the rehabilitation. These will include 10-15 minutes of content of landscapes such as beaches, flower fields, forests, and plateaus (Figure 2). The researcher is present when the VR is used and confirms, and records which content is viewed. The types of landscapes used will be changed regularly so that research participants can experience more than one type of content. The time of the home-visit rehabilitation will be about 40-60 minutes, and VR content will be provided during a part of that time. Rehabilitation will continue while the VR content is being experienced. To ensure the safety of the research participants, VR content will only be provided when they are in a supine or seated position, as wearing the VR equipment will block their full field of vision. Expected adverse events in this study will include pressure sores at the site where the VR equipment is worn, muscle strain from the neck to the shoulders (eg, pain, tightness, and heaviness) due to the load of the VR equipment, and discomfort from viewing VR images (VR sickness) [35], all of which are expected to be mild and tolerable. If any of these adverse events should occur, the VR will be stopped as soon as possible, the patient will be monitored, and medical attention will be sought if necessary.

Figure 2. The virtual reality content is viewed with Meta quest2 (YouTube virtual reality).

Data Collection

Outline

Baseline parameter measurements will be conducted on study participants before the start of the intervention. Baseline measurements will be taken during 3 usual home-visit rehabilitation as (without VR). VR applied home-visit rehabilitation will be carried out once a week, for a total of 10 times. Assessments will be conducted at the baseline, the end of the first intervention, the end of the fifth intervention, and the end of the tenth intervention. Parameter measurements in the study will include pain score, heart rate variability, range of motion, and various patient questionnaires and interviews to evaluate motivation, mood state, catastrophic thoughts of pain, and impressions about VR-applied rehabilitation. For the safety assessment of VR-applied home-visit rehabilitation, the presence and extent of symptoms related to the use of VR equipment and viewing of contents will be ascertained. Data will be collected by the researcher both at baseline and during the VR sessions. The researcher is present and observes the user during the rehabilitation visit, which includes the use of VR and collects and records a range of data. This ensures that the quality of the data collected is controlled. After the end of this clinical study, patients will receive home-visit rehabilitation as usual (without VR; Figure 3).

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Figure 3. Outline for data collection. BREQ-2: Behavioral Regulation in Exercise Questionnaire-2; HRV: heart rate variability; PCS: Pain Catastrophizing Scale; POMS 2: Profile of Mood State 2; ROM: range of motion; SF-12: Short-Form Health Survey; VR: virtual reality.

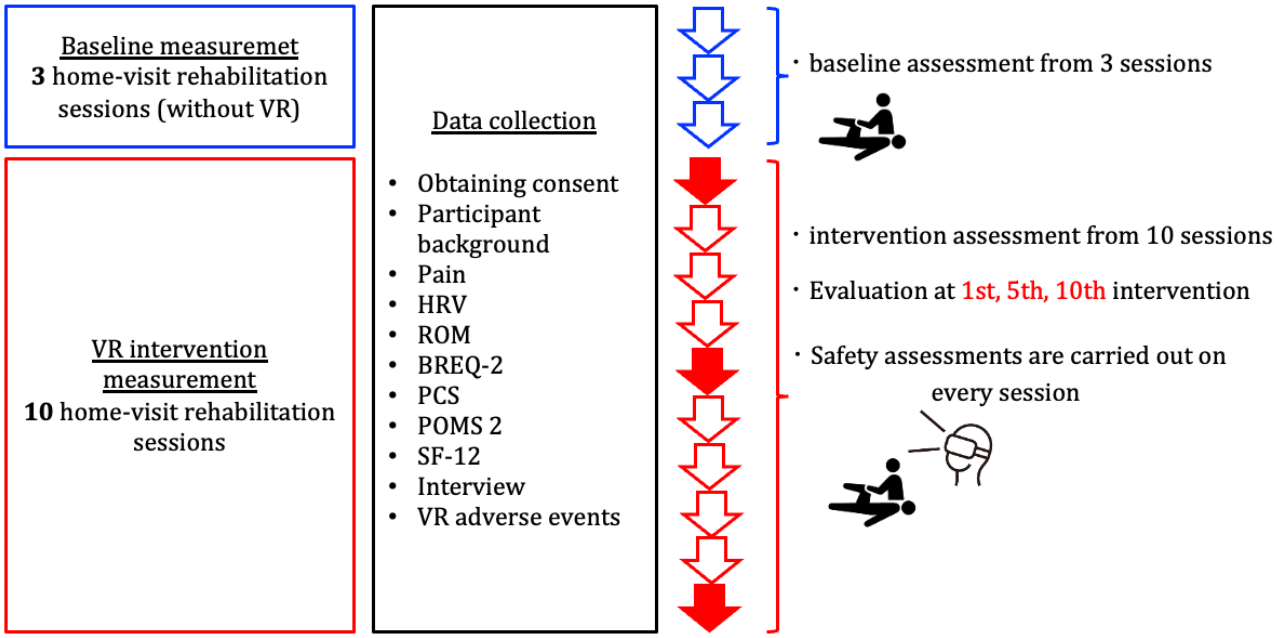

Variables

The primary variable is the change in pain from the baseline (before the VR interventions) to the tenth VR intervention. As pain is a subjective symptom of the study participants, it will be subjectively assessed by the Numerical Rating Scale (NRS) on a scale of 0-10, in which 0 indicates no pain at all and 10 indicates the most intense pain experienced so far [36]. The pain as the primary variable will be measured at 3 time points per rehabilitation session: before, during, and after the rehabilitation so that changes between time points will be evaluated.

Secondary variables are heart rate variability (HRV), range of motion (ROM) in the musculoskeletal system area where the pain occurs, motivation for rehabilitation (Behavioral Regulation in Exercise Questionnaire-2 [BREQ-2]), catastrophic thoughts of pain (PCS [Pain Catastrophizing Scale]), mood state (Profile of Mood State 2 [POMS 2]), and quality of life (Short-Form Health Survey [SF-12]).

HRV represents the ability of the heart to respond to physiological and environmental stimuli. Previous studies have shown the feasibility of HRV as a psychophysiological measurement for reactivity to stress [33]. HRV will be measured at the baseline and each VR intervention and changes from the baseline to the tenth intervention will be assessed.

ROM is the range in which each joint of the body can be physiologically exercised without injury or pain. It is one of the outcomes of rehabilitation and is also used to measure the effectiveness in patients with chronic pain [37,38]. ROM of the musculoskeletal system around where the pain occurs will be measured at the baseline and each VR intervention and changes from the baseline to the tenth intervention will be assessed.

The BREQ-2 is a 19-item scale based on self-determination theory to assess behavioral regulation in exercise. BREQ-2 asks questions relating to why they engage in physical activity and exercise, and their responses are measured on a 5-point Likert-type scale ranging from 1 (not true) to 5 (very true). The scale has 5 subscales measuring 5 types of exercise regulations, that are motivation, external regulation, introjected regulation, identified regulation, and intrinsic regulation [39]. The BREQ-2 will be applied at 4 time points, which consist of baseline, first, fifth, and tenth VR interventions and changes in scores between time points will be assessed.

The PCS assesses the extent to which participants experience magnification, rumination, and helplessness in response to their pain episodes [40]. The PCS has 13 items, each scored on a 5-point Likert scale from 0 to 4 (0: not at all, 4: all the time). The PCS is reported as a total composite score (range 0-52), with higher scores indicating greater catastrophic thoughts about pain. PCS scores will be measured at 4-time points, which consist of baseline, first, fifth, and tenth VR interventions, and changes in scores between time points will be assessed.

The POMS 2 questionnaire is used to monitor mood changes, particularly participants' psychological stress. This scale consists of subjective feelings in 6 different mood states (tension, depression, anger, fatigue, confusion, and vigor). A 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely), is used for each item. The higher scores indicate more pronounced emotions [41]. POMS 2 will be applied at 4-time points, which consist, of baseline, first, fifth, and tenth VR interventions, and changes in scores between time points will be assessed.

A 12-Item SF-12 is a health-related quality of life scale [42]. SF-12 consists of multiple questions to measure eight health concepts, that are physical functioning, limiting physical health problems, bodily pain, general health, vitality, social functioning, limiting emotional problems, and mental health. Information from all 12 items is used to construct physical and mental component summary measures [43]. The SF-12 will be applied at 3 time points, that are baseline, the fifth, and tenth

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VR interventions, and changes in scores between time points will be assessed.

Through interviews with study participants at the tenth intervention, the effects of VR-applied home-visit rehabilitation will be evaluated, including pain alleviation, promotion of motivation, improvement in mood state and pain catastrophic thinking, and patients' and families' impressions.

As part of the safety evaluation, the presence and degree of subjective symptoms will be checked using the NRS, which is expressed on an 11-point scale from 0 to 10, for pressure pain at the site where the VR equipment is worn, muscle strain from the neck to the shoulders due to the load of the VR equipment, and discomfort caused by viewing VR images (VR sickness) [35]. The adverse event NRS will be measured at each VR intervention.

Baseline measurements will be taken during 3 usual home-visit rehabilitation as (without VR). For pain and heart rate variability, the average of 3 rehabilitation visits on different days will be used as the baseline value. The joint range of motion and each questionnaire score will be measured once as a baseline.

The observation and examination items will be collected according to the schedule (Table 1).

Table 1. Schedule of the observation and examination.

	Baseline (home-visit rehabilitation)			Intervention period (VR applied home-visit rehabilitation)								
	1st	2nd	3rd	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Obtaining consent	✓												
Participant background	✓												
Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HRV[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ROM[b]	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BREQ-2[c]	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PCS[d]	✓			✓				✓					✓
POMS 2[e]	✓			✓				✓					✓
SF-12[f]	✓							✓					✓
Interview													✓
VR[g] adverse events				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]HRV: heart rate variability.

[b]ROM: range of motion.

[c]BREQ-2: Behavioral Regulation in Exercise Questionnaire-2.

[d]PCS: Pain Catastrophizing Scale.

[e]POMS 2: Profile of Mood State 2.

[f]SF-12: Short-Form Health Survey.

[g]VR: virtual reality.

Safety Evaluation

As part of the safety evaluation, the presence and degree of subjective symptoms will be checked for pressure pain at the site where the VR equipment is worn, muscle strain from the neck to the shoulders due to the load of the VR equipment, and discomfort caused by viewing VR images (VR sickness) [35]. Based on previous studies with patients at home, and also to measure the physical burden of wearing the head-mounted display, these items are measured using the NRS [44]. The adverse event will be measured at each VR intervention.

The condition of study participants will be observed before the start of VR use to check and assess for any problems in using VR; a researcher will be present at all times during the home visit rehabilitation, including the use of VR, to observe any changes in condition. If any participant develops adverse symptoms such as VR sickness at any stage before completing the VR session, the study will be terminated, and the participant will be excluded from the study. The study does not have a follow-up period after the VR sessions for all study participants; however, any patients who have adverse symptoms during the VR sessions will be monitored until their condition has recovered and stabilized.

Statistical Analysis

The analysis will include patients who participate in at least one VR-applied home-visit rehabilitation. The primary variable will be analyzed for the participants who completed the baseline and all 10 interventions. Baseline characteristics will be assessed using descriptive statistics. For both the primary and secondary

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variables, descriptive statistics (mean, SD) will be calculated for a single group and evaluated at a 2-sided 5% level of significance, with 1-way repeated measures ANOVA in the case of data with a 2-sided distribution and Friedman test for data without a normal distribution. Relevant qualitative data will be summarized and reported as appropriate. The data are analyzed in R version 4.3.2 (R Foundation for Statistical Computing).

Ethical Considerations

The study was approved by the Clinical Research Ethics Review Committee of Mie University Hospital (H2021-143) and registered as a clinical trial in "UMIN; University Hospital Medical Information Network" (UMIN000045039). All study participants were informed of the details of the study and gave face-to-face informed consent before the study began. Participants' data will be anonymized and managed so that personal information cannot be identified.

Results

Recruitment of participants began on February 22, 2022, and data collection is ongoing as of November 2024. The research results will be published in international peer-reviewed journals and through presentations at national and international conferences.

Discussion

Principal Findings

This study will lead to the development of new rehabilitation-based solutions for homebound patients who have difficulty obtaining adequate relief from chronic pain. A rehabilitation program with VR has been reported to alleviate chronic pain [21], and a mechanism of this alleviation is to distract patients from the pain by immersion in VR [19]. However, there is currently insufficient clinical evidence regarding the effects of VR for chronic pain. Especially in home-visit rehabilitation, the feasibility of using VR over the medium to long term and its effectiveness has not been fully clarified.

Existing chronic pain management measures, such as pharmacotherapy, intervention therapy, and psychotherapy, may be difficult to manage adequately because of the risk of side symptoms and the physical and psychosocial burden on the patient [16,17]. Therefore, there is a need for nonpharmacological chronic pain management measures that can be easily implemented at home.

In the current study, exercise-induced pain will be alleviated by using VR during home-visit rehabilitation, thereby increasing ROM. As increased ROM enhances the effectiveness of rehabilitation [45], chronic pain will be improved through rehabilitation. Furthermore, since pain relief with VR alleviates psychophysiological stress conditions [19], HRV should show a state of parasympathetic dominance in the activity of the autonomic nervous system [33]. The improvements in pain will also promote motivation, pain catastrophizing thinking, and mood state, measured by BREQ-2, PCS, and POMS 2, respectively [39-41], even in homebound patients who are difficult to motivate and have poor psychosocial health [9,10]. The experience of (simulated) natural landscapes brought about by VR will improve psychosocial factors in homebound patients, who infrequently leave their homes, and help improve quality of life in the medium to long term measured by SF-12 [42,43].

Therefore, this study will contribute to the development of novel rehabilitation-based solutions for homebound patients who have had difficulty obtaining adequate relief from chronic pain.

Although VR is generally considered to be a safe and noninvasive procedure with few side effects, the use of VR has been reported to induce VR sickness [35]. One must be aware of the potential occurrence of VR sickness and carefully observe the patient's condition during the administration of VR. It is assumed that many patients at home are older adults, which may be a barrier to the introduction of VR into home rehabilitation. For VR to be successfully applied to older people, careful induction sessions are important, and the process needs to be evaluated. Limitations of this feasibility study are the small number of cases as well as the lack of blinding and controls.

Conclusion

Future validation studies will consider conducting randomized controlled trials as clinical trials to verify efficacy.

Acknowledgments

We would like to thank the patients and families who participated in this study, as well as the medical staff at the collaborating institutions.

Data Availability

The datasets generated or analyzed during this study will not be publicly available but will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BREQ-2: Behavioral Regulation in Exercise Questionnaire-2

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HRV: heart rate variability
NRS: Numerical Rating Scale
PCS: Pain Catastrophizing Scale
POMS 2: Profile of Mood States 2nd Edition
ROM: range of motion
SF-12: Short-Form Health Survey
VR: virtual reality

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Protocol

Evaluation of the Development, Implementation, Maintenance, and Impact of 3 Digital Surveillance Tools Deployed in Malawi During the COVID-19 Pandemic: Protocol for a Modified Delphi Expert Consensus Study

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Abstract

Background: The COVID-19 pandemic has highlighted the importance of strengthening national monitoring systems to safeguard a globally connected society, especially those in low- and middle-income countries. Africa's rapid adoption of digital technological interventions created a new frontier of digital advancement during crises or pandemics. The use of digital tools for disease surveillance can assist with rapid outbreak identification and response, handling duties such as diagnosis, testing, contact tracing, and risk communication. Malawi was one of the first countries in the region to launch a government-led coordinated effort to harmonize and streamline the necessary COVID-19 digital health implementation through an integrated system architecture.

Objective: The aim of this study is to seek expert consensus using the Delphi methodology to examine Malawi's COVID-19 digital surveillance response strategy and to assess the digital tools using the World Health Organization mHealth (mobile health) Assessment and Planning for Scale (MAPS) toolkit.

Methods: This protocol follows the Guidance on Conducting and REporting DElphi Studies. Participants must have first-hand experience on the design, implementation or maintenance with COVID-19 digital surveillance systems. There will be no restrictions on the level of expertise or years of experience. The panel will consist of approximately 40 participants. We will use a modified Delphi process whereby rounds 1 and 2 will be hosted online by Qualtrics and round 3 will encompass a face-to-face workshop held in Malawi. Consensus will be defined as ≥70% of participants strongly disagree, disagree, or somewhat disagree, or strongly agree, agree, or somewhat agree. During round 3, the face-to-face workshop, participants will be asked to complete, the MAPS

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toolkit assessment on the digital tool on which they are experts. The MAPS toolkit will enable the panel members to assess the digital tools from a sustainable perspective from six distinct, yet complementary axes: (1) groundwork, (2) partnerships, (3) financial health, (4) technology and architecture, (5) operations, and (6) monitoring and evaluation.

Results: The ability of a country to collate, diagnose, monitor, and analyze data forms the cornerstone of an efficient surveillance system, allowing countries to plan and implement appropriate control actions. Malawi was one of the first countries in the African region to launch a government-led coordinated effort to harmonize and streamline the necessary COVID-19 digital health implementation through an integrated system architecture.

Conclusions: We anticipate findings from this Delphi study will provide insights into how and why Malawi was successful in deploying digital surveillance systems. In addition, findings should produce recommendations and guidance for the rapid development, implementation, maintenance, and impact of digital surveillance tools during a health crisis.

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KEYWORDS

delphi study; COVID-19; Malawi; surveillance; digital health; delphi; mobile health; mHealth; development; implementation; maintenance; impact; consensus; protocol; survey; expert; purposive sampling; epidemiology; descriptive statistics

Introduction

Background

Emergent zoonotic diseases have had disastrous global consequences, particularly in low- and middle-income countries (LMICs). LMICs are also impacted strongly by endemic and overlooked zoonotic illnesses [1]. Despite investments by the global health community, in increasing disease surveillance systems capacities across LMICs, initiatives need to be more cohesive and frequently fail to reach communities in remote rural areas [2]. Insufficient surveillance in such communities can lead to disease outbreaks being detected at a later stage and responded to ineffectively, thus, increasing the likelihood of pandemics inflicting greater damage due to latent amplification along with regional and global travel. The COVID-19 pandemic has highlighted the importance of strengthening national monitoring systems in order to safeguard a globally connected society, especially those in LMICs [3]. To combat the COVID-19 pandemic, local governments, nongovernmental organizations, and individuals have reused existing technologies and developed innovative solutions [4].

A 2022 study that conducted thematic synthesis of the World Health Organization intra-action review reports in 18 African countries noted that findings were suggestive that African countries responded quickly to the virus and should be commended for their efforts [5]. In particular, Africa's rapid adoption of digital technological interventions created a new frontier of digital advancement during crises or pandemics [6]. The use of digital tools for disease surveillance can assist with rapid outbreak identification and response, handling duties such as diagnosis, testing, contact tracing, and risk communication [6].

During the COVID-19 pandemic, the dominant type of digital surveillance in Africa was track and trace systems, which were largely obtained from telecommunications data and specific apps. However, during national lockdowns, nations such as Ethiopia and Sierra Leone implemented internet-based payment systems and electronic travel pass management to ensure distancing amongst travelers and to restrict movement to vital personnel [7]. Drones were used in Morocco, Sierra Leone, and Tunisia to send warnings and notifications, as well as to ask individuals on the street to provide their motives for being outdoors during lockdowns [8-10]. Furthermore, technologies that enable mass communication were used to disseminate messages relating to prevention measures. For example, a Moroccan startup launched a software based artificial intelligence bot that answered COVID-19–related inquiries in Arabic [11]. In addition, to preventative measures, multiple African nations implemented systems (such as national disease surveillance dashboards) to track the number of cases, testing, and deaths. Ethiopia designed smartphone apps for capturing personal identification data and temperatures at ports of entry, which were then used by a COVID-19 surveillance system for contact tracing [12]. Active community participation is required for the effectiveness of public health programs such as social distancing and mask-wearing. Early community engagement with technology and advances during the pandemic resulted in numerous contextualized approaches.

The COVID-19 pandemic had an immense impact worldwide, exposing significant flaws and vulnerabilities in our health care systems. Furthermore, the COVID-19 pandemic highlighted the significance of robust and well-functioning surveillance systems, given their role in local decision-making and worldwide knowledge exchange. The ability of a country to collect, collate, diagnose, monitor, and analyze data forms the cornerstone of an efficient surveillance system, allowing countries to plan and implement appropriate control actions. Malawi was one of the first countries in the region to launch a government-led coordinated effort to harmonize and streamline the necessary COVID-19 digital health implementation through an integrated system architecture.

In its Monitoring, Evaluation, and Health Information Systems Strategy, Malawi's Ministry of Health emphasized strengthening health information systems. Its primary goals were to establish interoperable digital systems that are loaded with high-quality data to promote data use in decision-making. The COVID-19 pandemic heightened the importance of this goal. It was a straightforward and economical move to use digital health tools

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to reinforce the Monitoring, Evaluation, and Health Information Systems Strategy objectives and expedite Malawi's COVID-19 response. Malawi's health system uses 54 digital health instruments, at least 20 of which have already been deployed for COVID-19 pandemic (Multimedia Appendix 1). The Ministry of Health Digital Health Division and the Public Health Institute of Malawi, with the assistance of Luke International and other development partners, rapidly created and deployed a suite of digital tools that aided the country in its COVID-19 response. This includes the One Health Surveillance Platform (OHSP), which is based on District Health Information Software 2 (University of Oslo). The OHSP was adopted as the single repository for COVID-19 interventions, including data for port of entry screening, case-based surveillance, contact tracing, confirmed case management and investigation, COVID-19 school assessment, COVID-19 e-Vaccine registry, and Integrated Disease Surveillance and Response reports (Multimedia Appendix 1). Furthermore, Luke International and its partners developed the Ministry of Health's COVID-19 National Information Dashboard, granting individuals with internet access the opportunity to review statistics in Malawi [13].

Goal of The Study

In this paper, we will seek expert consensus using the Delphi methodology to examine Malawi's COVID-19 digital surveillance response strategy, that is, the use of the following 3 digital tools.

Integrated Disease Surveillance and Response Case-Based Surveillance App Malawi

This application extends the existing infrastructure of electronic medical records and implements an electronic integrated disease surveillance and response system to facilitate real-time detection and reporting of notifiable disease cases. The application sends text alerts to all people under quarantine and thus, allows for the monitoring of people under quarantine.

Emergency Operations Center Call Center Exchange

The Emergency Operations Center (EOC) Call Center Exchange is a distributed call management system. It uses private automatic branch exchange for a more effective way of communication. The system improves the technical capacity to intelligently handle and manage calls, directing them to respective districts where they will be attended to by dedicated and trained district call center agents. This tool enhances the EOC to a modern solution that decentralizes the management of phone calls from the general public regarding COVID-19 pandemic.

One Health Surveillance Platform (by District Health Information System 2)

OHSP records and reports disease surveillance data in a holistic approach that involves human, animal (livestock and wild), and environmental aspects to disease surveillance. This web and mobile platform allows for patient screening, patient tracking and follow-up, contact tracing, case management, vaccine delivery and planning, and laboratory sample tracking.

Finally, we plan to assess the digital tools using the World Health Organization mHealth Assessment and Planning for Scale (MAPS) toolkit [14]. The MAPS toolkit is a robust "self-assessment and planning guide" that aims to advance conversations on how to scale up and maximize the impact of mobile health (mHealth) innovations [14]. Furthermore, the toolkit aims to optimize strategies to attain long-term sustainability.

Methods

Overview

This study will follow the Guidance on Conducting and REporting DElphi Studies [15].

Study Design

This study will use a modified Delphi technique that repeats a process of gathering and refining expert opinions until consensus is obtained. It is based on the concept that the opinions and predictions of an ensemble of experts are more reliable or accurate than those provided by individual experts [16]. The Delphi technique was chosen as the most appropriate study methodology to establish explicit consensus-based criteria where there is inadequate quantity or quality of existing evidence to develop evidence-based criteria [17]. Furthermore, the Delphi method is an iterative process technique that brings together the insights of various experts to establish a consensus and is used to generate future predictions, devise policy alternatives and find solutions. Our topic of study is under-research and so lacks existing evidence.

In the traditional Delphi process, there is no face-to-face interaction between the expert panel. However, we will undertake a modified Delphi process, in which round 3 will encompass a face-to-face workshop with the expert panel an approach which has been taken previously [18,19]. Notably, only those who completed both rounds 1 and 2 will be eligible to take part in the face-to-face workshop as these are the experts who can best speak on recommendations and feedback to the statements. This face-to-face workshop with experts who took part in the previous 2 rounds will facilitate discussion of the statements and recommendations in real-time by the experts, which will improve the efficiency of the consensus process whilst also maintaining anonymous voting [20]. During the group discussions of statements that did not reach consensus, experts will be advised not to reveal how they voted in the previous rounds. Furthermore, after finalization of the list of round 3 statements, experts will be asked to rerate the statements individually online using Qualtrics (Silver Lake) survey software to maintain anonymity amongst participants.

Experts who took part in rounds 1 and round 2 but are unable to attend the face-to-face workshop will be sent an email that asks them to provide feedback and recommendations to the statements, before the workshop. Any feedback provided by email from experts who are eligible but unavailable for workshop will be discussed and presented during the workshop. This process will ensure that all who are eligible to provide recommendations and feedback to the Delphi statements have an opportunity to do so.

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It should be noted that experts who did not complete round 1 and round 2 will not be eligible to participate in round 3. However, experts that have completed either round 1 or round 2 but not both rounds will be eligible to participate in round 3 of consensus but this will be through Qualtrics and not in person at the face-to-face workshop.

Finally, if there is no response to the Qualtrics survey, reminder emails, phone calls, text messages may be used to try to enhance response rates but ultimately with any research study, the response rate is based on the discretion of the respondent [21].

Study Setting

Delphi study rounds 1 and 2 will be conducted online through Qualtrics, a survey platform [20]. The Delphi study round 3 face-to-face workshop will be held at a site and location in Malawi convenient to the participants (Figure 1). This will be decided after recruitment and identification of consenting individuals in order to find a central location for all experts. Experts who are not eligible or unable to attend the face-to-face workshop will be able to rate the statements online through Qualtrics.

Figure 1. Delphi study flow diagram.

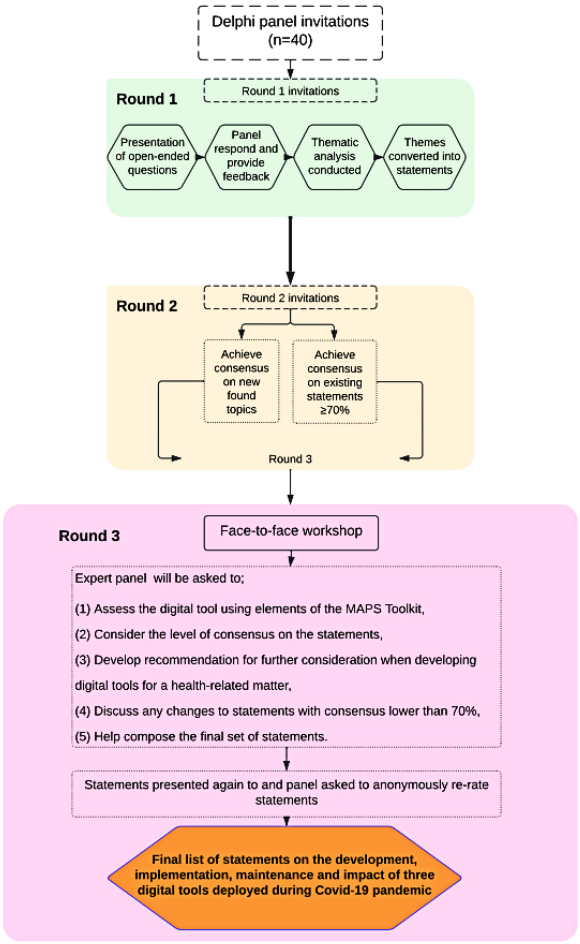

Study Participants

For this study, the participants will be referred to as an expert panel or panel of experts. In a Delphi study, there must be heterogeneity among the panel of experts. Participants must have first-hand experience (design, implementation, use, or maintenance) with COVID-19 digital surveillance systems. There will be no restrictions on the level of expertise or years of experience in their field of work.

The panel will consist of approximately 40 participants (Textbox 1).

Participants will be excluded if they lack the necessary expertise or are unable to make a commitment to being available for the duration of Delphi study rounds. If potential stakeholders are unable or decline to participate in the study, they will be invited to recommend a suitable alternative from their field.

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Textbox 1. Recruitment sources for study participants.

Ministry of Health (the below stakeholders report back to the Ministry of Health)

- Digital Health Division.
- Public Health Institute of Malawi.
- Border health officials.
- Integrated disease surveillance and response stakeholders.

Implementing entities

- District Health Offices.
- Central Monitoring and Evaluation Division.
- Non-governmental organizations: Elizabeth Glaser Pediatric AIDS Foundation, Luke International, Angle Dimension, and VillageReach.

Sampling Methods

Nonprobability purposive sampling will be used to invite participants (Figure 2). Purposive sampling techniques are used in each strategy to identify people who have first-hand knowledge of the phenomenon being studied, and as Patton [22] notes, it is the selection of "information-rich cases." Through peer recommendations and letters to appropriate professional groups, we will find relevant experts. We will get in touch with these organizations to obtain permission to send letters of invitation to their members. Snowball sampling will be implemented, which allows participants to recommend other persons with knowledge of COVID-19 digital systems [23].

Figure 2. Recruitment strategy.

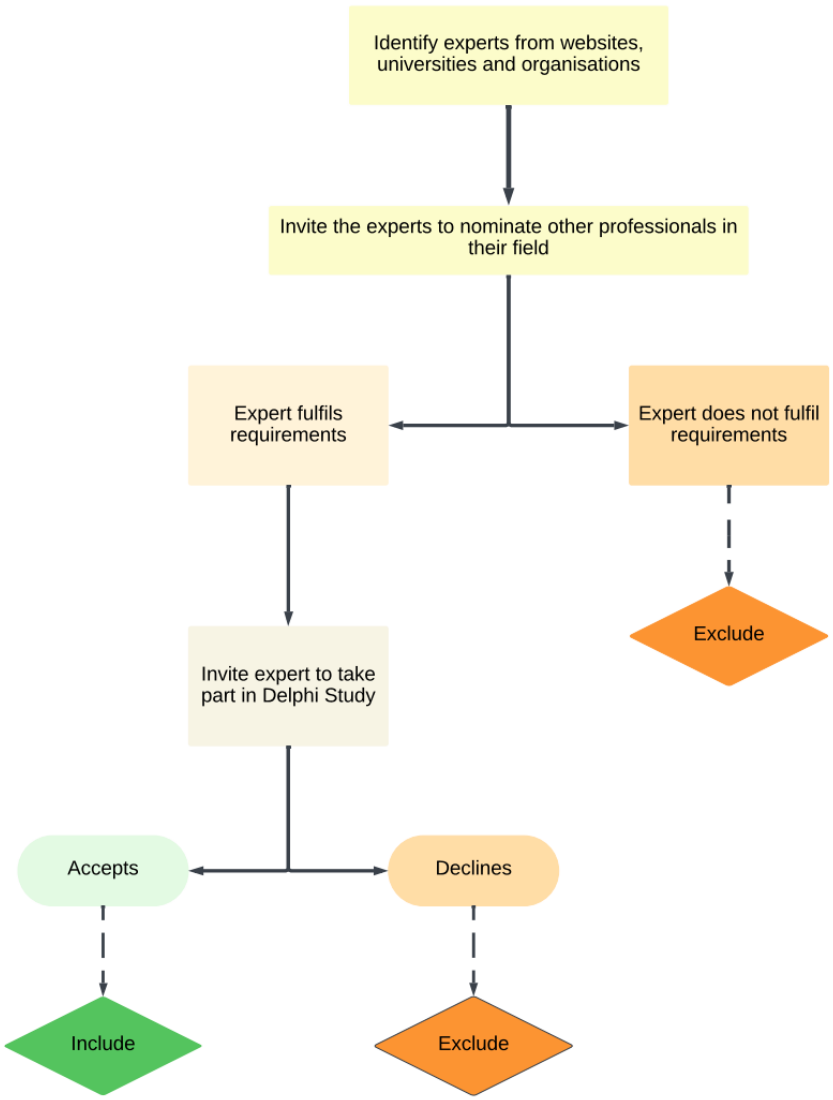

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Sample Size

There is no established standard for panel sample size, however it is widely agreed that the greater the number of participants, the greater the reliability of group judgements. Delphi technique panels range in number from 10 to over 1000, and there is no consensus or set of criteria about the appropriate size in the literature [24,25]. As there is no formal sample size calculation in Delphi studies, the literature was reviewed, in order to determine the most common and appropriate sample size whilst ensuring sufficient representation of the population. A 1995 study noted that the approximate size of a Delphi panel is generally under 50 and previous studies advise a panel of 40 as an overall rule [26,27]. Based on previous literature, the research team agreed on 40 experts to be included.

Recruitment

Representatives from each of the aforementioned stakeholder groups will be invited to participate in the Delphi study. We will email each of the stakeholders and provide an information sheet and consent form.

Information Sources and Steering Committee

For this study, the steering committee are the experts who will assist in the design and development of questions and statements for the Delphi rounds.

As this is a niche area with limited research, we did not conduct a formal literature search commonly seen in the Delphi process. Instead, the first step to preparing our Delphi study was to identify key terms relating to digital surveillance tools for COVID-19 pandemic. To do so, we engaged with the research team, which is comprised of persons who have or have previously worked in one of our stakeholder groups, have knowledge of digital surveillance tools, or are experienced in Delphi study design (Table 1).

Table 1. Delphi study steering committee members expertise.

Name (anonymized to maintain confidentiality of the committee)	Expertise
Member 1	• Epidemiology • Surveillance • Emergency response • Digital health development
Member 2	• Statistics
Member 3	• Public health • Epidemiology
Member 4	• Public health • Microbiology
Member 5	• Software developer • Digital health
Member 6	• Qualitative expertise
Member 7	• Qualitative expertise • Community health

The panel is composed of 4 members of the research team and 3 independent experts. These independent experts were recruited with the sole purpose of assisting with the development of the Delphi questions and statements. The experts were informed of the purpose of the study, the anticipated time they would be required to dedicate to the study and that their involvement would be voluntary. Meetings on Zoom (Zoom Video Communications), WhatsApp (Meta), and email were used to design and review feedback on the questions. In addition, the MAPS toolkit was used to help form the questions.

Overall, the steering committee will work collaboratively to reach an agreement on the Delphi survey format, statements, consensus thresholds, and stakeholder selection.

Data Collection

A Delphi study collects input from multiple expert panelists through a series of questionnaires or statements. In contrast to other data-gathering strategies, Delphi studies use processes of feedback (iterations) to build a consensus on a given topic. Given that the number of rounds in a Delphi can vary, there will come a time when additional agreement or consensus is either unnecessary or improbable to be obtained [28]. Whilst there has been no guideline on what constitutes an acceptable response rate, we do anticipate there will be a drop-off in the number of participants. The COMET handbook estimates that an appropriate response rate for each stakeholder group is around 80% [28]. The research team will endeavor to have a robust recruitment strategy to achieve this. However, for our study, as it is a niche area of expertise, response rate will not be a concern for reaching consensus and we will continue to launch subsequent rounds if the response rate is poor. With that said, we will report both the level of consensus and the response rate for each round so as to be as transparent as possible about our findings.

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Reminder emails, phone calls, text messages may be used to try to enhance response rates but ultimately with any research study, the response rate is based on the discretion of the respondent [21].

Consensus Definition

There are several approaches proposed to define the consensus criteria [28]. Consensus will be defined as ≥70% of participants strongly disagree, disagree, or somewhat disagree or strongly agree, agree, or somewhat agree [29].

As we are conducting a Delphi study on 3 digital tools, we will create 3 separate forms on Qualtrics for each of these tools. Stakeholders will be instructed only to complete the survey for the digital tool that they are experts on, and to ensure this, the experts will be emailed an anonymous link only for their designated digital tool. An information sheet will accompany each Delphi Round on the aims and procedures of this Delphi Study. The approach taken for this Delphi is the "all-rounds" approach whereby participants who do not respond to one are still invited to respond to others [30].

The decision to stop the Delphi process for a given topic will be based on reaching the consensus threshold or completion of 3 rounds (Figure 1).

Stage 1: First Round

Overview

Participants will receive an anonymous link to complete round 1 on Qualtrics. Round 1 will comprise a list of open-ended questions on the development, implementation, maintenance, and impact of each of the aforementioned digital tools that were designed by the steering committee. This is in line with traditional Delphi studies, whereby the initial round of a Delphi study starts with an open-ended questionnaire designed to elicit detailed information on the topic from the panel of experts [17]. Participants will be asked to add a comment, rationale, or suggestion for rewording if needed. Experts can also add free text suggestions regarding the design, implementation, maintenance, and impact of the digital tool.

Data Analysis

Responses to open-ended questions from the questionnaire will be summarized qualitatively using thematic analysis. Thematic analysis is a qualitative method that is used to identify, analyze, and report patterns or themes found within data [31]. For this Delphi study, we will adopt steps 1-6 of Braun and Clarke's guide to thematic analysis [31]. Data from Qualtrics will be extracted verbatim onto a Google Spreadsheet. One author (AD) will familiarize themselves with the data and generate the initial codes. Afterwards, we will create themes, review, and refine (research team). Furthermore, feedback from round 1 will be discussed by the study team and steering committee for potential incorporation into round 2.

Stage 2: Second Round

Overview

Themes identified from participant responses in round 1 will be used to generate statements for round 2 [30]. Round 2 will consist of a traditional structured questionnaire composed of statements hosted on Qualtrics. Participants will be presented with a 7-point Likert scale for each statement with the following options: strongly disagree, disagree, somewhat disagree, either agree or disagree, somewhat agree, and agree. There is an opportunity after each statement for additional remarks, and any statements with a consensus level less than the recommended threshold of ≥70% will be explored further in round 3 [32]. Statements with a consensus level less than the recommended threshold of ≥70% will be brought to the steering committee for review along with any feedback given by the panel. Participants will be asked to provide reasons for their disagreement with the statements if any.

Data Analysis

Central tendencies (means and medians) and levels of dispersion (IQR) will be computed from round 2 to present to participants in round 3.

Stage 3: Third Round (Face-to-Face Consensus Workshop)

Overview

Before round 3, results from round 2 will be summarized and circulated to the panel members, providing a summary of the level of group agreement (percentage of those who agreed or strongly agreed) and a summary of the submitted comments and suggested rewording of statements from round 2. Only the survey statements that do not achieve consensus from round 2 will be presented in round 3. Experts will be advised not to discuss how they rated the statements so to maintain anonymity for the previous rounds. The face-to-face workshop will last 2 days and facilitate real-time discussion, review, and modifications of the Delphi statements, a technique used in previous literature [33]. This workshop will include presentations by the research team on the findings from the 2 previous Delphi rounds and breakout sessions whereby stakeholders from a particular expertise will be grouped together. In groups they will be asked to (1) consider the phrasing and interpretation of the statements on the digital tools that they are experts in, (2) develop recommendations for further consideration when developing digital tools for a health-related matter, (3) discuss any changes to statements with consensus lower than 70%, and (4) help compose the final set of statements.

Following this review and finalization of the statements, participants will again be presented with a 7-point Likert scale for each statement with the following options: strongly disagree, disagree, somewhat disagree, either agree or disagree, somewhat agree, and agree.

Statements that meet the appropriate level of consensus will be included in a final list of recommendations for countries when developing, implementing, and maintaining digital health strategies during a health emergency or pandemic.

It should be noted that only participants who took part in rounds 1 and 2 will be eligible to take part in the face-to-face workshop. That is because experts who took part in both rounds will have a clear understanding of the statements being asked, improving

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the efficiency of the workshop as well as the discussion. Those who do not take part in both rounds 1 and 2, or are unavailable for the face-to-face discussion, will still be given the opportunity to rate the statements online through Qualtrics through an invitation link by email.

In addition, the panel will be asked to complete, in their expertise group, the MAPS toolkit assessment on the digital tool on which they are knowledgeable. The MAPS toolkit will enable the panel members to assess their digital tool from a sustainable perspective from six distinct, yet complementary axes: (1) groundwork, (2) partnerships, (3) financial health, (4) technology and architecture, (5) operations, and (6) monitoring and evaluation (Figure 3).

Figure 3. mHealth (mobile health) assessment and planning for scale toolkit-axes of scale taken from the World Health Organization mHealth Assessment and Planning for Scale toolkit.

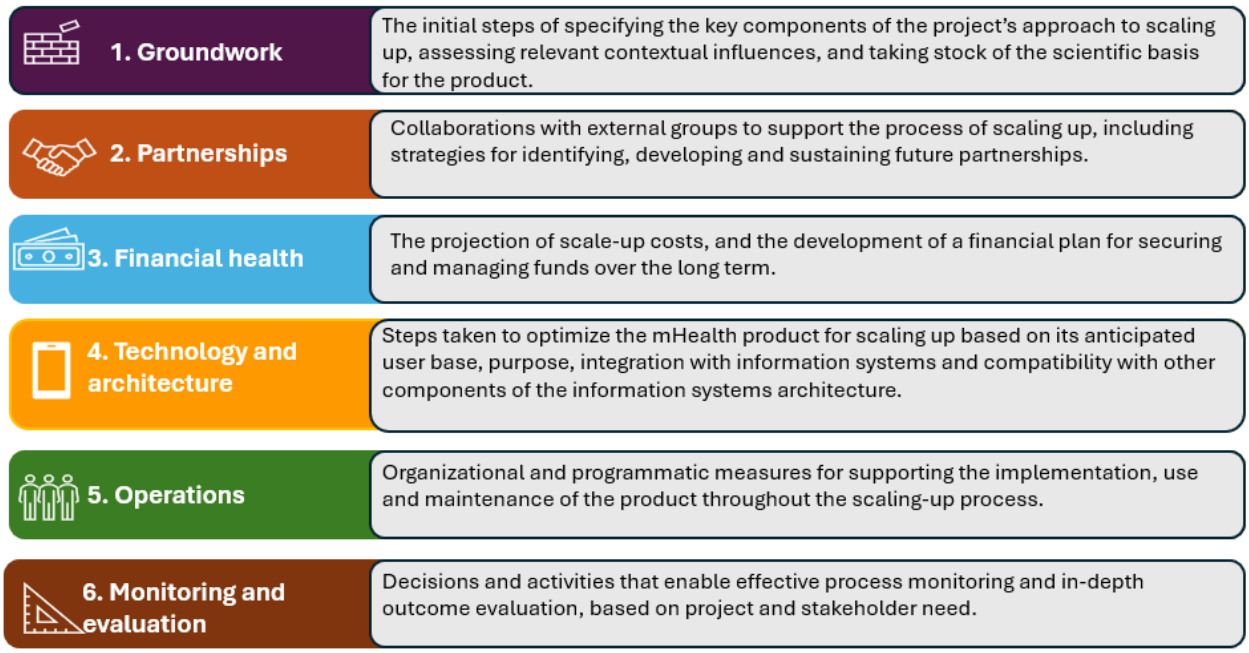

The MAPS toolkit works by participants responding to the self-assessment questions [14]. There are 2 suggested approaches to achieve this, either through an individual assessment or team assessment. For this modified Delphi study, participants will be grouped according to expertise and required to complete a team assessment of the digital tool which they knowledgeable on. It is recommended that the toolkit should take approximately 1.5-2 hours to complete in its entirety. The research team has allotted 3 hours for completion on day 1 of the workshop.

After the participants complete the MAPS Toolkit, the self-assessment questions scores will be calculated on 3 levels, the overall score (total score combining all axes), the axis scores (a separate score for each of the 6 axes of scale), and the domain scores (specific scores for the domains within each axis of scale).

The scoring procedures will enable the research team to explain the overall progress through the scaling up process, as well as their internal strengths and weaknesses in quantitative terms. The ability to compare ratings across axes and domains will assist the research team to identify which areas require additional improvement [14].

Data Analysis

Descriptive statistics will be used to summarize and analyze the data from Delphi rounds 2 and 3. This data includes characteristics of the participants, the number of participants who took part during each round, along with their demographic details, the median and mode for each item, an indication of the current level of consensus (based in the IQR), the summary of participant responses as to why they have ranked statements, on the 7-point Likert scale, in the way they did; and descriptive statistics (proportion or mean and SD where appropriate) will be used to summarize the individual responses to each statement in the Delphi round. The quantitative data, if appropriate, will be entered into SPSS for analysis and all experts' opinions will be weighted equally.

Descriptive statistics will be undertaken on the entire dataset after entering the data to provide a percentage of the overall response to each question. The median and IQR will be reported for each item. In addition, to investigate the qualitative data (open-ended questions), we will use rapid qualitative analysis. Statements that are the same or very similar will be amalgamated, and all comments will be grouped thematically.

Statements that reach consensus will be categorized according to the digital tool in which the statement relates to and will be mapped to one of the following concepts: development, implementation, maintenance, or impact. We will also subcategorize the statements according to the MAPS toolkit domains and axes. Furthermore, a figure will be designed that presents the flow of items through the Delphi process and presents the final ratings of statements for each of the 4 aforementioned concepts.

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Subgroup Analysis

A subgroup analysis will be conducted if feasible on respondents' profession, highest degree or education, and gender. For this study, gender refers to "socially constructed and enacted roles and behaviors which occur in a historical and cultural context and vary across societies and over time" [34].

This is to identify what statements are more likely to be endorsed based on a person's demographic data and to identify variances in justifications for rating statements.

Ethical Considerations

This study was reviewed and approved by the National Committee on Research in the Social Sciences and Humanities [NO. P.12/23/825] in Malawi. This study will conform to the Declaration of Helsinki [35].

Informed consent in writing from participants will be required before data collection starts. The investigators will support the participants to withdraw from the study at any stage of the research process if they wish to do so without giving reasons. Participants will be reminded that involvement in the study is entirely voluntary. By participating in this Delphi study, participants are contributing to important research on digital surveillance systems in Malawi. We do not anticipate any negative outcomes or risks from participating in this study. We do not intend to cause any distress to stakeholders, as this Delphi study will ask about their own experiences with these systems.

Individual rating of the statements for each round will be anonymous to the other participants. However, participants are identifiable to the research team. Participants are required to provide a full name at the start of each round, this is to allow the research team to follow up with incomplete or not started survey forms. This is stated in the participant information leaflet. It should be noted that the research team will deidentify any information provided after round 3 and before the final publication. No statements or ratings will be traceable back to the participants.

In addition, for the experts who are eligible and available to take part in the round 3 face-to-face workshop, support for travel costs will be provided. The amount of compensation for travel costs will be determined based on fuel expenses to and from the venue in Malawi.

Results

This study was reviewed and approved by the National Committee on Research in the Social Sciences and Humanities [NO. P.12/23/825] in Malawi. Round 1 invitations were sent on February 8, 2024. Round 2 invitations were sent on May 13, 2024. Data collection is ongoing.

Discussion

Expected Outcomes

This protocol describes a process to gather consensus and recommendations from leading experts in Malawi on digital tools deployed during the COVID-19 pandemic. This is an area of limited research and thus, comparison. However, we anticipate that the modified Delphi approach through open-ended round 1 questions and the option to participate in an in-person workshop in round 3 will allow for greater in-depth exploration of the digital tools deployed and improve the quality of this work.

We believe that the study findings will provide meaningful insights into stakeholders' perceptions of the effectiveness of these digital tools. In addition, this study will facilitate the development of recommendations on the development, implementation and maintenance of digital tools for future disease outbreaks. This study will also provide valuable insights and feedback on the digital tools through the application of the World Health Organization MAPS toolkit. The findings will inform implementers and foreign donors on digital health development initiatives and will help countries increase their disease surveillance capacity in the future.

Limitations

We foresee that a limitation will be the number of experts engaged in this research, the anticipated decline in response rate and incomplete responses. There will be 40 experts in total, which is approximately 13 for each digital tool. However, we hope that the ability to conduct the research online will make the questions and statements accessible to the experts and boost response rate. Furthermore, this consensus study focuses on the perspectives of the developers of the digital tools and does not incorporate the user experience of the digital tools.

Conclusions

In summary, global health epidemics, pandemics, and endemics can happen unexpectedly and therefore, there is a need for governments to ensure preparedness to tackle such occurrences. This research will encapsulate digital tool development and impact and facilitate the development of recommendations for future digital surveillance strategies.

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Authors' Contributions

AD and JOD coordinated the study. AD, JOD, HYL, KLJY, GBC, and JTSW contributed to the design and conception of the study. BC, SY, MK, and JTSW advised on recruitment of the expert panel. GBC, KC, IN, and JTSW advised on the recruitment of the steering committee and the design of the face-to-face workshop. AD and JOD contributed to the design of the tables and figures. BC, SY, MK, IN, KC, JTSW, and GBC edited and approved this final manuscript, and provided ongoing input about practicality of this study in the Malawian setting.

Conflicts of Interest

AD, JOD, HYL, KLJY, BC, KC, IN, GBC, and MK have no conflicts of interest to report. JTSW is working for the Ministry of Health and Luke International for COVID-19 responses as the Public Health Emergency Operation Centre manager and contributed to the related digital health solution development. However, he has no conflicts of interest in this study since the COVID-19 Public Health Emergency Operating Centre is now deactivated, and he has been dismissed from the EOC manager role. SY worked as Head of Digital Health during the COVID 19 pandemic and oversaw the implementation of the different technologies to sail through COVID-19 period. However, since he was moved to National Statistical Office, he is no longer overseeing such projects. This makes him have no conflict of interest in the study being proposed.

Multimedia Appendix 1
Mapping and matching digital health tools to strengthen Malawi's COVID-19 response. Table adapted from (Digital Health Systems to support pandemic response in Malawi - Squarespace 2021).
[PDF File (Adobe PDF File), 151 KB - resprot_v13i1e58389_app1.pdf]

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Abbreviations

EOC: emergency operations center
LMIC: low- and middle-income country
MAPS: mHealth Assessment and Planning for Scale

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mHealth: mobile health
OHSP: One Health Surveillance Platform

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Protocol

Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study

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Abstract

Background: Vitamin D deficiency has been associated with hypertensive disorders in pregnancy (HDP). The risk of developing HDP was reported to be further augmented among individuals with a vitamin D receptor (VDR) genetic variant. However, the reported roles of *VDR* variants in hypertensive disorders are inconsistent among different populations. Given the relatively higher incidence of vitamin D deficiency among Malaysian pregnant women and the high incidence of HDP in this population, we hypothesize that there may be associations between the risk of vitamin D deficiency and HDP with VDR genetic variants.

Objective: This paper outlines the protocol for a study to determine the association of vitamin D status and *VDR* sequence variants among Malaysian pregnant women with HDP.

Methods: This prospective study consists of two phases. The first phase is a cross-sectional study that will entail gathering medical records, a questionnaire survey, and laboratory testing for vitamin D status, with a planned recruitment of 414 pregnant women. The questionnaire will be utilized to assess the risk factors for vitamin D deficiency. The vitamin D status will be obtained from measurement of the vitamin D (25-hydroxyvitamin D_3) level in the blood. The second phase is a case-control study involving a Malay ethnic cohort with vitamin D deficiency. Participants will be divided into two groups with and without HDP (n=150 per group). Genomic DNA will be extracted from the peripheral blood monocytes of participants using the Qiagen DNA blood kit, and *VDR* sequence variants will be determined using polymerase chain reaction–high-resolution melting (PCR-HRM) analysis. Sanger sequencing will then be used to sequence randomly selected samples corresponding to each identified variant to validate our PCR-HRM results. The *VDR* genotype and mutation frequencies of *BsmI*, *ApaI*, *TaqI*, and *FokI* will be statistically analyzed to evaluate their relationships with developing HDP.

Results: As of December 2023, 340 subjects have been recruited for the phase 1 study, 63% of whom were determined to have vitamin D deficiency. In the phase 2 study, 50 and 22 subjects have been recruited from the control and case groups, respectively. Recruitment is expected to be completed by March 2024 and all analyses should be completed by August 2024.

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Conclusions: The outcome of the study will identify the nonmodifiable genetic components contributing to developing vitamin D deficiency leading to HDP. This will in turn enable gaining a better understanding of the contribution of genetic variability to the development of HDP, thus providing more evidence for a need of customized vitamin D supplementation during pregnancy according to the individual variability in the response to vitamin D intake.

Trial Registration: ClinicalTrials.gov NCT05659173; https://clinicaltrials.gov/study/NCT05659173

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KEYWORDS

gestational hypertension; preeclampsia; hypertensive disorder; vitamin D deficiency; vitamin D receptor gene polymorphism; vitamin D sequence

Introduction

Vitamin D deficiency is a global health issue affecting an estimated 1 billion people worldwide across all ethnicities and age groups [1]. Thus, vitamin D deficiency has become a pandemic despite the availability of sunlight in Asia, Africa, the Middle East, and Latin America. The most vulnerable populations at risk of vitamin D deficiency are pregnant women and their fetuses. Several studies have linked low vitamin D status with a higher risk of adverse short- and long-term health outcomes. In addition, risk factors such as dietary habits, cultural and religious practices such as wearing dark veils covering nearly all body parts that discourage sun exposure, and lack of government regulations for vitamin D fortification of foods further worsen the condition [2,3]

Hypertensive disorders in pregnancy (HDP) account for approximately 14% of all causes of maternal mortality globally. The spectrum of HDP includes gestational hypertension (GH); preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Preeclampsia is a complication of 2%-8% of all pregnancies worldwide, contributing to 16%, 9%, and 1.6%-2.5% maternal deaths globally, in Asia and Africa, and in Malaysia, respectively [4,5]. HDP is one of several disorders associated with vitamin D deficiency [6]. Vitamin D exerts its effect through the nuclear vitamin D receptor (VDR), and several single-nucleotide variants (SNVs; formerly single-nucleotide polymorphisms or SNPs) occur on the VDR gene, such as *BsmI*, *ApaI*, *TaqI*, and *FokI* SNVs. The *BsmI* and *FokI* variants of *VDR* have been reported to affect vitamin D binding and are associated with an increased risk of HDP [7].

In pregnant women, maternal 25-hydroxyvitamin D (25(OH)D) can freely cross the human placenta that expresses VDR and the enzyme CYP27B1, which converts 25(OH)D to its biologically active form 1,25-dihydroxycholecalciferol [8]. VDR is a protein comprising two functional domains (the N-terminal dual zinc finger DNA-binding domain and the C-terminal ligand-binding activity domain) and a linking region [9,10]. The gene encoding VDR is located on chromosome 12 (12q12-14) [11,12]. Several SNVs in the VDR gene have been associated with metabolic disorders and vitamin D deficiency to date, including rs1544410 (*BsmI*), rs7975232 (*ApaI*), and rs731236 (*TaqI*) [12].

Sequence variants in the VDR gene are associated with the dysregulation of metabolic biomarkers such as anthropometric parameters related to insulin resistance, obesity, and cardiovascular diseases, along with atherogenic lipid abnormalities in different populations [12,13]. Such metabolic dysregulation ultimately translates into complications in pregnancy with adverse health consequences for both the pregnant woman and the fetus. Vitamin D exerts its effect through the nuclear VDR. The *TaqI* variant, located at the 3′ untranslated region of the VDR gene, has been shown to affect mRNA stability and VDR expression in tissues. An SNV in *FokI* located near the promoter region causes altered VDR activity due to the change in the amino acid sequence of the protein [14]. A *FokI* variant of the VDR gene is also associated with upregulation of angiotensin II type I receptor and renin gene transcription, leading to hypertension [15]. A variant *BsmI* allele also influences *VDR* mRNA stability, resulting in a reduction in the amount of VDR protein produced in the tissues [16].

Accumulating evidence suggests that genetic variability involving variants of specific maternal susceptibility genes, such as those in the VDR gene, play vital roles in the pathogenesis of HDP [6]. An unfavorable *VDR* genetic background can significantly decrease the effectiveness of vitamin D action, thereby contributing to the development of HDP [6,17].

Moreover, the presence of a *VDR* sequence variant constitutes an important factor contributing to the individual susceptibility to the biological effects of vitamin D. HDP may be apparent in some pregnant women, whereas others present with a relatively milder sequela. Considering the influence of genetic variability and the roles of *BsmI*, *ApaI*, *TaqI*, and *FokI* variants in the etiopathogenesis of HDP, we aim to explore the possible association between the frequencies of these genetic variants and the incidence of HDP in Malaysian pregnant women. Given the estimated high prevalence of vitamin D deficiency among Malaysian pregnant women, we hypothesized that there are sequence variants in the *BsmI* and *FokI* VDR gene fragments (as the most common genotypes associated with HDP) of Malaysian pregnant women with vitamin D deficiency. We further explored associations with *ApaI* and *TaqI* variants given the relative lack of previous research on the potential associations of these genotypes with HDP.

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Methods

Objectives

The objectives of this prospective study are to (1) determine the prevalence of vitamin D deficiency and associated risk factors among Malaysian pregnant women; (2) determine the frequencies of *BsmI*, *ApaI*, *TaqI*, and *FokI* genotypes among Malay pregnant women with vitamin D deficiency and HDP; (3) understand and associate the distributions of *VDR* genotype and allele frequencies in relation to vitamin D deficiency among Malay pregnant women; and (4) identify mutations in the *BsmI*, *ApaI*, *TaqI*, and *FokI* VDR gene fragments among Malay pregnant women with HDP.

This study is divided into two phases. Phase 1 is a cross-sectional study involving Malaysian pregnant women to achieve objective 1, whereas phase 2 is a case-control study among Malay pregnant women to achieve objectives 2, 3, and 4.

Settings

This study will be carried out at Hospital Sultan Abdul Aziz Shah (HSAAS), a tertiary university hospital in Selangor, Malaysia. The hospital provides a range of health care services to the neighboring community and serves as the teaching hospital for the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. All pregnant women attending the Obstetrics and Gynaecology Department of HSAAS who fulfill the inclusion and exclusion criteria will be recruited between November 1, 2022, and March 31, 2024. A systematic random sampling method will be used to recruit the study participants for both the cross-sectional and case-control studies.

Cross-Sectional Study (Phase 1)

Participants and Data

To achieve objective 1, Malaysian pregnant women, at any stage of gestation, with a singleton viable pregnancy at the time of recruitment and who are literate in the English or Malay language will be recruited. Women with a multiple pregnancy and on vitamin D supplementation are excluded. The gestation stage will be determined from the first day of the last menstrual cycle or based on measurement of the fetal crown-rump length determined on an ultrasound scan. Pregnant women taking vitamin D supplements or those who have been diagnosed with chronic diseases that are known to affect vitamin D levels, such as autoimmune disease and cancer, are excluded from the study.

Clinical, sociodemographic, dietary intake, and anthropometric (height, weight, and BMI) data will be collected using a pro forma. The prepregnancy BMI (kg/m^2) will be calculated by dividing the weight (kg) by the square of the height (m^2). Weight will be determined from prepregnancy body weight recall or obtained from the woman's antenatal booking record along with the measured height. Participants will then be interviewed by a single trained interviewer to answer a validated questionnaire to determine their risk factors associated with vitamin D deficiency.

Validation of the Questionnaire

The questionnaire was adapted from the studies of Syed Nor et al [18], Jamil et al [19], and Humayun et al [20] (see Multimedia Appendix 1). Permission was obtained from all authors to adopt their questionnaires and translate them into the Malay language. The translation will be performed by two English-Malay-English translators before the validation test. A pilot test will be carried out among 40 pregnant women (approximately 10% of the calculated sample size) to assess the questionnaire's clarity of meaning, appropriateness of the words used, and its cultural acceptance. Participants recruited for the pilot testing will not be included in the study. The reliability will be measured by calculating the internal consistency and assessing the associations among questions. A Cronbach α value of at least 0.7 indicates good internal consistency of the questionnaire [21].

In addition, the content validity index (CVI) will be calculated to measure the validity of the questionnaire where the relevancy of questions will be assessed by three experts in the field. The item-level CVI will be calculated by assessing each question's validity, in which a score above 0.78 is considered acceptable [22]. The overall validity of the questionnaire will also be measured by calculating the scale-level CVI, in which a score above 0.9 is considered good [22].

Sampling Process

Approximately 5 milliliters of blood will be withdrawn and dispensed into a plain blood bottle for the measurement of $25(OH)D_3$ using an electrochemiluminescence immunoassay (Elecsys Vitamin D Total III assay). This assay kit includes a vitamin D–binding protein (VDBP) labeled with a ruthenium complex as the capture protein to bind $25(OH)D_3$ and $25(OH)D_2$. Cross-reactivity to 24,25(OH)D is blocked by a specific monoclonal antibody.

The sample will first be incubated with pretreatment reagents 1 and 2, where bound 25(OH)D is released from the VDBP. Subsequently, the pretreated sample is incubated with the ruthenium-labeled VDBP to form a complex between 25(OH)D and the ruthenylated VDBP. A specific unlabeled antibody binds to the 24,25(OH)D present in the sample and inhibits cross-reactivity to this vitamin D metabolite. During the third incubation, streptavidin-coated microparticles and 25(OH)D labeled with biotin are added. Unbound ruthenylated-labeled VDBPs become occupied, and a complex consisting of the ruthenylated VDBP and the biotinylated 25(OH)D is formed, which finally binds to the solid phase via the interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a specific voltage to the electrode then induces chemiluminescent emission, which is measured by a photomultiplier. The results are determined via a calibration curve that is specifically generated by a 2-point calibration process and compared to a master curve provided via the reagent barcode or e-barcode.

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Quality Control

Per-run control sera (deficient, insufficient, and normal) will be used for sample analysis. All laboratory analytical protocols will be performed with strict adherence to the quality control measures.

Classification of Vitamin D Status

The results will be further classified according to vitamin D status as deficient (30 nmol/L), insufficient (30-50 nmol/L), and normal (≥50 nmol/L), using the 2011 classification guidelines of the Institute of Medicine [23].

Case-Control Study (Phase 2)

Participants and Data

For the second phase of the study, we chose to focus on the Malay ethnic group, who make up the majority of the Malaysian population. Pregnant women of Malay ethnicity who are classified in the vitamin D deficiency group in phase 1 of the study will be recruited for phase 2. Those with a nonviable pregnancy or those who received a diagnosis of chronic hypertension prior to the current pregnancy will be excluded. The remaining participants will then be divided into two groups: those with HDP (GH, preeclampsia, eclampsia, HELLP syndrome) and those with blood pressure in the normal range.

Blood Collection and DNA Extraction

Approximately 5 milliliters of blood will be collected into ethylenediaminetetraacetic acid (EDTA) containers for genetic analysis. The blood samples will be transported to the laboratory under a cold chain. Immediately after collection, the genomic DNA will be extracted using the QIAamp DNA blood kit (Qiagen). The extracted DNA will be checked for purity using an ultraviolet spectrophotometer and the integrity will be checked by running the genomic DNA on a 2% agarose gel using triacetate-EDTA buffer in parallel with DNA ladders (all procured from Vivantis Sdn Bhd Malaysia). The genomic DNA with high quality will be stored at –20 °C pending genetic analysis.

VDR Genotyping

The polymerase chain reaction–high-resolution melting (PCR-HRM) technique will be used to amplify the VDR gene with specific primers. The amplified region of the VDR gene (amplicon) will be stored in a PCR tube. Sets of primers (procured from Apical Scientific and Biotechnology Sdn Bhd Malaysia) spanning the 5′-3′ region of the *VDR* sequence will be synthesized based on published sequences [24], which will be used to run the PCR-HRM analysis to detect *VDR* variants. The extracted DNA will be subjected to PCR-HRM following the manufacturer's protocol using the cycling conditions based on a previous report [24].

Principle of PCR-HRM

PCR-HRM analysis is a sensitive and specific technique for the detection of mutations on double-stranded DNA (dsDNA) samples (amplicons). First, the region of interest on the DNA is amplified in real time using specific primers prior to the HRM phase. The HRM process then begins with slow denaturation of the dsDNA with a temperature range of 50-95 °C in conjunction with an intercalating fluorescent dye, SYBR Green (Roche). When the melting temperature of the dsDNA is reached, the two strands "melt" apart. The midpoint of the melt curve is described as the point when 50% of the DNA is double-stranded and 50% is single-stranded. The shape of the curve is dependent on the characteristics of the dsDNA, which relate to whether it is the homozygous wild-type, homozygous mutant, or heterozygous wild-type and mutant genotype. When the two strands "melt" apart, the fluorescence level drops. As the HRM is monitored in real time, this curve offers a real-time picture of the characteristics of the DNA being tested.

Barcode-Tagged Sequencing Analysis

Barcode-tagged sequencing (BT-Seq) analysis, as a next-generation sequencing approach, will be used to verify the *VDR* SNVs identified among the Malay pregnant women with vitamin D deficiency and HDP according to the PCR-HRM results. BT-Seq services will be sought from TreeCode Sdn Bhd Malaysia. Ten amplicon samples will be selected from each of the identified *VDR* variants as representative samples to serve as the reference genotype for all SNVs detected in the PCR-HRM analysis. The analysis will be performed on each *VDR* variant amplicon that will be synthesized based on published primers spanning the four known VDR SNVs (*BsmI*, *ApaI*, *TaqI*, and *FokI*) using PCR [24]. The amplicons will be run on an agarose gel and the purified products will be cut from the gel before sending to the company providing the BT-Seq service. Discrimination of the three possible genotypes of each genetic variant (common homozygotes, heterozygotes, and rare homozygotes) in 4 distinct groups will be obtained from 180 samples by PCR-HRM analysis. A T-to-C transition in introns 8 and 9 will reflect the presence of SNVs in introns 8 and 9 for *BsmI* and *TaqI*, respectively; a C-to-T transition at the junction of intron 1 and exon 2 reflects the *FokI* variant; and the *ApaI* variant is reflected by a T-to-G transition in intron 8. The corresponding distribution of vitamin D status and the genotype frequency in Hardy-Weinberg equilibrium will be obtained for each SNV.

Sample Size Estimation

Total Sample Size

A total of 414 pregnant women will be recruited for the cross-sectional study (phase 1) to determine the prevalence of vitamin D deficiency and associated risk factors (objective 1). For phase 2, a total of 150 Malaysian pregnant women with HDP will be recruited as the case group and 150 normotensive Malaysian pregnant women with vitamin D deficiency will be recruited as controls.

Sample Size Calculation for the Cross-Sectional Study (Phase 1)

The sample size for the study was calculated using the following formula [25]:

$$n = (Z^2 \times p \times q)/d^2 \textbf{(1)}$$

where n is the minimum sample size, Z is the level of significance at the 95% CI (1.96), p is the prevalence rate, q = 1 − p, and d is the tolerable margin of error (5%).

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According to Woon et al [26], the prevalence of vitamin D deficiency among Malaysian pregnant women is 42.6%. Applying equation 1, the sample size is calculated as follows:

$$n = (1.96)^2 \times 0.426 \times (1 - 0.426)/(0.05)^2$$

$$n = (3.8416 \times 0.426 \times 0.574)/0.0025 = 376$$

Therefore, the minimum sample size required for the cross-sectional study after addition of a 10% attrition rate is approximately 414 Malaysian pregnant women.

Sample Size Determination for the Case-Control Study (Phase 2)

The minimum number of participants to be recruited in the case-control study was determined using the following formula [27]:

$$n = r + 1 \times P^* \times (1 - P^*) \times (Z_\beta + Z_{\alpha/2})^2/r \times (P_1 - P_2)^2 \textbf{(2)}$$

where r is the ratio of cases to controls (1 in this instance given the equal numbers in the two groups), P_1 is the proportion of exposed individuals in the cases, P_2 is the proportion of exposed individuals in the controls, P* is the effect size ($P_1 - P_2$), Z_β at 80% power is 0.84, and $Z_{\alpha/2}$ is 1.96 for a .05 significance level at the 95% CI.

According to Caccamo et al [6], the prevalence of vitamin D deficiency among women with GH (P_1) and that among pregnant women without hypertension (P_2) is 21% and 11%, respectively. Therefore, P* is determined to be 0.1 (0.21–0.11). Applying equation 2, the sample size is calculated as:

$$n = (1 + 1) \times (0.1) \times (1 - 0.1) \times (0.84 + 1.96)^2/1 \times (0.1)^2$$

$$n = 141$$

Considering dropout or missing samples, 10% attrition is added to the calculated sample size. Hence, our minimum number of participants in each group (cases and controls) was determined to be 150.

Ethical Considerations

The research protocol has been approved by the Ethics Committee for Research Involving Human Subjects of the Universiti Putra Malaysia (reference number JKEUPM-2021-915). The study will be conducted in accordance with the standards of human experimentation in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. This study protocol was also registered with ClinicalTrials.gov (NCT05659173). All eligible participants will be given a patient information sheet consisting of information about the study. Those who agree will be asked to sign a written consent form (available in both the Malay and English languages). Participation is voluntary and participants have the right to withdraw at any time without giving a reason. Any amendment to the protocol or documents will be submitted for review to the ethics committee. To preserve the privacy of the participants, any personal details will be removed from publications. Only anonymized and deidentified information will be made available in future manuscripts related to this work. All data of the study will be kept in a password-protected database on a password-protected desktop computer at the host organization and will only be accessible by the named researchers. As this is an observational cross-sectional and case-control study, there will be no compensation given to the participants given that the study is determined to be of low risk.

Data Analysis Plan

Data obtained from the study will be analyzed using SPSS version 27.0 (IBM Corp). Data entered will be checked for missing or suspicious values. These will subsequently be verified with the participants or omitted as missing values. Descriptive analysis will be used to summarize the sociodemographic data, anthropometric data, clinical data, vitamin D dietary intake, sun exposure, and physical activity. The prevalence of vitamin D deficiency will be expressed in frequency and percentage. The association with sociodemographic data will be analyzed using the χ^2 test, independent *t* test, and ANOVA where applicable.

We will report the comparative prevalence of *BsmI*, *ApaI*, *TaqI*, and *FokIVDR* genotypes among Malay pregnant women with vitamin D deficiency with and without HDP. Similarly, the distributions of *VDR* genotype and allele frequencies according to vitamin D deficiency among Malay pregnant women will be reported as a descriptive analysis. Any mutations found in the *BsmI*, *ApaI*, *TaqI*, and *FokI* VDR gene fragments among Malay pregnant women with HDP will also be described. The associations of vitamin D status, associated risk factors, and VDR genetic variants with HDP will be determined using multivariate logistic regression analysis. The level of significance will be considered at a threshold of $P \leq .05$ at the 95% CI.

Results

As of December 2023, a total of 340 subjects have been recruited for the phase 1 study. Preliminary analysis showed that 63% of the participants were vitamin D–deficient. Other analyses are pending. For the phase 2 study, 50 control subjects and 22 case subjects have been recruited to date. We are expecting to complete the recruitment by March 2024 and to complete all laboratory and questionnaire analyses by August 2024.

Discussion

Projected Significance

The study will provide information on the current prevalence and modifiable risk factors of vitamin D deficiency. The prospective associations of vitamin D deficiency with the study variables will be of immense benefit to physicians and public health experts in formulating policies related to vitamin D supplementation. The outcome will greatly advance our current understanding of vitamin D deficiency in Malaysia and at mechanistic level could be adopted by other low- and middle-income countries to tackle the widespread problem of vitamin D deficiency.

Additionally, this study holds promise for determining the influence of unchangeable genetic components that may impact

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vitamin D deficiency and its correlation with HDP. This will constitute a significant new development in the field. Determining the association of the genetic variants will enable gaining a further understanding of the roles of the nonmodifiable components contributing to the risk of vitamin D deficiency that lead to the development of HDP.

Strengths and Limitations

The sample size of this study is one of the highest among similar studies conducted in the study area performed to date [7,17]. In addition, the assessment of both modifiable and nonmodifiable risk factors of vitamin D deficiency will facilitate gaining a deeper understanding of cause and effect, as these factors relate not only to vitamin D deficiency itself but also involve associated genetic variants and the risk of developing HDP.

Potential limitations include bias in recall in answering the vitamin D food frequency components of the questionnaire given that these data are based on the self-reporting of participants. However, efforts have been made to ensure that these challenges are significantly tackled by conducting pre-enrollment interviews with pregnant women for eligibility before their inclusion in the study. As the study will be conducted in a tertiary hospital setting and a convenience sampling strategy is used, only subjects of interest that suit our inclusion criteria will be recruited. Thus, the results of this study may be influenced by the recruited participants group, which may not necessarily replicate the entire Malaysian population. Future studies should adopt a systematic random sampling strategy with a larger sample size and multicentered design to capture pregnant women from broader demographics, including those living in rural areas.

Conclusion

The outcome of this prospective study will determine both modifiable and nonmodifiable factors for vitamin D deficiency and will provide evidence to support targeted vitamin D supplementation programs. Furthermore, the study will help to enhance our understanding of the association of genetic variability in the VDR gene with the risk of developing HDP. These findings could bring together relevant stakeholders in government health authorities, food and drug administrations, and food manufacturing industries to contribute to the establishment of national intervention schemes for the screening, prevention, and treatment of vitamin D deficiency that would be customized for susceptible women of reproductive age.

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Data Availability

The data obtained and analyzed during the study will not be made publicly available due to privacy issues but will be available on reasonable request to the corresponding author.

Authors' Contributions

NIB, AAMJ, NN, and YI contributed to the study concept and design. The design of the laboratory analysis was further developed by NN and YI. YI drafted the manuscript with assistance from NIB and AAMJ along with input from NN at various stages. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[DOCX File , 21 KB - resprot_v13i1e53722_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the Ministry of Higher Education.
[PDF File (Adobe PDF File), 593 KB - resprot_v13i1e53722_app2.pdf]

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Abbreviations

25(OH)D: 25-hydroxyvitamin D
BT-Seq: barcode-tagged sequencing
CVI: content validity index
dsDNA: double-stranded DNA
EDTA: ethylenediaminetetraacetic acid
GH: gestational hypertension
HDP: hypertensive disorders of pregnancy
HELLP: hemolysis, elevated liver enzymes, and low platelets
HSAAS: Hospital Sultan Abdul Aziz Shah
PCR-HRM: polymerase chain reaction–high-resolution melting
SNV: single-nucleotide variant
VDBP: vitamin D–binding protein
VDR: vitamin D receptor

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Protocol

Patient Education and Decision Support for Long-Acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing with Ryan White HIV/AIDS Program Medical Case Management Programs in New York

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Abstract

Background: Long-acting injectable (LAI) HIV antiretroviral therapy (ART) presents a major opportunity to facilitate and sustain HIV viral suppression, thus improving health and survival among people living with HIV and reducing the risk of onward transmission. However, realizing the public health potential of LAI ART requires reaching patients who face barriers to daily oral ART adherence and thus can clinically benefit from alternative treatment modalities. Ryan White HIV/AIDS Program Part A medical case management (MCM) programs provide an array of services to address barriers to HIV care and treatment among economically and socially marginalized people living with HIV. These programs have demonstrated effectiveness in improving engagement along the continuum of care, but findings of limited program impact on durable viral suppression highlight the need to further innovate and hone strategies to support long-term ART adherence.

Objective: This study aims to adapt and expand Ryan White MCM service strategies to integrate LAI ART regimen options, with the larger goal of improving health outcomes in the populations that could most benefit from alternatives to daily oral ART regimens.

Methods: In 3 phases of work involving patient and provider participants, this study uses role-specific focus groups to elicit perceptions of LAI versus daily oral ART; discrete choice experiment (DCE) surveys to quantify preferences for different ART delivery options and related supports; and a nonrandomized trial to assess the implementation and utility of newly developed tools at 6 partnering Ryan White HIV/AIDS Program Part A MCM programs based in urban, suburban, and semirural areas of New York. Findings from the focus groups and DCEs, as well as feedback from advisory board meetings, informed the design and selection of the tools: a patient-facing, 2-page fact sheet, including *frequently asked questions* and a side-by-side comparison of LAI with daily oral ART; a patient-facing informational video available on YouTube (Google Inc); and a patient-provider decision aid. Implementation outcomes, measured through provider interviews, surveys, and service reporting, will guide further specification of strategies to integrate LAI ART options into MCM program workflows.

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Results: The study was funded in late April 2021 and received approval from the institutional review board in May 2021 under protocol 20-096. Focus groups were conducted in late 2021 (n=21), DCEs ran from June 2022 to January 2023 (n=378), and tools for piloting were developed by May 2023. The trial (May 2023 through January 2024) has enrolled >200 patients.

Conclusions: This study is designed to provide evidence regarding the acceptability, feasibility, appropriateness, and utility of a package of patient-oriented tools for comparing and deciding between LAI ART and daily oral ART options. Study strengths include formative work to guide tool development, a mixed methods approach, and the testing of tools in real-world safety-net service settings.

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International Registered Report Identifier (IRRID): DERR1-10.2196/56892

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KEYWORDS

HIV; implementation science; long-acting injectables; LAI; patient decision aid; medical case management; MCM; antiretroviral therapy; ART

Introduction

Since 1990, the federal Ryan White HIV/AIDS Program (RWHAP) has funded cities and counties (via Part A) to provide HIV medical care and support services for those without alternative resources. The RWHAP is an essential platform for reducing HIV-related health disparities and scaling up evidence-based strategies to strengthen the HIV care continuum [1,2]. RWHAP service recipients account for more than half of the people living with HIV in the United States [1,3-6], and approximately 75% of people receiving HIV medical care in the United States attend facilities with RWHAP funding [2]. The central role of the RWHAP in the US response to HIV has been reaffirmed in the Ending the HIV Epidemic Plan [7]. In New York (NY), RWHAP Part A (RWPA) services primarily represent people who identify as Black (53%) or Latinx (37%), which are groups disproportionately affected by the US HIV epidemic [8,9] and less likely to be virally suppressed once diagnosed with HIV [10]. Among those retained in HIV care in 2022, people enrolled in RWPA services in New York City (NYC) were less likely to be virally suppressed (83% vs 93%) or experience durable viral suppression (defined as all viral loads <200 copies/mL) in 2022 (71% vs 86%) as compared with other people living with HIV in NYC. RWPA medical case management (MCM) programs are specifically designed to reduce barriers to HIV care and treatment through the coordination of medical and social services and the provision of antiretroviral therapy (ART) adherence support. The NYC Health Department oversees RWPA MCM services to >4000 people living with HIV per year in 29 programs in NYC and the suburban and semirural Tri-County area (Putnam, Rockland, and Westchester) north of NYC. Although these programs have shown effectiveness in engaging people in HIV care and treatment, substantial room for improvement in HIV viral suppression outcomes remains, highlighting the need to further innovate and develop strategies to increase long-term ART adherence [11-15].

Long-acting injectable (LAI) ART has been heralded as a major biomedical advance that could close gaps in the HIV care continuum, minimize HIV transmission risk, reduce racial and ethnic HIV outcome disparities, and accelerate the end of the HIV epidemic by making viral suppression attainable for those who struggle with daily oral ART adherence. After phase 3 clinical trials found a long-acting cabotegravir and rilpivirine injectable combination (CABENUVA) to be comparable in safety and efficacy and superior in patient satisfaction to daily oral ART [16-19], the US Food and Drug Administration (FDA) approved a monthly CABENUVA regimen in January 2021 [20] and a bimonthly regimen in February 2022 [21]. LAI ART addresses some important adherence barriers by eliminating the requirement for daily dosing, and patients have also noted that it can remove the daily reminder or stressor of HIV status and mitigate the risk of inadvertent HIV status disclosures [22-30]. However, there are challenges in LAI ART implementation that must be systematically addressed. Commonly reported barriers for patients include concerns over effectiveness [31-36], side effects [31,32,35-37], dosing frequency [33,35,36], getting to a clinic for each injection [34,38,39], and use of needles [32,37]. Providers have voiced concerns related to staffing resources, organizational logistics, patient readiness for LAI ART, adherence to injection appointments, and injection tolerability [35,40,41]. In the face of these challenges, uptake of LAI ART since its FDA approval has fallen short of expectations. As of the end of September 2023, approximately 20,000 people in the United States (including Puerto Rico) were on CABENUVA (Cinthya Avalos Meléndez of ViiV Healthcare, email to author, December 14, 2023). This represents <2% of the approximately 1.1 million people living with diagnosed HIV in the United States and its dependent areas [42]. Optimizing the public health impact of LAI ART will require implementation science to identify and tailor interventions to facilitate LAI uptake and engagement, particularly for the most marginalized patients. Without the necessary groundwork to assess and promote access, acceptability, and uptake in underserved populations, biomedical innovations tend to benefit those who are already relatively advantaged and can even exacerbate health disparities [43-45].

This paper describes the protocol for a mixed methods study designed to prepare RWPA MCM programs for extending LAI ART options to patients who have struggled to achieve or maintain viral suppression on daily oral ART and who have been underrepresented in phase 3 clinical trials. Specifically, we summarize the formative and survey research stages completed to guide the selection and development of LAI ART–related educational and decision-support tools, and we

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present the methods for a pilot test to evaluate and refine these tools for future scale-up.

Methods

Study Overview, Aims, and Partners

The Assessing Perceptions and Preferences Around Long-acting Injectables study is organized into 3 consecutive phases of work, each of which corresponds to a specific aim: (1) elicit perceptions, barriers, facilitators, and expectations of LAI versus daily oral ART delivery options in focus groups with RWPA MCM patients, core staff, and prescribing providers; (2) quantify preferences and drivers of engagement in ART delivery and support strategies, including options for LAI and daily oral ART, via discrete choice experiments (DCEs) with approximately 200 patients and 200 providers; and (3) select and pilot strategies to promote LAI ART uptake, adherence, and impact in real-world care settings. Each aim corresponds to distinct data collection activities, as summarized in Table 1.

Table 1. Study data sources, participants, content, data collection periods, and purpose by aim.

Aim	Data source	Participants	Content	Time frame	Purpose
1	Focus groups	1. 16 MCM[a] providers (case managers, patient navigators, administrators, and a prescribing provider) 2. 5 MCM patients	1. Awareness and perceptions about LAI[b] ART[c] 2. Implementation barriers and facilitators (for providers) 3. Acceptability of LAI ART (to patients)	October to December 2021	Inform design of discrete choice experiments and gather preliminary data on LAI ART acceptability or concerns
2	Discrete choice experiment surveys	1. 177 MCM providers 2. 201 MCM patients	1. Preferred program features: type of ART, service location and mode, adherence support, rewards 2. Awareness and acceptability of LAI ART 3. Appropriateness and feasibility of LAI ART (for providers) 4. Case vignettes with questions about LAI ART candidacy and potential benefit (for providers)	June 2022 to January 2023	Understand drivers of decisions about ART regimens and adherence supports; quantify preferences for specific ART regimen, ART delivery, and ART adherence support or reinforcement options
3	Brief provider surveys	• 12 MCM providers (1 administrator and 1 direct service provider per partnering agency)	• Pilot intervention acceptability, appropriateness, and feasibility, and organizational readiness for implementation	3 rounds (baseline, midpoint, and final), May 2023 to February 2024	Quantify role of specific factors for pilot implementation using standard measures for comparison to the literature
3	Individual provider interviews	• 12 MCM providers (1 administrator and 1 direct-service provider per partnering agency)	• Providers' experience of the pilot, barriers and facilitators, or other factors for pilot tool implementation, and any recommendations	September 2023 to February 2024	Qualitatively assess pilot implementation factors and outcomes and desired changes to piloted tools
3	Program data on patients enrolled and pilot-related service delivery	• ≥180 MCM patients from 6 partnering agencies	• Patient descriptive data, assessments of patient ART regimen and adherence, and detail on pilot services delivered (tools and dates used, as well as patient responses on ART regimen choices)	May 2023 to January 2024, with follow-up on LAI ART adherence through September 2024	Quantitatively assess pilot implementation outcomes such as reach, effectiveness, adoption, and implementation and variation by agency, intervention condition, or stage of pilot

[a]MCM: medical case management.

[b]LAI: long-acting injectable.

[c]ART: antiretroviral therapy.

The study functions as an academic-government-provider collaboration, with a university-based lead agency working closely with a health department and 6 NY RWPA MCM service-provider agencies that were engaged as partners from the outset. The 6 provider agencies were purposively selected to represent the full range of NY RWPA MCM service settings (hospitals, community health centers, and social services community-based organizations) and the distinct geographic regions within the NY RWPA eligible metropolitan area. Three of the agencies have headquarters in NYC, which includes 5 counties: New York (Manhattan), Bronx, Kings (Brooklyn), Queens, and Richmond (Staten Island). The other 3 agencies

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have headquarters in the Tri-County area north of NYC: Westchester, Rockland, and Putnam. All 6 agencies had an annual caseload of at least 70 RWPA MCM patients at the time of the study proposal development. Although the FDA had not approved LAI ART until after the study proposal was submitted, LAI ART prescription was beginning when the project started and was being considered for some MCM enrollees at the partner agencies by the second year of the project in the months immediately preceding the pilot.

Completed Data Collection

Aim 1 Focus Groups

The first study phase was directed at eliciting patient and provider perceptions and expectations of LAI versus daily oral ART, including barriers and facilitators to LAI ART use or delivery. The focus group guide was designed to explore potential influences (organized by domain from the Consolidated Framework for Implementation Research; CFIR [46]) on LAI ART implementation outcomes. Implementation outcomes were defined using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) measures [47]. The primary purpose of the focus groups was to identify key intervention attributes (features of possible LAI ART implementation tools) to be included in the DCEs.

We set out to conduct focus groups of up to 9 participants each with NYC English-speaking patients, Tri-County English-speaking patients, Spanish-speaking patients, MCM administrators (who determine the use of program resources), MCM direct support service providers (who help develop and carry out patient care plans), and MCM program-affiliated primary care providers (who have the discretion to prescribe LAI ART). Patient focus group eligibility required being aged ≥18 years, currently enrolled in an RWPA MCM program at 1 of the 6 partnering agencies, comfortable conversing in Spanish or English, and virally unsuppressed (viral load ≥200 copies/mL) at most recent viral load test. Providers were eligible if they filled a core MCM role (administrator, support service provider, or prescribing provider) with any of the 6 partnering agencies. Provider focus group recruitment yielded 15 providers in 2 focus groups (administrators and support-service providers) plus 1 individual interview with a prescribing provider. Patient recruitment was more challenging and yielded 1 Tri-County participant and 4 NYC participants after no shows. Partner agencies had relatively few virally unsuppressed adults enrolled in MCM at the time of recruitment and noted that those patients were harder to engage in research. No Spanish-speaking patients were enrolled despite months of recruitment. Each participant received a US $25 gift card in appreciation of their time and input.

Focus group interview discussions were audio-recorded, transcribed, and coded in Dedoose using thematic analysis [48]. In a combined inductive-deductive approach, the qualitative analysts applied predefined codes derived from the CFIR and RE-AIM constructs and used grounded exploration to interpret category meanings [49] and attend to emergent themes salient to participants. Separately for patient and provider transcripts, initial codes were identified in an independent review of 1 focus group transcript by 2 study team members in dialogue with a senior investigator with extensive experience in conducting qualitative research. The draft (patient or provider) codebook was then independently applied to a second transcript, with discrepancies resolved in consensus sessions to optimize inter-rater reliability, yielding the final codebook that was applied to the entire data set. Findings were presented for study advisory board (AB) input and used for consensus- and evidence-based selection of 4 potential intervention attributes (with 3-4 levels each) for inclusion in the DCEs.

Patient and provider participants highlighted the potential for LAI ART options to reduce HIV stigma and adherence burden; providers noted that ART administration via injection by a health care worker offered protection against medication diversion. Both sets of participants mentioned COVID-19 vaccine-related attitudes and insurance preauthorization processes as barriers, and providers expressed concerns about the risks of missed injection appointments. Patients and providers desired more information and clearer messaging about LAI ART. The focus group participants also discussed MCM services that could be expanded to support LAI ART delivery: directly observed therapy, appointment transportation or accompaniment, reminder calls or texts, home visits, and financial incentives (eg, rewards for receiving an injection on time). These strategies, along with perceived LAI ART facilitators (less frequent injections, peer support, and postinjection follow-up communications from MCM staff) were integrated as treatment package features for the DCE surveys.

Aim 2 DCE Surveys

DCE Methods

DCEs offer an efficient means of assessing preferences and priorities for intervention-related attributes [50], which can guide intervention design and packaging to encourage uptake, engagement, and maintenance among the intended users. DCE participants are shown a series of choice sets juxtaposing ≥2 different hypothetical scenarios. Each scenario comprises intervention attributes, further defined by a number of levels, which are randomly combined to create hypothetical intervention alternatives. Participants are asked to choose the single preferred alternative for each choice set presented, recognizing the trade-offs between the desirable or undesirable characteristics of each. Through repetition of this process over several choice sets representing many possible combinations of attribute variations, investigators can identify which attributes and attribute levels participants value the most. Latent class multinomial logit regression is used to estimate utilities, which are measures of preference for levels within attributes. Positive utility values indicate greater preference.

DCE Survey Design

The aforementioned focus groups informed the team's selection of four attributes: (1) type of ART, (2) service location or mode, (3) adherence support, and (4) rewards. The latter 3 were alternative-specific attributes defined according to the type of ART (daily oral or LAI). Focusing on 3 implementation outcomes identified by Proctor et al [51] as salient during the adoption phase of an innovation-decision process, we also included the brief (4-item) *acceptability of intervention measure*

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(AIM) on the provider and patient survey and the *intervention appropriateness measure* (IAM) and the *feasibility of intervention measure* (FIM) on the provider survey [52]. Contextual items at the end of the patient survey covered prior awareness of LAI ART and any experience with LAI ART, and contextual items at the end of the provider survey covered the length of time delivering MCM and vignettes about hypothetical patients as potential candidates for LAI ART.

Survey Recruitment

Eligibility for the patient DCE survey required being aged ≥18 years and enrolled in RWPA MCM services at any of the 6 partnering agencies. As with the focus groups, contact attempts for patient recruitment were conducted through MCM program staff at the partnering agencies. Eligibility for the provider DCE survey required having an RWPA MCM care team job role (ie, case manager or care coordinator, patient navigator or community health worker, program administrator with duties beyond clerical or data support, or prescribing provider). Given the target of 200 participants per survey (patient or provider) and the availability of fewer than 50 eligible providers at the 6 partner agencies, all 29 RWPA MCM programs were engaged for the provider survey. We offered the provider survey in English and the patient survey in English, Spanish, and Haitian Creole.

Patient Survey Participants and Preliminary Results

From June 2022 through January 2023, 201 NY RWPA MCM patients with a median age of 54 years (IQR 42-62) and a median MCM enrollment of 31 months (IQR 11-45) completed the DCE. Most patients (183/201, 91%) were Black or Latinx, and 39.3% (79/201) identified as women. Three-quarters (151/201, 75.1%) self-reported perfect adherence to daily oral ART. A two-group latent class analysis identified a smaller subset of patients with a strong preference for daily oral ART and a larger subset preferring LAI ART. Both groups preferred higher value monetary incentives and transportation to primary care or injection appointments over other rewards or supports for adherence. At the time of the survey, 85.6% (172/201) of the participants reported taking daily oral ART. About half of the participants (104/201) indicated that they had heard of LAI ART before taking the survey, but only 4.5% (9/201) reported having tried it.

Provider Survey Participants

From July 2022 through January 2023, 177 NY RWPA MCM staff members completed the DCE. Most provider participants identified as women (127/177, 71.8%), were aged 40 to 59 years (92/177, 52%), and had been providing RWPA MCM services for >2 years (124/177, 70.1%). The largest racial or ethnic group among the participating staff was Latinx or Hispanic (73/177, 41.2%), followed by non-Hispanic Black or African American (50/177, 28.2%), and non-Hispanic White (32/177, 18.1%). The most frequent job types were patient navigator (68/177, 38.4%), case manager or care coordinator (46/177, 26%), program director (33/177, 18.6%), and prescribing provider (21/177, 11.9%). As of the end of 2023, data from the provider DCE survey were in the early analysis stage.

Advisory Board

After receiving notice of the grant award (April 2021), the study team convened an AB for input in July 2021; February, May, and November 2022; and January, April, and August 2023. AB members, who consult on study tools, implementation, results interpretation, and dissemination, include clinical and nonclinical direct-service providers and administrators (from all 6 partnering provider agencies and a seventh interested MCM agency); Health Department staff; external researchers; and members of the HIV Health and Human Services Planning Council of NY (RWPA community planning body). In the January and April 2023 meetings, AB members provided critical input on the tools for inclusion in the pilot, including feedback on the content and visual design of draft versions.

Pilot Testing of ART Regimen Decision-Making Supports

Selection and Design of Tools to Be Piloted

The third aim and phase of this study has focused on the synthesis and application of findings from aims 1 and 2 to develop LAI ART implementation tools and pilot test them with partnering agencies while gathering data to inform tool refinement for future research and scale-up. Tools were developed in consultation with the MCM program staff and other AB members familiar with MCM service settings, MCM patient needs, or decision-support processes. The selection and design of tools for the pilot study were guided by a combination of focus group findings, AB input, and preliminary patient DCE results. In addition to indirectly informing tool development by highlighting the attributes for inclusion in the DCEs, focus group findings and AB input directly influenced the study team's decision to develop patient-facing educational materials. The latter decision stemmed from the focus group participants' emphasis on the need for clearer messaging about LAI ART and AB members' requests for materials that could be reviewed by patients on their own. AB members called attention to a general lack of patient-facing materials about LAI ART beyond the drug manufacturer's consumer-directed materials, which partnering program staff viewed as unrelatable for many of their patients. Finally, the AB advocated for including a patient-facing video to present and compare ART regimen options in an engaging and entertaining medium while minimizing the time required during MCM visits for ART regimen-related education and decision-making processes.

The limited familiarity of patient DCE participants with LAI ART reinforced the need for clear, patient-facing educational materials describing LAI ART and directly comparing it with daily oral ART. Divergent patient preferences for daily oral versus LAI ART suggested a difference in perception between LAI ART phase 3 clinical trial participants and patients seen in our safety-net MCM program settings, which may reflect some of the patient-level factors limiting LAI ART uptake in practice. The mixed reception of LAI ART in the DCE reinforced the potential value of a decision-support tool to assist patients in weighing the advantages and disadvantages of available regimen types and assessing the fit of each option with their individual preferences, needs, challenges, and strengths as well as considering programmatic resources (such as transportation)

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that could reduce perceived barriers to treatment success. The study team developed a patient-provider ART regimen decision aid using the Ottawa Decision Support Framework [53] and tailored the tool to suit the RWPA MCM program context, the focus on ART regimen decisions, and the AB's emphasis on brevity and accessibility.

Pilot Trial Design

Primary data collection for the pilot has entailed brief provider surveys and semistructured provider interviews drawing upon the CFIR to assess factors (barriers and facilitators) for pilot tool implementation. In addition, we intend to use the provider interviews and program reporting on pilot enrollment and service delivery to evaluate pilot implementation outcomes, drawing upon RE-AIM measures: reach (types and numbers of patients enrolled), effectiveness (preliminary effects on LAI ART uptake and concordance between treatment plan pursued and patient choice as recorded on the decision aid), adoption (documentation of specific tools' use), implementation (alignment of reported tool use with study condition and guidance on tool use), and maintenance (ART adherence). This pilot study was designed as a nonrandomized, 2-arm trial of newly developed tools with ≥180 RWPA MCM patients. It was structured to allow comparison of an intervention arm including both patient education materials and the decision aid (*decision-aid arm*) with an intervention arm including only the patient education materials and usual care approaches (whatever agencies may already be doing) for ART regimen decision-making (*education-only arm*).

Study Setting and Participants

The pilot test was conducted at the 6 partnering RWPA MCM agencies. The characteristics and study arm assignments of the 6 agencies are summarized in Multimedia Appendix 1. Cluster (agency-level) assignment was used for this study to minimize crossover between intervention conditions and avert the logistical and ethical dilemmas posed by assignment strategies that require providers to administer, maintain, and track different investigator-assigned intervention conditions within a single patient caseload [54-56]. *Provider eligibility:* Pilot-related primary data collection was limited to English-speaking adults responsible for overseeing or delivering RWPA MCM services or prescribing ART for MCM patients at a partnering agency. At each agency, 1 administrative staff member (eg, program director) and 1 direct-service provider (eg, case manager, patient navigator, or prescriber) was engaged to participate in implementation-related data collection through brief surveys and semistructured interviews. *Patient eligibility:* Patients were enrolled in a partnering NY RWPA MCM program, aged ≥18 years, and able to understand materials in English or Spanish. Patient eligibility for an LAI ART prescription could not be directly assessed by the study team and could be assessed differently by different providers or third-party payers; it could also change over time with FDA label indications. However, the study team communicated to partnering programs that patients should not be included in the pilot if they had known or suspected resistance to cabotegravir or rilpivirine, as this was a contraindication for LAI ART available as of the start of this pilot study (CABENUVA). On the basis of AB feedback that translating pilot materials to Spanish without translating to Haitian Creole would be viewed as inequitable, and given a lack of remaining time or resources to provide translations for tools (including audio for the video) in 3 languages, the pilot study was launched with only English-language tool versions.

Intervention Conditions

Education-Only Arm

Participants received informational materials (including a fact sheet covering *frequently asked questions* [Multimedia Appendix 2] and a short video [Multimedia Appendix 3]) on their HIV treatment options and related support service options. These materials provide a comparison of the risks and benefits of LAI and oral ART regimens, set expectations about clinic visits, present information about side effects, and include additional resources to assist patients in preparing to discuss HIV treatment and support options with their care coordinator and prescribing provider. All materials are at or below an eighth-grade reading level, use graphics to bolster understanding for different levels of health literacy, and follow accessibility guidelines for font choice and size. Participants receiving this intervention were offered these materials by a care coordinator or patient navigator and were encouraged to review the materials on their own; they could also go over the materials with staff during an MCM program visit.

Decision-Aid Arm

Before or during an MCM visit, participants received informational materials (described in *Education-Only Arm* section) on HIV treatment types and related support service options. During an MCM visit, the participant and patient navigator or care coordinator reviewed the shared decision aid (Multimedia Appendix 4) to weigh the participant's treatment options and their fit to the participant's interests, needs, assets, and constraints. The tool facilitates and records patient-provider agreement on a treatment plan to be integrated into the broader MCM care plan signed by both the patient and provider. Figure 1 illustrates the 2 intervention conditions and the workflow for each.

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Figure 1. Intervention arms and workflows for the 2-arm pilot trial. eSHARE: Electronic System for HIV/AIDS Research and Evaluation.

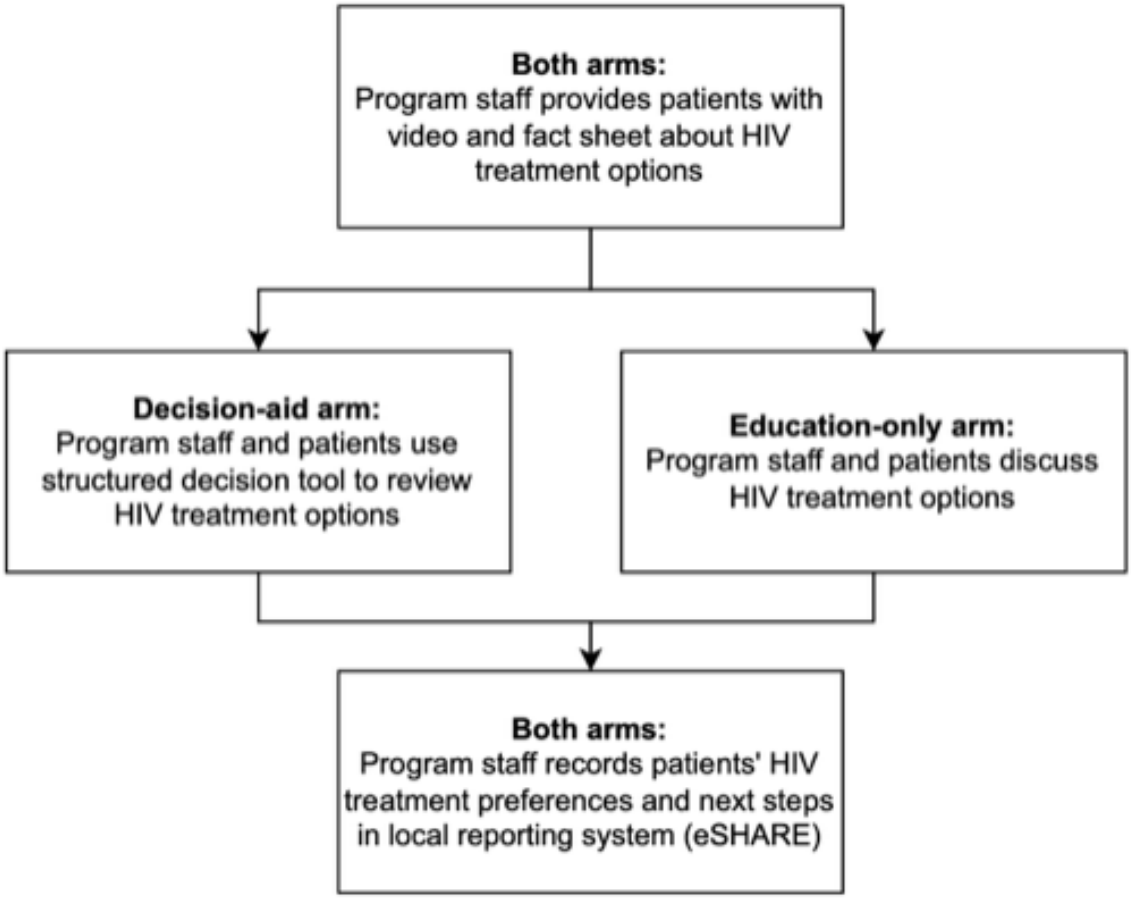

Nonrandom Assignment

We used purposive sampling to assign 3 of the 6 partnering RWPA MCM agencies to the decision-aid arm (which included the educational tools) and 3 to the education-only arm. Specifically, we ensured representation of at least 2 different agency types and MCM program sizes in each arm.

Blinding

Owing to the need to engage service providers in the intervention through study team–led activities (eg, orientation to the project-specific educational materials or the decision aid), study arm assignments were transparent to agency staff and study team members (though not to patients).

Data Collection and Management

Aim 3 (pilot testing) involved repeated primary data collection with 2 providers at each of the 6 partnering agencies and use of secondary data on pilot participants, service delivery, and outcomes. In aim 3 pilot interviews with the implementing providers, oral informed consent was obtained in advance of the interview session by phone or videoconference. The interviews were audio-recorded and transcribed for coding in Dedoose. Aim 3 provider survey data were collected and managed using the NYC Health Department REDCap (Research Electronic Data Capture; Vanderbilt University) server, a web-based application for designing and managing surveys. The REDCap survey data will be analyzed using R (version 4.3.2; R Foundation for Statistical Computing).

Patient data for the pilot are being drawn from the local RWPA data system, the Electronic System for HIV/AIDS Research and Evaluation (eSHARE), in the form of provider-reported enrollments, services, patient characteristics, assessed needs, regimen types, and adherence data required for fee-for-service reimbursement in NY RWPA MCM contracts. eSHARE has been updated by the NYC Health Department to include pilot tools so that partnering MCM agencies could enter pilot activities along with (and as distinct from) other MCM services. No patients were enrolled in the RWPA MCM programs solely for the pilot; rather, patients already enrolled in MCM could be eligible to receive pilot-related services (ART regimen-related information and decision support with the tools developed for the project), along with the array of other MCM services. All patient- and service-level data are protected according to the Centers for Disease Control and Prevention's physical and electronic data security and confidentiality policies [57]. Health Department staff extract and clean eSHARE data monthly, clean and freeze surveillance data sets quarterly, and conduct matches of the program to surveillance data semiannually. The deterministic matching algorithm has been described previously [58]. Through matching with surveillance data, patients are assigned a unique record number used to deduplicate data sets, which are stripped of personal identifiers before analysis.

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Study Outcomes

LAI Uptake (Primary Outcome)

The primary outcome is defined as the proportion of pilot participants who start LAI ART (whether initiating ART, transitioning from a prior regimen, or transitioning from a period of nonuse of ART). The denominator includes patients not already on LAI ART at the start of the pilot trial, and the numerator includes any of those in the denominator who began LAI ART during the trial. Using program-reported (eSHARE) data on regimen type, uptake will be measured continuously for up to 9 months (the duration of the pilot trial). *Concordance:* This outcome is defined as the proportion of participants whose intent (as documented via the decision aid) is carried through in terms of their subsequent treatment (self-administered daily oral ART, LAI ART, or some intermediate step such as directly observed therapy to meet the current FDA label requirement for viral suppression). Using eSHARE data on decision aid responses and subsequent regimen type or services related to ART adherence, concordance will be measured from the date of decision aid completion for up to 9 months. *LAI maintenance:* LAI maintenance is defined in terms of adherence to LAI ART, specifically the time from LAI initiation to first deviation from the injection schedule, among trial participants initiating LAI ART during the trial. A deviation includes any injection >1 week ahead of or 1 week after the treatment target date, where the injection target date depends on whether the prescribed regimen is monthly or bimonthly. Using eSHARE data on ART regimen type and adherence (as well as case closure owing to death), maintenance will be measured from the first report of LAI ART to the first reported deviation from the injection schedule or date of death from any cause, whichever comes first, assessed for up to 9 months from the first injection or up to 8 months of follow-up injections (counting from the first possible deviation from a scheduled follow-up injection).

Other Measures

To understand the influences on implementation, we assess provider-perceived acceptability, appropriateness, and feasibility of the tools at 3 points in the pilot: baseline, 4-5 months (midpoint), and 9 months (end of the pilot). Specifically, the provider survey includes the 4-item scales (AIM, IAM, and FIM) that were used in the provider DCE survey [52]. However, for the pilot survey, these 3 measures specifically refer to the pilot tools being implemented. The baseline and midpoint assessments also include a brief measure of organizational readiness for implementing change (ORIC), which captures commitment to change (5 items) and perceived efficacy to change (7 items) [59] based on the theory of organizational readiness for change [60]. As the ORIC measure is anticipatory, it is not part of the final assessment. The semistructured midpoint and end-of-pilot interviews elicit providers' experiences of the piloted tools, including barriers, facilitators, and suggested refinements. Interviews will lend context to the ORIC, AIM, IAM, and FIM results and guide tool refinements.

Sample Size, Data Analysis, and Power Analysis

The original target was to enroll 180 patients or 30 (on average) per partner agency. As of mid-November 2023, 205 patients were enrolled. Using eSHARE data, we will describe trial participant demographics (eg, gender, age, race or ethnicity, income, and housing status) overall and by intervention arm. We will compare LAI ART uptake and, among those starting LAI ART, adherence by intervention arm, to assess the effects of the fuller package with the decision aid versus education alone. We will use log binomial regression to estimate risk ratios for uptake and adherence by intervention arm with generalized estimating equations and a small sample correction (owing to the small number of clusters) to maintain the type I error rate while accounting for clustering by site. To the extent possible given our sample size, we will adjust for potential confounders captured in eSHARE.

The brief provider survey measures will be analyzed through a comparison of responses on the same measures over time (eg, to assess change in perceived feasibility), as well as comparison of responses by intervention arm, agency type, and participant role. AIM, IAM, FIM, and ORIC scores will also be analyzed in relation to the levels of pilot service delivery as documented in eSHARE. To understand the potential for sustainability and scale-up, we will explore qualitative provider interview themes related to the acceptability and feasibility of the intervention. Qualitative and quantitative analyses will be integrated by examining thematic patterns reflecting RE-AIM and CFIR implementation constructs as they explain observed implementation outcomes [61].

Our pilot was designed to assess implementation of the newly developed tools and inform tool refinements. Data from the pilot will be used to generate estimates of LAI ART uptake that can, in turn, inform sample size and power calculations for a larger, controlled study of the refined tools' implementation and treatment outcomes. Accordingly, data from the pilot study will be used to estimate the proportion of patients who start LAI ART and, among those initiating, the proportion who maintain LAI ART. With the original target of 180 patients (now exceeded), we will be able to estimate LAI uptake with precision (95% CI) with the levels of uptake described in Table 2.

Assuming that half of the people who initiate LAI ART maintain it at 9 months, we will have the abovementioned precision estimates for the scenario of 50% LAI ART maintenance across a range of different levels of LAI ART uptake.

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Table 2. 95% CIs for long-acting injectable (LAI) antiretroviral therapy (ART) uptake among pilot participants overall and maintenance estimates for those who start on LAI ART under LAI uptake percent assumptions.

LAI ART uptake, (%)	LAI ART uptake, 95% CI	LAI ART maintenance at 50%, 95% CI
5	2.7-9.2	22.7-77.4
10	6.4-15.2	29.0-71.0
15	10.5-20.9	32.4-67.7
20	14.8-26.4	34.5-65.5
30	23.8-37.0	37.0-62.9
40	33.1-47.3	38.8-61.3
50	42.8-57.3	39.9-60.1

Ethical Considerations

This study was approved by the NYC Department of Health and Mental Hygiene IRB (protocol 20-096) and registered with ClinicalTrials.gov (Identifier NCT05833542, preresults). The pilot trial was granted a waiver of patient informed consent in accordance with the pre-2018 requirements set forth in 45 CFR 46.116(d) based on its reliance on secondary data analysis. Any changes to trial eligibility criteria, outcome measures, or analysis plans would be mutually agreed upon between the principal investigators, vetted with the AB, and submitted to the IRB as protocol modifications.

Informed consent was obtained from each participant before their participation in primary data collection: focus groups, DCE surveys, provider pilot interviews, or provider pilot surveys. No individual incentive was offered for provider pilot interviews or provider pilot surveys. Each focus group participant and each DCE survey participant received a US $25 gift card.

The primary data collected for this study are stored on secured servers without participant names or other personal identifiers. Study records can be linked to individual participants only by study team members, who retain a separate key linking study identifiers to other identifiers (eg, eSHARE identifier codes). Patient names are stored in the most secured environment, accessible only to NYC Health Department staff authorized to view names and only during a time-limited, secured session in Citrix, which prohibits access to the internet, email, portable media such as flash drives, or printers. All records used in secondary analyses are also stripped of personal identifiers before their inclusion in data sets for analysis.

Results

The study was funded in late April 2021 and received official IRB approval in May 2021 under protocol 20-096. Focus groups were conducted in late 2021 and DCE data collection took place between June 2022 and January 2023. Patient education and patient-provider decision aid tools were developed by May 2023, and the trial continued through January 2024. Complete outcome data are expected by October 2024 and will be submitted for publication by December 2024. Study results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) extension to cluster randomized trials and disseminated through scientific conferences, peer-reviewed publications, and meetings with local stakeholders. The investigators have also been sharing this work with colleagues in other jurisdictions and will disseminate the findings via the Ending the Epidemic Dashboard website.

Discussion

Overview

As a biomedical advance that untethers HIV viral suppression from the requirement for daily medication adherence, LAI ART could greatly increase the opportunities for health, survival, transmission prevention, and health equity. However, realizing that potential will depend on reaching those who have difficulty achieving or maintaining viral suppression on daily oral ART regimens. In addition, at this relatively early stage of LAI ART availability through third-party payers, there is little information on how acceptable, appropriate, or feasible this treatment option may be for low-income, predominantly Black and Latinx patients and their HIV service providers. This study is designed to yield insights and field-tested strategies to help optimize the public health impact of LAI ART, with particular attention to the patient groups underrepresented in clinical trials, disproportionately burdened by HIV-related morbidity and mortality, and most able to benefit from gaining access to alternatives to daily oral ART. On the basis of the focus group participants' and AB members' calls for clear patient-facing information and findings of limited LAI ART familiarity and divergent ART regimen-type preferences among patient DCE participants, we prioritized the development and testing of a patient-facing fact sheet and educational video, along with a patient-provider decision aid to guide conversations about treatment options and related supports.

Limitations and Strengths

Agencies were purposively assigned to pilot intervention conditions (with the intent of balancing the characteristics of agencies represented in each condition) rather than through randomization. Additional limitations include a lack of blinding (of agencies, providers, or investigators) to the agencies' assignments and a lack of control over agencies', providers', or patients' exposure to other initiatives or interventions that may affect the outcome. We are aware of at least 1 other NY-based pilot test of LAI-related support strategies [62], as well as a NY State Department of Health clinical quality improvement committee focused on identifying and sharing LAI ART–related resources and best practices. However, the

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other NY-based pilot does not directly involve any of the agencies engaged in this trial. To our knowledge, our study is the first and only study to explicitly focus on the integration of LAI ART regimen options in RWPA or other RWHAP MCM service settings and the first to develop patient-directed LAI ART education materials or a patient-provider ART decision aid for use in an RWPA service population.

As with other HIV care quality improvement activities led by the NYC Health Department, agency participation is voluntary, meaning that agencies in the pilot could implement their assigned intervention condition incompletely or decline to implement. To address this limitation, we are tracking multiple implementation measures.

Conclusions

The United States National HIV/AIDS Strategy and National Institutes of Health have called for implementation science to produce evidence-based models of care [63,64]. Reviews of HIV care continuum research have also noted the need for practice-based evidence to inform program and policy development [65-67]. The implementation science design of this study has been selected to facilitate rapid research-to-practice translation of any LAI ART educational or decision-support tools that are found to be acceptable, feasible, and appropriate to these service settings and that show preliminary evidence of patient benefit. Through a robust academic-government-provider partnership, products from this study will be incorporated into local HIV services planning and delivery, as well as into future research.

Acknowledgments

This project was supported by the National Institutes of Health (NIH), grant number R34 MH 126809 (Project Officer Teri Senn), and by the Health Resources and Services Administration (HRSA), grant number H89HA00015 (Project Officer Axel Reyes). The authors would like to thank the 6 partnering provider agencies: State University of New York Downstate Health Sciences University (lead contacts: Lori Hurley and Antoinette Davis), La Casa de Salud (lead contacts: Mohammed Aldhuraibi and Pedro Gonzalez), Together Our Unity Can Health (lead contacts: Julian Palmer and Memunatu Attah-Issah), Open Door Family Medical Centers (lead contacts: Karin Palencia-Lua and José Miranda), Council on Adoptable Children (lead contacts: Denise Barrera and Katie Rivera), and Sun River Health (lead contacts: Aldonza Milian and Lisa Reid). This study also benefited from the support of other Ryan White Part A MCM service providers, Ryan White Part A participants, the HIV Health and Human Services Planning Council of New York, New York City Health Department HIV Care and Treatment Program leadership and quality management staff (Guadalupe Dominguez Plummer, Gina Gambone, Frances Silva, Grace Herndon, and Jacqueline Graham), and the Einstein-Rockefeller-CUNY Center for AIDS Research. The authors are indebted to Jennifer Carmona and Aimee Campbell, who provided early input critical to the grant proposal and the planning of the trial reported here. Finally, the authors would like to recognize the contributions of our other AB members and study team members (including Honoria Guarino, Will You, Chunki Fong, and Javier Lopez-Rios) to the larger Assessing Perceptions and Preferences Around Long-acting Injectables (APPLI) study and specifically the qualitative components and DCEs that guided the development of tools for pilot testing in the study's clinical trial phase. Generative AI (eg, ChatGPT) was not used in the ideation or in the writing process of this protocol. The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the official views of the funding agencies supporting this project. The NIH and HRSA are not involved in the study design, conduct, or products, or in the decision to submit this work for publication. The cited personal communication from ViiV Healthcare, indicating approximately 20,000 people in the US (including Puerto Rico) on CABENUVA, is based on an estimate derived from the use of information under license from the following IQVIA information service: National Custom Patient with National Longitudinal Patient (LRx) for the period ending 2023-09-29. IQVIA expressly reserves all rights, including rights of copying, distribution, and republication.

Data Availability

The full institutional review board protocol and statistical code will be made available upon request. The NY State Public Health Law prohibits the study team from releasing a public use data set containing information tending to identify the participants in its research. The NYC Health Department staff retain sole custody of study data sets and designated staff are available to answer any inquiries. Any questions or requests for additional information can be emailed to the study contact person.

Authors' Contributions

MKI is the health department (NYC Department of Health and Mental Hygiene [DOHMH]) principal investigator and led the conception of the overall study and the writing of the R34 proposal. RZ (City University of New York [CUNY]) reviewed and edited all drafts of the grant proposal, led the analyses on aim 2 of the larger study, and contributed substantively to the preparation of the manuscript. TA (DOHMH) supervised the DOHMH analysts' work on aims 1 and 3 of the larger study and contributed substantively to the study design and analysis plan. MP (DOHMH) and CE (DOHMH) conducted qualitative data collection for aim 1 and aim 3 and conducted qualitative analyses for aim 1. SGK (CUNY) and MMP (University of California, San Francisco [UCSF]) contributed substantively to the grant proposal and participated in ongoing planning. EAK (CUNY) contributed to the grant proposal and analysis plan and advised on study implementation. RZ (CUNY), TA (DOHMH), MP (DOHMH), and CE (DOHMH) prepared data, facilitated intervention implementation, participated in ongoing planning, and contributed to

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communication with service providers and other stakeholders while managing other aspects of the larger study. DN is the university-based, lead agency (CUNY) principal investigator and shares responsibility for the conceptualization and oversight of the overall study and this trial, serves as the primary contact with the grant funding agency, supervises CUNY team members on the grant, and guides dissemination. MKI drafted the manuscript, and all authors (MKI, RZ, TA, MP, CE, SGK, MMP, EAK, and DN) revised it for critically important intellectual content and provided the final approval of the manuscript.

Conflicts of Interest

The authors have reported only federal government grants to their institutions for this work. For work beyond this project, DN has received consulting fees from Gilead Sciences, Inc and Abbvie, Inc, and RZ, SGK, and DN have received research grant funding from Pfizer to their institution.

Multimedia Appendix 1
Partnering agency characteristics and intervention arm assignments for the pilot trial.
[DOCX File , 13 KB - resprot_v13i1e56892_app1.docx]

Multimedia Appendix 2
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot fact sheet.
[PDF File (Adobe PDF File), 109 KB - resprot_v13i1e56892_app2.pdf]

Multimedia Appendix 3
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot video.
[MP4 File (MP4 Video), 43202 KB - resprot_v13i1e56892_app3.mp4]

Multimedia Appendix 4
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot decision aid.
[PDF File (Adobe PDF File), 86 KB - resprot_v13i1e56892_app4.pdf]

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Abbreviations

AB: advisory board
AIM: acceptability of intervention measure
ART: antiretroviral therapy
CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials

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DCE: discrete choice experiment
eSHARE: Electronic System for HIV/AIDS Research and Evaluation
FDA: Food and Drug Administration
FIM: feasibility of intervention measure
IAM: intervention appropriateness measure
IRB: institutional review board
LAI: long-acting injectable
MCM: medical case management
NY: New York
NYC: New York City
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
RWHAP: Ryan White HIV/AIDS Program
RWPA: Ryan White HIV/AIDS Program Part A

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Protocol

Global Trends of Medical Misadventures Using International Classification of Diseases, Tenth Revision Cluster Y62-Y69 Comparing Pre–, Intra–, and Post–COVID-19 Pandemic Phases: Protocol for a Retrospective Analysis Using the TriNetX Platform

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Abstract

Background: The COVID-19 pandemic has sharpened the focus on health care safety and quality, underscoring the importance of using standardized metrics such as the *International Classification of Diseases, Tenth Revision* (*ICD-10*). In this regard, the *ICD-10* cluster Y62-Y69 serves as a proxy assessment of safety and quality in health care systems, allowing researchers to evaluate medical misadventures. Thus far, extensive research and reports support the need for more attention to safety and quality in health care. The study aims to leverage the pandemic's unique challenges to explore health care safety and quality trends during prepandemic, intrapandemic, and postpandemic phases, using the *ICD-10* cluster Y62-Y69 as a key tool for their evaluation.

Objective: This research aims to perform a comprehensive retrospective analysis of incidence rates associated with *ICD-10* cluster Y62-Y69, capturing both linear and nonlinear trends across prepandemic, intrapandemic, and postpandemic phases over an 8-year span. Therefore, it seeks to understand how these trends inform health care safety and quality improvements, policy, and future research.

Methods: This study uses the extensive data available through the TriNetX platform, using an observational, retrospective design and applying curve-fitting analyses and quadratic models to comprehend the relationships between incidence rates over an 8-year span (from 2015 to 2023). These techniques will enable the identification of nuanced trends in the data, facilitating a deeper understanding of the impacts of the COVID-19 pandemic on medical misadventures. The anticipated results aim to outline complex patterns in health care safety and quality during the COVID-19 pandemic, using global real-world data for robust and generalizable conclusions. This study will explore significant shifts in health care practices and outcomes, with a special focus

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on geographical variations and key clinical conditions in cardiovascular and oncological care, ensuring a comprehensive analysis of the pandemic's impact across different regions and medical fields.

Results: This study is currently in the data collection phase, with funding secured in November 2023 through the Ricerca Corrente scheme of the Italian Ministry of Health. Data collection via the TriNetX platform is anticipated to be completed in May 2024, covering an 8-year period from January 2015 to December 2023. This dataset spans pre-pandemic, intra-pandemic, and early post-pandemic phases, enabling a comprehensive analysis of trends in medical misadventures using the ICD-10 cluster Y62-Y69. The final analytics are anticipated to be completed by June 2024. The study's findings aim to provide actionable insights for enhancing healthcare safety and quality, reflecting on the pandemic's transformative impact on global healthcare systems.

Conclusions: This study is anticipated to contribute significantly to health care safety and quality literature. It will provide actionable insights for health care professionals, policy makers, and researchers. It will highlight critical areas for intervention and funding to enhance health care safety and quality globally by examining the incidence rates of medical misadventures before, during, and after the pandemic. In addition, the use of global real-world data enhances the study's strength by providing a practical view of health care safety and quality, paving the way for initiatives that are informed by data and tailored to specific contexts worldwide. This approach ensures the findings are applicable and actionable across different health care settings, contributing significantly to the global understanding and improvement of health care safety and quality.

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KEYWORDS

COVID-19; curve-fitting analyses; health care quality; health care safety; International Classification of Diseases, Tenth Revision; ICD-10; incidence rates; safety; TriNetX

Introduction

A wealth of scholarly research and empirical data underscores the imperative of prioritizing safety and quality in health care [1,2]. Seminal studies in the last 3 decades, such as the Canadian Adverse Events Study and the Harvard Medical Practice Study, have highlighted the rates of adverse events in health care settings, which led to severe, sometimes fatal, consequences for patients [3,4]. Moreover, research conducted in various international contexts has emphasized the necessity of rigorous safety protocols and the urgent need for continuous quality improvement plans [5-7]. The criticality of safety and quality in health care is not merely a theoretical construct but is supported by extensive research, governmental reports, and real-world implications [8]. Ensuring that safety and quality are at the forefront of health care delivery is pivotal for enhancing patient outcomes, reducing costs, and optimizing the effectiveness and efficiency of health care systems globally [9].

The COVID-19 pandemic has served as a watershed moment in the global health care landscape, profoundly influencing safety culture and catalyzing a renewed emphasis on quality improvement plans [10]. The unprecedented strain on health care systems worldwide has necessitated rapid adaptations in safety protocols, resource allocation, and patient care strategies. The pandemic has exposed vulnerabilities in existing health care infrastructures, compelling institutions to reevaluate and fortify their safety measures [11]. For instance, the critical importance of infection control has been magnified, leading to more stringent guidelines for personal protective equipment use, sanitation, and patient isolation [12]. Moreover, the pandemic has accelerated the adoption of telemedicine, which presents its own set of quality and safety considerations. The COVID-19 pandemic has also underscored the importance of data-driven approaches to safety and quality, as health care providers increasingly rely on real-time analytics to make informed decisions in a rapidly changing environment and use data to monitor improvements [13]. In essence, the COVID-19 pandemic has acted as a catalyst for a paradigm shift in health care safety culture, making the continuous improvement of quality not just an institutional goal but a global imperative.

In this evolving landscape of health care safety and quality improvement, the potential use of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) has gained significant attention [14]. *ICD-10* serves as a standardized coding system for diagnosing a wide array of medical conditions, thereby facilitating precise communication among health care providers and enabling robust data collection for research and policy development [15]. This standardization has further enabled the use of expansive data sets for retrospective analyses, thereby contributing to targeted quality improvement initiatives. For instance, platforms such as TriNetX leverage the *ICD-10* coding system to facilitate data-driven decision-making, offering health care institutions invaluable insights into areas requiring intervention or optimization [16]. Consequently, the *ICD-10* framework stands as a pivotal instrument in elevating the culture of safety and the data needed to guide quality improvement plans, particularly in the intricate health care landscape shaped by the ongoing COVID-19 pandemic.

Within the framework of *ICD-10*, the cluster Y62-Y69, designated for "Misadventures to patients during surgical and medical care," serves as a critical proxy for assessing patient safety and quality of care [17]. This particular cluster comprises an array of diagnostic codes that encapsulate a diverse spectrum of medical misadventures, ranging from lapses in sterile precautions to inaccuracies in dosage administration and contamination of medical or biological substances. Using these nuanced codes enables health care practitioners and academic researchers to undertake focused analyses to augment the

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standard of medical care. Critically, this categorization facilitates pinpointing potential vulnerabilities in existing safety protocols, thus providing empirically based insights that can be harnessed for the advancement of quality improvement strategies to improve safety.

In light of the urgent need to enhance safety and quality in health care, a comprehensive analysis focusing on the *ICD-10* cluster Y62-Y69 could offer invaluable insights. This research protocol articulates a methodical framework for examining longitudinal trends in the incidence rates associated with this specific cluster. Using the TriNetX platform, the study will encompass an 8-year period and use curve-fitting analyses. The choice of an 8-year time frame for this study serves multiple analytical purposes. First, it provides a sufficient number of data points to establish a robust trendline prior to the onset of the COVID-19 pandemic. These baseline data are crucial for understanding the pre-existing patterns and vulnerabilities in health care safety and quality, as captured by the *ICD-10* cluster Y62-Y69. Second, including data during the pandemic allows for an in-depth examination of how the health care systems adapted their safety protocols and quality improvement plans in response to the unprecedented challenges posed by COVID-19. Finally, extending the study into the postpandemic context offers a timely opportunity to assess the current state of health care safety and quality, including any lasting impacts or improvements catalyzed by the pandemic experience. Therefore, the 8-year span is methodologically sound and contextually relevant, enabling a comprehensive analysis that covers prepandemic, pandemic, and postpandemic phases.

This study aims to describe not only the linear trajectories of these rates but also the dynamics of their rate of change over time. This analytical focus has particular relevance in the context of health care systems' responses to the COVID-19 pandemic, a transformative event that has indelibly impacted global health care. The protocol specifies the analytical methodologies to be deployed, identifies the data repositories for consultation, and outlines the statistical models for rigorous data interpretation. Ultimately, this research protocol aims to provide a robust analytical framework capable of generating empirically substantiated findings regarding the past and current state of safety. The findings are designed to inform targeted interventions for the advancement of health care safety and quality.

Methods

Study Design

This study will adopt an observational, retrospective design, adhering to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. This is a big data study, leveraging the extensive and diverse data sets available within the TriNetX platform to provide a comprehensive analysis. The Gantt Chart for research activities presents a 6-month project timeline, where the initial 3 months are allocated to retrieving data. This is followed by a period of analysis spanning 2 months. Concurrently, starting in the third month and continuing through to the sixth month, a total of 3 months is devoted to meta-elaboration and scientific writing.

Setting and Data Source

Data will be extracted from the TriNetX platform, a global health research network that provides real-time access to clinical data. The platform's big data capabilities enable the analysis of large, complex data sets, thereby enhancing the robustness and generalizability of the study findings.

This retrospective analysis will be done using TriNetX, a global health research network providing a deidentified data set of electronic medical records regarding demographics, diagnoses, procedures, medications, laboratory values, genomics, and visits. This network comprises routinely collected, aggregated clinical data from around 130 million patients attending 107 health care institutions in 16 countries, with data spanning from 2008 to 2023.

Data include both inpatient and outpatient care. Clinical information is collected using widespread standard terminologies, such as Systematized Nomenclature of Medicine, Logical Observation Identifiers Names and Codes, and *ICD-10*. TriNetX is certified to the International Organization for Standardization 27001:2013 standard and maintains an Information Security Management System to ensure the protection of the health care data it has access to and to meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Security Rule.

The cohort for the study includes all patients aged 0 to 89 years old who underwent any *ICD-10-Clinical Modification* diagnosis during the period of observation. The *ICD-10-Clinical Modification* cluster Y62-Y69, which represents "Misadventures to patients during surgical and medical care," has been identified as the outcome of the analysis. The analysis of the incidence rate of the outcome in the years between 2016 and 2023 (4 years before and 4 years after the pandemic) will be conducted globally and for specific geographic areas: North America (United States); Latin America; Europe, Middle East, and Africa; and Asia-Pacific. This analysis will use the corresponding collaborative networks within TriNetX. TriNetX offers natural language processing capabilities, which use machine learning technology from Averbis (located in Freiburg in Breisgau, Germany) to search free text from clinical charts and other records specifically for the geographical areas in the United States.

The analysis will be applied to an oncological cohort and one with cardiovascular diseases to validate the results obtained in the initial phase of the research. The oncological cohort was determined using any *ICD-10* codes related to neoplasms (C00-D49). In contrast, the cardiovascular cohort was identified using codes related to Diseases of the Circulatory System (I00-I99).

The findings will be reported according to the STROBE guideline. One of the primary goals of STROBE is to ensure a clear and transparent account of the reporting of methods and results.

Study Period

The analysis will encompass 8 years of data, now divided into 3 distinct phases to align with the key periods of the COVID-19

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pandemic: from 2018 to 2019 (prepandemic phase), from 2020 to May 2023 (intrapandemic phase, aligning with the federal COVID-19 public health emergency declaration period), and from June 2023 to the end of 2023 (early postpandemic phase). This division allows for a precise examination of health care safety and quality trends during the prepandemic phase, the active pandemic phase as defined by the federal public health emergency declaration, and the immediate aftermath of the pandemic. This approach aims to provide a more detailed and contextually relevant understanding of the varying impacts of the COVID-19 pandemic, thus offering a comprehensive view of the health care landscape and its adaptation during these critical periods.

Variables of Interest

This study's primary variables of interest are the incidence rates associated with the *ICD-10* cluster Y62-Y69, a specific set of diagnostic codes designated for capturing "Misadventures to patients during surgical and medical care" [17]. This cluster is of particular importance as it serves as a critical proxy for assessing the safety and quality of health care delivery. It encompasses a wide range of medical misadventures, including but not limited to lapses in sterile precautions, inaccuracies in dosage administration, and contamination of medical or biological substances. Analyzing the incidence rates will enable a comprehensive evaluation of the health care system's performance in minimizing medical misadventures and informing targeted interventions for quality improvement and safety enhancement [18]. The limitations of these data are the self-reporting nature of documenting the "misadventures," with the potential for underreporting.

The incidence rate, which measures the rate of new or first-time cases, is calculated using a time-sensitive approach. The denominator for the incidence rate is the product of the number of patients in the incidence proportion denominator and the number of days covered by the time interval. This ensures that the incidence rate provides a dynamic view of how safety and quality are evolving over time. Importantly, the study also incorporates a "lookback period" to exclude patients who have experienced the event of interest prior to the study period, thereby focusing only on new cases.

Incidence rates are subject to stringent criteria, including demographic matching and time window overlaps, to ensure that the data are accurate and meaningful for targeted interventions. Furthermore, the study acknowledges the potential impact of date shifting by health care organizations to protect patient health information and takes this into consideration in the analysis.

Statistical Analysis

The primary aim of the forthcoming statistical analysis will be to decipher the linear and nonlinear trajectories of incidence rates, with a particular focus on understanding their rate of change over time. Special attention will be dedicated to evaluating the impact of the COVID-19 pandemic on these health care metrics.

The linchpin of the analytical strategy will be the application of curve-fitting analyses [19]. This advanced technique will enable researchers to construct models that elucidate the intricate relationships between the rates and the temporal variables. Specifically, polynomial regression models, including quadratic models, will be used to capture the complexity of the data trends. Quadratic models will be particularly useful for capturing nonlinear trends in the data. These models will be formulated based on the equation $y = ax^2 + bx + c$, where y represents the incidence rate; x represents time; and a, b, and c are coefficients to be estimated. The quadratic term ax^2 will allow us to understand the curvature in the data, providing insights into acceleration or deceleration trends over time. Model diagnostics, such as residual analysis and goodness-of-fit tests, will be conducted to ensure the appropriateness of the quadratic models.

Initially, curve-fitting analyses will be executed on an overall sample characterized by its extensive demographic and clinical diversity. Given the inherent heterogeneity of this sample, a rigorous validation process will be indispensable for confirming the generalizability and applicability of the observed trends.

A series of subgroup analyses will be undertaken to augment the robustness of the findings. These analyses will be stratified by various factors, including but not limited to geographic location. Data for these subgroup analyses will be sourced from the TriNetX network, which amalgamates health care data from a multitude of geographic regions. This approach will facilitate an assessment of the consistency of the observed trends across diverse subpopulations to bolster the external validity of the findings. Further stratification will be conducted based on prevalent epidemiological conditions in the fields of oncology and cardiovascular diseases. Within these conditions, specific groups identified with inclusion and exclusion criteria will be selected as they possess well-documented epidemiological profiles, serving as robust benchmarks for validation. Reperforming the curve-fitting analyses within these disease-specific cohorts will aim to corroborate the trends discerned in the overall sample.

Ethical Considerations

Human Subject Research Ethics Review and Approvals

The study uses data from the TriNetX network, which adheres to international and national data protection and privacy laws, including the HIPAA in the United States and the General Data Protection Regulation in the European Union. These compliance standards ensure that the data are reliably sourced and managed ethically. Each health care organization participating in the TriNetX network is committed to strict ethical standards, including obtaining informed consent for primary data collection with provisions for secondary analysis. Therefore, the study protocol has been approved by the institutional review board of Policlinico San Donato within the Ricerca Corrente funding scheme, affirming adherence to ethical standards and contribution to health care research. No external ethical committee review was deemed necessary due to the aggregated nature of the information, emphasizing the study's compliance with privacy and data protection principles inherent in its observational and secondary data analysis approach.

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Informed Consent for Secondary Analysis

The study involves secondary analysis of anonymized data sets obtained from organizations within the TriNetX network. It is important to note that the original informed consent obtained by these organizations (or their respective institutional review boards) allows for secondary analysis without requiring additional consent. This approach ensures that the use of the data respects and upholds the original consent and ethical approvals.

Privacy and Confidentiality Protection

The data included in the study, derived from the TriNetX platform, are aggregated to ensure that individual patient data are not directly used. This aggregation process, in conjunction with the initial ethical compliance by each participating health care organization, guarantees the protection of privacy and confidentiality. The data used in the research are anonymous and deidentified, following strict data protection principles.

Compensation

Compensation is not applicable in the study as it revolves around the secondary analysis of existing anonymized data sets. There is no direct participant interaction, so compensation for participants is not applicable.

Image and Supplementary Material Identification

No individual participants or user identification is possible in any images included in the manuscript or supplementary materials. The study design protects the privacy and anonymity of all individuals involved.

Anticipated Findings

The anticipated results of this comprehensive analysis focusing on the *ICD-10* cluster Y62-Y69 are expected to provide valuable insights into the safety and quality of health care delivery over the study period, spanning prepandemic, intrapandemic, and early postpandemic phases.

Regarding the incidence rates associated with the *ICD-10* cluster Y62-Y69, we anticipate that our analysis will reveal trends and patterns that can be attributed to various factors, including changes in safety protocols, resource allocation, and health care practices during the COVID-19 pandemic. Given the unprecedented challenges and adaptations required by health care systems worldwide, it is reasonable to expect that the pandemic may have had a significant impact on these rates.

In the prepandemic phase, our analysis aims to establish a baseline for the incidence rates, offering insights into the existing vulnerabilities in health care safety and quality captured by the *ICD-10* cluster. This baseline data will be crucial for understanding the context in which subsequent changes occurred.

During the intrapandemic phase, we anticipate observing fluctuations and shifts in the incidence rates. These changes may be indicative of the health care system's responses to the challenges posed by the pandemic, including heightened infection control measures, changes in patient care protocols, and resource allocation adjustments. The pandemic's impact on safety and quality may be reflected in the data.

In the early postpandemic phase, we expect to see how health care systems have adapted and evolved in response to the pandemic's challenges. It is possible that some changes implemented during the pandemic may persist or lead to improvements in safety and quality.

Furthermore, our analysis will include stratified subgroup analyses, which may reveal variations in trends across different geographic regions and within specific disease cohorts (oncology and cardiovascular diseases). These subgroup analyses will help identify whether the observed trends are consistent across diverse populations and clinical contexts. This study aims to provide a nuanced understanding of how the COVID-19 pandemic has influenced safety and quality in health care, as reflected in the incidence rates of the *ICD-10* cluster Y62-Y69. These findings will inform targeted interventions and quality improvement strategies, contributing to the ongoing efforts to enhance health care safety and quality in a rapidly evolving health care landscape.

Results

Our research, supported by the Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato (funds secured in November 2023), is currently advancing through the data collection stage. The compilation of data, facilitated by the global health research network TriNetX, is set to encapsulate a comprehensive 8-year timeframe extending from January 2015 to December 2023. This carefully curated dataset documents the healthcare landscape across three critical phases: before the COVID-19 pandemic (pre-pandemic), during the height of the pandemic (intra-pandemic), and the period following the emergency phase of the pandemic (early post-pandemic). Such temporal delineation is pivotal for our investigation into the trends and fluctuations in medical misadventures classified under the ICD-10 cluster Y62-Y69, offering a lens through which to view the nuances of healthcare safety and quality across different global healthcare contexts.

With data collection anticipated to be completed by May 2024, and final analysis expected by June 2024, our study is on track to fulfill its objective of dissecting the intricate patterns of medical misadventures during a period marked by unprecedented global health challenges. The results are anticipated to equip healthcare professionals, policymakers, and stakeholders with the insights necessary to fortify healthcare systems against future adversities, thereby enhancing the overall safety and quality of care delivered to patients worldwide

Discussion

Principal Findings

The primary expectation of this study is to elucidate the linear and nonlinear trajectories of incidence rates associated with the *ICD-10* cluster Y62-Y69 over time. Through the application of curve-fitting analyses, specifically quadratic models, we anticipate revealing intricate patterns in the data that may not be discernible through simpler linear models.

In the context of the COVID-19 pandemic, we expect to observe significant fluctuations in these rates, potentially manifesting

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as spikes or declines corresponding to various phases of the pandemic. These observations will be critical for understanding the pandemic's impact on health care safety and quality, particularly in medical misadventures. Furthermore, examining the postpandemic response to these rates will be of particular interest. These results will provide insights into the resilience and adaptability of health care systems in returning to prepandemic safety and quality levels or possibly achieving even better standards.

Upon conducting subgroup analyses, we expect that the trends observed in the overall sample will be validated in specific subpopulations. These subpopulations will be stratified by geographic location and specific epidemiological conditions within oncology and cardiovascular diseases. The validation of trends across these diverse subpopulations will lend greater credibility and generalizability to our findings.

Moreover, we anticipate that our stringent data selection criteria for validating the overall models will yield accurate and meaningful results. These results are expected to inform targeted interventions to improve the safety and quality of health care delivery, fulfilling the study's ultimate objective.

However, it is essential to acknowledge the limitations that may arise from the study. These could include potential biases in the original data documentation and collection and the challenges associated with interpreting complex statistical models. One specific limitation is the retrospective nature of the study, which may introduce recall bias and limit the ability to establish causal relationships. Retrospective studies often rely on existing records and data, which may not have been collected for research purposes, affecting the data's quality and completeness. In addition, despite the application of data selection criteria, the possibility of unmeasured or residual confounding factors cannot be entirely excluded. These factors might influence the observed associations and outcomes. This limitation is characteristic of retrospective studies and should be considered when interpreting our findings. Furthermore, we acknowledge the challenges associated with analyzing data from broad and heterogeneous geographic areas such as Europe, the Middle East, Africa, and Asia-Pacific. The diversity in health care systems, practices, and patient populations across these regions may limit the uniformity and specific applicability of our findings. This variation is important when interpreting our results and their implications in these diverse settings. We recognize this as a limitation of our study and suggest caution in generalizing the findings uniformly across these broad geographic areas.

Despite these limitations, the strength of this study lies in its use of global real-world big data. The TriNetX network provides a rich data set that captures a broad range of demographic and clinical variables, enhancing the study's generalizability and applicability. The use of real-world data allows for a contemporary understanding of medical misadventures, as it reflects on the complexities and variabilities inherent in everyday health care settings. This aspect is a significant advantage over controlled clinical trials, which often operate under idealized conditions that may not be representative of the real world.

Future research will focus on addressing these limitations and possibly using other advanced statistical techniques for a more in-depth analysis. For instance, machine learning algorithms could be used to identify hidden patterns and relationships in the data, providing a more comprehensive understanding of the factors influencing medical misadventures. In line with our future research directions, we aim to delve deeper into specific indicators like complications, side effects, mortality, and morbidity in subsequent studies. These indicators, when analyzed in homogeneous subgroups of patients with and without the presence of the *ICD-10* cluster Y62-Y69, could provide critical insights into the impact of medical misadventures on patient outcomes. This focus will augment our current understanding of relevant safety-related patterns and guide targeted interventions to mitigate such occurrences in health care settings.

Conclusions

The upcoming study is poised to offer a multifaceted exploration of the incidence rates associated with medical misadventures, as defined by the *ICD-10* cluster Y62-Y69. The research is designed to use advanced statistical models, such as quadratic equations, to capture both linear and nonlinear trends over time. This approach will be particularly illuminating in the context of the pre–, intra–, and post–COVID-19 pandemic analyses, a period in history that has introduced unique challenges and disruptions to health care systems globally. Global real-world data stand as a significant strength, offering a more pragmatic view of health care safety and quality that can typically be achieved through controlled clinical trials or other primary studies. The study's findings are anticipated to be of considerable value to health care professionals, policy makers, and researchers alike. The results will not only shed light on the current state of medical misadventures but also provide actionable insights for targeted interventions aimed at improving health care safety and quality.

Acknowledgments

This study was partially supported by Ricerca Corrente funding from the Italian Ministry of Health to Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

RC, MDM, EDS, SB, EG, and MD participated in the conceptualization and methodology of the protocol. RC, MD, and MDM drafted the manuscript, and all authors revised and approved the final version. LM and MAD are the colast authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the independent reviewers of the “Ricerca Corrente” fund of IRCCS Policlinico San Donato (Italy) and previous version of the protocol.
[PDF File (Adobe PDF File), 1367 KB - resprot_v13i1e54838_app1.pdf]

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Abbreviations

ICD-10: International Classification of Diseases, Tenth Revision
HIPAA: Health Insurance Portability and Accountability Act
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Effectiveness and Cost-Effectiveness of Survivorship Care for Survivors of Hodgkin Lymphoma (INSIGHT Study): Protocol for a Multicenter Retrospective Cohort Study With a Quasi-Experimental Design

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Abstract

Background: Hodgkin lymphoma (HL) occurs at young ages, with the highest incidence between 20 and 40 years. While cure rates have improved to 80%-90% over the past decades, survivors of HL are at substantial risk of late treatment–related complications, such as cardiovascular diseases, breast cancer, severe infections, and hypothyroidism. To reduce morbidity and mortality from late treatment effects, the Dutch Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations (BETER) consortium developed a survivorship care program for 5-year survivors of HL that includes risk-based screening for and treatment of (risk factors for) late adverse events. Even though several cancer survivorship care programs have been established worldwide, there is a lack of knowledge about their effectiveness in clinical practice.

Objective: The Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment (INSIGHT) study evaluates whether Dutch BETER survivorship care for survivors of HL decreases survivors' burden of disease from late adverse events after HL treatment and associated health care costs and improves their quality of life.

Methods: The INSIGHT study is a multicenter retrospective cohort study with a quasi-experimental design and prospective follow-up, embedded in the national BETER survivorship care infrastructure. The first BETER clinics started in 2013-2016 and several other centers started or will start BETER clinics in 2019-2024. This allows us to compare survivors who did and those who did not receive BETER survivorship care in the last decade. Survivors in the intervention group are matched to controls (n=450 per group) based on sex, age at diagnosis (±5 years), age in 2013 (±5 years), and treatment characteristics. The primary outcome is the burden of disease in disability-adjusted life years from cardiovascular disease, breast cancer, severe infections, and hypothyroidism. In a cost-effectiveness analysis, we will assess the cost of BETER survivorship care per averted or gained disability-adjusted life year and quality-adjusted life year. Secondary outcomes are BETER clinic attendance, adherence to screening guidelines, and knowledge and distress about late effects among survivors of HL. Study data are collected from a survivor survey, a general practitioner survey, medical records, and through linkages with national disease registries.

Results: The study was funded in November 2020 and approved by the institutional review board of the Netherlands Cancer Institute in July 2021. We expect to finalize recruitment by October 2024, data collection by early 2025, and data analysis by May 2025.

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Conclusions: INSIGHT is the first evaluation of a comprehensive survivorship program using real-world data; it will result in new information on the (cost-)effectiveness of survivorship care in survivors of HL in clinical practice. The results of this study will be used to improve the BETER program where necessary and contribute to more effective evidence-based long-term survivorship care for lymphoma survivors.

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KEYWORDS

research design; Hodgkin lymphoma; late effects of cancer treatment; survivorship care; screening; cost-effectiveness analysis

Introduction

Cardiovascular diseases (CVDs) and second malignancies, especially breast cancer, are well-known late complications of Hodgkin lymphoma (HL) treatment. The risks of CVD and breast cancer are highest in survivors of HL treated with chest radiotherapy with or without anthracycline-based chemotherapy [1-8]. In addition, survivors of HL may also face other late treatment effects such as severe infections, associated with (functional) asplenia [3,9], and hypothyroidism after neck radiotherapy [10,11]. Although improved chemotherapy and radiotherapy regimens have increased HL cure rates to 80%-90% over the past decades, the aforementioned treatment-related complications have led to excess morbidity and mortality in survivors of HL [3,4,12-14].

CVD risk is 4-6 times higher in survivors of HL treated in 1965-1995 than in the general population, with up to 50% cumulative CVD incidence 40 years after HL treatment [7]. Female survivors of HL who received chest radiotherapy in the aforementioned period have a 5 times higher breast cancer risk than women in the general population, with a 19% cumulative incidence 30 years after treatment [2]. In addition, infectious disease mortality in survivors of HL treated in 1965-2000 increased 8-fold compared to the general population [3]. Moreover, 25 years after HL treatment, the cumulative incidence of (subclinical) hypothyroidism was 44% in survivors treated between 1961 and 1989 [9]. Individual late treatment–related complication risks depend on the characteristics of patients and HL treatment (radiotherapy location, dose and volume, chemotherapy type and dose, and whether or not splenectomy was performed) and are expected to be lower in more recent treatment years as a result of improved radiotherapy techniques [2,3,5,7,9].

In 2009, the Dutch “Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations” (BETER) consortium, a collaboration between hemato-oncologists, radiation oncologists, nurse practitioners, epidemiologists, a general practitioner (GP), and patient representatives, was established. While HL generally occurs at a young age (with the highest incidence between 20 and 40 years) and survivors have a long life expectancy where they can develop late effects, structured survivorship care for adult survivors of HL was lacking. Structured survivorship care may lead to the early detection of (risk factors for) late adverse events, enabling timely intervention, possibly leading to a lower burden of disease due to late effects and better quality of life in survivors of HL [15,16]. Therefore, the BETER consortium developed a nationwide infrastructure of outpatient clinics where 5-year survivors of HL are screened for late adverse effects of lymphoma treatment according to nationally approved screening guidelines. Recommendations in the guidelines were based on the available scientific evidence in survivors of HL, and, if this evidence was absent, in other high-risk populations (eg, *BRCA* mutation carriers for breast cancer screening recommendations) or on expert consensus [17,18].

In 2013-2016, the first BETER clinics started inviting 5-year survivors of HL for risk-based screening for late treatment–related complications. Of note, setting up a BETER clinic requires a substantial effort, that is, identification and tracing of patients and setting up local infrastructure, including consulting specialists such as cardiologists [17]. Therefore, several Dutch lymphoma treatment centers were only able to start or will start inviting survivors of HL for survivorship care in 2019-2024.

Other cancer survivorship care programs, especially for survivors of childhood cancer (often also including survivors of childhood HL), have been established in several countries worldwide. However, there is a lack of knowledge about their effectiveness in clinical practice. Studies that evaluated the yield of late events in these programs, almost exclusively concerned with CVD and breast cancer screening results, lacked a comparison group or used hypothetical cohorts or simulation models to estimate the potential health benefits from structured survivorship care [19-25]. The effect of the implementation of cancer survivorship programs on survivors’ burden of disease, quality of life, and cost-effectiveness has never been assessed using real-world data. Therefore, in the Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment (INSIGHT) study, we aim to assess whether BETER survivorship care leads to reduced burden of disease from late adverse events after HL treatment, lower health care costs, better quality of life, and reduced health-related productivity losses compared to the absence of structured survivorship care.

Methods

Design

The INSIGHT study is a retrospective cohort study with a quasi-experimental design and prospective follow-up, embedded in the national BETER survivorship care infrastructure. The first BETER clinics started in 2013-2016 and the number of centers participating in the BETER program increased over the last few years; several centers started or will start a BETER

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clinic in 2019-2024. This provides the unique opportunity to evaluate the effectiveness of BETER survivorship care by comparing survivors who did and did not receive BETER survivorship care over the past 6-10 years (expected median follow-up of ~8 years). The intervention group will consist of 450 survivors of HL who were invited to first visit a BETER clinic in 2013-2016. The control group will consist of a matched group of 450 survivors of HL who were eligible for BETER survivorship care as of 2013-2016 but were not invited because they were treated in a lymphoma treatment center not starting a BETER clinic until 2019-2024 (Figure 1).

Figure 1. Schematic overview of the INSIGHT cohort study follow-up period among 5-year survivors of Hodgkin lymphoma in the Netherlands. BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations.

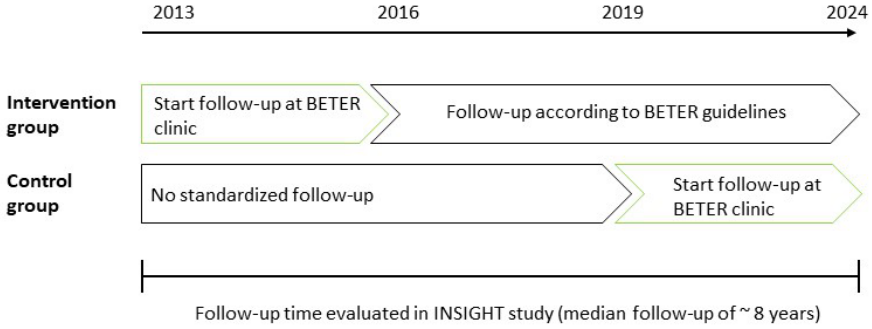

Study Population

According to the BETER guidelines, survivors of HL are eligible for survivorship care after completion of regular surveillance for HL recurrence (5 years after treatment), if they were 15-60 years at HL diagnosis, and are currently younger than 70 years of age. Figure 2 [17,18,26] shows a simplified overview of BETER eligibility criteria and the screening guidelines [17,18]. Survivors who do not have sufficient understanding of the Dutch language to complete the study survey, have developed an HL relapse during follow-up, whose vital status (and if alive current address) could not be verified, or who live abroad are excluded from the INSIGHT study.

Figure 2. Simplified overview of BETER screening guidelines for 5-year survivors of Hodgkin lymphoma in the Netherlands [17, 18] and guideline asplenia from the National Institute for Public Health and the Environment (RIVM) [26]. CT: chemotherapy; ECG: electrocardiogram; FT4: free thyroxine; MRI: magnetic resonance imaging; (NTpro-)BNP: (N-terminal pro–)B-type natriuretic peptide; RIVM: National Institute for Public Health and the Environment, RT: radiotherapy; TSH: thyroid stimulating hormone.

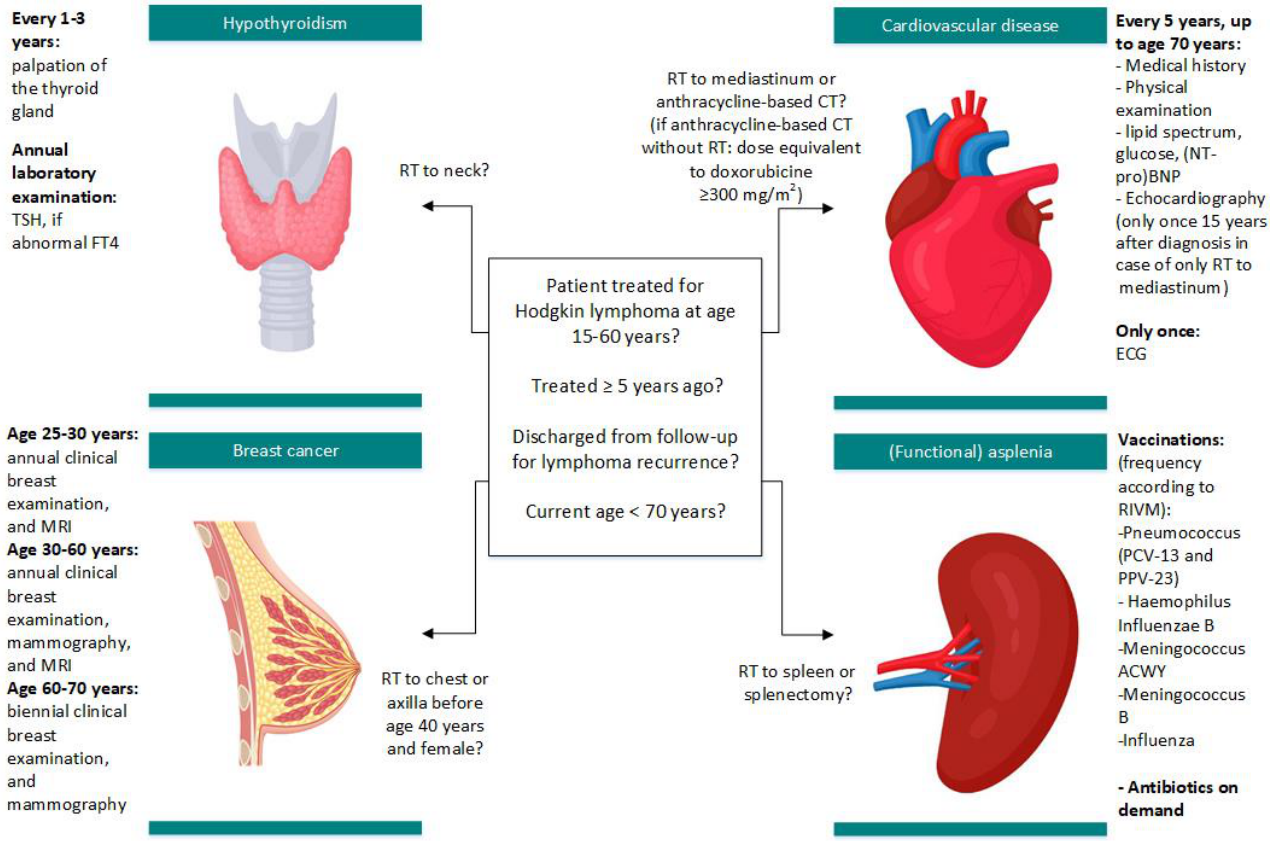

The study participants in the control group are matched to patients in the intervention group based on the following survivor characteristics: sex, age at diagnosis (±5 years), and age in 2013 (±5 years) and the following treatment

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characteristics associated with increased risk of CVD, breast cancer, hypothyroidism, and (functional) asplenia: chest radiotherapy (yes or no), neck radiotherapy (yes or no), spleen radiotherapy or splenectomy (yes or no), and anthracycline-based chemotherapy (yes or no). Controls are selected from the comprehensive database of the previously established retrospective cohort of lymphoma survivors treated in participating BETER centers between 1965 and 2012. This database contains information on basic survivor characteristics and detailed treatment data [17].

Outcomes

The primary outcomes of this study are the burden of disease (in disability-adjusted life years [DALYs]) from CVD including associated risk factors (Table S1 in Multimedia Appendix 1 [17,27-30]), breast cancer, severe infections (defined as fatal or requiring hospitalization) and hypothyroidism, the associated health care costs, and quality of life. In a cost-effectiveness analysis, the cost of BETER survivorship care will be weighed against averted or gained DALYs and quality-adjusted life years (QALYs). In order to assess indirect costs in both groups, health-related productivity losses and overall health care use will be calculated. Furthermore, the incidence rates (including stage and time since HL diagnosis) for the (risk factors for) late adverse events of interest (screen detected or nonscreen detected) will be compared between the intervention and control group.

The secondary outcomes of this study are BETER clinic nonattendance, guideline adherence, and knowledge and distress about late effects among survivors. Both the intervention and control group include survivors who attended the BETER clinic (attenders) and survivors who were invited for BETER survivorship care but chose to not attend (nonattenders). We will describe the reasons for nonattendance to BETER survivorship care and assess possible associations of nonattendance with socioeconomic status, health status, and other patient characteristics. This subanalysis will allow us to place our main study findings in perspective and possibly even improve future attendance rates. Survivors' socioeconomic status will be derived from their zip code based on data from Statistics Netherlands [31]. We assess the BETER clinicians' adherence to the guidelines by comparing the screening diagnostics that were performed in clinical practice to those that are recommended in the BETER guidelines. Finally, we will assess survivors' knowledge about the risk of late complications (risk perception) in both groups and investigate whether this knowledge comes with increased or decreased distress about their risk of late complications.

Follow-Up

For the intervention group, follow-up starts at the first BETER visit (or BETER clinic invitation date for nonattenders) and ends at the study inclusion of its matched control in 2019-2024 or at date of death, whichever comes first. For the control group, follow-up starts at the date their matched intervention group survivor started follow-up and ends at their first BETER visit (or BETER clinic invitation date for nonattenders), or, if earlier, at death. All study data will be stored for at least 20 years. This enables prospective follow-up of our cohort in order to study the long-term effects of screening on the incidence of late adverse events and the associated burden of disease.

Recruitment and Informed Consent Procedure

For the detailed recruitment and informed consent procedure, refer to the detailed informed consent procedure section in Multimedia Appendix 1. In brief, in intervention centers, study patients are identified and linked to the national Personal Records Database to verify survivors' vital status and current address. Subsequently, eligible survivors are invited for study participation by their (former) treating radiation oncologist or hematologist. In control centers, survivors who match an intervention group survivor are selected from the previously established cohort of survivors of HL from that specific center (Design section) [17]. Matched controls who are alive and do not experience adverse health outcomes in an advanced stage (eg, metastatic breast cancer or end-stage heart failure) are invited to the BETER clinic. After the invitation for BETER survivorship care, these controls are invited for study participation using the same procedures as for the intervention group. Survivors who do not respond to the study invitation will receive reminders; nonattenders receive 1 reminder approximately 4 weeks after the initial invitation and attenders receive 2 reminders after approximately 4 and 8 weeks, respectively. Survivors who died during follow-up are included without informed consent.

Data Collection

Basic survivor characteristics and detailed treatment information for the included survivors are extracted from the comprehensive database of lymphoma survivors treated in participating BETER centers between 1965 and 2012 [17]. For the INSIGHT study, we collect additional data from multiple sources: medical records, a survivor survey, a GP survey, and national registries. We provide explanations on each of the data collection procedures in the upcoming sections Medical Records, Survivor Survey, GP Survey, and Linkage With National Registries and in Figure 3.

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Figure 3. Data collection procedures for the INSIGHT cohort study at individual BETER survivorship care clinics for 5-year survivors of Hodgkin lymphoma in the Netherlands and planned linkages with national disease registries. BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations; NKI-AVL: The Netherlands Cancer Institute.

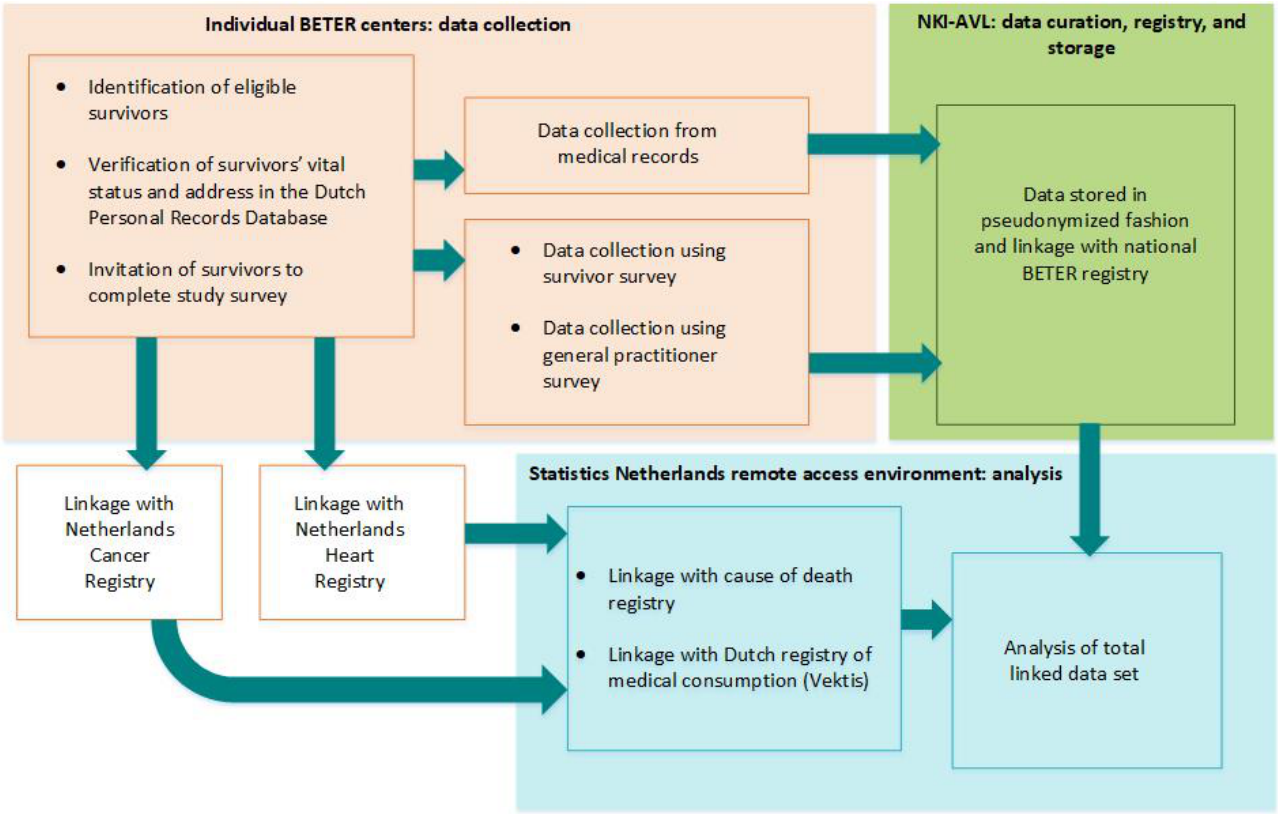

Medical Records

For attenders of the BETER clinics in the intervention group, complete follow-up data from the BETER clinic (ie, performed screening tests, results, diagnoses, and subsequent treatments) are collected from the medical records. For attenders in the control group, the date of the first BETER visit and the date of the last regular radiation oncology or hemato-oncology outpatient clinic visit are collected.

Survivor Survey

For attenders of the BETER clinics, the survivor survey includes, among others, the following standardized questionnaires: the EQ-5D-5L questionnaire yields utilities used to calculate QALYs, the 36-Item Short Form Health Survey is used to cross-sectionally assess the quality of life, and the Institute for Medical Technology Assessment Productivity Cost questionnaire is used to assess health-related productivity losses [32-34]. Textbox 1 shows an overview of the total study survey components for attenders of BETER care. The expected survey completion time for attenders of BETER care is 20-55 minutes depending on medical history. Nonattenders of the BETER clinics are asked to complete a survey that contains the following components: (1) a questionnaire assessing reasons to not attend a BETER clinic and possible screening or treatment for late effects elsewhere, (2) a short questionnaire on their current health status and lifestyle, and (3) the 6-item adapted version of the Cancer Worry Scale to determine distress associated with the increased risk of late effects [35]. The expected survey completion time for nonattenders is 10-25 minutes. Attenders in the intervention and control group receive the same survey; the same applies to the nonattenders in the intervention and control group.

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Textbox 1. Overview of Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment cohort study survey components for 5-year survivors of Hodgkin lymphoma who attended survivorship care at different Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations (BETER) centers in the Netherlands. The survey is completed by study participants at enrollment in the period 2021-2024.

- EQ-5D-5L questionnaire (a standardized questionnaire that yields utilities used for calculating quality-adjusted life years)
- 36-Item Short Form Health Survey (standardized quality of life questionnaire)
- Institute for Medical Technology Assessment Productivity Cost Questionnaire (standardized health-related productivity losses questionnaire)
- Medical consumption (including general practitioner care, hospital care, physiotherapist, psychologist, and psychiatrist consultations)
- Knowledge about late adverse effects
- Satisfaction with BETER care and perception of benefit and burdensomeness of BETER care
- 6-item adapted Dutch version of the Cancer Worry Scale to determine distress about late adverse effects
- Current health status (diagnoses of possible late effects, medication use, and lifestyle). These questions are only included when the last BETER clinic visit was > 6 months ago

GP Survey

Each survivor's GP is approached by the survivor's former treating radiation oncologist or hematologist with a request to provide information for the INSIGHT study. Each GP receives a short paper survey enquiring about the survivor's medical history of (risk factors for) CVD, severe infections, vaccination status, hypothyroidism, and, if applicable, cause of death. The GP receives 2 reminders in case of nonresponse.

Linkage With National Registries

For all survivors included in the study (intervention and control group), we will obtain information on the incidence of clinical events of interest through linkage with disease registries. Information on breast cancer diagnoses will be obtained from Netherlands Cancer Registry, information on cardiac interventions and disease episodes will be obtained from the Netherlands Heart Registry, information on hospital admissions for CVD and serious infections and total medical consumption will be obtained from the Dutch health care costs registration (Vektis), and for those who died during follow-up cause of death will be obtained from Statistics Netherlands [36-39]. Furthermore, linkage with the national BETER registry data, containing BETER questionnaire data, will be performed. The BETER questionnaire is completed by survivors before their first BETER visit and contains extensive questions about current health, medical history, and lifestyle, which helps health care providers focus on actual symptoms of late adverse effects and lifestyle during the consultation [17]. The questionnaire answers are registered in the national BETER registry for research into late effects of lymphoma treatment upon survivor's written informed consent [17]. Due to the privacy regulations of Statistics Netherlands, the final linked data set can only be accessed and analyzed in the protected remote environment of Statistics Netherlands.

Ethical Considerations

The study protocol was approved by the institutional review board of the Netherlands Cancer Institute (IRB21-115), and we complied with local ethical approval guidelines at all participating sites. Survivors who opted out of the use of their medical data for the INSIGHT study, or medical research in general, are excluded from the study (refer to the detailed informed consent procedure section in Multimedia Appendix 1). Participating survivors did not receive financial compensation. Patient-identifying information is pseudonymized at the participating sites before storage at the Netherlands Cancer Institute and before data analysis in the Statistics Netherlands remote access environment.

Statistical Analysis

Burden of Disease and Secondary Outcomes

DALYs for the conditions of interest are calculated as the sum of the "years of life lost" (YLL) due to premature mortality and the "years lost due to disability" (YLD) for people living with the condition: DALY=YLL+YLD. The YLL is calculated by the number of deaths multiplied by the standard life expectancy at the age at which death occurs. Standard life expectancy in the Netherlands is available from Statistic Netherlands [40]. To estimate YLD during the follow-up period, the number of cases in that period will be multiplied by the average duration of the disease and a weight factor (disability weight) that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead). Disability weights are extracted from the Global Burden of Disease Study 2019 or the most recent Global or preferably Dutch disability weight studies [41].

For continuous outcomes (eg, DALYs and health-related quality of life), multiple linear regression analysis will be used to study differences between the intervention and the control group. Important confounders will be controlled for by matching survivors in the intervention group to survivors in the control group based on patient and treatment characteristics, see Study population section. The influence of other potential confounders (eg, BETER hospital or socioeconomic status) on the regression coefficients will be examined, and these will be included in the model when associated with a ≥10% change in the regression coefficient.

For count data (eg, the incidence of late adverse events), negative binomial regression analysis or Poisson regression analysis (depending on the distribution of the data) will be used. To analyze the time between HL diagnosis and diagnosis of late adverse events, competing risk regression methods will be used, with death treated as a competing risk.

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Missing data will be handled by multiple imputation when data are missing (completely) at random. Data analysis will be performed in R and RStudio software (The R Foundation).

Sample Size Calculation

The complete sample size calculation including detailed substantiation can be found in the Detailed sample size calculation section in Multimedia Appendix 1. In brief, in an intention-to-treat analysis, taking a BETER clinic attendance rate of 65% into account (A Nijdam, unpublished data, 2016), the expected difference between the intervention and the control group is 0.40 acquired DALY over a follow-up period of 5 years (our expected median follow-up is longer). With a 2-sided significance level of .05 and 80% power to detect a difference of 0.20 SD (small effect size) and larger, we need 393 patients in each study arm. When we take a 15% loss to follow-up and incomplete data into account, we need 452 patients in each study arm.

Cost-Effectiveness Analysis

To compare direct and indirect health care costs between the intervention and the control group, the Dutch health care costs registration (Vektis) and the handbook of costing studies from the Dutch National Health Care Institute (ZorgInstituut) will be used [39,42]. The effects of BETER survivorship care in comparison to the absence of standardized follow-up will be expressed in costs/DALY and costs/QALY. QALYs are derived by health state utilities. A utility is a standardized score between 0 and 1, with 0 reflecting death and 1 perfect health, measured by the EQ-5D-5L questionnaire [33]. The cost-effectiveness analysis will be performed using a discrete event simulation, where we will incorporate several screening strategies. A discrete event simulation analysis on the patient level will be used to simulate the sequences of events that occur as a continuous process over time and to calculate the mean associated costs and QALYs [43]. Uncertainty around the results will be quantified using nonparametric bootstrapping and cost-effectiveness acceptability curves. These curves will show whether BETER survivorship care is cost-effective or not for various values of the Dutch society's willingness to pay for 1 QALY. A budget impact analysis will be performed to estimate the 5-year financial consequences of the implementation of BETER survivorship care in the Dutch health care system. The following factors will be accounted for in the budget impact analysis: screening costs, the potential number of survivors of HL eligible for screening, and the costs of treatment of late adverse events.

Results

The study was funded in November 2020 and approved by the institutional review board of the Netherlands Cancer Institute in July 2021. The first survivor was included in November 2021, and by November 2023, a total of 445 survivors were included in the study intervention group, and 34 survivors were included in the control group. We expect to finalize recruitment by October 2024, data collection by early 2025, and data analysis by May 2025.

Discussion

Principal Findings

BETER is an internationally unique comprehensive infrastructure for adult oncology survivorship care. The INSIGHT study evaluates the effect of the implementation of BETER survivorship care for survivors of HL on survivors' burden of disease from late adverse events, associated health care costs, and quality of life. It will result in important new information on the (cost-)effectiveness of survivorship care in survivors of HL in clinical practice. With our study results, we will be able to evaluate current BETER screening guidelines and adapt them accordingly, if indicated [17,18]. These study results can therefore be used to improve the BETER survivorship care infrastructure and contribute to more effective evidence-based long-term survivorship care for survivors of HL. Moreover, some results could possibly be extrapolated to other cancer survivors (eg, survivors of breast cancer treated with anthracyclines). Importantly, the knowledge gained in this study can be used to better inform survivors of HL about the possible benefits of screening.

If our study demonstrates the cost-effectiveness of BETER survivorship care, we expect that more hospitals in the Netherlands will be motivated to reallocate resources to overcome the organizational hurdles to implement survivorship care according to the BETER guidelines, thus improving implementation of BETER care.

Taking into account the increasing number of cancer diagnoses, improving survival rates, and increasing health care costs, it is essential to ensure that BETER survivorship care is feasible and cost-effective in the long term. If we are able to identify diagnostic tests that have little added value in terms of diagnostic yield and clinical benefit, we will look into leaving them out in future BETER guidelines. Our results may demonstrate that additional diagnostics not recommended in the guidelines, which do not contribute to the cost-effectiveness of BETER survivorship care, are routinely performed. Also, we may observe that survivors are recalled for surveillance more frequently than advised in the guidelines. We can then provide this feedback to the centers in question, as it is not only important to reduce costs but also to make sure we do not overmedicalize survivors of HL.

Strengths and Limitations

An important strength of this study is the quasi-experimental design, which takes advantage of the situation in which BETER care has been gradually implemented in different lymphoma treatment centers in the Netherlands over the past decade. This provides the unique opportunity to study the added value of BETER survivorship care by comparing survivors who did receive such care over the past 6-10 years with a matched comparison group that did not, thereby minimizing the risk of bias in our observational study. A second strength of this study is the comprehensive data collection on the incidence rates of late adverse events from multiple sources: survivors, survivors' medical records, survivors' GPs (and if necessary medical specialists), and national disease registries. This allows us to verify our data, in order to overcome uncertainties and selection

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bias related to patient-reported outcomes and potential missing data, for example, due to failed linkages. Third, very importantly, this study design provided us with a representative study population. As we have identified the entire cohort of 5-year survivors who were treated for HL in the centers participating in BETER, we can also include survivors who died during follow-up [17]. Moreover, we also include the data of survivors who did not respond to the invitation to visit the BETER clinic and those who did not respond to our INSIGHT study invitations. The only survivors not included in our study are those who explicitly objected to the use of their data for the INSIGHT study or medical research in general (expected 2%-7%). Including nonattenders of BETER care in this study enables us to accurately assess the total number of survivors eligible for BETER care and perform the cost-effectiveness analysis from a societal perspective of the Netherlands.

The first limitation of our analysis of patient-reported outcomes such as quality of life and risk perceptions is that our results can be affected by selection bias, as we expect 60%-70% of survivors to complete our study survey. A second limitation may be that our sample size calculation is based on a cumulative difference in the burden of disease of CVD, breast cancer, severe infections, and hypothyroidism. Therefore, we may have limited power to perform subanalyses of parts of the disease-specific screening guidelines separately. A third limitation is that we could only follow survivors treated for HL from 1971 to 2011 who were screened for late adverse events from 2013 onward. As late adverse events of interest may have already developed before the start of the BETER screening program in a substantial proportion of the included survivors, we may underestimate the yield and potential benefit of screening. Finally, the expected study follow-up of approximately 8 years may not be sufficient to accumulate enough events of interest to be able to detect a significant difference in the burden of disease between the groups. Therefore, we plan to prospectively follow our cohort and repeat linkages with disease registries after 5-10 years.

Comparison With Prior Work

The INSIGHT study is not only the first evaluation of survivorship care provided at BETER clinics but also the first cost-effectiveness study of structured cancer survivorship care worldwide that uses real-world data and focuses on multiple types of screening. Previous studies performed on survivors of HL and childhood cancer reported on the screening yield of 1 type of screening, lacked a valid comparison group, or used simulations models or hypothetical cohorts to study its cost-effectiveness [19-25,44].

For example, the study by Chow et al [23] reported on underdiagnosis and undertreatment of hypertension, hypercholesterolemia, and diabetes in adult survivors of childhood cancer at high risk of premature CVD in the United States Childhood Cancer Survivor Study cohort and compared the prevalence rates to the general population [23]. Furthermore, in the St. Jude Lifetime Cohort study of childhood cancer survivors, Armstrong et al [24] and Palmer et al [25] evaluated echocardiographic detection rates of impaired left ventricular ejection fraction and diastolic dysfunction, respectively [24,25]. Howell et al [44] described breast cancer cases detected in the United Kingdom national GP mammography screening program for survivors of HL and compared the findings (eg, stage) to breast cancer cases diagnosed in the general population. Although these studies provide valuable information, the results do not demonstrate the incremental value of screening due to the lack of a valid comparison group.

Chen et al [21] evaluated lipid screening and statin therapy in a hypothetical cohort of 30-year-old 5-year survivors of HL treated with chest irradiation. The authors compared no screening with screening at 1-, 3-, 5-, or 7-year intervals and used Markov models to calculate life expectancy, quality-adjusted life expectancy, and lifetime cost. Wong et al [20] simulated life histories using Markov health states to assess the effect of the implementation of echocardiographic screening followed by angiotensin-converting enzyme inhibitor and β-blocker therapy in survivors of childhood cancer on cost-effectiveness, life expectancy, QALYs, and the cumulative incidence of heart failure 30 years after a cancer diagnosis. An important limitation of the above-mentioned studies is that the actual efficacy of statins, angiotensin-converting enzyme inhibitors, and β-blockers in survivors of HL and childhood cancer is unknown and therefore had to be estimated based on assumptions. Furzer et al [22] used simulation models to evaluate the cost utility of 8 different breast cancer screening strategies for survivors of HL treated with chest radiotherapy, with annual magnetic resonance imaging and mammography from age 25 years onward as a reference (no comparison to population screening only). A limitation of this study is that model assumptions about the efficacy of breast cancer screening at young ages were mostly based on *BRCA1/2* mutation carriers, who are known to have different breast cancer tumor characteristics than other women [45].

The German Hodgkin lymphoma study group described the yield of hypothyroidism with thyroid-stimulating hormone screening in survivors of HL (median time since treatment 6 years, median follow-up of 70 months, IQR 12-243 months) [11]. Our study will examine the efficacy of thyroid-stimulating hormone screening after longer time intervals since HL treatment and will also provide longer follow-up after the start of screening. To our knowledge, no studies describing health gains from vaccinations or prescription of on-demand antibiotics in (functional) asplenic survivors of HL have been published. The current BETER afunctional spleen guideline is based on knowledge about patients who had a splenectomy for other indications and on the known increased mortality from infectious disease after spleen irradiation in survivors of HL [3,9,17,18,26]. This study will provide the opportunity to compare incidences of severe infections among survivors of HL who did and did not receive the recommended vaccinations and antibiotics.

Little is known about the effect of survivorship care on survivors' knowledge about late adverse effects and possible distress about these risks. Signorelli et al [46] performed a systematic review and described that attenders of survivorship care (compared to nonattenders) demonstrated increased knowledge about their treatment and diagnosis, and although not significantly, attenders tended to report more distress associated with the risk of late effects [46]. With our study, we can identify areas of insufficient risk perception in survivors of

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HL attending the Dutch survivorship program, with the aim of improving risk communication by BETER health care providers.

Conclusions

INSIGHT is the first evaluation of (cost-)effectiveness of structured cancer survivorship care for survivors of HL based on real-world data. It will result in new knowledge on the (cost-)effectiveness of survivorship care in lymphoma survivors in clinical practice. The results are expected to contribute to more effective evidence-based long-term lymphoma survivorship care and could also be of interest to other survivorship programs.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

EMJL participated in the study design and drafted this manuscript. BMPA, FEvL, and AN designed the study and supervised the drafting of this manuscript. JMZ and VPR participated in the study design and critically reviewed the manuscript. All authors read and approved the final manuscript and take full accountability for its content.

Conflicts of Interest

BMPA reports reimbursement costs for an oral presentation at the International Symposium on Hodgkin Lymphoma (2022) in Cologne, Germany.

Multimedia Appendix 1
Detailed informed consent and recruitment procedure, detailed sample size calculation, and overview of cardiovascular diseases and associated risk factors included in the INSIGHT study.
[DOCX File , 20 KB - resprot_v13i1e55601_app1.docx]

Multimedia Appendix 2
Project peer-review by funder.
[PDF File (Adobe PDF File), 4842 KB - resprot_v13i1e55601_app2.pdf]

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Abbreviations

BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations
CVD: cardiovascular disease
DALY: disability-adjusted life year
GP: general practitioner
HL: Hodgkin lymphoma

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INSIGHT: Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment
QALY: quality-adjusted life year
YLD: years lost due to disability
YLL: years of life lost

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Protocol

TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) Project: Protocol for an International Longitudinal Multicenter Study

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Abstract

Background: Nursing-sensitive events (NSEs) are common, accounting for up to 77% of adverse events in hospitalized patients (eg, fall-related harm, pressure ulcers, and health care–associated infections). NSEs lead to adverse patient outcomes and impose an economic burden on hospitals due to increased medical costs through a prolonged hospital stay and additional medical procedures. To reduce NSEs and ensure high-quality nursing care, appropriate nurse staffing levels are needed. Although the link between nurse staffing and NSEs has been described in many studies, appropriate nurse staffing levels are lacking. Existing studies describe constant staffing exposure at the unit or hospital level without assessing patient-level exposure to nurse staffing during the hospital stay. Few studies have assessed nurse staffing and patient outcomes using a single-center longitudinal design, with limited generalizability. There is a need for multicenter longitudinal studies with improved potential for generalizing the association between individual nurse staffing levels and NSEs.

Objective: This study aimed (1) to determine the prevalence, preventability, type, and severity of NSEs; (2) to describe individual patient-level nurse staffing exposure across hospitals; (3) to assess the effect of nurse staffing on NSEs in patients; and (4) to identify thresholds of safe nurse staffing levels and test them against NSEs in hospitalized patients.

Methods: This international multicenter study uses a longitudinal and observational research design; it involves 4 countries (Switzerland, Sweden, Germany, and Iran), with participation from 14 hospitals and 61 medical, surgery, and mixed units. The 16-week observation period will collect NSEs using systematic retrospective record reviews. A total of 3680 patient admissions will be reviewed, with 60 randomly selected admissions per unit. To be included, patients must have been hospitalized for at least 48 hours. Nurse staffing data (ie, the number of nurses and their education level) will be collected daily for each shift to assess

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the association between NSEs and individual nurse staffing levels. Additionally, hospital data (ie, type, teaching status, and ownership) and unit data (ie, service line and number of beds) will be collected.

Results: As of January 2024, the verification process for the plausibility and comprehensibility of patients' and nurse staffing data is underway across all 4 countries. Data analyses are planned to be completed by spring 2024, with the first results expected to be published in late 2024.

Conclusions: This study will provide comprehensive information on NSEs, including their prevalence, preventability, type, and severity, across countries. Moreover, it seeks to enhance understanding of NSE mechanisms and the potential impact of nurse staffing on these events. We will evaluate within- and between-hospital variability to identify productive strategies to ensure safe nurse staffing levels, thereby reducing NSEs in hospitalized patients. The TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) study will focus on the optimization of scarce staffing resources.

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KEYWORDS

adverse events; electronic health record; hospital care; no-harm incidents; nursing care; nursing-sensitive events; nurse staffing; patient safety; systematic record review

Introduction

Overview

The link between patient outcomes and adequate nurse staffing levels has been extensively studied internationally over the last 2 decades. To avoid negative patient outcomes, such as adverse events, adequate staffing levels and combinations of skills and grades are needed. In hospital settings, up to 77% of adverse events are attributed to nursing care [1]. Nursing-sensitive events (NSEs) are part of adverse events that are specifically affected, caused, and influenced by the processes or structures of nursing care, though nursing is not exclusively responsible [2]. Examples of NSEs are hospital-acquired urinary tract infections, pressure ulcers, pneumonia, or deep venous thrombosis [3]. NSEs may be accompanied by additional monitoring or treatment [4]. Compared to studies on adverse events and their characteristics, few studies include all types of NSEs and their prevalence, preventability, and severity [5]. A recently published study exploring NSEs in home care settings found that 73% of the NSEs were preventable, and approximately 37% resulted in temporary harm that required additional health care resources [6]. In addition to the burden on the patient, NSEs generate high medical costs by necessitating additional monitoring or treatment [5,7]. Different methods to identify and assess NSEs are available. Currently, there is no gold standard for identifying and assessing NSEs. However, retrospective record review (RRR) methods, such as the Global Trigger Tool [5] and the Harvard Medical Practice Study methodology [8], seem most promising. Compared to other methods (eg, critical incident reporting systems and patient safety indicators), record review facilitates the detection of more adverse events, thereby minimizing the underreporting of NSEs [9]. To prevent and reduce NSEs and ensure quality nursing care, appropriate nurse staffing levels are needed [8,10]. Nurse staffing refers to the number and qualifications of nurses relative to the care demands of patients, often expressed as staffing levels (eg, nurse-to-patient ratios), skill mix (ie, the composition of the nursing team in terms of qualifications), and grade mix (ie, educational levels of the nursing team) [9]. Providing optimal nurse staffing levels has been a challenge for health care systems worldwide. Having too few nurses increases the risk of NSEs and decreases the quality of care (F Gratwohl, N Grossmann, S Musy, and M Simon, unpublished data, September 2018) [11,12]; it also increases the risk of nurse burnout and job dissatisfaction, which impedes the recruitment and maintenance of the nursing workforce [13]. Evidence suggests that the occurrence of negative patient outcomes is related to staffing [14], but there is a lack of systematic reviews focusing on different types of NSE.

Despite studies that substantiated the link between nurse staffing and NSEs [14-16], operational and methodological challenges have limited the practical impact of this research. Typically, staffing studies describe only constant staffing exposure at the unit or hospital level without assessing individual patient-level exposure to nurse staffing during the hospital stay [17]. Methodological challenges include the omission of important variables (eg, shift patterns, skill mix, and patient turnover) [10,16]; common method variance (ie, dependent and independent variables derived from the same survey of nurses); and simultaneity, which refers to common-cause variables affecting both staffing and outcomes, such as patient severity [16]. Only a few studies have assessed nurse staffing and patient outcomes using a longitudinal study design [10,15,18], and most of these studies were single-center studies; there is a lack of multicenter or international studies allowing generalizability. Therefore, there is a need for multicenter longitudinal studies of the association between individual patient-level exposure to nurse staffing and all types of NSEs, with improved potential for generalization.

To advance the field, there is a strong need to determine the optimal intervention strategies for nurse staffing levels required to reduce the risk of NSEs. This study is the first step in generating data aimed at structuring and planning future intervention strategies.

Objectives

The overall aim of the TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) study is to investigate the association between NSEs and individual nurse staffing levels. The specific aims are as follows:

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1. To determine the prevalence, preventability, type, and severity of NSEs across sites using structured RRR methodology
2. To describe individual patient-level nurse staffing across hospitals
3. To describe the effect of nurse staffing on NSEs in hospitalized patients
4. To determine thresholds of safe nurse staffing levels and test them against NSEs in hospitalized patients

Methods

Design

TAILR is an international multicenter study with a longitudinal and observational research design, running from 2021 to 2025. Altogether, 4 countries are participating in the study: Switzerland, Sweden, Germany, and Iran. Those countries make up the international TAILR consortium. Except for Switzerland, all data will be collected within the TAILR study. For Switzerland, data from the CroWiS (Crowd Working in der Schweiz) study will be used for data collection and analyses. CroWiS is a multimethod study with the overall aim of investigating the effect of temporary nurses in Switzerland [19].

Setting and Sample

For the different countries, different numbers of hospitals and units are included in the TAILR study. The numbers of participating hospitals and units range from 1 to 4 hospitals and 4 to 21 units, depending on the country. Across all countries, 4 medical, surgical, or mixed units for each hospital are participating in the study, which is a total of 11 hospitals and 49 units. The study also includes acute care hospitals providing elective care. The inclusion criteria for units are as follows: they must have at least 10 patient beds and are either medical or surgical. Units with elevated levels of care, such as intensive or intermediate care, will be excluded, as these units have higher levels of staffing. In Sweden, 1 of the 4 hospitals is a pediatric hospital that is part of a university hospital providing adult care as well. For this pediatric hospital in the TAILR study, 9 units will be included. For pediatric care, neonatal care units will be included, but these data will be analyzed separately in the pediatric cohort. Table 1 shows the setting and sample information for each country.

During the 16-week observation period, 60 admissions will be randomly selected from all eligible admissions per unit and will be reviewed. For adult care, patients ≥18 years of age will be included. For pediatric care, no inclusion criteria for age will be applied. All patients must be hospitalized for at least 48 hours at a TAILR unit, and the admission record must be closed. The stay in the TAILR unit ends after patients have been discharged, when the length of stay exceeds 14 days or when patients are transferred from the TAILR unit for more than 12 hours. If the patient has a length of stay >14 days, the data collection ends at the end of day 14. If a patient is readmitted, this admission is considered a new admission.

Table 1. Number of hospitals, units, and patients, along with shift system information, including the number of shifts for each country and in total.

Country and hospital	Hospital, n	Units, n	Shifts per day, n	Patient admission, n	Number of shifts, n	
					Weekday	Weekend
Germany						
Acute adult care hospital	3	12	3-14	720	Minimum 2880	Minimum 1152
Iran						
Acute adult care hospital	1	4	3	240	1152	192
Sweden						
Acute adult care hospital	3	12	3	720	2880	1152
Pediatric care hospital	1	9	3	560	2160	864
Total	4	21	N/A[a]	1280	5040	2016
Switzerland						
Acute adult care hospital	3	12	3	720	2880	1152
All countries						
Acute adult care hospital	10	40	N/A	2400	Minimum 9792	Minimum 3648
Pediatric care	1	9	N/A	560	2160	864
Total	11	49	N/A	2960	Minimum 11,952	Minimum 4512

[a]N/A: not applicable.

Variables and Measurements

Patient Characteristics and NSEs

Patient characteristics (eg, age and sex), clinically relevant variables (eg, primary diagnosis and patient-based workload for activities of daily living), and NSEs will be collected from patient records using systematic RRR, inspired by commonly used RRR methods. For the collection of the type of NSEs, we will use a set of predefined events (eg, deficiencies in drug management, deterioration of vital signs, health care–associated

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infections, gastrointestinal impairment, pain, and pressure ulcer) based on a literature review [3,5,6,20]. Furthermore, there is an option to enter "other" NSEs in the patient record, which allows all types of NSEs to be included. In addition to the type of NSE, preventability, severity, timing, origin, and potential contributing causes will be assessed per NSE. For severity, a slightly modified version of the National Coordinating Council for Medication Error Reporting and Prevention will be used, ranging from "An event that reached the patient but did not cause harm" to "Contributed or resulted in the patient's death."

Staffing Assessment

The shift-level nurse staffing data of the participating units will be collected using routine data or data from unit schedules depending on the hospital. For each day and each shift during the observation period of 16 weeks, each registered nurse (RN), specialist RN, nurse with an associate nursing degree (AND), unqualified helper, and student or trainee directly involved in patient care on the unit will be considered in the staffing assessment. Informal caregivers will be excluded. The assessment also includes whether the staff member is a temporary worker on the unit. We define "temporary" as a staff member deployed from a different unit than the target TAILR unit, a hospital pool, or an external agency. We will not differentiate between temporary nurses who only work for a single or few shifts and nurses who are deployed for weeks or months. To identify shifts with missing nurses, we will clarify whether the number of staff on this shift was as planned or not. If not, the missing number of nurses stratified by nursing degree will be entered.

Patient Counts and Turnovers

To assess the workload of nurses in relation to patient turnover, routine data regarding the number of patients, discharges, admissions, and transfers will be collected. Moreover, we will assess the number of out-of-specialty patients to account for additional workload for nurses.

Unit Survey

The study-specific 26-item unit survey assesses the organizational characteristics of the participating units, such as size (bed count) and service line. Additionally, data about the used care system and the used system to describe nursing care demands, workload, or patient acuity will be part of the unit questionnaire.

Hospital Survey

The study-specific hospital survey (8 items) will be used to collect hospital-level characteristics and statistics, such as ownership status (eg, private, not-for-profit, and public) and type (ie, district, general, and teaching hospital), as well as regulation, financing, and provision of the hospital.

Survey Translation and Validity Testing

The study manual, surveys, and assessments were developed in English. For Germany and Iran, they were translated into German and Farsi (Persian), respectively. Using a modified Brislin protocol, a systematic translation process was conducted [21]. After translation, an expert panel review of bilingual clinical and research nurses fluent in each target language reviewed each item in terms of cultural adaptations. To ensure comprehensibility and to check for response patterns, the entire German and Farsi versions of the NSE assessment sheet were pilot tested with nurses of varying educational levels. For all language versions, adaptations were made, as necessary, for wording and clarity.

Data Collection

The data observation period started in 2022. The data collection covers an observation period of 16 weeks at each hospital, but the start dates for hospital enrollment will be staggered between and within countries. We opted for this stepwise approach to ensure proper supervision and optimal use of resources during the data collection process, considering unit availability. Data will be collected digitally or with paper and pencil.

In Sweden and Switzerland, the random sampling of 60 admissions per unit will be carried out at the end of the 16-week observation period. In Germany and Iran, to use the available data collection resources, a random sampling of 15 admissions for each unit occurred 4 times with an interval of 4 weeks. Therefore, the number of included admissions in Germany and Iran is the same as those in the other participating countries, that is, 60 admissions per unit within 16 weeks of observation. Data will be collected by the internal RNs of the corresponding hospital or RNs who have experience working in the corresponding hospital. All data collectors will receive standardized education with the study manual, PowerPoint presentations, test examples, test records, and discussion sessions. For data quality control, an RN experienced in research for comprehensibility and plausibility will monitor the entered data.

The shift-level staffing assessments will be collected every day (from Monday to Sunday) for every shift (ie, morning, afternoon, night, and intermediated shifts). In Germany and Iran, data will be entered directly into a cloud-based electronic data capture platform by the ward manager of the TAILR unit, a hospital internal RN or a research team member. All data collectors for staffing assessment will receive a 3-hour education session with test entries and discussion sessions. In Sweden, shift data will be generated automatically by the corresponding hospital staffing system. In Switzerland, staffing data will be manually extracted from hospital staffing systems and entered into a secure web platform by members of the research team.

The hospital- and unit-level surveys will be conducted retrospectively after the main data collection. Data will be collected using routine data. If no routine data are available, interviews between TAILR country-specific research group members, unit managers, and hospital managers will be conducted.

Data will be stored in a cloud-based database, with a server in the Netherlands, that complies with the European Union General Data Protection Regulation. Access to the platform is restricted to the TAILR research group members and data collectors at specific sites.

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Sample Size

We used 3 hospitals as the basis for sample size considerations. Assuming the same NSE rate of 36.4% as in a Swedish study [5], a sample size of 720 (95% CI 33.3%-39.5%) patients is expected (aim 1). A simulation (500 iterations per cell) of a 3-level generalized linear mixed model with a count variable for each shift above a low staffing threshold, with 15% of patients exposed to 1 or more shifts, was performed. We set the random effects at the unit and hospital level to 0.1, indicating an intraclass correlation coefficient (ICC) of 0.03. Based on an odds ratio of 1.10 and a sample of 60 patients per 4 units in 3 hospitals, the power was 100%. With a lower odds ratio of 1.07, representing the smallest effect of interest for a sample of 60 patients per 4 units in 3 hospitals, the power was still 0.91. As the ICC is unknown, we also assessed ICCs of 0, 0.06, and 0.15, resulting in the power ranging from 90% to 100% for both effect sizes, with a sample of 720 patients. Reducing the number of units to 3 per site, the total sample size was reduced to 540, with the power dropping to 70%-96%, depending on the specification. As the weights will only be known after the study has been conducted [22], this power calculation is based on a generalized linear mixed model without inverse probability weighting.

Data Analysis

Aim 1

A descriptive analysis of the prevalence, preventability, types, and severity of NSEs will be carried out. We will calculate the frequencies and percentages with 95% CIs for NSE type, severity, and preventability. We will calculate the prevalence of NSEs per 1000 patient days and 100 patient admissions. To determine the quality of the review process, we will assess interrater reliability between 2 primary reviewers from a random sample of every tenth of the admissions via the Cohen kappa (κ) coefficient for review stage 1. Agreement between reviewers is defined as (1) agreement on the presence of potential NSEs by calculating Cohen kappa and (2) agreement on the number of NSEs by calculating the weighted Cohen kappa, where high disagreement corresponds to high weights.

Aim 2

In the first step, a descriptive analysis of the numbers of patients and nurses and the patient-to-nurse ratios for different staff categories (eg, RNs, specialist RNs, nurses with ANDs, and unqualified staff) over time will be conducted. Extreme staffing shifts will be defined as those with 50% more or fewer patients per nurse for each unit based on the shift median.

In the second step, the workload will be modeled with the observed-over-expected (O/E) estimator. The O/E estimator is the observed number of nurse staff on a shift divided by the expected number of nurse staff based on the shift, patient, and unit characteristics; the O/E estimator is an extension of the adjusted staffing measure we used in a previous study [23]. For the O/E estimator, we will predict the number of different staff groups (eg, RNs, nurses with ANDs, and unqualified staff) with a multivariate generalized linear model of the Poisson family, with separate models for each unit. This model will take patient characteristics; primary and secondary diagnoses; shifts; and the number of patients, admissions, transfers, and discharges into account. The observed number of nurse staff per shift will be divided by the expected value derived from the multivariate generalized linear model. The O/E estimator will then be used to describe the staffing variability over time for each patient. Furthermore, the coefficients of the model will allow us to compare units, hospitals, and countries in terms of their nurse staffing provision.

Aim 3

We will evaluate the suspected causative effect of nurse staffing on selected NSEs using a directed acyclic graph describing the hypothesized mechanism over time (Figure 1). Directed acyclic graphs describe a set of time-invariant individual-level confounders, such as age (A) or sex (C), time-variant confounders, such as patient severity on a given shift ($L_{1...n}$); and the time-variant exposure variable of the O/E estimator for nurse staffing ($A_{1...n}$). The minimal adjustment set also includes the admission reason, which determines the unit to which a patient is admitted. To estimate the causal effects, 3 conditions need to be met. The first condition is the "exchangeability assumption." An uncontrolled variable that influences exposure and outcome would violate this assumption. As the supply side (ie, the available nurse staffing resources) is determined by the unit type and relatively fixed rosters, the exposure is primarily driven by the volatility of the demand side (ie, the patients admitted to the unit). Therefore, within units, the exchangeability assumption for the exposure should hold. Indeed, occupancy might influence patient admissions or discharges, potentially creating a backdoor path. We will, therefore, consider occupancy as a variable in a sensitivity analysis. Second, the "positivity" assumption is met by the design, as individual exposure to high- or low-staffed shifts occurs continuously throughout the index admission. We will use descriptive analysis to confirm this assumption. Last, the "consistency assumption" requires that the level of exposure is identical for all patients. Although consistency is provided in the way the exposure is operationalized, the nursing staff will allocate available time between patients according to their needs within shifts. The severity measure will partially account for this. We will use nurse activity data, which are available for some sites, to explore this issue. To estimate a causal effect of nurse staffing exposure on each NSE of interest, we will construct a marginal structural model using inverse probability weighting [24]. According to VanderWeele et al [25], a marginal structural model can assess the joint effects of time-varying exposure. To calculate the weights, we will use the R package "ipw" [26]. To fit the model, we will use a generalized mixed model of the binomial family with the lme4 package in R software (version R-4.3.3; R Foundation for Statistical Computing) [27].

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Figure 1. Directed acyclic graph of the staffing and nursing-sensitive events The graph describes a set of time-invariant individual-level confounders, such as age (A) or sex (C); time-variant confounders, such as patient severity on a given shift ($L_{1...n}$); and the time-variant exposure variable of the observed-over-expected estimator for nurse staffing ($A_{1...n}$). The minimal adjustment set also includes the admission reason (AR), which determines the unit to which a patient is admitted. Y: outcome.

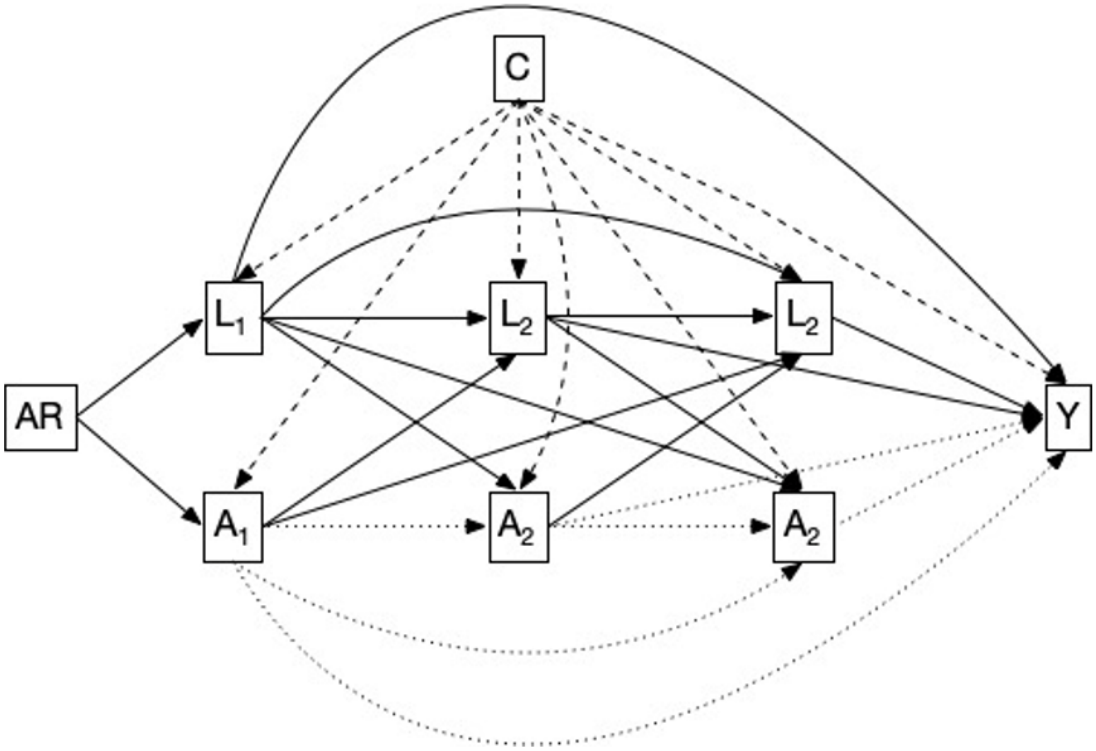

Aim 4

To help optimize and predict the necessary nursing staffing needs in hospitals to decrease NSEs, we will develop a simulation using the simmer package in R software. Simmer is a discrete-event simulation (DES) and automation software. DES is a flexible, computer-based modeling methodology characterized by the ability to simulate dynamic behaviors of complex systems and interactions between individuals, populations, and their environments. Compared with aggregate models without interaction, such as decision trees or Markov models, a DES can be more advantageous as an operational research technique to model complex systems at the individual level instead of the cohort level. After we have developed the DES model, we will test it against various data elements from our observational study, including the hospital bed size, number of nursing staff, patient flow structure, nursing practices, and NSEs. The process flow will be translated into a DES model, which will allow us to determine and validate the thresholds of safe nurse staffing levels.

Ethical Considerations

The TAILR study is compliant with the legal and ethical guidelines of the applicable federal, clinical (including participating hospitals), and academic partners (ie, universities and universities of applied sciences). Ethical approval for the proposed study has already been obtained according to national regulations (Germany [Ethik-Kommission Hochschule für Gesundheit, University of Applied Sciences Bochum]: 210602; Sweden [Swedish Ethical Review Authority]: TAILR.SE: 2021-04962; Iran [Ethics Committee of Kashan University of Medical Sciences]: TAILR.IR: IR.KAUMS.REC.1398.032; and Switzerland [Ethikkommission Nordwest- und Zentralschweiz]: CroWiS BASEC 2022-01121).

The study will follow all ethical standards of research conduct outlined in the Declaration of Helsinki and the General Data Protection Regulation for European countries. The project team will handle the patient- and unit-level staffing data with confidentiality. Each patient record included in the record review will receive a unique identification number, and the data in a cloud-based database will be pseudonymized. Participant names will not be disclosed. The published study data will be anonymous, and therefore, there will be no identification of individual participants. The study participants received no compensation.

Results

As of January 2024, the checking of plausibility and comprehensibility of patients' and nurse staffing data is ongoing in all 4 countries. Data analyses are planned to be completed by spring 2024, with the first results expected to be published in late 2024.

Discussion

This paper describes the study protocol for the TAILR study. TAILR is an international multicenter study with a longitudinal and observational design that will consider within- and between-hospital variability to identify productive and urgently needed strategies to ensure safe nurse staffing levels to reduce NSEs. More concretely, TAILR will provide important building

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blocks to address and overcome a critical patient safety issue, that is, the lack of staffing guidance in national health policy and at local organizational levels. TAILR provides a unique opportunity to better understand the mechanisms of NSEs and the potential impact of nurse staffing on NSEs. Collecting data on nurse staffing and its association with NSEs in multiple countries, the TAILR study aims to provide a new perspective on optimal nurse staffing levels in hospitals and a unique innovative template for the evaluation of the association between NSEs in patients and individual nurse staffing levels within the international context. This study addresses a gap in current research, as emphasized by repeated calls for research to inform health policies on safe nurse staffing levels [15,28]. This need has been increased due to the COVID-19 pandemic and the increasing pressures to develop and maintain the nursing workforce in the participating countries as well as other countries [29].

TAILR will act as a model for nurse-led improvement strategies for safe staffing within different countries. First, for the participating hospitals, TAILR will create transparency by providing comparative data. Moreover, we will be able to identify hospital structures and processes that facilitate and challenge safe nurse staffing. By conducting workshops with the participating hospitals and stakeholders, the best practices will be identified and described to create applicable solutions based on the study results. Second, based on the workshops with hospitals and stakeholders, TAILR will provide data to develop recommendations that provide cornerstones for safe staffing policies in a country-specific context. Beyond mandatory minimum nurse staffing levels, TAILR will provide highly granular data to describe operational gaps in nurse staffing, which remain undetected in aggregate analysis. Potential safe staffing policies must consider the service line and patient acuity as well as hospital-specific factors, such as nurse pools, clear distribution of nursing and nonnursing tasks between nurses with different educational backgrounds, and the systematic assessment and monitoring of nurse staffing and NSEs. Third, the international TAILR study will create research outputs for the participating countries as well as other countries. For (inter)national stakeholders and the members of the international TAILR consortium, the study results will enable the definition of global quality improvement strategies.

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Data Availability

The data that support the findings of this study are available from the corresponding authors, (SB, MU, and MS) upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the German Federal Ministry of Education and Research.
[PDF File (Adobe PDF File), 94 KB - resprot_v13i1e56262_app1.pdf]

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Abbreviations

AND: associate nursing degree
CroWiS: Crowd Working in der Schweiz
DES: discrete-event simulation
ICC: intraclass correlation coefficient
NSE: nursing-sensitive event
O/E: observed-over-expected
RN: registered nurse
RRR: retrospective record review
TAILR: Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels

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Protocol

Associations Between Stress, Health Behaviors, and Quality of Life in Young Couples During the Transition to Survivorship: Protocol for a Measurement Burst Study

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Abstract

Background: Cancer is a life-threatening, stressful event, particularly for young adults due to delays and disruptions in their developmental transitions. Cancer treatment can also cause adverse long-term effects, chronic conditions, psychological issues, and decreased quality of life (QoL) among young adults. Despite numerous health benefits of health behaviors (eg, physical activity, healthy eating, no smoking, no alcohol use, and quality sleep), young adult cancer survivors report poor health behavior profiles. Determining the associations of stress (either cancer-specific or day-to-day stress), health behaviors, and QoL as young adult survivors transition to survivorship is key to understanding and enhancing these survivors' health. It is also crucial to note that the effects of stress on health behaviors and QoL may manifest on a shorter time scale (eg, daily within-person level). Moreover, given that stress spills over into romantic relationships, it is important to identify the role of spouses or partners (hereafter partners) in these survivors' health behaviors and QoL.

Objective: This study aims to investigate associations between stress, health behaviors, and QoL at both within- and between-person levels during the transition to survivorship in young adult cancer survivors and their partners, to identify the extent to which young adult survivors' and their partners' stress facilitates or hinders their own and each other's health behaviors and QoL.

Methods: We aim to enroll 150 young adults (aged 25-39 years at the time of cancer diagnosis) who have recently completed cancer treatment, along with their partners. We will conduct a prospective longitudinal study using a measurement burst design. Participants (ie, survivors and their partners) will complete a daily web-based survey for 7 consecutive days (a "burst") 9 times over 2 years, with the bursts spaced 3 months apart. Participants will self-report their stress, health behaviors, and QoL. Additionally, participants will be asked to wear an accelerometer to assess their physical activity and sleep during the burst period. Finally, dietary intake (24-hour diet recalls) will be assessed during each burst via telephone by research staff.

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Results: Participant enrollment began in January 2022. Recruitment and data collection are expected to conclude by December 2024 and December 2026, respectively.

Conclusions: To the best of our knowledge, this will be the first study that determines the interdependence of health behaviors and QoL of young adult cancer survivors and their partners at both within- and between-person levels. This study is unique in its focus on the transition to cancer survivorship and its use of a measurement burst design. Results will guide the creation of a developmentally appropriate dyadic psychosocial or behavioral intervention that improves both young adult survivors' and their partners' health behaviors and QoL and potentially their physical health.

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KEYWORDS

young adult survivors; caregivers; dyadic; couple-based; stress; health behaviors; quality of life; transition to survivorship; measurement-burst

Introduction

Overview

Each year, more than 80,000 adolescents and young adults (aged 15-39 years) are newly diagnosed with cancer in the United States [1], and cancer is the leading cause of disease-related death among adolescents and young adults [2]. Mortality rates in adolescent and young adult patients with cancer have decreased over the past decade, and the 5-year relative survival rate for adolescent and young adult patients with cancer is 85.5% [3]. However, this high relative survival rate may mask the true burden of cancer among adolescent and young adult survivors. Although cancer and its treatment can be a traumatic event for any individual, it may be particularly so for adolescents and young adults because cancer can cause delays and disruptions in their successful developmental transitions across various domains of life: biological or physical (eg, cancer can cause hair loss, infertility, and weight change), psychological (eg, lack of control over life and disruption in progress toward life goals), educational or occupational (eg, disruption in education and unemployment), social or relationship (eg, problems in relationship with significant other and interference with plans for having children), and financial (eg, large debt and bankruptcy) [4-13]. Cancer and its treatment can also cause adverse long-term effects among adolescents and young adults (eg, premature or accelerated aging, cardiotoxicity, and second malignant neoplasms) [14,15] and heightened risk of chronic conditions (eg, cardiovascular disease, hypertension, diabetes, and asthma) [14,16,17], psychological issues (eg, depressive symptoms and fear of cancer recurrence), and lower quality of life (QoL) among adolescents and young adults compared with their peers without cancer [14,18].

Interest in and calls for research on adolescent and young adult cancer survivors have dramatically increased since 2006 when the Adolescent and Young Adult Oncology Progress Review Group published a report about the state of the science regarding cancer among adolescents and young adults [19]. However, adolescents and young adults affected by cancer still have vast unmet health care needs, including psychosocial care needs [7,20-23], and remain an understudied subgroup of patients with cancer. In addition, adolescent and young adult cancer survivors are often considered a single entity, and much of the existing data comes from studies that grouped adolescents and young adults together, although individuals in this age range may face different developmental tasks. Thus, the proposed study focuses on young adult survivors who were diagnosed with cancer at 25 to 39 years old [24], whose primary source of support is more likely to be romantic partners, whereas pediatric and adolescent survivors are more likely to depend on their parents. Due to a lack of existing studies specific to young adult survivors, the literature review below is based on studies among adolescent and young adult survivors.

Stress and Health Behaviors Among Young Adult Survivors

Overview

Strong evidence exists that engaging in healthy behaviors (eg, physical activity, low sedentary behavior, healthy eating, no smoking, no alcohol use, and quality sleep) is critical for cancer survivors' health, as it reduces the likelihood of cardiotoxicity, development of secondary cancers, cancer recurrence, and cancer-specific and all-cause mortality [25-28] and improves QoL [26,29]. However, young adult survivors report poor health behavior profiles. Specifically, young adult survivors report higher rates of unhealthy eating than their peers without cancer [14,16,30], and 26% of young adult survivors versus 18% of their peers without cancer report current smoking [14,16,30]. In addition, 50% to 90% of young adult survivors report at least some alcohol use [30], and 31% of young adult survivors report no leisure-time physical activity [14]. Further, approximately 40% of young adult survivors report experiencing sleep issues (eg, trouble falling or staying asleep in the previous week), and those who report difficulties with sleep also indicate higher levels of psychological distress [31].

While stress can substantially influence negative health outcomes [32] and poor health behaviors [33-35], it remains an understudied factor for young adult survivors' health behaviors. At present, almost nothing is known regarding the association between stress and health behaviors among young adult survivors. To better understand the association between stress and health behaviors in this survivor population, there are three crucial factors to be considered: (1) the transition from active treatment to survivorship; (2) interdependence between survivors and family caregivers, especially partners; and (3) within-person variabilities in stress and health behaviors.

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Transition From Active Treatment to Survivorship

Transitioning from active treatment to posttreatment care is critical to cancer survivors' long-term health. However, the transition is challenging because survivors are often lost to systematic follow-up, and opportunities to effectively intervene are missed [36]. Many people finish their primary cancer treatment being unaware of their heightened health risks and are ill-prepared to manage their future health care needs [36]. In particular, young adult survivors struggle with the transition; with the abrupt cessation of intensive support (feelings of abandonment); and with challenges regarding returning to work, study, and social or recreational activities, which is complicated by ongoing disease or treatment impacts and a collective dearth of knowledge and resources on how to cope with these challenges during this time [37]. Thus, beyond cancer or treatment-specific stress (eg, symptom burden and concerns about cancer recurrence), stress regarding postcancer life adjustment needs to be addressed to better understand young adults' survivorship outcomes.

Interdependence Between Survivors and Their Partners

Cancer is often considered a "we-disease" [38]; survivors and their families tend to react to cancer as an interdependent system in which they influence each other's health. As an example of this interdependence, stress experienced by a cancer survivor or by their spouse or partner (hereafter partner) can affect the QoL of the other person in the relationship [38,39]. Beyond cancer care demands and stressors shared with the survivor (eg, concerns about cancer recurrence or progression), partners of survivors may encounter various stressors in their everyday lives (eg, work deadlines and social obligations) that can spill over into the relationship. Thus, neglect of partners' stress and coping and failure to include partners in young adult survivorship interventions may provide only a partial understanding of QoL and the challenges of the transition to survivorship among young adult survivors who have partners. However, to date, to the best of our knowledge, none of the existing interventions developed for and tested among young adult survivors to enhance their psychosocial outcomes (eg, QoL and psychological symptoms) have targeted survivor-partner dyads [40].

Within-Person Variabilities in Stress and Health Behaviors

Although previous studies have significantly advanced our understanding of cancer survivorship issues among young adults, most of these studies were cross-sectional and therefore could not capture potential dynamic changes in stress, health behaviors, and QoL during the transition to survivorship. While a few prospective longitudinal studies in young adult survivors exist [41-44], assessment intervals tend to range between 6 and 12 months and assume that stress, health behaviors, and QoL are fairly stable in the short term. However, evidence indicates that an individual's stress and health behaviors may vary across days of a week [45-53], which may further explain reported short-term (eg, daily) within-person variations in QoL [54]. Moreover, within-person variations in stress, health behaviors, and QoL may exist in survivor-partner dyads [45,46]. Thus, global, aggregated measures of stress, health behaviors, and QoL at the between-person level or over longer time scales at the within-person level (eg, "How much were you stressed out in the *last week*?"; "How much did you drink alcohol in the *past month*?"; and "How was your overall QoL in the *past year*?") may fail to reveal subtle and dynamic changes in stress, health behaviors, and QoL that can occur over shorter time scales (eg, daily intervals) [55].

A measurement burst design can assess both the between- and within-person processes in stress, health behaviors, and QoL. The design incorporates bursts of intensive repeated assessment within a relatively short period of time (eg, daily) that are repeated longitudinally, over more widely spaced intervals (eg, every 3 months), which will enable us to investigate the interaction of within-person processes that transpire over different time intervals [56,57]. However, to date, no published studies have investigated the extent to which young adult survivors and their partners facilitate or hinder each other's short- and long-term adjustment during the transition to survivorship using the measurement burst design.

This Study

Overview

The overarching purpose of this study is to investigate associations between stress, health behaviors, and QoL at both within-person and between-person levels over the transition to survivorship in young adult survivors and their partners to identify the extent to which young adult survivors' and their partners' stress facilitates or hinders their own and each other's health behaviors and QoL. To examine both within-person and between-person changes, we will implement a measurement burst design [56,57], in which participants will be asked to complete a daily survey for 7 consecutive days (a "burst") 9 times over 2 years, with the bursts spaced 3 months apart. Thus, there will be 3 levels: day, burst (3-month interval), and person. We have the following specific aims.

Aim 1

Aim 1 is to determine the within-person effects of stress on health behaviors at both day and burst levels. We hypothesize that on days or during bursts when stress is high, individuals are more likely to report physical inactivity, unhealthy eating, poor sleep quality, smoking (current smokers only), or alcohol use (current drinkers only). We also hypothesize that on days or during bursts when partners' stress is high, survivors are more likely to report these unhealthy behaviors, and vice versa.

Aim 2

Aim 2 is to determine the within-person, day-level, and burst-level effects of stress on QoL and the effects of health behaviors on QoL. We hypothesize that individual's QoL will be high on days or during bursts when their stress is low, when they perform physical activity, and when their sleep quality is good. We also hypothesize that on days or during bursts when partners' stress is low, when partners perform physical activity, and when partners' sleep quality is good, survivors are more likely to report high QoL, and vice versa.

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Exploratory Aims

The two exploratory aims are as follows: (1) identifying 2-way cross-level interaction effects between day- or burst-level and person-level stress on health behaviors and QoL—in other words, we will examine whether the extent to which individuals' day- or burst-level stress influences their health behaviors and whether QoL is stable or varies depending on their average person-level stress; and (2) identifying 2-way cross-level interaction effects between day- or burst-level stress and person-level stable factors (eg, sex, race, age at diagnosis, and type of cancer) on health behaviors and QoL—that is, we will examine whether the extent to which individuals' day- or burst-level stress influences their health behaviors and whether QoL is stable or varies depending on their person-level factors.

Methods

Participants and Procedures

We aim to enroll 150 young adult survivors and their partners (ie, 300 individuals). Cancer survivors will be eligible if they (1) were diagnosed with cancer for the first time (ie, no previous history of cancer); (2) were a young adult (aged 25-39 years) at the time of diagnosis; (3) are within 3 months after the completion of treatment (eg, surgery, chemotherapy, and radiation therapy) with curative intent; (4) have no further planned cancer treatment (surgery, chemotherapy, radiation therapy, and immunotherapy) except for hormone therapy; and (5) have a valid phone number and email address. Survivors will be excluded if they (1) do not have significant others and (2) are unable to read, write, or speak English. Partners will be eligible if they (1) are aged ≥18 years; (2) are spouses or romantic partners (either married or not) cohabitating with the young adult survivor; (3) self-identify as the current primary caregivers of the young adult survivors; (4) are able to read, write, and speak English; and (5) have a valid phone number and email address.

During the study period, partners may change (because of separation, divorce, etc). If so, the current (ie, newly identified) partner (identified by the survivor, if applicable) will be contacted after permission is obtained from the survivor, and if interested and eligible, will be enrolled upon providing informed consent. We will record these changes in the dyads. If a member of a dyad drops out of the study, the other member will be asked to complete the study to investigate survivors' or partners' changes in stress, health behaviors, and QoL. If a survivor's cancer recurs during the 2-year study period, the dyad (ie, both the survivor and their partner) will be withdrawn from the study.

Cancer survivors will be recruited at The University of Texas MD Anderson Cancer Center. Potentially eligible survivors will be initially identified by research staff via electronic health records and will be contacted via telephone. Only those who are interested in the study will be further screened. If the survivor is eligible and interested, we will obtain the contact information of their partner for the partner's eligibility screening. If the partner is eligible and interested, the survivor-partner dyad will provide consent remotely via teleconferencing (eg, Zoom). We will also contact young adult cancer support groups and organizations through their websites and social media platforms to recruit non–MD Anderson cancer survivors. Interested individuals can submit a study interest form, and our research staff will contact them for phone screening.

All study procedures will be conducted remotely. After signed electronic consent forms are obtained, both survivors and partners will be asked to individually complete a baseline assessment in the form of a survey questionnaire via Research Electronic Data Capture (REDCap; Vanderbilt University), a secure, web-based app with controlled access designed to support data capture for research studies. This retrospective survey includes demographics, health status, stress, health behaviors, and QoL and will take approximately 1 hour to complete.

The daily survey will also be designed with REDCap, and the first daily survey period (ie, burst) will start within 10 days after completing the baseline survey. All participants will receive a survey link at 6 PM once per day for 7 consecutive days via their email; the brief 5-minute survey can be completed on the participant's electronic device (computer and smartphone). Survivors and partners will receive separate links and be asked to complete their daily reports in the evenings (before going to sleep) regarding stress, health behaviors, and QoL. Survivors and partners will be asked to complete assessments separately. Each survey link will be valid for only 12 hours. Thus, participants will not be able to submit data for a given day early, but they will be able to provide it the next early morning (until 6 AM). Regardless of when data are provided (that evening or the next morning), the questions will be specific to the person's experiences on the day the survey link is received.

During the burst, both survivors and partners will be asked to wear a blinded accelerometer (ActiGraph GT9X Link) on their nondominant wrist for 7 days and to engage in their daily routines as normal. The accelerometer with a prepaid envelope will be sent to the participants' residential address. After wearing the accelerometer for 7 days, participants will return the device using the envelope. Moreover, participants will be asked to choose 2 days (a day to recall a weekday's diet and another day to recall a weekend day's diet) over the 7 days when they are available for a dietary assessment (the Automated Self-Administered 24-hour Dietary Assessment Tool [58]). Participants will be told that research staff will call them on the selected days or times for the assessment.

Before each 7-day daily assessment period, participants will be asked to complete a retrospective survey similar to the baseline survey. We will mail out the accelerometer (with the prepaid envelope) in advance so that participants can wear the accelerometer and begin the 7-day daily survey without delays once they complete the retrospective survey.

Measures

Retrospective Survey Measures

Demographic and Medical Factors and Other Descriptive Factors and Covariates

Both survivors and partners will be asked about demographic (eg, sex, age, level of education and income, and marital or

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relationship status) and health and health care information (eg, existing comorbidities, health insurance, and height and weight to calculate BMI). Tumor characteristics will be obtained from self-report and medical records (for MD Anderson patients). Financial toxicity will be assessed with the Comprehensive Score for Financial Toxicity instrument [59], which consists of 12 items scored on a 5-point Likert scale and reveals high internal consistency and test-retest reliability (Cronbach α=.90) in patients with cancer. Financial toxicity will be assessed for both survivors and partners. For partners, the caregiving burden will be assessed with the short form of the Zarit Burden Inventory, a 12-item measure [60], which is validated among cancer caregivers [61]. Each question is scored on a 5-point Likert scale from 0 (never) to 4 (almost always). High scores represent a higher burden.

Stress

All participants will be asked to identify the most stressful event in the past 30 days (open-ended question). Then, the 4-item Perceived Stress Scale [62] will be administered; participants will rate each item from 0 (never) to 4 (very often).

Health Behaviors

For both survivors and partners, self-reported physical activity will be assessed with the Godin Leisure-Time Questionnaire [63], a brief measure assessing aerobic exercise, which is widely used in diverse populations including those with cancer [64]. In addition, we will assess strength exercise (eg, weight lifting and circuit training) with 1 item from the Health Information National Trends Survey [65]. Smoking will be assessed with items adapted from the Patient-Reported Outcomes Measurement Information System (PROMIS) Smoking Initiative [66] and the Health Information National Trends Survey [65], which include smoking behaviors (eg, "Have you smoked at least 100 cigarettes in your entire life?" [yes/no]; if yes, "How old were you when you first started smoking?"; and "Have you ever used an e-cigarette, even one or two times?" [yes/no]). Alcohol use will be assessed with 2 items from the Alcohol Use Disorders Identification Test–Consumption [67] asking about alcohol use frequency and quantity. Eating behaviors will be assessed with the validated, National Cancer Institute Diet History Questionnaire-III, which consists of 135 food and beverage line items and 26 dietary supplement questions [68]. Sleep will be assessed with the Pittsburgh Sleep Quality Index [69], an 18-item self-rated questionnaire that assesses the quality of sleep and sleep disturbances.

Relationship

Relationship will be assessed with 1 item measuring transformation of motivation [70] (indicating motivation for disease management is transformed from self-centered [eg, cancer is my/your problem] to relationship-centered [eg, cancer is our problem]) and with the 5-item Emotional Intimacy Scale, which showed good internal consistency (0.88) and test-retest reliability (0.85) [71].

QoL Measurement

For young adult survivors, we will use the 30-item satisfaction scale from the Late Adolescence and Young Adulthood Survivorship-Related Quality of Life (LAYA-SRQL) [72]. The LAYA-SRQL measure comprises 10 domains, including existential/spirituality, coping, relationship, dependence, vitality, health care, education/career, fertility, intimacy/sexuality, and cognition/memory. Participants can endorse "not applicable" if any item is not relevant to them. To reduce participants' burden, we will use 11 items (ie, approximately 1 item per domain). In addition, both survivors' and partners' QoL will be assessed with the 10-item PROMIS–global health (measuring physical function, pain, fatigue, emotional distress, and social health) [73] so that we can compare the level of QoL between survivors and partners.

Daily Survey Measures

Both survivors and partners will report the following.

Stress

Stress will be assessed by adapting a measure of daily recording of coping with everyday stressful events [74]. Specifically, participants will be asked to report the most stressful event or issue of the day in their own words. Then, the level of distress will be assessed with 1 item asking, "On a scale from 1 to 100 (where 100 is the maximum distress that you could imagine and 1 is a minor annoyance), how stressful would you rate this problem or situation?"

Health Behaviors

The objective level of physical activity will be assessed with the accelerometer, which has strong reliability and validity [75]. Participants will wear a blinded accelerometer on their nondominant wrist for 7 days to assess typical physical activity. The Godin Leisure-Time Questionnaire [63] and the strength exercise item [65] will be asked to assess self-reported physical activity. Dietary intake will be assessed via telephone (from research staff) on 2 preselected days with the Automated Self-Administered 24-hour Dietary Assessment Tool [58], which produces a healthy eating index. The accelerometer will also objectively assess sleep (eg, total sleep time, sleep percentage, and wake after sleep onset). Thus, subjective sleep quality (over the last night) will be assessed with 1 item ("How would you rate your last night's sleep quality overall?") adapted from the Pittsburgh Sleep Quality Index [69]. Daily smoking (yes or no) will be assessed only among current smokers. Daily alcohol use (yes or no) and number of drinks will be assessed only among current drinkers. All of these self-reported measures will be assessed among both survivors and partners, adapting the aforementioned measures with the stem "TODAY, ..."

Relationship

The aforementioned 1 item measuring transformation of motivation [70] and 3 items from the Emotional Intimacy Scale [71] will be assessed with the reference "TODAY."

QoL Measurement

We will assess survivors' QoL with the same 11 items from the LAYA-SRQL. Survivors will be asked to answer each item with the stem "Please indicate the extent to which you are satisfied with this aspect of your life TODAY." Participants can endorse "not applicable" if any item is not relevant to them. For both survivors and partners, the PROMIS-global health

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measure (4 items) [76] will also be assessed with the reference "TODAY."

Analytic Plans

We will first conduct extensive descriptive analyses of the retrospective and daily surveys over the 2-year period. Descriptive statistics, for example, means, SDs, and ranges for continuous measures, as well as frequencies and proportions for categorical variables, for the time-varying variables, will be calculated for each burst and for the 2-year period as a whole. Those of the baseline, person-level stable variables (eg, sex) will be calculated once. Preliminary bivariate analyses of the time-varying variables (eg, stress, health behaviors, and QoL) will be performed using within- and between-person correlations between them for each burst and for the 2-year period as a whole. Both correlations between an individual's own variables (eg, individuals' own stress and their health behaviors) and correlations between partners' and survivors' variables (eg, partners' stress and survivors' health behaviors) will be calculated.

For the aims of this study, we will design and fit mixed-effects multilevel models that adapt to the correlation structures of the underlying data process. For continuous (or near-continuous) outcomes (physical activity, eating behaviors, sleep, and QoL), linear mixed-effects models will be considered first, but depending on the distributional properties of the outcome (eg, skewed and censored), generalized linear mixed-effects models with proper distributions such as gamma or censored normal distribution and link functions such as log link will be used accordingly. For categorical outcomes (smoking and alcohol use), a logistic link function and binomial distribution will be used to build mixed-effects logistic regression models. All the models will be multilevel, incorporating burst-level trends, general day-to-day trends (centered), and deviations from the overall mean and day-to-day trends specific to burst (level 2) and to person (level 3) using random effects. Predictors will include survivors' and partners' day-to-day variables (person-burst-centered) to estimate within-person effects at level 1 and their burst-level variables (person-centered) to estimate within-person effects at level 2 (eg, the effect of day- or burst-level stress on health behaviors in Aim 1 and the effect of day- or burst-level health behaviors on QoL in Aim 2), their person-level (averaged) variables to estimate between-person effects at level 3, and a role variable to differentiate survivors' and caregivers' effects in each of those individuals' own effects and partners' effects using interaction terms. For the exploratory aims, 2-way interaction terms between the person-level variables (eg, person-level stress) and the day- or burst-level variables (eg, daily fluctuations of stress), as well as between-level stable demographic and clinical factors and the day- or bust-level variables, will be added to assess moderations for the individuals' day- or burst-level effects. Three-way interaction terms with the role variable added will be used to differentially evaluate each of those 2-way interactions for survivors and partners.

Within this modeling framework, the components of the aims can be estimated and evaluated. For Aim 1, various components of stress will be related to concurrent health behaviors, both within and between individuals and across survivors and partners. The effect of interest is the association between stress components and individual health behaviors (at the burst level and the day level within bursts). Smoking and alcohol use will each be assessed as an indicator of behavior (with a logistic link) and a magnitude of behavior (excluding nonsmokers and nondrinkers, respectively). Linear relationships will be tested, and if model diagnostics indicate a nonlinear fit, a smooth nonlinear association will be assessed. A similar construction will be considered for Aim 2, relating components of stress to QoL and components of behavior to QoL at the burst level and the day level within bursts. Similarly, for the exploratory aim, the effects of interest will be interactions of day- or burst-level stress and aggregate-scale person-level stress or person-level stable factors. For each model, there is a possibility of nonignorable dropout or mortality. To address issues of missingness, we will assume that loss to follow-up is missing at random. Within this context and under a small number of assumptions, the missingness due to death or dropout becomes missing at random and ignorable given the context of the model. The mixed-effects structure, in particular, is robust to many patterns of random missingness. With respect to mortality, we will implement the principal stratification approach [77], wherein participants are weighted by their propensity to survive the study period.

Sample Size and Power Calculation

Assuming a 20% rate of dropout, we expect to have at least 120 dyads complete the study. Most of our assessments will be measured by correlation. With 120 dyads, we expect to have at least 80% power to detect relationships with a partial R^2 of at least 0.26, which is a medium-large effect. A similar construction shows that the 80% detectable level of the partial F is 0.06, which is a small-to-medium effect. The partial F statistic is a scaled version of the partial F statistic in a nested analysis of variance comparison; the scaling factor is the ratio of the numerator's and the denominator's degrees of freedom [78]. As the modeling structure and relative effect sizes (and confidence bounds) will be of primary interest, we will not incorporate a multiple testing structure until the correlation between test statistics can be carefully assessed (which allows for less conservative testing criteria). The R library *pwr* was used in the calculation of these effect sizes.

Ethical Considerations

This study was approved by MD Anderson's institutional review board (Protocol 2021-0165). Written informed consent will be obtained from all participants. Study participant research data, which will be obtained for purposes of statistical analysis and scientific reporting, will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Participants will receive gift cards as compensation for their time and participation. Each participant will receive up to a US $35 gift card to complete a 7-day daily survey and wear an accelerometer (ie, US $5 gift card per day). Of the 7 days, participants must complete surveys and wear the accelerometer for at least 3 days to receive the compensation. Participants will also receive an additional US $15 gift card for

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completing both nutritional assessments and receive a US $40 gift card for each retrospective survey that they complete.

Results

We are currently recruiting participants, having initiated recruitment in January 2022. Recruitment and data collection are expected to conclude by December 2024 and December 2026, respectively. We expect to submit the main study results for publication in 2027.

Discussion

The aim of the proposed study is to investigate associations between stress, health behaviors, and QoL at both within- and between-person levels over the transition to survivorship in young adult survivors and their partners. To date, much is unknown regarding associations between stress, health behaviors, and QoL among young adult survivors. In particular, to the best of our knowledge, there is currently no existing study that investigates these associations among both young adult survivors and their partners. This will also be the first study that determines the interdependence of health behaviors and QoL between young adult survivors and partners, exploring how their stress levels may either facilitate or hinder their own and each other's health behaviors and QoL over the transition to survivorship.

This study has a few limitations. First, recruiting survivor-partner dyads, particularly survivors within a restricted age range (25-39 years old), can be a challenge. We will thoroughly review the recruitment progress, study refusal reasons, and work on addressing enrollment barriers. Second, participants' compliance may be a concern in this intensive longitudinal study. Over the course of the study, we will carefully monitor survey responses and consider reducing the number of retrospective or daily assessments if noncompliance is salient. Finally, this study addresses stress, health behaviors, and QoL of young adult survivors who have partners. Thus, the results of this study may not be generalized to all young adult survivors.

Despite these limitations, this study is novel and promises to generate new knowledge. Specifically, using a sophisticated research design—measurement burst—this study will allow assessment of both within- and between-person level changes in those variables and their relationships [56,57]. If the results of this study could reveal whether and on what time scales higher stress levels or certain types of stressors are associated with unhealthy behaviors and poor QoL, interventions such as just-in-time adaptive intervention [79] might be considered based on the findings. The focus on the transition to survivorship is another strength. By following up with the survivors over the course of 2 years after the completion of their cancer treatment, we can identify the time points when stress, health behaviors, and QoL begin to change (increase or decrease) during the transition. This information will help us target the right time to intervene for this understudied survivor group. Furthermore, the proposed study seeks to shift current individual-focused research in young adult survivors to relationship-focused exploration as it focuses on both survivors and their partners. Thus, the results of this study may guide the creation of a developmentally appropriate couple-based psychosocial or behavioral intervention that improves both young adult survivors' and their partners' QoL.

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Data Availability

The data sets generated during this study are not publicly available because they include sensitive information but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

LAYA-SRQL: Late Adolescence and Young Adulthood Survivorship-Related Quality of Life
PROMIS: Patient-Reported Outcomes Measurement Information System
QoL: quality of life
REDCap: Research Electronic Data Capture

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Protocol

Brief Parent-Child Substance Use Education Intervention for Black Families in Urban Cities in New Jersey: Protocol for a Formative Study Design

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Abstract

Background: Substance use continues to remain a public health issue for youths in the United States. Black youths living in urban communities are at a heightened risk of poor outcomes associated with substance use and misuse due to exposure to stressors in their neighborhoods, racial discrimination, and lack of prevention education programs specifically targeting Black youths. Many Black youths, especially those who live in urban communities, do not have access to culturally tailored interventions, leaving a critical gap in prevention. Since family is a well-known protective factor against substance misuse for Black youths, it is essential to create sustainable and accessible programming that incorporates Black youths' and their families' voices to develop a suitable prevention program for them.

Objective: We aim to understand the cultural and environmental level factors that influence substance use among Black youths and develop a prevention program to increase parent-child substance use education among Black families.

Methods: This study will take place within urban cities in New Jersey such as Paterson and East Orange, New Jersey, which will be the main study sites. Both cities have a large population of Black youths and this study's team has strong ties with youths-serving organizations there. A formative, qualitative study will be conducted first. Using the first 3 steps of the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing) framework we begin the development of an intervention for Black families. Three aims will be described: aim 1, collect qualitative data from Black parents and youths aged 11-17 years from parent-child dyads (N=20) on the challenges, barriers, and facilitators to communicating about substance use; aim 2, adapt a selected evidence-based intervention for Black families and develop a family advisory board to guide the adaptation; and aim 3 assess the feasibility of the intervention through theater testing, involving the family and community advisory board.

Results: This study is part of a 2-year research pilot study award from the National Institutes of Drug Abuse. Data collection began in May 2023, and for aim 1, it is 95% complete. All aim 1 data collection is expected to be complete by December 30, 2023. Data analysis will immediately follow. Aim 2 activity will occur in spring 2024. Aim 3 activity may begin in fall 2024 and conclude in 2025.

Conclusions: This study will be one of the few interventions that address substance use among youths and uses parents and families in urban communities as a protective factor within the program. We anticipate that the intervention will benefit Black youths not only in New Jersey but across the nation, working on building culturally appropriate, community-specific prevention education and building on strong families' relationships, resulting in a reduction of or delayed substance use.

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KEYWORDS

black families; parents; drug use; prevention; urban community

Introduction

Significance of This Study

While Black youths have lower rates of substance use than White and Hispanic youths, Black youths tend to have worse outcomes associated with substance use such as poor academic outcomes, involvement in the criminal justice system, and engaging in sexual risk behaviors while using drugs [1]. Despite the well-established association between parent-child communication and adolescent substance use, racial-specific differences among Black families compared to other racial-ethnic groups in parent-child drug use communication have received limited attention in intervention development. Thus, the adaptation of a race-specific parent-child substance use education intervention for Black families which can promote family bonding, communication, and supervision, as well as acknowledging racial and ethnic-specific norms, values, and pride, is necessary. In addition to racial stressors such as racial discrimination that Black families uniquely experience, it is essential for a racial-specific, strengths-based prevention intervention be used and adapted for urban Black youths and their families.

Background

Decades of research have established substance use as a public health concern among youths [2,3]. According to the National Survey on Drug Use and Health, approximately 24% of Black or African American people aged 12 years or older used illicit drugs in the past year, 10% were classified as having alcohol use disorder, and 10% were underage (aged 12-20 years) when drinking alcohol [4,5]. Whereas Black youths are more likely to start drinking at a later age than their peers and consume less alcohol [6,7], they also tend to experience more negative social consequences due to drinking compared to White youths [2,8,9]. Additionally, Black youths experience greater negative consequences from drug use, such as marijuana, compared to young men in other racial and similar socioeconomic status categories. Such consequences include increased accidents, illnesses, injuries, lower recovery rates from alcohol dependency, greater interpersonal issues, carceral issues, and economic challenges [10-13]. Black youths in urban settings tend to experience a unique set of stressors associated with their families, peers, and environment that in turn impact their mental health, school attendance and engagement, substance use, sexual health, and overall ways they cope with those stressors [14]. In addition to commonly cited risk factors for drug use among Black youths, especially those that live in urban communities such as exposure to community trauma, peer pressure, and neighborhood disorganization, research suggests that attending to the developmental concerns of Black youths also requires addressing the needs of the family unit [14].

Family as a Protective Factor for Black Youths

Family influences on adolescent development as well as substance use are well documented and the results across the board unsurprisingly point out that parents play a major role when it comes to affecting risk and protective behaviors [1]. In general, the more attentive, engaged, warm, protective, communicative, and close the relationship is, the more it will serve as a protective factor [1,15,16]. Parental bonding plays a protective role against youths using drugs while living in urban environments and parent-child communication is a significant protective factor for youths [15,16]. Our team found that parent-child communication about substance use and the parental modeling and communication of drug use within a neighborhood context were significant factors in reducing drug use and promoting abstinence among Black girls [17]. Other research by our team and others has demonstrated that youths report reduced use of drugs when they have positive relationships with their parents and communicate with their parents about sex [16-18]. However, very little research has specifically focused on family processes involved in drug use prevention among Black families. Salas-Wright et al [19] found that from 2002 to 2016, Black families who had lower socioeconomic status were less likely to discuss substance use education with their children. Most interventions addressing substance use have included large samples of White parents and children, which can result in gaps in prevention research focused on understanding significant cultural differences in family involvement and communication for Black families [16,20,21].

Challenges Within Black Families

While Black families are not homogenous, many Black youths who have negative consequences of drug use are exposed to traumatic conditions such as poverty, parental unemployment, parental drug use, neighborhood violence, and crime within their environments [22,23]. Within a family context, research has indicated that the more internal and external family stress that youths experience, the more elevated their mental health problems, use of drugs, and sexual risk behavior [7]. In addition, racism that Black youths and families experience can be a risk factor in Black families and a mental health stressor that can lead to substance use [23-26]. Little is known about the intersection of Black parent-child drug use communication and its influence on substance use outcomes in children. Consequently, it is essential to understand Black families' parenting practices and environment context to understand these practices' effects on youths' perception of substance use. This will avail the opportunity to create culturally sensitive and tailored interventions specifically designed to meet the unique needs of Black youths. This study protocol describes a race-specific parent-child substance use education intervention adapted for Black families called, "The Development of a Brief Parent-Child Substance Use Educational Intervention for Black

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Families." This brief intervention has the potential to guide future substance use interventions focused on Black families with a focus on strength-based and parent-child communication approaches. Considerable studies have validated that participation in culturally tailored family-centered preventative interventions for Black adolescents and their caregivers is associated with offsetting mental health risks, drug use, sexually risky behavior, and academic and behavioral challenges in Black adolescents [27-29]. There is a great need for researchers to develop culturally relevant prevention programs that are designed by and for Black families.

There is only one parent-child intervention that targets risky behaviors (ie, the Strong African American Families program [SAAF]) including substance use for Black families. To be more specific, SAAF is focused on improving family cohesion, dynamics, and communication for Black families and was adapted from the Strengthening Families Program [30]. However, it is 3 hours long and administered in 7 sessions, which may pose barriers described in detail below.

The SAAF program is one of the few prevention programs designed for Black or African American families. The SAAF program is a 7-session program designed for youths aged 10-14 years and their caregivers [30,31]. The goal of SAAF is to build on the strengths of African American families and support parents and youths during the transition from early adolescence to the teen years with a specific emphasis on helping young people avoid risky behaviors (eg, substance use). SAAF has shown positive health outcomes [27,32,33] and has been adapted to include condom education [32] and obesity and eating behaviors [34]. This study seeks to adapt the SAAF intervention to be applied in 2 urban cities in New Jersey: Paterson and East Orange, New Jersey. Both cities are considered urban and have a large population of Black people. This study's team also has long-standing partnerships with both cities and has experience in recruiting Black youths.

Barriers to Recruiting Black Families

Overview

Traditional family interventions often do not meet the needs of urban Black youths with substance use for a variety of reasons. Overall, parent interventions usually have high attrition [35]. A primary concern with the feasibility of existing parenting interventions is the difficulty ensuring that parents receive an adequate "dose" of the intervention. Adolescent substance use interventions involving parents that have been identified as "well-established" have generally ranged in intensity from 12 to 24 in-person sessions [36]. Further, studies with the highest retention rates of parents, [37] have relied upon home-based sessions or visits, an approach that is challenging to implement within residential facilities that are often short-staffed and financially constrained. Such high-contact interventions may also be difficult for parents of adolescents in substance treatment due to structural barriers related to lower socioeconomic status, such as limited transportation, lack of childcare, and competing demands [38]. Low attendance rates can be the result of busy work schedules and extracurricular activity schedules for youths, as well as a lack of motivation. While SAAF exists, there remain implementation challenges in recruitment for Black parents and children in urban communities. In studies that have used SAAF, a common challenge in scheduling has been mothers' varied work schedules [30]. Father involvement in the intervention is limited based on several studies that reported on this characteristic [39-41]. Additionally, the youths' fathers rarely participated in the prevention program even though they were invited to do so [42]. Although SAAF is a model intervention that has shown efficacy in improving knowledge, reducing risky behaviors, and improving mental health outcomes among African American families—there remain implementation challenges. For example, a 7-session intervention may not be feasible for urban Black families who are facing systemic and structural factors and are unable to commit to an intensive, time-consuming schedule. Given the knowledge researchers have on prevention interventions for Black youths and families, community-based approaches must be incorporated as community-based and culturally relevant interventions are the gold standard for urban communities [43]. Hence, the importance of adapting the intervention that can address the documented challenges and reach more Black youths and their parents.

Brief interventions, which are defined as interventions that have 4 or less number sessions, have been emerging as a strong option in substance use, frequently demanding less in terms of time and financial commitment, are one such potential resource for Black families. Brief interventions have shown efficacy in addressing youths' difficulties such as depression, anxiety, and substance use [44,45]. Specifically of substance use, meta-analytic reviews have found that brief interventions reduce risky drinking [46], and systematic reviews have found that brief-motivation building interventions are well established [36]. Our study aims are as follows:

Aim 1

We aim to collect qualitative data from Black parents and youths aged between 11 and 17 years from (N=20) parent-child dyads on the challenges, barriers, and facilitators to communicating about substance use. Recruitment will take place in partnership with community-based organizations and supportive family programs. Semistructured interviews will be conducted with adolescents and their parents to solicit their perspectives on identifiable strategies that have worked to discuss substance use within their family, barriers and facilitators to effective prevention programs, and specific community and cultural norms regarding youths' substance use.

Aim 2

We aim to adapt SAAF intervention using the first 3 phases of the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing) implementation framework, phases 1 and 2 which include a family and community advisory board (consisting of 3 parent-child dyads and 3 community leaders) will be developed to guide the adaptation of the intervention.

Aim 3

We aim to assess the feasibility of the intervention through theater testing, involving the family and community advisory

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board, we will enter step 3 of the ADAPT-ITT implementation framework.

Methods

Community Profile

Paterson, New Jersey

Paterson has a population of roughly 150,000 residents and is the third-largest city in New Jersey [47]. Over 90% of the city's population identify as either Hispanic (57.7%) or as African American or Black (34.7%) and nearly one-third are foreign-born residents [47]. The principal investigator's (PI's) work in the city shows that Paterson youths who drank alcohol during the past 30 days were 3 times more likely to smoke marijuana before being aged 14 years [48]. In terms of accessibility, 60% of Paterson youths purchased alcohol from liquor stores and 40% of Paterson adolescents also admitted to having adults purchase their alcohol from liquor stores [48]. Additionally, the city is currently facing an extreme opioid crisis with Paterson being ranked the 2nd city in New Jersey for the highest rate of heroin overdoses [49].

East Orange, New Jersey

East Orange is an urban city also located in Northeastern New Jersey and just 20 minutes away from Paterson. The city has one of the highest rates of drug overdoses in New Jersey and lacks youths' substance abuse rehabilitation and treatment centers [49]. East Orange also has the highest amount of Black people in the state of New Jersey (85%) [50]. In 2020, a total of 2434 (34%) of Essex County residents admitted for substance abuse treatment were female, 4375 (61%) were Black (non-Hispanic), and 31% of residents were aged younger than 18 years [51]. In our work with the city of East Orange, we conducted a qualitative study in East Orange, New Jersey, with a sample of 45 Black teen girls from the city who participated in focus groups with this study's team. Themes that arose involved (1) drug use being a major problem in their community, (2) peer pressure and mental health as a major risk factor, and (3) exposure to drugs in specific neighborhoods as an issue.

Framework for Adaptation

The ADAPT-ITT model is an implementation science framework that guides the adaptation of evidence-based interventions (EBI) for specific settings or populations [39,52]. ADAPT-ITT will be used to adapt the target interventions in partnership with a family and community advisory board, consisting of parents, caregivers, and leaders of family-based organizations in New Jersey.

The framework consists of 8 phases, each of which brings contextual nuances and constraints that determine how the phases are engaged and the timing of corresponding tasks: (1) assess the risk profile of Black families in participating cities: Paterson and East Orange, (2) decide on whether to adopt or adapt an EBI, (3) administer novel methods such as theater testing with families and children to facilitate the adaptation process, (4) plan on what aspects of the EBI need to be adapted and plan on how best to evaluate the adapted EBI, (5) identify additional topic experts to assist in the adaptation process, (6) integrate material from the topic experts to adapt the EBI, (7) train staff to implement the adapted EBI, and (8) test the adapted EBI.

Given the time and financial consideration, we will complete the first 3 tasks at the end of the pilot study. Using the ADAPT-ITT approach, we will first consult with Black families and stakeholders in cities that include a large population of Black people in New Jersey such as Paterson and East Orange to understand their unique challenges in discussing substance use with their children while also seeking their guidance on the development of a racial specific substance use parent-child intervention. A proactive approach, rather than a reactive approach, in the recruitment and retention of minority populations in research is necessary to build trust through community involvement, adapt to cultural norms, develop effective recruitment strategies, and through use of evidence-based practices to engage and retain participants effectively [53]. Therefore, we will use a proactive approach to recruit study participants, which will bring project staff into direct contact with potential participants [53]. This typically involves face-to-face contact with community leaders and organizations, as well as recruitment presentations and meetings in the community.

Study Design

We will conduct a formative qualitative study design consisting of semistructured individual interviews with (N=20) dyads of Black parents and their children. Qualitative data that will be collected from individual dyad interviews (parent-child) with Black families and children will be used to inform the data. Specifically, the research team will identify themes from data that center around challenges and barriers to drug use education and discussion within the family context and also will ask participants to provide examples of what they would like to see in a family-centered substance use intervention for Black families.

Eligibility

A parent who identifies as (1) Black, (2) of any age, (3) speaks and understands English, (4) resides in the state of New Jersey, and (5) has a child who identifies as follows. The child must identify as (1) Black, (2) aged between 10 and 17 years, (3) speaks and understands English, and (4) resides in a city that is classified as "urban" in the state of New Jersey. While our study team is primarily focusing on targeting 2 cities: Paterson and East Orange, based on need and our community partnerships, we are also open to including youths and families from other urban cities in New Jersey. The parent and child dyad must meet all criteria to be eligible for this study.

Ethical Considerations

This study was funded by a larger National Institute on Drug Abuse grant and approved by the Yale University Institutional Review Board in 2022 (2000032674). Due to the sensitivity of the research questions, we requested that written parental consent for youths younger than 18 years be waived for parents and youths and it was granted. All youths who participate in this study will receive a youths' information sheet, and parents and guardians will receive a parent information sheet. Youths

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must give verbal consent to participate in this study. We will obtain informed consent from all youths who meet the eligibility criteria and want to participate before they are enrolled in study activities. All participants will be paid US $50.00, in cash, at the end of each interview.

Aim 1

Overview

We aim to collect qualitative data from Black parents and youths aged between 11 and 17 years from parent-child dyads on the challenges, barriers, and facilitators to communicating about substance use.

Recruitment

Participation in this study will be strictly voluntary, confidential, and nondiscriminatory. This study will be advertised via posters and flyers located and circulated through community-based organizations, schools, and supportive family programs with which the PI has partnered. In addition, individual interviews with participants will also be recruited using social media sites, including Facebook, Instagram, and Twitter as needed. The PI and her research team are well known in the State of New Jersey and have strong partnerships with cities that have large Black populations such as East Orange and Paterson, New Jersey. During the duration of this study and afterwards, the PI and her research team still intend to conduct workshops and seminars about prevention for youths and girls and dissemination of research about the youths of color and parents specifically. The PI will continue to provide free workshops to youths and their families even if the youths refuse to participate in this study. We will first recruit parents through community organizations and at parent nights at local schools and then will recruit youths once data collection for parents has been completed. The second method of recruitment for this study will be with social media sites, including Facebook, Instagram, and Twitter. Participants will be asked to click on a link in the advertisement, which will take them to the Qualtrics (Qualtrics) web page where they will fill out a form with basic demographic information (age and race) and the parents' contact information (email and phone number). If participants meet eligibility criteria, a research staff member will contact the potential participant through email to send the information sheet for them to review and set up a time to contact them by phone to review this study and obtain verbal consent. If either the caregiver or the parent does not wish to be in this study or have their child participate in this study, no further contact will be made.

Individual interviews with parents and children will take place in 2 locations: through Zoom (Zoom Video Communications, Inc) where participants will be able to see and interact with each other, and in person with the aid of the community partners' space. Parents and children will be interviewed separately. Members of the research team will have prolonged engagement within the community to establish trust with participants. As of December 2023, recruitment for this study began in May 2023 and is 95% completed.

Qualitative Interview Outcomes

Qualitative methodology allows participants to discuss their lived experiences and can account for specific details that quantitative methods may not be able to attain. The research team will conduct semistructured individual interviews. Research questions will address the factors that contribute to substance use among youths in urban cities. The interview guide will consist of questions about substance use perception and knowledge, parent-child relationships, and their perception of educational resources for Black families.

Qualitative methodology allows for participants to discuss their lived experiences and can account for specific details that quantitative methods may not be able to attain. Research questions will address the unique contextual factors that contribute to substance use in Paterson (or East Orange), challenges in discussing substance use within their families and understanding what they would like to see in a parent-child substance use prevention intervention for Black families in their community. This component of this study focuses on three specific research questions: (1) What are the social and environmental contexts of substance use initiation? (2) What are the challenges to discussing substance use within the Black family? (3) What specific components do Black families need in a substance use prevention intervention in Paterson?

In qualitative research, data collection and data analysis occur inductively through the identification of recurring themes and patterns in transcripts, field notes, and analytic memos. A thematic analysis framework will be used for this study [54]. The thematic analysis allows researchers to highlight similarities and differences across groups of participants. The research staff will work from an essentialist or realist perspective that assumes participants' language reflects their experiences, meanings, and realities [54]. Meaningful analytical units will then be developed by using a coding scheme informed by dominant themes in the data. Topics will then be divided into several subtopics based on recurring themes within the larger topics, allowing for more in-depth analysis and complex understanding and interpretation of each theme. Each theme and subtheme will be assigned a code, and the codes will be compiled in a codebook.

A confirmability audit will be conducted where multiple coders will be used to analyze the data. Data from the interviews will first be analyzed by interviewers using open coding, whereby concepts were identified and labeled as they emerged from the data and across the interviews. Interviews will be transcribed and analyzed using NVivo (version 12; QSR International) software. The coding process will be inductive in nature and consist of categorization and grouping. Line-by-line coding will be used, and common themes will be grouped using a coding map created from NVivo to conceptualize the themes. At least a 90% interrater reliability will be achieved before codes and categories are developed. The categories that will be developed from the coding process will not be predetermined but rather formed during the coding process. After the initial coding of the data, the research team will summarize and organize the results in NVivo [55].

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Aim 2

Overview

We aim to adapt a family and community-based substance use prevention intervention for Black youths and families, which includes a family and community advisory board to guide the adaptation of the intervention.

Family and Community Advisory Board

After qualitative interviews, participants will be asked if they would like to be a member of the family-community advisory board, consisting of parents, caregivers, and leaders of family-based organizations in New Jersey. If the participant is interested, the research assistant will discuss this study with the guardian or parent and obtain informed written assent from the participants. For the focus group and individual interviews, the research assistant will discuss this study with the guardian or parent and obtain verbal assent from the participants. In describing this study to the participants, the purpose of this study will be to provide a strengths-based approach to build on the strengths of African American families and support parents and youths during the transition from early adolescence to the teen years with a specific emphasis on helping young people avoid dangerous behaviors (eg, substance use). If a participant or their guardian or parent indicates that they do not wish to participate, there will be no further involvement in this study. We will also obtain agreement from the appropriate administrator at the participating program. Findings from the qualitative study and approval from the board will aid in the adaptation of the intervention. Based on the current literature on Black families and available interventions, our study team decided to adapt an intervention that has been delivered to Black families: SAAF.

Intervention to Review and Adapt: SAAF Program

The SAAF program is an innovative preventative intervention program for African American youths and their families. This intervention translated research that identified racial discrimination on Black youths frequently developed into poor mental health, depression, early sexual activity, alcohol use, drug misuse, and behavioral issues [27]. Black youths who did not experience these negative health outcomes had supportive family relationships including emotional support, communicative parents, and high levels of potential control, which was identified as a protective factor [27]. While the initial SAAF program was designed for rural African American youths, it has since been successfully adapted across rural and urban settings. The intervention consists of 7 weekly gatherings lasting 2.5 hours in which caregivers and adolescents engage in discussions and activities led by community members. Caregivers focus on involved caregiving practices and providing consistent support to their adolescents. Adolescent topics include goal setting for the future, understanding who they are, dealing with early sexual desire, values, strategies for resisting peer pressure, and making good friends and choices. Caregiver topics include supporting adolescents, strict parental control, daily parenting, helping children achieve academically, encouraging racial pride, protection against negative behaviors, and maintaining adolescent-caregiver connection [28].

Aim 3

To assess the feasibility of the intervention through theater testing, involving the family and community advisory board, we will enter step 3 of the ADAPT-ITT implementation framework.

In this aim, we will use theater testing, an innovative methodology to pretest our EBI, with the feedback of stakeholders, including this study's team and advisory board, for intervention adaptation. Theater testing is commonly used for product testing in the areas of public service announcements; and television, video, and print advertisements [39]. ADAPT-ITT recommends no more than 5-20 participants to be involved in theater or pilot testing to receive adequate feedback and make substantive change in the intervention [52]. Out of 40 participants (20 parents and 20 children), we will invite 10-20 parent-child participants for theater testing. Participants will receive a demonstration of the product, in this case, the adapted intervention. Participants will then receive a questionnaire to provide feedback on their experience of the intervention. Documentation of participants' interaction and reactions to information and visual materials in a constrained time frame is a significant strength of theater testing. As the theater testing population is similar to the target population, this assessment will provide accurate information about the product (intervention).

Results

This study is part of a 2-year research pilot study award that received funding from the National Institute on Drug Abuse. Data collection for this study began in May 2023. The remaining year will focus on completing data collection, analysis, forming the family and community advisory board, and dissemination of results, and developing the intervention components. Moreover, data collection for aim 1 is 95% complete. We expect to complete all data collection for aim 1 on or before December 30, 2023. We will begin analyzing the data and consulting with our family and community advisory board beginning in February 2024. This study is funded by a research education grant from the Family Involvement in Recovery Support and Treatment Research Network, which is cofunded by the National Institute on Drug Abuse and National Institute of Neurological Disorders and Stroke (PI: AH: R24DA051946). The protocol outlines a pilot study funded through the research education grant (PI: IO). IRB approval was given in July 2022.

Discussion

Principal Findings

The goal of this study is to adapt a race-specific parent-child substance use education intervention for Black families living in urban cities in New Jersey which can promote family bonding, communication, and supervision, as well as acknowledge racial and ethnic-specific norms, values, and pride. The adaptation of this intervention will be co-designed based on the input of Black parents and their children and stakeholders. Through this approach, researchers will have an in-depth understanding to adapt evidence-based substance abuse prevention interventions

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for Black families' parenting practices and environmental context. Other studies have demonstrated that youths report reduced use of drugs when they have positive relationships with their parents and communicate with their parents about sex and drugs [16-18]. While limited research has specifically focused on family processes involved in drug use prevention among Black families solely, we anticipate reduced rates of substance use with positive parent-child communication drugs. We anticipate that study findings will provide more context on specific barriers that Black families face in their community around preventing drug use among their children. In addition, we anticipate that study findings will enhance this study team's knowledge of potential facilitators of substance use discussions that can be used in prevention interventions.

Further implications include an integrated community and health care provider approach to incorporate nurses within the school-based health setting and pediatric primary care settings. As nurses serve as members of one of the most trusted professions, nurses are positioned to positively influence outcomes with young Black youths as they can provide health care–related education, health promotion, prevention, and support through necessary medical treatment. By including medical and nursing professionals in this work, this project plans to take a more holistic approach to understanding the foundations of substance use and prevention in Black youths while building a community with parents and families. Nurse roles will help to expand the creation of a plan that maintains consistent outreach and sustainability by providing students with multiple opportunities to receive education and resources to integrate into the school culture.

Study Limitations

This is a formative study using qualitative individual interviews as a methodology. A limitation of this study is that data will be collected via self-report and subject to response bias.

Conclusions

This study aims to provide environmental level and culturally specific implications in implementation science regarding the use of adapted substance use prevention interventions guided by Black families, for Black families living in urban neighborhoods. The evidence from this study will be used for the preparation of a feasibility trial and a more robust and larger parent-children drug use prevention clinical trial specifically for Black families.

Acknowledgments

This study is funded by a research education grant from the Family Involvement in Recovery Support and Treatment Research Network, which is cofunded by the National Institute on Drug Abuse and National Institute of Neurological Disorders and Stroke (PI: AH: R24DA051946). The first author is funded by the National Institutes of Health Early Independence Award (PI: IO; DP5OD029636) and the National Institute on Drug Abuse Pioneer's Award (PI: IO; DP1DA058982).

Data Availability

The data sets generated and analyzed during this study are not publicly available due to confidential reasons but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Reviewers summary statement.
[PDF File (Adobe PDF File), 36 KB - resprot_v13i1e55470_app1.pdf]

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Abbreviations

ADAPT-ITT: Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing
EBI: evidence-based intervention
PI: principal investigator
SAAF: Strong African American Families

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Protocol

Assessing Functional Capacity in Directly and Remotely Monitored Home-Based Settings in Individuals With Chronic Respiratory Diseases: Protocol for a Multinational Validation Study

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Abstract

Background: Pulmonary rehabilitation is widely recommended to improve functional status and as secondary and tertiary prevention in individuals with chronic pulmonary diseases. Unfortunately, access to timely and appropriate rehabilitation remains limited. To help close this inaccessibility gap, telerehabilitation has been proposed. However, exercise testing is necessary for effective and safe exercise prescription. Current gold-standard tests, such as maximal cardiopulmonary exercise testing (CPET) and the 6-minute walk test (6MWT), are poorly adapted to home-based or telerehabilitation settings. This was an obstacle to the continuity of services during the COVID-19 pandemic. It is essential to validate tests adapted to these new realities, such as the 6-minute stepper test (6MST). This test, strongly inspired by 6MWT, consists of taking as many steps as possible on a "stepper" for 6 minutes.

Objective: This study aims to evaluate the metrological qualities of 6MST by (1) establishing concurrent validity and agreement between the 6MST and CPET, as well as with the 6MWT; (2) determining test-retest reliability in a home-based setting with direct and remote (videoconferencing) monitoring; and (3) documenting adverse events and participant perspectives when performing the 6MST in home-based settings.

Methods: Three centers (Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec in Québec, Groupement des Hôpitaux de l'Institut Catholique de Lille in France, and FormAction Santé in France) will be involved in this multinational project, which is divided into 2 studies. For study 1 (objective 1), 30 participants (Québec, n=15; France, n=15) will be recruited. Two laboratory visits will be performed to assess anthropometric data, pulmonary function, and the 3 exercise tolerance tests (CPET, 6MWT, and 6MST). Concurrent validity (paired sample t tests and Pearson correlations) and agreement (Bland-Altman plots with 95% agreement limits) will be evaluated. For study 2 (objectives 2 and 3), 52 participants (Québec, n=26; France, n=26) will be recruited. Following a familiarization trial (trial 1), the 6MST will be conducted on 2 separate occasions (trials 2 and 3), once under direct supervision and once under remote supervision, in a randomized order. Paired sample t test, Bland-Altman plots, and intraclass correlations will be used to compare trials 2 and 3. A semistructured interview will be conducted after the third trial to collect participants' perspectives.

Results: Ethical approval was received for this project (October 12, 2023, in Québec and September 25, 2023, in France) and the first participant was recruited in February 2024.

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Conclusions: This study innovates by validating a new clinical test necessary for the development and implementation of new models of rehabilitation adapted to home and telerehabilitation contexts. This study also aligns with the United Nations Sustainable Development Goals by contributing to augmenting health care service delivery (goal 3) and reducing health care access inequalities (goal 11).

Trial Registration: ClinicalTrials.gov NCT06447831; https://clinicaltrials.gov/study/NCT06447831

International Registered Report Identifier (IRRID): DERR1-10.2196/57404

(JMIR Res Protoc 2024;13:e57404) doi:10.2196/57404

KEYWORDS

chronic obstructive pulmonary disease; COPD; exercise capacity test; interstitial lung diseases; physiotherapy; rehabilitation; telerehabilitation; validation study; stepper test

Introduction

Background

Recent guidelines strongly recommend pulmonary rehabilitation for individuals with stable or acutely exacerbated chronic obstructive pulmonary disease (COPD) or with interstitial lung disease (ILD) [1]. Unfortunately, access to rehabilitation care remains limited in many countries, including Canada and France. Indeed, the latest available estimates indicate that only 0.4% of individuals in Canada and 8.6% of individuals in France with COPD have access to pulmonary rehabilitation programs [2,3]. The development of new and innovative health care models, including in rehabilitation, is urgently needed to address this health care gap that is only expected to worsen with the aging populations in most advanced economies [2,4]. Home-based rehabilitation and telerehabilitation are now increasingly considered as a solution to increase rehabilitation access in this population [1,4,5]. These programs are cost-effective alternatives to traditional ambulatory pulmonary rehabilitation models anchored in specialized hospital institutions [6,7]. Moreover, the effectiveness of home-based rehabilitation and pulmonary telerehabilitation programs has been demonstrated and is comparable to traditional rehabilitation models in individuals with COPD [8]. Yet, clinicians report the lack of validated functional exercise capacity tests for these new models of care as a major barrier for their implementation [9,10]. These tests are important to ensure safe, effective, and personalized exercise prescription during rehabilitation, and to monitor and document its effects [11,12].

The current gold standard for exercise capacity testing is maximal cardiopulmonary exercise testing (CPET), which is generally conducted on a cycle ergometer or a treadmill. These tests are designed to assess maximal physiological responses to exercise and thus require expensive equipment (eg, gas exchange analyzer and electrocardiogram) that are not easily accessible outside of specialized institutions. Moreover, these tests are not always representative of functional activities in daily life (eg, cycling may not be an activity of daily life for many individuals) [13]. Thus, functional capacity tests have been widely adopted in ambulatory rehabilitation settings [13,14]. To this effect, the 6-minute walk test (6MWT), which only requires an unobstructed corridor (≥30 meters), is among the most widely used [13,15]. Despite its simplicity, the 6MWT is not adapted to the realities of home-based and telerehabilitation settings. Indeed, limited available space inhibits its realization and has been highlighted as a barrier to the continuity of rehabilitation services during the COVID-19 pandemic [9]. It is therefore essential to validate functional capacity tests adapted to this new reality, such as the 6-minute stepper test (6MST). This test, strongly inspired by 6MWT, consists of taking as many steps as possible on a “stepper” for 6 minutes [16,17].

In individuals with COPD, initial studies indicate that the 6MST is reliable, as no significant difference in test results was found when repeated on consecutive days in a laboratory setting [16]. The 6MST is also valid, as the number of steps taken during the test is correlated with the total distance traveled during the 6MWT (r=0.56-0.87, P<.01), peak power during CPET (r=0.46, P<.01), and peak oxygen consumption during CPET (r=0.39, P<.01) [17,18]. Responsiveness to change following pulmonary rehabilitation has also been shown, with a minimally important difference estimated at 40 steps [19]. Finally, predictive equations have been computed to individualize aerobic training intensity using the 6MST [20]. However, to our knowledge, cardiorespiratory responses during the 6MST in individuals with COPD have not been formally compared with those during the 6MWT and CPET to date. This is particularly important when considering the development of home-based and telerehabilitation programs, as different cardiorespiratory responses to testing may elicit safety concerns. In individuals with ILD, there is limited evidence regarding the validity of the 6MST, as the number of steps taken during the test is correlated with the total distance traveled during the 6MWT (r=0.70, P<.01) [21]. Interestingly, in individuals with ILD, cardiorespiratory responses during the 6MST have been compared with the 6MWT. In this population, the 6MST leads to greater heart rate and ventilatory responses, and blood oxygen saturation remains higher during the 6MST [21,22]. Finally, as the 6MST has only been validated in laboratory or hospital settings, metrological properties in home-based settings with direct or remote (ie, videoconferencing) monitoring are currently unknown in individuals with COPD or ILD.

Objectives and Hypotheses

Overview

The overall aim of this project is to provide further evidence regarding the metrological properties of the 6MST in individuals with COPD or ILD. Specific objectives and hypotheses are described below.

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Objective 1

Objective 1 is to determine concurrent validity and the level of agreement (or bias) between peak cardiorespiratory responses and reported symptomology during the 6MST and CPET and the 6MST and 6MWT. The corresponding hypotheses are that peak cardiorespiratory responses and reported symptomology to the 6MST will be strongly correlated to those measured during CPET and the 6MWT (ie, concurrent validity), and that these values will be systematically lower than those measured during CPET (ie, presence of bias), but similar to those measured during the 6MWT (ie, no bias).

Objective 2

Objective 2 is to determine test-retest reliability for the 6MST in home-based settings under direct and remote (ie, videoconferencing) monitoring. The corresponding hypothesis is that measurement error will be minimal and intraclass correlations will be good and similar between direct and remote supervision.

Objective 3

Objective 3 is to determine the safety and the perception of the 6MST in individuals with chronic pulmonary diseases in home-based settings under direct and remote monitoring by collecting adverse events and qualitative feedback. The corresponding hypothesis is that the test will be safe (ie, absence of serious adverse events) and individuals will report a good level of overall satisfaction with the test, irrespective of the type of supervision.

Methods

Research Design

This research project comprises 2 studies resulting from an international collaboration between the Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec (CR-IUCPQ, Université Laval, Canada), the Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL, France), and FormAction Santé (France). Study 1 (objective 1) is a prospective, multicentric, quantitative, and validation study realized in an outpatient hospital setting at the CR-IUCPQ and the GHICL. Study 2 (objectives 2 and 3) is a prospective, multicentric, mixed methods, and validation study realized at the participants' homes in Québec (CR-IUCPQ) and in northern France (FormAction Santé).

Participants and Inclusion and Exclusion Criteria

A quota sampling method, based on disease and sex (ie, 1:1), will be used. All sample sizes were calculated a priori with an open-source calculator available on the internet or SPSS (IBM) [23]. Inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adults ≥40 years old
- Diagnosis of chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease Diagnostic Criteria 2 to 4) or of interstitial lung disease (>6 months)
- Clinically stable for ≥4 weeks

Exclusion criteria

- Interstitial lung disease associated with connective tissue disease and sarcoidosis (often accompanied by multisystemic effects)
- Unstable or severe cardiac condition
- Invalidating rheumatologic or neurologic condition
- Weight exceeding maximal limits of exercise equipment (eg, 130 kg for the stepper)
- Any other physical or medical condition limiting or contraindicating exercise testing
- Simultaneous participation in another study requiring changes in medication
- Recent pulmonary rehabilitation (≤1 year, potential learning bias for the 6-minute walk test and the 6-minute stepper test)
- For study 1 only: use of oxygen therapy (unable to provide oxygen therapy during testing due to limitation of gas exchange analysis equipment)
- For study 2 only: participation in study 1

For study 1, a mean difference of 0.28±0.32 L/min in maximal oxygen uptake between the 6MST and CPET was assumed, based on previous studies between the 6MWT and CPET [22,24]. To detect a difference of this amplitude with a paired sample *t* test, assuming a power of 80%, an α level of .05, and a dropout rate of 15%, 15 participants are needed. Fifteen individuals of each disease population (ie, COPD, n=15; ILD, n=15) will be included for a total sample of 30 participants (Québec, n=15; France, n=15), as cardiorespiratory responses to exercise are different among these populations [25].

For study 2, a minimal acceptable intraclass correlation coefficient of 0.5, and an expected intraclass correlation coefficient of 0.75, were assumed for the test-retest reliability of the 6MST. Assuming a power of 80%, an α level of .05, and a dropout rate of 15%, 52 participants (Québec, n=26; France; n=26) will be recruited. This calculated sample was taken as a

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whole, as test-retest reliability is not expected to be influenced by the type of respiratory disease.

Study 1: Procedures and Measurements

For study 1, in addition to a review of medical records, two 3-hour laboratory visits (separated by 6-18 days) will be conducted. Participants will be instructed to take all medications as usual, including inhalers. A summary of collected data and outcomes is presented in Table 1.

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Table 1. Data collected during study 1.

Measurements	Medical records	Visit 1	Visit 2
Sociodemographic			
Age	✓		
Sex	✓		
Pulmonary diagnosis	✓		
Comorbidities and risk factors	✓		
Anthropometric			
Mass (kg)		✓	
Height (m)		✓	
Composition (bioimpedance)		✓	
Leg length (cm)		✓	
Pulmonary function			
Spirometry		✓	
Plethysmography		✓	
DLCO[a]		✓	
CPET[b] on cycle ergometer			
Dyspnea (/10)[c]		✓	
Leg fatigue (/10)[c]		✓	
Absolute oxygen uptake (L/min)		✓	
Relative oxygen uptake (mL/kg·min)		✓	
Carbon dioxide excretion (L/min)		✓	
Minute ventilation (L/min)		✓	
Tidal volume (L)		✓	
Respiratory rate (breath/min)		✓	
Heart rate (bpm)		✓	
Blood oxygen saturation (%)		✓	
Blood pressure (mm Hg)		✓	
Québec only: inspiratory capacity (pre and post)		✓	
6MWT[a]			
Total distance traveled (m)			✓
Identical measurements as CPET			✓
6MST[e]			
Total number of steps			✓
Identical measurements as CPET			✓

[a]DLCO: diffusing capacity of the lungs for carbon monoxide.

[b]CPET: maximal cardiopulmonary exercise testing.

[c]/10: modified Borg Scale rating.

[d]6MWT: 6-minute walk test.

[e]6MST: 6-minute stepper test.

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Review of Medical Records

Medical records will be reviewed, and the information retrieved regarding participant sociodemographic characteristics will be age, sex, pulmonary diagnosis, medications, comorbidities, and cardiovascular risk factors. Physical activity level will be assessed using the Ricci and Gagnon questionnaire [26].

First Laboratory Visit

During the first laboratory visit, anthropometric measurements, pulmonary function tests, and CPET on a cycle ergometer will be performed.

Anthropometric Measurements

Anthropometric measurements will be composed of body mass, height, body composition (ie, lean and fat mass), and leg length. A standardized medical scale and stadiometer will be used to measure body mass and height, respectively. Body composition will be estimated by bioimpedance [27]. Leg length will be measured using a standard tape measure from the anterior superior iliac spine to the medial malleoli [28,29]. The mean of two measurements of the right leg will be used [28,29].

Pulmonary Function

Pulmonary function will be characterized by spirometry, lung volume assessment (plethysmography), and diffusing capacity of the lungs for carbon monoxide, following current guidelines [30-32]. Spirometry will be conducted first [30]. After a period of quiet breathing, participants will be instructed to inhale to total lung capacity and exhale quickly and forcefully to residual volume. Forced vital capacity and forced expiratory volume in 1 second will be recorded. The test will be repeated until an agreement of at least 5% is obtained for 3 measures of forced vital capacity. The mean values of these 3 tests will be recorded (forced vital capacity and forced expiratory volume in 1 second) [30]. Plethysmography will be conducted second [31]. Participants will be instructed to breathe quietly, hands on their cheeks, until end-expiratory lung volume is stable. The shutter will be closed near functional residual capacity, and participants will be instructed to conduct a series of gentle pants (between 0.5 and 1 Hz) in order to obtain at least 3 with adequate technique. The shutter will then be opened, and the participant will exhale to residual volume, followed by an inspiratory slow vital capacity maneuver. The test will be repeated until an agreement of at least 5% is obtained for 3 measures of functional residual capacity. The mean value of these 3 tests will be recorded (total lung capacity, slow vital capacity, inspiratory capacity, functional residual capacity, expiratory reserve volume, and residual volume) [31]. The diffusing capacity of the lungs for carbon monoxide will be measured third [32]. After a period of relaxed tidal breathing, participants will exhale slowly to residual volume, followed by a rapid inhalation to total lung capacity during which a standardized gas mixture will be provided (carbon monoxide, methane, oxygen, and nitrogen). Participants will be instructed to hold their breath for 8 to 12 seconds before exhaling to residual volume. The test will be repeated following a 4-minute rest period. At least 2 acceptable tests will be obtained [32].

Maximal Cardiopulmonary Exercise Testing

CPET will be performed on a cycle ergometer (Quinton Corival 400 in Québec and Ergoline Ergoselect 200 in France) in accordance with the current recommendations [33]. The protocol used is presented in Textbox 2. Briefly, following a warm-up, the work rate will increase by 10 to 15 watts per minute, following a ramp protocol, until the criteria for maximality is reached. The criteria for maximality will be those recommended by the American College of Sports Medicine and include abnormal cardiovascular responses or signs of ischemia, signs or symptoms of cerebral hypoxemia, marked pulsed blood oxygen desaturation (SpO_2≤80%), and at the request of the participant [34]. Participants will be asked to maintain a pedaling rate of 60±5 revolutions per minute. The modified Borg scale (/10) will be used to assess dyspnea and leg fatigue at rest before the test, during (every 2 minutes and at peak exercise), and after the test (5 minutes following the end of the test). Cardiorespiratory responses during the CPET will be monitored continuously using a breath-by-breath gas analyzer (Oxycon Mobile in Québec and Metamax 3B Cortex in France), an electrocardiogram, and an oximeter (Nonin). This equipment will provide data for absolute and relative oxygen uptake, carbon dioxide excretion, minute ventilation, tidal volume, respiratory rate, heart rhythm and rate, and pulsed oxygen saturation (SpO_2). Blood pressure will be measured manually before and after the test. In Québec only, inspiratory capacity will be measured before and within 10 seconds of the end of the test (sitting on the cycle ergometer and hands gripping the handlebars) and a reduction of more than 150 mL will confirm the occurrence of dynamic hyperinflation [35].

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Textbox 2. Protocol for CPET on the stationary cycle ergometer.

Resting phase

- Duration: ≥3 minutes (following equipment set-up)
- Resting measurements recorded during the last minute of this phase

Warm-up phase

- Duration: 3 minutes following resting phase
- Warm-up at an equivalent of 20 watts and at a pedaling rate of 60±5 revolutions per minute

Incremental phase

- Duration: 8 to 12 minutes
- Work rate: start at 20 watts and increase by 10 to 15 watts per minute (ramp)
- Pedaling rate: 60±5 revolutions per minute (stop test if individual falls under 50 revolutions per minute)

Recovery phase

- Total duration: 5 minutes
- Active phase (pedaling at 20 watts) for 2 minutes, followed by passive phase (quiet sitting) for 3 minutes

Monitoring

- Continuous: breath-by-breath gas analysis, electrocardiography, peripheral oxygen saturation (stop test if pulsed oxygen saturation ≤80% with symptoms, such as dizziness, nausea, etc)
- During the last minute of the unloaded phase, every 2 minutes during the incremental phase, immediately at completion, and at 5 minutes of the recovery phase: blood pressure, dyspnea (/10), and leg fatigue (/10)
- Pre- and postincremental phase (Québec only): inspiratory capacity

To address current international recommendations that require the test to be repeated twice, the first laboratory visit will end with a familiarization trial of the 6MWT for individuals who have not done the test during the previous 12 months (the 6MWT is routinely conducted during medical follow-ups in the centers in this study) [36,37]. Data from this familiarization trial will not be recorded (although vital signs will be monitored for safety).

Second Laboratory Visit

During the second laboratory visit, spirometry will be repeated to ensure the stability of the participants' health state (particularly relevant for individuals with COPD). Thereafter, the 6MST and 6MWT will be performed in a randomized order, separated by a rest period of at least 30 minutes.

The 6MWT will be performed in a leveled, unobstructed corridor in accordance with current recommendations [36,37]. Briefly, the 30-meter testing area will be marked at both extremities with brightly colored cones. Standardized instructions will be given before beginning the test, and standardized encouragements will be provided every minute during (see Textbox 3 for instructions in French used in this study) [36]. The total distance traveled will be collected to the nearest meter. Dyspnea, leg fatigue, and cardiorespiratory responses will be collected as described previously.

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Textbox 3. Standardized instructions and encouragements during the 6-minute walk test. See Multimedia Appendix 2 for the English version.

Standardized instructions in French

Le but de ce test est de marcher la plus grande distance possible pendant 6 minutes. Vous devrez réaliser des allers-retours dans ce couloir. Six minutes, c'est une longue durée, vous risquez de vous essouffler et de vous fatiguer. Vous pouvez choisir de ralentir ou d'arrêter, si nécessaire. Vous pouvez vous appuyer contre le mur pour vous reposer, mais recommencer la marche dès que possible.

Vous ferez des allers-retours en contournant les cônes orange. Vous devriez faire des virages rapides afin de poursuivre dans la direction opposée sans hésitation. Je vais vous montrer comment faire le virage, regardez-moi. (Démonstration)

Êtes-vous prêts à faire le test? Je vais compter le nombre d'aller-retour que vous faites et je vous dirai la durée restante toutes les minutes. Rappelez-vous, l'objectif du test est de marcher la plus grande distance possible pendant 6 minutes, mais vous ne devez pas courir. Je vais compter à trois et dire « GO ». Partez lorsque je dis « GO ».

Standardized encouragements in French

- C'est bien. Il vous reste 5 minutes.
- Continuez comme ça. Il vous reste 4 minutes.
- C'est bien. Vous avez fait la moitié.
- Continuez comme ça. Il vous reste seulement 2 minutes.
- C'est bien. Il vous reste seulement 1 minute.

The 6MST will be performed in accordance with the original description [16]. The test consists of taking the maximum number of steps on a stepper in 6 minutes. One step is counted for each complete flexion-to-extension movement of a lower extremity. The stepper used will be standardized and identical for all participants (Zinnor Mini Multifunctional Fitness Stepper [Zinnor] in Québec and Athletic Go Sport in France). Participants will be able to lightly touch a stable surface (ie, a wall) for balance, if needed. Participants will be allotted a 2-minute familiarization period, followed by rest (≥3 minutes seated), then will begin the test. Standardized validated instructions and encouragements, adapted from those of the 6MWT, will be provided (Textbox 4) [16,38]. Evaluators will ensure that complete lower extremity extension is reached during every step. The total number of steps will be automatically provided by the stepper. Dyspnea, leg fatigue, and cardiorespiratory responses will be collected as described previously.

Textbox 4. Standardized instructions and encouragements during the 6-minute stepper test. See Multimedia Appendix 3 for the English version.

Standardized instructions in French

Le but de ce test est de réaliser le plus grand nombre de pas possible pendant 6 minutes. Six minutes, c'est une longue durée, vous risquez de vous essouffler et de vous fatiguer. Vous pouvez choisir de ralentir ou d'arrêter, si nécessaire. Vous pouvez vous appuyer contre le mur pour vous reposer, mais recommencer l'exercice dès que possible.

Vous devez étendre complètement la jambe pour réaliser chaque pas. Le step doit toucher la base du stepper à chaque pas. Je vais vous montrer le bon mouvement, regardez-moi. (Démonstration)

Êtes-vous prêts à faire le test? L'appareil va compter le nombre de pas que vous faites et je vous dirai la durée restante toutes les minutes. Rappelez-vous, l'objectif du test est de réaliser le plus grand nombre de pas pendant 6 minutes. Je vais compter à trois et dire « GO ». Partez lorsque je dis « GO ».

Standardized encouragements in French

- C'est bien. Il vous reste 5 minutes.
- Continuez comme ça. Il vous reste 4 minutes.
- C'est bien. Vous avez fait la moitié.
- Continuez comme ça. Il vous reste seulement 2 minutes.
- C'est bien. Il vous reste seulement 1 minute.

Study 2: Procedures and Measurements

For study 2, in addition to a review of medical records, three 1-hour home visits (separated by 2-5 days) will be conducted. Participants will be instructed to take all medications as usual, including inhalers. Individuals who participated in study 1 will not be admissible for study 2 to reduce the risk of bias introduced by a possible learning effect with the 6MST. A summary of collected data and outcomes is presented in Table 2 and further described below.

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Table 2. Data collected during study 2.

Measurements	Medical records	Trial 1	Trial 2	Trial 3
Sociodemographic				
Age	✓			
Sex	✓			
Pulmonary diagnosis	✓			
Comorbidities and risk factors	✓			
Anthropometric				
Mass (kg)	✓			
Height (m)	✓			
General lower limb function				
SPPB[a] (/12)		✓		
6MST[b]				
Total number of steps		✓	✓	✓
Dyspnea (/10)[c]		✓	✓	✓
Leg fatigue (/10)[c]		✓	✓	✓
Heart rate (bpm)		✓	✓	✓
Pulsed oxygen saturation (%)		✓	✓	✓
Adverse events				
Minor		✓	✓	✓
Serious		✓	✓	✓
Semistructured interview				
Level of comfort during test				✓
Perception of safety				✓

[a]SPPB: Short Physical Performance Battery.

[b]6MST: 6-minute stepper test.

[c]/10: modified Borg Scale rating.

Review of Medical Records

Medical records will be reviewed, and the following information will be retrieved regarding participant sociodemographic characteristics: age, sex, pulmonary diagnosis, medications, comorbidities, and cardiovascular risk factors. Physical activity level will be assessed using the Ricci and Gagnon questionnaire [26].

First Trial

The first trial of the 6MST (familiarization trial) will be conducted at the participant's home with the therapist present. Preceding this trial, the Short Physical Performance Battery will be performed to obtain a general assessment of lower limb function [39].

The 6MST will be performed using a standardized portable stepper (same as in study 1) and following the same protocol as in study 1, including the 2-minute pretest warm-up period. However, full cardiorespiratory responses will not be measured. Instead, an oximeter (Nonin) will be used to monitor heart rate and SpO_2 continuously. Blood pressure, dyspnea, and perceived exertion will be measured pre- and posttest using the modified Borg scale (/10). For individuals on home oxygen therapy, oxygen flows will be titrated if SpO_2 falls below 88% during the test, with the aim of maintaining SpO_2 between 88% and 92%, while always respecting the flow limits of the prescribing physician's parameters. As in study 1, the test will be terminated if blood oxygen saturation falls to ≤80% accompanied by symptoms of hypoxia (such as dizziness, nausea, etc).

All adverse events will be recorded and graded according to the Common Terminology Criteria for Adverse Events, version 5 (United States Department of Health and Human Services), progressing from mild (1) to lethal (5) [40]. Textbox 5 presents the standardized grading used in this study. Adverse events are defined as any event that leads to (or could potentially lead to) prejudice to the participant or that inhibits the completion of the test. Examples include dyspnea, dizziness or nausea, close-call or fall events, musculoskeletal pain, chest pain, syncope, etc.

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Textbox 5. Classification of adverse events based on the Common Terminology Criteria for Adverse Events, version 5.

Grade 1: Mild

Mild adverse events are asymptomatic or with mild symptoms, or do not require intervention. Such adverse events include

- Musculoskeletal pain or injury (asymptomatic or mild)
- Joint effusion (asymptomatic or mild)
- Dyspnea with moderate exertion
- Productive cough with minimal production of sputum
- Wheezing with minimal symptoms
- Dehydration requiring increased oral fluid intake
- Hypoglycemia or hyperglycemia not requiring medical intervention
- Asymptomatic hypotension

Grade 2: Moderate

Moderate adverse events require minimal, local, or noninvasive intervention, or limit age-appropriate instrumental activities of daily living (preparing meals, doing the groceries, managing money, etc). Such adverse events include

- Musculoskeletal pain or injury limiting instrumental activities of daily living
- Joint effusion limiting instrumental activities of daily living
- Dyspnea with minimal exertion limiting instrumental activities of daily living
- Productive cough with moderate production of sputum or limiting instrumental activities of daily living
- Wheezing with moderate symptoms, or requiring medical intervention, or limiting instrumental activities of daily living
- Dehydration requiring intravenous fluids
- Hypoglycemia or hyperglycemia requiring intervention but no long-term changes in medical management
- Hypotension requiring nonurgent intervention
- Chest pain of palpitations related to exertion subsiding with rest

Grade 3: Severe

Severe adverse effects are medically significant but not immediately life-threatening, or require hospitalization, or limit self-care activities of daily living (bathing, dressing, using the toilet, feeding self, etc). Such adverse events include

- Musculoskeletal pain or injury limiting self-care activities of daily living
- Joint effusion limiting self-care activities of daily living
- Dyspnea at rest limiting self-care activities of daily living
- Productive cough with copious production of sputum or limiting self-care activities of daily living
- Wheezing with severe symptoms limiting self-care activities of daily living, or requiring oxygen therapy or hospitalization
- Dehydration requiring hospitalization
- Hypoglycemia or hyperglycemia requiring hospitalization or long-term changes in medical management
- Hypotension requiring intervention or hospitalization
- Syncope

Grade 4: Life-threatening

Life-threatening adverse effects require immediate and urgent intervention to avoid death. Such adverse events include

- Dyspnea (life-threatening) requiring urgent intervention
- Wheezing with life-threatening consequences or requiring urgent intervention
- Dehydration with life-threatening consequences
- Hypoglycemia or hyperglycemia with life-threatening consequences
- Hypotension (life-threatening) requiring urgent intervention
- Cardiac arrest

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Grade 5: Lethal

Lethal adverse effects lead to death and are generally a continuum of life-threatening events. Such adverse events include

- Dyspnea leading to death
- Wheezing leading to death
- Dehydration leading to death
- Hypoglycemia or hyperglycemia leading to death
- Hypotension leading to death
- Cardiac arrest leading to death

Second and Third Trials

The second and third trials of the 6MST will be performed in a randomized order, with either direct (therapist present at the home) or remote (therapist present through videoconferencing software, as in a telerehabilitation setting) monitoring. For the remotely monitored trial, another person (ie, family member, etc) will be present to ensure safety in case of emergency. The 6MST and adverse events will be, respectively, performed and collected as in the first trial (the only difference being the presence of the therapist through videoconferencing for one of the trials). The third trial of the 6MST will be followed by a semistructured interview using a guide created a priori. This interview will focus on the 2 themes, that are (1) level of comfort executing the test (ease of execution, symptoms, and anxiety) and (2) perception of safety (regarding test and home and telerehabilitation settings). The interview will be conducted in person or through videoconferencing software, depending on the randomization of the third trial.

Data Preparation and Analysis

All data will be stored in digital databases (REDCap [Research Electronic Data Capture] in Québec and OpenClinica in France) on secured servers at the participating research facilities (CR-IUCPQ and GHICL) following local protocols. Using a standardized thesaurus, research teams will enter data directly into both databases through remote access. With regard to data analysis, descriptive statistics will be used to summarize participant characteristics. For quantitative data, normality will be verified with Shapiro-Wilk tests and Q-Q plots. All statistical analyses will be completed using SPSS Statistics Version 28 (IBM) with a significance level set at $P<.05$. Graphical analyses will be conducted using Excel (version 2305; Microsoft Corporation) and qualitative analyses will be performed with Nvivio (version 14; Lumivero).

For objective 1, concurrent validity will be assessed using paired sample *t* tests (or Wilcoxon signed-rank tests) to verify whether peak cardiorespiratory (eg, oxygen consumption, minute ventilation, and heart rate) and symptomology (ie, dyspnea and leg fatigue) values obtained during the 6MST are comparable to the CPET and 6MWT. Pearson correlation coefficients (*r*) will also be calculated to quantify the strength of association between peak cardiorespiratory and symptomology values reached during the 6MST with those reached during the CPET and the 6MWT. Additional Pearson correlation coefficients (*r*) will be calculated to determine the strength of the association between the number of steps taken during the 6MST and peak oxygen consumption and heart rate reached during all 3 tests. The level of correlation will be interpreted as poor (≤0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.00) [41]. The agreement will be assessed with Bland-Altman plots and 95% limits of agreement (mean difference ± 1.96 SD of the difference) between peak cardiorespiratory and symptomology values reached during the 6MST and those reached during the CPET and the 6MWT [41].

For objective 2, reliability (trial 2 vs 3) will be assessed using paired sample *t* tests (or Wilcoxon signed-rank tests), Bland-Altman plots (with 95% limits of agreement), and intraclass correlations [42-44]. Intraclass correlations will be interpreted as poor (≤0.50), moderate (0.51-0.75), good (0.76-0.9), and very good (0.91-1.00) [44].

For objective 3, all minor and serious adverse events, for all trials, will be reported. The semistructured interviews will be voice-recorded and transcribed. Thematic content analysis will be used to analyze all verbatim [45]. Briefly, a combination of deductive (based on a priori interview guide) and inductive (based on data) approaches will be used to generate themes and subthemes. Coding will be conducted separately by 2 reviewers, who will compare their results and resolve discrepancies through discussion.

Ethical Considerations

This research project received ethical approval at the CR-IUCPQ on October 12, 2023 (2024-4075, 22380), and at the GHICL on September 25, 2023 (2023-A01571-44). All participants will provide written free and informed consent before enrollment. All information is provided in French and will be translated into English if needed. All data collected will be stored anonymously (coded numeric ID) on secured servers at participating research facilities. Participants will receive financial compensation in accordance with local standardized fees in participating research centers (value of approximately CAD $40[US $30] per laboratory visit and CAD $10 [US $7] per at-home visit).

Results

The first participant (study 1) was recruited on February 2, 2024, and will continue for a maximum of 12 months. Recruitment for study 2 is to follow the completion of study 1 and is expected to last for a maximum of 12 months. Data analysis will occur after, and results will be published in peer-reviewed journals.

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Discussion

Overview

This study aims to provide further evidence regarding the metrological properties of the 6MST in individuals with COPD or ILD. The 6MST is a clinically relevant functional capacity test that is specifically adapted for home-based models of care.

This research project innovates by being among the first to extensively evaluate the metrological properties of the 6MST in a diversified sample of pulmonary lung diseases. Moreover, this study is the first to evaluate the validity and safety of assessing exercise capacity using 6MST through direct and remote monitoring, mimicking home-based and telerehabilitation contexts. Since all the equipment required for the 6MST (ie, stepper) can easily be transported by a therapist, or even shipped to the patient, and requires very minimal space, this test is highly applicable in home-based rehabilitation models of care.

Knowledge derived from this research project will therefore contribute to addressing barriers currently hampering the wider adoption of these new models of care. Ultimately, this research project fits in a continuum of knowledge creation that aligns with the United Nations Sustainable Development Goals by contributing to augmenting health care service delivery (goal 3) and reducing health care access inequalities (goal 11).

Potential Challenges and Appropriate Mitigation Strategies

Certain potential changes were foreseen and the following mediation strategies will be put into place:

1. Changes in a participant's health status during the study could introduce bias in the results of repeated measures. To help reduce this risk, repeated testing conducted in the laboratory will be preceded by spirometry to ensure stability in health status. For testing conducted in the home-based settings, signs and symptoms of exacerbations will be collected before each repeated testing.
2. The steppers used in this study use hydraulic pistons to simulate the stepping movements. The resistance provided by the pistons is greater when the fluid inside them is cold and decreases progressively with use as the pistons heat. To avoid inducing a potential bias during repeated tests, a standardized 2-minute warm-up (familiarization) will be conducted followed by a standardized 3 minutes of rest before initiating the test trial. Participants will also be instructed not to use the stepper device other than when instructed to do so during testing.
3. Some participants may have trouble maintaining balance during the 6MST. Participants are allowed to touch a wall or other stable surface to assist in maintaining balance. Nevertheless, for home-based testing in the absence of the therapist (ie, videoconferencing), a third person (eg, family member) will be present to ensure safety. This person will also be instructed on how to react in case of emergency.

Strengths and Limitations

This research project has strengths and limitations that warrant consideration. With regard to strengths, first, sex parity will be assured and help limit bias, particularly related to the under-representation of people of the female sex in the pulmonary rehabilitation literature [46]. Second, the a priori calculation of sample sizes required will ensure sufficient statistical power to address the study's objectives. Third, the inclusion of several different and complementary statistical strategies will ensure adequate evaluation of the metrological properties of the included tests. Fourth, the multicenter and multinational nature of this study will improve its external validity and generalizability. Fifth, the inclusion of a mixed methods study design will help ensure that stakeholders (ie, individuals with pulmonary diseases) have input regarding the acceptability and use of the physical tests being validated in this research project. Finally, the publication of this protocol a priori will ensure accountability and any changes made a posteriori will be public knowledge and require justification.

With regard to limitations, first, only individuals with COPD and an ILD will be included in this study. This will limit its generalizability in the population with other pulmonary diseases (eg, asthma and cystic fibrosis). This methodological choice was made in an effort to reconcile feasibility (limited time and budget) and generalizability (ie, heterogeneity). Second, for study 1, participants will be required to perform several physical tests on the same day, potentially leading to fatigue that may alter performances. To address this, tests occurring on the same day are separated by a rest period and are randomized. Moreover, the research team has extensive experience with this type of protocol. Finally, regarding test-retest reliability in study 2, a learning effect is possible as the test will be conducted repeatedly. To limit this effect, the first trial of the test will exclusively serve as a familiarization trial. In addition, a 2-minute warm-up period is allotted before each trial. Nonetheless, as the learning effect may not be completely eliminated, randomization of the second and third trials is performed in order to limit a systemic effect on the test conditions (ie, with a therapist present or through videoconferencing software).

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Data Availability

The data sets generated and analyzed during this study are not publicly available to maintain participant confidentiality but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Fondation Institut Universitaire de Cardiologie et de Pneumologie de Quebec.
[PDF File (Adobe PDF File), 217 KB - resprot_v13i1e57404_app1.pdf]

Multimedia Appendix 2
The American Thoracic Society's recommended standardized instructions and encouragements for the 6-minute walk test that were translated to French in Textbox 3.
[PDF File (Adobe PDF File), 107 KB - resprot_v13i1e57404_app2.pdf]

Multimedia Appendix 3
The original English instructions proposed for the 6-minute stepper test that were translated to French in Textbox 4.
[PDF File (Adobe PDF File), 61 KB - resprot_v13i1e57404_app3.pdf]

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Abbreviations

6MST: 6-minute stepper test
6MWT: 6-minute walk test
COPD: chronic obstructive pulmonary disease
CPET: maximal cardiopulmonary exercise testing
CR-IUCPQ: Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec
GHICL: Groupement des Hôpitaux de l'Institut Catholique de Lille
ILD: interstitial lung disease
SpO_2: pulsed oxygen saturation

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Protocol

Implementation and Impact of Intimate Partner Violence Screening Expansion in the Veterans Health Administration: Protocol for a Mixed Methods Evaluation

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Abstract

Background: Intimate partner violence (IPV) is a significant public health problem with far-reaching consequences. The health care system plays an integral role in the detection of and response to IPV. Historically, the majority of IPV screening initiatives have targeted women of reproductive age, with little known about men's IPV screening experiences or the impact of screening on men's health care. The Veterans Health Administration (VHA) has called for an expansion of IPV screening, providing a unique opportunity for a large-scale evaluation of IPV screening and response across all patient populations.

Objective: In this protocol paper, we describe the recently funded Partnered Evaluation of Relationship Health Innovations and Services through Mixed Methods (PRISM) initiative, aiming to evaluate the implementation and impact of the VHA's IPV screening and response expansion, with a particular focus on identifying potential gender differences.

Methods: The PRISM Initiative is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) and Consolidated Framework for Implementation Research (CFIR 2.0) frameworks. We will use mixed methods data from 139 VHA facilities to evaluate the IPV screening expansion, including electronic health record data and qualitative interviews with patients, clinicians, and national IPV program leadership. Quantitative data will be analyzed using a longitudinal observational design with repeated measurement periods at baseline (T0), year 1 (T1), and year 2 (T2). Qualitative interviews will focus on identifying multilevel factors, including potential implementation barriers and facilitators critical to IPV screening and response expansion, and examining the impact of screening on patients and clinicians.

Results: The PRISM initiative was funded in October 2023. We have developed the qualitative interview guides, obtained institutional review board approval, extracted quantitative data for baseline analyses, and began recruitment for qualitative interviews. Reports of progress and results will be made available to evaluation partners and funders through quarterly and end-of-year reports. All data collection and analyses across time points are expected to be completed in June 2026.

Conclusions: Findings from this mixed methods evaluation will provide a comprehensive understanding of IPV screening expansion at the VHA, including the implementation and impact of screening and the scope of IPV detected in the VHA patient population. Moreover, data generated by this initiative have critical policy and clinical practice implications in a national health care system.

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KEYWORDS

screening; intimate partner violence; implementation; evaluation; national rollout; health care; quality improvement; veterans

Introduction

Overview

Intimate partner violence (IPV), including physical, sexual, and psychological aggression, is a significant public health problem with far-reaching consequences. Experiencing IPV is associated with serious negative physical and psychological outcomes among civilians and veterans alike [1,2]. Research shows that women veterans are at increased risk of experiencing violence in relationships compared to civilian women [1]. Moreover, IPV is common, yet critically understudied, among veteran men.

Reported rates of IPV experience vary widely across studies, largely due to methodological differences [3,4]. Although US women veterans are more likely to experience lifetime IPV than men (approximately 45% vs 36%), the prevalence of past-year IPV is similar, at approximately 30% [5]. Research has found that as many as 55% of women veterans experience IPV in their lifetimes [6]. Women's experiences of IPV are associated with adverse physical and mental health, including cardiovascular and respiratory problems, chronic pain, reproductive health challenges, posttraumatic stress, anxiety, depression, substance use, and elevated risk for suicide [2,7-10]. For veteran men, IPV experience is associated with poorer overall mental health; greater occupational impairment; and higher rates of depression, smoking, and heavy and binge drinking [11,12]. Despite high rates of IPV experience and adverse outcomes for men, little research has examined IPV screening and referral outcomes for this population. Moreover, although evidence demonstrates that transgender and nonbinary patients are at increased risk of IPV compared to cisgender patients [13,14], very little research has examined IPV screening and referral outcomes within this population [15].

The health care system plays an integral role in the detection of and response to IPV [16,17]. As such, the significant impact that IPV has on veterans across genders underscores the critical need for a comprehensive and effective health care response for patients seeking services through the Veterans Health Administration (VHA). In 2014, the VHA developed the national IPV Assistance Program to oversee and implement integrated services aimed at reducing the risk for IPV, including establishing IPV Assistance Program Coordinators at each Department of Veterans Affairs (VA) medical center across the country and providing clinical services and resources for IPV-related concerns through prevention, detection, and treatment [18]. Since the IPV Assistance Program's inception, the implementation of IPV screening and response among women veterans has been an important priority area for the program.

The VHA policy for IPV detection and response parallels and expands on recommendations put forth by the US Preventive Services Task Force [19]. VHA policy requires annual IPV screening for women of reproductive age, as well as other patients who belong to a recognized high-risk group (eg, patients who are homeless or underhoused, those with co-occurring disorders, and patients with disability [20]) and provision of support, resources, and referrals [20]. Accordingly, enhancing the implementation of IPV screening and response among the women veteran patient population has been a major priority of VHA clinical practice and research efforts over the last decade. A robust body of literature has shown that IPV screening of women veterans during health care visits is essential as patients are unlikely to spontaneously disclose IPV but will often report their IPV experiences when asked by a clinician in a sensitive manner [21]. Evidence also demonstrates that screening increases the identification of IPV and enhances women veterans' connections to and satisfaction with care, and women veterans report perceiving IPV screening as supportive, validating, and helpful [21-23].

However, there remain many system-level and clinician-reported barriers to screening women veterans, such as limited time and resources, discomfort in addressing IPV, lack of training, and competing priorities during health care visits [24,25]. Moreover, because the majority of IPV research and health care screening initiatives to date have targeted women, little is known about screening men for IPV, including men's perceptions and experiences of screening, their willingness to disclose IPV during screening, and clinicians' experiences and attitudes about screening men. These limitations highlight the need for a large-scale evaluation of IPV screening reach and effectiveness with men and patients of all gender identities to inform strategies for optimizing screening implementation across patient populations. To date, IPV screening implementation across health care systems, including the VHA, has targeted women of reproductive age and largely has occurred in primary care, obstetrics or gynecology, and urgent care settings. The recent VHA IPV screening expansion provides a unique opportunity for evaluation of the IPV screening and response protocol across VHA patient populations.

Expansion of IPV Screening

In response to growing evidence demonstrating that all VHA patient populations are at risk for experiencing IPV and associated negative health consequences (eg, men [12,26], women above reproductive age [27], and transgender and nonbinary veterans [13,14]), the VA National IPV Assistance Program has called for expanded IPV screening through the implementation of a "no wrong door" approach using the Relationship Health and Safety Clinical Reminder version 3 (RHS 3.0). This approach enables a patient-centered solution for detecting IPV such that patients are screened for IPV regardless of where they receive care within the health care system. The RHS 3.0 is a 2-part IPV screener, including a 5-item

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primary screen for IPV [28-30] and, if triggered, a 3-item secondary screen for risk of severe and potentially lethal IPV [31].

The RHS 3.0 was developed as a clinical reminder with a note template and approved for VHA enterprise-wide installation in August 2023. The clinical reminder prompts clinicians to screen women of reproductive age at least annually and is available and recommended for use with all patients outside of this target demographic, as well. Veterans can be screened for IPV and connected with support services wherever they present for care in the health care system, resulting in a "no wrong door" approach. The RHS 3.0 is administered using a standardized template in the electronic health record (EHR). Population health implementation support tools, such as clinical reminders and note templates, leverage standardization of the EHR to help systematize screening administration and data collection across a large patient population [32]. As the largest integrated health care system in the United States, the VHA serves over 9 million patients across 172 health care facilities [33], underscoring the importance of leveraging tools available in the EHR for reaching all patients who come into contact with the health care system.

To conduct IPV screening and complete the necessary clinical reminder steps, clinicians require training through an internet-based training module available to all VHA staff or through receiving training conducted by an IPV Assistance Program Coordinator. To support the adoption of the RHS 3.0 screening expansion, the IPV Assistance Program is combining a top-down approach, which includes disseminating education and materials throughout the VHA (eg, national live and recorded trainings, an IPV screening and response toolkit, and internet-based training modules), with facility-level implementation strategies at the discretion of local IPV Assistance Program Coordinators at each medical center.

A national screening expansion of this scale requires rigorous, systematic evaluation. Although prior work exists evaluating IPV screening implementation for women veterans in primary care settings [23-25,34-37], no effort to date has systematically evaluated the implementation of IPV screening among all patients across the entire health care system. Data are needed to assess the implementation of the screening expansion, as well as the impact of screening new patient populations. In this protocol paper, we describe the recently funded Partnered Evaluation of Relationship Health Innovations and Services through Mixed Methods (PRISM) initiative. The aims of this work are to (1) evaluate the implementation of the RHS 3.0 IPV screening and response to national expansion and (2) identify the impact of IPV screening and potential gender differences. Specifically, we will assess implementation outcomes across Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) domains and examine potential differences in outcomes by patient characteristics (eg, gender, age, race, ethnicity, sexual orientation, and marital status). To examine the "no wrong door" approach, we will also identify clinical settings most and least likely to adopt IPV screening, as well as yield disclosures during screening. We will examine the impact and potential gender differences by assessing service use and clinical outcomes following positive screens and exploring experiences and perceptions of clinicians who screened and patients who disclosed IPV during screening encounters.

Methods

Conceptual Framework

The PRISM initiative is guided by 2 robust implementation science frameworks—the RE-AIM (outcomes framework [38]) and the updated Consolidated Framework for Implementation Research (CFIR 2.0; determinants framework [39]). Although RE-AIM helps guide the organization of evaluation outcomes, it does not necessarily explain the conditions that influence variation in outcomes across the system, including among patient subgroups and clinical settings. The CFIR 2.0 is particularly helpful for structuring the exploration of contextual factors essential for the implementation of innovative programs, including at the VHA [40], making it ideally suited to guide the evaluation of multilevel factors that impact the implementation success of the VHA IPV screening and response national expansion. Integrating these 2 frameworks will support the assessment of implementation outcomes alongside understanding potential barriers and enablers of screening implementation, clinicians' experiences with IPV screening and patients' experiences with being screened (particularly among newly targeted patient populations, like men), and the implementation process overall.

Data Sources

Evaluation of the RHS 3.0 IPV screening expansion will include mixed methods data across VA health care facilities nationally. We will integrate quantitative and qualitative data sources, including EHR data and qualitative interviews (see Table 1 for a summary of data sources and outcomes). Quantitative data will be extracted from the VA's Corporate Data Warehouse (CDW), a centralized data repository that aggregates clinical, administrative, and financial data from the VA EHR across all 139 VA medical centers and satellite clinics [41]. Our evaluation sample will include all VHA veteran patients with at least 1 outpatient VHA health care encounter during the evaluation observation period. Qualitative data sources will include semistructured interviews with veterans, clinicians, and VA leadership from the national IPV Assistance Program. The development of the semistructured interviews was guided by the CFIR 2.0 domains. Specifically, clinician interviews will focus on CFIR 2.0 constructs related to the RHS 3.0 screening and response protocol itself, the outer and inner settings (ie, their clinics and facilities), responders' experiences and perceptions of the screening and response (including perceived impacts for patients), and the implementation process. Veteran interviews will also focus on their perceptions of being screened, including experiences with the screening process itself and resulting outcomes (eg, services offered or received).

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Table 1. Evaluation constructs, outcomes, and data sources.

Construct	Outcomes
Aim 1: implementation	
Reach: is the IPV[a] screening expansion reaching its intended target (all veterans)?	• Proportion of veterans screened out of those eligible for screening and representativeness of screening within the target population[b] • Differences and disparities between those who were and were not screened across patient characteristics (eg, gender, age, race, ethnicity, sexual orientation, and marital status)[b]
Effectiveness: is the RHS 3.0[c] screening expansion effective?	• Increased frequency of IPV detected among veterans[b] • Increased rate of referrals following screen positives[b] • Clinicians' and veterans' experiences with and perceptions of the RHS 3.0[d] • Unintended consequences of the RHS 3.0 rollout[d]
Adoption: what is the uptake of screening across VHA[e] facilities and clinical setting?	• Proportion of VHA facilities using the RHS 3.0[b] • Proportion of screenings completed using the RHS 3.0 across clinical settings[b] • Barriers and facilitators related to adoption of the RHS 3.0, guided by the CFIR[d,f]
Implementation fidelity: to what extent is the RHS 3.0 being implemented as intended?	• Degree of fidelity (ie, implementation per protocol)[b] • Contextual factors related to fidelity, guided by the CFIR[f]
Maintenance: is the RHS 3.0 expansion being sustained over time?	• Proportion of veterans screened overall and across patient subgroups (eg, gender) using the RHS 3.0 at years 2 and 3[b] • Percent of VHA facilities using the RHS 3.0 at years 2 and 3[b] • Number of unique clinicians using the RHS 3.0 at years 2 and 3[b]
Aim 2: impact	
Connection to and use of health care	• Health care use following positive screening; same day visits as a result of screening[b] • Engagement and retention in health care services following positive screens[d] • Sense of support and connection to VHA as a result of screening[d] • Satisfaction with the IPV screening encounter[d]
Connection to resources	• Use of VHA resources for social services or essential needs, such as housing, financial support, food resources, transportation, immigration services, legal aid, and law enforcement assistance (eg, restraining orders)[b]
Other clinical and health outcomes	• Identification and follow-up of high-risk IPV cases (ie, danger of lethality or serious injury)[b] • Number of safety plans completedb • Clinical decisions made or actions taken as a result of screeningd

[a]IPV: intimate partner violence.

[b]Indicates electronic health record data extracted from the corporate data warehouse.

[c]RHS 3.0: Relationship Health and Safety Clinical Reminder version 3.0.

[d]Indicates data resulting from qualitative interviews.

[e]VHA: Veterans Health Administration.

[f]CFIR: Consolidated Framework for Implementation Research.

Ethical Considerations

This evaluation is a quality improvement (QI) initiative jointly supported by the VA Care Management and Social Work Service's IPV Assistance Program; the VA Quality Enhancement Research Initiative (QUERI); and the IPV Center for Implementation, Research, and Evaluation (IPV-CIRE) at VA Connecticut Health care System. The PRISM Initiative was designed for internal purposes in support of VA QI as an internal operations evaluation designated as nonresearch by VA, thus not requiring institutional review board approval [42]. Empirical research conducted with data collected from this QI initiative was approved by the VA Connecticut Health Care System institutional review board (protocol #1792152).

Quantitative Procedures and Analyses

Quantitative data grounded in the RE-AIM outcomes will be extracted from the CDW and analyzed using a longitudinal observational design with repeated measurement periods at baseline (T0), year 1 (T1), and year 2 (T2) [38]. We operationalized reach as the proportion and representativeness of veteran patients who were administered IPV screening, and

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those administered the RHS 3.0 specifically, calculated as veterans screened out of those eligible for screening. Eligibility for screening was defined as having at least 1 VHA health care encounter during the observation period. To examine representativeness and potential disparities between those screened and not screened, we will use generalized linear mixed models (GLMM) to assess differences by patient characteristics (gender, age, race, ethnicity, sexual orientation, marital status, rurality, and housing instability status) over each of the 3 time points while specifying facilities as random effects to account for nesting [43,44]. We will also examine the change in the probability of being screened over time through GLMMs specifying facilities and patients as random effects. Additionally, we will examine whether the effect of time varies significantly across facilities. In post hoc analyses, we will investigate whether the change in the probability of being screened over time differs by patient characteristics.

Effectiveness, for this evaluation, focuses on determining the extent to which the RHS 3.0 expansion itself is effective. We defined the effectiveness of the expansion as whether there is an increase in the proportion of IPV cases detected, referrals offered, and universal education provided following the implementation of the RHS 3.0. Using the quantitative CDW data, we will calculate changes in the proportion of these factors following positive screens through the same GLMM process described above. Effectiveness will also be examined through the exploration of qualitative data regarding clinicians' and veterans' experiences with and perceptions of the RHS 3.0 and its potential unintended consequences. Adoption was operationalized as differences in screening uptake by facility and clinical setting [38]. We will combine stop codes, identifiers used by the VHA to track which clinic group and location provided a service, into meaningful categories of services (eg, primary care mental health, social work, etc) to examine descriptive statistics (frequencies and range) of screening uptake across medical center facilities and clinical settings. We will also assess adoption through an exploration of the barriers and facilitators related to IPV screening expansion via qualitative data.

Implementation fidelity was defined as the extent to which IPV screening and response procedures are implemented as intended (ie, per IPV Assistance Program guidelines) [20,38]. For example, we will identify the percentage of veterans screened out of those eligible, completion of the secondary screen based on positive primary screen responses, referrals offered, and universal IPV education provided. We will also explore contextual factors related to fidelity reported during qualitative interviews. Finally, to examine maintenance of the RHS 3.0 expansion, we will identify whether the proportion of veterans screened (and proportion screened across patient subgroups), percent of facilities using the RHS 3.0, and number of unique clinicians using the RHS 3.0 remains at, above, or below T0 levels during T1 and T2 [38].

In addition to examining the implementation of the IPV screening expansion, the PRISM initiative will evaluate the impact of expanded IPV screening on patients, clinicians, and the health care system as a whole. Unique from RE-AIM's effectiveness domain, which targets whether the screening expansion itself is effective, determining the impact of expanded screening will involve examining linkages between screening and connection and engagement to VHA services and resources. Leveraging available CDW data, we will examine patients' connection to, and use of, health care and social support services following IPV screening, including services for physical and mental health conditions and resources for social services or essential needs (see Table 1 for detailed description). Examination of CDW data will also enable the identification of responses to IPV cases identified as high risk for lethality or serious injury, including a number of safety plans completed or same-day consults placed. Additional analyses will include a calculation of the frequency of services received in the 60 days following a positive screen and the same day. We will determine associations between positive screens and health care or resource use by using GLMMs with facilities as random effects, controlling for service use in the 60 days prior to the screen. We will also examine rates of high-risk cases detected from secondary screener results and the proportion of safety plans completed among high-risk cases.

Qualitative Procedures and Analyses

Guiding Frameworks

We will use the CFIR 2.0 [39] as an organizational and explanatory determinants framework to (1) categorize multilevel factors critical to RHS 3.0 implementation across VHA facilities and clinical settings, (2) identify potential barriers and facilitators of implementation, and (3) examine the impact of screening on patients. The CFIR 2.0 includes 49 constructs across 5 overarching domains that have been shown to influence program implementation, and they are (1) innovation, (2) inner setting, (3) outer setting, (4) individuals, and (5) implementation process [39]. Following guidance to use constructs most salient for particular initiatives under study [45], we selected the most relevant constructs from the CFIR 2.0 and CFIR Outcomes Addendum [46] to guide the development of interview guides with veterans and clinicians and analyses of qualitative data for this evaluation. See Table 2 for a full list of CFIR constructs guiding qualitative data collection and analysis.

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Table 2. CFIR[a] domains and constructs for evaluation of the RHS 3.0[b] expansion.

Level and construct	C[c,d] or P[d,e]
Innovation characteristics	
Evidence strength and quality	C
Adaptability	C or P
Complexity	C or P
Outer setting	
External policies and incentives	C
Patient needs and resources	C or P
Inner setting	
Culture and climate	C
Compatibility	C
Relative priority	C
Access to information	C
Individuals: recipients (P) and deliverers (C)	
Self-efficacy	C
Need and appropriateness	C or P
Capability, opportunity, and motivation	C
Acceptability	C or P
Feasibility	C
Impact and outcomes	C or P
Process	
Tailoring strategies	C
Adapting	C

[a]CFIR: Consolidated Framework for Implementation Research.

[b]RHS 3.0: Relationship Health and Safety Clinical Reminder version 3.0.

[c]C: clinicians.

[d]Indicating which constructs will be reflected in corresponding interview guides.

[e]P: patients.

Patients

Leveraging EHR data, we will use purposeful sampling [47] to identify veteran patients who screened positive for IPV and created random stratified samples by gender and ensure patient presentation across geographical locations and clinical settings. We will generate batches of eligible veterans monthly to ensure that veterans are interviewed within 2 to 4 months of their screening encounter and have sufficient memory of the experience. We will send recruitment letters to those potentially eligible informing them of the study and inviting them to contact the study team to opt in or out of participation. Veterans with cognitive, language, or other impairments that prevent full participation in the study will not be eligible to participate. To ensure diversity in perspectives across interviews, we aim to include veterans from varying demographic backgrounds and experiences. We will encourage this diverse makeup by ensuring that our sample includes at least 20 women and 20 men, 25% racial or ethnic minority veterans, and 25% veterans aged 55 or older; we will also seek representation from each region of the country [48,49]. Recruitment will continue until we reach thematic saturation [50]. Interviews will be approximately 45 minutes and veterans will be compensated US $50 for their participation. Veterans' participation will be voluntary and their responses to interview questions will not be shared with any clinician providing them VHA services. Interview data will be presented using deidentified representative quotes and in aggregate through the development of qualitative themes.

Clinicians

We will leverage the EHR data to identify clinicians who used the RHS 3.0 to screen patients of all genders for IPV to create a roster of potentially eligible clinicians. Using this roster, we will ensure clinician representation across clinician discipline, geographical location, and clinical settings. We will reach out to potentially eligible clinicians via email informing them of the study, confirming that they have conducted at least 5 screenings with women and at least 5 with men, and inviting them to participate in a qualitative interview about their experiences and perceptions. We aim to include at least 25

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clinicians, although our final sample will be determined by thematic saturation [50]. Interviews will be 45-60 minutes in length.

National IPV Assistance Program Leaders

Using an established ethnographically informed method of guided discussion [51], we will conduct biannual 30-60 minute interviews with 3-4 key national IPV program leaders involved in supporting the RHS 3.0 expansion and program office partners, at the leaders' request. These discussions will enable us to systematically document and understand the implementation plan and process, as well as provide opportunities for the national implementers to engage in "periodic reflections" with our team [51]. Discussion notes will be coded to reflect key CFIR domains of interest and emergent themes, which will be analyzed in triangulation with our other qualitative data sources (ie, clinician interviews) and quantitative data (ie, CDW-based RE-AIM domains).

Qualitative Data Analysis

We will use a hybrid deductive-inductive thematic analysis approach [52] to analyze the qualitative data, with initial codes informed by specified CFIR constructs (Table 2). Interview transcripts will be coded and summarized, then consolidated into matrices by CFIR constructs. Multiple team members will conduct data analyses. Using a rigorous, team-based approach, we will complete the following steps: (1) develop a start list of codes based on the CFIR constructs and interview guides (to which we will add emergent codes); (2) code the transcripts; (3) transpose and systematize data into summary templates; (4) organize the data into matrices to note trends, similarities, and differences; and (5) synthesize into findings. As new codes arise, earlier transcripts will be recoded [53]. This iterative process will continue until all themes have been identified. Discrepancies will be resolved through consensus discussions [54]. Qualitative findings will support the planned evaluation by (1) describing conditions necessary for clinicians to effectively screen all veterans across health care settings and barriers to doing so; (2) identifying contextual factors that will inform future implementation strategies needed to enhance the expansion of the RHS 3.0; and (3) revealing veterans' experiences with, and outcomes related to, disclosing IPV during screening encounters, including the impact of screening on their health care and service use, satisfaction with the screening and response encounter, and sense of connection with VHA and clinicians.

Patient Engagement

This evaluation will include a Veteran Engagement Board (VEB) to accurately represent the complex and diverse experiences of veterans and ensure that our findings are meaningful and accessible to the patient population we are striving to serve [55]. Through the VEB, we will include veterans' voices and perspectives in each phase of the evaluation and aim to increase shared decision-making across a diversity of perspectives [56]. Although we will gain important knowledge through qualitative interviews with veterans to understand the impact of the RHS 3.0 screening and response protocol expansion on patients, involving veterans in research to understand their experiences differs meaningfully from engaging them in the research process to ensure that all phases of the work are veteran-centric and guided and informed by veteran perspectives. The VEB will actively inform the PRISM initiative through regularly occurring meetings and discussions focused on activities across all stages of the project (ie, planning, data collection, interpretation of results, and dissemination of findings).

Results

The PRISM initiative was funded in October 2023. We have developed the qualitative interview guides, obtained institutional review board approval, extracted quantitative data for baseline analyses, and began recruitment for qualitative interviews. Quantitative analyses will take place in 2024 (T0), 2025 (T1), and 2026 (T2). Qualitative interviews and analyses will take place between April 2024 and October 2025. Reports of progress and results will be made available to evaluation partners and funders through quarterly and end-of-year reports. Evaluation findings will also be intermittently disseminated through peer-reviewed journals and presentations at scientific meetings. All data collection and analyses across time points are expected to be completed in June 2026.

Discussion

This study protocol outlines a mixed methods evaluation of IPV screening expansion in the VHA, conducted in partnership with the VA National IPV Assistance Program. Findings generated from the evaluation of the IPV screening expansion will provide a comprehensive understanding of the reach, effectiveness, adoption, implementation, maintenance, and impact of the expanded IPV screening and response protocol, the RHS 3.0. Additionally, findings will determine the scope of IPV detected in the VA patient population through screening during routine clinical health encounters, knowledge essential to inform clinical practice and policy. These data will generate knowledge regarding IPV disclosures among subgroups of veterans previously not targeted for IPV screening (eg, men, women above reproductive age, and transgender and nonbinary veterans) and those from underserved or vulnerable populations, disparities in IPV screening and outcomes, and patient subgroups at heightened risk for IPV and IPV-related injury and lethality. Little research has examined IPV screening and referral outcomes within these populations, specifically among men and transgender or nonbinary patients (who are at increased risk of IPV compared to cisgender patients [13-15]). Because the majority of IPV screening initiatives to date have targeted women, this work will expand the field's knowledge regarding other subgroups' experiences and perceptions of screening and their willingness to disclose IPV during health care encounters.

One limitation of this national evaluation initiative is our ability to access data across all VA sites. The VA is currently undergoing an EHR modernization, including transitioning to a new EHR system [57]. These changes may impede our ability to identify and extract necessary data at VA sites that have transitioned to a new EHR system. Additionally, we are limited by our evaluation method. Although a staggered implementation

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rollout or use of control group sites may enhance evaluation by allowing for comparisons of strategies, the national IPV program partners are prioritizing a full-scale national rollout, currently underway, limiting the possibility of a staggered approach.

This initiative also has critical policy and clinical practice implications. Through the course of this project, we will develop essential evaluation tools for monitoring and improving screening implementation in the VHA over time. The VA's Office of the Inspector General identified the need for systematic and high-quality tracking of IPV-related programmatic outcomes data, particularly regarding IPV screening implementation outcomes [58], an area that this project will directly address. This evaluation will provide critically needed systems and clinical data to VHA policy leaders to inform national programming and enable tracking over time. Evaluation of the IPV screening expansion will result in recommendations for future IPV screening implementation initiatives and adaptations, including potential comparisons of implementation strategies for future studies leading to the optimization of IPV screening implementation across the health care system.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to requirements of compliance with government procedures. Those interested in deidentified data underlying this initiative can send an email request to the corresponding author.

Authors' Contributions

GAP, MED, and KMI conceptualized the study methodology and project administration. MRR, CP, MS, and CAB contributed to the statistical analysis plan, software, data curation, and visualization. LEB and SM provided supervision and mentorship. All authors contributed to the writing, review, and editing of the paper. All authors approved the paper.

Conflicts of Interest

None declared.

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Abbreviations

CDW: corporate data warehouse
CFIR 2.0: Consolidated Framework for Implementation Research
EHR: electronic health record
GLMM: generalized linear mixed models
IPV: intimate partner violence
IPV-CIRE: intimate partner violence Center for Implementation, Research, and Evaluation
PRISM: Partnered Evaluation of Relationship Health Innovations and Services through Mixed Methods
QI: quality improvement
QUERI: Quality Enhancement Research Initiative
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
RHS 3.0: Relationship Health and Safety Clinical Reminder version 3
VA: Department of Veterans Affairs
VEB: Veteran Engagement Board
VHA: Veterans Health Administration

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Protocol

Transgender-Specific Differentiated HIV Service Delivery Models in the South African Public Primary Health Care System (Jabula Uzibone): Protocol for an Implementation Study

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Abstract

Background: Almost 60% of transgender people in South Africa are living with HIV. Ending the HIV epidemic will require that transgender people successfully access HIV prevention and treatment. However, transgender people often avoid health services due to facility-based stigma and lack of availability of gender-affirming care. Transgender-specific differentiated service delivery (TG-DSD) may improve engagement and facilitate progress toward HIV elimination. Wits RHI, a renowned South African research institute, established 4 TG-DSD demonstration sites in 2019, with funding from the US Agency for International Development. These sites offer unique opportunities to evaluate the implementation of TG-DSD and test their effectiveness.

Objective: The Jabula Uzibone study seeks to assess the implementation, effectiveness, and cost of TG-DSD for viral suppression and prevention-effective adherence.

Methods: The Jabula Uzibone study collects baseline and 12-month observation checklists at 8 sites and 6 (12.5%) key informant interviews per site at 4 TG-DSD and 4 standard sites (n=48). We seek to enroll ≥600 transgender clients, 50% at TG-DSD and 50% at standard sites: 67% clients with HIV and 33% clients without HIV per site type. Participants complete interviewer-administered surveys quarterly, and blood is drawn at baseline and 12 months for HIV RNA levels among participants with HIV and tenofovir levels among participants on pre-exposure prophylaxis. A subset of 30 participants per site type will complete in-depth interviews at baseline and 12 months: 15 participants will be living with HIV and 15 participants will be HIV negative. Qualitative analyses will explore aspects of implementation; regression models will compare viral suppression and prevention-effective adherence by site type. Structural equation modeling will test for mediation by stigma and gender affirmation. Microcosting approaches will estimate the cost per service user served and per service user successfully treated at TG-DSD sites relative to standard sites, as well as the budget needed for a broader implementation of TG-DSD.

Results: Funded by the US National Institutes of Mental Health in April 2022, the study was approved by the Human Research Ethics Committee at University of Witwatersrand in June 2022 and the Duke University Health System Institutional Review Board in June 2023. Enrollment began in January 2024. As of July 31, 2024, a total of 593 transgender participants have been

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enrolled: 348 are living with HIV and 245 are HIV negative. We anticipate baseline enrollment will be complete by August 31, 2024, and the final study visit will take place no later than August 2025.

Conclusions: Jabula Uzibone will provide data to inform HIV policies and practices in South Africa and generate the first evidence for implementation of TG-DSD in sub-Saharan Africa. Study findings may inform the use of TG-DSD strategies to increase care engagement and advance global progress toward HIV elimination goals.

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KEYWORDS

HIV prevention; HIV care; pre-exposure prophylaxis; antiretroviral therapy; gender affirmation; transgender health

Introduction

HIV Among Transgender People

Transgender people are a key population with a disproportionate burden of HIV. Globally, transgender women have an estimated HIV prevalence of 19.9%, with 66-fold greater odds of HIV compared with other adults, a prevalence that has not decreased over the past decade despite the introduction of HIV pre-exposure prophylaxis (PrEP) [1,2]. Transgender men also face elevated HIV prevalence, with an estimated global prevalence of 2.6% and 6.8-fold increased odds of HIV [2]. South Africa has the largest HIV epidemic in the world, where more than 7 million people are living with HIV [3]. Approximately 17% of the general population of reproductive age adults have HIV, and prevalence is estimated to be 3-fold higher (58%) among transgender people [4]. A recent integrated biobehavioral respondent-driven sampling study (Botshelo Ba Trans [5]; N=888) estimated HIV prevalence in transgender women to be 46% in Buffalo City and Cape Town and 63% in Johannesburg [6-8]. Unfortunately, transgender men and nonbinary people have been largely overlooked in the HIV response, with no available prevalence data from South Africa.

Engaging transgender people in HIV care and prevention is necessary to reach global goals for ending the HIV epidemic by 2030. Global 2020 targets toward ending the HIV epidemic were missed and often left behind key populations, such as transgender people. For example, in 6 of 13 countries reporting HIV data on transgender people to the Joint United Nations Programme on HIV and AIDS (UNAIDS), less than half of transgender women were able to access HIV prevention services [9]. The Global AIDS Strategy 2021-2026 aims to leave no one behind in the HIV response [10]. Therefore, UNAIDS has set more ambitious targets for 95% of people with HIV to be diagnosed, 95% of diagnosed people with HIV to be on antiretroviral therapy (ART), and 95% of people with HIV on ART to achieve sustained viral suppression (ie, 95-95-95) by 2025 [11]. As key populations accounted for 65% of new HIV infections globally and 35% within sub-Saharan Africa in 2020, UNAIDS emphasized the importance of reaching key populations, including transgender people, to achieve these goals [12,13]. Because stigma and discrimination are known drivers of HIV, UNAIDS also set targets for 2025 that include <10% of health workers reporting negative attitudes toward key populations and <10% of key populations reporting experiences of stigma and discrimination [14]. However, interviews with >1400 transgender people in South Africa in 2023 revealed that only 7% felt safe and comfortable when accessing health care; 72% no longer get services because of disrespect from health facility staff; 65% reported that health facility staff were unfriendly; and 10% had been denied health care outright [15].

Although South Africa has the world's largest HIV epidemic, it has achieved 95% of people with HIV being aware of their status, 77% of people with HIV on ART, and 71% of people with HIV virally suppressed [3]. Unfortunately, South Africa does not disaggregate HIV continuum data for transgender people. In 2019, a study that combined data from transgender women and men who have sex with men in sub-Saharan Africa (including Cape Town and Soweto, South Africa) found that 56% of people with HIV knew their status, 34% were on ART, and 28% were virally suppressed [16]. Another combined study of transgender women and men who have sex with men in Johannesburg found that 47% were virally suppressed. Modeling data from 2021 indicate South Africa will not reach the HIV elimination threshold (incidence <0.1%) without engaging key populations [17]. Modeling has indicated that halving the rate of ART interruptions in South Africa would substantially reduce new infections, accelerating progress toward ending the HIV epidemic [18].

Available data among transgender men [19] and transgender women [20,21] have found suboptimal levels of ART adherence and viral suppression, even in high-income countries. For example, a US-based study of transgender men with HIV found that while 93% had been prescribed ART, only 60% maintained viral suppression over 12 months [19]. Similarly, a US study of transgender women found that while 80% reported ART adherence, only 59% achieved viral suppression [21]. Disaggregated data on viral suppression among transgender people in South Africa are scant. However, an observational cohort study, including 24 transgender women from South Africa, Kenya, and Malawi found that 25% of transgender women were virally suppressed at baseline and 62.5% were suppressed at 12 months [22].

UNAIDS 2025 targets call for 95% of people at risk for HIV acquisition to use combination HIV prevention, including PrEP [11]. However, PrEP uptake is low among transgender women. A large (N=728) US-based longitudinal study of transgender women's adherence to PrEP during periods of sexual risk (also known as prevention-effective adherence) found it to be <20% [23]. A smaller South African study (N=213) found that less than half of transgender women who were HIV negative reported they had heard of PrEP and only 11% reported taking PrEP

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[24]. Qualitative interviews with transgender women in the study (n=36) identified health facility-based antitransgender stigma as a barrier to care seeking [24]. While PrEP data on transgender men in sub-Saharan Africa are unavailable, research in high-income countries has found that PrEP-eligible transgender men report low PrEP use (approximately 11%) [25,26], and health care provider stigma is associated with decreased access to HIV prevention services [27]. Our team found no published data on PrEP engagement among gender nonbinary people.

Multiple studies with transgender people have concluded that stigma and limited access to gender affirmation are associated with increased HIV risk and low engagement in HIV care and prevention services [19,20,28,29]. Access to gender-affirming hormone therapy (GAHT) is a priority for many transgender people, often deemed more important than HIV care or prevention [30]. However, a recent study with transgender women in South Africa found that only 17% had access to GAHT [24]. Research has also found that the use of gender-affirming language by health care providers positively impacts transgender patients' health care experiences, quality of care, mental health, and likelihood of seeking preventive services [31].

Differentiated Service Delivery

Transgender-specific differentiated service delivery (TG-DSD) is a promising strategy to overcome barriers to HIV service engagement among transgender people. Differentiated service delivery (DSD) is a term used to refer to client-centered approaches that tailor HIV services to reflect the needs of specific populations [32]. Building blocks of DSD include adaptations to when (eg, frequency of clinical visits), where (eg, health facility or community), by whom (eg, nurses or community health workers), and what (eg, ART, PrEP, or counseling) services are offered based on the needs of the individual client [33]. When implemented at scale, DSD is intended to simplify and adapt HIV services across the prevention and treatment continuum in ways that better serve client needs, improve client outcomes, and reduce burdens on the health system [32]. UNAIDS 2025 targets call for 90% of people with HIV and people who face heightened vulnerability to HIV acquisition to be linked to people-centered, context-specific, integrated services, that is, DSD [11].

DSD sites may differentiate services according to client clinical characteristics (eg, newly diagnosed with HIV or stable on ART), subpopulations to which they belong (eg, pediatric, pregnant, or key population), and context in which they live (eg, concentrated versus generalized epidemic and rural versus urban setting) [33]. The World Health Organization (WHO) promotes the use of DSD for key populations to increase service acceptability, quality, and coverage, and reduce costs [34]. Facilities across sub-Saharan Africa have implemented a variety of DSD models for different subpopulations [35-37]. However, South Africa is the first in the region to implement TG-DSD models that tailor services to the specific needs of transgender people, including the need for GAHT.

As GAHT is a priority for transgender people, guidance on DSD for key populations from the WHO [38] and the International AIDS Society [33] recommend the inclusion of GAHT in DSD for transgender people. Promising research in Peru, Thailand, and the United States suggests that integration of GAHT services with HIV care and prevention can improve engagement with HIV services [39-42]. However, the evidence base is limited to case studies or protocols lacking outcome data [39,41,43,44], cross-sectional associations between the use of GAHT and engagement in HIV services [45,46], or outcomes and perceptions of services at a single site [40,42,47]. No published studies compare HIV outcomes at TG-DSD sites versus standard service delivery (SSD) sites, and no published studies of TG-DSD have been conducted in sub-Saharan Africa, the region with the greatest burden of HIV [35].

A recent review of DSD models called for a deeper understanding of their mechanism of effect and noted that while the success of DSD implementation may differ based on a variety of factors, few studies have evaluated comparative implementation or cost [48]. To inform ongoing efforts to achieve UNAIDS goals and leave no one behind, data are needed on the effectiveness of TG-DSD models for improving engagement in HIV services and on implementation barriers, facilitators, acceptability, feasibility, and cost.

Wits RHI demonstration sites provide a unique opportunity to evaluate TG-DSD in sub-Saharan Africa [49]. Over the last several years, Wits RHI has collaborated with transgender-led organizations in 4 municipal areas (Gauteng, Cape Town, Nelson Mandela Bay, and Buffalo City) in South Africa to implement a TG-DSD site in each area (n=4 sites). Each site integrates gender-affirming care, including GAHT, with a full package of facility-based and community-based (mobile) HIV care and prevention services, consistent with the WHO key population and DSD guidelines [49-51]. All staff members receive training on the provision of nonstigmatizing, gender-affirming services. Clinicians receive additional competency training in gender-affirming medical care. These real-world sites, currently supported by programmatic (nonresearch) funds from United States Agency for International Development, provide an important opportunity to conduct much-needed implementation research [32,34,52]. Findings will not only directly inform the future direction of DSD strategies in South Africa but also advance the knowledge base on *if* and *how* TG-DSD models work and the cost of implementation.

A robust evidence base supports DSD among nonkey populations. A systematic scoping review of DSD for HIV treatment included 40 publications (18 from South Africa) involving over 240,000 participants spanning 9 countries in sub-Saharan Africa [35]. The review found that a variety of DSD models were effective for improving viral suppression and retention in care compared with SSD. DSD improved acceptability and, in some cases, reduced the cost of care to clients. While these data provide a strong scientific premise for evaluating DSD models, none of the evaluated DSD models focused on key populations.

Study Aims and Hypotheses

This study, titled Jabula Uzibone (a Zulu phrase that can be translated into English as "be happy, see yourself"), is designed

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to fill an important gap in data on implementation, effectiveness, and cost of TG-DSD models in sub-Saharan Africa. It has the aims presented in Textbox 1.

Textbox 1. Jabula Uzibone study aims.

Aims

- Aim 1: assess the barriers, facilitators, acceptability, and feasibility of transgender-specific differentiated service delivery (TG-DSD).
- Aim 2: evaluate the effect of TG-DSD on viral suppression and prevention-effective adherence and test stigma and gender affirmation as mediators.
  - Hypothesis 1: rates of viral suppression (HIV RNA <50 copies/mL) are more likely to increase among transgender people on antiretroviral therapy (ART) at TG-DSD sites than among transgender people on ART at standard service delivery (SSD) sites over the 12-month study period.
  - Hypothesis 2: rates of prevention-effective adherence (measured by tenofovir levels >700 fmol/punch among participants on pre-exposure prophylaxis [PrEP] or no condomless intercourse among participants who are HIV negative and not taking PrEP) are more likely to increase among participants at TG-DSD sites than among those at SSD sites over the 12-month study period.
  - Hypothesis 3: stigma and gender affirmation will mediate relationships between service delivery models (TG-DSD vs SSD) and HIV outcomes (viral suppression and prevention-effective adherence).
- Aim 3: estimate the cost associated with TG-DSD versus SSD using a microcosting approach to determine the cost per service user served and per service user successfully treated at TG-DSD sites relative to SSD sites, as well as the budget needed for successful South Africa–wide implementation.

Methods

Overall Study Design

Jabula Uzibone is an observational, multisite, mixed methods, and prospective implementation study. To meet the first aim, we will assess the implementation of TG-DSD models and SSD models at the facility level using standardized observation checklists at 8 facilities (1 DSD site and 1 SSD site per area in all 4 areas). We will examine implementation, acceptability, feasibility, and barriers to and facilitators of TG-DSD via key informant interviews (KIIs; n=6 per site) with health facility staff. At the client level, we will conduct in-depth interviews (IDIs) with 30 transgender people (15, 50% from DSD sites and 15, 50% from SSD sites) drawn from the longitudinal cohort enrolled for aim 2 described in the next paragraph.

To meet the second aim, we will enroll a cohort of ≥600 transgender people and follow them for 12 months. Of the transgender people enrolled, ≥400 (66.7%) will be transgender people living with HIV. This will include ≥200 (50%) who receive ART at TG-DSD sites and ≥200 (50%) who receive ART at SSD sites in the same area as the TG-DSD sites. We will also enroll ≥200 transgender people without HIV. This will include ≥100 (50%) participants without HIV at TG-DSD sites and ≥100 (50%) without HIV at SSD sites in the same area as the TG-DSD sites. Each participant will complete a quarterly survey to assess engagement in HIV prevention and care, changes over time in experiences of gender affirmation, and experiences of stigma.

For participants on ART, we will measure HIV RNA levels (ie, viral load) at baseline and 12 months. For participants on PrEP, we will measure tenofovir levels at baseline and 12 months. For participants who are HIV negative and not on PrEP, we will assess self-reported condomless sex. Prevention-effective adherence is defined as being HIV negative and meeting one of the following criteria: (1) adherent to PrEP based on tenofovir levels, (2) self-report of consistent condom use in the prior 30 days, or (3) self-report of no anal or vaginal sex in the prior 30 days. Table 1 presents a list of data collection activities organized by level of analysis, participant type, and month of enrollment.

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Table 1. Data collection activities by level of analysis, participant type, and month of enrollment.

Level	Participant, n (%)	Baseline	Months 3, 6, and 9	Month 12
Facility level (n=8)				
TG-DSD[a] sites	4 (50)	Checklists	Quantitative survey	KIIs[b] (6/site, n=24)
SSD[c] sites	4 (50)	Checklists	Quantitative survey	KIIs (6/site, n=24)
Transgender people living with HIV (n=400)				
Care at TG-DSD sites	200 (50)	HIV RNA level	Quantitative survey	IDI[d] (n=15)
Care at SSD sites	200 (50)	HIV RNA level	Quantitative survey	IDI (n=15)
Transgender people without HIV (n=200)				
Care at TG-DSD sites	100 (50)	Tenofovir-level	Quantitative survey	IDI (n=15)
Care at SSD sites	100 (50)	Tenofovir-level	Quantitative survey	IDI (n=15)

[a]TG-DSD: transgender-specific differentiated service delivery.

[b]KII: key informant interview.

[c]SSD: standard service delivery.

[d]IDI: in-depth interview.

To meet the third aim, we will estimate the incremental costs of DSD implementation compared with SSD from the provider perspective by conducting a bottom-up analysis of the resources used and costs accrued by the TG-DSD cohort and comparing them to the costs of SSD established in recent studies [53,54]. We will also calculate the cost per successful outcome (suppressed viral load for those on ART and prevention-effective adherence for those without HIV) and the total budget required for a national roll out of TG-DSD.

Ethical Considerations

Ethics approval was received for this study from the University of Witwatersrand Human Research Ethics Committee (M220420) in June 2022 and from the Duke University Health System institutional review board (Pro00113320) in June 2023. All participants complete a written informed consent process, including the option to opt-out of participation, after eligibility screening and before any data collection activities. All data are collected in a private room at the study site or a private area (eg, mobile van) in the community. Name and contact information are collected in order to send reminders of follow-up study visits. However, personal identifiers are retained separate from study data. Each participant is assigned a unique anonymous study identifier that is associated with their data. Personal identifiers are only accessible by specific study staff who have permission to contact participants for reminder purposes. All study staff have been trained in human subjects protections and good clinical practices. Participants receive ZAR 300 (US $17) at the end of each study visit as well as light refreshments (eg, a sandwich).

Study Frameworks

This study uses the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) [55,56] implementation science evaluation framework and the gender affirmation framework [57]. Data collection and analysis for all aims are guided by RE-AIM. Key measures and analyses for aim 2 are also guided by the gender affirmation framework, a conceptual framework that outlines mechanisms by which TG-DSD is expected to improve HIV outcomes.

RE-AIM is often used to guide the evaluation of implementation strategies [55]. It is well-suited for studies of projects that are in the implementation process [56] and guides our selection of study measures [58]. The first 4 RE-AIM domains are listed in Textbox 2, with examples of research questions for each domain. These domains (reach, effectiveness, adoption, and implementation) are most applicable to this study, while the fifth domain, maintenance, will not be addressed.

Textbox 2. Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) domains applied in this study and example research questions.

Domains and example research questions

- Reach: Is the intervention reaching the desired population?
- Effectiveness: Does the intervention accomplish its goals?
- Adoption: To what extent are the people who should deliver the intervention participating?
- Implementation: To what extent is the intervention consistently implemented?

The gender affirmation framework provides a model for drivers of HIV outcomes. Gender affirmation is a process of recognition and support for one's gender identity [57]. Gender affirmation has 4 core facets: medical (eg, GAHT and surgery), psychological (eg, self-acceptance and sense of alignment with one's gender), social (eg, use of desired name and pronouns and wearing clothes associated with one's gender identity), and

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legal (eg, change of name and gender marker on legal documents) [59].

The gender affirmation framework posits that antitransgender stigma leads to social oppression and psychological distress. Social oppression reduces access to gender affirmation while psychological distress increases the need for gender affirmation. The gap between access and need drives behaviors that increase HIV vulnerability. Significant relationships between unmet gender affirmation needs and HIV risk behavior as well as ART interruptions are well documented [57,60-63]. This framework informs our hypothesis that TG-DSD will reduce stigma and increase gender affirmation, thereby increasing engagement in HIV services and improving HIV outcomes (ie, viral suppression and prevention-effective adherence) among transgender people. Our measures of stigma as well as medical (ie, GAHT) and psychological gender affirmation will be used to test hypothesis 3 for aim 2.

Transgender-Specific DSD Models

Wits RHI provides TG-DSD models at 4 sites. Of these, 2 (50%) are stand-alone sites and 2 (50%) are in park homes on an SSD facility campus. All TG-DSD sites offer GAHT in an integrated HIV and primary care package, which includes both facility-based (fixed) services and community-based (mobile) services. All services are free to clients.

Details of the care provided at those sites have been published elsewhere [49], and an overview is provided in Table 2 and Textbox 3. Each site employs peer navigators, community liaison officers, professional nurses, a social worker, a site manager, and community health workers. Each site also employs a sessional physician and psychologist. Services have been designed and delivered in collaboration with local transgender community–based organizations. All cadres of staff (clinical, nonclinical, professional, and lay) complete transgender sensitization training conducted by transgender-led community organizations. These trainings build staff skills in providing nonstigmatizing, transgender-friendly services. Trainings take place upon hire and routinely thereafter during in-service sessions.

Table 2. Wits RHI transgender-specific differentiated service delivery and models of care in South Africa.

	Guateng	Cape Town	Nelson Mandela Bay	Buffalo City
Model	Stand-alone	Stand-alone	Colocated with SSD[a]	Colocated with SSD
Population density	Urban	Urban	Peri-urban and rural	Peri-urban and rural
GAHT[b]	Provided on site	Provided on site	Provided on site	Provided off site

[a]SSD: standard service delivery.

[b]GAHT: gender-affirming hormone therapy.

Textbox 3. Components of Wits RHI transgender-specific differentiated service and their descriptions.

Service and description

- Clinical services: primary health care, sexually transmitted infection screening and treatment, tuberculosis screening, HIV treatment and prevention, and gender-affirming hormone therapy (GAHT)
- Ancillary services: psychosocial support, referral to postviolence care, legal support, and substance use services
- Full-time staff: 4 to 10 peer navigators, 0 to 2 community liaison officers, 1 social worker, 0 to 2 community health workers, 2 nurses, and 1 site manager
- Sessional staff: 1 physician and 1 psychologist
- Community partnerships: local transgender community organizations and local AIDS councils
- Community leadership: community advisory boards comprising transgender advocates and activists who guide and monitor services

Where possible, transgender people are appointed in all staff cadres. Most community health workers and peer navigators are transgender people. Program-specific Facebook (Meta Platforms, Inc) and WhatsApp (Meta Platforms, Inc) groups provide information on services and events to the community. Transgender-friendly health information, education, and communications printed materials are available.

Clinical services related to GAHT are provided only at the facility. The client comes to the facility monthly for the first 3 months on hormones for laboratory testing, side effect assessment, and dose adjustments. After the third month, when clients are on a stable dose, they return to see the medical provider at month 6, then every 6 months subsequently for monitoring. Multi-month dispensing of hormones is currently a challenge in South Africa due to stock shortages; therefore, clients on GAHT return monthly for dispensing visits only.

In addition to facility-based GAHT and HIV services, each TG-DSD site provides mobile HIV services in the community throughout their catchment area. These mobile services are offered in a van equipped with examination rooms and basic medical equipment. Mobile teams include a peer navigator, a community health worker, and a professional nurse. They offer primary health services, HIV testing and counseling, and multi-month dispensing of ART and PrEP.

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SSD Models

Public primary health care centers in South Africa provide SSD through a professional nurse-based, physician-supported infrastructure of >3500 clinics and community health centers, available within 5 km of more than 90% of the population and free at the point of care [64]. Primary health care centers are the first point of entry for health care access. These facilities provide a comprehensive package of basic services, including maternal, child, and reproductive health, and HIV and tuberculosis testing and treatment, including ART, screening and care for noncommunicable diseases, and treatment of common ailments. The primary health care system is supported by community teams, referred to as ward-based primary health care outreach teams. These teams are allocated to specific wards according to the size, geography, and social and structural considerations. They provide health information to the community, and screen and refer those who need further management to corresponding primary health care facilities [65]. Despite a progressive constitutional and legal framework, transgender people continue to face stigma and discrimination when they access SSD sites for health care [66-68]. GAHT is not available in public primary health care facilities. In general, access to GAHT is limited in South Africa, where it is only provided by specialist endocrinologists at tertiary facilities; and transgender people may face waiting times of up to 20 years or more to access gender-affirming surgery in the public sector [69,70].

Study Procedures

Facility-Level Eligibility, Recruitment, and Data Collection

We have enrolled all 4 Wits RHI TG-DSD sites listed in Table 2. In collaboration with district health departments, we have recruited 1 SSD site within the catchment area of each DSD site for a total of 4 TG-DSD sites and 4 SSD sites. SSD sites are similar to TG-DSD sites in urbanicity, socioeconomic status of the client population, and types of HIV services offered (ie, both ART and PrEP). We shared information about the study with the district and SSD site leadership and invited them to participate in the study. Study staff will visit all 8 recruited sites (TG-DSD and SSD) to complete a standardized observation checklist at baseline and 12 months. Checklist items include the number, type, and role of staff; content and frequency of staff training; facility hours, amenities (eg, number of rooms), and community outreach efforts; standard policies and procedures for delivery of HIV and sexually transmitted infection testing, PrEP, ART, and GAHT services, including, but not limited to counseling, prescribing, dispensing, laboratory monitoring, tracking, and visit frequency; sex and gender documentation on clinical forms and records; the number of transgender clients; number of transgender people prescribed GAHT; number of transgender people prescribed PrEP; number of transgender people prescribed ART; availability and use of psychosocial services; and cost of service delivery.

Leadership at each recruited site facilitate recruitment of 6 staff members per site (n=48) to complete a KII at baseline and 12 months. Eligible staff members are aged ≥18 years and work for 1 of the TG-DSD sites or a selected SSD site. We enroll 1 person in each role at each site, that is, peer navigator, community liaison officer, social worker, community health worker, nurse, and site manager. If a staff member leaves between baseline and 12 months, we will interview another person in the same role for the 12-month time point. We contact potential key informants via email or WhatsApp and invite them to participate.

An experienced qualitative researcher conducts the KIIs after the informed consent process. A semistructured KII guide will be used to organize the interview. KIIs last approximately 60 minutes and include open-ended questions that explore facilitators, barriers, strengths, and weaknesses of the DSD and SSD approaches and recommendations for improving service delivery. At the end of the qualitative interview, participants complete a brief, interviewer-administered quantitative tool measuring antitransgender stigma [71] and validated measures of intervention acceptability, feasibility, and appropriateness [72,73]. KIIs are audio-recorded with permission of the participant, and notes are taken during and after the interview to facilitate accuracy and appropriate analysis. Where possible, interviewers are fluent in local languages. When interpretation is required, a trained study staff member interprets during the interview.

We collect data on the costs of implementation at all TG-DSD sites by conducting a bottom-up analysis of the resources used and costs accrued by all transgender cohort participants who receive TG-DSD. We also collect facility-level data on overhead cost items, such as space, administration, and utility costs, and allocate these to the service and our cohort based on the number of visits. We use our extensive database of public sector prices and salaries, as well as information on staff levels at each site, to estimate the public sector costs; these are data we have used in other costing studies in South Africa [53,74,75].

In collaboration with local transgender organizations, trained transgender people recruit their peers from their social networks via social media posts, WhatsApp groups, and word-of-mouth. Eligibility criteria include age ≥18 years, identity as a gender different from the sex assigned at birth, and residence in the catchment area for 1 of the enrolled health facilities. Participants must either be living with HIV and prescribed ART or HIV negative and PrEP eligible (whether or not they are currently taking PrEP). We use stratified sampling to ensure enrollment of ≥400 participants on ART and ≥200 participants who are HIV negative. Within those strata, we further ensure that half are individuals who receive care at a TG-DSD site and the other half are transgender people who receive care at an SSD site in the same catchment area. We use quotas to ensure that no TG-DSD site makes up <20% of TG-DSD participants. At the enrollment visit, participants are rescreened for eligibility, including rapid HIV testing to confirm self-reported HIV status.

Client-Level Eligibility, Recruitment, and Data Collection

Participants complete study data collection visits with the study team in a dedicated room at the site or in the community. Over the 12-month study period, participants complete 5 study visits: baseline, 3, 6, 9, and 12 months. At each visit, trained study staff use electronic tablets to administer quantitative surveys lasting 30 minutes. Surveys assess the key measures listed in

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Table 3. Survey data are collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University), which synchronizes with the encrypted cloud-based server at Wits RHI, where it is stored for analysis.

Table 3. Key quantitative survey measures.

Construct	Measure	Citation
Implementation outcomes		
Acceptability	Acceptability of Intervention Measure	Weiner et al [73], 2017
Feasibility	Feasibility of Intervention Measure	Weiner et al [73], 2017
Appropriateness	Intervention Appropriateness Measure	Weiner et al [73], 2017
Enacted stigma		
Health facility stigma	Brief Health Facility Stigma Tool	Nyblade et al [71], 2013
Experienced stigma		
Transgender-specific stigma	Gender Minority Stress and Resilience measure	Testa et al [76], 2015
Intersectional stigma	Intersectional Discrimination Index	Scheim and Bauer [77], 2019
Gender affirmation		
Psychological	Psychological Gender Affirmation Scale	Sevelius et al [78], 2021
Prevention-effective adherence [23]		
Sexual behavior	"Have you had anal or vaginal sex in the past 30 days?"	—[a]
Condom use[b]	"How often did you use condoms when you had sex?"	—
PrEP[c] adherence[d]	"How many days have you missed PrEP pills in the last 30 days?"	—

[a]No relevant citation.

[b]This question is only asked of participants who report sex in the past 30 days.

[c]PrEP: pre-exposure prophylaxis.

[d]This question is only asked of participants who self-report taking pre-exposure prophylaxis.

At the baseline and 12-month visits, all participants have blood drawn by a professional nurse for laboratory analysis. Serums from participants on ART are tested for HIV RNA. HIV RNA levels <50 copies/mL are the threshold for viral suppression, consistent with South African national guidelines [79]. Dried blood spots from participants on PrEP will be tested for tenofovir diphosphate levels [80,81]. Levels >700 fmol/punch are consistent with ≥4 doses per week and will be used as a marker for adherence [82,83].

Thirty (5%) of the 600 enrolled transgender participants who complete the quantitative survey and laboratory analyses at baseline are invited to participate in longitudinal qualitative IDIs at baseline and 12 months. IDIs are most appropriate for eliciting detailed accounts of participant experiences and perceptions of service delivery models. The open-ended nature of IDIs provide the opportunity to more deeply explore issues relevant to the study aims. Embedding qualitative data collection within implementation research can enrich the understanding of how and why service delivery models work or do not work [84,85]. Longitudinal interviews are important to study how participants experience, interpret, and respond to the service delivery model over time [86].

We invite participants to take part in IDIs using stratified purposive sampling [87]. We stratify by care model, that is, 15 who receive care at TG-DSD sites and 15 who receive care from SSD sites. Within each stratum, we purposively sample to ensure diversity by HIV status, catchment area, and gender identity (transgender women, transgender man, and gender nonbinary). A topical guide structures the interview. Open-ended questions, followed by prompts, are used to elicit participant narratives. Study staff with training and experience in qualitative research conduct the IDIs. Each IDI explores perceptions of DSD versus SSD models of care, satisfaction or concerns related to type of care received, experiences with GAHT, if any, experiences with ART or PrEP, as appropriate, and recommendations for service improvement. Follow-up IDIs will explore how participant experiences and perceptions have changed over time and provide an opportunity to clarify earlier responses. With participant permission, all interviews are digitally audio-recorded. Interviewers write field notes and narrative summaries after each interview that supplement the transcripts. Participants' qualitative data are linked with the survey data to allow for integration with their quantitative measures of stigma and gender affirmation.

Participant tracking and retention rely on multiple strategies. At enrollment and each subsequent study visit, we document contact details for participants (eg, phone numbers, addresses, WhatsApp, and social media profiles) to communicate study reminders and re-engage participants who may miss a study visit. If participants are unable to come to the study site for data collection, research staff support retention by accompanying mobile health facility staff into the community and collecting study data there. We provide modest financial remuneration and refreshments to incentivize participation and retention. We

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have hired transgender study staff to create a welcoming and affirming environment for study participation. Gender-affirming stigma reduction training of research staff facilitates strong staff-participant rapport to encourage retention. Participants are provided a referral to counseling services if they demonstrate psychological distress while engaging with study staff.

Overall Approach to Data Analysis

Data analysis will include both qualitative and quantitative data. Table 4 outlines the relationships between the RE-AIM framework domains and the types of data to be collected.

Table 4. Relationship among the Reach, Effectiveness, Adoption, Implementation, and Maintenance domains; study aims; and data collection.

Domains (aim), levels, data type, and source	Example qualitative questions and quantitative measures
Reach (1)	
Facility	
Site checklist	Number of transgender people who receive GAHT[a], ART[b], or PrEP[c] from the site
KIIs[d] with health staff	What factors contribute to the engagement of transgender people at TG-DSD?
Adoption (1)	
Facility	
KIIs with health staff	What barriers and facilitators affected staff implementation of TG-DSD?
Implementation (1 and 3)	
Facility	
Site checklist	Number and type of staff and their roles in implementation. Availability of GAHT on site. Frequency of stigma reduction training. Cost of service delivery (infrastructure, labs, visits, etc)
KIIs with health staff	How was TG-DSD implemented and adapted over time? AIM[e], IAM[f], and FIM[g] implementation science measures
Client	
IDIs[h] with transgender participants	Tell me about the services you received at the site?
Effectiveness (2)	
Facility	
KIIs with health staff	What changes in use of HIV services (eg, ART and PrEP uptake and adherence) did you notice when TG-DSD was implemented? Health Facility Stigma Scale by Nyblade [71]
Client	
IDIs with transgender participants	Tell me about your experience receiving care at the site.
Survey with transgender participants	Intersectional stigma scale by Scheim and Bauer [77], Psychological Gender Affirmation scale by Sevelius et al [78], and GAHT use by self-report.
Laboratory test with transgender participants	HIV RNA level by serum analysis (for transgender participants on ART) and tenofovir level by DBS[i] (for transgender participants on PrEP)

[a]GAHT: gender-affirming hormone therapy.

[b]ART: antiretroviral therapy.

[c]PrEP: pre-exposure prophylaxis.

[d]KII: key informant interview.

[e]AIM: Acceptability of Intervention Measure.

[f]IAM: Intervention Appropriateness Measure.

[g]FIM: feasibility of intervention measure.

[h]IDI: in-depth interview.

[i]DBS: dried blood spot.

Qualitative interview (KII and IDI) recordings will be transcribed and translated into English. The transcripts, field notes, and narrative summaries will be uploaded into qualitative data management software, Atlas.ti (ATLAS.ti Scientific Software Development GmbH), to facilitate analyses. During regularly scheduled meetings, the study team will review field notes, transcripts, and summaries; discuss emerging themes; and revise interviewing and coding strategies, as needed.

Statistical analysis of quantitative data will be performed using Stata (StataCorp) and MPlus (Muthén & Muthén). Data exploration of key variables will be conducted to assess for implausible values and determine whether statistical assumptions

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(eg, normal distributions of data) for planned statistical analyses are satisfied. Categorical variables will be reported as frequencies and percentages, with means and SDs or medians and IQRs reported for continuous variables. Patterns of missing data will be examined, including testing for differences between participants with and without missing data. A series of sensitivity analyses will be conducted to evaluate the robustness of conclusions drawn from the primary models to departures from the missing at random assumption by comparing the magnitude of the primary effect. In the rare situation that >10% missing data is observed, we will use multiple imputation, as appropriate. We will specify 2-sided tests, .05 significance level (α=.05), and compute 95% CIs throughout.

Qualitative Data Analysis for Aim 1

Qualitative transcripts from the KIIs with health facility staff and IDIs with transgender people will be analyzed to assess barriers, facilitators, acceptability, and feasibility of TG-DSD. To identify preliminary results quickly, we will use a framework-guided rapid analysis in which transcripts are summarized in a structured template [88,89]. The template will include a section for each of the 4 aspects of this aim: barriers, facilitators, acceptability, and feasibility.

For full analysis, a priori codes based on the interview guides and key implementation constructs from RE-AIM will be used to generate the initial codebook [84]. A total of 2 independent analysts will code a subset of transcripts and meet weekly to discuss the textual context, update the codebook, assess interrater reliability, and generate analytic memos. Once the codebook is finalized, the remainder of the transcripts will be systematically coded. Code summaries will be consolidated into matrices by each category of variation (eg, site) to identify salient themes [90]. Any differences in code density will be explored after coding completion from baseline to 12 months and by site characteristics, such as district, urbanicity, and population size.

Codes and associated quotes will be examined within and across transcripts to identify patterns and recurrent themes related to the implementation constructs [91]. After preliminary findings have been shared with key stakeholders for member-checking [92], deductive in-depth content analyses will be conducted with open coding followed by focused coding. Once coding is complete, we will use visualization features of Atlas.ti to map out differences in code density by service delivery model.

To take advantage of the longitudinal nature of the data, we will apply multiple analytic approaches to the constant comparison technique as outlined by Lewis [93]. We will review the narrative summaries for each participant over time to look for within-individual changes. We will read across the transcripts for each period to look for themes unique to specific periods, and we will compare all data across service delivery models (TG-DSD vs SSD). Analytical memos will describe emergent themes and track the analytic process. Peer debriefing, triangulation with quantitative data, member-checking, and memos will support rigor [94].

Sample sizes for qualitative inquiries are designed to collect enough data to reach theoretical saturation, defined as the point at which no new themes emerge from ongoing data collection [95]. Samples sizes as low as 6 can achieve saturation when the study population is homogeneous. However, a sample size of 12 to 20 is typically needed, fewer for longitudinal studies. To account for diversity by site, role, gender identity, education level, etc, we have chosen a sample size of 48 individuals for KII participants, for a total data set of 96 KIIs (including baseline and 12 months). We have selected a smaller sample size of 15 per arm (n=30) for IDIs with transgender clients as they will share similarities which will produce a robust data set of 60 total IDIs for analysis.

Quantitative Data Analysis for Aim 1

Standardized checklists from DSD and SSD sites will be examined using descriptive statistics. We will perform chi-square tests or Fisher exact tests for associations between categorical variables. We will perform unpaired Student *t* tests to compare continuous variables or outcomes between 2 groups. We will perform Wilcoxon rank sum tests, if data are not normally distributed.

In the DSD sites, to assess acceptability and perceived feasibility of implementing the differentiated care model, staff at each implementing site will complete a brief survey with implementation outcome measures at 12 months. The Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure (FIM) will be used to quantitatively measure implementation outcomes related to the TG-DSD model [73]. Each measure consists of 4 items, with response options on a Likert scale from 1 (completely disagree) to 5 (completely agree), for a possible summary score range from 4 to 20. Higher scores indicate greater acceptability and feasibility.

Descriptive statistics will be used to characterize each measure overall and by site. On the basis of a score of 4 (agree) for all 4 items in the scale, a summary score ≥16 on each scale would be consistent with overall agreement that the strategy was acceptable or feasible, respectively [73]. Therefore, we will test the hypothesis that the overall mean score for each measure (AIM and FIM) is ≥16 using a 1-sample *t* test. If score data deviate from normality (skewed or nonnormal), we will conduct a 1-sample Wilcoxon signed test. We will conduct a secondary analysis to test for significant changes in baseline and 12-month scores across sites using paired sample *t* tests for normally distributed data or Wilcoxon signed rank tests if the data are nonnormal.

Using data from both study arms, facility-based stigma will be measured using the brief health facility stigma tool [71]. Each item includes 4 response options on a Likert scale that ranges from “never” to “most of the time.” Higher scores indicate greater facility-based stigma. Descriptive statistics will be generated as outlined earlier for the implementation outcome measures. We will compare mean summary scores at TG-DSD sites versus SSD sites at baseline and at 12 months, using 2-sample *t* tests if normally distributed or Wilcoxon rank tests if nonnormal. Exploratory analyses will include Pearson correlation analyses and bivariate regression to assess associations between site characteristics (eg, location and

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urbanicity), including facility-based stigma scores and the aforementioned implementation outcome scores.

Qualitative and Quantitative Data Integration for Aim 1

Qualitative and quantitative data will be integrated using results-based convergent synthesis in which they will be analyzed separately then merged using joint display [96-98]. Qualitative themes will triangulate and provide context for facility stigma scores and implementation measures. Data from the checklists will be integrated into the joint display to assess visually any relationships between site features and the relationship between TG-DSD and HIV outcomes. Integrated displays will be used to identify implementation patterns. The qualitative code density (frequency of each code) will be displayed by service delivery model (TG-DSD vs SSD). Visualization will facilitate identification of similarities and differences in participant experiences across models.

Data Analysis for Aim 2

We will use quantitative methods to evaluate the effectiveness of TG-DSD for viral suppression and prevention-effective adherence and to assess stigma and GAHT use as potential mediators. As noted earlier, our first hypothesis is that rates of viral suppression are more likely to increase among transgender people on ART at TG-DSD sites than among transgender people on ART at SSD sites over the 12-month study period.

The primary outcome measure is the proportion of transgender people on ART with viral suppression (HIV RNA <50 copies/mL). Descriptive analyses will summarize HIV viral suppression comparing participants at TG-DSD versus SSD sites as well as by gender identity at baseline and 12 months. Percent distributions will be computed for categorical variables and means, ranges, SDs, medians, and IQRs will be presented for continuous variables stratified by attendance at TG-DSD versus SSD sites. The primary estimate for this aim is the absolute difference in the change in proportion of virally suppressed during the study period between participants at TG-DSD sites and those at SSD sites. A difference-in-difference (D-i-D) analysis will be conducted to account for anticipated differences between groups at baseline (TG-DSD vs SSD). In addition, we will compare differences at 12 months considering baseline values to enhance the robustness of the estimators of the differences in the 2 groups.

A mixed-effects binomial model will be fit, where the binary viral load suppression status of each client is regressed on fixed effects for time (baseline vs 12 months), TG-DSD versus SSD site, the time by site model interaction, and client-level covariates (age and gender identity). In addition, random intercepts for each of the sites will be included in the model to account for within-site correlation. The D-i-D estimator is the estimated regression coefficient for the time by service delivery model interaction term. All models will account for clustering and be adjusted for relevant confounders in baseline covariates.

The second hypothesis is that rates of prevention-effective adherence are more likely to increase among transgender people who are HIV negative at TG-DSD sites than among those at SSD sites, over the 12-month study period. We will follow the same steps outlined above for the primary hypothesis. However, we define the outcome measure (prevention-effective adherence) as the proportion of (1) participants on PrEP with TFV levels >700 fmol/punch and (2) participants who are not on PrEP who report no condomless intercourse during the prior 30 days. The estimate will be the absolute difference in the change in the proportion who achieve prevention-effective adherence during the study period comparing those at TG-DSD versus SSD sites. In addition, we will estimate the difference between TG-DSD and SSD sites at 12 months, considering baseline values.

Clients who receive SSD services on enrollment may switch to TG-DSD over time, thereby reducing the sample size of the SSD arm and creating a threat to internal validity. To identify and account for switches over time, we will update information about where the participant is receiving care at every study visit. Participants who transfer from an SSD site to a TG-DSD site will be censored after the date of their last visit for the primary analysis. It would be inappropriate and unethical to require participants to continue receiving care at a specific site, therefore we will use careful tracking to inform an exploratory dose-response analysis that considers the amount of time a participant received care at the TG-DSD sites. The amount of time receiving care at the TG-DSD site will be the independent variable, with the change in outcome from baseline to 12 months as the dependent variable.

The third hypothesis is that stigma and gender affirmation will mediate relationships between service delivery models (TG-DSD vs SSD) and HIV outcomes (viral suppression and prevention-effective adherence). Mediation analyses will be used to investigate whether any association between service delivery models and HIV outcomes are significantly mediated by stigma (measured using Nyblade et al [71], Testa et al [76], and Scheim and Bauer [77] scales in Table 3) or gender affirmation (measured using the proportion of participants on GAHT and the Sevelius et al [78] gender affirmation scale in Table 4). Structural equation modeling will be used for this analysis. Structural equation modeling provides tests of the direct and indirect paths from the independent variable to the dependent variables [99]. The independent variable will be the service delivery model (TG-DSD vs SSD), and the dependent variables will be change from baseline to 12 months in the mediators (stigma and gender affirmation measures) and change from baseline to 12 months in the outcomes (difference in viral suppression and difference in prevention-effective adherence). Structural equation models will test direct paths (eg, from serviced delivery model to viral suppression) and indirect paths (eg, from service delivery model to stigma and from stigma to viral suppression). The basic model to be tested for this analysis is in Figure 1. We will assess standard fit statistics for the overall model: model chi-square, adjusted goodness of fit, comparative fit index, and standardized root mean square error of approximation.

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Figure 1. Structural equation model to test stigma and gender affirmation as mediators of relationships between service delivery type and HIV outcomes.

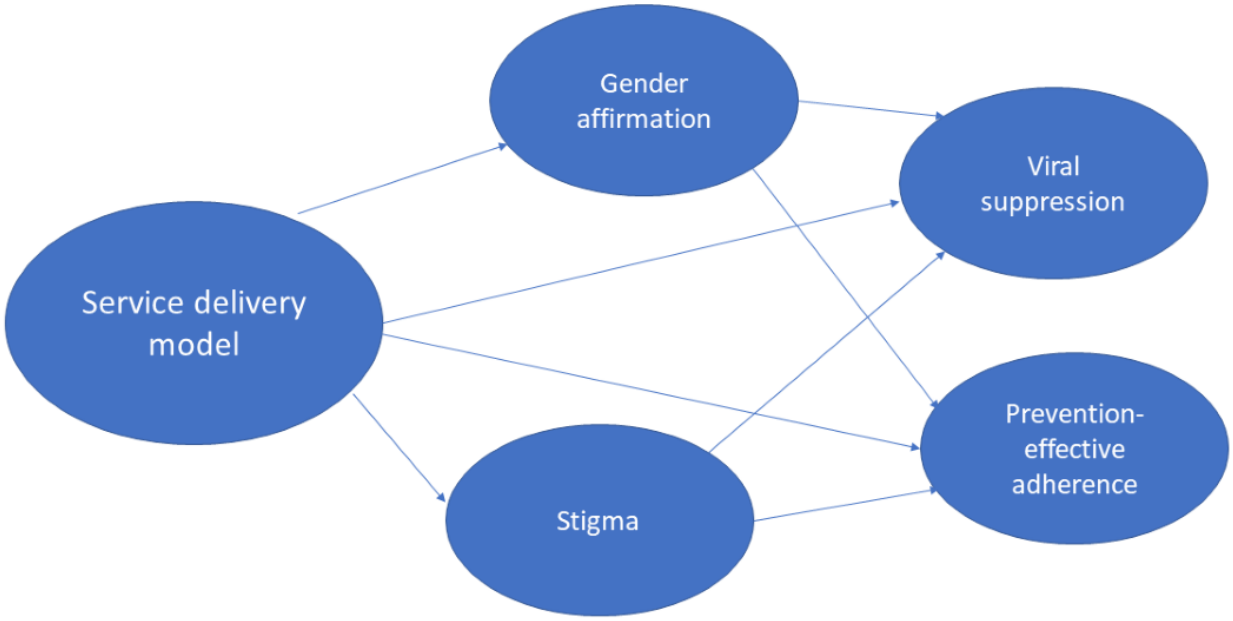

Exploratory Analyses for Aims 1 and 2

We will conduct 3 exploratory analyses. First, using longitudinal data from baseline, 3, 6, 9 and 12 months, we will perform mixed-effects regression modeling to analyze changes in stigma scores, psychological gender affirmation scores, and GAHT use over time by service delivery model. Mixed-effects regression is most appropriate for clustered longitudinal data as it captures correlations of repeated measures using random effects that describe cluster-specific trends over time [100]. Second, as sample size allows, we will assess HIV outcomes by subgroups. The D-i-D model, used to test hypothesis 1 and hypothesis 2, will be fit separately for subgroups defined by (a) gender identity, (b) sex assigned at birth, (c) individual care facility, and (d) colocated versus stand-alone TG-DSD sites. Third, the association between 12-month HIV outcomes (viral suppression rates and prevention-effective adherence rates) and implementation metrics from aim 1 will be examined graphically for the 4 TG-DSD sites by plotting the HIV outcomes at each site versus mean scores on the AIM, IAM, and FIM, respectively.

The use of D-i-D analyses implicitly assumes that TG-DSD sites are either comparable with SSD sites (other than the DSD approach) or that we can readily adjust for any differences. However, if we find that groups differ on important characteristics, we will use inverse probability of treatment weighting to adjust for the covariates in the effect estimation to mitigate potential bias.

Data Analysis for Aim 3

We will use the data from the microcosting exercise as well as existing data on SSD costs to estimate the incremental cost of TG-DSD over SSD from the health care system perspective. Integrating data collected for aim 2, we will then calculate the cost per successful outcome (defined as viral suppression for those participants on ART or prevention-effective adherence for the participants who are HIV negative at month 12) and the cost of producing an additional client with a successful outcome. Finally, using any available size estimates for the overall transgender population in South Africa [5], we will then calculate the total budget required for a national rollout of TG-DSD in South Africa, incremental to the country's HIV budget on which we will have real-time data.

Statistical Power

Power analyses and sample size calculations were based on the primary outcome of viral suppression (aim 2). No viral load data are available for transgender people in South Africa disaggregated from other key populations. The only South African data that includes transgender women and uses the current nationally recommended threshold for viral suppression includes cisgender men who have sex with men. Nonetheless, the study found a viral suppression rate of 47% [101]. One study of transgender people receiving TG-DSD in South Africa found that those on GAHT were 3 times more likely to be virally suppressed compared to transgender people who are not on GAHT [49]. This suggests an effect size of at least 20%. We consider an effect size as low as 15% to be clinically significant.

On the basis of the aforementioned data and clinical experience, we anticipate that current viral suppression rates will be approximately 65% at baseline, rising to 85% at 12 months among TG-DSD participants, and approximately 61% at baseline, rising to 66% at 12 months among SSD participants. This 20% difference from baseline to 12 months for TG-DSD participants and 5% difference from baseline to 12 months for SSD participants represents a difference in the absolute change in viral suppression rates of 15%. Using r=1, α=.05, power of 1− β=.80, and p_1=viral suppression in the SSD and p_2=viral suppression in the TG-DSD group and difference of $p_2 - p_1$=.15, the minimum sample per group will be 172 for both TG-DSD and SSD, for a total minimum sample size of 344. Adjusting for loss to follow-up of approximately 12%, a sample of ≥200 in each group, for a total of ≥400 transgender people on ART, provides adequate statistical power for planned analyses.

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Loss to follow-up is a challenge for any longitudinal study. We will make every effort to minimize loss to follow-up by collecting multiple forms of contact, reaching out monthly to update contacts, collecting data in the field as well as the study site, and providing remuneration for study participation. We are enrolling a larger sample size than required by the power calculations to allow for potential loss to follow-up without loss of statistical power.

Results

The Jabula Uzibone study enrollment began in January 2024. As of July 31, 2024, a total of 593 transgender participants have been enrolled: 348 are living with HIV and 245 are HIV negative. We anticipate baseline enrollment will be complete by August 31, 2024, and the final study visit will take place no later than August 2025.

Discussion

Expected Findings

We anticipate that the Jabula Uzibone study will demonstrate that TG-DSD is associated with higher rates of viral suppression and prevention-effective adherence compared with SSD. Furthermore, we expect qualitative and quantitative results to indicate that these associations are mediated by gender affirmation and stigma reduction. Importantly, we expect to find that broader implementation of key aspects of TG-DSD models, including cost, are feasible, acceptable, and appropriate.

Prior studies of DSD models support their effectiveness for improving retention in care and viral suppression for people living with HIV in sub-Saharan Africa [102]. However, the largest systematic review assessing DSD implementation barriers and facilitators excluded key populations [103]. This study will fill the critical gap in data on DSD for transgender people, a key population, as well as provide the first data on use of DSD for HIV prevention services.

Strengths and Limitations

This study is limited by its nonrandomized, observational nature. As TG-DSD is already being offered at Wits RHI sites in South Africa, sites cannot be randomized. While randomized controlled trials (RCTs) are considered the highest standard of scientific evidence, an RCT is not feasible in this situation. If an RCT were possible, it would run the risk of producing findings that cannot be replicated in less controlled settings. Jabula Uzibone will generate rich data on implementation strategies and intervention effectiveness in real-world conditions.

Assessment of prevention-effective adherence among participants who are HIV negative and not prescribed PrEP relies on self-reported sexual behaviors. Recall and social desirability bias may affect the accuracy of self-report. Despite this limitation, our choice to measure overall prevention-effective adherence (rather than limiting measures to tenofovir levels among participants on PrEP) allows for broader applicability of findings to the real lives of transgender people whose sexual behavior and indication for PrEP shift over time [23].

Conclusions

In addition to dissemination in scientific journals and relevance conferences, results from this study will be shared directly with both transgender community organizations and the National Department of Health in South Africa. Jabula Uzibone will provide actionable data to inform HIV policies and health facility practices in South Africa and generate the first evidence for implementation of TG-DSD in sub-Saharan Africa. Study findings also may inform how other countries could use TG-DSD strategies to increase engagement of transgender people in care and advance global progress toward HIV elimination goals.

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Data Availability

The data sets generated during this study will be available from the senior author upon reasonable request 1 year after the completion of data collection.

Authors' Contributions

TP, RB, NH, AP, and GM-R contributed to conceptualization. RB, GM-R, and CH contributed to data curation. TP, AP, and JI contributed to funding acquisition. JI, TP, AP, and GM-R contributed to the investigation. IM and TP contributed to methodology. JI, RB, TP, and AP contributed to the acquisition of funding resources. RB, CH, and GM-R contributed to project administration. RB contributed to the database software acquisition and development.
RB and GM-R were involved in supervision. TP wrote the original draft. All authors contributed to writing, reviewing, and editing the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institutes of Health.
[PDF File (Adobe PDF File), 77 KB - resprot_v13i1e64373_app1.pdf]

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Abbreviations

AIM: Acceptability of Intervention Measure
ART: antiretroviral therapy
D-i-D: difference-in-difference
DSD: differentiated service delivery
FIM: feasibility of intervention measure
GAHT: gender-affirming hormone therapy
IAM: Intervention Appropriateness Measure
IDI: in-depth interview
KII: key informant interview
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SSD: standard service delivery
TG-DSD: transgender-specific differentiated service delivery
UNAIDS: Joint United Nations Programme on HIV and AIDS
WHO: World Health Organization

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Protocol

Rethinking the Social Determination of Food in Chile Through Practices and Interactions of Actors in Food Environments: Nonexperimental, Cross-Sectional Study

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Abstract

Background: Food environments are crucial for promoting healthy and sustainable eating and preventing obesity. However, existing food environment frameworks assume an already installed causality and do not explain how associations in food environments are established or articulated, especially from an integrative and transdisciplinary approach. This research attempts to bridge these gaps through the use of Actor-Network Theory, which traces the relationship network between human (and nonhuman) actors in order to describe how these interact and what agencies (direct or remote) are involved.

Objective: This study aims to explain the practices and interactions of actors in food environments in order to approach the problem of unhealthy eating with a transdisciplinary approach.

Methods: This is a nonexperimental, cross-sectional study. Due to the complexity of the study phenomena, a mixed methods approach with 4 consecutive phases will be developed in Chile. Phase 1 involves a systematic literature review of food environment evidence since 2015, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol; phase 2 involves the application of a shortened version of the Nutrition Environment Measure Scale—Perceptions adapted to Chile (NEMS-P-Ch) in 2 neighborhoods with different socioeconomic levels; in phase 3, six focus groups in each neighborhood will be conducted to address social determinants such as gender, employment status, and migration; and in phase 4, participant observation and in-depth interviews will be used to analyze the direct and empirical exploration of the actors in their daily interaction with food environments. The triangulation and complementarity of the data will allow us to create a practical model about the practices and interactions of actors in their food environments, which reflects the complexity and transdisciplinary nature of the study.

Results: We have advanced in phases 1-3 of the study. In phase 1, a total of 109 manuscripts are being revised for data extraction. In phase 2, we applied the NEMS-P-Ch to 785 people, 49.4% (388/785) of whom belong to a low socioeconomic neighborhood. Participants from phase 2 are being contacted to participate in the focus groups (phase 3). By the end of July, we have conducted 6 focus groups with 5-11 participants.

Conclusions: This study will provide a comprehensive understanding of how individuals interact with their food environments, offering deep insights into the factors influencing their food-related decisions. In addition, the study aims to develop a model that more accurately reflects reality by examining not only the food environments themselves but also the interactions among various stakeholders within these environments and their daily practices. The findings of this study will offer evidence-based insights to inform public policies tailored to the specific territories and communities under investigation or those with similar characteristics.

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KEYWORDS

mixed methods; research design; food environments; food intake; obesity

Introduction

Unhealthy eating, characterized by a high intake of ultraprocessed foods (such as high-sugar foods and drinks and foods high in saturated and trans fats) and a low intake of fiber-rich foods (such as fruits, vegetables, and legumes), is a global public health challenge due to its association with obesity and noncommunicable diseases [1,2]. According to the World Health Organization, "three billion people cannot access safe, nutritious, and sufficient food" [2]. Data from the Global Nutrition Report indicate that people have a low intake of vegetables (40% below recommendation), fruits (60% below recommendation), whole grains (61% below recommendation), and legumes and nuts (between 68% and 74% of recommendation) [3]. However, red meat intake is more than 300% above the recommended amount [3]. Ultraprocessed foods represent between 50% and 60% of the daily energy that people consume, meaning that natural or less processed foods are being replaced by these foods [4,5].

Using a comparative risk assessment of 195 countries, the GBD (Global Burden of Diseases, Injuries, and Risk Factors Study) 2017 Diet Collaborators [6] discovered that dietary risk factors were responsible for 11 million deaths and 255 million disability-adjusted life-years in 2017. A recent review and meta-analysis showed that high exposure to ultraprocessed foods is associated with an increased risk of adverse health outcomes, such as cardiometabolic and mental disorders and mortality [7]. Addressing and solving the problem of an unhealthy diet requires a transdisciplinary approach, which goes beyond the biomedical or unidisciplinary methods that tend to oversimplify it.

The evidence indicates that environmental factors are the most relevant elements to explain an unhealthy diet and its consequences [8,9]. An individual will be able to perform some behaviors (eg, eat more fruits and vegetables) only if his or her environment is conducive to those behaviors (eg, if fruits and vegetables are available nearby and at affordable prices) [10-12]. This calls for conceptualizing food environments, of which several definitions exist [13,14]. One of the most recent and comprehensive is contained in the report written by the expert panel on food security and nutrition of the Committee on World Food Security, which defines food environments as *the physical, economic, political, and sociocultural context that frames consumers' interaction with the food system for the acquisition, preparation, and consumption of foods* [15]. This environment is formed by its physical configuration, sociocultural rules, networks of influence and determinations of public and private stakeholders, and the socioeconomic level [14]. It has also been established that food environments are essential for promoting the consumption of healthy and sustainable food, as well as for obesity prevention and improvements in people's quality of life [13,15,16].

The problem with the current food environment is that people are surrounded by obesogenic food environments, which are defined as the ones that bring together opportunities and conditions to promote unhealthy behavior patterns, thus leading to the accumulation of body fat in individuals and obesity in populations [17]. These obesogenic environments predominate in territories with lower socioeconomic levels, establishing unacceptable inequalities that are directly related to the differences in the prevalence of obesity among individuals and communities [18,19]. A recent literature review and meta-analysis showed that living in low socioeconomic neighborhoods increases the probability of being overweight by 31% (odds ratio 1.45, 95% CI 1.21-1.74; $P<.001$) and of being obese by 45% (odds ratio 1.31, 95% CI 1.16-1.47; $P<.001$), compared with high socioeconomic neighborhoods [20].

Chile has been fighting against unhealthy diet and obesity in its population for decades through several public policies [21]. Still, the latest National Health Survey 2016-2017 found that just 15% of the population met the recommendation of 5 servings of fruits and vegetables daily, 9.2% eat fish or other types of seafood, and 24.4% consume legumes at least twice a week [22]. According to the Pan American Health Organization, Chile is one of the countries with the highest sales of ultraprocessed foods in Latin America [16]. In addition, more than 85% of the population is sedentary. As a consequence, the prevalence of overweight, obesity, and morbid obesity affects 74.2% of the population. These conditions affect people's full development and their quality of life, decreasing the years of life that are free from disease and disability and increasing early mortality [23]. This context generates the need to seek new research and work approaches that provide a more comprehensive view, that is, one that goes beyond the traditional limits of only recommending specific behavior changes to people.

In 2016, Cerda et al [24] proposed a model of food environments for Chile through a set of definitions that propose 5 environments: domestic, institutional, street, restaurants (including restaurants, coffee shops, or similar), and supply. In this model, the domestic food environment is considered the starting point for the mobilization of the subjects to other environments. It also states that environments interact with each other and are crossed by cultural, economic, and social dimensions [24,25]. This model of food environments has served as a framework for Chilean policies such as the National Food and Nutrition Policy [26] and the National Health Strategy to establish the health objectives for the decade until 2030 [27].

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An interesting aspect of this model is that it breaks with the usual barriers of individual approaches and forces the integration of disciplines to understand the problem [28]. It also makes it possible to problematize actions in specific environments that are permeable to the daily routines of individuals and communities. In addition, the model includes cultural and social dimensions, which have a great influence on food preferences and practices, complicating the idea that people can "choose to live healthy" when, in fact, lifestyle choices are the result of a complex interaction between all the determining factors (particularly the food environment, the socioeconomic level, and cultural factors). The environment in which we live has a series of "traps" that make it difficult to maintain a healthy life, even when we know which behaviors are desirable [29].

Although there is evidence on some of the food environments in Chile, there are still some problems to be addressed so as to better understand how to determine these environments when analyzing people's nutritional health. Most studies continue to analyze environments associated with a more or less direct response variable (eg, BMI, food availability), although evidence shows that environmental influences on diet are complex, relational, and dynamic [30]. Generally, conceptual frameworks (including those related to social determinants of food and food environments) assume an already established causality while describing structural determinants that limit and restrict people's practices; thus, they do not explain how these associations are established or how they interact with each other. These frameworks also fail to explain how these determinations are embodied and structured in the practices of daily life, which contributes to the lack of understanding of, for example, those "traps that make it difficult to lead a healthy life." As the sociologist of science Bruno Latour [31] contends, these conceptual frameworks are assembled versions of the social aspect. Most of the work that has been done on food environments, according to Thompson et al [32], adopts a "black box" approach because it neither explores how residents of disadvantaged neighborhoods respond to their neighborhood's food environment nor what shapes these different responses beyond better or worse access to a wider range of foods. Turner et al [33] argue that in food environment research, the emphasis on interactions contributes to anchoring the framework of the food environment within the context of individuals' daily routines and behaviors, which influence their dietary habits, adding a more comprehensive point of view.

Moreover, the emergence of digital technology (especially during the COVID-19 pandemic) makes it necessary to reconsider the definitions of food environments, as this technology creates new ways of interacting *with* and *between* different environments. For instance, digital technology allows food sales and purchases, changes food availability, and ignores physical distance and time spent shopping, all while increasing marketing exposure by influencing choices, preferences, and food consumption [34].

These new approaches can be investigated through theoretical perspectives from social science. In the 1970s and 1980s, Actor-Network Theory (ANT) emerged from the work of Latour, Law, and Carron, who questioned the social models that conceal the type of associative dynamics of human (and nonhuman) actors (actants) [35]. ANT attempts to trace the network of relationships between these actors (objects, technology, ideas, devices, animals, vegetables, etc) in order to describe how they interact and which agencies (direct or remote) are involved [31]. This is possible through the traces left by relationships and interactions; however, it is not limited to those produced by human agents, as symmetrically, it also considers the traces produced by the environment itself and its objects [35]. According to Oña Serrano and Viteri Salazar [36], as a conceptual, methodological proposal, ANT would be particularly productive for addressing the complexity of the food system (including the food environment), its interactions, and the multiple economic, sociocultural, and internal and external environmental actors, allowing for a better understanding of the relationships between humans and nonhumans [35]. For Goodman [37], ANT allows food studies to be reframed by problematizing the ontological dichotomy between nature (nonhuman) and society. Following Latour [38], ANT proposes a framework in which interactions are conceptualized in terms of heterogeneous collective associations between elements of nature and elements of the social world, which are assembled in networks of actors. In this line, the agency is collective and relational, as well as a consequence of these hybrid networks between human and nonhuman actors.

Unlike social models that propose "coldly" assembled causal and deterministic structural relationships, ANT proposes the tracking of the actors when the relationships they establish with their environment are more unstable and "hot" [39]. For ANT, an actant (regardless of whether it is human or not) is so when it operates as a mediator for another actant. On the other hand, *tracking* the actors means following the rhizomatic network they build from their interactions with other actors (eg, humans, objects, food, institutions, and speeches, among others) and paying attention to how "they compose the social without previously imposing order on them" [31].

There is already some use of ANT in food studies. de Sowa and Busch [40] researched soy production and consumption in Brazil; Busch and Juska [41] analyzed global food system networks; and Lockie [42] used ANT to trace the interactions between organic food consumers in Australia and a holistic approach to the agri-food system. Most recently, Legun [43] followed an entire process ranging from apple production to their consumption to reflect on the role of technology in shaping food markets, while Stoddard and Cantor [44] used ANT to trace the web of vulnerability around the pork industry in North Carolina.

In this context, food environments represent a privileged space for monitoring networks and relationships between different actors, including those within the food environments themselves. Understanding these dynamics will contribute to comprehending the influence of food environments on diets and people's lives. It is necessary to understand these complex interactions of actors within food environments to determine how sociocultural factors affect these interactions and how they impact the configuration of daily practices and quality of life. Viewing these practices and interactions through a transdisciplinary lens allows for a comprehensive understanding of their complexity. Addressing not only the availability of healthy food, as well as the physical

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and economic access to it, but also food's relational, cultural, and social perspective would allow us to face its convoluted phenomenon in a multidimensional, intersectional, and transdisciplinary manner. This new knowledge could result in a better causal diagnosis, an update of the Chilean food environment model, and the proposal of evidence-based national and local public policies to better approach this complex problem.

To improve our understanding of what happens within the food environments, this study aims to explain the practices and interactions of actors in food environments in order to approach the problem of unhealthy eating with a transdisciplinary approach. To reach this aim, this protocol has the following objectives:

1. To describe people's practices *within* different food environments.
2. To describe people's interactions *with* different food environments.
3. To analyze the class, gender, and cultural determinants of food environment configurations.
4. To review the Chilean model of food environments, considering interactions, practices, determinants, and transdisciplinarity.
5. To generate recommendations for national and local food and nutrition public policy.

This project aims to answer the following question: How are practices and how do actors interact in food environments? We hypothesize that the practices and interactions of actors in food environments exceed the explanations provided by current theoretical models and require a transdisciplinary approach.

Methods

Research Design

This study follows a nonexperimental, cross-sectional, mixed methods study design, which aims to understand the complexity of actors' practices and interactions in food environments based on the Chilean model [24]. The mixed methods approach will be used for the purposes of triangulation and complementarity. Triangulation is used to visualize the same phenomenon with different methodological perspectives, while complementarity is applied for a broader, deeper, and more comprehensive social understanding of a complex phenomenon [45]. In addition, it will be sequential, so that the quantitative methodology will be used before the qualitative one [45].

The mixed methods approach proposed in this research and the use of ANT as the theoretical orientation enable the integration and transformation of knowledge from different perspectives, blurring disciplinary boundaries. Thus, it will contribute to defining, focusing, exploring, and understanding a complex phenomenon, which is the object of this study [46,47]. Finally, the study will be conducted in 4 phases described as follows:

Phase 1: Systematic Literature Review

A systematic literature review is being conducted to update conceptual elements about food environments and provide context for the subsequent phases of the study. The literature review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol [48]. The literature review aims to answer the question: What is new in the evidence of food environment that is not considered in the Chilean Model? To answer this question, we have selected 2 search strategies. First, during 2023, a general search about the food environment was conducted using the terms observed under "general search about food environment" shown in Textbox 1. The terms were searched in English and Spanish. Then, in 2024, a specific search was performed focusing on each food environment included in the Chilean model, using the terms under "search for specific food environments" shown in Textbox 1. In this last search, we also included terms related to the digital food environment and terms related to the influences of food environments.

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Textbox 1. Search terms used for the systematic literature review.

General search about food environment

"Food environment," "eating environment," "nutrition environment," "food availability," "food access," "social food environment," "community food environment," "retail food environment," "information nutrition environment," "obesogenic environment," "unhealthy food environment," "healthy food environment," "food shopping," "unhealthy/healthy food marketing (advertising)," and "food environment typology."

Search for specific food environments

Home food environment: "home food environment," "family and food environment," and "domestic food environment."

Restaurant food environment: "restaurants and food environment," "coffee shops and food environment."

Institutional food environment: "organization food environment," "educational institution (school/university/college/technical school food environment)," and "work food environment."

Supply food environment: "community food environment," "retail food environment," "neighborhood food environment," "urban food environment," "rural food environment," "harvest markets and food environments," "markets and food environments," "convenience store and food environment," and "market/convenience store/strip center and food grocery."

Street food environment: "street food environment," "food truck and food environment," and "community food environment."

Digital food environment: "digital food environment," "delivery and food environment."

Others: "women/children/adults and food environment," "agency and food environment," "migration and food environment," "social determinants of health and food environment," "socioeconomic level and food environment," "educational level and food environment," "gender and food environment," "social class/position and food environment," "time and food environment," "urban structure and food environment," "city and food environment," "geographic access and food environment," and "social food environment."

Papers were included if they were published after 2015 (when the Chilean food environment model was developed); they were in English, Spanish, or Portuguese; they were qualitative, quantitative, or mixed methods studies; systematic reviews; or other review types, meta-analyses, and reports. Papers were characterization or observational studies, all related to humans. Studies related to eating disorders, body image distortion, or specific food topics unrelated to food environments were not included. The search for papers was performed in academic databases such as Web of Science, Scopus, PubMed, SciELO, LILACS, and Cochrane. An additional nonacademic search was conducted in the databases of the World Health Organization, the Pan American Health Organization, and the Food and Agriculture Organization of the United Nations, among others. Finally, a specific search was conducted in journals that publish food environment research. The paper search was conducted from July 2023 to April 2024.

We hired 2 methodologists (DS and AR) and experts in systematic literature review to organize this phase. One methodologist (DS) carried out document identification (phase 1 in the PRISMA protocol). We hired 2 research assistants (LI and CZ) for conducting the document selection (phase 2). Both research assistants independently conducted the paper selection. Phase 1 and phase 2 were conducted using the Rayyan software [49]. Four researchers (the authors of this manuscript) are conducting the data extraction and analysis of the selected documents (phase 3), and they will conduct the data synthesis (phase 4). The 2 methodologists are supervising all the phases. Study quality will be evaluated by the 2 methodologists according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework [50].

Phase 2: Application of the Nutrition Environment Measure Scale—Perceptions Adapted to Chile Instrument

Participants

The participants were adults older than 18 years who performed some or any food purchases for their households. The participants were selected from households in 2 neighborhoods in the urban area of the metropolitan region, selected according to the communes' level of multidimensional poverty [51]: one with a high level of multidimensional poverty and the other with a low level of multidimensional poverty [52,53].

We excluded people who do not speak Spanish, who have lived in the country for less than 5 years, who have a disability that does not allow them to complete the project activities, or who follow a very restrictive diet either due to disease or by choice, as it may profoundly alter their relationship with the food environment.

For this phase, we expect to obtain people's perceptions of their food environments. Therefore, it is an exploratory phase. In consequence, to calculate the sample size, we assumed that there was an infinite population for each neighborhood and that the proportions of people living in those communes were unknown; therefore, unknown proportions and an error of 5% were used [54]. Also, we assumed a normal distribution. With this, a sample size of 384 people per neighborhood was calculated, meaning that, for the 2 neighborhoods, a sample of 768 participants was needed.

Instrument

In the Chilean food environment model, the domestic food environment is considered the actor's starting point and is described as one of the most complex environments due to the diversity of households that can be found [25]. It is also the main socialization space where most of the food preferences and traditions are defined, symbolized, transmitted, and

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reproduced [55]. Based on this context, the experiential work of this study begins with the application of an instrument based on the Nutrition Environment Measure Scale—Perceptions (NEMS-P) questionnaire developed by Green and Glanz [56], which evaluates the perceptions people have about their food environments and the practices they carry out there, starting in the home food environment. NEMS-P has been shown to be an easy-to-understand instrument [56], has good test-retest reliability (Kappa Index > 0.6 for most items), and acceptable internal consistency (Cronbach a values of 0.6-0.7). This instrument has been adapted to the Chilean food environment model and has been validated in this population by part of the team presenting this proposal [57]. The Nutrition Environment Measure Scale—Perceptions adapted to Chile (NEMS-P-Ch) had an acceptable reliability with Cronbach a values between 0.44 and 0.82 for the items [57].

Based on the psychometric analysis and the experience in previous research using the NEMS-P-Ch, we shortened this instrument to adapt it to the recommended time for conducting in-person surveys or questionnaires (25-30 minutes) [58]. This shortened version had 31 questions divided into six sections, similar to the original instrument: (1) home food environment; (2) food supply food environment; (3) eating out food environment (including restaurant and street food environment); (4) institutional or organization food environment (work or study places); (5) self-perception of body weight, health, and food; and (6) general household background. This short version of the NEMS-P-Ch has the same internal consistency as the larger version (data not yet published). Like the original NEMS-P, the shortened version of NEMS-P-Ch includes different types of items: direct response (eg, “On average, how many times a month do you eat in a restaurant?”), multiple choice (eg, “Regarding your meals at this place of study or work, you usually… a. Buy your meals there, b. Shop around this place, c. Bring food from home”), yes/no options (eg, “Could you tell me if any of the following foods were available in your home during the past week? Fruits such as oranges, bananas, apples, pears, peaches”), and Likert-type scales that evaluate the degree of agreement, appropriateness, importance, ease, or frequency (eg, “It is easy to buy fresh fruits and vegetables in my neighborhood: never, occasionally, almost always, always”).

Data Collection

The Microdata Center at the Universidad de Chile conducted the data collection. This center specializes in conducting national, regional, and local surveys [59]. Based on their previous experiences in survey research, they randomly selected 102 blocks in both neighborhoods: 50 from the low socioeconomic neighborhood and 52 from the high one. In each of these blocks, a trained team member did the census registration of all the addresses corresponding to homes in a database. From this list of addresses in the database, they randomly selected homes to visit. They randomly selected 12 homes per block in the low socioeconomic neighborhood and 14 in the high one. In addition, to ensure that they completed the sample size, they randomly selected 36% and 47% more homes in the low and high socioeconomic–level neighborhoods, respectively.

We trained 20 interviewers. These interviewers had experience in survey application and had worked for the Microdata Center. We conducted a 4-hour training program that included ethics (including consent process) and a question-by-question review and revision. In addition, we prepared a survey manual for the interviewers, which was sent to them by email before the training. This group of trained interviewers applied the NEMS-P-Ch in person from October to December 2023, visiting the selected homes in each neighborhood.

Data Analysis

Descriptive statistics will be applied for each of the scales included in the instrument. Items that describe food environments or people’s interactions with them were scored. Negative scores are given for less healthy food environments, while positive scores are given for the opposite. The perception of the environments between households in districts with different levels of multidimensional poverty will be explored by comparing the scores using the *t* test or the Wilcoxon-Mann-Whitney test, depending on whether the data meet the normality assumption [60]. We will also consider adjusting a multiple linear regression model for each of the perception scales, using the scale score as the response and the level of multidimensional poverty as a variable, controlling for other individual characteristics such as age, gender, and others [61]. Statistical analyses will be performed with SPSS (version 29.0; IBM Corp) software.

Phase 3: Conducting Focus Groups (2024-2025)

Participants and Sampling

The participants will be adults aged 18 years or older who (ideally) participated in phase 2. The sample determined will be by convenience. Participants who answered the NEMS-P-Ch by email or phone will be invited to participate in one of the focus groups. If we cannot complete the necessary sample for each focus group with the participants from phase 2, we will invite other people who meet the inclusion criteria from the corresponding neighborhood. We will ask for the collaboration of community members from the included neighborhood to invite other participants.

Data Collection

In this intermediate phase, we will conduct focus groups that are considered workshops with the actors for listening-conversation-reflection. Focus groups are a technique that aims to produce a set of social conversations based on group discussion of relatively focused topics [62]. The focus groups will analyze and interpret how actors’ meanings develop in their food environments and what the significant associations are, thus accessing the knowledge and perceptions that guide their decisions, choices, and actions, which leads to their configuration [62]. The focus group will also allow us to understand how food environments determine food behaviors from the point of view of those who interact in these environments. In this manner, we will be able to obtain, as ANT points out, *their* theories about what makes up the social component. The generation of the focus groups and the creation of the questions will be based on the results of phase 2 and on

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the background information emerging from the systematic literature review (phase 1).

A total of six focus groups will be carried out for each neighborhood participating in phase 2, distributed as follows: (1) a group with people who have a paid job, (2) a group with people without a paid job, (3) a group with Chileans only, and (4) a group with non-Chileans. Finally, there will be a group of (5) only men and (6) only women.

The focus groups will be conducted by trained personnel. The duration of each focus group will be a maximum of 1.5 hours (90 minutes), and between 5 and 8 people will be invited. Each focus group will be recorded and transcribed.

Data Analysis

The focus group recordings will be transcribed and reviewed by a team member to ensure the accuracy of the transcription. The information will be analyzed in accordance with the principles of the Grounded Theory of Strauss [62], which establishes three main moments: (1) *open coding*, whose main objective is to discover and develop a conceptualization that emerges from the data. This cellular approach to information, rather than global, reduces complexity and synthesizes the information from the construction of codes, which will be consistent with the research objectives; (2) *axial coding*, which articulates networks in order to relate concepts and analytical categories, establishing hierarchies with subcategories—properties and dimensions—around a category taken as the axis and which seeks to create schemes of understanding to advance toward analytical resolutions over descriptive ones; and (3) *final integration of findings*, which refers to the presentation of tentative explanations—some call this phase *selective coding* [63]. Atlas.ti (version 24; Cleverbridge GmbH) software will be used to provide technological support in the systematization of the large amount of information collected.

Phase 4: Ethnography (2025-2026)

Participants

The participants will be adults aged 18 years or older who (ideally) participated in phase 2 or 3 of this proposal. The sample for this phase will be selected according to the cases' representativeness and relevance. We will create profiles of participants (case studies) based on the findings of the previous phases. We will select subjects associated with characteristics and life conditions that stand out as distinctive and then select the determinant features of these subjects, that is, those with attributes that reflect meanings, decisions, and behaviors that are of interest for an in-depth study or situated knowledge to enhance the analysis of particular cases. Each profile will offer us an exhaustive and qualitative description of a specific situation or condition that not only involves a detailed understanding of what we intend to study but also provides the possibility of considering new aspects that may help us develop more relevant concepts. Likewise, it will allow us to identify key elements and variables that have an impact and that show the links between them, providing the phenomenon with an explanation that includes relationships, variability, and complexities to achieve an approach between the theories included in the theoretical framework and the reality under study.

Data Collection

Overview

Once the previous phases have been carried out, we will address the main principle of the ANT, which proposes "following the actors themselves" in order to trace the sites of production of interactions [31]. Through this ethnographic method, we can directly and empirically explore the actors' daily interaction with the food environments they operate in by using different sources and techniques combined to carry out a "field experience" and thus access the meanings and senses in a nondisruptive and contextualized manner [59]. For this purpose, the following will be carried out.

Participant or Ethnographic Observation

This technique refers not only to the act of looking but also to the act of observing critically and attentively [64]. It focuses on exploring the daily contexts in which the subjects of study develop by means of an in situ and systematic inquiry, in which the researcher is partially inserted. That is, he or she participates as an observer who acts as an external agent to the context being studied precisely to be able to capture the dimension of daily routines and practices [64]. Field notes and photographs will be taken by the research team.

In-Depth Interviews

We will use a conversational technique that is open, flexible, and reflexive, enabling a trusting and horizontal dialogue between researcher and interviewee [65]. A guideline of questions will be created and constantly reviewed for cultural appropriateness and questioning capacity in relation to the aspects of interest. Interviews will be conducted where people deem convenient, provided that these places are associated with the food environments they experience, such as the domestic and supply. These interviews will be audio recorded.

Ethnography

We will conduct 15 case studies, following Eisenhardt's principles, which state that it is possible to generate theorization between 4 and 10 cases [66]. The ethnography will be conducted for 4-5 hours, in 2-3 days (depending on the participant's availability), and especially in those moments when the participant is relating with food and food environments such as grocery shopping, cooking, commuting, among others. The ethnography will be conducted by trained personnel.

Data Analysis

Team members will transcribe the interview. A team member will review this transcription to ensure the accuracy. Field notes will be transcribed into a Word document. The qualitative data analysis will be carried out using Atlas.ti (version 24) software, following the Grounded Theory approach described before [63,67].

Triangulation and Complementarity of the Obtained Data

As a merged construction of the methodological process, triangulation will be carried out to understand the phenomenon

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with the use of data of a different nature whose priority is to compare [68] (1) level of complementation of relevant information to group dimensions and meanings; (2) levels of convergence of information to agglutinate common dimensions and generate categories and codes; and (3) levels of divergence of information to segment dimensions of meanings.

On the other hand, there will be elements of the quantitative data that will be complemented and deepened with the speeches and explanations found in the qualitative phase [45]. In other words, qualitative data will provide information that has not been collected by quantitative methodologies. We will be able to inquire about the "*why*" and the "*how*" of the visualized phenomenon, allowing a better understanding of it. In this sense, it is mainly in the data analysis where the mixture of methods will be carried out. In addition, through the qualitative information, we will be able to apply the ANT principles to understand the interactions between human and nonhuman actors that influence their decisions made in food environments (which will probably also appear in the quantitative data). In consequence, we will create the network of actants in food environments.

The information obtained through the triangulation and complementarity of the data, as well as ANT, will be useful to understand how actants and food environments cocreate everyday practices. It will thus enable us to create a practical model of the practices and interactions of actors in their food environments, reflecting the transdisciplinary approach of the study.

Ethical Considerations

This protocol was accepted on January 2023 and funded on June 1, 2023. Ethical approval was obtained on May 27, 2023, from the Ethics Committee of the College of Medicine, Universidad de Chile (#013-2023). Informed consent is obtained from all participants before the beginning of each study phase after explaining the activities they will participate in and their rights and duties. All participant data will be de-identified, and only aggregated group data will be presented in all reports of the study findings. Participants in phase 2 did not receive any compensation. Participants in phase 3 will receive transportation compensation of about US $10 (10,000 Chilean pesos), while participants in phase 4 will receive US $50 (50,000 Chilean pesos) for their time in the ethnography activities.

Results

Advances in Phase 1: Systematic Literature Review

For the general search, we retrieved 712 documents. For the specific search about each food environment in the Chilean Model, we retrieved 773 documents. As of May 2024, a total of 109 documents from both searches are in the data extraction phase. We will finish the systematic literature review by August 2024. The results are expected to be submitted for publication by the end of 2024.

Advances in Phase 2: Application of the NEMS-P-Ch Instrument

We applied the instrument to 388 participants in the low socioeconomic–level neighborhood and 397 from the high socioeconomic–level neighborhood, reaching a total sample of 785 participants. Participants have a median age of 51 years, with a minimum of 18 years and a maximum of 92 years. Participants from the low socioeconomic neighborhood were older than their counterparts (55 vs 47 years; P=.003).

Most of the participants were female (460/785, 58.6%), and 0.1% (1/785) perceived themselves as other gender. No differences between neighborhoods were found. Data analysis is planned to be finished by July 2024, and the first results are expected to be submitted for publication by the end of 2024.

Advances in Phase 3

Phase 3 started in July 2024 and will be finished by September 2024. By the end of July, 6 focus groups have been conducted: the groups of women, men, and nonworkers in both neighborhoods. Between 5 and 11 participants took part in the focus groups. Pending focus groups are planned for August and September 2024.

Pending Phase and Activities

Phase 4 will take place from November 2024 until September 2025. Data triangulation and integrative data analysis will occur from September 2025 to January 2026.

Discussion

Principal Findings

This study will examine what happens within food environments from a transdisciplinary perspective. Through its innovative feature, it will generate new experiential and practical knowledge of how the actors use, interact, and mobilize in their food environments and, in doing so, characterize the actors' food practices. We expect to find new elements of food environments that have not been described before and complex interactions between actors in these environments. These interactions go beyond a simple and traditional explanation of food practices. All this new knowledge will be translated into a new framework of food environments that will include updated information about the phenomenon and an integrated approach that allows an understanding of how people make decisions in food-related processes [33].

Chile has some definitions and concepts that allow a theoretical understanding of food environments as probable agents of poor nutrition in the population [25]. However, it is necessary to complement this theory by studying people's daily experiences, decisions, and interactions with their environments, an aspect not previously studied that can also serve as a model for other countries.

The study will be carried out using mixed methods, allowing a deeper investigation of the interaction and configuration of food environments, delving into the "why" and "how" of the visualized phenomenon. For Turner et al [33], using mixed methods research has the potential to fill the gap in our

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understanding of people's interaction with food environments. Previous studies have used mixed methods in food environment research [69-73]. However, these studies included exploring 1 food environment (most commonly, the retail food environment). This study will give information about the 5 food environments included in the Chilean model: home, organizational, street, restaurant, and supply food environments [25].

The use of ANT as a framework is also an innovation in the study of food environments. The complexity of this research problem forces us to look for answers through methodologies that go beyond fragmentary research, moving from linear observation to interactional observation. The ANT will allow us to innovate in studying the relationship between food environments and the actors (human and not human) moving inside and through them, turning this new information into an understandable framework [74].

Transdisciplinarity reorients scientific work and forces the integration of different areas of knowledge, promoting a symmetrical and dynamic relationship of perspectives that enrich traditional approaches and are projected through a prism, giving rise to new and innovative perspectives [75]. In this case, a dialogue between different medical disciplines and social science is assumed. Transdisciplinarity challenges us to a joint conceptual construction of the study problem, objectives, methodologies, analysis, and proposals. This type of research paves the way for the necessary and different points of view, allowing for the multiprofessional and intersector approach that this complex problem requires.

Despite the study's relevance and information quality, we acknowledge some limitations. First, this study will be conducted only in an urban region of Chile, leaving out other relevant elements from rural regions. In addition, our study does not include geographic information as most mixed methods research in food environments [69,73]. Finally, we will focus exclusively on the adult population residing in 2 neighborhoods within a single region of the country. Although these elements could enrich the understanding of the food environment, our study will represent an integral view of people's food practices and decisions from their home food environment to other environments where they move daily.

The results of this study will be disseminated through peer-reviewed publications in Web of Science journals and through abstracts, posters, and presentations at national and international conferences. The results will also be reported to local and national governments to inform policies. We will send infographics with the results to participants at each project phase. Finally, the study findings will be posted on the Transdisciplinary Group for Obesity of Populations website at the Universidad de Chile (GTOP-UChile) of which the authors are part [76].

Conclusions

This study will provide a holistic view of food environments. This study will present an integrated view of food environments and their configuration versus the fragmented view of the current Chilean model. In this context, this study will also open new challenges and lines of research on this subject. The new information shown in this study will help develop evidence-based and more comprehensive cross-sectoral public policies and create a new framework for food environments with an interactive approach between individuals and the environment. Like the previous Chilean model of food environments, this new one could be used to study food environments in other Latin American countries [75,77,78].

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Data Availability

The data generated from this study will be made accessible in the future to facilitate collaborative research inquiries. Requests for access must be formally approved by the principal investigators.

Authors' Contributions

PGE, LRO, CFM, and DER participated in the conceptualization of the study, the design of the methodology, and the acquisition of funding. PGE is in charge of project administration and supervision. PGE was in charge of the writing-original draft of the manuscript. LRO, CFM, and DER were in charge of writing-review and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Peer-review report by the Concurso Nacional de Proyectos FONDECYT Regular 2023 - Agencia Nacional de Investigación y Desarrollo (Chile).
[PDF File (Adobe PDF File), 85 KB - resprot_v13i1e62765_app1.pdf]

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Abbreviations

ANT: Actor-Network Theory
GBD: Global Burden of Diseases, Injuries, and Risk Factors Study
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
GTOP-UChile: Group for Obesity of Populations website at the Universidad de Chile
NEMS-P-Ch: Nutrition Environment Measure Scale—Perceptions adapted to Chile
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Multicomponent Intervention to Improve Acute Myocardial Infarction Care in Tanzania: Protocol for a Pilot Implementation Trial

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Abstract

Background: Although the incidence of acute myocardial infarction (AMI) is rising in sub-Saharan Africa, the uptake of evidence-based care for the diagnosis and treatment of AMI is limited throughout the region. In Tanzania, studies have revealed common misdiagnosis of AMI, infrequent administration of aspirin, and high short-term mortality rates following AMI.

Objective: This study aims to evaluate the implementation and efficacy outcomes of an intervention, the Multicomponent Intervention to Improve Acute Myocardial Infarction Care (MIMIC), which was developed to improve the delivery of evidence-based AMI care in Tanzania.

Methods: This single-arm pilot trial will be conducted in the emergency department (ED) at a referral hospital in northern Tanzania. The MIMIC intervention will be implemented by the ED staff for 1 year. Approximately 400 adults presenting to the ED with possible AMI symptoms will be enrolled, and research assistants will observe their care. Thirty days later, a follow-up survey will be administered to assess mortality and medication use. The primary outcome will be the acceptability of the MIMIC intervention, which will be measured by the Acceptability of Intervention Measurement (AIM) instrument. Acceptability will further be assessed via in-depth interviews with key stakeholders. Secondary implementation outcomes will include feasibility and fidelity. Secondary efficacy outcomes will include the following: the proportion of participants who receive electrocardiogram and cardiac biomarker testing, the proportion of participants with AMI who receive aspirin, 30-day mortality among participants with AMI, and the proportion of participants with AMI taking aspirin 30 days following enrollment.

Results: Implementation of MIMIC began on September 1, 2023. Enrollment is expected to be completed by September 1, 2024, and the first results are expected to be published by December 31, 2024.

Conclusions: This study will be the first to evaluate an intervention for improving AMI care in sub-Saharan Africa. If MIMIC is found to be acceptable, the findings from this study will inform a future cluster-randomized trial to assess effectiveness and scalability.

Trial Registration: ClinicalTrials.gov NCT04563546; https://clinicaltrials.gov/study/NCT04563546

International Registered Report Identifier (IRRID): DERR1-10.2196/59917

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KEYWORDS

myocardial infarction; Tanzania; sub-Saharan Africa; implementation science; quality improvement

Introduction

Overview

Acute myocardial infarction (AMI) is a leading cause of death and disability globally [1]. In sub-Saharan Africa (SSA), the burden of AMI is rising rapidly as the region progresses through its epidemiological transition [2]. Approximately 250,000 deaths, or 5% of all deaths in SSA each year, are attributed to AMI [3]. In an effort to curb the rising global burden of AMI, the World Health Organization has prioritized evidence-based AMI treatment with antiplatelet agents as a "Best Buy" for reducing noncommunicable disease morbidity and mortality [4]. Yet, AMI care remains under-studied in SSA [2,5-7], and there are currently no published studies from the region evaluating quality improvement interventions to increase aspirin administration in AMI [8,9]. In Tanzania, recent studies have shown that uptake of evidence-based AMI care is suboptimal. Specifically, in a northern Tanzanian emergency department (ED), we found that only half of adult ED patients with potential AMI symptoms undergo testing with electrocardiogram (ECG) or cardiac biomarker testing, only 23% of patients with AMI were treated with aspirin, and only 5% of patients with AMI were taking aspirin 30 days following their diagnosis [10-12]. Against this backdrop, AMI outcomes in Tanzania are currently poor: approximately 90% of AMI cases are misdiagnosed, and 30-day mortality among patients with AMI is 43% [12].

In response to these findings, an interdisciplinary design team consisting of providers from the study hospital and global experts in implementation science, emergency medicine, and cardiology, developed a multicomponent intervention to improve the uptake of evidence-based AMI care in Tanzania. Because there are currently no published interventions to improve AMI care in SSA [8], the design team chose to adopt a quality improvement intervention from Brazil (the ACS-BRIDGE intervention) [13,14]. The team chose this intervention due to its emphasis on both diagnosis and treatment, its multicomponent nature, its appropriateness for a resource-limited setting, its preliminary efficacy, and its congruence with local barriers to care [15]. Guided by formative qualitative data [15], the design team tailored the ACS-BRIDGE intervention to the local Tanzanian context using the ADAPT-ITT framework [16]. The result was the tailored intervention, Multicomponent Intervention to improve acute Myocardial Infarction Care (MIMIC). This pilot trial will assess the implementation outcomes of MIMIC as well as its impact on clinical care in a Tanzanian ED.

Study Aims and Outcomes

This study will assess the acceptability, feasibility, and preliminary efficacy of the MIMIC intervention in a single-arm pilot trial. The primary outcome will be the acceptability of the MIMIC intervention. Secondary implementation outcomes will include feasibility and fidelity; secondary efficacy outcomes will include (1) the proportion of participants with chest pain or shortness of breath who undergo diagnostic testing for AMI, (2) the proportion of AMI participants who receive aspirin, (3) 30-day mortality among AMI participants, and (4) the proportion of AMI participants adhering to aspirin at 30 days following study enrollment.

Methods

Adaptation

The process of developing the MIMIC intervention has been described in detail elsewhere [17]. Briefly, an interdisciplinary design team considered a wide range of published interventions to improve AMI care [8,13,18-25]. Two existing quality improvement interventions for AMI clinical care were considered most suitable for potential adaptation to the resource-limited Tanzanian health care context. In India, the ACS-QUIK trial aimed to improve AMI care, but did not demonstrate a significant reduction in mortality or cardiovascular events among patients, included strategies (such as electronic discharge order sets) that were not possible in Tanzania, and emphasized rapid percutaneous coronary intervention, which is not currently available in Tanzania [21]. For these reasons, the ACS-QUIK study was not selected for adaptation. The other intervention, ACS-BRIDGE in Brazil, successfully bolstered adherence to evidence-based AMI therapies, reduced in-hospital major cardiovascular events, and included low-cost strategies that were more feasible in Tanzania, so it was selected for adaptation [13]. However, the health care landscape in Tanzania is much different from Brazil, with fewer resources and less access to advanced cardiac care [26]. To address this, the MIMIC intervention was adapted to the resource-limited context of Tanzania over a 1-year period of discussion and refinement by an international team of experts in emergency medicine, cardiology, and implementation science [17].

Design

The MIMIC intervention is delineated in Figure 1. Briefly, the intervention consists of five key components: (1) a triage card that will be placed on the stretchers of patients with AMI symptoms by the triage nurse to prompt the physician to consider the diagnosis of AMI, (2) a pocket card summarizing the basic approach to AMI diagnosis and care that will be distributed to physicians and nurses, (3) a detailed web-based refresher module covering AMI diagnosis and care that will be required for all staff physicians and nurses, (4) educational pamphlets that will be distributed to patients with AMI and educational messages regarding AMI self-care that will be displayed on screens in the ED waiting room, and (5) a designated physician and nurse champion who will encourage the team and manage the delivery of all 5 intervention components. The full MIMIC intervention has been previously published. As described elsewhere, the patient education materials were piloted with patients from a range of educational backgrounds to ensure comprehensibility during the intervention development process [17].

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Figure 1. The MIMIC intervention for improving acute myocardial infarction care in Tanzania. AIM: acceptability of intervention measure; AMI: acute myocardial infarction; MIMIC: multicomponent intervention to improve acute myocardial infarction care.

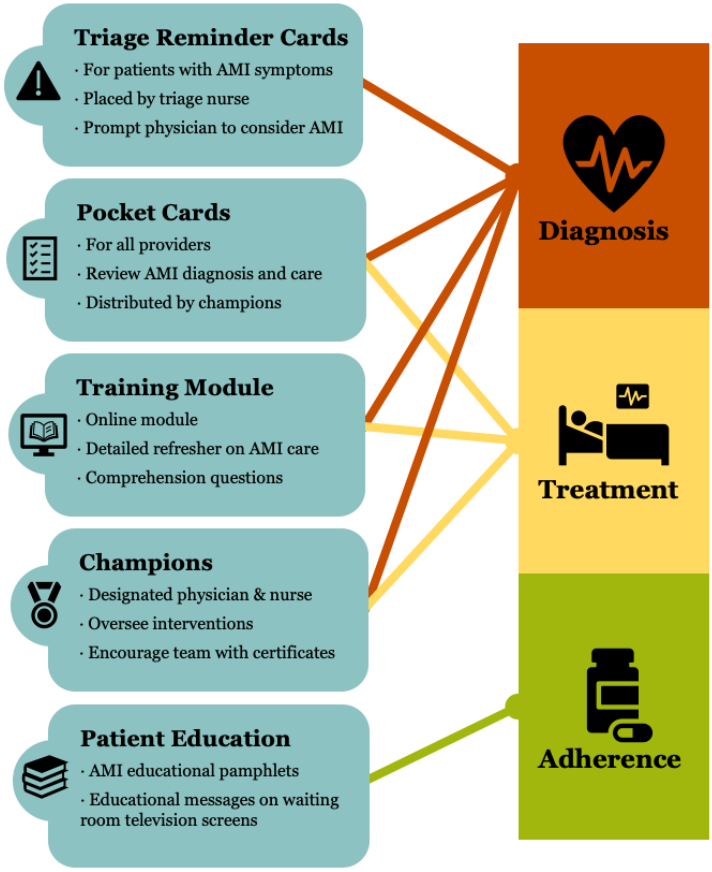

Study Setting

The study will be conducted at Kilimanjaro Christian Medical Centre (KCMC), a tertiary care center in Moshi, Tanzania. KCMC is a zonal hospital covering a catchment area of approximately 15 million persons and was the site of our preliminary studies identifying gaps in evidence-based AMI care [10-12,15,27]. KCMC is currently equipped with basic AMI diagnostic tools, including ECG machines, both point-of-care and laboratory-based troponin assays, and echocardiograms. KCMC is also currently well-stocked with basic AMI medications, including aspirin, clopidogrel, heparin, statins, nitrates, beta-blockers, other antihypertensives, and thrombolytics. Additionally, KCMC offers a dedicated outpatient follow-up clinic for patients with cardiac conditions like ischemic heart disease. However, KCMC presently does not have a cardiologist on staff and lacks the capacity for percutaneous coronary intervention or coronary surgery.

Study Sample

This pilot trial will be conducted in the KCMC ED for 1 year. Implementation outcomes (acceptability, feasibility, and sustainability) will be assessed primarily via in-depth interviews and surveys conducted with key stakeholders (physicians, nurses, patients, and administrators). Secondary efficacy outcomes will be assessed via observation of the care of patients who present to the KCMC ED with possible AMI symptoms during the study period. Based on the results of prior surveillance studies in the KCMC ED [11,12,28], we expect to enroll approximately 400 patients with chest pain or dyspnea in the KCMC ED over 1 year.

Inclusion and Exclusion Criteria

For in-depth interviews and surveys assessing implementation outcomes, eligible participants will be KCMC staff, including hospital staff and physicians and nurses working in the ED during the study period, as well as patients diagnosed with AMI in the KCMC ED during the study period. Patients younger than 18 years and those who were unable to provide informed consent were excluded from study participation. For ED patients whose care will be observed to assess secondary efficacy outcomes, eligibility criteria will be as follows: (1) KCMC ED patient presenting during the study period, (2) being 18 years or older, and (3) primary or secondary complaint of chest pain or dyspnea. Exclusion criteria will be as follows: (1) chest pain secondary to trauma, (2) self-reported fever, and (3) inability to provide informed consent. Consistent with prior AMI studies in Tanzania [11,12,28], these exclusion criteria were selected to exclude patients whose chest pain or dyspnea is unlikely to be due to AMI.

Recruitment

For surveys administered to hospital staff to assess implementation outcomes, members of the research team will approach physicians, nurses, and administrators to offer them participation in the study. To minimize disruptions to clinical care, research staff will approach staff during break periods, meals, or at the conclusion of their shift. Staff will be

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compensated 5000 Tanzanian shillings (approximately US $2) for their time completing the survey.

For in-depth interviews evaluating implementation outcomes, purposive sampling will be used to ensure participants from diverse backgrounds are included. Participants will be hospital staff, administrators, and patients from a variety of occupations, ages, genders, and educational backgrounds. Selected hospital staff and administrators will again be approached by research staff during their break periods and offered participation in the in-depth interviews. Moreover, selected patients will be contacted via telephone and offered participation. All in-depth interview participants will be compensated for their time (approximately US $2).

Procedures

MIMIC Implementation

The MIMIC intervention will be implemented by the clinical staff, not members of the research team. Following the initiation of MIMIC, the continuum of care received by ED patients with AMI will be directed by all 5 components of the intervention. Triage nurses will identify patients presenting to the ED with chest pain, dyspnea, or other possible AMI symptoms and will affix “ACS Suspect” cards to their stretchers. A list of possible AMI symptoms will be posted in the triage area to aid triage nurses in the identification of patients with possible AMI. The “ACS Suspect” cards serve as a notification to ED physicians, prompting them to consider the possibility of AMI and follow treatment protocols for the condition. ED physicians will also carry pocket cards that provide an overview of AMI diagnosis and serve as an accessible reference for treatment procedures. After being diagnosed with AMI, patients will also be provided an educational pamphlet that provides health literacy resources for AMI and cardiovascular disease prevention, including information on healthy diet, exercise, and medication adherence. In the event a patient is too ill to receive the pamphlet directly, the pamphlet will be given to a relative. All KCMC ED physicians and nurses will also be required to complete a web-based module providing an in-depth review of evidence-based AMI diagnosis and treatment. Staff will only be required to complete the module once, although they will continue to have access to the web-based module if they wish to return to it. Designated physician and nurse “champions” will also encourage team members to improve AMI care at daily staff meetings, ensure implementation of all intervention components, and recognize staff who provide outstanding AMI care with congratulatory certificates.

Provider Surveys

To assess acceptability and other implementation outcomes, trained research assistants will approach ED staff to administer provider surveys (Multimedia Appendix 1). These provider surveys will be administered beginning 1 month after intervention implementation, and survey administration will continue over the course of the trial period. Surveys will use the 4-item acceptability of intervention measure (AIM) [29] to evaluate provider perceptions of the acceptability of the MIMIC intervention. The survey will also include the 4-item Feasibility of Intervention Measure (FIM) [29] to evaluate feasibility. Additional survey questions will elicit provider opinions regarding specific components of the MIMIC intervention. Members of the research team will administer provider surveys to ED staff over the course of the pilot trial, with the goal of administering the survey to at least 90% of staff by the trial’s conclusion.

In-Depth Interviews

After initiation of the MIMIC intervention, research assistants will conduct in-depth interviews with providers, patients, and administrators to obtain additional qualitative data regarding the acceptability of MIMIC and other implementation outcomes. Interviews will be guided by a semistructured interview guide, informed by the Theoretical Framework for Acceptability, which encompasses 7 domains of acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy [30,31]. In-depth interviews will also explore stakeholder perceptions of the feasibility of the MIMIC intervention. Interviews will be conducted face-to-face in Swahili and will last approximately 1 hour. Interviews will be conducted until thematic saturation is achieved [32]. The epistemology informing these qualitative interviews is constructivist, recognizing that knowledge is constructed through the unique, lived experiences of providers, patients, and hospital administrators, in addition to the social interactions amongst them [33].

Observation of Intervention Fidelity

Trained research assistants will observe KCMC ED clinical care from 8 AM until 11 PM seven days per week during the trial period. They will observe and record the number of nurses who are using the “ACS Suspect” triage card and the number of physicians who have their pocket cards. Research staff will also monitor the web-based training module and record the total number of staff who complete the training during the trial period. Additionally, research staff will also observe the uptake of the patient educational pamphlets and triage cards, as described below.

Observation of Clinical Care

For 1 year following the initiation of MIMIC (September 1, 2023, to September 1, 2024), research assistants will enroll adult patients (age ≥18 years) presenting to the KCMC ED with a primary or secondary complaint of chest pain or shortness of breath. Written, informed consent will be obtained from all patients interested in participating. Following enrollment, a comprehensive approach will be taken to observe relevant testing and treatment procedures administered to the participants. Research staff will observe and record whether patients had an “ACS Suspect” triage card affixed to their stretcher and whether cardiac biomarkers and ECGs were obtained by the ED clinicians. The findings of all ED investigations, including cardiac biomarkers and ECGs when obtained, will be recorded. Additionally, physician-documented diagnoses will be transcribed directly from patients’ electronic medical records. Research staff will also observe and record all ED treatments, including aspirin administration, and will note whether the patient received an educational pamphlet.

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Enrolled patients will be contacted 30 days following enrollment to assess mortality and medication use. Medication use at 30 days will be determined by participant self-report. The 4-item AIM instrument [29] will also be administered to participants who received the educational pamphlet to discern patient perspectives on the acceptability of this component of the MIMIC intervention. Trained research assistants will conduct these 30-day follow-up assessments via telephone; when participants are unreachable by phone, a member of the study team will visit their home to administer the follow-up survey in person.

Implementation Outcomes

Primary Outcome: Acceptability

Implementation outcomes are summarized in Table 1. The primary outcome of this pilot trial will be the acceptability of the MIMIC intervention. Acceptability will be measured by the AIM instrument [29], embedded within the provider survey. The AIM instrument measures acceptability as an implementation outcome of an intervention, and it has shown substantial validity through rigorous psychometric assessment [29]. The AIM instrument is administered in survey format to respondents. Responses to each question are on a 5-point Likert Scale (Strongly Agree=5, Agree=4, Neutral=3, Disagree=2, Strongly Disagree=1). Responses of "Strongly Agree" (5) and "Agree" (4) are considered to indicate a more acceptable intervention. The responses to each question will be averaged to give an acceptability score between 1 and 5 for each respondent. The primary outcome will be the overall mean acceptability score among respondents. The AIM instrument does not have a validated cutoff score, although higher scores indicate greater acceptability [29]. Consistent with the approach of other studies that have used the AIM instrument, a mean acceptability score ≥ 4 will be considered indicative of acceptability for our study [34-42]. Acceptability will also be assessed via the qualitative data obtained from the in-depth interviews with key stakeholders, as described above.

Table 1. Implementation outcomes and measures.

Implementation outcomes [43]	Measures
Acceptability[a]	• Mean acceptability score on AIM[b] instrument administered via ED[c] provider surveys • Qualitative data obtained from in-depth interviews with hospital staff, administrators, and patients
Feasibility	• Mean feasibility score on FIM instrument administered via ED provider surveys • Total number of triage cards and pocket cards distributed and replaced • Number of ED providers unable to complete web-based module and average minutes required to complete training module
Fidelity	• Proportion of enrolled patients with chest pain or shortness of breath who are flagged with the red triage card, as determined by research staff direct observation. • Proportion of ED physicians receiving pocket cards and starting web-based training module • Proportion of patients with AMI receiving educational pamphlet
Penetration	• Proportion of ED triage nurses using red triage cards • Proportion of ED physicians using pocket cards • Proportion of ED physicians successfully completing training module • Proportion of AMI patients reading educational pamphlet
Costs	• Total costs of intervention, including costs of printing educational pamphlets, pocket cards, red triage cards, and congratulatory certificates over the course of the pilot trial

[a]Primary pilot trial outcome.

[b]AIM: acceptability of intervention measure.

[c]ED: emergency department.

Secondary Outcome: Feasibility

The feasibility of MIMC will be assessed through several methods. First, the 4-questions FIM instrument [29], integrated into surveys administered to KCMC ED providers, will assess feasibility. The FIM instrument measures feasibility as an implementation outcome of an intervention, and like the AIM instrument, has exhibited substantial validity [29]. Administered in survey format, responses to FIM questions will be measured using a 5-point Likert Scale and will be scored in the same manner as the AIM instrument described above.

Feasibility will further be evaluated from the qualitative data obtained from in-depth interviews with key stakeholders. Additional quantitative measures of feasibility will be obtained from observational data collected by the research team, including the total number of red "ACS Suspect" triage cards needing replacement due to loss or damage, the number of pocket cards requiring replacement, and the amount of time ED physicians and nurses took to complete the web-based training module (as self-reported on the provider survey).

Secondary Outcome: Fidelity

Implementation fidelity is defined by the extent to which an intervention is delivered as intended [44]. The fidelity of MIMIC will be assessed based on compliance with the intervention's 5 components. To gauge fidelity of the triage card component, the proportion of patients with chest pain or shortness of breath

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who are flagged with red triage cards will be observed (with the denominator being the total number of ED patients with chest pain or shortness of breath enrolled during the trial period). Similarly, measures related to pocket cards and the training module will be determined by the proportion of ED physicians who receive a pocket card and bring it to work at least once, and the number of ED staff who begin the web-based training module, respectively. These proportions will be determined by direct observation. Finally, the proportion of patients with a documented diagnosis of AMI receiving an educational pamphlet will be used as a measure of fidelity to MIMIC's patient education component.

Secondary Outcome: Penetration

Penetration will be measured by the proportion of ED triage nurses who use the red triage cards, the proportion of ED physicians who bring their pocket cards to work each day, the proportion of ED providers who complete the training module, and the proportion of patients with AMI who report having read their educational pamphlet by the time of their 30-day follow-up.

Secondary Outcome: Costs

All costs needed to implement MIMIC will also be monitored as a secondary implementation outcome. Expected costs will include printing educational pamphlets, pocket cards, triage cards, and congratulatory certificates. All amounts will be converted from Tanzanian shillings to USD for analysis.

Efficacy Outcomes

Secondary Outcome: AMI Testing in the ED

Early screening with ECGs and troponin testing has been shown to reduce morbidity and mortality among patients with AMI [45,46]. Therefore, the proportion of ED patients with chest pain or shortness of breath who receive an ECG and troponin testing in the ED will be evaluated as one efficacy measure of MIMIC. This proportion will be compared with the proportion of ED patients undergoing ECG and troponin testing for the period prior to implementation of the MIMIC intervention.

Secondary Outcome: Aspirin Treatment

Another efficacy measure will be the proportion of patients with AMI who are treated with aspirin in the ED. This proportion will be compared with preintervention observational data, as described above. For study purposes, patients with AMI will be defined as any patient with a physician-documented diagnosis of AMI or any patient meeting objective ECG and troponin criteria for AMI, as per the Fourth Universal Definition of Myocardial Infarction Guidelines [47]. Although not a formal outcome of this study, we will also observe the proportion of patients with AMI who receive heparin, P2Y12 inhibitors, and thrombolytics to inform future studies of the MIMIC intervention.

Secondary Outcome: 30-Day Mortality

Thirty-day mortality for patients with a documented diagnosis of AMI will be calculated and compared with preintervention observational data. Participants lost to follow-up will be excluded from this analysis.

Secondary Outcome: 30-Day Aspirin Use

The proportion of surviving participants with documented AMI diagnosis who report ongoing daily aspirin use at 30-day follow-up will also be a secondary efficacy outcome. This proportion will be compared with preintervention observational data; participants who died or were lost to follow-up will be excluded from this analysis.

Statistical Analysis

The main objective of this trial is to assess the acceptability of MIMIC, which will determined by calculating the mean AIM score. AIM scores will be gathered from all participants, including patients, ED providers, and administrators, and then divided by the total number of trial participants. Importantly, the AIM scores from participants will be assumed to be normally distributed and independent of each other. The overall AIM score will fall within a range of 1 to 5, with higher scores indicating greater acceptability. An overall mean AIM score of 4.0 will be considered to indicate acceptability, as described above.

The acceptability of MIMIC will also be examined via qualitative analysis of the content of in-depth interviews across stakeholders. Two independent coders will conduct thematic analyses of interview transcripts using NVivo (version 14; Lumivero) in an iterative cycle of coding, discussion, and consensus-building. The coders will be assumed to be consistent and reliable in their coding process, and the findings from the qualitative analysis will be assumed to be accurate representations of participants' views. Coders will use an inductive analytic approach, and disagreements among coders will be resolved by discussion and consensus-building. In the event a coding disagreement cannot be resolved by discussion, a third member of the coding team will serve as the tiebreaker. These thematic analyses will be guided by the Theoretical Framework for Acceptability [30].

Other implementation outcomes, such as fidelity and penetration, will be characterized by the proportion of participants receiving or complying with an intervention out of the total number of participants, as described above. In calculating these proportions, it will be assumed that the observations are independent of one another. Feasibility will be assessed through the FIM score mean and SD. To assess feasibility and costs implementation outcomes, the total number of resources allocated will be determined in place of proportions, as described above.

Efficacy outcomes will be used to assess the preliminary effectiveness of MIMIC. Pre-post analyses will be used to compare performance metrics from before and after MIMIC rollout to estimate the effect of the intervention on the 4 secondary efficacy outcomes listed in Table 2. Performance metrics from the preintervention and postintervention periods will be assumed to be independent of each other, and the conditions under which data were collected from each period will be assumed to be comparable.

To estimate effect sizes of the intervention, proportions of patients achieving each of the 4 key target efficacy outcomes will be compared from the preintervention period and postintervention period via Pearson chi-square test [48].

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Preliminary effectiveness will be reported as odds ratios with corresponding 95% CIs constructed directly from two-by-two contingency tables. Preintervention data will be taken from an observational study conducted immediately prior to MIMIC rollout (February 1, 2023 to September 1, 2023). No a priori assumptions will be made regarding effect size of MIMIC on any of the 4 outcomes.

Table 2. Efficacy outcomes and measures.

Efficacy outcomes	Measures
AMI[a] diagnostic testing	Proportion of patients with chest pain or dyspnea receiving ECG[b] and troponin testing in the ED[c]
AMI Care in ED	Proportion of patients with AMI treated with aspirin in the ED
Thirty-day mortality	Proportion of patients with documented diagnosis of AMI who die within 30 days of presentation
Outpatient aspirin use at follow-up	Proportion of patients with AMI taking daily aspirin 30 days after initial presentation

[a]AIM: acceptability of intervention measure.

[b]ECG: electrocardiogram.

[c]ED: emergency department.

Sample Size

No a priori assumptions will be made about the acceptability of the MIMIC intervention. There are currently approximately 70 total physicians and nurses working in the KCMC ED, and we will aim to administer the provider survey to at least 90% of the staff (63 total participants). Recent studies of the acceptability of other health care quality improvement interventions using the AIM instrument have reported SDs ranging from 0.4 to 0.8 when reporting the AIM score on a 5-point scale [49-51]. Assuming an SD of 0.6 in our study, a sample size of 63 participants would allow us to estimate the mean AIM score with a margin of error of ±0.2 with 95% CI.

Our observational study of ED care during the MIMIC pilot trial will be conducted for 1 year. Based on prior observational studies in the KCMD ED [11,12], we expect to enroll 400 patients with chest pain or dyspnea during the trial. The data generated from this pilot study will inform sample size calculations for a future clinical trial.

For qualitative interviews, approximately 35 participants will be recruited. This cohort will include 10 patients with AMI, 10 physicians, 10 nurses, and 5 hospital administrators. Final sample size will be determined by thematic saturation.

Data Management and Safety Monitoring

Data from electronic health records and clinical care observations will be systematically collected on encrypted tablets using the Open Data Kit platform (version 2024.1.3; ODK) and uploaded directly to a secure, encrypted server at KCMC. Interview transcripts will be recorded and stored on encrypted digital devices accessible exclusively to authorized research personnel. Thematic analysis of these transcripts will be conducted using the NVivo software, with measures in place to encrypt and safeguard data. All data will be password-protected to maintain strict confidentiality. Prior to accessing the data within these systems, research personnel will undergo prerequisite training to ensure compliance with data security protocols. The Principal Investigator (JTH) will oversee data management by conducting weekly queries and reviewing inputted data for accuracy and completeness.

Following MIMIC rollout, stringent safety monitoring measures will be put in place to ensure the safety of the intervention. Importantly, MIMIC will be implemented by ED providers rather than by research staff, so the primary focus on safety monitoring will be to ensure that research activities do not disrupt the regular operations of the ED. Therefore, research personnel will undergo mandatory training to strictly observe and refrain from interfering with the clinical care provided to patients with AMI within the KCMC ED. Furthermore, all interviews will be scheduled during break periods, mealtimes, or at the conclusion of shifts to minimize any potential disruptions to patient care.

The principal investigator (JTH) and local coinvestigator (FMS) will be responsible for conducting safety reviews of the MIMIC intervention and addressing any threats to patient safety that may arise. Any instances of serious adverse events occurring during the implementation of MIMIC will be documented and reported to the local institutional review board in accordance with established safety and ethics protocols.

A formal interim analysis will be conducted 6 months into the pilot trial. At this point, the investigator team (JTH, GSB, NMT, FMS, JPB, and BTM) will analyze intervention fidelity data and patterns of care for four key care processes: (1) the proportion of patients presenting with chest pain or shortness of breath to the ED who undergo testing for AMI, (2) the proportion of patients with AMI who receive aspirin in the ED, (3) the proportion of patients with AMI who are alive at 30 days, and (4) the proportion of patients with AMI who are taking aspirin at 30 days. As this study involves a quality improvement intervention, we do not anticipate any adverse events. If any adverse events do occur, they will be reported, as required, to the Institutional Review Boards at Duke Health, KCMC, Tanzania National Institute for Medical Research, and the National Institutes of Health. We do not anticipate any changes to the trial protocol, but if these occur, these changes will be reported to the Institutional Review Boards at Duke Health, KCMC, Tanzania National Institute for Medical Research; the ClinicalTrials.gov record will also be updated.

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Ethical Considerations

Ethical approval for this study was obtained from the Tanzania National Institute for Medical Research (NIMR/HQ/R.8a/Vol. IX/2436, Version 7, February 23, 2021), KCMC (Proposal 893, Version 7, December 21, 2020), and Duke Health (Pro00090902, Version 1.7, September 16, 2020). All study procedures will be in accordance with the Helsinki Declaration of 1975, as revised in 2000. Research assistants will obtain written, informed consent from all research participants, including patients and ED providers, prior to their enrollment. Consent forms will be available in both English and Swahili to ensure they are understood by participants. Participation will be entirely voluntary, and patients all patients will reserve the right to opt out of the study at any time. Participant privacy will be respected, and no identifying information about participants will be shared publicly. Research personnel will observe MIMIC interventions and will refrain from disrupting clinical care. ED staff who participate in in-depth interviews and staff surveys will be compensated 5000 Tanzanian shillings (approximately US $2) in exchange for their time completing interviews and surveys. All data will be anonymized and stored in a secure, encrypted system accessible only to authorized research personnel. All clinically actionable findings identified via patient health records and observations of patient care will be reported to the primary clinical team at KCMC. In addition, all serious adverse events occurring during the implementation of MIMIC will be reported to the local institutional review board.

Dissemination

Findings of this pilot trial will be disseminated among KCMC ED providers and hospital administrators via in-person conference meetings and presentations. Findings will also be published in peer-reviewed journals to inform broader audiences of implementation science interventions to improve AMI care in resource-limited settings. Trial results will be shared with local and national representatives of the Ministry of Health in Tanzania. If MIMIC is found to be acceptable, the findings from this study will inform a stepped-wedge, cluster-randomized trial to assess the effectiveness and scalability of the intervention across multiple health care facilities in Tanzania.

Results

This study was funded in February 2021 and received its final ethical approval from the Tanzania National Institute for Medical Research in February 2021. The KCMC ED staff began implementing the MIMIC intervention on September 1, 2023. As of April 2024, a total of 275 adult patients with chest pain or shortness of breath have been enrolled in the study. Enrollment is expected to be completed by September 2024 and all analyses are planned to be completed by October 2024. The first results are expected to be published by December 2024.

Discussion

With respect to implementation outcomes, we anticipate MIMIC to demonstrate high levels of acceptability, feasibility, and fidelity in the current trial. As for efficacy outcomes, we anticipate that MIMIC will enhance diagnostic testing rates among potential patients with AMI, increase the proportion of patients receiving aspirin, reduce 30-day mortality rates, and boost the proportion of patients with AMI adhering to aspirin 30 days post enrollment. More broadly, we anticipate that this will be the first study to investigate an evidence-based intervention aimed at improving AMI care in SSA. The study will also be the first in the region to assess an intervention aimed at increasing aspirin administration to patients with AMI—a World Health Organization “Best Buy” for mitigating noncommunicable disease morbidity and mortality [9].

However, it will be necessary to interpret the trial’s findings in light of its limitations. These include (1) the lack of a control arm, which limits the rigor of efficacy analyses, (2) use of pre-post comparisons for effectiveness outcomes, which may be subject to time-related confounders, and (3) unknown generalizability to settings beyond Tanzania.

If MIMIC demonstrates acceptability and effectiveness, then it may catalyze further research to implement similar interventions for emergency AMI care at a broader, more scalable level. Furthermore, the findings from this study will demonstrate the potential for rigorous implementation of scientific methods to enhance AMI care in SSA, especially with regard to aspirin administration. More broadly, this study will add to the growing body of research focusing on the effective and feasible translation of evidence-based procedures into practice within resource-limited settings.

Conclusions

In light of recent evidence suggesting that uptake of evidence-based AMI care is lacking in Tanzania, MIMIC holds promise as a valuable intervention that can improve AMI care delivery in the country. If MIMIC demonstrates successful implementation and efficacy outcomes in this pilot trial, then the results could pave the way for broader implementation of MIMIC in Tanzania and elsewhere in SSA, helping to mitigate the growing burden of AMI in the region.

Acknowledgments

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Data Availability

Data collected over the course of the pilot trial on MIMIC will be publicly available upon reasonable request to the corresponding author.

Authors' Contributions

JTH, FMS, BTM, GSB, JPB, and NMT conceptualized the pilot trial. JTH, VK, FS, JM, and FMS have overall responsibility for project supervision. JTH, FMS, FS, VK, JM, GSB, HBB, JPB, FOR, and NMT contributed to the design of MIMIC and its implementation outcome measures. FMS, FS, VK, BTM, and JM will provide project administration of the study trial. FOR drafted the manuscript. JTH acquired study funding. All authors contributed to the writing and approved the final manuscript.

Conflicts of Interest

JTH's institution received research grant funding from Roche Diagnostics for a study in which he was a coinvestigator. HBB reports research funding through his institution from BeBetter Therapeutics, Boehringer Ingelheim, Esperion, Improved Patient Outcomes, Merck, NHLBI, Novo Nordisk, Otsuka, Sanofi, Veterans Administration, Elton John Foundation, Hilton foundation, Pfizer He also provides consulting services for Esperion, Imatar, Novartis, Sanofi, Vidya, Walmart, Webmed, Janssen. He was also on the board of directors of Preventric Diagnostics. All other investigators have no other competing interests to declare.

Multimedia Appendix 1
MIMIC pilot trial provider survey. MIMIC: multicomponent intervention to improve acute myocardial infarction care.
[DOCX File , 19 KB - resprot_v13i1e59917_app1.docx]

Multimedia Appendix 2
Peer-review reports by the Mentored Patient-Oriented Research Review (MPOR) Committee - Heart, Lung, and Blood Initial Review Group - National Heart, Lung, and Blood Institute (NHLBI) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 151 KB - resprot_v13i1e59917_app2.pdf]

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Abbreviations

AIM: acceptability of intervention measure
AMI: acute myocardial infarction
ECG: electrocardiogram
ED: emergency department
FIM: feasibility of intervention measure
KCMC: Kilimanjaro Christian Medical Centre
MIMIC: multicomponent intervention to improve acute myocardial infarction care
SSA: sub-Saharan Africa

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Protocol

Investigating Exposure and Hazards of Micro- and Nanoplastics During Pregnancy and Early Life (AURORA Project): Protocol for an Interdisciplinary Study

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Abstract

Background: Micro- and nanoplastics (MNPs) are emerging pollutants of concern with ubiquitous presence in global ecosystems. MNPs pose potential implications for human health; however, the health impacts of MNP exposures are not yet understood.

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Recent evidence suggests that MNPs can cross the placental barrier, underlying the urgent need to understand their impact on reproductive health and development.

Objective: The Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics (AURORA) project will investigate MNP exposures and their biological and health effects during pregnancy and early life, which are critical periods due to heightened vulnerability to environmental stressors. The AURORA project will enhance exposure assessment capabilities for measuring MNPs, MNP-associated chemicals, and plastic additives in human tissues, including placenta and blood.

Methods: In this interdisciplinary project, we will advance methods for in-depth characterization and scalable chemical analytical strategies, enabling high-resolution and large-scale toxicological, exposure assessment, and epidemiological studies. The AURORA project performs observational studies to investigate determinants and health impacts of MNPs by including 800 mother-child pairs from 2 existing birth cohorts and 110 women of reproductive age from a newly established cohort. This will be complemented by toxicological studies using a tiered-testing approach and epidemiological investigations to evaluate associations between maternal and prenatal MNP exposures and health perturbations, such as placental function, immune-inflammatory responses, oxidative stress, accelerated aging, endocrine disruption, and child growth and development. The ultimate goal of the AURORA project is to create an MNP risk assessment framework and identify the remaining knowledge gaps and priorities needed to comprehensively assess the impact of MNPs on early-life health.

Results: In the first 3 years of this 5-year project (2021-2026), progress was made toward all objectives. This includes completion of recruitment and data collection for new and existing cohorts, development of analytical methodological protocols, and initiation of the toxicological tiered assessments. As of September 2024, data analysis is ongoing and results are expected to be published starting in 2025.

Conclusions: As plastic pollution increases globally, it is imperative to understand the impact of MNPs on human health, particularly during vulnerable developmental stages such as early life. The contributions of the AURORA project will inform future risk assessment.

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KEYWORDS

epidemiology; pregnancy; toxicology; microplastics; placenta; risk assessment

Introduction

Plastic is pervasive in both built and natural environments. Global plastic production was estimated to be 400.3 million tons in 2022, with most plastic generated for single-use purposes [1]. Despite growing regulatory efforts to reduce plastic production and increase recycling, global plastic production is projected to increase to 1100 million tons by 2050 [2-4]. The lifetime cost of the plastics produced in 2019 alone exceeded US $3.7 trillion, including expenses such as greenhouse gas emissions, waste management, and environmental cleanup, and without accounting for potential costs related to impacts on human health [5]. Small plastic particles are generated by weathering and degradation or intentionally produced [4,6]. These particles, including fibers, are categorized based on their dimensions, with those ranging from 5 mm to 1 µm referred to as microplastics (MPs), and those smaller than 1 µm termed nanoplastics (NPs) [6]. Although there is growing evidence of micro- and nanoplastics (MNPs) in air, drinking water, and food [7], the scale of MNP exposure and behavior in the human body remains uncertain [8]. Furthermore, the potential risk MNPs pose to human health is largely unknown [9,10].

MNPs represent a complex class of pollutants, with a range of physical-chemical properties, such as morphology, composition, density, and surface chemistry. Human health risk assessment of MNPs presents unique challenges, primarily due to the complexity and diversity of these particles [9]. Established risk assessment frameworks, for example, for engineered nanomaterials and chemical pollution, are likely inadequate to account for the complex characteristics of MNPs [11,12]. Recent inventories document more than 4000 substances used in plastic packaging and more than 10,000 plastic-associated compounds, including organic polymers, additives such as plasticizers, and nonintentionally added substances such as reaction by-products [13,14]. Furthermore, MNPs in ecosystems may form eco-coronas, which may subsequently absorb other environmental pollutants and potentially facilitate human exposure to additional pollutants [15]. Current measurement approaches inadequately capture the full extent of MNP-associated chemical exposures in humans, as they focus on a limited set of known chemicals.

Various analytical techniques have provided the first insights into human exposure to MNPs. There is growing evidence that MNPs can be detected in human tissues, including blood and placenta tissue [16-18]. Mass-based assessment of MNPs using high-resolution mass spectrometry coupled with pyrolysis (Py-GC/HRMS), chemical profile assessment, and complementary spectro-microscopic characterization have emerged as promising approaches [19-21]. However, most MNP exposure assessments to date have been small scale (ie, less than 100 subjects), proof-of-concept studies, and have primarily focused on MPs rather than NPs [17,18,22]. Critical analytical advancements are necessary to reduce the uncertainty and error

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of exposure estimates and to enable comprehensive risk assessment [11,23].

During gestation and early life, the developing fetus is highly vulnerable to environmental stressors, including chemical exposures, due to rapid organogenesis and developmental plasticity [24]. Disruption by environmental toxicants during this window of heightened susceptibility can have a long-lasting impact on the molecular and physiological phenotype and health later in life [25]. The placenta is a unique organ at the maternal-fetal interface that facilitates gas exchange and the transport of nutrients, hormones, and other solutes essential for fetal growth and development, while also supporting maternal health [26]. It has been observed that not only endogenous but also exogenous compounds, including engineered metallic and carbonaceous nanoparticles, can cross the placenta barrier [27,28]. Growing evidence supports the placental translocation of MNPs in in vitro, in vivo, and ex vivo models [29]. Furthermore, MNPs have recently been detected in human placenta tissue, amniotic fluid, meconium, and breastmilk [18,22,30-32]. Given that pregnancy and early life are periods of heightened susceptibility to environmental stressors, evidence supporting the potential for transplacental transport of MNPs [33,34] and early-life exposure via ingestion and inhalation [35] provide impetus for investigating the implications of MNP exposure during these periods.

To overcome these gaps in MNP research, the Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics (AURORA) research project aims to create a comprehensive framework for evaluating the health risks associated with MNPs during early-life stages [36]. Emphasis is placed on advancing analytical techniques for characterizing MNPs and evaluating their potential hazards during pregnancy and early life (Figure 1). This article provides an overview of the objectives, approaches, methodologies, strengths, challenges, and anticipated impacts of the AURORA project.

Figure 1. Overview of exposure assessment, sample types, and measurement techniques in AURORA. AAH-HRMS: alkaline-assisted hydrolysis with high resolution mass spectroscopy; AURORA: Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics; FaSTE-MPA: Fast, Single, Tissue Extraction for Multiplexed Plastic Analysis; LC-HRMS: liquid chromatography with high resolution mass spectroscopy; MNP: Micro- and nanoplastic; Py-GC/HRMS: pyrolysis gas chromatography high-resolution mass spectroscopy. Image created with BioRender.com [37].

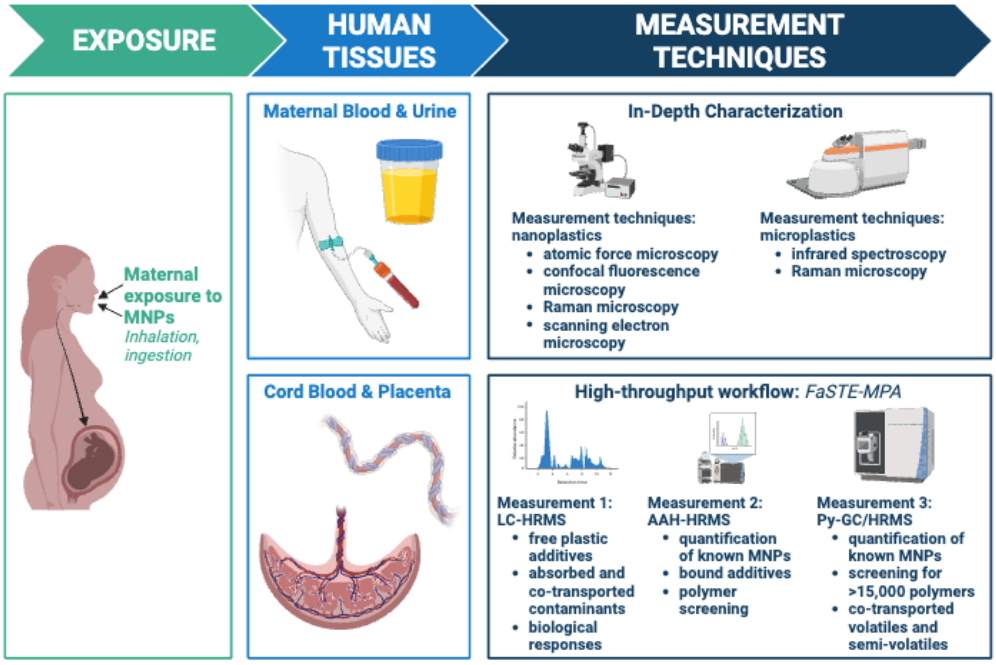

Methods

The AURORA project will address fundamental knowledge gaps about the effects of MNPs on early-life health and inform future human health risk assessment [36]. This 5-year project (2021-2026) is funded by the European Union through the Horizon 2020 program and is one of the five projects that forms the CUSP European research cluster to study the health impacts of MNPs [38].

Objectives

The AURORA project has five core research objectives:

1. Exposure characterization: to develop analytical methods for in-depth characterization of MNPs in maternal and fetal human sample matrices, including placenta.
2. Scalable exposure assessment: to develop high-throughput analytical strategies for quantitative assessment of maternal and prenatal exposure to MNPs and biomonitoring in human populations.
3. Experimental toxicology: to assess toxicity, toxicokinetics, and toxicodynamics of MNPs in experimental models, focusing on placental models.

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4. Epidemiology: to evaluate associations between MNP exposure and female reproductive and early-life health outcomes.
5. Advance risk assessment: to develop an actionable European framework for human health risk assessment of MNPs.

To address these objectives, the AURORA project was designed with an interdisciplinary approach, bringing together experts in nanoparticle characterization, inorganic chemistry, analytical chemistry, exposomics, exposure science, biology, toxicology, epidemiology, risk assessment, and science communication.

Study Populations and Samples

An extensive set of profiled human tissue samples, household samples, and biological markers and health outcomes will provide novel information about MNP exposure and health impacts. The AURORA project involves 2 richly phenotyped birth cohorts with unique biobanks, including placenta samples, and will establish a new cohort to assess determinants of MNP exposure.

The ENVIRonmental influence ON early AGEing (ENVIRONAGE) birth cohort has been recruiting pregnant women in the East Limburg Hospital, Genk, Belgium since 2010, and currently includes more than 2300 mother-child pairs [39]. This cohort was established to investigate the impact of air pollution and other environmental stressors on early biological aging. The Barcelona Life Study Cohort (BiSC) has recruited 1080 mother-child pairs residing in the Barcelona metropolitan area, Spain, during the years 2018-2021 with the overall aim of investigating the impact of the early-life exposome on maternal and child health and development [40]. Both cohorts collected fresh placenta tissue immediately after delivery. In addition to the standard biopsies sampled at fixed locations on the fetal and maternal side of the placenta [39], for a subset of women recruited since 2020, a de novo sample collection of the entire placenta was initiated with a sample collection procedure designed to minimize MNP contamination. In addition to placenta samples, cord blood, maternal urine, and blood samples from these cohorts will be analyzed to comprehensively characterize MNP exposures. To assess the impact of MNP exposures on maternal and early-life health, we will leverage the longitudinal assessments and novel health outcome data from the 2 birth cohorts, including markers of placental function, immune-inflammatory responses, oxidative stress, accelerated biological aging (telomere length), birth outcomes, and childhood growth and development.

Furthermore, a new cohort will be established in the Netherlands to assess determinants of MNP exposure, specifically among women of reproductive age (18-45 years). We will include 110 women living within 50 km of Utrecht, the Netherlands. Blood, urine, and household dust samples will be collected at baseline and after 3 months. In addition, a self-administered online questionnaire, taking approximately 15 minutes to complete, will be used to identify factors contributing to MNP exposure. This questionnaire will gather sociodemographic information, home environment characteristics, food consumption and preparation habits, as well as lifestyle and behavior patterns.

Quality Assurance and Quality Control

One of the considerations taken across the project is minimizing both primary MNP contamination during sample collection and secondary MNP contamination during processing and analysis with quality assurance and quality control (QA/QC) measures [41]. Plastic is commonly used for collecting biological samples and has many applications in laboratory settings. We use glass sample collection materials to collect de novo blood, cord blood, and urine samples and store placenta samples in aluminum foil. Cohort samples collected with plastic materials prior to the AURORA project will be compared to samples from the de novo collection to understand background contamination, and empty collection tubes will be analyzed to determine background MNP levels. In laboratory spaces, plastic is avoided and removed where possible, and work is done under a laminar flow hood. We implement QA/QC measures including field and procedural blanks at multiple stages of collection and analysis to account for any remaining background contamination. Quality control samples are prepared by spiking samples with known MNP concentrations to monitor the accuracy and performance of the method, ensuring the quality and reliability of the data across batches.

In-Depth Characterization of MNPs

The development of an analytical framework for the in-depth characterization of MNPs in maternal and fetal tissues is fundamental to providing measures of the particle characteristics potentially driving toxicological and health effects [9]. Key characteristics include particle quantity (mass and particle count), morphology (size, shape), chemical composition, surface chemistry, and state of degradation [19]. Low-throughput nondestructive particle-based approaches will be used for in-depth characterization.

Microscopic techniques are established for detecting and characterizing MNPs greater than ~1 µm in diameter [20]. However, additional advancements are required for the detection of NPs [20,21]. Thus, we will first focus on developing and applying innovative spectro-microscopic techniques, such as atomic force microscopy, confocal fluorescence microscopy, and scanning electron microscopy to characterize NPs [42,43]. To characterize MPs, we will leverage additional microscopy methods including Raman microscopy and infrared spectroscopy [44]. These methods will be optimized and validated using simple matrices (eg, salt and fresh water) to ensure the highest sensitivity before analyzing tissue samples.

Adding to the complexity of MNPs is that environmental MNPs undergo degradation, which makes understanding characteristics of MNPs at various stages of degradation essential for the identification of MNPs in complex matrices [45]. A vibrational spectroscopic library of MNPs from controlled degradation experiments will be established to facilitate identification of MNP type, regardless of MNP condition and state of degradation. Due to the complex nature of maternal and fetal tissues, sufficient sample digestion, filtration, and preconcentration is required to remove biological interferences prior to microspectroscopic analysis and imaging [46]. Tissue sample processing methods will be optimized to maximize sensitivity and minimize alteration of MNPs.

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The spectroscopic methods for in-depth characterization of MNPs will be developed and validated with commercial polystyrene (PS) spheres. However, the advancement of toxicological models requires the availability of well-defined, comparable, and representative MNPs that span a diverse range of polymers, sizes, and shapes [47]. Synthesis of suitable MNPs is necessary due to the limited commercial availability of MNPs, which currently predominately limits research to PS spheres [48]. The synthesis of MNPs via nanoprecipitation for the most common polymer types, both with and without fluorescent tagging for detection with fluorescence microscopy, will be performed to support the development and testing of the toxicological models. These fluorescent tags are designed not to leach, ensuring they remain nontoxic.

Scalable Exposure Assessment

The AURORA project will develop and apply a high-throughput analytical workflow to quantify MNPs in human tissues. High throughput, robust, and quantitative methods are essential for human biomonitoring and to conduct informative epidemiological studies [49,50]. We will use this approach to assess the mass concentration of MNPs and associated chemicals in maternal blood, urine, placenta, and cord blood. These metrics are chosen because they are useful for biomonitoring studies (maternal urine, blood) and suitable for early-life exposure assessment (birth cohorts: placenta and cord blood).

Our approach (termed Fast, Single, Tissue Extraction for Multiplexed Plastic Analysis: FaSTE-MPA) combines three HRMS platforms to enable systematic characterization of MNPs in complex matrices: (1) Py-GC/HRMS to characterize MNP levels and cotransported volatiles and semivolatiles, (2) alkaline-assisted hydrolysis with liquid chromatography HRMS (AAH-HRMS) to measure particle monomers and additives, and (3) untargeted liquid chromatography with HRMS (LC-HRMS) to characterize the metabolome for the presence of MNP constituents, additives, nonintentionally added substances, and biological response profiles [51,52]. Analysis by Py-GC/HRMS will provide mass concentration estimates of common plastic polymers including PS, polyvinyl chloride (PVC), polyethylene terephthalate (PET), polyamide (PA), polyethylene (PE), polypropylene (PP), polymethyl methacrylate (PMMA), and polycarbonate, as well as screen for other MNPs. Additionally, AAH-HRMS and LC-HRMS provide complementary information about both free and bounded plastic polymers and additives, such as phthalates. We will develop a comprehensive library containing the Py-GC/HRMS fingerprints of common MNP polymers and associated plastic additives. In this manner, maternal and prenatal MNP exposure and biological responses will be measured in 800 paired placenta and cord blood samples from the birth cohorts. Further, an in-depth investigation into the maternal-fetal transfer of MNPs from maternal blood to placenta to cord blood will be conducted in a subgroup of mother-child pairs, aiming to provide insight into kinetics and transfer efficiencies. Spatial distribution and accumulation of MNPs within the placenta will be assessed in a subset of placentas.

Despite the potential applications of Py-GC/HRMS for assessing MNPs, targeted Py-GC/HRMS is currently not routinely available in analytical laboratories designated for human samples. Furthermore, required sample volumes (currently >1 mL) may preclude its use in the analyses of precious biobanked samples. To identify the top chemical signals predicting MNP exposure, we will leverage untargeted HRMS data to build classification models for biomarkers exhibiting the highest sensitivity and selectivity for MNP exposure. These biomarkers will be used to establish a quantitative, targeted method that can be implemented in human biomonitoring studies (eg, Human Biomonitoring for Europe) and large-scale epidemiological studies. Results from these population-based studies are critical inputs for future etiological research and regulatory assessment of MNP exposure and health effects [10].

Hazard Assessment: Experimental Toxicology

Despite evidence suggesting that MNPs can cross the placental barrier, placental toxicokinetics and toxicity of MNPs remain largely unexplored [33,53-55]. Knowledge gaps in human placental transfer and toxicity of MNPs hinder comprehensive hazard characterization for early-life exposure [34]. We will apply a series of toxicological models for toxicokinetic and effect studies, focusing on the placental barrier and assessing the effects of MNPs on the placenta and the developing organism. Placenta is a morphologically and functionally complex organ; therefore, placental models with increasing level of complexity, that is, monolayers, cocultures, and placental perfusion, will be used to address the complex interplay between different placental cell types [34].

Considering the multitude of MNP characteristics, toxicity testing will be done in a tiered approach, using MNPs generated commercially and within AURORA (Figure 2). Many MNPs will be tested in the simple models, and based on uptake, transport and toxicity will be prioritized for further testing in more complex models. In Tier 1, toxicity end points (eg, cell viability, damage to the cell membrane, and oxidative stress) as well as uptake and transport of MNPs will be investigated in nonsyncytialized and syncytialized human choriocarcinoma cells (BeWo b30), representative of cytotrophoblasts and syncytiotrophoblasts, respectively [56]. In Tier 2, MNPs will be investigated with additional monolayer cell cultures, including the human adenocarcinoma cell line (H295R) and human trophoblast stem cells, as well as more complex coculture cellular models such as BeWo/Human umbilical vein endothelial cells (HUVEC) and BeWo/HUVEC/H295R triculture [57-59]. Tiers 1 and 2 will provide insight into a wide array of effects on placental integrity and function, immune response, endocrine functions, and other pathway perturbations. We will also perform mRNA sequencing and metabolomic analyses in selected samples to investigate system homeostasis.

Further investigations will focus on selected MNPs in a human placental perfusion model (Tier 3), the embryonic stem cell test with mouse embryonic stem cells (mES-D3; Tier 4), and the zebrafish embryo toxicity model (Tier 4). Transplacental transfer and toxicity markers will be assessed upon exposure to selected MNPs in the human placental perfusion model [60].MNP concentrations in perfusion media and tissue will be analyzed by Py-GC/HRMS and LC-HRMS analysis. Untargeted LC-HRMS and biological pathway analyses will be performed

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on the embryonic stem cell test and zebrafish embryos exposed to MNPs [61]. Placental and developmental toxicity markers upon MNP exposure will be compared with the health outcome assessments in the epidemiological studies.

Figure 2. Tiered approach to investigate transport, toxicokinetics and toxicity of MNPs (micro- and nanoplastics) in toxicological models with varying complexity, including in vitro placental models, human placental models, and developmental toxicity tests. HUVEC: human umbilical vein endothelial cells. Image created with BioRender.com [37].

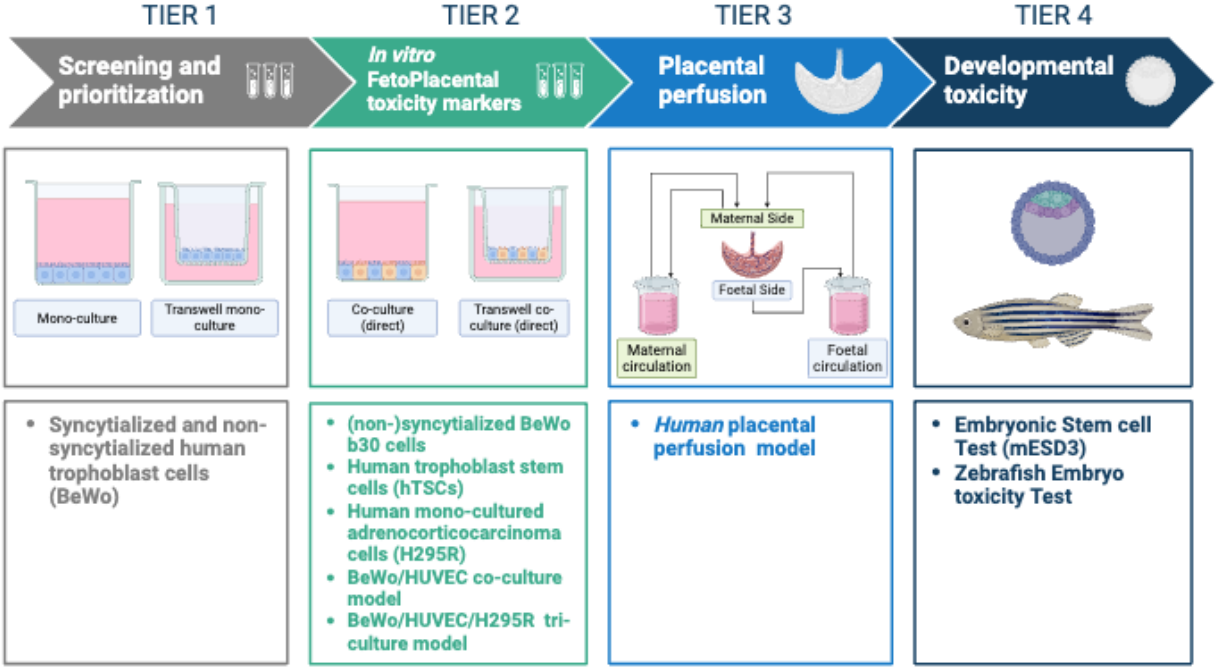

Epidemiological Studies

In epidemiological studies, we will evaluate the impact of MNPs and other plastic-related chemicals on multiple end points: (1) placental function; (2) system homeostasis; and (3) early-life growth and development (Figure 3). MNP exposure will be evaluated in 800 placenta samples from the ENVIRONAGE and BiSC cohorts. To examine the impact of (prenatal) MNP exposures on health, we will exploit the cohorts' longitudinal health assessments to generate novel data on exposure-health associations. The children currently span from new-born to 14 years of age.

When applicable, we will pool data from the 2 birth cohorts. We will use single-exposure-outcome regression modeling adjusted for covariates, as well as complementary exposure-wide modeling for MNPs and MNP-associated chemicals, including multivariable variable selection and machine learning approaches [62-64]. In addition, we will screen for associations between MNPs and metabolomic analytes to identify the overall biological alterations associated with MNP exposure and generate novel hypotheses on potential effects of MNPs [65,66]. Moreover, mediation analyses will be performed to evaluate system homeostasis markers, using models that accommodate multiple and high dimensional mediators [67,68].

Given that MNPs are a continuous exposure variable, the minimal sample size required to detect an effect for dichotomized outcomes depends on the prevalence of the outcome. The primary dichotomized outcomes to be examined are asthma and allergy, both prevalent in 5%-15% European pediatric populations [69-71]. Due to the absence of prior knowledge on the effect size of MNPs, we referred to a study which reported an increased risk of asthma (odds ratio [OR] 1.6-3.9) in Canadian children exposed to high phthalate concentrations in house dust [72]. Assuming a baseline outcome prevalence of 5%, an OR of 2, and a type I error of 0.05, the minimal statistical power obtained with 800 participants would be 0.77, which is deemed satisfactory. The statistical power for continuous outcomes is higher given the same sample size.

Identifying the contributing factors to MNP exposure levels provides insight into how MNP exposure may influence early-life health. Therefore, we will investigate determinants of MNP exposure, including maternal food consumption, sociodemographic and other lifestyle factors in the birth cohorts. The Dutch MNP exposure cohort, consisting of 110 women of reproductive age in the Netherlands, will allow for an in-depth assessment of the determinants of MNP exposure by combining levels of MNPs in blood, urine, and household dust samples, with a questionnaire investigating MNP exposure sources. We will assess the relative contribution of food packaging, food preparation methods, and indoor sources such as furnishing and frequency of cleaning to MNP and plastic-associated chemical body burdens.

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Figure 3. Overview of MNP (micro- and nanoplastic) exposure assessment and health outcomes to be evaluated in epidemiological studies in AURORA (Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics). Image created with BioRender.com [37].

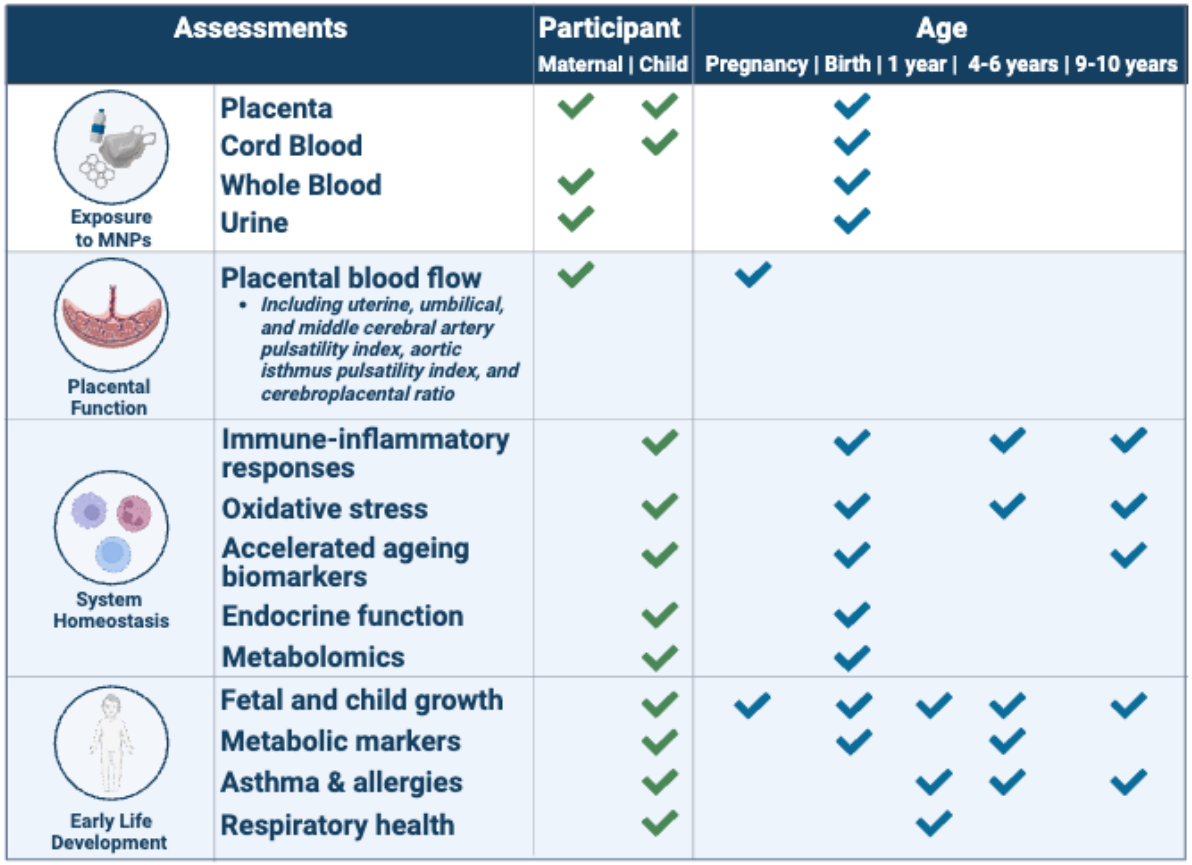

Risk Assessment

Risk assessment of MNPs is challenging, because MNPs constitute a very broad class of substances with diverse physiochemical properties, making it difficult to apply standard regulatory risk assessment approaches [12,73,74]. Evaluation of the exposure and hazard accounting for both the polymers and MNP-associated chemicals (ie, mixture effects) is essential [11]. Risk assessment of MNPs is also constrained by limited availability of reference materials, analytical challenges, and insufficient information about key characteristics of MNPs [11]. Further, hazard characterization is currently limited by lack of information about the accumulation, persistence, and kinetics of inhaled and ingested MNPs [10]. To understand early-life effects, risk assessment must consider the exposure rates for both the mother and the fetus.

We will build a framework for performing human risk assessment for MNPs with a focus on direct risk to the fetus and maternal-mediated risk, including via the placenta (Figure 4). A systematic evidence mapping approach will be applied to evaluate relevant literature from organizations such as the World Health Organization, European Food Safety Authority, Organization for Economic Co-operation and Development, National Institute for Occupational Safety and Health, and the published scientific literature, and critically evaluate the available regulatory tools for their relevance and adequacy for assessing the risks of MNPs. The framework we develop will integrate the project's updated methodologies and tools for assessing MNP exposures and risks from toxicological and epidemiological studies. Ultimately, we will determine the requirements to carry out a comprehensive risk assessment of MNPs and develop recommendations for advancing risk assessment for MNPs, focusing on early-life health.

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Figure 4. The anticipated output of the AURORA (Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics) project, which will contribute to the development of a human health risk assessment framework for evaluating the risks associated with MNP (micro- and nanoplastic) exposure in early life. Image created with BioRender.com [37].

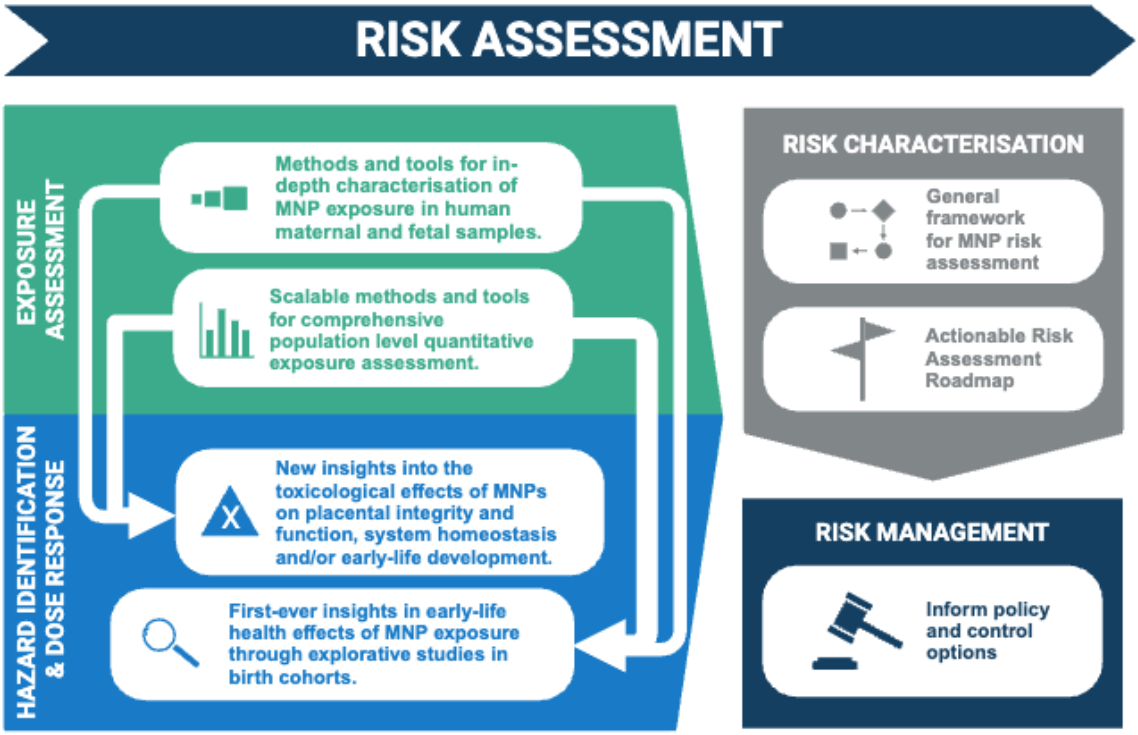

Ethical Considerations

The research activities of AURORA comply with international conventions and ethical codes, including the Declaration of Helsinki (2013) and the Declaration of Taipei (2016). Local ethics committees will support participating research groups to address all ethics requirements. Measures for personal data protection and confidentiality comply with the European Union General Data Protection Regulation (2016/679) and the FAIR (findable, accessible, interoperable, reusable) Data Principles [75].

The toxicological studies adhere to the 3R principles emphasizing nonanimal, in vitro cell, or alternative animal models [76]. Zebrafish fall outside the definition of animal models, eliminating the need for a specific ethical permit [77]. Human ex vivo placental perfusions with MNPs received ethics committee approval from the Research Ethics Committee of Hospital District of Northern Savo (952/2022). The ENVIRONAGE and BiSC cohorts are approved by the Ethics Committee of Hasselt University and East-Limburg Hospital (EudraCT B37120107805) and Comite de Etica de la Investigation Parc de salut Mar (No. 2018/8050/I), respectively. The Dutch MNP exposure cohort received ethics approval from the Medical Research Ethics Committee NedMec (NL81071.041.22). Adult participants in all cohorts provided informed consent for themselves and where applicable, for their children. An incidental finding policy is in place for all cohorts. All participants can withdraw from the study at any time, for any reason and without any consequences. Participants in the birth cohorts receive no compensation, whereas participants in the Dutch MNP exposure cohort receive a €25 (as of July 12, 2023 1 EUR=US $1.1135) gift card upon completion of the study.

Results

In the first 3 years of this 5-year project (2021-2026), the following progress has been made. As of September 2024, data analysis has begun and results are expected to be published starting in 2025.

In-Depth Characterization

We established a database consisting of infrared spectroscopy data measured on various polymers treated with different conditions; created a sample preprocessing workflow for measuring MNPs in complex human sample matrices, notably placenta; assessed the gaps in the current field of NP synthesis and fluorescent detection, synthesized NPs for 7 polymers including PVC, PS, PET, PA, PP, PMMA, and low-density PE using 2 fluorescent dyes; and summarized microspectroscopic techniques for measuring NPs [20].

Scalable Exposure Assessment

We advanced critical operational procedures for scalable biomonitoring of MNPs in placenta tissue and blood, including developing high-throughput and robust sample preparation based upon microwave-assisted extraction. We developed a comprehensive MNPs library containing the Py-GC/HRMS signal fingerprints of 39 common polymers, alongside relevant information on their associated plastic additives. Sample analysis for the characterization of maternal and fetal MNP exposure and biological response in the BiSC and ENVIRONAGE cohorts and spatial analysis of whole placentas is ongoing.

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Toxicological Hazard Assessment Studies

We reviewed the models for assessing placental uptake, transport, and toxicity of MNPs [34] and optimized the BeWo/HUVEC coculture model, and the BeWo/HUVEC/H295R triculture. The Tier 3 placenta perfusion model and the Tier 4 zebrafish and mESD3 models have also been optimized. Screening and prioritization of MNPs in Tier 1 and Tier 2 are ongoing, and Tier 4 experiments with zebrafish are in progress.

Epidemiological Studies

We recruited 110 participants for the Dutch MNP exposure cohort and collected blood, urine, and household dust samples. Sample collection from the birth cohorts for the epidemiological studies is complete; biobanked samples were selected from ENVIRONAGE, and de novo samples were collected from BiSC. Sample collection is complete for the spatial distribution study of MNPs in the placenta and ongoing for the study on the maternal-fetal transfer of MNPs. Follow-up of the birth cohorts is ongoing, and epidemiological analyses will proceed when MNP exposure estimates are available.

Risk Assessment Framework

We completed the systematic evidence mapping and initial roadmap addressing risk assessment for MNPs in early life, highlighting the current challenges and limitations [78]. This will be updated when results from AURORA-associated studies are completed, and with emerging external research and gaps in knowledge and future research needs will be identified.

Discussion

Principal Findings

The AURORA project brings together experts with diverse knowledge, from producing plastics and measuring plastics and associated chemicals, to quantifying the biological impacts of nanoparticles and chemicals on reproductive health and development in vitro, in vivo, and in humans, as well as experts in risk assessment and risk communication to assess exposures to and health effects of MNPs during the critical period of early-life development. Advancements in detection, quantification, and characterization of MNPs are crucial for understanding human exposure to MNPs. AURORA will develop complementary low-throughput nondestructive particle-based approaches for characterization of MNP properties and high-throughput Py-GC/HRMS mass-based measurements for scalable exposure assessment. Toxicological testing will provide foundational insight into the toxicity of a diverse range of MNPs in test systems with varying complexity. The epidemiological investigations will provide the first extensive evaluation of maternal and prenatal MNP exposures. While developing and applying the tools and methodological workflows, a risk assessment framework specific to MNPs will be established.

MNPs have recently been detected in human placenta tissue, meconium, amniotic fluid, and breastmilk, and cumulative evidence from aquatic species indicates reproductive effects of MNPs [18,22,30,32,79]. In mice, maternal exposure to microplastics has been demonstrated to induce placental dysfunction and result in metabolic disorders in both the placenta and fetus. [80,81]. The diverse in vitro and in vivo human placental models in AURORA show potential for more comprehensively assessing the potential hazards of MNPs in utero. Currently, research investigating the potential risk MNPs may pose to early-life health in mammals remains limited [18,22,30,32,79]. In recent small-scale human studies, an inverse association between MNPs in amniotic fluid and gestational age was found, and placental MNPs were linked to intrauterine growth restriction [82,83]. Our results will enrich the understanding of MNP exposure in human tissues and provide insight for the first time about health effects of MNPs during early life. Understanding the exposure and hazard of MNPs in early life is a crucial first step toward determining whether public health actions are needed and informing the urgency of regulatory responses to MNPs. As the burden of plastic in the environment increases, more evidence about how MNPs affect human health is essential [4,84].

Limitations

Given the complex nature of MNPs, there are challenging methodological advancements that need to be made during the project to accurately measure and evaluate early-life exposure to MNPs. Preliminary MNP measurements in human tissues suggest that exposure assessment is feasible; however, advancements in certain steps are necessary to develop workflows tailored to complex human matrices and ensure the reliability of exposure estimates. Additionally, the development of suitable test materials and workflows for toxicity testing, including dispersion protocols, requires significant methodological advancements. Another challenge we encounter is adequately addressing MNP contamination, which we do through the implementation of extensive QA/QC measures.

Dissemination

The results of the study will be published in peer-reviewed journals and further disseminated, for example, through webinars, and scientific conferences. Analytical protocols will be made available to the research community whenever possible. We will also engage with stakeholders, including health care professionals, industry, civil society organizations, and policy makers, using a multichannel approach including the project website, newsletters, press releases, workshops, and social media. We will liaise with the European Commission and its Joint Research Centre to ensure that the findings are translated into policy. We will publish open access, including analytical scripts. Data and metadata will be stored on the eNanoMapper [85] data repository.

Future Directions

AURORA supports the European Strategy for Plastics in a Circular Economy [86] by contributing to advancements of analytical methods for assessing thousands of chemicals, including potential unknown contaminants in future biodegradable and compostable plastics. The tiered approach for testing the toxicological effects of MNPs builds a framework for assessing the potential health impacts of measures taken under European policy. Aligned with the European Bioeconomy Strategy [87], AURORA addresses food and nutrition security,

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sustainable resource management, reduced reliance on nonrenewables, climate change mitigation, and European competitiveness. By providing novel information on health and safety risks of MNPs, AURORA will inform the development of safer plastics and bioalternatives for a circular economy.

Along with the gaps in health knowledge, policy and regulatory gaps must be addressed for systemic changes to be made. Harmonization of measurement techniques, exposure metrics, and terminology is essential to facilitate understanding between scientific and regulatory communities. Best practice is reporting both mass and particle counts, as will be done in AURORA [88]. Initiatives like an MNP-reporting guidelines checklist is a good example of moving MNP research forward in a valid, reproducible, and comparable way [89]. The harmonization of these key components will allow the newly generated research to collectively contribute to informing policy and control measures.

As the research on MNP and health is in its infancy, we acknowledge that not all open questions will be answered within AURORA or the CUSP cluster [38]. Therefore, in addition to the novel methods and tools and general framework for risk assessment of MNPs, we will develop an actionable risk assessment framework for MNP exposure in early life where the remaining knowledge gaps and priorities needed for comprehensively evaluating the impact of MNPs on early-life health are identified.

Conclusions

As plastic pollution increases globally, it is imperative to understand the impact of MNPs on human health, particularly during vulnerable developmental stages such as early life. The contributions of the AURORA project are important for understanding how MNPs may influence health in early life. We will advance the research field by advancing characterization and quantification methods, providing novel toxicological and human health outcome data, and ultimately design a risk assessment framework to inform future MNP research.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study. Data from this project will be shared in future publications and data repositories including eNanoMapper.

Authors' Contributions

JMB, HMD, MvD, MMF, JL, VL, FM, JM, TSN, PP, BMS-B., RV, MV, and DIW contributed to the conceptualization of the AURORA Horizon 2020 project application. MSPB, JvB, MB, EAC, AMD, PD, KSG, LDBM, ARR, NDS, RZ, and LZ played an important role in further developing the methodology once the project started. AMD and VL drafted the manuscript. All authors have read, revised, and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review.
[PDF File (Adobe PDF File), 246 KB - resprot_v13i1e63176_app1.pdf]

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Abbreviations

AAH-HRMS: alkaline-assisted hydrolysis with high resolution mass spectroscopy
AURORA: Actionable eUropean ROadmap for early-life health Risk Assessment of micro- and nanoplastics
BeWo b30: human choriocarcinoma cell line
BiSC: Barcelona Life Study Cohort
ENVIRONAGE: ENVIRonmental influence ON early AGEing
FAIR data: findable, accessible, interoperable, reusable data
FaSTE-MPA: Fast, Single, Tissue Extraction for Multiplexed Plastic Analysis
H295R: human adenocarcinoma cell line
HUVEC: human umbilical vein endothelial cells
LC-HRMS: liquid chromatography with high resolution mass spectroscopy
mES-D3: mouse embryonic stem cell line

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MNP: micro- and nanoplastic
MP: microplastic
NP: nanoplastic
OR: odds ratio
PA: polyamide
PE: polyethylene
PET: polyethylene terephthalate
PMMA: polymethyl methacrylate
PP: polypropylene
PS: polystyrene
PVC: polyvinyl chloride
Py-GC/HRMS: pyrolysis gas chromatography high-resolution mass spectroscopy
QA/QC: quality assurance and quality control

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Protocol

Effectiveness of a Person-Centered Interdisciplinary Rehabilitation Treatment of Post–COVID-19 Condition: Protocol for a Single-Case Experimental Design Study

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Abstract

Background: Patients with post–COVID-19 condition (PCC) experience a wide range of complaints (physical, cognitive, and mental), sometimes with high levels of disability in daily activities. Evidence of effective interdisciplinary rehabilitation treatment is lacking. A person-centered, biopsychosocial, interdisciplinary rehabilitation program, adapted to expert opinions and the patient's needs, was therefore developed.

Objective: This study aims to present a study protocol for a clinical trial to evaluate the effect of a new, person-centered, interdisciplinary rehabilitation treatment for PCC. It is aimed at improving participation in society and health-related quality of life in patients with PCC who perceive a high level of disability in daily activities or participation.

Methods: A total of 20 Dutch adults, aged 18 years or older, with high levels of disability in daily activities and participation in society will be included in this replicated and randomized single-case experimental design study, from October 2023 onward. The replicated and randomized single-case experimental design consists of 3 phases. The baseline phase is the observational period, in which no specific treatment will be given. In the intervention phase, patients will receive the new outpatient treatment 3 times a week for 12 weeks, followed by a 12-week follow-up phase. During the intervention phase, the treatment will be personalized according to the patient's physical, mental, and cognitive symptoms and goals. The treatment team can consist of a rehabilitation physician, physiotherapist, occupational therapist, speech therapist, and psychologist. The primary outcomes of the study are daily diaries, which consist of 8 questions selected from validated questionnaires (Utrecht Scale for Evaluation of Rehabilitation-Participation, EQ-5D-5L, and the Hospital Anxiety and Depression Scale). The other primary outcome measurements are participation in society (Utrecht Scale for Evaluation of Rehabilitation-Participation) and health-related quality of life (EQ-5D-5L). The secondary outcomes are physical tests and validated questionnaires aimed at physical, mental, and cognitive complaints. Effect evaluation based on daily assessments will include visual analysis, calculation of effect sizes (Nonoverlap of All Pairs), randomization tests, and multilevel analysis. In addition, other analyses will be based on ANOVA or a 2-tailed Student *t* test.

Results: Data collection for this study started in October 2023 and is planned to be completed in July 2024. The results will be published in peer-reviewed journals and presented at international conferences.

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Conclusions: This is the first study investigating the effect of an interdisciplinary rehabilitation treatment with a person-centered, biopsychosocial approach in patients with PCC. Our findings will help to improve the treatment and support of patients with PCC.

Trial Registration: German Clinical Trials Register DRKS00032636; https://drks.de/search/en/trial/DRKS00032636

International Registered Report Identifier (IRRID): DERR1-10.2196/63951

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KEYWORDS

rehabilitation medicine; postacute COVID-19 syndrome; quality of life; long COVID; COVID-19; multidisciplinary care; interdisciplinary care

Introduction

A COVID-19 infection, caused by the SARS-CoV-2 virus, typically causes respiratory tract illness [1]. In the Netherlands, there have been more than 8.5 million COVID-19 infections since December 2019 [2]. Although most patients with COVID-19 fully recover, about 10% to 20% of them retain symptoms after recovery from the initial SARS-CoV-2 infection [1]. Post–COVID-19 condition (PCC), commonly known as long COVID, is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these otherwise unexplained symptoms lasting for at least 2 months [3]. PCC can affect anyone exposed to the SARS-CoV-2 virus, regardless of their age or the severity of the original symptoms. Although the exact number of patients with PCC is uncertain, it is believed that more than 1.7 million people across Europe may have experienced it during the first 2 years of the pandemic (2020-2021) [3]. Common symptoms of PCC include fatigue, dyspnea, anosmia, muscle aches, headache, chest pain, palpitations, cognitive dysfunction, anxiety or depression, and sleep problems [4,5].

Persistent symptoms associated with PCC seem to harm physical and cognitive function, health-related quality of life (HRQoL), and participation in society [4,6]. According to the vision of health by the World Health Organization (WHO)—as presented based on the *International Classification of Functioning, Disability and Health*—functional impairments as a result of biomedical and psychosocial factors can reduce social participation, quality of life, and the ability to perform activities [7]. Therefore, it is possible that persistent complaints of PCC can be maintained by both (defined or still undefined) biomedical and psychosocial factors. This is consistent with findings from one of our earlier prospective cohort studies, in which survivors of COVID-19 in intensive care units (ICUs) who were admitted due to severe biomedical complications in this early phase of their illness were followed over time. Patients' levels of participation improved during the first year after ICU discharge [8]. But we also found that personal factors, such as less proactive coping, anxiety, or depression assessed 1 month after ICU discharge, appeared more predictive than biomedical (ICU-related) factors in indicating a delayed return to the patient's habitual level of participation during the first year. These findings suggest that rehabilitation treatment for survivors of COVID-19 in ICUs should focus on strengthening personal and environmental factors to improve functioning, participation in society, and quality of life and not just on biomedical complaints. Although these findings were specifically related to survivors of COVID-19 in ICUs [8], the same treatment components may also apply to patients with an initially milder course of COVID-19 infection who go on to develop PCC. This would be in line with the advice of the WHO, which recommends that rehabilitation treatment should have a human-centered, goal-oriented, and holistic approach designed to optimize functioning in individuals with health conditions or impairments in interaction with their environment [9]. Guidelines from the WHO and others recommend an interdisciplinary rehabilitation treatment for long-lasting complaints due to PCC with a high level of disability [9-11].

Recently, multiple studies on the effect of rehabilitation treatment in PCC were published. Two systematic reviews show an uncertain-to-positive effect of physical (pulmonary) training on functional exercise capacity, dyspnea, and quality of life [12,13]. Neither systematic review found any serious adverse events for any of the physical (pulmonary) training [12,13]. In addition, 2 experimental studies found no postexertional malaise or other adverse events due to physical activity [14,15]. However, a recent study showed changes in skeletal muscle structure in patients with PCC that are associated with a lower exercise capacity [16]. Another systematic review showed that a multidisciplinary rehabilitation treatment (multiprofessional, programs were ambulatory or inpatient) may have beneficial effects on fatigue, dyspnea, physical capacity, pulmonary function, quality of life, and daily life activities [17]. However, this evidence is very uncertain due to the low level of evidence, inconsistency in the results, varying treatment programs, and varying patient characteristics. Based on the biopsychosocial focus of PCC, psychological interventions such as cognitive behavioral therapy (CBT) or acceptance and commitment therapy (ACT) could also be useful. These would be aimed at increasing psychological flexibility or strengthening a person's resilience, depending on the patient's problem [18,19]. In a study by Kuul et al [20], CBT was effective in reducing fatigue complaints and improving physical and social functioning in patients with PCC. Furthermore, CBT seemed to be both feasible and accepted by patients with PCC [21]. In addition, in a study of Nikrah et al [22], ACT significantly increased the resilience and HRQoL of patients with PCC. In summary, although there has been research on rehabilitation treatments for PCC, the current understanding of the most effective rehabilitation treatment approach and the effects on participation levels and HRQoL is still limited.

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The precise cause of PCC remains unclear. A recent study by Appelman et al [16] showed changes in skeletal muscle structure, with severe exercise-induced myopathy and tissue infiltration of amyloid-containing deposits in the skeletal muscles of patients with PCC. Although there may be a somatic cause for PCC, a biopsychosocial approach seems promising for improving functioning in patients with PCC who perceive a high level of disability in daily activities and participation. It seems to be important to improve physical as well as mental resilience in order to optimize participation in society, despite health complaints due to PCC, by using a person-centered program focused on the various biopsychosocial factors of the patient and supported by a treatment plan from the entire interdisciplinary rehabilitation team. We therefore developed a new person-centered and tailored interdisciplinary rehabilitation treatment for patients with multiple health-related PCC complaints and high levels of disability in daily activities and participation. The treatment program is based on patients' and health care professionals' experiences and needs and on recommendations from the *European Physical and Rehabilitation Medicine* position paper [23]. This study aims to describe the replicated and randomized single-case experimental design (R-SCED) that is used to test the effectiveness of a 12-week, personalized, interdisciplinary rehabilitation treatment in secondary care and to evaluate changes in the recovery of participation levels and quality of life in patients with PCC.

Methods

Study Design

The design is R-SCED. This R-SCED study will use repeated measurements according to an AB follow-up design. In this design, patient functioning is closely monitored during a baseline phase (A), a treatment phase (B), and a follow-up phase. The length of phase A is 2 weeks. Phase B lasts for 12 weeks for all participants, and the follow-up phase lasts for 12 weeks. Figure 1 is a schematic presentation of the design, with treatment design and measurements (T0: beginning of phase A; T1: after completion of phase B; and T2: after completion of the follow-up phase). This R-SCED will be performed at Adelante Zorggroep, location MUMC+, which is an outpatient rehabilitation center in the south of the Netherlands.

Figure 1. Schematic presentation of the design: (left) the R-SCED design and treatment and (right) measurements. R-SCED: replicated and randomized-single case experimental design; T0: beginning of the baseline phase (phase A); T1: after completion of the treatment phase (phase B); T2: after completion of the follow-up phase.

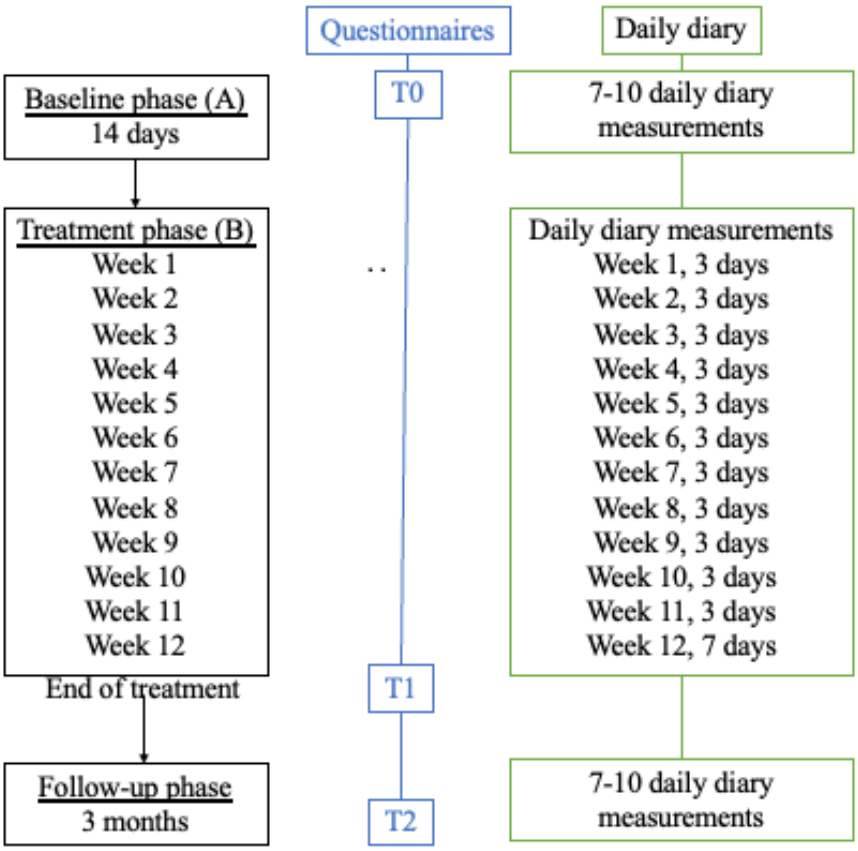

Ethical Considerations

The institutional review board of Maastricht University Medical Centre, University of Maastricht, approved this study (NL83848.068.23 or METC 23-008) in July 2023. All participants provided written informed consent. All personal data will be handled in accordance with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG). Participating patients will receive €75,00 after finishing the diaries and all the questionnaires.

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Eligibility Criteria

Adults, aged 18 years or older, having an indication for outpatient interdisciplinary rehabilitation treatment for PCC (high levels of disability in daily activities and participation based on the expert opinion of the rehabilitation physician) and with adequate Dutch literacy were eligible for inclusion. Participants will be excluded if PCC symptoms could be explained by an alternative medical disease or if they are not able to speak or read the Dutch language fluently; have no access to a smartphone, tablet, or computer; or have insufficient digital skills.

Regular Health Care Procedure

After referral by a general practitioner or medical specialist, the rehabilitation physician will invite the participant for a first consultation. This first consultation is for validating PCC complaints and their impact on daily life activities and participation. Biopsychosocial disabling factors will be identified and possibilities for psychological flexibility will be assessed. There will also be a medical examination, and other medical diseases will be excluded. If necessary, a referral to other medical specialists in secondary care will take place. Finally, education about PCC complaints and biopsychosocial factors for the participant and partner will be given [24]. During this consultation, a decision is made on whether there is an indication for an interdisciplinary rehabilitation treatment in secondary care. If an interdisciplinary rehabilitation treatment in secondary care is indicated and the participant meets the inclusion criteria, the rehabilitation physician will include the participant for the treatment and inform them about the aim and content of the study. Potential participants will have 1 week to reflect before deciding they want to participate. If the participant is willing to participate in the study, the study treatment protocol will start.

Baseline Phase (Phase A)

The baseline phase (phase A) is the control period of each participant. No specific treatment will be given during this period. The start of phase A is determined based on the start date of the interdisciplinary rehabilitation treatment and lasts 2 weeks. The number of days (7, 8, 9, or 10) a participant must fill in a daily diary during phase A will be randomized by a dedicated computer program (YourResearch). Phase B will start directly after phase A.

Treatment Phase (Phase B)

All participants will receive an outpatient interdisciplinary rehabilitation treatment in secondary care. This treatment aims to increase patients' levels of activity, participation in daily life, and HRQoL regardless of the level of complaints they experience. During phase B, participants are invited to fill in a daily diary for 40 days (Figure 1).

The treatment team consists of a rehabilitation physician, physiotherapist, occupational therapist, speech therapist, and psychologist. The team is experienced in interdisciplinary rehabilitation treatment with a biopsychosocial approach. Education has been given and supervision team meetings are planned monthly. For each participant, the content of the interdisciplinary rehabilitation treatment will be personalized according to the participant's individual physical, mental, and cognitive complaints and personal goals. As a result, input from the various disciplines can vary according to the participant's problem profile and needs. The individual goals are activity- and participation-oriented and determined during the intake with the rehabilitation physician and further specified during the treatment (eg, "being able to vacuum the entire house"). The Canadian Occupational Performance Measure (COPM), administered by an occupational therapist, will be used to support individual goal setting. The COPM was developed to set treatment goals based on problems experienced by the patient in daily activities [25,26]. The rehabilitation physician is the team supervisor and has final medical responsibility for the participants during the study period.

The interdisciplinary rehabilitation treatment lasts 12 weeks, with the patient receiving therapy approximately 3 half days per week (depending on their goals and initial capacity). In order to improve the level of functioning, the first 4 weeks consist of an assessment phase, in which the various disciplines gain insight into the participant's complaints, functional capabilities, and the potential to strengthen physical and mental resilience. After this first phase, a multidisciplinary consultation (MDC) takes place with all disciplines involved. During this MDC, an individual model explaining the level of COVID-19–related disability is proposed, based on the interaction of the disabling factors involved. The team will propose an 8-week treatment plan tailored to the patient's individual problems and goals. After this MDC, the patient will receive an interdisciplinary education from the treatment team in which the proposed individual explanatory model from a biopsychosocial perspective is discussed with the participant, including the hypothesized disabling factors that interfere with performing activities and participation in daily life. This education with a biopsychosocial approach is aimed at increasing mental and physical resilience despite the PCC complaints. Another MDC will take place in weeks 7 and 11 to discuss the progress in the treatment process and whether treatment goals or treatment plans should be adjusted. After each MDC, the rehabilitation physician provides all feedback to the participant and discusses the proposed plan according to principles of shared decision-making. If necessary, the rehabilitation physician will give additional biopsychosocial education. There will be a follow-up consultation with the rehabilitation physician after 3 months of completing the treatment phase.

The following are the commitment of disciplines within the interdisciplinary rehabilitation treatment and the contribution of the disciplines can vary according to the patient's profile and needs.

- Rehabilitation physician, at least 4 times (45 minutes for the first consultation, 15 minutes for a regular consultation): first consultation, after the MDC, and follow-up consultations.
- Physiotherapy, 2 times per week (each session takes 60 minutes), for improving physical performance such as physical condition and muscle strength through functional training and hydrotherapy and to guide in case of any pain- or tension-related complaints [11,27]. Patients are also encouraged to experience movement possibilities and will

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be encouraged to be as active as possible, regardless of the number and severity of complaints, particularly for valuable activities and social participation.
- Occupational therapy, 2 times per week (each session takes 60 minutes), for education in energy management and recognizing and pushing boundaries. The occupational therapist helps in resuming and building up daily activities (such as household duties, leisure activities, or work) despite the level of complaints [11,28].
- Speech therapy, 2 times per week (each session takes 30 minutes), for breathing exercises in case of dyspnea complaints, dysfunctional breathing, or dysfunction of the diaphragm [11].
- Psychotherapy, once a week (each session takes 60 minutes). To strengthen a person's resilience, first and second-generation CBT as well as third-generation CBT (ACT) will be applied. CBT aims to improve quality of life by strengthening individual resilience to cope with complaints [19,29]. The treatment can include a variety of techniques such as psychoeducation, verbal challenge techniques (learning to critically examine dysfunctional thoughts), behavioral experiments, skills training, breathing and relaxation exercises, stress management, problem-solving skills, and exercises to broaden sensory perception. The goal of ACT is growth in psychological flexibility [18]. The emphasis here is not on controlling and changing, but on accepting thoughts, behavior, feelings, and experiences such as negative physical experiences, fatigue, and pain.

Follow-Up Phase

The follow-up phase takes 12 weeks and starts directly after phase B. In the last 2 weeks of the follow-up phase, participants are invited to fill in a daily diary. The number of days (7,8, 9, or 10) a participant must fill in a daily diary during the last 2 weeks of the follow-up phase, will be randomized by a dedicated computer program (YourResearch). Phase B will start directly after phase A.

Assessment

Since PCC can affect different domains of functioning, measurements were chosen based on an integral vision of health and include body function impairments, activity limitations, and participation restrictions as well as personal factors, according to the *International Classification of Functioning, Disability and Health* [7]. All variables will be measured by daily diary items, validated questionnaires, and physical examination (Figure 1 and Tables 1-3). Based on design standards, the recommended minimum number of baseline measurements in an R-SCED study is 5 [30]. In this study, daily diaries will be completed for 7 to 10 days (baseline measurements) in phase A. In addition, there are 40 measurements during the rehabilitation treatment and a minimum of 7 to 10 follow-up measurements. The validated self-administered questionnaires will be collected at the start of phase A (T0), at the end of phase B (T1), and after 3 months of follow-up (T2). Participants will complete the questionnaires and the daily measurements with an app (YourResearch) on a computer or mobile device.

Table 1. Overview of the secondary outcome measurements: body function.

Secondary outcome measurements	Measurement instrument	T0[a]	T1[b]	T2[c]
Muscle strength	Muscle strength is a commonly used test for physical function [31]. A Jamar HHD[d] is used for handgrip muscle strength [32,33]. Muscle strength of the knee extensor or flexor is measured using a dynamometer (Biodex System 3 Pro Dynamometer) [34].	✓	✓	
Fatigue	MFIS[e]: this is a 21-item metric for fatigue severity. A total score is calculated as the sum of the subscale scores (0-84). Higher scores indicate higher levels of fatigue [35].	✓	✓	✓
Breathlessness	MRC[f] breathlessness scale: ranging from 1=no trouble with breathlessness to 5=I am too breathless to leave the house [36].	✓	✓	✓
Pain	NRS[g]: mean pain intensities in the last 7 days, ranging from 0 to 10 [37].	✓	✓	✓
Cognitive function	CFQ[h]: this is a 25-item self-report questionnaire. The total scores range from 0 to 100, with higher scores reflecting a report of more frequent cognitive errors in everyday life [38,39].	✓	✓	✓

[a]T0: beginning of baseline phase (phase A).

[b]T1: after completion of the treatment phase (phase B).

[c]T2: after completion of the follow-up phase.

[d]HHD: handheld dynamometer.

[e]MFIS: Modified Fatigue Impact Scale.

[f]MRC: Medical Research Council.

[g]NRS: Numerical Rating Scale.

[h]CFQ: Cognitive Failure Questionnaire.

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Outcome Measurement

Primary Outcome Variables

The primary outcome measurements are participation in society and HRQoL. A daily diary will be used, including a short (10-item) questionnaire to assess changes over time. The daily diaries consist of 8 questions selected from the validated questionnaires: Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P), EQ-5D-5L, and the Hospital Anxiety and Depression Scale (Multimedia Appendix 1). Each question is rated on a scale from 0 to 10. In addition, the daily dairy will focus on 2 most important individual goals (the participant will be asked to rate each goal on performance and satisfaction, on a scale from 0 to 10, based on the COPM score). The individual goals are determined by the patient, immediately after inclusion in the study.

Validated self-administered questionnaires will also be used. Participation in society will be assessed by USER-P. The USER-P consists of 3 subscales: the frequency of activities, the restriction subscale, and the satisfaction subscale. For all 3 subscales, the total score ranges from 0 to 100, with higher scores indicating better participation [40,41]. HRQoL is evaluated with the 5-dimension descriptive system (EQ-5D-5L) and the associated visual analog scale [42]. The EQ-5D-5L includes 5 domains, namely, mobility, self-care, usual activities, pain, and anxiety or depression. Each dimension is rated on a 5-level scale from “no problems” to “unable.” For the resulting 5-digit EQ-5D health profile, a weighted EQ index was calculated using Dutch reference values [43]. The EQ-5D-5L visual analog scale asks the participant to value their perceived health from 0=the worst imaginable health to 100=the best imaginable health, with higher scores indicating higher quality of life.

Secondary Outcome Variables

Secondary outcome variables are presented in Tables 1-3. Body function impairments (muscle strength, fatigue, breathlessness, pain, cognitive impairments), activity limitations (functional exercise, perceived limitations in daily life), participation (individual goals, activity and participation oriented), and personal factors (baseline characteristics, anxiety, depression, coping style and resilience) are assessed combined with physical examination and validated self-administered questionnaires. Details of the measurement instruments are also presented in Tables 1-3.

Table 2. Overview of the secondary outcome measurements: activity limitations and participation.

Secondary outcome measurements	Measurement instrument	T0[a]	T1[b]	T2[c]
Functional exercise	• 6MWT[d]: a submaximal exercise capacity by walking distance. The distance reached will be recorded in meters [44]. • STS[e]: for functional mobility, balance, and lower limb strength. Time in seconds is the main outcome [45,46]. • The 2-minute SCT[f]: a submaximal exercise capacity. The number of steps is the main outcome [47]. The 6MWT, STS, and SCT will be performed by an experienced physiotherapist.	✓	✓	
Perceived limitations in daily life	• PROMIS[g] physical function short form 8b: has 8 questions. Higher scores indicate better physical function [48,49]	✓	✓	✓
Individual goals, activity, and participation oriented	• COPM[h]: to set treatment goals based on problems experienced by the patient in daily activities and will be administered by an occupational therapist [25,26].	✓	✓	

[a]T0: beginning of baseline phase (A).

[b]T1: after completion of the treatment phase (B).

[c]T2: after completion of the follow-up phase.

[d]6MWT: 6-minute walk test.

[e]STS: Sit-to-stand test.

[f]SCT: stair climbing test.

[g]PROMIS: patient-reported outcomes measurement information system.

[h]COPM: Canadian Occupational Performance Measure.

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Table 3. Overview of the secondary outcome measurements: personal factors.

Secondary outcome measurements	Measurement instrument	T0[a]	T1[b]	T2[c]
Baseline characteristics	Age, sex, weight, education level, and marital status, as well as information about the time of COVID-19 infection, current complaints since the COVID-19 infection, the need for hospitalization due to COVID-19 infection, who diagnosed the post–COVID-19 condition, and previous treatments for the post–COVID-19 condition (open question and participant opinion).	✓		
Anxiety and depression	HADS[d]: this is a 14-item self-rated scale. The total score ranges from 0 to 21. A score ≥8 on either subscale is considered to be substantial anxiety or depression symptoms [50].	✓	✓	✓
Proactive coping skills	UPCC[e]: a 21-item self-assessment tool. The total score was the average for all item scores (range 1-4), higher scores indicate higher levels of proactive coping [51].	✓		
Resilience	BRS[f]: a 6-item questionnaire. The total score is the mean score of all answers (range 1-5). Higher scores indicate a better-developed ability of resilience [52,53]	✓		

[a]T0: beginning of baseline phase (phase A).

[b]T1: after completion of the treatment phase (phase B).

[c]T2: after completion of the follow-up phase.

[d]HADS: Hospital Anxiety and Depression Scale.

[e]UPCC: Utrecht Proactive Coping Scale.

[f]BRS: Brief Resilience Scale.

Sample Size Calculation

Experience from previous single-case experimental design (SCED) studies showed that the sample size varies between 6 and 27 participants [54-56]. One of our earlier prospective cohort studies was used in calculating the sample size. In this study, the USER-P was the primary outcome and improved in the first year after ICU discharge, [8]. In this cohort, the effect size based on changes in the level of participation appeared to be medium from baseline to 12 months follow-up (>0.5), with a statistical power of >0.8. Using the calculation tool developed by Bouwmeester and Jongerling [57] for SCED studies, with a medium effect size, the number of measurements, and accounting for loss-to-follow-up, 20 patients need to be included in this study. Patients withdrawn from the study will not be replaced. All analysis will be performed according to the "intention-to-treat" principle.

Statistical Analysis

Baseline and demographic characteristics will be presented in means (SD), medians (IQR), or percentages, as appropriate.

For our primary outcome measurements, the daily dairies, the statistical analysis will be performed using the Shiny app (KU Leuven) for single-case data analysis [58]. The following steps will be taken to test the effects of the intervention. First, in visual analysis, the within-case data of the daily dairies will be plotted and visually inspected per participant with respect to within-phase (eg, level, trend, variability) and between-phase characteristics (eg, immediacy of effect, overlap, consistency) [59]. Second, the percentage of nonoverlapping pairs between phases will be used to calculate the effect size of each participant. Nonoverlapping data between phases indicate performance differences between phases and is an important part of visual analysis in single-case research [60]. The Nonoverlap of All Pairs is an index of data overlap between phases in single-case research [60]. The Nonoverlap of All Pairs equals the number of comparison pairs showing no overlap, divided by the total number of comparisons. It can be calculated as an area under the curve [60]. Third, randomization tests will be performed to test the null hypothesis; that the interdisciplinary rehabilitation treatment has no effect on participation levels and HRQoL. The observations of the baseline phase will be compared to those of the intervention and follow-up phases, respectively (*mean phase A – mean phase BC = test statistic*, where C is the follow-up phase). Because the starting point of phase B (intervention) is randomly determined and the follow-up phase does not include any new intervention methods, phase B and the follow-up phase are combined. In case visual analysis suggests delayed effects, the randomization test will be repeated with lagged data until the lowest *P* value has been reached. Fourth, in a SCED study, 1 outcome is repeatedly measured in the same person. These replicated single-case experiments may be considered as multiple studies that can be combined using meta-analytical procedures [61,62]. To evaluate the overall changes in the daily diaries the daily data in phase A, phase B, and follow-up a multilevel analysis will be used to summarize the single-case data. Previously calculated effect sizes will be combined.

Missing data will be handled according to the randomized-marker method, in which all days of the diary that were not completed will be displayed as "N/A" (not applicable) [63].

For the other primary outcome measurements (USER-P and EQ-5D-5L) and the secondary outcome measurements, the results on T0, T1, and T2 will be computed as total scores on each questionnaire individually. Outcomes will be presented in

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mean (SD) or median (IQR), depending on the distribution. Outliers will be checked, defined as values more than 3 times the IQR from the median. The statistical analysis of the questionnaires will use repeated measures ANOVA in case of normal distribution or the Friedman test in case of nonnormal distribution. The statistical analysis of the physical examination will use the paired 2-tailed Student *t* test in case of normally distributed variables or the paired Wilcoxon test in case of nonnormally distributed variables. The significance level was set at *P*=.05, 95% CI. The statistical analysis will use IBM SPSS statistics version 26. No imputation will be made for missing data.

Data and Safety Monitoring

The risks attached to participating in this study are negligible and, in any case, no greater compared with other interdisciplinary rehabilitation treatments. A data safety and monitoring board has been appointed from de Clinical Trial Center Maastricht, with expertise in clinical trials. Monitoring includes informed consent forms, source data verification, and serious adverse events.

Results

This study was funded in June 2022. The institutional review board of Maastricht University Medical Centre, University of Maastricht, approved this study in July 2023. Participant recruitment started in October 2023 and was completed in July 2024. Data collection for this study is expected to be completed by January 2025. The analysis will be conducted after data collection has been completed. It is expected that the results will be published in spring 2025.

Discussion

Expected Findings

This study will assess the effectiveness of a new person-oriented interdisciplinary rehabilitation treatment in patients with PCC.

The WHO and other international guidelines recommend an interdisciplinary rehabilitation treatment for long-lasting complaints due to PCC with high level of disability [9-11,23]. Although the number of studies evaluating (interdisciplinary) rehabilitation treatments for PCC has increased [12,13,17], knowledge regarding the effect of these rehabilitation treatments on participation levels and HRQoL is still limited. It is expected that this personalized interdisciplinary rehabilitation treatment for patients with PCC, who perceive high levels of disability in daily activities and participation, will improve their level of participation and HRQoL and that physical, mental, and cognitive complaints will decrease.

Next, it is expected that this interdisciplinary rehabilitation treatment, when proven effective, can be implemented in other rehabilitation centers in the Netherlands and beyond. At the same time, we anticipate that patients and health care professionals will be satisfied with the interdisciplinary rehabilitation treatment. Depending on the results of the study, the interdisciplinary rehabilitation treatment can be further improved, based on information derived from a study of the experiences of patients and health care professionals. In addition, further research is necessary regarding the cost-effectiveness of the treatment, and when proven effective, further implementation studies will be facilitated to implement the program in current rehabilitation health care in the Netherlands and beyond. The results of the study will be published in peer-reviewed journals and presented at international conferences.

Strengths and Limitations

One strength of the study is its interdisciplinary approach. Various interventions (among others, physical training, energy management, breathing techniques, and psychological interventions) that may be effective in the treatment of PCC have been combined into a single interdisciplinary rehabilitation treatment program. Each patient is treated with a biopsychosocial approach aimed at improving physical and mental resilience and optimizing participation in society. Patients with PCC can experience various complaints such as fatigue and physical, mental, and cognitive complaints [5,64]. Patients included in this study experience high levels of disability in daily activities and low levels of participation, but the combination of their complaints may differ. An interdisciplinary rehabilitation treatment with a biopsychosocial approach tailored to a patient's complaints and goals, and which takes into account personal and contextual factors, therefore seems promising.

Another strength of the study is the chosen design: SCED [65]. Randomized controlled trials (RCTs) are seen as the gold standard for evaluating treatment effectiveness [66]. However, RCTs are time-consuming, and SCEDs seem to be a good alternative [67]. SCED studies are characterized by multiple measurements in a few participants, which allows a small sample size, whereas RCTs are based on a few measurement moments in many participants. Each patient functions as its own control and SCEDs are considered to be more compatible with clinical practice than an RCT [65,68]. A SCED can result in strong internal and external validity [65]. This study aims to evaluate the effect of a person-oriented interdisciplinary rehabilitation treatment, which makes a SCED most appropriate.

One limitation of the study is that a SCED may be resource intensive. The need for detailed observation and repeated measurements for a single participant can be demanding. A second limitation in using a SCED may be the generalizability of results. Since the focus is on a single participant or a small group, it may be hard to generalize the results to larger and more diverse populations. However, this interdisciplinary rehabilitation treatment was developed for a selected population, that is, patients with high levels of disability in daily activities and participation due to PCC. This selected group is a good fit for the design of a SCED study. Nevertheless, making conclusions about the effectiveness of the treatment in patients with less severe complaints needs further consideration. More research will be needed regarding the characteristics of patients who are more likely to benefit from the treatment.

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Conclusions

To our knowledge, this will be the first study to investigate the effect of an interdisciplinary rehabilitation treatment with a person-centered, biopsychosocial approach, to aim at improving social participation and HRQoL for patients with PCC. Our findings will help to improve the treatment and support of patients with PCC.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Daily diary, English translation.
[PDF File (Adobe PDF File), 45 KB - resprot_v13i1e63951_app1.pdf]

Multimedia Appendix 2
Peer-Review version 1 (including feedback on patient information letters and other medical-ethical documents) from the medical-ethical review board of Maastricht University Medical Centre, University of Maastricht.
[PDF File (Adobe PDF File), 227 KB - resprot_v13i1e63951_app2.pdf]

Multimedia Appendix 3
Peer-Review version 2 (including feedback on patient information letters and other medical-ethical documents) from the medical-ethical review board of Maastricht University Medical Centre, University of Maastricht.
[PDF File (Adobe PDF File), 178 KB - resprot_v13i1e63951_app3.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
CBT: cognitive behavioral therapy
COPM: Canadian Occupational Performance Measure
HRQoL: health-related quality of life
ICU: intensive care unit
MDC: multidisciplinary consultation
PCC: post–COVID-19 condition
RCT: randomized controlled trial
R-SCED: replicated and randomized single-case experimental design
SCED: single-case experimental design
USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation
WHO: World Health Organization

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Protocol

Efficacy and Safety of a Therapy Combining Sintilimab and Chemotherapy With Cryoablation in the First-Line Treatment of Advanced Nonsquamous Non–Small Cell Lung Cancer: Protocol for a Phase II, Pilot, Single-Arm, Single-Center Study

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Abstract

Background: Immunotherapy has significantly advanced lung cancer treatment, particularly in nonsquamous non–small cell lung cancer (NSCLC), with overall response rates between 50% and 60%. However, about 30% of patients only achieve a stable disease state. Cryoablation has shown potential to enhance immunotherapy by modifying the tumor's immune microenvironment through the release of antigens and immune factors. Addressing how to boost the immune response in these patients is critical.

Objective: This study aims to investigate the efficacy and safety of immunochemotherapy in combination with cryoablation as a first-line treatment for advanced NSCLC.

Methods: This is a phase II, pilot, open-label, single arm, single center, interventional study. Patients with stage IIIB to IIIC or IV NSCLC with T staging ranging from T1 to T2b will receive sintilimab (200 mg/m^2 every 3 weeks) and chemotherapy. After 2 cycles, the feasibility of cryoablation will be considered for those with stable disease by a multidisciplinary team. Cryoablation with 3 freeze-thaw cycles will be performed for the main lesion. The third cycle of systemic therapy will begin 7 (SD 3) days after cryoablation. A total of 20 patients will be enrolled. Treatment will continue until the disease progresses, there is unacceptable toxicity, a participant withdraws consent, other discontinuation criteria are met, or the study reaches completion. The primary objective is to assess progression-free survival (PFS). The secondary objective is to assess efficacy through duration of response, disease control rate, overall survival (OS), and the safety profile. The exploratory objective is to investigate and compare immune factor changes after 2 cycles of immunochemotherapy and at 1, 3, and 7 days after cryoablation. Survival time will be estimated using the Kaplan-Meier method to calculate median PFS and OS. Any adverse events that occur during the trial will be promptly recorded.

Results: The project was funded in 2024, and enrollment will be completed in 2025. The first results are expected to be submitted for publication in 2027.

Conclusions: This study will provide evidence for the efficacy and safety of the combination of immunochemotherapy and cryoablation as a first-line treatment for advanced NSCLC. Although it has a limited sample size, the findings of this study will be used in the future to inform the design of a fully powered, 2-arm, larger-scale study.

Trial Registration: ClinicalTrials.gov NCT06483009; https://clinicaltrials.gov/study/NCT06483009

International Registered Report Identifier (IRRID): PRR1-10.2196/64950

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KEYWORDS

cryoablation; immunotherapy; nonsquamous non–small cell lung cancer

Introduction

Lung cancer remains the most prevalent and lethal cancer worldwide. The 2022 Global Cancer Observatory report cites around 2.5 million new cases and 1.8 million deaths annually, which encompass all types of lung cancer, confirming its status as the deadliest cancer [1]. It is mainly categorized into 2 types: non–small cell lung cancer (NSCLC), which comprises about 85% of cases, and small-cell lung cancer. In recent years, significant breakthroughs have been made in targeted therapies and immunotherapies. Concurrently, the combination of local and systemic treatments has gained attention. According to the National Comprehensive Cancer Network (NCCN) guidelines [2], for NSCLC patients with oligoprogression after receiving tyrosine kinase inhibitors, local therapies can be incorporated alongside ongoing systemic tyrosine kinase inhibitor treatment for disease control. Studies with small sample sizes have confirmed that both oligoprogression and oligometastases benefit from local treatments [3-5]. The American Society for Radiation Oncology guidelines [6] recommend that for stage IV NSCLC patients with ≤5 oligometastases, up-front definitive local treatment of locoregional primary and all oligometastases should be performed after 2 to 3 months of standard systemic therapy. The BRIGHTSTAR (Brigatinib in Treating Patients With Stage IV or Recurrent Non-small Cell Lung Cancer Trial) study of local consolidative therapy [7,8] found that anaplastic lymphoma kinase (ALK)–rearranged mutation in advanced NSCLC patients who received targeted therapy for 8 weeks followed by local consolidative therapy prolonged the 3-year progression-free survival (PFS) rate compared to a consolidative therapy group (66% in a brigatinib group vs 47% in a crizotinib group, both with advanced ALK inhibitor–naive, ALK-positive non–small cell lung cancer). These studies indicate that sequential local treatment following systemic therapy provides an improved prognosis.

For advanced NSCLC without driver gene mutations, immunotherapy—specifically inhibitors targeting programmed death receptor 1 (PD-1) and its ligand (PD-L1)—has significantly improved patient outcomes. The 5-year overall survival rate has reached 20%, and even 40% in patients with high PD-L1 expression [9]. As a result, immunotherapy is recommended by the NCCN [2] as a standard first-line treatment for this type of lung cancer and has become a mainstream treatment option in clinical practice. Generally, for nonsquamous NSCLC, the objective response rate (ORR) to immunochemotherapy is around 50% to 60% [10-17], with approximately 30% of patients assessed as having stable disease. Sintilimab is a monoclonal antibody that targets PD-1 on T cells, blocking the PD-1/PD-L1 pathway. In NSCLC, sintilimab has been evaluated in a randomized, controlled phase III trial in China known as Oncology Program by Innovent anti-PD-1–11 [13]. This trial assessed the efficacy and safety of sintilimab combined with pemetrexed and platinum chemotherapy compared to a placebo in treating patients with locally advanced or metastatic nonsquamous NSCLC. The results showed that the combination sintilimab-chemotherapy group had significantly prolonged PFS compared to the placebo group, with a median PFS of 8.9 months versus 5.0 months (hazard ratio 0.482, 95% CI 0.362-0.643; $P<.001$). Additionally, the ORR in the combination sintilimab-chemotherapy group increased from 29.8% to 51.9%. Addressing how to enhance the immune response in these patients is crucial. Thus, the integration of local therapies with immunotherapy is gaining focus. The reasons for using local therapy are to (1) reduce tumor burden and minimize the possibility of metastasis and (2) adjust the immune microenvironment and boost the synergetic effect with immunotherapy.

In the NCCN guidelines, image-guided thermal (IGTA) therapy may be considered for those patients who are deemed “high risk”—those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. Recently, several studies have demonstrated that IGTA therapy combined with systemic therapy may improve survival [3,4,18]. Combining IGTA therapy and immunotherapy for a synergetic effect should be promising and deserves further investigation [19]. Cryoablation is a minimally invasive technique that uses extremely low temperatures to destroy cells in target tissues; it is commonly applied in treating various benign and malignant diseases, including tumors. This technique boasts benefits like ease of use, minimal intraoperative bleeding, and reduced postoperative pain. At temperatures below –20°C, most cells succumb, and below –50°C, cell death is nearly universal [20]. Cryoablation can cause extracellular ice crystal formation, leading to solute concentration and an osmotic gradient between the inside and outside of the cell, transferring intracellular water to the extracellular space, disrupting the local metabolic environment [21]. The crystals produced by freezing can generate local shear forces to disrupt the integrity of cell membranes, thereby causing lethal damage to the cells. After tumor cells are killed by cryoablation, the necrotic tumor cells at the lesion site release antigens, organelles, DNA, heat shock proteins, and other substances locally, triggering immune cells (such as dendritic cells) to engulf these substances, present antigens through major histocompatibility complex molecules, and costimulate and activate cytotoxic T cells, thus inducing a systemic antitumor immune response. At the same time, after cryotherapy, the levels of cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor [TNF]-α) in the serum significantly increase, also enhancing the immune response [20,22]. The synergetic effect of cryoablation and PD-1 blockade was explored in both allograft mouse lung cancer models and patients with unresectable NSCLC [23]. Cryoablation significantly increased circulating cluster of differentiation (CD) 8+ T cell subpopulations and proinflammatory cytokines in patients with early-stage NSCLC. In lung cancer cell allograft mouse models, an abscopal growth inhibition of contralateral, nonablated tumors was found. Analysis of single-cell RNA and T cell receptor bulk sequencing data revealed that cryoablation reprogrammed the intratumoral immune microenvironment and increased CD8+ T cell infiltration with a higher effector

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signature, interferon (IFN) response, and cytolytic activity. Mechanistically, cryoablation promoted an antitumor effect through the cyclic GMP-AMP synthase–stimulator of interferon genes–dependent type I IFN signaling pathway. In some small-sample-size clinical studies, patients who received cryoablation plus immunotherapy showed long short-term efficacy compared to monotherapy [24,25]. These studies suggest that cryoablation, as a form of local treatment, combined with immunotherapy, represents a new research direction. Nevertheless, the timing of sequencing therapy, and populations that can benefit from this approach, are still not clear. Further studies with better study designs and prospective cohorts are warranted. The purpose of the study is to evaluate the efficacy and safety of first-line treatment with sintilimab in combination with platinum-based doublet chemotherapy and cryoablation in patients with advanced nonsquamous NSCLC who have been assessed as having stable disease after 2 cycles of treatment.

Methods

Study Setting and Sample

This prospective, single-center, single-arm pilot study will be conducted in Shanghai Chest Hospital from July 2024 to July 2027. In our department, we see 100 to 120 new cases of advanced lung cancer per month, which may help us enroll enough patients for this study.

Eligible patients are all those who meet the inclusion criteria. Patients must have a primary lesion with a maximum diameter of <5 cm that is located in a relatively isolated location, not adjacent to major blood vessels or major structures, and deemed suitable for tumor debulking by ablation. After signing an informed consent form, eligible patients meeting the inclusion criteria are screened.

Patients receive sintilimab treatment combined with chemotherapy for 2 cycles, followed by tumor assessment. Patients assessed as having stable disease undergo cryoablation after the assessment. The systemic therapy continues within 7 (SD 3) days after cryoablation. There is currently no consensus on the timing of ablation and immunotherapy. According to the BRIGHSTAR study experience, implementing local consolidation therapy measures after a period of immunotherapy has been found to be feasible and effective. In a study of early-stage NSCLC, cytokines were found to increase from 3 to 7 days after cryoablation [23]. A phase I/II [26], multicenter, open-label, randomized study designed to evaluate the safety and efficacy of ablation combined with toripalimab versus toripalimab monotherapy in treated, unresectable hepatocellular carcinoma, in the first phase of the study, aimed to determine the superior regimen—ablation followed by immunotherapy on day 3 (regimen D3) or day 14 (regimen D14). The study found that regimen D3 resulted in a higher ORR. A 10-year real-world study [27] demonstrated that the combination of cryoablation and immunotherapy treatment showed good efficacy within 2 to 4 weeks. In another study [5], local treatment was administered 4 to 12 weeks after the end of immunotherapy for safety reasons. Taking into consideration patient compliance, safety, and departmental experience, we decided to perform the third cycle of immunotherapy treatment 7 (SD 3) days after cryoablation.

Immunotherapy combined with chemotherapy continues until the disease progresses, there is intolerable toxicity, a patient withdraws informed consent, a patient initiates another antitumor therapy, a patient dies, or a patient meets other criteria for treatment discontinuation specified in the protocol, whichever occurs first. The maximum treatment duration is 24 months.

Participants

Inclusion and Exclusion Criteria

Textbox 1 shows the inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years or ≤75 years
- Histologically or cytologically confirmed locally advanced (stage IIIB to IIIC), metastatic, or recurrent (stage IV) nonsquamous non–small cell lung cancer (NSCLC) (as per the

  International Association for the Study of Lung Cancer and the American Joint Committee on Cancer, 9th edition, tumor, nodes, metastasis lung cancer staging), with T staging ranging from T1 to T2b and the tumor not amenable to surgical treatment and definitive concurrent chemoradiotherapy, as well as not previously having received systemic treatment
- Maximum diameter of the primary lesion <5 cm and located in a relatively isolated area, not adjacent to major blood vessels or major structures
- Absence of epidermal growth factor receptor gene sensitizing mutations, and anaplastic lymphoma kinase gene fusion mutations confirmed with histopathology specimens
- At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1), with lesions located within previously irradiated fields considered measurable if confirmed to have progressed
- No prior systemic antitumor therapy for advanced/metastatic disease. Patients who have previously received platinum-based adjuvant/neoadjuvant chemotherapy, or definitive chemoradiotherapy for advanced disease, may be included if disease progression or recurrence has occurred at least 6 months after the end of the last chemotherapy regimen
- Patients with asymptomatic or stable symptomatic brain metastases may be included if they meet specific conditions: (1) measurable lesions outside the central nervous system, (2) absence of central nervous system symptoms or stable symptoms for at least 2 weeks, and (3) no need for corticosteroid treatment, discontinuation of corticosteroid treatment within 7 days before the first dose of study drug, or stable corticosteroid dose reduced to ≤10 mg/day prednisone (or equivalent) within 7 days before the first dose of the study drug
- Eastern Cooperative Oncology Group performance status of 0 to 1
- Expected survival >3 months
- Adequate organ function, with the following laboratory criteria: (1) absolute neutrophil count ≥1.5 × 109/L without granulocyte colony–stimulating factor use in the past 14 days and (2) platelet count ≥100 × 109/L without blood transfusion in the past 14 days

Exclusion criteria

- Pathologically confirmed small-cell lung cancer (SCLC), including lung cancer mixed with SCLC and NSCLC
- Diagnosed with malignancies other than NSCLC within 5 years before the first dose of the study drug (excluding cured basal cell carcinoma, squamous cell carcinoma of the skin, and/or in situ carcinoma)
- Previously having received therapy, including anti–programmed death receptor 1, anti–programmed death ligand 1, or anti–programmed death ligand 2, drugs or drugs targeting another T cell receptor for stimulation or coinhibition (eg, cytotoxic T-lymphocyte-associated protein 4, cluster of differentiation [CD] 134, or CD137)
- Active autoimmune diseases requiring systemic treatment within 2 years before the first dose of the study drug; alternative therapies (eg, thyroid hormone, insulin, or physiological corticosteroids for adrenal or pituitary insufficiency) are not considered systemic treatment
- Pregnant or lactating women
- Presence of any severe or uncontrollable systemic diseases
- Not fully recovered from any toxicity and/or complications caused by previous interventions before starting treatment
- A known history of HIV infection (ie, positive for HIV 1/2 antibodies)
- Untreated active hepatitis B (defined as positive hepatitis B surface antigen with hepatitis B virus DNA copy number exceeding the upper limit of normal values for the testing laboratory at the study center) or active hepatitis C virus infection (ie, positive for hepatitis C virus antibodies and hepatitis C virus RNA levels above the lower detection limit)
- Diffuse lesions in both lungs where ablation therapy cannot improve the condition
- Extensive pleural metastases with large amounts of pleural effusion
- Difficulty in needle puncture due to proximity of the tumor to major mediastinal vessels or difficulty in selecting a puncture path due to contrast agent allergy or patient noncompliance
- Severe impairment of lung function, with maximum ventilation <40%

Sample Size and Study Duration

The primary objective of this study is to evaluate PFS after adding cryoablation for tumors assessed as stable after 2 cycles of first-line treatment with sintilimab and platinum-based chemotherapy in driver-negative advanced nonsquamous NSCLC patients. Due to the lack of relevant literature regarding the PFS of advanced NSCLC patients who have undergone 2 cycles of immunotherapy and are assessed as having stable disease, this study is exploratory in nature. Therefore, a fixed sample size of 20 patients is set. The anticipated enrollment

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period for this study is 12 months, with a follow-up duration of 24 months.

Intervention

Sintilimab

Sintilimab (200 mg) is administered by intravenous infusion on day 1 of each cycle, with each cycle lasting 3 weeks, until disease progression, death, intolerable toxicity, withdrawal of informed consent, initiation of new antitumor treatment, or termination of treatment for other reasons, as specified in the protocol. The maximum treatment duration for sintilimab is 24 months.

Chemotherapy Regimen

Pemetrexed in combination with a platinum-based regimen is used. Pemetrexed (500 mg/m^2) is administered by intravenous infusion on day 1 of each cycle, plus either cisplatin (75 mg/m^2) or carboplatin (area under the curve 5) administered by intravenous infusion on day 1 of each cycle, every 3 weeks, for a total of 4 to 6 cycles. For patients who have not progressed after 4 to 6 cycles, maintenance therapy with pemetrexed monotherapy is continued at the same dose and schedule as before until disease progression, death, intolerable toxicity, withdrawal of informed consent, initiation of new antitumor treatment, or termination of treatment for other reasons, as specified in the protocol. The maximum treatment duration for pemetrexed is 24 months.

Cryoablation

For patients assessed as having stable disease after 2 cycles of medication, 1 session is performed under local anesthesia after assessment. The multidisciplinary team, including investigators and radiologists, evaluates the feasibility of tumor ablation based on the size, location, and proximity to major blood vessels. Criteria for eligible lesions include a maximum diameter <5 cm, a relatively isolated lesion location, and the lesion not being adjacent to major blood vessels or vital structures. Cryoablation is performed using a 17 gauge IceRod Plus 1.5 (Boston Scientific Corporation) cryoablation needle, guided by computed tomography (CT), avoiding nearby anatomical structures using the Visual-ICE cryoablation system (Boston Scientific Corporation).

Target Lesion Selection for Ablation

Assessment is conducted by a multidisciplinary team including researchers, ablation surgeons, and radiologists during the screening of eligible cases. The main lesion should be <5 cm. Based on tumor size, location, and vascular and adjacent structures, lesions that are assessed as debulkable are selected for cryoablation. For each patient, only the main lesion will be ablated. Debulking is needed when the tumor size exceeds 3 cm or when curative therapy cannot be performed. The ice ball might not cover the whole lesion, but should cover at least 80% of the tumor volume. The purpose is to reduce the tumor burden while the systemic therapy continues.

The cutoff value of 5 cm was chosen (1) for the generalizability of the study results and (2) because the study population comprises patients at stages IIIb to IV. The main purpose is to reduce the tumor burden and stimulate tumor immunity. Considering the heterogeneity of outcomes with different diameters of ablation, the researchers will strive to maintain a consistent ablation zone for patients.

Procedures

Cryoablation was performed with a minimum of 3 freeze-thaw cycles. The times for each phase were as follows: 3 minutes of passive thawing, 7 to 12 minutes of freezing, 5 minutes of passive thawing, and 7 to 12 minutes of freezing followed by active thawing. Each procedure was monitored with noncontrast CT imaging, typically at 3-to-5-minute intervals, to visualize the evolving ablation zone to avoid adjacent anatomical structures.

Outcomes

Primary Objective

The primary objective is to evaluate PFS after integrating cryoablation for tumors assessed as stable after 2 cycles of first-line treatment with sintilimab and platinum-based chemotherapy in driver-negative advanced nonsquamous NSCLC patients.

Secondary Objectives

The secondary objectives are to assess the ORR of patients, evaluate the disease control rate (DCR) of patients, assess the duration of response (DoR) of patients, and assess the OS of patients. The safety and tolerability of sintilimab in combination with cryoablation and platinum-based doublet chemotherapy will be recorded, including the incidence of adverse events, serious adverse events, and adverse events/serious adverse events that lead to treatment discontinuation.

The primary and secondary efficacy end points of this study are assessed by the investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and iRECIST. In case of any discrepancies, the investigators will consult a third party. The third party comprises a discussion group of experts in the same department (the team of experts performs teaching rounds every Monday morning).

PFS is defined as the time from ablation to disease progression or death from any cause. ORR is defined as the proportion of patients who have a partial or complete response to therapy. DCR is defined as the proportion of patients who have stable disease or a partial or complete response to therapy. DoR is defined as the time from ablation to disease progression or death in patients who achieve a complete or partial response. OS is defined as the time from ablation to death from any cause.

Exploratory Objective

The exploratory objective is a flow cytometry analysis of the peripheral expression of immune factors after 2 cycles of immunotherapy plus chemotherapy and at 1, 3, and 7 days after cryoablation. Peripheral blood samples of 2 ml each are collected. Changes in immune factors, including CD4+ T cells, naive CD8+ T cells (CD45RA+chemokine receptor [CCR] 7+), central memory CD8+ T cells (CD45RA− CCR7+), effector CD8+ T cells (CD45RA+ CCR7−), effector memory CD8+ T cells (CD45RA− CCR7−), IL-2, TNF-β, IFN-γ, IL-4, IL-6,

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IL-10, IL-11, IL-29, regulatory T cells, and matrix metalloproteinase–3 are explored using flow cytometry.

Statistical Analysis

All statistical analyses will be performed using SPSS (version 23 or higher; IBM Corp). Two-sided hypothesis tests will be used for all statistical tests, and comparisons between groups will provide 95% CIs and *P* values. Unless otherwise specified, continuous data will be described statistically using the mean (SD) or median (minimum, maximum), while categorical data will be described using frequencies (percentages). Cytokine changes before and after treatment will be tested with repeated ANOVA or the Friedman test as appropriate. Survival time will be estimated using the Kaplan-Meier method to calculate median PFS and OS (with the 95% CI), and survival curves will be plotted.

Data Management

The raw data will be captured using case report forms (CRFs; these are paper based) at the designated time. One data administrator, who is not affiliated with the research team and is blinded to group allocation, independently receives the completed CRFs and enters the raw data into a Microsoft Excel database. Simultaneously, they will input real-time data into ClinicalTrials.gov.

Ethical Considerations

Ethical approval to conduct this study has been obtained from the Research Ethics Committee of Shanghai Chest Hospital (IS24069) on June 28, 2024. Any substantial amendment to the study protocol will need to be approved by an ethics committee after being approved by the sponsor. Informed consent is obtained from participants and their ability to opt out is communicated to them. The data of patients are anonymized or deidentified. To ensure privacy and confidentiality, all records and files related to the study are kept in a secure location and are only accessible to members of the research team. The results will be published in peer-reviewed journals and presented at relevant national and international conferences. The study findings will also be disseminated through presentations at relevant academic forums.

Results

The project was funded in 2024, and enrollment will be completed in 2025. The first results are expected to be submitted for publication in 2027.

Discussion

Overview

Immunotherapy has established its position as a first-line treatment for NSCLC, with some patients still being assessed as having stable disease after a period of treatment. Nevertheless, several studies have confirmed that combining cryoablation with systemic treatments yields better outcomes. Niu et al [25] explored the efficacy of cryoablation treatment compared to palliative treatment in stage IV lung cancer. In their study, 98 lesions in 31 patients received cryoablation treatment, while 23 patients received palliative treatment. The results showed that the OS in the cryoablation group was significantly better than in the palliative treatment group (median OS: 14 months vs 7 months, $P \leq .001$). Multiple cryoablation treatments were found to improve OS more than a single cryoablation treatment (median OS: 18 months vs 14 months, $P=.04$). Another study [24] included 64 patients, including 32 patients who received argon-helium knife cryoablation combined with nivolumab treatment (the cryoablation-nivolumab group) and 32 patients who received cryoablation treatment alone (the cryoablation group). The results showed that short-term efficacy was better in the cryoablation-nivolumab group than the cryoablation group, with a statistically significant difference ($P<.05$). The DCR in the cryoablation-nivolumab group was 87.5%, compared to 62.5% in the cryoablation group ($P=.02$). The total number of T cells, CD8+ T cells, and CD4+ T cells significantly increased in the cryoablation-nivolumab group ($P<.05$), and both groups showed an increase in NK cell count after treatment ($P<.05$). Regarding lymphocyte function, the levels of IL-2 and TNF-β increased in the cryoablation-nivolumab group ($P<.05$), and the levels of IFN-γ increased in both groups after treatment ($P<.05$). These initial studies confirmed the efficacy of combining cryoablation and immunotherapy, but several questions regarding the combination therapy still need to be answered and clarified: how to maximize the value of the combination therapy, how to find the appropriate timing, and how to identify populations that could benefit. This study will help to clarify the mechanisms and optimal sequential timing of combining cryoablation with immunotherapy. Our study aims to improve the prognosis of patients by reducing the local tumor burden and stimulating the immune response. Should our study yield positive results, we plan to conduct a larger-scale, 2-arm study.

Principal Findings

This study will provide evidence for the efficacy and safety of the combination of immunochemotherapy and cryoablation as a first-line treatment for advanced NSCLC. Although it has a limited sample size, the findings of this study can be used in the future to inform the design of a fully powered, 2-arm, larger-scale study.

Limitations

There are risks inherent in the study design and conception. First, our sample size was not rigorously calculated; instead, a fixed sample size of only 20 was chosen, which is relatively small. Second, this is a single-center study, which may introduce bias in the results. Third, this is a single-arm study lacking a control group, which prevents comparative conclusions. These limitations are expected to be addressed in future research.

Conclusion

In conclusion, our study is pivotal in clarifying the timing of ablation and identifying the populations that might benefit from this treatment, and it lays the foundation for larger future studies.

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Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ZG and HZ contributed to conceptualization. ZG established the hypothesis and wrote the original proposal. JT, JQ, MM, and RQ contributed to data curation. JL and FP contributed to data analysis. BZ and TC helped improve the manuscript. HZ conducted manuscript review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Investigator-Sponsored Research Program (ISP) - Boston Scientific.
[PDF File (Adobe PDF File), 187 KB - resprot_v13i1e64950_app1.pdf]

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Abbreviations

ALK: anaplastic lymphoma kinase
BRIGHTSTAR: Brigatinib in Treating Patients With Stage IV or Recurrent Non-small Cell Lung Cancer Trial
CCR: chemokine receptor
CD: cluster of differentiation
CT: computed tomography
DCR: disease control rate
DoR: duration of response
IFN: interferon
IGTA: image-guided thermal

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IL: interleukin
NCCN: National Comprehensive Cancer Network
NSCLC: non–small cell lung cancer
ORR: objective response rate
OS: overall survival
PD-1: programmed death receptor 1
PD-L1: programmed death ligand 1
PFS: progression-free survival
RECIST: Response Evaluation Criteria in Solid Tumors
TNF: tumor necrosis factor

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Protocol

Exploring the Experiences of Times Without Care and Encounters in Persons With Dementia in the Swiss and German Nursing Home and Domiciliary Care Settings: Protocol for an Ethnographic Multimethods Study

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Abstract

Background: Persons with dementia spend a large part of the day without care and encounters, often without activity, as confirmed by numerous studies. However, no scientific analysis has examined how persons with dementia experience these periods. Such knowledge would be highly relevant for health care professionals and relatives to develop adequate strategies for dealing with times without care.

Objective: We aim to reconstruct times without care and encounters in persons with dementia in the nursing home and domiciliary care settings and develop a typology. This typology will address the lifeworld understandings of time and the ways of arranging the time of persons with dementia.

Methods: Our study is designed as an explorative, sequential multimethods investigation. We aim to systematically reconstruct times without care and encounters over a period of 36 months using ethnographic methods. Afterward, we will examine the resulting typology using a survey. To describe different social and caring cultures, practices, and arrangements, we will analyze time periods across all phases of dementia in (1) institutions exclusively caring for persons with dementia, (2) institutions where persons with dementia and those without live together, and (3) domiciliary care. For each type of care, our target is 10 intensive case observations. These observations will occur in both *participatory* and *nonparticipatory* ways. We video record selected situations and conduct situational conversations and interviews with persons with dementia and nurses. We are aiming for a minimum sample of 30 persons with dementia plus their caregivers (ie, relatives of people with dementia and professional caregivers). We will analyze data according to grounded theory methodology. Furthermore, we will perform a hermeneutic sequence analysis of selected text passages. To interpret the video material, we will conduct a video interaction analysis. To obtain complementary information about the newly developed typology, we will survey approximately 400 formal and 150 informal caregivers. We will summarize the ethnography and survey findings into an overall concept of times without care and encounters in persons with dementia. To fulfill the research objectives, our cross-disciplinary and cross-country team comprises researchers with expertise in nursing sciences, gerontology, sociology, psychology, and ethnography.

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Results: Our approach allows formulating statements about the nature, frequency, and prevalence of times without care and encounters in people with dementia across countries and types of care. Thus, we will contribute to making visible the lifeworld of persons with dementia. Our study commenced in March 2022 and will conclude in May 2025. The results are expected to be published in the fall of 2025.

Conclusions: Our research offers points of departure for the representative investigation of times without care and encounters in persons with dementia, for the development of diagnostic instruments, and for dealing critically with possibilities of interruption (eg, by developing targeted interventions).

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KEYWORDS

dementia; nursing homes; home nursing; home care services; nursing; ethnography; formal caregivers; informal caregivers

Introduction

Background

The diagnosis and progression of dementia are associated with lifeworld crises because the patterns of interpretation and action increasingly fail, and there is uncertainty and a lack of orientation [1,2]. Such crises arise and persist in the working and care worlds located in domestic-familial and institutional settings. For the most part, these crises receive political and social acceptance. Isolation, loneliness, helplessness, excessive demands, and despair, as well as the associated severe restrictions on basic rights and liberty, are characteristic of the lifeworld contexts experienced by persons with dementia and their caregivers [3-6].

Persons with dementia and their caregivers *navigate* a marginalized world characterized by the collapse of the structures of help, care, support, and relationships. The associated ethical conflicts and dilemmas are politicized and discussed in society. However, this does not change the affected persons' experience of crisis [7-12].

The issue of dementia has played an enormous role in the political, social, and scientific debate for several years. This is now reflected in the German-speaking population. As the German Dementia Barometer 2018 shows, the majority of the population feels well informed about dementia and believes that there are good opportunities for supporting persons with dementia [13].

However, at the same time, a marginalization of the dementia phenomenon is evident at various levels. The review by Lara et al [14] indicates the interrelation between subjectively experienced loneliness and the risk of developing dementia. According to the findings, people with a subjective feeling of marginalization are particularly affected by dementia. They feel socially excluded even before they are diagnosed. By contrast, the pathologization or stigmatization of persons with dementia as people that suffer from dementia increases their marginalization. Due to their varying degrees of loss of cognitive and communicative abilities, persons with dementia are less and less involved in social life in the sense of social participation. Caring for persons with dementia increasingly takes place in a social protective sphere [15] (eg, in a familial, dyadic care dependency or in a care facility). The social, restrictive area of protection results predominantly from a caring motivation or a benevolent compulsion" [16]. Country-specific differences could play a role here: in Switzerland, caring for and supporting persons with dementia in the institutional setting predominantly occurs in so-called protected and secured living areas [17,18]. Unlike in Germany, these protected living areas are usually isolated from other normal living areas. As a result, persons with dementia become even more fixed in place, immobile, and therefore isolated agents at the margin [19-21]. Persons with dementia enter a downward spiral due to inadequate cognitive, emotional, and sensory stimulation. This has a negative impact—on the course of dementia; the development of challenging behavior; the way of shaping relationships with their environment; and, above all, their physical, cognitive, and emotional states [22]. Almost on the basis of a conceptual justification and thus in a socially legitimized way, persons with dementia are isolated and immobilized [21,23]. This imposed solitude seems to support the *production* and *potentiation* of care dependency in persons with dementia [24,25]. The scientific and social discourse on this closed-door policy takes place internationally [17,26-29].

There are numerous empirical indications that persons with dementia in institutional care settings experience long periods of boredom and inactivity, along with associated phases of loneliness [21,30-36]. In addition, observational studies document the lack of activation of thoughts or behaviors and involvement of persons with dementia. Accordingly, during the majority of the observation periods, persons with dementia were found sitting alone, being inactive, resting, dozing, sleeping, or sitting or lying in front of the television set [35,37-39]. Persons with dementia spend an average of 5 hours a day asleep [40].

It should be noted that activity programs in inpatient care settings only take place to a limited extent [41]. Theurer et al [33] confirm institutionalized inactivity in their study on physical activity in institutional long-term care. Two observational studies [42,43] examined the activities of persons with dementia during the day in different long-term care settings. Both studies found significantly more activity and social interaction in specialized institutions. However, also in these settings, persons with dementia seem to spend a relatively large amount of time in nonpurposeful activity (eg, tapping on a table, rubbing hands for no reason, picking at clothing or objects, wandering, and mumbling) or inactivity. These findings are based exclusively on quantitative observational data and represent the researchers' perspective. As a result, it was not

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possible to draw conclusions about how people with dementia themselves perceive these periods of time. Therefore, there may be a difference in perspective [44].

In a Swedish ethnographic study addressing the situation in nursing homes, Harnett [45] described these periods of time as "respite spaces." A large part of the life of persons with dementia seems to consist of respite spaces. During these periods of time, persons with dementia neither communicate nor interact with nurses. They are not involved in interventions or routine processes. Harnett [45] advocated intensive investigation of these respite spaces to understand what they mean for people with dementia and their caregivers. Harnett [45] observed that persons with dementia not only passively submit to institutional events but also actively shape them—by using communicative strategies and entering into contact with each other. In respite spaces, persons with dementia seem to construct an intersubjectively shared reality of life. However, they usually do not organize their own daily routines—they see nurses as responsible for the social organization of a living unit [45]. In community rooms, they try to fulfill the shared expectation of sitting still and taking care of their own things [46]. By contrast, nurses' practices seem to be directed at *prompting* persons with dementia to sit as still as possible and mind their own business [46,47]. Other reasons for the low level of activity and involvement may be physical impairments, obstructive architecture (eg, large, noisy community rooms), and unfavorable design of the living environment. Limited time resources or a shortage of (nursing) staff might also play a role [48,49]. Together, these factors limit opportunities and choices to participate in activities and social relationships that persons with dementia consider important [50-52].

According to an explorative, Scandinavian study based on qualitative interviews with persons with dementia and nurses, persons with dementia wish to be more involved in activities and relationships. This is important for them to lead a dignified life [53]. By contrast, nurses often consider persons with dementia as inactive and unmotivated [51]. For their part, persons with dementia seek to engage in individual and group activities. These activities are important to them [53] and help them to live a meaningful and fulfilling life [54]. In addition, persons with dementia can experience and coconstruct their identity in activities that are meaningful to them [55]. Relationships characterized by respect and goodwill, in which they feel heard, understood, and accepted, are important for them [56,57]. In the domiciliary care setting, family caregivers also emphasize the importance of routines and sense-giving activities to maintain the continuity and stability of the care situation [58].

In times without care and encounters, persons with dementia may strive for activities that resemble to those generally described as leisure activities. Studies on the importance of leisure for persons with dementia are congruent with the sociopsychological concept of leisure [59]. According to Prahl [60], leisure has become a dominant area of modern societies. It refers to people's *free* time [60]. Leisure varies across social groups in terms of quantity and quality. For persons with dementia, access to leisure activities understood in this way is often difficult. They experience leisure time in increasing dependence on family members or other people. As a result, the leisure time of persons with dementia (as well as that of their informal caregivers) is condensed in terms of time and space.

However, engaging in or participating in activities considered leisure activities can have a positive impact on the well-being of persons with dementia and their families [59]. Leisure activities can be an opportunity for self-fulfillment. They allow persons with dementia to "be me, be with, make a difference, seek freedom, find balance, grow and develop and have fun" [61]. In relation to persons with advanced dementia, the literature does not generally refer to leisure activities but to meaningful activities. However, for the most part, meaningful activities coincide with leisure activities, as shown by a synthesis of qualitative studies on the perspective of persons with dementia regarding meaningful activities [62]. In a British grounded theory study, family caregivers emphasize the need to constantly reassess and adapt the goals, content, and types of activities that are meaningful for persons with dementia [58].

The authors of a meta-ethnography on the meaningful activities of persons with dementia underline the relevance of meaningful activities for a fulfilling life for persons with dementia [54]. They point out that these activities evolve and change with a person's identity [54]. Supporting meaningful activities for persons with dementia seems to be challenging for nurses. Nurses consider those activities as essential that reflect the interests of the person with dementia; activities should be personalized and fit into the social or physical environment. However, they face certain barriers preventing the introduction and implementation of meaningful activities: structural (barriers related to maintaining organizational routines), personal (barriers arising from insufficient specific knowledge of activities, roles, and habits before taking up employment in a nursing home), and interprofessional (barriers stemming from a lack of awareness of meaningful activities among professionals). Nurses also identify a low awareness of meaningful activities [63,64].

Times without care and encounters can also have a negative impact. Low levels of physical or cognitive activity may have a long-term influence on the progression of cognitive impairment and mortality in persons with dementia [65,66]. During periods of low social involvement, Cohen-Mansfield et al [23] found an increase in challenging behaviors, such as agitation, in persons with dementia, while Cohen-Mansfield and Golander [67] noted a rise in hallucinations [67]. It can be assumed that behind challenging behaviors are unmet needs—expressed in the form of behaviors [68]. Unmet needs arise from a lack of reciprocity of perspective between people with dementia and their (social) environment [69,70]. In their findings, Cohen-Mansfield et al [34] showed three main unmet needs of persons with dementia exhibiting challenging behaviors: (1) boredom or sensory deprivation, (2) loneliness or a lack of social interaction, and (3) the need for meaningful activities.

To obtain an idea of times without care in persons with dementia, it seems necessary to examine the structures of these periods of time. According to the phenomenological or pseudophenomenological findings of Honer [71], the lifeworld

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understanding of time in persons with dementia is characterized by confusion between the subjective and intersubjective perceptions of temporal structures. Persons without dementia can switch their thoughts between worldtime-related present, past, and future. By contrast, persons with dementia confuse the worldtime-related past with the present, which affects their perception of here-and-now-reality. The comments by Honer [71] indicate that the temporal structures of the lifeworld of persons with dementia differ from those of persons without dementia. In addition, persons with dementia experience time subjectively differently [71].

Dealing with times without care and encounters requires an exploration of their origins, subjective experiences, and the subjective attribution of meaning. This applies particularly to those times that are intersubjectively described as long periods of boredom and as supposedly destructive. These are conditional social categories of time, whose effects are described from a rather objective perspective. Little is known about their genesis [72], temporal perception [73,74], and meaning for persons with dementia [75,76]—and for formal or informal caregivers—as well as their relation to the past and the future [77].

There is a need to investigate these times and to examine how persons with dementia perceive them. It is not known how to interpret times without care and encounters from the perspective of persons with dementia. This knowledge is particularly important, given the different definitions of the term *need for care* in the assessment of care and support conditions in Germany and Switzerland. In the Swiss and German care systems, different instruments are used to identify care needs and record care and support times. These instruments refer to national definitions of the need for care. While the German concept is based on the degree of independence and abilities of the care recipient, the Swiss concept is focused on their support needs [78].

These conceptual logics result in different care services. One can assume that these conceptual logics influence the existence and experience of times without care and encounters [79,80]. Nevertheless, it would be premature to assume that these periods are generally undesirable, empty times that are frequently associated with distressing experiences. The periods could also be considered relaxing off time, allowing for *healing* contemplation in a condensed time—in the sense of time for oneself [42].

Times without care and encounters in persons with dementia are the focus of our explorative and sequentially designed multimethods ethnographic study [81-84]. We examine these periods of time across dementia phases in different institutional as well as domiciliary care arrangements in Switzerland and Germany. We want to clarify how people with dementia perceive and experience these times. It is unclear whether these times represent meaningfully definable periods of time—in the sense of periods of action—for people with dementia. We would like to close this research gap by investigating the way in which people with dementia act (or do not act) during these times without care and encounters.

Aim and Research Questions

The research objective of the study is to ethnographically reconstruct times without care and encounters from the perspective of persons with dementia themselves and from the point of view of formal or informal caregivers. For this purpose, we apply ethnographic methods [85-87].

We are thus exploring the different small social lifeworlds [88,89] of people with dementia.

In doing so, we investigate how people with dementia experience times without care and encounters in their respective lifeworlds. We are interested in investigating how people with dementia act in these times and what strategies they use to deal with these times.

These explorations deal with not only foreign world experiences but also familiar everyday phenomena. We therefore orientate ourselves to the methodological considerations of Honer [71] on lifeworld-analytical ethnography. Hitzler and Eisewicht [86] have developed these considerations further. In addition, focused ethnography according to Knoblauch [85] serves as guidance. Both ethnographic strands are methodologically pluralistic and presuppose reflexivity in the research process [90].

Lifeworld-analytical ethnography refers decidedly [86] to the mundane-phenomenological approaches of lifeworld analysis [91]. Therefore, we relate ourselves, among others, to the reflexive attempt of pseudophenomenology realized by Honer [71] for describing “demential world experiences”. Due to the cognitive limitations of persons with dementia, dementia-related world experience as a research subject is associated with considerable validity problems. Thus, we try to adopt a naïve point of view in the analysis. We attribute a pseudonatural status to the respective situations [92].

Furthermore, we conduct a supplementary survey to validate the interpretative typology developed from the ethnographic material. Specifically, we examine the provisions, regulations, and associated dimensions of the phenomenon of times without care and encounters in persons with dementia. With the survey, we also want to create a complementary information base. We hope to obtain additional information on the frequency, duration, and effects of times without care and encounters. This occurs particularly against the background of different national care systems, institutional and domiciliary arrangements, types of organizations, grade-mix specifications, and staffing principles for nursing homes [48,93,94].

With regard to the so far scarcely researched times without care and encounters, the fundamental question posed by Goffman [95] arises: “What is going on here?” Do persons with dementia address these time periods? If so, *how* do they talk about them? *How* do they experience and interpret these times? *How* do formal or informal caregivers experience and interpret these periods?

We are interested in exploring (across disciplines) how these periods of times without care and encounters are described (1) from the perspective of persons with dementia and (2) from the point of view of their formal or informal caregivers; we are also interested in (3) *whether* and *how* persons with dementia

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"appresent" (in the phenomenological sense) [96,97] these periods of time and how these times affect persons with dementia.

With regard to the individual perspectives, we explore the aspects outlined in Textbox 1.

Textbox 1. Aspects of individual perspectives explored in this study.

From the perspective of persons with dementia

- *Whether* and *how* persons with dementia individually and subjectively perceive and describe times without care and encounters
- *Which* verbal and nonverbal techniques and expressions they use to communicate about these times
- *Which* interpretations, wishes, intentions, and interests they express
- *What* persons with dementia do and *in which way* during times without care and encounters, *how* they use these times, and *whether* or *how* they prioritize their activities

From the point of view of the formal or informal caregivers of persons with dementia

- *Whether* and, if so, *how* formal and informal caregivers perceive and describe times without care and encounters
- *Which* verbal and nonverbal techniques and expressions they use to communicate about these times
- *Which* interpretations, wishes, intentions, and interests they express
- *How* they respond to perceived times without care and encounters and to the actions of persons with dementia

From the perspective of appresentation

- *How* times without care and encounters affect the physical, cognitive, and emotional states as well as the social interactions of persons with dementia
- *How* this effect manifests itself

Methods

Overview

We are guided by a hermeneutic sociology of knowledge that is based on the fundamental assumptions of social constructivism. According to this perspective, social reality is constructed by the everyday actors themselves (ie, in this case, the person with dementia). Our aim is therefore to reconstruct the construction of periods of care and those without care of people with dementia and translate them into scientific "second-order constructions" [98].

The project is scheduled to last 36 months. The work packages proceed partly in parallel, although mostly at different times and always in interdisciplinary dialogue. We interrelate the results of this work in an ongoing, reciprocal process and then gradually integrate them [99,100].

To do justice to the research interest, we organize the project on an interdisciplinary and multiprofessional basis. Of particular interest is the transnational use of the respective competence profiles, which are closely linked to the research questions. Expertise in the fields of nursing science, gerontology, sociology, and ethnography is located at the Eastern Switzerland University of Applied Sciences (Switzerland), the Fulda University of Applied Sciences (Germany), and the University of Applied Sciences Furtwangen (Germany). Expertise in cognitive psychology is located at the University of Geneva (Switzerland).

The cooperation between different sites and professions seems extremely useful and synergetic. It allows us to combine methodological competences for sociological, psychological, and practical nursing issues with expert knowledge concerning interaction-enabled and communicative action. In addition, the transnational research consortium can address national and international realities and relevancies as well as differences and similarities with regard to the questions posed.

Our research teams at the Eastern Switzerland University of Applied Sciences, University of Applied Sciences Fulda, and University of Applied Sciences Furtwangen are focusing on the ethnographic exploration of times without care and encounters on site. Our research team at the University of Geneva is focusing on the cognitive psychological parameters and is involved in the interdisciplinary and transnational fieldwork as well as in the survey. The respective analyses take place across locations and countries.

A combination of ethnographic observation and standardized survey procedures forms an adequate methodological approach to answer the research questions [101]. After the project installation, we explore the structures and dimensions of the lifeworld texture of time to appropriately reconstruct times without care and encounters in persons with dementia (Figure 1).

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Figure 1. Project overview.

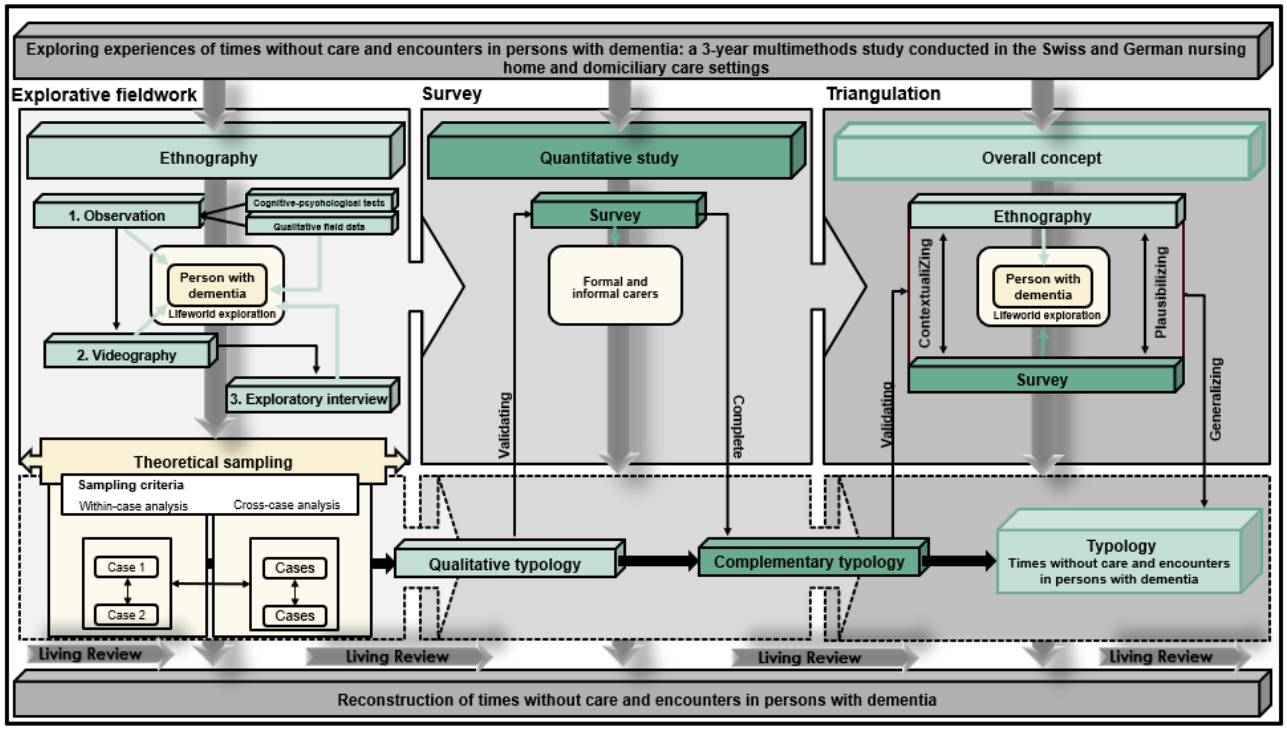

Ethical Considerations

Ethics approval was granted by the responsible ethics committees (Switzerland: Ethics Committee of Eastern Switzerland [BASEC 2021-02150 and EKOS 21/179]; Germany: Ethics Committee of the German Society of Nursing Science: 21-009, BL 1787/1-1, and KO 5965/2-1).

Participation in the survey is voluntary for all participants (persons with dementia as well as informal and formal caregivers). We ensure that all participants receive comprehensive and target group–specific information. The project team is aware that persons with dementia are individuals considered potentially (highly) vulnerable [102]. Inclusion in the sample only occurs if it is possible to obtain a declaration of consent from authorized and legal representatives. However, if it is obvious that a person with dementia refuses to participate in the research project, we respect this—regardless of their legal representatives' possible consent [79]. The design of the entire study and the proceedings ensure that participants face no exceptional risks. Participation takes place on the basis of ongoing consent [103,104]. All persons involved can withdraw from the project at any time. They can interrupt or cancel an observation. The designated research assistants have proven expertise in nursing and nursing science. They also have several years of research experience with persons affected by dementia. Therefore, they are able to pay sensitive attention to verbal and nonverbal signs of refusal or vegetative signs that may necessitate an immediate interruption or cancellation of the observation, interview, or video recording.

After the video recording, we review the footage with the persons with dementia and with their authorized representatives to confirm or revoke the previously granted release. However, our experience in previous projects shows that persons with dementia and their relatives use this option only occasionally—for various reasons.

In our view, it would be ethically unacceptable to pressure people to participate (and thus not respect their autonomy) or to withhold recordings from them.

It is crucial to ensure that the persons in question are aware of their option to codecide, to participate, and to access their data at any time—even later if they did not do so at an earlier stage. Being aware of the problems associated with videography involving persons considered (highly) vulnerable, we conduct prospective and retrospective ethical case discussions on the targeted video recordings. This occurs with the aim of ascertaining the presumed and situational will of the person with dementia and of complying with this will.

Against the background of (potential) vulnerability, we pay equal attention to providing comprehensive information to relatives about the voluntary nature of participation, the data collection methods, data protection, data analysis, data use, and data backup or archiving, as well as about the possibility of withdrawing consent and release.

The Research Team

The persons responsible for the project and the research assistants have many years of experience in qualitative or interpretative and quantitative research. They are also experienced in the care and support of persons with dementia. To achieve the necessary intersubjectivity, we discuss and analyze all data in the interdisciplinary and cross-location team. For this purpose, we conduct ongoing interpretation meetings and workshops. We document all interpretation sessions and workshops, transcribe them into extracts, and compile them into a protocol.

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Two nursing scientists advise and support the research team: Prof Dr Gabriele Meyer (Institute of Health and Nursing Science, Medical Faculty, Martin Luther University Halle-Wittenberg, Germany) and Prof Dr Hanna Mayer (Karl Landsteiner University of Health Sciences, Krems, Austria). Both have proven expertise in the field of dementia care research.

Exploration

The ethnographic exploration and identification of times without care and encounters involves a close observation of these periods. We also observe periods that immediately precede and follow those without care and encounters. To capture the behaviors and strategies of persons with dementia in these periods of time in a methodologically sound way, it is necessary to (1) observe them both in a *participatory* and *nonparticipatory* manner, (2) video record them, and (3) talk to persons with dementia or their caregivers. This involves situational conversations and follow-up qualitative interviews.

To validate the developed typology and to obtain complementary information on times without care and encounters, we subsequently conduct a standardized survey using a self-developed instrument (refer to the Detailed Methodological Outline subsection). Formal and informal caregivers take part in this survey, and we analyze their written statements (refer to the Detailed Methodological Outline subsection). Afterward, we synthesize the knowledge generated, and the associated combination of qualitative and quantitative research results in an overall model of times without care and encounters in persons with dementia (refer to the Detailed Methodological Outline subsection).

Research Field and Sample

We intend to collect data in the following settings:

- German and Swiss institutions in which persons *with* dementia live *separately* from those *without* dementia (segregation is explicitly envisaged as a concept [105])
- German and Swiss facilities in which persons *with* dementia and those *without* dementia live *together* (the concepts of integration and inclusion are explicitly envisaged)
- German and Swiss private households where persons with dementia reside [105]

In this study, we involve persons classified as dementia levels 3 to 7 according to the Global Deterioration Scale developed by Reisberg et al [106]. This means that we include persons with mild to severe loss of cognitive abilities.

As part of the observation procedures, we perform an initial screening by means of the Global Deterioration Scale [107]. We sample according to theoretical criteria and the principle of maximum and minimum contrast. Thus, we select people of different sexes and ages as well as with contrasting behaviors and care arrangements [108,109]. It is inherent to the strategy of theoretical sampling and maximum and minimum contrasting that the number of participants is determined during the research process. However, due to time constraints and the scope of the planned study, we plan 10 case observations per type of care. This corresponds to 30 case studies. The population of the planned survey (work package 3) includes formal and informal caregivers of persons with dementia in inpatient long-term care and domiciliary care settings in German-speaking Switzerland and Germany. We will analyze the data obtained through the survey using confirmatory factor analysis (CFA). While there are challenges in determining the statistical power and sample size for such an analysis [110], a widely accepted ratio is 10 cases per indicator variable [111]. We expect to generate approximately 50 indicator variables during the typology development, which would require a sample of 500 individuals. Accounting for a dropout rate of 10% [112], the recruitment of 50 additional individuals would result in a total required sample of 550 individuals. Given the difficulty of recruiting informal caregivers [113], we aim to recruit more formal than informal caregivers. We therefore plan to recruit an opportunity sample comprising approximately 400 formal (Germany: n=250, 62.5%; Switzerland: n=150, 37.5%) and 150 informal (Germany: n=100, 66.7%; Switzerland: n=50, 33.3%) caregivers.

Detailed Methodological Outline

Work Package 1: "Preparation"

The first work package, "Preparation" (2 months), focuses on preparing, organizing, and installing project structures. It also allows a comparison of the working methods of the interdisciplinary, multiprofessional, and transnational research team members. This work package also includes targeted sampling for the domiciliary care setting.

Work Package 2: "Explorative Fieldwork"

Overview

In the second work package (24 months in total), we collect data in the research field. We process and analyze data in parallel. The eight steps that make up this work package are detailed in the following paragraphs: first, participatory observations (4 months) in the respective institutions and households serve to identify times without care and encounters and determine the institutional sampling. In terms of research practice, we familiarize ourselves with the field and with the persons living and working in these settings. In return, persons in the field can become familiar with our research assistants. To this end, research assistants take on care and support tasks, depending on their own expertise. In some cases, they take part in the everyday lives of persons with dementia. In doing so, we develop preliminary hypotheses about the interpretation and effects of times without care and encounters, as well as about strategies for dealing with them.

Second, by means of nonparticipatory observations (structured and unstructured; 4 months) [87] in the institutional setting and by further participatory observations in the domiciliary care setting, we continue to identify times without care. We explore strategies for dealing with these periods on site or in situ, with the aim of formulating statements that are appropriate to the subject matter; for example, we document the time, duration, and frequency of these occurrences, as well as physical and verbal patterns of appresentation [96,97] (in the phenomenological sense), alongside the behavior and actions of persons with dementia during these periods. In addition, we capture upstream and downstream social times and

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worldtime-related events. These should reveal both communicative regularities and remarkable irregularities in the interactions between formal and informal caregivers or among fellow residents. In doing so, we further test and specify the assumptions we have made so far.

Third, we plan to perform structured nonparticipatory observations using Dementia Care Mapping (DCM) [114,115]. In this way, we intend to uncover worldtime-related processes and social-worldly predefined limits of the time budget [71] and the forms or types of interactions. We also identify the impact of times without care and encounters. On the basis of DCM analysis data, we narrow down the subsequent unstructured nonparticipatory observations to the identified periods of time. By means of focused and multiday observations, we further explore the periods of interest in greater depth. We also talk to persons with dementia *during* and *after* an observation. In situational conversations [71], we find out *if*,*how*, and *to what degree* of awareness persons with dementia frame and describe the situation in the sense of the fundamental question posed by Goffman [95]. Of note, DCM only takes place in an institutional context, not in the domiciliary care setting.

Fourth, the time periods of interest and the associated communication or interaction processes are both highly complex and ephemeral. We assume that the researchers influence the experience of time merely by *being present*, whereas the exploring person as such represents an intervention [116]. On the basis of this assumption, it is necessary to consider how the researcher influences the field. It is essential to clarify whether questions can be derived from the observations: what if the exploring person had not been there? How do persons with dementia coconstruct the situation? How would they have dealt with the situation? How do persons with dementia comment on the situation? What is the result of the situation? Is it possible to anticipate how persons with dementia would have spent the time if the researcher had not been present? Inevitably, the person exploring the field becomes the subject (or object?) of the analysis. Therefore, we video record times without care and encounters (4 months). Using videography [117], we record the range of expressive variants appearing on micro- and nanolevels (language, facial expressions, gestures, body orientation, voice pitch, and melody, as well as their interplay in interactions). Videography takes place in a targeted manner—after careful consideration within a framework that seems acceptable to the participants involved. Despite its clear benefits, videography is an invasion of privacy—it interferes with the leisure time of persons with dementia and with the private spheres of formal or informal caregivers. For this reason, we use the camera sparingly, in a focused way, and only to the extent strictly necessary to obtain answers to our research questions. We conduct at least 2 video recordings for each person recruited (60 in total). The findings from our previous observations guide and determine the selection of interactions to be video recorded [118,119]. In the context of domiciliary care, we involve informal caregivers in a participatory way as coresearchers in the videography process—with the aim of reducing possible reactance to the camera [120].

Fifth, to reconstruct the respective subjective views and explicable background knowledge of the formal or informal caregivers, we conduct exploratory interviews [71] over a period of 4 months. We want to gain insights into the caregivers' awareness of times without care and encounters. How do they understand these periods of time? Do they consciously use strategies to promote or reduce these periods? If so, which strategies do they use? In addition, we seek to find out the extent to which organizational framework conditions are beneficial or obstructive [121]. Which conditions are favorable or problematic according to the caregivers? Which options do they consider as desirable for solving difficulties in dealing with times without care and encounters? We orient ourselves toward the ideal of an interview that is minimally standardized but structured by means of a guideline. This is intended to ensure that the respondents are as open as possible in their responses, while at the same time maintaining the thematic focus of the interview [122,123]. We plan interviews, based on a semistructured interview guide [124], with at least 2 formal or informal caregivers per recruited person (60 interviews in total).

Sixth, in a further assessment step (parallel to steps 2 and 3), we use cognitive-psychological methods to determine the effect of times without care and encounters on the cognitive and emotional states of persons with dementia. Whenever possible, we use self-assessment tools for persons in the early stages of dementia. If self-assessment is impossible, data collection is based on proxies or an external assessment instrument. The repeated use of compact assessment tools (at least 4 assessments at 3-month intervals) allows us to document and examine changes. We focus on assessing the general cognitive state, emotional state, independence in activities of daily living, and perceived loneliness. We will use the Cognitive Telephone Screening Instrument [125] to assess the general cognitive state and the Geriatric Depression Scale [126] to evaluate emotional state in a global perspective; in addition, we will use the Short Depression-Happiness Scale [127] and the Self-Assessment Manikin scale [128] to capture momentary perspectives on emotional state. Furthermore, we will assess functional independence in everyday life (using the Index of Independence in Activities of Daily Living [129]) and perceived loneliness (using the De Jong Gierveld Short Scales for Emotional and Social Loneliness [130]). We also aim to evaluate mediators such as cognitive reserve (using the Cognitive Reserve Index questionnaire [131]) and desires or goals (by means of the Sense of Coherence questionnaire [132]). We will consider the social network of persons with dementia and their contact with this network [133]. Moreover, we will measure stress using the abbreviated Perceived Stress Scale [134].

Seventh, in the second phase of data collection (4 months), we conduct observations and video recordings. We also apply the knowledge gained from previous observations and interviews to currently observed situations. In this way, we clarify questions that remain unanswered. This relates to, for example, our more precise understanding of persons with dementia and their formal or informal caregivers. During this phase, we also perform observations at different times of the day. Whether it will be necessary at this point to focus specifically on certain times without care and encounters will depend on the findings obtained

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up to this point. We process and analyze the data collected in this stage and relate it to the analyses carried out so far.

Eighth, after the phase of direct fieldwork (4 months), we interrelate, compare, and contrast the findings and assumptions from the analyses of observations and interviews as well as video data and neuropsychological assessment data collected at different points of time.

Qualitative Data Analysis

We ensure the trustworthiness and credibility of our research by using a comprehensive process of documentation, an interpretation practice based on intersubjectivity, a uniform rule-based approach, a (trusting) proximity to the object of the research, a plurality of methods in data generation and analysis (ie, triangulation), and the continual reflection of the involved researchers [135].

To combine sampling, data collection, interpretation, and theory formation, we use grounded theory [109] as a corresponding [89] research approach in the sense of a hermeneutic grounded theory [136]. We document all observations in protocols and transcribe the audio data. After each step of data collection, we perform a successive overall review of the data which are initially open-coded, then axially coded, and finally selectively coded [109,137]. In addition, we deliberately select certain passages and subject them to additional hermeneutic sequence analysis [138-143]. In doing so, we relate the different observation situations and the interview statements to each other and compare them. Supplementary video data provide the necessary access to the complexity of the events of interest. They allow an in-depth, repeated evaluation by means of video interaction analysis [117,144]. This is of central importance for clarifying the questions raised in this context.

Our experience in analyzing video-recorded care interaction situations revealed that this method indeed allows us to capture important subtleties of communication and interaction that would otherwise have remained hidden. During the joint cross-site and cross-national interpretations [145], it is necessary to implicitly and explicitly triangulate different types of qualitative data with regard to their meaningful referential context [146]. We clarify *whether* and *how* they correspond, complement, or contradict each other. Furthermore, we retrace the referential contexts of events and actions thematized in the interviews and conversations. We also backtrack to events and actions that emerged in the participatory or nonparticipatory observations and in the video documentation.

Work Package 3: "Survey of Times Without Care and Encounters"

Overview

In this work package (14 months in total), we collect, edit, and analyze quantitative data. The design we chose is a standardized mixed modes survey (eg, web-based survey tool and paper-pencil version) directed at formal or informal caregivers. The questionnaire is based on the results of the ethnographic observations and the interviews. To test the questionnaire, we use a qualitative pretest procedure with expert validation [147]. The analysis involves multivariate statistical methods. The methodological approach, which involves five steps, is detailed in the following paragraphs: first, we develop the item batteries and case vignettes for the survey (over a 6-month period)—based on the elaborated typology and the associated phenomenal dimensions. This takes place in parallel and in coordination with work package 2. We test the instrument with 15 participants in a qualitative pretest procedure (interviews; 3 months) and adapt it accordingly. Participants must be aged at least 18 years to be included in the interview. We aim to ensure diversity among the participants, particularly regarding their educational backgrounds, professional experiences, and other relevant demographic factors (eg, sex and age). This approach intends to capture a wide range of perspectives and ensure a more comprehensive understanding of the topic. The project team is responsible for recruiting participants, with recruitment efforts coordinated to ensure diversity. We ask the participants to think aloud while filling in the survey (ie, the thinking-aloud method). The interviewer (ie, project member) will document these thoughts in protocols. Upon survey completion, participants are asked standardized questions (eg, whether there are terms they do not understand and whether the length of the survey is appropriate). The interviewer documents the answers in written form, and a project member evaluates the protocols. We discuss potential adjustments to the survey within the team before implementation.

Second, sample recruitment (3 months) occurs as part of an ad hoc procedure. To this end, we develop and implement a gatekeeper [148] system for recruiting in the institutional sector (nursing homes) and in the outpatient sectors (domiciliary care and self-help organizations, eg, Alzheimer Switzerland and the German Alzheimer Society). The target sample consists of formal and informal caregivers of people with dementia in Switzerland and Germany. To meet the inclusion criteria, caregivers must be aged at least 18 years. Formal caregivers should work in the institutional long-term care setting. These are the only criteria for inclusion.

Third, the survey (5 months) is designed as a mixed modes survey (web-based, written-postal, and telephone). Qualtrics (Qualtrics International Inc) will be used as the web-based survey platform [149].

Quantitative Data Analysis

The analysis (2 months) is based on descriptive and inferential statistical methods. First, we will analyze the survey data descriptively, thereby providing information on the sample characteristics (eg, the mean age of the study sample). Using CFA, we will test whether the model (hypothesized typology) fits our collected data. CFA belongs to the broader family of structural equation modeling and is typically used to validate the relationships between observed variables (indicators, ie, survey items) and underlying latent variables (factors, ie, typology) that are not directly measured [150]. Our null hypothesis is that the model (typology) will fit the data well, with the specified factor structure (or typology) accurately reflecting the real-world phenomena captured by our data. The alternative hypothesis posits that the proposed model does not fit the data, suggesting that the typology does not adequately represent the real-world phenomena and fails to capture the

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underlying constructs or relationships, as reflected in our data. CFA tests these hypotheses using model fit indices, such as the root mean square error of approximation or comparative fit index [150]. These indices help evaluate whether the null hypothesis (good fit) is reasonable or whether the alternative hypothesis (poor fit) is supported. A well-fitting model will have values within the acceptable ranges for these indices.

Work Package 4: "Overall Concept and Dissemination"

A triangulation focusing on convergence and complementarity [151] takes place in the fourth work package (6 months in total). For this purpose, we integrate the results of the ethnographic research and the survey. We analyze the results in cross-site, web-based group interpretations to determine whether and how they correspond, complement, or contradict each other. This occurs with the aim of contextualizing, plausibilizing, and, if necessary, generalizing the elaborated typology. The triangulation strategy paves the way to the concentrated final phase aimed at developing the overall theoretical concept for times without care and encounters in persons with dementia.

Work Package 5: "Living Literature Review"

A living literature review accompanies the project. The detailed methods are described elsewhere [152]. The specific aim of this review is to provide a continually updated overview of times without care and encounters from the perspective of persons with dementia and formal or informal caregivers. This can have a guiding function for data synthesis and interpretation. During the entire project, we conduct comprehensive systematic literature searches in MEDLINE, PubMed, CINAHL, PsycInfo, Ovid, and Web of Science Core Collection (citation-based searches and web searches). We include observational studies performed in the institutional or domiciliary care setting and published in English, French, or German, without restrictions on the year of publication. Studies have to address times without care and encounters from the perspective of persons with dementia and formal or informal caregivers. One reviewer screens titles, abstracts, and full texts and extracts data. We will present the key characteristics and results of the included studies in tabular form. Searches take place during the entire study (every 6 months for 2 years; 2023-2025) [152].

Results

The study started in March 2022 and ends in May 2025. It is underway as part of a lead agency process and has been funded by the Swiss National Science Foundation (200919) and the German Research Foundation (458561353).

The exploratory investigations associated with work package 2, the within-case analyses, and the location-related and cross-country cross-case analyses concluded in September 2024. The cross-national survey results will be available in December 2024. Work packages 4 ("Overall concept and dissemination") and 5 ("Living literature review") are scheduled for completion in April 2025.

Discussion

Summary

Our approach enables us to obtain information about the nature, frequency, and prevalence of the phenomenon of times without care and encounters. We will be able to make statements about how people with dementia and their caregivers experience and interpret these times for themselves. We will demonstrate how people with dementia act during these times and what purpose they pursue. The developed typology will provide the foundation for assessing these periods using a survey instrument, which can be validated in a follow-up project, with two intentions: (1) to assess times without care and encounters in a representative and reliable way with this instrument and (2) to develop a diagnostic instrument for nursing practice.

Furthermore, with this project, we would like to make a fundamental methodological contribution to advancing research *on* and *with* persons with dementia.

In the context of dementia care research, procedures for field research, intervention planning and implementation, and data collection require an extended framework of both care ethics and research ethics. However, at the same time, there are almost insurmountable problems of validity and generalization. The proposed research strategy envisages not only methodological and methodical triangulation but also data triangulation and researcher triangulation. In this way, we would like to contribute to the existing cross-disciplinary discourse on these problems. However, our research is limited by the fact that we are studying 2 relatively similar care cultures and cannot resolve validity issues. Nevertheless, this research represents an ongoing effort to understand and reconstruct the lifeworld of people with dementia.

Conclusions

With our research, we intend to pave the way for a qualitative assessment of lived times without care and encounters in persons with dementia and for scrutinizing organizational and professional practices. In doing so, we also ask about the need for change. However, expecting a priori a need for change with regard to all times without care and encounters seems to be inappropriate and paternalistic—despite initial scientific findings pointing in this direction. Therefore, it is our intention to present examples that have been described and proven as good practice.

In this research project, we shed light on the concepts of autonomy, well-being, independence, self-determination, and meaningful activities of persons with dementia in relation to the need for security and continuous attachment to formal and informal caregivers in times without care and encounters. The tensions involved in everyday dementia care will continue to intensify as social and human care resources become increasingly scarce. Against the background of the current political and social understanding of care, it is unlikely that the situation regarding times without care and encounters in persons with dementia, although considered worthy of change, will be addressed in a humane way. In a survey of nursing and care staff in Swiss care institutions, caregivers reported times when they had to keep residents waiting or were unable to offer them

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emotional support or engaging care [153]. Therefore, it seems essential to consider alternative interventions and possibly technical alternatives.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study. The results data will be deposited in publicly available repositories as requested by the funding agency (Swiss National Science Foundation).

Authors' Contributions

All authors made substantial contributions to the conception or design of this study. TB, JH, LA, UL, MD, and HMB drafted the manuscript. All authors revised it critically for important intellectual content and approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work have been appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Humanities and Social Sciences (Division I) - Swiss National Science Foundation (SNSF) (Switzerland).
[PDF File (Adobe PDF File), 401 KB - resprot_v13i1e58190_app1.pdf]

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Abbreviations

CFA: confirmatory factor analysis
DCM: Dementia Care Mapping

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Protocol

Understanding the Occurrence and Fate of Atmospheric Microplastics and Their Potential Risks to Human Health: Protocol for a Cross-Sectional Analysis

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Abstract

Background: Plastic pollution has reached an alarming magnitude, defining the contemporary era as the "Plastic Age." Uncontrolled plastic production and inadequate recycling processes have led to widespread contamination of the environment with micro and nanoplastics.

Objective: The study aims to assess the environmental and human health consequences of exposure to microplastic particles (MPs) and their additives among plastic recycling workers in Dhaka. Specifically, it focuses on mapping the management pathways of plastic waste from collection to disposal, analyzing the types of MPs in the environment, and assessing the potential health impacts on plastic recycling workers.

Methods: A cross-sectional exploratory study design was used, consisting of exposed and nonexposed groups in plastic recycling sites in Dhaka, Bangladesh. The study will establish possible associations between different health consequences and microplastic particle exposure with a systematic approach involving plastic recycling hot spot detection, management pathway mapping, and detecting the presence of environmental MP. MPs and heavy metals will be detected from environmental samples using fluorescence microscopy, Fourier-transform infrared spectroscopy, and inductively coupled plasma mass spectrometry. Human exposure will be assessed by detecting the metabolites of bisphenol and phthalates from urine samples using liquid chromatography–tandem mass spectrometry and thoroughly evaluating endocrine, reproductive, respiratory, and renal functions. The sample size was derived from the mean concentrations of urinary bisphenol and phthalates metabolites, requiring the participation of 168 respondents. A 1:1 exposure to nonexposed stratification would be sufficient to meet our study objectives, considering the conventional level of power and confidence interval. This study protocol (PR#22111) has received approval from the Research Review Committee and Ethical Review Committee of the icddr,b.

Results: The project was funded in August 2022. We started collecting environmental samples in January 2023 and completed participant enrollment, exposure survey, and biological sample collection by December 2023. We enrolled 84 adult plastic recycling workers with at least 5 years of exposure history and 84 nonexposed participants who were not involved with plastic

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recycling activities. Data analysis is currently underway, and the first results are expected to be submitted for publication in November 2024.

Conclusions: The findings would provide valuable insights into the adverse impacts of microplastic pollution on both the environment and human health, aiding in better understanding the extent of the issue.

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KEYWORDS

plastic exposure; microplastic; bisphenol; phthalate; heavy metals; health consequences; potential risk; cross-sectional analysis; pollution; nanoplastics; additives; plastic additives; health consequence; exposure; human exposure; plastic recycling; recycling activities

Introduction

Background

Plastic has become essential to our "throwaway" lifestyle. Due to its ubiquitous presence in our environment, the current era is better known as the "Plastic Age" [1]. In 2019, around 368 million metric tons of plastics were produced worldwide, which is expected to reach 33 billion tons by 2050 [2]. Plastic has invaded our natural resources and ecosystems to become a global environmental and public health threat. It is reported that 79% of global plastic products have yet to be appropriately recycled and are eventually released into landfills or natural environments [3]. About 0.8 million tons of plastic waste are generated annually in Bangladesh, among which 36% are recycled, 39% are landfilled, and the rest are considered leakage or unattended [4]. A study reported that 5 to 13 million metric tons of plastic waste was released into the ocean by 192 coastal countries in 2010 [5]. If urgent action isn't taken, the societal cost of plastic production could hit US $7.1 trillion by 2040, surpassing 2018's global health spending and the combined 2019 gross domestic product of Germany, Canada, and Australia [6].

Plastic degrades into powdery fragments and microscopic-sized plastics (less than 5 mm) called microplastics [7]. The pollution of the environment with degraded plastics and microplastics is an emerging concern attracting global attention [8]. Exposure to microplastic particles (MP) results in adverse outcomes, which can be classified into physical effects (such as those related to particle size, shape, and concentration) and chemical effects (involving harmful chemicals associated with MPs) [9]. Cox et al reported the presence of an average of 0.44 MPs/g of sugar, 0.11 MPs/g of salt, and 0.09 MPs/g of bottled water in the American diet [10]. Typically, humans consume 80 g of MPs/per day through fruits and vegetables that accumulate MPs through uptake from polluted soil [11]. Among numerous toxic chemicals, bisphenol and phthalates are most commonly used as plasticizers [12], where MPs work as vectors for these chemicals. Plastic and its additives harm human health and the environment [13,14]. Furthermore, many heavy metals like zinc, nickel, mercury, cadmium, and lead are present in plastic compounds as additives and pigments [15]. Long-term exposure to these metals has adverse health consequences [16-18]. In Bangladesh, MP was detected in different fish and shrimp species from the mangrove estuary and the Northern Bay of Bengal [19,20]. An abundant number of MPs were also detected in the beach sediments of Cox's Bazar, Bangladesh [21]. To our knowledge, limited research exists worldwide on the impacts of atmospheric microplastics, and the study of their human health impacts in Bangladesh is also scarce.

Proper plastic recycling plays a vital role in mitigating the environmental impact of plastic waste and promotes a sustainable future for generations to come. However, the mechanical friction and abrasion of the plastic recycling industries produce tons of MPs [22]. Plastic waste recycling and its harmful effects on human and environmental health should be adequately addressed in Bangladesh. Epidemiological studies indicate that plastic particles and their chemical additives (eg, bisphenol, phthalates, flame retardants, etc) may have adverse impacts on human health [23]. However, the underlying mechanism still needs to be clearly understood. Understanding the extent of environmental exposure to plastic additives and consequential health outcomes would provide valuable knowledge and help to develop effective control measures.

Objectives

The fundamental objective of this study is to determine the extent of environmental and human health consequences resulting from exposure to plastics (microplastics) and their associated additives. The specific objectives are (1) to identify the factors that determine the location of hot spots with higher exposures and concentrations of MPs in Dhaka city; (2) to map the management pathways of plastic waste in Dhaka city, specifically from collection to disposal; (3) to characterize the nature of plastics that entry into the environmental system of Dhaka city by identifying the types of MPs (composition, size, and shape), their sources, entry points, and contamination levels in different environmental samples; and (4) to evaluate the possible health impacts of MP exposure among workers in the plastic recycling industry.

Methods

Study Design and Participant Recruitment

We will use a cross-sectional exploratory study consisting of an exposed and a nonexposed comparison group. This study will be conducted at plastic recycling sites in Dhaka city. The research team will identify major plastic recycling sites. Participants will be recruited according to the following inclusion criteria: (1) workers involved in plastic recycling processes for at least 5 years and (2) aged 18 years or older at the time of data collection. We will exclude irregular part-time

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workers (eg, those who occasionally work in plastic recycling factories as day labor but primarily rely on other occupations for livelihood) and children under 18 years old. We will also exclude the participants who are on antibiotic treatment as it may mask symptoms of infection and alter the immune response [24,25]. Data collectors will clarify the study objectives, procedures, and intended outcomes to the participants and obtain written consent.

In addition, we will select a nonexposed control site within Dhaka city, where no plastic processing factory exists. Since plastic has become embedded in our daily lives, having a population free from plastic pollution's effects seems unreasonable. All nonexposed participants will be other occupational workers, including daily laborers, masons, carpenters, etc, who have had no exposure to the plastic industry.

Sample Size

We calculated the sample size based on the primary outcomes, including bisphenol and phthalate metabolites in biological samples. Mean concentrations of urinary bisphenol and phthalate metabolites from studies with similar outcomes were used [26,27]. Among the phthalate metabolites, urinary mono isononyl phthalate (MiNP) had a mean of 10.12 (SD 4.91) µg/L in plastic recyclers and 12.22 (SD 4.69) µg/L in the general population. The estimated sample size was 168 (84 per group) using the 2-sample mean test, considering 80% power and 95% CI.

Data Collection Methods

The detailed study activities by study objectives are discussed below.

Objective 1: Hot Spot Identification

Hot spot identification is the initial and crucial step in plastic waste management. The field team has identified the plastic recycling facilities across Dhaka and recorded the GPS coordinates. This data was compiled and analyzed using ArcGIS Pro mapping software (version 3.3; Environmental Systems Research Institute). The research team also sought permission from the plastic recycling factory owners to conduct the research within their facilities.

Objective 2: Mapping the Management Pathway

Plastics are typically distributed into three categories: (1) plastics in active use, (2) postconsumer managed plastic waste, and (3) mismanaged plastic waste [28]. Usually, plastic waste that is managed undergoes disposal methods such as recycling, incineration, or landfilling. However, improperly managed plastic waste is either discarded into the environment or inadequately disposed of and often ends up in rivers and oceans, contributing adversely to the ecosystem [29]. To identify the current challenges within Dhaka city's plastic waste management system, the research team will interview key informants involved in collection, refurbishment, reuse, crude recycling, and disposal. The team will collect information on who collects plastics, the primary source of collection (such as homes, institutions, dump sites, and transfer stations), the types of plastics collected, transportation methods to the recycling center, which part of plastics are reused and recycled, and the ultimate disposal site and methods of disposal (burying, incineration, or chemical melting). Purposive sampling techniques will be used, and data will be collected using 2 tools: in-depth interviews and key informant interviews. Sampling will continue until information redundancy or saturation is attained [30].

Objective 3: Quantifying the Extent of Environmental Pollution

The research team will collect different environmental samples, including floor dust and topsoil (0- to 5-cm depth) from the plastic recycling and dismantling sites, sediments from the water vicinity (lake, river, or pond) where such facilities are operated, and air samples (Table 1). The detailed sampling procedures are described below.

Table 1. Human participants and environmental sampling plan.

Environmental samples	Proposed number
Exposed group (proposed: n=84)	
Air	186
Nonexposed group (proposed: n=84)	
Soil	20
Dust	20
Sediment	10

Air Sampling

The field research team conducted air sampling at 2 plastic recycling industries or shops and 1 outdoor location for MPs and heavy metals (HMs) detection. Air sampling was performed using a filter-based low-volume $PM_{2.5}$ (particulate matter with a diameter less than 2.5 µm) sampler for heavy metal detection in nylon 6.6 filter paper, and a total suspended particulate (TSP) sampler was used for microplastic detection in the quartz fiber filter. The team set up $PM_{2.5}$ and TSP samplers in each selected industry or shop and outdoor location with a duration of 6 hours and a frequency of once every 6 days to assess the work-related exposure of factory workers. We collected air samples in both dry (January to March) and wet seasons (June to August) to explore seasonal variation. After sampling, quartz fiber filters were kept in glass filter holders and nylon filters in Ziplock bags. All the samples were placed in a cool box and kept at 4 °C till transported to the laboratory. The samples were preserved at a negative 20 °C temperature at the laboratory for future analysis.

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Soil Sampling

We will develop a 10×10 square meter grid map of selected plastics recycling factories to collect soil samples. The team will collect 20 soil samples from the selected areas of the grid map. We will identify the closest open-air bare soil surface using a whisk broom (nonplastic) and clean about 1 m^2 of area. Using the stainless-steel hand trowel, the clean surface will be divided into 6 equal quadrangles. A total of 6 subsamples will be collected from these quadrangles at depths ranging from 0-5 cm depth using a stainless-steel auger and placed in a metal tray. After thoroughly mixing the subsamples and removing stones and other nonsoil materials, approximately 100 g of soil sample will be enclosed in aluminum foil, put in a Ziploc bag, and labeled appropriately. Samples will be kept in a cooler box until they are carried to the laboratory, where they will be preserved at a negative 20 °C for later analysis.

Dust Sampling

The field team will collect indoor dust samples from the plastic recycling shop or industry where we have recruited our study participants. Our field research team will approach the shop or industry at the end of working hours but before cleaning to collect dust samples. We will sweep the floor under desks, shelves, and other areas, including furniture, machinery, and walls, collecting dust using a dustpan with a precleaned nonplastic brush. A 100-g sample will be obtained from the dust that remains after the sample has been mixed using a metallic hand trowel. These samples will be enclosed in aluminum foil, put in a Ziploc bag, and labeled appropriately. We will keep the samples in a cooler box until they are carried to the laboratory and preserve them at negative 20 °C for later analysis.

Sediment Sampling

The team will collect sediment samples from the nearest water body in the selected plastic recycling industries. Following the same 10×10-meter grid map, the field team will identify 10 sampling locations. Surface sediments will be collected at 0- to 20-cm depth using a metallic handheld sediment sampler. Samples will be collected in a glass jar labeled appropriately, put in a Ziplock bag, and transported to the laboratory for later analysis.

Environmental Sample Analysis

For microplastic detection from environmental samples, an adequate amount of samples will be combined with about 20 mL of 35% H_2O_2 and heated at 60 °C for an hour for organic matter removal. For density separation, 20 mL NaCl solution will be added, ultrasonicated for 20 minutes, and left overnight for organic matter removal. The top solution will be filtered through quartz and examined under an Oxion Inverso microscope (40× to 100×; Euromex Microscopen BV). The filter, post examination, will be stained using Nile red solution (1-5 mg/mL) and observed under green excitation fluorescence (540-580 nm). Microplastic sizing will be conducted using the ImageJ software (LOCI, University of Wisconsin).

Environmental samples will be analyzed for heavy metal detection using inductively coupled plasma mass spectrometry (ICP-MS) following the acid digestion method. Samples will be dried at 105 °C until reaching a stable weight, followed by disaggregation using a mortar and pestle and then sieving. Following the US Environmental Protection Agency (EPA) Method 3051, fine fraction samples weighing 0.3 grams will be subjected to acid digestion using a microwave oven digester. The resulting digested samples will be analyzed using an ICP-MS (NexION 2000, PerkinElmer).

Objective 4: Health Risk Characterization

Plastic particles enter the human body through inhalation, ingestion, and dermal contact [31]. In the human body, they cause oxidative stress [32,33], cytotoxicity [34,35], and even translocation to different tissues [36]. There is limited evidence on the direct human health effects of MP exposure, but mathematical modeling, animal studies, and in vitro cell cultures revealed potential health risks like altered metabolism, immune disruption, neurotoxicity, and reproductive toxicity [37]. Previous biomonitoring approaches have demonstrated the presence of bisphenol, phthalates, and other plastic additives and their metabolites in the human population. This study focuses on 2 common types of plastic additives: phthalates and bisphenol metabolites and various heavy metals. Based on the literature review, the human health systems most affected are identified and listed in Table 2. To assess the impact on human health, we will collect biological samples, conduct anthropometric measurements, measure blood pressure, and assess the lung function of study participants.

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Table 2. Major systems affected and the potential health impact assessment plan following exposure to microplastics and their additives.

Health systems and health-related outcome	Disease indicators	Biological sample	Procedure
Female reproduction			
Hormonal imbalance	• ↑ Progesterone, • ↑ LH[a]	Fasting blood	ELISA[b]
Undesirable pregnancy outcomes	• ↑ Risk of recurrent miscarriage, • ↑ Spontaneous preterm birth, • ↑ Preterm premature rupture of membrane	__[c]	Self-reported questionnaire
Male reproduction			
Hormonal imbalance	• ↓ Serum total testosterone • ↑ Prolactin	Fasting blood	ELISA
Sexual dysfunction and infertility	• ↓ sexual function, • ↓ sexual desire, • ↓ erectile ability, • ↑ premature ejaculation	—	Self-reported questionnaire
Endocrine			
Metabolic disorder (any 3 from the 5 features are suggestive of metabolic disorder)	• Height, weight, waist, and hip circumference	—	Anthropometry
Metabolic disorder (any 3 from the 5 features are suggestive of metabolic disorder)	• Triglycerides	Fasting blood	Semiautomatic biochemistry analyzer
Metabolic disorder (any 3 from the 5 features are suggestive of metabolic disorder)	• HDL[d] cholesterol	Fasting blood	Semiautomatic biochemistry analyzer
Metabolic disorder (any 3 from the 5 features are suggestive of metabolic disorder)	• Blood pressure	—	Automated blood pressure monitor
Metabolic disorder (any 3 from the 5 features are suggestive of metabolic disorder)	• Fasting blood glucose	Fasting blood	Hexokinase method
Thyroid function	• ↓T4[e], ↓TSH[f]	Fasting blood	ELISA
Respiratory			
Asthma	• ↓ Lung function	—	Spirometry
Renal			
Impaired renal function	• ↑ Albuminuria	Fasting urine	Dipstick test for albumin
Impaired renal function	• Urinary creatinine	Fasting urine	Automated hematology analyzer
Impaired renal function	• Urinary micro-albumin	Fasting urine	Automated hematology analyzer
Impaired renal function	• ↓ eGFR[g]	Blood	CKD-EPI[h] equation
Oxidative stress			
DNA damage	• 8-OHdG[i]	Fasting urine	ELISA

[a]LH: luteinizing hormone.

[b]ELISA: enzyme-linked immunosorbent assay.

[c]Not available.

[d]HDL: high-density lipoprotein.

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[e]T4: thyroxine.

[f]TSH: thyroid stimulating hormone.

[g]eGFR: Estimated Glomerular filtration rate.

[h]CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

[i]8-OHdG: 8-hydroxy-2-deoxyguanosine.

Biological Sample Collection, Assessment, and Survey

Upon informed consent, a trained team collected 50 mL of fasting urine samples in urine collection pots to detect bisphenol and phthalate metabolites [38]. Total bisphenol (free and conjugated) and phthalate metabolites will be determined by liquid chromatography–tandem mass spectrometry (LC-MS/MS) using the Agilent 6420 Triple Quad LC/MS System. The trained field team also collected 5 mL fasting venous blood samples using trace metal-free vacutainers, and an additional 3 mL was collected using a serum tube. All the samples were carried in a cooler box (4-8 °C) during transportation and stored in a negative 80 °C freezer until analysis.

We also developed a data collection tool and piloted it before applying it in the field. Our research team administered electronic questionnaires, gathering data across multiple domains. This includes general characteristics such as age, gender, income, education, and living environment, as well as detailed exposure histories and attitudes toward plastic waste. We also recorded lifestyle factors like smoking and medication, along with self-reported health conditions such as hypertension, diabetes, and liver diseases. Interviews were conducted at the participants' workplaces.

Blood Pressure Measurement

The team used an automated blood pressure monitor to assess the blood pressure of all participants, ensuring that all necessary precautions were taken care of. Participants were instructed to refrain from consuming caffeine (such as tea, coffee, and carbonated beverages), engaging in heavy physical activities, and smoking for at least 30 minutes before measuring blood pressure. They were then asked to rest for 5 minutes while seated on a chair with arm support. Different cuff sizes and calibrated instruments were used according to participants' age groups. Blood pressure measurements were conducted thrice, initially from the left arm, followed by the right arm, and then once more from the left arm. Systolic blood pressure and diastolic blood pressure readings were noted separately, and then the readings were averaged.

Respiratory Measurement

The research team collected information on smoking habits and medical history, including any previous diseases. The questionnaire inquired about acute symptoms, such as eye irritation, nasal congestion, sore throat, and headache. Lung function was assessed using a portable digital spirometer, adhering to standard operating procedures. Measurements encompassed forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow rate (PEFR).

Dietary Diversity Assessment

Previous research findings indicate that humans are commonly exposed to microplastics through inhalation, ingestion, and skin contact [23]. Thousands of chemicals and heavy metals are added to plastics as plasticizers; they enter the human body directly with microplastics. It was estimated that an American consumes an average of 39,000 to 52,000 MPs annually, where water was found to be the most prominent source [10]. Even our regular food items like chicken meat and fish were found to be contaminated with microplastics [39]. So, exploring environmental pollution and health consequences will be incomplete without a dietary assessment. Dietary diversity was measured considering the 1-week recall period. This assessment will guide us to the probable sources and help us measure the risks more precisely.

Statistical Methods and Data Analysis

Data analysis will be performed using the "R" programming language (version 3.5.2; R Foundation for Statistical Computing) and Stata (version 14; StataCorp). A codebook will be prepared based on data collection questionnaires. All variable labels, value labels, and composite variable calculations will be constructed using do files and "R" scripts. Throughout the data collection phase, quality control measures will be implemented. Any anomalies will be promptly addressed through discussion and resolution. Data will be summarized using descriptive statistical tools such as mean (SD)for quantitative symmetric variables, median (IQR) for quantitative asymmetric variables, and frequencies or proportions for qualitative variables. The chi-square test will be used to assess the association between 2 categorical variables [40]; independent *t* tests will be used to determine the significance of the differences between the means of 2 groups for normally distributed data [41], whereas the Kruskal-Wallis rank test will be used to compare the median between 2 groups or variables for non-normally distributed data [42]. After adjusting for the relevant covariates, inferential analyses such as regression and risk ratio will be calculated to draw more definitive conclusions. Confounding variables will be identified from the literature, and different types of bivariate analysis will be included in the regression model.

For qualitative data analysis, we will use ATLAS.ti (version 5.2; ATLAS.ti Scientific Software Development) to organize our data and conduct thematic analysis [43]. Our approach will begin with transcription and familiarization with interview content, followed by selecting significant quotations and identifying keywords. We will develop a coding system by iteratively reading and coding the transcripts to uncover patterns and themes. These coded segments will be entered into ATLAS.ti to facilitate theme identification and further analysis. Themes will be developed by grouping related codes and interpreting their meaning in context, aiming to construct a conceptual model that illustrates connections and insights from

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the data. Throughout this process, we will compare themes across interviews to ensure comprehensive coverage and triangulate findings for enhanced validity and reliability [44].

Ethical Considerations

The Research Review Committee (RRC) and Ethical Review Committee (ERC) of the icddr,b have reviewed and approved this study protocol (PR#22111). Eligible participants who consent to participate will be asked to provide written consent in the local language (Bengali). There will be no compensation for their participation in the research. Interviews will be conducted in private or in a comfortable setting to minimize the risk of confidentiality breaches. The interviewers will use culturally appropriate terminology and make every effort to ensure the subjects' comfort. Participants will be informed of their option to discontinue their participation in the study at any time if they feel uncomfortable. To protect participants' privacy, anonymous data sets without personal identifiers will be developed, and deidentified data will be used during storage, analysis, and dissemination.

Results

Overview

This project was funded in August 2022. Following approval from the RRC and ERC, the data collectors were recruited, and a comprehensive exposure survey and sample collection training was provided. Before starting fieldwork, we developed and piloted the data collection tool. We initiated air sample collection in January 2023 and completed this phase by August 2023. Simultaneously, biological sample collection and exposure surveys were started in June 2023 and completed by October 2023. Additional environmental samples, including soil, dust, and sediment from the exposure sites, were collected by May 2024. Data analysis is ongoing, and we anticipate publishing our first result by November 2024.

We successfully enrolled a total of 84 exposed and 84 nonexposed respondents, with sociodemographic information detailed in Table 3. The mean age of exposed respondents was 34 years (SD 6.47), slightly younger than the nonexposed respondents (mean 36, SD 13.3 years) population. The majority of the respondents were male, and almost half of them did not have any formal education across exposed and nonexposed groups. The BMI of nonexposed respondents was slightly higher than exposed respondents; however, this difference was not significant ($P \geq .05$).

Currently, all biological and environmental samples are undergoing analysis in the laboratory, and we anticipate obtaining the results by July 2024.

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Table 3. Participants characteristics of exposed and nonexposed population.

Characteristics	Exposed population (N=84), n (%)	Nonexposed population (N=84), n (%)	*P* value
Age in years, mean (SD)	34.3 (6.47)	35.7 (13.3)	.9[a]
Sex, male, n (%)	49 (58.3)	49 (58.3)	.01[b]
Education, n (%)			
No education	53 (63.1)	47 (56)	.19[b]
Up to primary school	28 (33.3)	28 (33.3)	.19
Above primary school	3 (3.6)	9 (10.7)	.19
Married, n (%)	72 (85.7)	71 (84.5)	.31[b]
Self-owned home, n (%)	29 (34.5)	32 (38.1)	.52[b]
Family members, mean (SD)	4.31 (1.92)	4.55 (1.70)	.39[a]
Monthly income (US $), median (IQR)	182 (136-255)	182 (168-273)	.05[c]
Households have their own, n (%)			
Television	0 (0)	1 (1.2)	.32[b]
Mobile phone	27 (32.1)	37 (44)	.11[b]
Refrigerator	37 (44)	46 (54.8)	.17[b]
Electric fan	82 (97.6)	83 (98.8)	.56[b]
Current smoker, n (%)	31 (36.90)	22 (26.19)	.14[b]
Alcohol consumption, n (%)	10 (11.9)	3 (3.57)	.04[b]
BMI (kg/m^2), median (IQR)	22.9 (19.5-25.6)	23.6 (21.4-26.4)	.66[c]

[a]Independent sample *t* test.

[b]Chi-square test.

[c]Mann-Whitney *U* test.

Dissemination

The study results will be disseminated to the Director General of Health and Family Services, the Department of Environment (DoE), and partnering civil society organizations in Bangladesh that are dedicated to addressing health and environmental issues, aiming to uphold environmental safety. Findings will be used to explore the boundaries and challenges of plastic recycling and management in Bangladesh. Furthermore, strategies at both technical and policy levels will be formulated alongside efforts to enhance public awareness of the environmental and health risks linked with plastic recycling. We will also develop initiatives to build capacity in this area. Abstracts will be prepared for international conferences to disseminate our findings globally, and manuscripts will be drafted and submitted to peer-reviewed journals for publication.

Discussion

Principal Findings

Several studies have examined the issue of plastic pollution in Bangladesh, with a primary focus on marine and aquatic environments. However, no study has investigated the potential human health impacts resulting from microplastic exposure [45]. Earlier evidence indicates the presence of MP in fish [20] and shrimp [46] from the northern Bay of Bengal. In addition, microplastics have been detected in sediments from Bangladesh's sea beaches and major rivers [47]. While exploring the sources of these microplastics, it was revealed that the plastic recycling industry also contributes due to the mechanical process and inadequate effluent treatments [48].

The presence of microplastic particles in our surrounding environment is evident, yet numerous unexplored aspects remain in measuring exposure and assessing health outcomes. While most of the health impacts have been hypothesized based on animal studies, only a few have been investigated through epidemiological research in humans. The proposed study aims to contribute evidence on human microplastic exposure and possible health impacts suggested by animal studies. In 2022, researchers from the Netherlands reported the first-ever detection of plastic particles in human blood, with 77% of the tested blood samples containing such particles [49]. Instead of directly detecting microplastic from biological samples, this study will focus on the metabolites of bisphenol and phthalates [50]. Furthermore, this study is designed to generate evidence on the presence of microplastic particles in environmental media, the extent of human exposure, and associated health outcomes. Collecting and analyzing a wide range of environmental sample types will contribute to a more comprehensive understanding

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of microplastic distribution in the environment and potential routes of human exposure. The results from this study will serve as a foundation for further research into monitoring the long-term ecological impacts of plastic debris. The multifaceted approach will also enhance the ability to develop targeted strategies for future mitigation and regulatory measures.

Nonetheless, this study has some limitations. We intend to identify the presence of bisphenol and phthalate metabolites in biological samples, representing an indirect method of assessing exposure. To address this limitation, we plan to collect environmental samples from the respondents' workplaces to detect the presence of MPs, which may validate our exposure assessment. This study is cross-sectional, from which causality between exposures and outcomes cannot be inferred.

Conclusion

The findings from this study could be valuable for regulatory authorities in understanding the magnitude of the problem. The proposed analysis of multiple systems, including hormonal, renal, lung function, and oxidative stress indicators, may enhance our understanding of the mechanism between exposures and biological responses. In addition, the detailed environmental investigation would provide initial evidence of contamination in the plastic industry, which might lead to negative consequences for the environment and human health. These findings could also be crucial in implementing occupational safety measures to mitigate adverse impacts, enabling informed decisions in formulating effective waste management and resource use strategies.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SSH and SMP developed the study concept. SMP, SSH, AS, and FJ developed the study design. AS, AB, NI, MR, ZI, MHK, RR, and MM provided input in environmental and biological sample collection and analysis. SSH and SMP provided input in statistical analysis. SSH drafted the paper, and all authors read and commented on it and agreed with the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Research Review Committee (RRC) - International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).
[PDF File (Adobe PDF File), 74 KB - resprot_v13i1e60289_app1.pdf]

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Abbreviations

DoE: Department of Environment
EPA: Environmental Protection Agency
ERC: Ethical Review Committee
FEV1: forced expiratory volume in one second

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FTIR: Fourier-transform infrared spectroscopy
FVC: forced vital capacity
HM: heavy metal
ICP-MS: inductively coupled plasma mass spectrometry
LC-MS/MS: liquid chromatography–tandem mass spectrometry
MiNP: mono isononyl phthalate
MP: microplastic particles
PEFR: peak expiratory flow rate
PM2.5: particulate matter with a diameter less than 2.5 μm
RRC: Research Review Committee
TSP: total suspended particulate

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Protocol

Development and Validation of a Novel Tool to Measure Medication Adherence for Noncommunicable Diseases in India: Protocol for an Exploratory Sequential Mixed Methods Multicentric Study

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Abstract

Background: In high-income countries, only 50% of patients treated for chronic diseases adhere to the prescribed treatment. This issue is even more pronounced in resource-limited countries. Medication adherence scales are simple, low-cost approaches to identify nonadherence in clinical practice. In India, nonadherence to medication varies from 18.7% to 74%, assessed using scales validated in the Western population, as there is no validated medication adherence tool contextualized to the Indian setting. The phrasing of questions in scales validated elsewhere and its interpretations may vary when applied in Indian patients unless accounting for the unique cultural, social, and economic factors influencing medication adherence in India. This could result in inaccurate reports of adherence behavior.

Objective: This study aims to develop and validate a novel medication adherence tool for select noncommunicable diseases (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, bronchial asthma, and coronary artery disease) in the Indian population.

Methods: An exploratory sequential mixed methods design will be used, beginning with a qualitative phase where the construct of the scale is defined and preliminary items are generated through a scoping review, focus group discussions, and in-depth interviews. This will be followed by the tool's development phase, including an expert panel review and item revision. Finally,

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a quantitative phase in 4 zones in India (North, South, East, and West) will be conducted to confirm and validate the newly developed scale.

Results: In the first phase, we will frame the construct definition and develop an inventory of potential items for the proposed medication adherence tool. In the second phase, item-level and scale-level content validity indices, along with content validity ratio, will be estimated. In the third phase, we will conduct an item reduction analysis and determine the scoring matrix and item weightage after expert review. We will assess the tool's psychometric properties, plot the receiver operating characteristic (ROC) curve to set an adherence cut-off score, and compute the construct validity and test-retest reliability from the quantitative survey.

Conclusions: A medication adherence tool for noncommunicable diseases, developed after ensuring it is ethnically, culturally, and linguistically appropriate incorporating stakeholder perspectives and validated in community settings, would offer a real-world perspective of adherence. The tool will have 2 versions for clinical practice and research, aiding policy makers in adopting tailored adherence policies.

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KEYWORDS

medication adherence; noncommunicable diseases; self-report; psychometric properties; validation; reproducibility of results

Introduction

India is undergoing an epidemiological health transition with an increasing burden of noncommunicable diseases (NCDs). NCDs contribute to approximately 5.87 million deaths, accounting for 60% of all deaths in India. This represents two-thirds of the total deaths caused by NCDs in the World Health Organization's South-East Asia Region [1]. In high-income countries, only 50% of patients treated for chronic diseases adhere to the prescribed treatment. This issue is even more pronounced in resource-limited countries [1]. The key contributor to the increasing burden of morbidity and mortality due to NCDs is patients' poor control status related to medication nonadherence [2]. Diabetes, hypertension, and bronchial asthma rank among the highest diseases reporting medication nonadherence [3,4]. Improving medication adherence requires assessment using a valid and reliable adherence scale, considering the various dimensions of adherence. Objective measures include pill counts, electronic monitoring, secondary database analysis, and biochemical measures, which are often impractical and resource-intensive. Subjective measures like self-reports and health care professional assessments rely on data, which could be influenced by social desirability and recall biases and might not capture complex cultural and socioeconomic factors. Nevertheless, they are cost-effective, nonintrusive, user-friendly, easy to administer, and can capture patients' concerns, helping individualize adherence interventions.

Globally, the psychometric properties of different medication adherence scales have demonstrated heterogeneous results when applied in different settings and disease conditions. Studies by Sakthong et al [5] and Zongo et al [6] reported that the Morisky Medication Adherence Scale (MMAS) demonstrated sensitivity as low as 51% and low reliability values in patients with type 2 diabetes mellitus (T2DM). The 5-item brief version of the Medication Adherence Report Scale (MARS-5) was found to be less sensitive in measuring medication adherence to asthma and other chronic disease conditions [7,8].

In India, nonadherence to medication varies from 18.7% to 74%, [2,9-11], which is assessed using scales validated in the Western population. Currently, we do not have a validated medication adherence tool contextualized to the Indian setting. The phrasing of questions in scales validated elsewhere and its interpretations may vary when applied to Indian patients unless accounted for unique cultural, social, and economic factors influencing medication adherence in India. This could result in inaccurate reports of adherence behavior.

The most commonly used adherence scales in these studies are the MMAS-4 and MMAS-8, Self-Efficacy for Appropriate Medication Use Scale, Beliefs about Medicines Questionnaire (BMQ), MARS, MARS-5, Hill Bone Compliance Scale, Adherence to Refills and Medications Scale (ARMS), and General Medication Adherence Scale [12-20]. However, these adherence scales have their own strengths and limitations. MMAS-8 has been extensively validated for a range of disease conditions. However, cost-related nonadherence and health system–related dimensions have not been explored in MMAS. Moreover, mandatory license fees preclude its widespread use in resource-limited settings. Scoring ambiguity (dichotomous response) can result in lower reliability estimates. The absence of validation in patients with low literacy levels (MMAS, BMQ, and MARS) is another factor that can affect the usability of these scales in resource-limited nations. Furthermore, few studies have considered the psychometric properties of adherence scales in the Indian context [21,22]. Concurrent validity against an objective measure of adherence has been assessed in only a few scales (BMQ).

Moreover, the linguistic validity of these translated versions of the tools has not been assessed by cognitive piloting considering the patient's perspectives and the acceptability of the tool. Measuring self-efficacy is an important factor in patient enablement to motivate and monitor their adherence behavior based on the scoring. However, this dimension of adherence behavior has not been explored in scales such as MMAS, MARS, and ARMS. Furthermore, India has mixed health care systems, where people's access to and use of medicines are dependent on their socioeconomic, cultural, and religious

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backgrounds. Out-of-pocket expenditure is an important area of health economics, especially in resource-limited countries where most patients pay direct medical costs [23,24]. Thus, the existing tools lack this important domain for measuring adherence. We aim to develop a novel indigenous medication adherence tool for select NCDs that is ethnically, culturally, and linguistically appropriate. The tool's various constructs will be developed after exploring expert opinions and patients' perspectives on adherence behavior. To ensure that the contents are relevant to the local population, the tool will be linguistically validated across different geographical zones in India. Unlike other medication adherence scales that have been validated in hospital settings, where patients are likely to be more adherent, we propose validating our tool in community settings, which would give a more accurate real-world perspective on adherence. This tool, which is envisaged to be developed in 2 versions, could be used across chronic disease conditions both in routine clinical practice (short version) and research settings (long version). This can help policy makers understand and identify reasons for nonadherence and then consequently adopt tailored policies to improve adherence. Thus, this study aims to develop a medication adherence tool and evaluate its psychometric properties to measure adherence for select NCDs in the Indian population. Furthermore, it aims to describe stakeholder perceptions of medication adherence through qualitative research.

Methods

Overview of the Study Design and Setting

The study will use an exploratory sequential mixed methods approach involving qualitative and quantitative components. This approach is widely recognized for its scale construct development and validation [25]. The study design includes three phases: (1) a qualitative phase defining the construct of the instrument; (2) an instrument development phase including item generation and revision; and (3) a confirming quantitative phase to test the instrument. In the qualitative phase, along with a scoping review, focus group discussions (FGDs), in-depth interviews (IDIs), and key informant interviews (KIIs) will be conducted among stakeholders to explore the scale construct and collect detailed information. The findings of the qualitative study will be systematically coded, and themes will be generated. These themes will be converted to scale items. In the instrument development phase, the resulting set of questions will be reviewed by a multidisciplinary team of experts. The items will then be reviewed for clarity and comprehension, and appropriate revisions will be made. After this process, the quantitative phase will begin, which will be conducted in 2 stages. A preliminary survey will be conducted to administer the new instrument among a sample of the target population with select NCDs. Item responses will be subjected to factor analysis to collect evidence for construct validity. Exploratory factor analysis with principal axis factor analysis will be used to retrieve the factors, reduce the items, and examine the factor structure. The strength of the factor loadings will indicate which items are the best, good, or acceptable on the scale.

In the second stage, the scale will undergo validation across 4 zones of India (North, South, East, and West). Our scale is designed to measure medication adherence among NCD patients in India, taking into account the significant cultural, social, and linguistic differences across regions. Scale evaluation will be carried out by examining the individual item and domain score to identify any floor and ceiling effect. Furthermore, concurrent validity against a gold standard will be estimated.

Study Procedure

Phase 1 (Qualitative): Defining the Construct and Generating the Item Pool

Initially, we will conduct a scoping review of the existing literature on medication adherence scales for NCDs validated in the adult population. This review of current global and Indian scenarios will help us methodically compile and analyze the evidence derived from the different medication adherence scales currently in use for NCDs. This will be done by considering their psychometric characteristics, including the delineation of quality benchmarks such as sensitivity, specificity, convergent validity, and reliability metrics. Furthermore, we will synthesize evidence on various medication adherence scales to identify their limitations, establish a working definition of medication adherence, determine the dimensionality of its constructs, and develop a list of potential items for creating a medication adherence scale tailored to the Indian context.

This process will be followed by FGDs, IDIs, and KIIs conducted across health centers in Kerala. Incorporating input from the target population when creating the questionnaire items will ensure that the resulting questionnaire accurately captures their perspectives. This process facilitates the inclusion of items that are acceptable, comprehensive, and relevant to the disease condition [26].

For FGDs, the participants will include staff members from primary health centers (PHCs) who have at least 2 years of experience managing NCD patients, including medical officers, staff nurses, pharmacists, health inspectors, public health nurses, and accredited social health activist workers. The selection of PHCs will be based on permission obtained from the health authorities and logistical considerations. The procedure for conducting FGDs is detailed in the FGD guide, provided in Multimedia Appendix 1. For IDIs, the participants will include patients with NCDs and their caregivers (1 adult and 1 older adult >60 years of age per disease condition). Participants will be recruited using convenience sampling. KIIs will include consultants specializing in NCDs from both government and private sectors, general practitioners, and NCD program officers. Details of the interview procedures are provided in the IDI and KII guides, included in Multimedia Appendices 2 and 3.

Data collected from these interviews and FGDs will undergo thematic analysis and triangulation to facilitate a more comprehensive understanding. Braun and Clarke's 6-step framework, including familiarization with data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report, will be used in our thematic analysis [27]. We will introduce triangulation by using multiple data sources and peer debriefing sessions and will

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consider member-checking where feasible. To ensure repeatability, we will document each stage of the analysis process to ensure minimal researcher bias. For confirmability, the findings will be supported by representative quotes from participants. The study context and participant characteristics will be comprehensively described to ensure generalizability.

This process will enable us to determine which items to add, delete, or modify from the initial questionnaire and identify potential additional domains of medication adherence for inclusion in the assessment tool. The outcome of this whole process will be the development of version 1 of the adherence tool. Figure 1 outlines the study procedure and data collection.

Figure 1. Study procedure and data collection. CVI: content validity index; CVR: content validity ratio.

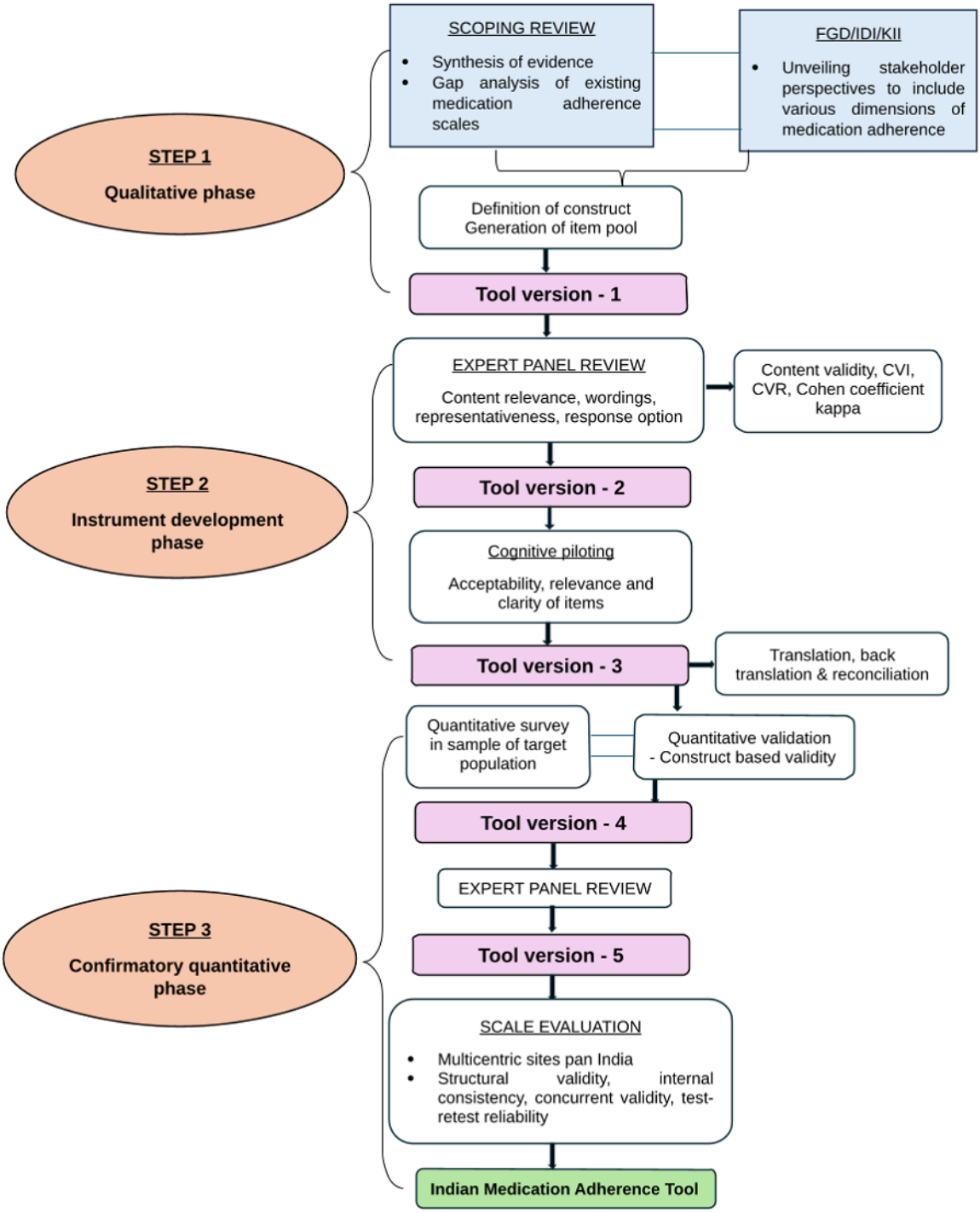

Phase 2: Instrument Development Phase

In this phase, evidence on the content-based validity of the proposed scale will be estimated to determine whether the items comprehensively represent the scale construct to be measured. This will be done by a panel of experts, whereby each item constituting the domain will be evaluated for content relevance, wording, representativeness, and response options. The expert panel will consist of 10 to 12 professionals from various disciplines, including physicians, cardiologists, pulmonologists, endocrinologists, general practitioners, and pharmacists. All

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panel members will be experienced in the construct of medication adherence and will be selected from across the 4 zones of India (North, South, East, and West).

Subsequently, the assessments will be quantified using formalized scaling and statistical procedures, including content validity ratio, content validity index, and Cohen coefficient kappa. Each item will either be accepted, rejected, or modified based on the results. This process will result in version 2 of the proposed tool.

The cognitive piloting (pretesting) of tool version 2 will be done in 2 rounds, with 1 participant from each disease condition under study in each round.

Cognitive piloting will ensure that the questionnaire assesses the acceptability, relevance, and clarity of the items. Cognitive piloting ensures that the questions are appropriately phrased, cover relevant areas, and maintain a logical flow. This step will also verify that questions are well-worded, understandable, and acceptable to participants before the main data collection [28]. Pretesting of the questionnaire will be conducted with participants who are not included in the study. Feedback from participants will be collected, and the questions will be rejected, amended, clarified, or augmented where necessary. This will comprise version 3 of the draft item tool. The translated version will undergo back translation and reconciliation before proceeding to the quantitative phase.

Phase 3 (Quantitative): Administering the Scale for Quantitative Validation in the Target Population

A quantitative survey will be conducted among a sample of the target population in the South zone, which serves as the field practice area for the lead site.

Inclusion Criteria

Participants will be individuals over 18 years of age undergoing drug treatment for at least 1 year for any of the select NCDs, including T2DM (oral antidiabetic drugs), hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and bronchial asthma.

Exclusion Criteria

Individuals with cognitive or psychological disorders, or debilitating illnesses that could impair their ability to respond will be excluded from the study.

Item Analysis and Expert Panel Review

Item responses will be analyzed via a series of statistical analyses for evidence of construct-based validity, including internal reliability (Cronbach alpha) and item correlations. Principal Axis Factor Analysis with oblique rotation will be used for item reduction, as this analysis allows for the removal of error variances and the correlation of extracted factors. The item reduction analysis will ensure that only parsimonious, functional, and internally consistent items are retained. Following this step, version 4 of the draft item tool will be finalized.

After item reduction, a second round of expert panel review (Delphi) will take place. The tool will be presented to a panel of experts to reach a consensus on the developed items and domains under which each item is categorized in the tool. Experts will also help with naming the domains and addressing any cross-loading factors on the same item, if applicable. This process will result in version 5 of the tool.

Scale Evaluation

The final version of the questionnaire (version 5) will be administered to a large representative sample of respondents from different zones across India to field test the tool's content, usability, and appropriateness for the target population. The study centers will be selected from the 4 zones across India. We will select centers that have both urban- and rural-attached facilities. Participants will be recruited purposively from these zones to ensure heterogeneity in socioeconomic, geographic, and cultural characteristics. The inclusion and exclusion criteria will be the same as those of the initial survey.

The final questionnaire will be translated into 4 different languages (Malayalam, Hindi, Assamese, and Marathi), followed by back-translation and reconciliation. The structural validity and internal consistency of the tool will be established at this stage. Individual item and domain scores will be examined for floor and ceiling effects. Sociodemographic details and medication adherence scores will be collected using the version 5 tool. The direct pill count will be assessed by a trained health worker after 2 consecutive visits at an interval of 30 days. In a subset of 10% (n=30) of participants from each site, we plan to provide a medication event monitoring system (MEMS) during the enrollment. We will then revisit these participants after 30 days to calculate the pill count. Wilcoxon signed-rank tests and Bland-Altmann analysis will be performed for each item, domain, and overall scale. Intraclass coefficients will be computed for domains and overall scale. This will establish the concurrent validity, sensitivity, and specificity of the new tool against the MEMS. If a participant is taking multiple medications, their pill-taking behavior will be assessed for only 1 medication. The scale will be readministered after 30 days for this subset in each zone to assess test-retest reliability. The criterion validity for the sample with hypertension will be estimated as a measure of blood pressure control. This will involve using the mean of 2 blood pressure readings taken 5 minutes apart.

Sample Size

For the qualitative phase, we will conduct between 4 and 5 rounds of FGDs until theoretical data saturation occurs. For IDIs, a total of 8 patients and 8 caregivers will be interviewed. For the KIIs, 3 treating physicians (1 consultant each from a private and a government sector, 1 general practitioner) and 1 district NCD program officer will be interviewed.

In the quantitative phase, the preliminary survey will be conducted among approximately 300 participants (between 8 and 10 respondents for each item). For the cross-sectional study across the 4 zones, for scale evaluation, the sample size was calculated based on a sensitivity of 0.81, with an absolute precision of 5% and a 95% CI. The total estimated sample size is 1200 [12]. We plan to recruit 300 participants from each of the 4 study sites located in different zones across India. This will be at a recruitment rate of 75 participants per disease condition studied per site.

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Data Management Plan

The data will be collected using structured case record forms (CRFs), which will be pilot-tested and validated. Relevant data will be captured on electronic CRFs and transmitted via the internet to the lead site. We will verify the data for appropriateness, run quality checks, and generate queries for clarification. Interviewers will be trained in data collection techniques, and interview times will be automatically logged. Regular supervisory visits and quality control protocols will be implemented. A quality assurance (QA) manager will monitor project activities, while the principal investigator and team will randomly check participant charts. The QA manager will independently perform source data verification, validate field visits, and review field diaries to assess data collection methods.

For the qualitative study, a descriptive content analysis of the transcripts will be carried out and subthemes will be generated. Thematic analysis and interpretive description will be done. NVivo software (version 12; QSR International) will be used to further analyze the qualitative data. In terms of content validity, the relevance of questions and ease of administration will be assessed and analyzed using item-level and scale-level content validity indices, as well as the content validity ratio, calculated with modified kappa statistics.

In the quantitative study, data will be entered into Microsoft Excel (IBM Corp) and analyzed using SPSS software (version 25; IBM Corp) for the tool validation and cross-sectional study. Item reduction will be carried out using exploratory factor analysis, including correlation matrix diagnostics, communalities, factor extraction based on eigenvalues, and factor identification based on factor loadings. Correlation matrices, the Kaiser-Meyer-Olkin test, the Bartlett test for sphericity, and determinant and individual measures of sampling adequacy will be used for establishing item adequacy for factor extraction and rotation. Cut-offs of item communalities will be determined iteratively, starting at 0.5 and, if necessary, reducing to no less than 0.3. The number of factors to retain will be identified using eigenvalues and scree plots, with factor loadings for individual items obtained from the pattern matrix. Wilcoxon signed-rank tests and Bland-Altmann analysis will be conducted for each item, domain, and overall scale. Intraclass coefficients will be computed for the domains and the overall scale. Adherence scores will be calculated as proportions using the validated tool.

Ethical Considerations

The study will be conducted after obtaining approval from the institutional ethics committee (reference no 64/23/IEC/JMMC&RI). All participants will be informed about the study's purpose and assured that participation is entirely voluntary. They will be told that refusing to participate will have no consequences and that they may withdraw at any time without providing an explanation. No incentives, other than contributing to scientific knowledge, will offered to encourage participation.

Participants will be given an information sheet summarizing key information about the study and data protection measurements. Written informed consent will be obtained from all participants, with privacy and confidentiality assured. The consent forms are attached in Multimedia Appendix 4. The consent process and participant protection measures will be documented following institutional and nationally mandated guidelines.

All information, including participant names, will be kept confidential. Only the principal investigator and selected project staff will access the data. Relevant data at the collaborator site will be captured on electronic CRFs using REDCap (Research Electronic Data Capture) and transmitted securely to the lead site. Hard copies of paper forms and documents will be stored securely under lock and key, while electronic data files will be downloaded and stored as password-protected files. Anonymized data files will be uploaded to cloud storage to ensure data privacy and confidentiality, protecting sensitive information from unauthorized access, misuse, or breaches. For this study's qualitative component, recordings of interviews and focused group discussions will be stored in secure folders with restricted access. Standard Good Clinical Practice (GCP) will be followed to ensure accurate, reliable, and consistent data collection.

Results

We will compute the item-level and scale-level content validity indices and content validity ratios to evaluate the validity of each item. Items will be then classified as rejected, accepted, or modified in phase 2 of the study. In phase 3, we will compute the Cronbach alpha and assess the contribution of each item to the extracted factors. Items that decrease alpha or do not contribute meaningfully will be scrutinized, with decisions made based on theoretical appropriateness, content validity ratios, and communality. Following an expert panel review, we will establish a scoring matrix and assign weightings to each item. This evaluation will lead to further adjustments, resulting in a final selection of items that will be accepted, modified, or rejected based on the review process. Furthermore, for the purpose of use in routine clinical settings, we will decide on 2 best fit global questions based on the consensus of the expert panel and content validity results. Construct validity for the sample with hypertension will be estimated as a measure of blood pressure control (mean of the 2 blood pressure values taken 5 minutes apart during the first visit). The scale will be readministered after 30 days for this subset in each zone to assess test-retest reliability.

The primary end point of the study will be the psychometric properties of the tool, including sensitivity, specificity, content validity index, content validity ratio, Cronbach alpha, and factor structure. Additionally, the receiver operating characteristic (ROC) curve will be used for determining cut-off score between adherent and nonadherent participants. The secondary end points will include the determinants of medication adherence from the perspectives of providers (doctors, pharmacists, nurses, and program officers) and end users (patients), as well as prevalence estimates of adherence for the conditions studied (T2DM, hypertension, CAD, COPD, and bronchial asthma).

The total duration of the study project is 36 months. In the first year, by February 3, 2024, evidence was synthesized from the existing literature. Focus groups and in-depth interviews for

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item generation for the proposed medication adherence tool were conducted between May 3, 2024, and July 3, 2024. In the second year, we will conduct an expert panel review and cognitive piloting by February 2, 2025, and the tool developed will be used for survey administration by April 2, 2025. The items will be further modified based on item reduction analysis by June 2, 2025, followed by a second round of expert panel review by August 2, 2025. For the final validation of the proposed medication adherence tool, we will conduct a cross-sectional study across the 4 zones across India between October 3, 2025, and April 2, 2026. We expect to publish our scoping review by November 2024, the stakeholder perspectives by September 2025, and the validation of the medication adherence tool at the end of year 3, by October 2026.

Discussion

Expected Findings

Currently, we do not have a validated medication adherence tool contextualized to the Indian setting. In low-resource settings, existing medication adherence scales should be used with caution due to the following reasons. First, most of these questionnaire scales were originally validated in Western contexts and may not be directly applicable in diverse settings like India. These scales should be assessed for cross-cultural equivalence, considering the varied linguistic, socioeconomic, and cultural extremes of literacy prevalent in India. The phrasing of questions in scales validated elsewhere and its interpretations may vary when applied among Indian patients. This will result in mixed findings on accuracy, reliability, and validity in patients with various chronic disease conditions.

Only a few studies have examined the psychometric properties of adherence scales such as MMAS, MARS, BMQ, and ARMS [12,13]. In Thailand [5], among patients with T2DM, MMAS-8 reported low sensitivity and predictive accuracy (51% and 43%, respectively), with a moderate specificity (64%). A study on the psychometric evaluation of MARS in caregivers of low-income, urban, African American children with poorly controlled asthma, conducted by Margolis et al [7], showed marginal fit in the Confirmatory Factor Analysis and a lack of associations with objective measures.

Scribano et al [29] reported that the Italian version of the MARS showed satisfactory internal consistency and test-retest reliability but showed low convergent validity. Furthermore, MARS has not been validated for use in patients with low literacy and does not assess self-efficacy. The cost factor, out-of-pocket expenditure, and patient self-efficacy dimensions of medication adherence were not considered in the ARMS. Additionally, the sensitivity and specificity of ARMS and the Self-Efficacy for Appropriate Medication Use Scale have not been reported and compared to clinical outcomes [14,18].

To address the limitations of existing medication adherence scales, we intend to examine the convergent validity of the new tool by comparing it with objective measures such as direct pill count and MEMS. Our novel, indigenously developed tool will include dimensions such as patient medication-taking behavior, comorbidity, pill burden, and aspects measuring self-efficacy. The proposed tool will be suitable for patients across all literacy levels. To accommodate patients with low literacy, some items will include pictograms to facilitate understanding and responses.

Furthermore, India has mixed health care systems, where people's access to and use of medicines are influenced by their socioeconomic status. Out-of-pocket expenditure is an important area of health economics, especially in resource-limited countries where most patients pay direct medical costs. Existing tools lack a consideration for this important domain when measuring adherence. Hence, the various characteristics of the proposed tool would be developed after considering expert opinions and patients' perspectives on adherence behavior. This will help us to assess various dimensions of adherence. The cost factor and out-of-pocket expenditure on medications will also be included as a dimension in our tool. To ensure that the contents are relevant to the local population, our tool will be linguistically validated across different geographical zones in India. Validation in community settings, as opposed to hospital settings, conducted in other preexisting tools, will provide real-world evidence on adherence. Moreover, we intend to develop a shorter version of the medication adherence tool, which could be integrated into routine clinical practice. Between 2 and 3 best-fit global questions in this short version will be selected after considering the content validity indices, expert consensus, and communality. This is a simple and rapid method for assessing medication adherence in point-of-care or clinical settings.

We acknowledge the potential limitations of our study and have outlined strategies to mitigate them. First, because our study will be conducted with specific populations, the findings may have limited generalizability and may not fully represent diverse population characteristics. To address this limitation, we will provide recommendations for future studies to test the findings in different contexts. Second, since our study relies on interviews/self-reported data, there may be potential recall bias or social desirability bias. To minimize these effects, we will use standardized, open-ended questions and ensure participant confidentiality. Third, researcher perspectives might affect the qualitative portion of the study. We plan to address this through reflexive data collection, analysis methods, and team discussions [30]. Finally, the timing of data collection might influence the findings, particularly if impacted by including seasonal factors or significant social events. We will consider these contextual influences while interpreting the results of our study.

Conclusion

A medication adherence tool for selected NCDs, developed to be ethnically, culturally, and linguistically appropriate through expert opinion and patient perspectives and validated in community settings, will provide a real-world perspective on adherence. The tool will have two versions for clinical practice and research, aiding policy makers in adopting tailored adherence policies.

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Data Availability

The data sets generated during and /or analyzed during the study are available from the corresponding author upon reasonable request.

Authors' Contributions

JT, MJ, PR, and JJC conceptualized the study. RPVP, MJ, and PR designed the analysis. The protocol was developed and registered by MJ, PR, and JT. FNF and NKJ designed the interventions. JT, MJ, PR, TSA, MB, AA, TGM, and PK generated the first draft of the manuscript. JT, JM, and PR wrote the manuscript. All authors reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group discussion guide.
[DOCX File , 20 KB - resprot_v13i1e60805_app1.docx]

Multimedia Appendix 2
In-depth interview guide for patients.
[PDF File (Adobe PDF File), 131 KB - resprot_v13i1e60805_app2.pdf]

Multimedia Appendix 3
In-depth interview guide for caregivers.
[PDF File (Adobe PDF File), 152 KB - resprot_v13i1e60805_app3.pdf]

Multimedia Appendix 4
Consent forms.
[DOCX File , 16 KB - resprot_v13i1e60805_app4.docx]

Multimedia Appendix 5
Peer-review report by the National Task Force (NTF) on Safe and Rational use of Medicines (SRUM) - Indian Council of Medical Research (ICMR) Central Coordinating Unit (CCU) (New Delhi, India).
[DOCX File , 280 KB - resprot_v13i1e60805_app5.docx]

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Abbreviations

ARMS: Adherence to Refills and Medications Scale
BMQ: Beliefs about Medicines Questionnaire
CAD: coronary artery disease
COPD: chronic obstructive pulmonary disease
CRF: case record form
FGD: focus group discussion
GCP: Good Clinical Practice
IDI: in-depth interview
KII: key informant interview
MARS: Medication Adherence Report Scale
MEMS: medication event monitoring system
MMAS: Morisky Medication Adherence Scale
NCD: noncommunicable disease
PHC: primary health center
QA: quality assurance
REDCap: Research Electronic Data Capture
ROC: receiver operating characteristic
T2DM: type 2 diabetes mellitus

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Protocol

Characterizing Emergency Department Disposition Conversations for Persons Living With Dementia: Protocol for an Ethnographic Study

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Abstract

Background: Almost 40% of persons living with dementia make an emergency department (ED) visit each year. One of the most impactful and costly elements of their ED care is the decision to discharge or admit them to the hospital—the "disposition" decision. When more than one reasonable option exists regarding a health care decision, such as the decision to admit or not, it often requires a complex conversation between patients, care partners, and ED providers, ideally involving shared decision-making. However, little is known about how these conversations are conducted and the real-world context in which they take place. Best practices in ED communication and shared decision-making for persons living with dementia and their care partners are limited.

Objective: This study aims to characterize current practices in ED disposition conversations for persons living with dementia and their care partners, informed by perspectives from patient and care partner participants.

Methods: This study will use an ethnographic design, including direct observation methods with a semistructured data collection tool to capture the ED encounter for up to 20 patient and care partner dyads, including all discussions about dispositions. Follow-up qualitative, semistructured interviews will be conducted with persons living with dementia and their care partners to explore specific observations made during their ED encounter, and to gain insight into their perspective on their role and elements of decision support used during that conversation.

Results: Data collection was initiated in October 2023, with 13 dyads recruited and observed as of July 2024. This study is expected to be completed by December 2024.

Conclusions: Novel methods can offer novel insights. By combining direct observation and follow-up interviews about an ED visit, our study design will provide insights into how ED disposition occurs in real-world settings for persons living with dementia. Findings can inform more patient-centered interventions for disposition decision-making.

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KEYWORDS

ethnography; direct observations; emergency medicine; dementia; caregivers

Introduction

Background

For persons living with dementia, emergency department (ED) visits often represent a sentinel event, with a significant risk of subsequent increased health care utilization and long-term care placement [1,2]. About 40% of the estimated 2.4-5.5 million US population living with dementia have an ED visit each year [3]. ED care for persons living with dementia can be challenging because these patients have more comorbidities and medications compared with their counterparts without dementia, and they frequently find the ED environment overstimulating and disorienting [4]. In many cases, they may not be able to provide a clinically actionable account of what brought them to the ED, in which case ED providers often rely on collateral information from care partners or anyone available.

Among the many decisions that are made over the course of an ED visit, one of the most difficult is the disposition decision; ED providers must balance the risks associated with hospital admission, including delirium and functional decline, against the risks of discharge, which may result in return visits to the ED and hospitalizations [5]. This decision has enormous implications for patient experience, outcomes, and costs of care and is especially intricate for persons living with dementia, as they have a higher risk of these adverse events compared with their counterparts without dementia [6].

In ED visits when this choice is not straightforward, a high-quality disposition decision would ideally involve input from the person living with dementia and their care partner through shared decision-making (SDM) [7]. While SDM is more widely used in other clinical contexts, it is a relatively new but growing concept in the ED setting, with great potential to ensure that ED decisions reflect the goals, preferences, and values of patients and their care partners [8,9]. Currently, there are no best practices or SDM tools to help guide these complex ED disposition conversations.

However, effective interventions to address the lack of best practices in SDM in this context will require real-world data about the context within which they are implemented, and we lack a fundamental understanding of how these conversations currently take place [10]. For example, to determine the optimal timing for an SDM tool, we need foundational data on current communication practices for disposition discussions (eg, is it addressed across multiple interactions over the course of an ED visit, or mostly at the very end?) [11]. To best facilitate participation from persons living with dementia and care partners, we need to understand what kind of decisional roles they each tend to take. To improve the degree of "sharing" during these discussions, we need to understand barriers and facilitators to participating in an SDM conversation around disposition (eg, are they invited to share their relevant values or preferences, is there sufficient time to make a decision?).

To address these gaps, the primary objective of this study is to use ethnographic methods to characterize current practices in disposition conversations for older persons living with dementia [12]. This will be augmented by follow-up interviews with patients and care partner participants to elicit their perspectives on observed barriers and facilitators to participation in these conversations. Direct observation methods are uncommon in emergency medicine research but can provide unique and nuanced information about health care processes and behavior that may not be captured by self-reported means such as surveys or participant recall in interviews [13]. It can facilitate researchers' understanding of how patients experience a specific event or circumstance. A previous scoping review on communication and SDM for persons living with dementia in the ED demonstrated regular use of interviews, focus groups, and survey methods [14]. To our knowledge, this will be the first use of direct observation methods with persons living with dementia in the ED setting.

Research Aims and Objectives

Aim 1

The first aim is to characterize discussions about ED disposition with persons living with dementia and their care partners using direct observation methods during ED visits, focusing on timing, decisional roles, and decision support strategies used in disposition conversations.

Aim 2

The second aim is to identify facilitators and barriers to participating in disposition decision-making for persons living with dementia and care partners. Informed by findings from direct observations in aim 1, we will conduct semistructured qualitative interviews with aim 1 participants. Interviews will ask participants about specific observations made from their encounter, to gain insight into their perspective on their role and elements of decision support used during that conversation.

Methods

Study Design

Overview

This ethnographic study design entails 2 largely concurrent, complementary phases [15]. Patient and care partner dyads will be recruited at the time of an ED visit, with direct observations using a semistructured data collection tool done during the ED visit that day. Follow-up interviews will be conducted within 48-72 hours of the observations, albeit dependent on the status of the patient given their health care needs and care partner availability.

This research plan is informed by the Ottawa Decision Support Framework (ODSF), a conceptual framework of decision-making commonly used in the development of patient decision aids [16,17]. The ODSF is guided by the premise that there are unmet decisional needs (eg, decisional conflict and

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unclear values) that, when addressed with "decision support," will improve decisional outcomes. As the focus of this proposal is to better understand current practices in decision support and sharing in decision-making, our study will be structured around elements that play a role in decision support in the ODSF.

Setting and Context

Data will be collected at the Durham Veterans Affairs Medical Center (DVAMC), a 251-bed tertiary care referral, teaching, and research facility affiliated with Duke University School of Medicine in Durham, North Carolina. The DVAMC ED evaluates and treats approximately 35,000 patients annually. The DVAMC ED achieved level 1 status (the highest level) of Geriatric ED accreditation from the American College of Emergency Physicians in June 2023 [18]. Of note, the DVAMC is also an Age Friendly Health System and working toward Geriatric Surgery Verification [19].

Researcher Characteristics and Reflexivity

Two researchers will screen patients for recruitment and perform data collection and analysis in this study. JS is a practicing emergency medicine physician at the DVAMC and a Health Services Researcher and brings an understanding of workflow and procedures in the DVAMC ED. MT is a qualitative data analyst in Health Services Research with a background in anthropology. Given the study design requiring immediate observational data collection after participant recruitment, the researchers also perform real-time screening in the ED and approach patients for consent before data collection.

Sampling Strategy

Inclusion criteria for patient and care partners include the following: (1) the patient is aged 65 years or older; (2) there is a dementia diagnosis documented in the electronic medical record (EMR); (3) the patient is community dwelling; (4) the patient or care partner (depending on the severity of a patient's dementia and if the patient has a legally authorized representative) is able to discuss disposition in English; and (5) the patient does not have a straightforward disposition based on study principal investigator–clinician review of initial triage note and vitals. Exclusion criteria include the following: (1) the patient has no care partner available in the ED; (2) the patient is triaged as Emergency Severity Index Level 1 (indicating a high-acuity patient that is very likely to be admitted); (3) the patient is not community dwelling; and (4) the patient has medical instability, acute altered mental status, or hyperactive delirium at the time of the ED visit (similarly indicative of a patient that is likely to be admitted). ED health care providers included may be attendings and residents, and any provider may be observed for multiple encounters if they care for more than one participant.

Recruitment Procedures

Trained observers will be stationed in the DVAMC ED for study recruitment. Eligible veterans and care partner dyads will be identified at the time of triage or check-in through monitoring the DVAMC electronic ED track board. Potentially eligible participants will first be identified using the EMR for inclusion and exclusion criteria. A documented diagnosis of dementia can be identified through several means, including International Classification of Diseases codes assigned to the patient's record, documentation in previous notes including outpatient visits or discharge summaries, or using the EMR search function with the query "dementia." These strategies were selected as those that best replicate the means by which ED providers often identify persons living with dementia in the ED clinical environment. For eligible participants, the study principal investigator will be contacted by the research staff to clinically review the nursing triage note and vitals as soon as they are available and make a determination as to whether the ED visit is likely to warrant deliberation about disposition by the average ED provider. Patients or care partners will not be approached before being placed in an ED room or while in the ED waiting room, given privacy concerns. When a potentially eligible patient has been assigned to an ED room on the electronic ED track board, the researchers will speak to the ED physician providers who will most likely care for that patient (based on room assignment location) to ask if they would be willing to delay their initial conversation for our consent process. If there are any concerns about this delay, we defer consent to allow for appropriate patient care. Of note, our protocol excludes any patients who are unstable or acutely agitated and thereby ensures that the time required for consent with the patient and care partner does not delay any crucial timely ED care. The patient and care partner are then approached to participate in the study after they have been placed in a private ED room.

Consenting Procedures

When the patient and care partner dyad are approached by the researcher, they are given a flyer that explains the study and asked if they would be interested in learning more about the study while they wait for a provider. With the targeted population of persons living with dementia, including those with moderate to severe dementia, their capacity to consent to research may significantly vary, although the severity of their dementia may not directly correspond to their capacity [20]. However, if this study was limited only to patients who had the capacity to provide consent, there is a significant risk that this would make the study population less representative. We acknowledge that persons living with dementia are a vulnerable population, and we will assess prospective participants' capacity to consent using the Evaluation to Sign Consent Scale, a measure developed to evaluate nursing home residents' ability to communicate and provide informed consent [21]. Of note, if the care partner at the bedside at the time of the ED visit is not the highest priority surrogate decision maker for the patient, the highest priority surrogate available at the time will be contacted for consent for the patient to participate, and the care partner at the bedside will additionally be consented for their own participation. If the person living with dementia is unable to fully appreciate key features of the protocol, the potential risks, or their rights to withdraw, we will ask the participant if they would like their highest priority surrogate decision maker or legally authorized representative (LAR) to provide consent. The person living with dementia will still provide assent to study staff explaining the procedures involved in the protocol in simplified terms. To respect the dignity of the participants living with dementia, we will also respect their dissent (which can

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include low levels of cooperation, demonstrating frustration, or passivity) in combination with proxy consent.

All participants that consent to participate in direct observations will be asked if they are also willing to participate in follow-up interviews, and we will additionally acquire their consent through written consent at that time. If any signs of discomfort are exhibited by the person living with dementia or it is requested, the researchers will stop the research process at that time.

Ethical Considerations

This research received approval from the DVAMC institutional review board (approval #1820207) in September 2023. For participating in this study, participants will receive US $50 for observations during the ED encounter and an additional US $50 for participating in follow-up interviews. While no identifying information is collected for the ED health professionals observed, written consent is also collected for them.

Data Collection

Direct Observations

The unit of observation is an interaction between the provider and the patient or care partner. Anticipating that each ED visit will include multiple discrete interactions between the patient or care partner, we will use continuous event sampling to collect data, meaning that all interactions are sequentially recorded during the ED visit [22]. Data will be collected from the time point of the first interaction after the patient has been placed in an ED room up until the point that a disposition decision is made. Observers will function as a "complete observer," meaning that the researcher observes what is occurring without interfering in routine care [22].

Data collection will occur through mobile positioning, in which the observer follows a person during a given activity or for a particular observation period [22,23]. As such, we will collect data as the patient and care partner move throughout the ED. The observers will station themselves in as unobtrusive a location as possible, ensuring that persons living with dementia and care partners are comfortable with their position. The data collection tool is a paper-based semistructured template, selected as it was thought to be less intrusive than typing on a keyboard if using an electronic form during an observation. Data will include the (1) date, (2) time, (3) location, (4) people present, (5) duration, and (6) contents of the discussions. Discussions will be captured using an open section for descriptive field notes. Descriptive fieldnotes can capture general observations, nonverbal communication such as facial expressions and demeanor, as well as paraphrased statements from the participants [12,24]. These notes will include topics such as who the physician is addressing during the conversation, the medical history of the patient, the reason for visit, and all components of the disposition discussion. Any interpretive notes (eg, that the care partner seems frustrated) will be clearly identified with "[closed brackets]" to demarcate this from the descriptive data. This approach leaves room for unanticipated findings or documentation of activities that are otherwise uncategorized. While the data collected during the encounter itself may be brief, the observer will fill in additional detail or add more thorough information after the encounter is over, with all notes written by the end of the day to minimize recall bias. Researchers will also write a postobservation reflection to summarize their overall impression of the ED encounter by the end of the day. Multimedia Appendix 1 presents the data collection tool template.

Baseline Data Collection

During a portion of the ED visit during which ED providers are not present, and no active patient care is taking place (eg, while waiting for test results), we will collect additional features of patients and care partners that may influence disposition decisions, including dementia severity by using the 5-minute, informant-based Dementia Severity Rating Scale [25,26]. To further describe the study sample, we will also measure patient demographics, income, health literacy through the Short Literacy Survey [27], and care partner burden (Zarit Burden Interview 4-item) [28]. Care partners will be asked to fill out the latter directly, instead of by interview.

Semistructured Interviews

Follow-up semistructured interviews will be conducted by the researcher who collected the direct observation data whenever possible. These will be scheduled at the time of the ED visit for participants who are discharged home. For participants who are admitted, a time to contact the care partner will be established, at which time the follow-up interviews can be scheduled. We aim to conduct 30- to 45-minute interviews with care partners and patients as much as possible. Interviews will be audio recorded and transcribed. For persons living with dementia, questions will be simple, with fewer planned questions and more probes to elicit details. Interview guides are structured around elements of decision support observed in aim 1. We may use specific observations and aim 1 results as prompts to elicit discussion and to gain insight into their perspective on their role and elements of decision support used. Multimedia Appendix 2 presents the interview guide templates.

Data Analysis

Overview

Our analytic goal is to characterize discussions about ED dispositions with persons living with dementia and their care partners, and to describe how different elements of SDM are used, informed by participant perspectives. Each participant unit will consist of a person living with dementia and their care partner, and for each of those, one unit of data will consist of one direct observation template and fieldnotes, 1 or 2 interview transcripts, and baseline demographic and clinical survey data. Data will be analyzed by the same 2 researchers performing data collection.

Data analysis for direct observations will be conducted using the constant comparative method, in which data collection and analysis are interrelated and carried out concurrently [29]. An initial codebook for each unit of data (encompassing the direct observation and interview data) was developed based on elements of SDM outlined in the ODSF and the research question. Analysts will independently code a minimum of 2 units of data and will refine the codebook based on findings.

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Postobservation reflections will also guide the development of the codebook. Data analysis will use iterative rounds of more focused coding to organize the initial coding results into themes. The data source (ie, direct observation notes, the patient interview, or the care partner interview) for each piece of data will be captured as well. We acknowledge that this analytic plan may change significantly depending on findings, particularly if there are little observational data regarding the discussion of the disposition decision—although this will be an important finding in and of itself.

Rigor and Trustworthiness

Multiple elements of this study design contribute to its rigor and trustworthiness [30]. To maintain credibility, we acknowledge the personal experiences of the researchers performing data collection and analysis as described above. In this case, using more than one coder increases study rigor and will allow for input by someone immersed in the ED environment as a clinician, as well as someone with a nonclinical perspective. This study also uses multiple data sources with observations and interviews to verify findings. We acknowledge that the selected patient population of veterans may limit the transferability, and this is to be further discussed as a limitation. To enhance dependability, we have created a detailed standard operating procedures document with changes documented. To address confirmability, we are creating postobservation reflections after each observation to document evolving thoughts during the research process, and this will also serve as a reference as needed to inform data analysis for each unit.

Patient and Public Involvement

Two sources of patient and public involvement were used in the design of this protocol. This study was funded by the Geriatric Emergency Care Applied Research Network 2.0 – Advancing Dementia Care (GEAR 2.0 ADC), a National Institutes of Health–funded program to support research to improve emergency care for people with dementia [31]. The initial grant application and study design proposal were reviewed by community reviewers involved in the GEAR 2.0 ADC program. Multimedia Appendix 3 presents a summary of peer-review findings. Based on their comments, we elected to make changes to the proposed protocol to expand the sample for the aim 2 interviews to all participants included in aim 1 and to expand the sample of persons living with dementia to all levels of dementia severity. As part of the GEAR 2.0 ADC grant program, we were also given the opportunity to consult with the University of Wisconsin's Community Advisors for Research Design and Strategies (CARDS) program [32]. This is a group of patient and care partner representatives recruited from community center programs to bring perspectives from diverse racial, socioeconomic, and educational backgrounds to all parts of the research process. While CARDS is not specific to dementia care, for this protocol, we specifically sought input into the ideal timing of when to approach patients and care partners for consent during the course of the ED visit, as well as the design of a recruitment flyer to use when first approaching patients and care partners in the ED.

Results

Data collection was initiated in October 2023. A total of 576 patients have been screened across 31 days of recruitment in the ED. Of those, 47 had a documented diagnosis of dementia, and 23 of those were eligible for inclusion. A total of 17 dyads were approached for consent. As of July 2024, a total of 13 dyads have been recruited. This study is expected to conclude by December 31, 2024.

Discussion

Expected Findings

We have designed this novel study to better understand communication practices for persons living with dementia in the ED. While this study is largely focused on the disposition conversation, using an open-ended direct observation tool to capture the clinical encounter will additionally allow us to collect rich, holistic data about the experience of ED care for persons living with dementia and their care partners. We aim to learn more about how disposition conversations take place in a real-world setting, who participates, and what elements of SDM are used or not used. Further, this open approach to direct observation data collection will also capture any number of possible findings, including the very real possibility that there will be a lack of formal discussion around the disposition decision altogether. Our results will be based on observation notes, observation reflections, and semistructured qualitative interviews. While data collection is ongoing, there have been some early lessons noted that merit discussion.

The research team has identified some early lessons related to the recruitment of patients for direct observation research in the ED setting, particularly that some flexibility is needed in the recruitment protocol. Our goal is to observe as many of the conversations between ED providers, patients, and care partners as possible, ideally including the very first conversation conducted involving introductions. As such, we seek to consent of patients and care partners for participation at the time of their ED visit, but before they are seen by any ED physician provider. An early concentration of planning for this protocol was focused on identifying the ideal timing to approach patients and care partners for consent and assent. Given that ED visits are typically for acute, unplanned care, we anticipate that some patients or care partners will understandably prefer to focus on initiating their medical care with their physician provider before they consider participation in research at the time of their ED visit. Our protocol is designed so that the researcher approaches patients and care partners for consent after they are physically moved to a private ED room and assessed by the assigned ED (nontriage) nurse for that room, but before they are seen by an ED physician provider. This typically represents a short time window and requires flexibility if the workflow changes. Our decision-making around this part of the protocol was informed by (1) the clinical experience of one of the researchers (JS) who is a practicing ED physician and (2) direct input from a patient and care partner advisory board. Overall, our approach is designed to prioritize patient care and safety, minimize intrusiveness to ED workflow, and maximize patient and care

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partner comfort with the timing of research procedures. However, we recognize that this particular ED workflow process may not be the norm in all EDs. As such, the ideal timing for the identification of eligible patients and the approach for consent may differ in other ED settings.

The research team has also identified several early lessons related to research with persons living with dementia and their care partners, some of which are also specific to the ED setting. For example, our protocol was written with several methods for screening ED patients specifically to identify those with dementia. Based on input from practicing clinicians on the research team, we elected to allow for the identification of a dementia diagnosis from multiple locations in the chart as this best mimics methods by which ED providers would look for a dementia diagnosis in a real ED encounter. This includes looking at the "problem" or "diagnosis" list on the patient's EMR cover sheet, using the medication list, looking at recent outpatient clinic visits or hospital discharge notes, and using the EMR search function. From early data collection, we have identified that most patients will have a diagnosis listed in outpatient visit notes, but it is not as consistently listed in the formal problem list for the patient. This is not surprising as documentation of a dementia diagnosis is well-known to be inconsistent in administrative data using formal diagnosis codes [33]. As such, research procedures for screening for persons living with dementia in real time in the ED will likely need to vary across different health systems that use other types of EMR programs.

In addition, we have found that the person who serves as the patient's formal LAR may not always be the same as the care partner at the bedside at the time of the ED visit. We anticipated that this may be a more likely scenario compared with other health care settings, given that ED visits are typically unscheduled, and so the patient's LAR may not be available at the time due to other commitments or having other reasons limiting their ability to attend an unplanned ED visit. As such, we created our protocol to accommodate a variety of consent and assent procedures with this in mind. From early data collection, we have found a variety of people serving as the care partners at the bedside—the majority have been spouses, but also have encountered the patient's children, in-laws, or family friends. Other studies involving persons living with dementia requiring consent and assent at the time of an ED visit will likely need to include similar approaches.

Limitations

We also note our study will have several anticipated limitations. As it takes place in a Veterans Affairs setting, this may limit generalizability. Given the demographic makeup of older veterans, we anticipate having predominantly male patients with (female) spousal care partners. We also note that the DVAMC has selected programs aimed at improving the coordination of care for community-dwelling veterans living with dementia, and patients participating in these programs may have access to specific resources that would impact the disposition decision [34]. Our protocol is also focused on capturing communication between patients, care partners, and ED physician providers, but we will not include observations of conversations with specialists consulted by the ED physician, which may mean we miss information conveyed to patients or care partners if the ED provider is not present. We also acknowledge that for this pilot study, patient recruitment will be conducted during business hours. This is typically when more hospital resources and consultants are available to ED providers, which may also influence the course of the ED visit and disposition decision.

Conclusions

Little is understood about how ED disposition conversations take place in a real-world ED setting and what elements of SDM are used (or not used) when caring for persons living with dementia and their care partners. This study uses direct observation methods to capture the entirety of the ED encounter and will be further informed by participant perspectives elicited by follow-up interviews. Results may be used to provide insights on timing, delivery, personnel, and format of a potential future SDM tool or decision aid for this clinical scenario.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to the nature of the research containing potentially identifying and sensitive patient information.

Authors' Contributions

Conceptualization and funding acquisition were performed by JS and SNH. The methodology was performed by JS, MH-G, GMF, NRS, and SNH. Data collection and analysis were completed by JS, MT, MH-G, and IG. Writing of original draft preparation was performed by JS and MT, with review and editing of the manuscript being completed by MH-G, GMF, IG, NRS, and SNH. Project administration was completed by JS and IG. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Direct observation notes template.
[PDF File (Adobe PDF File), 238 KB - resprot_v13i1e65043_app1.pdf]

Multimedia Appendix 2
Patient and care partner interview guides.
[PDF File (Adobe PDF File), 223 KB - resprot_v13i1e65043_app2.pdf]

Multimedia Appendix 3
Peer-review summary comments from The Geriatric Emergency Care Applied Research (GEAR 2.0-ADC) Community Review Committee (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 203 KB - resprot_v13i1e65043_app3.pdf]

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Abbreviations

CARDS: Community Advisors for Research Design and Strategies
DVAMC: Durham Veterans Affairs Medical Center
ED: emergency department
EMR: electronic medical record

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GEAR 2.0 ADC: Geriatric Emergency Care Applied Research Network 2.0 – Advancing Dementia Care
LAR: legally authorized representative
ODSF: Ottawa Decision Support Framework
SDM: shared decision-making

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Protocol

Improving Blood Pressure Control and Tobacco Use Cessation Intervention In Primary Care: Protocol for the Alabama Cardiovascular Cooperative Heart Health Improvement Project

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Abstract

Background: Alabama has the second highest rate of cardiovascular disease (CVD) mortality of any US state and a high prevalence of CVD risk factors such as hypertension, diabetes, obesity, and smoking. Within the state, there are disparities in CVD outcomes and risk factors by race or ethnicity and geography. Many primary care practices do not have the capacity for full-scale quality improvement (QI) initiatives. The Alabama Cardiovascular Cooperative (ALCC), which includes academic and community stakeholders, was formed to support primary care practices to implement QI initiatives to improve cardiovascular health. The ALCC is implementing a Heart Health Improvement Project (HHIP) in primary care practices with suboptimal rates of blood pressure (BP) control and tobacco use screening.

Objective: The study aimed to support primary care practices to increase BP control among adults with hypertension and increase rates of tobacco use screening and cessation intervention.

Methods: We are using a type 1 hybrid design to test the effects of the HHIP on BP control among adults with hypertension and tobacco use screening and cessation intervention, while collecting information on implementation. Primary care practices were recruited through existing practice networks and additional electronic and in-person outreach. To ensure participation from a broad range of clinics, we required at least 50% of practices to be Federally Qualified Health Centers or look-alikes and to include representation from practices in rural areas. At baseline, we collected information about practice characteristics and preintervention rates of BP control and tobacco use screening and cessation intervention. The QI intervention includes quarterly activities conducted over a 12-month period. The HHIP uses a multipronged approach to QI, including practice facilitation and technical assistance, on-site and e-learning, and improvement through data transparency. We will conduct a pre-post analysis to estimate the effects of the HHIP and whether there is an enduring change in outcomes after the 12 months of HHIP activities beyond what would be expected due to secular trends.

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Results: Practice recruitment took place between April 2021 and October 2022. After contacting 417 primary care practices, 51 were enrolled, including 28 Federally Qualified Health Centers or look-alikes; 47 practices implemented the HHIP. Among 45 practices that completed the baseline survey, 11 (24%) were solo practices, while 28 (62%) had 1-5 clinicians, and 6 (13%) had 6 or more clinicians. The median number of patient visits per year was 5819 (IQR 3707.3-8630.5). Practices had been in operation for a mean of 19.2 (SD 13.0) years. At baseline, the mean BP control rate was 49.6% and the rate of tobacco use screening and cessation intervention was 67.4%.

Conclusions: If successful, the ALCC and HHIP may improve the implementation of evidence-based guidelines in primary care and, subsequently, cardiovascular health and health equity in the state of Alabama.

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KEYWORDS

hypertension; primary care; quality improvement; tobacco use; smoking cessation; healthcare quality; quality of care; risk modification; cardiovascular disease prevention

Introduction

In the United States, cardiovascular disease (CVD) mortality declined dramatically beginning in the 1960s [1,2]. However, the decline has stalled since the 2010s, and national trends mask uneven progress by race or ethnicity and geography [2-5]. As a result, inequities in cardiovascular outcomes persist, and in some cases have widened, across racial, socioeconomic, and geographic lines [5,6].

Alabama has the second-highest rate of CVD mortality of any state in the nation [7]. The rate is even higher among non-Hispanic Black versus non-Hispanic White populations in the state and higher in rural versus urban counties [8,9]. Alabama also has a high prevalence of CVD risk factors such as hypertension, diabetes, obesity, and smoking [10,11]. The impact of these risk factors on health outcomes may be exacerbated by a lack of access to primary care. Compared with the top performing states (90th percentile), which have an average of 1 primary care physician per 1030 residents, Alabama has 1 primary care physician per 1540 residents, ranging from 1:930 to 1:10,080 depending on the county [12]. All but 5 of Alabama's 67 counties are deemed Primary Care Health Professional Shortage Areas by the Health Resources and Services Administration [13]. Few primary care practices have sufficient administrative support or the funding needed to facilitate full-scale quality improvement (QI) efforts.

To address these challenges, several organizations have provided services to support QI initiatives across the state, including the Alabama Primary Health Care Association (APHCA), QSource, and the Alabama Department of Public Health. In 2021, these organizations came together with academic partners from the Auburn University School of Pharmacy and the University of Alabama at Birmingham (UAB) Heersink School of Medicine to form the Alabama Cardiovascular Cooperative (ALCC) to support primary care practices across the state to implement QI initiatives to improve cardiovascular health. This paper describes the protocol for the ALCC's Heart Health Improvement Project (HHIP), a QI project implemented in 47 primary care practices to improve the assessment and management of cardiovascular risk factors, specifically hypertension and tobacco use. The HHIP will use a type 1 hybrid design [14] to test the effects of the HHIP on clinical outcomes at the practice level, including blood pressure (BP) control among adults with hypertension and tobacco use screening and cessation intervention, while collecting information on implementation.

Methods

ALCC Overview

The ALCC was formed to coordinate statewide efforts to reduce cardiovascular risk and disparities among individuals across the state of Alabama by supporting primary care providers, especially those in the most underserved areas of the state (Figure 1). Each of the organizations that is part of the ALCC has long-standing commitments to improving health outcomes in Alabama, broad statewide reach, and a shared belief that a coordinated effort to support primary care–based initiatives to improve cardiovascular health in Alabama could prove transformative. An Advisory Board, which includes representation from key stakeholders from multiple sectors across the state, helps inform the Cooperative's activities and sustainability plans through quarterly meetings and ad hoc communication. The Cooperative serves as a convener of stakeholders and maintains a repository of ongoing CVD-related initiatives and resources. The Cooperative is also implementing the HHIP in 47 clinics to improve rates of BP control and tobacco use intervention.

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Figure 1. Alabama Cardiovascular Cooperative Organizational Structure. CME: continuing medical education; CPE: continuing pharmacy education; HHIP: Heart Health Improvement Project; IRB: institutional review board; PI: principal investigator; VCoP: virtual community of practice.

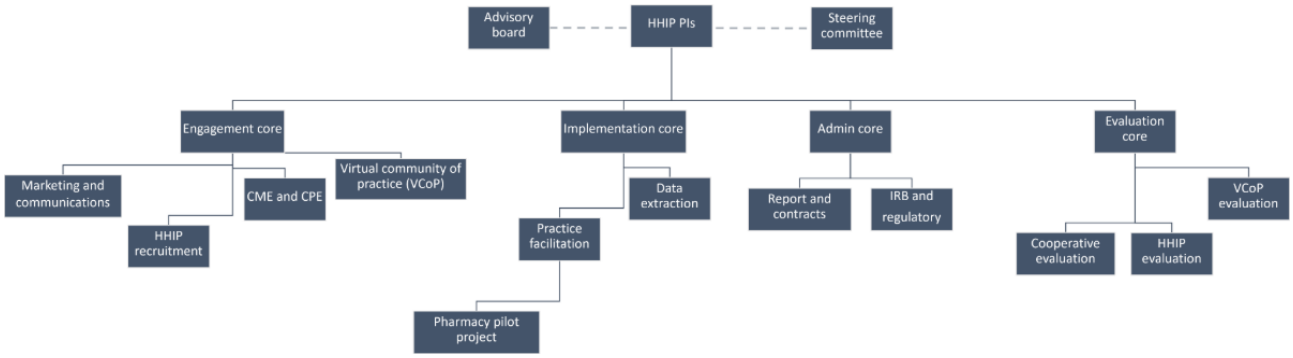

Figure 2. Heart Health Improvement Project primary care practice recruitment.

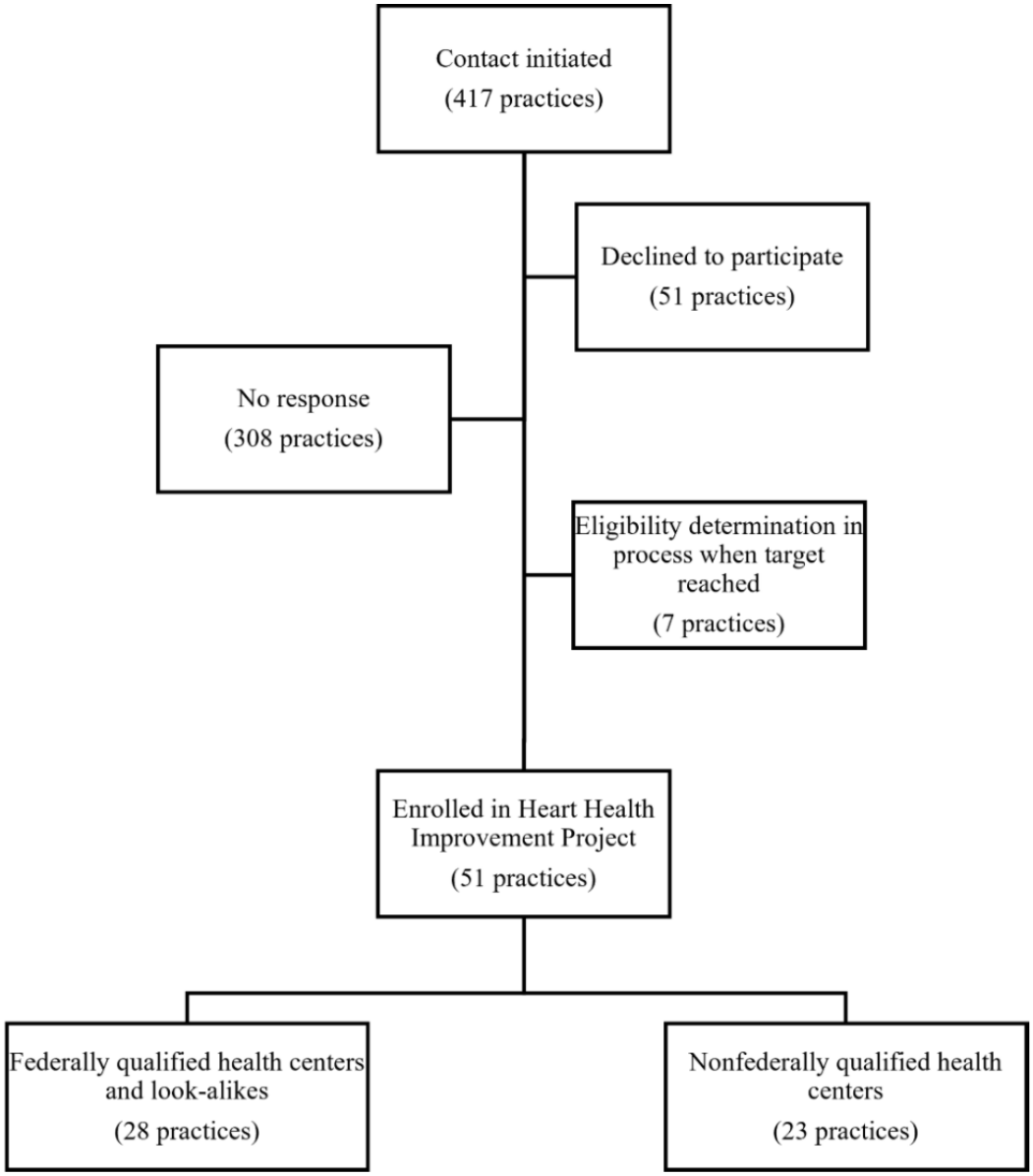

HHIP Overview

Approach to QI

The HHIP uses a multipronged approach to QI, including practice facilitation and technical assistance, on-site and e-learning, and improvement through data transparency. These strategies, described in further detail in this paper, were selected by the study investigators based on a review of patient-centered outcomes research. The HHIP is designed to build internal QI capacity and increase the implementation of evidence-based guideline recommendations for screening and treatment of cardiovascular risk factors. This project builds on the strengths

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and the previous and ongoing efforts of all Cooperative partners, such as (1) the Southeastern Collaboration to Improve Blood Pressure, a recent trial assessing the use of practice facilitation to improve BP control among adults with hypertension in primary care (UAB) [15]; (2) the Blood Pressure Self-Management Initiative (Alabama Department of Public Health); (3) expertise in promotion of best practices for pharmacotherapy (Auburn); as well as (4) ongoing QI initiatives in primary care (QSource and APHCA).

Study Design

The HHIP was initially designed as a "stepped wedge" in stages with groups of 10 practices randomly selected to begin the intervention each quarter. However, delays in practice recruitment did not allow for the randomization of practices by quarter, so we instead used a nonrandomized, pre-post design with primary care clinics as the unit of observation. Despite the design change, quantitative analysis of the effect of HHIP on measures of hypertension and smoking cessation will follow the general framework for the analysis of a stepped-wedge study. This includes using preintervention data from all practices to estimate secular trends—changes expected to occur without intervention, as well as estimating effects from the HHIP, and whether there is an enduring change in outcomes after the year of HHIP activities beyond what would be expected due to secular trends. Models will include random effects for sites and for patients to account for multiple patients nested within sites and the potential for multiple observations per patient. Secondary clinic-level analyses will use data aggregated each quarter by clinic.

Practice Recruitment

The Cooperative used several methods of recruitment including existing organization communication channels to recruit primary care practices for inclusion in the HHIP. First, we reached out to clinics in existing networks through the Alabama Practice-Based Research Network, the APHCA, and QSource, leveraging existing relationships for introductions. In addition, we created flyers and promotional materials to send to clinics through email and fax. We also conducted Google searches for clinics in designated areas to find additional practices to recruit while we were visiting enrolled sites. To ensure we reached a broad range of clinics, we aimed for at least 50% of our clinics to be Federally Qualified Health Centers (FQHCs) or look-alikes, which have an important role in increasing access to primary care in medically underserved areas, including rural communities [16,17].

For each practice that expressed interest in participation, we conducted an informational recruitment meeting to further explain the HHIP objectives and procedures. During this initial meeting, interested clinics completed readiness assessments using standardized questionnaires [18,19] and signed an informal letter of agreement to participate in the project. Following the initial meeting, the questionnaire scores and clinic information (eg, anecdotal patient demographics and clinic estimation of BP control rate) were shared with the Cooperative, and practices were voted on to be enrolled in the project. Once a practice was enrolled, a lead practice facilitator was assigned.

Practice facilitators scheduled and conducted a kick-off meeting for the practices that were enrolled in the HHIP. This kick-off meeting served as the start of the intervention where practices received additional information about practice facilitation, completed an "About Your Practice" survey, and initiated processes required to extract baseline data. Enrolled practices were also asked to identify a practice champion as part of the enrollment process. Practice champions are integral to the successful adoption of innovations within a practice, defined as "individuals who dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the intervention may provoke in an organization" [20]. The practice champion worked with the practice facilitator to schedule monthly touchpoints throughout the intervention period to implement and track the progress of quarterly QI activities. Clinics were compensated US $1500 for their time and participation in the intervention.

Intervention

Practice Facilitation

The HHIP implementation strategies included practice facilitation and technical assistance, on-site and e-learning, and improvement through data transparency, with practice facilitation serving as the foundation of the intervention. Practice facilitation is a flexible, tailored service aimed at assisting practices in implementing evidence-based care guidelines, thereby improving care quality and patient outcomes. Practice facilitators enable rather than direct QI activities, thereby building a practice's internal capacity for adapting clinical evidence to their practice context [21].

The practice facilitation intervention is built on the key driver model for care implementation [22] that was developed as part of the Improving Performance in Practice initiative and whose drivers focus on 4 components of Wagner's Chronic Care Model—delivery system design, decision support, clinical information systems, and self-management support [22-24]. As shown in Table 1, the facilitator guides the practices in targeting these key drivers to encourage practice-wide improvements in using registries, delivering planned care, using standardized care processes, and providing effective self-management support.

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Table 1. Key drivers and relationship to chronic care model.

Key drivers	Examples of QI[a] activities	Chronic care model components
Implement registry	• Determine staff workflow to support registry • Populate registry • Maintain registry	• Clinical information systems • Delivery system design
Use templates for planned care	• Determine staff workflow to support template • Use template with all patients • Update registry each time template is used and monitor its use	• Decision support • Delivery system design
Employ protocols	• Select and customize evidence-based protocols • Determine staff workflow to support protocol • Use protocol with all patients • Monitor use of protocols	• Decision support • Delivery system design
Provide self-management support	• Select patient education materials • Determine staff workflow to support patient self-management • Collaboratively set goals with patients • Monitor patient progress toward goals • Link patients with community resources	• Self-management support • Community resources

[a]QI: quality improvement.

The HHIP practice facilitators are used by organizations in the ALCC. Each of the facilitators received dedicated training delivered by HealthTeamWorks and the Agency for Healthcare Research and Quality Primary Care Practice Facilitation Curriculum to support practices to implement a change package [25]. The practice facilitators work with practices over a 1-year period, with at least monthly in-person (or by teleconference if necessary) visits and biweekly teleconferences with the practice champion and, additionally or instead, the QI team. At the start of the intervention, practices complete a self-assessment to measure quality indicators and identify the current level of QI implementation using the Key Drivers Implementation Scale (Multimedia Appendix 1) [26]. The self-assessments provide baseline data on practice performance as well as baseline data on practice capacity for QI (eg, generating reliable, valid performance data; seeking and integrating evidence-based guidelines into patient care; creating patient panels and using continuous QI processes involving care teams to identify and assist at-risk patients, and engaging patients and families to provide effective self-management support).

Following baseline assessments, practice facilitators guide practices to implement QI activities designed to achieve progress in each key driver area. These include activities such as using the electronic health record (EHR) to enable data collection, creating registries to track the implementation of evidence-based care, constructing a QI dashboard to enable ongoing reporting of process and outcome measures, establishing team-based care processes, and engaging patients and families to optimize their self-management goals. Practice facilitators encourage practices to conduct quarterly QI initiatives, beginning with a focus on hypertension control and moving to tobacco use cessation in at least 1 subsequent quarter.

e-Learning

The ALCC also uses e-learning to provide pragmatic guidance on cardiovascular risk reduction in primary care. As approved by Continuing Medical Education (UAB) and Continuing Pharmacy Education (Auburn) providers with access to cardiovascular experts, we offer accredited hours through asynchronous e-learning sessions for physicians and midlevel providers. Based on initial feedback regarding sessions, we also created sessions specific for staff members. Working closely with the ALCC, the UAB Division of Continuing Medical Education designed an initiative that is grounded in blended learning theory and creates a learning environment that fosters the adoption of new practices. The educational intervention focuses on topics critical to accurate patient risk assessment and appropriate guideline-concordant treatment of individuals at risk for CVD. Initial topics were identified by the Cooperative's Steering Committee.

A provider needs assessment was conducted with attendees at an Alabama Academy of Family Physicians meeting, which further informed the educational topics, preferred mode of delivery, as well as insights into what resources would be helpful for providers and their patients. Feedback from this survey was used in the development of a website (*Connecting2Health* website) where providers and patients can go to seek educational content and access community resources for cardiometabolic disease management and prevention within the state of Alabama.

We anticipate that providers who engage in these educational interventions will attain improved knowledge and skills in the effective use of risk assessment tools and care guidelines. Webinars and training modules are recorded, archived, and made available online as enduring continuing education materials.

Data Transparency

To promote data transparency, practice facilitators work with each practice to extract clinical quality measures. The practice facilitators are well-versed in the clinical aspects of cardiovascular care, as well as the technical aspects of an EHR and data flow. They work with each practice independently to establish the best ways to extract the necessary clinical data without creating a new burden to providers or staff.

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The ALCC contracted with the Consortium for Southeast Healthcare Quality (COSEHQ) to produce practice-level dashboards using data extracted from each practice's EHR, which allows clinics to review their progress toward improving BP control and tobacco use screening and cessation intervention throughout the intervention period. Practice facilitators review the practice dashboards with practice staff as an additional method of tracking progress across the intervention period.

Clinical Outcomes

Outcomes of the study were selected based on their associations with patient-level benefit (ie, cardiovascular risk reduction) and avoiding undue burden for practices or providers to measure (Table 2). BP-related outcomes included documentation of hypertension in the EHR when a patient has 2 or more readings with a systolic BP≥130 mm Hg or a diastolic BP≥80 mm Hg, which aligns with the 2017 American College of Cardiology and American Heart Association BP guideline recommendation for hypertension diagnosis [27]. Given the high cardiovascular risk associated with stage II hypertension (systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) and the prevalence of stage II hypertension in Alabama, the main outcome for intervention efficacy is BP control among adults with hypertension to <140/90 mm Hg. This is also the BP target used in the Centers for Medicare & Medicaid Services (CMS) 165 and National Quality Forum (NQF) 0018 clinical quality measure. Tobacco use outcomes were available through the EHR and included tobacco use screening and cessation intervention. The combined measure of tobacco use screening and cessation intervention aligns with the CMS 138 and NQF 0028 clinical quality measures.

Table 2. Heart Health Improvement Project primary blood pressure and smoking cessation clinical outcomes.

Outcome	Description	Practice target
Hypertension control	Number of patients between 18 and 85 years of age diagnosed with hypertension, and a BP<140/90 mm Hg (consistent with controlled stage II hypertension)	• ≥70% of patients diagnosed with hypertension who have controlled stage II hypertension (BP<140/90 mm Hg)
Tobacco use screening	All patients ≥18 years of age have smoking status updated within past 2 years	• ≥75% of patients have smoking status documented per practice • Rates of current smokers • Rates of former smokers who relapse • Rates of former and never smokers • Rates of secondary smoking exposure
Tobacco use counseling	Use of 4 Rs[a] to improve rates of smoking cessation	• EHR[b] documentation of smoking cessation counseling, referral to AL Quitline, medication documentation (including over-the-counter medication)
Tobacco use screening and counseling	Percentage of patients aged 18 years and older who were screened for tobacco use one or more times within 24 months and who received cessation counseling intervention if identified as a tobacco user	• 5-10% increase from baseline

[a]4 Rs: relevance, risks, rewards, roadblocks.

[b]EHR: electronic health record.

Measurement

Data on BP and tobacco use are available quarterly from the practice EHRs and retrospective EHR extraction provides preintervention data for all practices. In addition to clinical parameters, we collect data on age, race, and gender, as well as insurance status as available, to assess the impact of our program for these specific subgroups.

Statistical Analysis

The primary model for fixed effects without adjustment for any covariates will have the following structure:

$$Y=\beta 0+\beta 1(time)+\beta 2(HHIP\ exposure)+\beta 3(time\ after\ HHIP)$$

For the primary dichotomous outcomes of hypertension control and documentation of smoking status, Y will represent the log-odds of the binary outcome. In the model "time" will be considered as "calendar time" measured in quarters from the earliest quarter of baseline data and β_1 will be the estimate of the secular trend. "HHIP exposure" will similarly measure the cumulative number of quarters the practice was exposed to HHIP, ranging from 0 in the baseline period, to 4 after a year of HHIP and β_2 will be the estimate of the quarterly change due to HHIP. "Time after HHIP" will similarly quantify the period of follow-up after the year of HHIP and β_3 will be the estimate for any enduring effect of HHIP on rates after the intervention beyond what could be attributed to secular trends. A positive β_3 would indicate that outcomes continued to increase faster among practices after the HHIP intervention than would have been expected and would suggest a durable effect, while an estimate of β_2 that is not significantly different from 0 would

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be interpreted as practices returning to the change expected by secular trends. In the general framework, the effect due to HHIP will be considered statistically significant if the *P* value of the model coefficient is <.05.

Before analysis, we will consider smoothed scatter plots of outcomes over time and HHIP exposure; if any trends appear to be importantly nonlinear, we will consider these as categorical to most appropriately model the data. If this is the case, the overall test of the main hypothesis will be the significance of the coefficient for the full-year exposure to HHIP. The general model can be further adjusted for patient-level characteristics (eg, age, race, and gender) and practice-level characteristics (eg, urban vs rural, FQHC vs non-FQHC, Consolidated Framework for Intervention Research [CFIR] scores, and other implementation-related measures) and stratified analyses can be run using subsets of the data. Differential effects by subgroups (eg, race, gender, or practice types) will be tested using interaction terms.

Power and Sample Size Considerations

Statistical power was assessed using simulation methods based on the outcome of hypertension control. Briefly, data was simulated for 50 practices, with randomly generated practice-level baseline hypertension control rates of 50% with an SD of 4%. Secular trends were similarly generated for each practice with a mean yearly decrease of 1% with an SD of 0.05%. We assumed a mean effect due to HHIP of 2% per year (0.5% per quarter) assigned randomly with an SD of 1%. Simulations included a range of residual HHIP effects ranging from 0.5% to 1.5%. Simulated datasets began with creating data for 10,000 patients per practice using generating baseline status at random, then iterated forward with each practice's assigned secular trends and intervention effects, followed by the addition of random perturbations to model the high variability of BP measurements leading to changes in control status at each visit. For multiple iterations, 50 practices were randomly selected, along with a reduced sample of patients equal to 5 times the target sample size to reflect the fact that most patients will not have a visit in a given quarter (eg, if we expect to have data for 200 patients per practice per quarter, the data had an average of 1000 patients per practice). Finally, for each iteration, a random sample was drawn to reflect the mean of 200 patients per quarter. The mixed models were run on each iteration and power was estimated as the proportion of iterations in which coefficients were significant at the *P*<.05 level. We expect there to be >500 per patient per quarter, which would reflect <50 patients per week at a practice with a single practitioner so these power estimates should be highly conservative. Data from the Physicians Foundation in 2018 found that the average doctor sees 20 patients per day, so we could indeed expect >400 patients with hypertension per quarter for each physician [28]. Under these assumptions, there was >95% power for the HHIP effect with as few as 100 patients per site, which further suggests that we will have adequate power for analyses of patient subgroups analyses. Allowing for 400 patients per site provided 100% power for the secular trends and HHIP effect as well as 90% power for the 1% yearly residual increase from HHIP during follow-up. For analyses restricted to subgroups of practices, including only 25 practices with 400 patients per practice left >90% power for the secular trend and HHIP effect, but reduced power to 64% for the residual effect of HHIP during follow-up. Finally, in simulations of comparisons between subgroups (eg, race or gender), 50 practices with 400 patients per quarter per practice provide >80% power to detect a difference in yearly rates of 1.5% between groups (2% vs 3.5%) using a statistical interaction indicating that we will have adequate power for subgroup analyses. The outcomes related to smoking (principally documentation of smoking status) can be expected to have higher power based on higher baseline rates and greater control of the physicians (leading to lower variability in patient-level outcomes).

Evaluation of Implementation

The implementation outcomes evaluation will be guided by Proctor's Framework for Implementation Outcomes [29], and we will assess implementation using the CFIR [21,30]. Our proposed evaluation of the implementation of the HHIP will be guided by the tenets of realist evaluation. The realist evaluation approach recognizes that there are many interwoven factors operating at different levels within a setting, making this evaluation method a better approach to complex interventions than a more traditional, noncontextual cause and effect evaluation approach [31].

Realist evaluation investigates the "context-mechanisms-outcomes pattern configuration." Realist evaluation does not just consider outcomes to determine if an intervention is successful but analyzes the outcomes to discover if the speculated mechanism or context theories are confirmed. The overarching HHIP evaluation questions are: What works, for whom, in what way, to what extent, in what contexts, and how? To better understand context-specific mechanisms that may influence the successful implementation of HHIP, we will draw on a menu of constructs from the CFIR across 5 domains [21,30]. These domains include the (1) intervention characteristics, or aspects of the intervention that may have a positive or negative impact on implementation success, (2) outer setting, which includes the external forces that may influence successful implementation, (3) inner setting, which includes the organizational characteristics of the implementing organization, (4) characteristics of the individuals, including the knowledge, attitudes, beliefs, and personal attributes of those implementing, and (5) process of implementation, which refers to the stages of implementation and participation of key influencers in each of those stages.

Of the 39 constructs described in the CFIR, our evaluation will focus on the 23 constructs that are most relevant to this project (Table 3).

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Table 3. Consolidated Framework for Implementation Research (CFIR) domains and constructs to be evaluated.

Intervention	Outer setting	Inner setting	Characteristics of individuals	Process

• Complexity	• External policies	• Implementation
		  • Workflow
		  • Compatibility
		  • Learning climate
		  • Resistance to change
			• Knowledge and beliefs about the intervention	• Planning

• Relative advantage	• Peer pressure	• Leadership support	• Self-efficacy	• Reflecting and evaluating
• Strength of adaptability	• Patient needs • Cosmopolitanism	• Resources	• Individuals to deliver the intervention • Identification with the organization • Individual stage of change	• Champions • Opinion leaders • External change agents

Before implementation at each clinic, we administer the Organizational Readiness for Implementing Change (ORIC) survey, a psychometrically-validated instrument developed by Shea and colleagues [18], based on the constructs of Weiner's Organizational Theory for Implementation Effectiveness [32]. At baseline and again at the conclusion of the HHIP, the evaluation team will survey the participating chief medical officer, a senior practice leader, or the practice champion of each clinic using the 14-item Change Process Capability Questionnaire (CPCQ) to assess a practice's capacity to improve care using QI strategies [19].

Drawing on Proctor's Conceptual Framework for Implementation Outcomes, we will evaluate the implementation of the HHIP. Proctor et al [29] describe 8 implementation outcomes, including acceptability, appropriateness, feasibility, costs, adoption, fidelity, penetration, and sustainability. We will address the acceptability, appropriateness, feasibility, and sustainability of the HHIP with validated questionnaires [33,34]. Fidelity and penetration will be assessed with administrative data collected as part of delivering the intervention (eg, number and duration of contacts with clinic). In addition, we will use semistructured interviews, approximately 30 minutes in duration and conducted through Zoom (Zoom Communications, Inc), with clinic staff members and providers from 8 to 10 clinics. Guided by the CFIR, the interviews will focus on the context for implementing the HHIP. Table 4 describes the outcomes that we will measure and our method or measurement.

Table 4. Implementation outcomes and methods of measurement.

Outcome	Definition	Measure
Acceptability	Perception that a given innovation is agreeable, palatable, or satisfactory	Acceptability of Intervention Measure (AIM): 4-item validated instrument
Appropriateness	The perceived fit, relevance, or compatibility of the evidence-based practice for a given practice setting and that it well addresses a particular problem	Intervention Appropriateness Measure (IAM): 4-item validated instrument
Feasibility	The extent to which an innovation can be successfully used given the setting	Feasibility of Intervention Measure (FIM): 4-item validated instrument
Adoption	The intention to employ an innovation of evidence-based practice	Measured at the provider level, the number of clinicians who intend to employ the innovation
Fidelity	The degree to which an intervention was implemented as it was prescribed	Measured at the provider level, adherence to the protocol including dosage and delivery
Penetration	The integration of a practice within a service setting	The number of eligible providers and staff who use an innovation divided by the number of providers and staff eligible to do so
Sustainability	The extent to which a newly implemented innovation becomes maintained or institutionalized in a service setting	Clinical Sustainment Assessment Tool (CSAT): 47 items across 7 domains

Ethical Considerations

The study was approved by the Institutional Review Board at UAB (300006358 and 300007230). Each clinic entered into a business associate agreement with COSEHQ.

Results

HHIP Practice Recruitment

Practice recruitment took place between April 2021 and October 2022. We contacted 417 primary care practices in Alabama

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(Figure 2). Of those, 51 practices declined to participate, and an additional 308 practices did not respond to our outreach. We excluded 7 practices that were in the process of having their eligibility determined at the time we reached our target enrollment. We enrolled 51 practices into the HHIP, including 28 FQHCs or look-alikes. Practices were geographically distributed across the state (Figure 3).

Figure 3. Location of primary care practices participating in the Heart Health Improvement Project. Pins indicate practice locations. Counties shaded in blue are classified as rural by the Alabama Rural Health Association.

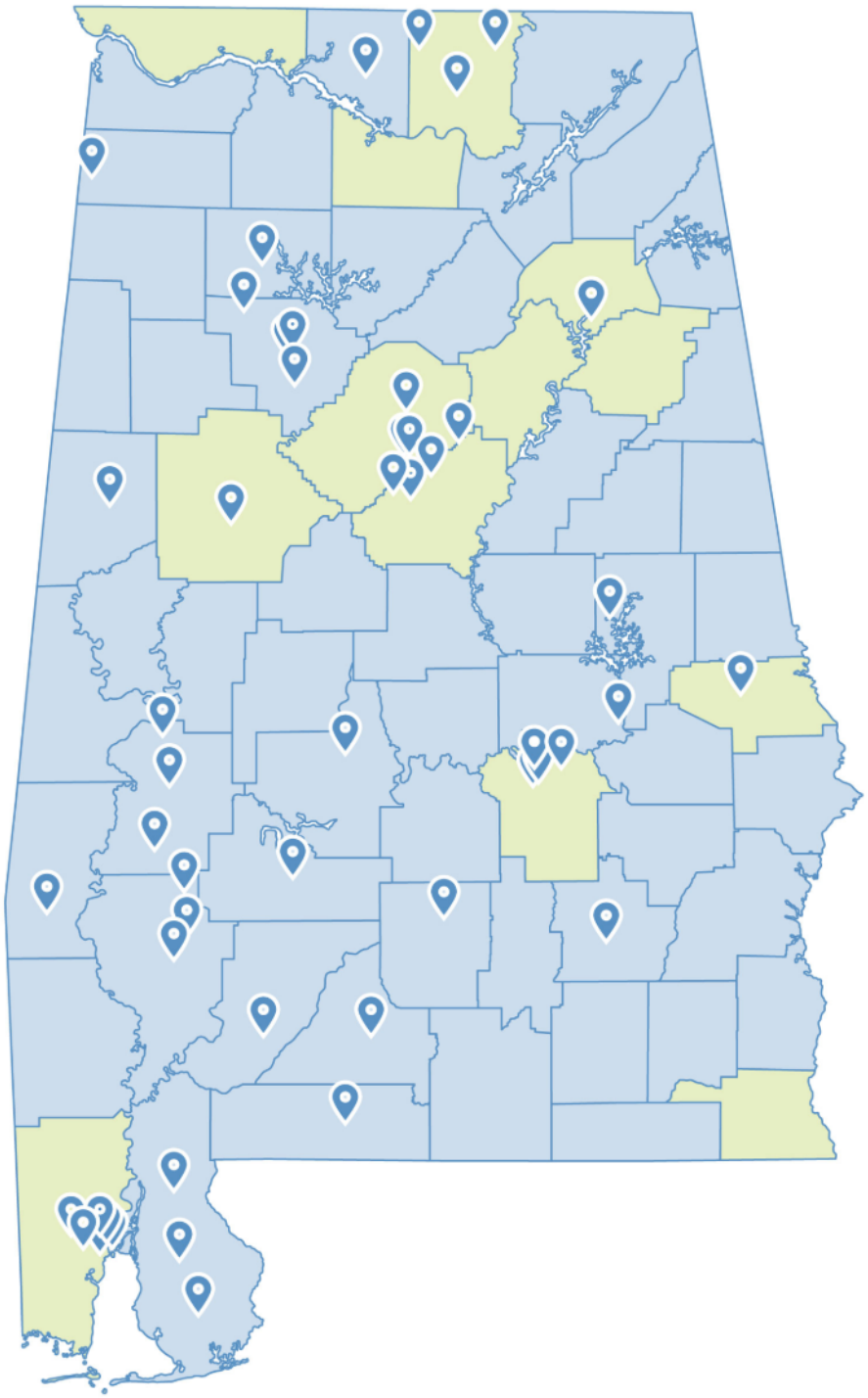

Of the 51 enrolled practices, 47 implemented the HHIP. Clinics that did not implement the HHIP included those that closed, lost a provider, or did not have sufficient staff time to dedicate to the intervention.

HHIP Practice Characteristics

Among HHIP practices that completed baseline practice characteristics, 24% (11/45) were solo practices, while 62%

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(28/45) had 1 to 5 clinicians, and 13% (6/45) had 6 or more clinicians (Table 5). The median number of patient visits per year was 5819 (IQR 3707.3-8630.5). Practices had been in operation for a mean of 19.2 (range 1-50) years. Half (23/46, 50%) were certified as Patient-Centered Medical Homes. Overall, 72% (33/46) of practices share patient information and 78% (36/46) have a designated quality reporter. Overall, 76% (34/45) were reporting CMS 165 for control of high BP, while 44% (20/25) were reporting CMS 138 for tobacco use screening and cessation intervention.

Table 5. Heart Health Improvement Project practice characteristics.

Characteristics	Summary statistics
Practice characteristics	
Practice size, n/N (%)	
Solo practice	11/45 (24)
2-5 clinicians	28/45 (62)
≥6 clinicians	6/45 (13)
Practice ownership—FQHC[a] or look-alike, n/N (%)	28/47 (60)
Single specialty, n/N (%)	24/42 (57)
Years of operation, mean (SD; range)	19.2 (13.0; 1-50)
Part of a network, n/N (%)	26/46 (57)
Number of visits per year, median (IQR)	5819 (3707.3-8630.5)
NCQA[b] certified PCMH[c], n/N (%)	23/46 (50)
Share patient health information, n/N (%)	33/46 (72)
Have a quality reporter for the practice, n/N (%)	36/46 (78)
Report CMS[d] 165[e], n/N (%)	34/45 (76)
Report CMS 138[f], n/N (%)	20/45 (44)
Baseline measures[g], %	
Blood pressure control rate	49.6
Tobacco screening rate	81.8
Tobacco cessation intervention rate	71.4
Tobacco screening and cessation intervention rate	67.4
Baseline questionnaires, mean (SD)	
Change process capability questionnaire	11.6 (14.3)
Organizational readiness for implementing change	4.2 (0.84)

[a]FQHC: Federally Qualified Health Center.

[b]NCQA: National Committee for Quality Assurance.

[c]PCMH: Patient Centered Medical Home.

[d]CMS: Centers for Medicare & Medicaid Services.

[e]CMS 165: controlling high blood pressure.

[f]CMS 138: tobacco use screening and cessation intervention.

[g]Baseline measures were calculated using data collected from January 1, 2021, to the start of the intervention period. Data on blood pressure control are from 46 practices and data on tobacco screening and cessation intervention are from 44 clinics.

The results shown above do not encompass all currently enrolled practices, only those who have completed the baseline practice characteristics survey measures.

Baseline measures of BP control and tobacco use screening and cessation intervention were calculated using data collected from January 1, 2021, to the start of the intervention period. At baseline, the mean BP control rate was 49.6%. The mean tobacco use screening rate was 81.8% and the tobacco use cessation intervention rate was 71.4%; the rate of tobacco screening and cessation intervention was 67.4%. The mean CPCQ score was 11.6 (SD 14.3) and the median ORIC score was 4.2 (SD 0.84).

Discussion

Expected Findings

The ALCC represents a unique partnership of clinical, public health, and academic institutions that have come together to

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support primary care practices to reduce cardiovascular risk and disparities by race or ethnicity and rurality that persist in the state. The ALCC's HHIP is a QI project that aims to improve the diagnosis and control of hypertension, documentation of tobacco use, and rate of tobacco cessation intervention in 47 primary care practices. We hypothesize that rates of BP control among adults with hypertension and tobacco use screening and cessation intervention will improve as a result of the HHIP, beyond what would be expected by secular trends.

Strengths of the HHIP include the multidisciplinary partnerships and multipronged approach to QI. Using evidence-based strategies, such as practice facilitation, on-site and e-learning, and data transparency, the HHIP intervention is designed to increase practices' internal QI capacity and promote sustainability. The practice facilitation intervention was designed using the key driver model for care implementation and is delivered by trained facilitators. In addition, there is a robust plan to evaluate implementation outcomes. The HHIP clinics include FQHCs and look-alikes, with a number of them in rural areas. Including these clinics in the HHIP is essential for reducing disparities in the management of cardiovascular risk factors.

Limitations of the HHIP included delays in recruiting clinics, in part due to the COVID-19 pandemic, which forced a change in design from a true randomized stepped wedge to a pre-post trial design. Variability in staffing across clinics also means that capacity for QI initiatives will vary, which has implications for intervention implementation as well as sustainability. During the HHIP, clinics experienced staffing turnover, including provider changes or retirements and changes in practice champions. Finally, availability of data from the EHRs is also variable since clinics have different EHRs, and even when the EHR is the same, clinics may have purchased limited packages.

Conclusions

If successful, the ALCC and HHIP may improve the implementation of evidence-based guidelines and, subsequently, cardiovascular health and health equity in the state of Alabama. The lessons learned can inform future primary care initiatives to improve cardiovascular health in the state of Alabama, as well as other state-based initiatives.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Data curation: JR
Formal analysis: JR
Funding acquisition: EAJ, ALC
Investigation: DH, KAS, LH, TH, SP, DR, MC, SAC, EAJ, ALC
Methodology: DH, KAS, LH, JR, TH, EAJ, ALC
Project administration: DH, TH, SP, EAJ, ALC
Supervision: EAJ, ALC
Writing – original draft: KF, DH, KAS, LH, JR, TH, EAJ, ALC
Writing – review and editing: KF, DH, KAS, LH, JR, TH, SP, SAC, EAJ, ALC

Conflicts of Interest

None declared.

Multimedia Appendix 1
Key Drivers Implementation Scale.
[DOCX File , 19 KB - resprot_v13i1e63685_app1.docx]

Multimedia Appendix 2
Peer review report from the AHRQ Special Emphasis Panel - Agency for Healthcare Research and Quality (USA).
[PDF File (Adobe PDF File), 104 KB - resprot_v13i1e63685_app2.pdf]

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Abbreviations

ALCC: Alabama Cardiovascular Cooperative
APHCA: Alabama Primary Health Care Association
BP: blood pressure
CMS: Centers for Medicare & Medicaid Services
CFIR: Consolidated Framework for Intervention Research
COSEHQ: Consortium for Southeast Healthcare Quality
CPCQ: Change Process Capability Questionnaire
CVD: cardiovascular disease
EHR: electronic health record
FQHC: Federally Qualified Health Centers
HHIP: Heart Health Improvement Project
NQF: National Quality Forum
ORIC: Organizational Readiness for Implementing Change
QI: quality improvement
UAB: University of Alabama at Birmingham

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Protocol

The Use of Medical Services for Low-Acuity Emergency Cases in Germany: Protocol for a Multicenter Observational Pilot Study

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Abstract

Background: The increasing number of requests for help for acutely ill patients and their management is a major problem in the health systems of many countries, but especially in Germany. Rescue coordination centers and ambulances in Germany are increasingly overloaded. As a result, rides as a part of rescue operations have been increasing in length for years, yet a relevant proportion of these operations represent low-acuity calls (LACs). The basic objective of this pilot study is the quantitative analysis of the potential misuse of requests to the rescue control center. Indications for alternative treatment options and how to handle these treatment options in nonacute, non–life-threatening health conditions, such as minor injuries or minor infectious diseases, will be assessed. The identification of these LACs is vital in order to prevent health care resources in emergency medical care becoming inadequate.

Objective: The overarching goal of this study is to determine the percentage of unnecessary rescue missions on site and subsequently to obtain an impression of the paramedics' assessment of alternative treatment options or alternative methods of rescue transportation.

Methods: This will be an exploratory, noninterventional, cross-sectional study with a quantitative approach. The study is multicentric, with 21 ambulances in 12 different locations. The data for this study were collected via a questionnaire, newly developed for this study, for rescue personnel. Additionally, secondary data from the responsible control center will be linked and processed in an initial descriptive analysis. This descriptive analysis will form the basis for a subsequent variance analysis.

Results: Data collection started as projected on September 18, 2023, and was ongoing until end of November 2023. We expect the documentation of several thousand rescue operations. We expect the following study results: (1) many unnecessary rescue operations, (2) immediate on-site assessment of correct care and treatment, and (3) patients' reasons for calling a rescue coordination center.

Conclusions: To our knowledge, this is the first observational study in which acute rescue operations are recorded on site. The focus of this study is on the trained paramedics' assessment of whether rescue operations are necessary or not. Additionally, alternative treatments, such as out-of-hours care service or primary care service, are shown for each individual case. The study also intends to cover the question of which factors are relevant and statistically significantly connected to the misuse of ambulances.

Trial Registration: German Register for Clinical Studies (Deutsches Register für Klinische Studien) DRKS00032510; https://drks.de/search/en/trial/DRKS00032510

International Registered Report Identifier (IRRID): DERR1-10.2196/54002

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KEYWORDS

emergency medical service; EMS; ambulance misuse; low-acuity calls; emergency department; paramedics; rescue operations

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Introduction

The number of outpatient medical treatment cases in Germany has been showing an upward trend for years [1]. Additionally, the number of rescue operations in emergency medical service (EMS) shows a continuous annual increase of about 5%, amounting to almost 16.5 million emergency ambulance and emergency missions in the 2016-2017 observation period [2-5]. This increase can also be observed in the number of rescue operations performed by the ambulance service and is similar in most European countries, as well as in the United States and Australia [6-9]. The steady increase can only partly be accounted for by demographic developments or geographical peculiarities [10,11]. Rather, a not inconsiderable proportion of EMS operations and the resulting transports to an emergency department (ED) do not seem to be indicated from a medical point of view [12-14].

In Germany, patients with minor ailments should generally be treated in medical on-call service centers out of hours when their own general practitioner (GP) is not available. GPs and specialists are obliged to work in medical on-call services; in some regions this is only out of hours, while in other regions it is 24 hours, 7 days a week. The medical on-call services are regulated by the Association of Statutory Health Insurance Physicians, that is, they are self-administered. Everybody, whether seriously or only slightly ill, can consult the ED as well as clinics and the EMS. EDs are also responsible for, preferably, emergency care but also for all other acute patient concerns. [15]. In addition to a lack of professional assessment on the part of those seeking help and ignorance of the responsibilities of the existing emergency and acute patient care structures [16,17], a variety of factors can lead to the EMS and ambulance service being alerted in nonurgent cases. Apart from the possibility of low-threshold and timely care by the ambulance service, these also include the patient-specific perception of their urgency as well as a personal need for safety [18]. Other circumstances that occasionally lead to avoidable requests for ambulance service include nursing home patients with ambulatory care–sensitive conditions, older people with many comorbidities not receiving timely outpatient consultation appointments, and people with mental health problems or somatoform disorders requiring psychological care [19-25].

The increased and undifferentiated use of the EMS means rising costs at the expense of social insurance [26] and a higher workload for emergency medical staff, who are exposed to an extremely high risk of burnout [27,28]. This also leads to overcrowded EDs and therefore to great difficulties treating patients efficiently and at a high quality outside of regular and scheduled consultations [29,30]. Besides this, the response time of the EMS tends to be more and more extended, and statutory provisions consequently cannot be observed [31,32]. Serious doubts concerning the capability of the EMS and the emergency medical system in general are being seen more and more in public debate in recent years.

German policy makers are now seriously addressing this issue after making some local short-term changes; for example, alert keywords have been restricted for ambulances on call. Recently, a German government commission proposed comprehensive modifications to the EMS. These call for extending the EMS's entitlement to services and fees for care and treatment of minor ailments on site, not just transportation (as before). The overall aim is to reorganize and expand the existing components of the EMS [33].

The aim of this prospective cross-sectional study is the quantitative analysis of unnecessary ambulance missions, in addition to the examination of indications for alternative care options in nonacute life-threatening situations instead of transport by the ambulance service to a hospital ED. Alternative health care options should be discussed to help improve care for acute patients and reduce the misuse of ambulances.

Methods

Aim

This study intends to quantify the fraction of low-acuity calls (LACs) in ambulance operations, focusing on alternative treatment options. For this purpose, the trial will evaluate how often EMS personnel rate a different, usually ambulatory treatment as being more suitable because a patient has a non–life-threatening health condition that does not require any urgent medical intervention. In addition, this study aims to identify and quantify the reasons why patients without a life-threatening medical condition or other medical indications are brought to an emergency room by ambulance instead of being transferred to a more suitable location for treatment. Therefore, the 2 main questions the study plans to cover are, first, what kind of treatment patients of the EMS need, if not emergency treatment and urgent conveyance to a hospital, and second, why patients may not receive adequate medical care. A quantitative approach is required to obtain an indication of the dimensions of these individual aspects, as there is usually no standardized documentation by the control center that goes beyond the point of "patient was taken to hospital/patient was referred to GP/refusal of transport/no patient was found," which represents only part of the actual situation. Furthermore, the study will collect and analyze data on operational statistics to determine if conditions like operation time, day of the week, accessibility to a GP, priority, and content of the alert (as set by the dispatcher in the control center) have an impact on the frequency of LAC operations. We will also evaluate socioeconomic factors, such as age and gender of the patient, as well as the impact of the operation area.

Design

The key feature of this exploratory, noninterventional, cross-sectional study is a web-based questionnaire (Table 1) for tablets or smartphones. In the first phase, each individual question on the web-based questionnaire was reviewed by an expert panel at the Department of General Medicine at Heidelberg University Hospital, and in the second phase, the questions were discussed with the heads of operations at the rescue coordination centers, as well as with selected paramedics. The focus was on the feasibility of this pilot study. When this study is rolled out (at large scale) there also will be analyses of interrater reliability.

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Table 1. Questionnaire for ambulance crews on emergency cases.

Item	Content
Operation number	• (Free text)
Patient gender	• Male • Female • Gender-diverse
Patient age group (years)	• 18-24 • 25-39 • 40-59 • 60-64 • 65-79 • ≥80
Operation time on a weekend day or holiday[a]	• Yes/no
Operation time during main opening hours of general practitioner care[b]	• Yes/no
Classification of operation area (number of inhabitants)	• Metropolitan (>100,000) • Urban (30,000-100,000) • Suburban (10,000-30,000) • Rural (<10,000)
Working diagnosis	• (Free text)
Treatment or procedure performed (multiple choices possible)	• Being conveyed to a hospital • Referral to a general practitioner or medical on-call service • Continuance at home • Patient refused being conveyed • Therapeutic measures performed • (Free text)
Appropriate treatment or procedure (multiple choices possible; no choice possible)	• Being conveyed to a hospital autonomously • Calling on the medical on-call service autonomously • Consulting the general practitioner for further care • Exclusively counseling • Counseling by telephone possible • Social caretakership • Being conveyed by a patient transport ambulance • (Free text)
Reasons for being conveyed to a hospital without medical indication (multiple choices possible; no choice possible)	• Missed transportation opportunity by patient or relatives • Patient insists on being conveyed by ambulance • Social indication • House call by general practitioner or medical on-call service indicated but not provided • Medical on-call service not favored by patient • Insecurity of team leader • Language barrier • (Free text)

[a]As defined by the state in which the operation took place.

[b]Main opening hours were defined as Monday, Tuesday, and Thursday from 7 AM to 7 PM, and Wednesday and Friday from 7 AM to 2 PM.

The members of the expert panel determined which crucial dimensions of medical emergency treatments will be queried, including (1) working diagnosis, which is the assessment made on site by the ambulance crew with consideration of diagnostics that can be carried out preclinically; (2) procedures, including the ambulance crew's approach to counseling, treatment, patient transport, and referral to other caregivers; (3) adequacy of care, that is, the assessment of the most suitable form of care, which is carried out by the ambulance crew based on the situation on site; and (4) problems that arise, that is, the evaluation of possible reasons why patients are not directed to the form of care that has been assessed as being most suitable.

The training of the paramedics consists of 5 vital elements. The important questions for assessing their concerns about possible rescue operations (Textbox 1) are described in in-person lectures. The five *W* questions are integrated in the questionnaire and special training is provided.

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Textbox 1. W questions and example cases.

***W* questions**

- Which typical use cases are presented?
- Who called? (Age and gender should be documented)
- Which concerns were stated? (Assessment of the emergency is an overarching goal of the study)
- When did the concerns occur? (Duration and assessment of the acute situation has to be included in the consideration)
- Where is the location? (Infrastructure, social environment, etc., should be documented)

Examples of possible rescue operation cases integrated into the training

- An ambulance is alerted with high priority because of high blood pressure and vertigo. On site, the crew can rule out current life-threatening conditions, only the blood pressure is slightly elevated beyond the patient's known level after an upsetting argument a few hours before. Anamnesis brings out that the patient is familiar with vertigo and does not have any new kinds of symptoms. So, the ambulance crew cannot find any indication for conveyance at this moment and offers the patient to stay at home unless new kinds of symptoms or decline of general condition occur. The patient prefers to do so, but his daughter presses him to "have a thorough checkup in hospital" and does not concede. The patient is conveyed to the nearest hospital. After the operation, the ambulance crew fills in the questionnaire, describes their working diagnosis as "slightly elevated blood pressure without further symptoms, known vertigo without current worsening" and picks "hospital conveyance" as performed procedure, "consulting the GP in the further course" as appropriate procedure and "patient insists on conveyance by ambulance" (which includes relatives) as reason for hospital conveyance without urgent medical indication.
- An ambulance is alerted under the heading "attendance operation for fire brigade". As there is no patient contact during the whole operation and therefore the operation is excluded from this study, the ambulance crew does not fill in the questionnaire.
- An ambulance and an emergency doctor's car are alerted with high priority because of acute chest pain. On site, the medical examination shows evidence for an acute myocardial infarction and the patient is quickly treated and conveyed to hospital for further treatment. After terminating the operation, the ambulance crew fills in the web-based questionnaire with the items 1-9 only, because they categorize their treatment as appropriate.
- An ambulance is alerted with low priority because of a headache on a Saturday. On site, they find a young woman who is healthy except for a cold that has been lasting for "already six days" accompanied by a sinusitis and a feeling of pressure in her head. The symptoms didn't change during the last days, and she was not satisfied by the advice of her GP and the request to await spontaneous recovery. The ambulance crew repeats the advice of the GP and recommends waiting and see and to contact the GP or alternatively the medical out-of-hours on-call service again if no improvement will occur. The patient insists on an immediate treatment, has never heard of the medical on-call service until now and claims not to be able to drive on her own, so the paramedics call the medical on-call service themselves and ask for a home call. After the operation, they fill in the web-based questionnaire, set their working diagnosis "headache associated with acute sinusitis", pick "referral to GP or medical on-call service" and "continuance at home" as performed procedure, "consulting the GP in the further course" and "exclusively counseling" as well as "counseling telephonically possible" as appropriate procedures and select "missing transportation opportunities by patient and relatives" and add "patient didn't know the medical on-call service" for reasons why the patient has not been directed to the appropriate caregiver straightforward.

We explained all phrases used in the questionnaire (Table 1) to precisely define the terms used. Examples for 2 terms are as follows: "social indication" means, for example, a single, immobile older person, a single mother, or a father of an ill child without his own car and without access to public transportation; "medical on-call service" means an on-call service in a suitable medical practice, self-managed by primary care physicians outside regular consultation hours or when a GP is not available.

The questionnaire will be completed once per operation by the ambulance crew, ideally in consultation with both or all 3 crew members and will represent the assessment of the most qualified crew member. The questionnaire can be filled in until the end of the operation.

The following types of operations are excluded: operations involving minor patients (aged <18 years), secondary transports or interhospital transfers, operations cancelled during the approach, operations with no patient found, provisional operations without a patient (eg, fire service operations), and operations in which the patient dies or is found dead on the incident scene. The inclusion and exclusion criteria are listed in Textbox 2.

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Textbox 2. Inclusion and exclusion criteria for emergency case recording.

Inclusion criteria

- Minimum of 1 ambulance involved in the operation (type C according to EN 1789)
- Crew members were recruited and briefed

Exclusion criteria

- Provisional operation without patient (eg, fire service operations)
- Secondary transport/interhospital transfer
- Cancellation during approach
- Minor patients (aged <18 years)
- Patient dies or is found dead on incident scene
- No patient found

Setting

The study takes place in the whole area of responsibility of the integrated emergency control center of Ludwigshafen, Germany. This covers an area of about 1200 km^2 and represents a point of call for over 620,000 inhabitants in 6 administrative districts and independent cities. Its dispatchers answer more than 210,000 calls per year, which result in more than 140,000 EMS operations (average 380 per day) and around 11,000 operations of the fire service annually. The control center has at its disposal 21 ambulances in 12 different locations, as well as 8 emergency doctor's cars, 1 rescue helicopter, and up to 28 patient transport ambulances (figures obtained via oral communication with the management team of the integrated EMS control center of Ludwigshafen on August 29, 2023). The area of responsibility, with its 6 administrative districts and independent cities, includes the core city of Ludwigshafen as the metropolitan zone, a few cities classified as urban regions, several smaller, suburban towns, and several remote rural townships [34]. The classification of the operation areas used in this survey can be found in Table 2.

Table 2. Operation areas of emergency crews.

Operation area	Description
Overall	The area around Ludwigshafen, a city in the federal state of Rhineland-Pfalz, Germany
Metropolitan	The core region of Ludwigshafen
Urban	The cities Speyer, Neustadt, and Frankenthal, as well as the districts Ruchheim and Maudach of Ludwigshafen
Suburban	The cities Bad Dürkheim, Grünstadt, Schifferstadt, Haßloch, Böhl-Iggelheim, Limburgerhof, Mutterstadt, and Bobenheim-Roxheim
Rural	All townships with less than 10,000 inhabitants

Participant Recruitment

All ambulance crew members under the responsibility of the integrated emergency control center of Ludwigshafen will have access to voluntary participation in this study. LMN, a doctoral student, will run several information sessions integrated into conferences at the individual rescue stations. Additionally, a written invitation with information will be sent to every employee via an email distribution list on the internal communications devices of the quality management system. It will include a thorough description of the study content, clarifications concerning the questionnaire, an informed consent form, and a link and QR code supplying access to the web-based questionnaire. Consent will be obtained in the web-based questionnaire; further participation is only possible after providing informed consent.

Data Collection

During the 10-week period of data collection, access to the web-based questionnaire is available 24 hours a day, 7 days a week. The questionnaire is accessible via the link or QR code and can be filled in using a personal computer, tablet, or smartphone. The questionnaire website has been built exclusively for the study by the department conducting the study. The EMS personnel are encouraged to capture as many operations as possible during this period. The acquisition of the data sets is not bound to a certain time frame after the operations. Although the ambulance crew members must complete the questionnaire only after finishing an operation, the data sets only have to be completed within the period of data collection. The data set of each recorded ambulance operation is directly sent to a dedicated study server within the Department of General Practice and Health Services Research of the University Hospital Heidelberg via secure internet protocols. After closing of primary data collection, additional information and secondary data provided by the control center will be combined with each completely collected data set for interpretation. This comprises the time of day of the alert, the priority of the alert, the keywords of the alert, and a specific feedback code from the ambulance.

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The scheduled course of the study is summarized in Figure 1.

Figure 1. Scheduled further course of study.

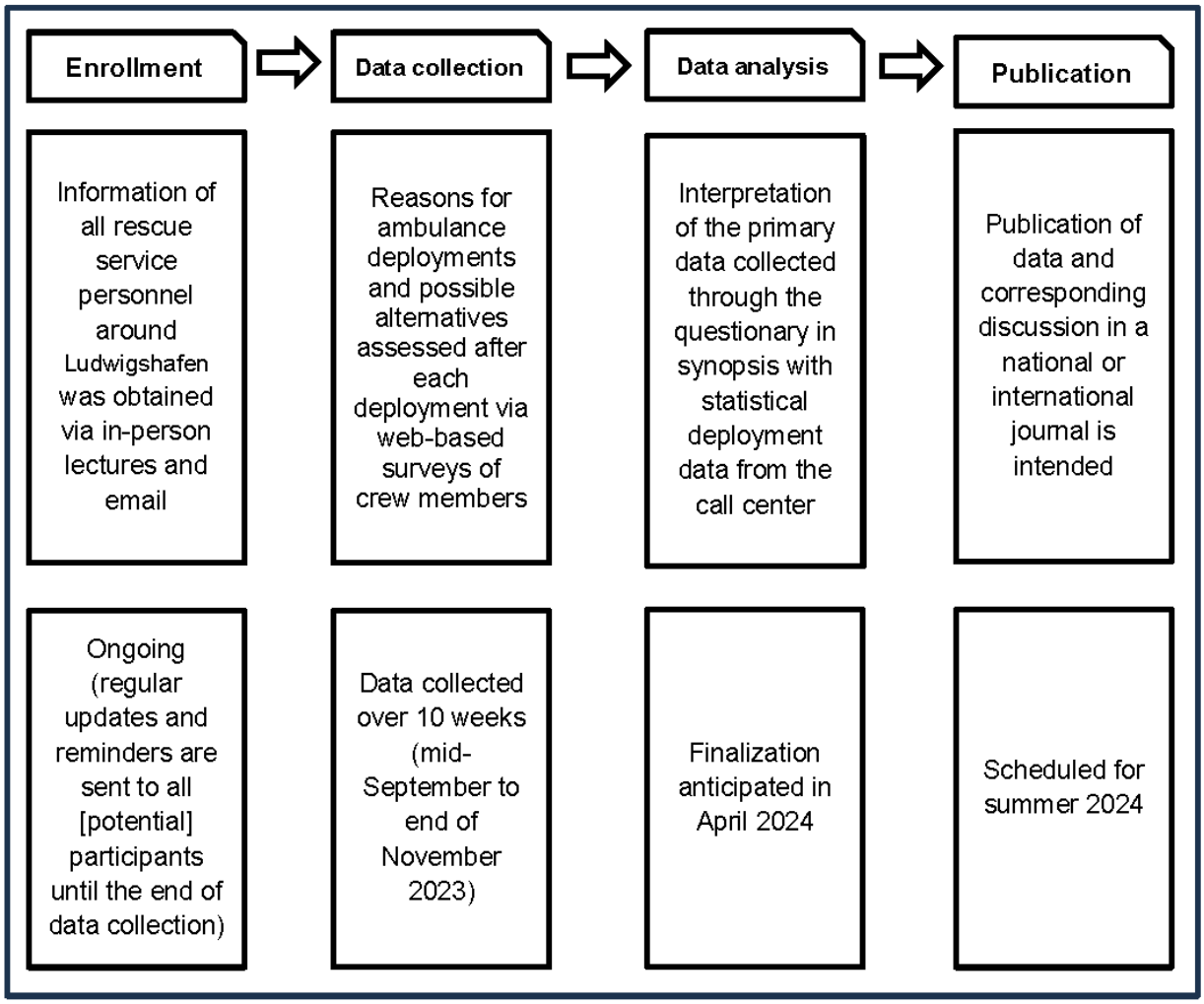

Research Staff

The research team consists of a doctoral student, several senior researchers, and a computer scientist employed at the Department of General Practice and Health Services Research of the University Hospital Heidelberg, Germany.

Data Management

Data management is performed by the data management team of the Department of General Practice and Health Services Research of the University Hospital Heidelberg. The secondary data are collected by the control center of Ludwigshafen and are unrelated to the described questionnaire; they are governed by their own data management team.

Each data set is directly sent to and filed on a dedicated study server in the Department of General Practice and Health Services Research of the University Hospital Heidelberg. This also applies to the required secondary data transferred from the control center. Data access is granted only to the research staff directly involved in data collection and analysis. There will be no passing on of the unprocessed data to any external institution. Additionally, secondary data from the responsible control center will be linked and processed in the initial descriptive analysis. This descriptive analysis will form the basis for the variance analysis (see Data Analysis section). Working diagnoses will be converted to *International Classification of Diseases, Tenth Edition* codes by a research physician. The free-text entries will be analyzed separately with qualitative methods to obtain a deeper insight into patients' motives for their behavior. Data storage and extraction will be performed with MySQL Community Server x64 (Oracle Corp).

Data Analysis

The two main outcomes for our analyses are the number and percentage of inappropriate emergency calls and the reasons for patients being conveyed to a hospital without a medical indication. This total numbers will be further subdivided according to the paramedics' assessments. Moreover, it is of interest if there are explanatory variables such as patient gender, patient age, operation area, and operation time in the data set that might be associated with inappropriate emergency calls or being conveyed to a hospital without a medical indication. This will be analyzed based on multivariable regression modeling [35]. To calculate frequencies, rates, and percentages, we will use the PROC SQL procedure in SAS (version 9.4, SAS

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Institute). To perform the multivariable analyses, we will use the PROC GENMOD procedure in SAS. For qualitative analyses, we will use MAXQDA (version 24.1, VERBI Software).

Ethical Considerations

The ethics committee of the University of Heidelberg revised and approved this study on May 30, 2023 (S-250/2023). The trial has been developed and will be executed according to all relevant national and international rules and regulations under the Declaration of Helsinki (2013 version) and International Council for Harmonisation Good Clinical Practice (E6, R2) guidelines. Consent from all participants will be obtained in the web-based form, and access to the questionnaire will be granted only after approval. Protocol modifications are not scheduled and are not foreseeable; if the need for them arises, they will have to be approved by the ethics committee. In case of modifications, a new study protocol will be released to all study participants via an official email. Due to the anonymous collection of data, participants do not have the choice to opt out after completing the questionnaire. Furthermore, as the questionnaire is anonymous, there is no possibility of inferring the identity of the participant or any other personal information. There is also no way to identify the personal data of patients using the secondary operational data provided by the control center. There is no compensation, financial or otherwise, provided to participants.

Results

Data collection started as projected on September 18, 2023, and was ongoing until end of November 2023. We expect the documentation of several thousand rescue operations. We expect that many of these rescue operations will be unnecessary. Our intention is to train paramedics to give an immediate on-site evaluation of the correct care and treatment. We hope to identify patients' reasons for calling a rescue coordination center so that we can give recommendations in advance on where to find the appropriate treatment options.

Discussion

To the best of our knowledge, this is the first observational study in which acute rescue operations are being recorded on site in Germany. This study was initiated to show how many inappropriate rescue operations, such as those for minor injuries or minor infections, take place in a defined study period. The assessment of these LACs is carried out directly on site by trained rescue personnel and not later in the clinic. The assessment is therefore supplementary and can provide information on operations without the need for a referral, which is a main strength of this study. Another focus is on a preclinical assessment to determine suitable, diverse alternatives to transport by ambulance to an ED for patient conditions that do not require urgent treatment.

One major intent of our study is to complement previous work, which includes several retrospective clinical evaluations and many qualitative studies, such as interview studies, on reasons for calling the EMS in LAC situations as seen through the eyes of patients, as well as of caregivers (mostly EMS personnel), and what circumstances encourage these calls [36-38]. It is known from previous data that around 30% to 35% of all rescue service operations transporting patients to the ED are rated as inadequate and unnecessary [5-8], so a similar proportion of operations with preferred alternative care methods is expected. Most of these inadequate EMS operations involve patients whose health conditions are assessed as being able to be adequately treated by a GP or in general outpatient care [6], which is why there may be a significant difference in the number of primary care–sensitive EMS operations depending on the general availability of and access to general practices and medical out-of-hours care [17]. Additionally, we anticipate that a certain number of transportation operations by ambulance for LACs will take place because of missing transportation alternatives, which has been found to be a relevant reason for ambulance misuse in previous work [39,40]. Previous studies have shown differences in the use of emergency services between urban and rural populations [41], as well as between groups with differences in relevant socioeconomic factors, such as age and personal mobility [42], which may be confirmed in this study.

Several limitations of this study should be noted. The whole system of EMS and acute patient care is complex and includes many variables that cannot be examined in this study. For example, the control centers' process for receiving emergency calls and dispatching ambulances plays a major role during all ambulance operations and the management of acute patients. Assessments of patients' health condition by dispatchers, EMS personnel, and the patients themselves may greatly differ [43]. Misclassification can occur due to different assessment standards because there are usually no uniform classification criteria. There are approaches to harmonizing the triage and dispatching process, such as an intervention in out-of-hours care call centers in Germany that started in 2017 [44], but currently there exist no mandatory and coherent structures in emergency or rescue coordination centers.

In general, studies concerning the EMS in Germany deal with limited generalizability because of huge regional differences in standard operating procedures for treatment, equipment, staffing of rescue resources, and laws and regulations [45]. This is due to the federal structure in Germany and the accountability for civil protection lying mostly with the federal states or even autonomously with the local authorities [46].

Another limitation is the risk of bias. Operations that the ambulance crew rates as having been inappropriately dispatched are more likely to be captured than operations that fulfill the original functions of the EMS. Additionally, recall bias could occur if the questionnaire is not filled in soon after the end of an operation. Our intention was, in any case, to document all rescue operations regardless of urgency.

Nevertheless, the results of this cross-sectional pilot study may form the basis of further evaluations of possible interventions and pilot projects, the implementation of additional services in urgent care, support for change in the way patients are treated, and political change concerning urgent care in general.

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Acknowledgments

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Data Availability

Restrictions apply to the availability of the additionally processed secondary data from the emergency call center of Ludwigshafen, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the emergency call center Ludwigshafen.

Authors' Contributions

LMN developed the study design as well as the questionnaire design and content. She organized the on-site process and implementation of the study at the rescue stations. She was a major contributor in writing the manuscript. RL was a supervisor and co-developed the study, particularly the research question of the study. He was also a major contributor in writing the manuscript. GL provided substantial assistance during the development of the study, especially in all points concerning data management, data privacy, and data analysis. AA and JS advised on the study and critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EMS: emergency medical service
ED: emergency department
GP: general practitioner
LAC: low-acuity call

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Protocol

Development and Testing of an Electronic Diabetes Diary Integrated With a Hospital Information System for Individuals With Type 2 Diabetes Mellitus: Protocol for a Mixed Methods Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is one of the leading noncommunicable diseases that require diabetes self-management (DSM) practices. This study proposes to develop a customized mobile health (mHealth) app integrated with a hospital information system (HIS) to enable real-time, two-way transfer of information between the patient and physician. The captured information in the electronic health record will facilitate physicians to have a chronological account of the patient's diabetes history and enable tweaking of the treatment.

Objective: The objectives of the study are (1) to develop the HIS-integrated Electronic Diabetes Diary (EDDy) per the end-user expectations at a tertiary care hospital in a south Indian state with a high prevalence of T2DM and (2) to evaluate and test adherence to EDDy in the management of T2DM.

Methods: The study will be carried out in 3 phases. Phase 1 involved in-depth interviews with primary end users to gather information regarding their expectations from the hospital-based EDDy. Phase 2 will use this information to develop a customized mHealth app using an iterative model of software development. Phase 3 will involve a pre- and posttest design; the developed app will be tested among consenting patients, where physicians will receive the patients' data through the HIS-integrated mHealth app. The pre- and posttest values will be analyzed for adherence leading to improvement in patients' self-management of blood glucose, user experience, glycemic control, and clinical utility.

Results: Phase 1 was completed on November 28, 2023. Phase 2 commenced in December 2023 and will end in May 2025. Phase 3 will follow afterward.

Conclusions: The proposed app will include a convenient and simple alert system that enables the patient to test glucose values at self-selected intervals, provide grading options to enter diabetic-related complications, enhance patients' knowledge of tracking and managing the complications of diabetes, and help in maintaining the visual representation of glucose values and complications. The simplicity and usability of the modules are its novelty, which may motivate the patients to keep track of their glucose values and help them attain better health outcomes.

Trial Registration: Clinical Trial Registry India CTRI/2023/03/051077; http://tinyurl.com/4tau4ndb

International Registered Report Identifier (IRRID): PRR1-10.2196/50732

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KEYWORDS

self-management of blood glucose; SMBG; diabetes self-management; DSM; personal health records; electronic diabetes diary; glycemic control; patient adherence; digital health

Introduction

In India, 11.8% of the population have diabetes per the National Diabetes and Diabetic Retinopathy Survey released by the Ministry of Health and Family Welfare in 2019, and this is projected to have a steady rise of 3.8% annually [1]. This prevalence is higher in the southern states and union territories of India [2]. *The Indian Glucose Monitoring Device Market Reports of 2020* [3] suggested that the use of glucometer was always on the rise, and it was specifically noticed that there was an exponential increase in its sale during the COVID-19 pandemic period. Technology-enabled self-management has been increasingly recommended, along with proper medication and lifestyle modification, to tackle diabetes. There are numerous diabetes managements apps available in the Google Play store; however, subscription to such apps is not proportional to the population with diabetes [4]. Literature from other parts of the world suggest that the adoption of digital diabetes-monitoring solutions is expected to reach 21% by 2027 [5].

Diabetes is an irreversible chronic condition that need to be well managed by altering lifestyles, food habits, and physical activities [6]. However, a standard diabetes management regimen may not be feasible to everyone around the globe, as each of these factors varies according to geographical locations and general living conditions [5]. Using customized information that is specific to the local lifestyle may be more effective and easier to ensure adherence. Existing literature suggests that nonadherence to treatment regimen and irregularity in following a diabetes-friendly lifestyle leads to poorly managed diabetes and poor disease outcomes [7]. To enhance the existing measures to manage T2DM, efficient methods needs to be formulated to ensure adherence to treatment regimen [8]. The success of such activities requires active involvement of the patients and caregivers. They should be motivated to follow T2DM management instructions from health care professionals.

This study setting already has an existing system of manual diabetes information documentation that expects its patients to record their self-management of blood glucose (SMBG) practices systematically and submit them to the treating physician during consultation. These glucose monitoring records are used by the physician to evaluate the patient's glycemic status and make appropriate clinical decisions. This study proposes to automate this process and make it more efficient for the patients and physicians. The proposed electronic diary is expected to reduce the loss of documented values, minimize errors, as well as motivate the patients to effectively make use of technology and manage their condition.

A pilot study was conducted to analyze the knowledge and attitude to digital diabetes management practices among 50 existing patients with diabetes, which indicated that ignorance and technological illiteracy are the main reasons behind nonuse of digital apps among them. Those who used digital apps, such as mobile health (mHealth) apps, suggested that the information available is more general in nature and that they find it difficult to navigate and comprehend the information, eventually leading to the discontinuation of its use.

Methods

Overview

The study will be carried out in the outpatient department (OPD) of the endocrinology department at a tertiary care hospital in a south Indian state, and it is divided into 3 phases. In phase 1, a qualitative study was conducted; in phase 2, the mobile app with be developed and integrated with a health information system (HIS); and finally, in phase 3, the developed app will be tested for its feasibility using a pre- and posttest design.

The study is based on the principles of the "theory of change," where stakeholders will be consulted through in-depth interviews (IDIs) to identify the deterrents to acceptance and adherence of electronic diabetes-monitoring practices, potential challenges, as well as ethical issues related to electronic information sharing. This feedback will provide the cues for the development of a customized electronic diabetes-monitoring system. The study would also attempt to identify the reasons that would lead to the discontinuation of electronic monitoring practices among patient with T2DM and address them by developing a more user-friendly mHealth app. This study will also analyze the patient acceptance of the mHealth app and their adherence to SMBG practices.

The model will then be developed and integrated with an HIS. Finally, it will be tested among patients with T2DM regarding their acceptance and adherence to using the Electronic Diabetes Diary (EDDy), its usability, contextual relevance according to user expectation, and clinical utility in terms of glycemic control.

Ethical Considerations

This study has been approved by the Institutional Ethics Committee (IEC; IEC No:223/2022). The participants personal information will be anonymized, and all privacy, confidentiality, and compensation policies will be adhered to as per the IEC guidelines.

Pilot Study

As a precursor to this study, a pilot study was conducted in a tertiary care hospital among 50 patients with T2DM to understand the existing personal record-keeping practices, the challenges they face, and their awareness of personal record keeping. The perception, expectations, and concerns of the target population were studied using a validated questionnaire survey. Patients with T2DM who are within the age group of 40-65 years were included in the study. The study setting encouraged patients with T2DM to document their SMBG values by providing a data sheet to enter the values and asking patients to bring it with them when they come for a doctor's appointment. It is a valuable tool for the doctor to assess the

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values and make better clinical decisions in the management of the disease.

A cross-sectional study was conducted, and a purposive sampling technique was followed to select the participants. A mixed-type questionnaire (both open- and close-ended questions) was used to collect data.

Phase 1

Study Design

IDIs with key stakeholders was carried out to identify the reasons for nonadherence, expectations from EDDy, and mandatory requirements to develop the intervention mechanism. The key stakeholders included the following participants:

- Patients with T2DM
- Their caregivers
- Treating doctors
- Diabetes counselors (includes nursing counselors, diet counsellors, and physiotherapists)

Sample Selection

The IDI participants were enrolled according to the following criteria: patients who own an Android smartphone and those who regularly attend doctor's appointments (ie, those who visit the OPD at least once in the last 6 months). Patients who are literate, can understand the local language (Kannada or Tulu) or English, aged 40-65 years, and have hemoglobin A_{1c} values between 7% and 10% were selected to ensure homogeneity. Patients with gestational diabetes and other terminal illnesses were excluded. The IDIs were conducted among the immediate caregivers of the patients (ie, those who are actively involved in the care of the patient). To understand the practical aspects of the treatment and management of patients, physicians, nurses, and counsellors were also interviewed.

Even with the availability of various diabetes management apps, studies suggest they are not very popular among the general population. The reason for this underuse and nonadherence, along with their expectations from mHealth apps, are the key areas that were addressed among patients with T2DM and their caregivers. The doctors and diabetes counselors were interviewed to understand the challenges they face while managing patients with T2DM and their SMBG practices.

IDI Process

The IDIs focused on the perspectives of patients with T2DM and their caregivers along with physicians and diabetes counselors who are actively involved in the care of patient with T2DM. Additionally, IT and health information management professionals were also consulted on ethical challenges and technical expertise. The IDI guide was designed based on the objectives of the study and the content was validated by experts. The IDI process is shown in Figure 1.

Qualitative data generated during the IDIs will be analyzed by using ATLAS.ti software (version 8; ATLAS.ti), and a report will be prepared. Based on the report, the researchers and the subject experts will identify the most feasible options that will be considered for incorporation into EDDy.

Figure 1. Process of the in-depth interviews (IDIs). IEC: Institutional Ethical Committee; IRC: Institutional Research Committee; KH: Kasturba Hospital.

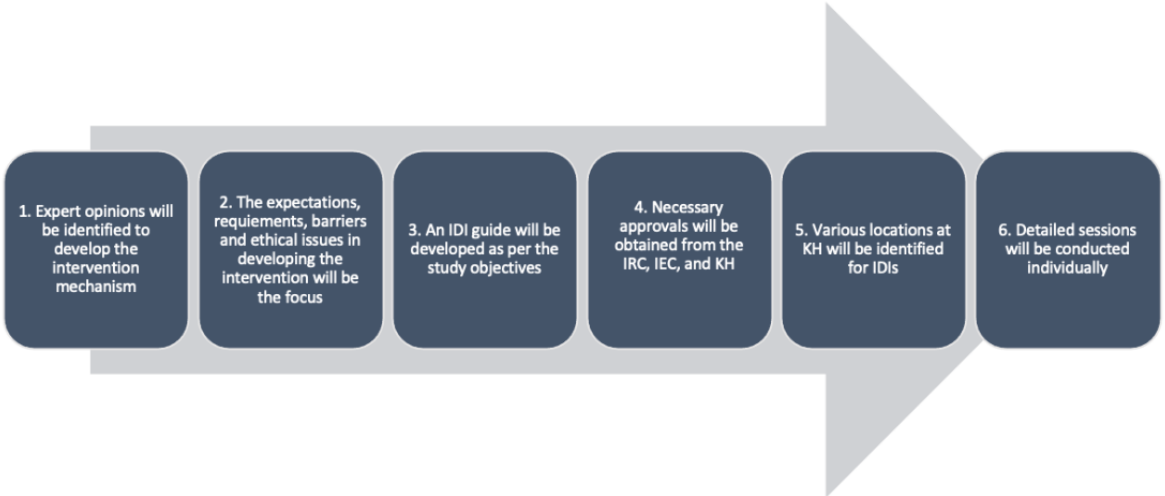

Phase 2

Development of EDDy

Phase 2 is the main part of this research, where the software will be developed based on inputs from the IDIs and the literature. The mobile app will be developed on Android Studio (Google) using an iterative model design.

The iterative model (Figure 2) is one of the Software Development Life Cycle models, where the development of a system goes through repeated cycles (iterative) and is conducted in smaller portions at a time (incremental) [9]. As and when the different modules of the app are developed, they will be tested and reviewed against the end user's expectation, and accordingly, modifications and further development will be done. This process will enable easier debugging and fixing of errors as and when tested.

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Figure 2. Iterative model of Software Development Life Cycle. EDDy: Electronic Diabetes Diary; HIS: hospital information system.

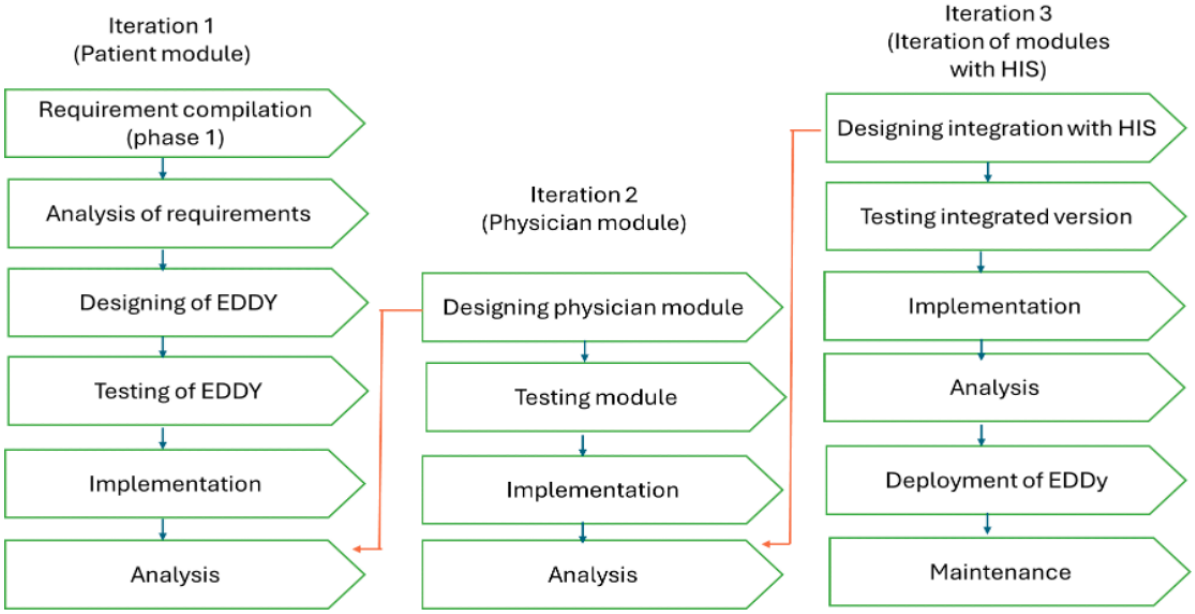

The development and testing of the app will involve development, pilot-testing, and debugging at each phase. Each iteration will be subjected to the development, testing implementation, and analysis of each component of EDDy. The components for incorporation into the software will be validated by the following experts:

- An endocrinologist
- Qualitative experts
- The IT team at the hospital

The expected pattern and time period for phase 2 are as follows.

System Development

Step 1: Requirements

This is the phase where the stakeholders' requirements are enquired and compiled, which was primarily covered in phase 1. The captured data will be systematically entered into Microsoft Excel for further evaluation.

Step 2: Analysis

The compiled information will be divided into feasible and nonfeasible items as per the system development and HIS-interfacing requirements. This step will be conducted with the researchers and technical experts.

Step 3: Designing and Development

This step will be done by a software developer with the support of a researcher. Once the feasible requirements are sorted and finalized by the researcher, the design of the app will take place. First, a prototype of the system will be developed, and the requirements for each module of the app will be determined. This step includes the coding of the app based on the design. Android Studio, an open-source program for Android software development, will be used to develop the proposed mobile app. The iteration process has 3 phases, where a patient module and a physician module will be designed, and integration with an HIS will be performed as depicted in Figure 2.

Step 4: Implementation

After development, each module of EDDy will be pilot-tested for its intended use. The modules will be connected to a web-based backend database application to help the validation of content, visualization, and analysis of the data collected.

Step 5: Testing and Quality Assurance

The developed app will undergo a standard testing and quality assurance process to identify and rectify any issues and bugs. Each module will be validated during testing to ensure its intended performance.

Step 6: Analysis of Feedback

A pilot test among 2 potential users will be carried out at each level of iteration, and user experience will be measured using a Likert scale on various aspects of the app's functionality. The parameters that will be measured during the piloting process will be the app's functionality, usability, accessibility, compatibility, and performance under real-life scenarios.

Once the app is fully developed and interfaced with an HIS, it will be installed in the respective systems of the stakeholders and tested for its performance. Gaps and technical glitches will be rectified at each phase.

Step 7: Deployment

The final app will be deployed among end users (patients and physicians).

Step 8: Maintenance

The final app will be integrated into an HIS. Once the module is fully functional, the study will proceed to phase 3.

Expected Outcomes From EDDy

The app is expected to improve the SMBG practices in patients with T2DM. EDDy is expected to motivate the use of the app (*acceptability*) and improve the user experience on the *contextual relevance*. The *ease* of using the customized system and a clinician's feedback mechanism through the physician

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module is expected to improve the *clinical utility* of the app. It is expected that adherence to using the app would improve compliance to treatment protocol, thus improving treatment outcomes.

The entry of information into EDDy can be done either by the patient or their caregiver. The entry of SMBG values by the patient is a standard clinical practice in patient management. The current practice is that these self-monitored blood glucose values (SMBG data) is maintained by the patient on a printed form provided by the hospital. It is standard practice that such SMBG data function as a mechanism that helps physicians to optimize medication in routine clinical practice [10].

A researcher will provide instruction to the patient or patient party on how data entry needs to be done on the app. Additionally, a built-in user manual will be provided with the system. This will be developed as a part of the app development. A multilingual *user manual* or *instructional videos* will be developed to assist the patient in using EDDy. The pictogram in Figure 3 represents the workflow of EDDy.

Figure 3. Prototype of EDDy.

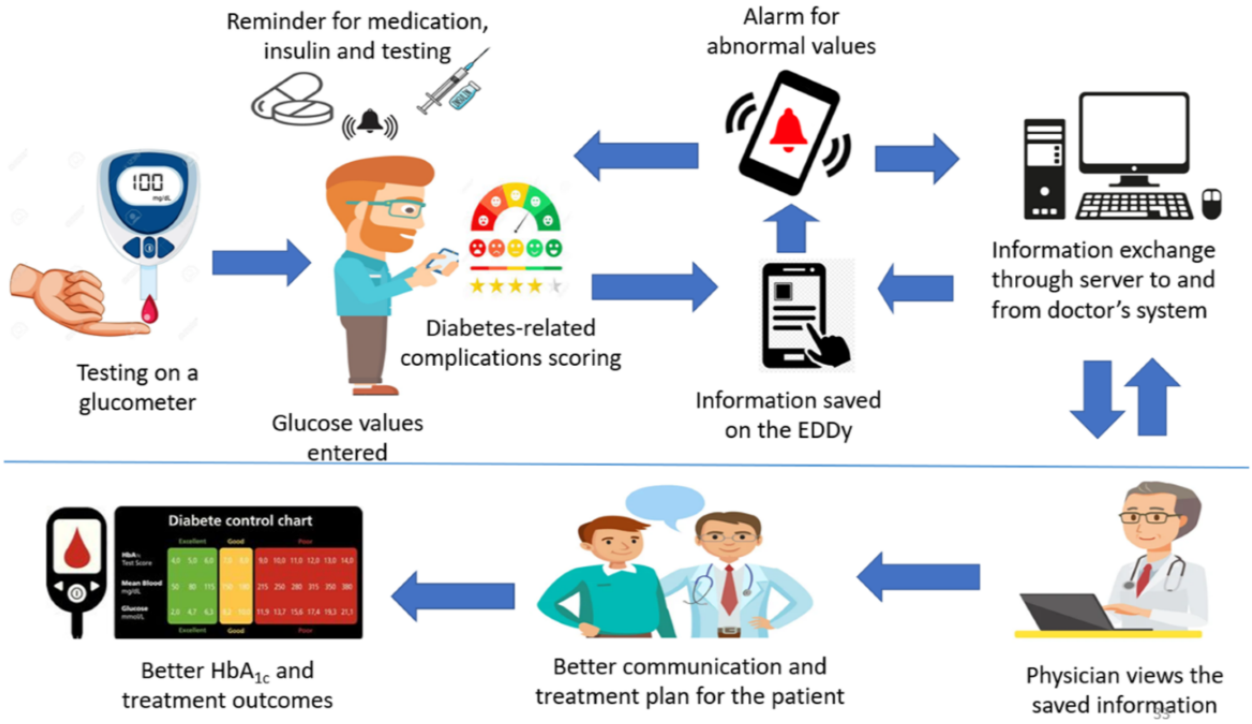

Phase 3

Study Design

Phase 3 will involve testing the adherence and usability of the developed app. This phase will use a pre- and posttest design among 48 patients with diabetes selected through purposive sampling.

At a 5% level of significance with 80% power and an effect size of 0.25, the minimum sample size required for a single-group, repeated measures study design involving 1 primary quantitative outcome (adherence) measured across 3 time points (preintervention, after 3 months, and after 6 months; correlation among repeated measures is 0.3) to understand the adherence to EDDy integrated with an HIS is 38 individuals. Incorporating a dropout rate of 20%, the minimum sample size requirement is 48 individuals.

The sample size was computed using G*Power (version 3.1.9; Universität Düsseldorf). The sample size may be amended (if required) based on pilot study findings.

The study setting will be the endocrinology OPD of a tertiary care hospital in coastal Karnataka, India.

Regarding study participants, patients with T2DM who have regular follow-up records will be considered for the study.

This study will analyze the adherence of patients with T2DM to EDDy in comparison to the existing manual method of documentation. Adherence will be evaluated in terms of the following:

- Adherence of entering SMBG values as predetermined by the patient: The study participants will be instructed to fix the frequency that they will monitor their blood glucose; based on this frequency, they will be prompted to conduct the glucometer testing and enter the values into EDDy. The values will be stored in the app and will be transferred to the server on a regular basis as the EDDy is integrated with an HIS.
- Adherence to diabetes self-management (DSM) practices: Pre- and posttest adherence to DSM practices will be analyzed using the same content-validated questionnaire.
- Adherence to routine blood investigations and screening regimen: Pre- and posttest adherence to periodic blood investigation and comorbidity screening will be analyzed.

The inclusion and exclusion criteria for sample collection will remain same as that of phase 1.

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Phase 3 will be evaluated in 3 intervals:

- First evaluation (preintervention): During enrollment into the study, the patients will undergo an entry survey using a content-validated questionnaire to analyze the current DSM and SMBG practices they follow.
- Second evaluation (follow-up): An interim follow-up will be conducted in the third month.
- Third evaluation (postintervention): The same questionnaire used in the first evaluation will be used to evaluate DSM and SMBG practices after the intervention.

The study participants will be provided with EDDy on their mobile phones and will be trained to use it along with standard diabetes care. Training materials will be a part of the app for patient's ready reference. The pre- and posttest process is shown in Figure 4.

Figure 4. Pre and Posttest Process of development of EDDy.

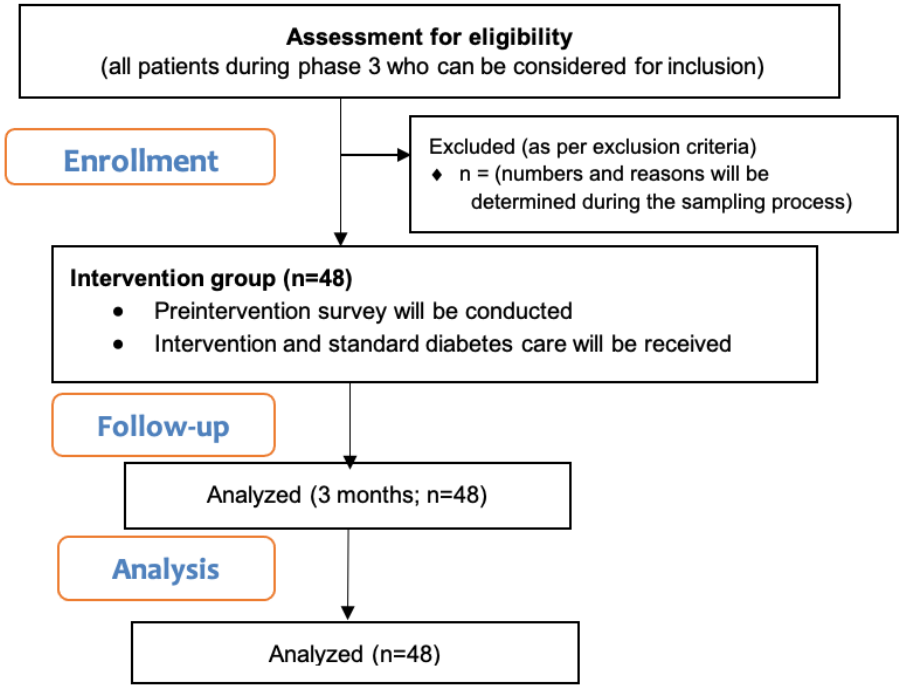

Analysis

Study participants will be followed up for 6 months and will be analyzed primarily for their adherence to using EDDy. It will be assessed based on patients' willingness to use it, the ease of use, their acceptance of EDDy in terms of the contextual relevance, and the clinical utility. The participants will undergo an exit survey at the end of the study period using a validated questionnaire. It will be specific for assessing the qualitative parameters such as *user experience*, *glycemic control*, *adherence leading to improvement in their SMBG*, and *clinical utility.*

The qualitative outcomes are as follows:

- Ease of use and adherence: User's perception on accessing the various modules in the app, ease of entering information, ease for retrieving information, and ease of comprehending information
- Glycemic control: Adherence in terms of regular monitoring and tracking of blood glucose values to keeps it under check, leading to well-managed T2DM
- Contextual relevance: Relevance of the contents of EDDy in terms of the user expectations and requirements as expressed in phase 1 of the study
- Adherence to SMBG and DSM practices: Reminders and alerts that ensure adherence to medications, insulin injections, regular glucose testing, and comorbidity screening
- Clinical utility: Improvement in treatment outcomes due to adherence to reminders or alerts and monitoring of blood glucose, adherence to medication, and follow-ups

The frequency will be tested based on the Diabetes Co-Conditions Screening Checklist provided by the Association of Diabetes Care & Education Specialists [11].

The following standard tools will be used for assessment, which are modified according to the study requirements and will be content validated by experts:

- Perceived Health Web Site Usability Questionnaire: A 12-item questionnaire that is validated for assessing the usability of health websites for older adults will be used [12].
- Diabetes Self-Management Questionnaire: It describes self-care activities related to diabetes. SMBG practices will be analyzed using this tool. A validated 12-item questionnaire to assess self-care activities associated with glycemic control will be used [13].
- A self-developed, content-validated questionnaire: Adherence will be evaluated, including the regularity of use; ease of use with respect to entering diabetes-related information such as regular testing and entry of glucose levels; adherence to medications or insulin doses; reporting of diabetes-related emergencies or complications, if any; and adherence to periodic screening such as laboratory

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investigations, peripheral neuropathies, retinopathy, diabetic foot, and BMI.

The physicians will be interviewed to assess the clinical utility of the app and their experience in using the app using a content-validated questionnaire.

Expected Outcomes

A customized mHealth app that provides adequate information specific to the T2DM management will be developed. This can lead to an effective intervention that will reduce the risk of a person diagnosed with T2DM from developing further disease complications, such as chronic kidney disease, diabetic foot, retinopathies, and peripheral neuropathies, thereby reduce the cost of health care expenditure.

Results

Pilot Study

Out of 50 patients with T2DM (aged 40-50 years), 22 (44%) documented their self-monitored glucose values, whereas the remaining 28 (56%) did not. The percentage score of sources used by patients with diabetes to document the values of self-care activities showed that most of the patients (n=21, 42%) were using a personal diary to document, whereas only 1 (2%) patient each used a diabetes app and mobile notes. Responses from patients with diabetes regarding the necessity of personal health information in diabetes management showed that 31 (62%) patients were not completely aware of personal health information management.

The study results reflected the perception of patients with T2DM about their personal health information documentation practices. Additionally, the study gave a brief outlook about the challenges and barriers that patients face during their DSM activities.

Study Status

Phase 1 was completed on November 28, 2023. Phase 2 of the study, which is the app development, commenced in December 2023 and will end by March 2025. The wireframe model of EDDy is shown in Multimedia Appendix 1. Phase 3 of this study will follow afterward, analyzing the effectiveness of adherence to the app and its usability.

Discussion

Pilot Study Findings

It was evident from the pilot study that there is a strong requirement to promote documentation of SMBG and DSM practices. Overall, the study concluded that there is a scope for strengthening DSM, knowledge development, and improved self-documentation practices by promoting personal health information practices among patients with diabetes. It has the potential to improve the quality of life of patients with diabetes by better promoting self-care.

Expected Findings

When considering a country such as India, which has a very diverse population belonging to different socioeconomic backgrounds, it is difficult to implement a standard practice to tackle a problem. Statistics show that out of 45% of Indians over 45 years of age, about 11.5% are diagnosed with diabetes or high blood sugar levels [3]. Patients belonging to this age group are comparatively less familiar with technology and digital apps. Understanding their requirements and developing a hospital-based electronic diary may promote its use and adherence among them and, eventually, all patients with T2DM.

Considering India's socioeconomic background, the requirements for this population need to be assessed from various angles. It can be demonstrated by analyzing the findings of the study conducted by Walle et al [14] among 422 patients with diabetes in Ethiopia. The study aimed at understanding the willingness of patients with diabetes mellitus to use mHealth app and its associated factors for self-care management in a low-income country as a precursor to digital health implementation in Ethiopia. The study concluded that the mHealth app developers should consider factors such as the patients' age, place of residence, internet connectivity, attitude, perceived ease of use, and perceived usefulness while developing similar apps [14].

The pilot study conducted to analyze the awareness of patients with T2DM also clearly stated that they were aware of the importance of SMBG and DSM practices and the availability of mHealth apps to help them manage their T2DM. However, they were not very keen on using it due to various personal factors.

It was evident from the findings that there is a clear requirement to generate awareness about T2DM management and the use of mHealth apps. It is equally important to understand the challenges that keep them from using available mHealth apps. Based on these observations, if an mHealth app can be developed and the information can be transferred to the patients' records in real time, it will be beneficial for both the patients and the doctors to better manage the condition.

Conclusion

The literature review and pilot study conducted suggests that an easily manageable, personalized diabetes-monitoring system for patients to do regular self-checks and that provides the end users with accurate data on the patient's diabetic history will be beneficial for better management of T2DM. It would enable better sharing of information between patients and doctors, thus improving the communication between patients and doctors, which is significant in the management of diabetes and leads to better treatment outcome. The available apps are not very popular among the end users as they find it difficult to use and understand the contents. To ensure better usability and adherence, a convenient and simple alert system that enables the patient to conduct glucose testing at intervals set by the patients themselves can be designed. The proposed app EDDy will provide grading options to enter the diabetic-related complications (such as neuropathy, retinopathy, diabetic ulcers, etc), thus alerting patients and doctors for prompt action. It is also expected to enhance patients' knowledge of tracking and managing the complications of diabetes and help in maintaining the visual representation of glucose values and complications. The simplicity and usability of the module are its novelty, which

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may motivate the patients to keep track of their glucose values and help them to attain better health outcomes.

Acknowledgments

The author would like to acknowledge the participants of the pilot study and Mr Prajwal L Salins and Ms Ashika Shetty.

Data Availability

As this is a study protocol, the results of the pilot study have been reported, and the data will be submitted as required.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Wireframe model of Electronic Diabetes Diary (EDDy).
[PDF File (Adobe PDF File), 225 KB - resprot_v13i1e50732_app1.pdf]

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Abbreviations

CTRI: Clinical Trial Registry of India
DSM: diabetes self-management
EDDy: Electronic Diabetes Diary
IDI: in-depth interview
IEC: Institutional Ethics Committee
HIS: hospital information system
mHealth: mobile health
OPD: outpatient department
SMBG: self-management of blood glucose
T2DM: type 2 diabetes mellitus

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Protocol

Enhancing the Efficiency of a Radiation Oncology Department Using Electronic Medical Records: Protocol for Preparing Radiotherapy

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Abstract

Background: Electronic medical records (EMRs) streamline medical processes, improve quality control, and facilitate data sharing among hospital departments. They also reduce maintenance costs and storage space needed for paper records, while saving time and providing structured data for future research.

Objective: This study aimed to investigate whether the integration of the radiation oncology information system and the hospital information system enhances the efficiency of the department of radiation oncology.

Methods: We held multidisciplinary discussions among physicians, physicists, medical radiation technologists, nurses, and engineers. We integrated paper records from the radiation oncology department into the existing hospital information system within the hospital. A new electronic interface was designed. A comparison was made between the time taken to retrieve information from either the paper records or the EMRs for radiation preparation. A total of 30 cases were randomly allocated in both the old paper-based system and the new EMR system. The time spent was calculated manually at every step during the process, and we performed an independent 1-tailed *t* test to evaluate the difference between the 2 systems.

Results: Since the system was launched in August 2020, more than 1000 medical records have been entered into the system, and this figure continues to increase. The total time needed for the radiation preparation process was reduced from 286.8 minutes to 154.3 minutes ($P<.001$)—a reduction of 46.2%. There was no longer any need to arrange for a nurse to organize the radiotherapy paper records, saving a workload of 16 hours per month.

Conclusions: The implementation of the integrated EMR system has resulted in a significant reduction in the number of steps involved in radiotherapy preparation, as well as a decrease in the amount of time required for the process. The new EMR system has provided numerous benefits for the department, including a decrease in workload, a simplified workflow, and conserving more patient data within a confined space.

(JMIR Res Protoc 2024;13:e51002) doi:10.2196/51002

KEYWORDS

efficiency; electronic medical records; Hospital Information System; protocol; radiation oncology

Introduction

The advantages of electronic medical records (EMRs) include facilitating medical process management, quality control, and the sharing of medical record data among different departments in a hospital, as well as reducing both costs and storage space for paper medical records [1,2]. The Ministry of Health and Welfare in Taiwan implemented a pilot program for the digitalization of medical records in 2002, and our hospital participated in this program to digitalize our medical records.

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However, due to the highly complex nature of the information contained in radiotherapy (RT) treatment plans [3,4], the paper records of RT are not easily integrated into the hospital information system (HIS) [5-7], causing operational difficulties for medical staff across different departments. These difficulties included obtaining information such as a patient's cumulative dose, fractionations, and frequency of treatment through our HIS. Additionally, searching for treatment history in paper records is a time-consuming and inefficient process that can lead to errors, especially as the records are handwritten. Moreover, the software used in a linear accelerator is independent of the HIS in most radiation oncology departments. Doctors and other medical personnel must use 2 different systems, which means they often have repeated tasks. For example, when a physician wants to write an RT certificate for a patient, information such as date of treatment, total dose, and frequency of treatment must be entered into a certificate manually, which is prone to errors and is time-consuming. Integrating the 2 systems would allow doctors to work more efficiently and serve more patients. Structured data can also be used for future quality control and clinical medical research. Furthermore, various monthly and annual reports in an integrated system can allow the department manager to effectively monitor the clinical load in the department, and the data can be used as a reference for manpower deployment and overtime budget application [8].

In line with national policy and the needs of our hospital, an EMR system for the radiation oncology department was established. This study examines how the integration of the RT EMR system with our HIS improved the efficiency of our department and the accuracy of the data. In this study, we demonstrated that by consolidating the 2 separate systems into 1, we were able to significantly increase efficiency, save time, and conserve valuable resources.

Methods

Overview

In January 2020, the first meeting was convened to discuss the implementation of EMRs. Representatives from various staff groups, including physicians, physicists, medical radiation technologists, nurses, and engineers, were appointed to discuss workflow arrangements and functional requirements. The preliminary system was completed in July 2020, followed by internet-based testing and debugging. The updated system was fully deployed in August 2020, replacing the old system entirely. We kept a monthly review of the system in order to debug or improve the user experience.

The first step involved reviewing the paper documents, including graphs, tables, and written records. Staff from different departments held monthly discussions in the Radiation Oncology Department conference room, and the records of our meetings were saved in our database for the future. Our staff and engineers discussed the feasibility of transforming each item into electronic records. In the paper documents, check marks were made under the date in the table upon completion of daily treatment. If daily treatment was not performed, the field would be left blank. The total number of treatment days was calculated manually. Following discussions with the engineers, key information, such as the radiation beam energy, radiation technique, planned target volume and dose, treatment date, and daily treatment status, were selected as items to be included in the electronic records.

The subsequent step involved educating physicians about how to input treatment plan information into the HIS. A new electronic interface was designed for physicians to input crucial data, such as the treatment intent, planned target volume, planned dose, and planned number of treatment days. These data would then be integrated into the EMR.

In addition, daily treatment progress was recorded automatically in the HIS. The total number of treatment days was controlled by the electronic treatment plan entered by the physician, thus preventing unnecessary dose delivery. The EMR retrieved the actual treatment dates from the HIS, thereby providing precise treatment progress information. After several adjustments, the final version of the EMR system was launched in the HIS (Figure 1).

Figure 2 shows the comparison of the preparation processes between paper record usage and the integrated electronic record system. In order to evaluate the results of our integration, a comparison was made between the time taken to retrieve information from either the paper records or the EMRs for radiation preparation. A total of 30 cases were randomly allocated in both the old paper-based (legacy) system and the new EMR system. The time spent was calculated manually at every step during the process, and we performed an independent *t* test to evaluate the difference. All statistical analyses were performed with SPSS (version 23; IBM Corp). A *P* value of <.05 was considered statistically significant. This study explores the benefits of converting paper medical records in the radiation oncology department into EMRs and integrating them with the hospital's existing electronic medical systems. It does not involve personal information or related ethical issues.

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Figure 1. The final version of the electronic medical record (EMR), including the records of the past treatment of patients, a review of their past treatment status, and a link to the latest EMRs for tracking their current condition. CBCT: cone-beam computed tomography; CT: computed tomography; ICD9: International Classification of Diseases, Ninth Revision; ICD10: International Statistical Classification of Diseases, Tenth Revision; OBI: on-board imaging.

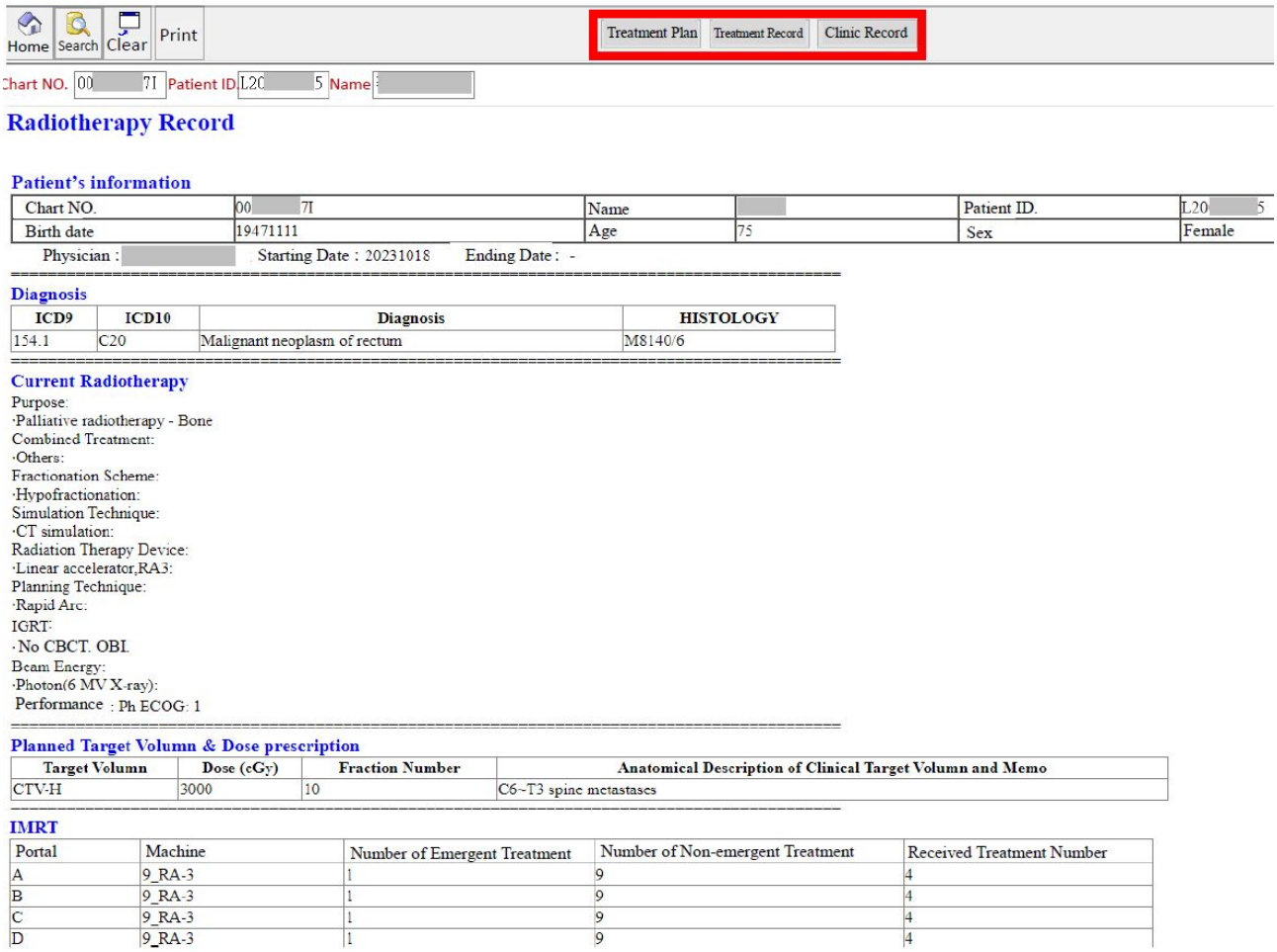
Home Search Clear Print

Treatment Plan | Treatment Record | Clinic Record

Chart NO. 00 7I Patient ID L20 5 Name

Radiotherapy Record

Patient's information

Chart NO.	00 7I	Name		Patient ID.	L20 5
Birth date	19471111	Age	75	Sex	Female

Physician : Starting Date : 20231018 Ending Date : -

Diagnosis

ICD9	ICD10	Diagnosis	HISTOLOGY
154.1	C20	Malignant neoplasm of rectum	M8140/6

Current Radiotherapy

Purpose:
·Palliative radiotherapy - Bone
Combined Treatment:
·Others:
Fractionation Scheme:
·Hypofractionation:
Simulation Technique:
·CT simulation:
Radiation Therapy Device:
·Linear accelerator,RA3:
Planning Technique:
·Rapid Arc:
IGRT:
· No CBCT. OBI.
Beam Energy:
·Photon(6 MV X-ray):
Performance : Ph ECOG: 1

Planned Target Volumn & Dose prescription

Target Volumn	Dose (cGy)	Fraction Number	Anatomical Description of Clinical Target Volumn and Memo
CTV-H	3000	10	C6~T3 spine metastases

IMRT

Portal	Machine	Number of Emergent Treatment	Number of Non-emergent Treatment	Received Treatment Number
A	9_RA-3	1	9	4
B	9_RA-3	1	9	4
C	9_RA-3	1	9	4
D	9_RA-3	1	9	4

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Figure 2. Comparison of the preparation processes between paper record usage and the integrated electronic record system. The integration of the electronic record system has led to a significant reduction in the time required for the radiation treatment preparation process. CT: computed tomography; HIS: hospital information system; OPD: outpatient department.

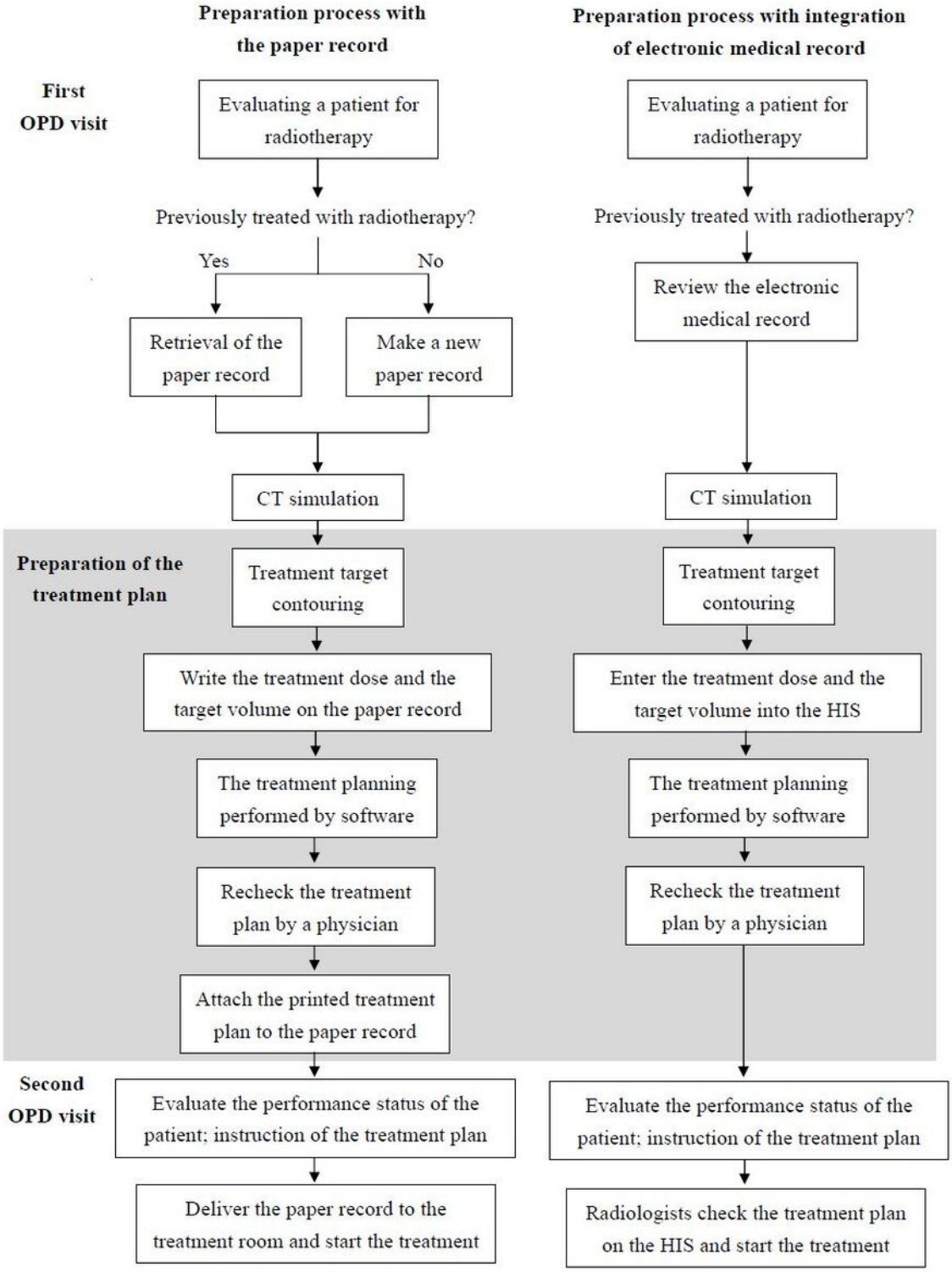

Ethical Considerations

Our research mainly focuses on the integration of the EMR system into the HIS and the efficiency of our new protocol in preparing RT records for new patients. The study does not involve personal or sensitive information related to human participants, so privacy and confidentiality protection considerations for human participants are not applicable [9]. There is no image or identifiable information related to an individual patient.

Results

Since launching in August 2020, the system has been highly used, with the number of medical records entered exceeding 1000 and continuing to increase. Integration of the system has

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meant that patient lists and their related information are now displayed (Figure 3), allowing physicians to easily check the treatment status of each patient. Physicians can also query the records of past treatments of patients, review their past treatment status, and link their latest EMRs to track their current condition. The new system can also export the files of all patients who have been treated in the past for the purpose of statistical analysis. Additionally, the number of treatment days for each patient can now be automatically calculated. The medical record writing format is now consistent among physicians.

As shown in Figure 2 the integration of the electronic record system has led to a significant reduction in the time required for the radiation treatment preparation process. The new protocol post integration of the EMR streamlines procedures by obviating the need for retrieving previous paper records or generating new ones. Physicians input treatment information directly into the HIS instead of transcribing it onto paper records, eliminating the necessity for printing treatment plans. In addition, physicians can scrutinize the treatment plan and monitor treatment progression seamlessly through the HIS. Radiologists, in turn, can access the treatment plan on the HIS and commence patient treatment, thereby economizing time previously spent awaiting the transportation of paper records. Specifically, the processing time has decreased from 286.8 minutes to 154.3 minutes (P<.001), representing a total reduction of 46.2%.

Figure 3. The list of patients and their related information created by our electronic medical record. Integration of the system allowed the patient lists and their related information to be displayed, allowing physicians to easily check the treatment status of each patient. RT: radiotherapy.

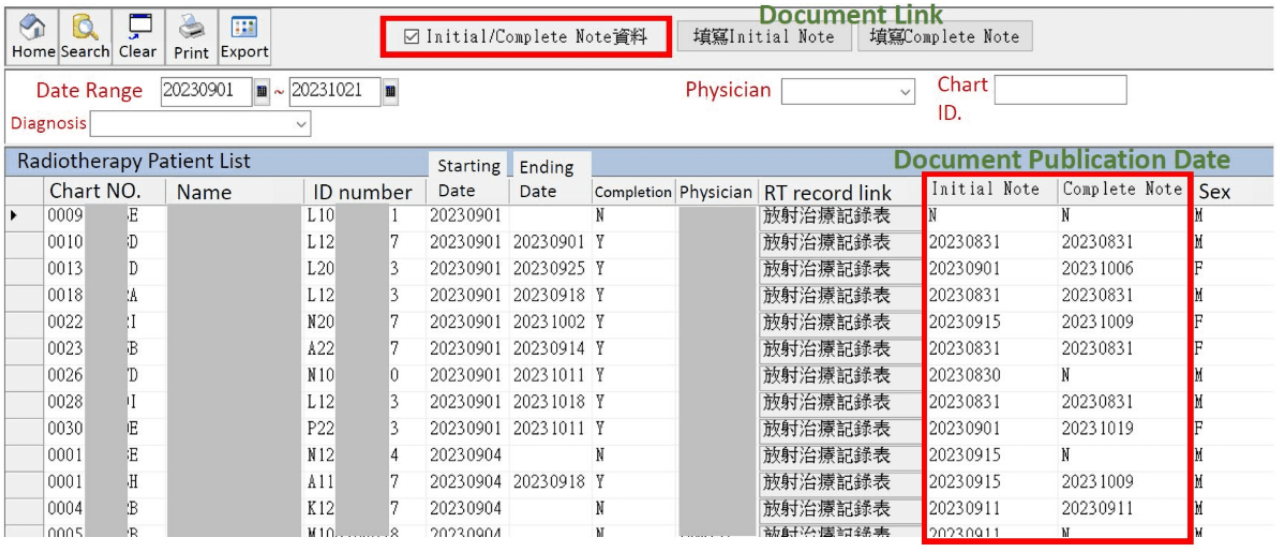

Discussion

Overview

Before the implementation of the EMR system, retrieving RT history was conducted manually, which was time-consuming and burdened nurses with a significant workload. The integration of the electronic system has simplified the process by eliminating several procedures and allowing physicians to instantly access RT records. Many new functions have also been added to this system.

First, the establishment of the new scheduling system allows physicians to modify the treatment schedules of new patients at any time. All staff in the department have the authority to modify the scheduling system. Second, the scheduling system has a hyperlink on the interface, which allows a doctor to view the patient's schedule while browsing the medical records, as well as edit the patient's RT notes. Third, a doctor can easily check the patient's status on the system. The patient list generated by the system can show information about a patient, including contact information, RT starting date or ending date, the number of treatments, and the completion status of RT notes.

The new electronic system has brought several benefits. First, it facilitates communication between physicians and other staff within the department. Clinical RT requires both intensive and extensive communication and cooperation among various groups of staff, including physicians, physicists, medical radiation technologists, nurses, and administrative personnel, in order to proceed smoothly. It is crucial that communication be both correct and instantaneous. With our system, a physician can enter the handover of a patient into the system, and a radiologist can read the handover before the treatment. Staff from different departments can also find the treatment details of a patient on the HIS.

Second, there is no longer a need to arrange for a nurse to organize the RT paper records, which saves a workload of 16 hours each month. Aguirre et al [2] concluded that electronic health records can minimize delays, increase health care workers' satisfaction, and decrease the chances of usability being compromised. Our study also showed that the integration of the radiation oncology EMRs and the HIS simplifies the workflow at our clinic (Figure 2), saving time spent performing radiation preparation procedures and enhancing efficiency. The protocol covered seamless transitions from one stage of the process to the next, ensuring that the entire workflow remained in compliance with standards for RT preparation. Furthermore, Chen et al [10] and Huang et al [11] showed that shortening the preparation time needed before the start of RT improved the treatment effect. Previous research has also shown that, with the assistance of an information system, the work process

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becomes smoother. Physicians can be given an automatic reminder or warning, which, in turn can shorten the necessary work preparation time from 12.2 days to 8.9 days [12].

Third, the statistical functions of this information system allowed the manager of the department to obtain accurate information on the number of people treated by each machine, as well as the number of fields per day, the number of simulations, the number of brachytherapy procedures, the number of people waiting for treatment, and the waiting time for each patient. The workload for each physician can also be monitored, and various monthly and annual reports allow the department manager to effectively trace the clinical workload in each treatment room. Monthly and annual reports can also be used as a reference baseline for manpower deployment and overtime budget applications [8]. Having mastery over these data can contribute to a better understanding of the operation of the department, and the information provided by the system can serve as important reference data for decision-making on issues such as whether to purchase new machines or modify manpower.

Additionally, the new system can assist with medical summary writing and education for a resident doctor. Each RT summary requires an average processing time of 10-15 minutes. Currently, with the new system, it only takes about 5 minutes to complete an RT summary because the detailed information on RT is automatically retrieved from the EMR. Doctors simply need to fill in the information about side effects and the treatment response. The system can also remind physicians to finish the initial note and to complete the RT summary when treatment is completed. For educational purposes, an electronic RT summary allows a resident doctor to quickly review the modifications from an attending physician and become familiar with the key points of the appropriate medical record [6,13].

Finally, at least 39,600 sheets of paper were used to prepare RT paper records per year, which is equal to 713 kg of carbon emissions. Furthermore, the demand for storage space tends to increase annually for paper records, but electronic records only require a relatively small physical space to store a large amount of patient data. The implementation of the improved EMR system has freed up space in our department that can now be put to better use. On the other hand, the number of our new patients increased annually. In 2020, we accommodated 1920 new patients, attended to 2118 newcomers in 2021, and extended our services to a total of 2230 fresh patients in 2022. Because the EMR system has decreased the number of radiation therapy transactions per day, physicians and nurses can manage clinical matters more efficiently, allocating more time for meaningful communication with patients. Furthermore, our department is relieved of the necessity to expand storage space for paper records as the EMR system adeptly conserves extensive patient data within a more confined space.

The system offers great flexibility for future expansion and can adapt to changes in clinical practice. We plan to improve the system by introducing an automatic patient registration system, a face recognition system, and an artificial intelligence scheduling system.

Limitations

The challenge of transitioning from paper records to electronic records remains high. The process is time-consuming and requires multidisciplinary team discussions. One limitation of our study is that the multidisciplinary team discussions only included engineers and staff in our department. Ideally, feedback and opinions should also have been collected from other departments in our hospital to improve our EMR system and make it more user-friendly. A survey to assess satisfaction with the new system will be conducted in the future. Any future studies should also have a larger sample size to validate our results. Furthermore, a comparison with other radiation oncology departments would be insightful.

Conclusion

The implementation of the integrated EMR system has resulted in a significant reduction in the number of steps involved in RT preparation, as well as a decrease in the amount of time required for the process. The new EMR system has provided numerous benefits for the department, including a decrease in workload, a simplified workflow, and conserving more patient data within a confined space.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

EMR: electronic medical record
HIS: hospital information system
RT: radiotherapy

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Protocol

Machine Learning Model for Readmission Prediction of Patients With Heart Failure Based on Electronic Health Records: Protocol for a Quasi-Experimental Study for Impact Assessment

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Abstract

Background: Care for patients with heart failure (HF) causes a substantial load on health care systems where a prominent challenge is the elevated rate of readmissions within 30 days following initial discharge. Clinical professionals face high levels of uncertainty and subjectivity in the decision-making process on the optimal timing of discharge. Unwanted hospital stays generate costs and cause stress to patients and potentially have an impact on care outcomes. Recent studies have aimed to mitigate the uncertainty by developing and testing risk assessment tools and predictive models to identify patients at risk of readmission, often using novel methods such as machine learning (ML).

Objective: This study aims to investigate how a developed clinical decision support (CDS) tool alters the decision-making processes of health care professionals in the specific context of discharging patients with HF, and if so, in which ways. Additionally, the aim is to capture the experiences of health care practitioners as they engage with the system's outputs to analyze usability aspects and obtain insights related to future implementation.

Methods: A quasi-experimental design with randomized crossover assessment will be conducted with health care professionals on HF patients' scenarios in a region located in the South of Sweden. In total, 12 physicians and nurses will be randomized into control and test groups. The groups shall be provided with 20 scenarios of purposefully sampled patients. The clinicians will be asked to take decisions on the next action regarding a patient. The test group will be provided with the 10 scenarios containing patient data from electronic health records and an outcome from an ML-based CDS model on the risk level for readmission of the same patients. The control group will have 10 other scenarios without the CDS model output and containing only the patients' data from electronic medical records. The groups will switch roles for the next 10 scenarios. This study will collect data through interviews and observations. The key outcome measures are decision consistency, decision quality, work efficiency, perceived benefits of using the CDS model, reliability, validity, and confidence in the CDS model outcome, integrability in the routine workflow, ease of use, and intention to use. This study will be carried out in collaboration with Cambio Healthcare Systems.

Results: The project is part of the Center for Applied Intelligent Systems Research Health research profile, funded by the Knowledge Foundation (2021-2028). Ethical approval for this study was granted by the Swedish ethical review authority (2022-07287-02). The recruitment process of the clinicians and the patient scenario selection will start in September 2023 and last till March 2024.

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Conclusions: This study protocol will contribute to the development of future formative evaluation studies to test ML models with clinical professionals.

International Registered Report Identifier (IRRID): PRR1-10.2196/52744

(JMIR Res Protoc 2024;13:e52744) doi:10.2196/52744

KEYWORDS

artificial intelligence; machine learning; readmission prediction; heart failure; clinical decision support; machine learning model; CHF; congestive heart failure; readmission; prediction; electronic health records; electronic health record; EHR; quasi-experimental study; decision-making process; risk assessment; risk assessment tool; predictive models; predictive model; Sweden; physician; nurse; nurses; clinician; clinicians

Introduction

Care for patients with heart failure (HF) causes a substantial load on the health care system. One of the prominent challenges associated with HF care is the elevated risk of readmissions within 30 days following initial discharge [1]. While this readmission risk underscores that patients receive life-saving care, it also encompasses implications of health care costs, patient's stress, and the impact of socioeconomic determinants on care outcomes [2]. The risk of readmission due to the worsening of HF symptoms is heightened by inappropriate treatment strategies, infectious complications, or prematurely executed discharges. Therefore, readmissions can be reduced by taking steps both during admission and hospitalization and post discharge to ensure compliance with care plans and improved treatment outcomes.

In current practice, clinicians make expert decisions, weighing in the probability of readmission of a patient by evaluating clinical data such as a patient's medical history, medication list, laboratory tests as well as social factors [3]. However, the process of assessing a patient's readiness for discharge introduces an element of subjectivity and uncertainty. Questions surrounding the probability of readmission emerge, prompting deliberation on optimal timing for discharge—whether immediately or with a slight delay. Additionally, the patient's social context plays a critical role; decisions must be made regarding the suitability of home care versus outpatient clinic assignment.

In pursuit of curbing health care costs and mitigating uncertainty novel risk assessment tools, often in the form of predictive models have been developed. Drawing upon statistical, conventional machine learning (ML), and deep learning methodologies, these tools are designed to identify patients at risk of hospital readmission [4-6]. Leveraging risk indicators such as age, illness severity, prior hospitalizations, and other factors, these models predict the likelihood of readmission within a specific time frame. Preventive approaches can then be developed and applied to target the identified high-risk patients. The profound potential for cost savings within the health care domain has fueled substantial interest in rigorous testing and validation of similar models, underscoring the imperative of optimizing patient care while securing resource efficiency.

In this project, our objective is to evaluate the applicability and potential benefits of a previously established ML model for predicting unscheduled readmission of patients with HF within 30 days after discharge from medical care [5]. This model has been further fine-tuned and tailored for practical integration and usage within clinical settings [3,7], encompassing the identification of potential barriers and enablers for implementing a clinical decision support (CDS) tool presenting the model output for clinical use. Refinement also encompassed the augmentation of the model with interpretability features and a comprehensive exploration of the optimal timing and manner in which the model's findings should be presented to users within the clinical domain [7]. The primary aim of the study outlined in this protocol is to investigate how the developed CDS tool alters the decision-making processes of health care professionals in the specific context of discharging patients with HF, and if so, in which ways. Additionally, the aim is to capture the experiences of health care practitioners as they engage with the system's outputs to analyze usability aspects and obtain insights related to future implementation.

Methods

Study Design

The design of this study used the principles of Template for Intervention Description and Replication [8] to support clarity of the description of the intervention and the replicability of its implementation. This study has a quasi-experimental design with a randomized controlled crossover assessment of 2 groups of physicians and nurses working in pairs. This study will be conducted within the health care settings of 1 region in Southern Sweden. The 2 groups will be presented with patient scenarios using purposeful sampling [9] on which they are to make decisions on subsequent care plans and treatment strategies.

HF Care Setting

An HF patient's referral to the hospital can occur through the emergency department, primary care, or home care services. Upon arrival, the patient is allocated to one of the medical departments within either of 2 hospitals in the included region possessing specialized cardiology units. Once admitted, a comprehensive care plan is made, considering the patient's symptoms, prior diagnoses, and relevant test results. This care plan also includes decisions regarding the appropriate timing for discharge. Within the framework of this study, this in-patient scenario, as detailed in a prior work [3], serves as the setting for HF care in which our investigation into the application of the CDS model takes place.

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Preparation for This Study

CDS Model

The model is based on comprehensive retrospective electronic health data in a Swedish region [10]. The cohort used for the development consisted of patients diagnosed with HF according to the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision;* I10.0, I42, I43, and I50), were residents, and receiving care in the region. The patients included were aged ≥40 years and had at least one admission after being diagnosed with HF between January 1, 2017, and December 31, 2019. All-cause hospitalization was considered. For each admission in the cohort, all patient's previous admissions within 5 years were considered from the time of admission as the medical history of the patient (look back period); these admissions are not considered as events in this study but were used only as historical data.

Besides demographic information, variables were collected out of electronic health data related to different categories. These categories can be detailed as follows: comorbidities in which patient conditions related to HF are traced back, for example, hypertension, diabetes, chronic kidney disease, and atrial fibrillation. Diagnoses (including procedures) and medications in the electronic health data system were represented according to standard schemas: *ICD-10-SE* (*Swedish version of the 10th revision of the International Classification of Diseases*) and Anatomical Therapeutic Chemical codes, respectively. Laboratory results were also used, including specific features for some laboratory tests, such as N-terminal prohormone of brain natriuretic peptide, sodium, potassium, ferritin, and estimated glomerular filtration rate. Variables were defined to indicate the level of abnormality in the obtained results of these laboratory tests. Following clinical feedback on model development, features associated with a patient's vital signs collected during the admission such as weight, heart rate, and blood pressure were also considered.

A conventional ML model was developed with *CatBoost*, which resembles gradient-boosting decision trees. The *CatBoost* model makes predictions using a series of decision trees, representing an explainable model [11]. In this study, the *CatBoost* python package (version 1.0.4) was used. The model was trained using a stratified 10-fold cross-validation, such that the training data were further divided into 10 parts where 90% (14,069) of data were used for training and 10% (1842) used for validation. Evaluation of the performance is based on commonly used performance measures such as sensitivity, specificity, F_1-score, receiver operating characteristic curves, the area under the receiver operating characteristic curve, and the area under the precision-recall curve. The performance of the model is presented in a retrospective ML study [7].

The Shapley Additive Explanations (SHAP) technique was adopted to provide more details behind the model decision regarding important features for readmission prediction [12]. SHAP works as a model-agnostic explanation tool and provides local (ie, patient-specific) as well as global explanations (ie, across patient cohorts). SHAP was used to compute explainability outputs for the selected patient scenarios, which were later used as input to the CDS tool. For each prediction, the most important features were listed that were positively or negatively driving toward the readmission risk. The explanations provided were assessed by physicians for clinical relevance.

Stakeholder Study

To prepare for the experiment, an interview study was performed to determine the potential barriers and facilitating factors for the implementation of the CDS tool. In total, 12 interviews with stakeholders were performed in a Swedish health care organization consisting of 2 hospitals, primary care, and partial home care. The views on the CDS tool were collected from different roles such as medical process leaders, medical specialists in cardiology, specialist nurses, physiotherapists, home care physicians, home care nurses, and administrative roles [3]. Interviews were transcribed and thematically analyzed to condense and categorize content.

Explainable Artificial Intelligence Design Process

A design process was carried out to create the user interface of the CDS tool. The initial phases included expert interviews, care process observations, and literature searches about the design of explainable artificial intelligence (AI) systems. There are several design problems to address in creating an interface for such a decision support system, for example, to understand who the intended users are and their needs, what information flows the system shall interact with, and in what part of the care process such information is relevant [13]. Therefore, an iterative design process was adopted, to move forward step by step, while generating and testing different design ideas.

Initial usability tests were conducted after generating a set of low-fidelity prototypes. In total, 5 clinicians (3 physicians and 2 nurses) were individually testing the different prototypes over recorded video calls. The tests evaluated if the prediction score and the explanation presented in the prototypes were understandable, and how clinicians perceived this information given the situation of an AI-model as the source. The tests gave important information on which language to use and what to display in the interface, which was the focus of the next iteration. The initial usability tests further raised questions about where this tool might be needed and who the users could be. Consequently, additional care process observations were made, which led to some changes to the definition of the target users and the place of potential implementation.

All usability test data were analyzed, categorized, and used as input for the further development of the prototype. Thereafter, additional usability testing was performed, following the same procedure as previous tests, however, focusing on exploring how to present more detailed information. Another 5 clinicians (three of them participated in the first usability tests) tested these prototypes over video calls. The outcome of this second round of usability tests was used as input to another design update before a high-fidelity prototype was created. This prototype was tested with 4 clinicians (2 physicians and 2 nurses who also participated in the previous tests).

As the last step of the prototype development, a series of design workshops were conducted with user experience resources, to finalize the prototype and set the details, before a smaller

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usability test was performed with 2 clinicians (1 physician and 1 nurse). Their input led to some minor interface changes, and now the development of the CDS tool could begin.

Scenario Creation

From the same data set used to develop the CDS model, 20 patients were selected to constitute the target population in this study by using stratified random sampling. The stratification was made to ensure that there are equal amounts of readmitted patients and control patients. For each of these 20 patients, scenarios comprising narrative reports and clinical data describing demographics, and clinical events and outcomes, including potential readmittance, were recreated retrospectively based on real patient historical data from the regional database of electronic health data.

Recruitment

The participants involved in the experimentation will include both physicians (n=6) and nurses (n=6) and will be recruited from the clinical staff at the 2 hospitals based on the following inclusion criteria: a minimum of 3 years of experience in the treatment of patients with HF, and currently active engagement in clinical practice within either of the 2 specialized cardiology departments in the region. This study will use purposeful sampling [9] for recruiting physicians and nurses according to the inclusion criteria, a process led by the hospital. Although there might be a limited availability of staff, physicians and nurses who were involved in the design of this study and the CDS model will be excluded from participation in this study, to prevent bias.

Experimentation and Data Collection

The experiment simulates the decision-making process of a patient's discharge, further treatments, and care plan, based on real historical data. Patient data for model output are preloaded into the CDS model. The participants will be randomly paired with 1 physician and 1 nurse in each pair, reflecting the real-world setup in the decision-making regarding the patient's potential readmission (Figure 1). Pairs will then be randomly assigned into test (n=3) and control (n=3) groups using simple randomization with stratification. The pairs in the test group will be given 10 scenario descriptions, patient electronic health record (EHR) data, and the CDS model output based on each of the 10 patients. The pairs in the control group will be given the same 10 scenario descriptions and EHR data but not the CDS model output. After making decisions based on the 10 scenario descriptions the test group and the control group will switch roles and 10 new scenario descriptions will be given to the groups, again with and without the CDS model output.

Figure 1. Flowchart for the randomized controlled cross-over design. CDS: clinical decision support; EHR: electronic health record.

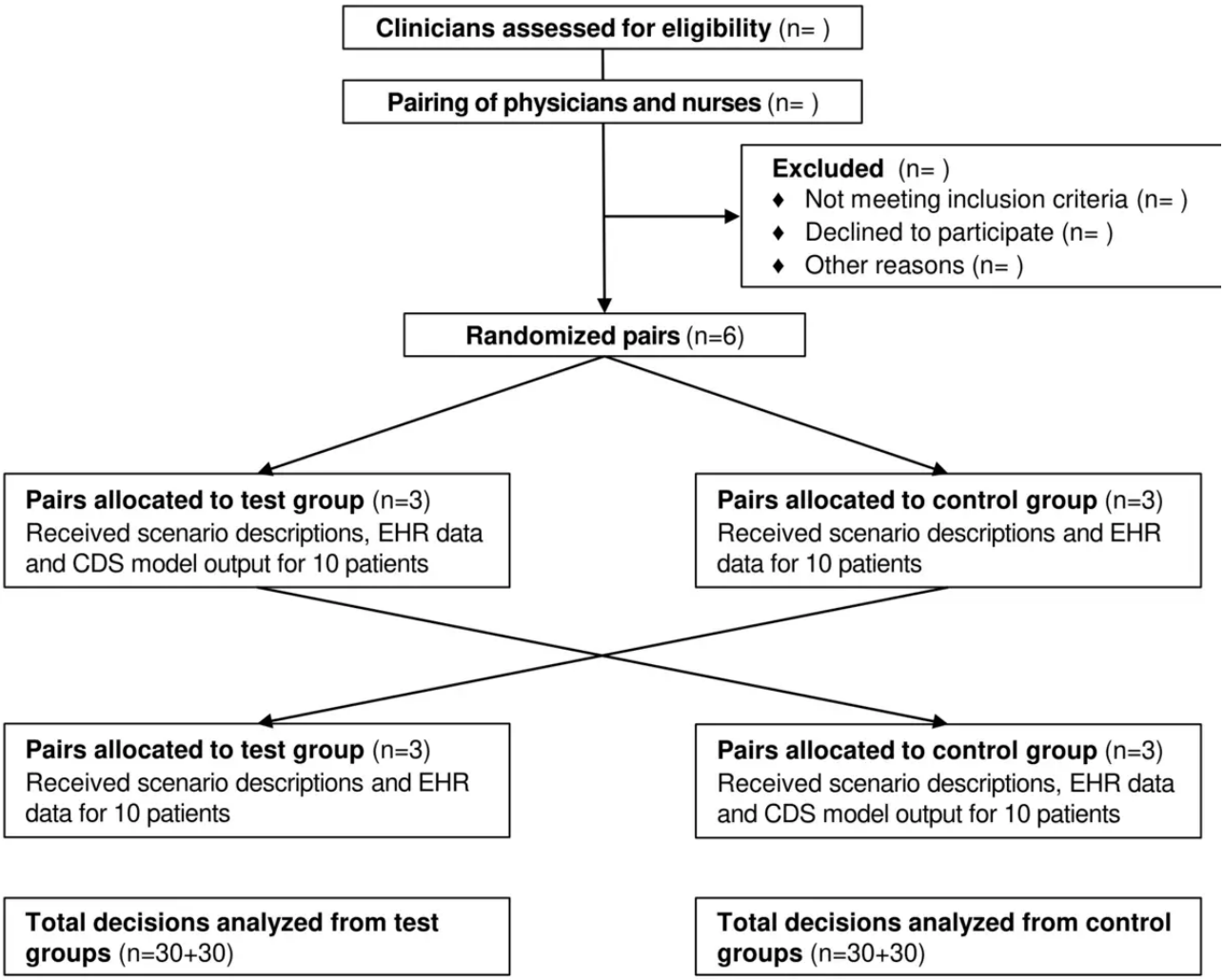

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Before the experiment, each group will be briefly trained in how the CDS model works and how to interpret its output [14,15]. The clinicians will be asked to think aloud so that both the conversation and reasoning during the decision process are recorded. The scenarios will be presented to the clinicians via a text document in a separate computer room at the hospital, and the CDS output in a web-based interface as depicted in Figure 2. The clinicians will be able to either make a decision or request for more information about the patient, which will be provided by an additional clinician who is part of the research group that will be in another room using a chat function on the local information system. This clinician is connected to the EHR system and has access to all patient data. The additional information can include admission notes, laboratory test results, and medication lists, and this procedure will be carefully explained to the clinicians before the experiment. This information will not be available from the beginning, to mimic the real-world information search between different systems or system modules and to research what level of information would be sufficient to decide in both groups; a clinician shall provide extra information about the patient only if requested. Every such request will be documented by the researchers present in the rooms together with the clinicians, observing the decision-making and the experiment. All clinical notes available in the experiment will undergo a deidentification process before this study. The decisions made by the participants will be noted by the observing researcher.

Figure 2. CDS model output showing readmission risk and explanations of model decision for a hypothetical patient. AI: artificial intelligence; CDS: clinical decision support; CDSS: clinical decision support system; HF: heart failure.

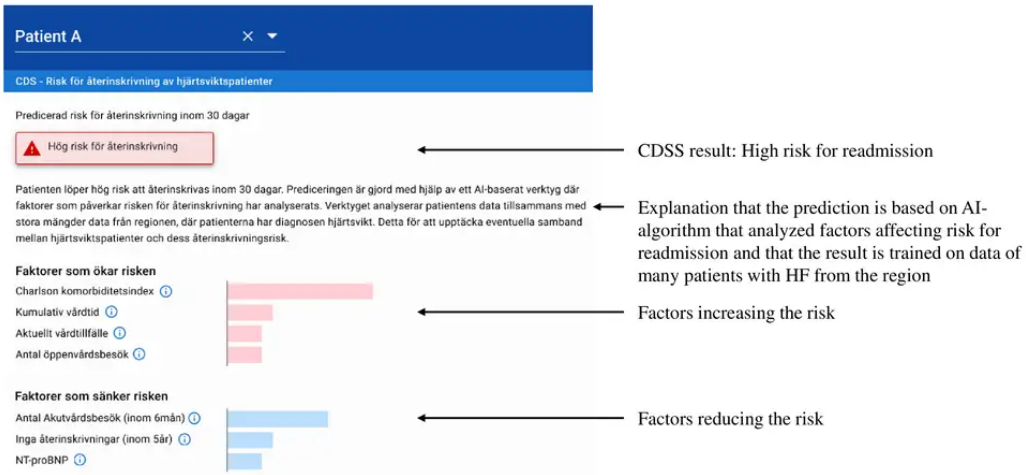

At the end of the experiment, each clinician will be interviewed individually by the researcher using the interview questions defined in Multimedia Appendix 1. The dialogue will be audio-recorded and transcribed verbatim.

Outcome Measures

A research-based evaluation framework specifically designed for AI-based decision-support systems [16] has guided and inspired the selection of the outcome measures for this study. The added value of the AI system will be assessed through a mixed methods evaluation design: process efficiency and patient-related outcomes shall be assessed using a quantitative approach, while quality, reliability, trust, and similar parameters shall be addressed through qualitative semistructured interviews. Table 1 provides details on the outcome measures selected for this study.

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Table 1. Outcome measures.

Outcome indicator	Goal	Analytic approach
Impact on decision-making		
Decision consistency	To explore decision consistency between the users and the CDS[a] model to research whether having the CDS model increases uniformity among the decisions taken compared to decisions without the model.	• Comparing the taken decisions: • Between the CDS model output and the test group to assess the extent of how much the users agreed with the model output. • Between test and control groups to assess similarity in decisions taken with and without the model output. • Potential decisions: • To discharge, with x, y, and z treatment. • Move to another department (which?). • Take additional tests for an extended investigation. • To send a referral or follow-up at outpatient clinical, primary care, or home care. • To stay for some more days.
Decision quality	To explore whether the CDS model could improve decisions.	• Comparing decisions taken by the test group with: • Historical data—what decision was actually taken for the patient and what event followed afterwards. • Control group's decisions on the same patients to control the influence of the experiment and set up over the decisions taken: do decisions differ from the test group and the historical data?
Work efficiency	To explore performance changes due to using the CDS model output.	• Measuring speed of decision-making for both test and control groups. Comparing the average speed between groups with and without CDS.
Impact on experience with decision-making		
Perceived benefits	Clinicians' attitude toward perceived benefit for patients and clinicians of AI[b].	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q1).
Knowledge	Knowledge sufficiency and possible gaps.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q5).
Confidence	Confidence in making decisions using the algorithm (trust in the algorithm and data, and self-confidence).	• Asking the participants in the test and control groups to take decisions for some patients with and without the CDS model output. Clinicians will be asked to rate their decision confidence and indicate to what extent the CDS output helped them using a 5-point Likert scale (1=not at all, 5=a great deal) [16]. • Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q3 and Q7).
Reliability and validity	How reliable and valid are the suggestions by the algorithm—perception?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q3).
Perceived service quality	How is the perception of the overall clinician-provided service perceived?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q2 and Q6).
Unintended consequences	Unintended consequences are foreseen.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q4).
Intention of use	Obtaining an indication of worthiness to continue developing the AI-based system.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q1, Q2, and Q6).
Implementation aspects		
Workflow integration	How integrable is the solution into the current workflows?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q4 and Q8).

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Outcome indicator	Goal	Analytic approach
Usability		
Perceived ease of use	Perception of the features, human-computer interface.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q5).

[a]CDS: clinical decision support.

[b]AI: artificial intelligence.

Data Analysis

The quantitative analysis will primarily employ descriptive statistics. The interview data to address the rest of the outcome measures shall be transcribed and thematically analyzed using the thematic coding scheme corresponding but not limited to the outcome measures of this study (Table 1) [16-18].

Ethical Considerations

This study conforms to the principles outlined in the Declaration of Helsinki and will fulfill the following requirements for research: information, consent, confidentiality, and safety of the participants, guided by the ethical principles of autonomy, beneficence, nonmaleficence, and justice. The anonymized patient data used in this study are available (2022-07287-02).

Patients whose data will be used for creating the scenarios will be informed through an advertisement on the university web pages and provided with the possibility to express a will to opt out of this study. The absence of an objection to the use of personal medical data in the research process will be considered as consent to participate.

All participants will receive written and oral information about the studies in which they are directly or indirectly involved. Participants will also be given information about the voluntary nature of the studies, confidentiality, and the ability to withdraw their consent at any time without having to justify why. All personal data will be registered according to the General Data Protection Regulation (GDPR2016/679) and the data will be stored per the Archive Act in Sweden (SFS1990:782).

Results

The project is funded by the Knowledge Foundation and is part of the Center for Applied Intelligent Systems Research Health research profile (280042), which started in July 2021 and ends in 2028. The profile conducts research projects in coproduction with industry about the development, design, and implementation of AI systems in health care. The project HF readmission prediction started in July 2021 and will end in June 2024.

The recruitment process will start in September 2023 and last until March 2024. First, the testing and fine-tuning of this study process using the prototype shall be conducted (planned for September 2023). Then, data will be collected and analyzed during the experiment from October 2023. This study's results are expected to be published. This research will involve several partners: Halmstad University (Sweden), Cambio AB (Sweden), and 1 Swedish region. This research aims to reduce avoidable readmissions of patients with HF.

Discussion

Principal Findings

This study focuses on the ML model for predicting unscheduled readmission of patients with HF within 30 days of discharge [5]. The purpose of the study described in this protocol is to assess the impact of this ML model on decision-making by health care professionals and to capture their experiences in using the model.

A quasi-experimental study shall be conducted with clinicians using the model and results shall be compared against a control group. Throughout the experiment, the researchers shall observe the decision-making process, take measurements, and collect feedback. Such knowledge shall increase an understanding of the potential impact on the decision-making, usability, perceived value if such a model is deployed, and willingness to use such tools in the future. Furthermore, this study will give practical insights into the factors that will potentially influence implementation that could be further used in the implementation process. In addition, concrete outcomes' measures are suggested which can assist in future developments of similar models.

This study has several limitations. First, although the CDS model output shall be provided as a digital interface, the system is not in this version integrated with EHR and it will not be possible to check the actual impact of the CDS model on the workflow. Second, the samples of admissions will be selected using stratified sampling where subgroups will be created for readmission labels assigned to patient encounters. The readmission rate in our data set is 21% (3334 out of 15,911 admissions), thus the chance to obtain enough examples where the readmission label is true will be very low. Accordingly, stratification will be used to divide the population data into 2 subgroups before sampling, then select 10 cases having true as a value for readmission label. Third, this study shall not assess the impact of the use of the model on the cost-efficiency or resource planning. Fourth, the presence of a researcher (an observer) in the computer room while clinicians assess the patient scenarios might influence the results.

To sum up, the findings from this study protocol shall contribute to the development and implementation of a CDS system based on ML models for readmission reduction. The results of this study will be presented at scientific conferences, seminars with professional organizations, articles for media outlets, and submitted to a scientific peer-reviewed journal specialized in health technology.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 13 KB - resprot_v13i1e52744_app1.docx]

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Abbreviations

AI: artificial intelligence
CDS: clinical decision support
EHR: electronic health record
HF: heart failure
ICD-10: International Statistical Classification of Diseases, Tenth Revision
ICD-10-SE: Swedish version of the 10th revision of the International Classification of Diseases
ML: machine learning
SHAP: Shapley Additive Explanations

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Protocol

An Approach to Potentially Increasing Adoption of an Artificial Intelligence–Enabled Electronic Medical Record Encounter in Canadian Primary Care: Protocol for a User-Centered Design

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Abstract

Background: Primary care physicians are at the forefront of the clinical process that can lead to diagnosis, referral, and treatment. With electronic medical records (EMRs) being introduced and, over time, gaining acceptance by primary care users, they have now become a standard part of care. EMRs have the potential to be further optimized with the introduction of artificial intelligence (AI). There has yet to be a widespread exploration of the use of AI in primary health care and how clinicians envision AI use to encourage further uptake.

Objective: The primary objective of this research is to understand if the user-centered design approach, rooted in contextual design, can lead to an increased likelihood of adoption of an AI-enabled encounter module embedded in a primary care EMR. In this study, we use human factor models and the technology acceptance model to understand the results.

Methods: To accomplish this, a partnership has been established with an industry partner, TELUS Health, to use their EMR, the collaborative health record. The overall intention is to understand how to improve the user experience by using user-centered design to inform how AI should be embedded in an EMR encounter. Given this intention, a user-centered approach will be used to accomplish it. The approach of user-centered design requires qualitative interviewing to gain a clear understanding of users' approaches, intentions, and other key insights to inform the design process. A total of 5 phases have been designed for this study.

Results: As of March 2024, a total of 14 primary care clinician participants have been recruited and interviewed. First-cycle coding of all qualitative data results is being conducted to inform redesign considerations.

Conclusions: Some limitations need to be acknowledged related to the approach of this study. There is a lack of market maturity of AI-enabled EMR encounters in primary care, requiring research to take place through scenario-based interviews. However, this participant group will still help inform design considerations for this tool. This study is targeted for completion in the late fall of 2024.

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(JMIR Res Protoc 2024;13:e54365) doi:10.2196/54365

KEYWORDS

primary care; electronic medical record; EMR; artificial intelligence; AI; contextual design; user-centered; design; electronic health record; EHR; Canada; Canadian; primary care; physicians; burnout; user; users; tools; provider-centered design; decision-making; AI tools; technology acceptance model; TAM

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Introduction

Background

In the Canadian health care system, primary care clinicians have played an integral role in providing continuity of patient care. Primary care clinicians are the first point of contact for patients and the health care system; their scope of work includes illness prevention, health promotion, diagnosis, treatment, rehabilitation, and counseling [1]. Approximately 93% of Canadian primary care physicians are using electronic medical records (EMRs) in their practice [2], which is a steep increase from the 37% of EMR use in 2009 [3]. An EMR can be defined as "a secure software system and its associated database. It is the record that primary care clinicians use within their practice environment to capture patient information such as a patient's family history, lab requests and results, cancer screening tests, emergency room visits, prescriptions, and more" [4]. EMRs were introduced and, over time, have gained acceptance and credibility for improving a primary care clinician's ability to provide care [5-7]. They have now become a standard part of care and are further supported through professional colleges and regulatory policies. EMRs have the potential to be further optimized with the introduction of artificial intelligence (AI). It is important to highlight how we can optimize and design AI in the primary care setting to ensure that it is ultimately supporting primary care delivery [5].

AI arguably has endless possibilities for application, which is what makes it both incredibly exciting and difficult to implement. With varying expectations and levels of comprehension, it is important to identify various stakeholders in the health care system and understand their expectations and intentions regarding AI in health care. The generalist approach and lack of specialization in a single system of the body make primary care a more difficult sector to embed AI into, in contrast to specific specialties such as oncology or diagnostic imaging. These areas of specialty allow data to be more specific, which makes the exploration of the use of AI more narrowly scoped than if it were primary health care [8]. The data available in health care are considered sensitive and highly personal. The way AI presents information to a clinician in an interaction has the potential to impact behaviors, including how decision-making is made [9-11]. Understanding human acceptance and the potential impact of a clinical encounter with the introduction of AI is a key milestone in enabling the industry to effectively predict the potential successes and barriers to AI-enabled products and services. A scoping review captured the various research foci related to AI in primary care research [8]. Its findings indicate that there has yet to be a widespread exploration of the use of AI in primary health care and how clinicians envision AI use to encourage further uptake [8]. This study supports the notion that research for primary care and AI is at an early stage of maturity [8]. Given the state of maturity, identifying the factors that influence the adoption of AI-enabled features in an EMR is essential to ensuring its acceptability by primary care clinicians.

The contextual design process will be used as the foundation of this research. Contextual design was first invented in 1988 and is continuously used in a wide variety of industries to drive innovative design [12]. Contextual design is a user-centered design process that uses techniques to analyze user data, drive ideation from the data, develop a design based on the data, and iterate these designs with the end users [12].

There are 3 distinct phases to contextual design as follows:

- Phase 1: Gathering user data. User-centered design recognizes that innovation starts with an understanding of the user by gaining an in-depth understanding of their tasks, motivations, intents, strategies, and detailed steps [12].
- Phase 2: Deriving insight from the data. Qualitative methods of understanding the data collected in Phase 1 are used to drive inductive insight into the design. This phase is further supported by other contextual design tools, such as affinity diagrams or experience models, to better articulate user design requirements [12].
- Phase 3: Taking data to design. This key phase involves translating the data to drive design thinking and visioning. Prototypes and mock-ups are redesigned with users to better fit their activities [12].

This process will be supported by the technology acceptance model (TAM) as a frame of reference. Although the TAM model has evolved in the last 30 years, the core of TAM remains focused on perceived ease of use and perceived usefulness [13]. Perceived ease of use and perceived usefulness influence attitudes and intentions, which can influence and predict user acceptance and adoption [13].

There is great potential and significant risk to advancing AI technologies in health care. The risk of embedding AI in an EMR encounter is disrupting an actively accepted and used tool that they perceive as a benefit to their performance [6,7]. Inappropriately introducing AI in the clinical encounter could impact its perceived usefulness, which could further deter the willingness and uptake of AI-enabled tools by primary care clinicians [14,15].

For the context of this research, the users are primary care health care providers (eg, primary care physicians, and nurse practitioners) in Ontario, Canada.

The primary objective of this research is to understand if the user-centered design approach, rooted in contextual design, can lead to an increased likelihood of adoption of an AI-enabled encounter module embedded in a primary care EMR. We are using human factor models and TAM to understand the results.

TELUS Health Partnership

To accomplish this, a partnership has been established with an industry partner, TELUS Health, to use their EMR, the collaborative health record (CHR). The CHR is TELUS Health's cloud-based EMR solution. The CHR has standard features such as the cumulative patient profile, free-text charting, custom forms, and electronic booking. However, it does have advanced functions, including streamlined clinical encounters, embedded virtual care, and real-time clinical and business intelligence.

The applicability of this proposed research is vast. This proposed work can demonstrate how to better optimize the use of AI-enabled products and services in the primary care setting,

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which is important given how the health care environment continues to evolve today. This can act as a key study that can inform some fundamental approaches to incorporating AI-enabled tools or services.

Methods

Overview

The approach of user-centered design requires qualitative interviewing to gain a clear understanding of users' approaches, intentions, and other key insights to inform the design process. This approach will be supported by qualitative methods to achieve the research objective. Several similar studies use a qualitative approach for user-centered design to inform technology acceptance in health care [14,16-19].

Preread material on AI and its capabilities within Canadian primary care has been developed for primary care clinicians to review in advance of the interviews.

Phase 1: Initial Interviews

All interviews will take place individually using a semistructured format comprising a standard set of scenarios with the ability to ask follow-up questions based on the participant's answer. This approach to interviewing enables a balance to provide purpose to the interview through the standard question set while also focusing the conversation on ideas and responses that can significantly inform the research and design considerations.

Several qualitative studies are conducted to inform contextual design in a clinical interaction. A number of these studies have demonstrated that anything over a total of 20 participants did not produce any significantly unique answers, which will inform our ability to reach data saturation with similar methods [16-18,20]. For this reason, we will recruit up to 20 participants in total. The participants will be comprised of primary care clinicians currently practicing in Ontario, Canada. Each participant will be asked to participate in the interview structure outlined below, with the potential for subsequent interviews to be requested based on input gathered at the secondary interview, primarily focused on validating findings from the first interview. All interviews will occur virtually using Microsoft Teams, where audio will be recorded and automatically transcribed through Microsoft Teams. Immediately after the interview, the interviewer will correct minor errors in the transcription.

Scenarios With the Primary Care Encounter Module

The goal is to understand a clinician's decision-making process through a clinical interaction with a patient and what key elements of workflow exist (eg, when do they document the clinical encounter, what do they consider distracting on their EMR screen, etc). Given the breadth and ambiguity of presentation in primary care, specific scenarios have been chosen focused on general approaches to primary care physician workflows. The primary module within the CHR that will be used for these interviews is the "Encounter." The Encounter module is where primary care clinicians spend the majority of their time documenting, even during a clinical visit. It captures information on patient responses to questionnaires, health history, examinations, assessment and planning, prescriptions, attachments, referrals, injections, follow-up items, and billing. Encounters require comprehensive information capture, making it an ideal module to focus on for added AI and its potential to impact how a physician captures a clinical encounter. Figure 1 shows the current structure of the Encounter module within the CHR.

Figure 1. The encounter module in the TELUS CHR in an empty state. CHR: collaborative health record.

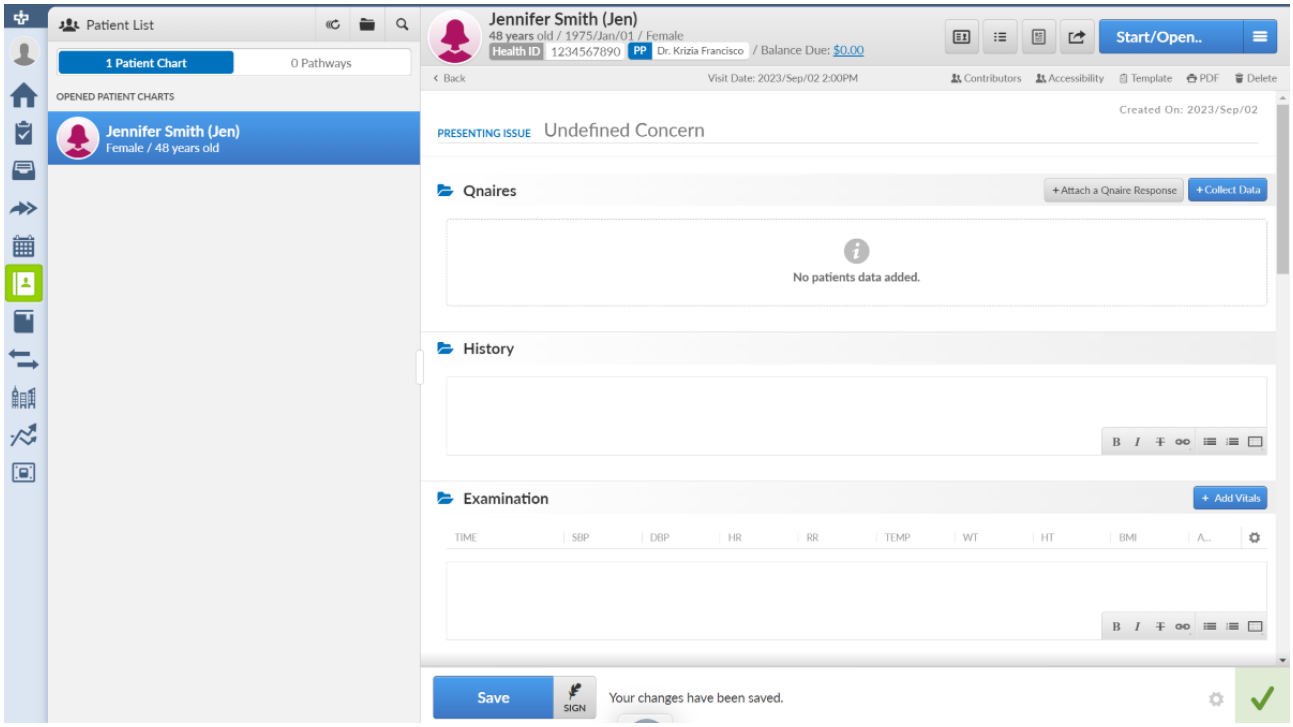

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Primary Care Physician Initial Interviews (Duration: 60 Minutes Total)

Part 1 (30 Minutes) Current State: Clinician

Overview

There will be an initial interview with the primary care physicians to understand their current approach to documenting clinical encounters during a visit. The goal is to establish a workflow of what clinicians use in their existing EMR for that particular scenario.

Scenario 1

Taylor Jones, a female patient aged 29, called your office 2 weeks ago requesting a visit related to her mental health. In preparation for her appointment, she was given a GAD7 to fill out at home; the results were then sent to your office, with a score of >15, indicating severe anxiety. This patient is now sitting in your office, and the encounter screen is open on your screen. What flow would you engage in? (eg, which sections would you expand first, what would you chart, and what are the questions you ask next).

Scenario 2

Alice Smith, a female patient aged 48, called your office with a suspected UTI. The last time she was prescribed an antibiotic for a UTI was over 2 years ago. The patient is now sitting in your office with this encounter screen open on your screen. What flow would you engage in? (eg, which sections would you expand first, what would you chart, and what are the questions you ask next).

Part 2 (30 Minutes; Scenario Exposure CHR Enabled With AI)

Overview

Physicians will be presented with the same scenarios as in the first interview, but now with an AI-enabled version of the CHR encounter. The objective is to understand how physicians will interact with the AI and whether it prompts differences in their workflow. Figure 2 shows example mock-ups that will be shown to primary care clinicians, demonstrating an AI-enabled version of the encounter module in the CHR. Scenarios 3 and 4 are the same as scenarios 1 and 2, except for adding an AI-enabled EMR encounter.

Figure 2. The AI-enabled version of the encounter in the CHR shown to clinicians during part 2 of the first interview. AI: artificial intelligence; CHR: collaborative health record; GAD7: Generalized Anxiety Disorder-7 Scale.

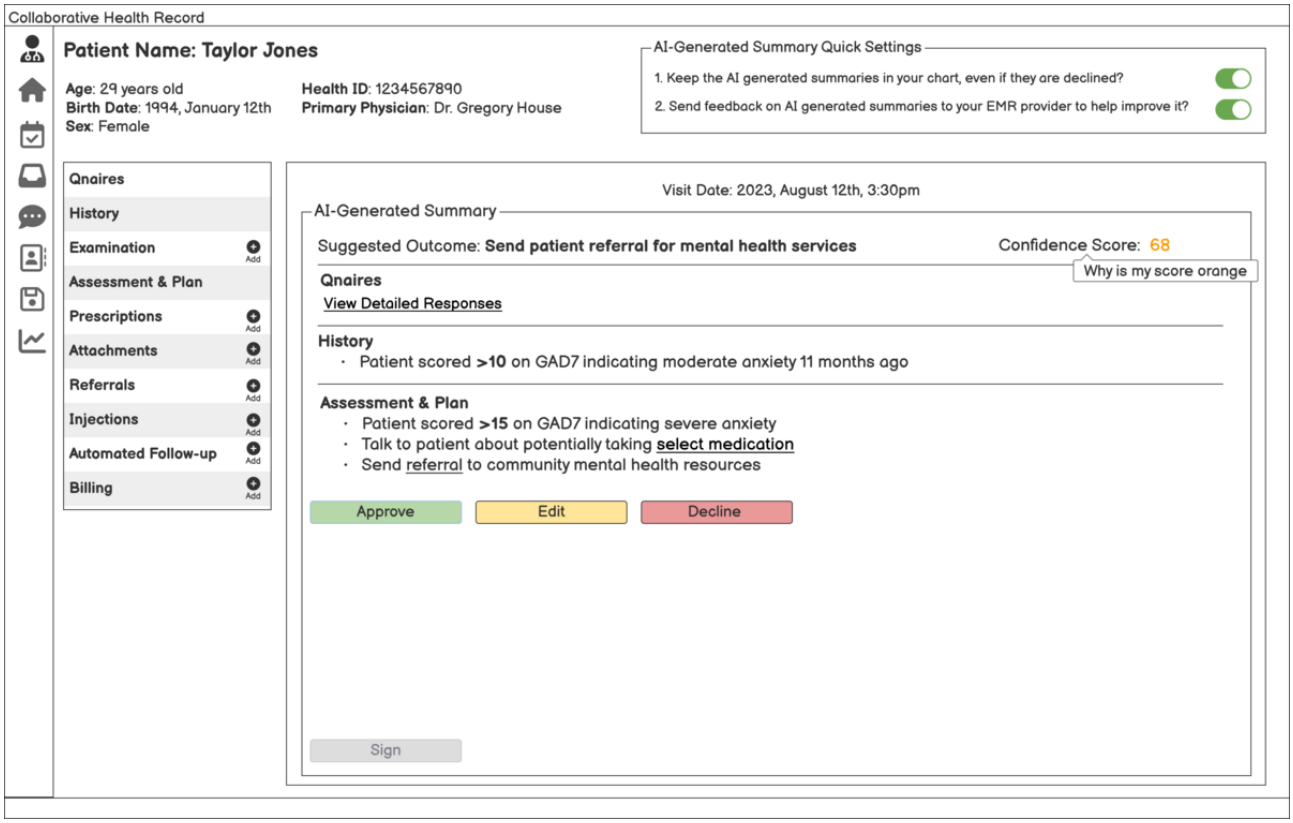

Scenario 3

Taylor Jones, a female patient aged 29, called your office 2 weeks ago requesting a visit related to her mental health. In preparation for her appointment, she was given a GAD7 to fill out at home; the results were then sent to your office, with a score of >15, indicating severe anxiety. Your EMR is now supported by AI, and before the patient's appointment, it processes the results and prepopulates your encounter. This patient is now sitting in your office, and the encounter screen is open on your screen. What flow would you engage in with the following screen? (eg, which sections would you expand first, what would you chart, and what are the questions you ask next).

Scenario 4

Alice Smith, a female patient aged 48, called your office with a suspected UTI. The last time she was prescribed an antibiotic

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for a UTI was over 2 years ago. Your EMR is now supported by AI, and before the patient's appointment, it processes the results and prepopulates your encounter. The patient is now sitting in your office with this encounter screen open on your screen. What flow would you engage in with the following screen? (eg, which sections would you expand first, what would you chart, and what are the questions you ask next).

This mock-up introduces the concept of an AI-generated summary for primary care clinicians. Key differences between this summary and a traditional EMR encounter are provided in Textbox 1.

Textbox 1. Key differences between the AI-generated summary and a traditional electronic medical record (EMR) encounter.

- A numeric confidence score. It is intentionally unspecified whether or not the suggested outcome confidence score is based on a large language model data set informed by best practice, the clinician's practice, or the organization's data set, as this is also a key design consideration that can be further explored in the interview.
- This also introduces the concept of "approve, edit, or decline" buttons in the EMR encounter to further understand how primary care clinicians want to interact with AI from a liability lens (eg, if a clinician declines what the AI is suggesting, do they want it to remain a part of the record? Or, if a clinician decides to edit the summary, do they want the chart to delineate what was AI-generated versus what was manually edited? Or do they view the note after it's been approved as their record is not distinguishable from what the AI suggested?).
- There are underlined actionable steps in this encounter (eg, "select medication"), demonstrating that the AI has not taken the further step of assigning a more specific medication to prescribe. Further probing clinicians on whether or not they think the AI has taken its suggestion too far, or not far enough.

Phase 2: Analysis and Reporting

The data collected throughout this research will be qualitatively analyzed concurrently with the interviews. This process aims to be deductive with the approach, supported by TAM, codes being sorted into one of 3 categories: perceived usefulness, perceived ease of use, and general attitudes towards using AI in health care practice. The coding techniques being applied are a result of the goals of the research being conducted. The codes discovered throughout the research will inform the various redesign approaches to an AI-enabled version of the CHR encounter. To provide further guidance related to AI-enabled primary care EMRs, key principles from design can be informed by a thematic analysis that results from the codes within the determined categories. A reporting guideline will be completed, the consolidated criteria for reporting qualitative research (COREQ), to further support the qualitative analysis [21].

The analysis will take place in the following way (Textbox 2):

The second and third steps in Textbox 2 are iterative and will be visited and then revisited numerous times until they become more refined and, as a result, more conceptual.

Textbox 2. Qualitative analysis.

- **Preliminary coding:** at this stage, the coding does not have to be accurate or final. The goal is to familiarize myself with the data that have been collected. Immediately after an interview, I will conduct preliminary coding, highlighting any significant quotes. At this stage, capturing ideas for analytic consideration while the study progresses is essential. These are vital first impressions that can provide a transitional link between raw data and codes [22].
- **First cycle coding:** the goal of the first cycle, once all interviews have been conducted, is to provide an initial analysis. Semantic coding will be used to do this. Specific segments of the interview data will be sectioned and labeled using either a word or a short phrase from that particular section of the data. Semantic codes do not require any interpretation beyond what the participants have said. These codes can be viewed as a description that only represents the content of the data as it has been communicated by the participant [22]. It is important at this stage that these initial codes provide enough context.
- **Sorting into categories:** categories were established based on the TAM and are indicative of the consolidated meaning that is being analyzed in the data. I am hopeful that the categories developed will be informative about the various design changes that can occur with an AI-enabled version of the CHR encounter.
- **Thematic analysis:** the outcome of the second and third steps is theme development. Coding and theming are not mutually exclusive procedures [22]. Themes are more descriptive versions of the categories discovered in the data. Theming data categorically provides descriptive detail about the patterns observed and constructed [22]. With the thematic analysis becoming a macro-representation of the patterns, these can be translated into fundamental principles that inform the future design of other AI-enabled digital tools in the primary care setting.

Phase 3: Develop User-Centered Design Requirements

The contextual inquiry methodology will be used to develop the user-centered design requirements. The principles of contextual inquiry enable the right type of interviewing to elicit design requirements, which include understanding the context, developing a partnership with the users, and engaging in the interpretation process. This method requires the researcher to assume a role similar to an "apprentice," where those being interviewed are experts in their own experiences. The introduction of AI technology within the CHR encounter for these common primary care visits is just 1 key component of a much broader process and experience that needs to be understood and considered. Contextual design is driven by the fact that products are always part of a larger picture, making this a suitable method to complement the proposed research [12]. The researcher minimizes the introduction of bias by moving through a continuous interpretation process; by engaging

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users in the interview process in sharing interpretation, they are typically quick to correct any misguided or misinterpretations that are shared.

The interview will provide initial exposure to an AI-enabled version of the CHR. Participants will be prompted to provide feedback on what they do and do not like about the interface or what they do and do not find helpful as a part of the interface. The interviews will also highlight critical experiences from participants and, through the contextual design approach, reveal intentions of what is not explicitly being said. This information will be interpreted and translated into design requirements which the redesigned mock-up interfaces will be based on. This information will be used to build personas to inform how these designs will be mocked up.

Phase 4: Redesign of an AI-Enabled Encounter Module in the CHR

Both categories and themes identified in the thematic analysis will be used to inform the redesign of an AI-enabled encounter module within the CHR. The goal is for the data to inform user-centered design requirements that accurately reflect the motivations, thoughts, and attitudes of the particular audience or participant. For example, what features on the output may be seen as adding friction and not providing value or purpose that can be presented differently?

Redesigns of the AI-enabled CHR will be completed in a low-fidelity wireframe using Balsamiq, focusing on functional design rather than aesthetic design. After phase 4 is completed, high-resolution wireframes that are consistent with TELUS Health's branding will be completed. TELUS Health will be involved in the iterative design process and will review the mock-up iterations before engaging in a usability study to refine designs further.

Usability Study

A usability study is required at this point in the process to select which of the redesigned AI-enabled mock-up interfaces are most usable and accepted. Based on other usability studies conducted with similar methods, 8-12 participants are considered reliable [23,24].

Participants will be given access to interactive wireframes using Balsamiq (Balsamiq Studios), accompanied by a system usability scale. As participants navigate the wireframes, open-ended questions will be asked to encourage further feedback on the redesigned interfaces. This system usability scale will be used to determine which of the redesigned outputs are best. Once this has been completed, the best designs will be mocked up using Figma (Figma Inc), a higher fidelity software that can more consistently reflect TELUS Health's CHR initial user-interface branding. These will then be presented in the secondary interview process. This method is well supported, efficient, and has a considerable amount of existing research to support its reliability.

Phase 5: Validate in a Secondary Interview (Duration: 60 Minutes)

Data gathered from the initial interview will be used to inform potential improvements that can be made. Alternative AI-enabled EMR encounter screens will be redesigned, mocked up, and presented to clinicians along with the scenarios they were presented during the initial interview. The goal is to understand whether or not the redesigned output was seen as an improvement from the initial designs in the first interview.

Recruitment of Participants

Targeted communications with well-known primary care networks will be used for recruitment (eg, primary care digital health networks, Association for Family Health Teams), in addition to direct emails to physicians or direct contact through social media platforms such as LinkedIn. The inclusion criteria for this study related to physicians is that they are primary care physicians actively practicing in Ontario. In addition, any other requirements outlined by the University of Waterloo's Office of Research Ethics will be implemented upon review of this research protocol application.

All participating primary care clinicians will be provided a one-time CAD $75 honorarium in the form of a VISA gift card in exchange for their valuable time and input.

Ethical Considerations

This study has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (43922). This application includes the formal consent letter that will be used to support the study and reiterate the confidentiality of participation, in addition to an oral consent script to be used with participants. Participants will be informed that transcripts of their interviews will be recorded and stored on an encrypted hard drive for a 7-year retention period in alignment with the University of Waterloo's best practice guidelines. Based on the feedback provided by this office, there may be minor changes made to the approach of this research study.

Results

As of March 2024, a total of 14 primary care clinicians have participated in this protocol, and their data have undergone the first phase of coding. The research team is assessing data saturation and strengthening the underlying theories that support this work related to the TAM. The results will be made available in a follow-up publication.

Discussion

Principal Findings

Some limitations need to be acknowledged related to the approach of this study. There is a lack of market maturity for AI-enabled EMRs in primary care, requiring research to take place through scenario-based interviews. Due to the limitation of risky investment in the actual development of an AI-enabled CHR, the proposed research would take place through scenario-based interviews with primary care clinicians and controlled exposure to mock-up interfaces of an AI-enabled CHR. This method can present several limitations. Given the lack of maturity in the use of AI-enabled EMRs in the Canadian primary care setting, it is difficult to provide users with a novel tool and not provide them with the guidance required to understand its use in a targeted context. This proposed research

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can continue to inform how standards compliance should be designed for AI-enabled tools, which can build credibility with clinicians over time.

There is also the limitation that scenario-based interviews limit our ability to observe and understand a person's natural use of the tool. There is still an opportunity to observe critical components of these tools that may cause a behavior change that can be isolated from other features of the proposed tool (eg, how only the output of a tool impacts a person's ability to make a decision). As the development of AI-enabled tools in primary care continues to mature, so will the ability to study and redesign their broader impact on clinical interaction.

In addition, the types of clinicians who choose to volunteer for this study may be more technically literate, which may not be representative of the general population's abilities or feedback related to using an AI-enabled tool in a diagnostic context.

Conclusions

This participant group will still help inform design considerations for this tool. However, if AI-enabled tools in the primary care domain gain more credibility, work needs to be done to understand the design implications for less tech-literate users. The proposed scenarios and methods will still gather the information required to inform key research questions and future design principles for AI-enabled tools in the primary care setting.

Research for primary care and the use of AI is at an early stage of maturity [8]. This research can contribute to assessing the real-world implications on primary care. This study is targeted for completion in late fall of 2024.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to the consent agreement that was established with all participants.

Conflicts of Interest

KMF is also employed with the industry research partner TELUS Health. To mitigate any conflicts of interest, a standard research partnership agreement has been signed by both parties indicating that the research results belong to the authors, and the research partner will only receive summaries and reports of the primary findings.

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Abbreviations

AI: artificial intelligence
CHR: collaborative health record
COREQ: consolidated criteria for reporting qualitative research
EMR: electronic medical record
TAM: technology acceptance model

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Protocol

A Novel Cognitive Behavioral Therapy–Based Generative AI Tool (Socrates 2.0) to Facilitate Socratic Dialogue: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Digital mental health tools, designed to augment traditional mental health treatments, are becoming increasingly important due to a wide range of barriers to accessing mental health care, including a growing shortage of clinicians. Most existing tools use rule-based algorithms, often leading to interactions that feel unnatural compared with human therapists. Large language models (LLMs) offer a solution for the development of more natural, engaging digital tools. In this paper, we detail the development of Socrates 2.0, which was designed to engage users in Socratic dialogue surrounding unrealistic or unhelpful beliefs, a core technique in cognitive behavioral therapies. The multiagent LLM-based tool features an artificial intelligence (AI) therapist, Socrates, which receives automated feedback from an AI supervisor and an AI rater. The combination of multiple agents appeared to help address common LLM issues such as looping, and it improved the overall dialogue experience. Initial user feedback from individuals with lived experiences of mental health problems as well as cognitive behavioral therapists has been positive. Moreover, tests in approximately 500 scenarios showed that Socrates 2.0 engaged in harmful responses in under 1% of cases, with the AI supervisor promptly correcting the dialogue each time. However, formal feasibility studies with potential end users are needed.

Objective: This mixed methods study examines the feasibility of Socrates 2.0.

Methods: On the basis of the initial data, we devised a formal feasibility study of Socrates 2.0 to gather qualitative and quantitative data about users' and clinicians' experience of interacting with the tool. Using a mixed method approach, the goal is to gather feasibility and acceptability data from 100 users and 50 clinicians to inform the eventual implementation of generative AI tools, such as Socrates 2.0, in mental health treatment. We designed this study to better understand how users and clinicians interact with the tool, including the frequency, length, and time of interactions, users' satisfaction with the tool overall, quality of each dialogue and individual responses, as well as ways in which the tool should be improved before it is used in efficacy trials. Descriptive and inferential analyses will be performed on data from validated usability measures. Thematic analysis will be performed on the qualitative data.

Results: Recruitment will begin in February 2024 and is expected to conclude by February 2025. As of September 25, 2024, overall, 55 participants have been recruited.

Conclusions: The development of Socrates 2.0 and the outlined feasibility study are important first steps in applying generative AI to mental health treatment delivery and lay the foundation for formal feasibility studies.

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KEYWORDS

generative artificial intelligence; mental health; feasibility; cognitive restructuring; Socratic dialogue; mobile phone

Introduction

Background

The use of digital mental health tools to augment traditional psychotherapies is becoming increasingly important due to a growing shortage of clinicians and other barriers to care (eg, cost and accessibility) [1-3]. Researchers have suggested that digital interventions can increase accessibility and reduce barriers to mental health care, offering flexible and scalable solutions [4,5]. To date, most of the existing digital mental health tools have relied on rule-based algorithms to provide mostly prescripted responses, at times resulting in these tools feeling less natural compared with dialogues with human therapists [6]. The ability of large language models (LLMs) to mimic human language provides the opportunity to build digital mental health tools that may feel more natural and engaging [7,8]. Building on recent advances relating to LLMs, our goal was to create and examine the feasibility of a generative artificial intelligence (AI) tool that can complement traditional cognitive behavioral therapies (CBTs) by facilitating a core therapeutic intervention: Socratic dialogue [9,10]. Developing the tool as a complement to traditional CBT allows it to fulfill basic functions, as other important therapeutic factors, such as other interventions or working alliances, can still be received through therapy. Given the current limitations of LLMs [7], our tool, Socrates 2.0, was designed to ultimately be used in conjunction with a licensed clinician to make the out-of-session CBT practice of evaluating one's thoughts more engaging compared with traditional worksheets. In this paper, we first describe our process of designing and completing the initial testing of Socrates 2.0, a multiagent tool built using LLMs. We then describe the protocol for a feasibility study to gather qualitative and quantitative data about users' and clinicians' experience of interacting with the tool.

Clinical Background

CBTs have been shown to be effective for a multitude of mental health disorders, including posttraumatic stress disorder, depression, and anxiety, among others [11]. A key intervention in CBTs is Socratic dialogue [9,10,12-15]. Although used in a wide variety of contexts beyond psychotherapy, the Socratic dialogue process therapists use is a collaborative approach to identifying and dismantling patients' unrealistic or unhelpful beliefs that lead to distress and the expression of psychopathology [9,10,12]. For example, in trauma-focused CBTs, such as cognitive processing therapy [12], common beliefs voiced by trauma survivors center on the perceived ability to have changed the outcome via different actions, such as "If I had dressed differently, I would not have been assaulted." The cognitive behavioral therapist's role using Socratic dialogue is to help the patient evaluate the specific belief in the context of the situation to which the belief refers, explore the factual support for the specific belief given relevant circumstances, and explore more realistic and helpful alternative beliefs [12].

Out-of-session practice (ie, homework) is common in CBTs and is often facilitated via worksheets that guide patients to identify, explore, and potentially challenge their thoughts using static Socratic questions. Although research demonstrates that learning and practicing skills via repeated practice and homework is important for symptom improvement [16-20], therapists frequently observe low homework completion rates in practice [21,22]. Possible reasons may include the challenging and noninteractive nature of the worksheets, the time it takes to complete them, and avoidance due to symptoms. We viewed the Socratic process as a good specific use case for an LLM-based tool that guides patients through this process. Given the advanced conversational abilities of LLMs [7], we hypothesized that the use of a tool such as Socrates 2.0 to facilitate Socratic dialogue could be feasible.

Design and Data Safety Considerations

To enhance user accessibility, the team prioritized ease of use in the design of Socrates 2.0. The aim was to create an intuitive interface, minimizing the need for therapists to extensively instruct patients on using the tool. After a straightforward log-in process, where users are reminded of the tool's limitations and prompted for their unique log-in credentials, the interface adopts a familiar chat layout. As shown in Figure 1, the initial interaction features Socrates introducing itself as an AI tool, preemptively clarifying its nonhuman nature. It then invites users to provide a belief they would like to explore or potentially change, a concept readily understandable within the context of CBTs.

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Figure 1. Socrates 2.0 user interface and dialogue example.

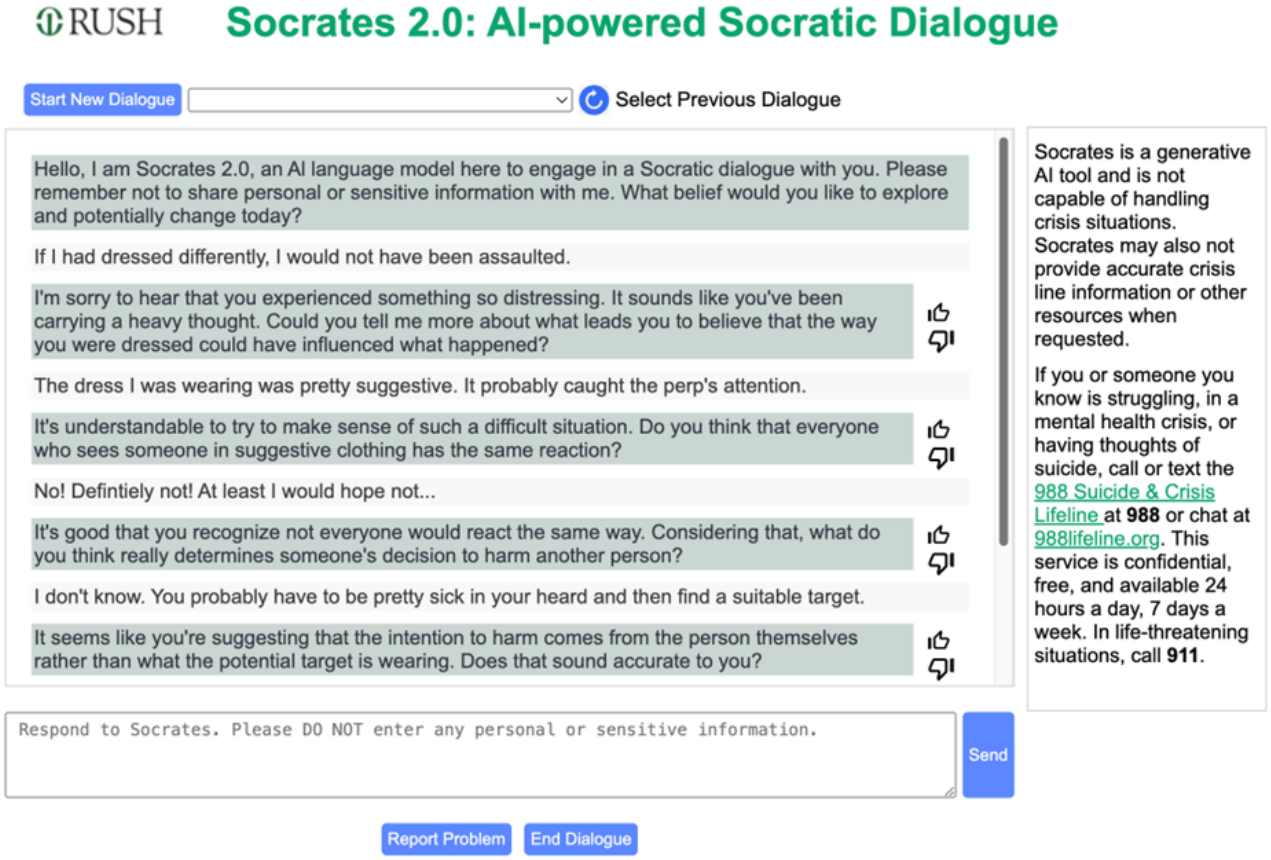

Recognizing LLMs' tendency to generate inaccurate content (hallucinations), information about this limitation and emergency contact details are prominently displayed (Figure 1). This constant visibility of the safety information and AI limitations ensures users are always aware and have necessary resources readily available during their interaction with Socrates. Additional design elements include a reminder in the text entry field against sharing personal information. Socrates 2.0 runs on our own instance of Microsoft Azure (Microsoft Corp) GPT4o (OpenAI) in the Road Home Program's dedicated resource group and Rush University Medical Center subscription. This is different from a public instance, such as simply connecting to ChatGPT via an application programming interface. The Microsoft Azure (Microsoft Corp) GPT4o (OpenAI) models are stateless, and no data (ie, user prompts or model-generated responses) are stored in the model. Moreover, none of the input or output data of the model or embedding and training data are used by other parties (eg, corporations and researchers). Socrates 2.0 was reviewed by our hospital's cybersecurity team and is fully compliant with Health Insurance Portability and Accountability Act and our hospital's data privacy policy. All user data are transferred through secure and encrypted https. All user data are always encrypted and then stored in databases. Users are also encouraged to refrain from providing personally identifiable information or personal health information when they log into Socrates 2.0's web interface to further decrease any potential risks.

Socrates 1.0

To create the first version of the tool, Socrates 1.0, the team initially used a zero-shot approach [23], prompting a single-agent model to engage the user in Socratic dialogue. Prompt engineering was facilitated by mental health treatment experts on our team with support from AI engineers. The resulting model was able to facilitate Socratic dialogue, but we noticed several issues, including model responses being overly elaborate or verbose, detracting from the natural flow of a therapeutic conversation. As exchanges became longer, Socrates 1.0 would also forget its role and get off task. We also noticed conversations would become cyclical and the model would get stuck in conversational loops. In addition to challenges with keeping conversations focused, it also became apparent that Socrates 1.0 struggled with determining when a user's belief had been explored or changed sufficiently to end the dialogue. Although human therapists do this relatively intuitively, monitoring session progress (ie, the extent to which a belief changes throughout the dialogue) and making decisions based on the progress (or lack thereof) are relatively advanced skills.

Socrates 2.0

To mitigate the aforementioned issues, we drew from real-world therapeutic processes and supervision experiences. We created a multiagent tool [24] by adding an AI supervisor and an AI external rater, which were designed to support the AI therapist in facilitating the dialogue without being visible to the user. All AI agents are based on GPT4o available through Microsoft Azure (Microsoft Corp); GPT4o was not fine-tuned for Socrates 2.0 (although GPT4o was used for Socrates 2.0, it is possible that similar performance could have been achieved using other available LLMs). The AI supervisor was designed to monitor the dialogue between the AI therapist and the user and provide real-time feedback to the AI therapist on how to improve the

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Socratic dialogue and keep the conversation focused. This process is similar to the bug-in-ear supervision method where human supervisors observe therapists' sessions and provide feedback in real time via a device in the therapists' ear [25]. Once the AI therapist receives the AI supervisor's feedback, it will integrate some of this feedback into future responses. Figure 2 shows the AI supervisor feedback in response to a dialogue and is taken from the developer version of Socrates 2.0, which differs from the production version in that it displays the external rater and supervisor feedback. In this example, following the monitoring of the ongoing exchange between the user and the AI therapist, the AI supervisor provides 3 concrete suggestions for improvement. As shown in Figure 3, the AI therapist's subsequent message incorporates the first of the 3 specific AI supervisor suggestions. By immediately incorporating AI supervisor feedback, the AI therapist can adjust the focus of the dialogue which can help improve the overall Socratic dialogue quality.

Figure 2. Socrates 2.0 artificial intelligence (AI) external rater and AI supervisor feedback. The first gray statement is from the AI external rater. The second gray statement in brackets is from the AI supervisor. Both responses are hidden from the user; this is a screenshot for illustrative purposes from the developer mode of Socrates 2.0.

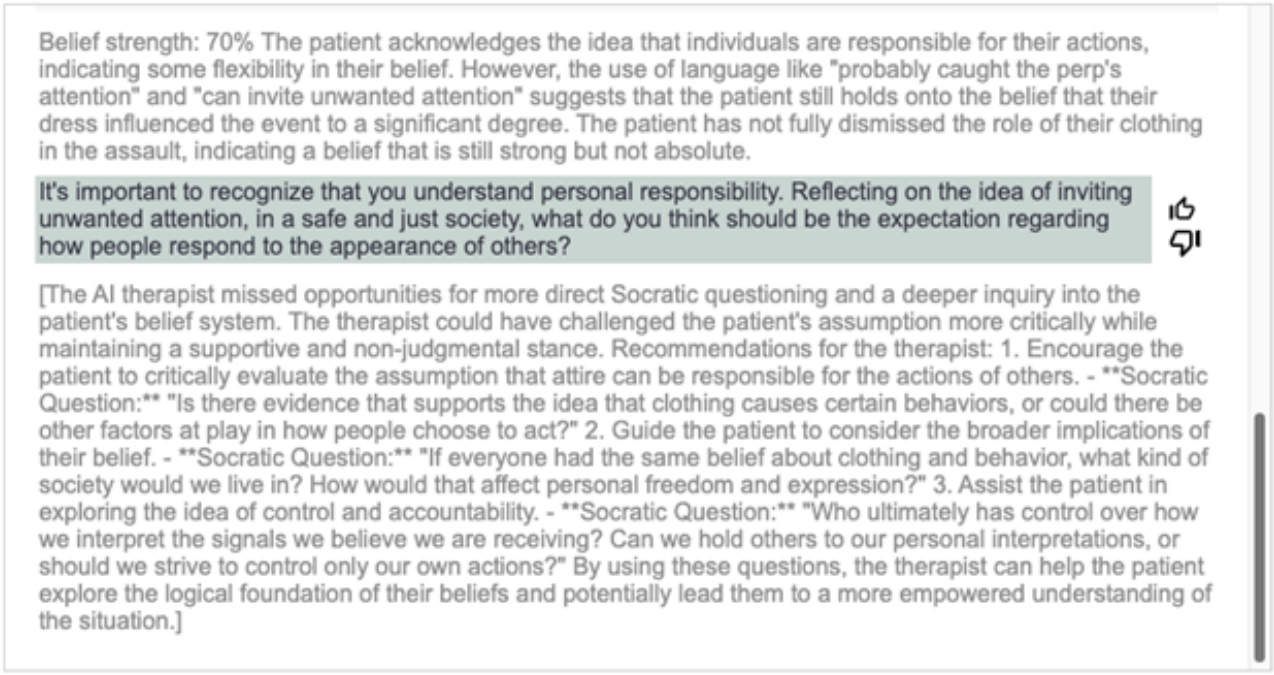

The AI external rater, which was designed to assess the dialogue progress by estimating the user's belief strength, is shown in Figures 2 and 3. When provided to the AI therapist, this information appears to aid in determining when the AI therapist needs to change the types of questions, such as in the case of an original belief not changing in strength or concluding sessions when the user's beliefs have meaningfully improved. Compared with Socrates 1.0, which did not include the AI external rater, the addition of the AI external rater appeared to drastically reduce the likelihood that the AI therapist would engage in infinite Socratic dialogue by providing belief change rating estimates.

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Figure 3. Socrates 2.0 integration of supervisor feedback. The gray statement without brackets is from the artificial intelligence (AI) external rater. AI external rater responses are hidden from the user; this is a screenshot for illustrative purposes from the developer mode of Socrates 2.0.

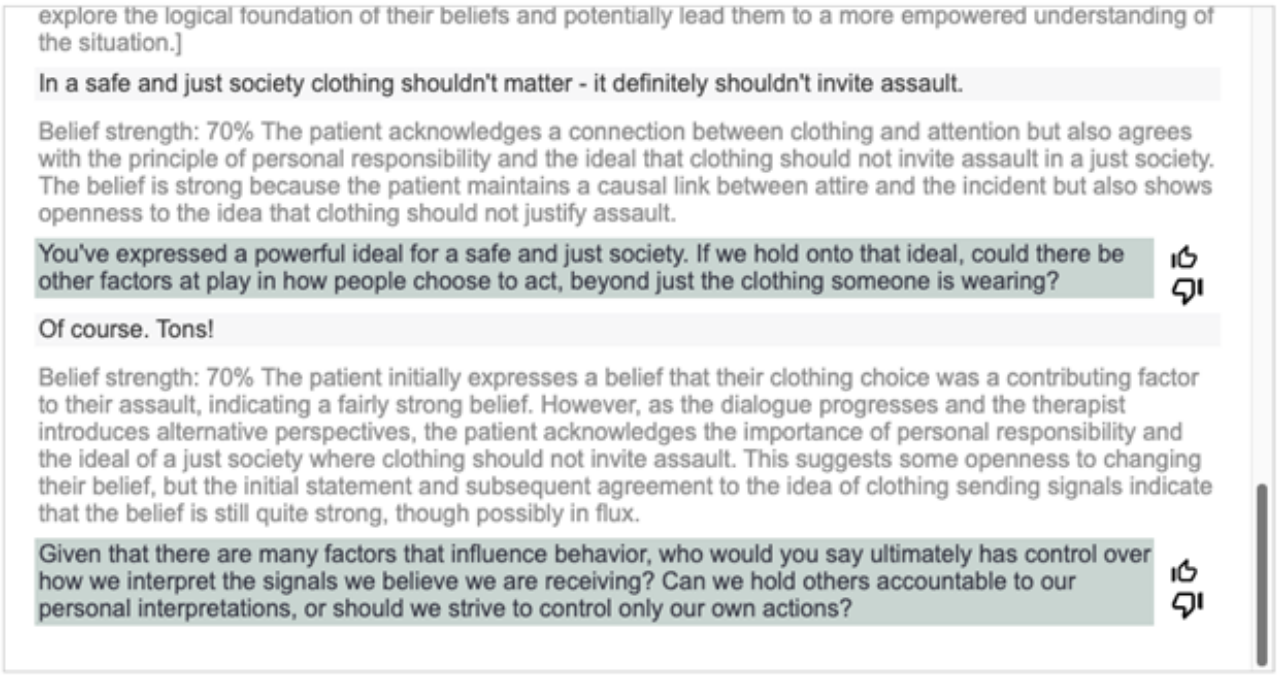

The interaction between the 3 AI agents is detailed in Figure 4. The average response time is approximately 2.11 seconds. To improve the experience and reduce wait times, the user sees the AI therapist respond as soon as it becomes available, even if the AI supervisor response, which takes approximately 7.69 seconds to generate, is still processing. The addition of multiple collaborative AI agents, which sets Socrates 2.0 apart from the original version, appeared to meaningfully impact the tool's behavior. Iterative prompt engineering was needed and used to improve the individual agent's behavior and how they worked together. For example, one key and somewhat comical issue the team needed to resolve via prompt engineering was LLM agents conversing with one another (eg, thanking each other for the valuable insights they each provided) in front of the user. Through the inclusion of multiple AI agents [24], CBT experts on our team felt as though Socrates 2.0 produced higher quality Socratic dialogue which seemed to resemble responses from a human therapist more closely.

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Figure 4. Socrates 2.0 artificial intelligence (AI) entity interactions.

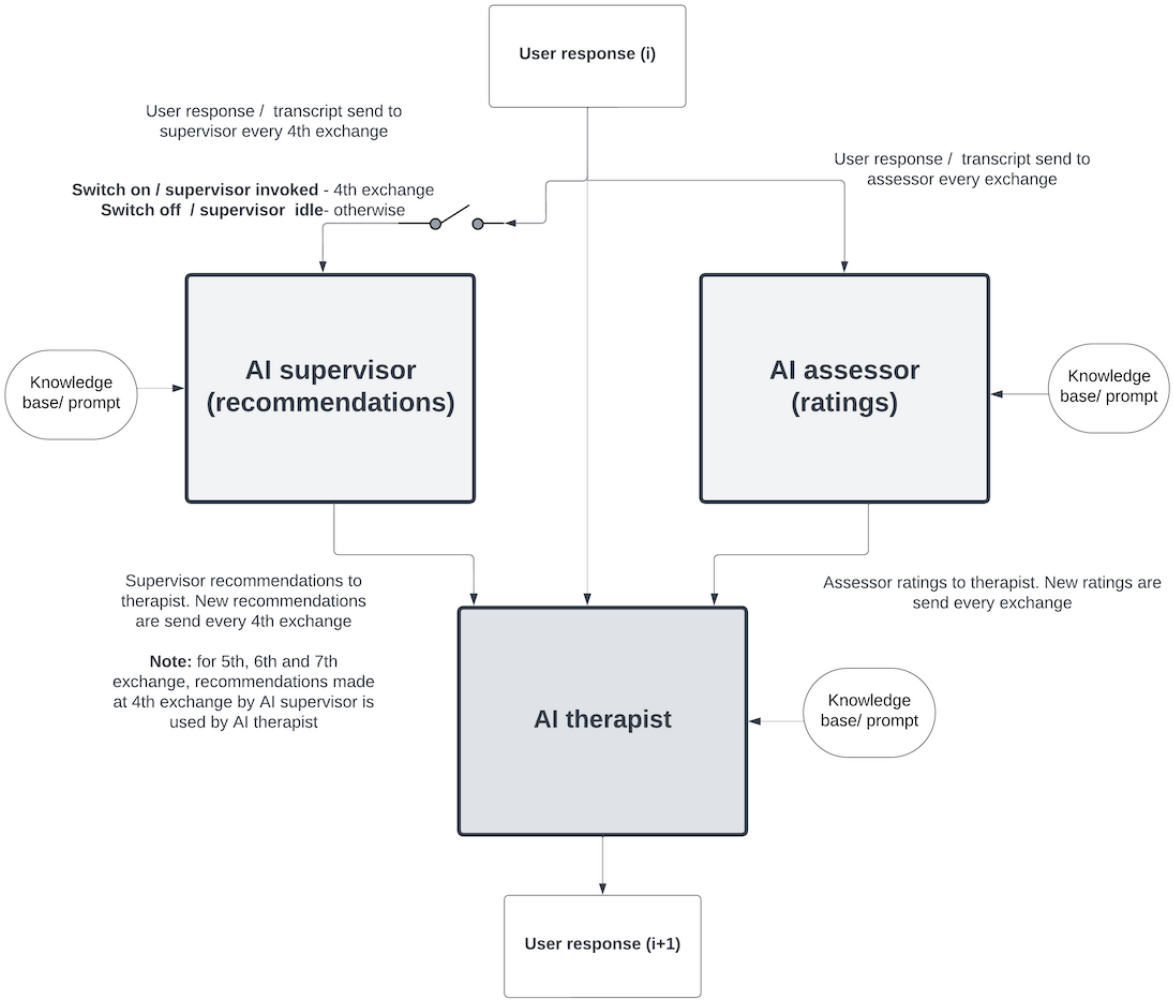

Initial Testing

Considering some of the known issues associated with LLMs, a key goal for our team was to ensure that Socrates 2.0 would not only provide users with a solid Socratic dialogue experience but also that it would not provide harmful responses [7]. This latter part was particularly important given its intended use in the context of mental health care. Our team's internal testing process involved engaging the AI in a diverse range of dialogues to assess the quality and appropriateness of its responses. In the absence of standardized methods to evaluate the response quality of generative AI tools in the context of mental health care, our team tested Socrates 2.0 across >500 conversational scenarios aimed at provoking potentially harmful responses, including the promotion of self-harm and harm to others, sexist and racist remarks, as well as other inappropriate therapeutic behaviors, such as flirting, among many other scenarios. The results were promising, showing that Socrates 2.0 generally avoided such responses. In extremely rare cases (<1%, n=1800 of test cases) where the tool was able to be triggered to provide undesired responses, the AI supervisor quickly (ie, usually within 3-4 exchanges) and effectively redirected conversations away from inappropriate content, further highlighting the benefit of multiagent tools.

Initial User Feedback

We first gave access to Socrates 2.0 to 6 trained clinicians at our academic medical center who are well-versed in Socratic dialogue. These clinicians had varying degrees of knowledge and comfort with AI tools for mental health. After engaging with Socrates 2.0, members of the study team elicited their feedback on the quality of the Socratic dialogue using a brief semistructured interview which asked about their overall impressions and potential usefulness when combined with clinical care and asked whether they could envision using the tool in their practice. Overall, clinicians were impressed with the quality of the interactions and found them comparable to that of a real-life clinician. Most (5/6, 83%) clinicians stated that they would consider using Socrates 2.0 with their patients, although it is important to recognize that these are clinicians who are used to adopting novel research-based tools and techniques.

We also elicited feedback from a community advisory board (CAB) made up of 6 members with lived experience of mental health disorders and CBTs. After having unlimited access to Socrates 2.0 for 1 week, study team members elicited qualitative feedback during a scheduled CAB meeting, by asking questions, such as "What was your overall impression of using Socrates 2.0?" and "What did you like or not like about engaging with

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Socrates?" The CAB's response to Socrates 2.0 was found to be overwhelmingly positive. They saw great value in being able to connect with the AI therapist at any time from anywhere:

> *I really like how it's always there- even in the middle of the night.*

Some specifically liked that it was not a real therapist, noting the following:

> *I feel like I can tell [Socrates 2.0] things I wouldn't say to a human therapist. I like feeling anonymous and it's non-judgmental.*

The CAB found the tool more engaging than common CBT worksheets and suggested they would be more likely to complete out-of-session practice assignments if it involved using Socrates 2.0. User data from that week showed that CAB individuals engaged with Socrates multiple times, with some users using Socrates for up to an hour at a time. The CAB also provided feedback on changes they would like to see with Socrates 2.0, many of which were cosmetic and accessibility-related changes ("I'd like the option to customize my experience, like changing font size, colors, and the background," "I want to be able to use voice rather than text"), which are currently in development for future versions of the tool.

Feasibility Study

Following the initial development of Socrates 2.0 and the obtained data from initial users, we devised a feasibility study to formally gather data about users' experience of interacting with the tool. The goal is to gather feasibility and acceptability data from both patients and clinicians, as information from both groups is critical to inform the eventual implementation of generative AI tools, such as Socrates 2.0, in mental health treatment. We designed this study to better understand how users engage with the tool, including the interaction frequency, length, and time, users' satisfaction with the tool overall as well as the quality of each dialogue and individual responses. Through the feasibility study, we also plan to obtain information about the ways in which the tool should be improved before it is tested in trials designed to examine the efficacy of Socrates 2.0.

Methods

Study Design

The study will use a mixed methods design, combining quantitative and qualitative methods to assess the feasibility of Socrates 2.0 from the perspective of users (ie, potential patients) and clinicians. The decision to obtain feedback from both users and clinicians was made so that our team could better understand how users would perceive the tool and to understand how clinicians could see integrating such a tool into their treatment. The mixed methods approach enables a comprehensive evaluation of the tool from multiple perspectives, providing quantitative feasibility, acceptability, satisfaction, and use of data for statistical analysis, as well as rich contextual data for a qualitative analysis of users' experiences and perceptions. The combination of quantitative and qualitative data captured throughout this study will be used to make further improvements to Socrates 2.0.

Individuals who consent will be asked to complete brief semistructured interviews and surveys before and after using Socrates 2.0. Users will be granted access to Socrates 2.0 for 4 weeks; clinicians will be granted free unlimited access to Socrates for 2 weeks. During the access period, individuals will be asked to use the tool at their convenience and as often as they wish. To maintain confidentiality, a unique identifier (ie, a combination of random numbers and letters) will be assigned to each participant. During the informed consent process, participants are informed of the potential risks, including loss of confidentiality if their dialogues were to be obtained by someone other than investigators. To help mitigate this risk, in addition to using unique identifiers that only the study team could link to the participant, users are reminded to not give Socrates 2.0 any identifying information about themselves when using the tool to further protect their identity.

Study Setting

The study will be conducted through the Road Home Program: National Center of Excellence for Veterans and Their Families at Rush University Medical Center in Chicago, Illinois. All qualitative interviews will be conducted via approved and secure video technology (eg, Microsoft Teams; Microsoft Corp), and quantitative feasibility, acceptability, and satisfaction data will be obtained via REDCap (Research Electronic Data Capture; Vanderbilt University) surveys emailed to participants.

Recruitment

A total of 100 users and 50 clinicians will be recruited to inform the eventual implementation of generative AI tools, such as Socrates 2.0, in mental health treatment. As Socrates is a web-based application and can be accessed via the internet from anywhere, recruitment is open to all individuals, not just patients and providers at Rush University Medical Center. Participants will be recruited from a variety of sources to ensure a diverse sample. Recruitment will occur via The New Normal, Rush University Medical Center's website, social media, and word of mouth.

Eligibility

Interested individuals will be screened for general eligibility and will be provided with an electronic version of the consent form. Individuals will be informed that they can contact the study staff before signing the consent form if they have questions. Individuals are eligible to participate in the study if they are aged ≥18 years and have reading and writing proficiency in the English language at least at the sixth-grade level. As Socrates 2.0 is a web-based application, participants must have access to a stable internet connection and a device, such as a computer, tablet, or smartphone, to use the tool and possess the basic technological skills necessary to navigate the tool effectively. In addition, participants must be willing to test and engage in Socratic dialogue with the tool. Aside from not meeting the inclusion criteria detailed earlier, there are no specific exclusion criteria. By having broader inclusion, we hope to be able to speak about the potential of the tool's feasibility for broader groups and have a more representative community sample. This information would then lend itself to

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more targeted and highly controlled studies of specific presenting concerns.

Measures: Users

Overview

Following the consent process, participants will be assessed using a combination of surveys and semistructured interviews before and after their 4-week engagement with Socrates 2.0. In addition, objective data based on their interactions with Socrates will be obtained by the research team. The specific data and timepoints at which the data are collected are detailed subsequently. Users and clinicians are asked to complete slightly different assessments; clinician measures are presented subsequently. Table 1 shows the study measures and timepoints for both the users and clinicians.

Table 1. Study measure descriptions and timepoints.

Measure	Timepoint	Purpose
User		
Demographics	Baseline	Characterization of sample
Patient Health Questionnaire-4	Baseline and 1-month follow-up	Assessment of depression and characterization of sample
Interaction Anxiousness Scale-3	Baseline and 1-month follow-up	Assessment of social anxiety and characterization of sample
PTSD[a] Checklist-4	Baseline and 1-month follow-up	Assessment of traumatic stress symptoms and characterization of sample
Obsessive-Compulsive Inventory-4	Baseline and 1-month follow-up	Assessment of obsessive-compulsive tendencies and characterization of sample
Washington Early Recognition Center Affectivity and Psychosis	Baseline and 1-month follow-up	Assessment of potential mania or psychotic symptoms and characterization of sample
System Usability Scale	1-month follow-up	Assessment of usability
Acceptability of Intervention Measure	1-month follow-up	Assessment of acceptability
Intervention Appropriateness Measure	1-month follow-up	Assessment of tool appropriateness
Feasibility of Intervention Measure	1-month follow-up	Assessment of feasibility
mHealth[b] App Usability Questionnaire	1-month follow-up	Assessment of ease of use, satisfaction, and usefulness
Working Alliance Inventory-Short Revised	1-month follow-up	Assessment of feelings of rapport and experiences with a therapist
Satisfaction	1-month follow-up	Assessment of satisfaction with overall use of Socrates
Engagement rates, completion rates, and API[c] token use	While using Socrates	Time using Socrates, length of dialogue, and number of tokens used during each exchange
Clinician		
Demographics	Baseline	Characterization of sample
System Usability Scale	2-week follow-up	Assessment of usability
Acceptability of Intervention Measure	2-week follow-up	Assessment of acceptability
Intervention Appropriateness Measure	2-week follow-up	Assessment of tool appropriateness
Feasibility of Intervention Measure	2-week follow-up	Assessment of feasibility
mHealth App Usability Questionnaire	2-week follow-up	Assessment of ease of use, satisfaction, and usefulness
Satisfaction	2-week follow-up	Assessment of satisfaction with overall use of Socrates
Engagement rates, completion rates, and API token use	While using Socrates	Time using Socrates, length of dialogue, and number of tokens used during each exchange

[a]PTSD: posttraumatic stress disorder.

[b]mHealth: mobile health.

[c]API: application programming interface.

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Demographic Characteristics

Participants will be asked to complete a brief demographic questionnaire at baseline asking them about their age, gender, sexual orientation, ethnicity, race, education, marital status, employment status, household income, and service member or veteran status. The information will be used to characterize the sample and to determine whether any of the participant characteristics are associated with feasibility, acceptability satisfaction, as well as the ways in which participants engage with Socrates 2.0.

Pre- and Post-Socrates 2.0 Mental Health Screening Assessments

Participants will be asked to complete brief validated self-report assessments for various mental health areas at baseline and after their month of access to Socrates 2.0. Mental health screening assessments will be used to characterize the sample, understand how mental health symptoms at baseline may impact engagement with the tool, and explore whether potential mental health symptoms change may be statistically associated with the use of Socrates 2.0. Brief screening assessments were chosen to reduce participant burden. To assess depression and generalized anxiety, participants will be asked to complete the Patient Health Questionnaire-4 [26]. The Interaction Anxiousness Scale-3 [27] will be administered to assess social anxiety. Obsessive-compulsive tendencies will be assessed using the Obsessive-Compulsive Inventory-4 [28]. Traumatic stress symptoms and potential manic or psychotic symptoms will be assessed via the Posttraumatic Stress Disorder Checklist-4 [29] and Washington Early Recognition Center Affectivity and Psychosis screen [30], respectively.

Before Engaging With Socrates

Participants will be asked to complete a brief semistructured qualitative interview with trained study staff. The interview is intended to better understand participants' familiarity with AI tools, mental health apps, and prior engagement with mental health services. Participants will be asked semistructured questions. Each semistructured question may be followed up with encouragers to expand on the answers participants provide. The questions are presented in Textbox 1.

Textbox 1. Semistructured interview questions and encouragers.

- Have you ever used an AI tool before?
  - If yes, what kinds? How often? For what purpose?
- Are you currently using, or have you used apps/tools for mental health before (eg, Headspace, Calm, BetterHelp)?
- Have you ever engaged with mental health services?
  - If yes, what kinds?
- Have you ever used an AI tool for mental health services?

Following the semistructured interview, the study staff will provide participants with an overview of Socrates 2.0 and walk them through how to use it. The study staff will ensure that participants can log into Socrates 2.0 and answer any questions they may have about using the tool. If requested by the participant, the study staff can be available to answer questions about the tool following the initial overview. The study staff will follow a brief script when introducing the tool, which encourages participants to use Socrates 2.0 as many times as they would like, at any time of the day. Clinicians will be encouraged to engage with Socrates 2.0 as if they were a patient.

While Engaging With Socrates 2.0

Participants can provide "thumbs up" or "thumbs down" ratings for responses that Socrates provides. This is optional and intended for participants to indicate particularly helpful or unhelpful responses.

After Engaging With Socrates 2.0

Participants will be able to complete a brief Likert-scale survey about their satisfaction with and the perceived helpfulness at the end of each exchange. Participants will also be provided with an option to provide any open-ended feedback they may want to share with the study team about the interaction.

One Month After First Engaging With Socrates 2.0

One month after first engaging with Socrates 2.0, participants will be asked to complete a brief survey containing validated measures to assess their experiences and be asked to participate in a semistructured qualitative interview. To assess participants' subjective assessment of usability, they will be asked to complete the System Usability Scale [31], which is a valid and widely used 10-item measure scored on a 5-point scale (strongly disagree to strongly agree). The Acceptability of Intervention Measure, Intervention Appropriateness Measure, and Feasibility of Intervention Measure [32] is a validated and widely used 12-item measure scored on a 5-point scale (completely disagree to completely agree) that will be administered to determine the perceived acceptability and feasibility of Socrates 2.0. Participants will also be asked to complete the Mobile Health App Usability Questionnaire [33], which is a validated and widely used 18-item measure scored on a 7-point scale (strongly disagree to strongly agree) that assesses ease of use, satisfaction, and usefulness of mobile apps. Finally, the Working Alliance Inventory-Short Revised [34], which is a validated 12-item measure scored on a 5-point scale (seldom to always or always to seldom) will be used to examine participants' experiences with their AI therapist. Participants will also be asked to complete a semistructured interview surrounding the questions

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presented in Textbox 2 to better understand their use and impressions of the tool

Textbox 2. Semistructured interview questions.

- What are your overall impressions of Socrates?
- How often did you use Socrates?
  - What prompted you to use Socrates in general and different times you did?
- What would you change about Socrates? Why?
- How would Socrates be helpful to you or other individuals?
  - Why might it not be helpful?
  - How likely would you be to use it going forward?
  - What would make you more likely to use it?
- Who do you believe could benefit most from Socrates?
- How would you present Socrates to others to make them interested and comfortable with checking out the tool?
- How do you think Socrates fits with mental health care?
- Has working with Socrates changed your perception on the utility of AI tools more broadly? (If so, how?)
- Is there anything else you would like to share that I have not asked you about?

Objective Use Metrics

Objective metrics, such as the frequency of use, number of exchanges, duration of interactions, and retention rates will be automatically collected via the tool and used to evaluate the feasibility of Socrates 2.0. Specifically, we will examine engagement rates to determine how often and how long users engage with the tool per session and in total over the study period, as well as determine the time since they last used the tool. We will also assess how often users complete the entire interaction or dialogue process with the tool. Finally, we will track LLM token use for each exchange to help with future cost estimations and performance evaluations.

Measures: Clinicians

As described earlier, both users and clinicians will be asked to participate. Clinicians will complete the same demographics survey, will have access to the same tool, and will be prompted to answer the same questions while using Socrates 2.0. However, unlike the users, clinicians will only be granted 2 weeks of access to Socrates 2.0. Our team determined that this would likely be sufficient time for them to form opinions and evaluate how the tool may fit with their therapeutic work. The team will obtain information about clinician characteristics, such as their experience (eg, number of years in the field), average caseload, populations with whom they work, and whether they are currently providing any interventions that involve cognitive restructuring or Socratic dialogue, among others. In addition, the team will ascertain the clinicians' familiarity with AI in mental health care. Using semistructured interviews, clinicians will be asked whether they have used AI tools before and whether they have recommended them to patients as well as which types of patients they believe may benefit the most and least from tools such as Socrates 2.0. The team will also ask clinicians about information they believe would be needed for them to feel comfortable recommending AI tools to patients and how AI tools fit with the clinicians' treatment philosophies.

Following their 2-week access to Socrates 2.0, clinicians will complete similar measures to the other users, including the System Usability Scale [31], Acceptability of Intervention Measure, Intervention Appropriateness Measure, Feasibility of Intervention Measure [32], and Mobile Health App Usability Questionnaire [33]. Clinicians will not be asked about the perceived working alliance with the AI therapist, as they were instructed to interact with the tool differently than actual users, such as by roleplaying some of their own patients to see what answers Socrates 2.0 provides. The semistructured interviews differ from those of the users as they are intended to generate information about clinicians' perceptions of the tool, aspects they would like to see changed, and how it could fit with their practice. Many of the questions are repeated from the pretool interview, such as questions surrounding the usefulness of AI tools such as Socrates 2.0 as well as which patients may be most and least likely to benefit from such a tool. Repeating interview questions will also enable the study team to determine whether the clinicians' perceptions and answers change after they have had the opportunity to engage with Socrates 2.0, as it may be more challenging for individuals to imagine what things could look like before directly interacting with the tool.

Statistical Analyses

Quantitative Data Analysis

Quantitative data such as the data from mental health screening assessments and the validated feasibility measures will be analyzed using appropriate descriptive and inferential statistics. Specifically, we will first characterize both the user and clinician samples based on demographic characteristics and the baseline mental health characteristics of the users. Descriptive statistics will also be used to detail the number of completed exchanges. Completeness of the entire interaction will be based on 2 criteria.

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Either the user clicks the End Dialogue button [rather than closing the window], which finalizes the dialogue, or the user makes statements during the dialogue that signal the end of the conversation. Examples of the latter include statements such as "Thank you. This was really helpful." After such statements, Socrates 2.0 generally inquires whether there is anything else that it can assist with. If the user ends the dialogue or closes the window at that point or replies suggesting that no further assistance is needed, the dialogue will be considered complete), responses to the assessments administered after using Socrates 2.0, as well as the overall use frequency, duration, and the use of tokens, among others. Any changes over time, such as for mental health symptoms, will be described via commonly-used effect sizes (eg, Cohen *d*), though it is important to note that this is not an effectiveness study and that the uncontrolled design precludes from determining whether any potential changes may be the result of engaging with Socrates 2.0 or external factors. Appropriate inferential statistics, such as multiple linear regression, will be used to determine whether certain demographic or baseline mental health characteristics were associated with the use of Socrates 2.0. We will also evaluate whether the use of Socrates 2.0 influenced assessment ratings, as it is possible that those who used the tool more regularly may have different perceptions of it than infrequent users.

Qualitative Data Analysis

Qualitative data will be analyzed using thematic analysis [35], a method for identifying, analyzing, and reporting patterns within data. The thematic analysis will begin with a meticulous process of data familiarization, where researchers immerse themselves in the data to gain a deep understanding of its content. Following this, data will be systematically coded, with codes representing the smallest units of meaning within the data that are relevant to the research questions. These codes will then be collated into potential themes, which are broader patterns of meaning that emerge from the coded data. Each theme will be reviewed and refined to ensure it accurately reflects the coded data and the overall dataset. The final step involves defining and naming themes, providing a detailed analysis of each theme, and the overall story the data tell about the research questions. All quantitative and qualitative analyses will be performed by approved study staff who have the necessary training.

Additional Safety Testing

Similar to previous safety testing, we will review interactions for any inappropriate behaviors, including discriminatory statements (racial, sexual, etc), responses that encourage harm of self or others, responses that elicit potentially identifying information from the participant (eg, information protected under Health Insurance Portability and Accountability Act), as well as general obviously inappropriate therapist behaviors, such as flirting with the patient. In addition, transcripts will be reviewed by trained CBT therapists to evaluate the general appropriateness of the responses to determine whether responses were potentially therapeutically inappropriate.

Ethical Considerations

The study procedures received approval from the Rush University Medical Center institutional review board (23083108). Each prospective participant will receive an electronic copy of the informed consent and have the opportunity to have any study-related inquiries addressed by members of the research team. Participation is contingent upon completion of the electronic consent process. Individuals who do not meet the study criteria or express a need for additional mental health resources will receive information from a member of the research team and be directed to appropriate support services.

Eligible participants will gain access to and receive an introduction to the tool. During both the informed consent process and the introductory session, participants will be informed that the research team does not actively monitor Socrates 2.0, and they should seek appropriate assistance in case of a crisis. Essential information, such as crisis helplines and instructions to dial 911 or visit the nearest emergency room, are prominently and permanently displayed on the main screen upon logging into Socrates 2.0 (Figure 1).

Before the start of the feasibility study, Socrates 2.0 underwent rigorous security testing by an external firm and was cleared for use by Rush University Medical Center's cybersecurity team. The results of this testing confirmed the security of the web-based platform, encompassing both access to the tool and the storage of the resultant data. These formal procedures aimed to minimize the risk of potential data breaches or losses. Usernames and passwords, generated by the research team using industry-standard protocols, will be linked to eligible participants via deidentified study participant codes. Access to the tool can be promptly revoked by the research team, if necessary. Through these measures, the team has tried to mitigate risks associated with conducting a feasibility study using a web-based platform.

Results

There are no results to report as of September 25, 2024. Enrollment started in February 2024 and is expected to continue until February 2025. All (ie, positive and negative) findings from this feasibility study will be presented in papers submitted to peer-reviewed scientific publications relevant to Socrates 2.0. Results will also be shared via presentations at scientific conferences as symposia and posters, as well as via Rush University Medical Center's website and social media. As of September 25, 2024, overall, 55 participants have been recruited.

Discussion

Principal Findings

Socrates 2.0 is one of the first functional multiagent generative AI tools intended to complement existing CBTs by engaging users in Socratic dialogue. The feasibility study will contribute to our understanding of whether and how individuals engage with Socrates 2.0 and whether they find their interactions to be beneficial. Importantly, the feasibility study will also provide important additional insights into the safety of the tool, expanding on previous safety testing. Moreover, this study will help us evaluate whether there are certain scenarios in which Socrates 2.0 does not perform as well as anticipated and will

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enable us to fine-tune future versions of the tool to improve its performance.

By incorporating feedback from clinicians, this study will provide valuable insights into the potential integration of generative AI tools, such as Socrates 2.0, into existing therapeutic practices. Positive findings could pave the way for subsequent studies evaluating the combined use of Socrates 2.0 and CBTs, potentially enhancing engagement compared with conventional worksheets and facilitating skill practice, leading to improved outcomes. Conversely, if the study yields negative results, indicated by low feasibility or satisfaction ratings or significant safety concerns, the feedback will be used to refine the tool further.

Limitations

The feasibility study has several limitations. First, although Socrates 2.0 is intended for use in mental health contexts, it is open to all users, not just patients with current or former mental health issues. This broad inclusion may impact feasibility, acceptability, and satisfaction ratings, potentially varying between those with and without diagnosed mental health conditions. To address this, we will administer screening assessments to gather mental health information and explore potential associations between symptom severity and feasibility ratings. Second, while Socrates 2.0 is primarily intended to complement CBTs by facilitating cognitive restructuring, this feasibility study initially evaluates it as a stand-alone tool. Using Socrates 2.0 as a complement to CBT enables the tool to fulfill a limited functionality (ie, engaging users in Socratic dialogue), while other core therapeutic elements, including working alliance and other therapeutic techniques, can still be received through the sessions with the human clinician. Thus, the obtained feasibility results from using Socrates 2.0 in isolation may differ compared with those that would be obtained following the integration with psychotherapy. Third, the study's description explicitly mentions testing a mental health–focused generative AI tool, which might deter users and clinicians less receptive to this novel technology from participating. Consequently, this self-selection bias could skew the findings related to feasibility, acceptability, and satisfaction. Finally, Socrates 2.0 was purposefully designed to facilitate Socratic dialogue. Therefore, the insights gleaned from this study will not be universally applicable to other generative AI–based mental health tools designed for different purposes.

Conclusions

The development of Socrates 2.0 marks a significant advancement in the use of generative AI in the context of CBT and mental health care more broadly. By combining multiple collaborative AI agents, Socrates 2.0 facilitates Socratic dialogue on a range of beliefs while minimizing common LLM issues such as looping. Initial positive user and clinician feedback suggests that generative AI tools, such as Socrates 2.0, could be feasible. However, formal studies, such as the feasibility study described in this paper, and tests of tools, such as Socrates 2.0 in conjunction with CBT are needed to better understand the true feasibility, as well as the potential risks and problems of generative AI tools as complements to CBT. Future studies should examine whether using LLMs would make out-of-session practice, such as examining one's thoughts, more engaging for patients than worksheets [21]. It should also be formally tested whether a generative AI tool would be able to engage patients in Socratic dialogue at least as well as a newly trained therapist, such as by providing therapists with transcripts and comparing the quality of subsequent human responses to those provided by AI. Finally, future studies should formally assess digital literacy, which could be an important factor that explains engagement with tools, such as Socrates 2.0. The outlined feasibility study will provide user and clinician feedback that can be used to evaluate the tool and further refine it for broader application and testing its efficacy with psychotherapy. We hope that the description of Socrates 2.0 and the associated feasibility trial will serve as a valuable model for other researchers and developers aiming to harness the power of AI in mental health [7].

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed.

Authors' Contributions

PH was responsible for the conceptualization, methodology, writing the original draft, and funding acquisition. SAP was responsible for conceptualization; methodology; writing, reviewing, and editing the manuscript; and project administration. YC was responsible for resources and data curation. ZA was responsible for resources and data curation and writing, reviewing, and editing the manuscript. DA was responsible for project administration. SP was responsible for resources; data curation; and writing, reviewing, and editing the manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CAB: community advisory board
CBT: cognitive behavioral therapy
LLM: large language model
REDCap: Research Electronic Data Capture

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Protocol

Assessing the Safety, User Acceptability, Dissemination, and Reach of a Comprehensive Web-Based Resource on Medications for Opioid Use Disorder (MOUD Hub): Protocol for a Development and Usability Study

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Abstract

Background: Medications for opioid use disorder (MOUD), such as methadone and buprenorphine, are the gold standard for opioid use disorder (OUD) treatment. Owing to various barriers, MOUD access and retention are low in the United States. The internet presents a digital solution to mitigate barriers, but a comprehensive and reliable resource is lacking. We present a user-friendly, web-based resource, the *MOUD Hub*, that provides reliable information on MOUD.

Objective: This study aims to assess the safety, acceptability, feasibility of dissemination, and reach of the *MOUD Hub* using focus groups and advertising on 1 key search engine and 1 social media platform.

Methods: This protocol describes the development of the *MOUD Hub* and the descriptive observational feasibility study that will be undertaken. The *MOUD Hub* uses motivational interviewing principles to guide users through the stages of change. The website provides evidence-based information from national health and substance use agencies, harm reduction organizations, and peer-reviewed literature. First, pilot focus groups with 10 graduate students who have lived experience with OUD will be conducted to provide feedback on safety concerns. Then, focus groups with 20-30 potential *MOUD Hub* users (eg, people with OUD with and without MOUD experience, friends and family, and health care providers) will be conducted to assess safety, acceptability, reach, and usability. Data will be analyzed using inductive thematic analysis. The website will be advertised on Google and MOUD-specific Reddit forums to assess dissemination, reach, and user acceptability based on the total user volume, sociodemographic characteristics, pop-up survey responses, and 1-year engagement patterns. This information will be collected through Google Analytics. Potential differences between users from Google and Reddit will be assessed.

Results: The *MOUD Hub* will be launched in January 2025. Data collected from 5 focus groups (approximately 30-40 participants) will be used to improve the website before launching it. There is no target sample size for the second stage of the study as it aims to assess dissemination feasibility and reach. Data will be collected for a year, analyzed every 3 months, and used to improve the website.

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Conclusions: The *MOUD Hub* offers an innovative theory-based approach, tailored to people with OUD and their family and friends, to increase access to and retention in MOUD treatment in the United States and provides broader harm reduction resources for those not currently in a position to receive treatment or those at risk of resuming illicit opioid use. Findings from this feasibility phase will serve to better tailor the *MOUD Hub*. After modifying the website based on our findings, we will use a randomized controlled trial to assess its efficacy in increasing MOUD access and retention, contributing to growing research on web-based interventions for OUD.

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KEYWORDS

opioid use disorder; medications for opioid use disorder; digital health; digital intervention; substance use; motivational interviewing; stages of change

Introduction

Medications for Opioid Use Disorders

The opioid crisis continues to drive mortality among adults, with >100,000 drug overdose deaths in the United States in 2022 [1]. Medications for opioid use disorder (MOUD) are the gold standard for treating opioid use disorder (OUD) and reducing fatal overdose risk [2]. However, MOUD treatment is highly underused in the United States, with only 22.3% of adults with an OUD receiving MOUD in the past year [3].

Treatment with MOUD is associated with a reduction in overdose and other-cause mortality. Methadone and buprenorphine have shown similar treatment outcomes [4,5] and retention rates among people undergoing treatment across gender and racial groups [6,7] and are effective among people using fentanyl [8,9]. MOUD treatment has also been shown to lower HIV and hepatitis C virus infection risk [10-13]. Beyond reducing mortality and drug use–related health harms, MOUD treatment is associated with an increase in social functioning and an overall increase in quality of life [14]. Therefore, its uptake is warranted to ameliorate the lives of people living with OUD.

Multiple barriers to access to and retention in MOUD treatment have been identified across US settings. Knowledge gaps represent a barrier for people living with OUD, including a lack of education on available treatment options and how to access care [15]. People living with OUD report experiencing social stigma and lack of support, self-stigma, and MOUD-related stigma when accessing treatment, including poor treatment by staff and rigid treatment structures [15]. Pregnant people have expressed the increased stigma and threats they experience when accessing care that create additional barriers for them [16]. Logistic concerns such as the cost of medications, long wait times, transportation issues, and fail-first abstinence programs have been listed as barriers to accessing MOUD treatment [15]. Accessing care is especially difficult for those in rural areas due to a lack of OUD services [17].

Web-Based Information Seeking

Given the stigmatized nature of OUD, people have been shown to seek information about detoxification, rehabilitation, and treatment through web-based resources as this offers more anonymity and confidentiality. We recently published a paper showing significant positive associations between the number of Google searches specific to help seeking for OUD (eg, “heroin detox” and “treatment for opioid use”) and indicators reflecting OUD prevalence, including the number of people receiving MOUD, the number of emergency department visits related to opioid overdose, and the number of fatal opioid overdoses across states in the United States [18]. These findings suggest that leveraging Google search algorithms could be used to effectively reach people in need of help for OUD. Similarly, web forums are a source of support, trust, and knowledge building among people living with OUD, including in the context of treatment seeking and maintenance [19]. Specifically, Reddit, a publicly available social media platform, has several subforums (known as subreddits) available to discuss and share information on opioid recovery (eg, r/OpioidRecovery, r/OpiatesRecovery, r/Methadone, and r/suboxone). As of August 13, 2024, these 4 subreddits reached >130,000 users.

Social media platforms and the internet provide a unique place for people to access information and help. People exist in different social surroundings, the first place being the home and the second place often being the workplace. Sociologist Ray Oldenburg coined the term third places, referring to the other spaces we occupy where ideas can be exchanged, community can be built, and relationships can be strengthened [20]. Examples of third places include gymnasiums, cafes, and churches. The internet has created a new web-based third place, where people can seek information, find community, and exist in ways in which they may not be able to in their first and second places. Unfortunately, public health agencies have not yet fully leveraged this resource, and much information on the internet is not based on evidence, resulting in the spread of misinformation. Misinformation has been found to spread more quickly, further, and more broadly than true and evidence-based information, as seen for vaccines during the COVID-19 pandemic [21,22]. Poor quality information on the internet has become a problem, hampering people’s ability to discern whether the information is true and providing unhelpful answers [19]. An internet resource for MOUD that offers clear, comprehensive, factual, and evidence-based information that is well tailored to the unique challenges people with OUD or their family and friends experience is necessary to increase uptake and retention.

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The MOUD Hub

We sought to create a web-based resource that provides user-friendly, reliable information to address barriers to MOUD at different steps of the care continuum, tailored to support both people living with OUD and friends and family in navigating the different stages of treatment and their respective challenges. We chose motivational interviewing (MI) as a guiding intervention. MI follows harm reduction principles to help promote progression along stages of the transtheoretical model of behavior change: precontemplation, contemplation, preparation, action, maintenance, recurrence (or relapse), and termination stages [23]. MI provides a nonjudgmental space that meets people where they are in managing their OUD and finding motivation toward behavior change.

We followed the Conceptual Framework of Access to Health by Levesque et al [24] to classify the different barriers across the MOUD care continuum, which maps onto the transtheoretical model of behavior change and consists of assessing one's health care needs, desire for care, seeking health care, reaching care, using care, and health care consequences. The Access to Health framework comprises 5 domains characterizing health care service: approachability, acceptability, availability and accommodation, affordability, and appropriateness. These domains are connected to the 5 abilities of persons to receive health care, which include the ability to perceive, seek, reach, pay, and engage.

Therefore, we developed the *MOUD Hub*, a web-based resource to help reduce barriers to accessing and remaining on MOUD care [25]. Our goal was to create a resource that would cater to all people with OUD, including those not yet considering treatment or having stopped treatment, to facilitate linkage to services and resources across multiple needs, such as prevention services, harm reduction tools, treatment resources, and social resources. This paper describes the protocol of how this website was conceptualized and created, along with how we plan to disseminate it and assess its feasibility by characterizing its reach, use patterns, and acceptability [26].

Study Objectives and Specific Aims

The main objective of this study is to assess the acceptability of using the website to address barriers to MOUD care and the feasibility of reaching people living with OUD and their friends and family. We first aim to gain feedback on the website's safety, acceptability, user experience, and usefulness. After receiving this feedback and making website adjustments, we aim to assess the volume of users, their key sociodemographic characteristics, their patterns of use (content accessed, time spent with different types of content, and frequency of use), and potential differences in users' characteristics when accessing the website from Google or Reddit. In addition, we aim to understand their views on the usefulness of the resources provided, to identify missing information and to collect web-based resources participants have found useful to further share them with the *MOUD Hub*.

Methods

Study Design and Setting

This descriptive observational feasibility study [26] will take place on a website called the *MOUD Hub* to investigate whether a theory-based website providing a comprehensive list of services can be helpful to people looking for information related to MOUD. The website will be advertised on Reddit opioid-related forums and through optimized Google searches with the theme of opioid use and recovery. Study outcomes will be assessed through pilot focus groups with students with lived experience of OUD who are involved in recovery groups or unions for people who use drugs, people living with OUD who have never received MOUD, people living with OUD who have experience with MOUD, family and friends of someone using opioids, and individuals who work with people living with OUD (eg, MOUD providers, counselors, and harm reduction workers); data on users will be collected in Google Analytics (Google LLC) and a pop-up survey on the website.

Team

The website was created with the help of professionals who have expertise in substance use disorders (SUDs). The website development process was led by a substance use epidemiologist, a social worker specializing in SUD, and a digital epidemiologist specializing in SUD. This process was supported by members of a community and scientific advisory board. A clinical psychologist and harm reduction psychotherapist who works as a counselor at a university, serves as a course instructor for SUD support group facilitation, and worked as a counselor at a harm reduction organization for 14 years helped operationalize the stages of change and MI components into the website and advised on accessibility (for Spanish speakers and people with visual impairments). A social worker who works with people with SUD in hospitals and counseling practices provided insight into the harm reduction resources included in the precontemplation and contemplation stages and helped ensure that key barriers to MOUD access were addressed in the preparation and action stages. An occupational therapist with experience working with transition-aged youth with SUD informed portions of the maintenance stage of change to improve retention in MOUD treatment, including supportive apps and resources. A harm reduction advocate and mental health program coordinator with lived experience as a family member of someone with OUD provided insight into and resources on what family and friends need during this process. A psychiatrist specialized in OUD and harm reduction verified information on the medications and best practices for the recurrence and termination stages. The community and scientific advisory board members brought a diverse perspective of the population living with OUD and helped provide feedback on the creation of the website throughout the process.

Intervention Description

MI and the Transtheoretical Model

Our *MOUD Hub* was built using a person-centered approach and following the principles of MI, which include partnership, acceptance, compassion, and evocation, to help individuals

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make decisions about their health, build a plan to problem-solve, and put them into practice. Regarding behavior change, MI is the most effective approach in changing SUD behaviors, compared to other behaviors, such as weight loss or increasing physical activity [27]. MI is a collaborative and goal-oriented style of communication that empowers people's capacity for change [28].

The *MOUD Hub* is not only for people living with OUD but also for their families and friends. Therefore, there are specific resources for family and friends to help them understand the progression to behavior change, needs and challenges that may arise, and how to best support themselves and people living with OUD in their treatment journey. Family and friends can use the MI skills to help them encourage people living with OUD who may be seeking resources. MI seeks to meet people where they are by acknowledging ambivalence and guiding the change process [29]. It avoids using the "righting reflex" or the need to fix what is wrong with people and steer them in the right direction [29]. These concepts were integrated into the website by acknowledging the stage of change a person is in. By doing this, we offered resources to reduce harm and incorporated language that might motivate "change talk" or ignite thoughts on wanting to change.

MI is usually conducted in a setting with an in-person meeting between counselor and client. Using this website as a virtual third place, we integrated the concepts of MI to encourage users to elicit behavior change independently. The website follows the transtheoretical model, or the stages of change, and incorporates the skills of MI within each stage [29]. The stages of change have been used to understand that people are more likely to change their behavior when it is intentional. The stages of change are not a linear process, and each stage requires different strategies to help individuals move through them [30]. Figure 1 shows how the stages of change are introduced on the website and how information on each stage populates when clicked. When using the transtheoretical model, most research focuses on the precontemplation, contemplation, and preparation phases and has found that using stage-matched interventions helps improve recruitment, retention, and progress [31]. While several web-based resources provide information on MOUD, to our knowledge, none cover the entire progression through the MOUD treatment continuum, including precontemplation and contemplation stages preceding engagement. In addition, the stages of maintenance and concerns such as substance use recurrence are rarely attended to in these interventions. We identified issues and challenges specific to each stage of change and resources that would benefit users in each stage. For more information on how the stages will be used and example pages of the website for each stage, refer to Multimedia Appendix 1.

Figure 1. A snapshot from the MOUD Hub's stages of change wheel. When users click on a specific stage, a pop-up appears with a brief quote and information related to that stage. Users can click "see more" and will be taken to the stage's specific page. MOUD: medications for opioid use disorder.

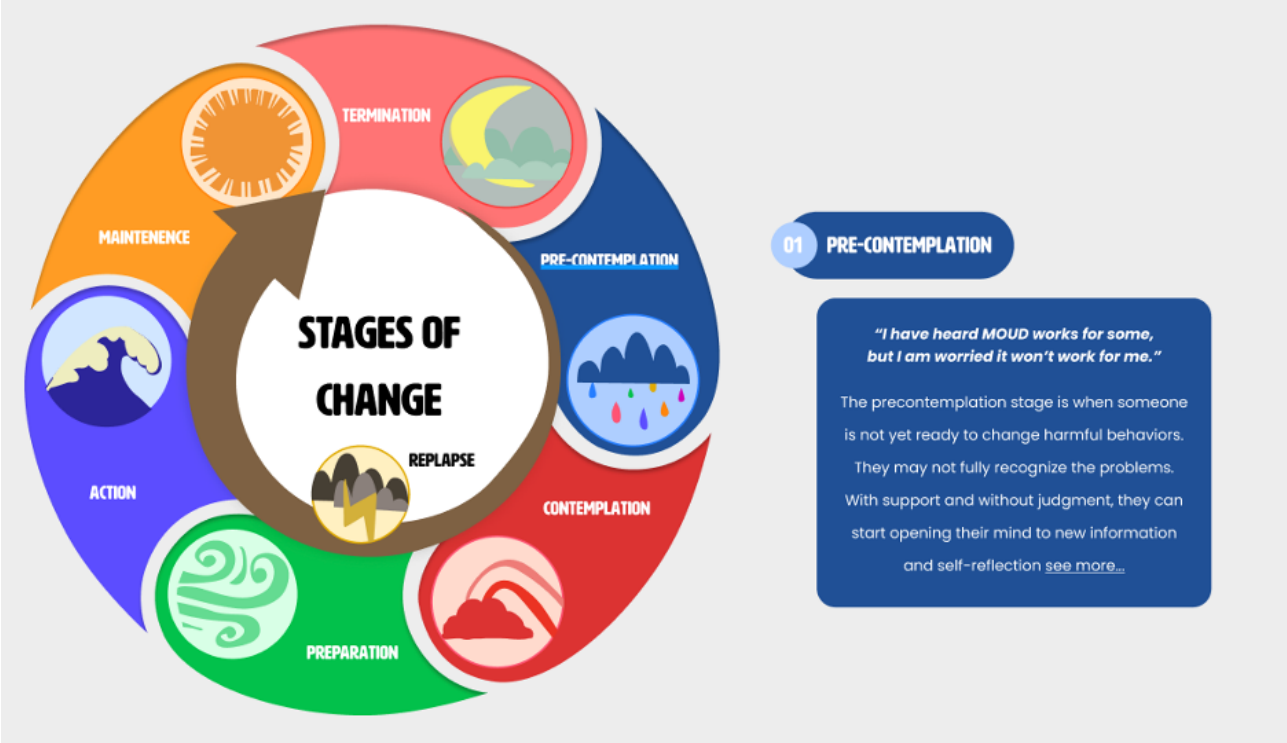

As in an MI session with a counselor, the *MOUD Hub* does not indicate to the user which stage of change they might be at and instead relies on their self-identification based on the stages' descriptions and associated quotes provided on the home page. The reasoning behind this is 2-fold. First, we wanted to stay aligned with the principles of MI, including the horizontal relationship between the client and the counselor and the respect for the client's capacity to identify the right tools for themselves (rather than a top-down educational approach in which the counselor informs the client of their condition and the steps they need to follow to resolve it). Second, some users might be friends or family of people living with OUD, and it might be harder for them to accurately complete an assessment, leading to inaccurate guidance. In both cases, this open approach might

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lead users to explore several stages before focusing on one stage, which could increase their understanding of the process of change.

Resources Provided and the Conceptual Framework of Access to Health

The *MOUD Hub* consists of a repository of evidence-based resources and links to web-based material to address barriers to MOUD treatment engagement and retention. To identify the challenges for which resources were needed, we conducted literature searches on MOUD barriers and facilitators and complemented these findings using insights from Reddit (A Almeida, personal communication, 2024). Specifically, natural language processing methods were applied to Reddit textual data to understand the main struggles faced by people who use MOUD throughout their treatment (A Almeida, personal communication, 2024). We used the results of the topic models that unveiled the main issues discussed in the r/Methadone and r/suboxone subreddits to guide sections of the *MOUD Hub* and help identify the resources needed. For example, the topic "Back to suboxone after relapse" guided the incorporation of links and materials in the *MOUD Hub*, elucidating the safest and best practices to resume suboxone treatment. The purpose of using this Reddit analysis to inform the website was to better cater to the needs of people seeking help on the web to address OUD, as their demographics and circumstances may differ from those not seeking help on the web.

Resources were obtained from verified sources that specialize in substance use, such as the Substance Abuse and Mental Health Services Administration, Centers for Disease Control and Prevention, and websites connected to the National Institute on Drug Abuse, as well as harm reduction organization websites, including the National Harm Reduction Coalition. Peer-reviewed papers were used as references for information to ensure that the content was based on evidence and supported by research. References are cited for every resource provided so that users can access information at its source.

Resources were selected to address the challenges that usually present at each stage of the transtheoretical model and were classified using the Access to Health framework, assessing resources' fit into the 5 dimensions, including approachability, acceptability, availability and accommodation, affordability, and appropriateness [24]. The corresponding abilities of persons were considered when assessing barriers and resources that would be helpful. Table 1 shows an overview of the stages, the barriers that people living with OUD face in each stage, and the resources shared to remedy those barriers. Each barrier and resource are connected to the domains of the Access to Health framework and the MI open-ended questions used to elicit behavior change. Figure 2 is an example of the main preparation stage page and its resources. Figure 3 is an example of a stage-specific check-in box that uses MI questions. Refer to Multimedia Appendix 2 for the complete series of web pages for all stages at website inception.

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Table 1. Stages of change and related barriers or issues as found in the literature, the resources provided to address these barriers, how the resource relates to the access to care framework, and relevant motivational interviewing (MI) questions included in the check-in box.

Stage of change and barrier or issue	Resources provided	Access to Health framework by Levesque et al [24]
Precontemplation stage[a]		
Limited understanding of OUD[b] [15]	• What is OUD? • What do opioids do to the brain?	• Ability to perceive
Lack of trust in MOUD[c] [15]	• MOUD myths dispelled	• Acceptability • Ability to perceive
Lack of knowledge or understanding of harm reduction [32]	• Harm reduction resources (safe injection practices, syringe services, overdose prevention, wound care, drug checking, HIV and HCV[d] testing)	• Approachability • Ability to perceive
Lack of readiness to start MOUD [32]	• Harm reduction resources to help in using drugs more safely	• Acceptability
Contemplation stage[e]		
Lack of knowledge of MOUD options [15,32]	• Resources and information on the different types of MOUD (methadone, buprenorphine, and naltrexone)	• Approachability • Acceptability • Appropriateness • Ability to perceive • Ability to seek
Strong preference for detox versus maintenance treatment [32,33]	• Web-based Information on detox (including risks) and advantages of maintenance	• Ability to perceive
Preparation stage[f]		
Lack of knowledge on where to access treatment [15]	• Treatment locator • Helplines	• Approachability • Availability and accommodation • Ability to seek
Logistic issues [15,32]	• Transportation help • Storing medication • Insurance coverage	• Acceptability • Affordability • Appropriateness • Ability to reach • Ability to pay
Stigma around OUD and MOUD [15,32]	• Preparing for stigma • Responding to stigma • Recovery support groups	• Acceptability • Ability to engage
Concerns about treatment during pregnancy [16,32]	• Information about benefits of treatment during pregnancy and relevant state policies	• Approachability • Ability to perceive
Action stage[g]		
Coping skills during early treatment [32]	• Information on different coping skills	• Approachability • Ability to perceive • Ability to engage
Dealing with side effects of medications [34]	• Resources on strategies to address side effects	• Availability and accommodation • Ability to perceive • Ability to engage
Lack of strategies to prevent recurrence [32]	• Creating a recurrence prevention plan	• Ability to engage
Maintenance stage[h]		

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Stage of change and barrier or issue	Resources provided	Access to Health framework by Levesque et al [24]
Lack of social support during treatment [15,32]	• Apps for support and MOUD support groups	• Appropriateness • Ability to engage
Trauma or mental health concerns [32]	• Mental health support and where to find mental health treatment	• Availability and accommodation • Ability to seek
Boredom when no longer using illicit opioids [32]	• Finding new sources of pleasure • Create a recurrence prevention plan	• Approachability • Ability to engage
Termination stage (ending MOUD)[i]		
Strong desire to terminate treatment	• Referring to a physician for support and to prevent overdose • Reiteration of the importance of long-term treatment	• Approachability • Acceptability • Appropriateness • Ability to perceive • Ability to engage
Recurrence (or relapse) stage[j]		
Stigma or shame around recurrence. The belief that recurrence is a "failure" [35]	• Research on recurrence as a natural occurrence of OUD and opportunity for readjustment	• Approachability • Ability to perceive • Ability to engage
Belief that recurrence is long-term	• How to return to treatment	• Approachability • Acceptability • Appropriateness
Lack of strategies to prevent recurrence [32]	• Create a recurrence prevention plan	• Ability to seek • Ability to engage
High risk of overdose during recurrence	• Revisit harm reduction resources	• Approachability • Ability to perceive

[a]Precontemplation stage MI check-in questions: readiness rulers [36]—How important is it for you to change your opioid use? What made you choose that number and not a lower one? What would help you pick a higher number? How confident are you in making this change? What would help you be more confident?

[b]OUD: opioid use disorder.

[c]MOUD: medications for opioid use disorder.

[d]HCV: hepatitis C virus.

[e]Contemplation stage MI check-in questions: How does your current opioid use affect your life, relationships, career, and future goals? How would treatment help you resolve some of those and help you achieve your goals?

[f]Preparation stage MI check-in questions: What are the ways to address some of the challenges you are worried you may face? What are the steps you may need to take to receive treatment?

[g]Action stage MI check-in questions: What has been working well for you? Are there any places that you need to strengthen to help your progress?

[h]Maintenance stage MI check-in questions: What challenges have you been encountering? What are practical ways to address them? Can you name 3 things that have improved since starting treatment?

[i]Termination stage MI check-in questions: readiness rulers [36]—How confident are you in making this change?

[j]Recurrence (or relapse) stage MI check-in questions: How has this relapse gotten me closer or farther away from my treatment goals? What do you think you need to help you in your next steps?

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Figure 2. A snapshot of the preparation stage home page of the MOUD Hub. Each stage has a home page with a description of the stage and a tailored affirmation at the top, followed by tabs for different themes relevant to the stage. For the preparation stage, the themes are where to obtain medications for opioid use disorder (MOUD), recovery support groups, transportation, pharmacy, cost of MOUD, storing medication, treatment during pregnancy, preparing for stigma, who can I call in a crisis, friends and family, and check in. SAMHSA: Substance Abuse and Mental Health Services Administration.

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Figure 3. An example of a check in box for the precontemplation stage. Each stage has a tailored check in with questions guided by the principles of motivational interviewing. Users will be able to answer the questions and download them to their personal devices.

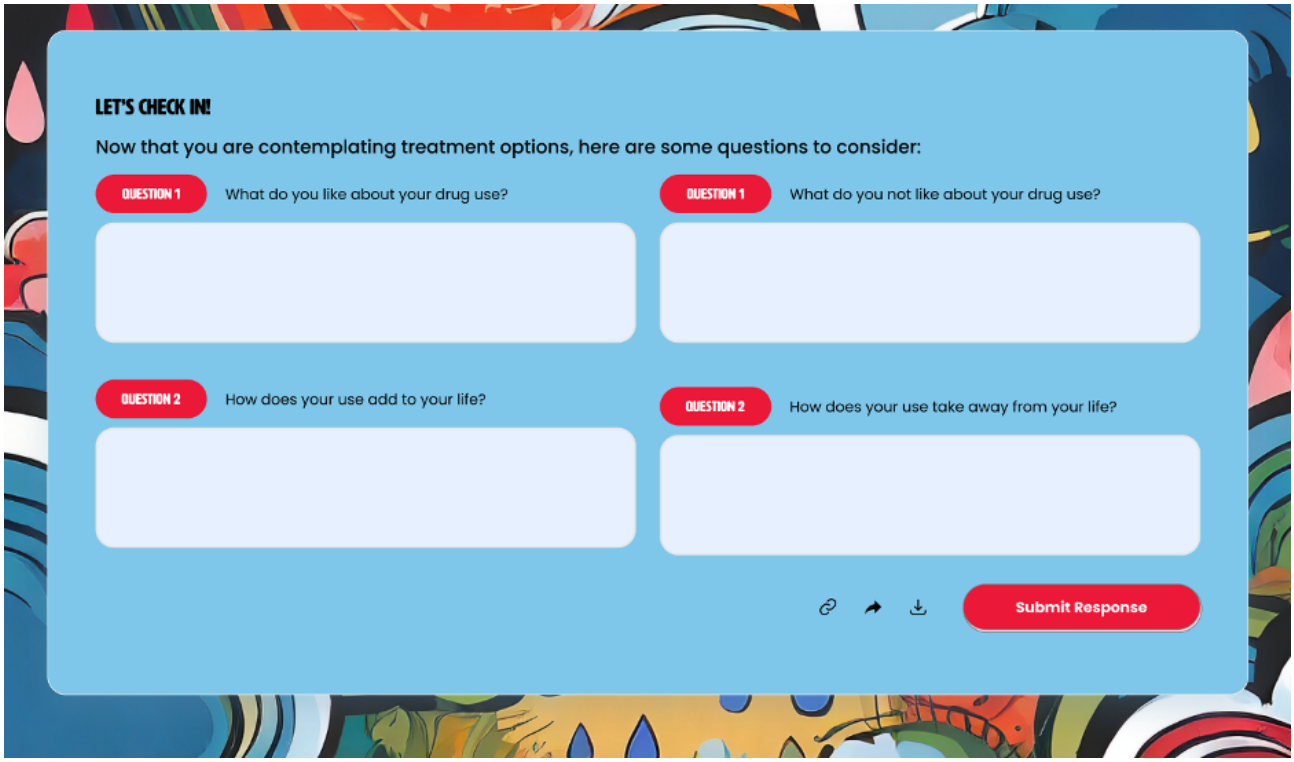

Apps deemed useful, such as the Calm App, were added as resources. Although we recognize that some apps may not be tested through randomized controlled trials, we chose those that have been based on helpful practices, such as mindfulness and harm reduction [37]. The *MOUD Hub* informs users that these apps may not be evidence based but that they might find some of them useful when trying to use coping skills for their treatment.

The website explicitly includes disclaimers regarding the fact that it does not offer medical advice; the language used, which in some instances includes terms from other resources that may be considered stigmatizing and for which we have used quotation marks; and noting that the resources are compiled rather than created by us (Multimedia Appendix 2).

Accessibility

The website has tabs to organize how users access the resources. For example, there is a "Languages" tab showing users how to set up and enable translations in their web browser if English is not their preferred language, as well as an "Audio" option that informs users on how to have the website read to them to reduce access barriers among those with vision or literacy concerns. The website was developed to be accessed from a computer and a mobile phone to increase accessibility.

Dissemination

The dissemination of the *MOUD Hub* will follow web-based marketing strategies, which harness interest in a topic, as expressed by internet searches or membership to specific social media networks, to promote the resource and increase its uptake. We will use internet searches on Google and leverage Reddit subreddits or discussions focused on opioid use recovery, treatment, and overdose prevention.

For Google, we will advertise this website in response to specific searches using sets of words described by Patton et al [18]. For example, when someone googles "opioid+treatment," they will see our advertisement. For Reddit, the website will be posted monthly in the subreddits of r/Methadone, r/suboxone, r/OpiatesRecovery, and r/Naloxone. We will advertise the *MOUD Hub* monthly and tailor the post to incorporate the month's most discussed topic. The monthly frequency of the posts is driven by the subreddits' constraints on the maximum number of research-related posts.

Recruitment, Sample, and Participants

To evaluate the safety and preliminary acceptability before advertising the website, we will first carry out pilot focus groups with 10 graduate students with lived experience of OUD, personally or through family and friends, and who are participating in recovery groups or unions for people who use drugs. In these focus groups, we will pay particular attention to safety and make changes to the MOUD Hub accordingly. Participants will be recruited by contacting UC San Diego and San Diego State University student recovery groups.

After the pilot focus groups have been conducted and relevant changes have been made, 4 additional focus groups will be conducted with people living with OUD who have never received MOUD; people living with OUD who have experience with MOUD; family and friends of someone using opioids (including people living with OUD); and individuals who work with people living with OUD, including MOUD providers, counselors, and harm reduction workers. Each focus group will aim to have 4 to 8 participants. Participants will be recruited from MOUD treatment centers, support groups for family or friends of people living with OUD, and harm reduction organizations in San Diego through email to ask for permission

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to share study fliers. The purpose of these focus groups will be to gain more in-depth knowledge on the safety and acceptability of the hub, user experience, and thoughts on its usefulness in improving MOUD access and retention.

For all focus groups, participants will have the option of engaging in a focus group either through Zoom (Zoom Video Communications) or in person. Inclusion criteria for participants include being aged ≥18 years and having at least one of the aforementioned experiences. Exclusion criteria include experiencing severe mental health issues and being unable to provide informed consent.

There are no eligibility criteria for the study when assessing the website's reach due to it being available for public access. We will be openly advertising it to people who make relevant Google searches or who are members of opioid-related subreddits. Similarly, there is no randomization, as all users can access the same website's content. We will be able to identify whether participants came from Reddit or Google and treat them as 2 different samples. This will enable us to investigate differences in user volume and characteristics when accessing the website through Reddit or Google and to evaluate the most appropriate platform for dissemination for future-related interventions.

There is potential for bias, including misclassification, self-selection, and response bias. It will not be possible to know whether users are experiencing OUD or searching for information for a loved one, limiting our understanding of the representativity of the sample by OUD experience and leading to potential misclassification bias. However, we will be able to know whether users clicked on resources specific to friends or family and whether they responded to the "check-in" questions directed at people living with OUD. In addition, the pop-up survey asks whether users are accessing the website for themselves or a friend or family member. This will provide us with an additional measure for the proportion of users who are seeking help for themselves versus for a friend or family member.

Effectively, all people accessing the website will self-select based on need or curiosity, and we will miss information from people living with OUD who are not seeking help for OUD or are not compelled to access the *MOUD Hub* when exposed to it. The demographics data will allow us to assess to what extent our sample is representative of the general population and the population experiencing OUD and fatal overdoses in the United States in terms of geography, age, and gender. We will also be able to assess whether users are accessing the website from Google, Reddit, or other sources, potentially representing different communities. While response bias is possible in the context of our pop-up survey, participation will be voluntary and anonymous, and therefore, this will be minimized. However, there will undoubtedly be self-selection bias among the group answering the survey, likely representing those most engaged in improving access to reliable MOUD information.

Outcomes and Measures

To evaluate the safety and acceptability of the *MOUD Hub*, we will conduct pilot focus groups with 10 graduate students belonging to recovery groups or unions for people who use drugs. We will lead 2 focus groups to explore safety-related issues, along with gaining feedback on the acceptability, content, and any additional information that should be provided on the website. Safety concerns will focus on, but will not be limited to, information that may potentially be triggering or misleading and stigmatizing language.

A total of 4 additional focus groups will be conducted with other groups to gain more in-depth knowledge on the acceptability of the hub, user experience, and thoughts on its usefulness, following improvements from the pilot focus group. The topic guide in Multimedia Appendix 3 will be used.

To evaluate the reach and use patterns of the website, we will use Google Analytics to collect data on the number of users, their characteristics, and their interactions with the website [38,39]. The website will be launched in January 2025, and we will collect data for evaluation for a year and look at the data in 3-month increments. With this iterative approach, we can adjust the website in real time.

Our protocol's outcomes and measures are shown in Table 2. We will first assess the dissemination reach of the website. The reach of an intervention is defined as "the absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative, intervention, or program, and reasons why or why not" [40].

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Table 2. Outline of the quantitative and qualitative measures that will inform the outcomes. Each measure is labeled with the information's source.

Reach	Acceptability
Quantitative measures	
Volume of users (GA[a])	Proportion of users who return to the website (GA)
Average time spent on the website (GA)	Acceptability of Intervention Measure questions (PS[b]; Figure 4)
The average number of resources the users clicked on in different stages (GA)	—[c]
Total number of times a resource was clicked within each stage (GA)	—
User demographics (age, gender, location, language, and accessing the website for themselves or for a friend or family member; GA and PS)	—
Qualitative measures	
Focus group interview guide assessing reach: Do you think people would use the website? Who do you think would use the website? (FG[d])	Open-ended questions about acceptability; for example, "What did you find most helpful?" and "What were you expecting to find that was missing?" (PS; Figure 4)
Focus group assessing who it would be useful in reaching: Who do you think would use this website the most? (People living with OUD, family, friends, SUD[e] professionals?)	Focus group interview guide assessing safety, acceptability, usability, and further feedback on usefulness. Example questions are "What are your overall impressions or thoughts on the website?" and "Is there something on the website you particularly liked/disliked?" (FG)

[a]GA: Google Analytics.

[b]PS: pop-up survey.

[c]No additional information.

[d]FG: focus group.

[e]SUD: substance use disorder.

We will measure the volume of users who access the website and user demographics to characterize who we are reaching. We will measure the average time spent on the website, the average number of resources the users clicked on, and the total number of times each resource was clicked on. This will help determine whether users genuinely engage with the website and identify which stages and specific resources are most relevant to them. Google Analytics provides data on how many users visit the website, when they visited, how long they stayed on the website and on specific pages, and what resources they clicked on, along with users' age, gender, location, and language preferences. Information on demographics, such as age and gender, and whether the users are visiting the website for themselves or for a friend or family member will also be asked in a pop-up survey that will appear when people leave the website (Figure 4).

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Figure 4. A pop-up survey that will be presented to users before they leave the website to collect demographic information and initial acceptability of the website. MOUD: medications for opioid use disorder.

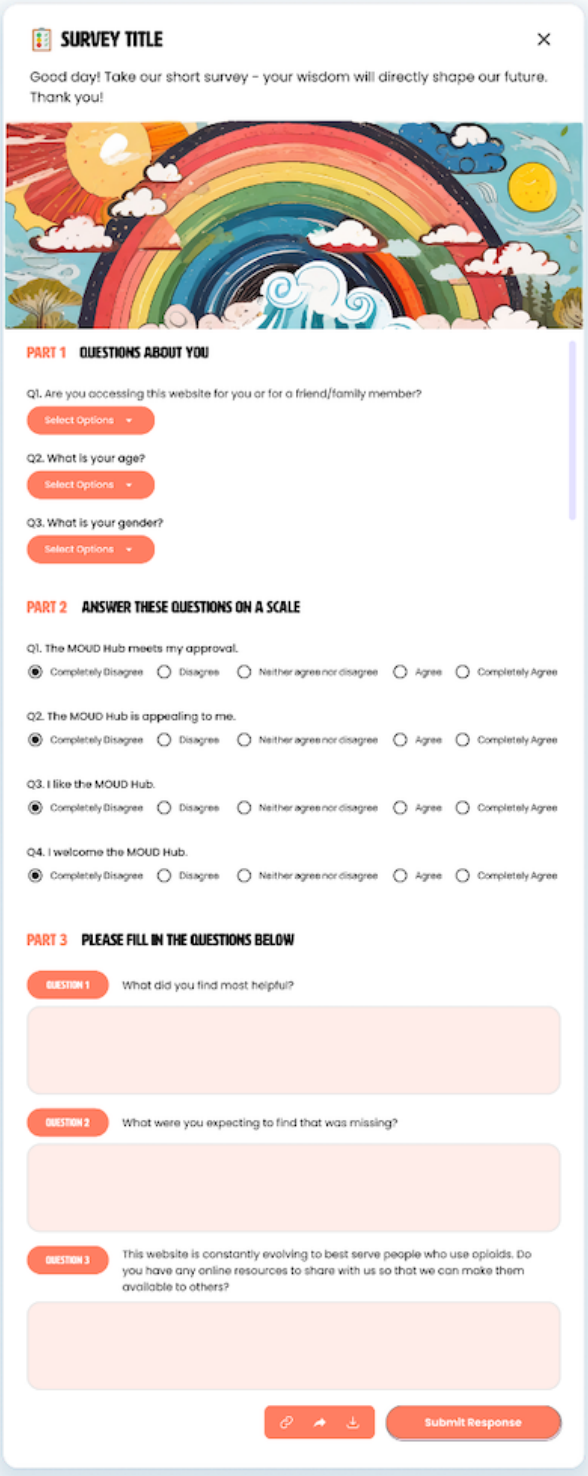

To further assess acceptability, we will measure the proportion of users who return to the website along with using the Acceptability of Intervention Measure [41]. The pop-up survey will ask closed- and open-ended questions to assess acceptability and identify additional relevant resources. The closed-ended questions will use the 4 questions from the Acceptability of Intervention Measure [41]. The open-ended questions will ask about ways in which they found resources helpful, whether there are other topics or questions that they expected to obtain information on but did not find anything relevant, and whether there are any other resources they would like to share with the broader community. Google Analytics tracks the number (and proportion) of people who are returning users, which will be used as another measurement of acceptability.

Finally, we will compare users who come from Reddit versus those who come from Google by looking at the volume of users

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from each source and their characteristics. The aforementioned outcomes will be assessed to compare the effectiveness of social media versus search engines in disseminating resources such as the *MOUD Hub.*

For the website's reach, we hypothesize that (1) users will most frequently click on links related to the precontemplation or contemplation phases of MOUD use, as opposed to links related to the preparation, action, and maintenance phases; (2) a substantial proportion of users (>25%) will be family members or friends of people who use opioids; (3) the volume of users referred through Google searches will be larger than that of users referred through Reddit; and (4) users referred through Reddit will spend more time on the website and click on a higher number of links than users referred through Google searches.

For acceptability, we hypothesize the following: (1) most users will find the resource useful and ratings will be significantly higher among acquaintances of people who use opioids than among people who use opioids themselves; (2) users with OUD will find the resource less useful; and (3) a large proportion of resources shared by users will lead to non–evidence-based information, including rehabilitation centers based on mandatory abstinence.

Data Collection and Management

For all focus groups, each potential participant will first do a Zoom screening session where the consent form will be read to them; basic sociodemographic information (ie, age, gender, and race or ethnicity) will be collected; and they will be asked about their availability for the focus group from a list of potential dates and times. The consent form outlines the study's components, the risks and benefits of enrollment, the length of time for the focus group process, the duration of the study, and contacts for the study and university should the participant have a question. As part of the consent form, participants will be informed that their "physical" identity will not remain anonymous with the other participants as they will see each other on Zoom or in person. Verbal informed consent will be obtained and recorded from eligible participants before starting the focus group.

Focus groups will be conducted either on Zoom or in person. For Zoom focus groups, each person will be sent an invitation to a password-protected Zoom room, and each will be added to the Zoom room one by one by the researchers, ensuring no names are shown on their profile. In-person focus groups will be hosted at UC San Diego, either in La Jolla or Hillcrest, depending on the participants' preference, in a private room where others cannot listen in.

For all focus groups, a topic guide has been created that covers topics of the websites' safety, acceptability, user experience, reach, usefulness, safety, and additional resources or suggestions that participants have (Multimedia Appendix 3). Focus groups will last for 60 to 90 minutes and will be audio recorded on a digital Dictaphone (no images or video will be recorded). Participants will be compensated with a US $20 debit card. Data from the focus groups will be kept on a password-protected computer with restricted access by the research team and transcribed.

Google Analytics will provide information on users' general demographics, site of origin (Reddit or Google), and the time spent on each web page. All data analyzed to investigate the *MOUD Hub* dissemination potential are from Google Analytics and website traffic. Google Analytics will provide details about the users, such as whether they are new or returning; their session on the website; what website pages they visit; page views; and bounce rates, which is when a user visits a website and leaves without interacting with any other pages [42]. Data will be stored on a password-protected computer with restricted access to the research team. Access to the Google Analytics data is username- and password-protected.

Statistical and Qualitative Analyses

Focus group transcripts will be analyzed using inductive thematic analysis. This inductive approach is useful when using direct questions to describe a particular experience and find common themes within data [43]. Two researchers will go through multiple coding iterations, with the first consisting of coding the data without preconceived categories. After the first round of coding, the researchers will decide on what codes to use and apply finalized codes using Atlas.ti (Lumivero) software [44]. Consistency will be achieved through regular team meetings, coding disagreements will be resolved through team deliberation, and code definitions will be enhanced as needed [45,46]. An in-depth review of coded data will lead to the identification of themes related to the safety, acceptability, and potential reach of the MOUD Hub and its hypothesized usefulness in improving access to and retention in MOUD treatment. We will then conduct member checking with selected participants to reduce the risk of data misinterpretation [47,48]. We will keep a log of suggestions and reasons regarding why they were or were not implemented.

Open-ended responses to the pop-up survey in the MOUD Hub will be analyzed on Atlas.ti software by the same 2 researchers using deductive-inductive thematic analysis based on the codebook developed for the analysis of the focus groups' data but allowing for new codes to emerge [49]. The same process will be followed to reach a consensus on the coding and to identify themes to answer our research questions.

Descriptive statistics will be conducted to assess the population that has accessed the website, their website of origin (Reddit or Google), how long participants were on the website, and how many pages they visited. Descriptive statistics will include the percentages, means, and SDs of age, gender, and geographic location of users. Descriptive statistics on how long participants were on the website and how many pages they visited will be measured by the total number of times the web page was visited, how many pages were visited, and the proportion of returning users. Descriptive statistics on the mean and SD of responses to the Acceptability of Intervention Measure will be assessed, with a mean between 4 and 5, corresponding to the "agree" and "completely agree" options in the scale, interpreted as users finding the website acceptable. We will produce CIs for each outcome.

Bivariate statistics, such as 1-tailed *t* tests, will be used to examine the difference in outcomes between users who come from Reddit and those who come from Google. Similarly, we

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will investigate differences in sociodemographic characteristics and use patterns of the website by conducting bivariate *t* tests. We will apply statistical tests to identify significant differences in the number of times each stage was accessed (vs all other stages) and in the number of times each specific resource was clicked on (vs other resources within that stage).

Ethical Considerations

Following implementation science guidelines, we will first assess whether this resource is acceptable and can be disseminated effectively and equitably before testing whether it can help with behavior change in a randomized controlled trial. Overall, there are minimal safety considerations at this time due to all resources provided coming from trusted sources and evidence-based studies that are accessible through web-based resources already. However, safety considerations will be thoroughly assessed during focus groups.

There is no disclosure from people accessing the website. Participants will not be identifiable as we will not collect personal identifiable information or geographical data that could exactly locate them. The resources and tools on the website are labeled as nonmedical advice, and participants are always informed to consult a physician. The study has been exempted by the University of California San Diego Institutional Review Board (protocol# 809353) due to the information being focused on the assessment of an educational resource as opposed to participants' personal experiences, and no personal identifying information will be collected. We will, nonetheless, take participants through an informed consent process for rigor and transparency.

Results

This research was funded by the National Institute of Health Avenir Award (NIH DP2 DA049295) in July 2019. The *MOUD Hub* will be launched in January 2025. We do not have a target sample size as this is a descriptive, observational, feasibility study aiming to gain information on the dissemination and reach of the website. Data will be collected for 1 year (from January 2025 to January 2026) and assessed in 3-month increments. Results based on the *Outcomes and Measures* section will be used to modify the website accordingly at each 3-month period. Results will show the evolution of the website and access patterns over time and will be published after the full year of assessment.

Discussion

Expected Findings

We have described our planned protocol for assessing the safety, acceptability, and reach of the *MOUDHub* website, which will be used as a resource guide for people seeking information on MOUD. This website is guided by harm reduction and MI principles, the stages of change, and Access to Health frameworks. We believe that it will be a helpful guide for those who experience barriers to accessing relevant information and care.

Our website includes information on evidence-based practices and interventions for users to consult and interact with. We believe that web-based platforms are a virtual third place for people to occupy and can provide knowledge and community building for those who may feel isolated and stigmatized. We expect to characterize users' interactions with the information provided and to gather their opinions on the usefulness of the resources for MOUD treatment.

Once these suggestions are incorporated into the website, we aim to conduct a randomized controlled trial to test the efficacy of the website in improving the uptake of and retention in MOUD. There are a few potential designs to help assess the intervention's efficacy. The first option would be to test the efficacy of the *MOUD Hub* by assessing differences in MOUD uptake and retention among people accessing the website. This could be done by recruiting participants on Reddit and Google based on their search for help, addressing their OUD, randomizing them to receive the *MOUD Hub* (ie, the intervention) or the Substance Abuse and Mental Health Services Administration website (ie, the control), and following up over time by asking them to fill in surveys regularly and obtaining access to their medical records to assess their treatment progress.

A more rigorous design would be to physically recruit participants and follow their treatment progress regularly. This type of analysis would allow us to compare efficacy among those stably housed and unstably housed to further assess whether a website is a helpful resource for those who might need to access the internet in public spaces versus the comfort of their own home.

Another possibility to assess the efficacy of the *MOUD Hub* could be to work with emergency departments. Participants could be those who are screened for an OUD, came in due to a recent overdose, or came in due to complications from their use. Participants would be randomly assigned to the *MOUD Hub* as a resource to learn more about MOUD in addition to the treatment-as-usual approach (eg, referral to OUD treatment) versus a treatment-as-usual approach only. Participants would be followed up to assess their uptake of (and retention in) MOUD.

Across study designs, qualitative interviews would be conducted to explore how the participants used the website, whether it impacted their decision to seek out MOUD, and whether it played a role in the participants taking and staying on the medication. This could inform future health research on whether a health information website that incorporates MI and the Access to Health framework can be more beneficial than those that only provide information.

A long-term goal will be to incorporate a discussion forum on the website for people to anonymously engage with others sharing similar questions and concerns, where they can share other resources, discuss their MOUD treatment, and offer support. There is potential for this website to become an "app" that can provide more personalized information and support for users, such as hotlines, trackers to help users see their progress, notifications to help keep users motivated, and space for reflections on their treatment.

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Limitations

One key limitation of this study is recognizing that not everyone has access to the internet, and thereby, some people will be excluded from using the *MOUD Hub*. Those most vulnerable often lack regular access to the internet. Therefore, if the *MOUD Hub* was successful in supporting access to and retention in MOUD treatment, it could exacerbate existing disparities in MOUD coverage by socioeconomic and housing status. However, among those who are unhoused or not working, the internet can be more accessible compared to physical services, with recent studies finding that >50% of adults experiencing homelessness have phones with internet access [50].

Web-based platforms offer a lifeline or support to people who may not be able to access health care regularly. The internet is a powerful tool in helping patients collaborate with their physicians by being more active in decision-making, preparing for their appointments, and facilitating communication [22].

Another limitation at this stage is that the website is not interactive, thus losing parts of the spirit of MI that can only be done through a person-to-person conversation. However, we are using elements of MI that might help the website users take the first step to receive the support needed. For example, we provide education and MI check-in questions tailored for each stage, including decisional balance questions and readiness and confidence rulers. Users will be encouraged to write their reflections on these questions in the space provided, and the website allows them to download their responses for them to keep. It is well established that information is not enough to elicit behavior change and that other issues take over when it comes to accessing SUD treatment (and other health interventions). However, we are providing concrete resources to address mistrust and logistical issues and ensuring that people with OUD, as well as their friends and family, are well equipped to understand how MOUD works and how to access and remain on treatment as an important first step.

Another limitation is that the *MOUD Hub* is not personalized at this stage, meaning that users cannot create a profile or track their progress. The website will not be able to follow a user's progress through the stages of change or keep a record of the resources that are useful for a specific person at a specific point in time. However, due to the website being in its first stages of development, this may be explored later and added to test whether personalization benefits users.

In addition, due to the website having a US-wide scope, the resources are general rather than specific to each setting, and it is up to the user to take steps to locate resources in their area if they are not included in the national MOUD, syringe service programs, or naloxone locators, for example. Finally, using Google Analytics poses a limitation as it estimates users' demographics through algorithms as opposed to self-report or routine databases.

Conclusions

This is the first website to provide comprehensive, reliable, and evidence-based sources on MOUD, considering all stages of change and catering to both people who use opioids and their friends and family. We trust this resource will increase awareness of MOUD, improve knowledge, dispel myths about its treatment effects, and support patients and families in accessing treatment. Future directions will focus on testing the efficacy of the *MOUD Hub* in increasing the uptake of and retention in MOUD.

Acknowledgments

AB, MJN, and AA were supported by the National Institute of Health Avenir Award (NIH DP2 DA049295) for this study. The authors are grateful to Jake Pelfrey for all his help and patience in building and fixing the MOUD Hub website beyond expectations.

Data Availability

The datasets generated during and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

MJN and AB conducted the literature review, developed the overarching study design, and drafted the manuscript. AA supported the search for resources for the website and the initial Reddit-based research to find what potential users would want to see on the website. JC, D Grelotti, BD, D Gann, KL, STP, and AA provided feedback and insight into the creation of the website and the manuscript. All authors contributed to editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional information on the stages of change.
[DOCX File , 154927 KB - resprot_v13i1e57065_app1.docx]

Multimedia Appendix 2

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High-fidelity snapshots of the web pages.
[DOCX File , 154926 KB - resprot_v13i1e57065_app2.docx]

Multimedia Appendix 3
Interview guide for focus groups to assess the website.
[DOCX File , 20 KB - resprot_v13i1e57065_app3.docx]

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Abbreviations

MI: motivational interviewing
MOUD: medications for opioid use disorder
OUD: opioid use disorder
SUD: substance use disorder

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Protocol

Development of a Web Platform to Facilitate the Implementation and Evaluation of Health Promoting Schools: Protocol for a Double Diamond Design Approach

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Abstract

Background: Health Promoting Schools (HPS) have emerged as a powerful framework to promote healthy behaviors in many countries. However, HPS still present several challenges, highlighting the excessive workload involved in the accreditation, design, implementation, and evaluation processes. In this sense, a resource to facilitate the implementation processes may have a positive impact on the support of HPS.

Objective: The aim of this study was to describe the co-design processes undertaken and resulting learnings to develop the Red Escuelas Promotoras de Salud (network of health promoting schools; REDEPS)-Gestion platform to facilitate the accreditation, design, implementation procedures, and evaluation processes of the Aragon's Health-Promoting School Network.

Methods: The Double Diamond Design Approach was used to co-design this web-platform. The different stakeholders that participated in this co-design, progressed through a 4-stage reflective phase, to discover, define, develop, and deliver the REDEPS-Gestion platform.

Results: Participants agreed that the functions of the REDEPS-Gestion platform should permit the management of both the educational centers and the administration such as accreditation processes, definition and review intervention projects, and preparation and review of the different progress reports to evaluate the HPS. Despite co-design being a well-established approach to creative practice, especially within the public sector, some challenges emerged during the co-design process, such as engaging and facilitating stakeholders' participation or the complexity of combining the interests of all stakeholders. This approach allowed us to identify the main barriers for future users and implement platform improvements.

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Conclusions: We hope that the REDEPS-Gestion platform will therefore be able to contribute to facilitating the implementation of HPS. The Double Diamond Design Approach used to co-design this web platform was an efficient and feasible methodological design approach. The REDEPS-Gestion platform will facilitate HPS implementation in Aragon as well as all the processes involving HPS. Future work will determine its effectiveness in improving HPS implementation.

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KEYWORDS

web platform; health promoting schools; co-design process; Double Diamond Design Model; implementation processes.

Introduction

The Health Promoting Schools Framework

The Health Promoting Schools Framework (HPS) is a very promising framework that provides a comprehensive strategic approach to the promotion of health in schools [1], involving a school environment that is constantly strengthening its capacity as a healthy setting for living, learning and working [2]. HPS reflect a holistic approach that goes beyond individual behavior since it also aims to change the whole system by strengthening the physical and social environment, including interpersonal relationships, school management, political structures, and teaching and learning conditions [3]. This approach can be seen as the result of overcoming traditional school-based health education, because it also implies a multicomponent framework that emphasizes improvements in educational outcomes as well as physical, social, and emotional well-being [4]. Internationally, HPS have been reported to have small, but positive effects on health behaviors and some aspects of social well-being [5].

Aragon's Health-Promoting School Network

Over the last decade, HPS have been implemented in many countries and different regional networks have been established. Spain belongs to the Schools for Health in Europe network foundation (SHE), which provides its members with the opportunity to further develop and sustain school health promotion in each country. Nevertheless, Spain lacks a national network, so each region has created its own. One of these is the HPS network in the region of Aragon in northeast Spain (Aragon's Health-Promoting School Network [ANHPS]). This network recognizes and supports schools that prioritize health and well-being as part of the educational curriculum, and encourages the development and dissemination of well-conducted interventions and specific activities [6]. In the 2022-2023 academic year, 215 accredited primary and secondary schools were involved in this network. In total, 30 are private schools, and the remainder are public schools. Together, they represent 20.4% of Aragon’s total primary and secondary schools [7]. In addition, 80.5% of teaching staff, 62% of nonteaching staff, and 90.2% of school students participate in the network. The intervention programs implemented in schools focus on the following areas of interest: life skills, physical activity, and nutrition [7].

Barriers and Challenges Identified in the Aragonese Context

Barriers and challenges have been found with respect to the implementation processes of ANHPS. The main ones would be the excessive workload involved in the accreditation, design and implementation processes, the lack of ongoing supervision of health promoting interventions, limited communication between the public administration (PAd) responsible for the ANHPS and the educational centers, and the need to evaluate interventions [8]. In this study, participants signaled the need to develop and use new evaluation and implementation tools. Perhaps for this reason, the WHO (World Health Organization) and UNESCO (United Nations Educational, Scientific and Cultural Organization) initiative [1] of “making every school a health promoting school” considers developing a web application for HPS monitoring and evaluation. Considering the above, it seems clear that there is a need for solutions and additional support.

The Importance of Participatory Approaches in Solving Problems in Health Promoting Schools Framework

Participatory approaches present the opportunity to do research “with” rather than “on” participants. Capacity building and community-level participation are important to enhance the efficiency and sustainability of health promotion programs [9]. The concept of “co-creation” has existed since well before the 1986 Ottawa Charter for Health Promotion, and it has been described diversely as community engagement and community-based participatory research [10]. In the context of schools, cocreation refers to inviting the school community and external stakeholders to participate in a design or problem-solving process [11]. It is also timely and key in school health promotion practices [9].

Among all the existing methodologies available to us, the Double Diamond Design Approach (DDDA) [12] has been used to develop service improvements in health and social care [13], patient-centered care in cancer treatment facilities [14], organizational medical care [15], and in the design process to co-develop the Active Schools framework [16].

The aim of this study was to describe the co-design processes undertaken and resulting learnings to develop the Red Escuelas Promotoras de Salud (network of health promoting schools; REDEPS)-Gestion platform, to facilitate the accreditation, design, and implementation procedures, and evaluation processes of the Aragon's Health-Promoting School Network.

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Methods

Participant Recruitment and Organization

This process began in September 2020, with the establishment of a steering committee (JZ, JJ, and GB-M) that met regularly throughout the development process. This steering committee was coordinated by the main researcher of the project. An experience-based purposive sampling was used by the steering committee, to identify different stakeholders' groups (DSGs) and participants that could be involved in the process [17]. Stakeholders included those individuals who were targeted by the intervention or policy, those involved in its development or delivery, and those whose personal or professional interests were affected (ie, all those with a stake in the topic). The steering committee identified participants from 5 DSGs [(1) Researchers (R): physical activity, nutrition, and addictive behaviors; (2) Representatives of the administration of the Government of Aragon, specifically from the Department of Health and Department of Education (PAd); (3) Aragonese network health promoting schools' coordinators (ANHPSC); (4) Aragon's Health-Promoting School Network' teachers (ANHPST); and (5) software developers; Table 1). Each stakeholder group was coordinated by one of its members. At least 1 member of the steering committee participated in the meetings of all the DSGs (Table 1).

The DSGs were organized into 3 different structures to develop the different design phases of the web platform: a first structure that involved all stakeholders, meaning that all stakeholders participated at the same time; a second structure (DSG) that involved various stakeholder groups (researchers, public health and education specialists -PAd-, ANHPSC, ANHPST, and software developer), meaning that these stakeholder groups participated separately; and a third structure multistakeholders' group that included the software developer group and the coordinators of the different stakeholders' groups.

The different structures were coordinated by the steering committee. Most meetings took place through Google Meet due to the COVID-19 pandemic situation.

Table 1. Key stakeholder characteristics (N=31).

Stakeholder groups	Participants from each stakeholder group, n	Proportion (%) of males/females	Approximate years in current professional role, mean
Researchers	17	47.1/52.9	15
PAd[a]	6	16.6/83.3	25
ANHPSC[b]	2	50/50	22
ANHPST[c]	3	66.6/33.4	12
Software developer	3	100/0	7
Total	31	48.3/51.6	16

[a]PAd: public administration.

[b]ANHPSC: Aragon's Health-Promoting School Network' coordinators.

[c]ANHPST: Aragon's Health-Promoting School Network' teachers.

Study Design

The DDDA [12] was used to guide the co-design process of the web platform (Figure 1). This methodology draws on recent discoveries on how to optimize both divergent (ie, creating choices) and convergent (ie, making choices) creative thinking processes [18]. The Double Diamond process consists of 4 phases (outline; Figure 1).

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Figure 1. The Double Diamond Design Approach used to develop the Red Escuelas Promotoras de Salud (network of health promoting schools)-Gestion platform.

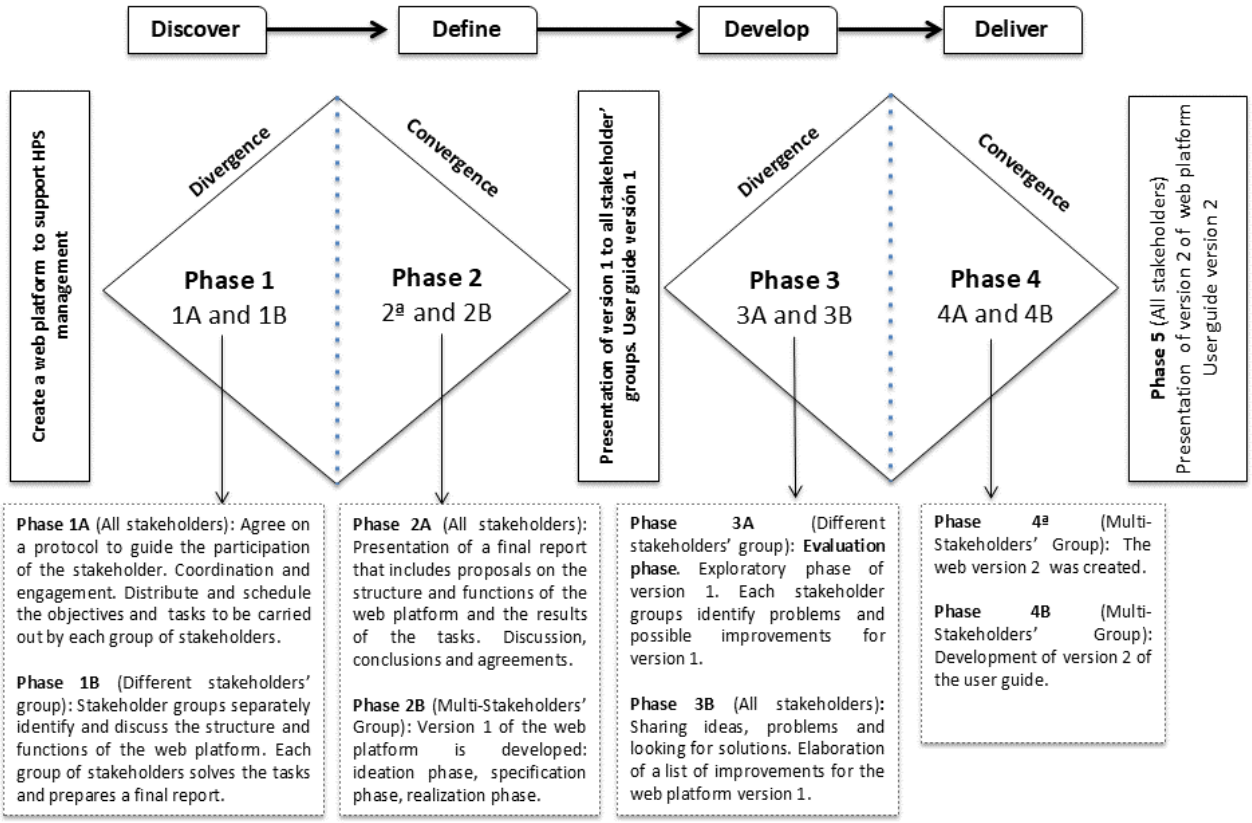

Discovery Phase

The stakeholder team explores problems or the target project to understand the target challenge. A protocol to guide the participation of the stakeholders is agreed. Problems and needs are explored, insights and user needs gathered, and ideas generated (ie, creative process and divergent thinking).

Definition Phase

In this phase, the team builds possible ideas and solutions (ie, prioritization of the ideas from the previous phase: convergent thinking).

Development Phase

Solutions are created and explored (ie, concepts and drafts are created and tested: divergent thinking).

Delivery Phase

The service is tested and evaluated (ie, the resulting content is finalized and delivered: convergent thinking).

The different phases of the process will be explained in the following sections.

Cocreation Procedures

A meeting was initially held (1 hour 30 min) with all the stakeholders. At that meeting, the objectives of the project and the justification for the need to design and develop a web platform to facilitate the management and evaluation of ANHPS were presented by the steering committee.

The different stakeholders that participated in this approach progressed through a 4-stage reflective process to discover, define, develop, and deliver an innovative solution to a problem [19], with different tasks (A/B) per phase.

Table 2 presents the different phases, the work structure used and the different stakeholder groups that participated.

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Table 2. Phases, work structure, and stakeholder groups.

Phases	Work structure	Engaged stakeholders
Discovery		
1A	All stakeholders	All stakeholders
1B	DSG[a]	Researcher, software developer, PAd[b]
Definition		
2A	All stakeholders	All stakeholders
2B	MSG[c]	At least one person representing each of the following groups: researcher, software developer, ANHPSC[d], ANHPST[e], PAd[b]
Development		
3A	DSG[a]	Researcher, software developer, PAd
3B	All stakeholders	All stakeholders
Delivery		
4A	MSG[c]	At least one person representing each of the following groups: researcher, software developer, ANHPSC[d], ANHPST[e], PAd[b]
4B	MSG[c]	At least one person representing each of the following groups: researcher, software developer, ANHPSC[d], ANHPST[e], PAd[b]

[a]DSG: different stakeholders' groups.

[b]PAd: public administration.

[c]MSG: multistakeholders' groups.

[d]ANHPSC: Aragon's Health-Promoting School Network' coordinators.

[e]ANHPST: Aragon's Health-Promoting School Network' teachers.

Each phase is explained in the following subsections.

Phase 1: Discovery Phase

Phase 1A (All Stakeholders)

The main objectives were to define the structure and functions of the web platform based on the previously identified needs and to specify the tasks to be carried out in the following phases by each stakeholder group involved. In this phase, the objectives, tasks, and calendar to be carried out by each of the stakeholder groups were presented and discussed. This phase was coordinated by the steering committee and developed through a 2-hour meeting. All stakeholders participated.

Phase 1B (Different Stakeholders' Group)

The main objective was to define the structure, components, and functions of the web platform. Each group of stakeholders (researcher, software developer, and PAd) solved these tasks and prepared a final report. The duration of this phase was 6 months. Each of the coordinators from the different stakeholders' groups were in charge of planning the necessary meetings to resolve the tasks assigned. The average number of meetings held by the different stakeholders' groups was 8, each one lasting for 2 hours. The main conclusions of these reports influenced the design of the platform and are described in the results section.

Phase 2: Definition Phase

Phase 2A (All Stakeholders)

The main objective was to present the different final reports, which include the structure, components, and functions of the web platform. This phase was coordinated by the steering committee and developed through a 2-hour meeting. Each stakeholder group (researcher, software developer, and PAd) presented its report with the results of the work from the previous phase, for discussion. Subsequently, the proposals were discussed to draw final conclusions. The conclusions of this phase allowed us to begin the design of the web platform. They will be explained in the Results section.

Phase 2B (Multistakeholders' Group)

The main objective was to develop version 1 (v1) of the web platform and of the user guide (v1) following the agreements and conclusions of the previous phase. These agreements and conclusions were materialized by the software developers.

The duration of this phase was 10 months, carrying out 18 work sessions, amounting to a total of 40 hours. A member of the steering committee acted as coordinator in all the work sessions.

Finally, this phase ended with a workshop (all stakeholders). In this workshop, the steering committee presented and explained v1 of the web platform and of the user guide, and the different stakeholders spent 1 hour exploring the web platform, and 30 minutes resolving any issues or problems.

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Phase 3: Development Phase

Phase 3A (Different Stakeholders' Group)

The goal of this phase was to determine how usable the web platform was for the stakeholder groups. This dimension was evaluated using quantitative methods such as an online questionnaire answered by each of the members of the DSG. The questionnaire was conducted remotely, and instructions were received by participants by email, together with a link to the website, as well as an online questionnaire that they could complete in their own time. Completion of all the items on the questionnaire was mandatory. The platform usability was evaluated through the following subdimensions: structure of the web platform, coherence, visibility, user interaction with the web platform, and content clarity (eg, usability items: "Does the platform present a clear structure that facilitates its use and meets the user's needs?"; Table 3). Furthermore, the questionnaire allowed us to add observations and suggestions to improve these dimensions.

Table 3. Subdimensions, indicators and items for usability evaluation.

Subdimension	Indicator	Evaluation
Structure	The contents are well organized with a well-defined hierarchy.	• Does the platform have a clear structure that makes it easy to use and meets the user's needs?
Coherence	The design of the platform, its sections, links, and content are presented in a coherent manner.	• Is the platform configured in a logical way to respond to the needs of each stage of the process?
Visibility	The headings and different sections (colors, saturation, and contrast are adequate for quick reading).	• Does the platform contain pleasing and attractive formats, colors, and fonts that make it easy to use with different devices?
Visibility	The menu is easily visible and accessible, and the platform allows the user to know where they are at any given time, or what section they are in.	• Is the menu easily accessible and identifiable? • Does the menu always remain visible to the user? • Does the user always know where he/she is on the platform?
Platform interaction	The platform is intuitive to use.	• Is the platform sufficiently intuitive that it does not require previous training to use if the user manual is followed?
Platform interaction	(Objective measurement)[a]. After logging in, the number of clicks needed to find the information within the platform is no more than 3.	—[b]
Clarity	The platform hosts clear, direct, and simple content, containing no irrelevant or superfluous information.	• Is the content of the platform relevant and presented in simple and easily understandable language?

[a]All indicators are evaluated by all stakeholders, except objective measurement, which is only assessed by IT developers.

[b]Not applicable.

Phase 3B (All Stakeholders)

In this phase, the results of the usability test were analyzed and discussed in order to discover if the original requirements were met.

These results were shared and discussed during a 2-hour work meeting, reflecting on the progress and the state of ideas compared with the work of v1. Similarly, suggestions for future improvements were made and considered. In addition, different work meetings were held with the various stakeholders to identify priority changes to this version.

Phase 4: Delivery Phase

Phase 4A (Multistakeholders' Group)

The goal of this phase was to apply the improvements identified in phase 3B and to create v2 of the web platform (a total of 20 hours invested).

Phase 4B (Multistakeholders' Group)

The goal of this phase was to create a new user guide (ie, v2) to facilitate the use of the new web platform version (2 two-hour work sessions).

Phase 5 (all stakeholders) took place at the end of phase 4b, holding a work session where v2 of the platform and the user manual were presented to all stakeholders involved in the project.

Ethical Considerations

This study is part of a research project called Health Impact Assessment Project in school population, supported by the Ministry of Science, Innovation and Universities of the Spanish Government (PID2019-105822RB-100). The co-design processes were approved by the Ethics Committee of Aragon (Comité de Ética de la Investigación de la Comunidad de Aragón [Research Ethics Committee of the Community of Aragon; CEICA], C.P. - C.I. PI20/357) and the ethical principles of the Declaration of Helsinki were followed. Participation was

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voluntary and information on meetings was provided in advance. Written consent was given to record the group sessions.

Results

Overview

The different phases of the co-creation process following the DDDA model allowed us to obtain different partial results, which we present below.

Discovery Phase Results (Phase 1)

In this phase, different issues were agreed upon:

(1) the level of involvement and participation of the different stakeholders throughout the process.

It was also agreed that, in line with the work of Pollock et al [20], the level of involvement and participation of the different stakeholders would be co-designed throughout the process, thus entailing maximum participation level. This fact makes all members of the development team equal, facilitating their participation in all development phases.

(2) the definition of the basic operation rules for the stakeholders, and the tasks to be carried out by each of the stakeholder groups during this phase.

As a result of the definition of the basic operation rules, it was agreed to appoint a coordinator for each stakeholder group, to schedule regular meetings of each of these groups, and plan the tasks to be carried out by them. These tasks were to review updated scientific evidence on their topics of reference, and to draft a report on the requirements and needs that the platform should meet.

(3) the main characteristics that should be considered in the design and development of the web platform.

These main characteristics were:

1. Platform usability: the web should offer a user-friendly platform on which all the procedures could easily be carried out (ie, accreditation, design and implementation of the programs, and evaluation process).
2. Communication platform: the web should offer a communication platform through which the previously named users could share the necessary information to carry out the different procedures.
3. Platform structure and functions: the structure of REDEPS-Gestion should allow the performance of the following actions explained in Textbox 1.

(1) Each educational center should be able to carry out a diagnostic evaluation (self-check) based on previously defined standards and indicators incorporated into the platform; (2) PAd should be able to check and give feedback to each educational center based on the results of the self-check; (3) each educational center should be able to carry out the accreditation process to be recognized as an HPS; (4) the PAd should be allowed to review the documentation provided by each educational center for the accreditation process and should decide whether or not to provide accreditation; (5) each educational center should be able to consult the result of its accreditation process; (6) if the educational center were accredited, start to define the HPS project for a 3-year period (a cycle); (7) the PAd should be able to review the projects defined by each HPS; (8) every academic year, each HPS should prepare a progress report, and during the third year, a final report should be delivered through the platform; (9) the PAd should be able to review the different progress reports; and (10) based on the review reports prepared by the PAd, each HPS should be able to request the renewal accreditation as a HPS, starting a new 3-year cycle. All these actions, which are part of the process and HPS life cycle, are implicit in the platform.

Textbox 1. Requirements of the REDEPS (Red Escuelas Promotoras de Salud)-Gestion platform.

- Each educational center should be able to carry out a diagnostic evaluation (self-check) based on previously defined standards and indicators incorporated into the platform.
- Public administration (PAd) should be able to check and give feedback to each educational center based on the results of the self-check.
- Each educational center should be able to carry out the accreditation process to be recognized as an health promoting schools (HPS).
- The PAd should be allowed to review the documentation provided by each educational center for the accreditation process and should decide whether or not to provide accreditation.
- Each educational center should be able to consult the result of its accreditation process.
- If the educational center were accredited, start to define the HPS project for a 3-year period (a cycle).
- The PAd should be able to review the projects defined by each HPS.
- Every academic year, each HPS should prepare a progress report, and during the third year, a final report should be delivered through the platform.
- The PAd should be able to review the different progress reports.
- Based on the review reports prepared by the PAd, each HPS should be able to request the renewal accreditation as an HPS, starting a new 3-year cycle.
- All these actions, which are part of the process and HPS life cycle, are implicit in the platform.

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Definition Phase Results (Phase 2)

The end results of this phase were the materialization of v1 of the web platform (ie, definition of the different stages, processes and responsible agents involved in the platform; Table 4) and the different itineraries, one for PAd and another for the educational centers (Figures 2 and 3).

The stages and processes previously described (Table 4) determine the structure and functions of the web platform, which include 2 different itineraries depending on the user (PAd role and ANHPSC role). These itineraries are specified in Figures 2 and 3.

Table 4. Final stages, processes, and responsible stakeholders of the web platform v1.

Stages	Processes	Responsible agent
Self-check	The self-check form allows the educational center to make a diagnostic evaluation in relation to the different standards and indicators previously defined from the Global Standards and indicators (WHO[a] and UNESCO[b] [1]; Multimedia Appendix 1).	ANHPSC[c]
Review of the self-check form. Self-check score	HPS[d] checks the self-check of the educational centers. The web platform assigns a score to the self-check and the educational centers review the score obtained.	ANHPSC[c], PAd[e]
HPS[d] accreditation process	This includes several steps. First, each educational center must enter its general data. Second, the application form must be filled out. Third, accreditation requirements (the educational center must complete the accreditation requirements requested by the web platform itself). Finally, a document is generated, including all the requirements requested to carry out the accreditation process.	ANHPSC[c]
Review of the documents for accreditation provided by the educational centers	The PAd[e] verifies that each educational center has correctly satisfied all the accreditation requirements.	PAd[e]
Educational centers consult the result of the accreditation process	Each educational center can check if it has been accredited.	ANHPSC[c]
Definition of the project	Each HPS[d] designs its project for three years.	ANHPSC[c]
Progress report	Each HPS[d] prepares an annual progress report.	ANHPSC[c]
Review of progress reports	Review of progress reports submitted by each HPS[d]. Analysis of the degree of compliance of the project.	PAd[e]
Renewal as HPS[d]	Depending on the degree of compliance achieved by the project, the PAd[e] will once again recognize the educational center as HPS[d].	PAd[e]
New project definition	If an educational center has been renewed as HPS[d], it redefines its project for the next 3 years (new cycle).	ANHPSC[c]

[a]WHO: World Health Organization.

[b]UNESCO: United Nations Educational, Scientific and Cultural Organization.

[c]ANHPSC: Aragon's Health-Promoting School Network' coordinators.

[d]HPS: health promoting schools.

[e]PAd: public administration.

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Figure 2. Educational centers itinerary: structure, functions, and processes in Red Escuelas Promotoras de Salud (REDEPS; network of health promoting schools)-Gestion (itinerary 1). HPSC: Health Promoting Schools Coordinators.

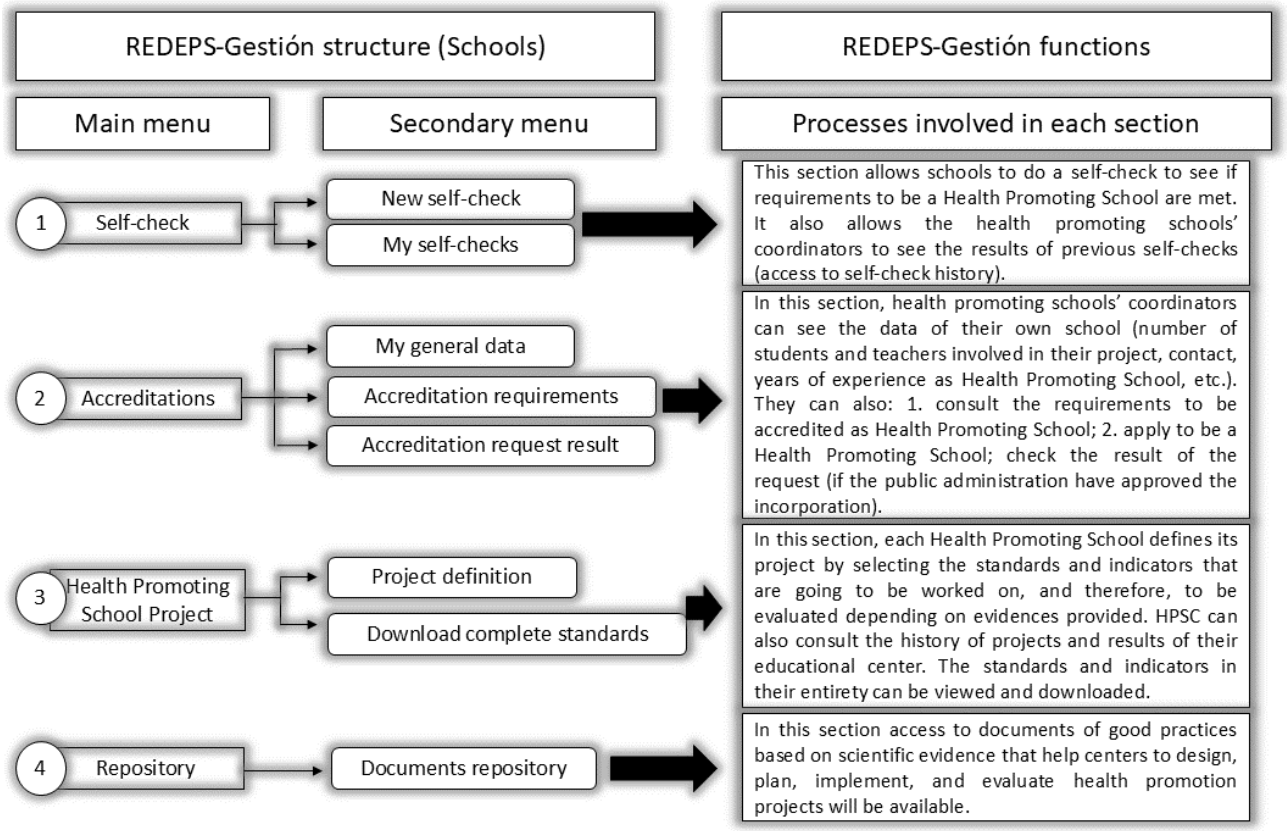

Figure 3. PAd itinerary: structure, functions, and processes in Red Escuelas Promotoras de Salud (REDEPS; network of health promoting schools)-Gestion (itinerary 2).

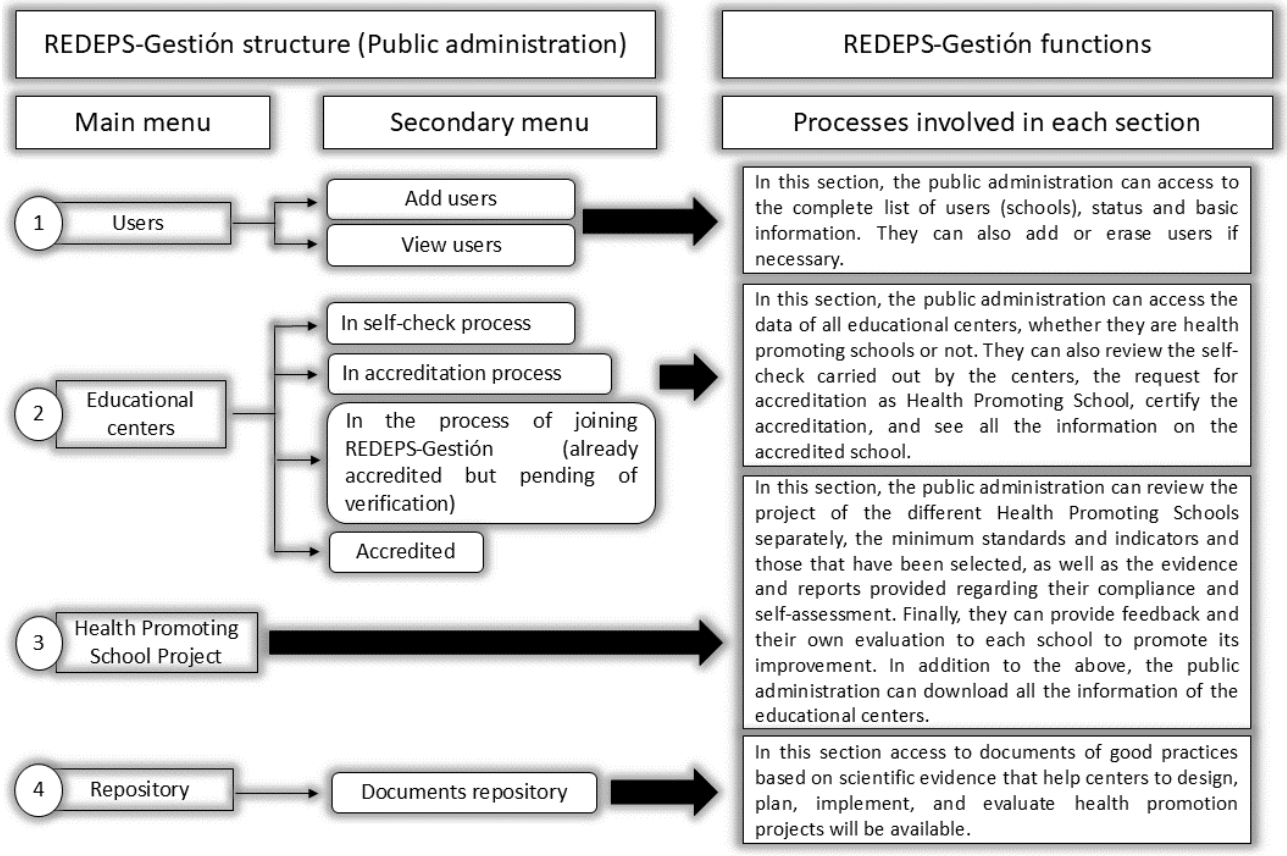

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Itinerary 1: Defined Structure, Functions, and Final Processes for Educational Centers on the Web Platform

The main objective of the first itinerary (Figure 2), corresponding to the educational centers, is to establish some commitments and objectives to improve health promotion in the educational center and context, involving the largest possible number of agents, providing evidence, and self-assessing. The main sections of the itinerary with their respective processes, presented in table 2, are the self-check section, the accreditation section, the project definition and evaluation section, and the consultation repository (support documents for evidence-based practice in health promotion).

Itinerary 2. Defined Structure, Functions, and Final Processes for PAd on the Web Platform

The second itinerary is associated with the PAd role. REDEPS-Gestion provides them with the ability to access information uploaded by the ANHPS, to review, analyze, and evaluate it and provide feedback and help when required. This itinerary (Figure 3) contains the following main sections: user management, HPS management (situation within the process), HPS project review and evaluation section, and finally, the only common section for both itineraries, the document repository. The preparation of standards and indicators to define and evaluate the intervention programs of the Aragonese health promoting schools based on the proposal of SHE [21], WHO, and UNESCO [1]. The final set of standards and indicators will serve as a reference for educational centers to define their projects, and for PAd to guide and evaluate them (Multimedia Appendix 1).

Development Phase Results (Phase 3)

In this phase, an evaluation of v1 of the platform was carried out by the different stakeholders. This first platform version was evaluated making an assessment of the degree of usability of platform v1 (yes, no, or sometimes).

The usability dimension obtained total fulfilment of 73.75% of the indicators.

Delivery Phase Results (Phase 4)

Based on the modifications identified in the previous phase, this phase entailed incorporating the changes to configure v2 of the platform and the user guide (Multimedia Appendix 2). Subsequently, this new version was presented to the different stakeholders.

Discussion

Principal Findings

This study describes the co-design processes undertaken and resulting learnings to develop a web platform to facilitate the accreditation, design, implementation procedures, and evaluation processes of the Aragon's Health-Promoting School Network. The REDEPS-Gestion platform was developed to achieve this objective.

Although HPS is a very promising framework, previous studies have identified barriers for the implementation of health programs in the context of HPS, such as the management of the different processes involved [22]. It seems clear that there is a need to provide solutions and support to facilitate these processes. Facilitating the HPS management (eg, accreditation and implementation) and evaluation processes can help to ensure the availability and improvement of institutional capacity (ie, educational centers and public administration), and to ensure the efficacy and sustainability of interventions.

The platform offers educational centers the possibility of finding out if they meet the requirements for accreditation and can apply to join. From the platform itself, educational centers will be able to define their project based on some standards and indicators offered by this resource. It also offers a responsible administration of HPS, as well as a review and evaluation of the projects presented by the different schools. REDEPS-Gestion also favors more fluid communication between both stakeholders.

Usability is commonly recognized as one of the most important factors in the quality of information systems [23]. The results indicate that more than 70% of those responsible for the administration and the agents of the educational centers consider that the platform presents a clear structure and responds to the needs of the HPS implementation processes. Based on the suggestions or remarks added to the questionnaire, improvements were made to the following aspects: (1) the colors of the platform were changed, scroll bars were added to some screens to speed up navigation, or the platform menu was changed to make it permanently visible, (2) alerts and warning windows, including relevant information, were incorporated for educational centers, and (3) some documents hosted on the platform that were essential for the accreditation process and project definition were modified. In addition, and to facilitate its use, 2 support elements were created, a complete user manual and training, mainly through video tutorials and face-to-face sessions.

Co-design approaches have become an integral part of various fields of public health, health education, and health promotion research. Several studies have already reported the efficacy of the use of co-design procedures [24-26], and that research co-design can benefit researchers [27]. These approaches have the potential to allow the production of deeper knowledge by incorporating the different perspectives and experiences of key actors closely related to the subject of the research [28].

Some challenges have emerged during the co-design process of the REDEPS-Gestion platform. Although engaging stakeholders is increasingly encouraged in co-design processes [29], our findings show that this may be difficult. We believe that a common understanding of each stakeholder's motives was important for the success of the project. In the implementation of the DDDA, the motivations of each of the participating stakeholders must be considered, as, on some occasions, we were able to verify disagreements between the representatives of the administration, the educational centers, and the researchers. Because of its difficulty, and despite the fact that, to allow for a high degree of engagement and interaction [30], we invited different stakeholders to take part in meetings rather than interviews or surveys, which are the most common methods used to engage stakeholders [31], the

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research team identified engagement and facilitation as key challenges. This may be because the meetings method entails too much time on behalf of stakeholders [32], especially because the DDDA requires divergent processes where different ideas are generated that need to be discussed and agreed upon. This can be time consuming. Therefore, the leadership of the meetings and the coordination of tasks by the steering committee is very important. In this sense, Tollyfield [33] describes how facilitation in co-design projects catalyzes receptive contexts that encourage engagement by creating a positive environment with mutual respect and equal partnership. Researchers who want to use co-design must be prepared for the extra time required, and the need for skills concerning engagement, communication, facilitation, and the negotiation and resolution of conflicts [34].

Lessons Learned

Several important learnings arose from this study. The DDDA is not a simple approach to guide the process of creating a web platform, particularly when the participation of different agents and interests must be combined in the development of the final product. One challenge identified was how to increase the degree of commitment of the different stakeholders. The work approaches throughout each stage of the process were fit for purpose, taking into consideration the needs of the HPS context and stakeholders involved, because they focus on the main aspects to be considered when developing a project, that is, defining and creating boundaries around problems as the aim is to create solutions. They also favor a dialogue between thinking styles, divergent creation/discovery and convergent analysis, synthesis, and decision-making. However, this process can take too much time. The importance of having a steering committee that coordinates the development of the different phases and the role of coordinator to lead the work of each different stakeholders' group. The fact that the research project leader participated in the steering committee as well as in the different meetings or work sessions proved to be of great value. This contributed to increased awareness of and support to the project. The complexity of the different tasks that comprise the convergent and divergent processes of this approach requires that meetings or work sessions be held in person. Most meetings (during the phases 1A, 1B, 2A, and 3B) took place through Google Meet due to the pandemic situation. This situation made the development of the different phases and tasks even more complex.

Strengths, Limitations, and Future Directions

The main strengths of this study were that through this website, all the processes to be carried out by both educational centers and the administration to implement HPS would be facilitated and the cocreative process used in the development of this website has allowed us to provide solutions to the main barriers identified by the different stakeholders with responsibility for the implementation of HPS.

However, the study is subject to some limitations. The main limitation is that the web platform is specific to the context of the region of Aragon (Spain), although it provides a useful tool that could be used in the different Spanish regions that implement HPS. Future research is needed to investigate how this web platform can be applied to another Spanish context. In co-design processes, it is also known that more time is required to advance, since a multitude of stakeholders are involved. This is a limitation, especially when the duration of the projects and their funding is insufficient.

In the near future, further improvements are expected to be incorporated into the platform. First, feeding a repository of materials, documents, and resources for teachers that guide educational centers in the design of health promotion programs, using best practices and evidence-based practices. Second, through the platform, the authors expect to incorporate the possibility for HPS students to be able to complete self-reported instruments that evaluate different health behaviors. These changes detected in health behaviors could help to further evaluate the effect of health promoting interventions carried out.

Conclusions

The REDEPS-Gestion platform will facilitate the implementation of HPS in Aragon. The DDDA used to co-design this web platform was an efficient and feasible methodological design approach, but several limitations and considerations must be taken into account when using it. Future work will determine its effectiveness in improving HPS implementation.

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Data Availability

No data has yet been generated since this project is ongoing. In the future, data will be available from the corresponding author on reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed standards and indicators for Health Promoting Schools.
[DOCX File , 17 KB - resprot_v13i1e52110_app1.docx]

Multimedia Appendix 2
REDEPS-Gestion user guide ES.
[PDF File (Adobe PDF File), 10502 KB - resprot_v13i1e52110_app2.pdf]

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Abbreviations

ANHPS: Aragon's Health-Promoting School Network
ANHPSC: Aragon's Health-Promoting School Network' coordinators
ANHPST: Aragon's Health-Promoting School Network' teachers
DDDA: Double Diamond Design Approach
DSG: different stakeholders' group
HPS: Health Promoting Schools Framework
PAd: public administration
REDEPS: Red Escuelas Promotoras de Salud
SHE: Schools for Health in Europe network foundation
UNESCO: United Nations Educational, Scientific and Cultural Organization
WHO: World Health Organization

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Protocol

The Effects of the Processing of Positive Memories Technique on Posttrauma Affect and Cognitions Among Survivors of Trauma: Protocol for a Daily Diary Study

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Abstract

Background: The Processing of Positive Memories Technique (PPMT) is a promising new treatment approach for posttraumatic stress disorder (PTSD), which involves detailed narration and processing of specific positive autobiographical memories. Indeed, preliminary case-series studies have found reductions in PTSD symptoms, negative affect, and negative cognitions among survivors of trauma who have received PPMT. However, PPMT's effects have not been investigated at the daily level. In this study, we describe the protocol for a study that will examine the daily-level impacts of PPMT in a trauma-exposed, nonclinical community sample.

Objective: This study uses an innovative research protocol that combines case-series design and daily diary approaches to examine changes in daily affect, daily cognitions, and daily PTSD symptoms pre- and post-PPMT. We hypothesize that at the daily level, in comparison to their own pre-PPMT levels, following the PPMT intervention, participants will report (1) a lower count of endorsed daily PTSD symptoms, (2) increases in daily positive affect and decreases in daily negative affect, (3) increases in positive affect reactivity to daily positive events, and (4) decreases in daily posttrauma cognitions.

Methods: We are currently recruiting participants (target n=70) from a metroplex in the southwest United States. Following a screening survey, eligible participants complete a preintervention baseline survey, followed by 21 daily surveys in their natural environments. Then, they receive 4 PPMT sessions on a weekly basis. After the conclusion of the PPMT intervention, participants complete a postintervention outcome survey and 21 daily surveys. To compare daily affect, daily cognitions, and daily PTSD symptoms before and after PPMT, we will use the daily diary report data and conduct multilevel random intercepts and slopes linear regression models.

Results: Data collection was initiated in March 2022 and is expected to end by June 2024. As of November 28, 2023, a total of 515 participants had consented to the study in the screening phase. No analyses will be conducted until data collection has been completed.

Conclusions: Study findings could clarify whether deficits in positive autobiographical memory processes may also characterize PTSD alongside deficits in traumatic memory processes. Furthermore, PPMT could be an additional therapeutic tool for clinicians to help clients reduce posttraumatic distress in their everyday lives.

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KEYWORDS

affect; case series design; cognitions; experience sampling; intensive longitudinal assessment; positive autobiographical memories; posttrauma health; posttraumatic stress disorder; trauma survivors

Introduction

Posttraumatic stress disorder (PTSD) is a psychological condition that can develop following exposure to traumatic events, characterized by intrusive thoughts and re-experiencing symptoms, avoidance of trauma reminders, negative cognitions and mood, and heightened arousal [1]. A proposed mechanism underlying the development and maintenance of PTSD is disruptions in the encoding, consolidation, and retrieval of negatively- and positively-valenced autobiographical memories [2-4]. Evidence suggests that survivors of trauma with PTSD report difficulties accessing and detailing positive autobiographical memories [5-7], akin to reported difficulties with traumatic autobiographical memories [8]. Unsurprisingly, PTSD interventions typically target the content, processes, and phenomenological characteristics of autobiographical memories [9,10]. While such trauma-focused interventions (eg, prolonged exposure and cognitive processing therapy) are effective for many survivors of trauma, a significant proportion of survivors of trauma do not respond to these treatments, and there is a high degree of dropout from these interventions [11]. This highlights the need to develop alternative therapeutic approaches.

While most PTSD interventions address engagement with only traumatic autobiographical memories, only a few other interventions address both traumatic and positive autobiographical memories or only positive autobiographical memories and have been shown to be effective. For instance, Memory Specificity Training (targeting one's ability to retrieve specific autobiographical memories irrespective of valence) is effective for PTSD and posttrauma distress [12,13]. Also, Broad-Minded Affective Coping, a positive emotion induction technique through the retrieval of positive autobiographical memories, improves mood among individuals with PTSD [14]. Such evidence suggests that a focus on positive autobiographical memories may be a helpful target in PTSD interventions.

The PTSD-Positive Memory Model [15,16] outlines that when survivors of trauma repeatedly retrieve, relive, and detail specific positive autobiographical memories, they may experience an improvement in PTSD symptoms, affect, and beliefs over time [15]. This model was foundational to the development of the Processing of Positive Memories Technique (PPMT), which is a 4- to 5-session intervention tailored to PTSD symptoms. During PPMT sessions, survivors of trauma are guided to narrate details of salient positive autobiographical memories; to access and strengthen positive values, affect, strengths, and thoughts associated with these memories; and to engage in positive affective, cognitive, and behavioral changes [17]. PPMT is influenced by positive psychology, a field that emphasizes factors and mechanisms that enhance psychological well-being rather than focusing solely on pathology [18,19]. PPMT draws from positive psychology interventions (eg, sharing positive narratives with others and using mental imagery to re-expereince positive events) [19-21] and from interventions that increase memory retrieval to improve mental health [22]. The detailed session-by-session content of PPMT is outlined by Contractor and colleagues [17].

Practicing PPMT may help survivors of trauma retrieve more positive autobiographical memories over time, which may also translate to retrieving fewer negative autobiographical memories. Consequently, survivors of trauma may be able to better contextualize and integrate traumatic autobiographical memories with existing beliefs [23] and with other memories [2,24], which in turn could aid recovery after a trauma [2,25]. Positive autobiographical memories may also become primary reference points to interpret experiences and influence self-concept [26-28]. Furthermore, by repeatedly retrieving positive autobiographical memories and associated content, survivors of trauma may lessen their focus on negative material, experience more positive affect, and downregulate negative affect [29-32]. This may be especially helpful for survivors of trauma who experience emotional distress from retrieving negative autobiographical memories. In turn, this improved affect may help survivors of trauma positively interpret events [29,33] and note more positive content in their thoughts [34]. Overall, retrieving positive autobiographical memories may improve well-being [35], resilience [36], and adaptive coping [37], serving as a reminder that there are positive values and thoughts to hold on to despite the hardships faced by survivors of trauma.

Pilot studies have shown that PPMT is feasible and may improve therapeutic outcomes for survivors of trauma. Using an experimental design, a 2-session modified-PPMT [38] and a 5-session PPMT protocol [39] were compared to a neutral memory condition among survivors of trauma. In the first study, authors found that participants who repeatedly narrated the content of positive autobiographical memories reported decreases in PTSD symptom severity and negative affect, as well as increases in positive affect across time compared to the control condition [38]. In the second study, authors found that survivors of trauma who repeatedly retrieved positive (and neutral) memories reported less PTSD and depression severity, fewer posttrauma cognitions, and improved affect [39]. Using an open-label pilot trial, the feasibility and effects of the 5-session PPMT were examined among 12 survivors of trauma [40,41]. The authors found that PPMT reduced PTSD symptoms, reduced negative affect, and improved regulation of positive affect, and there were good feasibility indicators for PPMT (eg, PPMT was acceptable).

Critically, no study has examined PPMT's effects using a larger community sample, nor has there been any exploration of whether PPMT is associated with postintervention changes in how survivors of trauma react to events in daily life. We can hypothesize that PPMT may impact individuals' daily-life affect and cognitions; these impacts represent hypothesized

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mechanisms through which PPMT may reduce PTSD symptom severity over time. Most studies examining PTSD intervention impacts use case-series designs, in which data are collected from a group of individuals pre- and postintervention and an aggregate assessment of symptomatology pre- and postintervention is conducted and compared. However, this approach has some noteworthy limitations. Affect, cognitions, and PTSD symptoms are dynamic and vary daily in response to trauma reminders and experiences [42-44]; thus, evaluating intervention effectiveness using 2 snapshot assessments of symptomatology is not sufficiently reliable or nuanced. Furthermore, case-series designs do not examine the daily-level mechanisms of change for an intervention. Given that PPMT may impact daily life affect, cognitions, and symptoms, it is crucial that the data enable an examination of these constructs at the daily level.

These limitations can be overcome by integrating case-series designs with a daily diary framework for the pre- and post-PPMT assessments. Daily diary studies are an intensive longitudinal data collection method in which participants provide daily reports of their experiences each day over a period of time. Compared to retrospective assessments, daily diary data are considered more ecologically valid as they are collected in an individual's everyday life rather than in a laboratory, more accurate and robust, and less vulnerable to recall bias [45]. Thus, the proposed study outlines information on the protocol of an ongoing study that combines case-series design and daily diary approaches to provide novel insights into PPMT's effects on daily-level cognitive and affective experiences. This approach can be conceptualized as a special subtype of case-series design that enables an examination of within-person changes at the daily level.

Specifically, the proposed study aims to use daily diary data pre- and post-PPMT to examine changes in daily PTSD, daily affect, and daily cognitions. We hypothesize that at the daily level, participants will report (1) a lower count of endorsed daily PTSD symptoms pre- to post-PPMT, (2) increases in daily positive affect and decreases in daily negative affect pre- to post-PPMT, (3) increases in positive affect reactivity to daily positive events (a within-person index of linear relations between daily positive events and daily positive affect) pre- to post-PPMT, and (4) decreases in daily posttrauma cognitions pre- to post-PPMT. The aim of this study is to detail the proposed research protocol and our hypotheses regarding daily PTSD, daily negative affect, and daily cognitions pre- and post-PPMT. As a supplementary analysis, we will examine if participants report a greater count of retrieved specific positive memories pre- to post-PPMT.

Methods

Study Design

The study involves four phases: (1) screening phase (eligibility survey), (2) preintervention phase (baseline survey and daily surveys), (3) intervention phase (PPMT and weekly surveys), and (4) postintervention phase (outcome survey and daily surveys). Figure 1 provides an illustration of the study procedure. All assessments are completed by participants using a computer or smartphone. Greene and colleagues [46] provide a detailed protocol for the questionnaires. Briefly summed up, following a web-based screening survey, eligible participants are asked to complete a preintervention phase baseline survey followed by 21 daily surveys in their natural environments. Then, they receive 4 PPMT sessions, completing 1 web-based survey per session and a feedback survey in the last session. After the conclusion of the PPMT intervention, participants are asked to complete a postintervention phase outcome survey and 21 daily surveys.

Figure 1. Study procedure: explaining the step-by-step process of the study.

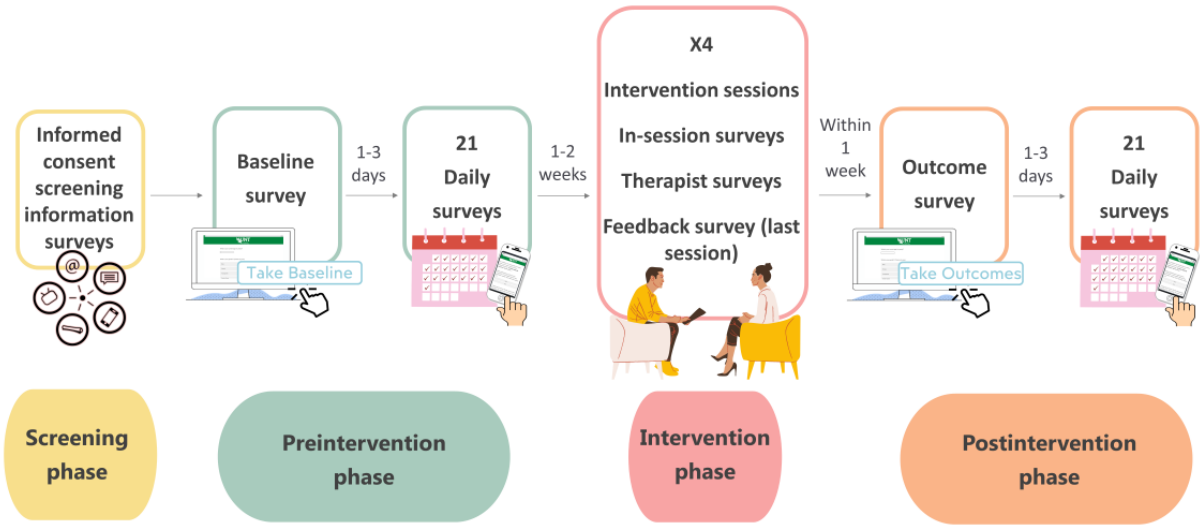

Participants

Participants (target n=70) are currently being recruited from a metroplex in the southwest United States through social media postings, flyers at businesses and public places, and university announcements since March 2022. The inclusion criteria are: (1) being aged between 18 and 65 years; (2) endorsing a trauma with posttrauma symptoms assessed by the Primary Care PTSD Screen for DSM-5 [47]; (3) access to an electronic device (eg, a computer or a smartphone) with internet capabilities; (4)

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working knowledge of English; (5) no active suicidal plan, suicidal attempt, homicidal plan, or homicidal attempt (past 3 months including current); (6) being a current resident of the Dallas Fort Worth metroplex; (7) not currently in therapy with a mental health provider; (8) willingness and availability to participate in approximately 10 weeks of this study (including 4 therapy sessions); and (9) willingness to be video-recorded during sessions for quality control purposes.

Procedure

Screening Phase

During this phase, interested participants complete an eligibility survey. First, they read the informed consent document (information about the study, eligibility criteria, compensation, benefits and risks to study participation, and steps to ensure data confidentiality) and provide electronic informed consent if they wish to participate. Next, they answer questions to determine eligibility. Eligible and consenting participants are automatically redirected to a separate survey, wherein they provide contact information for study purposes. Research personnel then contact eligible participants to provide more information on the study (eg, survey timelines and PPMT sessions). No compensation is provided for this study phase.

Preintervention Phase

Participants complete 1 baseline survey and 21 daily surveys as part of this phase. The baseline survey contains questions on demographics, trauma history, PTSD symptoms, and other psychological symptoms, as well as affect and cognitive processes (approximately 30-minute completion time). Eligible participants receive the baseline survey link by email at a date determined to be feasible based on contact with participants. Participants are given up to 48 hours to complete the baseline survey and are sent reminders if they do not complete the survey in a timely manner. Research personnel monitor survey responses for completion, response times to identify unfeasibly short times, accurate participant ID entry, therapy history to confirm they are not currently in therapy, and trauma history.

Participants who complete the baseline survey are asked to complete 21 daily surveys. The daily surveys include questions assessing daily PTSD symptoms, affect, cognitions, and events that occurred in the last 24 hours (approximately 3-5 minutes to complete each survey). The link to the first daily survey is emailed to participants within 1-3 days after completing the baseline survey. Participants receive daily surveys once a day at fixed intervals (at 7:00 PM each day) over a 21-day period, and they have until 11.59 PM to complete each daily survey. Participants are sent text reminders for survey completion to enhance compliance and are contacted if they miss any surveys.

Intervention Phase

PPMT is administered weekly as a 4-session protocol during the intervention phase. The sessions are scheduled within 1-2 weeks after completing the preintervention phase. In session 1, participants receive psychoeducation on PTSD symptoms, an overview of PPMT, and are assessed for psychological symptoms. Sessions 1-4 involve the detailed processing of a salient positive autobiographical memory to elicit "values, affect, strengths, and thoughts" related to that positive memory. Homework assignments include listening to an audio recording of that memory, completing a "values, affect, strengths, and thoughts" log, and engaging in a behavioral activity. In session 4, the therapist also reviews psychological symptoms and addresses termination. Following the completion of session 4, the participants complete a feedback survey on PPMT.

Postintervention Phase

Participants complete 1 outcome survey and 21 daily surveys as part of this phase. Within approximately 1 week after completing the intervention phase, participants complete an outcome survey. The procedural aspects of this phase mimic the preintervention phase. The outcome survey has questions similar to those of the preintervention phase baseline survey (without demographics and trauma history items and with different cue words for the measure examining the count of retrieved memories).

Dropout

Participants who do not complete the outcome survey after 2 days, consecutively miss 4 daily surveys, or miss more than 8 daily surveys (<60% of the daily surveys) in either the preintervention or postintervention phases are considered dropouts for this study, and they do not continue to receive survey links in order to avoid burdening participants with repeated requests to complete the surveys if they no longer wish to participate.

Study's Primary Measures

Overview of Primary Measures

In this section, we outline the measures that relate to the primary outcomes of this study. The primary outcomes of interest are daily positive affect levels, daily positive affect reactivity (within-person index of linear relations between daily positive events and daily positive affect [48]), daily negative affect levels, daily posttrauma cognitions, daily PTSD symptoms, and the number of retrieved specific positive memories as measured pre- and postintervention. Secondary measures (eg, difficulties in positive emotional regulation using the "Difficulties in Emotion Regulation Scale-Positive" and the severity of PTSD symptoms using the "PTSD Checklist for DSM-5") are also administered to allow for the assessment of possible mediators and moderators of treatment effects. Table S1 in Multimedia Appendix 1 [40,47,49-58] provides detailed information on all study measures (including measures for supplemental analyses).

Preintervention Phase Baseline Survey

The number of retrieved specific-positive memories is measured by the Autobiographical Memory Test (AMT) [49,59]. The AMT uses a cued memory recall technique involving the presentation of individual cue words, followed by a prompt to recall a personally meaningful and specific memory of an event that took place within any 24-hour period. For this study, participants are shown cue words and asked to retrieve a personal and specific memory of the cue-word-related event within 60 seconds [59]. The instructions were adapted from previous autobiographical memory studies [49,60,61]. In the preintervention baseline survey, we included 5 cues drawn from

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previous studies: friendly, happy, honest, kind, and humorous [62-64]. We will follow coding guidelines to categorize AMT responses [65,66]. AMT responses will be coded as specific (event that occurred at a certain place within 24 hours), extended (event that lasted >1 day), or categorical (summary of repeated events). AMT responses will also be coded as positive or nonpositive following the Coding and Assessment System for Narratives of Trauma [67]. Lastly, AMT responses will be coded as semantic associate (no personal memory) and omission (did not retrieve the memory within 60 seconds or was unable to recall a memory). The AMT demonstrates good psychometrics [68].

Preintervention Phase Daily Surveys

Daily negative and positive events are measured by asking participants to rate their most positive and negative events in the last 24 hours from 0 (not at all unpleasant) to 3 (very unpleasant) [50].

Daily affect levels (ie, positive and negative) are assessed by rating the extent of 4 positive (excited, cheerful, satisfied, and relaxed) and 6 negative (stressed, irritated, anxious, sad, hopeless, and insecure) emotions in the last 24 hours. These emotions were used in a previous daily diary study based on a theoretical circumflex of emotions. The study showed excellent between-person reliability and good within-person reliability [69]. In this study, responses are rated on a 5-point Likert scale ranging from 1 (very slightly or not at all) to 5 (extremely).

Daily posttrauma cognitions are measured by the Brief Version of the Posttraumatic Cognitions Inventory [51], which is a 9-item self-report measure assessing posttrauma cognitions. Responses are provided on a 7-point Likert scale ranging from 1 (totally disagree) to 7 (totally agree), with the time frame modified to “in the last 24 hours.”

Daily PTSD symptom severity is assessed using the Primary Care PTSD Screen for DSM-5 [47], which is a 5-item self-report measure with dichotomous “yes” or “no” items; the time frame is modified to “in the last 24 hours.” We will use the count of endorsed PTSD symptoms as a measure of daily PTSD symptom severity.

Postintervention Phase Outcome Survey

Similar to the preintervention phase baseline survey, the AMT is administered to examine the number of retrieved specific positive memories. Different cue words are used: peaceful, loyal, helpful, safe, and love [62-64].

Postintervention Phase Daily Surveys

The procedural aspects and measures mimic the preintervention phase daily surveys.

Participant Safety and Psychological Distress

There are minimal foreseeable risks associated with this study. Few participants may experience an increase in PTSD severity [70] or suicidal ideation [71], attributed to the sensitive nature of questions targeting trauma reactions and to PPMT itself. To address any such concerns, the study co-principal investigator (co-PI; a licensed clinical psychologist) is training all research personnel on considerations in administering assessments to survivors of trauma, providing clinical training and weekly supervision to study therapists, and training study therapists in anxiety-reduction techniques (eg, guided imagery). Furthermore, study participants receive information on mental health services.

To address any risk factors for self-harm, we are closely monitoring participants during PPMT to assess for any reported suicidal ideation, plan, or attempt (eg, administration of a depression measure every session). Furthermore, the study co-PI is training study therapists to conduct in-depth suicide risk assessments. In the event of suicidal ideation, plan, or attempt reported by participants in session, study therapists conduct a suicide risk assessment and consult with the supervising co-PI to determine if emergency services need to be contacted to ensure participant safety. Also, the participant or therapist may discontinue the study at any time should symptoms worsen or if the participant simply desires to withdraw. Lastly, we are providing information on community mental health centers offering 24-hour access to services and emphasizing contacting 911 or 988 in times of imminent risk.

Treatment Nonresponse or Relapse

Any treatment for posttrauma mental health is associated with some chance of failure to respond or relapse [72]. We are implementing the following procedures to address any such potential concerns. If a participant shows substantial increases in PTSD or depression severity or reports risk factors for self-harm during intervention sessions, we are providing mental health referrals immediately for alternate treatment options, including a 24-hour access local mental health center. Furthermore, research personnel are contacting participants when they miss appointments to check on their health status.

Intervention Training

Therapist Training

The study co-PI trained doctoral students (ie, study therapists) in PPMT. This training included a review of PPMT’s theoretical underpinnings, manuals, and fidelity checklists, as well as practice in PPMT administration. Furthermore, study therapists are required to follow detailed session protocols during each PPMT session. Research assistants were trained in PPMT fidelity ratings; ≥0.81 kappa coefficient and ≥0.8% percent agreement will be considered acceptable interrater reliability (IRR) [73].

Treatment Delivery

All sessions are being video recorded. The co-PI has reviewed all recorded PPMT sessions for 1 participant for each study therapist; she will continue to review 20%-50% of the video-recorded sessions as needed [74]. The co-PI is providing weekly group supervision to study therapists that involves case discussions and feedback.

Fidelity Ratings Across Raters

The authors have created fidelity checklists that include a list of proscribed PPMT components to be recorded as occurring or not occurring. Using these fidelity checklists, 2 trained evaluators will independently code video-recorded sessions for 18-20 participants. These data will be used to compute IRR estimates. If acceptable IRR estimates are not achieved, trained

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evaluators will code an additional 20% of sessions. Once acceptable IRR estimates are achieved, the evaluators will solely code the remainder of the treatment sessions for fidelity.

Adherence to PPMT Components

We will compute percentage adherence across sessions for each of the trained study therapists, with the recommended 80%-100% benchmark indicating high fidelity [74].

Data Analysis

Power Analysis

We conducted an a priori power analysis using the *EMAtools R* (Kleiman) package [75] for power curves for multilevel studies. The power analysis was based on two 3-week assessment bursts with 1 questionnaire per day and an estimated intraclass correlation coefficient of 0.36 based on a previous study on daily-level emotions, cognitions, and PTSD [76]. Analysis showed that 70 participants and up to 25% missing data would be sufficient to detect a medium effect size (d=0.5) with 80% power.

Analytical Plan

A paired sample *t* test will be used to examine changes in the count of retrieved specific-positive autobiographical memories pre- versus post-PPMT (comparing the preintervention baseline and postintervention outcome surveys). To examine changes in daily affect, daily cognitions, and daily PTSD symptoms, we will use the daily diary reports pre- and postintervention and conduct multilevel random intercepts and slopes linear regression models for each outcome variable using *MPlus 8*.3 (Muthén and Muthén), *nlme* (Pinheiro et al), and *lme R* (Bates et al) packages, comparing the models pre- and post-PPMT with and without demographic covariates (eg, gender, age, and education). We will also conduct exploratory analyses examining additional variables included in the study as predictors or moderators of post-PPMT outcomes (eg, count of trauma types previously experienced, PTSD severity at baseline, and difficulties in positive emotional regulation).

Missing Data

At the survey level, the web-based questionnaire has been set up with a prompt if questions have been skipped, with the option to continue the survey without completing a particular item or to go back and complete the skipped question. We anticipate a little missing data within the submitted surveys. We will treat surveys that have been submitted with missing data as complete for the purposes of determining dropout and participation compensation. An analysis will be conducted to investigate the pattern of missingness. If data are missing at random or missing completely at random, they will be handled by listwise deletion and models fit by maximum likelihood. If data are not missing at random, then missing data will be imputed using the MICE (van Buuren et al) package in R [77] and fit by maximum likelihood.

Ethical Considerations

The institutional review boards at the University of North Texas (#21-420) and the University of Haifa (#480/21) have approved this study. During the screening phase, interested participants read the informed consent document (information about the study, eligibility criteria, compensation, benefits and risks to study participation, and steps to ensure data confidentiality) and provide electronic informed consent if they wish to participate. Participants are then contacted by research personnel to re-explain any study procedures and obtain or confirm identifying information.

In terms of compensation, participants receive US $1.50 for each completed daily survey and US $10 each for completing each of the baseline and outcome surveys. Participants receive US $10 for completing each of the 4 PPMT session surveys and US $12 toward transportation costs cumulatively for all 4 (attended) intervention sessions. In order to incentivize participants to provide as much data as possible, participants who complete 36 surveys without any missing data receive an additional US $15. The total potential compensation for participation is US $150.

Participants provide personally identifiable information (eg, name and contact information), which is only used for scheduling purposes, study-related communications, and to connect data longitudinally. Each participant receives a unique and randomly generated ID number, which is used on all web-based surveys for this study. At no point is any personally identifiable information linked to participant data. Furthermore, deidentified data will be analyzed for the scientific dissemination of study findings.

Results

Year 1 of the study (October 2021-September 2022) was primarily devoted to recruiting and training research personnel, obtaining ethics approvals, and preparing to launch the study. Year 2 of the study (October 2022-September 2023) has been focused on participant recruitment and data collection. During Year 3 of the study (October 2023-September 2024), we will complete data collection from our targeted sample and start the data cleaning and analysis process. During Year 4 of the study (October 2024-October 2025), we will complete the data analyses and prepare planned scientific outputs (eg, publications and presentations).

Data collection was initiated in March 2022. As of November 28, 2023, a total of 515 participants had consented to the study in the screening phase. Of those, 258 (50.1%) participants were eligible, 92 (35.7%) of which gave their consent by phone and attempted the first daily survey of the study. Of the 92 participants who completed the first daily survey, a total of 58 (63%) participants completed all intervention sessions and ≥13 daily surveys (≥60% of the daily surveys), and 28 (30.4%) participants dropped out in various stages of the study, mostly before the PPMT intervention. As of November 29, 2023, a total of 6 (6.5%) participants are currently participating in various phases of the study. Data collection is expected to end by June 2024. No analyses will be conducted until data collection has been completed.

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Discussion

This study aims to examine the daily-level impacts of PPMT, a promising adjunct or alternative to traditional PTSD treatments, in a trauma-exposed, nonclinical community sample. This study combines a case-series design and a daily diary design to examine potential mechanisms of change in PTSD symptoms by assessing daily affect, daily cognitions, and daily PTSD symptoms before and after the PPMT intervention. This approach enables a more nuanced and ecologically valid exploration of changes as compared with retrospective aggregate assessments. We outline the research protocol for this study, including the hypotheses and the proposed analyses. When data collection has been completed (estimated date: June 2024), we will test our hypotheses that, at the daily level, in comparison to their own pre-PPMT levels, following the PPMT intervention, participants will report (1) a lower count of endorsed daily PTSD symptoms, (2) increases in daily positive affect and decreases in daily negative affect, (3) increases in positive affect reactivity to daily positive events, and (4) decreases in daily posttrauma cognitions.

The findings of this proposed study could have significant implications. Results could clarify whether deficits in positive autobiographical memory processes (eg, retrieval and encoding) may also characterize PTSD alongside deficits in traumatic memory processes [7]. If the study's hypotheses are confirmed, PPMT could be an additional therapeutic tool for clinicians to help clients with posttraumatic distress. Unlike other trauma interventions, PPMT exclusively targets positive autobiographical memories in treatment while redirecting attention away from negative content embedded in the positive memories. By uniquely combining positive and symptom-focused techniques and theories, PPMT aims to increase positive elements (eg, values, affect, and thoughts) while simultaneously decreasing PTSD severity [17].

There are some limitations to this study that should be considered. The study uses a self-report approach, which, although it reduces recall bias, is still subject to potential difficulties in the recall of experiences over the course of each day. Relatedly, while it reduces participant burden, the PC-PTSD measure is a PTSD symptom screener and usually is coupled with a comprehensive structured diagnostic interview for PTSD or a self-report measure assessing all 20 PTSD symptoms (which we do not do in this study due to the daily-level methodology and associated participant and time burdens). Furthermore, we are not gathering information on trauma characteristics such as the ages at which the trauma was experienced, the frequency or chronicity of each experienced trauma, or the time since the trauma has elapsed. Such information can impact posttrauma distress [78-80] and may moderate the impacts of PPMT in this study; hence, it should be empirically investigated in future research. In addition, while the research design of one assessment per day enables examination of changes in daily symptoms, affect, and cognition before and after the intervention, it does not have a sampling frequency nor sufficient power to examine fine-grained dynamic interactions between symptoms, affect, and cognition using even more complex modeling techniques. Lastly, our eligibility criterion permits individuals endorsing even 1 PTSD symptom at a clinical level to be included in the study. While such an approach accounts for impairment among individuals endorsing sub-threshold PTSD [81], it may also make it statistically difficult to detect any changes in PTSD symptoms (ie, the floor effect).

In conclusion, this study will contribute to the development of more personalized and alternative PTSD interventions for survivors of trauma who drop out or do not benefit from existing PTSD treatments. Further studies could examine PPMT as an ecological momentary intervention, wherein individuals receive daily reminders and instructions for engaging in therapy-relevant behaviors (eg, processing of positive memories). Such interventions can particularly benefit communities that do not have easy access to mental health services and are underserved in that regard [82]. Finally, this study will give insight into the mechanisms of change in the PPMT intervention through elucidating daily-level changes in affect, cognition, symptoms, and event reactivity.

Acknowledgments

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Data Availability

The data sets that will be generated through this study will not be publicly available due to the sensitive nature of the posttrauma daily-level data, however the corresponding author will make deidentified data available on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental table 1. Timeline information on measures.
[DOCX File , 25 KB - resprot_v13i1e51838_app1.docx]

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Abbreviations

AMT: Autobiographical Memory Test
co-PI: coprincipal investigator
IRR: interrater reliability
PPMT: Processing of Positive Memories Technique
PTSD: posttraumatic stress disorder

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Protocol

Microfragmented Fat and Biphasic Calcium Phosphates for Alveolar Cleft Repair: Protocol for a Prospective, Nonblinded, First-in-Human Clinical Study

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Abstract

Background: Biphasic calcium phosphates (BCP) may serve as off-the-shelf alternatives for iliac crest-derived autologous bone in alveolar cleft reconstructions. To add osteoinductivity to the osteoconductive BCPs to achieve similar regenerative capacity as autologous bone, a locally harvested buccal fat pad will be mechanically fractionated to generate microfragmented fat (MFAT), which has been shown to have high regenerative capacity due to high pericyte and mesenchymal stem cell content and a preserved perivascular niche.

Objective: Our primary objectives will be to assess the feasibility and safety of the BCP-MFAT combination. The secondary objective will be efficacy, which will be evaluated using radiographic imaging and histological and histomorphometric evaluation of biopsies taken 6 months postoperatively, concomitant with dental implant placement.

Methods: Eight patients with alveolar cleft (≥15 years) will be included in this prospective, nonblinded, first-in-human clinical study. MFAT will be prepared intraoperatively from the patient's own buccal fat pad. Regular blood tests and physical examinations will be conducted, and any adverse events (AEs) or serious EAs (SAEs) will be meticulously recorded. Radiographic imaging will be performed prior to surgery and at regular intervals after reconstruction of the alveolar cleft with the BCP-MFAT combination. Biopsies obtained after 6 months with a trephine drill used to prepare the implantation site will be assessed with histological and histomorphometric analyses after methylmethacrylate embedding and sectioning.

Results: The primary outcome parameter will be safety after 6 months' follow-up, as monitored closely using possible occurrences of SAEs based on radiographic imaging, blood tests, and physical examinations. For efficacy, radiographic imaging will be used for clinical grading of the bone construct using the Bergland scale. In addition, bone parameters such as bone volume, osteoid volume, graft volume, and number of osteoclasts will be histomorphometrically quantified. Recruitment started in November 2019, and the trial is currently in the follow-up stage. This protocol's current version is 1.0, dated September 15, 2019.

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Conclusions: In this first-in-human study, not only safety but also the histologically and radiographically assessed regenerative potential of the BCP-MFAT combination will be evaluated in an alveolar cleft model. When an SAE occurs, it will be concluded that the BCP-MFAT combination is not yet safe in the current setting. Regarding AEs, if they do not occur at a higher frequency than that in patients treated with standard care (autologous bone) or can be resolved by noninvasive conventional methods (eg, with analgesics or antibiotics), the BCP-MFAT combination will be considered safe. In all other cases, the BCP-MFAT combination will not yet be considered safe.

Trial Registration: Indonesia Clinical Trial Registry INA-EW74C1N; https://tinyurl.com/28tnrr64

International Registered Report Identifier (IRRID): DERR1-10.2196/42371

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KEYWORDS

microfragmented fat; calcium phosphate; bone regeneration; regenerative medicine; alveolar; bone grafting; bone; graft; alveolar cleft; surgery; surgical; perioperative; mouth; oral surgery; maxillofacial; jaw; oral pathology; oral; dentistry; dental; tooth; teeth; osteo; osteoconductive biphasic calcium phosphate; autograft; operation

Introduction

Alveolar cleft is defined as a bone gap in the primary palate from the nasal sill to the incisive foramen [1]. The defect occurs as a result of disruption of primary palate development between 4 and 12 weeks of gestational age, specifically in the frontonasal prominence [2]. The treatment protocol varies on the basis of the following factors: timing, surgical procedure, and grafting material. Secondary alveolar bone grafting (SABG) is the most preferred and successful method that is usually performed during the mixed dentition period (6-11 years), which allows the provision of support to teeth eruption and facial growth [1]. The iliac crest as a bone graft donor for alveolar cleft reconstruction has gained popularity since it was first introduced by Schmid [3] in 1954, and, in particular, for SABG procedures because it allows harvesting of large amounts of bone for alveolar cleft surgery [4]. Other bone graft sources include the cranium, tibia, and the mandibular symphysis [5]. However, several studies have reported risks of general postoperative complications using autografts, such as pain, prolonged hospital stay, and donor site–specific complications such as scarring, cutaneous nerve injury near the iliac crest, and hematoma after harvesting the cranial bone [6-9]. Therefore, alternative materials are being evaluated for alveolar cleft surgery.

Biphasic calcium phosphate (BCP) is a bioceramic that consists of 2 materials, hydroxyapatite (HA) and β-tricalcium phosphate, mixed in different ratios [10]. It is a biocompatible, easy-to-handle, safe material with a mineral composition comparable to that of human bone tissue [10]. BCP has been mixed in vivo and in vitro with autografts, inducing factors or cells to improve its osteoinductivity [11,12], also in the fields of dentistry and maxillofacial surgery [13-15]. Although calcium phosphate ceramic is not yet considered standard-of-care, it has been used for alveolar cleft reconstruction with satisfactory results [16], reportedly providing support for teeth eruption [17].

Adipose tissue is a source of mesenchymal stem cells, and adipose stem cells (ASCs) can be collected with minimum risk and discomfort from the buccal fat pad (BFP) [18]. The BFP surrounds the buccinators muscle and other superficial muscles such as the masseter, the zygomaticus major, and the zygomaticus minor [19]. Moreover, multiple studies have shown that the cell yield of ASCs per volume is at least 100-500 times that of mesenchymal stem cells in bone marrow aspirates [18,20]. Commonly, ASCs are prepared using enzymatic (collagenase) digestion which, however, is considered “more than minimal manipulation” of the cells by the US Food and Drug Administration and the European Medicines Agency [21]. An alternative method, which also takes considerably less time, involves processing the adipose tissue mechanically into microfragmented fat (MFAT) [22]. MFAT is reported to have similar or even higher secretory activity of regenerative growth factors and cytokines and pericyte content than an enzymatically derived stromal vascular fraction (SVF) [23]. In addition, the MFAT procedure can be applied even in regular hospitals because its harvesting and processing does not require a major invasive surgery, specialized equipment or expensive disposables, or good manufacturing practices–qualified cell culture expansion. Autologous application of MFAT has, among others, been used with success for clinical reconstructions in the maxillofacial area [24].

We hereby describe the protocol of a first-in-human clinical safety trial using BCP mixed with MFAT for alveolar cleft reconstruction. Our hypothesis is that the combination will be a safe, efficient, and effective alternative to conventional autograft since the osteoconductive BCP is supplemented by the regenerative capacity from the MFAT.

Methods

Study Design

This first-in-human surgical study can be classified as a “stage 1” study in accordance with the IDEAL (innovation, development, exploration, assessment, and long-term study) framework [25]. It is a single-center prospective clinical trial comprising 8 patients, assessing the safety of a combination of MFAT and BCP (BoneCeramic, Straumann) as bone graft material for alveolar cleft reconstruction. The BCP is a synthetic bone graft containing 60% HA and 40% β-tricalcium phosphate, a porosity of 90%, and an interconnected pore size of 100-500 µm. The BCP will be combined in a 1 g:1 cm^3 ratio with MFAT prepared from the patients’ own BFP, which is processed with a 1.2-mm single-use sizing transfer Tulip Gen II Nanofat Kit

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(Tulip Medical). The primary end point will be set at 6 months. At each follow-up visit, adverse events (AEs) or serious AEs (SAEs) will be documented, and clinical assessments will be performed at time points specified in the *Interventions* section. After these 6 months, a bone biopsy sample will be taken using a hollow drill during dental implant preparation and subsequently processed for histological or histomorphometric analysis (Figure 1). Finally, a report on safety and proof of concept with regard to bone formation will be made and published.

Figure 1. Simplified diagram of the study protocol (adapted from the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] checklist; Multimedia Appendix 1). BCP: biphasic calcium phosphate; MFAT: microfragmented fat.

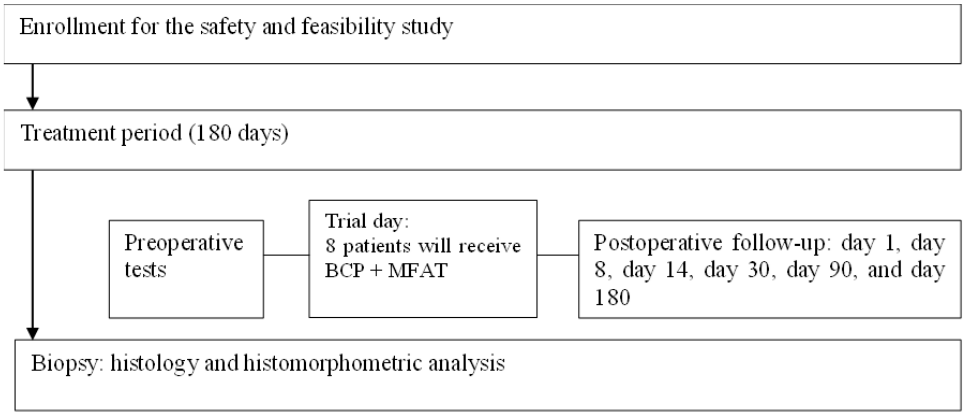

Ethical Considerations

The clinical trial protocol was approved by the ethical committee of Hasanuddin University, Makassar, Indonesia (1063/UN4.6.4.5.31/PP36/2019) and registered in the Indonesian trial registry (INA-EW74C1N). Informed consent will be obtained from candidates or their parents or legal guardians who are willing to join the trial after being fully educated about the trial procedure. This study complies with the principles of the Declaration of Helsinki. In the informed consent form signed by the patients or their legal representatives, consent to publish their data in a deidentified manner is included.

Inclusion and Exclusion Criteria

Patients will be included on the basis of the following criteria [26]: being healthy male or female participants aged ≥15 years, having unilateral alveolar cleft without any previous history of grafting procedures, being categorized as normal healthy patients for anesthetic risk per the American Society for Anesthesiologists' criteria, and having a normal blood count.

Patients will be excluded on the basis of the following criteria [26]: having poor oral hygiene with mouth plaques; having systemic disease; having systemic or local infection; having received chemotherapy, radiotherapy, immunosuppressives, or anticoagulants that may interfere with the healing process; having received bone growth–inducing factors, malnutrition, or active influenza; and being pregnant.

Interventions

Under general anesthesia and infiltration with lidocaine (1%) with epinephrine (1:100,000 dilution), the surgeon will identify the Stensen's duct with a lacrimal probe and make an incision 2-3 cm below the duct [27]. A dissection penetrating the muscles and the superficial fascia will allow spontaneous herniation of the BFP [27]. This procedure will be carried out bilaterally on both cheeks in order to obtain approximately 3 cm^3 of fat. After vasoconstrictor infiltration with epinephrine (1:100,000), a full mucoperiosteal flap spanning the first molar to the central incisor is lifted. After exposure of the full alveolar cleft and to separate the nasal layer from the oral mucosa, the tissue was meticulously dissected. Following the reflection of a palatal mucoperiosteal flap from either side of the cleft, the palatal tissues are elevated. The oronasal fistula is repaired cranially by elevating and suturing the nasal mucosa [4], thereby creating a pocket for BCP-MFAT deposition.

In parallel with the defect surgery, the harvested fat will be chopped into small pieces with a scissor and soaked in normal saline for 10-15 minutes. The normal saline then will be drained and the chopped fat will be processed into MFAT using 2 syringes (size 10 cm^3) connected with the 1.2-mm single-use sizing transfer Tulip Gen II Nanofat Kit in accordance with the manufacturer's protocol. MFAT will be mixed with BCP (Straumann Bone Ceramic) in a ratio of 1 g:1 cm^3 until it reaches homogenous consistency. The BCP-MFAT mixture will be placed as a graft material into the alveolar cleft defect. If the defect is large and requires more bone graft, another mixture will be prepared with the same mixing ratio. If necessary, a membrane will be used to cover the grafted defect. Finally, the defect will be closed by suturing the palatal mucoperiosteal flaps using absorbable sutures with 3-0 vicryl sutures for mucosa and 4-0 vicryl sutures for nasal reconstruction. All patients will be prescribed antibiotics and analgesics postoperatively.

AE Assessment

Any change in the health of subjects will be documented in their medical history, and required medical care will be provided. Any unexpected physical or laboratory change, symptom, or disease that occurs in a treated patient who has been administered the graft will be documented as an AE. An AE will be graded in accordance with the World Health Organization's classification [28] as either serious or nonserious based on its intensity. The Clavien-Dindo Classification of Surgical Complications will also be used in case of any incidence [29]. In the case of an SAE, a report will be made to the sponsor within 24 hours and to the ethical committee within

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3 days from the date of onset. If the SAE concerns severe toxicity or infection associated with graft products, the trial will be terminated immediately.

Sample Size

This is a first-in-human phase I clinical trial aimed to obtain insight on the safety and feasibility of the treatment with the BCP-MFAT combination. We assume that no SAEs or AEs will occur, based on our clinical experience with other applications of MFAT and the well-proven safety of BCP. Upon consultation with a statistician, a sample size of 8 individuals is expected to be sufficient for this trial.

Recruitment

Patients will be recruited from an existing database of the Hasanuddin University Dental Hospital, from general practices of Hasanuddin Dental Hospital and in the area around Makassar. Thereafter, we will determine whether the candidates fulfill the study's inclusion and exclusion criteria. Thorough assessment and training regarding the safety measurements at the research site at Hasanuddin University Dental Hospital will be performed prior to the trial by the ethical and surgical teams.

Since we did not want to enroll children in a safety study with this novel concept in clinical practice, we chose to only include older adolescent and adult patients, being themselves capable of decision-making. Within Indonesia, this age group is more common due to cultural and religious backgrounds causing abstinence from cleft surgeries.

The trial will be conducted at Hasanuddin Dental Hospital. All participants will be asked to sign an informed consent form after risks and possible complications of the procedure (eg, bleeding, infection, cheek asymmetry, parotid duct injury, possibility of facial nerve branches injury, and—although not likely—nonclosure) were appropriately communicated with the patient. Data will be handled and stored in a coded—that is, deidentified—format, so that data cannot be traced back to the patient without a decoding key, which is stored in a locked place and only accessible to the study's principal investigator. Implants will be offered free of charge.

Randomization and Blinding

Since this trial comprises only 1 type of treatment, no randomization or blinding to the treatment is possible.

Data Collection and Access

The research team will be informed about the rules and their responsibilities. All members of the research team, which will collect the data in accordance with the evaluation table (Table 1), will receive training on how data collection should be performed. The data manager will document the data in a patient-coded manner (ie, each patient will be assigned a study-specific code under which the data will be stored in order to conceal their identity), which will subsequently be handed over to the clinical evaluators and investigators. The primary end point is set at 6 months.

Table 1. Patients' assessments.

	Consent form	Orthopantomography	Cone-beam computed tomography or computed tomography	Physical examination	Complete blood count	Thermometry	Biopsy
Preoperative	✓	✓	✓	✓	✓	✓	
Operative day				✓		✓	
Postoperative day 1		✓		✓	✓	✓	
Postoperative day 8		✓	✓	✓	✓	✓	
Postoperative day 14				✓		✓	
Postoperative day 30				✓	✓	✓	
Postoperative day 90		✓		✓		✓	
Postoperative day 180		✓	✓	✓	✓	✓	✓

Posttrial Care

After the primary end point assessment, the participants will be followed up for an additional period of 3 years to ensure their safety and to record whether any delayed side effect occurs as a result of treatment with the BCP-MFAT combination, as previously done in a similar study [26].

Monitoring

Internal monitors of the Ethics and Research Committee, Faculty of Medicine, Hasanuddin University, will evaluate whether the data are accurately collected. Since negligible risk to the patient is expected as both materials (MFAT and BCP) have been tested in other clinical trials [16,17,24], no data safety monitoring board will be installed. A safety report will be submitted every year to the Medical Research Ethics Committee, Faculty of

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Medicine, Hasanuddin University. No interim analysis is deemed necessary.

Amendments

If deemed necessary, amendments to this protocol will be submitted to the ethical committee and competent authority and should be approved prior to implementation to ensure the safety and integrity of participants as well as the scientific value of the trial.

Evaluation Methods

Safety Assessment Based on Physical Examination and Laboratory Measurements

When an SAE occurs, it will be concluded that a combination of MFAT and BCP is not yet safe in the current setting. For AEs, if they do not occur at a higher frequency than that in patients treated with standard care (autologous bone) or can be resolved through noninvasive conventional methods (eg, analgesics or antibiotics), the combination of MFAT and BCP will be considered safe. In all other cases, combination of MFAT and BCP will not be considered safe yet.

Radiographic Analysis

To evaluate the success rate of the bone graft, the Bergland scale will be used [30]. This scale will evaluate the integrity and height of the alveolar bone graft and will classify bone height into 4 grades: grade I, bone height is almost normal; grade II, a bone height that is at least 75% of the interalveolar septum; grade III, a bone height of less than 75%; and grade IV, no evidence of bone integration [31].

Histological and Histomorphometric Analysis

Histological and histomorphometric analysis will be performed for at least 3 patients who received dental implants after alveolar cleft reconstruction, in accordance with previously published procedures [32]. Briefly, the implant preparation site will be developed using a trephine burr (2.0 mm × 10.0 mm in length) that allows biopsy specimen collection from the implant site without interfering with the regular procedure. The biopsy specimens will be fixed in 4% phosphate-buffered formaldehyde, dehydrated in an ascending series of ethanol, and embedded in 80% methylmethacrylate (BDH Chemicals) supplemented with 20% dibuthylphtalate (Merck), 8 g/L lucidol CH-50 L (Akzo Nobel), and 22 µL/10 mL N,N-dimethyl-p-toluidine (Merck). The biopsy specimens will be cut into 5-µm-thick sections and subjected to 2 different staining procedures (Goldner's trichrome and Tartrate-resistant acid phosphatase staining). Several histomorphometric parameters (bone volume, osteoid volume, graft volume, and number of osteoclasts) will also be measured for quantitative analysis [32]. Two trained examiners will perform the histologic and histomorphometric analyses. In case of dispute, the biopsies will be reanalyzed to reach consensus.

Statistical Analysis

Since this is a single-arm safety study, statistical analyses will not be performed.

Results

The primary outcome parameter will be safety after 6 months' follow-up, assessed by closely monitoring possible occurrences of AEs or SAEs, radiographic imaging, blood tests, and physical examinations. For efficacy, radiographic imaging will be used for clinical grading of the bone construct using the Bergland scale. In addition, bone parameters such as bone volume, osteoid volume, graft volume, and number of osteoclasts will be histomorphometrically quantified. We expect that the feasibility and safety of the procedure will be apparent, as well as its initial efficacy. Recruitment started in November 2019, and the trial is currently in the follow-up stage. This protocol's current version is 1.0, dated September 15, 2019.

Discussion

In recent years, there has been increasing interest in the use of adipose tissue for cleft lip and palate reconstruction [33]. Its applicability mostly relies on the quantity of the tissue, the ease of surgical harvesting, and the type of surgical reconstruction in which the tissue is used, for example, correction of cleft lip volume asymmetry [34,35], improvement of velopharyngeal insufficiency after cleft lip and palate repair [36,37], or as an extra flap in cleft palate repair [38-41]. In this study, we will make use of the BFP for bone reconstruction. The BFP is a specialized adipose tissue rich in vascular supply, which is easy to harvest via the oral cavity during an intraoral surgery with minimal morbidity and discomfort [42].

Until now, there are only few reports on the use of adipose tissue as a regenerative compound for bony cleft reconstruction—a phase I clinical trial conducted by Khojasteh et al [24] and an animal study using ASCs for alveolar cleft repair [43]. Both studies used collagenase digestion of the tissue and culture expansion to obtain ASCs for personalized cleft reconstructions. An alternative is the SVF derived from adipose tissue via collagenase digestion, which requires a shorter time frame and may yield similar stem cell–like quantities, allowing intraoperative applications [44,45]. A previous clinical study by Prins et al [44] showed that addition of SVF in an intraoperative setting to calcium phosphate ceramics had an additive value on bone formation, implying that SVF can provide osteoinductivity when combined with calcium phosphate. However, so far, regulatory issues and relative expensive SVF production procedures prohibit its wide applicability [22,23]. Mechanically processed fat or MFAT has emerged as a rapid processing alternative to SVF and is being considered minimally manipulated and thereby less regulation restricted [22,23].

This is the first in human study evaluating a combination of MFAT and biphasic BCP as a regenerative graft for alveolar cleft reconstruction [46,47]. BCP is a ceramic scaffold with a balanced ratio between the less-soluble HA and the more-soluble TCP that results in mechanical and biological properties to support bone and cartilage tissue production [48]. It is sufficient for bone reconstruction in non–load-bearing applications and already accepted as standard of care for certain maxillofacial reconstructions [49].

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Recently, calcium phosphate has been applied for alveolar cleft surgeries as well [16,17]. Patients within that study were treated at ages of 9-10 years, which is within the optimum age range for SABG [1]. However, we did not want to enroll children in a safety study with this novel concept in clinical practice. Therefore, although we realize that surgeries at a later age will (1) not make optimal use of the growth spurt and (2) may result in cases having larger or even critical size defects (which will not heal unless supplemented with grafts), we chose to only include older adolescent and adult patients, who are themselves capable of being involved in decision-making. We will perform this study in Indonesia because unoperated patients in this age group are difficult to find in Europe.

This is primarily a safety study, so the main conclusions of the study will be based on safety parameters, particularly on the occurrence of AEs or SAEs.

Acknowledgments

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Data Availability

The data generated in the course of this study will be presented in the main manuscript reporting on the trial outcomes in a deidentified manner or provided in a multimedia appendix coupled with that manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v13i1e42371_app1.pdf]

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Abbreviations

AE: adverse event
ASC: adipose stem cell
BCP: biphasic calcium phosphate
BFP: buccal fat pad
HA: hydroxyapatite
IDEAL: innovation, development, exploration, assessment, and long-term study
MFAT: microfragmented fat
SABG: secondary alveolar bone grafting
SAE: severe adverse event
SVF: stromal vascular fraction

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Protocol

Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study

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Abstract

Background: The aftermath of the COVID-19 pandemic continues to affect millions worldwide, resulting in persisting postvirus complaints and impacting peoples' quality of life. Long COVID, characterized by lingering symptoms like fatigue and mental illness, can extend beyond a few months, necessitating further research to understand its implications.

Objective: This study aims to quantify the degree of physical and psychological fatigue in patients following COVID-19 infection and examine its correlation with mental health disorders.

Methods: Using a consecutive nonrandom sampling technique, we will conduct a prospective cohort multicenter observational study in 5 Portuguese hospitals. Symptomatic adult patients with previous COVID-19 attending follow-up consultations will be enrolled. We will include patients who had mild, moderate, and severe acute disease. We will assess clinical outcomes related to COVID-19, including the type of respiratory support such as high-flow nasal cannula, noninvasive ventilation, and invasive mechanical ventilation. The exclusion criteria will include previous severe psychiatric disorders confirmed by a psychiatrist; refusal or inability to respond to the questionnaire; concomitant neurological disorder; persistent fatigue symptoms during the 6 months before infection; and the need for invasive mechanical ventilation during COVID-19 infection due to a high prevalence of postintensive care syndrome. Our primary outcome is the prevalence of fatigue in patients with post–COVID-19 depression and/or anxiety, as measured by the Chalder Fatigue Scale (CFQ-11) and the Hospital Anxiety and Depression Scale (HADS). The secondary outcomes will include an assessment of health-related quality of life via the EQ-5D questionnaire and an exploration of the prevalence of symptoms of posttraumatic stress disorder (PTSD) using the 14-item Posttraumatic Stress Scale (PTSS-14). We will also examine the association between mental health symptoms and the severity of acute COVID-19. The post–COVID-19 data will be collected at least 6 months after the positive test and no longer than 9 months during the clinical appointment.

Results: We expect our multicenter study on patients post COVID-19 to reveal a significant link between mental illness symptoms and both physical and psychological fatigue. Patients with heightened depression and anxiety may report increased levels of

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fatigue. Additionally, we expect to find persistent PTSD symptoms in a subset of participants, indicating the enduring psychological impact of the virus.

Conclusions: This study may underscore the need for integrated care addressing physical and mental health in patients post COVID-19. The observed connections emphasize the importance of considering mental well-being for long-term health outcomes. Despite study limitations, our findings contribute valuable insights for future treatment strategies and highlight the necessity for comprehensive mental health support in post–COVID-19 care. This research provides valuable insights into the mental health implications of COVID-19 and its impact on post–COVID-19 fatigue and the overall well-being of affected individuals.

Trial Registration: ClinicalTrials.gov NCT05323318; https://clinicaltrials.gov/study/NCT05323318

International Registered Report Identifier (IRRID): DERR1-10.2196/51820

(JMIR Res Protoc 2024;13:e51820) doi:10.2196/51820

KEYWORDS

SARS-CoV-2; coronavirus; COVID; long COVID; fatigue; tired; tiredness; anxiety; depression; PTSD; stress; quality of life; mental health; post-COVID-condition; neuropsychological; neuropsychology; psychological; long COVID-19; COVID-19; myalgia; correlation; impairment

Introduction

Despite the World Health Organization (WHO) declaration marking the end of the COVID-19 pandemic on May 5, 2023 [1], millions of people continue to have postvirus complaints. Moreover, the virus remains endemic in many parts of the world. Confirmed COVID-19 cases have exceeded 430 million globally, with 200 million in Europe alone [2]. The causative agent of COVID-19 is the novel SARS-CoV-2 [3]. Although, as the name implies, respiratory symptoms are acute, the term long COVID (or post-COVID syndrome or long-haul COVID-19) began gaining recognition in the scientific and medical communities after the first descriptions of long-lasting symptoms related to mental health, such as anxiety or stress after the first infection [4]. While the definition of long COVID is unclear, the most frequent symptoms are fatigue and dyspnea [5,6]. Other less typical symptoms include cognitive and mental disorders, headache, myalgia, chest and joint pain, smell and taste dysfunction, cough, hair loss, insomnia, wheezing, rhinorrhea, sputum, and cardiac and gastrointestinal issues [4]. These symptoms may persist for up to 6 months after hospital discharge, severely impacting patients' quality of life [7]. Since July 2021, long COVID is considered a disability under the *Americans With Disabilities* Act [8].

Per its definition, long COVID appears within 3 months after the onset of COVID-19, with symptoms lasting for at least 2 months that an alternative diagnosis [9] cannot explain, including, myalgic encephalomyelitis and chronic fatigue syndrome. However, studies have reported different persistent symptoms in contrasting durations and frequencies among survivors of long COVID [10,11]. Long COVID appears like other postviral syndromes observed in other coronavirus diseases. For example, symptoms of fatigue, myalgia, and psychiatric impairments have affected survivors of Middle East respiratory syndrome (MERS) and those with severe acute respiratory syndrome (SARS) for up to 4 years [10,12,13]. Even at 7-year and 15-year follow-ups, pulmonary and bone radiological complications were evident among a proportion of survivors of SARS who were predominantly younger than 40 years [10,14,15]. This is unsettling, as it implies that long COVID may extend beyond just a few months.

Fatigue, a primary persistent symptom of long COVID, has been reported in 10% to 70% of patients [16-19]. It is defined as "a decrease in physical or mental performance that results from changes in central, psychological, or peripheral factors due to the COVID-19 disease" [20]. Thus, post–COVID-19 fatigue depends on conditional and psychophysiological factors comprising the individual's task, environment, physical, and mental capacity, as well as the disease's central, psychological, and peripheral aspects [20].

While fatigue is not traditionally considered a neuropsychiatric disorder, it can be a symptom of many mental health conditions, such as depression, anxiety, and posttraumatic stress disorder (PTSD) [21,22]. Therefore, it is often included in discussions of mental health symptoms in post–COVID-19 syndrome [23]. The term "neuropsychiatric" often refers to a wide range of disorders affecting the brain and mental health. In contrast, "neuropsychological" refers to studying the relationship between brain function and behavior [24]. The primary focus of this study is on psychiatric symptoms, particularly depression and anxiety. However, we will also investigate PTSD, which is a neuropsychiatric disorder involving both neurological and psychiatric aspects. In addition, the health-related quality of life (HRQoL) assessment includes a section that evaluates aspects related to anxiety and depression. While not designed for diagnosing psychiatric disorders, this assessment can help gauge how these symptoms affect a person's overall quality of life, making it more of a general health assessment.

The current literature on long COVID and its mental sequelae has relied on self-reported symptoms through questionnaires administered either in-person or through telephone interviews to comply with public health guidelines. However, the correlation between these self-reported symptoms needs to be clarified. There is an obvious need to accurately characterize the mental sequelae of COVID-19 and the risk factors associated with these outcomes.

This study aims to quantify the degree of physical and psychological fatigue in patients post COVID-19 and assess the correlation of fatigue with other mental sequelae—particularly depression, anxiety, and PTSD. Furthermore, we aim to explore its impact on HRQoL.

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Our research questions for this study are outlined in Textbox 1.

Textbox 1. Research questions of the study.

Research Question 1 (primary outcome):

- Do patients with long COVID who experience depression and/or anxiety symptoms have a higher prevalence of fatigue?

Research questions 2 to 4 (secondary outcomes):

- Is there a correlation between the type of fatigue and depression and/or anxiety symptoms among patients post COVID-19?
- Is there a correlation between fatigue and the presence of PTSD symptoms in patients post COVID-19?
- Do patients with fatigue associated with mental health disorders have a lower health-related quality of life (HRQoL) after COVID-19?

Methods

Overview

This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [25]. This research is designed as an observational prospective cohort study.

Recruitment

Our study will be conducted in 1 private and 4 public Portuguese hospitals that have established follow-up post–COVID-19 medical consultations. Patients who meet the eligibility criteria will be invited to participate in the study at the end of their appointments in the follow-up clinics. This study will be conducted using a consecutive, nonrandom sampling technique.

Inclusion Criteria

Patients who cumulatively meet the following criteria will be eligible for inclusion: (1) ≥18 years; (2) previous case of COVID-19 at least 6 months after the diagnosis that is duly documented in the clinical record; (3) persistent symptoms after COVID-19 recovery, as defined by the WHO [9]; and (4) SARS-CoV-2 RNA confirmed by a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab or SARS-CoV-2 antigen confirmed with a nasopharyngeal swab by a health care professional within 7 days of initial symptoms.

We will implement multiple measures to exclude the possibility of second infections and ensure that the individuals included have persistent symptoms following their initial COVID-19 recovery. Our inclusion criteria stipulate that individuals must have a positive test result for SARS-CoV-2 RNA or antigen within 7 days after their initial infection. Additionally, we will conduct thorough reviews of medical records and clinical assessments to assess symptom presentation and timing, differentiating between persistent cases and new infections. In cases of uncertainty or potential overlap with new infections, we are prepared to conduct repeat testing, which may include RT-PCR and genomic sequencing for accurate classification.

Exclusion Criteria

Patients who meet the following criteria will be excluded from participation: (1) preexisting psychiatric disorders diagnosed by a psychiatrist before contracting COVID-19; (2) inability to respond to the questionnaire; (3) concurrent neurological disorders, such as stroke with sequelae, Alzheimer disease, and Parkinson disease; (4) individuals subjected to invasive mechanical ventilation during their COVID-19 infection; or (5) those experiencing persistent fatigue symptoms within the 6 months before SARS-CoV 2 infection.

The study design and inclusion criteria will be reviewed regularly to ensure they align with current best practices and the latest understanding of COVID-19. A patient enrollment flowchart is presented in Figure 1.

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Figure 1. Study flowchart. CFQ-11: Chalder Fatigue Scale; HADS: Hospital Anxiety and Depression Scale; PTSS-14: 14-item Posttraumatic Stress Scale.

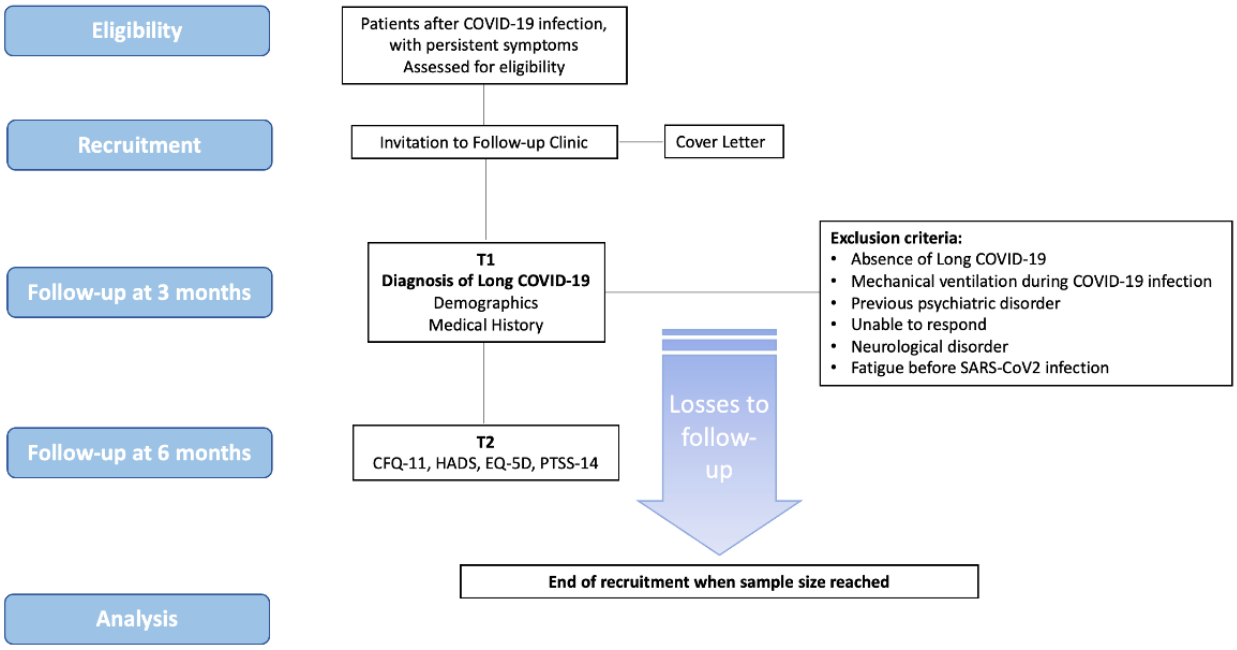

Data Collection

Data collection will take place during appointments at the long COVID follow-up clinics in all participating hospitals. Qualified clinical study staff will gather the data using a clinical research form (CRF) (Multimedia Appendix 1). These individuals comprise health care professionals, such as nurses, clinical research coordinators, and health care experts who have received appropriate training and have the necessary expertise to conduct data collection and assessments in a clinical research setting. Their training ensures adherence to research protocols and ethical guidelines, guaranteeing accurate and consistent data gathering during clinical appointments. Two months after hospital discharge, we will mail all patients a letter offering a follow-up consultation in the outpatient clinic. Patients who agree to attend will be offered 2 appointments, consisting of an anamnesis and a physical examination, and given several self-administered tests in the waiting room. We will allocate 15 minutes for the questionnaire completion in the waiting room. In the first visit (T1, 3 months), the following data will be additionally collected: demographic characteristics like age, sex, and BMI (kg/m^2); each participant's medical history, such as the date of the first positive COVID-19 test (PCR or antigen) and smoking, alcohol, and drug consumption status; comorbidities and usual medication intake; and screening of symptoms and severity of the acute disease. Data collection in the second visit (T2, 6 months) will include post–COVID-19 symptoms, the Chalder Fatigue Scale [26] (CFQ-11), the Hospital Anxiety and Depression Scale (HADS) [27], the 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID-19, and the EQ-5D [28] questionnaire.

Ethical Considerations

This study involves human participants and has adhered to all applicable ethical standards and procedures. The Algarve University Hospital Centre Ethical Committee approved this study (141/21; Multimedia Appendix 2). The patients' race will not be included in the study because the ethics committee did not approve this differentiation. A paper-based consent form was previously approved by the ethics committee. This consent form has 2 components: information for the participant (regarding the project) and declaration of informed consent (to date and sign, in case of acceptance). The informed consent procedure, mailed to potential participants, will provide them with detailed information about the study's objectives, risks and benefits of participation, and data management practices (Multimedia Appendix 3). The study will follow ethical guidelines and regulations related to informed consent, and participants will have the opportunity to ask questions and provide voluntary consent before enrolling. Participants will be given a month for reflection before written informed consent. As for data management, the study will implement a secure and confidential system that uses data encryption and secure storage procedures to protect participant confidentiality and comply with data protection laws and regulations. Only authorized individuals who have a legitimate need to access the data will be permitted to do so, and any data sharing will be done in compliance with the relevant ethical and legal requirements. As applicable, all procedures from this investigation followed the Declaration of Helsinki. All researchers will comply with the Data Protection Acts of their respective academic institutions.

Primary Outcome

Fatigue

A validated fatigue assessment tool will be used at the follow-up visit to capture a broader range of participants. This will provide a more comprehensive understanding of the relationship between fatigue and mental symptoms in individuals with long COVID. Fatigue will be measured using the CFQ-11 [26]. This is an

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11-item self-report measure of physical and mental fatigue. Participants rate their fatigue experienced over the past month compared to their usual energy levels using a 4-point Likert scale ranging from 0 (“less than usual”) to 3 (“much more than usual”) [29]. Scores range from 0 to 33. A bimodal version can also be calculated, where scores range from 0 to 11, with a cutoff score of 4 or more indicating a case of fatigue [29]. Reliability coefficients for the CFQ-11 have been shown to range between 0.8 and 0.9 [29-31] in both patients with chronic fatigue and the general population. This study will use only the Likert scale to reduce the risk of ceiling effect bias.

Secondary Outcomes

Depression and Anxiety

Symptoms of depression and anxiety will be assessed using the HADS [27], a practical, validated tool for assessing symptom severity in anxiety and somatic disorders in psychiatric and primary care settings and the general population [32]. This measure comprises 14 items, 7 measuring symptoms of anxiety and 7 measuring symptoms of depression. The scores are categorized into different ranges: 0 to 7 as “normal,” 8 to 10 as “mild,” 11 to 14 as “moderate,” and 15 to 21 as “severe.” The HADS questionnaire has been validated in many different languages and settings [32-34].

HRQoL Assessment

HRQoL will be assessed using the original EQ-5D questionnaire, which comprises 2 parts. The first part is the EQ-5D-3L questionnaire [28], a health state classification scheme of 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each having 3 alternatives (1=no problems, 2=moderate problems, and 3=severe problems). The combination of answers for the 5 items represents the health state (given as an index), ranging from 0 (worst possible health state) to 1 (best possible health state). The second part comprises the EuroQol Visual Analog Scale (EQ-VAS), which represents health states in a range from 0 (the worst possible health state) to 100 (the best possible health state). The EQ-5D can distinguish between the health conditions of patients with diverse injuries [35,36] and has been validated in several populations [37].

PTSD Assessment

This study includes an assessment of PTSD as a secondary measure. It aims to evaluate the potential impact of PTSD on the primary outcome of fatigue and provide a better characterization of the study population. Although previous PTSD to COVID-19 infection is an exclusion criterion, some participants may still have experienced PTSD symptoms after their COVID-19 infection, so evaluating the prevalence and severity of these symptoms in the study population could be relevant.

Given that the “gold standard” clinician-administered, semistructured psychiatric interviews to diagnose PTSD symptoms were not feasible during the workload of the COVID-19 follow-up clinic, we chose the patient-reported outcome instrument PTSS-14. This scale was developed based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria for PTSD and subsequently validated for patients following intensive care [38]. Patients were asked to assess the frequency of 10 common PTSD symptoms on a 7-point Likert scale from 1 (never) to 7 (always). Item scores were summed up to a total score (ranging from 10 to 70). A total score above 35 was suggested to indicate clinically relevant PTSD symptoms. A similar 14-item version of PTSS was later developed to reflect the changes in the fourth edition of the DSM (DSM-IV), where a cutoff value of 45 indicated presumable PTSD [39]. We modified the latter to include COVID-19 patients—whenever the term “intensive care unit (ICU)” appeared, we substituted it with “COVID-19.” We applied the same diagnostic cutoff to this adapted scale.

Association of Mental Illness Symptoms With the Severity of Acute COVID-19

COVID-19 severity will be categorized according to the WHO classification [40]. The classification includes the following: mild illness (mild symptoms without the radiographic appearance of pneumonia); pneumonia (having symptoms and the radiographic evidence of pneumonia, with no requirement for supplemental oxygen); severe pneumonia (having pneumonia, including one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or blood oxygen saturation level ≤93% while at rest and breathing room air); and critical cases (eg, respiratory failure requiring invasive mechanical ventilation or nasal high flow oxygen, septic shock, other organ failure occurrence, or admission to the ICU).

Statistical Analyses

The statistical analysis methodology is designed to align with the study’s defined objectives. All analyses will be conducted using SPSS (version 27; IBM Corp) and R (R Foundation for Statistical Computing) software. The analyses will be carried out in 5 phases, as outlined in Textbox 2.

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Textbox 2. The 5 phases of the statistical analyses carried out in this study.

- Phase 1: Characterization of the patient sample
  - 1.1. Sociodemographic analysis of the variables collected at T1 and the variables from the surveyed instruments at T2. This involves descriptive analysis, both univariate and bivariate, which will be differentiated by:
    - 1.1.1. Quantitative variables: mean and SD, coefficient of variation, and median and IQR
    - 1.1.2. Qualitative variables (nominal and ordinal categorical): analysis of distributions through absolute and relative frequencies, including absolute and relative accumulated frequencies
    - 1.1.3. Quantitative variables will be reported alongside appropriate tests for normal distribution to ensure the accuracy and validity of our statistical analyses.
  - 1.2. Bivariate and descriptive analysis using 2D tables will be calculated for all qualitative variables belonging to T1 with all instrument scores collected at T2: Chalder Fatigue Scale (CFQ-11), Hospital Anxiety and Depression Scale (HADS), 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID -19, and EQ- 5D plus recorded COVID-19 symptoms. The previous points will be reiterated in this bivariate context, utilizing the computational aid of split->file categorical variables in situations where one variable is metric and the other is categorical.
  - 1.3. Internal consistency and reliability analysis of the T2 instruments: calculation of the Cronbach alpha (general and partial) for all ordinal items and item subgroups differentiated by the subscales defined by the respective authors
- Phase 2: Determination of fatigue incidence caused by long COVID and its relationship with T1 and T2 variables
  - 2.1. Procedures for determining fatigue cutoff points in this cohort of patients:
    - 2.1.1. Bivariate analysis using optimal binning procedures for categorical variables (age class, sex, and BMI) with the total fatigue score, as well as partial scores of physical and psychological fatigue
    - 2.1.2. Multivariate analysis by constructing models in the format of decision trees via the CHAID (chi-square automatic interaction detection) algorithm [41], with total and partial fatigue scores as dependent variables
  - 2.2. Inferential analysis based on variables resulting from 2.1.1 and/or 2.1.2, considering the complexity of variables in T1 and T2:
    - 2.2.1. (1) Chi-Square tests to capture the association of categorical variables; (2) Shapiro-Wilk tests to verify the distribution of quantitative variables; (3) tests for comparing 2 or more population means: parametric analysis of variance (ANOVA) test and nonparametric (Kruskal-Wallis) test; and (4) correlation tests (Spearman or Pearson) to verify the degree of association between T2 instrument scales
- Phase 3: Determination of patient groups based on fatigue differentiation
  - 3.1. Conducting classification analysis using clustering techniques, specifically the 2-step cluster analysis, to explore variables with greater power in differentiating groups of patients
- Phase 4: Exploration of the best combination of T1 and T2 variables capable of discriminating patient fatigue levels through a discriminant multivariate analysis
- Phase 5: Investigation of the association between phase 3 groups and all T2 instrument scales using chi-square association tests

Power and Sample Size

We plan to conduct a prospective multicentric observational study to investigate the prevalence and severity of mental illness symptoms and fatigue in individuals with long COVID. Based on previous studies and expert opinion, we expect the prevalence of fatigue and mental symptoms in this population to be around 50% [42,43]. We aim to detect a minimum effect size of 0.2 with a power of 80% and a significance level of P=.05.

Using these assumptions, we performed a sample size power analysis using a 2-sample t test. We found that a total sample size of 200 participants (100 with adverse mental health symptoms and 100 without) would be required to detect the minimum effect size of 0.2 with 80% power and a significance level of P=.05. The required sample size was calculated using an a priori power analysis with an online calculator [44]. To compensate for a projected 25% loss to follow-up, we aimed for 250 participants.

We plan to recruit participants from multiple hospitals and primary care centers across Portugal, focusing on individuals who have been diagnosed with long COVID and are experiencing mental illness symptoms and/or fatigue. Recruitment will be closely monitored throughout the study to assess the pace at which participants are enrolled. The need for sample size adjustment will be determined based on the observed recruitment rates and the accumulating data. We plan to conduct an interim analysis after the recruitment of the first 100 patients.

Results

This study received no specific grant from any funding agency in public, commercial, or not-for-profit sectors. Recruitment began in October 2021 at Portimão Hospital and Alvor Hospital,

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in June 2022 at Faro Hospital and São Sebastião Hospital, and in October 2022 at Fernando Fonseca Hospital. The deadline for the end of the recruitment period in all centers was December 2023. The preliminary study results will be published in a peer-reviewed international medical journal after October 2023.

The study timeline is shown in Figure 2. This study is included as part of the first author's (LP) PhD thesis. The initial study results were presented at the PhD interview in November 2023. We aim to publish the study in an indexed scientific journal and present the results at national and international congresses.

Figure 2. Study timeline.

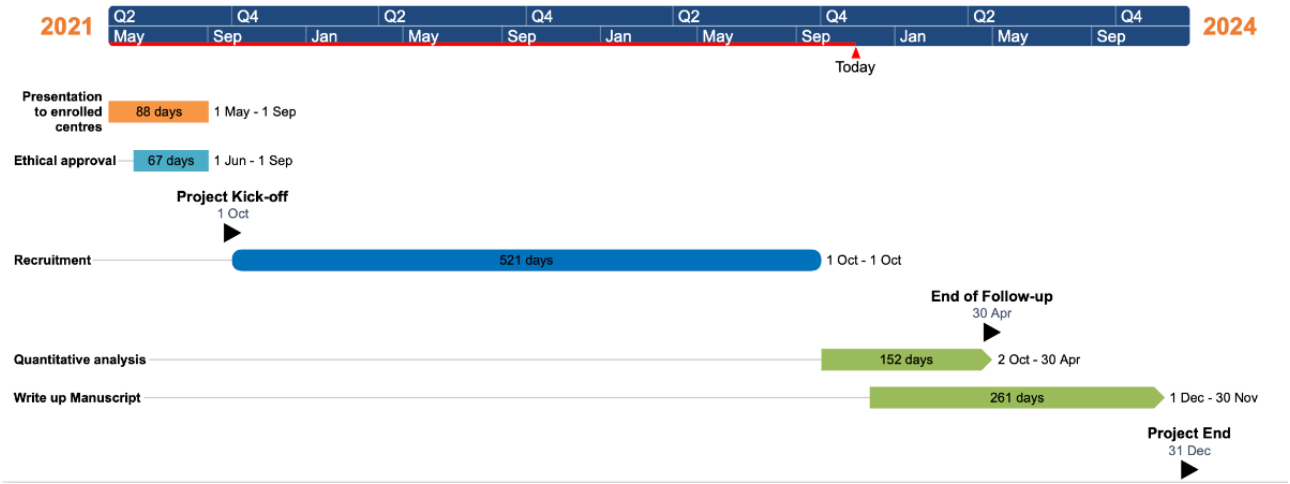

We plan to enroll 250 participants, including 100 with adverse mental health symptoms and 100 without, to explore the intricate relationship between adverse mental health symptoms and both physical and psychological fatigue in individuals recovering from long COVID. Preliminary analyses indicate a compelling connection, wherein patients who report heightened levels of depression and anxiety also tend to experience increased fatigue. These findings underscore the importance of considering mental health as a pivotal factor in understanding the enduring impact of COVID-19 beyond the acute phase. In addition to depression and anxiety, our study explores the persistence of PTSD symptoms in a subset of participants. Initial results suggest that, even after recovery from the acute phase of the infection, a proportion of individuals continue to grapple with the psychological repercussions of the virus. This observation aligns with emerging evidence suggesting a prolonged psychological impact of COVID-19, emphasizing the need for comprehensive mental health support for patients after contracting COVID-19. The identified links between mental health symptoms and fatigue have broad implications for the holistic care of this patient population. Understanding these connections can guide targeted interventions, emphasizing the importance of addressing mental well-being alongside physical recovery. As we delve deeper into the data and conduct further analyses, a more nuanced understanding of these relationships will emerge, informing future health care strategies and interventions.

Discussion

Expected Findings

As the COVID-19 pandemic ceases, more patients enter the chronic phase of the disease. Identifying groups at high risk of cognitive and psychiatric dysfunction may allow for targeted intervention to effectively meet their physical, neurological, and psychological health care needs. Our study, conducted in the aftermath of the COVID-19 pandemic, provides a unique opportunity to investigate the persisting health effects of the virus on those who have recovered from the acute phase of the disease. We specifically aim to explore post–COVID-19 fatigue and mental health disorders using specific tools to separate physical and psychological fatigue symptoms. We also use a prospective cohort multicenter study design, which is less prone to bias, and we aim to include both hospitalized and nonhospitalized patients, covering all degrees of acute COVID-19 severity. We anticipate that our research will reveal a significant association between the presence and severity of mental health symptoms, including depression, anxiety, and PTSD, and the degree of physical and psychological fatigue in patients following COVID-19. We expect to observe that patients experiencing more pronounced mental symptoms will report higher levels of physical and psychological fatigue.

The potential links between mental symptoms and fatigue suggest a connection between the mental well-being of patients post COVID-19 and their experience of fatigue, encompassing both physical and psychological dimensions. The existing research has indicated a high prevalence of anxiety and depression symptoms among patients hospitalized with COVID-19 infection, with a quarter of patients experiencing at least mild symptoms of acute stress disorder [42]. Moreover, a study conducted in Iran after the outbreak of COVID-19 found a correlation between the prevalence of chronic fatigue syndrome and PTSD [45]. The study reported that 5.8% of subjects experienced PTSD symptoms 6 months after the onset of SARS-CoV-2 infection. Interestingly, the study also noted that female sex was associated with a higher risk of fatigue. At the same time, variables such as oxygen saturation at admission, primary symptoms, ICU admission, and laboratory test parameters did not show a significant association with fatigue occurrence.

Based on these findings, we anticipate that patients post COVID-19 may exhibit more pronounced symptoms of

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depression and anxiety and heightened levels of physical and psychological fatigue. This insight emphasizes the importance of considering mental health as a crucial factor in understanding the long-term effects of COVID-19. It underscores that the impact of the virus extends beyond the acute illness phase and can manifest in persistent mental symptoms that influence patients' overall well-being. Moreover, it can imply that addressing anxiety symptoms in post–COVID-19 care may have a positive impact on reducing fatigue and improving patients' quality of life. We also aim to explore the prevalence and severity of PTSD symptoms in a subset of patients following COVID-19. While this is not the primary focus of our research, assessing the presence of PTSD symptoms in this study population allows for a better characterization of the patient group. Some participants continue to experience PTSD symptoms following COVID-19 infection, suggesting that the psychological impact of the virus can be long-lasting. These findings may shed light on the need for comprehensive mental health support for patients post COVID-19.

The implications of our potential findings are widespread. They underscore the importance of integrated care for patients post COVID-19 that addresses both physical and mental health aspects. Clinicians and health care providers will then be aware of the potential for persistent mental symptoms and their impact on patients' fatigue levels and overall HRQoL.

Limitations

Our study's limitations include the possibility of sampling bias, as individuals with more severe symptoms of fatigue or other mental health symptoms may be less likely to participate. This possibility could result in underrepresentation and bias within the study's findings. To minimize this, we will use diverse recruitment methods across multiple sites and collect data on participants' reasons for declining participation. We will also provide detailed information about the study and its potential benefits to participants while ensuring an ethical and respectful recruitment process sensitive to participants' health concerns and symptoms.

We also acknowledge the limitations related to our exclusion criteria and use of the CFQ-11, which has yet to undergo specific validation for patients with COVID-19. This recognition underscores the importance of future research endeavors to validate the applicability of the CFQ-11 within this patient population, despite its utilization in prior studies [46-48].

While there are valid concerns regarding the exclusion criteria and assessment of psychiatric disorders in our study—including the fact that assessing preexisting fatigue may be difficult—we have devised a plan to mitigate these concerns. We intend to meticulously collect detailed medical histories and review the medical records of all enrolled patients to ensure the precise application of the exclusion criteria. However, a notable limitation of our study arises from the absence of a baseline assessment conducted before the onset of COVID-19 infection. This absence impedes our ability to comprehensively evaluate the influence of COVID-19 on various health parameters, such as fatigue and mental health. The absence of a baseline assessment may also limit our capacity to distinguish between preexisting conditions and post–COVID-19 effects, which is a key consideration in understanding the full spectrum of the virus's impact on individuals. Additionally, while we acknowledge that the measurements used in the study are based on self-report—and therefore subjective—we emphasize that self-reported questionnaires are commonly used in scientific studies. These questionnaires hold significance in assessing the extent of physical and psychological fatigue in patients following COVID-19. Despite these limitations, our study is poised to make a significant contribution to the existing literature by shedding light on the impact of COVID-19 on mental health. This research has the potential to guide future treatment and management strategies, serving as a valuable resource for the health care community.

Conclusion

This study protocol outlines a critical investigation into the lingering physical and psychological effects of long COVID. It emphasizes the importance of understanding the ongoing health challenges individuals face even after recovering from the acute phase of the virus. This study's research questions focus on assessing the potential correlations of mental illness symptoms (ie, physical and psychological fatigue) among patients post COVID-19.

In the aftermath of a global pandemic, this research is timely and crucial. It has the potential to inform health care strategies and interventions that provide targeted and holistic care to individuals grappling with long COVID. Ultimately, this study aims to improve patient outcomes, enhance the quality of life for those affected, and contribute to broader efforts to address the multifaceted health implications of this unprecedented global crisis.

Authors' Contributions

LP conceptualized the study, wrote the first draft of the protocol, and planned the study. CR and RF helped write the first draft of the protocol. AB gave critical input throughout the study.
JB-E wrote the first draft of the protocol and gave critical input throughout the study. AM was responsible for the statistical planning and methodology. MD planned the study. All authors contributed to the manuscript and approved the submitted version. No generative artificial intelligence (AI) was used in any portion of the manuscript writing.

Conflicts of Interest

JB-E is an associate editor for BioMed Central (BMC) Medical Education and has received travel expenses from Medtronic for the "Save the Brain Initiative" training. The remaining authors have no conflicts of interest to disclose.

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Multimedia Appendix 1
Study clinical research form (CRF).
[PDF File (Adobe PDF File), 1865 KB - resprot_v13i1e51820_app1.pdf]

Multimedia Appendix 2
Ethical approval.
[PDF File (Adobe PDF File), 126 KB - resprot_v13i1e51820_app2.pdf]

Multimedia Appendix 3
Informed consent form.
[PDF File (Adobe PDF File), 119 KB - resprot_v13i1e51820_app3.pdf]

Multimedia Appendix 4
SPIRIT checklist.
[PDF File (Adobe PDF File), 75 KB - resprot_v13i1e51820_app4.pdf]

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Abbreviations

CFQ-11: Chalder Fatigue Scale
CRF: clinical research form
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EQ-VAS: EuroQol Visual Analog Scale
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
ICU: intensive care unit
MERS: Middle East respiratory syndrome
PTSD: posttraumatic stress disorder
PTSS-14: 14-item Posttraumatic Stress Scale
RT-PCR: reverse-transcription polymerase chain reaction
SARS: severe acute respiratory syndrome
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

The Impact of Forced Separations Between Women and Their Pets in Domestic Violence Situations and the Effectiveness of Crisis Response: Protocol for a Conceptual Framework

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Abstract

Background: Women are at high risk of experiencing trauma, guilt, and stress when forced to separate from their companion animals when fleeing domestic violence. Where little support is available for women and pets to stay together, women may be forced to delay leaving the abusive relationship or leave the pet with the abuser. Forced separation places both women and pets at substantial risk, where pets may be used as a coercive control measure. However, little evidence exists regarding the extent to which Australian services or policies offer support in these circumstances.

Objective: This research aims to increase the understanding and the impacts of forced separation between women and their pets in domestic violence situations. The research will investigate the effectiveness of service responses for both women and animals, aiming to develop a policy framework that guides service improvement with the goal of enhancing outcomes for women and pets fleeing domestic violence.

Methods: This protocol paper describes the process of developing a conceptual framework of 4 studies that include a scoping review, policy analysis, focus groups, and interviews that guide the design of the qualitative research project.

Results: A scoping review of the literature on forced separation from pets in domestic violence, natural disasters, and homelessness situations has led to the development of a conceptual framework that guided the design of the proposed study. The review also confirmed the necessity of the proposed research project in addressing the lack of Australian national frameworks and guidance available for women and pets seeking formal support in domestic violence situations. As of August 2023, supporting organizations have commenced the distribution of the research flyers. Expected data collection will be completed between August and October 2023. The results are expected to be published in June 2025.

Conclusions: Via a systematic process, the importance of the proposed study in improving the understanding of the impact of forced separation between women and their pets at times of domestic violence and the gaps in best supporting both women and their pets has been confirmed. A study design based on the learnings from previous studies and the focus of the current research has been finalized. The impact of the research project in developing an Australian national framework for best supporting women and their pets in crisis situations is anticipated.

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KEYWORDS

companion animal; domestic violence; forced separation; research protocol; animal welfare; pets; animal abuse; Australia; coercive control; victim; abusive partner; abusive; women; trauma; support; animal

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Introduction

In Australia, 69% of households live with a companion animal (pet), and 86% of households with a pet have children [1]. Dogs and cats are the most popular type of pets [1]. The main reason for living with a companion animal is companionship [1]. The relationship is considered beneficial both psychologically and physiologically for humans and animals [2]. Pets are a vital support system providing emotional support or strength at times of domestic violence [3]. Survivors in domestic and family violence situations often live in terror and face threats to themselves and their pets [4]. Sadly, women in domestic violence situations are often faced with the torturous decision to leave their pet with the perpetrator to seek safety or access temporary fostering, resulting in forced separation from their companion animal (Montgomery et al [5], in press), thus losing the emotional support normally received from the relationship [3].

Barrett et al [6] found that decisions to leave or stay in the relationship were impacted by the concerns for the animal's welfare, with 56% of women delaying leaving the relationship to protect their pet. Women with both children and pets were also found to delay leaving an abusive relationship out of concern for the pet's welfare [7]. Most women who delayed were forced to leave their companion animal with the perpetrator when they eventually fled to safety and 47% of women would have fled to safety with their companion animal if support was available [8]. Completing a safety plan when leaving domestic violence situations was often compromised due to a lack of pet-inclusive shelters, often leading to homelessness in order to stay with their pet [7]. When survivors are forced to leave their companion animals with the perpetrator, the risk of coercive control (such as monitoring a person's movements) increases where the companion animal is used as a coercive control tool [9]. The companion animal in this situation may be subject to continued maltreatment [9], often resulting in torture or death [10] and survivors experience additional guilt and trauma [3] as a result. Often, they consider returning to their partner for the sake of their companion animals' safety [8]. Where companion animals have survived domestic violence, signs of distress in the animal have been observed through behavioral changes, such as avoidance and vocalization [4,11]. Devastatingly, in Australia, such behavioral changes often result in euthanasia of the pet [4,11].

The emotional attachment between survivors of domestic violence and their pets may be substantial due to sharing the experience of abuse [4], which makes a deliberate act of cruelty or death of a companion animal particularly torturous [12]. While it is the case that domestic violence is a human issue that affects both men and women, it is recognized as a gender-based issue where men are more likely to perpetrate violence against women and is considered an epidemic problem that requires change in Australia [13]. A recent report on homicide in Australia [14] reveals that, from 1989 to 2020, the incidence of intimate partner homicide is consistently much higher for female survivors than male survivors. The most recent statistic (2019-2020) states that female individuals were the targets in 36 (80%) of the 45 intimate partner homicides. Considering Australia is one of the highest pet ownership countries in the world, where women with children are more likely to have a pet [15], it is vital to address the risks for survivors and their companion animals at times of forced separation because of domestic violence. In such a context, a research project has been developed to investigate the existing policy framework and relevant services that provide support to people and companion animals in domestic violence situations. This protocol paper will explain the process of confirming research gaps and determining research questions and will provide details of the overall project design to be used by the proposed project as informed by the learnings from previously published studies.

Methods

Overview

A scoping review [5] using the keywords "human-animal relationship/bond," "pets," "companion animals," "animal abuse," "violence," "homelessness," "housing," and "disasters," was conducted between March and August 2022. The review focused on identifying empirical studies on the human-animal relationship and crisis or situational change with no date limitation. The review was guided by Arksey and O'Malley's [16] framework for scoping reviews and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for scoping reviews [17]. English-language, scholarly peer-reviewed papers that included adults with a strong relationship with a pet and an event or change of situation were a criterion for the scoping review. All methodology types were accepted. Gray literature and certain animal types (rodents, wildlife, zoo animals, and working animals) were excluded. The papers were assessed on their ability to fit within the inclusion criteria. Five databases (MEDLINE Ovid, PsycINFO, Scopus, CINAHL, and Emcare Ovid) were searched, and a total of 42 scholarly papers that met the inclusion criteria were identified and included for data extraction. The scoping review mapped the concept of forced separation between people and their companion animals in areas of crisis or situational change and examined policies that included companion animals. The study design and methods used for the studies were also examined to inform the current project design. Please see the full list of papers included in the scoping review in the Multimedia Appendix 1 [3,4,6-11,18-51].

Scoping Review Findings That Informed the Development of the Protocol

The identified studies in [5] scoping review were predominately quantitative and conducted in the United States, with a focus on the co-occurrence of animal abuse and domestic violence. The lens of research has recently focused on the relationship and animal maltreatment or welfare concerns. Surveys and semistructured interviews were the common forms for collecting quantitative studies and qualitative data respectively. The average sample size consisted of 200 participants for quantitative studies and 20 participants for qualitative studies. The target population was predominantly female adults seeking refuge from domestic violence shelters and support services.

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The scoping review [5] confirmed a lack of support for both humans and animals at times of forced separation because of domestic violence. The oversights of the animals' safety and welfare showed that animals were being left with the abuser [18] and women delayed leaving a violent relationship to protect the companion animal [19]. Additional barriers that were identified included geographical locations, lack of available supports [19], lack of awareness of supports, and attachment or fear of separation from the companion animal [4]. As a result of these barriers, the risks to safety, health, and well-being for women, children, and their companion animals have increased.

The scoping review [5] findings revealed survivors were often reluctant to reach out to services due to a lack of trust in accessing support services, veterinary care, and law enforcement. A lack of trust was associated with a fear of being forced to separate from their companion animal [10,18,20,21]. The reluctance to access support, and the responsibility weighing on women to access supports [6,22] is highly concerning. Although many studies in the literature provided implications for service providers, no research was found that investigated the policy frameworks that provide support to people and companion animals in domestic violence situations at any system, organization, societal, or individual level [5].

Ethical Considerations

The following ethical considerations are guided by the Global Women's Institute for the Department of Foreign Affairs and Fair Trade [52], which provides recommendations for projects specific to researching women in domestic violence situations. Ethical approval was granted from the Human Research Ethics Committee (approval H9148). Participation in this study is voluntary and written and verbal consent will be obtained from every participant. The data will be retained for a minimum period of 5 years and will only be accessible to the research team. All data collected will be deidentified and pseudonyms will be provided. All audio recordings for both target populations will be erased after transcription. The primary target population will have the opportunity to review the transcriptions in writing via email. To avoid comprising anonymity and confidentiality for the primary target population, specific locations, age, occupation, culture, and religious discourse in the primary target will not be included in the narrative where there is potential to make the participant identifiable. Consent will be obtained verbally prior to the commencement of the focus group discussion and interviews. Participants are reminded of the voluntary nature of the study and their rights to not answer questions or withdraw their participation from the study. The focus group will be informed that confidentiality is not guaranteed and will be requested to anonymize discussions of their opinions and keep the group discussions private. Confidentiality and anonymity are provided to the interview participants.

Research Focus and Research Questions

The research aims to inform the Australian policy framework by investigating how support services operate across different contexts for adult women and their companion animals affected by forced separation to reduce negative impacts for both people and animals when fleeing domestic violence situations. The research aim will be achieved by the following two objectives:

1. Identifying the impacts of forced separation between adult female survivors of domestic violence and their companion animal's health, safety, and living conditions.
2. Identifying the existing strategies and support services, the perceived effectiveness of these strategies, and areas for improvement to develop recommendations that maximize support to people and their companion animals fleeing domestic violence situations.

The research seeks to answer the following two questions.

1. How does forced separation impact the domestic violence survivor and their companion animal under the existing policy and support framework in Australia?
2. What are the factors and how do these factors influence the extent that the benefits of the existing services currently available to people and their companion animals are realized?

A qualitative design will be used to address the gaps in the literature of a lack of national framework to guide pets and women in domestic violence; the impact of forced separation; and the roles, attitudes, and beliefs of seeking and providing services to better understand the impacts and perceptions of forced separation. The transformative paradigm views privilege and power as a social construction that is embedded through social, political, cultural, economic, gender, age, disability, race, and ethnicity. The transformative worldview is a suitable framework providing the lens of power and oppression with a focus on positive social change [53].

Conceptual Framework

Based on the findings of the scoping review [5] and the role of support services in preventing or minimizing adverse outcomes due to forced separation, a conceptual framework (Figure 1) was developed. The framework indicates that policy and adequate, effective support services are required to improve the outcomes for people and companion animals who must leave their homes because of domestic violence. The scoping review [5] confirms that a policy framework, key supports, and elements required to achieve these outcomes remain unclear. It is important to understand existing policies, support services or providers, and those who use the services in Australia so that improvements can be made to best support people and companion animals fleeing domestic violence. Guided by the conceptual framework created for this study, 4 steps (Figure 1, studies 1-4) need to be implemented to enrich our understanding of the key elements leading to the development of a policy framework on the forced separation of companion animals because of domestic violence that is relevant to the Australian context. The steps include:

1. A scoping review [5] of forced separation at times of crisis or situation (completed).
2. A policy or services analysis and a scanning of the key supports to humans and animals that will analyze the purpose; construction; implementation; and impacts to understand, evaluate, and provide meaning and context [54].

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3. Semistructured individual interviews with participants who have accessed a variety of support services (refuges, crisis services, animal welfare services, and mainstream such as women's legal services) will be conducted to increase the understanding and impacts of forced separation on people and companion animals.
4. Focus groups with staff and service providers will be conducted to understand and identify perceptions of the effectiveness and adequacy of service provision.

A critical analysis of steps 2-4 will be completed to compare the findings of the most common types of support, service gaps, and availability of services, leading to the development of an improved policy and support framework.

Figure 1. The conceptual framework. RQ: research question.

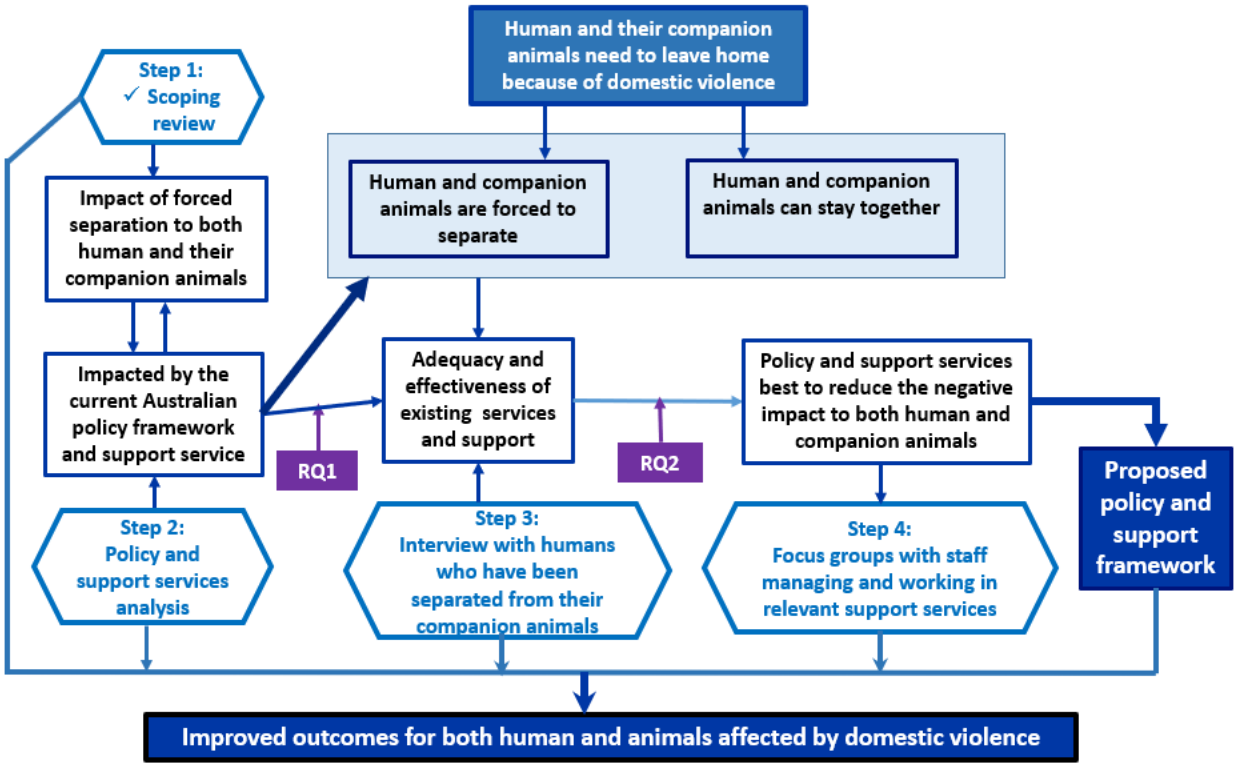

RQ 1: How does forced separation impact the domestic violence survivor and their companion animal under the existing policy and support framework in Australia?

RQ 2: What factors and how do these factors influence the extent that the benefits of the existing services currently available to people and their companion animals are realized?

Project Design and Method

Participants: Characteristics and Recruitment

The research project has 2 target populations. The primary target population is female individuals who have or have had considered themselves to have a strong emotional bond in a relationship with their companion animals; have experienced domestic violence; and have been forced to separate from their companion animals or sacrificed their own health, safety, and living arrangements to stay with the animals. The secondary target population is those who have not been directly affected by forced separation and domestic violence but have provided or are currently involved in providing professional support services to the primary target population. Due to the complex and sensitive phenomenon, both target populations are adults, 18 years and older [52].

Both target populations will be recruited through relevant domestic violence or animal welfare organizations. The organizations will be responsible for making direct contact with the potential participants via emails or organization-based advertisements. Potential participants will be encouraged to make direct contact with the principal researcher (first author) should they wish to participate in the study. Both target populations will be geographically recruited nationally across all states and territories in Australia. Due to financial and logistic constraints [55], both target groups are required to be fluent in the English language.

Sampling Strategy

Purposive sampling will be used to gather specific characteristics of survivors who have a strong emotional bond with their companion animals (primary target population) to maximize the richness of the data in addressing the research questions [56]. People who received an invitation from their perspective organization and made contact to participate in the study will need to fit the characteristics of either target population 1 or 2.

Key Stakeholders

To maximize the ethical sensitivity of the research, an advisory group of professionals in the field of domestic violence, advocacy bodies, and animal welfare organizations will be created [52]. Experts participating in the advisory group are

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excluded from the secondary target population. The principal researcher candidate and 2 research advisors will hold meetings via Zoom (Zoom Video Communications) prior to ethics submission and after analysis. The advisory group is sought for their expertise regarding sensitivity, recruitment pathways, research questions, and participation sheets. After the analysis, for advice on recommendations based on the findings from the study.

Data Collection Tools

In-depth individual interviews are best suited for "sensitive" populations [52] and web-based options may increase the participant response rate [57]. Hence, the primary target population will be invited to participate in individual semistructured, web-based interviews via Zoom. These interviews are expected to take around 1 hour and will be audio recorded. Focus groups are well suited to discussing beliefs, opinions, and attitudes surrounding programs [52], interventions, and service gaps [58]. Therefore, the secondary target population will be invited to participate in web-based focus groups with audio recordings via Zoom. There will be 4 focus groups nationwide. The focus groups are estimated to last 1 to 2 hours as it is important to allow time during the focus groups for rapport building and voicing opinions [56]. Both types of interviews will be professionally transcribed. Verbal and written consent to participate will be obtained from all participants. All participants will be given the opportunity to review a summary of the transcriptions prior to publication [59].

Sample Size

The average number of participants in related qualitative studies identified in the scoping review was 20 (Montgomery et al [5]). The method of the research project is designed to gather in-depth, rich data or high-quality dialogue [60]. Hence, between 12 and 20 participants will be sampled from the primary target group, with the final number of participants being guided by data saturation of main themes, and no new insights or issues are found [61]. The secondary target population will consist of 4 focus groups throughout Australia. When a group consists of high knowledge, a minimum of 4 participants are required to develop accurate information [62] and the probability of identifying themes with 6 participants is higher than 99% [63]. Due to the expertise and knowledge of the participants, there will be a minimum of 4 and a maximum of 8 participants to allow for space and reflection with each group member [56]. The number of participants for the target populations is supported by a recent systematic review of effective sample sizes for saturation in qualitative research [61].

Data Analysis

Interpretive work is required to identify meanings and themes from participants' opinions, perceptions, and experiences to meet the research aims and overall purpose. Thematic analysis will be used to provide a systematic approach to coding and conceptualizing themes [58]. Areas of analysis will include the impacts and outcomes of forced separation, accessibility of services, types of unmet needs, experiences of accessing services, and benefits of existing services. When the analysis of each step is completed, a critical analysis will be completed to aggregate the data [58] to provide a complete picture of the policy framework [54]. NVivo 12 software (Lumivero) will be used to facilitate the data analysis process.

Results

A scoping review of forced separation of companion animals in crisis situations has been completed, identifying the research gaps and guiding the research questions and design for the research project. As of August 2023, supporting organizations have commenced the distribution of the research flyers. Expected data collection will be completed between August and October 2023. The results are expected to be published in June 2025.

Discussion

Expected Findings

It is expected that the findings will identify the substantial issues experienced by women and pets in domestic violence situations such as psychological distress, grief, loss, and the complexity of decision-making when considering a pet. It is expected that women and pets need to be considered more seriously in Australia and the development of policies and services needs to include the consideration of pets in safety planning, accommodation, and long-term housing as their standard practice.

Comparisons With Prior Work

The research protocol builds on existing knowledge in the literature. We are unaware of any published national Australian frameworks or models that directly relate to responding to women and pets fleeing domestic violence. Previous literature indicates when women are seeking help to flee from domestic violence, the risk of safety increases for both women and their pets. In addition, the pet may be used as a coercive control measure, risking further abuse for both the woman and the animal [18]. The evidence indicates it is vital to address the increased risks to safety when fleeing domestic violence. The prospective data collection of service providers and women using domestic violence and animal welfare services in Australia, as we propose in this study, enables further understanding and development of an Australian framework that is embedded by those with lived experiences to improve outcomes.

Strengths and Limitations

Limitations include the small sample sizes that will not be generalizable to the wider populations, and the exclusion of non–English-speaking populations limits the ability of the research to understand the special needs of the linguistic and cultural populations [55]. The primary target population is recruited from service providers and is considered safe to participate. This is a limitation for women and pets in situations that did not seek formal service provision, had stayed in the relationship, or were not safe from abuse. Bias is more likely to occur in qualitative research than in quantitative methods, resulting in difficulty reaching true objectivity [59]. However, the strength of the qualitative design allows for flexibility and

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sensitivity in language, trust, rapport building, exploration of experiences, and collaboration within the community [58] and is appropriate for the study's aims.

Conclusions

A research project guided by a conceptual framework informed by the findings of the scoping review confirms 4 key studies required to better understand the strengths, needs, and gaps of existing policy and support services for women and pets fleeing domestic violence, and the impacts of forced separation from companion animals. Ultimately, the project will develop an Australian national framework that will develop and provide more relevant guidance for supporting women and their pets fleeing domestic violence situations to improve outcomes for both women and their companion animals in Australia.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

As the first author, JM developed the first draft of the manuscript guided by the senior author ZL. Both ZL and JL contributed to writing all sections of the manuscript and critically reviewed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of the scoping review articles by separation event.
[DOCX File , 33 KB - resprot_v13i1e52067_app1.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Validation of an Anti-Müllerian Hormone Cutoff for Polycystic Ovarian Morphology in the Diagnosis of Polycystic Ovary Syndrome in the HARMONIA Study: Protocol for a Prospective, Noninterventional Study

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Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women and is diagnosed using the Rotterdam criteria, including diagnosis of polycystic ovarian morphology (PCOM) by transvaginal ultrasound (TVUS). Due to high cost, availability, and the impact of the operator and ultrasound equipment on the reliability of the antral follicle count (AFC) by TVUS, an unmet need exists for a diagnostic test to determine PCOM without TVUS. A strong positive correlation between elevated anti-Müllerian hormone (AMH) levels and AFCs has been demonstrated in women with PCOS. In addition, recent updates to the international evidence-based PCOS guidelines state that serum AMH can be used as an alternative to TVUS-determined AFC, in the diagnosis of PCOM. The retrospective APHRODITE study derived and validated an AMH cutoff of 3.2 ng/mL for the Elecsys AMH Plus or Elecsys AMH assays (Roche) to diagnose PCOM in patients with PCOS.

Objective: This study aims to further validate, in an independent prospective cohort, the AMH cutoff (3.2 ng/mL) for PCOM determination, which was previously derived and validated in the APHRODITE study.

Methods: This large, prospective, multicenter, population-based, noninterventional study will evaluate the previously established AMH cutoff for the determination of PCOM during the diagnosis of PCOS using the Elecsys AMH Plus immunoassay in an independent population. Participants were women born between July 1985 and December 1987 in Northern Finland; the study partially links to the Northern Finland Birth Cohort 1986. We assessed the enrolled women, determined with the 2023 PCOS Guidelines, for current PCOS status and divided them by phenotype if positive. Each participant had 1 study visit to collect serum samples, record clinical data, and undergo a gynecological examination including TVUS. All data were collected by highly trained midwives or trained gynecologists. Sensitivity, specificity, and agreement measures were used to validate the previously determined cutoff in the whole population and in subpopulations based on phenotype and relevant demographic or clinical factors. The minimum target sample size was approximately 1800 women, including approximately 10% with PCOS.

Results: At the time of manuscript submission, participant recruitment had concluded, and 1803 women were enrolled into the study. Data collection is complete and biostatistical analysis is planned for 2023.

Conclusions: To limit variability, there were few TVUS operators and only 2 TVUS machines of the same type. Additionally, all women who were taking oral contraceptives were excluded from the primary analysis population. Selection bias was limited as this was a population-based study and participants were not seeking treatment for PCOS symptoms. Validating the AMH cutoff

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in a large, population-based study will provide further evidence on the utility of the Elecsys AMH Plus or Elecsys AMH assays in PCOM diagnosis as an alternative to TVUS. Measuring AMH for PCOM diagnosis could reduce delayed or missed diagnoses due to operator-dependent TVUS examinations.

Trial Registration: ClinicalTrials.gov NCT05527353; http://tinyurl.com/2f3ffbdz

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KEYWORDS

anti-Müllerian hormone; immunoassay; polycystic ovarian morphology; polycystic ovary syndrome; transvaginal ultrasound

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women and is characterized by symptoms of ovarian dysfunction and an excess of androgen, without other specific diagnoses [1-3]. PCOS is the primary cause of female anovulatory infertility and has metabolic, cardiovascular, and psychological implications [4-7]. The diagnosis of PCOS is based on the Rotterdam criteria [8,9], where 2 or more of the following conditions should be met: oligoanovulation or anovulation (OA), clinical or biochemical signs of hyperandrogenism (HA), a combination of both, and polycystic ovarian morphology (PCOM) based on transvaginal ultrasound [10] (TVUS; Figure 1).

Figure 1. Diagnostic criteria and phenotypes of PCOS based on the Rotterdam criteria. HA: hyperandrogenism; OA: oligoanovulation or anovulation; PCOM: polycystic ovarian morphology; PCOS: polycystic ovary syndrome.

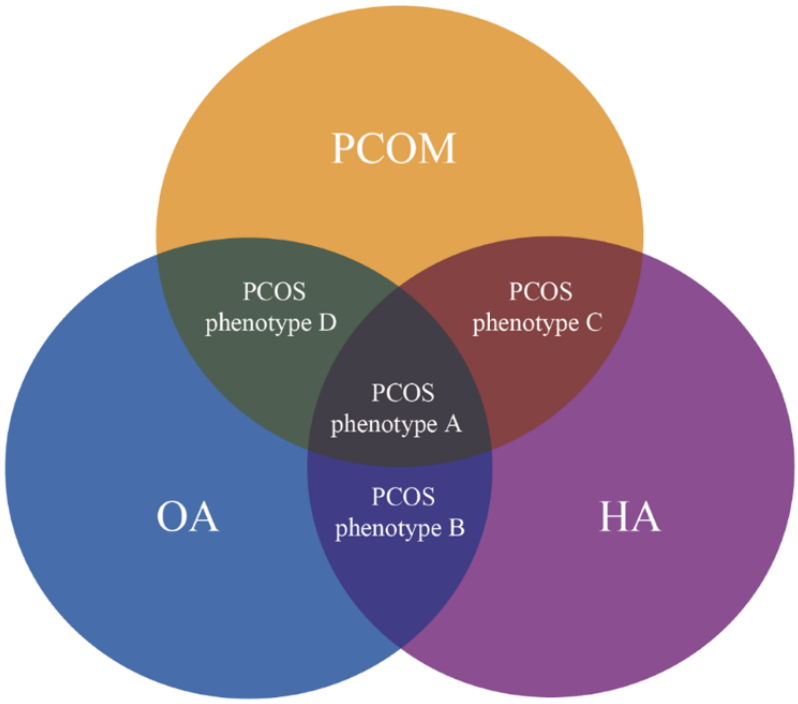

Criteria	Phenotypes			
	A	B	C	D
HA	✓	✓	✓	
OA	✓	✓		✓
PCOM	✓		✓	✓

According to the updated guidelines [9], the diagnosis of PCOM is based on a TVUS with a finding of ≥20 follicles of 2-9 mm in size in at least 1 ovary or increased ovarian volume ≥10 mL, but determination of the antral follicle count (AFC) by TVUS

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depends on the operator and ultrasound equipment used [11-17]. Due to the expense of the equipment and the regularity of updates needed, in addition to the very high level of specialized training required by operators, TVUS is not available for many physicians seeing women with symptoms of PCOS (eg, general practitioners, gynecologists, and endocrinologists). Thus, there is significant underdiagnosis of PCOS [18] along with a substantial delay in receiving a diagnosis [19-22]; therefore, an unmet medical need exists for a diagnostic test to determine PCOM without the need for TVUS.

Anti-Müllerian hormone (AMH) is a regulator of follicle recruitment from the primordial follicle pool and inhibitor of follicular growth that is expressed by granulosa cells in the preantral and small antral follicles [23,24]. Serum AMH levels correlate well with the 2-9 mm antral follicles found in TVUS examination in the diagnosis of PCOM [25,26]. Elevated levels of AMH are observed in women with PCOS [27-30], and a strong correlation between elevated levels of AMH and increased AFCs has been demonstrated [12,14,26,29], supporting the use of AMH as a biomarker for PCOM.

In the recent, retrospective, case-control APHRODITE study, a cutoff of 3.2 ng/mL for the Elecsys AMH Plus or Elecsys AMH assays (Roche Diagnostics International Ltd) was derived and validated to identify PCOM as part of PCOS diagnosis in women aged 25-45 years [28]. Moreover, a recent study reported the usability of the Elecsys AMH assay to identify PCOS cases in large epidemiological data sets [31]. All previous findings support the use of AMH measurement using the Elecsys AMH Plus assay as a substitute for AFC in the determination of PCOM, thereby reducing the need for TVUS procedures [28,32].

Since APHRODITE was a retrospective, case-control study that validated the derived cutoff in a population with an increased risk of PCOS, it is of interest to further validate the derived cutoff in a prospective, independent, population-based cohort. By validating AMH levels in a large, population-based study using the Roche Elecsys AMH Plus assay, we aim to provide clinicians with the ability to identify PCOM as part of a PCOS diagnosis using a simple blood test, thereby making diagnosis of the disorder more accessible in a primary care setting. Although it is not anticipated that TVUS as a diagnostic method for PCOM will be discarded from PCOS guidelines, AMH testing could be adopted as an alternative method, particularly in primary care.

Methods

Study Design

The prospective, multicenter, population-based, noninterventional HARMONIA (Human Anti-Müllerian Hormone for Diagnosis of PCOS) study aims to validate the AMH cutoff determined and validated in the APHRODITE study for the determination of PCOM during the diagnosis of PCOS using the Elecsys AMH Plus immunoassay. Study enrollment was conducted between May 2020 and October 2022 at 2 sites in Finland: Oulu University Hospital, Department of Obstetrics and Gynecology, Oulu, and Helsinki University Hospital, Helsinki.

Participants

The target population was women born in Northern Finland between July 1, 1985, and December 31, 1987; the study partially links to the Northern Finland Birth Cohort (NFBC) 1986 study population. The prevalence of PCOS in this population is expected to be approximately 10% when applying the diagnostic criteria for PCOS outlined in the 2018 international PCOS guideline [9,33]. The COVID-19 pandemic resulted in a lower enrollment rate than originally expected, and so the cohort was expanded to include a random cohort of women born in the same geographical area up to 18 months after those in the NFBC 1986, to ensure enrollment met the minimum target sample size of approximately 1800 individuals. As the study is population-based, all nonpregnant women from the target population were invited to participate in the study.

Participants were excluded if they were unwilling to undergo gynecological examination including TVUS, refused to have blood drawn, or did not consent to sharing their personal data with Roche Diagnostics International Ltd, who completed the AMH measurement and analysis. Additionally, women who were taking oral contraceptives at the time of study commencement will be excluded from the primary analysis population.

PCOS cases were defined as women fulfilling 2 or more Rotterdam criteria [8,9]. For each participant, the current PCOS status was assessed. PCOS positive cases were further divided into the following phenotypes: phenotype A (HA+, OA+, PCOM+), phenotype B (HA+, OA+, PCOM-), phenotype C (HA+, OA-, PCOM+), and phenotype D (HA-, OA+, PCOM+; Figure 1). PCOM in PCOS cases included the PCOS A, C, and D phenotypes. PCOS phenotype B cases by definition did not meet the criteria for PCOM based on TVUS (phenotype B accounted for approximately 3% of PCOS cases in the APHRODITE study) and were not included in the case group for the primary objective. Controls were defined as women with negative PCOM with an AFC <20, an ovarian volume <10 mL, and no other diagnostic features of PCOS according to the Rotterdam criteria.

Each participant had 1 study visit during which serum samples were collected through blood draw (taken at any stage of the menstrual cycle), clinical data (including questionnaire responses) were recorded, and a gynecological examination including TVUS (Ultrasound System HS60, Samsung Healthcare) was performed to determine PCOM status; all assessments were evaluated by a clinician (Table 1) [34]. All data were collected by highly trained midwives or gynecologists.

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Table 1. Baseline characteristics to be recorded by questionnaire and clinical assessment.

Baseline characteristic	Questionnaire	Clinical assessment
General information and medical history	• Participant identification and date of consent • Age at the study visit • Race • Education • History of radiation or chemotherapy (yes or no) or treatment • Long-term illnesses diagnosed by a doctor (self-reported) • Bothersome hair loss experience • Acne (former or current)	Confirmation of fasting for 12 hours before the clinic visit
Medication use	• Medication use (current) • Use and type of hormonal contraceptives (oral, patch, or intrauterine device; former or current)	N/A[a]
Intoxications	• Smoking (current, former, or never; number of cigarettes) • Alcohol (units per week)	N/A
Obstetric history	• Menarche • Cycle (regular, irregular, or absent) • Shortest and longest menstrual cycle length (days) • Last menstrual cycle • Number of live births, fetus mortus, miscarriages, extrauterine pregnancy, and pregnancy terminations • Fertility treatment • Breastfeeding status (no, exclusively, or partially) • Delivery within 6 months from the study visit	From the transvaginal ultrasound report: • Endometrial thickness • Visualization status of the ovaries • Ovarian length, width, height, and volume • Antral follicle count • Dominant follicle presence • Presence of corpus luteum and/or cysts >25 mm and/or other possible reason for increase of the ovarian volume
Anthropomorphic	• N/A	• Height • Weight • Waist circumference • Hip circumference • Systolic blood pressure or diastolic blood pressure • Gynecological ultrasonography (polycystic ovarian morphology) • Hirsutism (Ferriman-Gallwey-Score) • Acne severity grading (1-5) per the Global Acne Severity Scale [34]. Images of the participant will be assessed by a dermatologist

[a]N/A: not applicable.

Sample Processing

A total volume of approximately 5 mL of serum was collected using VACUETTE Tube 9 mL CAT serum clot activator tubes (Greiner Bio One) and stored at –80 °C. Aliquots were sent to the Nordlab in Oulu for measurement of testosterone by liquid chromatography-mass spectrometry (Sciex Qtrap 5500, Ab Sciex). Additional measurements were performed on-site at Oulu (testosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and prolactin) on the COBAS e 411 analyzer (Roche Diagnostics International Ltd), which was used to assess some of the PCOS criteria. Additional aliquots were shipped to Roche Diagnostics GmbH, Penzberg, Germany, for determination of AMH biomarker levels (Textbox 1). AMH levels were measured using the Elecsys AMH Plus assay on the COBAS pro e 801 analyzer (Roche Diagnostics International Ltd). The measuring range of the Elecsys AMH Plus assay is 0.01-23 ng/mL and the coefficient of variance for repeatability is less than 3% [35]. Participants with AMH levels more than 3.2 ng/mL (the cutoff determined and validated in the APHRODITE study [28]) were classified as AMH PCOM positive, and those with results ≤3.2 ng/mL were classified as AMH PCOM negative.

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Textbox 1. Laboratory parameters to be measured from blood samples.

Parameters to be measured

- Hemoglobin A1c
- Complete blood count
- Ferritin
- Fasting plasma glucose
- Fasting total cholesterol
- Fasting plasma high-density lipoprotein
- Fasting plasma low-density lipoprotein
- Fasting plasma triglycerides
- Plasma alkaline phosphatase
- Plasma albumin
- Fasting serum C-peptide
- Plasma alanine aminotransferase
- Plasma amylase
- Plasma aspartate aminotransferase
- Plasma bilirubin
- Plasma gamma glutamyltransferase
- Plasma creatinine
- Plasma uric acid
- Fasting serum insulin
- Serum high-sensitivity C-reactive protein
- Testosterone
- Sex hormone-binding globulin
- Follicle-stimulating hormone
- Luteinizing hormone
- Thyroid-stimulating hormone
- Prolactin
- Anti-Müllerian hormone
- Dehydroepiandrosterone sulfate

Data Analysis

At the time of publication submission, the trial was still underway, although data collection was complete. During the planned biostatistical analysis, baseline characteristics and biomarker data will be analyzed for all participants, and by PCOS phenotype and case or control groups. Additionally, the baseline characteristics will be compared between cases and controls using statistical tests, such as Mann-Whitney *U* tests or chi-square tests.

The primary objective of this study, conducted in the PCOM positive population, will be validating the AMH cutoff for PCOM determined in the APHRODITE study. Agreement measures will be calculated, and tables produced to estimate the performance (ie, sensitivity, specificity, and receiver operating characteristic curve) of the prespecified Elecsys AMH cutoff for the prediction of PCOM status. In addition, performance estimates (sensitivity, specificity, and agreement tables) of the Elecsys AMH Plus cutoff will be performed within subpopulations (phenotype and potentially relevant demographic or clinical factors).

Sample Size and Power

The total sample size for the primary analysis was a minimum of approximately 1800 women, of whom approximately 10% will be PCOS positive cases; however, some individuals may need to be excluded from the primary objective analysis due to hormonal contraceptive use. As PCOS phenotype B cases do not meet the criteria for PCOM based on TVUS, some PCOS cases will also be excluded. In addition, some women may need to be excluded if their PCOS or PCOM status cannot be determined (eg, due to the inability to adequately visualize the ovaries). Assuming a significance level of 0.05 (1-sided lower CIs) and a joint power of 80%, approximately 55-88 PCOS

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positive cases and approximately 164-262 PCOS negative cases are needed to achieve agreements of 65% and 70%, if the true percentages of agreement are 79%-82.5% and 78%-80%, respectively.

Ethical Considerations

The study complies with all relevant national regulations and institutional policies and was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval was provided by the Ethical Committee of the Northern Ostrobothnia Hospital District (EETTMK 47/2019), and all participants were required to give informed consent for the use of their collected data for scientific purposes. The trial was registered (NCT05527353) on September 2, 2022.

Results

The first patient provided consent on May 7, 2021, and the last patient provided consent on October 28, 2022; therefore, participant recruitment has been completed. At the time of manuscript submission, 1803 women had been enrolled into the study. Biostatistical analysis will commence later in 2023 and it is expected that the results will be published shortly thereafter.

Discussion

This is the first large, prospective, population-based study to validate an AMH level cutoff for determining PCOM status in the diagnosis of PCOS.

Strengths and Limitations

One strength of this study is that all data were collected by highly trained midwives and specialized gynecologists. The TVUS data is robust due to the limited number of TVUS experienced operators performing the ultrasound assessments, and the use of only 2 TVUS machines of the same type. In addition, while most studies on AMH testing are retrospective, using small, non–population-based cohorts from PCOS clinics, HARMONIA is a large, prospective, population-based study. Furthermore, there will be limited bias, as the study is population-based, and participants were not seeking treatment for PCOS symptoms. However, the study also has some limitations. The age of the participants is limited by the study's linkage to the NFBC 1986 (all participants are within a 3-year age range). In the APHRODITE study, it was also found that AMH levels decreased with age among PCOS cases and controls [28]; findings from this study should therefore be evaluated in the context of these results. Furthermore, due to the geographical location of the study and the fertile age of the participants, most women will be White (with a small minority, estimated below 3%, of indigenous Sámi people), and some will be taking hormonal contraceptives. It has also previously been shown that there is some biological variability in AMH during the menstrual cycle [36]. However, a longitudinal study conducted in a population-based cohort demonstrated that AMH may be used as a surrogate marker for identification of PCOM [37]. The samples in this study will be taken at any stage of the menstrual cycle; however, we anticipate that the small variation in cycle phases will not affect the diagnostic performance of the Elecsys AMH Plus assay. Furthermore, studies have shown that women with PCOS may have a higher body mass index, which could affect the precision of TVUS results [38,39]. In addition, the global COVID-19 pandemic may have caused selection bias during enrollment in the original NFBC 1986 population, although this factor applies to the entire cohort. The study results will be analyzed and interpreted in this context.

Benefits of the Study

By validating AMH levels in a large, population-based study, clinicians will be able to identify PCOM as part of PCOS diagnosis using a simple blood test. Thus, if TVUS is necessary only as a means to identify PCOM (rather than for other clinical reasons), this procedure can be replaced, thereby making the diagnosis of PCOM more accessible in a primary care setting. This would lead to much faster diagnoses for patients, as in some health care settings there would be no need to wait for referral, and only patients needing treatment for other specialized health care (eg, fertility, topical skin therapy, or psychological distress) would require referral to a specialist. This would also allow the common health impairments of the women affected to be viewed more holistically, rather than categorizing these women into an infertile population without further consideration of other adverse outcomes (eg, risk of developing type 2 diabetes mellitus or psychological distress). Testing AMH levels could also contribute to reducing missed diagnoses due to operator-dependent TVUS examinations. Following the validation of AMH levels in this study, we do not anticipate that PCOS guidelines will discard TVUS as a diagnostic method for PCOM, but rather advise that AMH testing be adopted as an alternative method.

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Data Availability

The data sets that will be generated or analyzed during this study will be available for academic research collaborations through the research group at the University of Oulu and the corresponding author on reasonable request. The Women's health study (WENDY) data can also be viewed [40].

Authors' Contributions

TP, DA, MH, JS, and RKA contributed to the study design and conception. TP and RKA acquired the data. TP, DA, MH, KB, JS, and RKA contributed to the data analysis and interpretation, provided critical review of the manuscript, and approved the final manuscript for submission.

Conflicts of Interest

TP received a research grant and honoraria from Roche, and fees or honoraria from Exeltis, MSD, Ferring, Gedeon Richter, and Organon. DA, JS, and MH are employees of Roche Diagnostics International Ltd. MH holds shares in F. Hoffmann-La Roche Ltd. KB is an employee of Roche Diagnostics GmbH. RKA has no competing interests.

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Abbreviations

AFC: antral follicle count
AMH: anti-Müllerian hormone
HA: hyperandrogenism
HARMONIA: Human Anti-Müllerian Hormone for Diagnosis of PCOS
NFBC: Northern Finland Birth Cohort
OA: oligoanovulation or anovulation
PCOM: polycystic ovarian morphology
PCOS: polycystic ovary syndrome
TVUS: transvaginal ultrasound

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Protocol

Let's Agree to Disagree on Operative Versus Nonoperative Treatment for Distal Radius Fractures in Older People: Protocol for a Prospective International Multicenter Cohort Study

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Abstract

Background: Distal radius fractures are the most frequently encountered fractures in Western societies, typically affecting patients aged 50 years and older. Although this is a common injury, the best treatment for these fractures in older patients is still under debate.

Objective: This prospective study aims to compare the outcome of operatively and nonoperatively treated distal radius fractures in the older population. Only patients with distal radius fractures for which equipoise regarding the optimal treatment exists will be included.

Methods: This prospective international multicenter observational cohort study will be designed as a natural experiment. Natural experiments are observational studies in which treatment allocation is determined by factors outside the control of the investigators but also (largely) independent of patient characteristics. Patients aged 65 years and older with an acute distal radius fracture will be considered for inclusion. Treatment allocation (operative vs nonoperative) will be based on the local preferences of the treating hospital either in Switzerland or the Netherlands. Hence, the process governing treatment allocation resembles that of randomization. Patients will be identified after treatment has been initiated. Based on the radiographs and baseline information of the patient, an expert panel of 6 certified trauma surgeons from 2 regions will provide their treatment recommendation. Only patients for whom the experts disagree on treatment recommendations will ultimately be included in the study (ie, for whom there is a clinical equipoise). For these patients, both operative and nonoperative treatment of distal radius fractures are viable, and treatment choice is predominantly determined by personal or local preference. The primary outcome will be the Patient-Rated Wrist Evaluation score at 12 weeks. Secondary outcomes will include the Physical Activity Score for the Elderly, the EQ questionnaire, pain, the living situation, range of motion, complications, and radiological outcomes. By including outcomes such as living situation and the Physical Activity Score for the Elderly, which are not relevant for younger cohorts, valuable information to tailor treatment to the needs of the older population can be gained. According to the sample size collection, which was based on the minimal

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important clinical difference of the Patient-Rated Wrist Evaluation, 92 patients will have to be included, with at least 46 patients in each treatment group.

Results: Enrollment began in July 2023 and is expected to continue until summer 2024. The final follow-up will be 2 years after the last patient is included.

Conclusions: Although many trials on this topic have previously been published, there remains an ongoing debate regarding the optimal treatment for distal radius fractures in older patients. This observational study, which will use a fairly new methodological study design, will provide further information on treatment outcomes for older patients with distal radius fractures for which to date equipoise exists regarding the optimal treatment.

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KEYWORDS

distal radius fracture; older patients; natural experiment; study protocol; observational study

Introduction

Distal radius fractures are the most common fractures encountered in Western societies, and they typically occur in patients aged 50 years and older [1,2]. Despite being so common, there remains an ongoing discussion on the best treatment for these fractures, especially in older patients, ranging from nonoperative treatment to complex surgery [3].

Previous studies have used varying definitions of "older people" and based this only on chronological age. However, the spectrum of physical demands and capabilities is wide among patients of the same age, which will likely be reflected in the satisfaction and outcome after treatment of distal radius fractures. Additionally, even frail patients may rely on a good function of the wrist to maintain independence if they, for example, require walking aids, and therefore need to fully weight bear on the upper extremity.

This study aims to compare the outcome of operatively and nonoperatively treated distal radius fractures in the older population by evaluating functional and radiological outcomes as well as range of movement, quality of life, and change in independence or living situation. By evaluating the quality of life and patient independency or living situation, we aim to gain more insight into outcomes after distal radius fracture in older patients while considering their individual functional demands.

Therefore, we have designed this study as a prospective international multicenter cohort study in which only patients with distal radius fractures for which equipoise regarding the optimal treatment exists will be included. The primary objective will be to compare clinical outcomes between older patients with distal radius fracture treated operatively and those treated nonoperatively.

Methods

Study Design

Although randomized controlled trials are generally considered the gold standard to investigate the effects of medical treatments, both patients and surgeons can have a strong preference for a certain treatment, which may limit the feasibility of a randomized controlled trial and therefore the generalizability of its results [4,5]. Provided possible incomparability of patients who receive different treatment modalities (ie, confounding) is adequately controlled for, observational studies could provide an alternative source of information.

A natural experiment design uses existing variation in treatment allocation (eg, due to practice variation). Natural experiments are observational studies in which treatment allocation is determined by factors outside the control of the investigators but also (to a large extent) independent of patient characteristics [6,7]. We assume the decisions regarding the treatment of distal radius fractures are largely influenced by the training of the treating surgeons. Since patients with a distal radius fracture generally visit the nearest hospital, treatment allocation is dependent on which surgeon is on call, which is likely independent on patient characteristics. Hence, the process governing treatment allocation arguably resembles that of randomization. Practice variation therefore provides an opportunity to conduct a natural experiment of the effect of operative versus nonoperative treatment of distal radius fractures. In order to further minimize the influence of patient characteristics on treatment decisions, a selection could be made of those patients for whom a panel of physicians disagree regarding the preferred treatment option (ie, for whom there clearly is a clinical equipoise). For these patients, both operative and nonoperative treatment of distal radius fractures are viable, and treatment choice is predominantly determined by personal or local preference.

This study is an international multicenter prospective observational cohort study for which patients will be identified after treatment has been initiated. Outcome data will be prospectively collected. Patients will be recruited from 5 hospitals in countries with a predominant preference for operative (Switzerland) and nonoperative treatment (the Netherlands).

Patient Population

Local investigators will review the list of patients seen in the emergency departments of the participating hospitals to identify eligible patients. The inclusion criteria are all patients 65 years and older with an acute (<14 days after injury) distal radius fracture treated at one of the participating hospitals.

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The exclusion criteria are no informed consent provided; patients transferred after initial operative treatment at a nonparticipating hospital; delayed presentation (>14 days after injury); insufficient follow-up (<12 months) or unavailable to follow-up due to residency in other hospital area; concomitant injury to the ipsilateral or contralateral upper extremity; cognitive impairment precluding answering questionnaires; non-German, non-English, and non-Dutch speaking; preexisting comorbidities that preclude operative treatment; pathological fractures; open fractures; and neurovascular injury requiring operative treatment.

Ethical Considerations

This study was approved by the ethics committee of Northwest and Central Switzerland (ID 2022-00142). It will be conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study has been registered on ClinicalTrials.gov (ID NCT05631314). The protocol was written in adherence to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline. A signed informed consent form is required prior to patient inclusion. The patients will be informed about the aim, content, and requirements of the study by the study leader or delegate either during an initial presentation or at a routine outpatient clinic appointment and will receive an information and consent form. The patients will be given the opportunity to ask questions and clarify any issues prior to giving their consent. No compensation or payments will be provided to project participants. Project data will be handled with the utmost discretion. They will be coded and a file to decode these data will be saved in the research folder only accessible by the principal investigator and project leaders.

Expert Panel

Following the identification of eligible patients and obtainment of informed consent, anonymous radiographs including key images of computer tomography scans if available, and baseline characteristics including information regarding comorbidities and activity levels (details below) will be made available on a secure web-based platform. This will allow the members of the panel to reach a "clinical" decision regarding their treatment recommendation. The panel will be blinded to the actual treatment received and the origin of the case.

The comorbidities, which will be reported to the experts, are cardiomyopathy including valvular disease, history of stroke or other brain injury with persistent neurological deficit, diabetes mellitus, cardiovascular disease, active malignancy, rheumatoid arthritis, and history of alcohol or drug abuse.

Additionally, the experts will be provided with information regarding the usage of the following medications: anticoagulant agents (vitamin K antagonists and new oral anticoagulants), immunosuppressants, and current chemotherapy.

The activity levels are independent, independent with support from family or district nurse or nursing home, and use of a walking aid prior to injury (no, walking stick, frame, and not mobile).

The expert panel will consist of 3 representatives from each "school." All panel members will be certified trauma surgeons. Half of them are generally in favor of conservative treatment ("school A"), while the others are generally in favor of operative treatment ("school B"). Patients will ultimately be included in the study if clinical equipoise is achieved, meaning 2 or more of the experts disagree with the rest of the panel. This is expected to result in 2 comparable groups for which clinical equipoise exists. The actual treatment the patient receives will continue as initially planned by the treating physician (see below).

Intervention

The decision whether operative or nonoperative treatment is chosen is left to the treating trauma surgeon as per the local standard of the participating hospital. Treatment will be initiated before the patient is approached for recruitment. Nonoperative treatment will consist of immobilization in a below the elbow cast for 4-6 weeks with or without prior closed reduction.

Operative intervention will be based on the treating surgeon's experience and preference. It will consist of open reduction and internal plate fixation using volar, dorsal, spanning or a combination of plates, or reduction (open or closed) and fixation with an external fixator with or without Kirschner wires. The participating hospitals in Switzerland will use the 2.4-mm distal radius plate system (Arthrex) for internal plate fixation. Perioperative management including anesthesia, antibiotics, and thromboembolism prophylaxis will follow the national guidelines. Postoperative care and immobilization will be decided by the treating surgeon. When possible, functional aftercare without immobilization will be allowed. Physiotherapy will be provided according to the local standards.

All patients (operative and nonoperative) will be reviewed in the outpatient clinic at 6 and 12 weeks as well as 1 year after treatment or surgery. In addition, patients will be contacted by phone 2 years after treatment or surgery.

Outcomes

Primary Outcome Measure

The primary outcome is the Patient-Rated Wrist Evaluation (PRWE) score measured at 12 weeks. This is a 15-item questionnaire that measures wrist pain and disability in activities of daily living. The score ranges from 0 to 100 with the best score being 0 [8,9].

Secondary Outcome Measures

Functional Outcome

Secondary functional outcome measures will include the PRWE at 1 year, Physical Activity Score for the Elderly, the Numerical Rating Scale for pain, and the EQ-5D-5L questionnaire. The Physical Activity Score for the Elderly is a questionnaire with multiple choice and open questions. The score combines information on household, leisure, and occupational activities. Based on duration, frequency, and intensity level of activities performed the previous week, a score is calculated ranging from 0 to 793, with higher scores reflecting more physical activity [10]. The EQ-5D-5L questionnaire is a questionnaire that measures general health status, with higher scores reflecting a better quality of life. It is based on 5 dimensions (mobility,

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self-care, usual activities, pain or discomfort, and anxiety or depression), which are rated on a scale with 5 levels. It also includes the EQ visual analogue scale for patients to state their self-rated health on a scale from 0 to 100, with 0 being the worst health imaginable [11]. The Numerical Rating Scale is a widely used scale to measure pain intensity, ranging from 0 (no pain) to 10 (worst pain imaginable) [4]. The living situation will be assessed at the first presentation, 6 weeks, 12 weeks, 1 year, and 2 years after injury. It will be defined as independent, independent with support from family, district nurse or similar, and nursing home. Range of motion of the wrist (dorsal extension, palmar-flexion, ulnar-, radial-abduction, pro-, and supination) as well as the finger-palm-distance will be assessed 12 weeks after injury. Additionally, the duration of surgery and the occurrence of intraoperative complications will be documented.

Complications

Complications will be assessed at every outpatient visit and after 2 years. They will include infection, nonunion, implant failure, complex regional pain syndrome, and any adverse event needing surgical intervention. For patients treated surgically, the need for implant removal will also be recorded. Infections will be defined according to the guidelines of The Centers for Disease Control and Prevention and subdivided into superficial incisional and deep infections. Deep infections will include both deep incisional and organ or space infections [5]. The diagnosis of complex regional pain syndrome is based on the Budapest clinical diagnostic criteria [12]. Nonunion is defined as a Radius union scoring system score greater than or equal to 6. It will be assessed 1 year after injury. The RUSS score evaluates union on dorso-volar and lateral radiographs by assigning a score of 0 to 2 on each cortex. Zero points are given if the fracture line is visible with no callus, 1 point if a callus is present but the fracture line is still visible, and 2 points if the fracture line is not visible and a bridging callus is present. In surgically treated cases, where the cortex is not visible due to the implant, a score of 0 is given to that cortex [13]. In case of doubt with regard to union, a computer tomography scan will be acquired. Patients with nonunion will be divided into 2 groups based on their symptoms (symptomatic vs asymptomatic).

Radiological Outcome

X-rays will be obtained as per standard hospital protocol at 6 and 12 weeks as well as 1 year after injury. The final radiological outcome will be determined 1 year after injury and will include union, radial inclination, volar tilt, carpal alignment, ulnar variance, and the presence and size of any step or gap in the articular surface.

Timeline and Recruitment

The recruitment procedure is visualized in Figure 1. The follow-up schedule for the patients and time point for the assessment of each outcome are listed in Table 1.

Figure 1. Flowchart of Patient Selection.

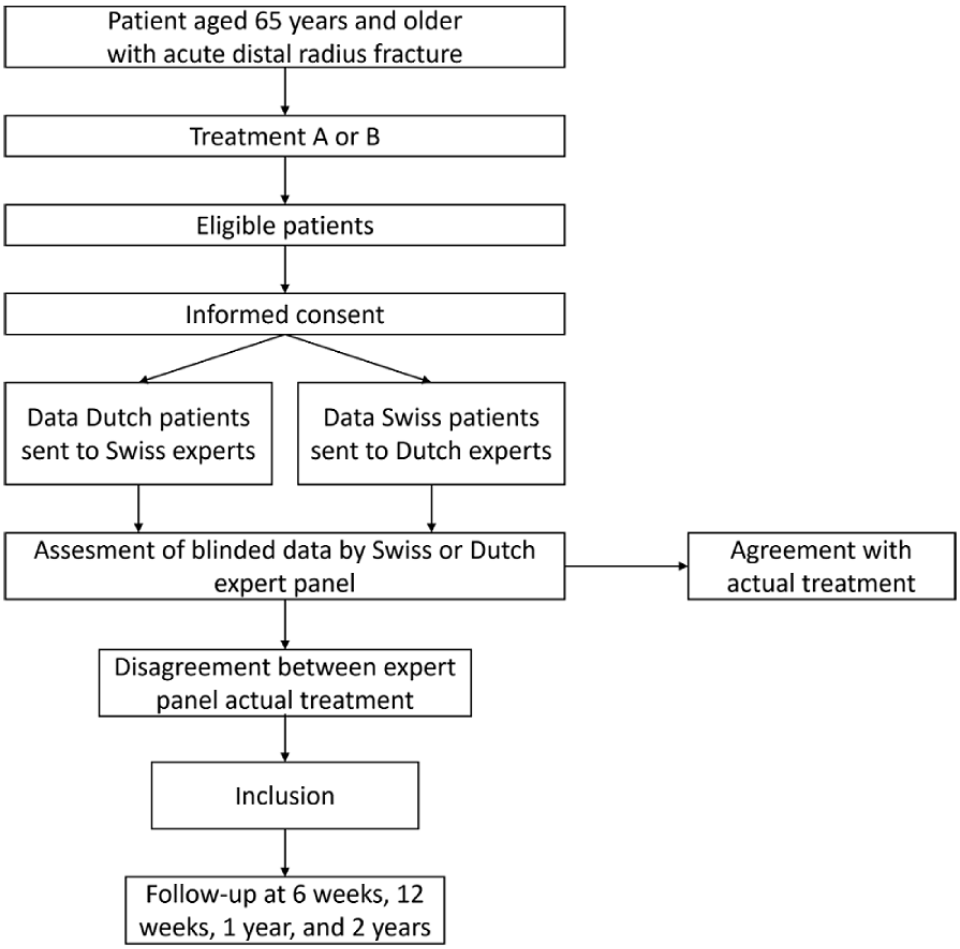

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Table 1. Outcome measures.

	First presentation	6 weeks	12 weeks	1 year	2 years
Outpatient clinic		✓	✓	✓	
X-ray	✓	✓			
PRWE[a]	✓		✓	✓	✓
PASE[b]	✓		✓	✓	✓
NRS[c] pain		✓	✓	✓	✓
ROM[d]			✓		
EQ-5D-5L	✓		✓	✓	✓
Complications		✓	✓	✓	✓
Living situation	✓	✓	✓	✓	

[a]PRWE: Patient-Rated Wrist Evaluation.

[b]PASE: Physical Activity Score for the Elderly.

[c]NRS: Numerical Rating Scale.

[d]ROM: range of movement.

Data Collection

In every participating institution, a project leader will fill in all the patient information in the secure web-based database on REDCap (Research Electronic Data Capture; Vanderbilt University). The original data will be collected from the institution's electronic patient records, the picture archiving and communication system, the different questionnaires, and pseudonymized prior to entry in the database.

Health care workers from the participating institutions will get access to REDCap, which enables centralized tracking of potentially eligible patients in compliance with the good clinical practice guidelines for electronic data collection. Every 2-4 weeks, this list of patients will be screened by the project leader, and explanatory and response variables will be entered on the study website. All data will be saved in a research folder that can only be accessed by the principal investigator and the project leader or leaders.

Sample Size Calculation

This study will be a noninferiority study, for which we assume that conservative treatment in older patients with a distal radius fracture is noninferior to operative treatment. The reason for choosing a noninferiority design is as follows. Operative treatment for distal radius fractures inherently exposes patients to additional risks of operation-related complications and costs. This is not the case for conservative treatment. If the study would demonstrate that both treatments are equal with regard to the primary outcome, it would automatically imply that patients should be treated with the lesser invasive treatment of the 2 (in this case, conservative treatment).

The sample size is based on the minimal important clinical difference of the PRWE score, which is 11.5 points (with an average SD 14). Using the minimal important clinical difference (11.5 points) as the noninferiority margin, a statistical significance threshold (α) of 5%, and a power of 90%, 32 patients per group are needed [14]. Taking into account a 30% loss to follow-up (due to the considerable age of the included study population), a total of 92 patients will have to be included, with at least 46 patients in each treatment group.

Statistical Analysis

The statistical software package SPSS (IBM Corp) will be used for analysis. All analyses will be performed according to the intention-to-treat principle. Multiple imputation will be used for missing values. Depending on their distribution, baseline characteristics will be described as means and SDs or median and IQR for continuous variables. Categorical variables will be reported as counts and percentages. Treatment groups will be compared using an independent Student *t* test (2-tailed) or chi-square test, as appropriate.

The primary outcome will be analyzed using a regression analysis with the 12 weeks PRWE score as dependent and treatment as independent variable. Potential confounders (notably age and fracture type) will be included as covariates in the model. Regression coefficients will be calculated with corresponding 95% CI. Regression analysis will also be used for analyzing the secondary outcomes with correction for the previously mentioned confounders.

Results

Patient enrollment started both in the Netherlands and Switzerland in July 2023. To date, 23 patients have given their consent in Switzerland and 59 in the Netherlands. The results of the first expert panel decisions are currently pending. Depending on the rate of equipoise, enrollment is expected to be completed after approximately 1 year. The final follow-up will be 2 years after the inclusion of the last patient.

Discussion

Despite many trials on this topic, the optimal treatment for distal radius fractures in older patients remains debated, and regional preferences continue to influence the treatment chosen. This

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provides the perfect situation to perform a natural experiment [6]. The Let's Agree to Disagree on Operative Versus Nonoperative radius study is a prospective international multicenter cohort study that will use a fairly new methodological study design [6]. One of the main benefits of this study design is that patients will be treated as per the local standards. We expect this to lead to high participation rates and prevent the negative effects of a learning curve. By limiting inclusion to those patients, for whom the expert panel disagrees on the treatment method, only those cases in which equipoise is attained are evaluated. We anticipate the 2 patient groups to be comparable as natural randomization based on geographical location will occur. Therefore, confounding is expected to be minimal. Additionally, multivariable analysis will be performed.

Many studies on the treatment of distal radius fractures in older patients have been published and yet no sound conclusion can be drawn. While some authors demonstrated a benefit of volar plating, others were unable to show a difference in functional outcomes between operative and nonoperative treatment [15-19]. Previous studies examined functional outcome based on patient-reported outcome measurements such as the PRWE score or Disabilities of the Arm, Shoulder, and Hand score. None of the studies used a score derived specifically for the older population or evaluated changes in independence or living situation despite the fact that these are very relevant issues for older patients. Additionally, information on the quality of life after treatment is lacking. This study aims to compare the outcome of surgically and nonoperatively treated distal radius fractures in older patients by not only evaluating functional and radiological outcomes but also quality of life and change in independency or living situation. Furthermore, a functional score that was specifically designed to assess the physical activity level of older patients will be used.

One limitation of this study to consider is the relatively new study design. The ratio of opposing opinions among the expert panel to define equipoise was set at 2:4. One could argue that a ratio of 1:5 or 3:3 might be a better choice. A previous study performed with ethical committee members examined which proportion of agreement on the merit of a new treatment was perceived by the members as ethically justifiable to perform a trial investigating the new treatment. This study showed a distribution of 1:4 to suffice for the members to deem the trial ethically justifiable [20]. Based on the findings of that study in combination with an equal number of experts from both regions, the ratio of 2:4 was chosen for this study.

In conclusion, this observational study, designed as a natural study, will provide valuable information on treatment outcomes for those older patients with distal radius fractures for which to date equipoise exists regarding the optimal treatment. By evaluating outcomes pertinent to the older population, such as quality of life and changes in living situation or independence, this study will help tailor treatment to the specific needs of older patients.

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Conflicts of Interest

None declared.

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Abbreviations

PRWE: Patient-Rated Wrist Evaluation
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial

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Protocol

Genomic, Proteomic, and Phenotypic Biomarkers of COVID-19 Severity: Protocol for a Retrospective Observational Study

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Abstract

Background: Health organizations and countries around the world have found it difficult to control the spread of COVID-19. To minimize the future impact on the UK National Health Service and improve patient care, there is a pressing need to identify individuals who are at a higher risk of being hospitalized because of severe COVID-19. Early targeted work was successful in identifying angiotensin-converting enzyme-2 receptors and type II transmembrane serine protease dependency as drivers of severe infection. Although a targeted approach highlights key pathways, a multiomics approach will provide a clearer and more comprehensive picture of severe COVID-19 etiology and progression.

Objective: The COVID-19 Response Study aims to carry out an integrated multiomics analysis to identify biomarkers in blood and saliva that could contribute to host susceptibility to SARS-CoV-2 and the development of severe COVID-19.

Methods: The COVID-19 Response Study aims to recruit 1000 people who recovered from SARS-CoV-2 infection in both community and hospital settings on the island of Ireland. This protocol describes the retrospective observational study component carried out in Northern Ireland (NI; Cohort A); the Republic of Ireland cohort will be described separately. For all NI participants (n=519), SARS-CoV-2 infection has been confirmed by reverse transcription-quantitative polymerase chain reaction. A prospective Cohort B of 40 patients is also being followed up at 1, 3, 6, and 12 months postinfection to assess longitudinal symptom frequency and immune response. Data will be sourced from whole blood, saliva samples, and clinical data from the electronic care records, the general health questionnaire, and a 12-item general health questionnaire mental health survey. Saliva and blood samples were processed to extract DNA and RNA before whole-genome sequencing, RNA sequencing, DNA methylation analysis, microbiome analysis, 16S ribosomal RNA gene sequencing, and proteomic analysis were performed on the plasma. Multiomics data will be combined with clinical data to produce sensitive and specific prognostic models for severity risk.

Results: An initial demographic and clinical profile of the NI Cohort A has been completed. A total of 249 hospitalized patients and 270 nonhospitalized patients were recruited, of whom 184 (64.3%) were female, and the mean age was 45.4 (SD 13) years. High levels of comorbidity were evident in the hospitalized cohort, with cardiovascular disease and metabolic and respiratory disorders being the most significant (P<.001), grouped according to the International Classification of Diseases 10 codes.

Conclusions: This study will provide a comprehensive opportunity to study the mechanisms of COVID-19 severity in recontactable participants.

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KEYWORDS

COVID-19; clinical research; multiomics; comorbidity; severity; electronic health record

Introduction

Background

COVID-19 has a wide spectrum of clinical severity, with approximately 60% of cases thought to be asymptomatic or mildly symptomatic and approximately 5% being critically ill [1]. A severe infection is characterized by respiratory and multiorgan failure [2]. There are several known demographic risk factors, such as age, male sex, diabetes mellitus, and obesity [3], and recently, high-risk genes and genetic variation have gained extensive attention [4-8]. Identifying further biomarkers that reflect the pathophysiology of the disease and aid clinical staff in recognizing COVID-19 severity is critical [9]. This would also help in the development of clinical management systems that can improve patient outcomes [10]. Early work focused on easily accessible laboratory indices, such as elevated C-reactive protein and D-dimer, among others, which have been helpful in the early management of high-risk patients [9,11]. These biomarkers are commonly recorded in electronic care records (ECRs), a technological development that allows the exchange of health information electronically, facilitating effective diagnosis, reducing medical errors, and providing safer care and research [12]. However, the limitations of routine laboratory biomarkers are well documented [13].

Early work also implicated angiotensin-converting enzyme 2 (ACE2) receptors and type II transmembrane serine protease in viral entry [14,15]. A recent genome-wide association study of 2000 critically ill patients [5] identified dipeptidyl peptidase 9, tyrosine kinase 2, and the antiviral restriction enzyme activators OAS1, OAS2, OAS3. To date, singleomic approaches have been used to identify genomic markers of COVID-19 severity [5,16-18]. Here, we seek to use multiomics analysis using 2 tissue types (blood and saliva) in combination with comprehensive ECRs and self-reported data to build one of the most extensive pictures yet.

Study Aims and Overview

The COVID-19 Response Study (COVRES; NCT05548829) aims to carry out an integrated multiomics analysis of factors contributing to host susceptibility to SARS-CoV-2 among a patient cohort of 1000 people from the geographically isolated island of Ireland. Because of differences in site, governance, and timelines, the protocol in the subsequent section describes the study to be carried out in Northern Ireland (NI-COVRES) by Ulster University and the Western Health and Social Care Trust (WHSCT) only. The Republic of Ireland component (Trinity College Dublin and St James Hospital Dublin) will be described separately.

Figure 1 shows an overview of the main stages and timeline with data for each participant (n=519) on the following: (1) disease status, (2) genome analysis, (3) transcriptome analysis, (4) proteome analysis, (5) methylome analysis, (6) microbiome analysis, (7) immune response, (8) patient history, (9) mental health, and (10) ECR and prospectively on 40 participants at 1, 3, 6, and 12 months postpositive polymerase chain reaction (PCR) analysis to assess persistent inflammatory and immune responses.

Figure 1. Stages of the COVID-19 Response Study implementation. ECR: electronic care record; NGS: next generation sequencing; QC: quality control; WGS: whole genome sequencing.

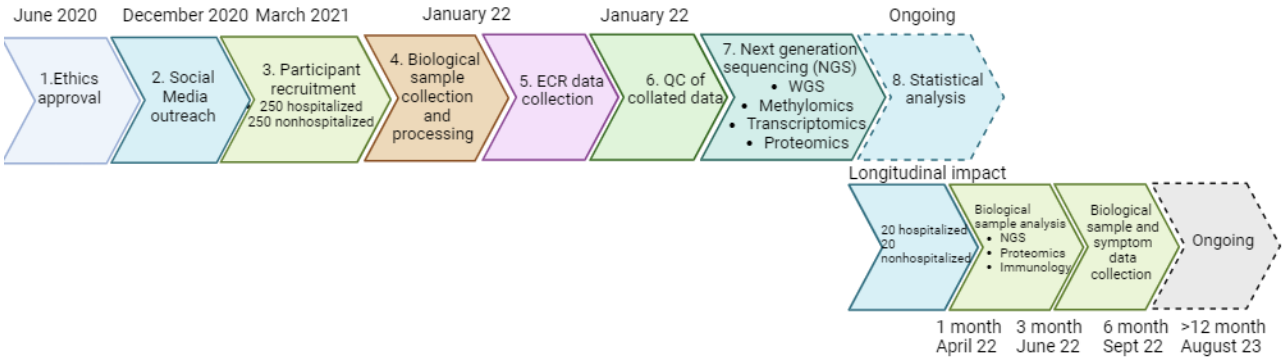

Methods

Status and Timeline of the Study

The main retrospective Cohort A recruitment commenced in December 2020 and was completed in March 2021 (trial registration; NCT05548829), except for the prospective Cohort B (ongoing). Integration of ECR record data was completed in January 2022 at the time of writing, and omics samples are being processed (Figure 2).

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Figure 2. Overview of the COVID-19 Response Study sample processing work flow. ECR: electronic care record; FBC: full blood count; GHQ-12: 12-item General Health Questionnaire; HLQ: Health Life Style Questionnaire; MSD: Meso Scale Discovery; PBMC: peripheral blood mononuclear cell; PCR: polymerase chain reaction; TCR: T-cell receptor; QC: quality control; WGS: whole genome sequencing.

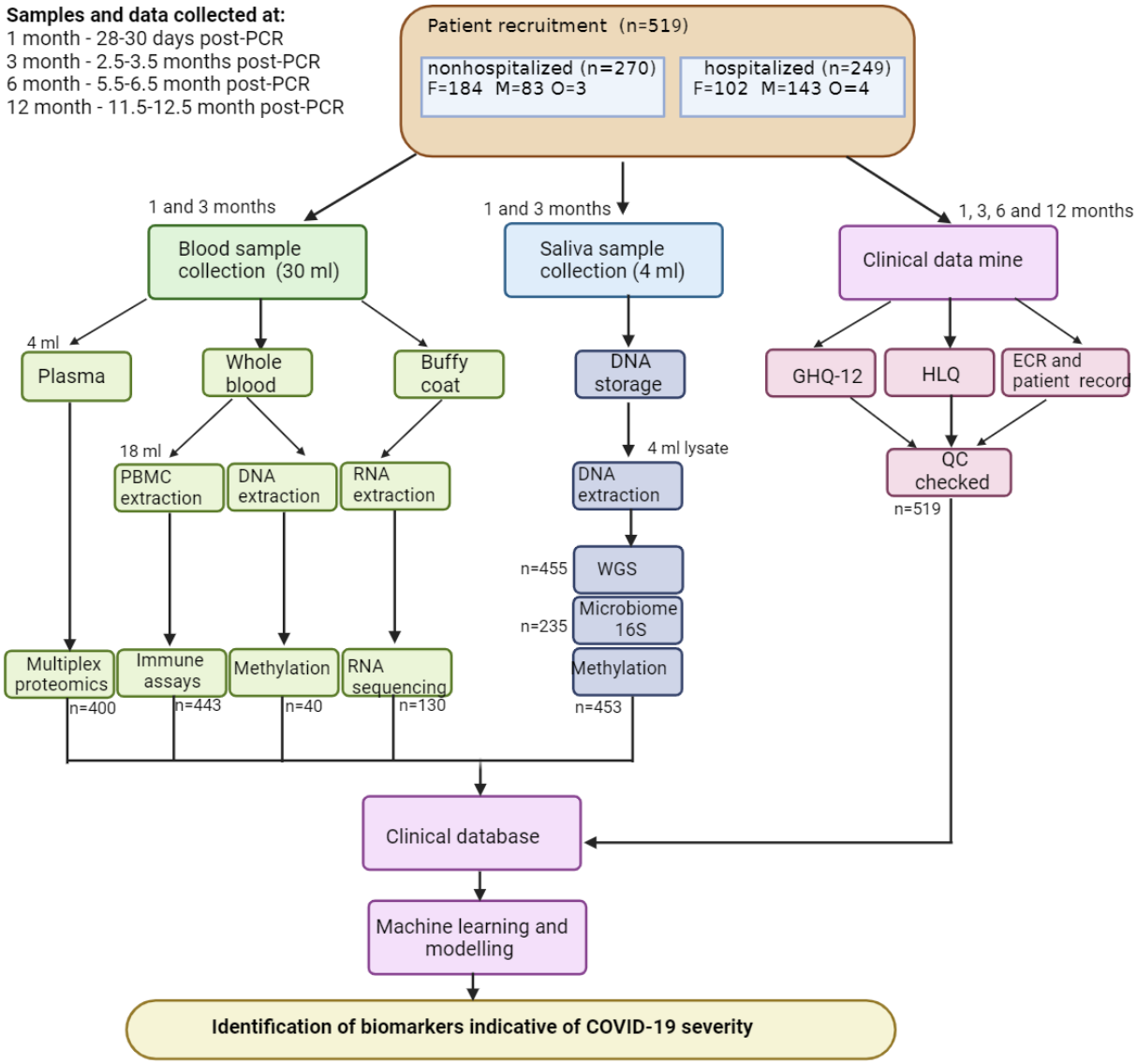

Ethical Considerations

Standard operating procedures and participant response questionnaires included standard operating procedures for saliva sample kit preparation, blood collection and processing, downstream sample processing, website management, data protection and participant contact. The COVRES was subsequently approved by the Health and Care Research Wales Ethics Service on July 14, 2020 (Research Ethics Committee ref 20/WA/0179). All the participants provided informed consent to participate.

Social Media Outreach

Social media content (on Twitter [subsequently rebranded X; Twitter, Inc] and Facebook [Meta Platforms, Inc]) and web page visuals were designed, with input from recovered patients, by the project principal investigators, including a range of infographics and short explanatory texts. Information was circulated to local and national news outlets (television, radio, and newspapers) across NI for recruitment purposes. Interested patients contacted the research team and were sent a patient information sheet. Appointments were then organized at least 24 hours later to obtain informed consent and samples.

Participant Recruitment With Inclusion and Exclusion Criteria

Inclusion criteria: patients had to be aged >18 years but could have any BMI or ethnic origin. Exclusion criteria: patients were excluded if they were aged <18 years and had any intellectual disabilities. Hospitalization status was determined if a patient attended or was admitted to the hospital within 14 days of a positive PCR result. Patients were also classified based on the World Health Organization (WHO) scale [19], which reflects severity over the duration of the patient's infection, regardless

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of hospitalization status. For example, a patient may have an overall WHO score of 5 and be classified as nonhospitalized as they attended the hospital >14 days from their positive PCR result. After receiving a participant information sheet, patients interested in participating provided written informed consent and were enrolled in the study. A self-report questionnaire established demographic information, lifestyle choices, family history of clinical disorders, and COVID-19 severity and symptoms. This was followed by a 12-item general health questionnaire to help ascertain the patient's mental health after the COVID-19 infection (Figure 2). This data was securely digitalized onto a bespoke database, CovresNIdb, generated on the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [19], to comply with the terms of the ethical considerations, the Human Tissue Act 2004, and general data protection regulations. This process is being repeated for Cohort B (prospective), consisting of 40 participants with stricter timelines followed (1, 3, 6, and 12 mo).

Biological Sample Processing

The WHSCT recruitment team coordinated sample collection appointments at hospital wards, Clinical Translational Research and Innovation Centre clinic rooms, or home visits. Participants and related study code numbers were predetermined depending on hospitalization and logged into encrypted clinical data sheets on a secure server to ensure full data traceability. All whole blood and saliva processing carried out includes recruitment numbers, sample collection types, sample processing, and downstream analysis; n numbers refer to patient numbers for specific omics analyses.

Isolation was carried out in a Category III containment hood with full personal protective equipment. Samples were not deactivated upon receipt or before processing. The participants provided 3×10 mL of whole blood and 2× saliva samples of approximately 2 mL each (Figure 2). Blood was extracted using 21G Vacuette safety needles (Greiner Bio-One Ltd, Gloucestershire) into 3×10 mL ethylenediaminetetraacetic acid–coated Vacuette tubes and centrifuged at 4000 rpm (4 °C) for 15 minutes. The buffy coat was extracted, washed, and stored for RNA sequencing (Figure 2). All samples were frozen at −80 °C; the time to freeze was <2 hours, and none showed signs of hemolysis. Saliva was collected using 1×DNA Genotek (DNA Genotek, Ottawa), Oragene DNA (OG-500), and 1×RNA (CP-190) collection tubes per participant. Samples were considered deactivated once lysed. Peripheral blood mononuclear cells were isolated using the Ficoll gradient separation methods as per [20].

Immune Assays

Whole blood was analyzed at 1 and 3 months post–positive PCR tests. Using the FACSAria III high-speed cell sorter (Becton Dickinson, Oxford, United Kingdom, software version 9) with an 85-µm nozzle fitted, whole blood and peripheral blood mononuclear cell samples were stained for T, B, and natural killer cell populations using CD45 PerCP-Cy5.5, CD3 FITC, CD8 APC-Cy7, CD4 PE-Cy7, CD19 APC, and CD16+CD56 PE (BD Biosciences) before erythrocyte lysis by PharmLyse (BD Biosciences) according to the manufacturer's instructions. T-cell subpopulations were measured using 2 defined panels: panel 1: CD3 FITC, CD4 PE-Cy7, CD8 BV605, CD30 APC, CD45RA V450, CD45RO BV786, and CD183 BB700; panel 2: CD3 FITC, CD4 PE-Cy7, CD8 BV605, CD69 APC, CD45 V450, CD127 BV786, CD152 BB700, CD25 R718, and FoxP3 PE. Cell surface staining was performed before fixing, permeabilizing, and FoxP3 labeling using the Transcription Factor Buffer Set (BD Pharmingen).

DNA Isolation

Saliva samples (whole-genome sequencing [WGS], methylome, and microbiome) were incubated for 2 hours at 56 °C, followed by DNA isolation using PrepIT L2P (DNA Genotek). DNA from whole blood (methylome) was isolated using the DNA Blood 200,360 prefilling H96 Kit (CMG-717, PerkinElmer), and 200 µL of whole blood on the Chemagic 360 system (PerkinElmer) was used. Microbial DNA was extracted from saliva aliquots using a modified protocol from Teng et al [21] using the DNeasy Blood and Tissue Kit (Qiagen). All extracted DNA was evaluated using the Qubit 3.0 fluorometer (Thermo Scientific) and the Nano Drop 1000 spectrophotometer (Thermo Scientific) and sequenced using the Invitrogen Quant-iT PicoGreen dsDNA Assay Kit (P7589) on the Hamilton Microlab Star before storage at −80 °C.

RNA Isolation

RNA was isolated from saliva using the Oragene RNA purification protocol and Qiagen RNeasy Micro Kit (Qiagen), and RNA was extracted from whole blood using the Chemagic 360 system (PerkinElmer) with the Chemagic RNA tissue 360 H96 Kit (CMG-1212). Purity and quantity were assessed, as described in the preceding section for DNA, but with the Invitrogen Quant-iT RiboGreen Assay Kit (R11490). Integrity (RIN) was determined using the Agilent 4200 TapeStation and the RNA ScreenTape (5067-5366), before storage at −80 °C.

Clinical Data

Self-Reported Data on Physical and Mental Well-Being

All participants completed 2 surveys as part of the trial. The 12-item general health questionnaire is a self-administered screening tool designed to detect current mental state disturbances in primary care settings; a score of ≥2 indicates a disorder. The health and lifestyle questionnaire is a survey tool designed by Ulster University to capture key health-related data not present in the ECR. The fields included COVID-19 risk factors, medications, comorbidities, hospitalization information, symptoms at admission, laboratory tests, family history, drinking status, and occupation. The same protocol is being followed for all prospective appointments (ongoing).

Clinical Database Development

The participants' consent forms, as well as data from the self-reported questionnaires, but with all personally identifiable information removed by the project's data controller as per general data protection regulations guidelines, were also recorded in the CovresNIdb database. The data were subjected to quality control (QC) by 2 independent researchers against the original sources. The same protocol is being followed for all prospective appointments (ongoing).

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Electronic Care Records

In addition to the self-reported data, consent was also provided by each patient to enrich the database by accessing their NI Electronic Care Record information held by the National Health Service. PCR positive dates, severity (hospitalized because of COVID-19 infection or recovered from COVID-19 infection at home), laboratory results (full blood count, blood pressure, lipids, C-reactive protein, glomerular filtration rate, and troponin), treatment administered, drugs prescribed within the last 6 months, and comorbidity and multimorbidity were recorded for each patient.

Omics Analyses

Genome Analysis

Whole-genome library preparation was performed using the Illumina TruSeq PCR Free Library Prep protocol (20015963) with an input amount of 1 µg on a Hamilton next-generation sequencing Star robotic workstation, and quality was assessed using the Roche KAPA Library Quantification Kit (7960298001) before pooling and sequencing (150bp PE) on an Illumina NovaSeq 6000 instrument using NovaSeq 6000 S4 Reagent Kit v1.5 (20028312), with a mean coverage of 30× as described previously [22]. Sequences are being uploaded to the European Genome-phenome Archive (EGA).

Methylome Analysis

Methylation analysis was performed on DNA samples from saliva (n=450) and whole blood (n=40) using the Illumina Infinium Methylation EPIC, largely as described previously [22]. Data were adjusted for known epigenetic covariates, and surrogate variable analysis was performed via the *sva* inference module [23]. Our in-house-developed tool, CandiMeth [24], will be used to streamline the methylation analysis of gene lists of interest.

Transcriptome Analysis

RNA sequencing library preparation was performed using the Illumina TruSeq Stranded Total RNA Library Prep Globin Kit (20020612) with an input amount of 100 to 1000 ng. Library preparation was automated and processed using a Hamilton next-generation sequencing Star, and quality was assessed using the Roche KAPA Library Quantification Kit (7960298001) and GX Caliper HS Assay (CLS 760,672, 760,517), run on Roche Lightcycler 480 II and PerkinElmer LabChip GX Touch analyzers, respectively. Libraries were pooled and sequenced (75bp PE) on an Illumina NovaSeq 6000 instrument using NovaSeq 6000 S2 Reagent Kit v1.5 (20028314), targeting 50M paired reads. Raw data binary base call format was demultiplexed and converted to the FASTQ format using BCL2FastQ (Illumina). Adapters were trimmed using Skewer [25], and QC was assessed using FASTQC. Spliced Transcripts Alignment to a Reference [26] was used to align reads to the reference genome (GRCh38/hg38) as well as to the transcriptome (version 25; GENCODE). The quality of the RNA alignment was assessed using Picard QC. Gene and isoform quantification will be performed using RNA-Seq by Expectation-Maximization [27], with prospective patient (1 and 3 mo) T-cell receptor sequencing completed following flow cytometry.

Microbiome Analysis

16S ribosomal RNA gene amplicons for sequencing by the Illumina MiSeq system (Illumina) were prepared using the V3 and V4 regions as described by Klindworth et al (2013), with sequencing performed in-house.

Proteome Analysis

Protein analysis of 400 plasma samples (baseline; 186 nonhospitalized and 214 hospitalized), 40 prospective (20 nonhospitalized and 20 hospitalized; 1 and 3 months postinfection), was outsourced to OLINK proteomics (OLINK, Uppsala, Sweden) using the Explore 384 Inflammation panel (Protein Proximity Extension Assay). Ethylenediaminetetraacetic acid plasma samples were thawed at room temperature (20 °C), and 45 µL of each plasma sample was (at random) pipetted into a LightCycle 480Multiwell Plate 96-well white PCR plates (product no. 04729692001; Roche Molecular Systems Inc) with 8 × wells left empty on each plate for internal controls to be added at OLINK. The samples were inactivated as per OLINK's protocol and shipped on dry ice (CO2, −78 °C). Only samples above 0.2 Normalized Protein eXpression and samples that deviated less than 0.3 Normalized Protein eXpression passed QC.

The Meso Scale Discovery plasma multispot assay system comprising V-PLEX COVID-19 serology panel 11, *total IgG*, and *ACE2 neutralization* assays was used to determine viral variant prevalence. Samples were prepared at 1:10 (ACE2) and 1:5000 (neutralization) for specific assays and then treated as described in [28].

The Roche COBAS Elecsys SARS-CoV-2 spike (S) protein receptor binding domain assay was used to determine SARS-CoV-2 antibody presence as per manufacturer's instructions.

Statistics

Univariate and Multivariate Analysis

Only patients from Cohort A (n=507) who had their BMI recorded in the database were selected for the odds ratio analysis. We considered the following risk factors: sex, age, BMI, and disease subgroups. First, univariate analyses (Fisher exact test) were performed to identify risk factors associated with COVID-19 severity.

P values for univariate analyses were generated using the Fisher exact test to compare the frequencies of each potential risk factor between nonhospitalized and hospitalized participants. Variables with a *P* value <.001, that is, sex, age <50 years and >50 years, and cardiovascular, respiratory, endocrine, and musculoskeletal comorbidities, were considered clinically relevant and entered into the multivariable logistic regression model. This and further analysis are being undertaken on Base-R software (R Project for Statistical Computing; version 4.2.2) using the Visdat library.

Demographics Table

The demographic table of the COVRES data (n=519) was generated using IBM SPSS Statistics for Windows (version 27; IBM Corp) [29]. Statistical analysis for the contingency table

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was undertaken using a Fisher exact 2-sided test to obtain the required *P* values, and CI rates were set at 95%.

Bioinformatic Analyses

Bioinformatic analyses will focus on using computational approaches to identify genomic, transcriptomic, proteomic, and clinical correlates of severity. Planned analyses primarily include the identification of clinical features, gene variants (host) or Expression quantitative trait loci, transcriptomic signatures, and cytokine profiles associated with disease severity, as well as the differential methylation among the host genomes of the severity groups.

Variant calling will use mathematical models from the Best Practices Genome Analysis Toolkit. Data are being stored according to genomic position in the Genuity Science Genomically Ordered Relational Database to facilitate rapid access by the Clinical Sequence Analyzer user interface and Sequence Miner visualization software. Initial data processing for methylome analysis will be carried out in *GenomeStudio* (version 3.2; Illumina) before the import of idat files into the RnBeads package [30] using RStudio (version 2022.02.0+443) on the R platform (version 4.1.2). QC will be performed using the *greedycut* algorithm, which involves the removal of probes with missing values and poor quality. For RNA-seq, gene and isoform quantification will be performed using RNA-Seq by Expectation-Maximization [27] before further analysis is carried out. 16S ribosomal RNA analysis has been previously described (refer to the preceding section), and OLINK data will be processed in R as per standard pipelines. WGS and transcriptomics data are to be deposited in the EGA pending and shared in collaboration with the International COVID-19 Host Genetics Initiative.

Results

Retrospective Cohort A Demographics

The main demographic characteristics are summarized in Table 1.

Table 1. COVID-19 Response Study Cohort A demographic information.

Cohort A demographics	Nonhospitalized (n=270)	Hospitalized (n=249)	Total (n=519)	*P* value[a]
Sex, n (%)				
Female	184 (64.3)	102 (35.7)	286 (55.1)	<.001
Male	83 (36.7)	143 (63.3)	226 (43.5)	<.001
Other	3 (42.9)	4 (57.1)	7 (1.3)	.72
Age (y) at diagnosis				
Age, mean (SD)	45.4 (13)	56.5 (12.7)	50.7 (14)	<.001[a]
<50, n (%)	169 (62.6)	67 (26.9)	236 (45.5)	<.001
>50, n (%)	101 (37.4)	182 (73.1)	283 (54.5)	<.001
Disease subgroup, n (%)				
Autoimmune[b]	12 (4.4)	26 (10.4)	38 (7.3)	.01
Metabolic[c]	33 (12.2)	94 (37.8)	127 (24.5)	<.001
Respiratory[d]	39 (14.4)	83 (33.3)	122 (23.5)	<.001
Cardiovascular[e]	32 (11.9)	100 (40.2)	132 (25.4)	<.001
Cancer[f]	7 (2.6)	21 (8.4)	28 (5.4)	.003
Gastrointestinal[g]	13 (4.8)	21 (8.4)	34 (6.6)	.11
Musculoskeletal[h]	23 (8.5)	58 (23.3)	81 (15.6)	<.001

[a]*P* value calculated using 2-sided Fisher exact test between nonhospitalized versus hospitalized patients. *P*<.05 was set as statistically significant (n=519); continuous variables used a 2-sided *t* test.

[b]Autoimmune or rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

[c]Metabolic and endocrine diseases including thyroid conditions, hypercholesterolemia, or other hyperlipidemia, gout, diabetes, and kidney disorders.

[d]Respiratory disorder and chronic lung diseases including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, sleep apnea, and pulmonary hypertension.

[e]Cardiovascular system disorders including angina, hypertension, stroke, peripheral vascular disease, balloon angioplasty or percutaneous coronary intervention, atrial fibrillation, venous thromboembolism, anemia, and chronic cardiac diseases other than hypertension.

[f]Cancer including leukemia, lymphoma, and malignant solid tumors, and to include current, past, and remission.

[g]Gastrointestinal disorders including gallbladder, liver disease, pancreatic disease, and Inflammatory bowel syndrome.

[h]Musculoskeletal diseases including osteoarthritis and ankylosing spondylitis, excluding subgroup 1 conditions.

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As expected, there was a significant difference in the mean age between hospitalized and nonhospitalized patients, as well as between sexes (both *P*<.001). Age bias was also evident, with 62.6% (169/270) of patients aged <50 years in the nonhospitalized subgroup (*P*<.001) and 73.1% (182/249) of patients aged >50 years in the hospitalized subgroup (*P*<.001). As expected, comorbidity incidence was higher in the hospitalized subgroup than in the nonhospitalized subgroup, with autoimmune (12/270, 4.4% nonhospitalized and 26/249, 10.4% hospitalized; *P*<.001), metabolic (33/270, 12.2% nonhospitalized and 94/249, 37.8% hospitalized; *P*<.001), respiratory (39/270, 14.4% nonhospitalized and 83/249, 33.3% hospitalized; *P*<.001), cardiovascular (32/270, 11.9% nonhospitalized and 100/249, 40.2% hospitalized; *P*<.001), and musculoskeletal (23/270, 8.5% nonhospitalized and 58/249, 23.3% hospitalized; *P*<.001) disorders of note. There were no differences between the cohorts for gastrointestinal disorders (Table 1).

Prospective Cohort B Demographics

Data collection is ongoing for 40 participants who are being followed up over 12 months: 20 (8/20, 40% female) hospitalized and 20 nonhospitalized (12/20, 60% female); sex distribution is not significantly different between subgroups (*P*=.21) but average age is (hospitalized: mean 52, SD 17.2 years; nonhospitalized: mean 45.2, SD 13.5 years; *P*<.001; Table 2).

In contrast to the initial recruitment, within this follow-up Cohort B, there was no age bias toward participants older than 50 years (*P*=.20). There was also no significant difference in vaccination status between hospitalization subgroups (*P*=.55), and only cardiovascular disease as a comorbidity was more prevalent in hospitalized patients (*P*=.02), although the numbers are small.

Table 2. COVID-19 Response Study Cohort B multivariate analysis of hospitalized versus nonhospitalized patients analyzing risk factors for COVID-19 severity.

Prospective Cohort B demographics	Nonhospitalized (n=20)	Hospitalized (n=20)	Total (n=40)	*P* value[a]
Female, n (%)	12 (60)	8 (40)	22 (50)	.21
Age (y) at diagnosis				
Age, mean (SD)	45.2 (13.5)	52 (17.2)	48.6 (15.6)	<.001[b]
>50, n (%)	7 (35)	11 (55)	18 (45)	.20
Vaccine status, n (%)	19 (95)	18 (90)	37 (93)	.55
Comorbidity, n (%)				
Autoimmune[c]	3 (15)	6 (30)	9 (23)	.26
Metabolic[d]	4 (20)	9 (45)	13 (33)	.91
Respiratory[e]	2 (10)	7 (35)	9 (26)	.58
Cardiovascular[f]	2 (10)	11 (55)	13 (33)	.02
Cancer[g]	0 (0)	4 (20)	4 (10)	.35
Gastrointestinal[h]	2 (10)	4 (20)	6 (15)	.38
Musculoskeletal[i]	3 (15)	7 (35)	10 (25)	.14

[a]*P* value calculated using 2-sided Fisher exact test between nonhospitalized versus hospitalized patients. *P*<.05 set as statistically significant (n=40); continuous variables used a 2-sided *t* test.

[b]Inclusion criteria for analysis: participants (n=40) were required to have a BMI score recorded.

[c]Autoimmune or rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

[d]Metabolic and endocrine diseases including thyroid conditions, hypercholesterolemia, or other hyperlipidemia, gout, diabetes, and kidney disorders.

[e]Respiratory disorder and chronic lung diseases including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, sleep apnea, and pulmonary hypertension.

[f]Cardiovascular system disorders including angina, hypertension, stroke, peripheral vascular disease, balloon angioplasty or percutaneous coronary intervention, atrial fibrillation, venous thromboembolism, anemia, and chronic cardiac diseases other than hypertension.

[g]Cancer including leukemia, lymphoma, and malignant solid tumors, and to include current, past, and remission.

[h]Gastrointestinal disorders including gallbladder, liver disease, pancreatic disease, and Inflammatory bowel syndrome.

[i]Musculoskeletal diseases including osteoarthritis and ankylosing spondylitis, excluding subgroup 1 conditions.

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Discussion

Principal Findings

The COVRES provides a novel opportunity to identify multiomics biomarkers from blood and saliva indicative of COVID-19 severity in NI and may provide unique insights into disease mechanisms and identify potential therapeutic targets. The maximum recruitment number (n=519) was reached, and various analyses are ongoing, including WGS and RNA sequencing, proteomic, microbiome, and methylation experiments. We have also collected detailed medical data using the NI Electronic Care Record that will be used to enrich the biomarker data [31]. All Cohort A participants were recruited over a 4-month period (December 1, 2020-March 31, 2021) during the pandemic peak, allowing homogeneous data collection from the same viral variant (B.1.1.7; Figure 1). Compared with other studies, the COVRES has a higher participant number and uses a significantly wider biomarker identification approach. This was achieved while significant pandemic restrictions were in place and was only possible because of our local health trust (WHSCT, National Health Service) collaboration, which facilitated patient access and enabled the recording of laboratory parameters that have not been possible in other studies [32]. A recent multiomics COVID-19 study used proteomics and metabolomics to screen 13 samples at 2 time points and found 10 significant proteins, 32 significant peptides, and 5 metabolites that were dysregulated in severe patients [33]. Recruitment for this study also occurred in early 2021, but the small sample size (n=13) brings into question the generalizability of the findings. Another multiomics study based in the United States sampled 128 individuals between April 6, 2020, and May 1, 2020, and conducted follow-up until June 2020. The authors quantified transcripts, proteins, metabolites, and lipids and made associations with clinical outcomes [34]. Links were made between platelet function, blood coagulation, endotheliopathy, and COVID-19 severity. Our study builds on these smaller studies and may offer increased statistical power and the potential to validate or compare the markers identified.

The COVRES was designed to recruit hospitalized (n=250) patients with COVID-19, classified as having a severe infection, and nonhospitalized (n=250) patients with COVID-19, classified as having a mild infection, within 3 months of sampling. It is worth noting that the recruitment of nonhospitalized patients with COVID-19 makes this cohort particularly valuable, as most trials have only involved patients who have been admitted to the hospital or those who have not [35,36], and few have investigated earlier stages of the disease process, such as preexposure or postexposure and outpatient treatment.

To maximize the impact and benefit to the scientific and health care communities, this study was designed to be cross-border, covering both NI and the Republic of Ireland. The global drive to identify clinical biomarkers of COVID-19 severity has led to many clinical studies and trials that have varied methodologies regarding different control groups, follow-up periods, omics of interest, and laboratory methodologies [37-39]. Studies have also been carried out in different geographic regions without any standardized operating procedures and have been powered according to different end points [40]. This variation makes reproducibility questionable, and it is difficult to apply the findings across geographic regions and variant periods. To align with as many studies as possible, COVRES participants have been classified according to the WHO [41], and to facilitate cross-border collaboration, we coordinated with Trinity College Dublin. We also plan to share our WGS data with the EGA for the advancement of science and improved public health outcomes.

The recruitment of nonhospitalized and hospitalized patients with COVID-19 in NI is the main strength of the COVRES and adds novelty to existing research regarding COVID-19 severity, with the majority recruiting patients based on a positive PCR test result regardless of hospitalization. Sex and age matching was considered, but an exact match was not achieved because of the complexities and limitations of COVID-19 presented regarding patient access [5]. The mean age of the hospitalized COVRES subgroup was 56.5 years (Table 1), which was slightly younger compared with a large UK-wide observational study [42] (20,908 hospitalized), which had a mean age of 62 years. There was no difference between sex (male 49%, female 51%), compared with our sample comprising 43.5% (226/519) men. Another smaller (n=429) UK study found the average age of hospitalized patients with COVID-19 to be 70 years and a male bias of 57%, which is close to our study. Corresponding with our study, they also found the average BMI to be 28 kg/m^2 (overweight-obese) and highly comorbid (Table 2), with the most common comorbidities being type-2 diabetes, hypertension, and respiratory disorders [42,43]. A previous study [43] in England is a good comparison for COVRES NI, as the recruitment protocols and cohort demographics are similar. The similarities in the data are promising and may indicate that our findings could be useful to the wider United Kingdom.

Limitations

COVRES participants were all sampled at a single time point, limiting our ability to assess genomic, proteomic, and immune biomarkers as the disease progresses. Future work will focus on obtaining follow-up samples to enable longitudinal analysis and assess the prognostic capability of markers of interest. Manual data input at some points increases the risk of human error [44], and although QC checks were carried out between 2 WHSCT staff members, there is an inherent risk of incorrect data.

It also needs to be considered that the COVRES cohort represents a COVID-19 population recruited in NI, and the demographics show a low representation of ethnic minority groups; therefore, data may not be able to be generalizable beyond White Irish and UK populations.

Conclusions

The COVRES offers a novel opportunity to study the multiomics mechanisms of COVID-19 severity in recontactable participants. This research has the potential to impact COVID-19 clinical decision-making and therapeutic development. Our WHSCT and industry collaborators enabled rapid and effective

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recruitment, allowing us to reach our goal of 500 participants and begin the analysis pipelines immediately. We hope that this paper will not only demonstrate the effectiveness of the study methodology but also raise awareness of the availability of this cohort among researchers in the field and promote future collaboration.

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Data Availability

Data and metadata will be stored according to the Ulster University policy on data management and sharing. Data will be available via Ulster University's Research Data Repository and in accordance with their Research Data Management Policy. Any personal and identifiable information will be redacted, and data queries will be addressed on an individual basis by the research team. Genomics data are being deposited in the European Genome-phenome Archive and will be available upon request.

Authors' Contributions

AE contributed to investigation, formal analysis, writing, resources, and supervision; DM, EC, BW, REI, M Bhavsar, SDZ and PS contributed formal analysis and data curation; SML contributed formal analysis and investigation; JM contributed to investigation, formal analysis and writing; MK and M Bhavsar contributed to conceptualization and project administration; VM contributed to conceptualization, project administration and supervision; TSR contributed to conceptualization, project administration, supervision, and funding acquisition; AJB contributed to conceptualization, project administration, supervision, funding acquisition and resources; EM contributed to conceptualization, project administration, supervision, and funding acquisition; DSG and CW contributed to conceptualization, project administration, supervision, funding acquisition, resources, and writing.

Conflicts of Interest

None declared.

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Abbreviations

ACE2: angiotensin-converting enzyme 2
COVRES: COVID-19 Response Study
ECR: electronic care record
EGA: European Genome-phenome Archive
NI: Northern Ireland
PCR: polymerase chain reaction
QC: quality control
REDCap: Research Electronic Data Capture
WGS: whole-genome sequencing
WHO: World Health Organization
WHSCT: Western Health and Social Care Trust

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Protocol

Development and Evaluation of a Community Health Program to Promote Physical Activity Among Vulnerable Community-Dwelling Older Adults: Protocol for a Prospective Cohort Study

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Abstract

Background: Vulnerable older adults have a high risk of morbidity and mortality. Regular physical activity (PA) can have a positive effect on the health and health-related behavior of this specific target group. However, evidence of the impact and feasibility of community-based PA promotion interventions for vulnerable older adults is still limited.

Objective: The BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung) study aims to evaluate the (1) impact as well as the (2) feasibility, acceptance, and usefulness of a 12-month low-threshold PA intervention program for community-dwelling vulnerable older adults.

Methods: For our population-based prospective observational cohort study, a total of 120 vulnerable older adults (aged 75 years or older) in the area of Chemnitz (Germany) will be recruited to participate in (1) weekly neighborhood-based low-threshold PA meetings with trained mentors (activity tandems) and (2) monthly exercise meetings led by trained exercise instructors. Within the intervention, participants will be encouraged to perform the PA independently. Participants will complete assessments, which will include questionnaires as well as objective measurements of their physical, cognitive, and psychosocial health at 3 different time points (baseline, 6 months after the start, and 6 months after the end of the intervention). Additionally, a process evaluation will be performed, including questionnaires and qualitative interviews, involving the participants, mentors, and municipal project partner representatives.

Results: The BeTaSen project process began in October 2021, with the start of data collection and intervention in August 2022 in the first neighborhoods of the city of Chemnitz. A total of 86 participants were recruited at the time of submission of the manuscript. Longitudinal results are expected by 2025.

Conclusions: This study's results will provide insights on (1) the PA behavior of vulnerable older adults as well as the impact of PA interventions on health-related outcomes such as cognitive, physical, and psychosocial health, and (2) the feasible and useful components of community-based PA interventions. Thus, this pilot study contributes to future recommendations and provides a basis for further research, such as the development of feasible and sustainable target group–specific interventions in community settings.

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KEYWORDS

acceptance; ageing; aging; cognitive; cohort; communal health promotion; community based; community dwelling; community-dwelling older adults; elder; elderly; exercise; feasibility; geriatric; gerontology; observational; older adult; older people; older person; physical activity; psychosocial health; psychosocial; vulnerable

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Introduction

Overview

The share of older adults in many European countries' total population is increasing [1]. Aging is associated with a number of physical and health-related changes, including a decline in physical and cognitive performance and an increase in neurodegenerative as well as cardiovascular diseases [2]. Furthermore, demographic developments and age-related increases in individual disease risk pose significant (health-related) economic and social challenges for aging societies. This manifests itself in increased hospitalizations [3] and financial burdens on both the health care system and private households due to rising health care costs [4]. Thus, healthy aging, for example, years of life spent in good health and the maintenance of well-being in old age, has enhanced attention in social and health systems [2]; investments in and programs to promote health are increasing in importance. According to current research, vulnerability in older adults (eg, poverty, loneliness, and a low level of education) can adversely affect the health behavior, morbidity, and mortality of older adults [5-9]. German adults with an income of less than 60% of the national average, for example, have a significantly reduced life expectancy compared to those with above-average incomes [8]. Consequently, it is crucial to focus, especially on these target groups, on health promotion programs.

Among other health-promoting interventions, recent studies confirm that regular physical activity (PA), for example, daily walks, can improve individual and biopsychosocial health among healthy as well as vulnerable older adults [10-16]. Moreover, regular PA can also have a positive impact on social connectedness [13], which in turn can improve older adults' cognitive and mental health and seems to be a relevant factor in successful aging [14]. Accordingly, regular PA can be considered a beneficial investment in individual health capital [15] and in healthy aging in general [11]. Furthermore, previous studies and systematic reviews have shown that PA interventions in community settings can improve older adults' physical function and level of PA [16-20], even in those who are vulnerable [16,20]. For example, Giné-Garriga et al [16] find that physical exercise interventions can improve physical function in frail older adults. Other studies conclude that such programs can have positive effects on older adults' cognitive and mental health [21,22]. Recently, studies investigated the impact of community-based PA interventions on older adults' cognitive, psychosocial, and physical health and on their PA behavior in German communities [23,24]. However, many studies involved mostly healthy older adults who did not belong to a vulnerable group, and current research does not address long-term implications or specific group differences.

Thus, more evidence is needed to confirm these positive impacts, especially on vulnerable older adults, and to implement subsequent health promotion programs. Furthermore, despite the well-known positive effects of regular PA, only a small fraction of older adults in Germany are sufficiently physically active in line with the recommendations of the World Health Organization (WHO) [25]. The WHO and the American College of Sports Medicine recommend adults aged 65 years or older perform moderate to vigorous endurance training for a minimum of 150 minutes per week (in bouts of at least 10 minutes each) [26], in addition to flexibility, strength, and balance training twice per week [25]. Among adults aged 65 years or older, 42% meet the recommendations for endurance training, while only 29% meet those for strength training [25]. In a German health monitoring survey, 36% of older adults aged between 60 and 69 years and nearly 45% of older adults aged between 70 and 79 years reported that they do not engage in any regular PA or exercise [27]. Several studies find that vulnerability, for example, a low level of education, physical restrictions, and poor health status, is negatively associated with older adults' PA level (eg, meeting the WHO's recommended level of PA) [25]. This specific group is thus exposed to severe health risks and potentially early care dependency [5-8]. Due to the high share of older adults who are physically inactive, feasible PA promotion programs targeted specifically at previously physically inactive or vulnerable older adults are especially relevant. To determine the feasibility and sustainability of PA programs targeted specifically at vulnerable older adults, further research on contributing factors and barriers is needed. The literature identifies several internal and external barriers for older adults' participation in PA programs: lack of information about PA offers, physical restrictions, lack of social support to begin with PA, lack of language skills and local accessibility, as well as financial costs [28]. Vulnerable older adults (eg, poverty, loneliness, and a low level of education) perceive high barriers to participation in health-related promotion programs, for example, PA programs [29]. In a systemic review, Franco et al [30] identified six major themes that may influence older adults' participation in PA: (1) social influences, (2) physical restrictions, (3) competing priorities, (4) access difficulties, (5) lack of awareness of the personal benefits of PA, and (6) motivation and beliefs [30]. Furthermore, current research recommends providing PA interventions in community settings for vulnerable older adults that are specifically tailored to the target group and embedded in their immediate social-spatial context (districts and neighborhoods) [31-33]. Moreover, previous studies have shown that personal interventions are particularly effective in promoting PA [34] and that motivators such as social and environmental support, convenience of location, and enjoyment of the activity seem to be relevant factors in interventions targeted at community-dwelling older adults [35]. These influencing factors should be considered when developing exercise interventions to promote PA and its associated positive health benefits among vulnerable community-dwelling older adults.

Some studies conclude that community-based PA programs for older adults are feasible, even over a longer period [36-38]. A systematic review carried out by Farrance et al [39], for example, finds long-term adherence rates of nearly 70% for community-based group exercise programs. Nevertheless, there is limited evidence about the long-term adherence measures included in these programs as well as participants' views [39]. Shvedko et al [40] assert that a PA intervention for community-dwelling older adults at risk of loneliness is accepted by older adults and is feasible. Crombie et al [41] also show that a community-based PA intervention is feasible for sedentary

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older adults. However, recent evidence about the feasibility and acceptance of community-based PA interventions and of the different components of such interventions, especially among vulnerable older adults, is limited.

In summary, evidence of the impact and feasibility of PA interventions on the health and health-related behavior of vulnerable community-dwelling older adults remains sparse. Therefore, research should focus on the health-related benefits of intervention programs that promote PA among vulnerable older adults as well as on how intervention programs tackle (internal and external) barriers that discourage the participation of vulnerable older adults in PA programs.

For this reason, the aim of this study is to investigate the impact and feasibility of a 12-month low-threshold targeted PA intervention program on community-dwelling vulnerable older adults. This study protocol describes the study's objectives, the design of the intervention, method, data collection, and considerations for analyzing the data from the PA intervention program of the study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung).

Research Objectives and Research Questions

The main goal of the BeTaSen study is to initiate, sustainably maintain, and promote an active and healthy lifestyle for vulnerable older adults who reside in Chemnitz.

The objectives of the BeTaSen study are described in subsequent paragraphs.

Evaluation of the impact of a 12-month low-threshold PA intervention program on health-related outcomes of vulnerable community-dwelling older adults. In this context, the main research questions are as follows: (1) What are the long-term outcomes for older adults after completing a 12-month, target group-specific community-based PA program? Older adults' PA behavior as well as their physical, cognitive, and psychosocial health are of particular interest in this regard. (2) Are any group differences evident in the long-term outcomes of a 12-month target group-specific community-based PA program among older adults (eg, gender, previous disease, and vulnerability)?

Analyzing the feasibility, acceptance, and usefulness of aspects of a community-based PA intervention for vulnerable community-dwelling older adults. In this context, the main research questions are as follows: (1) Which PA-promoting exercises and activities are considered useful by older adults? (2) Is a target group-specific 12-month PA program feasible for vulnerable community-dwelling older adults and the community setting? and (3) What factors promote or inhibit the successful implementation of a target group-specific PA program for vulnerable community-dwelling older adults?

Methods

Participants and Procedure

The pilot study is being implemented in the German city of Chemnitz. Chemnitz is the third-largest city in the federal state of Saxony in the southeastern part of Germany, with a population of 250,398 (in 2023) [42]. In 2022, nearly 30% of the population of Chemnitz was aged 65 years or older; 15% were aged 75 years or older [43]. In 2020, Chemnitz was the city with the highest median age in Europe (52 years) [44]. Forecast calculations expect that by 2030, the Chemnitz region will have the highest share of people aged 65 years or older (nearly 38%) in Europe [1]. According to population forecasts, the share of Chemnitz residents aged 80 years or older will also rise from 8% in 2018 to nearly 11% in 2030 [45]. Due to these demographic developments, there is an urgent need for target group-specific and low-threshold community health promotion programs (eg, PA interventions) to support the healthy aging of vulnerable older adults who live in the city of Chemnitz. This city was furthermore chosen due to its immediate proximity to the Technical University of Chemnitz, which is conducting the study, and its collaboration with the city of Chemnitz's health department, as well as support from various local partners (eg, citizen platforms).

The aim during the study period is to cover at least 4 out of 39 districts in Chemnitz, representing the city's average demographic age (>50 years) and lower socioeconomic districts (compared to the city of Chemnitz's average) [46,47]. The recruitment of participants is planned primarily due to collaboration with local partners. Announcements will be conducted in different communal facilities for older adults (eg, citizen online platforms, assisted living facilities, and citizens' meeting points) through flyers, at information events, in institutional newspapers, and in the personal conversations of the research team with targeted older adults as well as with staff of different social institutions. The study will be announced in various local and district newspapers, and flyers will be distributed in shops, for example, in bakeries and pharmacies. Additionally, older adults who had participated in previous studies and had consented to being informed about future studies will be contacted.

Eligibility to participate in the study will be determined in personal interviews by qualified staff based on the inclusion and exclusion criteria described below.

Inclusion and Exclusion Criteria

The study primarily targets older adults aged 75 years or older who can be considered vulnerable (eg, poverty, loneliness, physical restrictions, and a low level of education) and who reside in the city of Chemnitz.

Residents are eligible to participate in the study if they (1) have at least basic knowledge of the German language, (2) can independently travel to the assessment and intervention locations, which will be meeting points in close proximity to their home, and (3) provide informed consent to participate in the study.

Participants will be excluded from the study if they have a medical condition preventing them from engaging in regular PA or if they had a severe adverse health event within the last 6 months (eg, myocardial infarction, stroke, fracture, surgery, or pneumonia) to ensure their safety during the PA sessions. Additionally, participants will be excluded if they participate in other clinical trials as well as in regular PA programs at least

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twice a week (eg, regular gym visits or rehabilitation exercise programs) to address older adults who are less physically active and to analyze solely the impact of the intervention.

Study Design

The pilot study is designed as a population-based prospective observational cohort study and is being carried out in 4 different districts in the city of Chemnitz. The first screening for study eligibility will be assessed through a standardized telephone interview with, for example, questions about older adults' age, health conditions, and regular weekly PA exercises. Afterwards, participants will complete an assessment conducted by the research team in their direct neighborhood (eg, in the facilities of community centers), which includes questionnaires and objective measurements of physical and cognitive function and of psychosocial health. In addition to these measurements, participants will wear a pedometer for 7 consecutive days to assess their PA behavior. Measurements will take place at 3 different time points over an 18-month period, namely at the beginning (T1), at the end (T2), and 6 months after the end of the intervention (T3) (Figure 1).

The project was launched in October 2021 and will be completed in September 2025. The first participants were recruited in August 2022.

Figure 1. Study flow of the population-based prospective observational cohort study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung) with a study population of older adults (aged 75 years or older) living in Chemnitz, Germany. *Outcome evalution. **Process evaluation.

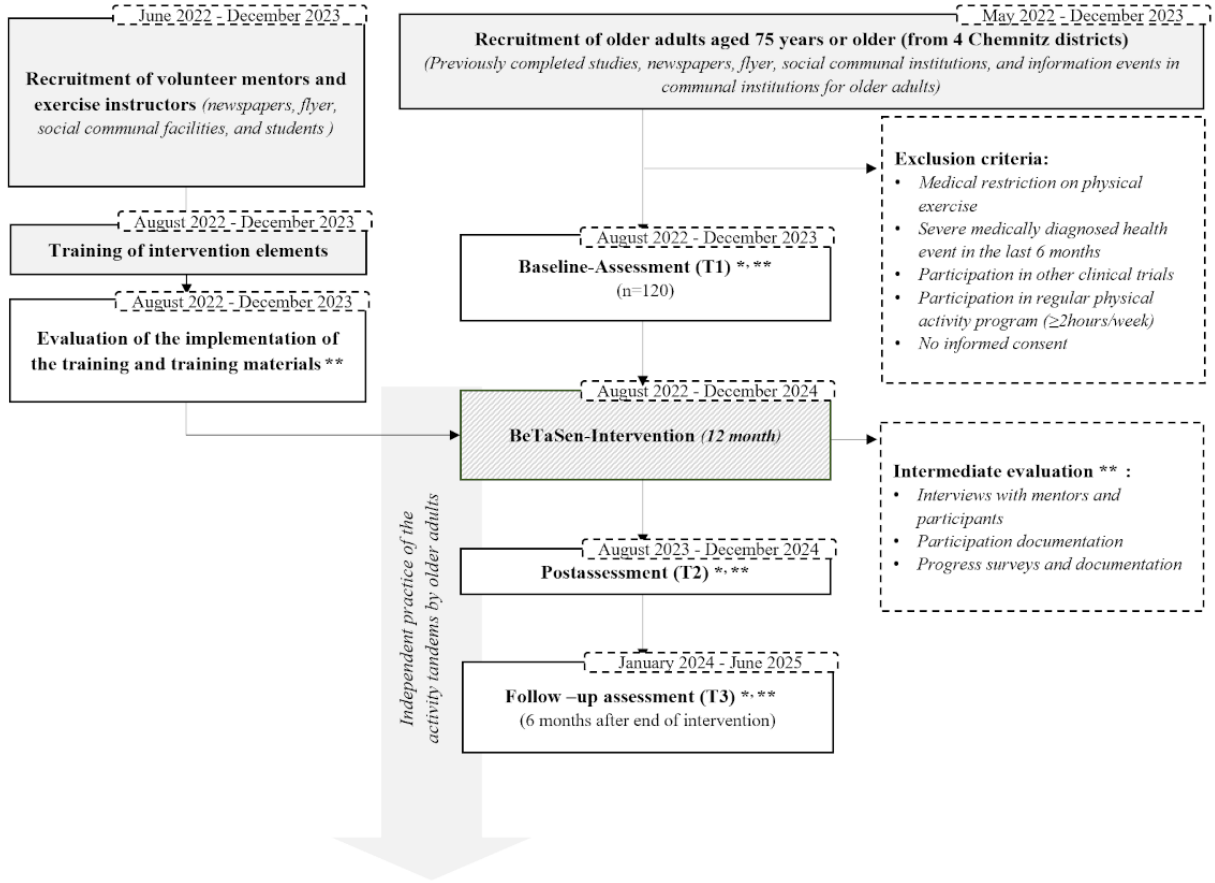

Design and Organization of a Physical Activity–Promoting Intervention

All participants will participate in the target group-specific community-based PA intervention. The pilot study's intervention period is 12 months per participating neighborhood. The participants will be encouraged to continue to engage in PA independently (Figure 2).

The intervention's main component will comprise regular PA meetings organized in so-called "activity tandems," which take place once a week for 30-45 minutes. One activity tandem will include 1 trained voluntary mentor and 3-4 older adults living in the same neighborhood. These activity tandems will primarily engage in low-threshold outdoor PA and exercise together in their neighborhood. For this, easily accessible locations such as urban lawns, walking paths, parks, and fitness trails will be used. In case of bad weather, the PA meetings will be organized in the meeting places of collaborating partners, for example, community centers. Due to the small group size, the content of each tandem lesson can be flexible and tailored to the individual participant's needs. For example, the exercises can be performed at different levels of intensity, or alternative exercises can be selected from a large PA-exercise pool. Additionally, monthly group meetings (eg, 3-4 activity tandems with a total of 12-16 older adults) will be organized in each neighborhood district in the intervention months 5-12 (Figure 2), which will be delivered by trained exercise instructors. In these group meetings, in addition to PA exercises, the following contents will be covered:

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knowledge about the positive effects of PA, goal setting and planning, barrier management, and motivational aspects, as well as the sustainable implementation of regular PA in everyday life. Measures like small group sizes, qualified mentors, support material (eg, first aid kits, pulse oximeters, Borg scales), and the accessible, familiar environment of the activity sessions ensure the safety and well-being of participating older adults.

Figure 2. Procedure of the population-based prospective observational cohort study BeTaSen's intervention over a period of 12 months; an example is shown for 1 district (study population: older adults aged 75 years or older living in Chemnitz, Germany). BeTaSen: Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung).

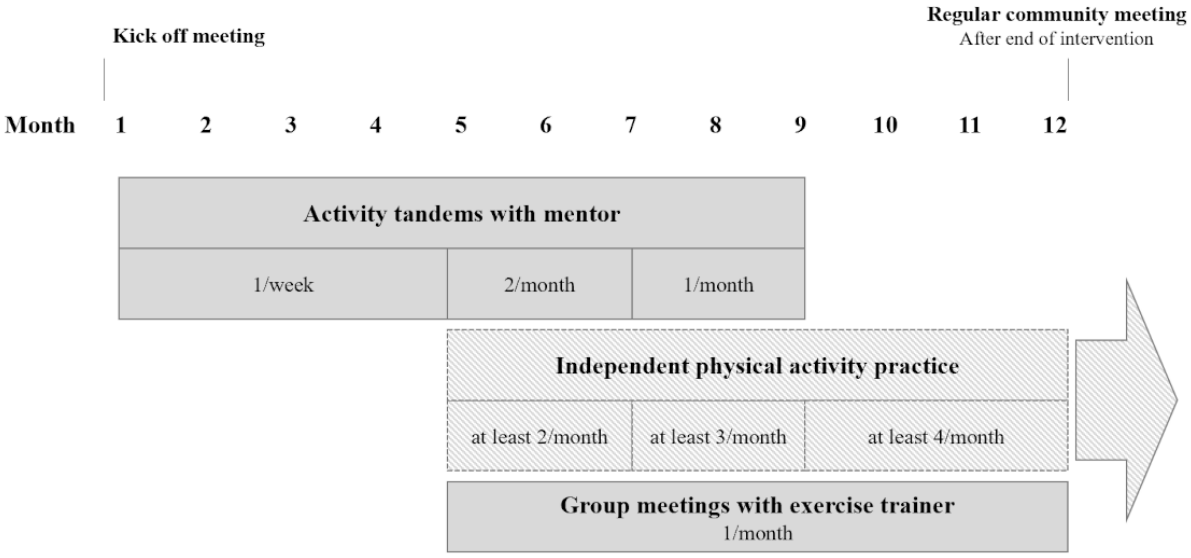

In total, around 6-8 activity tandems will be created in each of the 4 local districts (approximately 24-32 older adults per district). Thus, the goal is to reach a total of approximately 120 older adults residing in the city of Chemnitz during the project period.

Voluntary mentors (eg, volunteers from Chemnitz, students, and community center staff) will be recruited through various public channels (eg, newspapers, flyers, and mailing lists) in cooperation with municipal partners. The trained mentors should guide the activity tandem groups (eg, demonstrate PA exercises with the help of the manual and walk paths), ensure safety and well-being (eg, through individualized feedback), and encourage the older adults to do independent regular PA exercises. The mentors will also be responsible for communication and the planning of the activity tandem meetings. Researchers on the project team will instruct mentors in a workshop about how to conduct PA meetings, how to appropriately deal with the target group, and how to perform basic first aid procedures. In addition, mentors will be equipped with support materials, such as a manual that includes a range of various low-threshold PA exercises, an overview of district walkways, and additional exercise materials (eg, resistance bands and everyday objects).

The mentors will supervise and support the activity tandems once a week initially at the start of the intervention (intervention months 1-4), later once every 2 weeks (intervention months 5-6), and then once a month (intervention months 7-9). The older adults will thus be gradually encouraged to independently engage in weekly PA activity meetings, as from intervention month 10 onward, they will be prepared for basically independent implementation. Furthermore, older adults will be encouraged to actively participate in the activity tandems, for example, by choosing walkways or suggesting individual exercises. During the intervention period, participants will be given exercise material (eg, brochures) to continue regular PA in their activity tandem and on their own. To ensure that older adults do not overexert themselves as well as to enable them to get a better sense of their exercise limits, their oxygen saturation and heart rate (using a pulse oximeter; Orbisana Healthcare GmbH) as well as a subjective exertion rate (based on the Borg scale; [48]) will be measured at the beginning, middle (during physical exertion), and end of each activity tandem meeting. Based on these measures, participants will receive direct feedback, and the PA exercise intensity can be adjusted individually.

In line with previous literature and findings, the vulnerable target group's potential barriers should be carefully considered when developing the pilot study. To ensure low-threshold accessibility, the activity tandems and monthly group meetings will take place in the older adults' neighborhoods. District plans will be drawn up to identify sitting areas and public toilets, for example, and to pinpoint accessible walkway plans. The activity tandem's PA content will be designed to reflect daily life activities in a very playful, individualized, ability-oriented, and motivational way. Each unit can be freely designed by the mentors and older adults based on the PA, exercise materials, and recommendations provided. Each activity tandem unit should begin with a warm-up, and the components of strength, endurance, coordination, stretching, and relaxation should be addressed regularly in different sessions. In addition, the mentor should include knowledge transfer in each unit, for example,

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about the positive effects of PA. Moreover, participation in the PA intervention does not entail any financial costs (eg, materials and participation fees). To promote sustainable participation in the neighborhood meetings and to ensure that the PA meetings are tailored to the vulnerable target group, the activity tandems are purposely organized for a smaller number of older adults. The older adults and mentors of the activity tandems can coordinate the time and location of their weekly meetings flexibly on their own.

Measures

All participants will complete an assessment at baseline (T1), at the end of the 12-month intervention (T2), and 6 months after the end of the intervention (T3). Before each assessment, participants will be asked to fill out a self-administered questionnaire and, for the detection of objective PA behavior, will be given a pedometer to wear for 7 consecutive days. The questionnaire will assess the older adults' psychosocial and physical health and evaluate motivational aspects related to PA in a community setting. Sociodemographic information will be assessed within the questionnaire at T1 only, comprising target group-specific items from the German Health Interview and Examination Survey for Adults [49].

Further measurements will take place in communal facilities in the older adults' neighborhood and will be carried out by qualified staff members. Each assessment will start with the measurement of anthropometric data (height and weight) as well as the registration of current medication intake and existing diagnosed diseases via interview. Using the EQ-5D-3L questionnaire, the participants' subjectively perceived health status in terms of mobility, self-care, regular daily activities, pain, discomfort, anxiety, and depression will then be determined by interview (3 response options: no problems, some problems, and serious problems) [50]. Additionally, their general self-rated health status will be recorded using the vertical visual analog scale EQ-VAS (1-100) [50].

An additional process evaluation will be performed during the intervention period using questionnaires for participants (after a period of 4 weeks) and mentors (after the workshop, 3 months after the intervention). Furthermore, qualitative interviews and informal notes, reports, and documentation of the PA groups will also be obtained from the activity tandems as well as from group meetings (Table 1 for a summary of outcomes).

Table 1. Outcome measurements of the population-based prospective observational cohort study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung). T1 is baseline, T2 is the end of the intervention period (12 months), and T3 is 6 months after the end of the intervention (study population: older adults aged 75 years or older living in Chemnitz, Germany).

Assessment	Instrument or scale	Time of measurement
Outcome		T1, T2, T3
Physical function	• Short Physical Performance Battery (SPPB) • Handgrip strength (handgrip dynamometer)	
Physical activity	• OMRON Walking Style One 2.1. Pedometer (7 days) • PRISCUS-PAQ	
Psychosocial health	• German Depression Scale (DIA-S) • Items of Tilburg Frailty Indicator (TFI) • Items of social support questionnaire (F-SozU)	
Cognitive function	• Montreal Cognitive Assessment (MoCA)	
Process		
Feasibility	• Documentation of activity tandems and group meetings adherence rates • Qualitative interviews and self-administered questionnaire with older adults, mentors, exercise trainers, and communal partners	• Each activity tandem or group session • Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)
Usefulness	• Qualitative interviews and self-administered questionnaire with older adults, mentors, and exercise trainers	• Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)
Implementation (barriers and facilitators)	• Qualitative interviews and self-administered questionnaire with mentors, exercise trainers, and communal partners	• Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)

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The main activity and health-related outcomes will be addressed in the following subsections.

PA Behavior

PA behavior will be objectively assessed using the OMRON walking style one 2.1. pedometer (OMRON Cooperation) that records a person's steps, walked kilometers, kilocalories used, and aerobic steps per day over 7 consecutive days. Participants will be instructed to wear the pedometer on their hip during waking times as well as get information about the use and purpose of the pedometer. After the pedometer has been returned, the data will be transferred by study assistants to a Microsoft Excel (Microsoft Corporation) spreadsheet. Activity data for days with at least 500 steps will be included for further analysis, according to Meyer et al [51].

For a subjective evaluation of PA behavior, the PRISCUS-Physical Activity Questionnaire (PRISCUS-PAQ) for older adults aged 70 years or older will be assessed based on interviews during T1, T2, and T3 measurements [52]. PRISCUS-PAQ consists of 10 main items on sedentary behavior, daytime naps, cleaning, and other housework, cycling, gymnastics, group exercise, other PA, walks, and gardening. The total score of the PRISCUS-PAQ reflects the individual's energy expenditure (metabolic equivalent) during the previous week [52].

Physical Performance

The digital grip dynamometer (JAMAR Smart Hand Dynamometer; Performance Health Supply Inc) will be used to assess the participants' handgrip strength. During this test, participants sit upright in a chair without an armrest with their arm bent to 90°. A total of 3 trials are performed per hand, alternating between right and left, with a test duration of 3-5 seconds for each trial. The mean and highest values of the 3 trials for each hand will be analyzed [53]. Additionally, the dominant hand will be queried.

To prove the impact of the exercise intervention on participants physical performance, the widely used, highly reliable, and valid Short Physical Performance Battery (SPPB) will be used [54]. The SPPB includes balance (Romberg, Semi-Tandem, and Tandem), gait speed (4-meter walk), and chair rise tests. Each of these 3 SPPB components is scored from 0 (inability to carry out) to 4 (best performance). There is a potential range between 0 and 12, with higher scores indicating higher functional performance. Participants with cut-off points of less than or equal to 6 points will be classified as "poor performers." Whereas a score of 7-9 points will define the "moderate performers," and the "good performers" will have scores of 9 points or more [55]. In a systematic review and meta-analysis, the SPPB has been shown to be a predictive tool for all-cause mortality [56].

The 2-minute step test (TMST) [57] will be used to assess the participants' endurance capacity. The test starts with a 2-minute rest period. Participants will then stand in front of a wall and raise their thigh to be horizontal to the floor; a mark (strip) will be placed in the position corresponding to the middle of their thigh bone, between the kneecap and frontal prominent pelvis bone. Participants will be instructed to alternately lift their knees as often as they can over a 2-minute period, such that their knees reach the marked location. After completing the TMST, the researcher will record the participants' number of steps, or "steps," as an outcome measure. Before the start of the test, directly after, and 30 seconds after the end of the test, the participant's heart rate in beats per minute and measurement of oxygen saturation in percent (through a pulse oximeter) as well as a subjective rating of perceived exertion (through the Borg scale [48]) will be recorded.

Cognitive Function

The short screening tool Montreal Cognitive Assessment (MoCA) will be used to evaluate the participants' cognitive functions (eg, memory, attention, and basic functions). Participants who achieve a MoCA score between 26 and 30 points will be classified as cognitively healthy; those with a MoCA score of 19-25 will be considered to have mild cognitive impairment; and participants with a MoCA score of less than 19 will be defined as severely cognitively impaired [58].

Psychosocial Health

Psychosocial health outcomes will be assessed using modified, validated, and reliable instruments included in a self-administered questionnaire. Thus, the psychological and social domains of the Tilburg Frailty Indicator [59], the German depression scale for older adults, namely Depression im Alter Skala [60], and modified items of the Fragebogen zur sozialen Unterstützung (social support) [61] will be implemented.

Feasibility and Usefulness

The intervention's feasibility for older adults will be assessed quantitatively based on the adherence rate (number of completed activity tandems and group meetings) during the intervention period. Additionally, participants will be given their own documentation sheet to record their subjective well-being (using a 5-level smiley scale at the beginning, middle, and end of each session) and their level of satisfaction (using a 5-point Likert scale) with each activity tandem meeting. Additional self-administered questionnaires with items to subjectively rate the activity tandem's components will be implemented after every fourth unit. Using a 3-point Likert scale, participants will rate the difficulty of the particular intervention content (eg, strength, endurance, and coordination). In addition, they will be able to use the open response section to indicate which parameters they want to improve and what they want to achieve over the next 4 weeks. Six months into, at the end, and 6 months after the end of the intervention, participants will receive another self-administered questionnaire to assess the intervention's feasibility and sustainability and to identify the optimizing factors of the activity tandems and group meetings.

To evaluate the feasibility of volunteer mentors and the communal context, (1) mentor workshops will be anonymously evaluated using a self-administered questionnaire, and (2) mentors and community project partner representatives will be asked to fill out a self-administered questionnaire (eg, questions on perceived feasibility and sustainability).

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Implementation

To assess the implementation of the PA intervention, (1) self-administered questionnaires and (2) qualitative interviews will be conducted with mentors, participants, and community project partner representatives.

Data Management

Participant information will be recorded using an individual identification code. All hard copies will be stored at Chemnitz University of Technology in locked cabinets accessible only to project staff members. Electronic data will be stored on a secured, password-protected computer. The databases will not contain participant identifiers. The data linking participant identifiers and the individual identification codes will be stored separately. Data quality will be ensured through double data entry and range checks for data values. Only project staff members will have access to the final trial data set.

Statistical Analysis

SPSS Statistics (version 29; IBM Corp) and AMOS (version 29; IBM Corp) will be used for all quantitative statistical analyses. To determine the primary outcome at baseline (T1), the study population will be descriptively characterized using the following outcomes: demographics (eg, age, gender, family status, and income), anthropometric comorbidities, PA and health-related behavior (eg, smoking status and alcohol consumption), as well as physical, functional, cognitive, and psychosocial health status. Furthermore, participants' data at the end of the intervention period (T2) and 6 months after its end (T3) will be analyzed to evaluate the long-term impacts, feasibility, and usefulness of the PA intervention. Time effects, group differences (eg, age, gender, vulnerability, and sociodemographic conditions) in terms of physical, cognitive, and psychosocial health, interaction effects, as well as the intervention's feasibility and sustainability, will be analyzed using different parametric or nonparametric statistical methods such as the *t* test, Mann-Whitney *U* test, ANOVA, or Kruskal-Wallis test, depending on the number and size of the group, normal distribution, and homoscedasticity of the sample. Based on current evidence [6-8,25], associations and the strength of the relationship between 2 variables (eg, PA behavior and monthly income and adherence rate and level of education), correlation and regression analyses as well as adjustments for relevant covariates (eg, age, gender, and vulnerable criterion) will be performed. Additionally, multilevel analyses are planned to estimate, for example, the within-person impacts of the intervention program (eg, the impact of PA on well-being).

Qualitative interviews and focus group discussions will be protocolized by researchers and audio recorded, which will be transcribed afterwards. Qualitative data will be analyzed using a qualitative content analysis, according to Mayring and Fenzl [62], with the aim of structured processing of the material by coding relevant interview passages deductively in a theory-driven system of categories. Frequent text material that cannot be assigned to a deductive main category will result in the creation of new (inductive) main categories or subcategories [62]. The coding scheme will subsequently be supplemented with additional categories that emerge from the text material. These newly added categories will either be treated as subcategories of already existing categories or as new main categories. The text material will be coded with the help of MAXQDA (VERBI GmbH).

For this pilot study in the municipal area, the number of participants was calculated based on the project period and the project funding type in terms of feasibility within the study period.

Ethical Considerations

This study was approved by the Ethics Committee of the Chemnitz University of Technology, Faculty of Behavioral and Social Sciences, on May 19, 2022 (101547973). All study participants will be fully informed about the objectives and procedures of the study in German and will be requested to give written informed consent. Additionally, the informed consent contains information about the pseudonymized data collection for the study. Furthermore, the original informed consent allows the secondary analysis without additional consent.

Results

The intervention period of the BeTaSen study started in August 2022 in the first neighborhoods of the City of Chemnitz. Due to the planned staggered launches of the different activity tandems, cross-section data of all participants at T1 (approximately 120 older adults) and initial feasibility data 6 months into the intervention (approximately 60 older adults) will be collected until December 2023. Longitudinal results are expected in the first quarter of 2025. Qualitative and quantitative data on sustainable components for PA interventions among all participating vulnerable older adults are expected in December 2024, after T2, and 6 months after the end of the intervention (T3).

Discussion

The aim of the BeTaSen study is thus to develop, implement, and evaluate a target group-specific PA intervention for community-dwelling older adults living in Chemnitz, the city with the highest median age in Europe [44].

The intervention program was developed especially for the target group of vulnerable community-dwelling older adults on the basis of theoretical aspects [29-35] and considers potential barriers and facilitating factors for initiating and maintaining regular PA. Furthermore, the specific intervention design contains elements promoting long-term use (eg, increasing independent activity sessions over the intervention period, individual goal setting, and knowledge transfer of the effects of PA). Therefore, the intervention concept and their implementation are expected to contribute to (1) increasing or maintaining PA behavior, cognitive and physical function, as well as psychological parameters of older adults, and (2) the feasibility and sustainability of healthy aging in municipalities.

The results of the study will provide insights into (1) the PA behavior of vulnerable older adults as well as the impact of PA interventions on health-related outcomes such as cognitive, physical, and psychosocial health, and (2) feasible and useful

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components of community-based PA interventions. Thus, this pilot study bridges a research gap as it focuses on the PA-promotion of vulnerable community-dwelling older adults and implements a low-threshold health promotion concept that may have a sustained impact on the health and health-related behavior of this specific target group. Furthermore, the BeTaSen study will make an important contribution to the state of knowledge of average PA levels and health outcomes, as well as the impact, feasibility, and sustainability of such interventions. As the results of the study will provide insight into the demands, needs, and possible barriers of programs, it can provide a foundation for new interventions and how to deal with difficulties in their implementation.

During and at the end of the project period, interim results and findings will be summarized in information brochures and presented at municipal information events or scientific congresses. When interpreting the results, it should be considered that this research project does not have a randomized, controlled study design since the accessibility of the target group is very restricted and community-based PA programs should be accessible to vulnerable older adults over the entire study period. Nonetheless, the results of the study will provide insights into the within-person impacts of regular PA over a longer time period, and the study design comprises a low-threshold intervention for a highly relevant target population and allows "real-world" applicability. The results of the study will make an important contribution to the research field of aging and movement sciences as well as to the development of health-promoting structures, providing insights into the impact and implementation strategies of community health promotion programs for specific target groups like vulnerable older adults. In addition to publications in scientific journals, the impulses of the study will be implemented into municipal health policies and structures (eg, other neighborhoods, community centers, and health departments) after the end of the project period. Furthermore, the PA program can be distributed throughout Germany through cooperation with the Federal Centre for Health Education and thus shows a high potential for expansion.

Finally, the results will contribute to future recommendations and provide a basis for further research, such as the development of feasible and sustainable target group-specific interventions in community settings.

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Data Availability

Participants information and data sets generated during and/or analyzed during this study will be stored securely and identified by a coded ID number only to maintain participants' confidentially. Data will be available from the corresponding author on reasonable request.

Authors' Contributions

TA and KM conceptualized the study and conducted the project administration. TA conducted the visualization of the manuscript. TA, KZ, TS, and KM wrote and edited the original draft. TA and KM conducted methodology, investigation, and funding acquisition. KM is responsible for the supervision of the BeTaSen project. All authors read, critically revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BeTaSen: Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung
MoCA: Montreal Cognitive Assessment
PA: physical activity
PRISCUS-PAQ: PRISCUS-Physical Activity Questionnaire
SPPB: Short Physical Performance Battery
TMST: 2-minute step test
WHO: World Health Organization

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Protocol

Identifying and Validating Alcohol Diagnostics for Injury-Related Trauma in South Africa: Protocol for a Mixed Methods Study

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Abstract

Background: The burden of alcohol use among patients with trauma and the relative injury risks is not routinely measured in South Africa. Given the prominent burden of alcohol on hospital trauma departments, South Africa needs practical, cost-effective, and accurate alcohol diagnostic tools for testing, surveillance, and clinical management of patients with trauma.

Objective: This study aims to validate alcohol diagnostics for injury-related trauma and assess its use for improving national health practice and policy.

Methods: The Alcohol Diagnostic Validation for Injury-Related Trauma study will use mixed methods across 3 work packages. Five web-based focus group discussions will be conducted with 6 to 8 key stakeholders, each across 4 areas of expertise (clinical, academic, policy, and operational) to determine the type of alcohol information that will be useful for different stakeholders in the injury prevention and health care sectors. We will then conduct a small pilot study followed by a validation study of alcohol diagnostic tools (clinical assessment, breath analysis, and fingerprick blood) against enzyme immunoassay blood concentration analysis in a tertiary hospital trauma setting with 1000 patients. Finally, selected alcohol diagnostic tools will be tested in a district hospital setting with a further 1000 patients alongside community-based participatory research on the use of the selected tools.

Results: Pilot data are being collected, and the protocol will be modified based on the results.

Conclusions: Through this project, we hope to identify and validate the most appropriate methods of diagnosing alcohol-related injury and violence in a clinical setting. The findings from this study are likely to be highly relevant and could influence our primary beneficiaries—policy makers and senior health clinicians—to adopt new practices and policies around alcohol testing

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in injured patients. The findings will be disseminated to relevant national and provincial government departments, policy experts, and clinicians. Additionally, we will engage in media advocacy and with our stakeholders, including community representatives, work through several nonprofit partners to reach civil society organizations and share findings. In addition, we will publish findings in scientific journals.

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KEYWORDS

alcohol; diagnostic; surveillance; injuries; violence; road traffic; Africa; South Africa; alcohol misuse; alcohol diagnostics; addiction; mixed methods; trauma; risk; injury; diagnostic tools; diagnostic tool; clinical management; injury; injury prevention; accident; accidents

Introduction

Alcohol indicators obtained from patients seen in emergency departments or admitted to hospitals are one of the key and most cost-effective data sources for estimating the impact of alcohol on communities and health [1] to quantify problem drinking, alcohol-impaired driving, trauma readmissions, and premature death [2]. This assists in identifying high-risk groups that should be targeted for prevention. Effective monitoring of alcohol-related morbidity and mortality requires the collection of alcohol-related indicators, in which regular reports on the key predefined indicators are submitted by hospitals, primary health care units, or emergency services [3,4].

The contribution of alcohol to the global burden of disease is undisputed. In addition to risks such as noncommunicable diseases, infectious diseases, and mental health problems as a result of hazardous and harmful alcohol use [3], the trauma burden of intentional and unintentional risk of injury from alcohol is a major public health concern. Studies from sub-Saharan Africa have highlighted the impact of alcohol on injury and violence [5-8] and concerns over alcohol consumption and alcohol-attributable burden of disease. The lack of attention alcohol-related harm receives from policy makers has been raised [9,10], with calls for stronger and more effective alcohol control measures.

In South Africa, approximately a third (31.2%) of alcohol-attributable deaths in 2012 occurred as a result of injuries, while 15.9% and 12.8% of alcohol-attributable disability-adjusted life years were caused by road traffic injuries and interpersonal violence, respectively [11]. The adult per capita consumption of alcohol in South Africa is extremely high (64.6 g of absolute alcohol per drinker per day). Almost 6 out of 10 South African drinkers older than the age of 15 years are reported to engage in heavy episodic drinking [3], which is strongly associated with increased injury risk.

COVID-19, and the related alcohol bans in South Africa, has brought the impact of alcohol on trauma presenting to health facilities into sharp focus in the country [12]. Moultrie et al [13] and Barron et al [14] demonstrated how a total ban on alcohol during the COVID-19 pandemic resulted in significantly fewer injury deaths. However, the absence of routine and reliable alcohol-related injury surveillance data have been identified as a critical gap, and the government has had to rely on the South African Medical Research Council's (SAMRC) rapid mortality reporting [15] of all injury-related deaths and ad hoc surveillance studies [13,16] to demonstrate the association between the availability of alcohol and alcohol harm. This gap has substantially hindered the ability to provide regular information on changes in the pattern of alcohol-related injuries and limits the ability to measure the impact of policy changes, implementation, and enforcement.

As the country transitions from the COVID-19 crisis response, it is likely that there will be further pressure on the government—from civil society and health and social agencies—to implement more sustained intervention strategies to reduce harmful drinking and to monitor the impact of any interventions on the alcohol-related injury burden. This has highlighted the absence of practical, cost-effective, and accurate alcohol diagnostic tools in the South African trauma setting. Accurate measurement would improve surveillance and influence the clinical management of trauma, inform and improve government policies to address heavy drinking, and assess the impact of alcohol policy reform. The proposed study thus aims to determine the type of information that will be useful for stakeholders in the trauma care and injury prevention sectors, to validate the efficacy of a selection of alcohol diagnostic tools, and to explore their feasibility for wider provincial or national implementation as a routine source of information on the alcohol relatedness of injuries.

Methods

Study Design and Setting

We will use a mixed methods participatory approach across 3 work packages (WPs) to validate alcohol diagnostics for injury-related trauma and assess its use for improving national health practice and policy (Figure 1). Outcomes from this research will inform health practice, policy development, and sustained intervention strategies. A validation study will be conducted in the trauma unit of 2 public health facilities in the Western Cape Province. Further testing will be conducted in 1 hospital setting in the Western Cape Province. These 2 hospitals represent high injury caseloads, particularly for violence and road traffic injuries [17,18].

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Figure 1. Diagrammatic illustration of the 3 studies and anticipated outputs. AVIRT: Alcohol Diagnostic Validation for Injury-Related Trauma; GSH: Groote Schuur Hospital; MPH: Mitchell's Plain Hospital.

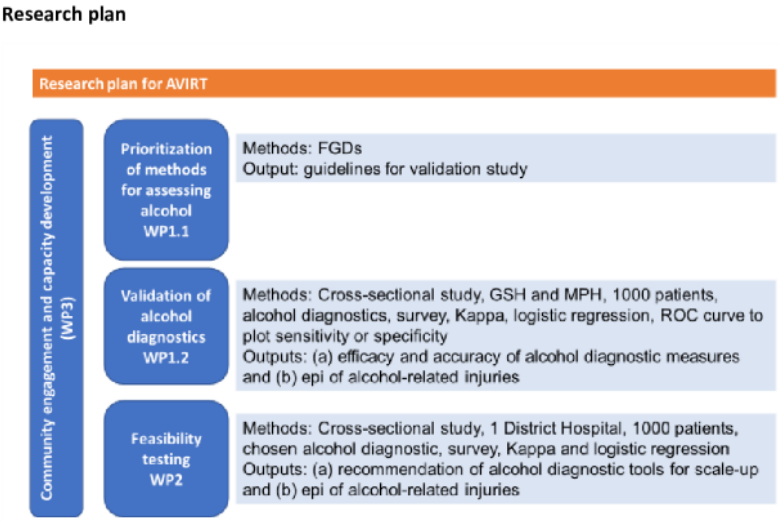

Research Plan

WP1: Prioritization and Validation of Methods for Assessing Alcohol Use

We will conduct focus group discussions (FGDs) with various stakeholders to ascertain the current alcohol assessment practice in hospitals and the type of information that could assist in the acute management of injured patients and measure alcohol use for public health surveillance. This will be followed by a cross-sectional study to validate the efficacy of three diagnostic tools: (1) clinical assessment, which is based on a clinician's observation of apparent intoxication classifies the alcohol status of a patient into 4 categories as per International Classification of Diseases, Tenth Revision (ICD-10) coding (Y91.0 mild, Y91.1 moderate, Y91.2 severe, and Y91.3 very severe) [19]; (2) breathalyzers provide an estimation of the ethanol content in the breath [20]; and (3) fingerprick test to provide a capillary blood reading in 1-2 minutes and is used to facilitate the clinical process, as well as the use of the ICD-10 Y91 coding [19].

These 3 index tests will be measured against venous blood testing for the presence of ethanol as the reference standard, for which we will use enzyme immunoassay [21] for testing of blood alcohol concentration (BAC). The analysis will be conducted by a private pathology laboratory.

This WP will also describe the epidemiology of alcohol-related injuries among trauma cases presenting at the emergency unit of the selected trauma units through a prospective study. Patients presenting to the trauma units for first-time treatment of their injuries will be interviewed to record patient demographics, the injury intent, and related mechanisms and will be tested for alcohol, using the aforementioned alcohol diagnostic tools. Prior to the validation study, a small pilot study will be conducted over 2 weeks to test the consent procedures, the study questionnaire platform, and the logistics surrounding the blood withdrawal and use of a courier to the contracted laboratory for centrifugation within the 2-hour limit to preserve the alcohol.

WP2: Field Testing Selected Diagnostic Tools

Guided by findings from WP1, the alcohol diagnostic tools will be field tested in a district hospital in a large suburb on the outskirts of Cape Town. This WP aims to test the suitability of validated alcohol diagnostic methods for routine use in a hospital trauma setting on a day-to-day basis.

WP3: Community Engagement and Capacity Development

Engagement with clinicians, operational stakeholders (eg, nongovernmental organizations and emergency services), and individuals working in the policy arena are key to the success of any policy change. These stakeholders will be engaged through the FGDs at the commencement and again at the end to include community and patient representation. Three sets of activities for this phase will thus include:

- Step 1: FGDs on the use of the recommended methods and what would be required for implementation and the role of the measure in health care provision;
- Step 2: workshops or webinars with stakeholders for input on findings and to convey recommendations for uptake and integration; and
- Step 3: community engagement and recommendations for uptake and integration within the health system.

Additionally, capacity development through linking research to policy and practice for increased commitment and support by the government to fund and implement further scale-up of this study in trauma facilities nationally will be threaded through the project.

Study Population and Sampling Procedure

The Applying Research to Policy and Practice for Health (ARCH) stakeholder mapping tool will be used to guide our mapping process [22] to identify stakeholders to participate in FGDs in WP1. FGDs will consist of approximately 6 to 8 participants each, and we anticipate holding 5 FGDs or until theoretical saturation is reached. We will start by making a list of stakeholders in the trauma or injury prevention and alcohol policy fields according to 4 categories: academic, clinical,

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operational, and policy stakeholders. Snowballing techniques from the initial core group will be used to identify additional stakeholders. Stakeholders will then be placed in a power-interest matrix based on the information outlined in the mapping [22] in order to categorize South African trauma and injury stakeholders according to their role in the professional landscape, to understand methods of engagement, and to lay out the proposed engagement strategy for the stakeholders throughout the project. FGDs will be exploratory and use a descriptive and contextual design [23]. Participants identified through this process will be invited to take part and required to provide informed consent before participation. FGDs with participants will take place over a 2-month period and will take place digitally to accommodate stakeholders in different locations. These FGDs will be guided by a semistructured interview sheet and run for between 45 and 60 minutes. They will be conducted by a trained facilitator in English.

For inclusion in the WP1 validation study, consenting patients presenting at the trauma units will be 18 years and older and injured <6 to 8 hours prior to arrival at the facility. All new consecutive admissions meeting the inclusion criteria will be tested for alcohol use. Unconscious, ventilated patients, and intoxicated patients with a breathalyzer (BrAC) test result >0.10 mg/L, who will be regarded as too intoxicated for informed consent, will require delayed consent to participate. Patients with severe cognitive impairment will be excluded. If the capacity to consent later is not regained, patients will be excluded. The required sample size to validate and assess the diagnostics' performance is estimated to be 1000 patients. This is based on the eligibility criteria and a targeted sample of cases stratified into a 5-level category variable of intoxication and ICD-10 Y91 severity (Multimedia Appendix 1). From prior studies [24], we expect that 40% will be ineligible for study entry, and a further 60% of the 600 eligible participants will have no alcohol detected or below 0.05 g/100 mL as the legal driving limit. The remaining 4 groups with a positive alcohol detection ("a patient who has a BAC reading of 0.05 g/100 mL" or above) will be closely monitored to ascertain that a minimum of 60 cases per BAC versus ICD-10 Y91/diagnostic measurements code category is captured. Using the expected 60%/40% split in zero versus positive for alcohol, we expect 360 zero alcohol and 240 alcohol-related cases; we do, however, expect that the distribution will vary across BAC categories.

Based on these assumptions, and to test a strict margin that the null hypothesis (k_0=0.7) and the alternative hypothesis (k_1=0.8) will be considered as substantial agreement, further input variables to determining the sample size included the 5 categories with frequencies equal to 0.6 (proportion of 0 alcohol cases) and 0.1 (for each proportion of the 4 remaining alcohol-positive categories). Based on this, we are expecting a sample size of 396 participants at 90% power. This power calculation is based on a significance level of P<.05. Hence, we expect our targeted sample of 600 eligible cases to be enough.

The same sampling strategy will be applied to select patients for the WP2 field testing of validated alcohol diagnostic tools in a district hospital trauma setting and estimated to be approximately 1000 patients. For WP2, the alcohol diagnostic tools will be used in separate data collection periods for ease of use. As the selected district hospital has a monthly average caseload of approximately 561 cases [18], we will plan to collect an approximate sample of 400 eligible cases for 1 alcohol diagnostic tool (breathalyzer), followed by a week's break, then for an additional 400 eligible cases to test a second diagnostic tool (fingerprick test) over the study's planned duration of 90 days.

For WP3, hospital staff from the validation of alcohol diagnostics and field testing will be invited to participate in FGDs (step 1). These will follow the same procedures described previously for the prioritization of methods, and we will include a summary of relevant updated study information. In step 2, national or provincial policy and health management stakeholders and the hospital staff from step 1 will be invited to participate in a feedback workshop to lobby for uptake and implementation nationally and provincially. They will be complemented by approximately 30 key public health, clinician, health management, injury prevention, and policy stakeholders identified using the ARCH stakeholder mapping tool. Step 2 will be held in a hybrid web-based and in-person workshop at the SAMRC in Cape Town after the FGD data have been analyzed. For step 3, we will work with the SAMRC Corporate and Marketing Communications division for policy brief, infographic, and short video design or production. This is for dissemination and engagement with community stakeholders, for research translation and recommendations to national or provincial policy and health management stakeholders, suggesting uptake and integration to other hospital trauma facilities.

Data Collection

The FGDs in WP1 will be conducted to explore stakeholders' knowledge and views on current alcohol indicators collected in trauma settings and gaps in the collection of indicators. We will also obtain opinions from these stakeholders about diagnostic tools, implementation barriers, facilitators, feasibility, acceptability and the appropriateness of collecting routine, and reliable injury surveillance and alcohol-related harm. The findings from this substudy will inform the study on the validation of alcohol diagnostic measures.

For the validation of alcohol diagnostics (WP1), a draft survey questionnaire was adapted from the WHO Collaborative Study on Injuries and Alcohol, a study validated across multicountry sites globally [24]. Information on the injury intent, mechanism, clinical screening according to ICD-10 code Y91, and breathalyzer analysis were retained with additions including the 2 alcohol diagnostic tools (the withdrawal of blood for testing and the fingerprick measure), time of blood withdrawal and fingerprick, the South African Triage Scale, an indication of delayed consent, referring hospital name (if applicable), and hospital folder number.

Fieldworker study nurses will be employed and trained on informed consent and completion of the survey content, and the questionnaire or data capturing on the Kobotools platform [25], using the study's electronic tablet devices. Fieldwork will occur over a 3-month period, with regular monitoring of the caseload

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to inform any adjustments to the schedule until the targeted sample of 1000 cases is achieved, of which 600 cases are estimated to be eligible. Study nurses will be required to work midweek during daytime hours as required and during night duty hours of 7 PM to 7 AM over weekends.

Blood samples will be couriered on a regular basis to a Pathcare laboratory near Groote Schuur Hospital. Preservation of the alcohol will be done by centrifuging the samples within 2 hours of blood withdrawal to separate the plasma from the serum and to have it sealed in a separately labeled tube for courier and analysis at a second Pathcare facility identified for blood alcohol testing.

For WP2, the survey questionnaire will be revised for the field testing phase of validated alcohol diagnostics with the addition of questions on the body region injured (head, face, neck, thorax, etc), the nature of injury (fracture, cut, bruise, concussion, etc), the selected alcohol diagnostic tools (Table 1), the patient's drinking history prior to injury, a self-assessment on alcohol intoxication, and information on socioeconomic status.

Table 1. Summary of alcohol diagnostic screening tool measures.

Alcohol diagnostics	Data source
• Clinical assessment: An observational assessment of alcohol intoxication conducted by a trained nurse or medical doctor. The assessment measures the severity of speech impairment, motor coordination, behavioral disturbances, etc through the use of a Likert scale (none to very severe) using ICD-10[a] Y91 codes	• WHO[b] evidence of alcohol involvement is determined by the level of intoxication (ICD-10 Y91 codes) [26]
• Active breathalyzer testing: The blood alcohol concentration measured in breath alcohol (BrAC) mg/L in exhaled breath through a straw. The minimum breath alcohol content detected is 0.03 mg/L BrAC. Alcohol can be detected up to 6-12 hours after the last drink. This method will not be used on ventilated patients • Passive breathalyzer testing: Exhaled breath for all patients to indicate the presence or absence of breath alcohol (yes or no)	• Dräger: SANAS-accredited breathalyzer screener used by blowing through a sterile mouthpiece for a digital reading (active) • Passive: indicate the presence or absence of breath alcohol (yes or no)
• Fingerprick test: Accurate measurement of capillary whole blood samples collected via fingerprick using a lancet. Results displayed in %BAC, mg/L, or µg/dL BrAC. The lowest level of detection is 0.03% BAC	• Fingerprick test: rapid blood alcohol meter
• Blood sample: Detecting the presence or absence of ethanol in the blood [27] using enzyme immunoassay. Venous blood was collected by qualified nurses in a sodium fluoride tube; alcohol levels were reported in g/dL	• Testing with a venous blood sample

[a]ICD-10: International Classification of Diseases, Tenth Revision.

[b]WHO: World Health Organization.

Fieldwork will be based on an idealized week, with a selection of hours across day- and nighttime, during the 3-month period. This is to ensure that the data are representative in terms of the facilities' operating conditions, which are expected to change by time of the month, hour, weekday or weekend, and so forth to assess the suitability of the alcohol diagnostic tools for possible national scale-up.

In WP3, FGDs with participants in step 1 will take place digitally to accommodate stakeholders in different locations. Interview guides will consist of open-ended questions to explore participants' views on the recommended methods, their thoughts on the requirements for implementation (provincially and nationally), and what the role of the measure would be in health care provision more broadly. Specific areas to discuss will include (1) intervention content; (2) intervention delivery; (3) strategies for addressing possible barriers to intervention delivery; (4) research questions around acceptability, feasibility, and sustainability of measuring alcohol-related trauma; and (5) strategies to generate local stakeholder buy-in. These areas of discussion will ensure appropriate information are collected that will inform national stakeholders on the benefits for the adoption of the recommended alcohol diagnostic screening tools for larger implementation [28].

For step 2, the findings from WP1 and WP2, as well as the FGD results from WP3 (step 1) will be shared in a workshop with researchers; clinicians and hospital managers; traffic officials; emergency medical services; police, pathology, and rescue services; and national and provincial policy makers. The output will be a framework to guide the implementation and scale-up of routine diagnostic measuring of alcohol-related trauma. Workshop participants will be asked to evaluate the usefulness of the workshop and their satisfaction with the outcome.

Data Analysis

WP1 and WP3 FGDs will be audio recorded and transcribed verbatim. Thematic analysis will be conducted based on deductive themes focusing on the exploration of current practices, implementation barriers, facilitators, feasibility, acceptability, and appropriateness of conducting alcohol diagnostics in public health facilities (WP1.1) and on acceptability, feasibility, and appropriateness of the recommended measure (WP3). The data will be managed using qualitative data analysis software NVivo (version 12; Lumivero)

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and will be presented in line with COREQ (Consolidated Criteria for Reporting Qualitative Research) guidance for reporting qualitative research [29].

For the validation of alcohol diagnostics in WP1 and WP2, data collection will be regularly monitored and managed by the study statistician. The blood alcohol analysis results will be merged into the main database using the unique case ID. The correlation coefficients of the continuous alcohol diagnostic measurements and the blood alcohol tests will be reported and represented graphically. A Kappa statistic [30] will be used to assess the level of agreement between BAC categories and the various alcohol diagnostic tests and the clinical assessment as per ICD-10 (International Classification of Diseases) Y91 codes. Taking into consideration that the alcohol diagnostic measures are ordinal responses, we will use ordinal regression to model the receiver operating characteristic (ROC) curve [31,32]. This diagnostic test plots sensitivity against the specificity of the alcohol diagnostics measures against the gold standard BAC. The area under the ROC curve will also be used to characterize the accuracy of the diagnostic tests, providing all information on its performance, instead of only a single estimate of the test's sensitivity and specificity. The trade-offs between the ROC curve's sensitivity and specificity can then be assessed to inform a decision threshold [33,34] for the alcohol diagnostic methods to be used in phase 2. Any level above 70%, sensitivity and specificity will be acceptable and is usually considered as "fair," followed by 80% as "good" and 90% as "excellent."

If multiple tests meet the same criteria, we will use the area under the curve to determine the best test. We will, however, proceed to test the feasibility of use for both the breathalyzer and the Fingerprick test if they meet the specified sensitivity and specificity criteria. Besides reporting the results of validating the alcohol diagnostic tools, descriptive statistics for analysis will include age and gender, followed by an analysis of the severity of the injury (assessed by the triage scale), the intent of the injury (violence, road traffic, unintentional, and self-harm), the related mechanism of injury (ie, gunshot, stabbing, pedestrian, driver, fall, etc), and BAC categories. Data analysis will be conducted on STATA (version 17; Stata Corp). Data will be presented in line with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidance for reporting cross-sectional studies [35].

For the field testing (WP2), we will follow the same data management and analysis procedures and packages as for the validation of alcohol diagnostics. Further analysis will include patient demographics, the nature of injury (fracture, sprain, open wound, burn, etc) and body region injured, the intent of the injury (violence, road traffic, unintentional, and self-harm) and the related mechanism of injury (ie, gunshot, stabbing, pedestrian, driver, fall, etc), and triage scale. We will use ordinal regression to analyze the severity of injuries (as indicated by the triage scale) as the outcome, and the level of intoxication (indicated as 0.05 g/100 mL and above) as one of the independent variables. In addition, a multinomial regression will be used to assess the association between the outcome as the type of injury with the level of alcohol intoxication. As information on drinking prior to injury will be recorded to determine the type of alcohol and volume consumed, the dose-response relation between the number of drinks consumed within 6 hours leading up to the injury and the relative risk of being injured will be analyzed and reported. Socioeconomic information on employment status, household income, and suburb of residence will be captured and used to inform alcohol policies.

For the workshop evaluation form in WP3, we will sum each evaluation item to create scores for the evaluation form and will summarize using mean with the SD or median with IQR.

Patient and Public Involvement

Clinicians are an important participant group and were involved in the initial design of the study and as coinvestigators. We will be using a participatory approach through stakeholder engagement initiated in the prioritization of methods to include community and patient representation; then incorporating a synthesis of findings from the validation of alcohol diagnostics and suitability testing to conduct qualitative research on the use of the recommended alcohol diagnostic method. Feedback will be sought on requirements for uptake and integration within the health system, which has a specific focus on community-based participatory research for study synthesis and recommendations. This final uptake activity is iterative and dependent on the outcomes of the formative work. Therefore, the study overall is geared to soliciting participant co-design.

Ethical Considerations

Ethical approval for the study has been granted by the research ethics committee of the South African Medical Research Council (EC005-2/2022) and approval from the Western Cape Health Department. Written informed consent will be obtained from all study participants, and all data will be anonymized. No compensation will be provided for study participation.

Results

Pilot data are being collected, and the protocol will be modified based on the results. The findings will be disseminated to relevant national and provincial government departments, policy experts, and clinicians. We will publish findings in scientific journals, engage in media advocacy, and share findings with our stakeholders, including community representatives, nonprofit partners, and civil society organizations.

Discussion

There is a lack of routine and reliable injury surveillance specifically alcohol-related harm data in South Africa to respond to the related trauma burden. Additionally, research to develop systems or reliable mechanisms to test alcohol-related trauma and to monitor the impact of interventions is lacking. Alcohol is an established risk factor for violence and injuries and accurately monitoring alcohol relatedness in response to interventions, policy changes, and so forth will be necessary to evaluate effectiveness as suggested by the WHO SAFER strategy of "*Monitoring*," 1 of 3 essential strategies aimed at government officials for the purpose of developing evidence-based alcohol policies and action plans to address alcohol harm [36]. The prominent role of alcohol in the trauma

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setting has become particularly pronounced during the COVID-19 lockdown, and this study will provide crucial evidence needed for the effective measurement of alcohol-related trauma to improve injury surveillance and clinical management. A few limitations of the study have been identified. First, expert stakeholders included in FGDs will be restricted to known contacts within the field. However, by using the ARCH stakeholder mapping tool to identify appropriate stakeholders, we are confident that we will involve relevant individuals, groups, organizations, and institutions and engage with them in a manner that can contribute to successful research uptake [22]. Second, the validity testing of the alcohol diagnostics will use enzyme immunoassay instead of the gold standard gas chromatography method. The detection of ethanol by gas chromatography, which has the advantage of being able to separate ethanol from other alcohol, is widely considered as the "gold standard" for alcohol measurement [21,27]. Due to the cost implications for this method of testing and the fact that we will not be using the results of this study in medicolegal cases, we will be using enzyme immunoassay [21] for testing of blood alcohol and will consider this as the gold standard for the purpose of this study. Third, validity testing at a tertiary hospital could influence the cut-off period to detect alcohol within the blood due to referrals from primary and secondary health facilities. However, the selected tertiary hospital was specifically selected as the site for validating the alcohol diagnostic tools, as it is a large tertiary hospital situated in Cape Town, South Africa, where the trauma unit is burdened by high injury caseloads, particularly for violence and road traffic injuries [16,17,37]. Through this study, we hope to identify and validate the most appropriate methods of diagnosing alcohol-related injury and violence in clinical settings. The findings from this study are likely to be highly relevant and could influence our primary beneficiaries—policy makers and senior health clinicians—to adopt new practices and policies around alcohol testing in injured patients.

Acknowledgments

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Data Availability

The data generated and analyzed during this study was subject to restricted consent from participants. The data can be made available by the corresponding author upon reasonable request.

Authors' Contributions

PPW and MP conceptualized the paper and are joint first authors. PPW, RM, and MMP developed the first draft. PPW, MP, MMP, IN, S Mhlongo, S Maqungo, CP, and RM edited the subsequent versions of the draft. All authors have reviewed and accepted the final version of the protocol and given their permission for publication. MMP, CP, and RM are joint last or senior authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Targeted sampling strategy with minimum sample requirement, prior to eligibility assumptions by blood alcohol concentration reading and Y91 code.
[PDF File (Adobe PDF File), 147 KB - resprot_v13i1e52949_app1.pdf]

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Abbreviations

ARCH: Applying Research to Policy and Practice for Health
BAC: blood alcohol concentration
COREQ: Consolidated Criteria for Reporting Qualitative Research
FGD: focus group discussion
ICD-10: International Classification of Diseases, Tenth Revision
ROC: receiver operating characteristic
SAMRC: South African Medical Research Council
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WP: work package

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Protocol

Group Acceptance and Commitment Therapy for Recovery From Psychosis: Protocol for a Single-Group Waitlist Trial

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Abstract

Background: Psychological interventions, along with antipsychotic medications, are recommended for adults diagnosed with a psychotic disorder. While initially designed to mitigate positive symptoms, psychological interventions targeting personal recovery were developed and aligned with the recovery framework that many mental health services have adopted. Acceptance and Commitment Therapy (ACT) for psychosis is one such intervention that shows promise when delivered in an individual format. There is preliminary evidence that ACT for psychosis in a group format improves recovery.

Objective: This trial aims to evaluate the effectiveness of the "Recovery ACT" group program on personal recovery among adults living with a psychotic disorder.

Methods: Our unfunded study is a multiagency, prospective, nonrandomized, waitlist control, single-group trial of the Recovery ACT group program. The program involves 7 weekly group sessions of 90 minutes duration and a 90-minute booster session held 1 month later. We intend to recruit 160 adults living with a psychotic disorder who enroll in a group that is offered as a routine clinical service at participating public mental health services in Melbourne, Victoria, Australia. The 4 assessment time points are 4-6 weeks before the start of the group program, at the start of the group program, at the end of the group program, and at the booster session. There is an optional midgroup assessment and follow-up study. The primary outcome is personal recovery. Secondary outcomes include participants' well-being and psychological flexibility processes. Qualitative data are also collected from participants and facilitators.

Results: Recruitment began in September 2019 and is ongoing until 2024, subsequent to a 24-month disruption due to the COVID-19 pandemic. As of the submission of this paper, 93 participants consented to the evaluation, 65 completed T1 measures, and 40 had a complete data set for the proposed analyses.

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Conclusions: This is the first trial evaluating the effectiveness of the Recovery ACT group program on personal recovery for adults living with a psychotic disorder. Findings will contribute to knowledge about psychosocial interventions for adults living with psychosis. This trial may also serve as an example of a partnership between clinicians and academics that can facilitate the translation of research into practice.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000223932; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000223932

International Registered Report Identifier (IRRID): DERR1-10.2196/49849

(JMIR Res Protoc 2024;13:e49849) doi:10.2196/49849

KEYWORDS

Acceptance and Commitment Therapy; ACT; group therapy; interventions; personal recovery; protocol; psychosis; psychotic disorders; public mental health services

Introduction

Background and Rationale

Schizophrenia spectrum disorders have a prevalence rate of 3.3 per 1000 individuals worldwide [1], with schizophrenia ranking as the twelfth most disabling disorder [2]. Psychotic disorders are typically first diagnosed in young adulthood and can run a chronic course [3]. About two-thirds of individuals diagnosed with a psychotic disorder continue to experience persistent psychotic symptoms despite adhering to antipsychotic medication regimens; about 20% do not respond at all [4]. In addition, there is a high prevalence of comorbid anxiety and mood disorders—about 40% experience anxiety [5,6] and 30%-80% experience depression [6,7]—and other challenges (eg, stigma and social exclusion) that impact well-being and functioning. Persisting psychotic symptoms, comorbid anxiety and depression, and other challenges not only contribute to an individual's level of distress and functioning but also impact a person's ability to fully engage in life [8], referred to as personal recovery [9].

For over 2 decades, psychological and psychosocial interventions have been internationally recommended as adjuncts to pharmacological interventions [10-13]. The leading evidence-based psychological intervention recommended for psychotic disorders is cognitive behavioral therapy for psychosis (CBTp). This intervention involves teaching skills to modify unhelpful thinking patterns that impact behavior [14] and primarily targets reduction in psychotic symptoms and, arguably, distress and functioning as well. While meta-analyses demonstrate that CBTp reduces psychotic symptoms (most notably positive symptoms) with a small effect size [15-17], CBTp does not appear to mitigate distress or improve quality of life [18]. The latter findings continue to be challenged [19,20]. Modifications of CBTp (eg, low-intensity CBTp [21,22] and group CBTp [23]) are promising, though they have yet to amass robust evidence to be recommended in treatment guidelines.

Another promising psychological therapy for psychotic disorders is Acceptance and Commitment Therapy (ACT). This approach involves developing psychological flexibility, which is the ability to be in conscious contact with the present moment, and the capacity to persist with or change behavior based on whether it aligns with one's personal values [24]. Psychological flexibility processes include willingness to be with mental experiences (thoughts, feelings, sensations, etc) instead of engaging in experiential avoidance; cognitive defusion (distancing or observing with openness and curiosity) with mental experiences; engagement in valued actions; and mindfulness (ie, awareness of the present moment) [24]. ACT adapted for individuals living with a psychotic disorder has been implemented in both inpatient and outpatient settings. There is emerging evidence [25] that this intervention not only reduces rehospitalization [26-28] but can also improve quality of life and personal recovery [29].

The first ACT for psychosis group intervention targeting quality of life and social functioning was a 4-session group (2-hour sessions run weekly) known as the "ACT for Life" program, a manualized protocol developed by researchers in the United Kingdom for adults living with psychosis [30,31]. An initial uncontrolled study evaluating this program at a community psychosis service in the United Kingdom [32] demonstrated small improvements in functioning and mood after group completion. A subsequent controlled study [33] demonstrated the positive effects of group participation on well-being over time and greater independence, as indicated by service use changes. Both studies demonstrated that the group was feasible and acceptable to adults living with psychosis.

Building on promising results from individual and group ACT programs for psychosis, the ACT for Life program was adapted for public outpatient mental health services in Melbourne, Victoria, Australia [34]. A pilot of the adapted program, referred to as "Recovery ACT," was implemented by public mental health service clinicians as part of their routine practice and evaluated using pre- and postgroup outcome measures together with qualitative feedback from facilitators and participating consumers [35]. Results from the uncontrolled pilot study involving 9 groups and 90 consumers demonstrated that the program and its evaluation were feasible, acceptable, and safe [35]. Significant increases in personal recovery, well-being, and psychological flexibility were observed from the start to the end of the program. The extent of consumer and clinician interest in the groups, both from the original agency and additional agencies, strongly indicated the feasibility of conducting a more extensive evaluation. Building on this momentum, our clinician-academic partnership agreed to conduct this more stringent trial by incorporating a waitlist control period and an established measure of personal recovery as the primary outcome.

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Objectives

The primary aim is to evaluate the effectiveness of the Recovery ACT group program on personal recovery for adults living with a psychotic disorder in routine clinical practice across public mental health organizations in Australia using a single-group, waitlist control design. A secondary aim is to evaluate the effect of the Recovery ACT group program on well-being and psychological flexibility processes (experiential avoidance, cognitive defusion, engagement in valued actions, and mindfulness). The research questions are as follows: (1) What are the clinical benefits and risks of the Recovery ACT group program for adults diagnosed with psychotic disorders as conducted in routine practice in Australia? (2) Are there changes in psychological flexibility processes due to participation in the Recovery ACT group program? (3) Are changes in psychological flexibility processes associated with changes in personal recovery and well-being?

The primary and secondary hypotheses are that the longitudinal trajectory of personal recovery and the secondary outcomes will not significantly change over the waitlist period, then will improve from the start to the end of the group program, and then improve at a less rapid rate from the end of the group to the booster session. A further hypothesis is that changes in psychological flexibility processes during the first half of the group program will be associated with changes in personal recovery and well-being in the second half of the group program.

Methods

Participants and Study Setting

We plan to recruit a minimum of 160 adults (aged between 18 and 65 years) who enroll in a Recovery ACT group program at 1 of 4 public mental health service study sites in Melbourne (NorthWestern Mental Health, St Vincent's Mental Health Service, Alfred Mental and Addiction Health, and Peninsula Health Mental Health Service). The target minimum number of participants at NorthWestern Mental Health is 95 participants, and 32 participants each at the other study sites. The overall recruitment target was based on the minimum sample size needed to complete the intended analyses and an anticipated 60% participant retention rate based on the pilot study [35].

The inclusion criteria are a primary file diagnosis of either schizophrenia spectrum disorder or other psychotic disorder, a mood disorder with psychotic features, or a substance-induced psychotic disorder; currently receiving outpatient mental health care at 1 of the study sites; and current enrollment in a Recovery ACT group program. The exclusion criteria are lack of capacity to consent to the evaluation; lack of proficiency in speaking and comprehending English; a file diagnosis of intellectual disability or borderline personality disorder.

Study Design

This trial is a multiagency, prospective, longitudinal, nonrandomized, waitlist control, single-group study among Australian adults diagnosed with a psychotic disorder who participate in a routine Recovery ACT group program. The design includes 4 assessment time points: the start of the waitlist period (approximately 4-6 weeks before the start of the group program), the start of the group program (0 weeks), the end of the group program (about 6 weeks after the start of the group program), and the booster session (about 10 weeks after the start of the group program). Some participants may complete outcome measures at the midpoint session (T2, which is 3 weeks after the start of the group program) if the study site is resourced to collect data at an additional time point. Quantitative data from facilitators about participants' clinical severity and clinical improvement will be collected before, during, and after the group program, as well as relevant demographic and clinical information collected at baseline from participants' electronic medical records. At either the end of session 7 or the booster session, participants will be asked to provide written consent for study personnel to contact them for a follow-up study. Facilitators will be invited to complete a semistructured interview with senior investigators after each group program to gather qualitative data about the feasibility of the group program in routine practice and to assist in the interpretation of the quantitative measures completed by participants. The protocol development addressed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendix 1) guidelines [36] and intends to adhere to the CONSORT (Consolidated Standards of Reporting Trials; Figure 1) criteria [37]. We retrospectively registered the trial with the Australian New Zealand Clinical Trials Registry; Table 1 lists the trial registration data set.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the Recovery ACT Trial. ACT: Acceptance and Commitment Therapy.

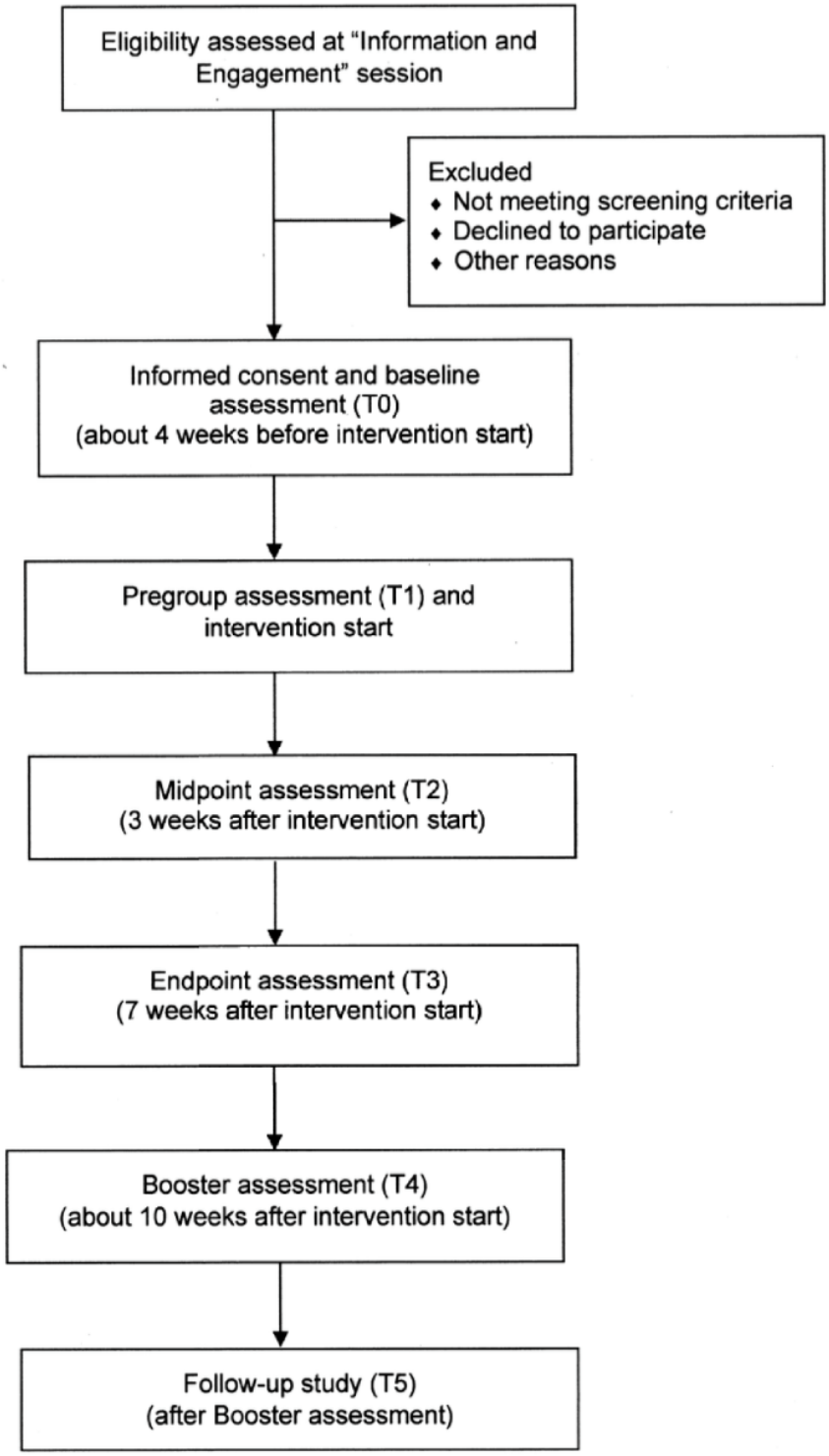

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Table 1. World Health Organization Trial registration data set.

Data category	Information
Primary registry and trial identifying number	ANZCTR, ACTRN12620000223932
Date of registration in primary registry	February 24, 2020
Secondary identifying numbers	UTN: U1111-1247-8144
Source of monetary or material support	Royal Melbourne Hospital, NorthWestern Mental Health
Primary sponsor	Royal Melbourne Hospital, NorthWestern Mental Health
Secondary sponsor	La Trobe University
Contact for public enquiries	Dr Eric Morris
Contact for scientific enquiries	Dr Marilyn Cugnetto
Public title	Acceptance and Commitment Therapy (ACT) Group Program for Recovery from Psychosis: A Multi-Agency Evaluation
Scientific title	A Multi-agency Evaluation of the Routine Practice of an Acceptance and Commitment Therapy Group for Recovery from Psychosis
Countries of recruitment	Australia
Heath conditions or problems studied	Psychosis, Mental Health, Schizophrenia
Interventions	Treatment: “Recovery ACT for Psychosis” Group Program; comparator or control: single group, waitlist control period
Key inclusion and exclusion criteria	
Inclusion criteria	Inclusion criteria: Out-patients aged between 18 and 65 years; have a primary file diagnosis of either a schizophrenia spectrum or other psychotic disorder, a mood disorder with psychotic features, or a substance-induced psychotic disorder; are currently receiving outpatient mental health care at one of the study centers; are self-referred or referred by clinical staff to a Recovery ACT group being conducted by a participating center.
Exclusion criteria	Exclusion criteria: lack of capacity to consent to this evaluation; lack of proficiency in speaking and comprehending English; file diagnosis of an intellectual disability (an intellectual development disorder) or borderline personality disorder.
Study type	Interventional
Allocation	• Nonrandomized trial • Intervention assignment: single-group • Masking: open (masking not used)
Primary purpose	Treatment
Phase	N/A[a]
Date of first enrollment	September 13, 2019
Target sample size	160
Recruitment status	Recruiting
Primary outcomes	Personal recovery
Key secondary outcomes	Well-being

[a]N/A: not applicable.

Procedure

Recruitment

Participants will be recruited from current consumers of the services enrolled in a Recovery ACT group program as part of their normal clinical care. Recovery ACT group programs are conducted at all 4 participating sites, either as part of a program of groups offered to consumers or as periodic opportunities. All sites follow the same recruitment plan. Recruitment will continue until the target is met, as long as the clinical services are willing to continue to support the evaluation. Facilitators will describe the group program and the evaluation study at staff meetings and with fellow clinicians at their study site to ensure they are aware that an evaluation of the program is occurring and that consumers will be invited but not obligated to participate. Facilitators will receive all referrals to the group program and contact potential consumers to schedule an “Information and Engagement” session to brief consumers about the group program and confirm their wish to attend. All consumers who enroll in the group program will be screened for eligibility to participate in the evaluation. Consumers who

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meet the eligibility criteria will be provided with an explanation of the study, an information sheet, and an evaluation brochure, and those who choose to participate will be required to provide written informed consent.

After the completion of a group program (after the booster session), senior investigators will invite facilitators to participate in a semistructured group interview for evaluation purposes and seek informed consent.

Due to the time elapsed from the initial consent process, all group members will be asked again at either session 7 or the booster session for permission and written consent to contact them in the future to invite them to participate in a follow-up study on the experience of participating in the group.

Intervention

The Recovery ACT group program includes 7 core sessions scheduled weekly and a booster session scheduled approximately 4 weeks later. The duration of all sessions is 90 minutes, and they are delivered in person. The intervention is an adaptation of the ACT for Life program [30] that centers on a core metaphor (passengers on the bus) [38] to facilitate consumers' engagement in value-based actions when relating to their internal experiences (eg, thoughts, feelings, and memories) once they become aware of the internal experiences and are able to defuse (or cognitive distance) from them. The group focuses on developing awareness of internal experiences through metaphors and mindfulness activities and building defusion skills. In the metaphor, the "bus" represents the consumer's life in the present moment, the "bus driver" is the consumer, and the "passengers" on the bus are the consumer's internal experiences. The topics covered during the core sessions include: introduction to noticing (mindfulness) of present experiences and values; enacting the core passengers on the bus metaphor and "specific, meaningful, adaptive, realistic, and time-framed" (SMART) goals; review of values, noticing, and willingness; identification of passengers and different ways of responding to them and development of noticing skills; passengers on the bus and changing relationships with words; review of values and encouragement of sharing value-guided actions; and review of key group messages. Brief contact with consumers between sessions is encouraged to promote completion of home practice and to encourage attendance.

There are no specified criteria for discontinuing or modifying the intervention, as this is an evaluation of a group program as conducted in routine clinical practice at local mental health services. Participants can choose to withdraw from the evaluation and remain in the group program. Participants may be withdrawn from the study due to a protocol violation or an adverse event.

Facilitators will be clinical mental health staff employed at a participating public mental health service who, where possible, have participated in an introductory ACT workshop and completed training in Recovery ACT. The group is led by 2 facilitators, one of whom is experienced (ie, has previously led a Recovery ACT group program) and adheres to the Recovery ACT group program manual [39]. Facilitators will be invited to attend a minimum of 3 "Support and Supervision" sessions while facilitating a group. The goal of these sessions is to enhance fidelity to the Recovery ACT group program manual [39]. In addition, facilitators will complete a fidelity log after each group session.

There are no restrictions on concomitant care and interventions, as this is an unfunded evaluation of the Recovery ACT group program that is already offered in routine clinical care at the participating public mental health services. To participate in the Recovery ACT program, participants must be receiving care at the respective public mental health service. As such, participants will receive provisions for ancillary and posttrial care at the public mental health service. The potential risks related to the study are deemed minimal. Facilitators are responsible for participants' clinical care during the group program, including distress related to study procedures. Participants have a key support clinician for out-of-group issues that may arise.

Outcomes

Timeline

The schedule of enrollment, interventions, and assessments is displayed in Figure 2. The quantitative self-report outcome measures are intended to be completed independently at the start of the waitlist period (T0, approximately 4-6 weeks before the start of the group program, typically at the "Information and Engagement" session), at the start of the group program (T1), at the end of the group program (T3, which is 6 weeks after the start of the group program), and at the booster session (T4, about 10 weeks after the start of the group program). Some participants may complete outcome measures at the midpoint session (T2, which is 3 weeks after the start of the group program) if the study site is resourced to collect data at an additional time point. Measures are completed after the group session, except for at T1, when participants complete measures before the start of the group to ensure no exposure to the program's content. Participants can request assistance from facilitators to complete the measures. Demographic and clinical information will be obtained from participants' electronic health records at T0 and will include their date of birth, gender, ethnicity, country of birth, highest level of educational attainment, highest level of employment, current employment status, primary mental health file diagnosis, co-occurring mental health file diagnoses, date of first contact with mental health services, number of listed episodes of outpatient mental health care, and number of psychiatric admissions.

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Figure 2. Schedule of enrollment, interventions, and assessments.

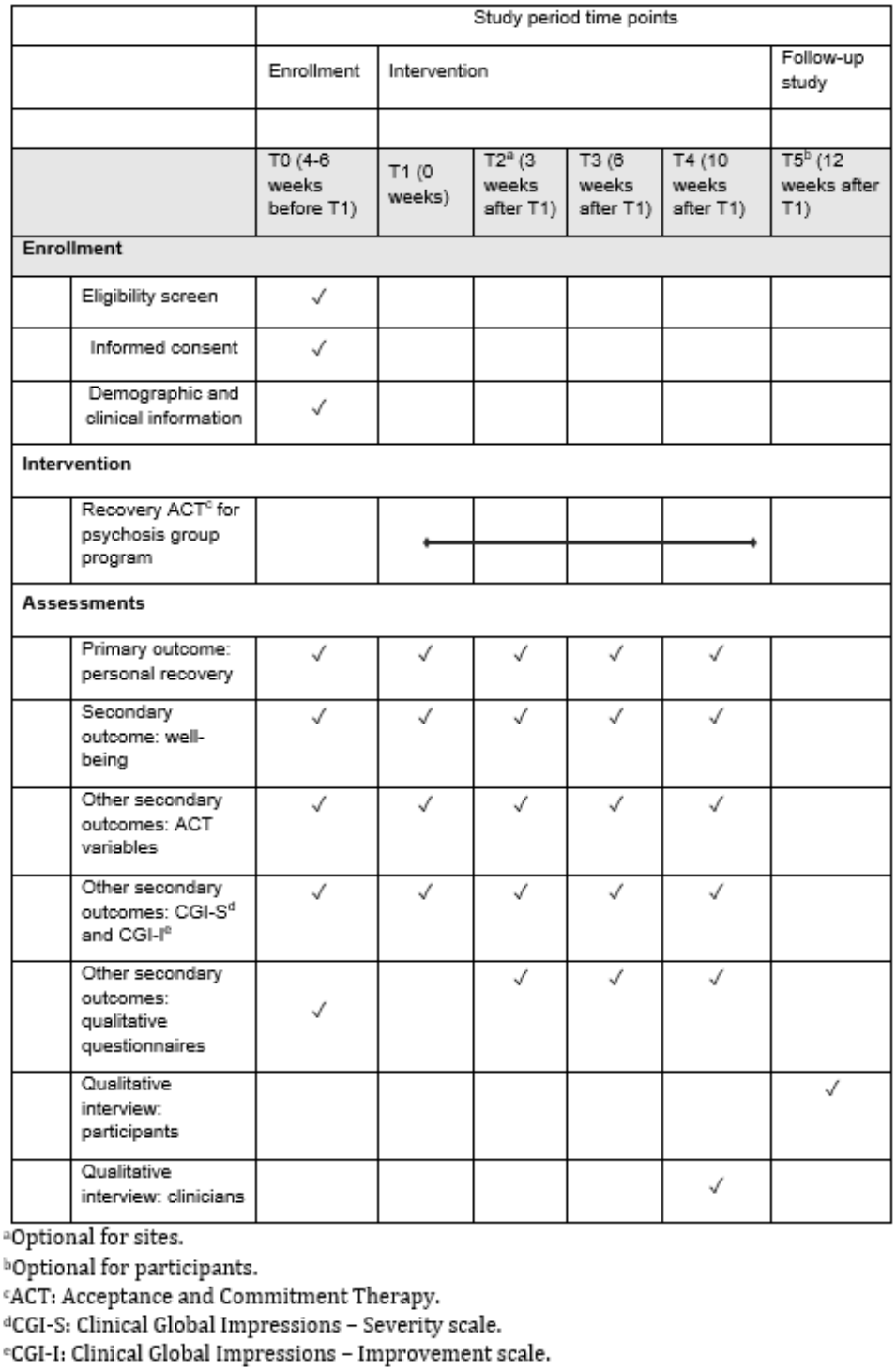

		Study period time points					
		Enrollment	Intervention				Follow-up study
		T0 (4-6 weeks before T1)	T1 (0 weeks)	T2[a] (3 weeks after T1)	T3 (6 weeks after T1)	T4 (10 weeks after T1)	T5[b] (12 weeks after T1)
Enrollment							
	Eligibility screen	✓					
	Informed consent	✓					
	Demographic and clinical information	✓					
Intervention							
	Recovery ACT[c] for psychosis group program		←	—	—	→	
Assessments							
	Primary outcome: personal recovery	✓	✓	✓	✓	✓	
	Secondary outcome: well-being	✓	✓	✓	✓	✓	
	Other secondary outcomes: ACT variables	✓	✓	✓	✓	✓	
	Other secondary outcomes: CGI-S[d] and CGI-I[e]	✓	✓	✓	✓	✓	
	Other secondary outcomes: qualitative questionnaires	✓		✓	✓	✓	
	Qualitative interview: participants						✓
	Qualitative interview: clinicians					✓	

[a]Optional for sites.
[b]Optional for participants.
[c]ACT: Acceptance and Commitment Therapy.
[d]CGI-S: Clinical Global Impressions – Severity scale.
[e]CGI-I: Clinical Global Impressions – Improvement scale.

Primary Outcome

The primary outcome is personal recovery, as measured by the 15-item version of the Questionnaire about the Process of Recovery (QPR) [40,41]. The 15-item QPR has good internal consistency (QPR total α=.89), fair to good test-retest reliability (QPR total intracluster correlation coefficient [ICC]=0.74), moderate sensitivity to change, and adequate convergent validity [42]. The QPR is a measure that assesses the 5 core processes of personal recovery that comprise the "Connectedness; Hope and optimism about the future; Identity; Meaning in life; and Empowerment" (CHIME) framework [43], which is currently the strongest conceptualization of personal recovery in serious mental illness. The Recovery ACT group program seeks to support change in these dimensions for participants.

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Secondary Outcomes

The secondary outcomes are well-being (Clinical Outcomes in Routine Evaluation 10 [CORE-10]) [44] and 4 psychological flexibility process variables, namely committed action (the Valuing Questionnaire's Progress scale comprised of items 3, 4, 5, 7, and 9) [45], mindfulness (Southampton Mindfulness Questionnaire) [46], cognitive defusion (Cognitive Fusion Questionnaire) [47], and experiential avoidance (Brief Experiential Avoidance Questionnaire) [48].

Other Clinical Outcomes

A facilitator will rate illness severity at enrollment and before the start of the group using the "Clinical Global Impression–Severity" scale and will rate illness improvement at the end of the group and at the booster session using the "Clinical Global Impression–Improvement" scale [49,50].

Consumer and Facilitator Feedback

Permission will be sought from participants to use their responses to routine qualitative feedback questions for evaluation purposes. These questions ask about their hopes and expectations for the group (at T0), helpful and unhelpful aspects of the group (at T2 and T3), requests for remaining sessions (at T2), and reflection on any perceived changes attributed to the group (at T3 and T4). The method of collecting these routine feedback responses is dependent on the site. The baseline feedback questions (at T0) are typically asked and recorded by a facilitator during the "Information and Engagement" session; the feedback questions at other time points are typically written responses by participants. Qualitative data about the group will be sought from facilitators who consent to participate in a semistructured interview after completing a group. The qualitative interview will assess the feasibility of the group, its evaluation in routine practice, and perceptions of the group program's effectiveness.

In addition, during the initial consent process, participants will be asked for written consent to contact them in the future to invite them to participate in a follow-up study involving a qualitative interview exploring their experience of participating in the group.

Statistical Methods and Sample Size

We intend to use an intention-to-treat sample to test a univariate latent growth curve model of the primary outcome from before the start of the waitlist period to the start of the group to the booster session in order to compare the trajectory over the waitlist period to the trajectory over the active treatment period. We selected this method of analysis to strengthen our estimations of associations due to the limitations of the nonrandomized study design chosen as the most realistic option for an evaluation of a program already in routine practice [51]. A minimum sample size of 90 is required to conduct the proposed growth curve structural equation model (5 observed variables and 2 latent variables) with an anticipated medium effect size (0.3), α set at .05, and power (1–β) at .80. Univariate latent growth curve models for each of the 5 secondary outcomes will also be tested. If there are sufficient data, we will test whether the trajectory of the 4 psychological flexibility process variables from the start of the group to the midpoint session (T1 to T2) is significantly associated with the trajectory of personal recovery (T2 to T4) using multivariate growth models. We do not predict a priori any differences associated with the study site. We intend to calculate the ICC after the data are collected to determine the relatedness of the data collected at different study sites.

Randomization and Blinding

This study is a nonrandomized (unblinded) trial that uses a single group, waitlist control, and a quasiexperimental design. All participants serve as their own control. The data for all participants on change in outcomes over the waitlist period (no active intervention) will be used to compare with the data on change in outcomes during the active intervention. The planned statistical methods will strengthen our conclusions. The risk of researcher bias is lessened by the self-report format of the primary and secondary outcomes and the opportunity for participants to submit questionnaires in a sealed envelope.

Data Collection and Management

The data will be collected using deidentified hardcopies of all evaluation documents (quantitative questionnaires completed by participants and facilitators, copies of qualitative feedback forms, and demographic and clinical information forms), and other trial documents (attendance records, fidelity logs, and recruitment logs). Facilitators will assist participants with questionnaire completion if needed. As facilitators will serve a dual role as clinical service providers and study personnel, participants will be provided a sealable envelope to return deidentified self-report questionnaires that will be reviewed by study personnel other than their facilitators if sealed (either at the site or by the study coordinator). If a participant does not attend a group session when data are collected, facilitators will attempt to schedule an appointment to complete study measures.

Deidentified data from hard copy evaluation documents will be entered into a password-protected electronic file maintained on secure computers by the study coordinator. A coding sheet with identifiable participant information will be saved as a password-protected electronic file on the sponsor site's server. Hard copies of consent forms and study documents will be kept in a locked filing cabinet at the Academic Psychology Unit located at the sponsor's site.

Data Monitoring and Adverse Event Reporting

Anticipated risks to participant safety due to participation in the evaluation and the group are deemed minimal based on pilot study data [35]. Therefore, there is no data monitoring committee, and there are no planned interim analyses to identify risks. Adverse events will be monitored by facilitators, site principal investigators, the coordinating principal investigator, and the Interagency Investigator Committee. An adverse event form and guideline are used.

An Interagency Investigator Committee led by the coordinating principal investigator meets quarterly to oversee the trial's progress, monitor any adverse events or serious adverse events related to the procedures or the group program, and discuss any necessary protocol modifications. A study coordinator is responsible for liaising with the site principal investigators, who

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are responsible for the evaluation at each site. In addition to the published Recovery ACT group program manual, evaluation procedure manuals were created to ensure that the protocol is adhered to by study personnel at all sites and over the course of the multiyear study.

Ethical Considerations

Melbourne Health's Human Research Ethics Committee (HREC/51498/MH-2019) provided ethics approval for this study. All methods will be performed in accordance with the relevant guidelines and regulations, and written, informed consent will be obtained from participants. The results of the main aim of the study will be published in a peer-reviewed scientific journal and submitted for presentation at clinical and scientific meetings and conferences. The coordinating principal investigator will oversee the publication and presentation of study results, including decisions about authorship. Participants are asked whether they would like to be informed of the main results of the study. Those who express interest and provide contact details will be provided with this information when it is available. Participants who complete quantitative outcome measures will be compensated with a US $6.54 department store voucher at each time point.

Results

Trial enrollment began in September 2019 and was originally planned to continue until at least March 2022. In March 2020, the Victorian Government in Australia introduced public health directions in response to the COVID-19 pandemic that derailed study progress as in-person groups were not permitted for over 20 months at some sites. While study recruitment and follow-up study procedures were broadened to allow for the use of telehealth, the group program format (in-person) was not changed as it would introduce significant variability to the study outcomes. As there remains notable interest from all stakeholders (investigators, facilitators, managers, and consumers), the study will continue to accept enrollments until at least 2024. As of the submission of the manuscript, 93 participants consented to the evaluation, 65 completed T1 measures, and 40 had a complete dataset for the proposed analyses. No data analysis has been conducted. Due to the uncertainty of the trial's viability due to the public health directions during the COVID-19 pandemic, the protocol's publication was delayed. The current protocol version is 8.0 (issue date: July 14, 2021).

Discussion

To our knowledge, this is the first trial in Australia evaluating the effectiveness of an ACT for psychosis group program on personal recovery outcomes. Although limited by the single-group design, its strength lies in the opportunity to evaluate effectiveness in routine practice. External validity is strengthened by the practice settings being spread across 4 public mental health networks in a large city, serving communities with a range of sociodemographic characteristics.

A randomized design was not feasible as the program is offered in routine practice [51], thus limiting causal conclusions. However, the quasiexperimental design includes a waitlist period that provides a baseline comparison to evaluate the effectiveness of the group program and can also allow for process analyses if sufficient data are collected. A further enhancement is a proposed qualitative follow-up study of the experience of the group program, intended to inform program development and assist in the interpretation of quantitative results.

A feature of note is the clinician-initiated origin of the evaluation and the forging of a partnership between clinicians and academics during a previous pilot evaluation that then led to the co-design and collaborative implementation of the trial [34]. This clinician-researcher partnership is likely to not only ensure the practical applicability of program modifications and the feasibility of study procedures, but may also lay the foundations for more rapid implementation into practice should the results warrant it. Nonetheless, as an unfunded study, the project is subject to significant risk of noncompletion as it relies on the participating mental health services supporting facilitators to undertake some evaluation tasks, services continuing to provide the group program over the proposed study period, and the support of the sponsor site to provide a study coordinator.

This study exemplifies an effectiveness-implementation hybrid trial [52]. If successful, the trial will further support psychosocial interventions to improve personal recovery among consumers who experience persisting psychotic symptoms.

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Data Availability

The data sets generated during or analyzed during this study are not publicly available as the authors do not have research participants' permission to share data.

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Authors' Contributions

JF was the initial coordinating principal investigator; EMJM is the current coordinating principal investigator. JF, EMJM, and MLC led the evaluation development, and all authors contributed. All authors contributed to either the conception, design, or acquisition of ethics and governance approval of the evaluation. MLC and JF were major contributors to writing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist (36).
[PDF File (Adobe PDF File), 250 KB - resprot_v13i1e49849_app1.pdf]

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Abbreviations

ACT: Acceptance and Commitment Therapy
CBTp: cognitive behavioral therapy for psychosis
CHIME: Connectedness; Hope and optimism about the future; Identity; Meaning in life; and Empowerment
CONSORT: Consolidated Standards of Reporting Trials
CORE-10: Clinical Outcomes in Routine Evaluation 10
ICC: intracluster correlation coefficient
QPR: Questionnaire about the Process of Recovery
SMART: specific, meaningful, adaptive, realistic, and time-framed
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e63249

Abstract

Background: Most new HIV diagnoses among cisgender women in the United States occur in the South. HIV pre-exposure prophylaxis (PrEP), a cornerstone of the federal Ending the HIV Epidemic (EHE) initiative, remains underused by cisgender women who may benefit. Awareness and access to PrEP remain low among cisgender women. Moreover, improving PrEP reach among cisgender women requires effectively engaging communities in the development of appropriate and acceptable patient-centered PrEP care approaches to support uptake. In a community-clinic-academic collaboration, this protocol applies an evidence-based community organizing approach (COA) to increase PrEP awareness and reach among cisgender women in Atlanta.

Objective: The aim of this study is to use and evaluate a COA for engaging community members across 4 Atlanta counties with high-priority EHE designation, to increase PrEP awareness, interest, and connection to PrEP care among cisgender women.

Methods: The COA, consisting of 6 stages, will systematically develop the skills of community members to become leaders and advocates for HIV prevention inclusive of PrEP for cisgender women in their communities. We will use the evidence-based COA to develop and implement a PrEP-specific action plan to create broader community change by raising awareness and interest in PrEP, reducing stigma associated with HIV or PrEP, and connecting women to sexual health clinics providing PrEP services. In the first 4 stages, to prepare for and develop action plans, we will gather data from one-on-one interviews with up to 100 individuals across Atlanta to capture attitudes, motivations, and influences related to women's sexual health with a focus on HIV prevention and PrEP. Informed by the community interviews, we will revise a sexual health curriculum inclusive of PrEP and community-centered engagement. We will then recruit and train community action team members to develop action plans to implement the curriculum during community-located events. In the last 2 stages, we will implement and evaluate COA's effect on PrEP awareness, interest, HIV or PrEP stigma, and connection to PrEP care among cisgender women community members.

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Results: This project was funded by the National Institutes of Health and approved by the Emory University institutional review board in July 2021. Data collection began in December 2021 and is ongoing. COA stage 1 of the study is complete with 70 participants enrolled. Community events commenced in November 2023, and data collection will be completed by November 2025. Stage 1 qualitative data analysis is complete with results to be published in 2024. Full study results are anticipated to be reported in 2026.

Conclusions: Through a community-clinic-academic collaboration, this protocol proposes to mount a coordinated approach across diverse Atlanta counties to strengthen HIV prevention for cisgender women and to create a sustainable systems approach to move new sexual health innovations more quickly to cisgender women.

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KEYWORDS

cisgender women; HIV prevention; community engagement; HIV; cisgender; United States; pre-exposure prophylaxis; PrEP; Ending the HIV Epidemic; awareness; community; community-based; prevention; community action team; HIV epidemic; evidence-based; participatory; community-engaged approach; community organizing approach; men who have sex with men

Introduction

Initiatives for ending the HIV epidemic in the United States must include cisgender women. Among ~37,000 people diagnosed with HIV annually in the United States, 19% are cisgender women, with the majority (~60%) of new HIV diagnoses among cisgender women occurring in the South [1,2]. Georgia has the highest rate of new HIV diagnoses (21% occur among cisgender women), and also has one of the highest rates of perinatal HIV infection [1,3]. HIV diagnoses among cisgender women in Georgia and nationally are more evenly distributed across age groups than in men, with magnified disparities by race or ethnicity [2,3]. This highlights the importance of women-tailored HIV prevention care, including pre-exposure prophylaxis (PrEP) to effectively reach all who may benefit. Within Georgia, the Atlanta metropolitan area accounts for over half of all annual HIV diagnoses [3], with 4 counties (Cobb, DeKalb, Fulton, and Gwinnett) identified as a high priority in the federal Ending the HIV Epidemic (EHE) initiative [4]. Reducing HIV in Atlanta is a public health priority, and cisgender women–tailored strategies will be necessary to achieve an end to HIV.

PrEP is dramatically underused by cisgender women. There has been wide-scale endorsement to bring PrEP use to scale through dissemination and implementation efforts in the United States since its approval in 2012 [5-8]. PrEP use has since steadily increased among men but remains flat in women [9]. PrEP is underused in women relative to need, especially in the Southern United States [10]. Women are <5% of US PrEP users, and account for only 2% of the estimated 176,670 cisgender women for whom PrEP is indicated [11,12]. The first steps for increasing PrEP uptake are ensuring that those who can benefit from PrEP are aware of it, and ensuring that PrEP is accessible in settings where they seek health care [13]. Unfortunately, PrEP knowledge is low among cisgender women in the United States, including in the Southern United States) [14-20] and among women's health care providers [21]. Encouragingly, cisgender women report interest in taking PrEP once informed [22,23], and women's providers are willing to prescribe PrEP once trained [21]. Our group previously investigated PrEP awareness and provider PrEP knowledge in 4 Atlanta family planning clinics that were not previously providing PrEP. Clients resided in 103 (91%) of 113 metropolitan Atlanta zip codes (the majority of clients resided in zip codes with HIV prevalence >1%) [14,24]. Only 95 (19%) of 500 cisgender women clients surveyed knew about PrEP, but after a brief provider training, 72 (66%) of 110 cisgender women with PrEP indicators received PrEP counseling during their visits. After receiving PrEP counseling, clients expressed interest in PrEP if it were offered on-site rather than through off-site referral. This study demonstrated the potential reach of sexual health clinics in high HIV burden areas as PrEP delivery sites.

However, PrEP delivery in publicly funded family planning clinics in the South remains low, despite clinical guidelines incorporating PrEP [25]. We previously surveyed nearly 600 providers or staff working in 286 Title X clinics across the South in 2018; only 22% of clinics provided any PrEP services (including through referral), and the Southeastern region (including Atlanta) had the fewest clinics offering PrEP [14,26].

Once clinic capacity for PrEP is built, it does not address low PrEP awareness among cisgender women. Lessons learned from the rollout of other prevention technologies, such as human papillomavirus vaccination [27] and new contraception methods [28], highlight the need to simultaneously address demand barriers that impede use [29]. We are learning that the same applies to scaling PrEP, particularly for cisgender women in Atlanta [14,15,24,26]. To date, efforts to scale PrEP in the United States have largely focused on PrEP awareness for men who have sex with men [8], despite continued low PrEP knowledge among women [15-20]. Our 2018 research found that once informed about PrEP, cisgender women in Atlanta wanted more information and widespread awareness-building specifically for women [30]. Thus, ending the HIV epidemic among women will require addressing uptake barriers through building interest in PrEP and promoting and connecting cisgender women to women-friendly PrEP clinics.

A comprehensive systems-level approach is needed to increase PrEP reach among cisgender women. To create a proactive solution for bridging the chasm from science to practice for PrEP use among cisgender women and building on our existing clinic-academic-community partnerships, we will innovatively

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use the Interactive Systems Framework (ISF) [31]. The ISF is a multisystem model to guide the dissemination and implementation of prevention programming through the work of 3 interactive systems, "prevention delivery" (implements the innovation in the real world), "prevention support" (provides training and technical assistance to users in the field), and "prevention synthesis and translation" (conducts research and distills information about innovations in user-friendly formats). The ISF has been used successfully by the Centers for Disease Control and Prevention (CDC) in their multisite capacity-building effort to reduce teen pregnancies in the United States [32], showing its feasibility for building prevention infrastructure to guide large-scale prevention efforts in the area of sexual health for women [32,33]. All 3 systems, and the different stakeholders who populate each system, interact to support each other toward a common goal, which is necessary to mount successful, sustainable, large-scale adoption of new prevention innovations (eg, PrEP, including long-acting PrEP).

The ISF provides a strong model to strengthen access to PrEP care, but it lacks equally robust attention to addressing PrEP awareness and interest. Thus, in this protocol, we innovatively supplemented the ISF with an evidence-based community organizing approach (COA), previously demonstrated effective for addressing underage alcohol use [34,35]. This evidence-based approach can create broader change across the community for any community challenge [36,37]. The COA consists of 6 stages of activities. The first stage is assessing the community through one-on-one conversations with citizens, typically done by a lead community organizer (LCO). The second stage is building the base, in which an action team of approximately 15 citizens is assembled. The action team members are not typically affiliated with formal prevention programs or HIV coalitions and do not need to hold formal positions of power. Rather they are everyday citizens—a retired teacher, minister, stay-at-home parent, coach, and so forth—who care deeply about preventing HIV. The action team is then trained by the LCO on strategies for reducing HIV, including PrEP, and how to take actions to advance those evidence-based strategies (eg, where individuals can go to get these services near them). In the third stage, expanding the base, the action team builds additional rings of supporters connected to the effort. In the fourth stage, the LCO and action team members develop an action plan, wherein they schedule strategic actions designed to accomplish specific organizing outcomes (eg, sharing at community events). Stage 5 involves implementing the plan and carrying out their planned actions. Stage 6 involves assessing results, celebrating accomplishments, and refining the next steps that were planned. Thus, this COA systematically develops the leadership skills of trusted community members to become leaders and advocates for HIV prevention inclusive of PrEP for women in their communities.

We propose to innovatively use this COA to systematically develop the leadership skills and HIV prevention knowledge of individuals to become community advocates for HIV prevention in metro Atlanta to reduce HIV or PrEP-related stigma, build demand for PrEP, and facilitate linkages to women-friendly PrEP clinics. We hypothesize that the COA is feasible to implement and that the PrEP action plan implemented as part of the COA will be associated with increased PrEP awareness and interest, decreased HIV or PrEP stigma, and increased awareness about where women or individuals can get PrEP among cisgender women community members.

Methods

Study Setting

We will implement the COA (Textbox 1) within the 4 Atlanta high-priority EHE counties, in partnership with SisterLove, an Atlanta-based women's HIV and reproductive justice community based organization (CBO) that is internationally recognized for raising sexual health and HIV awareness among women and has deep connections in the community, and additional CBOs identified through our formative work.

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Textbox 1. Description of the 6-stage community organizing approach.

Stage 1: assess community

Conduct one-on-one interviews to assess pre-exposure prophylaxis (PrEP) attitudes, motivations, and influences among key community members; use these findings to adapt a sexual health curriculum to address feedback.

Stage 2: build the base

Assemble "action teams" composed of approximately 15 individuals who work or reside across 4 metro Atlanta counties with the help of community-based organization partners and train them on an adapted sexual health curriculum.

Stage 3: expand the base

Identify individuals to engage during implementation (influencers to connect with to recruit women to attend workshops) and resources to contribute (eg, space to conduct the workshops).

Stage 4: develop an action plan

Schedule community education meetings across all 4 counties (5-10 per year per action team member) to reach diverse communities of cisgender women.

Stage 5: implement the action plan

Action team members conduct community events (~150 annually) using the adapted sexual health curriculum.

Stage 6: evaluate the action plan

Monitor the number of events, participant demographics, and fidelity to the sexual health curriculum; collect survey data to evaluate changes in PrEP awareness, interest, stigma, and reach.

Implementation of the COA

Preparing for Action (COA Stages 1-4)

We will first hire and train an LCO. In collaboration with the Emory team, the LCO will assess the community (COA stage 1) through one-on-one conversations with up to 100 individuals across Atlanta; ~25 per EHE county (collaborating CBOs will assist in identifying individuals such as opinion leaders, influential partners in their work, and diverse women in the community). Interviews will capture attitudes, motivations, and influences related to women's health and well-being, as well as their sexual health, with a focus on HIV prevention and PrEP. Interviews will be recorded and transcribed. Using an inductive coding approach, the LCO and Emory team members will code interviews and identify themes salient to address during COA implementation. We will then use findings to adapt SisterLove's existing sexual health curriculum (Healthy Love Workshop [38]) to address community feedback salient to PrEP use among women. Healthy Love is an evidence-based single-session, a small-group intervention for women with core content designed to increase participants' HIV and sexual health knowledge (including prevention strategies), risk perception, and self-efficacy to engage in HIV or sexually transmitted infection (STI) testing and preventative practices. The fundamental information within Healthy Love, specifically related to knowledge, risk perception, and self-efficacy for testing, will be retained, and updates will be made to incorporate information about PrEP.

Next, we will build the base (COA stage 2) by assembling action teams comprised of approximately 15 individuals who work or reside across all 4 counties with the help of CBO partners. Action teams will be essential for reaching diverse groups of women in their community and raising awareness, interest, and connection to PrEP via facilitating educational outreach. Action team members will be asked to commit to at least 1 year of engagement. They will be provided with an annual honorarium for serving in this role, and a certificate of appreciation from SisterLove and Emory teams acknowledging their significant role in reducing HIV in their communities. Action team members will work in coordination under the LCO, but each team will focus their implementation activities on their respective EHE counties. The LCO and SisterLove team will prepare the action teams with training on the adapted sexual health curriculum, supplemented with information on women-friendly places to access PrEP.

To expand the base (COA stage 3) action team members will identify individuals to engage during implementation and resources they might be able to contribute during implementation (eg, space for community education meetings to conduct adapted Healthy Love Workshop, audiences for meetings, and access to influencers to connect with to recruit women to attend meetings). As part of COA stage 4 (developing an action plan), the goal for each action team member is to arrange 5-10 community education events to be held per year in their EHE county. The LCO and action team members (supported by SisterLove and Emory teams) will schedule community education meetings reaching diverse communities of cisgender women, built on the unique reach of each action team member, across the 4 EHE counties.

Implementing and Evaluating the PrEP Action Plan (COA Stages 5-6)

Over 2 years, action team members will collectively conduct ~300 community events (~10 events per action team member per year) with an average of 10 community members attending each event. The action team members will facilitate their planned events (~2 hours each), following the adapted Healthy Love Workshop manual, with the assistance of the LCO, SisterLove, and the Emory team for data collection.

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To monitor the implementation of the PrEP action plan, we will use electronic monitoring logs to capture (1) the number of community events scheduled or conducted by each action team member with dates and locations recorded, (2) the number and demographics of participants at each event (gathered through attendance logs at events), and (3) the number of requests for scheduling other community meetings. A study team member will collect monitoring data at each event to ensure the accuracy and completeness of logs and use a fidelity checklist to record fidelity to the adapted sexual health curriculum for each event.

We will collect data via surveys from the ~3000 community event participants to evaluate changes in PrEP awareness, interest, stigma, and reach after participating in a community education event conducted as part of the PrEP action plan. Specifically, all cisgender women participants at community events will be asked to complete brief pre- and posttest surveys that include measures on demographics, knowledge and attitudes about PrEP [15], concerns or barriers to PrEP use [39], and PrEP or HIV stigma [40,41]. Upon arriving at the event, each participant will sign in (name, email, phone number, and social media usernames) on a study laptop. Two additional questions will be asked: (1) "Is it ok to contact you in a few months to ask a few follow-up questions about the workshop—you will receive a US $5 gift card for your time?" and (2) "What is your preferred way to be contacted—text, phone, or email?" Participants will then be assigned a unique identifier to be used in the pre- and posttest surveys which will be administered electronically using a QR code link. The study team member will verify the unique identifier used with the participant ID log which will be stored separately from the participant's contact information. Participants' pretest surveys will be collected at the onset of the event, and posttest surveys will be collected upon completion. Study staff will review surveys upon collection and encourage participants to complete any missing items. Approximately 3 months after participation, ~50% of participants (among those agreeing to be contacted) will be randomly selected per event to participate in a brief survey (via text, email, or phone). Survey questions will be yes or no items assessing PrEP reach since participation in the community event to determine whether the participants has (1) received HIV or STI testing, (2) gone to a clinic for sexual health services, (3) talked to a health care provider about PrEP, (4) started PrEP, and (5) shared information about PrEP with other women (if so, how many). See Table 1 for a full list of evaluation measures.

Table 1. Comprehensive evaluation of pre-exposure prophylaxis (PrEP) action plan implementation on PrEP awareness, interest, and connection to PrEP care.

Method	Data source	Timing	Evaluation measures
Action plan implementation monitoring	Electronic monitoring log to capture the number of events, number of participants, types of PrEP resources shared, and number of requests additional events	Completed for each community event	Number of community events conducted by each action team member; number and demographics of participants at each event; and number of requests for scheduling other community meetings
Fidelity to sexual health curriculum	Fidelity checklist to record fidelity to the adapted sexual health curriculum in real time	Completed for each community event	Overall and individual checklist item
Pre- and posttest assessment of events	Brief paper-pencil pre- and posttest survey completed by ~3000 cisgender women attending community events	All cisgender women who participate in community events before and after the event	Demographics, knowledge, and interest in PrEP, PrEP stigma and attitudes about PrEP, history of PrEP use, and knowledge of PrEP clinics
Follow-up survey after events	Random sample of 50% of community event participants who agree to be contacted will be sent a brief email or text survey	Three months after participating in a community event	Yes or no questions since event: (1) received HIV testing, (2) went to Title X clinic that provides PrEP, (3) talked to a doctor about PrEP, (4) started PrEP, and (5) shared information about PrEP with other women (if so, how many)
PrEP reach among cisgender women seen in area clinics	Number of PrEP prescriptions to cisgender women seen in PrEP-providing clinics shared in community event resource list	Quarterly before, during, and after community events	Changes in number of PrEP prescriptions to women per quarter among PrEP-providing clinics

Statistical Analysis Plan

Descriptive statistics will be conducted on monitoring and fidelity data by year for each of the 2 implementation years. Feasibility of the COA will be determined by (1) successful implementation of ~10 community events per year by each action team member (~15 members), (2) at least 100 community members reached by each action team member per year (as indicated by # of participants attending their events), and (3) high fidelity to the adapted Healthy Love by action team members per year (>80% fidelity: determined by fidelity checklist indicating >80% content completed per event).

For pre-post assessments, scores on scales will be computed according to published guidance [39-42]. Descriptive analyses and paired *t* tests or chi-square tests will be conducted to ascertain pre-post changes in PrEP awareness, interest, stigma, and knowledge of where to access PrEP. For follow-up surveys,

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descriptive statistics will summarize the connection between PrEP care, connection to HIV testing, and PrEP reach (ie, self-reported initiation of PrEP) among the subset of community event participants who complete a follow-up survey.

We will conduct exploratory logistic regression analyses examining the association between pre-post survey scores (PrEP knowledge, attitudes, barriers, stigma, and prior use of PrEP) on PrEP reach, including demographic factors as covariates. Finally, exploratory descriptive analysis will summarize changes in PrEP reach among cisgender women receiving care at publicly funded family planning clinics in the 4 Atlanta EHE counties (number of PrEP prescriptions to women per quarter among PrEP-providing clinics discussed or shared during community events) for each year before, during, and after PrEP action plan implementation. Given our design, it is not appropriate to conduct comparison tests for this analysis.

Ethical Considerations

This study was approved by the Emory University institutional review board (#00002950). For the community interviews which were all completed via video conferencing, a waiver of documentation of consent was obtained, and the interview was completed after verbal consent. Community interview participants received a US $50 gift card upon completion of an interview. Community event participants who complete pre-post assessments and follow-up surveys will provide written informed consent. Community event participants will receive a US $5 gift card for completion of the 5-item 3-month follow-up text or email survey.

Interviews are conducted by trained research staff and recorded with audio recording devices; we instruct individuals to avoid using their names during the interview. In the event an identifier is used in the recording, all personally identifiable information is redacted from the transcripts during data quality assurance procedures performed by the study team. All audio recordings are professionally transcribed by a trusted vendor with secure web-based file transmission procedures. After transcription, the study team reviews each transcription against the audio recording to ensure verbatim accuracy and to remove identifiable information from the transcripts during this quality assurance procedure. After all transcripts are quality-checked and saved, the audio recordings will be destroyed. A study log kept by the study team will document this process. Transcripts and audio recordings are only stored on secure, password-protected platforms. No personal identifiers will be stored for other data collection components, except to contact community event participants for follow-up surveys and distribute participant incentives. Personal identifiers will not be linked to any other data and will be destroyed as soon as survey invitations and participant incentives have been distributed.

Results

Study activities were funded by the National Institutes of Health (NIH) and was approved by the institutional review board in July 2021 and data collection began in December 2021 and is ongoing. From December 2021 to October 2022, we hired and trained the LCO and completed 70 community interviews with key stakeholders. Eligible participants worked or resided in Dekalb, Gwinnett, Fulton, or Cobb County in the state of Georgia and were able to provide verbal consent to participate. Participants were primarily female-identifying (n=64, 91%); of 70 total participants, 20 (29%) endorsed being a lay community member, while others reported community involvement through organizations or businesses (n=19, 27% members of a nonprofit organization; n=12, 17% staff at a clinic; n=4, 6% self-employed; n=4, 6% college students; and n=1, 1% affiliated with a faith-based organization). About 10% (n=7) of participants reported involvement in HIV support groups (n=5, 7%) or advocacy groups (n=2, 3%) as their community involvement. Of those who reported race and ethnicity (n=46, 66%), 35 (76%) identified as Black, 7 (15%) identified as White, and 4 (9%) identified as more than 1 race. A total of 4 (9%) participants reported Hispanic or Latino ethnicity which parallels HIV diagnoses by race or ethnicity in Georgia [3].

From October 2022 to December 2022, we analyzed interview data and identified important preliminary themes in these conversations including the need for broad-based, inclusive approaches to discussions about women's sexual health and HIV prevention with accurate, straightforward, and reliable content delivered by trusted, relatable members of the community in safe and easy to access spaces. From December 2022 to June 2023, we collaborated with SisterLove on the adaptation of the Healthy Love sexual health curriculum based on these preliminary community interview findings while taking care to retain fundamental information within Healthy Love, specifically related to HIV knowledge, risk perception, and self-efficacy for testing (COA stage 1). From February 2023 to July 2023, we recruited and trained a diverse group of 15 action team members and gathered feedback on the curriculum adaptation. Additional changes to the curriculum were made based on community feedback from July to August 2023. Community events commenced in November 2023 and data collection will be completed by November 2025. Full trial results are anticipated to be reported by July 2026.

Discussion

Principal Findings

Using a COA that engages and supports community members in educating other community members about their sexual health can broaden and enrich the awareness, and potentially the reach of, HIV prevention, testing, and PrEP into diverse networks of cisgender women. Our findings in assessing the communities in metro Atlanta thus far have affirmed the need for greater emphasis on women-inclusive initiatives delivered by individuals considered relatable within the community who are comfortable and knowledgeable about discussing sexual health with the overarching goal of creating safe spaces for authentic conversations. Taking this into consideration when forming action teams, the LCO, with the assistance of SisterLove and Emory partners, dedicated extra time and attention during stage 1 of the COA to identify, recruit, and train team members to ensure that teams remain representative of women of varying ages, races, ethnicities, and social networks living in EHE high priority counties in metro Atlanta.

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Adjustments in the protocol for the adaptation of the evidence-based Healthy Love curriculum by SisterLove, Inc were also made to include the opinions and feedback of the action team members on the revised curriculum content. Initial curriculum revisions were drafted to include content salient to data outcomes from the in-depth community interviews capturing attitudes, motivations, and influences related to women's sexual health, with a focus on HIV prevention and PrEP. The revised draft was then presented to action team members as a community event and their feedback was gathered and later incorporated into the final curriculum to guide action teams in facilitating health education community events.

Moving forward, we anticipate that the evidenced-based COA will be feasible, and participation in its community events will be associated with increases in PrEP awareness and interest, decreases in PrEP or HIV stigma, and greater knowledge about where women can go for PrEP care (eg, PrEP-providing Title X clinics). We also expect that participation in events will be associated with improved PrEP reach among women who participate. These findings will provide critical data related to the COA use to create a potentially sustainable community-engaged approach for disseminating information about new HIV prevention products from trusted members in the community inclusive of cisgender women.

Limitations

Action team members may discontinue participation over time. If this occurs, we will work with our collaborating CBOs and other action team members to recruit new individuals into this role. If a member withdraws before completing community events, other action team members, the LCO, and CBO staff will conduct the remaining scheduled events. We may encounter challenges related to the completion of the follow-up survey. If randomly selected individuals do not complete the survey, we will select another. We expect 90% will indicate willingness to be contacted, and we are only attempting to sample 50% of participants, so we are confident we can achieve our goal sample size.

Conclusions

Through a community-clinic-academic collaboration and innovative application of COA, this protocol proposes to mount a coordinated approach across diverse Atlanta counties to strengthen HIV prevention for cisgender women, and importantly, to create a sustainable systems approach to move new and sexual health innovations more quickly to cisgender women.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request upon completion of primary analyses.

Conflicts of Interest

None declared.

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Abbreviations

CBO: community-based organization
CDC: Centers for Disease Control and Prevention
COA: community organizing approach
EHE: Ending the HIV Epidemic
ISF: Interactive Systems Framework
LCO: lead community organizer
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

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Protocol

Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study

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Abstract

Background: Neonatal unit (NU) admissions for premature babies can last for months, which can significantly impact parental mental health (MH) with symptoms of depression, stress, and anxiety. Literature suggests fathers experience comparable MH symptoms to mothers. Family integrated care (FICare) is a culture where parents are collaborators and partners in caring for their hospitalized newborns. FICare improves infant outcomes and maternal MH. Similar reports on fathers are limited.

Objective: The primary aim of this study is to investigate the impact of supporting father or partner engagement in FICare of preterm infants on their MH up to 6 weeks postdischarge. The secondary aim is to investigate the impact on maternal MH.

Methods: This is a 2-phase study: phase 1 to gather baseline information and phase 2 to assess the impact of enhanced father or partner engagement in FICare on their MH, involving 2 NUs (tertiary and level 2). Enhanced FICare will be developed and introduced (eg, information booklet, workbook, classes, and a father peer-support group) alongside standard FICare practices. Father or partner MH will be assessed with semistructured qualitative interviews and validated questionnaires: Generalized Anxiety Disorder Assessment, Patient Health Questionnaire, and Parental Stressor Scale: Neonatal Intensive Care Unit from NU admission to 6 weeks postdischarge. Mothers will be assessed by focus groups and the same questionnaires. Descriptive statistics and appropriate comparative tests, such as the 2-tailed *t* test, will be used to analyze and compare phase 1 and 2 data. Qualitative data will be coded line by line with the use of NVivo (Lumivero) and thematically analyzed. Simultaneously, systematic reviews (SRs) of fathers' experiences of FICare and their MH outcomes will be conducted. The study was approved by the National Research Ethics Committee (22/EM/0140) in August 2022. A parent advisory group was formed to advise on the study methodology, materials, involvement of participant parents, and dissemination of study findings.

Results: A recent SR demonstrated that data saturation is likely to be achieved by interviewing 9 to 17 participants. We will study a maximum of 20 parents of infants born at less than 33 weeks' gestation in each phase. As of October 2023, the study was

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ongoing. The SR studies are registered with the PROSPERO database (324275 and 306760). The projected end date for data collection is July 2024; data analysis will be conducted in November 2024 and publication will occur in 2025.

Conclusions: The study aims to demonstrate the feasibility of using a father or partner-sensitive FICare model for parents of premature babies with a positive impact on their MH. It will demonstrate the feasibility of providing FICare to extremely premature babies receiving intensive care. This study may support the development of inclusive FICare guidelines for nonbirthing parents and their extremely premature infants.

Trial Registration: ClinicalTrials.gov: NCT06022991; https://classic.clinicaltrials.gov/ct2/show/NCT06022991

International Registered Report Identifier (IRRID): DERR1-10.2196/53160

(JMIR Res Protoc 2024;13:e53160) doi:10.2196/53160

KEYWORDS

family integrated care; FICare; neonatal intensive care unit; NICU; fathers; premature infants, mental health; pediatric; pediatrics; infant; infants; infancy; baby; babies; neonate; neonates; neonatal; premature; partner; couple; family care; NU admission; NICU admission; engagement

Introduction

In 2019, in England and Wales, 49,489 premature births were recorded, and the majority would have required a neonatal unit (NU) admission [1]. Scientific and technological advancements have led to significant reductions in mortality and morbidity for preterm infants [2], and now the importance of decreasing psychosocial morbidity for the family unit is being addressed. Admission of a critically ill baby to the NU is a deeply traumatic time for parents and may result in parental mental health (MH) difficulties during and after discharge [3,4]. Studies exploring paternal experiences in the NU highlight fathers feeling neglected and in a unique position of stress, trying to balance work and home life to allow the mother to focus on their sick baby [5]. As paternal and maternal MH are closely linked, supporting the fathers could also positively impact maternal MH [6,7]. A recent study has shown reduced paternal stress in relation to the provision of family integrated care (FICare) in single-family rooms, but it only included parents of babies who did not require intensive care [8].

FICare in the NU means that parents are partners and collaborators in the care of their hospitalized baby, rather than observers or visitors. They are included in decision-making and supported to feed, clean, and hold their baby as well as learning how to provide neurodevelopmental care [9,10]. FICare studies that have focused on mothers and infants demonstrate improved neurodevelopmental outcomes [11], improved breastfeeding rates [12], reduced infection rates, and improved maternal MH [13,14]. There is a paucity of similar research regarding fathers [15]. The impact of parental MH on children is a focus of the UK government's "First 1000 days of life" paper [16]. Implementation and improvements to FICare as a method of enhancing "parenting opportunity" are also highlighted in the National Neonatal Critical Care Review in England [17]. Synthesizing the evidence base surrounding the impact of paternal engagement addresses recommendations from National Health Service (NHS) England, the Cross Government 1001 Critical Days Campaign [7], the Neonatal Critical Care Transformation Review, and Care Quality Commission standards to increase the evidence base to support women and their families experiencing perinatal MH problems. This area currently costs the NHS an estimated £1.2 billion (equivalent to US $1.5 billion) per year [16,17]. The UK government has recently recognized the importance of maternal and paternal presence for babies in the NU via the Neonatal Care (Leave and Pay) Act, which achieved royal assent in May 2023 granting parents up to an additional 12 weeks of leave [18]. Hence, we developed a study protocol to investigate and enhance fathers' or partners' involvement in FICare and its impact on their MH.

This study will be the first to report on fathers' experiences of FICare in the NU with extremely premature babies. It will broaden the field of FICare research with respect to fathers from diverse social and cultural backgrounds and will highlight the needs of fathers in the NU. Therefore, it will demonstrate the value of designing a father- or partner-sensitive FICare program. This study will also generate evidence for the feasibility of the introduction of FICare from day 1 while preterm babies are receiving intensive care.

From here on, although the study refers to "fathers," all second parents of any gender or relationship status are included under this term throughout the remaining text.

Methods

Aims

This study aims to undertake an in-depth longitudinal study of the engagement of fathers or partners in FiCare and their experience and MH from NU admission to 6 weeks postdischarge of their premature baby born at 22 to 33 weeks' gestation.

Objectives

Our objectives are to (1) assess baseline fathers' experiences in the NU, their involvement in FICare, and MH status during babies NU admission up to 6 weeks postdischarge, (2) conduct systematic reviews (SRs) of published papers on "Fathers and FiCare in NU" and "Fathers' MH in the NU," (3) develop a program to enhance the involvement of fathers in FiCare, and (4) introduce the program developed to enhance fathers' involvement in FiCare and explore their experiences and effects on their MH.

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Outcomes

The primary outcome is paternal MH (stress) assessed by semistructured interviews.

The secondary outcomes are (1) maternal stress, assessed by the Parental Stressor Scale: Neonatal Intensive Care Unit (PSS:NICU) questionnaire; (2) paternal stress, assessed by the PSS:NICU questionnaire; (3) parental anxiety, assessed by the Generalized Anxiety Disorder Assessment-7 (GAD-7); (4) parental depression, assessed by the Personal Health Questionnaire-9 (PHQ-9); and (5); paternal engagement with FICare, assessed via interviews.

Study Design

This is a prospective, multicenter, and multiphase study. Phase 1 will assess baseline fathers' experiences in the NU, their involvement in FICare, and MH status during babies' NU admission up to 6 weeks postdischarge. Simultaneously, an SR of fathers' involvement in FICare and their MH outcomes will be conducted. A program to enhance the involvement of fathers in FICare will be developed using information from the phase 1 study, SR, existing DadPad or Imperial Family Delivered Neonatal Care app, and advice from the parent advisory group (PAG). In the phase 2 study, an enhanced father involvement program in FICare will be implemented and similar assessments as in phase 1 will be conducted (Figure 1). We will provide regular debrief sessions, and research updates or newsletters to keep staff engaged and supportive of the project. This support will be continued throughout the study.

This study has been registered with clinicaltrials.gov (NCT06022991) [19].

Figure 1. Participant flow chart. FICare: family integrated care; GAD-7: Generalized Anxiety Disorder-7; NU: neonatal unit; PHQ-9: Patient Health Questionnaire-9; PSS:NICU: Parental Stressor Scale: Neonatal Intensive Care Unit.

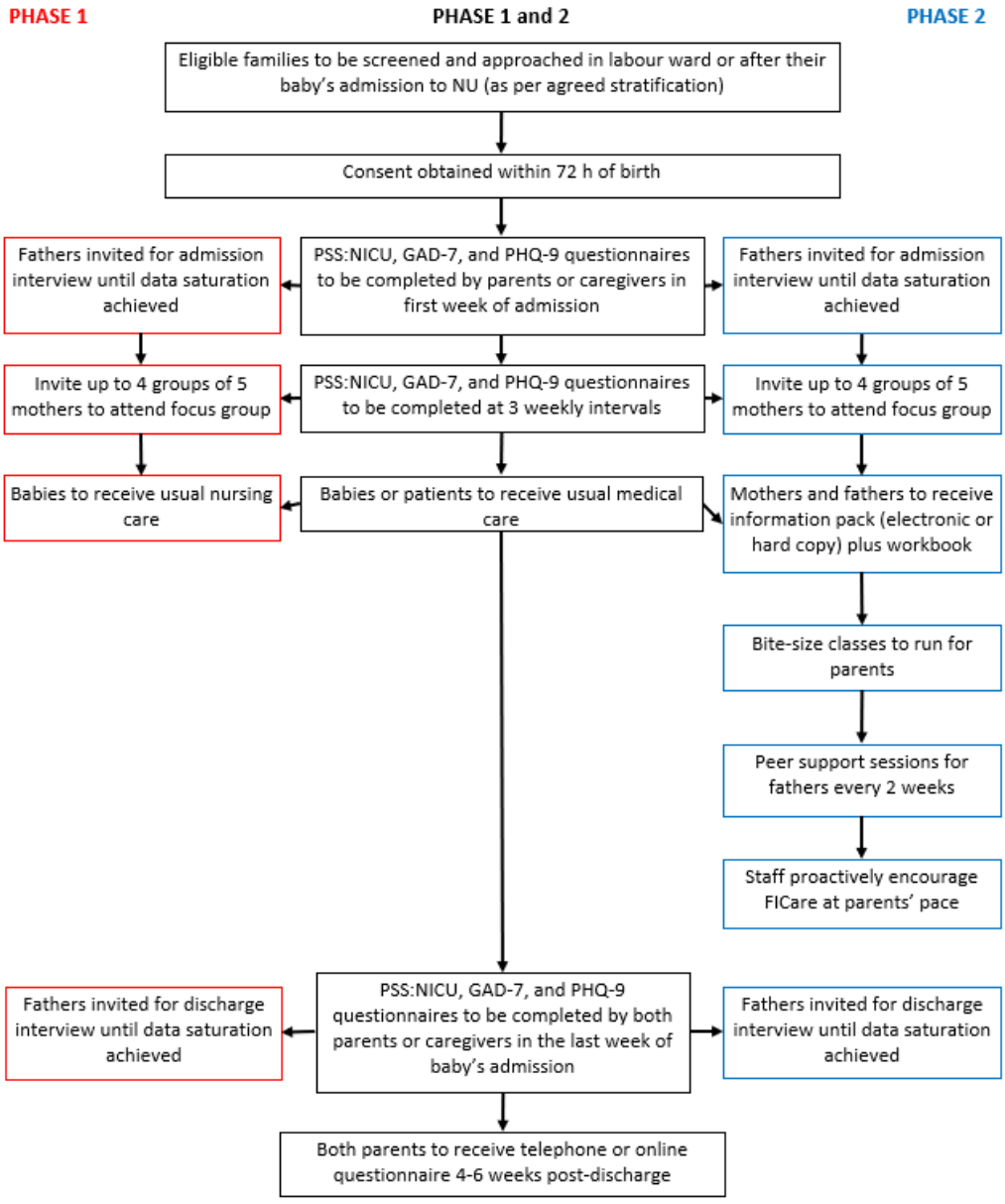

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Systematic Reviews

The SR studies have been registered on the PROSPERO database (324275 [20], 306760 [21]) and will follow a similar methodology. A literature search of health care databases including EMBASE, EMCARE, CINAHL, Medline, BNI, PYCHInfo, and Psychology and Behaviour, and a gray literature search will be conducted. Two independent researchers will screen the results at the title and abstract level against the eligibility criteria (Table 1), with mediation by a third researcher available for any disagreements to reevaluate the paper and come to a team agreement. The matrix method will be used for data extraction [22].

Table 1. Eligibility criteria for the systematic reviews.

	Fathers' mental health in the NU[a] [18]	Fathers and FICare[b] in the NU [19]
Studies published from January 1, 2000, to October 14, 2022	✓	✓
Full paper available in English	✓	✓
Study setting is the NU	✓	✓
At least 5 study participants	✓	✓
At least half of the participants are fathers	✓	✓
Addressed paternal mental health	✓	
Addressed FICare		✓

[a]NU: neonatal unit.

[b]FICare: family integrated care.

Study Centers

The study will be conducted at a tertiary NU (level 3) and a local NU (level 2), as defined by the Department of Health [23], in East London, United Kingdom. Average annual admissions are approximately 900 and 600 respectively, with parents from diverse ethnic and socioeconomic backgrounds. Both level 3 and 2 NUs are selected to show the feasibility of delivering enhanced father involvement in FICare in all NUs and the study findings are applicable to all levels of NUs. Although FICare culture is practiced at both sites, a formal program and expectations of FICare are not implemented.

Clinical Staff Involvement

The wider multidisciplinary team was consulted in the study design and consideration of phase 2 study materials. They included physiotherapists, clinical psychologists, occupational therapists, dieticians, and speech and language therapists along with neonatal nursing input. The London neonatal network care coordinator was also consulted regarding the study design and implementation.

Patient and Public Involvement

Patients and the public were involved in the design, conduct, reporting, and dissemination plans of the study. A PAG consisting of parents of preterm infants was developed. They consisted of a diverse socioeconomic and cultural mix of 4 fathers and a mother who had experienced the admission of their premature baby in the NU within the last 4 years. The PAG was involved in developing the study design. The PAG has reviewed and provided feedback on study materials, for example, participant information leaflet. A lay member is included as a coinvestigator (JB, Director of Inspire Cornwall CIC's Neonatal DadPad) of the study.

The PAG was consulted to advise on the burden of intervention and the time required to participate in the research. This has influenced the frequency of questionnaire administration and locations of interviews and focus groups. They will support the development of appropriate phase 2 materials for the information booklet, workbook, and education sessions. The PAG will also support the dissemination of the study findings to research participants, related charity bodies (eg, Bliss), and the wider neonatal community.

Study Participants and Recruitment

Parents of preterm infants will be recruited to the study.

Inclusion Criteria

The inclusion criteria are as follows: (1) parents of 22^{+0} to 32^{+6} weeks preterm infants; (2) infants aged 1 to 7 days; (3) infants with 2 primary caregivers (the father's or partner's participation in the study is a must, and participation from both parents is ideal), and (4) the parents should have conversational English.

Exclusion Criteria

The inclusion criteria are as follows: (1) infant with life-limiting conditions or no realistic chance of survival, (2) infant is likely to be transferred to nonparticipating center within 4 weeks of age, and (3) parents are younger than 16 years.

All parents with babies born between 22^{+0} and 32^{+6} weeks' gestation admitted to the participating centers at less than 7 days of age will be assessed for eligibility. A sequential recruitment strategy will be followed with all eligible parents from the date of recruitment opening until 20 parents have been recruited in each phase. Within each eligible parent, consent and recruitment of the father or partner is essential. Maternal recruitment in addition to the partner, is encouraged but not mandatory.

Sample Size

The sample size of the study is estimated based on qualitative study outcomes. A recent SR of qualitative study demonstrated that to achieve data saturation we need to interview 9 to 17 participants [24]. A focus group of 5 to 7 participants would be

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enough for in-depth conversations and 2 or more groups would increase the chances of successful data output [25].

In the first and second phases, up to 20 parents will be recruited (until the fathers' interviews reach data saturation). With a father and mother each, there could be 40 participants per phase. In total, there could be 80 participants in the study.

Phase 1 Study: Baseline Data Collection (9 Months)

Overview

Phase 1 will be conducted as follows: (1) Prior to the introduction of the study to wider NU clinical staff members, staff knowledge, experiences, and opinions about the role of fathers and FICare will be assessed by a questionnaire. (2) Once a parent is recruited, the PSS:NICU [26] and MH questionnaires (GAD-7 [27] and PHQ-9 [28]) will be given to complete within 7 days. (3) Fathers or partners will be invited to participate in 2 semistructured interviews, within 2 weeks of recruitment and immediately prior to discharge. The interviews will explore their MH, experiences of bonding with baby, understanding the neonatal environment, and reflecting on their service expectations. Based on the father's or partner's preference, interviews will be undertaken either in a private room on the NU or digitally via MS Teams at a mutually convenient time. Interviews will be digitally recorded and are anticipated to last up to 1 hour. Data saturation is expected at around 12-15 fathers. (4) The parents will be asked to complete the PSS:NICU, GAD-7, and PHQ-9 questionnaires at 3 weekly intervals, finishing on the week of discharge, to monitor their MH through their NU stay. (5) Up to 4 groups of 5 mothers will be invited to participate in a focus group to assess their wellbeing, experience of the NU, and their perspective on support for and from their partners. This will occur in a room in the NU at a time convenient to the mothers. Groups will be organized until data saturation is reached. (6) Telephone interviews and emailed questionnaires will be completed by parents at 4-6 weeks postdischarge to assess family confidence and bonding after NU discharge.

Description of Questionnaires Used

PSS:NICU Questionnaire

The PSS:NICU was originally developed in 1993 [26]. It assesses neonatal intensive care unit–specific stressors on a Likert scale. Each item can be scored from 0 to 5, with a maximum total score of 230 over the 46 items. Modified versions exist, but the original full-length questionnaire will be used for this study as all subsections are of interest with changes to be implemented.

GAD-7 Questionnaire

The GAD-7 is a 7-item self-administered questionnaire that assesses the presence and severity of symptoms of anxiety over the preceding fortnight. Scores range from 0 to 3 on each item, with a total score ranging from 0 to 21. There are established set points for mild, moderate, and severe anxiety [27].

PHQ-9 Questionnaire

The PHQ-9 is a 9-item self-administered questionnaire that assesses the presence and severity of symptoms of depression over the previous two weeks. It is scored in the same manner as the GAD-7 with total scores ranging from 0 to 27 and with established set points for mild, moderate, and severe symptoms [28].

Washout Period, Phase 2 Preparation (4 Months)

A program to enhance father participation with the FICare model will be developed using the existing Neonatal DadPad or Imperial Family Delivered Neonatal Care app. Both of these apps are currently used in several NHS Trusts to guide fathers through their NU journey. The phase 1 and systematic review findings, along with guidance from the PAG will inform our decision for what is best suited for our local population.

Teaching sessions will be undertaken to educate and upskill all clinical NU staff on the study aims, recruitment, phase 1 study findings, and upcoming phase 2 study, highlighting the importance of fathers' role in the FICare (eg, teaching parents how to safely give nasogastric feeds and nappy changes in a ventilated baby). In addition, there will be regular FICare teaching for staff, including encouragement of parents to attend ward rounds, and with guidance to parents in the workbook (Table 2).

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Table 2. Program to enhance father involvement in family integrated care.

Strategies	When	Who
Educational booklet or app, including • Introduction to the neonatal unit • Meeting the multidisciplinary team—tailored to the individual unit • Family integrated care • Taking care of yourselves • Routine care and "observations" • Breastfeeding • Developmental care • Medications • Nutrition and growth • Ventilation and breathing support • Cardiac (heart) conditions • Gastrointestinal and liver (gut) conditions • Brain development • Planning for discharge • Eyes	At parents' disposal	Both parents
Suggested tasks or workbook, including • Kangaroo care • Nappy changes in incubator • Mouth care and cleaning of baby • Reading of observations (heart rate, temperature, respiratory rate) • Helping to weigh baby • Bathing baby • Ward round participation	To work through at parents' pace	Both parents
Peer support sessions—led by specialist clinical psychologists or therapists	Every two weeks	Fathers[a,b]
Ward round participation	Daily	Both parents[a]
Bite-size education classes	2-3 per week at varying times including weekend	Both parents[a,b]

[a]Any parent in the unit is welcome to participate or attend.

[b]Sessions to occur at times to suit fathers with cultural, religious, family, and work obligations, as determined through phase 1 data collection.

Phase 2 Study: Enhanced Father Involvement in FICare (9 Months)

Once a family is recruited, the program developed to enhance the father's involvement in FICare will be implemented to take place at the parents' pace (Table 2). Materials will be freely available to the study participants in a format suited to their needs (electronic or paper copy). All interested parents are encouraged to attend the peer support sessions, ward round participation, and bite-size education classes.

The NU experience and MH status of both parents will be assessed as in the phase 1 study (Figure 1) including assessing their experience of the FICare program. At the end of the phase 2 study, staff knowledge, experiences, and opinions about fathers and FICare will be reassessed and compared with the start of the study.

Statistical Analysis

Qualitative data will be imported into dedicated software packages to facilitate analysis including NVivo (Lumivere) and SPSS (SPSS Inc). Interviews will be transcribed, following which the original recordings will be destroyed.

Interviews and Focus Groups

Data will be uploaded into NVivo to facilitate qualitative data management and thematic analysis. We will use several methods to minimize researcher bias during the study. All interviews will be conducted by 1 person (RR), who will maintain a reflexive diary through the study process. The transcripts will be independently coded by 2 researchers (RR and KG) to find repeated patterns of meaning which provide a detailed understanding of the perspective of the participants [29]. Both researchers will systematically code the data in detail and group them together into broader themes, with themes revisited to ensure that data saturation has been reached. These will then be grouped into broader themes generating a thematic map that will allow us to understand the parents' experiences in NU. The chief investigator (NA) will have control of the data and will be able to access the audio recordings of the interviews at all times to audit the quality of the interview process. Decision trails and coding trees will be used to ensure that coding and decision-making in data analysis are clear and transparent. Any discrepancies will be discussed with a third person (NA). Verbatim (anonymous) quotes will be shared with the results to allow the reader to determine whether the final themes reflect the data. Finally, the research team and participants will be invited to comment on the emerging or final themes during the data analysis.

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Questionnaires

For descriptive statistics, the median and mode scores of the PSS:NICU, GAD-7, and PHQ-9 will be used to describe the outcome of the questionnaires. For inference analysis, the difference in median for the PSS:NICU, GAD-7, and PHQ-9 at admission, discharge, and 6 weeks postdischarge will be compared between phase 1 and phase 2 using the Mann-Whitney test and the paired 2-tailed *t* test. The data will be checked for outliers and these will be corrected or removed. However, where these outliers are accurate, a nonparametric statistical analysis will be performed. Depending on the data type, missing data will be replaced with mean, median, or mode. In addition, regression and multiple imputations analysis will also be used to impute or generate missing values.

Staff survey questionnaire responses to individual questions will be presented as a percentage of individuals responding yes or no. The percentage of "yes" responses to each question by the staff at the start and end of the study will be compared by paired *t* test.

Data Storage and Availability

All patient-identifiable data will be stored in a locked office of the principal investigator (PI) of participating sites. Access to identifiable data will be restricted to the PI and research team. The paper questionnaires will be stored securely in a file kept in the locked research office and electronic versions will be stored in a password-protected NHS computer. The electronic version of questionnaires will be emailed by parents to a secure NHS email account. This will also be used if transcription or audio files need to be transferred with third-party transcription services. Third-party services will be vetted as per NHS standards to ensure data protection and confidentiality. The sponsor will have access to the pseudoanonymized data if requested. Anonymized data will be made available on request. Study data will be kept for up to 18 months after the study completion.

Potential Risk to Participants and Mitigation

Considering the nature of the study, it is unlikely to have any adverse events. However, fathers may feel the additional burden of fulfilling their expected NU obligations alongside their breadwinner role and feelings of guilt for being unable to fulfill the expectations set for them [30,31]. To mitigate this difficulty, there is flexibility in when and to what extent fathers would like to be involved in FICare set at their own pace. The questionnaires and interviews may be emotionally challenging. This is being mitigated by the option to attend peer support sessions run by an appropriately trained professional and all parents will have access to the local neonatal psychologist. Interview frameworks were reviewed by the PAG and neonatal psychologist. A protocol is in place for any participants exhibiting severe MH symptoms through questionnaire responses or other forms of communication. Adverse events will be reported to the chief investigator and local research and development office and follow research and development, protocols with consideration of modification of study procedures if required.

Adverse events in the hospital setting will follow local hospital protocols as well as escalation to study PI with consideration of modification of study procedures if required. The risk of psychological distress resulting from study participation has been minimized with the support of a specialist psychotherapist who reviewed the study design and materials. A protocol is in place for any parents exhibiting severe MH symptoms through questionnaire responses or other forms of communication. We do not anticipate any risks to parents as they are simply being encouraged to participate in standard FICare activities that already occur in the participating centers. There is an emphasis that this should occur at the parents' pace.

Dissemination

The study findings will be presented at neonatal and FICare conferences and published in medical and nursing journals. The study findings will also be shared with relevant charities (eg, Bliss), and the study participants if they wish. It will form the basis of a PhD thesis. The PAG will be involved in the dissemination of the study findings.

Ethical Considerations

Participants will be able to withdraw from the study at any point. Anonymized data gathered until this point will be retained for data analysis. Following each interview or focus group, parents will be given 2 weeks to withdraw their data from the study. The study was approved by Leicester, South Research Ethics Committee (22/EM/0140)in August 2022, and written consent will be obtained from participants (see participant information leaflets and consent forms in Multimedia Appendices 1 and 2).

Results

The study is currently ongoing. As of October 2023, 22 families, comprising 22 fathers and 17 mothers had been recruited. The SR studies have been registered with the PROSPERO database (324275 and 306760). The projected end date for data collection is around July 2024, data analysis will occur in November 2024, and publication of the study findings will occur in early 2025.

Discussion

This study will test the hypothesis that if fathers are facilitated to engage more with their baby on the NU and are better supported during the neonatal stay, both parents will experience fewer MH symptoms during their baby's hospitalization and up to 6 weeks postdischarge. Improving parents' MH is shown to allow greater parent-child bonding [32] and more sensitive responsiveness of mothers to their infants' cues [33]. Mothers engaged in the FICare model have greater confidence in caregiving at the point of discharge and seek less medical support after discharge [32]. It is anticipated that these results will translate to fathers or partners.

Unlike many other studies [12,33], this study includes parents of a wide gestational age range of premature infants, including extremely premature infants and those who are invasively ventilated and at the highest risk of adverse outcomes. This is vital as research has found that fathers find the fragile appearance of their premature infants causes significant stress

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[34]. A focus of the study methods will be to upskill NU staff to increase awareness and understand the importance of father engagement in FICare and their MH as well as the impact on mother and child, which is in line with the NHS Long Term Plan [17].

Limitations of the study include the need for conversational English. This is required to be able to complete the standardized questionnaires, participate in the interviews and focus groups, and to be able to engage with the phase 2 provisions. The language for the phase 2 materials will be kept as simple to ensure readability and understanding. Exclusion from recruitment based on language will be monitored. The perceived research burden may disproportionately impact parents who have older children, have a greater distance to travel, limited parental leave, or who do not have English as their first language. There may also be cultural barriers to overcome when discussing MH.

A prospective cohort study was the most practical and ethical study design. The sample size and the primary outcome of the study is based on the qualitative data. A bigger sample size will be required for the study to be based on the quantitative or questionnaire data. The quantitative or questionnaire data collected in this study is to support the qualitative data and to test the feasibility of collecting such data longitudinally.

The PSS:NICU questionnaire has been translated into many languages across the world [35,36], and is a well-used tool in neonatal research. It has been validated in mothers and fathers of NICU babies in the United Kingdom [37]. There are limited validated tools to assess paternal and maternal anxiety and depression in the postpartum or NU period. Therefore, simple screening tools that are validated in primary care and the general population for patients with a variety of backgrounds and stages of life were chosen [27,38,39].

Acknowledgments

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Data Availability

The deidentified data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NA, RR, and KG conceptualized the study. RR and NA prepared the first draft of the paper. All authors contributed to the study design, sample size calculation, and writing of the protocol for this study. All authors contributed to revisions of the manuscript and to the final version of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant information leaflet.
[DOCX File , 48 KB - resprot_v13i1e53160_app1.docx]

Multimedia Appendix 2
Consent form.
[DOCX File , 37 KB - resprot_v13i1e53160_app2.docx]

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Abbreviations

FICare: family integrated care
GAD-7: Generalized Anxiety Disorder-7
MH: mental health
NHS: National Health Service
NU: neonatal unit
PAG: parent advisory group
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
PSS: NICU: Parental Stressor Scale: Neonatal Intensive Care Unit
SR: systematic review

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Protocol

Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE): Protocol for a Translational Study

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Abstract

Background: Cutaneous T-cell lymphoma (CTCL) is a rare group of lymphomas that primarily affects the skin. Mycosis fungoides (MF) is the most common form of CTCL and Sézary syndrome (SS) is more infrequent. Early stages (IA-IIA) have a favorable prognosis, while advanced stages (IIB-IVB) have a worse prognosis. Around 25% of patients with early stages of the disease will progress to advanced stages. Malignant skin-infiltrating T-cells in CTCL are accompanied by infiltrates of nonmalignant T-cells and other immune cells that produce cytokines that modulate the inflammation. Skin infection, often with *Staphylococcus aureus*, is frequent in advanced stages and can lead to sepsis and death. *S. aureus* has also been reported to contribute to the progression of the disease. Previous reports indicate a shift from Th1 to Th2 cytokine production and dysfunction of the skin barrier in CTCL. Treatment response is highly variable and often unpredictable, and there is a need for new predictive and prognostic biomarkers.

Objective: This prospective translational study aims to identify prognostic biomarkers in the blood and skin of patients with MF and SS.

Methods: The Predictive and Prognostic Biomarkers in Patients With MF and SS (BIO-MUSE) study aims to recruit 120 adult patients with MF or SS and a control group of 20 healthy volunteers. The treatments will be given according to clinical routine. The sampling of each patient will be performed every 3 months for 3 years. The blood samples will be analyzed for lactate dehydrogenase, immunoglobulin E, interleukins, thymus and activation-regulated chemokine, and lymphocyte subpopulations. The lymphoma microenvironment will be investigated through digital spatial profiling and single-cell RNA sequencing. Microbiological sampling and analysis of skin barrier function will be performed. The life quality parameters will be evaluated. The results will be evaluated by the stage of the disease.

Results: Patient inclusion started in 2021 and is still ongoing in 2023, with 18 patients and 20 healthy controls enrolled. The publication of selected translational findings before the publication of the main results of the trial is accepted.

Conclusions: This study aims to investigate blood and skin with a focus on immune cells and the microbiological environment to identify potential new prognostic biomarkers in MF and SS.

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Trial Registration: ClinicalTrials.gov NCT04904146; https://www.clinicaltrials.gov/study/NCT04904146
International Registered Report Identifier (IRRID): DERR1-10.2196/55723

(JMIR Res Protoc 2024;13:e55723) doi:10.2196/55723

KEYWORDS

mycosis fungoides; Sézary syndrome; prognostic; predictive; protocol; translational study; cutaneous T-cell lymphomas (CTCL); skin microbiota; immunology; tissue microenvironment; epigenetics; quality of life; skin infection; Staphylococcus aureus; progression of disease; skin barrier; prognostic biomarkers; adult; adults; elderly; spatial; microbiological sampling; blood; study protocol

Introduction

Mycosis Fungoides and Sézary Syndrome

Cutaneous T-cell lymphoma (CTCL) is a rare group of lymphomas that primarily affects the skin [1-3]. The pathogenesis of CTCL is not yet fully understood [3]. The annual incidence of CTCL is 0.7 per 100,000. Mycosis fungoides (MF) is the most prevalent form and comprises 60% of CTCL, with a higher male incidence (1.6:1.0) and a peak age incidence between 50 and 74 years [4]. Since MF often has a chronic course, its prevalence is considerably higher. The skin lesions in MF can be patches, plaques, tumors, or erythroderma. Sézary syndrome (SS) is an aggressive leukemic variant of the disease and constitutes only 5% of CTCL; it is defined as a triad of erythroderma, lymphadenopathy, and the presence of neoplastic T-cells in peripheral blood [5]. The extent of the disease in the skin is measured according to the Modified Severity-Weighted Assessment Tool [6,7]. Both MF and SS are staged according to the same tumor-node-metastasis-blood (TNMB) classification, assessing the involvement of skin, peripheral lymph nodes, peripheral blood, and visceral organs [8].

Prognosis of MF and SS

The TNMB stage at diagnosis remains the most important prognostic factor [9,10]. Many patients with early stages of MF have an indolent disease with a 5-year disease-specific survival of 89% to 98% [8,11]. However, approximately 25% of patients with early stages of disease will later progress to advanced stages [4]. Patients with advanced stages of MF have a 5-year disease-specific survival of 18% to 56% associated with treatment failure [8,10]. The 5-year disease-specific survival of SS is 36% [3,8,10].

Multivariate analyses of cohorts of patients with MF and SS have identified potential adverse prognostic factors in the early stages of disease consisting of male gender, aged >60 years, plaques, folliculotropic disease, and stage N1/NX and negative prognostic factors for advanced disease consisting of male gender, aged >60 years, stages B1/B2 and N2/N3, and visceral involvement [12,13]. The presence of plaque lesions in the early stage of the disease, large cell transformation in the skin, and elevated lactate dehydrogenase are also identified as adverse prognostic factors [11,14,15]. Still, there is an unmet clinical need to identify which patients will progress to an advanced stage of disease, and there is a great need for new reliable prognostic markers.

Treatments for MF and SS

The therapeutic options for MF and SS range from skin-directed therapy (SDT) to systemic treatment, and the selection of appropriate treatment is primarily based on the stage of the disease. There are only a few randomized controlled trials for the treatment of MF and SS, and current recommendations for treatment are mainly based on consensus meetings and international guidelines [4,5,10]. The treatment of the early stages of MF aims at modulating the immune response in the skin through SDT, such as topical corticosteroids and UV light therapy. Local radiation therapy usually has a good effect in all stages. In early stages that are refractory to SDT or in advanced stages, systemic treatment is used, including retinoid derivatives, low-dose methotrexate, and interferon alfa. In patients with lymphoma cells expressing CD30, targeted chemotherapy with brentuximab vedotin can be used. Further, standard chemotherapy such as gemcitabine or doxorubicin can be used; however, this often results in only short remission periods. Extracorporeal photopheresis can be used in erythrodermic stages of MF and SS and mogamulizumab and alemtuzumab can be used in advanced stages of disease. Highly selected patients with advanced stages of disease can be considered for allogeneic stem cell transplantation. Histone deacetylase (HDAC) inhibitors such as vorinostat and romidepsin are approved by the US Food and Drug Administration but are not commonly used in Europe [16,17]. Total skin electron beam therapy can be used in widespread disease in the skin or before allogeneic stem cell transplantation. Treatment response is unpredictable, and there is an unmet clinical need to find reliable predictive markers.

Immunological Changes of the Microenvironment of CTCL in Skin and Blood

Early stages of CTCL derive from mature CD4+ T-cells, or rarely CD8+ T-cells, in the skin. The restriction to the skin suggests that the affected cells are dependent on the specific cutaneous microenvironment, including cytokines and adhesion molecules. Malignant skin-infiltrating cells are accompanied by infiltrates of nonmalignant T-cells and other immune cells. The infiltrating benign immune cells produce a variety of cytokines that modulate cutaneous inflammation and are important constituents of the local environment of the tumor, fostering proliferation, survival, and migration [3]. Attempts to associate a unique cytokine profile of the disease based on skin or blood samples have indicated that a shift from Th1 to Th2 cytokine production accompanies disease progression [18,19], but the mechanisms behind this shift are not completely known [20]. In the advanced stages of the disease, a reduction of

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skin-infiltrating CD8+ T-cells has been observed, as well as a shift toward M2 polarized macrophages and increased frequencies of NK cells and B-cells [21,22]. Other major immunological changes also facilitate the environment of the lymphoma cells and impair the host immunological defense [22]. The hypothesis of this study is to further explore these immunological changes through analysis of lymphocyte subpopulations in blood and skin together with cytokine expression in plasma through protein array analysis. We also hypothesize that we will detect other cells, molecules, and factors in the microenvironment of the tumor that could influence the clinical course of CTCL.

Epigenetic Modifications in CTCL

Regulation of DNA transcription is complex, and the mechanisms of regulation of DNA transcription in CTCL are partially unknown. HDACs can regulate the expression of genes and activities of transcription factors involved in malignant transformation and immune defense. HDACs act mainly through alteration of the structural components of chromatin by histone deacetylation, thus affecting the 3D conformation of DNA without changing or interrupting its sequence. Epigenetic drugs such as HDAC inhibitors have shown promising results in patients with advanced disease, emphasizing the impact of epigenetic regulators on the disease. Based on phase II data demonstrating long-term remission in 35% of heavily pretreated patients, HDAC inhibitors have been approved by the US Food and Drug Administration for second-line treatment of CTCL [16,17]. Although the dysregulated function of HDAC inhibitors may have an important role in malignant transformation and in the response to cancer treatment, the in vivo mechanisms behind the effects of HDAC inhibitors in CTCL are largely unknown. However, next-generation sequencing data have shown amino-acid or copy number alterations of 13 chromatin modifiers in 1% to 7% of CTCL cases, respectively, suggesting a mutation-driven epigenetic imbalance in CTCL [23]. Interestingly, HDAC inhibitors have been shown to reprogram the epigenome of host nonmalignant T-cells toward normal patterns, emphasizing the role of the host T-cells for therapy response [24,25].

Microbiological Changes and Skin Barrier Function in MF and SS

Skin infections, often with *Staphylococcus aureus*, are frequently seen in advanced stages of MF and SS. In patients who are immunocompromised, skin infections can lead to sepsis and death. Some studies indicate that a shift from Th1 to Th2 cytokine production and dysfunction of the skin barrier contribute to skin infections [26,27]. The underlying basis for the microbiological changes and the skin barrier function in CTCL need to be further elucidated for their potential role in the pathogenesis and progression.

Goals of This Study

The primary objective of this study is to identify serum-protein markers for 6-month progression-free survival (PFS) and to identify the immune cell profile in blood for 6-month PFS.

Secondary objectives are to identify the immune cell profile in the skin for 6-month PFS, analyze the lymphoma microenvironment in the skin for 6-month PFS, identify the skin barrier and skin microbiology profiles for 6-months PFS, and identify the epigenetic changes in lymphoma T-cells and host T-cells for 3 months PFS.

Methods

Study Design

The Predictive and Prognostic Biomarkers in Patients With MF and SS (BIO-MUSE) study is a translational prospective study, aiming to include 120 adult patients with MF and SS and a control group of 20 healthy volunteers (Figure 1). Sampling of each patient will be performed every 3 months for 3 years. The control group will be examined on 3 different occasions at least 2 months apart. This study is presently open at Skåne University Hospital and aims to open at Karolinska University Hospital. The multicenter study design enables other Swedish sites to be included, after further ethical approval.

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Figure 1. Study design of the BIO-MUSE study. BIO-MUSE: Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome; CT: computed tomography; DLQI: Dermatology Life Quality Index; IgE: immunoglobulin E; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; IL-1beta: interleukin-1beta; LDH: lactate dehydrogenase; MF: mycosis fungoides; mSWAT: Modified Severity-Weighted Assessment Tool; NRS: Numerical Rating Scale; sIL-2R: soluble interleukin-2 receptor; SS: Sézary syndrome; TARC: thymus and activation-regulated chemokine; TEWL: transepidermal water loss; TNMB: tumor-node-metastasis-blood.

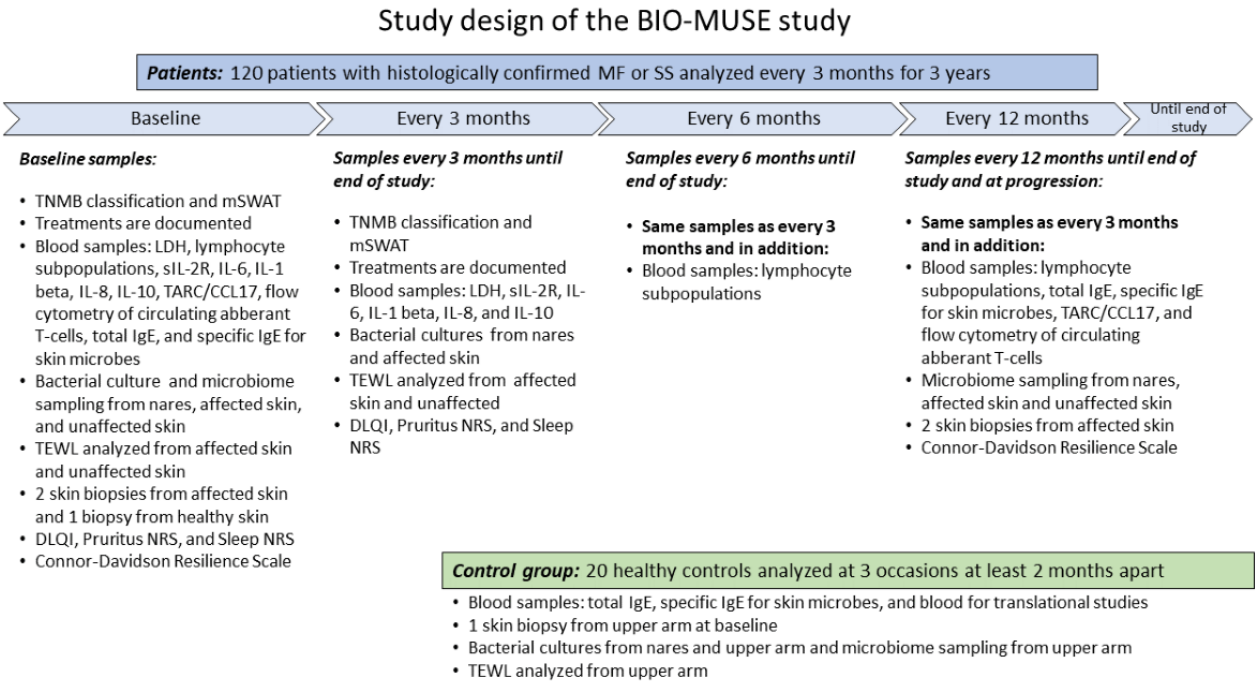

Ethical Considerations

This study's protocol is written per the Declaration of Helsinki and the International Council for Harmonisation's good clinical practice guidelines. This study was registered with ClinicalTrials.gov (NCT04904146) and approved by the Swedish Ethics Committee (2019-05130). Written informed consent will be obtained from participants according to the Declaration of Helsinki and International Council for Harmonisation's good clinical practice guidelines.

Eligibility Criteria

Inclusion criteria will be patients aged 18-100 years with histologically confirmed MF and SS (stage IA-IVB) and World Health Organization performance status 0-3. The inclusion criteria for the healthy control group will be healthy adults aged 18-100 years with World Health Organization performance status 0-2 and the absence of any malignant, autoimmune, or infectious disease. The exclusion criteria for both groups are psychiatric illnesses or conditions that could interfere with the ability to understand the requirements of this study.

Stage of Disease and Modified Severity-Weighted Assessment Tool

Patients will be staged according to the TNMB classification [8]. The extent of disease in the skin will be measured according to the Modified Severity-Weighted Assessment Tool [6,7]. Progression or regression will be defined as a shift from one stage to another.

Treatment of MF and SS

The treatments will be given according to clinical routine and national and international guidelines for MF and SS and participation in this study will not affect the choice of treatments. Ongoing treatments will be documented.

Blood Samples for Soluble Interleukin-2 Receptor, Interleukins, and Thymus and Activation-Regulated Chemokine/CCL17

Blood samples in patients will be analyzed for complete blood count, liver and kidney function, lactate dehydrogenase, soluble interleukin-2 receptor, interleukin-6, interleukin-8, interleukin-10, and thymus and activation-regulated chemokine/CCL17 (Multimedia Appendix 1).

Blood Samples for Analysis of Immunoglobulin E Against Specific Antigen

Total immunoglobulin E and specific immunoglobulin E for *S. aureus* enterotoxin A (m80), enterotoxin B (m81), toxic shock syndrome toxin-1 (Rm226), *Malassezia* (m227), and *Candida albicans* (m5) will be analyzed in patients and in the control group (Multimedia Appendices 1 and 2, respectively).

Blood Samples for Analysis of Lymphocyte Subpopulations

Flow cytometry of peripheral blood will be performed in patients to analyze the T-cell subpopulations including naive, effector, and memory T-cells (including Th1, Th2, and Th17 cells) and activated and regulatory T-cells. Monoclonal antibodies recognizing CD4, CD8, CD197, CD45RA, CD25, CD194, CD127, CD45RO, CD183, and CD196 will be used [28]. In

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addition, to evaluate the presence of clonal T-cells in peripheral blood and biopsies the following panel: T-cell receptor fluorescein isothiocyanate, TRBC1 phycoerythrin, CD16 electron coupled dye, CD2 PC7, CD3 BV421, CD4PC5.5, CD7 A700, CD8 KrO, CD26 allophycocyanine, and CD45 allophycocyanine-H7 will be used [29] (Multimedia Appendices 1 and 3, respectively).

Serum-Based Profiling of Immune-Related Soluble Proteins

Broad sets of serum-based protein profiling focused on immune-related proteins will be performed in patients. Global protein profiling will be performed using commercially available methods, allowing high-plex analyses of immune-related soluble molecules. State-of-the-art bioinformatic tools will be applied for preprocessing and analysis of data (Multimedia Appendix 1).

Assessment of Tumor Microenvironment by Digital Spatial Profiling and Single-Cell RNA Sequencing

To allow the study of the cellular tumor immune microenvironment, 2 biopsies from affected skin and 1 biopsy from unaffected skin, at least 5 cm away from affected skin, will be taken. In the control group, 1 skin biopsy is taken from the upper arm. The skin biopsies will be formalin-fixed and paraffin-embedded. In addition, blood will be drawn from patients and healthy controls and peripheral blood mononuclear cells will be cryopreserved.

Multiplex analyses of samples taken before and after progression have the potential to contribute to novel biological knowledge as previously discussed in a recent review by the group Kalliara et al [30] and will be performed in samples collected over time. In brief, in skin biopsies, Digital Spatial Profiling will be performed to study immune infiltration in CTCL and how it evolves during the progression of the disease [31]. Single-cell RNA and T-cell receptor sequencing will be applied to sorted CD3+ cells to follow the evolution of the malignant clone over time. Moreover, additional assessments of genetic and epigenetic changes in the tumor and tumor microenvironment will be performed in skin biopsies (Multimedia Appendix 1).

Assessment of Epigenetic Factors in Circulating Tumor Cells Compared to Normal and Host T-Cells

Cell sorting of CD3+ cells from peripheral blood in patients with blood involvement will be performed using FACSAria (BD, Bioscience). When possible, 2-3 million cells will be sorted from each patient to allow the preparation of DNA for epigenetic analysis and RNA for gene expression analysis. Analysis of histone modifications and chromatin accessibility will be performed by ChIP-seq (chromatin immunoprecipitation with sequencing) and ATAC-seq (assay of transposase-accessible chromatin with sequencing), respectively. Moreover, molecular profiling using nCounter analysis (NanoString Technologies, Inc) will be performed to profile cells through expression panels focused on immune profiling and proliferative signaling pathways (Multimedia Appendix 1).

Microbiological Sampling

Microbiological samples will be analyzed from affected skin and from unaffected skin 5 cm away from affected skin, preferably from the upper body, and from nares in patients. In the control group, the microbiological samples will be analyzed from the upper arm and from the nares (Multimedia Appendices 1 and 2, respectively).

Analysis of Skin Barrier Function

Skin barrier function will be measured as transepidermal water loss (TEWL) with a closed chamber TEWL meter, VapoMeter 300 (Delfin Technologies Ltd), according to guidelines [32]. TEWL will be measured on affected skin and on unaffected skin 5 cm away from affected skin, preferably from the upper body. TEWL will be measured on the upper arm in the control group (Multimedia Appendices 1 and 2).

Hematopathology of Skin, Lymph Node, Bone Marrow, and Tumor Biopsies

Hematopathology of skin biopsy will be performed in affected skin from patients and is optional from lymph nodes, bone marrow, and tumors (Multimedia Appendices 1 and 3).

Patient-Oriented Life Quality Measures

Patient-oriented life quality measures will be performed. The Dermatology Life Quality Index [33], Peak Pruritus Numerical Rating Scale [34], Sleep Numerical Rating Scale, and Connor-Davidson Resilience Scale [35] will be used (Multimedia Appendix 1).

Statistical Analysis

The sample profiles from patients with an early stage of disease (stage IA-IIA) will be compared to samples from patients with an advanced stage of disease (stage IIB-IVB) using multivariate analysis with principal component analysis. Individual samples will be compared between the groups using the Mann-Whitney *U* test. Other translational samples will be presented by descriptive statistics. Progression-free and overall survival will be presented using Kaplan-Meier plots.

Results

Patient inclusion started in 2021 and is still ongoing in December 2023, with 18 patients and 20 healthy controls enrolled. Until December 2023, a total of 2 included patients have declined further participation due to the extra visits in this study. Further, 2 patients have died from MF during this study. The publication of selected translational findings before the publication of the main results of the trial is accepted, and data analysis is in progress.

The evaluation of the stage of the disease will be observed every 3 months according to the TNMB classification, where the shift from one stage to another implies progression or treatment response. After the study, patients will be grouped as either early stage of the disease (IA-IIA) or advanced stage of the disease (IIB-IVB). The patients crossing over from the early stage of the disease to the advanced stage of the disease group will be analyzed both individually and as a group. Approximately 30% (36/120) of patients are estimated to be in

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the advanced stage of the disease group. The translational samples in the early stage of the disease group will be compared to samples from the advanced stage of the disease group. The treatments directed against MF are documented throughout this study. Excluded patients will be presented along with the final results. Depending on patient numbers, treatment data will be presented descriptively, or if possible, to support data on treatment predictive biomarkers.

Discussion

Principal Findings

This study aims to find potential predictive and prognostic biomarkers in patients with MF and SS. This study will investigate translational samples from skin and blood concerning the stage of the disease over time, which has the advantage of monitoring patients with consecutive samplings to be able to capture changes before and during a possible progression. This study will be able to compare differences in patients with early (IA-IIA) and advanced (IIB-IVB) stages of the disease. It will also be possible to analyze the data separately for patients with MF and SS, respectively. The translational samplings in this study are chosen to be able to detect changes in the immune system and in tumor cells, as well as changes in the skin barrier function and the skin microbiota. There is a clinically unmet need to find new predictive and prognostic biomarkers in MF and SS, and studies further exploring these areas are therefore a high priority. The research team, techniques, and management presented in this protocol have capacities to investigate new aspects and bring new knowledge to the field of CTCL. This study combines a multidisciplinary outpatient clinic with extensive translational research sampling, which has considerable potential to lead to true patient benefit.

Limitations

MF and SS are rare diseases, and the inclusion of the proposed number of patients in this study protocol may take considerable time. To reach the estimated number of patients in this study, inclusion will also start at Karolinska University Hospital, and to expand this study further, cooperations with other centers is ongoing. Another possible limitation is that the control group will be followed for a shorter period compared to the patients.

Comparison With Prior Work

The Prospective Cutaneous Lymphoma International Prognostic Index study is an ongoing international study of a confirmed early-stage MF cohort, which is being followed up to identify prognostic factors in the hope of providing better management and improving survival by identifying patients at risk of disease progression [36].

Conclusions

The BIO-MUSE study is a prospective translational study aiming to identify new prognostic and predictive biomarkers in blood and skin in patients with MF and SS.

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Data Availability

The data sets analyzed during this study are available from corresponding authors upon reasonable request.

Authors' Contributions

KD is the principal investigator of this study. EB and KD are responsible for including patients at Skåne University Hospital, Lund Sweden. HB is responsible for including patients at Karolinska University Hospital, Stockholm. AS is responsible for the microbiological translational part of this study. SE and ÅJ are responsible for the immunology translational part of this study. EB, AS, and KD were the major contributors to writing this paper. All the authors participated in the design of this study and read, commented upon, and approved this final paper.

Conflicts of Interest

EB has received lecturing fees from Novartis. AS has received lecturing and consulting fees from Sanofi, Pfizer, AbbVie, and LEO Pharma. KD has received honoraria from Kyowa Kirin, Roche, and Incyte, and is a shareholder and board member of Respiratorius AB. HB has received honoraria for serving on an advisory board from Kyowa Kirin and a lecturing fee from Janssen-Cilag.

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Multimedia Appendix 1
Translational samples and logistics for patients in the Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE) study.
[DOCX File , 22 KB - resprot_v13i1e55723_app1.docx]

Multimedia Appendix 2
Translational samples and logistics for the healthy control group in the Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE) study.
[DOCX File , 16 KB - resprot_v13i1e55723_app2.docx]

Multimedia Appendix 3
Planned assessments of hematopathology in the skin, lymph node, bone marrow, and tumor biopsies.
[DOCX File , 17 KB - resprot_v13i1e55723_app3.docx]

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Abbreviations

ATAC-seq: assay of transposase-accessible chromatin with sequencing
BIO-MUSE: Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome
CBC: complete blood count
ChIP-seq: chromatin immunoprecipitation with sequencing
CTCL: cutaneous T-cell lymphoma
HDAC: histone deacetylase
MF: mycosis fungoides
PFS: progression-free survival
SDT: skin-directed therapy
SS: Sézary syndrome
TEWL: transepidermal water loss
TNMB: tumor-node-metastasis-blood

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Protocol

A Bluetooth-Based Smartphone App for Detecting Peer Proximity: Protocol for Evaluating Functionality and Validity

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Abstract

Background: While ecological momentary assessment (EMA) is commonly used to study social contexts and social influence in the real world, EMA almost exclusively relies on participant self-report of present circumstances, including the proximity to influential peers. There is the potential for developing a proximity sensing approach that uses small Bluetooth beacons and smartphone-based detection and data collection to collect information about interactions between individuals passively in real time.

Objective: This paper aims to describe the methods for evaluating the functionality and validity of a Bluetooth-based beacon and a smartphone app to identify when ≥2 individuals are physically proximal.

Methods: We will recruit 20 participants aged 18 to 29 years with Android smartphones to complete a 3-week study during which beacon detection and self-report data will be collected using a smartphone app (MEI Research). Using an interviewer-administered social network interview, participants will identify up to 3 peers of the same age who are influential on health behavior (alcohol use in this study). These peers will be asked to carry a Bluetooth beacon (Kontakt asset tag) for the duration of the study; each beacon has a unique ID that, when detected, will be recorded by the app on the participant's phone. Participants will be prompted to respond to EMA surveys (signal-contingent reports) when a peer beacon encounter meets our criteria and randomly 3 times daily (random reports) and every morning (morning reports) to collect information about the presence of peers. In all reports, the individualized list of peers will be presented to participants, followed by questions about peer and participant behavior, including alcohol use. Data from multiple app data sets, including beacon encounter specifications, notification, and app logs, participant EMA self-reports and postparticipation interviews, and peer surveys, will be used to evaluate project goals. We will examine the functionality of the technology, including the stability of the app (eg, app crashes and issues opening the app), beacon-to-app detection (ie, does the app detect proximal beacons?), and beacon encounter notification when encounter criteria are met. The validity of the technology will be defined as the concordance between passive detection of peers via beacon-to-app communication and the participant's EMA report of peer presence. Disagreement between the beacon and self-report data (ie, false negatives and false positives) will be investigated in multiple ways (ie, to determine if the reason was technology-related or participant compliance-related) using encounter data and information collected from participants and peers.

Results: Participant recruitment began in February 2023, and enrollment was completed in December 2023. Results will be reported in 2025.

Conclusions: This Bluetooth-based technology has important applications and clinical implications for various health behaviors, including the potential for just-in-time adaptive interventions that target high-risk behavior in real time.

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KEYWORDS

Bluetooth technology; passive sensing; proximity detection; ecological momentary assessment; social influence; alcohol use; mobile phone

Introduction

Behavioral Influence in Social Contexts

Social context, which refers to immediate temporal, situational, and intrapersonal factors, is important for many health behaviors [1]. Understanding how context influences behavior is an essential first step toward the development of preventive interventions to reduce risk, as it provides essential information on why, with whom, where, and when a person engages in a particular behavior. For alcohol use, the health behavior we will focus on, the presence of peers is a highly influential contextual factor for all ages [2-6]. Recent studies have examined real-time information gathered about individuals and their environment [7-9] via purposeful, self-initiated reports or prompted reports [eg, ecological momentary assessment (EMA)]. Compared with retrospective recall, which can lead to error, EMA methods probe for participant reports in real time, leading to more accurate perceptions of behavior and allowing for the assessment of changes in the social context across a day [10]. However, while EMA as a method can help advance our understanding of the social context, it requires individuals to be both aware of and able to report peer presence or influence. Thus, there is value in research that relies less on self-report and more on passive assessment of the social context.

Use of Technology to Examine Social Contexts

There has been a rapid rise in the passive ambulatory assessment of behavior [11,12] using various technologies, including wearables for physical activity or heart rate [13,14] and alcohol biosensors [15,16]. In addition to wearable sensors, smartphones passively collect data from their built-in sensors in real time [17], including information on location and movement [18-20] and social interactions [20,21]. A smartphone-based technology with potential applications for understanding social contexts is Bluetooth, which is a ubiquitous connectivity protocol embedded in mobile phones and other wearable devices. Designed to underlie communication between digital devices, the unique characteristics of Bluetooth have enabled the development of software that can identify nearby Bluetooth beacons (eg, Apple AirTags or other transmitters, including smartphones themselves), allowing smartphone apps to assess the duration and frequency of interpersonal interactions [22-24].

Despite its promise, little research has applied Bluetooth technology to proximity sensing to study the social contexts of health behavior change. An epidemiological study used smartphone-based Bluetooth sensors to predict behavior change associated with disease spread [25], and another used Bluetooth-based proximity sensing to assess the relationships among sociability, sleep, and mood [26]. A recent study on alcohol use incorporated Bluetooth sensing to examine the social context of young adult drinking, in which the Bluetooth technology captured features such as the number of proximal devices and signal strengths [27]. Recently, researchers have evaluated the performance of Bluetooth-integrated methods to understand disease spread during the COVID-19 pandemic [28-30]. Our goal is to develop and evaluate the stability of a smartphone app that leverages a Bluetooth-based wearable sensing protocol to study the real-world social context of alcohol use but could be applicable to other behaviors in which social contexts act as key determinants.

Study Objective

The objective of this research is to develop technology that will allow for the passive detection of contact between individuals, and specifically between participants and their close friends. In this paper, we describe a smartphone app, Bluetooth-based beacons, and our planned procedures for evaluating the *functionality and validity* of the developed technology. In a companion paper [31], we describe our approach to evaluating participant responses to using the technology in a study on the social context of alcohol (ie, feasibility and acceptability). *Functionality* will be determined by evaluating the stability of the app (ie, low app crashes or other issues) and the success of the beacon detection protocol and app notifications across different devices and in different situations. We will collect data on functionality throughout the study, primarily using app-based data and secondarily using qualitative data from interviews with participants and peers at the completion of data collection. *Validity* will be determined by evaluating the concordance between beacon detection and participant EMA reports of peer presence data sources. Details of the project goals and methods for evaluating the goals are described in Table 1.

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Table 1. Project primary goals and methods for evaluating goals.

Goal	Definition	How determined	Data source
Functionality			
Beacon detection	Whether the peer beacons are detected by the participant app consistent with app settings	Tested in participant orientation to confirm that beacons are detected by participant phone	• Beacon Encounter data set • App Log data set
Beacon encounter notifications	Whether the app functions as expected, defined as delivering report notifications with the expected latency when beacon encounter criteria are met	An indication of notification sent by the server when actual encounters are identified	• Beacon Encounter data set • Participant Event data set
App overall stability	Whether the app functions as expected with minimal errors	App error reports (crash and reinstall) and participant error reports	• App Log data set • Participant EMA[a] report data set • Postparticipation interview
Phone and operating system differences	Whether differences across Android phone and operating system versions are noted	Information about participant phones and operating systems	• App Log data set • Baseline survey • Participant postparticipation survey and interview
Validity	Concordance between beacon detection and participant report of peer presence	Cross-classification of beacon encounter and participant self-report data	• Beacon Encounter data set • Participant EMA report data set • Participant postparticipation interview • Peer weekly surveys

[a]EMA: ecological momentary assessment.

Methods

Design

Young adults will participate in a 3-week protocol during which they will complete reports about interactions with peers, including (1) signal-contingent reports triggered by the presence of a Bluetooth beacon being carried by a participant-nominated peer, (2) random reports triggered in time blocks 3 times per day, and (3) a morning report. A baseline assessment will precede field data collection and will aid in identifying peers, and an interview at the end of the study will collect qualitative information and feedback about participant experiences.

Participants

We will recruit up to 5 participants for our pilot study, and we will recruit 20 participants in the main study, with a conservative estimate of 15 completing the full protocol. The inclusion criteria are as follows: (1) be able to read English, (2) own an Android smartphone with OS11 or newer and have it with them throughout the day (typical for the age group between 18 and 29 years), (3) have a data plan (limited or unlimited), (4) be willing to approach peers to participate, and (5) anticipate not deviating from their typical routine during the study period, including leaving the region (as this would likely reduce exposure to selected peers). Additional inclusion criteria related to our substantive research aims are as follows: (1) aged 18 to 29 years; (2) drinking alcohol with others at least once a week, including drinking >4 (women) and >5 drinks (men) per occasion at least once a week in the past month; and (3) not in or seeking treatment for substance use.

We restricted our project to Android phones because there were several barriers that emerged with iOS. First, iOS places significantly more restrictions on apps that can be put on users' phones and the methods by which those apps can be loaded onto devices. Relatedly, when provisional software is distributed via the developer side of the App Store, a very limited number of developer testing accounts are provided, limiting the ability to test the app. Second, iOS takes more control than Android over processes that run in the background of the phone, including notifications, which are critical to the functionality of the app. Third, with the availability of the Apple AirTag we were concerned that implementing an alternative Bluetooth Low Energy (BLE) signal detection network with a different beacon would appear in competition with first-party applications and thus our app would be precluded or significantly delayed in distribution via the App Store. Further, as app development for this project started during the COVID-19 pandemic, there was significant focus placed on using BLE for proximity detection by both Apple and Google, with Apple in particular restricting the use of some features. For these reasons, and given the available resources and time frame of the project, we decided early in the course of the project to exclusively develop for Android phones. We note, however, that while owning an Android phone is a requirement for participants, it is not a requirement for peers.

Procedures

Eligibility and Recruitment

Young adults will be recruited from the community through flyers, email listserves, and social media advertisements. A brief web-based screener will establish their initial eligibility. Eligible participants will provide contact information, and a research assistant (RA) will schedule the in-person baseline session.

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Participant Orientation and Baseline Assessment

A 90-minute in-person session will collect informed consent, demographic characteristics, and alcohol use data and identify possible peer participants. The RA will orient the participant to the project procedures, starting with installing the app on the participant's phone and recording device characteristics (device manufacturer, model, and Android operating system version). The RA will assist participants in changing settings on their phones to ensure the app will work optimally, including setting Bluetooth, location, nearby devices, and notifications to *on* or *allow*, and checking that settings that pause activity (eg, pause app activity if unused) or remove permissions are *off*. The RA will demonstrate the app interface, including showing the participants how to initiate reports and respond to notifications. The participants will navigate through each report, view examples of response types (radio buttons and text fields), and practice making entries. They will be instructed to respond as soon as possible after a prompt. We will explain that they are expected to keep their phone on, charged, and nearby. We will verify that the participants are not planning on traveling.

Peer Eligibility and Recruitment

The inclusion criteria for peers are as follows: (1) at least once a week in a typical week, having meaningful in-person social interaction with the participant. The alcohol-related inclusion criteria for peers are as follows: (2) between the ages of 18 and 29 years, and (3) drink with the participant at least twice a month in a typical month. While not all influential people with regard to alcohol use will be same-age peers, research indicates that same-age peers will most likely be present during drinking events (and in social interactions when drinking might occur) [32-34]. To identify possible peers, the RA will conduct a social network interview (SNI) that involves the participant nominating up to 10 people who they are close to, including friends, family members, or anyone they regularly spend time with in person who is close to their age [35,36]. The participants will report on the characteristics of these individuals, including their age, gender identity, whether they live together, relationship (friend, partner or significant other, casual acquaintance or coworker, sibling or cousin, other family member, and other), and frequency of meaningful social interaction ("How often in a typical month do you spend at least 15 consecutive minutes with this person?"). In line with the substantive study goals, we will also assess the frequency of the network member's drinking ("How many times in the past month do you think this person drank alcohol?") and the frequency of drinking with the person ("In the past month, how often did you drink with this person [while both of you were drinking]?"). For this protocol, we will ascertain the participant's perception of the willingness of the peer to participate in this study.

Working with the RA, the participants will identify 3 peers to be invited to participate in the study based on eligibility. During the baseline session, the participant will attempt to contact each of the 3 selected peers to invite them to participate. If the participant contacts the peer with the RA present and the peer agrees to hear more about the study, the participant will, with the peer's agreement, share the peer's contact information with the RA, who will then provide the peer with a web link to the study description and informed consent procedures and will communicate with the peer about their participation from that point forward. If the peer does not respond to the participant in the presence of the RA, the participant will send the peer a brief study description with the web link. If any peer who has received the project description does not respond after 3 days, we will move to the next person on the SNI list and ask the participant to make initial contact with the (new) peer. The participants will be given 5 days to recruit up to 3 peer participants.

Once a peer participant has consented to participate, the RA will arrange a time to give them the beacon and answer any questions. The beacon is 4.4 cm square and 1 cm thick (Figure 1). We will provide a small adhesive patch to allow the peer to attach the beacon to their phone and a ring to facilitate attachment to their keys if they choose. Peers will carry their beacon for 3 weeks of the project. Each beacon is assigned a unique ID that associates the beacon with the participant and peer. The smartphone app reports will begin for the participants once the beacons are distributed to their peers. The peer participants will complete web-based surveys at the end of each of the 3 weeks of data collection, in which they will indicate the days and time of day in the prior week they did not have their Bluetooth beacon with them and times in the prior week they were with the participant. This information will be useful for determining why a beacon was not detected.

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Figure 1. The beacons used in this research were asset tags from Kontakt.io.

EMA Reports

Overview

Our project will use a custom smartphone app for data collection, developed in conjunction with our developer, MEI Research [37]. The app, which is only available for Android phones, comprises 2 primary components: the participant-facing EMA report delivery component and a background process that continuously scans for the Bluetooth beacons. Researchers create EMA reports and adjust the settings using a web interface. Notification of random and beacon signal-contingent EMA reports is handled locally on-device, so internet connectivity is not needed for either report triggering or beacon detection to function. Content is delivered dynamically from the MEI Research server, which requires cellular or Wi-Fi connectivity. Data are synchronized with the server when the participant opens the app or activates the sync function.

Before the 21-day EMA phase, the names of the SNI-identified peers and information about their associated beacons are uploaded using the researcher-facing web interface into the app so that the customized list of peers is presented to each participant on EMA reports (refer to the examples in Figure 2). This list of peers will have a maximum of 6 names from the SNI. All peers carrying the beacon will be on the list; others on the list may have declined to carry the beacon or may not have been asked. First, names, nicknames, or initials are presented to maximize confidentiality during data collection. Updating this list can occur in real time without involving the participant, thereby avoiding protocol disruptions. EMA reports begin with an item measuring *peer proximity*: “Yesterday/In the past hour, who were you around for any length of time?” The friend list is presented to the participant for them to choose from, with branching logic used to determine the presentation of subsequent questions. The names or nicknames of peers are not included in the researcher data set; numeric peer IDs (also associated with beacon data) ensure deidentification.

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Figure 2. Screenshots of 2 items in the morning survey, first presented without answers (A) followed by the item with friends selected (B). Note that image B presents only friends that were selected in question A.

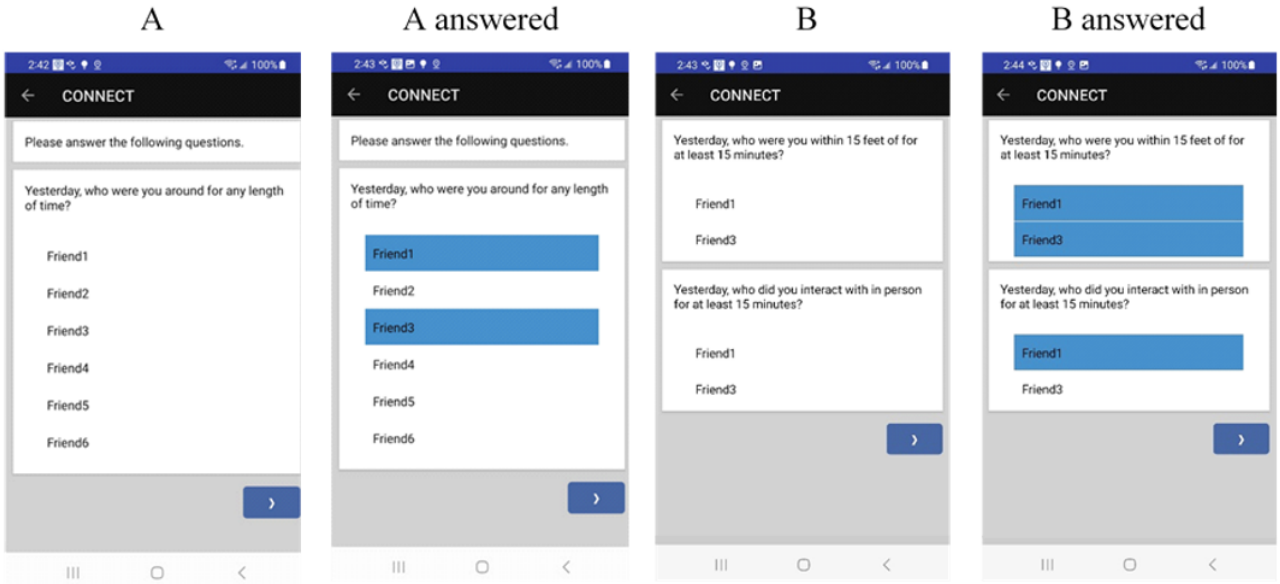

The participants will provide 3 types of EMA reports, completed in 1 to 3 minutes each.

Signal-Contingent

Signal-contingent reports are triggered by the app according to its detection of beacons carried by peer participants (refer to the subsequent section for details on beacon and trigger settings). We will not have constraints on times when these reports are prompted, and reports will expire (ie, will disappear from the app display) after 1 hour.

Random

Random reports are intended to sample experiences outside of drinking events and those prompted by signal-contingent reports, including peer contact and influence. The participants will receive 3 random EMA reports per day between 12 PM and 12 AM (12 to 6 PM, 6 to 9 PM, and 9 PM to 12 AM). We chose these intervals to optimize the measurement of alcohol use and exposure to peers. The participants will be informed of these intervals; missing data because of going to sleep is of low concern. Notifications will be followed by reminders at 15 and 30 minutes and will expire after 1 hour. The notification and in-app display for signal-contingent and random reports appear identical on the EMA app interface to minimize unintentional awareness of peer presence. Although there is no basis on which to project a compliance rate with beacon-triggered surveys, we expect a 70% or higher compliance rate with random surveys [31,38].

Morning

Morning reports will be completed by participants every day. The morning report is always available on the app, with a notification at 10 AM and reminders at 15 and 30 minutes thereafter. The EMA app prioritizes signal-contingent and random reports such that participants are not able to complete morning reports until any pending triggered reports are completed. The morning report items are identical to the signal-contingent and random reports but refer to *yesterday*, whereas the random and signal-contingent reports refer to *in the past hour*. In the morning reports, we also ask about prior-day app functionality related to participant experience (ie, *participant-related functionality*; "Were there times yesterday when you think our system was not working as you expected?"); those who indicate *yes* or *maybe* are asked to describe the issue in a text box. Items also identify possible missing data (eg, "Did you do any of the following yesterday?" with answers "You silenced your phone," "You turned your phone off," "You turned off notifications on your phone or for the EMA app," and "You turned off Bluetooth detection"). During the 3-week EMA period, the study staff will contact the participants once a week to check in, encourage compliance, and address technical issues as needed. The participants can also email, call, or text study staff at any time they have issues or questions.

Postparticipation Assessments

After the 3-week data collection period, the participants will complete a modified 15-item System Usability Scale (SUS [39]) with items adapted to our protocol that assess functionality (eg, "The app drained my battery" and "The app worked as expected") with response options on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree. We will also conduct a semistructured interview to clarify any reported functionality or validity issues. Before the interview, we will examine the participant's beacon encounter data and reports of peer presence, and during the interview, we will clarify discrepant information, including reconciling signal-contingent reports (ie, indicating beacon detection) at times when the participant did not indicate that the peer was present. We will also probe the reasons for noncompliance and whether triggered report noncompletion appears to be systematically related to peer presence. In this final session, participants will be told how to delete the app from their phone.

Ethical Considerations

Human Subject Protections

The procedures were approved by the Brown University Institutional Review Board (protocol number 2022003448).

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Informed Consent

The participants and the peer participants will complete informed consent, which includes reviewing detailed consent forms, discussion with the researcher, and documentation of consent.

Privacy and Confidentiality

All information obtained during the assessments will be confidential and will be used solely for research purposes. To protect the data and prevent unauthorized access, all EMA data will be encrypted and will remain so until it is accessed by the project staff using a username and password specific to this project. All files with participant-identifying information will be password-protected and stored separately from the data on a server accessed only by the project staff. To preserve confidentiality, we will deidentify data for both peers and participants using a numeric code. The participants will have the researcher provide credentials for the smartphone app that will not include their names, and we will encourage the participants to use phone passwords.

Compensation

Participants will be paid US $50 for attending the first session, US $5 per day for answering the EMA reports (at least 2 of 4 of the morning and random reports per day), and US $40 for attending the second session. The participants will also receive a weekly bonus of US $20 if they complete at least 80% of the random and morning reports. The most they can receive for participation is US $255. Peer participants will be compensated US $30 for each week they carry the beacon and answer the weekly survey questions, and US $10 for returning the beacon to the research team, so the most they can receive is US $100. All compensation will be provided in the form of an Amazon e-gift card.

Beacons and Parameters for Signal-Contingent Triggers

Beacon Selection and Features

We prioritized 4 criteria in the selection of the beacon used in this study: signal strength, robustness of the application programming interface, size and convenience of carrying, and battery life. The expected functionality of the beacon is primarily advertising (ie, one-way communication comprising transmission of small packets of data over fixed time intervals for detection and localization by a receiver—here, the EMA app used by the participants) [40]. Given these requirements, we selected BLE, an extension of the traditional Bluetooth protocol. Using BLE facilitated the optimization of our first criterion, signal strength. The Bluetooth protocol includes a feature called Received Signal Strength Indication, an indicator of the signal power received by a device detecting BLE signals. This feature, together with the specifications of the transmission source hardware, enables the computation of approximate positioning in the natural environment, including the estimation of distance [41,42]. Many hardware vendors provide these features; a subset of these vendors provides open, nonproprietary documentation of these values [43] and the ability to interface directly with the beacons through a robust application programming interface, our second criterion. After reviewing options, conducting testing, and consulting with the app developer, we selected Kontakt.io, a company with beacons that met the first 2 criteria and have form factors that can be attached to a phone or keyring to ensure that it is carried consistently. We extensively tested the options available from Kontakt.io and determined that the asset tag was most reliably detected by our app and by generic BLE scanner apps. Its battery life is 6 to 12 months and can be monitored on the internet; therefore, even with reuse, there should be no missing data attributable to a depleted battery.

We initially investigated whether we could build the system such that the Bluetooth on the peers' phones would be detected by the app on the participant's phone. For this, an app was needed that could use the BLE functionality within the participant phone to detect and identify the peer phone and prompt the participant to respond within the EMA app. One problem with using the peer phone as the BLE transmitter is that different Bluetooth hardware installed in different phones will report differing RSSI values for the same physical distance since this metric is contingent on the strength of the signal being sent out by the original device. This increases the complexity of the programming logic and would add error into what is a simple threshold check for beacons. Another issue is that we were unable to identify any phone-to-app software with an SDK available to use with our EMA app, whereas beacon detection SDKs were available. There were other considerations, including that in early developmental work concerns were raised by peers about installing an app on their phone, but the most critical were that the resources needed for phone-to-app detection were higher than the beacon-to-app model due to the initial development process, variability of operating systems and hardware, and required ongoing maintenance when relying on operating systems that evolve over time. The key benefits of beacon-to-app detection are the consistency of the technology and lower development costs when using an existing SDK.

EMA Report Triggering by Beacon Proximity

The protocol for peer proximity detection and subsequent triggering of reports involves the detection of *transient encounters* (ie, incidental, brief social interactions between the participant and a peer identified through signal detection), their conversion into *actual encounters* (ie, meaningful social interactions differentiated from incidental encounters using a time criterion), and their termination as *end encounters* (ie, discontinuation of meaningful social interaction; refer to Figure 3 for a representation of the process). The EMA app continuously scans the participants' environments for peer beacons. A transient encounter is recorded when the BLE proximity detection service integrated into our EMA app detects a beacon, defined as detecting a signal from a peer beacon that is at least as strong as the Received Signal Strength Indication criteria that correspond to our proximity criterion (ie, 15 ft, 4.6 m). The peer beacon advertising interval, which is the frequency at which beacons send out signals, was set to 1000 milliseconds (1 second) to ensure that the detection corresponds closely to real-world interactions. However, given that the detection of every signal from the peer beacon by the participants' device during the initial encounter period is not guaranteed, a window

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of time for the detection of this signal is needed to ensure that detection occurs (ie, that it is not missed, resulting in a false negative); this window was set at 2 minutes for the transient encounter.

A *transient encounter* is converted into an *actual encounter* when the beacon has been detected for at least 15 minutes (our definition of meaningful interaction) without being undetected (ie, gone) for >2 minutes. A signal-contingent report will be triggered upon the conversion of a transient encounter to an actual encounter. Critically, the algorithm that determines triggering by beacon proximity runs separately for each peer participant, such that a transient and actual encounter with a peer beacon can be initiated even when the participant is in an actual encounter with another peer. Given that there will be 3 peers carrying beacons, it is possible that up to 3 reports could be triggered at a time, although we do not anticipate that this will happen frequently. In addition, given our encounter parameters that require 60 minutes of nondetection before another encounter with the same beacon would occur (refer to the subsequent section for explanation), we do not expect the number of signal-contingent reports to be overwhelming but will evaluate this closely.

A separate criterion to end an actual encounter after 60 minutes of nondetection (vs 2 minutes for a transient encounter end) was selected. We selected 60 minutes to reduce spurious nondetection and accommodate behaviors such as going to the restroom or being in different rooms at a party (which may still be part of an ongoing meaningful interaction despite not meeting the proximity criterion). Although the duration of the time criteria (ie, 15 minutes for the actual encounter and 60 minutes for the end encounter) were somewhat arbitrary, the evaluation of the sensitivity and specificity of the criteria via concordance with self-report is a goal of the study. Subsequent work can trial different definitions based on study findings, as well as what contact is truly influential and whether the length of influential contact varies by relationship type. Table 2 presents our initial criteria (far-right column) based on the best judgment, but the criteria are modifiable within the researcher-accessed interface.

Figure 3. State flow diagram that incorporates the beacon detection, encounter definition, and notifications. PlotProjects is a service and application programming interface used by the app software for the Bluetooth beacon detection.

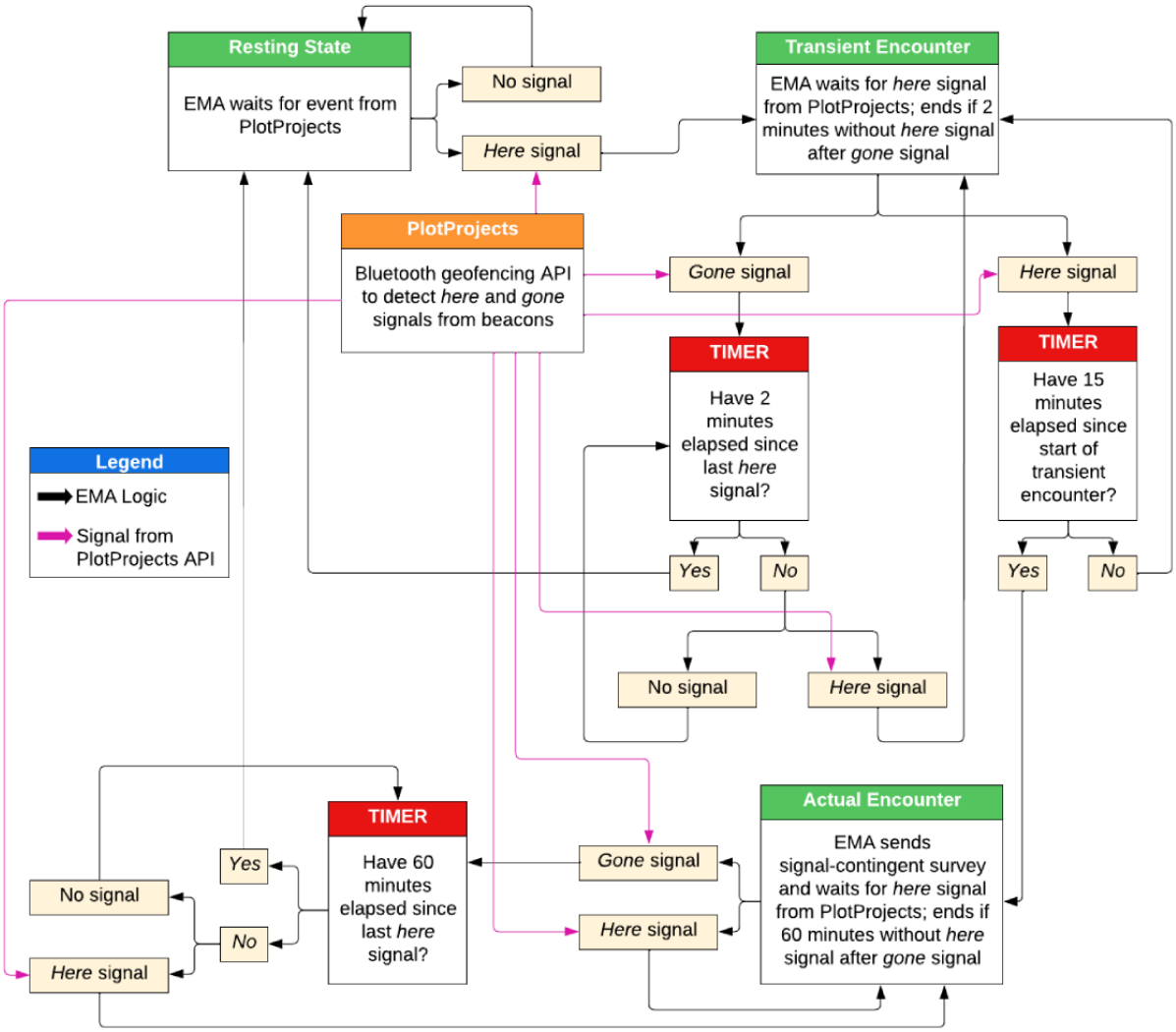

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Table 2. Transient and actual beacon encounter terms, definitions, and criteria.

Term	Definition	Criteria
Encounter	Incidental or purposeful social interaction between the participant and a peer is identified through BLE[a] signal detection with a predefined proximity criterion.	15 ft (4.6 m)
Start of a transient encounter	Brief social interaction. A transient encounter begins but does not constitute meaningful interaction until it converts to an actual encounter.	1000 milliseconds
End of the transient encounter	End of a brief social interaction is defined by a given time criterion. Intended to ensure that very brief encounters do not prompt a notification.	2 minutes without beacon contact
Start of an actual encounter	Meaningful social interaction defined by a given criteria of time. A transient encounter is converted to an actual encounter. An actual encounter triggers a signal-contingent report.	15 minutes of beacon contact with no periods >2 minutes without beacon contact
End of the actual encounter	Discontinuation of meaningful social interaction.	60 minutes without beacon contact

[a]BLE: Bluetooth Low Energy.

There are several technology-related considerations for the detection of meaningful interactions. First, an a priori definition of a meaningful social interaction had to balance sensitivity for detecting such events (addressing the *feasibility* of detecting social interactions) with specificity in excluding incidental, nonmeaningful interactions (and reducing the burden of responding to multiple signal-contingent reports). However, our a priori criterion of requiring 15 minutes for a transient encounter to be converted into an actual encounter will miss brief but meaningful interactions (eg, consuming a shot of hard alcohol together, offering alcohol). Importantly, we designed our protocol to minimize missing data associated with such events by including the assessment of past-hour peer presence in our random reports and past-day peer presence in our morning reports. This design will allow us to cross-tabulate the occurrence of self-reported interactions of even short duration (as recorded in the EMA report data set) with the occurrence of all beacon detections, including transient encounters (as recorded in the Beacon Encounter data set).

Data Sets and Calculated Variables

Overview

Data produced by the app, including information about encounter events, participant self-reported data, and metadata, are stored in several data sets. These data sets are supplemented by postparticipation self-report data from (non-EMA) surveys and semistructured interviews. Table 3 contains a description of the data sources; Table 1 links the data sources with the study goals and methods to the evaluate goals.

Table 3. Metadata and calculated variables and associated source data sets that will be used to evaluate research goals.

Metadata or calculated variable	Source data set					
	App log	Beacon Encounter	Participant events	Notification log[a]	EMA[b] report	Postparticipation
Participant ID	✓	✓	✓	✓	✓	✓
Peer ID (corresponds to beacon ID)		✓			✓	✓
Event or Report timestamp	✓	✓	✓	✓	✓	✓
Event type (eg, action delivered, participant report started, report response, and app synced)[c]	✓	✓	✓		✓	
Session ID (helps link together events from different data sets)		✓	✓	✓	✓	
Source of event (eg, morning or random report)			✓	✓	✓	
Corroborative self-report					✓	✓

[a]Contains only notifications for morning and random reports.

[b]EMA: ecological momentary assessment.

[c]Metadata recorded by the app and stored.

Further information about the source data sets are presented in the Multimedia Appendices 1-5.

App Log

This data set contains information about the app version used and (morning, random, beacon-triggered) report items that are programmed into the app. It also contains event types (eg, app opened and app synced) and errors (eg, when the operating system denies permission to the app). We will use information from this data set to determine that the app was installed correctly and that it was functioning as expected during the study.

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Beacon Encounters

Variables include participant ID, beacon ID, start and end timestamps of transient and actual encounters, the timestamp when the transient encounter was converted into an actual encounter, and the timestamp for when the report notification was sent. A unique session ID links the elements (start and end) of given (transient and actual) encounters.

Participant Events

Variables include participant ID and types of events (eg, report start, report submit, and report notification) with timestamps. The report start and submit timestamps are present for all reports, including random, morning, and signal-contingent reports. Report notification timestamps (1) duplicate the timestamp of the transient-to-actual conversion reported in the Beacon Encounter data set (which triggers a notification) and (2) indicate whether other notifications are for random or morning reports.

Notification Log

Variables include session ID, report type (ie, random and morning), and timestamps when timed notifications and reminders were scheduled to be sent.

EMA Reports

Data include participant responses to items in the signal-contingent, random, and morning reports, including indicators of who among their peers is or was present and self-reports about app functionality. For example, in each report, we ask, “Who did you interact with in person for at least 15 minutes?” The report type and timestamp will be used to ensure that data responses are aligned with information from other data sets and reports.

Postparticipation Data

Data from the postparticipation interviews and the SUS will be used to evaluate the app’s functionality. Participant interviews will also be used to investigate identified discrepancies between the beacon-derived data and participant reports (ie, validity) and will be supplemented with weekly survey day-level reports from peers about their proximity to participants.

Data Analysis Plan

Functionality of Beacon Detection by the Participant’s Smartphone

We will confirm the detection of the 3 beacons by the participant’s phone during the orientation. We expect to observe smartphone notifications for each beacon when the transient encounter is converted into an actual encounter (after 15 minutes). If notifications are not observed, we will examine the Beacon Encounter data set to determine whether transient encounters are being recorded (ie, whether the beacon is detected by the app) without being converted into an actual encounter. Functionality will be evaluated with 3 metrics: (1) the proportion of participants whose phones detect all beacons during the orientation, (2) the proportion of beacons detected by participant phones, and (3) the latency between exposing the participant phones to the beacons and the start of a transient and actual encounter. These observations will be systematically recorded and aggregated across beacons and participants.

Functionality of the Beacon Encounter Notifications

Data from the Beacon Encounter data set will be used to evaluate functionality in two ways: (1) the proportion of actual encounters for which a signal-contingent notification was shown as sent by the server in the Beacon Encounter data set, and (2) the mean latency in minutes between the conversion to an actual encounter and the sending of the signal-contingent notification. The functionality of notifications for random and morning reports will not be evaluated, as these are commonly used in EMA and are fully functional in the app.

Functionality Related to App Stability

The app log, the EMA data, and the end-of-study interview and survey will be used to assess the participant-experienced functionality. The app log contains details about the events that have occurred within the app, including information about app crashes and app reinstalls. Using data provided by participants in the morning report, participant-related functionality will be determined as follows: (1) the total count (ie, person-days) of participant-reported suspected functionality problems, (2) the person-level proportion of days of suspected functionality problems, and (3) aggregated item-level and overall mean scores on the adapted SUS. Open-ended feedback will also be obtained in the morning report as well as in the end-of-study interviews.

Functionality Related to the Phone and Operating System

The manufacturer, model, and Android operating system of the participant devices will be examined as moderators of the above metrics of functionality. The variables will be evaluated using a series of Mann-Whitney *U* tests (for means and counts) and chi-square tests (for comparing proportions) for each metric. Considering the small sample size, the groups will be driven by the sample of the device itself. For instance, the manufacturer could be binned to *Samsung* (or potentially *Google*) versus *all other manufacturers*; the model could be binned to *currently supported* (ie, receiving ongoing feature and compatibility updates) versus *legacy*; and the operating system could be binned to *Android 13* (the newest) versus *Android 11 or 12* (operating systems that were used during app development). Independent of group comparisons, descriptive findings on functionality will be aggregated for each manufacturer and operating system version.

Validity

We define validity as the concordance between encounters recorded in the Beacon Encounter data set and participant reports of peer presence recorded in the EMA reports (Table 4).

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Table 4. Beacon validity: cross-classification of beacon encounter and participant self-report data[a].

	Participant self-report data	
	Positive (participant reports peer within 15 ft, 4.6 m for 15 minutes)	Negative (participant does not report peer nearby)
Beacon detection		
Positive (signal-contingent trigger)	True positive: beacon detected and triggers signal-contingent report and participant reports peer presence in signal-contingent report (*sensitivity*)	False positive[b]: beacon detected and triggers signal-contingent report but participant does not report peer presence in signal-contingent report (*specificity; protocol criterion validation*). This could happen if: • delay or error in notification (*technology failure*) • peer is not actually present (*technology failure*) • peer is present with beacon but the index participant is not aware (*inaccurate index participant self-report*) • peer is present with beacon but not when the participant answers report (*limitation of detection settings*)
Negative (no signal-contingent trigger)	False negative[c]: 1. beacon never detected but participant reports peer presence on next EMA[d] random report (*sensitivity*). This could happen if: • peer is present with beacon but beacon is not detected (*technology failure*) • peer is present without beacon (*peer noncompliance*) • inaccurate index participant self-report 2. peer beacon is detected in transient encounter but criteria for actual encounter are not met so does not trigger signal-contingent report but participant reports peer presence on EMA random report (*specificity; protocol criterion validation*)	True negative: 1. beacon never detected and no report of peer presence on EMA random report (*sensitivity*) 2. peer beacon is detected in transient encounter but does not trigger signal-contingent report (criteria for actual encounter are not met) and no report of peer presence on EMA random report or morning report (*specificity; protocol criterion validation*)

[a]Concordance will be evaluated only when self-report EMA data are available. Therefore, beacon data collected when index participants are not compliant with random or signal-contingent reports will not be usable in the evaluation of concordance, as no self-report of peer proximity will be available.

[b]Reasons for false-positive signal-contingent triggers may not be known to the study team.

[c]Reasons for false-negative signal-contingent triggers may not be known to the study team.

[d]EMA: ecological momentary assessment.

False negative beacon detections will be evaluated in a series of steps: First, we will compute the proportion of (1) days and (2) random reports in which a participant reported peer presence (from the EMA data set), but a corresponding transient or actual encounter does not exist (from the Beacon Encounter data set). If a transient encounter, but not an actual encounter, is recorded, we will compute (3) the proportion of these false negative events that occurred because of the a priori selection of 15 minutes as the threshold delineating a transient versus an actual encounter (based on timestamps of encounter events in the Beacon Encounter data set). For the false negative events that are not associated with a transient encounter, we will further attempt to delineate the reason underlying this false negative as either technology-related (the peer was carrying the beacon but the beacon was not detected) or compliance-related (the peer was not carrying the beacon) by integrating self-report data on compliance from the peer weekly surveys. If sample size and base rates allow, we will also fit a series of generalized linear mixed models [44] regressing concordance at the person level (eg, sex and age) and proximal prior event level (eg, context and alcohol use) predictors to identify systematic factors associated with detection failure. *False positive* beacon detections, as indicated by the triggering of a signal-contingent report when the peer beacon is not present, have never occurred in preliminary testing. Given the factors needed to incur a false positive detection, which should only occur if beacon information was entered incorrectly by the research team, we believe that such events are highly unlikely. However, it is possible that a notification could be delayed by the operating system or other action (eg, if the index participant phone is off), which would result in the participant report being delayed, and thus the participant report would not confirm the peer presence. Beacon detection also could occur when a peer was present but the participant was not aware (eg, at a large party) or if the peer left the area before the participant answered the report. We will compute the proportion of signal-contingent reports in which participants deny a past-hour peer presence. We expect that the participant interviews and the peer surveys will be informative about the conditions under which false positives occur and will improve our understanding and measurement of peer proximity and influence. Ultimately, the detection of an encounter by the protocol when such an interaction did not occur from the participant's perspective provides critical information necessary for the computation of the specificity and positive predictive value of our detection protocol.

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Anticipated Sources of Missing Data

With various momentary assessment reports and passive data collection from multiple peers, the source of missing data is important to identify. We expect to have missing data owing to technical issues for the following reasons: (1) the beacons could stop sending a signal because of low battery or hardware failure; (2) the app could crash or be unable to send or receive data; (3) the phone operating system could update, resulting in the app or phone features not working as expected; or (4) the software detection algorithm may stop identifying encounter start and end signals. Missing data may also be because of participant or peer noncompliance, including the following: (1) participant nonresponse to EMA reports, (2) participant changing phone settings or status such that the detection of beacon signals or notifications is interrupted, or (3) peer failure to carry the beacon. Items in the morning report, postparticipation surveys and interviews, and the peer weekly survey will capture times when the participant or peer is aware of these issues occurring. While imperfect, this information should allow us to characterize situations in which the reason for missingness is known and thus maintain the missing-at-random assumption. Situations in which we are not confident about the reason for missing data will be investigated for systematicity using proximal prior predictors in the EMA data set to further maintain the missing-at-random assumption.

Results

Participant enrollment began in February, 2023. As of submission of the manuscript (June 2023), nine participants and 21 peers were enrolled, with data collection anticipated to finish in December, 2023. Data analysis will begin immediately upon completion of data collection.

Discussion

Principal Findings

The research described in this paper will advance the literature by developing and validating a passive detection system for situations in which social influence is important. While this Bluetooth-based technology could be applicable to many research, clinical, or community settings in which social contact is relevant, our substantive goal is to facilitate research characterizing the real-time social context of alcohol use and, in turn, to inform the timing and context of mobile-delivered interventions to reduce hazardous drinking [45,46]. In this paper, we describe our planned procedures for evaluating the functionality and validity of the system, which incorporates multiple components of functionality and uses data from the app and reports from participants and up to 3 of their close peers. Our approach to collecting user-reported information along with passively recorded data is consistent with recommendations for identifying high-risk events and the timing of real-time intervention [47].

Just-in-time adaptive interventions target behavior in the natural environment at a time when behavior is opportune for modification [48]. These tailored mobile-delivered interventions provide the right type and timing of intervention in response to real-time behavior, cognition, or context to prevent negative health outcomes [48-50]. Ideally, interventions could incorporate this BLE-based peer proximity approach to help people who are interested in changing behaviors by identifying contexts that confer greater risk (or alternatively, that protect against risk), alerting these people or others about the risk inherent in their present situation, and including encouragement and information about how to avoid the situation. This approach could be combined with other sensor technology, including location detection or geofencing using GPS to detect proximity to risky locations (eg, alcohol outlets), and other smartphone features (eg, the smartphone accelerometer to measure movement or engagement with messaging and texting apps) [27]. This study will provide much-needed information about the appropriate timing and context for just-in-time adaptive interventions in a scenario that is highly characteristic of young adult drinkers: consuming alcohol with close peers.

Limitations

Limitations related to technology include the need to build the system with a contracted app developer; to the best of our knowledge, there are no systems that researchers could use out of the box for person-proximity detection and EMA report triggering. The system only works with phones that use the Android operating system; iOS imposes barriers to the development of technologies and the distribution of test builds, whereas Android allows for the installation of third-party software outside of the context of Google Services (ie, sideloading). However, Android had multiple operating system updates while our project was under development; each update required a revision of the app and additional testing. This is an unavoidable element of app development that adds considerable time and resources to a project. We considered providing Android phones to participants who did not have them but had concerns that intermittent or limited use of a secondary phone would reduce both compliance and app functionality (eg, fewer notifications being sent to phones frequently in sleep mode). Another technology limitation is our inability to implement a minimum time interval between random and signal-contingent reports or to set a limit on the number of signal-contingent reports a participant receives. We will evaluate the average number of reports and intervals between reports and hope to include adjustments in future iterations.

Our design will not detect influential peers who are not carrying a beacon; therefore, its success will rely largely on how well our SNI identifies influential peers and whether they participate. Our procedures will also poorly detect friends who are influential through interactions other than in-person contact (eg, via social media or text). Influence could also occur more quickly than the time duration estimate that we defined in the protocol; this influential interaction would be missed. During all EMA reports, we collect information about peers who are present but not carrying a beacon (identified a priori) and peers who are present but not on the participant's selected peer list, which will help us to determine how successful our SNI selection process was and address some of the above limitations; we also expect that information collected in the postparticipation interviews will assist us in adjusting procedures for identifying influential peers.

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We are relying on self-report to a considerable extent in that we are using it as the ground truth for whether a beacon detection is accurate or not. Self-report can be inaccurate or missing, but it is the standard in the field for describing context and alcohol use, and there are no alternatives that we could use to compare to beacon detection. While we are confident that our informed consent procedure, the provision of a clear rationale to participants and peers, and confidentiality protections will minimize inaccurate reporting, it is possible that social desirability or other person-level or contextual effects in some situations will result in missing or inaccurate reports of peer presence or alcohol use [51,52]. We expect that we will not be able to identify the reason for some disagreements between beacon detection and self-report, but the very robust data sets will allow for sensitivity analyses that will help us identify and understand discrepancies. For example, with morning reports and sensor data, we can compare the concordance between beacon detection and self-report on drinking versus nondrinking evenings. The weekly web-based surveying of peers was designed to minimize burden (and thus increase the likelihood of peer inclusion), but may produce unreliable data about the time spent with the participant.

The success of this research relies on participant and peer compliance, as their reports are needed to evaluate every project goal. Although some degree of noncompliance with EMA is common [38], poor compliance would limit our ability to evaluate functionality (refer to Table 4 for details) independent of systematic bias owing to missingness in the data collected. Although our participant burden is consistent with the current practice in EMA research, our peers must consistently carry a small beacon. Our requirement that peers continuously carry a beacon will likely result in more missing data than if there were an app for peers to install on their phone (which would also be easier to do remotely). Finally, this type of work requires considerable staff time for participant and peer recruitment (up to 3 peers per participant), monitoring incoming EMA and beacon data, and data management and analysis.

Future Work

In addition to the evaluation described herein of functionality and validity, we are collecting participant feedback about our procedures, which will allow us to evaluate feasibility and acceptability. Together, this information will inform a large-scale study with a representative sample, a wider age span, and a broad representation of social context, permitting the study of dynamic intersections of multiple determinants of drinking behavior, including social context, location context, and individual factors (eg, craving, affect, and motivation) that underlie contextual influences [53].

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed in this protocol. Once data are generated, data sets will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Application (App) log data set.
[PNG File , 135 KB - resprot_v13i1e50241_app1.png]

Multimedia Appendix 2
Beacon encounter data set.
[PNG File , 206 KB - resprot_v13i1e50241_app2.png]

Multimedia Appendix 3
Participant events data set.
[PNG File , 280 KB - resprot_v13i1e50241_app3.png]

Multimedia Appendix 4
Notification log data set.
[PNG File , 298 KB - resprot_v13i1e50241_app4.png]

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Multimedia Appendix 5
Ecological momentary assessment report data set.
[PNG File , 314 KB - resprot_v13i1e50241_app5.png]

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Abbreviations

BLE: Bluetooth Low Energy
EMA: ecological momentary assessment
RA: research assistant
SNI: social network interview
SUS: System Usability Scale

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Protocol

A Community Needs Assessment and Implementation Planning for a Community Exercise Program for Survivors of Stroke: Protocol for a Pilot Hybrid Type I Clinical Effectiveness and Implementation Study

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Abstract

Background: Physical activity and exercise are important aspects of maintaining health. People with mobility impairments, including survivors of stroke, are less likely to exercise and at greater risk of developing or worsening chronic health conditions. Increasing accessible, desired options for exercise may address the gap in available physical activity programs, provide an opportunity for continued services after rehabilitation, and cultivate social connections for people after stroke and others with mobility impairments. Existing evidence-based community programs for people after stroke target cardiovascular endurance, mobility, walking ability, balance, and education. While much is known about the effectiveness of these programs, it is important to understand the local environment as implementation and sustainment strategies are context-specific.

Objective: This study protocol aims to evaluate community needs and resources for exercise for adults living with mobility impairments with initial emphasis on survivors of stroke in Richland County, South Carolina. Results will inform a hybrid type I effectiveness and implementation pilot of an evidence-based group exercise program for survivors of stroke.

Methods: The exploration and preparation phases of the EPIS (Exploration, Preparation, Implementation, and Sustainment) implementation model guide the study. A community needs assessment will evaluate the needs and desires of survivors of stroke through qualitative semistructured interviews with survivors of stroke, rehabilitation professionals, and fitness trainers serving people with mobility impairments. Additional data will be collected from survivors of stroke through a survey. Fitness center sites will be assessed through interviews and the Accessibility Instrument Measuring Fitness and Recreation Environments inventory. Qualitative data will be evaluated using content analysis and supported by mean survey results. Data will be categorized by the community (outer context), potential participants (outer context), and fitness center (inner context) and evaluate needs, resources, barriers, and facilitators. Results will inform evidence-based exercise program selection, adaptations, and specific local implementation strategies to influence success. Pilot outcome measures for participants (clinical effectiveness), process, and program delivery levels will be identified. An implementation logic model for interventions will be created to reflect the design elements for the pilot and their complex interactions.

Results: The study was reviewed by the institutional review board and exempt approved on December 19, 2023. The study data collection began in January 2024 and is projected to be completed in June 2024. A total of 17 participants have been interviewed as of manuscript submission. Results are expected to be published in early 2025.

Conclusions: Performing a needs assessment before implementing it in the community allows for early identification of complex relationships and preplanning to address problems that cannot be anticipated in controlled effectiveness research. Evaluation and

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preparation prior to implementation of a community exercise program enhance the potential to be successful, valued, and sustained in the community.

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KEYWORDS

community participatory research; need assessment; exercise; survivors of stroke; community; community need; exercise program; stroke; physical activity; PA; mobility impairments; impairment; mobility; health decline; group activity; group exercise

Introduction

Physical activity (PA) and exercise are important aspects of maintaining health and reducing the development and severity of chronic conditions [1]. PA can lower the risk of mortality and reduce the incidence of hypertension, diabetes, heart disease, and some cancers [1]. Older adults have additional benefits of improved quality of life and lower risk of falls [1]. People living with disability are at a greater risk for chronic health conditions and are less likely to exercise than their age-matched peers [2,3]. People with disabilities have limited access to exercise in order to mitigate their health conditions and improve their aerobic capacity [2,4].

For survivors of stroke, reduced PA additionally increases their risk for a recurrent stroke [3]. Up to 80% of the risk of recurrent stroke can be mediated by lifestyle factors including medication management, diet, and exercise [3]. Individuals after stroke with mobility impairments have poor movement economy and higher cardiovascular demands that increases their need to build aerobic capacity over their peers [5]. However, even after receiving inpatient rehabilitation services, deficits remain. After completing inpatient rehabilitation, 80% of stroke survivors can ambulate indoors, but only 27% can perform the essential skills of community ambulation [6]. Despite the remaining deficits, many do not receive additional care in the community [7]. A lack of services after rehabilitation to promote independent community living results in unmet needs for continued physical recovery [4,6,8].

In addition to the physical benefits of PA, structured exercise programs can provide social connection [9,10]. People living with disability, including survivors of stroke, are socially isolated and desire a sense of belonging and social participation [7,10,11]. Increasing accessible, desired options for exercise may address the gap in available PA programs, provide an opportunity for continued services after rehabilitation, and cultivate social connections for people after stroke and others with mobility impairments. Group exercise programs that focus on functional fitness for clinical populations are a worldwide fitness trend and are a suggestion of focus for fitness professionals by the American College of Sports Medicine [12].

Existing evidence-based community programs for people after stroke include Fitness and Mobility Exercise [13], Together in Movement and Exercise [14], and Fit for Function [15]. These programs target fitness with a varied focus on cardiovascular endurance, mobility, walking ability, balance, and education [13-15]. While much is known about the effectiveness of these programs, it is important to understand the local environment as implementation and sustainment strategies are context-specific.

The aim of this study protocol is to evaluate community needs and resources for general and group exercise for adults living with mobility impairments with initial emphasis on survivors of stroke in Richland County, South Carolina. Results will inform an action plan for a hybrid type I implementation study testing the effectiveness and implementation process of a modified evidence-based exercise intervention [16]. Involving the community in the needs assessment and performing the needs assessment with a systematic approach facilitates the success and sustainability of the program [17,18].

Methods

Overview

This project will address the study objective using the EPIS (Exploration, Preparation, Implementation, and Sustainment) framework, concepts of community-based participatory research, and the implementation research logic model [17-19]. The exploration and preparation stages of EPIS seek to determine health needs, identify barriers and facilitators, select an evidence-based program, determine program modifications, and create implementation strategies [17]. These stages are the focus of this protocol. The EPIS implementation and sustainment stages test the evidence-based program and the ability of the program to be maintained in the community after the research process ends [17]. The EPIS framework considers participants inside and outside the organization (inner and outer context) that will offer the community program, the academic and community partners that bridge these contexts, and the characteristics of the program itself [17]. Each stage is dependent on and related to the others [17].

The EPIS exploration and preparation stages (Figures 1 and 2) will be completed as part of this study and include three steps: (1) performing a needs assessment; (2) identifying determinants, selecting an evidence-based exercise program to address, and creating implementation strategies; and (3) determining mechanisms of action for the implementation strategies and their corresponding outcome measures, and creating a logic model [17,19]. Results will inform the implementation protocol and program pilot-testing as a separate study (EPIS implementation and sustainment stages; Figure 1 [17,20]).

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Figure 1. Applied EPIS (Exploration, Preparation, Implementation, and Sustainment) framework for implementation studies (adapted from Moullin et al [17], which is published under Creative Commons Attribution 4.0 International License [20]). The exploration and preparation stages will be completed as part of the current needs assessment for community group exercise for people after stroke. The exploration stage performs a needs assessment whose resulting determinants and strategies feed into the preparation stage that results in an implementation logic model and detailed protocol for the pilot study. The implementation and sustainment stages will be completed as a separate study and perform the pilot, evaluate the outcomes, and produce changes and further research for sustainment in the community.

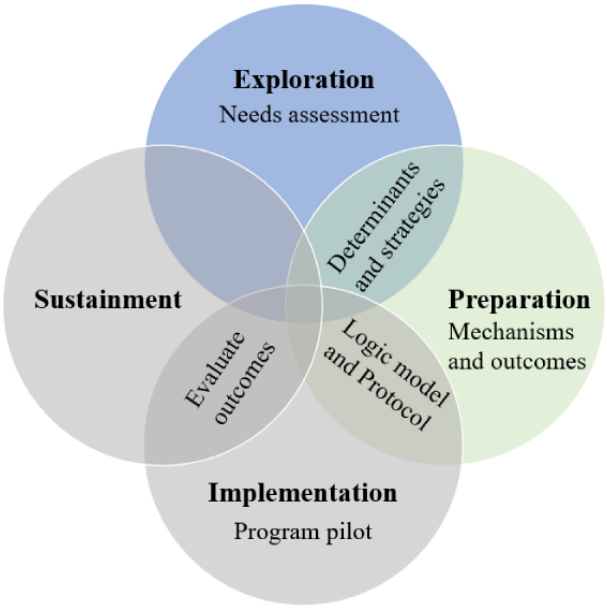

Figure 2. Steps to complete EPIS (Exploration, Preparation, Implementation, and Sustainment) framework: evaluation (blue-textured) and preparation stages (green-solid). This framework will be used as part of the needs assessment for a group exercise program for people after a stroke. Step 1 identifies the actions and data analysis of this study community needs assessment. Step 2 evaluates the results and selects the evidenced-based exercise program. Step 3 details the plans for pilot implementation including the mechanisms of action and the outcome measures.

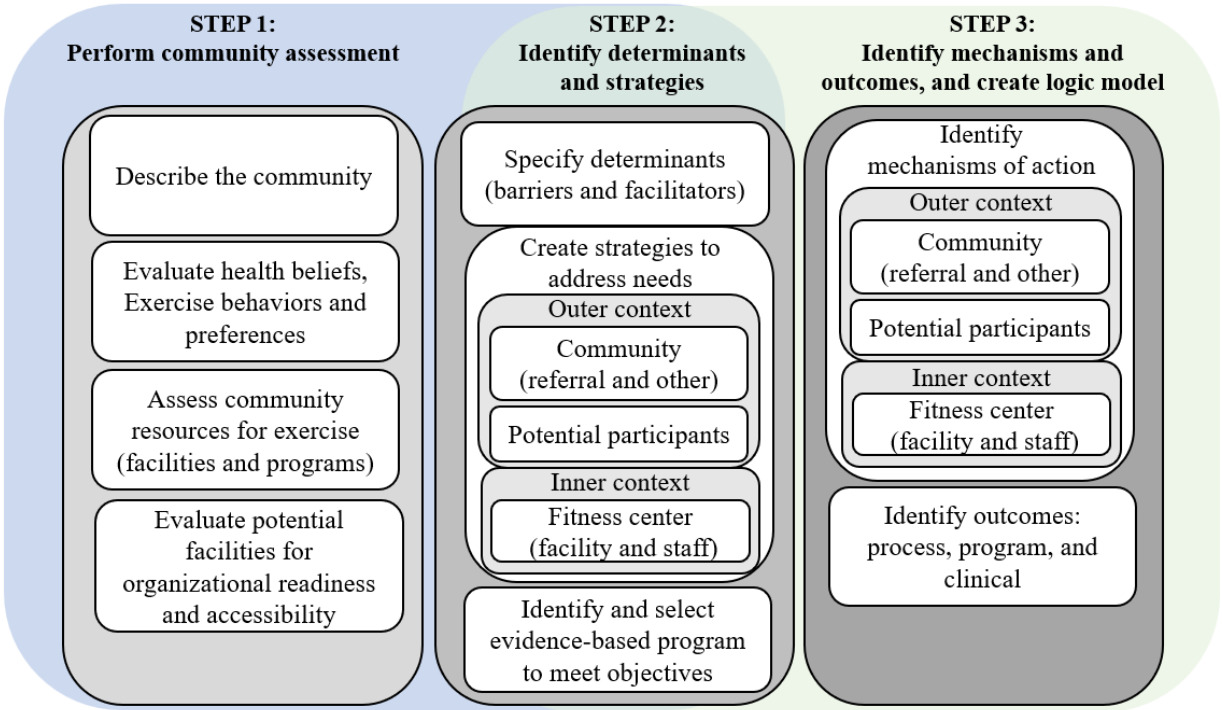

Step 1: Perform Community Assessment

Describe the Community

A literature review will provide perspective on the communities of Richland and Lexington Counties in South Carolina. Several resources will help provide demographics including United States Census data, Center for Disease Control American Community Survey and Center for Health Statistics, the Behavioral Risk Factor Surveillance System, and County Health Rankings. Prisma Health, the largest nonprofit health system serving Richland County SC, completed a community needs assessment in 2022. This assessment will provide data to

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describe the community health concerns and overall health priorities. General demographics, demographics of people living with disabilities, and demographics of survivors of stroke will be described.

Evaluate Health Beliefs, Exercise Behaviors, and Preferences

This step will use semistructured interviews with key stakeholders to assess the culture of the community around health beliefs and exercise behaviors and preferences both for people with mobility impairments and specifically for survivors of stroke. Individual or small group interviews will be conducted with targeted key organizational stakeholders which will include health care providers (physicians, rehabilitation providers, and cardiac rehabilitation providers), other nonprofit or public organizations serving people with disabilities (independent living support services, diabetes educators, vocational rehabilitation, and veterans' organizations) and fitness providers who currently serve people with mobility issues. After initial contact with stakeholders in each category, snowball sampling [21] will identify additional people or organizations to include.

Interview questions will relate to health needs, specific exercise needs, beliefs, contextual factors, exercise services, and gaps. Survivors of stroke will be interviewed in a focus group format at a community stroke survivor support group and additionally in small groups. Care partners will be invited to participate. Interview questions will be the same regardless of format or stakeholder (Textbox 1). Questions will be piloted in the first 2 interviews and revised as needed.

Sample goals are to collect data from a diverse set of viewpoints in order to adequately answer study aims [22]. A pragmatic approach targets 10-15 stakeholders and 10-15 survivors of stroke for the initial sample to achieve.

In addition to the questions in Textbox 1, the stroke survivors focus group will receive additional questions related to specific desires around group exercise (Textbox 2).

Once the focus groups and individual interviews are complete, a survey will be created based on the results. The survey will be distributed to a wider audience in the community and will evaluate desires for general and group exercises and the barriers and facilitators to participation. The survey will be distributed through stakeholder organizations and research contact lists for people with mobility impairments using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of South Carolina.

Textbox 1. Semistructured interview questions for stakeholders to evaluate community health services and exercise beliefs and behaviors as part of the community needs assessment for a group exercise program for people after stroke. Health care providers, organizations serving people with disabilities, fitness professionals, survivors of stroke, and care partners will be interviewed in individual, small group, or focus group formats.

Questions:

1. What is important to this community from a health and quality of life perspective?
2. What are the beliefs about access and treatment for ongoing health care needs?
3. What existing organizations and services address health care and quality of life needs?
    - What are they doing well?
    - What are the gaps in services?
4. What are the beliefs about and interest in exercise for this community?
5. What are the barriers and facilitators to exercise?
6. What are existing community resources for people to exercise and to engage in other ways to improve health?
    - Who is using these resources? Describe the people who engage.
    - What are they doing well?
    - What are the gaps in services?
7. What are your thoughts on funding to support exercise programming on-going? (organizational stakeholders)?

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Textbox 2. Semistructured interview questions to evaluate specific exercise interests and preferences for survivors of stroke only as part of the needs assessment for planning a community group exercise program for people after stroke. Interviews will occur in a focus group or small group format.

Semistructured interview questions on exercise interest and preferences (stroke survivors only):

1. What types of exercise activities would you be interested in (endurance, strength, balance/coordination, stretching, and relaxation) Examples given of each type of exercise.
2. In what formats (small group, larger group/Type of group based on mobility: seated vs standing, requiring assistance vs nonrequiring assistance, based on diagnosis or not based on diagnosis)
3. What type of facility (community fitness facility, private gym, community center, senior center, church center) and in what part of the county is desired?
4. How often and what time of day is preferred?
5. What do you think the benefits of an exercise program would be for you individually and others with stroke?
6. What do you think you will like about exercising in a group? What do you think you will dislike about group exercise?
7. What are factors currently and potentially impacting access and engagement in exercise?
    - Are you currently exercising, and if so, what are you doing, and if not, why not?
    - What do you like about exercise or movement?
    - What is your confidence in your ability to exercise independently? With instruction? With assistance?
        - If low confidence, what do you think would increase confidence?
    - How would you be able to get to a group exercise program (transportation)?
    - How much would you be willing to pay for an exercise program?

Assess Community Resources for Exercise

Using results from the community assessment and internet searches, the facilities and program resources available for group and individual exercise for people with mobility impairments in Richland County will be identified. Information gathered will include whether the facility or organization self-identifies as accessible and the goals and mission of the organization.

Evaluate Potential Facilities for Accessibility and Organizational Readiness

A subset of the listing of community resources will be evaluated in more detail to assess accessibility and general organizational readiness for new or modified exercise programs for people with mobility impairments (Textbox 3). Facility management, staff, and fitness providers will be interviewed to determine readiness for change. Interview questions were developed based on the components of the theory of organizational readiness for change [23]. The evaluation will include an accessibility evaluation using the Accessibility Instrument Measuring Fitness and Recreation Environments (AIMFREE) inventory [24].

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Textbox 3. Potential location for pilot group exercise program for people after stroke facility evaluation will include facility stakeholder (exercise instructors and management) semistructured interviews in individual or small group format and a comprehensive accessibility inventory.

Methods: (1) Stakeholder interview and (2) Accessibility Instrument Measuring Fitness and Recreation Environments (AIMFREE) accessibility inventory (Rimmer et al [24])

Facility stakeholder interview questions:

1. Describe the interest and priority in the organization to serve those with mobility impairments.
2. What is your openness to adding additional or modified programs for people with mobility impairments?
3. Describe your perception of your organization's ability to support an exercise program for people with mobility impairments both initially and ongoing.
4. What are the resources available to support new programming?
    - Describe your staff who could potentially support these new programs.
    - Would new staff need to be hired?
    - What are your anticipated barriers or facilitators?
    - What types of equipment and space would be available? At what time of day?

AIMFREE accessibility inventory:

The inventory includes both physical space accessibility and behavior and policy evaluations. The AIMFREE inventory can be obtained from the National Center on Health, Physical Activity and Disability (NCHPAD), nchpad.org. The following sections will be completed with the assistance of facility staff and a consultant with mobility impairments. Section E, which evaluates hot tubs, whirlpools, and saunas will be omitted.

- SECTION A: Access Routes and Entrance
- SECTION B: Equipment
- SECTION C: Information
- SECTION D: Locker Rooms and Showers
- SECTION F: Elevators
- SECTION G: Bathrooms
- SECTION H: Professional Behavior
- SECTION I: Professional Support and Training
- SECTION J: Policies
- SECTION K: Programs

Step 1: Data Analysis

Outer Context Description

A narrative summary of the neighborhood characteristics and priorities in the community based on the formal community statistics and health priorities review will be created to provide descriptive background for the remaining data. Community participants will be described with demographic descriptive statistics for each group (referral sources, health care providers, fitness providers, community organizations, and potential participants).

Inner Context Description

General descriptions of fitness facilities including location, program availability, inclusion as part of the mission, and goals of the organizations in Richland County will be summarized. For the subset of facilities that receive detailed reviews, a summary of each facility will be provided. The summary will include the AIMFREE findings.

Qualitative Thematic Analysis and Survey Analysis

Focus group and interview data will be analyzed using deductive-dominant qualitative content analysis using NVivo software (version 12; Luminvero Inc) [25-27]. Captured data will be open-coded and categorized for thematic analysis in the following levels: community (outer context), individual (outer context), and fitness center (inner context). At each level, needs/desires, resources, barriers, and facilitators will be defined by the responses to the categories in Table 1 by 2 researchers and combined by group review and discussion to resolve discrepancies. Any themes newly arising from the data outside of these categories will be included. Survey results will also be mapped to the same categories from Table 1 and combined in an evaluation matrix with the themes from the content analysis.

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Table 1. Categories of determinants and implementation strategies for results in the outer context and the inner context of the needs assessment for group exercise for people after stroke. Determinants categories will serve as the organizational structure for qualitative thematic data analysis and implementation strategies categories will serve as the planning structure for the implementation protocol.

Categories and levels	Determinants categories	Implementation strategies categories
Outer context		
Community	• Health care and other potential referral resources and the facilitators and barriers to referral • Other assistance needed from health care or community organizations to support potential new programs.	• Identify referral sources • Create strategies to address barriers to referral • Build strategies to address needs for health care or other community supports vital to the success of the program including champions
Potential participant	• General health and quality of life priorities, services, and organizations to meet related needs and gaps in services. • General exercise resources, use, beliefs, and priorities • General exercise desires and needs • Barriers and facilitators to exercise	• Strategies to address barriers and promote uptake and retention of potential participants
Inner context		
Intervention characteristics	• Group exercise desired format, types of exercise, and frequency	• Identify and select evidence-based exercise program
Organizational (fitness facility)	• Available facilities and programs already meeting the identified individual needs and desires • Accessibility of targeted facilities/organization (physical, behavioral, policy) including gaps and potential future needs • Organizational readiness for change	• Select an organization to pilot the program • Identify organizational strategies for staff, training, equipment, accessibility upgrades, and other needs • Identify an organizational champion

Step 2: Identify Determinants and Implementation Strategies

Following the EPIS framework, the preparation stage begins with specifying the determinants based on results in step 1. Determinants include contextual factors for the outer context (potential participants and community) and inner context (fitness facility), process components, and intervention components [19]. From the determinants, an evidenced-based exercise program will be selected, and implementation strategies for exercise programming and related services created (Figure 2 and Table 1) [19]. Implementation strategies are approaches to address the necessary modifications of the exercise program, the training and resources needed for the inner context, and any other required innovations to adapt to the local community.

All results of the qualitative content analysis, triangulation with survey data, and the determinants will be verified through member checking with updates made as necessary.

Step 3: Identify Mechanisms, Outcomes, and Create Logic Model

Identifying the mechanisms of action, selecting outcomes, and creating the logic model addresses the preparation step of the EPIS framework. Mechanisms of action are the implementation strategy processes to affect the outcomes [28]. Examples include education, skill building, efficacy, and motivation [28]. Finally, outcome measures for the participants (clinical effectiveness), implementation process (fidelity), and program components (service) will be identified. A logic model will be created based on the results of steps 2 and 3 to organize the determinants, implementation strategies, exercise programs, mechanisms of action, and outcomes. A logic model demonstrates the study design elements for the hybrid type I model and their complex interactions [19]. The standard logic model format by Smith et al [19] is presented in Figure 3 [19,20].

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Figure 3. The implementation research logic model standard form with intervention (adapted from Smith et al [19], which is published under Creative Commons Attribution 4.0 International License [20]). The logic model will serve as a roadmap for the implementation protocol for the evidence-based group exercise program for people after a stroke. Determinants include contextual factors, process components, and intervention components. Implementation strategies are actions to address the unique determinants through mechanisms of action (ie, education and skill building) to ensure success. Outcomes are process, program, and participant-driven.

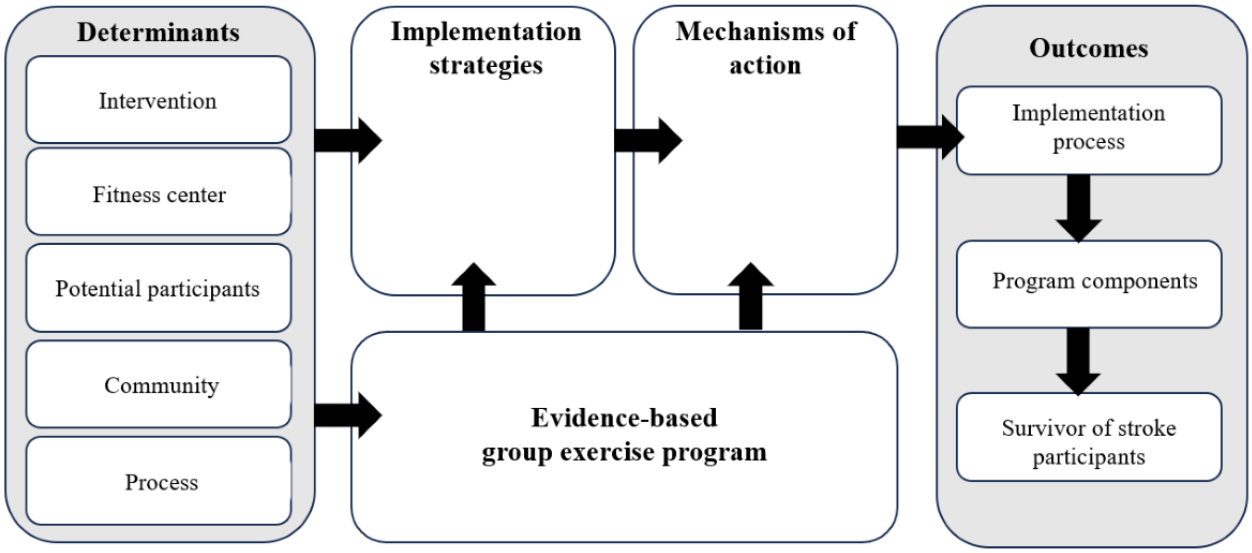

Ethical Considerations

The study has been reviewed by the University of South Carolina Institutional Review Board and classified as exempt human participant research. Letters of information are provided to participants outlining the study. Data will be collected and stored in REDCap cloud storage or other password-protected cloud storage at the University of South Carolina. Transcripts will be deidentified prior to data analysis. Participants will be compensated with a US $25 gift card upon completion of interviews.

Results

As of March 2024, the project is in process. The literature review has been completed. A total of 4 fitness professionals, 4 physical therapists, 1 physiatrist, 2 directors at Able South Carolina (a nonprofit community organization), 7 survivors of stroke, and 1 care partner have been interviewed. Two potential exercise facilities have been identified.

Discussion

Protocol Goals and Anticipated Outcomes

This protocol will evaluate the desires and needs of the local community for an evidence-based group exercise program for people after stroke and the planning required to implement the program. The use of community-based participatory research at the early stage of implementation planning will enhance the fit and success of the future community program [18]. Involving the community in the planning stages builds trust and identifies shared values toward a common goal [18]. The selection of the evidence-based program will be based on identified needs and desires [17]. The needs assessment will also provide a rationale for required modifications to the standard program [17]. If no evidence-based program meets the majority of the needs of the community, a unique program drawing on available evidence-based resources will be developed.

Performing a needs assessment before implementing it in the community allows for early identification of the complex relationships between the inner and outer contexts of a community program [17,19]. A result is an ability to preplan implementation strategies to address problems that cannot be anticipated in controlled effectiveness research. Capacity building, education and training, and recruitment and retention strategies will be identified and built into the action plan [17,19].

Study Strengths and Limitations

Using the EPIS framework, implementation mapping processes and the implementation logic model are strengths of this protocol [17,19,29]. The use of EPIS and related practical application tools creates a systematic approach to a complex task [17,19,29].

Potential study limitations include difficulty finding willing participants, reduced completion of surveys, and difficulty matching an evidence-based program to the needs of the community. These potential pitfalls are mediated by the ability to leverage existing academic-community relationships, multiple sources of data collection, and the existence of multiple potential evidence-based programs to choose from. Existing evidence-based community programs for people after stroke or for older individuals may be adapted through this process to meet the community's needs and desires.

Conclusions

Performing thorough evaluation and preparation prior to the implementation of a community exercise program will enhance its ability to be successful, valued, and sustained in the community. A robust process that includes community partners, applied theory, and implementation process tools enhance the protocol.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study

Conflicts of Interest

None declared.

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Abbreviations

AIMFREE: Accessibility Instrument Measuring Fitness and Recreation Environments
EPIS: Exploration, Preparation, Implementation and Sustainment
PA: physical activity
REDCap: Research Electronic Data Capture

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Protocol

Health Needs Assessment in Home-Living Older Adults: Protocol for a Pre-Post Study

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Abstract

Background: Conducting a health needs assessment for older adults is important, particularly for early detection and management of frailty. Such assessments can help to improve health outcomes, maintain overall well-being, and support older adults in retaining their independence as they age at home.

Objective: In this study, a systematic approach to health needs assessment is adopted in order to reflect real-world practices in municipal health care and capture the nuances of frailty. The aim is to assess changes in frailty levels in home-living older adults over 5 months and to examine the observable functional changes from a prestudy baseline (t1) to a poststudy period (t2). Additionally, the study explores the feasibility of conducting the health needs assessment from the perspective of home-living older adults and their informal caregivers.

Methods: Interprofessional teams of registered nurses, physiotherapists, and occupational therapists will conduct 2 health needs assessments covering physical, cognitive, psychological, social, and behavioral domains. The study includes 40 home-living older adults of 75 years of age or older, who have applied for municipal health and care services in Norway. A quantitative approach will be applied to assess changes in frailty levels in home-living older adults over 5 months. In addition, we will examine the observable functional changes from t1 to t2 and how these changes correlate to frailty levels. Following this, a qualitative approach will be used to examine the perspectives of participants and their informal caregivers regarding the health needs assessment and its feasibility. The final sample size for the qualitative phase will be determined based on the participant's willingness to be interviewed. The quantitative data consist of descriptive statistics, simple tests, and present plots and correlation coefficients. For the qualitative analysis, we will apply thematic analysis.

Results: The initial baseline assessments were completed in July 2023, and the second health needs assessments are ongoing. We expect the results to be available for analysis in the spring of 2024.

Conclusions: This study has potential benefits for not only older adults and their informal caregivers but also health care professionals. Moreover, it can be used to inform future studies focused on health needs assessments of this specific demographic

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group. The study also provides meaningful insights for local policy makers, with potential future implications at the national level.

Trial Registration: ClinicalTrials.gov NCT05837728; https://clinicaltrials.gov/study/NCT05837728

International Registered Report Identifier (IRRID): DERR1-10.2196/55192

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KEYWORDS

assessment; frailty; healthy aging; health care; home-living older adults; pre-post study; protocol

Introduction

Across the globe, the population is aging rapidly. There are around 1.4 billion people aged 60 years and older in the world today, and this figure will double by 2050 [1]. Norway is no exception to this demographic transition. It is anticipated that the number of people aged 65 years and older will exceed the population aged 0-19 years by 2030 [2]. As is widely known, the older segment of the population tends to have a higher prevalence of chronic diseases and disabilities [3,4]. This implies that the demographic shift could come at a great cost to older adults themselves and society [3,5]. Direct challenges at the societal level may include a strain on public finances and the welfare system, increased demand for health services, and rising health care costs [6,7].

One way to mitigate the impacts of an aging population is to support aging in place [8,9]. The term “aging in place” refers to meeting an older adult’s needs and supporting them to live independently or with some assistance in their own home for as long as possible [8]. Most older adults prefer to live at home because it enables them to maintain their independence, autonomy, and identity, as well as their connection to social support [10]. In addition to being the preferred choice for many older adults, aging in place is viewed as a cost-effective strategy for addressing the aging population’s needs, as it can reduce the expenses associated with institutional care [11]. Given these positive effects, encouraging older adults to continue living at home could be an essential part of the solution to meeting the challenges of population aging.

Many older adults are able to live independently without much support; others, however, may have age-related issues that prevent them from aging in place [12]. These age-related issues often lead to frailty, resulting in increased functional limitations, increased risk of falls, disability, institutionalization, hospitalization, and mortality [13,14]. As frailty progresses, efforts to mitigate, manage, or reverse this decline become increasingly difficult to implement [15]. Hence, there is a broad consensus on the importance of assessing frailty [14,16,17], particularly in relation to older adults aged 70 years and older [16,18]. In general, early assessment of frailty can prevent, reduce onset, or slow its progression in older adults [19], contributing to better quality of life and healthy aging [18,20].

There is currently no consensus on the definition of frailty [17,21]. At its simplest, frailty is a condition that indicates increased vulnerability to negative health outcomes [22]. Despite varying definitions, there is general consensus that frailty is multidimensional and involves complex interactions between physical, psychological, social, cognitive, and behavioral factors [17,19]. The diversity of definitions and the wide range of contributing factors also explain why there is a variety of measures of frailty [16,17].

Incorporating frailty into health needs assessments is, therefore, crucial, as this can help identify specific areas of need, set clear goals to meet those needs, and ultimately contribute to the health promotion of this population [23]. The term “health needs assessment” refers to a systematic method of identifying unmet health and care needs of a population, leading to agreed priorities and resource allocation that will improve health outcomes [24].

While our knowledge of frailty has improved [14], our understanding of the factors that contribute to frailty is still incomplete, and the understanding of how these factors relate to frailty is still limited [19]. These knowledge gaps are a clear indication that considerable efforts are still needed in this area.

Given the complexity of frailty as a construct and its enormous impact on the lives of older adults, adopting a collaborative approach is deemed essential to improving our understanding and achieving meaningful progress. This is further supported by research that highlights the benefits of fostering collaboration between health care professionals, individual service users, families, researchers, and other stakeholders to improve health service outcomes [25-27].

Such collaboration enables all relevant aspects of older adults’ health to be assessed, and essential information can be collected to develop effective, locally applicable, and relevant solutions [28]. With this in mind, we have established partnerships with health care professionals and other stakeholders in a Norwegian municipality, actively involving them in the planning and implementation phase of the project.

Interprofessional teams consisting of registered nurses, physiotherapists, and occupational therapists will be involved in this study. They will perform 2 health needs assessments of home-living older adults, initially at baseline and then after a period of 5 months. These assessments cover several factors, including physical (mobility and sensory), cognitive, psychological (depression), social (loneliness), and behavioral (alcohol consumption). The objectives of our study are 3-fold: first, to assess changes in frailty levels in home-living older adults over 5 months; second, to explore the observable functional changes from a prestudy baseline (t1) to a poststudy period (t2) and how these changes correlate to frailty levels; and finally, to gain deeper insight into the perspectives of older adults and their informal caregivers to enhance the feasibility

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of implementing this type of health needs assessment within municipal health and care services.

The research questions that guide the study are (1) What observable changes, if any, can be identified in the frailty levels of home-living older adults over a period of 5 months? (2) Are there identifiable changes in functions that can be observed from t1 to t2, and how these changes relate to frailty levels? and (3) What are the perceptions of home-living older adults regarding the feasibility of the health needs assessment, with regard to its content, delivery, and procedures?

Methods

Study Design

This pre-post study, registered on ClinicalTrials.gov (NCT05837728), is based on a case-only design to conduct health needs assessments, initially at the baseline and then after 5 months. The study is conducted as part of the research project "More good days at home: Advancing health-promoting practices in municipal health care services for older recipients of home care," funded by the Norwegian Research Council (320622).

To gain in-depth insights, we use a 2-step research process. In the first step, a quantitative approach will be applied to examine changes in frailty levels in home-living older adults over 5 months. In addition, we will examine observable functional changes from t1 to t2 and how these changes correlate to frailty levels.

Following this, a qualitative approach will be used to investigate the perspectives of participants and their informal caregivers concerning the health needs assessment and its acceptability.

Setting

This study is placed in the context of the Norwegian health care system, known for its universal health care. This system ensures everyone has equal access to health care regardless of socioeconomic status or geographical location [29]. The system is based on a clearly defined division of responsibilities between the local municipalities and the central government.

The local municipalities are tasked with organizing primary, preventive, and nursing care services [29] and are committed to providing the necessary health services, such as home and personal care, free of charge to all home-living older adults [30]. These services are universally available and tailored to the specific needs of each older adult. To access these services, older adults are required to submit an application to the district office in their municipality [31]. Once the application is submitted, it will be reviewed by health care professionals in the health and welfare services office. After this phase, the health care professionals will reach out to the older adults to proceed further.

While municipalities manage the above care services, central government oversees specialist care, which includes hospital services. This clear division ensures comprehensive health care for all citizens [29]. This study takes place in a municipality in Western Norway with a population of approximately 146,011. In this population, 9874 individuals are older adults aged 75 years or older [32].

Study Sample

Inclusion Criteria

To be eligible for the study, the older adults must be aged 75 years or older and have applied for municipal health and care services. These services may include medical emergency alarms, senior activity centers, home-based nursing services, and practical assistance with daily chores. In addition, older adults who received follow-up care after a hospital stay, were discharged from rehabilitation, or received emergency medical care are also eligible.

Exclusion Criteria

This study does not include home-living older adults who are younger than 75 years of age, have a cognitive impairment, or are undergoing palliative care. In this study, cognitive impairment refers to the inability to understand the study and provide informed consent to participate.

Recruitment

Participant recruitment was conducted in collaboration with 3 health and welfare service departments in a municipality in the western region of Norway between February 1 and June 26, 2023. Health care professionals purposively selected participants according to the eligibility criteria. During their initial phone contact with potential participants, health care professionals used their professional judgment to assess the individual's ability to understand the research project and provide informed consent to participate.

Subsequently, health care professionals asked a designated research team member, a nurse with experience in mental health, to obtain informed consent from those who meet the initial criteria. To ensure consistency in the process, the same nurse visited all potential participants for the consent process. Potential participants were then given time to consider this information before giving their written consent.

The design of our health needs assessment package includes a cognitive assessment. This approach ensures that participants identified with cognitive impairment in the first assessment are not included in the second assessment.

We aim to enroll 40 participants in the quantitative phase of this study, in line with the agreement made with the municipality at the beginning of the project, taking into account their resource limitations. In the next phase, which uses a qualitative approach, we plan to invite all 40 participants for an interview, with the actual number of interviews conducted depending on the participants' consent to participate. To capture diverse perspectives, we will strive to include a group of home-living older adults who differ in terms of age, gender, marital status, living situations, and health care needs.

The aforementioned sample size takes into account the limited resources available for the project, including budget constraints, personnel resources, and time limitations, while ensuring the collection of meaningful data to address the research questions.

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Data Collection

To respond to the diverse needs of older adults, we have interprofessional teams consisting of registered nurses, physiotherapists, or occupational therapists to carry out the health needs assessments. The assessment is conducted twice at the participant's home. To facilitate successful implementation, we provided simulation-based training and debriefings. We have also produced webinars available in Norwegian to enhance learning. The link to the webinars can be provided upon request. Our study is ongoing, so we will publish it upon completion.

The interprofessional teams will use an iPad (Apple Inc) to administer assessments covering the various factors—physical (mobility and sensory), cognitive, psychological (depression), social (loneliness), and behavioral (alcohol consumption). The collected data will be registered electronically and directly submitted to Services for Sensitive Data (*Tjenester for Sensitive Data* [TSD]) for secure storage and processing.

After the initial assessment, interprofessional teams will collaboratively review the results to determine whether, and to what extent, the older adult is eligible for assistance and to determine what type of support is available and appropriate for the individual [33]. Examples of such support include practical help with everyday tasks, provision of medical emergency alarms, access to walking aids, recommendations for physiotherapy sessions, referrals to hearing or vision centers, encouragement to participate in senior activity centers, and facilitating contact with primary care physicians.

After 5 months, the same interprofessional teams will conduct the second health needs assessment to determine whether the support provided at the first assessment is suitable for helping participants maintain their quality of life.

With regard to the qualitative approach, we will use 2 data collection methods in order to minimize mono-method bias [34]—in-depth individual interviews and dyadic interviews. We will use a general interview guide approach to collecting data from all the participants, which will give us the flexibility to modify or adapt questions based on responses to previous questions [35]. To maintain consistency, the topics and questions in the 2 interview methods will be identical and guided by the Theoretical Framework of Acceptability (TFA) proposed by Sekhon et al [36]. The questions will include, for example, (1) how the participant thinks and feels about the assessment, (2) what the participant thinks about the effort required to participate in this type of assessment, (3) the participant's understanding of the assessment process, (4) what benefits or value they believe the assessment will have for them, and (5) whether they feel the assessment was conducted respectfully or not. Finally, the interviews will be audio recorded and transcribed verbatim to ensure accuracy in the data analysis.

Measure Descriptions

The selection of measures was informed by a comprehensive review of existing literature, consultation with experts, and input from stakeholders involved in the project. Many of the measures have been validated in different contexts, including the Norwegian context. The study also includes novel scales that will be tested for validity within this particular sample of home-living older adults. The measures in the study are described below, and an overview is given in Table 1.

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Table 1. Overview of the measures used in the study.

Variables	Questionnaires and tests used in assessments
Demographics	
Gender	Male, female, or other?
Age	How old are you (years)?
Household	Do you live alone or with others?
Children	Do you have any children?
Residential suitability	Is your residence suitable for your needs?
Transportation	Do you use private or public transport?
Physical function	
Mobility: lower extremity function	To assess the lower extremity function, we will use the SPPB[a], a well-established instrument commonly used in home-living older adults [37-40]. The Norwegian version of SPPB, translated by Bergh et al [41], has been tested for reliability, and the result shows that it has high reliability when used by trained physiotherapists on older populations [42]. Other reasons for using SPPB are that it is fast, safe, and easy to administer; requires little training; and uses simple equipment [43]. The test assesses standing balance, walking, and rising from a chair. The result from the test is quantified by scores. In addition, the test is claimed to be highly sensitive to changes over time [37,44].
Sensory: hearing	To detect hearing impairment, we will use the KAS[b]-Screen interview guide [45]. The questions used in our study stem from the hearing and verbal communication or social life subscales. Previous evaluation and validation found this test to be an adequate tool for detecting hearing impairment in older adults and provides important information on how this impairment can affect the daily life of older adults [45,46].
Sensory: vision	To detect vision impairment, we will use a structured vision assessment tool called KROSS[c] developed by the University of South-Eastern Norway in collaboration with the Vestre Viken Hospital Trust and stroke survivor organizations. The KROSS tool includes assessments of visual acuity, visual field, eye alignment and movements, and visual in attention [47,48].
Cognitive function	
Cognitive function	To identify possible cognitive impairment, the Mini-Cog test will be used. This takes approximately 3 minutes to administer and consists of 2 cognitive tasks: 3-item word recall and a clock drawing test [49]. Mini-Cog was preferred to other cognitive screening tools because it is simple and concise, requires no special equipment, is easily incorporated into general practice and different senior settings, and has high sensitivity and specificity [49,50]. Additionally, it has been suggested that Mini-Cog performs well as a screening test among older adults in communities [51]. The Norwegian version of Mini-Cog was translated by Rostoft et al [52].
Psychological function	
Depression	To assess depression in old age, we will use the 4-item GDS[d]. Although other versions of GDS can be used to identify common symptoms of depression in older individuals, the 4-item GDS is reported to be most suitable for detecting depression in older adults who live at home [53,54]. Overall, the 4-item GDS has been shown to be a valid and reliable tool for evaluating depression in older adults, with a sensitivity of 100% and 62% specificity [54]. Another benefit of using this scale is that it is a relatively short scale, which reduces the burden on the respondent and the time it takes for health professionals to administer the test [54].
Social function	
Loneliness	The validated UCLA[e] 3-Item Loneliness Scale will be used to assess loneliness. This scale is designed to measure loneliness based on individual perceptions of how often a person feels (1) a lack of companionship, (2) left out, and (3) isolated from others [55]. In terms of reliability, this scale has been found to have good internal consistency, and test-retest reliability has shown that the scale produces consistent results over time [56,57]. In terms of validity, it was demonstrated that this scale correlates well with other measures of loneliness and discriminates well between loneliness and other constructs [55]. Additionally, this measure is chosen because it is quick to administer, has been used in large surveys, has been tested in older populations, and measures overall loneliness quite well [55,58]. The Norwegian version of this scale was translated by Arumugam et al [59].
Behavioral function	
Alcohol consumption	For a brief assessment of alcohol consumption, we will use the AUDIT[f] developed by the World Health Organization [60]. Our study will use AUDIT-4, which consists of 3 questions from AUDIT-C and the 10th item of the original scale [61]. In terms of reliability and validity, previous research with different samples has shown that AUDIT-4 has good internal consistency, criterion validity, and convergent validity [62,63].

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Variables	Questionnaires and tests used in assessments
Assessment of frailty	To assess frailty, we will use the CFS[g]. The CFS, a tool based on clinical judgment, assesses key areas such as multimorbidity, cognition, and other functional areas [64]. CFS has been shown to be a strong predictor of several outcomes, including falls, length of hospitalization, multimorbidity, and mortality [65]. The CFS was translated into Norwegian by Rostoft et al [66] and has been used to assess frailty in various settings in Norway, including emergencies and intensive care [67,68]. Its simplicity and predictive power in assessing physical health and potential outcomes for frail older adults [17,69] make it an appropriate choice for use in municipal health care settings.

[a]SPPB: Short Physical Performance Battery.

[b]KAS: *Kombinert Alvorlig Sansesvikt* (Combined Serious Sensory Impairment).

[c]KROSS: *Kompetanse om Rehabilitering Om Syn og Slag* (Competence, Rehabilitation of Sight after Stroke).

[d]GDS: Geriatric Depression Scale.

[e]UCLA: University of California, Los Angeles.

[f]AUDIT: Alcohol Use Disorders Identification Test.

[g]CFS: Clinical Frailty Scale.

Outcome Measures

This study has two primary outcome measures: (1) identifying changes in frailty levels of home-living older adults over a period of 5 months and (2) assessing any observed changes in functions from t1 to t2 and how these changes relate to the level of frailty.

In addition to the primary outcome measures, this study will also evaluate the feasibility of the health needs assessment. Emphasis will be placed on the acceptability of the assessment among older adults and their informal caregivers, as well as the practicality of implementation in relation to time and resource constraints.

Data Analysis

Quantitative Analyses

The statistical package SPSS (version 29; IBM Corp) will be used for all statistical analyses. Descriptive statistics will be used to provide an overview of the demographic variables. Given the exploratory nature of this study and the limited sample size, our analysis involves looking at the data from multiple perspectives. The aim is to uncover patterns and relationships that could inform the development of hypotheses for future studies.

To answer the research questions, we will first calculate descriptive statistics for changes in frailty levels between 2 time points, using mean and SD or median and IQR for a skewed distribution. This will be followed by paired comparisons using either 2-tailed *t* test or the Wilcoxon test. We will also examine the association between the changes in frailty and baseline levels by plotting and estimating correlation coefficients (Pearson and Spearman). We will further assess changes in functional variables and the bivariate associations between these changes and the change in frailty.

Qualitative Analyses

The interview transcripts will be read thoroughly and reread to ensure familiarity with the content. NVivo (version 12; Lumivero) software will be used to help organize and code the data. The data analysis will be carried out using a thematic analytical approach based on the guidelines of Braun and Clarke [70].

Patient and Public Involvement

In this study, older adult participants were not involved in developing the study design or objectives. The study design and objectives were developed by the researchers of this study in collaboration with the local municipality stakeholders. The Service User Association for Older Adults in Norway (*Pensjonistforbundet*) contributed insights to the grant application, which was successfully funded by the Research Council of Norway. Furthermore, details about the study design and recruitment procedures were provided to health care professionals prior to data collection.

Ethical Considerations

Ethics approval was obtained from the Regional Committees for Medicine and Health Research Ethics (REK) of West Norway on November 15, 2022 (523455). The project was subsequently approved by the Norwegian Agency for Shared Services in Education and Research (SIKT) on January 19, 2023 (100847), which ensures that adequate safeguards are in place to protect the privacy of participants and to maintain the confidentiality of data. This study will be conducted in accordance with the Declaration of Helsinki guidelines [71] from REK and the Data Protection Impact Assessment (DPIA). It will also be conducted under the principle of informed consent. Prior to data collection, all the participants who agreed to participate in the study will sign a consent form, which includes a description of the study, its objectives, and participants' involvement and rights. Participation in the study is entirely voluntary and participants can withdraw at any time. Additionally, participants are entitled to access the information documented about them and to make necessary corrections to any errors discovered.

Data Management

Overview

The project manager will supervise the day-to-day operation of the project and be responsible for ensuring that DPIA guidelines are followed.

Data Collected From the Frailty Assessment

The collected data will be registered electronically and directly submitted to TSD for secure storage and processing. The code list that links personal identification information to the

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individual participant will be secured by the project manager to ensure there is no unauthorized access to the information. Only the selected project team members will have access to the anonymized data sets. No other party will have access to the research data prior to dissemination. Furthermore, other paper-based research data will be anonymized and kept in locked cabinets or archives that are only accessible to project team members.

Data Collected From the Interview

Only a designated member of the research project and the project manager will have access to the audio files stored at Nettskjema. The interview will be transcribed into written text and all personal identifiers will be removed to ensure anonymity. The transcription will be shared with other project team members as appropriate. This data will be retained until December 31, 2026, and then deleted from TSD.

Results

The initial baseline assessments were completed in July 2023, and the second health needs assessments are ongoing. We expect the results to be available for analysis in the spring of 2024.

Discussion

Principal Considerations

Studies have documented that frail older adults have an elevated risk of negative health outcomes [13,14]. Early assessment of frailty in older adults is, therefore, crucial, and is recommended. Despite its recognized importance, assessing frailty is not considered a standard clinical practice in many health care systems [18], including in Norway [72]. This situation is understandable as such an assessment often requires significant resources, which many health care facilities lack [73].

Our study is carefully designed to reflect real-world applications and settings, with a particular focus on municipal health care in Norway, where health care professionals tend to have heavy workloads. These conditions pose a challenge to incorporating additional tasks, such as a frailty assessment, into routine health needs assessments. As mentioned earlier, older adults typically turn to their local municipality for home care services and health care professionals make home visits to assess their care needs. This assessment process uses the standardized tool (The Norwegian Information System for the Nursing and Care Sector [*Individbasert pleie- og omsorgsstatistikk*; IPLOS]), which was developed to optimize care needs assessments in Norway [33]. Despite being a standardized tool, IPLOS has been criticized for being too subjective, as assessments appear to vary widely among health care professionals [74].

In response to these challenges, we aim to refine the health needs assessment process to improve objectivity and consistency, and to highlight the critical needs to incorporate frailty assessments into routine municipal care practices. The path begins with selecting appropriate measurement tools that are meaningful and practical, and training interprofessional teams to implement them. Part of this training process includes the task of conducting assessments and discussing the results to make informed decisions.

Beyond integrating assessments, our study aims to shed light on the dynamic nature of frailty and provide a deeper understanding of the factors that impact its progression. This insight could potentially help older adults and their informal caregivers to manage frailty. Additionally, it can better prepare health care professionals to develop and implement strategies aimed at delaying and mitigating the progression of frailty.

Strengths and Limitations

This study has several strengths. First, it deepens our understanding of frailty as a complex condition and highlights how levels of frailty and related functional changes can differ. Moreover, because the study is designed to reflect the real-world settings and applications, it can help improve health care practices in the municipal sector. The involvement of local stakeholders in the municipality from the planning to the implementation phase ensures that the study remains relevant and applicable, thereby facilitating the translation of knowledge into practice. Additionally, the inclusion of home-living older adults' and their informal caregivers' perspectives can help facilitate improvement in the feasibility of the assessment.

As with other studies, this study has its limitations, particularly with regard to the relatively small sample size and the absence of a control group. This could lead to misinterpretation of the observed changes, either in the support or services for participants, other confounding factors, or due to a habituation effect over the 5-month period. Consequently, this limitation may also potentially impact the internal validity of the study, as well as the construct validity of the study [75]. To address this challenge, we will carefully compare our findings with those of previous studies investigating similar approaches to aiding the interpretation of outcomes.

Despite its inherent limitations, this study will serve as an important first step in developing a more systematic health needs assessment for home-living older adults and the development of health promotion strategies that can improve these older adults' quality of life.

Nonetheless, the results should be interpreted with caution due to the absence of a control group, the limited sample size, and the potential underrepresentation of all home-living older adults. These limitations suggest that the results indicate possible correlations and patterns, rather than confirming a definite relationship or establishing specific cause-and-effect relationships.

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Acknowledgments

The authors would like to express their sincere gratitude to the municipality health care professionals who participated and contributed to the design of this study. We would also like to acknowledge other local municipality stakeholders who supported us in planning the recruitment process and implementing the research project.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to ethical considerations inherent in this research but are available from the corresponding author on reasonable request.

Authors' Contributions

All authors made a substantial contribution to this work. FK contributed to the study design and protocol, drafting, writing original draft, and revising and refining the paper. BHL contributed to the study design and data collection tools and feedback and comments on the study protocol. GE contributed to the study design and data collection tools and feedback and comments on the study protocol. HKF contributed to the study design and data collection tools and feedback and comments on the study protocol. ID contributed to the data analysis and statistics and feedback and comments on the study protocol. SH contributed to the study design and collaboration between health care professionals and researchers. MS contributed to the study design, development of data collection tools, prepared all essential documentation for ethical approval, and participated in writing, commenting, and refining the paper. All authors read and approved the final version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

DPIA: Data Protection Impact Assessment
IPLOS: The Norwegian Information System for the Nursing and Care Sector (Individbasert pleie- og omsorgsstatistikk)
REK: Regional Committees for Medicine and Health Research Ethics
SIKT: Shared Services in Education and Research
TFA: Theoretical Framework of Acceptability
TSD: Services for Sensitive Data (Tjenester for Sensitive Data)

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Protocol

Carboplatin in Patients With Metastatic Castration-Resistant Prostate Cancer Harboring Somatic or Germline Homologous Recombination Repair Gene Mutations: Phase II Single-Arm Trial

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Abstract

Background: Approximately 20%-25% of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor a deleterious germline or somatic mutation in the homologous recombination repair (HRR) pathway genes, which is involved in the repair of double-stranded DNA damage. Half of these mutations are germline, while the remaining are exclusively somatic. While polyadenosine 5'diphosphoribose [poly (ADP-ribose)] polymerase inhibitors, such as olaparib and rucaparib, are effective in this subgroup, their widespread use is limited due to the associated high cost, especially in resource-constrained settings. Notably, platinum agents like carboplatin have exquisite sensitivity to cells with defective DNA repair machinery. Carboplatin, a conventional, inexpensive chemotherapeutic agent, offers a potential alternative treatment in such patients. Several retrospective small case series support this hypothesis. However, there are no prospective clinical trials of carboplatin in patients with mCRPC with HRR mutations.

Objective: The primary objective is to assess the objective response rate of 3 weekly carboplatin treatments in patients with mCRPC harboring deleterious mutations in the HRR pathway genes and previously treated with a taxane or a novel antiandrogen agent. The secondary objectives include progression-free survival, health-related quality of life, and safety profile of carboplatin.

Methods: Patients diagnosed with mCRPC harboring HRR pathway mutations previously treated with docetaxel or novel antiandrogen agents (abiraterone, enzalutamide, apalutamide, or darolutamide) or both will be eligible. Genes involved directly or indirectly in the HRR pathway will be tested. In this single-arm phase II study, we will screen approximately 200 patients to enroll 49 patients, and carboplatin (dosing at the area under curve=5) will be administered every 3 weeks until progression or intolerable side effects. The primary end point will be assessed as the proportion of patients with a reduction of serum prostate-specific antigen by more than 50% from enrollment. Secondary outcomes include progression-free survival—soft-tissue disease progression (by response evaluation criteria in solid tumors, version 1.1, and bone lesion progression using Prostate Cancer Clinical Trials Working Group 3 criteria), health-related quality of life during carboplatin treatment using the Functional Assessment of Cancer Therapy—Prostate questionnaire and the European Organisation for Research and Treatment of Cancer questionnaire and safety profile of carboplatin (National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0).

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Results: The trial started enrollment in September 2023. This trial is ongoing, and 12 patients have been recruited to date. All 49 participants will be enrolled according to plan.

Conclusions: This prospective phase II trial represents a critical step toward addressing the therapeutic gap in patients with mCRPC harboring HRR pathway mutations, particularly in demographic regions with limited access to poly (ADP-ribose) polymerase inhibitors. Outcomes from this study will inform clinical practice and guide future phase III randomized trials, ultimately improving patient outcomes globally.

Trial Registration: Clinical Trials Registry of India CTRI/2023/04/051507; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=Njc0NjU=&Enc=&userName=

International Registered Report Identifier (IRRID): DERR1-10.2196/54086

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KEYWORDS

carboplatin; mCRPC; prostate cancer; homologous recombinant gene repair; metastatic castration-resistant prostate cancer; incurable; deleterious mutation; synthetic lethality; tumor; DNA; low-income; middle-income; chemotherapeutic; drug; retrospective study; taxane; novel antiandrogen; single-arm study; health-related; quality of life; bone lesion

Introduction

Patients with metastatic prostate cancer are treated with androgen deprivation therapy, chemotherapeutic agents, or novel antiandrogen agents [1]. These patients eventually develop resistance to androgen deprivation therapy, and this state, known as castration-resistant prostate cancer, is incurable despite the advent of several newer therapies [2]. The therapeutic landscape for metastatic castration-resistant prostate cancer (mCRPC) includes chemotherapeutic agents, novel antiandrogen agents, and radioligand therapies [3].

Pritchard et al [4] reported that 11.8% of men with metastatic prostate cancer harbor deleterious germline mutations, primarily in *BRCA2*, followed by *ATM*, *CHEK2*, *BRCA1*, *RAD51D*, and *PALB41* genes. Subsequent studies evaluated the prevalence of deleterious somatic mutations within the homologous recombination repair (HRR) pathway in 25%-30% of patients with mCRPC [5]. Polyadenosine 5'diphosphoribose (poly [ADP-ribose]) polymerase inhibitor (PARP) inhibitors employ a strategy of synthetic lethality, inhibiting the base excision repair pathway, leading to the accumulation of unrepaired DNA breaks within HRR-deficient tumor cells, culminating in cancer cell death [6-8]. Olaparib, a PARP inhibitor, demonstrated an impressive 88% response rate in patients with mCRPC with HRR gene abnormalities, in contrast to a minimal 3% response in those without these mutations [9,10]. The pivotal PROfound trial supported these findings, leading to Food and Drug Administration approval for patients with mCRPC harboring HRR gene mutations [5]. Similar efficacy was observed with other PARP inhibitors, including rucaparib and talazoparib [11,12]. However, most patients with mCRPC harboring HRR gene mutations residing in low- and middle-income countries do not have access to PARP inhibitors due to the high cost.

Interestingly, HRR-deficient tumors also exhibit increased sensitivity to platinum chemotherapeutic agents (eg, carboplatin) due to their reliance on the HRR pathway for DNA double-strand break repair. This vulnerability has been exploited by platinum-containing treatments in breast and ovarian tumors [13,14]. Initial retrospective studies involving carboplatin in unselected patients with mCRPC showed encouraging efficacy, particularly within the subset carrying HRR gene alterations [15-17]. However, these studies are limited by several biases.

Despite a strong scientific rationale and encouraging preliminary data from real-world studies, no prospective study has been reported to assess the role of carboplatin in this subset of patients. Therefore, we planned this phase II single-arm study to evaluate the efficacy of carboplatin in patients with metastatic prostate cancer harboring mutations in the HRR pathway.

Methods

Objectives

This study is an investigator-initiated, prospective phase II, single-arm clinical trial. The primary objective of this study is to assess the prostate-specific antigen (PSA) response rate of 3 weekly carboplatin (dose at area under the curve 5) in patients with mCRPC harboring deleterious or likely deleterious mutations in the HRR genes and previously treated with a taxane or a novel antiandrogen (proportion of patients with more than 50% serum PSA decline).

The secondary objectives are to compare the effect of oral gabapentin with placebo on the following:

- Progression-free survival—soft-tissue disease progression (by response evaluation criteria in solid tumors, version 1.1) and bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 criteria)
- Health-related quality of life during carboplatin treatment (Functional Assessment of Cancer Therapy—Prostate questionnaire and European Organisation for Research and Treatment of Cancer questionnaire)
- The safety profile of carboplatin (National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0)

Study Setting

This study is being conducted in the outpatient department of Dr BR Ambedkar Institute Rotary Cancer Hospital, New Delhi, India, and the National Cancer Institute, Jhajjar, the 2 cancer blocks of the All India Institute of Medical Sciences, New Delhi, a central government-funded tertiary care teaching hospital.

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The catchment area includes an over 20 million population from the Northern states of India, with approximately 15,000 patients with cancer being treated every year.

Eligibility Criteria

All the following criteria must be met for enrollment:

- Histological diagnosis of prostate cancer.
- Serum testosterone <50 ng/dL within 28 days before screening.
- Documented current evidence of mCRPC, where metastatic status is defined as at least one documented metastatic lesion on either a bone scan, computed tomography, or magnetic resonance imaging scan.
- Prior treatment with docetaxel or at least one of the novel antiandrogen agents (abiraterone, enzalutamide, apalutamide, or darolutamide) or both.
- Mutation (germline or somatic) in the HRR pathway in either blood or biopsy samples.
- Written informed consent to participate.
- Eastern Cooperative Oncology Group performance status of 0-1.
- Aged older than 18 years.
- Adequate organ function:
  - Absolute neutrophil count ≥1.5 × 109/L
  - Hemoglobin ≥10.0 g/dL with no blood transfusions in the past 28 days.
  - Platelet count ≥100 × 109/L.
  - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN).
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) or alanine aminotransferase (serum glutamic pyruvate transaminase) ≤2.5 × institutional ULN unless liver metastases are present in which case, they must be ≤5 × ULN.
  - Subjects must have an estimated creatinine clearance using the Cockcroft-Gault equation for men of ≥40 mL/minute.

Patients with any of the following will be excluded from the trial:

- Patients with symptomatic brain metastases. A scan to confirm the absence of brain metastases is unnecessary in all patients.
- Patients with spinal cord compression, unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
- Patients are considered as poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include but are not limited to uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high-resolution computed tomography scan, or any psychiatric disorder that prohibits obtaining informed consent.
- Patients with a known hypersensitivity to carboplatin.

One of this study's investigators will obtain written informed consent from every patient before enrollment, during which the benefits and risks of participation will be informed in the local language (Hindi or English) that the patient comprehends. The study consists of two parts: (1) screening of tumor tissue or blood for mutations in the HRR pathway and (2) administration of carboplatin in patients found to harbor a deleterious or likely deleterious mutation in the HRR pathway.

Screening of mutations in the HRR pathway will be performed in the tumor tissue for the HRR genes using next-generation sequencing. The initial archived biopsy sample will be retrieved after informed consent is obtained. In patients where the initial biopsy sample is inaccessible or deemed to be of inadequate quality for next-generation sequencing, blood samples will be sent to assess germline mutations in the HRR pathway.

Interventions

Patients who agree to participate in this study will be tested for the presence of known deleterious mutations in the archived tumor tissue in genes involved directly or indirectly in HRR pathway: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *MSH2*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

Those found to have a pathogenic or likely pathogenic mutation in one of these genes will be treated with 3 weekly carboplatin. The dose will be calculated according to the estimated glomerular filtration rate determined by the Cockcroft-Gault equation and then administered at the area under the curve (5) with a dose capped at 750 mg per cycle. Chemotherapy will continue until progression (clinical, biochemical, or radiographic) or intolerable adverse events, whichever occurs earlier. If the patient misses a follow-up visit, this study's team will contact the patient and reinforce adherence to this study.

The relevant concomitant care permitted or prohibited during the trial includes the following. Palliative radiation for patients who develop urgent local complications in previously documented disease sites. The ideal gap between palliative radiotherapy and the first dose of carboplatin would be at least one week, and there would be no capping dose of palliative therapy.

Continuation of protocol therapy, if medically appropriate, should be discussed with the principal investigator at the site. The following medications and treatments are permitted in this study: (1) rescue medications for nausea or vomiting, (2) antibiotics, and (3) bisphosphonates or denosumab.

Certain medications may interact negatively with carboplatin or interfere with its effectiveness. The medications that may have significant interactions or should generally be avoided with carboplatin:

- Aminoglycoside antibiotics: these antibiotics, such as gentamicin or amikacin, may increase the risk of kidney damage when used concomitantly with carboplatin.
- Nonsteroidal anti-inflammatory drug: these drugs, including ibuprofen, naproxen, and aspirin, may increase the risk of bleeding or kidney damage when used concurrently with carboplatin.

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- Live vaccines: live vaccines, such as the measles, mumps, rubella vaccine or varicella (chickenpox) vaccine, should generally be avoided during chemotherapy treatment, including carboplatin. These vaccines contain weakened live viruses that may pose a risk to immunocompromised individuals.
- Other nephrotoxic drugs: carboplatin can cause kidney toxicity, and combining it with other medications that have nephrotoxic effects, such as certain antibiotics or antifungal medications, may increase the risk of kidney damage.
- Anticoagulant medications: combining carboplatin with anticoagulants such as warfarin or heparin may increase the risk of bleeding. Close monitoring of blood clotting parameters is essential if these medications must be used together.
- Vaccines containing weakened or killed viruses or bacteria: while certain vaccines may be necessary for specific situations, it is important to discuss with a health care professional, as the timing and administration of vaccines should be carefully considered during chemotherapy treatment.

There are no medications or treatments that are specifically prohibited during this study.

All concomitant medications will be recorded at the time of registration.

Patients meeting either of the following criteria will discontinue this study's treatment:

- Permanent discontinuation of carboplatin by treating physician (unacceptable toxicity or progression of underlying cancer).
- The investigator determines that continuing this study's treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety.
- Concomitant treatment that is not permitted.
- Failure to comply with the protocol. Suppose a patient consistently fails to attend scheduled assessments in this study. In that case, the investigator will determine the reasons and document the circumstances in the medical records as thoroughly and accurately as possible.
- The patient declines subsequent treatment or withdraws consent.

Posttrial care would be administered based on the treating physician's discretion. Patients will be followed up until disease progression. Data collected for this study comprise clinical characteristics obtained from hospital records and routine laboratory investigations, including but not limited to baseline demographics, outcome measures, treatment details, and adverse events.

Data Collection and Management

The research staff will collect data on site, using premade questionnaires on a paper case record form (CRF). All the parameters assessed in this study are defined a priori in a data dictionary, elucidating standards for data collection. Table 1 outlines the schedule of assessments.

Participating patients will be assessed before initiating a cycle of carboplatin-based chemotherapy and 3 weeks after the last dose of carboplatin. Subjects will be contacted by telephone if they miss their clinic appointment with the treating oncologist. Data entry will be done by using paper CRF. Data will be stored securely with limited access to authorized individuals. Biological samples will be collected as a part of this study at baseline. Formalin-fixed paraffin-embedded prostate tissue samples would be collected for HRR mutation testing. The patients' blood samples would also be collected for germline testing of HRR mutations.

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Table 1. Schedule of assessments.

	Screening	Baseline	Every cycle (3 weekly)	3 monthly
Informed consent	✓	—[a]	—	—
Serum testosterone	✓	—	—	—
Clinic assessment	—	✓	✓	—
Concomitant medications	—	✓	✓	—
Adverse events	—	—	✓	—
CBC[b]/LFT[c]/RFT[d]	—	✓	✓	—
Serum PSA[e]	—	✓	✓	—
Quality of life assessments	—	✓	✓	—
PSMA[f] PET[g] scan or CECT[h] chest abdomen and bone scan	—	—	—	✓

[a]Not available.

[b]CBC: complete blood count.

[c]LFT: liver function test.

[d]RFT: renal function test.

[e]PSA: prostate-specific antigen.

[f]PSMA: prostate-specific membrane antigen.

[g]PET: positron emission tomography.

[h]CECT: contrast-enhanced computed tomography.

Statistical Methods

The primary end point (confirmed PSA response rate) will be presented as a proportion to be tested against a 1-sided alternative.

Patient demographics, clinical and treatment characteristics, and other study outcomes will be described using mean, SD and range, or median, IQR and range for continuous variables, frequencies, and percentages for categorical variables, and the Kaplan Meier method for time-to-event variables. The effect sizes and 95% CIs will be presented where possible.

Simon's [18] 2-stage design will be used. The null hypothesis that the true response rate (serum PSA decline of more than 50%) is 20% will be tested against a 1-sided alternative. In the first stage, 24 patients will be accrued. If there are 5 or fewer responses in these 24 patients, this study will be stopped. Otherwise, 25 additional patients will be accrued for a total of 49. The null hypothesis will be rejected if 15 or more responses are observed in 49 patients. This design yields a type I error rate of 5% and a power of 90% when the true response rate is 40%.

To include 49 patients with mCRPC harboring HRR mutations, we must screen approximately 200 patients, assuming a 30% prevalence and tissue inadequacy of 20%. The type of HRR mutation will analyze subgroups. Regression models (using the Cox proportional hazards model) will be used for exploratory analyses.

Oversight and Monitoring

The principal investigator at the All India Institute of Medical Sciences, New Delhi, will coordinate this study and be responsible for data acquisition management and statistical analysis. Investigators from the Department of Medical Oncology at this study's site will constitute the trial steering committee. The trial steering committee will evaluate any serious adverse events and report promptly to the Institute Ethics Sub Committee for Monitoring of Adverse Events in Clinical Trials at the site. Guideline-based collection of adverse event data will be ensured. Additionally, serious adverse reactions will be reported on time to the Institute Ethics Sub Committee for Monitoring of Adverse Events in Clinical Trials at the site. There will be no compensation offered for adverse events or serious adverse events to participants. After the initiation of this study, the trial steering committee will regularly audit the process of consenting, protocol adherence, and data collection biannually. Additionally, the data may be audited or inspected by the Institute Ethics Committee. Amendments made to the protocol will be communicated on time to the Institute Ethics Committee and the Clinical Trials Registry of India. One protocol amendment has been done in which we added the European Organisation for Research and Treatment of Cancer prostate cancer 25 questionnaire to the assessment and included the option of contrast-enhanced computed tomography chest abdomen and bone scan in place of a prostate-specific membrane antigen–positron emission tomography scan.

This trial will be published in a peer-reviewed journal with individual investigators as authors. Full credit will be given to the collaborating investigators and research staff involved in this study. All authors will review and approve this paper before submission and comply with internationally accepted requirements. We also plan to present this study's results at major scientific meetings. The availability of results to all participants will be ensured.

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Ethical Considerations

The ethical approval has been obtained from the Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi who approved this study's protocol on April 20, 2023 (IECPG-255/20.04.2023). Informed consent of each participant in the local language will be taken. The identifying information of participants will be removed as much as possible. Each participant will be given a study identification number, and the CRFs will contain only the deidentified data. Consent forms (with identifying patient data) will be safeguarded in locked compartments at this study's site that can exclusively be accessed by authorized personnel. No monetary compensation will be provided to the enrolled participants. No identification of individual participants or users in any images of the paper or supplementary material is possible.

The protocol and final paper will be published as described by the International Committee of Medical Journal Editors guidelines. No professional writers will be employed to write the final paper. The supplementary material of the final paper will contain the full protocol. The deidentified data set and statistical code will be made available to the corresponding author at a reasonable request.

Results

The trial started enrollment in September 2023. This trial is ongoing, and 12 patients have been recruited to date. All 49 participants will be enrolled according to plan.

Discussion

Relevance of the Study

This prospective phase II study will provide efficacy data of carboplatin in patients with mCRPC with deficient HRR. If this study provides positive results, it will provide a treatment option for patients with mCRPC. Further multicentric phase III noninferiority trials may be conducted to compare the efficacy with PARP inhibitors. Importantly, this study will provide a rationale for using carboplatin in resource-limited settings worldwide.

The limitation of this study is that it will have a screen failure rate of around 70%, as the prevalence of deleterious mutations in the HRR pathway is approximately 30%. Further, the availability of tumor tissue and the quality of archived specimens can also impair the technical ability to detect mutations in the HRR pathway. Therefore, approximately 200 patients with mCRPC will be screened to enroll 49 patients in this study.

There had only been small retrospective trials for using carboplatin in mCRPC. This would be the first phase II trial to evaluate the efficacy of carboplatin in patients with metastatic prostate cancer harboring mutations in the HRR pathway.

Conclusions

This prospective phase II clinical trial addresses a critical unmet need in the management of patients with mCRPC harboring HRR gene mutations. With a focus on evaluating the efficacy of carboplatin, an affordable chemotherapy agent, this study holds promise as a new therapeutic option. The trial's approach builds upon the concept of synthetic lethality, harnessed by both PARP inhibitors and carboplatin. If successful, carboplatin could emerge as a practical and accessible treatment strategy for this specific patient subset, potentially improving their outcomes and quality of life. By bridging the gap between high-cost therapies and broader patient accessibility, this study can potentially transform the landscape of mCRPC treatment, offering hope to patients worldwide.

Acknowledgments

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Data Availability

The supplementary material of the final paper will contain the full protocol. The deidentified data will be available upon reasonable request to the corresponding author after the publication of the final results.

Authors' Contributions

RJ conceptualized the study and drafted and revised the manuscript. AK, Atul S, RKS, SK, Aparna S, BN, SAS, HKP, CJD, and A Seth conceptualized the study. AB conceptualized the study, designed the trial and statistical analysis, and drafted and revised the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Informed consent form.
[DOCX File , 15 KB - resprot_v13i1e54086_app1.docx]

Multimedia Appendix 2
Participant information sheet (PIS).
[DOCX File , 17 KB - resprot_v13i1e54086_app2.docx]

Multimedia Appendix 3
Participant informed consent form (PICF) Hindi.
[DOCX File , 36 KB - resprot_v13i1e54086_app3.docx]

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Abbreviations

CRF: case record form
HRR: homologous recombination repair
mCRPC: metastatic castration-resistant prostate cancer
PARP: polyadenosine 5'diphosphoribose (poly [ADP-ribose]) polymerase inhibitor
Poly (ADP-ribose): polyadenosine 5'diphosphoribose
PSA: prostate-specific antigen
ULN: upper limit of normal

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Protocol

Investigating SARS-CoV-2 Incidence and Morbidity in Ponce, Puerto Rico: Protocol and Baseline Results From a Community Cohort Study

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Abstract

Background: A better understanding of SARS-CoV-2 infection risk among Hispanic and Latino populations and in low-resource settings in the United States is needed to inform control efforts and strategies to improve health equity. Puerto Rico has a high poverty rate and other population characteristics associated with increased vulnerability to COVID-19, and there are limited data to date to determine community incidence.

Objective: This study describes the protocol and baseline seroprevalence of SARS-CoV-2 in a prospective community-based cohort study (COPA COVID-19 [COCOVID] study) to investigate SARS-CoV-2 infection incidence and morbidity in Ponce, Puerto Rico.

Methods: In June 2020, we implemented the COCOVID study within the Communities Organized to Prevent Arboviruses project platform among residents of 15 communities in Ponce, Puerto Rico, aged 1 year or older. Weekly, participants answered questionnaires on acute symptoms and preventive behaviors and provided anterior nasal swab samples for SARS-CoV-2 polymerase chain reaction testing; additional anterior nasal swabs were collected for expedited polymerase chain reaction testing from participants that reported 1 or more COVID-19–like symptoms. At enrollment and every 6 months during follow-up, participants answered more comprehensive questionnaires and provided venous blood samples for multiantigen SARS-CoV-2 immunoglobulin G antibody testing (an indicator of seroprevalence). Weekly follow-up activities concluded in April 2022 and 6-month follow-up visits concluded in August 2022. Primary study outcome measures include SARS-CoV-2 infection incidence and seroprevalence, relative risk of SARS-CoV-2 infection by participant characteristics, SARS-CoV-2 household attack rate, and COVID-19 illness characteristics and outcomes. In this study, we describe the characteristics of COCOVID participants overall and by SARS-CoV-2 seroprevalence status at baseline.

Results: We enrolled a total of 1030 participants from 388 households. Relative to the general populations of Ponce and Puerto Rico, our cohort overrepresented middle-income households, employed and middle-aged adults, and older children (P<.001). Almost all participants (1021/1025, 99.61%) identified as Latino/a, 17.07% (175/1025) had annual household incomes less than

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US $10,000, and 45.66% (463/1014) reported 1 or more chronic medical conditions. Baseline SARS-CoV-2 seroprevalence was low (16/1030, 1.55%) overall and increased significantly with later study enrollment time (P=.003).

Conclusions: The COCOVID study will provide a valuable opportunity to better estimate the burden of SARS-CoV-2 and associated risk factors in a primarily Hispanic or Latino population, assess the limitations of surveillance, and inform mitigation measures in Puerto Rico and other similar populations.

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(JMIR Res Protoc 2024;13:e53837) doi:10.2196/53837

KEYWORDS

cohort studies; COVID-19; epidemiologic studies; Hispanic or Latino; incidence; prospective studies; research methodology; SARS-CoV-2; seroprevalence

Introduction

After the first detection of SARS-CoV-2 in late 2019, the virus has become a significant threat to health and economies globally, particularly in populations with high economic inequality and low access to health resources and infrastructure [1,2]. In the United States, racial and ethnic groups with well-documented socioeconomic disparities have also been disproportionately affected by SARS-CoV-2, with the highest COVID-19 morbidity and mortality rates among American Indian or Alaska Native, non-Hispanic Black, and Hispanic or Latino populations [3,4]. Despite tremendous progress in our understanding of SARS-CoV-2 and the development of COVID-19 treatment and vaccines, control efforts have been hindered by the emergence of new, more contagious variants and vaccine hesitancy [5-9]. A better understanding of risk and risk factors for SARS-CoV-2 infection and transmission dynamics in minority groups and low-resource settings is needed to inform ongoing control efforts and develop strategies to improve health equity.

Puerto Rico, a Caribbean island and US Commonwealth, has a high prevalence of population characteristics associated with increased vulnerability to COVID-19. Among approximately 3.3 million Puerto Rico residents, almost all (99%) identify as Hispanic or Latino, and 43% live below the federal poverty level [10]. Additionally, risk factors for severe COVID-19, including older age and chronic disease, are higher among Puerto Ricans relative to residents of the continental United States, and economic crises and natural disasters have weakened the local health care infrastructure over the past decade [11-13]. As in many regions, facility-based public health surveillance and seroprevalence data from blood banks have been and continue to be the primary sources of SARS-CoV-2 incidence and prevalence data in Puerto Rico [14-16]. While valuable, these data are limited in depth and scope due to reliance on patient health care seeking behavior and passive reporting by providers and diagnostic laboratories. Systematic diagnostic testing and follow-up of a defined population can better capture the spectrum of COVID-19 disease, determine true infection rates, and help identify risk factors for infection and morbidity.

As part of the COVID-19 emergency response efforts, the US Centers for Disease Control and Prevention (CDC) supported multiple community-based cohort studies to better understand SARS-CoV-2 transmission and risk in different settings [17-19]. The ongoing Communities Organized to Prevent Arboviruses (COPA) cohort study in Ponce, Puerto Rico—implemented in 2018 through the collaboration of the Ponce Health Sciences University, Puerto Rico Vector Control Unit, and the CDC Dengue Branch (DB)—was identified as an existing platform that could be expanded to estimate SARS-CoV-2 community infection rates and other COVID-19 research objectives in the region. In June 2020, we implemented the COPA COVID-19 (COCOVID) study, a prospective, community-based cohort to investigate the incidence of and risk factors for SARS-CoV-2 infection and morbidity among COPA participants and other residents of 15 community areas.

In this study, we describe the protocol, baseline population demographics, and seroprevalence of SARS-CoV-2 in the COCOVID cohort. The study included weekly molecular testing and multiantigen serology testing at baseline and every 6 months for SARS-CoV-2. We also collected sociodemographic data, weekly mobility and personal preventive behavior patterns, COVID-19 vaccination status, symptoms, and long-term outcomes among individuals with and without incident SARS-CoV-2 infection during the study period. To date, few longitudinal COVID-19 studies with regular SARS-CoV-2 molecular testing have included the United States or Hispanic or Latino populations [20,21], and none have been conducted in Puerto Rico. Thus, data from the COCOVID study have the potential to enhance general knowledge of SARS-CoV-2 epidemiology in addition to providing unique insights into the COVID-19 epidemic in Puerto Rico, which may have implications for prevention efforts and future epidemics in geographically or demographically similar populations.

Methods

Ethical Considerations

Local ethics review and approval for the COPA project and COCOVID substudy protocols were obtained through the Ponce Medical School Foundation, Inc's institutional review board (study #171110-VR). CDC also reviewed COPA and COCOVID protocols and determined the activities were conducted in a manner consistent with applicable federal law and CDC policy (refer to 45 C.F.R. part 46; 21 C.F.R. part 56).

Adult consent, minor assent, and parental or guardian permission were obtained at enrollment and subsequent 6-month follow-up visits and documented using paper forms. The receipt of consent and assent for all participants was also confirmed daily and

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tracked electronically by study coordinators. All participants under the age of 21 years, the age of majority in Puerto Rico, were considered minors except for those emancipated by marriage or judicial decree. Before the interview or specimen collection, staff explained project activities and important points of informed consent to participants, answered any questions raised, and provided a paper copy of the consent form to the household. The household representative (an adult or an emancipated minor that was present at the time of visit) consented to provide household-level information and allow study staff to invite other household members to participate in the study.

All adults and emancipated minors (including household representatives) were asked to provide written consent for each of the following: providing contact information, responding to the COPA annual interview questions and providing blood and nasal swab specimens (where applicable), being contacted weekly for acute illness surveillance (AIS) and annually for cohort follow-up, responding to the COCOVID questionnaire and providing blood specimens every 6 months and nasal swabs weekly, storage of specimens remaining after testing for future studies, and permission for children for which they were the parent or legal guardian to participate in the same project activities.

The adult consent document requested a separate enumeration of each child for which they had parental or guardianship rights to account for any differences in the activities in which each child could participate. For minors aged between 14 and 20 years, written consent was obtained using a designated form simplified from the adult version. Verbal assent was documented in a designated form for minors aged between 7 and 13 years, and only parent or guardian consent was documented for minors aged between 1 and 6 years. All consent and assent forms and questionnaires were available in both Spanish and English and were written at an eighth grade or lower reading level.

This project involved the collection of personal identifying information and included safeguard measures to ensure the privacy and confidentiality of participants. Households and individual participants were assigned project-specific identifiers to track their location of residence and study status. Barcode stickers were used to link specimen tubes and paper forms to each participant's visit during the project. All specimens were securely transported to and stored at the study office site, the CDC DB, and other laboratory sites. All personnel involved in this study were required to complete ethics training requirements set by the institutional review board and adhere to an unwavering code of conduct regarding the confidentiality of patients' information.

Only study personnel have access to participant responses or laboratory results. Study questionnaires, laboratory test results, and other collected data are electronically stored in locations approved by the CDC for storage of personal data, including a limited-access encrypted server and shared drive within the CDC internal network, and, in the case of paper forms, in locked cabinets. Paper records will be maintained for at least 3 years and then destroyed. Where possible, deidentified data sets will be created and used for analysis, and individual participants will not be identified for any presentations or publications based on the study results.

For compensation for the time dedicated to the COCOVID study activities, participants received US $5 each week upon staff receipt of the completed weekly questionnaire and self-collected respiratory specimen, which was given in US $20 installments for every 4 successful transfers of weekly questionnaires and specimens. Participants also received US $20 at each study appointment (enrollment, 6 months, 12 months, 18 months, and 24 months) when they completed serum specimen collection and the questionnaire. If these appointments overlapped with COPA annual follow-up visits (enrollment, 12 months, and 24 months), an additional US $20 (between June 2021 and February 2022) or US $30 (between March and August 2022) in compensation was given for both activities for a total of US $40 or US $50.

Study Overview

In June 2020, we implemented the COCOVID substudy among residents of 15 community areas in Ponce. We aimed to enroll between 900 and 1000 participants for regular surveys and specimen collection, including weekly anterior nasal swab collection for SARS-CoV-2 polymerase chain reaction (PCR) testing and venous blood draws for multiantigen immunoglobulin (Ig) G antibody testing at baseline and every 6 months. Participants were also included in activities for the larger COPA cohort for at least the same period that they were active in the COCOVID study, including weekly reporting of acute COVID-19–like symptoms through SMS text message and additional SARS-CoV-2 PCR testing among symptomatic participants.

COPA Platform

The COPA study established an ongoing cohort of approximately 3800 participants in 38 community areas in Ponce, Puerto Rico (Figure 1) to measure the incidence and prevalence of arboviral infections and evaluate vector control interventions through a cluster randomized controlled trial design [22,23]. Recruitment activities are conducted primarily through house-to-house visits, and random selections of residences in each community area are made until sample size goals are reached or all residences have been approached for recruitment. Eligible individuals are aged between 1 and 50 years, spend 4 or more nights a week in the selected residence, and have no definite plans to move in the next 12 months. Follow-up is conducted annually and includes serum collection for antibody testing for dengue and the administration of a questionnaire (Figure 2). Cohort enrollment began in March 2018.

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Figure 1. Map of the 38 Communities Organized to Prevent Arboviruses (COPA) and 15 COPA COVID-19 (COCOVID) community cohort study cluster areas in Ponce, Puerto Rico.

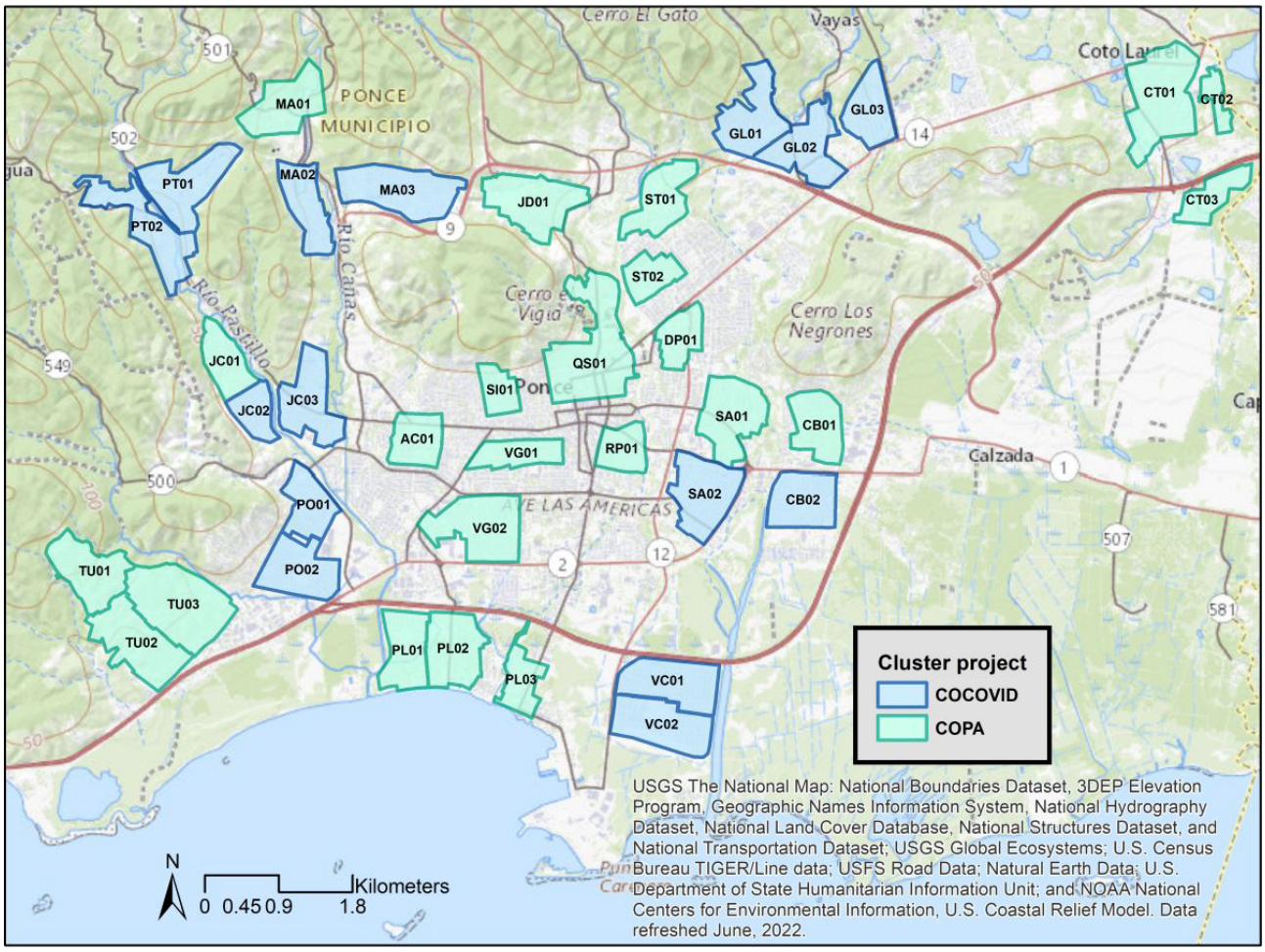

Figure 2. Timeline of key Communities Organized to Prevent Arboviruses (COPA) and COPA COVID-19 (COCOVID) cohort study activities in Ponce, Puerto Rico, between January 2020 and December 2022. CDC: Centers for Disease Control and Prevention; mo: months; PCR: polymerase chain reaction; PMSF: Ponce Medical School Foundation; yrs: years.

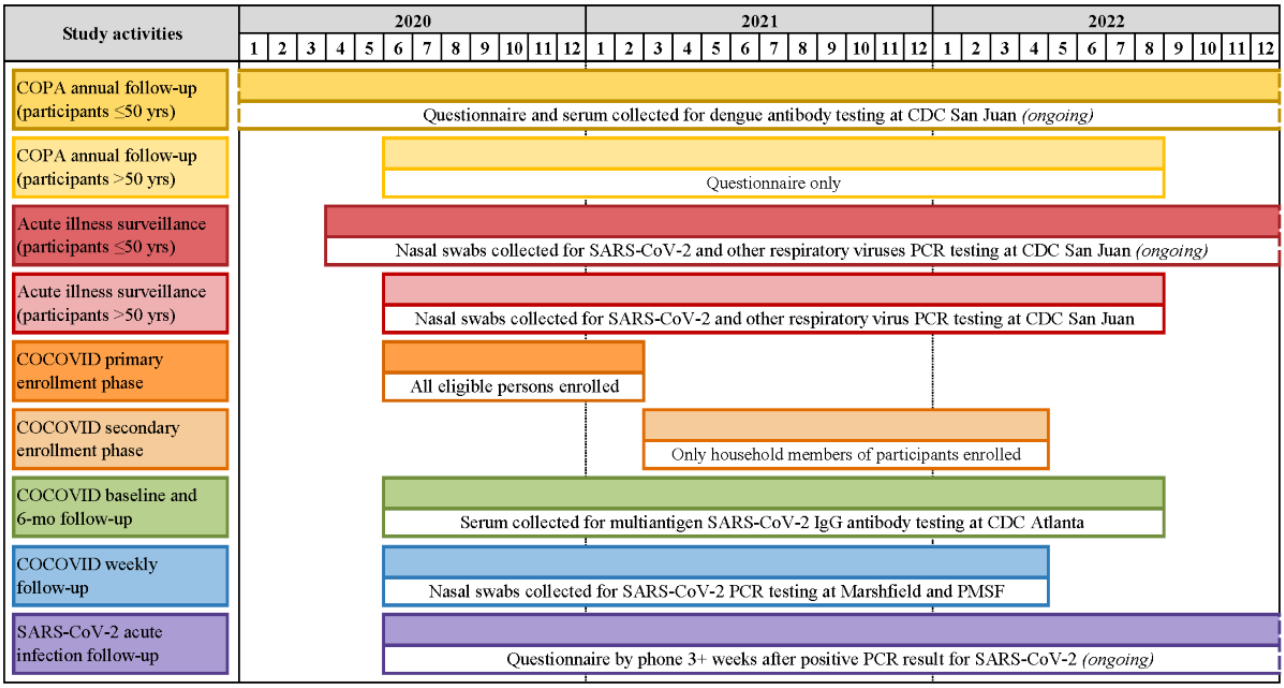

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In April 2020, questions related to risk and perceptions of COVID-19 were added to the annual questionnaire, and an AIS component was implemented (Figure 2). The AIS component is ongoing and uses an automated SMS text messaging system to contact adult participants weekly to inquire if any household members have experienced fever or other COVID-19–like symptoms (ie, cough, shortness of breath, sore throat, body pain, diarrhea, and loss of taste or smell) in the past 7 days (Figure 2). Participants that report fever are offered testing for dengue virus (DENV) by real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) testing in serum, and those that report any qualifying symptom are offered an anterior nasal swab for SARS-CoV-2 and other respiratory virus rRT-PCR testing. Beginning in December 2021, participants were also asked to provide an additional anterior nasal swab for SARS-CoV-2 rapid antigen testing. To ensure the consistency of the sample collection method for both tests, all nasal swabs are collected by a nurse or medical technologist. At the time of specimen collection, project staff also administer an AIS questionnaire on recent exposures, symptoms, and health care–seeking behaviors.

Study Population and Enrollment

Enrollment activities for the COCOVID substudy for COVID-19 began in late June of 2020. We initially selected 12 of the 38 COPA study communities for COCOVID activities, and an additional 3 community areas were added during the enrollment process to meet sample size goals (Figure 1). We prioritized the selection of community areas with high numbers of individuals aged 18 years or younger and those aged 50 years or older in COPA-participating households to increase the participation of these age groups. We also considered logistical priorities, including proximity to other selected clusters and ease of access to residential areas, in the selection process. Eligibility for COCOVID participation was expanded beyond that of COPA to include residents aged 50 years or older, in addition to spending 4 or more nights per week at a residence in a selected community area and having no definite plans to move in the next 12 months. COCOVID participants agree to participate in COPA annual follow-up questionnaires and, for participants aged between 1 and 50 years, the collection of blood specimens for arbovirus antibody testing for at least the substudy duration; participation in the AIS activities was not required for COCOVID enrollment.

Using a standardized script, study staff contacted households with 1 or more COPA participants by phone to explain the study, offer enrollment to eligible household members, and schedule an initial study visit to complete consent processes and data and specimen collection activities. Enrollment of all eligible household members was encouraged but not required, and participants were also asked to refer family and neighbors residing in the 15 community areas. The primary enrollment phase occurred between June 2020 and February 2021. Subsequently, only the enrollment of members of households with 1 or more active participants was permitted to avoid major changes to study logistics and increases in resource use (secondary enrollment phase, Figure 2). Following the completion of the primary enrollment phase, we planned to continue participants' weekly follow-up activities for a minimum of 12 months (through February 2022) and 6-month activities for a minimum of 18 months (through August 2022).

Sample Size Calculation

The sample size for the COCOVID substudy was based on the primary study objective of estimating community incidence of SARS-CoV-2 infection, which included allowing for comparisons by age group, accounting for potential similarity among participants within cluster areas, and assuming a cumulative incidence of infection of 10%-30% over the study period. Age groups were defined to allow infection risk comparisons of pediatric (1-17 years) and older adult (≥50 years) populations with the general population (18-49 years); gender-based sample size estimates were not made as we assumed our household-based recruitment methods would result in representative samples by gender. Our calculations assumed the enrollment of approximately equal numbers of participants across the 3 age groups and from the initially selected 12 community areas. Additionally, it was assumed that participants who were infected with SARS-CoV-2 before enrollment would not be at lower risk of further infection during the study period.

We expected a high coefficient of variation among the clusters for SARS-CoV-2 transmission, and calculations were made using a range of values from 0.5 to 0.8. We also expected a high intracluster correlation among the responses within a cluster due to the rapid spread of SARS-CoV-2, and calculations were made using values of 0.2 and 0.25. The precision of incidence is estimated by computing the 95% CI for 1 proportion in a cluster sampling design. Scenarios were run considering different cumulative incidence proportions with different intracluster correlations, coefficients of variation, and sample sizes for each cluster. Calculations showed that to reach a CI half width of 0.19 or less, a sample size of 215 participants per age group, or a total of 645 participants, was needed. To account for up to 20%-30% loss to follow-up (a high estimate to also allow for probable unequal recruitment across age groups) and an estimated 5% prevalence of previous SARS-CoV-2 infection at enrollment, we estimated that we needed to enroll a total of 900-1000 participants.

Baseline and 6-Month Follow-Up

Baseline and subsequent 6-month visits took place at the COPA central office facilities, a designated outdoor drive-through site, or the participant's home, depending on local social distancing regulations and participant preferences. After completing informed consent processes, study staff administered a questionnaire on chronic conditions, recent COVID-19 exposures, preventive behaviors, and, for participants that reported an acute COVID–like illness in the past 7 days, symptoms and health care seeking behaviors. Questions on COVID-19 vaccination status were added in January 2021, and questions on employment status and category, long-term COVID-19 symptoms (persisting or appearing more than 1 month after illness onset), and diagnosis of new chronic conditions after an acute SARS-CoV-2 infection were added in September 2021. A trained phlebotomist collected blood for multiantigen SARS-CoV-2 IgG antibody testing by venipuncture using aseptic techniques. Approximately 7.5 milliliters of blood were collected from participants aged between 1 and 4 years,

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and approximately 15 milliliters from participants aged 5 years or older.

To reduce study burden, COPA annual activities were conducted at the same time as COCOVID baseline and 6-month follow-up visits, where possible (Figure 2). In these cases, an additional ~7.5 mL of blood for dengue antibody testing were collected during the COCOVID visit for participants aged between 1 and 50 years, and the COPA annual questionnaire was administered to all participants by phone. This questionnaire included questions about household composition and income, demographics, employment status, and COVID-19 risk perception. The 6-month follow-up activities were conducted through August 2022 (Figure 2).

Weekly Follow-Up

Each week, participants self-collected (or had a parent or guardian assist them in collecting) a flocked swab of the anterior nares (anterior nasal swab) and completed a paper questionnaire on new or worsening symptoms, illness among household members, and behaviors such as leaving their home for activities with people outside of their household, places visited, mask use, and social distancing. Before distribution, a unique barcode label was applied to a specimen collection tube and corresponding weekly questionnaire, and questionnaires were prefilled with the participant's name, date of birth, and study identifier. At the enrollment appointment, the first weekly nasal swab specimen and accompanying questionnaire were completed under study staff instruction and supervision, and an initial 4-week supply of paper questionnaires and nasal swab specimen collection supplies were provided. Participants were asked to collect nasal swab specimens and fill out the accompanying questionnaire on a consistent day of the week within 0-12 hours of a scheduled transfer to study staff.

Study staff drove to the participating houses on an agreed-upon day and time for specimen and questionnaire pick-up each week. Households that were unavailable for scheduled pick-up (incidentally or always) were asked to drop off collected specimens and questionnaires at an agreed-upon day and time at the COPA office site. An automated SMS text-messaging system through Twilio MessagingX (Twilio, Inc) was used to send reminders to households on the day of their scheduled pick-up or drop-off for respiratory specimen collection, and study staff contacted participants by phone within 0-2 days if specimen and questionnaire receipt was delayed without notice and to resolve other issues related to received specimens and questionnaires, such as specimen leaks and missing responses. If scheduled receipt of a weekly respiratory specimen was delayed by 4 or more days, no additional opportunities for specimen transfer were offered, and the specimen was considered missing for that week. Additional 4-week supplies of respiratory specimen collection kits and questionnaires were distributed to participants as needed during pick-up and drop-off activities.

Weekly follow-up activities were initially planned to conclude in February 2022, after 12 months of the end of the primary enrollment period. However, investigators agreed to extend the weekly follow-up period due to an increase in SARS-CoV-2 transmission following the introduction of the Omicron variant in Puerto Rico. Study materials and funds were identified to permit a 2-month extension of weekly follow-up to a total of 98 weeks from June 2020 to April 2022 (Figure 2).

Follow-Up for Participants With Symptoms or SARS-CoV-2 Infection

Participants that reported fever, cough, shortness of breath, sore throat, body pain, diarrhea, or loss of taste or smell in the weekly questionnaires (or through the AIS SMS text message system) were asked to participate in a COPA AIS visit to collect additional samples for expedited testing for dengue, SARS-CoV-2, and other respiratory viruses and answer the AIS questionnaire.

Participants with a positive SARS-CoV-2 molecular test from nasal swab specimens collected during weekly COCOVID follow-up or as part of AIS were contacted by phone at least 4 weeks after specimen collection (depending on delays in receipt of positive test results) to complete a follow-up questionnaire on symptoms and illness duration, health care seeking behavior, travel, and other exposures before infection, and to take measures to prevent household transmission while sick (Figure 2).

Specimen Storage, Transport, and Testing

Participants were asked to store weekly anterior nasal swab specimens in their home refrigerators until they were transferred to study staff. Upon receipt of nasal swab specimens, staff stored them in the COPA laboratory refrigerator at 4 °C or according to current CDC specimen storage guidelines. Staff centrifuged whole blood specimens within 4 hours of collection to separate out serum and stored them in the COPA laboratory refrigerator until transport. Specimens were transported by a courier 3 times weekly from the COPA office site to the CDC DB laboratory in San Juan, Puerto Rico, for accessioning, processing, and storage at –70 °C. Frozen nasal swab specimens from COCOVID weekly collection activities were shipped every 1-3 months, and serum aliquots from COCOVID 6-month collection were shipped every 3-6 months to designated laboratories for testing.

Weekly nasal swab specimens were tested by multiplex rRT-PCR assays to detect SARS-CoV-2 RNA, including the Quidel Lyra SARS-CoV-2 Assay [24], Thermo Fisher Scientific TaqPath COVID-19 Combo Kit [25], Thermo Fisher Scientific TaqPath COVID-19, FluA, FluB Combo Kit [26], and Roche Cobas SARS-CoV-2 assay [27]. Cycle threshold values for assay targets were provided for positive specimens, and overall test result interpretations were provided for all tested specimens. Specimens collected between June 2020 and February 2022 were tested by Marshfield Labs in Marshfield, Wisconsin; those collected between March and April 2022 were tested by the Ponce Medical Sciences Foundation Immunology Reference Laboratory in Ponce, Puerto Rico. Whole genome sequencing is ongoing and being performed at CDC headquarters (Atlanta, Georgia) or DB laboratories for weekly nasal swabs that tested positive by rRT-PCR and have sufficiently low cycle threshold values for the nucleocapsid (N) protein target (≤30 for headquarters and ≤27 for DB laboratories). Information on the detected variant lineage (through Pangolin COVID-19 Lineage

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Assigner software version 3.1.7; Centre for Genomic Pathogen Surveillance) is provided in accordance with CDC guidance [28].

Serum specimens collected for baseline and 6-month follow-up visits were tested by the Luminex xMAP SARS-CoV-2 multiantigen IgG assay to detect previous infection with SARS-CoV-2 [29]. This assay has 3 antigen targets: the N structural protein, the S1 subunit, and the receptor binding domain (RBD), which are part of the spike (S) protein. Interim guidelines for SARS-CoV-2 testing from the US CDC recommend using anti-N IgG antibody testing to evaluate previous SARS-CoV-2 infection in vaccinated individuals, as COVID-19 vaccines are designed to encode the S protein or a portion of it. Thus, to reduce potential misclassification due to vaccination versus past SARS-CoV-2 infection, specimens were only determined to be positive if IgG antibodies against the N protein, in addition to those against at least 1 of the other 2 targets (S1 and RBD), were detected. The CDC Microbial Pathogenesis and Immune Response Laboratory in Atlanta, Georgia, conducted testing on all serum specimens collected during the study period.

Serum and nasal swab specimens collected for AIS activities were tested at the CDC DB laboratory. Serum samples were tested by the CDC DENV-1-4 rRT-PCR Multiplex Assay to detect RNA for DENVs 1, 2, 3, and 4 and by the DENV Detect IgM Capture enzyme-linked immunosorbent assay kit to detect IgM antibodies for DENV antigens [30,31]. Anterior nasal swabs were tested by an in-house respiratory virus rRT-PCR multiplex assay to detect RNA for SARS-CoV-2, influenza A and B viruses, parainfluenza viruses, adenovirus, respiratory syncytial virus, and human metapneumovirus. The DENV and respiratory virus rRT-PCR assays for AIS specimens were run weekly or more often, and participants with positive results were notified by phone and given recommendations on preventing transmission and following up with their health care providers as needed.

Data Collection and Management

Baseline and 6-Month Questionnaire

Between June 2020 and February 2022, the EpiInfo mobile app was used on Samsung tablets to administer the baseline and 6-month questionnaires and record responses, including participant identifiers and specimen collection data [32]. Beginning in March 2022, the Research Electronic Data Capture (REDCap; Vanderbilt University) mobile application was used to administer these questionnaires [33,34]. Paper questionnaire forms were available for use as a backup in case of electronic data collection failure. Paper forms were entered into the mobile app either daily or every 6 months as part of the data review and cleaning processes. Questionnaire data were transferred daily from tablets to a secure, limited-access CDC server through the Secure Shell File Transfer Protocol.

Weekly Questionnaire

A paper version of the weekly questionnaire was completed by participants and received by study staff at scheduled specimen pick-up and drop-off activities. Staff reviewed the form for completeness and filled out the laboratory section to accompany the corresponding weekly nasal swab specimen. After the specimens were transported to and accessioned by the CDC DB laboratory, the forms were scanned into the CDC laboratory samples database, where they underwent automated data extraction using Microsoft Azure Form Recognizer software or manual data entry in cases of software extraction failure [35].

Preliminary data cleaning was performed in EpiInfo or REDCap daily by study field staff and the data quality team. Additional data cleaning processes were performed weekly using the R environment for statistical computing (R Core Team) and involved data validation and standardization, including the identification of missing forms, data inconsistencies, and variable completeness [36]. Final data checks and standardizations were also performed using R statistical software at 6-month intervals to generate analytic data sets.

Data Analysis

Outcome Measures

The primary outcome measures of interest for this study are (1) the incidence of SARS-CoV-2 infection as defined by detection of SARS-CoV-2 RNA by PCR testing of participant specimens collected as part of weekly follow-up or AIS visits, and (2) the relative risks of incident SARS-CoV-2 infection by participant demographics, health history, and behaviors. Secondary outcomes included the (1) seroprevalence of SARS-CoV-2 defined by detection of N and either S1 or RBD IgG antibodies by enzyme-linked immunosorbent assay, (2) household attack rate among households with at least 2 participants and 1 participant with an incident SARS-CoV-2 infection, and (3) the frequency of illness characteristics and outcomes (ie, symptom status and severity, health care seeking, death, and post–COVID conditions) among participants with incident SARS-CoV-2 infections.

Planned Statistical Analyses

SARS-CoV-2 Infection Incidence and Risk Factors

Using the number of incident SARS-CoV-2 infection events detected through PCR testing divided by the total person-time at risk contributed, we calculated SARS-CoV-2 infection incidence rates overall and approximately every 6 months during the study period (between June 2020 and August 2022). We will also estimate the incidence rates separately for primary and secondary infections, during the circulation of major SARS-CoV-2 variants, and by COVID-19 vaccination status. We will use Poisson regression to estimate adjusted infection risks by age group, primary SARS-CoV-2 variant circulating at the time of infection, previous SARS-CoV-2 infection status, and COVID-19 vaccination status, and identify other potential risk factors for infection in our cohort. Household will be accounted for as a clustering effect in the regression, using the sandwich estimator framework to calculate a clustered SE [37]. We will extrapolate the cumulative incidence of SARS-CoV-2 infections in the cohort to the general population in the Ponce region during the study, using population age and sex estimates from US census data numbers, and compare this extrapolated estimate to surveillance data from the same time period.

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SARS-CoV-2 Infection Seroprevalence

Using the overall interpretation for the SARS-CoV-2 IgG antibody testing (positive only when N and either S1 or RBD antibodies are detected), we will estimate the seroprevalence of SARS-CoV-2 infection among participants of the COCOVID cohort approximately every 6 months during the study period, using specimens collected during those periods. The frequency of seroconversion, defined as a positive SARS-CoV-2 IgG antibody test result following a negative result, will be assessed over the study period at the individual and household level. For the period during which both PCR and antibody testing were occurring (between June 2020 and April 2022), we will compare the proportion of participants with seroconversion detected with SARS-CoV-2 incidence estimates from weekly PCR testing. This comparison will be used to evaluate the sensitivity and specificity of repeated serology testing at 6-month intervals in estimating infection incidence. We will also use the results of this comparison to inform estimates of SARS-CoV-2 infection incidence in the cohort that occurred between May and August 2022, when only SARS-CoV-2 IgG test results were available.

Household Attack Rate

We will assess potential household transmission of SARS-CoV-2 among households with at least 2 participating members and 1 participating member with an incident SARS-CoV-2 infection (index case) during study follow-up. Additional household cases will be defined based on the detection of SARS-CoV-2 RNA by PCR testing in a household member within 14 days of the index case. We will calculate a crude household attack rate from the proportion of additional cases among all household members deemed susceptible to acquiring SARS-CoV-2 infection from an index case. To account for household transmissions from nonindex cases and identify factors associated with household transmission, we will consider using a chain binomial transmission model to estimate the household attack rate and identify factors associated with increased and decreased likelihood of intrahousehold transmission [38,39].

Frequency of Illness Characteristics and Outcomes

Among COCOVID participants with incident infections, we will assess the frequency of symptomatic versus asymptomatic infection, self-reported symptoms, illness duration, health care seeking behaviors, and outcomes, including uncomplicated recovery, hospitalization, death, and the development of post–COVID conditions. If sample size permits, we propose using robust Poisson regression models to identify participant demographics, symptoms, and comorbidities associated with seeking care and being diagnosed with COVID-19, severe disease, and the development of self-reported post–COVID-19 conditions [40]. We will compare acute illness events reported in COCOVID weekly questionnaires associated with an incident SARS-CoV-2 infection to those not associated with SARS-CoV-2 infection to identify symptoms and symptom combinations that are highly indicative of infection [41].

Statistical Analyses of Baseline Data

In this study, we describe the baseline characteristics of the COCOVID cohort using data collected from questionnaires applied at COCOVID enrollment or within the previous year for participants previously enrolled in COPA. Frequency statistics are presented overall for the COCOVID cohort and compared to the populations of Ponce and Puerto Rico based on data from the US Census American Community Survey 2021 1-Year estimates [10,42]. Pearson chi-square tests were used for comparisons of the cohort population with those of Ponce and Puerto Rico at a household and individual level; multiple comparisons were conducted for variables with more than 2 categories, and Bonferroni-adjusted *P* values are presented. For the cohort population, individual frequency statistics were also presented by serological evidence of previous SARS-CoV-2 infection at baseline, as indicated by IgG antibody testing by timing of study enrollment, age group, sex, and annual household income. Pearson chi-square or Fisher exact tests, in the case of 1 or more expected values of <5, were used to compare categorical variables by baseline serostatus. A significance level of .05 was assumed for all comparisons, including following Bonferroni adjustment where applicable.

All analyses were conducted using R (version 4.0.4; R Core Team) [36].

Results

During the first phase of enrollment (between June 2020 and February 2021), a total of 1012 individuals from 388 households were enrolled in the COCOVID cohort; an additional 18 members of participating households were enrolled in the secondary enrollment phase, with the last participant enrolled in November 2021. Among 388 households with at least 1 COCOVID participant, 83.03% (1042/1255) of all household members were enrolled, with a mean of 3.2 participants per household; 40.27% (151/375) of households had an annual income under US $20,000 (Table 1). Of the 1030 total participants, 56.21% (579/1030) had previously participated in the COPA study, the mean age was 35.9 (range 1-97) years, and 53.40% (550/1030) were female (Table 2). Most participants identified as Latino/a (1021/1025, 99.61%) and Puerto Rican (1015/1024, 99.12%), and around two-thirds (682/1016, 67.13%) identified as White. There were 719 adult participants (aged 21 years or older; 69.8%) enrolled, of which approximately two-thirds had college or technical school degrees (197/716, 27.51%) or postgraduate study (278/716, 27.36%) and half were employed (380/717, 53.00%). More than half (389/719, 54.10%) of adult participants and 45.66% (463/1014) of all participants reported having been diagnosed with at least 1 chronic health condition.

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Table 1. Annual income of households with ≥1 participant in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

Annual household income (US $)[a]	Households with ≥1 COCOVID participant (N=388), n (%)	Households in Ponce municipality (N=50,007), n (%)	*P* value[b]	Households in Puerto Rico (N=1,165,982), n (%)	*P* value[b]
<10,000	61 (16.3)	16,659 (33.3)	<.001	286,499 (24.6)	<.001
10,000-19,999	90 (24)	9,783 (19.6)	.16	250,325 (21.5)	>.99
20,000-29,999	86 (22.9)	6,792 (13.6)	<.001	176,614 (15.1)	<.001
30,000-49,999	90 (24)	7,719 (15.4)	<.001	208,722 (17.9)	.01
>50,000	48 (12.8)	9,054 (18.1)	.04	243,822 (20.9)	<.001

[a]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

[b]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

Table 2. Demographics of all participants in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

	COCOVID study participant (N=1,030), n (%)	Ponce municipality residents (N=135,084), n (%)	*P* value[a]	Puerto Rico residents (N=3,263,584), n (%)	*P* value[a]
Age group (years)					
1-9	75 (7.3)	11,105 (8.2)	>.99	254,038 (7.8)	>.99
10-17	174 (16.9)	12,603 (9.3)	<.001	291,750 (8.9)	<.001
18-24	119 (11.6)	12,823 (9.5)	.20	316,387 (9.7)	.35
25-34	129 (12.5)	17,660 (13.1)	>.99	402,204 (12.3)	>.99
35-44	181 (17.6)	14,827 (11)	<.001	400,607 (12.3)	<.001
45-54	198 (19.2)	15,391 (11.4)	<.001	415,974 (12.7)	<.001
55-64	52 (5.1)	17,600 (13)	<.001	442,138 (13.5)	<.001
≥65	102 (9.9)	33,075 (24.5)	<.001	740,486 (22.7)	<.001
Female	550 (53.4)	70,555 (52.2)	.47	1,719,593 (52.7)	.67
Identify as Latino or Latina[b]	1021 (99.6)	134,560 (99.6)	.80	3,239,060 (99.2)	.27
Race[b]					
White	682 (68.9)	45,980 (34)	<.001	914,840 (28)	<.001
Black	102 (10.3)	5,171 (3.8)	<.001	200,391 (6.1)	<.001
Other	47 (4.7)	13,477 (10)	<.001	981,183 (30.1)	<.001
Multiple races	159 (16.1)	70,456 (52.2)	<.001	1,167,170 (35.8)	<.001

[a]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

[b]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

Compared to the overall populations of both Ponce and Puerto Rico, the COCOVID cohort population differed significantly by annual household income, age group, race, education level, and employment status (Tables 1-3). Households with at least 1 COCOVID participant more frequently belonged to middle income groups of US $20,000-US $29,999 (86/375, 22.93% in cohort vs 6792/50,007, 13.58% in Ponce and 176,614/1,165,982, 15.15% in Puerto Rico) and US $30,000-US $49,000 (90/375, 24.00% vs 7719/50,007, 15.44% and 208,722/1,165,982, 17.90%), and less frequently the highest, >US $50,000 (48/375, 12.80% vs 9054/50,007, 18.11% and 243,822/1,165,982, 20.91%), and lowest, <US $10,000 (61/375, 16.27% vs 16,659/50,007, 33.31% and 286,499/1,165,982, 24.57%), income groups (*P*<.05; Table 1). The cohort had relatively high proportions of participants in the age groups of 10-17 years (174/1030, 16.89% in cohort vs 12,603/135,084, 9.33% in Ponce and 291,750/3,263,584, 8.94% in Puerto Rico), 35-44 years (181/1030, 17.57% vs 14,827/135,084, 10.98% and 400,607/3,263,584, 12.28%), and 45-54 years (198/1030, 19.22% vs 15,391/135,084, 11.39% and 415,974/3,263,584, 12.75%), and low proportions of participants in the oldest age groups, 55-64 years (52/1030, 5.05% vs 17,600/135,084, 13.03% and 442,138/3,263,584, 13.55%), and ≥65 years (102/1030, 9.90% vs 33,075/135,084, 24.48% and 740,486/3,263,584, 22.69%; *P*<.001; Table 2). Cohort participants were more frequently identified as White (683/990, 68.99% in the cohort

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vs 45,980/135,084, 34.04% in Ponce and 913,840/3,263,584, 28.00% in Puerto Rico) or Black (102/990, 10.30% vs 5171/135,084, 3.83% and 200,391/3,263,584, 6.14%) and less frequently as another race (47/990, 4.75% vs 13,477/135,084, 9.98% and 981,183/3,263,584, 30.06%) or mixed race (159/990, 16.06% vs 70,456/135,084, 52.16% and 1,167,170/3,263,584, 35.76%; *P*<.001). For populations 25 years and older, cohort participants were less likely to have a less than high school education (38/659, 5.77% in cohort vs 19,235/98,553, 19.52% in Ponce and 488,780/2,401,409, 20.35% in Puerto Rico) and more likely to have some college or associate degree (186/659, 28.22% vs 21,209/98,553, 21.52% and 556,795/2,401,409, 23.19%) and a bachelor's degree or higher (268/659, 40.67% vs 31,402/98,553, 31.86% and 683,894/2,401,409, 28.48%; *P*<.001; Table 3). Additionally, cohort participants aged 25 years or older were more likely to be in the labor force relative to Ponce and Puerto Rico residents in the same age group, including in employed (356/644, 55.28% vs 35,976/98,553, 36.50% and 977,860/2,401,409, 40.72%) and unemployed groups (74/644, 11.49% vs 6037/98,553, 6.13% and 119,812/2,401,409, 4.99%; *P*<.001).

At enrollment, 1.55% (16/1030) of COCOVID participants were seropositive for SARS-CoV-2, of which the median age was 46 (IQR 33-51) years, 56.25% (9/16) were male, and half (50.00%, 8/16) reported chronic health conditions (Table 4). There was a significant difference in the timing of study enrollment among participants with and without baseline seropositivity for SARS-CoV-2, with a higher proportion of seropositive participants recruited in the later months of the study (*P*=.003). No significant differences by age group, sex, or household income were observed among participants that were seropositive and those that were seronegative at baseline.

Table 3. Education level and employment status of adult participants aged ≥25 years in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

	COCOVID study participants aged ≥25 years (N=662), n (%)	Ponce municipality residents aged ≥25 years (N=98,553), n (%)	*P* value[a]	Puerto Rico residents aged ≥25 years (N=2,401,409), n (%)	*P* value[a]
Educational attainment[b]					
Less than high school graduate	38 (5.7)	19,235 (19.5)	<.001	488,780 (20.4)	<.001
High school graduate or equivalent	167 (25.3)	26,707 (27.1)	>.99	671,940 (28)	.13
Some college or associate degree	186 (28.2)	21,209 (21.5)	<.001	556,795 (23.2)	.01
Bachelor's degree or higher	268 (40.7)	31,402 (31.9)	<.001	683,894 (28.5)	<.001
Employment status[b]					
Employed	356 (55.3)	35,976 (36.5)	<.001	977,860 (40.7)	<.001
Unemployed	74 (11.5)	6,037 (6.1)	<.001	119,812 (5)	<.001

[a]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

[b]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

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Table 4. Timing of study enrollment and demographics and of participants by serological evidence of previous SARS-CoV-2 infection at baseline, COPA COVID-19 (COCOVID) study, Ponce, Puerto Rico, between June 2020 and November 2021 (N=1030).

	Participants seropositive for SARS-CoV-2 at baseline (N=16), n (%)	Participants seronegative for SARS-CoV-2 at baseline (N=1014), n (%)	Prevalence of seropositivity for SARS-CoV-2 at baseline	*P* value
Timing of study enrollment				.003
June-August 2020	0 (0)	324 (32)	0	
September-November 2020	5 (31.3)	405 (39.9)	1.2	
December 2020–February 2021	10 (62.5)	268 (26.4)	3.6	
March 2021 or later	1 (6.3)	17 (1.7)	5.6	
Age group (years)				.24
1-17	1 (6.3)	248 (24.5)	0.4	
18-34	4 (25)	244 (24.1)	1.6	
35-49	5 (31.3)	301 (29.7)	1.6	
50-64	4 (25)	121 (11.9)	3.2	
≥65	2 (12.5)	100 (9.9)	1.9	
Sex				.46
Female	7 (43.8)	543 (53.6)	1.3	
Male	9 (56.3)	471 (46.5)	1.9	
Annual income for household (US $)[a]				.12
<10,000	3 (18.8)	172 (17)	1.7	
10,000-19,999	5 (31.3)	208 (20.6)	2.3	
20,000-29,999	0 (0)	234 (23.2)	0	
30,000-49,999	5 (31.3)	241 (23.9)	2	
>50,000	3 (18.8)	133 (13.2)	2.2	

[a]Participants that declined to respond were excluded from the denominator in percentage calculations (<3%).

Discussion

Few studies with prospective assessments of incident SARS-CoV-2 infections at the community level have been described to date, and none have been implemented in Puerto Rico or other primarily Latino or Hispanic US populations [17-19,43-45]. The COCOVID community-based cohort study provides a unique opportunity to assess SARS-CoV-2 infection incidence, risk factors, and outcomes in Puerto Rico and also help further characterize asymptomatic infections, household transmission, and serological and molecular testing dynamics. We were able to build the COCOVID study into an existing cohort study platform, allowing for rapid enrollment and the implementation of extensive data collection activities. Prospective follow-up through weekly PCR testing of participants and regular serology testing enabled comprehensive detection of SARS-CoV-2 infections within the cohort population. Additionally, our large sample size and extended follow-up period strengthened our assessment of SARS-CoV-2 incidence and outcomes by time-dependent factors, including lockdown measures, circulating SARS-CoV-2 variants, and COVID-19 vaccination status.

COCOVID surpassed its enrollment goal with 1030 participants with minimum sample size goals (n=215) reached in the 3 age groups of interest (1-17 years, 18-49 years, and ≥50 years). The cohort included participants with characteristics associated with increased COVID-19 morbidity risk [3,46,47], although sometimes with lower frequency than the general populations for Ponce and Puerto Rico. Consistent with these populations, almost all COCOVID participants identified as Latino/a. Chronic health condition prevalence was high among adults in the cohort and in accordance with estimates from the Behavioral Risk Factor Surveillance System [48]. The cohort had relatively low proportions of participants in the oldest (≥65 years) age group and households in the lowest (<US $10,000) annual income group compared to Ponce and Puerto Rico populations. However, these groups still accounted for at least 10% of cohort participants and households, respectively, which should facilitate adjusted analyses and extrapolation of results to the general population. SARS-CoV-2 seroprevalence at enrollment was low and increased among cohort participants enrolled later in the study period. The low but increasing seroprevalence of SARS-CoV-2 observed among study participants at baseline over time is consistent with surveillance data from the region [14]. As a result, there was a limited sample size to assess differences in SARS-CoV-2 seroprevalence by age group and other characteristics, and factors associated with the seroprevalence of SARS-CoV-2 infection will be explored more fully using follow-up data from the study.

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We did not use a formal sampling frame, but rather our sampling strategy was determined by logistic constraints to include a limited selection of community areas with primarily single-resident homes and no public housing or large apartment buildings. Additionally, most of our participants were previously enrolled in the larger COPA cohort, whose eligibility was restricted to participants younger than 50 years. This likely led to the observed oversampling of larger, middle-income households and employed, middle-aged adults and their children relative to the overall populations of Ponce and Puerto Rico. Additionally, individuals who agreed to enroll in COCOVID (and COPA) may be more concerned about disease risks and more likely to take measures to prevent SARS-CoV-2 infection than the general populations of Ponce and Puerto Rico. However, there was diversity across sociodemographic indicators in our study population, and the detailed data collected on household and individual characteristics and preventive behaviors can be used to adjust for these potential impacts on SARS-CoV-2–related outcomes and extrapolate our findings to the general population, where possible.

Despite tremendous progress in our understanding of SARS-CoV-2 transmission and control, including the development of effective vaccines, the persistence of health inequities and other challenges underpin the need for more comprehensive data to inform mitigation measures and prevent future outbreaks. The COCOVID study provides a valuable opportunity to investigate community and household SARS-CoV-2 infections in a primarily Hispanic or Latino population with diversity across several risk factors for COVID-19. Study methodology supports thorough detection of asymptomatic and symptomatic infections to help us better estimate the burden of SARS-CoV-2 in the region and assess the limitations of surveillance, which currently remains the primary resource for SARS-CoV-2 data for the island.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to data security and confidentiality guidelines determined by the study governance board, but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AIS: acute illness surveillance
CDC: Centers for Disease Control and Prevention
COCOVID: Communities Organized to Prevent Arboviruses COVID-19
COPA: Communities Organized to Prevent Arboviruses
DB: Dengue Branch
DENV: dengue virus
Ig: immunoglobulin

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N: nucleocapsid
PCR: polymerase chain reaction
RBD: receptor binding domain
REDCap: Research Electronic Data Capture
rRT-PCR: real-time reverse transcriptase–polymerase chain reaction
S: spike

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Protocol

Capturing the Dynamics of Homelessness Through Ethnography and Mobile Technology: Protocol for the Development and Testing of a Smartphone Technology–Supported Intervention

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Abstract

Background: US military veterans who have experienced homelessness often have high rates of housing transition. Disruptions caused by these transitions likely exacerbate this population's health problems and interfere with access to care and treatment engagement. Individuals experiencing homelessness increasingly use smartphones, contributing to improved access to medical and social services. Few studies have used smartphones as a data collection tool to systematically collect information about the daily life events that precede and contribute to housing transitions, in-the-moment emotions, behaviors, geographic movements, and perceived social support.

Objective: The study aims to develop and test a smartphone app to collect longitudinal data from veterans experiencing homelessness (VEH) and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless.

Methods: This study's design had 3 phases. Phase 1 used ethnographic methods to capture detailed data on day-to-day lived experiences of up to 30 VEH on topics such as housing stability, health, and health behaviors. Phase 2 involved focus groups and usability testing to develop and refine mobile phone data collection methods. Phase 3 piloted the smartphone mobile data collection with 30 VEH. We included mobile ethnography, real-time surveys through an app, and the collection of GPS data in phase 3.

Results: The project was launched in June 2020, and at this point, some data collection and analysis for phases 1 and 2 are complete. This project is currently in progress.

Conclusions: This multiphase study will provide rich data on the context and immediate events leading to housing transitions among VEH. This study will ensure the development of a smartphone app that will match the actual needs of VEH by involving

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them in the design process from the beginning. Finally, this study will offer important insights into how best to develop a smartphone app that can help intervene among VEH to reduce housing transitions.

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KEYWORDS

ethnography; homelessness; housing transitions; longitudinal data; military; mobile technology; smartphone; social support; veterans

Introduction

Background and Rationale

US military veterans are at greater risk of homelessness compared to their civilian counterparts [1,2]. Those experiencing homelessness are at increased risk of premature mortality, with a 2-decade–shorter life expectancy than the general population [3]. They experience an elevated burden of mental illness, substance use disorder, hypertension, and cardiovascular disease [4-6] as well as infectious diseases such as HIV or AIDS, tuberculosis, and hepatitis C [7]. Although homelessness is often episodic, it can occur over a long period of time for some. Commonly, those experiencing homelessness transition between different types of accommodations: homeless shelters, doubled-up with family or friends, or staying in places not meant for human habitation (eg, encampments, vehicles, and abandoned buildings) [1]. These frequent housing transitions likely exacerbate poor health, social well-being, and economic vulnerability [8,9]. There is a major gap in detailed, contextual knowledge of these transitions, such as information about in-the-moment emotions, behaviors, geographic movements, and perceived social support.

Having a greater understanding of these in-the-moment experiences may help inform efforts to better identify people who are at risk of an unexpected or unwanted housing transition and intervene to prevent a homeless episode. Without real-time information, it is difficult to understand the point-in-time contextual nuances of an individual's housing transition and provide support to mitigate these transitions. Previous work, whether quantitative or ethnographic, has been limited by the methodological difficulty of retrospectively gathering this type of contextual data about distinct points in time in the past [10,11]. Studies show that perceptions of emotions and behaviors are unreliable when gathered retrospectively [12,13]. Another factor that has limited understanding of the nuances of transition among veterans experiencing homelessness (VEH) is their lack of trust in people generally and in certain entities in particular (eg, "government") [14]. Previous research indicates that smartphones are already being widely used by homeless populations, and those populations view smartphones as a trusted source to communicate and receive information [15,16]. Smartphone technology shows promise for enhancing our understanding of short-term precipitants and helping us gain a better understanding of the in-the-moment experiences that lead to housing transitions.

Smartphone apps support the collection of real-time data, which involves the use of ecological momentary assessment (EMA). EMA allows researchers to measure participants' real-world emotions and behaviors in real-time in their natural environments [17]. Mood has been identified in numerous studies as being predictive of activity; it interacts with social support [18], is an indicator of daily stressors [19], and acts as a mediator of a variety of outcomes [20]. Additionally, technology such as GPS, which can be collected through smartphones, can provide accompanying information on daily changes in geographic movement. When analyzed with other data, this may provide insight on potential factors that precipitate a housing transition. Yet few studies have used smartphone apps to gather detailed, contextual knowledge on housing transitions among VEH. Notably, smartphone ownership among persons experiencing homelessness is growing and almost equivalent to that of the general population [21,22].

Thus, this study is among the first to design and test the feasibility and acceptability of a smartphone app that uses real-time surveys and GPS to collect longitudinal data from a population that is unstably housed. This protocol paper details the specific phases and methods used to prepare for and conduct a longitudinal smartphone data collection study with a sample of veterans.

Objective

We aim to develop and test a smartphone app to collect longitudinal data from VEH and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless.

Methods

Participating Institutions

The US Department of Veterans Affairs (VA) Center for Healthcare Organization and Implementation Research (CHOIR) leads the study. CHOIR invited university partners to participate to provide the types of additional expertise needed for this initiative. Joining the team are members of Boston University's Software and Application Innovation Lab (SAIL). SAIL is a professional research, software engineering, and consulting lab that acts as both a driver and a collaborative partner for computational and data-oriented research efforts. Also joining are RK, a demographer from the University of California Los Angeles, and NFS, a sociologist from the University of California Irvine. RK brings expertise in defining study populations, including extensive experience studying and conducting interventions for persons experiencing homelessness, and NFS has a depth of expertise in developing smartphone data collection tools for vulnerable populations.

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Design

This multistage study involves identifying the needs of VEH, designing an app, and pilot-testing it (Figure 1). Phase 1 involves repeated interviews over a 30-day period to understand app use and contexts of app use among persons at risk for or experiencing either chronic or recent homelessness. Phase 2 involves focus group discussions with VEH to members check the interview findings from phase 1 and develop survey questions to be used in the designed app. Additionally, user testing methods will be used to refine questions as needed. Lastly, in phase 3, we will test the feasibility and acceptability of the developed app with a sample of VEH.

Figure 1. Project design showing the 3 phases of the project. VEH: veterans experiencing homelessness.

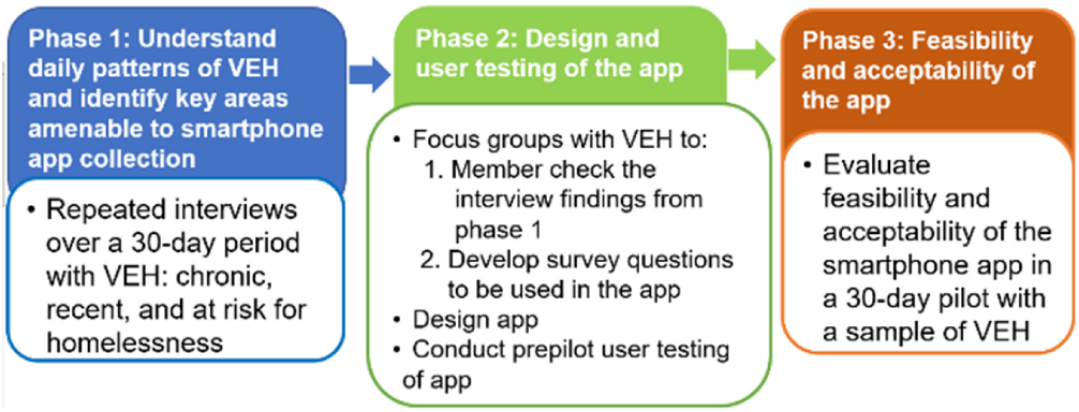

Study Settings

The study is being conducted at 2 locations in the northeastern region of the United States to achieve diversity in the participant samples. Site 1 is one of the VA health care system's 172 medical centers, located about 15 miles north of a major city. It is one of the largest providers of services to VEH and provides a range of health and social services to veterans living in suburban and rural areas. This site is a multiservice residential program serving veterans who are experiencing homelessness or at risk for homelessness. Site 2 is located in the center of a dense urban area. This site is a multiservice community-based residential program serving veterans who are experiencing homelessness and at risk for homelessness.

Phase 1: Understand Daily Patterns of VEH and Identify Key Areas Amenable to Smartphone App Collection

Sampling of Participants and Recruitment

Using a convenience sampling strategy, we will recruit participants from 3 locations with a range of experiences with homelessness, including chronic homelessness, a recent onset of homelessness, or being at-risk for homelessness. For the purposes of this study, we define chronic homelessness as having a pattern of multiple episodes (or a single long episode) of homelessness over an extended period (ie, a year or more). We define recent onset as newly homeless, with the period of homelessness having begun in the last 6 months but not having a history of being chronically homeless. Lastly, we define being at risk as being at imminent risk of losing one's housing [23]. Recruitment will begin with the study team hosting informational sessions, followed by sharing and posting flyers at the residential programs at sites 1 and 2. Those who express interest will be approached by study team members during informational sessions or later contacted by telephone. They will then be screened for their current homeless experience (chronic, recent-onset, and at-risk) to confirm that they meet eligibility criteria.

Procedures

A 30-day focused ethnographic data collection design will be used to understand the daily patterns of VEH and identify key areas amenable to smartphone app collection. Individuals will be interviewed multiple times over a 30-day period. This time frame will be consistent with the one planned for the phase 3 pilot study of smartphone-enabled data collection and will offer proof of the concept of engagement in this later work. The focused ethnographic approach will include four different types of interviews. Interview types will include (1) a baseline, historical interview (with structured and open-ended components) that will last between 60 and 90 minutes; (2) long interviews that will focus on a "special topic" (perceptions of health, social services, and technology, including the use of smartphones) of interest to the study and will last approximately 60 minutes; (3) a general short interview, twice a week, that will last approximately 15 minutes; and (4) a final follow-up interview to obtain feedback on participation in the multiweek study. Textbox 1 shows an overview of the interview schedule, and Textbox 2 shows a description of interview topics.

Both the long and short interviews will provide an opportunity to ask VEH their opinions about the most important things to ask on a regular basis that might influence stability in housing, how to ask about sensitive topics like substance use, and about potential concerns with answering questions through a smartphone app.

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Textbox 1. Phase 1 30-day illustrative interview schedule.

Weeks and interview schedule

- Week 1: baseline interview 1, short interview 2, short interview 3, and long interview 4
- Week 2: short interview 5, short interview 6, and long interview 7
- Week 3: short interview 8, short interview 9, and long interview 10
- Week 4: short interview 11, short interview 12, and final interview 13

Textbox 2. Interview types and the structured and unstructured ethnographic data collected over the course of the phase 1 30-day interviews.

Interview types and descriptions

- Baseline interview: This interview is designed to:
  - Gain a deeper understanding of participants' housing history using a modified Residential Time-Line Follow-Back Inventory [24].
  - Collect information on key social relationships, military experiences, and employment opportunities that may have influenced the life course of veterans experiencing homelessness.
  - Collect and record demographic information on a short survey form.
- Long qualitative interviews: longer "special topic" interviews to gain insights into 3 different topics
  - Physical and mental health (eg, perception of overall health, experience with physical and mental health conditions and the extent to which they impact everyday life, and perceptions of the impact of health conditions on housing stability) and its impact on housing stability.
  - Access to and use of social services (eg, places participants go for financial, logistical, or social support to meet needs, facilitators, and barriers to accessing different types of support, and perceptions of how support influences housing stability).
  - Use of technology (eg, types and uses of phones, including common apps and phone features).
- Short qualitative interviews: interviews will occur 2-3 times per week, last approximately 15 minutes, and happen between the longer special topic interviews. These interviews will explore participants' feelings, where they slept the night before, and any changes in their lives since the last conversation.
- Final interview: a 60-minute interview to obtain feedback from participants on the experience of engaging with a research team over a prolonged period.

Analysis Phase 1

Quantitative Data Analyses

Demographic characteristics like recent life experiences, homelessness episodes, overall health and health conditions, and social service use of participants will be entered into an Excel (Microsoft Corporation) spreadsheet. We will use descriptive statistics to summarize the characteristics of these participants.

Qualitative Data Analyses

All interviews will be professionally transcribed verbatim. Data will be analyzed using a Rapid Assessment, Response, and Evaluation approach [25], which uses a multidisciplinary team to collect different types of data that can be synthesized and analyzed iteratively and efficiently to generate an understanding of critical health and public health issues. Each participant in phase 1 will have a portfolio of data from their multiweek study period. Analysis will entail attention to both the cumulative story and key changes that might impact housing transitions or health. Once the transcript of each interview is available, a standardized template will be created to systematically summarize data with attention to transitions in housing and health for each participant. The summarized information will be examined to identify patterns, common concepts, and emerging ideas about current events and experiences that influence transitions in housing and health. For each participant, the lead interviewer will compile and analyze the portfolio of data. They will create a summary template that systematically synthesizes the data across the 4 weeks of data collection. This summary template will contain key fields such as transitions in housing and health for each participant, as well as key events such as fluctuations in mood and disposition, social networks, and experience with health and social services. After completion, a second team member, not involved in that participant's data collection, will review the summary template. The team will discuss the data until consensus is reached. This process will ensure consistency, clarity, and rigor. Following this process, team members will be designated to draft questions aligned with transitions in housing, health, and key events. These members will be instructed to first look for validated questions that may be appropriate. If none exist, they will draft questions for group review. Through a series of meetings, the full team will review all drafted questions and make decisions about which ones to include, exclude, and modify for a smartphone app format. This information will be used to inform phase 2 data collection and analysis.

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Phase 2: Design and User Testing of the App

Sampling of Participants and Recruitment

Phase 2 will use the same recruitment and consenting strategy as phase 1. Phase 2 focus group participants will be recruited from site 2.

Procedures

Focus Groups

Focus groups will take place at a nearby VA hospital and on-site at the residential program. These discussions will provide an opportunity to build on the phase 1 findings and further explore how to recruit, enroll, and retain VEH in a future, app-based study planned in the next phase. The focus group participants will be asked for their general perceptions of taking part in a research study that uses a smartphone app for data collection and recommendations regarding how to (1) introduce and explain a study that uses the collection of data through a smartphone app, (2) explain the ways in which privacy and confidentiality will be maintained, (3) ask about potentially sensitive topics, such as substance use and relationship conflict, and (4) assess capacity to participate using a smartphone app. Participants will also be provided a brief questionnaire to obtain specific information about their access to and use of technology generally, and specifically smartphones.

We will also inquire about what types of information participants would be willing to provide researchers through their mobile phones, the acceptability of having GPS locations tracked, and any locations where they would not want GPS. We will show the focus group participants a mockup data map of an individual's GPS generated locations and movements to facilitate discussion. We will also inquire about other data collection methods, such as passively collected call logs. We will share with participants mockups of what call log data would look like to researcher team members. We will also emphasize that there will be encryption built into the software to address concerns about privacy. Feedback from the focus groups will be used to adjust the prototype of the smartphone app and guide revisions to phase 3 protocols. Focus group discussions will last approximately 60 minutes and will be facilitated by one of the anthropologists on the study team.

Development and Usability Testing

Smartphone app development will be informed by data from phase 1 ethnographic and phase 2 focus group findings. Usability testing will involve 5 VEH participants reviewing app mockups. Participants will be asked to provide feedback about the home screen, survey screen layouts, survey response options, and settings screen. Usability testing will occur approximately 2-3 months after the focus groups, when the mobile app has reached functionality. SAIL team members will provide mobile phones preloaded with the app. A member of the study team with qualitative expertise will record notes in a data collection template about overall design, ease of use, and specific wording and phrases used in the app during usability testing. Participants will use a smartphone to complete a defined set of tasks, such as turning on the phone, turning GPS off and on, responding to EMA and survey questions, etc. We will follow usability protocols and assessments, including time to complete tasks, participant error rates, software errors, etc. The team member will also ask participants about the burden of answering questions and about issues of privacy and trust. The SAIL development team will incorporate lessons from focus groups and usability assessment into the final version of the smartphone app for the phase 3 pilot. Usability assessments will be conducted by research staff who have been trained in usability assessment procedures by the SAIL mobile development group.

Analysis Phase 2

Phase 2 Focus Groups

The phase 2 focus groups and mobile app design data will include (1) the use of focus groups to gather information about the frequency of data collection, privacy issues, and incentives, and (2) the use of both phase 1 ethnographic data and phase 2 focus group data to develop a smartphone app and perform app usability testing.

Qualitative Data Analyses

All focus groups will be professionally transcribed verbatim. Thematic analysis [26] will be used by the focus group leads to analyze the data, which will be shared with the full team for an analytic discussion. Transcripts will later be combined with the phase 1 data for a global discussion of implications for the phase 3 pilot.

Phase 3: Feasibility and Acceptability Pilot of the App

Sampling of Participants and Recruitment

Phase 3 will use the same recruitment and consenting strategies as the previous phases. Phase 3 participants will also be recruited from sites 1 and 2.

Procedures

Baseline Interview and Demographics

At enrollment in phase 3, study team members will conduct semistructured qualitative interviews to gather structured data on demographics, recent life experiences, homelessness episodes, overall health and well-being, impairments, supportive relationships, and technology use. During the interview period, participants will be guided on how to download the app and will be provided with an orientation on how to use the app. The baseline interview will last about an hour.

30-day Smartphone App Data Collection

We will recruit up to 30 participants who will use the app to daily answer survey questions related to housing transitions, health service usage, medication adherence, emotional states, and social relationships [27,28]. About 2 days a week (Wednesday and Saturday evening), participants will receive a longer app survey with additional questions about health care, substance use, and the ongoing quality of specific social relationships. The questions on substance use and social relationship quality will be based on data collected during the baseline survey and qualitative interview. We will also collect information on veterans' activity space (the local areas within which people move or travel over the course of their daily activities) and proximity to health or social services by using

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GPS [29]. GPS data will primarily be used to characterize the overall extent and variability of the activity space.

Follow-Up Interview

At the end of the 30-day pilot, a final follow-up interview will be conducted, using both structured and qualitative components. The interview will be conducted to document participant experiences and perceptions about the app data collection, including issues relating to trust, data security, maintaining phones, and the usability of EMA and mobile surveys. Participants will be allowed to view their survey and GPS data to offer insight into specific ambiguous survey responses and validate the general accuracy of the data set. This information will be used in a later analysis.

Analysis Phase 3

The phase 3 feasibility and acceptability pilot of mobile phone data will include 2 interviews (baseline and follow-up), as well as the mobile survey, GPS, and EMA data.

Qualitative Data Analyses

Baseline and final interview data will be organized and analyzed using the processes described in phase 1. The coding will closely follow the topics covered in the interview guide around performance and effort expectancy, social norms, facilitating factors, and trust.

Quantitative Data Analyses

First, we will use descriptive statistics to summarize the structured items collected from the baseline interviews, including information about participants' demographic characteristics, recent life experiences, homelessness episodes, overall health and health conditions, and social service use. Second, we will use sequence analysis to identify distinct patterns of housing transitions. Third, we will perform convergent integration of the qualitative and quantitative data to assess how contextual characteristics, including mood, activity space size, social support, medication adherence, and usage of health services, are related to housing transition patterns. Fourth, we will use mixed effects regression models to assess how daily changes in contextual characteristics are associated with daily experiences of housing stability (and major health events).

Ethical Considerations

Ethical approval was given by the VA Bedford Institutional Review Board (1626836-16), in accordance with VA guidelines. Written informed consent will be sought from all participants. Phase 1 participants will be provided written informed consent and will receive up to US $185 reimbursement over the course of the study (US $25 for the baseline, follow-up, and long interviews and US $10 for each brief interview). Phase 2 participants will receive US $25 upon completion of their focus group. Phase 3 participants will be offered US $30 for the baseline and follow-up interviews and US $5 per survey completed in the app for a possible total compensation of US $340. Study ID numbers will be assigned to participants to ensure confidentiality. We sought additional protections and obtained a federal Certificate of Confidentiality from the US National Institutes of Health because of the sensitive nature of the study discussions. Certificates of confidentiality protect the privacy of research subjects by prohibiting the disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. It is not possible to create a minimal data set with this qualitative data.

Results

The project was launched in June 2020, and as of December 2022, we had enrolled 10 participants for phase 1 and 9 participants for phase 2. Data collection and analysis for phases 1 and 2 are complete. This project is currently in progress.

Discussion

Principal Results

VEH are extremely vulnerable to experiencing housing transitions compared to their civilian counterparts [1,2]. A significant gap remains in research approaches to understanding the short-term precipitants and influences upon housing transitions. The use of smartphone apps can help fill the significant gaps in our knowledge, including, (1) the sequence of events leading up to and immediately after housing-related transitions; (2) information about the housing status of veterans not included in administrative systems, such as those who are living double-up or are street homeless; and (3) potential "early warning" signals gleaned from near-real–time reports of mood, activities, social support, and activity spaces (constructed from passively collected GPS data) that may presage increasing housing instability, a homelessness episode, or a major health event. This protocol paper details the specific phases and methods that will be used to develop and test a smartphone app to collect longitudinal data from VEH and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless. This multiphased research will provide contextual knowledge on how in-the-moment experiences precipitate housing transitions from the perspective of VEH.

Furthermore, engaging participants from a range of housing situations—street homeless, transitional housing, residential treatment programs, and shelters—in the development of the smartphone app will allow us to capture what VEH thinks is significant to include in the app, thus enhancing its potential uptake [30,31]. To our knowledge, this will be the first test of active and passive smartphone-enabled data collection applied to the study of homelessness among veterans. At a minimum, the information gained from this project will lay the groundwork for enhancements to clinical programs that incorporate smartphone data for early intervention or use smartphone tools for 2-way communication between patients and clinical teams to improve care access and engagement for vulnerable populations.

Limitations

While our design methods during phases 1 and 2 will offer rich and nuanced insights to guide the content and design of the smartphone data collection app, there are a few limitations worth noting. First, there are usually difficulties in contacting and recruiting certain VEH, which could bias this study because we

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may miss the most vulnerable and extreme cases. Thus, we will work closely with our staff at sites 1 and 2 to reduce selection bias. Second, VEH tends to report a lack of trust due to poor previous experiences with health care providers and mistrust of government institutions. We will try to establish a relationship of trust between the interviewer and VEH participants to obtain the most reliable data possible. Finally, although this will be an evaluation of VEH, our results may be applicable to non-VEH populations, contexts, and activities.

Conclusions

This multiphased study will provide rich data on the context and immediate events leading to housing transitions among VEH. This study will ensure the development of a smartphone app that will match the actual needs of VEH by involving them in the design process from the beginning. Finally, this study will offer important insights on how best to develop a smartphone app that can help intervene among VEH to reduce housing transitions.

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Data Availability

The underlying data for this study consists of in-depth, qualitative interviews with veterans experiencing homelessness. The data sets generated or analyzed during this study are not publicly available due to participant privacy but may be available from the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

CHOIR: Center for Healthcare Organization and Implementation Research
EMA: ecological momentary assessment
SAIL: Software & Application Innovation Lab
VA: Veterans Affairs
VEH: veterans experiencing homelessness

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Protocol

Supportive Care Needs in Chinese, Vietnamese, and Korean Americans With Metastatic Cancer: Mixed Methods Protocol for the DAWN Study

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Abstract

Background: Asian Americans with metastatic cancer are an understudied population. The Describing Asian American Well-Being and Needs in Cancer (DAWN) Study was designed to understand the supportive care needs of Chinese-, Vietnamese-, and Korean-descent (CVK) patients with metastatic cancer.

Objective: This study aims to present the DAWN Study protocol involving a primarily qualitative, convergent, mixed methods study from multiple perspectives (patients or survivors, caregivers, and health care professionals).

Methods: CVK Americans diagnosed with solid-tumor metastatic cancer and their caregivers were recruited nationwide through various means (registries, community outreach newsletters, newspapers, radio advertisements, etc). Potentially eligible individuals were screened and consented on the web or through a phone interview. The study survey and interview for patients or survivors and caregivers were provided in English, traditional/simplified Chinese and Cantonese/Mandarin, Vietnamese, and Korean, and examined factors related to facing metastatic cancer, including quality of life, cultural values, coping, and cancer-related symptoms. Community-based organizations assisted in recruiting participants, developing and translating study materials, and connecting the team to individuals for conducting interviews in Asian languages. Health care professionals who have experience working with CVK patients or survivors with metastatic solid cancer were recruited through referrals from the DAWN Study community advisory board and were interviewed to understand unmet supportive care needs.

Results: Recruitment began in November 2020; data collection was completed in October 2022. A total of 66 patients or survivors, 13 caregivers, and 15 health care professionals completed all portions of the study. We completed data management in December 2023 and will submit results for patients or survivors and caregivers to publication outlets in 2024.

Conclusions: Future findings related to this protocol will describe and understand the supportive care needs of CVK patients or survivors with metastatic cancer and will help develop culturally appropriate psychosocial interventions that target known predictors of unmet supportive care needs in Chinese, Vietnamese, and Korean Americans with metastatic cancer.

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KEYWORDS

Asian American; disparities; metastatic cancer; psychosocial; supportive care; unmet needs; well-being

Introduction

Overview

Cancer is the leading cause of death for Asian Americans, the fastest-growing US immigrant group projected to outnumber Hispanic or Latinx immigrants by 2065 [1]. However, only 0.17% of the National Institutes of Health (NIH)–funded clinical research studies have involved Asian American, Native Hawaiian, and Pacific Islander participants (1992-2018) [2], and other foundational funding sources show a similar disparity for Asian Americans [3]. Of the many mental and physical health topics requiring further investigation [3], metastatic cancer survivorship is a significant priority given that Asian Americans are often diagnosed with a distant stage of cancer [4] such as Chinese Americans and Korean Americans with later staged colorectal cancer [5,6]. While progress in treatments and earlier detection have improved cancer survival rates overall [7], metastatic disease remains the major cause of cancer mortality [8]. The provision of quality supportive care is needed for Asian Americans with metastatic cancer, yet very little is known about the needs and preferences of this population. While the National Cancer Institute has funded cancer survivorship science since 1996, a 2020 analysis of NIH-funded research in advanced or metastatic cancer survivorship reported no studies of Asian Americans with metastatic cancer, and past survivorship research typically focused on survivors without detectable disease or active treatment [9,10]. Moreover, Asian-heritage cancer survivors are more likely to experience care-quality disparities [11], with those who are foreign-born especially likely to report unmet supportive needs after controlling for demographic and socioeconomic factors, health system and health care access, and comorbidities [12].

Psychosocial care needs are particularly important to evaluate, as the highest level of psychosocial distress is found in patients with advanced stages of disease [13]. These include anxiety, depression, death anxiety, demoralization, and a perceived inability to cope effectively, which can result in poor quality of life and premature mortality [14,15]. Patients with metastatic cancer have different needs, goals, and physical and psychosocial symptoms compared to patients with earlier-stage cancer, with individuals with metastatic cancer facing greater uncertainty about their prognosis and fear of disease progression [10,16,17]. Evidence suggests early supportive care needs (ie, after diagnosis in active treatment) should also be examined, as it can result in better quality of life and a reduction in functionally impairing symptoms [18].

Chinese-, Vietnamese-, and Korean-descent (CVK) Americans experience greater cancer-specific mortality in contrast to other Asian ethnic groups [19-22] and likely experience difficulties accessing high-quality care due to 46%-60% reporting limited English proficiency [23]. Very little is known about CVK Americans' metastatic cancer survivorship and how similarities in philosophical traditions, values, and norms may guide distinct views about what is optimal for supportive care in metastatic cancer (eg, Confucian-heritage–based interdependent norms for East and Southeast Asian ethnic groups [24,25]). For example, Confucian-heritage individuals' self-concept often includes close others [26,27] and CVK patients' supportive care needs may be influenced by social harmony-based expectations such as self-sacrifice amid profound stress [28,29] or preferring indirect support [30] to minimize direct discussion of stigmatizing subjects such as cancer [31-33]. Supportive interventions or resources that allow for a reduction in directly verbalizing distress may be preferred (eg, writing [34] or use of web-based or social chat platforms [35]). As such, this generative study aimed to produce an initial glance at the supportive care needs and preferences of CVK patients or survivors. Multiple perspectives were sought as cancer survivorship care is coordinated across multiple levels, including close interpersonal relationships, health care organizational settings, and community settings [36]. This protocol outlines the multilevel assessment undertaken through multiple informants and study components.

Objectives

This study aims to present an embedded mixed methods study protocol for examining the supportive care needs and preferences of CVK patients or survivors with metastatic cancer through multiple informants (patients, caregivers, and health care professionals). To our knowledge, this is the first multiperspective study focused on Asian American metastatic cancer survivorship. This protocol will allow for an understanding of the components of the study, and findings from this study will refer to this protocol to showcase how community-engaged collaboration aided the development of culturally relevant, adapted psychosocial interventions or resources targeting known predictors of continued unmet supportive care needs.

Methods

Overview

We conducted a qualitative (QUAL) and quantitative (quan) convergent mixed methods study on supportive care needs with CVK survivors living in the United States and diagnosed with solid-tumor metastatic cancer (Figure 1). A convergent mixed methods design was selected to provide a rich description of supportive care needs, including any similarities or discrepancies in self-reporting through interview or survey assessment. The strength of a convergent design is its ability to collect both qualitative and quantitative data simultaneously and promptly, which fits well with the generative "snapshot" purpose of this study given the lack of knowledge about conducting research with this understudied population diagnosed with stage IV cancer. With guidance from a qualitative expert (coauthor MKS), the qualitative portion was prioritized to engage an understudied population of cancer survivors who may face cancer-related stigma due to cultural beliefs about cancer. We invited survivors' caregivers to provide their perspective on survivors' supportive care needs through interviews. Health

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care professionals' perspectives on the supportive care needs of CVK metastatic cancer patients or survivors and their families were also examined qualitatively. All study materials were matched to participants' language preferences in English, traditional Chinese, simplified Chinese, Vietnamese, and Korean.

Figure 1. Convergent mixed methods design and timeline. CVK: Chinese-, Vietnamese-, and Korean-descent; QOL: quality of life; SCN: supportive care need; SCNS-ST-9: Supportive Care Needs Survey-Screening Tool.

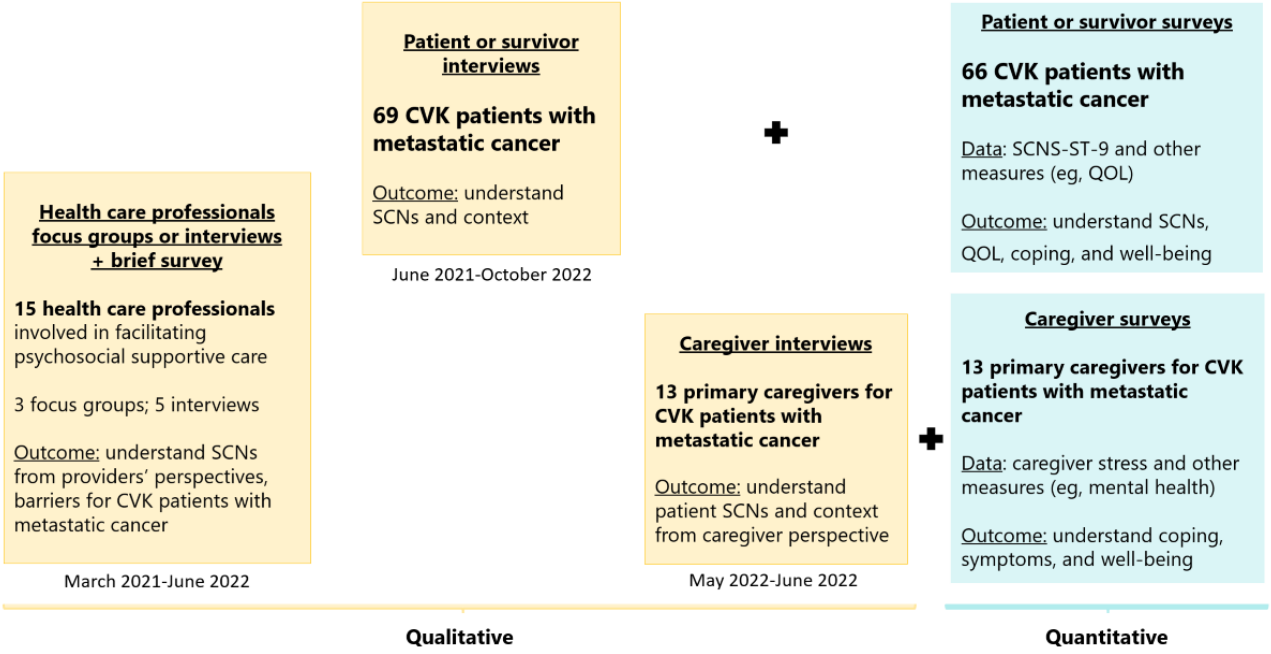

Participants

The study population included CVK individuals with solid-tumor metastatic cancer and caregivers (aged ≥18 years) living in the United States. Patients or survivors and caregivers were primarily recruited through partnered community outreach and supplemented by the University of California, San Francisco CARE (Collaborative Approach for Asian Americans, Native Hawaiians, and Pacific Islanders Research and Education) Registry and the University of California, Los Angeles (UCLA) Cancer Registry. Trained bilingual research assistants who speak English and Chinese (Mandarin or Cantonese), Vietnamese, or Korean called potential patient or survivor and caregiver participants to introduce and explain the study, screen for eligibility, and obtain consent for participation. Patient or survivor and caregiver participants received a US $90 e–gift card upon completing all parts of the study (brief demographic questions, interview, and survey). Patient or survivor participants who started the study but were unable to complete it, or declined to further participate for health reasons were also sent US $90 e–gift cards for their efforts. Health care professionals received a US $100 e–gift card upon completing the study.

Eligibility Criteria

The inclusion criteria for patients or survivors were (1) individuals diagnosed with de novo or recurrent, stage IV, solid tumor metastatic cancer; (2) self-identifying as Chinese, Vietnamese, or Korean and fluent in English, Korean, Cantonese, Mandarin, or Vietnamese; (3) aged 18 years or older; and (4) living in the United States. The inclusion criteria for caregivers were (1) individuals who self-identified or were patient- or survivor-identified as the primary caregiver (a close relative, friend, or partner who is doing most of the work to help take care of daily activities or medical care) for a person diagnosed with de novo or recurrent solid tumor metastatic cancer; (2) aged 18 years or older; and (3) living in the United States. If any patient or survivor or caregiver reported a diagnosis of schizophrenia or bipolar disorder, post hoc exclusion was to be considered based on any evidence of cognitive impairment presented to the research team during interactions or interviews. Health care professionals were eligible if they (1) were involved in facilitating patients' connection to or providing supportive care; (2) have been practicing at their medical or health center-related organization for 6 months or more; and (3) regularly worked with or have worked with at least 2 Chinese, Vietnamese, or Korean American patients with metastatic cancer.

Recruitment

Patient or survivor participants were initially recruited from the Greater Los Angeles Area and Orange County in Southern California. Recruitment was expanded nationwide due to limitations in reach and access resulting from the study being conducted during the height of the COVID-19 pandemic. Advertising and community outreach were focused on locations with a greater presence of Chinese, Vietnamese, and Korean communities (Los Angeles-San Gabriel Valley region, San Francisco Bay Area region, Buena Park, La Palma, Little Saigon area in Orange County, Irvine, Houston, Seattle, New York, etc). A majority of participants were recruited through flyers and community outreach (community organizations, churches, temples, libraries, community centers, senior centers, and ethnic supermarkets), physician referrals, doctor's offices, hospices, coverage on ethnic television, radio, or newspapers, social media

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(Facebook and Instagram), and word-of-mouth. Partner community organizations (Chinese American Coalition for Compassionate Care [CACCC] 美華慈心關懷聯盟 and the Vietnamese American Cancer Foundation [VACF] H i Ung Th Vi t M) helped increase word-of-mouth recruitment by using their websites, social media, and radio broadcasts to publicize the research. VACF lay navigators actively distributed study flyers with their community during the organization's events, such as the drive-by COVID-19 relief resource distribution. Participants were also later recruited through the University of California, San Francisco CARE Registry and the UCLA Cancer Registry when open to non-COVID-19 research. Recruitment efforts for caregivers began with paired dyads for more focused qualitative synthesis; thus, we first recruited through patient or survivor participants who identified their primary caregivers and gave assent for contact. Following this, the research team sought to recruit caregivers unpaired with patient or survivor study participants.

Health care professionals were recruited through the Describing Asian American Well-Being and Needs in Cancer (DAWN) Study community advisory board members' referrals of those who may best understand the supportive care needs of CVK adults with metastatic cancer, based mostly in Southern California.

Analysis Plan

The patient or survivor and caregiver interviews were transcribed in English, Mandarin, Cantonese, Korean, and Vietnamese. Asian language transcripts were translated, and English transcripts will be analyzed. The health care professional interviews and focus groups were transcribed in English. All transcription and translation work was reviewed and corrected by the multilingual research team. All qualitative data will be examined for thematic content with reflexive thematic analysis [37,38]. Reflexive thematic analysis is a theoretically flexible approach that allows for the presentation of shared meaning in data by emphasizing researcher reflexivity as a key process in the analysis and acknowledging that the findings are embedded in this context [37,38]. Self-reflexivity will be emphasized before and throughout the analysis and interpretation. Coders and the principal investigator (JHJK) will discuss the influence of their backgrounds and preconceptions and keep memos for a record of analysis and interpretations. As the lead investigator (JHJK) approaches research with a critical realist framework and is a clinical psychologist with knowledge of mental health service use disparities, cultural variations in symptomatology and coping, and stressors faced by immigrant families, findings are likely to be influenced by this perspective.

The research team will first familiarize themselves with the data through independent reading of the interview transcripts and generate initial codes and candidate themes to engage in reflexive thematic analysis. Inductive "bottom-up" coding will be completed first for a full description of participants' perspectives and experiences. Then, deductive "top-down" coding will be performed centered on the research question and any relevant supportive oncology concepts of additional significance. Themes will be reviewed and refined to best represent participant perspectives. Seeking saturation and minimum sample sizes is not compatible with reflexive thematic analysis, and our sampling was pragmatic and acceptable within reflexive thematic analysis (ie, the research team sought to conduct as many qualitative data collections as possible during the project period). Self-reported supportive care needs, demographics, and medical variables will also be summarized with univariate statistics. Chi-square tests will examine any differences in supportive care needs (eg, US- or foreign-born). Joint display results will be produced for the supportive care needs described by CVK patients or survivors. For the health care professionals' parallel-format focus group and interview data, candidate themes were compared across the focus group data and interview data to arrive at final themes.

Data Management and Confidentiality

When participants enrolled in the study, they were assigned a random study ID number to label self-report and interview data. Self-report and interview data were further deidentified. Any potentially identifying records are kept password-protected on a secure server. All analyses will be reported as aggregate data or in an anonymized format for qualitative excerpts.

Data Collection Overview

Patients or Survivors and Caregivers

After obtaining consent, self-reported demographic information (eg, age, sex, ethnicity, education level, income, length of US residency, language use, religion, employment status, insurance status, and subjective social status captured using the community version of the MacArthur Scale of Subjective Social Status [39]), acculturation level (from the Brief Acculturation Scale for Hispanics [40]), and cancer history (eg, type of metastatic cancer, diagnosis date, and treatments) were collected by telephone immediately following the screening call or at another scheduled time. Following the demographic and cancer history questions call, participants were scheduled for a 1-1.5-hour interview over telephone or videoconference through Zoom (Zoom Video Communications). When scheduling and sending reminders for the interview, participants were asked to secure a private location where they could speak freely and confidentially, in addition to a suggestion to use headphones for added privacy. Participants' privacy and comfort with their interview location were confirmed before beginning the interview. In the rare circumstance that the participant needed another location for continued privacy for the interview, participants were offered a break period or to reschedule to continue the interview in a confidential manner. After the interview, participants completed a 30-minute survey on paper or a web-based survey within 1 week of the interview. All participants were encouraged to complete their survey on the same day as the interview, in one sitting, if possible, within 1 week from the interview date. They were reminded to complete the survey through their preferred method of communication. Participants with lower literacy were supported by trained bilingual research assistants over the phone. Caregivers underwent the same study process as patients or survivors (brief demographic questions through phone, 1-hour interview, and 30-minute survey).

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Health Care Professionals

Health care professionals were provided study information sheets with the opportunity to ask questions about eligibility before scheduling the 1-hour focus groups or interviews led in English by the principal investigator. Focus groups and parallel key informant interviews took place over Zoom. Focus groups were composed of a minimum of 3 health care professionals to allow for greater depth of responses from each participant attending the focus group, as well as to accommodate scheduling restrictions imposed by their COVID-19 workload. The three focus group compositions were balanced out as much as possible: (1) social worker, bilingual radiation oncologist, and bilingual medical oncologist; (2) social worker, bilingual medical oncologist, and medical oncologist; and (3) chaplain, bilingual hematology oncologist, hematology oncologist, and bilingual medical oncologist. Following the focus groups, parallel-format key informant interviews were the only feasible way to gain additional perspectives due to time limitations from health care professionals' COVID-19 workload—this alternate participation option was pursued when health care professionals could not otherwise participate in the focus groups. In reminders before the interview, participants were asked to secure a private location where they could speak freely and confidentially and were suggested to use headphones for added privacy. Before beginning each focus group or interview, health care professionals confirmed their eligibility and provided oral or web-based survey consent. They also confirmed privacy and comfort with their location of remote participation. The demographics of health care professionals were collected before the interviews through a brief demographic questionnaire on the web. Self-reported demographic information includes age; profession; sex; ethnicity; years since clinical licensure; years since obtaining an MD degree; hospital or clinic affiliation; months employed at the institution, hospital, or clinic; if bilingual in Chinese, Vietnamese, or Korean and if using the endorsed language in clinical practice; years working with patients with metastatic cancer; the number of CVK patients with metastatic cancer seen in the past month and per month before COVID-19; and level of comfort caring for CVK patients with metastatic cancer.

Semistructured Guides for Qualitative Data

Patients or Survivors and Caregivers

All interviews were conducted using semistructured topic guides. Interviews were conducted in English, Chinese (Cantonese or Mandarin), Vietnamese, and Korean by language-matched, trained interviewers and the principal investigator. Interviews lasted 60-90 minutes for both the patients or survivors and their caregivers. Interviews took place through Zoom or telephone calls and were audio-recorded with participants' permission. The main research question domains for patients or survivors and caregivers were (1) cultural influence on coping, needs, and preferences; (2) cultural fit and adequacy of existing or offered supportive care after diagnosis; (3) unmet supportive care needs (physical vs emotional priorities); and (4) psychosocial intervention or resource preferences (modality and timing). Supportive care needs explored included informational, patient care support, daily living, physical, psychological, or emotional, as well as how people's social lives (interpersonal relationships, marriage, sexuality, and spirituality) were affected. Caregivers were asked to provide information regarding their own experiences as well as the patient's or survivor's experiences in these domains and their insights about patients' or survivors' needs. Caregivers were also asked about how their relationship with the patient or survivor had changed or stayed the same if they were married or in a committed relationship. In the fourth domain, participants were asked to rank potential psychosocial interventions based on perceived helpfulness for patients or survivors with metastatic cancer of their ethnicity: writing privately, a website or blog for close family or friends, social media with close family or friends, peer education or support, and professionally trained counseling. Images representing each type of intervention were provided for participants to reference during the interview. For interviews in which participants mentioned end-of-life or openness about mortality, and time permitting, patients or survivors were shown an image of CACCC's Heart to Heart Café cards to ask for their thoughts regarding a culturally based intervention for end-of-life discussions with family or friends. This last intervention image was presented in a tailored manner for each individual because of ethical concerns raised by community and scientific advisors given the known stigma and taboo related to the end of life in Asian cultures [31], the limited scope of the project, and the lack of culturally and linguistically matched supportive or counseling resources available to all participants.

Health Care Professionals

A semistructured interview guide was developed and used for the focus groups and interviews in English. All participants were asked the same questions per the interview guide by the same facilitator. Domains of inquiry included (1) any difference in care provided for CVK patients with metastatic cancer; (2) challenging scenarios for CVK patients with metastatic cancer; (3) health care professionals' perceptions of the most important unmet supportive care needs, barriers to meeting those unmet needs, and potential solutions; and (4) the type of supportive care that would be most helpful and culturally appropriate. Focus group participants were scheduled for an individual follow-up interview if there were any comments to probe for additional clarifying information. Focus group participants' thoughts were shared with parallel-format individual interview participants, as appropriate, to elicit their reactions and thoughts as would occur if they had participated in a focus group.

Survey Measures for Quantitative Data

Overview

All measures for the study were provided in English, Chinese (traditional or simplified), Vietnamese, or Korean. If not already available or needing wording modification, simplified and traditional Chinese, Vietnamese, and Korean versions of measures were developed using a rigorous translation methodology. A total of 2 independent forward translations, 1 independent back translation, and reconciliations of translations were completed with feedback from community partner organization representatives and bilingual research team members from each language group. Feedback from the Chinese,

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Vietnamese, and Korean community organization representatives included identifying the best phrasings for the United States context while maintaining the meaning of the original English measure. If not in the public domain, permission was obtained from the measure authors.

Patients or Survivors

The primary survey for a convergent mixed methods examination of patients or survivors with metastatic cancer's supportive care needs was measured by the Supportive Care Needs Survey-Screening Tool [41]. The Functional Assessment of Cancer Therapy General-7 measure was used to assess quality of life [42]. Participants' other patient-reported outcomes were assessed with the National Comprehensive Cancer Network distress thermometer [43], an 8-item Patient Health Questionnaire Depression Scale for depression [44], Generalized Anxiety Disorder Scale for anxiety [45], the Multidimensional Fatigue Symptom Inventory-Short Form physical subscale for fatigue [46], the 6-item Impact of Event Scale for cancer-specific traumatic stress [47], the pain intensity, enjoyment of life, general activity 3-item scale for pain assessment [48], and the 2-item Sleep Condition Indicator for sleep disturbance [49]. Considering the importance of coping in determining quality of life and other patient-reported outcomes, coping was evaluated using the Brief Coping Orientation to Problems Experienced Inventory [50] and the Emotional Approach Coping Scales (emotional processing and emotional expression) [51]. The Mental Health Continuum Short Form examined well-being [52], and other resilience factors were examined with the Gratitude Questionnaire-6 [53], the mindfulness subscale of the Self-Compassion Scale [54], the preparedness subscale of the Quality of Life at the End of Life-Cancer measure [55], the UCLA 3-Item Loneliness Scale [56], and the Social Provisions Scale [57].

We also measured additional exploratory concepts related to cultural factors that may affect supportive care needs and quality of life among CVK adults with metastatic cancer. The Asian American Values Scale was modified as a brief 9-item pilot version to assess how much participants valued family collectivism, conformity to norms, and emotional self-control [58], alongside the harmony subscale of the Brief Collectivism Questionnaire [59]. Other culturally relevant concepts measured include ambivalence of emotional expression with the 4-item Ambivalence Over Emotional Expressiveness Questionnaire [60], internalized metastatic cancer-related stigma (modified Lung Cancer Stigma Inventory subscale) [61], self-perceived burden upon others [32,62], the patient's level of sacrifice for their family using a modified Sacrifice for Close Others Scale [63], and a question about lifetime experience of personal or sociopolitical trauma. All measures were completed in one survey assessment after the interview.

Caregivers

Caregivers filled out the same surveys as patients or survivors for cancer-related coping, mental and physical health symptoms, resilience factors such as gratitude, and cultural values. Additionally, their caregiving relationship was measured with the 4-item Quality of Caregiver-Care Recipient Relationship [64,65] and caregiving stress was measured with the Caregiver Intrapsychic Stress and Strain Scales [66]. All measures were completed in one survey assessment after the interview.

Partnered Community Involvement

The study was conducted in collaboration with community organizations that were cultural and community-based advisors for the research and supported all nonengaged aspects of the study such as prioritizing research questions, informing the design of the study including participant eligibility criteria, recommending culturally relevant concepts to assess (eg, stigma or burden), translating study materials, reviewing the ethics of the research procedures, supporting recruitment efforts, and recommending bilingual research assistant candidates for interviewing participants. The CACCC (美華慈心關懷聯盟) is a coalition in Cupertino, California that addresses issues related to serious illnesses in the Chinese American community and partnered for the Chinese portion of the study. The VACF (H i Ung Th Vi t M) in Orange County, California is an organization that provides cancer education, resources, and services and is involved in research and advocacy for cancer prevention to improve quality of life and outcomes in the Vietnamese community and partnered for the Vietnamese portion of the study. The DAWN Study community advisory board comprising multidisciplinary health care professionals (psychology, oncology, palliative care, or public health), patient advocates, and community-based organizational representatives, also contributed to the development and conduct of the study through quarterly meetings. For example, the eligibility criteria for all participants were informed through community advisory board discussions, with the minimal length of employment for health care professionals set at 6 months for the health care professional to have had time to adjust to their health care system and be able to provide an "insider" perspective. The community advisory board included at least one bilingual representative with cultural knowledge relevant to CVK patients and their families.

Ethical Considerations

Institutional review board approval was obtained from UCLA (20-001554) and the University of California, Irvine (1541;2391). Oral or web-based informed consent was obtained from all participants in this study. Nonregistry-based patient or survivor participants completed a web-based screening and consent form, or expressed interest through email or phone and oral consent was obtained over the phone by trained research assistants. Registry-based patient or survivor participants received a letter or email with the study information sheet and a postage-paid postcard to indicate their interest. Research team members followed up with all potentially eligible registry-based patients or survivors to complete the screening and oral consent by phone if participants had not completed the web-based screening and consent on their own. For all participants who consented through a web-based survey, we ensured informed consent by verbally reconfirming an understanding of the purpose of the study, what participation entails, and rights as participants at the beginning of the first portion of the study.

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Results

The study was funded for 2 years, from June 2020 to June 2022, by the NIH-National Cancer Institute with supplement funding from the UCLA Institute of American Cultures and Asian American Studies Center. Recruitment began in November 2020, and data collection was completed in October 2022. A total of 74 patients or survivors enrolled in the study from various US states (66 from California, 3 from Texas, 2 from Washington, 1 from Delaware, 1 from Nevada, and 1 from Connecticut); 69 patients or survivors completed the interview, and 66 patients or survivors completed both the interview and survey. A total of 13 caregivers enrolled in the study (12 from California and 1 from Washington) and completed all portions of the study. All 13 caregivers were linked with a patient or survivor participant in the study; no unlinked caregivers joined the study. A total of 15 health care professionals enrolled in the study, resulting in 3 focus groups and 5 parallel-format interviews. No post hoc exclusions were necessary. We completed the remaining data management in December 2023. A manuscript on health care professionals has been accepted, and manuscripts for convergent mixed method results for patients' or survivors' supportive care needs and caregiver perspectives will be submitted in 2024.

Discussion

This study is one of the first to examine the unmet supportive care needs of Asian Americans with metastatic cancer through interviewing patients or survivors, caregivers, and health care professionals for a more comprehensive understanding, using culturally and linguistically appropriate study materials and community-based participatory research principles. The perspectives of interested parties, which include patients or survivors, caregivers, community members, and health care professionals, will help advocate for this understudied population and inform the next steps to develop, test, and disseminate supportive care resources and interventions that are culturally relevant. By studying adults from Confucian-heritage cultures, this study may uncover cultural factors to be considered in the provision of supportive care. However, given the focus on only CVK adults, the results of this study may not apply to other Asian ethnicities that do not share a Confucian heritage. This research design may be adaptable for other understudied Asian Americans with metastatic cancer to facilitate quality care and intervention development.

Strengths of this study include the involvement of the community through their active participation from the design of the study to the analysis, interpretation, and dissemination of results. Multidisciplinary community advisors who closely work with metastatic cancer survivors and community-based organizations shaped the study to be more culturally appropriate. All steps of the research were available in English, Chinese, Vietnamese, and Korean, and the study was designed to be flexible around participants' schedules (including evenings and weekends) and remove the burden of transportation by being remote.

Challenges encountered in this study include technological and logistical difficulties in offering multiple modalities for participation. Considering that some participants had limited familiarity with technology such as Zoom and SMS text messaging and relied on telephone calls, it was challenging, at times, to connect with individuals to complete every part of the study. Another challenge faced was during the recruitment process, as some participants did not know the staging of their cancer. Diagnoses needed to be clarified through caregivers or with detailed follow-up questions about where the cancer had spread. Though every effort was made to ensure privacy, confidentiality, and independence in participant interviews, one patient strongly preferred that their caregiver be present. Given the patient's physical supportive needs and sporadic difficulty with speech due to cancer, this patient's decision was honored. An explanatory discussion of the research process ensured understanding from both the patient and caregiver that interview and survey responses should be the patient's most direct and honest thoughts. We included this dyad in the study as they were otherwise eligible, and it was deemed the most ethical route per community advisors' recommendations. Lastly, due to COVID-19, opportunities to establish community-based relationships in person were unavailable, and future research participation may be even more plentiful with such efforts. In particular, partnering with locally based community-based organizations and research registries outside of California will be key to reaching a broader US sample, as the majority of the participants in this study were from California.

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Data Availability

The data sets generated during this study are not publicly available. The original consent for study participants did not state such an intention to share the data publicly with others outside of the research team, and some participants are no longer reachable for a reconsent procedure. Confidentiality of participants is of utmost priority, and upon review of the data, there is a possibility that, with known collaborators on this project, demographic characteristics, diagnostic information, interview response patterns, and details, in combination, could make participants recognizable to others in the smaller Asian American network serving metastatic cancer patients or survivors, to participants' health care providers, or to participants' colleagues. Therefore, only restricted data reviews may be discussed with the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CACCC: Chinese American Coalition for Compassionate Care
CVK: Chinese-, Vietnamese-, and Korean-descent
DAWN: Describing Asian American Well-Being and Needs in Cancer
NIH: National Institutes of Health
UCLA: University of California, Los Angeles
VACF: Vietnamese American Cancer Foundation

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Protocol

Leveraging AI and Machine Learning to Develop and Evaluate a Contextualized User-Friendly Cough Audio Classifier for Detecting Respiratory Diseases: Protocol for a Diagnostic Study in Rural Tanzania

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Abstract

Background: Respiratory diseases, including active tuberculosis (TB), asthma, and chronic obstructive pulmonary disease (COPD), constitute substantial global health challenges, necessitating timely and accurate diagnosis for effective treatment and management.

Objective: This research seeks to develop and evaluate a noninvasive user-friendly artificial intelligence (AI)–powered cough audio classifier for detecting these respiratory conditions in rural Tanzania.

Methods: This is a nonexperimental cross-sectional research with the primary objective of collection and analysis of cough sounds from patients with active TB, asthma, and COPD in outpatient clinics to generate and evaluate a noninvasive cough audio classifier. Specialized cough sound recording devices, designed to be nonintrusive and user-friendly, will facilitate the collection of diverse cough sound samples from patients attending outpatient clinics in 20 health care facilities in the Shinyanga region. The collected cough sound data will undergo rigorous analysis, using advanced AI signal processing and machine learning techniques. By comparing acoustic features and patterns associated with TB, asthma, and COPD, a robust algorithm capable of automated disease discrimination will be generated facilitating the development of a smartphone-based cough sound classifier. The classifier will be evaluated against the calculated reference standards including clinical assessments, sputum smear, GeneXpert, chest x-ray, culture and sensitivity, spirometry and peak expiratory flow, and sensitivity and predictive values.

Results: This research represents a vital step toward enhancing the diagnostic capabilities available in outpatient clinics, with the potential to revolutionize the field of respiratory disease diagnosis. Findings from the 4 phases of the study will be presented as descriptions supported by relevant images, tables, and figures. The anticipated outcome of this research is the creation of a reliable, noninvasive diagnostic cough classifier that empowers health care professionals and patients themselves to identify and differentiate these respiratory diseases based on cough sound patterns.

Conclusions: Cough sound classifiers use advanced technology for early detection and management of respiratory conditions, offering a less invasive and more efficient alternative to traditional diagnostics. This technology promises to ease public health burdens, improve patient outcomes, and enhance health care access in under-resourced areas, potentially transforming respiratory disease management globally.

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KEYWORDS

artificial intelligence; machine learning; respiratory diseases; cough classifiers; Tanzania; Africa; mobile phone; user-friendly; cough; detecting respiratory disease; diagnostic study; tuberculosis; asthma; chronic obstructive pulmonary disease; treatment; management; noninvasive; rural; cross-sectional research; analysis; cough sound

Introduction

Respiratory diseases impose a significant burden on individuals, communities, and health care systems worldwide. These conditions, which encompass a wide range of disorders such as tuberculosis (TB), asthma, chronic obstructive pulmonary disease (COPD), and lung cancer, not only diminish the quality of life for affected individuals but also lead to substantial economic and health care costs particularly in low- and middle-income countries [1]. Patients with respiratory diseases often struggle with symptoms like coughing, shortness of breath, and chest pain, which can limit their ability to perform daily activities and enjoy a normal life [1,2]. The burden of respiratory diseases extends beyond the physical aspect, as they are frequently associated with emotional distress and psychological challenges, contributing to diminished overall well-being for patients and their families.

From a public health perspective, respiratory diseases account for a significant portion of global morbidity and mortality. The World Health Organization (WHO) reports that respiratory infections alone are responsible for millions of deaths each year, particularly affecting vulnerable populations such as children, the elderly, and individuals with compromised immune systems [3,4]. Moreover, the economic costs associated with respiratory diseases are staggering, encompassing medical expenses lost productivity due to illness, and the burden on health care systems. For instance, the total spending across all respiratory conditions increased by US $71.7 billion in the United States by 2016 from 170.8 billion in 1996 with asthma and COPD contributing US $35.5 billion and US $34.3 billion, respectively, of the total increase [3]. TB, asthma, and COPD are said to be common and rising public health burdens in Africa [5]. Preventive measures such as smoking cessation, improved air quality and vaccination are critical to alleviating this burden, as they can reduce the incidence and severity of respiratory diseases and ultimately improve the overall health and well-being of populations around the world [3]. However, respiratory diseases are relatively neglected in sub-Saharan Africa with no tangible public health programs to address them [5,6]. Consequently, the provision of health care for respiratory diseases appears suboptimal and this was further compromised by the COVID-19 pandemic [5].

Taking TB as an example, the WHO continues to emphasize the need for early detection as a strategic approach for reducing the risk of transmitting the disease to others, improving health outcomes, and reducing distress and economic hardship at the family level [7,8]. Much emphasis is now placed on user-friendly, inexpensive, and contextually feasible diagnostic tools that can effectively identify people who probably have active TB [7,8]. Consequently, countries like Tanzania have started incorporating some of the WHO recommendations about using new user-friendly digital techniques for managing TB into their policies. However, due to the need for improved quality of health care workers with essential knowledge and skills, real adoption of such technologies is still less than intended.

The emergence of the COVID-19 pandemic profoundly impacted the diagnosis and management of other respiratory diseases. With health care systems overwhelmed by the surge in COVID-19 cases, resources, personnel, and laboratory capacities were often diverted away from routine health care services, including the diagnosis of respiratory conditions such as TB, asthma, and COPD [5]. For example, most guidelines recommended limiting the use of pulmonary function tests for fear of transmission of COVID-19 which constrained the use of spirometry testing further compromising the diagnosis of chronic respiratory diseases [9]. Furthermore, the fear of contracting COVID-19 in health care settings led many individuals to postpone or avoid seeking medical care for respiratory symptoms, resulting in delayed diagnoses and exacerbation of preexisting conditions [5]. Diagnostic tests and imaging equipment were sometimes repurposed for COVID-19 testing, leaving fewer resources available for the timely detection of other respiratory ailments. As a result, there has been a concerning backlog in the diagnosis of respiratory diseases, potentially leading to worsened health outcomes and increased burden on health care systems as they work to catch up on missed diagnoses and treatments.

One promising avenue for improving the diagnosis of respiratory diseases is the analysis of cough sounds, which can carry valuable information about the underlying respiratory condition. Most importantly, the recent developments in artificial intelligence (AI) and machine learning (ML) have heightened the need for the application of these powerful tools in the diagnosis of respiratory diseases, particularly, through the development of cough sound classifiers [10,11]. These sophisticated algorithms have the capacity to analyze and interpret patterns within cough sounds, providing valuable insights into a patient's respiratory health [10-17]. By training AI models on large data sets of cough audio recordings from both healthy individuals and those with respiratory conditions such as TB, asthma, or COPD, it becomes possible to identify distinctive acoustic signatures associated with different diseases [12-17]. These AI-driven cough classifiers can discern subtle variations in cough frequency, duration, intensity, and spectral characteristics, enabling early and accurate disease detection [12-17]. A good example of how AI and ML have been proven useful is the documentation of their effectiveness in Western countries toward the detection of TB [12], COVID-19 [13,14], asthma, COPD [15,16], and even pertussis [17] and their values have extended beyond sound classification to interpreting and analysis of medical imaging for TB detection [18,19]. Moreover, the noninvasive nature of cough audio analysis makes it a convenient and cost-effective diagnostic tool, particularly in resource-constrained settings [12-17]. Patients can record their cough sounds using smartphones or dedicated devices, and these

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recordings can then be processed by AI algorithms for rapid assessment [20-22]. The potential for remote monitoring is especially valuable in the context of respiratory diseases, as it allows for continuous tracking of a patient's condition and response to treatment.

Coughing is a common indication of respiratory illnesses, resulting from a forceful release of air from the air passages. Nevertheless, the impact of coughing on the respiratory system is recognized to be variable [23,24]. For instance, lung ailments can lead to either constriction or blockage of the airways, which can affect the sound characteristics of coughing [24]. Furthermore, it has been suggested that the glottis behaves differently under various pathological conditions, allowing for the differentiation of coughs associated with asthma, bronchitis, and pertussis [25]. As a result, the automatic classification of acoustic signals linked to cough to detect respiratory diseases like TB, asthma, and COPD seems to be a reasonable scholarly endeavor to pursue. Research suggests that conditions such as TB, asthma, and COPD exhibit specific temporal patterns and frequencies in coughing, which can be effectively analyzed with advanced technology [26,27].

As AI and ML continue to advance, the accuracy and precision of cough audio classifiers are expected to improve and may outperform standard tests enhancing their use in both clinical practice and public health initiatives. For example, a recent study in Europe indicated that the sensitivity and positive predictive value of the AI-based algorithm were superior to pulmonologist-based diagnostic category allocation in each of the 8 disease groups evaluated [28]. In essence, these technologies hold great promise in revolutionizing the way we diagnose and manage respiratory diseases, offering early intervention, personalized treatment, and improved patient outcomes. However, a major shortfall with the application of AI and ML is that they have not been fully exploited in cough audio classification in rural African contexts. Given the burgeoning interest in leveraging AI or ML for health care advancements, there is a critical need for empirical research to explore their potential applications in rural African settings. The gap in noninvasive, efficient diagnostic tools for respiratory diseases in low-income Africa necessitates urgent attention. This study aims to develop and assess an AI-powered cough audio classifier designed to detect respiratory conditions in rural Tanzania. Through a systematic approach to collecting and analyzing cough sounds in outpatient settings, this research aims to improve disease identification accuracy and efficiency, offering accessible, user-friendly diagnostic solutions to support health care providers in low-income areas.

Methods

Design

This is nonexperimental cross-sectional research with the primary objective of collection and analysis of cough sounds from patients with active TB, asthma, and COPD in outpatient clinics to generate and evaluate a noninvasive cough audio classifier. The study combines innovative applications of AI or ML to develop cough audio classifiers using data collected from patients with active diseases and evaluation of the classifiers in routine care against the reference standards. To achieve this, a four-phase research process will be implemented involving (1) cough sound collection for 12 months (phase 1), (2) cough sound analysis and algorithm development for 12 months (phase 2), (3) development of cough audio classifier for 6 months (phase 3), and (4) evaluation of cough audio classifier for 18 months (phase 4). The expected primary outcomes are contextualized user-friendly AI-powered cough audio classifier and a rate of patients with active respiratory diseases notified and linked to treatment. The expected secondary outcomes are health care workers' experience with a cough audio classifier, including perspectives on the acceptability, feasibility, and cost of using a cough audio classifier. The comparison of the cost incurred to implement the audio classifier will be compared to the standards of care. The feasibility indicators will include the perceived acceptability and satisfaction of health care providers and patients toward the cough audio classifier. Findings from this study will be useful in further refinement of the cough audio classifier and definitive trials in the broader community. The research will increase the pool of health experts with skills in the application of AI or ML developing diagnostic tests in Tanzania. It is expected that the cough audio classifier if found effective during future definitive trials, can be trademarked.

Settings

The study will take place across the Shinyanga Region of Tanzania. The Shinyanga Region, predominantly rural with less than 5% urban residency, is detailed further in my prior research [29,30]. More specifically, the study will be conducted in 30 facilities including Shinyanga Referral Hospital, Shinyanga Municipal Hospital, Shinyanga District Council Hospital, Kolandoto Hospital, Kahama Municipal Hospital, Jakaya Kikwete Hospital, Kishapu health centre (HC) Mwadui Hospital, Nindo Dispensary, Tinde HC, Samuye HC, Ngokoro HC, Kambarage HC, Imani Dispensary, Inspire Dispensary, Mwawaza Dispensary, Kizumbi Dispensary, Bubiki Dispensary, Polisi Dispensary, Lubaga Dispensary, Consolata Dispensary, Majengo Dispensary, Maganzo Dispensary, Mwamalili Dispensary, Mwamalili Dispensary, Golden Grace Dispensary, Masekelo Dispensary, Kanisa la Kiinjiri la Kilutheri Tanzania Lutheran Dispensary, Old Shinyanga Dispensary, and Chamaguha Dispensary. These sites are purposefully selected considering ownership (public, private, and faith-based organization), location (urban, peri-urban, and rural), level (hospital, health center, and dispensaries), and access to a wealthy number of clients presenting with coughs. The focus on rural settings stems from the commitment of the principal investigator (PI) to enhancing primary health care [29]; challenges in diagnosing TB, asthma, and COPD due to limited diagnostics; the value of co-designing [30] a cough audio classifier with rural inputs for cultural relevance; and Shinyanga's clear, low-noise environment for optimal cough sound recording.

Study Implementation

Overview

The study implementation is concisely illustrated in Figure 1. A concise summary is provided.

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Figure 1. Study implementation framework.

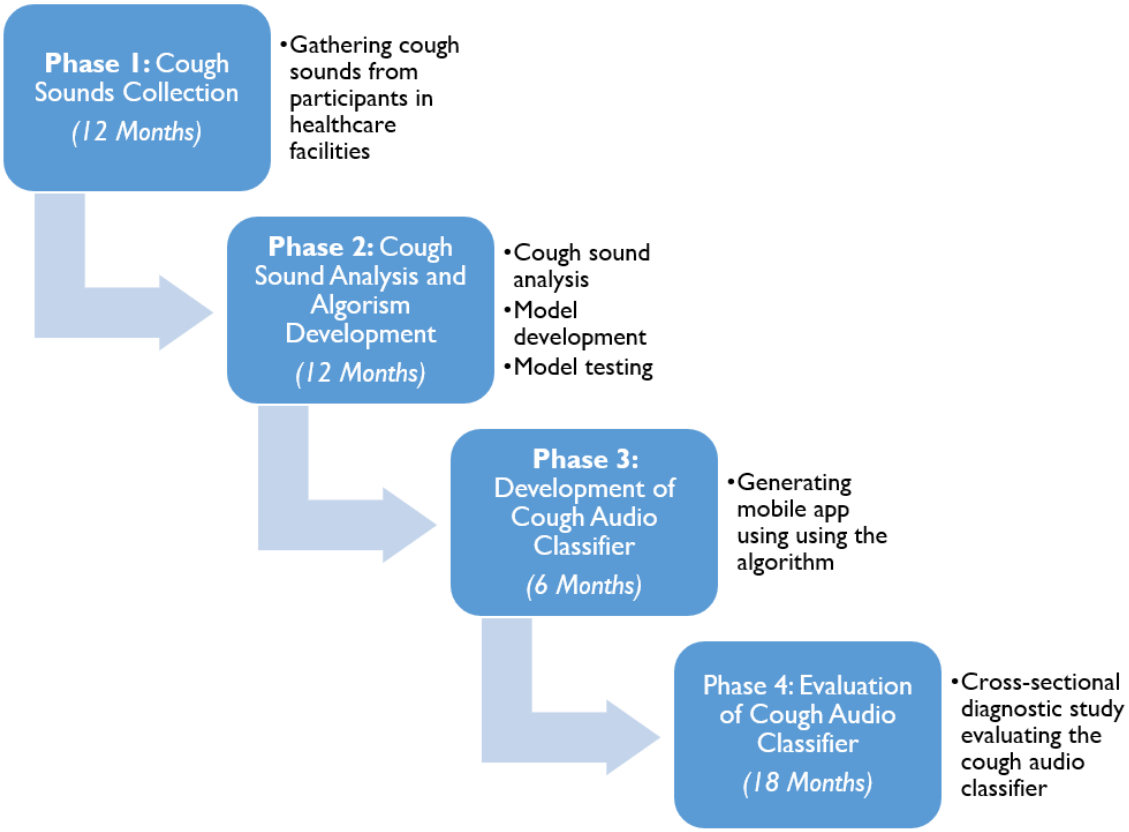

Phase 1: Cough Sounds Collection (12 Months)

The procedures for cough sound collection are adapted from previous research in South Africa [12] considering local contexts. More specifically, cough sound data will be collected from health care facilities using specialized cough sound recording devices equipped with high-quality microphones in a dedicated cross-ventilated room. These devices will be nonintrusive and user-friendly, ensuring patient comfort and compliance. Patients with active TB, asthma, and COPD will be identified in the outpatient department (OPD) clinics and directed to the recording room. During the recording sessions, patients will be instructed to cough into the device several times, producing a diverse set of cough sounds. All audio recordings will be conducted by a health care provider, in selected health care facilities during regular clinic hours, who are trained to operate the recording device. The recording room will not be fitted with additional soundproof materials to mimic the clinical environment where the diagnostic procedures for patients with TB, asthma, and COPD are performed. A comprehensive summary of the audio sound capturing process is detailed in Multimedia Appendix 1 [11,12,31-36].

The research team will adhere to ethical guidelines and ensure the privacy and well-being of participants. The inclusion criteria for patients whose cough sounds will be collected include patients who are older than 18 years of age and with a clinical diagnosis of TB, asthma, or COPD diseases. The exclusion criteria will be patients who provide no consent and those unable to provide a cough sound. The decision to exclude children younger than 18 years of age from our study was driven by the extensive consent process required for minors, compounded by our limited resources. Additionally, previous research has highlighted challenges in collecting cough sounds from this demographic [37-39].

Phase 2: Cough Sound Analysis and Algorithm Development (12 Months)

Once the cough sound data are collected, advanced signal processing and ML techniques will be used to analyze and classify the cough sounds associated with each respiratory disease. By comparing the acoustic features and patterns among the 3 conditions (TB, asthma, and COPD), the study aims to develop a robust algorithm for automated disease discrimination. A proposed approach for audio classification is using TensorFlow applying Librosa software (Librosa Organization) described previously [11,40]. Librosa is an open-source Python package for music and audio analysis and can provide the data and the sampling rate which plays a vital role in audio classification since different sounds have different sample rates [40]. A comprehensive summary of the procedures for cough sound analysis, algorithm or model development, and testing has been summarized in Multimedia Appendix 2 [11,12,34,35,40-46].

The emerging model will be checked whether it correctly predicts the cough sounds. The expected outcome of this process is a reliable model that can assist the research team in developing a mobile app to help health care practitioners identify TB, asthma, and COPD based on cough sound patterns.

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Phase 3: Development of Cough Audio Classifier (6 Months)

The developed models for TB, asthma, and COPD will need to be integrated into a noninvasive and user-friendly diagnostic tool. Under the guidance of developers, the development of a mobile app for TB, asthma, and COPD detection will involve the deployment of the developed models to Android with TensorFlow Lite [47]. The sample app will be cloned from GitHub, the sound classification Android app will be imported into Android Studio, and the model will be added (both the soundclassifier.tflite and labels.txt) into the src/main/assets folder replacing the example model that is already there and the app will be built and deployed on the Android device.

Phase 4: Evaluation of Cough Audio Classifier (18 Months)

This will be a cross-sectional diagnostic study evaluating the cough audio classifier for active TB, asthma, and COPD triage and case detection against the reference standards. Clients attending OPD clinics at rural health care facilities and suspected of having TB, asthma, and COPD as per national guidelines will be included in the study, upon written consent. Data will be collected from each of the participating facilities. The results of recorded cough using a cough audio classifier will be compared with the current standard of clinical assessment, spirometry, peak expiratory flow (PEF), GeneXpert, culture and sensitivity, chest x-rays (CXR), clinical assessment, and the specificity and predictive values will be calculated.

Study Design

The study will be a multicenter hospital-based validation cross-sectional diagnostic study evaluating the cough audio classifier for active TB, asthma, and COPD triage and case detection in routine care against the reference standards. This study will involve consecutively enrolled suspects who will be closely evaluated to define their illness. The diagnostic accuracy of automated smartphone-based cough audio will be compared among TB, asthma, and COPD cases and controls. Cases include participants who meet “Definite” or “Probable” TB, asthma, and COPD criteria. Controls include participants who presented with symptoms potentially suggestive of TB, asthma, and COPD, but were not started on treatment and had full clinical resolution at follow-up or had an alternative diagnosis confirmed.

Study Area

The evaluation study will be conducted in similar study settings and the 30 health care facilities in which cough sounds were collected in Shinyanga Region (phase 1).

Participants Recruitment

Patients attending OPD clinics and meeting all eligibility criteria listed in the eligibility criteria will be referred to the study’s research staff primarily by the treating medical officer or nurses during triage at OPD. Once enrolled, participants will be retained in the study by telephone reminders. Research assistants will call the participant to arrange follow-up visits and reminder calls will be placed prior to the expected follow-up visit appointments. If there is significant difficulty with participant retention, the possibility of using community health care workers to conduct home visits will be explored. The participant will be reimbursed for the cost of travel to or from the follow-up appointments.

Eligibility Criteria

Overview

There will be no exceptions to eligibility requirements at the time of enrollment. Questions about eligibility criteria will be administered prior to attempting to enroll the participant. The eligibility criteria for this study have been carefully considered. Patients not meeting the criteria will not be enrolled in the study. Participants will be considered eligible for enrollment in this study if they fulfill all the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

The criteria for inclusion are (1) patients aged older than 18 years and presenting with cough; (2) clients attending outpatient clinics in the selected study sites; and (3) clients suspected of having tuberculosis, asthma, and COPD as per national guidelines—prioritizing those with cough of any duration.

Exclusion Criteria

The exclusion criteria are (1) refusal to participate and (2) clients who started prescription medications.

Sample Size Estimation

This evaluative study will collect and analyze data for all patients receiving TB, asthma, and COPD care, starting from screening, and ending with the starting of treatment or preventive therapy. A sample size of 348 for each disease condition (a total of 1044) was obtained using the Buderer formula for sensitivity and specificity [48]. Using tuberculosis as an example, the reported sensitivity of 0.98and specificity of 0.84 of using AI in detecting *Mycobacterium tuberculosis* [49,50] and the prevalence of pulmonary TB of 0.335 among patients with presumptive TB [51] were used to compute this sample size at 0.05 precision and 0.1 attrition.

Where n is the required sample size, SN is the anticipated sensitivity, α is the size of the critical region ($1-\alpha$ is the confidence level), $Z1-\alpha 2/$ is the standardized normal variate corresponding to the specified size of the critical region (α), and L is the absolute precision.

Participants’ Service Flow

Patients’ TB, asthma, and COPD service flow all project activities will be consistent with the service standards as outlined in the national policies and guidelines. Currently, in Tanzania, patients’ access to TB, asthma, and COPD services is mainly through facility-based health services. The flow of patients starts with screening for symptoms and signs. Participants who screen positive for TB, asthma, and COPD symptoms (presumptive clients) are either assessed clinically first and referred directly to the laboratory within the same or outside facility for diagnosis (for TB) or receive medical treatment after medical assessments

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and investigations (for asthma and COPD). Specifically for TB, health providers then order sputum for smear microscopy or GeneXpert and the sample is collected at the referring entry point or at the laboratory, depending on the client volume and human resources at the site. When the sputum sample is negative, a CXR is ordered to support clinical radiological diagnosis. Sputum samples with positive results are sent to the TB clinic service provider who then liaises with the requesting clinician (at various service delivery points) to ensure that the patient receives their result and initiates TB treatment. Patients may be waiting for their result (same-day diagnosis) or be given an appointment to return to the requesting clinician for follow-up. CXR results are interpreted by trained clinicians if available at the facility level, or by the district TB coordinator. For asthma and COPD, a clinical diagnosis may be made by an attending clinician and medications initiated, occasionally after excluding TB where diagnostic facilities are available.

Clinical Evaluations

A variety of clinical assessments will be conducted, encompassing the collection of demographic and medical data, anthropometric measurements, chest auscultations, spirometry, PEF, and clinical specimen collection. A comprehensive overview of these clinical evaluations is described in Multimedia Appendix 3 [52,53].

Data Management and Analysis

Data Management

Study personnel will be given in-service training by the PI about forms and study procedures before the start of the study and given in-service training periodically throughout the study. Data collection is the responsibility of the research assistants at the site under the supervision of the PI. During the study, the PI will maintain complete and accurate documentation for the study. Data analysis will be the responsibility of the PI, under the mentorship of a biostatistician.

Each subject will be assigned a unique patient ID number. The forms that contain the subjects' names, dates of birth, and contact information will be kept in the PI's office and filed in a secured cabinet. A key linking each participant to their patient ID will be created and kept secured by the PI. All case report forms (CRFs) will be reviewed for accuracy, clarity, and completion, and by the data entry staff for completion. Study-related laboratory reports will be reviewed and signed off by a PI. Data reported on the CRF that are derived from source documents or chart reviews should be consistent with the source documents or the discrepancies should be explained.

Data Capture

Data will be captured using paper CRFs or electronic CRF and transcribed into a secure, password-protected, electronic database. Data capture will be ongoing throughout the period of the study. It is expected that participant CRFs will be reviewed and entered electronically directly or within 7 days of completion of the visit. Data quality control measures will be instituted as outlined in the standard operating procedures, in accordance with data quality control procedures at the study site.

Types of Data

Identifiable information including name and contact information will not be stored electronically, but only on paper. A coded CRF-compliant, secure, password-protected electronic database will house the demographic data, clinical data (including current and past medical history), and laboratory outcome measures (including results of study-related tests or procedures).

Analysis for Outcomes

Results of recorded cough using cough audio classifier will be compared with clinical assessment, GeneXpert, culture and sensitivity, spirometry, PEF and sensitivity, and specificity and predictive values will be calculated. These measures will be collected simultaneously among patients and will serve as benchmarks for comparison purposes. The analysis will be generated for cost, facilitators, and barriers to implementing the cough audio classifier for TB, asthma, and COPD screening in rural community settings.

Audio Classifier-Diagnostic Test

A binomial test will be used to test whether the sensitivity of the audio classifier using the previously reported cut-off is less than 0.8, and receiver operating characteristic analysis will be explored to determine if another cut-off should be used in this patient population. Logistic regression models will be used to determine whether an audio classifier contributes additional information to predicting TB, asthma, and COPD in the presence of clinical and laboratory predictors. Variable assessment will be based on a likelihood ratio test, in which the likelihood of the reduced model will be compared to the likelihood of the full model. As a primary summary measure of discrimination, we will use the c (for concordance) index, a measure that is identical to the area under the receiver operating characteristic curve when the end point is binary.

Risk Factor Analysis

The study will use a similar strategy as described. All models will be adjusted for baseline medical and demographic characteristics of the subjects. Data will be also summarized with respect to the primary and secondary outcome measures, demographics, and baseline characteristics. Quantitative variables will be summarized with standard descriptive statistics while frequency tables will summarize categorical variables. All analyses will be performed in STATA (StataCorp). Before analysis, the outcome will be examined for skew and kurtosis to determine the need for standard transformations to meet normal distribution assumptions. All *P* values are 2-sided and considered statistically significant at a level of .05.

A deductive thematic analysis approach will be used for qualitative data [54] on the barriers and facilitators of cough audio classifier acceptance using NVivo software (Lumivero). More specifically, data transcription and translation will occur simultaneously by the research assistants. After transcription and translation, the interview transcripts will be cross-checked by the PI to ensure that the participants' worldview was not lost during translation. The interview transcripts will then be deidentified, and pseudonyms generated for each participant. The data will then be uploaded into NVivo software for thematic coding. The PI will deductively generate an initial list of codes

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from data extracts of the first 3 transcripts. Then, these codes will be reviewed by the research team who had independently reviewed selected transcripts generating a consensual list of codes. The PI will continue coding the rest of the transcripts, refining, and generating more codes upon coming across a new segment of data that could not fit into the initial codes. Codes will then be sorted into potential subthemes and themes, followed by collation of all relevant coded data extracts within identified themes. Throughout coding and refinement, the peer consultation will be maintained to reflect on the subthemes and themes generated.

Ethical Considerations

The study complies with the principles of the Declaration of Helsinki, as amended by 59th World Medical Association General Assembly, Seoul, Korea, October 2008. It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice and applicable local laws and guidelines. The study protocol, information, and consent documents will be submitted to the National Institute for Medical Research (Tanzania) for review and approval. Permission will be sought from the President's Office Regional and Local Administrative Government (PORALG), the national TB and leprosy programme (NTLP), and participating health facilities. A comprehensive overview of the informed consent process, along with measures for ensuring confidentiality and data protection, is outlined in Multimedia Appendix 4.

Results

Participants Demographics

The first section of the results will summarize the demographics of participants involved in cough sound collection and evaluation of the cough audio classifier. Participants' gender; age; primary occupations; marital status; presence and duration of cough and other TB, asthma, and COPD symptoms and TB contact and family history; current or chronic medications; and comorbidities are some of the demography that will be presented in a tabular form.

Phase 1: Cough Sounds Collection

The findings will encapsulate a compilation of various cough sounds gathered during the collection process. This compilation will encompass a spectrum of cough characteristics, including frequency, duration, and intensity. Additionally, a summary of the extensive database comprising cough audio recordings, intended for use in subsequent phases, will be provided.

Phase 2: Cough Sound Analysis and Algorithm Development

The findings regarding the methodology and procedures used to analyze patterns and correlations within the cough sound data set, facilitating algorithm development, will be outlined. Additionally, the process, methodologies, and findings related to the initial algorithm development, distinguishing between different cough sounds, and identifying potential classification markers, will be detailed. Furthermore, a summary of the steps taken to refine the algorithms and improve accuracy and efficiency in identifying distinct cough patterns will be provided.

Phase 3: Development of Cough Audio Classifier

The findings will encapsulate an overview of the process and methodologies leading to the successful creation of a functional cough audio classifier, designed as a smartphone-based app, derived from the refined algorithms developed in phase 2. The summary will outline the procedures used to assess the classifier's capacity to accurately differentiate between various types of coughs, specifically identifying those associated with conditions. Similarly, it will highlight the process for evaluating the classifier's adaptability across a broad spectrum of cough variations and its potential for real-time implementation.

Phase 4: Evaluation of Cough Audio Classifier

The study will present findings from a performance evaluation aimed at assessing the accuracy, sensitivity, and specificity of the cough audio classifier in a real-world setting. These results will encompass an evaluation of the classifier's feasibility, acceptability, user experiences, and efficiency among health care providers and patients. Additionally, the study will present findings from a comparative analysis of the cost-effectiveness and practicality of implementing the cough audio classifier in contrast to existing standard practices.

Collectively, these key results from each phase will significantly contribute to a comprehensive understanding of the cough audio classifier's feasibility, accuracy, and its potential for real-world applicability, as developed within this study.

Discussion

Principal Findings

The study aims to enhance the management of TB, asthma, and COPD in health care facilities involved in the research. It aligns with existing patient care pathways for TB, asthma, and COPD by focusing on improving diagnostic capabilities through the integration of services and decentralization, thereby reinforcing referral systems within and between health care facilities. The anticipated primary outcome is the development and validation of a noninvasive, mobile-based cough sound classifier for detecting TB, asthma, and COPD. This research will report on the practical evaluation of the acceptability and effectiveness of the cough audio classifier, with a particular focus on its applicability in rural primary health care settings.

Comparison to Prior Work

The scholarly community is increasingly interested in the potential of AI or ML technologies for developing diagnostic tools. This research aims to develop and explore the feasibility, acceptability, and efficacy of using AI or ML to create cough audio classifiers in Tanzania, marking the first pilot project of its kind in the region. The results of this study will be benchmarked against findings from previous research on cough audio classifiers, some of which have been reviewed in the context of this protocol [13-22], to provide a comparative analysis and contribute to the evolving field of AI or ML applications in health care diagnostics.

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Strengths and Limitations

This study represents a groundbreaking effort in the development and evaluation of a noninvasive, user-friendly AI-powered cough audio classifier for 3 respiratory diseases within low-income rural settings. However, conducting a study in rural Tanzania may encounter several limitations. First, access to technology poses a significant challenge. Rural areas may lack the necessary technology infrastructure, including stable internet connections, cough audio processors, reliable power supply for devices, or access to smartphones or suitable devices required for the AI-powered application. To mitigate these challenges, efforts will be made to leverage financial and nonfinancial resources within and beyond Aga Khan University. Second, data quality and quantity could be limited. The availability and quality of cough audio data for training the AI model might be insufficient or biased in rural settings, potentially affecting the model's accuracy. To address this, institutionalized quality assurance measures will be implemented to ensure high-quality data collection. Additionally, the study duration will be adjusted to ensure the collection of sufficient data. Third, language and cultural considerations might impact the classifier's accuracy. The AI model may not be optimized to recognize local dialects or variations in cough sounds due to cultural or linguistic differences. To partly address this, global AI and ML experts and processing protocols will be used to ensure accurate cough audio processing. Fourth, the study targets adults aged 18 years and older, primarily due to the complexities of the consent process, resource constraints, and the difficulties associated with collecting cough audio sounds from children. Given the pilot nature of this research, subsequent studies may consider including children as participants. Consequently, the study aims to exclude participants who have taken prescription medications. This exclusion criterion is based on the premise that prescription medications can markedly modify the characteristics and severity of cough sounds, thereby influencing the precision of our cough audio classifier. Given that certain prescription medications might be available over-the-counter within the study environments, there is a potential for this criterion to substantially diminish the sample size. In response to this challenge, we have expanded the number of health care facilities involved and extended the period of data collection to mitigate the impact on our sample size and ensure robust data acquisition. Finally, limited health care infrastructure in rural areas, including a scarcity of health care facilities and skilled personnel, may hinder the effective implementation of the AI-powered classifier. To counter this, health care workers involved in the study will receive adequate training before engaging in the research. Recognition is made that addressing these limitations are crucial to ensure the successful development, implementation, and evaluation of the AI-powered cough audio classifier for respiratory condition detection in rural Tanzania.

Future Directions

The findings of this study will have a range of social impacts. Although there is a lack of common definitions, conceptualizations and practical tools addressing the acceptability of technological health innovations in sub-Saharan Africa [55], an acknowledgment is made that social and cultural contexts have a significant impact on how humans behave both positively and negatively [56]. This is also the case when we are addressing the adaptation to new innovations among health care providers and community members. Common barriers to acceptance of health innovations may include intrapersonal and interpersonal, community, organizational, and policies or enabling factors [57,58]. Intrapersonal factors encompass attitude, fears, level of income, self-efficacy, and education level, which could play both roles as facilitators and barriers when it comes to the acceptability of these new techniques. For example, a recent review noted fear of a loss of professional autonomy and difficulties in integrating AI into clinical workflows as factors hindering their acceptability [57]. Public fears toward health innovations that they are not fully aware of may also promote negativity toward them [58]. Some of the interpersonal factors include social or family roles and responsibilities, norms, stigma, and community influence. Individuals and communities are seen to be more open to innovations when the intervention is supported by influential people within their communities [58]. Challenges are expected on the issue of acceptability among health care workers and the community since it is a new technology introduced and this can cause some reluctance. Additionally, the issue of smartphone use can be a challenge as some potential health care professionals may not be willing to use their personal devices for clinical diagnostic tasks and patients might not own the smartphone where the app will be installed. Similarly, the sharing of smartphones in the family and at the community level for self-diagnosis can be a potential for spreading communicable respiratory diseases if proper hygiene is not observed. Therefore, this study will navigate through these factors and ensure that they are well-addressed to maximize our outcomes. The focus will be on integrating the end users in the early stages of AI development, offering needs-adjusted training for the use of AI in health care and providing adequate infrastructure [57]. Furthermore, health care providers will be trained as trainer of trainers from the start of the study as they tend to easily pave the way, and consideration of gender roles, ensuring both males and females can participate equally.

Furthermore, the findings will have implications on health economics. Scaling up TB, asthma, and COPD services to achieve national and global targets requires an optimization of available funding. To identify and address the available inefficiencies and consider new interventions at the national level; information on the cost of services is of great necessity. There is a scarcity of data on the cost and technical efficiency of using mobile health (mHealth) for early TB, asthma, and COPD detection in rural communities that once done can aid in the achievement of national goals. Thus, we aim to gather health economics data to assess total and unit costs, cost structure, and cost drivers of this technology provision. The purpose of the health economics component of this study is to inform priority setting within the health sector. This will cover resource allocation across an overall budget or total resource envelope from the health provider's perspective that focuses on costs incurred by the implementing partner but also assesses the costs of services and consumables from other providers (eg, national program) in both financial and costs.

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Patient and household expenditures including productivity losses have been barriers to accessing and retention in care. In consultations with health economists, a plan is to collect data on both direct and indirect patient-incurred costs using questionnaires. The study is expected to estimate direct costs incurred by patients such as those related to transport, as well as indirect costs, in terms of productivity losses, related to access to care as well as due to illness-related absenteeism. Together with data on service usage and socioeconomic background, we will be able to analyze patient costs and equity considerations in access and use of care. The study will generate a comprehensive picture of the costs of using mHealth-based cough audio triage testing for active pulmonary TB, asthma, and COPD in health facilities in high-burden settings in Tanzanian communities.

Dissemination Plan

The dissemination of findings will involve communication with key stakeholders, regular reporting through the pertinent channels of the funding agency and the Tanzanian Ministry of Health, engagement in local and international forums, and publication through peer-reviewed open-access journals. By using a methodical and systematic approach to disseminating the study's findings, this research aims to contribute to the expanding knowledge base regarding the use of AI and ML in developing noninvasive diagnostic tools. These tools are designed to assist health care professionals in effectively identifying and distinguishing various diseases, not only within Tanzania but also broadening their application beyond geographical boundaries.

Conclusions

Cough sound classifiers harness the power of advanced technology to offer a promising solution for the early detection and efficient management of various respiratory conditions. By accurately analyzing cough sounds, these innovative tools can identify potential illnesses at an earlier stage than traditional diagnostic methods, facilitating timely intervention and reducing the need for more invasive procedures. This approach not only has the potential to significantly alleviate the burden on public health systems by streamlining the diagnostic process but also aims to improve patient outcomes through faster and more accurate diagnosis. Moreover, the use of cough sound classifiers can democratize health care access, particularly in under-resourced areas, by providing a cost-effective and easily deployable tool for community health workers and primary care settings. Ultimately, the integration of this technology into clinical practice could transform the landscape of respiratory disease management, offering a scalable and efficient solution to global health challenges.

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Data Availability

Some data sets generated and analyzed during this study will not be publicly available due ethical reasons and a need to protect participant privacy but will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Procedures for capturing cough sounds.
[DOCX File , 588 KB - resprot_v13i1e54388_app1.docx]

Multimedia Appendix 2
Procedures for model development.
[DOCX File , 34 KB - resprot_v13i1e54388_app2.docx]

Multimedia Appendix 3
Guidelines for clinical evaluations.
[DOCX File , 31 KB - resprot_v13i1e54388_app3.docx]

Multimedia Appendix 4
Informed consent process, confidentiality, and data protection.

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[DOCX File , 30 KB - resprot_v13i1e54388_app4.docx]

Multimedia Appendix 5
Sample transcript of conversation with generative artificial intelligence.
[PDF File (Adobe PDF File), 68 KB - resprot_v13i1e54388_app5.pdf]

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Abbreviations

AI: artificial intelligence
COPD: chronic obstructive pulmonary disease
CRF: case report form
CXR: chest x-ray
HC: health centre
mHealth: mobile health
ML: machine learning
NTLP: national TB and leprosy programme
OPD: outpatient department
PEF: peak expiratory flow
PI: principal investigator
PORALG: President's Office Regional and Local Administrative Government
TB: tuberculosis
WHO: World Health Organization

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Protocol

Exploring the Pathways of Diabetes Foot Complications Treatment and Investigating Experiences From Frontline Health Care Professionals: Protocol for a Mixed Methods Study

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Abstract

Background: Diabetes affects more than 4.3 million individuals in the United Kingdom, with 19% to 34% developing diabetes-related foot ulceration (DFU) during their lifespan, which can lead to an amputation. In the United Kingdom, every week, approximately 169 people have an amputation due to diabetes. Preventing first-ever ulcers is the most effective strategy to reduce the occurrence of diabetes-related amputations, but research in this space is lacking.

Objective: This protocol seeks to document the experiences and perspectives of frontline health care professionals who work with people who have diabetes and diabetes-related foot problems. Special attention is given to their perceptions of barriers to effective care, their views about barriers to effective and inclusive engagement with people with diabetes, and their experience with the first-ever DFU. Another aspect of the study is the focus on whether clinical management is affected by data sharing, data availability, and interoperability issues.

Methods: This is a mixed methods explanatory protocol, which is sequential, and its purpose is to use the qualitative data to explain the initial quantitative data collected through a survey of frontline health care professionals. Data analysis of quantitative data will be completed first and then synthesized with the qualitative data analysis. Qualitative data will be analyzed using the framework method. This study will use joint displays to integrate the data. Ethical approval has been granted by the ethics committee of Staffordshire University.

Results: The quantitative data collection started in March 2023 and will close in May 2024. The qualitative interviews commenced in November 2023 with volunteer participants who initially completed the survey.

Conclusions: This study's survey focuses on data interoperability and the interviews focus more on the perspectives and experiences of clinicians and their perceived barriers for the effective management of diabetes foot ulcers. Including a geographically relevant and diverse cohort of health care professionals that spans a wide range of roles and care settings involved in diabetes-related foot care is very important for the successful application of this protocol. Special care is given to advertise and promote participation as widely as possible. The qualitative part of this protocol is also limited to 30-40 interview participants, as it is not realistic to interview higher numbers, due to time and resource constraints.

International Registered Report Identifier (IRRID): DERR1-10.2196/54852

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KEYWORDS

diabetic foot; first-ever diabetic foot ulcer; qualitative research; quantitative evaluation; surveys and questionnaires; telephone interviews; primary care; community care; acute care; education of patients; foot ulcer; exploration; diabetes; foot ulceration;

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United Kingdom; diabetic foot ulceration; DFU; amputation; complication; complication; perspectives; experiences; health care professionals; barrier; barriers; effective care; foot care; primary ulcers; quality of life

Introduction

Currently, there are more than 4.3 million people diagnosed with diabetes in the United Kingdom [1], and 19% to 34% of them will develop diabetes-related foot ulceration (DFU) in their lifetime [2]. Out of all DFUs, the literature reports that 10% to 56% will result in amputation [3]. In the United Kingdom, every week, approximately 169 people have an amputation due to diabetes [4,5]. The total direct cost of DFU and diabetes-related foot amputations in England alone is between £837 million (US $1.25 billion) and £962 million (US $1.20 billion) and is steadily rising every year [6]. DFU costs the National Health Service (NHS) more than the 3 most common types of cancer combined [6]; hence, DFU is a major challenge for the financial sustainability of the NHS, and effective prevention could significantly reduce its burden.

Understanding the barriers to effective care and their regional variability is critical for service improvement, leading to fewer diabetes-related foot complications and fewer lower limb amputations [7,8]. A survey of health care professionals working with diabetes-related foot complications, conducted in 2018, highlighted delayed access to specialist care as the most important barrier for effective diabetes-related foot care [9,10]. The key contributors to this problem, which were noted by the responders, included inadequate funding and issues in the areas of referral pathways, patient care, and education [9]. More specifically, about half of the responders indicated a lack of necessary resources. Regarding referrals, the responders of that survey identified inefficiencies in the referral pathways leading to preventable delays. In the area of patient care, the survey indicated a lack of coordination and standardization leading to suboptimal care. The responders also noted that the lack of or ineffective patient education compromises their ability for self-care and leaves them unaware of when to seek help [9].

Structured diabetes education programs are extremely important for promoting effective engagement with health care services and for effective self-management of diabetes-related foot complications [11,12]. To be effective, education needs to be offered to people with diabetes as well as to their families or caregivers [11,12]. It also needs to be designed and delivered in a culturally competent manner [13].

People from ethnic minority groups or socioeconomically disadvantaged communities are disproportionately affected by diabetes and diabetes-related foot complications, experiencing higher morbidity and mortality than majority populations or more affluent communities [13]. Understanding the barriers to effective engagement with these groups is extremely important for effective diabetes-related foot care as well as for robust clinical research.

There is overwhelming evidence that populations from geographical regions that are more actively involved in clinical research tend to benefit from it the most. These benefits include the early adoption and tailoring of new highly effective approaches to care that translate to lower disease prevalence and better patient experience [14,15]. At the same time, regional variations in research participation indicate that the areas and communities with the highest diabetes prevalence are also the least likely to participate in research [16,17]. Ineffective communication and engagement with underserved communities are among the key contributors to this disconcerting discrepancy [14,15], highlighting even further the need to address barriers to effective communication and engagement. Understanding the perceptions of health care professionals about these barriers and how these can be overcome can be helpful to this end.

An exciting new approach for effective DFU care proposed in current literature is to shift medical attention from the management of active DFU to supporting people with diabetes to remain ulcer-free for longer. This can be achieved by focusing efforts to prevent the first-ever DFU from happening [18-20].

Preventing first-ever ulcers (also known as primary ulcers) is the most effective way to reduce the number of diabetes-related amputations and protect the quality of life of people with diabetes. This is because 40% of people with healed first DFU reulcerate within a year (60% reulcerate within 3 years), which significantly increases the risk for amputation [2]. The first-ever DFU incidence is also associated with a 250% increase in the 5-year risk of death [21,22].

Integrated care that combines frequent specialist screening with education and offloading interventions (eg, the use of therapeutic footwear or orthoses) is currently used to prevent recurrent DFU [11,23,24] and is likely to be effective also for the prevention of first-ever ulcers. However, their blanket use across all people with diabetes is practically impossible due to the sheer number of people at risk of their first-ever DFU [18,20,25].

According to current international guidelines, a person with diabetes is considered to be at high risk of DFU when they have had their first-ever DFU or diabetes-related amputation [11,26]. However, as it stands, there is no established method to determine when someone is at high risk of developing their first-ever DFU [11].

Clinical research is needed to develop effective strategies to target preventative care for those at imminent risk for first-ever ulceration [11]. However, studying first-ever ulcers remains significantly more challenging than studying recurrent ulcers. This is due to the scarcity of current and geographically relevant data in the literature to support the design and implementation of research in this area. Moreover, due to their relatively low incidence rate [25], any research on first ulcers is likely to require relatively larger numbers of participants, highlighting the need for effective and inclusive recruitment strategies. To maximize the chances of success, research protocols should be informed by the experience of the health care professionals who will have to lead and deliver this research. This includes identifying strengths to be used and limitations and perceived barriers to participation and recruitment to be addressed [9,27].

In this context, this protocol aims to capture the experience and views of frontline health care professionals working with people

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with diabetes-related foot complications regarding previously identified barriers to effective care from the literature [9]. These barriers may include the effectiveness of referral pathways, the efficiency of communication between disciplines and NHS services, and the adequacy of patient education The experience of frontline health care professionals regarding the first-ever DFU will be also captured to inform clinical research toward more effective DFU prevention.

The primary objective is to identify the potential areas of improvement regarding DFU care delivery and patient-clinician engagement.

The secondary objectives are to (1) model qualitatively the lived experiences of frontline health care professionals about diabetes foot care and (2) develop a theoretical model that describes the interaction between their lived experience and identified barriers to effective care and engagement with people with diabetes.

Methods

Study Design

In agreement with the Equator's Network mission to improve the reporting of health care research, and in the absence of a comprehensive checklist for mixed methods study design, we have adopted the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, given that our study is observational [28]. The STROBE statement covers cohort, case-control, and cross-sectional studies and we will follow the relevant statement's sections about the cohort (for our qualitative data) and cross-sectional (for our quantitative data) studies.

This study uses pragmatism and a mixed methods approach, which has been previously used and supported in the field of health informatics [29,30]. The rationale behind choosing mixed methods is that, based on our pragmatic approach, the best way to achieve the aims and objectives was to mix both quantitative and qualitative data, which complement each other enhancing the results of the study [31,32]. This study uses an explanatory design that is sequential, and its purpose is to use the qualitative data to explain the initial quantitative data.

The study has two main components: (1) a survey and (2) semistructured interviews. This study prioritizes the qualitative data as they are used to explain and enhance the findings of the quantitative data [32]. Interview participants were purposefully recruited from the survey responders, mixing the data-gathering methods. Figure 1 illustrates the mixed methods sequential explanatory design stages of this study.

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Figure 1. A schematic of the proposed mixed methods sequential explanatory study to capture the experiences and perspectives of frontline health care professionals working in the National Health Service (NHS) in the area of diabetes foot complications. Data collection started in March 2023 and is expected to end in May 2024. PPI: patient and public involvement.

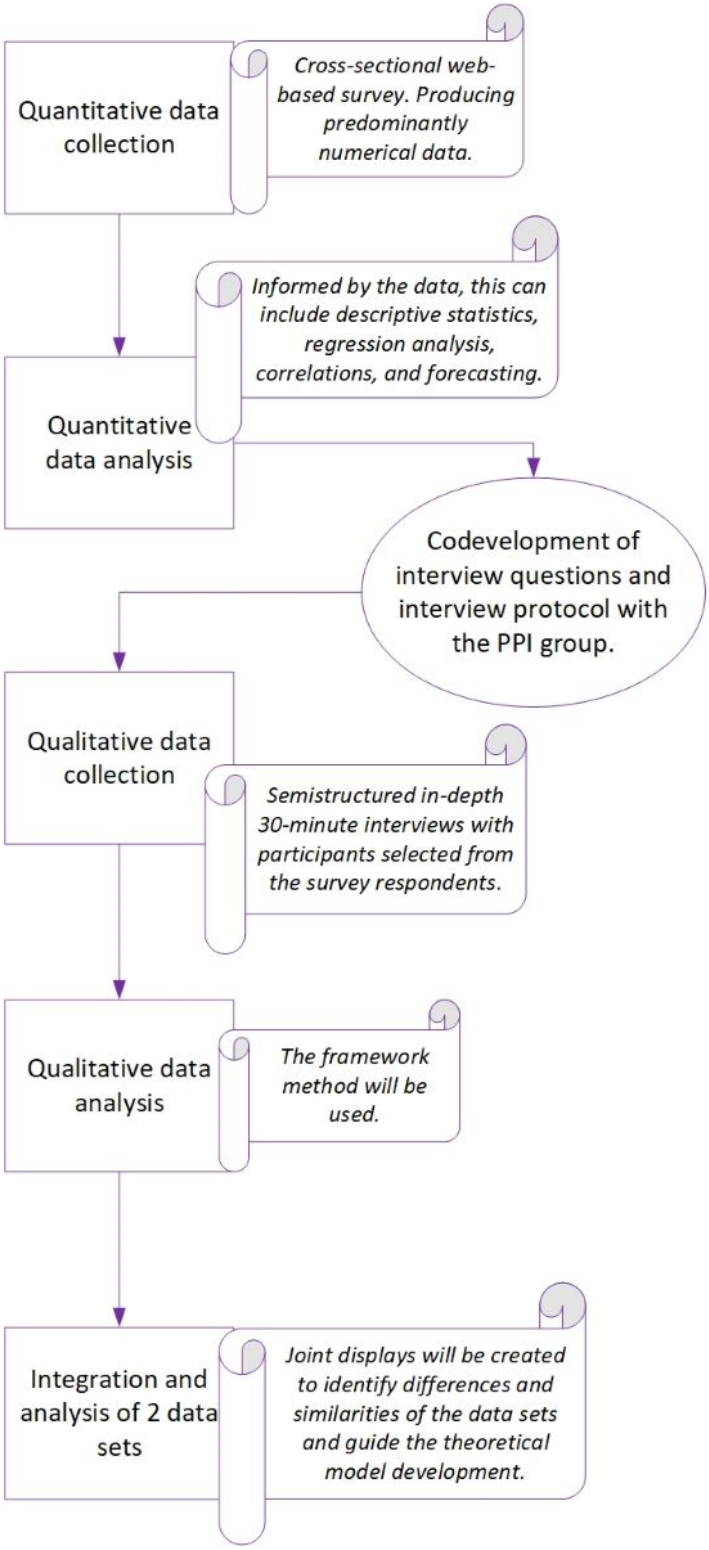

Patients, Sampling, and Recruitment

Recruitment will occur in 2 stages. The first stage includes the recruitment of survey respondents. We aim to attain between 188 and 270 responses that are required for a maximum assumed error of 6% to 5% (90% Cis), respectively [33].

A recruitment strategy, which encompasses a number of different avenues, has been established to enable us to reach out to a diverse audience and maximize the chances of meeting the required target. This includes the distribution of leaflets in relevant scientific conferences, press releases, social media announcements, and dissemination through a network of collaborating NHS trusts and UK universities (and their alumni

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associations) that train health care professionals involved in diabetes foot care. Invitation to participate in this survey was also disseminated through the Staffordshire and Shropshire Health Economy Research Partnership [34] through the National Institute for Health and Care Research Clinical Research Network West Midlands [35], special interest groups on diabetes funded by the National Institute for Health and Care Research (Diabesity group), and NHS integrated care boards.

The survey, which is used during this first stage of recruitment, is also used to obtain permission to contact respondents for interviews for the second stage of recruitment. The interviewees will be divided into 3 main cohorts based on their professional work setting (primary, community, or acute care) to discover and model differences in DFU care delivery across contexts. As this study aims for the greatest variation in demographic distribution, the sampling is purposeful [32,36,37]. We intend to interview around 30-40 health care practitioners since the "gold standard" for a purposive sample is to achieve theoretical saturation. It is impossible to predict an absolute number for theoretical saturation; however, based on prior experience and published recommendations, we believe these figures are reasonable given our objectives, scope, and methodology [32,36,38,39].

The interview participants' selection was based on the following criteria in importance ranking to ensure variation in (1) roles within the care pathway for diabetes foot complications, (2) gender, (3) years of experience, and (4) age group.

Inclusion criteria are (1) participant is willing and able to give informed consent for participation in the study, (2) people aged 18 years or older, and (3) any grade or discipline of health care professional working in diabetes foot care.

Exclusion criteria are (1) inadequate spoken English or unable to participate in a web-based interview, (2) health care professionals who are not working in the diabetes foot care field, and (3) health care professionals not working in NHS.

An assumption has been made that everyone who fills the survey and understands English well. Nonetheless, if we suspect that the interviewee's English comprehension and articulation are inadequate, we will exclude them and replace this interview.

Measures

This project will collect quantitative and qualitative data via a web-based survey and further qualitative data from the same group via web-based or telephone interviews.

The survey design was cocreated in conjunction with a patient and public involvement (PPI) group of people with diabetes and diabetes foot complications. The first draft of this survey was cocreated with the 10 health care professionals who also face validated and pilot-tested it. Those health care professionals included a diabetologist, 3 general practitioners, and 6 podiatrists who worked in community, acute, and primary care settings. The survey design can be found in Multimedia Appendix 1. We plan to publish the results of the survey after the analysis is concluded.

Microsoft Excel (Microsoft Corp) will be used for descriptive statistics, while SPSS (IBM Corp) will be used to conduct inferential statistical tests, such as regression analyses and other data-driven tests to assess the association between factors.

For the qualitative component of this protocol, we shall conduct single semistructured interviews (maximum 40 minutes) to explore user experience about the DFU clinical pathway barriers, clinician-patient communication issues, and research participation. We will obtain informed consent and the interviews will be audio recorded and fully transcribed. The interview guide (Multimedia Appendix 2) followed the structure of the NHS Integrated Research Application System guidelines, and it was cocreated with our PPI group.

The framework method [40] will be used for the qualitative data analysis, allowing themes to be produced both inductively (from the interviews) and by adding themes that originate from the survey. The framework method is systematic, comprehensive, and data driven, but it is also adaptable and allows facts to be shown visually [40,41]. The framework method has step-by-step instructions for application, and this study aims to adhere to Gale et al [41] recommendations.

For coding, NVivo (QSR International) will be used. An independent researcher will code a portion of the files (around 25%), and after comparing the themes, the interrater reliability score will be calculated. Following the coding of half of the transcripts, a framework with well-defined and grouped together codes will be created and applied to the remaining transcripts [41]. During data merging, the qualitative data will be interpreted alongside the quantitative.

Having arranged the quantitative and the qualitative data in a format based on thematic relevance to allow merging, further integration will be needed. This study will use joint displays to integrate the data in a similar fashion and to gain a better understanding of the complexity of the observed phenomena [42]. The combined display, should the data collection permit such integration, will have rows representing the participants and columns representing each theme (obstacles in DFU care delivery and research engagement issues, etc), along with the quantitative variables (years of experience, type of employment, etc). This approach may help us better understand the roles of individual themes as enablers or barriers to effective patient care.

Ethics Approval

Ethical approval for this study has been granted by Staffordshire University's ethics committee (approval: SU_22_113). All participants provide informed consent before any quantitative or qualitative data are collected.

All potential responders to the survey are first required to read through the participant information sheet and to fill a specific consent form before accessing the main body of the survey. To ensure that no quantitative data are collected without consent, the participants can only access the survey if they agree to all consenting questions (see consent form in Multimedia Appendix 1).

Consenting to take part in the quantitative part of this mixed methods study does not directly qualify a person to participate also in the follow-up interviews. A separate consenting process

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was followed to this end. More specifically, at the end of the survey, it is explained that based on their responses the research team might want to invite them to take part in a semistructured interview. It is explained that the purpose of this interview will be to ask some more specific questions regarding their response to the survey and that the interview will be on the web or over the phone (see follow-up in Multimedia Appendix 1). The questionnaire responder is then asked to indicate whether they consent to be contacted again to arrange the interview. Answering "no" to this question brings the survey to an end, enabling the responder to submit their answers for analysis. Answering "yes" reveals an additional question where the responders are asked to provide their contact details before submitting their survey responses for analysis and exiting the survey. If they are selected to take part in the qualitative data collection, participants who consent to be contacted again are invited to take part in the semistructured interviews. Consent to be interviewed and to have the interview recorded and transcribed is verbally confirmed at the start of each interview. No qualitative data are recorded for survey responders who do not consent to be contacted again. In addition, no qualitative data are recorded for survey responders who consent to be contacted again but fail to provide explicit consent to be interviewed.

All collected personal information will be kept confidential on a password-protected computer. Only members of the research will have access to this information. The contact details of the people who consent to be contacted again will be used to arrange and conduct the interviews and they will be deleted at the end of data collection. Special care will be given during dissemination to ensure that all data are presented in an anonymized form so that no identification of individual participants is possible.

No compensation or financial incentive will be provided to survey responders. Participants taking part in an interview will receive a £10 (US $12.5) shopping voucher.

PPI Involvement

People with diabetes and diabetes foot complications have been involved throughout this research to increase transparency, minimize bias, and maximize clinical relevance. All members of the PPI group were recruited based on posters displayed in Stoke-On-Trend community areas and general practitioner practices as well as social media posts. The selection criteria involved people with diabetes and diabetes foot complications, who are consenting adults, and able to express their opinions.

Early in the design of this study, our aim, objectives, and areas of focus of the survey were discussed within a group of 4 people with diabetes and diabetes foot complications. The final questionnaire was designed based on their feedback. The initial core PPI group has since been extended to include 9 people with diabetes and diabetes foot complications. This extended PPI focus group met at Staffordshire University in June 2023 to discuss plans for the semistructured interviews. Discussions in this meeting enabled identifying topics and specific questions that were important to them. These were then included in the interview script. The final interview script was shared with the members of the PPI group during a separate web-based meeting to ensure that their feedback was correctly used.

Results

So far, this study has had 223 respondents in the web-based survey, and the interview invitations have started. We have invited 30 participants for the interviews, and based on their willingness to be interviewed and their responses, we will keep inviting interviewees, within reason, until theoretical saturation is reached. The study's data collection will close in May 2024. Initial data analysis has commenced, with results expected to be published by the end of 2024.

Discussion

The protocol presented here aims to capture the experience and views of frontline health care professionals working with people with diabetes-related foot complications. Emphasis is given to previously identified barriers to effective care regarding the effectiveness of referral pathways, the efficiency of communication between disciplines and NHS services, and the adequacy of available resources and patient education [9]. This protocol also recognizes the need to help people with diabetes remain ulcer-free for longer [18-20]. With this in mind, the experience of frontline health care professionals regarding the first-ever DFU will be also captured to inform clinical research toward more effective DFU prevention.

To this end, a mixed methods explanatory protocol will be implemented. This protocol is sequential, and its purpose is to use qualitative data to explain the initial quantitative data collected through a survey of frontline health care professionals. Data analysis of quantitative data will be completed first and then synthesized with the qualitative data analysis. Compared to relevant literature, this protocol can offer a more comprehensive overview of the perceptions of frontline clinicians regarding diabetic foot care. It is also the first to include the perspective of health care professionals working in primary care [9].

Regarding the limitations of this protocol, even though special care is given to advertise and promote participation as widely as possible, it is likely that dissemination through institutions that are participating in this research will be more effective, leading to greater numbers of responders. These institutions are based in England, and most of them are based in West Midlands. The inability to attain responses with a representative spread across the country could limit the representativeness of results. This study is also limited to the 30-40 interview participants, as it is not realistic to interview higher numbers, due to time and resource constraints.

Once completed, this study can offer new insight into potential improvements regarding DFU care delivery and patient-clinician engagement toward reduced DFU and amputation rates. It will also provide a contextual evidence base for further studies related to DFU care delivery and DFU care workflow.

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Acknowledgments

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Data Availability

The data that will be collected as part of this study will be made available upon reasonable request sent to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey.
[PDF File (Adobe PDF File), 1675 KB - resprot_v13i1e54852_app1.pdf]

Multimedia Appendix 2
Interview guide.
[PDF File (Adobe PDF File), 660 KB - resprot_v13i1e54852_app2.pdf]

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Abbreviations

DFU: diabetes-related foot ulceration
NHS: National Health Service
PPI: patient and public involvement
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Real-World Registry on the Pharmacotherapy of Multiple Myeloma and Associated Renal and Pulmonary Impairments in the Greater Gulf Region: Protocol for a Retrospective Real-World Data Study

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Abstract

Background: Multiple myeloma (MM) is the second-most common cancer among hematological malignancies. Patients with active disease may experience several comorbidities, including renal insufficiency and asthma, which may lead to treatment failure. The treatment of relapsed or refractory MM (RRMM) has been associated with multiple factors, causing a decline in progression-free survival as well as overall survival with subsequent lines of therapy. Data about the characteristics of this group of patients in the Greater Gulf region are lacking.

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Objective: The primary objective of this study is to describe the disease characteristics and various treatment approaches or regimens used in the management of patients with RRMM in the Greater Gulf region.

Methods: We will conduct a regional, retrospective study collecting real-world and epidemiological data on patients with MM in countries of the Greater Gulf region. Medical records will be used to obtain the required data. Around 150 to 170 patients' records are planned to be retrospectively reviewed over 6 months without any cross-sectional or prospective intervention. Cases will be collected from Saudi Arabia, the United Arab Emirates, Kuwait, Oman, and Qatar. Descriptive as well as analytical statistics will be performed on the extracted data. The calculated sample size will allow us to estimate the percentages of RRMM cases with acceptable precision while complying with the challenges in light of data scarcity. We will obtain a comprehensive description of the demographic profile of patients with MM; treatment outcomes; the proportion of patients with MM with renal impairment and asthma, chronic obstructive pulmonary disease, or both at the time of diagnosis and any subsequent point; and data related to treatment lines, regimens, and MM-associated morbidities.

Results: Patient medical records were reviewed between June 2022 and January 2023 for eligibility and data extraction. A total of 148 patients were eligible for study inclusion, of whom 64.2% (n=95) were male and 35.8% (n=53) were female. The study is currently in its final stages of data analysis. The final manuscript is expected to be published in 2024.

Conclusions: Although MM is a predominant hematological disease, data on its prevalence and patients' characteristics in the Greater Gulf region are scarce. Therefore, this study will give us real-world insights into disease characteristics and various management approaches of patients with MM in the Greater Gulf region.

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KEYWORDS

Greater Gulf region; multiple myeloma; pulmonary dysfunction; renal impairment; RRMM; Real-world data

Introduction

Overview

Multiple myeloma (MM) is a malignant clonal cancer of plasma cells of the bone marrow that results in an overproduction of huge amounts of light- and heavy-chain monoclonal immunoglobulins [1,2]. In 2020, MM was revealed as the second most predominant hematological malignancy, representing about 10% of hematologic cancers [1], with 176,404 new cases and 117,077 deaths detected worldwide [3]. The hallmark of monoclonal immunoglobulins in MM is the monoclonal protein (M protein), named after its monoclonal properties, detected in patients with MM's serum and urine [2]. The potential uncontrolled growth of these plasma cells causes destructive bone lesions, kidney injury, anemia, and hypercalcemia [4]. About 15% to 30% of patients have the clinical presentation of hypercalcemia with concomitant renal insufficiency caused by precipitated monoclonal light chains in the collecting tubules [5,6]. However, in asymptomatic patients, the disease is accidentally discovered after detecting anemia or hyperproteinemia [1]. Moreover, around 10% of patients with MM showed a previous history of asthma or chronic obstructive pulmonary disease (COPD). The treatment of MM involves the use of steroids; standard chemotherapy (including cyclophosphamide, melphalan, and bendamustine); proteasome inhibitors such as bortezomib and ixazomib [7]; anti-CD38 monoclonal antibodies (eg, daratumumab and isatuximab), and autologous stem cell transplantation (ASCT) [8].

Guidelines have approved anti-CD38 monoclonal antibodies simultaneously with lenalidomide and dexamethasone for treating relapsed or refractory MM (RRMM) following their remarkable efficacy. Alongside clinical disease complications, the treatment of patients with RRMM relied on 3 key points: the duration of response (DoR), progression-free survival (PFS), and overall survival (OS) reduction with successive lines of therapy [9].

MM shows a socioeconomic burden on the patients as well as their families. Rare data regarding MM in the Middle East have been detected [10]. Nevertheless, the United Arab Emirates (UAE) and Qatar were among the countries with the largest prevalence of MM cases and deaths over the past 30 years across the world [11].

Rationale

The primary objective of this study is to detect the associated characteristics of patients with RRMM and the treatment landscape in the Greater Gulf region. The secondary objectives are to describe MM disease history; assess the prevalence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region; assess the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region, both at diagnosis and throughout the disease course; describe renal response (overall, per treatment line and regimen for patients with renal impairment); describe the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen); and reveal the percentage of patients with RRMM who are eligible for ASCT.

Methods

Overview

Due to the rarity of MM, this study will be a regional, retrospective study aimed at collecting real-world and epidemiological data from patients with MM's medical records in countries in the Greater Gulf region. In addition, the study will describe the demographic characteristics and treatment

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landscape of patients diagnosed with RRMM who have relapsed at least once and maximally 3 times before study entry in the 2 years leading up to data collection. Medical records will be checked for eligibility, and data will be retrieved from all participating countries, including Saudi Arabia, the UAE, Kuwait, Oman, and Qatar.

Participants for whom medical records will be eligible for inclusion, review, and analysis must fulfill the following criteria: male or female patients with RRMM who have relapsed at least once and a maximum of 3 times before study entry in the 2 years leading up to data collection. Patients should be 18 years or older, male or female, diagnosed with RRMM (first, second, and third relapses only, who had 1-3 previous lines of treatment) within a maximum of 2 years before data collection time, and have complete patient medical records from MM diagnosis to date of death or medical abstraction. Patients will be excluded as follows: patients not undergoing treatment for MM or newly diagnosed patients (first-line patients); patients with a history of other malignancies; pregnant patients or those planning for pregnancy; or patients with end-stage renal disease.

This study is based on the secondary use of data; expedited reporting of adverse events or adverse drug reactions is not required. However, the sponsor will report all safety observations made during the conduct of the study in the study report.

All of the data will be obtained from the available records as shown in Textbox 1.

Textbox 1. Study flowchart. All the data will be obtained from the available records. Data will be collected from Saudi Arabia, the United Arab Emirates, Kuwait, Oman, and Qatar.

Evaluation or data points in patients' records

- *Inclusion and exclusion criteria*
- *Patient characteristics*: nationality, gender, age, and race
- *Multiple myeloma (MM) disease history*: year of diagnosis, diagnostic method used, levels of heavy-chain immunoglobulin, hematological biomarkers, other laboratory findings, and symptoms before diagnosis (if available)
- *Cytogenetic abnormalities*
- *MM-associated morbidities*: renal impairment (estimated glomerular filtration rate values or other kidney function tests) and pulmonary impairment (including asthma and chronic obstructive pulmonary disease)
- *Lines of treatment used*: first-line regimens (at diagnosis), second-line regimens (after first relapse), third-line regimens (after second relapse), and fourth-line regimens (after third relapse)
- *Treatment regimens*: monotherapy or combination therapy
- *Reasons for treatment change or discontinuation*
- *Eligibility for stem cell transplant*
- *Lenalidomide refractoriness status*
- *Treatment outcomes*: dates of progression, relapses, and requiring treatment escalation (due to refractoriness or relapse)
- *Time to progression*
- *Minimum residual disease negativity (if applicable)*

Data sources include—but are not limited to—hospital records (medical, clinic, and pharmacy) and office charts; memoranda; evaluation checklists; laboratory reports, radiology reports, and imaging data (eg, ultrasonography and scans on film or digital media); computer printouts; and any other documentation regarding the patient (including the patient diary).

Based on the study by Lecat et al [12], 71% of patients with RRMM became refractory to lenalidomide after an initial response. Considering an observed percentage of 71% (120.7/170) with an absolute precision of 8% and a 95% CI, a sample size of a minimum of 150 patients was calculated based on the below formula:

To estimate an observed percentage of 50% (85/170) with an absolute precision of 8% and a 95% CI, the sample size for this retrospective study was estimated to be 170 patients with the assumption that 10% (15/150) of enrolled patients would not be valuable for the primary analyses due to missing values or unfulfilled inclusion and exclusion criteria.

It is planned to review the medical records of the 170 patients from all participating countries, including Saudi Arabia, the UAE, Kuwait, Oman, and Qatar.

The final study will include 15 medical centers distributed as follows: 10 in Saudi Arabia; 3 in the UAE; and 1 medical center each from Qatar, Oman, and Kuwait.

This study is categorized as a Group E study with no applicable individual case safety reporting; however, either aggregate analysis may provide safety conclusions of interest for the product or, even if the analysis is not intended for safety purposes, it may raise a safety signal. Any potential safety signal will be transmitted to the company's pharmacovigilance department.

All data collected will be analyzed appropriately, and statistical analysis will be carried out by SPSS (version 18 or higher; IBM

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Corp). The associated characteristics of RRMM will be described using frequency and percentage with a 95% CI. Other variables will be described using the mean (SD) for continuous variables and counts for categorical variables. Patients' variables will be compared using Mann-Whitney-Wilcoxon tests for continuous variables and chi-square for categorical variables. A probability value of less than 5% (P<.05) will be considered significant.

Primary Analysis

The associated characteristics of RRMM will be described using frequency and percentage with a 95% CI. This analysis will be descriptive and will be conducted on the eligible patients who fulfill the inclusion criteria and who have been selected during the specified study period.

Secondary Analysis

The disease history for MM will be assessed using frequency and percentage with a 95% CI. This analysis will be descriptive and will be conducted on eligible patients. The incidence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region and the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region will be presented using incidence density rates. Comparison will be done using Mann-Whitney-Wilcoxon tests for continuous parameters and chi-square for categorical parameters. The description of renal response (overall, per treatment line and regimen for patients with renal impairment), the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen), and the percentage of patients with RRMM who are eligible for ASCT will be described using frequency and percentage. Univariate and multivariate analyses will be conducted on lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region and other variables collected.

This section provides specifications for preparing the final statistical analysis plan, which will be issued before the database lock. Therefore, any differences compared to this statistical section should be identified and documented in the final statistical analysis plan.

Statistical Analysis

The data will be analyzed using SPSS version 26 software. Categorical variables will be reported as frequency (n) and percentage (%), while quantitative variables will be reported using descriptive measures such as mean, SD, and range. The chi-square test will be used to determine the association of different risk factors with treatment regimens. A value of P<.05 to determine the significance level will be used. Multivariate logistic regression analysis will be used to analyze the relationship between the dependent variable and multiple predictors or independent variables. PFS and OS will be used accordingly.

Ethical Considerations

This study is being conducted in accordance with the principles established by the 18th World Medical Assembly in Helsinki in 1964, along with all subsequent amendments [13]. All patient data will be handled anonymously to ensure patient confidentiality. In accordance with the institutional review board (IRB) approval obtained for this study, there is no requirement for informed consent. The final study will include 15 medical centers, distributed as follows: 10 in Saudi Arabia; 3 in the UAE; and 1 medical center each from Qatar, Oman, and Kuwait. IRB approvals were obtained from the participating countries. In Saudi Arabia, approval was obtained from Mouwasat Hospital under the IRB NCBE- KACST (H-05-D-12) on October 10, 2022; the Directorate of Health Affairs-Aseer Region (REC-15-06-2022) on June 20, 2022; King Faisal Specialist Hospital and Research Center under IRB 2022-47 on June 22, 2022; King Fahad Medical City under 2 hospitals—Al Mana Hospital (King Fahad Medical City approval as an external site, IRB 22-212E in December 2022) and Alkhobar Comprehensive Cancer Center (22-212 IRB 22-212) on July 26, 2022; King Saud University-Medical City under 22/0626/IRB on August 23, 2022; Prince Mohammed bin Nasser Hospital under 22058 on June 28, 2022; and King Abdullah International Medical Research Center-Al Ahsa and King Abdullah International Medical Research Center-Riyadh (IRB: 1519/22) on August 31, 2022. In UAE, approval was obtained from Burjeel Hospital (DOH/CVDC/2022/1473) on August 11, 2022; Cleveland Clinic Abu Dhabi (DOH/CVDC/2022/1622) on November 10, 2022; and Sheikh Shakhbout Medical City, Abu Dhabi, UAE (DOH/CVDC/2022/740) on April 28, 2022. In Oman, approval was obtained from Sultan Qaboos University Hospital (SQU-EC/174/2022 MREC#2801) on July 13, 2022. In Kuwait, approval was obtained from the ethics committee in the Ministry of Health (2022/1988) on May 17, 2022. In Qatar, approval was obtained from the National Center for Cancer Research (MRC-02-22-37) on October 2, 2022.

Data Analysis

Upon completion of this study, a comprehensive description of the demographic profile of patients with MM, including age, gender, and other relevant data, will be obtained. As well, data on patients undergoing different treatment modalities and regimens, including monotherapy or combination therapy, both overall and for each treatment line, will be collected. Additionally, information on the DoR and time to progression (TTP), both overall and within different treatment lines, will be gathered. This includes assessing the percentage of patients with lenalidomide-refractory in the first, second, and third relapse settings. The study will record the history of MM, including the duration of the disease, laboratory levels of biomarkers, and symptoms before diagnosis. Furthermore, we will investigate the proportion of patients with MM with renal impairment and asthma, COPD, or both at the time of diagnosis and at any point thereafter. These data will be collected for each treatment line and regimen. The changes in estimated glomerular filtration rate and other relevant parameters from baseline to evaluate renal response (whether it remains stable, improves, or worsens) will be analyzed. In addition, information on the proportion of patients prescribed lenalidomide at each treatment line and the treatment regimen for patients with lenalidomide-refractory will be retrieved. TTP and DoR among patients with lenalidomide-refractory in different treatment lines and regimens will be calculated according to the International Myeloma Working Group criteria [2]. For instance, the DoR

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will be calculated in the subpopulation experiencing treatment response from the date when the response is first met to the date of the first documented progression, whereas the TTP will be calculated as the length of time from the date of diagnosis or the start of treatment for a disease until disease progression. Moreover, the proportion of patients eligible for ASCT at any time after diagnosis will be determined. The definitions of "relapsed" and "refractory" MM have been varied across clinical studies. While some studies have defined "relapsed" as those patients with recurrent malignancies following a remission or patients who were positively affected by rescue therapy yet experienced disease progression during their follow-up with or without maintenance therapy, others have defined patients with "refractory" MM as those who have a failed response (or showed a limited response) to rescue therapy or who progress within 60 days of their last regimen [14,15]. This study will assess the used definitions and their impact on the OS and PFS of the included patients.

Compliance

RAY-Contract Research Organization (CRO), a third party delegated by Sanofi, is solely responsible for taking all reasonable steps to ensure the proper conduct of the protocol regarding ethics, protocol compliance, and the integrity and validity of the data recorded on the case report form (CRF). The primary responsibility of RAY-CRO is to assist the investigating site in maintaining high standards of ethical, scientific, technical, and regulatory quality throughout the study.

At regular intervals during the study, the site will be contacted, through monitoring visits, letters, or telephone calls, by a representative of the monitoring team to review study progress, investigator and patient compliance with study protocol requirements, and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized by the investigator: IRB approval, documentation and reporting, and quality of data in the CRF.

The main duty of the monitoring team of RAY-CRO will be to assist the investigator and the sponsor in maintaining high ethical, scientific, technical, and regulatory standards throughout the study. Regular monitoring visits, letters, or telephone calls will be made to the site to review study progress, investigator and patient compliance with study protocol requirements, and any emerging issues. During these visits, the investigator will be scrutinized on, but not limited to, the following points: IRB approval, data documentation, and the quality of data in the CRF.

Results

Patient medical records were reviewed between June 2022 and January 2023 for eligibility and data extraction. A total of 148 patients met the study inclusion criteria, of whom 64.2% (n=95) were male and 35.8% (n=53) were female. The study is currently in its final stages of data analysis, and the final manuscript is expected to be published in 2024.

Discussion

Summary

This study is expected to provide reliable data on MM and associated renal and pulmonary impairments in the Greater Gulf region, through the collection of real-world and epidemiological data from the medical records of patients with MM in countries in the Greater Gulf region. In addition, the study will describe the demographic characteristics and treatment landscape of patients diagnosed with RRMM who have relapsed at least once and maximally 3 times before study entry in the 2 years leading up to data collection. All patients who have relapsed at least once and a maximum of 3 times before study entry in the 2 years leading up to data collection will be included. The incidence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region, the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region, renal response, the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory, and the percentage of patients with RRMM who are eligible for ASCT will be presented.

Expected Outcomes and Comparisons With Previous Work

Although MM has been detected at increasing rates in some countries of the Greater Gulf region [11,16], fewer studies have been conducted regarding low-income countries, including the Middle East and North Africa [17]. Nevertheless, the treatment of MM, largely in relapsed cases, poses major challenges. Although new drugs and other therapeutic interventions enhance the prognosis of MM, the availability of these drugs is limited across the Middle East [18]. Hence, this study will provide an overview of the treatment regimens and associated patient characteristics in Greater Gulf countries. Regardless of updated national guidelines established in the Greater Gulf countries, a deficiency in complete data to guide the decision makers of local patients is detected. Educational gaps arise, and bespoke initiatives are required to help oncologists individualize the treatment and translate the evidence-based endorsements into real-world practice [19,20]. With this study, we hope to elucidate the incidence of lenalidomide-refractoriness among patients with RRMM and the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen) to guide physicians with the best treatment options and better survival outcomes.

Patients who experienced a ≥25% increase in serum or urine M protein have a biochemical relapse, are considered asymptomatic, and are closely monitored without treatment [21]. In contrast, patients with high-risk disease, including those with negative cytogenetics, suboptimal response to previous treatment, or aggressive disease at diagnosis [22], or those who exhibit a rapid escalation in serum or urine M protein levels, for instance, a doubling time of 2 months or less, should initiate therapy immediately [23]. It is expected that if our patients reveal symptomatic relapse, it should be managed based on the criteria of the International Myeloma Working Group. We hope that this study can provide us with the actual management

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procedures followed in each country and the consequent responses of those patients.

Regarding the demographic data for MM, age is considered a crucial prognostic factor for patients with MM. Patients aged above 50 years at diagnosis usually exhibit significantly shorter median survival times than younger patients [24]. Nevertheless, recent MM therapy protocols have improved the clinical outcome, particularly in patients younger than 70 years [24,25], while the survival advantage has been recently detected in older patients [26]. This controversial conclusion regarding the improved survival in the older population with MM could be due to the detected variability of the age range included in interventional clinical trials (ie, aged between 60 and 65 years) and the median age of patients with MM at diagnosis (usually around the age of 70 years) in other studies. The median time for diagnosis for these patients usually ranges between 2 and 4 years [23]. According to a study conducted in Jordan, the median age of the included patients was 62 years, the mean OS was 74 months, and the median survival was 38 months [17]. Our anticipated results will provide us with a clear indication of the age range and the influence of age on the prognosis and survival of those patients.

In addition, patients older than the age of 75 years exhibit an increased cumulative incidence of renal insufficiency and cardiovascular disease, from 47.7% at MM diagnosis to 67.8% at the first relapse exhibited. Moreover, in patients with MM aged 75 years or older, the risk of relapse post–second-line therapy increased significantly and alternated by time to the next treatment [11]. Nevertheless, younger patients have exhibited better survival than older populations, particularly those younger than 40 years of age, where they are rarely detected with such comorbid diseases [27]. Additionally, geriatric assessments were recommended to be incorporated into routine clinical practice at the diagnosis of MM and for the exclusion of differential diagnoses in the very elderly. This approach aims to achieve optimum therapy and the adjustment of both dosing and regimens for improved effectiveness and tolerability [28]. As such information is missed among patients with MM in the Greater Gulf countries, this study shall provide us with more details regarding the prognosis of patients aged over 75 years with renal insufficiency, cardiovascular diseases, or both; their management procedure; and the effect of younger age over survival.

For lenalidomide-refractoriness among RRMM, improvement in renal function in patients with RRMM and renal impairment following lenalidomide- or dexamethasone-based treatment has been revealed by many studies [29-31]. Similarly, patients with MM presented with asthma or COPD showed significantly longer time from first- to second-line treatment. Additionally, the OS from first-line therapy was remarkably lower among patients with COPD, with a statistically significant decline in the OS from second-line therapy [32]. As no previous studies in the Middle East and North Africa region have provided the effect of first- or second-line treatment on patients with associated asthma or COPD, this study will assess the OS and PFS in those patients and compare the influence of first- or second-line therapy on survival.

Limitations

Anticipated limitations of this study include the heterogeneity of management guidelines among the included countries, which may restrict the results obtained from real-world data by reflecting actual practice, influenced by patient compliance and environmental factors rather than solely by the efficacy of the drugs. Furthermore, despite the relative consistency of first-line therapy in the countries of the Gulf Cooperation Council, several different treatment options become available after the first relapse. This study may not be able to comprehensively capture the multiple factors influencing the selection of specific regimens at the first stage of progression. Additionally, the proportion of patients receiving anti-CD38 monoclonal antibody therapy such as daratumumab or isatuximab, which has significantly transformed the MM treatment landscape, remains relatively limited to date.

Conclusion

This study will provide a more comprehensive understanding of the management of MM in the Greater Gulf region, with a particular focus on the renal and pulmonary complications that may arise. We will delve into the wider significance of this study, addressing potential predisposing factors and their implications for clinical practice and public health in the region. This study seeks to shed light on how the insights gained can inform healthcare strategies and ultimately enhance the quality of care for patients with MM in this specific geographic area.

Acknowledgments

The authors would like to thank Dr Shimaa Ragab, from RAY-CRO, for her valuable editorial support. The authors also acknowledge Dr Omar M Hussein and Dr Reham Elgarhy, from RAY-CRO, for their valuable review and guidance. The study is conducted by Sanofi Saudi Arabia, Tahlia Street, Nojoud Center, Gate C, Jeddah, Saudi Arabia. Sanofi will provide the basic study material (study outline and protocol template) needed for RAY to develop the study materials, including protocol information, data collection items, a review of the medical manuscript, and approval for journal submission. Furthermore, in accordance with local and international regulations, Sanofi Saudi Arabia will be responsible for the monetary funding for the study conducted and publication, and RAY Clinical Research Organization will ensure operational execution. Also, we confirm that this study protocol was revised by the representative of Sanofi before submission.

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Data Availability

Data will be presented in the main manuscript or additional supporting files whenever possible. After completing the study, the data obtained during and/or analyzed during this study will be available upon request through the corresponding author. The authors hereby state that no generative artificial intelligence was used in any portion of the manuscript writing.

Authors' Contributions

The principal investigator for this study is AN, who developed the initial draft of the protocol. Further versions were edited by A Alshehri, A Alhejazi, BU, GE, and HM, while IM, KAF, MA, MS, and RG reviewed the content and development of the paper. All authors provided inputs for the study protocol and approved the final version of the manuscript after their revisions.

Conflicts of Interest

MR and MZC are employees at Sanofi. The authors have no further conflicts to declare.

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Abbreviations

ASCT: autologous stem cell transplantation
COPD: chronic obstructive pulmonary disease
CRF: case report form
DoR: duration of response
IRB: institutional review board
M protein: monoclonal protein
MM: multiple myeloma
OS: overall survival
PFS: progression-free survival
RRMM: relapsed or refractory multiple myeloma

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TTP: time to progression
UAE: United Arab Emirates

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Protocol

Tobacco Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED): Protocol for a Noninterventional Observational Study

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Abstract

Background: In the last few years, several nicotine products have become available as alternatives to smoking tobacco. While laboratory and limited clinical studies suggest that these devices are less toxic compared to classic tobacco cigarettes, very little is known about their epidemiological impact. Visiting the emergency department (ED) often represents the first or even the only contact of patients with the health care system. Therefore, a study conducted at the ED to assess the impact of these products on health can be reliable and reflect a real-life setting.

Objective: The aim of this noninterventional observational study (SMOPHED study) is to analyze the association between the severity of clinical presentation observed during ED visits among patients using various nicotine products and the subsequent outcomes, specifically hospitalization and mortality.

Methods: Outcomes (hospitalization and mortality in the ED) will be examined in relation to various patterns of nicotine products use. We plan to enroll approximately 2000 participants during triage at the ED. These individuals will be characterized based on their patterns of tobacco and nicotine consumption, identified through a specific questionnaire. This categorization will allow for a detailed analysis of how different usage patterns of nicotine products correlate with the clinical diagnosis made during the ED visits and the consequent outcomes.

Results: Enrollment into the study started in March 2024. We enrolled a total of 901 participants in 1 month (approximately 300 potential participants did not provide the informed consent to participate). The data will be analyzed by a statistician as soon as the database is completed. Full data will be published by December 2024.

Conclusions: There is substantial debate about the harm reduction potential of alternative nicotine products in terms of their smoking-cessation and risk-reduction potential. This study represents an opportunity to document epidemiological data on the link between the use of different types of nicotine products and disease diagnosis and severity during an ED visit, and thus evaluate the harm reduction potential claims for these products.

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KEYWORDS

NEWS; National Early Warning Score; emergency department; smoking; nicotine/tobacco use; electronic cigarettes; heated tobacco products

Introduction

Smoking-related diseases are a well-known group of pathologies that are responsible for 8 million deaths per year globally [1]. Despite numerous restrictions, taxation, and communication campaigns, there are still more than 1.3 billion smokers globally. Quitting smoking remains one of the most cost-effective methods to reduce health risks. However, the success rate of smoking cessation methods remains low in real-world settings [2-5]. Additionally, a substantial proportion of smokers are unwilling to use smoking cessation services but would prefer switching to a less harmful alternative product [6,7]. In the last few years, several alternatives to smoking nicotine products have become available, which are commonly referred to as electronic nicotine delivery systems (ENDS), namely e-cigarettes and heated tobacco products (HTPs). While laboratory and limited clinical studies suggest that these products reduce exposure to toxins and may thus reduce health risks [8-12], very little is known about their epidemiological impact.

Several studies have demonstrated a high proportional cigarette smoking prevalence in patients presenting to the emergency department (ED), which is higher than the prevalence in the general population [13-19]. This is expected considering the disease burden caused by smoking, which might result in more ED visits for smokers compared to nonsmokers. Current smoking as well as smoking relapse were found to be significantly associated with ED visits [20-24]. Access to the ED often reflects the first or the only contact of patients with the health care system; thus, the ED visit represents an opportunity to record smoking and nicotine use patterns. However, no studies have systematically recorded use patterns for ENDS in relation to ED visits. Considering the growing popularity of these products and the limited epidemiological evidence on their health effects, a detailed recording of use patterns for all nicotine products is important to monitor their use prevalence, health care system burden, and epidemiological impact.

The National Early Warning Score (NEWS) is a standardized tool used for assessing and responding to acute illness in patients admitted to the ED [24]. The NEWS is based on a straightforward aggregate scoring system, assigning scores to routine physiological measurements taken when patients either present at or are monitored in the hospital. The scoring system is based on six key physiological parameters: (1) respiration rate, (2) oxygen saturation, (3) systolic blood pressure, (4) pulse rate, (5) level of consciousness or new confusion (alert, verbal, pain, unresponsive [AVPU] scale), and (6) temperature.

For patients accessing the ED, the NEWS aids triage nurses in determining the appropriate urgency level for patient examination, which is represented by color codes. This stratification is based on the severity and urgency of the patient's condition.

The aim of this study is to accurately document the patterns of smoking and nicotine product use, including ENDS, in patients visiting the ED. A key focus is to investigate whether the use of ENDS is associated with any measurable differences in disease severity and outcomes compared to conventional tobacco smoking among these patients.

Methods

Study Design

The Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED) study is an observational study with no intervention or randomization, analyzing the association between the patient's health condition during an ED visit as well as the outcome (hospitalization and death) and different patterns of nicotine products use. Specifically, the study will explore relevant associations according to the smoking and ENDS product use status (current, former, and never use). The pilot phase of the study will take place at a single clinical center, aiming to evaluate its feasibility and analyze the results. Upon successful completion, there are plans to expand the study into a multicenter format involving a national network comprising 10-12 EDs.

Study Population

Inclusion and exclusion criteria are summarized in Textbox 1. Participants will be recruited among patients presenting at the ED of Policlinico Teaching Hospital of Catania, Italy, in 1 month during the diurnal shift. Only patients that access the ED for a nontraumatic reason will be screened, since it is unlikely that smoking or use of other nicotine products can have any causal effect on accident incidence and subsequent diagnosis. The study will take place during daytime working hours owing to organizational constraints. Typically, our ED admits approximately 70-80 patients for nontraumatic issues during a daytime shift, which runs from 8 AM to 8 PM.

We calculated the expected sample size for the study based on available national and regional statistics, providing a practical approach to estimating the study's sample size. The current and former smoking rates in Sicily are estimated at 22.5% and 13.3%, respectively [25], while the combined prevalence of combustion-free products use (e-cigarettes and HTPs) stands at approximately 5% [26]. Considering the annual Catania ED access rate of 80,000 (monthly access rates of 6000-6500) [27], we anticipate recruiting no less than 1500 current smokers and 1000 former smokers per month. Additionally, we expect to enroll no less than 350 users of combined e-cigarettes/HTPs

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per month (dual usage is estimated at approximately 50% of the total). Since approximately 70 patients per day access the ED during the diurnal shift for nontraumatic reasons, we expect to enroll approximately 2000 participants in 1 month.

Textbox 1. Inclusion and exclusion criteria for study participation.

Inclusion criteria

- Adult (aged≥18 years)
- Ability to understand and sign the informed consent form

Exclusion criteria

- Accessed the emergency department for a traumatic accident
- Pregnancy

Ethical Considerations

The study will be conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Ethical clearance for this protocol was obtained through the ethical review board "Comitato Etico Catania 1" at Policlinico Teaching Hospital of Catania (84/2023/PO del Registro dei pareri del CE) on April 17, 2023. If any amendments to this protocol are required, the chief investigator will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or nonsubstantial. Any substantial amendments will be submitted to the research ethics committee for approval before implementation. Informed consent from study participants will be obtained by the investigators through relevant forms. A dedicated website will be created for the study. This website will respect the General Data Protection Regulation policy. Every study team member will access the site with a personal and unique ID and password. The website will create two different databases to guarantee participants' privacy. The first database will record the fiscal code of the participant and will assign a unique ID. The second database will anonymously record the data from each participant using only the participant's ID. It is necessary to create two databases so that additional information on outcomes or other missing data will be recorded at a later time.

Patients will be asked for authorization to use their clinical data in an anonymous format, in accordance with the current privacy directives related to access to the ED. The informed consent model will be shown to participants who must be able to understand and sign it as an inclusion criterion to participate in the study. All collected informed consent forms will be stored at the ED of Policlinico Teaching Hospital of Catania. No financial or other incentives will be provided to the participants.

Data Collection

On arrival at the ED, each patient undergoes a triage phase. A nurse is usually responsible for evaluating the severity of the health condition and the priority for clinical assessment (unless the patient enters the ED by ambulance under a red code). The nurse usually performs this task by collecting vital signs and recording the patient's medical history. This information is then used to assign a color code representing the priority for further assessment. The patient then waits for the medical evaluation in a dedicated room where nurses can monitor the clinical condition of all attending patients. Participants who meet the inclusion criteria will be recruited during this phase and will be administered an electronic questionnaire (see Multimedia Appendix 1) about their smoking and nicotine product use habits and their medical history. This questionnaire serves to typify the patient's use phenotype and quantify exposure to each product.

In addition to the questionnaire, medical data recorded at the triage phase, such as the NEWS, heart rate, blood pressure, blood oxygen saturation, respiratory rate, temperature, and fraction of inspired oxygen, will be collected.

After the assessment and management of each patient in the ED, the final diagnosis, final disposition, and color code at discharge or admission to a ward will be recorded (see Table 1). To avoid compromising the health of patients with severe disease requiring urgent medical attention, potential participants who arrive at the ED under a red code (ie, with a severe acute illness) will be asked to participate only after they are stabilized (ie, the questionnaire, NEWS, and vital signs will be recorded later).

Based on the responses to the questionnaire, participants will be divided in the following 5 smoking subgroups to facilitate analysis: (1) current tobacco smoker, (2) former tobacco smoker, (3) former tobacco smoker now using e-cigarettes and HTPs (exclusive use), (4) current tobacco smoker also using e-cigarettes and HTPs (dual use), and (5) never smokers or e-cigarette/HTP users.

After 1 month, data in the electronic case report form (eCRF) will be extracted for the statistical analysis.

Since the ED is usually very crowded, four study team personnel will work on the study and will screen and recruit patients during the waiting period before the medical examination. The study team will interview potential participants in a dedicated room within the ED area to guarantee privacy. The initial survey will last approximately 5 minutes per patient. This is a reasonable time to collect product use information from each participant. After the medical visit and final disposition, compilation of the eCRF will be completed as provided by the study protocol, with each study member collecting all necessary information about the patients' outcome (discharge or admission to a ward) by the end of their shift. Some patients may stay in the ED beyond the length of a diurnal shift; in such a case, the data will be collected the day after their arrival. Some patients might access the ED

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two or more times during the study. To avoid double entries, only the first visit will be included for analysis in the study. The eCRF database will reply with an error if we try to recruit a patient with the same fiscal code a second time (a fiscal code is a unique identifying code in Italy, and it is mandatory to be recorded for each patient during the triage phase in the ED).

Table 1. Data to record in the electronic case report form.

Data type	Value/units
NEWS[a] calculated at the patient's triage phase (conventionally, patients with an acute condition will be recorded as being at high risk, corresponding to NEWS>7)	0-17
Vital signs recorded during triage	
Heart rate	Beats per minute
Blood pressure	mmHg
Blood oxygen saturation	%
Respiratory rate	Breaths per minute
Body temperature	°C
Fraction of inspired oxygen	%
Smoking questionnaire	See Multimedia Appendix 1
Medical history and drug use history	Textual
Length of stay in the ED[b] or in the hospital (if admitted))	Hours and minutes, or days if admitted
Final diagnosis of discharged patients	Textual
Final disposition	Admitted/discharged
Final diagnosis of admitted patients	*ICD-9*[c] codes

[a]NEWS: National Early Warning Score.

[b]ED: emergency department.

[c]*ICD-9: International Classification of Diseases, 9th edition.*

Endpoint and Outcomes

The primary endpoint of the study is the association between the NEWS and product use phenotypes. Our hypothesis is that use of ENDS may be associated with a lower NEWS compared to cigarette smoking. If our hypothesis will be confirmed, the study will be replicated as a multicenter study to validate our findings.

Secondary outcomes will be hospital admissions (vs discharge) and length of stay in the ED and in the hospital (if admitted). Moreover, we will compare the prevalence of acute diseases known to be related to smoking between groups, specifically stroke, acute myocardial infarction, peripheral artery diseases, chronic obstructive pulmonary disease, asthma, and respiratory infections.

Statistical Analysis

Descriptive analysis will be performed by presenting numerical data as mean (SD) and categorical data as n (%). Patients will be classified according to product use as a current tobacco smoker, former tobacco smoker, former tobacco smoker now using e-cigarettes and HTPs (exclusive use), current tobacco smoker also using e-cigarettes and HTPs (dual use), and never smokers/never e-cigarette or HTP users.

Univariate comparisons will be performed using χ^2 tests for categorical variables and the Kruskal-Wallis H test for the NEWS. Regression analyses will be performed to examine the association between the use of different types of products and the NEWS as well as secondary outcomes. Demographics, including age, sex (male or female), and educational level, as well as past medical history will be included as independent variables. Since the majority of ENDS users report current or past smoking, the smoking status of these users will also be recorded along with those who do not report any ENDS use. Therefore, the analysis will be adjusted for the smoking status of ENDS users. Additionally, secondary analyses will be performed for never-smoking ENDS users, if a sufficient number of such participants will be available. All analyses will be performed using SPSS v.25 (IBM) and a P value <.05 will be considered statistically significant.

Dissemination

The intention of the authors is to disseminate the results of the study through articles in high-quality, peer-reviewed journals and through conference abstracts.

Results

In March 2024, we have enrolled a total of 901 participants (approximately 300 potential participants did not provide the informed consent to participate). The data will be analyzed by a statistician as soon as the database is completed. Full data will be published by December 2024.

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Discussion

This protocol was designed to evaluate the impact of smoking and the use of other nicotine products on ED visits, including the respective clinical diagnoses and outcomes. Smoking is a leading preventable cause of morbidity and mortality. It is estimated that tobacco use accounts for 3%-6% of all ED visits and 5%-16% of total hospital expenses [28-30]. Smokers with preexisting diseases such as diabetes and asthma are more prone to ED visits than nonsmokers with similar conditions [23,31].

The smoking prevalence among patients at the ED surpasses that of the general population [16,18], indicating the ED as a key setting for managing smoking-related health issues. In recent years, there has been an intense debate about the harm reduction potential of ENDS. Some studies have shown their effectiveness in smoking cessation [32], yet there is scarce epidemiological evidence on the clinical impacts of noncombustible nicotine products. This study will be the first to explore the link between the use of various nicotine products and ED visits, as well as their association with urgent care needs for smoking-related disease.

Approximately one decade ago, our research group conducted the ECLAT study, which was the first randomized controlled trial that established the efficacy and the safety of e-cigarettes as smoking substitutes [33]. Since then, a newer generation of e-cigarettes, which are more efficient in nicotine delivery and more appealing, have shown encouraging results in clinical and real-world settings [34-41]. Therefore, they may represent a viable alternative for individuals unable or unwilling to quit smoking using approved methods. Nonetheless, it is important to thoroughly investigate and document the potential risk-reduction potential of these products in a clinical context.

Little epidemiological evidence exists on the harm reduction potential of ENDS. This study thus represents an opportunity to document epidemiological data on the link between the use of different nicotine products and disease severity during an ED visit, as well as clinical outcomes and associations with specific (ie, smoking-related) diseases. Besides further exploring the epidemiological impact of ENDS on diseases related to smoking, the implications of this study are also directly related to understanding the currently unknown burden of these products on emergency care resource use, particularly in the context of the well-known substantial effects of smoking on increasing ED visits. The systematic tracking of the impacts of nicotine use in this study will help to highlight the magnitude of tobacco and nicotine use in the community in relation to access to emergency health care services, and will enable those responsible for tobacco control policies, programs, research, and surveillance to assess the situation and inform decision-making.

This study, currently conducted in a single hospital, serves as a pilot phase, aiming to evaluate its feasibility and analyze the results. The ultimate objective is to expand this research to additional EDs within a national network.

Documenting the association between ENDS use and ED visits will provide insights on both local and central policy levels, especially when we consider that emergency and urgent care systems struggle with major challenges in developed countries with crowding, long waiting times, and, in general, increasing numbers of ED visits [42]. Therefore, it is important to examine factors associated with ED visits and adverse outcomes, and to assess if ENDS affect the ED burden in a different manner to smoking. At the same time, this study may document the need for routinely recording nicotine use habits for all patients accessing the ED instead of the current norm of recording smoking status only.

This study has several limitations. The brief period of recruitment and the use of only one study site may introduce sampling bias due to seasonality and locality. Therefore, this study may have limited generalizability to all Italian EDs. However, as mentioned above, this represents a pilot study with the purpose of further expanding the protocol to more regions and several EDs from other hospitals. While it is possible to verify exposure to tobacco smoke by measuring exhaled carbon monoxide and exposure to nicotine by measuring salivary cotinine, logistical and financial restrictions within the short duration of an ED presentation, as well as the urgent nature of attendance requested in the ED, preclude us from performing an objective assessment of the smoking status. Although self-report of smoking status has been shown to be accurate in the ED setting [17], a systematic review (despite including studies outside the ED setting) showed some discrepancy between self-report and objective assessment [43]. In addition, determining nicotine exposure would not help to distinguish between the use of tobacco cigarettes and noncombustible nicotine products. Moreover, the responses to questions on past smoking and nicotine use habits may be introducing recall bias. Finally, the exclusion of patients in a critical state who need urgent care will be compensated by a subsequent request to participate in the study once they are stabilized.

In conclusion, this study protocol addresses the need for additional epidemiological evidence on the effects of ENDS on health, with clinical endpoints. The ED setting represents an opportunity to record smoking and nicotine habits, assess the burden of different products, and provide guidance for interventions at both the personal and systematic level.

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The members of the SMOPHED Study Group are Simone Aliotta, Noemi Contino, Adriana Scalia, and Manuela Leonardi. They are affiliated to the Department Of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

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Conflicts of Interest

RP has received the following EU and governmental competitive grants: U-BIOPRED, AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Ministero dell'Università e della Ricerca (MUR) Piano Nazionale Ripresa Resilienza (PNRR) 3277/2021, PNRR 341/2022, and PNRR 411/2021 funded by NextGenerationEU of the European Commission. RP has also received investigator-initiated grants from Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl, Duska Therapeutics, and Forest Laboratories. He is founder of the Center for Tobacco Prevention and Treatment and of the Center of Excellence for the Acceleration of Harm Reduction at Catania University. He has been consulting for Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbook royalties from Elsevier and Edra Publishing. He is also Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4) and scientific advisor at RIDE2Med Foundation. The other authors declare no competing interests related to this research.

Multimedia Appendix 1
Questionnaire to be administered to patients.
[DOCX File , 19 KB - resprot_v13i1e54041_app1.docx]

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Abbreviations

AVPU: alert, verbal, pain, unresponsive
eCRF: electronic case report form
ED: emergency department
ENDS: electronic nicotine delivery system
HTP: heated tobacco product
NEWS: National Early Warning Score
SMOPHED: Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department

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Protocol

Detection of Urinary Misfolded Proteins for Imminent Prediction of Preeclampsia in Pregnant Women With Suspected Cases: Protocol for a Prospective Noninterventional Study

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Abstract

Background: Preeclampsia (PE) is one of the most common hypertensive diseases, affecting 2%-8% of all pregnancies. The high maternal and fetal mortality rates of PE are due to a lack of early identification of affected pregnant women that would have led to closer monitoring and care. Recent data suggest that misfolded proteins might be a promising biomarker for PE prediction, which can be detected in urine samples of pregnant women according to their congophilia (aggregated) characteristic.

Objective: The main purpose of this trial is to evaluate the value of the urine congophilia-based detection of misfolded proteins for the imminent prediction of PE in women presenting with suspected PE. The secondary objectives are to demonstrate that the presence of urine misfolded proteins correlates with PE-related maternal or neonatal adverse outcomes, and to establish an accurate PE prediction model by combining misfolded proteins with multiple indicators.

Methods: At least 300 pregnant women with clinical suspicion of PE will be enrolled in this prospective cohort study. Participants should meet the following inclusion criteria in addition to a suspicion of PE: ≥18 years old, gestational week between 20+0 and 33+6, and single pregnancy. Consecutive urine samples will be collected, blinded, and tested for misfolded proteins and other PE-related biomarkers at enrollment and at 4 follow-up visits. Clinical assessments of PE status and related complications for all participants will be performed at regular intervals using strict diagnostic criteria. Investigators and participants will remain blinded to the results. Follow-up will be performed until 42 days postpartum. Data from medical records, including maternal and fetal outcomes, will be collected. The performance of urine misfolded proteins alone and combined with other biomarkers or clinical variables for the prediction of PE will be statistically analyzed.

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Results: Enrollment started in July 2023 and was still open upon manuscript submission. As of March 2024, a total of 251 eligible women have been enrolled in the study and enrollment is expected to continue until August 2024. Results analysis is scheduled to start after all participants reach the follow-up endpoint and complete clinical data are collected.

Conclusions: Upon completion of the study, we expect to derive an accurate PE prediction model, which will allow for proactive management of pregnant women with clinical suspicion of PE and possibly reduce the associated adverse pregnancy outcomes. The additional prognostic value of misfolded proteins is also expected to be confirmed.

Trial Registration: Chinese Clinical Trials Registry ChiCTR2300074878; https://www.chictr.org.cn/showproj.html?proj=202096

International Registered Report Identifier (IRRID): PRR1-10.2196/54026

(JMIR Res Protoc 2024;13:e54026) doi:10.2196/54026

KEYWORDS

preeclampsia; misfolded protein; congophilia; noninvasive; prospective

Introduction

Background

Preeclampsia (PE) is one of the most common hypertensive diseases in pregnancy, characterized by elevated blood pressure accompanied by proteinuria or organ damage after 20 weeks of gestation [1]. The incidence of PE is approximately 2%-8% worldwide [2,3], and each year, an estimated 76,000 women and 500,000 fetuses die from PE and related complications [4]. Symptoms of PE are not specific, including headache, visual impairment, upper abdominal pain, and shortness of breath, among others. In severe cases, PE may develop into eclampsia, which involves seizures or coma [5-7]. PE may also lead to placental abruption; intrauterine growth restriction; hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets (ie, HELLP syndrome, a life-threatening liver and blood clotting disorder); and other serious health consequences for both the pregnant woman and fetus [8,9]. To date, the treatment of PE has mainly involved the use of antihypertensive medications such as methyldopa, labetalol, and hydralazine to lower blood pressure and prevent further maternal complications [10-12], and magnesium sulfate is also administered to prevent seizures in severe cases [13]. However, the only curative treatment of PE is to deliver the placenta. The current clinical strategy for PE is focused on the early screening and close monitoring of high-risk pregnancies, since low-dose aspirin therapy has proven to be effective in reducing the risk of developing PE by 62% [14]. Although potential biomarkers and ultrasonic techniques for detecting PE have been evaluated in recent decades, none has adequate positive or negative predictive value for the prediction of PE [15-17].

With increasing knowledge of the condition, six stages of PE have been proposed [6]. Defective placentation (stage 3) results in oxidative stress, and placental-derived products are released into the maternal blood (stage 4) before PE is diagnosed (stage 5). Recently, an increased level of misfolded proteins in the urine has been identified in patients with PE [18], suggesting that PE might share pathophysiologic features with recognized protein misfolding disorders such as Alzheimer disease. In patients with PE, misfolded proteins such as amyloid beta and transthyretin can accumulate in the circulation to exert neurotoxic effects and activate inflammatory cascades, leading to endothelial dysfunction and oxidative stress. Buhimschi et al [18] demonstrated that a dot test using Congo Red, a synthetic diazo dye with specific affinity for misfolded proteins, to visualize this aggregation feature (ie, congophilia) for detecting the presence of misfolded proteins in urine could serve as a promising diagnostic tool for PE. Li et al [19] subsequently developed a simple and rapid point-of-care testing (POCT) tool to detect the presence of misfolded proteins in urine based on visual observation, which achieved an overall sensitivity of 73.6% that reached up to 83% for severe PE cases.

The traditional approach for PE screening is to identify risk factors based on maternal demographic characteristics and medical history; however, this approach can only identify 35% of total PE cases and 40% of preterm PE cases, with a false-positive rate of approximately 10% [20,21]. A noninvasive laboratory method involving measurement of the ratio of soluble FMS-like tyrosine kinase 1 (sFLT-1) to placental growth factor (PlGF) in the urine proved to be effective in PE diagnosis, achieving a sensitivity of 70%-72.5% with a 5%-14% false-positive rate [22,23]. Thus, combining urine PlGF and sFLT-1 testing with other biomarkers may yield the best predictive performance.

In this trial, we will test a new congophilia-based detection method alone or combined with clinical variables and other urine biomarkers to predict the onset of PE before its clinical manifestation. This work can therefore help clinicians better identify PE earlier, enabling the proactive management and monitoring of pregnant women who exhibit signs or symptoms of PE but do not meet the current diagnostic criteria.

Objective

The primary objective of this study is to assess the short-term predictive potential of the new congophilia-based detection tool for PE onset in pregnant women with a clinical suspicion of PE. That is, we aim to confirm whether the urine misfolded protein level can be used to rule in or rule out PE in the short term. The secondary objectives are to evaluate whether the urine misfolded protein level correlates with PE-related maternal or neonatal adverse outcomes and to establish an accurate PE prediction model by combining misfolded protein values and multiple indicators.

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Methods

Study Design

This is a prospective noninterventional clinical trial planned in accordance with the principles of evidence-based medicine using the PICO (patient, problem, or population; investigated condition; comparison; and outcome) criteria. The study procedure is outlined in Figure 1.

Figure 1. Flowchart of participants with suspected preeclampsia (PE) in the trial. Eligible pregnant women will be enrolled, and consecutive urine samples will be collected at each visit. Urine samples will be blinded and tested for misfolded proteins and other PE-related biomarkers. No intervention according to the test results will be introduced. Required clinical information will be collected from patients' medical records. crea: creatinine; PlGF: placental growth factor; sFLT-1: soluble FMS-like tyrosine kinase 1; TPUC: Total Protein in Urine.

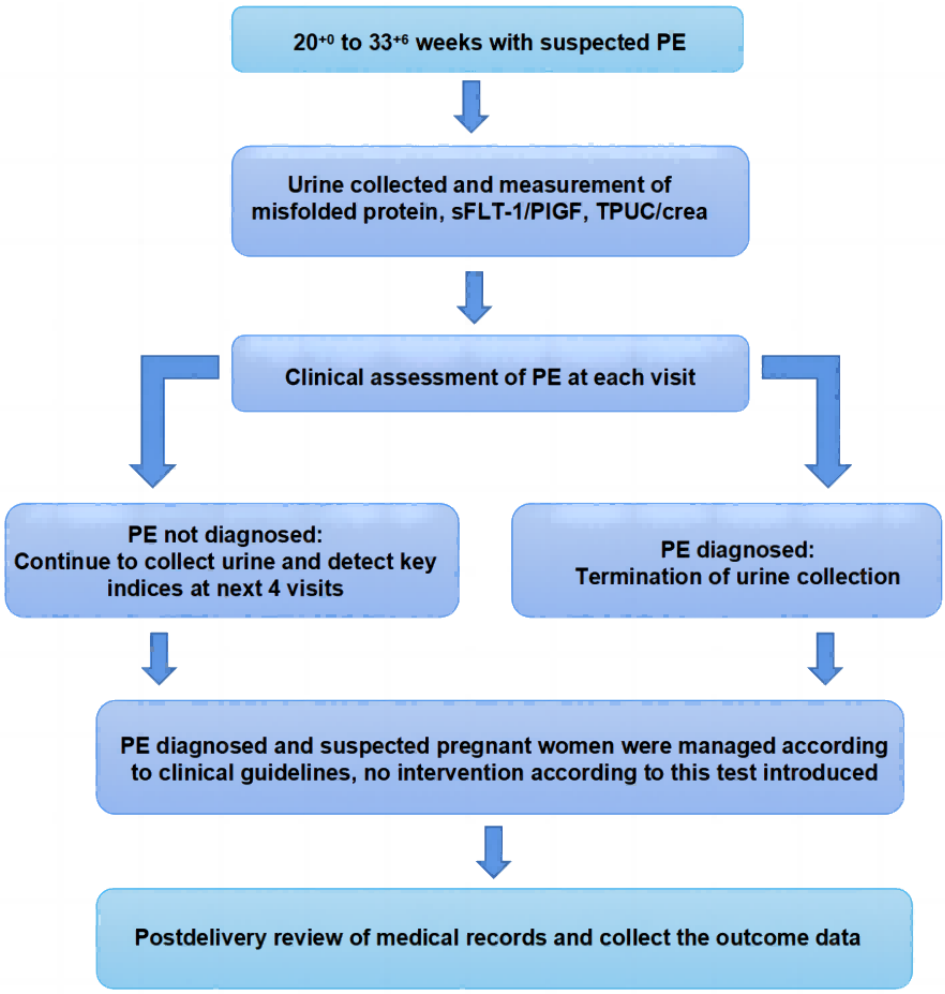

Ethical Considerations

The trial is being conducted in accordance with ethical principles derived from the Declaration of Helsinki and is in line with Good Clinical Practice and applicable regulatory requirements. The clinical research ethics committee of Women's Hospital, School of Medicine, Zhejiang University has reviewed the trial protocol, and full ethical approval has been granted (IRB-20230198-K). Each woman identified as eligible for the study is required to give written informed consent, including but not limited to, for primary data collection and secondary analyses of research data prior to inclusion in the trial.

Apart from sample collection and required assessments during follow-up, the study does not involve any further impact on the patients' clinical procedures. The patients' PE status will be kept confidential from laboratory technicians, and neither the investigator nor the patient will know the detection results, which ensures that the clinical therapeutic scheme and pregnancy outcomes will not be affected.

Recruitment

Potential participants will be identified by the research team from the antenatal clinic at Women's Hospital, School of Medicine, Zhejiang University. Eligible women must meet all inclusion criteria without violating any of the exclusion criteria (Textbox 1) and will be provided with the participant information and consent form to sign. A research team member will provide a verbal explanation of the trial, including a description of the trial processes, the voluntary nature of the trial, and that a decision of whether or not to participate will not affect normal clinical care. No trial-related procedures will be performed on any individual without their prior written informed consent. All participants will be followed up until 42 days postpartum.

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Textbox 1. Inclusion and exclusion criteria for determining trial eligibility.

Inclusion criteria

1. Aged ≥18 years.
2. Gestational week 20+0 to 33+6.
3. Signed written informed consent.
4. Single pregnancy.
5. Clinically suspected preeclampsia (PE), meeting one or more of the following criteria:

(i) new onset of elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥80 mmHg);

(ii) aggravation of preexisting hypertension (increase of more than 30 mmHg systolic/15 mmHg diastolic from the basic blood pressure in patients without hypertension, or a significant increasing trend or increase beyond the controlled level based on the original treatment for patients with hypertension);

(iii) new onset of proteinuria (no urinary tract infection);

(iv) one or more clinical symptoms indicate suspected PE (other possible causes have been ruled out): upper abdominal pain, headache with impaired vision, fetal growth restriction, thrombocytopenia (platelets count<100×10^9/L), liver function impairment (elevated blood concentrations of liver transaminases up to twice the normal concentration), and renal impairment (serum creatinine>1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease).

Exclusion criteria

1. Confirmed diagnosis of PE/chronic hypertension with PE (superimposed PE).
2. Confirmed diagnosis of eclampsia.
3. Confirmed diagnosis of hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets (HELLP syndrome).
4. Fetal chromosomal abnormalities.
5. Concomitant participation in another clinical study.
6. Received investigational intervention drugs in the past 3 months.
7. Visible hematuria.
8. Preexisting renal disease.

Sample Size

The target negative predictive value (NPV) is 99% and the target positive predictive value (PPV) is 54.0%. A positive test rate of 15% is assumed. The Type I error is set to .05. A sample size of 280 should be sufficient to detect NPV>90% and PPV>25% with 80% power. Therefore, at least 300 eligible participants will be included in this study considering a dropout rate of 6%. To avoid an overrepresentation of cases of late-onset PE, no more than 50% of the enrolled participants will be at 32 weeks gestation or above and no less than 20% of the enrolled participants will be at gestational week below 28+0 at inclusion.

Study Groups: Classification of Cases and Controls

Standard diagnostic criteria [24,25] for PE are new onset of hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg measured on two occasions at least 4 hours apart) and new-onset proteinuria (≥300 mg/day or protein/creatinine ratio ≥0.3 mg/dL) after 20 weeks of gestation. Diagnostic criteria in the absence of proteinuria include any of the following: (1) thrombocytopenia (platelets count<100×10^9/L); (2) liver function impairment (elevated blood concentrations of liver transaminases to twice the normal concentration); (3) renal insufficiency (serum creatinine>1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); (4) pulmonary edema; and (5) central nervous system abnormalities or visual disturbances.

Cases are defined as patients who develop PE at any time between the first visit to 6 weeks (42 days) postpartum.

Controls are patients who do not develop PE throughout the pregnancy and up to 6 weeks (42 days) postpartum.

Outcome Measures

The primary outcome is the onset of PE after study inclusion. The secondary outcomes are the following maternal and fetal adverse outcomes: maternal death, pulmonary edema, acute renal failure, cerebral hemorrhage, cerebral thrombus, disseminated intravascular coagulation, eclampsia, HELLP syndrome, rupture of placenta, placental abruption, perinatal death, stillbirth, intrauterine growth restriction, small for gestational age, respiratory distress, necrotizing enteritis, intraventricular hemorrhage or subdural and cerebral hemorrhage, neonatal hypoxic encephalopathy, or periventricular leukomalacia. In addition, the date and mode of delivery, fetal weight, and Apgar score are important outcome measures.

Data Collection

Participant data for this study will be collected by investigators and input into an electronic case report form (eCRF). The data will be verified by the principal investigator when suspicious

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data entries are noted. The data manager will check the completion of the data for final analysis. The study will include 6 visits plus a postpartum documentation. The first visit starts at enrollment, followed by 4 visits once a week when participants come for their routine prenatal examinations. There will be one visit at delivery as well as one postpartum documentation. On occurrence of pregnancy complications, further visits are possible. The clinical data to be collected during each visit are summarized in Table 1. The time interval between two consecutive visits could be 7±2 days, and adherence to the time schedule is crucial for incorporating participant data into the final analysis.

Table 1. Summary of the data collection procedure and timeline.

Data collected	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Delivery	Postpartum	Unscheduled visit
Inclusion/exclusion criteria	✓							
Informed consent	✓							
General baseline feature	✓							
Chronic history	✓							
Pregnancy history	✓							
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓
BMI	✓	✓	✓	✓	✓			✓
Blood pressure	✓	✓	✓	✓	✓		✓	✓
Sampling and detection	✓	✓	✓	✓	✓			✓
Preeclampsia assessment	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory parameters (blood and urine)	✓	✓	✓	✓	✓			✓
Sonographic data	✓	✓	✓	✓	✓			✓
Delivery outcome						✓		
Pregnant woman status						✓	✓	
Fetal/neonatal status						✓	✓	

Sampling and Detection

Urine Sampling and Storage

All enrolled participants will be provided with a sterile cup to collect no less than 5 milliliters of midstream urine at each visit. The sampled urine tubes will be frozen and stored at –20 °C no later than 4 hours after collection. Samples will be shipped frozen to a local laboratory for further analysis.

Urine Coding

At enrollment, each participant will be assigned a specific study number to protect their anonymity. The leading principal investigators will ensure that the participants' anonymity is maintained in the trial database and during the whole research process. Samples collected from one participant at one time will be labeled with the same number to allow tracking and identification of any aliquot prepared from the original urine and for sample programming in laboratory analyzers. The test results will be held securely and separately from the eCRFs, ensuring that clinical decisions will not be influenced by the test results.

Laboratory Detection

Urine samples will be thawed at room temperature and centrifuged at 3000 rpm for 10 minutes. The supernatant will be used for detection.

Urine misfolded proteins will be detected by Pre-Eclampsia Detection Kit (CercaTest RED, Shuwen, China) since misfolded proteins can selectively bind to the Congo Red dye. When a mixture of the Congo Red and urine from a pregnant woman is loaded onto a chromatographic column mounted in a detection cuvette, the presence (positive) or absence (negative) of misfolded proteins can be determined based on the color of the eluent in the cuvette. The eluent will also be applied for quantitative measurement using the HACH DR1900 instrument by detecting the absorbance at a wavelength of 520-600 nanometers.

PlGF and sFLT-1 levels will be detected by the Elecsys PlGF and Elecsys sFlt-1 detection kits (Roche, Germany), respectively. The total urine protein/creatinine ratio will be detected by the Total Protein in Urine/CSF (TPUC) Kit and Creatinine Kit (Mindray, China), all according to the manufacturers' instructions.

Selection of Predictor Variables

According to the objective of this study, the misfolded protein level in urine will be considered as a predictor candidate for PE onset or adverse outcomes. Other preset variables include: (1) demographic factors, including high-risk factors of PE; (2) urine biomarkers reported in the literature; (3) medication; and (4) routine clinical variables or laboratory tests in daily practice (Textbox 2). The determination of valid variables will be based

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on the statistical analysis results with a significance level of $P<.05$.

Textbox 2. Preset variable candidates for model development.

Demographic factors

- Age
- BMI
- Conception mode
- Parity
- Preexisting hypertension, diabetes, autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome)

Urine biomarkers

- Misfolded proteins
- Placental growth factor
- Soluble FMS-like tyrosine kinase 1
- Total protein
- Creatinine

Medication

- Aspirin
- Antihypertensive drugs

Routine clinical variables or laboratory tests

- Blood pressure
- Aspartate aminotransferase
- Lactate dehydrogenase
- Serum creatinine
- Proteinuria (spot urine protein, 24-hour urine protein)
- Uterine artery pulse index

Statistical Analysis

All variables will be compared between case and control groups. Either parametric or nonparametric tests will be applied for continuous variables and χ^2 tests will be used for categorical variables. Receiver operating characteristic analysis will be used when applicable. Univariable or multivariable logistic regression will be applied to develop the prediction models. All *P* values will be two-tailed. The statistical analysis will be run on SPSS version 27 (IBM) statistical software.

Results

The study is currently in the patient recruitment phase. Study recruitment started in July 2023. As of March 2024, a total of 251 pregnant women with clinical suspicion of PE have been enrolled in the trial, who will be continuously followed up and monitored for their PE status until 42 days postpartum. Statistical analysis is scheduled to start after all participants reach the follow-up endpoint and complete clinical data are collected.

Discussion

Study Implications

Many potential PE biomarkers have been identified using samples from patients with a confirmed diagnosis of PE in comparison with samples obtained from normal pregnancies, which represents a convenient and pragmatic approach for biomarker identification. Although these studies have generated excellent candidate biomarkers for PE detection, there has been less focus on biomarkers that can be used in PE risk prediction. It is possible that biomarkers that are differentially expressed in patients with PE versus those without will fail in a predictive verification study. Thus, a prospective cohort with an uncertain subsequent PE status would provide the best avenue for exploring PE prediction models. To our best knowledge, this is the first prospective study to explore the predictive value of a congophilia-based detection tool in pregnant women with a clinical suspicion of PE in China. The study will be conducted in a high-quality tertiary hospital focused on women's health. Maternal age of 35 years or older; nulliparity; and preexisting hypertension, diabetes, and autoimmune diseases (eg, systemic lupus erythematosus and antiphospholipid syndrome) are the main high-risk factors for PE [25] and will be included as

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predictive variables in our analysis. High-risk pregnant women are recommended to use low-dose aspirin to prevent PE; therefore, it is appropriate to consider medication with aspirin as a variable candidate. The crucial biomarkers of PE [22,23], such as PlGF, sFLT-1, and routine clinical variables or laboratory tests, are also under evaluation to build a prediction model. Another important feature of this study is the use of blinding, which ensures that the participants' laboratory data have no influence on the diagnosis of PE as well as the clinical decisions of treatment.

PE remains one of the most severe pregnancy complications associated with substantial maternal and perinatal morbidity. With current pregnancy trends of advancing age and obesity, the morbidity of PE might increase inevitably in the future. Since the only definitive treatment for PE is to terminate the pregnancy, early screening and continuous monitoring during pregnancy are particularly important for pregnant women with high risk of PE. No effective screening test for PE has been identified. The commonly used clinical screening methods are mostly based on blood samples with precise instruments [26-28], which limits the ability for home self-inspection and timely identification of the disease. Congophilia detection represents a promising new approach for the detection of PE by targeting the misfolded proteins in urine, providing a simple, rapid, and cost-effective method for early diagnosis of this complex condition. This method can be performed using small volumes of urine and no additional instrument is needed, making it suitable for use in resource-limited settings and even as a potential home self-test. Therefore, the affordable, noninvasive, and simple use of this POCT detection tool will enable its wide accessibility for bedside use in a central hospital, low-resource settings, and even at home, which would significantly reduce the serious socioeconomic burden attributed to PE.

Limitations

Although use of a prospective cohort in undiagnosed populations provides the best avenue for discovering predictive biomarkers, these markers or their combinations must be rigorously validated in internal/external cohorts to ensure their potential for PE prediction. The single-center nature of this study and prospective recruitment may imply the potential for selection bias. In addition, the enrollment was mainly conducted at prenatal clinics, and this might introduce selection bias regarding the severity of disease, as women with sudden onset of organ complications are more often seen at the emergency clinic. Therefore, future investigations with larger populations, along with assessment of the long-term outcomes of infants will be necessary to ensure the accuracy of the prediction model obtained in this trial and to establish the clinical utility of this tool for routine use in pregnancy care.

Conclusions

This study aims to provide comprehensive evidence on urine misfolded proteins alone or combined with other indicators as a short-term predictive tool for PE. Accurate prediction of PE will allow for proactive management of pregnant women with clinical high risks, and possibly reduce the adverse maternal and fetal outcomes and health care costs associated with hospitalization.

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Authors' Contributions

All authors contributed to the overall study design and specific methodologies. The main idea of this study was conceived by XL and XB in collaboration. They jointly take responsibility for the integrity of the data and the accuracy of the data analysis. MY and XY prepared the first draft of the manuscript with considerable input from HT, YT, and JF, and revised the manuscript based on the feedback of other authors. YW, YF, JS, YN, YY, YW, and PL will carry out the recruitment and data collection. All authors have critically reviewed, edited, and approved the final version of the manuscript.

Conflicts of Interest

XL, XY, and MY are employed by Shuwen Biotech. The other authors have no conflicts of interest to declare.

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Abbreviations

eCRF: electronic case report form
HELLP: hemolysis, elevated liver enzymes, and low platelets
NPV: negative predictive value
PE: preeclampsia
PICO: patient, problem, or population; investigated condition; comparison; and outcome
PlGF: placental growth factor
POCT: point-of-care testing
PPV: positive predictive value
sFLT-1: soluble FMS-like tyrosine kinase 1

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Protocol

Gait Features in Different Environments Contributing to Participation in Outdoor Activities in Old Age (GaitAge): Protocol for an Observational Cross-Sectional Study

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Abstract

Background: The ability to walk is a key issue for independent old age. Optimizing older peoples' opportunities for an autonomous and active life and reducing health disparities requires a better understanding of how to support independent mobility in older people. With increasing age, changes in gait parameters such as step length and cadence are common and have been shown to increase the risk of mobility decline. However, gait assessments are typically based on laboratory measures, even though walking in a laboratory environment may be significantly different from walking in outdoor environments.

Objective: This project will study alterations in biomechanical features of gait by comparing walking on a treadmill in a laboratory, level outdoor, and hilly outdoor environments. In addition, we will study the possible contribution of changes in gait between these environments to outdoor mobility among older people.

Methods: Participants of the study were recruited through senior organizations of Central Finland and the University of the Third Age, Jyväskylä. Inclusion criteria were community-dwelling, aged 70 years and older, able to walk at least 1 km without assistive devices, able to communicate, and living in central Finland. Exclusion criteria were the use of mobility devices, severe sensory deficit (vision and hearing), memory impairment (Mini-Mental State Examination ≤23), and neurological conditions (eg, stroke, Parkinson disease, and multiple sclerosis). The study protocol included 2 research visits. First, indoor measurements were conducted, including interviews (participation, health, and demographics), physical performance tests (short physical performance battery and Timed Up and Go), and motion analysis on a treadmill in the laboratory (3D Vicon and next-generation inertial measurement units [NGIMUs]). Second, outdoor walking tests were conducted, including walking on level (sports track) and hilly (uphill and downhill) terrain, while movement was monitored via NGIMUs, pressure insoles, heart rate, and video data.

Results: A total of 40 people (n=26, 65% women; mean age 76.3, SD 5.45 years) met the inclusion criteria and took part in the study. Data collection took place between May and September 2022. The first result is expected to be published in the spring of 2024.

Conclusions: This multidisciplinary study will provide new scientific knowledge about how gait biomechanics are altered in varied environments, and how this influences opportunities to participate in outdoor activities for older people.

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KEYWORDS

walking; aging; environment; biomechanics; kinematics; spatiotemporal; gait; GaitAge; observational cross-sectional study; gerontology; geriatric; geriatrics; older adult; older adults; elder; elderly; older person; older people; ageing; aging; health disparities; health disparity; assessment; assessments; physical test; physical tests; interview; interviews; biomechanic; activities; outdoor; activity; movement analysis; analysis of walk; posture; free living

Introduction

Overview

The ability to walk is a key issue in maintaining independence in old age. Walking difficulties hinder the ability to manage tasks of daily life and may lead to the need for help and an increased risk of disability and institutionalization [1,2]. With increasing age, changes in gait are common [3]. Walking speed declines with increasing age [4], due to changes in step or stride length, as well as slower cadence. Changes in ankle, knee, and hip motion and center of pressure are also common [4,5]. Gait variability, defined as fluctuations in spatiotemporal characteristics between steps increases with age [3,6] and is associated with increasing risk of developing mobility difficulties [7].

Spatiotemporal and kinematic parameters of gait provide important information, but outcomes are usually based on a treadmill or laboratory overground gait, which may be significantly different from walking outdoors. Only a few studies have examined differences in gait biomechanics between laboratory and outdoor circumstances among older people. In the studies of Schmitt et al [6] and Renggli et al [8] significant differences in several spatiotemporal parameters were found between outdoor walking and treadmill walking. On a treadmill, a decrease in walking speed, an increase in double support duration, shorter stride length, and decreased cadence were found compared to outdoor walking [6,8]. While these assessments provided knowledge about issues such as fall prediction [9] many uncertainties remain. For example, the environment where the activity takes place is typically not recorded, so it is not known whether changes in gait represent a response to some specific environmental demand or whether it is an expression of a person's usual performance. Taking into account environmental features, and using wearable sensors, such as inertial measurement units (IMUs) at the same time could add important information about walking speed and body orientation that is needed to understand how people move and adapt to challenges encountered in different environmental circumstances.

The ability to adapt gait to environmental demands may be crucial for preventing or reducing restrictions in participation on outdoor activities. The concept of life-space mobility gives us an idea about how well people are able to access different community amenities, attend different events, or be physically active, thus describing a person's opportunities for participation outside the home [10]. Life-space mobility refers to the spatial area in which a person moves in daily life, taking into account distance, frequency, and any assistance needed for movement. Restrictions in participating in out-of-home activities are known to correlate, for example, with functional limitations, pain, depression, and chronic conditions [11-13]. Previously it has also been shown that life-space mobility correlates with, for example, quality of life [14,15], physical functioning, and autonomy [16], and that restrictions on it may lead to cognitive decline [17,18], falls and fractures [19], nursing home admission [20], or even mortality [21]. However, research on the association between gait parameters and the impact on life-space mobility is scarce.

Study Objectives

The aim of the "Gait features in different environments contributing to participation in outdoor activities in old Age (GaitAge)" project is to study whether IMUs are valid for detecting traditional (gait cycle event timings) and novel (heading and torso angle) gait parameters among older people in laboratory and outdoor environments. We will focus on how gait parameters change when walking on a treadmill in a laboratory compared to an outdoor environment and in a hilly environment compared to walking in a level outdoor environment. Finally, we will study whether alterations in gait parameters in different environments are associated with outdoor participation (measured via life-space mobility and physical activity) in older people when health and demographics are taken into account.

Methods

Recruitment

Our target was to recruit a total of 40 participants for the study. First, we invited 15 participants from our pilot study conducted between May and June 2021 (not published), who had given their permission to contact them again. These participants were recruited through the University of the Third Age in Jyväskylä by advertising in a public lecture in May 2021. They were contacted again in April 2022 to enquire about their interest in taking part in this study. All of them were willing to take part in the study and met the inclusion criteria.

Additional recruitment to reach a total of 40 participants was done in June 2022 through 5 central Finland senior organizations. Leaders of these organizations were contacted via email and were asked to forward an information letter and invitation to all members of the organizations. Those members who were interested in taking part in the study were asked to contact researchers via email or by phone, after which a short phone interview was scheduled.

A researcher called potential participants and conducted a short telephone interview to screen their suitability and to confirm their willingness to participate. Inclusion criteria were community-dwelling, at least 70 years of age during the current year, able to walk at least 1 km without assistive devices, able

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to communicate, and living in central Finland. Exclusion criteria were the use of mobility devices, severe sensory deficit (vision and hearing), neurological conditions (eg, stroke, Parkinson disease and multiple sclerosis), and memory impairment (Mini-Mental State Examination [MMSE]≤23) [22]. Memory impairment was assessed during the initial phone interview by asking about diagnosed memory illness and screened with an MMSE test during the first research visit to the laboratory.

Recruitment continued until 40 participants who met the inclusion criteria and were willing to participate were reached.

Data Collection

The data collection procedure is shown in Figure 1. Data collection took place between May 27, 2022, and September 28, 2022. The data collection protocol included two visits (1) indoor walking measurements and interviews that were conducted at the University of Jyväskylä sport and exercise laboratory and (2) approximately 4 days later, outdoor walking measurements were conducted at the local sports track and hilly terrain next to the sports track. For some participants, the time between indoor and outdoor walking measurements was longer than 3 days due to weather conditions, as it was not possible to perform outdoor measurements when it was raining. One participant was not able to participate in outdoor measurements because of a nonstudy-related injury after the laboratory measurements. All the measurements and interviews were conducted by research group members with help from research assistants trained for the task.

Figure 1. Data collection protocol of GaitAge project. IMU: Inertial measurement unit; MMSE: Mini-Mental State Examination.

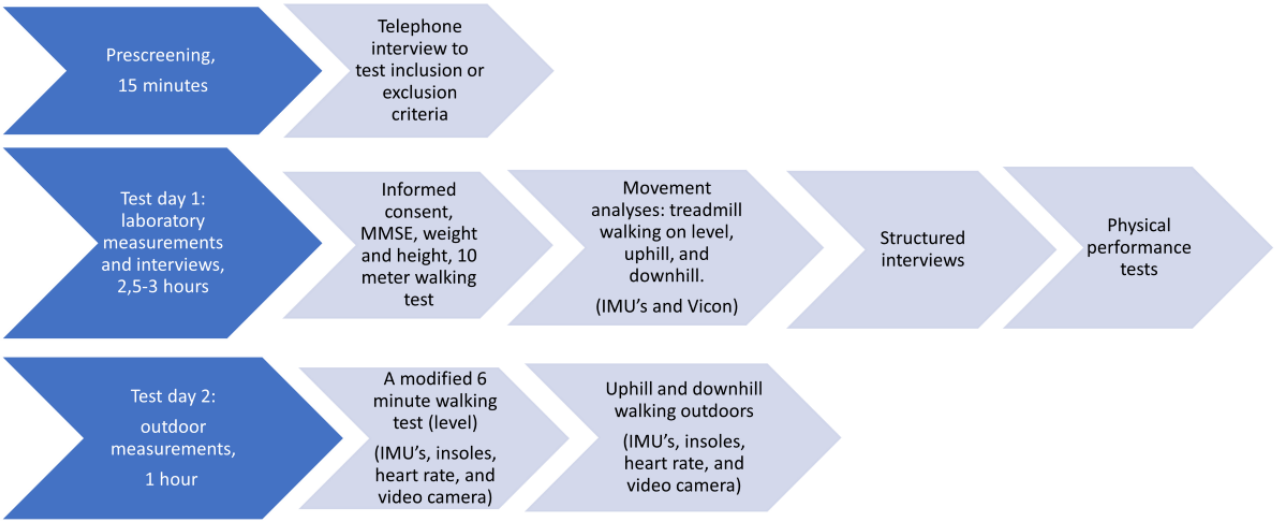

Laboratory Measurements and Interviews

Overview

For the indoor research visit, participants were instructed to wear sneakers or running shoes and clothes that were suitable for physical activity, preferably as tight as possible to facilitate the attachment of reflective markers for 3D motion analysis. If the participant did not have shorts or tight leggings, they were provided with tight shorts. Participants were instructed to eat a light meal or breakfast and to avoid alcohol use 24 hours before the measurements.

At the start of the research visit, the MMSE test was conducted and written informed consent was obtained. Participants had the possibility to ask questions about the study and the study protocol was explained to them. After that, weight and height were measured.

10-Meter Walking Test

Indoor walking tests started with a 10-meter walking test to identify participants' walking speed. The time in seconds was measured using photocells placed 10 meters apart in a hallway. Participants were instructed to walk through the photocells at their usual walking speed, starting 2 meters before the first pair of photocells and stopping 2 meters after the second pair of photocells. The test was done once by each participant. Time was changed into walking speed (in m/s) and this information was used to determine the speed for the subsequent treadmill tests.

Next-Generation Inertial Measurement Units

After the 10-meter walking test, next-generation inertial measurement unit (NGIMU) devices (x-io Technologies Limited) were attached. NGIMU is an IMU sensor that includes a triple-axis accelerometer (±16 g; 400 Hz sample rate), triple-axis gyroscope (rotations ±2000°/s; 400 Hz sample rate), and triple-axis magnetometer (magnetic field ±1300 µT). NGIMUs also include analog inputs (8-channel; 0-3.1 V; 10-bit; 1 kHz sampling rate). One NGIMU including housing has dimensions of 56×39×18 mm and weighs 46 g. A total of 8 NGIMU devices were attached to participants with Velcro straps and leukoplast tape.

NGIMUs were placed on both legs above the third metatarsal, on the lateral mid shank, anterior thigh 5 cm above the knee joint, and to the middle of the spine just above the spina iliaca posterior superior and upper half of sternum.

VICON 3D Motion Analysis

3D motion capture (Vicon Motion Systems) was used to obtain ground truth values for indoor walking tests. A total of 16 Vicon Vero cameras were positioned around the space where treadmill walking took place. A total of 26 reflective markers were

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attached to participants with 2-sided tape and secured with leukoplast tape and a self-adhesive bandage (Textbox 1). Data were sampled using Nexus software (Vicon Motion Systems).

Textbox 1. Placement (right and left legs and sides of the body) of the reflective markers for indoor 3D motion analysis.

- Hallux
  - Top of hallux nail
- Toe
  - Proximal head of second metatarsal
- Heel
  - Heel, at the same level as toe marker
- Ankle
  - Lateral malleoli
  - Medial malleoli (used only for calibration)
- Shank
  - Midway along the shank, laterally (left and right)
- Knee
  - Knee extension—flexion axis and lateral side
  - Knee extension—flexion axis and medial side
- Thigh
  - Midway between KNEE marker (lateral side) and spina iliaca anterior superios (SIAS)
- SIAS
- Spina iliaca posterior superior
- Thoracic vertebrae 10
- Cervical vertebrae 7 (C7)
- Sternum
  - Lowest part of the sternum
- Clavicula
  - Between the heads of clavicula

NGIMUs and Vicon data were synchronized with an analog trigger, which sent simultaneous pulses to the master NGIMU (400 Hz) and to Nexus software (1000 Hz).

Treadmill Walking Tests

Level Treadmill Walking

First, a safety harness was put on the participant. Second, the participant walked on the treadmill (Gymstick Walking Pad Pro 44 cm×120 cm) for 1-5 minutes for familiarization. Treadmill speed was gradually increased in increments of 0.5 km/h until the participant's walking speed from the 10-meter test was achieved or when the participant indicated that he or she did not wish to increase the speed. Participants were allowed to take support from the front and side rails if necessary for balance at any point during assessments, but they were not allowed to hold the rails during the full measurements.

After familiarization, the treadmill was stopped. The actual test started with 5 seconds of standing still in an anatomical posture. When starting, the speed was gradually increased toward the speed obtained from the 10-meter walking test and once achieved, the participant was asked to walk for 3 minutes at that speed. After 3 minutes, the treadmill was slowed down and the participant was asked to stand again for 5 seconds in an anatomical posture.

Uphill and Downhill Treadmill Walking

The treadmill was inclined or declined by 5° to correspond with the slope of the outdoor hilly walking tests. The order of test (incline or decline first) was randomly determined by a random number generator. The test speed was determined based on 1-5 minutes of walking at the new gradient, whereby participants were asked to indicate their self-selected speed for uphill or downhill walking. The actual test started with 5 seconds of

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standing still in an anatomical posture. Then the speed of the treadmill was gradually increased to the test speed, and participants walked for 2 minutes at that speed. After 2 minutes, the treadmill was stopped, and participants again stood for 5 seconds in an anatomical posture.

Structured Interviews

Overview

Following the walking tests, interviews were conducted including structured questions and questionnaires.

Demographic Information

Demographic information included age, gender, perceived financial situation (from very poor to very good), highest educational status, living arrangements (living alone, with spouse, or with someone else), type of housing (apartment block, row house, semidetached, or detached house), and time of residence in the current house.

Health Condition

Health condition was determined via self-report (5-point scale from good to poor) [23] and by asking about illnesses diagnosed by a doctor from a list of chronic conditions, including different cardiovascular, respiratory, musculoskeletal, and eye diseases, hearing impairment, diabetes, cancer, and incontinence and an open-ended question about any other physician-diagnosed chronic conditions. In addition, participants were asked about whether they had artificial joints and if so, in what joint [23].

Functional Vision

Functional vision was assessed using a 7-item vision function questionnaire (VF-7) [24], which is a modified version of the 14-item vision function questionnaire (VF-14) [25]. The VF-7 comprises 7 activities dependent on functional vision and is validated for use in patients with cataracts. Patients are asked how much difficulty they have doing each activity, with or without glasses. The activities are reading small print; seeing steps, stairs, or curbs; reading traffic, street, or store signs; doing fine handwork; cooking; watching television; and driving in darkness. Each question is scored 4, 3, 2, or 1, respectively, if the participant has no, little, moderate, or a great deal of difficulty performing the activity, and 0 if the participant is unable to perform the activity due to poor vision. If a patient does not do an activity for reasons other than his or her vision, the item in question is not included in the scoring. The final score is obtained by averaging responses across all the relevant activities and multiplying by 25. Scores range from 0 (representing maximum impairment) to 100 (representing no impairment).

Trail-Making Test

Trail-making test (TMT) was used to measure executive functioning [26]. The TMT consists of 2 parts. Part A involves drawing connective lines between circles that are spread over a sheet of paper and are numbered from 1 to 25. Part B involves drawing connective lines between circles including numbers and letters in order (1-A-2-B-3-C-4-...etc). Participants are asked to draw the lines as fast as possible without lifting the pen from the paper. The researcher pointed out possible errors as they occurred and the participant continued doing the task. The time to complete the task was recorded. The maximum accepted time for part A was 100 seconds, and for part B 240 seconds or 4 mistakes.

Depressive Symptoms

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (CES-D) [27] and balance confidence was assessed with the Activities-specific Balance Confidence scale [28]. History of falls during the previous 12 months was self-reported and separated into injurious and noninjurious falls [29].

Outdoor Mobility

Life-Space Mobility

Life-space mobility was assessed with the Finnish version of the University of Alabama at Birmingham Study of Aging Life-Space Assessment (LSA) [10,30]. The LSA establishes self-reported movement patterns according to specific life-space levels, ranging from within one's dwelling to beyond one's town during the 4 weeks preceding the assessment. For each level of life-space (bedroom, home, outside home, neighborhood, town, and beyond town), participants are asked how many days within a week they attained that level and whether they needed help from another person or used assistive devices. A life-space mobility score was calculated (range 0 to 120), reflecting distance, frequency, and independence of movement. Higher scores indicate a larger life-space.

Environmental Features

Environmental features near the participant's home were assessed using "Perceived environmental barriers for outdoor mobility" (PENBOM) questionnaire [31] and with self-evaluation of the home neighborhood environment, including questions about distances to services, closest grocery store, and walking and cycling routes [23].

Physical Activity

Self-reported level of physical activity was assessed with a 6-point scale [32] modified from Grimby [33] and Mattiasson-Nilo et al [34]. The levels varied from "1" hardly any activity and mostly sitting to "6" performing competitive sports.

Walking Ability and Walking Modifications

Walking ability and walking modifications were evaluated using a standardized questionnaire [35]. The participants were asked whether they had difficulties in walking 2 km with response options (1) able to manage without difficulty, (2) able to manage with some difficulty, (3) able to manage with a great deal of difficulty, (4) able to manage only with the help of another person, and (5) unable to manage even with help. Regarding walking modifications, participants were asked "Have you noticed any of the following changes in walking 2 km?" The response options (yes or no) concerned reduced walking frequency, having given up walking 2 km distances, walking more slowly, and resting while walking the 2 km distance.

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Physical Performance Tests

Physical performance tests were performed after the interviews. Lower extremity performance was assessed using the short physical performance battery (SPPB) test following the guidelines of the Finnish Institute of Health and Welfare [36,37], which includes 3 subtests, static balance in 3 different positions, 4-meter walking time, and 5 repetitions of sit-to-stand. The balance test was performed without shoes. The walking test was performed at the usual speed and the sit-to-stand test was performed as fast as possible. Both these tests were performed with shoes on. The possible use of a walking aid during the test was also recorded. All subtest results were recorded in seconds and scored from 0 to 4 points, leading to a maximum of 12 points. Higher SPPB test scores indicate better lower extremity performance.

Functional Mobility

Functional mobility was assessed with the Timed Up and Go (TUG) test [38]. In the TUG test, the participant stands up from a chair, walks 3 meters, turns around, walks back, and sits on the chair. The TUG test was performed twice at the usual walking speed, with the shoes on. Time in seconds was measured using a stopwatch. Both results were recorded, and the best result (shorter time in seconds) was used. A lower TUG test time indicates better mobility.

Treadmill walking tests took approximately 1.5 hours including attachment of NGIMUs, instructions and walking tests with breaks, after which the participant had a 15-30 minute coffee break. Interviews and physical performance tests took approximately 45-60 minutes per participant. The total duration of the research visit to the sport and exercise laboratory was 2.5-3 hours.

Outdoor Measurements

Overview

Walking tests outdoors were performed approximately 4 days after the laboratory visit. Participants were instructed to wear good walking shoes (trainers, running shoes, etc) and clothes suitable for physical activity. Outdoor tests were conducted only on days with suitable weather conditions (no rain), thus for some participants the time between indoor and outdoor measures was longer than 4 days (range 2-20).

First, participants were equipped with NGIMUs, force-sensitive resistor (FSR)–insoles and a wrist-worn heart rate monitor (Polar Vantage M, Polar, Finland). The same set and placement of NGIMUs were used as in the treadmill walking tests. FSR-insoles were made with two FSRs (18 mm diameter and active area 12.7 mm), which were attached with tape to a thin insole (1-2 mm) and placed under the heel and ball of the foot. The size of the insole was modified according to each participant's feet and FSR-insoles were inserted in participants' shoes replacing the insoles they had in their own shoes. The participants reported that they did not notice having the insoles in their shoes, thus the insoles are not likely to affect the gait parameters. The FSRs were connected to a battery-powered open-source Internet of Things development board (M5StickC PLUS, Interlink Electronics) and force data were sampled at 200 Hz via the board's 12-bit analog-to-digital converter. Internal clocks of the development boards were synchronized before each measurement using an external button connected to the digital pins of the boards. FSR-insoles were connected to a custom mobile phone app via Bluetooth low-energy connection.

The heart rate monitor was placed on the participant's right wrist. The heart rate was measured to monitor exertion during the outdoor walking tests. A GoPro 9 Hero camera (120 Hz; GoPro Inc) was attached to a modified stroller which was pushed alongside the track. A second GoPro Hero camera was placed at the end of the walking track. NGIMUs and GoPro cameras were synchronized with a trigger device, which sent an analog signal to the master NGIMU and simultaneously turned on a light visible by both cameras. For camera calibration, a 5-second video was filmed of a checkerboard calibration matrix located at the same distance from the camera as the participant's walking route.

A Modified 6-Minute Walking Test

Participants walked along a 70 m long route (Figure 2) at the sports track (synthetic track surface) for 6 minutes at a self-selected speed. Rating of perceived exertion was assessed using the Borg scale (range 6-20; 6=no exertion, 20=completely exhausted) [39] at the beginning of the test, after 3 minutes and at the end of the test. A research assistant moved the camera and stroller alongside the participant at a distance of 3.46 meters from the midline of the participant's route. After 6 minutes of walking, the test was stopped and distance was measured to the nearest meter.

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Figure 2. Route of a modified 6-minute walking test performed at a sports track.

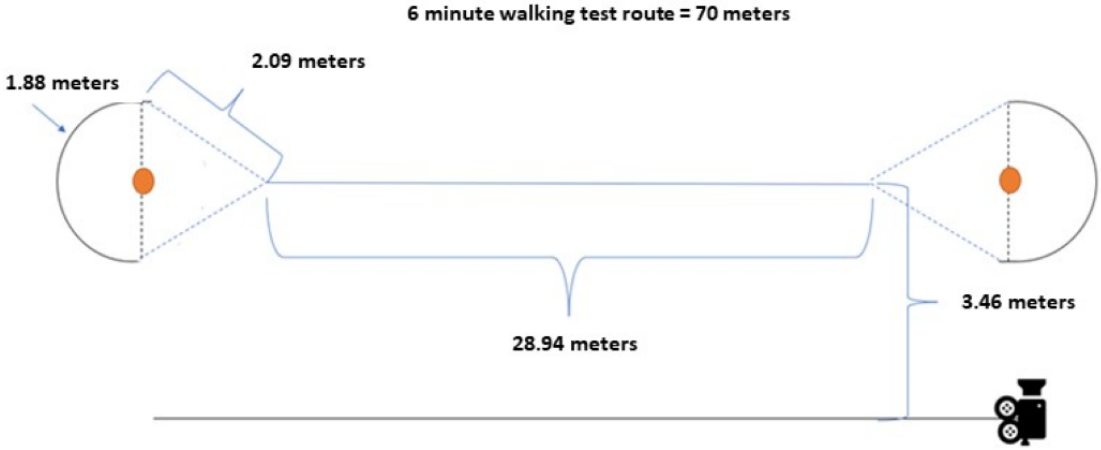

Uphill and Downhill Walking Outdoors

A walking test in a hilly environment was performed next to the sports track. The steepness of the hill was 5°, and the ground surface was asphalt.

The participants walked at self-selected speed downhill for 20 meters and then after a short break (approximately 10 seconds) walked 20 meters uphill. Downhill and uphill trials were repeated 5 times, that is, 100 meters walking both ways. A research assistant moved the camera and stroller alongside the participant and a second researcher walked behind the participant for safety. Rating of perceived exertion was assessed after every 20 meters, and the heart rate was recorded with the heart rate monitor. Rest breaks were taken between trials as needed.

Data Analysis

Gait Parameters

Several gait parameters will be derived from IMU data. For example, step duration; step length; stance phase duration; swing phase duration; cadence; gait speed; variability of step, swing, or stance duration; and asymmetry of step, swing, or stance duration.

Step duration is defined as time and step length as the length between 2 consecutive contralateral heel strikes. Stride duration is defined as the time between 2 ipsilateral heel strikes. Swing duration is calculated as the time between consecutive toe-off and heel strike of the same foot, and stance duration as the time between consecutive heel strike and toe-off of the same foot. Cadence is defined as steps per minute and step velocity as step length divided by step duration. Variability in gait parameters (within-person differences in steps) is calculated as SD or coefficient of variation (SD divided by mean multiplied by 100%) of certain parameters per participant.

To calculate gait parameters from different IMUs we will use algorithms published in previous literature (eg, [40-43]). New algorithms are developed when necessary.

Vicon Data

Exported 3 dimension motion data are analyzed with open-source Mokka software (Motion kinematic & Kinetic analyzes, biomechanical tool kit, GitHub), where heel strikes and toe-offs are manually determined. In treadmill walking, heel strikes are set to the last frame before the heel marker starts to move backward in the image, that is, at the most anterior point. Toe-offs are set to the last frame before the hallux marker starts to move proximally, that is, at the most posterior point in the image. These analyses are performed by 2 researchers and similarity of identifications is ensured by checking agreement on data. In case of disagreements, event timings are discussed and agreed upon together. Events are then exported to Matlab (b2022; The MathWorks, Inc).

GoPro Camera Data

The GoPro camera data were used as a reference to validate the IMU's in the outdoor environment. From outdoor video data, heel strike and toe-off events and step length are digitized and identified manually. The heel strike is denoted as the first frame when the shoe touches the ground after the swing phase. Toe-off is determined as the last frame when the distal end of the shoe is still on the ground. These analyses are performed by 2 researchers and similarity of identifications is ensured by checking agreement on data. In case of disagreements, event timings are discussed and agreed upon together. ShotCut software (Meltytech, LLC) is used to mark event timings, which are copied to an Excel file (Microsoft Corporation). Timings are converted from frames to seconds using Matlab (MathWorks) and Excel.

Statistical Analyses

To test the validity of IMU sensors, we will use Bland-Altman plots and intra-class correlation coefficients. To compare gait parameters in different environments, we will use appropriate statistical methods depending on data properties, which may include *t* tests and repeated measures ANOVA and mixed effect models. Linear regression analyses are used to study associations with life-space mobility and physical activity. Other statistical testing will be performed where appropriate.

Data Management

All data are handled and registered according to the Finnish Personal Data Act and the European Union Data Protection Act. All data are recorded and analyzed without direct personal recognition information. The research material is carefully

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maintained, documented, and stored in password-protected organizational servers.

Ethical Considerations

The study was conducted according to good scientific and clinical practices as laid down by the Declaration of Helsinki. All participants were informed carefully about the study, and they gave their written informed consent prior to any measurements. Data collection included no invasive or potentially physically or psychologically harmful elements beyond what one might experience in everyday life. Only people who were personally able to consent were recruited. Research assistants conducting the data collection were trained for study procedures and the safety of participants during the measurements was ensured. Participants had the possibility to withdraw from the research at any point without any consequences. The ethics committee of the JAMK University of Applied Sciences approved the study (JAMK/40/13.02/2021; January 11, 2021).

Results

The GaitAge data collection is completed. A total of 40 participants participated in indoor measurements and 39 of them in outdoor measurements. Participants were on average 76.3 (range 69-92, SD 5.45) years of age, 65% (n=26) of them were women, and all of them reported being able to walk 2 km without difficulties.

Gait data analyses are underway, and the first results reporting findings of the validation of NGIMUs is expected to be published in spring 2024.

Discussion

Principal Findings

Our project features several strengths. First, for example, a comparison of gait parameters in an outdoor environment and on a treadmill in a laboratory provides fundamental knowledge for studies aiming to use gait parameters to predict progressive neurological problems. We will report how older adults adapt their gait according to variable environmental demands. This study provides findings that can change our view of person-environment interaction processes by providing detailed information about changes in gait parameters in level, uphill, and downhill walking. Second, we will assess whether changes in gait biomechanics induced by environmental demands influence possibilities for general participation in outdoor activities of older people by combining information on gait parameters with life-space mobility. Third, we will explicitly focus on person-environment interaction at the individual level, which will create new study hypotheses and give new perspectives on research in environmental gerontology. Fourth, the study sample of 40 older adults with a comprehensive data set (several walking measures with IMUs, 3D motion analyses and video data, questionnaires, and physical performance tests) will have a multidisciplinary impact by providing information about objective and subjective aspects of gait and mobility in old age.

It should be noted that the study population included older adults without major mobility difficulties or neurological conditions, so the results cannot be generalized to clinical populations. There are also some limitations in the study protocol that will be taken into consideration in forthcoming analyses, for example, differences between measurement protocols for level treadmill walking (3 minutes) and outdoor walking (6 minutes). We will also need additional longitudinal studies to determine whether possible changes in gait in different environments are predictive of changes in mobility capacity.

Conclusions

This research will provide answers to major research questions about the role of the environment in outdoor mobility in old age. This research project could serve as a reference for future research on gait among different patient groups and will serve as a baseline for a longitudinal study, with the aim of exploring whether changes in gait parameters in different environments can be used as early signs of declining health and restricted participation in outdoor activities.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author (MR) upon reasonable request.

Authors' Contributions

MR, TF, and NC performed the concept and design. All authors took part in acquisition of data, drafting the paper, critical revision of the paper, and approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

CES-D: Center for Epidemiologic Studies Depression scale
FSR: force-sensitive resistor
IMU: inertial measurement unit
LSA: Life-Space Assessment
MMSE: Mini-Mental State Examination
NGIMU: next-generation inertial measurement unit
PENBOM: perceived environmental barriers for outdoor mobility
SPPB: short physical performance battery
TMT: trail-making test
TUG: Timed Up and Go
VF-7: 7-item vision function questionnaire
VF-14: 14-item vision function questionnaire

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Protocol

Patient Partnership Tools to Support Medication Safety in Community-Dwelling Older Adults: Protocol for a Nonrandomized Stepped Wedge Clinical Trial

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Abstract

Background: Preventable harms from medications are significant threats to patient safety in community settings, especially among ambulatory older adults on multiple prescription medications. Patients may partner with primary care professionals by taking on active roles in decisions, learning the basics of medication self-management, and working with community resources.

Objective: This study aims to assess the impact of a set of patient partnership tools that redesign primary care encounters to encourage and empower patients to make more effective use of those encounters to improve medication safety.

Methods: The study is a nonrandomized, cross-sectional stepped wedge cluster-controlled trial with 1 private family medicine clinic and 2 public safety-net primary care clinics each composing their own cluster. There are 2 intervention sequences with 1 cluster per sequence and 1 control sequence with 1 cluster. Cross-sectional surveys will be taken immediately at the conclusion of visits to the clinics during 6 time periods of 6 weeks each, with a transition period of no data collection during intervention implementation. The number of visits to be surveyed will vary by period and cluster. We plan to recruit patients and professionals for surveys during 405 visits. In the experimental periods, visits will be conducted with two partnership tools and associated clinic

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process changes: (1) a 1-page visit preparation guide given to relevant patients by clinic staff before seeing the provider, with the intention to improve communication and shared decision-making, and (2) a library of short educational videos that clinic staff encourage patients to watch on medication safety. In the control periods, visits will be conducted with usual care. The primary outcome will be patients' self-efficacy in medication use. The secondary outcomes are medication-related issues such as duplicate therapies identified by primary care providers and assessment of collaborative work during visits.

Results: The study was funded in September 2019. Data collection started in April 2023 and ended in December 2023. Data was collected for 405 primary care encounters during that period. As of February 15, 2024, initial descriptive statistics were calculated. Full data analysis is expected to be completed and published in the summer of 2024.

Conclusions: This study will assess the impact of patient partnership tools and associated process changes in primary care on medication use self-efficacy and medication-related issues. The study is powered to identify types of patients who may benefit most from patient engagement tools in primary care visits.

Trial Registration: ClinicalTrials.gov NCT05880368; https://clinicaltrials.gov/study/NCT05880368

International Registered Report Identifier (IRRID): DERR1-10.2196/57878

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KEYWORDS

primary care; medication safety; communication; patient engagement; human factors; medication; safety; engagement; support; community dwelling; older adults; elderly; protocol; patient safety; self-management; ambulatory; medications; tool; tools; effective; medication safety; data collection; decision; decision making; care; self-efficacy; engagement tool

Introduction

Background

Health care encounters are opportunities for health care professionals (HCPs) to work productively with patients and families to address risks in medication use in ambulatory settings [1,2]. This study assesses a systematic redesign of time-limited primary care encounters to improve medication safety. Adverse drug events (ADEs) account for 6.1 emergency department visits per 1000 population each year in the United States and 38.6% of these visits require hospitalization [3]. Medication safety is recognized as a significant area for improvement by the World Health Organization ("Medication without Harm") [4]. The National Action Plan for ADE Prevention [5] highlighted ADEs associated with insulins, opioids, and anticoagulants, such as those from hypoglycemia, opioid misuse, injurious falls, and bleeding. Older adults are especially vulnerable to ADEs with nearly double the risk compared to younger populations [3]. Patients' roles (including families in this protocol) are critical to medication safety in ambulatory settings [6-8]. An analysis of insulin-related emergency department visits identified patient self-management as the most common precipitant to insulin-related hypoglycemia and errors—patients incorrectly managed their food intake and insulin products at home [9]. Leading contributors to benzodiazepine adverse events were nonmedical use (56%) and self-harm (30%) [10].

Major gaps have been identified in patient and family engagement in medication safety in ambulatory settings [11-15], including cultural barriers that disrupt engagement between HCPs, patients, and families; lack of patients' experience and skills in working with HCPs; and unclear expectations of patient roles in clinical encounters. Older adults often do not take advantage of existing systems for safe medication management practices at home, even for high-risk medications [16]. Patients often have an unvoiced agenda, especially related to concerns, side effects, and uncommunicated methods of managing their conditions [17]. Interventions to bridge these gaps in patient engagement include patient coaching prior to visits [18]; providing patients with instructional brochures, training videos, or prompts of questions to prepare for visits [19-21]; encouraging patients to bring medications and questions to visits [2]; and encouraging patients to ask questions [22-24]. One patient portal-based intervention focused on a dual approach of a previsit agenda-setting questionnaire followed by in-person coaching to prepare for encounters with HCPs [19].

This project uses the patient work system model [25]. The model, similar to those that study and improve the work performance of HCPs [26], focuses on the health-related work of patients and nonprofessionals. The concept of patient work systems broadens the scope for medication safety interventions to encompass patients' home environments [25], including setting expectations and clarifying the roles of patients and families [27], using community resources [28], and incorporating patient perspectives in medication safety improvement [29].

Although the inventions reported so far address several gaps in patient and family engagement, integrated approaches are lacking to systematically target key elements of the joint patient-professional collaborative work to achieve productive interactions. A redesign that acts on multiple aspects of collaborative work is needed to help patients and HCPs set expectations for their partnership appropriate to each patient, along with tools to support collaborative work, and skills training appropriate for the time and resource constraints typical in primary care encounters. Specific aspects of collaborative work are not usually recognized, such as psychological safety in the mostly hierarchical patient-HCP relationship, severe limitation of time, lack of training and knowledge of teamwork concepts, and limited tools for self-efficacy.

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Objectives

The primary objective of this study is to assess the impact of a set of patient partnership tools that redesign primary care encounters to encourage and empower patients to make more effective use of those encounters to improve medication safety. Two notable features of the tools are (1) to encourage patients to tell, not just ask, primary care professionals (PCPs) about their medication use at home; and (2) to empower PCPs with tools to nudge patients to become active partners. The tools were developed to leverage the longitudinal relationship between patients and PCPs, instead of focusing on 1-time exposure to the tools. Comparison will be made between usual clinical processes as the control and redesigned clinic processes as the intervention.

Methods

Ethical Considerations

The human participant research protocol was approved by the University of Texas at Arlington Institutional Review Board under a reliance agreement for all study sites (protocol number and version UTA 2019-0439.25 approved on May 10, 2023; contact information: University of Texas at Arlington, Arlington, Texas, US, Angela Luna, IRB Specialist, Office of Regulatory Services, angela.luna@uta.edu). Documentation of patient consent was waived; verbal consent was sufficient and required for data collection (approved verbal consent scripts in Multimedia Appendix 1). The clinics determined that the interventions were part of their standard of care process once implemented. A data and safety monitoring board was appointed with one of the authors (RAY) as the lead to review any adverse events, protocol deviations, and issues with recruitment. The lead physician of each study site was included in the board. Quarterly reviews by the board will be conducted. The trial was registered with ClinicalTrials.gov (number NCT05880368 on May 26, 2023). The clinical leaders at each clinic will decide the types of primary care visits to be included in the interventions, such as annual wellness, disease management follow-up, or acute visits. The leaders will be asked to include all English- or Spanish-speaking patients who are at least 50 years old and have 5 or more medications listed in their electronic health records (EHRs). During each study period, requisite numbers of eligible patients will be recruited by a study coordinator to participate in data collection.

Study Design

The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Multimedia Appendix 2) [30]. The study is a nonrandomized, cross-sectional stepped wedge cluster-controlled trial with 1 private family medicine clinic and 2 public safety-net primary care clinics each composing their own cluster (for a total of 3 clusters). There are 2 intervention sequences with 1 cluster per sequence and 1 control sequence with 1 cluster. We planned the study as a cluster trial because randomization of patients is not feasible when the clinical processes are changed for all patient visits once interventions are in place, not for individual visits. One control sequence is included in the clinic with no intervention planned.

Study Settings

The 3 clinics were in urban settings in a Southwest metropolitan area of the United States. All clinics predominantly serve patients with low socioeconomic status. One clinic is private with 1 family medicine physician. The other 2 clinics are public and part of a safety-net health system with family medicine residency training programs with approximately 15 primary care providers. The clinical and administrative leaders agreed to participate and to the timelines for data collection and implementation.

Interventions

Process redesign will be facilitated by two partnership tools: (1) a 1-page visit preparation guide given to relevant patients by clinic staff before seeing the provider, with the intention to improve communication and shared decision-making, and (2) a library of short educational videos that clinic staff encourage patients to watch on medication safety. The intervention design approach aimed to address multiple elements of collaborative work systems during primary care clinic visits to improve medication safety while minimizing the additional demands on busy PCPs and patients. The tools are expected to be used during typical patient wait times in the exam room and thus are expected to have minimal impact on throughputs. The following goals were considered during the design process: (1) to change collaborative work culture by clarifying patients' roles in contributing to medication use preferences, information accuracy, and in being prepared to participate in shared decision-making; (2) to explicitly recognize fear and reluctance in patient-professional communication by using concepts from the psychological safety literature in teamwork; (3) to set an expectation and to support learning the basics of medication use, such as the refill process and knowledge about tools to reduce unintentional errors; and (4) to encourage problem-solving in community settings, such as contacting pharmacists, who are generally more accessible than primary care providers, with medication-related questions. Participatory design methodologies [31,32] were used in the design and formative evaluation of the tools with older adults and PCPs. Iterative testing was conducted with users, both patients and PCPs. A qualified medical writer wrote the scripts for the videos. Health literacy and patient education experts edited the final versions of the visit prep guide and the scripts for the videos.

The visit preparation guide (Multimedia Appendix 3) contains three sections: ("ask") a list of question prompts for patients to consider about their medications, including one about deprescribing [33]; ("tell") a list of prompts for patients to communicate their medication management views, practices, and concerns; and ("expect") a set of behaviors to encourage collaborative work. The "ask" section had its origin in the approaches used in "Ask Me 3" [23] and EHR-based pre-encounter medication reconciliation [19], with a focus on barriers to self-efficacy in medication use. The "tell" section was designed to overcome communication barriers, such as fear of telling providers about nonadherence with medication regimens. The "expect" section is designed to provide means for providers to recognize and encourage patient collaborative actions, such as bringing medications to clinic visits [34].

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The educational videos are less than 2 minutes each in length. The topics and learning objectives are based on interviews, focus groups, professional organization recommendations, and surveys with older adults and PCPs. The final set has 5 videos (length in min:sec): (1) working with your doctor (1:25); (2) taking medicine safely at home (1:33); (3) learning about your medicines (1:36); (4) working with your pharmacist (1:34); and (5) reading prescription labels (1:23). The videos are delivered in exam rooms on touchscreen tablets mounted to either the wall or portable stands.

There is no compensation to patients or clinicians for using the study tools. Participating clinics consider the interventions to be part of their standard of care once implemented, with no plans to compensate for any potential harm because of the trial.

Strategies to Improve Adherence to Interventions

Five points ("moments") of patient encounters during a typical office visit were identified to redesign clinical processes for enhanced patient partnership. The moments all present opportunities for PCPs to partner with patients to improve medication safety and were used to train PCPs on how to incorporate the interventions in the visit process. Two behavioral economics principles were used in developing sample scripts for PCPs: benefits appeal and psychological incentives [35].

1. Rooming, by medical assistants, sets the expectation for active partnership through benefits appeal and psychological incentives. Script examples include "This guide may help you be prepared. Check the items and give it to the doctor" and "I watched all these videos and I like them all. They are very short but will really help you."
2. Greeting, by providers, recognizes and encourages preparation in the patient work system with psychological incentives. Script examples include "Did you bring your meds? Great. I like it when you are prepared!" and "I see you are trying to be prepared. Very good."
3. Agenda setting, by providers, recognizes and encourages collaborative work through psychological incentives. Example scripts include "You used the prep guide. Thank you!" and "Thank you for telling me about your meds! I like it when we can work together better."
4. Closing, by providers, recognizes and encourages patient learning and engagement with psychological incentives. Example scripts include "Did you watch the videos here? Do you want to learn more?" and "That was a good visit – you are a 5-star patient today."
5. Discharge, by medical assistants or nurses, encourages learning through psychological incentives and group effects. Scripts examples include "It is great that you are trying to learn more about your meds" and "We can help you better by working together."

At the discretion of the clinics, gifts of token values are given to patients by staff or providers as part of psychological incentives. Examples of gifts are water bottles, band-aid holders, pill boxes, and medication bags, with a bulk purchase value of about US $1 per item. Staff and providers are informed that although they are encouraged, they are free to decide whether to use the tools and to adapt the suggested partnership enhancement scripts in their clinic encounters.

Outcomes

The primary outcome is self-efficacy in medication use in community settings. Self-efficacy will be measured by a validated tool: Medication Use and Self-Efficacy (MUSE) [36]. MUSE has eight items with a 5-point Likert scale, ranging from "1 – strongly disagree" to "5 – strongly agree": (1) It is easy for me to take my medicine on time; (2) It is easy to remember to take all my medicines; (3) It is easy for me to set a schedule to take my medicines each day; (4) It is easy for me to take my medicines each day; (5) It is easy for me to ask my doctor questions about my medicine; (6) It is easy for me to understand my doctor's instructions for my medicine; (7) It is easy for me to understand instructions on medicine bottles; and (8) It is easy for me to get all the information I need about my medicine. We replaced the word "pharmacist" with "doctor" given that our focus is on interventions in primary care settings. The MUSE score is the sum of the individual responses to the 8 items and ranges between 8 and 40, with 40 indicating "strongly agree" for all 8 items.

Secondary outcomes are a combination of patients' and PCPs' views on communication, collaborative work, and medication reviews. For patients, we will assess their views on collaborative work with seven items selected from five previously published instruments: (1) I know what each of my prescribed medications does (from Patient Activation Measure [37]); (2) I worry about drug interactions between the medications I take (from Medication-Related Problems [38]); (3) During the visit, I was asked to talk about any problems with my medicines or their effects (from Patient Assessment of Chronic Illness Care [39]); (4) During the visit, I was asked questions, either directly or on a survey, about my medicine habits (from Patient Assessment of Chronic Illness Care); (5) I understand what my doctor expects of me regarding my medicines (Psychological Safety Measure [40]); (6) If I make a mistake with my medicines, my doctor does not hold that against me (from Psychological Safety Measure); and (7) My doctor knows the vitamins and supplements I take (from Home Medication Experience Questionnaire [41]).

For providers, we will record the results of medication reviews in a medication review form and capture collaborative work during the visit. The medication review form was adapted from a toolkit published by the Agency for Health Care Research and Quality [42]. The medication review form measures regimen issues (contraindications, drug-drug interactions, and duplications); patient self-management issues (taking expired medications, taking incorrectly, failure to refill, and missed follow-up visits or lab testing); making changes without communicating with the primary care provider (making changes in medications, stopping a prescription, and stopping a supplement); and discrepancies in the medication record (taking medications not in the record, taking medications different from the record, medications active in the patient's record but not taking, or incorrect dose information). For each issue identified, we asked the providers whether they believed it presented a risk to medication safety (no risk, minor risk, or major risk). The collaborative work activities captured are medication changes made in the visit (removal of expired medications, updating prescriptions, replacing prescriptions, prescribing new

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medications, regimen simplification, deprescribing, and changes in total number of medications); whether a caregiver is present, and if not, if a caregiver would be helpful; whether the patient brought their prescription and nonprescription medications to the visit; whether the patient knows why and how to take their medications; practices in engaging patients (agenda setting, creating or updating medication list with patients, and using teach-back techniques); and issues impeding the collaborative work (health literacy, language barriers, cognitive impairment, lack of a caregiver, not enough time, patient not knowing their medications).

All outcomes will be assessed immediately after the conclusion of a clinic visit. A research coordinator will survey consenting patients and give a paper form to the provider to collect data on primary and secondary outcomes. Implementation-related measures will be collected in terms of monthly use of the visit preparation guide and access logs of the video library. Protocol deviations will be reported and addressed per University of Texas at Arlington policies.

Study Timeline

Cross-sectional measurements will be taken at 6 time periods of 6 weeks each and will include a transition period of no data collection for intervention clinics (Table 1). Sample sizes will vary by period and cluster. We powered the trial according to the stepped wedge design (clinics A and B only) so that the additional data from the control clinic would add to the power as a supplement. The control clinic is in the same health system as one of the intervention clinics and shares a similar patient population and staff. Using a stepped wedge design allows for the implementation of the intervention at different time points in each clinic, thus providing logistical advantages (like maximizing resources for implementation) and controlling for biases from trends in patient care [43].

Table 1. Design of the nonrandomized, cross-sectional stepped wedge cluster-controlled trial with the schedule of enrollment, interventions, and assessments.

Timepoint (6 weeks[a])	Study period					
	P_1	P_2	P_3	P_4	P_5	P_6
Study sites[b]						
Clinic A	CTRL[c]	N/A[d]	INT[e]	INT	INT	INT
Clinic B	CTRL	CTRL	N/A	INT	INT	INT
Clinic C	CTRL	CTRL	CTRL	CTRL	CTRL	CTRL
Enrollment						
Eligibility screen	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Informed consent	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Interventions						
Visit Prep Guide	N/A	Clinic A	Clinics A and B	Clinics A and B	Clinics A and B	Clinics A and B
Educational Videos	N/A	Clinic A	Clinics A and B	Clinics A and B	Clinics A and B	Clinics A and B
Assessments						
Medication use self-efficacy	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Medication review	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Collaborative work	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C

[a]Timepoint is in 6-week periods (P_1-P_6), total 36 weeks.

[b]Study sites (nonrandomized).

[c]CTRL: control.

[d]N/A: not applicable (transition period for implementation; no data collected).

[e]INT: intervention.

Sample Size

The study is a superiority trial, on the hypothesis that interventions will improve patients' self-efficacy in medication use. We powered the trial to detect a difference of 3.8 units on the MUSE scale from pre to postintervention, with a pooled SD of 4.7 (standardized effect size of 0.79) based on a validation study on MUSE [36] using a 2-tailed significance level of 0.05. Power analysis was computed using the R package (version 4.1.0; University of Washington) swCRTdesign [44] via a web-based tool [45]. The transition period was excluded from the sample size calculations. We used 0.07 for intracluster correction and 0.9 for cluster autocorrelation based on study design recommendations [46,47]. With power set at 80%, the

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requisite numbers of visits to collect data for each period are in Table 2, with a total sample size of 405.

Table 2. Sample size calculation. Sample size is the number of visits, not the number of patients, using a cross-sectional design.

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
Clinic A	15	N/A[a]	35	20	15	15
Clinic B	30	50	N/A	45	30	30
Clinic C	20	20	20	20	20	20

[a]N/A: not applicable (transition period with no data collection efforts).

Recruitment

During each 6-week data collection period, study coordinators will work with study clinics to select recruitment days and identify up to 4 eligible visits per provider on those days. Only 2 visits per provider per shift will be enrolled to avoid disrupting care. Providers will be recruited and consented, informed of identified visits on selected data collection days, and asked to obtain verbal consent from the patients in identified visits to be approached by the study coordinator. The coordinator will then recruit and consent the patient. Patient and clinician participants will be compensated US $10 and US $25, respectively, for each data collection encounter.

Assignment of Interventions and Blinding

Because of the nature of the assessed interventions, we consider blinding not possible for patients or PCPs. Research coordinators who collect data are not blinded to the interventions as they may see interventions, but they are instructed to conduct data collection in consistent procedures regardless of intervention status.

Data Management and Confidentiality

All primary and secondary data collected will be entered into Research Electronic Data Capture (REDCap; Vanderbilt). A quarterly data review will be carried out to assess potential issues with data collection, including missing data and duplicate records. No personal identifying data will be collected.

Statistical Methods for Primary and Secondary Outcomes

Hierarchical models will be used to assess the impact of the interventions on primary and secondary outcomes. Hierarchical models, including linear mixed models, have been described and recommended for use in testing for intervention effects in cross-sectional stepped wedge designs [48,49]. The effect of the intervention is subject to confounding with time due to the staggered entry in stepped wedge designs, and thus the hierarchical modeling structure captures time trends and accounts for the effects of clustering within clinics. Should there be ceiling or floor effects with the total MUSE scores, responses to individual items will be explored. No interim analysis will be conducted. Social determinants of health will be evaluated, including sex, age, race, ethnicity, preferred language, educational level attained, self-reported health literacy, insurance status, and study clinics (private vs public). Associations of these variables with primary outcomes will be assessed, as we anticipate social determinants of health may affect the impact of the interventions. Selected social determinants of health will be assessed through subgroup analyses and model adjustment.

Descriptive statistics, such as medians, IQRs, and proportions, will be tabulated, overall and within clinics, to understand the distribution of the study population. Potential confounding variables were specified prior to data collection and include patient demographics, social determinants of health, time, and clinician. Confounding variables will be evaluated and controlled for in the analysis primarily through model adjustment or stratification. Because the intervention is confounded by time, the model will account for time period as a covariate in the statistical model, following recommendations on mixed models for stepped wedge trials by Li et al [48]. In addition, we included an extra clinic as a control group to assess changes over time in the absence of the intervention.

The study protocol is publicly registered and fully available. Participant level-data will not be made available. Statistical code will be made available upon request.

Dissemination Plan

A writing group will lead publication efforts in peer-reviewed journals and professional conferences. Reports will follow the CONSORT (Consolidated Standards of Reporting Trials) statement and its extensions (for both cluster randomized trials and nonpharmacological interventions) and follow journal authorship guidelines. We will also report implementation-related findings such as uptake patterns of tools over time and qualitative feedback from clinicians and patients at the study sites.

Results

The study was funded in September 2019. The trial started on April 10, 2023, and continued until December 15, 2023. The 3 study sites were in urban settings in a Southwest metropolitan area of the United States. All clinics predominantly serve patients with low socioeconomic status. One clinic is private with 1 family medicine physician. The other 2 clinics are public and part of a safety-net health system with family medicine residency training programs with approximately 15 primary care providers. As of February 15, 2024, we enrolled 405 patients. Data analysis is currently underway and the first results are expected to be submitted for publication in 2024.

Discussion

The trial aims to assess the impact of a set of patient partnership tools that redesign primary care encounters on patient

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self-efficacy in medication use in community settings. Secondarily, the trial will provide information on the systematic approach to patient partnership enhancement in collaborative work during primary care visits, from both the patients' and providers' perspectives. We expect the tools and associated process changes in primary care clinics to improve several components of the collaborative work system in terms of self-efficacy, tools, and skills. The intervention is unique compared with prior approaches, such as generic videos on open communication between patients and HCPs or EHR-based tools to help agenda setting [19,22]. If adoption proves successful and MUSE scores rise, the trial will support the innovative approach to improve medication safety in ambulatory settings by improving the value of primary care through collaborative work and partnership. The trial will be carried out in clinics serving vulnerable populations with poor indicators for social determinants of health. The combination of a private family medicine clinic and a primary care clinic in a public safety-net hospital system will provide evidence about the applicability of the approach in a wide range of clinical settings. In addition to the visit prep guide and videos, the trial will also generate other tools for implementation, such as training for PCPs to engage the patient work system and thus improve self-efficacy and ultimately medication safety.

Both the intervention and the assessment approaches are based on collaborative work concepts not previously used to increase patient engagement. Psychological safety in the hierarchical relationship between patients and providers and the clarification of roles and responsibilities have been absent in prior interventions. Although prescribing decisions are important aspects of medication safety, the intervention targets barriers to successful self-management in the patient work system, including patients' home environments.

The trial design has several strengths. The assessment collects data to illuminate both the patient's and PCP's perspectives immediately after an office visit. The data include both patient-centered safety outcomes such as self-efficacy and clinical outcomes such as risks posed by issues identified during medication review. The data also include process measures on collaborative work like psychological safety. The studied patient population is on 5 or more chronic medications and thus is a high-risk group.

The trial has several limitations. Data on ADEs are not collected. Future studies are needed to assess the longer-term impact. The trial is limited in time and thus longitudinal data are not collected on the potential long-term impact of the partnership tools (ie, the impact of repeated exposure over years). The modality of tools (paper visit preparation guides and exam room videos on tablets) is limited and does not leverage consumer and EHR technology in communication and in learning. The number of study clinics is small. However, with stepped wedge design, we expect to control some of the confounding variables, such as seasonality.

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Data Availability

The data sets generated and analyzed during this study are not publicly available to protect patient confidentiality but may be available from the corresponding author upon reasonable request. The assessment instruments and intervention tools are available for noncommercial use.

Authors' Contributions

YX was responsible for writing the protocol, acquiring funding, and planning the study. ZNH, KMD, KGF, APG, RAY, and SB participated in cowriting the protocol. ZNH coordinated data collection procedures across study sites. KMD, KYC, YZ, LK, JW, KGF, AME, APG, SIP, AIA, RAY, and DS were involved in codeveloping intervention tools. JLR, KMS, SIP, AIA, and MAC participated in codeveloping assessment concepts. KGF, APG, RAY, DS, and MJ played a role in coplanning for the study. KGF and SB were responsible for designing the study. KGF, AME, and RAY were involved in recruiting study sites.

Conflicts of Interest

KYC has a potential research conflict of interest due to a financial interest with companies Hewlett-Packard Enterprise, Boostr and DecisionNext. A management plan has been created to preserve objectivity in research in accordance with UTA policy. The authors have no further interests to declare.

Multimedia Appendix 1

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Verbal consent scripts.
[PDF File (Adobe PDF File), 136 KB - resprot_v13i1e57878_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 34 KB - resprot_v13i1e57878_app2.docx]

Multimedia Appendix 3
Patient visit guide (English).
[PDF File (Adobe PDF File), 184 KB - resprot_v13i1e57878_app3.pdf]

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Abbreviations

ADE: adverse drug event
CONSORT: Consolidated Standards of Reporting Trials
EHR: electronic health record
HCP: health care professional
MUSE: Medication Use and Self-Efficacy
PCP: primary care professional
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Predictive Noninvasive Single-Nucleotide Variation–Based Biomarker Signature for Resectable Pancreatic Cancer: Protocol for a Prospective Validation Study

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Abstract

Background: Single-nucleotide variations (SNVs; formerly SNPs) are inherited genetic variants that can be easily determined in routine clinical practice using a simple blood or saliva test. SNVs have potential to serve as noninvasive biomarkers for predicting cancer-specific patient outcomes after resection of pancreatic ductal adenocarcinoma (PDAC). Two recent analyses led to the identification and validation of three SNVs in the CD44 and CHI3L2 genes (rs187115, rs353630, and rs684559), which can be used as predictive biomarkers to help select patients most likely to benefit from pancreatic resection. These variants were associated with an over 2-fold increased risk for tumor-related death in three independent PDAC study cohorts from Europe and the United States, including The Cancer Genome Atlas cohorts (reaching a P value of 1×10^{-8}). However, these analyses were limited by the inherent biases of a retrospective study design, such as selection and publication biases, thereby limiting the clinical use of these promising biomarkers in guiding PDAC therapy.

Objective: To overcome the limitations of previous retrospectively designed studies and translate the findings into clinical practice, we aim to validate the association of the identified SNVs with survival in a controlled setting using a prospective cohort of patients with PDAC following pancreatic resection.

Methods: All patients with PDAC who will undergo pancreatic resection at three participating hospitals in Switzerland and fulfill the inclusion criteria will be included in the study consecutively. The SNV genotypes will be determined using standard genotyping techniques from patient blood samples. For each genotyped locus, log-rank and Cox multivariate regression tests will be performed, accounting for the relevant covariates American Joint Committee on Cancer stage and resection status. Clinical follow-up data will be collected for at least 3 years. Sample size calculation resulted in a required sample of 150 patients to sufficiently power the analysis.

Results: The follow-up data collection started in August 2019 and the estimated end of data collection will be in May 2027. The study is still recruiting participants and 142 patients have been recruited as of November 2023. The DNA extraction and genotyping of the SNVs will be performed after inclusion of the last patient. Since no SNV genotypes have been determined, no data analysis has been performed to date. The results are expected to be published in 2027.

Conclusions: This is the first prospective study of the *CD44* and *CHI3L2* SNV–based biomarker signature in PDAC. A prospective validation of this signature would enable its clinical use as a noninvasive predictive biomarker of survival after pancreatic resection that is readily available at the time of diagnosis and can assist in guiding PDAC therapy. The results of this study may help to individualize treatment decisions and potentially improve patient outcomes.

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KEYWORDS

single-nucleotide polymorphism; SNP; single-nucleotide variation; SNV; pancreatic ductal adenocarcinoma; PDAC; noninvasive biomarker; survival; resection; prospective validation

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most frequent type of pancreatic cancer and one of the most lethal malignancies due to a tendency for early local invasion and high metastatic potential [1,2]. Despite this aggressive phenotype, PDAC shows a wide range of biological features, whereby early recurrence is observed in some patients who undergo pancreatic resection, whereas long-term cancer-free survival can be achieved in others [3-5]. It is considered that such individual oncologic courses and the response to personalized treatment plans can be predicted by gaining a more comprehensive understanding of human germline genetic variation [6,7]. Importantly, this genetic information can be found in the germline DNA and thus does not require a tumor biopsy or the technically demanding isolation of circulating tumor cells. Instead, samples can be easily obtained by a simple and cheap blood or saliva test at any time during diagnostic workup or treatment, offering a noninvasive predictive biomarker available at the time of diagnosis. Indeed, this type of personalized medicine is no longer a fantasy but a maturing reality. In other cancer types, including acute lymphoblastic leukemia, colorectal cancer, lung cancer, and breast cancer, the genotyping of certain single-nucleotide variations (SNVs; formerly SNPs) is recommended by the US Food and Drug Administration [8].

A growing body of evidence suggests that inherited genetic variants can also be used to predict cancer-specific patient outcomes and guide therapy for patients with pancreatic cancer. Specifically, in a retrospective analysis, we identified a germline variant in the CD44 gene (rs187115) that can serve as a predictive biomarker to help select patients who are likely to benefit from pancreatic resection [9,10]. More recently, we performed a genome-wide screen for inherited variants that affect survival in patients with PDAC based on existing biological knowledge about the regions where the genetic variants reside [11]. This search for high-frequency polymorphic variants that affect tumor-related survival and either result in an altered protein structure and function or reside in known regulatory noncoding genomic regions has identified two clinically relevant sequence variants in functional regions of genes that are known to regulate cancer progression, invasion, and metastasis [11]. Specifically, regulatory variants within *CHI3L2* (rs684559) and *CD44* (rs353630) were found to be associated with an over 2-fold increased risk of tumor-related death in two independent retrospective PDAC study cohorts from Europe and the United States (hazard ratio [HR] 0.38, 95% CI 0.27-0.53; $P=1\times10^{-8}$, q value<.05) [11].

Taken together, these retrospective studies have demonstrated the potential of polymorphic sequence variants to identify a subset of patients with high-risk pancreatic cancer associated with a very low survival probability that might be eligible for inclusion in clinical trials of new therapeutic strategies, including neoadjuvant chemotherapy protocols and novel adjuvant systemic regimens. In addition, the findings from these studies suggest that the biological knowledge about these SNVs could help guide the development of such individualized genomic treatment strategies.

However, despite their robustness, the described results have not yet been validated prospectively and it is unclear whether these observations can be independently replicated in a controlled clinical setting.

Methods

Study Aim, Design, and Setting

This project is designed as a one-arm prospective controlled clinical study that aims to validate the association of the previously identified SNVs in the CD44 and CHI3L2 genes with PDAC survival after tumor resection. We aim to use a prospective cohort of patients with PDAC who will undergo pancreatic resection at our established network of three cantonal hospitals (Departments of Surgery at the Cantonal Hospital of Winterthur, Cantonal Hospital of Lucerne, and the Triemli Hospital in Zurich) in Switzerland. The study outline is depicted in Figure 1.

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Figure 1. Study outline. A planned sample of 150 consecutive patients with histopathologically confirmed resectable pancreatic ductal adenocarcinoma (PDAC) will be treated at three designated Swiss hospitals according to the best standard of care and prospectively included in the study. The first patient was included in August 2019 and the recruitment is ongoing. The estimated end of data collection is May 2027. The survival analysis using the single-nucleotide variation (SNV) genotyping data after DNA extraction from the blood collected at the time of inclusion will be performed after completion of the follow-up of all patients to ensure that all study participants and physicians are fully blinded with regard to the SNV genotypes of the patients. AJCC: American Joint Committee on Cancer.

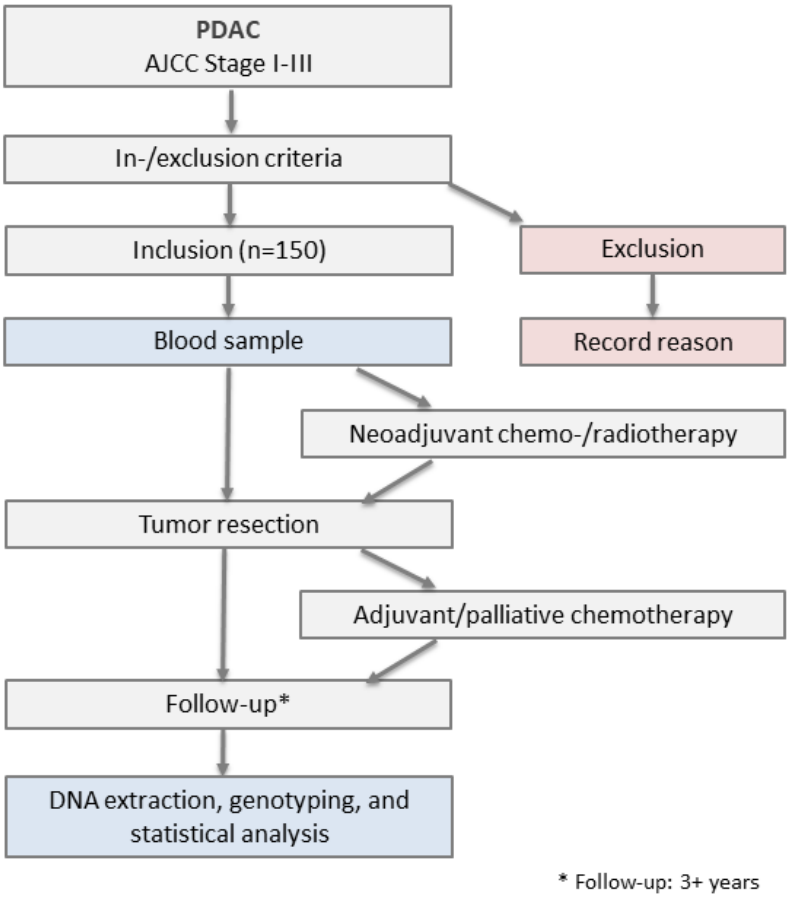

Participant Characteristics

Patients with a diagnosis of a pancreatic tumor mass that is either biopsy-proven or highly indicative of PDAC will be recruited before surgery in the outpatient clinics of the participating centers after completed standard preoperative evaluation of a pancreatic cancer diagnosis and assessment of tumor resectability according to the best standard of care and the following criteria: (1) pancreatic tumor mass either biopsy-proven or highly indicative (as assessed by preoperative magnetic resonance imaging, computed tomography, and/or endoscopic ultrasound imaging) of PDAC in the head or tail of the pancreas; (2) tumor, node, and metastasis stage c/uT1-4, c/uNx, cM0 (according to the 7th edition of the American Joint Committee on Cancer staging system); (3) open or minimally invasive pancreatic resection, including conversion laparotomy; (4) underwent primary tumor resection; (5) received neoadjuvant chemotherapy and/or radiochemotherapy; (6) previously underwent pancreatic resection for reasons other than PDAC; (7) age≥18 years; and (8) provided written informed consent. Patients who subsequently successfully undergo tumor resection and whose diagnosis of PDAC is confirmed by histopathological examination of the resected specimen will be included in the study. All patients who fulfill these criteria will be included, regardless of the tumor resection margins (R0, R1, R2) and regardless of intra- or postoperative mortality.

The presence of one of the following criteria will lead to the exclusion of the patient: (1) any histopathological entity other than PDAC, including but not limited to adenocarcinoma of the papilla of Vater, acinar cell carcinoma, distal cholangiocarcinoma, and neuroendocrine tumors such as neuroendocrine carcinoma; (2) metastatic disease, including intraoperative findings confirmed by histopathological examination (cM1, pM1); (3) previous pancreatic resection for PDAC and presenting either with local recurrence or a second primary tumor in the pancreatic remnant, but not yet included in the study; (4) age<18 years; and (5) did not provide written informed consent. With respect to exclusion criterion (3), individuals who had already been included in the study at the time of the first resection of a PDAC will not be excluded from the study retrospectively because of a local recurrence or a second primary tumor but will continue to receive follow-up. All patients that will be excluded from participation will be recorded together with the reason for the exclusion.

Endpoints and Data Collection

The primary endpoint of the study is tumor-related survival. Secondary endpoints include recurrence and overall survival.

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The exact type and timing for data and blood sample collection are detailed in Table 1. The estimated total duration of the study is 5 years, including the scheduled 3-year postoperative follow-up.

Table 1. Type and timing of data and blood sample collection.

Data and timing of collection	Screening	Surgery	Early postoperative period	Follow-up
Visit	1	2	3	4, 5, and 6
Time	Preoperative	day 0	1 week postoperative	1, 2, and 3 years
Participant information and informed consent	✓			
Medical history	✓			
Inclusion/exclusion criteria check	✓			
Blood collection	✓			
Surgical procedure		✓		
Histopathological data			✓	
Recurrence/survival data				✓

All cases will be presented at interdisciplinary tumor board meetings at each participating center pre- and postoperatively. All patients will be offered standard-of-care multimodal treatment at the discretion of the interdisciplinary tumor board at each participating center. The operation will be performed according to the group assignment by senior surgeons only, who have extensive experience in pancreatic resections. All surgeries will be performed at the Departments of Surgery at the Cantonal Hospital of Winterthur, Cantonal Hospital of Lucerne, and the Triemli Hospital in Zurich. The follow-up of the patient will be recorded for at least 3 years after tumor resection. Data collection will be completed using the hospital records or by contacting the patient's general practitioner or oncologist; thus, no additional appointments in the outpatient clinic will be required for study purposes.

Power of the Study

Sample size calculations were performed in G-Power 3.1 software (Heinrich-Heine University, Germany) based on the results of the previously mentioned retrospective studies according to the ability to detect an HR>2 between genotypes [9-11]. With the use of a two-sided α level of .05 and considering a dropout rate of 10% as well as a potential additional error margin of 10%, 150 patients are required to obtain 80% power to detect a difference in cancer-related survival between genotypes.

Statistical Analysis

A parametric two-sided Student *t* test and a two-tailed Mann-Whitney *U* test will be used to compare data distributions in groups with normally distributed data and data that deviate from a normal distribution, respectively. The Fisher exact test will be used to calculate frequency distributions in cross-table analyses. Kaplan-Meier survival curves (log-rank test) and Cox proportional hazards models will be calculated to assess and compare survival times. All statistical analyses will be performed using R and SPSS software.

Ethical Considerations

The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and the requirements of the Swiss regulatory authority. The study was approved by the local ethics committee (Kantonale Ethikkommission Zürich, BASEC-Nr. 2019-00178) on April 18, 2019. All patients will be asked to sign a written informed consent form that has been approved by the ethics committee, which describes in detail the aims and methods of the study as well as lists all potential risks posed to the participants. Privacy and confidentiality are fully ensured since the study data are anonymous and deidentified. All data relevant to this study will be coded (including biological material and health-related personal data), safely protected, and recorded in a digital format using a GCP-compliant electronic data capture system. The study participants will receive no financial compensation for participating in the study.

Results

The follow-up of the patients started in August 2019. The estimated end of data collection is May 2027. Recruitment is ongoing. As of November 2023, 142 patients have been recruited.

The DNA extraction and genotyping of the SNVs will be performed after the inclusion of the last patient. The data analysis will be performed at the end of follow-up of the last patient. Since no SNV genotypes have been determined, no data analysis has been possible to date. The results are expected to be published in 2027.

Discussion

This is the first prospective study of the clinical value of *CD44* and *CHI3L2* SNV–based biomarkers in PDAC after tumor resection. The design of this study enables minimizing the biases

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inherent in retrospective trials, such as selection or publication biases. Moreover, akin to a randomized controlled trial designed to compare clinical interventions, both the study participants and all physicians involved in the treatment of the included patients will be fully blinded by determining the SNV genotypes and analyzing the results only after the completion of follow-up of all patients. Such a prospective validation of these biomarkers would allow for their clinical use as a predictive signature of survival after pancreatic resection that can be readily available at the time of PDAC diagnosis.

The main limitation of the study is the heterogeneity of the patient group with regard to the neoadjuvant and adjuvant treatment(s) the individual participants will receive. These treatments are known to affect patient outcomes, including cancer-related survival as the main endpoint of this study. However, this heterogeneity also reflects real-world clinical practice and should thus provide a robust biomarker that can be applied to all patients with PDAC who undergo resection of their tumors, regardless of the chemoradiotherapy they individually receive. Another limitation is the disruption of administrative and processes during the COVID-19 pandemic. However, since patients diagnosed with pancreatic cancer received adequate treatment without major delays and were included consecutively in this study during this disruptive period, the effect on the study results should be negligible.

The genotype of the identified SNVs can be determined before the start of any treatment by a technically simple blood or even saliva test, which can then be used to identify patients who are at higher risk for faster tumor progression [6,9]. Other prognostic factors currently in use or suggested to be useful in a clinical setting such as completeness of resection, lymph node involvement, or postoperative carbohydrate antigen 19-9 serum levels can only be precisely determined after surgical resection and therefore have limited relevance to treatment decisions [12]. In contrast, SNV-based biomarkers can guide preoperative treatment decisions such as the decision to perform neoadjuvant chemotherapy in patients with an aggressive tumor biology or can affect adjuvant treatment protocols. The results of this prospective study may lead to improved patient outcomes in patients with PDAC that is amenable to resection.

Authors' Contributions

NS and LFG designed the protocol and drafted the manuscript. All other authors participated in the design of the study and are local investigators at the Cantonal Hospital of Winterthur, Cantonal Hospital of Lucerne, and the Triemli Hospital in Zurich. All authors were involved in editing the manuscript and approved the final text of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

GCP: Good Clinical Practice
HR: hazard ratio
PDAC: pancreatic ductal adenocarcinoma
SNV: single-nucleotide variation

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Protocol

Impact of an Automated Population-Level Cirrhosis Screening Program Using Common Pathology Tests on Rates of Cirrhosis Diagnosis and Linkage to Specialist Care (CAPRISE): Protocol for a Pilot Prospective Single-Arm Intervention Study

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Abstract

Background: People with compensated cirrhosis receive the greatest benefit from risk factor modification and prevention programs to reduce liver decompensation and improve early liver cancer detection. Blood-based liver fibrosis algorithms such as the Aspartate Transaminase–to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) index are calculated using routinely ordered blood tests and are effective screening tests to exclude cirrhosis in people with chronic liver disease, triaging the need for further investigations to confirm cirrhosis and linkage to specialist care.

Objective: This pilot study aims to evaluate the impact of a population screening program for liver cirrhosis (CAPRISE [Cirrhosis Automated APRI and FIB-4 Screening Evaluation]), which uses automated APRI and FIB-4 calculation and reporting on routinely ordered blood tests, on monthly rates of referral for transient elastography, cirrhosis diagnosis, and linkage to specialist care.

Methods: We have partnered with a large pathology service in Victoria, Australia, to pilot a population-level liver cirrhosis screening package, which comprises (1) automated calculation and reporting of APRI and FIB-4 on routinely ordered blood tests; (2) provision of brief information about liver cirrhosis; and (3) a web link for transient elastography referral. APRI and FIB-4 will be prospectively calculated on all community-ordered pathology results in adults attending a single pathology service. This single-center, prospective, single-arm, pre-post study will compare the monthly rates of transient elastography (FibroScan) referral, liver cirrhosis diagnosis, and the proportion linked to specialist care in the 6 months after intervention to the 6 months prior to the intervention.

Results: As of January 2024, in the preintervention phase of this study, a total of 120,972 tests were performed by the laboratory. Of these tests, 78,947 (65.3%) tests were excluded, with the remaining 42,025 (34.7%) tests on 37,872 individuals meeting inclusion criteria with APRI and FIB-4 being able to be calculated. Of these 42,025 tests, 1.3% (n=531) had elevated APRI>1 occurring in 446 individuals, and 2.3% (n=985) had elevated FIB-4>2.67 occurring in 816 individuals. Linking these data with FibroScan referral and appointment attendance is ongoing and will continue during the intervention phase, which is expected to commence on February 1, 2024.

Conclusions: We will determine the feasibility and effectiveness of automated APRI and FIB-4 reporting on the monthly rate of transient elastography referrals, liver cirrhosis diagnosis, and linkage to specialist care.

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International Registered Report Identifier (IRRID): DERR1-10.2196/56607

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KEYWORDS

noninvasive tests; cirrhosis; population health; screening; liver cirrhosis; liver; compensated; risk factor; pathology; population based; liver screening; prevalence; hepatocellular carcinoma; transient elastography; FibroScan

Introduction

Background

Liver cirrhosis is a major global public health threat; from 1990 to 2017, the global estimate of compensated cirrhosis prevalence increased from 66 million cases to 112 million cases [1], and liver cirrhosis directly causes millions of deaths each year due to liver failure and liver cancer [2,3]. Without timely treatment of chronic liver disease of any cause, individuals are at risk of developing liver cirrhosis [4].

People with compensated cirrhosis receive the greatest benefit from risk factor modification and prevention programs to reduce liver decompensation and improve early liver cancer detection [1]. Curative options are available for early-stage hepatocellular carcinoma; however, most cases are diagnosed at an advanced stage and median survival is only 18% [5], highlighting the importance of early diagnosis [6]. Early-stage liver hepatocellular carcinoma can be identified through surveillance with 6 monthly liver ultrasounds in people with cirrhosis. It is, therefore, imperative that novel population-based screening strategies are explored to identify people with cirrhosis early to facilitate timely linkage to specialist care, including liver cancer surveillance programs.

Transient elastography (FibroScan) has revolutionized the diagnosis of cirrhosis for people with liver disease, providing a noninvasive alternative to liver biopsy [7]. However, at a population level, transient elastography is an unsuitable screening method for cirrhosis due to limited access and cost. Blood-based biomarker algorithms that use readily available blood test parameters, such as the Aspartate Transaminse (AST)–to-Platelet Ratio Index (APRI) [8] and Fibrosis-4 (FIB-4) index [9], have, therefore, been developed as an affordable, accessible screening tool for liver cirrhosis that can triage the need for transient elastography [10].

Prior Work

Studies in the United Kingdom have used specialized software to automate reflex FIB-4 calculation and reporting on frequently requested blood tests in primary care practice, to increase the diagnosis of people with liver disease and link them to specialist care within public-funded National Health Service networks of the United Kingdom [11,12]. While the iLFT (Intelligent Liver Function Testing) program has proven effective, it requires significant resourcing and may be challenging to translate to privately funded primary care models in countries such as Australia. In contrast, automated reporting of liver fibrosis indices such as APRI and FIB-4 on routinely ordered blood tests by pathology providers does not require specialized software or resourcing and facilitates broad accessibility of results to patients and health workers.

Study Goal

In this study (CAPRISE [Cirrhosis Automated APRI and FIB-4 Screening Evaluation]), we will determine the feasibility and effectiveness of automated APRI and FIB-4 reporting and provision of brief liver cirrhosis information on the monthly rate and proportion of transient elastography referrals, liver cirrhosis diagnosis, and linkage to specialist hepatology care. We have partnered with a large pathology service in Victoria to pilot a population-level liver cirrhosis screening package, which comprises automated calculation and reporting of APRI and FIB-4 on routinely ordered blood tests and provision of brief information about liver cirrhosis and a web link for transient elastography referral.

Hypothesis

Automated calculation and reporting of APRI and FIB-4 on routinely ordered blood tests and provision of information about liver cirrhosis, including a link for transient elastography referral, will increase the diagnosis of liver cirrhosis and linkage to specialist care.

Objectives

The primary objectives of this study are given below.

First, this study aims to measure the monthly rate and the number (proportion) of individuals with APRI greater than 1.0 and FIB-4 greater than 2.67 among people who undergo automated APRI and FIB-4 calculation on blood test events performed through a single Australian pathology service.

Second, this study aims to measure the monthly rate of transient elastography referrals received after the introduction of automated APRI and FIB-4 reporting, compared with the preintervention period.

Third, this study aims to measure the monthly rate and the number (proportion) of transient elastography tests performed in those with an elevated APRI and or FIB-4 score during the intervention period, compared with the preintervention period.

Fourth, this study aims to measure the monthly rate and the number (proportion) of individuals with APRI greater than 1.0 or FIB-4 greater than 2.67 that have cirrhosis range median stiffness (kPa) confirmed on FibroScan.

Finally, this study aims to measure the number (proportion) of individuals with cirrhosis range FibroScan during the intervention period that is linked to specialist care, compared with the preintervention period.

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The secondary objective of this study is to describe the sociodemographic factors associated with (1) APRI greater than 1.0 and FIB-4 greater than 2.67, (2) attendance at FibroScan appointment, (3) cirrhosis diagnosed on FibroScan, and (4) linkage to specialist care.

Methods

Ethical Considerations

A waiver of consent was granted for this study by the institutional ethics committee (St Vincent's Hospital Melbourne human research ethics committee project ID 81922, Local Reference LRR 315/21).

Study Methodology

Study Design

A pilot, prospective, single-arm, intervention approach was followed for this study.

Study Setting

This study was conducted at the FibroScan clinic of a single tertiary center linked to a large pathology service, which provides both public and privately funded pathology services for the general population in regional and urban areas of Victoria, Australia.

Primary Outcome Measurement

The primary outcomes prospectively commenced on August 1, 2023, for 6 months before intervention and will continue until the conclusion of the intervention period on July 31, 2024. The impact of the intervention will be determined by comparing primary outcome measures during the intervention period to the 6 months prior to the intervention (standard of care).

Definitions

Comparator Group (Standard of Care)

Currently, APRI and FIB-4 scores are not routinely reported anywhere in Australia. Prior to the intervention, blood tests will be reported per standard of care. APRI and FIB-4 scores will be calculated automatically by the pathology service from the start of the study but will not be reported to ordering clinicians until the intervention period. FibroScans are requested through a paper-based referral form by general practitioners or specialists, which is then faxed to the hospital for triage and booking.

Intervention (In Addition to Standard of Care)

St Vincent's Pathology automatically calculates and reports APRI and FIB-4 scores if platelet count, alanine transferase (ALT) level, and AST level are requested together in a single blood test by primary care physicians. This is provided free of charge. The result will be reported to the requesting primary care physician (both in paper format and online), along with a brief interpretation of the APRI and FIB-4 results, their relevance to liver cirrhosis screening, and a web link for further web-based information. No additional testing or appointments are scheduled as part of this study in addition to the standard of care.

Two separate pathways will be used by St Vincent's Pathology to notify clinicians of our new APRI and FIB-4 reporting format approximately 1 month prior to the commencement of the intervention period. (1) The St Vincent's Pathology standard liver function test result report will include a comment stating that APRI and FIB-4 scores will be reported as of the date of project commencement. (2) There will be a new banner included on the St Vincent's Pathology website notifying clinicians of the availability of automatic reporting of APRI and FIB-4 scores on blood test events and the date that this reporting will commence. This will have a web link to further information on the APRI and FIB-4 score, as well as information about chronic liver disease.

The additional information on the website includes (1) how APRI and FIB-4 are calculated and how it is used, (2) how to interpret the APRI and FIB-4 result, (3) what further tests would be recommended if someone has an abnormal APRI result, (4) further general information about chronic liver disease and liver cirrhosis, and (5) a link to a web-based referral form for the St Vincent's Hospital FibroScan service to book a confirmatory FibroScan to determine whether the patient has liver cirrhosis.

Recruitment

All individuals aged 18 years and older who have liver function tests and full blood count requested by a community-based health worker and performed at St Vincent's Pathology between August 1, 2023, and July 31, 2024, will be recruited. There will be no active recruitment of participants for this study.

This study is an evaluation of a health system–wide introduction of routine reporting of APRI calculation, information on liver cirrhosis, and a web link through St Vincent's Pathology to improve the quality of care for people with liver disease; therefore, no individuals will individually consent to participate. No personally identifying information will be collected and all data supplied to the research team will be deidentified by St Vincent's Pathology and transient elastography booking and reporting teams, respectively. Variables including 10-year age category, sex, and postcode will be collected as part of the study but will not allow identification of individuals, as they are broad categories expected to contain more than 1000 persons per strata per month during the study period.

The exclusion criteria of this study include children aged 18 years or younger and blood tests performed during a hospital inpatient stay, or requested by hospital outpatient service, defined by St Vincent's Pathology records (blood collection site).

Study Timeline

Preintervention Period

Between August 1, 2023, and January 31, 2024, St Vincent's Pathology will prospectively collect data on all ALT, AST, and platelet count test results conducted, and APRI and FIB-4 scores will be automatically calculated by the St Vincent's Pathology data management system, but not reported to the ordering clinician. These data will be prospectively collected from St Vincent's Pathology by a member of the study team, along with exposure variables outlined above. During the same time period,

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outcome measures per month will be prospectively collected from the St Vincent's hospital electronic medical records by a member of the research team (number of FibroScan referrals, number [proportion] of scheduled FibroScan appointments attended, number [proportion] diagnosed with cirrhosis, and number [proportion] linked to specialist care).

Intervention Period

From February 1, 2024, to July 31, 2024, St Vincent's Pathology will commence inclusion of automatic calculation of APRI and FIB-4 score reporting on all pathology blood testing events where an AST, ALT, and platelet count are ordered. St Vincent's Pathology will provide for these testing events: (1) the APRI result, (2) the FIB-4 result, (3) an explanation of what APRI and FIB-4 measure and what cutoffs are used to define cirrhosis, and (4) recommendations for further investigation of elevated APRI or FIB-4 with transient elastography (FibroScan) and performance of a liver disease screen if underlying liver disease is not known. In addition, a web link to the St Vincent's Pathology website for liver disease and cirrhosis information page will be included on all blood test reports where APRI and FIB-4 are calculated, with a provided URL link to a unique St Vincent's Hospital FibroScan referral form. This link will be distinct from the standard fax-based St Vincent's FibroScan referral form to allow measurement of referrals specifically generated in response to St Vincent's Pathology APRI or FIB-4 score calculations during the study period.

Statistical Analysis Plan

Outcome Measures

Data will be analyzed per test event and per individual tested.

Primary outcomes of this study include the number of APRI and FIB-4 scores calculated on blood test events conducted during the study period, overall and per month; the number (proportion) of APRI scores that are greater than 1.0 and FIB-4 scores that are greater than 2.67; number of FibroScan referrals overall and per month, operationalized as number of completed FibroScan referrals generated online using the recommended St Vincent's Pathology FibroScan referral link on the request slip, or St Vincent's Pathology APRI or FIB-4 calculation web page referral form link; number of individuals with an APRI greater than 1.0 or FIB-4 score greater than 2.67 who undergo a FibroScan test at St Vincent's Hospital Melbourne overall and per month; proportion of individuals with an APRI greater than 1.0 or FIB-4 score greater than 2.67 who undergo a FibroScan test at St Vincent's Hospital Melbourne; the number of individuals per month who undergo FibroScan at St Vincent's Hospital Melbourne who have cirrhosis diagnosed (liver stiffness measurement >12.5kPa); the number (proportion) of individuals with an APRI greater than 1.0 or FIB-4 score greater than 2.67 who have cirrhosis confirmed by FibroScan; the number (proportion) of individuals with etiology-specific cirrhosis range FibroScan results that are referred to the specialist liver clinic; and the number (proportion) of individuals with etiology-specific cirrhosis range FibroScan results that attend to the specialist liver clinic appointment.

The secondary outcomes of this study include the number (proportion) of individuals, stratified by age category, sex, and postcode who have elevated APRI greater than 1.0 and FIB-4 score greater than 2.67, attend the FibroScan clinic for further testing, have etiology-specific cirrhosis range FibroScan scores (kPa), and attend a liver specialist clinic appointment.

Exposure Variables Collected

Sex, age category (deciles), socioeconomic status of residence (defined by Australian Bureau of Statistics Socio-Economic Index Areas [SEIS] data matched to postcode), urban versus regional place of residence (defined by SEIS data matched to postcode), and liver disease indication recorded on FibroScan requests will be collected.

Analysis Methods

The number of APRI and FIB-4 scores generated and the proportion of APRI and FIB-4 scores in the cirrhosis range will be described overall and rates per month will be calculated.

The number (proportion) of individuals with an elevated APRI or FIB-4 who are referred for a FibroScan will be described overall and per month; and the number of FibroScan referrals after the intervention will be compared with the number of FibroScan referrals prior to the intervention by logistic regression modeling (time series analysis with the timepoint of interruption defined as February 1, 2024, when the reported APRI score intervention was introduced).

Similarly, the number (proportion) of individuals with an elevated APRI or FIB-4 who are referred for a FibroScan and who attend their FibroScan appointment, overall and per month, will be described and compared with the number (proportion) of FibroScan appointments attended prior to intervention using linear regression modeling, as well as the number (proportion) of individuals with FibroScan results in cirrhosis range that are referred and attend specialist liver clinic appointments.

The number and proportion of individuals with an elevated APRI or FIB-4 who had cirrhosis confirmed by FibroScan will be described, and sensitivity, specificity, and positive and negative predictive values of APRI for cirrhosis determined by confusion matrix. The area under the receiver operating characteristic curve of APRI and FIB-4 for cirrhosis diagnosis will also be calculated by receiver operating characteristic analysis.

The bivariate distribution of sociodemographic (sex, age category, and urban or regional place of residence [defined by postcode using SEIS data]) and clinical variables (liver disease indication) within the proportion of people with elevated APRI and FIB-4 score, who attend FibroScan testing, have elevated FibroScan results, and attend the liver specialist clinic will be determined and compared with their counterparts using chi-square test for categorical data, 2-tailed Student *t* test for parametric continuous data, and Wilcoxon rank-sum test for nonparametric continuous data as appropriate.

A 2-tailed *P* value of .05 will be used as the significance threshold for all analyses. All analyses will be performed using STATA (version 17; Stata Corporation).

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Sample Size Justification

We have conducted a preliminary analysis of the number of AST and platelet count testing events that were performed at St Vincent's Pathology over a 12-month period (2019). These data showed approximately 11,000 people known to St Vincent's hospital clinics, and a further 4400 people in the community that had AST and platelet count testing events, that would have allowed APRI calculation to be performed, proving the feasibility of reaching large numbers within the community for cirrhosis screening.

For the comparison of rate of referral for FibroScan before and after the intervention, we estimate that we will be powered to detect a 10% difference in rates of FibroScan referral before and after the intervention. For the logistic regression analyses to determine the difference in proportion of APRI scores leading to referral before and after providing cirrhosis information and FibroScan referral link information (overall and by subgroup), and for determining the proportion of FibroScan referrals that are attended (overall and by subgroup), we are powered to detect a 5% or greater difference between the intervention and historical control groups with power 90% and a sample size of 1100 per subgroup. The above numbers of more than 15,400 individuals having APRI calculations within 12 months suggest that we will be adequately powered to explore our end points including stratified by sex, urban versus rural place of residence, age category, socioeconomic quartile of place of residence, and indication for FibroScan (all of which are expected to have >1000 individuals in each subgroup).

Results

As of January 2024, in the preintervention phase of this study, a total of 120,972 tests were performed by the laboratory. Of these tests, 78,947 (65.3%) tests were excluded, with the remaining 42,025 (34.7%) tests on 37,872 individuals meeting inclusion criteria with APRI and FIB-4 being able to be calculated (Figure 1). Of these, 1.3% (n=531) had elevated APRI greater than 1 occurring in 446 individuals, and 2.3% (n=985) had elevated FIB-4 greater than 2.67 occurring in 816 individuals (Table 1). Linking these data with FibroScan referral and appointment attendance is ongoing and will continue during the intervention phase.

Data analysis is expected to begin following 6 months of intervention in August 2024, and the publication of results will then follow.

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Figure 1. Flow diagram of current data from the preintervention period of blood tests performed at St Vincent's Pathology and included in the interim analysis. ALT: alanine transferase; AST: aspartate transferase; FBC: full blood count; LFT: liver function test.

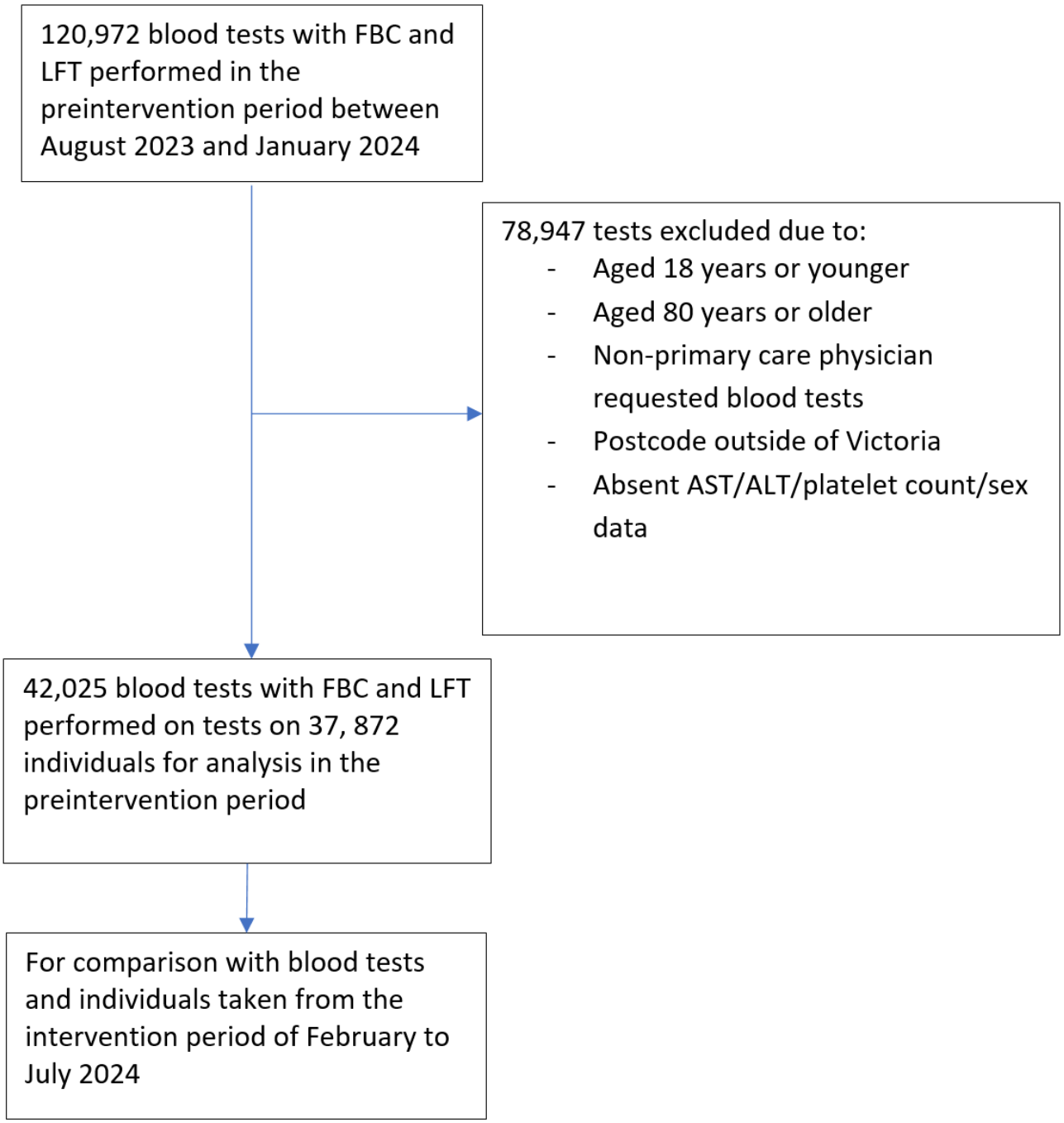

Table 1. Proportion of blood tests and individuals with elevated Aspartate Transaminse–to-Platelet Ratio Index (APRI)and Fibrosis-4 (FIB-4) values.

	Total test events (n=42,025), n (%)	Individuals (n=37,872), n (%)
Elevated ALT[a]	16,760 (39.9)	15,285 (40.4)
Elevated APRI>1	531 (1.3)	446 (1.2)
Elevated FIB-4>2.67	985 (2.3)	816 (2.2)

[a]ALT: alanine transferase.

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Discussion

Scientific Contribution

The results from this study will contribute to knowledge gaps surrounding the prevalence of individuals with compensated cirrhosis in a community setting and the use of services instigated through primary care.

Strengths and Limitations

This study will determine the feasibility, effectiveness, and implementation requirements of a population-level screening program for liver cirrhosis in Australia.

Strengths of this study include its prospective study design and large population-based cohort, which is representative of the Australian population.

Automated liver fibrosis index calculation and reporting by pathology services using frequently requested blood tests is a low-cost, potentially scalable approach to population-level liver cirrhosis screening and may also raise awareness of chronic liver disease among health workers and the community.

Study limitations include the limited set of clinical and demographic variables available from routinely collected pathology data to inform risk factors for cirrhosis on a population scale.

Resource requirements and logistics of specialist referral may limit the scalability of blood test–based cirrhosis screening on a population level.

Conclusions

In summary, we aim to test the feasibility of determining the prevalence of elevated noninvasive tests, APRI, and FIB-4 and the use of services that would aid in the diagnosis of liver cirrhosis and linkage to specialist care.

Acknowledgments

This study is funded by a St Vincent's Foundation grant, Gilead Sciences Australia Fellowship (JEF, 2021), and in-kind support from St Vincent's Pathology.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

JH has received investigator-initiated research funding (Gilead Australia Fellowship 2017) and speaker fees (2017) from Gilead Sciences, as well as speaker fees and investigator-initiated research funding from Eisai (2020 and 2021). JEF has received investigator-initiated research funding (Gilead Australia Fellowship 2021).

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Abbreviations

ALT: alanine transferase
APRI: Aspartate Transaminse–to-Platelet Ratio Index
AST: aspartate transferase
CAPRISE: Cirrhosis Automated Aspartate Transaminse–to-Platelet Ratio Index and Fibrosis-4 Screening Evaluation
FIB-4: Fibrosis-4
iLFT: Intelligent Liver Function Testing
SEIS: Socio-Economic Index Areas

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Protocol

Finite Element Analysis of Pelvic Floor Biomechanical Models to Elucidate the Mechanism for Improving Urination and Defecation Dysfunction in Older Adults: Protocol for a Model Development and Validation Study

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Abstract

Background: The population is constantly aging, and most older adults will experience many potential physiological changes as they age, leading to functional decline. Urinary and bowel dysfunction is the most common obstacle in older people. At present, the analysis of pelvic floor histological changes related to aging has not been fully elucidated, and the mechanism of improving intestinal control ability in older people is still unclear.

Objective: The purpose of this study is to describe how the finite element method will be used to understand the mechanical characteristics of and physiological changes in the pelvic cavity during the rehabilitation process, providing theoretical support for the mechanism for improving urination and defecation dysfunction in older individuals.

Methods: We will collect magnetic resonance imaging (MRI) and computed tomography (CT) data of the pelvic cavity of one male and one female volunteer older than 60 years and use the finite element method to construct a 3D computer simulation model of the pelvic cavity. By simulating different physiological states, such as the Valsalva maneuver and bowel movement, we will verify the accuracy of the constructed model, investigate the effects of different neuromuscular functional changes, and quantify the impact proportions of the pelvic floor muscle group, core muscle group, and sacral nerve.

Results: At present, we have registered the study in the Chinese Clinical Trial Registry and collected MRI and CT data for an older male and an older female patient. Next, the construction and analysis of the finite element model will be accomplished according to the study plan. We expect to complete the construction and analysis of the finite element model by July 2024 and publish the research results by October 2025.

Conclusions: Our study will build finite element models of the pelvic floor of older men and older women, and we shall elucidate the relationship between the muscles of the pelvic floor, back, abdomen, and hips and the ability of older adults to control bowel movements. The results of this study will provide theoretical support for elucidating the mechanism for improving urination and defecation dysfunction through rehabilitation.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400080749; https://www.chictr.org.cn/showproj.html?proj=193428

International Registered Report Identifier (IRRID): DERR1-10.2196/56333

(JMIR Res Protoc 2024;13:e56333) doi:10.2196/56333

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KEYWORDS

elderly; older adults; pelvic cavity; finite element analysis; biomechanical model; protocol; urination; incontinence; aging; bowel dysfunction

Introduction

With the aging population, approximately 1.4 billion people were aged 60 years and older in 2022, which is expected to double by 2050 worldwide [1]. The majority of older people experience numerous underlying physiological changes with increasing age, leading to functional decline. Urination and defecation dysfunction are the most common impairments in older age. In China, the prevalence of urinary incontinence was 74.8% among older women [2] and 54.4%-60.0% among hospitalized older patients [3,4], while older men are at a higher risk of severe fecal incontinence than older women [5]. Furthermore, a systematic review and meta-analysis reported that the global prevalence of constipation in older adults was 18.9% (95% CI 14.7%-23.9%) [6]. Urination and defecation dysfunction play a crucial role in determining care dependence among older adults. Further, these factors contribute to the increase in susceptibility to negative emotions in older adults and burden among their caregivers [7]. Therefore, addressing the toileting needs of older adults is a pressing global challenge that requires immediate attention and a comprehensive solution.

Factors affecting the ability to control urination and defecation are mainly divided into 3 parts, including the pelvic floor muscle group, core muscle group, and sacral nerve. Rehabilitation training methods, including pelvic floor muscle training, biofeedback, electrical stimulation, magnetic stimulation, and vibrational stimulation, can enhance neural regulatory ability and muscle strength, thus improving dysfunction in urination and defecation [8,9]. The rehabilitation training methods and intensity are quantitatively related to neural control and muscle strength parameters. It is crucial to quantify this relationship to explain the mechanism underlying improvement in dysfunction in urination and defecation. At present, an analysis of histological changes in pelvic floor tissue related to aging has not been fully elucidated; hence, the mechanism underlying enhancement of bowel control in older adults remains unknown.

Finite element analysis is a technique to simulate the mechanical properties of an object by dividing it into discrete elements and creating a numerical calculation model to represent its behavior [10], and it could potentially reveal the mechanism for improving bowel control. Therefore, we aim to use a finite element model to identify the relationship among rehabilitation training methods, intensity, and parameters related to neural control and muscle strength, ultimately determining the mechanism by which urination and defecation dysfunction can be improved in older people.

Methods

Ethical Considerations

This study has been approved by the Biomedical Ethics Committee of Capital Medical University on June 5, 2023 (registration number 2023-079). The implementation of this study complied with relevant ethical requirements, and the study participants signed informed consent forms before undergoing medical imaging. Participation in this study is completely voluntary, and the participants may refuse to continue participating in this study at any time without any negative impact on their medical care. We shall retain all information about the study participants, including their identity, general information, medical history, results of magnetic resonance imaging (MRI) and computed tomography (CT) imaging, etc. Only authorized researchers, ethics committees, and research project approval departments can access records related to this study. The names of research participants will not appear in any public materials, reports, or articles related to this research. The study participants receive free pelvic floor MRI and CT examinations in this study, and upon completion of data collection, they will receive a corresponding compensation of 1000 CNY (approximately US $138).

Patient Involvement

In this study, one man and one woman both aged ≥60 years will be included. Eligible participants are required to have good physical health, normal daily living abilities, normal cognitive abilities, normal communication skills, normal pelvic floor function, and no urination and defecation dysfunction (Figure 1). Inclusion and exclusion criteria are outlined in Multimedia Appendix 1.

Clinical data will be collected at a hospital in Beijing. Demographic information will be collected, encompassing gender, age, BMI, and the frequency and characteristics of daily bowel and bladder movements. Their health conditions will be also captured, consisting of hypertension, diabetes, heart disease, stroke, Alzheimer disease, arthritis, osteoporosis, chronic obstructive pulmonary disease, tumors, and vision or hearing problems.

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Figure 1. Flowchart of the participant recruitment process. CT: computed tomography; MRI: magnetic resonance imaging.

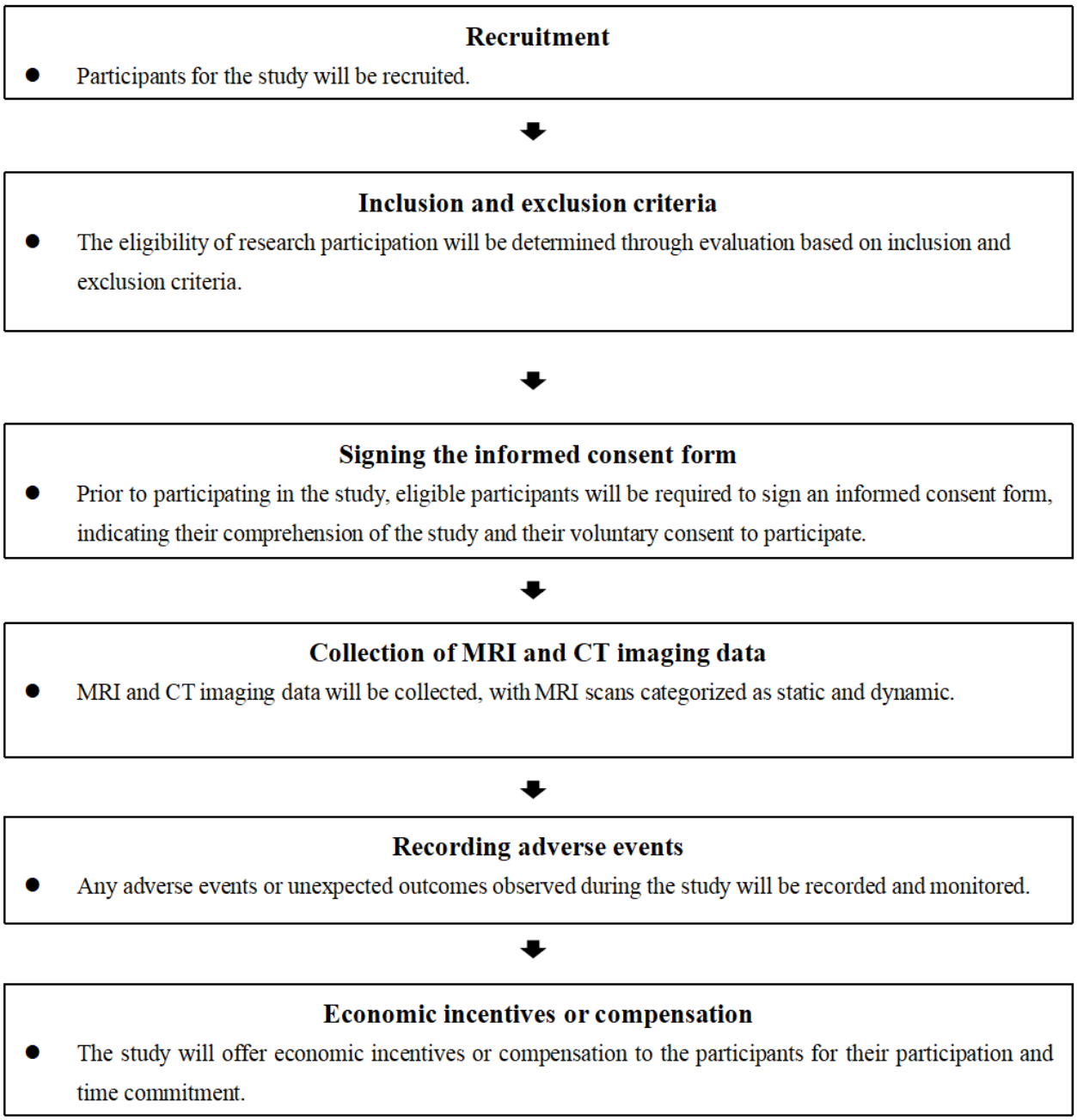

Software and Hardware

The computer CPU has an Intel (R) Core (TM) i5 processor, with a 64-bit operating system, 16 gigabytes (GB) of memory, 500-GB hard disk, and 900-GB external hard disk. The software involved in medical imaging analysis include Mimics (Materialise NV), Geomagic Studio (3D Systems Inc), and Abaqus (Dassault Systèmes). Mimics and Geomagic Studio are used for 3D model building; Abaqus is used for 3D model processing and biomechanical finite element analysis.

Collection of MRI and CT Image Data

Participants will be scheduled for MRI and CT imaging, with the goal of acquiring medical imaging data pertaining to the organs of the pelvis, bones, and muscles associated with defecation and urination.

Due to the similar density of pelvic muscles, fascia, and other tissues, distinguishing them in CT and ultrasound imaging is challenging. MRI is the most recognized and important imaging modality [11]. However, CT has a higher resolution for bone tissue, so CT scanning of pelvic bones and MRI scanning of pelvic floor muscle tissue are used for medical imaging. The data from both scans are combined to construct a finite element model of the study participants' pelvic cavity. Multimedia Appendix 2 provides detailed descriptions of the steps and receipt collection methods for static MRI, dynamic MRI, and CT imaging. Dynamic MRI will include Kegel movements and Valsalva maneuvers, providing a comparison for subsequent finite element model validation. Images will be acquired by skilled doctors from the MRI and CT departments, and the collected imaging data will be evaluated by radiologists with ≥5 years of experience in diagnosis using pelvic MRI and CT

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imaging. In cases of poor image quality, a rescan will be performed to obtain a clear image.

Establishment of 3D Images

Data Import

The original MRI and CT imaging data will be imported into the medical image analysis software Mimics. This software will automatically generate the 3 views: cross-sectional, coronal plane, and sagittal plane views. To ensure optimal 3D reconstruction results, we will select the sagittal plane corresponding to the MRI and CT scanning section for further editing. CT and MR images of the older man and woman are shown in Figures 2-5.

Figure 2. Magnetic resonance image of the older male participant. H: head.

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Figure 3. Computed tomography image of the older male participant. HLA: head left anterior.

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Figure 4. Magnetic resonance image of the older female participant. H: head.

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Figure 5. Computed tomography image of the older female participant. HLP: head left posterior.

Selecting Thresholds and Segmenting Images

The brightness and contrast of 2D images will be adjusted. Additionally, 2 experienced radiologists specializing in diagnosis using pelvic MRI and CT imaging will collaboratively outline the organs, bones, muscles, and muscle groups in each cross-sectional image to reach a consensus. When accessing the designated interface, we will perform threshold adjustments to accurately select the required organs, bones, muscles, and muscle groups. A self-set threshold method will be used to maximize the selection of these structures while minimizing interference from adjacent tissues. We will first use CT image data to outline skeletal parts including the hip bone, sacrum, coccyx, and femur, and then use MRI data to outline the pelvic floor muscle group, abdominal muscle group, back muscle group, hip muscle group and organ parts. The final data will combine bone parts, muscle group parts, and organ parts.

Generation of 3D Images

We will use the calculate 3D function in Mimics to directly obtain the corresponding 3D solid geometry model including

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organs, bones, muscles, and muscle groups, and then the model will be exported in stereolithography format.

Edge Processing

The initially created 3D image is relatively rough and will be enhanced through the smoothing function in Mimics to reduce the angles of points or edges, making the edges smoother, improving the overall appearance of the 3D image.

Establishment of the 3D Model

We will import the 3D image into the reverse engineering software Geomagic Studio and then generate a solid 3D model of the pelvic cavity, which can be used for finite element analysis through computer gridding and surface fitting. The final 3D pelvic floor model will include several parts such as the pelvis, bladder, urethra, uterus, vagina, rectum, levator ani muscle, perineum, and uterosacral ligaments.

Validation of Finite Element Models

During the finite element modeling process, it will be essential to validate the effectiveness of the finite element model. We will adopt 2 methods to validate the finite element model. The first method is the geometric verification method, we will compare the dynamic effects simulated by the established finite element model of the pelvic floor with the pelvic floor movements performed by actual subjects during dynamic MRI, for example, Kegel movements and Valsalva maneuvers, to determine whether the internal pressure and bladder deformation align. The second method is the validation of results obtained from the literature. The model will be validated through comparison with previous literature.

Finite Element Model Mechanism Analysis

Building the Finite Element Model

Import a 3D Model

We will import the Standard ACIS Text file into Abaqus and convert it to a mesh model.

Volume Meshing

Volume meshing is crucial in constructing finite element models and conducting numerical simulations. Due to the complexity of the solid model that needs to be meshed, partitioning it into regular volume meshes is challenging. Therefore, we will use Abaqus' free meshing method, which automatically generates a hybrid mesh consisting of triangles, tetrahedra, and hexahedra by dividing different tissues. The mesh will be divided into different forms based on the anatomical characteristics of each pelvic floor structure. If a satisfactory grid cannot be constructed for the local area, the model is locally fine-adjusted and iterated repeatedly until a high-quality grid is obtained.

Assignment of Material Properties

Once the 3D solid model is constructed, Abaqus will be used to assign mechanical properties, such as the elastic modulus, the Poisson ratio, element type, number of elements, and ligament strength to each constituent element, resulting in a model with defined mechanical characteristics. This study aims to determine the material characteristic parameters of the pelvic organ, skeleton, individual muscle and muscle groups, as well as each ligament, using relevant literature sources.

Constraining of Boundaries

When analyzing static structural mechanics, the muscles are in close proximity to various tissues. To replicate the model's deformation under specific loads, the boundary must be adequately constrained to prevent nonconvergence caused by displacement uncertainty. The z-axis displacement of all nodes in the finite element model of the pelvic floor system should be restricted, and base constraints should be applied to the vagina, perineal body, rectum, levator ani muscle, pubic bone, and sacrococcygeal bone.

Application of Loads

Solid 3D elements can be used in static structural mechanics analysis. The surface loads from the participants can be applied to the finite element model's surface. The model can undergo finite element analysis under different states and various load patterns. Integrating neuromuscular physiological information and medical imaging data into computer simulation models allows for simulating the effects of various stimulation methods, locations, and intensities on urinary and bowel control.

Currently, there are 5 known rehabilitation training methods for improving bowel function including pelvic floor muscle training, biofeedback, electrical stimulation, magnetic stimulation, and vibration stimulation. We have summarized the muscles corresponding to 5 types of rehabilitation training based on the literature contained in Multimedia Appendix 3. After completing the construction of the finite element model, we will conduct specific finite element analysis under different simulation plans. We will simulate the effects of muscle enhancement or weakening corresponding to the 5 types of rehabilitation training. The study simulated a 25%, 50%, 75%, 100%, normal, 25%, 50%, 75%, 75%, and 95% increase in muscle capacity by changing the correlation coefficient of elastic modulus to 1.25 times, 1.5 times, 1.75 times, 2 times, 1 time, 0.75 times, 0.5 times, 0.25 times, and 0.05 times, respectively. The main outcome measure of the study is the Mises stress cloud map and stress region of the area of interest in the finite element model of older adults under different simulation plans. The second outcome comprises the retrovesical and anorectal angles used to reflect the ability of older people to control their bowel movements. Among them, the retrovesical angle is the angle formed by the median sagittal plane of the bladder floor and the long axis of the urethra, and the anorectal angle is the angle between the longitudinal axis of the anal canal and the posterior wall of the rectum above the levator ani muscle.

By comparing the changes in outcome measures under different parameter settings, our objective is to maximize the improvement of urination and defecation dysfunction while identifying the optimal muscle and neural parameters. This analysis will help quantify the relationship between rehabilitation training coordination, neural control, muscle strength, and other relevant parameters (Figure 6). It will provide insights into the mechanisms underlying the improvement of urination and defecation dysfunction in older adults.

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Figure 6. Schematic diagram of the mechanisms of enhanced defecation ability.

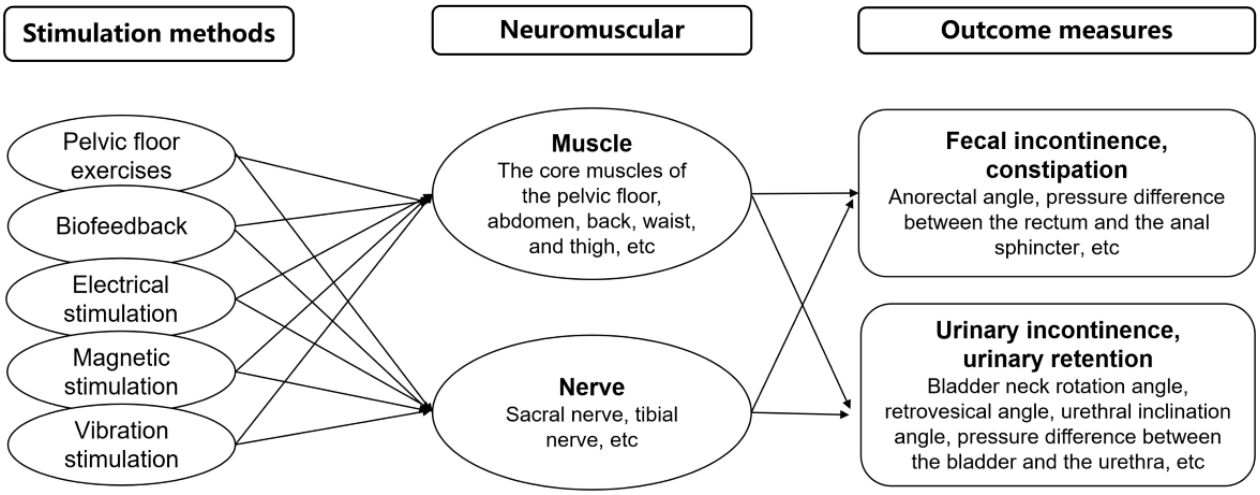

Results

We have registered the study in the Chinese Clinical Trial Registry (ChiCTR2400080749). After obtaining ethical approval, we recruited the study participants. As of January 13, 2024, we have completed the collection of MRI and CT imaging data for an older man and woman. Thereafter, the finite element model will be established as intended. We expect to complete the construction and analysis of the finite element model by July 2024 and publish the research results by October 2025.

Discussion

Principal Findings

Our study aims to generate finite element models of the pelvic floor of older men and women and derive the relationship among the muscles of the pelvic floor, back, abdomen, and hips and the ability of older adults to control their bowel movements. Pelvic floor issues significantly impact the quality of life and overall health of older adults, which plays a crucial role in determining care dependence among them. Given the most common problem of urination and defecation dysfunction among older people, which has still not been effectively addressed from a mechanistic perspective, our study will innovatively adopt finite element analysis to establish, validate, and further analyze the finite element model for pelvic floor function to address the aforementioned issues.

Finite element analysis is a reliable research method that has been verified by many studies [12-16], and it can reflect the condition of the human body. Finite element analysis has been widely adopted for urethral support function [17], injury in levator ani muscles, occurrence of pelvic floor diseases during vaginal delivery [18], and assessing the mechanism of posterior vaginal prolapse [19]. The finite element model can simulate biomechanical processes, avoiding the implementation of a complex interventional study. For our study, finite element models of urinary incontinence, urinary retention, constipation, and fecal incontinence for older adults will be established to simulate their real pelvic floor tissue and muscles. When designing and developing the finite element model, we shall consider simulating the structure and function of the real human body as much as possible. Professional doctors experienced in imaging diagnostics will outline the bones and muscles based on actual high-resolution MRI and CT imaging data to ensure consistency between the constructed finite element model and real human body structure as much as possible. In addition, we will also invite relevant experts in anatomy, rehabilitation medicine, physiology, bioengineering, and nursing to guide our subsequent finite element analysis to ensure that we can truly reflect the structure, function, and existing problems of the pelvic floor of older adults. It is notable that some studies on finite element models of the pelvic floor for urinary incontinence only recruited young postpartum women [20,21], which might have had an impact on the models' adaptability. Older people are at a higher risk of incontinence and constipation due to decreased muscle strength, relaxation and reduced elasticity of pelvic floor tissues, and hormonal level alterations than their younger counterparts. Consequently, variations may arise in the anatomical structure, muscle tone, and elasticity of the pelvic floor, as well as in the material properties of the finite element model. There is currently a scarcity of pelvic floor finite element models for analyzing fecal incontinence, constipation, urinary incontinence, and urinary retention in older men and women, and our study can bridge this gap.

In addition to model construction, this study also intends to validate the effectiveness of the constructed model, which has been overlooked in many studies [22]. The validation part is crucial as it is closely related to the accuracy of the results of subsequent finite element analysis. Finite element analysis allows for quantitative assessment of the adaptability of pelvic floor structures to various mechanical loads. To address research questions, the finite element model can simulate 5 different rehabilitation training methods, including exercise training, biofeedback, magnetic stimulation, electrical stimulation, and vibration stimulation. By comparing the changes in the outcome indicators of defecation under different parameter settings, the optimal muscle and nerve parameters are determined to maximize the improvement of defecation dysfunction. This quantifies the relationship between the collaborative rehabilitation training methods and parameters such as neural control and muscle strength and reveals the mechanism

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underlying enhancement of control of defecation in older adults [11]. A realistic pelvic model based on MRI of asymptomatic women was established by Peng et al [17], wherein the combined weakening effect of the 3 components of the levator ani muscle exceeded the sum of the weakening effects caused by each individual component. The levator ani muscle group demonstrated good coordination by providing urethral support in a nonlinear additive manner. Therefore, it is reasonable to speculate that the interaction between muscles and nerves involves a more complex correlation rather than just a linear additive relationship. Our research will explore how to maximize the enhancement of pelvic floor muscle and nerve function in older adults to further improve urinary and bowel dysfunction. Research findings in the finite element analysis section will offer novel evidence to comprehend the physiological changes and mechanical characteristics of the pelvic cavity in older individuals, as well as provide theoretical support for elucidating the mechanisms underlying the improvement in urination and defecation dysfunction among them. Future studies can explore the potential of using the computer simulation model of the pelvic floor, as detailed in this paper, in the advancement of novel technologies for diagnosing and treating pelvic diseases in older individuals. In addition, our results can be extended to 3D printing and virtual reality systems to assist teaching practice. These would serve as key steps for transforming our research findings into practical applications.

This study describes a logical, rigorous, and scientific research protocol. However, the limitation of this study is the absence of statistical analysis. Due to individual variations, data on pelvic floor anatomy from the 2 participants may not comprehensively reflect the changes and characteristics observed in the broader population of older adults. Nevertheless, in initial stages of the study or due to resource constraints, the MRI and CT data from these 2 participants can be used to generate a preliminary pelvic model. Future studies can design and construct finite element models that contain more pelvic floor data of older adults. Alternatively, selecting different populations of older adults, such as those with urinary incontinence or those with disabilities, may be the next research direction.

Conclusions

Finite element analysis offers the advantages of low risk, cost-effectiveness, and quantifiable metrics. This study encompasses the construction and validation of finite element models, as well as the analysis of their mechanisms. Our results will elucidate the correlation between muscular function and bowel control ability. Our findings will contribute theoretical insights into the mechanisms underlying enhancements in urinary and fecal control through rehabilitation, ultimately aiming to improve the quality of life of older adults.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be made available by the corresponding author on reasonable request.

Authors' Contributions

The study was conceived and designed by all the authors. RW, GL, and LJ conceptualized the study and designed its methodology. RW and JZ drafted the initial version of the manuscript, with all authors contributing to the investigation and subsequent review and editing. LG managed the resources for the study, while LJ and CL handled the study's administration. LJ secured the funding for the study. RW, JZ, GL, and LJ provided additional supervision and contributed to the editing and approval of the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study eligibility criteria.
[DOCX File , 19 KB - resprot_v13i1e56333_app1.docx]

Multimedia Appendix 2
Scanning methods of static magnetic resonance imaging (MRI), dynamic MRI, and computed tomography.

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[DOCX File , 16 KB - resprot_v13i1e56333_app2.docx]

Multimedia Appendix 3
Muscles corresponding to five rehabilitation trainings for four types of urinary and defecation dysfunction.
[DOCX File , 15 KB - resprot_v13i1e56333_app3.docx]

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Abbreviations

CT: computed tomography
GB: gigabyte
MRI: magnetic resonance imaging

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Protocol

Detecting and Understanding Social Influence During Drinking Situations: Protocol for a Bluetooth-Based Sensor Feasibility and Acceptability Study

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Abstract

Background: High-risk alcohol consumption among young adults frequently occurs in the presence of peers who are also drinking. A high-risk drinking situation may consist of particular social network members who have a primary association with drinking. Fine-grained approaches such as ecological momentary assessment (EMA) are growing in popularity for studying real-time social influence, but studies using these approaches exclusively rely on participant self-report. Passive indicators of peer presence using Bluetooth-based technology to detect real-time interactions have the potential to assist in the development of just-in-time interventions.

Objective: This study seeks to examine the feasibility and acceptability of using a Bluetooth-based sensor and smartphone app to measure social contact in real-world drinking situations.

Methods: Young adults (N=20) who drink heavily and report social drinking will be recruited from the community to participate in a 3-week EMA study. Using a social network interview, index participants will identify and recruit 3 of their friends to carry a Bluetooth beacon. Participants will complete a series of EMA reports on their own personal Android devices including random reports; morning reports; first-drink reports; and signal-contingent reports, which are triggered following the detection of a beacon carried by a peer participant. EMA will assess alcohol use and characteristics of the social environment, including who is nearby and who is drinking. For items about peer proximity and peer drinking, a customized peer list will be presented to participants. Feedback about the study protocol will be ascertained through weekly contact with both index and peer participants, followed by a qualitative interview at the end of the study. We will examine the feasibility and acceptability of recruitment, enrollment of participants and peers, and retention. Feasibility will be determined using indexes of eligibility, enrollment, and recruitment. Acceptability will be determined through participant enrollment and retention, protocol compliance, and participant-reported measures of acceptability. Feasibility and acceptability for peer participants will be informed by enrollment rates, latency to enrollment, compliance with carrying the beacon, and self-reported reasons for compliance or noncompliance with beacon procedures. Finally, EMA data about peer proximity and peer drinking will support the validity of the peer selection process.

Results: Participant recruitment began in February 2023, and enrollment was completed in December 2023. Results will be reported in 2025.

Conclusions: The protocol allows us to examine the feasibility and acceptability of a Bluetooth-based sensor for the detection of social contact between index participants and their friends, including social interactions during real-world drinking situations. Data from this study will inform just-in-time adaptive interventions seeking to address drinking in the natural environment by providing personalized feedback about a high-risk social context and alerting an individual that they are in a potentially unsafe situation.

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KEYWORDS

Bluetooth technology; passive sensing; social influence; alcohol use; ecological momentary assessment; social network; feasibility; acceptability; mobile phone

Introduction

Background

Alcohol use typically begins and escalates between the ages of 16 and 20 years, and prevalence rates for heavy drinking and related consequences are the highest among those aged between 18 and 25 years compared with all other age groups [1]. During this time of emerging adulthood, individuals spend approximately 10 hours per week socializing with their friends [2], and many of these interactions occur in the context of alcohol use. Young adult drinking most frequently occurs in a social context, in groups, and with close friends [3-5]. Moreover, youth who drink in social settings consume more alcohol than they do when drinking alone [6,7] and report more alcohol-related consequences such as interpersonal violence, risky sexual behavior, and driving under the influence of alcohol [8,9]. Thus, understanding how peers influence and interact with each other during drinking situations is of utmost importance.

Influence of Peers on Drinking

Survey research demonstrates that regular exposure to peers who value alcohol use and support heavy drinking is associated with higher adolescent alcohol use [10] and that in young adulthood, the proportion of alcohol-consuming friends is concurrently and prospectively associated with an individual's drinking [11-13]. The expansion of social networks during young adulthood and the increase in proximity and salience of same-age peers [14-16] may exacerbate increases in alcohol use during this time [17].

A high-risk drinking situation may consist of particular social network members who have a primary association with drinking. Influential peers, colloquially known as "drinking buddies," have many traits that are characteristic of close friends, including frequent contact, relationships of long duration, and high levels of emotional and concrete social support [18,19]. The presence of these individuals in one's social network confers additional alcohol-related risk, even after controlling for the number of drinkers in the network [20-22]. Heavy drinking could potentially be triggered by the presence of these influential peers in close proximity. The presence of influential peers could be a single key indicator of heavy-drinking situations. In addition, peers are a frequently cited source of alcohol [23,24] often by directly offering alcohol [25] or by pressuring others to drink [26].

Examination of Drinking Contexts Using Technology

Ecological momentary assessment (EMA) involves repeated sampling of individuals' behaviors and experiences in real time and in naturalistic settings [27]. As data are collected in situ, findings are more generalizable to real-world, real-life experiences and processes [27]. Data also are less prone to retrospection bias [28]. Individuals are better at recalling their cognitions and behavior across a day compared with weekly or monthly retrospective reports [29]. EMA reports show poor concordance with timeline follow-back assessments, and EMA data have been demonstrated to both overestimate [30] and underestimate [31] the number of drinks relative to timeline follow-back assessments. EMA designs also allow for the examination of changes in a behavior over time and across contexts and permit within-person comparisons. For example, researchers can test whether there are unique differences in the social context on days that a person drinks alcohol versus on days they do not drink alcohol. EMA has been used to examine situational predictors of drinking behavior, including social context (with whom) and physical context (where) [32-34]. However, there are 2 primary limitations of EMA when applying it to study peer influence. First, individuals must be actively aware of and be able to report about peer influence. Second, there is a significant bias toward recent and salient peer proximity when self-reported [35]. Owing to these 2 significant limitations, there is value in research that relies less on self-report and more on passive assessment.

App-based ambulatory assessment of behavior is on the rise [36,37], with smartphones collecting multiple types of data from built-in sensors in real time [38]. Examples of passive sensing in alcohol research include transdermal alcohol biosensors to continuously measure alcohol consumption [39,40] and heart rate variability to study associations with stress and anxiety [41]. EMA studies in the tobacco and cannabis fields have used geographic EMA methods to passively capture contextual changes as individuals move through their days [42-44]. These methods combine EMA with real-time mobile geographic location tracking technology obtained through GPSs and geographic information systems. A drinking report can be triggered when an individual enters a specific zone (a geofence), reducing the burden on the individual to self-initiate reports in this location. Thus, there is support for work that identifies and targets high-risk situations based on a link between a given context and substance use.

However, despite the well-established importance of peer influence on alcohol use, no extant studies have used passive assessment to understand the real-world social contexts of drinking. As a ubiquitous low-power connectivity feature embedded in mobile phones and many other wearable sensors, Bluetooth provides a possible method to study peer contact in settings in which peers are influential. Specifically, Bluetooth-based transmitters or beacons (eg, Apple AirTags or other transmitters including smartphones) have unique addresses that can be identified by Bluetooth receivers (eg, smartphones),

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and thus, Bluetooth beacons carried or worn by individuals can be used with smartphone apps to assess the duration and frequency of interpersonal interactions [45]. Only few studies have used Bluetooth sensors to study health behaviors [46,47], including COVID-19 spread [48-50], but to the best of our knowledge, passive sensor technology has not been used to investigate the social context of alcohol use.

Study Objective

This study aims to evaluate the feasibility and acceptability of (1) using a social network interview (SNI) to identify influential drinking peers and (2) using a Bluetooth-based sensor for the detection of contact between heavy drinkers and their peers. In a companion paper, we have described the technology that uses Bluetooth-based sensors to detect social contact [51]. Together, these papers summarize the procedures for a study that will develop and test the utility of a Bluetooth-based sensor to detect contact between individuals in drinking studies. The methods for evaluating feasibility and acceptability are described in Table 1.

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Table 1. The study's primary goals and methods for evaluating feasibility and acceptability.

Participants and goals	Definition	Method of evaluation	Data source
Index participant			
	Feasibility		
	Proportion of screened respondents who are eligible based on the inclusion criteria	• Number of eligible respondents among all respondents who completed the screening survey	• Screening survey • Indexes of consent and enrollment
	Proportion of screened respondents ineligible due to mobile phone operating system	• Number of respondents eligible based on the screening survey, excluding the reason of not having an Android phone	• Screening survey • Indexes of consent and enrollment
	Time required to enroll index participants	• Number of months from start of recruitment to reaching the desired sample size	• Indexes of consent and enrollment
	Duration between notification and survey completion	• Time elapsed between signal-contingent report notification and EMA[a] survey completion and submission	• EMA report notification and data time stamps
	Acceptability		
	Proportion of eligible index participants who enroll in the study and who participate in the study	1. Number of respondents who enroll in the study among all the eligible respondents 2. Number of respondents who participate in the study among those who enroll (defined as the proportion of enrolled participants for whom eligible peers are identified and enrolled) 3. Postscreening self-reported reasons for nonparticipation	• Screening survey • Indexes of consent and enrollment
	Retention of index participants through the study protocol—defined as high retention rate at 90%	• Number of index participants completing the study protocol among those who enrolled	• Project tracking database • Postparticipation interview
	Index participants' compliance with project procedures—defined as typical completion rate of EMA reports for substance use research—75% for signal-contingent and random reports [52]	1. Separate indexes of number of signal-contingent and random reports completed among those expected 2. Total number of triggered signal-contingent and random reports will be considered to evaluate the impact of participant burden on compliance	• EMA report notification and data time stamps • Postparticipation measure of reasons for noncompliance
	Index participant ratings of the functionality and utility of the EMA app	• High ratings on system utility measures and few reports of barriers to use	• EMA morning report of previous-day app errors • Postparticipation measures (adapted System Usability Scale and interview)
Peer participant			
	Feasibility and acceptability		
	Peer consent and enrollment rate	1. Proportion of eligible peers who consent 2. Proportion of peers who consent but do not enroll 3. Peer self-reported reasons for nonparticipation after providing consent	• SNI[b] • Indexes of consent and enrollment
	Peer retention	• Number of peers completing the study protocol (completing the weekly surveys and end-of-study survey) among the peers enrolled in the study	• Peer participant weekly surveys • Postparticipation peer interview
	Acceptability		

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Participants and goals	Definition	Method of evaluation	Data source
	Peer evaluation of protocol	• Initial reactions to participation request, privacy concerns, and perceived impact on behavior or relationship with peer	• Postparticipation peer interview
	Compliance with beacon procedures, defined as the peer carrying the beacon with them throughout the study	1. Self-reported noncompliance, defined as the number of days and times when peer participants report not carrying the beacon 2. Self-reported reasons for not carrying the beacon	• Peer weekly surveys • Postparticipation peer interview
Feasibility			
	Time required to enroll peers following identification by participant	• Average time required to enroll first, second, and third peer	• Indexes of consent and enrollment
	Enrollment of 3 peer participants per index participant	• Total number of eligible peers who enroll	• Indexes of consent and enrollment
	Bluetooth beacon return rate	• Proportion of peer participants who return their beacon	• Project beacon log
Validity			
	Successful identification of influential drinking peers	• Proportion of participant drinking episodes in which peers identified during the SNI were present	• SNI • Project beacon log • EMA report data
	Successful selection of influential drinking peers to carry beacons	1. Proportion of drinking episodes in which a beacon-carrying peer was noted as present 2. Proportion of drinking episodes in which a beacon-carrying peer influenced the participant's drinking (offering alcohol or refilling a drink)	• SNI • Project beacon log • EMA report data

[a]EMA: ecological momentary assessment.

[b]SNI: social network interview.

Methods

Design

Young adults from the community will be recruited to participate in a 3-week EMA study with 3 peers. During the baseline session, participants will complete a battery of self-report measures and a research assistant (RA)–led SNI (described in the following sections) and will download a smartphone app. During the SNI, participants will identify influential peers, 3 of whom will carry beacons. Each day during the study, index participants will report about their own drinking behavior, which of their peers are nearby, and whether their peers are drinking using the smartphone app. At the end of the study, index participants will participate in a semistructured interview during which we will collect qualitative information, including feedback about their experiences in the study. Peers who carry sensors will complete weekly surveys and an interview at the end of the study to collect additional information about feasibility and acceptability.

Participants

We will recruit 20 participants, anticipating that 15 (75%) will complete the data collection process. Participant inclusionary and exclusionary criteria include the following: (1) aged between 18 and 29 years; (2) a minimum of 1 nonsolitary drinking day per week, including 1 heavy-drinking episode (≥4 drinks for women and ≥5 drinks for men) per week in the past month; (3) able to read English; (4) own an Android smartphone with an operating system (OS) of version 11 or newer and carry it throughout the day; (5) have a data plan (limited or unlimited); (6) are willing to approach peers to participate; (7) not in or seeking treatment for substance use; and (8) no plans to travel for an extended period or other significant deviations in routine.

Procedures

Eligibility and Recruitment

We will recruit young adults from the community, including both college-attending and non–college-attending young adults. Recruitment methods will include social media advertisements, flyers posted in retail establishments and on public streets, and notifications and email listserves at local universities. Advertisements will describe the study, including that participants will be asked to identify peers to be included in the study and will refer respondents to a brief Qualtrics screening survey, which will establish initial eligibility. Those who are eligible will be redirected to a separate survey where they will

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provide their contact information. Eligible individuals who decline to participate will be directed to an anonymous survey with a checklist of reasons for nonparticipation (eg, do not understand the study; do not think they have friends who would be willing to participate; Multimedia Appendix 1).

Participant Orientation and Baseline Assessment

An RA will schedule the 90-minute in-person baseline session, during which the index participants will complete the informed consent process, a brief battery of self-report measures, and the RA-led SNI. The RA will assist the index participant in downloading and logging into the EMA app and in adjusting the mobile phone settings and permissions. The RA will also demonstrate the EMA reports.

Participants will complete 4 types of EMA reports on their own personal Android devices via the PiLR platform application developed by MEI Research. *Signal-contingent* reports are triggered by the app following its detection of a beacon carried by a peer participant when a peer comes within approximately 15 feet from the index participant for at least 15 minutes. *Random* reports are intended to sample experiences throughout the day; index participants will receive 3 random reports per day between noon and midnight (distributed across 3 blocks of time: noon to 6 PM, 6 PM to 9 PM, and 9 PM to noon). *Signal-contingent* and *random* reports will have identical notifications in the app and will assess identical information, so that participants cannot differentiate between the two; both reports will assess alcohol use and the presence of and drinking by peers identified in the SNI. Participants will be instructed to complete these reports in response to notifications as soon as possible. *Morning* reports will be completed by participants every day, with the app providing a reminder at 10 AM. These reports will ask the participant about the previous day with items similar to those in the random and signal-contingent reports (ie, measuring who of their nominated peers they have spent time with and whether they have consumed alcohol). *Drinking event–contingent* reports will be initiated by participants when they start their first drink. Over the course of the study, study personnel will contact participants several times a week via SMS text message and as needed to check the progress, encourage compliance, and address technical issues. In addition, RAs will schedule weekly phone calls with participants to ensure that all issues and questions are addressed. We will ask participants to keep their mobile phone *on* and charged and not to change the mobile phone during the study period and will encourage the use of mobile phone pins or passwords.

After the 3-week EMA assessment is completed, we will conduct a 60-minute end-of-study qualitative phone interview with index participants to determine their reactions to participating in the study; any hesitation about participating; and their opinions about the EMA assessment, the Bluetooth beacon technology, and the peer selection process. Participants will also complete several end-of-study survey measures about their experience (Multimedia Appendix 1). We will assess whether the index participants changed any of their behaviors or interactions with others due to their participation in the study. Research staff will review the information about peer presence reported during the 3-week period with the participant. Index participants will be instructed about how to delete the app from their mobile phone at the end of the study, and their log-in credentials to the app will expire on their last day of data collection.

Measures and Peer Selection

Baseline Survey

A web-based survey will assess sociodemographics including sex, gender, age, racial and ethnic groups, living arrangement, and college or employment status. *Alcohol consumption* will be measured using a series of items adapted from National Institute on Alcohol Abuse and Alcoholism [53] including past-year and past-month frequency of alcohol use and heavy alcohol use, typical quantity of use, maximum number of drinks, frequency of intoxication, and age of first use. *Alcohol consequences* and alcohol problems will be assessed using the Brief Young Adult Alcohol Consequences Questionnaire [54,55] and Alcohol Use Disorders Identification Test [56], respectively. A measure of *physical context*, stratified based on time of day (day, evening, or late at night), will assess drinking across the various locations (all that apply) with options such as your home (house, apartment, dorm, or residence hall), friend's place, restaurant, bar, nightclub, and pub. A measure of *social context* (who do you drink with) will assess frequency (0=*never/almost never* to 4=*almost always/always*) in which the participant spends time (1) together without drinking; (2) together drinking; (3) together getting drunk; and (4) as a "drinking buddy" across various people such as roommates and housemates, romantic partner, boyfriend, or girlfriend, and classmates or coworkers. The frequency of *obtaining alcohol from various sources* will be assessed (0=*never* to 2=*frequently*), with options such as buy it at a store, available at a party, and someone gives it to me. Social norms will include *descriptive norms* (number of close friends and same-age peers who drink alcohol and get drunk monthly) and *injunctive norms* (perceived approval of drinking by a close friend and same-age peer) [57]. A 20-item measure of *drinking motives* assesses reasons for drinking alcohol related to coping, conformity, enhancement, and social reasons (0=*never/almost never* to 4=*almost always/always*) [58]. *Other substance use* (tobacco, Juul or vaping, marijuana, and illicit drugs) will be assessed. We will collect measures of *impulsivity* (18-item measure of sensation seeking [59,60]) and *drinker identity* such as "drinking is part of my self-image" (Alcohol Self-Concept Scale [61]).

SNI With Index Participants

The SNI entails asking the index participant to name up to 6 people of their age who are important to them. These people may be friends, family members, or anyone who they regularly spend time with in person [62,63]. Age, gender, residence (eg, do you live together) of network members, relationship type (eg, family or friend), and frequency of meaningful social interaction ("How often in a typical month do you spend at least 15 consecutive minutes with this person?") will be collected. In addition, we will assess the alcohol use of the peer, including the following: (1) frequency of drinking ("How many times in the past month do you think this person drank alcohol?") and (2) frequency of drinking with the peer ("In the past month, how often did you drink with this person [while both of you

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were drinking]?"). Finally, using a yes or no format, we will assess whether participants think the network member would be interested in carrying the beacon for the research study.

Peer Selection

During the baseline session, following the completion of the SNI, the RA will work with the index participants to identify 3 peers to ask to carry the beacon. The three inclusionary criteria for peers to carry the beacons are as follows: (1) aged between 18 and 29 years, (2) frequency of meaningful in-person social interaction is at least once a week in a typical week, and (3) drinking with the peer at least twice a month in a typical month. During the baseline session, with the assistance of the RA, the index participant will try to contact each of their selected peers via SMS text message, phone call, or video chat. If during the session, the index participant is able to contact the peer and the peer is interested in learning more about the study, the index participant will provide the contact information of the peer to the RA, and then, the RA will send the peer an authenticated Qualtrics link. The Qualtrics link will contain an explanation of the study and informed consent. If the peer does not respond to the index participant during the baseline session, the participant will send the peer a brief description of the study with the Qualtrics link. Peers who do not provide consent will be asked to complete a checklist indicating the reasons for declining to participate, which immediately follows the consent form (eg, "not enough time"; "do not trust that the research won't be tracking them"; Multimedia Appendix 1). Index participants will be given 5 days to recruit a maximum of 3 peers to carry the beacons; participants who are unable to *identify* influential peers or are unwilling to contact peers in the orientation session will be withdrawn from the study. Index participants who are unable to *recruit* at least 1 peer to participate will not complete the EMA portion but will complete the end-of-study interview, as it collects information about the recruitment and peer selection process. If any peer who has been contacted has not responded to the participant within 3 days, we will inform the participant to contact the next peer on their SNI-identified list. The end goal is to have 3 peers who can carry the beacon, but we expect that we will need to make contact with >3 peers for some participants. To maintain confidentiality, index participants will not be directly told by the project staff which of their friends participated in the study. Peers who have declined to carry the beacon or were not asked to participate will still be listed as a peer in the EMA reports. Although we will not explicitly tell the index participant that they may participate in the full study with <3 peers, if we are unable to identify 3 peers or the peers are nonresponsive to the research team, at that point, we will inform them that they only need 1 peer to consent to participate for them to participate in the full study.

Once the set of SNI-identified peer participants have provided consent, each peer will be contacted by the project staff to schedule a time to receive the beacon and ask any questions. Each beacon is assigned a unique ID, which associates the beacon with the index participant and the peer. Peer names and unique beacon IDs will be uploaded into the EMA software, so that a customized list (maximum of 6 names) is presented to each participant for all EMA reports (asking whether any of their friends are nearby) and signal-contingent reports triggered by beacon detection can be associated with the correct peer. Peers on the list presented to the index participant may be carrying the beacon, or they may have declined to carry the beacon or not have been asked. This list can be updated in real time without involving the participant to avoid protocol disruptions.

The EMA reports will begin for index participants once the beacons are distributed to peers or within 5 days, whichever comes first. As up to 3 peers can be given a beacon, 3 signal-contingent reports could be triggered at a time (eg, if all the peers who were given a beacon come into contact with the participant at the same time); however, we do not anticipate that this will occur regularly. At the end of each week of data collection, peer participants will complete a brief web survey, and at the end of the study, they will complete a phone interview and return the beacon.

EMA Report Measures

The EMA measures are presented in Multimedia Appendix 1. The *random and signal-contingent reports* will appear identical on the EMA application to minimize unintentional awareness of peer presence. These reports will assess peer presence, participant drinking, and peer drinking and influence. *Index participant drinking* will be measured using questions about the number of drinks consumed, time at which drinking started and stopped, and level of perceived intoxication ("How intoxicated do you feel?"). Peer-related assessments will begin with a stem item measuring *peer proximity*: "In the past hour, who have you been around for any length of time?" The list of up to 6 most influential friends as determined in the SNI will be presented to the index participant, and they can select the names of their friends. Subsequent questions will present a revised list of friends according to which the friends were selected. Figure 1 presents screenshots of the sample survey flow. We will assess whether the index participant was within 15 feet from the peer for at least 15 minutes and whether they interacted with the peer in-person for at least 15 minutes. *Peer drinking and heavy drinking and drunkenness* will be measured using 2 items: "Of the people you were with in the past hour while you were drinking, who was also drinking?" and "Of the people you were with in the past hour, who was drinking heavily or was drunk?" *Direct and indirect peer influence* on participant drinking will be measured using questions about drink offers ("In the past hour, has anyone offered you a drink?"), suggestions to drink ("In the past hour, has anyone suggested that you should drink?"), and provision of alcohol to drinkers ("In the past hour, did anyone refill your drink or get you a new drink?"). Following affirmative answers, these 3 questions will be followed by determinations of whether the individuals selected were friends on the index participant's peer list; if they are included in the peer list, the names of the peers indicated as present are shown.

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Figure 1. Survey flow.

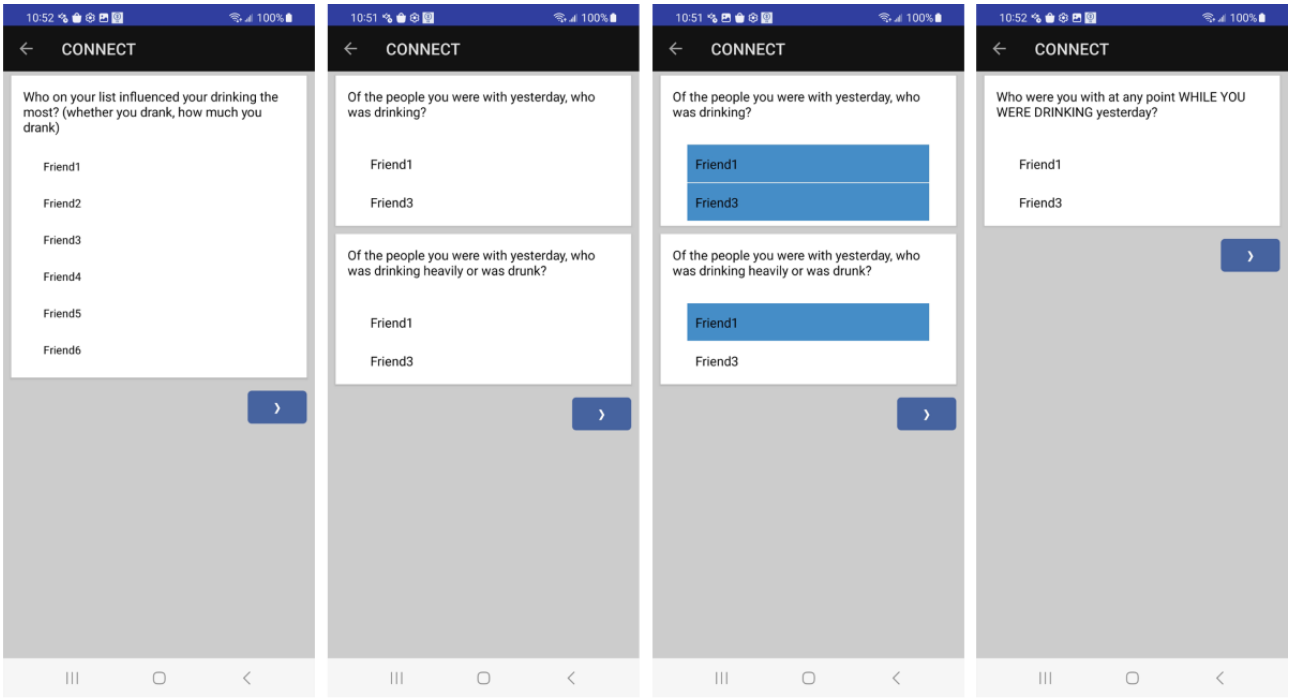

The *morning report* will be identical to the signal-contingent and random reports but will refer to "yesterday," whereas the signal-contingent and random reports will refer to "in the past hour." Morning reports will also assess the total number of drinks taken on the previous day and the start time and end time of drinking. In addition, the morning report will include items measuring noncompliance and the mobile phone's operational state as indicators of participant acceptability (Table 1) and possible reasons for missingness that could inform missing data analysis [64], including options such as silenced their mobile phone, turned off Bluetooth detection, mobile phone battery died, and mobile phone on battery or power saver mode (refer to Multimedia Appendix 1 for the full set of responses). We will also ask participants whether they did not complete a previous-day report because of their drinking, with response options such as no; yes, because I missed a notification; and yes, because I chose not to respond to a notification.

The *first-drink report* will focus specifically on alcohol involvement, including any drinking, heavy drinking, and drunkenness of peers. Again, we will query about people included and those not included in the peer list for specific actions, including offers of drinks. We will focus on the first drink because it is an index event that participants can identify and quickly answer questions about. We will not require additional momentary reports about that drinking event given that this information (including who was there at any time) is reported in the next-day morning report and we are cognizant of participant burden.

Peer Weekly Surveys

Peer participants will receive a link to a brief web-based survey at the end of each week. Peers will indicate days and time of day (day, evening, and late night) in the previous week they did not have their beacon with them, times in the previous week they spent time with their friend and drank with their friend, and whether they had difficulty in finding a place to keep the beacon or any problems in carrying the beacon with them.

Postparticipation Assessments

As part of our evaluation of acceptability, poststudy semistructured interviews will be conducted with index participants and peer participants. For index participants, we will solicit feedback about the peer recruitment process and the study protocol, including the frequency and timing of the EMA reports. Specifically, these interviews will ask participants about (1) identifying and inviting peers to participate, (2) using the app for answering EMA reports, and (3) appropriateness of contact from researchers and compensation for participating. Questions will also pertain to the usefulness of the technology from the participant's perspective, including applications of the peer proximity technology to risky contexts (eg, heavy-drinking situations), and the usefulness of this technology for safety concerns in the context of heavy drinking. In addition, index participants will complete a modified 15-item System Usability Scale [65], with items adapted to our protocol that assess acceptability (eg, "I didn't like that I had to change settings on my phone to use the app"). The System Usability Scale response options range on a 5-point Likert scale from 1=*strongly agree* to 5=*strongly disagree*.

For peer participants, we will collect the initial reactions to being asked to participate (reasons and concerns about participating), privacy concerns, adequacy of compensation, and perceived impact on the behavior of or relationship with the friend. We will also obtain feedback about the beacon, including ease of carrying the beacon with them every day and whether they would prefer to download an app in lieu of carrying the beacon. Multimedia Appendix 1 presents the full set of postparticipation assessments and peer measures.

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Ethical Considerations

Procedures were approved by the Brown University institutional review board (protocol 2022003448).

Index participants and peer participants will complete the informed consent process, which includes reviewing detailed consent forms, discussion with the researcher, and documentation of consent.

All information obtained during assessments will be confidential and used solely for research purposes. To protect data and prevent unauthorized access, all EMA data will be encrypted and will remain so until they are accessed by the project staff using a username and password specific to this project. All files with participant-identifying information will be password protected and stored separately from the data on a server accessible only to the project staff. To preserve confidentiality, we will deidentify data for both index and peer participants using a numeric code. Participants will have researcher-provided credentials for the smartphone app that will not include their names, and we will encourage participants to use mobile phone passwords.

As this protocol involves the passive assessment of social contexts and reporting about the behaviors of proximal others, considerable care was taken during the design phase to maximize confidentiality and increase participant comfort with responding. First, index participant reports inherently identify peers by presenting their names during daily reports. To preserve confidentiality, peer names are replaced by ID numbers in the analytic data sets and are thus unavailable for reidentification. Second, index participants' discomfort associated with reporting about peer behavior will be minimized by ensuring that index participants understand that the smartphone app only records when it is within the range of the beacon and that no other information about their friend is recorded. We will protect peers against coercion by identifying eligible peers during the SNI but recruiting these peers without the presence of the index participant. To further reduce coercion, whether peers agreed to participate or were enrolled into the study will not be disclosed to the index participants unless the peer participant discloses this information themselves. It is possible that participants will identify which of their friends are participating in the study or will even encourage their friends to participate. We will also inform the peer participants that we will never share information about them or their weekly survey and interview responses with the index participant. To protect against peers' discomfort about their friend's smartphone app detecting their presence, we will clarify that no passively assessed information (eg, geolocation) other than peer presence is recorded.

Index participants will be paid US $50 for attending the baseline session, US $5 per day for answering the EMA reports, a weekly bonus of US $20 if they complete 80% of the random and signal-contingent reports, and US $40 for attending the exit interview. The highest compensation they can receive for participation is US $255 (compensation for peer participants is described below, following the section on peer selection). Peer participants will be compensated US $30 for each week they complete the weekly survey and interview and US $10 for returning the beacon to the research team. The highest compensation the peer participants can receive is US $100.

Expected Results

Table 1 shows the list of project goals, how these goals are defined, the metric by which those definitions are evaluated, and the data source for each goal.

Analytic Plan: Feasibility and Acceptability of Recruitment; Enrollment of Participants and Peers; Compliance; and Retention

The *feasibility* of recruiting index participants will be determined based on three indexes: (1) proportion of people who meet the inclusionary criteria among those who complete the screening survey, (2) proportion of screened respondents who are ineligible due to mobile phone OS (eg, iOS instead of Android), and (3) time required to reach the desired sample size. The *feasibility* of complying with the protocol is determined based on the time elapsed between receiving a signal-contingent report notification and EMA survey completion and submission. The *acceptability* of the procedures for index participants will be determined based on four indexes: (1) proportion of eligible individuals who enroll and participate in the study after reading a written explanation of the study—we will also calculate postscreening, self-reported mean ratings of reasons for nonparticipation and inspect each item as a measure of poor acceptability; (2) number of index participants completing the full study protocol compared to the number of index participants enrolled in the study; (3) proportion of completed reports among the total number of possible reports (morning and random reports only) and number of expected reports based on the project beacon log (signal-contingent reports only) and latency (in minutes) between triggering and completing a given report, calculated separately for random and signal-contingent reports (we will also examine whether compliance systematically varies as a function of timing and number of reports within a day); and (4) mean ratings on system utility measures and barriers to use, including ratings about the functionality and utility of the EMA app.

We will explore the *feasibility* and *acceptability* of recruitment and retention of peers. Feasibility will be determined based on three indexes: (1) total number of peers who are asked to carry the beacon, number of peers who provide consent, and number of peers who enroll, calculated across the full sample; (2) time required to recruit the first, second, and third peer by calculating the duration of time between baseline assessment and peer consent; and (3) whether 3 peer participants are successfully enrolled for each index participant. We will also informally explore best practices for enrolling peers with respect to timing (time required to make contact) and mode of contact (eg, text, call, or face to face). The feasibility of retaining peers will be determined based on the number of enrolled peers completing the study protocol (weekly surveys and end-of-study survey) among the number of peers enrolled in the study. Mean ratings of peer reasons for nonparticipation will be calculated similarly, and each item will be inspected.

The *feasibility* and *acceptability* of beacon procedures for peers will be determined based on two indexes: (1) number of days and times the peer carried the beacon with them and (2)

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proportion of distributed beacons that are returned to the study staff. Mean ratings of reasons for noncompliance with beacon procedures will also be calculated, and each item will be inspected.

Analytic Plan: Validity of the Peer Selection Process

We will use 3 indications of whether (up to 6) influential peers were selected during the SNI and whether (up to 3) influential peers were selected to carry Bluetooth beacons, supporting the *validity* of our protocol. First, data from all EMA reports will be used to calculate the proportion of drinking episodes reported by the participant in which they reported that ≥1 of their listed peers were present. Second, we will calculate the proportion of drinking episodes in which the participant indicated that the present peers were also drinking. Third, when a participant indicates that someone (1) offered them a drink, (2) suggested they drink, (3) refilled their drink, or (4) influenced their drinking, the proportion of these peers who were included in the participants' peer list (vs not included) will be computed. As these latter experiences could show low rates in some participants, we will combine them.

Attrition, Nonresponse, and Missing Data

We will investigate person-level correlates of attrition for both index and peer participants by comparing the proportions of participants completing each week of the study (ie, days 7, 14, and 21) across baseline demographic and behavioral factors. We expect compliance with the study protocol to be consistent with current estimates (ie, approximately 75%; refer to the meta-analytic review across substance use studies using EMA designs by Jones et al [52]). Time-varying predictors of nonresponse will be examined within a conceptual framework that considers the impact of participant characteristics, protocol burden (eg, number of notifications received), and situational factors (eg, context and behavior) [66]. We will regress attrition or missingness onto these variables at their appropriate level of analysis and use the identified predictors of systematic missingness to inform future analyses to help maintain the missing-at-random assumption.

Power

Although our sample size of 20 is similar to that of other pilot studies using EMA [67,68] and power to detect moderate-size, level-1 effects exceeds 0.80 (conservatively assuming 70% missingness and a binary grouping variable with an even split), we are likely underpowered for formal tests of moderation [69]. Instead, we will descriptively explore differences in SNI members' presence in drinking events across sex (across all SNI members) and peer consent (across SNI members selected to carry beacons) by performing stratified analyses.

Data Analysis and Dissemination

Data management and analysis will be conducted after all data have been collected, and findings will be reported in manuscripts submitted thereafter.

Results

Participant enrollment began in February 2023. As of submission of the manuscript (June 2023), a total of 9 participants and 21 peers were enrolled. Data collection was completed in December 2023. Data analysis began immediately upon the completion of data collection. Results will be reported in 2025.

Discussion

Summary

In this paper, we describe a protocol that advances the literature by leveraging a newly developed Bluetooth-based detection system to understand influential social contact during real-time drinking situations. Understanding how young adults engage with and feel about this technology is important for determining whether just-in-time interventions using Bluetooth-based sensing can be implemented. Furthermore, evaluating whether the peers who are most influential on an individual's drinking behavior can be identified and are willing and compliant in carrying a Bluetooth beacon is necessary in determining the feasibility of this protocol to identify situations where the index individual is most at risk.

Study Implications

Most interventions aimed at reducing youth drinking are delivered distal in time to actual drinking events. Unfortunately, programs that neglect the socioecological context in which risky behaviors occur may have limited effectiveness, in part due to constraints on an individual's ability to make sound decisions in a highly charged typically social context [70,71]. However, in recent years, there have been targeted efforts to reduce drinking in the natural environment, at a time when behavior is opportune for modification [72-76]. In just-in-time interventions, also referred to as ecological momentary interventions, individuals receive intervention components at specific moments throughout the day to increase health-promoting behaviors and reduce risky behavior [77-79]. However, although studies have identified effective just-in-time content across domains of health behavior [77], there is limited information about the appropriate timing or context in which to intervene.

Beckjord and Shiffman [80] have recommended using a combination of EMAs and ecologic momentary interventions where the delivery of real-time intervention is predicated on user-reported contextual data as well as passively recorded data to coincide with high-risk events. Some of the challenges with using self-reported EMA data as the antecedent for just-in-time intervention include the risk for systematic user noncompliance with EMA during high-risk events (eg, not reporting drinking events) and the need for burdensome EMA algorithm development, high use of devices (eg, geolocation leading to battery drain), and considerable monitoring by researchers, which may limit dissemination and impact [80]. Making just-in-time intervention content contingent on passive sensing overcomes many of these barriers and could facilitate timely delivery of intervention content that is less reliant on user interaction. Future interventions could incorporate Bluetooth-based sensor technology to help individuals who are trying to reduce their alcohol use. This technology could notify an individual through a smartphone or smartwatch that they need to be mindful of their alcohol intake. For example, personalized feedback could be provided when a "risky" peer

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is nearby and could alert the individual that they are in an unsafe situation, similar to smartwatch vibrations after a period of inactivity [81] or tailored messaging that are provided based on geolocation [82]. Our passive sensing approach could effectively complement geographic EMA by identifying both influential high-risk social contexts (peers) and high-risk physical contexts (locations). A friend or accountable individual could also be alerted that the participant is in a risky situation.

Challenges and Limitations

There are several limitations in our protocol related to index participant behavior. It is possible that our use of a 15-minute criterion for a meaningful interaction will be inaccurate, resulting in, for example, us not detecting an influential encounter between a participant and a peer that is too brief to trigger a report. The decision to trigger signal-contingent reports after 15-minute interactions was based on a trade-off between sensitivity and burden. While meaningful social interactions <15 minutes that influence drinking may occur, triggering signal-contingent reports after shorter durations would yield more triggered reports, leading to potential disengagement (longer latency between trigger and completion of report) or noncompliance with the study protocol [52]. Although we plan to examine the relationship between burden and compliance in this protocol, future studies should systematically examine these trade-offs. We will query both behavior in the past 15 minutes and in the past hour in an attempt to accommodate delayed compliance.

Another potential limitation related to index participant behavior that is inherent to all substance use studies using ambulatory methods is the possibility that noncompliance is associated with the use of the substance itself. Participants may miss notifications when they are highly intoxicated [83]. Thus, we might expect alcohol use as reported at the survey level or day level to be associated with nonresponse. We will assess this potential reason for missing self-report data by examining the relationship between compliance with triggered or random reports and past-day drinking as reported in the morning report and self-reported reasons for missing a previous-day report as reported in the morning report. Intoxicated participants also may not recognize or record that a friend was present or influenced their drinking (eg, by offering alcohol or refilling a drink), resulting in underreporting of important peer interactions. Furthermore, there may be systematic noncompliance that is related to drinking context (eg, lower response rates when drinking in social situations such as loud parties or bars); this also can be explored using self-reported EMA data. However, one strength of this protocol is the capability to *passively* detect interactions with proximal peers without the need for self-report. Technological limitations precluded the suspension of random reports after a signal-contingent report is triggered or vice versa. Thus, it is possible for both random and signal-contingent reports to be triggered around the same time, resulting in the index participant being notified to complete multiple identical reports. We expect this will happen infrequently. Although triggering of multiple signal-contingent reports may increase participant burden and increase the likelihood of nonresponse to a survey, detection of these unique social interactions by the smartphone app and completion of these reports will yield greater resolution of index participants' social contexts and is critical to validate the overall protocol.

Next Steps

This proof-of-concept study supports a long-term line of research characterizing the real-time social context of hazardous drinking, in turn informing the timing and context of mobile phone–delivered interventions to reduce hazardous alcohol use among young adults. Feasibility, acceptability, and initial substantive data will inform a large-scale study including participants with a wider age span and broader representation of social context, permitting the study of multiple dynamic determinants of drinking behavior including social and physical context, craving, affect, and motivation [84]. Passive peer detection can be used with other passive technology such as GPS (geolocation) for identification of localized risk, accelerometers for gait sensing, and ambient noise recording to evaluate the situational risk associated with social interactions. It can also be integrated with alcohol biosensors or other more objective measures of intoxication (eg, balance and gait assessed passively by the smartphone) to fill the gaps in reporting related to noncompliance or underreporting of alcohol use.

This protocol involves carrying Bluetooth beacons and requires Android OS smartphones, but future studies should explore the possibility for peers to download an app instead of carrying a beacon (which use the mobile phone's Bluetooth feature to transmit a unique signal similar to the beacon) and to use Apple phones; however, this approach may be technologically limited by host OSs that restrict the development of features that duplicate extant commercially available products (eg, iOS and AirTags). Finally, although the proposed study targets peers associated with increased risk for alcohol use, future studies could also consider peers who are protective against heavy drinking. We hope that this proof-of-concept study stimulates future studies that leverage passive technology to understand the social nature of young adult drinking and ultimately reduce alcohol-related harms.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study. Once data are generated, data sets will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Assessment battery.
[DOCX File , 327 KB - resprot_v13i1e50650_app1.docx]

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Abbreviations

EMA: ecological momentary assessment
OS: operating system
RA: research assistant
SNI: social network interview

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Protocol

The Daily Experiences of Hispanic and Latinx Dementia Caregivers Study: Protocol for a Fully Remote Daily Diary Observational Cohort Study

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Abstract

Background: The Hispanic and Latinx community is disproportionately affected by Alzheimer disease and related dementias (ADRDs). In the United States, approximately 8.5 million caregivers of individuals with ADRDs identify as Hispanic and Latinx people, and caregiving-related stress and burden place caregivers at elevated risk for poor mental health outcomes, as well as loneliness and social isolation. To date, there is limited knowledge about the daily stress experiences of Hispanic and Latinx caregivers. Given this knowledge gap, it is critical to examine how personal, cultural, and contextual factors influence daily stress, mental health, and resilience over time among Hispanic and Latinx ADRD caregivers.

Objective: The goal of this protocol report is to present the rationale, methodology, planned analytical strategy, progress completed to date, and implications of future findings for “Nuestros Días” (Spanish for “our days”), a fully remote daily diary (DD), observational cohort study examining the day-to-day experiences of Hispanic and Latinx ADRD caregivers.

Methods: The study will recruit a cohort of up to 500 Hispanic and Latinx caregivers of individuals living with ADRD. Participants will complete measures assessing contextual, individual-level, and cultural factors at 3 intervals (enrollment, 6 months, and 12 months). Each of the timepoints will be followed by 21 days of DD surveys to report on daily stress, stress moderators, and mental health variables.

Results: Data collection began in March 2023 and is projected to end in December 2026. As of March 2024, we have enrolled 60 caregivers in the Nuestros Días study, 78.9% (n=15) of whom are Spanish speakers. The current completion rate for DD surveys is 79.4%, averaging approximately 18 surveys out of 21 completed. We expect to enroll 10 to 15 participants per month moving forward to achieve our enrollment goal.

Conclusions: Results from this study will identify which Hispanic and Latinx ADRD caregivers, and under what circumstances, appear to be at the greatest risk of experiencing poor mental health outcomes over time. This study represents a critical step forward in providing key guidance to develop effective, culturally sensitive interventions to support the health and well-being of

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Hispanic and Latinx ADRD caregivers, a historically underrepresented and underserved population in aging and caregiving research.

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KEYWORDS

dementia; caregivers; Hispanic; Latinx; mental health; daily diary; longitudinal; protocol; observational cohort study; cohort; Alzheimer's disease; Alzheimer; stress; burden; mental health; loneliness; well-being

Introduction

Background

The prevalence of Alzheimer disease and related dementias (ADRDs) among the Hispanic and Latinx populations is 1.5 times higher than among non-Hispanic White populations [1]. Hispanic and Latinx adults exhibit an earlier onset of ADRDs and more severe symptoms at the time of diagnosis than other ethnic and racial groups [2,3]. Moreover, the presence of comorbidities, such as diabetes, heart disease, and hypertension, among Hispanic and Latinx individuals with ADRDs introduces further health complexities, exacerbating ADRD-related symptoms and accelerating functional decline [4]. Despite facing worse health outcomes and increased disability, nursing home admissions are lower among older Hispanic and Latinx individuals, suggesting increased reliance on informal caregiving [5].

Notably, Hispanic and Latinx ADRD caregivers exhibit poorer mental health outcomes compared with non-Hispanic White ADRD caregivers [6-9]. However, a limited understanding of the daily stressors and dynamic predictors of changes in mental health over time exists. Prior investigations into the mental health of Hispanic and Latinx ADRD caregivers have reported inconsistent results, likely due to varying quality of evidence across studies, which highlights the need for more in-depth research [10]. This inconsistency may arise from dynamic interactions between contextual, individual-level, and unique cultural factors contributing to within-person variability.

Conventional between-group designs and cross-cultural comparisons may not fully capture such within-group variability, thus potentially masking important factors driving mental health outcomes over time. Previous studies on caregiver mental health have found daily variations in mental health [11]. The emerging evidence of daily mental health experiences exemplifies the necessity to examine day-to-day variations in these experiences—especially among populations that may be disproportionately impacted by ADRDs and caregiving-related stress.

To address this gap, the Nuestros Días (Spanish for "our days") study implements a daily diary (DD) approach, offering a novel and comprehensive method to understand the day-to-day stress and mental health experiences of Hispanic and Latinx ADRD caregivers. Daily diaries provide granular data that can determine intricate patterns and nuances that might be otherwise missed in broader survey methods [12]. Examining daily experiences can reveal how specific events or triggers may lead to heightened stress or emotional arousal, allowing for a more holistic understanding of the factors influencing an individual's well-being. As such, when studying the mental health of Hispanic and Latinx ADRD caregivers, DD studies can provide invaluable insights and further directions for ecologically relevant and culturally tailored interventions to support the well-being of Hispanic and Latinx ADRD caregivers.

Study Aims

Overview

The following report presents the design for the Nuestros Días study, a comprehensive and innovative investigation involving Hispanic and Latinx ADRD caregivers, who will be asked to complete measures assessing contextual, individual-level, and cultural factors at 3 intervals within a year (enrollment, 6 months, and 12 months). Subsequently, participants will engage in 21 days of diary surveys measuring daily caregiving experiences and mental health outcomes. The DD methodology encompasses various assessment techniques enabling researchers to investigate individuals' experiences, behaviors, and situations in their natural environments, nearly in real time, and through repeated measurements spanning from a few days to months. Daily diaries have been previously used to quantitatively examine the day-to-day experiences of dementia caregivers including daily stress and well-being [13-15]. Overall, this research design enables the exploration of intraindividual variability (eg, fluctuations in daily experiences) and interindividual differences (eg, variations within distinct groups such as those with high levels of familism or religiosity vs those with low levels) and potential relationships among them [16]. Moreover, this design facilitates the identification of distinct groups within a population that aggregate-level estimates may not accurately capture [16,17]. The 3 study aims are as follows.

Examine Factors Influencing Daily Mental Health Experiences

The objective of this aim is to identify daily factors that increase (ie, risk factors) or decrease (ie, protective factors) the daily odds of experiencing moderate or severe depression and anxiety symptoms among Hispanic and Latinx ADRD caregivers.

Characterize Mental Health Developmental Trajectories

The objective of this aim is to investigate the developmental course of depression- and anxiety-related symptoms among Hispanic and Latinx ADRD caregivers over 12 months.

Identify Predictive Factors for Distal Health Outcomes

The objective of this aim is to examine the association between developmental trajectories of depression- and anxiety-related symptoms with levels of resilience and with distal health

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outcomes (eg, overall physical, mental, and social health) among Hispanic and Latinx ADRD caregivers.

Methods

Overview of the Study Design

This multi-time scale study will test the hypothesis that contextual, individual-level, and cultural factors influence daily and long-term mental health patterns among Hispanic and Latinx ADRD caregivers. Participants (N=500) will be asked to complete surveys measuring contextual, individual-level, and cultural factors at 3 time points (ie, enrollment, 6 months, and 12 months). Immediately after completing each survey, participants will complete 21 days of DD surveys evaluating caregivers' day-to-day caregiving experiences and mental health (for a total of 63 diary surveys across the 3 sampling periods).

Ethical Considerations

The study procedures were approved by the University of Alabama at Birmingham institutional review board (IRB-300008710). The study was deemed to be minimal risk, and a waiver of written consent was approved. Participants will be provided a study information sheet with details about the study's purpose, procedures, risks, and contact information. Participants are informed that all data will be kept deidentified and that no questions regarding immigration status will be asked.

Participant Eligibility Criteria

The target population for the study is English- and Spanish-speaking Hispanic and Latinx ADRD caregivers across the United States. The sample eligibility criteria are guided by AARP's definition of family caregivers [18] and the sampling frame for family caregivers used by the National Institute on Aging–funded REACH trials [19].

Inclusion criteria are as follows: (1) the caregiver is 18 years or older; (2) the caregiver identifies as Hispanic or Latinx descent; (3) the caregiver provides informal care to a spouse/common-law partner, parent, or grandparent (or in-law; 60 years or older), living with dementia; (4) the caregiver assists with at least 2 instrumental activities of daily living or 1 activity of daily living; and (5) the caregiver lives with or shares cooking facilities with the care recipient.

The target sample includes any type of dementia (ie, Alzheimer and frontotemporal dementia) reported by the caregiver, and this will be accounted for in the analytic models. The AD8 questionnaire is being used to determine dementia eligibility status [20], as this is a valid and reliable measure with excellent discriminant validity to distinguish between normal cognition and mild cognitive impairment or dementia. A cutoff score of 2 or greater (ie, cognitive impairment is likely to be present) on the AD8 will be used to determine eligibility. Participants will have the option of completing the study in the language of their choice (ie, either English or Spanish).

Exclusion criteria are as follows: (1) admission to a nursing home or institutional care for the care recipient planned within the next 6 months, (2) the caregiver is terminally ill, and (3) the caregiver does not have reliable internet access.

Participant Recruitment Strategies

Several strategies are in place to facilitate participant recruitment (Textbox 1). All of the recruitment materials have been developed in English and Spanish. As part of our analytical strategy, we will examine the effectiveness of each recruitment strategy including participant characteristics, reach, number of participants enrolled via each method, and costs associated with each strategy. We will also examine demographic differences that arise from the different recruitment methods used to identify possible selection biases.

Textbox 1. Overview of strategies to facilitate recruitment for the Nuestros Días ("our days"): the daily experiences of Hispanic and Latinx dementia caregivers study.

Print recruitment

Newsletter advertisements tailored for senior centers and newspapers serving the Hispanic and Latinx communities. Advertisements include basic information about the study and contact details.

Radio-based recruitment

Advertisements on local Spanish-speaking radio stations in select cities. Advertisements include basic information about the study, as well as contact details.

Digital-based recruitment

Social media campaign with a marketing agency to program study advertisements to appear in the feed of social media sites including Facebook and Instagram. Once individuals click on the "Sign up" button in these ads, they are directed to an initial screening survey that includes questions to verify if the user meets the study eligibility criteria. In addition, we have developed a website for this study with support from the University of Alabama School of Nursing's strategic marketing and communications team.

Community outreach recruitment

Partnership development with local organizations nationwide serving the Hispanic and Latinx community, as well as people living with dementia and their caregivers (eg, Alzheimer Association local chapters and the Area Agencies on Aging).

Registry-based recruitment

Registration of this study on sites that share information about ongoing research studies with potentially eligible participants (eg, Alzheimer Association's registry, Family Caregiver Alliance's registry).

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Remote Data Collection Procedures

Eligibility Screening and Enrollment

The eligibility screening process is completed via web and involves a 3-step approach and requires administrative confirmation at each step. All recruitment materials include a link to complete an initial eligibility screening questionnaire. This questionnaire includes prompts to assess whether the potential participants meet the study eligibility criteria specified above. In addition, participants' IP addresses are recorded and screened by study personnel to prevent fraudulent responses. This screening process is supported by tools such as Scamalytics [21] or WhatIsMyIPAddress.com [22].

Study personnel then verify participants' responses and those eligible to take part in the study receive the study information sheet with details regarding study participation. This study has a waiver of consent due to its low-risk nature, and all participants are asked to acknowledge they have reviewed the information sheet.

Afterward, participants are sent a link to complete a verification questionnaire. This questionnaire includes similar prompts as the initial eligibility screening questionnaire, and serves as an information verification step, as responses from both questionnaires are cross-referenced by study personnel. This process aims to minimize the risk of enrolling fraudulent participants, as well as potential software bots. Participants deemed eligible after this verification procedure are then called by a member of the study team to confirm their enrollment in the study as part of the third and final step. During this call, participant contact information and eligibility are verbally verified one last time. In addition, the start dates for the surveys are confirmed by the study team members during this call. This step also helps ensure that only real participants who meet the eligibility criteria are enrolled in the study.

Data Collection

All data are collected using REDCap (Research Electronic Data Capture; Vanderbilt University), and accessed via the REDCap Consortium. REDCap is a web-based data collection platform aimed to securely support a variety of data management tasks including data tracking, manipulation, export, and others [23,24]. Participants are sent links to complete surveys to the email address provided during enrollment. All surveys are sent at 7 PM in the participant's respective time zone. First, they are prompted to complete a 40-60 minute baseline questionnaire (see Table 1 for measures).

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Table 1. Brief descriptions of measures organized by construct for the traditional, longer-recall surveys that participants complete at baseline, 6 months, and 12 months in the Nuestros Días ("our days"): the daily experiences of Hispanic and Latinx dementia caregivers study.

Construct	Measure	Description
Demographics[a]	N/A[b]	Basic demographic information, including age, gender identity, sex assigned at birth, native language, country of origin, race/ethnicity, sexual orientation, marital status, education, employment, income, medical insurance, time spent as a caregiver, and relationship to the care recipient, as well as the following questions about the care recipient: age, gender identity, race/ethnicity, education, insurance, type of dementia diagnosis, and other chronic conditions.
Caregiving-related stress	BSD[c] [25,26]	Twenty items reflecting different domains of BSD (restlessness, mood, memory, care resistance, hallucinations and delusions, verbal and physical aggression, disinhibition, repetition, safety) with stress appraisals reported on a 5-point Likert scale. Items were adapted from several established instruments because they represent the diversity of types of symptoms rather than overarching conceptual constructs.
Caregiver burden	Zarit burden inventory-short form [27]	Twelve items on a 5-point Likert scale measuring dimensions of personal strain and role strain related to caregiving (α=0.88).
Noncaregiving related stress	Perceived stress scale [28]	Ten items on a 5-point Likert scale measuring perceptions of unpredictability, lack of control, and overload in one's life (α=0.78).
Family stress	Family caregiver conflict scale [29]	Eight items on a 4-point Likert scale measuring caregiving-related conflicts between caregivers and other family members (α=0.93).
Financial stress	Financial subscale of the caregiver reaction assessment [30]	Three items on a 6-point Likert scale measuring caregiving-related financial strain (α=0.83).
Caregiver demands	N/A	Single item asking how many hours of care per week they provide to the PLWD[d].
Relationship quality[a]	Relationship closeness scale [31]	Six items on a 4-point Likert scale measuring relationship quality between caregiver and care recipient (α=0.90).
Coping strategies[a]	Brief-COPE Inventory[e] [32]	Adapted scale with 14 items on a 4-point Likert scale measuring situational coping including strategies of avoidance, problem-solving, and seeking informational support at the personal level (α=0.83-0.91).
Social support	PROMIS[f] social health SF [33-35]	Measures perceptions of emotional (4 items), informational (4 items), and instrumental support (4 items) on a 5-point Likert scale.
Social isolation	PROMIS SF[g] social isolation scale [33,34]	Four items on a 5-point Likert scale measuring perceptions of social isolation.
Emotion regulation[a]	Emotion regulation questionnaire [36]	Ten items measuring cognitive reappraisal (6-items, α=0.83) and expressive suppression (4- items, α=0.79) using a 7-point Likert scale.
Alcohol use[a]	AUDIT[h] [37]	Ten items measuring alcohol use (α=0.83).
Cultural values[a]	Mexican American cultural values scale [38]	Adapted scale includes 36 items on a 5-point Likert scale measuring cultural values including fatalism, familism support, familism obligation, familism reference, religion, and traditional gender roles.
Acculturation[a]	Brief acculturation scale for the Hispanic population [39]	Four items on a 6-point Likert scale measuring acculturation in language use, media, and ethnic social relations (α=0.94) [40].
Discrimination[a]	Everyday discrimination scale [41]	Nine items on a 6-point Likert scale measuring experiences of racism and discrimination (α=0.88).
Overall health	PROMIS global health scale [42]	Ten items on a 5-point Likert scale measuring overall physical and mental health.
Depressive symptoms	Patient health questionnaire [43]	Nine item–questionnaire on a 4-point Likert scale measuring severity of depression symptoms and suicidal ideation (α=0.86-0.89).
Anxiety symptoms	General anxiety disorder questionnaire [44]	Seven items on a 4-point Likert scale measuring the severity of anxiety symptoms (α=0.92).
Resilience	Resilience scale for adults [45]	Adapted scale includes 14 items on a 7-point Likert scale measuring resilience with 3 subscales (perception of self, planned future, and structured style).
Decision-making involvement	Decision-making involvement scale for individuals with dementia and family caregivers [46]	Ten items measuring the degree of a caregiver's involvement in the everyday decisions of a person living with dementia (α=0.85).

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Construct	Measure	Description
Social media use habits	N/A	Six items assessing social media platforms of choice, duration of use, frequency of checking, and preferred device to engage with social media over the past 6 months. In addition, passive and active social media use are measured with questions based on SMAQ[i]; (α *for* active=0.845 and α for passive=0.853) [47].
Social media automaticity	Self-report behavioral automaticity index [48,49]	Four items measuring daily habitual behavior patterns regarding social media use (α=0.92).
Social media self-regulation	Bergen social media addiction scale, [50] the social media self-control failure scale, [51] and the generalized problematic internet use scale [52]	Three items from 3 different instruments assessing self-regulation abilities when using social media.

[a]Only administered in the baseline questionnaire.

[b]N/A: not applicable.

[c]BSD: behavioral symptoms of dementia.

[d]PLWD: people living with dementia.

[e]COPE: coping orientation to problems experienced.

[f]PROMIS: patient-reported outcomes measurement information system.

[g]SF: short form.

[h]AUDIT: alcohol use disorders identification test.

[i]SMAQ: social media activity questionnaire.

The initial DD survey period begins 1 day after completing the baseline questionnaire. Participants receive an email reminder once a day for 21 consecutive days to complete the diary surveys, and each email contains the REDCap link to complete the surveys. The diary surveys are expected to take 10-15 minutes to complete (see Table 2 for measures). The collection period for the diary surveys is set between 7 PM and 11 PM (in the participants' respective time zones) to reduce recall bias. Participants receive 3 hourly reminders via email during the data collection window to encourage completion of DD surveys. If participants do not complete DD surveys 3 days in a row, a study personnel member reaches out to the participant via phone call or email to assess continued interest in study participation, as well as any study engagement barriers and reprogram DD surveys as appropriate.

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Table 2. Brief descriptions of measures for the daily diary surveys organized by construct for the Nuestros Días ("our days"): the daily experiences of Hispanic and Latinx dementia caregivers study.

Construct	Measure	Description
Caregiving-related stress	BSD[a] [25,26]	20 items reflecting different domains of BSD (restlessness, mood, memory, care resistance, hallucinations and delusions, verbal and physical aggression, disinhibition, repetition, safety) and the perceived stressfulness of each symptom reported on a 5-point Likert scale. Items were adapted from several established instruments because they represent the diversity of types of symptoms rather than overarching conceptual constructs.
Noncaregiving related stress	Daily stress inventory [53]	Adapted scale includes 7 items measuring daily stressors.
Coping strategies	Brief-COPE Inventory[b] [32]	Fourteen items that measure self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame (α=0.83-0.91).
Social support	Social support scale [54]	Adapted scale includes 11 items measuring daily social support and resources (emotional support, instrumental support, and informational support).
Social isolation	PROMIS social isolation scale SF[c] [33,34]	Four items measuring perceptions of social isolation.
Discrimination	Everyday discrimination scale [41]	Nine-item scale measuring experiences of racism and discrimination (α=0.88).
Depression symptoms	PROMIS emotional distress—depression scale SF[c] [33]	Four items measuring common symptoms associated with depression.
Anxiety symptoms	PROMIS emotional distress—anxiety scale SF[c] [33]	Four items measuring common symptoms associated with anxiety.
Suicidality	Paykel suicide scale [55]	Adapted scale includes 5 items measuring daily suicidal ideation.
Social media use habits	N/A[d]	Six items assessing daily use of social media, including platforms used, preferred platform, time spent on social media, and passive and active social media use behaviors.
Social comparison	N/A	Two items based on previous literature [56] that assess social comparison when using social media and feelings experienced afterward.

[a]BSD: behavioral symptoms of dementia.

[b]COPE: coping orientation to problems experienced

[c]SF: short form.

[d]N/A: not applicable.

A total of 6 months following the baseline questionnaire and initial diary study, participants repeat this process in the second wave of data collection with a 6-month follow-up questionnaire and a second set of 21 DD surveys. In the third wave of data collection, participants repeat this process 12 months after the initial wave of data collection in addition to a third set of 21 DD surveys (Figure 1).

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Figure 1. Overview of the data collection schedule for the Nuestros Días ("our days"): the daily experiences of Hispanic and Latinx dementia caregivers study. Participants first complete a screening and verification process to determine eligibility and identify potentially fraudulent responders. Then, participants completed 3 waves of data collection (baseline, 6 months, and 12 months). At each wave, participants complete traditional, longer-recall surveys measuring contextual, individual-level, and cultural factors followed by 21 days of daily diary surveys measuring day-to-day caregiving and mental health experiences.

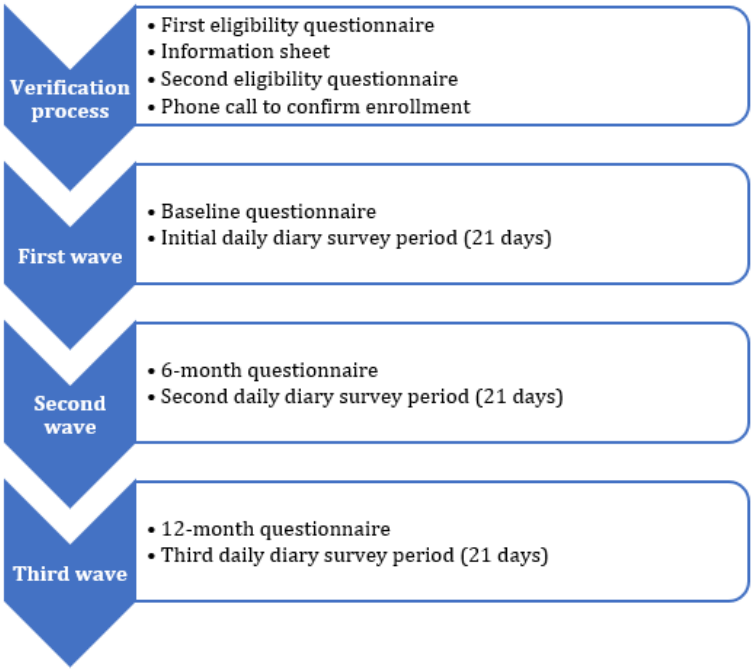

Data Analysis Plan

All data will be exported from REDCap and analyzed using various statistical software platforms, for example, SAS (SAS Institute Inc), SPSS (IBM Corp), R (R Core Team), and STATA. (StataCorp). First, univariate and bivariate approaches will be used to examine outstanding issues with the DD survey data including outliers and missing data. Descriptive statistics and data distributions will be evaluated to ensure values are within reasonable limits and evaluate potential issues of nonnormality and collinearity. A false discovery rate approach [57] will be used to adjust for multiple inferences when appropriate. To ensure the validity and reliability of the proposed measures in our sample, we will perform psychometric testing on all measures as part of our analytical strategy including measures that were adapted for the purposes of this study. The main analytical approaches for each of the study's specific aims are detailed below.

For aim 1, the objective is to identify daily protective and risk factors that impact the daily odds of depression and anxiety symptoms among Hispanic and Latinx ADRD caregivers. Generalized linear mixed modeling (GLMM) accounting for the nesting of diary survey data within participants will be used to examine associations between contextual, individual-level, and cultural factors and daily mental health (ie, depression and anxiety-related symptoms).

In aim 2, the main goal is to investigate the developmental course of depression and anxiety symptoms among Hispanic and Latinx ADRD caregivers over 12 months. To achieve this, we will use group-based trajectory modeling (GBTM) [58] to identify clusters (ie, trajectory groups) of daily mental health symptom occurrence over time and determine personal and cultural factors that predict group membership. We will follow current best practices in GBTM [59] for model selection.

For aim 3, the purpose is to examine the association between developmental trajectories of depression and anxiety symptoms with levels of resilience and distal health outcomes. We will use regression modeling with the trajectories identified in aim 2 and posterior probabilities to make prognostic predictions of overall physical health and clinically significant depression and anxiety at 12 months. We will also examine levels of resilience at baseline, 6- months, and 12 months as a time-varying covariate for these relationships [58].

Sample Size and Power Considerations

For the planned aim 1 analyses, the design proposed in this study will collect a maximum of 31,500 data points across 500 participants with 63 observations per participant (21 days x 3 sampling periods). Assuming a 0.2 uniform probability of dropout over the 12-month study period and an average of 80% diary completion, the expected datapoint collection is 22,680 datapoints (500×16.8+450×16.8+400×16.8). Further assuming, 2 equally sized groups, an intraclass correlation of 0.4 (ie, average correlation between any 2 repeated measurements on the same individual), a standardized outcome (eg, stress and depression), and an adjusted significance level of 0.025, the expected effective sample provides 80% power to detect a time-averaged between-group difference (*d*) of 0.19 [60]. Under similar assumptions for intraclass correlation and significance level, regarding within-cohort changes in standardized outcomes between sampling periods (eg, baseline vs 6 months, each with up to 21 observations per participant) the expected effective

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sample size provides 80% power to detect a within-cohort change (*d*) of 0.04.

For aims 2 and 3, there are no established guidelines for assessing power or determining appropriate sample sizes for GBTM as these are exploratory analyses and the number of resulting trajectories is not known a priori. In previous studies [61] evaluating depression symptoms, discrimination, and ethnic identity among Latinos, a sample of 91 participants was sufficient to detect variations in depressive symptoms. In another study [62] using GBTM, a sample of 94 caregivers of individuals with malignant brain tumors was sufficient for a 2-group trajectory model of caregiver depression and anxiety. Considering that precision is expected to increase with a greater number of data points [63], we expect the target sample size of 500 participants will yield enough precision and power for our planned analyses. Further, GBTM falls under the umbrella of growth mixture models. Previous literature on growth mixture models suggests that a sample size of 500 is sufficient for the Bayesian information criterion and sample-size adjusted Bayesian information criterion to accurately identify the correct number of latent growth trajectories [64].

Results

We started recruitment and data collection in March 2023. Enrollment numbers following 12 months of recruitment are shown in Table 3. We have enrolled 60 family caregivers in this study, most of them are Spanish speakers (75%). Overall, 51 participants have completed the first wave of data collection and 5 are currently completing data collection, either for the baseline extended survey or DD surveys. A total of 5 participants withdrew from the study after enrollment; 3 of them did not complete the baseline survey and 1 stopped responding to the daily surveys; the research team was not able to contact these individuals via phone or email, so we do not have any further information on the reason for withdrawal; 1 participant requested to be removed for the study because of personal reasons. As shown in Table 3, the completion rate for the DD surveys is 84%, equivalent to 900 daily surveys completed for the whole sample.

Table 3. March 2023 through March 2024 enrollment data for the Nuestros Días ("our days"): the daily experiences of Hispanic and Latinx dementia caregivers study.

Characteristic	Participants (n=60), n (%)
Study implementation numbers	
English speakers	15 (25)
Spanish speakers	45 (75)
Participants in progress	4 (7)
Participants completed wave 1	51 (85)
Participants withdrawn	5 (8)
Overall DD[a] data collection progress	
Total participants started DDd	51 (85)
Total number of DDs completed	900 (84)
Total number of DDs expected	1071 (100)
Completion rate	84

[a]DD: daily diary.

Participants who have completed the first wave of data collection responded to 18 DD surveys on average, out of the 21 DD surveys expected. Our goal is to have 70 participants by the end of April 2024. We estimate to enroll 10-15 participants per month from this date forward to successfully accrue our yearly recruitment goals.

Discussion

Principal Results

This study addresses a critical gap in the literature by implementing an innovative design and analytical strategy to test the hypothesis that contextual, individual-level, and cultural factors influence daily and long-term patterns of mental health outcomes among Hispanic and Latinx ADRD caregivers. With cases of ADRDs rapidly increasing among Hispanic and Latinx individuals [8,65,66], the number of Hispanic and Latinx caregivers is consequently growing. Given that Hispanic and Latinx adults develop ADRDs at a younger age and experience complex comorbid conditions, as well as more severe symptomatology than other racial or ethnic groups, Hispanic and Latinx caregivers are uniquely susceptible to increased caregiving stress that can negatively impact mental health outcomes. Thus, a better understanding of the dynamic interactions between risk and protective factors will contribute to the identification of modifiable targets to inform ecologically valid and culturally responsive interventions that will better support Hispanic and Latinx ADRD caregivers.

To our knowledge, this is the first study to provide an in-depth examination of how daily and enduring caregiving-related stress and burden influence the mental health of Hispanic and Latinx ADRD caregivers. This examination is conducted based on the novel application of the protective factor model of resilience. In this model, promotive resources (eg, coping strategies and

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cultural values) can either reduce risk or improve other protective factors [67,68], and resilience is defined as the capacity for positive adaptation despite adversity [69-71]. Thus, resilience theory provides a strengths-based framework to understand why some caregivers report better mental health outcomes than others despite similar risk exposures. While most studies to date have primarily relied on the stress-process model [72] to inform clinical recommendations, small effect sizes have been repeatedly reported in interventions based on this model [73,74]. The measures included in this study align with domains of the protective-factor model of resilience frameworks including promotive resources/assets and risk factors, that decrease vulnerability to caregiving-related stress and increase resilience over time. Therefore, the results from this study will help inform the development of novel resilience-based interventions to support the well-being of Hispanic and Latinx ADRD caregivers.

In addition, the application of advanced analytical strategies, such as GBTM, allows for a thorough evaluation and understanding of caregivers' mental health trajectories over time in this understudied population. Further, a subsequent evaluation of the predictive utility of the identified trajectories will allow us to identify which caregivers, under what circumstances, are at risk of developing clinically significant depression and anxiety over time, and which caregivers are resilient. Finally, findings from the Nuestros Días study will translate into key guidance for targeted and culturally responsive behavioral interventions to mitigate the negative effects of caregiving-related stress on Hispanic and Latinx ADRD caregiver mental health.

Limitations

Although results from the Nuestros Días study will provide compelling directions for future research and tailoring of clinical interventions for caregivers' mental health, several limitations should be taken into consideration.

First, concerns may be raised regarding the potential burden of completing daily surveys. Although we acknowledge that the study design may appear intensive, it provides a rich in-depth examination of day-to-day changes to the variables of interest, and previous studies [15] using this methodology report good compliance along with unsolicited positive feedback from participants. The daily surveys currently take an average of 10-15 minutes to complete, and the study is purposefully designed to minimize participants' burdens while supporting the successful completion of the study aims. However, we acknowledge that there could be a potential tendency for participants to provide random answers to DD assessments due to inconvenience. To identify these scenarios, research team members will monitor the DD data to preliminarily identify randomly completed questionnaires.

Second, in the case of low variability in daily mental health measures, we will explore alternative analytical approaches as appropriate (eg, using the single-item questions instead of converting them to a count of symptoms). It is possible to observe low variability in caregivers' depression and anxiety scores due to either cultural perceptions of mental health or consistently elevated rates of these symptoms at the baseline assessment. To address this concern, we will create a symptom burden score for each period based on the number of days that each participant reported having anxiety and depression symptoms.

Third, the possibility of missing data is a ubiquitous limitation, particularly in longitudinal quantitative research; however, we will use analytical methods [75] (ie, GLMM and GBTM) robust for missing data and will appropriately evaluate patterns of missingness to prevent model misspecification. We also use maximum likelihood estimation to estimate the parameters of the models. Maximum likelihood estimation accounts for data missing at random by estimating the marginal probability of observing a variable given the available data [76]. Finally, we will examine nonparticipant issues (eg, technical failures) and compare the means of observed variables for responders and nonresponders across days, periods, and participants.

Fourth, given the longitudinal nature of the study design, attrition is an additional limitation to consider. To address this concern, we have implemented strategies to keep participants engaged between sampling periods. For example, we mail birthday and holiday cards to participants enrolled in the study. We also send out reminder letters 1 month prior to the 6-month and 12-month data collection waves and place reminder phone calls 1 week before data collection begins. If any mail is returned as undeliverable, we will follow up with an alternate contact provided by the participant upon enrollment. Similarly, after 1 week of 3 unsuccessful attempts to reach the participant at the 6- and 12-month timepoints, we will follow up with the alternate contact. Previous research [77,78] has found that such strategies increase retention over single strategies. If these strategies are unsuccessful, we will identify participants lost to attrition, reopen recruitment, and match the new participants to the lost participants on several demographic variables. Finally, we will use Leigh et al's approach [79] of specifying an instrumental variable to test whether the likelihood of attrition influences the relationship between key independent measures and mental health outcomes.

Comparison With Prior Work

Previous studies on Hispanic and Latinx ADRD caregivers have identified important factors that influence the risk of poor mental health outcomes (eg, physical health, family support, and acculturation) [8,80-83]. However, the dynamic relationships among these individual, contextual, and cultural factors, as well as their effects on caregivers' mental health progression over time, remain relatively unknown among Hispanic and Latinx caregivers. A recent study [62] examining psychological distress among family caregivers of individuals with malignant brain tumors found a trajectory of decreasing psychological distress over 12 months following diagnosis, suggesting psychological adaptation and increased flexibility over time. Such mental health patterns over time are unknown among Hispanic and Latinx ADRD caregivers, which presents a missed opportunity to determine when caregivers are at most risk for developing depression and anxiety.

In addition, while numerous studies [6-10] have observed elevated levels of depression among Hispanic and Latinx caregivers, findings are not consistent across studies, and these

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discrepancies may be due to the dynamic nature of mental health outcomes, as well as temporal variations in risk or protective factors, yet unexamined in Hispanic and Latinx ADRD caregivers. Further, previous research [61,84-87] has found a high degree of variation in the effects of cultural factors on mental health outcomes. These inconsistencies may be due to the heterogeneity within the culturally, genetically, and regionally diverse Hispanic and Latinx subgroups (eg, Mexican, Puerto Rican, Cuban, and Central American), thus emphasizing the importance of implementing innovative design and analytical strategies to disentangle the within-group variability in this population.

The Nuestros Días study overcomes these limitations and addresses these gaps through the multi-time scale design described and the combination of GLMM and GBTM strategies. Results from this study will identify modifiable intervention targets and at-risk groups, thereby providing foundational knowledge to inform evidence based on the care of Hispanic and Latinx ADRD caregivers.

Conclusions

In summary, the Nuestros Días study aims to address gaps in the knowledge about the influence of contextual, individual-level, and cultural factors on daily and long-term patterns of mental health of Hispanic and Latinx ADRD caregivers through the implementation of an innovative design and analytical approach. Results from this study will contribute to the development and testing of culturally responsive, resilience-based behavioral interventions to support the well-being of Hispanic and Latinx ADRD caregivers.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ADRD: Alzheimer disease and related dementia
DD: daily diary
GBTM: group-based trajectory modeling
GLMM: generalized linear mixed modeling
REDCap: Research Electronic Data Capture

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Protocol

Erlotinib or Gefitinib for Treating Advanced Epidermal Growth Factor Receptor Mutation–Positive Lung Cancer in Aotearoa New Zealand: Protocol for a National Whole-of-Patient-Population Retrospective Cohort Study and Results of a Validation Substudy

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Abstract

Background: Starting in 2010, the epidermal growth factor receptor (EGFR) kinase inhibitors erlotinib and gefitinib were introduced into routine use in Aotearoa New Zealand (NZ) for treating advanced lung cancer, but their impact in this setting is unknown.

Objective: The study described in this protocol aims to understand the effectiveness and safety of these new personalized lung cancer treatments and the contributions made by concomitant medicines and other factors to adverse outcomes in the general NZ patient population. A substudy aimed to validate national electronic health databases as the data source and the methods for determining patient eligibility and identifying outcomes and variables.

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Methods: This study will include all NZ patients with advanced EGFR mutation–positive lung cancer who were first dispensed erlotinib or gefitinib before October 1, 2020, and followed until death or for at least 1 year. Routinely collected health administrative and clinical data will be collated from national electronic cancer registration, hospital discharge, mortality registration, and pharmaceutical dispensing databases by deterministic data linkage using National Health Index numbers. The primary effectiveness and safety outcomes will be time to treatment discontinuation and serious adverse events, respectively. The primary variable will be high-risk concomitant medicines use with erlotinib or gefitinib. For the validation substudy (n=100), data from clinical records were compared to those from national electronic health databases and analyzed by agreement analysis for categorical data and by paired 2-tailed *t* tests for numerical data.

Results: In the validation substudy, national electronic health databases and clinical records agreed in determining patient eligibility and for identifying serious adverse events, high-risk concomitant medicines use, and other categorical data with overall agreement and κ statistic of >90% and >0.8000, respectively; for example, for the determination of patient eligibility, the comparison of proxy and standard eligibility criteria applied to national electronic health databases and clinical records, respectively, showed overall agreement and κ statistic of 96% and 0.8936, respectively. Dates for estimating time to treatment discontinuation and other numerical variables and outcomes showed small differences, mostly with nonsignificant *P* values and 95% CIs overlapping with zero difference; for example, for the dates of the first dispensing of erlotinib or gefitinib, national electronic health databases and clinical records differed on average by approximately 4 days with a nonsignificant *P* value of .33 and 95% CIs overlapping with zero difference. As of May 2024, the main study is ongoing.

Conclusions: A protocol is presented for a national whole-of-patient-population retrospective cohort study designed to describe the safety and effectiveness of erlotinib and gefitinib during their first decade of routine use in NZ for treating EGFR mutation–positive lung cancer. The validation substudy demonstrated the feasibility and validity of using national electronic health databases and the methods for determining patient eligibility and identifying the study outcomes and variables proposed in the study protocol.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12615000998549; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368928

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KEYWORDS

epidermal growth factor receptor; erlotinib; gefitinib; lung cancer; retrospective cohort; study protocol; validation

Introduction

Background

Over the last 20 years, advances in the understanding of the molecular basis of lung cancer have led to new diagnostic and treatment practices being introduced into routine care [1], but their everyday impact in general patient populations is undefined. Such improvements in lung cancer care have been an important priority because lung cancer is a major cause of death globally [2] and a significant contributor to ethnicity-related health inequity in Aotearoa New Zealand (NZ) [3] and elsewhere. Starting in 2010, the epidermal growth factor receptor (EGFR) kinase inhibitor drugs erlotinib and gefitinib were introduced into routine clinical use in NZ for the treatment of advanced lung cancer [4]. Before their introduction, clinical trials of erlotinib and gefitinib had demonstrated substantial therapeutic benefits in patients with EGFR mutation–positive lung cancer, with >50% reduction in the risk of disease progression in pooled analyses of randomized trials [5]. These clinical trials also highlighted major safety concerns with erlotinib and gefitinib due to serious adverse drug reactions [6], including interstitial lung disease, renal failure, hepatotoxicity, severe diarrhea, gastrointestinal perforation, and skin and ocular disorders [7,8]. Regulatory studies [9,10] also alerted to the potential interaction of erlotinib and gefitinib with other medicines, expected to lead to adverse outcomes from treatment. Some medicine interactions were expected to reduce lung cancer treatment effectiveness by reducing systemic exposure to erlotinib or gefitinib from their concurrent use with gastric acid suppressants [11,12] or cytochrome P450 enzyme inducers [13,14]. Other medicine interactions were expected to increase serious adverse events by increasing erlotinib or gefitinib systemic exposure from their concurrent use with cytochrome P450 enzyme inhibitors [14,15]. Other medicine interactions were expected to increase the risk of gastrointestinal perforation from concurrent use with nonsteroidal anti-inflammatory drugs or systemic corticosteroids or bleeding from prolongation of the international normalized ratio from concurrent use with coumarin anticoagulants [16,17]. Despite these expectations, the effectiveness and safety of these new personalized lung cancer treatments in the general population of NZ patients has not yet been described, and the contributions made by concomitant medicines and other factors to the occurrence of adverse outcomes remain to be defined in this setting of routine care. As clinical trials underreport harm from anticancer drugs [18] and assess their efficacy under ideal rather than everyday circumstances [19], large-scale observational studies such as the one described in this protocol are required to fully understand the safety and effectiveness of cancer treatment in real-world settings. Recent reports illustrate how real-world studies of new personalized lung cancer treatments can be informative about their effectiveness and safety in general patient populations [20] and unrepresented patient groups [21] as well as the impacts of concomitant medicines [22].

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Studies using routinely collected health administrative and clinical data can provide insights into the everyday impacts of new treatment pathways, but their data sources and study methodology first need to be validated [23]. In NZ, cancer registration, hospital discharge, mortality registration, and pharmaceutical dispensing data are collected in national electronic health databases [24], thereby providing potentially useful sources of information for studies of the impacts of routine cancer care. However, bias may be introduced from errors in data recording or in the methods used for identifying the cases and health outcomes of interest, which may limit the validity of study findings. This potential for bias may be controlled in part by quantifying errors inherent in study methodology and data sources by comparison against a reference standard, such as clinical records [25].

Objectives

The purpose of this paper is to present the study protocol and results of a validation substudy for a planned retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib during the first decade of their use in NZ for treating advanced EGFR mutation–positive lung cancer. The overall objective of the study described in this protocol is to understand the effectiveness and safety of new personalized treatments in the general population of NZ patients with lung cancer and the contributions made by concomitant medicines and other factors to adverse outcomes in this setting of routine care. The study protocol and results of the validation substudy are detailed in the following sections.

The specific aims of the study are to (1) determine the effectiveness and safety of erlotinib and gefitinib for the treatment of EGFR mutation–positive lung cancer in the entire cohort of all patients treated in NZ over a 10-year period, (2) identify serious adverse events and assess their expected association with erlotinib and gefitinib in these patients, (3) determine the prevalence and patterns of the concomitant use of other medicines with erlotinib or gefitinib in these patients, and (4) assess whether the combined use of other medicines was associated with serious adverse events or reduced lung cancer treatment effectiveness in these patients treated with erlotinib or gefitinib.

Methods

Study Design

This study will be a national, population-based, observational, data-linkage, retrospective cohort study that will analyze routinely collected administrative and clinical electronic health data. The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000998549).

Study Group

This study will have a whole-of-population sample comprising a single group of patients treated with erlotinib or gefitinib for EGFR mutation–positive lung cancer who were first dispensed erlotinib or gefitinib before October 1, 2020, and followed thereafter until death or for at least 1 year.

Setting

NZ had a resident population of approximately 4.4 to 5.1 million people during the period of the planned retrospective study. NZ residents were eligible for state-funded health care, including prescription medicines whose state subsidies were managed by the NZ government agency Te Pātaka Whaioranga–Pharmac [26]. From October 1, 2010, to December 31, 2013, Te Pātaka Whaioranga–Pharmac fully funded erlotinib in NZ as a second-line treatment for advanced non–small cell lung cancer without any requirement for EGFR mutation testing. From August 1, 2012, Te Pātaka Whaioranga–Pharmac fully funded gefitinib in NZ as a first-line treatment for advanced EGFR mutation–positive non–small cell lung cancer. On May 1, 2013, the National Health Committee of the NZ Ministry of Health issued recommendations for EGFR mutation testing in NZ, including that all patients with non–small cell lung cancer should be tested at diagnosis as part of standard pathology processes, except those confidently diagnosed with squamous carcinoma. From January 1, 2014, Te Pātaka Whaioranga–Pharmac restricted funding for erlotinib in NZ to the treatment of advanced EGFR mutation–positive non–small cell lung cancer.

Eligibility Criteria

Inclusion Criteria

Patients will be eligible for inclusion in the retrospective cohort if they were (1) diagnosed with EGFR mutation–positive lung cancer; (2) dispensed erlotinib and gefitinib first before October 1, 2020; and (3) followed thereafter until death or for at least 1 year.

Exclusion Criteria

Patients will be excluded from the retrospective cohort if they had (1) a dispensing of erlotinib or gefitinib before positive EGFR mutation test results became required for state subsidies for erlotinib (starting January 1, 2014) and gefitinib (starting August 1, 2012) in NZ, (2) no notification of a diagnosis of nonsquamous non–small cell lung cancer in the NZ Cancer Registry, or (3) an unactionable or unknown EGFR mutation subtype.

Proxy Criteria for the Initial Assessment of Patient Eligibility

As EGFR mutation test results were not systematically recorded in national electronic health databases, proxy criteria were developed for identifying an initial pool of potentially eligible patients. According to these proxy criteria, patients will be potentially eligible for inclusion if they were first dispensed gefitinib on or after August 1, 2012, or erlotinib on or after January 1, 2014, which was when positive EGFR mutation test results first became required for access to state-subsidized erlotinib and gefitinib in NZ. Patients dispensed erlotinib before January 1, 2014, or gefitinib before August 1, 2012, will be excluded because of uncertainty about their EGFR mutation status at the time of commencing treatment with erlotinib or gefitinib. A further assessment of potentially eligible patients will be undertaken according to the aforementioned inclusion and exclusion criteria. The validity of these proxy criteria for

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an initial evaluation of patient eligibility was assessed in the validation substudy (Multimedia Appendix 1).

Data Sources and Linkage

Eligible patients will be identified first in national electronic dispensing records of erlotinib and gefitinib (Figure 1). Subsequently, the data required for the study will be compiled from these dispensing records and other sources (Figure 1). Use will be made of routinely collected health administrative and clinical electronic data sourced from various national electronic health databases, including (1) the New Zealand Cancer Registry, which is a population-based register of all legally mandated notifications of cancer diagnoses and deaths in NZ and includes all cancer types except nonmelanoma skin cancer; (2) the Pharmaceutical Information Database, which contains payment and claims information from pharmacists for state-subsidized community pharmaceutical dispensings in NZ; (3) the National Mortality Collection, which contains information on all deaths registered in NZ and includes the dates and underlying cause of death; and (4) National Minimum Dataset (Hospital Events), which is a national collection of public and private hospital discharge information for day patients and inpatients in NZ. Individual-level data on eligible cohort participants will be compiled from these various national electronic health databases by deterministic data linkage using each participant's unique National Health Index number. Additional data on eligible cohort participants may be sourced from regional data repositories or clinical records, such as EGFR mutation subtype and testing methodology.

Figure 1. Flow diagram of the assembly of a retrospective cohort and compilation of data from national electronic health databases for a study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor (EGFR) mutation–positive lung cancer in Aotearoa New Zealand (NZ).

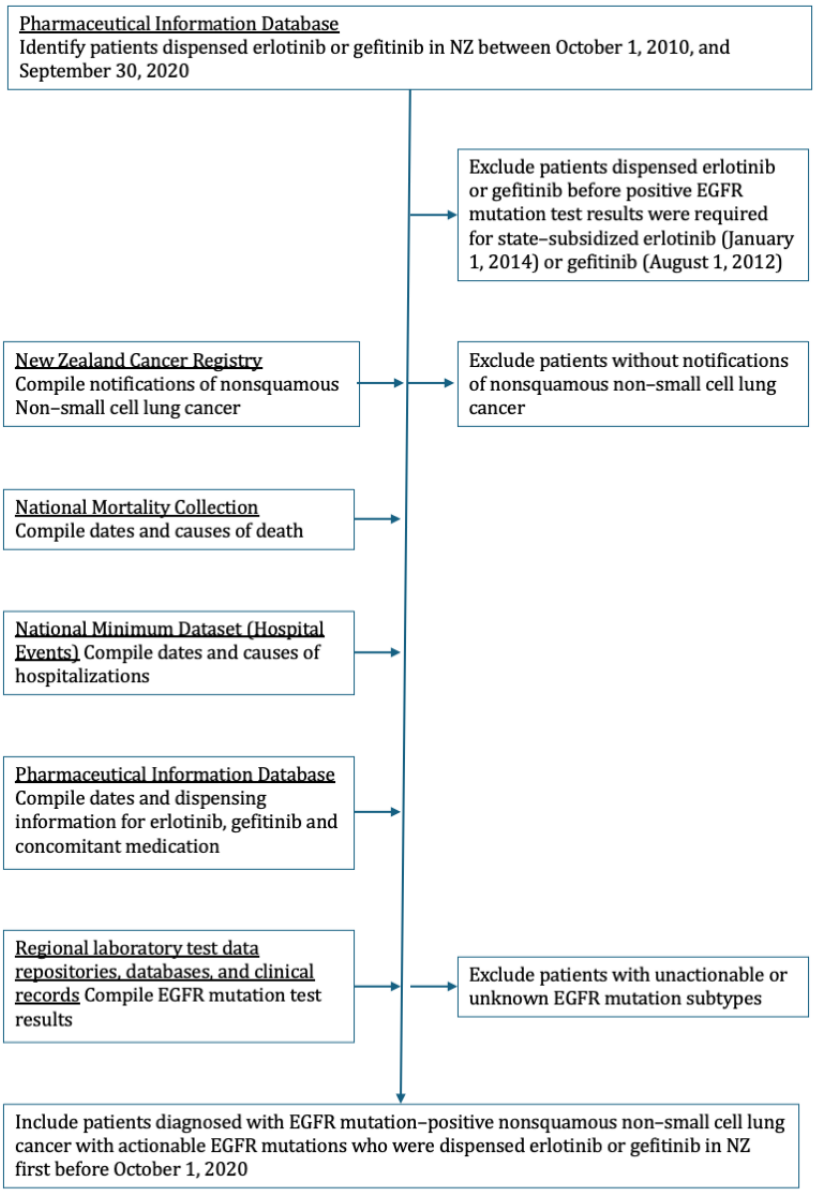

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Outcomes

Primary Effectiveness Outcome

The primary effectiveness outcome measure will be time to treatment discontinuation with erlotinib or gefitinib. Prescriber guidelines [7,8] recommend uninterrupted daily treatment, with erlotinib and gefitinib continued for as long as it is safe and tolerable, and the patient is responding. In clinical trials of EGFR kinase inhibitor drugs for the treatment of advanced EGFR mutation–positive lung cancer, time to treatment discontinuation correlated well with progression-free survival [27], which is an important and common end point used in oncology trials to measure the efficacy of a drug. Time to treatment discontinuation is also less impacted by subsequent treatments and other factors that confound the effects of study treatment on overall survival. For this study, time to discontinuation of treatment with erlotinib or gefitinib will be defined as the duration between the dates of first dispensing and last treatment with erlotinib or gefitinib. The date of last treatment with erlotinib or gefitinib will be calculated by adding the number of days' treatment with erlotinib or gefitinib dispensed at the last dispensing to the date of this last dispensing, except when death occurred before the calculated date of last treatment, in which case the date of last treatment will be the date of death. Participants with no known dates of last treatment or death will be censored at the date of their last known treatment. The validity of national electronic health databases as the source of key dates determining time to treatment discontinuation was assessed in the validation substudy (Multimedia Appendix 2).

Primary Safety Outcome

The primary safety outcome measure will be serious adverse events. For this study, serious adverse events will be defined as death or hospitalization during or within 30 days of stopping treatment with erlotinib or gefitinib, when the primary cause of death or hospitalization was non–cancer related. Cancer-related hospitalizations and deaths will be excluded from serious adverse events because lung cancer progression and death are expected outcomes during palliative treatment of advanced lung cancer with erlotinib or gefitinib. Cancer-related hospitalizations and deaths will be identified from the International Classification of Diseases, Tenth Revision (ICD-10), codes (C00-D48) for the main cause of hospitalization or death in national electronic discharge summary and mortality databases. The validity of national electronic health databases for identifying serious adverse events was assessed in the validation substudy (Multimedia Appendix 1).

Secondary Effectiveness Outcome

The secondary effectiveness outcome measure will be overall survival. Overall survival will be defined as the duration between the dates of the first dispensing of erlotinib or gefitinib and death from any cause. Participants with no known date of death will be censored at the date of their last known pharmaceutical dispensing or hospital discharge. The validity of national electronic health databases as the source of dates determining overall survival was assessed in the validation substudy (Multimedia Appendix 2).

Secondary Safety Outcomes

A secondary safety outcome measure will be interruption, reduction, or substitution of treatment with erlotinib or gefitinib. Prescriber guidelines recommend administering erlotinib 150 mg or gefitinib 250 mg once daily orally continuously without interruption except in the event of serious adverse drug reactions when erlotinib or gefitinib are recommended to be withheld, dose reduced, discontinued, or substituted by another treatment [7,8]. Such changes in dosing may signal significant safety concerns. Treatment interruption will be defined as when the total number of days of treatment with erlotinib and gefitinib dispensed was less, by ≥7 days, than the time to treatment discontinuation defined from the start and end dates of treatment with erlotinib or gefitinib. Treatment reduction will be defined as when the daily dose of treatment was reduced and substitution when erlotinib was changed to gefitinib, or vice versa. The validity of national electronic health databases for identifying patients with interruptions, reductions, or substitutions of treatment with erlotinib or gefitinib was assessed in the validation substudy (Multimedia Appendix 1).

Another secondary safety outcome will be serious adverse drug reactions. Serious adverse drug reactions are a subgroup of serious adverse events (primary safety outcome measure) known to be associated with erlotinib or gefitinib. Adverse drug reactions known to be associated with erlotinib or gefitinib monotherapy are listed in Textbox 1. They were identified in the warnings and precautions sections of the latest Food and Drug Administration drug label for erlotinib and gefitinib or as recorded elsewhere within their latest Food and Drug Administration drug label as being consistently increased compared to placebo in controlled trials of erlotinib or gefitinib monotherapy [7,8]. For this study, serious adverse drug reactions will be defined as those known to be associated with erlotinib or gefitinib monotherapy (Textbox 1) that resulted in death or hospitalization during or within 30 days of stopping treatment with erlotinib or gefitinib. Patients experiencing serious adverse drug reactions will be identified from the ICD-10 codes for the main cause of hospitalization or death during the relevant time period in national electronic discharge summary and mortality databases. The ICD-10 codes corresponding to adverse drug reactions known to be associated with erlotinib and gefitinib are shown in Textbox 1. The validity of national electronic health databases for identifying patients with serious adverse drug reactions to erlotinib or gefitinib was assessed in the validation substudy (Multimedia Appendix 1).

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Textbox 1. Adverse drug reactions known to be associated with erlotinib or gefitinib, with their corresponding International Classification of Diseases, Tenth Revision (ICD-10), codes, compiled for a national retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor mutation–positive lung cancer in Aotearoa New Zealand.

Adverse drug reactions known to be associated with erlotinib or gefitinib and the corresponding ICD-10 codes

- Decreased appetite: R63.0
- Dehydration: E86
- Diarrhea: A09.9, K52.1, and K52.9
- Dyspnea: R06.0
- Electrolyte abnormalities: E87.1-E87.5, E87.6, and E87.8
- Gastrointestinal perforation: K22.3, K25.1, K25.2, K25.5, K25.6, K26.1, K26.2, K26.5, K26.6, K27.1, K27.2, K27.5, K27.6, K28.1, K28.2, K28.5, K28.6, K63.1, K57.0, K57.2, K57.4, K57.8, K82.2, and K83.2
- Hemorrhage in patients on warfarin: D68.3
- Hepatotoxicity: R94.5, K71.0-K71.9, and K72.0-K72.9
- Interstitial lung disease: J70.2-J70.4 and J84.9
- Nausea and vomiting: R11
- Ocular disorders: H00.0-H22.8
- Renal failure: N14.1, N14.2, M14.4, N17.0-N17.9, N18.1-N18.9, and N19
- Skin and subcutaneous tissue disorders: L00-L99.8
- Stomatitis: K12.0-K13.7

Other Secondary Outcomes

Another secondary effectiveness outcome measure will be lung cancer–specific survival, measured from the start date of treatment with erlotinib or gefitinib until the date of death from lung cancer. Participants who died of causes other than lung cancer will be censored at their date of death. Participants with no known date of death will be censored at the date of their last known pharmaceutical dispensing or hospital discharge. Another secondary safety outcome measure will be non–cancer-related mortality, defined as when the primary cause of death was non–cancer related. For the analysis of non–cancer-related mortality, participants whose death was caused by cancer will be censored at their date of death. Participants with no known date of death will be censored at the date of their last known pharmaceutical dispensing or hospital discharge. As the primary cause of death is not systematically recorded in clinical records, these secondary outcome measures were not formally validated.

Variables

Primary Variable

The primary variable will be the use of high-risk concomitant medicines during treatment with erlotinib or gefitinib. High-risk concomitant medicines will be those listed in Stockley's Interactions Checker [28] with alerts to potential interaction with erlotinib or gefitinib, excluding natural health products, recreational drugs, foods, nonprescription medicines, medicines not used in NZ, medicines whose interaction is expected to result in only a mild or no effect, and topical formulations (Therapeutic group 2 or 3: ID numbers 105, 1011, 1019, 1033, 2810, 2824, 2851, 3103 and 10404; Textbox 2). High-risk concomitant medicines will be categorized according to whether their potential interaction is expected to (1) reduce systemic exposure to erlotinib or gefitinib, (2) increase systemic exposure to erlotinib or gefitinib, (3) increase the risk of gastrointestinal perforation, (4) increase international normalized ratio and bleeding risk, (5) increase interacting drug exposure and toxicity, or (6) alter the distribution and excretion of erlotinib or gefitinib (Textbox 2). Concurrent use will be defined as the dispensing of high-risk concomitant medicines at any time during treatment with erlotinib or gefitinib. The validity of national electronic health databases for identifying concurrent use of high-risk concomitant medicines was assessed in the validation substudy (Multimedia Appendix 1).

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Textbox 2. High-risk concomitant medicines, categorized by their expected adverse outcome from potential interaction with erlotinib or gefitinib, compiled for a national retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor mutation–positive lung cancer in Aotearoa New Zealand.

Expected adverse outcome from potential drug interaction and high-risk concomitant medicines

- Reduced exposure to erlotinib or gefitinib: antacids, bosentan, calcium carbonate, carbamazepine, cimetidine, dabrafenib, efavirenz, enzalutamide, famotidine, lansoprazole, mitotane, nevirapine, omeprazole, oxcarbazepine, pantoprazole, phenobarbital, phenytoin, primidone, ranitidine, rifabutin (erlotinib only), rifampicin, sodium bicarbonate, sorafenib, and temozolomide (erlotinib only)
- Increased exposure to erlotinib or gefitinib: aprepitant, atazanavir, bupropion (gefitinib only), cinacalcet (gefitinib only), ciprofloxacin (erlotinib only), clarithromycin, cobicistat, ethinylestradiol (erlotinib only), crizotinib, darunavir, diltiazem, erythromycin, fluconazole, fluoxetine (gefitinib only), imatinib, itraconazole, ketoconazole, lopinavir, methoxsalen (erlotinib only), mexiletine (erlotinib only), neratinib (erlotinib only), nilotinib, paclitaxel (gefitinib only), paroxetine (gefitinib only), posaconazole, ritonavir, terbinafine (gefitinib only), verapamil, and voriconazole
- Increased risk of gastrointestinal perforation (considered a class effect but specified only for erlotinib and not for all systemic corticosteroids in Stockley's Interactions Checker): aspirin, betamethasone, budesonide, celecoxib, cortisone, dexamethasone, diclofenac, docetaxel, etoricoxib, fludrocortisone, hydrocortisone, ibuprofen, indometacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, methylprednisolone, naproxen, paclitaxel, parecoxib, prednisolone, prednisone, sulindac, tenoxicam, and tiaprofenic acid
- Increased international normalized ratio and bleeding risk: acenocoumarol, phenindione, and warfarin
- Increased interacting drug exposure and toxicity: alprazolam (erlotinib only), etoposide (erlotinib only), irinotecan, simvastatin (erlotinib only), teriflunomide (gefitinib only), triazolam (erlotinib only), vemurafenib (gefitinib only), vinblastine, vincristine, vindesine, and vinorelbine
- Altered distribution and excretion of erlotinib or gefitinib: amiodarone (erlotinib only), azithromycin (erlotinib only), ciclosporin (erlotinib only), and vemurafenib (erlotinib only)

Secondary Variables

A secondary variable will be comorbidity. Comorbidity will be assessed using a previously validated pharmacy-based comorbidity index for patients with cancer [29] with further adaption for this study. Comorbid conditions will be identified from community pharmaceutical dispensing records for a 9-month period starting 1 year before the commencement of treatment with erlotinib or gefitinib. A total of 19 comorbid disorders will be identified according to the dispensing of ≥1 specific pharmaceuticals or those from specific therapeutic groups, as shown in Multimedia Appendix 3. The number of comorbid disorders for each patient will be summed without weighting. The validity of national electronic health databases for identifying comorbidities was assessed in the validation substudy (Multimedia Appendices 1 and 2).

Other secondary variables, which will be used in patient characterization and analyses of exploratory factors, covariates, and confounders, will include age, the date of diagnosis, the date of death, gender, ethnicity, the place of domicile, tumor morphology, the basis of diagnosis, notifying laboratory, the extent of disease, tumor stage, tumor grade, deprivation index, rurality, EGFR mutation subtype, EGFR test method, smoking status, clinical stage, and performance status.

Statistical Analysis

The process of assembling the retrospective cohort will be illustrated using a flow diagram to show the number of patients at each stage of the process, including those who were examined for eligibility, were included in the study, completed follow up, were included in the analysis or not included, and the reasons for noninclusion. Descriptive statistics will be used to analyze the demographic profiles, clinical characteristics, and treatment received by the assembled retrospective cohort. To determine the effectiveness and safety of erlotinib and gefitinib in the cohort (aim 1), time to event effectiveness (time to discontinuation of treatment with erlotinib or gefitinib, overall survival, and lung cancer–specific survival) and safety outcome measures (non–cancer-related mortality) will be analyzed using Kaplan-Meier curves and Cox proportional hazards modeling to generate summary survival statistics (median, 1-year, and 2-year survival, as well as 95% CIs) and examine predictive factors. To identify and assess serious adverse events (aim 2), summary tables and descriptive statistics will be used to display the number and percentage of patients with serious adverse events by ICD-10 code and their known association with erlotinib or gefitinib. To determine the prevalence and patterns of concomitant medicines use (aim 3), summary tables and descriptive statistics will be used to display the number and percentage of patients administered medicines concomitantly by individual specific medicine, therapeutic class, and expected adverse outcome of potential interaction with erlotinib or gefitinib. To analyze associations between high-risk concomitant medicines use and the effectiveness and safety of erlotinib and gefitinib (aim 4), study participants will be stratified according to whether they were exposed or not exposed to high-risk concomitant medicines. Differences between participants exposed to high-risk concomitant medicines and those not exposed in proportions of patients experiencing serious adverse events will be analyzed by chi-square tests and multivariable regression models. Differences between participants exposed to high-risk concomitant medicines and those not exposed in time to event end points will be analyzed using Kaplan Meier curves and Cox proportional hazards modeling. Exploratory analyses may examine associations between the use of concomitant medicines and serious adverse events or poor survival outcomes using different definitions of concurrent exposure, individual medicines, the therapeutic classes of medicines, and patient subgroups such as those defined by ethnicity. Sensitivity analyses may be undertaken, for example, to assess effects on the outcomes of modifying patient eligibility criteria.

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Sample Size Considerations

With an expected cohort of between 800 and 900 eligible participants, with ≥750 events, the study will have 80% power (=.8) for detecting with statistical significance (=.05) differences in time to treatment discontinuation (primary effectiveness outcome measure) with hazard ratios of ≤0.76 between the groups, each including between 20% and 80% of the whole cohort. With an expected rate of serious adverse events (primary safety outcome measure) of ≥10% and complete serious adverse event data on at least 75% of the eligible cohort participants, the study will have 80% power (=.8) for detecting with statistical significance (=.05) differences of at least 2-fold in serious adverse event rates between the groups, each including between 20% and 80% of the whole cohort.

Validation Substudy

To validate national electronic health databases as the source of data for this study protocol and the aforementioned methods for determining patient eligibility and identifying the key outcomes and variables of interest, the validation substudy was undertaken in a subgroup of potentially eligible patients. From a source population of 532 patients identified in national electronic dispensing records as having been dispensed erlotinib or gefitinib in the northern region of NZ between October 1, 2010, and September 30, 2020, a total of 100 (18.8%) patients were randomly selected for this validation substudy. The northern region includes the Auckland, Counties Manukau, Waitemata, and Northland district health areas and one-third of the national population. The validation substudy was restricted to northern region patients because their clinical records were available to the investigators for manual review. A gold standard set of data was compiled for each validation substudy patient by manual review of their clinical records, including their EGFR mutation test status. These results were compared to those generated by study methods applied to data compilations from national electronic health databases. As the primary cause of death was not systematically recorded in clinical records, fatal and nonfatal serious adverse events were validated separately. In addition, fatal serious adverse events were validated without the requirement of being non–cancer related and termed for this purpose as *potential serious adverse events that were fatal*. Categorical data were analyzed by agreement analysis and numerical data by paired 2-tailed *t* tests. A sample size of 100 patients for the validation substudy was expected to be adequate for defining levels of overall agreement with 95% CIs of –10% to +10%.

Ethical Considerations

Ethics approval for this research was obtained from the New Zealand Ministry of Health Northern B Health and Disability Ethics Committee (13/NTB/165/AM02). All procedures will be conducted in accordance with the relevant ethics guidelines (eg, the Declaration of Helsinki). As this research will retrospectively analyze routinely collected data and not involve direct contact with patients, the human participants included in this retrospective cohort study will not be able, or required, to give informed consent. Requirement for informed consent was considered impractical and undesirable by the researchers, ethics committee, and governance groups who approved the study. Patient confidentiality will be maintained by holding any identifying information as password-protected data spreadsheets or as hard copy data in secure facilities only accessible to approved research or clinical personnel whose employment contracts include obligations regarding patient confidentiality.

Results

Validation of Categorical Data

Validation analyses for categorical data are shown in Multimedia Appendix 1. For the determination of patient eligibility, the comparison of proxy and standard eligibility criteria applied to national electronic health databases and clinical records, respectively, showed overall agreement and κ statistic of 96% and 0.8936, respectively. For the identification of nonfatal serious adverse events, the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 93% and 0.8526, respectively. For the identification of potential serious adverse events that were fatal, the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 100% and 1.0000, respectively. For the identification of interruptions, reductions, or substitutions of treatment with erlotinib or gefitinib, the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 94% and 0.8764, respectively. For the identification of serious adverse drug reactions, the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 97% and 0.8529, respectively. For the identification of the use of high-risk concomitant medicines with erlotinib or gefitinib (primary variable), the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 95% and 0.8717, respectively. For identifying comorbidities, the comparison of national electronic health databases and clinical records showed overall agreement and κ statistic of 93% and 0.7779, respectively.

Validation of Numerical Data

Validation analyses for numerical data are shown in Multimedia Appendix 2. To validate national electronic health databases as the source of key dates for determining time to discontinuation of treatment with erlotinib or gefitinib (primary effectiveness outcome) and overall survival, the dates of the first dispensing of erlotinib or gefitinib, last treatment, and death were compared to those in the clinical records. For the dates of the first dispensing of erlotinib or gefitinib, national electronic health databases and clinical records differed on average by approximately 4 days with a nonsignificant *P* value of .33 and CIs overlapping with zero difference. For the date of last treatment with erlotinib or gefitinib, national electronic health databases and clinical records differed on average by approximately 6 days with a nonsignificant *P* value of .46 and 95% CIs overlapping with zero difference. For the dates of death, national electronic health databases and clinical records differed on average by <1 day with a nonsignificant *P* value of .57 and 95% CIs overlapping with zero difference. For the number of comorbidities, national electronic health databases and clinical records differed on average by <1 comorbidity but

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with a marginally significant *P* value of .03 and 95% CIs almost overlapping with zero difference.

Current Status

As of May 2024, the main study is ongoing.

Discussion

Summary

The research project described in this protocol will provide important new information about the everyday impacts, both beneficial and harmful, arising from the introduction of erlotinib and gefitinib into routine clinical use for treating advanced EGFR mutation–positive lung cancer in NZ a little more than 1 decade ago. Previous studies in this area have been limited to evaluations of the impact and uptake of the introduction of EGFR mutation testing in the northern region of NZ [4,30-32]. Currently, few data exist on the effectiveness and safety of erlotinib and gefitinib in the general NZ patient population and on the contributions made by concomitant medications and other factors to adverse outcomes in this setting of routine care. Such new real-world and NZ-specific data are likely to provide deeper insights into the harms profiles of erlotinib and gefitinib and to have important implications for clinical practice and patient-centered care; for example, if the study establishes associations between adverse outcomes and the use of concomitant medicines, an awareness of these data could influence the clinical practices of health care professionals who prescribe or dispense erlotinib, gefitinib, or other medicines for use concomitantly with erlotinib and gefitinib in NZ or elsewhere. The data will also inform new health policies, such as those concerning state subsidies for newer-generation EGFR kinase inhibitor drugs that have gained regulatory approvals for marketing but remain unfunded in NZ since erlotinib and gefitinib were introduced into routine care approximately 1 decade ago.

In the validation substudy, we showed that the methods proposed in the study protocol, when applied to data compiled from national electronic health databases, were valid for determining patient eligibility and identifying the outcomes and variables of interest to this retrospective cohort study. Compared to gold standard data sets compiled by a manual review of clinical records, the results generated by the study methods applied to data compiled from national electronic health databases showed good levels of agreement in categorical data, such as patient eligibility, serious adverse events, and the use of high-risk concomitant medicines, and generally small and statistically insignificant differences in numerical data such as the dates required for the estimation of time to treatment discontinuation. These results support the validity of the methods described in the study protocol and the robustness of the findings that will be generated and eventually reported.

Strengths

The strengths of the research protocol include its large population-based sample, internal validity, national generalizability, and the unique patient cohort. We envisage recruiting almost all eligible patients from throughout NZ in a whole-of-patient-population cohort, thereby eliminating selection biases and assembling one of the largest national cohorts of this type to be reported to date [33-37]. However, few of these previous studies have evaluated serious adverse events from erlotinib and gefitinib and their association with the use of concomitant medication in real-world settings. The use of national electronic health databases that use consistent data collection methodology will give confidence that the study results will be generalizable to all NZ patients and regions. Previous studies have highlighted striking geographic and ethnic variations in EGFR mutation–positive lung cancer [38,39]. As NZ is a multiethnic society, with the largest global populations of Indigenous Māori and Pacific people, this study will provide important new information of international interest about treatment outcomes in these understudied groups.

Limitations

The limitations of the study protocol include potential biases from errors inherent in the use of routinely collected data; for example, the safety outcomes for the study protocol assume that the coding of hospital admissions and deaths is always complete and accurate, whereas this is not necessarily the case. Further limitations of the retrospective study design include that, unlike in prospective randomized studies, it will not be possible to assess causality or control for confounding variables. The study design also assumes adherence to the treatment regimens as recorded in dispensing records and provides no practical method for assessing compliance. Another limitation is the historical perspective of the study protocol, which will evaluate the impacts of treatment that occurred between 2 and 12 years ago and may now be of limited relevance to current clinical practice. For the initial assessment of patient eligibility, the study protocol infers EGFR mutation status indirectly from pharmaceutical dispensing records rather than directly from EGFR mutation test results, which could have introduced bias. The findings of the study may not be generalizable outside NZ because of limited external validity and a shift in standard EGFR treatments to targeted therapies that have superseded gefitinib and erlotinib. However, if the study establishes associations between adverse outcomes and the use of concomitant medicines, these findings could have important implications for the use of erlotinib or gefitinib in other countries or for the use of other anticancer kinase inhibitor drugs susceptible to similar medicine interactions [40]. The limitations of the validation study included its small sample size and the resulting wide CIs for the levels of agreement, κ statistic, and other statistical parameters.

Conclusions

In conclusion, a protocol is presented for a planned study that seeks to describe the safety and effectiveness of erlotinib and gefitinib during the first decade of their routine clinical use in NZ for treating EGFR mutation–positive lung cancer in a national whole-of-patient-population retrospective cohort. An exploratory substudy has demonstrated the feasibility and validity of using national electronic health databases and the study methodology developed for determining patient eligibility and identifying the outcomes and variables of interest for this study.

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Acknowledgments

The authors thank Luisa Bituin for data collection from clinical records for the validation study. This study has been funded by the Health Research Council of New Zealand (19-450).

Data Availability

All aggregate data (ie, counts) required for replicating the calculation of proportions, and so on, will be made available within manuscripts. Individual patient-level data cannot be shared publicly because they will contain identifying patient information. Ethics and legal requirements, which limit data access and sharing to maintain patient confidentiality and privacy, have been imposed upon us by the New Zealand Ministry of Health ethics and governance committees.

Authors' Contributions

PSA, JB, GL, LC, MA, BL, SD, DH, STT, ME, PH, and MJM were responsible for project conceptualization, study protocol development, and grant applications. PSA and MJM were responsible for the validation substudy. GL, LC, ME, BL, SD, DH, BM, EB, JW, RL, MA, and MJM were responsible for the provision of clinical data, oncology expertise, and knowledge transfer. JB was responsible for research pharmacy expertise and knowledge transfer. Epidemiology and biostatistical expertise was provided by PSA, STT, and ME. Māori leadership was provided by GL and PH. All authors reviewed and edited the draft and final versions of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Validation of national electronic health databases as the source of categorical data for a national retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor mutation—positive lung cancer in Aotearoa New Zealand.
[PDF File (Adobe PDF File), 27 KB - resprot_v13i1e51381_app1.pdf]

Multimedia Appendix 2
Validation of national electronic health databases as the source of numerical data for a national retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor mutation—positive lung cancer in Aotearoa New Zealand.
[PDF File (Adobe PDF File), 27 KB - resprot_v13i1e51381_app2.pdf]

Multimedia Appendix 3
Comorbidity definitions by pharmaceutical dispensing for a national retrospective cohort study of the safety and effectiveness of erlotinib and gefitinib for treating advanced epidermal growth factor receptor mutation-positive lung cancer in Aotearoa New Zealand. Italicized names and ID numbers to be used in searches of dispensing records.
[PDF File (Adobe PDF File), 85 KB - resprot_v13i1e51381_app3.pdf]

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Abbreviations

EGFR: epidermal growth factor receptor
ICD-10: International Classification of Diseases, Tenth Revision
NZ: Aotearoa New Zealand

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Protocol

Body Composition and Energy Expenditure in Youth With Spina Bifida: Protocol for a Multisite, Cross-Sectional Study

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Abstract

Background: Obesity prevalence in youth with spina bifida is higher than in their typically developing peers. Obesity is associated with lifelong medical, psychological, and economic burdens. Successful prevention or treatment of obesity in individuals with spina bifida is compromised by (1) the lack of valid and reliable methods to identify body fat in a clinical setting and (2) limited data on energy expenditure that are necessary to provide daily caloric recommendations.

Objective: The objectives of this study will be to develop 2 algorithms for use in youth with spina bifida in a clinical setting, one to model body fat and one to predict total daily energy expenditure. In addition, physical activity and dietary intake will be described for the sample.

Methods: This multisite, prospective, national clinical study will enroll 232 youth with myelomeningocele aged 5 to 18 years (stratified by age and mobility). Participants will be enrolled for 1 week. Data obtained include 4 measures of body composition, up to 5 height measures, a ramped activity protocol, and a nutrition and physical activity screener. Participants will wear an accelerometer for the week. On the final study day, 2 samples of urine or saliva, which complete the doubly labeled water protocol, will be obtained. The analysis will include descriptive statistics, Bland-Altman plots, concordance correlation, and regression analysis.

Results: The study received extramural federal funding in July 2019. Data collection was initiated in March 2020. As of April 2024, a total of 143 (female participants: n=76, 53.1%; male participants: n=67, 46.9%) out of 232 participants have been enrolled. Data collection is expected to continue throughout 2024. A no-cost extension until November 2025 will be requested for data analysis and dissemination of findings.

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Conclusions: This study furthers previous pilot work that confirmed the acceptability and feasibility of obtaining alternate height, body composition, and energy expenditure measures. The findings from this study will enhance screening, prevention, and treatment of abnormal weight status by facilitating the accurate identification of youths' weight status category and recommendations of daily caloric needs for this population that is at higher risk of obesity. Furthermore, the findings have the potential to impact outcomes for youth diagnosed with disabilities other than spina bifida who experience similar challenges related to alterations in body composition or fat distribution or measurement challenges secondary to mobility issues or musculoskeletal problems.

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KEYWORDS

obesity; overweight; body composition; energy expenditure; doubly labeled water; spina bifida; children; adolescents; wearable device

Introduction

Background

Obesity in Spina Bifida

The prevalence of obesity is as high as 50% of youth and 64% of young adults with spina bifida (SB) [1]. Youth with obesity often remain obese as adults, increasing their risk of morbidity and mortality [2]. Obesity is associated with lifelong medical, economic, and psychological burdens [3-6].

SB is a birth defect involving an incomplete closure of the spine that occurs in 3.5 per 10,000 live births [7]. The higher incidence of youth with SB having obesity can be attributed to characteristics inherent in the condition, including (1) a lower percentage of lean mass and lower basal metabolic rate (BMR), (2) decreased function in the lower extremities that can alter the individual's mobility dependent on the level of the spinal lesion, and (3) an overall reduced energy expenditure (although exact amounts are not quantified) [8-11]. Muscle hypoplasia and decreased growth and height velocity can further exacerbate the high percentage of body fat and is accentuated with the youth's advancing age, higher level of lesion, and decreased mobility status [11-14]. Carrying excess body fat with SB increases the risk of decubitus ulcers, skin breakdown, social isolation and rejection, and surgical complications. It further decreases an individual's mobility and the ability to self-manage their condition, undermines independence, and creates unnecessary barriers for caregivers who assist with daily care [15-18]. In addition, obesity creates the same risk of obesity-related comorbidities as in the typically developing (TD) population, including type 2 diabetes, metabolic syndrome, and cardiovascular disease [19-22], highlighting the need for obesity prevention. Thus, obesity in youth with SB places them in double jeopardy for poor physical health, creates additional barriers to independence, and can worsen the underlying conditions associated with the disability [18,23-27]. The focus on youth is important when addressing obesity-related issues because the prevention and treatment of obesity begin in childhood, when weight-related behaviors and habits are being formed and can promote successful weight management as the youth ages [19].

To address obesity in youth with disabilities, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) convened a group of experts in obesity and disabilities that identified barriers to healthy weight status in youth with disabilities and developed a research agenda to address the problem [28]. Two research priorities were identified: (1) the need for a clinically available, accurate measure of obesity; and (2) data on energy expenditure [28].

Specifically, the group recommended that the obesity measure to be developed be valid, reliable, and feasible for use in the clinical setting [28]. The group also highlighted the methodological concerns of using BMI in youth with disabilities, including the difficulties associated with accurately measuring the height of youth who primarily use wheelchairs and cannot stand independently and have inherent differences in body composition related to their diagnosis [28]. Accurate height measurement is an integral component of many body composition measures. The need for data related to energy expenditure was based on the dearth of information available specific to youth with disabilities and the lack of understanding of the impact that a physical disability has on youths' energy requirements and nutrient needs [28].

Routine screening for obesity risk and documenting weight status is recommended for all youth and is integral for preventing and treating obesity and promoting health [19]. However, commonly used measures of body fat have been normed on the TD population [29] and often require measurement of height [30]. Individuals with SB have a decreased height velocity, atypical body habitus (eg, abnormal water and fat distribution and varying degrees of muscle atrophy), and orthopedic complications (eg, contractures, kyphosis, or scoliosis) that make it difficult to obtain an accurate height measurement [10,11,13,14,31-35]. The characteristics inherent in SB, along with measures normed on the TD population and reliance on the height measurement, lead to inaccurate body fat measurements or delayed identification of abnormal weight status for youth with SB.

Measurement of Body Composition

Proposals to modify the BMI [14,36] or use alternative measures of height or body composition to increase the accuracy of body fat assessment in SB have been made [10,12,30-32,37-42]. However, these modifications or alternative measures have yet to be tested in a sufficiently large sample, thereby limiting their application in this population. The benefits of BMI (eg, ease of

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use and cost-effectiveness) have prompted suggestions to adjust the BMI graph percentiles or obesity cutoff points for individuals with physical disabilities. One proposal suggested lowering the BMI graph percentiles by 50% for youth with higher-level lesions to improve obesity identification [14]. In 29 adolescents with physical disabilities (n=3 with SB), it was reported that using a more conservative cutoff point for obesity of 19 kg/m^2 (female individuals) and 20 kg/m^2 (male individuals) versus graph percentiles increased the classification accuracy [36]. However, these approaches have not been validated. The underlying need for an accurate height within a BMI calculation and other body composition measures has led to suggestions for using surrogate measures of height or length (eg, arm span, recumbent length, tibia height, and ulnar length) [14,30,43-45].

Beyond BMI, alternative body composition measures (eg, waist circumference, skinfolds, and bioelectrical impedance analysis [BIA]) that fulfill the requirements for being clinically available, cost-effective, and previously used in TD youth [46-52] or small samples of youth with SB [9,10,31,32,36,38,53] are promising but need further testing in larger samples. Alternate methods of estimating body fat with higher accuracy (eg, isotope dilution technique, dual x-ray absorptiometry [DXA], underwater weighing, and magnetic resonance imaging) are available [54,55] but are not easily accessible, cost-effective, or pragmatic for performing in a clinic setting or on an ongoing basis to monitor body weight trends [27].

Measurement of Energy Expenditure

Subsequent to the accurate identification of percentage of body fat, the need to provide anticipatory guidance on daily energy (kcal) requirements is essential to obesity prevention and treatment. Total energy expenditure is the combination of the individual's BMR, thermic effect of food, physical activity energy expenditure, and the cost of growth in children [56]. The total daily energy expenditure (TDEE) is the average energy expended in a 24-hour period. Weight management strategies are based on the overly simplified premise of energy balance (ie, energy in [nutritional intake] must equal energy out [energy expenditure] to maintain weight [57]). When there is a balance deficit, a change in weight will occur (eg, energy in>energy out=weight gain). Although more complex than this, knowledge of TDEE is essential to accurately guide energy requirements specific to daily caloric intake.

In the TD population, estimated energy requirement equations based on the child's sex, height, and weight are used to determine average calorie needs per day [58]. Unfortunately, these equations are based on the metabolic rate and reference height and weights of TD youth, which are not applicable for youth with SB. In fact, the use of these equations would grossly overestimate the energy needs of youth with SB, resulting in overfeeding and further weight gain [34]. There is evidence supporting that youth with SB have a reduced energy expenditure, but the amount has not been specified [8,31,32,34,59]. Similar to body composition measurement, preliminary studies in small samples have been conducted but need to be tested in larger samples with validated criterion measures of energy expenditure [31,32,34]. Evidence-based information on TDEE is key to future research endeavors, including creating and testing interventions for weight management.

Stable isotope techniques are reliable methods for measuring energy expenditure and body composition within a 2-compartment model comprising fat-free mass (FFM) and fat mass (FM). The doubly labeled water (DLW) technique is widely recognized as a gold-standard tool for measuring TDEE [60]. This method involves the ingestion of water containing 2 stable isotopes, deuterium (^{2}H) and oxygen-18 (^{18}O), which act as tracers when ingested. The dosage of DLW is determined based on the individual's body weight. The analysis is performed on the individual's body fluids (saliva, blood, or urine) through isotope ratio mass spectrometry to measure the elimination of the tracers over a specific time frame [60]. The difference in the elimination rate of the tracers from the body allows for the calculation of carbon dioxide production, a product of energy metabolism that is used to compute TDEE [60]. Furthermore, the added tracers can also be used to estimate the individual's total body water (TBW) through the isotope dilution technique. Equations are typically applied to DLW-derived TBW to determine body fat percentage, an age-related adjustment for chemical maturation of FFM.

Pilot Studies

This study furthers previous pilot work that examined the feasibility of obtaining multiple height and body composition measures and then used these measures to generate preliminary models to predict FM as measured using a DXA scan in 15 youths aged 4 to 18 years with SB. A total of 4 measures of height (segmental, arm span, recumbent, and standing height [if able]) and 5 body composition measures (Bod Pod, 7-site skinfold, traditional BMI calculation, BIA, and DXA) were found to be feasible to obtain and generally accepted by participants [61]. A second pilot study examined the feasibility of completing different measures of energy expenditure and activity using a metabolic cart, portable calorimeter, accelerometers, and DLW in 36 youths with SB (n=18; 9 ambulatory and 9 who primarily used a wheelchair for mobility) and Down syndrome (n=9) and a control group of TD youth (n=9) without chronic illness. DLW analysis was found to be feasible (34/36, 94% of participants completed the protocol), and accelerometers were worn without concern. The DLW used urine and saliva as samples, with each being feasible and acceptable. Results showed that, when matched for FFM, the recommended daily caloric intake based on TDEE averaged 800 calories less per day for the participants with SB who primarily used a wheelchair (P=.001) as compared to the controls [62].

The objective of this study was to provide a method of measurement that accurately assesses body fat and the estimation of energy expenditure in youth with SB in a clinical setting.

Study Aims

This national study is convening a sample of 232 youths with SB to complete the following aims.

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Aim 1

The first aim is to develop an algorithm that accurately models body fat percentage and categorizes weight status in youth with SB using clinically feasible, cost-effective, and efficient measures of body composition (4-site skinfolds, waist circumference, and BIA) or surrogate height measures (arm span, recumbent, knee height, and ulnar length). The subaim is to examine whether mobility status, sex, BMI using surrogate height, and pubertal status are important determinants in the model and determine whether corrections are needed for these variables.

Aim 2

The second aim is to measure TDEE using DLW and develop a prediction equation for the energy requirements of the sample. The first subaim is to examine average TDEE based on age, sex, and mobility status (walks or primarily uses a wheelchair), and the second subaim is to develop an equation based on actual TDEE to predict energy requirements using a best-fit model based on FFM, sex, age, mobility status, assistive device use, and height or weight. The exploratory aim is to describe the dietary intake and the physical activity frequency and duration in youth with SB using a nutrition screener, physical activity screener, and accelerometers. This exploratory aim provides a preliminary understanding of obesity-related behaviors, which is currently lacking for this population.

Methods

Study Design

A multisite, prospective cross-sectional study of youth with the most severe form of SB, myelomeningocele, is in progress. The project is being conducted collaboratively through 4 regional pediatric SB programs.

Setting

The SB programs from across the country were strategically chosen based on (1) the ethnic and geographic representation of clinic patients, (2) broad research experience with this vulnerable population, (3) participation in the Centers for Disease Control and Prevention National Spina Bifida Patient Registry (NSBPR), and (4) the ability to recruit the needed sample size. After the COVID-19 pandemic, during the initial implementation phase of the protocol, one of the original sites withdrew after data collection challenges and was replaced by an alternate site. In total, 3 of the 4 sites use their associated clinical and translational science institutes' research unit for study visits, and the fourth uses their designated clinical research setting. Each site has a predetermined recruitment goal based on its patient enrollment. The NSBPR investigators at each site have established routine communication patterns, annual meetings, and a history of collaboration to determine, gather, and evaluate data collected through the registry. Each site recruits and collects data on its predetermined number of participants and has coinvestigators and staff to support their roles.

Sample Characteristics

On the basis of the data from the NSBPR [7], we estimated that 1399 youth are seen yearly in the 4 participating SB programs. Among these, we expect approximately 81%, or 1133, to be diagnosed with myelomeningocele. Of those, 725 (64%) are expected to be aged between 5 and 18 years and eligible for recruitment. On the basis of the NSBPR data [7], we expect our sample to be approximately 52% female.

This study has a targeted enrollment of 232 youths (aged 5-18 years) diagnosed with myelomeningocele-type SB. Purposive sampling is being used to achieve a minimum of 60 youths who identify as being Hispanic or Latino and 116 who primarily use a wheelchair for mobility. Participants are stratified by age (5-11 years and 12-18 years) and mobility status (ambulates independently vs primarily uses a wheelchair for mobility) to increase the usefulness of the study findings to both mobility groups (Table 1). Once the collection is complete for a subgroup, sites will be notified to stop recruiting for that specific mobility status, age, or ethnicity.

Table 1. Sample stratification (N=232).

	Ambulatory		Wheelchair	
	Sample, n (%)	Minimum Hispanic, n (%)	Sample, n (%)	Minimum Hispanic, n (%)
Aged 5-11 years	58 (25)	15 (6.5)	58 (25)	15 (6.5)
Aged 12-18 years	58 (25)	15 (6.5)	58 (25)	15 (6.5)
Total	116 (50)	30 (12.9)	116 (50)	30 (12.9)

The chosen age range (5-18 years) allows for representation of 2 developmental stages that include prepubertal and pubertal status; children in these groups were successful at following the protocol during the pilot study. In addition, the initial age of 5 years was chosen based on the likelihood of being able to cooperate with the study protocol. The end cutoff point of 18 years was chosen because many youth transfer to an adult SB program at that time.

The specific inclusion of minority groups provides a more accurate representation of the population of youth with SB and makes the findings more useful as obesity prevalence has been documented as varying by ethnic descent [3]. To accommodate participants who do not speak English, interpreters are sufficiently budgeted for, and all study materials are professionally translated into Spanish.

Inclusion and Exclusion Criteria

The inclusion criteria are (1) youth aged between 5 and 18 years diagnosed with myelomeningocele and (2) English or Spanish speakers (interpreters will be provided).

Participants are excluded from the study if they meet one or more of the following criteria that either interfere with their

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ability to complete the protocol or compromise the study results: (1) a medical restriction to a 6-hour fast, (2) pregnancy, (3) expectation to participate in abnormally vigorous and out-of-the-ordinary activity during the 7-day test period, (4) living or traveling >200 miles from the study site during the week before or during the protocol, (5) use of supplemental oxygen, (6) a pacemaker, (7) blood transfusion or intravenous infusion of >500 mL of intravenous fluids the week before the test date or expectation to do so during the 7-day test period, (8) claustrophobia or predisposition to the sensation of claustrophobia (for sites including a resting metabolic cart assessment), and (9) an active viral or bacterial illness during the initiation of the 7-day protocol (if study participants are ill during their in-person study visit, they are rescheduled).

Recruitment

Recruitment is conducted by the participating pediatric SB programs, their surrounding communities, and national organizations (eg, Spina Bifida Association) through newsletters, social media, and referrals from family members and health care providers. It is reiterated during and within the consent and assent process that participation is completely voluntary and that there will be no consequences if individuals do not take part or complete the study.

Recruitment processes used in the previous pilot studies were effective in achieving targeted participation and are being replicated. Recruiting strategies include institutional review board (IRB)–approved advertisements that are posted and distributed within clinics, locations where families congregate, and special events that focus on families with disabilities. In addition, the advertisements can be mailed to patients enrolled in the participating SB programs, shared through social media sites such as X (formerly known as Twitter) and Facebook, and posted on the websites of relevant professional organizations. Within the clinic, a Permission to Contact Form is used, which allows a family (if interested) to indicate where, how, and when they would like to be contacted to discuss the study further. Recruitment materials include a pictorial orientation study manual (in print and web-based), modified from that of our initial pilot study, explaining the study protocol and measurements so that families can make an informed decision to participate. By using SB programs as our recruitment sites, families that have an ongoing relationship with the program can participate in this study in a familiar environment.

Participant Reimbursement

To reimburse the families for their time and cost of participation in the study, each family is offered a US $100 gift card for completing the first-day (<5 hours) appointment and a US $150 gift card when the day-7 urine specimens and accelerometers are returned to the study site. The second gift card is sent only after the day-7 samples are received. All supplies and prepaid shipping mailers are provided to the family before their departure on day 1. Early in the implementation process, unanticipated transportation and childcare issues were encountered by a subset of sites. Due to this concern, an amendment was submitted to allow for an additional voucher of up to US $125 per the site's discretion to accommodate families who expressed interest in participating in the study but acknowledged barriers (eg, lack of transportation, distance to the clinic requiring a hotel stay for an early-morning visit necessary due to fasting for the child, or childcare), along with local parking vouchers if relevant. The request and reason for use are documented by each site. Study dates are on weekdays and include flexible appointment times to meet the needs of the families. Morning appointments are recommended based on the need for a minimum 6-hour fasting status before testing.

Retention Strategies

Retention of study participants (to complete the full 7-day protocol) is enhanced by replicating strategies successfully used in our pilot studies, including the provision of (1) a comprehensive explanation of what the study entails (aided by the pictorial recruitment manual) so that the family can make an informed choice to participate, (2) flexible scheduling options, (3) clear instructions provided verbally and in print when they leave on day 1, and (4) all materials needed for the collection and the return of the day-7 urine samples and accelerometers with prepaid mailing labels and supplies. To enhance retention and completion of data collection, a call or SMS text message is made or sent to the family on day 5 or 6 to remind them of the final samples needed on day 7 and review instructions and answer questions. The final retention aid is that the second gift card is not sent to the family until the day-7 sample collections are received. The process and requirements for receipt of the second gift card are discussed during their day-1 visit, which we believe may support study retention.

Measures and Instruments

Table 2 outlines vital signs and anthropometrics, Textbox 1 provides a listing of body composition and energy expenditure measures, and Textbox 2 provides study instruments. All instruments and study materials are available in English and Spanish. Specific training, orientation, and validation checks are completed for data collectors along with the provision of a study manual with detailed instructions supported with pictures. For all measures, a standardized process is followed to obtain the measure, and an open comment box is available for the data collector to provide additional details related to any challenges encountered (eg, orthopedic complications) to be considered during analysis. In total, 2 of the measures, DXA and resting metabolic rate through a resting metabolic cart, are only being collected at the lead principal investigator's site to provide a subset of participants to be examined as a secondary validation assessment for the DLW. The decision to use this site for these additional measures was made as the measures were successfully collected during the pilot work at this site.

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Table 2. Vital signs and anthropometrics.

Measure	Procedural operations
Vital signs	Baseline heart rate, blood pressure, and respiratory rate are obtained.
Weight (measured to the nearest 0.1 kg)	
Body weight	Participant removes shoes, extra clothing (jackets), and assistive devices and is weighed on a medical-grade calibrated standing or wheelchair scale. After, the wheelchair is weighed separately and subtracted from the total weight of participant and wheelchair. If braces are needed to safely stand, the youth is weighed with the braces on (total weight), and then the braces are removed and weighed alone. The weight of the braces is subtracted from the total weight to obtain the final youth weight.
Height (measured to the nearest 0.1 cm)	
Standing	If able to stand independently and safely, the participant removes shoes or assistive devices and stands erect to the best of their ability with their back and heels against a wall-mounted stadiometer. The stadiometer arm is brought to the top of the youth's head.
Arm span	Participant abducts shoulders 90° and fully extends arms and hands. A flexible tape measure is placed posteriorly from the tip of the middle finger to the tip of the opposite middle finger with staff on each side to assist with outstretching of arms perpendicular to the body. Each measure is obtained 3 times, and the average is used.
Recumbent length	Participant lies supine on a length board on a flat surface. The measure is taken from the crown of the head to the base of the feet. Staff assists with leg extension or ankle dorsiflexion if there are orthopedic issues. Each measure is obtained 3 times, and the average is used.
Knee height	With the participant seated with the knee at a 90° angle, the fixed blade of the caliper is placed at the distal end of the calcaneus and the sliding blade is placed on the anterior side of the distal condyle of the femur, with the caliper shaft aligned with the tibia [30]. Each measure is obtained 3 times, and the average is used.
Ulnar length	While the participant is seated, the forearm rests on the table with the palm down, fingers extended, and elbow bent 90° to 110°. A measure is taken from the elbow (olecranon process) to the wrist (styloid process) with an anthropometer or measuring tape [44]. Each measure is obtained 3 times, and the average is used.

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Textbox 1. Body composition and energy expenditure assessment.

Measure and procedural process

- Waist circumference: measure at 2 different landmarks—the umbilicus and immediately above the right iliac crest at the midaxillary line—using a flexible tape measure. Measures are obtained in recumbent position and standing (if able to stand) and to the nearest 0.1 cm 3 times, and the average is used.
- Bioelectrical impedance analysis (BIA): confirm no vigorous physical activity, food, or substantial drink for a minimum of 3 hours. Using an InBody S10 BIA machine, place electrodes on the youth's extremities and have them sit for 10 minutes before the first measure. Manually input the youth's height and weight and then obtain the measure (approximately 40 seconds to complete). Repeat assessment using the average of each height measure (standing, arm span, recumbent, knee height, and ulnar length).
- 4-site skinfolds: skinfold calipers are used to pinch fat at 4 body landmarks (triceps, biceps, suprailiac, and subscapular). Each skinfold measure is obtained 3 times, and the average is used.
- Doubly labeled water (DLW): verify a minimum of 6 hours of fasting or light fluid ingestion. Approximately 1-3 oz of DLW (dosed on body weight) are consumed. After drinking the DLW, 50 mL of drinking water are added to the empty bottle and consumed by the youth. On day 1, urine or saliva specimens are collected at baseline (before DLW) and hours 1 (discarded), 3 (kept), and 4 (kept) after consuming DLW. The family collects 2 urine or saliva specimens 1 hour apart on day 7 with the provided supplies and mails the specimens back to the study site.
- Dual-energy x-ray absorptiometry (DXA; only site 1): before the scan, female participants are screened for risk of pregnancy per hospital policy. If there is risk of pregnancy, the participant does not undergo DXA scan and continues with the remainder of the protocol. If the study participant has metal implants, they are excluded from the DXA scan as this is a contraindication. External artifacts are removed (eg, buttons, zippers, and jewelry). Hospital scrubs will be available if needed. With the participant lying supine on the open DXA table, the scan arm passes over the participant's body in a series of transverse scans from head to toe. If there is no risk of pregnancy in the parent, they are allowed to remain with the youth during the scan but asked to remain 1 meter away from the scanner.
- Resting metabolic cart (only site 1): this noninvasive test uses indirect calorimetry to measure resting metabolic rate [63]. This portable unit measures the concentration of oxygen and carbon dioxide in air streams entering and exiting a clear canopy tented over the youth. The participant lies quietly for 30 minutes before and during the test while respiratory gas exchange is measured and averaged. The youth is able to watch television with their parent from the bed with external distractions (eg, noise and lights) minimized.
- Accelerometer—measured physical activity: physical activity is measured using the ActiGraph GT3XP-BT accelerometer (ActiGraph LLC) provided on day 1 to be worn for the following 7 days on the participant's nondominant wrist and removed during water activities (eg, swimming and bathing) [64-67]. Raw data at 30 Hz are collected and converted to counts for analysis. During day-1 testing, participants perform a timed ramped protocol based on the individual's perceived exertion at baseline, light, moderate, and vigorous intensity levels aided by a validated pictorial perceived exertion chart that commiserates with their mobility status (eg, wheelchair or walking) [68].
- Heart rate monitor: heart rate during the timed ramped protocol is recorded using an electrocardiogram-based heart rate monitor (Polar H7; Polar Electro Inc) mounted on the participants' chest with an elastic band. Recorded heart rate is time stamp synced with the accelerometer data to provide a reference of measured physical activity intensity.
- Fat-free mass (FFM): FFM (kg) = total body water (TBW; kg)/hydration factor of FFM based on the child's age and sex [69]. FFM comprises all body components except fat or adipose tissue [54]. FFM contains 73.2% water in healthy adults, but in children, the hydration of FFM is higher and is based on age and sex as listed in the study by Fomon et al [70].
- Fat percentage: fat percentage=100 – (body weight – [TBW/hydration factor of FFM]). The hydration factor is based on the child's age and sex [69]. Fat percentage is defined as the percentage of body weight that is fat. The equation uses the hydration factor of FFM for children in the work by Fomon et al [70].
- TBW: TBW = ($[N_O/1.007] + [N_D/1.043]$)/2, where N_i= ([W × A/a] × [ΔDD/ΔBW])/1000 – cumulative fluid intake (kg) [60]. The water content of the body at birth is 70% to 75% but decreases in adulthood. Water (intra- and extracellular) is contained exclusively within the FFM [60]. The TBW is determined by measuring and adjusting the dilution space of oxygen-18 (N_O) and deuterium (N_D) in the body water pool using nonaqueous exchange values of 1.007 and 1.043 for each isotope, respectively. In the calculation, N_i is the dilution space for each isotope, "W" is the amount of water used to prepare the diluted dose, and "a" is the amount of isotopes used in the dilution. "A" is the dose of DLW consumed by the participant, ΔDD is the isotope enrichment measured in diluted dose, and "ΔBW" is the plateau enrichment measured in body water based on day 0 [60].
- Total energy expenditure (TEE) and total daily energy expenditure (TDEE): TEE (kcal/day) = rCO_2x (1.106 + 3.94/RQ). TEE is the total energy used by our body to maintain life [71], including basal metabolic rate, the thermic effect of food, and physical activity (and growth in children) [56]. In the TEE calculation, the rate of carbon dioxide production (rCO_2) is based on the body's elimination of isotopes (rCO_2= 0.4554 × TBW × [(1.007 × k_O) – (1.043 × k_D)] × 22.26, in which 22.26 is the gas constant for carbon dioxide in L/mol), and RQ is the respiratory quotient estimated from typical diet [72]. In our study, TEE is measured over 7 days and averaged to obtain the TDEE.

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Textbox 2. Instruments.

Pubertal status

- Youth pubertal status by parent report is based on a pictorial and written definition of Tanner stages 1 to 5 (development of external genitalia for male individuals and breast development for female individuals).
- Tanner stage 1=prepubertal and stages 2 to 5=pubertal. The purpose for this study is not specificity of stage but to discern prepubertal vs pubertal stages. Parent report of youth was valid when compared to health care provider assessment (r=0.75 to r=0.87; P≤.001;k=0.13-0.55) [73].

Screener—measured nutrition

- Block Kids Food Screener (version 2; NutritionQuest, 2007). The screener is self-administered to the child with parent assistance, as needed. The screener takes approximately 10 to 12 minutes to complete [74]. This 41-item screening instrument assesses intake by food group by amount (3-point scale) and frequency (6-point scale) consumed in the last 7 days. When compared to 24-hour dietary recalls, they were correlated between 0.526 for vegetables and 0.878 for potatoes. Bland-Altman plots indicated no systematic difference between the 2 based on food groups [75].

Function

- Pediatric Evaluation of Disability Inventory–Computerized Adaptive Test (PEDI-CAT; CREcare, LLC; 2007). The PEDI-CAT measures abilities in the ages of 2 to 21 years in 3 functional domains—daily activities, mobility, and social or cognitive—and a responsibility domain. Uses the item response theory statistical model to estimate the ability from a minimal number of most relevant items. It has positive reliability (intraclass correlation coefficient=0.96-0.99) and discriminant validity between children with and without disabilities (P<.001) and a mean completion time of 12.66 (SD 4.47) minutes [76].

Screener—measured physical activity

- Block Kids Physical Activity Screener (NutritionQuest, 2003). This 9-item screening tool assesses the frequency (6-point scale) and duration (4-point scale) of physical and sedentary activity in the last 7 days. The tool was validated for children aged 8 to 17 years, so it is not used with our participants aged 5 to 7 years. It takes approximately 5 minutes to complete.
- When used to estimate kilocalories based on weight, age, intensity, frequency, and duration in 48 children against an accelerometer, partial correlations (controlling for age and weight) were significant (r=0.56; P<.001) [77].
- Without a validated measure of physical activity for youth with disabilities, special considerations are taken with this instrument, and accelerometers are used to obtain an objective measure of activity. Participants are directed to substitute wheelchair options in the questions (ie, substitute wheeling for walking). We added 1 question asking youth to share any activities performed in the last 7 days that were otherwise not captured.

Demographic form (parent completed)

- Youth demographics include age (month and year), ethnicity, gender, level of education, participation in school health service plan, level of lesion, mobility status, assistive devices used for mobility, and concurrent diagnoses.
- Parental or legal guardian demographics include age, marital status, relationship to child, family income, educational level, ethnicity, and work status.

Post–day 1 survey

- Parents complete questions related to measurements performed during day 1, weight management in children with spina bifida, stress, and quality of life. The child (aged ≥12 years) completes 3 questions related to quality of life.

Patient-Reported Outcomes Measurement Information System (PROMIS) parent-proxy peer relationships

- A validated PROMIS questionnaire that includes 7 questions related to the child's peer relationships is answered by the parent using a 5-point scale from never to almost always.

Accelerometer and sample collection log

- A 2-page log is provided to the family before leaving the day-1 visit. This log allows for the documentation of when the accelerometer was not worn and why, any unusual notes (eg, illness or unusual activities), and reminders for the day-7 urine or saliva sample collections.

Procedures

After agreeing to participate (see the *Recruitment* section), consenting and assenting is completed, and a 5-hour morning appointment on day 1 is scheduled. A reminder call is placed to the family before the visit to review the study protocol and fasting requirements and answer any questions. On the day of the visit, the fasting status of the child is confirmed, and standard-of-care vital signs are obtained, including a baseline heart rate, blood pressure, and respiratory rate. The youth's weight (wheelchair or standing based on mobility status) is obtained and used to verify the accurate dosing of DLW.

A baseline urine or saliva sample (participant's choice) is obtained. The method of urine collection depends on the youth's home bladder regimen. If they typically perform clean intermittent catheterization, catheters are provided for them (or their parent) to collect urine; if they typically void, a clean catch in a clean urine hat is completed. If they prefer to provide a

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saliva sample, they are asked to collect 2 to 3 mL of saliva in a tube.

After baseline urine or saliva sample collection and measurement of weight, DLW is dosed based on the youth's weight and provided to the youth (1-3 oz depending on the youth's weight) in a sterilized bottle provided by the laboratory and requested to be consumed using a straw. After drinking the DLW, 50 mL of drinking water are added to the empty DLW bottle and swished around, and the youth is asked to drink the added water to ensure that the DLW was completely consumed. Subsequent urine and saliva collection are conducted at hours 1 (only urine), 3, and 4 after consumption of DLW. The hour-1 sample is collected but discarded as the urine is not isotopically equilibrated with body water at this time and no saliva is collected at this time. The hour-3 and hour-4 samples are collected, timed, and saved for analysis. After hour 1 or between hours 1 and 3, the youth is offered a small snack that is consistent with the caloric requirements (≤250 kcal) of the DLW protocol, such as a granola bar, prepackaged snack, or small can of PediaSure supplement, and up to 8 oz of water.

Between timed urine or saliva samples, up to 5 measures of height (stadiometer [if able to stand], arm span [adjusted by level of lesion], recumbent length, knee height, and ulnar length) and 3 additional measures of alternative body composition beyond DLW (waist circumference, 4-site skinfold, and BIA) are collected. In addition, for participants at site 1, the child has a resting metabolic cart and a DXA scan performed in the hospital's radiology department if no contraindications are present (eg, metal implants in the body). The resting metabolic cart measurement is completed as the resting metabolic rate is the largest contributor to TDEE. The DXA scan is used to address potential age-related variation in bone mass and hydration and provides coefficients between the DXA and TBW, eliminating concern of variance [69]. All sites conduct a ramped protocol while the study participant wears an accelerometer on their nondominant wrist and a heart rate monitor. The ramped protocol includes walking or wheeling in their wheelchair (based on ambulatory status) for set periods at different levels of intensity (eg, sedentary, light, and moderate to vigorous). Activities include 5 minutes each for sitting quietly and playing with Legos for arm movement, walking or wheeling slowly, and walking or wheeling at a normal pace. The final activity includes walking or wheeling at a fast pace for 6 minutes. After each activity, the child is asked to rate their perceived level of exertion using a pictorial scale [68].

Parents complete the demographic form, including a report of the youth's Tanner stage, a post–day 1 survey that includes questions on the measurements performed and weight management in children with SB, the Patient Reported Outcomes Measurement Information System parent-proxy peer relationships questionnaire to assess their child's peer relationships, and the Pediatric Evaluation of Disability Inventory–Computerized Adaptive Test survey related to their child's function. Youths, with parental assistance as needed, complete the nutrition screener and physical activity screener. The physical activity screener was developed for youths aged 8 to 18 years, so youths aged between 5 and 7 years will not be assessed using this instrument.

Before the end of the day-1 appointment, the family receives a "participant kit" containing all materials needed for urine or saliva collection at home: sterile urine cups and urine hats or saliva collection tubes, labels with participant ID number and space for time and date of collection to be completed, and appropriate-sized catheter if the participant uses it. In addition, the participants are asked to continue wearing the accelerometer provided on their nondominant wrist for the following 7 days. They are provided an accelerometer wear and sample collection log to document when and why the accelerometer was removed and reminders for day-7 urine or saliva sample collection. At the end of the day-1 visit, the family receives a US $100 gift card in return for their time and travel, a US $25 hospital cafeteria voucher, and any additional site-specific gift cards (eg, parking or travel).

On day 7, the participants are asked to collect 2 urine or saliva samples 1 hour apart as close to their original appointment time of day as possible. Families keep urine or saliva samples refrigerated until they are able to mail them back along with their accelerometer to their original collection site using prepaid and addressed mailers and packing materials that are provided. After the study team receives the final samples, the family is mailed their second and final gift card for US $150. The gift card at the end of the study is emailed or mailed based on the participants' preference. If mailed, the cards are sent through the US Postal Service and require a signed signature for receipt of mail. Table 3 provides a summary of the protocol.

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Table 3. Study protocol overview.

Study date	Description
Before day-1 study date	
Recruitment	• Recruit participants and obtain consent and assent. • Study team members complete enrollment questions as to their assessment of whether the recruited participant enrolled in the study or chose not to and the possible reasons.
Preparation	• Confirm appointment date and time, fasting requirements, no active illness, catheter size, and estimate of youth body weight.
Day 1—appointment day with participant	

Day-1 study visit	• Consent and assent, if not completed during recruitment.
	  • Obtain body weight × 1.
	  • Obtain pre-DLW[a] baseline urine or saliva sample. Sample is timed and stored.
	  • Provide DLW based on body weight.
	  • After DLW consumption, obtain urine or saliva at hour 1 (discard), hour 3 (time and store), and hour 4 (time and store).
	• Between urine or saliva collections, obtain height, body composition, and additional measures:
	  • Arm span, recumbent length, ulnar length, knee height, and stadiometer (if able to stand; each × 3) are obtained.
	  • Waist circumference and skinfold measures (each × 3); bioelectrical impedance analysis with each height measure are obtained.
	  • Vital signs (heart rate, blood pressure, and respiratory rate) are obtained.
	  • Ramped protocol of perceived exertion while wearing an accelerometer and heart rate monitor are obtained.
	  • Resting metabolic cart is obtained at 1 site.
	  • DXA[b] scan is obtained at 1 site if no medical contraindications are present.
	• Snack:
	  • Provide snack option (meal replacement drink [PediaSure] or prepackaged snack [≤240 kcal] and ≤8 oz of water) to the participant.
	• Surveys:
	  • Parents complete demographics, PEDI-CAT[c], post–day 1 survey, and Tanner stage of youth questions.
	  • Youth aged 8-18 years (with parent assistance as needed complete the Block Kids Physical Activity Screener.
	  • Youth aged 5-18 years (with parent assistance as needed) complete the Block Kids Food Screener.
	• Before leaving the clinic:
	  • Provide the family with the Participant Kit; review materials and day-7 urine or saliva collection, mailing instructions, and research team contact information.
	  • Remove the heart rate monitor.
	  • Review the use of the accelerometer to be worn on the nondominant wrist for 7 days except when bathing, swimming, or showering.
	  • Provide a US $100 gift card, a US $25 cafeteria gift card, and any additional site-specific gift cards to the family for day 1.

Day 5 and 6	• Call or SMS text message to family to remind them to collect day-7 urine samples and review mailing instructions for urine or saliva samples and accelerometers to be mailed back to the collection site.
Day 7	• Family collects 2 urine or saliva samples and mails back samples and accelerometer.
After day 7	• Upon receipt, confirm obtaining samples and accelerometer. Disinfect the accelerometer; process samples; and complete study documentation, including notification that the final gift card can be sent to the family.

[a]DLW: doubly labeled water.

[b]DXA: dual x-ray absorptiometry.

[c]PEDI-CAT: Pediatric Evaluation of Disability Inventory–Computerized Adaptive Test.

Data Analysis

Descriptive statistics, including mean, SD, median, and range, will be calculated for each variable or measurement. When analyzing arm span, knee height, ulnar length, waist circumference, and skinfolds, additional analysis or equations will be used based on the literature [30,38-41,43-48,50-52,78,79]. For BMI (kg/m^2) and bioelectrical impedance measures, the average of each surrogate height measure will be used. Arm span can be used as a direct measure

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of height if there is no leg muscle mass loss (low-level lesions), or it can be modified if there are higher-level lesions and variations in leg muscle mass. If there is partial leg muscle loss (midlevel lesions), arm span × 0.95 can be used; with high-level lesions and complete leg muscle loss (thoracic-level lesion), arm span × 0.90 will be used. We will consider use of the measured arm span with and without the adjustment based on the level of lesion for our analysis. For knee height, 3 prediction equations developed for use with individuals with mobility impairment (cerebral palsy and Duchenne muscular dystrophy) [43-45] will be used. For ulnar length, a prediction equation using the ulnar length and age of the youth will be used [44].

For aim 1, Bland-Altman plot analysis and concordance correlation will evaluate the agreement between DLW body fat percentage and modified BMI, waist circumference, BIA, and skinfold measures. This marginal association analysis will also provide information for the relationship between different measures (linear, quadratic, and nonlinear association). To construct an algorithm that can predict body fat percentage, we will first choose the measures of skinfold thickness at 4 sites in our base model using the equations by Jackson and Pollock [79], Slaughter et al [51], and Gurka et al [78] that have been successfully applied to several adolescent populations [80]. To further improve accuracy, we will construct linear gender-specific regression models by considering the modified BMI (eg, weight or arm span and weight or ulnar length), FFM, waist circumference, mobility status, race, age, or pubertal status as potential predictor variables. Stepwise linear regression and all-possible-subsets regression procedures will be used to develop prediction equations. Potential interactions between age, race, and other variables will be examined. The Mallow Cp statistic and the Schwarz-Bayesian criterion will be used to select the appropriate models. The resulting predicted body fat percentage is a weighted sum of a subset of those potential predictors, where the weights are the parameter estimates associated with each predictor in the regression model. Predictive accuracy will be evaluated using the mean square error through a 10-fold cross-validation; all the samples will be randomly split into 10 parts, 9 folds of the samples will be used to build the regression model, and the remaining hold-out samples will be used to test the predictive accuracy between the predicted and DLW body fat percentage. This procedure will be repeated until all the samples are tested. Upon completion of our body fat percentage algorithm, we can use the distribution of this metric to categorize weight status (obesity, overweight, and normal weight) by selecting appropriate cutoff points. The determination of cutoff points to use for the categorization of the weight status was thoughtful and deliberate. While there are no accepted cutoff points for body fat percentage to define obesity or other weight categories for youth, we will use cutoff points based on body fat percentages correlated to BMI percentiles presented by McCarthy et al [81] that are age specific to account for the growth and development of the child. We will use the agreed-upon criteria for categorizing weight status: body fat percentage between 85% and 94% for overweight, ≥95% for obesity, and 5% to 84% for normal weight [19].

For aim 2, we will predict TDEE by estimating BMR and physical activity level and using these as our primary predictors. Several BMR equations from cross-sectional studies with good model performance (ie, R^2=0.7-0.8) have been reported [82] that mainly used age, FFM, FM, and weight as key predictors. Thus, we will use those as our base model predictors and further consider height, race, gender, assistive devices used in ambulation, pubertal status, and mobility as potential predictors. Furthermore, the subset of 42 participants who will undergo a resting metabolic cart to measure resting energy expenditure will provide additional data to construct an equation for predicting TDEE in SB. The model selection procedure and predictive accuracy will be evaluated as described in the statistical methods for aim 1. Once the best BMR equation is identified, TDEE will be estimated as a weighted sum of estimated BMR and physical activity level. To handle the missing data issue, regression analysis will be conducted under multiple imputation under the missing-at-random (MAR) assumption [83]. Sensitivity analysis will be conducted to check for potential violation of the MAR assumption [84]. Simulation under MAR will be conducted to quantify the efficiency loss, defined as $1 - E(\hat{Y}[X^*] - Y)2/E(\hat{Y}[X] - Y)^2$, where X^* represents the observed data and X is the data with missingness. The exploratory aim based on the Block food and physical activity screeners will be analyzed through NutritionQuest. Descriptive analysis on frequency and duration of physical activities, sedentary activity, and youths' dietary intake by food groups and servings will be presented. Raw accelerometer data are collected at 30 Hz and converted to counts through ActiGraph's proprietary software (ActiLife; ActiGraph LLC). Analysis will include calibration of individualized activity counts aided by 20-minute ramped protocol data based on the perceived exertion of the youth and measured heart rate. The Block Kids Physical Activity Screener will complement the objective accelerometer data.

Power Analysis

The power calculation was based on the increased coefficient of determination (R^2) from a baseline simple linear model to a multivariate model that regresses body fat percentage on potential predictors (ie, alternate height, BMI, race, and age). Pilot studies from the literature suggest that the correlation between the body fat percentage measured using DLW and alternate height (arm span and recumbent length) is in the range of approximately 0.6 to 0.7 (R^2=0.36-0.49). As we will use 10-fold cross-validation to construct our predictive models for 2 gender groups, a sample size of 94 (232/2 × 0.9 × 0.9) achieves 90% power to detect an increase of $R^2 \geq 0.066$ (0.078) attributed to 1 (2) independent variable(s) using an F test with a significance level of .05. The variables tested are adjusted for 1 independent variable in the simple linear model with an R^2 of 0.36. We assume that 10% of the participants will not complete all measures based on pilot data. Because it is likely that we will include >2 additional variables in the final model, the proposed sample size will have sufficient power to detect a clinically meaningful increase in R^2.

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Data Storage

Data are collected and stored using REDCap (Research Electronic Data Capture; Vanderbilt University) [85]. Through REDCap, individual levels of privilege and access can be granted to study team members based on need. This database provides menu-driven options and built-in checks and generates reports. All data are checked for accuracy through biweekly reports run by the lead study coordinator. Signed consent or assent forms are kept in a locked file cabinet in the office of each site's lead investigator and are separate from deidentified study data. REDCap projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by team members, with planning assistance from the administrator. The development and testing process results in a well-planned data collection strategy. The REDCap server is housed in a local data center of the lead study coordinator, and all web-based information transmission is encrypted with a 256-bit Secure Sockets Layer certificate. Data backups are performed nightly and stored in a separate location.

Ethical Considerations

This human participant study was reviewed and approved by the Western IRB–Copernicus Group (20190134). Informed consent from a parent or legal guardian for all participants and assent for participating children aged ≥7 years is obtained by a trained staff member who has experience working with children. All documents are IRB approved and provided in English and Spanish based on the needs of the family. During the consent and assent process, it is reiterated that participation is voluntary and that there will be no consequences if they do not participate or complete the study. Signed consent and assent forms are kept in a locked file cabinet in each lead site investigator's locked office, and a copy is provided to each family. The confidentiality and privacy of the participants' information is protected by deidentifying the data and through the use of a secure, encrypted, and password-protected database for storage. Compensation for participation is provided using gift cards at 2 time points of the protocol. The monetary value reflects the participants' time and effort required to complete the study protocol. To reduce family burden, an optional gift card of up to US $125 is available if needed to support travel costs to the study site or associated childcare costs. The amount is determined by each site based on their geographical region, distance to the study site, and associated travel costs.

Results

This study was funded in July 2019, and training and study preparation occurred until February 2020. Data collection was initiated in March 2020 but then halted due to the COVID-19 outbreak, with a staggered and slow reintroduction initiated in September 2020 based on each organization's policies and state mandates. During the COVID-19 outbreak, a 6-month midproject extension was provided by the funding agency that extended our study end date to November 30, 2024.

Recruitment challenges after the COVID-19 pandemic have persisted. While the incidence of COVID-19 has diminished across the United States, secondary effects are noted. This includes an increased turnover of research staff and a reduced number of patients being seen in the clinical setting for in-person appointments. At the beginning of the fourth year of the grant (December 2022), one of the 4 clinical sites withdrew secondary to increased challenges related to enrollment of participants. A new data collection site was added to replace the discontinued site. A subaward was successfully executed, and the site's involvement was reviewed and approved by the IRB of record and at their local level. The team was onboarded with one-on-one training and set up with equipment required for the protocol. This process was completed over a 5-month period, with initiation of data collection occurring in late spring 2023.

As of April 2024, a total of 143 participants (female participants: n=76, 53.1%; male participants: n=67, 46.9%; Hispanic participants: n=52, 36.4%) have been enrolled. Recruitment and enrollment strategies are anticipated to continue until year 5, with a planned request for a no-cost extension year (December 2024-November 2025). The no-cost extension year will be used to complete analysis and initiate dissemination. Cleaning of data and preliminary analysis have begun and support a low rate of missing data and retention of participants throughout the 7-day protocol.

Discussion

Expected Findings

The aims of this study are to develop 2 algorithms for use in youth with SB in a clinical setting, one to model body fat and one to predict TDEE. In addition, the physical activity and dietary intake of the sample will be described. To increase the generalizability of the findings, the goal is to recruit a diverse sample of youths aged between 5 and 18 years who are diagnosed with myelomeningocele, the most severe type of SB. This population has an increased prevalence of overweight and obesity that influences their physical health, mobility, and level of independence.

Data cleaning and preliminary analysis have documented that there are limited missing data and a high retention of study participants who start the protocol. Current enrollment of 61.6% (143/232) of the proposed sample is on target to reach the goal of including 25.9% (60/232) of participants who self-identify as Hispanic.

Challenges encountered have primarily centered on COVID-19. Since this research project was funded, the COVID-19 pandemic drastically altered clinical programs and, thus, recruitment and data collection. COVID-19 affected the number of health care staff in all settings, resulting in overloads, reduced clinical activities, and unexpected vacancies in key clinic management and study personnel, thus hampering the implementation of the project in some sites. Although each of the clinical sites' research compliance mechanisms differed, research at all sites was completely suspended for multiple months, with variability by site for resumption of research activities (recruitment and data collection). Each program or organization limited the number of research personnel allowed in clinical settings and the scope of recruitment activities upon resumption, which varied by site. In addition, telehealth drastically reduced clinic attendance in some settings. Finally, travel to sites for training

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and validation of data collection was challenged by the pandemic.

Although a 6-month extension of year 2 was obtained from the funding agency (National Institutes of Health/NICHD), recruitment remained variable and reduced at each of the study sites. Concurrent to the disruption of clinical processes for conducting research, families experienced challenges with school programs altering attendance and having multiple children at home, and more clinic participants lived a substantial distance from the clinic than was originally anticipated. Families voiced concerns about (1) childcare as clinical and research settings were allowing only 1 adult and no siblings to attend data collection, (2) the risk of public mass transit, (3) the cost of alternative transportation, and (4) difficulty traveling to the data collection site for early-morning appointments necessitated by the 6-hour preappointment fast. These concerns prompted amendments to the study protocol related to participant reimbursement and discontinuing data collection at 1 site and adding a new site.

Despite the unforeseen challenges, the strengths of this study are notable. We are the first to convene a sample of youth with SB to develop an algorithm that incorporates clinically available, cost-effective, but not yet validated measures of height or body composition to accurately model body fat percentage in this population and estimate TDEE. In addition, the purposive recruitment from clinics located in different regions allows for stratification by age and mobility status and provides representation of ethnicity while providing an adequately powered sample to test the aims. The use of DLW, a validated noninvasive measure, as the criterion for body fat percentage and TDEE increases the study's rigor. The use of a DXA scan in a subgroup of the sample allows for a second comparison of body fat percentage and FFM between DLW and DXA, decreasing concerns of depending on a 2-compartment body water method in this unique population. Limitations include the lower-than-expected enrollment at the time of this publication. The team continues to strategize on methods to further recruitment and enrollment within the timeline of the grant. The findings will enhance the screening, prevention, and treatment of an abnormal weight by facilitating the accurate identification of the youths' weight status and allow for recommendations of daily caloric needs to be provided for this population at a higher risk of having obesity. With the ability to accurately estimate body fat percentage, we can accurately categorize weight status and monitor weight trends longitudinally. Furthermore, our findings in youth with SB have the potential to impact outcomes for youth diagnosed with disabilities other than SB who experience similar challenges related to alterations in body composition or fat distribution or measurement challenges secondary to mobility issues or musculoskeletal problems. The NICHD research agenda that prioritized weight management for youth with disabilities was not limited to SB but included youth with a variety of intellectual and physical disabilities [28]. The successful execution of this study, methodological approach, and dissemination of the findings will shift current research and clinical practice paradigms as well as raise awareness for the need to conduct future studies in this area. Furthermore, the measures used in the proposed research will serve as a framework for use with children in other diagnostic categories and, thus, will make a major contribution to science.

Dissemination of the study findings will be a priority. Outcomes will be shared with national SB organizations (ie, Spina Bifida Association); the Centers for Disease Control and Prevention NSBPR national and international conferences focused on SB, weight management, and developmental disabilities; manuscripts; and individual and family organizations. Future directions for this work will be to test the application of these algorithms in youth with SB and expand this work to adults with SB. The outcomes of this study will also be implemented in weight management interventions.

Conclusions

This innovative study will provide 2 clinically accessible and feasible algorithms related to body fat and TDEE. The lack of an accurate clinically available and cost-effective method to measure body fat and the inability to provide daily caloric recommendations obstruct the advancement of the science of weight management of youth with SB. These foundational deficiencies significantly impede successful prevention and treatment of obesity for this vulnerable population. The outcomes of this study will advance the science of weight management in individuals with disabilities, address national research priorities, and shift clinical practice paradigms.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study protocol.

Conflicts of Interest

None declared.

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Abbreviations

BIA: bioelectrical impedance analysis
BMR: basal metabolic rate
DLW: doubly labeled water
DXA: dual x-ray absorptiometry
FFM: fat-free mass
FM: fat mass
IRB: institutional review board
MAR: missing-at-random
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NSBPR: National Spina Bifida Patient Registry
REDCap: Research Electronic Data Capture

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SB: spina bifida
TBW: total body water
TD: typically developing
TDEE: total daily energy expenditure

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Protocol

Gender Inequalities of Health and Quality of Life in Informal Caregivers in Spain: Protocol for the Longitudinal and Multicenter CUIDAR-SE Study

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Abstract

Background: The aging population and increased disability prevalence in Spain have heightened the demand for long-term care. Informal caregiving, primarily performed by women, plays a crucial role in this scenario. This protocol outlines the CUIDAR-SE study, focusing on the gender-specific impact of informal caregiving on health and quality of life among caregivers in Andalusia and the Basque Country from 2013 to 2024.

Objective: This study aims to analyze the gender differences in health and quality of life indicators of informal caregivers residing in 2 Spanish autonomous communities (Granada, Andalusia, and Gipuzkoa; Basque Country) and their evolution over time, in relation to the characteristics of caregivers, the caregiving situation, and support received.

Methods: The CUIDAR-SE study uses a longitudinal, multicenter design across 3 phases, tracking health and quality of life indicators among informal caregivers. Using a questionnaire adapted to the Spanish context that uses validated scales and multilevel analysis, the research captures changes in caregivers' experiences amid societal crises, notably the 2008 economic crisis and the COVID-19 pandemic. A multistage randomized cluster sampling technique is used to minimize study design effects.

Results: Funding for the CUIDAR-SE study was in 3 phases starting in January 2013, 2017, and 2021, spanning a 10-year period. Data collection commenced in 2013 and continued annually, except for 2016 and 2020 due to financial and pandemic-related challenges. As of March 2024, a total of 1294 participants have been enrolled, with data collection ongoing for 2023. Initial data analysis focused on gender disparities in caregiver health, quality of life, burden, perceived needs, and received support, with results from phase I published. Currently, analysis is ongoing for phases II and III, as well as longitudinal analysis across all phases.

Conclusions: This protocol aims to provide comprehensive insights into caregiving dynamics and caregivers' experiences over time, as well as understand the role of caregiving on gender inequality in health, considering regional variations. Despite limitations in participant recruitment, focusing on registered caregivers, the study offers a detailed exploration of the health impacts of caregiving in Spain. The incorporation of a gender perspective and the examination of diverse contextual factors enrich the study's depth, contributing significantly to the discourse on caregiving health complexities in Spain.

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KEYWORDS

caregivers; gender equity; sex differences; health status; quality of life; longitudinal studies; multicenter studies

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Introduction

Caregiving in the International and Spanish Context

In recent decades, Spain has witnessed significant demographic changes, marked by an aging population and a notable prevalence of disability among older adults [1]. With the highest percentage of older adults in the Organisation for Economic Co-operation and Development (OECD), at 5% older than 80 years, Spain's aging population is expected to double by 2050, leading to a 6-fold increase in public spending on long-term care (LTC) [2]. In addition, Spain is home to 4,380,000 people with disabilities as of 2020 where over 2 million receive personal or supervised care [3].

In the context of this study, informal care is defined as care activities carried out by people in the dependent person's immediate environment (relatives, friends, or neighbors), in a nonprofessional manner and who do not receive remuneration for the work they do (although they may sometimes benefit from financial benefits). Informal care is a pillar of LTC systems among OECD countries [4]. It is estimated that across 23 OECD countries, around 14% of people over 50 provide informal care on a daily or weekly basis [4]. In the European Union, it is estimated that between 12% and 18% of the adult population aged 18-75 years provide informal care on a daily or weekly basis [4]. Informal caregivers in Spain formed 12.4% of working people aged 18-64 years [5]. Spain's LTC landscape encompasses family-centric caregiving, often supplemented by domestic service employment, particularly among immigrant women [6]. Regional variations in this trend stem from differing government priorities, provision levels, labor market dynamics, and caregiving cultures.

Gender Differences in Informal Caregiving and Its Impact on Health and Quality of Life

The nature of informal caregiving includes its lack of visibility and social recognition. This informal caregiving is tied to personal relationships, domestic in nature, and predominantly carried out by women, which leads to being undervalued socially and economically [7]. Most of the informal care across 25 OECD countries is performed by women, where women represent 60% of daily caregivers [4]. The share of women caregivers is higher in South European OECD countries, with women being 76% of daily informal caregivers in Spain [4]. Gender roles are key, with women in Spain mainly taking on caregiving responsibilities, in addition to handling domestic tasks and sharing close kinship ties with those they care for [8-10].

Gender disparities extend to the type and amount of care provided. Women caregivers are more likely to provide personal care, companionship, and monitoring, often in intensive ways, while juggling family and work obligations, in comparison to men [11]. Despite its societal importance, caregiving can negatively impact caregivers' physical and mental health due to chronic stress from the physical and emotional burden [11-14]. Factors such as the cared-for person's disability type and behavioral issues, especially dementia, alongside the care type and intensity, contribute to caregiver stress and health issues [11-19]. These effects on health can manifest as poor physical health, mental health challenges, unhealthy habits, and even premature death [11-19]. Variables like gender, age, socioeconomic status, and social support play a role in moderating these effects [11]. However, population-based studies show that almost one-third of caregivers do not experience negative impacts, particularly in the early caregiving stages [20].

Caregiving also affects other quality of life dimensions. It often reduces employment opportunities, leads to fewer work hours, and increases temporary work, affecting women more than men, and potentially increasing poverty risk [9,21]. Survey data in Spain highlight a higher prevalence of health, professional, economic, and personal problems due to the higher burden of caring [22]. The unequal burden on women's daily lives leads to higher stress, overload, and risk factors for their health [23-26]. Various studies confirm this pattern, indicating more psychiatric morbidity, depression, and poorer health perception among women caregivers [22-26]. However, while existing research underscores these trends, there is a need for further exploration through quantitative and qualitative methods [27].

Need for Follow-Up and Longitudinal Studies

While existing evidence highlights caregiving's impact on health and quality of life, many studies experience limitations like small sample sizes and cross-sectional designs, often lacking control over confounding factors, such as education or socioeconomic status. To comprehensively address these issues, longitudinal studies are imperative. These studies not only counter cross-sectional biases, such as the "healthy caregiver" bias, but also track caregivers' health and quality of life changes over the caregiving journey [28]. Additionally, a deeper understanding of varied caregiving experiences and their effects on caregivers' health is crucial [19]. Longitudinal research on these aspects remains limited in the Spanish context, and the factors influencing the impact of caregiving over time still require in-depth exploration.

The Importance of Crisis Contextualization

In recent decades, women's engagement in the workforce and formal care services for dependents have surged, yet the ongoing crisis is bucking this trend by shifting caregiving responsibilities back to households [29]. The reduction in formal care services may intensify informal caregiving, potentially overburdening caregivers. With escalating unemployment, particularly affecting women, the adverse impacts of caregiving on employment and finances will worsen, especially in a landscape of diminished public support services. This scenario is expected to detrimentally affect caregivers' health and well-being, especially among women [30]. Vulnerable groups like older adults, minors, dependents, and women will bear amplified health-related repercussions during crises [31]. Effective support networks, both formal and informal, can mitigate these effects, highlighting the importance of evaluating how informal networks, mainly family-based, impact women's health and quality of life as primary caregivers [32]. The study at hand was initiated in 2013, amidst the repercussions felt in the following years after the 2008 economic crisis which was then further compounded by the COVID-19 pandemic [33]. These 2 crises set the contextual

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background for the study, and therefore it is important to acknowledge these significant events' relevance in the realm of caregiving, and subsequently, in the study.

The CUIDAR-SE Study

CUIDAR - SE is the acronym derived from the terms care and follow - up ("cuidar" and "seguimiento" in Spanish) and is the abbreviated name of the project titled "Longitudinal study of women and men caregiver's health and quality of life in Andalusia and the Basque Country." This study was designed to analyze the effects of caregiving on different aspects of life, including health, in a sample of women and men providing informal care in Spain.

Its longitudinal analysis of quantitative data, with data collected 3 times every 12 months, in each of the 3 phases, allows the study to capture caregivers' experiences during both crises and their ongoing repercussions.

The CUIDAR-SE study also incorporates a gender approach in all its aspects, meaning not only in analysis with sex-disaggregated data but also in its design. The study was designed to conduct comparisons between women and men. This gender perspective has not been found as a focus in previous studies and therefore illustrates the study's importance.

Furthermore, this study is multicentric in nature. There are notable differences between the 2 contexts at hand. Andalusia (south of Spain) has been characterized in the last decades by being a "familistic regime with subsidized public support," with support primarily focused on economic benefits. Whereas in the Basque Country (north of Spain), following an "optional familist" model, other social protection services have been further developed to support care and there is a high participation in the domestic market [6,7]. In 2023, the public dependency system, in both regions, has granted more services to support care than economic benefits [34].

As the economic crisis impacts all regions, Andalusia appears to experience more pronounced effects than the Basque Country, potentially accentuating these disparities further. Consequently, this investigation is apt for addressing these dynamics in both contexts. The multidimensional approach facilitated by a multicenter design enriches the study's uniqueness and significance.

Objective

To analyze the gender differences in health and quality of life indicators of informal caregivers residing in 2 Spanish autonomous communities (Granada, Andalusia, and Gipuzkoa; Basque Country) and their evolution over time, in relation to the characteristics of caregivers, the caregiving situation, and the support received.

The CUIDAR-SE study is divided into 3 phases, currently in the CUIDAR-SE III phase. Each phase has its respective specific objectives demonstrated in Textbox 1.

Textbox 1. Specific objectives of the 3 phases of CUIDAR-SE study.

Phase I

- Describe the characteristics of the care situation and the indicators of health and quality of life at different times in the care process.
- Analyze the changes (evolution) produced in the health and quality of life of informal caregivers over time.
- Study the differences in the health and quality of life of women and men informal caregivers and their associated factors in relation to the characteristics of the informal caregivers.
- Compare the health and quality of life of women and men caregivers, as well as its evolution, in 2 different national contexts: Granada and Gipuzkoa.

Phase II

- Study the evolution of health-related quality of life and the burden of caregivers, based on the informal and formal support (financial benefits and services) received, analyzing the differences between women and men caregivers.
- Estimate the economic value of informal care time and its evolution during the care process, as well as the differences in this value depending on the sex of the caregivers, the support received, and the characteristics of the care provided (tasks and intensity).
- Compare the 2 provinces studied, the evolution of health-related quality of life and the burden of caregivers based on the formal and informal support received, and the economic value of care.

Phase III

- Analyze the evolution of perceived health, morbidity in chronic pathologies, and the mental health of women and men caregivers, based on the characteristics of the care provided and the support they receive.
- Know the differences between women and men informal caregivers in the use of health services for their own health needs, their medication use, and the evolution at different moments of the care process.
- Analyze the evolution of the problems derived from care, in women and men caregivers, related to aspects of health, work and professional, economic, leisure, free time, and family life, depending on the characteristics of the care they provide and the support they receive.
- Study the support needs experienced by women and men caregivers at different times in the care process, depending on the characteristics of the care they provide and the formal and informal support they receive.
- Compare Granada and Gipuzkoa the health indicators studied, use of health services, medication use, and problems and support needs exposed in the previous objectives.

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Methods

Design

This study is a multicenter (Granada, Andalusia, and Gipuzkoa; Basque Country) longitudinal repeated measures study where the caregiver population is followed up at 3 moments in time known as waves, each 12 months in duration, for each phase (I, II, and III) of the CUIDAR-SE study that initiated in 2013 and is ongoing.

Participants

Participants are composed of all persons aged 18 years or older living in family dwellings in the provinces of Granada and Gipuzkoa who provide unpaid care for a person in a situation of dependency and are co-inhabiting with the individual or not, among other criteria (Textbox 2).

Agreements with the institutions were made to ensure the availability of data on caregivers. From the registries listed (Textbox 2), participants for each phase of the CUIDAR-SE study have been selected using multistage randomized cluster sampling using municipalities as primary units, census sectors as secondary units, and caregivers as final units. The initial sample size calculations were 1180 people, however, due to resource limitations, the sample size was reduced, remaining an equal sample size in terms of sex and province (Table 1).

For each subsequent phase, participants who expressed their willingness to collaborate in future phases were retained. The ongoing follow-up involves the same initial cohort of participants, with the exception of additional individuals recruited during the inception of CUIDAR-SE II to address attrition observed at the conclusion of CUIDAR-SE I.

Textbox 2. Inclusion and exclusion criteria for participants in the CUIDAR-SE study.

Inclusion criteria

- Registered in the records of caregivers available in the health districts of Granada (Primary Care Health District) or in the Gipuzkoa Provincial Council (Social Services Registry) at the time of the beginning of the phase.

Exclusion criteria

- Presents characteristics that prevent answering the questionnaire in its language or a change of address is foreseen that prevents follow-up.

Table 1. Sample sizes and sex distribution of the phases of the CUIDAR-SE study (2013-2024).

Phase and waves	Gender		
	Men, n	Women, n	Total, n
Phase I			
2013	265	345	610
2014	208	259	467
2015	155	199	354
Phase II			
2017	361	478	839
2018	259	351	610
2019	184	254	438
Phase III			
2021	96	165	261
2022	57	98	155
2023 ongoing	51	99	150

Participant Recruitment and Follow-Up

The persons selected are initially contacted by means of a letter by those responsible for the registries, by which they will ask for permission from the persons contacted to participate in the study. Once permission is obtained, a member of the research team contacts the participants to describe the scope and objectives of the study, resolve their doubts, guarantee their participation, and request their consent. At the time of data collection, signed informed consent forms are collected. For those who do not consent, basic information is obtained to characterize their refusal to take part in the study.

Participant follow-up occurs at baseline, at 12 months, and at 24 months, for each phase of the CUIDAR-SE study. No new participants will be included after the start of each wave of the study. Participants may leave the follow-up process due to the following cases: (1) end of the follow-up period, (2) death of the caregiver, (3) definitive cessation of the caregiving situation (death or recovery of the cared-for person or cessation of the caregiver's role due to other circumstances), (4) relocation of

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residence outside the provinces of the study, and (5) any other circumstance that makes it impossible to locate the caregiver. The information collected on participants who have left the follow-up will be incorporated into the analysis if they have participated in at least 2 moments of measurement.

Survey Questionnaire Instrument

The questionnaire developed for the study "Health care in the domestic setting: care and caregivers in Andalusia" by García Calvente, 1999, proved useful to identify the health impact of caregiving tasks and its application in this project is considered very appropriate [10]. This questionnaire was updated and adapted to the objectives of the CUIDAR-SE study, considering, among other things such as context, the perception of the new aids instituted under the development of the Spanish Dependency Law. In addition, the scales EuroQol, the DUKE-UNC of 11 categories, the ZARIT scale of burden, and the GOLDBERG of 12 categories were selected for inclusion in the study questionnaire due to their widespread use in similar research endeavors and validation for use within our study context [35-38].

The finalized questionnaire was piloted during CUIDAR-SE phase I in a sample of 20 participants belonging to both provinces to guarantee its comprehension and adequacy. A summary of the structure of the questionnaire can be found in Table 2. The questionnaire was also later complemented with questions found in the 2008 EDAD; a survey on disability, personal autonomy, and situations of dependency conducted by the National Statistics Institute of Spain [39].

Table 2. Structure summary of the finalized questionnaire of the CUIDAR-SE study.

Block	Questionnaire structure	Subsections
I	Household structure and people in care	• Section A: Household structure • Section B: General characteristics of the care recipient
II	Characteristics and intensity of care	• Section C: Type of care (care tasks) • Section D: Specific tasks related to the use of health services for the care recipient • Section E: Frequency, intensity, and duration of care • Section F: Other domestic and care workloads of the caregiver • Section G: Burden
III	Support, needs, and demands	• Section H: Social support • Section I: Informal care support • Section J: Formal care support • Section K: Needs and demands
IV	General and mental health status	• Section L: General state of health • Section M: Morbidity, mental health, and medication use • Section N: Use of health services • Section O: Preventive practices • Section P: Healthy habits • Section Q: Satisfaction with life
V	Consequences of care on health and quality of life	• Section R: Impairment of health • Section S: Professional and labor aspects • Section T: Economic aspects • Section U: Aspects of leisure, free time, and family life • Section V: Perception of positive effects of care
VI	Contingent economic evaluation of care	—[a]
VII	Sociodemographic	—

[a]Not available.

Data Collection

A survey technique is used by conducting a personal interview with the caregiver, using the questionnaire. The questionnaire is applied by means of a personal interview at the caregiver's home, or, when this is not feasible, in-person at a care center (health or social services center, depending on the province). The interview is conducted by specially trained interviewers from a company specializing in nationwide surveying.

The research team provided training workshops to interviewers at the Andalusian School of Public Health, oriented toward understanding the structure and layout of the questionnaire and to provide context for the questions asked in the questionnaire. There is continual interaction between the research team and the interviewers during fieldwork, establishing a quality control protocol.

COVID-19 Implications

The collection was not completed in 2020 due to the COVID-19 pandemic, and therefore the first wave of phase CUIDAR-SE III was performed subsequently in 2021, 2022, and is currently ongoing. In-person interviews were replaced with telephone interviews using computer-assisted telephone interviewing in

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2021 and onward. Certain variables were eliminated to reduce the length of the telephone questionnaire, and questions regarding COVID-19 were added to explore different dimensions of the COVID-19 pandemic and their impact on self-perceived caregiver health and other aspects of life. This new questionnaire was piloted among 60 members of the current cohort to ensure the comprehensibility of each item and appropriate interview duration.

Data Analysis

The sampling units of the multistage randomized cluster sampling previously mentioned are stratified to reduce study design effects. Municipalities are stratified by size where allocation is proportional to the population of each corresponding municipality, and caregivers are stratified by sex. Data cleaning and aggregation of variables are conducted in accordance with the study objectives.

Every wave undergoes two kinds of analyses: (1) a cross-sectional analysis which includes descriptive and associative analysis between dependent and independent variables (Tables 3 and 4), using bivariate and multivariate logistic regression, and (2) a longitudinal analysis using multilevel analysis. Analysis with a gender perspective is also conducted. All analyses are performed in SPSS (IBM Corp).

Bivariate analysis is used to determine the prevalence of each dependent variable in relation to the independent ones. The respective associations are analyzed by logistic regression analysis with adjustment for age. Multivariate logistic regression analysis with calculation of odds ratios is performed to determine the likelihood of poor health (or another situation of quality of life) according to caregiving characteristics.

A combined model including men and women caregivers with adjustment for all other variables was built to analyze the association between sex and health or quality of life. Forward stepwise selection is used to add variables shown to be significant in the bivariate analysis and other relevant variables from the theoretical model. The same variables are used to build separate models for men and women caregivers to explore factors associated with the studied dependent variable. The magnitude of association in the 3 models is estimated using odds ratios with a CI of 95%. Variance inflation factor analysis rules out multicollinearity between the variables.

Table 3. Three categories of dependent variables: (1) health and health-related quality of life, (2) other dimensions of quality of life, and (3) economic value of informal care.

Category and dependent variables	Description
Variables related to health and health-related quality of life	
Health-related quality of life	EuroQol: EQ-5D-DL is a self-assessed questionnaire comprised of a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [35]
Perceived health	Likert: bad, fair, good, very good, and excellent
Deterioration of health because of care	Yes/no
Experiences a chronic disease	Yes/no, number and type of chronic diseases experienced
Mental health	GHQ-12[a] scale [38]
Lifestyles	Presenting unhealthy behaviors in at least one of the following factors: alcohol consumption, smoking, hours of sleep, physical activity, and diet
Burden	Zarit Caregiver Burden Scale validated for use in the Spanish population, consists of 22 questions and 5 possible answers scored from 1 to 5, which establishes 12 different degrees of overload depending on the score obtained: without overload, light overload, and intense overload [37]
Use of health care services	Yes/no, number and type of health care service used
Medication use	Yes/no, number and type of medications, prescribed or not
Variables related to other dimensions of quality of life	
Problems derived from care, in work, economic, leisure, and family life	Yes/no
Time to care for self, derived from care	Yes/no
Variable related to economic value of informal care	Value according to the willingness to pay for care and value according to the willingness to be compensated for care

[a]GHQ-12: 12-item general health questionnaire.

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Table 4. Three categories of independent variables: (1) caregiver characteristics, (2) caregiving situation, and (3) support received.

Category and independent variables	Description
Caregiver characteristics	
Sex	Male/female
Age	Continuous
Province of residence	Granada/Gipuzkoa
Place of residence	Rural/urban
Education level	Without studies: lower than primary, primary: EGB[a]/elementary, high school: FP[b]/BIP[c]/higher high school, superior: university or others
Employment situation	With paid work or without paid work
Social class	Five categories according to the occupation and according to the National Classification of Occupations of 1994 [40]
Health status prior to caregiving perceived	Good (excellent, very good, and good) and deficient (regular and bad)
Relationship between care recipient and the caregiver	Spouse/partner, child, father/mother, other
Lives with the care recipient	Yes/no
Caregiving situation	
Characteristics of the care recipient	
Sex	Male/female
Age	Continuous
Degree of dependency	Moderate dependency, severe dependency, and great dependency
Cognitive impairment or behavioral problems	Yes/no
Caregiving characteristics	
Type of tasks	Personal care, physical mobility, domestic or accompanying tasks within the home and in use of health services, care related to sickness, and tasks outside the home
Intensity	Daily hours of care
Frequency	Weekly days of care
Duration of care	Years of caring
Number of dependent people cared for	Number
Support received	
Informal support	Unpaid support from family or social environment: yes/no
Formal support	Formal support received in the last 12 months, financial benefit (FB) or home help (HH): without FB or HH, with FB without HH, without FB and with HH, with FB and HH.
Perceived social support	DUKE-UNC Social Support Index with 11 items validated for use in the Spanish population: low support if score ≤ 32, high social support if score >32 [36].

[a]EGB: Educación General Básica.

[b]FP: Formación Professional.

[c]BIP: ___.

To explore both how individual and group level factors influence trends observed over time, the combination of a longitudinal analysis using multilevel methods is used. The effect of the independent variables on each of the dependent variables is done by means of generalized linear mixed models of a binomial response when the dependent variable is qualitative, or Gaussian when the dependent variable is quantitative. This methodological approach allows for both the analysis of temporal variability in the measurements and heterogeneity among individuals, incorporating random effects into the model coefficients.

A contingent economic evaluation is performed as part of phase II, of which the methodology can be found in other papers from our research group [41].

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Ethical Considerations

The CUIDAR-SE study is conducted according to the guidelines outlined by the Declaration of Helsinki and the law for the protection of patients' rights (Law 15/2002). Clinical data are not collected as part of this study. Data collection procedures ensure confidentiality, with participant identifiers encrypted using numerical codes managed solely by the research team. These measures are implemented in strict accordance with the data protection laws and regulations in force (Organic Law 3/2018 of December 5, Protection of Personal Data and guarantee of digital rights). Ethical approval was granted by the Research Ethics Committee of Granada (Andalusia [Acta 2/2020]) and the Research Ethics Committee of Euskadi (Basque Country [PI2020068]). Participants provide their written informed consent to participate in the study and are assured anonymity and confidentiality. All data exchanges adhere to the most up-to-date European Union and national data protection regulations.

Results

The CUIDAR-SE study received funding for each phase of the study starting with phase I in January 2013, phase II in January 2017, and phase III in January 2021 to fund the ongoing 10-year project. Data collection started in 2013 and has continued every year, excluding 2016 due to financial constraints and 2020 due to the COVID-19 pandemic. Total enrollment for the CUIDAR-SE study as of March 2024 stands at 1294 participants. Data collection for the year 2023 is ongoing. There has been ongoing data analysis, initiated after the first wave of data collection in phase I, which investigates gender disparities in caregiver health, quality of life, burden, perceived needs and services, and support received. Results from the first phase have been published [21,41-44]. Currently, work is underway on the data collection of phase III, the data analysis of phases II and III, and on the longitudinal analysis of all phases.

Discussion

Contributions of the CUIDAR-SE Study

The CUIDAR-SE study is a pivotal research initiative that will delve into the multifaceted world of caregiving in Spain. With a rigorous longitudinal approach that encompasses 3 waves of data collection at 12-month intervals, for 3 different phases, the CUIDAR-SE study provides the opportunity to capture the evolving experiences of caregivers. Starting in 2013, against the backdrop of the 2008 economic crisis and later with the global COVID-19 pandemic, this temporal perspective enables a comprehensive understanding of caregiving impacts that appear with time within the context in which it occurs. Another distinctive feature of the CUIDAR-SE study is its commitment to incorporating a gender perspective in its design and analysis. This emphasis extends beyond sex-disaggregation of data, to a holistic integration of gender considerations, setting it apart from previous research endeavors in this domain and in Spain. By facilitating gender-based comparisons, the study allows for differential experiences of women and men caregivers to be captured, adding depth to the understanding of caregiving dynamics. Moreover, the CUIDAR-SE study's multicenter nature with collaboration between research groups with extensive involvement in the field of caregiving, positions it as a pioneering effort. The variation in caregiving contexts between the Andalusia and Basque Country regions allows for a more complex understanding of how different social norms, economic structures, and varying social service support systems influence caregiving.

While other longitudinal studies exist in this field, our study enhances the value of longitudinal design by integrating a gender perspective and fostering multicenter collaboration. This approach provides unique insights into the interplay of major societal events, regional contexts, and gender dynamics, thereby enriching the understanding of caregiving experiences and caregivers' roles more broadly.

Limitations

The CUIDAR-SE study, although primarily quantitative in nature, recognizes the value of incorporating qualitative methodologies to delve deeper into the impact of crises and social norms on caregiving. Past endeavors by the research team have involved the use of qualitative methods within this domain [45]. This experience underscores the team's commitment to continuing this methodological integration in future studies, with the aim of augmenting the findings of the CUIDAR-SE investigation and mitigating this methodological limitation. The prospect of incorporating mixed method approaches in future research endeavors holds substantial potential for enriching discourse within this field.

An important constraint inherent in longitudinal studies is that of lower-than-expected recruitment rates. Such limitations can impede the study's capacity for conducting comprehensive analyses and may introduce survival bias, particularly prevalent in studies of extended duration. To address this concern, the CUIDAR-SE study has used corrective measures, including a comparative examination of baseline characteristics between participants lost to follow-up to those retained within the study cohort. In addition, recruitment efforts during the inception of the CUIDAR-SE II phase aimed to replenish the participant pool with individuals with comparable characteristics to those recruited at the study's outset. We emphasize for future longitudinal studies of a long duration to prioritize not only a substantial initial sample size but also to consider budget allocations initially to accommodate potential recruitment challenges.

Participant recruitment, conducted through registration in the Primary Care Health District and Social Services Registry of Granada and Gipuzkoa, respectively may introduce variances in baseline characteristics. Methodological efforts are undertaken during the analysis phase to ensure the comparability of participants from the different regions, thereby homogenizing the study population. This is achieved by considering factors such as the degree of dependency of the person receiving care, the financial support received, and various sociodemographic characteristics of caregivers.

Another limitation of the CUIDAR-SE study is that all participants are solely registered caregivers. However, it is posited that individuals who opt not to register with the

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corresponding health district or social services registry likely allocate minimal time to caregiving or are of lower caregiving intensity. Thus, the caregiver profile in our study is that of a long-term caregiver providing high-intensity care. Extrapolation of future study results should be to caregivers with a similar profile, who we believe should be the priority target for support interventions.

Conclusions

The CUIDAR-SE study offers a thorough exploration of caregiving, using a longitudinal design across 3 waves of data collection. Its focus on gender dynamics and collaboration between regions provides valuable insights into caregiving experiences. While recruitment limitations exist, the study's emphasis on long-term caregivers highlights the need for crucial support interventions. Ultimately, CUIDAR-SE stands as a pioneering effort aimed at addressing the intricate facets of caregiving, not only within Spain, but also in other countries where caregivers' health and quality of life are similarly impacted.

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Data Availability

The data sets generated during and analyzed during this study are available from MMGC main researcher of the CUIDAR-SE Study.

Authors' Contributions

MMGC and MDRL conceived and designed the study and planned the strategy for analyzing and interpreting the results. MMGC coordinated the research team and obtained funding. MDRL supervised the fieldwork and data quality control. DJM drafted the manuscript and made substantial contributions to its writing. All authors have reviewed successive versions of the manuscript and have approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

LTC: long-term care
OECD: Organisation for Economic Co-operation and Development

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Protocol

Effect of Menstrual Cycle and Hormonal Contraception on Musculoskeletal Health and Performance: Protocol for a Prospective Cohort Design and Cross-Sectional Comparison

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Abstract

Background: Women of reproductive age experience cyclical variation in the female sex steroid hormones 17β-estradiol and progesterone during the menstrual cycle that is attenuated by some hormonal contraceptives. Estrogens perform a primary function in sexual development and reproduction but have nonreproductive effects on bone, muscle, and sinew tissues (ie, ligaments and tendons), which may influence injury risk and physical performance.

Objective: The purpose of the study is to understand the effect of the menstrual cycle and hormonal contraceptive use on bone and calcium metabolism, and musculoskeletal health and performance.

Methods: A total of 5 cohorts of physically active women (aged 18-40 years) will be recruited to participate: eumenorrheic, nonhormonal contraceptive users (n=20); combined oral contraceptive pill (COCP) users (n=20); hormonal implant users (n=20); hormonal intrauterine system users (n=20); and hormonal injection users (n=20). Participants must have been using the COCP and implant for at least 1 year and the intrauterine system and injection for at least 2 years. First-void urine samples and fasted blood samples will be collected for biochemical analysis of calcium and bone metabolism, hormones, and metabolic markers. Knee extensor and flexor strength will be measured using an isometric dynamometer, and lower limb tendon and stiffness, tone, and elasticity will be measured using a Myoton device. Functional movement will be assessed using a single-leg drop to assess the frontal plane projection angle and the qualitative assessment of single leg loading. Bone density and macro- and microstructure will be measured using ultrasound, dual-energy x-ray absorptiometry, and high-resolution peripheral quantitative computed tomography. Skeletal material properties will be estimated from reference point indentation, performed on the flat surface of the

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medial tibia diaphysis. Body composition will be assessed by dual-energy x-ray absorptiometry. The differences in outcome measures between the hormonal contraceptive groups will be analyzed in a one-way between-group analysis of covariance. Within the eumenorrheic group, the influence of the menstrual cycle on outcome measures will be assessed using a linear mixed effects model. Within the COCP group, differences across 2 time points will be analyzed using the paired-samples 2-tailed *t* test.

Results: The research was funded in January 2020, and data collection started in January 2022, with a projected data collection completion date of August 2024. The number of participants who have consented at the point of manuscript submission is 66. It is expected that all data analysis will be completed and results published by the end of 2024.

Conclusions: Understanding the effects of the menstrual cycle and hormonal contraception on musculoskeletal health and performance will inform contraceptive choices for physically active women to manage injury risk.

Trial Registration: ClinicalTrials.gov NCT05587920; https://classic.clinicaltrials.gov/ct2/show/NCT05587920

International Registered Report Identifier (IRRID): DERR1-10.2196/50542

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KEYWORDS

estrogens; oestradiol; progesterone; calcium; musculoskeletal health; hormonal contraceptive

Introduction

Background

Women of reproductive age experience cyclical changes in endogenous sex steroid hormones during the menstrual cycle. These hormones regulate and support the production, release, and fertilization of the ovum. 17β-estradiol, the predominant estrogen in women of reproductive age, is produced by the ovaries during the early stages of the menstrual cycle. Progesterone is secreted by the *corpus luteum*—the discarded sac of the ovum—after ovulation and stimulates endometrial growth in preparation for fertilization in the later stages of the menstrual cycle. Growth and release of ova are regulated by the anterior pituitary hormones—follicle-stimulating hormone and luteinizing hormone (LH)—under the influence of gonadotropin-releasing hormone [1].

Hormonal contraceptives (HCs) are made from synthetic forms of estrogens or progesterone, in some instances combined in varying concentrations. They prevent pregnancy by disrupting the release of gonadotropin-releasing hormone, suppressing ovulation, and altering the uterine lining to impair egg implantation. Consequently, the majority of HCs reduce circulating endogenous sex steroid hormones [2]. The most commonly used HC is the combined oral contraceptive pill (COCP), but long-acting reversible contraceptives (LARCs) containing progestin only, administered by subcutaneous implant, intrauterine system (IUS), or intramuscular injection, are increasingly popular methods [3]. Some studies have measured temporal patterns of sex steroid hormones during the menstrual cycle [4] and in COCP users [5,6], but data are lacking in LARC users.

HCs are also used medically to reduce or suppress menstrual bleeding in those experiencing conditions such as endometriosis [7] and by female athletes and servicewomen to delay or prevent menstrual bleeding [8,9]. However, there is growing concern that the noncontraceptive effects of estrogens on bone, muscle, and metabolism may influence injury risk and physical performance [10]. Estrogens are essential to bone health; women who experience conditions with lower estrogens, such as postmenopausal women [11] and those with functional hypothalamic amenorrhea [12], have lower bone mass compared with eumenorrheic (EUM) women. The influence of HCs on bone mass and bone stress injury risk is less clear [13], although biochemical markers of bone resorption and formation are lower in COCP users compared with EUM women [14-16]. The use of the COCP may decrease bone remodeling by a reduction in endogenous estrogens or indirectly by a synthetic estrogen-mediated reduction in *free* insulin-like growth factor I (IGF-I) [17].

Osteogenesis is the formation of new bone tissue performed by osteoblasts. Bone resorption is the process by which osteoclasts break down bone tissue, releasing calcium and other minerals into the circulatory system. Biochemical markers of bone resorption and formation reflect metabolic processes in bone, but they do not provide quantitative data on calcium status. A total of 6 naturally occurring calcium isotopes exist (^{40}Ca, ^{42}Ca, ^{43}Ca, ^{44}Ca, ^{46}Ca, and ^{48}Ca). Bone formation favors the uptake of lighter calcium isotopes and subsequently causes the composition of urine to shift toward an isotopically heavier state [18]. If bone resorption is the dominant metabolic process and calcium is excreted from the bone, the calcium isotopic composition of the urine becomes lighter [19]. Low estrogens increase bone resorption, but the effect of estrogen status on calcium homeostasis (ie, whether calcium is being deposited or lost from bone), measured from ^{44}Ca:^{42}Ca isotopes, is not known.

Traditionally, bone strength has been inferred from measures of areal bone mineral density (aBMD) with dual-energy x-ray absorptiometry (DXA). DXA is not portable and emits ionizing radiation, and an alternative ultrasound-based method may provide valid hip and spine aBMD measurements that can be used in field-based scenarios. Additionally, peripheral quantitative computed tomography (pQCT; volumetric bone mineral density and structure) and impact microindentation provide additional, and possibly superior, estimates of bone strength in vivo in young adult healthy women compared with DXA [20]. Preliminary data using pQCT in female soldiers indicate differential effects of COCP and non-HC use on tibial adaptations during arduous training [21], with implications for stress fracture risk. High-resolution pQCT (HRpQCT) offers

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more detailed information on bone strength based on bone microstructure [22]. Hypoestrogenic athletes have poorer bone microarchitecture and higher stress fracture risk compared with their EUM counterparts [12,23], while female military recruits taking progestin-only contraceptives experience blunted tibial adaptations to military training compared with COCP and EUM women [24].

Anterior cruciate ligament injury risk is highest mid-cycle in EUM athletes [25,26], with a lower risk in COCP users [26], suggesting a role of estrogens. In skeletal muscle, estrogens are purported to exert beneficial effects, and low estrogens status can impair muscle strength and growth [27,28]. Menstrual bleeding and HC use can influence iron status, including the prevalence of iron deficiency, through excessive iron loss or by mediating hepcidin production, an acute-phase protein that impairs iron absorption. Understanding the effects of the menstrual cycle and hormonal contraception on musculoskeletal health and performance will inform contraceptive choices for physically active women to manage injury risk.

Aims and Hypotheses

There is limited evidence for the overarching effects of estrogen on bone and calcium metabolism and musculoskeletal performance and even fewer studies investigating the impact from chronic use of HCs. Our primary aims are to (1) investigate the effect of menstrual cycle phase on bone and calcium metabolism, and musculoskeletal health and performance in EUM, non-HC users (EUM group); and (2) investigate the effects of HC use on bone and calcium metabolism, and musculoskeletal health and function. Our secondary aims are to (1) determine the validity of an ultrasound-based method of measuring hip and spine aBMD compared with "gold standard" DXA and (2) compare calcium and bone metabolism, reproductive hormones, and musculoskeletal function between the pill phase and non-pill phase of COCP use.

This study will test the following hypotheses in 2 study designs. Menstrual cycle phase (within-groups design): (1) calcium and bone metabolism is decreased during the ovulatory phase compared with other phases; and (2) muscle strength and tissue mechanical properties differ across the menstrual cycle. HC use (between-groups design): (1) calcium and bone metabolism is higher in the implant and injection groups compared with IUS (which exerts localized effects) and EUM (ovulatory phase) groups, and lower in the COCP group; (2) estradiol and progesterone are lower in HC users compared with the EUM group during the ovulatory phase; (3) bone macro- and microstructure, muscle strength, and tissue properties are different in HC users compared with the EUM group; and (4) calcium and bone metabolism, reproductive hormones, and musculoskeletal function are different between the pill phase and non-pill phase of COCP use.

Methods

Recruitment

Biochemical markers of bone and calcium metabolism and measures of musculoskeletal health and performance will be obtained in physically active women who are EUM (n=20) or HC users taking or administered COCP (n=20), implants (n=20), IUS (n=20), or hormonal injections (n=20). Participants will be aged 18-40 years; have stable body mass (defined as no change in self-reported body mass ≥5% over the previous 3 months); have a BMI between 18 and 30 kg/m^2; have a regular menstrual cycle of 24-35 days in length; have not been taking any HC in the last 12 months (EUM group); have used the COCP for at least 12 months (COCP group); have used the IUS continuously for at least 2 years (IUS group); have used the implant continuously for at least 12 months (implant group); or have used the hormonal injection continuously for at least 2 years (injection group). Participants will be excluded if they have diagnosed premature ovarian insufficiency; are pregnant; are less than 2 years post partum; have given birth to more than 2 children; demonstrate evidence of disordered eating (defined as ≥20 on the Eating Attitudes Test-26 items) or have a self-reported eating disorder; report menstrual disturbance (amenorrhea or oligomenorrhea: <9 menstrual cycles in previous 12 months); are a habitual smoker (defined as ≥10 cigarettes per day); are taking any medication known to affect bone or calcium metabolism (eg, treatment for thyroid disorders); have a self-declared history of heart, liver or kidney disease, diabetes or thyroid disorder; self-report a bone injury in the previous 12 months; or have a total 25-hydroxyvitamin D (25(OH)D)<30 nmol/L at prescreening. Finally, any participants not in the injection group who report a history of using the hormonal injection will also be excluded from participation. We will aim to recruit matched sample sizes; however, some HC options are less common, and the study may be unable to achieve the desired sample size. Researchers have stated an end point for data collection of August 2024, giving 2.5 years of recruitment. If any group is underpowered, the sample achieved will be presented to mitigate influences from different time periods. An overview of the study schedule is illustrated in Figure 1; proposed biochemical markers of reproductive health and bone health are listed in Table 1.

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Figure 1. Study design schematic for (A) eumenorrheic women with an example 28-day cycle and (B) combined oral contraceptive pill users. Calcium balance represents a urine sample; biochemistry indicates a blood sample; bone health and function represents dual-energy x-ray absorptiometry scan, high-resolution peripheral quantitative computed tomography scan, and EchoLight ultrasound; muscle and tendon function represents muscle strength testing, MyotonPRO, and single-leg drop; and health and lifestyle represents questionnaires.

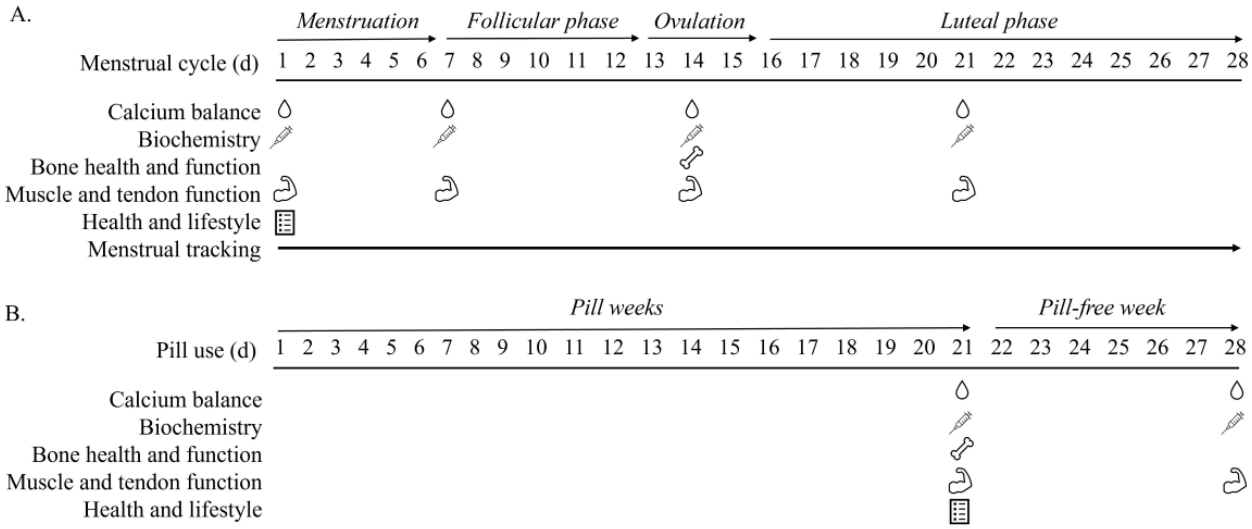

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Table 1. Proposed biochemical measurements.

Biochemical measurements	Measurement time points, n		
	EUM[a] group	COCP[b] group	Other HCs[c,d] group
Reproductive, stress, and metabolic hormones			
Estradiol	4	2	1
Progesterone	4	2	1
Luteinizing hormone	4	2	1
Follicle-stimulating hormone	4	2	1
Testosterone	4	2	1
Sex hormone–binding globulin	4	2	1
Cortisol	4	2	1
Cortisol-binding globulin	4	2	1
Insulin-like growth factor I (IGF-I)	4	2	1
IGF-binding protein 1	4	2	1
IGF-binding protein 3	4	2	1
Prolactin	4	2	1
Relaxin	4	2	1
Free thyroxine (FT4)	4	2	1
Free triiodothyronine (FT3)	4	2	1
Thyroid-stimulating hormone (TSH)	4	2	1
Androstenedione	4	2	1
Dehydroepiandrosterone sulfate	4	2	1
Bone			
C-terminal telopeptide of type 1 collagen	4	2	1
Bone–specific alkaline phosphatase	4	2	1
Amino terminal propeptide of type 1 procollagen	4	2	1
Osteoprotegerin	4	2	1
Receptor activator of nuclear factor κβ ligand	4	2	1
Iron			
Hepcidin-25	4	2	1
Ferritin	4	2	1
Soluble transferrin receptor	4	2	1
Hemoglobin	4	2	1
Vitamin D			
Total 25-hydroxyvitamin D (25(OH)D)	2	2	2
Free total vitamin D (25(OH)D)	1	1	1
Total 24,25-dihydroxyvitamin D	1	1	1
1,25-Dihydroxyvitamin D	1	1	1
Vitamin D–binding protein	1	1	1
Intact parathyroid hormone	4	2	1
Phosphate	4	2	1
Calcium			
^{44}Ca:^{42}Ca ratio	4	2	1

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Biochemical measurements	Measurement time points, n		
	EUM[a] group	COCP[b] group	Other HCs[c,d] group
Albumin-adjusted calcium	4	2	1
Ionized calcium	4	2	1

[a]EUM: eumenorrheic.

[b]COCP: combined oral contraceptive pill.

[c]HC: hormonal contraceptive.

[d]Other HCs include the hormonal injection, hormonal implant, and hormonal intrauterine system.

All participants will attend a prescreening visit to confirm eligibility and to complete familiarization with the muscle strength and functional movement testing protocols. Thereafter, the EUM group will attend the laboratory on 4 occasions, COCP users will attend the laboratory on 2 occasions, and LARC users on 1 occasion (Figure 1). The first visit for the EUM group will be scheduled on day 2 of the menstrual cycle (ie, the second day of the menstrual bleed), according to the predictions based on their cycle length (see the *Menstrual Cycle Tracking* section). As the predictions may not be exact, the first day of the menstrual bleed will be recorded, and we will accept participant testing between day 1 and day 3 of their menstrual bleed. The second visit will be scheduled at the midpoint between day 1 of the menstrual cycle and predicted ovulation. The third visit will be scheduled to coincide with ovulation, predicted from the first day of menses and then determined in *real time* from a urine test for ovulation (LH stick, Clear Blue Advanced Digital) on the days around predicated ovulation. The final visit will be scheduled between ovulation and menstruation (for a 28-day cycle, day 21) as determined by the fertility tracker. Study visits will be scheduled on days 21 (end of active pill phase) and 28 (end of pill-free week) for COCP users (Figure 1B) and at one point in time for hormonal implant, IUS, and hormonal injection users (not represented in Figure 1).

Ethical Considerations

This study received ethical approval from the Ministry of Defence Research Ethics Committee (1042/MODREC/20) in September 2020. Participants will be provided with an information sheet at least 24 hours before consenting to participation and given a verbal description of the study. Written informed consent will be obtained at the start of the first testing session. Adverse events and reactions will be reported to the trial committee and considered by a minimum of 3 trial committee members.

All data will be handled in accordance with the project's data management plan and in compliance with the General Data Protection Regulation. All raw data will be pseudonymized during the trial. Anonymized data will be uploaded to the active research data storage system at Nottingham Trent University for a minimum of 10 years following the completion of the study. Data access rights will be provided only to the relevant members of the research team.

Measurements

Menstrual Cycle Tracking

Menstrual cycle phase and length will be monitored in the EUM group; many participants may already be using a menstrual tracking app, which will aid in cycle prediction using historical cycle length data.

Participants will be asked to report day 1 of menses, and all subsequent laboratory visits will be planned according to their reported cycle length. To verify the predicted phases of the menstrual cycle, the EUM group will be given urine dip stick tests (LH surge test) to test for ovulation between days 10 and 15 of the menstrual cycle for a 28-day cycle to ensure that testing occurs during the ovulatory phase. Women will be scheduled for testing at their *predicted* ovulation but will be *actually* tested once they also produce a positive LH test; we expect these dates to coincide. If a woman does not ovulate during the testing cycle, she will be invited to retest the following month.

Venous Blood and Urine Sampling

Venous blood samples will be taken in a resting state after an overnight fast. For the EUM group, blood will be drawn at 4 time points: menses (days 1-3), midfollicular phase (day 7, for women with a 28-day cycle), ovulation phase (day 14 for women with a 28-day cycle), and midluteal phase (day 21 for women with a 28-day cycle). For COCP users, samples will be obtained on day 21 of the pill cycle and the final day of the pill-free week (day 28). LARC users will be tested at a single time point. First-void urine samples will be taken at the same time points as venous blood samples.

Biochemical Analyses

Analysis of biochemical markers of reproductive status, bone resorption and formation, and iron status (Table 1) will be performed at the Bioanalytical Facility, University of East Anglia (Norwich, United Kingdom), according to manufacturers' instructions and under Good Clinical and Laboratory Practice conditions. Metabolites will be analyzed using the COBAS automated platform (Roche Diagnostics) for 17β-estradiol (pmol/L), follicle-stimulating hormone (U/L), LH (U/L), procollagen type 1 N-terminal propeptide (g/L), phosphate (mmol/L), intact parathyroid hormone (pmol/L), beta carboxy-terminal cross-linking telopeptide of type 1 collagen (g/L), osteocalcin (g/L), albumin-adjusted calcium (mmol/L), IGF-I (ng/mL), prolactin (ng/mL), free thyroxine (pmol/L), thyroid-stimulating hormone (mIU/L), ferritin (g/L), soluble transferrin receptor (nmol/L), and IGF binding protein 3

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(ng/mL). Liquid chromatography tandem mass spectrometry will be used for measurement of serum testosterone (nmol/L); androstenedione (nmol/L); dehydroepiandrosterone sulfate (nmol/L); cortisol (nmol/L); progesterone (nmol/L); 25(OH)D3/D2; 24,25-dihydroxyvitamin D3/D2 (nmol/L) [29]; 1,25-dihydroxyvitamin D3/D2 (pmol/L); and hepcidin-25 (ng/mL). Plate-based enzyme-linked immunosorbent assay will be used to analyze bone-specific alkaline phosphatase (U/L; MicroVue, Quidel Corp.), relaxin (pg/mL), and IGF-binding protein 1 (R&D Systems, Inc.; pg/mL). All assays will be performed with an inter- or intra-assay precision coefficient of variation (CV) of <10% across their respective assay ranges. The performance of 25(OH)D and 1,25-dihydroxyvitamin D assays is certified by the vitamin D external quality assessment scheme [30].

Hemoglobin and ionized calcium will be measured by a portable blood analyzer (iStat Alinity). Bone calcium balance will be measured in first-void urine samples, determined from the ratio of naturally occurring stable calcium isotopes (^{44}Ca:^{42}Ca). Total calcium and the stable calcium isotopes ^{42}Ca and ^{44}Ca will be analyzed using methods described elsewhere [31].

aBMD Measurement

Whole-body, right hip, and lumbar spine aBMD and whole-body fat mass and lean mass will be measured from a DXA scan (Lunar iDXA, GE Healthcare). Participants will be asked to remove excess jewelry and to wear shorts and a T-shirt. Scans will be performed on day 14 for the EUM group, day 21 for COCP users, and on the sole visit for LARC users.

Ultrasound

A nonradiating ultrasound technique (EchoLight, EchoLight S.p.a.) for measuring aBMD at the hip and lumbar spine will also be used in this study. The Royal Osteoporosis Society has recognized the technique as a clinical tool for measuring hip and spine aBMD, but there is no published research validating this technique in young, healthy adults. The site-specific aBMD readings from the ultrasound will be compared with those derived from DXA to validate the use of this equipment in future research. EchoLight ultrasound will be performed on day 14 for EUM, day 21 for COCP users, and the sole testing day for LARC users.

Bone Macro- and Microstructure

Bone microstructure, geometry, and volumetric density of the right tibia (distal 4% and 30% sites from the endplate) and radius will be assessed using HRpQCT (XtremeCT II, Scanco Medical AG). Trabecular and cortical volumetric bone mineral density and geometry, trabecular microarchitecture, cortical porosity, and estimated mechanical strength will be calculated for each scan. HRpQCT scans will take place on day 14 for the EUM group, day 21 for COCP users, and on the sole visit for LARC users.

Bone Material Properties

Reference point indentation will be performed on the flat surface of the medial tibial diaphysis using the handheld portable OsteoProbe (ActiveLife). The OsteoProbe is used to measure skeletal material mechanical properties by creating microindentations (150-260 µm depth) in the bone [32]. Reference point indentation will take place away from the main testing schedule for 1 day per month. The menstrual cycle phase and COCP status at the time of testing will be recorded.

Muscle and Tendon Characteristics

Measurements of muscle and tendon characteristics (see the *Muscle Strength*, *Functional Movement Testing*, and *Tissue Characteristics* sections) will be performed on every testing visit: days ~1, 7, 14, and 21 in the EUM group (equivalent to menses and midfollicular, ovulation, and midluteal phases), days 21 and 28 in the COCP group, and on the sole visit for the other HC groups.

Muscle Strength

Isometric and dynamic leg strength will be assessed using an isokinetic dynamometer (Biodex System 4 Pro, IPRS Mediquipe). For the isometric strength test, the participant will perform 2 submaximal warm-up reps of increasing effort followed by 3 maximal isometric contractions in extension, sustained for 5 seconds at 90° of knee flexion, with a 90-second rest period between each contraction. For the dynamic strength test, participants will complete 6 maximal repetitions in extension and flexion at 60°/s. Muscle endurance will be assessed by 15 maximal repetitions in extension and flexion at 180°/s. At least 3 minutes of rest will separate each test. Participants will be given verbal encouragement throughout the tests.

Functional Movement Testing

Participants will perform a single-leg drop to evaluate knee and ankle stability. From a raised platform, participants will stand on one leg with their arms crossed across their chest and “hop off” the platform, landing on the same leg. A total of 3 “hops” will be performed on each leg, with stability assessed using the qualitative assessment of single leg loading [33]. The frontal plane projection angle will be calculated by measuring the angle between the line from the proximal thigh to the midpoint of the knee joint and the line from the knee joint to the midpoint of the ankle, at the frame corresponding to maximum knee flexion [34].

Tissue Characteristics

Stiffness (N/m), tone (inferred from frequency; Hz), and elasticity (logarithmic decrement) of the *rectus femoris*, patellar tendon, *soleus*, *gastrocnemius*, and Achilles tendon will be measured in the rested state using digital palpation (MyotonPRO, Myoton AS). Participants will lie supine for the *rectus femoris* and patellar tendon measurements, and prone for the *soleus*, *gastrocnemius*, and Achilles tendon measurements using standardized protocols to ensure reliable recordings [35]. The MyotonPRO will be held perpendicular to the skin and 5 low-force (0.4 N) and short (15 ms) mechanical impulses applied, leading to oscillations of the underlying tissues from which stiffness, tone, and elasticity are derived. The MyotonPRO device records the CV between the 5 mechanical impulses within each set and displays this as a percentage next to each parameter. If any parameters are over a CV 3% threshold, the measurement will be repeated.

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Health and Lifestyle

Eating Attitudes Test 26-Items

The Eating Attitudes Test-26 item questionnaire will be completed at baseline and will be used for screening energy deficiency as a key risk factor for musculoskeletal health [36].

Habitual Calcium Intake

A food frequency questionnaire will be completed by participants on the final study visit to calculate habitual energy and calcium intake over the study period.

Statistical Analyses

The required sample size was calculated in G*Power 3 based on testing the null hypotheses: (1) there will be no change in calcium balance across the menstrual cycle; and (2) there will be no difference in calcium balance between the EUM group and HC users. There are no data examining calcium balance across the menstrual cycle. We anticipate a moderate to large effect size based on reported differences in calcium balance between women with low (anorexia nervosa patients) and normal estrogen (control participants; −50, SD 116 vs 77, SD 69 mg/day; *d*=2.27) [37], circulating blood calcium between the luteal and follicular phases (9.29, SD 0.52 vs 10.08, SD 0.48 mg/dL; *d*=1.08 [38]; and 2.1, SD 0.2 vs 2.3, SD 0.2 mg/dL; *d*=1.00 [39]), and urinary calcium excretion between the luteal and follicular phases (2.1, SD 1.5 vs 3.8, SD 2.2 µM/min; *d*=0.90) [40]. We estimate that between 8 and 17 participants are required to detect a significant main effect of time for calcium balance across the menstrual cycle (measured at 7 time points) with a moderate to large effect size (eta squared 0.06-0.14), an α of 0.05, and a 1– of 0.80.

All continuous data will be checked for normality using a Shapiro-Wilk test and by visually checking for skewness and kurtosis. Markers of bone and calcium metabolism, reproductive function, and musculoskeletal health will be compared between contraceptive groups with a one-way between-group analysis of covariance (EUM [day 14] vs COCP [day 21] vs hormonal implant vs IUS vs hormonal injection groups) controlling for age, lean body mass (for bone measures only), physical activity, total 25(OH)D, and previous hormonal injection use. Categorical data from questionnaires will be analyzed using a chi-square test to test for differences between lifestyle, prior HC use, menstrual cycle history, and dietary choices between groups. Nonnormally distributed data will be tested using a Kruskal-Wallis test. Significant main effects of the group will be followed up with post hoc 2-tailed *t* tests with a Bonferroni correction (or Mann-Whitney *U* test for nonparametric data). Paired-sample 2-tailed *t* tests will be used to compare markers of bone and calcium metabolism, and reproductive and musculoskeletal function across the 2 time points in COCP users. Markers of bone and calcium metabolism, reproductive function, and muscle strength and tendon function will be compared between days in the menstrual cycle for the EUM group with a linear mixed effects model with the restricted maximum likelihood estimator to allow incorporation of incomplete data. Time will be the fixed effect (day 1 vs day 7 vs day 14 vs day 21), and a random intercept will be assigned to participants to account for the nonindependence of repeated measures. The significance of the fixed effects from each model will be determined with Sattherwaite degrees of freedom. The normality of the residuals for each model will be checked visually by plotting the residuals against the fitted values and from Q-Q plots. In the event of a significant main effect of time, pairwise comparisons with Holm-Bonferroni corrections and Kerward-Roger degrees of freedom will be used on the linear mixed effects model to identify differences between time points. A Bland-Altman plot will be used to assess the agreement between aBMD measured by ultrasound and DXA. Differences will be considered statistically significant at an α level of $P<.05$ with post hoc *P* values corrected for multiple comparisons.

Results

The research was funded in January 2020, and data collection started in January 2022, with a projected data collection completion date of August 2024. The number of participants that have consented at the point of manuscript submission is 66. It is expected that all data analysis will be completed and results published by the end of 2024.

Discussion

Primary Findings

HC use is highly prevalent among servicewomen [41]. Military training is physically arduous, particularly for women [42], who experience a greater risk of musculoskeletal injuries and stress fractures than men [43]. Previous studies have shown that HC choice may inhibit skeletal adaptation to military training [24,44] and may increase stress fracture risk [45]. These studies have combined progestogen-only methods and do not report effects on muscle and soft tissue, which are limitations this study aims to address. There are limited data on the influence of contraceptives on musculoskeletal health and performance. We aim to characterize the musculoskeletal health and function of regularly menstruating women across the menstrual cycle and compare the outcomes of women using different types of HCs. These data are principally needed to understand the potential musculoskeletal injury risk (or protection) from the use of HCs in female military personnel, but the findings will have applications across wider physically active occupational groups and for female athletes and may be incorporated into public health guidance for the general population. Understanding the effects of estrogens and progesterone or progestogen on musculoskeletal health and performance will inform contraceptive choices for women and improve our understanding of the musculoskeletal risks of contraceptive use and the menstrual cycle stage.

Strengths

Through the use of strict eligibility criteria, we will be able to control for factors that may affect the study outcomes, including age, BMI, pregnancy and postpartum status, bone injury, length of HC use, pathologies affecting hormonal functions (eg, thyroid disease), and specific HC type. This is one of the first studies of its kind to investigate such a broad range of HCs and consider all 4 phases of the menstrual cycle for physical performance assessment.

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Limitations

The cross-sectional study design prevents standardized and controlled administration (frequency and dose) of HCs in the COCP group, and the self-selection of hormonal contraception across groups may introduce selection bias. A randomized control trial design of HC interventions was not considered feasible for this research due to the length of time needed to elucidate meaningful effects, the impact on lifestyle and health care for participants, and the invasive procedures for the administration of LARCs. Functional movement—visually assessed from the location of the midpoint of the knee and ankle using video footage—may also be subject to observer bias; this bias will be minimized by using a single trained observer. Investigators will also be involved in the testing of all study participants and will not be blinded to HC groups.

Future Directions

The research findings are expected to support the education of women in the military and policy for HC choices. The authors also anticipate identifying additional research needs for the wider impacts of long-term HC use. Investigating injury risk in association with HC use or the impact of HCs during arduous training would be particularly relevant in a military setting. These data also have important implications for exercising women in the general population. An exploration of the lasting effects post-discontinuation of HCs focused on musculoskeletal health and fertility would enhance the research in this field.

Dissemination Policy

The trial results will be reported to the Ministry of Defence upon completion of all data collection and analysis. The evidence provided by this study will inform servicewomen of the effects of different HC options on their physical strength and performance and guide the decisions of health care professionals when prescribing HCs. With the approval of the Ministry of Defence, the results will be published in several formats, including, but not limited to, peer-reviewed journals, press releases, and conferences.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available as they are held under license by The Ministry of Defence but are available from the corresponding author on reasonable request and with the permission of The Ministry of Defence.

Authors' Contributions

The study was designed by RLD, SLW, KAMW, TJOL, and JPG. The manuscript was written by RLD, SLW, KAMW, SJM, TJOL, JCYT, and JPG. Data collection was coordinated by SJM, RLD, SLW, KAMW, and TJOL alongside members of the Army Health and Performance Research team. Biochemical analyses will be carried out by AE, JCYT, and WDF. All authors read and approved the final version of the manuscript. This is work is principally being conducted by government scientists employed by the Ministry of Defence, United Kingdom. This study was funded by the Ministry of Defence (Army) in January 2020.

Conflicts of Interest

RLD, SLW, KAMW, SJM, and TJOL are employed by the UK Ministry of Defence as defence scientists. AE is employed as a consultant scientist for Osteolabs GmbH, which is contracted for biochemical analysis on this trial. JPG is employed by the UK Ministry of Defence as a principal scientist and defence principal investigator on this trial.

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Abbreviations

25(OH)D: hydroxyvitamin D
aBMD: areal bone mineral density
COCP: combined oral contraceptive pill
CV: coefficient of variation
DXA: dual-energy x-ray absorptiometry
EUM: eumenorrheic
HC: hormonal contraceptive
HRpQCT: high-resolution peripheral quantitative computed tomography
IGF-I: insulin-like growth factor I
IUS: intrauterine system
LARC: long-acting reversible contraceptive

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LH: luteinizing hormone
pQCT: peripheral quantitative computed tomography

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Protocol

Childhood Gender Diversity and Mental Health: Protocol for the Longitudinal, Observational Gender Journey Project

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Abstract

Background: Prepubertal transgender, nonbinary, and gender-diverse (TGD) children (ie, those asserting gender identity, expressing gender-role behavior outside of culturally defined norms for their sex registered at birth, or both) are presenting in greater numbers to pediatric gender clinics across the United States and abroad. A large subset of TGD children experiences gender dysphoria, that is, distress that arises from the incongruence between gender identity and sex registered at birth. A lack of consensus exists regarding care for prepubertal TGD children due, in part, to a dearth of empirical research on longitudinal developmental trajectories of gender identity, role behavior, and gender dysphoria (when present).

Objective: The objective of this National Institutes of Health–funded study is to provide evidence to inform clinical care for prepubertal TGD children by establishing a US longitudinal cohort (N=248) of prepubertal TGD children and their caregivers that is followed prospectively at 6-month intervals across 18 months.

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Methods: At each timepoint, clinical and behavioral data are collected via web-based visit from child and caregiver reporters. Latent class analysis, among other methods, is used to identify subgroups and longitudinally characterize the gender identity and gender-role behavior of TGD children. These models will define longitudinal patterns of gender identity stability and characterize the relationship between TGD classes and mental and behavioral health outcomes, including the moderating role of social gender transition (when present), on these associations.

Results: Baseline data collection (N=248) is complete, and the identification of TGD subgroups based on gender identity and expression using latent class analysis is anticipated in 2024. The completion of all 4 waves of data collection is anticipated in July 2024, coinciding with the start of a no-cost study extension period. We anticipate longitudinal analyses to be completed by winter 2024.

Conclusions: Through a longitudinal observational design, this research involving prepubertal TGD children and their caregivers aims to provide empirical knowledge on gender development in a US sample of TGD children, their mental health symptomology and functioning over time, and how family initiated social gender transition may predict or alleviate mental health symptoms or diagnoses. The research findings have promise for clinicians and families aiming to ensure the best developmental outcome for these children as they develop into adolescents.

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KEYWORDS

transgender; prepubertal; mental health; gender identity; development; childhood; protocol; observational; gender; children; gender-diverse; United States; dysphoria; TGD; transgender, nonbinary, and gender-diverse; symptoms; diagnoses

Introduction

A Call for Lifespan Research on Gender-Diverse Children

Increasing numbers of prepubertal transgender, nonbinary, and gender-diverse (TGD) children, asserting and expressing a gender identity outside of culturally defined norms related to their sex registered at birth [1], are presenting to pediatric gender clinics across the United States and abroad [2-4]. Prepubertal TGD children continue to remain a poorly understood and understudied population in the United States. This trend remains despite a 2011 National Academy of Medicine (formerly the Institute of Medicine) [5] report, “The Health of Lesbian, Gay, Bisexual, and Transgender People,” which explicitly called for longitudinal cohort studies that incorporate a life-course perspective to examine experiences of gender-diverse individuals across developmental stages.

Gender Dysphoria Prevalence and Course Among TGD Youths

A subset of TGD children experience gender dysphoria (GD), distress that arises from the incongruence between gender identity and sex registered at birth [6]. In 2013, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; *DSM-5*) replaced the now-obsolete diagnosis of gender identity disorder (GID) with GD [6]. In contrast to GID, GD presented greater diagnostic specificity by shifting toward gender identity incongruence and away from simply “cross-sex” behavior by requiring both (1) incongruence between gender identity and sex registered at birth and (2) the presence of distress associated with gender incongruence. Implied by these more stringent GD diagnostic criteria is that some proportion of children assessed and studied in the era of GID may have been falsely diagnosed. Yet, in the *DSM-5*, the theorized etiology, epidemiology, and course of GD were informed by older studies of clinic-referred samples of Dutch and Canadian children who met GID diagnostic criteria [7,8].

Nonetheless, in the absence of research based on the more recent GD criteria, conclusions from research based on GID have been influential in guiding clinical decisions. One oft-cited statistic is that most prepubertal children with GID no longer met criteria for the condition by adolescence or adulthood, and instead developed to be cisgender and sexual-minoritized individuals (eg, gay and lesbian); likely an artifact of the less stringent GID criteria [8-12]. Another finding suggested that only children who satisfied most or all GID diagnostic criteria were more likely to “persist” in endorsing these symptoms in mid to late adolescence thereby meeting treatment eligibility for gender-affirming hormone therapy [9]. TGD children are not eligible for gender-affirming medical interventions (ie, pubertal suppression and gender-affirming hormone therapy) prior to Tanner stage 2 when the first physical signs of puberty occur according to the objective classification system by which physicians track pubertal development [13-15]. The validity of findings from those studies has since been questioned due to notable sampling limitations and methodology for measuring and evaluating gender status in prepubertal children [16]. Concerns have been raised that the absence of more recent research on GD has yielded proliferate misinformation that informs legislative efforts to challenge gender-affirming policies within schools or health care [17].

This study is designed to longitudinally examine gender development and GD (when present) among TGD. Such findings would significantly inform clinical perspectives that may, in turn, inform treatment eligibility standards of gender-affirming medical care for youths with GD who have entered puberty (eg, pubertal suppression and gender-affirming hormone therapy).

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To Affirm or Not to Affirm: Discordant Clinical Approaches to Prepubertal GD

The perspective of a gender health professional as to (1) the extent to which gender identity among prepubertal TGD children is stable over time and (2) the extent to which GD in prepubescence can be reliably predictive of GD into Tanner 2 and beyond may inform the extent to which they support a caregiver facilitating a prepubertal social gender transition in a pediatric patient. A social gender transition is an approach led by caregivers in an effort to address GD in transgender and nonbinary children through various reversible social interventions (eg, by changing the first name, gender pronouns, and manner of dress and grooming) [14]. Emergent empirical findings suggest potential mental health benefits of social gender transition in prepubertal transgender and nonbinary children [18,19]. Informed by this research, as well as expert consensus, the current standards of the World Professional Association for Transgender Health support social transition for prepubertal TGD children on an individualized basis, with the understanding that gender identity can evolve and change over time [13]. However, no known research has observed mental health effects of social gender transition, when present, at more than 3 timepoints across childhood.

Social Gender Transition and Its Mental Health Correlates

In the absence of longitudinal outcomes on psychosocial health, prepubertal social gender transition remains controversial. This controversy may be further sustained by findings from the previously mentioned research that imprecisely examined children with GID and spuriously suggested that, in most cases, these children did not continue to experience GID upon reaching puberty [20,21]. Those unaware of these studies' limitations may believe without question that most prepubertal children do not continue to assert a transgender or nonbinary identity beyond puberty and that a prepubertal social gender transition is premature and a potential source of emotional harm when a child wishes to transition back to a gender consistent with their sex registered a birth. However, 2 cross-sectional studies of transgender and nonbinary children aged 3-12 years [19] and 6-14 years [18] suggest that social gender transition may be a psychosocially protective factor for transgender and nonbinary children. In both studies, nonclinical samples of transgender and nonbinary children who underwent family initiated social gender transition exhibited age-normative depressive and anxiety symptoms with anxiety rates slightly higher than controls (ie, cisgender siblings and age-matched controls) but still well below a clinical level. Beyond these cross-sectional studies that used cisgender children as comparison groups, there is a need to longitudinally examine mental and behavioral health outcomes in a "within-group" fashion. For example, it is important to examine the mental health outcomes of prepubertal transgender and nonbinary youths who are socially transitioned compared to those who are not.

Mental Health Correlates Among TGD Children

Beyond the existing studies is the need to longitudinally examine mental and behavioral health outcomes (both positive and negative) in prepubertal TGD children in the United States including the extent to which family rejection or support factors may moderate these outcomes. The existing body of scientific evidence documenting the health and well-being of prepubertal TGD children is sparse, but studies to date suggest transgender and nonbinary children may experience and be at risk for developing mental health problems. One Canadian study found that 47% to 89% of transgender and nonbinary children experienced problem behaviors in the clinical range, per caregiver report [21]. Another study found that 52% of prepubertal TGD children with GID met diagnostic criteria for at least one additional psychiatric condition, more often internalizing (anxiety, depression) than externalizing (attention-deficit/hyperactivity disorder, oppositional defiant disorder) in nature [22]. Several factors have been found to contribute to these co-occurring conditions including lack of family acceptance and support, family risk factors for mental health problems, and peer or community social ostracism. Consistent with this formulation, numerous studies of transgender and nonbinary adolescents have suggested that distress related to GD may contribute to disproportionate psychosocial adversity including depressive symptoms, low life satisfaction, self-harm, isolation, homelessness, incarceration, posttraumatic stress, and suicidal ideation and attempts [23-27]. Without appropriate support, as they age into young adulthood, transgender and nonbinary youths are likely to face economic and societal marginalization, incarceration, and physical abuse leaving them at significantly higher risk for substance use, violence, acquisition of HIV, other sexually transmitted infections, and homelessness [23,25,28,29]. Attention must be placed on research that can inform clinical practice early in the developmental process with all prepubertal TGD children, possibly serving as preventive interventions in the face of these later risk factors.

Gender Journeys: Gender Identity Development in Prepubertal TGD Children

A dearth of empirical evidence exists on the extent to which prepubertal TGD children understand their gender. Gender constancy refers to a child's ability to report their gender identity stably and consistently over time, irrespective of changes in gender-typed activities or appearances [30]. Based on developmental research to date (and samples presumed to consist of non-TGD children), gender constancy is considered to be achieved by age 4-7 years, and it is foundational to the formation of knowledge structures (ie, gender schemas) that inform how children learn gender-role norms and mores [31]. At the time of this study protocol's development, only one known study assessed gender cognition in prepubertal TGD children, using a cross-sectional design, and found that transgender and nonbinary children were comparable to cisgender controls in gender-cognition ability [32]. This finding suggested that prepubertal transgender and nonbinary children may reach gender development milestones at periods similar to those theorized among cisgender children. Nonetheless, without longitudinal observation of prepubertal TGD children, there is no empirical basis for understanding important milestones of gender development in these children. The features of these milestones include the extent to which patterns of gender identity development, gender expression, and role behavior are stable

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over time, and what factors predict continuity or change in these patterns as children age.

Responding to a Call: A Study of Prepubertal GDC

This study's principal investigators (PIs; ie, MAH, DC, and DE) and coinvestigators (ie, RG, JO-K, and SMR) comprise a multidisciplinary team of clinician-scientists affiliated with the 4 enrolling sites. These sites are US gender centers considered national leaders delivering similar models of multidisciplinary pediatric care and include the University of Southern California (USC) and the Center for Transyouth Health and Development at Children's Hospital Los Angeles (CHLA; MAH, formerly and JO-K), Northwestern University (NU) and the Gender & Sex Development Program at Ann & Robert H. Lurie Children's Hospital of Chicago (LCH; DC and RG), University of California San Francisco (UCSF) and its Child and Adolescent Gender Center at Benioff Children's Hospital (DE and SMR), and University of California Los Angeles (UCLA) and its Gender Health Program at UCLA Health (MAH, presently). An additional site—the Gender Multispecialty Service at Harvard Medical School's Boston Children's Hospital (HMS/BCH; ACT and DC)—withdrew in year 2, prior to initiation of enrollment, due to the absence of a qualified behavioral clinician-scientist PI to replace the original site PI (ACT), who had relocated to a liberal arts university with no gender clinic affiliate. All authors are veteran investigators in Trans Youth Care United States (TYCUS), an ongoing, longitudinal, observational study of psychosocial and anthropometric outcomes of gender-affirming medical care among TGD adolescents (R01HD082554-06A1). With this adolescent cohort research already underway, our study team was well-suited to recruit a cohort of prepubertal TGD children in further response to the 2011 National Academy of Medicine Report calling for rigorous lifespan research aimed at understanding the health implications of approaches to gender-affirming care.

Gender Journey Project's Overarching Goal and Specific Aims

The goal of this study, Gender Journey Project, is to provide evidence to inform clinical care for prepubertal TGD children. We are pursuing 3 scientific aims over an 18-month observational period, collecting behavioral data from prepubertal TGD children and a primary caregiver at 6-month intervals to (aim 1) describe characteristics of gender identity and expression in a cross-section of prepubertal TGD children to inform clinical classification and care, (aim 2) describe and characterize longitudinal patterns of gender identity development and gender expression to inform the timing of clinical intervention, and (aim 3) longitudinally characterize the relationship between identity-expression-dysphoria profiles and mental and behavioral health outcomes—both negative (eg, GD and externalizing behaviors) and positive (strengthened resilience and social confidence)—and the moderating role of social gender transition (when present) on these relationships.

Methods

Study Design

This ongoing study uses a longitudinal, observational multisite design to better understand prepubescent trajectories of gender diversity (identity and behavior), GD, mental health, and well-being among a cohort of TGD children. Participants include a TGD child and 1 caregiver who were studied prospectively over an 18-month period.

Community Engagement

At several junctures throughout the study period, our team used community-engagement methods in the form of Key Informant Advisory Boards, a participant feedback survey, and a feedback item in the finalized child and parent surveys to help tailor methods of the study protocol to our target population while also seeking to limit participant burden. The 3 separate Key Informant Advisory Boards were each comprised of a distinct group: TGD youths (slightly older than our target population but who may have been eligible for participation if not for their age), caregivers of TGD youths, and licensed mental health clinicians with expertise in pediatric gender health. Board members provided input on the study visit structure and measure selection; youth members named the study. In the first 8 weeks of baseline data collection, immediately after completing their baseline study visit, 12 caregivers and 7 child participants agreed to complete a 15-minute participant feedback survey for which they were each paid US $10 via a reloadable cash card (eg, ClinCard) that, although issued to the caregiver, is shared by the child and caregiver. Caregivers were eligible to participate without their child and vice versa. The survey objective was to elicit participant feedback on several aspects of study participation (eg, screening and informed consent or assent procedures, usability of the computerized and survey-delivery format, basic understanding of the study content, and the overall sequencing of the study visit). Finally, in the subsequent survey versions used at all study periods, we included an open-ended item to capture additional participant feedback.

Study Population and Recruitment

A total of 248 prepubertal TGD children and their caregivers are enrolled in the study. Participants were recruited nationally through a number of pathways, including seeking gender-affirmative mental health care for GD at any of the 4 affiliated sites, referred from local community providers, or self-referred. Initially, we anchored enrollment to the 4 sites (and community referrals local to each) before eventually widening recruitment nationally to help meet enrollment goals in the final year.

To be considered eligible for enrollment, children must have met criteria that include: residing in the United States, a caregiver-reported history of gender-nonconformity for at least the past 6 months or a GD diagnosis per *DSM-5* criteria, Tanner stage 1 pubertal development (ie, lack of pubertal development) per structured prescreening by caregiver or child, aged 6-13 years, the ability to understand English, access to a computer with webcam, microphone and internet capabilities, willingness to provide informed assent, and a caregiver willing to provide

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caregiver permission for the child to participate. The exclusion criteria include prior use of gonadotropin-releasing hormone agonist to suppress puberty, the presence of serious psychiatric symptoms that would impair abilities to assent or complete baseline, or being visibly distraught. Adults considered eligible must: be a primary caregiver of the child participant, be at least age 18 years, have the ability to read and understand English, have access to a device with internet capabilities, and have the ability to provide informed consent on their and the child participant's behalf. Caregiver exclusion criteria include the presence of serious psychiatric symptoms, being visibly distraught, and being under the influence of alcohol or substance use.

Ethical Considerations

The institutional review board (IRB) of the record is UCLA (10-00029) through a single-IRB agreement established to include USC/CHLA, NU/LCH, and UCSF. Prior to the primary author's (ie, Contact PI) relocation to UCLA from USC/CHLA in the third quarter of the project period's third year, IRB approval was granted to NU/LCH and UCSF under a reliance agreement established through the USC/CHLA IRB (19-00108). Study staff members conducted informed consent and assent procedures with each child-caregiver dyad via video-conferencing software. These procedures consisted of reviewing respective forms to, first, obtain child assent, and then, caregiver consent. The caregiver was present for both assent and consent procedures, while children were given the option to stay or be dismissed once caregiver consent procedures began. Children and caregivers signed forms electronically using the electronic signature tool. All enrollment and survey data collected is electronically stored, under policies compliant with the Health Information Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act. Child and caregiver participants are each provided US $25 after completion of their respective study visits. These reimbursements are disbursed to a reloadable cash card immediately following the completion of the study visit.

Data Collection and Measures

Overview

To accommodate public health social-distancing requirements, study visits are all conducted remotely. Caregiver report measures are collected remotely through a computer-assisted self-completed survey. Child report measures are collected remotely through a computer-assisted survey conducted by a research associate over a video-conferencing platform.

Domains Common in Child and Parent Surveys

Child and caregiver surveys are completed at baseline, 6, 12, and 18 months. Both surveys include domains assessing the child participant's GD-specific experiences (including feelings about primary sex characteristics and other aspects of anatomy), mental health, and social relationships. Caregiver participants completed the survey in 40-65 minutes. Child participants completed the survey in 50-90 minutes, due to the increased time of the child survey's verbal administration, as well as multiple 3- to 5-minute breaks issued to the child throughout. Caregiver and child participants complete their respective surveys privately and typically not during the same visit because the caregiver participant is advised to be available to research associates throughout the child's remote study visit if needed. Caregiver participants are given up to 72 hours after the child's study visit is completed to complete the caregiver survey.

Domains Specific to Child Survey

Unique to the child survey is a domain related to implicit gender cognition. At the advice of community informants, child participants are only asked items pertaining to the child's suicidality and perceptions of anatomy if, during informed assent, the child and their caregiver elect for the child to receive these items during the survey. In cases when suicidality items are endorsed in either the caregiver or child surveys, a research associate checks in with participants to determine whether professional mental health support is needed and whether the study visit should continue or be postponed. At the end of the visit and at the start of the subsequent study visit 6 months later, an additional check-in occurs regarding child safety.

Domains Specific to Caregiver Survey

Unique to the parent survey are additional domains related to caregiver stress, caregiver support related to child gender diversity, medical information about the child, the impact of COVID-19 on the family, and demographics. Caregivers also complete the Brief Problem Monitor for Ages 6-18 [33], an empirically validated measure for rating children's internalizing and externalizing problems.

Statistical Analysis

Overview

Existing research on TGD youths largely uses variable-centered approaches to data analysis (eg, regression, factor analysis, and structural equation modeling) with a focus on relationships among variables (eg, to predict outcomes) to study how indicators are related to latent constructs (eg, factors) and how constructs relate to independent and dependent variables. More recently, research on TGD youths has capitalized on advances in person-centered methods using latent class analysis (LCA) [27,34-36]. The conceptual impetus for this shift is that individuals may differ in their development and timing as to when they assert or express diverse gender identities. Informed by the recognition that person-centered methods are of high utility for epidemiological and clinical research by allowing the effects of risk factors, outcomes, as well as treatment modalities, to vary across subgroups of youths, latent class models will serve as the primary analytic method in this study.

Aim 1: Characteristics of Gender Identity and Gender-Role Behavior Among Prepubertal TGD Children to Inform Clinical Classification and Care

To address this aim, separate latent class models will be estimated for caregiver and child ratings of gender identity and gender expression using indicators from the gender development scale (J Strang et al, unpublished, 2016). An LCA describes how the probability of endorsing a set of observed categorical variables or indicators may vary across groups of individuals where group membership is not observed [37-39]. For example, youths who are transgender and identify as either male or female

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(ie, binary transgender youths) are hypothesized to endorse different indicators than nonbinary youths. For this aim, we focus on the measurement model only (ie, the relationship between the gender identity and expression indicators and the categorical latent variable). Using a structural equation modeling approach, the circle in Figure 1 refers to a categorical latent variable representing the discrete number of latent groups and the boxes represent observed variables, which can serve as (1) latent class indicators "U" (ie, gender identity indicators), (2) predictors of class membership "X" (eg, sex registered at birth), or (3) distal outcomes "Z" (eg, mental and behavioral health outcomes) associated with each latent class. As mentioned earlier, group membership itself is not an observed variable. To this end, models with an increasing number of groups are estimated and compared based on recommended fit indices [40-42]. In addition to statistical fit indices, model selection will also be informed by the substantive interpretability of the groups, as well as considerations of parsimony with respect to the number of model parameters. A selected latent class model will indicate the "optimal" number of groups, the number of individuals in each group, and group-specific response profiles for parent and child ratings.

Figure 1. A latent class model with covariates (X) and a distal outcome (Z). C: latent class variable; U: latent class indicators; X: covariates; Z: distal outcomes.

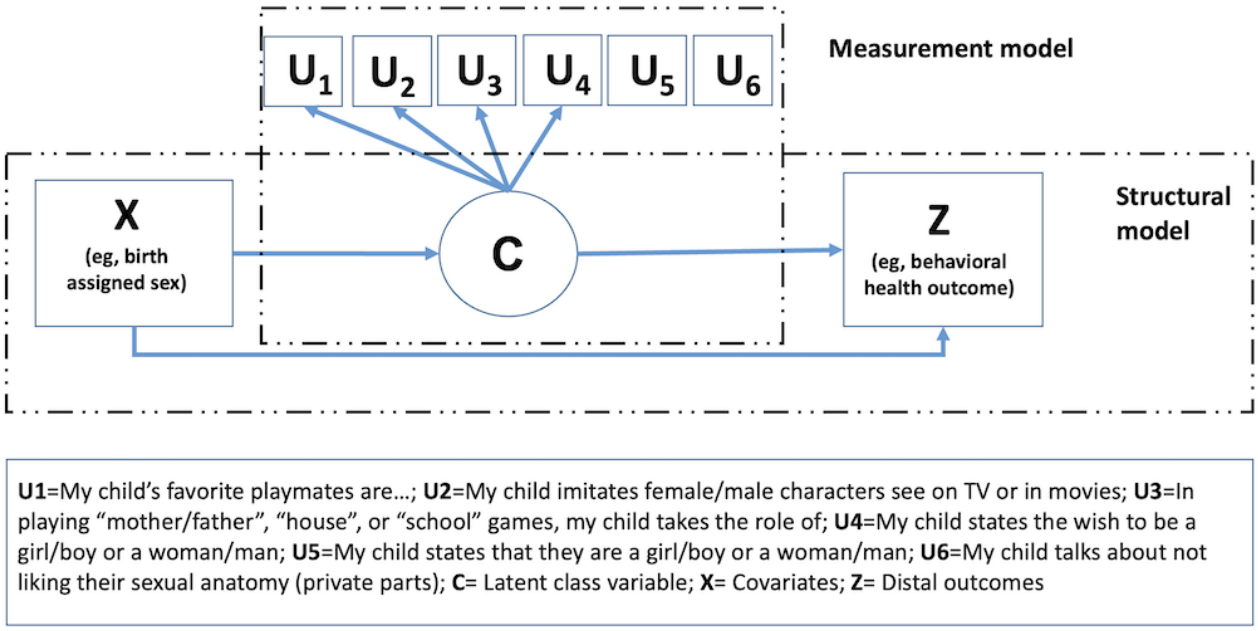

Aim 2: Characterize Longitudinal Patterns of Gender Identity Development and Gender-Role Behavior to Inform Timing of Clinical Intervention

To address this aim, a longitudinal extension of LCA will be implemented, namely latent transition analysis (LTA) [43-45] (Figure 2 [43]). Building upon the timepoint-specific LCA models, models from 2 or more waves are linked to study individual transitions from a gender diversity profile at 1 wave to the same or different profile at the subsequent wave. Generally, transitions can be described in terms of "stayers" (ie, transitioning to the same profile at a later wave) and "movers" (ie, transitioning to a different profile at a later wave). We hypothesize two types of movers, that is, (1) those who transition to a profile that was observed at a prior wave, and (2) individuals who transition into a profile that is newly evolved at a later wave. LTA models can be estimated after 2 rounds of data collection. When more than 2 waves of data are available, the lag-1 model can be extended to assess other lag models. For example, it is possible to explore whether profiles at baseline directly influence profiles at 12 months (ie, 2 timepoints later). In addition, it is important to assess whether transition probabilities are stationary (constant across waves) or whether there is evidence for more likely transitions occurring at certain time points, for example, due to pubertal onset after baseline. Another reason certain transitions may be more likely is the possibility that families may make a treatment decision to suppress or "pause" the child's pubertal development during the course of this study, or potentially support a social gender transition. Such influences can be further explored by adding covariates to the model, as discussed in more detail below.

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Figure 2. Latent transition model with time-invariant (X) and time-variant (Y) covariates. TGD: transgender, nonbinary, and gender-diverse.

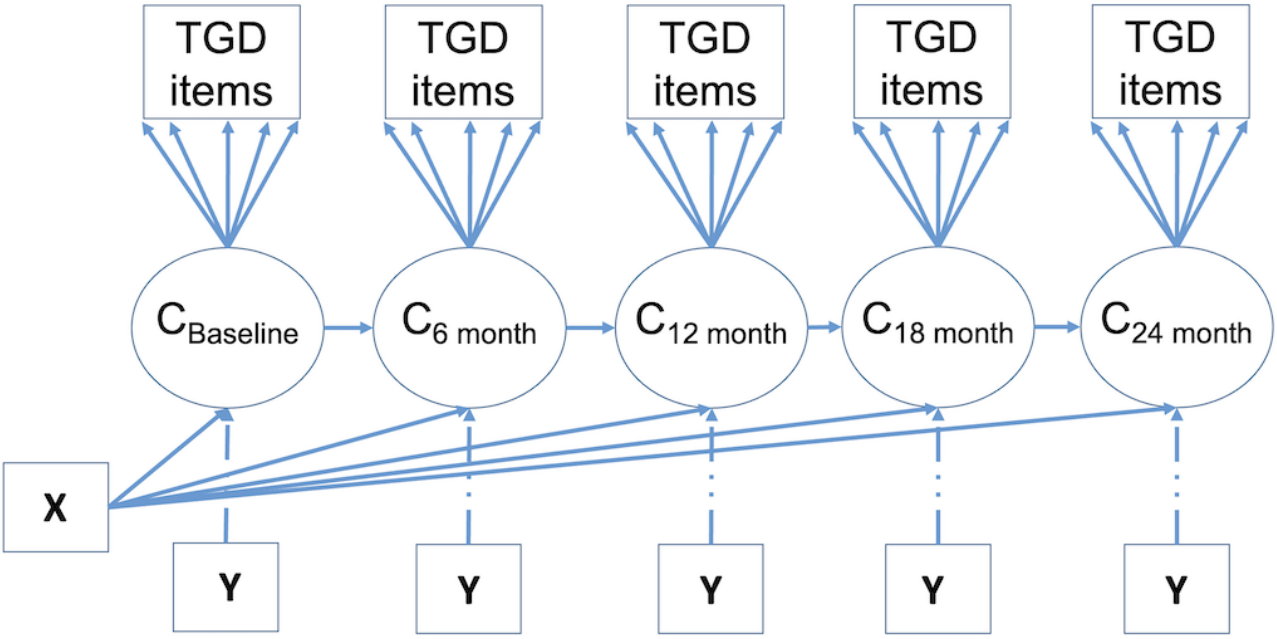

Aim 3: Longitudinally Characterize the Relationship Between Identity-Expression-Dysphoria Profiles, Mental and Behavioral Health Outcomes, and the Moderating Role of Social Gender Transition (When Present) on These Relationships

To address this aim, selected mental and behavioral health variables are included as outcomes in the wave-specific LCA models (Figure 1). As discussed earlier, the inclusion of outcomes is part of a comprehensive substantive model assessment strategy. If distinct TGD child profiles do not differ with respect to outcomes, their theoretical fit must be questioned. To ensure the correct timing, LCA profiles are related to outcomes measured at *t*+1. This model essentially resembles a linear (for continuous outcomes) or logistic (for categorical outcomes) regression model with a categorical latent predictor variable (ie, TGD child profiles). In addition, the effect of outcome differences by latent class profile can be assessed in conjunction with outcome differences by covariates (Figure 1). This can help to differentiate the contribution covariates and profiles make in explaining differences in outcomes. In other words, we can assess whether covariates at *t*–1 explain or overwrite any differences in outcomes associated with profile membership. For this scenario, a latent class profile at *t*+1 is simultaneously regressed on the baseline profile and a baseline predictor variable. Both effect paths are parameterized by a multinomial logistic regression. It is furthermore possible to assess the extent to which the influence of covariates is moderated as a function of profile membership. For example, we can assess the effect of family initiated social gender transition on mental health outcomes for each latent class profile of TGD children.

Power

To arrive at credible estimate inputs for the power calculations, data from a small sample (n=34) were analyzed. These data were drawn from measures administered as part of the standard of care for all patients aged 12 years and younger who presented to the Lurie Children's/NU multidisciplinary Gender Development Clinic, a subspecialty clinic established in July 2013. Latent class analyses identified 3 distinct groups. Of the 34 cases in the sample, 21% (n=7) fit with what we termed a "gender fluid" profile (ie, moderate levels of gender-diverse behavior and low to moderate levels of gender identity incongruence), and 27% (n=9) fit with what we termed a "gender-nonconformity" profile (ie, high levels of gender diverse behavior and low degree of gender identity incongruence). The largest group (n=18, 53%) consisted of youths with both high levels of gender-nonconforming behavior and high levels of gender identity incongruence (ie, transgender youths).

A minimum sample size of 100 is needed to detect a medium effect of a continuous covariate on both gender identity profiles. With a sample size of 248, a small effect on membership in the gender nonconformity group can be detected. A minimum sample size of 200 was needed to detect a medium effect of a binary covariate on membership in the gender nonconformity group. To detect a medium effect for the gender-fluid group, a minimum sample size of 300 is required. In summary, with a targeted sample size of 248, the proposed study is sufficiently powered to detect, at minimum, a medium covariate effect for membership in both profiles. Since full information maximum likelihood estimation will be used, all youths who contribute information for at least 1 wave will be included in the analysis and thus loss to follow-up does not alter the conclusions from this power analysis [46].

Results

Baseline Sample

When originally proposed, sites in each of the 4 cities were to recruit 80 cases to contribute to the overall sample (N=320). Upon withdrawal of the Boston site, sites in the remaining 3

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cities were responsible for recruiting a one-third greater sample than their original target. Study recruitment closed in November 2022, and the last baseline survey was completed in January 2023. Our baseline sample includes 248 child participants (78% of our original target of n=320). The average age of the child baseline sample is 8.42 (SD 1.75; range 6-13) years. Of the child participants, 69% (n=171) are registered male at birth and 31% (n=77) are registered female at birth. Preliminary child race or ethnicity data were collected from caregivers and indicate that 52% (n=128) of the sample is non-Hispanic or non-Latine White; 14% (n=34) of the sample is Hispanic or Latine; 17% (n=43) of the sample is bi- or multi-racial; and, non-Hispanic or non-Latine Black (n=1) and Asian (n=1) participants each comprised less than 1% of the sample. Race and ethnicity data for 34 participants (14%) were not reported by caregivers. Of the caregiver sample, 89% (n=214) of the sample is registered female at birth and 12% (n=30) of the sample is registered male at birth, with about 2% (n=4) not reporting registered sex at birth. All intervals of study visit follow-up are now underway.

Extenuating Challenges to Study Enrollment

We consider it a great success to enroll 248 child and parent participants given several challenges that coincided with enrollment efforts. First, were the many emergent and muddying challenges associated with the COVID-19 pandemic, the onset of which coincided with the original launch of study enrollment. Originally, the study procedures were to occur entirely in person at research facilities located at each study site. A child participant and the caregiver participant were to complete their respective surveys privately during the same visit. Significant delays were borne out of the subsequent quarantine, the overall "new normal" of socially distanced interaction, and fit-and-start patterns that emerged alongside new viral variants. The most notable challenges included institutional months-long halting of human participant research, as well as staffing shortages that affected the productivity of IRB and research compliance offices; a 6-month delay in starting data collection to overhaul study procedures from entirely in-person to entirely remote; and delays in visits due to illness of a child participant, a caregiver participant, or a study staff member. Second, was the withdrawal of the Boston site (ie, HMS/BCH) at the end of year 2. At that point, HMS/BCH had not started enrollment due to delays in obtaining IRB reliance with USC/CHLA. Consequently, its withdrawal significantly increased recruitment demand at the 3 remaining sites. Third, was a 6-month pause in recruitment during the relocation of the Contact PI and coordinating center from 1 Los Angeles academic medical center with an affiliated gender program (ie, USC/CHLA) to another (UCLA).

Discussion

Principal Product

This paper describes the protocol of a research study that seeks to longitudinally observe a national cohort of prepubertal TGD children (and a caregiver) with the aim of expanding empirical knowledge pertaining to gender development and cognition in prepubertal TGD children, their mental health and functioning over time, and how family initiated social gender transition may predict or alleviate mental health symptoms. This study will use state-of-the-art measures and use statistical advances in person-centered analytical approaches (ie, LCA and LTA) to address inconsistencies in prior studies, which have focused primarily on variable-centered approaches. This study expands on the current collaboration of TYCUS study investigators to include a younger and understudied cohort of prepubertal TGD children. The average age of our 248 baseline child participants is 8 (SD 1.75) years, the sample is predominately White (non-Hispanic or Latine), and over two-thirds registered male at birth.

An analysis of sample characteristics is beyond the scope of this protocol paper, but ostensibly, the sample resembles clinic-derived samples of TGD children which were largely White and with more registered males at birth referred for care at younger ages and more often than registered females at birth, with ratios ranging from 6:1 (Canada), 4:1 (the United Kingdom), 3:1 (the Netherlands), and 2:1 (NU/LCH) [2,47]. Although our sample is not clinic-derived, its composition may be similar to that of previous studies given its affiliation with prominent 4 academic gender health centers.

Limitations

The protocol described here is not without limitations. It is certainly a limitation that our sample is somewhat racially homogeneous, which may present challenges to how we evaluate our hypotheses within and between racial subgroups. In addition, in collecting data from and about only 1 caregiver, we are limited in our ability to examine the effects of attitudes and influences of additional caregivers (when present) on our outcomes of interest. Last, given the observational design of our study, its findings will have limited generalizability.

Conclusions

Limitations aside, the current researchers anticipate expanding the investigation into a program of research that examines the experiences and needs of TGD youths from early childhood through early adulthood. This study sets up an ideal framework to continue collecting longitudinal data from the cohort recruited for this initial work, and further elucidate the developmental complexities of this population to complement findings from the TYCUS study.

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Data Availability

The data sets generated by and to be analyzed during this study are not yet publicly available due to ongoing data cleaning or due to not having yet been completed but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BCH: Boston Children's Hospital
CHLA: Children's Hospital Los Angeles
DSM-5: Diagnostic and Statistical Manual of Mental Health Disorders (Fifth Edition)
GD: gender dysphoria
GID: gender identity disorder
HMS: Harvard Medical School
IRB: institutional review board
LCA: latent class analysis
LCH: Lurie Children's Hospital
LTA: latent transition analysis
NU: Northwestern University
PI: principal investigator
TGD: transgender, nonbinary, and gender-diverse
TYCUS: Trans Youth Care United States
UCLA: University of California Los Angeles
UCSF: University of California San Francisco
USC: University of Southern California

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Protocol

Preventing Cognitive Decline in Older Latino Adults With HIV Through a Culturally Tailored Health Promotion Intervention: Protocol for a Single-Arm Pilot Trial

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Abstract

Background: Older Latino adults with HIV are at increased risk for mild cognitive impairment and earlier onset of aging-related cognitive decline. Improvements in cognitive functioning and cognitive outcomes are possible among people with HIV who adopt health promotion behaviors. However, health promotion interventions for older Latino adults with HIV have not been extensively used or widely recognized as viable treatment options. Happy Older Latinos are Active (HOLA) is a multicomponent, health promotion intervention that is uniquely tailored for older Latino adults with HIV.

Objective: This study aims to (1) determine the feasibility and acceptability of an adapted version of HOLA aimed at improving cognitive functioning among older Latino adults with HIV; (2) explore whether HOLA will produce changes in cognitive functioning; (3) explore whether HOLA will produce changes in activity, psychosocial functioning, or biomarkers of cognition; and (4) explore whether changes in activity, psychosocial functioning or cognitive biomarkers correlate with changes in cognition, while accounting for genetic risk for dementia.

Methods: A single-arm pilot trial with 30 Latino (aged 50 years and older) men and women with HIV was conducted to assess feasibility, acceptability, and preliminary effects on cognition. Participants were assessed at 2 time points (baseline and postintervention) on measures of neurocognitive and psychosocial functioning. In addition, blood samples were collected to determine biomarkers of cognition at baseline and postintervention. Successful recruitment was defined as meeting 100% of the targeted sample (N=30), with 20% (n=6) or less of eligible participants refusing to participate. Adequate retention was defined as 85% (n=25) or more of participants completing the postintervention assessment and acceptability was defined as 80% (n=38) or more of sessions attended by participants.

Results: Participant recruitment began on February 22, 2022, and was completed on August 15, 2022. The last study visit took place on February 20, 2023. Data analysis is currently ongoing.

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Conclusions: Encouraging findings from this exploratory study may provide a blueprint for scaling up the HOLA intervention to a larger cohort of older Latino adults with HIV who may be currently experiencing or are at risk for HIV-related cognitive challenges.

Trial Registration: ClinicalTrials.gov NCT04791709; https://clinicaltrials.gov/study/NCT04791709

International Registered Report Identifier (IRRID): DERR1-10.2196/55507

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KEYWORDS

Latinos; HIV; AIDS; cognitive decline; health promotion; intervention; protocol; single-arm; pilot trial; prevention; older; cognitive impairment; impairment; treatment; dementia; psychosocial; men; women; cohort

Introduction

Older Latino adults with HIV are disproportionately affected by the HIV epidemic and comorbid health challenges at increasing rates [1-4]. Although Latino adults represent approximately 19% of the US population, they account for 21% of new HIV infections, and 20% of those living with the virus. These disparities become even more pronounced among older Latino adults [4] with HIV incidence rates for Latino individuals in the United States being 5 times as high compared to their non-Latino White counterparts [1]. Additionally, Latino individuals with HIV are diagnosed later in life with approximately 17% of them receiving their diagnosis after the age of 50 [1]. These inequities already contribute to poorer HIV-related and general health outcomes among older Latino adults with HIV and will continue to magnify with the "greying of the epidemic" [5].

Older Latino adults with HIV are uniquely at risk for experiencing deleterious neuropathological and neurocognitive sequelae within the context of aging due to the co-occurrence of aging-related cognitive impairments and depression [1,2,4,6]. Although advancements in HIV treatment (eg, antiretroviral therapy [ART] over the past 2 decades have greatly improved the longevity and health of people with HIV [7], neurocognitive impairments are observed in approximately half of people with HIV [8]. Nonpathological cognitive impairments— or age-related cognitive changes—have been well-documented in numerous aging [7,9,10] and HIV-centered studies [7,11-13]. Although HIV-related dementia is uncommon in the era of highly effective ART [10,14-16], people with HIV remain susceptible to both cortical and subcortical insults that facilitate cognitive impairments [17,18]. For example, in 1555 adults with HIV from across the United States, Heaton et al [8] found that 52% of people with HIV experienced measurable cognitive impairments, with 33%, 12%, and 5% experiencing asymptomatic neurocognitive impairment, mild neurocognitive disorder, and mixed neurocognitive disorder, respectively.

Such cognitive impairments may be attributable to a diverse set of factors related to HIV pathogenesis and progression. These factors include HIV-induced death of glial cells; elevated cortisol levels and inflammation caused by HIV; age- and HIV-associated comorbidities; and ART-induced metabolic complications such as hypercholesterolemia and insulin resistance [15,17,19-23]. In a cross-sectional study of middle-aged and older veterans with HIV, Justice et al [24] found a high prevalence of cognitive impairments (eg, speed of processing, memory). Furthermore, these cognitive challenges are more acutely exacerbated among older adults with unsuppressed viral load [25] and may even present as early as 1-year post-HIV acquisition [26-29].

Older Latino adults with HIV encounter distinct challenges in cognition that stem directly from the intersection of mental health challenges (eg, depression), HIV, and general aging-related cognitive impairment. Ethnic differences have been found in speed of processing, memory, and reasoning/executive functioning—the cognitive domains most often impacted by HIV-related challenges—with older Latino adults with HIV experiencing higher rates of impairment in these aspects of cognition [4,6,10,20,30-45]. Depression, which has also been identified as an independent risk factor for cognitive impairment, has been reported at 5 times the rate among older Latino adults with HIV than in the general population [6,7,45]. The causes of depression among older Latino adults with HIV are multifaceted. Two of the most influential contributing factors may be stigma and resultant loneliness due to social rejection and withdrawing from society [6,46].

There are many social and lifestyle factors that contribute to declining cognitive reserve within the context of HIV. For example, when Fazeli et al [31] examined the relationship between lifestyle factors and the prevalence of cognitive impairment in people with HIV, they found that if participants were physically active (ie, engaged in any strenuous exercise in the past 72 hours), socially and or behaviorally activated, and mentally stimulated (ie, working full- or part-time), participants had a greatly reduced likelihood of presenting with cognitive impairment [31]. This observation parallels findings in the cognitive aging literature that supports the notion that disengaging from a sedentary lifestyle is good for both one's physical and cognitive health [47]. Self-reported sedentary behavior is associated with greater odds of impaired learning, motor function, and memory in adults with and without HIV [48]. Moreover, people with HIV who reported regular physical activity over 2.5 years maintained better neurocognitive function even when compared with sedentary adults without HIV [49].

Physical activity is known to produce structural and cellular changes within the brain including promoting angiogenesis, synaptogenesis, neurogenesis, and dendritic remodeling [48-52]. Several theories suggest that physical activity stimulates the release of a number of factors from adipose tissue and skeletal

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muscles that produce these changes in the brain. Many of the molecules suspected to potentiate this process include myokines or cytokines (interleukin [IL]-15), adipokines (irisin and adiponectin), and neurotrophic factors (brain-derived neurotrophic factor [BDNF], insulin-like growth factor 1 [IGF-1], and vascular endothelial growth factor [VEGF]), which are detected in the blood [52]. Such biomarkers can be used to determine the impact of physical activity on brain health, and possibly function [52].

The salience of cognitive impairment among older Latino adults with HIV suggests that health promotion interventions—defined as behavioral interventions that use counseling strategies to equip participants with the necessary knowledge and skills to modify and sustain a healthy diet, increased physical activity, or healthy weight—are well-aligned with their needs and may provide a practical approach to address them. Health promotion is safe, and the benefits for older Latino adults with HIV who are pharmacologically burdened is well documented [45]. Similarly, improvements in both cognitive functioning and outcomes are possible among people with HIV who adopt health promotion behaviors [12]. However, despite such encouraging evidence, health promotion interventions for midlife and older Latino adults with HIV have not been extensively used or widely recognized as viable treatment options, perhaps due to the fact that the majority of older Latino adults with HIV are more likely to be sedentary and not as actively engaged in pursuing changes in their physical activity compared to their non-Latino White counterparts [53].

Happy Older Latinos are Active (HOLA) is a multicomponent, health promotion intervention that incorporates a moderate intensity group walk, uniquely tailored for older Latino adults with HIV. Informed by behavioral activation and social learning theory [54,55], HOLA builds on prior research [56] using health promotion to prevent depression and anxiety in older Latino adults. Through physical activity and engaging in pleasant and meaningful activities, behavioral activation helps older Latino adults with HIV break the cycle of inactivity and social withdrawal to improve cognitive and psychosocial functioning. To complement this process, we use the constructs of observational learning, reinforcement, and enhanced self-efficacy postulated in social learning theory [55]. The personal relationship between the participants and the community health worker (CHW) is an important factor that helps to motivate, model, and maintain health behavior change. The CHW holds the individuals accountable, and individuals hold themselves accountable to the group, providing additional motivation to engage in the intervention. Figure 1 depicts the conceptual framework of HOLA.

HOLA is feasible and acceptable among older Latino adults [56]. Notably, results from a previous pilot study suggested that participants who engaged in the intervention expressed interest in learning more evidence-based methods to prevent cognitive decline, even though HOLA had not previously been piloted with a focus on cognition. To address this gap, a single-arm trial was conducted using HOLA with older Latino adults with HIV to assess feasibility, acceptability, and preliminary effects on cognition. The 4 specific aims of this single arm trial were (1) to determine feasibility and acceptability of an adapted version of HOLA aimed at improving cognitive functioning among older Latino adults with HIV and incorporating activity tracking; (2) explore whether there are cognitive differences in HOLA participants between baseline and posttest assessments; (3) explore whether participation in HOLA results in changes in activity, psychosocial functioning (depression, anxiety, and social support) or biomarkers of cognition (myokines or cytokines [IL-15], adipokines [irisin and adiponectin], neurotrophic factors [BDNF, IGF-1, and VEGF]) between baseline and posttest assessments; and (4) explore whether changes in activity, psychosocial functioning, or cognitive biomarkers correlate with changes in cognition, while accounting for genetic risk for dementia (apolipoprotein E [APOE] ε4 carrier status).

Figure 1. HOLA conceptual framework. CHW: community health worker; HOLA: Happy Older Latinos are Active.

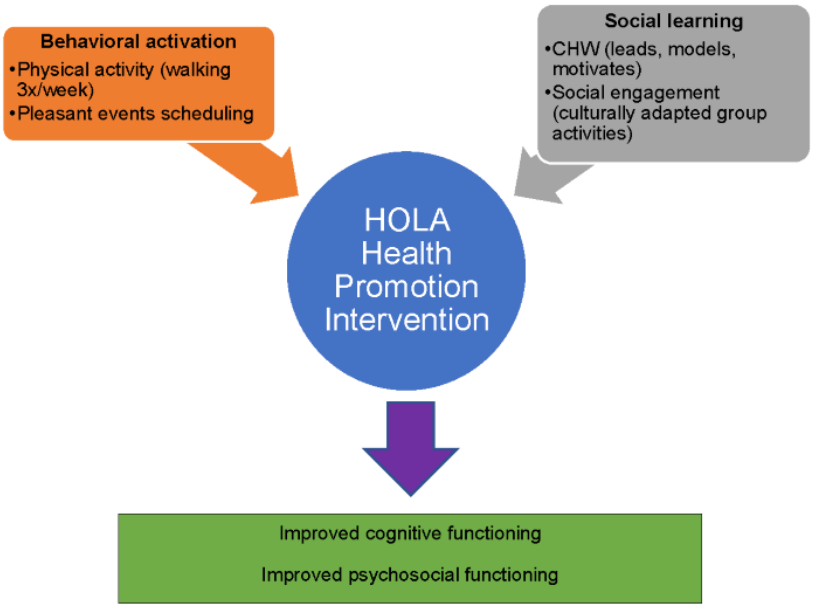

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Methods

Study Design

In this study, 30 older Latino adults with HIV aged 50 years and older were enrolled in a single arm trial to assess the feasibility and acceptability of the HOLA health promotion intervention and to identify preliminary intervention effects on cognitive functioning. The mean age at baseline was 61.7 (SD 6.0) years, and the sample was predominantly men (60%; n=18). Participants were assessed at 2 time points (baseline and 16 weeks post intervention) on measures of neurocognitive and psychosocial functioning. Blood samples were collected to assess biomarkers of cognition. Consistent with recommendations from biostatistical workgroups funded by National Institutes of Health (NIH) [12], this pilot study was not powered to test hypotheses. Participants were recruited from the Center for HIV and Research in Mental Health which serves as a consent to contact database, to efficiently and ethically contact eligible participants who receive HIV care at the University of Miami or Jackson Health System HIV Clinic [57].

Participants

Inclusion and exclusion criteria for study participation are outlined in Textbox 1.

Notably, the age of 50 years was chosen as a cutoff for 2 reasons. First, more than half of individuals affected by HIV in the United States are aged 50 years or older [2]. Second, in HIV infection, patients aged 50 years and older have poorer immunological response to ART and poorer survival. This age has been used to define medically advanced age in HIV-infected people [58]. Because of the longitudinal study design, participants planning to move outside of the South Florida metropolitan area within 6 months of enrollment or not living in stable housing (eg, group home) were excluded. All participants read and signed an informed consent form approved by the University of Miami institutional review board (IRB).

Textbox 1. Criteria for Happy Older Latinos are Active (HOLA) study participation.

Inclusion criteria

- Self-identify as Latino
- Aged 50 years or older
- Been diagnosed with HIV
- Maintained virological suppression (viral load <200 copies/mL)
- Volunteer informed consent
- Have medical clearance by a physician to participate in a physical activity intervention.

Exclusion criteria

- Have a diagnosis of any neurodegenerative disorder or dementia (Parkinson disease, Alzheimer disease, vascular, frontotemporal dementia) or significant cognitive impairment as indicated by a Telephone Interview for Cognitive Status score <30.
- Have other conditions that could impact cognitive functioning or testing (eg, legally blind or deaf)
- Currently undergoing radiation or chemotherapy.
- History of brain trauma with a loss of consciousness greater than 30 minutes.
- Contraindications to physical activity outlined in the American College of Sports Medicine standards or severe medical illness that precludes them from safely participating in a health promotion intervention.
- Unable to complete 10-meter walk test.

Measures and Assessment Protocols

Table 1 describes the measurement battery and assessment schedule.

The neurocognitive battery represents the domains that are used to classify cognitive impairment. These cognitive performance tests are norm-based, allowing us to detect performance comparisons to one's age and education level. Multiple equivalent versions of these tests are available which reduces the potential confound of practice effects. Study measures were administered in either English or Spanish (using certified translations), according to the participant's preference. Trained bilingual research assistants (RAs) conducted all assessments in private offices at the University of Miami or Jackson Health System HIV Clinic. A licensed neuropsychologist trained and supervised the RAs using a multistep process. First, the training focused on understanding test administration procedures, scoring guidelines, and potential difficulties of the specific tests that were to be administered. Second, the RAs observed the neuropsychologist administer the assessment battery. The RAs then practiced administering the test under direct supervision before transitioning to conducting the assessments on their own. The neuropsychologist would conduct interreliability checks and provide regular feedback and address any errors.

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Table 1. Measurement battery.

Criteria	Instrument
Screening and background variables (administered at baseline only)	
Cognitive screen	TICS[a] [59]
Walking ability	10-meter walk test [60]
Demographics	CLaRO[b] demographics form
Acculturation	Bidimensional acculturation scale [61]
Psychosocial functioning (administered at baseline and 16 weeks)	
Depression severity	PHQ-9[c] [62]
Anxiety severity	GAD-7[d] [63]
Perceived social support	Multidimensional Scale of Perceived Social Support [64]
Physical activity and characteristics (administered at baseline and 16 weeks)	
Waist and hip circumference	Direct measurement
Physical activity	GPAQ[e] [65]; Fitbit activity tracker
Neurocognitive functioning (administered at baseline and 16 weeks)	
Speed of processing	Trail making test A [66-69]
Attention or working memory	WAIS-III[f] spatial span [69,70]
Learning	BVMT-R[g] trials 1-3 [71,72]
Memory	BVMT-R delay [71,72]
Verbal fluency	Animal fluency [24,73]
Executive function	Trail making test B [66-69,73]
Motor	Grooved pegboard (dominant and nondominant) [74]
Participant feedback (administered at 16 weeks)	
Participant satisfaction	CSQ-8[h] [75]

[a]TICS: Telephone Interview for Cognitive Status.
[b]CLaRO: Center for Latino Health Research Opportunities.
[c]PHQ-9: Patient Health Questionnaire-9.
[d]GAD-7: Generalized Anxiety Disorder-7 Scale.
[e]GPAQ: Global Physical Activity Questionnaire.
[f]WAIS-III: Wechsler Adult Intelligence Scale-III.
[g]BVMT-R: Brief Visuospatial Memory Test, Revised.
[h]CSQ-8: Client Satisfaction Questionnaire-8.

At the end of the intervention, participants' satisfaction with the intervention was measured using the 8-item Client Satisfaction Questionnaire-8 [75]. At the end of the Client Satisfaction Questionnaire-8, there are 2 open-ended questions that allow participants to state in their own words what they liked most about the intervention and what they liked the least. Answers to these questions will be used to identify modifications needed in the design of a larger, ensuing hypothesis testing study.

Biological Data Protocol

Blood draws took place at the University of Miami or Jackson Health System HIV Clinic prior to starting baseline assessments. Approximately 20 mL (2 tablespoons) of blood was collected by a trained phlebotomist at both time points to assay biomarkers of cognition: myokines or cytokines (IL-15), adipokines (irisin and adiponectin), and neurotrophic factors (BDNF, IGF-1, and VEGF). APOE status, a genetic marker of dementia risk, was collected at baseline only. The biomarkers were assayed at the University of Miami Center for AIDS Research Laboratory Sciences Core using a commercially available enzyme-linked immunosorbent assay.

Description of the HOLA Intervention

HOLA is a multicomponent health promotion intervention for older Latino adults. The first component consists of 2 manualized social and physical activation sessions. Prior to beginning the group walk phase, each participant met

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individually with a CHW for a 30-minute physical and social activation session to (1) educate participants about the goals of the intervention; (2) provide information surrounding cognitive functioning, age-related memory loss versus dementia, how their comorbidities impact cognition, and ways they can prevent cognitive decline; (3) motivate participants to engage in physical activity; (4) increase participants' social activities; (5) identify potential obstacles that may interfere with meeting the demands of the intervention; and (6) brainstorm ways to overcome these obstacles. Participants met again individually with the CHW for 30 minutes after week 8 to discuss progress of physical and social activity goals. These meetings were typically held in the participants' homes.

HOLA's second component is a group walk, led by a CHW for 45 minutes, 3 times a week, for 16 weeks. Walks were conducted with a group of 6 participants at a centrally located public park. Each walk began with 10 minutes of stretching and warm up and followed by 25 minutes of moderately intense walking. The group walk concluded with a 10-minute cooldown phase of stretching.

The third component consists of scheduling pleasant events, which offers a means to generalize the intervention into the participants' everyday lives and relationships. During the cool-down phase of each walking session, the CHW asks each participant to identify a pleasant event that they intended to do with another person before the next meeting. Subsequent sessions start with participants reporting on how effectively they implemented their pleasant event plan while the CHW and the group provided positive reinforcement and feedback.

Cultural values and beliefs were included in the formative phases of HOLA to ensure that it addressed sociocultural influences that have a role in the health of older Latino adults. First, recruitment, intervention, and assessment materials were available in English and Spanish, and we added further cultural components to the social and physical activation manual by including Latino relevant metaphors, values, and cultural proverbs (dichos). Second, our recruitment strategies focused on relationship building given the fear, mistrust, and stigmatizing attitudes in the Latino community toward participation in clinical research. Specifically, we emphasized the Latino cultural values of personalismo (the cultural value that emphasizes social relationships and the mutual respect that those in the relationship have for one another) and confianza (trust and familiarity). Third is the use of CHWs. Since CHWs possess an intimate understanding of the community, they understand cultural values and norms and know how to incorporate them in order to promote health and health outcomes. Moreover, older Latino adults with HIV may feel more comfortable divulging personal information to someone from their own community, allowing them to communicate with study personnel in their preferred language and in a manner in which they feel comfortable.

CHW Training and Supervision

The CHW in this study worked on a previous HOLA trial [76] and was already trained to deliver the HOLA intervention using a detailed manual of operations. A clinical psychologist met weekly with the CHW to provide supervision and give one-on-one corrective feedback as needed to ensure that what was being delivered was fully consistent with the intervention as designed. Furthermore, all planned and unplanned contacts were recorded. This involved the CHW documenting the following variables for each contact with a participant: date, duration, type of session, initiator of contact, planned or unplanned contact, reason for contact, and activities engaged in.

Data Analysis

For this pilot study, we evaluated the feasibility of recruitment, assessment procedures, retention, acceptability, and implementation of HOLA in a sample of older Latino adults with HIV (aim 1). Consistent with recommendations from biostatistical workgroups funded by NIH [39], this pilot study was not powered to test a hypothesis; therefore, we did not complete a power analysis. Successful recruitment was defined as meeting 100% of the targeted sample (N=30), with 20% (n=6) or less of eligible participants refusing to participate. Adequate retention was defined as 85% (n=25) or more of randomized participants completing the postintervention assessment, and acceptability was defined as 80% (n=38) or more of sessions attended by participants.

To explore changes in neurocognitive impairment (memory, reasoning or executive functioning, speed of processing; aim 2), and general activity, psychosocial functioning, and biomarkers of cognition (aim 3), a 1-way ANOVA will be used to illustrate the change in scores from baseline to postintervention in all the outcome measures. General linear modeling will be used to explore whether changes in psychosocial functioning or cognitive biomarkers (myokines or cytokines [IL-15], adipokines [irisin and adiponectin] and neurotrophic factors [BDNF, IGF-1, and VEGF]) correlate with changes in cognition, while accounting for genetic risk for dementia (APOE ε4 carrier status). Due to the small sample size, APOE genotypes will be collapsed into ε4 carrier status carriers and non-ε4 carriers (aim 4).

Given that depression and cognitive functioning are closely linked, it is possible that improvements in cognitive functioning could be due to reductions in depressive symptoms. Therefore, to understand better the intervention effect on cognitive functioning, we will use generalized estimating equation with a log link function and Poisson distribution. The model will estimate the incident rate ratio for cognitive functioning outcomes at follow-up versus baseline. All generalized estimating equation models will include time as the main effect and control for gender, age, socioeconomic status, years of education, and depression severity at baseline as covariates. In addition, a mediational analysis will be done using structural equation models to determine whether intervention effects, if detected, are influenced by depression.

Ethical Considerations

Approval from the University of Miami IRB was obtained on May 14, 2021 (IRB ID 20201202). In addition, the trial was registered in the ClinicalTrials.gov database on March 5, 2021 (NCT04791709). All study procedures were conducted according to good clinical practice and all other relevant

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regulatory guidelines. Participants were informed that they may end their participation in the study at any time without affecting access to any other services they were receiving. Participant payments were graduated such that participants received US $25 on the baseline visit and US $35 on the follow-up visit (total honoraria: US $60). They also got to keep the tracking device.

Completed data were entered into password secured databases by authorized staff. All electronic data were deidentified and stored in password-protected files on servers at the University of Miami Miller School of Medicine Department of Psychiatry and Behavioral Sciences. For each data file, a code number was assigned, and the master list, linking code numbers with names, was stored separately. At the conclusion of the project, the record linking the assigned research number and participant identity will be destroyed. No participant will be identified within any published report. Each member of the research team was certified and trained in maintenance of confidentiality and data compliance standards.

Results

Participant recruitment began on February 22, 2022, and was completed on August 15, 2022. The study was completed on February 20, 2023. Data analysis is currently ongoing with a goal of completion by late December 2023 and a paper submission during the third quarter of 2024.

Discussion

Expected Findings

To the best of our knowledge, this is the first study to adapt a culturally tailored health promotion intervention for older Latino adults with HIV to improve physical, mental, and cognitive health. Findings from this pilot study will help to identify whether the HOLA health promotion intervention is (1) feasible and acceptable to a group of older Latino adults with HIV, and (2) potentially efficacious in bolstering brain health in this underserved group. Encouraging findings from this exploratory study may provide a blueprint for scaling up HOLA to a larger cohort of older Latino adults with HIV who may be currently experiencing or at risk for HIV-related cognitive challenges.

There are several benefits to this single arm pilot trial. At the individual level, older Latino adults with HIV may acquire and practice health behaviors that lead to improved well-being by participating in this intervention. Similarly, engaging with this intervention offers older Latino adults with HIV the opportunity to receive support, advice, encouragement, and feedback from a trained CHW and other participants who are peers with similar lived experiences as themselves. Continued psychoeducation on physical, mental, and cognitive health from the CHW as well as emotional, instrumental, informational, and appraisal support from peers may help participants gain enhanced motivation to take control of their health while also increasing psychological well-being and self-efficacy.

This project has direct public health implications at the societal level. Findings from this research may offer insight into how a health promotion intervention could improve cognitive functioning among older Latino adults with HIV with implications for dementia prevention. Similarly, older Latino adults, particularly those with HIV, are at increased risk for developing depression and anxiety compared to their White age-matched peers. Therefore, based on the intervention's focus on facilitating activity and increasing social support among older Latino adults with HIV, HOLA may chip away at social isolation among participants through opportunities for socialization and relationship-building with peers, leading to general mental health improvements in the long-term. In addition to improving the general well-being of older Latino adults with HIV, the development of more efficacious interventions that stave off cognitive and mental health challenges prior to their onset among this group is cost-effective and reduces future health care burden costs. Ultimately, approaches such as the HOLA intervention shift the attention toward preventing morbidity rather than treating it.

Finally, this study is highly relevant and responsive to the NIH priority to "maintain or improve the cognitive performance of all adults," especially for those "populations experiencing the greatest disparities and risks in cognitive health" [77]. This project shares the same values as both the NIH Cognitive and Emotional Health Project and the Healthy Brain Initiative (a national road map to maintaining cognitive health) and offers a noninvasive technique to improve cognition in adults with HIV, a major challenge currently facing the field [17].

Limitations

This study has some limitations. First, it targeted older Latino adults with HIV living in the southeastern United States; therefore, study findings may not be generalizable to older Latino adults with HIV living in other parts of the United States or globally. Second, participants were older Latino adults with HIV who were engaged in HIV care and living who have a suppressed HIV viral load. In order to support older Latino adults with an unsuppressed HIV viral load, this intervention may need to be tailored to accommodate them. Third, participants who were not living in stable housing were excluded from the study. Including participants who were not living in stable housing—which typically make up a fairly large portion of people living with HIV—would have provided interesting and useful information about whether they would have been able to attend the intervention and how they would have fared in the study. However, given that we only had 1 year to recruit 30 participants and run them through a 16-week intervention, we had to make the most efficient use of our time. Therefore, the decision was made to only include participants who were stably housed. We intend to remove this criterion in a subsequent, adequately powered trial. Fourth, the study was not powered to test for intervention effects. However, any effects that are found to be statistically significant would be encouraging. Nonetheless, this single-arm pilot study used a sound methodological approach, and, if successful, data gleaned will advance the field of HIV-related cognitive impairment among older Latino adults with HIV.

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Generative artificial intelligence was not used in any portion of the manuscript writing.

HG was affiliated with the Department of Public Health Sciences at the University of Miami at the time of the trial and is currently affiliated with the Department of Psychiatry and Mental Health at the University of Cape Town.

Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

DEJ was involved in conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, and writing—original draft, review, and editing. EJR was involved in methodology, validation, visualization, and writing—original draft, review, and editing. EW was involved in involved in methodology, formal analysis, visualization, and writing—original draft, review, and editing. HG was involved in investigation, methodology, project administration, supervision, and writing—original draft, review, and editing. YP was involved in data curation, formal analysis, methodology, project administration, and writing—original draft, review, and editing. DMG was involved in involved in validation, visualization, and writing–original draft, review, and editing. SLB was involved in conceptualization, methodology, resources, supervision, and writing–original draft, review, and editing. JHJ was involved in visualization and writing—original draft, review, and editing. VBZ was involved in conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, and writing—original draft, review, and editing.

Conflicts of Interest

None declared.

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Abbreviations

APOE: apolipoprotein E
ART: antiretroviral therapy
BDNF: brain-derived neurotrophic factor
CHW: community health worker
HOLA: Happy Older Latinos are Active
IGF-1: insulin-like growth factor 1

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IL: interleukin
IRB: institutional review board
NIH: National Institutes of Health
RA: research assistant
VEGF: vascular endothelial growth factor

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Protocol

The Association Between Physical Distancing Behaviors to Avoid COVID-19 and Health-Related Quality of Life in Immunocompromised and Nonimmunocompromised Individuals: Patient-Informed Protocol for the Observational, Cross-Sectional EAGLE Study

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Abstract

Background: Immunocompromised individuals are known to respond inadequately to SARS-CoV-2 vaccines, placing them at high risk of severe or fatal COVID-19. Thus, immunocompromised individuals and their caregivers may still practice varying

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degrees of social or physical distancing to avoid COVID-19. However, the association between physical distancing to avoid COVID-19 and quality of life has not been comprehensively evaluated in any study.

Objective: We aim to measure physical distancing behaviors among immunocompromised individuals and the association between those behaviors and person-centric outcomes, including health-related quality of life (HRQoL) measures, health state utilities, anxiety and depression, and work and school productivity impairment.

Methods: A patient-informed protocol was developed to conduct the EAGLE Study, a large cross-sectional, observational study, and this paper describes that protocol. EAGLE is designed to measure distancing behaviors and outcomes in immunocompromised individuals, including children (aged ≥6 mo) and their caregivers, and nonimmunocompromised adults in the United States and United Kingdom who report no receipt of passive immunization against COVID-19. We previously developed a novel self- and observer-reported instrument, the Physical Distancing Scale for COVID-19 Avoidance (PDS-C19), to measure physical distancing behavior levels cross-sectionally and retrospectively. Using an interim or a randomly selected subset of the study population, the PDS-C19 psychometric properties will be assessed, including structural validity, internal consistency, known-group validity, and convergent validity. Associations (correlations) will be assessed between the PDS-C19 and validated HRQoL-related measures and utilities. Structural equation modeling and regression will be used to assess these associations, adjusting for potential confounders. Participant recruitment and data collection took place from December 2022 to June 2023 using direct-to-patient channels, including panels, clinician referral, patient advocacy groups, and social media, with immunocompromising diagnosis confirmation collected and assessed for a randomly selected 25% of immunocompromised participants. The planned total sample size is 3718 participants and participant-caregiver pairs. Results will be reported by immunocompromised status, immunocompromising condition category, country, age group, and other subgroups.

Results: All data analyses and reporting were planned to be completed by December 2023. Results are planned to be submitted for publication in peer-reviewed journals in 2024-2025.

Conclusions: This study will quantify immunocompromised individuals' physical distancing behaviors to avoid COVID-19 and their association with HRQoL as well as health state utilities.

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KEYWORDS

SARS-CoV-2; social isolation; patient participation; patient-reported outcome measures; quality of life; immunosuppression; respiratory tract infection; cost of illness; surveys and questionnaires; protocol

Introduction

Background

Recent estimates suggest that there are >14 million immunocompromised individuals in the European Union [1] and approximately 19 million immunocompromised individuals in the United States [2,3]. Relative to their immunocompetent peers, immunocompromised individuals are at an increased risk of SARS-CoV-2 infection [4]. Moreover, despite the availability and use of COVID-19 vaccines, immunocompromised individuals have a higher risk of hospitalization and death from COVID-19 [5-8] due in part to their suboptimal responses to those vaccines [9-11].

Early in the pandemic, governments worldwide implemented a number of public health nonpharmacological interventions (NPIs) to ease hospital demand; slow down the spread of SARS-CoV-2; and protect high-risk groups, including immunocompromised individuals [12,13]. Interventions included *lockdowns*, travel restrictions, compulsory mask wearing, stay-at-home or other isolation policies, and physical distancing measures [12,13]. The US and UK governments advised immunocompromised individuals to maintain physical distancing, wear masks, avoid crowds, and keep up to date with COVID-19 vaccinations [14-16]. However, the population of immunocompromised individuals is heterogeneous—the degree of immunosuppression depends on the underlying disease or the duration of the condition and the type of immunosuppressive treatment [3,17-19]. Moreover, there is a lack of consensus on how severity should be categorized among immunocompromised individuals (eg, who should be considered moderately vs severely immunocompromised) [9-11,15]. To date, this heterogenous population, together with inconsistencies in how governments and physicians advised NPIs, has created uncertainty for immunocompromised individuals as to what they should be doing to keep safe [14,20,21]. While conducting interviews with the patient authors of this protocol (after protocol development), a common statement was that "life was never static—we (immunocompromised individuals) had to adapt to an ever-changing landscape."

Although NPIs effectively reduce the risk of SARS-CoV-2 infection [22], the psychosocial impact of such measures is unclear [23]. While there were some cases in which immunocompromised individuals reported that NPIs had a positive impact on family life, health care access, and mental health [24,25], for many immunocompromised individuals, NPIs led to negative effects on mental and physical functioning in areas such as exercise, social support, independence, sleep, daily routines, anxiety, and continuity of care [23-29]. As an example of disrupted continuity of care, in the interviews conducted after protocol development, the patient authors noted that COVID-19–related restrictions caused delays in cancer diagnosis and subsequent treatment initiation. In addition,

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support from family members was disrupted when those family members were infected with SARS-CoV-2. The patient authors also described an increased sense of isolation caused by being unable to spend time with family members and friends. This view is reinforced in studies among the general population, which have also shown that NPIs were linked to negative impacts on work and career progression among participants from the United Kingdom, Italy, Malaysia, and Thailand [30].

Although government-imposed restrictions officially ended in 2022 for the United Kingdom and the United States (primarily due to effective vaccination programs in the general population), COVID-19–related hospitalizations and mortality remain disproportionately higher in immunocompromised individuals than in nonimmunocompromised individuals [31-33]. In the United Kingdom, people at high risk of severe COVID-19 outcomes (including immunocompromised individuals) were advised in September 2021 to take the same measures for avoiding SARS-CoV-2 infection as the general population, albeit with some additional precautions (no further updates have been issued as of November 2023) [15,34]. Nevertheless, current guidelines are challenging for many immunocompromised individuals, who perceive that their life cannot return to *normal* despite the rest of the world appearing to do so [35]. As of April 2022, UK data showed that 69% of individuals at high risk of severe COVID-19 were still taking extra precautions against COVID-19 and 13% were practicing physical distancing (including social isolation) and other self-protective behaviors [31].

Previous research on the psychosocial effects of physical distancing and social isolation for COVID-19 avoidance has focused on government-imposed restrictions, reflecting the *lockdown* period early in the pandemic [23,24,26-29]. There is little published research describing the broader impact of physical distancing and social isolation on the lives of immunocompromised adults, adolescents, and children (and their caregivers), whose distancing behaviors are no longer government imposed but rather voluntarily practiced based on medical recommendations or individual choices. In addition, the phenomenon of post–COVID-19 condition, also known as Long COVID, has not been extensively studied in immunocompromised individuals. While it has been established that post–COVID-19 condition has a detrimental impact on health-related quality of life (HRQoL) among the general population, the impact of post–COVID-19 condition among immunocompromised individuals is not well characterized [36,37].

Objectives

Given these gaps in knowledge in the *postlockdown* setting, the EAGLE Study was designed to describe the association between physical distancing to avoid COVID-19 and HRQoL in immunocompromised adults, adolescents, and children (and their caregivers) in the United States and the United Kingdom.

In addition to these gaps in knowledge, most existing scales for measuring physical distancing do not target the extent to which a person may engage in various distancing behaviors specifically to avoid COVID-19 [38-44]. In 2020, Prachthauser et al [45] developed the Social Distance Scale (version 1), a brief, self-reported screening measure of adherence to social distancing and self-protective behaviors in pandemic situations; however, this scale was developed during the *lockdown* period and was aimed at the general population rather than high-risk groups. Furthermore, while the evidence for its measurement properties is limited, only its structural validity was assessed (solely via an item reduction–driven exploratory factor analysis, which was overly mechanical), and none of its resulting scales had good (r>0.9) consistency-based (Pearson correlation) test-retest reliability (2 scales had r<0.7); internal consistency, known-group validity, and convergent validity were not assessed. Moreover, the scale's development and validation were only conducted with undergraduate students, with approximately 30% of the respondents excluded from analyses due to aberrant response patterns [45]. As such, it was deemed inappropriate for the context of the EAGLE Study, which aimed to rigorously assess the physical distancing behaviors of immunocompromised individuals of all ages at a point in time in which behaviors were practiced voluntarily rather than according to government mandates. Accordingly, the de novo Physical Distancing Scale for COVID-19 Avoidance (PDS-C19) was developed for this study to capture the extent of physical distancing behaviors. The psychometric properties of the PDS-C19 will also be assessed in the EAGLE Study. This paper summarizes the protocol of the EAGLE Study, entitled "An Observational Cross-sectional Survey to Describe the Association Between Socially Isolating to Avoid SARS-CoV-2 Infection and Health-Related Quality of Life in Immunocompromised Individuals and Nonimmunocompromised Individuals," which was finalized and approved on October 17, 2022. The study sponsor is AstraZeneca, which contracted IQVIA to conduct the study (AstraZeneca study code: D8850R00013).

Methods

Patient Participation in Study Design

To inform how physical distancing behaviors and any associated burden should be captured from a patient's perspective in future studies, 4 web-based qualitative focus groups [25] and 2 web-based asynchronous patient forums (personal communication by TM, 2023) were held with people at high risk of severe COVID-19, including immunocompromised individuals (and caregivers, where applicable).

The 4 web-based focus groups were held between April and July 2022. In these focus groups, people at high risk of severe COVID-19 were asked to describe the reasons and the extent to which they engaged in physical distancing and social isolation behaviors. Data from these focus groups were interpreted using deductive and inductive analysis [46]. Participants conveyed that these behaviors depended on their personal circumstances, the medical advice they had received, the availability of local services, and the prevalence of SARS-CoV-2 in their area. The impact on HRQoL of practicing these behaviors was also documented in these focus groups [25]. These insights and impacts were developed into a conceptual model of COVID-19 avoidance and protective behaviors that helped direct the development of the PDS-C19.

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The 2 patient forums were held between July and August 2022 with people at high risk of severe COVID-19, some of whom had previously participated in the focus groups. These forums also helped direct the development of the PDS-C19 (personal communication by TM, 2023).

Study Design

The EAGLE Study is a noninterventional, observational, cross-sectional survey of immunocompromised adults, adolescents, and children and the caregivers of immunocompromised children or adolescents living in the United States and the United Kingdom. Individuals who are not immunocompromised will be included as a reference group for nonformal comparisons and benchmarking purposes. The EAGLE Study is designed to capture the perspectives of individuals with and without immunocompromising conditions via self-report or child-caregiver (proxy) report at a point in time for each study participant during the COVID-19 pandemic. This will include some retrospective assessments to capture perspectives earlier in and before the COVID-19 pandemic. Physical distancing behaviors to avoid COVID-19 will be captured using the newly developed PDS-C19 instrument. HRQoL and health state utilities will be captured using previously validated instruments.

Participants

In this study, immunocompromised individuals are defined as individuals with a moderate to severe immune compromise due to a medical condition or reported use of immunosuppressive treatments [16,47]. The categories of immunocompromising conditions and treatments are based on the UK government and US Centers for Disease Control and Prevention (CDC) guidelines [16,47]. Accordingly, based on their conditions, immunocompromised individuals will be grouped as follows: (1) blood cancers, (2) solid tumors (on active treatment), (3) solid organ or stem cell transplants, (4) end-stage kidney disease, (5) primary immunodeficiency disorders, (6) immunosuppressant treatments, (7) HIV infection (uncontrolled), (8) COVID-19 vaccine contraindications, and (9) other. While those with COVID-19 vaccination contraindications are not generally considered immunocompromised, they will be considered as immunocompromised for the purposes of the EAGLE Study because they are not protected by vaccination and, therefore, may remain susceptible to severe COVID-19 outcomes. The “other” category is included to ensure that those who do not know the exact categorization of their immunocompromising condition are not excluded from the study.

To be eligible to take part in the study, participants are required to meet all the inclusion criteria and none of the exclusion criteria (Table 1).

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Table 1. Inclusion and exclusion criteria.

Criteria	Adults (aged ≥18 y)	Adolescents (aged 13-17 y) and children (aged 6 mo to 12 y)
Inclusion criteria		
Individuals with immunocompromising conditions	• At least 1 specified immunocompromising condition or treatment within 2 months before study enrollment	• At least 1 specified immunocompromising condition or treatment within 2 months before study enrollment
Individuals without immunocompromising conditions	• No specified immunocompromising conditions, treatments, or history of an immunocompromising condition or treatment since January 2020	• No specified immunocompromising conditions, treatments, or history of an immunocompromising condition or treatment since January 2020
Caregivers of immunocompromised children or adolescents	• Formal caregiver (ie, a parent or legal guardian) of the child included in the study • Living (at least some of the time) with the child included in the study • If the caregiver's child is aged ≥5 years: willingness and ability to provide consent for their child to participate in the study in addition to assent from the child or adolescent	—[a]

All individuals	• Age of ≥18 years
	• Residence in one of the eligible study countries
	• Ability to read and understand English (United States and United Kingdom) or Spanish (United States)
	• Willingness to complete a 30- to 45-min web-based survey related to feelings, health, living situation, and other descriptive questions within 1 week of the survey becoming available to them
	• Willingness and ability to provide consent to participate in the study
		• Age of 6 months to <18 years
		• Residence in one of the eligible study countries
		• Have a formal caregiver who meets the caregiver eligibility criteria
		• For children aged ≥5 years:
		  • Ability to understand English (United States and United Kingdom) or Spanish (United States) at a level typical for their age, with caregiver assistance if needed
		  • Willingness and ability to complete questions appropriate for their age about feelings and health and simple descriptive questions lasting <15 min, with caregiver assistance if needed
		  • Willingness and ability to provide assent to participate in the study

Exclusion criteria		
All individuals	• Participation in a clinical trial for experimental or investigational treatments for immunocompromising conditions and preventions or treatments for SARS-CoV-2 infection or COVID-19 • Hospitalization or admittance to an inpatient facility at recruitment • History of administration of tixagevimab or cilgavimab or any other passive immunization therapy for COVID-19 (history of vaccination against COVID-19 is acceptable)	• Participation in a clinical trial for experimental or investigational treatments for immunocompromising conditions and preventions or treatments for SARS-CoV-2 infection or COVID-19 • Hospitalization or admittance to an inpatient facility at recruitment • History of administration of tixagevimab or cilgavimab or any other passive immunization therapy for COVID-19 (history of vaccination against COVID-19 is acceptable)

[a]Not applicable.

Sample Size Calculation

Due to the descriptive nature of the study, no formal sample size or power calculations were conducted. Instead, an estimate based on an initial feasibility assessment was used to inform the sampling of key groups of interest and to achieve a reasonable representation of both the breadth of immunocompromising conditions and types and extent of physical distancing behaviors.

From an initial feasibility assessment conducted in early 2022 to test the survey approach for the EAGLE Study, 22% of adults with immunocompromising conditions reported that they were practicing physical distancing behaviors. Accordingly, a pragmatic sample size of 1400 immunocompromised adults was chosen for the EAGLE Study to ensure that the study would include approximately 300 socially isolating adult participants. Assuming that the prevalence of social isolation in adolescents and children is half that of the adult sample (11%), a sample size of 1818 adolescents and children was also chosen to ensure that approximately 200 adolescent and child participants would

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be currently socially isolating. The group of 1818 adolescent (aged ≥13 y) and child (aged <13 y) participants will be split in a ratio of approximately 1:1 to ensure roughly equal representation of adolescents and children. In addition to the immunocompromised participants, approximately 300 nonimmunocompromised adults, 100 nonimmunocompromised adolescents, and 100 nonimmunocompromised children (and the caregivers of these adolescents or children) are planned to be recruited to serve as an informal reference group for benchmarking purposes. Therefore, the total planned sample size for the EAGLE Study is 3718 (approximately 3218 immunocompromised and 500 nonimmunocompromised) participants, counting each adolescent- or child-caregiver pair as 1 participant. All adolescent and child participants will have a corresponding caregiver who, in addition to assisting or serving as proxy for their child, will complete some survey questions as a participant themselves. The planned sample size for each group is shown in Table 2.

Table 2. Planned sample size by age group and immunocompromised status[a].

Age group (y)	Immunocompromised status, n		Total (N=3718), n
	Yes (n=3218)	No (n=500)	
Adults (≥18)	1400	300	1700
Adolescents (13-17)	909	100	1009
Children (0.5-12)	909	100	1009

[a]All nonadults will have a corresponding caregiver (n=2018). The “children” age group comprises the following subgroups: older children (aged 8-12 y), young children (aged 5-7 y), toddlers (aged 2-4 y), and infants (aged 0.5-<2 y).

Recruitment

Participants in the United States and United Kingdom are planned to be recruited via the patient recruitment agency Global Perspectives. To diversify participant recruitment, multiple direct-to-patient channels will be used (Figure 1). The eligible population will comprise 2 sets of participants: 1 set recruited through patient panels and networks (approximately 30%) and 1 set recruited through clinician referral, patient advocacy groups, and social media (approximately 70%). Child (or adolescent) and caregiver pairs will be recruited together (ie, both the child [or adolescent] and their caregiver must meet their respective eligibility criteria to participate in the study).

Potentially eligible individuals will be provided with information about the study and invited to participate via email with a unique link to a screening questionnaire to determine eligibility (Figure 1). Respondents who provide consent and pass the screening will be given access to the web-based study survey questionnaires. Completion is requested within 1 week to reduce the possibility of daily changes affecting survey responses while allowing sufficient time and pauses to complete the survey.

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Figure 1. EAGLE Study flowchart. IRB: institutional review board; PAG: patient advocacy group.

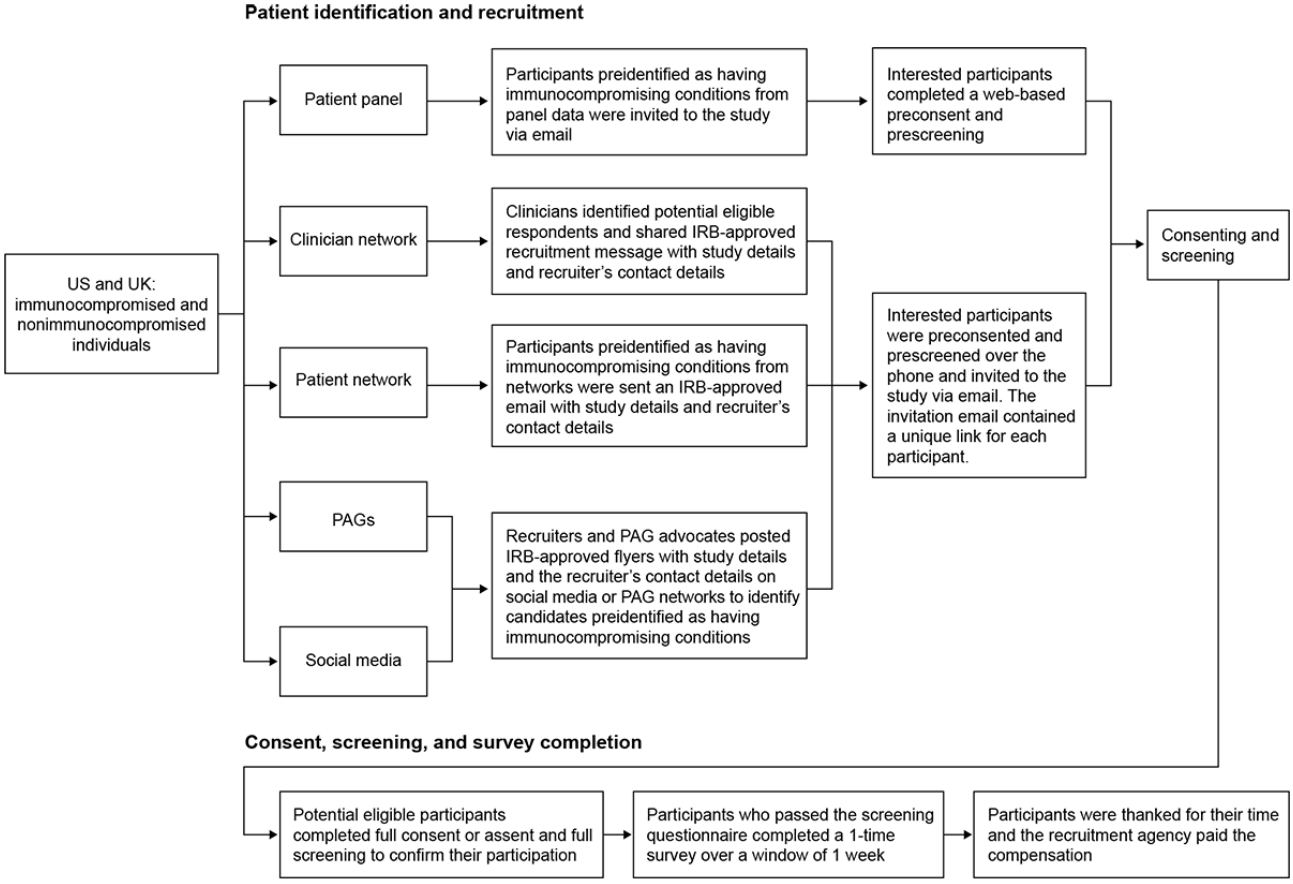

Confirmation of Immunocompromising Diagnosis or Treatment

To verify that participants represent the spectrum of immunocompromising conditions that exist in real-world settings, a random subsample from the total study sample will be asked to provide confirmation of diagnosis (COD) via a medical document showing proof of either immunocompromising diagnosis or treatment. To calibrate the total number of COD invitations needed to achieve a 25% random sample from the immunocompromised population, the first 100 immunocompromised participants enrolled into the study will be invited to provide COD; the resulting acceptance rate will be used to calculate the number of COD invitations to extend. Participants who provide COD information will receive additional compensation at an institutional review board (IRB)–approved rate.

Objectives and Outcomes

Broadly, the EAGLE Study has two parts: (1) psychometric validation of a new behavioral measure of physical distancing for COVID-19 avoidance (the PDS-C19) and (2) outcome analysis to explore the associations between the PDS-C19 measure and various HRQoL and utility measures collected as part of the survey.

Psychometric validation of the PDS-C19 will be conducted before outcome analyses using either an interim or randomly selected subset of approximately 1000 participants. The psychometric validation methods are detailed in the *Statistical Analysis* section.

The primary objective of the EAGLE Study is to describe the association between physical distancing to avoid COVID-19 and the HRQoL measures and health state utility values for immunocompromised adults. The secondary objectives are to describe the association between physical distancing and various HRQoL and utility measures among the other EAGLE Study participants. The specific study objectives and outcome measures are presented in Table 3.

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Table 3. Outcome analysis: study objectives, population, and outcome assessments.

Objective and population	Outcome assessments
Primary objective summary	
To describe the associations between physical distancing to avoid COVID-19 and *HRQoL*[a,b] and *health state utilities*	
Immunocompromised adults (aged ≥18 y)	• The association between the PDS-C19[c] score or scores and the following: SF-12v2[d] [38], QDIS-7[e,f], and DMOL[g] item instruments [39] and the EQ-5D-5L [40] and SF-6D[h,i] (based on the SF-12v2) instrument [41]
Secondary objectives	
To describe the association between physical distancing to avoid COVID-19 and *HRQoL*	
Immunocompromised adolescents (aged 13-17 y); older children (aged 8-12 y)	• The association between the PDS-C19 score or scores and the PedsQL[j] Generic Core Scales[k] and DMOL item instruments
Young children (aged 5-7 y); toddlers (aged 2-4 y)[l]	• The association between the PDS-C19 score or scores and the PedsQL Generic Core Scales[k] [48]
Infants (aged 6 months-<2 y)[l]	• The association between the PDS-C19 score or scores and the PedsQL Infant Scales [42]
Caregivers (aged ≥18 y)[m]	• The association between the PDS-C19 score or scores and the PedsQL FIM[n] instrument [49]
To describe the association between physical distancing to avoid COVID-19 and *health state utilities*	
Immunocompromised adolescents (aged 13-17 y)	• The association between the PDS-C19 score or scores and the EQ-5D-5L instrument
Older children (aged 8-12 years); young children (age 5-7 y)[l]	• The association between the PDS-C19 score or scores and the EQ-5D-Y[o] instrument
Caregivers (aged ≥18 y)[m]	• The association between the PDS-C19 score or scores and the EQ-5D-5L instrument
To describe the association between physical distancing to avoid COVID-19 and *anxiety and depression*	
Immunocompromised adults (aged ≥18 y) and adolescents (aged 13-17 y) and caregivers (aged ≥18 y)[m] of immunocompromised adolescents and children	• The association between the PDS-C19 score or scores and the HADS[p] [43]
To describe the association between physical distancing to avoid COVID-19 and work and school productivity impairment	
Immunocompromised adults (aged ≥18 y) and caregivers (aged ≥18 y) of immunocompromised adolescents[q] and children	• The association between the PDS-C19 score or scores and the WPAI+CIQ:SHP[r] instrument [44]
Adolescents (aged 13-17 y)	• The association between the PDS-C19 score or scores and the WPAI+CIQ:SHP (CIQ[s] questions only) and PedsQL Generic Core Scales
Children (aged 5-12 y)	• The association between the PDS-C19 score or scores and the PedsQL Generic Core Scales
To describe the association between physical distancing to avoid COVID-19 and *HRQoL, health state utilities, anxiety and depression, and work and school productivity impairment*	
Nonimmunocompromised adults, adolescents, and children and caregivers[m] of immunocompromised adolescents and children	• The association between the PDS-C19 score or scores and all outcomes as reported by the immunocompromised individuals
Exploratory objective summary	
To describe the background frequency of symptoms similar to post–COVID-19 condition and describe the differences in background frequency of these symptoms between group or groups of immunocompromised individuals and group or groups of nonimmunocompromised individuals	

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Objective and population	Outcome assessments
Immunocompromised and nonimmunocompromised adults, adolescents, and children	• The frequency and differences in frequency of post–COVID-19 condition symptoms regularly over the past 4 weeks as measured using questions developed for this study • Note that confirmation of post–COVID-19 condition diagnosis will not be captured in this study

[a]Items in italics highlight key outcomes.

[b]HRQoL: health-related quality of life.

[c]PDS-C19: Physical Distancing Scale for COVID-19 Avoidance.

[d]SF-12v2: 12-item Short Form Health Survey version 2.

[e]QDIS-7: 7-item Quality of Life Disease Impact Scale.

[f]Mapi Research Trust [50].

[g]DMOL: Direct Measure of Loneliness.

[h]SF-6D: Short Form 6 Dimension.

[i]The SF-6D will be derived from the SF-12v2 instrument.

[j]PedsQL: Pediatric Quality of Life Inventory.

[k]Mapi Research Trust [51].

[l]Solely proxy reported; proxy version 1 for the EQ-5D-5L (caregiver's opinion).

[m]For themselves, not via proxy.

[n]PedsQL-FIM: PedsQL Family Impact Module.

[o]EuroQol Group, the Netherlands [52].

[p]HADS: Hospital Anxiety and Depression Scale.

[q]Only school-related questions administered.

[r]WPAI+CIQ:SHP: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problem (avoiding COVID-19).

[s]CIQ: Classroom Impairment Questions.

PDS-C19 Measure

Targeted literature reviews conducted in April 2022 did not identify any existing fit-for-purpose scales for measuring physical distancing and social isolation behaviors specifically in relation to the avoidance of SARS-CoV-2 infection or COVID-19. Therefore, the de novo PDS-C19, a self- and observer-reported behavioral scale, was developed; the PDS-C19 will be used in the EAGLE Study to measure physical distancing to avoid SARS-CoV-2 infection and, thus, prevent COVID-19. The PDS-C19 contains questions that capture both the extent (frequency) of current physical distancing behaviors for a 4-week recall period and more distant retrospective recall of onset of current behaviors. These questions were based on distancing behaviors practiced by immunocompromised individuals to avoid SARS-CoV-2 infection. The behaviors were identified from public guidance for physical distancing, existing surveys from previous studies capturing data on social isolation during the COVID-19 pandemic, other social isolation scales, and the 4 patient focus groups [25]. The questions on physical distancing behaviors developed for the PDS-C19 were informed by and evaluated in 2 separate, web-based, debriefing patient forums involving 24 individuals at high risk of severe COVID-19 (23 patients in the first forum, of whom 22 patients returned in the second, follow-up forum [personal communication by TM, 2023]). Most participants in the second patient forum agreed that the physical distancing behaviors in the scale were relevant to their experience (n=19/22, 86.4%; personal communication by TM, 2023). The structural validity of the PDS-C19 will be assessed as part of this study. Further information about the PDS-C19 can be made available upon request to the corresponding author.

Health Outcomes

Health outcome data related to the primary and secondary study objectives will be collected via previously validated age-specific HRQoL and related instruments (ie, the 12-item Short Form Health Survey version 2, Quality of Life Disease Impact Scale, Pediatric Quality of Life Inventory, Hospital Anxiety and Depression Scale, Direct Measure of Loneliness, and Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problem) and health state utility instruments (ie, the EQ-5D-5L, EQ-5D-Y, and Short Form 6 Dimension; Table 2). Patient-reported outcome (PRO) measures were selected by reviewing the social isolation literature to identify validated outcome measures used in similar studies and qualitative research describing the impacts of COVID-19 and social isolation. External clinical, health economic, and PRO experts (n=5) provided additional input. Direct input from immunocompromised individuals was also sought via the 4 patient focus groups. This helped conceptualize physical distancing and social isolation behaviors and their impact on HRQoL [25]. Regarding the PDS-C19 instrument, the PROs and the survey questions were evaluated in the 2 web-based, debriefing patient forums on HRQoL involving individuals at high risk of severe COVID-19. The aim was to assess the relevance and comprehensibility of the survey questions and implement feedback from forum members.

The PRO measures chosen for inclusion in the study cover a range of outcomes theorized to have a potential association with

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physical distancing behaviors. In addition, the chosen PRO measures are fit for purpose (ie, previously validated and appropriate for the context of use), well established, and available and licensable for use.

Finally, all the PRO measures to be used incorporate a recall period of ≤4 weeks, with most being 4 weeks and the remainder being 1 week or momentary (ie, current) at a time point within the 4-week PDS-C19 recall period.

Exploratory Outcomes

A brief set of survey questions was developed to capture the frequency of signs and symptoms reported in individuals with symptoms similar to those of post–COVID-19 condition. However, to minimize bias in answering these questions, no survey question will directly ask about post–COVID-19 condition diagnosis, either self-reported or confirmed. At the time of protocol finalization in October 2022, there was no international consensus on the definition of post–COVID-19 condition; thus, these survey questions are based on post–COVID-19 condition guidance issued by the UK National Health Service, the US CDC, and a report from the US Department of Veterans Affairs [53]. As recommended by the National Health Service and US CDC, the questions related to symptoms similar to those of post–COVID-19 condition are written in lay language appropriate for self-reporting within a 4-week retrospective recall period.

Study Survey Questionnaire

The study survey questionnaire is a 1-time, web-based, self- or proxy-administered set of questions comprising validated, age-appropriate PRO measures and study-specific questions that capture HRQoL outcomes, physical distancing behaviors, and key contextual data related to potential confounders (including demographic and socioeconomic factors). Input from the 4 web-based focus groups comprising individuals (including caregivers of immunocompromised children or adolescents) at high risk of severe COVID-19 informed the development of the survey questionnaire [25]. The languages of the survey questionnaire for study conduct are English (United States and United Kingdom) and US Spanish. The survey questionnaire is designed to be completed on any electronic device with an internet connection and is expected to take 30 to 45 minutes to complete.

PRO measures relating to the study's primary objectives are placed toward the beginning of the survey questionnaire. Questions designed specifically for this study, which will collect more detailed and specific information, are positioned after (and within the same section as) the relevant PRO measures. Age-specific versions of the survey questionnaire for infants, toddlers, young children, older children, and adolescents have been designed with age adaptations to language and question content. Surveys are designed so that children aged ≥5 years can respond to questions on their own with assistance from their caregiver if needed, whereas all questions for toddlers (aged 2-4 y) and infants (aged <2 y) are directed toward caregivers only. The survey is structured so that children will complete questions about themselves first, allowing the caregiver to continue with other questions about the child or about themselves. Younger age groups have fewer questions to answer, whereas older age groups have progressively more questions to answer.

Statistical Analysis

An interim or randomly selected subset of approximately 1000 participants stratified by immunocompromised status, age group, sex, and country will be partitioned from the main sample to serve as a psychometric validation sample for the PDS-C19. This subset will be further split into an exploratory factor analysis sample to identify underlying relationships between PDS-C19 items and a confirmatory factor analysis sample to test whether the scale structure or structures identified via the exploratory factor analysis is supported. After establishing the structural validity and scoring of the PDS-C19, the following psychometric properties will be evaluated: internal consistency, known-group validity (how well the scale can differentiate between groups that are known to differ), and convergent validity (how well the scale relates to other measures to which it is expected to be related).

Figure 2 provides a flowchart for the overall statistical analysis using the final measurement model and scoring for the PDS-C19 developed as part of the psychometric analysis. After examining the Pearson correlations between PDS-C19 and the PRO scores (all scales are continuous), for immunocompromised respondents, prespecified structural equation models with partially latent variables will be fit to test hypothesized direct and indirect relationships between expected predictors of physical distancing (PDS-C19), other risk mitigation behaviors, and PRO measures. In addition, multiple regression analyses, with each PRO as a univariate dependent outcome, will examine the direct relationship between the PDS-C19 and the PROs controlling for other covariates (Figure 2).

Descriptive statistics for the various categorical and continuous health outcome scores and other survey items will be reported by age group and immunocompromised status. For each age group, descriptive analyses may also be reported univariately by immunocompromised category (immunocompromised participants only), country, and language (US and UK English vs US Spanish). The descriptive analyses may also be reported by categorized PDS-C19 scores. A statistical analysis plan for the EAGLE Study will be approved before conducting any analyses.

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Figure 2. Outcome analysis flow diagram for primary and secondary objectives. CFA: confirmatory factor analysis; EFA: exploratory factor analysis; HBM: health belief model; MI: modification index; PDS-C19: Physical Distancing Scale for COVID-19 Avoidance; PRO: patient-reported outcome; SEM: structural equation modeling.

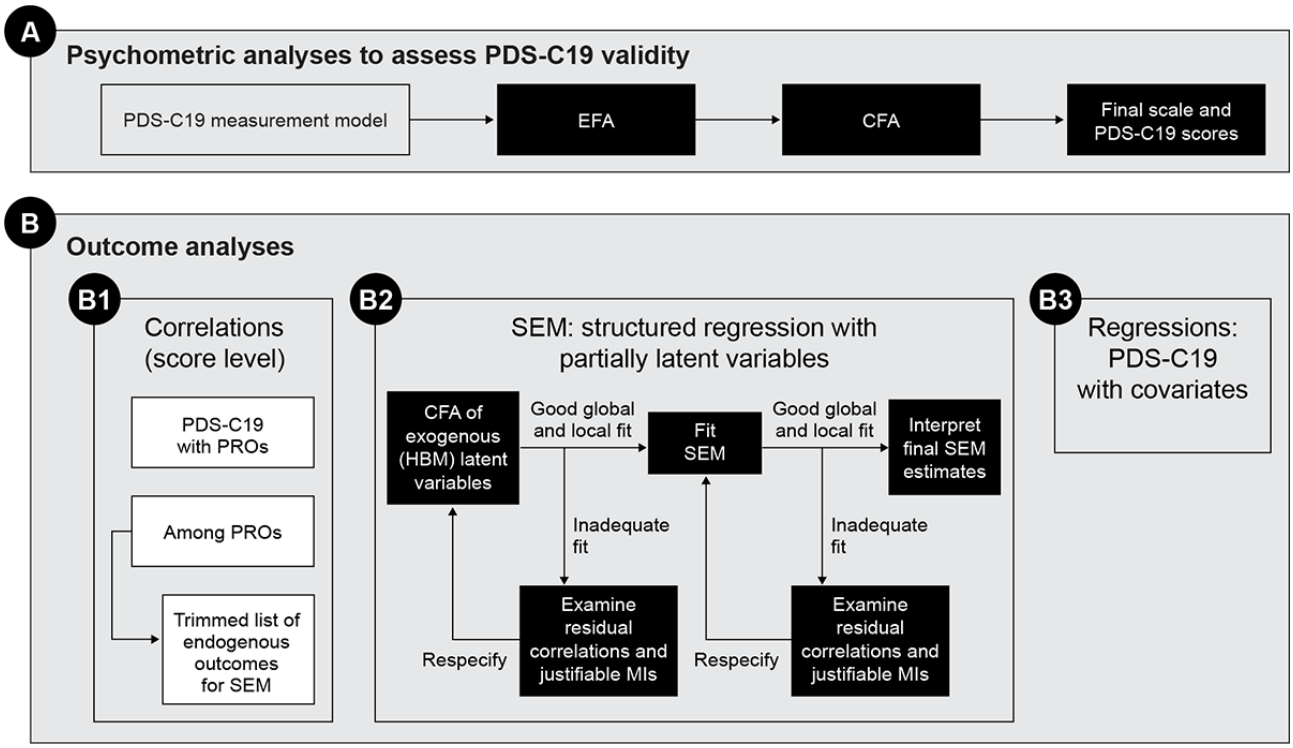

Ethical Considerations

The EAGLE Study protocol and informed consent material were approved by the Western Institutional Review Board–Copernicus Group on November 15, 2022 (tracking 20226100), and those materials adhere to ethical principles consistent with the Declaration of Helsinki, guidelines for good pharmacoepidemiology practice, and applicable regulations and guidelines governing medical practice and ethics in the relevant countries. The UK regulatory authorities do not require local IRB approval for the conduct of this type of study. The final protocol and participant consent forms and all study recruitment and advertising materials will be implemented based on the IRB approval. In accordance with local regulations and ethical principles originating in the Declaration of Helsinki, participants will be required to provide informed consent electronically before being granted electronic access to the study and will be allowed sufficient time to consider participation. By signing and completing the electronic consent form, participants will consent to their data being used in the study unless they withdraw voluntarily for any reason and at any time. The consent form incorporated wording that complies with relevant data protection and privacy legislation. Consenting participants authorize the collection, use, and disclosure of their personal data by the third-party recruitment agency and by study team members, as necessary, for the purposes of the study. The consent form explains that study data will be stored in a secure computer database with confidentiality to be maintained in accordance with local data protection law or laws.

This study does not involve any safety objectives, and thus, adverse event reports will not be actively solicited. However, any incidental reports of adverse events regarding study sponsor products from study participants passively received by study staff during the course of the study will be reported to the study sponsor as per local country requirements and, as and when applicable, to the relevant regulatory authorities. After completing the survey questionnaires, participants will be compensated for their time based on a rate approved by the relevant IRB. Participants can discontinue at any time but will only be compensated after survey completion.

Results

Participant recruitment and data collection were planned from December 2022 until June 2023, with all data analyses and reporting planned to be completed by December 2023. Results are planned to be submitted for publication in peer-reviewed journals in 2024-2025 and presented at national and international scientific conferences.

Discussion

Expected Findings

Following the end of government-imposed restrictions implemented to control COVID-19, the voluntary physical distancing behaviors practiced by immunocompromised individuals to prevent COVID-19 are still not well characterized. However, there is evidence suggesting that many of these individuals continue to practice physical distancing and social isolation behaviors similar to those required during government-imposed restrictions [25]. Emerging research published by the University of Liverpool during the EAGLE Study conduct has shown that immunocompromised individuals report higher levels of worry (due to COVID-19) and lower levels of mental health and well-being than the general

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population in the *postlockdown* setting [54]. The EAGLE Study will build on this research by comprehensively evaluating the associations between engaging in physical distancing behaviors for COVID-19 avoidance and HRQoL among immunocompromised individuals of all ages in the *postlockdown* era.

Strengths

A key strength of the EAGLE Study is that its design was informed by input from immunocompromised individuals and from a group of individual expert advisors. Specifically, the self-reported physical distancing behaviors, HRQoL concepts, PRO instruments, and other survey items incorporated into the study were all informed by feedback from multiple stakeholders: clinical and health economic experts; specialists in HRQoL research; experts in the development, validation, and use of PRO instruments; and individuals at high risk of severe COVID-19 who contributed their insights over 4 focus groups and 2 forums. This study will provide the opportunity to use a randomly selected subsample of the EAGLE Study to refine the de novo PDS-C19 and its scoring via structural validity analyses and evaluate the instrument's psychometric properties before its use in outcome analyses. The PDS-C19 will be a valuable tool for future studies and may serve as a framework that can be adapted for other infectious diseases.

Other strengths of the study design include the planned large sample size, inclusion of participants from 2 countries, inclusion of participants of nearly all ages, and the speed of data collection and subsequent analyses. A very large sample size will likely provide sufficient statistical power for the numerous analyses planned and should provide representation of key subgroups in this heterogeneous population. Due to this representation, we are more likely to obtain stable point estimates for these subgroups. In the midst of a pandemic, there is a need to balance credible study duration with the need for rapid research and data interpretation. The cross-sectional study design allows for more rapid data analysis and reporting than would be afforded by a longitudinal design while still providing valuable information about the relationship of interest.

Multiple channels of participant recruitment, a process that will involve prescreening and telephone calls with potential participants, and broad inclusion criteria are additional merits of the EAGLE Study. By requesting, collecting, and assessing confirmation of immunocompromising diagnosis information from a randomly selected large proportional subsample, it will also be possible to determine the level of representativeness of the study data regarding the broader immunocompromised population. In this study, HRQoL will be assessed using both validated, generic HRQoL instruments and instruments that are adaptable to specific conditions. Specific survey questions, all of which underwent multiple stages of development and testing, will be used to complement and help contextualize the main study findings. The study primarily focuses on the current (at the time of the survey: December 2022 to June 2023) and recent (within a 4-week period before the survey questionnaire completion) period for physical distancing and HRQoL outcomes. Choosing a recall period of within 4 weeks was considered appropriate to capture aspects of HRQoL and distancing behaviors less likely to be influenced by possible momentary fluctuations in health or daily activities.

Limitations

In terms of evaluating the measurement properties of the PDS-C19 instrument, the cross-sectional study design precludes assessing the instrument's test-retest reliability and sensitivity to change or what score change could serve as a threshold for meaningful change. For the EAGLE Study outcome analyses, inferences are also limited by the cross-sectional design. In the absence of longitudinal and other formal comparative data, causality or impact should not be inferred from any associations identified between physical distancing behaviors and other measures. At best, results can be deemed consistent with causal hypotheses. Nonetheless, the data from this study can serve as a strong basis for inferring possible causality and impact that could be demonstrated in future longitudinal studies.

As with all self-reported data, there is also the possibility of information bias, whereby participants may give inaccurate information based on their recall abilities, time frame of reference, and method of survey administration. Despite taking measures to ensure that the participant sample is representative of the real-world population, the influence of selection bias is possible such that the recruited participants might not be fully representative of the many categories and types of immunocompromising conditions (particularly rare ones) or of the nonimmunocompromised population. Furthermore, the web-based recruitment process may skew the sample toward individuals who are more familiar with electronic devices and browsing the internet. Another potential limitation is that the representativeness of subgroups may be reduced by the broad inclusion criteria (such as a wide age range and inclusion of many different immunocompromising conditions and categories). It is also possible that individuals with more severe immunocompromising conditions may be more invested in their underlying condition than those with milder immunocompromising conditions, meaning that those with a more severe immunocompromising condition are perhaps more likely to participate in research. In addition, we do not have prospectively collected baseline or other comparative data on physical distancing behaviors before the emergence of COVID-19, and there is no evidence of how physical distancing behaviors measured using the PDS-C19 are related to the risk of SARS-CoV-2 infection.

Conclusions

This study will investigate the associations between physical distancing and social isolation to avoid COVID-19 and HRQoL and health utility measures in immunocompromised and nonimmunocompromised adults, adolescents, and children and the caregivers of immunocompromised adolescents and children. This study will also explore symptoms similar to those of post–COVID-19 condition in this population.

Following the finalization of this protocol, in May 2023, the World Health Organization declared COVID-19 an established and ongoing health issue that no longer constitutes a public health emergency of international concern [55]. However, there remains uncertainty around emerging and future SARS-CoV-2

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variants, for which the transmission rates and case-to-fatality ratios are unknown or undercharacterized. In interviews with patient authors consulted for this protocol, it was noted that the end of government-imposed restrictions poses an even greater challenge for immunocompromised individuals, who must continue to take extra measures to protect themselves from infection. COVID-19 has substantially changed the way in which immunocompromised individuals live their lives.

This study will quantify and characterize the diverse HRQoL burden associated with physical distancing practices to avoid COVID-19 by immunocompromised and nonimmunocompromised individuals and caregivers of immunocompromised children and adolescents. It is anticipated that the data generated in the EAGLE Study will help inform future planning and recommendations by public health authorities and may be used directly in health technology assessments and health economic modeling. The data are also expected to be useful in developing guidelines for health care providers and immunocompromised individuals regarding the risks versus benefits of physical distancing to avoid COVID-19.

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Authors' Contributions

Study conceptualization was undertaken by PW, TAH, RTCY, SA, JLS, ST, and MK. Data curation was carried out by GS and MK. Funding, funding acquisition, investigation, and resourcing were undertaken by MK. Formal analysis and visualization were carried out by JM. The methodology was developed by PW, TAH, TM, SV, JCM, AL, JLS, JWV, PAP, JEW Jr, and MK. Project administration was undertaken by TAH, GS, and MK. Supervision was undertaken by PW, TAH, ST, and MK. Validation was carried out by JCM and MK. All authors contributed to the writing, review, and editing of the manuscript.

Conflicts of Interest

At the time of the start of the patient recruitment, Global Perspectives was an independent company. Global Perspectives has since been acquired by IQVIA. JWV holds the copyright and the trademark for the Pediatric Quality of Life Inventory and receives financial compensation from the Mapi Research Trust, which is a nonprofit research institute that charges distribution fees to for-profit companies that use the Pediatric Quality of Life Inventory. JEW Jr. holds the copyright for the Quality of Life Disease Impact Scale. JCM, TM, and MK are employees of IQVIA and may hold stock or stock options. IQVIA provided research services for AstraZeneca for this study. PW was employed by IQVIA under contract with AstraZeneca at the time of study conduct and is now an AstraZeneca employee. PW, TAH, SV, SA, GS and ST are employees of AstraZeneca and may hold stock or stock options in that company. RTCY is an employee of P95 currently under a contract with AstraZeneca. JLS is an employee of Severens HTA Consultancy and may hold stock or stock options. He received study materials from IQVIA Ltd and consulting fees from AstraZeneca for the study design. PAP has received consulting fees from AstraZeneca for the study design. JEW Jr. is an employee of John Ware Research Group, Inc, and may hold stock or stock options.

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Abbreviations

CDC: Centers for Disease Control and Prevention
COD: confirmation of diagnosis
HRQoL: health-related quality of life
IRB: institutional review board
NPI: nonpharmacological intervention
PDS-C19: Physical Distancing Scale for COVID-19 Avoidance
PRO: patient-reported outcome

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Protocol

Effects of Auditory and Visual White Noise on Oculomotor Inhibition in Children With Attention-Deficit/Hyperactivity Disorder: Protocol for a Crossover Study

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Abstract

Background: In attention-deficit/hyperactivity disorder (ADHD), poor inhibitory control is one of the main characteristics, with oculomotor inhibition impairments being considered a potential biomarker of the disorder. While auditory white noise has demonstrated the ability to enhance working memory in this group, visual white noise is still unexplored and so are the effects of both types of white noise stimulation on oculomotor inhibition.

Objective: This crossover study aims to explore the impact of auditory and visual white noise on oculomotor inhibition in children with ADHD and typically developing (TD) children. The study will investigate the impact of different noise levels (25% and 50% visual, 78 dB auditory), and performance will be evaluated both with and without noise stimulation. We hypothesize that exposure to white noise will improve performance in children with ADHD and impair the performance for TD children.

Methods: Memory-guided saccades and prolonged fixations, known for their sensitivity in detecting oculomotor disinhibition in ADHD, will be used to assess performance. Children diagnosed with ADHD, withdrawing from medication for 24 hours, and TD children without psychiatric disorders were recruited for the study.

Results: Data collection was initiated in October 2023 and ended in February 2024. A total of 97 participants were enrolled, and the first results are expected between September and November 2024.

Conclusions: This study will examine whether cross-modal sensory stimulation can enhance executive function, specifically eye movement control, in children with ADHD. In addition, the study will explore potential differences between auditory and visual noise effects in both groups. Our goal is to identify implications for understanding how noise can be used to improve cognitive performance.

Trial Registration: ClinicalTrials.gov NCT06057441; https://clinicaltrials.gov/study/NCT06057441

International Registered Report Identifier (IRRID): DERR1-10.2196/56388

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KEYWORDS

white noise; attention-deficit/hyperactivity disorder; eye tracking; cognitive performance; auditory; visual; oculomotor; child; children; protocol; crossover study; impairment; impairments; psychiatric disorders; cross modal; sensory stimulation; eye movement; noise

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder and one of the most common psychiatric disorders among children, affecting up to 5.3% of children around the world [1]. ADHD is characterized by developmentally inappropriate and impairing inattentiveness that may include hyperactive or impulsive behavior, highly associated with executive function deficits that cause impairments in school and difficulties with social interactions [2,3].

People with moderate to severe ADHD are commonly medicated with stimulants or nonstimulants [4], with stimulant treatment being more common due to larger effect sizes and less side effects [5]. The effects of stimulants have shown to be beneficial on several symptoms and impairments associated with ADHD, such as increased risk for other psychiatric disorders, substance use, increased risk for accidents and injuries, and antisocial behavior [6,7]. However, there are several side effects of stimulant medication; evidence for improved effects on learning processes and cognitive impairments commonly connected to ADHD varies [7,8]. Multimodal treatment, that is, medical treatment combined with nonmedical treatment and support, is thus recommended [9].

White noise exposure has been shown to improve cognitive performance in various cognitive tasks [10,11], both in neurotypical controls [12,13] and in particular for children with ADHD [14-16]. White noise is an information-dense and meaningless random signal produced by a stochastic process with a flat or constant power spectrum, that is, the same amount of energy (dB) remains over the entire frequency band [17].

To explain noise benefit among inattentive children, our point of departure is the moderate brain arousal (MBA) model proposed by Sikström and Söderlund [18]. The MBA model relies on the phenomenon of stochastic resonance (SR) where weak signals can be reinforced by external noise exposure [19]. Due to low levels of extracellular dopamine, people with ADHD have a small signal-to-noise ratio [20,21] making it hard to differentiate between the target signal and the surrounding noise [18]. By introducing the right amount of external noise in the right millisecond, through the sensory system, the noise can interact with the signal through the phenomenon of SR. It can thereby reinforce the signal and increase the signal-to-noise ratio, leading to improved cognitive performance in various tasks [14,22].

While white noise stimulation is suggested to be applicable to all modalities [18], auditory noise is the most studied and provides several demonstrations for the benefits of white noise stimulation [10,11]. For example, children with poor attention abilities or ADHD have displayed improved working memory during white noise exposure of around 80 dB [14-16]. When exposed to 70 dB white noise, an increased reading pace has also been demonstrated in this group [23]. In contrast, Allen and Pammer [24] did not find any white noise effects from noise played at “medium volume” in children with ADHD, nor did Metin et al [25] find any effects on decision-making from pink noise stimulation in the same group. When studying neurotypical adults, white noise demonstrated the ability to enhance new word learning, recognition accuracy, and word recall at 70 dB [26-28] and Awada et al [12] showed that white noise presented at 45 dB improved sustained attention, accuracy and speed of performance, while white noise presented at 65 dB improved working memory but also increased stress levels. This may indicate that different levels of auditory white noise are beneficial for different cognitive processes and may affect neurologically differentiated groups in different ways.

Other types of sensory white noise are less studied. However, in a group of children with reading disorder (RD) and phonological decoding difficulties, a common comorbidity to ADHD, visual white pixel noise stimulation has demonstrated improved reading and memory capacities [29], while a recent study using stochastic vestibular stimulation could not find any effects of white noise stimulation on visuo-spatial tasks [30].

The evidence for improved cognitive performance from cross-modal white noise stimulation is somewhat inconsistent and while working memory performance seems to be the most responsive to noise stimulation, there are other executive function deficiencies in ADHD that affect cognitive performance. Along with working memory deficits, diminished inhibitory control is a core symptom of ADHD, and also one of the most pervasive executive impairments [31]. Inhibitory control is a broad term referring to the ability to suppress nonproductive behaviors and cognitive processing. Deficiencies in inhibitory control in ADHD have been associated with several neural dysfunctions that affect different functional aspects [32-34]. For example, manual and oculomotor inhibitory controls are suggested to be independent processes, and diminished ocular inhibitory control is demonstrated to be a stronger predictor for impulsivity than manual inhibitory control [35]. Oculomotor inhibitory control has been suggested to be a more sensitive measurement in characterizing the performance of individuals with ADHD, and the use of eye tracking could thereby be a more efficient tool to study the disorder, compared with manual inhibitory control [36-38].

There are several paradigms used to assess oculomotor inhibitory control, where memory-guided saccades (MGS) and prolonged fixations (PFs) are the 2 most sensitive measurements [37,39]. In MGS, anticipatory errors reflect difficulties in inhibiting stimulus-driven responses, and even without any distractors ADHD leads to difficulties in maintaining fixation in PF [37].

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Aim and Objectives

With the main objective to shed further light into whether cross-modal sensory stimulation can be an effective tool to improve executive function, we here focus on eye movement control in children with ADHD. This study aims at comparing the effects of auditory and visual noise stimulation during 2 visual attention tasks. This study will be the first to investigate the effects of visual white pixel noise stimulation on children with ADHD, while the study will add to the research on auditory white noise stimulation by using a new assessment method in relation to noise stimulation. Based on the MBA model, the hypotheses are that noise stimulation will be beneficial for children with ADHD while impairing for TD children. We also hypothesize that TD children will outperform children with ADHD without noise stimulation and any such differences between TD and ADHD will be removed by the noise. The hypotheses are visualized in Figure 1.

As a secondary objective, by assessing different levels of visual white pixel noise, we expect to find an inverted U-shaped curve in accordance with the MBA model [18] and previous findings on visual noise stimulation [29].

Figure 1. Hypotheses: (1) Children with ADHD will improve performance during noise stimulation, (2) TD children will get impaired performance by noise stimulation, (3) TD children have higher performance than ADHD children without noise stimulation, and (4) the difference between TD and ADHD will be diminished by noise stimulation. ADHD: attention-deficit/hyperactivity disorder; TD: typically developing.

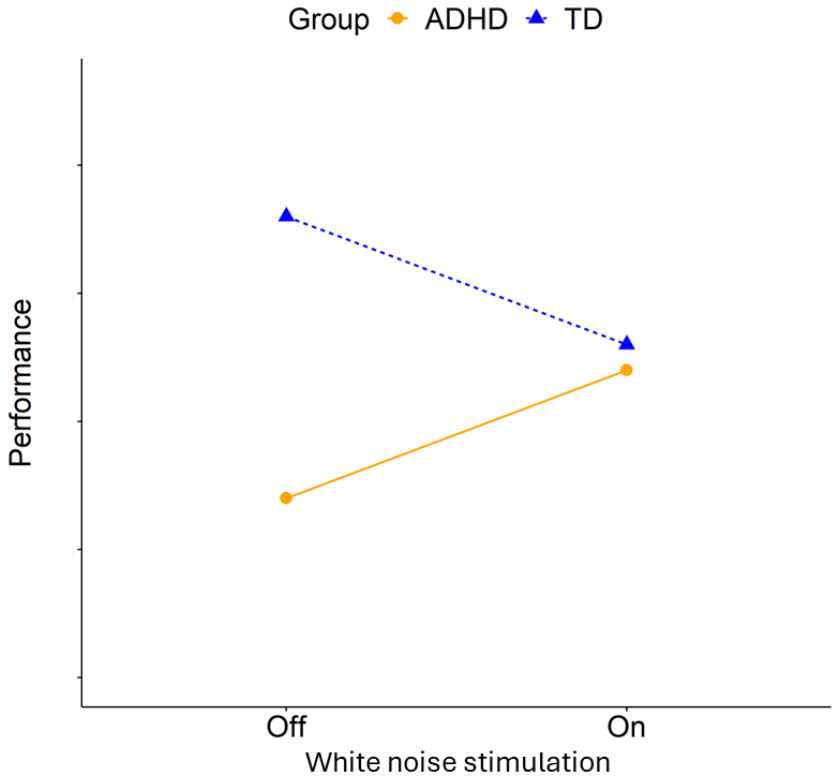

Methods

Design

This crossover study has 2 groups, children with ADHD and TD children, performing MGS and PF tasks while being exposed to different levels of either auditory or visual white noise. The tasks will be performed in the order of 2 assessments of MGS (7 min), 4 assessments of PF (4 min), and ending with 2 assessments of MGS (7 min), with planned breaks in between.

During the experimental session, the participants will be exposed to 2 levels of visual noise (25% and 50%) and 1 level of auditory noise (78 dB). The noise levels are chosen based on previous research on visual and auditory noise stimulation. During auditory noise, optimal noise benefit for children with ADHD has been found in the range of 75-80 dB [14-16]. In children with RD, the optimal visual white pixel noise level has been found to be at medium levels [29]. Following an inverted U-shaped curve, too little or too much visual white pixel noise deteriorated performance for the children with RD. Here, we apply 3 levels of visual noise to enable replication of those findings.

Performance on the tasks will be evaluated during noise stimulation and compared with performance without any noise stimulation. Thus, the participants will perform each task 4 times, one in each noise condition. The order of the noise stimulation between the tasks will be randomized and counterbalanced among participants. Recruitment was active between October 2023 and February 2024.

Study Population

The recruitment of children with an ADHD diagnosis was carried out in the outpatient child and adolescent psychiatry clinic in Lund, Sweden. Children aged 7-15 years, diagnosed with ADHD according to international guidelines following the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [2], were asked to participate in the study. With the goal to recruit a naturalistic sample for the study, children

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with all types of ADHD severity and with both combined, predominantly inattentive or predominantly hyperactive-impulsive type, were included in the study. Two authors (EC-K and PT), senior consultants in child and adolescent psychiatry, confirmed all diagnoses. Participants currently on medical treatment (methylphenidate) for their ADHD had to comply to withdraw their medication for 24 hours before the study. Exclusion criteria include medicating with other substance than methylphenidate and not being willing to withdraw from medication during assessment.

TD children, without any previous record of a psychiatric disorder, in the same age range as the ADHD group, were recruited from local schools in the district. Exclusion criteria for the control group is to have a neurodevelopmental diagnosis.

Background information on all participants was collected using the SNAP (Swanson, Nolan, and Pelham) rating scale and the Five-To-Fifteen-revised (5-15R) assessment, given by legal guardians. The SNAP rating scale is an assessment tool for symptoms of inattention and impulsivity or hyperactivity in ADHD, that stems from the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) criteria [40]. The SNAP rating scale contains 9 questions regarding inattentiveness and 9 questions regarding impulsive or hyperactive behavior that is rated on a 0 to 3 rating scale where 0=not at all, 1=just a little, 2=quite a bit, and 3=very much. The rating will be used to validate the ADHD and control groups. The 5-15R assessment consists of 181 statements concerning day-to-day situations, structured to map skills and behavioral patterns in children aged 5 to 17 years [41]. It is used for examining behavioral problems and possible developmental disorders and questions can be answered by selecting 1 of the 4 ratings from no, a little, a great deal, and very much.

Test Battery

Memory-Guided Saccades

The goal of the MGS task is to focus on a central point on the screen until it disappears. The central point consists of a blue (1°) disc with a red (0.2°) disc in the middle. Following Caldani et al [42] and Mahone et al [43], the center point is visible for a randomized time interval. After 2000-3500 milliseconds, with unpredictable timing, a white disc (1°) flashes in 1 of the 4 directions on the screen for 300 milliseconds with a 10° radius from the central point. That is, the disc flash is either directed at 45°, 135°, 225°, or 315°, with the current target randomly selected in 1 of the 4 directions of the screen [44]. The participant is instructed to keep focusing on the central point until the central point disappears, 2000-3500 milliseconds after stimulus (white disc) presentation. The participant is then instructed to make a saccade to the remembered position of the white disc. After 1000 milliseconds of center point extinction, the white disc reappears for 1000 milliseconds and the participant is instructed to make a corrective saccade to the correct position (Figure 2). The assessment consists of 30 trials.

Figure 2. In the memory-guided saccade task, the participant will be asked to look at the central fixation point as long as it is visible and not look at a white disc but remember its placement. When the central point vanishes, the participant should move their eyes to the remembered location of the white disc as fast as possible and stay there until it reappears.

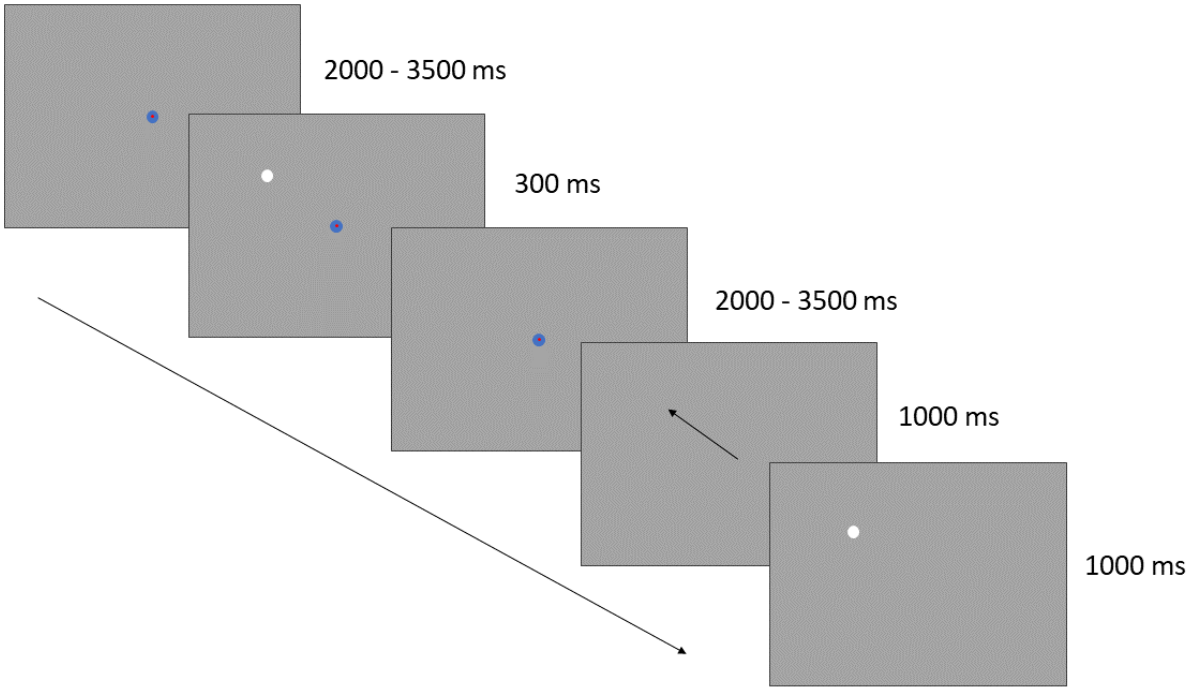

Prolonged Fixation

During a PF task, the participant is asked to maintain their focus on a central fixation point presented on the screen for 60,000 milliseconds (Figure 3). The central point has the same appearance as in the MGS task, that is, a blue (1°) disc with a red (0.2°) disc in the middle. The participant is instructed to return their gaze to the fixation point as soon as possible if they deviate from it.

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Figure 3. In the prolonged fixation task, the participant will be asked to focus on a central fixation point for 1 minute.

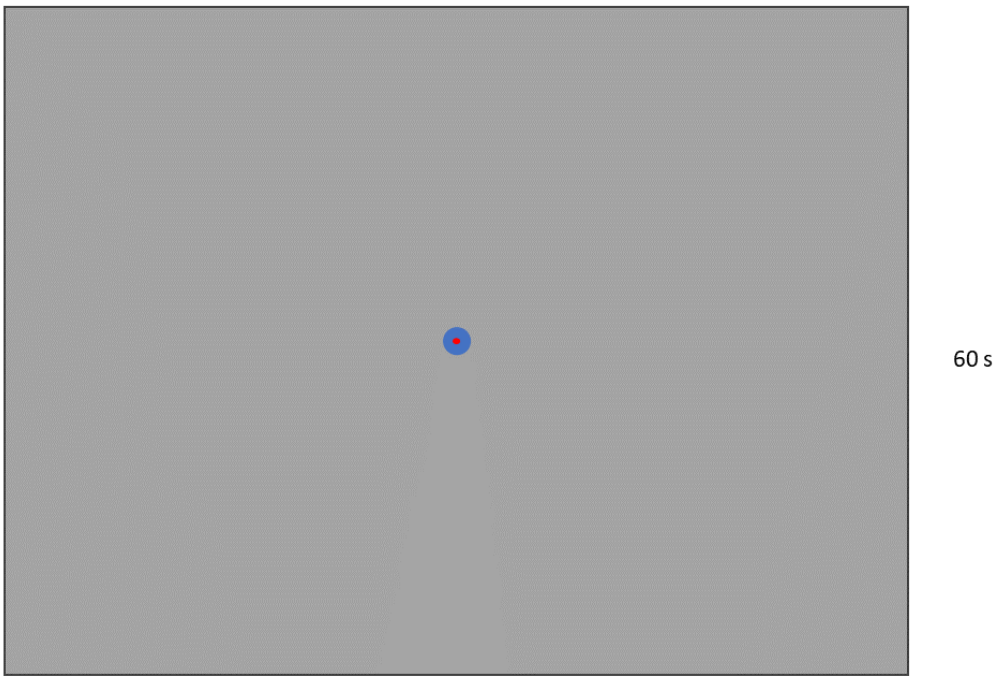

Intervention

Auditory White Noise

Auditory noise will be presented through a pair of RØDE NTH-100M earphones at 78 dB. The noise is generated from a uniform distribution U[0, 255]. To generate a stereo signal, 2 arrays drawn from such distributions are used, 1 for each channel. The audio file is sampled at 48,000 Hz, digitized to 16 bits, and saved in the .wav format. The noise level will be calibrated before each experimental session with a UNI-T UT351/352 sound level meter. Each pair of headphones will be separately calibrated when connected to the computer where the assessments are performed.

Visual White Pixel Noise

Visual noise is added to each pixel in the stimulus image by blending it with a transparent image of the same size with noise drawn from a uniform distribution U[0, 255], where 0 represents black and 255 represents white. The noise is controlled by the level of transparency of the noise image. For instance, a noise level of 100% would result in only noise and hide the stimulus image, whereas a noise level of 0% would not add any noise to the stimulus image at all. In this study, we will use noise levels of 25% and 50% (Figure 4).

Figure 4. The visual white pixel noise at 0%, 25%, and 50%.

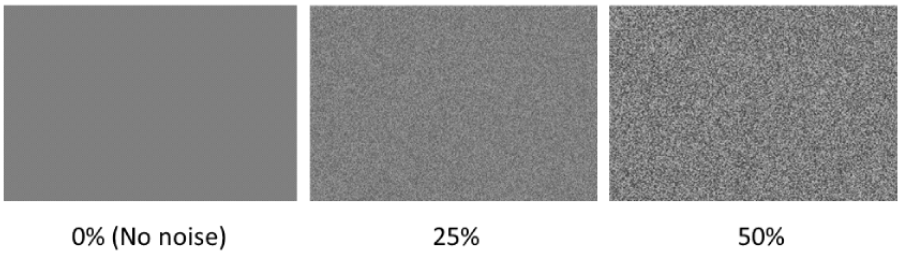

Measures and Data Collection

The study will take place at the Humanities Lab at Lund University, which has a digital classroom without any windows, equipped with 16 Tobii Pro Spectrum eye trackers (firmware: 2.6.1-orbicularis-0). Using a chin rest, participants will be placed 63 cm in front of an Eizo Flexscan EV2451 screen and be using a pair of RØDE NTH-100M earphones, connected to a desktop computer running Windows 10 (Microsoft Corp; Figure 5). Eye positions will be recorded at 600 Hz in horizontal and vertical gaze positions for both eyes, where (0,0) corresponds to the top-left on the screen and (1,1) corresponds to the low-right. The eye trackers will be calibrated with the default option in the Titta Toolbox (v.2.0.2) [45].

The dependent variables in the MGS task include (1) anticipatory saccades and (2) visuospatial working memory. Anticipatory saccades are saccades made before the extinction of the central fixation point and reflect the ability of response inhibition. Anticipatory saccades are classified as existing or nonexisting by the saccadic latency from central fixation point disappearance. Visuospatial working memory is assessed by saccadic accuracy or gain, that is, the distance between the saccade endpoint and the target. In the PF task, the dependent

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variable is intrusive saccades, that is, the number of deviations from the central point.

To ensure that participants understand the MGS task, a thorough presentation will be made before participants are asked to take a seat at one of the screened-off stations in the eye tracking lab. We will use similar instructions to describe the task as Mahone et al [43]: “As long as the center fixation point is visible, look only at the center point. Do not look at the flash when it occurs. When the center fixation point goes out, then immediately look to the place where you saw the flash.” All participants will then take part in a training session before data collection starts. The training measures performance by assessing correct and incorrect responses on the MGS and will be classified as successful if the participant has 3 or more correct responses, out of 5. A correct response is defined as maintaining the gaze within an area of interest of the central point until the point disappears and then moving the gaze to an area of interest of the place where the white disc was shown. If the participant has less than 3 correct responses, the test leader will give an additional instruction on how the task should be performed and the participant must redo the test. The training proceeds until the test leader is ensured that the participant understands the task.

Then, following the study design, the MGS assessment will be randomly performed in 2 of the 4 noise conditions (no noise, auditory white noise, visual white pixel noise 25%, and visual white pixel noise 50%) before a planned break. During the break, participants are instructed on the second assessment, PF, which will be performed once in each noise condition. Participants will then have a second planned break before completing the final 2 MGS assessments, securing assessments in all noise conditions. The noise conditions will be counterbalanced among participants.

To gather individual objective assessments of the tasks and interventions, participants will be asked to fill out a form inquiring about their experiences of performing the tasks. The answers will be used to examine whether there are any associations between the experiences of the different noise stimulation types and performance. The questions will focus on 3 areas and be divided into 5 questions, rated on a Likert scale. The first 2 questions will regard whether the participants experience the task as easier or harder when listening to or watching the noise. The third and fourth questions regard whether they experience the noise as uncomfortable or pleasant when listening to or watching it. The last question inquires whether they experience the tasks as boring or fun.

Figure 5. Each participant will be placed 63 cm in front of a screen and Tobii Pro Spectrum eye tracker, wear a pair of earphones, and rest their head on a chin rest during the assessments.

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Ethical Considerations

Ethical permission for the study is granted from the Swedish Ethical Review Authority (EPN 2023-02476-01) and the study is registered at ClinicalTrials.gov (NCT06057441). All legal guardians of the participating children will sign a written informed consent before the study, all children aged 14 years or less will have to orally agree to participate while children aged 15 years will leave a written informed consent. All participants were informed that discontinuing participation could be done without giving any specific reason or any following consequences. Data will be anonymized, kept confidential, and managed in accordance with the Data Protection Act, General Data Protection Regulation policies, and the Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). Data will be stored and secured both physically and electronically and will be accessible to the study team only.

Statistical Considerations

Sample Size

Power calculations are based on previous studies of auditive noise effects from our group [15,29] in combination with a review on oculomotor inhibition during MGS and PF [37]. To demonstrate an improvement of stimulation with sensory noise, equivalent to half an SD on intrusive saccades on PF, approximately 15 individuals per group are required to achieve a power of 0.80 with a *P* value of .05. The study aimed at including at least 60 participants, 30 in the ADHD group and 30 TD children.

Data Analysis Plan

Background information will be used to classify groups in the data. SNAP scores will be used to statistically validate the TD and ADHD group while the 5-15R assessment and task evaluation will be used in an investigative order to identify other subgroups than the patient and control group. For example, reading ability and motor performance are of interest. Söderlund et al [29] identified noise benefits in children with reading disability and vestibular dysfunction has been identified as more common in children with neuropsychiatric disorders than healthy controls [46] which may have an effect on cognitive functioning [47].

The dependent variables, such as (1) anticipatory saccades in MGS, (2) visuospatial working memory in MGS, and (3) intrusive saccades in PF, will be analyzed using regression analysis and ANOVA in relation to the noise stimulation. Anticipatory saccades in MGS will be assessed through latency and classified as either correct or incorrect. All MGS onsets ≤80 milliseconds [42] from central fixation point extinction will be classified as incorrect. Saccadic accuracy will initially be classified as being correct or incorrect by the saccade being made in the right direction (1 of the 4) and then, by the gain of the saccade, that is, the amplitude of the saccade divided by the Euclidean distance from origin to target. In the PF task, saccades with an amplitude larger than 4° [48,49] will be counted as intrusive and deviant from the central fixation point. Only the left gaze position from the recorded eye tracking data will be used for the analysis. Data analysis will be conducted in R (R Core Team).

Results

Data collection was initiated in October 2023 and ended in February 2024. A total of 97 participants were enrolled in the study. The first results are expected between September and November 2024.

Discussion

With hypotheses grounded in the MBA model [18], this study will investigate the effects of auditory and visual white noise on oculomotor control in children with ADHD and TD children. The hypotheses are as follows: (1) noise stimulation will be beneficial for children with ADHD, (2) TD children will be impaired by noise, (3) TD children will outperform the ADHD group without any noise stimulation, and (4) noise stimulation will remove such differences.

In accordance with previous research [37,39], we expect the ADHD group to perform more anticipatory saccades, have poorer saccadic accuracy in the MGS task, and make more deviations from the fixation point in the PF task in the no-noise condition, compared with the TD children group. We also expect both noise modalities to remove the differences in performance between the groups. However, we do not have any hypotheses regarding differences between the modalities.

There has only been one previous study, to our knowledge, investigating the effects of visual white pixel noise stimulation. In a study by Söderlund et al [29], where they studied reading performance during stimulation with both auditory white noise and visual white pixel noise in children with RD, the visual white pixel noise had a larger impact on performance than the auditory noise. Since RD is a common comorbidity to ADHD, similar effects may also be found in this study. However, whether our results will be in line with these findings or not might depend on several factors.

The noise in the study by Söderlund et al [29] was applied in the same modality as the stimuli (visual), which could be more beneficial on performance than if noise and task were presented in different modalities. Here we will use only visual tasks, which, in accordance with the study by Söderlund et al [29], could potentially be affected more by visual noise than auditory noise. On the other hand, in accordance with assumptions of the MBA model, numerous experiments have shown that the SR effect works cross-modal [12,15,50]. In that sense, modality should not affect performance, only the intensity of the noise. Since noise benefit can be plotted as a reversed U-shaped curve, where too little or too much noise is detrimental to performance, the MBA model postulates that the level of noise should affect performance to a larger extent than modality [18]. Accordingly, by using several visual noise levels, that is, 0%, 25%, and 50%, we should be able to map out the inverted SR U-curve for both ADHD and TD children, as previously demonstrated by Söderlund et al [29].

Another aspect to consider when studying white noise stimulation is the nature of the task performed. Previous research on auditory white noise has found support of noise benefits on several executive functions; however, not all tasks seem to be

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affected [10]. Most studies have investigated working memory performance in relation to white noise stimulation and there are only 2 previous studies of white noise stimulation in relation to inhibitory control or impulsive behavior, with somewhat contradictory results. In 1 study of impulsive behavior, where children with ADHD had to choose between a smaller reward sooner or a larger reward later, no beneficial effects from noise stimulation were found [25]. On the contrary, children with ADHD displayed improved inhibitory control, as measured by performance on a go or no-go task, during auditory white noise stimulation in another study [14]. Here, we argue that the tasks used in this study are more similar to the go or no-go task than the one measuring impulsive behavior and, thus, expect to find beneficial effects of white noise stimulation in accordance with the results from Helps et al [14]. We even argue that, by assessing MGS and PF through eye tracking, we will be able to investigate the association between brain mechanisms and behavior during white noise stimulation with a high temporal resolution [51]. The method will enable measuring responses to task demands on a moment-by-moment basis and provide a more precise measure of the effects of white noise stimulation than previously used cognitive tasks [51].

The population studied also needs to be considered during noise stimulation. ADHD consists of large heterogeneity and several comorbidities [1] that could potentially affect the effects of white noise stimulation. Due to the heterogeneity, there is often large variability in psychometric test results within ADHD [52] and it is not certain that the TD group will outperform the ADHD group in the no-noise condition.

To what extent such factors affect the way external noise interacts with internal noise levels is still too early to say, since the mechanisms behind noise benefit are still unknown. However, the MBA model postulates that external white noise and internal neural noise are additive through the phenomenon of SR and that there are individual levels of optimal noise for each person. This implies that children with ADHD generally benefit from larger amounts of external noise [18]. However, not all children seem to be affected by noise stimulation. For future work, it would be valuable to investigate different subgroups of ADHD to potentially find mechanisms that would further guide the application of white noise stimulation.

This study aims at supporting the continuation of white noise research. There is often little detail on how the noise is generated in different studies and such details might affect the results. We will improve this by making the code to generate and present the noise publicly available after the study is completed.

Conclusions

This research will offer new insights into the effects of auditory and visual white noise on oculomotor behavior in children with ADHD and TD children. The results will shed light on the potentially differential effects of auditory and visual noise on oculomotor control and working memory in both groups, with potential implications for understanding how noise can be used to improve cognitive performance.

Acknowledgments

The authors gratefully acknowledge Lund University Humanities Lab and thank participants for their time and contribution to the study. This research was funded by Aktiestinsen (grant AS2018-0001) and Thure Carlsson Foundation.

Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions

EJ and MN, in collaboration with EC-K, PT, PG, and GS are responsible for the overall conception and design of the study. MN is responsible for creation of software and assist EJ with study methodology, data curation, and proposed analyses. EJ, MN, PT, and EC-K are involved in study implementation. PG, GS, and EC-K received the funding to implement the study. EJ drafted the original manuscript alongside with preparing figures. All the authors participated in the review and revision of the manuscript and approved the final manuscript to be published.

Conflicts of Interest

None declared.

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Abbreviations

5-15R: Five-To-Fifteen-revised
ADHD: attention-deficit/hyperactivity disorder
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders, (Fifth Edition)*
MBA model: moderate brain arousal model
MGS: memory-guided saccades
PF: prolonged fixation
RD: reading disorder
SNAP rating scale: Swanson, Nolan, and Pelham rating scale
SR: stochastic resonance
TD: typically developing

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Protocol

Effectiveness and Acceptability of Cognitive Behavioral Therapy and Family Therapy for Gaming Disorder: Protocol for a Nonrandomized Intervention Study of a Novel Psychological Treatment

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Abstract

Background: Gaming disorder (GD) is a new official diagnosis in the *International Classification of Diseases, 11th Revision*, and with its recognition, the need to offer treatment for the condition has become apparent. More knowledge is needed about the type of treatment needed for this group of patients.

Objective: This study aims to evaluate the effectiveness and acceptability of a novel module-based psychological treatment for GD based on cognitive behavioral therapy and family therapy.

Methods: This study is a nonrandomized intervention study, with a pretest, posttest, and 3-month follow-up design. It will assess changes in GD symptoms, psychological distress, and gaming time, alongside treatment satisfaction, working alliance, and a qualitative exploration of patients' and relatives' experiences of the treatment.

Results: This study started in March 2022 and the recruitment is expected to close in August 2024.

Conclusions: This study evaluates the effectiveness and acceptability of a psychological treatment for patients with problematic gaming behavior and GD. It is an effectiveness trial and will be conducted in routine care. This study will have high external validity and ensure that the results are relevant for a diverse clinical population with psychiatric comorbidity.

Trial Registration: ClinicalTrials.gov NCT06018922; https://clinicaltrials.gov/study/NCT06018922

International Registered Report Identifier (IRRID): DERR1-10.2196/56315

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KEYWORDS

gaming disorder; psychological treatment; CBT; cognitive behavioral therapy; family therapy; effectiveness; acceptability; gaming; addiction; mixed method design; video games; leisure activity; Sweden; young adult; teenager; internet gaming disorder

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Introduction

Background

Playing video games is a common leisure activity, with 68% of those aged 13-16 years and 55% of those aged 17-18 years in Sweden reporting that they play regularly [1]. Among adults, 49% of men and 37% of women have played video games in the past 12 months, of whom 13% played daily [2]. While video gaming is a source of enjoyment for many, some individuals develop problems related to their gaming that negatively impact their well-being and everyday functioning. The research focusing on problematic gaming behavior, its impact on well-being and daily functioning, and potential treatments is still in its early stages of development.

In 2015, internet gaming disorder (IGD) was included in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-V*) as a potential diagnosis in the section for disorders requiring further research [3]. In 2018, gaming disorder (GD) was included as an official diagnosis in the *International Classification of Diseases, 11th Revision* (*ICD-11*) [4]. GD is defined by a lack of control over one's gaming behavior, prioritizing it over other activities, and continuing to play despite negative consequences, which results in increased psychological distress or problems with daily functioning. GD as a psychiatric disorder has been criticized by researchers who are concerned about the risk of medicalizing normal behavior, stigmatizing gaming, and pathologizing children's everyday activities. They argue that sufficient evidence does not yet exist and that the criteria developed are overly based on other addiction disorders [5].

The global prevalence of GD is estimated to be 0.5% to 15% [6] and varies across studies and regions, with higher reported prevalence in Asia [7]. In a Swedish survey study, the prevalence rate was estimated to be 1.2% [8]. A meta-analysis of prevalence studies with a total of 226,247 individuals showed a global prevalence of 1.96% in all age groups; however, most of the included studies focused on adolescents and young adults [9]. There is high comorbidity with other psychiatric diagnoses, such as depression, anxiety, and obsessive-compulsive disorder [10-12], as well as neuropsychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [13,14]. Individuals with GD also demonstrate a heightened risk for suicidal ideation, sleep disturbances, poor academic performance, weaker emotional regulation, and poorer executive functioning [15-19]. Similar patterns have been observed in a Swedish context, where individuals who engaged heavily in gaming, both highly engaged gamers and gamers with problematic gaming behavior, experience loneliness and psychological distress [8,20]. In a 4-year longitudinal study, Hygen et al [21] observed no direct correlation or causation between IGD and mental health problems in children. They suggest that the concurrent emergence of these problems can be attributed to shared underlying factors.

GD is most common among male adolescents and young adults [9]. Time spent gaming is a weak predictor of symptoms of GD [22]. Research instead highlights gaming motives as crucial predictors of GD. Gaming used as an escape or coping mechanism is notably linked to severe problematic gaming behavior [23]. Several social factors are associated with GD in children and adolescents. Studies have shown that poorer quality relationships in the family are associated with increased severity of problem gaming [24]. A meta-analysis by Coşa et al [25] that investigated the parental factors for IGD showed that the lack of parental involvement and supervision, as well as family conflict and inadequate social support, are correlated with IGD. Paradoxically, some studies showed that overly strict restrictions can sometimes exacerbate the problem [25].

To date, the majority of studies have focused on various forms of cognitive behavioral therapy (CBT) as potential treatments for GD, and the results suggest that CBT is effective for GD [26-28]. Important studies on CBT for GD include CBT for internet addiction [29], CBT combined with family therapy (FT) [30], CBT combined with psychoeducation for parents [31], short-term treatment for internet and computer game addiction (STICA) [32], *Professioneller Umgang mit technischen Medien* (Professional Use of Technical Media; PROTECT+) [33], and relapse prevention [34]. Kim et al [28] conducted a network meta-analysis and found that despite the scarcity of intervention studies incorporating FT for GD, its combination with CBT may be a promising way to maximize treatment efficacy. Bonnaire et al [35] argue that it is important to involve parents in the treatment of GD because several studies link GD to the family environment and parent-child relationship. Multidimensional FT has been tested in a randomized controlled trial (RCT) for adolescents with IGD [36]. In comparison to FT treatment as usual, there were no significant differences between groups, although there were only 42 participants. Nonetheless, the whole group improved significantly from baseline to 12 months after treatment.

In conceptualizing our psychological treatment, we draw upon self-determination theory, which posits that 3 intrinsic needs—relatedness, competence, and autonomy—motivate behavior [37]. Research suggests that games proficiently satisfy these needs [38]. Given that individuals with GD often engage in gameplay to escape or cope, it may indicate a deficiency in need fulfillment within their real-world interactions, thereby further intensifying the allure of gaming [23,39]. We propose that these individuals have an imbalance within their motivational systems: an overactive threat system that deters engagement with the world outside gaming, coupled with a reward system tuned to gaming incentives. It is therefore important to strengthen individuals' capabilities in meeting their needs in activities outside of gaming. Furthermore, considering the prevalence of gaming issues among adolescents, it is crucial to acknowledge the developmental and familial context in which problematic gaming behaviors manifest [24]. Individuals with GD often face difficulties in addressing their problematic behavior independently, which emphasizes the necessity of developing a systemic family-inclusive approach to treatment [35,40].

There is a call for more RCTs of psychological treatments for GD [26]. While efficacy trials offer high internal validity due to their controlled environments, they often deviate from clinical practice, which decreases the generalizability and applicability

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of the findings. Meanwhile, RCTs may not reflect real-world scenarios, as patients with comorbidities are often excluded and clinicians are directed to adhere strictly to a manual and limit parallel interventions [41]. Effectiveness trials, in contrast, evaluate treatments in standard clinical practices, embracing a broader patient demographic and intervention flexibility. This approach increases the relevance and generalizability of the findings. Meta-analyses suggest that, while efficacy trials often report larger treatment effects, the outcomes from effectiveness trials may be more representative of what clinicians can expect in their practice [42,43]. Our objective was to develop and evaluate a treatment within the local health care system to ensure its practical applicability in that setting, which was the reason we chose to carry out an effectiveness trial.

Considering the promise of combining CBT with FT to enhance the effects of psychological treatment, we aim to develop and evaluate the effectiveness of a novel module-based psychological treatment in a naturalistic setting that integrates interventions from CBT and FT for GD.

Aims and Objectives

This 1-group, nonrandomized intervention study aims to evaluate the effectiveness and acceptability of a novel psychological treatment for GD offered to patients recruited at the outpatient clinic Gamingprojektet Maria Malmö in Sweden. The specific objectives of this study are, first, to evaluate the effectiveness of the psychological treatment in terms of changes in symptoms of GD, psychological distress, and time spent gaming. The second objective is to evaluate the acceptability of the treatment in terms of treatment satisfaction and working alliance. In addition to this objective, a qualitative study will be conducted focusing on exploring patients' and relatives' experience of the psychological treatment. The third objective is to explore how clinicians use and relate to a manual for psychological treatment of GD. It will be explored by evaluating which modules clinicians use in the treatment, how many sessions they spend on each module, and the total number of sessions required for each treatment.

Methods

Study Design and Setting

This study has a single group with a pretest, posttest, and 3-month follow-up design, as well as measures at each session. It is conducted in routine care and the participants are treatment-seeking patients. This study will be carried out at a single site, Gamingprojektet Maria Malmö, which is an outpatient clinic for problematic gaming behavior and GD in Skåne, Sweden. The participants will be offered a module-based psychotherapy that is a combination of interventions from CBT and FT. The treatment will be given by psychologists with a 5-year education in clinical psychology and psychotherapy, social workers with 1-year training in psychotherapeutic counseling, and psychotherapists with 2.5 years training in psychotherapeutic counseling. The treatment can be given as an individual treatment with the patient, a family treatment with only the parents, or a family treatment with both the parents and the patient. Most treatments will be conducted with 1 clinician per treatment, but exceptions can be made if there is a high level of conflict between the patient and the parents. Assessment points include baseline, which is the assessment period; the start of therapy (pretreatment period); the end of therapy (posttreatment period); and the follow-up after 3 months. In addition to these quantitative measures, we will also conduct qualitative interviews with patients and relatives about their views on the outcome, acceptability, and eventual negative experiences of the treatment, which will be presented in a separate paper.

A Transparent Reporting of Evaluations With Nonrandomized Designs 2004 flow diagram [44] of this study's design is shown in Figure 1. This study is registered with ClinicalTrials.gov (NCT06018922). Recruitment started March 17, 2022, and will close on August 30, 2024.

Figure 1. Recruitment and flow diagram (TRENDS). TRENDS: Transparent Reporting of Evaluations With Nonrandomized Designs.

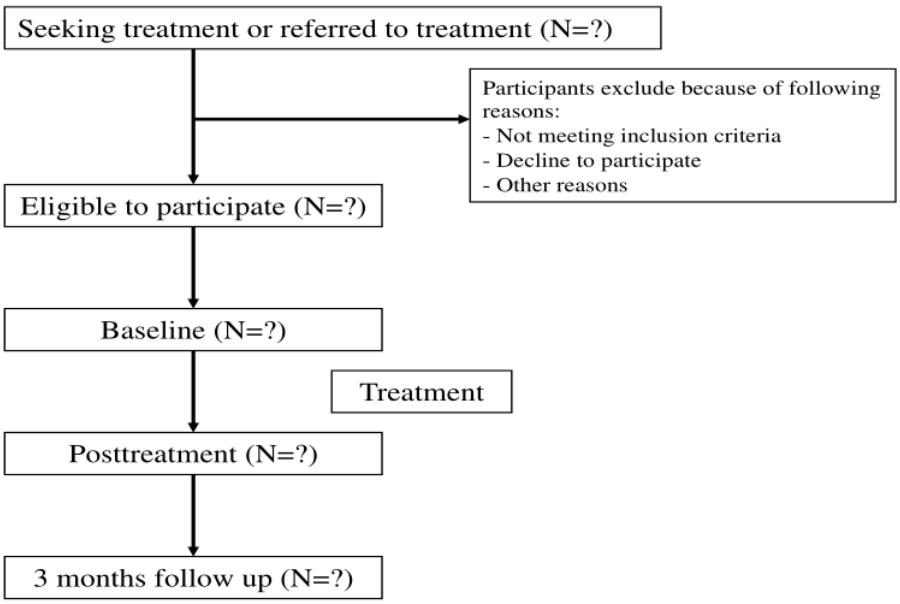

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Recruitment

All patients who seek treatment or are referred to Gamingprojektet for GD treatment will be invited to participate in this study. The first patient was recruited in March 2022, and extensive work has been conducted to spread information about the clinic, both directly to the citizens by paid advertising on social media, public transport, billboards, and newspaper articles to reach inhabitants of Skåne county, and a campaign directed at professionals in the public health care system, in the school system, and social services. Patients come to the clinic either via self-referral or through referral from health care practitioners, schools, and social services. The health care system in Sweden is mostly government-funded, and all visits to this clinic are free of charge.

Eligibility Criteria

This study aims to conduct a naturalistic effectiveness trial designed to include a representative group of patients; hence, inclusion and exclusion criteria are minimal. The inclusion criteria for participation include (1) being aged 13 years or older; (2) seeking treatment for problematic gaming behavior or GD as a patient or as a parent on behalf of their child; and (3) the patient's gaming is affecting their well-being, daily functioning, or creating conflicts in the family.

The exclusion criteria for participation are (1) somatic or psychiatric disease that is contraindicating or severely complicates the implementation of the intervention (eg, ongoing psychotic, manic episode, or neuropsychiatric condition with severe disability) and in which case the patient is referred on from the clinic, and (2) the patient or parent (if the patient is aged younger than 15 years) is not able to read and communicate proficiently in Swedish.

Treatment

The treatment that is studied is a novel psychological treatment developed by the researchers specifically for GD and is a combination of interventions from CBT and FT. The treatment is planned for approximately 15 sessions. However, it can be completed earlier if the patient chooses or extended beyond if the patient and clinician deem it necessary. The treatment is module-based with 10 individual modules and 7 family modules. The aim is to adapt each therapy and choose several modules, somewhere between 1 and 6 modules, depending on the patient's age, family system, functioning, and case formulation. The modules have been developed by reviewing common interventions from CBT and FT, as well as other psychological treatments for GD. The modules are described in Textboxes 1 and 2.

Textbox 1. Individual modules.

1. *Alternative activities to gaming (behavioral activation)*: helping the patient engage in other activities in addition to gaming, and problem-solving in session to increase the likelihood of engaging in other activities.
2. *Daily structure*: helping the patient create a clear and sustainable daily routine. For example, waking time, when to eat, when to do chores, and when to go to bed.
3. *Basic needs—nutrition, exercise, and sleep*: assisting the patient in developing better habits by providing psychoeducation about food, exercise, and sleep and planning together to change habits related to these basic needs.
4. *Impulse control*: identifying triggers for gaming, learning to delay acting on impulses, distracting oneself, and finding other behaviors that fulfill similar functions.
5. *Emotion regulation*: providing patients with psychoeducation about emotions, practicing recognizing their emotions, reflecting on how to manage strong emotions, and then practicing using these strategies at appropriate times.
6. *Working with thoughts*: working with the patient to relate more freely to their thoughts, not seeing them as truths and thereby reducing their reactions to them. This involves psychoeducation about thoughts, practicing how to approach them in therapy, and planning worry time.
7. *Social anxiety*: providing psychoeducation about common thoughts and mechanisms in social anxiety and exposure to situations where these thoughts and anxiety arise.
8. *Procrastination*: identifying procrastination behaviors and practicing strategies to manage these behaviors.
9. *Relationships and conflict management*: communication exercises and how the patient can handle conflicts with loved ones more helpfully.
10. *Problem-solving*: teaching the patient a step-by-step problem-solving strategy.

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Textbox 2. Family modules.

1. *Psychoeducation about gaming*: parents receive information about games, how they are played, and common motives for gaming. The purpose is to make parents more curious about gaming, focus more on the positive aspects of gaming, and understand how their children are gaming.
2. *Alternative activities to gaming*: helping parents engage their children in activities other than gaming, a form of behavioral activation. Specifically, starting with activities that children want to do and that can fulfill similar needs as gaming. Further, discussing the "activity plate model," that is, what else they need in their lives besides gaming and how to incorporate it into their everyday life.
3. *Positive time together*: working to reduce conflicts in the family and creating more positive time together free from demands and conflict. This includes trying to avoid unnecessary conflicts, practicing positive communication, and acknowledging things that work.
4. *Demands and capabilities*: often, children have difficulties that parents are unaware of, or parents generally set higher demands on children than they can handle which increases the risk of the child turning to gaming to avoid the demands. We work to help the family to identify the right level of demands, and what support the patient needs to succeed in the tasks given to them.
5. *Making agreements in the family*: providing information and practicing together with the family on how to make agreements together and set boundaries. It is essential for children to feel listened to and participate in the discussion, even though parents may have the final say. This is performed by practicing concrete steps in making agreements together, first in the session together and then the family does it by themselves.
6. *Setting boundaries with emotional validation*: practicing how parents handle situations where they need to set boundaries for their children. The focus here is on becoming aware of their own and their children's feelings and validating the children's emotional experiences. The aim is to stay present with the children's emotions without trying to problem-solve, eliminate the feelings, or escalate the conflict.
7. *Conflict management*: discussing how to handle situations where emotions become overwhelming in the family system. Often, it involves temporarily stepping back from the situation and revisiting the situation at a later point.

Outcome Measures

This study consists of children, adolescents, and adults, as well as their parents. The patients will have different outcome measures depending on whether they are children (aged 13-15 years) or adults (aged 16 years and older). When the patient is a child, some outcome measures will also be collected from parents. An overview of outcome measures and assessment points is shown in Tables 1 and 2.

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Table 1. Measures' and measurements' points for adults, aged 16+ years.

Measure	Outcome	Assessment	Treatment period			
		Baseline	Pretreatment	Weekly	Posttreatment	Month 3
CORE-OM 34[a]	Primary	✓	✓		✓	✓
GDT[b]	Primary	✓			✓	✓
IGDS9-SF[c]	Primary	✓			✓	✓
Time spent gaming	Primary	✓	✓	✓	✓	✓
How do you feel?	—[d]			✓		✓
Demographic	—	✓				
MINI[e] interview	Secondary	✓			✓	
GAF[f]	Secondary	✓			✓	
NODS-PERC[g]	Secondary	✓			✓	
Social media disorder	Secondary	✓			✓	
Game motives	Secondary	✓			✓	
Emotion regulation	Secondary	✓			✓	
Alcohol use	Secondary	✓			✓	
Substance use	Secondary	✓			✓	
Harm severity of gaming	Secondary	✓			✓	
Working alliance	Acceptability					
Treatment satisfaction	Acceptability					

[a]CORE-OM 34: Clinical Outcomes in Routine Evaluation–Outcome Measure 34 questions.

[b]GDT: Gaming Disorder Test.

[c]IGDS9-SF: Internet Gaming Disorder Scale–Short-Form.

[d]Not applicable.

[e]MINI: Mini International Neuropsychiatric Interview.

[f]GAF: Global Assessment of Functioning.

[g]NODS-PERC: National Opinion Research Centre Diagnostic Screen for Gambling Disorders–Preoccupation, Escape, Risked Relationships, and Chasing.

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Table 2. Measures' and measurements' points for children, aged 13-15 years.

Measure	Outcome	Assessment	Treatment period			
		Baseline	Pretreatment	Weekly	Posttreatment	Month 3
RCADS[a]-child	Primary	✓	✓		✓	✓
RCADS-parent	Primary	✓	✓		✓	✓
GDT[b]	Primary	✓			✓	✓
IGDS9-SF[c]	Primary	✓			✓	✓
GAIT[d]-parent	Primary	✓			✓	✓
Time spent gaming	Primary	✓	✓	✓	✓	✓
How do you feel?	—[e]			✓		
Demographic	—	✓				
MINI[f]-kid interview	Secondary	✓			✓	
CGAS[g]	Secondary	✓			✓	
NODS-PERC[h]	Secondary	✓			✓	
Social media disorder	Secondary	✓			✓	
Game motives	Secondary	✓			✓	
Emotion regulation	Secondary	✓			✓	
Alcohol use	Secondary	✓			✓	
Substance use	Secondary	✓			✓	
Harm severity of gaming	Secondary	✓			✓	
Working alliance	Acceptability				✓	
Treatment satisfaction	Acceptability				✓	

[a]RCADS: Revised Child Anxiety and Depression Scale.

[b]GDT: Gaming Disorder Test.

[c]IGDS9-SF: Internet Gaming Disorder Scale–Short-Form.

[d]GAIT: Gaming Addiction Identification Test.

[e]Not applicable.

[f]MINI: Mini International Neuropsychiatric Interview.

[g]CGAS: Children's Global Assessment Scale.

[h]NODS-PERC: National Opinion Research Centre Diagnostic Screen for Gambling Disorders–Preoccupation, Escape, Risked Relationships, and Chasing.

Primary Outcome Measures

Overview

The primary outcome measures are symptoms of GD, psychological distress, and time spent on gaming in the last week.

Adults

Symptoms of GD are measured with both the Gaming Disorder Test (GDT) [45] and the Internet Gaming Disorder Scale–Short-Form (IGDS9-SF) [46]. The GDT consists of 4 questions that cover the criteria for GD in *ICD-11* and is answered on a 5-point Likert scale, from 1 to 5. The total score is 20 and the suggested cutoff is that all questions are answered with 4 or 5. The IGDS9-SF consists of 9 questions that cover the criteria for IGD in the *DSM-V*, with an additional question added about craving, and is answered on a 5-point Likert scale, from 1 to 5. The total score for the original IGDS9-SF questions is 45. The suggested cutoff point based on an Italian clinical sample is 21 [47]. Psychological distress is measured by the Clinical Outcomes in Routine Evaluation–Outcome Measure 34 questions (CORE-OM 34). The CORE-OM 34 contains 34 questions about subjective well-being, symptoms (anxiety, depression, and physical problems), life functioning, and risk of suicide [48]. It is answered on a 5-point Likert scale, from 1 to 5. The last primary outcome measure is how much time the patient has spent on gaming in the last week, where the patient themselves approximates how much time they have spent gaming.

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Children

Symptoms of GD are measured with the GDT, IGDS9-SF, and Gaming Addiction Identification Test [49]. The Gaming Addiction Identification Test is a parent assessment with 17 questions that is answered on a 5-point Likert scale, from 1 to 5. It also contains a question about the estimated time spent gaming per day. Psychological distress is measured by the Revised Child Anxiety and Depression Scale (RCADS) [50] child and parent self-report. The RCADS contains 47 items assessed on a 5-point Likert scale, from 1-5, for children and parents, covering subscales for social phobia, panic disorder, general anxiety disorder, obsessive-compulsive disorder, separation anxiety, and depression. Scores are compiled into 2 totals: one for combined anxiety and depression, and another for exclusively anxiety-related symptoms. The RCADS is globally recognized in research and clinical settings for its strong psychometric reliability [50]. Lastly, the children estimate how much time they have spent gaming during the last week.

Secondary Outcome Measures

Overview

The secondary outcome measures are psychiatric comorbidity, everyday functioning, emotional deregulation, problematic social media behavior, gaming motives, symptoms of problem gambling, alcohol use, substance use, harm severity of gaming, therapeutic alliance, and treatment satisfaction.

Adults

Psychiatric comorbidity is measured by semistructured interviews by a clinician with the Mini International Neuropsychiatric Interview which assesses common psychiatric diagnoses from the *DSM-V* and *International Classification of Diseases, 10th Revision* (*ICD-10*) [51]. Everyday functioning is measured by clinicians using the Global Assessment of Functioning [52], where the clinician assesses everyday function on a 1-100 scale. Emotional dysregulation is measured using the Difficulties in Emotion Regulation Scale-16 [53], which consists of 16 items. Problematic social media use is measured with the Bergen Social Media Addiction Scale, which contains 6 questions answered on a 5-point Likert scale, from 1 to 5, about salience, mood modification, tolerance, withdrawal, conflict, and relapse [54]. Gaming motives are assessed using the Motives for Online Gaming Questionnaire, which contains 27 questions answered on a 5-point Likert scale, from 1 to 5 [55]. The questionnaire assesses 7 motivational factors: escape, coping, competition, social, skill development, fantasy, and recreation. Problem gambling is measured with the National Opinion Research Centre Diagnostic Screen for Gambling Disorders–Preoccupation, Escape, Risked Relationships, and Chasing, consisting of 4 questions about gambling problems throughout one's lifetime, focusing on preoccupation, chasing losses, escape, and the social consequences of gambling, answered on a binary scale. If the participant endorses any item, it indicates problem gambling [56]. To assess the level of alcohol consumption, we use the Alcohol Use Disorders Identification Test-Consumption scale, 3 questions, which focus on the frequency and quantity of alcohol consumption [57]. To measure substance use behavior, a drug identification list consisting of 10 common substances is given to the patients from which they indicate whether they have ever used said substance, and if so, how often. Gaming-related harm severity was assessed by questions about how the patient's gaming impairs their ability to function in school or work, everyday situations at home, social activities, free time, and family life. The scale ranges from 0 (indicating no harm or minimal impact) to 10 (signifying severe harm) on how gaming impairs their function in the 5 parts of their everyday life. The therapeutic alliance is measured by the Working Alliance Inventory Short, which contains 12 questions about the alliance in the therapeutic relationship [58]. Further, 9 additional questions were developed by the research team and included regarding patient treatment satisfaction.

Children

In total, 2 of the instruments are different between the children and adults. Psychiatric comorbidity is measured by using the Mini International Neuropsychiatric Interview for Children and Adolescents [59]. Everyday functioning is measured by the clinician using the Children's Global Assessment Scale [60], where clinicians assess everyday function on a scale from 1 to 100.

Additional Measures

Data concerning demographics, what games they are playing, everyday gaming behavior, social life, family life, psychical health, sleep and eating habits, as well as symptoms of ASD and ADHD, are gathered at baseline to provide a comprehensive picture of the treatment-seeking sample. For the adults, ASD symptoms will be measured with Ritvo Autism and Asperger Diagnostic Scale 14 [61]. Symptoms of ADHD will be measured by the Adult ADHD Self-Report Scale part A, which contains 6 items, and it has been found that these questions are the most predictive of ADHD [62]. For children, patient-reported symptoms of ASD and ADHD are measured with Ritvo Autism and Asperger Diagnostic Scale 14 and Adult ADHD Self-Report Scale, respectively. Likewise, parent-reported child ASD and ADHD symptoms are measured using the Autism Quotient [63] and Swanson, Nolan, and Pelham [64] scales, respectively. After each treatment session, the patients will answer 4 questions: rating their psychological well-being on a 1-10 scale, reporting how much time they have spent gaming the last week, rating how much their psychological distress depends on their gaming on a scale of 1-10, and the reporting of how helpful they found this treatment session on a 1-10 scale. After treatment, the patients will be asked whether they have received any parallel interventions during the treatment and whether they will seek further help for their problems. Before treatment begins, the patients' current medications will be documented. During the posttreatment assessment, any changes to their medications during the treatment will be recorded. These changes will be reported at the group level in the final paper.

Sample Size

This study is performed in routine care and a naturalistic setting, which means that how many participants can be recruited is dependent on how many patients seek treatment at the said outpatient clinic. We aim to conduct semistructured interviews

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with at least 20 participants, both patients and parents, or until data saturation is reached.

Statistical Analysis and Power Analysis

We will present descriptive statistics (eg, proportions, means, SD, and medians) and bivariate correlation measures for variables collected at baseline. To assess the overall effect of the treatment phase (baseline, postintervention, and follow-up) on primary (eg, GD symptom burden, psychological distress, and time spent gaming) and secondary continuous outcome measures, we will conduct repeated measures mixed-effect ANOVA with time as a fixed factor and patient as a random factor; post hoc pairwise comparisons with Bonferroni corrections will be conducted to determine differences in outcome variables across treatment phases. This approach is essentially equivalent to repeated measures ANOVA but will enable us to control individual variability and perform analyses including all cases provided each patient has 1 valid pre- or postoutcome value. In addition, we will conduct logistic mixed-effect model analyses to assess the effect of time on binary outcome measures (ie, symptom improvement).

All tests will be 2-sided with the α level set at .05. Based on previous CBT-based therapy studies for GD that indicate medium-to-large effect sizes from pre- to posttest for symptom burden, time playing, and mental health improvement [32], we estimate that a minimum of 28 participants would be required to achieve 80% power to detect such differences across all outcome measures (Cohen f=0.25). To accommodate a potential attrition rate of 30%, we will enroll a minimum of 37 participants for quantitative analyses. Follow-up univariate logistic regressions will be conducted to explore which baseline characteristics are predictive of participant symptom improvement, defined by subcutoff scores for the GDT, IGDS9-SF, and CORE-OM 34 follow-up. Planned analyses will be conducted apropos of missing data patterns and modified accordingly when needed. The results will be reported as means and odds ratios, respectively, with 95% CIs.

Qualitative Component

To bolster our quantitative findings and refine our treatment model, our project will integrate a qualitative component. This phase will consist of semistructured interviews with patients and their relatives, exploring their thoughts and experiences of GD and the psychological treatment they underwent. The interviews will center on gaining insights into their comprehension of GD, their perceptions of the treatment's effectiveness, its acceptability, and whether it appropriately addressed their needs. Furthermore, the interviews will probe into the mechanisms of change, exploring participants' experiences with individual or family-focused aspects of the treatment.

Interviews will be conducted by staff with knowledge of qualitative interview methodology and will be recorded and transcribed verbatim. Initially, we will remove person identifiers and pseudonymize the data. Further, 2 researchers will independently acquaint themselves with the data and identify potential themes. These will then be jointly reviewed and defined, culminating in their formal naming and clarification. Quotes will be translated to English via a back-translation procedure in collaboration with an independent bilingual party to ensure accuracy.

Ethical Considerations

This study is approved by the Swedish Ethical Review Authority (reference: 2021-06666-01, 2022-03-17). Subsequent amendments have been approved (reference: 2023-03112-02; 2023-03112-02, reference: 2023-03112-02; 2023-06-05, and reference: 2023-06393-02; 2023-11-08). We estimate that this study poses little or no risk for the participants, especially since this study is carried out in routine care. The patient's choice to participate in the research will not impact the treatment they receive and they will go through the same assessment before and after treatment regardless of whether they take part in the research or not. All participants will give written consent to participate in this study and may withdraw at any point. For patients aged 13 and 14 years, the children will give assent and parents will give written consent.

Participants' Safety

This study is integrated into routine care, ensuring that standard clinical safety procedures are adhered to. There are weekly meetings where the clinicians discuss treatment progress and potential adverse events. The patients answer a questionnaire where they rate their psychological well-being at every treatment session, and the clinicians monitor these forms, which enables them to detect a change in the patients' well-being. If a patient starts deteriorating in psychological distress, develops a new psychiatric disorder, or has emerging suicidal ideation, it will be addressed in the ongoing psychological treatment. If necessary, an experienced psychiatrist is available to adjust medication or assess the need for inpatient care.

Data Management

Personal and identifiable data will be collected from patients. All collected data will be stored securely, with the physical documents being stored in locked cabinets and digital data behind firewalls and only be accessible by the clinicians and researchers. The data from all patients will be compiled in a database with study ID. This study ID will be recorded in a document, which will be stored separately from the physical and digital data and can only be accessed by 1 member of the research team.

Dissemination

Findings will be published in peer-reviewed journals, at research conferences, and disseminated to the general public.

This study will be reported per the Transparent Reporting of Evaluations With Nonrandomized Designs statement. The primary objective is to compose a key scientific paper concentrating on the efficacy and acceptability of the treatment. Subsequent studies within the research project will include qualitative interviews and analysis to explore the experiences of both patients and their relatives with the treatment. Additional papers may also emerge, delving into predictors and moderators influencing treatment outcomes.

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Results

This study started on March 17, 2022, and recruitment is planned to end on August 30, 2024. The first results are expected in 2025.

Discussion

Principal Findings

This study will evaluate the effectiveness and acceptability of psychological treatment for patients with problematic gaming behavior and GD about symptoms of GD and psychological distress and time spent gaming. This study will be a 1-group, pretest-posttest with a follow-up design including at least 37 patients undergoing psychological treatment at an outpatient clinic specialized in GD. The treatment is module-based and is based on CBT and FT. The treatment will be given as individual sessions with the patient sessions, family sessions, sessions with parents, or a combination of the three. The duration of the therapy provided to each patient can vary, ranging from 5 to 20+ sessions based on the case formulation of the patient and the progression of the therapy.

This study is important in several aspects: this study has a high external validity since it is conducted in routine care. Due to that, this study ensures that the results are relevant for a diverse clinical population with patients with high comorbidity with other psychiatric conditions. The treatment consisting of standard CBT and FT interventions not only roots this study in well-established therapeutic techniques but also indicates that, should the results be positive, the treatment protocol can easily be adopted by other clinics. Moreover, this study's origins in actual clinical practice underscore its commitment to real-world effectiveness, emphasizing the value of learning directly from clinical experiences and spreading that knowledge.

There are feasibility and exploratory elements to this study. The patients answer questions about satisfaction and working alliance with the therapist at the posttreatment assessment. There are also planned qualitative interviews with the patients and relatives of the patients regarding their view of the treatment, important components of the treatment, if anything should change, and the patient-clinician relationship.

Limitations and Strengths

The primary limitation of this study is its single-arm design, with 1 intervention group and no control group. This design makes it hard to draw any definitive conclusions about the effectiveness of the treatment, as opposed to potential influences from the patient–health care professional interactions or the natural course of the disorder's reduction over time. However, we can compare our results with outcomes from other studies on treatment for GD. Several factors influenced our decision to pursue a single-group trial design. First, we anticipated recruitment challenges given that this study would be conducted at a newly established clinic. Ethical considerations also played a part; we felt it imperative to offer the best possible treatment to those seeking assistance, rather than withholding potential benefits for the sake of a control group. There is no established treatment for GD, and therefore, we could not have another treatment arm in this study. Due to recruitment challenges, in terms of few patients seeking treatment for GD and a lack of awareness about the newly opened clinic, we decided not to use a waiting list control group. Lastly, given this study's exploratory nature, our objective was to evaluate the treatment in a real-world setting, examine how many sessions the clinicians often offer, and which of the modules are most often used.

Conclusion

In summary, this study aims to evaluate a novel psychological treatment for GD in a naturalistic setting, using a 1-group pretest and posttest design.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available because this study's ethical review does not allow for study data to be in a public repository. Requests to access the data sets should be addressed to PB.

Authors' Contributions

PB, SN, KO, AH, and ECK designed this study and, together with JA and MA, contributed to the recruitment and data collection. PB drafted the protocol. All authors read and approved the final paper. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of Interest

AH has employment at Lund University, sponsored by the state-owned Swedish gambling operator Svenska Spel. AH also has research funding from the research council of the Swedish state monopoly for alcohol, Systembolaget AB. None of these bodies had any role in, or influence on, this study. The authors alone are responsible for the content and writing of this paper. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
CBT: cognitive behavioral therapy
CORE-OM 34: Clinical Outcomes in Routine Evaluation–Outcome Measure 34 questions
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FT: family therapy
GD: gaming disorder
GDT: Gaming Disorder Test
ICD-10: International Classification of Diseases, 10th Revision
ICD-11: International Classification of Diseases, 11th Revision
IGD: internet gaming disorder
IGDS9-SF: Internet Gaming Disorder Scale–Short-Form
PROTECT+: Professioneller Umgang mit technischen Medien (Professional Use of Technical Media)
RCADS: Revised Child Anxiety and Depression Scale
RCT: randomized controlled trial
STICA: short-term treatment for internet and computer game addiction

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Protocol

EXploring Patterns of Use and Effects of Adult Day Programs to Improve Trajectories of Continuing Care (EXPEDITE): Protocol for a Retrospective Cohort Study

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Abstract

Background: Adult day programs provide critical supports to older adults and their family or friend caregivers. High-quality care in the community for as long as possible and minimizing facility-based continuing care are key priorities of older adults, their caregivers, and health care systems. While most older adults in need of care live in the community, about 10% of newly admitted care home residents have relatively low care needs that could be met in the community with the right supports. However, research on the effects of day programs is inconsistent. The methodological quality of studies is poor, and we especially lack robust, longitudinal research.

Objective: Our research objectives are to (1) compare patterns of day program use (including nonuse) by province (Alberta, British Columbia, and Manitoba) and time; (2) compare characteristics of older adults by day program use pattern (including nonuse), province, and time; and (3) assess effects of day programs on attendees, compared with a propensity score–matched cohort of older nonattendees in the community.

Methods: In this population-based retrospective cohort study, we will use clinical and health administrative data of older adults (65+ years of age) who received publicly funded continuing care in the community in the Canadian provinces of Alberta, British

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Columbia, and Manitoba between January 1, 2012, and December 31, 2024. We will compare patterns of day program use between provinces and assess changes over time. We will then compare characteristics of older adults (eg, age, sex, physical or cognitive disability, area-based deprivation indices, and caregiver availability or distress) by pattern of day program use or nonuse, province, and time. Finally, we will create a propensity score–matched comparison group of older adults in the community, who have not attended a day program. Using time-to-event models and general estimating equations, we will assess whether day program attendees compared with nonattendees enter care homes later; use emergency, acute, or primary care less frequently; experience less cognitive and physical decline; and have better mental health.

Results: This will be a 3-year study (July 1, 2024, to June 30, 2027). We received ethics approvals from the relevant ethics boards. Starting on July 1, 2024, we will work with the 3 provincial health systems on data access and linkage, and we expect data analyses to start in early 2025.

Conclusions: This study will generate robust Canadian evidence on the question whether day programs have positive, negative, or no effects on various older adult and caregiver outcomes. This will be a prerequisite to improving the quality of care provided to older adults in day programs, ultimately improving the quality of life of older adults and their caregivers.

Trial Registration: ClinicalTrials.gov NCT06440447; https://clinicaltrials.gov/study/NCT06440447

International Registered Report Identifier (IRRID): PRR1-10.2196/60896

(JMIR Res Protoc 2024;13:e60896) doi:10.2196/60896

KEYWORDS

adult day care centers; aged; program evaluation; cohort studies; routinely collected health data

Introduction

Across the globe, societies are struggling to meet the needs of an aging population [1-5]. The increasing prevalence of dementia [6-8] and comorbid chronic conditions [9,10] lead to complex care needs [9,10] and to greater family or friend caregiver burden [11-14] (ie, "the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical, and spiritual functioning" [15]). In response, health systems provide a range of ongoing care and supports to older adults and their caregivers—in Canada commonly referred to as continuing care [2,16]. Continuing care can be provided in an older adult's private home, in the community (eg, an adult day program), or in a variety of congregate care settings including independent living, retirement homes, supportive or assisted living, or nursing homes (NHs) [17,18]. Governments have identified NHs as a major driver of public continuing care costs [17,19-21]. To mitigate pressures on public continuing care systems, and to meet aging in place preferences of older adults and their caregivers [22-24], reforms have implemented aging in place strategies. These strategies largely include (1) reserving NH care to those with the most complex care needs, and (2) improving access to an array of publicly funded continuing care options in the community [2].

Adult day programming is such a continuing care option to support aging in place [25-32]. Older adults in need of continuing care usually attend these programs for parts of the day, returning to their homes overnight (but overnight services are provided by some day programs). As this literature illustrates [25-32], the number of days a person attends a day program can vary widely, depending on the program and health jurisdiction, from a couple of days or month to daily attendance. The amount of time an individual attends also varies from a few hours or day to all day, or sometimes during nights, and so do admission criteria, supports and services offered, and funding models.

Despite these variations, day programs have unique characteristics that set them apart from other continuing care options. Day programs employ care staff and admit people with a certain level of support needs [30,33]. This distinguishes them from senior or community centers [34] and creative arts programs [35], which are open to independent older adults, do not employ care staff, and are organized more informally. Unlike home care [36] or in-home respite [37], day programs serve groups of older adults in a setting external to the attendee's home [30,33], supporting social interactions and caregiver respite [32]. Unlike geriatric day hospitals, which provide medical, therapeutic, and rehabilitative care for a few weeks [38], day programs prioritize social and recreational activities, and they do so for long term (often for months or years) [30,33]. Day program services and supports usually include transportation; meals; recreational activities (eg, playing games, musical activities, crafting, and painting); socializing with other clients and day program staff; physical, cognitive, and spiritual activities; social work counseling; and case management support. Personal, nursing, and medical care are often not provided, or only to a limited extent, depending on the program and health system.

Recent literature reviews [28-32,39] reveal a growing body of evidence that suggests that day program attendance may be associated with attendees' improved mental health, cognition, loneliness, quality of life, perceived health, physical functioning, use of polypharmacy, and mortality. These reviews also suggest that attendance may be associated with older adults' delayed admissions to congregate care, reduced risk for hospitalization, improved caregiver burden, and caregivers' feelings of competence, mental health, and well-being. However, reviews point to inconsistent findings, methodological limitations, and substantial heterogeneity of included studies. For example, a Canadian 1-group pre-post study suggested that Geriatric Depression Scale scores decreased (fewer depressive symptoms) from 5.0 at admission to a day program to 3.3 at discharge (P=.007). A quasi-experimental study comparing depressive

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symptoms between day program attendees with dementia and nonattendees with dementia in the United States [40] found no group differences. However, on days of attendance, the proportion of caregivers who reported depressive symptoms for attendees decreased over time (from 32/133, 24% to 25/133, 19%; $P<.02$). A Canadian randomized controlled trial [41] found no difference in depressive symptoms between day program attendees and wait-listed nonattendees.

Across the literature, four key knowledge gaps persist: (1) we generally know little about the characteristics of day program attendees and nonattendees, or about those with different patterns of use. (2) We lack longitudinal data on changes in the aforementioned outcomes. (3) Generally, the methodological quality of available studies is poor [32], and we lack robust, large-scale, longitudinal evidence of older adult day programs on day program attendees—especially those living with dementia. With few notable exceptions [42,43], we especially lack current research on Canadian day programs with most research originating from the US or Canadian studies often dating back several decades [25,26,44]. (4) Differential effects of day programs on persons with multiple, intersecting vulnerabilities are poorly understood, despite inequity concerns [39,45-47]. Advanced age puts individuals at risk of ageism; physical and cognitive disabilities may expose them to ableism; the majority of older adults and their caregivers are women, often experiencing gender inequities; and giving and receiving care are associated with substantial health care costs, disproportionally affecting those with low income [48]. Racism or transphobia or homophobia can further increase these pressures, severely affecting older adults and their caregivers [49,50].

Our study will address these knowledge gaps comprehensively, rigorously, and simultaneously. We will address the following 3 research objectives:

1. Explore patterns of day program use (eg, variations in time to first attendance, monthly hours of attendance, ongoing versus interrupted attendance, and total time of day program exposure), using latent class analyses (LCA), and compare the frequency of each latent use class between provinces and over time.
2. Compare older adults' demographic, social, and health characteristics (eg, age, sex, physical or cognitive disability, area-based deprivation indices, and caregiver availability or distress) by day program use or nonuse class, province, and time.
3. Assess whether, compared with a propensity score–matched control group of nonattendees, day program attendees enter care homes at later points in time; use emergency, acute, or primary care less frequently; experience less cognitive and physical decline; have better mental health; and have less distressed caregivers. We will assess potential modification of these effects by day program use or nonuse class, age, sex, and social determinants of health (eg, area-based deprivation indices).

Methods

Study Design

Using an integrated knowledge translation (iKT) approach [51,52], we partnered with a cross-Canadian team of experts to design this population-based retrospective cohort study (ClinicalTrials.gov; NCT06440447) covering the Canadian provinces of Alberta, British Columbia, and Manitoba, and we will collaborate with our experts throughout the study. Experts include older adults (some with dementia), their caregivers, Alzheimer societies, caregiver organizations, day program staff and managers, and government and health system decision makers. They will provide intimate knowledge of day programs, and the experience of attending them or caring for an attendee, which will help us interpret and contextualize our findings. We will use deidentified clinical and health administrative data from each of the 3 provinces. Our study will follow the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [53], and the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) [54] guidelines. Provincial data policies require data to remain in each respective province, preventing linkage across provinces and analyses of all data in one place. Therefore, in-house data analysts with each provincial health system will carry out the analyses separately with shared protocols and programs.

Setting and Sample

Our study settings are community-based continuing care systems. Each province provides access to a range of publicly funded community-based continuing care services, including adult day programs [55-63]. Each provincial health system determines and enacts access criteria and provides services (directly or via contracted providers) [55-63]. Day program eligibility is assessed in each province, using comparable processes, criteria, and assessments (ie, the Resident Assessment Instrument—Home Care [RAI-HC], a standardized, valid, reliable assessment tool [64]) [60,65,66]. To be eligible, attendees need to have not only some care dependency but also the ability to cope to some extent with activities of daily living, ambulate or transfer with no or minimal assistance, be continent or independent in managing continence products, exhibit no or easily manageable responsive behaviors, and either be alone for extended periods or have a caregiver who requires respite. Our study cohort will include all individuals aged 65 years or older with an initial RAI-HC assessment completed between January 1, 2012, and December 31, 2021. We will follow everyone until they move into a care home, are lost to follow-up (eg, because of death, moving out of province, loss of public insurance eligibility), or until December 31, 2024 (the end of the period covered by our data). That will allow for a care trajectory of at least 3 years (for those with an initial RAI-HC assessment in December 2021), enabling us to assess the number and characteristics of individuals with different day program use patterns, and compare them with those who were never exposed to a day program.

Sample Size Calculation

The yearly average number of completed RAI-HC assessments is ~20,000-30,000 in Alberta, ~34,000-39,000 in British

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Columbia, and ~10,000 in Manitoba [67]. About 50% of those assessed receive a reassessment within 12 months and another 10%-30% receive a reassessment after >15 months [68]. There are 89 publicly subsidized day programs in Alberta (~3300 spaces per day), 95 in British Columbia (~1500 spaces per day), and 70 in Manitoba (~1000 spaces per day) for a total of 254-day programs with 5800 spaces on any given day. Some day program users do not attend daily, but only 1 or a few days per week, so the number of unique attendees exceeds the number of spaces per day. This corresponds to >20,000 attendees per year (>200,000 within the study period), each with multiple assessments. Our study sample size will be large enough to detect small effects sizes. With Cox proportional hazards models, adjusted for covariates explaining an assumed 25% of effect variance (a=.05; power=0.8) [69], we require a total sample of 1327 participants to detect a hazard ratio for admissions to care homes of 0.6 (as can be expected based on a similar Canadian study [42]) in favor of day program attendees. Similarly, Kelly [43] was able to detect significantly fewer emergency department visits and hospital admissions per day among 812 day program attendees compared with 812 propensity score matched to nonattendees. Our expected sample size will be considerably larger than for those previous studies, allowing for complex statistical modeling.

Data Sources

For each individual in our cohort, designated provincial health system analysts will link all records available within the study time frame from the following databases: (1) regional continuing care registries, documenting when an individual starts or stops receiving any community-based continuing care, including day programs, how these services change over time, and when an individual is admitted to a care home. (2) Population registries for each participant's demographic data. (3) RAI-HC assessments [64], completed annually for people receiving long-term home care (60+ days), and to determine day program eligibility. The RAI-HC will provide data on older adults' medical conditions, functional dependence, pain, cognitive impairment, mood, and behavioral problems. It also includes information on a person's marital or partnership status, caregiver availability, whether that caregiver lives with the older adult, and caregiver distress. Additional caregiver characteristics are not included in the available provincial databases, posing a limitation to our quantitative analyses. However, a related prospective cohort study that we are conducting in Ontario will allow us to link comprehensive caregiver and older adult data, and we are currently conducting additional qualitative research that will illuminate how caregiver characteristics may affect day program use and outcomes. (4) Discharge abstract database (DAD) for information on all inpatient hospital stays, including diagnoses and length of stay. (5) National Ambulatory Care Report System (NACRS) for all emergency department visits and diagnoses. In British Columbia, we will use the physician payment file in addition, since NACRS is not collected in all emergency departments [70]. (6) Pharmaceutical information on outpatient prescription medications filled through a community pharmacy and covered by provincial drug formulary. (7) Care provider claims data for health service claims submitted for payment by health care providers (eg, general practitioners, nurse practitioners, geriatricians, geriatric psychiatrists, neurologists, therapists) to obtain information on general and specialist health services used by participants.

Study Variables

Exposure

Our exposure will be different patterns of day program use or nonuse, based on information from the provincial continuing care registries, documenting the dates a person starts or stops attending a day program, days of attendance, and the duration of each visit. Day program use patterns will be determined, using LCAs (see *Statistical Analyses* section) [71]. We will categorize three continuous variables as low, low-moderate, high-moderate, or high use, using sample distribution quartiles: (1) time between first RAI-HC assessment and first attendance of a day program; (2) average number of hours of day program attendance (ie, total number of hours spent in a day program divided by the number of times attended); and (3) total number of days a person attended a day program. LCAs will also include a categorical variable, indicating whether a person consistently attended a day program or whether there were longer periods (several weeks) of nonattendance. Nonuse will be defined as no day program exposure at any time during a person's continuing care trajectory.

Study Outcomes

The data sources noted above enable us to examine a range of important study outcomes. Data on the time between a person's first RAI-HC assessment and admission to a care home will come from provincial continuing care registries. Symptoms of depression will be assessed using the validated RAI-HC Depression Rating Scale [72], with scores ranging from 0 to 14 and a cut point of 3 or higher representing clinically meaningful depressive symptoms [72,73]. We will capture physical and cognitive decline, using validated RAI-HC scales [64]: the Activities of Daily Living Hierarchy (ADLh) Scale [74] and the Cognitive Performance Scale (CPS) [75]. Both scales range from 0 (no impairment) to 6 (maximum impairment), and our outcomes will be dichotomous, indicating any increase (vs no change or a decrease) between the previous and follow-up measurement in each of these scales. Using care practitioner claims data, we will generate rates of different types of primary and specialist care use (eg, family physician, specialists, nursing practitioner, and allied health providers). We will use the DAD and NACRS databases to generate rates of emergency department registrations, hospital admissions, and days in hospital (including alternative level of care) [43]. Rates will be stratified by day program use or nonuse pattern.

Demographic, Social, and Health Characteristics

These will include older adults' age, sex, marital or partnership status (population registries and RAI-HC), physical disability (ADLh Scale score of >3), and cognitive impairment (CPS score of >3). Available data sets include only a binary variable on biological sex (male or female) and no nonbinary information on gender identity. We will also include RAI-HC measures of caregiver availability (item G1e) and burden (items G2a-c). Finally, we will include 4 publicly available area-level measures from the Canadian Index of Multiple Deprivation [76,77]:

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residential instability (eg, housing insecurity, overcrowding, and frequent moves), economic dependency (high number of older adults, children younger than 15 years, and persons receiving government transfers), ethnocultural composition (eg, immigrants and racialized individuals), and situational vulnerability (eg, indigenous peoples, dwellings needing major repairs, and low education). Using Statistics Canada data, each measure is derived for 54,775 geographical dissemination areas, using 17 variables. Quintile-based ranks for each of the indices (1=least deprived to 5=most deprived) will be assigned to individuals based on their home's postal code [77].

Propensity Score–Matching Variables

To compare outcomes between day program attendees and nonattendees, we will use propensity score matching [78] (for details, see Statistical Analyses section). Propensity scores aim to ensure a similar distribution of baseline variables among treatment (day program attendees) and control (nonattendees)—akin to what random assignment aims to accomplish in randomized trials [78]. Since we lack evidence on differences between day program attendees and nonattendees, our objective 2 analyses will be key to informing the selection of the exact covariates that will form the propensity score. We will derive covariates for day program attendees from the RAI-HC day program eligibility assessment (index date). For each day program attendee, we will identify potential matches as nonattendees whose first RAI-HC assessment was completed within ±3 months of the attendee's index date (ie, admission to long-term home care at about the same time). This RAI-HC assessment will provide the relevant covariates to enable propensity score matching with day program attendees as of their index date.

Our first set of matching covariates will be RAI-HC variables used by health systems to determine day program eligibility [60,65,66]: physical functioning (ADLh Scale), cognition (CPS), behavioral symptoms (Aggressive Behavior Scale [79]), bladder or bowel continence (items I1, I3), availability of a caregiver (item G1e), and caregiver distress (items G2a-c). This will ensure that control participants are potentially eligible to a day program. Possible reasons for nonattendance include the lack of day program spaces, preference not to attend, inability to afford the required copayments, or not receiving a day program referral. Our experts assure us that the pool of potential matches far exceeds that of attendees, supporting the feasibility of this study and underscoring the lack of day program spaces. This approach excludes individuals whose care needs are either too low or too severe for day program eligibility, but it minimizes confounding by the matched variables and ensures comparable groups at baseline [80-82]. Finally, we will include a second set of matching covariates: health and social characteristics identified in objective 2 by which attendees and potentially eligible nonattendees differ and that overlap sufficiently between attendees and nonattendees (eg, age, sex, type or duration of publicly funded community care received before the matching index date, and deprivation indices).

Additional Covariates

Additional covariates for model adjustment will come from RAI-HC, DAD, NACRS, pharmaceutical, and claims records (eg, geriatric syndromes, medical diagnoses, and prescribed medications). We might also adjust for additional community care services (eg, in-home respite and home care).

Statistical Analyses

Objective 1: Explore Patterns of Day Program Use

Using our day program cohort, we will conduct LCAs to determine the number of different day program use patterns, using the 4 variables described in the exposures section. LCAs are widely used to identify subgroups by clusters of characteristics (ie, parameters of day program use) [71]. In collaboration with our experts and guided by relevant literature, we will prespecify the expected number of classes. We will carry out LCAs separately in each province. We will run models with the prespecified number of classes, and with 1, 2, and 3 more and fewer classes than the number prespecified [71]. We will compare the fit between models, using bootstrap likelihood ratio tests [71], and select a final model that reflects the same number and types of classes in each province, balancing theoretical, conceptual, and statistical considerations. To assess temporal changes in the number of day program attendees within each use pattern, and differences between provinces, we will report and graphically plot the proportion (95% CI) of individuals within each latent class by quarter and province.

Objective 2: Compare Older Adults' Characteristics by Day Program Use, Province, and Time

Using our full cohort of day program attendees and nonattendees, we will descriptively assess the distribution of sample characteristics over time and by province. In each province and quarter, we will report and plot graphically the proportion (95% CI) of individuals with each characteristic, stratified by day program use class versus nonuse. Using general estimating equations (GEEs) [83], we will assess whether the number of persons with each characteristic has changed over time and whether characteristics are associated with older adults' day program use or nonuse pattern. We will run a separate GEE model for each characteristic within each province, with the respective characteristic as individual-level outcome. We will run binary logistic regressions for dichotomous variables (eg, sex) and ordinal regressions for categorical variables (eg, residential instability quintile). Models will account for repeated measures within individuals and include the independent variables year of assessment (to assess change in social determinants over time), use or nonuse class (to assess differences in social determinants by day program use), and an interaction between year and use or nonuse (to assess how social determinants differed between use and nonuse patterns by year). Using random-effects mixed regression models, we will pool provincial effects statistically. Other Pan-Canadian studies, such as the Canadian Network for Observational Drug Effect Studies [84], have successfully applied this approach and developed rigorous protocols to minimize bias and maximize consistency of regional analyses.

Objective 3: Assess Effects of Day Programs

To create a propensity score, we will run a logistic regression for each province with day program attendance or nonattendance as the dependent variable and adding matching covariates. We

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will use one-to-one matching (1 matched nonattendee for every attendee) [78]. We will use matching without replacement [85] and apply an optimal caliper matching algorithm [86]. As per best practice recommendations [87], we will use a caliper width of 0.2 of the SD of the propensity score's logit. If this matching approach does not allow us to achieve a sufficient sample size, we will use propensity score quintiles for matching.

We will compare sample characteristics and study outcomes between attendees and nonattendees in every year and province, using bivariate statistical tests (eg, chi-square test or Fisher exact test for categorical variables, *t* tests, or ANOVAs for continuous variables, and their nonparametric equivalents if variables violate statistical assumptions). To assess the effect of day program exposure on time to care home admission, we will specify a multilevel time-to-event model with a health region–level random effect [88]. Health systems in each of the 3 provinces are divided into 5 health regions [89-91], and regional policies may cause clustering effects that our models must account for. Each model will include day program use or nonuse class as independent variable and will be adjusted for time-varying variables. These will include matching variables, if appropriate (ie, in case of group differences in matching variables over time or due to missing data) [80-82] and, if needed, additional covariates (eg, demographics, social determinants, medical or functional conditions, and non–day program community care). Covariates that differ between attendees and nonattendees with a *P* value of ≤.15 in the bivariate analyses will be considered for inclusion. We will add covariates stepwise, one-by-one, and remove those that cause collinearity issues or decrease model fit. As in objective 2, we will pool provincial effects statistically, using random-effects mixed regression models.

Using GEEs and a similar approach as for the time-to-event models (including separate models in each province and statistical pooling of their effects), we will assess whether the other study outcomes differ by day program use or nonuse pattern. Models will include each study outcome of interest as a dependent variable, day program use or nonuse class and time of assessment as independent variables, and similar covariates (using the same stepwise approach) as the time-to-event models. Models will also include a random term to account for repeated measures within individuals. The choice of a link function will be informed by the nature of the variable and theoretical and empirical considerations. For example, the number of hospital, emergency department, or physician visits has been shown to follow a zero-inflated negative binomial distribution, sometimes requiring an offset for the natural logarithm of person-time [92]. For continuous outcomes (eg, days spent in hospitals), we will use an identity link function, and for dichotomous outcomes (eg, presence or absence of depressive symptoms), we will use a logit link function. All models will apply multiple imputation in case of missing data, which we expect to be small based on our previous work with the administrative health care data sources used in this study.

Ethical Considerations

We received ethics approvals from the York University Ethics Review Board, Human Participants Review Sub-Committee (e2022-412, December 1, 2022), the University of Alberta Health Research Ethics Board—Health Panel (Pro00127850, February 3, 2023), and the University of British Columbia Research Ethics Board (H24-01435, August 1, 2024), and we are in the process of obtaining ethics approval from the University of Manitoba Health Research Ethics Board.

Results

Funded by an endowed research chair, the Helen Carswell Chair in Dementia Care (July 1, 2022, to June 30, 2027), this will be a 3-year study (July 1, 2024, to June 30, 2027). Starting on July 1, 2024, we will work with the 3 provincial health systems on data access and linkage, and we expect data analyses to start in early 2025.

Discussion

Principal Findings

Older adults, caregivers, and health systems urgently need solutions to empower older adults to receive care at home for longer [93]. There are few feasible solutions that target both, the older adult in need of care and their family or friend caregiver, but day programs are one of them [30,33]. Despite the knowledge that day programs could fill an immense and costly care gap [27-33,37,39,45-47,94,95], we lack the research needed to inform policy and drive practice change to make day programs more available [30,33]. This study will generate robust Canadian knowledge on whether day programs have positive, negative, or no effects on outcomes that matter most to older adults, their caregivers, and health systems. For example, day programs aim to support older adults and their caregivers to avoid or delay care home admissions; reduce or avoid costly and unnecessary emergency, acute, or primary care use; and improve the health and well-being of older adults and their caregivers [27-33,37,39,45-47,94,95]. However, the international research is inconclusive on whether or not day programs are effective in accomplishing these aims [27-33,37,39,45-47,94,95], and we especially lack robust, longitudinal, and cross-provincial Canadian research [25,26,44]. Therefore, this study will provide critical knowledge that is urgently needed by health systems. First, we will determine how many persons are attending day programs in the 3 participating Canadian provinces, what their patterns of use look like, whether these patterns have changed over time, and similarities and differences of these patterns between provinces. Second, we will assess how characteristics of older adults who attend day programs differ from those who do not attend day programs. Finally, we will assess whether day programs are effective in delaying admissions to care homes, reducing emergency, acute and primary care, and in improving various outcomes related to older adults' health and well-being.

Our iKT approach, in which we have been closely partnering with older adults (some with dementia), their caregivers, Alzheimer societies, caregiver organizations, day program staff and managers, and government and health system decision makers, will ensure that our research addresses issues that these groups have deemed a priority. It will further facilitate rapid translation of these findings into policy and practice changes. Results will be disseminated in a variety of ways. Staying true

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to our iKT approach, we will invite, encourage, and empower our experts to participate in, coauthor, or lead these activities (to the extent our experts wish to be involved and have capacity to do so).

Limitations

While this study has various important strengths, including the use of comprehensive, population-based, cross-provincial health administrative data, and application of robust statistical methods, there are some limitations. First, important variables, such as older adult quality of life, various social determinants of health, or day program characteristics, are not available in the administrative health care data available to us. Second, the health administrative data used in this study do not allow for identification of caregiver health administrative data, preventing linkage of caregiver and older adult data. Therefore, our team currently also carries out a prospective cohort study (ClinicalTrials.gov; NCT06496945) in which we will collect these missing variables to fill the mentioned gaps. Finally, quantitative data may suggest the presence or absence of an effect, but they may be more limited in explaining the mechanisms leading up to the effect or the reasons of the lack of an effect. Our program of research includes a realist literature review and comprehensive qualitative work to address the lived experience of older adults and their caregivers in day programs and the "how and why" of day program effects (or the lack thereof).

In webinars in years 2 and 3, researchers, trainees, and experts will copresent key research findings on specific topics, such as effects of day programs in general (ie, on individuals with dementia, caregivers, and health systems); variation of day program effects in various equity-deserving groups or by day program characteristics; or jurisdictional differences in day program structures, policies, characteristics, and effects. Thirty to 50 additional experts (not members of our advisory committee) will be invited to participate per webinar, including provincial or regional health system policy makers, Alzheimer Societies, caregiver organizations, day program operators or managers or staff, individuals with dementia, and caregivers. In particular, webinars will offer the opportunity for discussion about relevance of findings within and across jurisdictions and for cross-provincial learning (learning health systems).

Researcher, trainee, and expert team members will also codevelop a series of briefing documents that highlight key messages of our research. Documents will target health system policy makers and day program operators and managers. They will be a valuable tool to support desired directions and action post project funding. In year 2, we will hold a series of workshops to engage experts in a facilitated, deliberative process of developing alternative approaches that improve day program effects on individuals with dementia, their caregivers, and health systems.

We are planning the preparation of several peer-reviewed manuscripts (cocreated by researchers, trainees, and experts). Publications might include (among others) (1) this research protocol of our study; (2) a manuscript comparing the number and characteristics of day program attendees over time and across participating regions; (3) a comparison of older adults by day program use or nonuse stratified by health region; and (4) several papers (~3-5) on the effects of day programs on older adults. Team members will give presentations at conferences within Canada (eg, Canadian Association for Health Services and Policy Research, Ontario Long Term Care Association, National Health Leadership Conference, Canadian Alliance for Long Term Care, Canadian Association on Gerontology, and Congress of the Humanities and Social Sciences) and internationally (Gerontological Society of America, International Association of Gerontology and Geriatrics). Experts will be invited to participate in symposia, copresent, or lead presentations.

In year 3, key messages will be used to develop various lay summaries and an easily accessible, animated summary project video that can also be used for educational training on aging in place and care of individuals with dementia and their caregivers in the community. These will be posted on our study website and on our team members websites.

In conclusion, this study will identify essential elements of day programs and how they can be improved. We will provide critical evidence for health systems to help them leverage the full potential of day programs to provide appropriate care, prevent inequities, and mitigate the need for emergency, hospital, and congregate care. Ultimately, we will improve the quality of life of older adults (including those with dementia) and their caregivers, alleviate caregiver burden, and reduce social costs associated with poor health and well-being. Future studies will expand this research to additional health jurisdictions.

Acknowledgments

We would like to thank all members of the Helen Carswell Chair in Dementia Care Advisory Committee, who helped us identify important research priorities (including the population-based, retrospective cohort study proposed here) and in conceptualizing and designing this study. This study is funded by the Carswell Family Foundation, which funds the Helen Carswell Chair in Dementia Care, held by MH. The funder has had no role in designing this study and preparing or approving this publication, and the funder will have no role in accessing and analyzing the administrative health care data, and in publishing or approving future manuscripts.

Data Availability

This study uses population-based clinical and administrative health care data, routinely collected, and owned by the participating health regions. Provincial data policies do not allow for public sharing or access of these data. Data are not allowed to be removed

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from regional repositories. Guided by the study team, data in each region will be analyzed by health data analysts employed by the respective health care system. Study findings will then be pooled across health regions, using shared protocols and statistical codes. Access may be granted to those who meet prespecified criteria for access, available at on the websites of (1) the Alberta SPOR SUPPORT Unit (AbSPORU) [96] (email: absporu@albertainnovates.ca), (2) Population Data BC [97] (email: dataaccess@popdata.bc.ca), and (3) Shared Health Inc [98] (email: SHResearch@sharedhealthmb.ca).

Authors' Contributions

MH is the lead investigator of this study, and CJM, AU, MBD, ZG, and SA are coleads. MH, CJM, AU, MBD, ZG, SA, RB, WB, JB, TD, LG, HN, ASMR, KT, and KG helped conceptualize the study and to design the study methods. MH wrote the original draft, and CJM, AU, MBD, ZG, SA, RB, WB, JB, TD, LG, HN, ASMR, KT, and KG critically reviewed and edited various iterations of the manuscript. All authors approve of the manuscript in its current form and agree to be accountable for all of its contents.

Conflicts of Interest

None declared.

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Abbreviations

ADLh: Activities of Daily Living Hierarchy Scale
CPS: Cognitive Performance Scale
DAD: discharge abstract database
GEE: general estimating equation
iKT: integrated knowledge translation
LCA: latent class analysis
NACRS: National Ambulatory Care Report System
NH: nursing home
RAI-HC: Resident Assessment Instrument—Home Care
RECORD: REporting of studies Conducted using Observational Routinely-collected health Data
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Piloting the Inclusion of the Key Populations Unique Identifier Code in the South African Routine Health Information Management System: Protocol for a Multiphased Study

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Abstract

Background: The global community has set an ambitious goal to end HIV/AIDS as a public health threat by 2030. Significant progress has been achieved in pursuing these objectives; however, concerns remain regarding the lack of disaggregated routine data for key populations (KPs) for a targeted HIV response. KPs include female sex workers, transgender populations, gay men and other men who have sex with men, people who are incarcerated, and people who use drugs. From an epidemiological perspective, KPs play a fundamental role in shaping the dynamics of HIV transmission due to specific behaviors. In South Africa, routine health information management systems (RHIMS) do not include a unique identifier code (UIC) for KPs. The purpose of this protocol is to develop the framework for improved HIV monitoring and programming through piloting the inclusion of KPs UIC in the South African RHIMS.

Objective: This paper aims to describe the protocol for a multiphased study to pilot the inclusion of KPs UIC in RHIMS.

Methods: We will conduct a multiphased study to pilot the framework for the inclusion of KPs UIC in the RHIMS. The study has attained the University of Johannesburg Research Ethics Committee approval (REC-2518-2023). This study has four objectives, including a systematic review, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (objective 1). Second, policy document review and in-depth stakeholder interviews using semistructured questionnaires (objective 2). Third, exploratory data analysis of deidentified HIV data sets (objective 3), and finally, piloting the framework to assess the feasibility of incorporating KPs UIC in RHIMS using findings from objectives 1, 2, and 3 (objective 4). Qualitative and quantitative data will be analyzed using ATLAS.ti (version 6; ATLAS.ti Scientific Software Development GmbH) and Python (version 3.8; Python Software Foundation) programming language, respectively.

Results: The results will encompass a systematic review of literature, qualitative interviews, and document reviews, along with exploratory analysis of deidentified routine program data and findings from the pilot study. The systematic review has been registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42023440656). Data collection is planned to commence in September 2024 and expected results for all objectives will be published by December 2025.

Conclusions: The study will produce a framework to be recommended for the inclusion of the KP UIC national rollout. The study results will contribute to the knowledge base around the inclusion of KPs UIC in RHIMS data.

Trial Registration: PROSPERO CRD42023440656; https://tinyurl.com/msnppany

International Registered Report Identifier (IRRID): PRR1-10.2196/55092

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KEYWORDS

key populations; unique identifier code; biometric; biometrics; alphanumeric code; routine health management information system; health management; management; protocol; mixed methods study; South Africa; human immunodeficiency; immunodeficiency; HIV; AIDS; transgender; epidemiology; data extraction; HIV transmission

Introduction

Background

HIV/AIDS continues to be a leading global health tragedy regardless of international and local initiatives to address the epidemic [1]. Globally, it is estimated that 38.4 million people are living with HIV at the end of 2021 [2]. According to the sixth South African National HIV Prevalence, Incidence, and Behavior survey, South Africa had approximately 7.8 million people living with HIV, indicating 12.7% HIV prevalence in 2022 [3]. Globally, key populations (KPs) and their sexual partners accounted for 70% of HIV infections in 2021 [4]. In South Africa, HIV prevalence among KPs varies noticeably, ranging from 60% among female sex workers, 37.5%-43% in men who have sex with men and transgender people, to 21.8% in people who inject drugs [5-9].

South Africa is among the countries that have committed to the Global AIDS Strategy 2021-2026 to end AIDS as a public health threat by 2030 [10]. Monitoring progress toward the 2030 agenda for sustainable development, endorsed in 2015, faces challenges regarding data disaggregation [11]. To reach these targets, a vigorous routine health information management system (RHIMS) must provide disaggregated data for proper planning, resource allocation, progress reporting, and accountability [11,12]. In South Africa, RHIMS does not include a unique identifier code (UIC) for KPs. Therefore, routine data cannot be disaggregated by the latter. There is thus a necessity for improving the current RHIMS in South Africa to guarantee KP data disaggregation to improve targeted resource allocation reporting and accountability inclusive of KPs. To address this deficit globally, in 2017, the World Health Organization (WHO) launched consolidated guidelines on the adoption and implementation of UIC for improved person-centered HIV patient monitoring and case surveillance [13-15]. However, less than one-third of Sub-Saharan Africa (SSA) countries, including Kenya, Uganda, Ghana, Mali, Burkina Faso, Togo, Burundi, Liberia, and Malawi, have adopted those guidelines and started implementing KPs UIC through alphanumeric codes and biometric systems [16-21].

Reports from those countries cited issues, such as knowledge of the technology behind biometric devices and their benefits, trust in health care providers, data privacy, and confirmed confidentiality, as critical facilitators to biometric UIC uptake among KPs [22-26]. Barriers noted included generalized fear of the unknown, personal data might end up in the hands of police, doubt about the technology implications, interrupted power supply, poor network coverage, system technical glitches, such as system failures, computer or software errors, lack of technical expertise, shortage of resources, poor funding, and maintenance cost of UIC systems [27-34]. Some studies suggested combining biometric fingerprint identification with alphanumeric codes to enhance feasibility, particularly in African rural areas. However, alphanumeric codes may lead to duplicates as some clients may change addresses, phone numbers, and names or may provide different spellings, or incorrect date of birth different from what they used during admission.

South Africa has a strong economy, advanced information and communication technology infrastructure, and reasonable advocacy for KP's rights compared to some countries that have adopted the KP UIC. The adoption of KPs UIC in South Africa must be acceptable, affordable, and feasible, given the well-resourced status. This protocol pursues to undertake a comprehensive assessment of the prevailing status of RHIMS in SSA, appraising the level to which the incorporation of UICs for KPs has been embraced, as well as an assessment of how the current RHIMS is designed for capturing and monitoring HIV in South Africa and what evidence can be generated from it to guide the incorporation of KPs UIC into RHIMS.

Research Questions

The following research questions will be addressed:

- What is the status quo on existing RHIMS that have incorporated KPs UIC in SSA?
- Does the monitoring and evaluation documents, tools, and guidelines incorporate UIC for KPs in South Africa?
- How is the current RHIMS designed for capturing and monitoring HIV in South Africa?
- How can the KP UIC be incorporated into RHIMS?

Methods

Overview

This is a multiphased study including a systematic literature review (objective 1), policy document review and in-depth interviews with stakeholders (objective 2), exploratory data analysis for the deidentified HIV data set (objective 3), and finally, the piloting of the RHIMS framework to understand how the KPs UIC can be incorporated in RHIMS (objective 4).

The study is part of a doctoral study by the first author which has attained the University of Johannesburg (UJ) Higher Degrees Committee and UJ Research Ethics Committee (REC) approval (REC-2518-2023). The doctoral study is linked to 2 larger studies in the South African Medical Research Council/UJ Pan African Centre for Epidemic Research Extramural unit, namely harnessing big heterogeneous data to evaluate the potential impact of HIV responses among KPs in generalized epidemic settings in SSA (REC-1504-2022) and assessing COVID-19 impacts on HIV prevention and treatment continuum (REC-1781-2022), which also obtained ethics approval from UJ REC.

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Methods for Objective 1

Aim

To conduct a systematic review of existing gray and published literature on the RHIMS and how the data is captured in SSA.

The methods for this objective consist of study setting, design, study selection and screening, assessment of study quality, data extraction, and analysis.

Study Setting

This objective focuses on reviewing published and gray literature from January 2013 onwards, on successes, barriers, and facilitators for implementing KPs UIC in SSA.

Study Design

The systematic review will be conducted in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [35] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) register (registration CRD42023440656).

Search Strategy

Two reviewers (MR and EP) will develop a search strategy using key terms in the research questions and consultation with the UJ librarian. For each key term, a medical subject heading term will be developed and combined with Boolean operators: "AND," "OR," and "NOT" during the title search [36]. The medical subject headings terms and keywords will be used to develop the search strategy. The population, intervention, comparison, and outcome framework will guide the development of search terms and keywords. Electronic search databases will comprise, but not limited to Google Scholar, MEDLINE (via Ovid or PubMed), PLoS, and Medicine Web of Science. Keywords, such as "key populations," "men who have sex with other men," "MSM," "female sex workers," "FSW," "SW," "people who use drugs," "PWUD," "people who inject drugs," 'PWID," "lesbian," "gay," "bisexual," "transgender and queer or questioning," "LGBTQ," 'district health information system," "RHIMS," "UIC," "unique patient identifier code," "biometric scanner," "alphanumeric code," and "SSA," will be used to build search strategy (Multimedia Appendix 1). Gray literature will be searched from Google, Google Scholar, WHO, Global Fund, PEPFAR/USAID, government department websites, conference proceedings, policy documents, and institutional repositories of KP organizations. Additionally, we will search the reference lists of all identified reports and papers for additional studies. Two reviewers (MR and EP) will vote independently on each reference. In case of differences, a third member (RNP-M) will be asked to give input and make the final decision based on the reviews of the 2 members.

Quality Assessment

The critical appraisal skills program systematic review checklist will be used after the screening to assess the quality and bias in each of the selected papers. The checklist investigates the validity, precision, and generalizability of the research [37]. Using appropriate quality assessment techniques, each paper that will be included in this review will have its methodological and research quality evaluated. Two team members (MR and EP) will independently evaluate the complete text and abstracts of the qualifying papers using the inclusion and exclusion criteria, as well as a predetermined and agreed-upon score criterion for each evaluation using Covidence (Veritas Health Innovation).

Study Selection

Inclusion and exclusion criteria will be used to ensure the consistent exclusion of studies that do not address the research questions. The eligibility criteria will ensure that the selected and included studies have the relevant data required to answer the research questions. EndNote 21 (Clarivate Analytics) reference manager software will be used to manage the references. Covidence software for systematic reviews will be used with two reviewers voting independently on each reference. In case of differences, a third member will be asked to give input and make the final decision based on the reviews of the two members.

Data Extraction

A standard extraction tool generated through Covidence software will be used to capture key indicators of interest to organize eligible papers. The information to be extracted for each paper will include the author or authors, publication year, settings, country, study method, sample size, indicators of interest, population details, and data sources.

Data Analysis

Thematic analysis will be used to assess results from the systematic review. A narrative summary of the results will be developed, and tables will be used to show specific details of the analysis.

Methods for Objective 2

Aim

To conduct a formative assessment of the RHIMS and its stakeholders with respect to the inclusion of KP UIC in terms of operations, challenges, vulnerabilities, considerations, opportunities, and policies for improvement and its policy in South Africa.

This objective will use in-depth interviews and document reviews.

Methods for In-Depth Interviews With Stakeholders

Study Setting

The stakeholder interviews will be conducted in any province in South Africa depending on where the identified stakeholder will prefer to be interviewed. Only the interviewer, interviewee, and a trained study assistant or note-taker will be present during all face-to-face interview sessions. For privacy purposes, separate and private rooms within the office premises will be used for the interview.

Study Design

An exploratory study design involving in-depth interviews with stakeholders will be used.

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Study Population

The stakeholders will comprise of policy makers and managers from various institutions working closely with the KP program including the KP community, government officials, the research community, health information or data managers, health care providers, civil society organizations, private sector, nongovernment organizations, international and local funders, and political leaders.

Study Sample

A purposive sample size of 20 key stakeholders who work or interact with the RHIMS and KPs will be invited to take part in the interviews using a semistructured questionnaire. However, the sample size may change depending on when saturation is reached. Study participants will be aged 18 years and older; working with the RHIMS and KPs programs in South Africa.

Data Collection

In-depth interviews will be conducted with stakeholders using a semistructured questionnaire. A trained study assistant will assist the researcher with data collection during the interview. The interviews will be audio-recorded with the participant's consent. Participants will be informed that participation in the study is completely voluntary, and they have the freedom to withdraw from the study at any time. Interview notes will be taken during the interviews to back up the audio-recorded data in case of equipment failure. Each interview is expected to last for 20-30 minutes.

Data Analysis

The qualitative data from the in-depth or semistructured interviews will be captured and analyzed using ATLAS.ti (version 6; ATLAS.ti Scientific Software Development GmbH) [38]. Data will be analyzed by content through a thematic approach. The 6 stages of the thematic approach comprising data familiarization, coding, identification, review, naming the major themes, and compiling the final report will be applied [39]. Interview transcription, translation, and coding will form part of an iterative process. For content analysis, a "directed content analysis" methodology will be followed, in which codes are chosen both prior to and after analysis [40,41]. A priori codes will be developed using ATLAS.ti software based on previous research findings and theory [38]. Coding will be done independently by 2 researchers (EP and MR). Intracoder reliability will be assessed prior to entry into the final codebook. Close-ended questions will be analyzed descriptively, reporting proportions and percentages where possible.

Methods for Program Document Review

Documents to be searched and analyzed will include RHIMS policies, protocols or guidelines, reports, program logs, performance ratings, funding proposals, procedures, meeting notes or minutes, and strategic reports on HIV-related data for KPs. These documents may be in the form of hard or soft (electronic) copies.

Inclusion and Exclusion of the Documents

Overview

Documents that were published in the last 10 years to date; reporting on the South African RHIMS, written in English will be included. This will include documents in both public and private domains. Documents that were published before the year 2013 and non-English will be excluded.

Data Collection

Documents will be searched from South African government and nongovernment organization websites. Furthermore, websites of key multilateral organizations of interest (eg, Global Fund, UNAIDS, WHO, Centre for Disease Control and Prevention Africa, and PEPFAR) will be conducted to find more information. To complement the web-based document search, relevant individuals in government and nongovernmental organizations will be contacted to request unpublished reports that are not available in the public domain. An Excel (Microsoft Corp) data extraction tool for document review activity will be used to document outcomes. The Excel spreadsheet will have column headings containing the document name, type, source of the document, the year it was released, purpose, target audience, and summary of key content related to this study.

Data Analysis

Qualitative document analysis will be conducted to provide insight into how various official documents recognize KPs HIV data collection and reporting. Thematic content analysis will be used to identify themes emanating from the documents that will be reviewed.

Methods for Objective 3

To conduct an exploratory analysis of the deidentified routine program data to understand the nature and structure of RHIMS data, outputs, and the implications thereof.

Study Design

Using a retrospective observational descriptive design, the analysis will focus on the District Health Information System HIV program data set covering the years 2021 to 2023, aiming to summarize and interpret the data to uncover patterns, trends, and insights. The data will be sourced from the National Department of Health (NDoH) and will encompass demographic information (age, gender, geographic location), clinical data (HIV diagnosis dates, cluster of differentiation 4 counts, viral load measurements), and treatment details (antiretroviral therapy [ART] initiation dates, regimen types, adherence measures, and virological outcomes).

Study Population

The study population will consist of individuals whose information is captured within the deidentified HIV routine program data set sourced from the NDoH. This data set includes individuals diagnosed with HIV, with recorded demographic, clinical, and treatment details. Encompassing a diverse array of individuals across various age groups, genders, geographic locations, and clinical profiles, the population offers a comprehensive representation of how HIV data is documented within the national health management information system.

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Sampling

Random sampling will be used to select a representative subset of records from the deidentified HIV routine program data sourced from the NDoH. The sample will include facilities from all 9 provinces and 52 health districts in the country. This method aims to ensure comprehensive coverage of the population while minimizing bias and enhancing the generalizability of the study findings.

Data Collection

A standard data extraction tool will be used to extract deidentified data from the HIV database as an export file. Data for this objective will be collected from the deidentified HIV routine program data set maintained by the NDoH. A data sharing agreement will be submitted to the NDoH to request deidentified HIV-related data. The data sharing agreement will be accompanied by a list of HIV-related data elements and indicators that are collected by NDoH at the facility level in South Africa. These HIV-related elements and indicators are listed in the National Indicator Data Set, which is a document outlining the list of indicators and elements introduced by the NDoH that every public health facility is required to capture and report. Data cleaning procedures will be implemented to address any missing values or inconsistencies, ensuring the integrity and reliability of the data set. Strict measures will be taken to protect patient confidentiality, including the removal of personal identifiers, and access to the data will be restricted to authorized personnel only.

Data Analysis

This objective will use an exploratory-descriptive approach to analyze deidentified HIV routine program data. Exploratory data analysis will be conducted using Python 3.11.4 programming language. The analysis will include univariate nongraphical (central tendency, spread skewness, and kurtosis), multivariate nongraphical, univariate graphical (histograms, stem-and-leaf plots, boxplots, and quantile-normal plots), and multivariate graphical (scatterplots, run charts, multivariate charts, Bubble charts) outputs. A data deduplication process will be undertaken to eliminate multiple records that pertain to the same individual. When unique identifiers are available, we will use exact matches to ascertain whether records belong to the same person. However, in cases where unique identifiers are absent, we will use matching algorithms to calculate the probability of multiple records belonging to the same person.

Methods for Objective 4

To pilot the inclusion of the KPs UIC in RHIMS in South Africa using findings from objectives 1, 2, and 3.

Study Design

Drawing insights from objectives 1, 2, and 3, an integrated framework will be developed, by adapting the PRISMA framework. This framework will undergo a pilot phase within selected health care facilities. During this pilot, primary health care registers and clinical stationery will be adjusted to include UICs for KPs. Over the course of 1 month, these refined tools will be used to gather comprehensive data on HIV testing, ART initiation, ART outcomes, viral load collection, and suppression.

To evaluate the feasibility of UIC integration into data collection tools, semistructured qualitative interview questionnaires will be administered to testers or lay counselors, data captures, and clinicians.

Study Setting

The framework will undergo a pilot phase in Gauteng province, specifically in the Tshwane district, where both KPs are served, and high HIV burden facilities exist. The district's notable HIV prevalence renders it an optimal setting for assessing the framework's effectiveness. Focusing on high-burden facilities will ensure a comprehensive representation of health care settings, offering valuable insights applicable to wider contexts.

The framework will be pilot-tested among health care providers, data captures, and HIV testers or lay counselors who are 18 years and older and employed within the selected facilities. Additionally, the population will encompass individuals accessing health care services at the selected facilities.

The individuals need to be on permanent employment or contract employment beyond the duration of the piloting to avoid participants discontinuing from the study because of employment termination. By including various personnel, the study intends to capture a wide range of experiences and perspectives, facilitating a thorough evaluation of the framework's feasibility and effectiveness in real-world health care settings.

Data Collection

A semistructured questionnaire will be used to collect feedback from the pilot sites. Trained researchers will conduct face-to-face interviews with HIV testers or lay counselors, data captures, and clinicians at each pilot facility. The interviews will be recorded to ensure the accurate capture of participants' responses and insights. Conducted in an environment conducive to open and sincere dialogue, participants will have the opportunity to provide additional comments or insights beyond the structured questionnaire. This approach allows for a comprehensive understanding of the pilot implementation process, enriching the evaluation with nuanced perspectives.

Data Analysis

Qualitative data analysis will be carried out following similar steps outlined in objective 2 for semistructured interviews with stakeholders.

Ethical Considerations

Ethical guidelines will be adhered to throughout the research process. Ethics approval has been secured from the UJ for the Research Ethics Committee (UJ REC) for this study (REC-2518-2023). Furthermore, since human participants will be used in the study, several principles will be adhered to, enhancing the norms and standards of ethics, as well as aligning with the guidelines of the Protection of Personal Information Act 4 of 2013 (POPIA). These principles are elaborated further in this section. With regards to objectives 2 and 4 (stakeholder interviews and pilot site), the participants will be informed about the study's methodology and procedures using the study information letter in line with the POPIA. The participants will further be provided with a personal information letter detailing

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the personal information that will be collected during the study according to the POPIA and thereafter be asked to sign the personal information consent form acknowledging that they have understood the information contained in the personal information letter. Before taking part in the study, all participants will be asked to give written informed consent. The interviews will be audio-recorded with the participant's consent. Participants will be told that participation in the study is completely voluntary and will be allowed to withdraw their consent at any stage of the study. For privacy purposes, separate and private rooms within the office premises will be used for the interview. Only the interviewer, interviewee, and note-taker will be present during all face-to-face interview sessions. The interview will be solely done in the interest of the research topics. The interviews will commence with a brief introduction of the study objectives, introducing the interviewer, and reading the privacy declaration form. In line with the POPIA, information will not be analyzed using participant's names, but pseudo names will be used in the analysis where verbatim quotations are applied. Since anonymized data cannot be considered completely anonymous, necessary provisions will be taken to remove any identifying information or avoid reidentification. For example, a pseudonym will be assigned to each participant, ensuring that the interview transcript does not contain any identifying information. This will also be consistent with UJ's data sharing and processing policies for the use of secondary data.

Results

As of June 2023, the systematic review protocol was registered with PROSPERO (CRD42023440656). The results will encompass a systematic review of literature, qualitative interviews, and document reviews, along with exploratory analysis of deidentified routine program data and findings from the pilot study. Prior to commencing the study, formal authorization will be secured to conduct stakeholder interviews and access deidentified HIV programmatic data. Data collection will commence in September 2024 and expected results for all objectives will be published by December 2025.

Discussion

Principal Findings

This study will significantly contribute to enhancing HIV management and addressing the epidemic among KPs in South Africa and beyond, ultimately improving health outcomes and reducing disparities. Integrating UICs for KPs into RHIMS in South Africa will enhance HIV monitoring and programming by enabling the identification of HIV trends among specific KP groups, offering insights crucial for tailoring interventions to address their unique needs. Consolidating the principal findings of all 4 objectives, this study will provide a comprehensive understanding of the UIC implementation landscape, encompassing successes, challenges, and opportunities across SSA. Furthermore, it will furnish valuable insights into the operational, technical, and policy aspects of UIC integration into RHIMS. The systematic literature review will not only shed light on RHIMS implementation challenges and facilitators for UIC integration but also garner best practices, and comparisons to prior studies, potentially expediting the implementation process while mitigating errors through lessons learned from countries that failed to incorporate UICs successfully. Formative assessments of RHIMS and stakeholder perspectives will refine strategies for engagement and policy development, fostering collaboration among diverse stakeholders and ensuring a unified approach to UIC integration. The exploratory analysis of routine program data will yield crucial insights into existing RHIMS data structures and trends, guiding further enhancements and optimizing data use for evidence-based decision-making. The integration of the KPs UIC allowing for the disaggregation of data to include marginalized KPs will contribute to the Government's achievement of the Sustainable Development Goals 2030 agenda of leaving no one behind.

This study's strengths lie in its comprehensive approach, involving diverse stakeholders across multiple objectives, potentially yielding valuable insights into UIC integration. However, limitations include context-specific findings, challenges related to data quality, potential implementation barriers, and scope constraints.

The future direction of this study entails extending the integration of KPs UICs into other government information management systems in South Africa and other SSA countries. Subsequent research efforts could focus on assessing the sustained impact of this integration on HIV monitoring, programming, and health outcomes among KPs, while also exploring advancements in technology and methodologies to optimize data collection and analysis within RHIMS for more effective public health interventions.

Concerning our dissemination plan, we aim to publish study findings under each objective in peer-reviewed journals. Summary reports will be distributed to key stakeholders, policy makers, and relevant organizations to ensure broad visibility and use of the study outcomes.

Conclusions

This study will produce a framework to recommend the national rollout of KPs UIC inclusion. The results will contribute to the knowledge base on integrating KPs UIC into RHIMS data, leading to data optimization, complete reporting, and improved programming.

Acknowledgments

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responsibility of the authors and does not necessarily represent the official views of the SAMRC. This work is conducted under the auspices of the SAMRC/University of Johannesburg Pan African Centre for Epidemics Research Extramural Unit.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

RNP-M, EP, and MR conceived the protocol. MR wrote the first draft of the protocol. RNP-M and EP extensively reviewed the protocol. RNP-M and EP were responsible for the supervision of the manuscript. All authors read and approved the submission of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[PDF File (Adobe PDF File), 30 KB - resprot_v13i1e55092_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
KP: key population
NDoH: National Department of Health
POPIA: Protection of Personal Information Act
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
REC: Research Ethics Committee
RHIMS: routine health information management system
SSA: Sub-Saharan Africa
UIC: unique identifier code
UJ: University of Johannesburg
WHO: World Health Organization

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Protocol

Establishing Priorities for Improving Data Collection and Measurement of Mental Health and Well-Being of Adolescents With Special Educational Needs Within Nonmainstream Schools: Protocol for a Delphi Study

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Abstract

Background: There are more than 1.5 million children and young people in England with special educational needs (SEN), with over 160,000 young people in the United Kingdom attending a special school or alternative provision (AP) setting. Young people with SEN have been found to be at risk for poorer mental health and well-being than non-SEN peers. However, there is a range of both school-related and research challenges associated with identifying difficulties in a timely manner.

Objective: This Delphi study aims to determine a list of stakeholder priorities for improving school-based measurement of mental health and well-being among young people with SEN, at an aggregated level, within secondary special school or AP settings. A secondary objective is to inform the implementation of school-based well-being surveys, improve engagement in special schools or AP settings, and improve survey response rates among children and young people with SEN.

Methods: A mixed methods Delphi study will be conducted, including a scoping review and preliminary focus groups with school staff members and researchers to establish key issues. This will be followed by a 2-round Delphi survey to determine a list of stakeholder priorities for improving the measurement of mental health and well-being at an aggregate level within special schools and AP settings. A final stakeholder workshop will be held to discuss the findings. A list of recommendations will be drafted as a report for special schools and AP settings.

Results: The study has received ethical approval from the University College London Research Ethics Committee. The stage 1 scoping review has commenced. Recruitment for focus groups will begin in Autumn 2024. The first round of the Delphi survey will commence in early 2025, and the second round of the Delphi survey in the spring of 2025. The final workshop will commence in mid-2025 with final results expected in late 2025.

Conclusions: There is a need for clear recommendations for special schools and AP settings on priorities for improving the measurement of mental health and well-being problems among young people with SEN. There is also a need for recommendations to researchers implementing school-based well-being surveys, including the #BeeWell program, to enable them to improve their engagement in special schools and AP settings and ensure surveys are accessible.

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KEYWORDS

special educational needs; special schools; alternative provision; mental health; well-being; school-based measurement

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Introduction

Background

There are over 1.5 million children and young people in England with special educational needs (SEN) [1]. SEN covers a range of needs including speech, language, and communication needs; learning disabilities, autistic spectrum disorder, and attention-deficit/hyperactivity disorder; and social, emotional, and mental health needs [1].

There are high levels of co-occurrence between SEN conditions, which make it helpful to consider "special educational needs" as an umbrella term. For example, attention-deficit/hyperactivity disorder has been found to co-occur with conditions, including oppositional defiant disorder, conduct disorder, autism, anxiety, and coordination problems [2,3]. Likewise, autism has been found to co-occur with anxiety, disruptive, impulse-control, and conduct and depressive disorders [3].

Young people (adolescents aged 11-18 years) with SEN are at an increased risk of mental health problems [4], have lower levels of well-being than children without SEN [5,6], experience a more difficult transition to secondary school [7,8], and are more likely to experience bullying [9].

Many young people with SEN attend special schools or alternative provision (AP) settings, which are nonmainstream schools that cater to the different needs of young people. Special schools are those with specific educational provisions for young people with SEN or disabilities, while AP settings, which include pupil referral units (PRUs), are education settings for children and young people who are unable to attend a mainstream school for reasons such as being permanently excluded or having an illness that prevents them from being educated in a mainstream setting. In 2022-23, there were nearly 150,000 children with SEN in state-funded special schools and 4000 in nonmainstream special schools [10]. There were an additional 13,000 young people with SEN in state-funded AP settings and PRUs [1].

Most schools in the United Kingdom are taking steps to identify the mental health and well-being needs of their pupils. A report by the Department for Education found that 73% of special schools and 77% of AP settings carried out universal data collection on mental health [10]. However, large-scale school-based mental health and well-being surveys have been found to have barriers to implementation relating to competing school priorities, a lack of time and resources, and schools feeling overwhelmed by the number of competing surveys [11]. Recent research recommended that a program for school-based identification of mental health and well-being in mainstream primary school settings should (1) aim to identify children with the full range of severity of difficulties, (2) have opt-out parental consent, (3) educate staff members and children, and (4) provide a link between identified need and available support [12].

A school-based mental health and well-being survey, the #BeeWell program, found the administration of school-based surveys more challenging in special schools and AP settings. This was considered to be due to a high turnover of pupils, which made it difficult for schools to get necessary data-sharing agreements, consent, and resources in place in the time frame [13]. Likewise, due to smaller pupil numbers and lower response rates, which hindered the attainment of minimum data reporting thresholds, detailed aggregated well-being reports could not always be shared with special schools and APs [13]. This challenge is not unique to #BeeWell; other studies have had challenges with low numbers of young people with SEN in existing datasets [5] or did not collect data on SEN [14].

While there are general challenges with school-based measurement of mental health and well-being at an aggregate level, there are also challenges specific to identifying the mental health and well-being needs of children and young people with SEN. One such challenge is being able to distinguish between mental health difficulties and characteristics of special educational needs [15]. Hence, early warning signs can be missed, leading to late identification of issues [16]. Young people in AP settings may have their mental health needs viewed as behavioral issues, and there may be an overfocus on "challenging" behaviors rather than looking at the underlying emotional causes of behaviors [17,18].

Some children with SEN, particularly those with speech, language, and communication needs, may have difficulties in expressing their distress or describing negative events, such as bullying [19]. There may be difficulties relating to staff training and knowledge about mental health and well-being [15,18]. Young people with SEN may need help from school staff in completing surveys, which can be labor-intensive [20].

In addition, there is a lack of consensus on the most appropriate mental health and well-being measures for young people with SEN [21], particularly for those with intellectual or learning disabilities. A COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) systematic review of well-being measures for young people with intellectual disabilities found no measures that they could recommend for use [22]. However, more recently, an intellectual disability version of the Short Warwick–Edinburgh Mental Wellbeing Scale (ID-SWEMWBS) and KIDSCREEN-10 (ID-KIDSCREEN10) showed good psychometric properties [23].

Aim and Objectives

This study aims to identify the challenges associated with conducting school-based surveys to measure the mental health and well-being of young people with SEN in secondary special schools and AP settings. It aims to reach a consensus among researchers and special school and AP staff on what the priorities are for improving data collection and measurement of mental health and well-being in these settings.

The findings will be used to draft guidelines for special schools and AP settings about improving the measurement of mental health and well-being issues among young people with SEN. These findings will also be used to make recommendations for school-based surveys to improve the engagement and response rates of special schools and AP settings in the future.

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Methods

Design

This Delphi study will have a mixed methods design, including a scoping review and preliminary qualitative focus groups, with secondary special school and AP staff members and researchers in the field of mental health and SEN, to establish key issues relating to the measurement of mental health and well-being problems in SEN settings. This will be followed by a 2-round Delphi survey in the spring of 2025 to determine a list of the most important stakeholder priorities for improving the measurement of mental health and well-being at an aggregate level within these settings. A final follow-up workshop will be held in mid-2025 to discuss and reflect on the findings and provide additional information and context to the priority guidelines. It will be used to establish a list of the top 10 priorities if the final list from the Delphi survey rounds is long.

The Delphi method was chosen as it is useful for topics where there is a large amount of experiential knowledge among different expert groups and has frequently been used in mental health research [24-26]. The Delphi method was recently used in a similar study on stakeholder priorities for developing a program for mainstream school–based identification of mental health problems in mainstream primary schools [12].

It will also allow an agreement to be reached across different stakeholders (eg, special school and AP staff and researchers in different UK regions) about the priorities for addressing commonly faced issues in identifying mental health and well-being of young people with SEN at an aggregate level, which will be applicable to a wider range of special schools and AP settings. The Delphi method aims to make practical recommendations that can be implemented, and as the process is iterative, it allows participants to reflect on and revise previous responses, which is not possible in interviews or focus groups [24,27].

Stakeholders and Setting

Participants and Recruitment: Focus Groups

Purposive sampling, which is a commonly used qualitative sampling technique to capture those who are especially knowledgeable about an area of interest (in this case, school-based measurement of mental health and well-being), will be used to recruit participants for the focus groups [28]. There will be 2-3 focus groups, each consisting of 5-8 participants: at least 1 focus group with school staff members and 1 focus group with researchers.

Participants for the “school staff” focus groups will be those working with adolescents with SEN in special schools or AP settings (including PRUs). These participants will be recruited from the sample of 38 special schools and AP settings who are currently taking part or have previously taken part in the #BeeWell study in Greater Manchester and Hampshire, Isle of Wight, Portsmouth, and Southampton. A smaller number of 5-10 schools will be contacted in the first instance, and further schools will be contacted based on responses and the need for additional participants. Targeted recruitment will be considered if there is a lack of representation from a particular school setting (eg, PRUs).

Initial contact to recruit school staff for focus groups will be made to school staff by an email sent by the #BeeWell project managers of Greater Manchester and Hampshire, Isle of Wight, Portsmouth, and Southampton. Individuals who are interested in participating will be encouraged to contact the researcher by email.

Participants for the “researchers” focus group will be those working in the field of SEN and mental health or on school-based mental health data collection (including researchers who have worked on the #BeeWell program but who are not associated with this study) and educational psychologists. These participants will be identified through purposive sampling, including from relevant university research groups such as UCL’s Centre for Research in Autism and Education or the University of Warwick’s Centre for Research in Intellectual and Developmental Disabilities.

Focus groups will aim for a maximum diversity of participants from different school settings, different regions, and different professional backgrounds.

Participants and Recruitment: Delphi Survey Rounds

To reach the minimum number of 50 responses needed in the round 2 survey, with anticipated dropout between rounds, a minimum of 100 participants will be recruited for the Delphi survey round 1. This will be approximately 50 school staff and 50 researchers or experts in mental health and SEN, including educational psychologists. There is no general consensus for the optimal number of participants to recruit in a Delphi study [29], but smaller sample sizes are preferred because the aim of the Delphi study is to establish a consensus between expert participants, rather than providing cross-sectional representation [30]. Furthermore, 1 review found that nearly 50% of Delphi studies had fewer than 40 experts [31].

School staff participants will be recruited from the special schools and AP settings who have been involved with the #BeeWell study in Greater Manchester and Hampshire, Isle of Wight, Portsmouth, and Southampton. Every special school and AP setting with previous #BeeWell involvement will be invited to complete the survey to capture a wide range of views. Participants will be those with knowledge of the school’s involvement with #BeeWell or with the implementation of school-based surveys on mental health and well-being. This study aims to have approximately 5-10 responses from each group of frontline teachers, special educational needs coordinators, head teachers, or other school leadership staff.

As in the focus groups, researcher participants for the Delphi survey will be identified through purposive sampling and snowball sampling of professionals in a research background, including university academic staff, who have published on mental health and SEN, and professionals in research policy or practice.

Participants will be recruited through email. Email addresses will be obtained from publicly available sources (eg, through author information on published journal papers or university

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staff lists). A general recruitment email will also be sent to research groups (eg, UCL's Centre for Research in Autism and Education). Participants will be encouraged to forward the survey to colleagues with knowledge in the field of school-based measurement of mental health and well-being and SEN.

The perspectives of young people with SEN will also be incorporated as part of an associated study (UCL REC ethics approval project 26477/001). Young people with SEN, aged between 11 and 16 years, will be recruited from #BeeWell special schools and AP settings (more details are given in the "Phase 1: Delphi Survey Development" section below).

Phase 1: Delphi Survey Development

Identifying the issues will be a 2-stage process. Stage 1 will involve a minimum of 2 focus groups. The first group will have between 5 and 8 school staff, and the second will involve 5-8 researchers or experts in mental health and SEN. If interested participants are unable to join the focus groups, they will be offered the opportunity to take part through individual interviews or a qualitative open-ended survey.

Focus groups will explore the barriers and facilitators to the measurement of mental health and well-being issues among children and young people with SEN in special schools or AP settings at an aggregate level. Focus groups will also incorporate questions about school-based surveys, such as the #BeeWell program, and improvements that could be made to the implementation of these surveys to improve special school and AP engagement and response rates.

Focus groups and interviews will be audio-recorded on an encrypted Dictaphone, and the audio recordings will be sent to an external transcription service for transcription.

Stage 2 will involve a scoping review to identify previously published literature on the school-based measurement of mental health and well-being problems among young people with SEN. The scoping review will explore the issues associated with school-based data collection and measurement, including the mental health and well-being measures that are validated for use in these settings. It aims to determine whether there are specific challenges referenced in the literature relating to the measurement of mental health and well-being problems within these settings (eg, staff time to implement surveys, barriers relating to parents opting out).

The perspectives of young people with SEN will also be incorporated during phase 1 Delphi survey development. Interviews with young people will be analyzed for any themes or nuances that have not been captured by the focus groups or the scoping review, such as young people's feelings about their school collecting mental health and well-being data and issues surrounding data anonymity. As with the focus groups and scoping review, themes that emerge from interviews with young persons will be written into items for improvement of school-based measurement of mental health and well-being.

Data Analysis

Thematic analysis of focus group data will be carried out to identify statements for the Delphi survey. The process is based on a previous Delphi study [32]:

1. Audio recordings will be securely transferred to an external transcription service. Written transcriptions will be anonymized (removing names and identifying information) before qualitative data analysis is carried out.
2. Within the data, concepts generated from the discussion on issues will be extracted and grouped into categories. For example, themes may emerge about issues relating to "staff time," "staff training," "accessibility of mental health surveys," "validated mental health and wellbeing measures," or "communication barriers." Themes might include those that are more general issues relating to special school and AP settings and themes that are more specific to research methods.
3. Issues related to school-based measurement of mental health and well-being among children and young people with SEN that emerged from the scoping review will also be categorized into items in the same manner as focus group discussions and sorted into the overall key themes.
4. Each key concept will be written as individual items for improvement, to create a provisional list of items for the Delphi survey. Each item will relate to only 1 idea and will be worded as a practical factor relating to an improvement that can be made in the measurement of mental health and well-being in school that can be rated on a Likert scale of importance from 1 (not important at all) to 9 (very important). For example, survey items may be "How important is it for adequate staff time to be available to assist young people with completing surveys?" "How important is it for accessible surveys for young people with SEN to be available?" "How important is it for school staff to have training on measuring the mental and wellbeing of young people with SEN?" and "How important is it for special schools or AP settings to have external support for implementing mental health and wellbeing surveys?"
5. The draft survey statements will be refined with input from an expert advisory panel with members drawn from both UCL and the University of Manchester.
6. A Delphi survey is then created by compiling a list of statements (grouped into themes) related to the research aims and objectives.

Phase 2: e-Delphi Survey

Round 1

The first round of the Delphi survey will be piloted with 2-5 individuals from the #BeeWell advisory panel and colleagues at the UCL, to ensure clarity of statements and that there is no overlap between statements. The survey will be hosted on Qualtrics.

Invitations to complete the survey will be emailed to participants in early 2025, including those who participated in round 1 of focus groups, but also a wider number of participants from special schools and AP settings and researchers.

Participants will be emailed individually, and they will be reminded of the purpose of the study and asked to provide consent to take part in the survey, at the start. They will be informed about how to rate the statements and the importance of completing the Delphi survey in both rounds 1 and 2.

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In the survey, participants will be asked for demographic data (age, gender, ethnicity, job role, and length of time in their field). They will then be asked to rate statements relating to issues on school-based data collection and measurement of mental health and well-being, on a Likert scale of importance from 1 (not important at all) to 9 (very important). A 9-point scale was chosen to be more sensitive to different scores, than a 5 or 7-point scale. As in a similar Delphi study, scores of 7-9 will be considered "important" issues, scores of 4-6 as "neither important nor unimportant," and scores of 1-3 as "unimportant" issues [12].

The survey will include an open-textbox at the end for participants to recommend something that was not covered by the survey. Participants will have up to 3 weeks to complete the survey and will be sent up to 2 reminders to complete it.

Data Analysis

The results of the round 1 Delphi survey will be used to generate the survey for round 2. Statements will be considered to have reached a consensus if >70% of participants rated the statements unimportant (scores of 1-3) or important (scores of 7-9) and the statement's IQR is less than or equal to 2, which has been done in a similar Delphi study [12]. Statements that reached consensus as "unimportant" will be dropped from the round 2 survey.

Any additional statements that were recommended by participants in the free textboxes in the round 1 survey will be reviewed by the researchers to ensure they are within the scope of the study, clearly worded, and are dissimilar to existing statements [25]; if they meet these criteria, they will be included in the next Delphi round.

Survey Round 2

Respondents of the round 2 survey who rate at least 50% of the statements will receive an invitation to the round 2 survey. Participants will receive feedback on the round 1 scores of all aggregated responses (ie, the aggregated scores from special school staff, AP and PRU school staff, researchers, and educational psychologists) as a median group-level score, alongside information about how they rated the statements.

In the round 2 survey, participants will be able to rerate the level of importance of the statements considering this feedback. As in round 1, participants will have 2-3 weeks to complete the survey and will be sent up to 2 reminder emails.

Data Analysis

As in round 1, statements will be deemed to have reached consensus if >70% of participants rated the statements unimportant (scores of 1-3) or as important (scores of 7-9) and the statement's IQR is less than or equal to 2 [12].

All statements that achieve consensus as being "important" will be included in the final list of priorities for schools and researchers on improving school-based measurement of mental health and well-being.

Final Follow-Up Workshop

A final follow-up web-based workshop will be held in early 2025 to discuss and reflect on the findings. The workshop will be used to establish a list of the top 10 priorities if the final list from the Delphi survey rounds is long. The workshop will aim to have 8-10 participants from a range of settings and UK regions recruited from those who completed both rounds of the Delphi surveys. The workshop will be recorded and transcribed to provide additional information and context to the priority guidelines.

Ethical Considerations

This study will follow the Code of Conduct for Research of University College London. Ethics approval for this study was granted by the UCL Research Ethics Committee (REC; project 26477/002). This research project is allied to the #BeeWell program, which was reviewed and approved by The University of Manchester's REC (reference 2021-11133-18179). The #BeeWell program introduced a youth-developed well-being survey to 187 secondary schools, including special schools and AP settings, across Greater Manchester in 2021. In Autumn 2023, #BeeWell began its rollout in Hampshire, the Isle of Wight, Portsmouth, and Southampton, with plans to extend further after 2024. There are 3 versions of the #BeeWell survey that include questions across the domains and drivers of well-being: a full version, a short version, and a widget symbol version, which was developed in consultation with young people in special school and AP settings.

Informed Consent

Participants will be provided with a detailed information sheet and privacy notice before participation in the research. For the focus groups, the consent form will be hosted on Microsoft Forms, the link to which will be sent along with the participant information sheet ahead of the focus groups. Participants will be informed that due to the nature of focus groups, full anonymity cannot be guaranteed for this stage of the Delphi study.

For the Delphi survey rounds, participant information and privacy notices will be explained within the web-based survey form, which will be hosted on Qualtrics. Consent for completing the surveys 1 and 2 will be obtained in the web-based surveys.

Privacy and Confidentiality

Participants will receive a privacy notice before involvement, which will state how their data will be collected, used, and stored. Names and identifying information of the participants, such as their school, will not be associated with their responses.

Due to the nature of focus groups, full confidentiality of responses cannot be guaranteed. However, participants will be informed about this in the participant information sheet and will be reminded at the start of the discussion to not discuss the focus group with others.

Individual schools or respondents will not be named in any outputs, and findings will be aggregated. It will not be possible to identify any individual survey responses within papers or reports.

Compensation Details

School staff who participate in the focus groups will receive a £25 (US $33) voucher for participation.

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Results

The stage 1 scoping review has commenced as of March 2024. The scoping review protocol is registered on the Open Science Framework [33].

Recruitment for focus groups will begin in Autumn 2024. The first round of the Delphi survey will commence in January 2025, and the second round of the Delphi survey in the spring of 2025. The final workshop will commence in mid-2025. Expected results will be published in late 2025.

Discussion

Anticipated Findings and Potential Impact

It is anticipated that this study will be able to identify a set of stakeholder agreed-upon priorities for special schools and AP settings and researchers, to be able to improve the measurement of mental health and well-being problems among young people with SEN. A report for special schools and AP settings will be written to provide feedback on the study's findings related to priorities.

A set of guidance will also be written to make recommendations for the introduction or development of school-based mental health and well-being surveys, such as #BeeWell, to be more inclusive of special schools and AP settings and ensure a good response rate from young persons with SEN.

Strengths and Limitations

The strength of this Delphi study is the range of stakeholders that will be included. It will include the perspectives of special school and AP staff who have direct experience with the challenges of trying to identify mental health and well-being problems among children and young people with SEN, along with other professionals working in the field of mental health and SEN, including educational psychologists. It will also incorporate the perspectives of young people with SEN themselves, who are being interviewed as part of an associated study.

As school staff will be recruited from specific schools who participated in the #BeeWell program, in 4 regions of the United Kingdom (Greater Manchester and Hampshire, the Isle of Wight, Portsmouth, and Southampton), it is acknowledged that results may be less applicable to other UK schools more widely. To minimize this risk, this study aims to recruit from different schools and include professionals from other areas who were not associated with the #BeeWell program.

Taking a multi-methods approach, including the qualitative focus groups in round 1, will generate a deeper understanding of some of the challenges that special schools and AP settings face when trying to understand the mental health and well-being problems faced by their students rather than just drawing on the literature.

Conclusions

There is a strong need to identify some of the problems that special schools and AP settings face regarding measuring the mental health and well-being of adolescents with SEN. This Delphi study aims to establish a set of priority recommendations for improving school-based measurement of mental health and well-being, which have been agreed upon by stakeholders in special school and AP settings and researchers in mental health and SEN.

It also aims to make recommendations to researchers implementing school-based well-being surveys, including the #BeeWell program, to enable them to improve their engagement in special schools and AP settings, ensure surveys are accessible, and increase survey response rates of young people with SEN.

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Authors' Contributions

The study protocol was designed with input from all authors (MCJ, JD, and STL). MCJ wrote the manuscript, JD and STL provided edits, and all authors approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AP: alternative provision
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
ID-KIDSCREEN10: intellectual disability version of KIDSCREEN10
ID-SWEMWBS: intellectual disability version of the Short Warwick–Edinburgh Mental Wellbeing Scale
PRU: pupil referral units
REC: Research Ethics Committee
SEN: special educational needs

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Protocol

Objective Analysis of Traditional Chinese Medicine Syndrome Differentiation of Patients With Diabetes and Prediabetes: Protocol for a Nonrandomized, Exploratory, Observational Case-Control Study Using Digitalized Traditional Chinese Medicine Diagnostic Tools

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Abstract

Background: Diabetes and prediabetes are diagnosed differentially by Western and Chinese medicine. While Western medicine uses objective laboratory analysis of biochemical parameters to define the severity of diabetes and prediabetes, Chinese medicine uses a comprehensive approach that integrates observation, inquiry, pulse palpation, and tongue diagnosis. The medical information collected is then categorized into different syndromes. However, traditional methods of pulse and tongue diagnoses used to determine syndrome differentiation are highly subjective and skill dependent.

Objective: This study aims to identify the gap in conventional traditional Chinese medicine (TCM) diagnostic techniques for syndrome differentiation analysis using contemporary diagnostic devices. We devised a protocol for a nonrandomized, exploratory, observational case-control study with equal allocations in 5 arms to investigate the syndrome differentiation of diabetes and prediabetes. We hypothesize that the TCM syndrome differentiation of diabetes and prediabetes in the tropical climate may differ from that defined based on the Chinese demographic. We also speculate that the high-frequency spectral energy may reflect a difference in pulse wave intensity and density between the healthy and diabetes groups.

Methods: A total of 250 eligible participants will be equally assigned to 1 of 5 arms (healthy or subhealthy, prediabetes, diabetes, prediabetes with hypertension and dyslipidemia, and diabetes with hypertension and dyslipidemia). Participants aged 21-75 years, of any sex or race, and have been diagnosed with diabetes (fasting plasma glucose [FPG] of 7 mmol/L, or 2-hour plasma glucose [2hPG] of 11.1 mmol/L) or prediabetes (impaired FPG of 6.1-6.9 mmol/L, or impaired glucose tolerance with an 2hPG of 7.8-11 mmol/L) will be included. The Health Evaluation Questionnaire, Physical Activity Questionnaire, sugar intake assessment, Constitution in Chinese Medicine Questionnaire, radial pulse diagnosis, and tongue diagnosis will be performed in a single visit. ANOVA for continuous data and chi-square tests of independence will be used for categorical data assessments, with a level of $P<.05$ considered significant.

Results: The recruitment is in progress. We anticipate that the study will conclude in June 2025. As of July 15, 2024, we have enrolled 140 individuals.

Conclusions: To the best of our knowledge, this is the first study to use contemporary TCM diagnostic instruments to map expert and empirical knowledge of TCM to its scientific equivalents for the purpose of evaluating the syndrome differentiation

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of diabetes. We designed this protocol with the exploratory goal to examine objectively the syndrome differentiation of patients with diabetes and those with prediabetes using TCM diagnostic technologies. The data collected and evaluated under standardized conditions using these contemporary diagnostic devices will exhibit a higher degree of stability, hence yielding dependable and unbiased results for syndrome differentiation. Thus, our findings may potentially increase the accuracy of identification, diagnosis, treatment, and prevention of diabetes and prediabetes through a system of targeted treatment.

Trial Registration: ClinicalTrials.gov NCT05563090; https://clinicaltrials.gov/ct2/show/NCT05563090

International Registered Report Identifier (IRRID): DERR1-10.2196/56024

(JMIR Res Protoc 2024;13:e56024) doi:10.2196/56024

KEYWORDS

diabetes; dyslipidemia; hypertension; prediabetes; traditional Chinese medicine syndrome differentiation; pulse diagnosis; tongue diagnosis; tongue; diabetic; protocol; diagnostic tools; diagnostic system; accuracy; diagnosis; treatment; prevention; questionnaire; sugar intake; physical activity; health evaluation

Introduction

Definition

Diabetes mellitus is one of the top 10 leading causes of mortality, presenting a significant burden on global public health [1]. The International Diabetes Federation estimates that the global diabetes prevalence among individuals aged 20-79 years will increase from 10.5% (536.6 million) to 12.2% (783.2 million) in 2045 [2]. Prediabetes (intermediate hyperglycemia), characterized by a glycemic level between normal glucose tolerance and diabetes, maintains a high risk of developing diabetes, with an annual conversion rate of 5%-10% [3]. Table 1 provides the World Health Organization (WHO) diagnostic standards defined for diabetes and prediabetes [4]. The American Diabetes Association also states that the glycated hemoglobin A_{1c} (HbA_{1c}) level should be at or above 6.5% for diabetes and between 5.7% and 6.4% for prediabetes [5]. The projected global prevalence of patients with impaired fasting glucose and impaired glucose tolerance is 6.5% (414 million) and 10.0% (638 million), respectively [5].

Table 1. The WHO[a] definition of diabetes and prediabetes.

Type and test	WHO criteria	
Diabetes		
FPG[b]	≥7.0	126
2hPG[c]	≥11.1	200
Intermediate hyperglycemia (prediabetes)		
IFG[d]		
FPG	6.1-6.9	110-125
2hPG	<7.8	140
IGT[e]		
FPG	<7.0	126
2hPG	7.8-11.1	140-200

[a]WHO: World Health Organization.

[b]FPG: fasting plasma glucose.

[c]2hPG: 2-hour plasma glucose.

[d]IFG: impaired fasting glucose.

[e]IGT: impaired glucose tolerance.

Prevalence of Diabetes and Prediabetes in Singapore

A local study concluded that between 2010 and 2035, the prevalence of prediabetes and diabetes among Singapore residents is expected to increase by more than 2-fold, from 434,685 to 903,596 and from 373,104 to 823,802, respectively. The incidence of prediabetes and diabetes is respectively projected to increase gradually from 15.5% to 24.9% and from 13.3% to 22.7% [6]. The number of patients with diabetes in Singapore is projected to grow to 1,000,000 in 2050 [7]. It is noted that Indians have the highest prevalence of diabetes in Singapore at 17.2%, followed closely by Malays at 16.6%, and Chinese at 9.7% [8].

Progression of the Disease

Prediabetics have a 5%-10% chance of progressing to diabetes and a higher risk of developing complications such as early

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nephropathy, small fiber neuropathy, early retinopathy, and risk of macrovascular disease [3,9,10].

Adults with diabetes have double the chance of contracting heart disease and stroke [11,12]. Patients with diabetes are also prone to developing kidney failure and blindness from diabetic retinopathy [13,14]. Hyperglycemia could cause neuropathy, foot ulcers, and limb amputation [15,16]. In 2021, the proportion of diabetes-related deaths in Singapore under the age of 60 years was 31.4% [17]. In addition, the total diabetes-related health expenditure worldwide in 2021 amounts to US $966 billion [17]. In Singapore, 11% of the total health care budget is set aside for diabetes [18]. It is to be noted that diabetes tends to hinder employment and productivity, putting more stress on the economy [19,20].

Different Diagnostic Approaches From Western and Chinese Medicines

The diagnosis of diabetes and prediabetes in Western and Chinese medicines differs in the approach, methodology, and fundamental principle. Objective laboratory analysis of biochemical parameters such as fasting plasma glucose (FPG), HbA_{1c}, and oral glucose tolerance tests play a crucial role in the diagnosis of diabetes in Western medicine [21]. In addition, salivary biochemical analysis is also used as a diagnostic tool for diabetes [22,23]. Diabetes and prediabetes result from inadequate insulin secretion or insulin resistance.

In contrast to Western medicine diagnostic criteria, traditional Chinese medicine (TCM) uses a different approach in the diagnosis of diabetes and prediabetes. TCM uses a unique diagnostic system to determine the underlying causes of the symptoms and devise individualized treatment plans to restore balance and promote health. Conventionally, TCM practitioners examine the patient's body appearance, tongue and radial pulse characteristics, medical history, and symptoms to provide a comprehensive and holistic analysis of the disease syndrome. The syndrome differentiation is an assemblage of clinical manifestations resulting from the disharmony or imbalances of the body's yin and yang, qi, and blood [24].

The ancient Chinese name of diabetes in the TCM classic "*Huang Di Nei Jing*" is known as "*xiao-ke*" [25,26]. Table 2 summarizes the syndrome differentiation of "*xiao-ke*" in the current *TCM Internal Medicine Textbook* [27].

Table 2. Classification of "xiao-ke (消渴)" based on syndrome-etiology differentiation.

Type of syndrome and classification	Main clinical manifestations	Other symptoms
shang-xiao 上消		
Excess lung heat and fluid deficiency 肺热津伤	Polydipsia	Dry mouth and tongue, frequent polyuria, excessive sweating with dysphoria. The tongue tip is red with a thin yellow coating. Surging and rapid pulse.
zhong-xiao 中消		
Excess stomach heat 胃热炽盛	Polyphagia, weight loss	Thirst, excessive urine, dry stool. Yellow tongue coating. Slippery and forceful pulse.
Qi and yin deficiency 气阴亏虚	Polydipsia	Diarrhea, with normal appetite or poor appetite, lassitude, weak limbs, and weight loss.
xia-xiao 下消		
Kidney yin deficiency 肾阴亏虚	Polyuria	Excessive, turbid, sweet urine, weak and sore back and knees, fatigue, dizziness, tinnitus, dry mouth and tongue, dry skin, skin itch. Red tongue with faint coating. Fine and rapid pulse.
Yin and yang deficiency 阴阳两虚	Polyuria	Frequent turbid urination may even pass urine upon water intake, haggard complexion, dry ears, weak and sore back and knees, cold limbs, aversion to cold, impotence, or irregular menstruation. Pale, white, and dry tongue. Sunken, fine, and weak pulse.

TCM provides individualized treatment plans based on the syndrome differentiation and body constitution to address the root causes of illness and promote overall well-being.

Comparing the Western medicine and TCM diagnostic approaches in diabetes and prediabetes highlights their complementary strengths. Western medicine excels in precise diagnosis and blood sugar management, while TCM offers a holistic perspective focusing on underlying imbalances. Integrating these approaches could offer a more comprehensive approach to managing diabetes and prediabetes.

Current Possible Gaps in Syndrome Classification of Diseases

It should be noted that the syndrome classification was developed using China's demographic data. We speculatively believe that this could be notably dissimilar from countries with tropical climates like Singapore due to the region's specific geographical and meteorological characteristics. Local research on the body constitution of a multiracial population revealed that qi-deficiency, phlegm dampness, and damp heat were the 3 most prevalent conditions [28]. Another local study reported a significant difference in the syndrome differentiation of knee osteoarthritis, wherein a much higher proportion (51%) of these patients experience spleen and kidney deficiencies with dampness syndrome compared to only 4.2% of those in China [29].

Conventional TCM Diagnostic Techniques

Moreover, the conventional techniques of diagnosis which rely solely on the clinical judgment, finger sensitivity, and visual

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accuracy of the TCM practitioner can result in inconsistent diagnoses and treatment [30,31]. For instance, the practitioner uses the index, middle, and ring fingers to simultaneously or separately palpate the bilateral radial pulses at *cun* (distal), *guan* (middle), and *chi* (proximal) locations corresponding to each viscus on each wrist (Figure 1) [31].

Figure 1. (A) Location of cun, guan, and chi pulses on the radial artery. (B) Modern pulse sphygmograph and its application output in graphical and quantitative measures. (C) Application output indicating (a) palpating pressure; (b) pulse wave; (c) pulse rate per 6 seconds; (d) intensity and density of the wave spectral energy; and (e) quantitative measures of spectral energy, energy proportion, and spectral energy ratio.

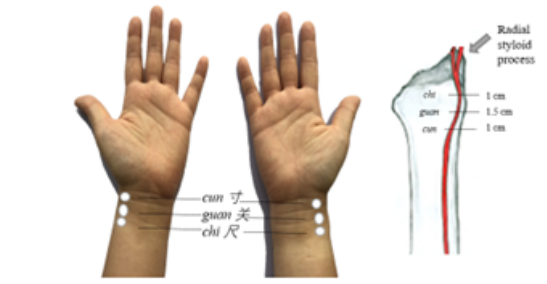

Left	Pulse	Right
Heart	*cun*	Lung, chest
Liver, gallbladder	*guan*	Stomach, spleen
Kidneys, lower abdomen	*chi*	Kidneys, lower abdomen

(A) Location of *cun*, *guan*, and *chi* pulses

(B) The pulse sphygmograph

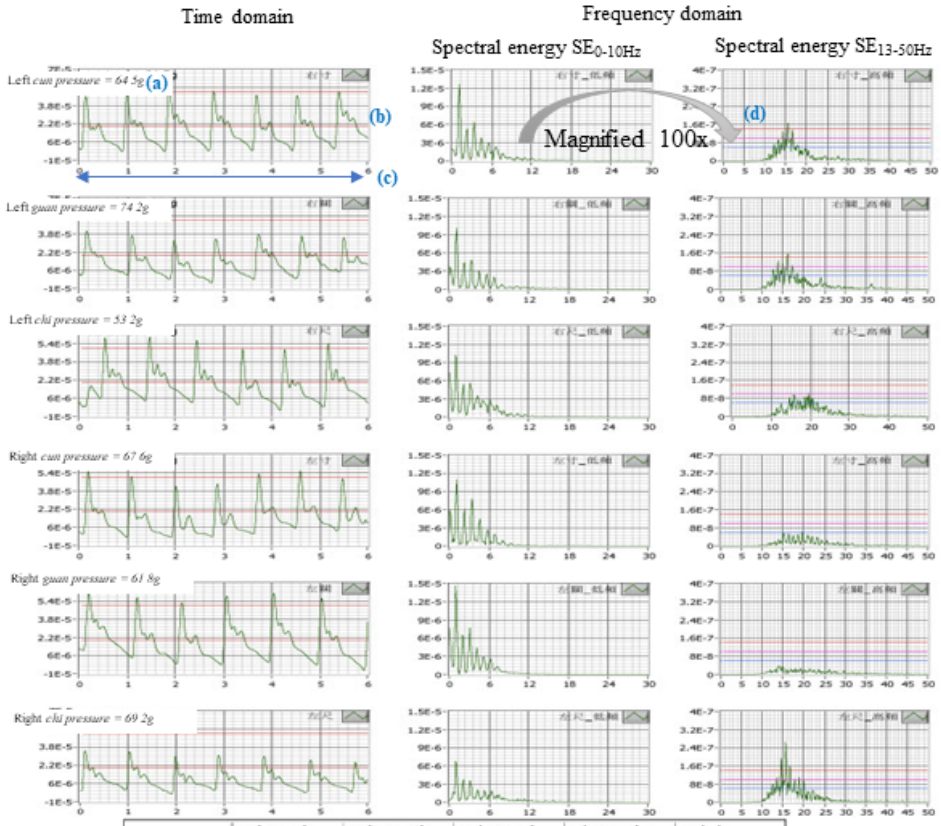

Pulse	FFT(0~10Hz)	FFT(10~50Hz)	FFT(13~50Hz)	EP(10~50Hz)%	SER(10)
Left *cun*	2.490E-10	9.240E-13	1.239E-13	0.370	269.500
Left *guan*	1.638E-10	8.840E-13	1.181E-13	0.537	185.312
Left *chi*	2.728E-10	7.159E-13	1.008E-13	0.262	380.986
Right *cun*	2.446E-10	1.039E-13	3.138E-14	0.042	2354.996
Right *guan*	3.834E-10	1.988E-13	1.312E-14	0.052	1929.033
Right *chi*	8.684E-11	1.100E-12	2.055E-13	1.251	78.927

(e)

(C) Application output

Historical TCM references list 28 common pulse profiles seen in clinical practice [32]. Each radial pulse profile, with its distinct characteristics in the pulse depth, rate, waveform, density, and intensity, can reveal physiological or pathological changes in the human body [33]. For instance, Jeon et al [34] investigated pulse wave variation during the female menstrual cycle and reported that string-like or slippery and rapid pulses

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were seen. Subjective evaluations have been demonstrated to influence the diagnosis and treatments [31].

Aside from pulse diagnosis, tongue diagnosis is essential in distinguishing TCM syndromes. The practitioner examines the physiological and pathological changes in the tongue and associates them with specific viscera. Figure 2 provides the relationship between the tongue position and the viscera (*zang-fu*) systems. However, because observations are based on the physician's judgment and can be easily influenced by environmental factors such as lighting and colored food, they can be highly subjective and inaccurate [35].

Figure 2. Relationship of the tongue and the respective viscera in TCM concept and tongue imaging analysis. TCM: traditional Chinese medicine.

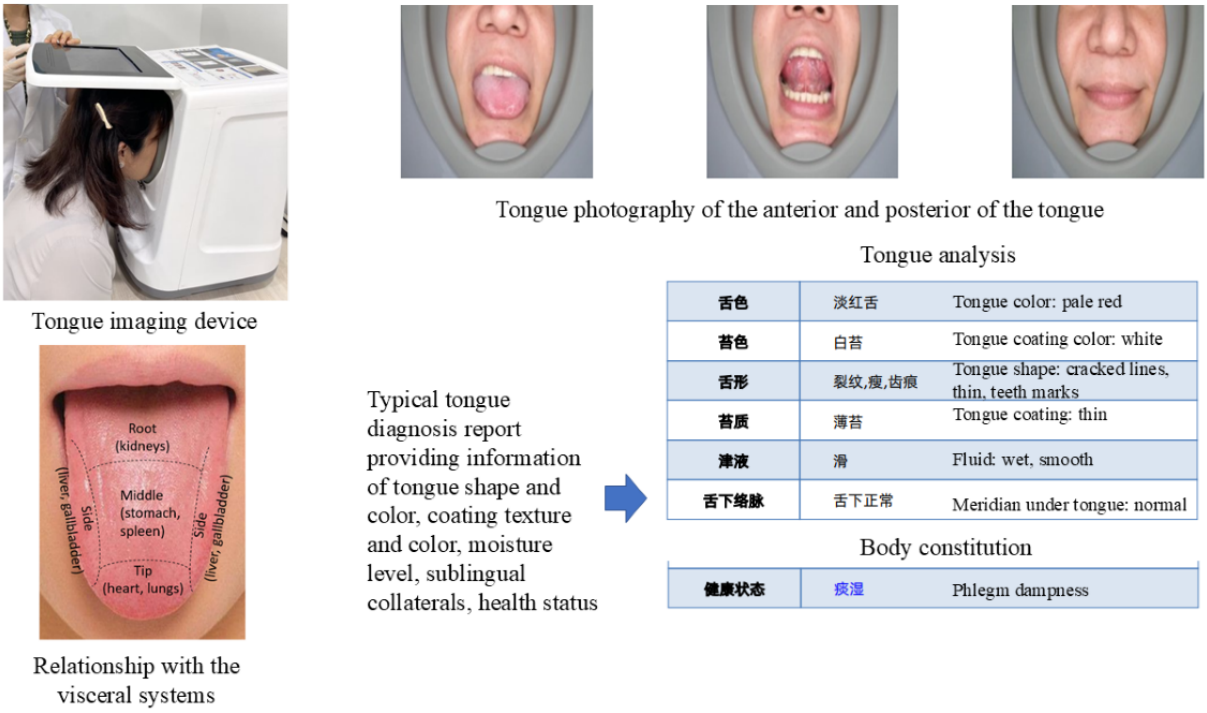

Specific Aims and Hypothesis

This study aims to identify the gap in syndrome differentiation between the subjective and objective TCM diagnosis. We devised a protocol for a nonrandomized, exploratory, observational case-control study with equal allocations in 5 arms to investigate the syndrome differentiation of diabetes and prediabetes. We hypothesize that the local TCM syndrome differentiation of diabetes and prediabetes in the tropical climate may differ from that defined based on the Chinese demographic. We also speculate that the high-frequency spectral energy ($SE_{13\text{-}50Hz}$) may reflect a difference in pulse wave intensity and density between the healthy and diabetes groups. We will validate the syndrome differentiation using contemporary technologies such as the tongue imaging device and the pulse sphygmograph. An objective diagnosis of the tongue could be achieved with the advancement of artificial intelligence and imaging technology [36,37]. Images of the tongue captured with the tongue diagnostic device will then be processed through an algorithm for comparison and analysis against standard tongue diagnosis images (Figure 2). Furthermore, the development of pulse sphygmographs has enabled the digitalization of pulse assessment. Researchers investigated quantitative analyses of pulse profiles in the time and frequency domains [30]. The development of these quantitative and graphical representations of the pulse profiles in the 6-pulse positions is a significant step toward transforming traditional pulse diagnoses into scientific and objective assessments (Figure 1) [31].

The objective assessment will potentially increase the accuracy of the identification, diagnosis, and prevention of diabetes and prediabetes through a targeted treatment system tailored to the local population.

Methods

Study Design and Setting

This nonrandomized, exploratory, observational case-control study integrates the concept of TCM diagnostic methods with contemporary tools in an effort to provide an unbiased perspective on the syndrome differentiation of patients with diabetes and those with prediabetes, and, as a result, provide a guideline for the treatment options specifically targeted at the local population.

The research will be conducted between September 2022 and April 2025 at the Singapore Chung Hwa Medical Institution after obtaining approval from the Parkway Independent Ethics Committee (PIEC; reference: PIEC/2022/003). This study is registered under ClinicalTrials.gov (NCT05563090). Figure 3 depicts the study flow diagram.

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Figure 3. The study flow diagram. DIA: diabetes without hypertension or dyslipidemia; DIAHD: diabetes with hypertension and dyslipidemia; HEA: healthy or subhealthy; PRE: prediabetes without hypertension or dyslipidemia; PREHD: prediabetes with hypertension and dyslipidemia; TCM: traditional Chinese medicine.

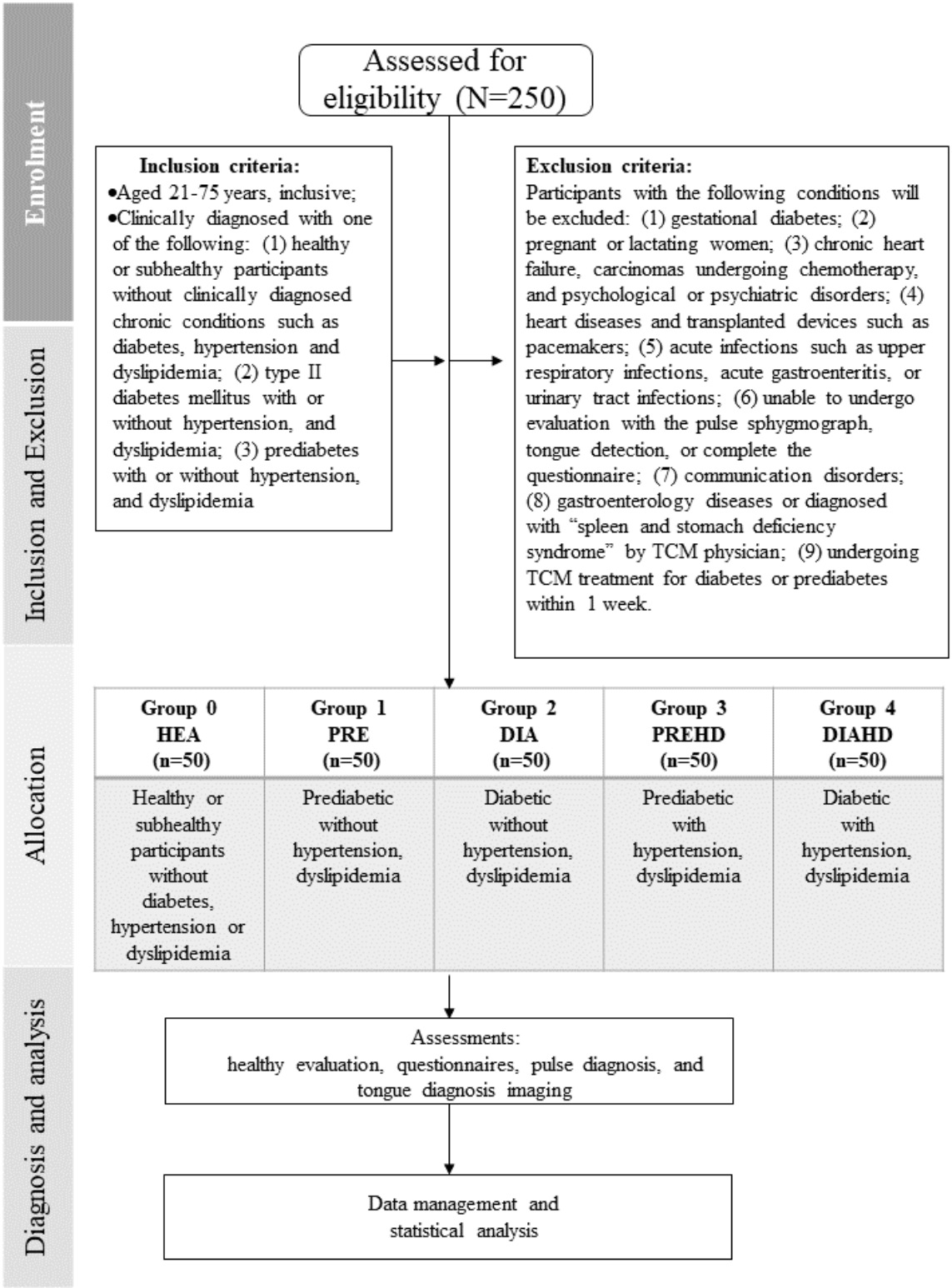

Recruitment of Participants

To ensure a sufficient sample size for statistical analysis of the diabetic and prediabetic syndrome differentiation, we intend to recruit 250 participants who will be equally assigned to one of 5 arms. The groups are as follows: group 0: healthy or subhealthy without diabetes, hypertension, or dyslipidemia; group 1: prediabetes without hypertension or dyslipidemia; group 2: diabetes without hypertension or dyslipidemia; group 3: prediabetes with hypertension and dyslipidemia; and group 4: diabetes with hypertension and dyslipidemia. Primarily, recruitment is conducted through physician referrals, as well as recruitment posters on the institution's bulletin boards and social media. Participants can register through the digital registration form, while the screening and enrollment will be conducted by

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the study team. The list of potential participants will be consolidated, and the research assistant will contact the participants to guide them through the informed consent process. Written consent will be collected when informed consent has been explained to the participant in a language they can comprehend. The participants will have the opportunity to decline enrollment at any time, and they are not required to present a justification for doing so. A study ID based on the grouping will be assigned after screening and enrollment according to the inclusion and exclusion criteria. The first 50 participants who qualify for each of the 5 groups and complete the screening process will be included, and recruitment for that particular group will cease once the target number is reached. This ensures that each of the 5 groups has an equal number of participants, allowing for balanced and effective statistical analysis.

Enrollment criteria include: (1) demographic: aged 21-75 years, of any sex or race; (2) clinical conditions include diabetes that have been clinically diagnosed by Western medical professionals (FPG7.0 mmol/L, 2-hour plasma glucose [2hPG]11.1 mmol, or HbA_{1c}>6.5%) with or without hypertension and dyslipidemia, prediabetes that have been clinically diagnosed (impaired fasting glucose of FPG 6.1-6.9 mmol/L or impaired glucose tolerance with 2hPG of 7.8-11.0 mmol/L); and (3) control group consists of participants who are healthy or subhealthy and do not have any significant health-related issues, such as clinically diagnosed chronic conditions like diabetes, hypertension, or dyslipidemia. The health evaluation form will be used to confirm that they (1) do not have a family history of diabetes and (2) have not had unusually high FPG levels detected within the last year.

Participants with the following conditions will be excluded from our study: (1) gestational diabetes; (2) pregnant or lactating women; (3) chronic heart failure, carcinomas undergoing chemotherapy, and psychological or psychiatric disorders; (4) heart diseases and transplanted devices such as pacemakers; (5) acute infections such as upper respiratory infections, acute gastroenteritis, or urinary tract infections; (6) unable to undergo evaluation with the pulse sphygmograph, tongue detection, or complete the questionnaire; (7) communication disorders; (8) gastroenterology diseases or diagnosed with “spleen and stomach deficiency syndrome” by TCM physician; and (9) undergoing TCM treatment for diabetes or prediabetes within 1 week.

To protect the confidentiality of personal information, a unique identifier will be used. The principal investigator will maintain a list of study participants and their identification codes.

Study Procedure and Outcome Measures

Table 3 shows the study schedule for enrollment and assessment, which may take between 0.5 hours and 1 hour in a single visit. The assessment and evaluations will take place in a temperature-controlled environment of 25 °C. The study team has undergone training by the principal investigator on the use of questionnaires, pulse sphygmograph, and tongue diagnostic devices to reduce interphysician variability.

Table 3. The study schedule.

	Enrollment	Allocation	Postallocation	
Timepoint	$-t_1$	0	t_1	t_2
Registration				
Digital registration	✓			
Enrollment				
Informed consent	✓			
Eligibility screen	✓			
Allocation		✓		
Intervention			N/A[a]	N/A
Assessment procedure (0.5-1 hour)				
Health evaluation (vital signs, blood sugar levels, BMI, medications, symptoms)			✓	
Questionnaires (Physical Activity Questionnaire, Sugar Intake, and CCMQ[b])			✓	
Pulse diagnosis				✓
Tongue diagnosis imaging				✓

[a]N/A: data are not applicable or not available.

[b]CCMQ: Constitution in Chinese Medicine Questionnaire.

Health Evaluation

Each participant’s age, sex, ethnic race, body weight, height, blood sugar level (including blood glucose in fasting, 2hPG or HbA_{1c} results if available from the patient’s regular blood test report), and health status, including medication prescription, will be recorded. Participants who have been clinically diagnosed as prediabetic or diabetic will be asked to present their blood test results from 3 months prior to or after the assessment date. The study team will contact the participant following the study if the blood test results are not available at the time of assessment. The primary objective of collecting

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these data is to enable the study team to determine whether the diabetic or prediabetic disorders are under control and if there is a correlation with the syndrome being studied. The information that will be gathered is as follows.

- Vital signs: The Omron Automatic TIC Blood Pressure Monitor HEM-7130 will be used to assess vital signs, including systolic blood pressure, diastolic blood pressure, and pulse rate.
- BMI: After measuring height and weight, the BMI will be calculated and documented.
- Medications: Western and Chinese medications consumed by the participant will be recorded to identify possible interventions and correlations for TCM syndrome differentiation.
- Existing symptoms will be collected to determine the potential correlation with TCM syndrome differentiation.

Physical Activity Questionnaire and Sugar Intake

The Physical Activity Questionnaire, adapted and modified from the Singapore Prospective Study Program Physical Activity Questionnaire, will be used to record the level of physical activity during the past 3 months. The Singapore Prospective Study Program Physical Activity Questionnaire evaluates physical activities including transportation, leisure time activities, occupational physical activities, and household activities. This questionnaire was validated against the International Physical Activity Questionnaire in a multiethnic population of Chinese, Malays, and Indians residing in Singapore. It was concluded to show good validity and repeatability for vigorous activities [38].

Metabolic equivalent task (MET) levels will be used to compare the average energy expenditure in each group. The 1 MET unit, which represents the energy expended while sitting quietly, is equivalent to 3.5 ml of O_2 per kg body weight per minute or 1.2 kcal per minute for a 70-kg individual [39]. Moderate intensity refers to physical activity that is performed between 3 and <6 times the intensity of rest (METs), while vigorous intensity is defined as physical activity that is performed at 6.0 or more METs [38]. The WHO Physical Activity Guidelines (2020) recommend a minimum of 150-300 minutes of moderate-intensity aerobic physical activity per week and engaging in muscle-strengthening activities at moderate or greater intensity on at least 2 days a week to stay physically active [40]. Those who reach a high level of physical activity per week perform vigorous-intensity activity on at least 3 days of 1500 MET-minutes per week, or 7 or more days of activities of a minimum of 3000 MET-minutes. While those with a moderate level of physical activity per week perform 3 or more days of vigorous-intensity activity of at least 20 min/day, or 5 or more days of moderate-intensity activity of at least 30 min/day, or 5 or more days of activities achieving a minimum of at least 600 MET-minutes/week. Participants who do not meet any of the above criteria would be considered inactive.

Additionally, weekly sugary food and beverage consumption will be documented. This will aid in identifying the risk variables involved and the association between the body constitutions and various forms of "*xiao-ke*" based on TCM syndrome differentiation.

The Constitution in Chinese Medicine Questionnaire

Based on TCM principles, the Chinese Medicine Questionnaire (CCMQ), which was established in 2009 by the China Association of Chinese Medicine, will be used to evaluate the body constitution of each participant. This questionnaire consists of 60 questions divided into nine categories of body constitution: (1) balanced, (2) qi deficiency, (3) yin deficiency, (4) yang deficiency, (5) phlegm dampness, (6) damp heat, (7) blood stasis, (8) qi stagnation, and (9) inherited special constitution. Each category has 7 or 8 questions. A 5-point Likert scale that quantitatively assesses the body characteristic is adopted, and the original score is obtained by summing the categorized items. The adjusted score is derived by: 100 [(original score – number of questions) / (number of questions 4)]. The scoring algorithm indicates the likelihood of a particular type of body constitution with a higher score. A subscale criterion of at least 30 points will be used to classify the body composition [41]. Table 4 provides the recommended assessing criteria [42].

Lu et al [41] concluded that the CCMQ is capable of measuring the 9 body constitutions with reasonably good construct validity and reliability. Another study reported that the reproducibility using the Spearman correlation coefficient for the subscales ranged from 0.76 to 0.90, indicating good repeatability and quantitativeness [43].

Table 4. Assessing criteria of CCMQ[a].

Adjusted score of balanced constitution	Total adjusted score of 8 unbalanced constitution	Body constitution
≥60	<30	Balanced constitution
≥60	30-39	Balanced constitution but leaning toward the unbalanced constitution with a score ≥40
≥60	≥40	Unbalanced constitution with a score ≥40
<60	≥40	Unbalanced constitution with the highest score
<60	30-39	Prone to an unbalanced constitution with the highest score

[a]CCMQ: Constitution in Chinese Medicine Questionnaire.

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Pulse Sphygmograph

The Asia Plus Pen Pulse Analysis System Model PPAS-93 (Asia Plus Biotech Co, Ltd) will be used to identify pulse profiles.

The PPAS-93 is a noninvasive device that comprises a high-precision pressure sensor pen and a pulse analyzer. The high-precision pressure sensor pen is a portable handheld pen that digitalizes the biological signal of the radial pressure pulse wave and provides graphical analysis using fast Fourier transformation. This electronic gadget incorporates a high-precision pressure sensor, a filter, an amplifier, and a signal recording card connected to signal analysis software. The sampling rate is 3000 Hz, and the frequency response is between 0.1 and 50 Hz.

With the participant sitting in a relaxed position, the *cun*, *guan*, and *chi* pulses of each hand will be assessed using the sensor pen with appropriate vertical pressure. The result will be recorded when the best spectrogram displays the highest amplitude. A summation of SE in the 0-10 Hz ($SE_{0\text{-}10Hz}$), 10-50 Hz ($SE_{10\text{-}50Hz}$), and 13-50 Hz ($SE_{13\text{-}50Hz}$) frequency ranges will be obtained. Figure 1 depicts the pulse sphygmograph and its application output.

The time domain analysis examines the amplitude and shape of the arterial waveform such as surging, slippery, fine, and thready [30]. The pulse rate per minute can be determined by the number of waves in 6 seconds multiplied by 10. This will determine the rate such as a rapid or slow pulse. The frequency domain analyzes the variation of SE in the radial pulse waves [30]. The quantitative measures can assess the intensity and density of the SE, providing insight into the deficiency, repletion, coldness, heat, or dampness syndrome. An in-depth examination of both the time and frequency domains will be conducted to deduce the associated syndrome-etiology differentiation of *xiao-ke* (Table 2).

Tongue Diagnosis

The China Artificial Intelligence Health Status Identification System Model YZKJ-SMZY-1AI will be used to image and analyze the participant's tongue. The noninvasive device captures the image of the tongue through an inbuilt camera supported by light-emitting diode lighting within the device within 15 seconds. A monitor connected to the imaging instrument would display real-time video feedback on the tongue's position. Using an artificial intelligence system, the photographs of the face, tongue, and sublingual collaterals will be examined and compared with typical images of tongue analysis within 10 seconds. Figure 4 depicts the analytical details of the tongue, including the shape and color of the tongue, the texture and color of the tongue coating, the moisture level of the tongue, and the sublingual collaterals. The body constitution and syndrome differentiation will be analyzed and recorded. Figure 5 provides some examples of body constitutions and syndrome differentiation reported from the system. The results will be reconciled with the pulse diagnosis and CCMQ.

Before evaluation, the participants will be instructed to abstain from tongue scraping, smoking, and consuming caffeinated beverages such as coffee, tea, and cola, as well as dairy products such as milk, yogurt, and cheese, which may alter the tongue diagnosis.

Figure 4. Analytical details of the tongue diagnosis.

Tongue analysis	Description
Tongue color	Pale, light red, red, crimson, dark purple, purplish, blue-purple
Tongue shape	Enlarged, thin, prickly, spotted, cracked, teeth-marked, flaccid, stiff
Coating colour	White, light yellow, yellow, scorched yellow, grey, black
Coating texture	Thin, thick, curd-like, greasy, peeled, scanty, no coating
Moisture	Moist, slippery, dry, rough
Sublingual collaterals	Normal, blue-purple and thick, short but thin and pale

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Figure 5. Tongue analysis examples of body constitutions and syndrome differentiation.

Body constitution	Normal	Phlegm dampness	Dampness heat and blood stasis	Excessive heat	Qi deficiency
Tongue color	Pale red	Pale red	Pale red	Red	Pale
Tongue shape	Normal	Normal	Normal	Teeth mark	Teeth mark
Coating color	White	White	Pale yellow	White	White
Coating texture	Thin	Thick, greasy	Greasy	Thin	Thin
Moisture	Moist	Moist	Moist	Moist	Moist
Sublingual collaterals	Normal	Normal	Blue-purple	Normal	Normal
Syndrome	Balanced	Cold dampness accumulating in the spleen	Dampness heat and blood stasis	Excessive Heat	Qi deficiency
			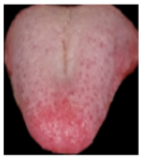		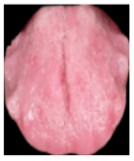

Syndrome Differentiation

The syndrome differentiation of *xiao-ke* will be based on the objective assessment results analyzed from CCMQ, tongue, and pulse diagnosis regardless of the participants' group status. Data collection under standardized conditions using contemporary diagnostic devices is expected to enhance stability and reliability in syndrome differentiation. This approach effectively minimizes bias and eliminates the necessity for blinding in our study design.

Ethical Considerations

The final clinical trial protocol version 1.8 dated August 1, 2023, was reviewed and approved by the Parkway Independent Ethics Committee (PIEC/2022/003). Important protocol modifications will be communicated to all study staff via emails and meetings after PIEC approval. Informed consent will be obtained from all participants by investigators who are approved by the ethics committee. The participants will be given the right to reject participation at any time. The collected data will be deidentified. Reimbursement in the form of cash vouchers will be provided to the participants upon completion of the study.

Data Management and Monitoring

Without interference from the study sponsor, the data will be monitored by the principal investigator and the study team. Each participant will be assigned a distinct identifier upon enrollment to guarantee the confidentiality of their information.

The reports generated by the tongue diagnosis imaging device and pulse sphygmograph will be stored as PDFs. Each participant's information will be documented in an encrypted Microsoft Excel spreadsheet for comparison purposes. No data will be omitted over the duration of the trial. Outliers and missing data will be identified to ensure data quality. All the assessment and evaluation results will be digitized and archived in Microsoft SharePoint with a password-protected database available exclusively to the research staff for at least 6 years following the conclusion of the study before being discarded by the principal investigator.

We anticipated that the study would be completed within the allotted time frame and that there would be no significant participant safety concerns. Consequently, a data monitoring committee and stopping guidelines are unnecessary. Interim analysis may be conducted without stopping the study.

There are no possible risks and side effects from this study as the diagnostic assessments are noninvasive. Hence, adverse events associated with the study are not anticipated.

Statistical Analyses

The baseline variables (age, sex, height, body weight, BMI, and blood sugar levels), MET-minutes for physical activity, scoring of body constitution, pulse assessments, and tongue analysis results will be compared between the five groups.

Using ANOVA, we will compare the variances across the means of the $SE_{13\text{-}50\ Hz}$ value from the pulse sphygmograph between each group and the control. Analysis of covariance will also be used to assess the group differences while controlling for potential confounding variables such as gender, age, BMI, physical activity levels, and others. Using the Bonferroni test for post hoc multiple comparisons, the mean values will be compared and corrected. Chi-square tests will also be used to do the comparative analysis of the body constitutions or syndromes between the objective and subjective assessments. All tests will be 2-tailed and $P<.05$ will be considered statistically significant. We will use STATA (standard edition version 18.0; StataCorp LLC) for the analysis.

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Sample Size Calculation

In an earlier 3-arm study to investigate the relationship between dyspepsia and rhinitis conducted by Huang et al [44] with 42 participants assigned to each group, there was a significant difference in the high-frequency pulse SE ($SE_{13\text{-}50Hz}$) between the control and experimental groups. Huang et al [45] also compared the radial pulse wave characteristics of hypertensive patients against healthy individuals with 46 patients in each group using the same device. Other investigations using the pulse tonometric device indicated a sample size of 25 with an expectation of 5% type 1 error, 80% power, and 5% drop rates based on the mean and SD derived from a study conducted by Huang et al [46,47]. Although there is limited prior data on the investigation of syndrome differentiation and pulse diagnosis of diabetes and prediabetes, we anticipate that a sample size of 50 in each group will provide adequate power to detect statistical significance.

Retention of Trial Documents

In a secure storage facility, the principal investigator will maintain all source documentation (including evidence of research eligibility, history and physical findings, and diagnostic test results), as well as ethical review records and other regulatory documentation. The documents should be available for inspection and duplication by authorized parties. The study coordinator will ensure that all documentation is current and up to date.

Results

Recruitment has been in progress since September 2022.

Discussion

Expected Findings

We anticipate that diabetes and prediabetes with or without hypertension and dyslipidemia would have different body constitutions compared to healthy individuals. The prevalence of specific TCM syndrome differentiation may be more common in countries with hot and humid tropical climates, albeit it may differ from the Chinese demographic.

TCM diagnosis is a comprehensive approach that integrates observation, inquiry, pulse palpation, and tongue diagnosis. Finger sensitivity required for palpating radial pulses and precise visual assessment of the tongue are fundamental to accurately detecting variations in the pulse and tongue quality in TCM diagnosis. However, traditional methods of syndrome differentiation are highly subjective and skill dependent. The interpretation of pulse quality and tongue characteristics can differ across practitioners based on their clinical training, experience, and personal bias. This may result in observations lacking clinical significance. To mitigate subjectivity and provide impartial evaluations, we designed this protocol to examine the syndrome differentiation of patients with diabetes and those with prediabetes using contemporary TCM diagnostic technologies. The data collected and evaluated under standardized conditions using these contemporary diagnostic devices are expected to yield stable and unbiased results. This standardized assessment will facilitate more consistent and reliable syndrome differentiation, which is crucial for both clinical practice and research. Thus, our findings may enhance the accuracy of the identification, diagnosis, treatment, and prevention of diabetes and prediabetes through targeted approaches, potentially improving patient outcomes and management effectiveness. Additionally, we will explore and analyze the correlation between TCM syndrome differentiation and WHO diagnosis criteria for diabetes. Establishing the reliability of contemporary TCM diagnostic tools sets the stage for their broader adoption in clinical practice and enables future research into individualized treatment plans based on objective TCM syndrome differentiation. Some of the following study challenges are expected.

Sufficient Sample Size

Estimating the sample size for a TCM study, especially when using diagnostic devices investigating syndrome differentiation and pulse diagnosis, can be indeed challenging. There is currently limited preexisting data specifically focusing on the syndrome differentiation and pulse diagnosis in the context of our study. Since this study is a pilot investigation into the TCM syndromes in patients with diabetes and those with prediabetes using digital diagnostic instruments, we used prior studies conducted by Huang et al [44,45] as a reference to estimate the required sample size. These studies used the older model of pulse sphygmograph to investigate the pulse characteristics of chronic conditions such as hypertension, dyspepsia, and rhinitis as well as healthy individuals.

Recruiting Eligible Participants

The recruitment of eligible participants is undoubtedly the most crucial, challenging, and unpredictable component of clinical research. Aside from the main strategies such as physician referral, recruitment posters, and social media, publicity can also be disseminated through newspapers, health magazines, or health education to promote awareness and public interest, following the necessary ethical approval. Furthermore, a lack of sufficient knowledge about the study process or clinical trial benefits can be one of the primary barriers to research recruitment. To overcome this barrier, we ensure to provide good communication to the physicians and participants through the designs of advertising posters, health studies, and informed consent. In addition, we reduce the study burden by providing flexibility and accommodation on research visits.

Conclusions

To the best of our knowledge, this is the first study to use contemporary TCM diagnostic instruments to map expert and empirical knowledge of TCM to its scientific equivalents for the purpose of evaluating the syndrome differentiation of diabetes. In addition to identifying the pulse wave and tongue morphology, both devices are also capable of distinguishing the TCM body constitution and syndrome differentiation through the processing of the identified characteristics by their artificial intelligence algorithm. We will compare and contrast the outcomes of the digital analysis and the CCMQ.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

HPN and CMH, who are accountable for the design and methodology of this protocol, contributed equally as the first authors. HPN and CMH will be responsible for the ultimate decision to terminate the trial and the manuscript's final clearance. HPN authored this manuscript. Protocol execution is performed by HPN, SYC, and YHL. THG has assisted in the development of several questionnaires. KYP has critically reviewed the manuscript. MJP has reviewed the statistical plans. All authors will have full access to the study's interim and final results, will contribute to the protocol's refinement, and will approve the final publication.

Conflicts of Interest

None declared.

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Abbreviations

2hPG: 2-hour plasma glucose
CCMQ: Constitution in Chinese Medicine Questionnaire
FPG: fasting plasma glucose
HbA1c: glycated hemoglobin A1c
MET: metabolic equivalent task
PIEC: Parkway Independent Ethics Committee
SE: spectral energy
TCM: traditional Chinese medicine
WHO: World Health Organization

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Protocol

Analyzing the Influence of Video Game and Music Engagement on Technical Skills Acquisition in Dental Students in Preclinical Phase: Protocol for a Prospective, Controlled, Longitudinal Study

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Abstract

Background: The practice of dental surgery requires a few different skills, including mental rotation of an object, precision of movement with good hand-eye coordination, and speed of technical movement. Learning these different skills begins during the preclinical phase of dental student training. Moreover, playing a musical instrument or video game seems to promote the early development of these skills. However, we found that studies specifically addressing this issue in the field of dental education are lacking.

Objective: The main aims of this study are to evaluate whether the ability to mentally represent a volume in 3D, the precision of gestures with their right and left hand, or the speed of gesture execution is better at baseline or progresses faster for players (video games or music or both).

Methods: A prospective monocentric controlled and longitudinal study will be conducted from September 2023 and will last until April 2025 in the Faculty of Dental Surgery of Nantes. Participants were students before starting their preclinical training. Different tests will be used such as Vandenberg and Kuse's mental rotation test, the modified Precision Manual Dexterity (PMD), and performing a pulpotomy on a permanent tooth. This protocol was approved by the Ethics, Deontology, and Scientific Integrity Committee of Nantes University (institutional review board approval number IORG0011023).

Results: A total of 86 second-year dental surgery students were enrolled to participate in the study in September 2023. They will take part in 4 iterations of the study, the last of which will take place in April 2025.

Conclusions: Playing video games or a musical instrument or both could be a potential tool for initiating or facilitating the learning of certain technical skills in dental surgery.

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KEYWORDS

video game; music practice; dental education; technical skills; simulation; video games; music; preclinical skills; dental students; dental student; pre-clinical phases; longitudinal investigation; dentistry; gestures; gesture; preclinical training; training; protocol; tool; tools; cognitive skills, mobile phones

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Introduction

Background

The last 50 years have seen the emergence of playful practices such as video games, which are now an integral part of the digital cultural landscape. As a result, demographic changes have led to the emergence of a new generation of learners who live in a rich and accessible digital environment, surrounded by computers and smartphones. As a result, this generation is now more sensitive to and interested in the use of video games than previous generations seemed to be [1]. Today, video games have become one of the most popular leisure activities among young adults. Many studies are now focusing on the effects of this ludic practice, particularly in terms of learning. Some articles seem to suggest a link between the development of psychomotor and cognitive skills and the practice of video games [2]. Research dating back to the early 1980s has consistently shown that playing video games (regardless of genre) enables players to acquire faster reaction times, better hand-eye coordination, enhanced psychomotor skills, and improved self-esteem [3-5]. These elements have been found in various fields, including medical education. For example, a study using video games on the Nintendo Wii console showed bimanual improvement in surgery, including an increase in the precision of nondominant hand movements [6,7].

Video games may reduce the time required for medical students to acquire or improve surgical skills [1,8-10]. Some studies have also shown that previous video game experience improves baseline performance on a laparoscopic simulator and that student players have better visuospatial awareness when using the simulator [11,12]. Thus, playing video games would significantly reduce reaction time without compromising the precision of the technical gesture. An increase in execution speed has been observed in various tasks outside the gaming situation [8,13]. To date, no study seems to have evaluated the beneficial effects of video games on the preclinical training of dental students. However, precision, speed of execution, and 3D volume representation are skills that are required to perform dental treatment [14].

In addition, the first traces of musical practice date back to prehistoric times, approximately 35,000 years ago. Over the centuries, music has been listened to, played, and then analyzed in empirical studies that have demonstrated the benefits of playing a musical instrument, such as the development of cognitive and psychomotor skills, improved visuospatial skills, and bimanual dexterity, and better hand-eye coordination [15,16]. In a health care setting, a prospective cross-sectional study of 51 medical students evaluated the influence of previous musical experience on surgical skills in terms of speed and quality of performance. Students with previous musical experience performed better than nonmusicians [15]. Another study of 30 medical students evaluated the influence of previous musical experience on laparoscopic suturing tasks and found increased performance speed in musicians [17]. Furthermore, surgical and musical practice appear to share common cognitive skills such as accuracy of motor performance, integration of multimodal sensory and motor information, hand-eye coordination, spatial visualization, intense concentration, short reaction time, and efficient mental rotation [18].

The nonsurgical skills developed by playing a musical instrument appear to be similar to those developed by playing video games. These similar nonsurgical skills have been compared to assess their impact on surgical skills. A cohort study of 57 students using a simulator showed that subjects exposed to both video games and playing a musical instrument had higher psychomotor skills [18]. The influence of music, as opposed to video games, has been demonstrated in microsurgery [19]. However, some studies have shown no improvement in surgical or microsurgical performance in video game players and musicians [20,21].

Consequently, there is currently no consensus in the literature on the impact of these leisure activities on learning in medical education. Furthermore, there is no previous study of this issue in the context of dental education.

Study Objectives

In this context, the aim of our study is to evaluate the impact of certain leisure activities, such as playing video games or playing a musical instrument, on the learning of technical skills by dental students. Using baseline measurements, we will observe whether initial skills differ between students who engage in one of these 2 leisure activities and those who do not. Subsequently, longitudinal monitoring will allow us to follow the development of students' learning of these three skills, that are (1) mental rotation of an object, (2) precision and hand-eye coordination, and (3) speed of execution, according to their leisure activities.

Methods

Study Design and Setting

The purpose of this protocol is to establish a study that would be prospective, monocentric, controlled, longitudinal, and conducted at the Faculty of Dental Surgery in Nantes from September 2023 to April 2025.

Study Population

The study population includes second-year surgical students who started their studies in September 2023 and have not yet started preclinical training with simulation-based placements. These students are followed until the end of their simulation training, that is, the end of the third year.

Sample Size

The planned number of subjects included in the study would be 86, representing a full year's intake at our faculty.

Eligibility Criteria

Inclusion criteria are that the participants must be major dental surgery students enrolled in their second year at the Faculty of Dental Surgery of Nantes. Exclusion criteria are that the student is a minor, repeats a year in the second year, or does not agree to participate in the study. Inclusion or exclusion criteria will be reviewed by the investigator for each subject after completion of the preliminary questionnaire, that we created for this study,

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in the case report form (CRF). They must give verbal consent after being informed about the study by the investigators. The student must not have any particular physical or mental condition that prevents them from carrying out their practical training under the same conditions as other students. This information was collected on the basis of a previous medical diagnosis, according to the student's statements.

Demographic characteristics were collected using the preliminary questionnaire completed by the participants at the start of the study. This allowed us to collect data such as gender, age, and leisure habits.

Allocation

Based on the answers to the preliminary questionnaire, the students are divided into different groups according to their music or video game experience. Assignment of the subject to the "video game players" group if the student describes an hourly habit of playing action video games (first-person shooter or role-playing games) based on 0-60 minutes per week for occasional players, 61-300 minutes per week for moderate players, or more than 300 minutes per week for regular players. These values were used in a 2016 study to link the time spent playing video games to children's mental health and cognitive and social skills [22].

Assignment of the subject to the "music players" group if the student describes an hourly habit of using a musical instrument based on 0-60 minutes per week for occasional players, 61-300 minutes per week for moderate players, or more than 300 minutes per week for regular players. These values are used to be consistent with those used to define a video game player profile. The methods used in other studies to define a music player were either too subjective or too complicated to implement. The different groups "video game players," "music players," and "nonplayers" can thus be constituted.

Study Timeline

This study therefore consists of 4 phases of investigation: the first, which serves as a baseline evaluation, and the subsequent phases at 6 months, 1 year, and 2 years, which are useful for measuring the progress of the different groups during the preclinical phase of dental surgery studies, which in this case lasts 2 years. The timetable for the study is shown in Figure 1. It shows the various tests carried out during each measurement period. Each experimental session takes place on a single day. Each phase of the study takes place over the course of a day, in 4-time slots of 1 hour and 40 minutes each, with the total number of students divided into 4 groups of about 20.

Figure 1. Flow Chart of the Study Procedure.

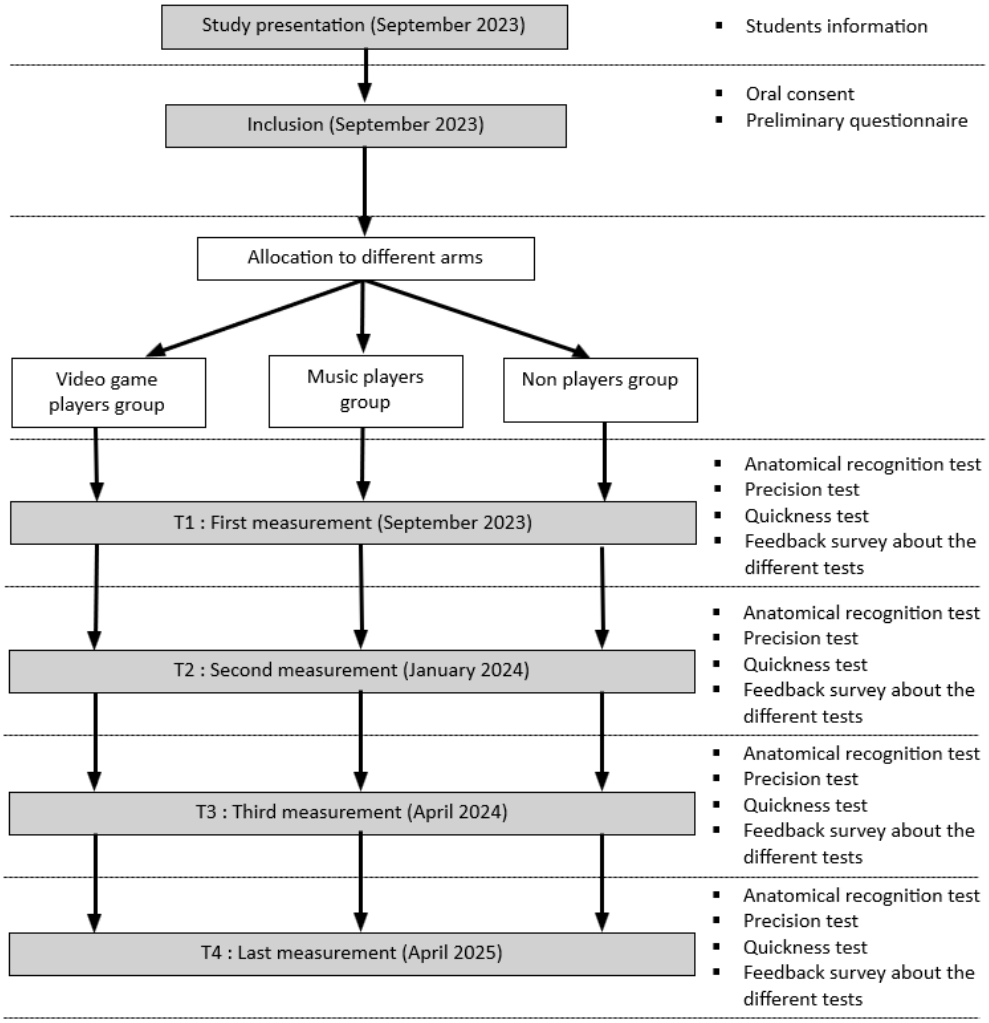

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Outcomes

We aim to assess whether the initial level and development of preclinical skills over the 2 years of preclinical education show superior or faster progress among students identified as "music players" or "videogames players" compared with "nonplayers." To achieve this, our study will focus on 3 main objectives to compare the progress of these different groups over time.

Objective 1

Objective 1 was to assess baseline measures and learning progress between the "players" group (video games or music or both) and "nonplayers" in their ability to mentally visualize 3D volumes. Comparative analysis of mean test scores will be conducted at all 4 planned stages.

The evaluation criterion will refer to the score obtained from Vandenberg and Kuse's mental rotation test [23], which was used in 2009 to measure the spatial representation skills of dental students [14] (Figure 2). The stimuli are 3D structures consisting of a line of 9 to 10 cubes angled at 3 points. Some of the presented items consist of identical stimuli that can be matched by rotation in the frontal or sagittal plane. The other items are pairs of completely different stimuli. Each item consists of 5 figures, a model placed at the left end of the line, and 4 structures to the right of the model, among which the subject must indicate those that resemble the model. There are always 2 correct answers for each item. The test consists of 20 items divided into 4 pages of 5 items each. For half of the items, the incorrect figures are rotations of the mirror image of the model, while the other half are rotations of 1 or 2 other structures. For high school and university students, the author recommends limiting the time to 6 minutes, that is 2 3 minutes [23]. A total of 2 points are awarded for each line with 2 correct choices, 1 point if only one of the drawings is selected and is correct, 0 points if 1 of the 2 choices is correct and the other is not, or if both are incorrect. This system eliminates the effect of random answers. We allow 3 minutes for each of the 2 sections of the test, with 10 items per section. The maximum possible score for this test is therefore 40. The purpose of these tests is to assess the student's anatomical representation skills and how they develop over the year according to the student's profile. At the end of this first test, the student fills out a feedback questionnaire on this anatomical recognition test.

Figure 2. Sample items for the Vandenberg mental rotation test.

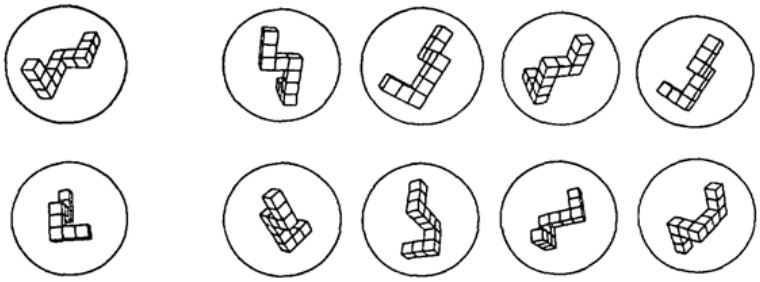

Objective 2

Objective 2 was to assess baseline measures and learning progress between the "players" group (video games or music or both) and "nonplayers" in terms of precision of hand gestures using both right and left hands (eye-hand coordination). A comparative analysis of the average scores of the corresponding test will be conducted across all 4 phases.

The evaluation criterion will relate to the result obtained in the modified Precision Manual Dexterity (PMD) test as described by Bowers et al [24] (Figure 3). The test consists of penetrating 80 targets printed on a sheet of paper stretched over a soft surface as accurately as possible using a hand-held 15/100 steel endodontic hand file, with the right hand on the 4 rectangles on the right side of the sheet (ie, 40 targets) and with the left hand on the 4 rectangles on the left side of the sheet (ie, 40 targets). This allows us to test students with both hands (dominant or nondominant) [7,21]. The test sheet is divided into 8 target areas, each containing 10 randomly placed targets, the diameter of which has been increased to 1 mm, the initial PMD test using optical aids, and magnification 8 and 2.5. A scoring system is used to assign a total score to the test sheet: 3 points if the penetration point is completely in the target, 2 points if the penetration point is at least 50% on the target, 1 point if the penetration point is at least 50% off the target, 0 points if the penetration point is completely off the target. A prepunched sheet with a score of 240, the maximum for each hand, is used as a reference for scoring and compared with the player's sheet using the backlight. The maximum total score is 120 points for the right hand and 120 points for the left hand. The accuracy of the subject's gesture is the parameter evaluated. At the end of this second test, the subject fills out a feedback questionnaire on this hand-eye coordination test.

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Figure 3. Modified Precision Manual Dexterity test.

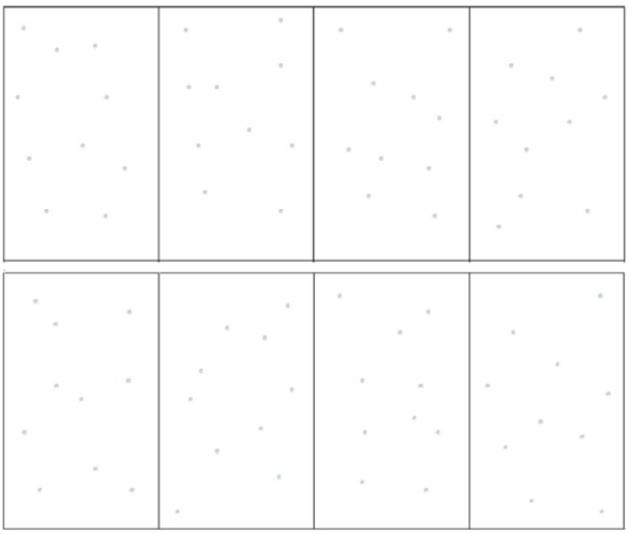

Objective 3

Objective 3 was to assess baseline measures and learning progress between the "players" group (video games or music or both) and "nonplayers" in terms of speed of gesture execution. A comparative analysis of the average scores of the corresponding test will be performed at each of the 4 stages.

The assessment criterion will relate to the time taken by the student to perform a complete pulpotomy on a mandibular permanent molar. The test is performed on practical models mounted on preclinical simulation mannequins or "phantoms." A 3D printed model of the permanent tooth (right permanent mandibular first molar) in resin with a space simulating the pulp chamber is used to best simulate a real clinical situation (Figure 4). Just before performing the technical procedure, subjects are given appropriate instructions and success criteria. For each student, the investigators record the time (in minutes) required to perform the pulpotomy correctly. The parameter evaluated in this test is therefore the speed of performance, by comparing the average time taken by the groups during the recordings. At the end of this third test, the subject fills in a feedback questionnaire on this pulpotomy test.

Figure 4. Stereolithography file of a 3D printed model of the permanent tooth.

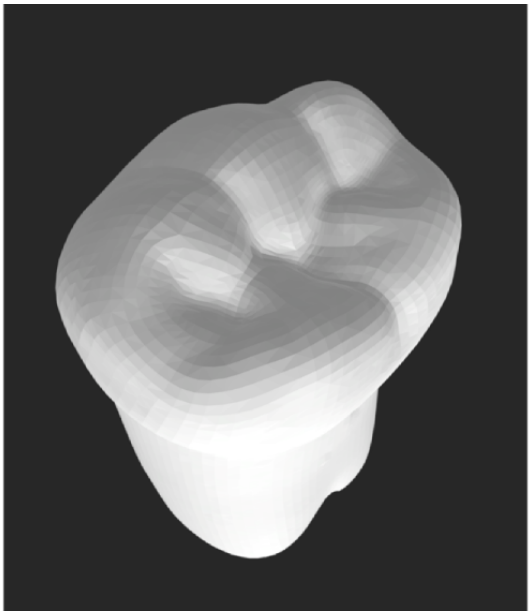

Data Collection

Identification of Participants

Investigators agree to keep the identity of research participants confidential by assigning them a code. This code will be used for all CRFs. It is the only information that can be used to identify the participant. Therefore, this study will be conducted in a single-blind fashion. Anonymization of participants in the CRF was carried out by the investigators at the time of enrolment.

Each student's personalized CRF contains their answers to the anatomical recognition test, the time taken for the speed test, and their score on the accuracy test, for all 4 iterations.

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Statistical Analysis Plan

A descriptive analysis of the sample will be performed using counts and percentages for categorical variables and means and SD for continuous variables. Missing data will not be imputed. Depending on the size of the samples of video game and music players, nonparametric statistical tests will be used to compare the mean scores on the 3 different tests at the 4 planned stages. A comparison of the mean scores on the feedback questionnaire for each test is made at each of the 4 stages. Each comparison will be made for the categories of "video game players" versus "video game nonplayers" and "music players" versus "music nonplayers" groups. A total of 2 researchers, JT and CG, will be single-blinded, meaning they will not know which group the students belong to, to enter data and analyze results. The data collected will be described as median, SD, and IQR. For nonparametric data, the statistical test appropriate to the size of the groups (Mann-Whitney *U* test) will be used to compare medians between groups. The significance level was set at 5%. The data collected are compared between the different groups. Qualitative data from the intervention will be entered into Microsoft Excel (version 16.86).

Ethical Considerations

Our protocol was reviewed and approved by the Ethics, Deontology, and Scientific Integrity Committee of the University of Nantes, France (institutional review board approval number IORG0011023). All procedures performed in this study will be in accordance with the ethical standards of the Ethics, Deontology, and Scientific Integrity Committee of the University of Nantes and with the Declaration of Helsinki of 1964 and its subsequent amendments. Informed consent will be obtained from each student participating in the study.

Results

All 86 nonrepeating second-year dental surgery students were enrolled in the study in September 2023. The first and second run of the study has already been completed and will result in an interim analysis. The next will take place in April 2024 and the last in April 2025. We plan to publish the baseline data on the influence of playing video games and a musical instrument separately for September 2024. A final publication including the influence of these 2 practices (jointly or separately) and the evolution of their impact over the 2 years of preclinical training is also planned for September 2025.

Discussion

Principal Findings

Playing video games and practicing some musical instruments seem to be promising ways to improve manual dexterity and cognitive skills. Our aim is to investigate the relevance of playing these activities in the context of learning dentistry. Specifically, we aim to determine whether regular video games or musical instrument practice has a positive impact on the baseline preclinical performance of novice dental students. In addition, our study aims to determine whether these "video game players" and "music players" students progress more quickly in their preclinical skills than their "nonplayers" peers.

Public Health Impact

The acquisition of technical skills in dental students is critical to their future effectiveness as health care providers. Understanding these skills through innovative methods, such as video games and music engagement, can lead to better-prepared graduates who are proficient in performing complex dental procedures. This has a significant public health impact as it can lead to better oral health outcomes and overall health for the population.

Existing Literature

Numerous studies have investigated various methods to enhance technical skills in medical and dental education. For example, the use of simulation-based training has been widely documented for its effectiveness in improving clinical skills. However, there is limited research on the impact of video games and music on technical skills acquisition. Some studies have suggested that video games can improve hand-eye coordination and cognitive skills, which are essential for dental procedures. Similarly, music has been found to enhance concentration and reduce anxiety, potentially leading to better performance in skill-based tasks.

Rationale for Studying Dental Students

Dental students were chosen for this study because their training requires a high level of manual dexterity and precision. The preclinical phase is a critical period during which students develop foundational technical skills that they will use throughout their careers. By focusing on dental students, we aim to explore innovative methods to enhance these essential skills during this formative stage. In addition, dental students represent a homogeneous group in terms of educational background and training requirements, allowing for more controlled and consistent study conditions.

Study Methodology

The decision to conduct a prospective, monocentric, controlled, longitudinal study was made to ensure rigorous and reliable results. A prospective design allows us to observe the effects of video games and music engagement over time, while a controlled setup helps in comparing the intervention group with a control group to determine the specific impact of the interventions. A monocentric study conducted at the Faculty of Dental Surgery in Nantes provides a consistent environment and resources, facilitating detailed monitoring and data collection over the study period from September 2023 to April 2025.

Strengths

Our study has a few strengths, including its innovative aspect, as it does not appear that similar work has been carried out in dental education. In addition, it is a longitudinal study, which should allow us to monitor the results obtained at the beginning and follow their evolution in the different groups. In addition, the participants started the study before starting any dental surgery training, whether theoretical or practical, to limit any possible bias. The tests used to assess the participants had been tried and tested in previous studies.

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Limitations

As the study is monocentric, it might be interesting to distribute the preliminary questionnaire to other French faculties to confirm that our sample is representative of our target population.

Plan of Dissemination

We will publish all results in peer-reviewed international journals indexed in Web of Science or Scopus databases and present them at national and international conferences. Depending on the interest and importance of the results and the relationship between music and video game playing and preclinical skills, a decision may be made to disseminate the results in the form of one or more articles.

Conclusion

In France, dental students present very heterogeneous profiles at the beginning of their university studies to become dental surgeons. Coming from different recruitment systems and scientific or nonscientific backgrounds, their knowledge and technical skills seem to be uneven. The results of our research could potentially make it possible to tailor students' practical workload according to their needs of formation, by focusing on their leisure activities, such as video games and music. This knowledge could facilitate personalized support for students who are not naturally talented and require more diligent training. Finally, this work could argue for the integration of video games and music into medical education, based on evidence of their benefits in a learning context. We are currently in a situation where the number of students continues to grow while the university infrastructure does not allow us to accommodate any more. Identifying learner profiles and adapting the simulation time required for each would allow us to optimize the training of our students and manage the availability of facilities as effectively as possible.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

TP, RC, and SS contributed to the design and methodology of the study. AG was responsible for statistical analysis. JT and CG contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
PMD: Precision Manual Dexterity

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Protocol

Toward Physiological Detection of a "Just-Right" Challenge Level for Motor Learning in Immersive Virtual Reality: Protocol for a Cross-Sectional Study

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Abstract

Background: Motor learning, a primary goal of pediatric rehabilitation, is facilitated when tasks are presented at a "just-right" challenge level—at the edge of the child's current abilities, yet attainable enough to motivate the child in persistent efforts for success. Immersive virtual reality (VR) may be ideally suited for "just-right" task challenges because it enables precise adjustments of task parameters in motivating environments. Rehabilitation-specific VR tasks often use dynamic difficulty algorithms based on task performance to personalize task difficulty. However, these approaches do not consider relevant cognitive processes that could also impact "just-right" challenges, such as attention and engagement. Objective physiological measurement of these cognitive processes using wearable sensors could support their integration within "just-right" challenge detection and prediction algorithms. As a first step, it is important to explore relationships between objectively and subjectively measured psychophysiological states at progressively challenging task difficulty levels.

Objective: This study aims to (1) evaluate the performance of wearable sensors in a novel movement-based motor learning immersive VR task; (2) evaluate changes in physiological data at 3 task difficulty levels; and (3) explore the relationship between physiological data, task performance, and self-reported cognitive processes at each task difficulty level.

Methods: This study uses the within-participant experimental design. Typically developing children and youth aged 8-16 years will be recruited to take part in a single 90-minute data collection session. Physiological sensors include electrodermal activity, heart rate, electroencephalography, and eye-tracking. After collecting physiological data at rest, participants will play a seated unimanual immersive VR task involving bouncing a virtual ball on a virtual racket. They will first play for 3 minutes at a predefined medium level of difficulty to determine their baseline ability level and then at a personalized choice of 3 progressive difficulty levels of 3 minutes each. Following each 3-minute session, participants will complete a short Likert-scale questionnaire evaluating engagement, attention, cognitive workload, physical effort, self-efficacy, and motivation. Data loss and data quality will be calculated for each sensor. Repeated-measures ANOVAs will evaluate changes in physiological response at each difficulty level. Correlation analyses will determine individual relationships between task performance, physiological data, and self-reported data at each difficulty level.

Results: Research ethics board approval has been obtained, and data collection is underway. Data collection was conducted on December 12, 2023, and April 12, 2024, with a total of 15 typically developing children. Data analysis has been completed, and results are expected to be published in the fall of 2024.

Conclusions: Wearable sensors may provide insights into the physiological effects of immersive VR task interaction at progressive difficulty levels in children and youth. Understanding the relationship between physiological and self-reported cognitive processes is a first step in better identifying and predicting "just-right" task challenges during immersive VR motor learning interventions.

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(JMIR Res Protoc 2024;13:e55730) doi:10.2196/55730

KEYWORDS

virtual reality; pediatric rehabilitation; physiological data; engagement; just-right challenge

Introduction

Overview

Virtual reality (VR) systems enable users to interact with virtual environments using body movements. Virtual environments can be categorized as immersive or nonimmersive [1]. Immersive VR is viewed in a head-mounted display (HMD) that provides a stereoscopic 3D viewing medium in which visual display changes in a natural way with head movements [2]. User movements are tracked by handheld or body-worn sensors to enable interaction with virtual objects. In contrast, nonimmersive VR is viewed on a 2D flat-screen display. VR incorporates evidence-based motor learning principles (such as multisensory feedback and abundant repetitions) and engaging immersive environments that may motivate children to adhere to repeated practice [3-5]. The use of nonimmersive VR has demonstrated effectiveness toward a variety of motor outcomes in pediatric rehabilitation [6]. With recent advances in immersive VR interaction abilities and the development of more lightweight and lower-cost HMDs, the use of immersive VR has become more attractive in pediatric rehabilitation, as complete visual immersion may enhance presence [7,8]. Several studies have established the feasibility of using immersive VR in pediatric rehabilitation, and there is preliminary evidence for the effectiveness of immersive VR interventions in promoting motor learning outcomes in children with disabilities [5]. While more information about the safety of long-term use in children younger than 12 years of age is required, recommendations for use with this age group include short periods of use punctuated by frequent breaks [9]. While the integration of immersive VR in clinical practice is in its early stages, a greater understanding of the potential unique advantages of immersive VR as a therapeutic intervention may support efforts at evidence-based integration.

One potential benefit of immersive VR is its potential to achieve a "just-right" task difficulty level during motor rehabilitation. A "just-right" task challenge is [3]:

> *structured so children are required to persist with and problem solve tasks in order to achieve success, however, they are not so difficult that the child loses interest, gives up, or fails the challenge*

The "just-right" challenge is an important rehabilitation concept, evident across different disciplines, populations, and functional goals [10]. The concept of the "just-right" challenge is associated with the "challenge point framework" developed by Guadagnoli and Lee [11]. The authors theorize that an optimal degree of functional task difficulty for an individual with a specific level of skill will lead to optimal learning conditions, with evidence demonstrating the effectiveness of practice at this "challenge point" to improve motor learning [12]. Related to this framework are efforts to examine psychological factors that influence practice adherence, such as motivation [13]. Therapists working with children who require repeated, long-term rehabilitation interventions may struggle to keep them motivated to engage in the persistent efforts required to improve skills beyond current ability levels [14]. Novel and engaging virtual tasks and environments can help in that regard. In addition, VR applications custom-developed specifically for rehabilitation enable precise task difficulty selection, titrating task parameters to meet individual children's ability levels more precisely than is possible in the real world. For these reasons, immersive VR may provide an ideal practice modality to target "just-right" challenges during motor skill learning. Currently, therapists use objective task performance indicators and subjective judgments of a child's affective state when making difficult decisions targeting "just-right" challenges. This makes the presence of a therapist necessary to propose a "just-right" challenge. Some VR applications use automatic dynamic difficulty algorithms with performance-based decision rules to adjust task difficulty based on performance, in a similar way to the challenge point framework [15,16]. These algorithms are useful in situations where the therapist is not present to contribute clinical judgment, such as in telerehabilitation. However, the therapist brings additional important judgments outside of optimal task difficulty. Since the "just-right" challenge depends not only on performance (ie, how successful the learner is at accomplishing the task) but also on the learner's motivation to persist in their efforts to succeed, it makes sense to consider how children's cognitive processes can contribute to a "just-right" challenge. For example, a task difficulty level that is outside of a child's abilities might be "just-right" for a child who is motivated to succeed and who enjoys being challenged, while a different child might be discouraged by failure and require a difficulty level closer to their abilities. Having an objective means of measuring proxies of these cognitive processes could supplement performance results in algorithms determining the "just-right" challenge in telerehabilitation. Psychophysiology is defined as the scientific study of the relationship between physiological and cognitive processes [17]. Measuring psychophysiological state in real time is possible with wearable sensors. Houzangbe et al [18] present a novel method for quantifying the "just-right" challenge in immersive VR based on psychophysiological data and performance variables. The authors outline the potential variables of interest and present hypothesized thresholds for the "just-right" challenge. Wearable sensors are an active research area in the pediatric population, mainly explored for measuring activity level and movement for physical rehabilitation [19]. However, multiple barriers still limit their usage [20,21], including difficulty with the placement of adult-sized sensors and movement artifacts during intense activities. Very little research has been done on the use of physiological sensor

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wearables (eg, heart rate [HR] and electroencephalography [EEG]) with pediatric populations. Existing studies are conducted in a static condition [22], or are missing details about the potential impact of movement artifacts on data integrity [23]. More evidence is required to understand potential data loss and data quality issues in wearable sensors when children undertake movement-based tasks [24]. The protocol described in this paper for this pilot study is focused on the feasibility of detecting variation in psychophysiological states in children during a new motor learning task in immersive VR. As such, it is centered around capturing objectively differing difficulty levels rather than identifying a "just-right" challenge. The study is the first step in a larger long-term research goal to train machine learning models to identify "just-right" challenges based on task performance and psychophysiological data. Although the interest of this study is in the "just-right" challenge during motor skill learning in children with motor impairments, typically developing children are included in this pilot study to capture a wider range of performance abilities in immersive VR.

Objectives and Hypotheses

Objective 1

The objective is to evaluate the performance of (1) the electrodermal activity (EDA) and HR sensor and (2) the EEG 13-lead sensor in children undertaking a new motor learning task in immersive VR.

Hypothesis 1.1

Data loss will be less than 10%.

Hypothesis 1.2

A total of 70% of collected data will meet predetermined thresholds for data quality.

Objective 2

The aim is to evaluate changes in physiological data at 3 immersive VR task difficulty levels.

Hypothesis 2

EDA number of peaks per minute, HR, level of engagement, cognitive workload and concentration measured through EEG, average time of eye pursuit of the interactable objects, and average number of eye blinks per minute will differ between difficulty levels.

Objective 3

The aim is to explore the relationship between physiological data, task performance, and self-reported measures of engagement, cognitive workload, physical effort, and attention or focus at each task difficulty level.

Hypothesis 3.1

Self-report ratings will correlate positively with their corresponding physiological data at each of the 3 difficulty levels. Specifically, first, the EEG engagement index will positively correlate with the self-reported engagement score. Second, EEG cognitive workload will positively correlate with the self-reported cognitive workload score. Third, EEG concentration and average time of eye pursuit data will positively correlate with the self-reported concentration score. The average blink rate will negatively correlate with the self-reported concentration score. Finally, physical activity measured through acceleration data will positively correlate with self-reported physical effort scores.

Hypothesis 3.2

Levels of arousal, measured through HR and EDA data, will correlate negatively with task performance.

Methods

Ethical Considerations

This research project has been approved by the research ethics board of the Sainte-Justine University Hospital Research Center (2022-3881). We will send the informed consent form via email to potential participants; signing will occur at the study session after providing the opportunity to ask questions. The informed consent document explains why participants are invited to participate, the purpose of the project, the number of participants involved, and the age range. Finally, there is an optional section allowing participants to choose whether they agree to the secondary usage of their data for future research and whether their data will be made available.

Privacy and Confidentiality Protection

Participant data will be deidentified using codes, and only the research team will have access to the code linking participants' information to the collected data. On the informed consent form, parents have the option to grant permission for the use of deidentified images and videos of the participants for scientific communication and training purposes.

Setting

Data collection will take place at the Technopôle for Pediatric Rehabilitation of the Marie Enfant Children's Readaptation Center of the Sainte-Justine University Hospital Center in Montréal, Canada.

Study Design

This study uses the repeated measure within-participant experimental design.

Participants

Inclusion and Exclusion Criteria

A total of 15 typically developing children aged between 8 and 16 will be invited to participate. Inclusion criteria are cognitive, visual, and auditory abilities necessary to follow instructions and interact with the VR task. Exclusion criteria are photosensitive seizures, visuospatial deficiencies, and known cardiac problems. Interested participants will complete the cybersickness susceptibility questionnaire's non–time-sensitive questions [25]. Since the experiment is performed seated, and the virtual environment does not move independently of the head movements, there is a limited risk of cybersickness. Children displaying 4 or more (out of 18 total) indicators of susceptibility to cybersickness (any "yes" answer in the yes-no

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questions and any rating of 1 in the Likert scales) will be excluded from participation.

Recruitment

Typically developing children will be recruited through social media advertisements. Participants and their parents will provide assent and consent, respectively.

Sample Size Calculation

This pilot study is not powered for effectiveness. For the analysis of repeated measure correlations, using the method developed by Bakdash and Marusich [26], with a presumed strong effect of task difficulty, 3 data points (the 3 different levels of difficulty), 15 participants in total are sufficient to reach a power of 0.80. This pilot study will determine the effect size to power a subsequent larger data collection.

Novel Motor Learning Task in Immersive VR: Ball Bounce

Ball bounce is a custom-developed unimanual task built in Unity3D (Unity Technologies) that requires the player to consecutively bounce a virtual ball on a virtual paddle. The task takes place in a fantasy environment composed of floating islands and castles. The VR controller is represented in the virtual environment by a paddle (Figure 1). The user views a ping-pong–sized ball hovering directly in front of them at their eye level. When the user squeezes the controller trigger finger, the countdown starts and the ball is dropped. When the paddle enters in contact with the ball then the ball will bounce according to regular physics reaction. If the ball hits the ground, it disintegrates, and a new ball is generated and appears at eye level of the player at its initial position. A trial is started when a new ball is generated and starts falling. The trial ends when the ball hits the floor, automatically triggering a new ball to appear. Consecutive ball bounces during each trial are counted in the scoreboard and the highest number of bounces is displayed.

Figure 1. (A) The virtual environment. (B) The participant's view.

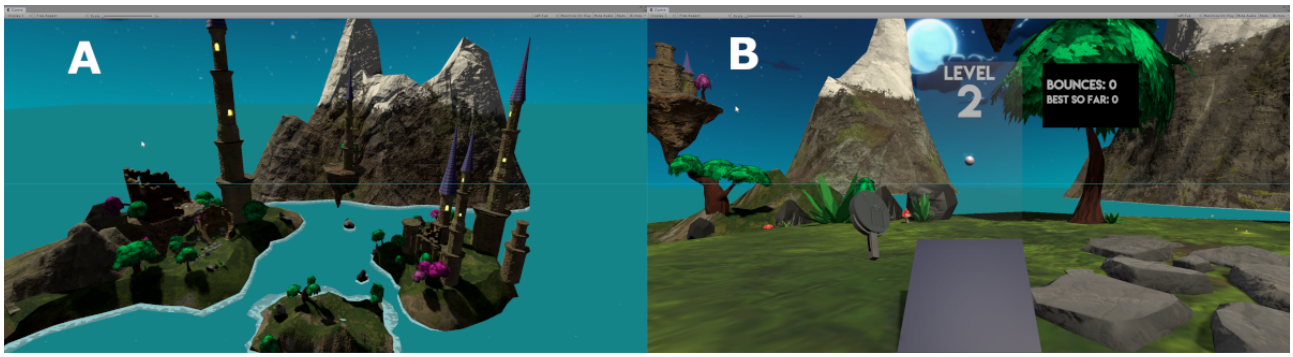

Task difficulty is modulated through Unity's physics engine global gravity parameter. The ball is coded as a physical object and gravity modulates its speed. There are 10 difficulty levels, ranging from 10% of real-life gravity to 100% of real-life gravity; each progressive difficulty level has a 10% step increase. The virtual environment does not change across difficulty levels. The impact of gravity manipulation on perceived task difficulty was confirmed through preliminary testing with 5 typically developing children.

Study Procedures

Overview

Figure 2 outlines the study protocol. After completing a study demographic form, the participant is outfitted with the HMD and the data collection devices.

Participants will be asked to sit still for 5 minutes to calculate baseline resting state data. They will then receive task instructions Participants play with their dominant hand. All participants are asked to limit the movements of the nontask hand. Participants will first complete a 1-minute tutorial to familiarize them with the environment and the gameplay. The tutorial is set at a minimal level of difficulty (gravity is set to 10% of its real value). When participants are ready, they can click any button on the controller to start the game.

Participants will play for 3 minutes at the medium level of difficulty (gravity set to 50%) to evaluate their baseline task abilities. Depending on the participant's performance during this baseline session, the starting difficulty will be set at a very easy level, an easy level, or a medium level. This personalization optimizes task difficulty progression to participant abilities. Visual representation of the difficulty selection and evolution is detailed in Figure 3. Participants then complete three 3-minute gameplay sessions at progressively challenging gravity manipulation levels, with breaks in between sessions. This number of gameplay sessions was chosen to limit the effects of fatigue. We chose not to counterbalance task difficulty presentation in order to better reflect real-world task learning conditions in which instructors increase task difficulty parameters as performance improves.

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Figure 2. Overview of the data collection protocol.

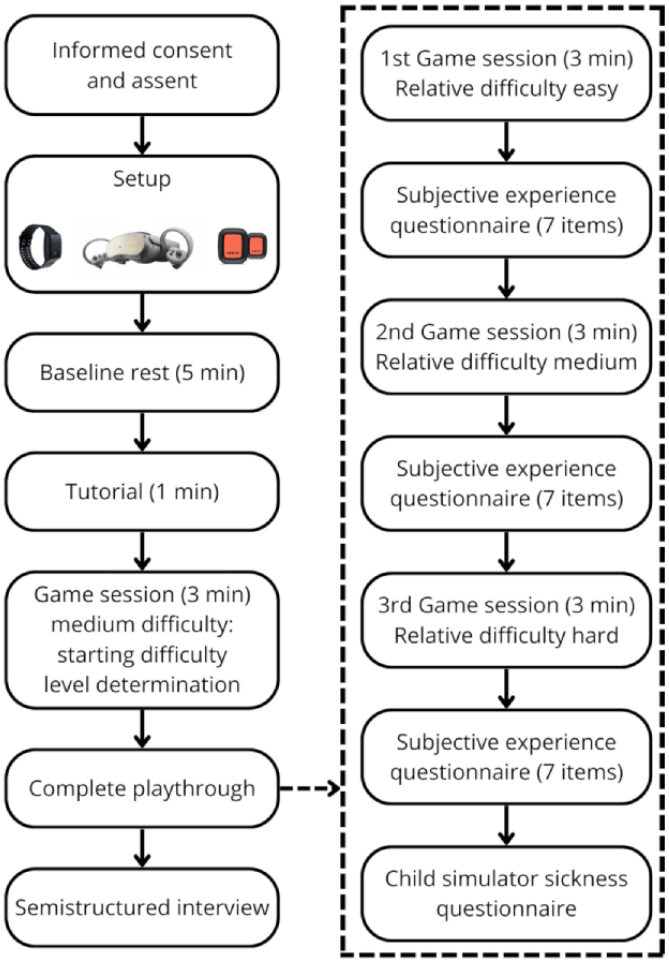

Figure 3. Difficulty selection and progression depending on baseline evaluation.

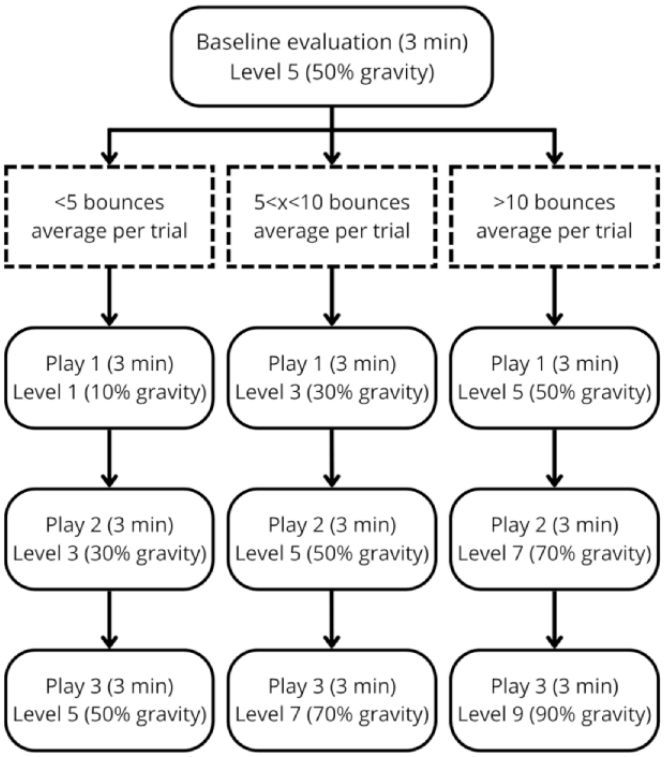

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After each 3-minute play session, the participant removes the HMD and answers a study-specific questionnaire asking them to rate agreement with 7 statements (1 statement per construct) about their engagement, attention or focus, cognitive workload, physical effort, self-efficacy, and motivation. Statements are presented on a 7-item Likert scale with anchors on "strongly disagree" and "strongly agree." First, engagement—2 questions inspired by the Independent Television Commission-Sense Of Presence Inventory [27] whose scores are averaged as (1) I enjoyed myself during this level and (2) I felt involved in the displayed environment. Second, attention or focus—I am completely focused on the task at hand (question derived from the Flow Short Scale [28]). Third, cognitive workload—during the task I did a lot of thinking and figuring out (questions derived from the revised National Aeronautics and Space Administration [NASA] Task Load Index [TLX] for children [29]). Fourth, physical effort—during the task I had to do a lot of physical effort (question derived from the revised NASA TLX for children [29]). Fifth, self-efficacy—I think I can do well at a more difficult level. Finally, motivation—I wanted to work harder to improve my performance or I tried hard to improve my performance (question derived from the Pediatric Motivation Scale [30])

The resting period between each 3-minute play session is between 3 and 5 minutes, and participants can request a longer break as needed. At the end of the session, participants complete the Child Simulator Sickness Questionnaire [31]. Participants will receive a CAD $25 (US $1=CAD $1.37) gift card as a token of appreciation for their participation in the study.

Data Collection Instruments

Task Performance

Participants will wear a Pico 4 Enterprise HMD. Performance data are collected within the Unity task—for each trial, the position of the paddle when the ball hits it and the maximum elevation of the ball after each hit is captured. The number of consecutive hits is calculated. To be considered as a valid bounce the ball must reach a height of at least 15 cm. Task performance is defined as the ratio of error over the total number of bounces attempted (number of errors divided by [number of bounces + number of errors]) during the 3-minute trial.

EEG Analysis

A Kaptics (Corporation) EEG with 12 Ag/AgCl dry electrodes is integrated into the Pico4 headgear. The electrodes are placed in the configuration—Fp1, Fp2, AFz (bias), F3, Fz, F4, C3, Cz (reference), C4, O1, Oz, O2. The Kaptics custom-developed application computes the psychophysiological metrics of (1) mental engagement level, measured with the engagement index, which is calculated through beta and alpha bands, based on the work of Coelli et al [32]; (2) cognitive workload, which is calculated through changes in theta and alpha bands, based on the work of Di Flumeri et al [33] and Zammouri et al [34]; and (3) concentration, which is measured through changes in beta bands, based on the work of Lim et al [35].

Eye-Tracking

The Pico Neo 4 Enterprise has an integrated Tobii eye tracker. Oculometry correlates with attention to a task [36]. The average time per trial of eye pursuit of the ball will be used as a metric of focused attention. Eye pursuit will be computed as the amount of time when performing the VR task, during which the direction of the eyes intersects with the areas of interest (volumes englobing respectively the ball and the paddle). A lower blink rate will be indicative of a higher focused attention [36].

Movement Quantity

The continuous position of the virtual paddle in the virtual environment is saved at a frame rate of 60 Hz. From the consecutive 3D positions recorded, the total amount of displacement will be computed to get the total amount of motion during the virtual task.

EDA and HR

Participants will wear an Empatica E4 sensor equipped with a photoplethysmography sensor and an EDA sensor. EDA, a recognized marker of arousal [37], will be computed as the average number of peaks per minute for each 3-minute play period using pyEDA, an open-source Python toolkit (Python Software Foundation) [38]. HR is also a proxy for arousal [37]. HR in beats per minute will be averaged over each gameplay. The changes in the level of arousal will be computed to determine the intensity of the physiological response. With an optimal level of engagement, arousal should be average [37]. If arousal is too high it can be interpreted as a sign of frustration rather than engagement.

Upper Extremity Movement Quality

As an exploratory measure, participants will wear XSens DOT inertial measurement units on the active forearm and on the chest to capture upper limb movement smoothness. Movement smoothness is measured through acceleration data. Less smooth movements are characterized by fluctuations in velocity, causing local maxima in the velocity profile. It is classified as an acceleration metric since the calculation of this metric is in the acceleration domain [39]. The lower the number of local maxima recorded the smoother the movement is. The average number of local maxima per minute will be computed as an exploratory measure to look for differences in movement at the different levels of difficulty.

Data Processing

Empatica data are stored in the smartwatch during the experiment and then downloaded to a computer for analysis. EDA data will be filtered using a low-pass Butterworth filter (frequency of 1 Hz and order of 6). EEG signals processed by Kaptics are filtered using a band-pass filter between 0.5 and 45 Hz and then zero-mean normalized. Kaptics uses the subspace reconstruction method to remove motion artifacts [40].

Analyses

Overview

Quantitative statistical analyses will be performed using SPSS (IBM Corp) for ANOVA, correlations and graphical output and R (R Foundation for Statistical Computing) for the usage of the repeated measure correlation (rmcorr) package [26]. Confidence level will be set at 95%. Descriptive statistics will be presented as counts, means, and standard differences by level of difficulty. Demographic categorial data will be presented as means and

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standard differences by age, gender, and Gross Motor Function Classification System level.

Objective 1

The aim is to evaluate the performance of the physiological sensors in children undertaking a new motor learning task in immersive VR.

Identify Data Loss

The acceptable data loss threshold per measure will be set as 10% of the total data collection time for each of the 3 gameplay sessions. The expected output of data differs by sensor according to frequency. The amount of recorded data, for each 3-minute level, over expected output will be computed to measure the percentage of data loss.

1. EDA: Empatica frequency is 4 Hz
2. HR: Empatica HR value frequency is 1 Hz
3. Eye-tracking: Data will be collected at a fixed frequency (60 Hz). When the HMD is unable to accurately detect the eyes of the participants, the values are reported as 0.

Data Quality

For each 3-minute level, the amount of aberrant data will be computed for each sensor. The percentage of aberrant data over the total amount of collected data will then be computed.

First, the quality of EDA data is assessed following the two criteria of [41] (1) the total range of valid EDA data is 0.05-60 µS (data outside this range will be considered aberrant) and (2) an EDA change of more than ±10 µS/s between any 2 consecutive values is considered aberrant.

Second, HR—the minimal valid value of HR data is 60 beats per minute [42], while the estimated maximum valid value is 194 beats per minute [43]. Data outside this threshold will be considered aberrant. Changes in HR between any 2 consecutive values superior to ±3 beats per second will be considered aberrant [44].

Objective 2

Evaluate changes in physiological data at 3 immersive VR task difficulty levels. To examine intraindividual changes in averaged physiological data at baseline and the 3 difficulty levels, a repeated measure ANOVA will be performed for each dependent variable, with the level of difficulty as the within-subject factor. Sensitivity analysis will be done using the Friedman test, due to the small sample size. Eta squared will be reported as the measure of effect size.

Objective 3

The aim is to explore the relationship between physiological data, task performance, and self-reported measures of engagement, cognitive workload, physical effort, and attention or focus at each task difficulty level.

To determine the intraindividual relationship between physiological data and self-reported data, the Pearson product-moment correlation, and the Spearman rank correlation will be performed, to explore linear and monotonic relationships. The complete correlation matrix will be reported (with correlation coefficient as effect sizes and *P* values). At each difficulty level, correlations will be explored between (1) the level of engagement computed from the EEG data and the averaged self-reported score of engagement, (2) the level of attention computed from the EEG data and the self-reported score of attention, (3) the level of attention computed from the eye tracking data (time of pursuit and average blink rate) and the self-reported score of attention, (4) the level of cognitive workload computed from the EEG data and the self-reported score of cognitive workload, and (5) the average amount of movement of the virtual paddle and the self-reported score of physical effort.

Testing to evaluate parallel slopes between conditions will be undertaken [45]. If parallel slopes are identified, a repeated measure correlation (rmcorr) will be performed [26]. The rmcorr method can handle repeated measures data without violating independence assumptions or averaging data. It is ideally suited to assess association in intraindividual relationships between paired measures. Visual analysis [46], as well as statistical inference (regression coefficients and *P* values) will be reported. We will report visual analyses, as well as statistical inference (regression coefficients and *P* values) results.

Results

Study recruitment is underway. The Centre hospitalier universitaire Sainte-Justine research ethics board approved this work (2022-3881) in the spring of 2023. Data collection was conducted on December 12, 2023, and April 12, 2024, with a total of 15 typically developing children. Data analysis has been completed, and results are expected to be published in the fall of 2024.

Discussion

Principal Findings

Targeting “just-right” task challenges during rehabilitation interventions is anchored in evidence-based motor learning principles [3]. Wearable sensors can enable objective measurement of psychophysiological states related to difficulty progression during motor skill learning. A better understanding of wearable sensor task performance during movement-based tasks in children is required [24]. The current state of knowledge on wearable sensor use in pediatric rehabilitation is limited to inertial measurement units and accelerometers [19]. Very few studies have explored the potential of wearable physiological sensors to understand children’s engagement during VR-based interactions [22]. This study will evaluate relationships between physiological data and children’s self-reports during the practice of a novel motor learning task in immersive VR at different task difficulty levels. Findings from this pilot study will inform subsequent work, which could include collecting physiological and self-report data with a child with a motor impairment who progresses at their own pace through task difficulty levels in immersive VR and asking children to self-identify when they perceive the challenge to be “just-right.” If objective and subjective data are correlated, this training data could be used to build a machine learning model to predict the “just-right” challenge based on the combination of thresholds of different variables, using the subjective self-report of the “just-right”

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challenge to correctly label the corresponding physiological data. As proposed by Houzangbe et al [18], combining the success rate of a task with psychophysiological levels of engagement, arousal, cognitive workload, and attention could lead to the objective identification of conditions necessary to reach personalized "just-right" challenges. In the longer term, embedding this model within immersive VR motor learning tasks may enable real-time decision-making about task difficulty level to achieve and maintain "just-right" task challenges. Subsequent work can also compare different types of VR tasks to assess the reproducibility of the results and their generalization.

Potential Limitations

The small sample size of this pilot study limits the scope of the conclusions. Results will inform the calculation of the effect size required to power subsequent data collection. Using commercial physiological wearable sensors may lead to more compromised data quality as compared to medical-grade equipment. This limitation is balanced by cost and accessibility benefits. Choosing not to counterbalance task difficulty presentation introduces potential learning or fatigue effects. Using short house-made motivation and focus questionnaires is required as longer validated questionnaires are impractical following short gameplay sessions.

Conclusions

This is the first step in a program of research exploring factors influencing children's user experiences during motor skill learning in immersive VR. Immersive VR hardware and software are rapidly developing and lowering in cost, increasing their potential as an accessible telerehabilitation modality. If the difficulty of immersive VR tasks can be adapted to "just-right" challenges in the absence of therapeutic decision-making, they may be evidence-based, accessible, and personalized telerehabilitation interventions. Being able to identify, quantify, and predict "just-right" challenges can contribute to a future of precision rehabilitation [19] where VR, physiological sensors, and AI models can provide personalized interventions in clinic and home-based contexts.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the design of the study protocol. SH wrote the first draft of the paper, and all authors contributed to the subsequent versions. SH developed and integrated the data collection tools from the virtual reality software.

Conflicts of Interest

None declared.

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Abbreviations

EDA: electrodermal activity
EEG: electroencephalography
HMD: head-mounted display
HR: heart rate
NASA: National Aeronautics and Space Administration
TLX: Task Load Index
VR: virtual reality

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Protocol

Outcomes of Patients With Early and Locally Advanced Lung Cancer: Protocol for the Italian Lung Cancer Observational Study (LUCENT)

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Abstract

Background: Lung cancer, predominantly non-small cell lung cancer (NSCLC), remains a formidable challenge, necessitating an in-depth understanding of evolving treatment paradigms. The Italian Lung Cancer Observational Study (LUCENT) addresses this need by investigating the outcomes of patients with early and locally advanced lung cancer in Italy.

Objective: With a focus on real-world data and patient registries, this study aims to provide comprehensive insights into clinical, psychosocial, and economic impacts, contributing to informed decision-making in health care.

Methods: LUCENT is a prospective observational multicenter cohort study enrolling patients eligible for minimally invasive manual, robot-assisted, or traditional open surgery. The study will develop a web-based registry to collect longitudinal surgical, oncological, and socioeconomic outcome data. The primary objectives include performance assessment through the establishment of national benchmarks based on risk-adjusted outcomes and processes of care indicators. The secondary objectives encompass economic and psychosocial impact assessments of innovative technologies and treatment pathways. The multicenter design ensures a diverse and representative study population.

Results: The evolving landscape of NSCLC treatment necessitates a nuanced approach with consideration of the dynamic shifts in therapeutic strategies. LUCENT strives to fill existing knowledge gaps by providing a platform for collecting and analyzing real-world data, emphasizing the importance of patient-reported outcomes in enhancing the understanding of the disease. By developing a web-based registry, the study not only facilitates efficient data collection but also addresses the limitations of traditional methods, such as suboptimal response rates and costs associated with paper-and-pencil questionnaires. Recruitment

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will be conducted from January 01, 2024, to December 31, 2026. Follow-up will be performed for a minimum of 2 years. The study will be completed in the year 2028.

Conclusions: LUCENT's potential implications are substantial. Establishing national benchmarks will enable a thorough evaluation of outcomes and care processes, guiding clinicians and policymakers in optimizing patient management. Furthermore, the study's secondary objectives, focusing on economic and psychosocial impacts, align with the contemporary emphasis on holistic cancer care. Insights gained from this study may influence treatment strategies, resource utilization, and patient well-being, thereby contributing to the ongoing refinement of lung cancer management.

Trial Registration: ClinicalTrials.gov NCT05851755; https://clinicaltrials.gov/study/NCT05851755. ISRCTN 67197140; https://www.isrctn.com/ISRCTN67197140

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KEYWORDS

lung cancer; quality of life; observational study; economic aspects; multicenter study

Introduction

Background and Rationale

Most lung cancer cases involve non-small cell lung cancer (NSCLC), while small cell cancer represents the minority of cases. To date, limited percentages of NSCLC cases are diagnosed in the early stage (in which patients are potential candidates for surgery, possibly followed by chemotherapy, to reduce the risk of recurrence) or in the locally advanced stage (in which the treatment is based on the use of chemotherapy, radiotherapy, and possibly, upon their completion, immunotherapy). The therapeutic strategy in patients with advanced NSCLC has changed in recent years. Until about 10 years ago, chemotherapy was the only option available; however, it was characterized by limited effectiveness. In recent years, the 2 crucial therapeutic "revolutions" we have witnessed in medical oncology (molecularly targeted drugs and then immunotherapy) have played essential roles in treating these patients. Some molecularly targeted drugs (primarily epidermal growth factor receptor [EGFR] inhibitors and then drugs directed against other molecular alterations) are superior to chemotherapy as a first-choice treatment, but the use of these drugs is limited to cases in which the tumor has those specific molecular alterations. Molecular analyses aimed at identifying these alterations in the tumor tissue represent a fundamental part of the diagnosis, which precedes the best treatment choice for each patient. In the next few years, we will probably see the continuation of those therapeutic "revolutions" mentioned above with the availability of new molecularly targeted drugs. These approaches will increase the therapeutic possibilities to be used in sequence after the failure of the approaches already available today [1]. Still, in some cases, they will allow a "targeted" treatment in the presence of molecular alterations for which no target drugs are available in clinical practice until now. Immunotherapy first established itself (about 5 years ago) as an effective treatment in patients who had already failed chemotherapy [1]. Subsequently, it was proven to be superior to chemotherapy as the first-choice treatment in cases characterized by high expression of the PD-L1 marker. Finally, significant results have been obtained in recent years by combining chemotherapy and immunotherapy, even in patients with low or absent PD-L1 expression. It is conceivable that in the coming years, based on a series of clinical trials recently conducted or still in progress, innovative drugs (targeted therapies and immunotherapy) will have essential roles in the treatment of early stages of cancer (used before surgery or after surgery) to reduce the risk of disease recurrence and hopefully increase the chances of recovery. The 5-year survival rate of lung cancer is low (16% in men and 23% in women), and it is at the bottom of the survival ranking, reminding us that, despite the critical progress made in recent years, there is a long way ahead regarding its treatment [2-4].

Globally, there is an increasing trend to use real-world data to inform decision-making in health care, and patient registries are regarded as a typical example of real-world data. A patient registry can be defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" [5,6]. While regulatory agencies can use real-world data collection for postmarketing surveillance and risk assessment, payers and reimbursement agencies are consistently considering real-world evidence to make or revise their recommendations. To this end, the information collected in patient registries can extend from appropriate treatment strategies to effectiveness and cost-effectiveness assessments in real-world clinical practice [7,8].

Furthermore, achieving and maintaining optimal well-being and health-related quality of life (HRQoL) have become essential objectives of cancer treatment, rehabilitation, and aftercare across the cancer continuum. The availability of patient-reported outcomes (PROs) is critical in achieving these goals. In the past, patient registries have provided clinicians and researchers with a wealth of clinical data (eg, stage and primary treatment) on cancer patients. However, data on PROs are not yet routinely available. PROs have been collected using paper-and-pencil questionnaires, with suboptimal response rates, high costs, and overall process efficiency. Online administration of questionnaires has several advantages compared with paper-and-pencil questionnaires, including convenience for the participant, potentially significant cost savings, data collection efficiency, and high data quality [9-12].

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Therefore, we propose to develop a web-based registry to collect longitudinal data on the clinical, psychosocial, and economic impacts of lung cancer treatment in Italy.

Objectives

Primary Objectives

The project involves a web-based registry developed to facilitate data collection and evaluation of several different surgical, oncological, and socioeconomic outcomes of lung cancer patients diagnosed in early and locally advanced stages in Italy.

The primary objective is to generate data relevant to performance assessment through the development of national performance benchmarks based on the analysis of risk-adjusted outcomes and the processes of care indicators (eg, How does individual center X compare to the national standard in terms of length of stay for a certain subgroup of patients?).

Secondary Objectives

The registry can be used simultaneously for multiple studies with different purposes. Among the secondary objectives are the following: (1) Economic impact assessment of innovative technologies or treatment pathways (eg, Do different surgical medical devices influence health care resource utilization for a single episode of hospitalization?) and (2) Psychosocial impact assessment of innovative technologies or treatment pathways, for example, minimally invasive surgery (eg, Do new targeted treatments have a beneficial or adverse impact on PROs?).

Trial Design

The Italian Lung Cancer Observational Study (LUCENT) is a prospective observational multicenter cohort study enrolling lung cancer patients who are candidates for minimally invasive manual, robot-assisted, or traditional open surgery. This study aims to investigate the outcomes of patients with early and locally advanced lung cancer in Italy. By using real-world data and patient registries, the study seeks to provide comprehensive insights into the clinical, psychosocial, and economic impacts of lung cancer treatment. The study's observational nature allows for data collection in a naturalistic setting without intervention or manipulation by the researchers. The list of collaborating institutions has been provided in Multimedia Appendix 1.

Methods

Study Setting

This multicenter study will include community clinics and academic centers located in Italy. This protocol has been presented in compliance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [13].

Eligibility Criteria

Inclusion Criteria

The inclusion criteria are as follows:

- Diagnosis of lung cancer: Patients must meet the following criteria for the diagnosis of lung cancer: (1) confirmation of lung cancer through histopathological examination or imaging studies and (2) specific ICD-10 codes for lung cancer that include but are not limited to C34.0 (main bronchus), C34.1 (upper lobe, lung), C34.2 (middle lobe, lung), C34.3 (lower lobe, lung), C34.8 (overlapping lesion of the lung), and C34.9 (lung, unspecified).
- Age criteria: Patients must be aged 18 years or older at the time of enrollment.
- Informed consent: Patients must provide written informed consent to participate in the study.
- Communication requirement: Patients should provide an email address at the time of enrollment for follow-up communication and the exchange of questionnaires.
- Language proficiency: Patients should be able to understand and communicate in Italian.

Exclusion Criteria

The exclusion criteria are as follows:

- Language proficiency: Patients are unable to understand or communicate in Italian.

Who Will Take Informed Consent?

Qualified health care professionals will conduct the informed consent process at each participating institution in this study. These professionals will ensure that potential participants are fully informed about the study's purpose, procedures, and possible risks and benefits, and their rights as participants. They will also address any questions or concerns raised by the participants and obtain written informed consent from those who voluntarily choose to participate in the study. The informed consent process will adhere to ethical guidelines and regulatory requirements to safeguard the rights and well-being of the participants.

Additional Consent Provisions for the Collection and Use of Participant Data and Biological Specimens

We will conduct the trial according to the ICH Good Clinical Practice (GCP) guidelines. Accurate and consistent records are essential to a cooperative study.

The clinical and surgical data collected in a standardized endorsed data set can be downloaded locally and used for internal quality analyses or institutional research. The data collection methodology will use a website platform that meets international data privacy protection standards and rules. Notably, data are anonymously reported, independently accessed, and encrypted for other users.

For joining the database, the login of each institution will be provided after downloading and completing an application form from the project homepage and directly sending an email to the study coordinator. Investigators will access the patient medical records and enter the required data into the database. Protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized research project oversight.

In compliance with the ICH-GCP guidelines, the investigator or institution will maintain all electronic case report forms, all source documents that support the data collected from each

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subject, all study documents as specified in ICH-GCP Section 8 (Essential Documents for the Conduct of a Clinical Trial), and all study documents as determined by the applicable regulatory requirements. The investigator or institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 25 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained longer if required by the applicable regulatory requirements or an agreement with the sponsor. The sponsor is responsible for informing the investigator or institution when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or withdraws from the responsibility of keeping the study records for other reasons, custody must be transferred to a person who will accept the duty. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before obtaining written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

Interventions

Explanation for the Choice of Comparators

The choice of comparators in this study is driven by the need to assess and compare various surgical interventions for lung cancer patients. The study aims to enroll patients eligible for minimally invasive manual, robot-assisted, or traditional open surgery, reflecting the diverse landscape of surgical approaches in clinical practice.

The rationale for including these comparators is rooted in the evolving nature of lung cancer treatment, where different surgical modalities are employed based on factors such as tumor characteristics, patient condition, and advancements in surgical techniques. Minimally invasive surgeries, including robot-assisted procedures, have gained prominence for their potential benefits, such as reduced postoperative pain, shorter hospital stay, and quicker recovery compared to traditional open surgery.

By including these comparators, this study seeks to evaluate and compare the outcomes of these diverse surgical interventions. This comprehensive approach allows for a nuanced understanding of the effectiveness and potential differences in results associated with each surgical modality. It also enables the study to contribute valuable insights into the evolving landscape of lung cancer treatment, guiding future clinical decisions and optimizing patient care.

The choice of comparators aligns with the study's overarching objective to generate data for performance assessment. This provides a basis for national benchmarks and facilitates a thorough analysis of outcomes and care processes. This approach ensures that the study captures the diversity of surgical practices in the real-world setting, reflecting the dynamic nature of lung cancer treatment and contributing to the broader knowledge base in the field.

Intervention Description

The interventions in this study encompass a spectrum of surgical approaches for lung cancer patients diagnosed in the early and locally advanced stages.

Regarding the rationale for intervention selection, the choice of interventions reflects the diversity of surgical practices in treating lung cancer. Each intervention has its advantages and considerations, and the study aims to evaluate and compare their outcomes comprehensively. Including minimally invasive and robot-assisted surgeries acknowledges the evolving landscape of surgical techniques, aligning with the contemporary emphasis on reducing patient morbidity and improving recovery.

Patients meeting the inclusion criteria will be assessed for eligibility, and the choice of intervention will be based on factors such as tumor characteristics, patient condition, and the surgeon's expertise.

Qualified and experienced health care professionals will perform the surgical procedures at participating institutions. Data related to the interventions, perioperative details, and postoperative outcomes will be systematically collected through the web-based registry developed for the study.

Criteria for Discontinuing or Modifying Allocated Interventions

The criteria for discontinuing or modifying allocated interventions in LUCENT are established to ensure participants' safety and well-being while maintaining the study's integrity. These criteria are designed to address unforeseen circumstances, emerging patient-related factors, or changes in clinical status. The discontinuation or modification of interventions will be considered under the following events:

- Medical emergencies: If a participant experiences a medical emergency during or after the intervention, the allocated intervention may be discontinued or modified to address the emergent health situation. The treating health care professionals will decide on the situation and prioritize the participant's health and safety.
- Adverse events (AEs): In the case of unexpected AEs related to the allocated intervention, the study protocol allows for the discontinuation or modification of the intervention to mitigate potential harm to the participant. AEs will be monitored, documented, and reported according to the study's safety monitoring procedures.
- Participant withdrawal: If a participant chooses to withdraw from the study or requests a change in the allocated intervention, their decision will be respected. Withdrawal may be due to personal reasons, differences in health status, or other factors influencing the participant's willingness to continue with the allocated intervention.
- Protocol deviation: Any deviation from the study protocol deemed necessary for the participant's well-being may lead to modification or discontinuation of the allocated intervention. Protocol deviations will be documented and

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reported according to the study's data management and reporting procedures.
- Clinical judgment: Health care professionals, in consultation with the principal investigator, may exercise clinical judgment to modify or discontinue the allocated intervention if unforeseen clinical circumstances arise that warrant such actions. Decisions will be made based on the best interests of the participant and in adherence to ethical and safety considerations.
- Loss to follow-up: If a participant loses access to follow-up or cannot adhere to the scheduled assessments and interventions, modifications may be considered based on the available information. It is crucial to note that any discontinuation or change of allocated interventions will be thoroughly documented, and the reasons for such actions will be reported in the study records. Additionally, these decisions will be communicated to relevant stakeholders, including the study participants and institutional review boards, ensuring transparency and adherence to ethical standards. The criteria outlined aim to balance participant safety with the scientific rigor of the study.

Strategies to Improve Adherence to Interventions

The following strategies will be implemented to optimize and enhance adherence throughout the study:

- Patient education and informed consent: Clear and comprehensive education about the study, its purpose, and the importance of adherence will be provided during the informed consent process.
- Multidisciplinary team engagement: A multidisciplinary health care team, including surgeons, nurses, and support staff, will be involved in patient education and engagement.
- Regular communication: Normal communication channels will be established between health care providers and participants to address any concerns, provide ongoing support, and reinforce the importance of adherence.
- Patient-centered decision-making: Patients will be involved in decision-making regarding their treatment to foster a sense of autonomy and ownership in the intervention process.
- Monitoring and feedback: A robust monitoring system will be implemented to track participant progress and intervention adherence.
- Patient support programs: Support programs, including psychological support and resources, will be offered to address the emotional and psychological aspects of the intervention.
- Use of technology: Technology, such as mobile apps or online platforms, will be leveraged to provide educational materials, reminders, and real-time support.
- Continuous participant engagement: Strategies will be implemented to maintain participant engagement throughout the study, including newsletters, educational materials, and updates on study progress.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Adherence to interventions is crucial for scientific validity and participant well-being. The following strategies will be implemented to optimize adherence throughout the study: clear and comprehensive education during informed consent, and emphasizing the study's purpose and the importance of adherence. Patients will be informed about the potential benefits, highlighting their contribution to advancing knowledge in lung cancer treatment. A multidisciplinary health care team, including surgeons, nurses, and support staff, will be involved in patient education and engagement. A collaborative approach ensures consistent information and support from various health care professionals. Treatment plans will be tailored to individual patient needs and preferences to enhance buy-in and motivation to adhere to the protocol. Patient-specific factors, such as lifestyle and cultural background, can improve adherence. Regular communication channels will be established between health care providers and participants to address concerns, provide ongoing support, and reinforce the importance of adherence. Telehealth or virtual platforms will be implemented for follow-up consultations to facilitate continuous communication. Patients will be included in decision-making to foster a sense of autonomy and ownership in the intervention process. Shared decision-making can enhance commitment and adherence to the chosen intervention. A robust monitoring system will be implemented to track participant progress and adherence. Timely feedback will be provided to participants on their progress. Acknowledgment of their contributions is considered positive reinforcement. Support programs, including psychological support and resources, will be offered to address the emotional and psychological aspects of the intervention. Support programs help patients to cope with challenges, fostering a positive attitude toward the intervention. Technologies, such as mobile apps and online platforms, will be adopted to provide educational materials, reminders, and real-time support. Technology can enhance engagement and facilitate communication between participants and health care providers. Flexibility will be offered in scheduling interventions to accommodate individual participant preferences and logistical considerations. Flexible scheduling can reduce barriers to adherence and increase overall participant satisfaction. Strategies will be implemented to maintain participant engagement, including newsletters, educational materials, and updates on study progress. This will ensure that participants feel connected and valued as contributors to the research endeavor.

Provisions for Posttrial Care

The provisions for posttrial care in LUCENT are designed to ensure that participants receive appropriate medical attention and support even after their active involvement in the study has concluded. The posttrial care plan prioritizes the well-being of participants and addresses any ongoing medical needs that may arise. The key provisions for posttrial care include the following:

- Continuity of standard medical care: Participants will continue to receive standard medical care for lung cancer as per established clinical guidelines, irrespective of their involvement in the study. The study team will facilitate the seamless transition of participants back to routine medical care provided by their health care providers.
- Access to study-related information: Participants will continue to have access to information related to the study,

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including summaries of study results, as they become available and appropriate for dissemination.
- Follow-up assessments: If any scheduled follow-up assessments or evaluations are part of the study protocol extending beyond the active trial period, participants will be informed about and encouraged to attend these follow-up appointments.
- AE monitoring: During the posttrial period, the study team will continue to monitor and address any AEs or complications related to the study interventions or procedures.
- Referral to specialists: If participants require specialized care or additional medical attention beyond the scope of the study, appropriate referrals to specialists will be facilitated.
- Communication and support: Participants will be provided with the contact information of the study team or a designated point of contact, allowing them to reach out with any questions or concerns about their participation or posttrial care.
- Emergency procedures: Clear procedures will be in place to manage any emergent medical situations that participants may face after the conclusion of the trial, with appropriate guidance on seeking urgent medical attention. The posttrial care provisions emphasize the ethical responsibility of the study team to prioritize participant welfare beyond the active study period. By providing ongoing support, access to information, and coordination with standard medical care, the study aims to ensure a comprehensive and ethical approach to the well-being of participants even after their active involvement in the observational study has ended.

Ethical Considerations

The study protocol has received approval from ISMETT Palermo (IT) (IRRB/04/23 20/04/2023). All participants will provide informed consent before participating in the study. Participants will be informed that study findings may be published, and their confidentiality will be maintained.

Results

Outcomes

A comprehensive set of outcomes will be evaluated to gain insights into the clinical, psychosocial, and economic impacts of lung cancer treatment in Italy. The outcomes are categorized into primary and secondary objectives.

Primary Objectives

The primary objectives are as follows:

- Performance assessment: (1) Development of national performance benchmarks based on the analysis of risk-adjusted outcomes and processes of care indicators; and (2) Evaluation of individual centers compared to national benchmarks for specific subgroups of patients.

Secondary Objectives

The secondary objectives are as follows:

- Economic impact assessment: Examination of the financial implications of innovative technologies or treatment pathways for lung cancer.
- Assessment of health care resource utilization for different surgical medical devices during a single episode of hospitalization.
- Psychosocial impact assessment: Investigation of the psychosocial impact of innovative technologies or treatment pathways, such as minimally invasive surgery.
- Assessment of PROs to determine the impact of new targeted treatments on quality of life.

Additional Outcomes and Considerations

The additional outcomes and considerations are as follows:

- Longitudinal clinical outcomes: (1) Analysis of long-term clinical outcomes related to the chosen surgical interventions; and (2) Evaluation of recurrence rates, overall survival, and disease-free survival among participants.
- PROs: (1) Collection of PROs related to well-being, quality of life, and psychosocial factors; and (2) Utilization of online administration of questionnaires to enhance efficiency and data quality.
- Health care resource utilization: (1) Examination of the utilization of health care resources, including hospital stay, postoperative care, and associated costs; and (2) Identification of factors influencing resource utilization and potential areas for improvement.
- Treatment decision patterns: (1) Analysis of the patterns in treatment decisions, considering factors such as tumor characteristics and patient preferences; and (2) Exploration of the factors influencing the choice of surgical interventions.
- Patient characteristics and demographics: (1) Documentation of patient demographics, including age, gender, and other relevant characteristics; and (2) Analysis of how patient characteristics may influence treatment outcomes and decision-making.
- AEs and complications: Monitoring and documentation of AEs and complications related to the chosen interventions; and (2) Evaluation of the safety profile of different surgical modalities.

Participant Timeline

Recruitment will be conducted from January 01, 2024, to December 31, 2026. Follow-up will be performed for a minimum of 2 years. The study will be completed in the year 2028. The assessments at baseline and follow-up are presented in Table 1.

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Table 1. Study assessments.

Assessment	Baseline	Follow-up
Visit month (from inclusion)	Yes	No
Informed consent	Yes	No
Check if patient meets the inclusion/exclusion criteria	Yes	No
Medical history	Yes	No
Physical examination, including weight	Yes	No
Hematology	Yes	No
Blood chemistry	Yes	No
Radiological assessment	Yes	No
Clinical variables	No	Yes
Health-related quality of life	Yes	Yes
Direct and indirect costs	Yes	Yes

Sample Size

LUCENT adopts a nonspecific sample size approach, allowing for the inclusion of eligible participants based on the defined criteria. The study aims to enroll a diverse and representative sample of lung cancer patients diagnosed in early and locally advanced stages to capture a comprehensive range of outcomes and experiences. Participants meeting the inclusion criteria will be recruited consecutively from participating institutions to ensure a systematic and unbiased selection process. The study will involve multiple centers across Italy to enhance the diversity and generalizability of the study findings. Data collection will be facilitated through a web-based registry developed for the study, allowing for standardized and centralized data collection from various participating sites.

Recruitment

Recruitment involves the following:

- Collaboration with health care institutions: Forge partnerships with a network of health care institutions across Italy.
- Multidisciplinary team engagement: Involve a multidisciplinary team, including thoracic surgeons, oncologists, and research staff, in the recruitment process.
- Patient advocacy groups: Partner with patient advocacy groups focused on lung cancer. Leverage these groups to disseminate information, support recruitment efforts, and enhance community trust.
- Continuous communication: Maintain open and continuous communication with potential participants throughout the recruitment period.
- Address concerns, provide clarifications, and emphasize the value of their contribution to research.
- Regular site meetings: Conduct regular meetings with site staff to share best practices, address challenges, and reinforce recruitment strategies. Foster a collaborative and motivated research team.

The study aims to achieve adequate participant enrollment by combining these strategies, ensuring a diverse and representative sample to meet the target sample size within the specified recruitment period.

Assignment of Interventions: Allocation

Sequence generation, concealment mechanism, and implementation are not applicable as this is a nonrandomized observational study.

Assignment of Interventions: Blinding

The blinding approach is as follows:

- Participants: Owing to the nature of the surgical intervention, participants and those directly involved in their care can access the assigned intervention. It is challenging to blind participants and health care providers involved in surgical procedures.
- Care providers: Surgeons, health care providers, and clinical care teams responsible for delivering the interventions will not be blinded. Their awareness of the assigned surgical approach is essential for providing appropriate care.
- Outcome assessors: Outcome assessors will be blinded to the assigned interventions, particularly those collecting objective clinical data and endpoints. This includes individuals responsible for assessing recurrence rates, overall survival, and disease-free survival.
- Data analysts: Data analysts involved in the statistical analysis of study outcomes will be blinded to the assigned interventions. Blinding at this stage helps ensure unbiased data interpretation.
- Statistical team: The statistical team responsible for analyzing and interpreting the study results will conduct blinded analyses to prevent potential bias in reporting.
- Data monitors and auditors: To maintain objectivity, data and external auditors may also be blinded to treatment assignments during monitoring and auditing activities.

Procedure for Unblinding if Needed

Unblinding will only occur under predefined circumstances where knowledge of the treatment assignment is deemed crucial for participant safety or well-being. Only authorized personnel, such as a designated unblinding officer, will access confidential information regarding treatment assignment. The unblinding

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officer will be independent and not involved in the study's day-to-day management or the participants' direct care. The unblinding process will be secure, ensuring only authorized personnel can access information that reveals treatment assignment. Access to unblinded information will be password-protected and restricted to authorized individuals. The unblinding officer will maintain updated emergency contact information for each participant. In an emergency, the unblinding officer can quickly and efficiently communicate the relevant treatment assignment to the appropriate health care providers. All instances of unblinding, including the reason for unblinding, will be thoroughly documented. Documentation will include the date, time, individuals involved, and the specific circumstances necessitating unblinding. A clear communication plan will be established to ensure that unblinding occurs promptly and reaches the relevant individuals in emergencies. Records of unblinding events will be securely stored and kept separate from the primary study database. Access to these records will be restricted to authorized personnel and regulatory authorities, as necessary. Unblinding events and the reasons for unblinding will be promptly reported to the relevant ethical review boards and regulatory authorities. Following any unblinding event, the study team will reassess the blinding procedures to determine if modifications are needed to prevent similar situations in the future. Participants involved in an unblinding event will be promptly notified of the situation, and clear and accurate information about the intervention they received will be provided.

Data Collection and Management

The plans for the assessment and collection of outcomes are as follows:

- Longitudinal clinical outcomes: Regarding assessment, long-term clinical outcomes, including recurrence rates, overall survival, and disease-free survival, will be assessed through regular follow-up visits and medical records review. Regarding collection, outcome assessors will collect data during scheduled follow-up visits, and data entry personnel will ensure accurate and timely recording in the study database.
- PROs: Regarding assessment, patient-reported well-being and quality of life outcomes will be assessed using online questionnaires. Regarding collection, participants will be provided access to secure online questionnaire-completion platforms. Data will be automatically recorded in the study database.
- Health care resource utilization: Regarding assessment, health care resource utilization, including hospital stay and postoperative care, will be assessed through medical records and billing data. Regarding collection, data collection personnel will extract relevant information from medical records, and billing data will be obtained and recorded for economic analyses.
- Treatment decision patterns: Regarding assessment, patterns in treatment decisions, considering tumor characteristics and patient preferences, will be assessed through medical records and clinician interviews. Regarding collection, data collection personnel will document treatment decisions in the study database based on comprehensive reviews of medical records.
- Economic and psychosocial impact: Regarding assessment, economic and psychosocial impact assessments will be conducted through standardized tools and interviews. Regarding collection, trained personnel will administer economic and psychosocial assessments, and the results will be recorded in the study database.
- AEs and complications: Regarding assessment, continuous monitoring and medical records review will assess AEs and complications. Regarding collection, data collection personnel and safety monitoring teams will document AEs and complications in the study database.
- Stratification factors: Regarding assessment, stratification factors, including tumor stage and patient demographics, will be assessed at baseline. Regarding collection, data collection personnel will collect baseline information during participant enrollment and document it in the study database.
- Data quality assurance: Regarding assessment, regular audits and validation checks will continuously monitor data quality. Regarding collection, data management personnel will conduct routine quality checks to ensure the accuracy and completeness of the collected data.
- Data security and confidentiality: Regarding assessment, data security and confidentiality measures will be assessed through regular reviews and audits. Regarding collection, data management personnel will implement encryption, access controls, and other security measures to protect participant information.
- Reporting and analysis: Regarding assessment, reporting and analysis plans will be periodically reviewed and updated as needed. Regarding collection, the statistical team will conduct blinded data analyses to generate reports for internal and external stakeholders.

The plans to promote participant retention and completion of follow-up are as follows:

- Participant engagement initiatives: Implement a comprehensive plan to maintain ongoing communication and involvement. Regularly update participants on the study progress, key findings, and importance of their continued participation.
- Clear communication of study benefits: Communicate the potential benefits of the study to participants. Emphasize the contribution of their data in advancing scientific knowledge and improving lung cancer treatment strategies.
- Educational materials: Develop and distribute educational materials explaining the importance of follow-up assessments. Provide resources that enhance participants' understanding of the study's objectives and their role in contributing to research.
- Participant reminders: Implement a system of reminders for upcoming follow-up visits, assessments, and questionnaire completions. Use multiple communication channels, including emails, phone calls, and text messages, to ensure participants are aware of and prepared for scheduled activities.

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- Flexible follow-up options: Offer flexible options for follow-up assessments, including virtual visits or alternative locations. Accommodate participant preferences to reduce barriers to attendance.
- Incentives for follow-up: Provide reasonable incentives for participants to complete follow-up assessments. Ensure that incentives comply with ethical guidelines and do not compromise the voluntary nature of participation.
- Dedicated study coordinator: Study coordinators will be a consistent point of contact, addressing participant queries and concerns.
- Continuous feedback loop: Establish a constant loop by soliciting participant feedback on their experiences.

Data Management

The LUCENT data management process adheres to rigorous standards to ensure accuracy, integrity, and confidentiality. Standardized data collection forms will gather information consistently across all participating centers. Electronic data capture systems will be employed for efficient and accurate data entry. Regular checks and validations will be implemented to ensure the accuracy and completeness of the collected data. Data quality will be systematically monitored to identify and promptly address any discrepancies or errors. Secure and encrypted servers will be used to store electronic data. Access controls will be implemented to restrict unauthorized access to sensitive information. Stringent security measures, including encryption and secure authentication, will safeguard participant data. Compliance with relevant data protection regulations and guidelines will be maintained. Data will be shared according to appropriate ethical and legal frameworks if applicable. Access to data will be regulated to ensure privacy and confidentiality. A data monitoring committee will ensure that the study is conducted with the highest ethical and scientific standards.

Confidentiality

The aspects of confidentiality are as follows:

- Participant confidentiality: Assign unique identifiers to participants to anonymize data while maintaining linkage to individual records internally. Implement strict access controls to restrict data access to authorized personnel only. Define user roles and permissions based on the principle of least privilege to limit access to specific data sets.
- Data encryption: Apply encryption protocols to protect stored and transmitted data. Encrypt sensitive information to prevent unauthorized access in case of a security breach.
- Confidentiality agreements: All personnel involved in the study must sign confidentiality agreements. Emphasize the importance of respecting participant privacy and the confidential nature of study data. Store physical and electronic data in secure environments. Implement measures such as locked cabinets for physical documents and secure servers for electronic data.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial/Future Use

There will be no collection, laboratory evaluation, or storage of biological specimens.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

The demographic and baseline characteristics and follow-up outcomes will be described as mean, SD, median, and range for continuous variables, and percentage for categorical variables. Descriptive statistics will be calculated for the whole sample and by relevant subgroups (age, gender, diagnosis, etc). Statistically significant differences across groups will be detected using 1-way ANOVA. Multiple linear regression will be performed to investigate the impact of participant characteristics on short- and medium-term outcomes.

This study will use the official Italian EQ-5D-5L questionnaire to measure health and quality of life. The EQ-5D-5L descriptive system includes 5 dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD). Each dimension is articulated into 5 severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems (or unable to). Consequently, 3125 (55) possible health states are determined by response combinations and identified with a unique 5-digit number ranging from perfect health (“11111”) to the worst state (“55555”). Each health state will be converted into a single index value from 0 (assigned to death) to 1 (perfect health state), using predefined preference weights collected at the population level.

All statistical analyses will be performed using R software (R Project for Statistical Computing).

Interim Analyses

Interim analyses will be conducted at predetermined intervals to assess the study’s safety, efficacy, and futility. The analyses will be planned to coincide with critical milestones, such as the completion of a specific percentage of follow-up assessments or the occurrence of a predefined number of events. An independent data monitoring committee will be established to oversee interim analyses. The data monitoring committee will consist of experts in the field, statisticians, and clinicians who are not directly involved in the day-to-day conduct of the study. The data monitoring committee will have exclusive access to interim results. Unblinded provisional data will be shared with the data monitoring committee for their assessment of safety, efficacy, and overall study progress.

Clear stopping guidelines will be established in advance, outlining the criteria for stopping the trial. Controlling guidelines will include considerations for both safety and efficacy, with predefined thresholds for statistical significance. The trial may be stopped for the following reasons:

- Efficacy: If interim analyses demonstrate overwhelming evidence of benefit, meeting predetermined criteria for early success.
- Safety: If there is a significant safety concern, meeting predefined criteria for harm.
- Futility: If interim analyses indicate that the study is unlikely to achieve its primary objectives.

The principal investigator and the steering committee will take the final decision to terminate the trial. The steering committee,

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comprising key study investigators, will consider the data monitoring committee's recommendations and ultimately take a decision.

A clear communication plan will be in place to ensure timely and transparent reporting of interim results to relevant stakeholders. Communication channels will be predefined to facilitate the efficient dissemination of information. Any decision to stop the trial will be promptly reported to relevant ethical review boards and regulatory authorities. Transparent reporting ensures compliance with ethical standards and regulatory requirements.

Methods for Additional Analyses

Other studies, including subgroup and adjusted analyses, will explore variations in treatment effects among different patient subgroups. Adjusted analyses will account for potential confounding factors, such as baseline characteristics and comorbidities, that may influence study outcomes. Statistical methods, such as regression models and stratification, will be employed to assess the impact of variables on study outcomes.

Predefined subgroup analyses will be based on key demographic and clinical variables, such as age, tumor stage, and treatment modality. Criteria for conducting subgroup analyses will be established to avoid data-driven post hoc analyses, and exploratory analyses may be performed to generate hypotheses for future research. Sensitivity analyses will assess the robustness of findings by varying assumptions or statistical methods.

Multiplicity issues in subgroup analyses will be addressed by adjusting significance levels and applying appropriate statistical corrections, such as Bonferroni adjustments, to control for type I errors. Guidelines for interpreting additional analyses will be established, distinguishing between confirmatory and exploratory findings. Reporting standards will be adhered to, and results will be presented with effect sizes, CIs, and *P*-values for transparency and reproducibility.

The findings of additional analyses will be reviewed to ensure methodological rigor and validity. Publication policies will be defined, and any deviations from the original study protocol will be disclosed. Additional analysis findings will be communicated to relevant stakeholders, including study sponsors, regulatory authorities, and the scientific community, providing context for interpretation and discussing the implications on the overall study results.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

The primary analysis will adhere to the intention-to-treat (ITT) principle with consideration of participants based on their randomized treatment assignment. Protocol nonadherence, such as deviations from the assigned treatment, will be captured and addressed in sensitivity analyses, including per-protocol analyses.

Sensitivity analyses will be conducted to assess the impact of protocol nonadherence on study outcomes. These analyses may include per-protocol analyses, where only participants strictly adhering to the protocol are considered, providing insights into the robustness of the primary ITT analysis.

Multiple imputation methods will be employed to handle missing data. Missing data patterns will be carefully examined, and imputation models will be used to estimate missing values based on observed data, enhancing the completeness of the data set. The missing data mechanism will be assessed to inform the selection of appropriate imputation methods with consideration of mechanisms such as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).

Imputation models that account for variables associated with missing data, including baseline characteristics, treatment assignment, and relevant covariates, will be developed. The number of imputations will be specified to ensure sufficient imputations to capture uncertainty associated with missing data, commonly using 5 or 10 imputations.

Sensitivity analyses will compare results from the imputed data set with those from observed data to assess the impact of imputation on study outcomes. The methods used to handle missing data will be reported in study publications, transparently communicating any assumptions made during imputation and their potential implications on the study findings.

External validation of imputation models will be considered to enhance the generalizability of imputed data. Collaboration with statistical experts will be sought to ensure the appropriateness and rigor of the chosen methods for handling missing data, with input from experts during the planning phase to adapt methods as needed based on recommendations.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

LUCENT has plans to make the full study protocol publicly accessible, allowing interested parties to review the details of the study. Additionally, the intention is to grant public access to the participant-level data set, promoting transparency and openness in sharing study data. The statistical code used for data analysis will also be made available to the public, allowing researchers and analysts to understand and evaluate the study's statistical methods.

For dissemination, reputable data-sharing platforms or repositories will be considered to host the protocol, participant-level data set, and statistical code. The study will ensure compliance with ethical standards and legal requirements when granting public access, prioritizing participant confidentiality. Evaluation of embargo periods before public release may allow researchers involved in the study to publish primary findings before more comprehensive access is granted.

Clear documentation outlining the terms and conditions for using the participant-level data set and statistical code will be developed. This includes guidelines to ensure responsible and ethical use of the shared data. To enhance the visibility and accessibility of study-related information, collaboration with reputable data repositories or platforms specializing in hosting and sharing research data will be sought.

Effective communication strategies will be implemented to inform the research community and the public about the

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availability of the study protocol, participant-level data set, and statistical code. Continuous updates will ensure the most recent protocol version and related materials are accessible to the public. The study aims to foster transparency, collaboration, and reproducibility in research by sharing key study components openly.

Oversight and Monitoring

The composition of the coordinating center and trial steering committee will be decided. Moreover, the composition of the data monitoring committee, its role, and its reporting structure will be decided.

AE Reporting and Harm

A systematic approach will be employed to collect AEs, encompassing solicited and spontaneously reported events. A standardized assessment process will be in place to evaluate the severity, causality, and expectedness of each noted AE, with clearly defined criteria for categorizing events as serious AEs.

Reporting mechanisms for solicited and spontaneously reported AEs will be established, and investigators and site personnel will receive training on proper reporting procedures. The study will have a robust system for managing AEs, including immediate actions for severe or unexpected events. It will provide appropriate medical intervention and follow-up for affected participants.

Thorough documentation of each AE will be maintained, including details about onset, duration, resolution, and any actions taken. Data on AEs will be included in study reports and publications. AEs meeting the criteria for reporting to ethics committees and regulatory authorities will be promptly communicated following local regulations and ethical guidelines.

Consideration may be given to establishing a safety monitoring committee to independently review and assess safety-related data and provide recommendations for the trial's continuation, modification, or termination based on safety considerations.

During the informed consent process, participants will be informed about potential risks and AEs associated with the trial interventions. Regular communication with participants will be maintained to encourage reporting any AEs experienced during the study.

A comprehensive data safety and monitoring plan will be developed, outlining procedures for collecting, assessing, reporting, and managing AEs. The plan will be followed diligently to ensure the highest standards of participant safety.

AE reporting procedures will undergo continuous review, allowing for adaptation based on emerging safety data or changes in the risk-benefit profile of the trial interventions.

Frequency and Plans for Auditing Trial Conduct

Trial conduct will be audited at planned intervals throughout the study. Procedures for auditing will be detailed to comprehensively examine aspects such as protocol adherence, data integrity, participant safety, and regulatory compliance. The auditing process will be independent of investigators and the sponsor, possibly involving external auditors or separate entities to maintain objectivity.

The scope of audits will cover various aspects, including adherence to the study protocol, informed consent processes, data collection and management procedures, monitoring of AEs, and regulatory compliance. Site selection for audits will be based on risk assessment with consideration of factors like the number of enrolled participants, data quality, and historical site performance, with both random and targeted site selection strategies.

Comprehensive audit reports will be generated, documenting findings, observations, and any identified deviations from the study protocol or regulatory requirements. Recommendations for corrective actions will be included in these reports. In response to audit findings, corrective and preventive measures will be implemented promptly, with collaboration between the study team and auditors to address identified issues.

Audit results, including findings and actions taken, will be communicated to relevant stakeholders to ensure transparency and accountability. The auditing process will be part of the continuous monitoring and improvement framework of the study, informing ongoing quality assurance measures to enhance the overall integrity of the trial. As required, significant audit findings impacting participant safety or data integrity will be reported to regulatory authorities to maintain regulatory compliance.

Plans for Communicating Important Protocol Amendments to Relevant Parties

A transparent communication strategy will be employed to disseminate information about essential protocol amendments. Significant changes will be notified directly to principal investigators, site personnel, and ethical committees (research ethics committees/institutional review boards). Participants will be informed of modifications that may impact their involvement, emphasizing explicit and understandable communication to maintain trust.

Trial registries will be promptly updated to reflect any protocol changes, ensuring accurate documentation of amendments, including modifications to eligibility criteria, outcomes, and analyses. Journals and publications, if applicable, will be notified of protocol amendments to align with reporting guidelines, and manuscripts will accurately reflect the final protocol.

Regulatory authorities will be informed following local regulations, maintaining timely and compliant reporting for regulatory approval and oversight. Continuous updates will be provided to all relevant parties, ensuring awareness of the study's evolving nature.

Thorough documentation of protocol amendments and associated communications will be maintained for internal use, audits, and regulatory inspections. A feedback mechanism may allow stakeholders to seek clarification or provide input on protocol changes, fostering open communication and collaboration within the research environment.

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Dissemination Plans

The main results of this clinical study will be published in a peer-reviewed scientific journal.

One of the study chairs will write the final publication based on the final analysis performed by the principal investigators.

Co-authors will be the study's principal investigators who participate in designing and drawing up the research project. Investigators of foreign centers may be included as authors depending on their contribution to patient assessments and scientific input.

Discussion

The protocol outlined in LUCENT presents a robust framework for conducting a comprehensive observational study focused on lung cancer patients in Italy. The study's emphasis on real-world data collection and patient registries provides a valuable opportunity to gather longitudinal data on various aspects of patient care and outcomes, particularly in the context of minimally invasive surgery for lung cancer. One key strength of the protocol is its adherence to the ITT principle, ensuring that participants are analyzed based on their randomized treatment assignment. By incorporating sensitivity analyses to address protocol nonadherence and employing multiple imputation methods for handling missing data, the study demonstrates a commitment to rigor and transparency in data analysis. Furthermore, the protocol's plan for auditing trial conduct at regular intervals, independent of investigators and sponsors, underscores the importance of maintaining data integrity, participant safety, and regulatory compliance throughout the study. The comprehensive audit reports and corrective actions in response to findings reflect a proactive approach to quality assurance and risk management. The protocol also highlights the importance of transparent communication regarding protocol amendments, ensuring that relevant parties are informed of any significant changes that may impact the study's conduct or outcomes. By prioritizing clear and explicit communication with participants, ethical committees, and other stakeholders, the study aims to uphold trust and accountability in its research practices. Regarding data sharing and dissemination, the protocol outlines plans to make the full study protocol, participant-level data set, and statistical code publicly accessible. By leveraging reputable data-sharing platforms and repositories, the study aims to promote research transparency, collaboration, and reproducibility while prioritizing participant confidentiality and ethical data use. Overall, the LUCENT protocol demonstrates a comprehensive and meticulous approach to conducting an observational study in lung cancer research. By incorporating robust methods for data analysis, quality assurance measures, and transparent communication strategies, the study sets a strong foundation for generating valuable insights into the outcomes of lung cancer patients undergoing minimally invasive surgery in Italy.

While the LUCENT protocol presents a comprehensive framework for investigating the outcomes of lung cancer patients in Italy, several limitations should be considered. The study's reliance on voluntary participation may introduce selection bias, as patients who agree to participate will differ systematically from those who decline. This could impact the generalizability of the findings to the broader population of lung cancer patients. Despite rigorous data collection processes, the accuracy and completeness of the collected data may be subject to human error or inconsistencies across participating centers. The study's focus on lung cancer patients in Italy may limit the generalizability of the findings to other populations with different health care systems, demographics, or treatment practices. Maintaining high follow-up rates over the study duration may be challenging, particularly if patients experience barriers to participation or drop out due to personal reasons. Lower follow-up rates could introduce bias and affect the validity of longitudinal outcome assessments. The absence of external funding for LUCENT may pose challenges regarding resource allocation, data collection, and study implementation. Limited resources could impact the scale and scope of the study, potentially affecting its ability to achieve comprehensive and robust outcomes. While the protocol emphasizes obtaining informed consent and ethical approval, ethical considerations concerning data privacy, participant confidentiality, and potential risks to participants' well-being must be monitored and addressed throughout the study. The study's reliance on specific surgical approaches and centers in Italy may limit the external validity of the findings, particularly in regions with different health care infrastructure or surgical practices. Collaboration with international partners could enhance the study's external validity.

Data Availability

Data and materials related to the study are available upon request.

Authors' Contributions

LB, OC, and RC are the principal investigators; they conceived the study and led the proposal and protocol development. FZ, ML, AB, and LS contributed to the study design and proposal development. LB was the lead trial methodologist. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Collaborating institutions.
[DOCX File , 25 KB - resprot_v13i1e57183_app1.docx]

Multimedia Appendix 2
SPIRIT checklist.
[DOC File , 116 KB - resprot_v13i1e57183_app2.doc]

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Abbreviations

AE: adverse event
GCP: Good Clinical Practice
HRQoL: health-related quality of life
ITT: intention-to-treat
LUCENT: Italian Lung Cancer Observational Study
NSCLC: non-small cell lung cancer
PRO: patient-reported outcome

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Protocol

The Rutgers Omnibus Study: Protocol for Quarterly Web-Based Surveys to Promote Rapid Tobacco Research

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Abstract

Background: Rapid and flexible data collection efforts are necessary for effective monitoring and research on tobacco and nicotine product use in a constantly evolving marketplace. The Rutgers Omnibus Survey (1) provides timely data on awareness and use of new and emerging tobacco products among adults in a rapid manner, (2) provides a platform for measurement experiments to help develop and refine measures of tobacco use that reflect the current marketplace, and (3) generates pilot data for grant applications and scientific manuscripts.

Objective: This study aims to document the first 2 years of the Rutgers Omnibus Study through the reporting of methodology, fielding summaries, and sample characteristics.

Methods: Launched in February 2022 and fielded quarterly thereafter, we survey convenience samples of 2000 to 3000 US adults aged 18-45 years recruited from Amazon Mechanical Turk (MTurk) using the MTurk Toolkit by CloudResearch. The questionnaire includes core and rotating modules and is designed to take approximately 10 minutes to complete through Qualtrics. The fielding duration is approximately 10 days per wave. Each wave includes both unique and repeating participants, and responses can be linked across waves by an anonymous ID.

Results: Sample sizes ranged from 2082 (wave 8, December 2023) to 2989 (wave 1, February 2022), and the 8-wave longitudinal dataset included 10,334 participants, of whom 2477 had 3 or more data points. The cost per complete at each wave was low, ranging from US $2.46 to US $3.27 across waves. Key demographics were consistent across waves and similar to that of the general population, while tobacco product trial and past–30-day use were generally higher.

Conclusions: The Rutgers Omnibus Study is a quarterly survey that is effective for rapidly assessing the use of emerging tobacco and nicotine products and can also be leveraged to conduct survey experiments, generate pilot data, and address both cross-sectional and longitudinal research questions.

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KEYWORDS

survey; tobacco; nicotine; young adults; adults; protocol; Rutgers Omnibus Study; Amazon Mechanical Turk; MTurk

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Introduction

Tobacco companies in the United States have undergone dramatic changes in the marketing and manufacturing of tobacco. Whereas tobacco control efforts have historically focused on cigarette smoking, the marketplace has evolved to include numerous products such as electronic nicotine vaping devices and "tobacco-free" nicotine pouches. Today, the tobacco marketplace is in constant flux, with the emergence of new products, flavors, and packaging styles on a regular basis [1,2], and tobacco use patterns are changing in turn [3,4].

Traditional health behavior surveys, such as the Behavioral Risk Factor Surveillance System (BRFSS), have been slow to respond to the changing marketplace. The most recent BRFSS survey (2022) did not include questions about the newest products, and the limited data about tobacco that are collected are typically not available for many months after data collection. Tobacco-centric surveys, such as the Population Assessment of Tobacco or Health Study (PATH), the National Youth Tobacco Survey (NYTS), and the Tobacco Use Supplement to the Current Population Survey (TUS), have improved our ability to monitor perceptions and use of a wider variety of products, but each wave of data takes months to collect and even longer to release for public analysis. While these studies are ideal for generating nationally representative, generalizable estimates of tobacco use, they are not well suited for rapid and flexible data collection to capture changes in tobacco products, tobacco marketing, and tobacco use in the United States.

With the growing variety of tobacco and nicotine products, there is a critical need to develop and test valid and precise measures for assessing use patterns and perceptions. For example, an investigation into measures of modern oral nicotine product use found substantial variation in the phrasing of questions about these products, calling for the development of common and validated measures [5]. However, large national survey systems are not suited for this purpose. Instead, smaller studies that use convenience samples are sufficient for conducting survey methods experiments [6]. Similarly, academic researchers can also use convenience samples to generate pilot data in support of a funding proposal. However, developing and fielding a separate study for each measurement question or pilot inquiry is both time and cost prohibitive.

In response to these methodological challenges, we designed the Rutgers Omnibus Survey, a serial web-based survey of adults aged 18-45 years designed to capture awareness and use of new and emerging tobacco products. The Rutgers Omnibus Survey serves 3 major functions. First, it provides timely data on the awareness and use of new and emerging tobacco products among adults in a rapid manner. Second, it provides a platform for measurement experiments to help develop and refine measures of tobacco use that reflect the current marketplace. Finally, it generates data to serve as pilot data for grant applications and timely scientific manuscripts among investigators at the Rutgers Institute for Nicotine and Tobacco Studies. The aim of this paper is to document the first 8 waves of the Rutgers Omnibus Survey protocol and describe the characteristics of the study samples.

Methods

Overview

The Rutgers Omnibus is fielded quarterly; although there are minor differences across waves, the primary aspects of survey development and administration are consistent. Each wave's survey is programmed in Qualtrics, a secure web-based survey program, and extensively tested by research staff. All waves recruit a convenience sample of individuals aged 18-45 years from Amazon Mechanical Turk (MTurk), an internet-based crowdsourcing platform that has been used successfully in a number of previous studies related to tobacco use and perceptions [6-10]. We targeted this age range to increase the probability of capturing individuals who use a variety of tobacco and nicotine products, given that prevalence tends to be higher among younger adults, particularly for emerging products [4,11]. Recruitment, informed consent, data collection, and remuneration take place entirely through the internet following the same procedures. We will describe the general protocol and address key differences across waves as necessary.

Questionnaire

The Rutgers Omnibus consists of a core set of items that appear in all waves as well as rotating and 1-time supplemental question modules. The core items that appear in every iteration of the study include batteries on every and current (daily, some days, rarely, and past 30 days) use of cigarettes, electronic nicotine delivery systems, cigars (including traditional and premium, cigarillo, and filtered), smokeless tobacco (ie, moist snuff, chew, and snus), and modern nicotine products (eg, nicotine pouches). Each survey also contains items about product brands and flavors and exposure to tobacco advertising, an item capturing whether respondents have purchased tobacco or nicotine products that are different from their usual products in the past 30 days, and standard demographic questions. Rotating modules that are included periodically include question sets about cessation from tobacco use; product risk perceptions and social norms surrounding tobacco use; use of heated tobacco products, alcohol, and marijuana; use of coupons to purchase tobacco products; and mental health status.

One-time batteries may be added to a wave on an ad hoc basis for the purposes of generating pilot data or testing survey questions. Examples of such modules include split-sample experiments testing the impact of question wording, randomized experiments exploring variations in warning labels and ad features, and items that expand upon the core batteries by examining them in greater depth.

At all waves, the questionnaire is designed to take approximately 10 minutes to complete, depending on the number of products a respondent report using.

Recruitment, Data Collection, and Data Quality

Omnibus participants are recruited from among eligible workers on MTurk using the MTurk Toolkit by CloudResearch (formerly known as TurkPrime), in order to enhance control over data quality [7]. CloudResearch regularly monitors MTurk worker engagement in order to identify individuals who are most likely to provide high-quality data. For all waves, we specify the

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following eligibility parameters: aged 18-45 years, located in the United States, and identified as high quality by CloudResearch-approved participant status. We further specify that CloudResearch should block workers coming from suspicious geocodes and duplicate IP addresses, as well as verify the country location of workers. Finally, CloudResearch ID numbers are assigned in place of participants' Amazon ID numbers to ensure anonymous participation.

Individuals who meet all eligibility criteria receive an invitation in the form of an MTurk Human Intelligence Task. The Human Intelligence Task briefly describes our survey, and interested workers can choose to participate by clicking on a link to the survey, which is programmed in Qualtrics. Before beginning the survey, respondents must provide informed consent and verify their age. While the Omnibus is not designed to be a panel study, previous participants are eligible to complete a later wave.

Upon completing the survey, respondents are assigned a randomly generated redemption code, which they then submit to the CloudResearch platform in order to claim payment. Redemption codes entered on the platform are compared with the list of codes that were generated by Qualtrics to verify participation before payment is issued.

Sample Size and Composition

At each wave, our primary goal is to collect high-quality data rapidly, to facilitate efficient monitoring of tobacco and nicotine product features and use. For this reason, we have no prespecified target sample sizes and instead target a fielding period of approximately 10 days. However, in waves that include a supplemental split-sample experiment, we have extended the fielding period in order to recruit enough participants to yield adequate statistical power, approximately 2500 participants. We decided to exit the field based on a combination of fielding duration, reaching a target sample size, and daily yield.

As the Omnibus is not primarily designed to be a panel study, a secondary goal at each wave is to maximize participation among eligible workers that have not taken part in previous waves of the study. CloudResearch enables the exclusion of individuals who have completed previous study waves. We have used this feature iteratively, whereby excluding some or all previous participants at a survey's launch and slowly increasing the pool of previous participants, starting with the oldest iteration of the study (eg, allowing those who had participated in wave 1 but no subsequent waves), as the rate of daily participation declines.

Ethical Considerations

The Omnibus protocol was reviewed by the Rutgers institutional review board and approved as exempt, category 2(i), because it involves ordinary survey procedures and data are collected such that participants' identities cannot be readily ascertained. All participants are presented with an informed consent document, which includes that participation in the survey and responding to any questions therein are completely voluntary, before beginning the study; consent is indicated by clicking "I Agree" (clicking "I Do Not Agree" will terminate the survey). No identifying information is collected by the survey and CloudResearch ID numbers are assigned in place of participants' Amazon ID numbers to ensure anonymous participation. Verified respondents in waves 1 through 6 were paid US $1.50 for completing the survey, which is consistent with similar MTurk tasks and a rate of approximately US $9 per hour; compensation was increased to US $2.00 beginning in wave 7 to combat slowed recruitment.

Statistical Analysis

Although data collection is anonymous, we are able to identify unique (participated in 1 wave only) and repeated respondents (participated in multiple waves) according to participants' anonymized CloudResearch ID numbers. Therefore, we are able to maintain single-wave, serial cross-sectional (all waves, unique individuals only), and longitudinal (all waves, linked by anonymous ID) datasets, enabling a variety of analyses including cross-sectional and longitudinal studies. At each wave, cost per complete was calculated by dividing the total amount paid to CloudResearch, including participant incentives and additional fees charged by CloudResearch, by the final number of participants for each wave of the survey.

Results

The study launched in February 2022 and proceeded approximately quarterly thereafter. As shown in Table 1, the total number of participants ranged from 2082 (wave 8) to 2989 (wave 1), and the percentage of respondents who were new to the Omnibus survey, after wave 1, ranged from 70.5% (wave 2) to 19.9% (wave 6). The cost per complete at each wave was low, ranging from US $2.46 to US $3.27. The serial cross-sectional dataset for waves 1-8 contains 5822 participants, of whom all have participated in exactly 1 wave. The longitudinal dataset for waves 1-8 includes 10,334 participants, of whom 2477 had 3 or more data points.

Table 2 summarizes the demographic and tobacco use characteristics of Omnibus participants by wave, which have been largely consistent throughout the study. The majority of participants in each wave were aged 25-45 years, non-Hispanic White, and college educated, and about 55% to 60% were female. Roughly three-quarters of participants in each wave had ever smoked cigarettes, and prevalence of past–30-day smoking ranged from 32% to 36.3%. The trial of e-cigarettes was reported by nearly half of each wave's participants (range 45.3%-49.9%), with past–30-day prevalence ranging from 19% to 24.4%. Of those who reported ever smoking cigars, almost 60% of each sample, past–30-day prevalence ranged from 12% to 14.8%. Smokeless tobacco product use was less common, with trial and past–30-day use ranging from 14.8% to 17.7% and from 3.3% to 5.6%, respectively. Finally, the nicotine pouch trial ranged from 5.5% to 8.5% over the 8 waves, while past–30-day use increased from 0.8% in wave 1 to 4.2% in wave 8.

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Table 1. Fielding summary, Rutgers Omnibus Study waves 1-8 (February 2022 to December 2023).

Wave	Month and year	Total participants, N	New participants, n (%)	Cost per complete (US $)
1	February 2022	2989	2989 (100)	2.48
2	May 2022	2964	2091 (70.5)	2.49
3	August 2022	2526	1679 (66.5)	2.46
4	December 2022	2307	1243 (53.9)	2.46
5	February 2023	2530	877 (34.7)	2.46
6	May 2023	2518	501 (19.9)	2.46
7	August 2023	2174	443 (20.4)	2.87
8	December 2023	2082	503 (24.2)	3.27

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Table 2. Sample demographic and tobacco or nicotine product use characteristics at each wave, Rutgers Omnibus Study waves 1-8 (February 2022 to December 2023)

	Wave 1 (n=2989), n (%)	Wave 2 (n=2964), n (%)	Wave 3 (n=2526), n (%)	Wave 4 (n=2307), n (%)	Wave 5 (n=2530), n (%)	Wave 6 (n=2518), n (%)	Wave 7 (n=2174), n (%)	Wave 8 (n=2082), n (%)
Age range (years)								
18-24	323 (10.8)	308 (10.4)	283 (11.2)	239 (10.4)	230 (9.1)	210 (8.3)	176 (8.1)	144 (6.9)
25-34	1363 (45.6)	1360 (45.9)	1142 (45.2)	1023 (44.3)	1074 (42.5)	1118 (44.4)	940 (43.2)	870 (41.8)
35-45	1303 (43.6)	1296 (43.7)	1101 (43.6)	1045 (45.3)	1226 (48.5)	1190 (47.3)	1058 (48.7)	1068 (51.3)
Sex								
Male	1297 (43.4)	1325 (44.7)	979 (38.8)	927 (40.2)	1110 (43.9)	1030 (40.9)	886 (40.8)	807 (38.8)
Female	1691 (56.6)	1639 (55.3)	1546 (61.2)	1377 (59.8)	1419 (56.1)	1487 (59.1)	1288 (59.2)	1275 (61.2)
Race and ethnicity								
Non-Hispanic White	1527 (68.2)	2026 (68.4)	1722 (68.2)	1547 (67.1)	1699 (67.2)	1687 (67)	1444 (66.4)	1400 (67.4)
Hispanic	206 (9.2)	281 (9.5)	278 (11.0)	243 (10.5)	283 (11.2)	261 (10.4)	236 (10.9)	205 (9.9)
Non-Hispanic Black	231 (10.3)	310 (10.5)	259 (10.3)	236 (10.2)	256 (10.1)	272 (10.8)	227 (10.4)	228 (11.0)
Non-Hispanic Asian	161 (7.2)	209 (7.1)	146 (5.8)	152 (6.6)	174 (6.9)	168 (6.7)	143 (6.6)	126 (6.1)
Non-Hispanic other	24 (1.1)	30 (1.0)	25 (1.0)	31 (1.3)	22 (0.9)	19 (0.8)	19 (0.9)	19 (0.9)
Non-Hispanic multiracial	90 (4.0)	107 (3.6)	94 (3.7)	98 (4.3)	96 (3.8)	111 (4.4)	105 (4.8)	100 (4.8)
Education								
High school graduate or below	387 (13.0)	395 (13.3)	316 (12.5)	312 (13.5)	316 (12.5)	324 (12.9)	309 (13.1)	269 (12.9)
Associate degree or some college	947 (31.7)	979 (33.0)	916 (36.3)	811 (35.2)	813 (32.1)	816 (32.4)	719 (33.3)	697 (33.5)
Bachelor’s degree	1185 (39.7)	1170 (39.5)	918 (36.4)	842 (36.5)	985 (38.9)	977 (38.8)	832 (38.4)	801 (38.5)
Master’s degree or above	469 (15.7)	420 (14.2)	375 (14.9)	341 (14.8)	415 (16.4)	401 (15.9)	314 (15.2)	315 (15.1)
Cigarettes								
Ever	2271 (76.0)	2242 (75.6)	1873 (74.2)	1694 (73.4)	1905 (75.3)	1888 (75.0)	1634 (75.2)	1554 (74.6)
Past 30 day	1086 (36.3)	992 (33.5)	834 (32.0)	787 (34.1)	903 (35.7)	898 (35.7)	765 (35.2)	691 (33.2)
e-Cigarettes								
Ever	1453 (48.6)	1478 (49.9)	1280 (50.7)	1150 (49.9)	1205 (47.7)	1196 (47.5)	973 (44.8)	943 (45.3)
Past 30 days	707 (23.7)	707 (23.9)	615 (24.4)	561 (24.3)	599 (23.7)	573 (22.8)	468 (21.5)	396 (19.0)
Cigars								
Ever	1795 (60.1)	1782 (60.1)	1483 (58.7)	1380 (59.8)	1484 (58.7)	1493 (59.3)	1219 (56.1)	1194 (57.3)
Past 30 days	418 (14.0)	426 (14.4)	355 (14.1)	328 (14.2)	332 (13.1)	372 (14.8)	263 (12.1)	250 (12.0)
Smokeless tobacco								
Ever	493 (16.6)	522 (17.7)	442 (17.5)	429 (18.6)	444 (17.6)	371 (14.8)	323 (14.9)	332 (16.0)
Past 30 days	98 (3.3)	100 (3.4)	81 (3.2)	100 (4.3)	142 (5.6)	104 (4.1)	74 (3.4)	69 (3.3)
Nicotine pouches								
Ever	165 (5.5)	217 (7.3)	147 (5.8)	165 (7.2)	156 (6.2)	155 (6.2)	156 (7.2)	178 (8.5)
Past 30 days	25 (0.8)	79 (2.7)	53 (2.1)	64 (2.8)	86 (3.4)	78 (3.1)	68 (3.1)	87 (4.2)

Discussion

Principal Findings

The Rutgers Omnibus is fielded quarterly, beginning in February 2022, among an internet-based sample of US adults aged 18-45 years recruited from vetted MTurk workers through CloudResearch. Although a convenience sample, MTurk samples have fairly good geographic distribution, and the distribution of key demographic and socioeconomic characteristics are comparable to the US general population [6-8]. For the purposes of researching tobacco and nicotine product use, our MTurk samples have been particularly useful,

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with trial and past–30-day use prevalence exceeding those in national surveillance studies. For example, e-cigarette trial was reported by about 24% of the 2022 BRFSS sample, and current use by only 5%, as compared with nearly half and one-fourth of our samples, respectively [12]. Indeed, while Omnibus samples are not representative of all US adults, they are ideal for reaching individuals who use or are exposed to various emerging tobacco products. Moreover, we are able to recruit 2000 to 3000 participants for each wave within 10 days of fielding at a low cost and process the data for analysis immediately, making Omnibus especially useful for rapid monitoring and timely research of emerging products.

A key feature of the Rutgers Omnibus is our ability to generate both cross-sectional and longitudinal datasets while still maintaining the anonymity of participants. Although new workers join each month, the pool of eligible workers that have never participated in a Rutgers Omnibus survey shrinks with each iteration of the study. While including an increasing number of repeating participants requires vigilance for evidence of worker fatigue and panel conditioning [13], it has the advantage of producing data that can be used for multiple types of analyses.

The frequency and rapidity of the Omnibus study also make this a useful source of pilot data for project planning and grant proposals, as well as survey methods experiments. Requests to add supplemental measures to a specific wave of data collection, granted on an ad hoc basis, have resulted in several scholarly works and support for numerous grant proposals since the study's inception [9,10].

Limitations

This protocol is not without limitations. First, as a convenience sample of MTurk workers with unknown selection probability, the results of Omnibus analyses cannot be considered representative of all US adults or of adults aged 18-45 years. However, it is worth noting that such inferences are not necessary in the context of rapid surveillance when the goal is to identify signals rather than estimate population prevalence. In addition, representative samples are not necessary for survey experiment studies, where the focus is on maximizing internal validity, or for generating pilot data.

A second limitation is the potential for panel conditioning, especially as the pool of unique MTurk workers becomes smaller over time. However, existing evidence indicates that panel conditioning is most likely when study waves take place 1 month apart or less, and the literature on panel conditioning across study waves that are less frequent, such as ours, is divided [14]. To combat this, we have begun applying strategies to reduce the impact of conditioning, including diversification of questions wave to wave and reduction in survey length, with a focus on fielding rapidity over target sample size. As well, we have the ability to exclude repeated participants for primary or sensitivity analyses.

Conclusions

The Rutgers Omnibus Study is a quarterly rapid survey that can also be leveraged to conduct survey experiments, generate pilot data, and address both cross-sectional and longitudinal research questions. Future waves of data collection will continue to follow this protocol.

Data Availability

The datasets generated during and/or analyzed during this study are not publicly available because our informed consent did not specify the secondary use of the data.

Authors' Contributions

CDD initially conceived the study, and all authors contributed to its design and oversight. MTBM wrote the first draft of the manuscript, and all authors participated in the review and approval of the manuscript for publication.

Conflicts of Interest

OG has received consulting fees from the National Academy of Science, Engineering, and Medicine. The other authors have no conflicts of interest to declare.

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Abbreviations

BRFSS: Behavioral Risk Factor Surveillance System
MTurk: Amazon Mechanical Turk
NYTS: National Youth Tobacco Survey
PATH: Assessment of Tobacco or Health Study
TUS: Tobacco Use Supplement to the Current Population Survey

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Protocol

A Self-Administered Eating Behavior Scale for Patients With Heart Failure Living at Home: Protocol for a Mixed Methods Scale Development Study

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Abstract

Background: The prevalence of heart failure (HF) is increasing worldwide, with the associated mortality rates rising consistently. Preventing HF progression requires adherence to restricted sodium intake alongside sufficient and balanced nutritional consumption. For patients at home, preparing nutritionally balanced meals is essential, either self-assisted or with the aid of close individuals. Patients with HF frequently experience decreased exercise tolerance, depression, anxiety, and social isolation, which interfere with eating behaviors, leading to inadequate dietary habits. However, measures focusing on the determinants of eating behavior among patients with HF are currently lacking.

Objective: This study aims to develop a self-administered scale to assess the eating behaviors of patients with HF living at home (Self-Administered Eating Behaviors Scale for Heart Failure [SEBS-HF]).

Methods: This study encompasses 3 phases. Phase 1 involves identifying factors influencing eating behaviors in patients with HF. First, a literature review will be conducted using PubMed and CINAHL databases. The specified literature will be analyzed qualitatively and inductively. Additionally, verbatim transcripts obtained from semistructured interviews of patients with HF and medical experts will be qualitatively analyzed. Based on the Phase 1 results, a preliminary scale will be constructed. In Phase 2, cognitive interviews will be conducted with patients with HF and experts; the preliminary scale will be used to qualitatively evaluate its content validity. After validation, the scale will be used in Phase 3 to conduct a cross-sectional study involving patients with HF. In Phase 3, data will be collected from clinical records and self-administered questionnaires or scales. After conducting a preliminary survey, the main survey will be conducted. The reliability and validity of the scale will be assessed using statistical methods.

Results: The first phase of this study commenced in September 2023, and by May 2, 2024, a total of 7 patients with HF and 6 expert professionals were enrolled as study participants. The draft creation of the scale will be completed in 2024, and the content validity evaluation of the draft scale is expected to be finished by early 2025. The third phase will begin its investigation in mid-2025 and is expected to be completed by late 2025, after which the SEBS-HF will be published.

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Conclusions: The development and use of this scale will enable a more comprehensive evaluation of the factors influencing eating behaviors in patients with HF. Thus, medical and welfare professionals should provide appropriate support tailored to the specific needs of patients with HF.

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KEYWORDS

heart failure; eating behavior; self-care; patient-reported outcome measures; International Classification of Functioning, Disability, and Health (ICF)

Introduction

Heart failure (HF) is a clinical syndrome characterized by signs and symptoms resulting from a structural or functional impairment in ventricular filling or blood ejection [1]. HF is a global pandemic, with its prevalence steadily increasing globally, coupled with a consistent increase in associated mortality rates [2]. The prevalence of HF in Japan is estimated to be between 2.2% and 6.5% [3], with HF-related deaths accounting for 6.3% of all mortalities [4]. Given the context of a super-aged society, Japan is currently facing an HF pandemic [5].

Effective self-care for patients with HF primarily involves medication adherence, dietary habits, and physical activity [1]. Self-care measures, such as the European Heart Failure Self-care Behavior Scale (EHFScBS) [6] and the Self-Care of Heart Failure Index (SCHFI) [7], are widely recognized. A Japanese version of the EHFScBS has been developed and used [8]. Patients who adhered to appropriate self-care, as indicated by their EHFScBS scores, had significantly fewer hospitalizations due to all causes than those who did not [9]. The EHFScBS and SCHFI, which include dietary habits as part of self-care, primarily evaluate patient adherence.

Dietary recommendations for preventing HF progression and its associated adverse events are based on balancing sodium restriction with adequate nutrient intake [1]. Concerning low-sodium diets, large-scale randomized controlled trials have demonstrated that stringent sodium restrictions have limited benefits [10]. Therefore, a moderately low-sodium diet and adequate nutritional intake are recommended. However, a low-sodium diet often leads to inadequate intake of macronutrients and micronutrients [11,12]. HF comorbidities, including malnutrition, are known to affect prognosis adversely [13]. In addition, maintaining a balanced diet after discharge from the hospital is crucial to prevent HF progression. Home dietary management entails selecting suitable ingredients and meals, purchasing and preparing them, and making associated decisions. The term “eating behavior” broadly encapsulates these series of actions and decision-making processes [14].

The Brief Dietary Psychosocial Scale (BDPS) is an instrument that targets adolescents and adults, focusing on psychosocial factors and external environments that influence healthy dietary habits, such as the consumption of fruits, vegetables, fiber/whole grains, and fats [15]. The BDPS assesses whether individuals perceive the benefits they derive from a healthy diet, whether they are trying to maintain or change to a healthy diet, whether they are receiving social support for the diet, whether healthy food ingredients are physically and economically accessible, and whether they are enjoying following a healthy diet. The reliability of this scale has previously been evaluated in patients with HF [16].

The Dietary Sodium Restriction Questionnaire (DSRQ) is designed to assess attitudes, subjective norms, and perceived behavioral control related to dietary sodium restriction in patients with HF and hypertension [17]. Of the 3 DSRQ subscales, the subjective norms are predictive factors for adherence to a low-sodium diet [18].

The Burden Scale In Restricted Diets (BIRD) is a specific instrument developed to assess the burden of low-sodium diets in patients with HF [19]. This questionnaire comprises 14 candidate items for the following dietary-related domains: organization, pleasure, leisure, social life, vitality, and self-rated health.

The International Classification of Functioning, Disability, and Health (ICF) is a framework developed by the World Health Organization that categorizes and describes the health and disability status of individuals [20]. Under the ICF framework, eating behavior pertains to activities and participation domains. Patients with HF often experience decreased exercise tolerance [21], depression, and anxiety [22], which fall under the domains of body function and structure, and social isolation [23], included in the environmental factors domain. These conditions among patients with HF may hinder the eating behaviors necessary for proper home dietary management, potentially leading to acute decompensated HF.

Existing measures, such as the BDPS, DSRQ, and BIRD, focus on factors influencing healthy eating and low-sodium diets but lack a perspective on eating behaviors and do not focus on the body functions and structures domain in the ICF, corresponding to decreased exercise tolerance in HF.

Despite these reasonable hypotheses, measures focusing on the eating behavior determinants among patients with HF are currently lacking. Therefore, this study aims to develop and validate the Self-Administered Eating Behaviors Scale for Heart Failure (SEBS-HF) to assess the dietary habits of patients with HF living at home.

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Methods

Design and Study Population

This study was designed in accordance with the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) Study Design checklist for patient-reported outcome measurement [24] and the COSMIN methodology for evaluating the content validity of patient-reported outcome measures [25]. The qualitative descriptive investigation in this study adheres to the guidelines outlined in the COREQ (Consolidated Criteria for Reporting on Qualitative Research) checklist [26].

The criteria for identifying patients with HF in this study are defined as follows. The eligible population includes patients aged ≥18 years with symptomatic HF (stage C), according to the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines [1]. Under the Japanese long-term care insurance system, individuals aged ≥65 years are assessed and classified into 7 levels of care needs based on their activities of daily living, cognitive function, and medical conditions. For patients aged ≥65 years, only those yet to receive long-term care certification or those who fall within the range of "Requiring Help 1" to "Long-term Care Level 1" will be included. This is because the SEBS-HF is aimed at home-based patients with HF who can self-manage their diet to some extent, focusing on individuals who are relatively independent but may still require minimal assistance.

The exclusion criteria are as follows: living in care facilities, assisted living facilities, or nursing homes; aged ≤65 years with a disability certificate unrelated to cardiac dysfunction; undergoing hemodialysis because of dietary restrictions different from those of patients with HF; chronic respiratory diseases because of symptoms similar to HF such as reduced exercise tolerance; and mental illnesses because of the potential impact on eating behaviors.

Patients with HF eligible for this study will be recruited from either outpatients or inpatients at the medical institutions where the coresearchers are affiliated and the medical institutions collaborating in this study. Specifically, patients who are attending or admitted to the cardiology departments of these medical institutions will be included.

Experts will be recruited through the network of the principal investigator and coresearchers, and snowball sampling of the initially recommended experts.

Study Composition

Overview

This study is composed of 3 phases (Textbox 1).

Textbox 1. Composition of the study.

Phase 1: Scale draft creation using qualitative descriptive method

- Extraction of factors influencing eating behavior through literature review
- Extraction of factors influencing eating behavior through semistructured interviews with patients
- Extraction of factors influencing patients' eating behavior through semistructured interviews with experts
- Itemization and creation of the scale draft from the scale items obtained

Phase 2: Evaluation of the scale draft's content validity by patients and experts

- Evaluation of the scale draft's face validity and revision of the draft through semistructured interviews with patients
- Evaluation of the comprehensibility, relevance, and inclusiveness of the scale draft and revision of the draft through semistructured interviews with patients
- Evaluation of the relevance and inclusiveness of the scale draft and revision of the draft through semistructured interviews with experts

Phase 3: Evaluation of the reliability and validity of the scale draft through a cross-sectional survey

- Preliminary investigation
- Primary investigation
- Analysis of the data obtained from the primary survey using statistical methods and evaluation of the reliability and validity of the scale draft

Phase 1

In Phase 1, a qualitative descriptive investigation will be conducted to create a preliminary scale.

Phase 1-1

A literature review will be performed to identify factors influencing eating behaviors. For this literature review, the approach by Kraus et al [27] will be followed, and PubMed and CINAHL databases will be used as literature sources. We will consider primary research articles written in English, published within the last 10 years, and available as full texts for our analysis. Keywords such as "heart failure," "eat," "behavior," "diet," "food," "meal," "sodium," and "preparation" will be incorporated in the search to specifically target relevant articles in the context of this study. Additionally, references cited within the selected literature will be manually searched, and any articles identified as relevant to the eating behaviors of patients with HF will be included in the analysis based on their context or titles. The selected literature will be analyzed qualitatively and inductively. Descriptions of factors influencing the eating

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behaviors of patients with HF will be extracted from each source. To maintain the meaning and content, these descriptions will be standardized consistently to illustrate how various factors influence the eating behaviors of patients with HF. The extracted descriptions will be categorized based on their similarities and differences. Multiple researchers will review and verify the categorization to ensure reliability and validity.

Phase 1-2

Semistructured interviews with patients with HF will be conducted to gather insights into the factors influencing their eating behaviors. Interviews will be conducted in person according to an interview guide. Verbatim transcripts generated from the interviews will be returned to the participants for verification and to obtain their comments. Demographic and clinical information, such as age, sex, New York Heart Association (NYHA) functional classification [1], height, weight, HF history, hospitalization due to HF, other medical conditions or history, details of medications, and whether patients received nutritional guidance, will be extracted from their medical records. Information on participants' living arrangements, employment status, perceived financial status, use of community resources, means of transportation to grocery stores, frequency of cooking meals and meal delivery services, presence of cohabitants, and essential characteristics of cohabitants will be collected using a self-administered questionnaire to obtain more data. The age distribution of the targeted patients will encompass the entire age range susceptible to HF, including a minimum of 1 participant aged <50 years, 1 participant in their 60s, and 2 participants each in their 70s and 80s, totaling at least 6 individuals.

Data obtained from medical records and self-administered questionnaires will be analyzed using simple aggregation. Interview transcripts will be collected verbatim and analyzed using Sandelowski's qualitative descriptive approach [28]. The analysis will commence once the data from the 6 patients with HF have been collected. Transcript data collected verbatim from subsequent participants will be included in the analysis, and the process will continue until theoretical saturation is achieved. The analyses will be conducted independently by 2 researchers.

Phase 1-3

Semistructured interviews will be conducted with experts to gather insights into the factors influencing the eating behaviors of patients with HF. The interviews will be conducted following an interview guide, either in person or online. Transcripts generated verbatim from the interviews will be returned to the experts for verification and to obtain their comments. The target experts for the interviews will consist of 6 members, 1 from each specialization area:

1. Certified physicians of the Japanese Society for Clinical Nutrition, specializing in cardiology
2. Certified nurse in chronic HF care
3. Clinical nurse specialist in chronic disease care
4. Certified HF educator
5. Nutrition support team (NST)-specialized therapist
6. Visiting nurse

The NST-specialized therapist and visiting nurse will target individuals with extensive experience caring for patients with HF. Verbatim transcripts from the interviews will be analyzed using Sandelowski's qualitative descriptive approach [28]. The analysis will be conducted independently by 2 researchers.

Based on the results obtained in Phase 1, a set of scale items and a Likert rating scale will be constructed as preliminary scales.

Phase 2

In Phase 2, cognitive interviews with patients with HF and experts will be conducted, using a preliminary scale to evaluate its content validity. The COSMIN guidelines recommended having a sample size of at least 7 participants for qualitative evaluation of content validity [25]. If any issues with the scale are identified through the assessments conducted in Phases 2 and 3, they will be modified as appropriate.

Phase 2-1

The surface validity of the preliminary scale will be assessed through semistructured interviews with patients with HF. Patients with HF will be recruited from a population different from the one used in the previous investigation. The participants will consist of at least 7 individuals, including 1 individual in their 50s and 60s and 2 individuals each in their 70s and 80s. Cognitive interviews and analysis will follow the approach proposed by Willis [29]. Cognitive interviewing allows us to understand respondents' thought processes and identify issues with the scale. This approach involves asking participants to verbalize their thought processes while answering, allowing researchers to detect misunderstandings, ambiguities, and cognitive difficulties. This method ensures the face validity of the scale. The interview guide will be developed based on the questionnaire items created for the preliminary scale. The interviews will be conducted in person following this procedure:

1. Explaining the purpose of measuring the scale to the patients.
2. Showing patients the items on a preliminary scale and requiring them to provide written responses to each question.
3. Once responses are obtained, we will orally confirm the thought process that the patients underwent when answering the questions (think-aloud).
4. We will verbally probe and confirm the content of the question items in more detail, checking if the initial responses align (verbal probing).
5. Steps (2)-(4) will be repeated for all question items.
6. Verifying that no important content relevant to the patient is missing across the entire scale.

The verbatim transcripts obtained from the interviews will be analyzed from the following perspectives:

1. Were there any doubts or concerns regarding the content of the questions?
2. Were the intended responses obtained from the question items?
3. Were there any ambiguities or unclear language expressions in the question items or response choices?

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4. Were there any deficiencies in the questions regarding important content relevant to the participants themselves?

The analysis will be conducted independently by 2 researchers.

Phase 2-2

The clarity, relevance, and comprehensiveness of the preliminary scale will be assessed through cognitive interviews, involving at least 7 patients with HF included in the previous investigations. The interview guide will be developed based on the questionnaire items created for the preliminary scale. The interviews will be conducted in person following this procedure:

1. Participants will read and respond to the paper-based scale.
2. Orally confirming how participants understood the content of the scale questions.
3. Verbally confirming if the scale questions were relevant to their own experiences.
4. Steps (1)-(3) will be repeated for all the question items.
5. Verifying that no important missing content in the scale is relevant to the participant's experiences.

Transcripts will be created verbatim from the interviews, and the assessment will revolve around examining the clarity of each question item, its relevance to patient situations, and the presence of any pertinent information that might be missing. The analysis will be conducted independently by 2 researchers.

Phase 2-3

The relevance and comprehensiveness of the preliminary scale will be assessed through cognitive interviews with experts. The investigation will involve 7 experts, including 6 experts identified in Phase 1-3, and an additional expert who is a nursing faculty member experienced in scale development. These 7 experts will be the target participants and will be distinct from those involved in previous investigations. Interviews will be conducted either in person or online.

1. Participants will read the scale on paper.
2. The questionnaire items will be checked for their relevance to patients with HF.
3. If any questionnaire item is perceived as lacking relevance, its reasons will be investigated.
4. The overall scale will be reviewed to ensure that important content related to patients with HF is not missing.
5. The reasons for perceiving the content as insufficient will be confirmed if it was perceived as such.

Transcripts will be created verbatim from the interviews, and the assessment will revolve around examining its relevance to the patients' situations and the presence of any pertinent information that might be missing. The analysis will be conducted independently by 2 researchers.

Phase 3

We will use the scale scrutinized in Phase 2 to conduct a cross-sectional study involving patients with HF. Data will be collected from the clinical records and self-administered questionnaires or scales. The items are listed in Textbox 2. A cross-sectional survey consisting of preliminary and primary investigations will be conducted. The collection of clinical records data will be conducted with the approval of the medical institution's ethics review board. After obtaining this approval, consent from the eligible patients for their participation in the study will be requested. Clinical records will then be collected from the medical institutions where the co-researchers are affiliated or from the collaborating medical institutions, with the cooperation of both the co-researchers and collaborating researchers.

Textbox 2. Inventory of data obtained from the cross-sectional survey in Phase 3.

Clinical record

- Age, sex, New York Heart Association (NYHA) classification [1], height, weight, heart failure (HF) history, hospitalization due to HF, other existing medical conditions, medical history, medications, and whether nutritional guidance was provided

Self-administered questionnaire of lifestyle situations

- Living arrangements, employment status, perceived financial status, use of community resources, means of transportation to grocery stores, frequency of cooking meals on own, frequency of using meal delivery services, presence of cohabitants, essential characteristics of cohabitants, and frequency of meals prepared by a cohabitant or home helper

Self-administered scales

- The preliminary Self-Administered Eating Behaviors Scale for Heart Failure (SEBS-HF)
- The Japanese version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)
- The Japanese version of the European Heart Failure Self-care Behavior Scale (EHFScBS)
- Established scales for assessing criterion-related validity

Preliminary Investigation

Data will be collected using clinical records, self-administered questionnaires, and the preliminary SEBS-HF. To confirm normality, the sample size will be approximately 30 [30]. In addition, data will be collected from patients attending collaborating medical institutions. The principal investigators collaborating at these institutions will select patients based on established eligibility criteria. Once informed consent has been obtained, the patient's clinical records will also be collected. A survey set, which includes the self-administered questionnaire and preliminary SEBS-HF, will be provided along with a return envelope for data collection. Calculations will be made from the acquired data to determine the mean scores, standard

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deviations, and individual item score distributions. Normality tests will be also performed. Moreover, potential ceiling and floor effects will be examined based on the mean and standard deviation.

Primary Investigation

The reliability and validity of the data acquired from the primary investigation will be examined using statistical methods (Table 1).

Table 1. Statistical analysis procedures and considerations for assessing reliability and validity.

Statistical analysis	Procedure
Descriptive statistics	Measure means, SDs, and frequencies
Normality assessment	Conduct a Shapiro-Wilk test, which calculates a test statistic based on the observed data and compares it against the Shapiro-Wilk distribution.
Item analysis	Evaluate ceiling and floor effects and perform item-total correlation analysis. Items with a correlation coefficient r <0.3 or >0.7 may be considered for removal or integration [31].
Internal consistency	Calculate Cronbach α coefficient. A coefficient of ≥0.7 is considered to indicate internal consistency [32].
Structural validity	Perform an exploratory factor analysis to ascertain the degree of shared variance among the items and elucidate potential factor groupings. The factor structure established through exploratory factor analysis is assessed with confirmatory factor analysis to check its fit with data from a different population.
Criterion validity	Calculate descriptive statistics for the external criterion scale and confirm normality. Then, calculate the correlation coefficient between the criterion scale and the scale under development. The validity is evaluated based on the value of the correlation coefficient.
Construct validity	Calculate the correlation coefficient between subgroups to verify hypotheses. In this scale, it is assumed that aging and the decline in physical and mental functions due to HF[a] symptoms will affect eating behavior negatively. Therefore, verification will be done using age, NYHA[b] classification [1], and certification of care-need level subgroups.
Measurement error	Calculate the intraclass correlation coefficient, SE, and detectable minimum change for the total scale and subscale scores obtained from the first and second tests. The sample size should be >50 participants to verify measurement error. An intraclass correlation coefficient of ≥0.7 is considered to indicate stability [33].

[a]HF: heart failure.

[b]NYHA: New York Heart Association.

In addition to the data collection methods used in the preliminary investigation, the primary investigation will incorporate the test-retest method to assess measurement error and establish scales to evaluate criterion-related validity. In the test-retest method, participants will initially respond to the SEBS-HF and then provide their responses again 2 weeks later. To assess the criterion-related validity of the SEBS-HF, we will select the Medical Outcomes Study 36-Item Short-Form Health Survey [34] and the EHFScBS [8] as external measures. We will request the study participants to provide their responses to these instruments. If more suitable external measures are available when the survey commences, we may opt to use them.

The maximum likelihood method and promax rotation will be used in the exploratory factor analysis. The factor loadings obtained will enable commonality assessment among the questionnaire items. Items with a factor loading exceeding a certain threshold will be selected. Consideration will be given to the excluded items that did not meet this threshold or loaded on multiple factors. If items are excluded, a factor analysis will be performed again.

The factor structure established by exploratory factor analysis will be examined to fit the data collected from different populations. This will be performed using goodness of fit indices (goodness-of-fit index, adjusted goodness-of-fit index, comparative fit index, and root mean square error of approximation) to evaluate the appropriateness of the model. If the fit does not meet specific standards, a review of the questionnaire items or reconsideration of the exploratory factor analysis will be needed.

According to the COSMIN guidelines [24], the sample size should be 5-7 times the number of scale items and not <100. Assuming the scale had 30 items, we planned to include more than 150 participants in the primary investigation. Data from different populations are required to conduct exploratory and confirmatory factor analyses. Therefore, the total sample size should exceed 300 participants.

Ethical Considerations

In Phases 1 and 2, before starting interviews of patients with HF and experts, the research participation details will be explained using a document and written informed consent will be obtained. Consent can be withdrawn within certain time limits by signing and returning a withdrawal form or by email. As compensation for participating in the research, patients with HF received a gift card worth approximately US $20, and experts received a gift card worth approximately US $35 upon the completion of each interview.

In Phase 3, when distributing the set of survey forms to the eligible patients with HF, the research participation details will be explained using a document, and consent will be obtained in a similar manner. The set of survey forms will include a small gift as a token of appreciation for participating in the research.

The Ethics Review Board of the Graduate School of Nursing at Sapporo City University approved this study. The first phase

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of the investigation had already been approved by the Ethics Review Board (No. 4, 2023) on August 30, 2023. This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki.

Results

In the first phase of this study, a literature review was conducted to extract factors influencing eating behavior in patients with HF. On January 26, 2024, a comprehensive search using keywords such as "HF," "diet," "eating behavior," "meal prep*," and "culinary" was performed in databases including PubMed and CINAHL. This search yielded a total of 4145 articles. Relevant literature was selected based on the examination of titles and abstracts to extract the factors influencing eating behavior among patients with HF.

As of May 2, 2024, a total of 7 patients with HF and 6 experts have already been enrolled as study participants.

The draft creation of the scale is scheduled to be completed in 2024, and the evaluation of the content validity of the draft scale is expected to be finished by early 2025. The third phase will begin its investigation in mid-2025 and is expected to be completed by late 2025, after which the SEBS-HF will be published.

Discussion

Expected Findings

This study aims to develop the SEBS-HF to evaluate the eating behaviors of patients with HF living at home. This section discusses how SEBS-HF development might improve the eating behaviors of patients with HF living at home.

Given the concerns surrounding the relationship between malnutrition and adverse outcomes in patients with HF, proper dietary management has emerged as a pivotal factor in enhancing prognosis [35].

Minimal barriers to eating are desirable to maintain appropriate dietary management. According to the ICF framework, negative aspects of body functions and structures, environmental, and personal factors, can affect eating behaviors, which are included in the activities and participation domains. In other words, characteristics specific to heart failure patients, such as frailty [36], depression, and social isolation [37], are expected to influence eating behaviors negatively. Therefore, the SEBS-HF will be designed to quantitatively evaluate and assess the impact on eating behaviors specific to heart failure patients through self-administered evaluations.

Through self-administered evaluations, patients can identify their strengths and weaknesses. Additionally, sharing the evaluation results from the SEBS-HF with medical and welfare professionals can pave the way for individualized patient-centric support. Such assistance enhances the patient's ability to manage their diet appropriately and leads to improved well-being.

Furthermore, as the SEBS-HF is quantified using a Likert scale, if a correlation between the results and adherence to dietary habits and readmission due to acute decompensated HF becomes evident, it could serve as a potent predictor.

Notably, a significant number of patients with HF may have dementia, which affects their self-care. The SEBS-HF is specifically designed for patients with HF who manage their diet at home, without accounting for those patients who require additional assistance because of conditions such as dementia.

Limitations

This study will verify the reliability and validity in accordance with the COSMIN guidelines [24,25], but there are some limitations. First, a longitudinal study must evaluate the responsiveness of the measure or the process of validating the ability of the instrument to detect changes in the measured construct over time. Second, interpretability, which implies setting cutoff values, will not be measured. Following SEBS-HF development, we aim to evaluate the clinical importance of factors such as adherence to dietary habits and readmission due to acute HF to determine appropriate cutoff points. Finally, the cross-cultural validity of the SEBS-HF, explicitly designed for Japanese, remains to be assessed in different linguistic and cultural contexts.

Conclusions

The development and use of this scale will enable a more comprehensive evaluation of the factors influencing eating behaviors in patients with HF. Patients will be able to conduct self-assessments using this scale. Sharing the results with health care professionals will allow patients to identify eating behavior issues, potentially improving dietary adherence. Therefore, medical and welfare professionals will provide appropriate support tailored to their patients' needs.

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Data Availability

The data collected or analyzed during the course of this study will not be made available to third parties. However, upon reasonable request, associated questionnaires and protocols used in the study may be provided by the corresponding author.

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Authors' Contributions

DK conceptualized the study, collected and analyzed data, administered the project, and wrote the original draft. A Hiyama, MM, and A Hinotsu conceptualized the study and contributed to data analysis. MT, NS, SA, SK, and KK recruited and selected patients and experts for interviews. All authors reviewed and edited the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BDPS: Brief Dietary Psychosocial Scale
BIRD: Burden Scale in Restricted Diets
COREQ: Consolidated Criteria for Reporting on Qualitative Research
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
DSRQ: Dietary Sodium Restriction Questionnaire
EHFScBS: European Heart Failure Self-care Behavior Scale
HF: heart failure
ICF: International Classification of Functioning, Disability, and Health
NST: nutrition support team
NYHA: New York Heart Association
SCHFI: Self-Care of Heart Failure Index
SEBS-HF: Self-Administered Eating Behaviors Scale for Heart Failure

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Protocol

Multidimensional School-Based and Family-Involved Interventions to Promote a Healthy and Sustainable Lifestyle (LIVELY) for Childhood Obesity Prevention: Study Protocol

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Abstract

Background: Childhood obesity has become a significant public health concern over the past 2 decades, posing multifactorial challenges, including modifiable factors like dietary habits, physical activity, screen time, and sleeping habits. Prevention efforts require a comprehensive approach comprising educational interventions, collaboration among multidisciplinary teams, and community engagement. Since schools play a central role in children's lives, they are the ideal setting for promoting healthy habits.

Objective: The LIVELY (Multidimensional School-Based and Family-Involved Interventions to Promote a Healthy and Sustainable Lifestyle) study will assess the prevalence of overweight and obesity in primary school children and identify contributing factors within families. Additionally, it aims to implement and evaluate a multidimensional, multidisciplinary intervention to foster a sustainable and healthy lifestyle, ultimately working toward preventing obesity in school-aged children.

Methods: During the school year, each class will be individually involved in a multidimensional educational intervention covering the topics of healthy, sustainable nutrition and lifestyle. Children will also participate in a multimedia lab where they will create an animated cartoon. The lectures will engage them through various methods, including direct instructions, games, and drawing activities, to stimulate and enhance their learning and involvement.

Results: Data collection began in October 2023 and will last until the end of October 2024. A sample of 227 children from 14 classes was included in the study. The mean age was 8.9 (SD 1.2) years, and 48% (n=110) were males. Among the overall sample, 18.1% (n=41; 95% CI 13.7%-23.7%) were overweight, while 5.3% (n=12; 95% CI 3%-9%) had obesity. Males had a higher prevalence of obesity than females (9.1%, n=10 vs 1.7%, n=3, *P*=.03, respectively). Otherwise, the prevalence of central obesity was similar between the two (*P*=.329). Data analysis and the presentation of the complete results will be available after the end of 2024.

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Conclusions: The study could lead to the structuring of an educational intervention model in school settings aimed at preventing childhood obesity. Moreover, it could help raise awareness of childhood obesity and help prevent this public health issue.

Trial Registration: ClinicalTrials.gov NCT05966051; https://clinicaltrials.gov/study/NCT05966051

International Registered Report Identifier (IRRID): DERR1-10.2196/57509

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KEYWORDS

childhood obesity; school education; family education; healthy lifestyle; sustainability; primary prevention; nutritional intervention; physical activity; community engagement; lifestyle habits; socio-economic status; LIVELY study

Introduction

Background

Childhood overweight and obesity have emerged as public health crises, reaching a global dimension [1]. Overweight and obesity prevalence estimates from the fifth round of Childhood Obesity Surveillance Initiative (COSI) data collection (2018-2020), conducted in 33 countries of the World Health Organization (WHO) European Region, indicate that 29% of children aged 7 to 9 years are living with overweight, including 12% with obesity, with Italy ranking fourth highest [2].

Primary factors contributing to obesity in Europe—unhealthy dietary habits, lack of physical activity, high screen time, and poor sleep habits—stand as prominent drivers of preventable fatalities, chronic illnesses, and economic health burdens among young people. These modifiable determinants have been particularly challenged during the COVID-19 pandemic, across all population age groups, including children. The lockdown significantly impacted children's lifestyle habits, contributing to increased sedentary behavior, extended screen time, and higher consumption of calorie-dense and sugary foods [3].

Total screen time, time spent on television, and time spent on the computer are positively correlated with overweight/obesity among children [4]. The pandemic has heightened the use of technology platforms, on the one hand, to facilitate communication and, on the other hand, to facilitate virtual education. Indeed, it has been reported that screen time has increased by about 5 hours per day compared to the pre–COVID-19 period [3]. However, this has exacerbated sedentary habits and increased snack consumption, resulting in weight gain [5]. Prolonged screen time can also affect the quality and quantity of sleep hours [6]. Inadequate sleep negatively influences several aspects of children's and adolescents' lives, including physical and mental health and school performance [7]. Inadequate sleep is also correlated with increased cardiometabolic risk, leading to the onset of impaired fasting blood glucose, dyslipidemia, and increased blood pressure [8]. Along with excessive screen time, inadequate sleep is also associated with unhealthy eating behaviors. This could lead to an increased risk of obesity and overweight as evidenced by recent meta-analyses [9,10]

In such a sensitive and complex scenario, where many factors play a central role in maintaining good health conditions, more evidence-based policies, economic investments, and integrated programs are required [11,12]. In the past decades, several childhood abatement interventions have been carried out to address this issue, but increasing regional and global prevalence trends show that those have had little success [2,13,14]. Scientific evidence described how the "eat less, move more" attitude is too simplistic, and no single intervention can be successful in halting the advancement of the obesity epidemic. Therefore, modern policy actions have been prompted into executing integrated programs, which take into consideration: (1) multicomponent approaches including nutrition, physical activity, sleep hygiene, and so on; (2) multilevel efforts, including individual children, families, and school; and (3) multi-setting interventions, such as primary care clinics, homes, and community centers to prevent, contain, and manage childhood overweight and obesity [2,15,16].

Adherence to the Mediterranean diet (MD) and lifestyle represents a further piece of the puzzle as the primary prevention strategy for obesity recognized by many relevant scientific societies [17]. However, MD adoption has decreased in the past decades in most WHO member states, including countries in the Mediterranean basin and among younger individuals belonging to lower socioeconomic classes [18-20]. According to estimates of the most recent COSI data collected (2018-2020), less than half (43%) of the children in the WHO European Region consumed fresh fruit daily, and even less (34%) ate vegetables daily [2]. According to these data, their level of physical activity remains poor as well. Overall, 40% of children did not spend any time during the week doing sports, while 43% of children aged 6 to 9 years had at least 2 hours a day of screen time, with the prevalence reaching 76% on the weekends [2].

Italy is no exception. The transition toward Western dietary patterns, based on ultraprocessed foods and a sedentary lifestyle, is the consequence of numerous sociocultural and economic factors, such as an increased cost of living, changes in gender roles in society, urbanization, and globalization [21]. In particular, children of migrant backgrounds often shift away from traditional eating habits, increasing their consumption of processed foods, likely due to economic barriers [20,21]. As of January 1, 2020, Italy had 1.3 million children of migrant background aged 0 to 17 years, so it is clear that instilling nutritional education and promoting healthy lifestyle habits within this population group is crucial for reducing childhood obesity rates in the coming years [22].

Since establishing healthy dietary habits at an early age may prevent the onset of chronic diseases later in adulthood, schools have been recognized as powerful settings to provide nutritional and healthy lifestyle education and execute targeted interventions [15,23].

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Archero et al [24] conducted a 2-month cross-sectional study in Novara, including 3 primary and 2 secondary schools, to assess the association between MD and weight status. The authors found a higher prevalence of overweight and obesity and a lower adherence to MD in children attending primary school compared to other schools. Another cross-sectional study was conducted by Paduano et al [25] to investigate the physical/sedentary activities of first-year primary school children in Modena and their association with overweight/obesity and dietary habits. The authors found that 3 out of 4 children spent less than 7 hours a week engaged in physical activities, while 63.9% dedicated 2 or more hours a day to sedentary activities. Recently, the Italian National Institute of Health, in collaboration with the Ministry of Health, implemented a project, called "Maestra Natura" [26] aimed at promoting healthy lifestyles and improving knowledge about food and nutrition in elementary school children. The results showed a significant improvement in knowledge (P <.001) in the intervention group compared to the control group.

Despite several actions carried out to counteract childhood obesity in Italy [24-26], the rising incidence of obesity demonstrates that the measures adopted have been ineffective at achieving their short- and long-term goals [27]. In this context, the LIVELY (Multidimensional School-Based and Family-Involved Interventions to Promote a Healthy and Sustainable Lifestyle) study aims to address the prevalence of overweight and obesity among primary school children and its determinants, as well as to set up and evaluate the feasibility of a multidimensional school-based educational intervention for preventing childhood obesity.

Study Objectives

Primary Objective

The study's primary objective is to investigate the prevalence of overweight and obesity among primary school children, as well as its determinants, including the children's clinical history and lifestyle habits, and their families' socioeconomic status, environmental influences, and behavioral factors.

Secondary Objectives

The secondary aims are to (1) evaluate the feasibility (in terms of satisfaction, learning, and organizational impact) of a multidimensional school-based educational intervention aimed at promoting a healthy and sustainable lifestyle to prevent childhood obesity; and (2) assess changes in children's diet and lifestyle, as well as in family behavioral attitudes, at 6 and 12 months after the intervention.

Methods

Study Design and Overview

LIVELY is a single-arm pre-post study (without a control group). The study is being conducted by a multidisciplinary team consisting of researchers from the Istituto di Ricerche Farmacologiche Mario Negri IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) of Milan and the Laboratory of Dietetics and Clinical Nutrition from the University of Pavia.

Study Setting

LIVELY is being carried out at Istituto Comprensivo "Luigi Cadorna," a public primary school with a strong multiethnic component in northwest Milan, Italy. The study will run from October 2023 until October 2024. Figure 1 shows the study flowchart and timeline.

Figure 1. Study flowchart with timeline.

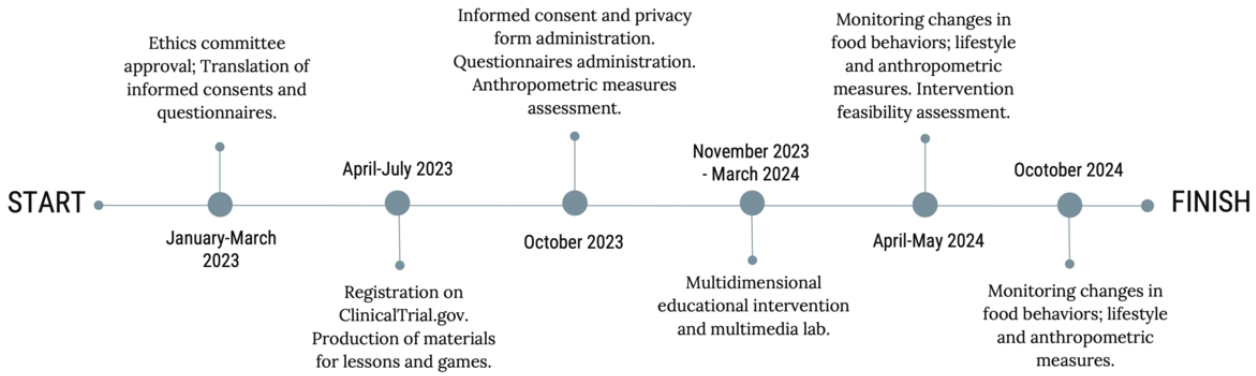

Selection Criteria

The target population for the study was children from 5 to 12 years of age, of both sexes and any ethnicity, and their families. Only children whose parents or legal guardians approved and signed the informed consent were included.

Recruitment

The multidisciplinary team organized an initial meeting at the participating school to introduce the project to the dean and teachers. Teacher representatives took charge of presenting the project to the families of the various classes. Interested families were provided with a study information sheet, which was translated into different languages (Arabic and English) to accommodate the school's diverse, primarily Arabian, population. Teachers in participating classes distributed informed consent and privacy forms in the families' native languages. Signed documents were required from all families before their children could participate.

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Ethical Considerations

The LIVELY study was approved by the Fondazione IRCCS Istituto Neurologico Carlo Besta Ethics Committee (protocol 11) in January 2023. It follows the principles of the Declaration of Helsinki and complies with all relevant privacy and confidentiality regulations concerning the participants' data. Written informed consent was obtained from parents or legal guardians before data collection. Each participant was assigned a unique code to link their data securely while protecting their identity.

Outcome Measures

Details of the data collected from the children and their families throughout the study period are summarized in Table 1.

Table 1. Summary of outcome measures collected from the participating children and their families[a].

Data collection points and outcomes	Baseline (T0)	6 months (T1)	12 months (T2)
Anthropometry measurements			
Weight	✓	✓	✓
Height	✓	✓	✓
Waist circumference	✓	✓	✓
Bicep circumference	✓	✓	✓
Questionnaires			
Sociodemographic information about the parents			
Household composition	✓	✓	✓
Ethnicity	✓		
Education	✓	✓	✓
Job	✓	✓	✓
Health	✓	✓	✓
Smoking and drinking habits	✓	✓	✓
Household food habits	✓	✓	✓
Sociodemographic information about the children			
Age	✓		
Attended class	✓		✓
Health conditions	✓	✓	✓
Children's diet and lifestyle information			
Adherence to Mediterranean Diet	✓	✓	✓
Consumption of ultra-processed foods	✓	✓	✓
Water consumption	✓	✓	✓
Sleep habits	✓	✓	✓
Screen time habits	✓	✓	✓
Project evaluation			
Feasibility of the project (satisfaction, learning, and organization)		✓	

[a]The table shows all the outcome measures that will be collected at baseline (T0), 6 months (T1), and 12 months (T2) after the start of the study from the participating children and their families.

Anthropometric Measurements and Weight Status Classification

A team of trained nutritionists conducted the initial assessment of the children's anthropometric measurements at T0, with plans to reassess these measurements at T1 and T2.

The children's weight was measured using the same digital scale (Tanita Corp). Before standing on the scale, the children were asked to remove their shoes and to wear just trousers and a T-shirt. Body weight was recorded to the nearest 0.1 kilogram. Height was measured using a portable altimeter (Seca GmbH & Co) and recorded to the nearest millimeter. Waist circumference (WC) was measured midway between the lower rib and the iliac crest to the nearest 0.5 cm, while the circumference of the nondominant bicep was measured with the forearm flexed 90°, between the acromion process and the olecranon to the nearest 1 cm.

BMI was expressed as BMI *z* score by referring to the growth curves proposed by the WHO that classify children as having underweight, normal weight, overweight (BMI by sex and age

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greater than 2 SDs), or obesity (BMI greater than 3 standard deviations) [28]. The software Anthro and AnthroPlus (both developed by the World Health Organization) were used to calculate BMI *z* score for the children [29].

The waist-to-height ratio (WHtR) was calculated as WC divided by height, both expressed in centimeters. For the definition of central distribution of adiposity, we adopted the discriminatory value of 0.5 for WHtR [30-32], which corresponds to the 85th percentile of our sample [33,34]. Pupils were separated into 2 groups: the first one included children with WHtR <0.5 (normal distribution of adiposity), while the second one included children with WHtR ≥0.5 (central obesity).

Data Collection

Overview

A case report form (CRF) was used to collect information regarding the children and their household and to investigate all the determinants of overweight and obesity (Multimedia Appendix 1). Referring teachers distributed the CRF in paper format to each child participating in the study in the family's native language and collected them once they were filled out by the parents.

Sociodemographic Information

Sociodemographic and socioeconomic information about the family (household composition, ethnicity, parents' education, job, health, smoking and drinking habits, and household food habits) and the children (age, attended class, health conditions, and practices related to child feeding) were collected through a structured questionnaire at the beginning of the school year (T0).

Diet and Lifestyle

Information regarding the child's eating habits and lifestyle were assessed at T0 through a structured questionnaire administered to the parent or legal guardians. The same questionnaire will be administered at 6 months (T1) and 12 months (T2) after the beginning of the study to assess changes in children's eating and lifestyle habits in relation to the educational content addressed in the classrooms during the intervention.

Specifically, the Mediterranean Diet Quality Index for Children and Adolescents (KIDMED) [35,36] questionnaire was used to assess adherence to the MD and provide an overview of the children’s consumption of major food groups (fruits, vegetables, pasta and cereals, legumes, fish, meat, and dairy products). The questionnaire also gathered details about the number of meals consumed, use of the school cafeteria, sweeteners in tea or milk (eg, sweetened cocoa, sugar, or honey), consumption of whole foods, and intake of ultraprocessed foods (NOVA classification) [37,38]. In the absence of a validated questionnaire to assess children's lifestyle, questions were structured based on the 2018 Centro di Ricerca Alimenti e Nutrizione (CREA) Guidelines [39] to assess hydration level and the WHO guidelines [40] to assess physical activity, sleep habits, and screen time.

Multidimensional Educational Interventions

Lessons and Games

During the school year, each class participates in a multidimensional educational intervention focused on healthy and sustainable nutrition and lifestyle. This intervention is being led by experienced staff, including nutritional biologists and registered dietitians, and was integrated into Civic Education lessons during regular school hours. From October 2023 to March 2024, 6 lectures plus a multimedia workshop are scheduled, covering topics such as macronutrients, micronutrients, the digestive system, the food pyramid, the healthy eating plate, and lifestyle (including sleep habits, screen time, and physical activity).

Researchers visit the school 3 days a week, working with 2 classes per day: one during the first 2 hours of the morning and another in the 2 hours before lunch. Each 2-hour session takes place every 4 weeks and is divided into 2 parts: 30 to 40 minutes of direct teaching using interactive slides, followed by 80 to 90 minutes of playful activities tailored to the children's age group. Activities include crossword puzzles, hangman, and memory games focused on the topics discussed. Another proposed activity involves depicting an unmarked food pyramid and magnetic cards depicting different foods; the goal was to stick the cards at the correct pyramid level (eg, ultraprocessed foods at the top of the pyramid). The children are also asked to come up with combinations of foods to achieve a healthy, balanced plate. At the end of each lecture, to increase family involvement and reinforce learning, a summary slide of each lesson is sent to the parents. Multimedia Appendix 2 includes the teaching presentation used for the second lecture on micronutrients, along with 2 summaries provided to the parents.

Multimedia Workshop

After the first 5 lessons, in which children will have learned the basics of healthy and sustainable nutrition, a multimedia workshop will be conducted to create an animated cartoon. This activity, designed by the Officine Creative of the University of Pavia, aims to foster discussions about healthy eating, promote creative narrative reflection, and document the activities carried out in class.

The goal is to reinforce the content learned in previous lessons, stimulate motivation and discussion among the students, and guide them through character design and the creation of shared dramaturgies.

The children, divided into small groups, are asked to draw a humanized food item, giving it a name, distinguishing features, personality, and clothing (Multimedia Appendix 3). Based on their drawings and character descriptions, each group will then develop a dramaturgy. To help structure these stories, the children will use “story inventor” cubes, with each side of the cube displaying typical fairy tale elements, such as the setting, the helper, the magical object, or an unexpected event. Each image on the cube thus serves as a prompt for the creation of shared dramaturgies. The images and tales produced by the children will be collected, processed, and animated using augmented reality techniques, allowing the children to experience the stories they created in a dynamic, immersive

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way. Table 2 summarizes the lectures and activities proposed for the intervention.

Table 2. Summary of the lectures and activities proposed during the interventiona.

Lectures title	Covered topics	Games/activities	Lecture aim	Time period
1. Macronutrients	Carbohydrates, proteins; lipids; water	True or false; crossword puzzle; game of sets; rhyming riddles	Learn what macronutrients are, their functions, importance to our bodies, and what foods they are present in. Know the importance of water, main functions, and daily intake.	November 2023
2. Micronutrients	Vitamins and minerals	Rhyming riddles; the hangman's game; memory game	Learn what micronutrients are, their functions, their importance to our bodies, and what foods they are present in.	November to December 2023
3. Digestive system	The pathway of food from the mouth to the esophagus, to the stomach, to the intestines; the enzymes involved; and where major macronutrients are absorbed	World search; true or false; rhyming riddles; a vision of a short cartoon on the digestive system; human anatomy labeling game	Learn what happens to food when we eat, what path it takes inside our bodies, how food is digested, and how nutrients are absorbed.	December 2023
4. Food pyramid	Composition of the food pyramid; frequency of food consumption; ultraprocessed foods; food labels	Rebus; food pyramid sorting game; riddles	Learn the frequency of food consumption; know the foods to consume every day and those to consume only occasionally. Learn what ultraprocessed foods are and learn how to read food labels.	January 2024
5. Healthy eating plate	Plate composition; how to compose a healthy dish; importance of breakfast; seasonality of fruits and vegetables	Create your own healthy dish game; Find the Odd One Out game; Find the Missing Part game	Learn how to compose a balanced, healthy dish; learn about alternatives for each part of the dish (fiber, carbohydrates, and protein); learn how to compose a healthy dish on your own by choosing seasonal foods.	January to February 2024
6. Lifestyle	Sleep habits; screen time; physical activity	True or false; riddles; complete your healthy day activity	Know what good habits are to stay healthy and lead an active lifestyle; know the difference between moderate and intense physical activity and related examples; learn how much time should be devoted to these activities; know how many hours of sleep a child needs and what are good habits before sleeping; know what is the limit of screen time and what alternative activities are.	March 2024
7. Multimedia lab	Drawing and storytelling	Drawing a humanized food and proposing a dramaturgy	Work on the content learned in previous lessons, activate motivation and discussion among students; work on character design and the creation of shared dramaturgies.	February to March 2024

[a]The table presents the various lectures and activities that make up the educational intervention given during the LIVELY project. For each lecture, the topics covered, the games or activities planned, the learning objective, and the time period are described.

Evaluation of the Project

The evaluation of educational interventions will aim to analyze and interpret relevant aspects of the multidimensional intervention. It will involve both the school team (teachers) and the recipients (children and families) participating in the LIVELY project and will be conducted at the end of the school year (T1).

The feasibility of the multidimensional educational intervention at school will be assessed in terms of satisfaction, learning, and organization. Three main areas of evaluation of educational interventions will be distinguished, namely, satisfaction (by children, families, and teachers), learning (by children), and organizational impact in the work context (by teachers).

The children's and their families' satisfaction will be assessed through an ad hoc questionnaire investigating the level of

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appreciation regarding the proposed activities. The children's knowledge of the topics covered in the lessons (healthy and sustainable nutrition and lifestyle) will be collected through age-appropriate questionnaires (true/false items, multiple-choice items, insertion) or short compositions, depending on their age group. This assessment will help us determine whether the concepts explained in the lessons have been learned and whether the educational model used is appropriate for the target population. The overall satisfaction and organizational impact of the interventions will be evaluated by teachers through an ad hoc structured questionnaire, which will explore the following issues: (1) usefulness (definition and consistency/congruence of the multidimensional interventions with the project objectives, (2) usefulness of the interventions and materials prepared), (3) didactics (competence and appropriateness of the teaching techniques of the study teams addressed to the subjects, support received by the study teams during the implementation of the activities), (4) organization, and (5) services (timing, facilities and appropriateness of the schools' premises). In addition, teachers will be asked to refer to the reproducibility of the intervention in other classrooms or schools. All items in the questionnaire will be rated on a Likert-type scale.

Sample Size Calculation

This type of study did not require a sample size calculation, but we expected to enroll about 300 to 350 children aged between 6 and 12 years from 15 to 20 classes (in primary school and in the first class of secondary school) based on the availability/willingness of teachers to participate and the resources.

This would allow us to estimate the prevalence of overweight and obesity between 23% and 24%, with a 20% relative precision and within a 95% CI. These data are in line with those observed in the Okkio alla Salute 2019 survey in the Lombardy region [41].

Statistical Analysis

Descriptive analysis will be performed to summarize the baseline characteristics of the involved children according to normal weight, overweight, and obesity classifications. Descriptive data were expressed as counts (percentages) for categorical data and as means (SD) for continuous variables. The means for continuous variables were compared using independent group *t* tests when the data were normally distributed; othewise, the Mann-Whitney test was applied. Categorical variables were compared using the chi-square test. Main determinants of overweight/obesity among children will be investigated according to clinical conditions, dietary patterns, physical activity habits, and environmental and behavioral (family) conditions collected at the baseline using logistic/multinomial regression models.

Specifically, according to the questionnaire results and the information collected in the CRF, children will be identified as “fully adherent,” “partially adherent,” or “poorly adherent” to the WHO recommendations regarding eating and lifestyle habits [42].

The obesogenic environment will be investigated by summarizing all information collected with an appropriate index by assigning a score ranging from 0 (least obesogenic) to 100 (most obesogenic). Each item will be assigned a score from 0 to 1: variables that were considered positive aspects of the environment (grocery, stores/superstores, exercise opportunities) will be reverse scored so that a lower score for these variables indicates a healthier environment. Variables that are considered negative aspects (fast food restaurants, food budgets at home, using a car to go to school) will be scored as is, so a higher score indicates an unhealthy environment. The final index will be calculated by summing up the score for the single items and then normalized to lie between 0 and 100.

Indices for each dimension and an aggregate index will also be calculated to assess the level of satisfaction with the training intervention, learning and overall knowledge of the topic, and the intervention’s organization and reproducibility. Multivariate statistical analysis will be used to investigate general and specific quality dimensions and factors, and it will be correlated with the other aforementioned measures. Changes in dietary and lifestyle habits in the children, behavioral attitudes of their families, and the children's anthropometric measurements will be assessed at 6 (T1) and 12 months (T2) starting from baseline. All results will be stratified by sex and age groups.

Results

Preliminary Results

Recruitment lasted throughout October 2023. Out of the 275 children from the 14 classes participating in the project, 227 whose parents approved and signed the informed consent were included in the study.

The mean age was 8.9 (SD 1.2) years, and 48% (n=110) were males. Children from the 14 classes were distributed as follows: 5.3% (n=12 children) from the second year (1 class), 33.9% (n=77 children) from the third year (5 classes), 15.9% (n=36 children) from the fourth year (2 classes), and 44.9% (n=102 children) from the fifth year (6 classes). No first-graders took part in the project. Data related to demographic data, including age, ethnicity, weight, height, BMI *z* score, and WHtR are shown for the total population and by sex in Table 3.

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Table 3. Demographic characteristics of the study population[a].

Characteristics	Study population			*P* value
	Total (n=227, 100%)	Male (n=110, 48%)	Females (n=117, 52%)	
Age (years), mean (SD)	8.9 (1.2)	8.9 (1.2)	8.9 (1.1)	0.975[b]
Age range (years)	6-12	6-12	7-12	
Place of birth, n (%)				0.091[c]
Italy	170 (79.3)	83 (75.5)	97 (82.9)	
Europe	10 (4.4)	9 (8.2)	1 (0.9)	
South America	11 (4.8)	6 (5.5)	5 (4.3)	
Africa	23 (10.1)	10 (9.1)	13 (11.1)	
Asia	3 (1.3)	2 (1.8)	1 (0.9)	
Ethnicity, n (%)				0.858[c]
Caucasian	83 (36.6)	44 (40)	39 (33.3)	
North African	80 (35.2)	35 (31.8)	45 (38.5)	
Latin American	31 (13.7)	16 (14.5)	15 (12.8)	
Asian	20 (8.8)	9 (8.2)	11 (9.4)	
Black African	4 (1.8)	1 (0.9)	3 (2.6)	
Mixed	9 (4)	5 (4.5)	4 (3.4)	
Attended class, n (%)				0.640[c]
First-year class	0 (0)	0 (0)	0 (0)	
Second-year class	12 (5.3)	8 (7.3)	4 (3.4)	
Third-year class	77 (33.9)	36 (32.7)	41 (35)	
Fourth-year class	36 (15.9)	17 (15.5)	19 (16.2)	
Fifth-year class	102 (44.9)	49 (44.5)	53 (45.3)	
Anthropometric measurements, mean (SD)				
Weight (kg)	35.86 (10.53)	35.27 (10.5)	36.41 (10.57)	0.419[b]
Height (cm)	136.33 (8.74)	135.85 (8.38)	136.75 (99)	0.420[b]
Waist circumference (cm)	65.19 (11.37)	65.22 (10.95)	65.15 (11.79)	0.966[b]
Bicep circumference (cm)	22.11 (41)	21.72 (4.12)	22.47 (3.89)	0.159[b]
WHtR[d]	0.48 (07)	0.48 (07)	0.48 (07)	0.666[b]
BMI *z* score	0.87 (1.42)	0.87 (1.55)	0.87 (1.30)	0.971[b]
BMI z score classes, n (%)				0.025[c]
Underweight	5 (2.2)	4 (3.6)	1 (0.9)	
Normal weight	169 (74.4)	80 (72.7)	89 (76.1)	
Overweight	41 (18.1)	16 (14.5)	24 (21.4)	
Obesity	12 (5.3)	10 (9.1)	3 (1.7)	
Central obesity, n (%)				0.329[c]
WHtR <0.5	150 (66.1)	76 (69%)	74 (63%)	
WHtR ≥0.5	77 (33.9)	34 (31%)	43 (37%)	

[a]Table shows the demographic and anthropometric characteristics of the overall study population and then divided between male and female students. Categorical variables are presented as n (%), and continuous variables are presented as mean (SD).

[b]*P* value of the *t* test between male and female students.

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[c]*P* value of the chi-square test between male and female students.

[d]WHtR: waist-to-height ratio.

The percentage of normal weight, overweight, and obesity (defined by BMI *z* score) and central obesity (according to the WHtR cut-off) is reported in Table 4. Among the overall sample, 18.1% (n=41; 95% CI 13.7%-23.7%) were overweight, while 5.3% (n=12; 95% CI 3%-9%) were obese. Male students had a higher prevalence of obesity than female students (9.1% vs 1.7%, *P*=.03 respectively). Conversely, the overall prevalence of central obesity was similar between male and female students, respectively (31% vs 37%, *P*=.329).

Table 4. Weight status prevalence according to BMI z score and its relation to WHtR[a] in male and female students.

Participants	Total, n (%)	WHtR <0.5, n (%)	WHtR ≥0.5, n (%)
Males	110 (100)	76 (69)	34 (31)
BMI *z* score (WHO[b])			
Underweight	4 (3.6)	4 (5.3)	0 (0)
Normal weight	80 (72.7)	71 (93.4)	9 (26.5)
Overweight	16 (14.5)	1 (1.3)	15 (44.1)
Obesity	10 (9.1)	0 (0)	10 (29.4)
Females	117 (100)	74 (63)	43 (37)
BMI *z* score (WHO)			
Underweight	1 (0.9)	1 (1.4)	0 (0)
Normal weight	89 (76.1)	71 (95.9)	18 (41.9)
Overweight	24 (21.4)	2 (2.7)	23 (53.5)
Obesity	3 (1.7)	0 (0)	2 (4.7)

[a]WHtR: waist-to-height ratio.

[b]WHO: World Health Organization.

The second data collection was completed in June 2024 (T1), and the last data collection will be completed by the end of October 2024 (T2). Data analysis and a presentation of the complete results will be available after the end of 2024.

Discussion

Overview

The rising prevalence of obesity worldwide represents a growing burden of noncommunicable diseases (NCDs) and a significant public health issue due to increasing public service health costs [13,18,43]. To prevent the early onset of NCDs in younger populations, additional policies, treatments, and financial investments must be made to contrast the growing pandemic of childhood obesity [44-46]. Based on scientific research [15], preventing childhood obesity requires a multifaceted approach including multiple areas of intervention. Therefore, it is essential to develop and carry out integrated programs that could cover a variety of topics (nutrition, physical activity, sleep hygiene, etc) at various levels (individual, family, school, and institutional) [47].

The LIVELY study enrolled 227 school-age children attending an elementary school in a multiethnic neighborhood in north Milan, Italy. Classes from the second to the fifth grade were included. No first-grade class joined the project because the availability of children to follow the lesson could not be optimal. This was because, during the first year of elementary school, children were just beginning to learn how to read and write, leading primary school teachers to abstain from participating in the project.

In line with previous studies [24-26], our preliminary results showed a high prevalence of overweight/obesity among the enrolled children, at 24% (n=26) for the male students and 23% (n=27) for the female students, with a higher prevalence of obesity among males (*P*=.007). Interestingly, the prevalence of central obesity was similar between the 2 sexes (*P*=.329).

Study Strengths

A child's diet and physical activity can be significantly influenced by their surroundings, particularly family and school [48]. To date, many programs have been developed to prevent obesity in children, but the overall impact of these is questionable and does not include long-term follow-up measurements [24-26]. Thus, the LIVELY study has significant strengths. First, interventions involving different actors (children, families, teachers) and multidisciplinary professional expertise will be implemented, allowing us to address the different determinants of childhood obesity. Second, frontal lectures and games relating to the subject matter will be adapted to all age groups, dividing the children into 2 groups—first and second graders in one group, and third to fifth graders in the other. The strong multicultural component of the sample will be considered by involving them in stimulating and bonding activities. Third, an interactive digital lab will be developed to maximize learning outcomes by taking advantage of the children's digital skills. Fourth, attention will be given to the

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opinions of all participants (children, parents, and teachers) to assess the feasibility and reproducibility of the project.

Study Limitations

There are several possible obstacles to this research in real-world contexts; some that we can foresee now and others that will be managed as they arise. We have already encountered 2 main challenges. The first challenge comprised the teachers' active involvement and participation. Some teachers expressed that they found it difficult to include new lectures in the already tight teaching schedule as all classes are conducted during regular school hours and included within the Civic Education class period. However, it was possible to overcome this obstacle by involving the school principal and explaining to teachers the importance and impact of the project since the topics covered are not part of the regular school curriculum and will cover current and important issues such as sustainability and planetary health. Moreover, this approach aligns with the Sustainable Development Goals outlined in the 2030 Agenda for Sustainable Development, adopted by all United Nations Member States, and integrated into Civic Education curricula by the Italian Ministry of Education in 2020. The second challenge concerned the large multicultural component of the sample, as language barriers can play a critical role. To minimize this obstacle, most of the tools concerning completion by families (informed consent, releases, and questionnaires) were translated into 3 different languages (Italian, English, and Arabic).

We anticipate challenges with family compliance in completing the self-administered questionnaires. To address this, we plan to make phone calls to the families to fill in the questionnaires or enter the missing data with the support of trained staff. Another challenge may arise from the difficulty in collecting data at 12 months from children transitioning from 5th grade to 6th grade, as they will be changing school locations. We plan to mitigate this issue by maintaining contact with teachers and parents. In addition, through satisfaction questionnaires, the project's various stakeholders will be given a voice to highlight the strengths and address any critical issues through different perspectives.

Conclusions

The LIVELY study will provide key insights into the prevalence of overweight and obesity in a primary school setting and identify their main determinants. It is expected to benefit the study population by conveying, through a multidisciplinary, multiprofessional, and reproducible approach, the basics of a healthy and sustainable lifestyle. The ultimate goal is to reduce—and altogether prevent—childhood obesity.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to prior authorization from the Istituto di Ricerche Farmacologiche Mario Negri (IRCCS) of Milan, the data controller complying with the General Data Protection Regulations (GDPR). Data sharing is restricted to comply with the regulations of the European Economic Area (EEA). As such, data sharing with entities or individuals located outside the EEA is not foreseen.

Authors' Contributions

CF, MB, IA, and MVC conceived and designed the study and acquired the funding. HC peer-reviewed the study design. SB and EK drafted and wrote the manuscript. All the authors critically reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Case report form.
[PDF File (Adobe PDF File), 459 KB - resprot_v13i1e57509_app1.pdf]

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Multimedia Appendix 2
Lectures on micronutrients.
[PDF File (Adobe PDF File), 6163 KB - resprot_v13i1e57509_app2.pdf]

Multimedia Appendix 3
Multimedia lab activity example.
[DOCX File , 114 KB - resprot_v13i1e57509_app3.docx]

Multimedia Appendix 4
SPIRIT Checklist.
[PDF File (Adobe PDF File), 87 KB - resprot_v13i1e57509_app4.pdf]

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Abbreviations

COSI: Childhood Obesity Surveillance Initiative
CREA: Centro di Ricerca Alimenti e Nutrizione
CRF: case report form
CVD: cardiovascular disease
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
KIDMED: Mediterranean Diet Quality Index for Children and Adolescents
LIVELY: Multidimensional School-Based and Family-Involved Interventions to Promote a Healthy and Sustainable Lifestyle
LDNC: Laboratory of Dietetics and Clinical Nutrition
MD: Mediterranean diet
NCD: noncommunicable disease
WC: waist circumference
WHO: World Health Organization
WHtR: waist-to-height ratio
UNESCO: United Nations Educational, Scientific and Cultural Organization

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Protocol

Noninvasive, Multimodal Inflammatory Biomarker Discovery for Systemic Inflammation (NOVA Study): Protocol for a Cross-Sectional Study

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Abstract

Background: Prolonged systemic inflammation is recognized as a major contributor to the development of various chronic inflammatory diseases. Daily measurements of inflammatory biomarkers can significantly improve disease monitoring of systemic inflammation, thus contributing to reducing the burden on patients and the health care system. There exists, however, no scalable, cost-efficient, and noninvasive biomarker for remote assessment of systemic inflammation. To this end, we propose a novel, multimodal, and noninvasive approach for measuring inflammatory biomarkers.

Objective: This study aimed to evaluate the relationship between the levels of inflammatory biomarkers in serum (gold standard) and those measured noninvasively in urine, sweat, saliva, exhaled breath, stool, and core body temperature in patients with systemic inflammation.

Methods: This study is a single-center, cross-sectional study and includes a total of 20 participants (10 patients with systemic inflammation and 10 control patients). Eligible participants provide serum, urine, sweat, saliva, exhaled breath, and stool samples for biomarker analyses. Core body temperature is measured using a sensor. The primary end point is the level of C-reactive protein (CRP). The secondary end points are interleukin (IL)–1β, IL-6, IL-8, IL-10, and tumor necrosis factor-α levels. The tertiary end points are fractional exhaled nitric oxide, calprotectin, and core body temperature. Samples will be collected in 2 batches, enabling preliminary analysis of the first batch (patients 1-5 from each group). The full analysis will include both batches. CRP and cytokine levels will be measured using enzyme-linked immunosorbent assay and electrochemiluminescence immunoassay. For statistical analysis, the Shapiro-Wilk test will be used to evaluate the normality of the distribution in each variable. We will perform the 2-tailed *t* test or Wilcoxon rank sum test to compare the levels of inflammatory biomarkers between patients with systemic inflammations and control patients. Pearson and Spearman correlation coefficients will assess the relationship between inflammatory biomarkers from noninvasive methods and serum biomarkers. Using all-subset regression analysis, we will determine the combination of noninvasive methods yielding the highest predictive accuracy for serum CRP levels. Participants' preferences for sampling methods will be assessed through a questionnaire.

Results: The study received ethics approval from the independent research ethics committee of Canton Zurich on October 28, 2022. A total of 20 participants participated in the study measurements. Data collection started on February 22, 2023, and was completed on September 22, 2023. Participants were on average 52.8 (SD 14.4; range 24-82) years of age, and 70% (14/20) of them were women. The analysis results reporting findings are expected to be published in 2025.

Conclusions: This study aims to evaluate the feasibility of noninvasive, multimodal assessment of inflammatory biomarkers in patients with systemic inflammation. Promising results could lead to the creation of noninvasive and potentially digital

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biomarkers for systemic inflammation, enabling continuous monitoring and early diagnosis of inflammatory activity in a remote setting.

International Registered Report Identifier (IRRID): DERR1-10.2196/62877

(JMIR Res Protoc 2024;13:e62877) doi:10.2196/62877

KEYWORDS

systemic inflammation; chronic inflammation; inflammatory biomarkers; biofluids; serum; urine; sweat; saliva; exhaled breath; stool; C-reactive protein; interleukin; IL-1β; IL-6; IL-8; IL-10; tumor necrosis factor; TNF-α; fractional exhaled nitric oxide; calprotectin; core body temperature; noninvasive biomarker; multimodal biomarker; remote monitoring; surrogate biomarker; rheumatology; chronic inflammatory disease

Introduction

Chronic systemic inflammation is a persistent upregulation of inflammatory activity as a result of prolonged exposure to a pathogen or autoimmune dysfunction. Prolonged systemic inflammation is associated with the disease onset and progression of various chronic inflammatory diseases such as rheumatoid arthritis, spondyloarthritis, or systemic lupus erythematosus [1].

Current standardized practice to assess the presence of systemic inflammation and inflammatory disease activity is based on serum biomarkers obtained from a blood test [2]. Increased levels of proinflammatory markers such as the C-reactive protein (CRP) and interleukin (IL)–6, IL-8, and tumor necrosis factor (TNF)–α are closely associated with active inflammation and disease progression in cardiovascular and autoimmune diseases [3]. The serum CRP is found to be the most precise and objective measurement and is regularly assessed at routine hospital visits to confirm the clinical diagnosis, classification of disease activity, and treatment decisions in chronic inflammatory diseases. In the case of rheumatoid arthritis, for instance, clinicians determine the current state of disease activity and treatment response based on aggregated information of the inflammatory biomarker levels from a blood test (eg, CRP), physical assessment (eg, joint counts), and composite score (eg, Disease Activity Score-28) obtained during a routine visit [4,5]. While blood tests provide valuable information to diagnose, screen, and monitor various inflammatory biomarkers and clinical conditions, this procedure has three distinct disadvantages: (1) it is invasive and burdensome to patients, (2) it requires trained personnel and is not feasible for self-administration, and (3) real-time monitoring or at-home measurements are not available. In addition, there are a limited number of studies and insufficient evidence to support the validity of detecting CRP or cytokines noninvasively.

Existing studies assess only specific disease populations, biofluids, or biomarker types, limiting the generalizability of findings to a wide patient population of systemic inflammation. Urinary CRP, for example, is mostly researched in patients with urinary tract infections, other urologic conditions, or rejection of transplanted kidneys [6,7]. Likewise, fractional exhaled nitric oxide (FeNO), a product of metabolic and inflammatory processes in the human body, is largely investigated in cancers and respiratory diseases such as asthma, but rarely in other systemic inflammatory conditions [8,9]. Fecal calprotectin is a well-established biomarker for inflammatory bowel disease, yet its clinical relevance to other inflammatory diseases remains largely unexplored [10]. Recent studies have shown encouraging results including significant associations with serum calprotectin in patients with spondyloarthritis compared with matched controls and increased serum calprotectin levels correlated with disease activity in both rheumatoid arthritis and axial spondyloarthritis [11,12]. Furthermore, chronic inflammation contributes to the disruption of homeostatic control mechanisms, such as core body temperature, and results in increased vulnerability to homeostatic dysregulation and diseases [13]. Yet, the underlying mechanisms responsible for this connection are not yet fully understood.

Noninvasive assessment of inflammatory biomarkers could overcome the limitations of the invasive blood draw and improve the lives of patients with chronic inflammatory diseases by enabling continuous disease monitoring. This study demonstrates the potential to use noninvasive methods for developing accessible and less invasive diagnostic tools. These advancements would alleviate multiple burdens from blood tests, contribute to patients' self-management, and add significant value to clinicians and caregivers by enabling meaningful treatment and effective prevention of future events, a step toward population-wide measurement and personalized prevention.

To date, however, there exists no scalable solution that allows patients to gauge one's inflammatory state remotely. As a result, many patients might postpone contacting their physicians until late during a disease progression or even until the next routine visit to evaluate inflammatory symptoms and the CRP level. This delay may not only impact negatively on patients' quality of life but also cause unanticipated consequences or harm in some cases. An option of remotely monitoring symptoms and inflammatory activity could empower patients toward self-management, increase comprehension of the disease, and thus, ensure engagement in treatment adherence and timely intervention.

To address this research gap, we propose a proof-of-concept feasibility study (NOVA study) to evaluate the relationship between the levels of serum inflammatory biomarkers and those measured noninvasively in urine, sweat, saliva, exhaled breath, core body temperature, and stool in patients with systemic inflammation. We hypothesize that the levels of inflammatory biomarkers measured noninvasively in various biofluids can be used to detect and monitor disease activity and are associated with inflammatory biomarkers measured in serum through a

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blood test. Once this link is established, it would pave the way to the development of digital biomarkers for real-time disease activity prediction and monitoring of the effectiveness of treatments through scalable, cost-effective, and patient-oriented digital solutions. The proposed study aims at targeting the following three main research questions: (1) to what extent is systemic inflammation measured by serum CRP associated with the CRP measured non-invasively in urine, sweat, and saliva? (2) to what extent is systemic inflammation measured by serum cytokines (ie, IL-1β, IL-6, IL-8, IL-10, and TNF-α) associated with cytokines measured noninvasively in urine and sweat? and (3) to what extent is systemic inflammation measured by serum CRP and cytokines associated with noninvasive measures of FeNO from exhaled breath, calprotectin from stool, and core body temperature?

Methods

Study Design and Participants

The NOVA study is a 2-group, cross-sectional, single-center observational study aiming to recruit 20 individuals among the hospitalized patients from the rheumatology ward of University Hospital Zurich. The systemic inflammation group and the control group will include 10 participants each. The inclusion criteria are adult persons (aged 18 years or older) who have provision of written informed consent. Patients with systemic inflammation are defined as patients with the inflammatory syndrome (ie, CRP>5 mg/L). The control patients are patients who do not have an inflammatory syndrome (ie, CRP≤5 mg/L). Exclusion criteria are patients with active psychiatric or mental disorders (ie, clinically relevant depression, dementia, and Alzheimer disease), alcohol abuse, or other substance abuse; patients needing immediate treatment with glucocorticoids or other drugs for the suppression of the inflammation until study procedures can be performed; those with language barriers or incapable of understanding and signing an informed consent form; and those with other factors that impair daily functions and make adherence to the study protocol impossible.

Procedures

Recruitment

Figure 1 shows the study procedures of the NOVA study. A clinician will conduct a prescreening to identify planned and emergency admissions and check if they have increased CRP levels. In case a patient is deemed eligible for the NOVA study, the clinician or study nurse will contact the patient, hand out a study flyer and a patient information sheet, and ask if they are willing to participate in the study following good clinical practice guidelines. Participants will have 24 hours or overnight to consider study participation before providing informed consent.

Figure 1. A schematic of NOVA study procedures.

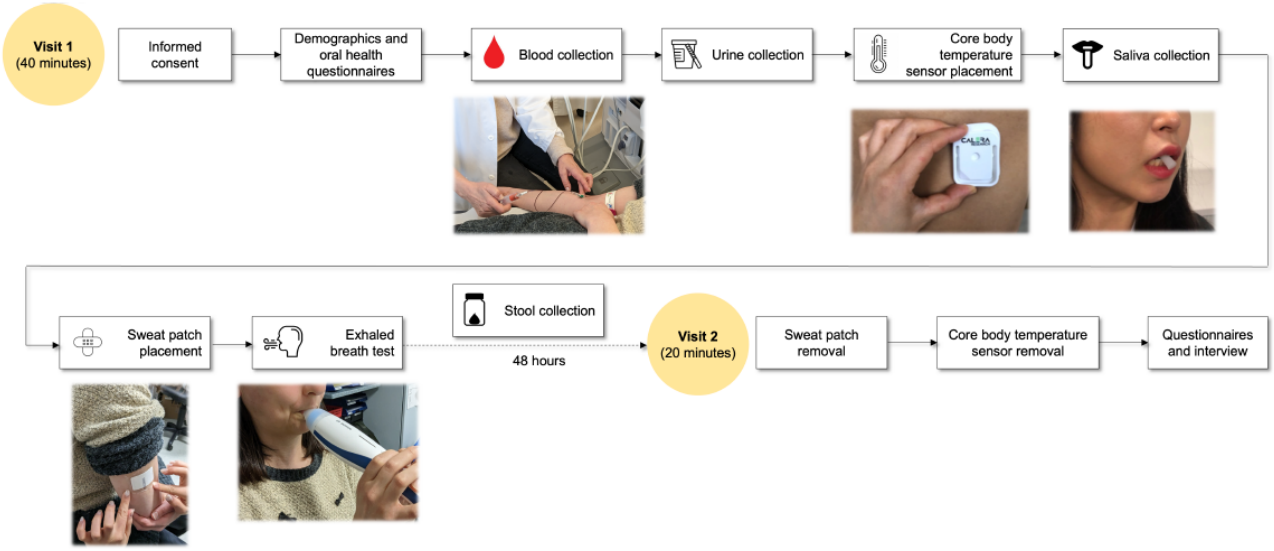

Visit 1 (Study Measurements)

Study Measurements

The study measurements will either take place in the patient's room or in the clinical examination room available on the ward and are estimated to take approximately 40 minutes. Participants will complete the following steps under the guidance of the study nurse and a researcher from the Centre for Digital Health Interventions (CDHI).

Informed Consent

If the eligible patient agrees to participate in the study, a study nurse will explain the study objectives and procedures. The patient will review the informed consent form and sign it.

Baseline Questionnaire

Participants will fill out the questionnaires (Multimedia Appendix 1) to provide information on demographics, oral health, and previous history of surgeries and hospitalizations in the past year.

Blood Collection

A trained nurse will perform a standard venipuncture, drawing the required blood tubes for the chemistry parameters and

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cytokine analysis. Upon completion, participants will answer a short questionnaire assessing their experience and impression of the blood draw. This questionnaire will be repeated after each sampling method (Multimedia Appendix 2). The blood samples will be centrifuged and aliquoted into cryovial vials according to the laboratory instruction, frozen within 1 hour of collection, and preserved in sterile tubes at −80 °C until analysis.

Urine Collection

Midstream urine samples will be collected in sterile containers. Immediately after collection, we will perform a dipstick test (ie, Roche Combur Test Strip) to exclude samples with relevant bacterial contamination. The suitable samples will be centrifuged and aliquoted into cryovial vials according to the laboratory instruction, frozen within 1 hour of collection, and preserved in sterile tubes at −80 °C until analysis.

Core Body Temperature Sensor Placement

The CDHI researcher will attach a core body temperature sensor (eg, greenTEG CORE) to the upper body or chest area approximately 20 cm below the armpit using a heart rate monitor strap or medical patch. The sensor will be collected at the follow-up meeting.

Saliva Collection

Saliva samples are collected using an absorbent swab. Participants will place an absorbent swab (ie, Salimetrics SalivaBio Oral Swab) underneath the tongue for 3 minutes followed by direct disposal to a collection tube. Salivary samples will be transported to a storage unit within 1 hour of measurement and refrigerated at –80 °C until the analysis.

Sweat Patch Placement

The CDHI researcher will attach 2 sweat patches (ie, PharmChek Sweat Patch) on the participants' arms or abdomen for sweat collection following the manufacturer's instructions. Participants will be informed of the dos or do nots for the next 48 hours. The sweat patches will be collected at the follow-up meeting.

Exhaled Breath Test

Participants will complete FeNO measurements in exhaled breath using the "Bosch Vivatmo me" device. All measurements will be repeated twice per participant. "Bosch Vivatmo me" is a breathalyzer designed to measure airway inflammation based on the FeNO level detected in exhaled breath.

Stool Sampling Instruction

Participants will be provided a guide for collecting stool samples.

Visit 2 (Follow-Up Meeting)

Participants will be scheduled for a 20-minute follow-up meeting after 48 hours after study measurements. At this meeting, the CDHI researcher will remove the sweat patch and the core body temperature sensor, collect the stool sample, and conduct an interview on overall experience and preferences comparing sampling methods (Multimedia Appendix 3). Collected sweat patches and stool samples will be refrigerated at –80 °C until the analysis. The follow-up meeting will occur either in the patient's room or the clinical examinations room available on the ward.

Patient Instructions

If participants agree to participate in this research project, they are asked to adhere to the specifications and requirements of the research project through the protocol. First, from 2 hours before study measurement to saliva collection: refrain from eating, drinking coffee, or acidic or sweet liquids, chewing gums, brushing teeth, using mouthwash and smoking. Second, from study measurements to follow-up meetings: avoid hot tubs, tanning booths, prolonged exposures in a sauna, or sweat lodges. Normal activities such as bathing, showering, swimming, and exercising are permitted. When drying the area where the sweat patch is applied, gently pat the area with a towel instead of rubbing the area.

Measurements

End Points

The primary endpoint of this study is the level of CRP. Secondary end points are the levels of inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-10, and TNF-α. Tertiary end points are FeNO, calprotectin, and core body temperature (Figure 2).

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Figure 2. An overview of study measurements and end points. CRP: c-reactive protein; FeNO: fractional exhaled nitric oxide.

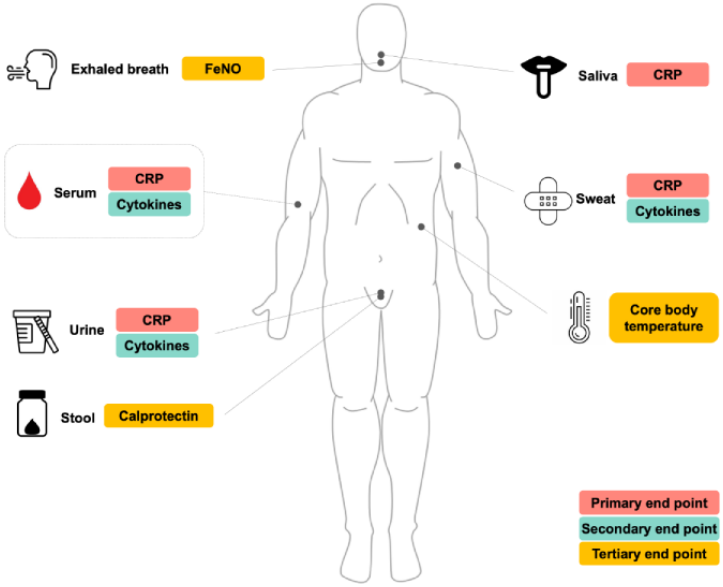

Additional Information

As described in Textbox 1, we will collect additional information on patient characteristics and demographics, disease characteristics (eg, disease diagnosis, age at diagnosis, disease duration, and comorbidities), medications (eg, type, duration, and dose), measures of disease activity and functional outcomes (eg, Disease Activity Score-28 with CRP for rheumatoid arthritis, Bath Ankylosing Spondylitis Disease Activity Index for spondyloarthritis, Disease Activity in Psoriatic Arthritis for psoriatic arthritis, and Systemic Lupus Erythematosus Disease Activity for systemic lupus), oral health (eg, fasting, teeth status, and presence of oral diseases), and previous histories of surgeries and hospitalizations. To standardize the results of measured biomarkers, we will measure creatinine, albumin, and total protein levels in serum and urine and report the excretion of each urinary protein as a ratio between the concentration of the respective protein and urinary creatinine in a similar manner to albumin and creatinine ratio.

Textbox 1. Additional information.

Baseline characteristics

- Demographics: age, sex, race, marital status, employment status, education, weight, height, BMI, blood pressure, smoking status, and comorbidities

Disease characteristics

- Disease diagnosis, age at diagnosis, disease duration, disease activity, and functional outcomes

Medications

- Type, duration, and dose

Oral health

- Status of fasting, brushing teeth, chewing gums, smoking, and drinking
- Bleeding gums and presence of oral diseases

Prior history

- Hospitalization within 1 year
- Surgical operation within 1 year

Sample standardization

- Creatinine, albumin, and total protein levels in serum
- Creatinine, albumin, and total protein levels in urine

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Sample Size Calculation

Since there is no previous knowledge or evidence of the outcome measures in this context, we calculate the sample size based on the following assumptions and considerations. First, we compute the sample size based on the serum CRP level to make sure that differences in CRP level are significant between both study groups. Second, we refer to studies of adult patients diagnosed with rheumatoid arthritis, which is one of the most prevalent systemic inflammatory diseases. CRP also plays a pivotal role in disease assessment and inflammatory activity in rheumatoid arthritis, which makes it a suitable choice of disease for exploring the sample size [14,15].

Bechman et al [16] reported that the serum CRP levels in patients with rheumatoid arthritis in systemic inflammatory states (ie, medium and high disease activity) range from 5 to 9 (SD 3.0) mg/L. Lillegraven et al [17] reported that the serum CRP levels in patients in the nonsystemic inflammatory state (ie, remission) range from 2 to 3 mg/L. Based on these results, it is plausible to conclude that we will observe a 3 to 6 mg/L difference in serum CRP levels comparing systemic inflammation versus nonsystemic inflammation among patients with rheumatoid arthritis. On this basis, and assuming 80% of power, 5% of type I error, and equal variance in groups [18], a sample size of 10 participants per group is required to detect a difference of 4 (SD 3.0) mg/L in serum CRP levels with (Table 1). Considering dropout and missing data, the sample size required may be increased by 10% to 20%.

Table 1. Sample size calculation.

Difference of means between groups	Pooled SD and sample size				
	SD 1.0	SD 2.0	SD 3.0	SD 4.0	SD 5.0
2 mg/L	6	17	37	64	100
3 mg/L	4	9	17	29	45
4 mg/L	3	6	10	17	26
5 mg/L	3	4	7	12	17

Statistical Analysis

Descriptive analysis will report the mean and SD for continuous variables and the count and percentage for categorical variables. The 2-tailed *t* test and the chi-square test (or Fisher exact test if expected n<5) will be used for univariable analysis. In addition, the Shapiro-Wilk test will be used to evaluate the normality of the distribution in each variable. We will perform the 2-tailed *t* test (or Wilcoxon rank-sum test, if nonnormal) to compare the levels of inflammatory biomarkers between patients with systemic inflammations and controls. Subsequently, analyses of covariance or multiple regressions will be conducted to examine whether the mean biomarker level differs significantly between patients with systemic inflammation versus controls, adjusting for confounding factors such as baseline characteristics and oral health. Secondary and tertiary end points will be analyzed analogously. We will compute Pearson and Spearman correlation coefficients to assess the relationship between inflammatory biomarkers from noninvasive methods and serum biomarkers. For core body temperature data, the repeated measures correlation method will be performed to assess the association [18]. Participants' preferences for 7 sampling methods will be assessed using a questionnaire, with rankings quantified on a scale from 1 (most preferred) to 7 (least preferred). To determine if combining noninvasive methods improves predictive accuracy of systemic inflammation, we will use an all-subset regression analysis. The combination of methods that yields the highest adjusted R^2 values for predicting serum CRP levels will be considered the optimal model. Statistical analysis will be performed with R (R Core Team) or Python (Python Software Foundation). Statistical significance is set at 2-sided P<.05.

Biomarker Analysis

Due to the pilot nature of this study, it is difficult to estimate the precise time required to complete study recruitment and data collection. To overcome this limitation and enable preliminary data analysis, samples will be collected and submitted for biomarker analysis in 2 batches as described in Figure 3. Samples from the first half of the participants (ie, patients 1-5 from each group) will be collected and submitted to laboratories for the biomarker analyses (batch 1). Batch 2 will consist of samples from the second half of the participants (ie, patients 6-10 from each group). This will provide us with information on the accuracy of our estimated sample size and allow us to make corrections with regard to the planned number of patients to be included. Full data analysis will be conducted including the entire samples. Serum CRP, serum cytokines, and fecal calprotectin will be analyzed in the in-house laboratories of University Hospital Zurich according to the laboratory procedures. The levels of urinary CRP, urinary cytokines, salivary CRP, sweat CRP, and sweat cytokines will be determined at Swiss BioQuant. Noninvasive CRP levels will be quantified by the enzyme-linked immunosorbent assay according to instructions provided by the manufacturer. Noninvasive cytokines will be analyzed using electrochemiluminescence immunoassay.

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Figure 3. Proposed biomarker analysis. CRP: c-reactive protein; FeNO: fractional exhaled nitric oxide.

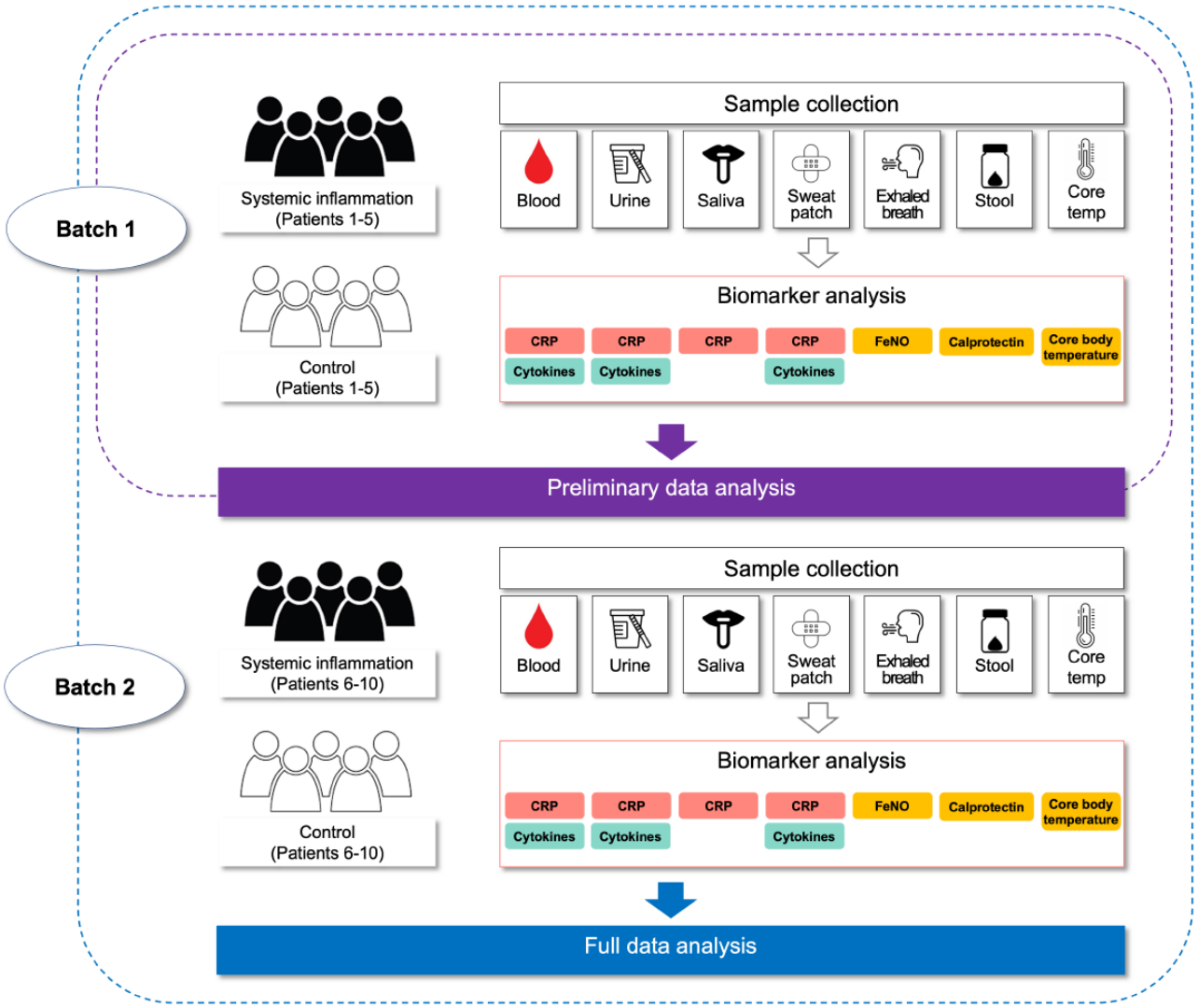

Data Management

Project data will be handled with the uttermost discretion and are only accessible to authorized personnel who require the data to fulfill their duties within the scope of the research project. Participant data will be encrypted. The participant identification list will be stored separately from the study records and only accessible by a dedicated data manager, who was not involved in the study. On the case report forms and other project-specific documents, participants are only identified by a unique participant number. Access and changes to documents and data servers will be logged and traced. Data will further be backed up on encrypted drives and safeguarded in a key-locked cupboard.

Ethical Consideration

This study received ethical approval from the independent research ethics committee of Canton Zurich on October 28, 2022 (BASEC-Nr: 2022-01386). This research project will be conducted in accordance with the protocol, the Declaration of Helsinki, the principles of good clinical practice, the Human Research Act, and the Human Research Ordinance, as well as other locally relevant regulations. All participants will provide written informed consent before they participate in the study. Participation in the study is fully voluntary, and withdrawal from the study is possible at any time.

Results

The study received ethics approval from the independent research ethics committee of Canton Zurich on October 28, 2022. A total of 20 participants participated in the study measurements. Data collection started on February 22, 2023, and was completed on September 22, 2023. Participants were on average 52.8 (SD 14.4, range 24-82) years of age, and 70% (14/20) of them were women. The analysis results reporting findings are expected to be published in 2025.

Discussion

Principal Findings

This study aims to investigate the noninvasive assessment of inflammatory biomarkers in patients with systemic inflammation. We hypothesize that inflammatory biomarkers measured noninvasively in urine, sweat, saliva, stool, core body temperature, and exhaled breath are significantly associated with serum biomarker levels. The study will also examine if

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the multimodal, noninvasive approach yields stronger associations and increases the predictive ability of serum biomarker levels compared with a single noninvasive method. Furthermore, we anticipate that assessing individual preferences for different noninvasive methods provides valuable insights into patients' acceptance when implemented in real-life settings.

Comparison to Previous Work

Prior work has explored the detection of inflammatory biomarkers in urine, saliva, and sweat. Researchers reported that elevated urinary TNF-α level is correlated with chronic inflammation and endothelial dysfunction in obese adolescents [19]. A study by Galhardo et al [20] measured CRP and IL-6 in saliva to predict sepsis diagnosis in hospitalized patients in an intensive care unit setting. Hladek et al [21] analyzed inflammatory cytokines including IL-6, IL-10, and TNF-α collected using sweat patches among 49 young and older adults. More recently, researchers developed a wireless patch for the real-time electrochemical detection of the CRP in sweat and assessed the evaluation in patients with chronic obstructive pulmonary disease [22]. While these studies have provided valuable insights, they implement a single biofluid modality, where detection accuracy may be highly variable depending on the presence of local inflammation (eg, urinary tract infection), environmental factors (eg, ambient temperature), or biomarker characteristics (eg, diurnal variation). Furthermore, previous research has primarily involved healthy individuals or specific disease types, with limited work addressing systemic inflammation. Our study differs by adopting a multimodal approach using easy-to-collect samples and focusing specifically on patients with systemic inflammation, thus addressing a significant gap in the existing literature.

Study Implications

Systemic inflammation is a major contributor to chronic inflammatory diseases, which are responsible for more than 50% of worldwide deaths today. Given its low-grade, persistent, and chronic nature, continuous monitoring and early diagnosis of exacerbations are especially important for patients with systemic inflammation. Currently, there is no scalable solution for remote assessment of inflammatory status, often leading many patients to delay timely interventions until symptoms become severe or until their next routine visit. Although clinical guidelines for disease management and treatment are well established, many patients still encounter unanticipated exacerbations resulting in pain, worsened symptoms, and reduced quality of life. Thus, this proof-of-concept study provides an important avenue for exploring the feasibility of noninvasive inflammation assessment. To our knowledge, this is the first study to simultaneously collect and measure inflammatory biomarkers from 6 different noninvasive methods and evaluate their associations with serum biomarkers. Establishing these relationships would provide the basis for digitizing measurement for serum biomarkers, such as for CRP, contributing to the creation of a digital surrogate biomarker. Once digitized, this approach could lead to the development of a scalable, cost-efficient sensor, allowing a timely and rapid monitoring of inflammatory activity. This advancement is particularly relevant given the ever-rising incidence of systemic inflammatory conditions and the urgent need for precise and remote monitoring tools.

Strengths and Limitations

A key strength of our study is that we collect 6 distinct types of body fluids in addition to blood from the same individual and perform a biomarker immunoassay assessment through comprehensive testing. A proposed multimodal approach not only increases the precision and sensitivity of detected associations but also offers new insights into patients' experiences or preferences related to different sampling methods. Second, we include different types of inflammatory biomarkers (ie, CRP, interleukins, calprotectin, FeNO, and core body temperature) as the sensitivity of detection varies by molecules and biofluid types. As opposed to existing research with a single outcome, we seek to contribute to the current literature by assessing multiple endpoints that have been acknowledged to have a direct or indirect association with the gold standard. Third, we minimize an unanticipated temporal or circadian influence or medication effect in the inflammatory state by obtaining blood and noninvasive samples simultaneously. To achieve simultaneous sampling, we propose an efficient workflow of study procedure that enables us to complete study measurements and the follow-up meeting within a total of 1 hour. Fourth, it is the first to implement noninvasive, continuous monitoring of core body temperature for 48 hours to associate the temporal pattern of body temperature with inflammatory activities in systemic inflammation. Finally, we obtain additional information on patient and disease characteristics, disease activity, medications, comorbidities, and oral health questionnaires and adjust statistical models for potential confounding.

This study will have limitations. With the pilot nature of the study, no longitudinal measurements will be collected. Given the nature of the cross-sectional study, we are not able to establish causal relationships from observed associations. In addition, our study involves a relatively small size at a single study site among hospitalized patients at a University hospital, which may limit the generalizability of our findings to a real-world patient population. Nevertheless, this proof-of-concept study offers novel insights into the digitization of inflammatory biomarkers and directions for future research opportunities. If this proof-of-concept study yields successful results, a longitudinal, prospective cohort study is warranted.

Dissemination Plan

We are committed to reporting the study results through peer-reviewed journals and presentations to disseminate key findings and learnings to various clinical and scientific communities.

Conclusion

This study aims to evaluate the feasibility of noninvasive, multimodal assessment of inflammatory biomarkers in patients with systemic inflammation. Promising results could lead to the creation of noninvasive and potentially digital biomarkers, enabling continuous monitoring and early diagnosis of inflammatory activity in a remote setting.

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Acknowledgments

We would like to thank Lucia Fleckenstein, Vanessa Loew, and Caroline Evers for their contributions to participant recruitment and data collection.

Data Availability

The datasets generated and analyzed during this study are not publicly available due to patient confidentiality but may be available from the corresponding author upon reasonable request.

Authors' Contributions

JS, SM, EF, OD, and FB contributed to conceptualization. JS, SM, EF, OD, and FB performed methodology. JS, SM, EF, OD, and FB contributed to project administration. EF and OD managed resources. JS and SM performed supervision. JS wrote the original draft. JS, SM, RD, EF, OD, and FB contributed to writing, reviewing, and editing the manuscript.

Conflicts of Interest

OD has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, Horizon, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Prometheus, Redxpharma, Roivant, and Topadur. OD was issued a patent for “mir-29 for the treatment of systemic sclerosis” (US8247389, EP2331143). RD has served as speakers bureau for Actelion; served on an advisory board for Boehringer-Ingelheim; and has received grants/research support from Pfizer, Actelion, and Iten-Kohaut foundation and congress participation support from Amgen. SM has received congress participation support from AstraZeneca. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Baseline questionnaire (in German).
[PDF File (Adobe PDF File), 38 KB - resprot_v13i1e62877_app1.pdf]

Multimedia Appendix 2
Questionnaire on assessment of sampling methods (in German).
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e62877_app2.pdf]

Multimedia Appendix 3
Questionnaire on preference for sampling methods (in German).
[PDF File (Adobe PDF File), 249 KB - resprot_v13i1e62877_app3.pdf]

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Abbreviations

CDHI: Centre for Digital Health Intervention
CRP: C-reactive protein
FeNO: fractional exhaled nitric oxide
IL: interleukin
TNF: tumor necrosis factor

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Protocol

The COSMOS Registry of CytoSorb Hemoadsorption Therapy in Critically Ill Patients: Protocol for an International, Prospective Registry

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Abstract

Background: Extracorporeal blood purification with CytoSorb has been increasingly used as an adjunctive therapy in several hyperinflammatory critical care conditions, as well as to remove elevated levels of myoglobin or bilirubin in patients with rhabdomyolysis or liver failure. Despite the increasing worldwide use of hemoadsorption, data from large international multicenter studies are still lacking.

Objective: The COSMOS (CytoSorb Treatment Of Critically Ill Patients) registry is a company-sponsored registry by CytoSorbents Corporation and CytoSorbents Medical Inc. and will provide a data repository and reporting infrastructure for the surveillance of CytoSorb use in real-world critical care settings in an unselected, critically ill patient population. The gathered data will serve as a comprehensive resource to assess the effects of such therapy on patients’ management.

Methods: The international COSMOS registry is collecting prospective data for patients treated with CytoSorb during routine care in various critical care indications, based on the decision of the treating physicians. Data are collected at baseline, during CytoSorb therapy, 24 hours thereafter, at discharge from the intensive care unit and the hospital, and on day 90. Key outcomes assessed include change in inflammatory biomarkers, vasopressor requirements, fluid balance, organ function and organ support, length of intensive care unit and hospital stay, occurrence of adverse events, and mortality.

Results: The COSMOS registry started with the inclusion of the first patient on July 15, 2022, and is now actively enrolling in 4 countries (Germany, Spain, Portugal, and Italy), with plans to expand to other countries outside of Europe. An initial readout is planned for presentation at an international Critical Care conference in 2024.

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Conclusions: The COSMOS registry is intended to provide comprehensive real-world data on patient outcomes with CytoSorb in various critical care indications, thereby contributing to optimization of patient selection, timing of initiation, and dosing of hemoadsorption treatment.

Trial Registration: ClinicalTrials.gov NCT05146336; https://clinicaltrials.gov/study/NCT05146336

International Registered Report Identifier (IRRID): DERR1-10.2196/55880

(JMIR Res Protoc 2024;13:e55880) doi:10.2196/55880

KEYWORDS

extracorporeal blood purification; CytoSorb; hemoadsorption; hemoperfusion; adsorption; hyperinflammation; sepsis; septic shock; liver failure; rhabdomyolysis; hospital care; mortality

Introduction

Background and Rationale

Prolonged and excessive inflammation, characterized by the persistent release of several mediators into the blood stream in response to different stimuli, is believed to contribute to multiple organ failure, leading to a high risk of mortality [1,2]. Blood purification has been increasingly used for treating critically ill patients with excessive inflammation and can be considered as an umbrella for different procedures, subdivided into hemofiltration, hemoadsorption, and plasma-processing techniques, including plasmapheresis and plasma exchange [3-5].

The concept of hemoadsorption refers to the adhesion of circulating molecules such as cytokines to the surface of the respective sorbent material. Different hypotheses have been developed to explain possible beneficial effects of removing such mediators from the bloodstream, including lowering pro- and anti-inflammatory mediators below a threshold to limit organ damage [6] and restoration of a cytokine gradient between tissue- and blood-promoting leukocyte chemotaxis [7]. This pathophysiological rationale and the growing number of clinical studies have led to the hypothesis that reducing inflammatory mediators within the systemic circulation could restore immune homeostasis and positively affect patient outcomes. Currently, there are several extracorporeal technologies available that offer potential benefits in blood purification for managing life-threatening conditions. These include CytoSorb (CytoSorbents), oXiris (including the AN69-ST; Baxter), Jafron HA-series (including HA-230, HA-280, HA-330, HA-330-II, and HA-380; Jafron), Seraph 100 Microbind Affinity Blood Filter (Seraph100; ExThera Medical), and Polymyxin B hemoperfusion (PMX-HP; Toraymyxin, Toray Medical Co., Ltd.). These devices vary in their specific modes of action and target substances for removal, approved indications, and documented clinical experiences, including any potential impact on drug removal [8-10].

The CytoSorb device is a Conformité Européenne labeled whole blood hemoadsorption device. The device was registered in 2011, and the number of patients treated with CytoSorb has continued to grow.

A recent randomized controlled trial (RCT) in healthy volunteers provided definitive mechanistic evidence of CytoSorb's ability to decrease systemic cytokine levels after intravenous administration of endotoxin in an established sepsis model [11]. These findings support the approved indications of CytoSorb therapy for the treatment of a variety of clinical conditions in which excessively high plasma levels of inflammatory mediators occur, such as septic or vasoplegic shock, acute respiratory distress syndrome (ARDS), and critical illness requiring extracorporeal membrane oxygenation (ECMO) therapy. Additional application fields for CytoSorb include use of the device for removal of elevated levels of bilirubin and myoglobin in patients with life-threatening conditions, such as liver failure [12] or rhabdomyolysis [13], as well as the intraoperative removal of ticagrelor and rivaroxaban during cardiothoracic operations with cardiopulmonary bypass [14].

Despite the increasing worldwide use of blood purification therapies, large international, multicenter studies and robust evidence of clinical outcome improvement are still lacking [15,16]. Consequently, questions about the appropriate application modalities, especially regarding timing and dose, remain unanswered. Also, some conflicting data showing neutral or even negative outcomes have been published, underlining the need for further conclusive evidence generation [17-19]. A recent systematic review showed no mortality benefit of the therapy in a very heterogenic patient group and underlined the need to systematically identify patients likely to respond to the therapy with clinical benefits in a reproducible manner [16].

The hemoadsorption device can be easily integrated into concomitant continuous renal replacement therapy or into a dedicated hemoperfusion circuit (Figure 1), as well as into a bypass within the ECMO circuit or a cardiopulmonary bypass circuit.

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Figure 1. Setup integration of CytoSorb into different platforms: (A) hemoperfusion; (B) continuous renal replacement therapy (CRRT) predialyzer; (C) CRRT postdialyzer; and (D) extracorporeal membrane oxygenation with bypass.

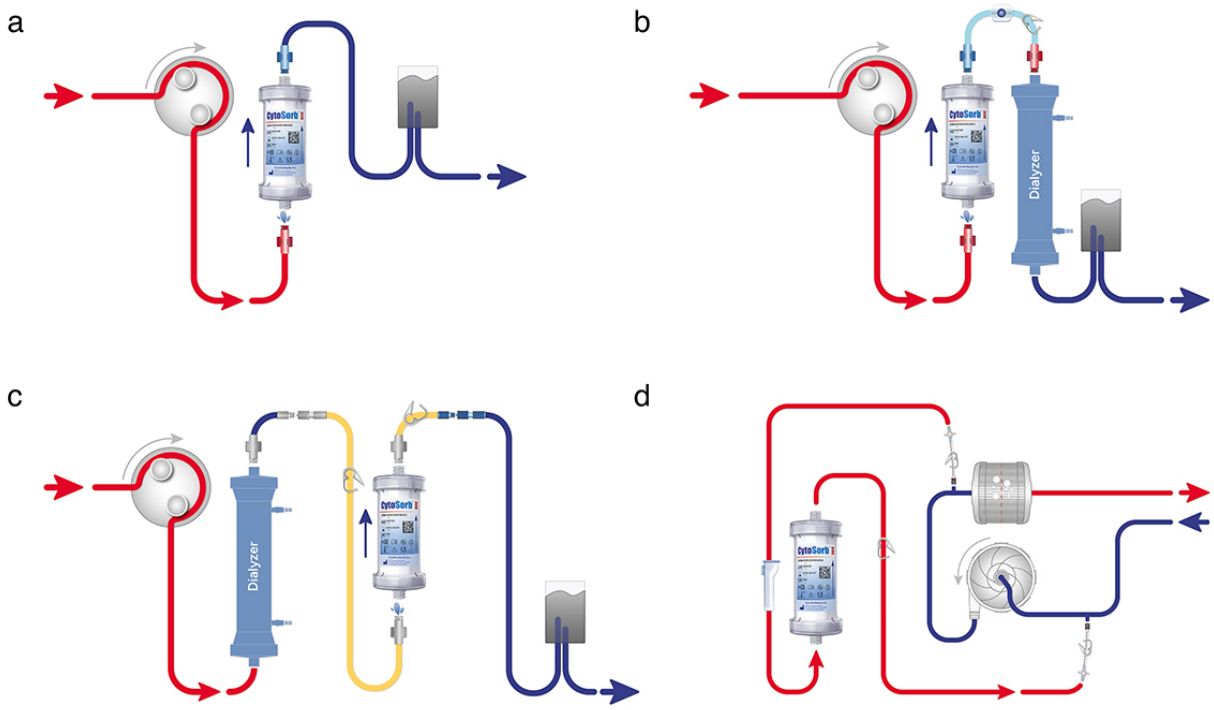

Objectives of the COSMOS Registry

The aim of the COSMOS (CytoSorb Treatment Of Critically Ill Patients) registry is to capture real-world clinical use patterns and clinical outcomes associated with the utilization of the CytoSorb device and to help further refine best practices for the therapy. There is a well-known heterogeneity of treatment effects in critically ill patients [20], which is why collecting registry data is a valuable tool, making it easier to identify those patients who would potentially benefit most from the therapy. Also, treatments of critically ill children are included as a predefined subcohort, allowing the collection of multicenter data, thereby expanding the available evidence derived from single-center reports on limited patient numbers. Additionally, the registry will also serve as a crucial part of the postmarket clinical follow-up measures as required by Medical Device Regulation [21].

Methods

Study Setting

The COSMOS registry is an ongoing, observational, prospective, and international data collection platform for patients receiving CytoSorb devices during routine clinical care. Site selection was performed according to experience with the hemoadsorption therapy (total number of treatments per year), usual indications for use, estimated patient number contributions, experience in study conduct and electronic data collection, as well as personnel capacity and overall interest in participation based on a dedicated site qualification questionnaire. The treatment strategy and patient's management are determined by the physician and not by the registry protocol. For all site personnel, including the principal investigator, subinvestigators, and clinical research coordinators, training on the latest hemoadsorption therapy recommendations is provided to ensure that the users are aware of the current understanding of best practice with CytoSorb and consider these aspects in their decision-making on therapy management [22,23]. Additionally, each investigator is encouraged to review the most recent CytoSorb instructions for use to assess contraindications, warnings, and precautions for treating potential patients. In order to best represent real-world practice and to avoid selection bias, sites are asked to include consecutive patients receiving the CytoSorb device. All clinical data from critically ill patients treated with the device after the date of approval of the institutional review board (IRB) or independent ethics committee (IEC) are considered "prospective data."

The registry collects patient-level data with the use of the CytoSorb device in the following different clinical indications (Table 1).

The study may be discontinued at the discretion of the investigator (or designee) or sponsor if any of the criteria mentioned in Textbox 1 are met.

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Table 1. Different indications for CytoSorb included in the COSMOS (CytoSorb Treatment Of Critically Ill Patients) registry.

Category	Clinical indication
Hyperinflammation	• Septic shock • Hemophagocytic lymphohistiocytosis • CRS[a] • Chimeric antigen receptor therapy CRS
Cardio and pulmonary	• Cardiogenic shock • Acute respiratory distress syndrome • Lung failure with venovenous extracorporeal membrane oxygenation and cardiac failure with extracorporeal life support system
Liver and kidney	• Acute liver failure or acute-on-chronic liver failure • Rhabdomyolysis
Infectious disease	• COVID-19 • Influenza • Dengue
Others	• Postoperative vasoplegic shock • Burns • Pancreatitis • Overdose drug removal

[a]CRS: cytokine release syndrome.

Textbox 1. Study discontinuation criteria.

- Medical or ethical concerns
- Safety issues pertaining to adverse device events (ADEs) or serious adverse events (SADEs) unknown to date
- Changes in accepted clinical practice making the continuation of a registry unwise
- Difficulties in patient recruitment
- Sponsor's decision

Eligibility Criteria

The registry population will be comprised of critically ill patients, including children who undergo treatment with the CytoSorb device as part of their routine clinical care. To best represent real-world practice and avoid selection bias, participating sites will ideally include all patients receiving the CytoSorb device consecutively, without preselection (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- CytoSorb device utilization
- Informed consent for prospective registry participation

Exclusion criteria

- Use of CytoSorb device for antithrombotic drug removal only
- Intraoperative use of CytoSorb device during cardiac surgery only

Ethical Considerations

This registry is being conducted in accordance with International Organization for Standardization (ISO) 14155:2020; the Declaration of Helsinki; the standards of Good Clinical Practice, as defined in the International Conference on Harmonization E6 Guideline for Good Clinical Practice; as well as all other local legal requirements. Prior to initiation of the registry, IRB and IEC approval must be received for the protocol, sample informed consent form (ICF), and any other documents that pertain to patient information and recruitment methods such as advertisements. All subsequent protocol amendments and changes to the ICF must also be submitted and approved by the IRB and IEC. The initial international ethics approval at Vall D'Hebron University Hospital, Barcelona, Spain, is

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PR(AG)86/2022. Each center must obtain approval from its responsible IRB before activation.

To collect in-hospital and postdischarge data, the investigator or designee must obtain a signed, IRB- and IEC-approved ICF from patients or their legally authorized patient representatives when the patient is identified as a potential candidate for the registry (refer to Multimedia Appendix 1 for the ICF). Consent is obtained either from the patient or, according to standard procedures in emergency situations, via the legally authorized patient representative. The ICF contains all the elements required by ISO14155:2020 and only includes data collection, as the indication of treatment with CytoSorb itself is solely at the discretion of the treating physician. In cases where patients are unable to give consent, a declaration of consent must be obtained from a legal representative, taking into account the patient's presumed willingness. The legal representative may be an authorized representative appointed by a power of attorney or a court-appointed caregiver (health care task group) according to local regulations. For children, dedicated ICFs are provided. Patients who are not able to give their consent initially but who become able to during their stay in hospital will be informed about the registry when they are able again to consent, and then the written informed consent on participation in the registry is obtained. Any patient has the right to withdraw from the registry at any time without penalty or loss of benefit. There is no direct financial compensation for participants.

For each enrolled participant, an electronic case report form (eCRF) will be maintained. All clinical data will be extracted from medical records by the site investigator(s) and their designees. Data accuracy will be verified by centralized monitoring. Data will be entered in a deidentified manner; that is, patients who consented will be assigned a consecutive patient identification only traceable by the site. The eCRF will be available for inspection by the sponsor and its designees before, during, and upon completion of the registry. Patient rights regarding information, correction, deletion, and general handling of data will be respected according to the European General Data Protection Regulation. A full data readout is performed at least annually. The data are treated confidentially at all times and are protected against unauthorized access. In the event of premature termination of the registry, no further data will be collected. Transmission of registry-related data, for example, for statistical analysis, to countries with a level of data protection that may differ from that of the European Union, such as the United States, takes place exclusively in deidentified form. This ensures data confidentiality, as data cannot be assigned to a specific or identifiable actual person. Publication of the results of the registry study will be in anonymous form only.

Data Capture and Outcomes

As per the registry protocol, there are no prespecified assessments or medical treatments to be performed other than a follow-up telephone call at 90 days (plus an additional 20 days if needed for administerial reasons) after the start of CytoSorb treatment. Data collection is performed based on medical chart review and transcription of deidentified data collected from hospital admission through discharge. The following key parameters are included (Textbox 3).

Data from the following time points will be collected if available (Textbox 4).

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Textbox 3. Key parameters.

- Demographics
- Baseline characteristics including Acute Physiology And Chronic Health Evaluation II score, respective Pediatric Index of Mortality-3 score for children, and Charlson Comorbidity Index score
- Indication for CytoSorb treatment
- Details on the extracorporeal circuit used (eg, type of platform, blood flow rate, and anticoagulation regimen), integration of CytoSorb, and duration of treatment
- Changes in Sequential Organ Failure Assessment scores or subscores and Pediatric Logistic Organ Dysfunction-2 score for children
- Changes in inflammatory biomarkers (C-reactive protein, procalcitonin, leukocytes, interleukin-6, and other interleukins)
- Laboratory results from hematology, chemistry, coagulation, and arterial blood gas analysis as well as additional drug level measurements
- Duration of organ support therapies (number of days on extracorporeal membrane oxygenation or extracorporeal life support system, number of days on continuous renal replacement therapy, number of days on mechanical ventilation, and number of days on concomitant procedures like therapeutic plasma exchange)
- Daily fluid balance
- Vasopressor requirements (type, dose, and duration)
- Ventilation parameters
- Liver disease assessment (eg, hepatic encephalopathy, bilirubin, bile acids, model for end-stage liver disease score, respective pediatric end-stage liver disease score for children, European Association for the Study of Liver—Chronic Liver Failure score, Maddrey score, and Lille score)
- Acute kidney injury assessment, including Kidney Disease Improving Global Outcomes severity score and myoglobin and creatine kinase levels for rhabdomyolysis
- Critical illness polyneuropathy
- Cumulative blood products
- Concomitant therapies including plasmapheresis and medication
- Length of intensive care unit (ICU) and hospital stay
- ICU and in-hospital mortality
- Safety performance of CytoSorb device, including collection of any unexpected serious adverse device effects
- Cases of device deficiency
- Long-term follow-up on day 90 (+20) including 90-day mortality and cause of death
- Study exit: vital status and registry exit date

Textbox 4. Data collected.

- Baseline (at intensive care unit [ICU] admission)
- Before start of CytoSorb therapy (maximum 24 hours prior)
- During CytoSorb therapy
- After CytoSorb therapy (maximum 24 hours afterward)
- At discharge from ICU
- At discharge from hospital
- Follow-up on day 90 (+20)

A device deficiency is defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance, including malfunctions, use errors, and inadequate labeling [22]. Following the same standardization, a serious adverse device event (SADE) is defined as an adverse device event (ADE) that has resulted in any of the consequences characteristic for a SADE, with an unexpected SADE (USADE) being defined as a SADE that by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. SADE and USADE will immediately be analyzed by the sponsor regarding possible root cause and possibility of reoccurrence. In addition, all statutory reporting duties will be fulfilled. In the case of USADE, the investigator has the same notification duties and reporting timelines as for SADE.

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Analysis and Statistical Methods

Descriptive statistics and patient data listings will be used to summarize the data. Continuous variables will be summarized by nonmissing values (n), mean and SD (in case of normal distribution), median, 25th and 75th percentiles (in case of nonnormal distribution), and minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Stratification of descriptive categories within treatment groups may occur if such elaborations are thought to be useful. Inferential statistical tests may be used, as appropriate, with an α critical value of .05 to indicate statistical significance. Inferential statistical tests will be 2-sided, unless specified otherwise. Also, 95% CIs may be used to compare event rates to a historical and clinically meaningful standard or to investigate the course of biomarkers (or certain laboratory values) after CytoSorb therapy. Multivariate analysis may be used to determine independent predictors of study outcomes. Missing data is unavoidable for critically ill patients treated in the intensive care unit (ICU). The principle of analyses is to only include the nonmissing observations. For inflammatory biomarkers or laboratory values that are highly associated with the use of hemoadsorption devices, sensitivity analyses will be performed by applying a multiple imputation method under the missing-at-random assumption.

Unless specified otherwise, minimum and maximum will be displayed to the same level of precision as the observed value. Mean and median will be displayed to 1 level of precision greater than the observed value. The SD and SE will be displayed to 2 levels of precision greater than the observed value. All *P* values will be rounded to and displayed as 3 decimals. If a *P* value less than .001 occurs, it will be shown in tables as <.001.

Results

The COSMOS registry is an international registry executed in countries where the device is approved and routinely used in everyday clinical practice. It started with the inclusion of the first patient on July 15, 2022. There is no prespecified sample size for the registry, but the current estimation is that with annual enrollment of approximately 300 patients, the registry can reach up to 3000 patients in 10 years. The COSMOS registry is now actively enrolling in 4 countries (Germany, Spain, Portugal, and Italy), with plans to expand to other countries outside of Europe. As of August 1, 2024, a total of 199 patients are included in the registry.

Discussion

Overview

The previous CytoSorb international registry collected patient data from May 2015 to December 2020 and was independently led as an investigator-initiated project by the Centre for Clinical Studies at the Jena University Hospital, Germany [24]. At its closure, 46 sites had included a total of 1434 patients showing improvements in cardiovascular and pulmonary Sequential Organ Failure Assessment scores and a reduction in procalcitonin, C-reactive protein, and interleukin-6 levels [24]. However, several important parameters were not captured, for example, lactate and hemodynamic data, due to a lack of knowledge of hemoadsorption treatment characteristics at the time of conceptualization of the project. Also, the definition of sepsis and septic shock changed in 2016 [25]. Furthermore, other indications for blood purification, including bilirubin and myoglobin removal, were not yet covered at the time by the Conformité Européenne label and were therefore not considered in the initial design of the Jena registry.

Existing literature in the field of CytoSorb treatment mainly consists of smaller studies, case series, and case reports [16], including studies that showed neutral or negative results [17-19]. In the following paragraphs, we summarize the current understanding of the pathophysiology and rationale behind the most common use of CytoSorb in critically ill patients. Of note, so far, evidence is still scarce with a lack of larger RCTs in the field. In general, pooled analysis of such heterogenous patient groups is difficult, especially given the methodological limitations of these studies [26].

Septic and Vasoplegic Shock

The clinical conditions of sepsis and septic shock arise from a dysregulated host reaction to an infection, causing organ malfunction. The excessive release of inflammatory mediators beyond the local area in response to the infection characterizes the syndrome, leading to an overshooting inflammatory response from the host (known as a cytokine storm). However, comprehension of the fundamental pathophysiology behind organ and especially vascular dysfunction, including inadequate vascular response to vasoconstrictors (vasoplegia) caused by sepsis, remains incomplete. Existing data support the concept of sepsis-associated cytokine release as the driving force in refractory vasoplegic shock [27,28]. Both sepsis and septic shock represent 2 of the main causes of death in ICUs worldwide [29,30]. This considerable mortality is at least in part attributable to the inadequacy of current treatment options. The only causal therapeutic options are comprised of infectious source control and antibiotic therapy, while stabilization of the cardiac and respiratory systems is considered supportive measures. However, there are several reasons why CytoSorb therapy might be able to provide benefits for critically ill patients in the ICU who develop severe organ dysfunction due to a dysregulated immune response (ie, often termed as “hyperinflammation” and “cytokine storm”). Existing clinical data on the use of CytoSorb hemoadsorption in patients with sepsis support the concept that a reduction in inflammatory mediators, but certainly also of other, yet unknown substances, can result in improved hemodynamics, reduced needs for catecholamines, reversal of shock, and improved outcomes [31-33]. The effect of hemoadsorption therapy on mortality as a primary end point has not yet been evaluated in a prospective randomized manner, but retrospective studies suggest significant survival benefits in the CytoSorb-treated group compared to matched controls [34,35]. Next to sepsis, vasoplegic shock also occurs in the context of noninfectious triggers such as polytrauma, severe burns, severe acute pancreatitis, and cardiogenic shock [29,36]. Additionally, vasoplegic shock is commonly seen postoperatively after cardiac and other major surgeries [37,38]. Patients with postoperative vasoplegia will be included in this

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registry; however, intraoperative use of the device during cardiac surgery will not be included. The separate STAR (Safe and Timely Antithrombotic Removal) registry is dedicated for the indication of intraoperative antithrombotic removal with CytoSorb hemoadsorption (NCT04976530).

ARDS and ECMO

ARDS is characterized by bilateral interstitial edema of the lungs, resulting from increased capillary leakage. If the condition advances to severe ARDS, one sole lifesaving option available is frequently ECMO. Nevertheless, this approach is expensive, burdensome, and exceedingly invasive, requiring specialized personnel, and is typically only available in specialized facilities. It is crucial to note that the application of ECMO itself may exacerbate the underlying hyperinflammatory state [39]. Recent reports also suggest that patients treated for severe ARDS who received blood purification treatment show improvements in oxygenation, as evidenced by an increased partial pressure of oxygen to fraction of inspired oxygen ratio [40-44].

COVID-19

Based on the emerging knowledge that hyperinflammation may play a key role in respiratory failure in patients with COVID-19, CytoSorb therapy has been used in this setting with over 7500 patients treated worldwide (as of December 2021), including the United States under Food and Drug Administration–issued emergency use authorization [45-49]. The recently released results from the multicenter US CytoSorb therapy in COVID-19 registry showed high survival in the most critically ill patients requiring life support on ECMO [43,50]. The same rationale for using CytoSorb in COVID-19 also applies to other viral infectious etiologies leading to severe respiratory failure, such as dengue fever or influenza [51-55].

Liver Failure

Currently, the medical world fundamentally distinguishes between acute liver failure (including hyperacute or fulminant) and acute-on-chronic liver failure, but all types of liver failure are associated with very high mortality irrespective of the presence of preexisting liver disease [56,57]. For most patients, the only definitive treatment is liver transplantation, but availability is limited. Several artificial liver support systems have been used with the aim of bridging by detoxification in patients with liver failure [56]. CytoSorb has been shown to be effective for the removal of bilirubin [12,58,59] and bile acids [60,61].

Rhabdomyolysis

Additionally, hemoadsorption therapy has been increasingly used to remove myoglobin [13,62,63]. In cases of rhabdomyolysis, efficient removal of myoglobin is crucial to protect the patient from acute kidney injury as well as for organ recovery [64].

Furthermore, children will also be included in the registry, capturing additional specific parameters such as Pediatric Index of Mortality-3 and Pediatric Logistic Organ Dysfunction-2 scores. The instructions for use of the CytoSorb device do not specify patients' age limitations but only mention that for treatment of patients weighing less than 45 kg, discretion should be used. The minimum treated body weight, reported in the literature, is 3.5 kg [65]. An ongoing multicentric observational study in Italy (CYTOPED) has already demonstrated safety and feasibility of the use of CytoSorb in the first 50 children and will allow further investigation into other aspects of the therapy in this patient cohort [66].

Responsibilities and Dissemination

A scientific committee has been established to provide scientific oversight of the registry. This is led by the registry's principal investigator and composed of internationally recognized investigators and experts in the different application fields of extracorporeal blood purification as well as the sponsor's medical director of the trial. The scientific committee will be responsible for any changes to the registry design, the decisions for interim data analyses according to the statistical analysis plan, and the data readout strategy, including presentations at medical conferences and publications. Reports of the annual evaluations of the registry data and retrospective inspection of their own data will be made available to the participating registry centers. The scientific committee and the sponsor may appoint other independent committees to resolve specific problems such as verifying patient classification, adverse events adjudication, or publication policy. Operational execution of the trial will be performed by a contract research organization (EvidentIQ), with oversight and management performed by the sponsor's clinical team.

Strengths and Limitations

The COSMOS registry is a high-fidelity, systematic data collection platform for CytoSorb treatment across multiple critical care indications and highly representative of real-world practice [33,42,67]. Real-world evidence (RWE), as captured with registries, is particularly useful for expanding the evidence base to encompass populations of patients who are not well represented in RCTs but who may benefit from the intervention in question. RWE is also critical in the setting of complex, rapidly evolving treatments or overall rare indications, where RCT design cannot answer all the relevant questions or is not feasible. RWE is essential to better define a treatment's safety profile under routine clinical conditions, particularly in the longer term. These uses enhance clinical knowledge and patient care with approved agents and devices. While RWE has many uses, it also has its limitations [68]. Efforts are being made to develop best practices for the mitigation of common biases in the design of real-world studies. These include ensuring that the data collected are comprehensive, accurate, and complete, by using validated data sources and conducting a thorough evaluation of the quality of data sources to assess their reliability and validity. Also, we aim to include a diverse study population to ensure that the results are generalizable to different patient groups. Engaging with all stakeholders to inform study design and ensure the research addresses relevant and meaningful questions is crucial for valid results of this registry.

Conclusions

The intent of the COSMOS registry is to inform data-driven optimization of CytoSorb therapy across a broad variety of indications and to provide important safety information fulfilling

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regulatory requirements on postmarket surveillance. Furthermore, the current design of the COSMOS registry allows the potential for future registry-embedded RCTs [69] to answer specific prespecified hypotheses, a process that will require separate protocols, consent, and ethics approval.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study. Data management plan, annotated electronic case report forms, and informed consent forms are available on request.

Authors' Contributions

Conceptualization was done by FST, TK, JS, and RF; methodology was developed by FST, TK, and RF; writing and original draft preparation were done by FST, TK, and RF; writing, review, and editing were done by JH, AK, FMB, GB, DT, JLT, and ED; visualization was done by TK; and supervision was done by ED and RF. All authors have read and agreed to the published version of the manuscript. CytoSorbents Corporation and CytoSorbents Medical Inc. are the funding sources.

Conflicts of Interest

FST, GB, JH, AK, JLT, DT, and RF have consulting contracts with CytoSorbents Corporation and CytoSorbents Medical Inc. TK and JS are full-time employees of CytoSorbents Europe GmbH. ED is full-time employee of CytoSorbents Corporation and CytoSorbents Medical Inc.

Multimedia Appendix 1
Informed consent form.
[PDF File (Adobe PDF File), 253 KB - resprot_v13i1e55880_app1.pdf]

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Abbreviations

ADE: adverse device event
ARDS: acute respiratory distress syndrome
COSMOS: CytoSorb Treatment Of Critically Ill Patients
ECMO: extracorporeal membrane oxygenation
eCRF: electronic case report form
ICF: informed consent form
ICU: intensive care unit
IEC: independent ethics committee
IRB: institutional review board
ISO: International Organization for Standardization
RCT: randomized controlled trial
RWE: real-world evidence
SADE: serious adverse device effect
STAR: Safe and Timely Antithrombotic Removal
USADE: unexpected serious adverse device effect

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Protocol

Effectiveness of Ayush Rasayana A and B on the Quality of Life of Older Adults: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: With advancing age among older adults, the associated debilities increase, indicating a deteriorating health status as there is a gradual loss of muscle mass, strength, and functionality. *Ayush Rasayana* A and B are coded Ayurvedic medicines developed from herbal extracts. This study has been planned to prevent debilitating conditions and improve the quality of life (QOL) in older adults.

Objective: This study aimed to assess the effectiveness of *Ayush Rasayana* A and B on the QOL, quality of sleep, and functionality of older adults, along with the tolerability of the intervention.

Methods: This was a multicenter, open-label, cluster randomized controlled trial conducted with 720 participants aged 60 to 75 years. The participants were divided into 2 groups (intervention and control), with both receiving Ayurvedic ancillary treatment for 3 months. The intervention group additionally received 10 g of *Ayush Rasayana* A orally once daily at bedtime for 6 days, followed by 1.5 g of *Ayush Rasayana* B orally twice daily before food for the remaining 84 days. The assessment criteria included the Older People's Quality of Life Questionnaire Brief, Katz Index of Independence in Activities of Daily Living, Pittsburgh Sleep Quality Index, Five Times Sit-to-Stand Test, and shoulder and scapular movements. Any change in hematological and biochemical parameters and occurrence of treatment-emergent adverse events were also assessed during the study period.

Results: The recruitment of the participants started in December 2023, and the final follow-up was completed in April 2024. Out of the total 720 enrolled participants, 686 (95.3%) completed the study up to the last follow-up.

Conclusions: This study may provide evidence-based data to establish preventive treatment protocols for enhancing the QOL and functionality among older adults. The study results may also be helpful for the planning of interdisciplinary health policies for improving the health conditions of different populations

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KEYWORDS

Ayush Rasayana A; Ayush Rasayana B; cluster-randomized trial; geriatrics; Ayurveda; quality of life; complementary and alternative medicine

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Introduction

Background

The aging population in India is a major concern across social, political, and economic spheres. The older adult population in India is growing 3 times faster than the general population, which is attributed to the increased life expectancy [1]. A total of 27.72% of the older adult population reported having a medical condition, either short term or chronic [2]. With advancing age, there is a gradual loss of muscle mass, strength, and functionality. Studies show that chronic morbid conditions such as musculoskeletal disorders impact the quality of life (QOL) in multiple dimensions [3]. The prevalence of age-related diseases is on an upward trend, and its management is limited at this age owing to less reciprocation and multiple underlying disorders [4]. In addition to causing symptoms of structural and functional deficiencies, these age-related illnesses cause a reduction in the older adults' total functional ability and a variety of limitations. The aging process is brought about by the damage inflicted on biological macromolecules, which act as endogenous damaging agents, creating a state of oxidative stress. This accumulated damage in cells over time leads to the loss of function or functional impairments in the body [5]. Reduced quality of sleep and increased prevalence of sleep disorders are common in advanced age. Studies show that older people have low sleep quality, and it is often associated with a lower QOL [6]. Aging is inevitable, and there is an urgent need to find interventions that help reduce the incidence of debilitating age-related diseases and promote QOL.

Ayurveda endures as a traditional and extensive discipline of traditional Indian medicine used to promote health, prevent illness, and treat physical ailments via *Jarachikitsa* or *Rasayana*. The medicines, food products, and lifestyle-related factors that enhance the quality and longevity of life have been termed *Rasayana* [7]. It is a rejuvenation therapy that has been said to impede the aging process (*Vayasthapanam*), lengthen life expectancy (*Ayushkaram*), improve intelligence (*Medha*), build strength (*Bala*), and prevent disease development [8]. According to various studies, the *Rasayana* drugs possess potent antioxidant activity when combined with dietary supplements and rejuvenators. It reacts negatively with oxidative stressors, which are what lead to the production of various free radicals [9,10]. The study drugs—*Ayush Rasayana* A and B—are coded Ayurvedic medicines; are developed from herbal extracts that have rejuvenating properties as per the classical Ayurveda textbooks; and are effective in improving health-related QOL, functional capacity, and cognition [11]. This study is planned as a multicenter, double-arm, cluster randomized controlled trial to assess the effectiveness of *Ayush Rasayana* A and B on the QOL of older adults in the selected populations.

Objectives

The primary objective of the study is to assess the effectiveness of *Ayush Rasayana* A and B on the QOL of older adults. The secondary objectives include the assessment of the quality of sleep and functionality in the study population, along with the assessment of the tolerability of the intervention during the study period.

Methods

Study Design

The study was an open-label, multicenter, parallel-group, cluster randomized controlled trial conducted in 2 groups with an allocation ratio of 1:1.

Study Participants

Inclusion Criteria

Participants aged 60 to 75 years were selected for the study from the identified Scheduled Caste (SC)– or Scheduled Tribe (ST)–dominant areas regardless of gender. They needed to be ambulatory, be clinically stable with or without medication, have a score of 5 or more in the Katz Index of Independence in Activities of Daily Living, and be willing to provide written informed consent for their participation in the study for 3 months.

Exclusion Criteria

Participants with blood pressure ≥160/100 mm Hg, hemoglobin A_{1c} (HbA_{1c}) ≥8%, serum thyroid-stimulating hormone >10 mIU/mL with or without medication, elevated liver enzymes (aspartate transferase and/or alanine transaminase >2 times of the upper normal limit), impairment of renal function (defined as serum creatinine>upper normal limit), or BMI <23 or >30 kg/m^2 were excluded from the study. Those who have a history of serious cardiac dysfunction or pulmonary dysfunction (patients with asthma and chronic obstructive pulmonary disease); those with cancer or chronic inflammatory conditions, including but not limited to chronic infection like tuberculosis, leprosy, HIV, and collagen vascular diseases; participants on hormone replacement therapy, steroid therapy, chemotherapy, or immunosuppressive therapy; and participants with alcohol use disorder were not enrolled. Those with a diagnosis of any severe cognitive or psychiatric illness, neurological disorders, hemorrhagic diseases, or coagulation disorders within 90 days before the screening were also excluded. Participants who were currently on any drugs that affected the cognitive or physical function, on any nutritional supplements or any Ayush or folk medicine for maintaining the QOL, or with any other condition that the investigator thought could jeopardize the study were also excluded from participation.

Withdrawal Criteria

Study participants who developed any serious adverse events, developed any condition mentioned in the exclusion criteria during the study period, and were not compliant with the protocol or not willing to continue in the study were free to withdraw from the study. Detailed justification for withdrawal of the participant were prepared, indicating the line of further management, if required. The sponsor and ethics committee were informed within the appropriate time as per Ayush Good Clinical Practice guidelines.

Study Setting

The study was conducted as a part of the public health care program, through 17 peripheral institutes under the Central Council for Research in Ayurvedic Sciences (CCRAS), Ministry

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of Ayush, Government of India. For the Ayurveda Mobile Health Care Programme under Scheduled Caste Sub Plan, areas predominantly dwelled by SC population were selected by 8 institutes located at Agartala, Gwalior, Patna, Chennai, Vijayawada, Jammu, Guwahati. and Bangalore, while for the Tribal Health Care Research Programme under Tribal Sub Plan, areas predominantly dwelled by ST population were identified by 9 institutes located at Cheruthuruthy, Bangalore, Nagpur, Gangtok, Ahmedabad, Bhubaneshwar, Kolkata, Mumbai, and Jammu. The participants were screened through outreach outpatient departments, medical camps, and door-to-door visits.

Study Intervention

Participants from both groups (intervention and control) were provided with ancillary care through Ayurveda for 90 days. In the intervention group, along with ancillary care, 10 g of *Ayush Rasayana* A in powdered form were administered orally with lukewarm water, once daily after food at bedtime for the first 6 days starting from the day of enrollment, and 1.5 g of *Ayush Rasayana* B were administered orally per day in 2 divided doses (2 capsules of 375 mg each) with lukewarm water, before food for 84 days (from the 7th day onward up to the 90th day of enrollment).

Ancillary care was defined as the care needed by research participants but not necessary to ensure scientific validity, prevent study-related harms, or address study-related injuries [12]. The medicines for ancillary care were procured from Indian Medicines Pharmaceutical Corporation Limited, Ministry of Ayush, Government of India. The dose and duration of ancillary care medicine were decided by the investigator based on the clinical presentations mentioned in the protocol. The study interventions *Ayush Rasayana* A and B were coded Ayurvedic formulations developed by the CCRAS (Table 1). These drugs were manufactured by the Central Ayurveda Research Institute Ayurveda Pharmacy, Jhansi, Uttar Pradesh, India (Figures 1 and 2).

Table 1. Ingredients of the intervention (Ayush Rasayana A and B).

Study drug	Ingredients
Ayush Rasayana A	• Harītakī (Terminalia chebula Retz) • Sanāya (Cassia angustifolia Vahl) • Yashtimadhu (Glycyrrhiza glabra Linnaeus) • Rock salt
Ayush Rasayana B	• Amalaki (Phyllanthus emblica Linnaeus) • Asvagandha (Withania somnifera [Linnaeus] Dunal) • Gudūcī (Tinospora sinensis [Loureiro] Merrill)

Figure 1. Image of the study intervention: Ayush Rasayana A, procured from the manufacturer.

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Figure 2. Image of the study intervention: Ayush Rasayana B, procured from the manufacturer.

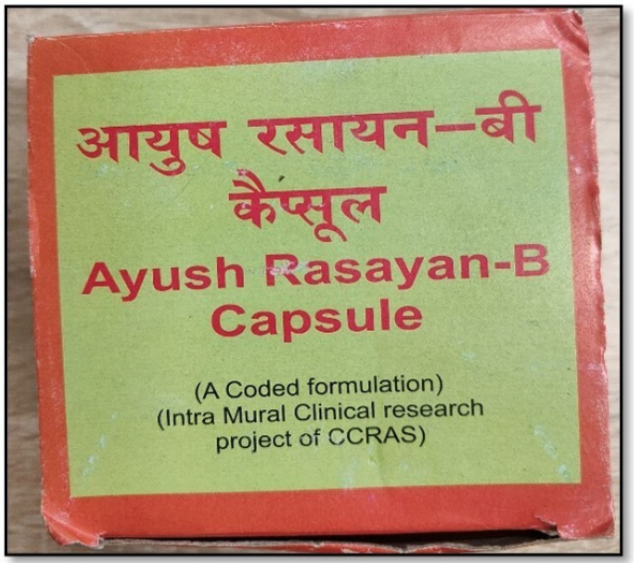

Outcome Measures

The primary outcome measure was the change in the QOL of the older adults, assessed by Older People's Quality of Life Questionnaire-Brief (OPQOL-BRIEF) at baseline and on the 34th day, 62nd day, and 90th day. The secondary outcome measures included any change in the Katz Index of Activities of Daily Living, Pittsburgh Sleep Quality Index (PSQI), Five Times Sit-to-Stand Test, shoulder joint mobility, hematological and biochemical parameters (complete blood count, liver function test, and renal function test), and the occurrence of treatment-emergent adverse events during the study period at the baseline and on the 90th day.

The OPQOL-Brief is a short measurement for QOL developed from the OPQOL-35 questionnaire [13]. It contains 13 questions scored from 1 (strongly agree) to 5 (strongly disagree) based on the response from the participant. The total score is calculated after reverse coding the positive items so that higher scores represent higher QOL. The Katz Index of Activities of Daily Living is a dichotomous scoring tool used for measuring independence in older adults. It measures the functional independence of a person, assessing self-care tasks under 6 domains: bathing, dressing, toileting, transferring, continence, and feeding [14]. The PSQI is a widely used scale comprising a combination of Likert-type and open-ended questions in 7 components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction—each with scores ranging from 0 to 3. Higher PSQI scores indicate more acute sleep disturbances, thus a lower quality of sleep [15]. The Five Times Sit-to-Stand Test is a measure used to assess functional independence and mobility. It evaluates the time required to stand as rapidly as possible from a sitting posture for 5 repetitions; the shorter the time taken by the person, the better the functional condition [16]. The change in shoulder joint mobility is assessed through simple physical maneuvers for the active range of movements: active abduction, and external and internal rotations. Each maneuver is assessed separately by 3-point scales for the range of mobility (fully able=3, partially able=2, and unable=1) and pain on movement (no pain=1, some pain=2, and lots of pain=3) on both sides. A sum score for all 3 maneuvers on each side is estimated for the range of movement and pain separately.

The schedule of enrollment, administration of study intervention, assessments, and follow-up visits are shown in Figures 3 and 4.

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Figure 3. Flow diagram depicting the study schedule for the assessment of effectiveness of Ayurvedic intervention in the QOL of older adults through the cluster randomized controlled trial. ADR: adverse drug reaction; QOL: quality of life.

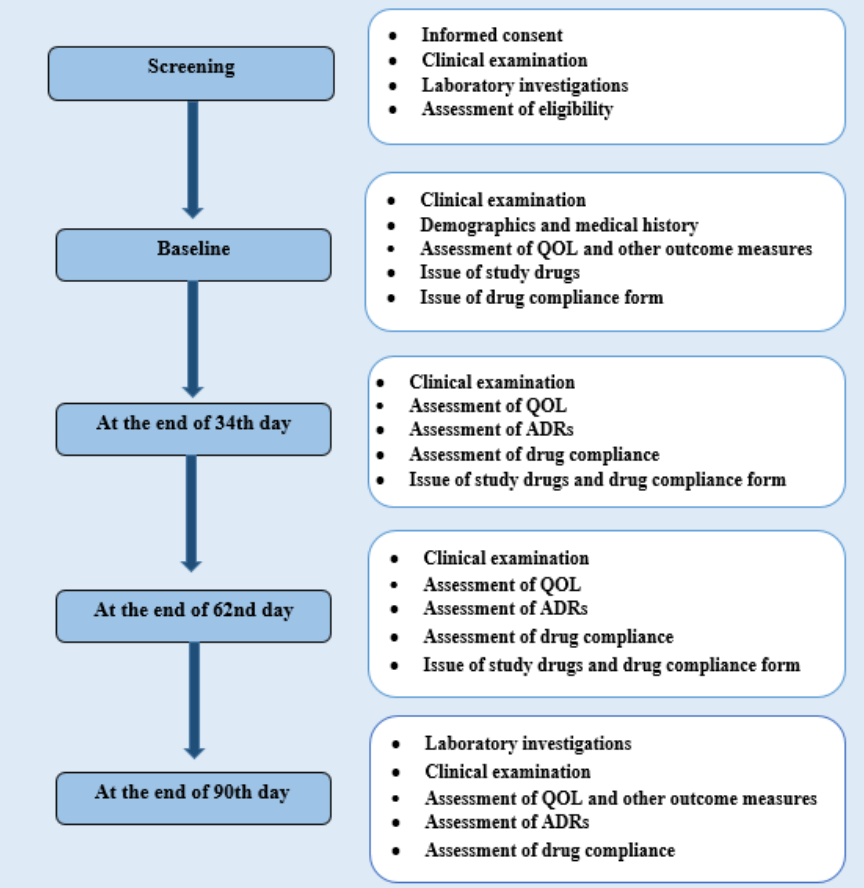

Figure 4. CONSORT (Consolidated Standards of Reporting Trials) diagram depicting the enrollment, allocation, and follow-up visits for the assessment of QOL in older adults through the cluster randomized controlled trial. QOL: quality of life.

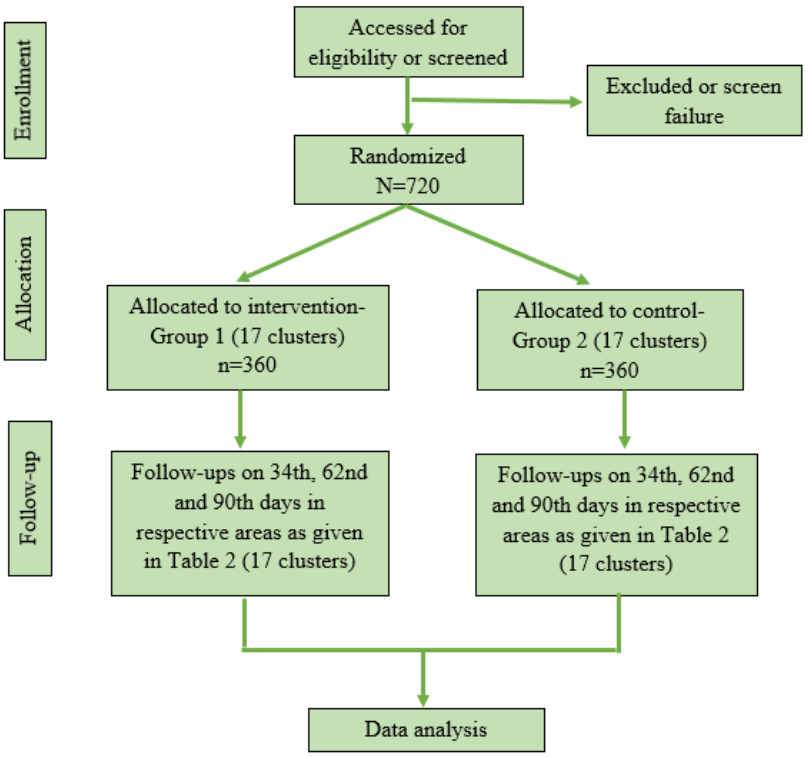

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Sample Size

A change of 9 points on the OPQOL-Brief was expected in the intervention group (*Ayush Rasayana* A and B) compared to 6 points in the control group. With an SD of 8 points and a 95% CI, a sample of 150 participants per group would be needed to achieve 90% power. The estimates for the intervention group and SD were based on the results of a previously published study [11]. Considering the design effect of 2 clusters in this randomized controlled trial and an attrition rate of 20%, a sample size of 360 participants per group was needed. The sample size of each center needed to be 20 in each of the 2 groups. Therefore, the total sample size for each group was calculated as 360 for 18 study centers, and for the 2 groups, the total sample size was 720 (360 × 2). Therefore, a total of 720 participants were intended to be enrolled in the study. Initially, the sample size was calculated for 18 centers, and later on, 1 center was withdrawn from the study and the remaining sample size was distributed to the other centers as per Table 2.

Table 2. Sample size distribution at 17 study centers for the evaluation of Ayush Rasayana A and B in older adults.

Area and location of the center	Sample size, n
Scheduled Tribe–dominated areas (8 centers and 16 clusters)	
Agartala	44[a]
Gwalior	44[a]
Patna	44[a]
Chennai	44[a]
Vijayawada	44[a]
Jammu	40[b]
Guwahati	40[b]
Bangalore	40[b]
Total	340
Scheduled Caste–dominated areas (9 centers and 18 clusters)	
Cheruthuruthy	44[a]
Bangalore	44[a]
Nagpur	44[a]
Gangtok	44[a]
Ahmadabad	44[a]
Bhubaneswar	40[b]
Kolkata	40[b]
Mumbai	40[b]
Jammu	40[b]
Total	380

[a]Clusters with a sample size of 22 in each group.

[b]Clusters with a sample size of 20 in each group.

Randomization

The preexisting groups of the population in the selected areas were identified and divided into 5 clusters at each center as per the geographical demarcation. Of these, 2 clusters were randomly assigned to either the intervention or control group by a cluster randomization chart, prepared using a computer-generated sequence by the statistics department of the CCRAS. The participants were recruited through door-to-door surveys, outreach outpatient departments, and medical camps from the selected clusters by the investigators at each study center using voluntary sampling.

Blinding

The study was open label in execution; therefore, blinding was not done.

Data Collection

The investigators complied with the requirements for all assessments and data collection. The demographic data, clinical history, details of concomitant medications, and outcome

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parameters were documented. During follow-ups, the occurrence of any symptom and need for any rescue medication were recorded**.** Data capture for this study was planned to be in both hard copies of the case report form (CRF) and an electronic format. All source documentation supporting entries into the CRFs was maintained, and data were checked for consistency, omissions, and any apparent discrepancies. After the completion of the study, the data will be analyzed and published without disclosing the personal identification of the participants.

Concomitant and Rescue Medication

The drug or medications administered to treat the participant's additional illness were noted by the study investigators. The participant continued any concomitant therapy for diabetes mellitus, hypertension, or any other disease during the study, which were not specifically excluded. Any medical emergency would have been relieved with the administration of any rescue drug. This would have been properly documented in the CRF.

Statistical Analysis

After data collection, verification of its accuracy and limits will be done. The filtered data will be utilized for additional analysis and interpretation. Categorical variables (eg, bowel movement: regular or irregular) will be reported as number (percentage), and the analysis of the pretrial-posttrial outcome will be done by a McNemar chi-square test. Continuous variables (eg, score and laboratory parameter) will be analyzed by a 2-tailed paired *t* test or Wilcoxon test as per the distribution of data in the pretrial-posttrial situation. Categorical variables will be analyzed through a chi-square test in the between-group comparison. Continuous variables will be analyzed through a 2-tailed unpaired *t* test or Mann Whitney *U* test in the between-group comparison. The assessment parameters assigned in more than 2 follow-ups will be analyzed using the r-ANOVA, Friedman test, or Cochran *Q* test. Continuous data with normal distribution will be represented as mean (SD), and data without normal distribution will be represented as median (IQR). The 5% level of significance will be used throughout the analysis. The SPSS (version 26.0l IBM Corp) software will be used to conduct the analysis.

Monitoring

To ensure strict adherence to the study protocol and correct documentation of the data, CCRAS headquarters monitored the progress of the study. The CCRAS representatives and regulatory authority monitors visited the investigators to inspect the facilities and various records of the clinical study (eg, CRFs and other pertinent data), ensuring that participant confidentiality is respected. The Clinical Monitoring Committee was responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. Any problems detected in the course of these monitoring visits, including delays in completing CRFs, were resolved by the committee.

Ethical Considerations

The study was conducted according to the national ethical guidelines for biomedical and health research involving human participants (2017); Indian Council of Medical Research; and Good Clinical Practice guidelines for Clinical Trials in Ayurveda, Siddha, and Unani Medicine, 2013. The recruitment started after obtaining approval from Institutional Ethical Committees from all the study centers (the approval details for all 17 centers are shown in Multimedia Appendix 1) and registration in Clinical Trial Registry-India (CTRI/2023/06/054204; dated June 20, 2023). Before initiation, local authorities of the selected sites were informed about the program and the study. The written informed consent for their participation in the study was obtained from each participant after explaining the study in detail in their regional language. The privacy and confidentiality of every participant will be protected, and all the data will be stored in password-protected Microsoft Excel formats accessible to the authorized personnel only. All study participants were insured under Clinical Trial Insurance CTI policy, which covered any adverse events that may occur during the study.

Protocol Amendments

Any modification from the study protocol were executed after prior approval from the Institutional Ethical Committees.

Results

The recruitment of the participants started in December 2023, and the final follow-up was completed in April 2024. Out of the total 760 enrolled participants, 686 (95.3%) completed the study up to the last follow-up. The study findings will be disseminated in peer-reviewed journals after the completion of data analysis.

Discussion

Expected Findings

The proposed study will evaluate the effectiveness of *Ayush Rasayana* in improving the QOL, quality of sleep, and functionality of older adults. Previous research [11] conducted on healthy volunteers between the ages of 60 and 75 years has shown that these interventions are likely to be effective in enhancing the physical endurance, QOL, and cognition of older adults, thus improving their general well-being. The study used the World Health Organization QOL-BREF questionnaire and the 6-minute walk distance as efficacy measures for 6 months. The study suggests a beneficial effect of the drugs on the aging process [11]. This study is being conducted to substantiate the effectiveness and realize the full potential of the intervention in comparison with a control group.

Ayush Rasayana A contains 3 herbal ingredients—*Harītakī* (*Terminalia chebula* Retz), *Sanāya(Cassia angustifolia* Vahl), and *Yashtimadhu* (*Glycyrrhiza glabra* Linnaeus)—that are described as having mild laxative properties. Systemic biocleansing or *Samsodhana* is one of the prerequisites for the *Rasayana* procedure as per Ayurvedic textbooks [17]. The intake of the laxative drugs for 6 days before administering the *Ayush Rasayana* B drug will help purify the body and correct digestion and absorption.

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After this, *Ayush Rasayana* B, containing the *Rasayana* drugs such as *Asvagandha (Withania somnifera* [Linnaeus] Dunal), *Amalaki (Phyllanthus emblica* Linnaeus), and *Gudūcī* (*Tinospora sinensis* [Loureiro] Merrill), is administered. *Asvagandha* has been proven to have antistress, neuroprotective, antitumor, antiarthritic, analgesic, and anti-inflammatory properties and is useful in different clinical conditions such as dementia, memory loss, stress-induced diseases, Parkinson diseases, etc [18]. *Amalaki* is one of the important rejuvenator drugs, either alone or as a chief ingredient in many polyherbal formulations, mentioned in Ayurveda classics. The consumption of *Amalaki* have been proven to be beneficial in age-related health conditions owing to its immunomodulatory, antioxidant, cytoprotective, antitussive, and gastroprotective properties. In vivo and in vitro studies conducted on *Amalaki Rasayana* have demonstrated improved exercise tolerance and significant improvement in fatigue time in treadmill exercise in aging rats [19]. The results from a study of *Amalaki Rasayana* on healthy volunteers suggest that it may prevent erosion of telomeres in older adults and promote healthy aging [20]. *Gudūcī* is one of the widely used medicinal plants in Ayurvedic formulations, which is reported to have antioxidant, antistress, hepatoprotective, immunomodulatory, anti-inflammatory, antiarthritic, antidiabetic, antiperiodic, antispasmodic, antiallergic, antineoplastic properties, etc [21] The beneficial effects of *Gudūcī* in reducing stress-induced damage in aging cells have been demonstrated in in vivo studies [22]. *Gudūcī* is one of the drugs mentioned as effective in improving intellect and cognition. The aqueous extract of *Gudūcī* significantly improved memory status in rats along with reducing oxidative stress, indicating its beneficial effect on age-related memory and cognitive functions [23]. Thus, a combination of these 3 herbal drugs in *Ayush Rasayana* B is expected to bring about improved QOL in older adults if provided after proper purification using *Ayush Rasayana* A.

Limitations of the Study

This was a multicenter clinical study focused on older adults. The research was conducted within the framework of a public health program, which constrained the opportunity for detailed, specific laboratory investigations. The duration of intervention was short, and follow-ups without intervention were not included in the study design.

Conclusion

The administration of *Ayush Rasayana* A and B has the potential to improve older adults' QOL owing to the proven *Rasayana* properties of the ingredients. This study will help provide evidence-based data to establish preventive treatment protocols for enhancing the QOL and functionality among older adults. The results of the study could be beneficial for the development of public health programs in the older adult population. The study results may also be helpful for the planning of interdisciplinary health policies to improve the health conditions of different populations.

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All authors declared that they had insufficient funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. *JMIR Publications* provided article processing fee (APF) support for the publication of this article.

Data Availability

Data maintained by the central biostatistical monitoring team of the council will be made available in accordance with ethical guidelines for biomedical research and provisions of the council, as feasible.

Conflicts of Interest

The study drug is developed by the funding agency (Central Council for Research in Ayurvedic Sciences [CCRAS]), and the investigators are the employees working under the CCRAS, Ministry of Ayush, Government of India.

Multimedia Appendix 1
Institutional Ethical Committee (IEC) approval details of the study centers.
[DOCX File , 13 KB - resprot_v13i1e58186_app1.docx]

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Abbreviations

CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: case record form
HbA1c: hemoglobin A1c

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OPQOL-BRIEF: Older People's Quality of Life Questionnaire-Brief
PSQI: Pittsburgh Sleep Quality Index
QOL: quality of life
SC: Scheduled Caste
ST: Scheduled Tribe

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Protocol

Relatives' and Intensive Care Unit Personnel's Perspectives of Care in Organ Donation: Protocol for a Multiple Methods Study

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Abstract

Background: In organ donation from deceased donors, the interaction between the donor's relatives and intensive care personnel is an important factor. The organ donation (OD) process is complex, and patients' relatives play a vital role. Intensive care professionals need knowledge about how relatives perceive and experience the process to create a caring environment and support them throughout. Therefore, this collaborative project aims to explore both relatives' and intensive care personnel's perspectives of care in deceased organ donation in Scandinavia.

Objective: This study aims to (1) investigate donor relatives' satisfaction and ICU personnel's perception of their own professional competence and (2) explore donor relatives' and ICU personnel's experiences in the OD process to design for care and support in OD.

Methods: This protocol outlines a Scandinavian (Norway, Sweden, and Denmark) project, including 4 work packages. Work package 1 started in 2023 with the translation and validation of the Family Satisfaction in the Intensive Care Unit questionnaire into a Danish version and the translation of the Professional Competence in Organ Donation Questionnaire into a Swedish and Danish version. A cross-sectional survey measuring Scandinavian relatives' perception of support in and satisfaction with the organ donation process and a cross-sectional survey measuring Scandinavian intensive care personnel's competence in organ donation are the foundation for work package 2 (2024). The data from both surveys will be analyzed using descriptive and comparative analysis. The results will inform the interview guides in qualitative studies (work packages 3 and 4). Participants in the quantitative study will be invited to participate in in-depth interviews. In work package 3, in-depth interviews will be conducted to illuminate relatives' experiences in the organ donation process. The interviews will be analyzed using thematic analysis, according to Braun and Clarke. In work package 4 (2025-2026), 1 qualitative design study will be conducted to illuminate ICU personnel's experiences. Furthermore, the results from work packages 2 and 3 will inform the development of specific programs for care, support, and communication in the organ donation process.

Results: The project was funded by the Norwegian Organ Donor Foundation in 2022 and Scandiatransplant in 2023. The Norwegian Nurses Organisation supports the project by funding a PhD student. The PhD student was employed by the University in Agder in May 2024.

Conclusions: This project will provide new knowledge that will assist us in designing and establishing programs for care, support, and donor relatives' involvement in OD processes.

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KEYWORDS

organ procurement; qualitative research; public health; patient-reported outcome; organ donation; organ care; perspectives; donors; intensive care personnel; Scandinavia; donor relatives; family satisfaction; descriptive analysis; comparative analysis; organ harvesting

Introduction

Background

Organ donation (OD) is essential for organ transplantation, the lifesaving treatment for patients with terminal organ failure. However, worldwide, there is a gap between the need for organs and the number of deceased organ donors [1,2]. In 2023, there were 2210 new notifications on the transplant lists in Scandiatransplant, the organ exchange organization for the Nordic countries. Although 1982 people received an organ from a deceased donor, as many as 1627 people were still waiting for an organ by the end of the year. Many of the patients on transplant lists will either be withdrawn from the list due to deteriorating health or die while waiting for an organ [3]. The process of procuring organs from a deceased donor is complex, and patients' relatives play a vital role [4-7]. It starts with the admittance of the patient to the emergency department, followed by failed treatment attempts and declaration of death in the intensive care unit (ICU), and finally, organ procurement in the operating theatre. In the months after the donation, donor relatives are offered a follow-up conversation initiated by the ICU personnel [6,8-10].

Whether to become a deceased organ donor is an individual decision [11-14]; yet, in most cases, ICU personnel ask the deceased's relatives for an interpretation of the deceased's preference and decision regarding organ donation. As OD often is the result of sudden and unexpected death, relatives are not prepared. They find themselves in a devastating situation facing the sudden death of a loved one, and they may have many thoughts regarding the usability of the body, the purpose of the donation, and the notions of meaning and hope in this tragedy [5,15,16]. Hence, the ICU personnel's competence in communication and the OD process is crucial when there is a potential deceased donor (DD) in the ICU [17-20]. To gain more knowledge about relatives' needs and the ICU personnel's competence in OD processes, we conduct a Scandinavian collaborative project in Norway, Sweden, and Denmark. These neighboring countries are cooperating partners in Scandiatransplant, have a common history, and the health care system and culture are fairly similar. This project involves users who have personal experiences they want to share. One of them, Anne Stine, lost her husband in an accident. At the ICU, the question about organ donation was raised. She says: "Even if we knew Niels' wishes related to organ donation, it was crucial that the health personnel had a humble, respectful approach to the topic. One of the most important issues is enough time to be able to get used to the idea that someone close to you has passed away. Time to take a decision. The way it is communicated can be decisive" [21].

Qualitative studies investigating relatives' experiences with OD in general show that they may have difficulties understanding and dealing with the severity of the situation and that their relationship with the intensive care staff is of great importance [10,15,22-24]. Lack of comprehension can present a challenge, and understanding the process helps people reconcile with their decision [10]. Furthermore, the prolonged interventions necessary to enable OD can be misleading and make it difficult to understand brain death [17]. Relatives of ICU patients are at increased risk for long-term health impairments such as anxiety, depression, and complicated grief [25,26]. In the OD process, in which all treatment is deemed futile, and the patient becomes a potential DD, a lack of knowledge can make donation a fearful experience [27]. Hence, the ICU personnel have a multidimensional responsibility to create a caring environment and provide correct and comprehensive information to accommodate relatives' understanding and to prevent psychological impairment. At the same time, this cooperating, caring relationship enables organ donation and ensures that there are organs available for patients waiting for organ transplantation [4,6,28].

Organ Donation Methods

The OD process has traditionally taken place after the patient has been declared dead by neurological criteria, what is known as donation after brain death (DBD) [1]. In these cases, the patient is declared dead while the heart and lungs are still functioning, and vital organs can be preserved by medical treatments. Hence, the patient's family members may perceive that their loved one is still alive [17]. To meet the excessive demand for donor organs, organ donation after circulatory death (DCD) has been introduced to complement DBD. The former can be performed in a controlled context (controlled donation after circulatory death [cDCD]) when treatment is deemed futile, and death cannot be determined by neurological criteria [1,2,29]. In these cases, following the decision to withdraw life-sustaining therapies, the family members witness the controlled death of the patient [22]. Thereafter, the family must leave the room quite rapidly, and the organ donation procedure is performed. This OD method is now available in Scandiatransplant's member countries, Norway, Sweden, Denmark, and Finland [13,30]. There is a significant need for further knowledge about relatives' experiences related to both methods of OD.

Relatives' Satisfaction With Care and Decision-Making

The quality of health care services must be evaluated using ongoing measurement of satisfaction [31,32], which is lacking in organ donation research. Previous studies [32-35] have investigated relatives' satisfaction with care and decision-making support in the ICU, with results showing that there is potential for improvement. When it comes to the process of OD, relatives are the unique source of information about satisfaction in end-of-life care in the ICU. Studies investigating donor families' psychological well-being [36-38] have shown that donation may have a beneficial effect on the bereavement process, whereas negative feelings related to organ donation might increase the symptoms of posttraumatic stress [38]. None

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of the studies described above focuses on how the process in the ICU is perceived by the relatives. In Belgium, Poppe et al [39] investigated the quality of communication and emotional support during the organ donation process. Most relatives reported receiving emotional support; however, the support decreased during the process.

ICU Personnel's Competence in the OD Process

ICU personnel, both physicians and nurses, are responsible for identifying a potential donor and partaking in donor management and care for the next of kin. However, OD is a rare event, and in line with international research [40-44], scarce experience and insufficient competence in approaching next of kin and medical aspects regarding OD have been reported in previous Norwegian studies [45-47]. Internationally, education programs have been developed to enhance the quality of the communication and emotional support offered during the donation process [48,49]. In Norway, Sweden, and Denmark, there are similar interdisciplinary programs where ICU personnel are educated in the OD process. The education programs include donor management and communication; however, as far as we know, their effect has not been evaluated. All 3 countries have donor-responsible doctors and nurses at their donor hospitals, and in some regions or hospitals, there are specialized nurses in organ donation. Any hospital may initiate the donor process; however, in Norway, organ retrieval is allowed only at hospitals the health authorities have certified.

Needs Description

There is a lack of studies exploring experiences related to both DBD and cDCD, and few studies have investigated relatives' perspectives on care and support during the organ donation process, including aftercare of relatives in general [50]. There is also a lack of knowledge about ICU personnel's professional competence and experiences related to the 2 donation methods. To our knowledge, no previous research focusing on donor relatives' or ICU personnel's experiences and perceptions of care, decision-making, and support across ICUs in Scandinavia exists, despite the longstanding cooperation in organ exchange within Scandinavian countries. The cDCD method of organ donation has recently been reintroduced in the Nordic countries as a complement to DBD. Consequently, we have a unique opportunity to explore relatives' experiences in both groups. This project will allow us to identify aspects that might influence relatives' perceptions of the OD process. These aspects will form the basis of future work to enhance ICU personnel's competence in care and support for relatives when OD is an option. Therefore, there is a need to assess perceptions of and satisfaction with care, decision-making, and support during the organ donation process in Scandinavian ICUs.

Aim and Research Questions

Overview

The overall aim of the project is to explore relatives' and ICU personnel's perspectives of care and support in OD in Scandinavia by increasing the acknowledgment of family involvement and designing programs for care and support in OD, both DBD and cDCD, including donor relatives' aftercare.

Research Questions

1. What is donor relatives' satisfaction with care, decision-making, and support in the OD process?
2. What are donor relatives' experiences in the OD process?
3. What is ICU personnel's perception of their own professional competence in the OD process?
4. What are ICU personnel's experiences in the OD process?

Methods

Overview

This project consists of 4 work packages and includes 2 quantitative studies to assess relatives' and ICU personnel's perceptions of the organ donation process and 2 qualitative studies to explore relatives' and ICU personnel's experiences and perspectives related to the 2 methods of OD. The studies will be the basis for designing and implementing follow-up programs to improve clinical practice in organ donation across Scandinavian countries (Figure 1). The project started in 2023 and will be completed in 2028.

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Figure 1. Work packages. Wp: work package; FS-ICU: Family Satisfaction in the Intensive Care Unit; PCODQ: professional competence in organ donation questionnaire; ICU: intensive care unit.

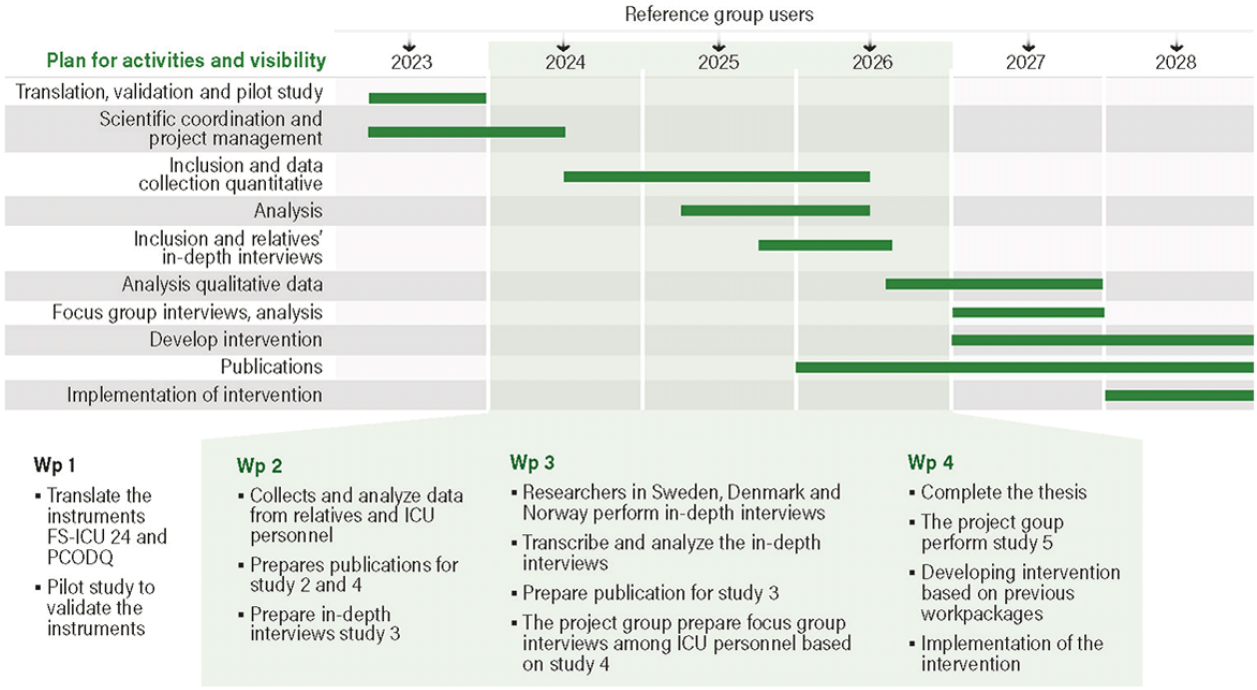

Work Package 1: Translation and Validation of Instruments (2023)

The translation process followed recognized guidelines for forward and backward translation [51,52]. A reference group reflects the perspectives of the donor relatives and of health care professionals in the ICU. The project group consists of members from the 3 countries. The Swedish and Danish research team members will act as gate openers in the clinical field. The Danish team performed the translation of the instrument Family Satisfaction in the Intensive Care Unit (FS-ICU) 24 into Danish and will test it in a pilot study (study 1). The Danish version of FS-ICU will be tested for content and internal consistency using Cronbach's alpha during the spring of 2024 and will be published in a separate scientific paper. The project group members in Sweden and Denmark approved the translation of the instrument measuring ICU personnel's competence in the respective languages. Validation will be performed accordingly.

Work Package 2: Assessment of Relatives' Perceptions of and Satisfaction With Care, Decision-Making, and Support, and ICU Personnel's Professional Competence in the Organ Donation Process (2024-2025)

Overview

Assessment of donor relatives' perceptions of care in and satisfaction with the OD process by using the FS-ICU 24 questionnaire developed by Heyland and Tanmer [32,33,53] will start in 2024 (study 2). Simultaneously, ICU personnel's perception of their own professional competence in OD will be assessed (Study 4) by using the professional competence in organ donation questionnaire (PCODQ) developed by Meyer et al [47].

Study Design

Study 2: across-sectional survey to explore relatives' satisfaction and perceptions of the OD process will be conducted consisting of the following information.

Demographics such as relatives' nationality, gender, age, relation to the donor, and donation-specific questions.

The FS-ICU 24 questionnaire will assess donor relatives' satisfaction [32]. The questions concern the perception of care, communication with the ICU staff, the quality of information, and perceptions of the decision-making process. The items are scored on a 5-point Likert scale from ranging from poor to excellent. The questionnaire was used in a Norwegian cross-sectional study [33] to measure satisfaction with care and decision-making in the ICU and psychometrically tested in a Norwegian context [54]. Even though the questionnaire was not developed to scope the donor relatives' satisfaction we will use it in this project.

Setting and Recruitment

In Sweden and Denmark there are OD registries where the public may opt-in or opt-out, while in Norway a person may register their attitude on the national health website; however, it is not a formal OD registry. As the transplantation and organ donation acts in all 3 countries states that the deceased will should be followed, the relatives have an interpretative role in the OD. Former relatives involved in OD processes in a Scandinavian ICU in the last 2-24 months will be invited to participate. There are approximately 100-200 deceased donors a year in the respective countries. Relatives describe OD as a distinctive experience that does not fade over time. Hence, we anticipate that an inclusion period of 2-24 months will be sufficient. We will establish a network of ICU personnel to recruit eligible participants. Based on power calculation

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statistics, we will need a sample of 92 relatives from each country. Furthermore, to allow for dropouts, we will include an extra 20%. Thus, we aim to enroll 110 individuals from each country.

Relatives who were involved in a DBD or cDCD process for a close family member in an ICU in Norway, Sweden, or Denmark will be included. We will include relatives with experiences from DBD or cDCD in all 3 countries. They can be included even if the decision-making process resulted in no donation. Children younger than 18 years, relatives without the capacity to consent, and persons who are not able to understand Scandinavian languages will not be invited to participate.

Data Analysis

The FS-ICU scale will be recoded into scores ranging from 0 to 100, (0=poor, 25=fair, 50=good, 75=very good, and 100=excellent). Transforming item scores to a 0-100–point scale makes the values more meaningful and more appropriate for statistical analyses. We will perform descriptive and comparative analyses. Descriptive analyses will be generated for family members' demographics and for scores on perceptions of and satisfaction with care. We will use multiple linear regression analysis to identify adjusted associations between care, communication support, and family satisfaction. The data will also be stratified by country to check for any differences among the 3 countries.

Study 4: across-sectional survey to explore ICU personnel's perception of their competence in organ donation will be conducted consisting of the following information.

Background variables include profession, specialization, type of hospital, experience in OD, both care and communication and clinical experience in the ICU.

ICU personnel's professional competence in OD will be measured by the PCODQ [47]. The questionnaire consists of 32 items exploring the different dimensions of theoretical, practical, ethical, and socially mediated knowledge of professional competence on a 5-point Likert scale.

We also assess what they perceive as most important for developing their own professional competence in OD.

Setting and Recruitment

The network of ICU personnel will assist in recruiting eligible personnel. The ICUs vary in terms of size and site, such as university, regional, or local hospitals. ICU personnel at university and regional hospitals may have more experience in organ donation than those at local hospitals. The practice and approach may also vary between countries and hospitals. ICU physicians and nurses who have been involved in at least 1 OD will be recruited in ICUs in the 3 countries. They will receive an invitation letter, which will include information about the study and a consent form by email. Those who consent to participate will receive an electronic questionnaire.

Data Analyses

An independent samples *t* test will be used to test differences between ICU physicians and nurses. Regression analysis will be used to test potential associations between background variables and perception of professional competence. One-way ANOVA will be used to test potential differences between ICU personnel in the 3 countries. Cronbach α will be performed to test the validity of the Swedish and Danish versions of PCODQ.

Work Package 3: Qualitative In-Depth Interviews to Gain Insight Into the OD Process From Relatives' Own Perspectives (2025)

Overview

Study 3: to capture the relatives' experiences in the OD process, we will use a qualitative design with in-depth interviews. In-depth interviews can provide rich information about the OD process from the relatives' own perspectives. The results from the cross-sectional survey in Study 2 will allow us to identify areas that need further in-depth exploration, and a semistructured interview-guide will be developed based on previous studies [5,16] and the cross-sectional study.

Study Design

Recruitment

We will recruit participants among eligible relatives who accept an invitation attached to the survey (study 2). Approximately 6 or 7 participants from each country will be purposively selected based on the areas identified in Study 2 as needing further exploration. We will include 20 participants altogether.

Data Collection

Interviews with former donor relatives will be conducted in Norway, Sweden, and Denmark. The interviews will be conducted by the PhD student in Norway and by the core researchers in Sweden and Denmark. By interviewing relatives about their experiences during and after the OD process, themes and items found in the quantitative study (study 2) can be further explored, and new phenomena might be revealed. The interviews will be recorded by a recorder recognized for research and transcribed by native-speaking transcribers in Norway, by the PhD student, and in Sweden and Denmark by a professional service.

The time and place of the interviews will be chosen in accordance with the participants' preferences.

Data Analysis

The qualitative data will be analyzed using a thematic analysis (TA) comprising an interpretative approach, according to Braun and Clarke [55]. The 6 steps of TA are (1) get familiar with the data by reading, rereading, and searching for patterns across the dataset; (2) coding; (3) searching for themes across the codes; (4) reviewing the themes; (5) defining and naming the themes; and finally (6) relating the results to the research question and the existing literature. The TA was chosen as it is flexible and allows for the search of patterns and meaning across the dataset.

The NVivo software (Lumivero) will be used for qualitative analysis.

Work Package 4: Exploring ICU Personnel's Experiences and Designing a Plan to Implement the

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New Knowledge Obtained in the Previous Stages in Intensive Care Settings (2026-2027).

Overview

Studies 2-4 will be completed, and the project group will conduct a qualitative study to gain insight into ICU personnel's experiences in the OD process (study 5).

Study 5: qualitative study to explore ICU personnel's experiences in DBD and cDCD processes. We will use focus group interviews to gain a variety of perspectives on OD. In contrast to individual interviews, focus group interviews use group dynamics to acquire qualitatively good data about the participants' experiences and opinions. Furthermore, the advantage of using focus groups is that the participants consider their own views in the context of others [56].

Study Design

Recruitment

Both ICU physicians and nurses from the respective countries who participated in the cross-sectional survey and agreed to participate in the qualitative study will be invited to participate.

Data Collection

The results from the 3 previous studies will inform the development of a semistructured interview guide. A Norwegian researcher will moderate the focus group interviews in Norway and participate in the focus group interview, while a Swedish and Danish researcher will moderate in the respective countries.

Data Analysis

The project group will perform a thematic analysis [55] to identify themes and patterns.

Implementation

The knowledge gained from studies 2-5 will form the foundation of specific follow-up programs for care, support, and communication throughout the OD process, starting during the ICU stay and decision-making process and ending with an aftercare intervention.

Ethical Considerations

Overview

The project has ethical approval from the Regional Ethical Committee (REK sør-øst C 502704) and Sikt (445633) [57]. To ensure appropriate ethical considerations throughout the study phases, we will follow the World Medical Association (WMA) Declaration of Helsinki [58]. This project involves relatives who might be vulnerable. The participants will receive oral and written information about the project. The researchers will act with sensitivity when it comes to disclosure of aspects of lived experience that would normally be kept private [59]. Throughout the project phases, we will be special attentive to the risks of psychological burdens and possible re-traumatization. If there is a need for further psychological support, the project members will establish an appropriate support team.

Clinical staff members will provide information sheets to relatives who are potential participants, and the survey will be sent directly by the clinic using their registered contact information. We will use web survey software to ensure the participants' anonymity. Relatives and ICU personnel who wish to participate in the interview studies will return their replies and completed questionnaires. All participants will be able to withdraw their consent to participate at any time during the process, and we will ensure confidentiality and anonymity in reporting throughout the research process. No names of individuals or hospitals will be exposed in the interview transcriptions or reporting. The transcriptions will be treated confidentially and be kept under lock and key at the University in Agder. The project partners have clear guidelines and regulations for collecting, storing, and processing research data. All data will be collected according to the European General Data Protection Regulation [60]. The University in Agder and project partners will establish data-sharing agreements as needed. All data will be treated in strict adherence to the regulations of the data protection officers at the University in Agder and project partners.

Contingency Plan

In order to meet any problems, we have established an expert group consisting of professionals in organ donation or intensive care from the 3 countries in addition to the research group.

Results

The project was funded by the Norwegian Organ Donor Foundation in February 2022 and Scandiatransplant in March 2023. The Norwegian Nurses Organisation decided to support the project by funding a PhD student for 4 years. The PhD student was employed by the University in Agder on May 1, 2024. The recruitment will start during the autumn of 2024.

Discussion

Principal Findings

This research is novel because no previous research has focused on relatives' experiences and perceptions of care, decision-making, and support or ICU personnel's perceptions of their professional competence in OD processes across ICUs in Scandinavia, despite the long-existing cooperation in organ exchange. By conducting this study, aspects that might influence relatives' and ICU personnel's perceptions of OD processes can be identified. These aspects will form the basis of future work to improve care and support for relatives when OD is an option.

The cDCD method has recently been reintroduced in the Nordic countries as a complement to DBD. Consequently, we have a unique opportunity to explore the experiences of relatives in both groups. In addition, the perspectives on processes that did not lead to organ donation need to be illuminated.

The new knowledge obtained through the 2 studies reflecting the relatives' perspectives will inform efforts to increase professional competence in the organ donation process and to prepare ICU personnel for meeting relatives in the future. Based on this knowledge, and the knowledge we will obtain about ICU personnel's perception of their own professional competence and their experiences in OD, we plan to organize

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regional workshops to develop systems that can ensure appropriate support and aftercare for donor relatives [16,18,33,40,47]. A more uniform approach towards OD seems to be beneficial [9,18,40]. Furthermore, it seems important that the relatives of the donors understand the OD process. Support during the process and aftercare, where the relatives have the opportunity to ask questions and receive information both about the OD process and the result of the donation, may reduce a potential burden [5,7,10,17,25]. Relatives are important ambassadors; their communication about the topic, their experiences, and their stories will influence their social surroundings. These experiences can be decisive for others' responses to the question of organ donation [16]. To share this knowledge and raise public awareness, the Division of Communication at the University in Agder will offer coaching for publishing feature (op-ed) stories in the press [61].

Strengths and Limitations

This project has several strengths; one important strength is that it will include donor relatives and ICU personnel from 3 Scandinavian countries. Another important strength is that the cross-sectional surveys will provide a broad understanding of relatives' perceptions of and satisfaction with care and support, as well as of ICU personnel's professional competence in the OD process. Using both quantitative and qualitative methods enables both broad and in-depth insight.

One limitation is the different ICU cultures and resources in the Scandinavian countries, which might be a challenge in recruiting participants on the one hand, but on the other hand, might be a strength in the interpretation of the results.

Both relatives and ICU personnel will be anonymous participants in the surveys, and the project members will not be active participants in the recruitment. This might be another limitation as there will be no control over who has been invited to participate or any possibility of a reminder.

Conclusion

This project will provide new knowledge that will assist us in designing and establishing programs for the care of both potential donors and their relatives. Furthermore, support and donor relatives' involvement in OD processes will be emphasized.

Patient and Public Involvement

To ensure the project's relevance, 4 family members who have been involved in the organ donation process are included. Their contribution in planning during the different phases of the project is invaluable. They all have unique experiences that are essential in developing the interview guide for the in-depth interviews. Furthermore, their previous experiences as relatives of deceased organ donors will provide a different perspective than the researchers, and they will be involved in the analysis and interpretation of the results and the dissemination of the new knowledge.

An ICU physician and 1 ICU nurse from 2 donor hospitals in Norway will also participate in the reference group to provide the perspective of health professionals and contribute to the dissemination of new knowledge.

Another member of the reference group is a woman with a kidney transplant. She is a local team leader of the Norwegian Association for Kidney Disease and Transplantation. She has a broad network and provides yet another perspective to this research project.

Dissemination

The study results will be disseminated through publications in international peer-reviewed journals, presentations at national and international conferences, and in forums for intensive care health care professionals.

Acknowledgments

This work was supported by the Norwegian Organ Donor Foundation and Scandiatransplant. There was no use of generative artificial intelligence in any part of the preparation of the manuscript.

Data Availability

The datasets used and/or analyzed during this study are not publicly available due to General Data Protection Regulation laws but are available from the corresponding author on reasonable request and with permission from the Norwegian Centre for Research Data.

Authors' Contributions

GF and KBM conceptualized the study and designed the details with substantial contributions from GR. GF and KBM wrote the study protocol. GF is the principal investigator. KBM prepared the first draft of the manuscript. GF and GR contributed to the critical revision of the manuscript. The corresponding author attests that all listed authors meet the authorship criteria, and no others who meet the criteria have been omitted.

Conflicts of Interest

None declared.

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Abbreviations

cDCD: controlled donation after circulatory death
DBD: donation after brain death
DCD: donation after circulatory death
DD: deceased donor
FS-ICU: Family Satisfaction in the Intensive Care Unit
ICU: intensive care unit
OD: organ donation
PCODQ: professional competence in organ donation questionnaire
TA: thematic analysis
WMA: World Medical Association

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Protocol

Bystander Response and Out-of-Hospital Cardiac Arrest Outcomes (Bro. Study) in 3 Gulf Countries: Protocol for a Prospective, Observational, International Collaboration Study

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Abstract

Background: : Globally, there is significant variation in the out-of-hospital cardiac arrest (OHCA) survival rate. Early links in the chain of survival, including bystander cardiopulmonary resuscitation (CPR) and the use of an automated external defibrillator at the scene, are known to be of crucial importance, with strong evidence of increased survival rate with good neurological outcomes. The data from the Middle East are limited and report variable rates of bystander CPR and survival. It is crucial to get prospective, reliable data on bystander response in these regions to help plan interventions to improve bystander response and outcomes.

Objective: This international collaborative study aims to describe the characteristics, including bystander interventions and outcomes, of OHCAs brought to hospitals enrolled in the study from Abu Dhabi, United Arab Emirates; Doha, Qatar; and Muscat, Oman. It also aims to describe the strength of the association between bystander response and OHCA outcomes, including the return of spontaneous circulation, survival to hospital admission, survival to discharge, and good neurological outcome at discharge in the local context of low bystander CPR rates.

Methods: This multicenter, prospective, noninterventional observational study (Bro. Study) will be conducted at the emergency departments of 4 participating tertiary care hospitals in 3 countries. The data will be collected prospectively according to the Utstein style (a set of internationally accepted guidelines for uniform reporting of cardiac arrests) on demographic variables (age, sex, nationality, country, participating center, and comorbidities), peri–cardiac arrest variables (location, witnessed or not, bystander CPR, use of automated external defibrillator, time of emergency medical services arrival, initial rhythm, number of shocks, and time of prehospital CPR), and outcome variables (return of spontaneous circulation, survival to discharge, and neurological outcome at discharge and 3 months). Univariate and multivariate analysis with logistic regression models will be used to measure the strength of the association of bystander interventions with outcomes using SPSS (version 22).

Results: Data collection began in November 2023 and will continue for 2 years, with publication expected by early 2026.

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Conclusions: Bystander response to an OHCA is critical to a favorable outcome. The reliable, baseline bystander CPR data will be a cornerstone in the team's next planned projects, which are to qualitatively identify the barriers to bystander CPR, conduct a scoping review of community interventions in the Gulf and other Asian countries, and design and implement strategies to help improve the bystander CPR rate in the community.

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KEYWORDS

out-of-hospital cardiac arrest; cardiac arrest outcomes; bystander response; cardiopulmonary resuscitation; CPR; automated external defibrillator; AED; survival to discharge; emergency medical services; prehospital care; Utstein style

Introduction

Background

Out-of-hospital cardiac arrest (OHCA) represents a substantial public health challenge, contributing significantly to morbidity and mortality across societies [1]. Timely and coordinated responses from the community and prehospital emergency medical services (EMS) are crucial in mitigating OHCA-related fatalities [2]. The early components of the chain of survival, comprising early recognition of cardiac arrest, prompt activation of EMS, provision of high-quality cardiopulmonary resuscitation (CPR), and timely defibrillation, are widely acknowledged as pivotal factors associated with increased rates of return of spontaneous circulation (ROSC) and improved neurological outcomes upon hospital discharge [2].

Notably, family members or bystanders assume a critical role in initiating this chain of survival by administering early and effective CPR. A systematic review and meta-analysis underscore the importance of swift delivery of evidence-based interventions by witnesses, with bystander CPR yielding a number needed to treat of 17 in areas with low baseline bystander CPR rates [3]. Studies show that bystander CPR can be associated with a 3-fold increase in survival with good neurological outcomes. Early use of an automated external defibrillator (AED) individually doubles the chance of survival and good neurological outcome [3,4]. Bystander CPR is also associated with higher rates of first shockable rhythm and higher survival rates, including survival with good neurological outcomes [4]. Enhanced care at pivotal junctures in the chain of survival is paramount, given the substantial patient volume before irreversible neurological damage occurs [5].

Discrepant survival rates following OHCA are documented globally, indicative of varying levels of effectiveness in community and prehospital EMS responses [6]. Such disparities are reflected in the variability of reported bystander CPR rates and AED use worldwide, with observed correlations between response efficacy and survival rates [7]. A recent study in Australia found lower rates of training and willingness to do CPR and use AED among migrants in Australia [8]. Regional studies have identified spatial disparities in bystander CPR rates, suggesting the potential for tailored CPR training strategies to address such discrepancies effectively [8].

A recent systematic review found that long-term survival and favorable neurological outcomes were lower in Asian and Middle Eastern countries than in European and North American countries [7]. Globally, there are examples of the focus on improvement in bystander CPR and AED use that improved all the relevant outcomes of OHCA [9]. Development of community-integrated response in Ireland over a period of 5 years increased the bystander CPR rate from 69% to 81%, improved the ROSC rate from 23% to 26%, and increased the survival to discharge from 6.3% to 7.2% with a cerebral performance score of 1 or 2 in most of them [10]. In the Pan-Asian Resuscitation Outcomes Study, implementing a dispatch CPR mechanism improved the rate and quality of bystander CPR, resulting in a measurable increase in survival with favorable neurological outcomes [11].

The Middle East and South Asia exhibit significantly lower OHCA survival rates and bystander CPR rates than global averages, with bystander CPR rates varying widely within the region [12,13]. One paper reported a bystander CPR rate of 30% [12], while another reported 5.1% [14]. The rate of AED use was reported to be less than 3% in Gulf Cooperation Council (GCC) countries. These variations underscore the complexity of OHCA management in the region, necessitating tailored interventions and further research to improve care and enhance survival rates.

While international literature underscores the critical importance of early CPR and defibrillation, a lack of uniform OHCA data reporting from the Middle East contributes to a limited understanding of regional OHCA dynamics.

Unique demographic, spatial, and cultural factors in the Middle East may influence bystander and community responses to OHCA, necessitating context-specific interventions. For example, in the United Arab Emirates (UAE) until 2019, there has been a lack of Good Samaritan laws to legally protect a layperson who attempts to provide first aid and resuscitation to an unconscious patient. Favorable laws have been introduced, but their favorable impact on community response is yet to be achieved and measured. Studies from the Middle East also report an alarmingly young median age of 51 years among patients with OHCA [15,16]. Furthermore, the absence of comprehensive in-hospital documentation practices aligned with Utstein guidelines in many Gulf countries underscores the region's persistent data gaps surrounding OHCA.

In light of these challenges, our study aims to enhance the clinical documentation of OHCA cases in line with Utstein and cardiac arrest registry standards, facilitating comprehensive data collection from prehospital and hospital sources. By examining the association between bystander CPR and AED use with

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OHCA outcomes, including ROSC, survival to discharge, and favorable neurological outcomes, we seek to provide critical insights into local OHCA dynamics in the Middle East. These baseline data will inform future research endeavors to address barriers to early CPR in the community and implement targeted strategies to optimize OHCA response and outcomes. Given the current low baseline bystander response rates and OHCA survival outcomes, we anticipate that improving bystander CPR rates will lead to tangible enhancements in survival rates with favorable neurological outcomes upon discharge.

Aims

Primary Outcome

The primary outcome is to describe the characteristics, including bystander interventions and outcomes, in OHCAs brought to hospitals enrolled in the study from Abu Dhabi, UAE; Doha, Qatar; and Muscat, Oman.

Secondary Outcome

The secondary outcome is to describe the strength of the association between bystander response and OHCA outcomes, including the ROSC, survival to hospital admission, survival to discharge, and good neurological outcome at discharge in the local context of low bystander CPR rates.

Methods

Study Design

This study (Bro. Study) adopts a prospective, observational, descriptive design conducted through international collaboration across 3 GCC countries.

Setting

The international collaborative effort involves prospectively recording nontraumatic OHCA data upon presentation to emergency departments. Prehospital information from EMS and hospital records will be collected prospectively in the emergency department. Where feasible, information will also be gathered directly from prehospital records.

Study Period

Data will be prospectively collected from November 1, 2023, to October 31, 2025. During this period, based on historical caseloads, the study is expected to include over 2000 cases of OHCA across the participating hospitals.

Inclusion Criteria

The study will include all patients with nontraumatic cardiac arrest aged >18 years who are transported to participating emergency departments from non–health care facilities during the study period, wherein either bystanders or EMS provided prehospital resuscitation.

Exclusion Criteria

Patients meeting the criteria for undeniable death as declared by EMS at the scene, where neither bystander nor EMS resuscitation was attempted and no resuscitation was performed in the emergency departments, will be excluded from the study.

Data Collection Protocol

The emergency departments of Tawam Hospital, Al Ain, Abu Dhabi; Sheikh Shakhbout Medical City Abu Dhabi; Hamad General Hospital Doha; and Sultan Qaboos University Hospital Oman will collect data according to the Utstein style, a set of internationally accepted guidelines for uniform reporting of cardiac arrests. Ad hoc forms have been added to the existing electronic records to capture core and supplemental data per the International Liaison Committee on Resuscitation consensus guidelines [17]. Table 1 details the parameters to be collected. The details of the variables and response options for collecting data on OHCA are outlined in Multimedia Appendix 1.

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Table 1. Key parameters.

Variables	Parameters
Demographic variable	• Age • Sex • Nationality • Country • Presenting hospital • Comorbidities
Peri–cardiac arrest variables	• Location • Witnessed status • Bystander CPR[a] • AED[b] use • EMS[c] arrival time • Initial rhythm • Prehospital shocks • Prehospital CPR time
Post–cardiac arrest variables	• ROSC[d] • Survival to discharge • Neurological outcome at discharge • Neurological outcome at 3 months

[a]CPR: cardiopulmonary resuscitation.

[b]AED: automated external defibrillator.

[c]EMS: emergency medical services.

[d]ROSC: return of spontaneous circulation.

Prehospital Data

Prehospital resuscitation data will be prospectively collected using the Utstein-style international guideline data form from EMS. Only 1 center electronically transfers this data to hospital records; efforts are ongoing to implement this feature across all participating hospitals. A standardized handover sheet was designed for recording findings, which are promptly entered into electronic data following resuscitation. The parameters to be collected are detailed in Table 1.

In-Hospital Data

In-hospital data on patients with OHCA will be systematically collected upon emergency department arrival using a report form designed for this study, adhering to Utstein guidelines. This form captures patient status (pulse, breathing, and cardiac rhythm), defibrillation details (number of shocks), use of mechanical CPR devices, advanced airway interventions (type specified), and vascular access types (intravenous, intraosseous, or central line) for medication administration (eg, epinephrine, atropine, amiodarone, lidocaine, bicarbonate, and dextrose).

Outcome Data

Outcomes will be recorded prospectively, including ROSC, survival to discharge, and neurological status, using the Cerebral Performance Category scale at discharge. Residents involved in the study will collect this data following clear guidelines to ensure consistent and accurate entry. The same doctor who took the EMS handover and participated in the OHCA management will make electronic notes.

Data Quality and Standardization

To ensure quality control and standardization across the 3 centers, personnel from 3 research teams will regularly review the collected data for consistency and accuracy, providing feedback to the participating centers. Regular meetings will align team members with study protocols and Utstein-style guidelines. Periodic audits will identify and rectify discrepancies or deviations, ensuring high data quality and uniformity across all participating centers. A full-time research assistant is recruited to look after these processes using the research grant fund.

EMS Characteristics of Participating Hospitals

Doha, Qatar

The Hamad Medical Corporation Ambulance Service is Qatar's sole ambulance provider, servicing a population of 3 million. Key units include Alpha (basic ambulance), Charlie (critical care), and Delta (supervisory). A hub-and-spoke model ensures rapid response, with a median EMS response time of 6-8 minutes [18].

Abu Dhabi, UAE

The Abu Dhabi Civil Defence Authority provides emergency services to 3.8 million residents. Units include basic (staffed by emergency medical responders and emergency medical technicians), advanced life support ambulances (staffed by advanced care paramedics and paramedics), and critical care ambulances (staffed by critical care paramedics).

Muscat, Oman

The Public Authority for Civil Defense and Ambulance, managed by the Royal Oman Police, oversees EMS.

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Ambulances are staffed with advanced emergency medical technicians and specialized drivers. The goal is a response time of 10 minutes in urban areas and 20 minutes in rural areas [19].

Ethical Considerations

The study was approved by the Abu Dhabi Health Research and Technical Ethics Approval Committee on March 2, 2023, under the reference DOH/CVDC/2023/490 and by the Tawam Human Research Ethics Committee on May 2, 2023, under the reference KD/AJ/939.

The trial will follow the ethical guidelines established in the Declaration of Helsinki and the Belmont Report (1979).

Results

The project successfully secured funding in 2023. Data collection commenced on November 1, 2023, and will be conducted prospectively over 2 years, concluding on October 31, 2025. The research findings will be published in a peer-reviewed academic journal, with the anticipated release in the first quarter of 2026.

Discussion

Expected Findings

This study anticipates a low incidence of bystander CPR and, correspondingly, very low use of AEDs within community settings in the Middle East. Given this context, favorable outcomes among patients with OHCA, even those who received bystander CPR, are expected to be limited. Such limitations may be attributed to delays in the initiation of CPR, thereby reducing its overall effectiveness. A critical barrier to addressing this issue is the lack of reliable and updated regional data, which complicates efforts to assess and improve cardiac arrest outcomes accurately. Previous research has reported a wide range of survival rates following OHCA, varying from 5.1% to 30%.

This study will focus on outcomes for patients who experienced witnessed cardiac arrests and received bystander CPR. Positive findings within this subgroup may suggest that increasing the prevalence and quality of bystander CPR, particularly in witnessed cases, could substantially enhance survival rates for OHCA, as supported by existing literature [9,10].

This study will analyze OHCA outcomes across 3 countries to provide insights for policy makers, guiding evidence-based policy development and community interventions [20].

Future Plans

This investigation represents the initial phase of a 4-year, multiphased international collaborative research initiative to improve community health outcomes by examining bystander involvement in OHCA cases across 3 GCC nations. The goal of following sequential research is to implement strategies to enhance OHCA outcomes within the community.

1. Assess the current rates of bystander-administered CPR, AED use, and survival rates in the study regions compared to global benchmarks through a prospective, descriptive analysis of OHCA cases, which is the primary focus of this phase
2. Conduct a qualitative analysis of facilitators and barriers to bystander responses during OHCA incidents in the Al Ain region
3. Identify community-based interventions to increase bystander CPR rates in GCC countries, drawing on findings from the first 2 studies and a review of international literature on community interventions that improve OHCA outcomes in the GCC and Asia
4. Evaluate the effectiveness of community interventions by comparing bystander willingness, CPR rates, and OHCA survival rates against baseline rates established in the initial phase over 1 year
5. Establish a nationwide cardiac arrest registry in the study regions

Limitations

Data collection will occur during the EMS handover to the resuscitation team. However, potential recall bias may arise among EMS personnel if pertinent information is not explicitly documented at the scene. Moreover, within the study region, EMS systems exhibit variability in response and documentation protocols, thereby influencing the quality and completeness of reported information. Consequently, missing data will inevitably arise, necessitating the use of complete case analysis and multiple imputations to address this issue. To overcome this limitation, robust guidance for handover documentation is provided to all the participating centers.

The prospective hospital-based design of the study means that sample size estimation depends on expected presentations to participating hospitals, which is potentially smaller than that in retrospective studies using registry data. While this design improves data reliability, it may limit the study's ability to robustly measure secondary outcomes, such as establishing strong associations between variables and outcomes, particularly if AED use in the community is very low.

Direct access to prehospital records may not be possible in all participating centers. Currently, in 1 participating country (Qatar), prehospital records are directly uploaded to hospital records. In the other 2 countries, such integration is not yet complete. This might lead to variable access to prehospital records and, consequently, missing data. Prospective data collection at the time of handover will mitigate this limitation.

Patients who were declared dead at the scene by EMS have been excluded from the study; hence, subsequent study findings will not include outcomes for patients whose care is terminated in the field.

Conclusions

This investigation marks the first international collaborative research effort among 3 neighboring Gulf countries. The study aims to produce up-to-date and reliable data on bystander response and its association with survival rates for OHCA within the Middle Eastern context. The findings will aid in planning and implementing community-based interventions to enhance outcomes, including establishing cardiac arrest registries.

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Data Availability

The datasets generated and analyzed during the study will be available from the corresponding author (MF) upon reasonable request.

Authors' Contributions

MF, KB, and EHD conceptualized this study. MAJ, FKH, SA, and MF are responsible for data collection at their respective study centers. OAN coordinated the integration of data collection forms into electronic health records. MF drafted the initial protocol. All authors have reviewed and approved the draft. MF and KB oversee the overall quality and integrity of the project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Out-of-hospital cardiac arrest variables and response options.
[PDF File (Adobe PDF File), 39 KB - resprot_v13i1e58780_app1.pdf]

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Abbreviations

AED: automated external defibrillator
CPR: cardiopulmonary resuscitation
EMS: emergency medical services
GCC: Gulf Cooperation Council
OHCA: out-of-hospital cardiac arrest
ROSC: return of spontaneous circulation
UAE: United Arab Emirates

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Protocol

Methodology for Biological Sample Collection, Processing, and Storage in the Newcastle 1000 Pregnancy Cohort: Protocol for a Longitudinal, Prospective Population-Based Study in Australia

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Abstract

Background: Research in the developmental origins of health and disease provides compelling evidence that adverse events during the first 1000 days of life from conception can impact life course health. Despite many decades of research, we still lack a complete understanding of the mechanisms underlying some of these associations. The Newcastle 1000 Study (NEW1000) is a comprehensive, prospective population-based pregnancy cohort study based in Newcastle, New South Wales, Australia, that will recruit pregnant women and their partners at 11-14 weeks' gestation, with assessments at 20, 28, and 36 weeks; birth; 6 weeks; and 6 months, in order to provide detailed data about the first 1000 days of life to investigate the developmental origins of noncommunicable diseases.

Objective: The study aims to provide a longitudinal multisystem approach to phenotyping, supported by robust clinical data and collection of biological samples in NEW1000.

Methods: This manuscript describes in detail the large variety of samples collected in the study and the method of collection, storage, and utility of the samples in the biobank, with a particular focus on incorporation of the samples into emerging and novel large-scale "-omics" platforms, including the genome, microbiome, epigenome, transcriptome, fragmentome, metabolome, proteome, exposome, and cell-free DNA and RNA. Specifically, this manuscript details the methods used to collect, process, and store biological samples, including maternal, paternal, and fetal blood, microbiome (stool, skin, vaginal, oral), urine, saliva, hair, toenail, placenta, colostrum, and breastmilk.

Results: Recruitment for the study began in March 2021. As of July 2024, 1040 women and 684 partners were enrolled, with 922 infants born. The NEW1000 biobank contains 24,357 plasma aliquots from ethylenediaminetetraacetic acid (EDTA) tubes, 5284 buffy coat aliquots, 4000 plasma aliquots from lithium heparin tubes, 15,884 blood serum aliquots, 2977 PAX RNA tubes, 26,595 urine sample aliquots, 2280 fecal swabs, 17,687 microbiome swabs, 2356 saliva sample aliquots, 1195 breastmilk sample aliquots, 4007 placental tissue aliquots, 2680 hair samples, and 2193 nail samples.

Conclusions: NEW1000 will generate a multigenerational, deeply phenotyped cohort with a comprehensive biobank of samples relevant to a large variety of analyses, including multiple -omics platforms.

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KEYWORDS

pregnancy cohort study; biobanking protocol; toenails; blood; microbiome; urine; hair; pregnancy; cohort study

Introduction

Research into the developmental origins of health and disease provides compelling evidence that adverse events during the first 1000 days of life from conception can impact life course health, increasing the risk of metabolic risk factors [1,2], such as obesity [3], diabetes [4], hypertension [5], cardiovascular disease [6], asthma [7,8], allergies [9,10], and adverse neurodevelopmental [11,12] and mental health [13-15] outcomes. Despite decades of research, we still lack a complete understanding of the mechanisms underlying some of these associations. Australian pregnancy and birth cohorts have provided excellent contributions to pregnancy health and developmental research over the past 3 decades, with over 17 pregnancy or birth cohorts to date [16]. Since the inception of these studies, there have been significant advances in technologies, increasing our understanding of the underlying biological mechanisms driving the pathogenesis of disease. For example, the rapidly expanding use of "-omics," such as genomics, transcriptomics, proteomics, and metabolomics, has contributed to identifying complex traits underlying health outcomes with greater accuracy than standard clinical approaches [17].

The Newcastle 1000 Study (NEW1000) is a comprehensive pregnancy cohort study based in Newcastle, New South Wales, Australia, which will provide detailed data about the first 1000 days of life to investigate the developmental origins of noncommunicable diseases [18]. The multiomics design of NEW1000 intends to provide detailed, longitudinal, multisystem phenotyping and serial sample collection for analyses of the genome, microbiome, epigenome, transcriptome, fragmentome, metabolome, proteome, exposome, and cell-free DNA and RNA. A critical element of biorepositories is standardized collection, handling, and storage of samples to ensure reliable results through analyses of high-quality samples [19]. In addition, the use of a suitable informatics system is recommended to ensure accurate tracking of inventory [20]. This manuscript describes the methodology used to collect, process, and store samples in NEW1000, with the intent to facilitate the access and use of these resources upon request.

Methods

Study Design

NEW1000 is a prospective, population-based, longitudinal pregnancy cohort study. Stage 1 (2021-2025) will involve recruitment of 500 pregnant participants and their partners per year for 5 years. The importance of the first 1000 days of life from conception is reflected in the number of assessments during this stage. Each family will be seen 5 times during pregnancy (14, 20, 28, 36, and 40 weeks' gestation), at birth, 1-2 days postnatally, then again 6 weeks, and 6 months postpartum. Stage 2 will involve further postnatal follow-up of the families at 12, 24, and 36 months of age. Stage 3 will involve long-term follow-up of the cohort through face-to-face appointments, questionnaires, and data linkage to establish a deeply phenotyped pregnancy cohort from early gestation through adulthood. The focus of this manuscript will be the protocol and methodology of biological sample collection and biobanking for stage 1 of the study, and recruitment and assessment processes have been previously published [18]. NEW1000 has been designed for standardized collection of blood, urine, saliva, buccal swabs, microbiome swabs, toenails, and hair samples from the mother, father (or partner), and infant. In addition, cord blood, placenta, and colostrum samples will be collected at birth, and breastmilk samples will be collected 6 weeks and 6 months postpartum (Figure 1).

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Figure 1. NEW1000 stage 1 biological sample collection timepoints. NEW1000 aims to provide a comprehensive database for use in traditional analysis and emerging -omics platforms. Expanded uses denote the intended platforms and appropriate approaches based on the collection methods highlighted in the manuscript. e: epigenomics; f: fragmentomics; g: genomics; mb: microbiomics; m: metabolomics; NEW1000: Newcastle 1000 Study; p: proteomics; t: transciptomics.

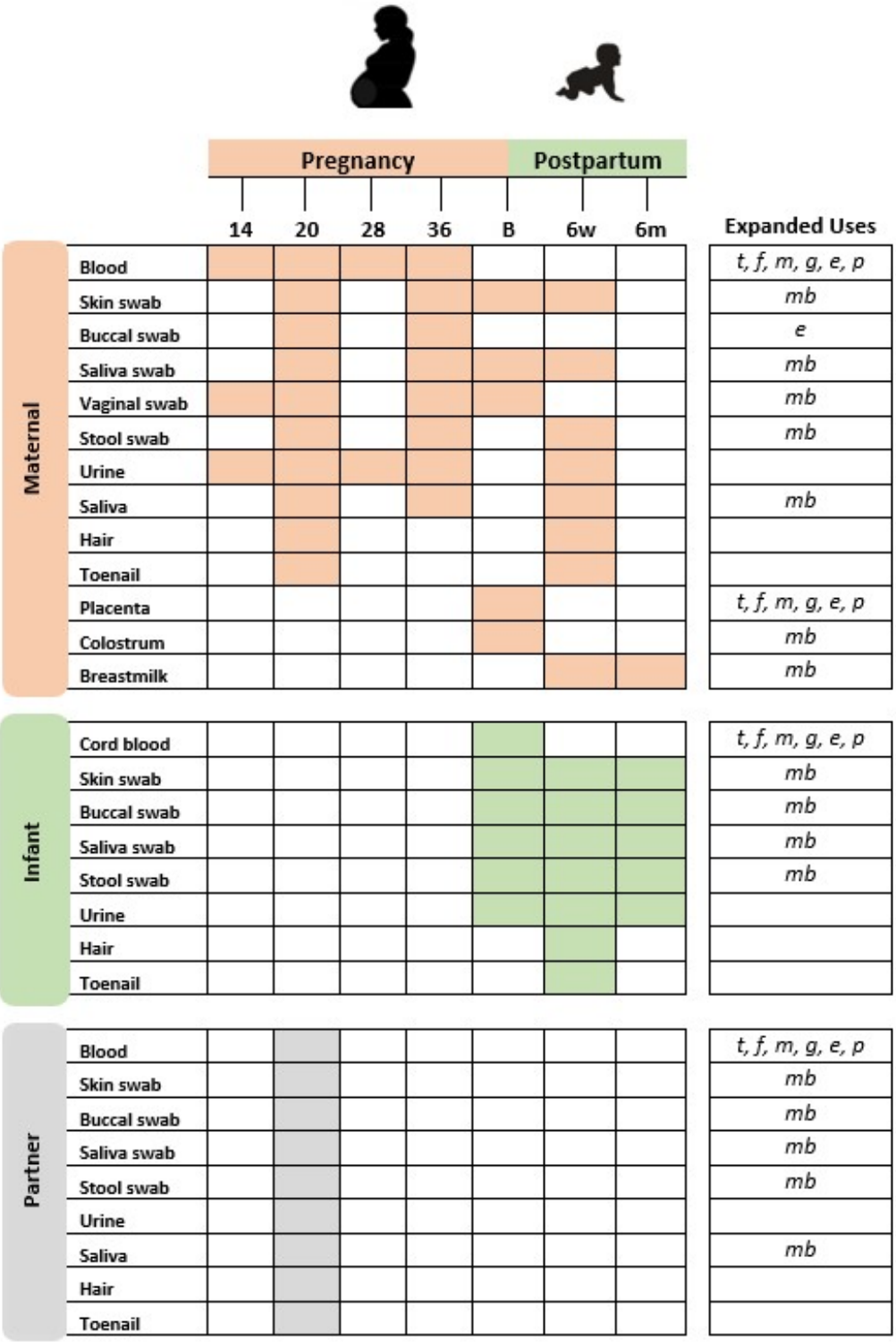

Blood Samples

The use of human blood within biomedical research, particularly biomarkers, is a significant resource and commonplace in the discovery and diagnosis of clinical conditions. Biomarkers have been defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” [21]. In addition to the traditional use of biomarkers, there is emerging evidence to support the use of genetic biomarkers for precision medicine—that is, their application for diagnosis, prognosis, and personalized treatment options based on an individual’s genetic profiling [22]. NEW1000 will collect a comprehensive panel of blood and

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blood products to facilitate all avenues of biomarker research, including traditional approaches and downstream genetic or multiomic analyses. Isolating such biomarkers will allow for the prediction of adult disease in the earlier stages of life and thus provide the potential for advancements in precision medicine.

Collection of Blood Samples

Collection of blood samples will be according to the recommended order of draw (Multimedia Appendix 1): the Vacuette serum tube (silica-coated clot activator and polymer gel; Greiner Bio-One) for use in routine clinical chemistry and hormone tests, serology, and immunohematology; the Vacuette heparin plasma tube (lithium heparin coated) used for clinical biochemistry tests; Vacuette ethylenediaminetetraacetic acid (EDTA) tubes (containing K2 EDTA anticoagulant) used for hematological procedures, such as complete blood counts and blood typing and plasma isolation, to allow for multiomics analyses; and the PAXgene blood RNA tube (containing 6.9 mL of RNA stabilization additive; BD Biosciences) used to stabilize intracellular RNA to yield accurate and reproducible gene expression data [23]. Maternal blood samples will be collected at 14-, 20-, 28-, 36-, and 40-week appointments, as well as 6 weeks postpartum. Partner blood samples will be collected at the 20-week appointment, and cord blood will be collected at birth. Adult blood samples to be collected include 8 mL in one 8 mL Vacuette serum tube; 4 mL in one 4 mL Vacuette heparin plasma tube; 18 mL in two 9 mL Vacuette K2 EDTA tubes; and 4 mL of cord blood in one 4 mL Vacuette EDTA tube. The buffy coat, containing white blood cells and platelets, an important source of genomic DNA that can withstand long-term storage [24], will be extracted from centrifuged Vacuette EDTA tubes. In addition to these tubes, 2.5 mL (draw volume) in 1 PAXgene blood RNA tube will be collected for maternal blood samples at 14-, 20-, and 28-weeks' gestation. Thus, each family will have the potential to donate blood that totals up to 68 aliquots within their first year of the study that can be used for traditional and nontraditional -omics techniques.

Adult Blood Samples

Using a tourniquet on the arm above the cubital fossa, a research nurse will locate a suitable vein and clean the site with an alcohol swab. Samples will be collected via a 21G sterile luer and holder with a retractable needle, commonly used during venipuncture as the smaller gauge reduces discomfort and prevents hemolysis. Once all tubes are filled and the needle removed and retracted for safe disposable, a sterile injection pressure pad will be applied to the collection site.

Cord Blood Samples

The placenta will be placed in a sterile specimen dish postbirth. If umbilical cord blood gas analysis is required as part of clinical care, it will be obtained prior to research samples. A large cord vein will be located and cleaned using an alcohol swab to remove any maternal blood. An 18G needle will then be inserted into the vein, and a 10 mL syringe will be used to draw a blood sample, which will be put into a 4 mL EDTA tube.

Processing and Storage of Blood Samples

The subsequent sections will discuss the methodology of processing, separation, and storage of plasma, serum, and the buffy coat from the EDTA, serum, lithium heparin, and PAXgene blood tubes (Figure 2).

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Figure 2. Flow diagram for processing of blood samples. *Lithium heparin plasma can be divided evenly between two 2 mL cryovial tubes if there is >2 mL of plasma. Purple boxes indicate the processing flow of EDTA tubes, green boxes depict lithium heparin tubes, and pink boxes show serum tubes. ac: acceleration; dc: deceleration; EDTA: ethylenediaminetetraacetic acid.

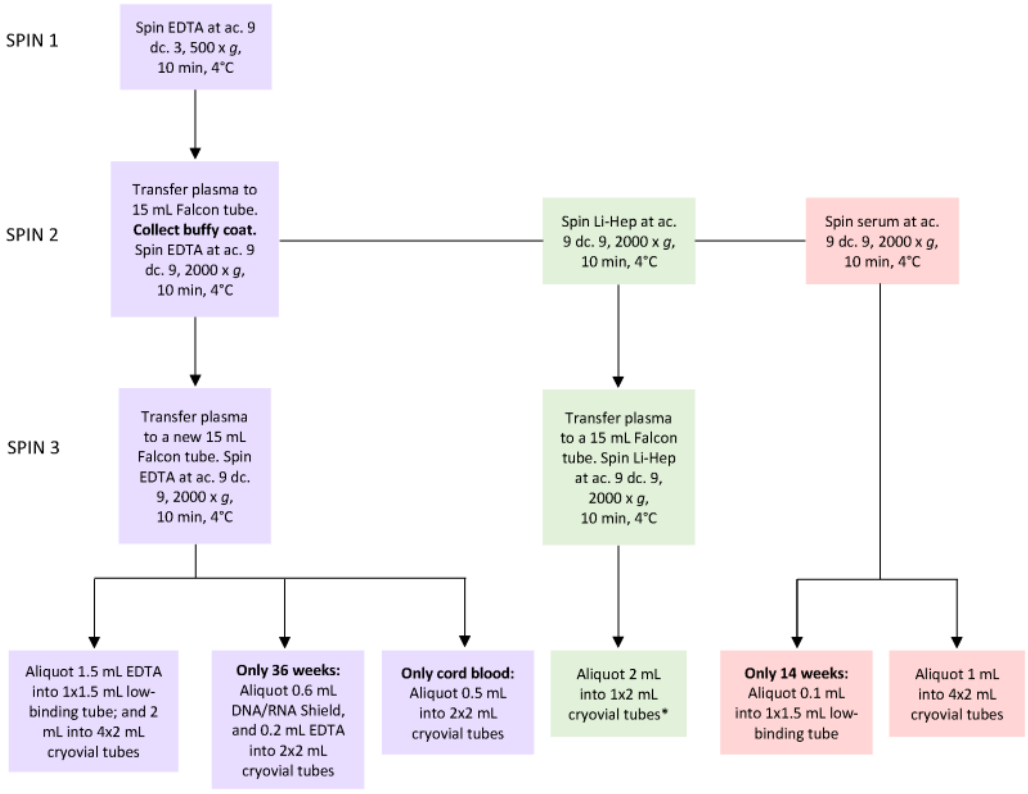

Plasma

Samples will be inverted 5-10 times to ensure adequate mixing of blood with the EDTA anticoagulant [25] and centrifuged under the following conditions: 10 minutes at 500 ×*g* at 4 °C, with an acceleration of 9 and a deceleration of 3. All but approximately 0.2 mL of plasma (reserved for the buffy coat; Figure 3) will be aliquoted into one 15 mL Falcon tube and subjected to a second centrifugation step for 10 minutes at 2000 ×*g* at 4 °C, with an acceleration of 9 and a deceleration of 9. Plasma will be aliquoted into a new sterile 15 mL Falcon tube (Corning) and centrifuged again according to the same conditions as the previous spin and the pellet discarded. The remaining plasma will then be aliquoted: 1.5 mL plasma into one 1.5 mL low-binding Eppendorf tube, with the remaining plasma evenly distributed among four 2 mL cryovial tubes. For 36-week appointments, 0.2 mL plasma will be transferred into two 2 mL cryovial tubes containing 0.6 mL of DNA/RNA Shield solution prior to the plasma being distributed into the four 2 mL cryovial tubes. Cord blood samples will be subjected to the same centrifugation conditions; however, a smaller quantity of plasma will be obtained. Approximately 0.5 mL of plasma will be placed into one 1.5 mL low-binding Eppendorf tube and two 2 mL cryovial tubes. When extracting plasma, approximately 0.2 mL will be reserved (in each tube) for the buffy coat. Aliquots will be stored at –80 °C until required for analysis, and the OpenSpecimen database will be updated to include these aliquots.

Figure 3. Centrifugation of whole blood to separate blood components (figure created in BioRender): plasma; buffy coat, which contains white blood cells and platelets; and hematocrit (red blood cells).

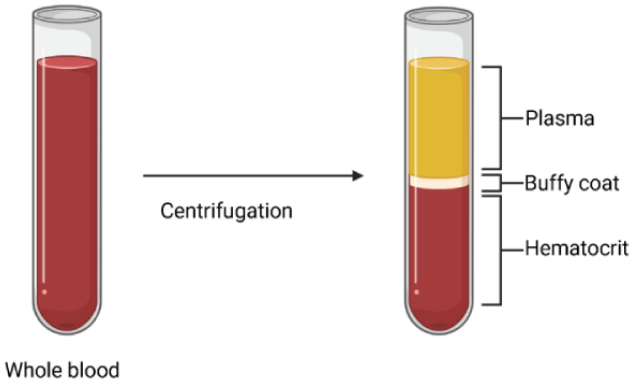

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Buffy Coat

A sterile 3 mL Pasteur pipette will be used to aliquot the buffy coat from both 9 mL Vacuette EDTA tubes (one 4 mL Vacuette EDTA tube for cord blood), along with the remaining 0.2 mL of plasma and a small portion of red blood cells into one sterile 2 mL cryovial tube. The tubes will be stored frozen at –80 °C until required for analysis, and OpenSpecimen will be updated to include these aliquots.

Serum

Samples will be inverted 5-10 times to activate the silica clotting agent [25] and then kept upright at room temperature for 20 minutes to allow clot formation. Afterward, the samples will be centrifuged under the following conditions: 10 minutes at 2000 ×*g* at 4 °C, with an acceleration of 9 and a deceleration of 9. The serum will be subsequently aliquoted: 1 mL into four 2 mL cryovial tubes and, for 14 weeks' gestation only, approximately 0.1 mL into one 1.5 mL low-binding Eppendorf tube. Aliquots will be stored frozen at –80 °C until required for analysis, and OpenSpecimen will be updated to include these aliquots.

Lithium Heparin

Samples will be inverted 5-10 times to ensure adequate mixing of blood with the heparin anticoagulant [25] and centrifuged under the following conditions: 10 minutes at 2000 ×*g* at 4 °C, with an acceleration of 9 and a deceleration of 9. All the plasma will be aliquoted into one 15 mL Falcon tube and subjected to a second centrifugation spin under the same conditions as the previous spin. All the plasma will then be aliquoted into one 2 mL cryovial tube or divided evenly between two 2 mL cryovial tubes if there is >2 mL of plasma. Aliquots will be stored at –80 °C until required for analysis, and OpenSpecimen will be updated to include these aliquots.

PAXgene Blood RNA

Samples will be kept upright at room temperature for a minimum of 2 hours before being stored at –30 °C overnight, and OpenSpecimen will be updated to include the samples. The following morning, the samples will be transferred from –30 °C to permanent storage at –80 °C until required for analysis.

Urine Samples

Urine can be used for the detection and analysis of proteinuria, bacteria, infections, toxicology, renal function, and nutrient markers [26-28]. Midstream urine samples will be requested at 14, 20, 28, and 36 weeks' gestation and 6 weeks postpartum from enrolled women. Partner samples will be collected at 20 weeks. Adult samples will be self-collected in 70 mL sterile specimen jars and aliquoted into four 2.0 mL sterile CryoGen CLEARLine cryotubes (Biosigma) for storage at –80 °C. Additional urine will be stored in 15 mL Falcon tubes at –80 °C. Infant urine samples will be collected 6 weeks and 6 months postpartum using a cellulose pad insert to collect urine during appointments. The insert will be collected at the end of the appointment, and urine will be extracted using a specialized press device, then aliquoted into 2.0 mL sterile cryotubes, and stored at –80 °C.

Saliva Samples

Human saliva is a complex biofluid that is readily available, can be collected noninvasively, and can be used for a number of diagnostic and biomedical research-based analyses [29]. Saliva has been used to study proteomics, with proteins often closely reflecting those seen in plasma, as approximately 30% of salivary proteins originate in the blood [30]. As such, saliva is emerging as a common alternative to blood in genetic research and polymerase chain reaction (PCR)–based genotyping [31]. Further, steroid hormone concentrations and fluctuations are often assessed in salivary samples via enzyme-linked immunosorbent assay (ELISA) or liquid chromatography–mass spectrometry (LC-MS) [32,33]. Salivary cortisol concentrations, routinely studied in animal and human studies, have been validated with serum cortisol concentrations [34-36]. As stressful experiences in early life are linked to numerous adverse developmental outcomes, accurate biospecimen collection for assessment of these pathways within any longitudinal cohort is critical [37,38]. Therefore, saliva will be an important forward-looking and versatile sample within the NEW1000 biobank, providing an often-overlooked biological sample for accessing and validating a multitude of biological markers. Investigating the response to stressors, such as maternal anxiety, depression, and familial and sociodemographic adversity [37,39-41], and external and environmental factors, such as COVID-19, lockdowns, or natural disasters [42,43], will provide a baseline for future long-term programming studies in children and adults.

Collection, Processing, and Storage of Saliva Samples

Maternal saliva samples will be self-collected at home on the morning of the 20- and 36-week appointments. Partners will provide a saliva sample at 28 weeks. Participants will be instructed to collect samples within 20 minutes of waking up, before food, drink, or other substances are consumed and before teeth are brushed, to enable assessment of baseline levels of biomarkers and stress hormones, such as cortisol. To maximize the collection amount, participants will be instructed to let saliva accumulate in the mouth without swallowing for 1 minute and then to passively drool the accumulated saliva into a sterile 5 mL screw-cap collection tube (Sarstedt Australia). Samples will be processed by centrifugation in 5 mL collection tubes for 10 minutes at 2000 ×*g* at 4 °C prior to being placed into two 2 mL cryotubes using a sterile 3 mL Pasteur pipette. Duplicate aliquots will be implemented to minimize the need for freeze/thaw and provide an alternative or complimentary examination to blood samples. Samples will be routinely kept at –80 °C for long-term storage [15].

Buccal Swabs

Recent studies have highlighted the potential advantages offered by buccal swabs when assessing epigenetics, DNA methylation, and genome-wide studies [44-46], most notably the uniformity of the epithelial cell type present compared to other samples [45,46]. Critical to collection of samples for multiomic analyses, buccal samples have recently been used to assess the predictive nature of epigenetics in preterm birth [45], providing a valuable addition to the biobank.

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Collection, Processing, and Storage of Buccal Swabs

Maternal buccal swabs will be collected at 20 and 36 weeks' gestation and 6 weeks postpartum; paternal samples at 20 weeks; and infant samples at birth, 6 weeks postpartum, and 6 months postpartum. Prior to collection, adult participants will be asked to refrain from eating, drinking, chewing gum, brushing teeth, or smoking for at least 30 minutes. Participants will be instructed to remove a sterile swab from the tube, ensuring the tip does not touch any surfaces, and rub the swab on both sides of their inner cheek for 60 seconds, rotating the end several times to collect skin cells. Once the collection is completed, the participants will be instructed to remove the swab, being careful the swab tip does not touch the teeth, lips, or any other surface, then place the swab directly into the collection tube, and close the lid firmly. Collection of infant buccal swabs will be completed by a research midwife or nurse.

Microbiome Samples

The microbiome plays a central role in health and disease, contributing to the development and regulation of metabolic and immune functions [47,48]. From birth, the microbiome changes in response to host and environmental factors [49]. Disruptions in the early life microbiome can negatively impact a wide range of health outcomes [50,51]. Beginning at birth, complex host-microbe-environmental interactions help shape host metabolism, immune and gastrointestinal tract system development, and behavior [47,48], setting the biological foundation for future disease susceptibility [52]. The first colonizers of the infant gut are determined during and immediately after birth when the infant is exposed to microbial communities from the mother and the external environment. The subsequent maturation of the microbiome is dynamic and highly individualized during the first 2 years of life [53]. During this time, multiple factors influence the microbiome structure and function, including the maternal microbiome across surfaces and fluids the infant is exposed to, such as the vagina, skin, saliva, and breastmilk [54].

The maternal microbiome undergoes substantial remodeling during pregnancy that can promote metabolic changes, such as weight gain and insulin insensitivity [55], and promote neonatal growth. Maternal host-microbe interactions contributing to infant health remain poorly understood. Comprehensive studies to address this knowledge gap are critical in order to develop microbiome-targeted strategies to improve pregnancy outcomes and infant health [56]. Although recent studies have provided important insights into microbiome development in early life [51,53,57,58], these studies are limited due to small samples sizes. This cohort aims to alleviate these matters and provide a comprehensive and well-characterized data set using which future studies can elucidate the mechanisms and complex interactions behind maternal and infant microbiomes in fetal development and the onset of disease later in life.

Collection, Processing, and Storage of Microbiome Samples

Vaginal Microbiome

A self-collected vaginal swab for the vaginal microbiome and a swab of the transvaginal probe cover (postscan) will be requested from each participant, which will provide an upper and a lower vaginal microbiome specimen/sample for assessment. Low vaginal swabs will be self-collected at 14 and 36 weeks' gestation and during early labor using a standardized health services protocol [55]. Participants will be instructed to wash their hands prior to twisting the cap to break the seal on the sterile swab provided (Copan), being careful the swab end does not touch any other surfaces. With their other hand, they will gently spread the labia and insert the tip of the swab about 5 cm into the vaginal opening, pointing the tip of the swab toward their lower back while relaxing their muscles. The swab should be gently rotated and then held against the vaginal wall for 10-20 seconds. Participants will then remove the swab without it touching the outer skin and return it to its original tube, ensuring the cap is snapped shut. Swabs will be transported immediately to the laboratory and the swab tips cut into 2 mL screw-cap tubes and snap-frozen in liquid nitrogen before being transferred to a –80 °C freezer until extraction [59].

Skin Microbiome

Skin microbiome samples will be collected by a sterile swab dipped in 0.15M sodium chloride solution and firmly applied and rotated on the skin for ~60 seconds (chest of the mother/father and cheek of the baby) [60]. Swabs will then be transported immediately to the lab and the swab tips cut into 2 mL screw-cap tubes and snap-frozen in liquid nitrogen before being transferred to a –80 °C freezer until extraction [59]. Maternal skin swabs will be obtained at 20 and 36 weeks' gestation and at birth; partner swabs at 20 weeks; and infant swabs within 24 hours of birth, 6 weeks postpartum, and 6 months postpartum.

Oral Microbiome

Participants will be asked to refrain from eating, drinking, chewing gum, brushing teeth, or smoking for at least 30 minutes before sample collection. Participants will be provided with a sterile swab and asked to collect a saliva sample by rubbing and rotating the swab along the teeth, applying similar pressure as brushing their teeth, and then placing the swab under the tongue for 30 seconds to collect saliva. Participants will be instructed to ensure the swab does not touch their lips or other surfaces prior to placing it back in the sterile tube and securing the lid. Swabs tips will be cut into 2 mL screw-cap tubes and snap-frozen in liquid nitrogen before being transferred to a –80 °C freezer until extraction [59]. Maternal saliva swabs will be obtained at 20 and 36 weeks' gestation and 6 weeks postpartum, partner swabs at 20 weeks' gestation, and infant swabs 6 weeks and 6 months postpartum.

Gut Microbiome

Collection kits developed by Microba Life Sciences will be used to collect stool samples. This kit consists of an easy-to-use swab and preservation with a liquid-free preservation solution, which is temperature-stable for up to 7 days [61]. A prelabeled swab collection kit will be provided to participants, who will use the sterile swab to collect fecal matter from soiled toilet paper after a bowel movement. Instructions on the amount needed for correct sampling will be provided as part of the self-collection pack. Samples remain stable at room temperature for up to 7 days, allowing participants to collect their sample

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several days prior to their next appointment and bring the sample in the provided packaging to their next appointment. Maternal fecal swabs will be obtained at 20 and 36 weeks' gestation; partner swabs at 28 weeks' gestation; and infant swabs, where possible, within 24 hours of birth, 6 weeks postpartum, and 6 months postpartum. Swabs will be stored in a –80 °C freezer until analysis.

Measurement of Environmental Exposure

Substances such as endocrine disrupting chemicals, heavy metals, and pesticides are persistent in the environment, leading to human exposure through diet, the household, the workplace, and ambient surroundings [62]. Maternal exposure to environmental contaminants during pregnancy renders the fetus susceptible to indirect exposure and the associated negative health impacts during critical periods of development [63,64]. These health impacts can be diverse and long lasting, with effects including altered human chorionic gonadotropin (hCG) secretion, intrauterine growth restriction, reduced birth weight, and alterations of the neonatal gut microbiome and metabolome [63-66]. Collection and storage of nail and hair clippings for use as a biomarker of environmental contaminant exposure are ideal due to the noninvasive nature of sampling, the ability to assess cumulative exposure, and the ease of long-term storage and handling [67]. Additionally, when substances are deposited into keratin-rich tissues, their levels remain unchanged, allowing for measurement of long-term cumulative exposure over a period of 6-12 months [67,68]. This is of critical importance to the value of these samples as human nails develop at ~10 weeks of gestation. Thus, collection and analysis of infant nail samples early postpartum can enable an estimate of exposure over the span of pregnancy as a whole, compared to blood or urine samples that only provide insight into a short span of time, usually up to a few days [68].

Toenails

Analysis of nail samples has proven effective for a range of environmental contaminants, including heavy metals, such as mercury and arsenic; endocrine disrupting chemicals, such as bisphenol A; and other industrial chemicals, such as chlorinated paraffins and per- and polyfluoroalkyl substances (PFASs) [67-71]. Thus far, studies that have used toenail sample analysis in infants have primarily focused on heavy metal exposure, correlating detected levels with maternal dietary exposure from 8 weeks postdelivery through 36 weeks from maternal and infant toenails at prenatal and postpartum time points. Collecting toenail samples to analyze environmental contaminant exposure is a promising yet underused tool, with the detection of an expansive range of harmful contaminants yet to be addressed in the context of fetal exposure and gestational cohorts.

Collection, Processing, and Storage of Toenail Samples

Participants will be directed to self-collect toenail clippings after a bath or shower, with cleaned clippers or scissors (maternal and partner samples at 20 weeks' gestation and maternal and infant samples 6 weeks postpartum). Participants will be instructed to cut toenails as close to the nail bed as comfortable over a clean piece of paper or tissue, with at least 2-3 mm of clippings from each toenail being obtained. The tissue or paper will be folded at the edge of each side to enable ease of transfer into a provided self-sealing envelope to be stored in a dry place at room temperature.

Hair Samples

Similar to toenails, hair samples can provide information about toxicology, exposure to heavy metals, harmful chemicals in the environment, and alcohol and illicit substance use. Hair may also be used as a biomarker in chronic stress and certain pathological conditions [72]. As evidenced by the assessment of cortisol concentrations, 3 cm of hair growth from the scalp represents retrospective activity of the hypothalamic-pituitary-adrenal (HPA) axis in the preceding 3 months [73]. A small amount of hair cut close to the scalp is an easily accessible, noninvasive sample that can be obtained with high compliance from many populations [74,75].

Collection, Processing, and Storage of Hair Samples

Maternal and partner hair samples will be requested at 20 weeks' gestation and maternal and infant samples 6 weeks postpartum. Hair will be parted with a comb horizontally on the crown of the head, and a 2-3 mm section of hair below will be sectioned off and, aiming for at least 3 cm of length, cut with sharp hair-cutting shears as close to the scalp as possible. For hair less than 3 cm in length, a 4-5 mm section of hair will be collected. The cut end of the hair will be fastened with medical tape. Samples will be stored, flat, in foil within an envelope and stored in a dry, dark place at room temperature. Hair samples can be stored in this way for several years, with little to no degradation [73-75].

Placental Samples

Placental samples have previously been used in biomedical research using traditional measures, such as gene and protein work, to interrogate physiology and disease, although rarely in sample sizes cohort studies provide. As methodologies facilitate more comprehensive work, such as genome-wide association studies, proteomics, and metabolomic analysis across more diverse populations, it is critical to maintain high standards of collection and storage to ensure reproducibility. Maintaining accurate and thorough records of placental samples enables the transfer of samples upon request, ensuring use of the cohort, independent evaluation and validation, and creative approaches to reproductive research. As such, in this cohort, we aim to establish a well-characterized and thorough process for consistent and accurate collection to ensure quality. Placentas will be collected as close to birth as possible and taken immediately to the laboratory for processing. Eight individual samples per placenta will be collected, encompassing both the membrane and the villous tissue, in both fixed and frozen format, to obtain the utility and quantity to assess multiple measures per sample (Figure 4).

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Figure 4. Overview of collection process for placental samples (figure created in Biorender). PBS: phosphate-buffered saline.

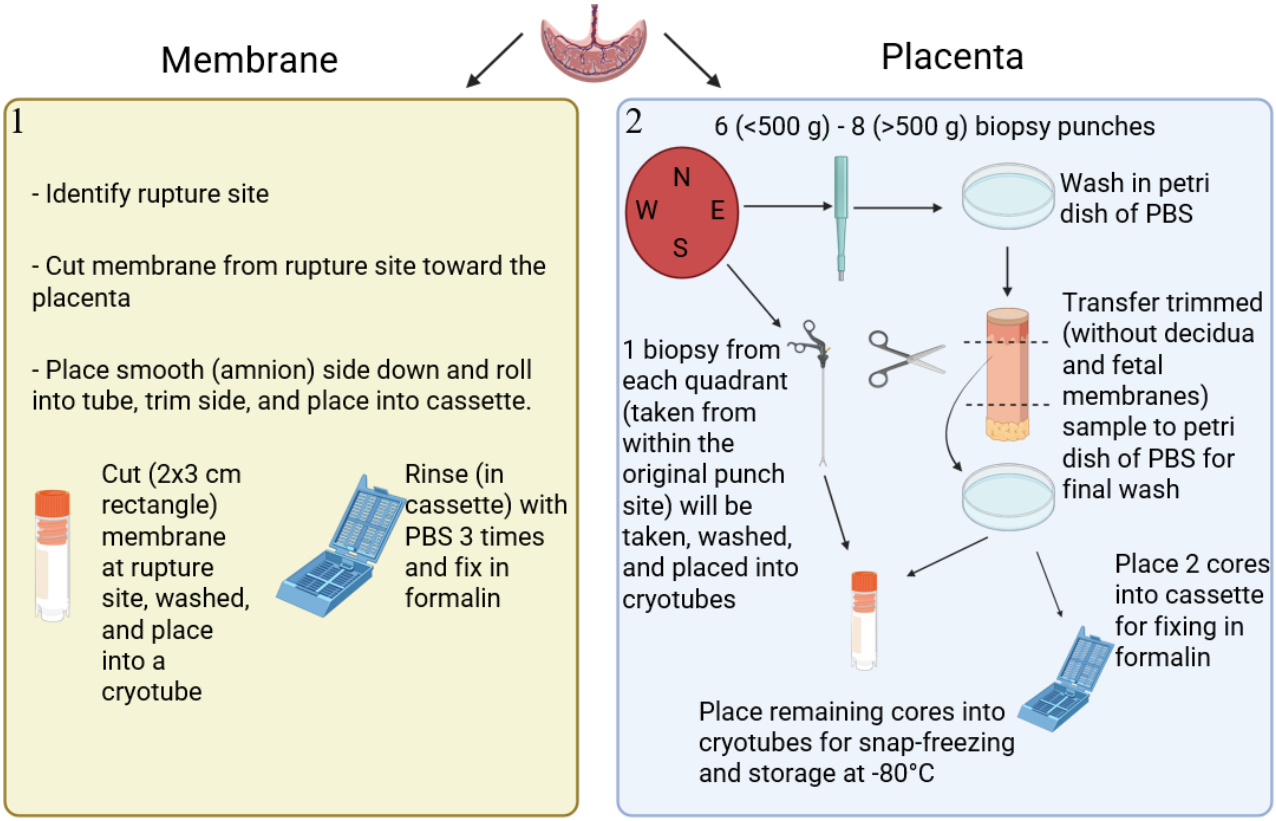

Membrane Collection, Processing, and Storage of Placental Samples

Placental weight and processing time will be recorded. As the membrane must be repositioned or removed prior to placental villous core sampling, the fetal membrane will be collected first. The site of rupture will be ascertained and a cut made posteriorly to collect a 2 × 3 cm^2 section, which will immediately be washed in ice-cold phosphate-buffered saline (PBS) tablets (Gibco) at pH 7.45) and then dabbed on Kimwipes (Kimtech) to remove excess PBS prior to being snap-frozen in 2 mL cryotubes. For subsequent storage, samples will be frozen at –80 °C until required for analysis. In addition to frozen samples, a section of rolled membrane approximately 2 × 5 cm^2 will be obtained from the rupture site. This membrane strip will be washed in ice-cold PBS prior to placing the amnion face down on a Kimwipe, and forceps will be used to gently roll the sample. Each edge of the membrane roll will then be subjected to trimming with scissors and placed into an immunohistology embedding cassette (TechnoPlas). The cassette containing the fetal membrane roll will then be placed into a 70 mL specimen pot and subsequently washed 3 times in PBS and placed on a rocker in formalin at 4 °C overnight. Following fixation, formalin will be removed and replaced with a PBS/sodium azide solution (0.1M PBS with 0.05% sodium azide) to prevent bacterial growth for long-term storage. Fixed samples will be stored for the long term at 4 °C.

Villous Collection, Processing, and Storage of Placental Samples

The number of samples obtained from the placenta will be determined by the weight of the placenta and whether clinical histopathology examination has been requested. Placentas<500 g will have a maximum of 6 sample cores, while in placentas>500 g, up to 8 cores may be collected. This is to ensure that all placental integrity can be maintained upon returning the placenta to histopathology for subsequent clinical macro- and microscopic evaluation. Core samples will be obtained numerically from each of the 4 quadrants (north, south, east, and west) of the placenta (Figure 4) in a process adapted from Burton et al [76]. Cores will be gathered by an 8 mm biopsy punch (Kai) and immediately placed in a petri dish filled with ice-cold PBS, ensuring that the samples are washed gently and thoroughly to minimize maternal blood carryover. Samples will be transferred to a new petri dish containing ice-cold PBS, where scissors will be used to exclude the fetal and maternal membranes. Following this, 4-6 samples (depending on placental weight) will be placed into 1 screw-cap 2 mL cryotube and snap-frozen in liquid nitrogen. Due to limited samples, tissue will not be homogenized immediately prior to being frozen, although we will form a representative cross section once the samples are frozen within the tubes. Tubes will be stored frozen at –80 °C until required for analysis. The remaining core samples will be placed in immunohistology embedding cassettes and fixed and stored, as described before. In addition to whole placental samples, individual biopsies will be obtained from the initial core sites via Klini Tischler (3 × 7 mm^2 jaw) biopsy tool. Samples will be rinsed in PBS, dabbed dry, and placed in

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uniquely labeled and barcoded individual Eppendorf tubes (1.5 mL) to represent their respective quarter.

Biobanking

NEW1000 is a large-scale cohort study. Each family will donate dozens of biological samples, thus contributing to an extensive biospecimen data set. One family could donate up to 150 aliquots of biospecimens within their first year, equating to 75,000 aliquots for the first 500 families. The need to accurately and efficiently store and retrieve samples for subsequent analysis is critical. The NEW1000 biobank will ensure accurate processing, storage, and tracking of all specimens. "Biobanking" is a term used to describe large-scale biospecimen collection and storage within a biorepository [77]. For effective management, biobanking software—known as the laboratory information management system—can be implemented. One such platform that uses this software is OpenSpecimen, an open source database that aims to ensure that extensive sample collection, research, and derivation of meaningful data are as streamlined as possible, allowing researchers to obtain high-quality biospecimen data [78]. As OpenSpecimen is highly configurable, it provides a customizable platform that will suit the needs of the study. Each participant will have a deidentified participant identification number and a profile that contains all relevant medical information pertaining to each gestational time point. All biospecimens collected as part of the study will be barcoded and scanned into the NEW1000 biobank according to each participant's visit date. Additionally, OpenSpecimen can be integrated with other applications or instruments, such as REDCap [78]. This will ensure that all biospecimens are accounted for and easily retrieved upon request for future studies.

Ethical Considerations

This study was approved by the Hunter New England Local Health District Human Research Ethics Committee (December 8, 2020; 2020/ETH/02881). All participants provided written informed consent. All proposed projects using NEW1000 data or biological samples will be required to submit an initial application to the NEW1000 Executive Committee and have relevant ethics and safety clearances from the Hunter New England Local Health District Human Research Ethics Committee prior to the release of any deidentified data or biological samples.

Results

Recruitment for the study began in March 2021. As of July 2024, 1040 women and 684 partners were enrolled, with 922 infants born. The NEW1000 biobank contains 24,357 plasma aliquots from EDTA tubes, 5284 buffy coat aliquots, 4000 plasma aliquots from lithium heparin tubes, 15,884 blood serum aliquots, 2977 PAX RNA tubes, 26,595 urine sample aliquots, 2280 fecal swabs, 17,687 microbiome swabs, 2356 saliva sample aliquots, 1195 breastmilk sample aliquots, 4007 placental tissue aliquots, 2680 hair samples, and 2193 nail samples.

Discussion

Summary

NEW1000 provides a robust and deeply characterized cohort with a comprehensive biobank of samples relevant to a large variety of -omics platforms. This manuscript provides a detailed description of collection and storage procedures used within the NEW1000 cohort. Study design, consumer engagement, demographics of the participants, study setting, governance structure, recruitment process, inclusion and exclusion criteria, and nonbiological data collection in the form of questionaries are discussed elsewhere [18]. The breadth and depth of biological samples and data have the potential to generate new and exciting research outcomes and improve the health of future generations. Potential uses for the data include investigations into the early origins of disease, with data collected from early pregnancy through 6 months within the current stage of the study. Planned follow-up of the cohort at 12, 24, and 36 months is underway, with a focus on child development.

Conclusion

The Newcastle 1000 Study (New1000) is designed as a resource for collaboration, with data linkage, or implementation of a substudy within the cohort, including a new clinical trial, observational study, or intervention. Applications to access New1000 are highly encouraged and outlined in depth [79]. All proposed research projects will be subject to a review process prior to approval. Each application will be reviewed by the NEW1000 Management Group and Executive Committee. The NEW1000 Executive Committee meets face to face on a quarterly basis; however, if there is a need for a project submission to be reviewed outside of this time, frame reviews can be completed electronically. Please allow 6-8 weeks for an application to be reviewed. Data and biosample access requests will be reviewed fortnightly by the study management group. All data and biosample access requests will be cross-referenced with project forms and ethics approvals. If approved, the study manager will liaise with the study data manager and the lead investigator to arrange transfer of deidentified data and samples. The time of data extraction and transfer may vary according to the number and type of data and samples requested.

Acknowledgments

JJF coordinated the concept of the paper 0and wrote the draft manuscript. TG is the lead project administrator, coauthored the manuscript, and provided revision and editing. NAC contributed to the visualization of the manuscript and coauthored the manuscript. EJ, SJD, AEP, GKC, ECH, KEW, RGSK, JJH, and KGP contributed to the study protocol and manuscript sections in their respective fields of expertise. CEP is the study director and was responsible for the study protocol on which the manuscript was based and contributed the conceptualization, writing, review, and editing of the manuscript. The Newcastle 1000 Study is supported by philanthropic donations through the Hunter Medical Research Institute.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
"Order of draw" chart.
[PDF File (Adobe PDF File), 456 KB - resprot_v13i1e63562_app1.pdf]

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Abbreviations

EDTA: ethylenediaminetetraacetic acid
ELISA: enzyme-linked immunosorbent assay
LC-MS: liquid chromatography–mass spectrometry
NEW1000: Newcastle 1000 Study
PBS: phosphate-buffered saline

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Protocol

Factors Influencing Outcome After Shoulder Arthroplasty (FINOSA Study): Protocol of a Prospective Longitudinal Study With Randomized Group Allocation

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Abstract

Background: There is an increasing need for evidence-based postoperative rehabilitation strategies to optimize patient outcome. Knowledge of potential prognostic factors could steer the development of rehabilitation protocols and could result in better treatment outcomes and higher patient satisfaction.

Objective: This study aimed to investigate which potential prognostic factors predict baseline shoulder pain and function and its evolution in the first 2 years following surgery, in patients with total shoulder arthroplasty. The secondary objective is to investigate which potential prognostic factors predict baseline quality of life and its evolution in the first two years following surgery.

Methods: To reach the aims of this project, a prospective longitudinal study, running from January 2020 to March 2025, will be carried out with a follow-up of 48 months. Patients will be randomized based on sling wear. We will study factors such as shoulder function, patient expectations, psychosocial factors, lifestyle factors, sling wear, soft tissue integrity, and physiotherapy treatment. Test moments will take place preoperatively, at 6 weeks, 12 weeks, 6 months, 12 months, and 24 months. Descriptive statistics will be used to describe the patient population characteristics. Based on literature review, expert opinion, and univariate analyses, potential prognostic factors will be chosen as covariates. A mixed regression model for repeated measures will be used to assess both the evolution of the Shoulder Pain and Disability Index within persons from baseline over time and the differences in evolution between participants. Correlation analyses will be used to investigate associations between the other outcome measures such as the Constant and Murley Score, shoulder range of motion, shoulder muscle strength, and proprioception, and the primary outcome measure, the Shoulder Pain and Disability Index score. Potential prognostic factors not included in the model will be presented in a descriptive manner.

Results: Data collection started in January 2020. In April 2023 the sample size was reached. Data collection will end in April 2025. Analyses will follow when data collection is completed.

Conclusions: Knowledge of potential prognostic factors will have implications toward better rehabilitation strategies of patients after total shoulder arthroplasty.

Trial Registration: ClinicalTrials.gov NCT04258267; https://clinicaltrials.gov/study/NCT04258267

International Registered Report Identifier (IRRID): DERR1-10.2196/56522

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KEYWORDS

shoulder arthroplasty; influencing factors; rehabilitation; arthroplasty; shoulder; FINOSA-study; evidence based; post-operative rehabilitation; rehabilitation protocols; shoulder pain; clinical outcomes; geriatrics; longitudinal study; shoulder dysfunction

Introduction

Over the last decade, the number of shoulder arthroplasty procedures have more than doubled in the United States [1,2]. Based on registered studies in Australia, the United States, and Europe, the incidence is vastly increasing [1,3-5] with the demand being projected to rise with 755.4% from 2015 to 2030 [6]. Reasons for this large increase in number of shoulder arthroplasty procedures include amongst others, the good clinical outcomes, the expanding indications for reverse shoulder arthroplasty and the growing elderly population [2,7-11].

Due to this substantial boom, there is an increasing need for evidence-based postoperative rehabilitation strategies to optimize patient outcome. However, the consensus in literature is currently lacking. The only evidence-based consensus is that rehabilitation is believed to have an important impact on patient outcomes, and that there is need for high quality prospective longitudinal research [12,13]. Insight in potential prognostic factors, both modifiable and nonmodifiable is needed to improve the outcome of rehabilitation [14]. Modifiable factors are factors that can be influenced by changing the treatment approach, while in nonmodifiable factors, this is not possible. These different factors may both explain the variety of postoperative outcome satisfaction and might play an important role in the rehabilitation after shoulder arthroplasty, for example, age [15-17], gender [15-17], preoperative shoulder function [18,19], patient expectations [20-23], indication for arthroplasty [24], lifestyle factors, psychosocial factors [25,26], patient characteristics [18,23,24,27], and soft tissue integrity [28,29]. However, at this moment it is not clear to which extent these factors have a relevant influence on postoperative outcome [14]. Knowledge of potential prognostic factors could steer the development of rehabilitation protocols and could therefore result in better treatment outcomes and higher patient satisfaction. Studies on (non) modifiable potential prognostic factors for outcome after shoulder arthroplasty are clearly needed [12,14]. Therefore, the objectives of this study are as follows:

- Primary objective: to investigate which potential prognostic factors predict baseline shoulder pain and function measured with Shoulder Pain and Disability Index (SPADI) and the evolution of SPADI in the first 2 years following surgery, in patients with total shoulder arthroplasty.
- Secondary objective: to investigate which potential prognostic factors predict baseline quality of life measured with Short Form 36 (SF-36) and the evolution of quality of life in the first 2 years following surgery, in patients with total shoulder arthroplasty.

We will study factors such as shoulder function, patient expectations, psychosocial factors, lifestyle factors, sling wear, soft tissue integrity, and physiotherapy treatment.

To reach the aims of this project, a prospective longitudinal study will be carried out over 48 months, starting from January 2020 up to March 2025. The reporting of this protocol is in line with the SPIRIT statement recommendations.

Methods

Study Setting

Data will be collected monocentric in the shoulder surgery unit of the orthopedic surgery department of AZ Monica in Antwerp, Belgium, starting from January 1, 2020. The estimated ending time of data collection will be 2 years after including the last patient. To standardize the procedure and minimize the effect of different surgeons on outcome, a single fellowship trained shoulder specialized surgeon [OV] will perform all shoulder arthroplasty procedures.

Preoperatively, after being scheduled for a total shoulder arthroplasty, all patients, regardless of the indication for surgery, except for acute fractures, are approached by the principal researcher. The principal researcher will ask the patients to participate right before the surgery. When patients agree to participate, the first measurements will be taken immediately after signing the informed consent. Patients are thoroughly informed about the study before obtaining written consent. The informed consent can be found in Multimedia Appendix 1. The appointments will take place on the following time points: on average 1-2 hours before surgery, at 6 weeks post surgery, at 12 weeks post surgery, at 6 months post surgery, at 12 months post surgery, and 24 months post surgery.

All patients will undergo the same testing procedure. Measurements will be carried out by 2 researchers [AC and ADM]. Each researcher was trained in performing these measurements. Parallel to this study, a reliability study regarding these measurements is ongoing. To ensure adequate follow-up, the consultation schedule of the orthopedic surgeon will be followed. At every time point, patients plan the next consultation with the orthopedic surgeon.

Eligibility Criteria

The population of interest includes patients undergoing an anatomical or reverse total shoulder arthroplasty, both from traumatic and nontraumatic origin. Inclusion criteria are adult men and women scheduled for a primary total shoulder arthroplasty. Exclusion criteria are patients scheduled for revision surgery, acute fractures, patients not understanding the Dutch language, surgeries where perioperative complications occur, and patients that cannot be randomized.

Surgical Intervention

The deltopectoral approach will be used in all patients. If applicable, hardware from previous surgery will be removed and a resection of the subdeltoid adhesions will be done. In all

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cases, a tenodesis of the long head of the biceps will be performed just above the upper border of the pectoralis major tendon using a suturing technique. A tenotomy of the subscapularis tendon will be performed 1 cm from its insertion on the minor tuberosity. In stiff shoulders, the subscapularis tendon is peeled-off starting more lateral at the bicipital groove. Both subscapularis tendon and capsule will be released toward medial, and a resection of the contracted anterior capsule will be performed. After dislocation of the humeral head, resection of osteophytes on the humeral head will be done. For anatomic total shoulder arthroplasty, a resection of the humeral head with an extramedullary guide will be performed at the anatomic neck following the anatomical version and inclination. For reverse total shoulder arthroplasty, a resection of the humeral head at 145° inclination and 10° retroversion is performed with the use of an intramedullary guide.

After exposure of the glenoid surface, labrum and osteophytes of the glenoid are removed and any remaining cartilage on the articular surface of the glenoid is removed. In anatomic total shoulder arthroplasty, the glenoid surface is reamed and a hybrid anatomical glenoid (combination of central ingrowth post and cemented peripheral pegs) is then placed in the preoperatively planned position. For reverse total shoulder arthroplasty, a standard baseplate with central post and 2 peripheral screws is positioned in the preoperatively planned position and a glenosphere is placed. Then the humeral side is finished. For anatomic total shoulder arthroplasty, a stemless, uncemented component is positioned using an anatomically sized humeral head. For reverse total shoulder arthroplasty, the proximal humeral canal is prepared for a stemmed, uncemented humeral component. After reduction the subscapularis tendon is anatomically repaired using a transosseus suturing technique in anatomic total shoulder arthroplasty. In reverse total shoulder arthroplasty, the subscapularis is only repaired if reduction of the tendon is possible in 30° of external rotation and the posterior remnants of the rotator cuff are intact.

Outcome Measures

We selected the outcome measures based on the available literature and clinical expertise. Shoulder pain and shoulder function will be measured using the SPADI, which is the primary outcome measure. Quality of life measured with the SF-36, is the secondary outcome measure. Other measured outcomes are shoulder pain and function measured with the Constant and Murley Score (CS), the Visual Analogue Scale (VAS), active shoulder range of motion, shoulder muscle strength, and proprioception of the shoulder. The last outcome measure is patient satisfaction, measured with a self-developed questionnaire.

To measure shoulder pain and function, the SPADI [30] has shown a good internal consistency and test-retest reliability, with a Cronbach α of 0.94 and Intraclass Correlation Coefficient of 0.89 (95% CI 0.83-0.93). The questionnaire is divided in 2 subscales, a pain subscale with 5 statements, and a disability subscale with 8 statements. Every statement must be scored with a number between 0 and 10, with 0 being “no pain” or “no effort” and 10 being “the worst pain” or “so difficult that help is needed”. The overall SPADI score will be used and is calculated: ([sum of all statement scores]/130)×100. This self-administered questionnaire is available in Dutch, and is designed to measure pain and disability associated with shoulder pathology in different clinical settings [31].

Shoulder pain will be measured with the VAS (0-100). Patients will be asked to score the average pain they experience during rest and during shoulder movement on a drawn line of 100 mm, with answers ranging for 0-100. With 0 showing “no pain” and 100 showing “the worst pain.” Shoulder pain and function will be measured with the CS, validated and reliable in patients with shoulder dysfunction [32,33]. We used a Dutch translation, which is not yet validated. A score will be calculated between 0-100, with 100 being a more functional patient.

To measure the active shoulder range of motion, 7 active range of motion measurements of the shoulder will be measured (Table 1). All measurements will be performed in sitting position to avoid compensatory movement of the trunk. A gravity inclinometer will be used during this procedure (Plurimeter, Dr Rippstein). First, anteflexion, abduction, and abduction in the scapular plane will be measured [34]. These measurements are expressed in degrees. After that, both internal rotation and external rotation will be measured. The participant must reach behind his back and is asked to try to go as far up as possible with his thumb to measure functional glenohumeral internal rotation. The position of the thumb will be noted following an ordinal scale (Table 1) [34]. To measure the functional glenohumeral external rotation, the participant is asked to try and put his hand in his neck. The position of the hand will be noted following an ordinal scale (Table 1) [32]. At last, internal rotation and external rotation glenohumeral range of motion will be measured in the horizontal plane. The participant rotates the arm upward and downward, performing a glenohumeral internal and external rotation. Both measurements will be measured with the inclinometer and expressed in degrees.

To measure the shoulder muscle strength, 5 different muscle strength measurements of the shoulder will be performed in sitting position to avoid compensatory movement of the trunk (Table 2). A handheld dynamometer (HHD, Microfet) is used. During all muscle strength measurements, the participant is asked to hold the position while the rater applies a force with the HHD. The rater’s force will be increased until the participant’s arm moves, or the participant indicates the maximal force is reached. During muscle strength measurement of internal and external rotation, the rater can provide stabilization at the distal end of the humerus with the nontesting hand. It is important that the participant does not move his or her elbow medially of laterally. All these muscle strength measurements are expressed in Newton.

The joint positioning sense test and force sensation test measured participant’s ability to actively reproduce an active positioning of the arm and to actively reproduce target forces with shoulder muscle contraction, respectively. To measure the proprioception, the joint positioning sense and force sensation will be measured (Table 3). First, the joint positioning sense will be measured in 4 different angles. The participant is asked to engage a movement of the shoulder in his or her own tempo with eyes open. The rater says “stop” when the shoulder is in the previous

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decided position (criterion angle), and the participant holds this for 3 seconds to become aware of the position. The participant will then be asked to return to the starting position and to close his or her eyes. Then the participant is asked to reproduce the same position or angle (reproduced angle) with his or her eyes closed for 3 seconds and to give a sign when he or she thinks the angle was reached. This will be repeated 2 times. The degrees will be noted and the absolute difference between criterion and reproduced angle (reproducing error) will be taken as measure for proprioceptive accuracy [35]. To measure the force sensation for internal and external rotation, the HHD will be used. To begin the force sensation measurement the participant is asked to produce 50% of the maximally voluntary contraction, calculated from the muscle strength test (see above), while receiving visual and verbal feedback regarding the force being produced. When the participant reaches the target force, he or she will be asked to hold it for 3 seconds to become aware of the force. After 3 seconds, the participant is instructed to relax and to close their eyes so the visual feedback would be removed. Then the participant is asked to reproduce the force. The participant will be asked to verbally indicate when he or she reaches the target force. This will be repeated 2 times and the reproducing error in degrees will be calculated by the absolute difference between criterion force and reproduced force, which is taken as measure for proprioceptive accuracy [36].

Patient satisfaction will be measured with a self-developed questionnaire, adapted from the study of Swarup et al [22]. This questionnaire consists of 8 questions in Dutch, regarding the satisfaction of the patient in terms of pain, function, and quality of life.

Quality of life will be measured with the SF-36 [37,38]. This is a self-administered validated survey of patient health, comprising mental health as well as physical health, available in Dutch [39].

Table 1. Active shoulder range of motion measurements.

Range of motion measurement	Position participant	Position hand of participant	Position inclinometer	Unit
Glenohumeral anteflexion	Sitting	Pointing upward to ensure consistent rotation	Ventral on distal humerus, perpendicular to the plane of motion	Degrees
Glenohumeral abduction	Sitting	Pointing upward to ensure consistent rotation	Lateral on distal humerus, perpendicular to the plane of motion	Degrees
Glenohumeral abduction scapular plane	Sitting	Pointing forward to ensure consistent rotation	Ventral on distal humerus, perpendicular to the plane of motion	Degrees
Functional internal rotation	Sitting	—[a]	No inclinometer used	Ordinal scale: hand on the lateral side of the major trochanter, thumb behind buttocks, thumb toward contralateral SI joint, thumb toward L3, thumb toward T12, or thumb between scapulae[b]
Functional external rotation	Sitting	—[a]	No inclinometer used	Ordinal scale: hand not in neck or hand only to mouth, hand in neck but elbow pointing forward, hand in neck and elbow ½ open, hand in neck and elbow completely open, hand in neck and patient can extend elbow to 90° of flexion (hooray), and hand in neck and patient can extend the arm to complete elevation[c]
Internal rotation in horizontal plane	Sitting	Elbow in 90° of flexion, palm of the hand downwards	Middle of dorsal forearm	Degrees
External rotation in horizontal plane	Sitting	Elbow in 90° of flexion, palm of the hand downwards	Middle of dorsal forearm	Degrees

[a]—: not applicable.

[b]See Multimedia Appendix 2 for visual representation of the ordinal scale for functional internal rotation.

[c]See Multimedia Appendix 3 for visual representation of the ordinal scale for functional external rotation.

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Table 2. Shoulder muscle strength measurements.

Isometric muscle strength measurement	Position participant	Position hand of participant	Position HHD[a]	Direction of applied force (HHD[a])	Unit
Anteflexion 90°	Sitting, shoulder in 90° of anteflexion, and 30° in frontal plane toward abduction, arm extended	Palm of the hand downwards	Dorsal on distal forearm	Downward orientated	Newton
Anteflexion	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Ventral on humerus	Posterior orientated	Newton
Abduction	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Lateral on humerus	Medial orientated	Newton
Internal rotation	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Medial on distal forearm	Lateral orientated	Newton
External rotation	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Lateral on distal forearm	Medial orientated	Newton

[a]HHD: handheld dynamometer.

Table 3. Proprioception measurements.

Proprioception measurement	Position participant	Position of hand	Position inclinometer or HHD[a]	Unit
Joint positioning sense test 45° ± 10° anteflexion	Standing with elbow extended	Thumb pointing upward to ensure consistent rotation	Attached on ventral side distal humerus	Repositioning error in degrees
Joint positioning sense test 90° ± 10° anteflexion	Standing with elbow extended	Thumb pointing upward to ensure consistent rotation	Attached on ventral side distal humerus	Repositioning error in degrees
Joint positioning sense test 45° ± 10° abduction	Standing with elbow extended	Thumb pointing forward to ensure consistent rotation	Attached on lateral side distal humerus	Repositioning error in degrees
Joint positioning sense test 90° ± 10° abduction	Standing with elbow extended	Thumb pointing forward to ensure consistent rotation	Attached on lateral side distal humerus	Repositioning error in degrees
force sensation test internal rotation (50% MIVC)	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Medial on distal forearm, force lateral orientated	Reproducing error in Newton
force sensation test external rotation (50% maximally voluntary contraction)	Sitting, arm by the side of the trunk with elbow 90° of flexion	Thumb pointing upward to ensure consistent rotation	Lateral on distal forearm, force medial orientated	Reproducing error in Newton

[a]HHD: handheld dynamometer.

Patient Characteristics

Age, gender, comorbidities, previous surgery, and indication for surgery are collected from the medical records of the patient. Body weight and length will be asked during every consultation.

Potential Prognostic Factors

Patient characteristics such as body weight and body length, to calculate the BMI. Preoperative shoulder function including shoulder range of motion, shoulder muscle strength, and proprioception of the shoulder before surgery (Tables 1-3).

Soft tissue integrity of the different muscles around the shoulder joint will be collected from the surgeon's report and from previous surgeries. The shoulder muscles of interest are the rotator cuff muscles, biceps brachii muscles, and triceps brachii muscles. Soft tissue will be scored a 1 if it is damaged either through injury of previous surgery (open or arthroscopic surgery). Soft tissue will be scored 0 if it is not damaged, and no previous surgery has occurred.

Patients' expectations will be measured with a self-developed questionnaire, based on the HSS Shoulder Surgery Expectations Survey [20]. This survey consists of 17 questions, in Dutch, regarding postoperative expectations of symptom relief, physical function, and psychosocial function. Both spectrum and importance of expectations are measured, in less than 5 minutes. Each question has the following 5 possible responses: "very important," "somewhat important" "a little important," "I do not expect this," and "this does not apply to me."

Sling wear is also a possible prognostic factor. Patients will be randomized preoperatively in 2 groups with varying immobilization period. Patients in the first group (delayed

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mobilization group) will be wearing a sling for 6 weeks, the first 4 weeks an abduction sling, followed by 2 weeks of adduction sling. Patients in the second group (early mobilization group) will be wearing an adduction sling for 4 weeks. If a patient cannot be randomized in one of the 2 groups, the patient will be excluded from the study. For example, if a longer immobilization period is needed (complications during surgery, bone grafts used, etc.). Raters will be blinded from the sling wear throughout the whole observation period.

Psychosocial factors**,** including anxiety, depression, pain catastrophizing, and self-efficacy will be measured. Anxiety and depression will be measured by the Hospital Anxiety and Depression Scale [40]. This is a validated, self-administered questionnaire, available in Dutch, measuring anxiety as well as depression using 14 items. The items are scored on a 4-point Likert scale (0-3), the total score ranges from 0-21, whereas 0 means no depression or anxiety disorder and 21 means probability for anxiety or depression disorder, with a cut-off of +8 [41,42]. Pain catastrophizing will be measured with the Pain Catastrophizing Scale [43], a validated for low back pain, self-reported questionnaire that can be completed and scored within 5 minutes, available in Dutch [44,45]. This questionnaire consists of 13 items in which patients are asked to reflect on painful experiences and indicate feelings and thoughts about this pain. The questions are scored on a 5-point Likert scale, ranging from 0 (not at all) to 4 (always). Self-efficacy will be measured by the Pain Self-Efficacy Questionnaire, a validated, self-administered questionnaire with an excellent internal consistency, available in Dutch [46,47]. The questionnaire consists of 10 items whose are scored on a 7-point Likert scale, depending on how confident the patient is about a particular activity, despite the pain, 0 being not confident at all and 6 being completely confident. A total score will be calculated ranging from 0 to 60, with 60 indicating greater levels of confidence dealing with pain.

Lifestyle factors, including physical activity, smoking behavior, sleep, and drug and alcohol usage. Physical activity will be measured by the International Physical Activity Questionnaire – *long version* [48]. This is a valid and reliable questionnaire, available in Dutch [49]. Smoking behavior, sleep, and drug and alcohol usage will be objectified using a self-developed questionnaire. Drug usage will also be collected from the medical record. An overview of measurements per time point can be found in Table 4.

Physiotherapy treatment will also be objectified. Physiotherapists treating the patients included will be sent a questionnaire. The number of physiotherapy sessions during the first 6 weeks will be listed, as well as the number of given home exercises. The ratio between these 2 numbers indicates whether patients did perform predominantly more physiotherapy sessions or more home exercises. All patients will get the same information regarding postoperative rehabilitation. The first 2 weeks, a home-exercise program will be followed, explained by the inpatient physiotherapist. After 2 weeks the patient will be asked to visit the outpatient physiotherapist of their choice. An overview of measurements per time point can be found in Table 4.

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Table 4. Overview of measurements per time point.

Measurements	Type	T1 (preoperative)	T2 (6 weeks postoperative)	T3 (12 weeks postoperative)	T4 (6 months postoperative)	T5 (12 months postoperative)	T6 (24 months postoperative)
Patient characteristics							
Age	Medical records	X	—[a]	—[a]	—[a]	—[a]	—[a]
Gender	Medical records	X	—[a]	—[a]	—[a]	—[a]	—[a]
Comorbidities	Medical records	X	—[a]	—[a]	—[a]	—[a]	—[a]
Previous shoulder surgery	Medical records	X	—[a]	—[a]	—[a]	—[a]	—[a]
Indication for surgery	Medical records	X	—[a]	—[a]	—[a]	—[a]	—[a]
Outcome measures							
Shoulder function	• SPADI[b]	X	X	X	X	X	X
	• VAS[c]	X	X	X	X	X	X
	• CS[d]	X	X	X	X	X	X
	• ROM	X	X	X	X	X	X
	• Strength	X	—[a]	X	X	X	X
	• Proprioception	X	—[a]	X	X	X	X
Patient satisfaction	Self developed questionnaire	—[a]	X	X	X	X	X
Quality of Life	SF-36[b]	X	X	X	X	X	X
Potential prognostic factors							
Patient characteristics	• Body weight	X	X	X	X	X	X
	• Body length	X	X	X	X	X	X
Preoperative shoulder function	• ROM	X	X	X	X	X	X
	• Strength	X	—[a]	X	X	X	X
	• Proprioception	X	—[a]	X	X	X	X
Patient expectations	Self developed questionnaire	X	—[a]	—[a]	—[a]	—[a]	—[a]
Soft tissue integrity	Surgery report	—[a]	—[a]	—[a]	—[a]	—[a]	—[a]
Sling wear	Randomization	X	—[a]	—[a]	—[a]	—[a]	—[a]
Psychosocial factors	• Anxiety and depression (Hospital Anxiety and Depression Scale)	X	X	X	X	X	X
	• Self-efficacy (Pain Self-Efficacy Questionnaire)	X	X	X	X	X	X
	• Catastophizing (Pain Catastrophizing Scale)	X	X	X	X	X	X

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Measurements	Type	T1 (preoperative)	T2 (6 weeks postoperative)	T3 (12 weeks postoperative)	T4 (6 months postoperative)	T5 (12 months postoperative)	T6 (24 months postoperative)
Lifestyle factors	• Drug usage	X	X	X	X	X	X
	• Physical activity (International Physical Activity Questionnaire – long version)	X	X	X	X	X	X
		X	X	X	X	X	X
		X	X	X	X	X	X
	• Smoking behavior	X	X	X	X	X	X
	• Sleep						
	• Alcohol use						
Physiotherapy treatment	Questionnaire	X	X	X	X	X	X

[a]—: not applicable.

[b]outcomes used in the mixed-models analysis.

[c]VAS: Visual Analogue Scale.

[d]CS: Constant and Murley Score.

Participant Timeline

The participant timeline is shown in Figure 1.

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Figure 1. Participant timeline.

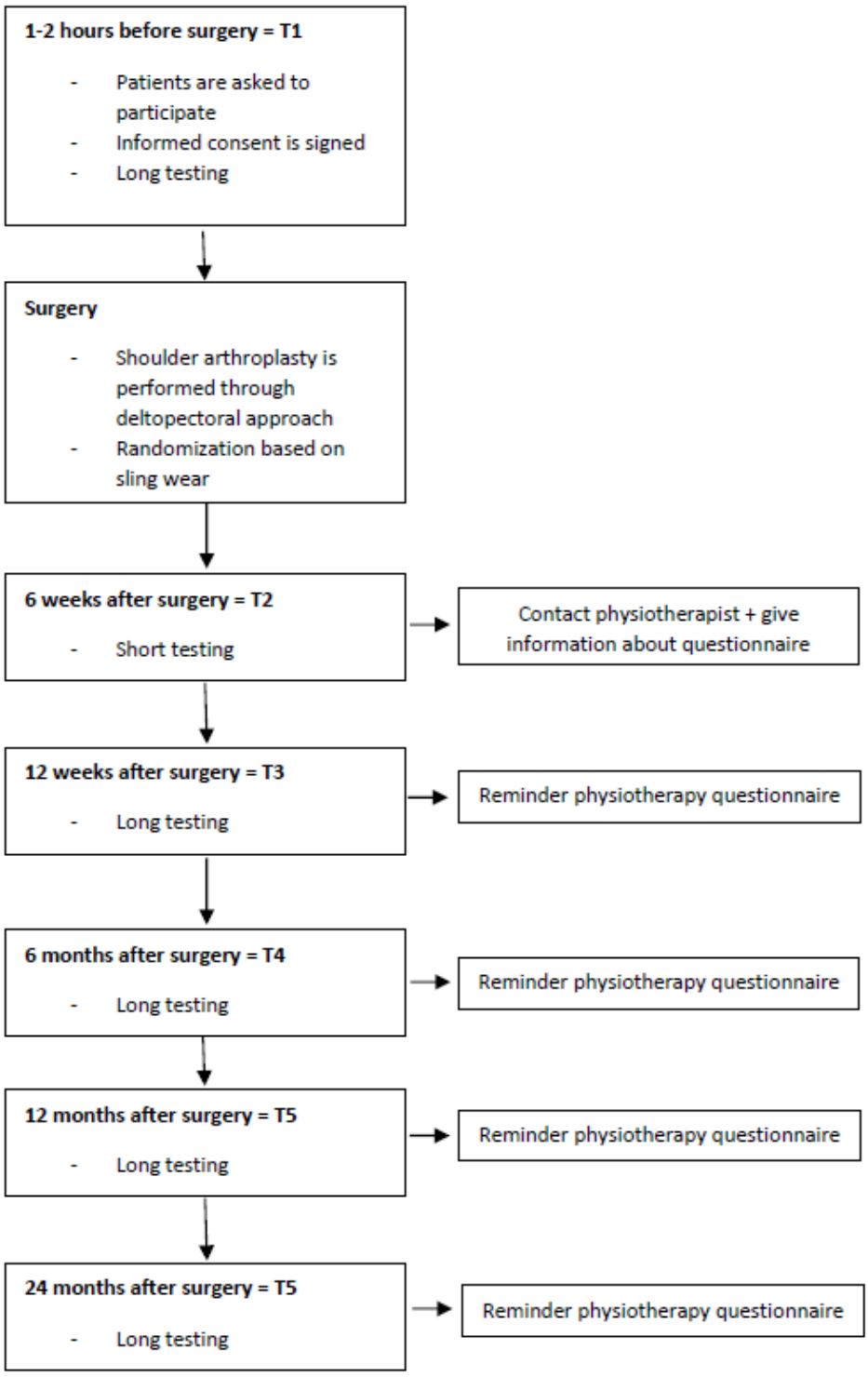

Sample Size

Considering a mixed regression model for repeated measures and using a moderate effect size that is still clinically relevant (20 points average decrease in SPADI score), inclusion of 5 covariates, confidence level (α=0.05), and desired power (90 %), the required total sample size is calculated to be 43 participants per group (Edland method, R package longpower 1.0-11) [50-52]. The SD of the SPADI measurements is set at 18, and is estimated from the SD measured in previous studies [31]. The variance of the residuals cannot be estimated from previous studies, but this variance only has a very limited effect on the sample size. It doesn't change the result of the power calculation and is not included in this analysis. Given the expected dropout rate of approximately 12.5%, a total number of 97 patients will be needed. The power is set at 90% to minimize the chance of making a type II error.

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Statistical Methods

Statistical analyses will be performed using SAS Studio (version 9.4; SAS Institute Inc). Level of significance is set at P=.05. Descriptive statistics will be used to describe the patient population. Based on literature review, expert opinion and univariate analyses potential prognostic factors will be chosen as covariates. A mixed regression model for repeated measures will be used to assess both the evolution of the SPADI score and the SF-36 score within persons from baseline over time and the differences in evolution between participants. This type of model has the advantage that the assumption of sphericity can be relaxed. Sphericity will probably be violated, as both the SPADI score, and SF-36 score at baseline and at all the different time points will probably have different variances. Second, using mixed models it is not necessary to have complete datasets to produce accurate results. Multiple imputation of missing values is thus not needed. All available data of a participant can be used in the model estimation, even if people missed a visit. Another advantage is that it is possible to simultaneously examine within and between person phenomena that might contribute to change in outcome. A fourth advantage is that the correlation between observations within persons over time is adequately addressed [53]. One assumption that must be checked is normality of the residuals, using a Shapiro-Wilk test. If these residuals are not normally distributed, an appropriate transformation will be performed first, or a nonlinear mixed model will be used.

Correlation analyses will be used to search for correlations between the other outcomes measured such as CS, shoulder range of motion, shoulder muscle strength, and proprioception and the primary outcome measure, SPADI. Potential prognostic factors not included in the model will be described.

Data Management

Two separated and secured computers will be used. Patients will be given a specific number characteristic. The respective number-patient relation will be stored on another external hard drive remote from the data computer.

The primary investigator [AC] will perform all data analysis. An independent statistician [TS] will guide the primary investigator in performing statistics.

Ethical Considerations

The central and local ethical committees of the University Hospital Antwerp and AZ Monica approved this study (B300201942512; 19/48/559). The present study underlies the principles of the Helsinki Declaration. Only data of patients who gave informed written consent to the project will be considered for analysis. The coding list of target data will be saved in a secured folder on an external hard drive. Only the project leader, study nurse, principal investigator, and second investigator have access to it. Between the members of the research team only coded and deidentified data will be shared.

The research team is committed to full disclosure of the results of the study. The results of the study will be disseminated for research purpose at different conferences and as published articles in peer reviewed journals. Findings will be reported in accordance with international guidelines, and we aim to publish in high impact journals. Given the multitude of outcome parameters, results will be divided over several papers.

Results

Data collection started in January 2020. In April 2023, the sample size was reached. Data collection will end in April 2025.

Due to the COVID-19 pandemic, the duration to reach the sample size was rather long. Between March 2020 and July 2020, and between October 2020 and December 2020, all nonurgent surgeries were postponed and even consultations were cancelled. Therefore, no new patients could be included, and the follow-up of some patients could not be reassured. An overview of the timeline can be found in Figure 2.

Figure 2. Timeline of study flow.

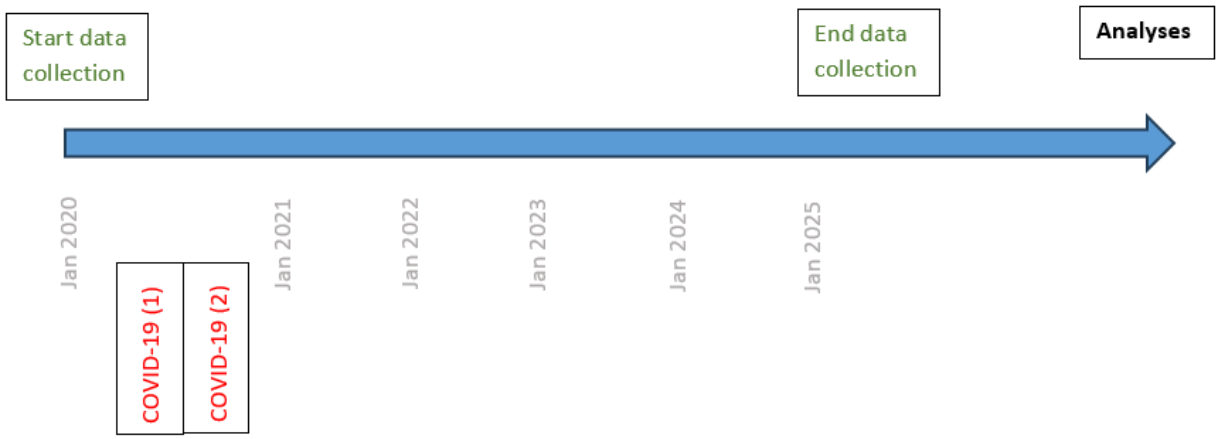

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Discussion

Principal Findings

The aim of this study is to investigate which prognostic factors could possibly predict baseline shoulder pain and function, and quality of life, and the evolution of shoulder pain and function, and quality of life in the first 2 years after a total shoulder arthroplasty surgery. A broad spectrum of factors is studied. This is the first longitudinal study to investigate the possible prognostic factors in patients with a shoulder arthroplasty with adequate power. The longitudinal design will allow us to follow patients over 24 months, which makes it possible to analyze and compare the measurements at 6 time points. Only 1 orthopedic surgeon performed the surgeries. This means the surgical technique is not one of the factors that must be taken into account. Parts of the surgery that do differ between patients are taken into account, such as subscapularis handling, and take-down and repair of muscles. The surgery, preoperative screening, postoperative consultation schedule, and everyday practice is the same in each of the included patients. The questionnaires the HSS Shoulder Surgery Expectations Survey and a self-developed questionnaire, adapted from the study of Swarup et al [22] were translated to Dutch for the purpose of this study. Therefore, their validity in the Dutch-speaking population has yet to be established.

As previously mentioned, the amount of shoulder arthroplasty procedures is rising. In contrast with knee and hip arthroplasties, more follow-up consultations with the orthopaedic surgeon are planned with total shoulder arthroplasties. Patients return to regular consultations at the defined timepoints which minimizes the loss to follow-up. Knowledge of potential prognostic factors will have implications toward better rehabilitation strategies of patients after total shoulder arthroplasty**.** With the modifiable potential prognostic factors analyzed, we could change strategies to try and change the outcome. Also, nonmodifiable factors are of interest. We could educate these patients to change or monitor the patient expectations to increase the quality of the outcomes.

Data Availability

The datasets generated during this study will be made available after analyses from the corresponding author on reasonable request.

Authors' Contributions

OV, FS, and AC worked on the conceptualization of the manuscript. FS, OV, TS, and AC worked on the methodology. The investigation was done by AC and ADM. The work was supervised by FS and OV. AC wrote the original draft, and FS, OV, TS, and AC reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent.
[DOCX File , 48 KB - resprot_v13i1e56522_app1.docx]

Multimedia Appendix 2
Visual representation of the ordinal scale for functional internal rotation.
[PNG File , 65 KB - resprot_v13i1e56522_app2.png]

Multimedia Appendix 3
Visual representation of the ordinal scale for functional external rotation.
[PNG File , 83 KB - resprot_v13i1e56522_app3.png]

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Abbreviations

CS: Constant and Murley Score
HHD: handheld dynamometer
SPADI: Shoulder Pain and Disability Index
SF-36: Short-Form 36
VAS: Visual Analogue Scale

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Protocol

Vientiane Multigenerational Birth Cohort Project in Lao People's Democratic Republic: Protocol for Establishing a Longitudinal Multigenerational Birth Cohort to Promote Population Health

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Abstract

Background: Rapid global population growth and urbanization have led to an increase in urban populations in low- and middle-income countries. Although these urban areas have generally better health outcomes than lower-income rural areas, many environmental, social, and health challenges remain. Vientiane, the capital of Lao People's Democratic Republic (Lao PDR), has approximately 1.5 of the 7.5 million Laotian population (2022) and provides a unique opportunity to examine health outcomes among socioeconomically diverse populations in the rapidly urbanizing context of the country.

Objective: The aim of the Vientiane multigenerational birth cohort (VITERBI) project is to (1) establish a multigenerational birth cohort in Vientiane capital, Lao PDR, which is representative of the local population, (2) serve as the basis for additional observational (ie, cross-sectional) and intervention studies that promote population health in Vientiane province, and (3) investigate the social, epidemiological, and medical problems of public health importance to Lao PDR.

Methods: VITERBI is a prospective multigenerational birth cohort. The study population is structured around children born between July 1, 2022, and June 30, 2023, who reside in Chanthabuly, Sikhottabong, Sangthong, or Mayparkngum districts of Vientiane. Whenever possible, children and their mothers are enrolled during pregnancy; nonreported pregnancies are enrolled after birth. The cohort plans to enroll 3000 pregnant women and their children and the infants' fathers, grandparents, and great-grandparents for a total study population of approximately 13,000 individuals. Participants will be followed throughout the life course with a range of data collected, including demographics, behavior, diet, physical activity, physiology, neurodevelopment, health history, quality of life, environmental exposures, depression, anxiety, stress, resilience, household characteristics, obstetric history, birth outcomes, and various living and dementia scales for older adults. Biomarkers collected include height, weight, blood pressure, and hemoglobin levels. Currently, no statistical analyses are planned.

Results: As of April 2024, this study has enrolled 3500 pregnant women and 4579 family members. Study participation is ongoing until May 2025 at minimum, with the goal to extend follow-up until 2050.

Conclusions: The study cohort will be used as a basis for further observational (cross-sectional, longitudinal) and intervention studies. It also serves as a tool to investigate social, epidemiological, and medical problems of public health importance to Lao PDR, which will contribute to broader understanding of regional and international contexts.

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KEYWORDS

Lao PDR; birth cohort; growth and development; mental health; dementia; exercise; behavior; aging; intergenerational; noncommunicable disease; hypertension; longitudinal cohort; low- and middle-income countries; maternal health; pregnancy; antenatal care; peripartum; postpartum; child health; infant health

Introduction

The Lao People's Democratic Republic (Lao PDR) is a socialist republic in southeast Asia, bordered by China, Vietnam, Cambodia, Thailand, and Myanmar. In 2018, Lao PDR was home to approximately 7 million people and at least 47 distinct ethnic groups [1]. Roughly half (52.5%) of the population identify as ethnic Lao [1], and one-third (35.6%) live in an urban area [2]. The majority of the urban population reside in the capital city of Vientiane [3]. Historically, Lao PDR's economy has relied heavily on agriculture; more recently, tourism, foreign investments, and foreign aid have supported Lao PDR's major economic growth—with an estimated 7% growth rate in gross domestic product between 2011 and 2017 [4]. In 2011, the World Bank changed Lao PDR's economic status from a low income to lower middle-income economy [5].

Despite the rapid recent economic growth in Lao PDR, many environmental, social, and economic factors contribute to the high rates of mortality and morbidity [2]. Lao PDR reports a high incidence of infectious diseases, including malaria [6,7], dengue [8], Japanese encephalitis [9], typhoid [10], and tuberculosis [7,11]. Parasitic diseases endemic to Lao PDR, including schistosomiasis, soil-transmitted and food-borne helminthiases, and taeniasis, are classified by the World Health Organization (WHO) as neglected tropical diseases, and these disproportionately impact impoverished communities and women and children, engendering broader social and economic consequences [12]. Only 55% of the Laotian population has access to safe drinking water, which increases the frequency of preventable water-related diseases [13,14]. In recent decades of economic development, noncommunicable diseases have increased significantly, among which diabetes mellitus, cardiovascular disease, and various cancers are of particular concern in Lao PDR.

Maternal and child health is a strong predictor for population health and the development and sustainability of economies [15]. Lao PDR has the highest maternal mortality rate in Southeast Asia—estimated between 400 and 600 deaths for every 100,000 births from 2000 to 2008 [16]. Approximately 2 in 5 children younger than 5 years have moderate or severe stunting [17]. On average, a child of poor health will have a lower education attainment and earn a lower income, usually following a similar social and health trajectory as the mother [18]. Although the determinants of maternal and child health are vast and multifaceted, epidemiologic research utilizes several indicators to measure the maternal and child health status of a country, such as low birth weight, maternal morbidity, and antenatal or postpartum care attendance [19].

Maternal and child health indicators are useful tools for guiding public health strategies to improve population health; however, collecting data on maternal and child health alone is not sufficient to understand the health needs of populations. Intergenerational health and wealth beyond the mother also directly influence the life course trajectory of children [20-22]. Mental health problems in childhood are directly related to both the parents' and grandparents' mental health history and current mental health status [23]. Children born into socioeconomically disadvantaged families are more likely to have problems with language and reasoning, and similar challenges are found among family members within 2 generations of the family lineage [24]. Epigenetic modifications for various diseases, including gestational diabetes, are impacted by both family genetic backgrounds and environmental factors [25], highlighting the importance of combining intergenerational and individual maternal and child health data.

To date, only a few cohorts exist in Lao PDR or Vientiane. A prospective, community-based cohort study in Vientiane (N=4885 participants, 995 households, 25 villages) was conducted from 2015 to 2016 to monitor influenza-like illnesses and its causative pathogens [26]. Another prospective cohort study in Vientiane (n=1000 pregnant women) was conducted from 2013 to 2015 to investigate the association between maternal morbidity, small for gestational age, and fever [27]. To the best of our knowledge, there are currently no active cohort studies covering all age ranges in this setting.

Our Vientiane multigenerational birth cohort (VITERBI) is the first multigenerational birth cohort created in the urban and semiurban districts of Vientiane capital, Lao PDR, focused on intergenerational health and life course trajectories of children, their parents, grandparents, and great-grandparents. Cohort data will be analyzed to quantify key health challenges and gaps across population groups, ultimately to develop interventions and social impact programs for the improvement of population health.

VITERBI has 3 main aims:

1. Establish a multigenerational birth cohort in Vientiane capital, Lao PDR, which is representative of the local population.
2. Serve as the basis for additional observational (ie, cross-sectional) and intervention studies that promote population health in Vientiane province.
3. Investigate the social, epidemiological, and medical problems of public health importance to Lao PDR, including intergenerational prevalence of overnutrition and undernutrition, access to antenatal care, adult access to health care, prevalence and predictors of communicable and noncommunicable diseases within families, the current status of geriatric care, and its socioeconomic determinants.

Methods

Study Design

The VITERBI cohort will be established in the Vientiane capital of Lao PDR and is a prospective longitudinal birth cohort study

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enrolling children (during pregnancy), their parents, and relatives up to 3 generations (maternal and paternal grandparents and great-grandparents). Four districts of Vientiane capital were purposely selected based on overall socioeconomic status: Chanthabuly and Sikhottabong are 2 districts located in urban areas of high socioeconomic status, while Sangthong and Mayparkngum are 2 districts located in the semiurban, less developed areas of low socioeconomic status.

Participants

The target sample size for the VITERBI cohort is 3000 children and their relatives (~13,000) across 4 selected districts. Index women (ie, pregnant women and the first participant enrolled within a family) are eligible for recruitment if they live in Vientiane capital in 1 of the 4 study districts; had an expected due date or gave birth between July 1, 2022, and June 30, 2023; do not plan to permanently move outside the study area; do not have a medical, intellectual, or psychological disability; and agree to participate with a signed informed consent. If the participant is younger than 18 years, a legal representative will additionally need to sign the informed consent. Whenever possible, women will be enrolled during pregnancy; however, women who were not enrolled during pregnancy will be enrolled shortly after birth by using a modified late enrollment questionnaire.

Index women are tracked with a unique VITERBI ID number within the project database. All subsequent family ID numbers retain the number associated with the index woman in addition to their specific unique ID (Figure 1). Thus, all unique personal ID numbers assigned to family members of the child will be associated with the original ID number of the index woman. The ID numbers also indicate the district of residence of the index woman.

Enrollment data from each family member will be used to construct a family tree based around the index woman and child (Figure 2). All enrolled members will be followed up for a minimum of 1 year, with the ambition to extend the follow-up period until 2050. Members of the established cohort will also be recruited and enrolled into additional studies, as they arise.

Figure 1. Participant ID interpretation of the Vientiane multigenerational birth cohort (VITERBI) participants.

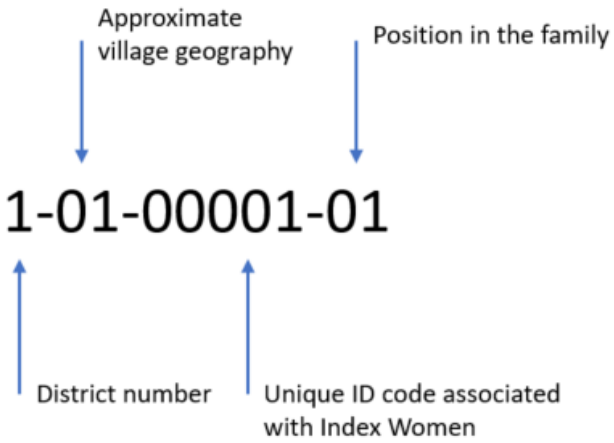

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Figure 2. Family tree of the index women of the Vientiane multigenerational birth cohort (VITERBI). DOB: date of birth.

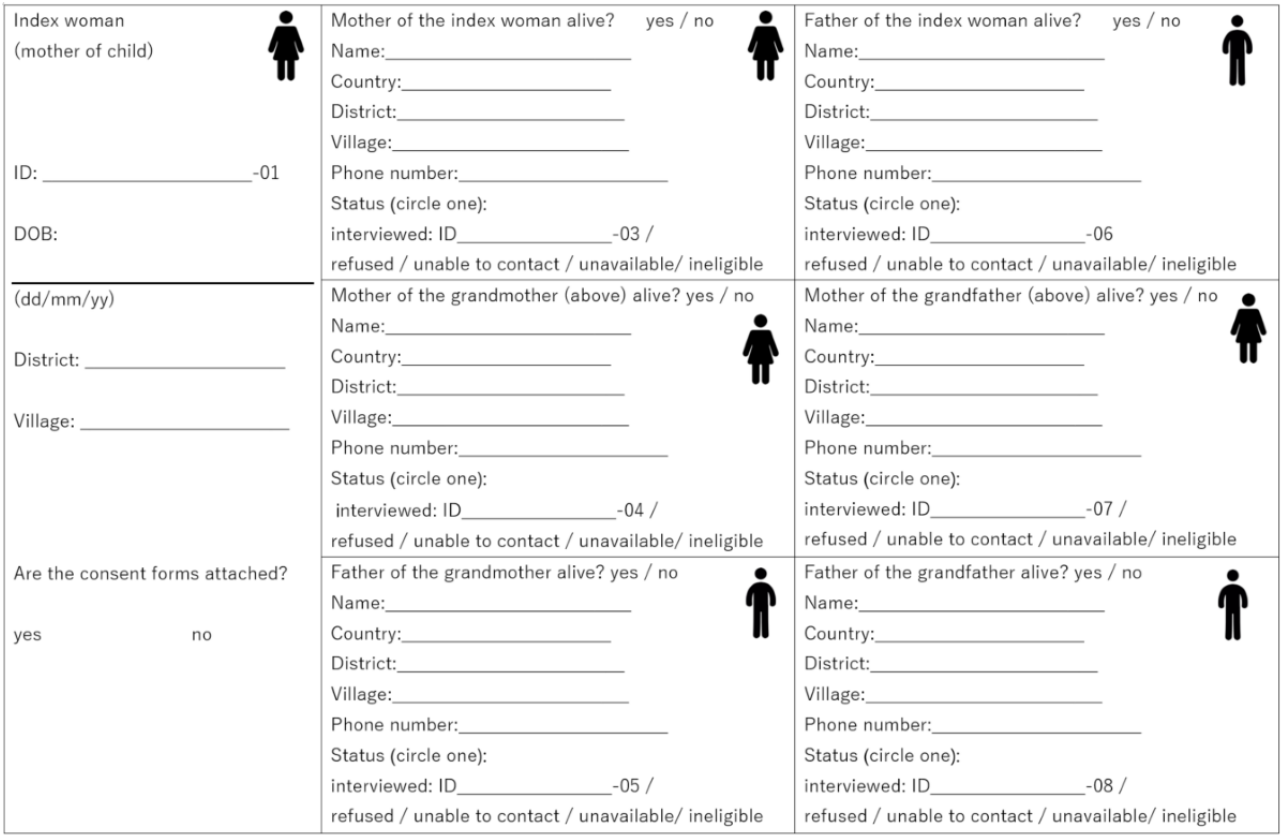

Ethics Approval

Ethics approval for this study was obtained from the Ethics Commission of Northwestern and Central Switzerland (EKNZ, 2020-00037) and the National Ethic Committee of Health Research, Ministry of Health, Lao PDR (035/NECHR). This research project will be conducted in accordance with the protocol, Declaration of Helsinki [3], Swiss Human Research Act, and Swiss Human Research Ordinance [1] as well as other locally relevant regulations.

Informed Consent

Eligible participants will be visited initially by study staff. The purpose of this study and its procedures will be explained to participants, and a written informed consent will be obtained. Pregnant women will give consent for themselves and their newborns. For minors (age<18 years), both the pregnant woman and her parents will provide consent. For participants who are illiterate, there will be an additional witness who is not part of the study team. Participation is voluntary, and patients have the right to withdraw from the study at any given point in time with no further obligations. If the participant withdraws at any time, their data will be deleted. Confidentiality of information will be assured to the participants. All participants younger than 18 years are considered vulnerable populations according to the Lao PDR legislation. If the respondent is underage and agrees to participate, he/she needs the authorization of a parent or legal guardian who cosigns the study informed consent.

Recruitment

We used a variety of sampling methodologies to identify all births between July 1, 2022, and June 30, 2023. To start, we embedded VITERBI recruitment strategies within the existing Laotian health care system. In Lao PDR, public health care services are delivered according to administrative levels, that is, central/national, provincial, district, and village, which operate under the centralized Ministry of Health. We recruited eligible pregnant women from hospitals operating at all 3 levels of care available in Vientiane capital: central/national, district, and village. Health care staff at public health care facilities at the central and district levels facilitate recruitment by notifying VITERBI staff of eligible participants and connecting consenting individuals with VITERBI staff.

VITERBI staff are assigned in teams to 1 of the 4 study districts to conduct recruitment. VITERBI staff partner with local staff working in public health and governance at both the district and village levels through institutional relations formalized by the Lao Tropical and Public Health Institute, a Lao governmental research entity administered by the Lao Ministry of Health. These partnerships involve working closely with key informants such as hospital leadership, health care providers, public administrators, village health volunteers, and local leaders of all administrative levels. Local collaborators generally keep more granular records (eg, unofficial village census) than national partners and maintain situational awareness of their populations' health status. Key informants from each village within the 4 study districts work alongside VITERBI staff to identify and recruit potential participants. VITERBI staff regularly visit antenatal care clinics known to serve populations that reside in the study districts to recruit eligible women. Enrollment and all data collecting activities of the VITERBI cohort study are coordinated from a central office at the Lao Tropical and Public Health Institute.

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Women who were not enrolled during pregnancy are enrolled postpartum to increase enrollment coverage. Birth records are obtained from central hospitals and local health centers to identify recent births that occurred within the cohort window. Staff attempt to contact these women who were neither enrolled nor declined a previous recruitment attempt during pregnancy. Study staff also obtain vaccination records from central health entities to cross-check infant enrollment with both on-time and postpartum recruitment and attempts to recruit women who do not appear in either channel (Figure 3). Access to these records is facilitated by the Lao Tropical and Public Health Institute through the Ministry of Health. Formal birth records obtained from hospitals and vaccination records from the National Immunization Program are used to evaluate recruitment rates. Increasing the overall enrollment coverage of eligible women (prepartum and postpartum) assures that the cohort represents the target population.

Index woman enrollment is the cornerstone for subsequent enrollment of the child's relatives. In the field, VITERBI staff work closely with the index women to construct family trees detailing relatives of the child who are alive, eligible (living in the 4 study districts), and available to take part in the study. The family tree document guides staff recruitment efforts by providing basic demographic (name, age, and relationship to the child) and contact information of all family members who can be included. As we recruit additional family members, we anticipate their input will continue to guide recruitment and interview of subsequent members by reviewing the family tree document.

Figure 3. Enrollment pathway of the Vientiane multigenerational birth cohort. VITERBI: Vientiane multigenerational birth cohort.

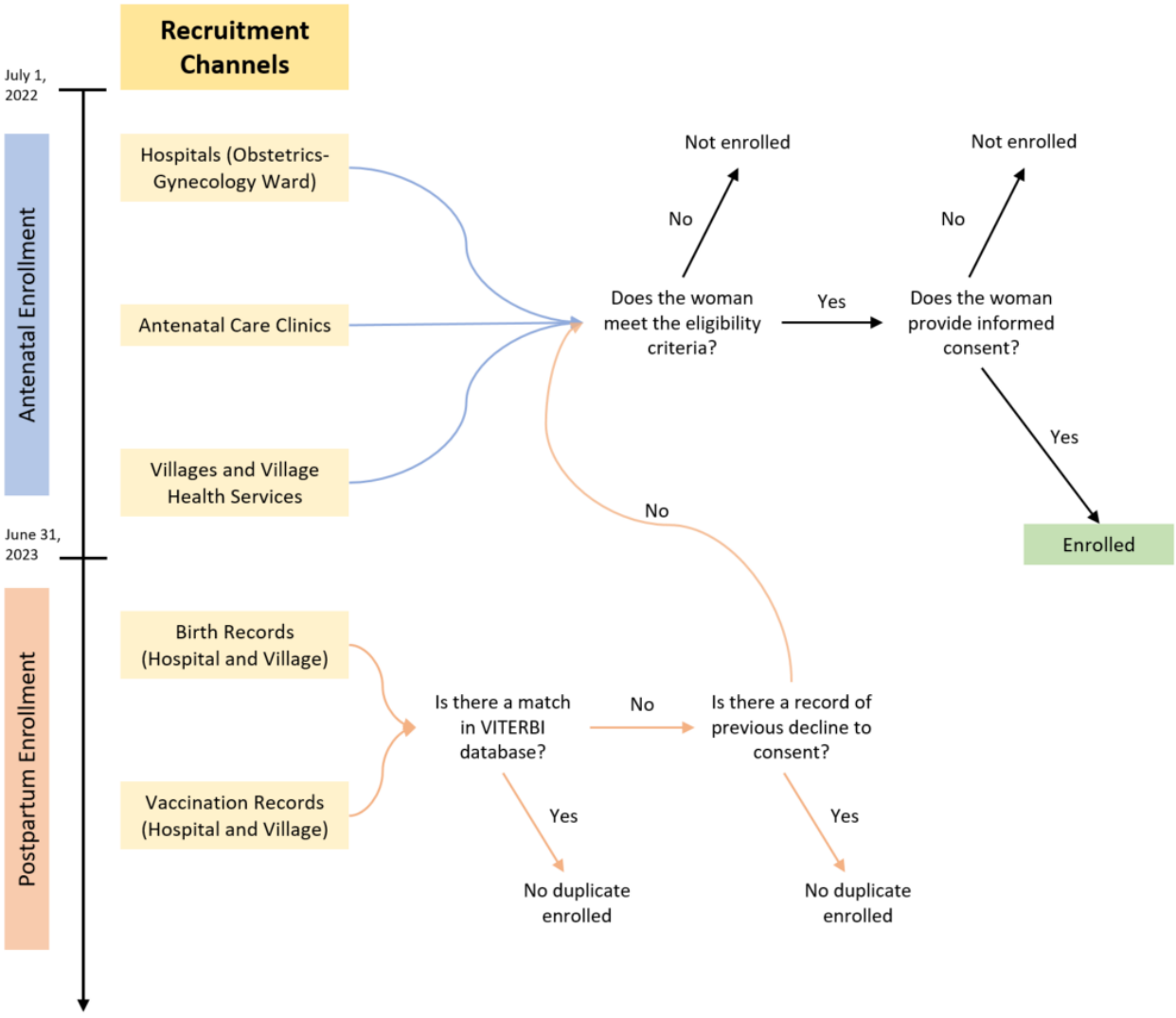

Data Collection Instruments

The VITERBI study has a total of 6 questionnaires: (1) child enrolled during pregnancy (ie, index women), (2) child enrolled after birth (late enrollment), (3) postpartum form to collect birth outcomes, (4) adult questionnaire for the child's father, grandparents, and great-grandparents, (5) a short questionnaire for family members who are incapacitated or have a cognitive impairment, and (6) household characteristics. Table 1 shows extensive information about the data collection instruments. All surveys are administered in-person via tablets by trained staff in the field and uploaded remotely to a web-based server at the end of the workday. Each questionnaire is briefly described below but can be accessed by reasonable request.

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Table 1. Data collection for each participant in the Vientiane multigenerational birth cohort (VITERBI).

Question type	Participants					
	Index mother	Late enrollment	Index mother postpartum	Adult[a] (<60 years)	Adult[a] (≥60 years) with no cognition problem	Adult[a] (≥60 years) with cognition problem
Demographics	✓	✓		✓	✓	✓
Employment	✓	✓		✓	✓	
Obstetric history	✓	✓		✓[b]	✓[b]	
Antenatal care	✓	✓				
Prenatal supplementation	✓	✓				
Tobacco use	✓			✓	✓	
Alcohol consumption	✓			✓	✓	
General diet	✓			✓	✓	
Dietary salt	✓			✓	✓	
Handwashing practices	✓			✓	✓	
Raw food consumption	✓			✓	✓	
Physical activity	✓			✓	✓	
Transportation	✓			✓	✓	
Sedentary behavior	✓			✓	✓	
Pattern recognition and digit span	✓			✓	✓	
Disability	✓			✓	✓	
History of raised blood pressure	✓			✓	✓	
History of diabetes	✓			✓	✓	
History of raised cholesterol	✓			✓	✓	
History of cardiovascular disease	✓			✓	✓	
Experience of pain and arthritis	✓			✓	✓	
Chest pain	✓			✓	✓	
Cervical cancer screening	✓			✓[b]	✓[b]	
Health history	✓			✓	✓	
Environmental exposure	✓			✓	✓	
Family survival history	✓	✓		✓	✓	
Quality of life	✓			✓	✓	
Depression, anxiety, stress	✓			✓	✓	
Resilience	✓			✓	✓	
Recent birth outcomes		✓	✓			
Breastfeeding initiation, exclusivity, duration		✓	✓			
Postpartum depression		✓	✓			
Postpartum medical visit		✓	✓			
Instrumental Activities of Daily Living Scale					✓	✓
Activities of Daily Living						✓
Revised Hasegawa Dementia Scale					✓	✓
Physical measurements						
Blood pressure	✓	✓	✓	✓	✓	
Heart rate	✓	✓	✓	✓	✓	

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Question type	Participants					
	Index mother	Late enrollment	Index mother postpartum	Adult[a] (<60 years)	Adult[a] (≥60 years) with no cognition problem	Adult[a] (≥60 years) with cognition problem
Weight	✓	✓	✓	✓	✓	
Height	✓	✓	✓	✓	✓	
Waist circumference	✓	✓	✓	✓	✓	
Hip circumference	✓	✓	✓	✓	✓	
Leg length	✓	✓	✓	✓	✓	
Trunk length	✓	✓	✓	✓	✓	
Mid-upper arm circumference	✓	✓	✓	✓	✓	
Hemoglobin	✓	✓	✓	✓	✓	

[a]Relation to the child: father, grandmother, grandfather, great-grandmother, and great-grandfather.

[b]Women only.

Index Women

Women enrolled during pregnancy were asked about their pre–pregnancy weight in kilograms, antenatal care, obstetric history, and plans for infant feeding. If enrollment occurred after birth, a shortened questionnaire was provided so as not to interfere with the mother-infant bonding (late enrollment questionnaire).

Postpartum Interview

The postpartum questionnaire obtains information about the child's birth outcome, health status, and general obstetric and postpartum experiences. Breastfeeding initiation and duration are assessed using questions from the Infant Feeding Practices Survey II [28]. Postpartum depression is assessed using the Edinburgh Postnatal Depression Scale [29]. Only when the women moved to a district outside the VITERBI catchment area were the questionnaires completed via telephone.

All Adult Family Members

Utilizing validated questionnaires, we compiled an extensive interview to assess population characteristics. Each questionnaire includes the following information: demographic information; behavioral measurements for tobacco use, alcohol consumption, diet, and physical activity; health history; physical measurements, including blood pressure, height, weight, and waist circumference; sections from the WHO stepwise approach to surveillance [30]; hemoglobin levels by using the HemoCue Hb 301; family survival history; self-rated general quality of life [31]; environmental exposures to pesticides and cooking conditions; general mental health assessed using the Depression Anxiety Stress Scales [32,33]; cognitive status using progressive matrices [34] and the digit span [35]; and resilience levels [36]. Only women are asked the cervical cancer screening question from WHO stepwise approach to surveillance [30].

Older Adults (Aged 60 Years or Older)

Individuals aged 60 years or older complete additional aging-related modules: Activities of Daily Living (ADL) and Instrumental Activities of Daily Living Scale are assessed using the Barthel [37] and Lawton [38] index, respectively. The Revised Hasegawa Dementia Scale [39] is used to assess cognitive impairment. If there is any indication that the adult is cognitively unable to complete the full-length interview, a short questionnaire only including these indicators was included. The main caretaker would answer questions regarding ADL. Only ADL was assessed among adults who had a main caretaker.

Household Questionnaire

The Demographic and Health Surveys Phase 8 Questionnaire for household characteristics is used to assess access to drinking water, toilet facilities, mosquito net use, wealth and assets, food security, and use of social services.

Retention of Participants

We collect a variety of contact information to reduce participant attrition. Participants provide their first and family names, address, phone number, email address, village leader name, temple or religious organization, and the contact information of a family member or close friend. In addition, we provide a small gift for participation. Immediately after the physical examination during baseline interview, all participants receive their biometric test results. Results include blood pressure, hemoglobin levels, and waist and hip circumference values. Results are explained during the session by licensed medical personnel (eg, staff nurses) and written on an information pamphlet for future reference. If the test results are abnormal, participants will be referred to their local health center for treatment. In addition, all participants who complete the baseline questionnaire receive a small gift (ie, hand soap) that equates to approximately US $1.

Data Management

All questionnaires and data management are conducted in Open Data Kit (ODK). ODK is an open-source Android app that supports mobile data collection services. ODK Collect replaces paper forms used in survey-based data gathering and can be utilized without network connectivity. It supports a wide range of question types and answer formats. All data collection will occur offline on password-protected Android devices. Data connectivity will only be used to send data collected in the field at the end of the workday, when the data collection staff are in

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network range. Data storage is on a local secured server at Swiss Tropical and Public Health Institute by using the ODK Aggregate server.

Statistical Analyses

The main goal of our study is to provide descriptive epidemiologic information on the current health status of a representative, purposive sample of children and their families in Vientiane province, Lao PDR. This includes incidence and prevalence estimates, geospatial maps displaying disease distributions, and factors of health and health behaviors (ie, accessing health care). Currently, no statistical analyses are planned. However, any additional research study will submit a separate institutional review board application.

Results

As of April 2024, this study has enrolled 3500 pregnant women and 4579 family members. Study participation is ongoing until May 2025 at minimum, with the goal to extend follow-up until 2050. The cohort has already served as a basis for additional observational and intervention studies that promote population health in Vientiane province: (1) VITERBI GUT, a prospective birth cohort studying the link between early life malnutrition, the microbiota, and metabolic health [5] and (2) a randomized controlled trial providing social transfers to increase exclusive breastfeeding and promote maternal and child health [40].

Discussion

Multigenerational prebirth cohorts provide in-depth information about pregnancy, infants, early childhood, intergenerational health and wealth cycles, and etiology for specific diseases. Conducting longitudinal cohort studies in low-and middle-income countries provides unique challenges that are often not seen in high-income nations.

One key challenge in the specific context of Vientiane capital is the lack of robust information technology systems that would facilitate official data sharing and provide patients with personal records. Although decentralized operations might improve health system equity in hard-to-reach places subject to remote conditions and limited infrastructure, widespread deficiency of interfacility and interagency communication also results in fragmentation of the health system [41]. The VITERBI recruitment methodology employs diverse strategies in an attempt to reach eligible women and their families across different channels of the public health care and municipal systems. Of note, the recruitment efforts of women seeking and receiving care at 2 national facilities, Mother and Child Hospital and the maternity ward of Mahosot Hospital, yielded higher enrollment compared to province-level and district-level facilities. Face-to-face contact with local health staff and officials is an effective strategy for identifying eligible participants, as centralized data sharing and communication are not effective strategies in Lao PDR. Although record-keeping may vary between villages and districts, local staff generally have knowledge and records—both formal and informal—of pregnancies within their jurisdiction. Basing their work out of one of the study districts for prolonged periods, VITERBI staff are able to develop consistent partnerships with local staff at both the district and village levels. This strategy is particularly useful in recruiting women who may not be accessing health services within the previously described VITERBI contact circuit (eg, who are accessing private services or are not accessing any health care services).

Despite the varied and often fragmented channels for identifying and recruiting eligible participants, close collaboration with stakeholders at all levels, detailed study coordination from our team, and adaptive communication and working strategies have helped increased enrollment. Although there likely remains untapped avenues for reaching and recruiting eligible women, the previously described methods currently push the operational limits of our administrative and fieldwork staff. These staff members contend with the need for persistent communication with local health authorities, receive redundant and disorganized population data, and work around convoluted timelines set by administrative bottlenecks. These challenges emphasize the need to develop adaptable workflows with flexible coordination and strong collaboration among the staff.

Further challenges to producing a clean and robust database for a cohort of this magnitude include maintaining record completeness and reconciliation between the web-based questionnaire database and physical forms. When physical forms are collected (eg, participant consent forms, family trees) from the field, they are submitted biweekly to the main office to be double-checked and filed. This check is essential to ensure that no duplicate ID numbers have been assigned to different index women—an error that occurs due to misprinting of questionnaire codes associated with the IDs and the dissemination of misprinted forms to interview staff working in different groups in different areas of the same district. Duplicate ID numbers are detected by thorough check of the physical forms and then amended in the web-based database by manually assigning a new unique VITERBI ID in ODK.

All forms, including physical consent and contact forms alongside digital survey forms, must be checked for completeness. Then, physical and web-based forms must be compared with one another to ensure essential information (name, date of birth, contact phone number, district of residence, etc) match to the best of our ability. The Lao language and naming system presents unique challenges, as there is no standard Romanization, and often an individual is identified by an informal name that does not match legal or medical records. These factors result in multiple spellings of the same name in English translation and several names being associated with one individual. Often, informal names are quite generic, which can lead to confusion if there are no additional formal names or surnames listed for the participant. For this study, we collate all the records and associate as much identification information as is available with the unique VITERBI ID numbers. Thus, we rely on the index numbers to identify participants.

Many lessons learned from VITERBI can be used for other cohort studies in low-resource settings. These lessons include:

1. Local capacity building and continuous strengthening is essential. A thorough training of all research staff is critical for minimizing data collection errors. Creating sustainable

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institutional partnership for comparative cohorts of mutual benefit for different partners is also key for future research.
2. Building trust with local leaders facilitates identification of participants and creates community ownership of the cohort goals.
3. In minority populations such as the Hmong ethnic group in Vientiane, utilizing local staff that reflect the community population who act with high cultural competency from villages or neighborhoods is important for engaging difficult-to-reach populations.
4. Flexibility and creativity in research staff are key. Participant identification is difficult, and the local study staff may need to adapt recruitment strategies in order to engage the population. Many of the villagers were only available in the evenings or on weekends, creating the need for staff to stay for long periods of time within the community.
5. Study instruments need to be reflected across many different age and ethnic groups. The multigenerational aspect of the cohort calls for a multidisciplinary team to ensure cohesion across study questions.
6. The medical system is overburdened, and medical records are not digitized. Collecting handwritten ledgers to identify and track children and their mothers is time-intensive and requires a formal data tracking system.

Each community offers unique challenges. In low-resource settings where longitudinal studies are more difficult, such data would often be the most beneficial for population health. For this exact reason, additional longitudinal studies should be conducted in these settings. Although the researcher should not be complacent in recognizing the specificity of the study setting, the methods and lessons described here may prove relevant in the formation of future studies in the Lao PDR context and beyond.

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Data Availability

Data sharing is not applicable to this paper, as no datasets were generated or analyzed during this study.

Authors' Contributions

JTW, SK, NP-H, PO, SS, and GF made substantial contributions to the conception and design of this study and contributed to the acquisition of data and revised the manuscript. JTW, MS-H, VO, SK, LS, SS, PO, and GF provided project administration and supervision. JTW and MS-H drafted the manuscript. All authors revised and approved the submitted version and have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and the resolution documented in the literature.

Conflicts of Interest

None declared.

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Abbreviations

ADL: Activities of Daily Living
Lao PDR: Lao People’s Democratic Republic
ODK: Open Data Kit
VITERBI: Vientiane multigenerational birth cohort
WHO: World Health Organization

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Protocol

Assessment of Health and Well-Being Effects Associated With the Challenging Drinking Water Situation in the Gaza Strip: Protocol for a Cross-Sectional Household Survey Study

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Abstract

Background: The water supply in the Gaza Strip, Palestine, has been unstable and under strain for decades, resulting in major issues with drinking water quality, reliability, and acceptability. In 2018, between 25% and 30% of Gazans did not have regular access to running water. The progressive deterioration of water infrastructure and concerns over the quality of piped water have resulted in a complex mix of drinking water sources used in the Gaza Strip. The challenges of safe water provision in the Gaza Strip could potentially have severe adverse effects on the population's health and well-being.

Objective: The main objectives of this survey are to determine the quality of drinking water at the household level and to investigate the association of various health outcomes with water quality at the household level in the Gaza Strip.

Methods: We conducted a cross-sectional household survey in the North Gaza, Gaza, and Rafah governorates between January and March 2023. We selected a subsample of households from a representative cross-sectional survey conducted in the Gaza Strip in 2020 with persons aged 40 years and older. From each household in the 2023 survey, we invited 3 individuals (2 older than 40 years and 1 between 18 and 30 years) to participate. The face-to-face interview included questions on drinking water, mental health and well-being, self-reported diagnoses for selected diseases, use of antibiotics, and knowledge about antimicrobial resistance. Additionally, we measured each participant's blood pressure. We sampled drinking water from each household and analyzed the samples for microbial contamination, nitrate, sodium, and mineral content.

Results: In total, we visited 905 households and interviewed 2291 participants. In both age groups, more female participants were interviewed. A total of 56.60% (914/1615) were aged ≥40 years, and 58.9% (398/676) were aged between 18 and 30 years. We obtained water samples from nearly all households (902/905, 99.8%). The results are expected to be published in several papers in 2025.

Conclusions: The extensive survey components, coupled with drinking water testing and building on an existing survey, allowed us to identify a broad set of potential impacts on health and well-being and to track changes over time. This study intends to identify humanitarian and development interventions that could impact the population served most. However, we completed data collection before the escalation of violence in October 2023. Given the impact of the still ongoing conflict, the initial intent of

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this work is no longer valid. However, the results emerging from the survey may still serve as a valuable baseline to assess the impacts of the current escalations on physical and mental health and on drinking water quality. In addition, our findings could provide important information for rebuilding the Gaza Strip in a more health-promoting way.

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KEYWORDS

drinking water; water quality; households survey; noncommunicable diseases; protracted conflict; humanitarian crisis; Gaza Strip; well-being

Introduction

Background

Water quality has decreased drastically in Gaza, Palestine, over the past 2 decades. While nearly all residents had access to improved water 25 years ago, between 25% and 30% of Gazans did not have regular access to running water in 2018 [1]. The destruction and deterioration of water infrastructure and concerns over the quality of piped water have resulted in a complex constellation of different types of drinking water sources being used in the Gaza Strip.

In addition to the weak infrastructure and reliability, there are major issues with drinking water quality. Only about 4% of the water from groundwater wells falls within the World Health Organization (WHO) limits for nitrate and chloride. Only 1 in 10 wells was below the threshold for nitrate (50 mg/L) and 2 in 10 wells were below the threshold for chloride (205 mg/l) [2]. Four out of 5 municipal wells did not comply with the safety threshold for salinity (250 mg/L), and most of the coastal area is affected by seawater intrusion into the aquifers [2,3]. A recent study found that groundwater salinity has increased by 31% and nitrate has decreased by 20% in some wells over the past 20 years [4]. The pollution of groundwater and drinking water with toxic chemicals, such as pesticides and heavy metals, is unknown. Approximately 70% to 80% of people in the Gaza Strip are estimated to use desalinated water as their main source for drinking and cooking [5]. However, the desalinated water that many households purchase as an alternative to groundwater is not free from contamination. Studies ranging from 2014 to 2021 found that piped water, as well as water from desalination plants, exhibited high levels of microbial contaminants, including fecal coliforms [6,7]. In a study conducted in 2018, 17% of the samples were positive for fecal coliforms [3]. A study testing water from various sources found *E coli* in 6.9% of the samples [8]. Additionally, nitrate levels in desalinated water are a concern, with 13% of samples exceeding the WHO safety threshold [9].

Climate change is likely to further exacerbate water quality and availability in the Gaza Strip with an expected increase in the average temperature between 1 and 1.5 °C by 2050 [10,11]. In the same time frame, the number of days above 30 °C is anticipated to increase by 60%, along with the increasing sea level, pushing seawater intrusion into the aquifer farther inland [10,11]. Annual rainfall could decrease by up to 20%, while extreme weather, such as heavy rainfall in winter will be more frequent, increasing the frequency of flooding events [10]. Moreover, it is expected that the southern part of the Gaza Strip will be at increased risk of chronic annual drought events due to much lower precipitation conditions than other areas in the Gaza Strip [12].

The significant microbial pollution in the Gaza Strip's drinking water raises public health concerns. Fecal coliform poses a severe risk for the transmission of water-borne diseases, encompassing various pathogens causing mild infections like acute diarrhea to severe conditions such as chronic diarrhea, dysentery, hepatitis A, typhoid, and cholera [13]. The high microbial pollution is particularly of concern in light of the high levels of antimicrobial resistance (AMR) found in bacteria isolated from human and environmental samples taken at hospitals, farms, and coastal waters [3,14-16]. AMR further complicates the treatment of some of these infections, posing a particularly pertinent public health problem [17].

Additionally, the levels of physicochemical parameters in water sources in Gaza are a public health concern. High nitrate pollution in most drinking water sources indicates that the Gazan population is at an increased risk for a range of severe diseases, such as colorectal cancer, thyroid disease, neural tube defects, and infant methemoglobinemia [18]. Sodium levels in municipal drinking wells of the Gaza Strip are above the permissible limits for consumption [19]. An excess intake of sodium can lead to a range of adverse health effects, including obesity, hypertension and subsequent stroke, coronary heart disease, renal disease, osteoporosis, and others [20-24]. Additionally, low mineral content in drinking water, such as calcium and magnesium, has been found to have various adverse health impacts. Associated health risks include an increased risk of cardiovascular disease [25-30], caries [31,32], osteoporosis [33,34], and various cancers [35-40]. A recent study in the Gaza Strip showed an association between the consumption of desalinated water and osteoporosis [41]; this is highly relevant because of the high consumption of desalinated water in this area [5].

Beyond the physical health effects, the dire water situation in the Gaza Strip can also affect its people's mental health and cognitive functions through different pathways [42]. Insecurity about water quality and availability, as well as potentially high water prices, can trigger stress and affect well-being. Chronic stress is linked to severe and interlinked physical and psychological health problems, including depression and anxiety disorders and associated cardiovascular diseases [43,44]. Additionally, the lack of water can cause fatigue, which impacts mood stability and cognitive function and can increase anxiety or irritability [43]. Dehydration can further contribute to

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difficulties in concentration, reaction time, memory, and reasoning [43,44].

Knowledge Gaps and Objectives

The existing evidence highlights numerous potential public health risks in the Gaza Strip, with persistent knowledge gaps in associated health determinants and outcomes. Water quality is primarily assessed at the source (eg, groundwater wells and desalination plants), neglecting the mixing of water from different sources, water distribution systems, and water tanks widely used for storage. Inadequate distribution and improper storage practices can further contribute to contamination, while possible treatment at the household level before consumption can improve water quality. Evidence of the magnitude of health conditions related to low drinking water quality (eg, diarrhea, diseases related to high nitrate or sodium, and conditions related to low mineral consumption) is incomplete. Additionally, there are no data on the presence of AMR pathogens in Gazan household drinking water. There are insufficient data on practices and knowledge of antibiotics and AMR among the population, which is important to better address the multisectoral challenge of emerging AMR. Addressing these gaps in an integrated manner at the individual and household levels is crucial for targeted AMR interventions and prioritized health initiatives. Quantifying water-related health conditions will allow us to estimate the impact of the water system on public health. This improved understanding of the impact of water quality and availability on health could help in priority setting and identifying potential targeted interventions in the water sector.

Against this background, in 2019, the International Committee of the Red Cross (ICRC) initiated a health impact assessment of selected essential services (electricity, water, wastewater, and food security) in the Gaza Strip to help inform strategic priorities for its interventions. This paper presents the protocol of a household survey conducted as part of the ICRC-mandated health impact assessment in early 2023. The main objectives of the household survey are to determine what contaminants (eg, microbial contamination, nitrate, sodium, and mineral content) persist in drinking water at the household level and to investigate the health conditions (eg, kidney disease, osteoporosis, methemoglobinemia, and mental health issues) associated with water quality at the household level. Ultimately, this will provide a more comprehensive understanding of the interplay between drinking water, health conditions, and mental health in the Gaza Strip. Data collection was completed before the escalation of violence in the Gaza Strip in October 2023. While some of the findings from the survey might not be relevant anymore, the results can provide a baseline for future research. Additionally, the results and conclusions may still be relevant for other areas with similar challenges in humanitarian contexts.

Methods

Project Design

We conducted a cross-sectional household survey in the Gaza Strip from January to March 2023. For the 2023 survey, we revisited a subsample of households from a survey conducted in 2020. This minimized the potential burden on study participants while maximizing synergies with the existing data. Additionally, this study design allowed for more in-depth analyses, including an assessment of changes over time, as we could use selected indicators from the 2020 survey as a baseline for the 2023 survey. The 2020 survey was a representative, cross-sectional, anonymous household survey carried out by Al-Quds University, the American University in Beirut, Imperial College in London, and Juzoor, a Palestinian nongovernmental organization (NGO). It included 4576 people from 2443 households and focused on dietary patterns and noncommunicable diseases (NCDs). The study population was comprised of persons older than 40 years living in all 5 governorates of the Gaza Strip. Using a systematic cluster random sampling method, the 2017 Population and Housing Census served as the sampling frame to select enumeration areas for each governorate [45]. A total of 163 clusters proportionate to the population size of the 5 governorates were selected. In each cluster, 15 households were sampled, and in each household, 1 eligible female and 1 eligible male were interviewed [45]. The 2020 survey is described in more detail in 2 publications from Abu Hamad et al [45] and Basu et al [46].

Ethical Considerations

Ethical approval was granted by the Helsinki Committee of the Palestinian Health Research Council in the Gaza Strip (June 6, 2022; PHRC/HC/1141/22), the Ethikkommission Nordwest- und Zentralschweiz (January 9, 2023; AO_2022-00076), and the ICRC internal Ethics Review Board (January 26, 2023; proposal no 2301_JAN and validation reference LDPCORE 23/00006-CGB/bap). The Ministry of Interior and the Ministry of Health in Gaza also reviewed and approved the survey tools and the full study protocol.

The household survey involved no collection of biological samples and only a minimal time burden on participants. The survey collected data on mental health, which can be sensitive. However, the questionnaire survey merely assessed the participants' mental health status. No traumatic events were discussed, and no in-depth discussion of any mental health problems took place, thereby reducing the potential burden on participants. The participants received no direct benefits but were compensated with a box of dates for contributing to the survey with their time and providing a water sample.

All participants in the household survey were required to sign an informed consent form prior to participation in the study. The informed consent explained the content and purpose of the study, stated clearly that participants were free to withdraw at any time without any consequences, and informed them that the data might be used and shared with other researchers in anonymized form. Participants' names and addresses were used only for recruitment, with access restricted to field coordinators and interviewers. Each participant was assigned an identification number, which was used for data entry, analysis, and coding of water samples. All primary data were anonymized upon entry. The anonymized data will be archived on secure servers at the Swiss Tropical and Public Health Institute for 10 years after the project's completion.

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Study Setting, Population, and Sampling

The study was conducted in the North Gaza, Gaza, and Rafah governorates to represent the diversity of settlements in the Gaza Strip. The Gaza Governorate, with Gaza City as its capital, is the economic and administrative center of the Gaza Strip. It is home to a socioeconomically diverse population and has an extremely high population density of 13,000 inhabitants per square kilometer. In Rafah, the southernmost governorate of the Gaza Strip, a large part of the population lives in poverty, many of them refugees and rural people. Saltwater intrusion into the aquifer is particularly problematic in Rafah, and water quality parameters, such as nitrate levels, are the worst in all areas of the Gaza Strip [47]. North Gaza is frequently affected by violent escalations with Israel. Poverty levels are similar to Rafah, making the area particularly vulnerable to the health effects of poor water quality. Large parts of the land are used for agriculture, and wastewater irrigation projects are being implemented in North Gaza. The main wastewater collection facility is located in the north.

For this survey, we sampled a subset of the previously conducted 2020 survey. We used stratified random sampling to select the study population for the 2023 survey from a complete list of households included in the 2020 survey. In total, we included 905 households proportional to the population in the 3 study areas. Figure 1 shows the distribution of clusters in the Gaza Strip visited in the household survey. For each cluster, we visited between a minimum of 12 and a maximum of 15 households and interviewed between 1 and 3 participants in each household.

Figure 1. Study clusters included in the household survey in the Gaza Strip. In each cluster, up to 15 households were included in the survey.

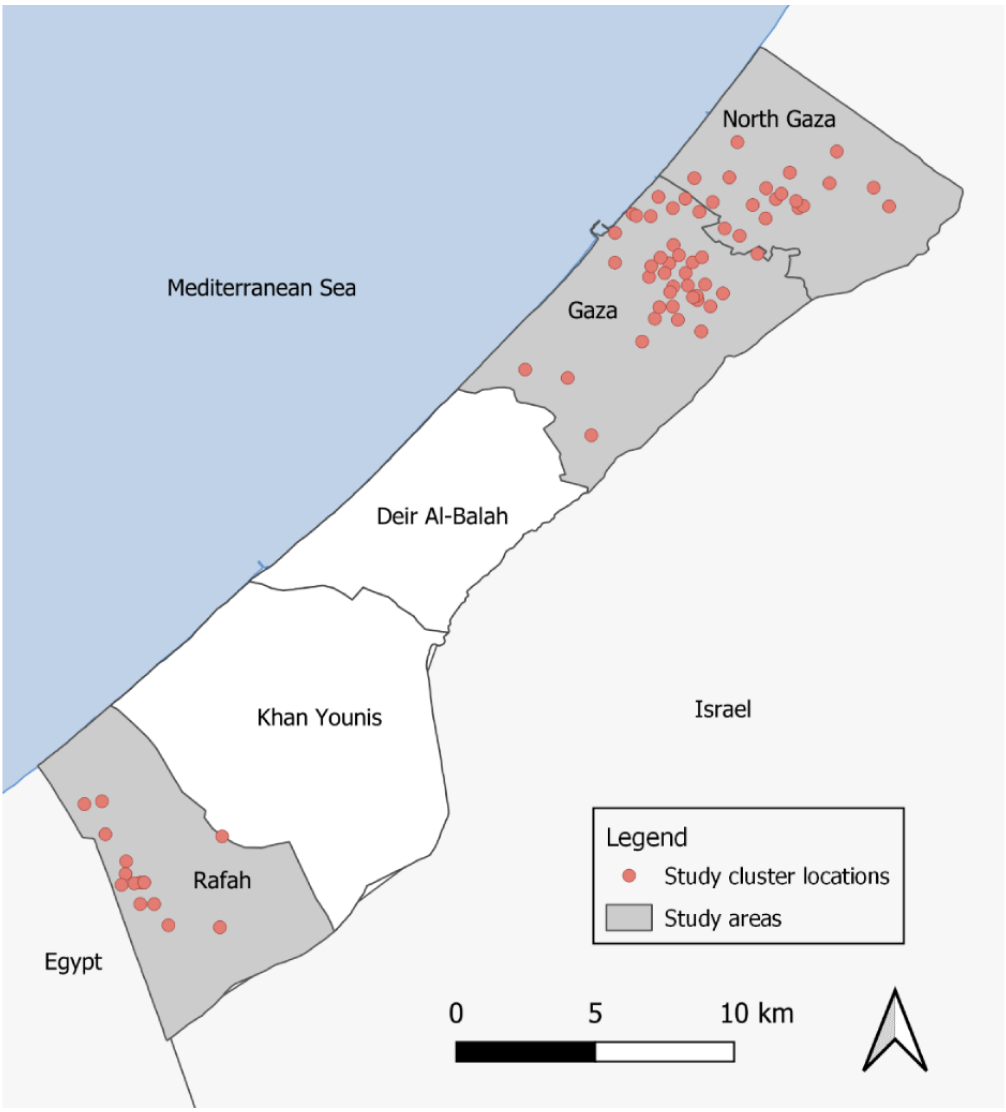

We invited all respondents from the 2020 survey in the selected households to participate in the 2023 study. For a household to be eligible for inclusion in the 2023 survey, at least one of the respondents from the 2020 survey needed to be present. Otherwise, we revisited the household up to 4 times before they were considered lost to follow-up. If the original respondents had moved since the 2020 survey or refused to participate, we replaced the household with another yet unsampled household in the same cluster. If only 1 original participant was present or agreed to participate, we replaced the second respondent with a new participant over the age of 40 years in the same household.

Additionally, we randomly selected 1 respondent between 18 and 30 years from any available household members in that age group present at the time of the survey. If none were available in the initial household, an additional household in the same

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building was randomly selected. To select the additional household, the floor and apartment door were randomly selected. In case there was no available respondent between 18 and 30 years in the additionally selected household, the procedure was repeated. No additional respondents were selected if no respondents between 18 and 30 years of age were available in the whole building.

Before starting the study, all interviewers were trained in the interview process, the correct measurement of blood pressure, and the correct collection of water samples. Additionally, the questionnaire was piloted to ensure participants understood the questions correctly. Two field workers visited each household. All field workers were female and had been part of the 2020 survey team. Having female interviewers visiting the households made participation for female household members easier and more comfortable, as they could remain without a headscarf. The survey was administered face-to-face, with the interviewer capturing data electronically on a tablet.

The sample size calculation was based on the objective of estimating the prevalence of various NCDs. For the questionnaire survey, we assumed a prevalence of 50% as the most conservative assumption. The respondent groups (ie, females and males above 40 years and additional household members between 18 and 30 years) will be analyzed separately. Therefore, the resulting sample size indicates the required number of individuals in each group. The sample size was calculated using the following formula:

where Z is the z-value (1.96, corresponding to a 95% CI), P is the expected prevalence (50%), d is the precision (5%), deff is the design effect (2), and RR is the response rate (0.9), based on nonresponse rate in the baseline survey (96.6%) and the estimated proportion of respondents remaining at the same location since the baseline survey (95%). The resulting sample size was 854 households, which we rounded up to 900, corresponding to 2700 respondents (1800 aged 40 years and older and 900 aged 18 to 30 years), in the best-case scenario.

Survey Modules

The 2023 household survey consisted of three modules: (1) a questionnaire, (2) blood pressure measurements, and (3) a drinking water sample. Figure 2 displays an overview of the 3 modules and the components of each.

Figure 2. The 3 modules of the 2023 household survey and their components: questionnaire (green), drinking water sample (blue), and blood pressure measurements (red).

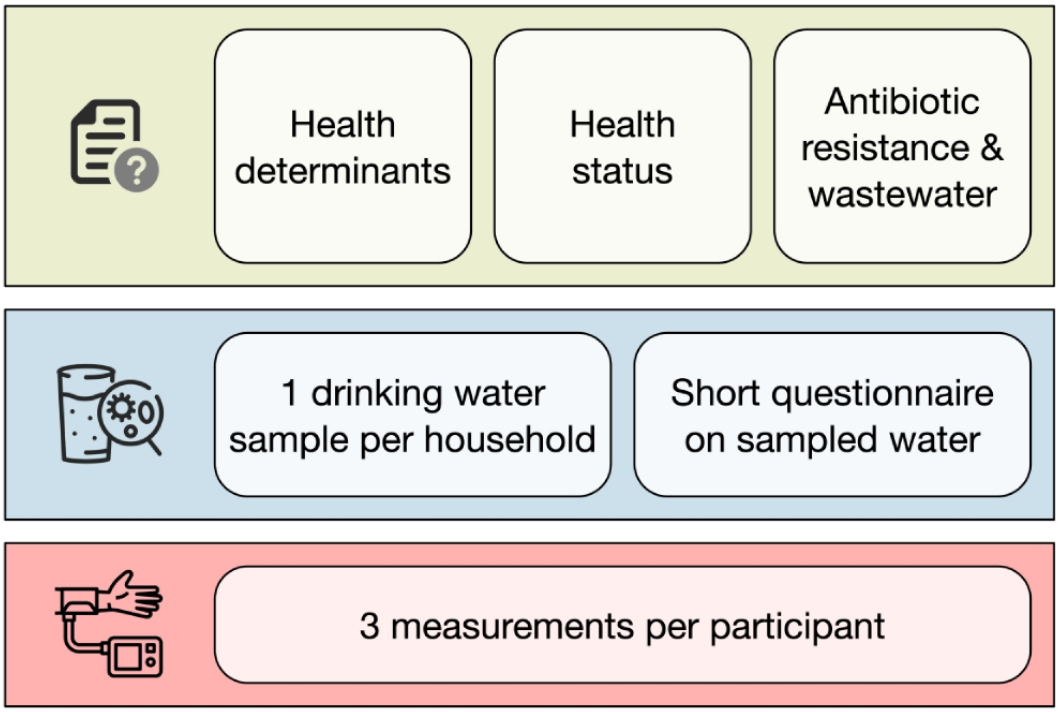

The questionnaire consisted of 3 major components, which are outlined in Textbox 1.

When applicable, we used and sometimes adapted established questionnaires and survey items to build this questionnaire. Table 1 lists the different questionnaires used for the household survey. For most of the questionnaire, not all the questions were applied in our household survey. The column *survey items included in our questionnaire* lists the items from the respective questionnaire that we adopted and included in the survey.

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Textbox 1. Components of the questionnaire.

1. Health determinants: drinking water source, storage, and consumption; recreational activities (eg, swimming in the sea) and perception of the environment; and social network
2. Health status: self-reported mental health and well-being, and self-reported diagnoses/diseases for selected noncommunicable diseases (NCDs) and communicable diseases, including reports of diarrheal symptoms among participants and children under 5 years in the household, as reported by parents
3. Consumption of antibiotics, knowledge about antibiotics and antimicrobial resistance (AMR), attitudes toward wastewater irrigated crops, and perception of the environment on the influence of health

Table 1. Overview of established questionnaires used in the household survey questionnaire.

Questionnaire name	Survey items included in our questionnaire	Source

Multiple Indicator Cluster Surveys (MICS): Water quality testing questionnaire	• Water sources for
	  • Drinking
	  • Cooking
	  • Hygiene and bathing
	• Treatment of water at the household level
		UNICEF[a], MICS6[b] Questionnaire, Water Quality Testing Questionnaire, 2020 [48]

Household Water Insecurity Access Scale (HWIAS)	• Water availability and quantity • Water safety and quality • Emotions related to water access and security	Tsai et al (2016) [49]
The WHO[c] STEPwise approach to noncommunicable disease risk factor surveillance	History of selected NCDs[d]: • Raised blood pressure • Diabetes • Raised total cholesterol • Cardiovascular diseases • Chronic respiratory diseases • Cancer	Household survey 2020: Abu Hamad et al (2022) [45]; Sibai et al (2009) [50]; WHO STEPs [51]
WHO Oral Health Questionnaire for Adults	• Oral health and hygiene • Dental health and hygiene	WHO, Oral Health Surveys - Basic Method (2013) [52]
Questionnaire on Self-Reported Skin Complaints	• Skin complaints and irritations • Skin diseases	Dalgard et al (2003) [53]
General Health Questionnaire 12-Items (GHQ-12)	• Mental disorders • Mental health problems • Mental disturbances • Psychosocial health	Anjara et al (2020), Goldberg et al (1997), Goldberg and Hillier (1979) [54-56]
Health-Related Quality Of Life (WHOQOL-BREF)	• Quality of life and well-being • Individuals' perceptions of their position in life	WHO Program on Mental Health-WHOQOL User Manual, 1998 [57]
Antibiotic Resistance: Multicountry Public Awareness Survey	• Antibiotics use and knowledge • Antimicrobial resistance knowledge	WHO, Antibiotic resistance: multicountry public awareness survey (2015) [58]
Attitudes Toward Wastewater Reuse	• Attitude toward wastewater reuse and wastewater irrigated crops • Perception of water and environment	Friedler et al (2006) [59]

[a]UNICEF: United Nations Children's Fund.

[b]MICS6: Multiple Indicator Cluster Survey, 6th round.

[c]WHO: World Health Organization.

[d]NCD: noncommunicable disease.

Following the interview, we measured each participant's blood pressure using oscillatory blood pressure monitoring devices. For each participant, we took 3 measurements with a break of at least 3 minutes between each measurement. We asked participants to follow a standardized protocol to ensure standardized blood pressure measurements. Participants had to refrain from eating or drinking for at least 30 minutes and ensure their bladder was empty before the measurement. Prior to the

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measurement, participants had to sit comfortably in a supported position for a minimum of 5 minutes. During the measurement, they had to keep both feet flat on the ground, with their legs uncrossed. The arm with the cuff was rested at chest height on a table and the cuff was put on bare skin. Finally, there was no talking during the measurement to minimize potential disturbances. The field workers advised participants with high blood pressure (systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg) to visit a doctor for further assessment.

Additionally, we collected a drinking water sample in all households for subsequent analyses. The samples were tested for 9 common water quality parameters (Table 2) by the Coastal Municipalities Water Utility laboratory in Gaza City. We took the sample from the source the respondents usually use for drinking. The field workers collected approximately 100 ml using sterile containers and stored the samples in a cool box between 4 and 6 °C. Within 6 hours, the samples were transported to the laboratory and analyzed within 30 hours of collection. We collected an additional sample from 10% (90/902) of the households and analyzed the sample at a different laboratory for quality control. In each household, we administered a brief questionnaire to collect data regarding the water source and any filtration or purification methods used in the household. The questions were based on the water quality testing questionnaire from the Multiple Indicator Cluster Survey, 6th round (MICS6) [48].

Table 2. Overview of measured water quality parameters.

Water quality parameter	Abbreviation	Unit
Total coliform	TC	CFU/100 ml
Fecal coliform	FC	CFU/100 ml
Nitrate	NO_3-N	mg/L
Sodium	Na^+	mg/L
Calcium	Ca^{2+}	mg/L
Magnesium	Mg^{2+}	mg/L
pH	pH	N/A[a]
Electrical conductivity	EC	µS/cm
Total dissolved solids	TDS	mg/L

[a]N/A: not applicable.

Among households whose water tested positive for fecal coliform in the first round of sampling, we selected 90 for a second round of water sampling. The selection was based on high fecal coliform counts, geographic distribution, and drinking water sources. We took the second sample 4 weeks after the first sample and analyzed it for AMR bacteria. Of these 90 households, we selected 10 (11%) for additional water chain testing. Starting from the point where household members accessed their drinking water, we followed the water chain and took a sample at each potential contamination site. Examples of sample locations are the kitchen faucet, the rooftop storage tank, the pipe from a water tanker truck, and the refill pipe at a desalination plant. The number and location of water samples taken varied for the water chain testing depending on the drinking water source used in the households.

Data Analysis

Data analysis will be performed with R and RStudio software (R Foundation for Statistical Computing) [60,61]. We will include questionnaires with missing data as long as 75% of the questionnaire has been filled out. When using data from the 2020 and 2023 surveys, we will only include participants who took part in both surveys. As the first step, we plan to focus mainly on descriptive analyses to give an overview of the data gathered. We will treat water quality variables as continuous variables and compare them to national and international water quality guidelines. If needed, we will apply log transformations to meet normality distribution requirements. Further, we will compare the results of the water analysis across different water sources and investigate potential reasons for observed differences between water sources. In the second analysis step, we will compare water quality and water-related health conditions. This will include integrating data from the 2020 survey to investigate changes in health status over time. We will analyze health determinants (other than water quality) and health outcomes as either dichotomous (eg, presence of diabetes) or categorical (eg, type of water treatment) using Pearson chi-square tests to compare groups. We will use linear or logistic regression models to explore associations between health determinants and outcomes, depending on whether the outcome variable is continuous or dichotomous. We will specifically assess associations such as microbial pollution with diarrheal disease, nitrate levels with cancer and kidney disease, and low mineral levels with osteoporosis. Since our analyses are hypothesis-driven, we will not apply adjustments for multiple testing. Additionally, we intend to delve into the mental health burden among residents in both the 2020 and 2023 surveys, aiming to investigate temporal trends or disparities. We will explore the determinants of mental health within the Gaza Strip, considering various socioeconomic, environmental, and psychosocial factors that could influence mental well-being by including data from the 2020 and 2023 survey and external data sources such as data from ACLED (Armed Conflict Location and Event Data) [62]. As part of the health impact assessment,

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we collected additional data on AMR in different sectors of the Gaza Strip. We will combine these findings with the AMR data from household drinking water and survey responses on antibiotic use and AMR awareness to provide a clearer overview of the scale of the AMR issue in the Gaza Strip. Taken together, these analyses will provide a comprehensive understanding of the complex interplay between water quality, health outcomes, and mental well-being in the Gaza Strip.

Results

The household survey was initiated on January 24, 2023, and the final interviews were administered on March 7, 2023. We visited a total of 905 households, interviewed 2291 participants, and collected water samples in 99.7% (902/905) of the households (Figure 3). Data analysis was still ongoing at the time of submission. We plan to conclude the data analysis in early 2025 and expect to publish the results in several peer-reviewed papers in the course of 2025.

Figure 3. Study area and population in the 2020 and 2023 survey.

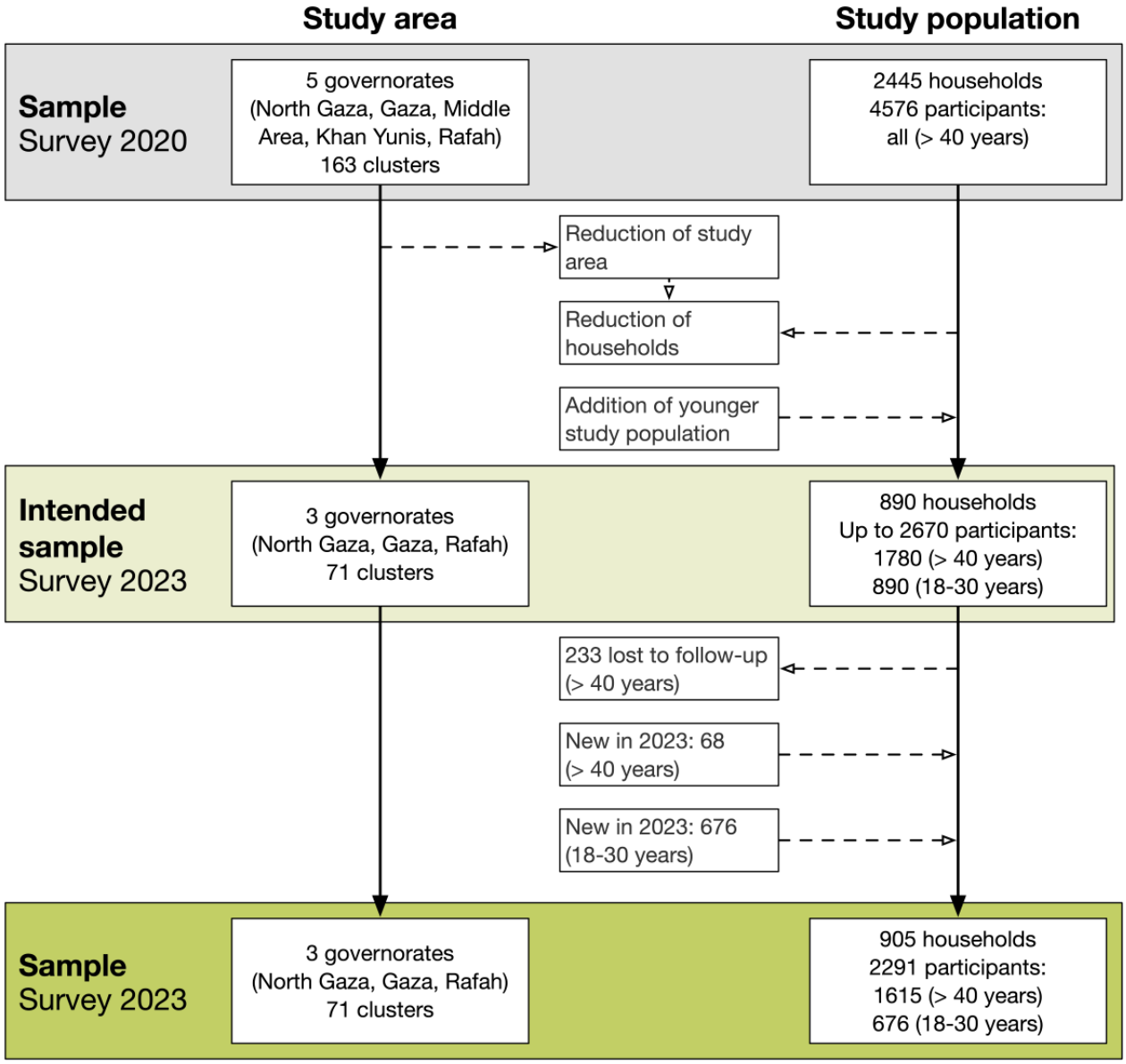

Table 3 shows an overview of the participants' characteristics from the 2023 household survey compared with those from the 2020 survey. In 2023, 70.50% (1615/2291) of the participants were aged 40 years and older, and 29.51% (676/2291) were between 18 and 30 years old. Moreover, 95.79% (1547/1615) of the participants aged 40 years and older in 2023 were already part of the 2020 survey. The follow-up rate in 2023 was 77.01% (1615/2097) compared to the 2020 sample in the same study area. In both age groups in 2023, more female participants were interviewed, with 914 out of 1615 (56.6%) in the first group and 398 out of 676 (58.9%) in the second group. This is similar to the participants of the 2020 survey, where 53.13% (1071/2016) were female. A more detailed overview of participant characteristics by governorate is available in Table S1 in Multimedia Appendix 1.

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Table 3. Description of participants in the 2023 household survey and comparison with participants in the 2020 survey.

Characteristic	Study year	
	2023	2020
Number of households	905	1065
Number of participants	2291	2016
≥40 years age group		
Number of participants	1615	2016
Same as 2020, n (%)	1547 (95.79)	—[a]
Female, n (%)	914 (56.60)	1071 (53.13)
Age, mean (years), min-max	59 (40-89)	57 (40-118)
Refugee, n (%)	1044 (64.64)	1332 (66.07)
18-30 years age group		
Number of participants	676	—
Female, n (%)	398 (58.9)	—
Age, mean (years), min-max	23 (18-30)	—
Refugee, n (%)	419 (62)	—

[a]Not applicable.

Discussion

Expected Findings

This paper describes the design and methodology of a household survey conducted in the Gaza Strip between February and March 2023. We conducted a survey in 905 households with 2291 participants and collected 902 drinking water samples in the Gaza Strip, achieving a follow-up rate of 77.01% (1615/2097) with the participants from the 2020 survey.

Using the results from the water samples, complemented with recent data on groundwater quality, we aim to provide a comprehensive overview of the water quality in the Gaza Strip in early 2023 and identify potential risks for public health. Previous studies and measurements suggest high levels of chemical and some microbial contamination in groundwater wells and the drinking water system [3,6,7]. We expect to find similar results in our measurements at the household level, but in contrast to previous studies, we can directly link water quality to health at the individual level. The widespread use of desalinated water may result in low levels of essential minerals such as magnesium and calcium, which may have implications for public health. However, this issue has only been investigated in a few studies on the Gaza Strip. Compared to the 2020 survey, we expect only an increase in the prevalence of NCDs that corresponds to the 3-year increase in the study population's age. Having data on the mental health status of our study populations from 2020 and 2023 will allow us to study the mental health change over this time. Findings from previous studies report a high level of mental health burden in the population, and we assume our results to be similar for mental health [63,64]. Taken together, the upcoming results of our project will provide a thorough understanding of the relationships between water quality, health, and mental well-being in the Gaza Strip, as they were before the current escalation of violence.

Strengths and Limitations

One strength of our study lies in integrating data from a previous survey on the participants' health status. This approach allows us to observe trends over time and gain a more detailed understanding of the health burden within the Gaza Strip. This will help us identify a broad set of potential impacts on health and well-being and track changes over time. An additional strength is our sampling of water at the household level, which allows us to test the water that the participants consumed rather than sampling further up the water chain, after which contamination could occur before consumption.

Our study also has several limitations. The main limitation is the cross-sectional design of the survey. While we have data from 2020 and 2023, we only have data from one survey for several important questions. Most of the health outcomes included in the survey are NCDs, which develop over the course of a person's life. We lack data on long-term water quality from several years back, as well as data on health outcomes prior to 2020. This temporal alignment means that we cannot establish causation between water quality and health outcomes based on the current dataset. All health information collected in the survey is self-reported and not from medical diagnoses. To limit wrong answers, we used validated questionnaires that have been used in many contexts to screen for NCDs and other health statuses.

The survey was completed in March 2023 before the escalation of violence in October 2023. Many houses and much of the infrastructure have been destroyed, negatively impacting the physical and psychological health of the residents of the Gaza Strip. While the situation in the Gaza Strip has completely changed and some of the findings may not be relevant anymore, our study could serve as a valuable baseline for future research evaluating the impacts of the escalations. Furthermore, the findings from this survey may still be relevant for other areas

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with similar challenges linked to drinking water in humanitarian contexts.

Conclusions

The data collected in this survey will provide valuable insights into drinking water quality at the household level and its potential impact on the health and well-being of people in the Gaza Strip as the situation stood in early 2023. The results emerging from this study may serve as a baseline for future research that seeks to assess the impact of the current escalations on water quality and physical and mental health. Additionally, the results from this study can provide information regarding the water system from a public health perspective, which could be useful in rebuilding the Gaza Strip. Collaborative efforts involving government agencies, NGOs, and international partners will be essential in addressing the complex challenges facing water, sanitation, and public health in this process.

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Data Availability

The data collected and generated during data collection and analysis of this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

MSW, DD, CB, BAAH, TVG, and FS contributed to the conceptualization of the study. CB, MSW, BAAH, TVG, RR, and DD contributed to the implementation of the investigations and project administration. CB, DD, BAAH, and BNO contributed to data curation and writing (original draft and visualization). MSW, BAAH, and NP contributed to supervision, while TVG, FS, and RR contributed to the funding acquisition. CB, DD, MSW, BAH, TVG, FS, RR, BNO, and NP all reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant characteristics in the 2020 and 2023 surveys by governorate.
[DOCX File , 37 KB - resprot_v13i1e63415_app1.docx]

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Abbreviations

ACLED: Armed Conflict Location and Event Data
AMR: antimicrobial resistance
ICRC: International Committee of the Red Cross
MICS6: Multiple Indicator Cluster Survey, 6th round
NCD: noncommunicable disease
NGO: nongovernmental organization
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Ultrasound-Guided High-Intensity Focused Ultrasound Combined With PD-1 Blockade in Patients With Liver Metastases From Lung Cancer: Protocol for a Single-Arm Phase 2 Trial

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Abstract

Background: While immunotherapy has revolutionized oncological management, its efficacy in lung cancer patients with liver metastases remains limited, potentially due to the unique immunosuppressive microenvironment of the liver. Local liver treatment has been shown to enhance the immunotherapy response, and high-intensity focused ultrasound (HIFU), a minimally invasive local treatment, has demonstrated promising results in combination with immunotherapy. However, clinical data regarding HIFU in lung cancer with liver metastases are limited.

Objective: We designed the HILL (Ultrasound-Guided High-Intensity Focused Ultrasound Combined With PD-1 Blockade in Patients With Liver Metastases From Lung Cancer) study to investigate the effectiveness and safety of HIFU in combination with immunotherapy for lung cancer with liver metastases.

Methods: The HILL study is a single-armed, single-center, phase 2 clinical trial that will enroll 30 patients with lung cancer and liver metastases. The treatment regimen involves administering HIFU to liver metastases 1 week before the first dose of a programmed cell death protein (PD)–1 blockade, which is then administered every 3 weeks. The primary aim is to determine the overall response rate based on immune-related response criteria. Secondary aims include safety, progression-free survival, overall response, overall survival, and quality of life. Exploratory studies will also be conducted using whole blood, plasma, archival cancer tissue, and tumor biopsies during progression or relapse to identify potential biomarkers.

Results: The study was funded on March 14, 2022, and received ethical approval on April 27, 2022. Clinical trial registration was completed by June 10, 2022, with participant recruitment beginning on July 10, 2022. Data collection commenced on July 14, 2022, with the enrollment of the first patient. By April 2024, 6 participants had been recruited. The results are expected to be published in December 2026.

Conclusions: This study seeks to improve treatment outcomes for lung cancer patients with liver metastases by combining HIFU and PD-1 inhibition. The study also aims to identify potential biomarkers through exploratory research that can aid in selecting patients for optimized outcomes in the future.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2200061076; https://www.chictr.org.cn/showproj.html?proj=170967

International Registered Report Identifier (IRRID): DERR1-10.2196/59152

(JMIR Res Protoc 2024;13:e59152) doi:10.2196/59152

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KEYWORDS

high-intensity focused ultrasound; programmed cell death protein; PD-1 blockade; liver metastases; lung cancer; immunotherapy; treatment efficacy; quality of life; HILL study

Introduction

Lung cancer is the second most frequently diagnosed tumor and the largest cause of cancer-related fatalities globally, accounting for roughly 1 in 10 (11.4%, 2.2 million) new cancer cases and 1 in 5 (18%, 1.8 million) deaths annually [1,2]. Immunotherapy, a landmark breakthrough in cancer treatment, has revolutionized the field of oncology, contributing to a recent accelerated decline in lung cancer mortality [3,4]. Encouraging clinical trial results with immune checkpoint blockade (ICB) have demonstrated the efficacy of this approach in lung cancer, leading the US Food and Drug Administration to approve programmed cell death protein (PD)–1 inhibitors for all stage III to stage IV lung cancers [3].

Nevertheless, a substantial proportion of patients fail to benefit from immunotherapy, particularly those with lung cancer liver metastases [5]. The existence of baseline liver metastases in patients with lung cancer has been connected with a reduced response to immunotherapy. In the Checkmate 017 and Checkmate 057 trials, the 3-year overall survival (OS) rate for subgroups of patients with lung cancer liver metastases treated with pembrolizumab was 8%, as compared to a 3-year OS of 17% across all enrolled patients [6]. Similarly, in the Keynote 001 trial among patients with non–small cell lung cancer (NSCLC), liver metastasis was linked with a decreased treatment response and shorter progression free survival (PFS) in comparison to patients without liver metastasis [7]. In patients with NSCLC with similar PD-L1 expression, tumor burden, and mutational burden, the presence of liver metastases was linked with reduced OS regardless of age, sex, or treatment modality. [8,9]. Liver metastases are independently associated with a poorer response to immunotherapy, primarily due to the liver's unique immunosuppressive microenvironment [10]. The liver processes a vast array of harmless dietary antigens daily, necessitating a state of immune tolerance [11]. Metastatic lesions in the liver further enhance this immunosuppressive milieu. Liver metastases highly express integrin receptors, including cluster of differentiation [CD] 44 and lymphocyte function–associated antigen-1, which promotes the sequestration of activated peripheral T cells into the liver, thereby reducing T cell distribution abnormalities [12]. Additionally, liver-infiltrating myeloid cells in metastatic lesions induce T cell apoptosis via the Fas-FasL pathway, resulting in T cell depletion [13]. This extensive antigen-specific T cell exhaustion drives immunosuppression in preclinical models and cancer patients with liver metastases, leading to the enlargement of metastatic lesions and a poor response to immunotherapy [14].

Local treatment of liver metastases may be practical to counter this tumor-permissive immune microenvironment. Radiation therapy (RT) that targets the liver can both inhibit immune-suppressing myeloid cells and boost T cell immunity [13,15]. A preclinical study showed that mice treated with a combination of RT and immunotherapy demonstrated remission of both liver and subcutaneous tumors and considerably increased survival [13]. In another report, a White patient aged 64 years with chemotherapy-resistant metastatic lung adenocarcinoma who received local RT to one of the liver metastases combined with immunotherapy generated a therapeutically effective antitumor immune response [16]. Therefore, we propose that localized therapies targeting hepatic metastases, such as RT, may enhance the efficacy of ICB in patients with liver metastases.

Based on an understanding of tumor–immune system interactions, oncologists categorize tumors as "hot" (high immune cell infiltration, high immune scoring) or "cold" (low infiltration, low immune scoring) based on the type, density, and location of immune cell infiltration. This classification has been validated in patients with tumor, demonstrating its predictive value for tumor recurrence and survival outcomes [17]. In "cold" tumors, the efficacy of ICB is markedly poor, often resulting in no response or excessive adverse reactions [18]. High-intensity focused ultrasound (HIFU) can create a favorable temporal window for immunotherapy to turn previously immunologically "cold" tumors into immune-reactive "hot" tumors. HIFU uses specialized ultrasonic focusing equipment to generate focused ultrasound beams that penetrate the skin and tissue to form focal points deep within the body. At these focal points, the ultrasound intensity is extremely high, generating heat that can rapidly elevate the temperature of exposed tissues above 60°C. When this exposure lasts longer than 1 second, most cells within the tissue undergo immediate irreversible death, minimizing potential damage to surrounding nontarget tissues [19]. The thermal ablation effect of HIFU induces coagulative necrosis in tumor tissues by moving the focal point, thereby rapidly reducing tumor burden and locally releasing tumor antigens. Unlike RT, HIFU can be safely reapplied without increasing systemic toxicity risks, allowing clinicians to administer multiple local treatments even in the event of local tumor recurrence.

As a method for real-time imaging and noninvasive local thermal ablation, HIFU is being developed as an alternative to conventional oncologic therapy for a variety of solid malignant tumors, such as liver, kidney, and bone tumors [20-22]. In a rat tumor model of refractory neuroblastoma, HIFU in combination with immunotherapy significantly improved the antitumor response, increasing the survival rate from 0% to 62.5% [23]. The combination's proposed mechanism of action is shown in Figure 1. In a syngeneic mouse model of epithelial breast cancer, Silvestrini et al [24] also found that immunotherapy combined with HIFU treatment could significantly reduce the number of macrophages and bone- and marrow-derived suppressor cells in tumor tissues, and it could promote the polarization of monocytes to the M1 type. In addition, it significantly upregulated PD-L1 in CD45+ cells and CD8+ T cells generated by IFN-γ, thereby enhancing antitumor immunity.

However, data on the combination of HIFU and immunotherapy in patients with lung cancer with liver metastases is limited.

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The HILL (Ultrasound-Guided High-Intensity Focused Ultrasound Combined With PD-1 Blockade in Patients With Liver Metastases From Lung Cancer) study intends to investigate the therapeutic efficacy and safety of PD-1 blockade in conjunction with HIFU.

Figure 1. Hypothesis diagram of the research mechanism of HIFU enhancing immunity. HIFU, high-intensive focus ultrasound; TAAs, Tumor Associated Antigens; DAMPs, damage associated molecular patterns; APC, Antigen Presenting Cells.

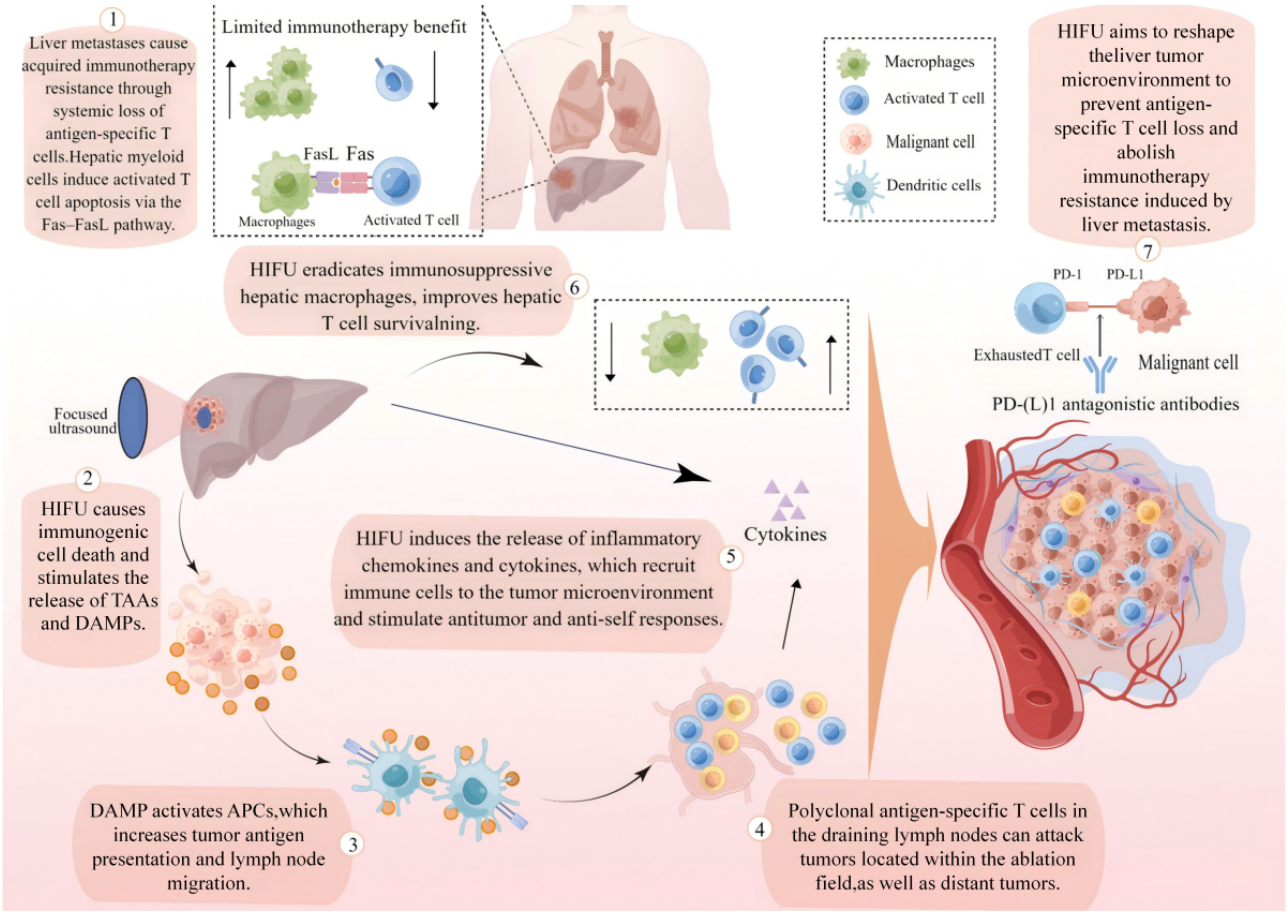

Methods

Ethical Considerations

The trial has received ethics approval from Xiangtan Central Hospital Ethics Committee (2022-04-001). All participants provide full informed consent to participate in HILL. The data of the enrolled participants were kept strictly confidential and were anonymized for deidentification. The participants are exempted from any fees for ultrasonic monitoring. The trial is conducted in conformity with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Design

The HILL study is a single-center, single-arm, phase 2 trial conducted with lung cancer patients with liver metastases (Chinese Clinical Trial Registry ChiCTR2200061076). Recruitment for the research began on July 10, 2022, and it is expected to be completed in June 2025.

Eligibility Criteria

The inclusion criteria are as follows: (1) age 18-75 years; (2) histologically or cytologically confirmed NSCLC; (3) liver metastases confirmed by abdominal imaging, such as computerized tomography (CT) or magnetic resonance imaging (MRI); (4) negative for epidermal growth factor receptor and anaplastic lymphoma kinase, as assessed by polymerase chain reaction or next-generation sequencing; (5) Eastern Cooperative Oncology Group performance status 0-2; (6) at least 2 measurable lesions according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1) guidelines ; (7) asymptomatic (identified as being without significant symptoms at baseline, judged by the investigator as not requiring steroids and/or local treatment) or symptomatically stable brain metastases (without significant symptoms after local treatment, such as RT, and at least 7 days free from steroids and/or anticonvulsant therapy at the time of enrollment); (8) requirement for immunotherapy; (9) liver metastases (confirmed by imaging and multidisciplinary tumor board consultation) that can be treated with HIFU; (10) agreement to use effective contraception during the beginning of the trial and 90 days after the dose; (11) written informed consent.

Exclusion criteria for patients are as follows: (1) mixed lung cancer, including neuroendocrine tumors or sarcoma; (2) history of other malignancies within 5 years; (3) effusions of the third space that cannot be drained or otherwise treated; 4) severe interstitial pneumonia or severe diffusion dysfunction; (4) liver function with Child-Pugh grade C; (5) history of immunodeficiency disease necessitating long-term treatment

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with glucocorticoids; (6) history of acute cardiovascular or cerebrovascular disorders, including acute cerebral infarction and acute coronary syndrome, within the last month; (7) pregnant or lactating women; (8) life expectancy 3 months or less.

Intervention

Eligible patients will receive HIFU on liver metastases and PD-1 blockade therapy. Given the potential immunomodulation effect of HIFU, ablation of metastatic liver lesions was planned to take place within no more than 7 days of immunotherapy. The PD-1 blockade was injected repeatedly every 3 weeks for 6 cycles. The combination of immunotherapy and ablation was administered once in week 1. The study schema provides a comprehensive summary (Figure 2). Patients who are considered to have obtained clinical benefits, including a complete response (CR), partial response (PR), or having achieved stable disease (SD), will be allowed to continue PD-1–blocking medicines (every 3 weeks) for up to 2 years beyond the end of the trial. Patients with progressive disease will exit the trial or undergo re-ablation with HIFU according to their choice. Re-ablation will be performed in liver metastases without changing the immunotherapy regimen, and the efficacy will be evaluated 3 weeks later. If the treatment outcome is progressive disease, the patient will be withdrawn from the study. If the outcome is SD, PR, or CR, the patient will be treated and followed up. The standard PD-1 blockade treatment plan for advanced lung cancer with liver metastases will be used, as determined by the investigators and based on clinical guidelines.

Whole blood, plasma, archived cancer tissue, and tumor biopsies will be taken for exploratory research. Given the stability and availability of the test, peripheral blood will be obtained for lymphocyte subsets and the levels of 12 cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-10, IL-17, interferon [IFN]-α, IL-1β, IL-2, IL-5, IL-8, IL-12P70, IFN-γ, IL-4) will be measured before and after HIFU treatment. Tumor biopsy tissue will be embedded in paraffin and analyzed for immune cell infiltration and PD-L1 expression. This information will help us determine whether the medication modifies the diversity of immune response and whether these changes are reflected in the blood. This could aid in the selection of predictive biomarkers for patients in future trials by connecting immunological alterations to clinical symptoms.

Figure 2. Details of the scheduling for all planned blood sampling and tumor imaging operations during the trial to document the treatment's safety and efficacy. Palliative radiation therapy for liver metastases and other immunotherapy treatments will not be performed. CT: computerized tomography; DCR: disease control rate; HIFU: high-intensity focused ultrasound; ORR: overall response rate; PD: programmed cell death protein; PFS: progression free survival.

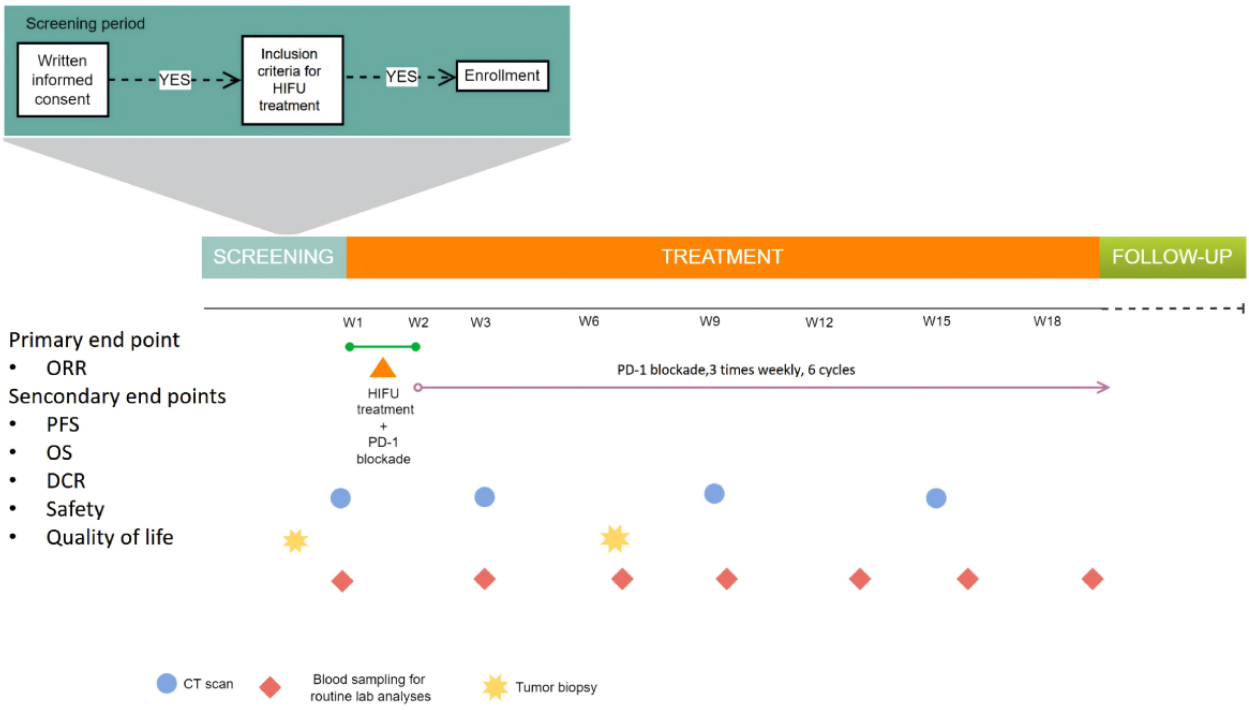

Focused Ultrasound Ablation

Patients were chosen according to the following HIFU treatment inclusion criteria: (1) suitability for anesthesia and sedation, (2) visibility in diagnostic sonography, (3) accessibility (maximum of 11 cm between the skin and the deepest tumor sections), (4) absence of extensive scarring or extensive calcifications along the acoustic route, and (5) absence of metal clips following surgery. Ultrasound-guided HIFU will be performed with a HIFU system (the Focused Ultrasound Tumor Therapeutic System [model-JC200]; Chongqing Haifu Medical Technology Co Ltd), with the patient in a lateral position. Operational details were chosen with reference to previous studies [25,26]. Prior to HIFU treatment, ultrasound localization is required to assess the safety of the patient's acoustic channel and the accessibility of the treatment target area to determine the treatment regimen. Gastrointestinal preparation is required the day before HIFU treatment, similar to the preparation before colonoscopy. To

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minimize skin damage caused by HIFU, the treatment area should be shaved and moisturized on the day of surgery. The patient is given general anesthesia by a qualified anesthesiologist. During treatment, ultrasound can be used to detect the distance between the treated lesion and the edge of the lesion and the surrounding vulnerable structures (eg, the intestinal and biliary stents) in real time to prevent complications caused by heat. The power of HIFU ablation will be adjusted in real time according to the treatment.

If a patient has multiple liver metastases, HIFU ablation should not be performed on more than 3 lesions at once to ensure patient safety and tolerance. If there are more than 3 liver metastases, it is possible to ablate the largest 3 first, monitor the remaining lesions, and ablate them again if necessary.

End Points

Overall response rate (ORR) is the primary end point. The secondary end points are PFS, OS, disease control rate, safety, and patient-reported outcomes, including the results of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 and Quality of Life Questionnaire–Lung Cancer Module 13. MRI or CT examinations will be administered at the start point, week 3, and each 6 weeks following. According to the RECIST1.1 and the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), tumor response and adverse events will be evaluated and recorded during therapy and within 28 days after the last dose, respectively. Telephone checks will be conducted every 3 months until the end of the trial, death, or loss to follow-up.

After illness progression or withdrawal from the trial's treatment, the use of anticancer medication will be recorded. ORR is the proportion of enrolled patients with a CR or PR based on imaging. PFS is the length of time between enrollment and the occurrence of disease progression. OS is the duration between enrollment and death.

Monitoring

The effectiveness and safety of the treatment will be evaluated by an independent reviewer annually. The monitoring committee will monitor the trial's safety, adherence to protocol, and progress and will modify the protocol as necessary and determine the need for early termination of treatment.

Statistical Analysis

The 2-stage minimax design of Simon was chosen for sample size estimation. With an ORR of 17% or less, HIFU with PD-1 blocking as a combination therapy will be deemed useless or uninteresting; With an ORR of at least 37%, this regimen will warrant further investigation. At a significance level of .05, an analysis with 80% power will require a sample size of at least 30 patients, with 14 during the initial phase and 16 in the next. At the end of the first stage, if 2 or more patients have responded, the second stage can be carried out. If this does not happen, the study has to end. At the end of the study, if at least 8 of 30 patients respond, it will be taken to indicate that the combination therapy is beneficial and worthy of further investigation.

In accordance with the concept of "intention to treat," all individuals who are given a minimum of 1 injection of the trial medication and undergo effectiveness assessment will be included in efficacy analyses. All patients who are injected with a minimum of 1 dose of the research medication and have a minimum of 1 safety report will be included in the safety analysis. Once we have recorded baseline features, tumor responses, patient-reported outcomes, and adverse events, we will produce descriptive statistics, including Kaplan-Meier survival curves. There will be no data imputation for missing data.

Results

The study was funded on March 14, 2022, and received ethical approval on April 27, 2022. Clinical trial registration was completed by June 10, 2022, with participant recruitment beginning on July 10, 2022. Data collection commenced on July 14, 2022, with the enrollment of the first patient. By April 2024, 6 participants had been recruited. The results are expected to be published in December 2026.

Discussion

The HILL study is a phase 2 single-arm trial investigating the efficacy and safety of combining HIFU with PD-1 blockade immunotherapy in patients with lung cancer and liver metastases. Although ICB has yielded promising response rates in lung cancer, its impact on liver metastases remains constrained by the unique immune microenvironment of the liver. This challenge has spurred the search for more effective therapeutic strategies [27]. Local treatments such as RT can modify the liver's tumor microenvironment, potentially enhancing the effects of ICB-based therapies. As a minimally invasive, repeatable approach, HIFU has seen extensive use in the treatment of solid tumors. We hypothesize that the combination of HIFU with PD-1 inhibition may enhance the clinical response in patients with lung cancer liver metastases. Indeed, HIFU has demonstrated the ability to modulate the tumor microenvironment and stimulate antitumor immunity in both preclinical and clinical settings [28-30].

Preclinical studies across various tumor types demonstrate that HIFU, when combined with immunotherapy, increases the expression of IFN-γ and granzyme B in the distant tumor microenvironment, enhances CD8+ T cell activation, augments tumor cell lysis, and extends survival [24,31-33]. These findings suggest that HIFU may potentiate the effects of immunotherapy. A study by Yang et al [34] involving 14 patients with liver metastases from malignancies treated with HIFU and immunotherapy found that this combination was feasible and safe, achieving an ORR of 21.4%. However, only 3 participants had lung cancer, limiting conclusions about the combination's effectiveness specifically for lung cancer liver metastases.

Peripheral blood samples are frequently used in clinical trials for biomarker identification due to the challenge of obtaining tissue specimens. To ensure reliability and accessibility in clinical settings, we selected 12 cytokines and lymphocyte subpopulations as biomarkers. These markers are part of routine

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clinical testing and ensure consistency in results. Clinically relevant findings from these analyses could be quickly implemented. Lymphocyte subpopulations—including T cells, B cells, and natural killer cells—are measured to reflect immune changes, as peripheral blood lymphocytes correlate with immunotherapy efficacy and may reflect synergistic effects of combined treatments [35,36]. Cytokines play a critical role in cancer-immune interactions, influencing multiple aspects of metastasis [37]. The 12 cytokines studied are linked to T cells and macrophages—key immune cells within the tumor microenvironment—and provide an indirect assessment of antitumor treatment efficacy. Therefore, investigating changes in these cytokines during therapy may yield clinically valuable biomarkers.

This study uses HIFU, a local treatment widely used for liver cancer that causes minimal tissue damage and uses external ultrasonic focusing and real-time monitoring, ensuring a high degree of safety and allowing for repeated applications. HIFU's influence on the tumor microenvironment can activate antitumor immunity, potentially enhancing the benefits of immunotherapy for patients with lung cancer liver metastases. The trial aims to assess the safety and efficacy of this combination therapy, offering a potential new treatment approach. Additionally, biomarker analysis will seek to identify markers that could improve future therapeutic outcomes. However, the study has limitations. The small sample size may affect the generalizability of the results. The single-arm design could introduce bias, and while HIFU and PD-1 blockade have shown promise individually, their combined efficacy and safety remain to be fully determined.

In summary, this study targets an unmet clinical need for patients with lung cancer liver metastases, taking into account their distinct pathophysiology and the limited benefits of immunotherapy in this population. By investigating the effects of HIFU combined with immunotherapy on the liver tumor microenvironment, this trial seeks to provide novel therapeutic options for these patients

Acknowledgments

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors were involved in the preparation of this manuscript. CH, JZ, MYJ, and WZC designed the protocol. MYJ is the principal investigator of the study. CH, XH, FFG, HL, LY, and LP prepared the manuscript and CH prepared Figures 1 and 2. JZ, QF, WX, MYJ, and WZC revised the manuscript. CH, JZ, MYJ, and WZC are responsible for interpretation of the data. XH, FFG, LP, HL, LY, and MYJ are responsible for patient recruitment. JZ, QF, and WX are responsible for the HIFU treatments. CH, LP, and QF are coordinating the collection of biological samples. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CD: cluster of differentiation
CR: complete response
CT: computerized tomography
HIFU: high-intensity focused ultrasound
HILL: Ultrasound-Guided High-Intensity Focused Ultrasound Combined With PD-1 Blockade in Patients With Liver Metastases From Lung Cancer
ICB: immune checkpoint blockade
IFN: interferon
IL: interleukin
MRI: magnetic resonance imaging
NSCLC: non–small cell lung cancer
ORR: overall response rate
OS: overall survival
PD: programmed cell death protein
PFS: progression free survival
PR: partial response
RECIST1.1: Response Evaluation Criteria in Solid Tumors 1. 1
RT: radiation therapy
TNF: tumor necrosis factor

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Protocol

Consistent and Correct Use of Condoms With Lubricants and Associated Factors Among Men Who Have Sex With Men from the Ghana Men's Study II: Protocol for a Mixed Methods Study

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Abstract

Background: Men who have sex with men (MSM) experience a disproportionate burden of HIV infection globally, including in Ghana. The use of condoms with lubricants correctly and consistently plays a vital role in reducing the number of new HIV infections among MSM. However, there are concerns about the consistent and correct use of condoms and lubricants among MSM in Ghana. In this regard, there is a need to understand context-specific factors associated with consistent and correct condom use with lubricants.

Objective: This study aims to determine the current scope of consistent and correct use of condoms with lubricants, associated factors, interventions, and user- and service-related challenges on correct condom and lubricant use among the MSM population in Ghana.

Methods: The study will use a mixed methods study approach. First, a retrospective analysis of the Ghana Men's Study II data set involving 4095 MSM will be conducted to determine the scope of consistency and correct use of condoms with lubricants as well as associated factors. The data will be imported into STATA (version 17; StataCorp LLC) to treat missing data and outliers before the analysis. Bivariate and multivariate logistic regression analyses will be conducted to determine the associated factors of consistent condom use with lubricants. All statistical analyses will be done at a 95% CI, with significant differences at $P<.05$. Second, in-depth interviews with a purposive sample of about 15-20 stakeholders will also be conducted to understand contextual issues regarding the factors identified, identify existing interventions for correct condom and lubricant use, user and service-related challenges, and how best to address those challenges from the stakeholders' perspectives. For qualitative data, thematic analysis will be conducted using Atlas.ti version 23.1.1.

Results: Qualitative and quantitative results will be triangulated together with systematic review results, and key findings will be highlighted and used to guide the development of a predictive model for improving correct and consistent condom use with lubrication among MSM. This protocol paper, part of a doctoral study by the first author (RA), received approval from the Research and Ethics Committee of the University of Johannesburg on May 10, 2024. Data collection commenced on August 20, 2024, and the expected results will be published by October 2025.

Conclusions: Results from qualitative interviews and secondary data analysis will be triangulated to develop a predictive model to strengthen the correct and consistent use of condoms with condom-compatible lubricants among MSM and other key population groups in Ghana and other parts of sub-Saharan Africa for future pandemic preparedness, policy making, and targeted budget allocation.

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KEYWORDS

men who have sex with men; consistent condom use; HIV; Ghana Men's Study; condom; Ghana; Africa; mixed methods; protocol; lubricant; qualitative; quantitative

Introduction

HIV infection is still an issue of public concern in sub-Saharan Africa, where many young adults engage in unprotected and transactional sexual relationships and also report inconsistent condom use [1]. Key populations (KPs), particularly men who have sex with men (MSM), female sex workers, people who inject drugs or people who use drugs, and transgender people, are disproportionally affected by the HIV burden [2]. In 2022, KPs and their sexual partners accounted for more than half (55%) of new HIV infections in sub-Saharan Africa [3]. Recent studies have shown that less effort has been made to reduce the incidence and prevalence of HIV in MSM in both underdeveloped and developed countries [4-6]. Men who have sex with men are more likely to contract and transmit HIV because they are more stigmatized and hidden, especially in low- and middle-income countries [7,8], aggravated by inadequate access to essential prevention materials such as condoms and lubricants [9].

In Ghana, HIV prevalence among MSM remains a major concern (18.1%) despite the remarkable decline in the number of new HIV infections among the general population (1.68%) [10]. The risk of HIV transmission in unprotected anal sexual activity is about 18 times higher than in unprotected vaginal sex [11,12], and 70% of this risk can be lessened by the consistent and correct use of condoms with lubricants [12]. According to model simulations, since 1990, the use of condoms consistently with lubricants has averted about 117 million new HIV infections [13,14]. Consistent use of condoms with lubricants to reduce the number of new HIV infections among MSM is a public health priority and an important component of prevention programs globally [11,12]. This is defined as using a new condom for each act of oral, anal, and vaginal sex during the whole sex act, ensuring that one uses ample lubricant during vaginal and anal sex, and removing the condom immediately after ejaculation to prevent spillage [11].

National estimates show that only 48.2% of MSM consistently and correctly use condoms during penetrative anal sexual intercourse with other male partners, compared with 29.7% of women [10]. This shows that consistently using condoms with condom-compatible lubricants (CCLs) correctly among MSM may be influenced by context-specific factors. Without proof of these factors, it will be impossible to address the underlying HIV prevention needs of MSM as well as other KP groups in Ghana. Further, there is inadequate consolidated data on the consistent use of condoms with CCLs and their associated factors among MSM in Ghana. This article therefore describes a protocol to determine the consistency of the correct use of condoms with CCLs and associated factors among MSM in Ghana as well as to identify existing interventions for correct condom and lubricant use, user and service-related challenges, and how best to address those challenges from the perspectives of the stakeholders. This study aims to determine the current scope of consistent condom use with lubricants and associated factors, as well as to develop a predictive model to improve the correct and consistent use of condoms with CCLs among MSM and other KP groups in Ghana, particularly for future pandemic preparedness, policy making, and funds allocations.

Methods

Overview

This is a mixed methods study involving retrospective analysis of secondary data and in-depth interviews with stakeholders. The reason for choosing a mixed methods study approach is that the secondary data analysis will help to determine the current scope of consistent and correct use of condoms with CCLs and associated factors among the MSM population in Ghana while interviews with stakeholders such as MSM, MSM representatives, program managers, and health service providers will also provide in-depth knowledge and understanding of the factors that will be identified during the secondary data analysis. The interviews will also help to provide useful information to address the challenges associated with the consistent and correct use of condoms with lubricants from the perspectives of both users and service providers.

Methods for Retrospective Analysis of the Ghana Men's Study II

Study Setting

The Ghana Men's Study II was conducted in Ghana, located in the West African subregion, with 16 administrative regions and 261 districts [15]. The study was done in 2017 across the then 10 regions of Ghana. The population of Ghana has an estimated 55,000 MSM with 18.1% HIV prevalence compared with 1.6% in the general population [16-18].

The Ghana Men's Study II was conducted in 2017 by the Ghana AIDS Commission (GAC), a supraministerial and multisectoral body established under the chairmanship of the president of the Republic of Ghana to provide HIV, tuberculosis, and sexually transmitted infections services to MSM, transgender, adolescents, young women, and other high-risk KP groups in Ghana, mainly supported by the Global Fund and the United States President's Emergency Plan for AIDS Relief.

Study Design

A retrospective analysis of the Ghana Men's Study II data set will be carried out to determine the scope of consistent and correct use of condoms with CCLs and associated sociodemographic, behavioral, socioeconomic, and structural factors among MSM.

Sample

The Ghana Men's Study II included MSM who were biologically male, were aged ≤18 years (ie, inclusive of men aged 18 years), had consensual sex with another male partner in the last 12 months (self-reported), and lived, worked, or socialized in any one of the study regions of Ghana. Transgender

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women were eligible if they were biologically male and had intercourse with another male individual within the previous 12 months.

MSM were recruited using respondent-driven sampling, which is a widely used variant of snowball sampling where respondents are chosen not from a sampling frame but from a social network of existing participants of the sample. Incentives were provided for participation and the recruitment of others [19]. The size of the sample was determined based on the surveillance goal of following significant changes in the HIV epidemic over some time, that is, between rounds of the integrated biological and behavioral surveillance survey. The survey treated each of the sites as a distinct survey, with the size of the sample required to track any changes at each of the locations [10]. A sample size of 500 MSM for each region was calculated by factors such as the estimated period of the recruitment, funding, the highly risky nature of such studies, and, most importantly, the ability to measure the most important indicators using Ghana Men's Study I estimates with 80% power at a 95% confidence level [10]. A total sample size of 4095 MSM were recruited for the Ghana Men's Study II. The target sample generated an exact estimate of the anticipated equilibrium distribution for each of the indicators (change in sexual behavior, ie, the prevalence of always using condoms at the last sexual intercourse) to identify a 10%-15% increase (ie, from 48.4% to 53.4%) or decrease (28.4% to 23.4%) in the indicators based on the ability to measure significant program effort between surveys and HIV prevalence, with an expected projection of 34.3% [10]. For further details on the sample, please refer to earlier publications [10,20]

Data Collection

The primary outcome of the study is consistent condom use with lubricants at last sexual intercourse, measured as the number of participants with one or more intimate partners during the past 12 months (sexually active participants) [10]. The secondary outcomes are factors associated with consistent condom use with lubricants. The study will examine sociodemographic, behavioral, socioeconomic, and structural characteristics for the secondary outcomes. Data were collected on sociodemographics, condom and lubricant use, consistency of use, accessibility of condoms and lubricants, condom and lubricant use at last sex with a male or a female, and the consistency of condom and lubricant use ("always used a condom with lubricants" or "not always using condom with lubricants") among MSM in Ghana during penetrative anal sex with other men, among others (Table 1). The GAC collected data through the MSM Comprehensive HIV Prevention Programme [10]. The questionnaire was administered through a computer, with respondents having the option of completing it using computer-assisted personal interview software [10]. The data will be secured from the GAC and used only for this study. The data were captured on the GAC's electronic database and stored on a secure server with encryption and user access control. All the collected data were stored in a respondent-driven sampling-A-compatible format. The Bryant Research System was used to oversee and coordinate the collection of data to ensure anonymity, privacy, and confidentiality [10].

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Table 1. Description of variables to be assessed from the 2017 Ghana Men's Study II data set. Adopted from the Ghana Men's Study II questionnaire [10].

Variable name	Variables	Variable descriptions	Variable recode
Dependent variables (condoms and lubricants use)			
Condom use	Used a condom at last sexual intercourse	• Yes • No • No response	• Yes • No
Lubricant use	Used a lubricant at last sexual intercourse	• Yes • No • No response	• Yes • No
Condom use with lubricants	Used a condom with lubricants at last sexual intercourse	• Yes • No	• Yes • No
Consistent use of condoms with lubricants	• Used condom with lubricants consistently • "Always used a condom", "frequent condom use", and "consistently used a condom" are synonymous with condom use consistency during sexual activities	• Yes • No	• Yes • No
Consistent use of condoms with condom-compatible lubricants	Used condoms with condom-compatible lubricants consistently	• Yes • No	• Yes • No
Consistency of correct condom use with lubricants	Used condoms with lubricants correctly and consistently	• Yes • No	• Yes • No
Factors associated with condom and lubricant use	• Positively associated factors of condom use • Negatively associated factors of condom use	• Sociodemographic factors • Behavioral factors • Economic factors • Structural factors.	• Sociodemographic factors • Behavioral factors • Economic factors • Structural factors.
Factors that affect condom and lubricant use by classification: independent variables (sociodemographics)			
Age	Respondent's age	Integer	• ≥18 years • 20-24 years • 25-29 years • 30-34 years • 35-39 years • 40-44 years • 45-49 years • 50-54 years • 55-59 years • ≥ 60 years
Education	The educational level of the respondents	• No formal education • Basic education • Secondary education • Tertiary education	• No formal education • Basic education • Secondary education • Tertiary education
Occupation	The employment status of participants	• Unemployed • Self-employed • Government employed • Private-sector employed	• Unemployed • Self-employed • Government employed • Private-sector employed
Factors that affect condom and lubricant use by classification: independent variables (behavioral factors)			

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Variable name	Variables	Variable descriptions	Variable recode
Behavioral factors	Behaviors that affect condom and lubricant use	• Number of sexual partners • Condom-carrying • Drug use or sex under the influence of drugs • HIV testing behavior • Trust for a sexual partner • Seeking counseling on risk reduction. • Dislike condom use • Unplanned sexual intercourse	• Number of sexual partners • Condom-carrying • Drug use or sex under the influence of drugs • HIV testing behavior • Trust for a sexual partner • Seeking counseling on risk reduction • Dislike condom use • Unplanned sexual intercourse
Structural factors	Structural factors that influence condom and lubricant use	• Physical and sexual violence • Access challenges • Low-quality products (eg, condoms) • Distribution challenges • Practical difficulties with using condoms such as breakage • Misinformation about condom use • Interference with sexual pleasure • Access to free condoms	• Physical and sexual violence • Access challenges • Low-quality products (eg, condoms) • Distribution challenges • Practical difficulties with using condoms such as breakage • Misinformation about condom use • Interference with sexual pleasure • Access to free condoms
Socio-economic factors	Socio-economic factors affecting condoms and lubricant use	• Financial incentives for sexual intercourse • Socioeconomic vulnerability • Financial stability	• Financial incentives for sexual intercourse • Socioeconomic vulnerability • Financial stability

Data Analysis

The Ghana Men's Study II data set will be imported into STATA (version 17; StataCorp LLC) for data cleaning and processing before conducting statistical analysis. The data will be disaggregated by sociodemographic characteristics, condom use, condom use at last sex, consistent condom use with a male or female sexual partner or both, consistent condom use during insertive or receptive anal sex, consistency of correct condom use with lubricants, consistency of the correct use of condoms with CCLs, and associated factors (sociodemographic, behavioral, structural, and socioeconomic factors) that promote or hinder condom and lubricant use consistency. Descriptive statistics will be performed to describe the demographic characteristics of MSM. Continuous variables will be reported as means with SD and categorical variables as percentages. We will conduct bivariate and multivariate logistic regression analyses to identify significant associations between consistent condom use with lubricants and sociodemographic factors, behavioral factors, and structural and socioeconomic factors. All statistical analyses will be done at a 95% CI, with significant differences at $P<.05$.

Concerning the choice of specific statistical test, one of the objectives of this study is to test for the associated factors of consistent condom use with lubricants hence our choice of Bivariate and Multivariate logistic regression analysis. After bivariate analysis, multivariate logistic regression analysis will be done to exclude all confounding factors to determine the factors that are associated with consistent and correct use of condoms with lubricants.

Methods for In-Depth Interviews With Stakeholders

Study Design

An exploratory study design of in-depth stakeholder interviews will be conducted, using a semistructured questionnaire (Multimedia Appendix 1).

Study Population

The stakeholders will comprise MSM and MSM representatives from various institutions who work closely with KPs, including the KP community, program managers, HIV health care service providers, and civil society organizations.

Sample

A purposive sample of about 15-20 key informants [20,21] of the various stakeholders that offer interventions, HIV prevention programs, and services to improve consistent and correct use of condoms and lubricants among MSM will be purposively selected to participate in the study. The sample size given is aimed at getting diverse views from a range of stakeholders and the number of key informants (15-20) is not fixed. It will increase until the saturation point is reached. Textbox 1 shows the inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria for stakeholder participation in interviews on interventions for condoms and lubricant use [1].

Participants

- Men who have sex with men (MSM), MSM representatives, HIV health care service providers, program managers, and civil society organizations

Inclusion criteria

- Individuals working in the HIV field as health care providers, program developers, policy makers, and beneficiaries aged 18 years and above
- They should be willing to provide informed consent to take part in the study
- They should have been working in the area of HIV control and prevention (ie, condom and lubricant use) for at least 1 year or more
- They should be employed in the field at the time of the interviews
- They should be knowledgeable on the subject matter
- They should speak English or the local language

Exclusion criteria

- Individuals younger than 18 years
- Individuals who did not provide informed consent to take part in the study
- Individuals working in the area of HIV control and prevention for less than a year
- Individuals who cannot speak English or the local language
- Individuals who are not knowledgeable on the subject matter
- Individuals who are not interested in the subject matter

Participant Recruitment

The recruitment of stakeholders for this objective will be done with the support of the GAC, which has an extensive track record of working with MSM structures, leaders, and organizations. For MSM, the recruitment process will not be event-based recruitment however, a direct approach will be used to contact MSM individually. A known GAC staff member will approach potential MSM participants who were previously involved in GAC studies or activities. The GAC will provide an introductory support letter to each potential participant. If a potential participant agrees to participate in the study, they will be given the researcher's contact details for engagement at a convenient time. The GAC will inform participants to feel free to contact them if they have any issues before, during, or after the study. The researcher will also be required to give feedback to GAC about any concerns or progress updates weekly in writing. The GAC will ensure that whatever concerns are raised by the participants are promptly addressed. The GAC will emphasize that participation in the study is voluntary and that participants may feel free to leave the study at any time. For the other stakeholders, in addition to the above-mentioned introductory letter, the researcher will write a letter of invitation to participate in the study. The invitation letter will specify the inclusion and exclusion criteria, especially emphasizing anonymity, privacy, confidentiality, and voluntary participation. The letter will specify that the interviews will not be focusing on their personal lives but rather on stakeholder views as officials working in the HIV field. This will be mentioned to ensure that participants are assured of protection against social, physical, or psychological vulnerabilities.

Data Collection

The in-depth interviews will be conducted to elicit information on factors associated with condom use, the programs or initiatives and policies on the consistent and correct use of condoms and lubricants, user and service-related challenges, and how these challenges can be addressed among MSM and other stakeholders. Interviews will be administered face-to-face in a private room for participants' privacy and will take place at a time and location that is most convenient for them. During face-to-face interview sessions, only the interviewer, interviewee, and note-taker will be present. During the interviews, only the interviewer (researcher), interviewee, and a trained note-taker will be present during all face-to-face interview sessions. For privacy purposes, a separate private room within their premises of choice will be used to conduct the interviews.

The interviews will commence with a brief introduction of the study objectives, introducing the interviewer, and reading the privacy declaration form. The participants will be asked to voluntarily engage in interview questions. The interviews will focus mainly on the study objective and probing questions will be used where necessary to get a deeper understanding of their views. Each interview is expected to last for about 45 minutes. No personal or identifiable information will be disclosed throughout the study The interviews will be recorded verbatim and supported by tape recording for accuracy purposes. Field notes will also be taken to supplement the recorded information. Data will be coded to generate themes and subthemes, where possible.

Data Analysis

Data will be captured on Atlas.ti (version 23.1.1) and will be coded using an inductive approach. A comprehensive overview

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of the entire data will be done to become familiar with its content. Before analyzing the data, the interviews will be transcribed; thereafter, the entire dataset will be read to generate codes. Data will be coded using Atlas. ti and intercoder agreement will be used to deal with discrepancies. Patterns from created codes will be used to formulate themes and subthemes where necessary. After this, a consensus on the themes and subthemes will be reached before further analysis. Finally, themes will be defined and named; then, the data analysis will be carried out. Thematic content analysis will be used to analyze open-ended questions, whereas closed-ended questions will be analyzed descriptively, reporting proportions and percentages.

Ethical Considerations

This study protocol will use deidentified data from the Ghana Men's Study II dataset secured from the GAC. After the data analyses, the preliminary results will be stored securely on a memory stick with an access code. The results of this study will only be reviewed by the researcher and the research team. All the data used in this study will be managed in compliance with the Protection of Public Information Act. Furthermore, all the data generated from the PhD study will be stored for 5 years after the completion of the study.

The results to be published will not have any identifiable information. This protocol paper is part of the doctoral study of the first author (RA) and has received ethics approval from the Research and Ethics Committee (REC-2742-2024) (Multimedia Appendix 2) of the University of Johannesburg. Furthermore, this study also falls under a broader research project at the South African Medical Research Council (SAMRC)/the University of Johannesburg (UJ) Pan African Centre for Epidemic Research (PACER) Extramural Unit funded project, namely Harnessing Big Heterogeneous Data to Evaluate the Potential Impact of HIV Responses Among KPs in Generalized Epidemic Settings in Sub-Saharan Africa (REC-1504-2023).

Before obtaining consent, the study participants will be provided with the full research details before participating in the qualitative study. These include the objectives, methods, anticipated benefits, and possible risks of the research. Written informed consent will be taken in a private room at a convenient time, and location, and on an individual basis with the researcher and the note taker. The content of the consent form will be read out to the participants and ensure that they understand and ask for their consent. The decision to participate will solely rest on the participant and no form of coercion, deceit, or influence will be used on them. Participants will be informed that their participation in the study is voluntary and that they have the right to withdraw from the study if they so choose at any moment, for any reason, and without any repercussions or prejudice. There will be contact information for the researcher and the supervisor available should any questions or concerns arise about the research and the research participant's rights. This study will only involve individuals with a complete willingness to participate. Before participation, all participants will be asked to sign the informed consent form, protection of public information consent for the collection of information, and consent to audiotape the interviews to confirm their complete willingness to participate in the study.

To ensure the confidentiality of the study participants, a private room will be used for the interview, and the interview will be conducted at a time and location suitable to participants. During interviews, only the interviewer, interviewee, and trained note-taker will be present during all face-to-face sessions. The note-taker will sign a confidentiality agreement to ensure that no information is divulged without the permission of the participant. We will ensure that pseudonyms are used for each participant and that no identifiable information will be found in the interview transcripts. Steps will be taken to control data accessibility and all interview recordings and paper-based data collection materials will be secured under lock and key.

For participants' safety, the study will be entirely anonymous; at no point or time will names or identifying information of the MSM be collected. The GAC, which has an extensive track record of working with MSM structures and leaders, will lead the recruitment process. As outlined in the participants' recruitment section, there will be no organized meetings with MSM groups to avoid any risk of exposure. There will be no campaigns for MSM to join the study and no social marketing of the study. The use of any type of media, including TV and radio advertisements, will be avoided. A direct approach will be used to contact MSM individually. A known GAC staff member will approach potential MSM participants previously involved in GAC studies or activities. The GAC will provide an introductory support letter to each potential participant. If a potential participant agrees to participate in the study, they will be given the researcher's contact details for engagement at a convenient time. The GAC will inform participants to feel free to contact them if they have any issues before, during, or after the study. The researcher will also be required to give feedback to GAC about any concerns or progress updates weekly in writing. The GAC will ensure that whatever concerns are raised by the participants are promptly addressed.

In addition, there is also a trust relationship between the GAC and MSM that has been nurtured and grown for over 2 decades of HIV programming among MSM who receive the full range of HIV services in all 16 regions of the country. The program is founded on public health and human rights principles with well-established protective mechanisms, developed and implemented in strong collaboration with the Ghana Police Service and other law enforcement agencies. As part of this collaboration, the Ghana Police Service adopted and integrated public health and human rights principles into its pre- and in-service training curricula to prepare the personnel for the effective protection of KPs. The police service also established national and regional steering committees to coordinate and oversee the protection of KPs, including MSM throughout the country. A special unit of the police service with officers trained in public health and human rights principles handles all MSM-related cases in the country just to ensure their protection. The protection efforts of the police service are complemented by trained paralegals and pro-bono lawyers who work closely with the police to ensure the protection and uphold of the dignity of MSM who find themselves on the wrong side of the law. The strong partnership and collaboration with the police service will

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be used to as well protect any study participant who may be involved in any adverse incident.

Results

The results will encompass analysis of deidentified data from the Ghana Men's Study II dataset, as well as in-depth stakeholder interviews, to determine the current scope of the consistency of correct condom use with lubricants and the associated factors among the MSM population in Ghana. Results from the secondary data analysis will be presented in tables and interpreted by using odds ratios and *P* values. For the qualitative interviews, we will do interpretation by making a list of key themes and subthemes. Each theme that arises during the coding process will be reviewed to identify similarities and differences in responses from participants. Relationships between themes to determine how they are connected will be considered. Key findings will be highlighted and used to guide the development of a predictive model for improving correct and consistent condom use with lubricants among MSM. This protocol paper is part of a doctoral study by the first author (RA), which received approval from the Research and Ethics Committee of the University of Johannesburg on May 10, 2024. Secondary data analysis commenced on August 20, 2024, and all expected results will be published by October 2025.

Discussion

Principal Findings

Consistency of the correct use of condoms with CCLs is very crucial in preventing new HIV infections among MSM and other KP groups in Ghana and across the globe. The study will use a mixed methods study design, retrospective data analysis, and stakeholder interviews. The rationale for this approach is that the secondary data analysis will elicit information on the scope of consistent and correct condom use with CCLs and associated factors among MSM while interviews with the stakeholders will also provide in-depth knowledge and understanding of the factors that will be identified during the secondary data analysis. The interviews will also help to provide useful information to address the challenges associated with the consistent and correct use of condoms with lubricants from the perspectives of both users and service providers. Findings from the study will be triangulated to develop a predictive model to improve the consistency of the correct use of condoms with lubricants among MSM and other KP groups [22-25]. This study corroborates the findings of another study conducted by Newby et al [26], which proposed the development of a future-definitive trial to reduce the occurrence of sexually transmitted infections by improving the correct and consistent use of condoms.

Results from this study will help to address a significant gap in understanding sexual health practices among the MSM population in Ghana. This study will also provide useful information essential for developing targeted interventions and policies to mitigate the impact of HIV on public health. By using predictive modeling techniques, this study has the potential to increase awareness and promote safer sex practices among MSM, ultimately informing evidence-based strategies for HIV prevention and control.

The monitoring and evaluating HIV prevention framework and the SMART (specific, measurable, attainable, realistic, and timely) tool will serve as a guide for developing the model. The SMART tool allows users to capture, manage, and map data from studies or surveys that can be analyzed to understand behavioral changes over time as well as understand the factors responsible for the changes. Positively associated sociodemographic factors, behavioral factors, structural factors, and socioeconomic factors of consistent condom use with lubricants will be triangulated to develop the model.

Regarding the dissemination plan, we intend to publish the study findings for each objective in a peer-reviewed journal with a high impact factor and readership by October 2025. A report summarizing the findings will be made available to stakeholders, policy makers, and relevant organizations to ensure that the correct and consistent use of condoms with CCLs is widely practiced among all KP groups and the general public.

Strengths and Limitations

The retrospective analysis being undertaken relies on data from the Ghana Men's Study II, which uses rigorous scientific methods successfully used in the Ghana Men's Study I to ensure scientific rigor, comparability, and consistency. For example, a sample size calculation was done to ensure that the study sample was large enough to enable the generalization of the study results to the MSM population. The sample size was calculated based on the estimated MSM population size in Ghana. Multiple methods were used to recruit MSM to ensure that diverse MSM groups are represented in the study, thus enhancing the applicability of the study's findings to MSM broadly. The same validated tools used in Ghana Men's Study I were used in Ghana Men's Study II to ensure the reliability and validity of the study results. Researchers in the Ghana Men's Study received training to enable them to elicit information; however, subjectivity bias cannot be ruled out. Data collection tools were administered in local languages to ensure a proper understanding of the questions. The possibility of information bias may not be ruled out given that self-reported information was used.

In addition, qualitative interviews will be used to elicit rich, in-depth information on some of the findings emanating from the secondary data analysis. Further, a systematic review will be conducted to understand the status quo. The secondary data, qualitative data, and narrative analysis from the systematic review will be triangulated. The use of a mixed methods approach will mitigate the inherent limitations of a retrospective study design.

Conclusion

This study will provide data to inform the design of a predictive model through stakeholder interviews and secondary data analysis to strengthen the correct and consistent use of condoms with CCLs among MSM and other KP groups in Ghana and other parts of sub-Saharan Africa. The outcome of this study could also inform the government of Ghana how best to support HIV prevention programs to meet the health care needs of KP groups in Ghana. This will enable the government of Ghana to

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reach its health goals, conforming to the third goal of the Sustainable Development Goals.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

RA, EP, KA, and RNP-M contributed to conceptualization. RNP-M and EP performed validation. RA and EP wrote the first draft. RA, EP, KA, and RNP-M contributed to writing, reviewing, and editing. RNP-M, KA, and EP performed supervision. RA handled project administration. RNP-M handled funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 18 KB - resprot_v13i1e63276_app1.docx]

Multimedia Appendix 2
Research and ethics approval letter.
[PDF File (Adobe PDF File), 92 KB - resprot_v13i1e63276_app2.pdf]

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Abbreviations

CCL: condom-compatible lubricant
GAC: Ghana AIDS Commission
IBBS: integrated biological and behavioral surveillance survey
KP: key population
MSM: men who have sex with men
PACER: Pan African Centre for Epidemics Research
SAMRC: South African Medical Research Council
UJ: University of Johannesburg

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Protocol

Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study

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Abstract

Background: Older adults comprise a substantial proportion of the US population requiring support during disaster events. Previous research demonstrates that older adults are resilient but deficient in disaster preparedness and lacking in community engagement. There is a gap in high-quality research in this area.

Objective: This study aims to fill this gap by developing a 4-phase intervention to improve mobility and balance, decrease fall risks (mitigation), increase knowledge of disaster preparedness (preparedness), improve community emergency operation plans (response), and improve self-efficacy in disaster recovery (recovery) for older adults.

Methods: This is a community-based, 10-month study in a large Midwestern urban and suburban location targeting community-dwelling older adults. The 4 phases of interventions address mitigation, preparedness, response, and recovery—aspects improving outcomes from disaster events. In total, 4 to 6 one-hour seminars each month are provided to community-dwelling older adults to improve disaster preparedness and recovery planning. A critical incident packet with resources on essential information such as medications, a communication plan, evacuation resources, and supplies was started and is being reviewed. Preintervention surveys are orally given, with research assistants aiding in any difficulties the participants have. After the surveys, 2 individual 20-minute presentations separated by a short break for snacks and initial completion of their disaster plan preserve the older adult's attention. Mitigation efforts to improve mobility and safety are offered with 10 visits to the older adults' residences, adapting physical activity and balance exercises to the individual's needs. To address response needs, the emergency operations plans for 2 of the major cities are being amended for specific functional needs and access guidelines. Measurements include accelerometers to assess improvement in mobility, fall risk assessments, an abbreviated Federal Emergency Management Association Household Survey, an assessment for disaster engagement with partners tool, a brief pain inventory assessment, and the General Self-Efficacy Scale. We analyze data descriptively and compare pre- and postintervention data for each phase with paired-samples *t* test and other nonparametric techniques (proportion tests and Wilcoxon signed-rank tests). Overarching objectives prioritized during this intervention include underscoring respect for the experience and resilience found in older adults and engaging them in specialized roles to support their communities during disaster events.

Results: The intervention was funded in July 2023; enrollment began in November 2023 and is continuing. We will conclude data collection by July 2025. Published study results can be expected in early 2025.

Conclusions: With improved disaster preparedness, mobility, recovery planning, and inclusion as a resource in community disasters, older adults are expected to be safer and be able to age in place. If successful, future studies will focus on outreach and sustainability. This study will serve as a model for older adult disaster preparedness and community involvement.

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KEYWORDS

older adults; disaster preparedness; emergency preparedness; disaster protocol; disaster engagement; disaster recovery; personal preparedness; community dwelling older adults; elderly; aging in place; activities in daily life; resiliency; community health

Introduction

Older adults experiencing disaster events are disproportionately at risk for morbidity and mortality [1,2]. This population is increasing to 1 in 5 Americans by 2050 [3], with 39.5% needing equipment to perform activities of daily life [4]. The Federal Emergency Management Association (FEMA) Household Survey on disaster preparedness [5] reported a disconnect between the older adult population's perception of preparedness and their preparedness actions, prompting FEMA to urge communities and emergency managers to focus on and empower this population to meet their unique situations and challenges before disasters. FEMA's survey results found a lack of planning for disasters, preparing for evacuation, family communication, participation in drills, and involvement with their community and neighbors among American older adults. Evidence suggests that while older adults are more resilient in disasters [6], they are also more isolated [7]. The National Academies of Sciences [8] reports isolation is exacerbated during disaster events, recommending improved connection with communities. Due to time horizons (the sense of how much time is left in life), older adults are uniquely susceptible to disaster mental health issues [9]. Mental health and lack of access to medical care post disaster require specific attention for this population. After Hurricane Sandy, Corley et al [10] found that older adults had increased anxiety, stress, and posttraumatic stress disorder.

Current risk management efforts focus on preparedness, mitigation, and planning for recovery, along with acute response to the disaster event [3]. While literature is scarce and dated on interventions that improve disaster preparedness and self-efficacy, Ashida et al [11] noted some convincing evidence of positive outcomes from postpreparedness education. Pre-event decisions should be planned before the disaster event to improve peace of mind and individual response times [12]. In addition, this population is motivated by a need to feel valued rather than expendable [13]. Older adults have had experience with disasters, wars, and challenges in their lives, expertise which may be reflected in the data supporting their increased resilience in emergencies [14,15]. They provide experience from previous successes or learning from previous failures, giving value to the older adults and hope to survivors. There are 1 primary and 4 secondary hypotheses for this study. The primary hypothesis is that the interventions will show significant improvement in disaster preparedness knowledge for community-dwelling older adults from the pre- to postintervention survey. This will be supported by four subhypotheses: (1) mitigation: the intervention will demonstrate improved mobility and safety from before to after the intervention; (2) preparedness: the seminar interventions will demonstrate significant improvement in household disaster readiness measured by the FEMA Household Survey [5] from before to after intervention; (3) response: the collaboration between supporting disaster management organizations will improve interagency teamwork and communication after the intervention as measured by the Assessment for Disaster Engagement with Partners Tool (ADEPT); and (4) recovery: the self-efficacy of community-dwelling older adults will statistically improve from before to after the intervention.

Methods

Study Design

Overview

This is a 4-phase, quasi-experimental study conducted in a Midwestern US metropolitan area. Population includes all community-dwelling older adults, defined as those equal to or older than 65 years of age living independently. Support from 12 organizations, including public health departments, emergency management councils, regional support councils, and disaster volunteer organizations, was obtained. Partner organizations provide a host location and recruitment for the seminars through organizational emails, flyers, and word of mouth. Childcare is offered, allowing older adults who are babysitting during daytime hours to attend. The 4 seminars include Spanish interpretation and materials. The option for study involvement is voluntary and private. The 4 phases follow disaster phase principles and are mitigation, preparedness, response, and recovery.

Mitigation

To improve mobility and mitigate the loss of life during disasters, we are recruiting a sample of older adults to participate in a 10-week, perspective, pre- and posttest, fall prevention and physical activity intervention.

Preparedness

Four seminars per month are being given for 1 hour with a PowerPoint presentation on disaster preparedness, decision making, communication, and county state resources available. The Your Very Personal Preparedness Inventory (Multimedia Appendix 1) [16] begins with assistance from a research assistant, ending with the presentation of a red critical information packet to be stored at their home for emergencies. In addition to the personal preparedness inventory, the critical information packet includes Your Guide to Emergency Preparedness in the Greater Kansas City Region (Multimedia Appendix 2), My Communication for Disaster Recovery (Multimedia Appendix 3), and My Action Steps to Avoid: Disaster Recovery Scams (Multimedia Appendix 4). All are welcome to attend whether they opt in for the study or not. In total, 2 test seminars were held to obtain feedback from

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participants on the value of the information given and the method of delivery. Feedback included having more interaction and making the information more concrete and less abstract.

The study participants orally consented and then asked for an abbreviated version of the FEMA Household Survey. The seminar presentation (Multimedia Appendix 5) is then presented to the participants. One week after the seminar, the same research assistant phones the participant and asks the same questions. All answers are documented in Qualtrics XM, a secure encrypted data gathering and analyzing program, for confidentiality. Media releases for educational sharing of photos are signed upon entering the seminars.

Response

Two city emergency management departments and 8 community support organizations and coalitions were engaged to participate in a review of their current emergency operations plan with a focus on improving integration of older adult needs. The organizations agreed to participate in writing before beginning work with the research team. Research assistants were then provided with copies of organization emergency plans and participated in discussions with stakeholders to create organization-specific recommendation guides based on current literature and community assessments to address identified challenges for older adults. Members of leadership and registered personnel of participating organizations were asked to rate their organization's level of partner engagement by completing the ADEPT [17] through an email survey before engaging in the plan review and again after the research team presented their recommendations at the close of the project. Responses to both surveys were recorded in Qualtrics XM and compared with measure changes in 4 domains of partner engagement: communication outreach and coordination, resource mobilization, organizational capacity building, and partnership development and maintenance.

Recovery

As in the preparedness phase, four 20-minute seminars per month, in conjunction with the preparedness seminars, are also delivered to community-dwelling older adults on disaster recovery. Similarly, this phase of the project underwent 2 test seminars with nearly identical feedback to that of the preparedness phase. A team of research assistants collected oral consent from participants and administered the General Self-Efficacy Scale (GSES) [18] before the seminar. As an intervention study, research assistants re-administer the GSES through phone 1 week after the seminar to examine any changes in perceived self-efficacy pertaining to disaster recovery. Oral responses are recorded in Qualtrics XM by the research assistants.

Ethical Consideration

All phases were submitted and approved by the University of Missouri-Kansas City institutional review board (2094344, 2097949, 2098365, and 2098527). Preparedness, response, and recovery were deemed exempt since identification of individuals was only for follow-up phone call communication and all data were and are deidentified after the 1-week follow-up phone call. The mitigation research review was expedited and approved due to the length of the intervention being over 2 hours. No compensation other than snacks was given.

Description of the Intervention

Overview

"Seniors' Positive Impact on Community Emergencies" is a community-based intervention targeting community-dwelling older adults aged 65 years or older. The program's intent is 3-fold: To improve disaster preparedness for older adults whose independent living does not afford them the protections of extended care facilities, improve community involvement and respect for the known experiential depth of our older populations, and create a safer environment during disaster events by reducing fall hazards in the home. There is an overabundance of literature on the need for specific interventions during disasters [4,12,19,20] but few to no studies conducted on the effect of interventions to improve this situation.

Mitigation Programming

At enrollment, participants are provided an accelerometer to assess baseline physical activity for 1 week; research assistants determine a time to visit the participant's home to collect the accelerometer and to conduct the first home visit. During the first session, research assistants assess home fall hazards using the Fall Prevention Checklist [21]. In response to the checklist, research staff developed a plan with the participant to modify their home environment to prevent fall risks increase mobility for a safe evacuation and have a safer home environment. A balanced assessment is also conducted using the Timed Up and Go test (TUG) [22]. In addition, research assistants and participants develop small, realistic physical activity goals for the 10-week intervention using the Go4Life goal-setting worksheet [23]. Potential goals include doing balance or chair exercises, walking around their home, and walking outside for 10-30 minutes. A research assistant goes to the participant's home once per week for 1 hour to exercise with the participant. Measures are reassessed at the conclusion of the intervention for a posttest comparison.

Preparedness Programming

The 4 seminars per month are given with a 20-minute Microsoft PowerPoint interactive session and a 15-minute time block in which research assistants provide help completing the participants' critical information packet and individualizing it for their community. The following disaster preparedness subjects are the content included: statistics on the cost and incidence of natural disasters, alerts versus warnings, decisions such as shelter-in-place or evacuation, supplies, disaster pet rescue, communication plans, transportation, medication, important documents, and medical equipment. These subjects all prepare the community-dwelling older adults so that they can act quickly if a disaster occurs. The critical information packet includes the booklet: Your Very Personal Preparedness Inventory [16], Your Guide to Emergency Preparedness in the Greater Kansas City Region [24] from the area emergency managers, and a sheet of resources particular to the area where the seminar is being given. It also includes an individual sheet with contact information or unique disaster details for the participant and their family, and a credit-card-sized magnifier

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so that all information can be easily viewed. During the breaks, a disaster go-bag with essential supplies is displayed near the refreshments with a list of basic go-bag needs.

Response Programming

Upon establishing partner agency enrollment, the researchers begin by introducing the ADEPT survey, explaining its goals, and distributing it electronically to emergency response community members [17]. This provides a baseline of current engagement metrics as reported by agency partners. Researchers then collaborate with emergency managers and community stakeholders to conduct a comprehensive review of current emergency operations plans for the participating municipalities. Research assistants also perform a community needs assessment identifying and verifying current resources for community-dwelling older adult populations and a literature review of evidence-based practices and model emergency operations plans addressing the needs of older adults, allowing guide designers to creatively incorporate older adults as contributing support resources in the construction of their recommendations. Research assistants then present their findings and recommendation guides in training seminar format at designated organizational meetings to inform and educate collaborators. After the presentation of these seminars and deliverables, participating agency leadership and affiliated members are resurveyed with the ADEPT inventory to assess reported engagement changes post intervention.

Recovery Programming

The 20-minute recovery seminars include a Microsoft PowerPoint presentation with the following content: defining disaster recovery, discussing common challenges in the recovery phase, explaining the role of FEMA in recovery, and descriptions of local disaster recovery centers, and other community resources. The presentation concludes by reminding participants that they are survivors and not victims in disaster recovery because they have resilience and are assets to their communities. In addition to the PowerPoint presentation, participants will also receive 2 handouts: one that provides information on recommended actions to avoid disaster recovery scams and another that provides communication resources for disaster recovery.

Measures

Demographic Variables

The older adults' demographic variables are measured by self-reporting questions at baseline. They are asked name and phone number for the follow-up survey access, age, sex, and zip code, worded identically to the FEMA Household Survey [5] questions.

Mitigation Measures

Home fall hazards are assessed before and after the intervention using the Fall Prevention Checklist [21]. The Fall Prevention Checklist assesses multiple aspects of a participant's home, including stairs, loose carpets, handrails, etc. To assess balance before and after the intervention, the TUG assessment is used [22]. The TUG asks participants to get up from a chair, walk to a place marker about 10 feet away, return, and sit back down. The baseline level of physical activity is assessed using a Garmin Vivofit 4 wrist-mounted accelerometer for 1 week before the intervention [25]. At the end of the 10 weeks, the participant is asked to wear the Garmin device again for 1 week to assess physical activity after the intervention.

Preparedness Measures

Before and 1 week after the disaster preparedness seminars, an abbreviated version of the FEMA Household Survey [5] is orally administered by research assistants and documented in Qualtrics XM. FEMA Household Survey [5] questions are copied with permission verbatim from the original survey for national norming comparison. To abbreviate the survey to increase acceptance, disasters not appropriate for the Midwest such as tsunamis; types of alerts; and specific disaster questions such as coastal flooding, earthquake, etc, were removed. The time average for taking the oral survey is 13 minutes.

Response Measures

Partner engagement is assessed before and after the intervention using the ADEPT instrument [17]. The ADEPT survey assesses the impact on partner engagement relationships using a 15-item set of ordinal scale questions across 4 domains: communication outreach and coordination, resource mobilization, organizational capacity building, and partnership development and maintenance. This tool was validated using internal consistency reliability, and reasonable interitem reliability for the 4 hypothesized dimensions (Cronbach α=.71-.88). These dimensions were confirmed through correlation and factor analysis (Varimax rotation) [17]. Completion time is approximately 15 minutes. A link to the Qualtrics XM survey form is emailed to a roster of affiliated collaborator members at the beginning of the project and again at the end of the project after the presentation of community-dwelling older adult recommendation guides. The survey population includes disaster response organization leadership, members, and stakeholders. The survey form includes an electronic statement of consent and requires participants' affirmative submission of their data to opt into the study. The survey form also collects demographic data that include the participant's name, contact phone, and affiliated organization and role. To support response fidelity in a comparatively small sample population, participants receive 1 follow-up email reminder to complete the survey 1 week after distribution and 1 phone call reminder 2 weeks after distribution for each survey. If no response is received from either prompt, an in-person visit from a research assistant may follow to confirm opportunity awareness. The researchers do not use coercive methods to obtain survey responses; participation must remain strictly voluntary. Further, participant identifiers should not be used in analysis reporting and remain undisclosed.

The GSES [18] is a 10-question survey that generates ordinal-level responses pertaining to self-efficacy. Self-efficacy in this context refers to, "a person's belief in his or her capability to successfully perform a particular task" [26]. After obtaining oral consent from participants, research assistants briefly define the meaning of disaster recovery and explain that participants will answer each question in the context of the particular task of recovering from a disaster. As previously mentioned, participants receive follow-up surveys through phone from the

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research assistants 1 week after the recovery intervention that are recorded in Qualtrics XM.

Deidentified data collected from these measures may be made available to researchers upon request from the corresponding author after completion of the project.

Statistical Analysis

Data preparation and analysis will be conducted in R (R Core Team) [27] using a variety of base and add-on libraries available through the Comprehensive R Archive Network [28]. In preparing the data, we will examine missing responses to identify the mechanism most likely responsible for the missingness to determine the appropriateness of multiple imputation procedures for data recovery [29,30]. In analyzing the data, we will examine the descriptive statistics for all measured variables, evaluate the reliability of the instruments used to measure the constructs of interest and perform appropriate cross-sectional and repeated measures analyses to address the aims guiding the project. Specifically, we will examine the associations between constructs measured at each wave using appropriate correlation techniques, such as Pearson, Spearman, or phi correlation, to adequately account for the distributional characteristics of the variables. In addition, we will examine changes to the constructs of interest (eg, knowledge, self-efficacy, physical activity) using repeated measures techniques that account for the scale of measurement (eg, categorical, continuous) and distributional characteristics (eg, approximate normality), such as the paired-samples 2-tailed *t* tests, repeated measures ANOVA, Wilcoxon signed-rank test, or a generalized estimating equation. We will test for statistical significance against an α threshold of .05.

Results

This study began in November 2023 and will continue through July 2025 (20 months). Trial seminars occurred in December 2023 with the feedback of increasing interaction and delivering concrete actions for disaster response based on location, community, and individual needs. This was incorporated before the study. Results will be communicated to the professional community by publications, and results will also be given in presentation form to stakeholders, organizations, and governmental entities. Published study results can be expected in early 2025.

Discussion

Expected Findings

With the older adult population increasing, it is important to support efforts that allow aging in place. This decreases loneliness and provides a sense of security [31,32]. Older adults are more vulnerable during disasters due to mobility, cognitive, and functional needs [1,33,34]. This study tests community-based interventions to improve household disaster literacy and community awareness of these specific needs while using the population's resilience to improve community response.

Like related studies, we expect to find statistically significant improvements in mobility, preparedness, collaboration between response organizations, community involvement, and self-efficacy will be demonstrated. For example, this project is similar to the Japan Earthquake project, providing support for older adults. Miyadera et al [35] in Japan conducted a quasi-experiment trial of 89 older adults aged 65 years or older that targeted improvements in physical activities in daily life. The older adults' quality of life was significantly improved ($P<.01$, effect size 0.51) when focused program interventions were administered. Ashida et al [36] studied 194 members in a Midwestern community. After an Emergency Network Form was completed with assistance, they found statistically significant gains in nonfamilial networks and emotional support.

Limitations and Strengths

Limitations of this study include self-reporting surveys, which are subjective, with no control group to assess if the interventions influenced participants. Randomization was not used in this convenience sample. Isolated community-dwelling older adults are difficult to reach, resulting in a population already prone to action during disasters and not the general population.

Strengths include support from emergency managers, public health departments, disaster response agencies, faith-based organizations, and regional governmental organizations. The overarching respect and noted value of this population in all study endeavors results in community inclusion and interaction. The acceptance and feasibility of this study occurring in their own communities allows participation from community-dwelling older adults that is often overlooked.

Conclusion

Disaster preparedness of community-dwelling older adults is a priority for many organizations in the United States. Research on the effectiveness of interventions to improve older adults' safety before, during, and after disasters is lacking. This protocol describes an all-encompassing project to improve postdisaster outcomes by addressing mitigation, preparedness, response, and recovery factors that influence disaster outcomes for this population. Further research needs to be conducted in this area with this population.

Acknowledgments

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Authors' Contributions

SWL, JL, AG, KS, JC, and SC contributed to conceptualization. JL and SC performed data curation. SWL, JL, AG, KS, JC, and SC conducted formal analysis. SWL managed funding acquisition. SWL, JL, AG, KS, JC, and SC performed an investigation. SWL, JL, AG, KS, JC, and SC performed the methodology. SWL, JL, AG, KS, JC, and SC handled project administration. SWL, JL, AG, KS, JC, and SC managed resources. SWL, JL, AG, KS, JC, and SC performed supervision. SWL, JL, AG, KS, JC, and SC conducted validation. SWL, JL, AG, KS, JC, and SC performed visualization. SWL, JL, AG, KS, JC, and SC wrote the original draft. SWL, JL, AG, KS, JC, and SC performed writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Your Very Personal Preparedness Inventory.
[PDF File (Adobe PDF File), 2273 KB - resprot_v13i1e58895_app1.pdf]

Multimedia Appendix 2
Your Guide to Emergency Preparedness in the Greater Kansas City Region.
[PDF File (Adobe PDF File), 8929 KB - resprot_v13i1e58895_app2.pdf]

Multimedia Appendix 3
My Communication for Disaster Recovery.
[PDF File (Adobe PDF File), 116 KB - resprot_v13i1e58895_app3.pdf]

Multimedia Appendix 4
My Action Steps to Avoid: Disaster Recovery Scams.
[PDF File (Adobe PDF File), 164 KB - resprot_v13i1e58895_app4.pdf]

Multimedia Appendix 5
Seminar presentation.
[PPTX File , 30895 KB - resprot_v13i1e58895_app5.pptx]

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Abbreviations

ADEPT: Assessment for Disaster Engagement with Partners Tool

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FEMA: Federal Emergency Management Association
GSES: General Self-Efficacy Scale
TUG: Timed Up and Go test

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Protocol

Incentivizing Rural Work Preferences Among Specialist Physicians: Protocol for a Discrete Choice Experiment

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Abstract

Background: Retaining specialist physicians in rural parts of India poses a fundamental challenge, which affects the health care system's functionality and provision of standard health care services. There has been an acute shortfall of specialist physicians in the fields of medicine, pediatrics, obstetrics and gynecology, and surgery at rural community health centers. This necessitates urgent policy focus to address the shortages and design effective rural retention strategies. In this study, which uses a discrete choice experiment (DCE), individuals choose from multiple-choice preferences that resemble hypothetical job descriptions.

Objective: DCEs are a quantitative approach to assessing several aspects of job selection. This study aims to develop a detailed plan of a DCE method used to determine specialist physicians' job choices. This protocol outlines the DCE method, which uses an exploratory sequential mixed methods research design to understand specialist physicians' preferences and design reward packages that would effectively motivate them to work in underserved regions.

Methods: The qualitative phase of the study involved identifying job attributes and their corresponding levels for the DCE. We followed a meticulous process, which included reviewing relevant literature, performing qualitative pilot work, conducting in-depth individual interviews, and consulting with medical and health experts. The quantitative phase involved generating a D-efficient orthogonal fractional factorial design using Ngene software to create choice scenarios using the identified job factors and their corresponding levels. The generated choice scenarios were blocked into 6 versions in 6 blocks. The DCE was undertaken among final-year postgraduate medical residents and specialist physicians from several health care facilities in Rajasthan. Various statistical models will be applied to explore the response variability and quantify the trade-offs that participants are willing to make for nonmonetary features as a substitute for adjustments in the monetary attribute.

Results: After the ethics committee's approval of the study, the qualitative data collection phase occurred from September to December 2021, while the quantitative phase took place from May to August 2022. Six attributes and 14 levels were identified and established through qualitative surveys. The experimental design resulted in 36 choice situations, which were grouped into 6 blocks. The preliminary investigation demonstrated that the instrument was valid and reliable. Statistical data analysis has been initiated, and the principal findings are expected to be disseminated in January 2025.

Conclusions: The protocol provides a systematic framework to assess specialist physicians' preferences regarding working in rural health care centers. This research has the potential to substantially influence the future of rural health care by laying the foundation for understanding specialist physicians' choices, which will help design future incentive schemes, policy interventions, and research.

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KEYWORDS

discrete choice experiment; specialist physicians; community health centers; rural retention; policy interventions

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Introduction

Background

Several low- and middle-income countries (LMICs) experience massive deficits and uneven distribution of health care workers. This matter has been additionally exacerbated by the collapse of health care systems in LMICs and the global policy climate [1]. To attain the objective of universal health coverage, the supply of health care workers should be improved, alongside an effort to improve their distribution, accessibility, performance, and productivity [2]. However, such attempts are severely compromised by a lack of health care professionals motivated to practice in rural locations in LMICs [2]. To achieve the objective of universal health coverage in 2030, a total of 54 million health care workers are still needed, based on the recommendation by the World Health Organization of having 44.5 health care workers per 10,000 people [2]. According to the World Health Organization estimate, there was a global shortage of 17.4 million health care workers in 2013, of whom 2.6 million were physicians. Achieving the United Nations' Sustainable Development Goal 3 of ensuring good health and well-being for all necessitates addressing the addressing the significant financial and policy implications of the dearth of health care professionals [2], particularly specialist physicians, in rural regions [1].

Rising Attrition of Specialist Physicians in the Rural Public Health Sector: Indian Context

The availability of human resources (HR) is among the top crucial requirements for the effective operation of rural health services [3]. In India, the majority of health professionals are located in metropolitan areas, resulting in a severe scarcity of health care providers for the rural population [4]. Factors such as poor governance and underinvestment in the public health system in rural areas drive health workers to migrate to urban areas in search of better salary structures, good living conditions, proper working environments, better accessibility to use equipment and educational facilities for children, and greater transparency in HR policies [4-9]. International outmigration of health professionals also dramatically impacts the domestic health workforce's availability [10]. Prior research has demonstrated that physicians raised and educated in cities were unwilling to take rural postings. The primary reasons attributed to their choice (an unwillingness to work in rural areas) were the limited scope of occupational growth opportunities, a lack of accountability, issues with access to the necessary medical resources needed to perform their jobs adequately, and the absence of appropriate work policies in the health system [11]. To improve the retention rates of specialist physicians in the rural health system, it is necessary to implement strategies that involve regular rotations between rural and urban job placements [11]. In addition, other factors such as intermittent electricity, poor road connectivity, an unreliable public transport system, and inadequate educational facilities also discourage specialist physicians from relocating to rural and remote regions, which is evident from the substantial number of vacant jobs [1,12-16]. A recent study revealed that specialist physicians were willing to relocate from rural community health centers (CHCs) to towns, cities, or district headquarters to live with their families [17].

Specialist Physicians in the Rural Health Care Sector: Status as of March 31, 2022

In the Indian public health care sector, many sanctioned positions remain vacant, especially for specialist physicians at rural CHCs [3,4]. The country is grappling with a shortage of specialist physicians in rural CHCs, estimated at 79.5% according to the Rural Health Statistics Report 2021-2022 [3]. The Ministry of Health and Family Welfare has been facing persistent challenges in ensuring the availability of specialist physicians at most of the rural CHCs across the country. As of March 31, 2022, only 541 out of India's 5480 operational rural CHCs had all 4 specialist physicians [3]. Throughout the past few decades, the Ministry of Health and Family Welfare and the Department of Health and Family Welfare (at the state level) have used a range of measures to retain staff in different Indian states [11]. These retention strategies have included mandatory rural postings, linking postgraduate program enrollment to rural positions, and offering specific financial incentives [11]. However, there is still a lack of information on acquiring a more comprehensive understanding of the evidence-based strategies required to resolve this issue further and design potential solutions.

The statistics on the vacancies of specialist physicians at rural CHCs are presented in Table 1.

The specialist physicians' shortage profoundly impacts the distribution of rural health care services in the nation [3,4]. Their limited availability and uneven allocation in rural CHCs can lead to higher rates of newborn and maternal fatalities, contributing to a more significant burden of disease [17]. Thus, addressing vacancies in the public sector necessitates immediate policy focus [4] to guide essential policy measures to enhance the delivery and administration of health care services in rural areas.

Table 1. Vacancies of specialist physicians at rural community health centers (CHCs; N=10,000)[a].

Area of specialty	Nationwide vacancies at rural CHCs, n (%)	Vacancies as per infrastructural requirements at rural CHCs, n (%)
Medicine	6750 (67.5)	7910 (79.1)
Surgery	7190 (71.9)	8320 (83.2)
Pediatrics	6970 (69.7)	8160 (81.6)
Obstetrics and gynecology	6300 (63)	7420 (74.2)

[a]Source: Rural Health Statistics Report 2021-2022 [3].

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The Use of Discrete Choice Experiments in Health Workforce Research

Discrete choice experiments (DCEs) were first used in market research, transportation, and environmental economics and later applied to investigate outcomes of interest in health care [18-22]. The DCE methodology identifies health workers' preferences for a job based on its attributes. It is valuable for policy makers seeking to examine the most effective combinations of incentives or policy choices to promote health workers' employment in underserved regions, particularly rural regions [9,23,24].

This protocol provides a detailed research method for a DCE, which will be used to quantify specialist physicians' preferences for rural job incentives in Rajasthan. Rajasthan is among India's largest states, considering its geography and cultural diversity [25], and it is currently facing a massive shortage of specialist physicians at rural CHCs [3].

Research Objectives

The study will investigate the motivational job attributes valued by final-year postgraduate residents, who exhibit a higher propensity to quit their occupations and stay for shorter durations in rural areas, and specialist physicians, given the huge number of vacancies in the public health system. This will help policy makers understand the behavioral choices influencing and shaping specialist physicians' decisions to accept rural postings. The study will specifically address the following research objectives:

1. To identify the significant job attributes valued for working in rural CHCs in Rajasthan
2. To identify the number of monetary incentives or job attributes traded off for other nonmonetary incentives or job attributes for working in rural CHCs in Rajasthan through willingness-to-pay (WTP) analysis
3. To develop incentive packages to increase the attraction and retention of specialist physicians in rural CHCs in Rajasthan as part of a retention strategy

Methods

Research Design

The study research method used an exploratory sequential (qualitative+quantitative) mixed methods research design [26] to assess the incentive preferences and motivations of final-year postgraduate medical residents and specialist physicians to work in rural CHCs in Rajasthan. The survey tool for the study was constructed in 2 phases: qualitative and quantitative. The research design for the study protocol is provided in Figure 1.

Figure 1. Summary of the discrete choice experiment (DCE) research design. KI: key informant.

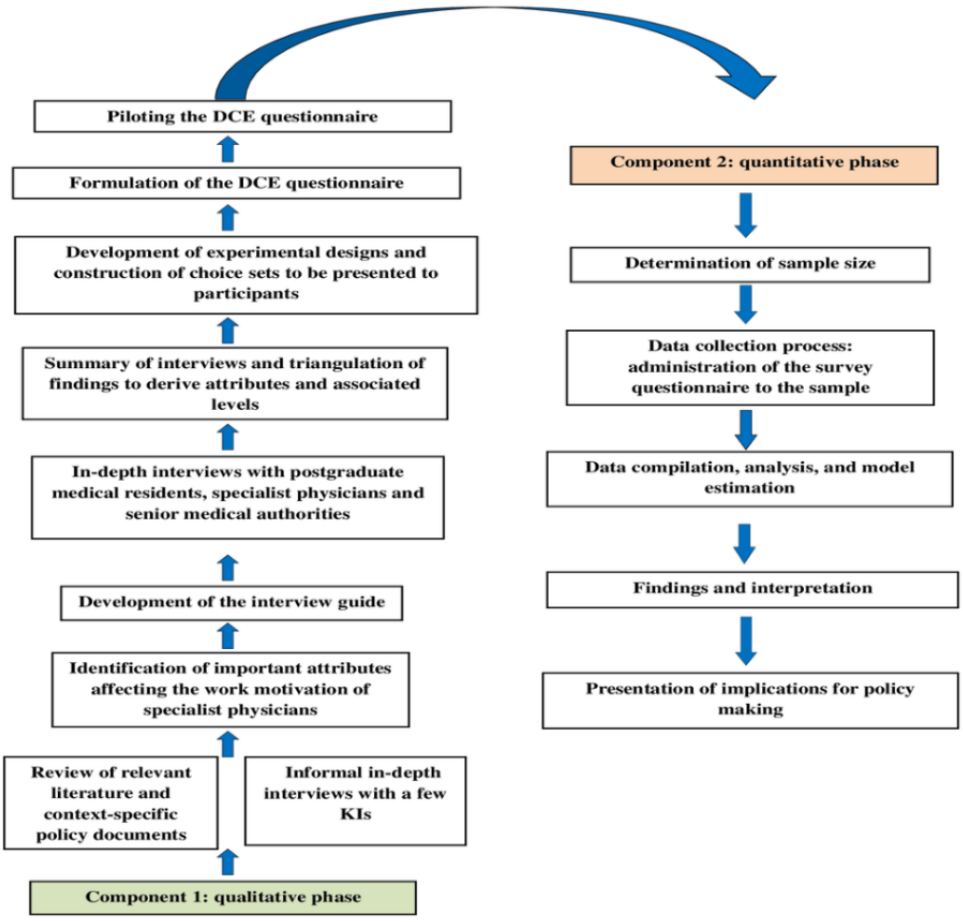

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Overview of DCEs

DCEs are a precise and quantifiable method for gathering choices [9,27]. They are rooted in the theory formulated by Lancaster [28], which posits that commodities and services may be characterized by their fundamental properties, and the merit they hold for an individual is decided by a blend of these features. This approach involves providing participants with various choice profiles resembling hypothetical job alternatives and asking them to make selections. Every profile has multiple attributes that describe the job alternatives, and each attribute has multiple potential levels. Job descriptions are commonly merged to form decision sets, where participants are directed to pick the most appealing work profile. The analysis of participants' selections among several alternatives allows for determining the relative significance of these attributes [22].

DCE and the Theoretical Framework

The DCE method is theoretically based on random utility theory, where individuals are reasonable decision makers with perfect discrimination ability to maximize utility relative to their choices [9,24,29].

The equation presented after this paragraph shows how the perceived value of an option (i) in a set of choices (C_n) for an individual (n) is broken down into 2 parts. First, there is a systematic component, which depends on the attributes of the options $V(X_{in}, \beta)$. Second, there is a random component (ε_{in}), representing variations in preference that are not accounted for. This approach facilitates the incorporation of variations in desires across individuals, which can impact their decision-making.

$$U_{in} = V(X_{in}, \beta) + \varepsilon_{in} \quad \textbf{(1)}$$

In the DCE method, it is assumed that an individual (n) will pick option (i) only if it provides the highest utility compared to all other options in the set (C_n). This logical decision-making process ensures that the chosen option truly offers the most value to the individual:

(2)

where y_{in} is a choice indicator equal to 1 if alternative i is chosen and 0 otherwise.

Study Settings

Rajasthan, located in India's western region, is one of the country's largest states in terms of geographic area. It spans 342,239 square kilometers, accounting for 10.4% of the country's total land area [25]. It is home to 68.6 million people, representing 5.7% of India's population. The state comprises 33 districts and 44,672 villages, with 75.13% of the population residing in villages [25,30]. Rajasthan faces an HR scarcity, with a shortage of 1939 specialist physicians for the 616 functioning CHCs [3]. In 2019, Rajasthan's health system had only 22.02% (25,056/113,742) of the required physicians (both general and specialist) [31]. Hence, the scarcity of specialist physicians, particularly in the rural regions of Rajasthan, is a significant issue that hampers the efficient provision of health care services in such areas [32].

Development of the DCE

To develop the DCE for the study, published recommendations in the literature were followed, including identifying criteria for acceptable research methodologies [33-36], implementing the suggestions on constructing the study's design [36-39], and adhering to guidelines on the appropriate statistical methods [40].

Phase 1: Qualitative Phase

One crucial aspect of building a DCE is determining the subject matter's pertinent qualities. Attributes are usually identified by collecting primary and secondary data to customize the DCE for the specific study environment [34].

Identification of Job Attributes and Allocation of Associated Levels

To guide the selection of job attributes and their associated levels in a DCE, an extensive examination of existing literature and the use of qualitative methods of inquiry is advisable [23]. An attribute is a characteristic that describes a product, treatment, or decision. Levels are allocated to each attribute to define its range. Identifying attributes and their associated levels is vital for formulating job choices and designing the survey questionnaire, essentially guided by insights gained through qualitative research [23]. However, including excessive attributes and levels may overwhelm participants, impairing their decision-making abilities and potentially biasing the results. Qualitative research plays a significant role in defining attribute levels that are both pertinent and actionable for policy purposes [23,41]. Attributes and levels for DCE design were developed following the procedure outlined in recommended literature [34-39].

Development of the Interview Guide

To initially explore and identify key themes associated with the challenges of retaining specialist physicians in rural areas, an exploratory pilot investigation was conducted in Rajasthan to develop a semistructured interview guide [23]. The interview guide was developed in 2 phases. In the first phase, 8 key informants (KIs) were interviewed. These KIs consisted of a group of second- and third-year postgraduate medical residents, specialist physicians working in rural and urban CHCs, and other medical experts. In the second phase, expert consultations and open-ended interviews were conducted with senior administrative authorities, including health officers as well as directors and joint directors of state health institutions, to check and confirm the themes and the major rural retention challenges existing in the real-life situations. This guide was also informed by a review of relevant literature on health HR and various policy documents. This inquiry helped in building out new themes and reviewing and modifying the existing themes resulting from an emergent research design. The pilot testing allowed us to refine and assess the questions' clarity and wording, as well as the effectiveness and appropriateness of the content in the interview guide. The final interview guide (Multimedia Appendix 1) encompassed topics related to individual job circumstances and experiences, the professional

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demands of the workplace, factors influencing the choice between rural and metropolitan settings, and instances of both satisfaction and dissatisfaction reported by participants. The guide also contained the relevant probes needed to elicit the desired information.

Sampling and Raw Data Collection

Using the semistructured interview guide, 21 telephone in-depth interviews were conducted in Rajasthan to attain data saturation. The interviews involved a varied cohort comprising specialist physicians; postgraduate medical residents; specialist physicians from the fields of medicine, pediatrics, surgery, obstetrics and gynecology (OB-GYN); and senior medical authorities with extensive experience in the public health care sector spanning 25 to 30 years. A purposive sampling technique was adopted to choose participants from several districts in Rajasthan, such as Sikar, Jhalawar, Jodhpur, Bikaner, Jaipur, Bhilwara, Jhunjhunu, and Nagaur. The choice of these districts was made to include a wide variety of geographic areas and work environments to maximize the diversity of the data. Of the 21 interview participants, 15 (71%) were male, and 6 (29%) were female; furthermore, 2 (10%) were retired senior medical officials with 25 to 30 years of experience in the field, 9 (43%) were specialist physicians employed at rural CHCs, 6 (29%) were specialist physicians employed at government district hospitals, and 4 (19%) were postgraduate medical students. To ensure data quality, notes were taken during the interviews to keep track of the information. The selection of participants from these specific specialty areas was deliberate because there existed a notable scarcity of specialist physicians within the state's public health infrastructure.

Data Analysis

The interviews were transcribed from recorded conversations in the native language, and transcripts were meticulously analyzed using ATLAS.ti software (version 7.5.18; ATLAS.ti Scientific Software Development GmbH) [42]. Open coding was performed to identify the major concepts and themes emerging from the in-depth interviews. The codes were grouped into discrete clusters for each transcript and constantly compared across all transcripts. Simultaneously, memos were drafted to document the participants' descriptions, together with the feelings, interpretations, and reactions that they associated with ongoing occurrences in their present lives.

Establishing the List of Job Attributes and Associated Levels

An important focus of a DCE is to thoroughly examine the optimal number of attributes in the pilot study because including too many attributes and levels may lead participants to use simplistic decision-making processes. This could result in information overload, which can create a cognitive burden and lead to inaccurate assessments of trade-offs. In studies addressing labor challenges in LMICs, the number of attributes has typically ranged from 5 to 8, with 8 being the highest [43-45].

An open coding process was used to examine and organize the job attributes, revealing the following predominant themes across all interview transcripts: physical working conditions, the structure of residential quarters, HR policies in the health system, salary and related rural financial schemes, skill development training, children's schooling and the provision of recreational activities, transportation facilities, sanctioned staff capacity at rural CHCs, and health center locations. These themes were further narrowed down into categories to generate job attributes, and the analysis of the characteristics and range of these categories resulted in the creation of the associated levels for each attribute.

To determine the attribute levels for a DCE, several authors [38,46-50] have suggested incorporating fewer levels for each attribute to minimize measurement error. On the basis of the provided information and the established norms in the research field, 2 or 3 levels for each attribute were included.

An extensive iterative process, followed by a ranking procedure, was used to generate a final list of potential job attributes and their corresponding levels as identified by the participants (refer to the Results section), with the attributes and associated levels ranked by them in ascending order of relevance. This was further examined and discussed with the KIs to strengthen the accuracy and trustworthiness of the findings.

In addition, peer debriefing sessions were conducted within the research team to validate the final list of attributes and levels. Through a process of consensus, a definitive set of attributes, along with their associated levels, were determined. Finally, the participants were again asked to express their expectations regarding the impact of each attribute on their choice of rural job preferences. These preexisting expectations were later used to assess the theoretical validity of the questionnaire in subsequent stages. The insights gathered at each stage informed the next stage, specifically regarding triangulating the data collected across different phases [49,50].

Phase 2: Quantitative Phase

Overview

The quantitative phase of the study involved constructing choice sets by combining various job attributes and their corresponding levels using different experimental designs. This process required the generation of different statistical experimental designs to optimize D-efficiency, maximize level balance and orthogonality, and minimize the estimated SEs across the parameter estimates for the job attributes [23,51]. Using Ngene software (version 1.3; ChoiceMetrics), different experimental designs were constructed to create choice sets for the study [23,51].

Number of Choice Sets

To proceed, hypothetical employment options, consisting of various combinations of attributes and their associated levels identified as relevant, must be created and offered to participants. [13,23]. Most health workforce studies suggest using between 7 and 16 choice sets as a feasible range [34].

In this study, we administered 15 choice sets to each participant, a quantity considered to be sufficiently minimal to prevent excessive cognitive burden while still providing high statistical precision.

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Developing an Experimental Design: Blocking and Choice Set Creation

The next phase in developing an experimental design involves determining the choice sets and applying blocking. Blocking, a technique commonly used in DCEs, entails partitioning lengthy experimental designs into groups of equal magnitude [47,51].

Initially, a comprehensive factorial design was generated, resulting in 144 potential choice scenarios (10,296 potential choice tasks) by considering various combinations of job attributes. However, due to practical constraints, presenting so many choice situations to participants was deemed impractical. Therefore, a fractional factorial design of 24 choice scenarios with different D-errors on repeated runs was created. To ensure that the statistical requirements of orthogonality, attribute-level balance, and minimal overlap were met, a simultaneous orthogonal fractional factorial design [51] comprising 36 choice scenarios was developed and optimized to minimize D-error.

Next, a blocked orthogonal fractional factorial design [51] was used to organize the 36 choice scenarios into 6 blocks. Each block contained 6 hypothetical job scenarios to be presented to participants. Subsequently, a mathematical pairing of scenarios was conducted using a pair-wise design, resulting in the development of 90 unique choice sets divided into 6 blocks, each containing 15 (17%) distinct choice sets. We used a randomization technique to randomly assign participants to 1 of the 6 blocks, with each receiving 15 choice sets to respond to. Before being incorporated into the survey tool, all choice sets underwent thorough evaluation for relevancy. Each choice task comprised an unlabeled design featuring 2 work profiles, “Job 1” and “Job 2,” without specifying whether they were rural or urban. Furthermore, a general opt-out alternative was included in the questionnaire to enhance accuracy and minimize errors in parameter estimations [23]. In addition, 2 supplementary dominance choice sets were included to serve as rationality or internal consistency checks in the final questionnaire version, where 1 alternative outperformed the other in every domain and was anticipated to be selected by a reasonable decision maker. Participants who did not pass the dominance tests were excluded from the final analysis.

Attribute-Level Balancing

Attribute-level balancing ensures that each level of an attribute is equally represented in the experimental design [33-36,47]. When creating choice sets, it is essential to consider how the levels of attributes are distributed. Care was taken when designing choice sets using Ngene software [51] to ensure maximum attribute-level balance through the use of the correct algorithms outlined in the software manual.

DCE Survey Instrument Design

Creating a comprehensive survey instrument for a DCE involves interconnected assessments centered on attribute identification and selection, experimental design construction, and decision environment considerations [35]. The DCE survey instrument aimed at presenting participants with various job scenarios across different choice sets and eliciting their preferences based on changing job characteristics. The survey introduction included the study topic, the researcher’s name and institute, the study objectives, and the intended use of the results. The survey was divided into 3 main sections:

- Section 1 presented different choice sets, each containing hypothetical job situations with varying attributes, such as workplace infrastructure, salary, staffing levels and workload at CHCs, residential facilities, workplace location, and transfer and promotion policies. Each choice set included 2 job alternatives labeled “Job 1” and “Job 2,” allowing participants to compare and choose between them.
- Section 2 featured a mix of subjective and objective questions to encourage participants to express their opinions briefly on the issues and factors influencing their expectations and decisions regarding rural postings.
- Section 3 gathered sociodemographic information about the participants, including personal details and relevant socioeconomic variables.

Piloting the Survey Questionnaire

In accordance with econometric guidelines [23], a pilot study was undertaken with a sample of 30 (71%; female: n=12, 40%; male: n=18, 60%) participants out of 42 recruited participants to assess their comprehension of job attributes and associated levels, as well as their level of engagement in responding to the choice tasks provided. On the basis of the feedback received, there was minimal necessity to alter the attributes, levels, or questions presented. Nevertheless, minor alterations were implemented to the demographic profile component of the questionnaire, and an additional segment was introduced to evaluate participants’ socioeconomic status. Furthermore, the quality control of the pilot questionnaire was evaluated through various validity and reliability assessment methods along with the feedback forms [47,52]. Of note, these 30 participants involved in the pilot study were not included in the final data collection sample.

Validity and Reliability of the Design

In this study, the evaluation of the instrument design’s dependability and accuracy was comprehensive, with 7 methodologies used based on the proposed criteria [46,47] (Figure 2). These methodologies were chosen with the specific purpose of assessing the measurement validity of the design [46,47]. Content validity was initially addressed by formulating attributes and associated levels using precise qualitative techniques, such as conducting in-depth interviews. This ensured the inclusion of significant characteristics and levels for most participants. Later, during the in-depth interviews, participants were asked about their expectations regarding the influence of each level on individual preferences. This was considered a preexisting preference expectation and was analyzed to test the direction of the coefficients [46,47].

Two tests were used to check the reliability of the measurement. Test-retest reliability was used to evaluate the consistency of the participants’ responses throughout the survey, where the participant was presented with the same choice problem again, known as a repeat-choice task. The stability was evaluated based on the ratio of individuals who responded consistently across the repeat-choice tasks [53,54]. To assess the consistency of the

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versions, a fixed-choice problem was incorporated into the design, which was kept consistent throughout all 6 blocks.

To assess the design's choice validity, a within-set monotonicity test was incorporated to evaluate whether participants preferred inferior levels of a characteristic over superior ones [55,56].

The second test, task nonattendance, identified individuals who consistently selected profiles from 1 specific alternative across all choice sets, considered task nonattendance [55,56].

To evaluate the reliability of the choices, we used the consistency test proposed by Sen [56], which comprises 2 principles: the expansion and contraction principles [23,55]. The expansion principle involved an initial task with 2 options ("Job 1" and "Job 2"), followed by a subsequent task with 3 options ("Job 1," "Job 2," and "None of the above"). The expansion feature is satisfied when a participant who selects "Job 1" does not choose "Job 2" in the subsequent challenge. The contraction principle was applied by presenting participants with an initial choice task consisting of 3 options ("Job 1," "Job 2," and "None of the above"), followed by a subsequent test with 2 options ("Job 1" and "Job 2"). The contraction feature is satisfied when a participant who first chose "Job 1" in the choice task also selects "Job 1" in the subsequent task. The final analysis did not include participants who were absent throughout the task and did not respond coherently to the dominant alternatives. This procedure was essential to guarantee the precision and dependability of the findings, resulting in a final pilot sample size of 30 (71%) participants out of 42 recruited participants

Figure 2. Tests for assessing the reliability and validity of the instrument.

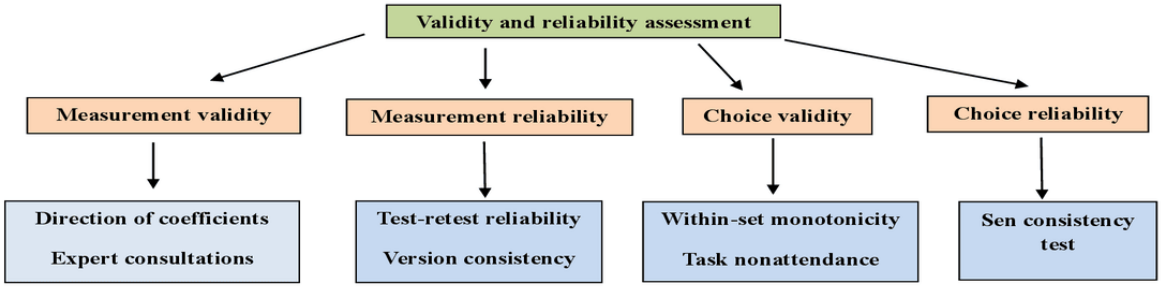

Study Population and Eligibility Criteria

Once the pilot study was completed, the proposed survey was administered to 2 groups of participants. The first group included final-year medical residents undergoing postgraduate specialty training in medicine, pediatrics, surgery, and OB-GYN at government and private medical colleges in Rajasthan and preparing to enter the health care industry. The second group consisted of specialist physicians who had been working in rural CHCs in Rajasthan for 6 to 7 years.

The selection of participants for the study considered both geographic and sex diversity. The age range of participants, spanning from >30 years to ≤50 years, was intentionally varied to encompass both young postgraduate residents and older individuals who embarked on postgraduate training later in their careers. This diverse age distribution was maintained to investigate how evolving priorities throughout the life course influence motivations to work in rural health care settings.

Participants aged >50 years were excluded from the study. In addition, we excluded health professionals from other disciplines, such as nurses, midwives, paramedical staff, laboratory technicians, and specialist physicians from other specialties, who were employed at rural health facilities within the state. Furthermore, the study did not include specialist physicians in medicine, pediatrics, surgery, and OB-GYN working at rural CHCs who had pursued Diplomate National Board certification.

Sample Size and Recruitment

A multistage stratified random sampling method [57] was used to recruit 156 participants from various government and private medical facilities and rural CHCs in Rajasthan, following the sample size calculations recommended for DCEs.

In research focusing on individual choices in DCEs, sample size determination typically follows the rule of thumb [35,58-63]. According to this rule, the predicted sample size is the minimum feasible quantity [58,59]. The rule of thumb proposed by Johnson and Orme [60,61] suggests that the sample size required for main effects depends on the number of choice tasks (t), the number of alternatives (a), and the number of analysis cells (c), as per the equation: $N > 500 \times c / (t \times a)$. For this study, with t=90 (total choice tasks), a=3 (alternatives: "Job 1," "Job 2," and "Unable to decide"), and c=3 (the largest number of levels for any attribute), the minimum sample size was determined.

In addition, it is recommended to include at least 20 participants per questionnaire version to estimate reliable choice models [35,62,63]. Following these guidelines for DCEs [35,58-63], a minimum sample size of 120 participants was required to cover the 6 questionnaire versions.

Data Management and Statistical Analysis

The survey data from both participant groups were combined for quantitative analysis. The responses from the 156 participants will be assessed using Stata (version 17.0; StataCorp LLC) [64]. Digital data security measures were implemented, including encryption and restricted access.

The utility function incorporated predictor variables representing 6 job attributes, informed by the qualitative design of the DCE. Participants' choice behavior regarding job acceptance at rural locations is the outcome variable, categorized into "Job 1" and "Job 2." Participants' choices will be evaluated based on various

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demographic and socioeconomic factors to assess their impact on decision-making.

In the DCE analysis, the probability of choice will be modeled as a function of job attributes. The effect size of each attribute will be determined by beta coefficients while controlling for other predictors at a 5% significance level. These coefficients will elucidate the individual contribution of each predictor to the model, indicating the magnitude of its impact on choice behavior when adjusted for other attribute levels and covariates.

Various statistical models (conditional logit model and fixed effects and random effects panel logit models) will be used to calculate the outcome measure. Predictor variables and covariates will be systematically entered into the regression equation based on their predicted importance.

The coefficients table for levels and covariates will be presented alongside relevant statistical measures, such as pseudo-R^2, log-likelihood test, and the Akaike information criterion, to evaluate the model's goodness of fit. Apart from the main regressions, calculations for WTP will be conducted for attribute levels. WTP quantifies the salary a participant is prepared to forgo to obtain a higher level of another job attribute, determined by the ratio between the coefficients of nonmonetary and monetary attributes [23]. This measure offers valuable insights to inform policy decisions [23,65-68].

Ethical Considerations

The research obtained approval from the institutional ethics committee of the Indian Institute of Public Health Gandhinagar (TRC/2021-22/14). Administrative permission was granted by the Secretary of the Department of Medical, Health & Family Welfare and the Department of Medical Education, government of Rajasthan.

Due to the COVID-19 pandemic, participants recruited for the initial phase received the consent form and information sheet on the web before the qualitative interviews. They provided verbal consent for participation and recording during this phase. Telephone interviews were conducted attentively, with participants informed of their right to end the conversation at any time. For the second phase, involving the quantitative survey, participants provided written informed consent. Distinct codes were used for participant identification to maintain confidentiality. The study adhered to ethics guidelines and ensured the confidentiality of all participants.

Results

Overview

The collection of qualitative data occurred between September and December 2021, followed by the quantitative data collection phase conducted between May and August 2022, using diverse recruitment methods. The selected attributes (and the number of associated levels) derived from the qualitative phase of the study included workplace infrastructure (2 levels); salary, including rural retention bonus (3 levels); staffing levels and workload (2 levels); residential facilities (3 levels); workplace location (2 levels); and transfer and promotion policies (2 levels; Table 2).

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Table 2. List of attributes and their associated levels in the discrete choice experiment.

Attributes and levels	Description
Workplace infrastructure	
1	Basic infrastructure
2	Advanced infrastructure
Salary (including rural retention bonus)	
1	Current government salary
2	Current government salary+25% increase in rural retention bonus
3	Current government salary+50% increase in rural retention bonus
Staffing levels and workload	
1	Fully staffed CHC with moderate workload
2	Understaffed CHC with heavy workload
Residential facilities	
1	Provision of well-developed residential quarters, not free of charge
2	Provision of substandard residential quarters with limited facilities, but free of charge
3	No residential quarters provided but house rent allowance provided
Workplace location	
1	≥30 km from the current place of residence or hometown (30-149 km)
2	≥150 km from the current place of residence or hometown (150-269 km)
Transfer and promotion policies	
1	Substantial more rational policies based on seniority or genuine personal and medical needs, along with time-bound promotions
2	Ad hoc policies based on current practices and norms

Construction of Choice Sets

Using a blocked orthogonal fractional factorial design, attributes and associated levels derived from the qualitative phase of the study resulted in a construction of 90 unique choice sets partitioned into 6 blocks, each containing 15 (17%) distinct choice sets. A sample of a choice set is provided in Textbox 1.

For the final data analysis, the sample comprised 156 individuals, categorized into 4 specialist physicians' groups: medicine (n=58, 37.2%), surgery (n=34, 21.8%), pediatrics (n=32, 20.5%), and OB-GYN (n=32, 20.5%). Statistical analysis of the data has been initiated, and the findings are expected to be disseminated in January 2025.

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Textbox 1. Sample choice set.

Job 1

- Workplace infrastructure: basic infrastructure
- Salary (including rural retention bonus): current government salary+50% increase in rural retention bonus
- Staffing levels and workload: fully staffed community health center (CHC) with moderate workload
- Residential facilities: provision of substandard residential quarters with limited facilities, but free of charge
- Workplace location: ≥150 km from the current place of residence or hometown (150-269 km)
- Transfer and promotion policies: substantial more rational policies based on seniority or genuine personal and medical needs along with time-bound promotions.

Job 2

- Workplace infrastructure: advanced infrastructure
- Salary (including rural retention bonus): Current government salary+25% increase in rural retention bonus
- Staffing levels and workload: fully staffed CHC with moderate workload
- Residential facilities: Provision of well-developed residential quarters, not free of charge
- Workplace location: ≥30 km or more from the current place of residence or hometown (30-149 km)
- Transfer and promotion policies: ad-hoc policies based on current practices and norms.

Which of these 2 jobs do you prefer?

- Job 1
- Job 2
- Unable to decide

Results of the Validity and Reliability Assessment

A preliminary investigation was performed using a conditional logit regression model, as mentioned in the existing literature on model specification [33,69]. The analysis was performed using Stata software (version 17.0) [64]. The results were analyzed using the beta coefficients and their related 95% CIs. A significance level of 5% was used. The model demonstrated a suitable fit for DCE (pseudo-R^2=0.09) [23,47]. The findings indicated that all job attributes except advanced workplace infrastructure and substandard residential facilities significantly explained the preferences for rural jobs (P<.05). The results aligned with the preexisting preference expectations, demonstrating the theoretical validity of the design (Multimedia Appendix 2).

The findings indicated that 71% (30/42) of the participants consistently selected repeat-choice tasks, suggesting satisfactory reliability throughout the pilot survey (Multimedia Appendix 3). It was further found that the design exhibits version consistency because there was no remarkable variation between the blocks in selecting alternatives for the fixed-choice tasks. Furthermore, the study revealed that 30 (71%) of the 42 participants made rational decisions by choosing the dominant alternative. As a result, the design's within-set monotonicity was confirmed. The task nonattendance rate was 29% (12/42), which is within an acceptable range for a DCE. Of the 42 participants, 30 (71%) based their selections on the consistency principles proposed by Sen [56], suggesting satisfactory decision reliability. Hence, the data from 29% (12/42) of the participants who were found to have not attended to the task were excluded from the final analysis due to inadequate information. Most of the participants concurred that the design was understandable (30/42, 71%) and that the questionnaire was easy to respond to (30/42, 71%).

Discussion

Summary

Investing in increasing the number and accessibility of the health workforce is currently the most crucial area in India requiring policy attention [4]. The protocol presented herein seeks to bridge this knowledge gap by addressing the significant shortage of specialist physicians, a critical segment of the health care workforce, informing future policy interventions in Rajasthan, one of India's largest states. This study uses a novel approach—DCE—to generate valuable, actionable, and policy-relevant data to improve the retention of specialist physicians in rural regions. Prior research on health HR in India has predominantly focused on general physicians, nurses, and midwives, while neglecting the importance of specialist physicians [5,7,70-72].

This study provides a thorough approach for performing a DCE and analyzes the findings of an initial survey conducted to assess the effectiveness of the study design before its complete adoption.

The pilot tests present a comprehensive overview of the essential procedures for determining job attributes and associated levels, generating choice sets, defining the utility model, selecting labeled and unlabeled choices, and implementing the design.

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This study used a diverse array of methodologies to assess the efficiency of the design. Attributes were identified throughout the qualitative phase of the study through a meticulous iterative procedure involving in-depth interviews. However, the qualitative analysis revealed unique characteristics and levels specific to the location [73,74], which may add bias to the findings when examined in the broader context. With the incorporation of various attributes and associated levels, several experimental designs were created using an orthogonal fractional factorial design to create choice sets that guaranteed orthogonality, balance, and little overlap between attribute levels. Generic label options were used to create choice sets. Although specific labeling more accurately reflects individual preferences and actual choices, generic labeling is preferable for analyzing the trade-offs among multiple characteristics [38].

The direction of the coefficients validates the theoretical validity, demonstrating that the instrument effectively assesses participants' choices [47,74] and that the attributes have been assigned appropriate levels, allowing for effective trade-offs [23]. Furthermore, the outcomes of the reliability and validity evaluations of the design indicate that it exhibits response efficiency [47].

By conducting a DCE, this study will serve as a cornerstone in providing a systematic and comprehensive understanding of several job characteristics, individual traits, and the importance of work incentives for specialist physicians in rural areas. This study's findings will inform and shape judicious policy measures concerning implementing attractive work incentive schemes to attract and retain specialist physicians in rural areas. This will allow policy makers and health care administrators to refine their strategies for managing attrition and talent migration, thereby facilitating the development of a policy evaluation framework and planning health care HR for the state.

Strengths and Limitations

The primary advantage of a DCE involves its experimental nature, which allows for recording participants' preferences under controlled experimental conditions, which helps to gain insight into how attribute changes affect individuals' choices. Second, the job attributes and their corresponding levels were produced by performing comprehensive and precise objective evaluations, enhancing the design quality and result validity. The study identifies a wide variety of job characteristics that can be modified and adjusted to suit the preferences of specialist physicians in different national and international scenarios. Furthermore, pilot research was conducted using established frameworks to develop a thorough strategy for designing and assessing the quality of the DCE instrument.

While DCEs offer benefits, their implementation presents numerous challenges. At first, the study provided participants with hypothetical work options developed using qualitative research to collect relevant attributes. By using experimentally determined hypothetical alternatives during qualitative interviews, it became feasible to examine the participants' "expressed preferences" rather than their "revealed preferences." Moreover, the primary constraints of DCE methodologies stem from the cognitive challenge posed by the intricate assortment of options presented in bundles that encompass numerous attributes and levels. This can present several intricate trade-off questions to optimize statistical efficiency. Furthermore, the DCE's distinct emphasis on specialist physicians guarantees that the results are particularly relevant to this group.

Dissemination of Study Findings

The results of this study will be shared through various platforms, such as scholarly journals that undergo peer review, conferences, and policy briefs. A concise summary of the findings will be made available to the participants on demand.

Future Directions

Further research is necessary to fully understand the broader context in which specialist physicians operate and the influence of the sociopolitical environment on their professional independence within the rural health care system to improve the retention and job satisfaction of rural specialist physicians. It is essential and equally important to further investigate and examine the factors that influence the uneven distribution and scarcity of female specialist physicians. To optimize the allocation of scarce monetary resources and conduct thorough assessments of policy initiatives, it is necessary to consider their costs, the accuracy of cost information, funding sources, and long-term sustainability. To comprehend the expenses linked to the policy intervention, a financial assessment of all resources used in executing the intervention is necessary.

Conclusions

This study offers a comprehensive process for building the DCE instrument and presenting the findings of instrument pilot testing. This study also demonstrated a unified and thorough framework that may be applied in future research endeavors. This study will be helpful in investigating the job factors needed to understand this issue thoroughly. Moreover, the study findings will aid in designing rural intervention packages, essential in promoting relevant policy measures to address the high turnover rates of specialist physicians in Rajasthan. In addition, it will offer valuable evidence to guide future policy interventions globally, facilitating the creation of incentive packages aimed at attracting and retaining specialist physicians in rural and underserved areas of LMICs.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AJ was involved in conceptualization, data curation, methodology, resources, software, formal analysis, investigation, and writing the original draft. JP contributed to the conceptualization and reviewing and editing the manuscript. AP provided input on conceptualization and reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[PDF File (Adobe PDF File), 166 KB - resprot_v13i1e59621_app1.pdf]

Multimedia Appendix 2
Conditional logit regression analysis (pilot survey).
[DOCX File , 24 KB - resprot_v13i1e59621_app2.docx]

Multimedia Appendix 3
Outcomes of reliability and validity assessments of the design.
[DOCX File , 20 KB - resprot_v13i1e59621_app3.docx]

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Abbreviations

CHC: community health center
DCE: discrete choice experiment
HR: human resources
KI: key informant
LMICs: low- and middle-income countries
OB-GYN: obstetrics and gynecology
WTP: willingness-to-pay

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Protocol

Evaluating the Impact of Assistive Technologies on Individuals With Disabilities in Benin: Protocol for a Cross-Sectional Study

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Abstract

Background: A significant proportion of individuals with disabilities in resource-limited countries require at least 1 assistive technology (AT) device to enhance their functioning and autonomy. However, there is limited evidence regarding the actual needs of AT users in these regions concerning the adequacy of ATs.

Objective: This research aims to assess the effects of ATs on AT users in a resource-limited country.

Methods: A cross-sectional study will be conducted in Benin, a sub-Saharan African country, using a nonprobability sample of AT users. Participants will undergo evaluation using standardized tools to assess their psycho-affective status, satisfaction with ATs, perception of the functional effects of ATs, well-being, and quality of life. Additionally, a survey based on the World Health Organization's rATA (rapid assistive technology assessment) tool will be conducted to gather sociodemographic and other data concerning the use of ATs. The findings will be organized and discussed using the Consortium on Assistive Technology Outcomes Research taxonomy, focusing on aspects related to the effectiveness and social significance of ATs, as well as the subjective well-being of AT users.

Results: The process of identifying potential participants began in August 2024, and data collection is scheduled to start in January 2025 and continue for 12 months.

Conclusions: This research will provide an overview of the effects induced by the use of ATs, as well as describe the profile of AT users in Benin. To our knowledge, this will be the first study to examine the impact of ATs in Benin. It will therefore make a significant contribution to the existing data on the use of ATs in sub-Saharan Africa.

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KEYWORDS

assistive technologies; assistive technology assessment; individuals with disabilities; disabilities; cross-sectional study; well-being; quality of life; effects; Benin

Introduction

The global population of individuals with disabilities is rapidly increasing, and assistive technologies (ATs) are emerging as substantial supports for these individuals [1,2]. ATs facilitate the social inclusion and involvement of people who are disabled [2], while also enabling them to maintain an optimal level of independence. Accordingly, the World Health Organization

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(WHO) has recognized access to appropriate ATs as a fundamental human right for all individuals who require them [2,3]. In 2022, a joint report by the WHO and the UNICEF (United Nations Children's Fund) estimated that over 2.5 billion individuals living with various disabilities required at least 1 AT to improve their functioning and autonomy [2]. Additionally, this report states that most of these individuals reside in low- and middle-income countries, particularly in sub-Saharan Africa [2]. Unfortunately, only a small percentage—ranging from 5% to 15%—of these individuals have actual access to ATs [4]. Based on a recent analysis of 252 studies carried out in resource-limited countries, the provision and supply of ATs appear to be disproportionately influenced by the type or function of the AT [4]. For instance, there appears to be a lower availability of ATs designed for hearing and communication compared to those designed for mobility [4]. The lack of financial resources and unstructured institutional policies are the main reasons for the observed issues with the accessibility and availability of ATs in these countries [4,5].

National and international nongovernmental charities are working to provide ATs to disadvantaged populations [2,6]. However, a significant proportion of these ATs are often misused or abandoned by beneficiaries due to insufficient consideration of their actual needs [2,6]. Similarly, there is limited literature on the impact of ATs on the quality of life (QoL) and well-being of users, especially in resource-limited regions.

It follows that it is essential to conduct comprehensive in-depth documentation of the effects of ATs to address concerns regarding the paucity of data on ATs.

Most conceptual frameworks or taxonomies designed to understand the effects of using ATs describe these effects as multifaceted and multidimensional, considering both the users and their environments [7]. For instance, the Consortium on Assistive Technology Outcomes Research (CATOR) provided a taxonomy that covers 3 broad domains—effectiveness, social significance, and subjective well-being—in which the impacts of ATs can be classified [8]. The domains of this taxonomy cover various objective and subjective aspects of an AT user's overall life.

Thus, ATs can help individuals with disabilities to perform daily tasks and personal care activities [2,3,9,10]. ATs can reduce the difficulties experienced by these individuals, improve their QoL, and broaden the range of useful and enjoyable activities in which they wish to participate [2]. For example, ATs such as wheelchairs and walking aids (canes or walkers) are designed to enhance mobility and promote accessibility for individuals with disabilities in various environments [11]. Moreover, ATs can reduce the workload of family caregivers of individuals who are disabled [12-14].

The advantages and disadvantages of ATs are generally assessed based on specific indicators that can predict the QoL and overall well-being of AT users [15,16]. These indicators include satisfaction [17], the psychosocial impact of AT use [18], and the perception of functional benefits [19]. Furthermore, they provide information on the opinions of AT users concerning their expectations regarding the use of AT. More specifically, they provide information on the impact of AT on users' daily lives per functional independence, performance, productivity, willingness to try new things, ability to take risks or take advantage of life's opportunities, self-confidence, and ability to adapt to life [19-21]. Numerous studies in high-income countries have used them to predict long-term AT use or AT abandonment [22-26]. In sub-Saharan Africa, very few studies have focused on some of the indicators described above [21,27,28].

To our knowledge, there is no data on the use of ATs in Benin, nor on such indicators, despite the increase in the number of people who are disabled recorded in successive censuses [29]. Thus, understanding the real needs of these individuals per the adequacy of ATs in this country remains a genuine challenge. This research aims to document the literature on this issue by evaluating these indicators among AT users in Benin.

Methods

Study Design, Participants, and Recruitment

A cross-sectional study will support this research project, using a nonprobability sample of AT users in Benin. The participants will be evaluated by multiple teams of recruiters, with two recruiters assigned to each department in Benin. Recruiters will be selected based on specific criteria: (1) being a health professional, (2) having experience in participant recruitment, and (3) fluency in French and one of the local languages spoken in the covered area. They will receive training on the questionnaires and assessment methods that will be used in this study. Participants will be identified through the Fédération des Associations des Personnes Handicapées du Bénin (FAPHB). FAPHB is a national network that brings together all associations of individuals who are disabled, whether they use ATs or not, residing in one of Benin's regions or departments. FAPHB maintains a register of individuals who are disabled and who are regularly identified as such. A formal request will be made to FAPHB to establish contact with those among them who use ATs. In addition, participants will be recruited from hospital rehabilitation units and community rehabilitation centers across various regions in Benin. Before recruitment, authorization will be requested from these centers. Textbox 1 displays the inclusion and exclusion criteria that will be followed.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Individuals with disabilities resulting from neurological, trauma, musculoskeletal or orthopaedical disorders, or visual or hearing impairments
- Be aged 18 years or older
- Daily use of 1 or more AT (eg, wheelchair, walking sticks, walking aid or walker, external prosthesis, hearing aid, visual aid, or orthosis) for at least 6 months
- Be able to complete questionnaires in French or participate in support interviews to complete them

Exclusion criteria

- Presence of preexisting psychological conditions before using ATs
- Use of ATs for a short period or irregularly

Sample Size

The planned sample size for this study was calculated using the Cochran formula with a margin of error of 5% and an unknown population of AT users. A total of 384 participants will need to be recruited to allow for the generalization of our future results. A description of how this estimate was calculated is provided in Multimedia Appendix 1. Given that there are 12 departments in Benin, a maximum of 32 potential participants could be recruited from each department. However, the number of participants to be recruited in each region will be weighted according to the density of each region. For example, in the most populous departments (ie, urban and semiurban cities), more than 32 participants could be recruited, and in the least populous departments (ie, villages and small cities), fewer than 32 participants could be recruited on an equitable basis to achieve the desired sample size.

Data Collection and Procedures

Once identified, AT users will be contacted by phone or met in person (at their homes or in rehabilitation centers) to receive a brief explanation of this study's project. Participants who wish to take part in this study will receive a detailed information letter describing this study's protocol. Assessments will be scheduled according to participants' availability and will last approximately 1 hour. Regular breaks will be scheduled to minimize the risk of fatigue during assessments.

First, a form will be used to collect sociodemographic data from participants, including age, sex, gender, and level of education, as well as information about their use of ATs.The form is based on specific items from the rATA (rapid assistive technology assessment) developed by the WHO and published in 2022. The goal of the rATA is to provide a quick assessment of the needs, demands, supply, and satisfaction of AT users [30].

Second, the participants will undergo assessment using standardized tools or methods to determine their psycho-affective status, satisfaction with the assistive devices, perception of the functional effects of the devices, well-being, and QoL. These outcome measures have been selected from among the most widely used worldwide, according to the different domains and subdomains of the CATOR taxonomy (Figure 1 [8]). The following section describes the selected instruments:

- Psychosocial Impact of Assistive Devices Scale (PIADS): The French version of the PIADS will be used in this study [31]. This 26-item self-report questionnaire aims to evaluate the effects of ATs on functional independence, well-being, and QoL [32]. It was developed in response to the need for a simple, reliable, and valid scale that could be applied generically to all categories of AT [25]. The PIADS is an appropriate instrument for developing and testing theories regarding the psychosocial factors that may influence the use of AT [25]. It is widely used in clinical and research settings due to its ability to detect major changes in the acceptability of ATs and to predict their cessation or discontinuation [22-24]. A recent systematic review has demonstrated the robustness of the PIADS, with satisfactory conclusions drawn regarding its psychometric properties, including content validity, structural validity, internal consistency, criterion validity, test-retest reliability, and construct validity [18]. It is composed of three subscales: Competence: 12 items describing the user's perceived functional capacity, independence, productivity, and performance [20,32]; Adaptability: 6 items that measure an individual's motivation to take risks, seize opportunities, and try unusual things [20,32]; and Self-esteem: 8 items reflecting self-confidence, feelings of power and control, and emotional well-being [20,32]. Each item is evaluated using a 7-point Likert scale, ranging from –3 for the most negative impact to +3 for the most positive impact. A score of 0 indicates no impact or change [32].
- Quebec User Evaluation of Satisfaction With Assistive Technology 2.0 (QUEST-2.0): It aims to measure satisfaction with a wide range of assistive devices and asks users how satisfied they are with the specific characteristics of their assistive device [17,33]. It comprises 12 questions, 8 of which assess the device's characteristics, including weight, size, length, width, fit, safety, durability, ease of use, comfort, and effectiveness [17,33]. The remaining 4 questions evaluate satisfaction with the service provided, including appliance maintenance and repair, professionalism, and follow-up [17,33]. Participant satisfaction with the AT used is evaluated on a 5-point scale, ranging from "not at all satisfied" to "very satisfied." Additionally, participants are required to select the three most important characteristics of the AT used. A recent systematic review assessed all available versions of QUEST,

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including QUEST 2.0, and concluded that it has good reliability and validity [17].

- Measurement of perceived functional benefit: The functional benefit of AT use will be measured according to the method of van der Heide and de Witte [19]. This will be based on the following 2 questions, using the visual analog scale graduated from 0 to 100. For example, if the AT involved is a wheelchair, the questions will be formulated as follows: (Q1) "How would you rate your ability to get around?" and (Q2) "Imagine you don't have a wheelchair; how would you rate your ability to move around?" The difference between the 2 scores obtained for these 2 questions (Q1 and Q2) represents the perceived functional benefit of using AT. A score of 0 indicates no perceived functional benefit. A score between 0 and 50 indicates a moderate perceived functional benefit, while a score of 50 or higher indicates a significant perceived functional benefit.
- Satisfaction With Life Scale (SWLS): The French version of SWLS [34] by Diener and colleagues [35] will be used. It consists of 5 statements measuring general satisfaction with one's own life on a scale of 1 to 7 points [34,35]. SWLS has demonstrated favorable psychometric properties, including construct validity, internal consistency, and reliability [35]. It is suitable for use with individuals of varying ages [35].
- Hospital Anxiety and Depression Scale (HADS): Anxiety and depression symptoms will be assessed using HADS, which comprises 14 items scored from 0 to 3. Seven questions relate to anxiety and 7 to depression, giving two scores with a maximum score of 21 [36]. HADS has also demonstrated good psychometric properties across different language versions [37].
- World Health Organization Quality of Life (WHOQOL-BREF): WHOQOL-BREF is one of the most used tools to assess a person's QoL. It consists of 26 questions and assesses 4 domains: physical health, mental health, social relationships, and environment [38]. The scores for the different domains should be considered separately, as this questionnaire does not provide an overall score [38]. WHOQOL-BREF is widely used in clinical and research settings due to its reliability and validity [38].

In the case where participants fail to respond to all questions on the various questionnaires, they will be contacted without delay to ascertain the reason for this and to update the data accordingly. Otherwise, their data will not be included in the analysis.

Figure 1. Selection of evaluation tools and methods based on the CATOR taxonomy. AT: assistive technology; CATOR: Consortium on Assistive Technology Outcomes Research; HADS: Hospital Anxiety and Depression Scale; ICF: International Classification of Functioning, Disability and Health; PIADS: Psychosocial Impact of Assistive Devices Scale; rATA: rapid assistive technology assessment; VAS: visual analog scale; WHOQOL-BREF: World Health Organization Quality of Life.

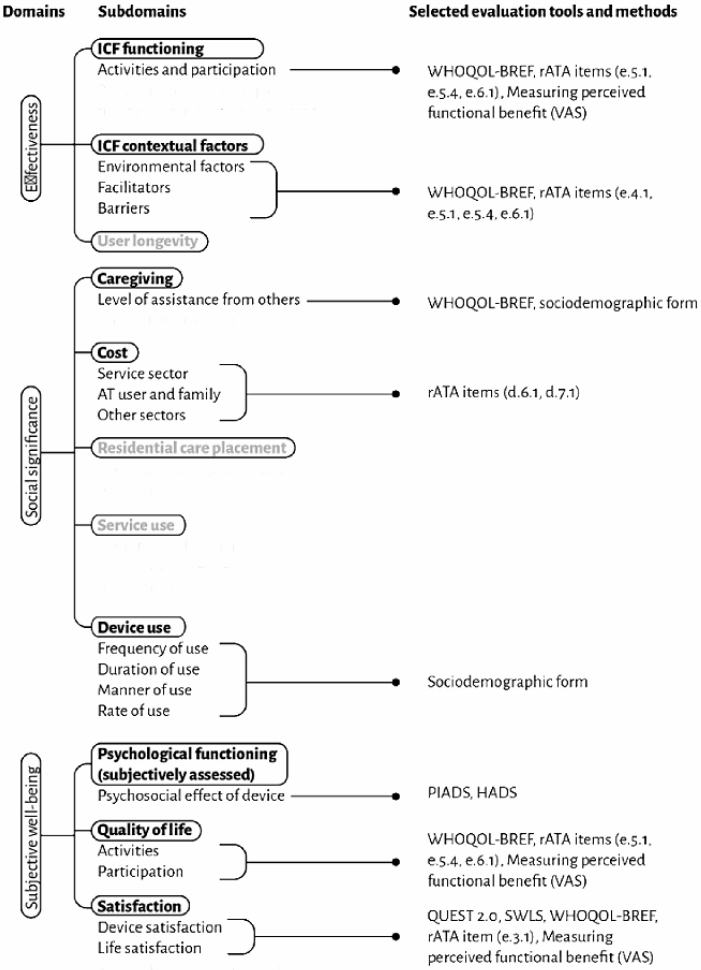

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Ethical Considerations

The intended study was approved by the Research Ethics Committee of the University of Parakou in Benin (257/2024/CLERB-UP/P/SP/R/SA) and will be conducted per the prescribed guidelines. There will be no financial compensation for this study, and each participant will be required to sign a consent form before being assessed. All data collected as part of this study will be treated as strictly confidential. Participants will be identified by a number to preserve their anonymity. Files will be securely kept and destroyed after 5 years from the end of data collection. Personal information will not be disclosed in public documents, and all necessary precautions will be taken to avoid any disclosure.

Data Analysis

The data from completed questionnaires will be entered into Microsoft Excel 2021 (Microsoft Corp) to create a database, which will then be analyzed using IBM SPSS Statistics (version 26; IBM Corp) software. The results will be presented in tables and figures to highlight the sample's particularities. Descriptive statistics such as frequency, percentage, mean and SD, or median (IQR) will be used to summarize sociodemographic data. Student *t* test or one-way ANOVA will be used to compare normally distributed numerical variables. Pearson or Spearman correlation coefficients will be used to determine any relationships between variables. Multivariate linear regressions will be used to determine any associative links between the measured variables.

The main results of the assessments using the different outcome measures described above will be organized using the CATOR taxonomy on aspects relating to the effectiveness and social significance of the use of ATs, as well as the subjective well-being of users [8], as shown in Figure 1. The evaluations will be limited to the fully dark-written CATOR domains and subdomains (Figure 1). In CATOR domain 1 (effectiveness), the different impacts and implications of ATs use in everyday activities and participation in social or community life, as well as environmental barriers and facilitators, will be reported. A quantitative assessment of the level of assistance received from others in the installation and use of ATs will be reported in CATOR domain 2 (social significance). This will also include an evaluation of the cost, frequency, rate, duration, and manner of use of ATs. Finally, the CATOR domain 3 (subjective well-being) will encompass all the results of the assessment of the psychosocial impact of ATs, satisfaction with ATs and with life, and overall QoL. The relationships between the results obtained in the 3 domains will be investigated to gain a more comprehensive understanding of the profile of AT users in Benin.

Results

The process of identifying potential participants began in August 2024, and data collection is scheduled to start in January 2025 and continue for 12 months.

Discussion

Relevance and Strengths of this Study

Given the growing importance attributed to worldwide data regarding the use of ATs by individuals with disabilities in their daily lives [2], it is imperative to assess these devices across diverse settings or environments to ascertain their real effects on the lives of these individuals, especially in resource-limited countries. Understanding these effects could be useful for selecting ATs, involving potential users in the decision-making process, and enhancing the accessibility of ATs in line with global priorities defined by WHO and UNICEF [2]. We therefore intend to evaluate the effects of ATs in Benin, a sub-Saharan African country where there are no data on AT users. To achieve this aim, an exhaustive research project has been drawn up based on the CATOR taxonomy and the use of standardized tools, the most widely used and documented in the literature. In addition, sociodemographic data will be gathered using specific items from the rATA, a recently developed and WHO-certified instrument designed to assess AT users worldwide [30].

The CATOR taxonomy provides a diversified classification of the findings of all forms of AT and is adaptable to all types of populations with disabilities. It provides a more objective view of the various effects of using ATs and leads to the identification of any problems encountered by users. Its use in our study guarantees a holistic structuring of our future results, which could easily be discussed with existing data in the literature.

Limitations

It is worth noting a few limitations in the design of this study. One of these limitations is that it was not possible to plan the assessment of the users who will be included in this study on all the aspects described in the CATOR taxonomy. These include aspects such as body functions, longevity, use of care services, and use of long-stay residences (Figure 1). A more specific design is required to evaluate these different aspects. In addition, the impact of ATs on caregivers' workloads will not be evaluated in depth. This is a topic that could be the subject of a future study. Another limitation is that the convenience sampling method to be used may limit the generalizability of our results. However, the fact that we plan to recruit participants from all regions of the country may strengthen the relevance of our future results.

Dissemination Plan

After completing this study, the results will be disseminated through various ways, including oral and poster presentations at national and international scientific conferences. Additionally, at least 2 scientific articles will be published in peer-reviewed journals.

Conclusion

This research project aims to contribute to the advancement of knowledge on ATs in sub-Saharan Africa, with a particular focus on Benin, where there are currently no data available. The findings of this study will constitute the inaugural investigation

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into the use of ATs in Benin. They may serve as a basis for future research in this field.

Acknowledgments

The research team would like to thank Isaac Laguna Munoz, BDes, MSc, for his valuable contribution to the design of this protocol. This research received no external funding.

Authors' Contributions

OLGA had the original idea, administered the project, supervised, conceptualized, carried out the writing, and prepared the original draft. OLGA and SJMC-c handled the methodology. OLGA, SJMC-c, PMM, and ASH did the validation. OLGA and ASH worked on the review and editing of this paper. OLGA, SJMC-c, PMM, and ASH visualized this paper. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cochran formula and sample size calculation.
[PDF File (Adobe PDF File), 158 KB - resprot_v13i1e60869_app1.pdf]

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Abbreviations

AT: assistive technology
CATOR: Consortium on Assistive Technology Outcomes Research
FAPHB: Fédération des Associations des Personnes Handicapées du Bénin
HADS: Hospital Anxiety and Depression Scale
PIADS: Psychosocial Impact of Assistive Devices Scale
QoL: quality of life
QUEST: Quebec User Evaluation of Satisfaction With Assistive Technology
rATA: rapid assistive technology assessment
SWLS: Satisfaction With Life Scale
UNICEF: United Nations Children's Fund
WHO: World Health Organization
WHOQOL-BREF: World Health Organization Quality of Life

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Protocol

SARS-CoV-2 Infections in a Triad of Primary School Learners (Grades 1-7), Their Parents, and Teachers in KwaZulu-Natal, South Africa: Protocol for a Cross-Sectional and Nested Case-Cohort Study

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Abstract

Background: In low- and middle-income countries (LMICs) such as South Africa, there is paucity of data on SARS-CoV-2 infections among children attending school, including seroprevalence and transmission dynamics.

Objective: This pilot study aims to assess (1) the prevalence of self-reported or confirmed SARS-CoV-2 prior infections, COVID-19 symptoms (including long COVID), seroprevalence of SARS-CoV-2 antibodies, and general/mental health, (2)

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longitudinal changes in SARS-CoV-2 seroprevalence, and (3) SARS-CoV-2 acute infections, immune responses, transmission dynamics, and symptomatic versus asymptomatic contacts in a unique cohort of unvaccinated primary school learners, their parents, teachers, and close contacts in semirural primary school settings.

Methods: Learners (grades 1-7) from primary schools in KwaZulu-Natal, South Africa, their parents, and teachers will be invited to enroll into the COVID kids school study (CoKiDSS). CoKiDSS comprises 3 parts: a cross-sectional survey (N=640), a follow-up survey (n=300), and a nested case-cohort substudy. Finger-prick blood and saliva samples will be collected for serological and future testing, respectively, in the cross-sectional (451 learners:147 parents:42 teachers) and follow-up (210 learners:70 parents:20 teachers) surveys. The nested case-cohort substudy will include cases from the cross-sectional survey with confirmed current SARS-CoV-2 infection (n=30) and their close contacts (n=up to 10 per infected participant). Finger-prick blood (from all substudy participants), venous blood (from cases), and nasal swabs (from cases and contacts) will be collected for serological testing, immunological testing, and viral genome sequencing, respectively. Questionnaires covering sociodemographic and general and mental health information, prior and current SARS-CoV-2 symptoms and testing information, vaccination status, preventative behavior, and lifestyle will be administered. Statistical methods will include generalized linear mixed models, intracluster correlation, descriptive analysis, and graphical techniques.

Results: A total of 645 participants were enrolled into the cross-sectional survey between May and August 2023. A subset of 300 participants were followed up in the follow-up survey in October 2023. Screening of the participants into the nested case-cohort substudy is planned between November 2023 and September 2024. Data cleanup and analysis for the cross-sectional survey is complete, while those for the follow-up survey and nested case substudy will be completed by the third quarter of 2024. The dissemination and publication of results is anticipated for the fourth quarter of 2024.

Conclusions: This study provides data from an LMIC setting on the impact of SARS-CoV-2 on school-attending learners, their parents, and teachers 3 years after the SARS-CoV-2 pandemic was declared and 21-24 months after resumption of normal school attendance. In particular, this study will provide data on the prevalence of self-reported or confirmed SARS-CoV-2 prior infection, prior and current symptoms, seroprevalence, changes in seroprevalence, SARS-CoV-2 transmission, SARS-CoV-2 adaptive immune responses, and symptoms of long COVID and mental health among a triad of learners, their parents, and teachers.

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KEYWORDS

COVID-19; SARS-CoV-2; learners; seroprevalence; long COVID; transmission dynamics

Introduction

Since the onset of the COVID-19 pandemic, an estimated 75.3 million (21%) children and adolescents <20 years of age have tested positive globally [1]. In South Africa, like many low- and middle-income countries (LMICs), there is a significant population youth bulge: children aged <20 years and children attending primary school make up almost 37% and 28% of the populations, respectively [2]. In their last publicly available report, the National Institute of Communicable Diseases, South Africa, reported that as of December 4, 2021, individuals aged ≤19 years comprised 14.8% of the SARS-CoV-2 tests, 12.5% of laboratory-confirmed COVID-19 cases, 5% of all COVID-19–associated admissions, and 0.7% of COVID-19–associated in-hospital deaths [3]. In most LMICs, children aged <12 years were not offered SARS-CoV-2 vaccines and not prioritized for SARS-CoV-2 testing. In this context, the long-term impact of the COVID-19 pandemic on children requires investigation.

SARS-CoV-2 seroprevalence studies provide an estimate of SARS-CoV-2 antibodies and thus better insight into overall infections, given that access to viral diagnostic testing and testing among mild and asymptomatic cases may be low [4]. In South Africa, during the COVID-19 pandemic, 3 cardinal community studies have reported SARS-CoV-2 seroprevalence among adults and children (Table 1), with an overall increase in the seroprevalence with each successive wave [5-7]. Further, all studies reported that the seroprevalence in adolescents is analogous to that reported in adults, while young children had lower seroprevalence compared to adolescents and adults. Noteworthily, children constituted only a fraction of the sample size in all 3 seroprevalence community surveys (ie, ~55%, 10%, and 20%, respectively) [5-7]. To our knowledge, there is paucity of data reporting the seroprevalence of SARS-CoV-2 among primary school-age children in school settings in South Africa.

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Table 1. Summary of SARS-CoV-2 seroprevalence studies in South Africa.

Study	Period	Variant of concern	Study setting	Participants (n)	Children and adolescents (n)	Age groups	SARS-CoV-2 infection/seroprevalence among children	SARS-CoV-2 infection/seroprevalence among adults
Cohen et al [5], 2022	July 2020 to August 2021	Beta and Delta variants	Mpumalanga and North West (2 provinces)	1200	664	<5 years of age (n=154, 12.8%) 5-12 years of age (n=340, 28.3%) 13-18 years of age (n=170, 14.2%) 19-39 years of age (n=265, 22.1%) 40-59 years of age (n=168, 14%) ≥50 years of age (n=103, 8.6%)	49% (75/154) in <5 years of age[a] 60% (205/340) in 5-12 years of age[a] 78% (132/170) in 13-18 years of age[a]	62.3% (165/265) among 19-39 years of age[b] 68.5% (115/168) among 40-59 years of age[b] 55.3% (57/103) among ≥50 years of age[b]
National household-based population seroprevalence survey of SARS-CoV-2 antibodies report [6]	November 2020 to February 2021 and April 2021 to June 2021	Beta and Delta variants	Western Cape, Eastern Cape, Northern Cape, Free State, Kwazulu-Natal, Northwest, Gauteng, Mpumalanga, and Limpopo (9 provinces in South Africa)	13,212	1363	Children<12 years not included 12-17 years of age (n=1363, 10.3%) 18-35 years of age (n=4494, 34%) 36-49 years of age (n=3060, 23.2%) >50 years of age (n=4294, 32.5%)	23.2%, (95% CI 19.2-27.8), 12-17 years of age[c]	17.3% (95% CI 15.0-19.9) among 18-35 years of age[d] 20.1% (95% CI 17.6-22.8) among 36-49 years of age[d] 21.3% (95% CI 19.1-23.7) among >50 years of age[d]
Madhi et al [7], 2022	October 2021 to December 9, 2021	Omicron	Gauteng (1 province)	7010	1375	<12 years of age (n=753, 10.7%) 12-17 years of age (n=622, 8.9%) 18-50 years of age (n=4047, 57.7%) >50 years of age (n=1588, 22.7%)	56.2% (95% CI 52.5-59.7) among <12 years of age[c] 73.8% (95% CI 70.2-77.1) among 12-17 years of age[c]	73.6% (95% CI 72.2-74.9) among 18-50 years of age[d] 79.7% (95% CI 77.6-81.5) among >50 years of age[d]

[a]SARS-CoV-2 infection among children.

[b]SARS-CoV-2 infection among adults.

[c]SARS-CoV-2 seroprevalence among children.

[d]SARS-CoV-2 seroprevalence among adults.

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Initial evidence suggested that children and adolescents are susceptible to infections with ancestral SARS-CoV-2 but at a reduced risk of severe illness or death relative to adults [8]. However, the subsequent Delta and Omicron variants have been more infectious in children than previous variants [9]. A retrospective study in China (n=2135) demonstrated that up to 90% of the pediatric cases were asymptomatic, mild, or moderate [10]. The majority of children hospitalized with severe COVID-19 were unvaccinated or had additional comorbidities such as type 2 diabetes or obesity [11]. A study in the United Kingdom reported that children with underlying neurodisabilities or multiple comorbidities are vulnerable to hospital admission or death [12]. Similar to adults, children and adolescents can also experience long COVID, the frequency and characteristics of which are still under investigation [13].

Studies have focused on differentiating the SARS-CoV-2 immune response between adults and children. In response to SARS-CoV-2 exposure or infection, children elicit a stronger mucosal innate immune response, which facilitates viral clearance [14-22], a lower level of neutrophilia that has previously been associated with microangiopathy and thrombosis [18,20], and a difference in cytokine profiling with a reduced tendency to trigger a cytokine storm [18,19,21-24]. With reference to adaptive immunity, higher lymphocyte counts with a higher proportion of naïve T cells, T regulatory cells, and T follicular helper cells have been reported [24-27]. Additionally, there are conflicting data on mucosal and serum antibody levels reported in children [18-20,24,28-32], and there are discordant reports on the durability and sustainability of the nucleocapsid antibody response in children after infection [33-35]. The Texas Coronavirus Antibody Response ongoing survey reported that 95% of the previously infected children of 5-19 years of age tested positive for nucleocapsid antibodies at the onset of the study and continued to have nucleocapsid antibodies up to 6 months later [36]. SARS-CoV-2 variants have evolving mechanisms to evade host immune defenses; intermittent testing to understand immune response in children exposed to or infected with SARS-CoV-2 infection may contribute to providing key insights into the pathogenesis of severe COVID-19.

During the COVID-19 pandemic, decisions on school closures varied widely between and within countries [37]. Children play a critical role in the transmission of respiratory viruses such as influenza, and school closures were partly guided by such evidence [38,39]. However, the epidemiological benefits of school closures on the transmission of SARS-CoV-2 remain elusive. There are conflicting data on the transmission of SARS-CoV-2 from children to children and from children to adults [40-45], with a lower prevalence of infection reported in younger children [46-48], with studies focusing primarily on household transmissions, while the role of schools remains unclear [47,49]. Young children infected with SARS-CoV-2 have viral loads in their respiratory tract similar to those of adolescents and adults [50,51]. School infection control measures played a role in decreasing outbreaks in some countries [52-54], but cluster outbreaks were reported among children in several provinces of South Africa when schools fully opened in 2022. Hence, further evaluation is needed to determine whether children (and the school setting) play a more substantive role in the community spread of SARS-CoV-2, especially in LMICs.

The overall aim of the COVID kids school study (CoKiDSS) is to assess SARS-CoV-2 prior infection, prior and current COVID-19 symptoms, seroprevalence, acute infection, transmission, immune responses, and symptoms of long COVID among a unique cohort of learners in grades 1-7, their parents/guardians, and teachers in the KwaZulu-Natal province of South Africa. The objectives of this study are shown in Table 2. Here, we describe the research study, its implementation processes, methodology, and expected results.

Table 2. COVID kids school study objectives.

Objective	Description
Primary objective	• Objective 1: To assess the prevalence of self-reported confirmed SARS-CoV-2 prior infections, prior and current COVID-19 symptoms, and seroprevalence of SARS-CoV-2 antibodies in the overall triad of learners (grades 1-7), their parents/guardians, and teachers.
Secondary objectives	• Objective 2: To determine the prevalence of long COVID-19 symptoms, general health and mental health in participants overall, and by SARS-CoV-2 antibody status. • Objective 3: To determine the longitudinal changes in SARS-CoV-2 seroprevalence and symptoms in a subset of participants who are followed up.
Exploratory objectives	• Objective 4: To conduct viral genome sequencing and describe transmission dynamics in a subgroup of 30 consenting SARS-CoV-2–positive individuals from the learner-parent-teacher triad and up to 10 of their close contacts. • Objective 5: To determine the proportion of previously asymptomatic contacts who test SARS-CoV-2–positive above. • Objective 6: To investigate B-cell and T-cell responses in the subgroup of 30 SARS-CoV-2–positive individuals enrolled and correlate these with symptoms.

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Methods

Study Setting

This study will be conducted within the catchment areas of the South African Medical Research Council (SAMRC)'s Verulam Clinical Research Site (CRS) based in the Verulam suburb of the eThekwini district in KwaZulu-Natal. The KwaZulu-Natal province has the second largest population in South Africa, with an estimated 11.3 million people; 43% of the population are younger than 18 years [2]. The province is divided into 1 metropolitan municipality (eThekwini Metropolitan Municipality; Durban) and 11 district municipalities. Verulam is an urban area in the northern part of eThekwini Municipality in close proximity to the iLembe district municipality. Approximately 94% of the school-age children between 5 and 17 years are in school in this municipality [3]. The catchment areas of the Verulam CRS comprise urban, periurban, and rural localities. In South Africa, the COVID-19 pandemic evolved against a backdrop of longstanding tuberculosis and HIV epidemics. KwaZulu-Natal has the largest burden of HIV and tuberculosis infections [55], and of the 9 provinces in South Africa, KwaZulu-Natal had the third highest cumulative number of COVID-19 cases recorded as of June 29, 2022 [56].

Study Design

This pilot study will implement a cross-sectional survey, follow up a subsample of survey participants, and conduct a nested case-cohort substudy in a preselect number of primary schools within the catchment area of the Verulam CRS in KwaZulu-Natal. Participating learners from primary schools (grades 1-7), their parents/guardians, and teachers will be invited to enroll in the CoKiDSS cross-sectional survey from May to August 2023 (primary objective 1; Figure 1). The cross-sectional survey will be conducted over 6 consecutive school weeks (window ±3 weeks; Figure 1). A subset of participants from the cross-sectional survey will be invited to participate in the follow-up survey (secondary objectives 2 and 3), with repeat SARS-CoV-2 antibody testing (3-4 months later from October 2023) until the desired sample is achieved (Figure 1). Saliva samples will be collected and stored from the first 10% (65/645 and 30/300, respectively) of the participants enrolled across the cross-sectional survey and in the follow-up survey for future testing. The nested case-cohort substudy (exploratory objectives 4-6) aims to enroll 30 cross-sectional survey participants with confirmed current SARS-CoV-2 infection—preferably all or at least 20 children (Figure 1) from November 2023 to September 2024. The follow-up survey will allow us to monitor the dynamics of SARS-CoV-2 seroprevalence. Long COVID will also be assessed in the cross-sectional and follow-up surveys as well as in the nested case-cohort substudy. Participants in the cross-sectional survey will have 1 study visit, while participants in the follow-up survey will have 2 study visits (Figure 1). During the follow-up survey, participants lost to follow-up will not be replaced.

Figure 1. Study design, objectives, and data collection. CRF: case report form; DBS: dried blood spot; PCR: polymerase chain reaction.

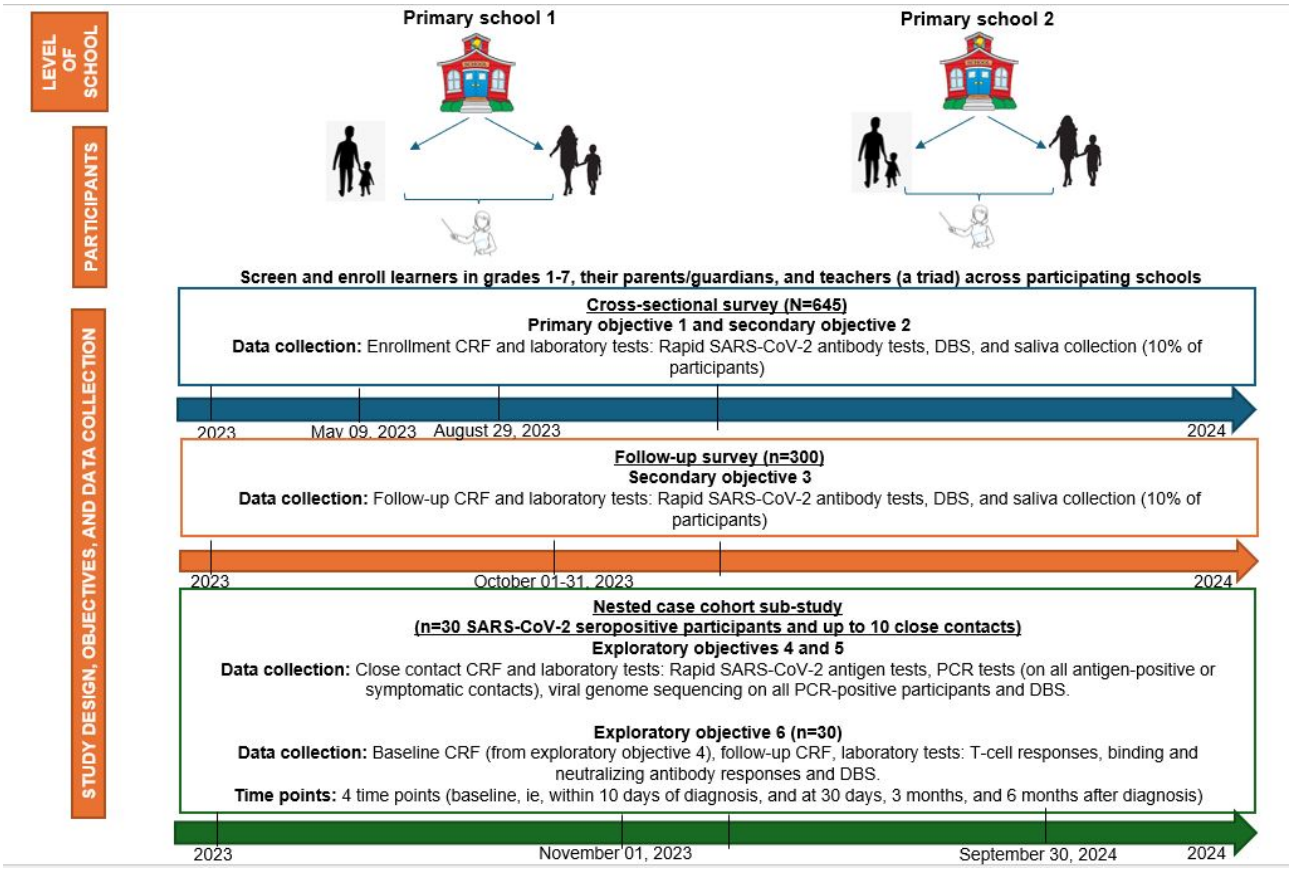

For objectives 4-6, the first 30 participants in the cross-sectional surveys (learner/parent/teacher) who test SARS-CoV-2 polymerase chain reaction (PCR)–positive (30 children or at least 20 children) identified through the school or existing

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linkages with the National Institute of Communicable Diseases/National Health Laboratory Services will be invited to enroll into the exploratory substudy (nested case-cohort substudy; Figure 1). These participants are referred to as the primary positives. To assess transmission dynamics (objective 4) and proportion of asymptomatic cases (objective 5), all close contacts of the 30 primary positives (30 SARS-CoV-2 PCR-positive participants) up to a maximum of 10 contacts will be tested with a South African Health Products Regulatory Authority–approved SARS-CoV-2 point-of-care antigen test, and a swab will be sent to the National Health Laboratory Services for a SARS-CoV-2 PCR test. Only 1 swab will be collected from children who are primary positives or close contacts. For the primary positives and their PCR-positive contacts, remnant swabs will be sent for viral genome sequencing (objective 4; Figure 1). To assess B-cell and T-cell immune responses (objective 6), the primary positives (30 SARS-CoV-2 PCR-positive participants) will also provide venous blood at baseline (ie, within 10 days of a positive SARS-CoV-2 test), 30 days, 3 months, and 6 months post diagnosis (nested case-cohort substudy; Figure 1). Dried blood spot samples will be collected from all participants enrolled in the cross-sectional and follow-up surveys as well as the nested case-cohort substudy for future antibody testing.

Study Populations

The inclusion and exclusion criteria for the school, school-age learners, their parents or guardians, and teachers are summarized in Table 3.

Table 3. Inclusion and exclusion criteria for the school, learners in grades 1-7, their parents/guardians, and teachers.

Participant and part of the study	Inclusion criteria	Exclusion criteria
School		
Cross-sectional and follow-up surveys and nested case-cohort substudy	• Primary schools within the catchment areas of the Verulam South African Medical Research Council clinical research site in eThekwini, KwaZulu-Natal, South Africa.	• Special schools, learner referral units, and education colleges. • Schools where other school-based COVID-19 studies are already being conducted. • Small school size with <40 learners per grade in grades 1-7.
Learners, parents/guardians, and teachers		
Cross-sectional survey	• Learner must be attending school in person. • A parent/guardian is only eligible if his/her child is eligible and participating in the study. • A teacher is only eligible if the teacher teaches at a participating school. • For learners <18 years of age, a parent/guardian is able to provide consent. • For learners 8 to <18 years of age, the learner can provide assent. • For learners 7 years of age, only parental/guardian consent is required. • Willing for study staff to obtain routine SARS-CoV-2 results from National Institute of Communicable Diseases/National Health Laboratory Services.	• Learners 8 to <18 years of age who are unable to provide appropriate informed assent. • Parent excluded if learner already has 1 parent enrolled in the study. • Learner does not anticipate completing the school year in the selected school. • Learners with physical or intellectual challenges. • Learners who, in the opinion of the principal investigators or designees, will be at risk if they participate in this study.
Follow-up survey	• Same criteria as for cross-sectional survey • Learner must be attending school in person during the 2023 academic year. • Willing to be followed up once and to give blood during follow-up.	• Same criteria as for cross-sectional survey.

Ethics Approval

This study has been approved by the SAMRC Human Research Ethics Committee (EC018-9/2022) and the South African Department of Basic Education (national and provincial) and the South African Department of Health (provincial). Written informed consent will be obtained from parents or guardians of participating learners and from all participating parents/guardians and teachers. Additionally, assent will be obtained from children aged 8 to <18 years. All participants will be reimbursed with a voucher valued at R 300 (US $16), in accordance with local ethics guidance to cover the cost of time, inconvenience, and expenses.

Schools: Sampling and Sample Size

For objectives 1-6, a convenience sample of schools will be selected. In the first stage, a sampling frame of all public primary schools within the Verulam CRS catchment areas will be developed. Attempts will be made to obtain the head counts in these schools and number of classes. Only large schools (≥40 learners per grade in grades 1-7) able to contribute to the sample size will be shortlisted (short list 1) and their principals approached to ascertain interest. From short list 1, schools whose

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principals are agreeable to study participation will be identified (short list 2), and a sample of 2 primary schools will be selected from short list 2. We will expand to additional selected primary schools if needed, until the enrolment target is reached.

Madhi et al [7] demonstrated a seroprevalence of 56.2% (95% CI 52.6%-59.7%) among children younger than 12 years in a seroepidemiological study conducted from October to December 2021 [7]. We opted to be more conservative due to the waning immunity anticipated in unvaccinated children or those who did not receive the booster dose almost 2 years after the pandemic. The sample size calculations for this study were based on estimating seroprevalence rates with a specific degree of precision. Specifically, the was used, where DE refers to the design effect, p refers to the estimated prevalence, and d to the margin of error. A sample size of 640 will allow us to estimate seroprevalence rates in the combined group of 40% and greater with a margin of error of 6%, accounting for a design effect of 2.5 and assuming a 5% α. The survey is designed to be stratified by school, with class defining the cluster. We expect a minimum of 40 clusters in total across the 2 schools with an average cluster size of 16. In Figure 2, we have illustrated the margin of error for estimation under various sample sizes assuming all the other aforementioned parameters are fixed. As depicted in Figure 2, a reduction in the sample size below 600 will result in a greater margin of error (lower precision) larger than 7%.

A review of 14 studies indicated that long COVID symptoms varied from 4% to 66% among children and adolescents [57]. A cohort of 300 individuals will enable us to estimate the prevalence rates of long COVID at follow-up, 45% or greater with a 7% margin of error, accounting for a 20% loss to follow-up rate, and a maximum design effect of 1.2. Tables 4-5 summarize the sample size allocation for the respective surveys. The nested case-cohort substudy sample size is described in Table 6.

Figure 2. Margin of error for various sample sizes assuming a fixed prevalence of 40% and design effect of 2.5. MOE: margin of error.

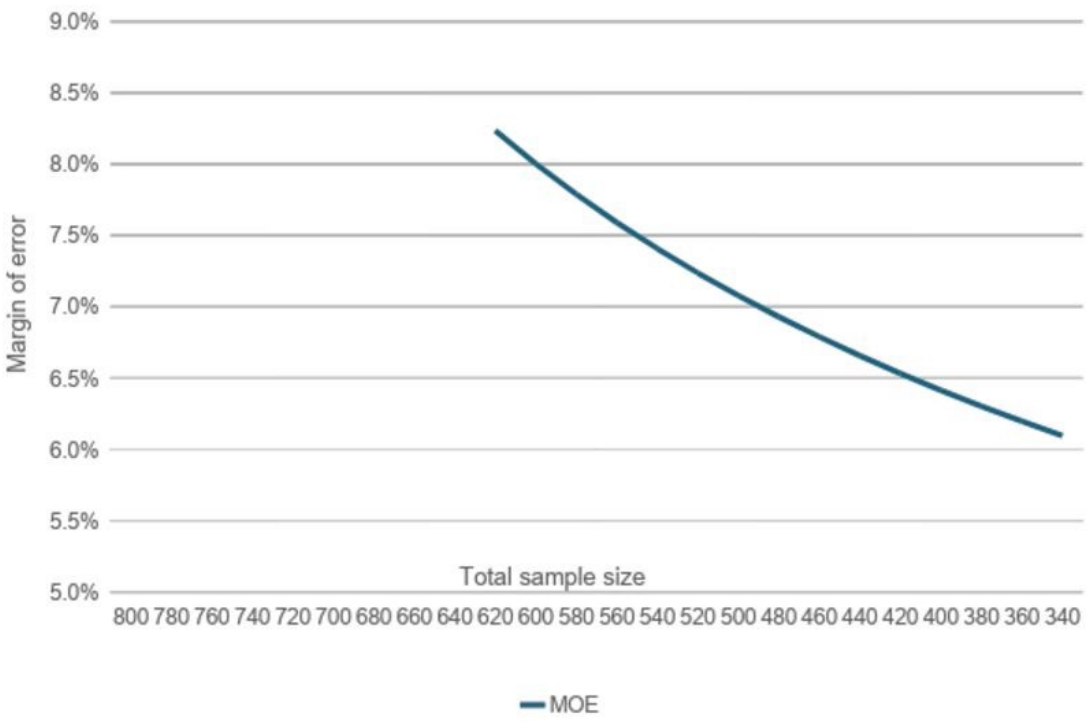

Table 4. Sample size allocation of primary school learners, parents, and teachers for the cross-sectional survey (N=640).[a]

Sample	Grade						
	1 (n=91)	2 (n=91)	3 (n=91)	4 (n=91)	5 (n=92)	6 (n=92)	7 (n=92)
Learners (n=451)	64	64	64	64	65	65	65
Parents (learner: parent, 3:1) (n=147)	21	21	21	21	21	21	21
Teachers (learner: teacher, 11:1) (n=42)	6	6	6	6	6	6	6

[a]The sample size might vary by ±10 people per group (learner, parent, teacher).

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Table 5. Sample size allocation of primary school learners, parents, and teachers for the follow-up survey (n=300).[a]

Sample	Grade						
	1 (n=43)	2 (n=43)	3 (n=43)	4 (n=43)	5 (n=43)	6 (n=43)	7 (n=43)
Learners (% of cross-sectional survey ~50%) (n=210)	30	30	30	30	30	30	30
Parents (% of cross-sectional survey ~50%) (n=70)	10	10	10	10	10	10	10
Teachers (% of cross-sectional survey ~50%) (n=20)	3	3	3	3	3	3	2

[a]The sample size might vary by ±5 people per group (learner, parent, teacher).

Table 6. Sample size allocation for the nested case-cohort substudy.

Participants	Value, n
SARS-CoV-2–positive learners across grades 1-7	20-30
SARS-CoV-2–positive parents/teachers	0-10
Close contacts	10 per positive participant

Study Procedures

Stakeholder Engagement

A strong community engagement program is underway to assist with buy-in and recruitment for the study among the Department of Basic Education, school principals, school governing boards, teachers, and parents/guardians of learners in grades 1-7. Schools that agree to participate will be asked to register and complete a short questionnaire.

Participant Recruitment and Follow-Up

Informed consent will be sought from teachers and from parents/guardians for their own/their children's participation. Simplified informed consent forms were piloted to evaluate their understanding of the study and implications of the study. Assent will also be obtained from children aged 8 to <18 years, and participation will be contingent on obtaining both assent and parental consent. Only parental consent will be required for 7-year-old children. Flexible systems will be used to engage with parents, including weekend meetings and interviewer-administered or self-administered parental questionnaires. Multiple learners from one family can participate, but separate consent will be sought for each learner. Recruitment for the cross-sectional survey commenced on May 9, 2023, and was completed before the end of August 2023. The follow-up survey will follow up the first 210 learners, 70 parents, and 20 teachers who consent to follow-up at least 6 weeks after the first interview and after a school holiday. SARS-CoV-2–positive participants enrolled in the immunological substudy will be followed up for 6 months.

Data Collection

Questionnaire data will be gathered from school principals or a substitute member of the school senior leadership team, teachers, and parents/guardians of the primary school learners (in grades 1-7) (Table 7 and Multimedia Appendices 1-7).

Information will be collected on sociodemographic and basic health information; use of nonpharmacological measures; COVID-19 vaccination status of learner, parent/guardian, and teacher; household structure and COVID-19 history; symptoms of long COVID; household exposures; lifestyle; and preventive behavior related to the pandemic since January 2020 (see Multimedia Appendices 1-6). Parents/guardians will complete all the study case report forms on the children's behalf (Multimedia Appendices 3 and 4).

Additionally, information will be collected on the learner's lifestyle, mental health, and well-being. The Revised Children' Anxiety and Depression Scale will be used to determine the internalizing symptoms of anxiety and depression among children and young adolescents enrolled in this study (see Multimedia Appendix 7) [58]. If the tool triggers negative memories in participants, these participants will be referred to a counsellor at the nearest health care facility. Samples will be collected from participants as outlined in Table 7 and described in Multimedia Appendix 8.

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Table 7. Summary of data collection.

Participant	Cross-sectional and follow-up survey	Nested case-cohort substudy	
		Immunology	Transmission dynamics
School principal or senior school leadership	Questionnaire about number of learners, number of staff, and nonpharmaceutical interventions	N/A[a]	N/A
Learner/parent/teacher triad	Questionnaire at baseline and follow-up (if applicable) about contacts/nonpharmaceutical interventions/symptoms of long COVID. Blood draw to determine seroprevalence (rapid antibody test), dried blood spot for anti-S IgA/IgG, anti-N IgG, neutralizing antibody and antibody titers. Saliva samples will be collected in 10% of participants and stored if applicable.	N/A	N/A
Primary positives identification and follow-up within 10 days, 30 days, 3 months, and 6 months of a positive SARS-CoV-2–positive test	N/A	Questionnaire at baseline and follow-up (if applicable) about contacts/nonpharmaceutical interventions/symptoms of long COVID. Blood draw to determine seroprevalence (rapid antibody test), dried blood spot for anti-S IgA/IgG, anti-N IgG, neutralizing antibody and antibody titers. Saliva samples will be collected in 10% of participants and stored if applicable.	Telephonic questionnaire to identify contacts. Initial swab sent for viral genome sequencing.
Contacts of the primary positives	May or may not be included in the cross-sectional and follow-up surveys.	N/A	Questionnaire + rapid antigen test + polymerase chain reaction + dried blood spot

[a]N/A: not applicable.

Data Management

Data will be collected in research electronic data capture, a secure web-based application hosted by the SAMRC. More information on this platform can be found elsewhere [59,60]. Research electronic data capture access will be restricted to CoKiDSS personnel. A lookup function will be created in research electronic data capture to link/track participants enrolled in the cross-sectional survey, follow-up survey, and nested case-cohort substudy. This will be useful if the close contact is already a participant in the study.

Biospecimen Management

Samples will be stored at the HIV and other Infectious Diseases Research Unit, SAMRC, biorepository. The Laboratory Data Management System program developed by Frontier Science is used by the HIV and other Infectious Diseases Research Unit biorepository and is a storage module that conforms to US Food and Drug Administration, 21 Code of Federal Regulations part 58 and 11 [61]. The program is utilized to manage specimen tracking, inventory storage, and specimen shipment.

Data Analysis

We will perform descriptive analysis of participant sociodemographic, lifestyle, and behavior information. Total seroprevalence and cumulative incidence (ie, total number of reverse transcription-PCR–confirmed infections in official statistics per population) will be calculated and compared as well as age-specific and time-specific estimates. The total numbers of learners in the respective grades per school will be used for poststratification so that the estimates are representative of the demographics in KwaZulu-Natal, which will be incorporated via weights. The prevalence prior and current COVID-19 symptoms and seroprevalence will be presented with 95% CIs, where standard errors will be computed via jackknife methods. Within the cohort, changes in seroprevalence, symptoms, mental health, and physical health will be assessed using generalized linear mixed models, considering the within-individual correlation of responses as well as the hierarchical structure of the data. The clustering of seropositivity within classes and school will be quantified using the intracluster correlation. To analyze the exploratory objectives, the following statistical methods will be employed: (1) means with standard deviations or medians with interquartile ranges (as appropriate depending on the distribution) will be presented for continuous data, (2) the graphical presentation of continuous outcomes will be undertaken using box plots, (3) bar charts will be used to represent categorical data across groups of interest, and (4) the correlation between variables will be addressed using 2-way scatterplots with the presentation of Spearman correlation coefficient.

Patient and Public Involvement

Several school principals were consulted during the development of the protocol to ensure the feasibility of the planned study procedures. Early feedback was collected from learners and parents invited to participate to adapt the communication strategies and channels. Further feedback will also be collected

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from enrolled learners and school principals during the cross-sectional survey to adapt the follow-up survey. Results of individual tests will be communicated to the participants, and overall study results disseminated to participating schools. Findings will be disseminated to the South African Department of Basic Education and Department of Health.

Results

Recruitment for the cross-sectional survey occurred between May and August 2023, and a total of 645 participants were enrolled. Three hundred participants were followed up in the follow-up survey implemented in October 2023. Screening of the participants into the nested case-cohort substudy is planned between November 2023 and September 2024. Data cleanup and analysis for the cross-sectional survey is complete. Data cleanup and analysis for the follow-up survey and nested case substudy will be completed in the third quarter of 2024. The dissemination and publication of study findings is anticipated for the fourth quarter of 2024. The abovementioned activities and timelines are outlined in Multimedia Appendix 9.

Discussion

Anticipated Main Findings of This Study

We anticipate that this study will find high SARS-CoV-2 seroprevalence, especially among teachers and parents, despite low reported SARS-CoV-2 infections and low prevalence of long COVID-19 and that transmission dynamics will favor parent-child transmission.

Contextualization of the Anticipated Results

The direct impact of COVID-19 on child and adolescent mortality is limited, with these age groups accounting for a meagre 0.4% (over 17,400) of COVID-19 deaths worldwide as of March 2023 [1]. However, according to UNICEF (United Nations Children's Fund), children and adolescents bear the brunt of the indirect effects of the COVID-19 pandemic, including more households plummeting into multidimensional poverty, exacerbating the hardships of children living in the poorest countries, augmenting the learning crisis, threatening child survival and death, increasing child malnutrition, and deprivation and disruptions in health services [62]. Hence, the harms associated with school closures were profound. CoKiDSS is centered around the school rather than community settings, as schools play a critical role in a child's learning and development, and in many countries, schools also provide access to immunizations, health care, and nutritional services.

In LMICs, among children aged 5-13 years, there is a paucity of data on SARS-CoV-2 infections, including seroprevalence and transmission dynamics. In South Africa, 3 cardinal community studies have been published to date, reporting SARS-CoV-2 seroprevalence among adults and children [5-7]. However, the last serosurvey was conducted in December 2021 during the Omicron wave, and children constituted a small proportion of the study population [7].

CoKiDSS will provide data on the impact of COVID-19 on school-attending children ~36 months after the pandemic was declared and 21-24 months after the resumption of normal school attendance. In particular, data will be provided on the prevalence of confirmed prior SARS-CoV-2 infections, prior and current COVID-19 symptoms, seroprevalence of SARS-CoV-2 antibodies, prevalence of long COVID symptoms, and general and mental health in a triad of learners, their parents/guardians, and teachers in the current COVID-19 endemic. The longitudinal design will allow a description of the temporal trends of immunity to SARS-CoV-2. Presently, in South Africa, children aged 5-11 years are only eligible to receive SARS-CoV-2 vaccination if they are at risk of developing severe COVID-19. The CoKiDSS data will provide a better understanding on the natural protection within this population and could potentially guide local vaccination strategies.

Strengths and Limitations

This study is the first study of SARS-CoV-2 infections in a school setting within a high HIV/tuberculosis prevalence LMIC. Thus, it will provide information on the impact of COVID-19 on schools, learners, teachers, and parents in these settings, and could guide future responses to pandemics within these settings. However, this study is not without challenges and limitations. Given the limited geographic area and number of schools, the findings may not be representative of all South African schools. In order to recruit a triad of learners in grades 1-7, their parents, and teachers, several rounds of engagement may be needed, resulting in oversampling or undersampling at schools. This study will assess SARS-CoV-2 seroprevalence by using a qualitative SARS-CoV-2 point-of-care antibody test. It is possible that the qualitative antibody assessment is below the threshold of conferring immunity. We would, however, prefer to use a minimally invasive test in this vulnerable population. Notwithstanding these, this study will contribute to the limited body of knowledge on the effect of the COVID-19 pandemic on school-attending children 21-24 months after resumption of normal school attendance.

Dissemination Plan

The study objectives and outcomes will be disseminated to participants, community, and other stakeholders, including the South African Department of Health and South African Department of Basic Education (district, provincial, and national levels), regulatory bodies, research organizations, community members, and participants. Additionally, the information linked to this study will be shared by the community staff with the participating school principals and members of the school governing board as well as the community advisory board/community working group members. The results of this study will be disseminated via virtual methods and face-to-face meetings. Communication methods will include the use of SMS text messaging to mobiles, monthly telephone calls with community advisory board members, hand delivery of relevant written material, email, Microsoft Teams, and social media platforms (WhatsApp). These methods will contribute to ongoing community acceptance of the study and trust in the research team and the program.

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Acknowledgments

We are grateful to the South African Medical Research Council (grant SAMRC-RFA-GIPD-03-2021) and the European Union Horizon Europe program under the project “EU-Africa Concerted Action on SARS-CoV-2 Virus Variant and Immunological Surveillance” (grant 101046041) for funding this pilot study. Views and opinions expressed are, however, those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. Additionally, we would like to extend a huge thank you to the study participants and the communities that participated.

Data Availability

Data availability will need to be requested from the corresponding author. The request will be considered a concept note, and the reason for data access will be required. Data will only be shared after the minimum papers have been written by the authors. Data will be made publicly available on the South African Medical Research Council website after all the main papers have been published.

Authors' Contributions

RD and AG conceived, designed, and wrote the manuscript. TC, BD, ZG, ES, TR, NM, DFN, SP, AB, VM, PLM, WAB, TdO, and NM contributed to reviewing and critiquing the manuscript. TR and KM were responsible for the statistical design and data management plan for the study, respectively. All authors read and approved the final manuscript. There were no conflicts of interest. No artificial intelligence was used in developing this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Principal enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 168 KB - resprot_v13i1e52713_app1.pdf]

Multimedia Appendix 2
Teacher enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 401 KB - resprot_v13i1e52713_app2.pdf]

Multimedia Appendix 3
Parent of learner enrollment and follow-up e-case report form.
[PDF File (Adobe PDF File), 745 KB - resprot_v13i1e52713_app3.pdf]

Multimedia Appendix 4
Parent of learner enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 460 KB - resprot_v13i1e52713_app4.pdf]

Multimedia Appendix 5
Close contact case report form.
[PDF File (Adobe PDF File), 149 KB - resprot_v13i1e52713_app5.pdf]

Multimedia Appendix 6
Nested case-cohort substudy case report form.
[PDF File (Adobe PDF File), 253 KB - resprot_v13i1e52713_app6.pdf]

Multimedia Appendix 7
Learner mental health case report form.
[PDF File (Adobe PDF File), 439 KB - resprot_v13i1e52713_app7.pdf]

Multimedia Appendix 8
Detailed data collection.

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[DOCX File , 20 KB - resprot_v13i1e52713_app8.docx]

Multimedia Appendix 9
Study timeline.
[DOCX File , 16 KB - resprot_v13i1e52713_app9.docx]

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Abbreviations

CoKiDSS: COVID kids school study
CRS: clinical research site
LMIC: low- and middle-income country
PCR: polymerase chain reaction
SAMRC: South African Medical Research Council
UNICEF: United Nations Children's Fund

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Protocol

Examining Caregiver Practices During Adolescent Outpatient Alcohol Use and Co-Occurring Mental Health Treatment: Protocol for a Dyadic Ecological Momentary Assessment Study

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Abstract

Background: Caregiver-involved treatments for adolescents with alcohol use disorder and co-occurring disorders (AUD+CODs) are associated with the best treatment outcomes. Understanding what caregiving practices during treatment improve core adolescent treatment targets may facilitate the refinement and scalability of caregiver-involved interventions. Caregiving is dynamic, varying by context, affect, and adolescent behavior. Caregiver-involved treatments seek to change momentary interactions between caregivers and their adolescents. Accordingly, this protocol outlines a dyadic ecological momentary assessment (EMA) study to examine caregiving practices during AUD+CODs treatment and their associations with adolescent core treatment targets (eg, alcohol craving and use, motivation to reduce or stop drinking, and internalizing and externalizing symptoms).

Objective: This paper aims to describe the methods for examining momentary caregiving practices and adolescent core treatment targets during adolescent outpatient AUD+CODs treatment.

Methods: We will recruit 75 caregiver-adolescent dyads from outpatient mental health clinics providing AUD+CODs treatment. Eligible families will have an adolescent who (1) is aged between 13 and 18 years; (2) meets the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, diagnostic criteria for AUD; (3) is enrolled in outpatient treatment at the time of recruitment; and (4) has a legal guardian willing to participate in the study. Caregivers and adolescents will complete an eligibility screening, followed by a baseline assessment during or as close as possible to the second week of treatment. During the baseline assessment, caregivers and adolescents will receive formal training in EMA procedures. Next, caregivers and adolescents will complete a 15-week EMA burst design consisting of three 21-day EMA periods with 3-week breaks between periods. Throughout the study, participants will also complete weekly reports regarding the skills learned or practiced during therapy. The three overarching aims to the proposed study are as follows: (1) examine momentary caregiving practices (eg, support, monitoring, substance use communication quality) and their associations with core treatment targets, (2) examine how these associations change throughout treatment, and (3) examine whether a caregiver report of learning or practicing parenting- or family-focused behaviors in treatment sessions is associated with changes in the use of caregiving practices in daily life.

Results: The proposed study was informed by a pilot study assessing the feasibility and acceptability of dyadic EMA during adolescent AUD+COD treatment. Some benchmarks were met during this study (eg, ≥80% caregiver retention rate), although most benchmarks were not (eg, adolescent [772/1622, 47.6%] and caregiver [1331/1881, 70.76%] random prompt compliance

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was below the ≥80% target). Data collection is anticipated to begin in December of 2024. The proposed study is designed to be completed over 3 years.

Conclusions: Examining momentary caregiving practices using EMA has important implications for refining and scaling caregiver-involved interventions for AUD+CODs so that families who would benefit from caregiver-involved treatments can have access to them.

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KEYWORDS

adolescent; caregiver; ecological momentary assessment; alcohol; co-occurring disorders treatment; treatment; older adult; aging; alcohol use; mental health; assessment; protocol; alcohol use disorder; drinking; substance use; data collection

Introduction

Adolescent Alcohol Use Disorder and Co-Occurring Disorders

> *Caregivers are the ultimate role models for children. Every word, movement, and action has an effect. No other person or outside force has a greater influence on a child than the caregiver.* [Bob Keeshan]

More than 750,000 adolescents in the United States aged between 12 and 17 years have alcohol use disorder (AUD), according to current estimates [1]. Among adolescents who present for AUD treatment, >80% have a co-occurring mental health diagnosis [2,3]. Youth with AUD and co-occurring disorders (AUD+CODs) exhibit poor family functioning, low treatment motivation and engagement, poor treatment outcomes, and high rates of returning to substance use [4-6]. Although treatments for adolescents with AUD+CODs yield small, short-term benefits, caregiver-involved treatments are associated with the best outcomes [7,8]. This mirrors findings for caregiver-involved treatments for myriad adolescent mental health conditions (eg, depression and conduct disorder) [9]. Throughout this paper, we use the term *caregiver* to reflect that figures other than biological parents (eg, grandparents and stepparents) can serve as caregivers for youth in treatment. To date, limited work has examined caregiver behaviors during adolescent AUD+CODs treatment [10]. Building on theoretical and empirical research from clinical and developmental science emphasizing the importance of studying caregiving practices in the moment [11-13], this protocol describes the rationale and methods for a study seeking to address a central yet unanswered question: What specific caregiving behaviors during caregiver-involved treatment for AUD+CODs contribute to improved outcomes?

Caregiver Involvement in AUD+CODs Treatment

Caregiver involvement in adolescent services is positively associated with adolescent treatment engagement, motivation, retention, and outcomes [9,14-20]. Moreover, adolescent AUD treatments that involve caregivers have been found to reduce co-occurring externalizing and internalizing symptoms [21-24]. These findings align with evidence that caregiving practices mediate adolescent treatment for internalizing (eg, depression and anxiety) and externalizing (eg, attention-deficit/hyperactivity disorder and oppositional defiant disorder) conditions that often co-occur with adolescent AUD [25]. Consequently, current guidelines identify caregiver-involved adolescent AUD+CODs treatment as a best practice [8].

Research examining what caregivers are doing in their routine environments during the course of treatment to promote improved youth outcomes is at a nascent stage [26,27]. Moreover, although multiple evidence-based treatments (eg, cognitive behavioral therapy, family-based therapies, and multicomponent therapies) call for the involvement of caregivers in some capacity [26,28-31], typical community-based practices for treating adolescents with AUD+CODs do not involve caregivers [8,32-34]. Structural barriers to delivering caregiver-involved treatments in outpatient settings include the high costs of the training required for family-based treatments, session frequency and duration, and highly manualized protocols with limited flexibility [8,26,35]. These barriers may affect youth considered the most vulnerable whose families have limited knowledge, access, and resources to complete caregiver-involved treatments [26,36,37]. One way to advance treatment options for youth is to identify the specific caregiving practices (ie, change-promoting parenting behaviors) during AUD+CODs treatment that most strongly relate to positive changes in core treatment targets. By isolating these behaviors, we can develop scalable and targeted caregiving interventions to maximize those treatment ingredients that yield the highest impact while mitigating required resources [38].

Unfortunately, most of what we know about how caregiving behavior relates to adolescent AUD outcomes derives from observational studies of adolescents without AUDs and not in treatment [39]. To our knowledge, only 7 studies have assessed caregiving behaviors as putative mechanisms of adolescent substance use treatment outcomes [20,40-45], and only 1 of them assessed caregiving behavior during treatment [40]. In the study, growth in parental monitoring from baseline through 12-month follow-up predicted decreased growth in substance use from baseline to 12-month follow-up [40]. Although the study provides additional support for the importance of caregiver behavior to treatment outcomes, the study design did not prospectively examine how caregiving during treatment predicts outcomes [40]. Moreover, the study, like virtually all caregiving-AUD research [39,46], operationalized caregiving via assessments spaced months apart that aggregated caregiving behaviors across weeks or months [11,47]. Harnessing the impact of caregivers to boost adolescent AUD outcomes in the most impactful and efficient way requires methods that capture

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how caregiving behaviors, in real time in daily life, relate to core treatment targets during therapy.

The Need for Moment-Level Caregiving Assessments

Dynamic system theory posits that momentary interactions between a caregiver and their child create a reciprocal interaction system (ie, relationship pattern) that impacts long-term adjustment [11,48,49]. In a treatment context, this suggests that examining how caregivers act toward their children during AUD+CODs treatment is critical to understanding long-term treatment outcomes. A growing body of work from developmental science highlights the importance of studying caregiving behaviors and their associations with the indicators of adolescent adjustment at a more refined timescale [50-53]. Consistent with dynamic systems theory, these studies have found caregiving practices to vary from moment to moment depending on context, affect, and adolescent behavior [11-13]. Importantly, emerging research indicates that associations between caregiving practices and adolescent adjustment indicators do not generalize across different timescales [54]. In other words, capturing caregiver practices and adolescent adjustment on broader time courses (eg, monthly) may not representatively encode what occurs moment to moment in daily life.

Core adolescent AUD+CODs treatment targets, such as treatment motivation [55,56], alcohol craving [57-59], substance use [59,60], and internalizing and externalizing symptoms [61-63], vary considerably within and across days. Understanding improvements prompted by caregiver-involved treatments for adolescent AUD+CODs requires momentary assessments that can capture and correlate the dynamic nature of caregiving and adolescent treatment targets. Ecological momentary assessment (EMA) provides a methodology to study caregiving behaviors and evaluate their impact on adolescent functioning in real time [64,65]. EMA has been suggested to minimize recall bias, memory heuristics, and demand characteristics that can occur in caregiving research [64,66-68]. It has the unique ability to go beyond looking at how caregiving predicts behaviors across families (between-family associations) and provides rich data on how changes in a caregiver's behavior relate to changes in their adolescent's behavior in real time in the family's daily life (ie, within-family associations [64]). Despite the developmental salience of these dynamic associations, no research has examined these momentary associations between caregiving practices and adolescent behavior during AUD+CODs treatment.

The Proposed Study

The proposed protocol aims to examine caregiving practices, in the moment, during adolescent community outpatient AUD+CODs treatment. To advance our understanding of caregiving practices that promote improvements in core treatment targets, the proposed study has 3 overarching research aims and corresponding hypotheses.

Aim 1 is to examine momentary associations between caregiving practices and core treatment targets. Hypothesis 1 is that momentary *caregiver reports* of caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices will be positively associated with *adolescent reports* of motivation to reduce or stop drinking and positive affect and negatively associated with alcohol craving, alcohol use, and internalizing and externalizing symptoms. Momentary *caregiver reports* of caregiver-adolescent conflict will be negatively associated with *adolescent reports* of motivation to reduce or stop drinking and positive affect and positively associated with alcohol craving, alcohol use, and internalizing and externalizing symptoms.

Aim 2 is to examine changes in the strength of the associations between caregiving practices and core treatment targets over the course of treatment, consistent with treatment perspectives arguing that skill use should be more effective across time [69]. Hypothesis 2 is that aim 1 associations for caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices will become stronger over the course of AUD+CODs treatment as caregivers and adolescents learn and practice skills over the course of treatment. Aim 1 associations for caregiver-adolescent conflict will become weaker as caregivers and adolescents learn and practice skills to better manage conflict in the moment.

Aim 3 is to examine whether the use of family-focused therapy techniques are associated with changes in the use of caregiving practices. Hypothesis 3 is that caregiver reports of learning or practicing family-focused therapy techniques in therapy will be prospectively positively associated with increases in caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices and with decreases in caregiver-adolescent conflict.

Methods

Target Population and Recruitment

The adolescents eligible for Project Momentary Assessment of Parenting Practices (MAPP) will be those who (1) are aged between 13 and 18 years; (2) meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, diagnostic criteria for AUD; (3) are enrolled in outpatient treatment at the time of recruitment; and (4) have a caregiver willing to participate in the study. Considering that >80% of adolescents with an AUD presenting to treatment have a co-occurring mental health condition [2,3]—and consistent with current dimensional conceptualizations of psychopathology [70]—a formal diagnosis of a co-occurring condition will not be required for eligibility. Exclusion criteria will include (1) adolescents exhibiting acute psychosis and (2) adolescents or caregivers who are unable to read or comprehend the study forms in English or Spanish (eg, consent procedures).

Seventy-five dyads will be recruited from 5 community-based mental health clinics treating adolescents with co-occurring conditions in Massachusetts. On average, these clinics have 9 (SD 7.36, range 3-20) therapists working with adolescents with co-occurring conditions and have the capacity to see 159 (SD 123.74, range 50-350) adolescents per year. Across these mental health clinics, several treatments are offered, including the adolescent community reinforcement approach (A-CRA; all 5 clinics), trauma-focused cognitive behavioral therapy (1 clinic),

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eye movement desensitization and reprocessing (1 clinic), and home-based services (1 clinic). A-CRA is the preferred treatment model endorsed by the Office of Youth and Young Adult Services in the Bureau of Substance Addiction Services, Massachusetts. Caregiver involvement varies across settings and treatments, with examples of caregiver involvement being weekly family therapy sessions for home-based services and 2 formal caregiver sessions in A-CRA.

Before recruiting families, the study team will provide presentations to each partnering clinic about the study so that clinicians can inform their clients about the study and answer any questions they may have. At each clinic, recruitment will occur using flyers that will be distributed to all new adolescent clients and their caregivers. In line with recent recommendations for facilitating compliance and building rapport in EMA research with adolescents [71], the flyers will also briefly introduce the Project MAPP research team and include pictures of team members. Interested families will be able to notify study staff if they are interested in participating and would like to complete an eligibility questionnaire through a QR code on the flyer. This method of recruitment was selected so that no clinic needs to provide the study team with any protected health information.

Ethical Considerations

Overview

Project MAPP has been received Boston University ethics committee approval (7636E). Consent, for adolescents who are aged 18 years and caregivers, as well as parental permission and assent, for adolescents who are aged <18 years, will be obtained from all dyads before participation in Project MAPP. Adolescents and caregivers can each earn up to US $570 (refer to the next subsection for details).

Compensation Structure

Adolescents and their caregivers will each be compensated US $30 for completing the baseline study visit. Adolescents and their caregivers deemed ineligible during the baseline visit will each be compensated US $15 for their time. Both adolescents and their caregivers will be compensated US $1.25 per completed EMA survey during the 9 weeks of EMA and US $1.25 per morning report during non-EMA weeks. Adolescents and their caregivers will be eligible for a US $10 bonus for maintaining a weekly EMA compliance rate of ≥75%. During the weeks when the dyads are not completing EMA, they will be eligible for US $5 bonuses if their morning report compliance rate is ≥75%. Adolescents and caregivers will be compensated US $2 for each mental health update report they complete. The total possible amount a participant can earn is US $570. Adolescents and their caregivers will receive gift cards from, for example, Amazon, Walmart, and Target, as compensation. This compensation structure is similar to that of prior studies with adolescents and their caregivers [62,72].

Procedure and Protocol

Figure 1 provides an overview of the study components of Project MAPP. Project MAPP consists of two components: (1) an eligibility screening and baseline assessment and (2) an EMA burst design (Figure 2). All components of Project MAPP will be conducted remotely via Health Insurance Portability and Accountability Act (HIPAA)–compliant video communication platforms.

Figure 1. Proposed study design overview. EMA: ecological momentary assessment. *Participants will still complete morning reports and mental health update reports during the two 3-week breaks from random prompts.

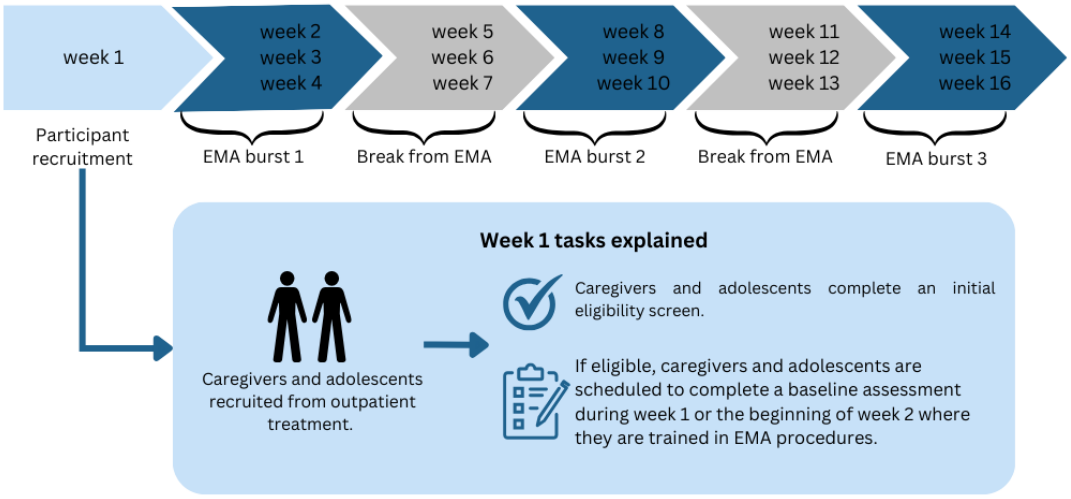

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Figure 2. Ecological momentary assessment (EMA) procedures for the proposed study.

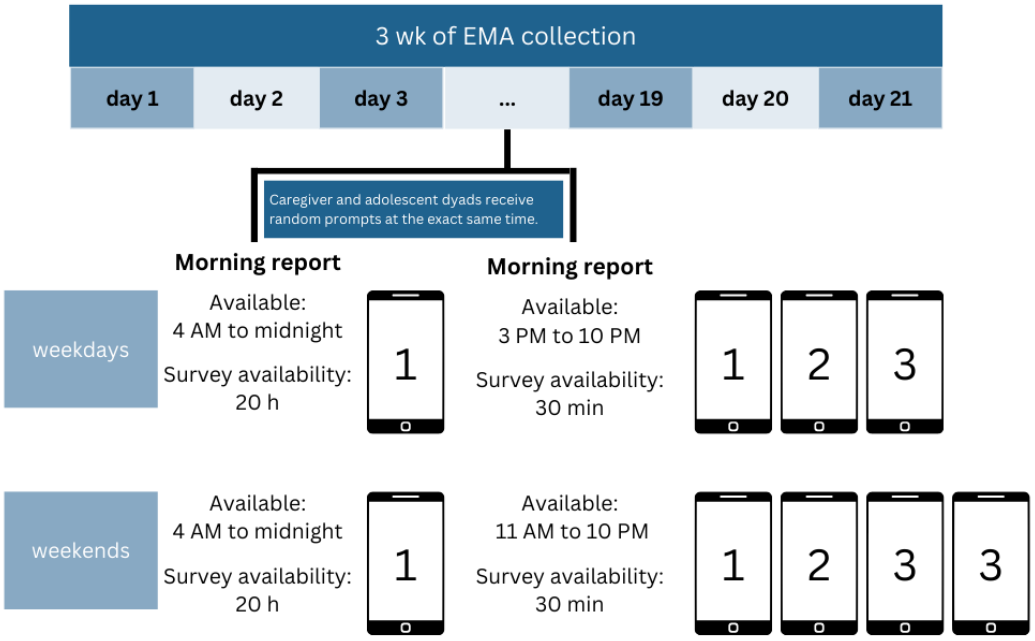

Baseline Study Visit

Figure 3 provides an overview of the procedures for the baseline study visit. Eligible dyads interested in participating in Project MAPP will be scheduled for their baseline assessment session during the second week of their treatment. If dyads are unable to schedule the study visits during the second week of treatment, they will be scheduled as close to the second week of treatment as possible. The baseline session will be offered in 2 formats: In format 1, dyads complete consent, assent, and parental permission forms; complete a formal assessment for AUD; complete baseline assessment measures, including a timeline followback (TLFB) interview for the adolescent; and are trained in EMA study procedures. In format 2, adolescents and caregivers complete all components of the baseline other than the baseline assessments, which they can complete at their own convenience within 72 hours of the baseline session.

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Figure 3. Order of procedures for the baseline study visit. EMA: ecological momentary assessment; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Aged Children; TLFB: timeline followback.

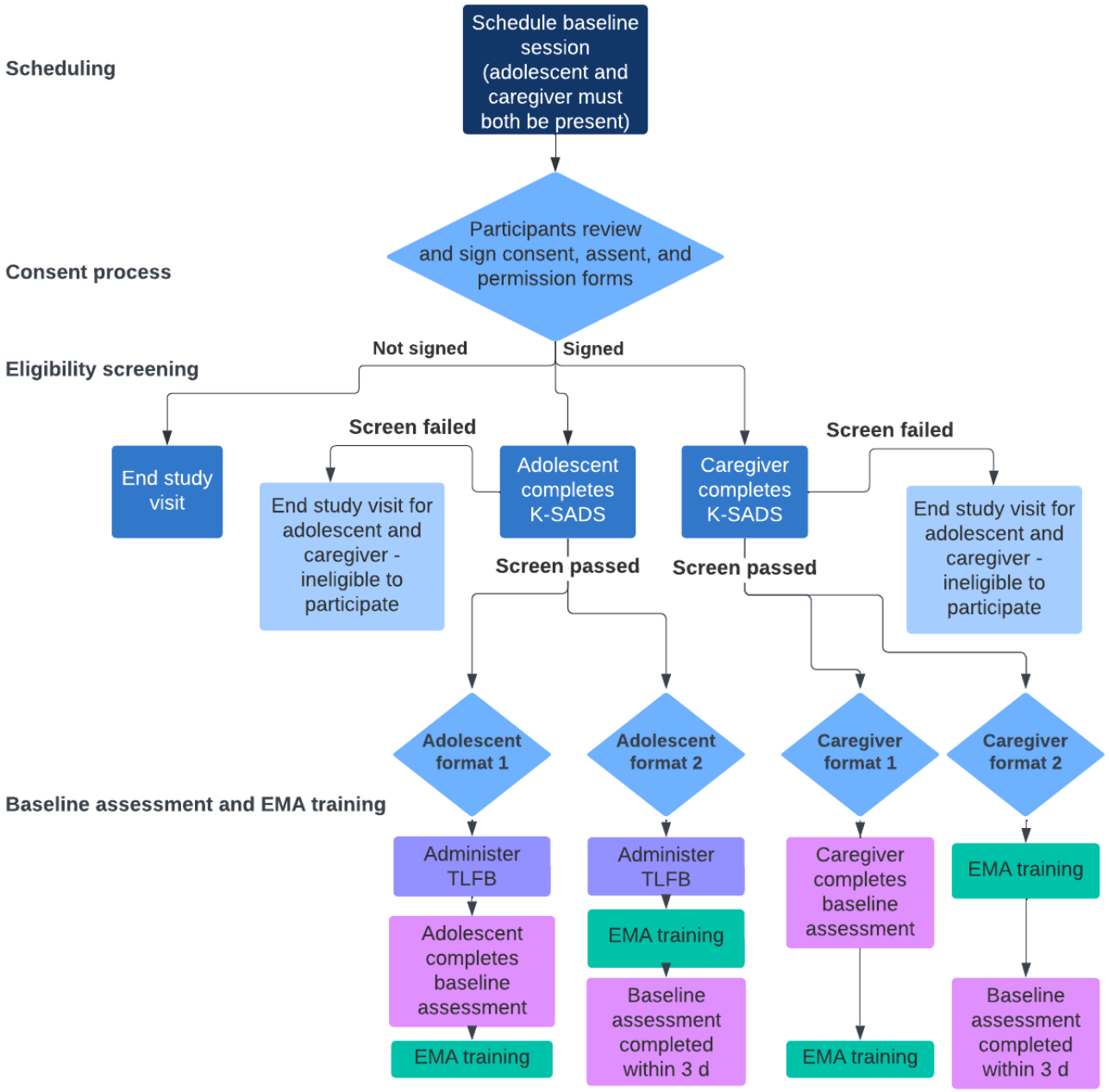

These 2 options are provided to accommodate caregiver and adolescent preferences and time constraints.

For both formats, after completing the consent (for caregivers aged ≥18 y and adolescents aged 18 y), parental permission (for caregivers of adolescents aged <18 y), and assent (for adolescents aged <18 y) procedures, adolescents and caregivers will each complete the Schedule for Affective Disorders and Schizophrenia for School-Aged Children in separate web-based breakout rooms to formally assess for adolescent AUD [73]. Dyads will be notified that they are not eligible for Project MAPP if the adolescent does not meet the diagnostic criteria for AUD, and they will be compensated for their time. Eligible adolescents will complete a 30-day TLFB assessing their alcohol and other substance use (eg, cannabis and nicotine) in the past 30 days. The TLFB is a gold standard assessment for capturing alcohol and other substance use behaviors [74,75].

In format 1 of the baseline visit, caregivers and adolescents will next complete an assessment battery measuring demographic information (eg, age, gender, and family composition) as well as validated self-report measures of the EMA parenting domains and the treatment outcomes of interest (Table 1, column 3). A strength of the parenting measures selected for this study is that they contain parent- and adolescent-report versions, attenuating concerns regarding demand characteristics in parenting measures [76]. Internalizing and externalizing mental health symptoms will be measured continuously using the Child Behavior Checklist and the Youth Self-Report, which are measures from the Achenbach System of Empirically Based Assessment (Table 1) [77,78]. In format 2, adolescents and caregivers will complete these measures on their own time within 72 hours of completing the baseline visit.

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Table 1. Baseline assessment measures and schedule of ecological momentary assessment (EMA) for the constructs of interest.

Construct	Baseline assessment measure	EMA reporter		EMA report	
		Teen	Caregiver	MR[a]	RP[b]
Parenting					
Parental communication	• Network of Relationships Inventory [79] • McMaster Family Assessment Device [80] • Parenting Styles Circumplex Inventory [81]	✓	✓		✓
General parenting practices	• Parental Monitoring Questionnaire [82] • Issues Checklist [83] and Conflict Tactics Scale [84] • Alabama Parenting Questionnaire [85] • Parental Locus of Control [86]	✓	✓		✓
Alcohol- and other substance-specific parenting practices	• Substance-specific parenting measure [87,88] • Alcohol-Specific Socialization Practices [89] • Alcohol-Specific Communication Scale [90] • Substance Use Communication Quality [91]	✓	✓	✓	✓
Core treatment targets					
Treatment motivation	• University of Rhode Island Change Assessment [92]	✓	✓	✓	✓
Alcohol and other substance craving	• Alcohol Urge Questionnaire [93] • Marijuana Craving Questionnaire–Short Form [94] • Questionnaire of Vaping Craving [95] • Tobacco Craving Questionnaire–Short Form [96]	✓		✓	✓
Alcohol and other substance use	• Timeline followback [97] • Fagerström Test for Nicotine Dependence [98] • Penn State Electronic Cigarette Dependence Index [99] • Substance Problem Index–Adolescent [100]	✓	✓[c]	✓	✓
Internalizing and externalizing symptoms	• Youth Self-Report and Child Behavior Checklist [77] • Affective Reactivity Index [101]	✓	✓	✓	
Context					
Location	—[d]	✓	✓		✓
Individuals present	—	✓	✓		✓
Current activity	—	✓	✓		✓

[a]MR: morning report.

[b]RP: random prompt.

[c]Caregiver will be asked questions about their knowledge of their child's past-day alcohol and other substance use in addition to questions about their own use.

[d]Not applicable.

For both formats 1 and 2, the last component of the baseline study visit consists of EMA training. Participants will be instructed to download the EMA software, created using a MetricWire platform (MetricWire Inc), and register for Project MAPP. Research assistants will use an EMA training manual developed for adolescent alcohol and other drug EMA research

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[102,103]. First, adolescents and caregivers are walked through a MetricWire demonstration survey. Research assistants walk participants through completing question types that they will encounter (eg, check boxes, typed responses, and Likert-scale items) and answer any questions that participants may have. Second, participants are led through completing a problem survey report. These surveys are intended for participants to use when they experience any difficulties with the MetricWire app. In addition, research assistants demonstrate the messaging feature of MetricWire where participants can contact any study staff if they have questions or issues with the EMA software. Third, to facilitate the reporting of standard drinks of alcohol, research assistants walk adolescents through a standard drink training on MetricWire. This survey, which is available throughout the study, includes detailed information on what constitutes a standard drink of alcohol.

As the last step of the baseline visit, research assistants will walk participants through a series of procedures intended to maximize the ease of completing the EMA protocol and EMA compliance. These procedures consist of study staff reviewing times where participants are unable to complete EMA (eg, during work or extracurricular activities) and informing participants that they do not have to complete EMA surveys during these periods and that these surveys will not count against their compliance. Furthermore, participants are instructed not to complete EMA surveys when it would be unsafe or uncomfortable (eg, when driving or when a caregiver or peer is looking over their shoulder). Research assistants also inform participants that they will receive push notification reminders, SMS text messages, and telephone calls to facilitate their EMA compliance (greater detail on these procedures is provided in the subsections that follow). Finally, research assistants will inform participants that they will be in frequent contact with them to help facilitate EMA compliance and address any questions that may arise [104]. EMA compliance will be calculated in two ways: (1) total accountable EMA compliance (total number of EMA surveys completed/total number of EMA accountable surveys—accountable surveys refer to reports where an adolescent or caregiver could have completed the survey but did not; this will be the primary means of examining EMA compliance) and (2) total EMA compliance (total number of EMA surveys completed/total number of EMA surveys).

EMA Burst Design and Content

Overview

Caregivers and adolescents will complete 9 weeks of EMA after their baseline study visit session over the course of three 21-day EMA burst periods (Figure 1). Figure 2 provides a detailed overview of the EMA procedures for each study day. The EMA protocol will consist of 2 assessment types, which are discussed in the following subsections.

Morning Reports

Morning reports will be interval-contingent recordings whereby adolescents and caregivers answer questions each morning about caregiving practices; adolescent internalizing and externalizing symptoms; and adolescent past-day alcohol, cannabis, and other substance use (refer to Multimedia Appendix 1 for a complete list of morning report items). Morning reports will be available each day from 4 AM to 11:59 PM. If a participant has not completed the morning report, they will receive push notifications at 11 AM and 3 PM asking them to complete their morning report. Participants will receive an SMS text message at 6:30 PM asking them to complete their morning report if it has not been completed yet. Morning reports were selected over evening reports to reduce substance use recall bias because most adolescent alcohol use occurs in the late evenings [105,106].

Random Prompts

Random prompts (signal-contingent reports) will occur at random intervals from 3 PM to 10 PM during the school week and from 11 AM to 10 PM during the weekend. Blocks will be delivered randomly in 140-minute intervals during weekdays and 165-minute intervals during weekends to yield 3 and 4 random prompts per day, respectively. These numbers of prompts have been found to be manageable for adolescents and caregivers [107]. Participants will be alerted to their random prompts through push notifications on their mobile phones, and the random prompts will be programmed to ensure that they do not occur within a 30-minute window of each other. Participants will receive a push notification asking them to complete the random prompt after 10 minutes if it has not been completed yet. If a participant does not complete the random prompt after 20 minutes, they will receive a text message asking them to complete the random prompt and notifying the participant that they have only 10 minutes left to complete the assessment. Considering that the overarching goal of the protocol is to study caregiving practices in the moment, the random prompts will be delivered to caregivers and adolescents at the same time and will be available for 30 minutes. A concern with a longer window to complete random prompts is that there could be a larger temporal lag between adolescent- and caregiver-reported behaviors (eg, a caregiver completes the random prompt immediately and then the adolescent completes the random prompt after 50 min).

Multimedia Appendix 1 contains a complete list of the Project MAPP EMA items. Caregivers and adolescents will be asked whether they had contact (eg, in person, via SMS text message, or on the telephone) with each other since the last random prompt and complete the measures of caregiver communication as well as general and alcohol-specific caregiving, assessing these behaviors since the last random prompt. Random prompts are commonly used to assess social interactions in EMA research [108-110]. Each random prompt will capture any substance use since the last report, the time use began and ended, and the amount consumed (Table 1). The random prompts will also capture adolescent treatment motivation, alcohol craving, affect, and contextual information (eg, who they are with).

EMA Participant-Tracking Procedures

High levels of EMA compliance are essential to obtaining high-quality data that can rigorously answer the questions outlined in this protocol. The proposed study will implement the following procedures to maximize EMA compliance: (1) As noted in the Baseline Study Visit subsection, the dyads will be trained during the baseline visit by research assistants on using MetricWire and review the times when participants are

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unable to answer prompts and should not answer prompts (eg, when driving). (2) Research assistants will monitor the EMA compliance of all participants daily. (3) Participants will be contacted frequently through the MetricWire messaging feature or SMS text message, based on their preference, to receive EMA compliance feedback. (4) On the morning of the fourth day of each 7-day EMA week period, participants will be sent a message noting whether they are on pace to earn a US $10 bonus for maintaining a weekly compliance rate of ≥75%. For participants who are below the 75% threshold, they will be informed of the number of surveys they need to complete during the remainder of the week to earn the US $10 compliance bonus. (5) At the end of each study week, research assistants will reach out to participants by text message or telephone call, depending on participant preference, to review the participants' EMA compliance from the last week, discuss missed surveys and whether there were any reasons for missed surveys, and inquire whether there were any issues that occurred with the EMA software. (6) Information from procedures 3 to 5 will be shared with all Project MAPP staff on an internal messaging service (eg, Google Chat or Slack). This will help ensure that the entire study team is aware of any emerging issues with EMA compliance and that plans can be discussed early on to address any compliance issues. In addition, this information will be reviewed at weekly Project MAPP study meetings.

Mental Health Update Reports

Considering that aim 3 seeks to examine whether the use of family-focused therapy techniques are associated with changes in caregiving practices, Project MAPP requires a means of collecting information on what is occurring in weekly therapy sessions. The mental health update report will collect information, weekly, on the skills that adolescents and caregivers are learning in outpatient therapy. These reports will capture skills learned or practiced in therapy, caregiver involvement in the session, therapeutic alliance, and the degree to which caregivers support their adolescent's mental health and treatment goals (refer to Multimedia Appendix 1 for a complete list of items). The skills that caregivers and adolescents learn or practice in session will be assessed using the Therapy Process Observation Coding Scale–Self-Reported Therapist Intervention Fidelity for Youth [111], modified for caregiver and adolescent self-reports. This measure captures adolescent-oriented skills (eg, emotion regulation, managing negative thinking, and behavioral activation) and caregiver and family-oriented skills (eg, communication skills, consistent rules, and consequences). When adolescents or caregivers report that an adolescent missed their weekly therapy session, they will complete the mental health update report, which will include specific items assessing why they missed their therapy visit along with most of the constructs assessed in the mental health update report for attended sessions (Multimedia Appendix 1).

Unfortunately, only approximately 4 in 10 individuals of any age who present to substance use services complete treatment [112]. This number may be lower for adolescents [113]; for example, whereas the average outpatient treatment protocol is 16.5 sessions, youth only attend 3.9 sessions on average [114]. Acknowledging the high dropout rates in adolescent outpatient treatment, this study will retain dyads where the adolescent drops out of treatment. If an adolescent or caregiver reports that the adolescent dropped out of treatment, they will complete a version of the mental health update report assessing the reasons for discontinuing treatment, alternative recovery supports that the adolescent is receiving, caregiver support of the adolescent's mental health and substance use, the use of skills learned from therapy or other recovery supports, and experiences of minority stress (refer to Multimedia Appendix 1 for a complete list of items). Dyads where the adolescent successfully completes treatment will also complete the same version of the mental health update report but not be administered questions regarding the reasons for discontinuing treatment (Multimedia Appendix 1).

The mental health update report will be available every Saturday starting at 4 AM. Reminders for the mental health update will follow the same schedule as those for the morning reports. If the participant does not complete the mental health update on Saturday, the mental health update will be available to complete on Sunday.

Statistical Analyses

Data Analytic Approach

The proposed EMA protocol will generate a large database with clustered data. The aims of Project MAPP require a data analytic approach that can accommodate the clustering of reports (level 1) within participants (level 2), the unique timing of reports for each participant in the study, and missingness. Aims 1 and 2 will be assessed using group iterative multiple model estimation (GIMME), an analytic approach that was designed for clustered data [115]. GIMME will be used to model contemporaneous and temporal associations between caregiving practices and adolescent treatment targets [115]. A benefit of GIMME over traditional multilevel modeling techniques for intensive longitudinal data is that it uses a data-driven technique to estimate person-specific networks consisting of both lagged and contemporaneous associations based on unified structural equation modeling. GIMME will be conducted using the R package *gimme* [116].

Descriptive Statistics

Descriptive statistics (eg, means and SDs) will be reported for all focal predictors and outcomes noted in aims 1 to 3. Intraclass correlation coefficients (ICCs) will be calculated for these variables to characterize the degree of variation across participants (ie, between-person variation) and across days or moments (ie, within-person variation) in these constructs. In addition, multilevel growth modeling, conducted separately for each focal predictor (eg, caregiver support) and outcome (eg, alcohol craving) will examine mean level change in caregiving behaviors and core treatment targets over the course of the study.

Examine Momentary Associations Between Caregiving and Core Treatment Targets (Aim 1)

Overview

Hypothesis 1 is that momentary *caregiver reports* of caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices will be positively associated with *adolescent reports* of motivation to

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reduce or stop drinking and positive affect while negatively associated with alcohol craving, alcohol use, and internalizing and externalizing symptoms. Momentary *caregiver reports* of caregiver-adolescent conflict will be negatively associated with *adolescent reports* of motivation to reduce or stop drinking and positive affect while positively associated with alcohol craving, alcohol use, and internalizing and externalizing symptoms. GIMME will be used to model contemporaneous and temporal associations between parenting practices and adolescent core treatment targets [115]. Default settings will predominantly be used across models. Specifically, we will allow autoregressive paths to be freely estimated; and the inference criteria for path pruning will use a Bonferroni correction of α=.05/N, where N is the number of individuals [117,118]. Data will be standardized within GIMME. GIMME uses full information maximum likelihood to account for observations with missing data.

GIMME 1: Positive Affect, Negative Affect, Alcohol Craving, Motivation to Reduce or Stop Drinking, and Alcohol Use Outcomes

Random prompts during the 9 weeks of EMA will be used to examine the contemporaneous and prospective associations of caregiver support, caregiver-adolescent conflict, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices with positive affect, negative affect, alcohol craving, motivation to reduce or stop drinking, and alcohol use. Signal-contingent reports that occur after alcohol use each day will be excluded due to adolescent substance use altering parenting behaviors [87]. Although affect, craving, motivation, and use will serve as the central outcome variables, they will also predict caregiving behaviors in the model because GIMME estimates contemporaneous and lagged associations between all variables in the network. Bidirectional associations will not be included for alcohol-specific caregiving practices because GIMME currently does not support dichotomous outcome variables; therefore, we will be restricted to examining how the use of alcohol-specific caregiving practice (0=*practice not used* and 1=*practice used*) is associated with contemporaneous and future affect, craving, motivation to reduce or stop drinking, and alcohol use.

If there are a sufficient number of observations per participant, sensitivity analyses using the analytic approach in aim 2 (confirmatory subgroup GIMME [CS-GIMME] [119]; for details, refer to the Examine Changes in the Strength of the Associations Between Caregiving Practices and Core Treatment Targets Over the Course of Treatment [Aim 2] subsection) will compare these associations in reports before versus after adolescent alcohol use to understand how alcohol use may alter these relationships.

GIMME 2: Outcomes for Internalizing and Externalizing Symptoms

Morning reports from the 15 weeks of data collection (Figure 1) will be used to examine the contemporaneous and prospective associations of caregiver support, caregiver-adolescent conflict, caregiver monitoring, substance use communication quality, and alcohol caregiving practices with internalizing and externalizing symptoms. Caregiver support, caregiver-adolescent conflict, caregiver monitoring, substance use communication quality, and alcohol caregiving practices will be taken from the random prompts and averaged within day. These analyses will examine associations between caregiving practices and internalizing and externalizing symptoms within day and across days.

Examine Changes in the Strength of the Associations Between Caregiving Practices and Core Treatment Targets Over the Course of Treatment (Aim 2)

Hypothesis 2, aim 1, is that associations for caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices will become stronger over the course of AUD+CODs treatment as caregivers and adolescents learn and practice skills over the course of treatment. Aim 1 associations for caregiver-adolescent conflict will become weaker as caregivers and adolescents learn and practices skills to better manage conflict in the moment. We will use CS-GIMME [119], an extension of GIMME that can model subgroup-level associations within predefined subgroups (ie, EMA burst periods). Subgroups will be defined as EMA burst periods 1, 2, and 3. The CS-GIMME algorithm searches across EMA bursts (ie, group level) for contemporaneous and lagged associations that improve model fit for most of the individuals. Consistent with prior work, the subgroup-level cutoff (ie, in the 3 separate burst periods) will be 51% [120,121], meaning that paths will be included in subgroup networks if they improve fit for at least 51% of the subgroup. Finally, GIMME estimates effects for each individual. Conceptually, this information indicates whether the strength of the associations between caregiving and core treatment targets becomes more frequent (ie, more families demonstrate associations between parenting behaviors and core treatment targets) and whether these associations become stronger across treatment. CS-GIMME will be conducted separately for the 2 sets of outcomes outlined in aim 1. Of note, whereas CS-GIMME for model 1 in aim 1 will be based on burst periods, the CS-GIMME for model 2 in aim 1 will be based on 5-week periods (ie, study weeks 2-6, 7-11, and 12-16).

Examine Whether the Caregiver-Reported Use of Family-Focused Therapy Techniques Is Associated With Changes in Parenting Practices (Aim 3)

Hypothesis 3 is that caregiver reports of learning or practicing family focused therapy techniques in therapy will be prospectively positively associated with increases in caregiver support, caregiver monitoring, substance use communication quality, and alcohol-specific caregiving practices and with decreases in caregiver-adolescent conflict. Multilevel modeling will be used to predict caregiving practices using EMA data. Repeated observations (level 1) will be nested within participants (level 2). Caregiver support, caregiver-adolescent conflict, caregiver monitoring, substance use communication quality, and alcohol caregiving practices will be predicted by techniques learned or practiced in therapy from mental health reports. Caregiving practices will be averaged across therapy weeks (eg, caregiver support will be averaged between therapy sessions X and X+1) to allow for prospective associations between skill receipt and subsequent use. Separate multilevel models will be conducted for each caregiving practice.

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Power Calculations

Aims 1 and 2

The ability to detect effects in GIMME analysis is a function of the number of time point numbers, rather than sample size. Simulation studies have found that GIMME can adequately detect signal from noise and recover accurate group and individual models when there are a minimum of 10 participants and 60 time points (advisable) per person [118,122]. Recent work suggests that the direction of associations is best recovered in GIMME when autoregressive parameters are strong and when there are 100 observations per person [123]. Over the course of the 9 weeks of EMA, there will be 207 random prompts and 112 morning reports. For random prompts, participants would have to complete 29% (60/207) and 48.3% (100/207) of their assessments to reach recommended observations per person for GIMME. For morning report–based analyses (ie, examining internalizing and externalizing symptom outcomes), participants would have to complete 53.6% (60/112) and 89.3% (100/112) of their morning reports to reach recommended observations per person for GIMME.

Aim 3

Assuming a power level of 0.8, a small or medium ICC, and 75% compliance with mental health update reports, the minimum detectable effect sizes for level-1 direct effects in the multilevel model would be 0.15 if the participant retention rate is 93% and 0.17 if the retention rate is 67% [124]. Assuming a power level of 0.8, a small ICC, and 75% compliance with mental health update reports, the minimum detectable effect sizes for level-2 direct effects would be 0.43 with a 93% retention rate and 0.49 with a 67% retention rate [124]. For a medium ICC, the minimum detectable effect sizes for level-2 direct effects would be 0.36 with a 93% retention rate and 0.41 with a 67% retention rate. Considering that the direct effects of interest for aim 3 are level-1 effects, the proposed study would be powered to detect small effects between therapy techniques and the use of caregiving practices.

Results

Pilot Work

As part of a National Institute on Alcohol Abuse and Alcoholism K99 award (K99AA030030), a pilot trial was conducted to assess the acceptability and feasibility of conducting a 7-week EMA study with caregiver-adolescent dyads, in which the adolescent is receiving AUD+CODs treatment in an intensive outpatient treatment program. The acceptability and feasibility benchmarks for the K99 phase are presented in Table 2. Whereas some core benchmarks were met during the K99 pilot study (ie, retention rate ≥80% for caregivers), most of the benchmarks were not met. These included a targeted enrollment rate of ≥75% versus the actual dyad enrollment rate of 62% (16/26), retaining 75% (12/16) of the adolescents versus an 80% target retention rate, EMA random prompt completion rate of ≥80% versus adolescents completing 47.6% (772/1622) and caregivers completing 70.76% (1331/1881) of the random prompts, and a morning report compliance rate of ≥80% versus adolescents completing 55.5% (361/651) and caregivers completing 91.3% (601/658) of the morning reports. The proposed study, which would be funded through the R00 portion of this National Institute on Alcohol Abuse and Alcoholism Pathways to Independence R00 award, contains modifications based on the information learned from the K99 phase, which are discussed in detail in the Methods section (Table 2; Multimedia Appendix 2).

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Table 2. K99 pilot study benchmarks and corresponding R00 proposed changes.

K99 benchmark	Outcome	Proposed R00 protocol modification
Target enrollment rate of ≥75%	Of the 26 eligible adolescent-caregiver dyads, 16 (62%) were enrolled	• Considering that 20.5% of the adolescents did not participate due to citing the severity of their co-occurring symptoms or they went to a higher level of care before their baseline study visit, the R00 phase will recruit from community outpatient substance use clinics, a lower level of care • Whereas the K99 phase only recruited from a single clinic, the R00 phase will recruit from 5 community clinics; the larger potential participant pool across the 5 community clinics will facilitate meeting the recruitment goals of the R00 phase even if enrollment rates fall below the threshold of ≥75% of eligible dyads
Retain ≥80% of the adolescents and caregivers from the baseline assessment through the completion of the 7-week EMA[a] protocol and discharge assessment	100% of the dyads were retained during the 7-week EMA period; 75% (12/16) of the adolescents and 81% (13/16) of the caregivers completed the discharge session	• Considering that 50% of the adolescents did not complete the discharge session because they were being provided a higher level of care (ie, inpatient hospitalization or residential treatment program), the R00 phase will recruit from community outpatient substance use clinics, a lower level of care
Completion of ≥80% of the random prompts	Across the 7-week EMA period, adolescents completed 47.6% (772/1622) and caregivers completed 70.76% (1331/1881) of the random prompts	• Adolescent EMA data linearly declined by week (refer to Multimedia Appendix 2), with a large decrease in compliance between weeks 3 and 4; for the R00 phase, EMA will be administered through a burst designb wherein dyads will complete 3 weeks of EMA, have a 3-week break, complete 3 weeks of EMA, have a 3-week break, and then complete 3 weeks of EMA • To improve compliance, EMA random prompts will only be sent to adolescents and their caregivers from 3 PM to 10 PM during weekdays to avoid prompts being delivered during school hours (this modification will lead to 1 less random prompt each day during weekdays) • The compensation structure will be modified in the R00 phase; in the K99 phase, participants were compensated when they completed 3 out of 5 surveys per day, whereas in the R00 phase, participants will be compensated for each survey they complete (moving to this compensation schedule will incentivize participants to complete surveys even when they can only complete 1 or 2 prompts per day)
Completion of ≥80% of the morning reports	Adolescents completed 55.5% (361/651) and caregivers completed 91.3% (601/658) of the morning reports	• As noted in the modifications based on random prompt compliance, participants were only compensated if they completed 3 out of 5 surveys per day; if participants were unable to answer 3 random prompts (eg, because they were driving or were at school), they may not have completed their morning report because there was no financial incentive to do so; to address this, the R00 phase will compensate participants for each survey they complete, including morning reports

[a]EMA: ecological momentary assessment.

[b]Whereas intensive outpatient programs have more limited and standardized treatment durations, community outpatient clinics vary in their length of treatment. Whereas some of the partnering R00 clinics deliver the 12- to 14-session manualized treatment—the adolescent community reinforcement approach (A-CRA)—others see their adolescent clients for a year or longer. In addition to using a burst design to help increase random prompt compliance, a 15-week burst design EMA study will fully capture the length of treatment for clinics delivering A-CRA and to sample a sufficient period of treatment (ie, almost 4 months) to appropriately test the aims of the R00 phase.

Proposed Study Timeline

No data have been collected for the proposed study. Data collection is anticipated to begin in December of 2024. Project MAPP will take place over the course of 3 years. Study startup tasks (eg, training study staff) will occur during months 1 to 3, and data collection will occur during months 4 to 30. On the basis of this recruitment time frame, the study will need to enroll approximately 3 dyads per month to meet the recruitment goal of 75 dyads. Data checks to ensure the quality of the data will be performed weekly throughout data collection as will data cleaning procedures. Beginning in month 31, by which time most of the data collection will have occurred, data preparation and analysis will be performed for the primary aims of Project MAPP.

Discussion

Summary

Project MAPP seeks to advance our knowledge of how caregiver involvement in AUD+CODs treatment improves outcomes by examining (1) momentary associations between caregiving practices and core treatment targets (eg, motivation to reduce or stop drinking and alcohol craving), (2) changes in the strength of the associations in aim 1 to understand whether caregiving practices become more effective over the course of therapy, and (3) whether learning and practicing family-focused therapy techniques in session are associated with changes in the use of caregiving practices in real time in daily life outside of therapy. Information from this study will hopefully aid clinical practice by informing which caregiving practices positively change adolescent core treatment targets on a more refined and clinically aligned timescale. In contrast to existing caregiving research

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that indicates that greater monitoring before treatment is associated with improved outcomes [125], the proposed study will be able to determine whether caregiver use of monitoring strategies in the moment protects their children from using substances. Data from this study will be on a timescale most relevant to caregivers and clinicians who want to know what caregivers can do during a specific moment in time to promote well-being and mitigate risk for their teens when in treatment [126,127].

Additional Questions of Interest

In addition to testing the primary aims of Project MAPP, we intend to use the data from this study to advance knowledge on associations across multiple timescales (eg, the association between learning or practicing skills and then using them outside of therapy). Theoretical and empirical papers in psychological science have raised awareness of the importance of timescale [54,128]. Aims 1 to 3 of Project MAPP focus on momentary (aims 1 and 2) and proximal (ie, weekly; aim 3) associations. It remains an open empirical question as to whether these are the most appropriate timescales to better understand caregiving processes during treatment; for example, aim 3 will examine whether caregiver skills learned in therapy are associated with the use of caregiving practices in the week after therapy. Alternative timescales (eg, lags of half a week, 2 weeks, 1 month, and the entire study period) may better capture the relationship between learning or practicing skills in therapy and implementing them outside of therapy.

Aims 1 to 3 emphasize the unidirectional role of caregiving behaviors on adolescent core treatment outcomes. A large body of research demonstrates that caregiving and adolescent behavior influence one another reciprocally across time [129-131]. Changes in adolescent core treatment outcomes during AUD+CODs treatment may be a function of improvements in adolescent behavior, which result in improved caregiving behaviors. In turn, these caregiving improvements facilitate positive changes in adolescent treatment outcomes. Furthermore, caregiver involvement in treatment may facilitate treatment outcomes by enhancing the effectiveness of skills that adolescents learn during therapy. Learning or practicing specific skills in therapy, such as emotion regulation strategies, may be more strongly associated with reduced mental health symptoms among adolescents whose caregivers monitor their behavior or are responsive to them. Project MAPP is designed to test alternative mechanisms of positive outcomes, such as these examples, in addition to the primary aims of the study.

Limitations

Although Project MAPP represents an important extension to caregiving research during AUD+CODs treatment, the proposed study will still contain several limitations. First, the study will recruit only a single caregiver per adolescent. Caregiving research has demonstrated unique effects of separate caregivers (eg, unique effects of mothers vs fathers [132]). By not including all caregivers responsible for the adolescent, Project MAPP will miss important information regarding what some caregivers are doing during AUD+CODs treatment. Second, caregivers and adolescents will be repeatedly asked questions about caregiving practices, skill use, treatment motivation, and substance use. There is the possibility for reactivity—that repeated assessments systematically alter caregiver and adolescent behaviors or attitudes [133,134]. Without the inclusion of a control condition (ie, a group of dyads in which the adolescents are receiving treatment who do not receive EMA), Project MAPP will not be able to determine the extent of reactivity to the EMA burst design protocol. Third, given that adolescents and their caregivers will be participating in outpatient treatment, which can last more than a year, Project MAPP will not be able to sample all of an adolescent's time in AUD+CODs treatment. Finally, there are many caregiving practices associated with adolescent substance use [39]. Capturing all these practices via EMA would not be feasible. The selection of caregiving practices was based on the core elements of caregiver-involved interventions for adolescents [8,32] and EMA caregiving research from community samples [53,135].

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Data Availability

All data collected from Project Momentary Assessment of Parenting Practices will be available through the National Institute on Alcohol Abuse and Alcoholism data archive.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ecological momentary assessment items for Project Momentary Assessment of Parenting Practices.
[DOCX File , 151 KB - resprot_v13i1e63399_app1.docx]

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Multimedia Appendix 2
Pilot study ecological momentary assessment compliance by study week.
[DOCX File , 36 KB - resprot_v13i1e63399_app2.docx]

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Abbreviations

A-CRA: adolescent community reinforcement approach
AUD: alcohol use disorder
AUD+COD: alcohol use disorder and co-occurring disorder
CS-GIMME: confirmatory subgroup group iterative multiple model estimation
EMA: ecological momentary assessment
GIMME: group iterative multiple model estimation
HIPAA: Health Insurance Portability and Accountability Act
ICC: intraclass correlation coefficient
MAPP: Momentary Assessment of Parenting Practices
TLFB: timeline followback

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Protocol

Spread and Scale of the Integrated Nutrition Pathway for Acute Care Across Canada: Protocol for the Advancing Malnutrition Care Program

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Abstract

Background: A high proportion of patients admitted to hospital are at nutritional risk or have malnutrition. However, this risk is often not identified at admission, which may result in longer hospital stays and increased likelihood of death. The Integrated Nutrition Pathway for Acute Care (INPAC) was developed to provide clinicians with a standardized approach to prevent, detect, and treat malnutrition in hospital.

Objective: The purpose of this study was to determine if the Advancing Malnutrition Care (AMC) program can be used to spread and scale-up improvements to nutrition care in Canadian hospitals.

Methods: A prospective, longitudinal, mixed methods design is proposed to evaluate the spread and scale of INPAC best practices across Canadian hospitals using a mentor-champion model. Purposive and snowball sampling are used to recruit mentors and hospital champions to participate in the AMC program. Mentors are persons with experience improving nutrition care in a clinical setting and champions are health care providers with a commitment to implementing best care practices. Mentors and champions are trained digitally on their roles and activities. Mentors meet with champions in their area monthly to support them with making practice change. Champions created a site implementation team to target practice change in a specific area related to malnutrition care and use AMC program-specific tools and resources to implement improvements and collect site information through quarterly audits of patient charts to track implementation of nutrition care best practices. An online community of practice is held every 3-4 months to provide further implementation resources and foster connection between mentors and champions at a national level. A prospective evaluation will be conducted to assess the impact of the program and explore how it can be sustainably spread and scaled across Canada. Semistructured interviews will be used to gain a deeper understanding of mentor and champion experiences in the program. The capabilities, opportunities, and motivations of behavior model will be used to evaluate behavior change and the Kirkpatrick 4-level framework will facilitate assessment of barriers to change. Aggregated chart audits will assess the impact of implemented care practices. Descriptive analyses will be used to describe baseline mentor and champion and hospital characteristics and mentor and champion experiences; Friedman test will describe these changes over time. Directed content analysis will guide interpretation of interview data.

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Results: Data collection began in September 2022 and is anticipated to end in June 2025, at which time data analysis will begin.

Conclusions: Evaluation of the AMC program will strengthen decision-making, future programming, and will inform program changes that reflect implementation of best practices in nutrition care while supporting regional mentors and hospital champions. This work will address the sustainability of AMC and the critical challenges related to hospital-based malnutrition, ultimately improving nutrition care for patients across Canada.

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KEYWORDS

malnutrition; nutrition screening, nutrition assessment; hospital; malnutrition care; nutrition; acute care; clinicians; mixed-methods design; decision making; mentor-champion model; virtual training; peer support; virtual community of practice

Introduction

Disease-related malnutrition is prevalent and observed in up to 1 in 2 patients admitted to hospital in Canada [1]. Patients with malnutrition at time of admission are at increased risk of longer length of stay, increased cost of care, disability, morbidity, and mortality [1-3]. Nutrition interventions are associated with improved clinical outcomes including survival [4-6] in patients at nutrition risk or with malnutrition, yet not all patients in need receive nutrition support [1]. The problem of disease-related malnutrition is not unique to Canada; it is an ongoing clinical issue that continues to lack recognition, detection, and treatment in hospitals globally [7,8].

To identify nutrition risk and malnutrition in the hospitalized setting, all patients, regardless of age, body shape and size, should be screened [9]. Several validated tools for nutrition screening exist [10,11]; yet, screening rates vary greatly across hospitals and units [12,13]. It is recommended that patients who screen positive for nutrition risk receive a complete nutrition assessment and appropriate nutrition intervention from a registered dietitian [14], although this practice is not widely implemented [15]. Without standardized nutrition care practices, patients at nutrition risk and those with malnutrition are not identified and may not be referred to a dietitian when needed [1,8,13].

The foundational work required to begin standardizing nutrition care practices in Canadian hospitals has been underway since 2010 (Figure 1). To improve the identification and treatment process for patients at nutrition risk or with malnutrition, best practices were developed and strategies to combat hospital malnutrition were implemented [14-20]. Specifically, the evidence-informed and consensus-based Integrated Nutrition Pathway for Acute Care (INPAC) was developed to support clinicians with addressing nutrition-related gaps in care [21]. This pathway is an algorithm based on minimum clinical practice standards required for prevention, detection, and treatment of malnutrition for patients admitted to medical and surgical units and is a means to standardize nutrition care practices related to screening, assessment, interventions and follow-up [14,22,23].

Figure 1. Overview of malnutrition care initiatives by the Canadian Malnutrition Task Force. INPAC: Integrated nutrition pathway for acute care.

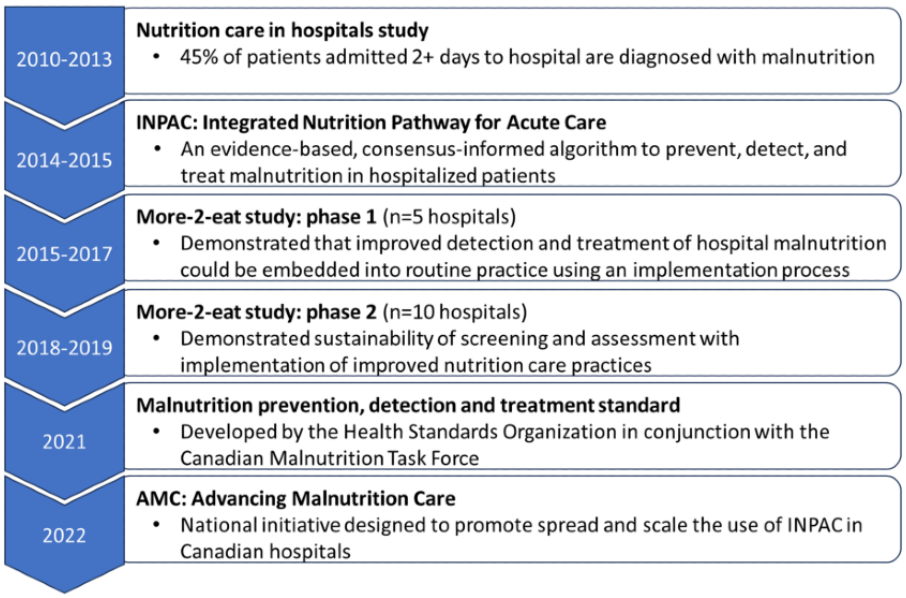

INPAC was tested for feasibility and effectiveness in 2 phases and demonstrated that medical and surgical units in hospitals across 8 Canadian provinces could implement INPAC components such as nutrition risk screening on admission (Figure 1) [15,16,24-26]. In 2021, the Health Standard Organization published a national malnutrition standard (Malnutrition Prevention, Detection, and Treatment - CAN/HSO 5066:2021(E)) [9]. The components of the standard are based

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on INPAC, recognizing the importance of systematizing nutrition care. The standard provides hospitals with best practices that support the detection, treatment, and prevention of malnutrition and improve health outcomes of hospitalized patients [9].

The Advancing Malnutrition Care (AMC) program was developed as a way to spread implementation of INPAC and scale use of the malnutrition standard to improve nutrition care practices in hospitals across Canada [27]. By spread, we are referring to the replication of INPAC implementation from one hospital to the next [28]. By scale, we are referring to development of the infrastructure to support implementation of INPAC and support national use of the malnutrition standards [28]. AMC uses a mentor-champion model to engage and train regional mentors and connect them with hospital champions to both spread and scale nutrition care best practices across Canada in a feasible and effective way. The purpose of this study is to determine if the AMC program can be used to spread and scale-up improvements to nutrition care in Canadian hospitals. The following research questions will be used to evaluate AMC:

1. Is virtual training effective to support mentor and hospital champion capability to implement improved nutrition care practices in Canadian hospitals?
2. What implementation strategies do hospital sites use and what is the impact on nutrition care practices?
3. Does the AMC program increase mentor and champion opportunity, motivation, or confidence for implementing practice change? What are mentor and champion experiences with AMC?
4. What barriers and facilitators do mentors and champions experience related to their implementation roles?
5. Does a virtual community of practice support spread and scale of AMC?
6. How does the qualitative interview data on mentor and champion experiences further explain the impact of the AMC program on the quantitively measured improved nutrition care practices?

Methods

Advancing Malnutrition Care Program Implementation

Design and Objectives

The AMC Core Team recruits, trains, and supports regional mentors, typically dietitians or managers with experience improving nutrition care in a clinical setting and connects them with hospital champions who are typically front-line clinical dietitians. The AMC Core Team supports a quarterly national community of practice to enhance mentor-champion capacity building for implementation and oversees AMC program evaluation (Figure 2). About 20 mentors and 75 hospital champions will be recruited from approximately 20 hospitals across Canada. Having 75 champions across Canadian provinces will support our understanding of a mentor-champion model among health systems in Canada. As this is an existing program being evaluated, a sample size calculation is not necessary to support the sample required to address the research questions. The flow of mentors and champions through the AMC program is described in Figure 3.

Figure 2. Advancing Malnutrition Care program design. AMC: Advancing Malnutrition Care.

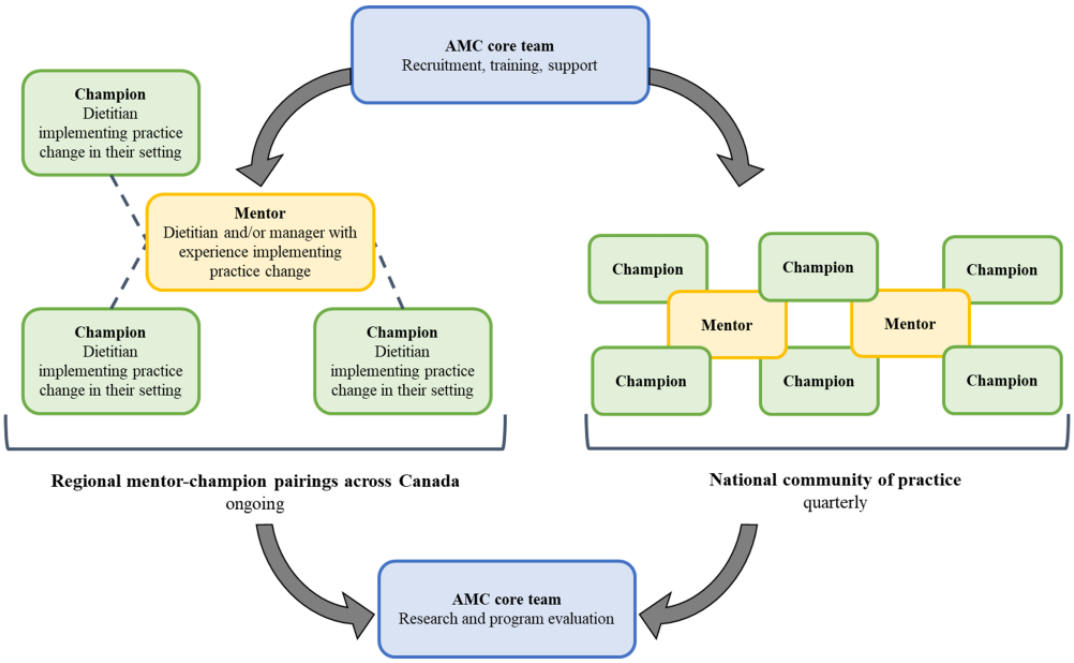

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Figure 3. Mentor and champion flow through the Advancing Malnutrition Care program. AMC: Advancing Malnutrition Care; N/A: not applicable.

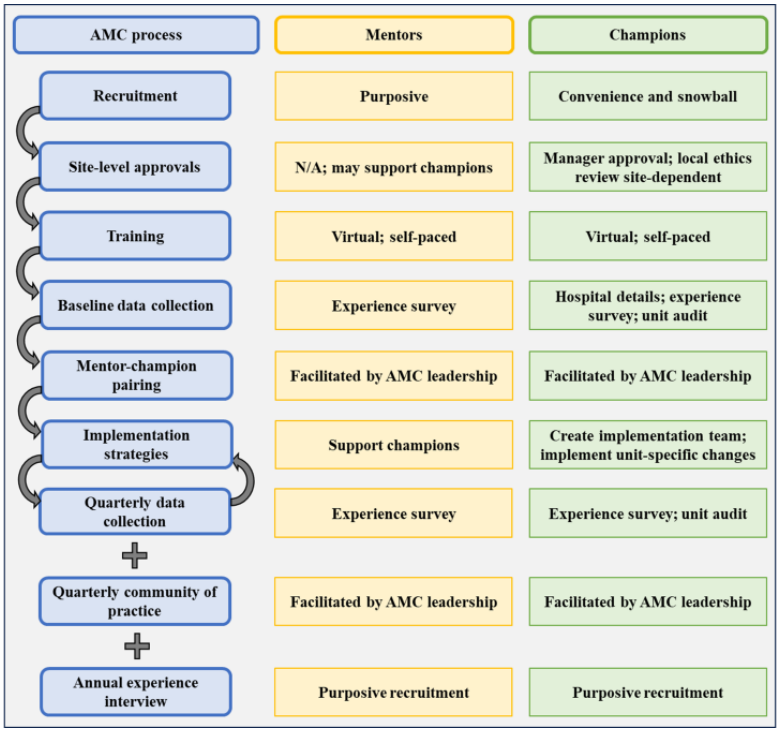

The objectives of the AMC program are to (1) virtually train regional mentors and develop their mentorship and coaching capabilities to support champions with implementing improved nutrition care practices; (2) virtually train hospital champions and develop their capacity to implement change in their practice setting; and (3) facilitate and support ongoing INPAC implementation efforts.

Theoretical Foundation and Frameworks Guiding the Advancing Malnutrition Care Program

An integrated knowledge translation model was used to design AMC [29]. This model uses a collaborative approach by researchers and decision makers. The knowledge to action process [30] is used to implement strategies and move through stages of the action cycle. This model was previously used with the More-2-Eat studies and is applied with AMC [15,31]. Theories of behavior change are also applied to the implementation strategies, with the overall program informed by the Behavior Change Wheel, a method for characterizing behavior change centered around sources of behavior delimited by intervention functions and policy categories [32]. The sources of behavior of this model include capabilities, opportunities, and motivations of behavior (COM-B model) and are interacting to produce behaviors that influence intervention and policy [32]. Strategies to support hospital champions with implementing INPAC in their hospital settings are drawn from the Expert Recommendations for Implementing Change taxonomy—a consensus-based compilation of implementation strategies [33].

Recruitment and Participants

Mentors are purposefully recruited based on their previous involvement with the More-2-Eat studies or other hospital implementation experience. A recruitment email message was sent to Canadian Malnutrition Task Force networks and further disseminated to professional networks (ie, Canadian Nutrition Society) to recruit hospital champions. AMC program information and request for hospital champions is advertised on the Canadian Malnutrition Task Force website [34] and social media feeds; is presented at national conferences and webinars; and shared through snowball sampling. Enrolment is ongoing and responsive to new opportunities. Mentors may also recruit hospital champions from their networks using the general email recruitment message and poster provided by the AMC research team. Ideally, mentors will have a passion for addressing malnutrition care in a hospital setting, demonstrated commitment to successful implementation of INPAC, experience making practice changes and a keen desire to help others, enthusiasm, and capacity to support INPAC implementation, and an understanding of the local hospital and regional contexts. The role of the mentor includes receiving mentorship training from AMC leadership; supporting hospital champions in their region with implementation of INPAC; facilitating mentor-champion meetings and where necessary, one-on-one meetings; participating in quarterly national community of practice meetings; debriefing with AMC leadership at occasional AMC mentor meetings; and completing baseline and quarterly surveys. Mentors may choose to assume a dual role as mentor and hospital champion.

Ideally, hospital champions will have a passion for addressing malnutrition care; enthusiasm and capacity to drive the implementation process; an understanding of the local hospital context; and a commitment to implement best practices and participate in a mentorship model to improve hospital nutrition care. Their role includes completing training on INPAC implementation and sustainability; implementing INPAC practices in their units; receiving guidance from an AMC mentor on how best to implement INPAC; undertaking quarterly patient chart audits to assess changes in practice, and feeding back results to relevant hospital teams (eg, site implementation team);

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sharing progress with AMC mentors; participating in quarterly national community of practice sessions; completing baseline and quarterly surveys.

Training

The AMC leadership developed virtual orientation and training modules based on implementation science, behavior change theory, and real-world experience from the More-2-Eat projects [15-17]. Modules were reviewed by the AMC Core team and are used by mentors and hospital champions before the start of implementation efforts. Mentor training is focused on mentorship and behavior change, including the role of mentors in the AMC program, how to support hospital champions with implementation of INPAC, and sharing strategies for a meaningful and successful mentor-champion partnership. Mentor training is self-paced and takes approximately 2 hours to complete. Mentors have the option to review the hospital champion training materials.

Hospital champion training is focused on INPAC as an algorithm to support malnutrition care, strategies to implement INPAC, how to support behavior change, including the role of hospital champions and mentors, strategies for getting started, developing buy-in and engagement, adoption of changes into routine practice, using behavior change strategies, and collecting data and feeding it back to relevant teams, to support adoption of change in routine practice. Hospital champion training is self-paced, spread over 3 modules, and takes approximately 3 hours to complete.

Both mentors and champions complete a behavior change training module focused on how to implement practice change that aligns with INPAC. This module reviews the basics of change, with a focus on the COM-B model [32], the Behavior Change Wheel [32], and action steps related to the "Plan Do Check Act" [35] model for change.

Mentor-Champion Pairing

The AMC leadership pairs hospital champions with a regional (eg, health systems) mentor. The purpose of the mentor-champion pairing is for mentors to guide hospital champions through implementation efforts, advise on implementation challenges, celebrate implementation successes, and support practice change in the study unit. Based on the number of champions that are paired with a mentor, the mentor will choose to host individual or group mentor-champion meetings. These meetings occur in-person or virtually on a monthly or bimonthly basis, depending on the location of the mentor and hospital champions and their preferences and implementation needs. The AMC leadership can facilitate the first mentor-champion meeting; subsequent meetings are arranged by the mentor-champion pair.

Implementation

Champions are encouraged to first create a site implementation team with select individuals (eg, nurses, physicians, dietitians, food service personnel, and key management personnel) involved in the targeted practice change (eg, improving rates of nutrition risk screening at admission). The number of members and composition of this team can be fluid and may change as specific INPAC activities are implemented. Hospital champions also work with team members on their hospital units to make improvements to nutrition care based on INPAC and the malnutrition standard. The AMC program provides champions with resources and tools (eg, spreadsheet to collect audit data with automated feedback graphs) to support implementation of improved practices. Champions work with their site teams and are encouraged to use the Plan-Do-Check-Act cycle [35] to implement improved nutrition care practices, following a schedule that is feasible for their unit. At the start of the AMC program, champions typically concentrate their implementation efforts on nutrition risk screening and nutrition assessment for those screened at risk, as these practices drive all other nutrition care within INPAC [14,16]. When nutrition risk screening and assessments are routinely integrated into patient care, implementation efforts are focused on other INPAC activities (eg, food intake monitoring), while still conducting occasional checks to make sure screening is maintained.

Community of Practice

An online national community of practice occurs every 3-4 months and is hosted by the AMC leadership. The community of practice offers mentors and champions the chance to receive further education related to implementation and connect with peers across the country to foster continued motivation for the program. The community of practice is also an opportunity to address common challenges, promote the implementation of further INPAC activities, and discuss strategies for sustainable malnutrition care practices amongst a group of like-minded individuals. Topics discussed at community of practice sessions evolve based on challenges and needs identified by mentors and champions.

Anticipated Time Commitments and Timelines

There are multiple factors that can largely influence the time it takes to implement nutrition care practices in a hospital setting, including staffing restraints, organizational priorities and culture, barriers, facilitators, and baseline nutrition care practices. The fluidity of these factors is a barrier to precisely determining the time commitment affiliated with the mentor and champion roles. In addition, the role of mentors and champions is likely to evolve as the program ages. In general, implementation of nutrition risk screening and standardized nutrition assessment is expected to occur over a duration of 12-18 months.

The AMC program began recruiting mentors in April 2022 and champions in September 2022. The first community of practice was held in September 2022 and was structured based on previous implementation work from the More-2-Eat study [17]. The AMC program is anticipated to continue for several years with new hospitals, champions and mentors joining over the time. AMC leadership expects that timeline flexibility will be needed to accommodate shifting priorities, staffing restraints, barriers, and reduced hospital capacity secondary to public health emergencies or other constraints.

AMC Program Evaluation

A prospective, longitudinal, convergent parallel mixed methods design is being used to evaluate the AMC program [36]. The

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COM-B model is built into many of the data collection tools and strategies used in AMC (eg, interview guide designed to understand mentors' and champions' experiences) and will be used to evaluate behavior change, including change over time. Kirkpatrick's 4-level framework will also be used to assess mentor and champion barriers to change by measuring their reaction to the training, learning of best practices, use of implementation strategies, and practice changes made [37]. Mentors and hospital champions are the primary participants in this program evaluation. Patient-level data that will be used for chart audits to assess the impact of improved nutrition care practices will be obtained by the hospital champion and transmitted to the AMC program team in an anonymized aggregated format, thus, patients are not considered "participants" in this program evaluation.

Baseline Data Collection

After AMC program training, mentors and hospital champions complete a baseline survey before the mentor-champion pairing and implementation of nutrition care practices (Table 1). Data collection is completed through a secure on-line platform (Qualtrics). The baseline surveys take approximately 30 minutes to complete and are voluntary. Mentors and hospital champions have the option to skip over any questions that they prefer not to answer. Hospital champions also complete a survey to describe their hospital and baseline nutrition care practices. This survey takes approximately 10 minutes.

After baseline surveys are complete, hospital champions complete a unit audit to determine nutrition care activities of patients since admission. Ideally, the chosen units will have an engaged health care team interested in implementing improved nutrition care practices and a minimum of 20 beds with longer stay patients (≥3 days) who are suitable for prevention, diagnosis, and treatment of malnutrition (ie, nonpalliative, pregnant, or postpartum). One weekday (eg, Tuesday) is selected as the audit day and data collection for the audit is conducted over a short time period (ideally 1-2 days) to capture current nutrition care practices. All patients on the chosen unit on the audit day are to be included in the audit process. Resources including an audit tool and audit tracking spreadsheet are provided by AMC leadership to facilitate the audit process. Alternatively, champions are encouraged to use their electronic medical record to populate an audit report, if available. Results from the audit are for internal hospital use only and are not shared with the AMC leadership. Rather, aggregated data from the unit audit will be transmitted to the AMC program in the form of an audit summary (eg, number screened at admission). It is anticipated that the unit audit will take up to 8 hours to complete if done by hand and submitting the audit summary through the online platform will take 10 minutes. Hospitals that have electronic medical records and can pull some or all of these data routinely will use this method for the audits. Hospital champions are encouraged to share these results with their implementation teams and site leadership to initially demonstrate a reason for change, and then to demonstrate if their change efforts are having an impact. Data collected aim to be beneficial for individual hospitals while the aggregate data deepen our understanding of the overall effectiveness of the AMC program.

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Table 1. Overview of data collection tools used in evaluation of the Advancing Malnutrition Care program.

Data collection tool	Baseline		Quarterly		Annually	
	Mentors	Champions	Mentors	Champions	Mentors	Champions
Experience survey						
Demographics						
Age group, gender, racial background, professional role, length of time working in the hospital, and geographical region	✓	✓				
Implementation experience						
Implementing nutrition care practices and using a mentor-champion model	✓	✓				
Behavior change						
Measures of capability, opportunity, motivation, and confidence in being a mentor or champion	✓	✓	✓	✓		
Hospital details survey						
Hospital and unit(s) names, unit type(s), bed capacity, and staffing details		✓				
Implementation status of nutrition care best practices related to INPAC[a]						
Status of screening, assessment, weight and food intake monitoring, use of energy-dense or protein-dense supplement with medication, and discharge planning		✓				
Unit audit summary						
Number of patients: in the audit, screened for nutritional risk, at nutritional risk, with a nutritional assessment (ie, SGA[b]) completed, who scored SGA A, B and C, with food intake monitoring recorded, and with body weight measured within 48 hours of admission		✓		✓		
Average timing of: SGA from screening (in days), nutritional screening from time of hospital admission		✓		✓		
Frequency of specific actions taken to improve nutrition, that is, nutritional interventions		✓		✓		
Site progress survey						
Summary of implementation activities undertaken on their units				✓		
Semistructured interviews					✓	✓

[a]INPAC: integrated nutrition pathway for acute care.

[b]SGA: subjective global assessment.

Quarterly Data Collection

Approximately 3 months after baseline data collection, and quarterly thereafter, AMC leadership sends the mentor or champion a reminder to repeat the experience survey to solicit changes in their experiences. Hospital champions also complete a site progress survey and a summary of implementation activities undertaken to track site implementation progress (Table 1).

Qualitative Data Collection

The baseline hospital champion and mentor surveys provide an opportunity for the participant to indicate interest in being part of a future interview. One year after the start of implementation and approximately yearly afterward, select interested mentors and hospital champions may be asked to take part in an interview to gain a deeper understanding of their experiences with the AMC program and learn of strategies that they feel would enhance the program. Specifically, topics center on the mentor-champion relationship, COM-B, reimplementation, and program sustainability and scale (Multimedia Appendix 1). Due to the potential number of mentors and champions participating in AMC, all who express interest in participating in an interview may not be invited to do so. Interview participants will be based on trying to attain regional, hospital, and champion diversity. Mentors and champions will complete a separate informed consent process if invited to participate in an interview. Interviews will be conducted virtually or by phone and are expected to last 30-45 minutes. Closed captioning transcription will be used for web-based interviews and telephone audio files

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will be transcribed by a member of the research team or an independent professional transcriptionist.

Statistical Analyses

Analyses described herein are related to the stated research questions; it is anticipated that additional secondary analyses will be completed. Briefly, analyses will include descriptive summaries (eg, means, SDs, and frequencies) of baseline mentor, champion, and hospital characteristics and mentor and champion experiences. Friedman test will be used to describe changes in mentors' and champions' experiences and their capability, motivation, and opportunity for implementing change over time (eg, at baseline and quarterly thereafter). Implementation of nutrition care practices will be summarized and compared between time points (eg, baseline and final audit) using chi-square tests to compare the proportion of patients who received selected nutrition care practices (eg, screening, weight monitoring, food intake monitoring) to provide insight into the sustainability of practices implemented. All data will be in aggregate form and no participant will be identifiable. Quantitative analyses will be conducted using SPSS (version 28.0.1.1; IBM Corp), GraphPad Prism Version 10.0.2, and Excel (Microsoft Corp).

Transcribed interview data will be checked by the interviewer [KF]. The COM-B model [32] will be considered when deductively coding data line-by-line. Directed content analysis [38] will guide the process of using the COM-B model to develop themes, which will be informed, described, and supported with quotes from the data. A summary of emerging themes will be reviewed with a minimum of 2 other researchers and will be mapped to the Behavior Change Wheel [32] to describe mentors and champions experiences with the AMC program and inform any changes needed. Qualitative data analyses will be conducted using Excel and NVivo 14. All data will be stored in a secure Faculty of Health server for use by the Nutrition and Aging Lab. VPN access is required to access this server. Folders and files will be encrypted and only available to AMC program evaluation investigators.

Ethical Considerations

This study is approved by the University of Waterloo Human Research Ethics Board (ORE 44153). Written informed consent is obtained from mentors and hospital champions before data collection. Mentors and hospital champions create and submit a unique 9-digit identifier to be used during the data collection process to link responses while maintaining anonymity. Participating hospital sites determine on an individual basis if local research ethics board approval is required for hospital champions' participation in the AMC program.

Prospective mentors and hospital champions who indicate interest in the AMC program will receive an electronic package that includes a detailed written and video description of the AMC program, a study information letter, and a consent form. Consenting champions will receive an electronic package that includes a memorandum of understanding and a data sharing agreement that is signed by the hospital site and the University of Waterloo. This process ensures that the hospital understands data collection that will occur, and how the hospital will be acknowledged in publications that result from the AMC program.

Results

Data collection started in September 2022 and is projected to be completed by June 2025. As of August 2024, a total of 19 mentors and 46 champions had enrolled in the AMC program. Data analysis is projected to begin in July 2025, and results are expected to be published in 2026.

Discussion

Anticipated Outcomes

Evaluation of the AMC program is anticipated to inform the applicability of a mentor-champion model to spread and scale implementation of nutrition best care practices in Canadian hospitals. To date, few studies have observed, documented, and evaluated the process of spread and scale of a health innovation using a web-based mentor-champion program. To our knowledge, this is the first study to document and report on the national spread and scale of a malnutrition care initiative using a mentor-champion model. The documented success of 10 diverse hospitals implementing change to prevent, detect and treat malnutrition [15-17] suggests feasibility for spread and scale across Canadian hospitals.

The focus of the AMC program is on nutrition risk screening, assessment, and intervention in a hospital setting. The AMC program is unique as it is training mentors to support regional site hospital champions in their implementation efforts whereas mentorship in the More-2-Eat studies was provided through central administration [26]. The mentorship and implementation skills developed by all those involved in the AMC program also aim to boost confidence in how to be a mentor, how to change practice, and ultimately, how to make a difference in their own hospital and across the country. The AMC program aims to support hospital teams across Canada to address critical challenges related to hospital-based malnutrition, and ultimately improve nutrition care for patients across the country. Several of the educational goals (eg, improving clinical performance, recommending practice change, and offering decision-making support) align with the goals of academic detailing [39], and may provide an additional lens through which to consider the evaluation of this work. In contrast to the evaluation outlined herein, academic detailing conducts evaluation beyond changes in the decision-making process and also assesses the impact of education on patient-centered outcomes and resource use [39]. These are evaluation metrics that should be considered in future work and supplemented with data collection methods that capture the patient perspective (eg, interviews) on the impact of improved nutrition care on their stay.

Strengths and Limitations

A strength of the AMC program and corresponding evaluation is the incorporation of models (eg, COM-B model [32]) and frameworks (eg, Kirkpatrick 4-level framework [37]) across stages of program development, implementation, and evaluation. Furthermore, the program includes hospital sites of various sizes, across Canadian provinces, and includes various in-patient

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units. These strategies support the generalizability of our findings, which will ultimately be determined based on the final number and demographics of participating sites. Our approach to program evaluation uses a mixed methods approach and will deepen our understanding of program effectiveness from both quantitative and qualitative perspectives. The lack of control sites for comparison during the evaluation process may be viewed as limitation although previous work in Canada has highlighted the prevalence of nutrition risk screening in hospital and has documented the need for improved implementation practices related to nutrition care [1,15-17,23].

Conclusions

Evaluation of the AMC program will help support implementation of program changes aimed to positively impact nutrition care interventions. Mentors and champions are needed to implement sustainable nutrition care best practices, and this evaluation allows a deeper understanding of their experiences with the AMC program and will inform our ongoing efforts to spread and scale the AMC program, sustainably, across Canada. Ultimately, the lessons learned, and the tools developed by the AMC program and this evaluation, will aim to support optimized nutrition care for all patients.

Acknowledgments

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Data Availability

The datasets generated during and/or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

HK, CL, RD, RN, LG, JPA, and KLF contributed to conceptualization; HK, CL, RN, LG, and KLF managed methodology; KLF and RD handled project administration; HK contributed to supervision; KLF wrote the original draft; HK, CL, RD, RN, LG, and JPA contributed to writing—review and editing.

Conflicts of Interest

KLF reports honoraria from Abbott Nutrition; LG reports honoraria from Baxter, Fresenius Kabi, Takeda; consultancy with Baxter, Fresenius Kabi, Takeda, and Abbott Nutrition; research funds from Baxter, Fresenius Kabi, and Takeda; HK reports honoraria from Nestle Health Sciences; CL, RD, RN, JPA declare that they have no competing interests.

Multimedia Appendix 1
Advancing Malnutrition Care mentor and champion interview guide.
[PDF File (Adobe PDF File), 169 KB - resprot_v13i1e62764_app1.pdf]

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Abbreviations

AMC: advancing malnutrition care
COM-B: capabilities, opportunities, and motivations of behavior
INPAC: Integrated nutrition pathway for acute care

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Protocol

Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study

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Abstract

Background: Family and community nurses (FCNs) play a crucial role in delivering primary care to patients within their homes and communities. A key aspect of their role involves various health interventions, which are influenced by their unique competencies, such as health promotion, advanced clinical knowledge, and strong interpersonal skills. However, it is essential to understand which specific health outcomes these interventions impact to better understand the relationship between FCNs' skills and the health results.

Objective: This study aims to outline the steps we will take to develop a set of core outcomes. These outcomes will be particularly sensitive to the health interventions carried out by FCNs, providing a clearer picture of their practice's impact.

Methods: A Delphi survey will be used for this research, conducted from January to December 2024. The process will involve 5 steps and input from 3 stakeholder categories. These stakeholders will help identify a preliminary list of outcomes that will form the basis of our core outcome set (COS).

Results: This guideline will be beneficial for a wide range of stakeholders involved in COS development, including COS developers, trialists, systematic reviewers, journal editors, policy makers, and patient groups. As of January 2024, we have successfully completed the first stage of the study, with the stakeholder group approving the reported outcomes and assigning participant lists for each stakeholder group.

Conclusions: This study will provide a roadmap for identifying the key health outcomes influenced by the interventions of FCNs. The multistakeholder, multiphase approach will ensure a comprehensive and inclusive process. Ultimately, the findings will enhance our understanding of FCNs' impact on health outcomes, leading to more effective primary care strategies and policies.

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KEYWORDS

clinical knowledge; core outcomes set; Delphi survey; family and community nurse; health interventions; health promotion; primary care; stakeholder engagement

Introduction

Family and community nurses (FCNs) provide primary care services to patients within their homes and communities [1]. Their core activities span a broad spectrum of primary services, including health promotion and primary, secondary, and tertiary prevention, focusing on the health and well-being of communities and populations [2]. These specialized professionals are crucial as they deliver accessible and comprehensive primary care services to individuals and communities, particularly in underserved areas and communities with high rates of chronic diseases [3]. Hence, they play a pivotal role in promoting health, preventing disease, and managing chronic conditions by fostering close collaborations with other health care providers to ensure comprehensive patient care. Although various outcomes linked to the activities of FCNs have been described in recent literature [4-8], a formal core outcome set (COS) is yet to be established [9].

Even though FCNs are primarily employed in primary care settings, they have been recognized as key connectors between the various levels of care and health care providers involved in primary, secondary, and tertiary care levels [10]. Primary care is the first level of contact between a patient and the health care system, focusing on illness prevention, health promotion, and the diagnosis and treatment of common conditions [11]. Secondary care involves specialized medical care provided by health care professionals such as specialists, nurses, and technologists, involving more complex medical procedures and treatments in health care facilities [12]. Tertiary care refers to specialized and complex medical and surgical treatments provided by specialized health care providers in specialized centers. In this intricate scenario, FCNs facilitate a smooth transition of care between the various levels of care in a typical patient journey, addressing the challenges of chronic diseases by providing preventive care, health education, and referrals to specialists when necessary [13,14]. This ability to provide comprehensive care and coordinate with other health care providers enables FCNs to ensure that patients receive seamless and effective care across different health care system levels [15].

The curricular competencies of FCNs, as described in recent literature through the ENhANCE project [16], are primarily based on health promotion, high relational competencies, skills, and advanced clinical knowledge. These competencies define the health domain of FCNs as a specific FCN health intervention. According to Caruso and colleagues [16], to frame an integrated view of the complex relationship between curricular competencies and health outcomes, it is necessary to clarify which specific health outcomes are susceptible to the domains described in defining the role of FCNs.

In essence, aligning a specific domain with a health outcome is crucial for 2 main reasons. First, it allows health care providers and policy makers to determine the effectiveness of the FCN role [17]. Second, linking specific domains to specific health outcomes enables the measurement and comparison of the impact of different domains, thereby informing decisions about which domains are most effective for improving health outcomes [18]. Moreover, matching interventions to outcomes helps ensure that resources are used effectively and efficiently [19]. Health care providers and policy makers can prioritize resource allocation and improve health outcomes for the greatest number of people by focusing on domains that impact health outcomes. Lastly, matching domains to outcomes also promotes accountability and transparency in health care [18]. By clearly documenting the impact of domains on health outcomes, health care providers and policy makers can demonstrate their commitment to improving health and provide evidence of their progress toward this goal. However, even though the nature and classification of the health domain provided by FCNs are clearly recognized in the literature (eg, ENhANCE Project - European Curriculum for Family and Community Nurses) [15], the health outcomes that are susceptible to those interventions remain largely undefined and poorly described, and no COS has been defined in relation to the FCNs [9].

A COS is a standardized and agreed-upon set of outcomes that should be measured and reported in all studies of a particular condition or intervention [20]. A COS helps ensure that the most important and relevant outcomes are measured and reported consistently across studies, allowing for meaningful comparison and synthesis of results [20]. Developing a COS involves a systematic and collaborative process involving stakeholders such as patients, health care providers, researchers, and policy makers. The goal is to identify the most important outcomes, starting from a defined framework and developed from the perspective of patients, ensuring that these outcomes are relevant and meaningful to all stakeholders [20,21].

A COS can improve the quality and comparability of research by standardizing the measured and reported outcomes, informing clinical decision-making, and supporting evidence-based health care. It can also help to reduce the risk of selective reporting of outcomes and publication bias, leading to a more comprehensive understanding of the impact of a domain on health outcomes [20,21]. This COS is therefore labeled as the Family and Community Nursing Core Outcomes Set (FCN-COS), using the approach proposed by Moher and colleagues [22]. This protocol will develop FCN-COS sensitive to the health interventions that characterize the practice of FCNs. The objectives of the study are to (1) determine a consensus with a Delphi survey regarding an FCN-COS and (2) develop an FCN-COS sensitive to the health domains that characterize the practice of FCNs involving stakeholders such as patients, health care providers, researchers, and policy makers.

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Methods

Design

This protocol is designed to incorporate a multimethod and multiphase approach from January to December 2024. It adheres to the recommendations of the "Core Outcome Measures in Effectiveness Trials" (COMET) Handbook (version 1.0) [23] and the Guidance on Conducting and Reporting Delphi Studies (CREDES). The development of the FCN-COS guideline will commence in January 2024 and will be carried out in 5 stages.

- Stage 1: compilation of a preliminary, evidence-based list of reviewed outcomes for consideration in the FCN-COS.
- Stage 2: execution of a web-based Delphi survey to validate the classification and work toward a reporting guideline for FCN-COS.
- Stage 3: conducting a final web-based consensus meeting to identify the definitive outcomes for inclusion in the FCN-COS reporting guideline.
- Stage 4: development of a high-quality reporting guideline and a detailed explanatory document, transforming final FCN outcomes into definitive outcomes and domains.
- Stage 5: Postdevelopment activities, including pilot-testing and dissemination of the results.

The process will involve 3 categories of stakeholders: health care professionals, methodological experts, and service users. These stakeholders will contribute to identifying the preliminary list of proposed outcomes, participate in the Delphi survey rounds, contribute to the consensus meeting, and review the materials produced for disseminating the results.

Stage 1

Preliminary List of Outcomes

The practice of FCNs has significantly contributed to the development of comprehensive health interventions. The preliminary list of proposed outcomes is based on the Classification Clinical Care Classification System (CCC, version 2.5), which provides standard terminology for outcomes and domains, facilitating the documentation of nursing assessments in home care settings. This classification comprises 176 nursing diagnoses, including 60 primary outcomes and 116 diagnostic subcategories. The outcomes included in the preliminary list are defined using existing taxonomies [24], supplemented by a summary of outcomes from a recent systematic review [9] (Multimedia Appendix 1 [5,8,13,25-36]). Additionally, the literature review that will serve as a foundation for developing a preliminary list of outcomes [9] will be updated with specific searches in MEDLINE, CINAHL (EBSCO), Global Health (Ovid), Scopus, and Web of Science. The steering committee will approve the final list of outcomes. The Delphi survey will present the outcomes within each domain to participants in a random order.

Preliminary Consensus Meeting

A preliminary consensus meeting has been arranged to define specific methodological aspects of the Delphi survey among the authors of the study protocol. Specifically, an initial web-based consensus meeting was held to define domains. The preliminary outcomes are based on the CCC (version 2.5) taxonomy [24], serving as an evidence-based classification to initiate the preliminary FCN-COS. These preliminary outcomes, developed in the home care setting, have been identified as a crucial starting point [24].

Moreover, a web-based meeting was held in the designing phase of the protocol to discuss strategies for mitigating the risk associated with a low response rate to the Delphi survey. Before starting with the Delphi survey, a brief video will be disseminated among the participants to familiarize them with the project, particularly focusing on the timeline and rounds of discussion.

Stage 2

Delphi Surveys

A web-based Delphi survey will be started to generate consensus regarding the preliminary list of outcomes. We will use the Delphi technique to obtain consensus from the panel of participants through 2 rounds of discussions. Therefore, the first round of discussion will take place from the outcomes identified in the previous stage, inviting participants to add further outcomes not included in the preliminary outcomes. Outcomes identified during the first round will be included in the second round of the Delphi process outcome item. The second round of discussion will take place to provide feedback and identify further outcomes from participants. More precisely, participants will reevaluate their original rating from the first round by including the other participants' overall rating for each outcome. An outcome will be included in the final FCN-COS with a consensus equal to or greater than 80% in all stakeholder groups rating the outcome as critically important.

Participants: Panel Composition

We plan to involve various stakeholder groups, each contributing a balanced mix of skills and competencies. These groups include health care professionals in primary care, health care researchers, nurses actively involved in nursing regulatory authority boards, and service users. The first group will consist of individuals who have experienced primary nursing care within the past 2 years. The second group will focus on research methods to provide robust support for the Delphi survey methodology. Service users will offer feedback based on their experiences in primary care.

Recruitment Process

Potential participants will receive personal emails explaining the project and its objectives. Before initiating the survey, we will organize a web-based meeting to help participants better understand the project's aim. We will then ask them to complete the first round of the Delphi survey within a 2-week time frame. Participation in the survey is optional, and informed consent will be obtained from those who choose to participate. Each participant will be assigned a unique identification number for the 2 rounds of the Delphi survey. We will request the contact authors from each FCN-COS developer stakeholder group to invite their coauthors to provide feedback. This approach ensures that we gather opinions from both clinical and methodological experts in FCN-COS development. At the end of the 2-week

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period, we will send reminders to participants to complete the survey.

We will collect demographic data, including age, profession, years of experience, educational background, and previous experiences with COS development. Each stakeholder who completes the first round of the Delphi survey will be invited to participate in the second round. We will obtain their name and informed consent to be recognized as a member of the Delphi group in the publication resulting from this research.

Delphi Scoring and Software

The reporting guideline outcomes listed will use a 9-point scale, with 1-3 labeled as not important for inclusion in the COS, 4-6 labeled as important but not critical for inclusion in the COS, and 7-9 labeled as critical for inclusion in the COS [37]. Participants will also be allowed to score "maybe" if they are unable to offer an opinion as to whether the reporting guideline outcome is important or not. An electronic survey format called "web-based" will be used for managing the Delphi surveys [23].

Data Analysis

Descriptive statistics will be used for each survey round to determine the overall scores for each stakeholder group, considering the 3 categories (not important, important but not critical, and critical) to determine whether outcomes are critical for the FCN-COS. Only responses from participants who will rate at least 50% of the outcomes will be included in the analysis. By comparing the distribution of the mean overall scores from the second Delphi round between participants who attended the consensus meeting and those who did not, selection bias between the Delphi procedure and the consensus meeting (see Stage 3 section) will be evaluated. Data analysis will be performed using SPSS Statistics for Windows (version 28; IBM Corp).

Stage 3

Consensus Meeting

The stakeholder group of 100 people will be included in a web-based interactive consensus meeting. The consensus meeting will be represented through a short study overview as outcomes reported by each stakeholder group. The outcomes where the consensus meeting is reached will be considered first to ratify those results. If a consensus meeting is reached for other outcomes, they will be considered according to the stakeholder groups. An opportunity to discuss each outcome will be given to all participants, defined by an anonymous scoring method, between the ones defined at the consensus meeting. Stakeholders will define the final outcomes based on the review of the responses from Delphi participants. The consensus meeting will be fundamental to identifying the outcomes included in the reporting guideline for FCN-COS development. If 70% of the consensus meeting participants favor the outcome's inclusion, it will be considered consensus. The best form of communication in the consensus meeting will be determined by comprising methods of feedback (eg, track changes) and ensuring disagreements' resolution. In the end, a written report after the consensus meeting will be circulated for comment.

Delphi Round 1

Each outcome will be presented to reflect the outcomes' clarity or ambiguity [23]. Every participant will be asked to score each outcome, and after that, they could add any other outcomes they believed to be added to develop FCN-COS. The research group will revise the entire reporting list of outcomes. Each outcome will have a summarized view, including the scored outcome and its distribution. All outcomes will be carried forward to round 2. The response rate of participants as all the participants completed the survey compared to the sent email invitations. The incomplete answers will also be monitored.

Delphi Round 2

In the second round, each participant who participated in the first round will be shown the number of respondents and the distribution of scores for each outcome. They will be asked to rescore the outcome of the other Delphi participants and to justify any reason for an eventual change (eg, if a participant changed their score from "not critical" to "critical" in the second round). For each outcome, the number of participants who have scored it and the distribution of scores will be summarized. When the second round is completed, the attrition bias will be considered by comparing 2 groups of the first and second rounds. A comparison will be developed between participants who completed the second round and those who completed only the first one. Changes in participants' scores will also be examined, and the reasons for changes between the 2 rounds will be summarized.

Consensus Definition

A consensus will be defined and obtained before participants take part in the Delphi survey, as previously recommended. Reporting outcomes will only be prioritized if they reach 80% of the support from participants scoring "critical" (ie, score 7-9) [23].

Stage 4 (Development of Reporting Guideline and Explanatory Document and Procedure)

The aim of the explanatory document is to provide the background, rationale, and justification for the FCN-COS. This document will be developed concurrently with the reporting guidelines.

In stage 4, stakeholders will concentrate on the development of the reporting guideline for studies developing COS and the accompanying explanatory document. Additionally, a draft recommendation will be created to explain the origin of the outcome (whether from stakeholders or the Delphi survey), the level of consensus achieved (through the Delphi survey and consensus meeting), and a brief rationale for inclusion. The expert panel will review the document and provide feedback on the guideline and explanatory document as needed. The FCN-COS guideline will undergo several revisions until the final draft is deemed complete.

Stage 5 (Pilot-Testing of the FNC-COS)

In the end, in stage 5, we will test the draft completed in the previous stage. Authors will be invited to test the FNC-COS, and the more experienced COS developers will review the

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guidelines to improve it. Their feedback will be reached through an anonymous survey incorporated into the final COS guideline.

Ethical Considerations

The University of Pavia Review Board has been consulted and confirmed ethical approval for this study (number 02/int/2023/CdS).

Results

In this study, a comprehensive FCN-COS will be developed through a rigorous multiphase approach. COS developers, trialists, systematic reviewers, journal editors, policy makers, and patient groups will benefit from the COS development, as it will aim to improve the quality and comparability of future research by standardizing, through 5 distinct stages, the measurement and reporting of outcomes in the field of family and community nursing. As the first stage of the study will be successfully completed, with the stakeholder group expected to approve the reported outcomes and assign participant lists for each stakeholder group, this significant milestone will signify the initial step toward establishing a standardized framework for measuring and reporting outcomes in family and community nursing research, which will inform future clinical decision-making and enhance research quality and comparability in this vital domain. The Delphi survey approach will be a sound method for soliciting input from a wide range of stakeholders, including health care professionals, researchers, and service users. The surveys will aim to establish consensus on the importance of various outcomes. This iterative process will be instrumental in refining the list of outcomes and ensuring that the most critical outcomes are identified. The consensus meeting will mark a critical juncture in the development of the FCN-COS. Bringing together a diverse group of stakeholders for an interactive discussion will ensure that the final outcomes selected truly reflect a collective consensus, as well as the development of the reporting guideline and explanatory document. The involvement of an expert panel in reviewing and revising these documents will ensure their quality and clarity. The pilot-testing stage will represent a valuable step in validating the FCN-COS. Inviting authors and experienced COS developers to test the guideline and provide feedback will be a practical approach to identifying any potential issues or areas for improvement. Their insights will contribute to the refinement and usability of the FCN-COS.

Discussion

Overview

To date, no FCN-COS has been developed, and its development could aid in organizing and understanding various interventions within the family and community context [9]. The establishment of FCN-COS will enhance the organization and improvement of FCN interventions, shedding light on the impact of the FCN on health outcomes within a broader family and community context.

This proposed protocol for developing and the future FCN-COS is essential to comprehend how nursing domains are defined by FCN interventions. An example is the “role relationship,” such as parenting skills to ensure child protection. Multidisciplinarity in the health care setting is a priority to ensure continuity of care, involving various health care professionals to better guarantee community health. This can be better illuminated through the FNC-COS, starting from the preliminary version of FCN-COS. The preliminary version of FCN-COS is a crucial starting point. This classification is vital to prioritize the most relevant interventions for FCNs in practice and guide the development of a consensus-based set of core interventions using a Delphi survey approach [24]. This can help ensure that nurses are equipped with the most relevant and evidence-based interventions to provide high-quality care to families and communities.

FCNs provide primary care services to patients in families and communities [1]. Their core activities cover a wide range of primary services, from health promotion to primary, secondary, and tertiary prevention, focusing on the health and well-being of communities and populations [2]. These specialized professionals are important because they provide accessible and comprehensive primary care services to individuals and communities, particularly in underserved areas and communities with high rates of chronic diseases [3]. The FCN is a key role that can bridge the gap between home care settings and hospitals, with autonomy as a self-regulated profession [15]. For this reason, this Delphi process aims to develop a standardized classification of FCN interventions emerging from the unique needs and contexts of FCN practice. In particular, as the FCN’s clinical practice develops in primary, secondary, and tertiary care, defining FCN-COS is a priority that has not yet been developed [9].

The FCN-COS derived from stage 1 is based on the national and international literature [9], and it will need to be adapted for country-specific use in Italy. This will be developed by engaging with a panel of participants in Italy, using a Delphi approach, to define the classification and identification of any outcomes that may be more or less relevant to FCN practice in Italy. In other words, this proposal will be developed as the result of the implementation of the next phases of the protocol to ensure that the FCN is relevant and applicable to the unique needs and contexts of FCN practice in Italy.

Expected Results From the Delphi Study

Having an FCN-COS is highly relevant to sustaining health promotion and salutogenic interventions in the family and community context [2]. FCN-COS is fundamental to try to fill the gaps about the current unavailability of FCN-COS in the Italian context [9]. This protocol, even if developed in Italy, will be fundamental for the international context. In particular, we focused on the international literature review to define the preliminary outcomes of the FCN-COS [9]. After the preliminary outcomes, stage 1 of the study will follow. A standardized scheme of classification and a precise hierarchical classification of interventions are fundamental to facilitate assessments [21].

Furthermore, the social recognition of the FCN could be strengthened by the definition of a COS shared between health care professionals, even internationally [9,24]. The Delphi survey allows the illumination of experts’ opinions through a

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series of iterative questionnaires to reach a consensus on defining FCN-COS. The Delphi survey will be conducted ensuring the anonymity of the panel of participants. This is fundamental to reduce the impact of dominant personalities in the debate and decreasing peer pressure [38]. In this sense, every answer will be equally weighted, and the feedback process allows experts to develop a precise idea between one round and another, letting them know the previous ratings of the survey [39].

Limitations

The methodology used is the main limitation in defining FCN-COS. This approach limited the possibility of elaborating on in-depth views of the panel composition about the FCN-COS. However, a web-based system should help researchers optimize the response rate. Despite this, developing the best possible FCN-COS could be possible through future further validation studies to verify the defined FCN-COS in relation to measurable patient-level outcomes and to the previously developed FCN-COS.

Conclusion

The Delphi survey is fundamental to developing a COS sensitive to the health interventions that characterize the practice of FCNs. The FCN-COS will be developed as the main turning point, which can determine a greater quality and comparability of research, inform clinical decision-making, and support evidence-based health care. Furthermore, FCN-COS will be fundamental to define FCN as an emerging health care professional in the field of nursing.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SR, CA, and RC conceptualized the study. All authors developed the first draft of the manuscript and are involved in the data collection. All authors contributed to the development of the study protocol and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary list of outcomes.
[DOCX File , 107 KB - resprot_v13i1e51084_app1.docx]

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Abbreviations

CCC: Clinical Care Classification System
COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
CREDES: Guidance on Conducting and Reporting Delphi Studies
FCN: family and community nurse
FCN-COS: Family and Community Nursing Core Outcomes Set

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Original Paper

Content Validity and Psychometric Properties of the German Version of the Holm and Cordoba Urinary Tract Infection Score for Uncomplicated Urinary Tract Infections in Women: Protocol for a Validation Study

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Abstract

Background: Uncomplicated urinary tract infections (UTIs) in women are among the most common bacterial infections in primary care. Given the health threats related to the overuse of antibiotics, alternative options are of increasing importance. Patient-reported outcome measures are valuable tools for including the patients' perspective when evaluating the efficacy of these strategies. Aiming to identify a suitable instrument to measure the severity and bothersomeness of UTI symptoms in women, we performed a systematic review of the literature and identified the Holm and Cordoba Urinary Tract Infection Score (HCUTI), which measures the severity, bothersomeness, and impact of uncomplicated UTIs on daily activities. This instrument showed sufficient content validity but needs translation and further validation before it can be used in German research.

Objective: For use in the German setting, we aim (1) to perform translation and linguistic validation of the HCUTI and (2) to evaluate content validity and psychometric properties of the German version of the HCUTI in a population of women with uncomplicated UTIs.

Methods: The HCUTI will be translated and linguistically validated using the dual-panel method. This process involves a bilingual translation panel and a lay panel to check the comprehensibility of the translation. Content validity of the translated questionnaire will be assessed using cognitive interviews according to the criteria for good content validity as recommended by the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) group involving women with uncomplicated UTIs and health care professionals. Subsequent psychometric validation of the German version of the HCUTI in a population of women with uncomplicated UTIs will include the assessment of structural validity, internal consistency, test-retest reliability, construct validity, responsiveness, and interpretability.

Results: Results of the translation and linguistic validation process and the results of the content validity study were obtained in September 2023 and will be published separately. Data on the psychometric properties of the German version of the HCUTI are anticipated in mid-2024.

Conclusions: We expect that data from the content validity study will provide important suggestions for potential modifications of the HCUTI for use in the German setting. The final version of the questionnaire will be used for the assessment of its psychometric properties in a large population of women with uncomplicated UTIs.

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KEYWORDS

uncomplicated urinary tract infections; patient-reported outcome measures; PROM; PROMs; content validity; psychometric properties; patient reported; validity; validation; urology; urinary; urinary tract infection; UTI; psychometric; scale; score; scoring; assessment; women's health; internal medicine; women; urinary tract infections; bacterial infection; primary care; infection

Introduction

Background

Patient-reported outcome measures (PROMs) are increasingly used in medical research and patient care since researchers, clinicians, and decisions makers are becoming increasingly aware that the patients' perspective is crucial when evaluating the efficacy of treatments and the quality of health services [1]. PROMs are standardized questionnaires for the assessment of information on health outcomes directly from the patient, including symptoms, physical, emotional, and social functioning, or multidimensional constructs such as health-related quality of life (HRQoL). Initially developed for use in research, the application of PROMs has expanded involving various domains of patient care including clinical decision-making and the evaluation of treatment strategies [1].

In primary care, uncomplicated urinary tract infections (UTIs) are among the most common bacterial infections in women and an important public health problem [2,3]. UTIs are generally self-limiting but commonly treated with antibiotics since they are bothersome, and antibiotic treatment leads to a more rapid resolution of symptoms [4,5]. Given the health threats related to conservative antibiotic treatment, the development of alternative treatment options is of increasing importance, and evaluating these strategies by considering the patients' perspective is a high priority. For this purpose, PROMs are valuable tools. For uncomplicated UTIs, several disease-specific instruments have been developed and validated, assessing symptom burden [6,7], the impairment of daily activities [6,8], and HRQoL [6]. The selection of a PROM is guided by content-related considerations, including the construct to be measured and the target population, but it is also essential to consider the quality of the measurement properties of available instruments. Aiming to facilitate the selection of high-quality PROMs for research and patient care, the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) initiative has suggested a methodology for conducting systematic reviews of PROMs [9]. This includes the assessment of the methodological quality of single studies on measurement properties of PROMs using the COSMIN risk of bias checklist [10] and the evaluation of the quality of measurement properties of the PROMs themselves.

A systematic review of the quality of measurement properties of available PROMs for uncomplicated UTIs using the COSMIN methodology was performed [11]. Among the identified PROMs measuring symptom severity and bothersomeness, the Acute Cystitis Symptom Score (ACSS) [6] and the Urinary Tract Infection-Symptom and Impairment Questionnaire (UTI-SIQ-8) [7] can be recommended for use (COSMIN category A). Capturing the broadest spectrum of outcomes, the assessment revealed that the Holm and Cordoba Urinary Tract Infection Score (HCUTI) [12] is a promising tool that warrants further validation (COSMIN category B). The HCUTI comprises 43 items on 3 subscales measuring the following aspects over a 7-day period: symptom severity (18 items), bothersomeness (18 items), and impact on daily activities (7 items). All items are rated on a 4-point Likert scale ranging from 1=none to 4=a lot. The instrument is available in Danish and has sufficient content validity. Data on other important measurement properties, for example, structural validity, are not yet available, indicating the need for further validation studies before the instrument can be used.

Objectives

The objective of this work is to perform translation and linguistic validation of the HCUTI for use in the German setting and to evaluate content validity and psychometric properties of the German version of the HCUTI in a population of women with uncomplicated UTIs. The protocol aims (1) to describe the translation process of the HCUTI from Danish into German language and the linguistic validation, (2) to describe the content validation of the translated HCUTI, and (3) to describe the psychometric validation of the German version of the HCUTI. The timeline is presented in Figure 1.

Figure 1. Study schedule.

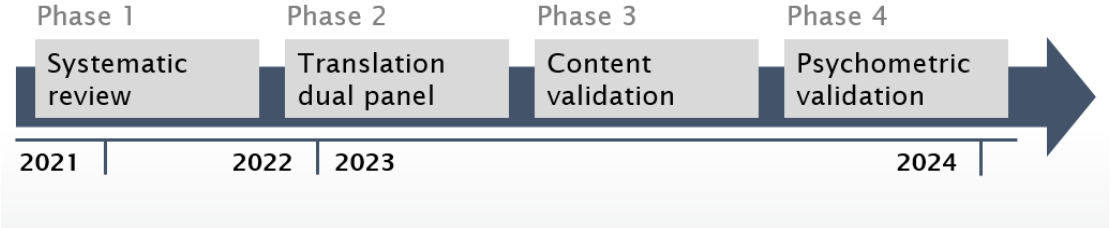

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Methods

Translation and Linguistic Validation

The HCUTI will be translated from Danish into German language using the dual-panel method [13]. A bilingual translation panel consisting of 4 nonprofessional persons fluently speaking Danish and German will perform the translation in a web-based meeting. A bilingual person with a medical background will moderate the session under the guidance of the study team, and discussion points and decisions about the wording of the single items will be protocolized. To ensure that the original meaning of the items is maintained, the developer of the HCUTI will participate in the translation process. Based on the translations of the single members of the panel, consensus will be sought about the wording during the session. Subsequently, a lay panel involving 4 German native-speaking women who have experienced uncomplicated UTI in their lifetime will review the translation regarding comprehensibility of the instructions, items, and response options, also in a web-based meeting. Changes in wording will be documented in minutes, and the session will be additionally audio recorded for later analysis. Two members of the research team will adapt the questionnaire according to the results of the lay panel. This procedure will result in the German version of the HCUTI, for which content validity and psychometric properties will be assessed.

Assessment of Content Validity

Overview

Following a qualitative approach, the content validity of the German version of the HCUTI will be assessed in cognitive interviews with affected women and interdisciplinary experts.

Recruitment of Participants

Women with uncomplicated UTIs will be recruited through the study team's network. Women being at least 18 years of age who have been diagnosed with uncomplicated UTI in the past 3 years will be included. Experts from relevant disciplines including family practice, urology, gynecology, nursing, health sciences, and psychosomatic medicine will be also recruited through the study team's network.

Procedure

Content validity will be assessed in accordance with the COSMIN criteria [10]. These criteria were developed in 2016 in a Delphi study among 159 experts from 21 countries including participants with expertise in qualitative research, development and evaluation of PROMs, and different professional backgrounds such as clinicians [14]. COSMIN provides a detailed, standardized, and transparent methodology, thereby promoting the selection and use of high-quality PROMs in research.

In individual semistructured interviews, women with uncomplicated UTIs (n=7) and health care professionals (n=7) will complete the questionnaire. The aim is to assess the relevance, comprehensiveness, and comprehensibility of the instructions, items, response options, and recall period from the women's and experts' perspectives. Two trained interviewers will conduct the interviews in a web-based meeting or in-person session following a standardized interview topic guide (Multimedia Appendix 1). The results will be documented for each item using a Microsoft Excel (Microsoft Corp) sheet. All interviews will be recorded and transcribed verbatim. Two researchers will perform data analyses using thematic analyses to identify problems related to relevance, comprehensiveness, and comprehensibility. Single items will be modified if at least 3 interviewees make a specific comment on that item. If required, the questionnaire will be adapted based on the results of the interviews, and all items will be tested in their final form in further qualitative interviews with women with uncomplicated UTIs.

Assessment of Psychometric Properties

Overview

Once the content validation has been carried out and the final version of the HCUTI has been accepted by the interviewees and experts in terms of relevance, comprehensiveness, and comprehensibility, the psychometric validation study will be carried out in a quantitative web-based survey. For this purpose, the final HCUTI will be used in the target population, and the measurement properties will be analyzed using the survey data set.

Recruitment of Participants

A web-based survey targeting a sample size of >200 will be carried out. The study procedure is displayed in Figure 2. Women with uncomplicated UTIs will be recruited in practices for family medicine, urology, and gynecology. Women being at least 18 years of age with a confirmed diagnosis of acute cystitis or uncomplicated UTI (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes N30.0, N30.9, and N39.0) will be included. Women with complicated UTI and women with insufficient German language skills will be excluded. Participating women will complete the survey at 3 measurement points: baseline (day 1, before treatment), follow-up 1 (day 2), and follow-up 2 (day 5). Subsequent data analyses on psychometric properties will include the assessment of structural validity, internal consistency, test-retest reliability, construct validity, responsiveness, and interpretability. All analyses will be performed in accordance with the criteria of the COSMIN group [9].

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Figure 2. Procedure of the psychometric validation study.

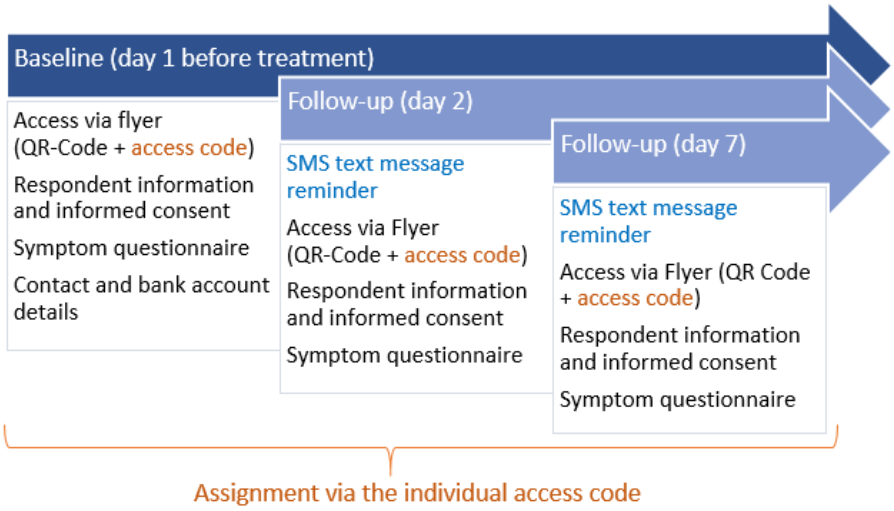

Data Analyses

Structural Validity

Structural validity is defined as the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured [15]. Unidimensionality refers to whether the items in a scale or subscale measure a single construct and is an assumption for internal consistency. The HCUTI is hypothesized to measure symptom severity, bothersomeness, and impact on daily activities, suggesting the unidimensionality of the 3 subscales. Structural validity will be assessed using item response theory and Rasch analysis. Confirmatory factor analyses will be performed to test the unidimensionality of the 3 subscales. The assessed parameters according to the criteria for good measurement properties as recommended by the COSMIN group are depicted in Textbox 1.

Using Rasch analysis, the resulting dimensions will be tested for differential item functioning, which is a method for analyzing measurement equivalence. Differential item functioning of an item is present if the item response differs across groups (eg, sex and race), controlling for an estimate of the construct being measured [16].

Textbox 1. Parameters and criteria for the assessment of structural validity.

- Unidimensionality: Comparative fit index or Tucker-Lewis index or comparable measure >0.95 or root mean square error of approximation <0.06 or standardized root mean square residual <0.08
- Local independency: Residual correlations among the items after controlling for the dominant factor <0.20 or Q3's<0.37
- Monotonicity: Item characteristic curves will be generated for each item; adequate-looking graphs are required or item scalability >0.30
- Model fit: Item response theory: χ^2>0.01 and Rasch: infit and outfit mean squares ≥0.5 and ≤1.5 or *Z* - standardized values >–2 and <2

Internal Consistency

Internal consistency is defined as the extent to which items within an instrument measure various aspects of the same characteristic or construct and is commonly evaluated using Cronbach α [17]. Given unidimensionality, we will analyze Cronbach α for the 3 subscales of the HCUTI. Cronbach α≥.70 is considered sufficient.

Test-Retest Reliability

Test-retest reliability is the degree to which test scores remain unchanged when measuring a stable individual characteristic on different occasions [18]. For the assessment of test-retest reliability, patients will complete the HCUTI before treatment (baseline) and at days 2 and 5 after baseline assessment. To define stable patients, an anchor question from the ACSS [6] on change in symptom severity will be included. Patients are asked if they have perceived any changes in their symptoms. This item is rated on a 5-point Likert scale as follows: 0=now I feel back to normal (all symptoms have gone away), 1=now I feel much better (majority of symptoms has gone away), 2=now I feel only somewhat better (majority of symptoms is still present), 3=no changes, now I feel about the same (no changes in my symptoms), and 4=now I feel worse (my condition is worse).

Based on the rating, participants are categorized into 3 groups as improved, unchanged, or worsened. Test-retest reliability will be assessed for patients whose symptom severity has not changed. The degree of agreement will be assessed using intraclass correlation coefficients. An intraclass correlation coefficient >0.70 is considered sufficient.

Construct Validity

Overview

Construct validity is the degree to which a measurement instrument assesses the intended construct and involves the evaluation of the relationship between the instrument and comparator instruments measuring the same, similar, or dissimilar constructs [10]. To determine construct validity,

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hypotheses are formulated a priori, and these hypotheses concern comparisons with other outcome measurement instruments and differences in scores between "known" groups.

Comparison With Other Outcome Measurement Instruments

To determine the convergent validity of the HCUTI, the following comparator instruments will be administered:

The UTI-SIQ-8 is a self-administered questionnaire designed to assess symptom severity and bothersomeness of uncomplicated UTIs with 4 items each. The symptom severity scale is rated on a 5-point Likert scale ranging from 1=not at all to 5=very strong, and the bothersomeness scale is rated on a 5-point Likert scale ranging from 1=not at all to 5=very severe.

The ACSS comprises 4 domains assessing typical symptoms, differential diagnosis, quality of life, and additional symptoms. We will use 2 items of the quality-of-life subscale assessing the impact of UTI symptoms on daily activities and social activities. These items are rated on a 4-point Likert scale ranging from not 0=affected at all to 3=extremely affected.

The EQ-5D-5L is a generic instrument for the measurement of self-reported health status and HRQoL [19]. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has five response levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=unable to or extreme problems. The EQ-5D-5L further includes a vertical EQ visual analog scale capturing the respondents' overall assessment of their health on a scale ranging from 0=worst possible health you can imagine to 100=best possible health you can imagine).

Correlations of the subscales of the HCUTI with the comparator instruments will be examined. A priori formulated hypotheses are tested using Spearman rank correlation coefficients. Following the recommendations of the COSMIN group, correlations with instruments measuring similar constructs should be ≥0.5 (high). Correlations with instruments measuring related but dissimilar constructs should be between 0.3 and 0.5 (moderate). Correlations with instruments measuring unrelated constructs should be <0.3 (low). The hypothesized associations are depicted in Table 1.

Table 1. Hypothesized associations between the subscales of the HCUTI[a] and the comparator instruments.

Comparator instruments	HCUTI subscales		
	Symptom severity	Bothersomeness	Impact on daily activities
UTI-SIQ-8[b] symptom severity	High	Moderate	Moderate
UTI-SIQ-8 bothersomeness	Moderate	High	Moderate
ACSS[c] daily activities item	Moderate	Moderate	High
ACSS social activities item	Moderate	Moderate	High
EQ-5D-5L			
Index: quality of life	Moderate	Moderate	High
Mobility	Moderate	Moderate	Moderate
Self-care	Moderate	Moderate	Moderate
Usual activities	Moderate	Moderate	Moderate
Pain or discomfort	High	Moderate	Moderate
Anxiety or depression	Low	Low	Low
EQ VAS[d]: health status	Moderate	Moderate	Moderate

[a]HCUTI: Holm and Cordoba Urinary Tract Infection Score.

[b]UTI-SIQ-8: Urinary Tract Infection-Symptom and Impairment Questionnaire.

[c]ACSS: Acute Cystitis Symptom Score.

[d]VAS: visual analog scale.

Comparison Between Subgroups (Known-Groups Validity)

Since no clinical ratings or controls will be available due to the design of the study, known-groups validity of the HCUTI will be examined using Kruskal-Wallis test to compare the symptom severity score at baseline assessment between different age groups. We hypothesize no significant differences in symptom severity across age groups.

Responsiveness

Responsiveness to change is defined as the ability of an instrument to detect change over time in the construct to be measured [20,21]. For the assessment of responsiveness, external criteria such as patient reports are needed to determine whether the patient's condition has improved, worsened, or not changed. For symptom severity, the anchor question from the ACSS will be used. We will further include a global rating of change item, which is rated on a 7-point Likert scale as –3=much worse, –2=moderately worse, –1=a little worse, 0=no change, +1=a

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little better, +2=moderately better, or +3=much better. This item will be also used to assess changes in bothersomeness and changes in impact on daily activities. Based on the rating of the anchor questions, participants are categorized into 3 groups as improved, unchanged, or worsened. Analyses on responsiveness will be performed at days 2 and 5 after the baseline assessment.

First, we will examine the sensitivity of the HCUTI to changes in patients whose severity of illness has changed. Spearman rank correlations between change scores in the anchor questions and change scores in the subscales of the HCUTI will be calculated to examine if the anchors can be considered as appropriate (>0.3) [22]. Second, receiver operating characteristic curves will be used to assess the ability of the HCUTI subscales to distinguish between patients who have experienced different changes in their condition severity. For this analysis, patients will be grouped based on the anchor question as follows: participants with improvement in symptom severity, bothersomeness, and impact on daily activities ("a little better," "moderately better," or "much better") versus participants with no change or worsening in symptom severity, bothersomeness, and impact on daily activities ("no change," "a little worse," "moderately worse," or "much worse"). Area under the curve values >0.70 indicate sufficient discrimination between groups [9]. The points on the curve maximizing sensitivity and specificity are considered the optimal cutoff value for differentiating between responders and nonresponders. Third, following the construct approach, we hypothesize that improvement in the symptom severity scores of the HCUTI from baseline assessment to days 2 and 5 is related to improvements in the impact on daily activities and social activities as measured with the ACSS. We further hypothesize that improvement in the symptom severity scores of the HCUTI from baseline assessment to days 2 and 5 is related to improvements in the EQ-5D-5L index score and the EuroQol visual analog scale score. Spearman correlation coefficients will be calculated to assess the degree of association between the measures of change. We expect correlations ranging from 0.30 to 0.50.

Interpretability

Interpretability refers to the ease of deriving meaning from an instrument's scores. Interpretability is not considered a measurement property but is an important characteristic for the clinical application of an instrument. Data on the interpretation of changes in the scores are based on the minimal important difference (MID), which denotes the smallest score or change in score that would likely be important from the patient's or clinician's perspective [22]. We will estimate the MID for the 3 subscales of the HCUTI between baseline assessment and days 2 and 5 using an anchor-based approach, a distribution-based approach, and an integrated approach.

Using the anchor-based approach, the MID will be calculated by selecting patients who reported that they felt "a little worse" and "a little better" on the anchor questions. The mean change in scores of the HCUTI subscales in these groups will be calculated.

Applying the distribution-based approach, the MID is estimated based on the distribution of observed scores in the study population at baseline using 2 criteria: half SD and SE of measurement (SEM) [22]. According to these criteria, a change of more than one-half of the outcome score's SD is considered a MID [23]. The SEM is calculated as follows: $SEM=\sigma x\sqrt{(1-rel)}$, where σx=SD of the scale or subscale and rel=reliability of the subscale (internal consistency). A value of 1 SEM is used as a cutoff value for determining the MID [24].

The integrated approach combines the anchor-based approach and the distribution-based approach, taking into account the advantage of both an external criterion and a measure of variability [25]. To determine the MID, the upper bound of a 1-tail 95% CI for the mean score change in the "no change" group is used. The following formula will be used: mean score change in the patient group that did not change+1.645×SE. Patients will be equally grouped as using the classical anchor-based approach.

Ethical Considerations

The study has been approved by the Ethics Committee of the University of Magdeburg, Germany (19/23) and conforms to the principles of the Declaration of Helsinki. Written informed consent is obtained from all participants. The copyright holders gave permission to use the HCUTI for translation and validation. Data collected in the translation process; the content; and the psychometric validation study, including meeting minutes, transcripts, audio records, and survey data are stored in a pseudonymized way. An independent trusted third party at the Medical Faculty of the University of Magdeburg manages data containing personally identifiable information (consent forms and personal data required to pay incentives) and stores these data separately from the study data. A financial incentive is paid to all participants as follows: 50$ for participation in the dual panel or content validity study; 40$ for patients participating in the psychometric validation study; 100$ for physicians participating in the psychometric validation study + 10$ for each included patient.

Results

Results of the translation and linguistic validation process and the results of the content validity study were obtained in September 2023 and will be published separately. Data on the psychometric properties of the German version of the HCUTI are anticipated in mid-2024.

Discussion

Expected Results

The increasing research activities in the development of alternative approaches to conventional antibiotic treatment of uncomplicated UTIs indicate the need for high-quality PROMs to evaluate the efficacy of these strategies. This study will provide data on the content validity and psychometric properties of the German version of the HCUTI. We expect that the German version of the HCUTI is a valid and reliable PROM for the assessment of the symptom severity, bothersomeness, and impact of uncomplicated UTIs on daily activities in women. A tool with sufficient measurement properties that can be used

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for the evaluation of novel therapeutic strategies in the German setting will be available.

Challenges

For participation in the web-based survey for the psychometric validation of the HCUTI, strict inclusion criteria in terms of physician-diagnosed cystitis or uncomplicated UTIs according to the respective *ICD-10* codes are applied. This requires collaboration with physicians and is time-consuming. For the recruitment of participating practices, a comprehensive approach is planned, including personal contacts of the study team, personal invitation letters, contact with professional associations, conferences of local physicians, and publications in local medical journals. An incentive will be paid to all participating physicians. To keep the effort for the physicians during data collection as low as possible, they will be asked to confirm the diagnosis on a prepared form and to hand the study information out to the eligible women. The study information includes all data required for study participation, and the women can participate in the survey independently.

In view of the planned analysis, in particular regarding structural validity, responsiveness, and interpretability, a sufficient sample size must be obtained. To maximize the participation rate and minimize the dropout rate, an incentive will be paid to the participating women. For the follow-up assessment, a reminder will be sent via SMS text message to enable prompt completion of the questionnaire using a mobile device. The study procedure will be pretested to evaluate the feasibility of the procedure and the implementation of the survey in LimeSurvey (LimeSurvey GmbH).

To draw attention to our research activities, information on our study, possibilities for participation, and current results will be published on a regular basis at the Institute of Social Medicine and Health Systems Research's website, X (formerly known as Twitter) account, and other social media platforms.

Acknowledgments

This work is funded by Bionorica SE, Germany. The study sponsor has no role in the design of the study, data collection, data management, data analysis, data interpretation, and issues regarding the publication of results.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CA, KP, and SN contributed to the conceptualization of the study. KP designed the study protocol and drafted the paper. All authors were involved in revising the draft.

Conflicts of Interest

CA received institutional funding for the submitted work and consultancy fees from the Dr Wolff Group, Bionorica SE, Sanofi, Incyte Biosciences, RHEACELL, and LEO Pharma.

Multimedia Appendix 1
Interview guide.
[DOCX File , 27 KB - resprot_v13i1e49903_app1.docx]

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Abbreviations

ACSS: Acute Cystitis Symptom Score
COSMIN: Consensus-based Standards for the selection of health Measurement Instruments
HCUTI: Holm and Cordoba Urinary Tract Infection Score
HRQoL: health-related quality of life
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
MID: minimal important difference

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PROM: patient-reported outcome measure
SEM: SE of measurement
UTI: urinary tract infection
UTI-SIQ-8: Urinary Tract Infection-Symptom and Impairment Questionnaire

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Protocol

Screen Use Time and Its Association With Mental Health Issues in Young Adults in India: Protocol for a Cross-Sectional Study

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Abstract

Background: Screen use time has increased in the past decade owing to the increased availability and accessibility of digital devices and the internet. Several studies have shown an association between increased screen use time and mental health issues such as anxiety and depression. However, studies in the young adult population—a demographic with high screen use—and in low- and middle-income country settings are limited.

Objective: This protocol describes a study that aims to measure self-reported screen use times and patterns in young adults (18-24 y) in India and assess if increased screen use time is associated with poorer mental well-being.

Methods: This protocol describes a cross-sectional study of a pan-India, web-based convenience sample of young adults (18-24 y) with access to digital devices with a screen and a minimum of secondary school education. Participants will be recruited through people in the professional networks of the investigators, which includes pediatricians. The survey will also be distributed via the social media pages of our organization (X [X Corp], Instagram [Meta], Facebook [Meta], etc). Sociodemographic details will be collected through a questionnaire designed by the authors; screen use time and patterns will be assessed using an adaptation of the Screen Time Questionnaire to include data on different apps and websites used on digital devices; and mental health parameters will be gauged using the Warwick-Edinburgh Mental Well-Being Scale, Generalized Anxiety Disorder Scale, Perceived Stress Scale, and Patient Health Questionnaire. For statistical analysis, we will consider the following variables: (1) the primary independent variable is screen use time; (2) other independent variables include age, gender, residence: rural or urban, educational qualifications, employment status, stress associated with familial financial status, average sleep time, number of people living in a house or rooms in that house, BMI, substance use, and past psychiatric history; and (3) dependent variables include mental well-being, depression, anxiety, and perceived stress. To quantify the association between screen use time and mental health, we will perform a Bayesian multivariate multiple regression analysis that models the possibility of multiple alternative hypotheses while accounting for relevant sociodemographic covariables.

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Results: The survey instrument has been designed, and feedback has been obtained from the domain experts and members of our organization whose profile is similar to the potential study participants. The final data received after this study has been conducted will be analyzed and shared. As of January 2023, we have not yet initiated the data collection.

Conclusions: Based on the findings of this study, we will be able to establish a correlation between device- and use-specific screen use time and various mental health parameters. This will provide a direction to develop screen use time and mental health guidelines among young adults.

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KEYWORDS

mental health; India; screen use; computer use; screen time; depression; stress; anxiety; low- and middle-income country; LMIC; questionnaire; survey; instrument; young adult; mental well-being; cross sectional; internet use; phone use; young adults

Introduction

Screen use time has steadily increased in the 21st century with increased availability of and easy accessibility to digital devices and the internet [1]. Adults and even children spend a large portion of their days on different screen-bearing devices including smartphones, tablets, laptops, computers, televisions, etc [1]. The recommended screen use time limit is considered to be 2 h/d [2]. However, studies have shown that screen use time has increased to as much as 7 h/d in groups aged 8-18 years in the United States [3]. As screens become increasingly integral to peoples' social and professional lives, there is a rise in health-related concerns. Previous studies conducted in the United States and China have shown that increased screen use time has been associated with physical and mental health issues including increased incidence of anxiety and depression [2,4-6], sleep problems, and obesity [7]. Further, screen use times have only increased during the COVID-19 pandemic, making the issue a greater health research priority [8].

In 2021, the number of smartphone users in India reached 492.78 million, which accounts for about 16.93% of the total users worldwide [9]. Hence, it is timely to conduct studies to evaluate screen use time and its effects in low- and middle-income countries such as India with an increasing number of screens and large young (emerging) adult populations. Previously, screen use and its health impacts have been studied across multiple countries including the United States, China, and Canada. One study found the average daily screen use time to be between 1.73 hours on weekdays and 2.52 (SD 1.49) hours on weekends among children (mean age 7.4, SD 2.76 y) in Australia, which is higher than the recommended screen use time per Australian government guidelines. The guidelines suggest a screen use time of less than an hour for toddlers and preschoolers [10]. In Canada, the average screen use time was 1.78 (SD 1.52) h/d among adults. This study aimed to study the association between sedentary screen use time and neighborhood walkability, which showed that higher screen use time was found in individuals who did not have access to walkable neighborhoods [11]. The association between depression and screen use time is known to exist in different populations. For example, a study with college students in China has noted that the odds of depression were 1.76 times greater among those with over 2 hours of daily screen use time compared to those with lower use times [6]. Similarly, a study on Canadian youth found a significant correlation (R=0.212; P<.01) between sedentary total screen use time and depression severity [2]. Studies in India have focused on measuring screen use time and its correlation with various demographic factors, sleep problems, and mental health issues such as depression among adolescents [12,13]. Screen use time in children aged <5 years has been studied to assess its association with developmental delay [14]. These studies however do not use comprehensive activity-based screen use time. They also do not include the use of multiple mental health screening tools.

This study aims to measure the time spent on and patterns of screen use in individuals aged 18-24 years living in India. This study will probe into the different types of screen use–related factors such as types of devices, time and quality of engagement, and purpose of use. Young adults are of particular interest as behaviors adopted during developing years can persist and develop into chronic diseases [4,6]. This study includes a compilation of various existing mental health screening tools, which will help identify the presence of anxiety, depression, and stress. The hypothesis that increased screen use time is associated with various mental health problems including overall mental well-being, depression, anxiety, and perceived stress will be tested, while controlling for a wide range of possible confounders. A study such as this, with a comprehensive screen use time scale for different devices and compilation of multiple mental health screening tools, has not been conducted in India before. It could provide valuable data to help understand the public health impact and design preventive strategies for mental health issues due to increased screen use (Textbox 1).

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Textbox 1. Design for this study's plan.

Question

- Is screen use time associated with mental health disorders (mental well-being, depression, anxiety, and perceived stress)?

Hypothesis

- On the contrary to a single alternative hypothesis in the frequentist approach, the Bayesian approach gives a probability distribution for multiple alternative hypotheses. Therefore, we aim to test the influence of all the independent variables on the dependent variables.

Sampling plan (eg, power analysis)

- We plan to perform a sequential Bayes factor (BF) design analysis. We will start with initial design priors for the variables, draw an initial sample size of N_{eff}, and calculate the BF for the alternative models relative to the null model.

Analysis plan

- We will perform a Bayesian multivariate multiple regression analysis. We will use a default prior (normal distribution) from the RStudio package *rstanarm*, which is weakly informative, that is, the prior distribution is scaled based on the actual range of the outcome variables, and this will reduce the uncertainties in the posterior probabilities. Therefore, we plan to start with these default priors and then make some adjustments to the distributions as per our data set requirements.

Interpretation given to different outcomes

- Obtaining a $BF_{10} \geq 30$ would imply that the screen use time, combined with other sets of predictors in that model, is strongly correlated with mental well-being, depression, anxiety, and perceived stress.

Methods

Ethical Considerations

This study will adhere to ethics regulations that are standard for noninterventional studies involving human participants in India. Ethics committee approval was obtained from the National Institute of Ayurveda, Jaipur, Rajasthan, India, on September 1, 2021 (IEC/ACA/2021/02-12), under NKO affiliated with the Department of Kaumarbhritya Balroga, National Institute of Ayurveda, Jaipur, Rajasthan, India. The approval has been signed by the Institutional Ethics Committee member secretary Dr Sumit Nathani (Associate Professor, National Institute of Ayurveda, Jaipur). Given that this study involves web-based data collection and storage, special attention will be given to data confidentiality and security. The confidentiality of each participant will be maintained throughout this study's period as access to the raw data on participants will be available only to the members of this study's team. Further, the questionnaire will not have any personal identifiers (name and date of birth) that would reveal the identity of the participants. The responses generated will be automatically transferred to a datasheet stored in the cloud-based service—Google Drive (a third-party trusted and commonly used data storage platform)—owned by the Association for Socially Applicable Research (ASAR) administration account and can be accessed only by this study's team members.

Pilot Data

No pilot data has been collected till now.

Design

Recruitment and Data Collection

This will be a cross-sectional, web-based survey study conducted using a pan-India convenience sample. Participants will be recruited by investigators and people in their peer and professional networks. Additionally, the survey will be distributed through social media platforms that are popular in India such as WhatsApp (WhatsApp LLC), Facebook (Meta), Instagram (Meta), X (X Corp), etc. The survey will be posted on ASAR social media channels and those of collaborators regularly every 2 weeks for 6 months. The frequency will be adjusted based on the number of participants recruited in each such round. Concurrently, the social media channels will be modified and other web-based channels of dissemination will be explored. The survey will also be sent via email and SMS text messaging by investigators to people in their peer and professional networks. Our investigators are located in different regions in India, which will ensure nationwide coverage. A snowballing strategy will be used. Participants who have responded to the survey and people in the investigators' networks will be requested to send the survey instrument further to people who might be eligible for study participation. Additionally, the survey will also be distributed through the higher education institutes that investigators routinely collaborate with.

The survey will be distributed in the form of Google Forms. Participants are expected to take about 10-15 minutes to complete the entire questionnaire. Once started, the participants will be able to resume the survey at any point later on, but we will recommend completing the survey in 1 week. Reminder emails will not be sent as the email IDs will be kept confidential. Additionally, participants will be directed to upload screenshots of their screen use time from their phones to assess objectivity. A step-by-step guide on how to upload the screenshot will be included in the questionnaire.

Data collection will be conducted for 12 months with the form being live for this duration. Eventually, survey data will be transferred to an external hard drive owned by the ASAR whose access is restricted to study investigators.

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Inclusion and Exclusion Criteria

Participants for this study will be young adults aged 18-24 years from India who have access to digital devices with a screen (television, personal computer, laptop, tablet, or smartphone), those who have completed secondary school (10th standard passed), and those who have the basic knowledge of English reading and writing. Individuals aged younger than 18 years and aged older than 25 years will be excluded. Individuals who do not currently reside in India and have not resided in the last 12 months in the country, individuals who do not have access to digital devices with a screen, and those who have less than a secondary school education or have failed the 10th standard will be excluded.

Survey Instruments

All the survey questions will be made compulsory in the Google Form to avoid incomplete entries. The questionnaire consists of 114 questions across 4 parts. The first part is the introduction of this study and consent form for the participants. The second part is for the demographic and baseline details, including age, gender, residence (rural or urban), state, educational qualifications, employment status, the stress associated with familial financial status, average sleep time, number of people living in a house or rooms in that house, BMI, substance use, and past psychiatric history. This part of this study has been designed by the investigators, in line with other questionnaire-based surveys. The third part is the Screen Time Questionnaire [15]. The questionnaire from the cited study takes into consideration 2 types of screen use times. First, screen use time is the primary activity, which is defined as the main activity you are engaged in rather than using a television or other screens in the background while performing another activity such as cooking or exercising. Second, background screen use time is defined as the use of a television or another screen near you while performing other activities such as exercising, cooking, and interacting with family or friends. To obtain an accurate estimate of screen use time, we have modified the questionnaire by adding questions to measure differential screen use time. This will be measured by asking participants to enter the number of hours and minutes spent on screen-bearing devices (eg, televisions, mobile phones, laptops, etc) on various activities such as entertainment (eg, Netflix [Netflix], Amazon Prime [Amazon.com, Inc], YouTube [Google LLC], etc), gaming, social media (eg, WhatsApp, Facebook, X, etc), web-based classes or learning, or shopping websites (eg, Amazon, Myntra [Flipkart], etc). The fourth part is for mental health screening tools for well-being, depression, anxiety, and stress. Existing mental health screening tools will be used as they are without any modification [16]. The Warwick-Edinburgh Mental Well-Being Scale [17] will be used to assess mental well-being. This is a 14-item self-administered questionnaire, where each item is scored from 1 to 5 with a total score of 70. The interpretation of the scoring will be done according to the guidelines set by the National Health System Health Scotland [18]. The Patient Health Questionnaire will be used to assess the presence and severity of depression. This is a 9-item self-administered questionnaire, where each question is scored from 0 to 3. Patient Health Questionnaire scores of 5, 10, 15, and 20 represent the presence of mild, moderate, moderately severe, and severe depression, respectively [19]. The Generalized Anxiety Disorder Scale will be used to screen for the presence and severity of anxiety. This is a 7-item self-administered questionnaire, where each question is scored from 0 to 3. Scores of 5, 10, and 15 represent mild, moderate, and severe anxiety, respectively [20]. The Perceived Stress Scale [21] will be used to assess the perception of stress in an individual. It is a 10-item self-administered scale, where each item is scored from 0 to 4. Scores from 0 to 13 are considered low perceived stress. Scores from 14 to 26 are considered moderate stress. Scores from 27 to 40 are considered high perceived stress. At the end of the questionnaire, participants will be provided with mental health resources such as helplines, emergency numbers, etc.

The survey is coded using Google Forms. The questionnaires included in the survey have been reviewed by a psychiatrist and a psychologist. The first 3 parts of the survey have been adapted as per the feedback from ASAR members, who match the profile of the eligible participant population and guided the adaptation process. A copy of the survey instrument is presented in Multimedia Appendix 1.

Statistical Analysis

Research Question and Hypothesis Testing

Our main research question is whether screen use time is associated with mental health issues such as mental well-being, depression, anxiety, and perceived stress. Before stating our formal hypotheses, we present the list of independent and dependent variables and their abbreviations that will be referred to in this section.

The primary independent variable or predictor is screen use time (T), which will be calculated per individual for the full week (5 weekdays, 5 weeknights, and 2 weekend days) as $5 \times (T_{\text{per weekday}} + T_{\text{per weeknight}}) + 2 \times (T_{\text{per weekend day}})$ in minutes. Other independent variables include age (A), gender (G), residence (rural or urban; R), educational qualifications (E), employment status (EM), financial status (S), average sleep time (SL), number of people living in a house or rooms in that house (P), BMI, history of substance use (SU), and past psychiatric history (PPH). The outcomes or dependent variables will include mental well-being (MWB), depression (DEP), anxiety (ANX), and perceived stress (PS) as measured by the mental health screening tools mentioned above. Our null hypothesis is that there is no association between screen use time (T) and mental health issues (MWB, DEP, ANX, and PS), that is:

H0: [MWB, DEP, ANX, PS] ~ 1

Contrary to having a single alternative hypothesis in the frequentist approach, the Bayesian approach allows for probability distributions for multiple competing alternative hypotheses. Therefore, we aim to test the influence of all the abovementioned independent variables on the dependent variables through the following alternative hypotheses:

H1: [MWB, DEP, ANX, PS] ~ T

H2: [MWB, DEP, ANX, PS] ~ T + A

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H3: [MWB, DEP, ANX, PS] ~ T + A + G

H4: [MWB, DEP, ANX, PS] ~ T + A + G + R

H5: [MWB, DEP, ANX, PS] ~ T + A + G + R + E

H6: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM

H7: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM + S

H8: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM + S + SL + P

H9: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM + S + SL + P + BMI

H10: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM + S + SL + P + BMI + SU

H11: [MWB, DEP, ANX, PS] ~ T + A + G + R + E + EM + S + SL + P + BMI + SU + PPH

Sampling plan

We plan to perform a sequential Bayes factor (BF) design analysis. Since this study does not use the traditional frequentist null hypothesis testing, there is no need to determine the power or minimum sample size a priori. We will start with initial design priors for the variables, draw an initial sample size of N_{eff}, and calculate the BF for the alternative models relative to the null model. We will then sequentially increase our sample size until the BF (relative to the null model, BF_{10}) for the best-fit model, that is, the model with the highest posterior probability, becomes greater than or equal to 30. Obtaining a $BF_{10} \geq 30$ would imply that screen use time is strongly correlated with mental health issues with a high posterior probability. Data collection will be continued until the end of 12 months. No optional stopping rule is required as it has been previously argued that under Bayesian formalism, the strength of the evidence is not associated with the decision to terminate data collection [22].

Analysis Plan

To ensure high data quality, we will use some basic exclusion checks before the analysis. The entire response entry (ie, participant) with at least 1 missing variable from any of the dependent and primary independent variables will be excluded. We will also exclude the responses that give entries with unrealistic screen use time (T), for example, exceeding 24 h/d. Data collection for different variables will be done in such a way that the candidates will have to fill in all the answers or choose out of multiple options provided. This would be useful for avoiding incomplete or missing data. The screenshots containing screen use time uploaded by the participants will be used as a secondary screen to further exclude the unrealistic responses.

Bayesian multivariate multiple regression analysis will be performed. The list of independent and dependent variables is provided under hypothesis testing. Before conducting the analysis, it has been assumed that the independent variables are not correlated with each other. After receiving the data from the survey, a correlation analysis between all the covariables will be performed first. The independent variables or covariables that have a strong correlation (Pearson r=0.7-1.0) with the primary independent variable will be dropped to reduce model complexity.

A default prior (normal distribution) from the RStudio (Posit) package *rstanarm* will be used, which is weakly informative [23], that is, the prior distribution is scaled based on the actual range of the dependent variables, and this will reduce the uncertainties in the posterior probabilities. Therefore, the analysis will be started with default priors with subsequent adjustments to the distributions as per the data requirements. The other backup prior that could be used is the standard Jeffreys-Zellner-Siow prior, which follows a Cauchy distribution and can model skewed real-world associations better.

After the prior distributions are finalized, there are 2 methods. First, these priors will be used to initialize the Bayesian multimodel inference using linear regression based on the Bayesian adaptive sampling methodology [24]. This methodology can be applied through a graphical interface tool, JASP (The JASP Team), which is based on the *BAS* package in R (R Foundation for Statistical Computing). This will enable prediction of the plausibility of each model, based on their posterior probability distributions. The BF for a particular model will be finally computed using this posterior probability relative to the posterior probability of the null model. Second, the *stan_glm* function in *rstanarm* can be continued to fit Bayesian generalized linear regression models. This package follows a Markov chain Monte Carlo technique to explore a desired posterior probability distribution. The advantage of using *rstanarm* is that it fits a wider range of models as compared to JASP.

Results

The survey instrument has been created by designing a demographic questionnaire, compiling various existing mental health screening tools, and adapting an existing screen use time questionnaire. The instrument was reviewed by domain experts for feedback. This study will be funded by the National Institute of Ayurveda, Jaipur, India. As of January 2023, we have not yet initiated the data collection and the results obtained will be updated in this section accordingly.

Discussion

Principal Findings

This study aims to find the presence and magnitude of the association of screen use time used for different activities such as education, social media, web-based shopping, and entertainment with depression, anxiety, perceived stress, and general mental well-being while adjusting for confounders. We hypothesize that there is a positive correlation between screen use time and mental health issues such as depression, anxiety, and high levels of perceived stress. There is some support for this hypothesis from existing studies across different study populations and age groups.

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Comparison to Prior Work

A meta-analysis included 16 studies conducted in North America, Australia, and countries in Asia and Europe; the group aged 5-18 years shows a curvilinear dose-response between screen use time and the risk of depression, with or without increasing screen use time per day [3]. A study conducted in India among 16,292 adolescents and young adults in the group aged 10-19 years to examine the association between screen use time and sleep problems showed that screen use time increased with increasing age; with average screen use time being about 25 min/d for male and female individuals aged 12 years to about 150 min/d in male individuals and 50-100 min/d in female individuals aged 23 years [13]. A study involving 380 undergraduate college students in India showed that students with internet addiction (measured by Young's Internet Addiction Test) had significantly higher depression, anxiety, and stress than those without internet addiction [25]. A community-based study with participants in the aged 10-19 years group in India found that the mean screen use time was 3.8 hours on weekdays and 3.9 hours on weekends [12]. This study also showed that there has been an increase in the use of digital devices apart from television such as mobile phones.

A meta-analysis including a total of 19 studies from the United States, Australia, Singapore, Sweden, China, Brazil, Ghana, India, South Korea, Russia, and Mexico showed an odds ratio of 1.28 (95% CI 1.17-1.39; $P<.01$) between screen use time–based sedentary behavior and depression [2]. A systematic review of reviews in the age group of <3 years, which included a total of 29 studies from the United States, countries in Europe, and Asia, showed that high screen use time is associated with low measured health-related quality of life and higher depressive symptoms [26]. A study establishing a relationship between screen use time, physical activity, and obesity in adolescents in the United States showed high predicted obesity incidence was associated with high screen use time [27]. A prospective study done in Denmark in 435 adolescents who were followed up for a period of 12 years showed that each additional hour per day spent watching television or screen viewing was associated with 1.64 (95% CI 1.18-2.27) and 1.58 (95% CI 1.18-2.12), respectively, greater odds of prevalent depression in young adulthood, and dose-response relationships were indicated [28]. A study among 926 US adults found that there were significant associations ($\chi^2=14.96$, $P<.001$) for heavy (median time: 17.5 h/d or 1050, IQR 900-1290 min/d) and moderate (median time: 11.25 h/d or 675, IQR 615-750 min/d) screen use with BMI compared to light (median time: 7 h/d or 420, IQR 328.50-480 min/d) use [7]. The relation between device-specific screen use time and health-related behavior has been studied by Vizcaino et al [7], which shows that heavy users (17.5 h/d) have the highest perceived stress scores.

Strengths and Limitations

While studies showing a correlation between screen use time and mental health have been conducted, the strength of this study is that it studies device-specific screen use time and its relation with depression, anxiety, and perceived stress. The correlation between activity-specific screen use time and the mentioned mental health parameters will also be studied.

This study has the following limitations. First, this study uses a self-reported questionnaire due to which there might be some self-reporting bias. The questionnaire includes questions that ask the participants to recollect information based on their past experiences due to which there could also be recall bias. We are applying a secondary screen by asking participants to upload a screenshot of the screen use time settings on their phones. Since this question is not compulsory, all the participants might not upload it.

Future Directions

The exponential rise in screen use time warrants further investigation of its effect on mental health. Studies done in India focus largely on adults and adolescents. The age group that will be studied in this protocol is unique. The findings of this protocol could be used to establish healthy activity-based screen use time. Strategies and guidelines for the prevention of mental health disorders can be established.

Acknowledgments

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Authors' Contributions

Conceptualization was done by SD, SPD, SZ, and SG. Formal analysis was done by SZ and AM. PG, NKO, and SS acquired funding. The investigation methodology was accessed by SPD, SD, AS, and SZ. Project administration was performed by SPD, SD, and SZ. Resources were obtained by SG, NKO, SS, and SZ. The software was handled by AM and SZ. Supervision was done by SPD, NKO, and SG. Validation was handled by SD and SZ. Visualization was done by SD, AS, AM, and SZ. Original draft preparation was written by SPD, SD, AS, and AM. The writing was reviewed and edited by all authors.

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Conflicts of Interest

SZ serves on the boards of the Association for Socially Applicable Research (ASAR) and Nirvana. SZ also represents ASAR on the Maharashtra State Mental Health Policy Drafting Committee and has received honoraria from Harvard Public Health Magazine, The Wire, The Hindu, and Think Global Health. SPD is a founding member of ASAR and previously served on its board.

Multimedia Appendix 1
Example questionnaire.
[DOCX File , 39 KB - resprot_v13i1e39707_app1.docx]

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Abbreviations

ASAR: Association for Socially Applicable Research
BF: Bayes factor

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Protocol

Developing and Validating a Self-Care Self-Efficacy Scale for Oral Anticoagulation Therapy in Patients With Nonvalvular Atrial Fibrillation: Protocol for a Mixed Methods Study

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Abstract

Background: Oral anticoagulation therapy (OAC) is the cornerstone treatment for preventing venous thromboembolism and stroke in patients with nonvalvular atrial fibrillation (NVAF). Despite its significance, challenges in adherence and persistence to OAC regimens have been reported, leading to severe health complications. Central to addressing these challenges is the concept of self-efficacy (SE) in medication management. Currently, there is a noticeable gap in available tools specifically designed to measure SE in OAC self-care management, while such tools are crucial for enhancing patient adherence and overall treatment outcomes.

Objective: This study aims to develop and validate a novel scale aimed to measure self-care self-efficacy (SCSE) in patients with NVAF under OAC, which is the patients' Self-Care Self-Efficacy Index in Oral Anticoagulation Therapy Management (SCSE-OAC), for English- and Italian-speaking populations. We also seek to assess patients' SE in managing their OAC treatment effectively and to explore the relationship between SE levels and sociodemographic and clinical variables.

Methods: Using a multiphase, mixed methods observational study design, we first conceptualize the SCSE-OAC through literature reviews, patient focus groups, and expert consensus. The scale's content validity will be evaluated through patient and expert reviews, while its construct validity is assessed using exploratory and confirmatory factor analyses, ensuring cross-cultural applicability. Criterion validity will be examined through correlations with clinical outcomes. Reliability will be tested via internal consistency and test-retest reliability measures. The study will involve adult outpatients with NVAF on OAC treatment for a minimum of 3 months, using both e-surveys and paper forms for data collection.

Results: It is anticipated that the SCSE-OAC will emerge as a reliable and valid tool for measuring SE in OAC self-care management. It will enable identifying patients at risk of poor adherence due to low SE, facilitating targeted educational interventions. The scale's validation in both English and Italian-speaking populations will underscore its applicability in diverse clinical settings, contributing significantly to personalized patient-centered care in anticoagulation management.

Conclusions: The development and validation of the SCSE-OAC represent a significant advancement in the field of anticoagulation therapy. Validating the index in English- and Italian-speaking populations will enable personalized patient-centered educational interventions, ultimately improving OAC treatment outcomes. The SCSE-OAC's focus on SCSE introduces a novel approach to identifying and addressing individual patient needs, promoting adherence, and ultimately improving health outcomes. Future endeavors will seek to extend the validation of the SCSE-OAC across diverse cultural and linguistic landscapes, broadening its applicability in global clinical and research settings. This scale-up effort is crucial for establishing a universal standard for

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measuring SCSE in OAC management, empowering clinicians and researchers worldwide to tailor effective and culturally sensitive interventions.

Trial Registration: ClinicalTrials.gov NCT05820854; https://tinyurl.com/2mmypey7

International Registered Report Identifier (IRRID): PRR1-10.2196/51489

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KEYWORDS

oral anticoagulation therapy; nonvalvular atrial fibrillation; self-care; self-efficacy; medication adherence; patient-centered education; scale development; validation; psychometrics; atrial fibrillation; education; development; anticoagulation; prevention; stroke; medication; management

Introduction

Overview

Oral anticoagulation therapy (OAC) represents the primary and secondary prevention choice for venous thromboembolism and stroke in patients with nonvalvular atrial fibrillation (NVAF) [1]. As a life-long treatment, OAC is prescribed for various clinical indications, such as heart failure, congenital heart disease, hematological disorders, and peripheral vascular disease, affecting approximately 2% of the Western population. Despite its efficacy, the quality of anticoagulation control remains a challenge, impacting patient safety, efficacy in preventing thromboembolic events, and overall well-being. With an aging population, OAC use is expected to increase due to the equally increasing prevalence of AF [1].

Research has highlighted patients' low adherence and persistence to OAC, leading to preventable thromboembolic and hemorrhagic complications like stroke and bleeding. Addressing the underlying health determinants of patient adherence is essential to develop personalized patient-centered educational interventions [2]. Among these determinants, patients' self-efficacy (SE) plays a crucial role in empowering patients to actively engage in self-care management. SE is associated with patient knowledge and motivation, enabling timely medication intake and self-care activities even under uncertain and challenging conditions [3-5], and will contribute to shared decision-making in OAC treatment [6].

Despite the extensive research on the OAC population, inconsistent results and underreporting of SE persist [3]. One of the main reasons for this inconsistency is the heterogeneity of tools used to measure SE in this specific context. Existing tools, such as the Chronic Disease Self-Efficacy (CDSES) [7], General Self-Efficacy (GSE) [8], and Self-Efficacy for Appropriate Medication Use Scale (SEAMS) [9], have a broad focus and are not tailored to assess the specific SE aspects relevant to OAC self-care management. Consequently, there is a need for a dedicated tool that can capture these challenges and optimize OAC treatment outcomes. In other words, the effects of SE measured using broad tools on specific OAC outcomes might be misleading because the available general tools are not fit to measure aspects of SE that might impact anticoagulation control safety and other OAC-specific results in anticoagulation therapy management, as stated in a recent study [10].

Self-Care Self-Efficacy Framework

A self-care self-efficacy (SCSE) framework emerges as a valuable theoretical model for developing a measure of OAC-specific SE by being rooted in the middle-range theory of self-care for chronic illness [11,12] and Bandura's [13] social cognitive theory. In this framework, the SCSE is the patient's confidence in self-care maintenance (actions to maintain physiological stability), monitoring (efforts to detect signs and symptoms), and management (actions to address functional health behaviors) [14].

The SCSE framework can help researchers and clinicians effectively address OAC-specific challenges related to self-care behaviors in patients undergoing OAC treatment. This approach facilitates the creation of a theory-grounded SE scale that can discern and evaluate complex situations in the context of OAC. These situations involve the behaviors patients need to adhere to maintain physical and mental stability over time (maintenance), monitor signs and symptoms, and implement appropriate actions for symptom management (management) [11,12]. Consequently, the SE within this framework will assess a patient's confidence in performing these demanding self-care tasks associated with OAC, encompassing decision-making processes, cognitive functioning, and overall health literacy [11,12].

For example, some behaviors investigated within the 3 domains of self-care may reflect how well patients respond to tailored education and preparedness. Other behaviors might address shared challenges in maintaining a healthy status, monitoring changes in the body and mental well-being while on OAC treatment, and making informed decisions in response to unexpected changes. As the project expands, these behaviors could be further tested and integrated into OAC-specific self-care measures. Therefore, developing the Self-Care Self-Efficacy Index in Oral Anticoagulation Therapy Management (SCSE-OAC) aims to offer a comprehensive and nuanced understanding of patients' SE in managing their OAC treatment effectively by using and incorporating the SCSE framework.

Aims

This study aims to address the current gap in measuring SE in OAC treatment for NVAF. Existing measurement tools need more specificity and sensitivity to the unique challenges of OAC treatment, as recently highlighted [10]. To address this gap, the primary aim of this research protocol is to outline the design

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and methodology required to develop the SCSE-OAC in adults with NVAF. The study will provide cross-cultural validity and reliability of the developed measures for both English and Italian-speaking populations.

The secondary aim of this research protocol is to guide analyses to comprehensively describe patients' SCSE levels in managing OAC for each native-speaking group participating in the study. The data collection rounds designed to validate the SCSE-OAC (primary aim) will lay the groundwork for future investigations into potential associations between patients' SCSE and their sociodemographic or clinical variables. These findings will be instrumental in tailoring and implementing effective patient-centered educational interventions, ultimately enhancing adherence to OAC treatment and optimizing health outcomes.

Methods

Study Design

Following the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement, a multiphase, mixed methods observational, and cross-sectional study design will be used. Additionally, the COSMIN (Consensus-based Standards for selecting health status Measurement Instruments) guidelines will be used to evaluate the measurement properties of SCSE-OAC [15].

As depicted in Figure 1, the study will be structured into three main phases (1) conceptualization phase (phase 1), (2) validation phase (phase 2), and (3) reliability phase (phase 3). Phase 1 aims to establish a preliminary item's pool for the SCSE-OAC and ensure cross-cultural validity for each native-speaking country involved in the research, encompassing both Italian and English versions. The focus of phase 2 is to provide evidence of the internal validity of the SCSE-OAC for each language group. In phase 3, the stability and consistency of the SCSE-OAC over time will be assessed.

Figure 1. Gantt chart of the research activities related to the development and validation of the scale.

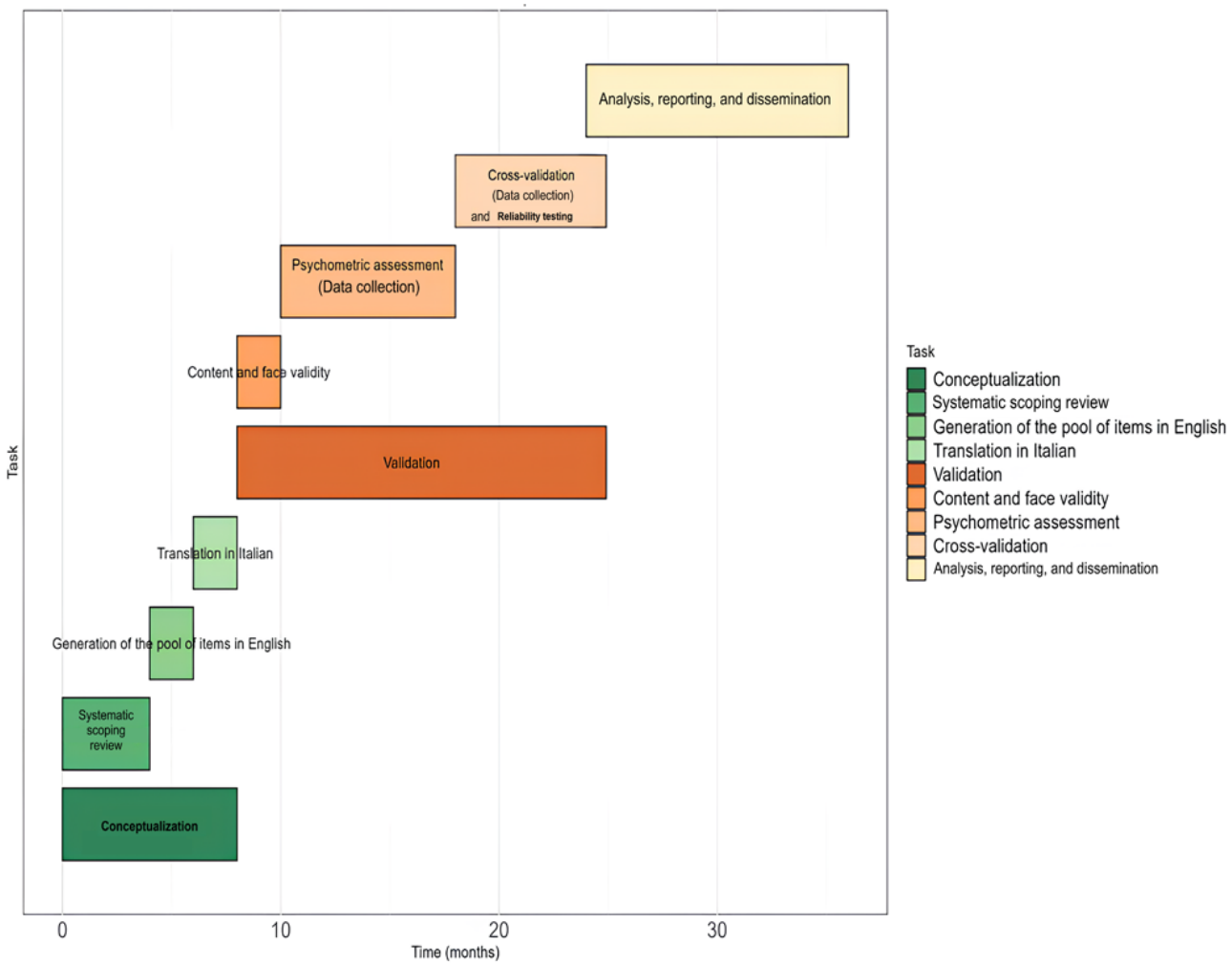

Phase 1: Conceptualization

In this initial phase (conceptualization), the primary objective is to generate a comprehensive list of behaviors that patients should perform in their daily self-care management of OAC. Specifically, we aim to develop a measure of patients' SCSE, which pertains to their confidence in successfully executing appropriate self-care behaviors to address the unique challenges associated with chronic OAC treatment [16,17]. A total of 3

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key substeps will be undertaken to achieve the primary aim of this study, using a mixed methods approach that integrates qualitative and quantitative methodologies to create the first version of the SCSE-OAC.

The first substep entails a systematic scoping literature review, which will help identify existing challenges and issues related to OAC self-care management in adults with NVAF as reported in previous researches. In the second substep, a group of patients with OAC treatment experience will be engaged to validate and potentially modify the initial set of behaviors identified in the literature review [18]. Similarly, in the third substep, input from health care experts with expertise in OAC management will be sought to further validate and refine the list of challenges or issues. Subsequently, the provisional version of the SCSE-OAC will be subject to cross-translation and cultural adaptation to ensure its relevance and applicability in the validation phase (phase 2) of the study.

More precisely, the systematic scoping literature review will be performed through the main academic research databases (PubMed, CINHAL, Scopus, and Web of Science) to identify the key pool of patients' challenging behaviors in OAC management. In this stage, the "Population, Concept, Context" (PCC) framework will be used to develop the queries for each database [19,20] and be consistent with the framework to conduct scoping reviews [21].

In the second substep of this phase, purposive sampling of adult outpatients (18 years of age or older) with NVAF treated in OAC for at least 3 months will be involved in a small focus-group discussion to share the most relevant challenges they lived or perceived in the self-care management of OAC. In the methodology for our focus group discussions, we have chosen to start with a base number of 5 participants. This decision is grounded in qualitative research practices where smaller groups could facilitate more in-depth discussions, allowing each participant ample opportunity to share their experiences and insights [22]. This size is considered sufficient to begin exploring the range of patient perspectives on managing OAC, particularly given the specialized nature of the topic and the targeted patient population [22]. However, recognizing the importance of achieving comprehensive data saturation, our approach is designed to be flexible and iterative. After the initial focus group with 5 participants, we will continuously assess the information gathered for new and recurring themes. If additional perspectives are needed to achieve saturation—where no new information is observed in the data—we will conduct subsequent rounds of focus groups, incorporating more participants as required. This iterative process ensures that our research captures a full spectrum of patient experiences and challenges related to self-care management of OAC, thus enhancing the validity and applicability of our findings [23]. Therefore, a group of voluntary patients will be identified for each country involved in the study (Italy and Australia). A bilingual-trained moderator will be identified to guide the discussion for each patient group. Finally, a list of OAC challenges by patients' views will be integrated with the literature review results, and the advice from the interviewed patients will contribute to defining the items' wording. This phase is anticipated to end in October 2024.

After the patients' focus-group discussion, a panel of experts (ie, physician, nurse, and pharmacist) will assess the relevance of each OAC-specific required behavior (item) identified in the previous phases. A multidisciplinary group of bilingual health care professionals with a minimum of 1 year of clinical experience in OAC management will be asked to rate the relevance of each item (ie, OAC challenges) on a 4-point Likert scale (1: completely disagree and 4: completely agree). Therefore, an overall interrater agreement among experts will be assessed through the Fleiss kappa index, and a value of more than 0.40 might be acceptable in a sample size ranging from 6 to 50 experts. Any divergence will be solved with consensus discussion.

In the last substep of phase 1, the provisional English version of the SCSE-OAC will be in parallel translated and cross-culturally adapted for each native-speaking country involved in the study (ie, Italian). Therefore, an independent group of bilingual experts will be involved in an iterative forward-backward translation process to ensure that the final version of the scale will be conceptually and linguistically correct and understandable to people of all levels of education by being culturally acceptable. Brislin's translation procedure will be followed [24]. More specifically, 2 expert bilinguals who are native speakers of the target language will translate the English version of the SCSE-OAC into the Italian language, and a third expert will review the 2 translations to achieve the best possible reconciled translation. After that, another 2 bilingual experts who are native speakers of the target language with fluency in English will be involved in the back-translation of the previously reconciled translation to the original language (ie, Italian back to the English language). The results of all 3 tasks (translation, reconciliation, and back-translation) should be forwarded to a permanent panel of experts or translation coordinator to review the process. As a result of the translation process, 2 translated versions of SCSE-OAC will be available (1) SCSE-OAC for the Italian-speaking patients' group and (2) SCSE-OAC for English-speaking patients' group. At the end of this translation process, a pilot test will be performed to assess the readability and comprehensibility of the items for each native-speaking group (10-15 patients). Therefore, each patient group will be asked to fulfill the preliminary translated version of SCSE-OAC and highlight any items that are not clear to them. All comments and suggestions will be taken into account. This phase is anticipated to end in December 2024.

Phase 2: Validation

This second phase (ie, validation phase) aims to define the construct intended to be measured, providing evidence of psychometrics validity for each translated version of SCSE-OAC. Two main substeps will be performed (1) content and face validity and (2) construct validity.

According to the COSMIN guideline, the content validity of the scale will be assessed based on the key criteria of relevance, comprehensiveness, and comprehensibility. In other words, each item will be analyzed by patients and health care professionals for content, meaning, wording, and format. As per the relevance criteria, we will ask to judge the items' relevance for the construct of interest (ie, SCSE) on a 4-point

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Likert scale (1=not relevant, 2=somewhat relevant, 3=quite relevant, and 4=highly relevant), with the following question

> *Please evaluate the relevance of the following self-care behaviors in managing your oral anticoagulation medication. Which behaviors do you find relevant to your daily life with OAC treatment?*

Content validity index (CVI) will be computed at the item and overall scale (ie, I-CVIs and S-CVI), considering a critical threshold value equal to 0.70 for I-CVIs and 0.80 for S-CVI. For each native-speaking country, a minimum of 15 patients will be enrolled to participate in the study.

The patients' eligibility criteria will be adult outpatients (18 years of age or older) with ongoing treatment with OAC at the time of the investigation, with a primary clinical indication for long-term OAC for NVAF, treated for at least 3 months, and who are willing to participate in the study. Instead, patients with cognitive decline (ie, Six Item Screener Test with lower than 4 points) will be excluded. Likewise, a convenience sample of 10 voluntary professionals from all relevant disciplines (ie, physician, nurse, and pharmacist) with documented clinical experiences in OAC for at least 1 year will be involved. Sociodemographic and professional variables will be considered to provide a sample description. Finally, an open-ended question will be included to assess the comprehensive and comprehensibility criteria. More specifically, participants will be asked to evaluate whether the items together comprehensively cover the construct of interest and if the population of interest clearly understands the items and response options to evaluate the face validity. The responses will be systematically analyzed, coded, and compared through a qualitative content analysis approach. Data collection will be done through an e-survey.

Following the achievement of content and face validity, 3 forms of validity will be tested—structural, cross-cultural, and criterion validity. As per the structural validity, we will assess the dimensionality of the construct to be measured (ie, SCSE) by factor analysis. However, no clear hypotheses about the underlying dimensions of the construct in the OAC population are available. Therefore, a 2-fold cross-validation will be performed for each language group, using explorative factor analysis (EFA) to explore relationships between observed variables and underlying factors and identify the most plausible psychometric structure and confirmatory factor analysis (CFA) to confirm the most plausible structure derived from EFA. More specifically, the overall sample for each language group will be randomly resampled to generate a subsample A for performing EFA (roughly 50% of the original sample) and subsample B for performing a CFA using the most plausible psychometric structure derived from EFA (using the second 50% of the original sample).

Sample Size for Phase 2

In the field of factor analysis, the sample size estimation for allowing researchers to perform factor analysis properly is based on a rule of thumb supported by the Monte Carlo simulation study of enrolling 10 patients per item and per language group [25]. As a result, the final required sample size will be based on the version of the SCSE-OAM derived from the content validity phase because it depends on the number of items encompassed in the scale. Considering previous similar research in patients with heart failure, 10 items were developed for measuring SCSE for adults with heart failure. We hypothesized a similar number of items. In this case, 100 patients per language group will be necessary for EFA and subsequently for CFA.

Study Procedures for Cross-Sectional Data Collections

The 2 data collection rounds required for achieving construct validity will be performed using an e-survey or paper form based on patients' preferences. E-survey is a more accessible and practical approach to gathering data from the desired group using a web survey link. The paper form will be delivered to patients in OAC who will prefer this approach. Considering that some patients could be older, the paper form could overcome the possible challenges that they could have in using an e-survey approach. A preidentified health care professional will oversee patients' enrollment, get informed consent, and perform data management and monitoring. Each obtained paper form or electronically collected data will be registered (or transferred in the case of data collected via SurveyMonkey [SurveyMonkey Inc]) in REDCap (Research Electronic Data Capture) software (Vanderbilt University; ie, electronic case-report forms). REDCap works as a web-based repository of the data collected. Both SurveyMonkey and REDCap are compliant with the European General Data Protection Regulation.

Eligibility Criteria for Phase 2

Inclusion criteria for participation in the study are (1) the patients must be aged 18 years or older, (2) have a confirmed diagnosis of NVAF, (3) be outpatients, and (4) have been receiving any OAC for at least 3 months before enrollment. Additionally, patients must provide informed consent. Exclusion criteria are those who have been treated with OAC for a brief period and are not on treatment anymore (ie, less than 3 months), patients with serious comorbidities (ie, Charlson Comorbidity Index, CCI >4), patients who have suspended OAC for surgery in the last 3 months, and those with cognitive impairment (assessed using a 6-item screener <4). Furthermore, a core set of sociodemographic and clinical variables will be collected to comprehensively describe the study sample.

Measurements for Phase 2

The study will collect data on sociodemographic and clinical variables to comprehensively understand the participants. Sociodemographic variables will include age, sex (male or female), marital status, educational level, occupation status (employed or unemployed), socioeconomic status (income exemption—yes or no), and the country of the participants. Regarding clinical variables, the study will record the duration of OAC treatment, the type of OAC used (direct and indirect OAC), and the clinical condition that led to the prescription of OAC. For patients treated with vitamin K antagonists, the study will assess the time in therapeutic range (%) over the last 3 months to determine the effectiveness of treatment. Additionally, the occurrence of thromboembolic or hemorrhagic complications during OAC treatment within the last 3 months will be documented for both direct and indirect OAC users. In addition

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to the sociodemographic and clinical variables previously outlined, our study will also collect data on the number and types of other medications that participants are taking concurrently with their OAC. This inclusion acknowledges polypharmacy as a critical factor in the management and outcomes of patients with NVAF.

A total of 2 scoring systems, the CHA_2DS_2-VASc score [26] and the HAS-BLED (Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) bleeding score [27] will be used to assess the risk factors associated with stroke and bleeding, respectively. The CHA_2DS_2-VASc score will help identify patients with a higher risk of stroke, where scores greater than 5 indicate a risk higher than 6.7%. On the other hand, the HAS-BLED bleeding score will be used to assess the risk of bleeding, with scores equal to or higher than 3 indicating a high risk of bleeding. By capturing these variables, the study aims to provide a comprehensive and detailed description of the participants in the research, enabling a thorough analysis of SCSE in OAC management.

Data Analysis

The relevant number of factors to be retained in EFA data analysis will be done on the parameters of scree-test, parallel analysis, and factor rotation. More specifically, in the parallel analysis, if the eigenvalue of the original data's factor is greater than the average of the eigenvalues of the parallel factor, that factor is retained. Likewise, the item retention will be assessed using factor loadings evaluations, where items with loadings >.40 will be retained. The structural model derived from EFA has to be used for both language groups in the CFA data analysis. The goodness of each model fit will be assessed based on the indexes of root-mean-square error of approximation (RMSEA; <.01) "excellent fit;" (<.05) "good fit;" (<.08) "mediocre fit;" comparative fit index (CFI) and Tucker-Lewis Index (TLI; >.90) and (>.95) [17,18]; SRMR (<.08) [19]; and chi-square test [25]. Furthermore, the multivariate normality of each model will be checked with the Mardia test, supposing that the multivariate skewness and kurtosis are significant. In the case of normality violation, a robust maximum likelihood estimator will be used.

After estimating the baseline model of scale for each language group, we will perform the Multi-Group Confirmatory Factor Analysis (MGCFA) to assess the cross-cultural validity. In other words, we will assess if the configural, metric, and scalar structure of SCSE-OAM is equivalent across 2 different language groups (English vs the Italian language). Achieving multi-group equivalence is pivotal to generating meaningful cross-group comparisons. Testing the measurement invariance means following a series of iterative analytical steps that bring from the largest model (where each language group has its parameters) to the more restricted one (where all the parameters are equal across the language group). This process stops when the model comparison is significant (ie, the large model fits the data significantly better than the more restricted one). A chi-square difference test will be performed to compare each model with the previous one to check whether a stronger invariance assumption holds. Data analysis will be performed in MPlus (Muthén & Muthén; version 8.1).

Clinical variables (ie, time in therapeutic range and absence of hemorrhagic and thromboembolic complications) will be used to estimate the cutoff points of adequate versus inadequate patients' SCSE and assess criterion validity, which is the degree to which the score of the SCSE-OAM is an adequate reflection of good anticoagulation control. Sensitivity and specificity analyses will be performed under the receiver operator characteristic curve by using time in the therapeutic range and absence of hemorrhagic and thromboembolic complications as dichotomic outcomes (if the distribution of the outcomes will allow researchers to perform this analysis).

Phase 3

The third phase of this research protocol focuses on evaluating the reliability and internal consistency of the SCSE-OAM over time. This phase, which is anticipated to end by December 2025, aims to ensure the stability of the developed scale. Two main criteria will be used for this assessment—internal consistency and reliability.

For internal consistency, the degree of interrelatedness among the items of the SCSE-OAM will be evaluated using Cronbach α. This index will be calculated for each unidimensional subscale, as well as for the overall scale. A Cronbach α value equal to or greater than 0.70 will be considered acceptable, indicating a strong internal consistency.

In assessing reliability, a test-retest study design will be used to determine the stability of the SCSE-OAM over time. After a 2-week interval, the second group of patients randomly selected from the previous one (sample B for CFA) will be asked to resubmit the SCSE-OAM. The minimum sample size for this test-retest reliability study will be set at 16 patients, with a power of 80%, a minimally acceptable reliability of 0.60, an expected reliability of 0.90, and α level of 0.05, considering a potential dropout rate of 10%. In addition to the scale responses, relevant clinical variables, such as the number of complications and any changes in the treatment regimen, will be collected to assess patients' stability over time. The intraclass correlation coefficients with a 95% CI will be calculated using a 2-way random-effects model to evaluate the scale's stability. This model enables us to assess the consistency of the SCSE-OAM when rated by different raters with characteristics similar to the selected raters in this study. By conducting this reliability phase, the research aims to validate the SCSE-OAM as a reliable and consistent tool for measuring SCSE in the context of OAC management.

Ethical Considerations

This research protocol has obtained ethics approval from the Ethical Committee of Ospedale San Raffaele (164/INT/2022) and will be conducted in accordance with the principles outlined in the Helsinki Declaration, Good Clinical Practice, and European law on the right to privacy (GDPR 679/2016). The confidentiality of all collected data will be strictly ensured during both data collection and analysis, with information analyzed in an aggregate manner to protect participants' identities. Ethics approval will be obtained from each

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participating institute, with Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato acting as the owner of the data.

Informed consent will be a mandatory requirement for every participant enrolled in the study, and health care professionals will be responsible for providing clear and detailed information about the study's objectives to the participants. Participants will have the right to withdraw their informed consent at any point during the study without facing any repercussions or penalties. This research prioritizes the protection of participants' rights, privacy, and well-being, adhering to ethical guidelines and ensuring that the study is conducted with the utmost integrity and respect for all individuals involved.

Results

The forthcoming validation of the SCSE-OAC is poised to significantly advance our understanding of SE in managing OAC among patients with NVAF. Anticipated results are expected to affirm the scale's robust validity features, including its construct, criterion, and content validity, affirming its reliability across diverse patient demographics. Through exploratory and confirmatory factor analyses, the SCSE-OAC is projected to exhibit a coherent factor structure that aligns with theoretical expectations, reinforcing its use as a psychometrically sound tool for assessing SCSE in OAC.

Subsequent analyses are anticipated to unveil significant correlations between SCSE scores derived from the SCSE-OAC and key clinical outcomes, such as medication adherence rates, incidence of bleeding or thromboembolic events, and overall patient quality of life. These findings will underscore the critical role of SE in the self-management of OAC, suggesting that higher SE levels are associated with improved health outcomes and adherence behaviors. Moreover, the study is expected to elucidate the relationship between SE scores and sociodemographic characteristics, including age, education, and health literacy, providing valuable insights into how these factors may influence patients' confidence and capabilities in managing their treatment regimens.

The significance of this study extends beyond the validation of a novel measurement tool. It promises to contribute substantially to the field of patient-centered care in anticoagulation management by offering health care professionals a reliable means to assess and enhance SE among their patients [1]. The SCSE-OAC will enable targeted educational and supportive interventions designed to bolster self-management skills by identifying, for instance, patients at risk of poor adherence due to low SE; therefore, mitigating risks associated with suboptimal treatment adherence. Furthermore, the scale's validation across different languages and cultural contexts is anticipated to facilitate its global applicability, paving the way for its adoption in varied clinical settings and among diverse patient populations.

Discussion

Principal Findings

This research protocol addresses a critical gap in OAC management by focusing on developing and validating SCSE for OAC treatment (SCSE-OAC). OAC is an internationally recommended treatment for patients with NVAF and plays a crucial role in preventing venous thromboembolism and stroke while requiring the adjustment of lifestyle to the chronic treatment that requires adherence [2,9,28]. However, low levels of adherence and persistence to OAC have been observed by previous research [29], leading to potentially preventable thromboembolic and hemorrhagic complications [30]. Understanding the determinants underlying patients' adherence to OAC, particularly their SE, is of paramount importance to designing personalized patient-centered educational interventions. The SCSE-OAC, being a specific and theory-grounded tool, will aid in capturing patients' confidence in performing self-care behaviors and provide insights into the challenges they face in OAC management. Consequently, the study's findings will contribute significantly to enhancing treatment adherence, safety, and overall health outcomes for patients with NVAF.

The study aims to provide a comprehensive SCSE-OAC for English- and Italian-speaking populations through a multiphase and mixed methods research design. In the conceptualization phase, a systematic literature review will help identify challenges and issues in OAC self-care management. Subsequently, qualitative and quantitative methodologies involving patients and experts will refine the initial items' pool. The validation phase will focus on establishing the internal validity of the SCSE-OAC using Cronbach α, ensuring the tool's reliability and consistency. Additionally, a test-retest reliability study will assess the stability of the SCSE-OAC over time. Overall, the study is expected to yield a robust and culturally adapted SCSE-OAC that can be applied to evaluate patients' SE levels in OAC management for each native-speaking group involved in the research.

While previous studies have examined determinants of OAC adherence [29], the SCSE-OAC represents a novel contribution to the field. The SCSE-OAC could provide a more focused and contextually relevant assessment of patients' self-care behaviors in OAC management because it will adopt a specific theoretical framework and develop a theory-grounded measure of SE. Existing tools used to measure SE have been diverse and general, lacking specificity for the challenges specific to OAC treatment [10]. The SCSE-OAC's development and validation will enhance the field's understanding of SE's role in OAC management and could contribute to the implementation of tailored patient-centered educational interventions, ultimately improving treatment outcomes.

Limitations

Several limitations may be encountered during the course of this research. First, despite the efforts made to include a diverse sample of patients, there might be some variations in the characteristics of participants from different geographic regions, potentially impacting the generalizability of the findings. Additionally, self-reported data may be subject to recall bias or social desirability bias, potentially affecting the accuracy of the responses. Moreover, the reliance on patients' self-assessment for some clinical variables, such as complications during OAC treatment, might introduce some subjectivity to the data. We

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also have to acknowledge that the study's cross-sectional design limits the ability to establish causality between patients' SE and specific health outcomes.

An additional limitation to note is the geographical scope of our study, which initially includes participants from Italy and Australia. The choice to focus on these 2 countries was primarily driven by logistical and feasibility considerations, including the availability of research networks and resources to support the study's implementation. While this focus provides valuable insights into the SCSE of patients managing OAC in these regions, it may not fully capture English speakers' linguistic and cultural nuances in Europe, such as those in Ireland or the United Kingdom. We acknowledge that the distinct differences in Australian English compared to UK English, along with varying health care systems and patient education practices, could influence the generalizability of our findings to other English-speaking populations. Therefore, we will extend the validation phase of our project to include researchers and participants from other countries who wish to contribute to this body of knowledge. Interested parties are encouraged to contact the authors for potential collaboration, allowing authors to evaluate and integrate scaling-ups of the project accordingly. This adaptive approach aims to enhance the SCSE-OAC's applicability and relevance across broader linguistic and cultural contexts, addressing an acknowledged limitation of this study design.

Conclusions

This research protocol describes the development and validation of the SCSE-OAC in adults with NVAF by using a multiphase and mixed methods approach, guided by the SCSE framework, to ensure cross-cultural validity and reliability for both English and Italian-speaking populations. The SCSE-OAC will address the crucial need to assess patients' confidence in managing their OAC treatment, enabling tailored patient-centered educational interventions and ultimately improving treatment adherence and health outcomes. These interventions are anticipated to markedly enhance treatment adherence and health outcomes, representing a significant stride in OAC management. The study will introduce a novel perspective in identifying and addressing individual patient needs, thus fostering better adherence and improving health outcomes, highlighting the importance of SCSE. The forthcoming efforts to validate the SCSE-OAC across diverse cultural and linguistic landscapes will amplify its applicability in global clinical and research settings and crucially contribute to establishing a universal standard for assessing SCSE in OAC management. This endeavor is pivotal for empowering health care professionals and researchers globally to devise efficacious and culturally attuned interventions.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available in the Zenodo repository once the study is completed.

Conflicts of Interest

None declared.

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Abbreviations

CCI: Charlson Comorbidity Index
CDSES: Chronic Disease Self-Efficacy
CFA: confirmatory factor analysis
CFI: comparative fit index
COSMIN: Consensus-based Standards for selecting health status Measurement Instruments
CVI: content validity index
EFA: explorative factor analysis
GSE: General Self-Efficacy
HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
MGCFA: Multi-Group Confirmatory Factor Analysis
NVAF: nonvalvular atrial fibrillation
OAC: oral anticoagulation therapy
PCC: Population, Concept, Context
REDCap: Research Electronic Data Capture
RMSEA: root-mean-square error of approximation
SCSE: self-care self-efficacy
SCSE-OAC: Self-Care Self-Efficacy Index in Oral Anticoagulation Therapy Management
SE: self-efficacy
SEAMS: Self-Efficacy for Appropriate Medication Use Scale
STROBE: Strengthening the Reporting of Observational studies in Epidemiology
TLI: Tucker-Lewis Index

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Protocol

Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies Using AI (QUADAS-AI): Protocol for a Qualitative Study

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Abstract

Background: Quality assessment of diagnostic accuracy studies (QUADAS), and more recently QUADAS-2, were developed to aid the evaluation of methodological quality within primary diagnostic accuracy studies. However, its current form, QUADAS-2 does not address the unique considerations raised by artificial intelligence (AI)–centered diagnostic systems. The rapid progression of the AI diagnostics field mandates suitable quality assessment tools to determine the risk of bias and applicability, and subsequently evaluate translational potential for clinical practice.

Objective: We aim to develop an AI-specific QUADAS (QUADAS-AI) tool that addresses the specific challenges associated with the appraisal of AI diagnostic accuracy studies. This paper describes the processes and methods that will be used to develop QUADAS-AI.

Methods: The development of QUADAS-AI can be distilled into 3 broad stages. Stage 1—a project organization phase had been undertaken, during which a project team and a steering committee were established. The steering committee consists of a panel of international experts representing diverse stakeholder groups. Following this, the scope of the project was finalized. Stage 2—an item generation process will be completed following (1) a mapping review, (2) a meta-research study, (3) a scoping survey of international experts, and (4) a patient and public involvement and engagement exercise. Candidate items will then be put forward to the international Delphi panel to achieve consensus for inclusion in the revised tool. A modified Delphi consensus methodology involving multiple online rounds and a final consensus meeting will be carried out to refine the tool, following which the initial QUADAS-AI tool will be drafted. A piloting phase will be carried out to identify components that are considered to be either ambiguous or missing. Stage 3—once the steering committee has finalized the QUADAS-AI tool, specific dissemination strategies will be aimed toward academic, policy, regulatory, industry, and public stakeholders, respectively.

Results: As of July 2024, the project organization phase, as well as the mapping review and meta-research study, have been completed. We aim to complete the item generation, including the Delphi consensus, and finalize the tool by the end of 2024. Therefore, QUADAS-AI will be able to provide a consensus-derived platform upon which stakeholders may systematically appraise the methodological quality associated with AI diagnostic accuracy studies by the beginning of 2025.

Conclusions: AI-driven systems comprise an increasingly significant proportion of research in clinical diagnostics. Through this process, QUADAS-AI will aid the evaluation of studies in this domain in order to identify bias and applicability concerns. As such, QUADAS-AI may form a key part of clinical, governmental, and regulatory evaluation frameworks for AI diagnostic systems globally.

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KEYWORDS

artificial intelligence; AI; AI-specific quality assessment of diagnostic accuracy studies; QUADAS-AI; AI-driven; diagnostics; evidence synthesis; quality assessment; evaluation; diagnostic; accuracy; bias; translation; clinical practice; assessment tool; diagnostic service

Introduction

Despite many promises, the integration of artificial intelligence (AI)–centered systems into clinical workflows has been limited thus far. In the current paradigm, diagnostic investigations require interpretation from expert clinicians in order to generate a diagnosis and subsequently determine management. However, diagnostic services across the world are overburdened with unmanageable workloads, which exceed workforce capacity [1]. In order to address this, diagnostic AI systems have been characterized by regulators and technologists as medical devices [2] that may achieve diagnostic accuracy comparable to that of an expert clinician, while concurrently alleviating health-resource use, helping to reduce medical errors. Indeed, the majority of health care–related AI systems that have reached regulatory approval belong to the field of medical diagnostics [3]. As seminal primary research studies arise on the theme of AI diagnostics [4,5], there has been a concomitant rise in secondary research studies that amalgamate the findings of comparable studies.

Although systematic reviews serve an important role in summarizing evidence, the vast majority related to AI diagnostic accuracy have been conducted in the absence of an AI-specific methodological quality assessment tool [6]. AI diagnostic accuracy studies are methodologically distinct from traditional diagnostic accuracy studies as they comprise distinct methods, analyses, and outcome measures that mandate specific considerations when assessing quality [7]. Currently, the most commonly used instrument for the methodological assessment of secondary research studies remains the quality assessment of diagnostic accuracy studies (QUADAS-2) tool [8]. It is a quality assessment tool designed for use in systematic reviews, initially developed in 2003 [9] and updated in 2011; its use is strongly encouraged by many biomedical journals. It consists of four key domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. These domains allow researchers to undertake a structured appraisal of a research study's internal validity (biases) and external validity (applicability), respectively. The absence of a robust quality assessment tool in the AI field not only hinders efficient quality appraisal at an evidence synthesis phase but has considerable downstream effects as key stakeholders, such as policy makers, regulatory officials, technologists, and health care professionals, are unable to effectively evaluate the translational potential of these nascent technologies.

We propose an AI-specific extension, termed AI-specific QUADAS (QUADAS-AI), that aims to provide researchers and policy makers with a framework to appraise methodological quality in systematic reviews evaluating the diagnostic accuracy of AI. This work is complementary to the Standards for Reporting Diagnostic accuracy studies (STARD-AI) [10] and QUADAS-3 initiatives. QUADAS-AI is being coordinated by a project team and a steering committee consisting of clinician scientists, computer scientists, journal editors, Enhancing the Quality and Transparency of Health Research (EQUATOR) Network representatives, regulatory leaders, epidemiologists, statisticians, industry leaders, funders, health policy makers, legal experts, and bioethicists. Given the global reach of this class of technologies and the transformative potential in clinical diagnostics, we view that connecting global stakeholders is of the utmost importance for this initiative. This study aims to produce a novel quality assessment tool (QUADAS-AI) that accounts for the specific considerations required for the appraisal of AI diagnostic accuracy studies.

Methods

Overview

This protocol has benefitted from the experience and expertise of members of the project team and steering committee who have previously led the development of seminal quality assessment tools over the past 2 decades. These include QUADAS and QUADAS-2 for diagnostic accuracy studies, risk of bias in systematic reviews (ROBIS) for systematic reviews [11], and prediction model risk of bias assessment tool (PROBAST) [12] for prediction modeling studies. Moreover, there is shared learning from the development of AI-specific reporting guidelines and risk of bias tools, including STARD-AI [10] and PROBAST-AI [13]. The development of QUADAS-AI can be distilled into 3 broad stages, as previously delineated [14]. Given the pressing need for suitable quality assessment standards of diagnostic studies in this field, development is projected to finish by the end of 2024.

Stage 1

Project Organization

QUADAS-AI is being undertaken by a project team and a steering committee. The project team consists of the founder of QUADAS (PW), the lead for the STARD-AI initiative (HA), and a clinician scientist (AG). The project team is responsible for identifying members of the steering committee, candidate item generation, undertaking the online surveys for the modified Delphi consensus process, organizing the consensus meeting, drafting the QUADAS-AI tool and accompanying documents, coordinating the piloting of the draft QUADAS-AI tool, and leading the dissemination process.

The steering committee was created in order to provide diverse stakeholder guidance in this process, as well as to identify additional experts to invite for the consensus response and draft the final QUADAS-AI tool. The steering committee currently comprises approximately 15 members and consists of health care professionals, computer scientists, epidemiologists,

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statisticians, regulatory officials, health policy leaders, and industry leaders. These individuals were identified through their notable work in the fields of (1) diagnostic accuracy research, (2) AI in health care, and (3) applied health policy.

Defining Scope

The scope of QUADAS-AI has been defined by the project team and steering committee through a discussion framed around questions previously proposed [14]. It was predetermined that QUADAS-AI, as per previous iterations of the tool, would focus on the methodological quality of AI diagnostic accuracy studies. This study is complementary to the ongoing QUADAS-3 initiative, which is the next iteration of QUADAS and is currently led by one of the study authors and the project team (PW). If a draft of the QUADAS-3 becomes available during the development of QUADAS-AI or any substantial updates are anticipated in comparison to QUADAS-2, we will base the QUADAS-AI tool on the QUADAS-3 structure; otherwise, we will instead focus on QUADAS-2. Discourse related to the (1) assessments related to the risk of bias (internal validity), (2) assessments related to applicability (external validity), (3) tool structure, and (4) rating system is a dynamic process that will be open to adaptation throughout stage 2 of the study.

Stage 2

Item Generation

In order to generate a candidate list of items to enter the modified Delphi consensus process, the project team will undertake a mapping review, a meta-research study, a scoping survey with a global panel of experts, and a patient and public involvement and engagement (PPIE) exercise.

Mapping Review

A mapping review of both academic and nonacademic literature has been undertaken in order to identify key considerations in the development of QUADAS-AI. An electronic database search of MEDLINE and Embase was conducted through Ovid (Wolters Kluwer). This process was augmented by nonsystematic searches using traditional search engines for gray literature, social networking platforms, as well as personal paper collections highlighted by members of the project team. The extracted material was broadly classified into four categories: (1) general considerations regarding diagnostic accuracy studies and AI, (2) evidence and statements suggesting modifications to current items, (3) evidence and statements suggesting additions of items, and (4) evidence and statements suggesting the removal of specific items.

Meta-Research Study

As previously noted, there have been no studies examining the adherence and suitability of QUADAS-2 for the appraisal of AI diagnostic accuracy study quality. Therefore, a meta-research study was carried out to evaluate the adherence of AI diagnostic accuracy systematic reviews to the existing QUADAS-2 tool. This study demonstrated that there is incomplete uptake of quality assessment tools, as well as inconsistent reporting of bias in AI-diagnostic accuracy systematic reviews, with just over half of the studies using QUADAS-2. This study also identified key biases and features unique to AI diagnostic accuracy studies. These will contribute to the formulation of candidate items for addition or modification.

Online Scoping Survey

The project team and steering committee will undertake a survey of an international panel of experts in order to identify potential further items or modifications that warrant inclusion in QUADAS-AI. A diverse and independent panel of experts will be identified by the Project Team and Steering Committee from the various stakeholder groups outlined above. They will be provided with an information sheet describing the study and asked to participate in an online questionnaire. Participants will be asked to consider whether each item on the existing QUADAS-2 tool should be retained, removed, or modified in the QUADAS-AI tool. Free-text sections will allow participants to express their thoughts on each item as well as suggest modifications or further considerations. Furthermore, participants will be asked to comment on additional candidate items or considerations produced from preceding rounds of the item generation process.

PPIE Exercise

Finally, a focus group will be conducted with patients and members of the public who have expressed an interest in participating in forums related to digital health and AI. The objective of these discussions is two-fold: (1) to further identify issues not uncovered during previous evidence generation steps and (2) to gain further understanding of the perceived importance to the public of specific items that have been raised thus far. These discussions will be conducted remotely using Zoom (Zoom Video Communications).

An expert facilitator will lead a discussion on the current uses of AI in health care, including considerations on the aims of QUADAS-AI and the important items that the participants deem to be important to capture during the study process. As stakeholder discussions will be conducted virtually on Zoom, anonymized post hoc discussion transcripts will be retained.

Collation of Items

The project team and steering committee will group items from the item generation phase into domains and subsequently word items as signaling questions. An online discussion among the project team and members of the steering committee will be held to further refine the domains and signaling questions into a draft tool, which will then enter the Delphi consensus process for approval and refinement.

Modified Delphi Consensus Process

We will adopt a pragmatic modified Delphi consensus methodology. The Delphi consensus methodology is a well-established method of obtaining a collective opinion from a group of experts through a series of questionnaires; each one refined based on feedback from respondents on a previous version [15]. We will conduct the Delphi consensus process in a similar way as described in the STARD-AI protocol [10].

Participants from across the world are invited to join the QUADAS-AI Consensus Group on account of their expertise as clinician-scientists, computer scientists, journal editors, EQUATOR Network representatives, epidemiologists,

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statisticians, health technology industry leaders, funders, health policy makers, legal experts, and bioethicists. The steering committee will identify potential participants from their wider professional network or experts who have made significant contributions to their respective fields. Invited experts will be provided with a written invite detailing the study and given a 6-week timeframe to respond. Those who accept the invitation will be invited to complete each round of the modified Delphi consensus process and will be acknowledged as an author, within a group authorship model, in the publication that arises from this study. Studies of similar scope and breadth, such as STARD-AI, recruited over 150 participants from varied backgrounds across the world. A similar number is anticipated for QUADAS-AI.

During each phase of the modified Delphi consensus process, participants will use a 5-point Likert-like scale to evaluate each item (1—very important, 2—important, 3—moderately important, 4—slightly important, and 5—not at all important). The threshold for consensus will be predefined at ≥75%. Items that achieve ≥75% ratings of 1 or 2 will be put forward for discussion in the final round, which will occur in the form of an online teleconference meeting. Items that achieve ≥75% ratings of 4 or 5 will be excluded. Items that do not meet the 75% consensus threshold will advance to the next phase of the Delphi process. Participants will also have the opportunity to propose additional items that they believe warrant discussion in future rounds through open-ended responses.

In subsequent rounds, the survey will be composed of items for which consensus was not achieved and any new items suggested in prior rounds. Each item will be accompanied by a reminder of the participant's last rating and the average rating from all participants in the prior round. This allows participants to reconsider their initial evaluations with the benefit of understanding the perspective of the wider group. Items that have not reached a consensus will be put forward for discussion in the following rounds until a consensus is reached. We will conduct descriptive statistical tests on the results for each round (median, range, mean, percentage agreement, and consensus).

Once a consensus is reached, there will be a final meeting between a small group of the project team and the steering committee to finalize the structure and content of the QUADAS-AI tool based on feedback from the Delphi consensus. The primary objective is to develop a draft version of the QUADAS-AI tool. As recommended in the Core Outcome Measures in Effective Trials (COMET) handbook, the nominal group technique, a highly structured group interaction framework, will be used to aid this process [16,17]. Following a brief introduction and explanation of the purpose of the meeting by the facilitators, participants will discuss the inclusion and exclusion of candidate items and share any comments until all contributions are exhausted. This discussion phase will be led by the facilitators to ensure that the discussion will not be dominated by any one individual and be as neutral as possible [18].

The first 2 rounds of the modified Delphi consensus process will be conducted as online surveys using the Delphi Manager software (version 4.0; Embarcadero Technologies), which is developed and maintained by the COMET initiative. The final meeting to draft the QUADAS-AI tool will be conducted using Zoom. All data are pseudo-anonymized and no identifiable data will be published.

Development of the Quality Assessment Tool, Statement, and Explanation and Elaboration Document

Upon completion, the project team will construct the initial QUADAS-AI tool. The draft tool, with an accompanying statement, will be shared among the wider steering committee in order to discuss its content and, therefore, allow the steering committee to suggest additions, subtractions, or modifications as they see fit.

Piloting Among Experts and Nonexperts

Upon completion of the first draft of the QUADAS-AI tool, we intend to organize multiple rounds of piloting among expert and nonexpert users (QUADAS-AI Pilot Group). The main aim of these piloting sessions is to test the tool's usability, as well as identify items that are considered to be vague, ambiguous, or perceived to be missing. We intend to undertake this process among health care professionals, computer scientists, expert statisticians, journal editorial boards, key industry stakeholders, regulatory leaders, as well as policy experts. Interviews among this QUADAS-AI Pilot Group will be undertaken in order to ensure that a granular level of feedback is attained for points of discussion. Members of the pilot group will not be part of the steering committee or have previously participated in the consensus process in order to provide an independent opinion. We anticipate around 20 to 30 members will be recruited. Experts and nonexperts within the Pilot Group will be acknowledged by name as author, within a group authorship model, in the publications that arise from this study.

In conjunction with this piloting process, the project team will prepare the explanation and elaboration document, to provide rationale for the domains, structure, and items associated with the tool.

Stage 3: Dissemination

Overview

Following the piloting phase, the final proposed amendments to QUADAS-AI will be discussed among the project team and the steering committee. Once consensus has been reached through email correspondence, the documents will be disseminated.

We strongly anticipate that the dissemination strategy will be principally tailored toward five groups of stakeholders: (1) academia, (2) policy, (3) guidelines and regulation, (4) industry, and (5) patient-representative bodies. Although a significant amount of material will cross over between stakeholders, creating stakeholder-specific material is considered to be the most meaningful way of achieving impact.

Academic Stakeholders

We aim to publish the QUADAS-AI tool, the accompanying statement and the explanation and elaboration document in an open-access format in a high-impact, peer-reviewed journal. In order to further complement this, we aim to create

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specialty-specific discourse regarding QUADAS-AI through focused editorials in pertinent journals. These journal editors will also be actively encouraged to endorse the use of QUADAS-AI as part of their peer review process. Translations of the tool in various languages are also encouraged in order to further broaden the scope of its impact. We urge interested parties to contact the corresponding author for further information about the translation policies.

Policy Stakeholders

We are in close collaboration with organizations such as Public Health England, National Health Service (NHS) Digital, National Institute for Health and Care Excellence (NICE), and the NHS Accelerated Access Collaborative (AAC) and their wider network to ensure that the tool will form part of their health technology assessment pathways.

Guidelines and Regulatory Stakeholders

QUADAS-AI has been co-designed with senior figures from the United States Food and Drug Administration (FDA) and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA). While they do not represent the views of either organization, these steering committee members have a high-level understanding of how QUADAS-AI may be constructed to achieve maximal real-world impact.

Industry Stakeholders

We will present QUADAS-AI to a broad range of health technology companies, ranging from start-ups, small, and medium-sized enterprises to multinational corporations, so that their product pipelines may accommodate this.

Public and Nonspecific Stakeholders

Ensuring that the core material is available in an open-access fashion, through a CC-BY license, is paramount to achieving general impact. In addition, we aim to publish papers in mainstream media and attain distribution through nontraditional means (eg, social networking platforms, webinars, podcast episodes, and blog posts).

Ethical Considerations

Ethics approval for the study has been granted by the Joint Research Compliance Office at Imperial College London (21IC6664). Written consent will be gained for all participants in the online scoping survey, PPIE, Delphi consensus process, and checklist piloting.

Results

As of July 2024, the project team and steering committee have been established, as has the scope of the project. The study is currently in the item generation phase (stage 2), and the mapping and meta-research reviews have been completed. We aim to conduct the scoping survey of experts, PPIE, and Delphi consensus process by the end of 2024 and publish the statement by the first quarter of 2025 for stakeholder use.

Discussion

QUADAS-AI will be a consensus-derived quality assessment tool that will allow readers to critically appraise the risk of bias and the applicability of study findings in systematic reviews of diagnostic accuracy studies using AI. By providing a framework to evaluate the methodological quality of studies, stakeholders will be in a better position to assess the evidence base and potential for clinical translation of AI-driven diagnostic tools.

AI technology will likely be integrated into several clinical workflows within the next decade in order to enhance patient care and improve clinical outcomes. Specifically, clinical diagnostics has emerged as a key area that has gathered significant interest from global clinical, academic, and industry communities. The importance of evidence synthesis becomes increasingly evident as rapidly advancing AI technology continues to be applied within the diagnostic field; this is typically achieved with systematic reviews to draw clinically relevant conclusions from summarized findings. Therefore, robust methods to evaluate evidence synthesis will be fundamental to the clinical development and implementation of AI technologies as the research community continues to harness the unique ability of AI to generate and process ever-increasing amounts of health data. However, given the notable flaws in using current quality assessment tools, there is a pressing need to develop an AI-specific quality assessment tool that can suitably assess the unique nature of AI diagnostic accuracy studies. We hope that this international, multistakeholder consensus approach will sufficiently address the unique considerations of AI technology, and will ultimately provide a useful tool for clinical, academic, policy, regulatory, and industry stakeholders.

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Data Availability

Datasets generated or analyzed during this study are available on reasonable request from the corresponding author.

Authors' Contributions

AG, VS, PW, PB, AD, and HA developed the concept and methodology of the study. AG and VS drafted the paper. All authors read and approved the paper.

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Conflicts of Interest

AD is the Executive Chair for Preemptive Health and Medicine, Flagship Pioneering. HA is the Chief Scientific Officer of Preemptive Health and Medicine, Flagship Pioneering. VC is an employee of Alphabet. All other authors declare no conflicts of interests.

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Abbreviations

AAC: Accelerated Access Collaborative
AI: artificial intelligence
COMET: Core Outcome Measures in Effective Trials
EQUATOR: Enhancing the Quality and Transparency of Health Research
FDA: Food and Drug Administration
MHRA: Medicines and Healthcare products Regulatory Agency

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NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PPIE: patient and public involvement and engagement
PROBAST: prediction model risk of bias assessment tool
QUADAS: quality assessment of diagnostic accuracy studies
QUADAS-AI: artificial intelligence–specific quality assessment of diagnostic accuracy studies
ROBIS: risk of bias in systematic reviews
STARD-AI: Standards for Reporting Diagnostic accuracy studies

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Protocol

Evaluating the Appropriateness of Podcasts to Improve the Knowledge and Awareness of Selected Health Topics Among Undergraduate General Nursing Students: Protocol for an International Feasibility Study

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Abstract

Background: Podcasts have proven to be a successful alternative source of educational material for students. Given the ability to listen to podcasts 24/7 and while on the go, this technology has the potential to provide informative and educational material to a large number of people at any given time. Podcasts are usually freely available on commonly used mobile devices, such as smartphones, laptops, and tablets.

Objective: This paper describes the impact of health-related podcasts as an intervention tool to support the knowledge and awareness of nursing students on a given topic.

Methods: Pre- and postpodcast questionnaires will gather data regarding the participants' knowledge and awareness of two topics—gestational diabetes and mental health. This intervention will be tested on general nursing undergraduate students. The total number of students (N=2395) from the participating universities are broken down as follows: (1) University College Cork (n=850) and the University of Galway (n=450) in Ireland, (2) Mzuzu University in Malawi (n=719), and (3) University of Fort Hare in South Africa (n=376).

Results: The study received ethical approval from the University College Cork Ethics Committee (2022-027A1). The approval obtained from University College Cork sufficed as ethics coverage for the University of Galway in Ireland. Ethics approval was also received from the Mzuzu University Research Ethics Committee (ID MZUNIREC/DOR/23/28) and the Inter-Faculty Research Ethics Committee of the University of Fort Hare (ID CIL002-21). Data collection is currently underway and will continue until the end of February 2024. The quantitative and qualitative data are expected to be analyzed in March 2024.

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Conclusions: Results from this study will allow for an investigation into the impact of podcasts in different settings: a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi). The data gathered from this feasibility study will provide more clarity on the potential utility of podcasts as an intervention tool. We will gather data regarding listener demographics (eg, country of residence, age, gender, and year of study).

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KEYWORDS

podcasting; podcast; nursing student; gestational diabetes; mental health; health; knowledge

Introduction

Overview

The term “podcast” has been used since approximately 2004. It originally stemmed from 2 terms “iPod” and “broadcast” [1]. The groundbreaking iPod device from Apple pioneered the mobility of digital audio information. Although the iPod has never been the only device used for podcast listening, it swiftly grew into one of the most prominent listening devices [2]. A podcast can be listened to on any digital audio listening device, including a computer that supports audio file playing. Therefore, podcasts can be listened to 24/7 and while on the go. These combined attributes have dramatically increased the use of podcasts over the last 20 years [3]. During this period, podcasts have been regarded as effective medical educational instruments [4,5]. Thus, the accessibility and open access of podcasts may be hugely attractive to higher education institutes as a method of teaching and learning.

Chin et al [6] (2017) showed that after listening to the extracurricular audio podcasts on health-related topics, students who completed the study experienced a significant and probably educationally relevant improvement in their knowledge. This aligns with the results of Mitchell et al [7] (2021), which showed an overall increase of 11.54% in knowledge attainment in undergraduate nursing students after listening to a podcast on delirium [7]. Overall, these studies demonstrate the impact of podcasting on knowledge attainment in third-level education.

A study of the literature in 2017 further highlights that podcasts are a popular source of educational material for a wide range of health care professionals, including junior doctors, nurses, and medical students [4]. In particular, third-level nursing education is an area of health care that calls for sophisticated critical thinking abilities and decision-making processes, which may likely influence clinical competency. University staff members can find themselves searching for new and creative ways to present material in an engaging fashion as the demands on their time and the availability of innovative tools for use in nursing education expand. The implementation of podcasting in nursing education is one strategy to enhance learning, as discussed in the literature. Recent research conducted in Northern Ireland on podcasting to improve undergraduate nursing students’ awareness of Parkinson Disease found that “podcasting as an educational resource for undergraduate student nurses is a successful way of developing knowledge for PD [Parkinson disease]” [8].

There has been a rise in research being conducted on podcasting in nursing education [9]. Despite this, there is limited research being undertaken on the use of podcasts in Africa, even though podcasting is a great topic of conversation among interested African communities. Surveys completed by the Reuters Digital News Report that included 2 African countries highlighted that 33% of participants were considered regular podcast users [10]. Notably, 50% believed that podcasts are more informative in terms of providing a better understanding of issues compared to traditional media platforms [10].

This research will allow for an investigation into the impact of podcasts on knowledge and awareness in different settings—a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi).

Knowledge and awareness have often been used synonymously, but in this study, a distinction between these 2 interchangeable words is set. Knowledge has been described as “the fact or condition of knowing something with familiarity gained through experience or association,” the “acquaintance with or understanding of a science, art, or technique,” and “the range of one's information or understanding” [11]. Awareness has been described as “knowledge and understanding that something is happening or exists” [12]. In our study, awareness will be defined as having heard of a term or topic, while knowledge will be defined as a deeper understanding of the area.

The podcast topics are as follows:

Pregnancy

According to the World Health Organization (WHO), approximately 800 women died every day from pregnancy and childbirth-related avoidable causes in 2020 [13]. Of note, nearly 95% of these maternal deaths took place in low- and low-to-middle–income countries, such as Malawi [13]. This highlights the need to raise awareness of pregnancy risk factors, complications, and services available for women to access the care they need.

Gestational Diabetes

The WHO describes gestational diabetes as “hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes,” which occurs during pregnancy [14]. Worldwide, 21.3 million pregnancies are linked to hyperglycemia, and of these, 18.4 million pregnancies are linked to gestational diabetes mellitus [15]. Furthermore, it is estimated that more than 90% of hyperglycemia cases in pregnancy occur in low- and middle-income countries [16]. Gestational diabetes can impact both the fetus and the mother. Long-term

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implications for children include an increased risk of obesity and metabolic disruption [17]. Furthermore, women who experience gestational diabetes are at risk for developing type 2 diabetes later in life [17]. This demonstrates that gestational diabetes a potentially preventable condition can have a huge societal burden and devastating long-term outcomes.

HIV/AIDS

The WHO figures highlight how HIV infection remains a significant global health concern with 40.1 million deaths occurring to date [18]. Approximately, 650,000 persons died in 2021 as a result of HIV-related causes, and by the end of 2021, an estimated 38.4 million people were living with HIV [18]. Nearly 60% of new HIV infections worldwide occur in the WHO African Region [18]. The HIV infection is incurable. However, owing to accessibility to effective HIV prevention, diagnosis, treatment, and care, especially for opportunistic infections, HIV infection has evolved into a manageable chronic health disease, allowing those who have it to live long and healthy lives. Unfortunately, the disease continues to take many lives despite the availability of treatment and hence it is an important podcast topic to discuss to increase knowledge and awareness.

Cervical Cancer

According to global estimates, there were 604,000 new cases and 342,000 deaths from cervical cancer in women worldwide in 2020 [19]. New cases of cervical cancer and deaths from cervical cancer that occurred in low- and middle-income countries accounted for around 90% of the global total deaths in 2020 [20]. Nearly 50% of high-grade cervical precancers are caused by 2 human papillomavirus types (16 and 18) [20]. This is an important topic to discuss as cervical cancer is curable if detected early and treated effectively. Preventing cervical cancer is more affordable with the human papillomavirus vaccine, precancer lesions screening, and treatment.

Malnutrition

The WHO defines malnutrition as “undernutrition (wasting, stunting, underweight), inadequate vitamins or minerals, overweight, obesity, and resulting diet-related noncommunicable diseases” [21]. A total of 462 million adults are underweight, compared to 1.9 billion who are overweight or obese [21]. Undernutrition is a contributing factor in about 45% of deaths in children younger than 5 years and mostly takes place in low- and middle-income countries [21]. The prevalence of childhood obesity and overweight is also rising in these same nations. The global burden of malnutrition has substantial and long-lasting effects on people and their families as well as on communities, nations, and the economy; therefore, greater conversation around this area is imperative.

Mental Health

As evidenced by the inclusion of mental health in the United Nations Sustainable Development Goals [22], there has been growing recognition of the crucial role mental health plays in achieving global development goals in recent years [23]. According to Arias et al [24] (2022), 418 million disability-adjusted life years or 16% of all disability-adjusted life years worldwide could be attributed to mental diseases in 2019. Overall, this confirms that the need for action on mental health topics is paramount.

Objective of the Feasibility Study

This paper explores the impact of health-related podcasts as an intervention tool to support the knowledge and awareness of nursing students on a given topic. To address this objective, we aim to answer the following questions:

1. Can podcasts support listeners' knowledge of global health topics?
2. Is knowledge attainment from podcasts different across Ireland, South Africa, and Malawi?
3. Is podcasting effective for supporting awareness in nursing students on global health diseases and issues?

Methods

Research Design

This pre- and postpodcast intervention is a feasibility study. Feasibility studies facilitate researchers’ evaluation of whether an intervention is suitable to undergo additional investigation or whether the concepts and conclusions can be applicable and sustainable to the population [25]. A feasibility method was chosen for this study due to the lack of previously published studies on this specific intervention.

Type of Study and Setting

This study mainly involves quantitative data, but qualitative data will be synthesized for the 1 open-ended question on the survey tool. These questionnaires will be created and managed using Google Forms, as it is compliant with the General Data Protection Regulation. Microsoft Excel will be used to capture qualitative and quantitative data and to execute descriptive statistics in the form of percentages and frequencies [26]. This study will be carried out from March 2023 until March 2024.

The selected podcast topics revolve around global health concerns that exhibit significant variations in understanding and practices across different countries. This is intended to enable in-depth podcast discussions and survey questions that can yield insights into how nursing students use the podcasts. These podcast topics have been chosen to encompass a diversity of health-related topics affecting both high- and low-income countries.

To date, the recordings of the podcasts have been conducted. Video and audio files for 2 out of the 6 podcasts will be available for the study participants. Despite only 2 podcasts being chosen for research purposes, all 6 podcasts will be disseminated on platforms including but not limited to YouTube and Spotify. The podcasts’ duration ranges from approximately 30 to 60 minutes each. Each podcast discusses the risk factors, symptoms, and treatment or management of the global health topic.

Each podcast was created with a panel of international experts along with a chair (AD and BC). The 2 podcasts selected for the study are the gestational diabetes podcast and the mental health podcast. As this is a voluntary feasibility project, we only have the resources to examine 2 of the podcasts. Upon completion of this research, we will determine if podcasting is

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an effective method of increasing knowledge and awareness attainment. If the results are positive, we will conduct a broader survey, which will include members of the public and not just nursing students, and will release more podcasts. In addition, mental health and gestational diabetes are widespread issues normally taught in depth in nursing schools and are not confined by geographical locations or socioeconomic status. Likewise, these podcasts had the best audio quality, conversation flow, and in-depth discussion, as decided by the research team. It is evident from the literature that gestational diabetes is a global phenomenon that can impact people from Ireland, South Africa, and Malawi and have potentially long-term preventable implications [16,17]. Similarly, mental health is a global health concern that is gaining increasing attention due to the addition of mental health in the Sustainable Development Goals and the disability-adjusted life years that are attributable to mental disease [23,24]. The selected global health topics are on the list of the top 10 global public health challenges to track in 2023 [27].

Measurement Tools

For the gestational diabetes podcast, a 5-item "Yes-No-I don't know" awareness questionnaire and a 27-item "Yes-No-I don't know" knowledge questionnaire were developed by the researchers. For the mental health podcast, a 4-item "Yes-No-I don't Know" awareness questionnaire and a 26-item "Yes-No-I don't know" knowledge questionnaire were developed by the researchers. The gestational diabetes podcast has 1 additional survey question on awareness and knowledge compared to the mental health podcast, as the podcast discussion on gestational diabetes covered additional items beyond those initially prepared in the semistructured podcast guide.

The knowledge questionnaires for each of these podcasts will address 3 key themes: risk factors, symptoms, and services or treatments. Examples of the questions asked can be found in Table 1.

The only qualitative question asked at the end of each podcast is the following:

"Do you have any further comments on the podcast (duration or formatting), questions asked, or recommendations for future podcasts?"

Table 1. Example of questions asked on knowledge and awareness.

Topic	Area being assessed	Examples of question asked before and after the podcast
Gestational diabetes	Knowledge	Is obesity or BMI a risk factor for gestational diabetes mellitus?
Gestational diabetes	Awareness	Have you heard of metformin?
Mental health	Knowledge	Is a history of mental illness in a blood relative family member a risk factors for mental illness?
Mental health	Awareness	Are you aware of risk factors for mental health problems?

Study Population

The study will collect data from undergraduate general nursing students from 4 universities located across Ireland, South Africa, and Malawi.

Sampling and Sample Sizes

The sample will consist of a cohort of undergraduate nursing students from University College Cork (UCC) and the University of Galway (Ireland), the University of Fort Hare (South Africa), and Mzuzu University (Malawi). These students will be recruited through invitation via the university they are attending. Entry into the study will be entirely voluntary.

The main aim is to compare the pre- and postpodcast scores on knowledge and awareness differences with a paired 2-tailed *t* test. The inputs that will be used are the expected mean (SD) of the paired differences. As this is a feasibility study, a formal sample size calculation is not required [28].

Inclusion and Exclusion Criteria

Exclusion criteria include those who are unable to complete the web-based questionnaires due to a lack of internet connection. These surveys are solely available via Google Forms and are thus inaccessible without an internet connection. Participants will be excluded if they are not a current resident and a registered undergraduate general nursing student of Ireland, South Africa, or Malawi and do not agree to consent to the study. As this is a feasibility study, we are targeting a small cohort of individuals who are convenient to the research team. Inclusion criteria encompass those aged 18 years and older.

Data Collection and Management

Questionnaires will be made using Google Forms, which are stored on UCC's Microsoft OneDrive. The questionnaires will include closed-ended questions using a point scale, with points given to the tick-the-box answers of "Yes", "No," or "I don't know." These questionnaires will be distributed to UCC (Ireland), University of Galway (Ireland), University of Fort Hare (South Africa), and Mzuzu University (Malawi). Regarding the data collection, the investigators will not seek names or emails from the participants, and the data will be fully anonymized. Fully anonymized data are achievable in this study, as participants are not required to complete two different surveys. The pre- and postpodcast questions are on a single Google Form, separated only by the embedded podcast file (not 2 separate survey forms), allowing a direct comparison of survey responses without requiring participant contact details. Once the survey is submitted, the option to withdraw will no longer be available. Answers to our survey (questionnaires) will be stored on UCC-supplied Google Forms and uploaded to OneDrive. Data on knowledge and awareness will be collected from both pre- and postpodcast surveys. Information on gender,

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age, year of study, and the university the student is attending will also be stored, along with the consent forms. The UCC-supplied OneDrive will also be used during data collection and data analyses due to the ability to store data generated on the cloud automatically. Data will be stored for a minimum of 10 years. The data will be controlled by the UCC study members. General Data Protection Regulation will be observed at all times with all information anonymized.

Data collection tools will be structured according to the research themes outlined as follows:

Podcast Knowledge

Participants will be asked about their knowledge of the global health topic by assessing knowledge of symptoms, risk factors, and treatment options associated with the disease. The Google Forms will present an individual question on symptoms, risk factors, and treatments and ask respondents to indicate whether they are symptoms, risk factors, and treatment options of the condition with response options "Yes," "No," or "I Don't know." For the prompted symptoms items, "No" and "I Don't Know" responses will be combined and scored 0, and "Yes" responses will be scored 1. Total scores for prompted awareness of warning signs and risk factors as well as knowledge of symptoms, risk factors, treatment options, government policies, or screening programs will be calculated by adding the recorded responses together.

Podcast Awareness

To achieve this objective, terms on awareness will focus on whether participants have previously heard of terminology associated with the specific podcast and are aware of services available for that health topic or whether they have heard of the condition or disease. With regard to awareness assessment, a scoring system will be implemented. For each question item, "No," and "I Don't Know" responses will be combined and scored 0, and "Yes" responses will be scored 1.

Data Analysis

Microsoft Excel and Google Forms will be used to capture raw quantitative data and to execute the descriptive statistics in the form of percentages and frequencies. Descriptive statistics, including percentages, means, and standard deviations will be calculated for participants' survey responses. For the pre- and posttest analysis, a paired 2-tailed *t* test analysis for the questions that assess medical knowledge will be performed. The means of both the pre and posttests will be calculated. The pretest will act as the control, and therefore, *P* values will be determined to identify if the results are statistically significant. This analysis will enable the observation of whether the podcasts were an effective intervention tool by examining a higher posttest mean score. Significance will be defined as $P<.05$.

This is an international feasibility study, and it would be of great interest to analyze participants' country of residence in conjunction with the level of knowledge and awareness gained from the podcast to give us an insight into which country would benefit most from this form of audio learning. To conduct this, we will perform a subgroup analysis in SPSS. Furthermore, men and women have been shown to learn differently, with women preferentially being auditory learners [29]. Therefore, a subgroup analysis on gender will be carried out on SPSS. This research will help to clarify whether podcasting is a useful educational resource that is of benefit to both sexes as an alternative source of learning [30].

For this study, we only have 1 open-ended question, which is "Do you have any further comments on the podcast (duration or formatting), questions asked, or recommendations for future podcasts?" We will conduct a thematic analysis of the responses to open-ended questions [31]. To analyze and describe the comments, a coding frame will be developed. If responses contain 2 or more different statements, these statements or sentences will be coded separately or line by line.

Ethical Considerations

The study received ethical approval from the UCC's Social Research Ethics Committee (ID 2022-027A1). The approval obtained from UCC sufficed as ethics coverage for the University of Galway in Ireland. Ethics approval was also received by the Mzuzu University Research Ethics Committee (ID MZUNIREC/DOR/23/28) and by the Inter-Faculty Research Ethics Committee at the University of Fort Hare (ID CIL002-21) in South Africa. The study will conform with the precepts of the Declaration of Helsinki on Human Rights of 1975. This research will involve participation through remotely answering survey questions and listening to podcasts. The survey is available in the English language only, as it is the official language in Ireland, Malawi, and South Africa. Participation in this research is not likely to cause any harm or pose a risk to the study participants' well-being.

Informed consent will be explicitly sought from the study participants at the beginning of the survey, and participants are required to be 18 years of age and older. Only undergraduate nurses can take part in this research. Participate confidentiality will be upheld throughout the study process. To maintain confidentiality, no emails, names, or contact information will be required.

The study data will be stored on a password-protected laptop to which only the research team will have access. Participation in this study is entirely voluntary, and participants retain the right to withdraw their participation and data at any time while filling out the survey. However, once the survey is submitted, participants cannot withdraw because the survey is anonymous, and we can therefore not identify who completed the survey. Participants will not receive remuneration or compensation for taking part in the study.

Results

Data collection is currently being conducted and will be carried out until February 2024. The quantitative and qualitative data are expected to be analyzed by March 2024.

Discussion

Comparison With Prior Work

This study, to the best of our knowledge, is the first podcast intervention study to compare the impact of podcasting on

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nursing education internationally. This is extremely pertinent considering the changing landscape of third-level education, the impact of web learning, and the shift away from conventional approaches [32]. This study may highlight the idea that the next generation may be keener on using this technology, as they have grown up with e-learning and internet-based content.

The implementation of podcasting in nursing education is a strategy that has been considered in previous literature. O'Connor et al [33] (2020) identified that the next generation of nursing students has grown up with technology and thus are mostly learners with diverse digital literacy abilities and perhaps a need for interactive, learner-centred courses. Fortunately, podcasting is emerging as a viable educational option. Abate [34] (2013) demonstrated that when undergraduate nursing students listened to a segmented podcast, they had increased scores on multiple choice exams and case study tests, compared to face-to-face lectures and unsegmented podcasts. Likewise, Burke and Cody [35] (2014) reported that 86% of undergraduate nursing students felt that podcasts enriched their learning, and an astonishing 94% of these students would recommend podcasting for other courses.

Expected Findings

This study will investigate the impact of informational podcasts on the attainment of knowledge and awareness in undergraduate nursing students. It will provide valuable insights into the impact of podcasts in education settings across different countries. We anticipate that results from this study could illuminate whether educational podcasts serve as an impactful learning resource for undergraduate nursing students.

Future Research

Other populations apart from undergraduate general nursing students should be included in further studies to determine the appropriateness of this intervention across third-level education. If the results are positive, this feasibility study will be used to inform future research on podcasting in third-level education.

Strengths and Limitations

The role of social media platforms as a medium to deliver education has been under development for several years. This research will provide a clear contribution focusing on the impact of one such platform—YouTube—for undergraduate nursing students in the areas of knowledge and awareness on a set of given topics. This research is international and will enable a greater understanding of the usefulness of podcasts in a high-income country (Ireland) compared to middle-to-low-income countries (South Africa and Malawi). Nonresponse is one of the limitations of this study. Pre- and postpodcast questionnaires are planned to be administered before and after listening to a podcast recording. This may cause participants to become mentally fatigued and not fill out the questionnaire following the podcast, resulting in a reduced response rate. Another limitation of this study is selection bias. For this study, only general undergraduate nursing students will be used to gather information, and thus, they could skew the results due to the level of knowledge they should already have from their undergraduate studies. The generalisability of the study may be limited by the cohort only being composed of nursing students.

Conclusions

Results from this study will allow for an investigation into the impact of podcasts in different settings, a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi). The data gathered from this feasibility study will provide more clarity on the potential utility of podcasts as an intervention tool. We will gather data regarding listener demographics (ie, country of residence, age, gender, and year of study) to ascertain the outreach of the podcasts, which could shape future studies on podcasts as an educational tool. If the results of our study are positive in terms of an increase in knowledge and awareness, we hope to identify other populations that might benefit from this sort of educational resource.

Acknowledgments

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Data Availability

The media data that support the methodology of this study are openly available on Figshare [36]. This is covered by the Creative Commons Attribution license (CC BY 4.0 license).

Authors' Contributions

AD, BC, JOD, and GBC contributed to the design and development of podcasts. LC, GBC, AD, BC, and COM assisted with study recruitment and advertisement. RB, STR, AD, BC, JOD, GBC, COM, and LC edited and reviewed the manuscript. All members of the research team approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

UCC: University College Cork
WHO: World Health Organization

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Protocol

Comparison of Spontaneous Pushing and Directed Pushing During the Second Stage of Labor Among Chinese Women Without Epidural Analgesia: Protocol for a Noninferior Feasibility Study

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Abstract

Background: Maternal pushing during the second stage of labor could influence labor progress and maternal-neonatal outcomes. Although the image of health care providers directing the laboring women to push during the second stage of labor could be commonly observed globally, this practice is not sufficiently researched and is questioned regarding its effectiveness and outcomes on the mother and baby. Meanwhile, a strategy referred to as "spontaneous pushing," which supports women to push by following their bodily urges, has been evaluated in several trials. However, in China, spontaneous pushing is not common practice. Notwithstanding the evaluation of spontaneous pushing, there is a lack of high-quality evidence to support either strategies of directed pushing or spontaneous pushing.

Objective: This study aims to test the feasibility of a future randomized controlled trial to compare the effects of spontaneous pushing and directed pushing during the second stage of labor for maternal and neonatal outcomes in China.

Methods: A nonrandomized, single-group, noninferiority feasibility study will be conducted in a public hospital in Hebei Province, China. In total, 105 women meeting the selection criteria will be recruited to receive the intervention (spontaneous pushing), while 105 sets of medical notes from women who received routine care (directed pushing) will be identified and reviewed to compare outcomes for both cohorts. A mixed methods approach will be used to assess primary outcomes (feasibility and acceptability) and secondary outcomes (effectiveness).

Results: Data collection took place between May and October 2023. A total of 110 women were invited to participate in the intervention of spontaneous pushing. Midwives' interviews were conducted and will be transcribed for analysis in March 2024. The data analysis is planned to be completed by May 2024.

Conclusions: This feasibility study will provide important information by conducting a full-scale clinical trial in the future as well as the potential facilitators and barriers of it. A future randomized controlled trial is likely to have considerable policy and funding impacts regarding pushing management during the second stage of labor and improvement in women's childbirth experience.

Trial Registration: Chinese Clinical Trial Register ChiCTR2300071178; https://tinyurl.com/mudtnbft

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International Registered Report Identifier (IRRID): DERR1-10.2196/55701

(JMIR Res Protoc 2024;13:e55701) doi:10.2196/55701

KEYWORDS

spontaneous pushing; directed pushing; labour stage, labour; labor; obstetric; obstetrics; child; birth; delivery; second; feasibility study; China; Chinese; women; protocol; maternal-neonatal outcomes; maternal; healthcare; labouring women; cohort; effectiveness; Midwives; midwife; midwifery; childbirth

Introduction

Background

To achieve physiological childbirth, it is acknowledged that sound maternity practice should aim primarily at giving every woman an opportunity to achieve normality if that is what women choose [1]. More recently, a clinical practice that supports a woman to follow their bodily desire to push during the second stage of labor has been evaluated in several clinical trials [2-5]. This practice is called "spontaneous pushing." However, this is not a new practice; rather, it is a return to previous practice because it is believed that women in the past gave birth unaided. During spontaneous pushing, a woman takes several breaths in between pushes and is encouraged to give several short pushes throughout the duration of 1 uterine contraction [6]. This could occur with open and closed glottis, depending on women's preference [6]. Evidence from a systematic review confirmed that spontaneous pushing did not necessarily lead to a longer duration of the second stage of labor [7]. In addition, women in the spontaneous pushing group are less likely to experience an extended episiotomy and cesarean birth during labor [8].

Meanwhile, in most hospital settings around the world, directing a woman to push during labor is commonly observed [7]. This is usually called "directed pushing." In this context, women are required to follow specific instructions from health care providers and to push in the Valsalva maneuver, involving taking deep breaths and pushing long and hard with closed glottis [7]. At the beginning of the last century in resource-rich countries, promoters of natural birth introduced and advocated this way of directed pushing [9]. They believed that directed pushing could expedite the second stage of labor and avoid the use of forceps, which was commonly used at that time [10]. However, subsequent findings revealed that directed pushing unfavorably alters maternal physiology and contributes to adverse fetal outcomes [11], including poor fetal acid-base balance [12], fetal heart rate increase or decrease [13], low umbilical cord pH and partial pressure of oxygen levels [14], low Apgar scores at 1 and 5 minutes [12], and decreased cerebral oxygenation [15].

Effective spontaneous pushing during the second stage of labor contributes to satisfactory labor progress and improved maternal and neonatal outcomes. The World Health Organization [16] recommends that women in the expulsive phase of the second stage of labor should be encouraged and supported to push spontaneously. Both the Association of Women's Health, Obstetric and Neonatal Nurses and the American College of Nurse-Midwives advocate the use of spontaneous pushing as best practice, which is consistent with physiological birth practices and evidence improved outcomes [17,18]. In a Chinese context, spontaneous pushing has been recommended by a national guideline by the China Maternal and Child Health Association titled *Clinical Practice Guideline for Normal Birth*. The guideline recommends that "women are 'allowed' to push (spontaneously) during a uterine contraction" [19]. Despite the guideline, the routine practice of directed pushing remains in China. Spontaneous pushing is only conducted in an extremely small proportion of hospitals [20]. More evidence is needed to narrow down the gaps between practice guidelines with clinical routine practice. Consequently, high-quality original trials are required to further explore the evidence on pushing management and outcomes in the Chinese context.

Aims

As this study will involve a change of practice in the Chinese context, it is ethically required to conduct a feasibility study before a full-scale randomized controlled trial (RCT) can be performed. Additionally, this study will be conducted as part of a PhD candidature; hence, there are time constraints. This study aims to test the feasibility of a future RCT to compare the effects of spontaneous pushing and directed pushing during the second stage of labor for maternal and neonatal outcomes.

This study will include (1) the preparation program for midwives and (2) the implementation of spontaneous pushing during the second stage of labor for women and a comparison with normal standard care (directed pushing).

Objectives

The primary objective is to test the feasibility of a future RCT to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes. The secondary objective is to explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor.

Methods

Study Design

This feasibility study is a nonrandomized, single-group, noninferiority trial. All participants will receive the intervention (spontaneous pushing). A mixed methods approach will be used to assess the primary and secondary outcomes. This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Multimedia Appendix 1) [21].

Table 1 illustrates the objectives, outcomes, and the corresponding study design. Tables 2 and 3 illustrate the chart of the study designs, visits, and assessments for both women

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and midwives. The flow diagram (Multimedia Appendix 2) demonstrates the enrollment, allocation, follow-up, and assessment process for women to compare the effectiveness of the intervention.

Table 1. Objectives, outcomes, and study design.

Objectives and outcomes	Study design
Primary objective: To test the feasibility of a future RCT[a] to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes	
Feasibility: recruitment rates, retention rates, and attendance rates of participants	Quantitative study design
Acceptability: women's and midwives' perspectives and acceptability of the intervention	Quantitative study design (survey for women) and qualitative design (interviews for midwives)
Secondary objective: To explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor	
Maternal and neonatal outcomes	Quantitative study design

[a]RCT: randomized controlled trial.

Table 2. Chart of the study design, visits, and assessment for women.

Time point	Visit 1: during late pregnancy at clinics	Visit 2: at clinics or admission to the prenatal ward	Visit 3: during the second stage of labor	Visit 4: within 2 hours after birth	Visit 5: during the stay in the postnatal ward
Recruitment					
Eligibility screening	✓	✓			
Informed consent	✓	✓			
Intervention					
Spontaneous pushing			✓		
Assessment					
Case report forms				✓	
Survey for women					✓

Table 3. Chart of the study design, visits, and assessment for midwives.

Time point	Visit 1: before the preparation program	Visit 2: during the preparation program	Visit 3: during women's labor	Visit 4: at the end of the study
Recruitment				
Eligibility screening	✓			
Informed consent	✓			
Intervention				
Preparation program for midwives		✓		
Support women's spontaneous pushing			✓	
Assessment				
Focus group interview for midwives				✓

Sample Size Determination

One of the objectives of the feasibility study is to gain estimates for a sample size calculation in a future RCT [22]. Although a formal sample size calculation is not necessarily needed in a feasibility study, the sample size was calculated based on the duration of the second stage of labor as a parameter outcome in previous studies. Statistical power analysis was used to estimate sample size in PASS (version 15.0; NCSS LLC, USA) software with statistical power at 90%, α at .05, and dropout rate at 20%. The sample size was calculated to be 105 in each group. Based on clinical judgment and the number of laboring women eligible in the site-specific hospital, a sample size of 105 is set for each group.

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To cover all 4 shifts of the roster, a total of 6 midwives will be recruited to deliver the intervention. All the midwives recruited to the study will be interviewed at the end of the study to assess midwives' acceptability and experience participating in the study.

Setting

This study will be conducted in a single Birth Centre in the Fourth Hospital of Shijiazhuang, Hebei Province, China. The economic status of the population and the medical resources of Hebei Province is at the average level among all the provinces in China [23], with an annual live birth rate of 762,376 in 2019 [24]. The chosen hospital has one of the largest numbers of annual birth rates in Hebei Province with around 15,600 births in 2022. The default pushing strategy at this hospital is directed pushing, which also aligns with most other hospitals in China.

Participants

All participants will be recruited from the Fourth Hospital of Shijiazhuang, Hebei Province, China. In total, 105 women will be recruited to receive the intervention. At the same time, 105 sets of medical notes will be identified, and relevant information will be extracted to compare health outcomes between the 2 cohorts. These medical notes will be from women who received standard care, that is, "directed pushing" during the second stage and met the same selection criteria as the women in the spontaneous pushing group. The women whose notes will be reviewed will not be recruited into this study, but permission has been obtained from the site-specific hospital to examine the deidentified medical notes. The demographic data, that is, age and the parity and labor care section of the medical notes will be reviewed and examined and parity in 2 cohorts will be matched for further comparison.

Six midwives will be recruited to support spontaneous pushing. They will be rostered to cover all 4 shifts of the roster to ensure that every recruited woman will be supported to push spontaneously by a recruited and trained midwife. All recruited midwives will be interviewed for the qualitative study part.

Eligibility Criteria

The eligibility criteria for women and midwives are presented in Textboxes 1 and 2. The medical note audit will include women who received directed pushing during the second stage of labor and met the same eligibility criteria as the women in the spontaneous pushing group.

Textbox 1. Eligibility criteria for women.

Inclusion criteria

- Older than 18 years of age
- Gestation 37+ weeks at birth
- Single, healthy fetus in cephalic presentation
- No complications during labor

Exclusion criteria

- Administered epidural analgesia
- Any medical or obstetric complication affecting second-stage management
- Unable to comply with guidance
- Undergo cesarean birth during labor

Textbox 2. Eligibility criteria for midwives.

Inclusion criteria

- Qualified with a certificate in maternal and neonatal care by the Ministry of Health, People's Republic of China
- Employed at the Birth Centre of the Fourth Hospital of Shijiazhuang, Hebei Province, China
- Providing care at the birth site
- Willing to participate (not allocated by a manager)
- Have at least 1 year of postregistration practice

Exclusion criteria

- Unwilling to participate
- Allocated by a manager to participate
- Doula or other nonregistered lay birth support person

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Recruitment

Recruitment of Women

The researcher (JY) will approach and recruit women into the study during their third trimester of pregnancy. This will allow the women to have enough time to read the information leaflet for the study, ask any questions, and make an informed decision about participating in the study without any undue pressure.

The study will be advertised using posters and information leaflets in the antenatal services of the hospital. The researcher (JY) will approach women while they are in the waiting room awaiting their appointment and will talk to them about the study assessing their willingness to receive further information about the study. Verbal information and a written information sheet outlining the study will be provided to the women to take home and review again before their next visit. At the women's subsequent visit, the researcher (JY) will meet women who are willing to participate, provide them with an opportunity to ask any further questions about the research, and seek their consent to participate in the study by asking them to sign a consent form.

Recruitment of Midwives

Study information will be shared at one of the midwives' regular meetings or workshops and written information will be provided. Midwives will be encouraged to take the information sheet home to review, and those interested in participating in the study will be encouraged to contact the research team.

Upon permission, recruited midwives will be recruited to participate in a preparation program, which will be in a workshop format. The workshop will help to prepare them to provide care to women in the spontaneous pushing group. At the end of the study, the midwives will all be invited to attend a focus group interview to gain their views and thoughts about the implementation of the study, the intervention, and their experience of participating in the study. Midwives will not be rewarded for participating in the study. With permission from the birth center manager, the participation of midwives will occur during their normal working hours.

Patient and Public Involvement

Patients and the public were not directly involved in the development of this protocol. However, the development of the research question and the preparation program content are in accordance with the previously published studies on laboring women's and midwives' experiences and priorities.

Ethical Considerations

Ethics Approval

All the methods will be performed in accordance with the relevant guidelines and regulations. The protocol is approved by 2 ethical committees, the University of Technology Sydney Medical Research Ethics Committee (ETH22-7072) and the Health Research Committee from The Fourth Hospital of Shijiazhuang, Hebei Province, China (20230064). All participants will be provided with informed written consent prior to their enrollment in the study. Deidentified findings of this study will be shared locally via staff forums and education sessions in China; shared through peer-reviewed journal publications, international conferences, and seminar presentations; and included as part of the first author's (JY) PhD thesis.

Informed Consent

Informed consent from both women and midwives will be obtained. A member of the research team (JY) will discuss the study with the women and midwives and provide them with details about the study and obtain written consent. All participants will not receive any type of compensation from the study.

All women participating in the study will be given a study code number, and this will be documented in their medical records and all study documents. A sticker with the logo of this study will be tagged in the top right corner of the participant's medical notes. This will help midwives identify the recruited women when they arrive at the birth center in labor.

Participants' Safety and Withdrawal

A participant (including laboring women or midwives) may choose to withdraw from the study at any time. With consent, data before participant withdrawal will be retained and used in data analysis. Participant withdrawal may happen for several reasons, including but not limited to the following: (1) participant decision, (2) inability to comply with study procedures, and (3) the occurrence of what the participant perceives as an intolerable adverse effect.

In addition, the chief researcher (KB) will exclude a participant if it is considered necessary for any reason, including but not limited to (1) clinical decision, (2) ineligibility (either arising during the study or retrospectively having been overlooked at screening), (3) significant protocol deviation, and (4) significant noncompliance with intervention.

The nature and reason for the withdrawal or discontinuation will be recorded.

Intervention

Preparation Program for Midwives

Before the commencing of the study, a preparation program will be provided to the recruited 6 midwives. The program was developed and informed by the research team's midwifery experience, engagement with the literature and a systematic review [8].

The aim of the midwifery preparation program is to provide midwives with comprehensive and evidence-based practice information on the management of pushing in particular the management of spontaneous pushing during the second stage of labor. This will ensure that midwives feel confident to support women with spontaneous pushing during the second stage of labor. The program will run over 3 weeks and will include 6 sessions, and 5 hours in total over 3 weeks. The training plan is displayed in Table 4.

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Table 4. Preparation program for midwives.

Week and session	Topic	Details	Duration (min)
Week 1			
Session 1	Induction	• Introduction of the project and the research team • Midwives to introduce themselves and discuss their expectations of the program, allowing the researcher to answer any questions they may have • The procedure of the feasibility study • The role of the midwife in the feasibility study • Time for question and answers	50
Session 2	Review of the current evidence	• Pushing during the second stage of labor: a scoping review • Directed pushing vs spontaneous pushing: meta-analysis • Discussion	40
Week 2			
Session 3	How to support spontaneous pushing	• Standard procedures of directed pushing management • Strategies to support spontaneous pushing • Comparison of spontaneous pushing and directed pushing • Simulation in pairs • Time for question and answers	90
Session 4	Q&A: Expectations or questions on pushing management	• This session will be conducted digitally using the social media app Tencent meeting • In this session, midwives will be encouraged to share their expectations or questions on managing the second stage of labor • Questions about the process of the study will be answered by the researcher	30
Week 3			
Session 5	Further discussion of the research and participant withdrawal options	• A brief recap of the research and refresh of the training content (highlight the items that directly relate to midwives) • Safety and distress protocol will be explained to midwives • Withdrawal options and their procedures will be explained to midwives	30
Session 6	Scenario-based learning and practice	• Scenario-based learning • Time for question and answers	50 minutes

Strategies to Support Spontaneous Pushing During Labor

Spontaneous pushing encourages a woman to push following her bodily instincts. A standardized step-by-step procedure may not be suitable for every laboring woman. The following strategies are shown to facilitate the spontaneous pushing during labor: (1) encourage woman to select the most comfortable position for her during pushing [7]; (2) offer information about progress of her labor and about any sensations she may feel [25]; (3) affirm to the woman how well her body is working and encourage her to work with and listen to her body urges [25]; (4) support the woman to wait for pushing urges, instead of coaching her to push immediately when the contraction begins [25]; (5) support the woman to push with open glottis, including sighing, moaning, or even crying [26]; and support and encourage the woman to give several short pushes (usually 4 to 6 s) instead of 1 long push (8 to 10 s or even longer) [27].

Outcomes

Overview

The outcomes measured will include 3 domains: feasibility, acceptability, and effectiveness.

Primary Outcomes

The primary outcomes will include (1) feasibility (recruitment rates, retention rates, and attendance rates of participants) and (2) acceptability (women's and midwives' perspectives and acceptability of the intervention).

Secondary Outcomes

Secondary outcomes will include the duration of the second stage of labor, maternal pushing position, mode of birth, rates of cesarean birth, perineal laceration, the rates of episiotomy, newborn Apgar scores, rates of newborn resuscitation, and rates of transfer to the neonatal intensive care unit. Table 5 illustrates the primary and secondary objectives, outcomes, criteria for success, methods for analysis, and measurement tools.

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Table 5. Primary and secondary outcome criteria, analysis, and measurement.

Objectives, outcomes, and criteria for success	Methods of analysis	Measurement or tool
Primary objectives: To test the feasibility of a future RCT[a] to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes		
Recruitment		
Complete recruitment within 6 months	Descriptive	Researcher work log
Women recruited/women accessed×100% > 10%	Descriptive	Researcher work log
Number of women recruited/number of women who bring Information Sheet home×100% > 30%	Descriptive	Researcher work log
Retention		
Loss of follow-up under 30%	Descriptive	Researcher work log
Number of women who completed spontaneous pushing during labor/number of women recruited×100% > 30%	Descriptive	Researcher work log
Number of women who completed the postnatal questionnaire/number of women who completed spontaneous pushing during labor×100% > 80%	Descriptive	Researcher work log
Attendance of participant		
Percentage of completion of all sessions of midwives' preparation program (midwives) > 80%	Descriptive	Researcher work log
Acceptability of the "intervention"		
Overall score of the questionnaire survey above 4 out of 5 (Childbirth Experience Questionnaire above 3 out of 4)	Descriptive	Questionnaire survey
Midwives' focus group	Framework analysis method	Qualitative data
Secondary objectives: To explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor		
Duration of the second stage of labor		
From full cervical dilation to the birth of the baby	Mean (SD) or medians for continuous variables	Case report forms
Mode of birth		
Normal vaginal birth, forceps extraction, vacuum extraction, breech delivery, and cesarean birth	n (%) for categorical variables	Case report forms
Perineal laceration		
Intact, I degree, II degree, III degree, and IV degree	n (%) for categorical variables	Case report forms
Episiotomy		
Mediolateral episiotomy, midline episiotomy, and intradermal suture	Mean (SD) or medians for continuous variables	Case report forms
Apgar score		
Apgar scores in 1 minute, 5 minutes, and 10 minutes after birth	Mean (SD) or medians for continuous variables	Case report forms
Admission to neonatal intensive care unit		
Newborn transferred to the neonatal intensive care unit because of any emergency	Mean (SD) or medians for continuous variables	Case report forms
Neonatal resuscitation		
Resuscitation strategies following China Neonatal Resuscitation Guideline	Mean (SD) or medians for continuous variables	Case report forms

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[a]RCT: randomized controlled trial.

Data Collection

Overview

The primary and secondary outcomes will be measured using a combination of qualitative and quantitative methods. Three data collection tools will be used during this process.

Case Report Form

A self-designed case report form (CRF) will be used by the researcher (JY) to extract the effectiveness outcomes from a woman's medical notes. These will include the duration of the second stage of labor, maternal pushing position, mode of birth, rates of cesarean birth, perineal laceration, rates of episiotomy, newborn Apgar scores, rates of newborn resuscitation, and rates of transfer to the neonatal intensive care unit. The researcher (JY) will also record on the work log the name of the midwife who supported the recruited woman with spontaneous pushing. As the maternal pushing position is not routinely recorded in medical notes, the researcher (JY) will ask the midwife about a woman's pushing position during labor and will record it on the CRF. Midwives will also be advised to record the maternal pushing position in the labor notes during the preparation sessions.

Survey for Women

A questionnaire with closed-ended and open-ended questions will be used to explore women's satisfaction with pushing, their childbirth experience, and their experience in joining the study. The researcher (JY) will access women during their stay in the postnatal ward for the completion of the survey. In case women withdraw from the study, for personal or medical reasons, a withdrawal note will be recorded in their CRF.

Focus Group With Midwives

The focus group with the midwives will form the qualitative part of the study. At the end of the intervention phase of the study, midwives will be invited to attend a face-to-face focus group to share their experience of supporting women with spontaneous pushing and their experiences of being part of the study. The discussion will be moderated by a senior researcher (HL) from the research team and will be guided by several open-ended questions.

As the primary objective of this study is to explore the feasibility of a future RCT, it is important to fully understand how midwives and women feel about the intervention, the procedure, and the enablers and barriers. The questions in the surveys for women and interviews for midwives will focus on the perceptions of both the women and midwives during the pushing phase of labor as well as their experience of being part of the study.

After a lengthy literature search, it was evident that there was no validated survey tool available that would meet the aims of this study. Therefore, the survey for women was developed based on the principles and domains advocated by Bowen et al [28], Section B "Childbirth Experience Questionnaire" in the survey for women is a freely available tool, which has been published in English and validated in Chinese by Zhu et al [29].

Data Analysis

The data in this study include both quantitative and qualitative data. For quantitative data, "intention-to-treat" analysis will be used. Statistical description will be conducted by the description of mean value, SD, number of cases, and percentage. Pearson chi-square test will be conducted for categorical variables. Independent group 2-tailed *t* test will be conducted for continuous variables. The threshold for statistical significance will be set at .05. For qualitative data, a framework method will be used, which is commonly applied for the thematic analysis of interview transcripts [30]. After a verbatim transcription of the audio recording, the framework method will help to create and apply an analytic framework in the data analysis process in 5 steps (data familiarization, framework identification, indexing, charting, mapping, and interpretation) [31]. The quantitative and qualitative data will be combined in order to compile recommendations from the feasibility in order to conduct a future RCT.

Results

This study will provide both quantitative and qualitative data on the feasibility of a future RCT, including the rate of and ease of recruitment, retention, and attendance of participants during the process. Qualitative results from midwives' focus group interviews will be presented to illustrate midwives' acceptability of the intervention. In addition, a series of labor and birth outcomes will be compared to explore the effectiveness of the intervention.

Data collection took place between May and October 2023. A total of 110 women were invited to participate in the intervention of spontaneous pushing. Midwives' interviews were conducted and will be transcribed for analysis in March 2024. The study is expected to conclude in May 2024.

Discussion

Principal Findings

This is a protocol for a study assessing the feasibility, acceptability, and effectiveness of spontaneous pushing during the second stage of labor among Chinese women without epidural analgesia.

A challenge for this study may likely be the recruitment of laboring women. One of the exclusion criteria for women in this study is "administered epidural analgesia" (Table 3). A large proportion of recruited women may be excluded due to the use of epidural analgesia during labor. The epidural analgesia rate varies from one hospital to another in China [32]. However, the most recently noted rate within the study hospital was around 65% for primiparous women. Despite the anticipated high loss rate of laboring women, this exclusion criterion is set based on the underpinning midwifery philosophy that labor and birth under the use of epidural analgesia is not considered a physiological process. The International Confederation of

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Midwives [33] states that "Normal birth is where the woman commences, continues and completes labour with the infant being born spontaneously, in the vertex position at term, without any surgical, medical, or pharmaceutical intervention." The use of epidural analgesia inhibits nerve conduction by blocking painful impulses from the nerves [34]. Although epidural analgesia is considered to be an effective way of pain relief in labor and birth [35], blocking of pain impulses also blocks other impulses conducted by the nerves, including pushing or bearing down urges. At the same time, the "intervention" in this study, spontaneous pushing, encourages laboring woman to feel their bodily urges and push in their most effective way. From this perspective, women who used epidural analgesia during labor may have difficulty feeling their pushing instinct, and hence, they are excluded from this study. The criteria of excluding women who used epidural during labor does not mean to influence women's choices for their pain relief methods. The reasons for this criteria item will be explained beforehand to women to avoid their potential shame of the use of epidural analgesia during labor.

Strengths and Limitations

A strength of this study is the mixed methods that will be used to measure outcome assessment, including quantitative data for effectiveness outcomes and focus group data for acceptability and feasibility outcomes. Another strength of the protocol is that a detailed preparation program for midwives is developed to support spontaneous pushing during labor. A potential limitation of the study is that participants will be both primiparous and multiparous women as we assume that a larger proportion of primiparous women will use epidural analgesia during labor, which will exclude them during the study. Another limitation of the study will be the risk that crossover in clinical context may occur where midwives may facilitate spontaneous pushing when taking care of women from routine practice groups.

Conclusions

This feasibility study will be used to evaluate the feasibility of conducting a full-scale RCT in the future as well as providing an opportunity to explore the potential facilitators and barriers of implementing an RCT. A future RCT will aim to compare the maternal and newborn outcomes between directed pushing and spontaneous pushing in women without epidural analgesia during the second stage of labor. The findings in this study are likely to have considerable policy and funding impacts regarding pushing management during the second stage of labor in line with the World Health Organization's recommendation to improve normality during labor and improve a woman's childbirth experience.

Acknowledgments

The first author (JY) would like to acknowledge the scholarship supported by the China Scholarship Council. This proposed research is being undertaken as a PhD degree and the candidate and supervisors all contributed to the research.

Data Availability

Data sharing is not applicable to this paper currently as no data sets were generated or analyzed during this study.

Authors' Contributions

JY drafted the manuscript protocol. KB and H Roth contributed to the study design and editing. DA and HL helped with the study design. H Rong was a major contributor in assessing the study protocol in hospital settings. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 78 KB - resprot_v13i1e55701_app1.pdf]

Multimedia Appendix 2
Flow diagram.
[PDF File (Adobe PDF File), 103 KB - resprot_v13i1e55701_app2.pdf]

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Abbreviations

CRF: case report form
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials

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Protocol

Evaluating a Remotely Delivered Cardio-Oncology Rehabilitation Intervention for Patients With Breast Cancer (REMOTE-COR-B): Protocol for a Single-Arm Feasibility Trial

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Abstract

Background: Exercise rehabilitation is a promising strategy for reducing cardiovascular disease risk among patients with breast cancer. However, the evidence is primarily derived from programs based at exercise centers with in-person supervised delivery. Conversely, most patients report a preference for home-based rehabilitation. As such, there is a clear need to explore strategies that can provide real-time supervision and coaching while addressing consumer preferences. Evidence from cardiac rehabilitation has demonstrated the noninferiority of a smartphone-based telerehabilitation approach (REMOTE-CR) to improve cardiorespiratory fitness in people with cardiovascular disease compared to a center-based program.

Objective: This study aims to assess the feasibility, safety, and preliminary efficacy of the REMOTE-CR program adapted for patients with breast cancer at risk of cardiotoxicity (REMOTE-COR-B). We will also assess the satisfaction and usability of REMOTE-COR-B.

Methods: We will conduct a single-arm feasibility study of the REMOTE-COR-B program among patients with stage I-III breast cancer who are at risk of cardiotoxicity (taking treatment type and dose, as well as other common cardiovascular disease risk factors into account) and who are within 24 months of completing primary definitive treatment. Participants (target sample size of 40) will receive an 8-week smartphone-based telerehabilitation exercise program involving remotely delivered real-time supervision and behavior change support. The platform comprises a smartphone and wearable heart rate monitor, as well as a

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custom-built smartphone app and web application. Participants will be able to attend remotely monitored exercise sessions during set operating hours each week, scheduled in both the morning and evening. Adherence is the primary outcome of the trial, assessed through the number of remotely monitored exercise sessions attended compared to the trial target (ie, 3 sessions per week). Secondary outcomes include additional trial feasibility indicators (eg, recruitment and retention), safety, satisfaction, and usability, and objective and patient-reported efficacy outcomes (cardiovascular fitness, quality of life, fatigue, self-reported exercise, self-efficacy, habit strength, and motivation). Adherence, feasibility, and safety outcomes will be assessed during the intervention period; intervention satisfaction and usability will be assessed post intervention; and objective and patient-reported efficacy outcomes will be assessed at baseline, post intervention (2-month postbaseline assessment), and at follow-up (5-month postbaseline assessment).

Results: Recruitment for this trial commenced in March 2023, and 7 participants had been recruited as of the submission of the manuscript. The estimated completion date for the project is October 2024, with results expected to be published in mid-2025.

Conclusions: The REMOTE-COR-B intervention is a novel and promising approach to providing exercise therapy to patients with breast cancer at risk of cardiotoxicity who have unique needs and heightened safety risks. This project will provide important information on the extent to which this approach is satisfactory to patients with breast cancer, safe, and potentially effective, which is necessary before larger-scale research or clinical projects.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621001557820; www.anzctr.org.au/ACTRN12621001557820.aspx

International Registered Report Identifier (IRRID): DERR1-10.2196/53301

(JMIR Res Protoc 2024;13:e53301) doi:10.2196/53301

KEYWORDS

breast cancer survivor; breast cancer; cancer survivor; cancer; cardiac rehabilitation; cardiac; cardiotoxicity; cardiovascular disease; digital health; efficacy; exercise; exercise; feasibility; fitness; rehabilitation intervention; rehabilitation; safety

Introduction

With increased rates of breast cancer survival, especially beyond 5 years, there is now an increased need to focus on the late adverse effects of cancer treatment [1,2]. The adverse impact of cancer treatment on cardiovascular health is one such late effect [3]. Cardiovascular disease (a group of heart and blood vessel disorders [4]) is now a leading cause of death among survivors of breast cancer, and survivors of breast cancer have a higher risk compared to the general population [3,5]. In addition to the overlapping risk factors of cancer and cardiovascular disease, including obesity and physical inactivity [6], the cardiotoxic nature of common breast cancer treatments (including chemotherapy, radiotherapy, and human epidermal growth factor receptor [HER]–targeted therapy) is a contributing factor to this increased risk [3]. Anthracycline-based chemotherapy and trastuzumab are of particular concern, being associated with a 5-fold increase in the risk of heart failure compared to treatment without these agents [7].

Exercise rehabilitation focused on increasing cardiorespiratory fitness is a promising strategy for reducing cardiovascular disease risk among survivors of breast cancer [8]. Lower fitness is associated with an increased risk of cardiovascular disease and all-cause mortality in the general population [9], and fitness declines have been observed during cancer treatment. Following breast cancer, major cardiovascular events tend to emerge initially around 4 years after adjuvant treatments, with a second peak around 10 years post treatment [10]. A recent study in over 4000 women, 12 years after a diagnosis of breast cancer, found that increased physical activity (equivalent to approximately 3 hours of brisk walking per week or ≥9 metabolic equivalent task hours [MET-hrs]) was associated with a 56% reduced risk of cardiovascular events (including heart failure, myocardial infarction, angina, coronary revascularization, peripheral arterial disease, carotid artery disease, transient ischemic attack, stroke, and cardiovascular death) when compared to women who exercised less (<9 MET-hrs per week) [11]. To date, over a dozen randomized controlled trials have demonstrated that exercise rehabilitation can effectively increase cardiorespiratory fitness among survivors of breast cancer [8]. Alongside consistent evidence from randomized controlled trials that exercise also improves quality of life and physical functioning [12], this evidence has led to exercise being recommended in guidelines as a routine part of cancer management [13,14].

While the evidence for exercise rehabilitation improving fitness among survivors of breast cancer is strong, it has primarily been derived from center-based exercise rehabilitation programs, where participants receive real-time in-person supervision. However, reliance on center-based delivery is likely to limit accessibility and uptake [12], as many survivors of breast cancer report a preference for home-based rehabilitation [15]. Even with this preference, it is important to ensure participant safety as well as the suitability and individualization of exercise prescriptions. Particularly because exercise trials typically recruit more “well” survivors of cancer, who are generally younger, less likely to be obese, and who are more physically active (ie, rarely include those most at-risk of cardiovascular disease) [16]. As such, there is a clear need to explore noncenter-based delivery models that can provide real-time supervision and coaching to optimize safety, particularly for high-risk patients with breast cancer (eg, those at high risk of cardiovascular disease). Evidence from the cardiac rehabilitation setting suggests that the use of sensors and mobile technologies is a promising strategy for reducing cardiovascular disease risk

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among survivors of breast cancer, warranting investigation [17,18].

Maddison et al [19] developed a smartphone-based exercise telerehabilitation program (REMOTE-CR) that allowed participants to receive real-time remote exercise supervision and coaching from an exercise professional. A noninferiority, randomized trial (n=162) compared REMOTE-CR to a 12-week center-based exercise cardiac rehabilitation program in people with cardiovascular disease [19]. At the 12-week follow-up, REMOTE-CR was shown to be noninferior to center-based exercise cardiac rehabilitation on maximum oxygen uptake (VO_2max; adjusted mean difference [AMD] 0.51, 95% CI 0.97-1.98 mL/kg/minute). At longer-term follow-up (24 weeks), participants allocated to REMOTE-CR were also more likely to be participating in physical activity than those allocated to the center-based program (ie, less sedentary time: AMD –62, 95% CI –118 to –5 minutes/day) [19]. Importantly, per capita costs for delivering REMOTE-CR were 70% lower than center-based exercise cardiac rehabilitation, and although more adverse events were self-reported by the REMOTE-CR group during the intervention period, none were severe, and the majority (42/50, 84%) were not related to program participation. The same approach could be adapted for use in a cardio-oncology setting. However, the extent to which it would be feasible, safe, and effective (ie, positively impact fitness outcomes) for survivors of breast cancer at risk of cardiotoxicity, given their unique needs and risk profile, is unknown.

The overall aim of this study is to determine the feasibility of the REMOTE-COR-B program, a smartphone-based telerehabilitation exercise program for survivors of breast cancer at risk of cardiotoxicity. The secondary objectives of this trial are to determine satisfaction with and usability of REMOTE-COR-B, as well as potential effects on cardiovascular fitness that can be used to inform future, adequately powered trials.

Methods

Ethical Considerations

Ethics clearance was obtained by the Peter MacCallum Cancer Centre Ethics Committee (HREC/60412/PMCC-2020). Informed consent will be obtained from all participants involved in the trial. Participants will be assigned a study ID number. All study materials will be coded with the ID number only. Only the research team will have access to the study database, which contains the information needed to link ID numbers with identifiable information. Participants will be provided with an AUD $25 (US $16.32) gift card at the end of each assessment as an incentive to complete outcome assessments and in acknowledgement of their time. Participants will also be reimbursed for travel expenses or parking costs for attendance at each appointment.

Trial Design

A single-arm feasibility study will be conducted to determine the feasibility, safety, and preliminary efficacy of REMOTE-COR-B (protocol version 7; date August 24, 2023). The trial has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621001557820). The study protocol is reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [20], and the intervention is described according to the Consensus on Exercise Reporting Template (CERT) [21]. Study materials are available on the Open Science Framework [22].

Eligibility and Recruitment

The inclusion and exclusion criteria are provided in Textbox 1. Eligibility will be confirmed using medical data and patient interviews, as appropriate.

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Textbox 1. The inclusion and exclusion criteria for the study.

Inclusion criteria

- A diagnosis of stage I-III breast cancer.
- At risk of cardiotoxicity according to predetermined criteria (taking treatment type and dose as well as other common cardiovascular disease risk factors into account, including age, obesity, and the presence of other comorbidities; Figure S1 in Multimedia Appendix 1 [3,6,23-27]).
- Completion of primary definitive anticancer therapy within the last 24 months (which may be surgery, radiotherapy, or chemotherapy depending on the treatment pathway; participants who received both adjuvant and neoadjuvant treatment are eligible).
- Generally participating in less than the REMOTE-COR-B exercise target (ie, <150 minutes of moderate to vigorous intensity aerobic activity per week over <3 sessions per week) [13,14,28].
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 [28]
- Having sufficient reading and writing English skills is required for understanding the participant information sheet and study participation instructions.

Exclusion criteria

- Participants who have been diagnosed with metastatic (stage IV) or recurrent breast cancer.
- Those who have a medical condition where exercise or cardiopulmonary exercise testing is contraindicated (eg, unstable angina, uncontrolled heart failure, or asthma) [21].
- Having an implanted cardiac device [21].
- Being unable to provide informed consent.
- Being unable to fully participate in study assessments due to cognitive or physical impairment.
- Participating in another exercise study or exercise program with similar goals.
- Participating in a clinical trial that presents safety or contamination issues for either trial (to be assessed by the Steering Committee).

Eligible participants will be identified by the breast cancer clinical and research staff at the Peter MacCallum Cancer Centre and the Royal Melbourne Hospital. Potentially eligible patients will receive an email through the REDCap (Research Electronic Data Capture [29,30]) platform and will be provided with an information pack (including a study flyer and participant information and consent form). Patients can indicate their interest in the trial through the REDCap platform or by direct contact with the research team. Trial staff will contact interested patients to provide a verbal explanation of the project and its procedures, answer patients' questions, and complete the eligibility screening. Following confirmation of eligibility, trial staff will obtain informed consent to participate in the study through REDCap, and the baseline assessment will be scheduled. Participants can withdraw from the study at any time without reason or consequence. In addition, the investigator may discontinue a patient from the study at any time if the investigator considers it necessary for any reason.

Adapting the REMOTE-CR Intervention

For this study, REMOTE-COR-B was adapted from the original REMOTE-CR platform, which is described in detail elsewhere [31]. In brief, the base platform comprises a smartphone and wearable sensor (currently compatible with BioHarness 3, Zephyr Technology, and H10, Polar Electro), as well as a custom-built smartphone app and web application. The platform facilitates remotely supervised exercise prescriptions that are delivered, monitored, and coached in real-time by an exercise professional. The participant's heart rate and geospatial data are displayed in the smartphone app for self-monitoring and streamed to a web server for review by an exercise professional (along with single-lead electrocardiogram [ECG] data, which are not visible to the participant in the smartphone app). The participant can also use the app to report "red flag" symptoms during exercise (chest pain, breathlessness, and dizziness), allowing the exercise professional to stop the session, make contact, and direct as needed. The exercise professional provides individualized audio coaching, feedback, and social support throughout the session, which is delivered to participants through earphones (text-to-audio feature) to optimize usability. At the end of an exercise session, participants are prompted to report their perceived exertion using the app. Outside of real-time interaction, participants can record exercise training for self-monitoring, receive behavior change education through direct messaging, review all recorded exercise performance data, and set or review goals to encourage behavior change.

Adaptations of REMOTE-CR for Breast Cancer

Following consultation with consumer representatives and the advisory committee, the following changes were made to the base platform for the REMOTE-COR-B trial: (1) expansion of the symptom reporting list to include common breast cancer treatment-related side effects and symptoms (Figure 1); (2) prompts for participants to report their symptoms at the start of each exercise session; (3) ability to report Rating of Perceived Exertion (RPE) both during and after exercise to enhance tailoring of prescription and coaching; (4) expansion of the heart rate data display to include beats per minute (BPM; the raw measurement unit) in addition to heart rate reserve, to allow use when a lack of maximal exercise testing precludes calculation of heart rate reserve; (5) revisions to the behavior change education to provide additional positive reinforcement, breast

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cancer–specific content, and messages focused on planning, habit formation, and autonomous motivation; and (6) alternative options for wearing the heart rate monitor if chest irritation or pain is an issue (ie, delay enrollment post treatment, use an adhesive to place the sensor on an unaffected area or at a different location that yields sufficient signal quality, or monitor intensity exclusively through RPE).

Figure 1. Expanded symptom reporting list in REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer.

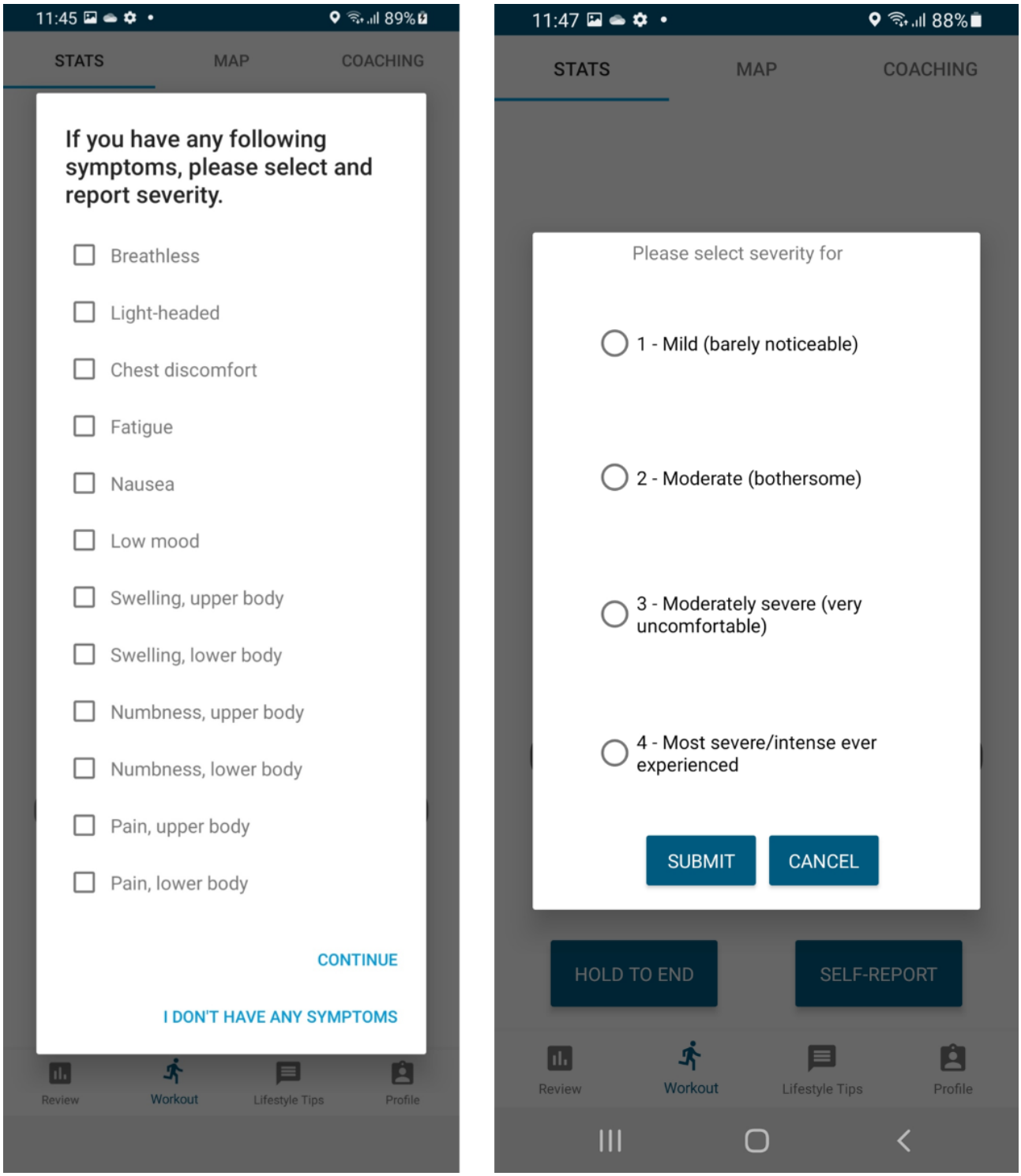

The Remote-COR-B Intervention

The REMOTE-COR-B intervention will be delivered over a period of 8 weeks and involves remotely delivered individualized exercise prescriptions, real-time supervision, and behavior change support (eg, goal setting and supportive messages). The aim of the intervention is for participants to attend 3 remotely monitored aerobic exercise sessions per week, with self-directed exercise encouraged (where appropriate) on ≥2 other days to align with current aerobic recommendations for patients with cancer (ie, 150 minutes of moderate to vigorous intensity activity per week) [13,14,28]. The REMOTE-COR-B trial will emphasize aerobic activity, given the focus of the intervention on improving cardiovascular fitness [14,28]. The

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intervention is summarized below and described in detail according to the CERT requirements in Table S1 in Multimedia Appendix 2 [21,32,33].

Exercise Prescription

Each participant will be provided with an individualized and progressive exercise prescription based on their age, previous and recent exercise habits, motivation, personal goals, attitudes, values, treatment, and support. Exercise prescription components will include frequency (3 remotely monitored sessions per week), duration (20-60 minutes per session), and intensity (moderate: 40%-60% heart rate reserve [HRR] and RPE 3-5 [34]), with the aim of increasing peak oxygen consumption (VO_2peak). Intensity will be monitored through a combination of HRR and RPE if complete baseline cardiopulmonary exercise testing (CPET) is available (more details are provided in the "Secondary Outcomes" section), or BPM and RPE if baseline CPET is unavailable.

The progression of exercise prescription components will typically occur in the following order: duration, intensity, frequency (additional to remotely monitored sessions), and will be gradually increased as tolerated by the individual, with consideration to symptom status, fitness level, exercise response (based on heart rate data and RPE), and each participant's goals [35]. During the first half of the intervention (ie, weeks 1-4), exercise intensity targets will typically range from RPE 3 to 4 ("moderate" to "somewhat hard") and between 40% and 50% HRR [34]. In the second half of the intervention (ie, weeks 5-8), exercise intensity targets will typically range from RPE 4 to 5 ("somewhat hard" to "hard") and between 50% and 60% HRR [34]. The preferred mode of exercise is walking, though participants may choose other land-based aerobic activities (eg, cycling, jogging, and exercise videos).

Remote Monitoring and Supervision

Participants will be able to attend remotely monitored exercise sessions during set operating hours each week, scheduled in both the morning (eg, between 6 AM and 10 AM) and evening (eg, between 5:30 PM and 7:30 PM). Participants can complete exercise in any location with an active broadband connection (mobile, Wi-Fi, or Bluetooth). The REMOTE-COR-B mobile app collects heart rate and single-lead ECG through a Polar H10 heart rate transmitter (loaned to participants throughout the study), location, distance, and speed through location services integration, as well as symptoms and RPE through self-report. These data are then transmitted to a cloud-based server and displayed on a companion web application in real-time. Exercise professionals remotely monitor all data in real-time through the web application, provide participants with real-time individualized coaching feedback and support through their smartphone app (through alerts, messages, or telephone calls), respond to adverse events if required, provide postexercise feedback, and modify exercise prescriptions as needed.

Behavior Change Support

Participants will receive behavior change education and support during the 8-week intervention period through push notifications (2-4 per week) delivered through the REMOTE-COR-B mobile app (Figure 2). The messages are based on social cognitive [36], self-determination [37], and habit theories [38] (Table S1 in Multimedia Appendix 2 outlines the specific strategies). Additionally, participants are encouraged to use the built-in data visualization features of the app to review their exercise performance data and set and review goals to encourage behavior change.

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Figure 2. Example of behavior change support in REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer.

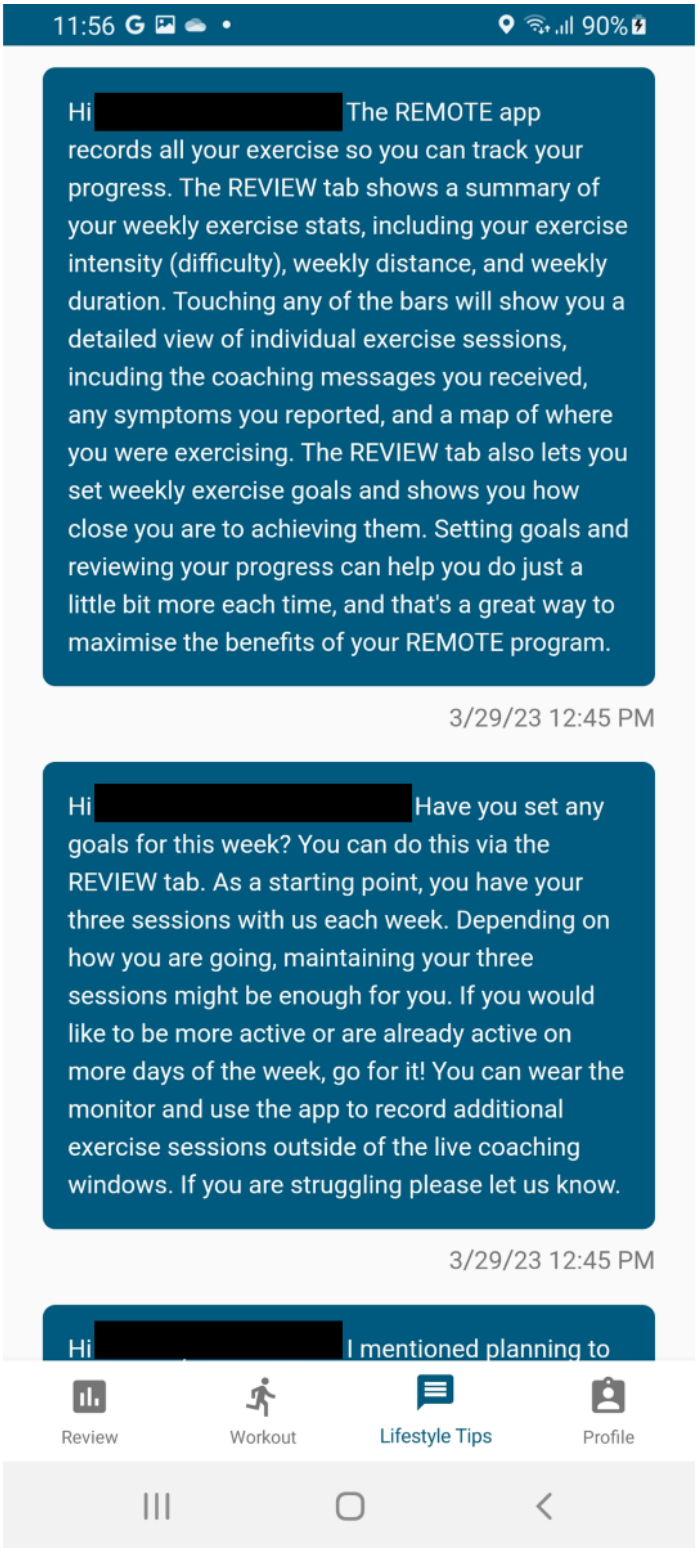

Outcomes and Assessment Timing

Data relating to intervention delivery outcomes (eg, adherence, feasibility, and safety) will be collected during the 8-week intervention (Table 1). Satisfaction and usability will be assessed post intervention. Objective and patient-reported efficacy outcomes will be assessed at baseline (within 24 months post completion of primary definition treatment), post intervention (2-month postbaseline assessment), and at follow-up (5-month postbaseline assessment). Demographic and medical data will be collected at baseline through self-reports and medical records. Criteria of success for core feasibility, usability, safety, and efficacy outcomes have been prespecified and are outlined below.

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Table 1. Schedule of enrollment, intervention, and assessments for REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer (based on the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] guidelines) [20].

Time point	Study period				
	Enrollment (prebaseline)	Intervention period			Follow-up
		Baseline (0 months)	Intervention (2 months)	Postintervention (2-month postbaseline)	Follow-up (5-month postbaseline)
Enrollment					
Cardiotoxicity screen (including treatment information)	✓				
Eligibility screen	✓				
Informed consent	✓				
Interventions					
Single-arm exercise			✓		
Assessments					
Demographic information	✓	✓			
Intervention adherence			✓		
Feasibility	✓	✓		✓	✓
Safety		✓	✓	✓	✓
Intervention satisfaction				✓	
Intervention usability				✓	
CPET[a]		✓		✓	✓
ISWT[b]		✓		✓	✓
Quality of life		✓		✓	✓
Fatigue		✓		✓	✓
Self-reported exercise		✓		✓	✓
Psychological mechanisms		✓		✓	✓

[a]CPET: cardiopulmonary exercise testing.

[b]ISWT: incremental shuttle walk test.

Primary Outcome

Adherence will be assessed through the number of remotely monitored exercise sessions attended compared to the trial target (ie, 3 sessions per week). Previous research suggests ≥70% adherence is satisfactory to achieve fitness gains [8,12]. As such, participants will be considered adherent to the intervention if they complete ≥17 of 24 remotely monitored exercise sessions.

Secondary Outcomes

Trial Feasibility

Trial feasibility is assessed based on rates of screening, consent, device ownership, retention, and missing data across all assessment points. Prespecified cut points indicating feasibility include cardiac dysfunction risk level is accessible for ≥80% of cases identified; ≥60% of those invited to participate agree to complete eligibility screening [39]; the recruitment goal is reached within the allotted time (1 year); retention is ≥60%; and outcome data are collected for ≥80% of enrolled participants at both the postintervention and follow-up assessments (this is in line with retention observed by the chief investigator Maddison et al [19] in the REMOTE-CR trial).

Safety

Adverse events will be assessed through the frequency and severity of adverse events reported during remotely monitored exercise sessions, any unsupervised exercise sessions, and exercise testing sessions (as outlined in the "Cardiovascular Fitness: VO_2peak" section). Severity will be graded according to the Common Terminology Criteria for Adverse Events 5.0 and the National Health and Medical Research Council guidelines for safety monitoring and reporting [32,40]. Participants will be instructed to immediately report any adverse events that occur during the intervention period (during either supervised or unsupervised exercise sessions) to the study staff (ie, exercise professionals or study coordinators); these will be recorded. All adverse events reported to study staff will be communicated to the study coordinator and the coordinating principal investigator as soon as possible and recorded. The coordinating principal investigator will be responsible for ensuring serious adverse events are reported to the ethics committee and trial sponsor within the appropriate time frames. Participants can also retrospectively report adverse events during the postintervention and follow-up surveys. The trial will be deemed safe if no grade ≥3 adverse events attributed to

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participating in the research project are reported. During the intervention period, participants can also self-report symptoms (new, ongoing, or worsening) through the smartphone app at the beginning and end of every exercise session (supervised and unsupervised). Any changes in symptomology will also be recorded.

Satisfaction and Usability

Satisfaction with the intervention and perceived intervention usability will be assessed using the validated 8-item Client Satisfaction Questionnaire (0-32) [41] and the 10-item System Usability Scale (0-100) [42]. The intervention will be deemed satisfactory and usable if mean scores are ≥24 and ≥68, respectively. Issues with wearing the heart rate monitor due to cancer treatment-related discomfort will also be discussed and recorded by the study coordinator in a study-specific form.

Cardiovascular Fitness: VO2peak

Cardiovascular fitness (VO_2peak) will be assessed through CPET and an incremental shuttle walk test (ISWT). The CPET will occur at the Peter MacCallum Cancer Centre (conducted by Peter MacCallum staff) and will involve participants exercising on an exercise bike against increasing resistance, during which time gas exchange analysis will be conducted to measure anaerobic threshold and VO_2peak. Blood pressure and 12-lead ECG will be monitored for signs of an adverse cardiac response. VO_2peak is a gold-standard measure for objectively assessing cardiorespiratory fitness and is an important clinical end point in this population because it is a strong predictor of adverse cardiovascular events and mortality [11]. A change in VO_2peak as small as 6% can be clinically meaningful in terms of cardiovascular outcomes among patients with chronic systolic heart failure [43]. We expect an average improvement in VO_2peak of ≥10%, as this is comparable to what has been achieved in posttreatment supervised exercise interventions among patients with breast cancer [44-46]. Additionally, this level of change is used clinically in a heart failure setting as indicating a clinically meaningful improvement in outcomes [47,48] and is associated with improved health-related quality of life in patients with breast cancer [46].

The ISWT is a valid and reliable field walking test to assess functional exercise capacity [49,50] and is shown to be moderately correlated with CPET-assessed VO_2peak (r=0.61) [51]. Due to possible COVID-19–related difficulties with performing CPETs on all participants, an ISWT will also be performed (conducted by trial staff), as the equipment is easily transportable and the test can be completed outdoors (potentially necessary if a home visit is required due to COVID-19 restrictions and a suitable indoor location is not available). Participants are required to walk around 2 cones placed 9 meters apart (a total of 10 meters of flat course) in time to a set of auditory beeps. Initially, the walking speed is very slow, but each minute, the required walking speed progressively increases. The test concludes when the participant cannot achieve the required speed, experiences clinical indications for test termination, or wishes to stop. The number of shuttles is recorded. Only standardized instructions will be used [50], the walking track will be kept the same for all tests for a participant, and no encouragement will be given throughout. An improvement of ≥48 meters from baseline to postintervention will be considered clinically significant [49]. The intervention will be deemed potentially efficacious for improving cardiovascular fitness if clinically significant changes in VO_2peak (≥10%) or meters walked in the ISWT are achieved.

Quality of Life

Quality of life will be assessed using the validated 38-item Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire [52]. Total health-related quality of life (0-148) and subscale scores (physical, social, emotional, and functional well-being) will be calculated. A clinically important change in total quality of life has been defined as a 6% increase between baseline and postintervention [53].

Fatigue

Fatigue will be assessed using the validated 13-item Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) questionnaire [54]. All items are summed to create a single fatigue score (0-52). A clinically important change in the FACIT-Fatigue has been defined as a 6% increase between baseline and postintervention [53,55].

Self-Reported Exercise

Self-reported exercise will be assessed using the validated 3-item Godin Leisure-Time Exercise Questionnaire (GLTEQ) [56]. Using the GLTEQ, participants self-report how often in the previous 7 days they completed ≥15 minutes of strenuous, moderate, and light physical activity. The number of bouts at each intensity is then multiplied by the corresponding MET value and summed to create a Leisure Score Index (LSI). The proportion of participants considered sufficiently active will also be reported, determined based on prespecified LSI scores (<14 units=insufficiently active or sedentary; between 14 and 23 units=moderately active; and ≥24 units=active or “meeting criteria for being physically active”) [56,57].

Psychological mechanisms

Potential mediators of intervention effects will be assessed, including self-efficacy (Multidimensional Self-Efficacy for Exercise Scale [58]), habit strength (self-reported habit index [59]), motivation type (Behavioural Regulation Questionnaire [60]), and autonomy-supportive exercise environment (The Perceived Environmental Supportiveness Scale [61]).

Data Analysis

Sample Size

We aim to recruit 40 participants over the course of 12 months. This sample size is considered sufficient to test the feasibility of delivering the intervention and other key trial parameters [62]. Notably, with this sample size, we will also have reasonable precision for estimating intervention adherence. For example, with a sample size of 40, if the average adherence rate observed in the study is 70%, we can be sure with 95% confidence that the true population proportion is between 56% and 85%; the 95% CI is ≥14.2. Given the potential reach of the intervention and the fact that adherence to current technology-based behavior change programs is 50% [39], this

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finding would warrant further investigation. The target sample size is also equivalent to approximately 20%-30% of the sample size needed to adequately power (80%) a future definitive trial to demonstrate noninferiority in VO_2peak changes between groups (a *P* value of .05); based on differences observed in our formative work [19] and a systematic review [8].

Statistical Methods

The data will be presented descriptively where appropriate; this includes most feasibility outcomes (eg, recruitment rate, proportion of missing data, usability, and satisfaction), including the primary outcome (ie, adherence to the intervention), and safety outcomes (eg, number of adverse events, proportion of serious adverse events).

Changes in VO_2peak, patient-reported outcomes (quality of life and fatigue), and physical activity behavior will be examined in exploratory analyses at all assessment time points using mixed model repeated measures analyses. Unadjusted and age- and treatment pathway–adjusted models will be conducted with standardized coefficients reported with 95% CIs to aid interpretation of clinical significance rather than *P* values given a lack of statistical power. The choice of modeling link will be informed by residual diagnostics. The data for withdrawn participants collected before study withdrawal will be retained for use in intention-to-treat analyses, unless requested otherwise by the participant.

Further exploratory analyses may include (1) examining changes in the proposed psychological mechanisms (eg, self-efficacy) from baseline to postintervention; (2) examining associations between the proposed mechanisms and the study outcomes (eg, adherence to exercise sessions and cardiorespiratory fitness); and (3) examining associations between participant characteristics (potential moderators) and intervention adherence (sessions and intensity), as well as changes in VO_2peak. Given the small sample size and absence of a control group, a formal mediation analysis or moderation analysis will not be undertaken (as per Baron and Kenny [63]). However, the collection of these data will assist with determining the feasibility of mediator and moderator assessment in a larger trial, where a formal mediation analysis and moderator analysis may be undertaken.

Data Management

The data will be preferentially recorded in electronic case record forms (CRF) and through surveys using REDCap data management software, only accessible to trial staff. Hard copy forms will also be available if necessary (stored in a locked filing cabinet). Data collected through hard copy will be scanned and uploaded to REDCap and the secure study network drive as soon as possible. Hard copies will be shredded once the data are safely stored electronically (including a scan of the original). All data will be exported from REDCap at the end of the trial and stored on a password-protected network drive at the University of Melbourne for at least 5 years after the publication of the results. Deidentified data may be shared indefinitely through sites like Open Science or Figshare to ensure scientific transparency and to share knowledge with others.

Results

The recruitment for this trial began in March 2023, and 7 participants had been recruited as of the submission of the manuscript. Recruitment issues were encountered early, and changes to the prespecified protocol (ACTRN12621001557820) have been made to aid recruitment. The original eligibility criteria for the trial required participants to have completed primary, definitive anticancer therapy within 3-12 weeks. In addition, only anthracyclines and no other types of chemotherapy were considered in the cardiotoxic risk assessment. After screening potential participants, it became clear that recruitment would be slower than expected and that many patients at risk of poor heart health would not be eligible for the trial. Before enrolling the first participant, the eligibility criteria were amended so that participants could be up to 6 months post definitive treatment, and a wider range of evidence-based risk factors for cardiotoxicity and cardiovascular disease would be considered (Figure S1 in Multimedia Appendix 1 [3,6,23-27]). A second objective fitness test (the ISWT) was also added, which can be conducted outside of the hospital setting in case COVID-19 disruptions impact access to CPET assessments. Following these changes, the first participant was enrolled in March 2023.

Additional changes have since been made to the protocol to further aid recruitment. These include expanding screening opportunities to identify potentially eligible participants, streamlining the recruitment procedure through REDCap to reduce burden on hospital staff, and expanding eligibility criteria to include patients up to 24 months post definitive treatment. This amendment was recently approved, and the estimated completion date for the project is October 2024, with results expected to be published in mid-2025. Any future protocol amendments will be reported in the main outcomes publication and registered on the Australian New Zealand Clinical Trials Registry.

Discussion

The original intervention underpinning this trial has demonstrated efficacy and noninferiority compared to gold-standard in-clinic cardiac rehabilitation [19]. The adaptation of this intervention for patients with breast cancer who are at risk of cardiotoxicity is a novel and promising approach to providing accessible exercise therapy. This trial will address the extent to which this approach is satisfactory to patients with breast cancer, safe, and potentially effective, given the unique needs and risk profile of this group. The findings will be used to inform features of a future, adequately powered efficacy trial, including but not limited to eligibility and recruitment strategy, app features and functions, and delivery preferences (eg, session timing) [64]. Trial findings might also be used to inform the implementation of this approach in breast cancer services, given that remote strategies are needed now and the strong evidence-based basis behind the base software (REMOTE-CR). By publishing this protocol, we aim to ensure transparency around prespecified outcome criteria, inform

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interested parties of the upcoming trial, and aid replication and critical review of study methodology.

Acknowledgments

This study is funded by a National Breast Cancer Foundation grant. TLJ is supported by a postdoctoral fellowship partly funded by the grant. CES is supported by a Victoria Cancer Agency Mid-Career Fellowship. LE is supported by a Victoria Cancer Agency Early Career Research fellowship. JCR received a National Heart Foundation of Australia Postdoctoral Fellowship (102585). ALS is supported by the National Heart Foundation of Australia Future Leader Fellowship (award ID 106025).

The University of Melbourne is the sponsor for the trial. The trial sponsor has responsibility for the quality and integrity of trial data, ensuring appropriate approvals are obtained before the commencement of the trial, and patient safety.

Data Availability

The data sets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

CES, JCR, SH, LD, and RM obtained study funding. CES led protocol development with support from all authors. CES led adaptation of the intervention software, with support from JCR, RB, and IH and feedback from SH, LE, RM, and LD. TLJ developed the exercise prescription protocol with input from LE, SH, and LD. CES, TLJ, JCR, and RM developed the behavior change content, which was reviewed and revised by RDB and IH. RDB and IH provided consumer input to the study. SN, RDB, FHJ, and ALS provided clinical expertise in developing cardiotoxicity eligibility criteria. HI oversees cardiopulmonary exercise testing at the Peter MacCallum Cancer Centre. SN and RDB oversee participant recruitment at the study sites. CES and TLJ wrote the original draft of the manuscript. All named authors reviewed, had input into revisions, and approved the final manuscript. Generative AI was not used in any portion of the manuscript writing.

Conflicts of Interest

JCR and RM are inventors of the telerehabilitation platform being examined in this study. They do not receive any related benefits over and above their normal salary.

Multimedia Appendix 1
Cardiotoxicity criteria.
[DOCX File , 17 KB - resprot_v13i1e53301_app1.docx]

Multimedia Appendix 2
Exercise prescription principles of the REMOTE-COR-B trial (based on Consensus on Exercise Reporting Template).
[DOCX File , 27 KB - resprot_v13i1e53301_app2.docx]

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Abbreviations

AMD: adjusted mean difference
BPM: beats per minute
CERT: Consensus on Exercise Reporting Template
CPET: cardiopulmonary exercise testing
CRF: case record forms
ECG: electrocardiogram
FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FACT-B: Functional Assessment of Cancer Therapy-Breast
GLTEQ: Godin Leisure-Time Exercise Questionnaire
HER: human epidermal growth factor receptor
HRR: heart rate reserve
ISWT: incremental shuttle walk test
LSI: Leisure Score Index
MET-hrs: metabolic equivalent task hours
REDCap: Research Electronic Data Capture

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RPE: Rating of Perceived Exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VO2max: maximum oxygen uptake
VO2peak: peak oxygen consumption

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Protocol

Assessing and Improving the Care of Patients With Heart Failure in Ghana: Protocol for a Prospective Observational Study and the Ghana Heart Initiative-Heart Failure Registry

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Abstract

Background: Heart failure (HF) is a leading cause of morbidity and mortality globally, with a high disease burden. The prevalence of HF in Ghana is increasing rapidly, but epidemiological profiles, treatment patterns, and survival data are scarce. The national capacity to diagnose and manage HF appropriately is also limited. To address the growing epidemic of HF, it is crucial to recognize the epidemiological characteristics and medium-term outcomes of HF in Ghana and improve the capability to identify and manage HF promptly and effectively at all levels of care.

Objective: This study aims to determine the epidemiological characteristics and medium-term HF outcomes in Ghana.

Methods: We conducted a prospective, multicenter, multilevel cross-sectional observational study of patients with HF from January to December 2023. Approximately 5000 patients presenting with HF to 9 hospitals, including teaching, regional, and municipal hospitals, will be recruited and evaluated according to a standardized protocol, including the use of an echocardiogram and an N-terminal pro-brain natriuretic peptide (NT-proBNP) test. Guideline-directed medical treatment of HF will be initiated for 6 months, and the medium-term outcomes of interventions, including rehospitalization and mortality, will be assessed. Patient data will be collated into a HF registry for continuous assessment and monitoring.

Results: This intervention will generate the necessary information on the etiology of HF, clinical presentations, the diagnostic yield of various tools, and management outcomes. In addition, it will build the necessary capacity and support for HF management in Ghana. As of July 30, 2023, the training and onboarding of all 9 centers had been completed. Preliminary analyses will be conducted by the end of the second quarter of 2024, and results are expected to be publicly available by the middle of 2024.

Conclusions: This study will provide the necessary data on HF, which will inform decisions on the prevention and management of HF and form the basis for future research.

Trial Registration: ISRCTN Registry (United Kingdom) ISRCTN18216214; https:www.isrctn.com/ISRCTN18216214

International Registered Report Identifier (IRRID): DERR1-10.2196/52616

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KEYWORDS

clinical; cross-sectional; epidemiology; Ghana; heart failure; heart; management; medium-term; monitoring; mortality; outcome; patient data; prevention; protocol; teaching; treatment

Introduction

Overview

Heart failure (HF) is a costly, multifaceted, and life-threatening syndrome characterized by significant morbidity and mortality. Globally, HF affects 64 million people, with a prevalence of 1%-2% of adults in the general population and an estimated incidence of 1-20 cases per 1000 person-years [1].

Sub-Saharan Africa (SSA) has no population-based data; however, in-hospital prevalence ranges from 9.4% to 42.5% [2,3]. HF in SSA mainly affects young people and middle-aged individuals, occurring in people aged between 36 and 62.4 years [4]. It poses a substantial disease burden, with high mortality, rehospitalization rates, and health care costs, primarily attributable to readmissions and prolonged hospitalization periods of 11-13 days [3,5,6].

HF contributes significantly to Ghana's cardiovascular disease burden, with a worse prognosis and a more malignant course [7,8]. It is a leading cause of death among Ghanaian adults; yet, there is a paucity of data on the epidemiological profiles, treatment patterns, and survival rates of patients with HF in Ghana [9-11]. Single-center studies indicate a high prevalence of HF in Ghana [7,8,12].

The diagnosis of HF in most patients is primarily based on clinical manifestations due to the limited availability of diagnostic equipment. Ghana has few cardiologists, who are mainly located in tertiary hospitals [13]. In addition, there is a lack of HF education and training for physicians and nonphysician health workers. While HF management teams or multidisciplinary teams for HF management are the gold standard model for the delivery of care, these teams are nonexistent in Ghana, and most health facilities lack resources for long-term patient follow-up, such as diagnostic equipment, dedicated HF clinics, and protocols [14-17].

A national network of heart failure management teams (NNHFMT) will be established as part of the Ghana Heart Initiative's efforts to improve cardiovascular disease care in Ghana to help mitigate the burden of HF. The NNHFMT is tasked with building the capacity of both secondary and tertiary levels of care to promptly and effectively identify and manage HF by creating heart failure management teams (HFMTs) and establishing a national registry for HF and HF clinics that will be integrated with routine clinical services to provide long-term follow-up and care. The establishment of HF clinics and a national registry will fill a significant gap in HF care and research by providing the most recent epidemiological, management patterns, and medium-term outcomes data on HF.

Objectives

The primary objective of this study is to determine the epidemiological characteristics and medium-term outcomes of HF in Ghana by outlining the epidemiological and clinical characteristics of patients with HF in Ghana, identifying the underlying causes, evaluating the medium-term outcomes of HF in Ghana, and identifying the factors that predict hospitalization and mortality in patients with HF in Ghana. This study also aims to build capacity in the care of patients with HF and form the basis for a national registry for HF in Ghana.

Methods

Overview

An NNHFMT consisting of physicians, nurses, and researchers from 9 collaborating hospitals in Ghana was constituted to achieve the study objectives, with each institutional HFMT led by a cardiologist, 2 supporting cardiologists or physicians, and 2 nurses. The HFMTs will establish HF clinics and integrate them into the routine services of their hospitals; recruit patients with HF and manage them per guidelines and algorithm; and create awareness and train other personnel in the 9 centers on the diagnosis and management of HF. These institutions include 5 teaching hospitals, 3 regional hospitals, and 1 municipal hospital. They include the Korle-Bu Teaching Hospital (KBTH), Komfo Anokye Teaching Hospital (KATH), Tamale Teaching Hospital (TTH), Ho Teaching Hospital (HTH), Cape Coast Teaching Hospital (CCTH), Bono Regional Hospital, Presbyterian Hospital-Agogo, Kumasi South Hospital, and the Effia Nkwanta Regional Hospital (Figure 1) [18].

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Figure 1. Map of Ghana showing the location of collaborating centers. Source: Ghana Statistical Service, 2020.

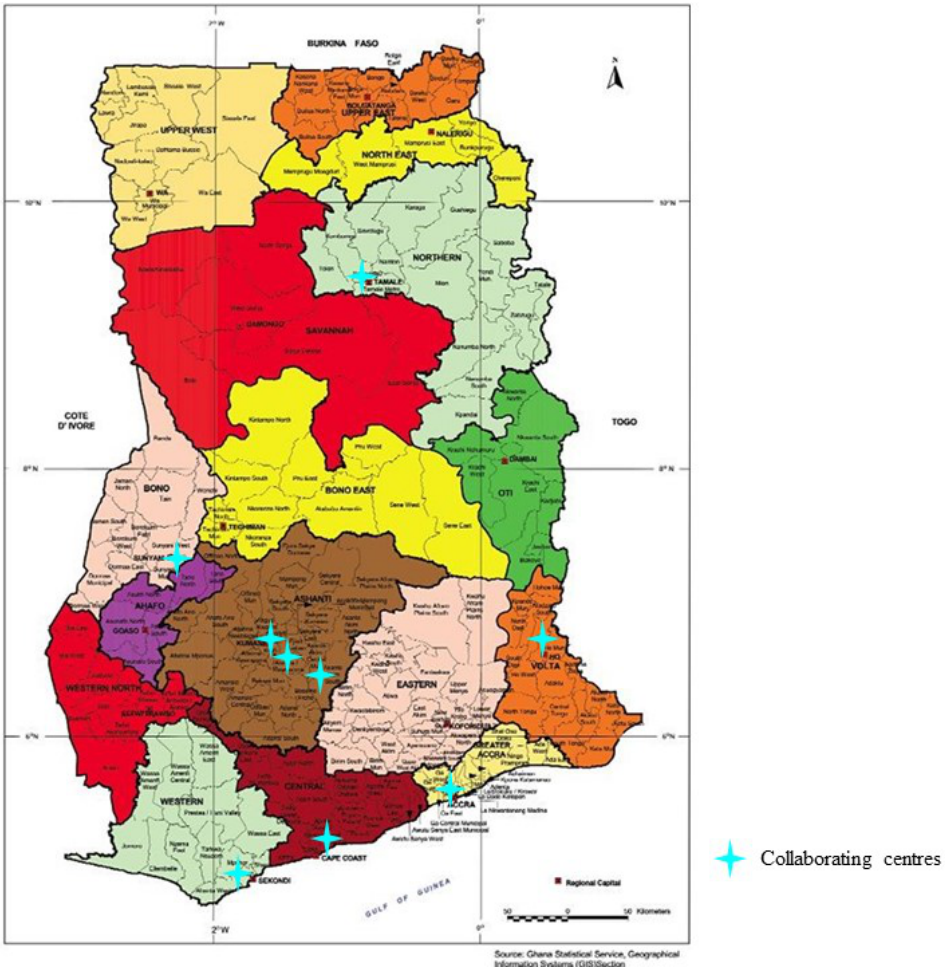

Study Design

This is a prospective, multicenter, and multilevel observational study of patients with HF. Patients presenting with HF will be recruited and evaluated according to a standardized protocol. Guideline-directed treatment for HF will then be prescribed after the diagnosis has been confirmed. The study will conduct a serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and transthoracic echocardiogram for all participants for free, while the cost of treatment and other investigations will be borne by study participants as in routine care. Patients will be followed up prospectively for 6 months to determine the medium-term outcomes of interventions (Figure 2).

Patients will be recruited through the collaborating institutions' emergency rooms, admission wards, and established HF clinics from January to December 2023. The HFMTs of the 2 leading teaching hospitals in Ghana, KBTH and KATH, will be trained using a facilitators' training manual, which will be developed from current international HF guidelines. KBTH and KATH will then provide mentorship and training to the other collaborating hospitals. The HFMT of KBTH will train members of the HFMTs from the TTH, HTH, and Effia-Nkwanta Regional Hospital, while the HFMT of KATH will also train the HFMTs of CCTH, Bono Regional Hospital, Presbyterian Hospital-Agogo, and Kumasi South Hospital. The study will begin in the KBTH and KATH in January 2023, while the other 7 sites will begin recruitment in July 2023, and all areas will end enrollment in December 2023.

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Figure 2. Chart outlining study design.

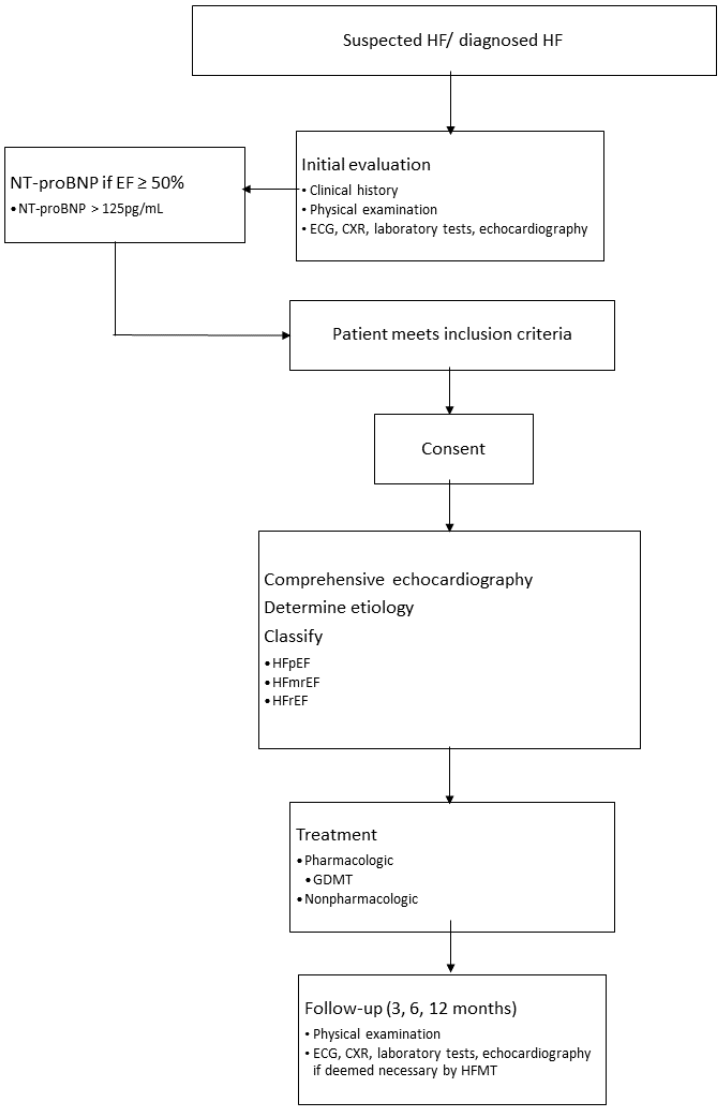

Study Population

Study participants will include patients aged 13 years or older who present with HF in the collaborating hospitals and consent to participate in the study. Patients with a life expectancy less than the expected duration of the registry due to non-HF comorbidities will be excluded.

Based on our estimation of a sample size of 5000 participants, we would be able to determine the mortality and hospitalization rate at 6 months with a 95% CI and a precision of ±1%. Each participating center will recruit 556 participants.

Recruitment of Study Participants

Participants will be recruited through the various departments or units of the collaborating institutions. All patients diagnosed with HF or suspected of having HF will be referred to the HFMTs for evaluation and enrollment. A total of 2 sensitization workshops will be organized at collaborating institutions during the study period: 1 before participants' enrollment and 1 midway through participant recruitment.

Data Collection

Data collection comprises administering questionnaires, reviewing medical records, physical examinations, imaging investigations, including chest x-rays and echocardiography, electrocardiography, and laboratory tests. The methods for data collection in this study are identical in all locations, following standardized operating manuals and tools.

Diagnosis of HF

The diagnosis of HF will be made using a modified diagnostic algorithm adopted from the 2021 European Society of Cardiology Guidelines to diagnose and treat acute and chronic HF (Figure 3) [19]. The diagnosis of HF will be made based on the presence of typical symptoms of HF and objective evidence of cardiac dysfunction and categorized into three phenotypes: (1) heart failure with reduced ejection fraction (HFrEF), (2) heart failure with mildly reduced ejection fraction (HFmrEF), and (3) heart failure with preserved ejection fraction (HFpEF) based on the left ventricular ejection fraction (LVEF) [19].

All patients with typical symptoms and specific signs of HF and LVEF≤40% will be categorized as HFrEF, while patients with LVEF of 41%-49 % will be categorized as HFmrEF.

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HFpEF will be diagnosed in patients presenting with typical symptoms and specific signs of HF and LVEF≥50%, the presence of elevated natriuretic peptides (NT-proBNP≥125 pg/mL), and objective evidence of cardiac structural and functional abnormalities consistent with the presence of left ventricular (LV) diastolic dysfunction or raised LV filling pressures. Objective evidence of structural or functional abnormalities includes the following:

- LV mass index ≥95 g/m^2 (female), ≥115 g/m^2 (male), and a relative wall thickness >0.42.
- Left atrial volume index >34 mL/m^2 in sinus rhythm (SR) and the presence of atrial fibrillation (AF) left atrial volume >40 mL/m^2.
- E/e' ratio at rest >9.
- NT-proBNP >125 (SR) or >365 (AF) pg/mL OR BNP >35 (SR) or >105 (AF) pg/mL.
- Pulmonary artery systolic pressure >35 mm Hg or tricuspid regurgitant velocity at rest >2.8 m/second.

Figure 3. Modified diagnostic algorithm for heart failure (HF). BNP: brain natriuretic peptide; ECG: electrocardiogram; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction.

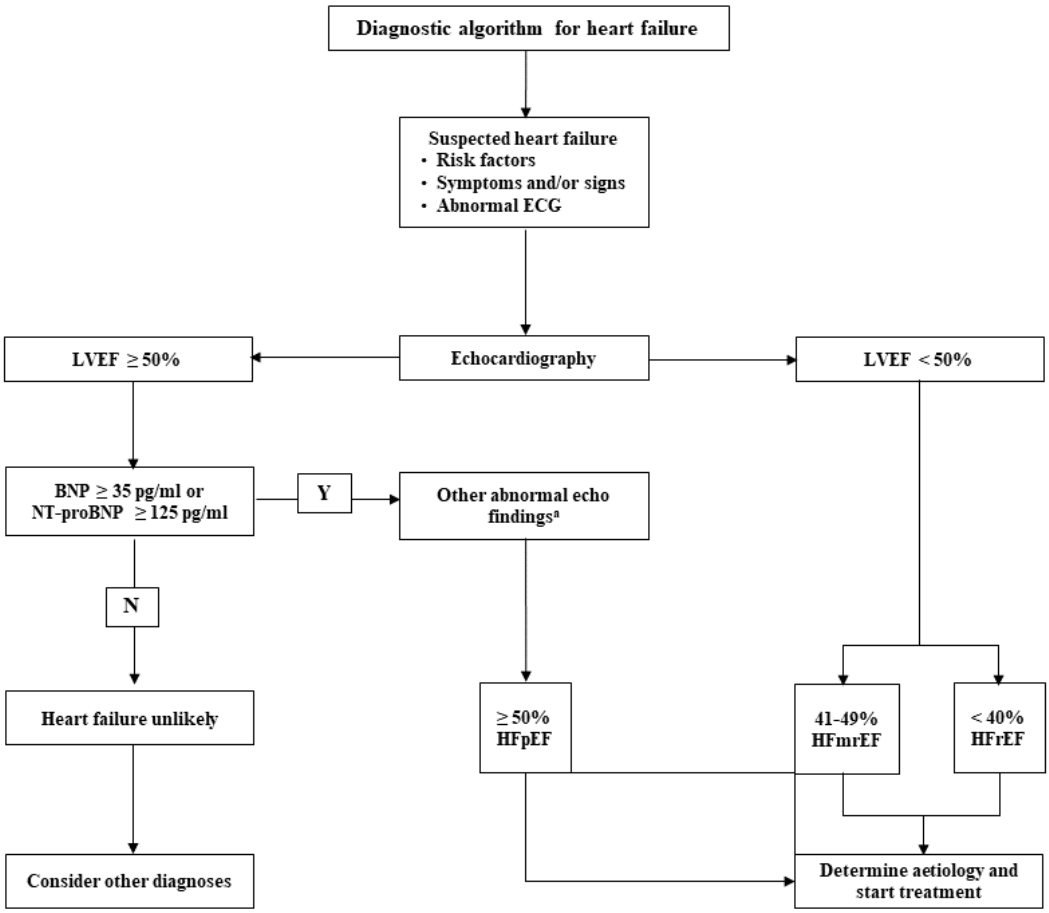

Etiology of HF

The etiology of HF will be determined based on the history, physical examination, laboratory, electrocardiographic, echocardiographic findings, and other imaging modalities (Table 1).

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Table 1. Heart failure (HF) etiology and clinical characteristics.

Etiology of HF	Clinical characteristics	Specific investigations
Hypertension [20-22]	• Persistent elevated systolic BP[a] ≥140 mm Hg and diastolic BP ≥90 mm Hg • Presence of HMOD[b] • Current or previous use of antihypertensive medications	• 24-hour ambulatory BP • Plasma metanephrines and renal artery imaging • Serum renin and aldosterone • TTE[c]
Coronary artery disease [23]	• HF and ACS[d] • A pre-existing history of CCS[e] • Features suggestive of significant CAD[f] on coronary angiography or other imaging	• Invasive coronary angiography • CT[g] coronary angiography • Imaging stress tests (echo, nuclear, and CMR[h])
Valvular heart disease [24]	• Primary valve disease, for example, aortic stenosis • Secondary valve disease, for example, functional regurgitation • Congenital valve disease, for example, bicuspid aortic valve and mitral valve prolapse	• TTE/ TEE[i]/ stress echo • CT/ CMR
Rheumatic heart disease [25,26]	• Primary valve disease, for example, mitral stenosis and mitral regurgitation • Atrial fibrillation	• TTE/ TEE/ stress echo
Dilated cardiomyopathy [27,28]	• Unexplained dilated cardiac chambers with increased left ventricular mass index	• CMR, genetic testing • Trace elements, toxicology, LFTs[j]
Arrhythmia-induced cardiomyopathy [29]	• Mean heart rate above 100 beats per minute • Atrial fibrillation • Premature ventricular contractions burden equal to or greater than 10% • No other cause of LV dysfunction identified	• Ambulatory ECG recording • Electrophysiology study, if indicated
Congenital heart disease	• History of congenital heart disease • Incidental diagnosis of congenital heart disease during investigation for HF	• TTE/ TEE • CMR
Other etiologies of HF [19]	• Clinical features diagnostic of restrictive cardiomyopathy, arrhythmogenic cardiomyopathy, peripartum cardiomyopathy, endomyocardial fibrosis, cor pulmonale, infiltrative cardiomyopathy, pericardial disease, LV noncompaction cardiomyopathy, and toxin-induced cardiomyopathy.	• Serum electrophoresis and serum free light chains. • Echo, CMR, CT-PET[k], endomyocardial biopsy, Serum angiotensin-converting enzyme, fluorodeoxyglucose-PET, and chest CT • Right and left heart catheterization

[a]BP: blood pressure.

[b]HMOD: hypertension-mediated organ damage.

[c]TTE: transthoracic echocardiogram.

[d]ACS: acute coronary syndrome.

[e]CCS: chronic coronary syndrome.

[f]CAD: coronary artery disease.

[g]CT: computed tomography.

[h]CMR: cardiovascular magnetic resonance.

[i]TEE: transesophageal echocardiogram.

[j]LFT: liver function test.

[k]PET: positron emission tomography.

Treatment of HF

A modified treatment algorithm adopted from the 2021 European Society of Cardiology Guidelines for treating acute and chronic HF (Figure 4) will be used in the treatment of patients [19].

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Figure 4. Modified treatment algorithm for treating HFrEF and HFmrEF. a: a replacement for ACE-I/ARB (angiotensin receptor blocker); ACE-I: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; CRT-D: cardiac resynchronisation therapy with a defibrillator; CRT-P: cardiac resynchronisation therapy pacemaker; HFmrEF: heart failure with mildly reduced ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; ms: milliseconds; SR: sinus rhythm.

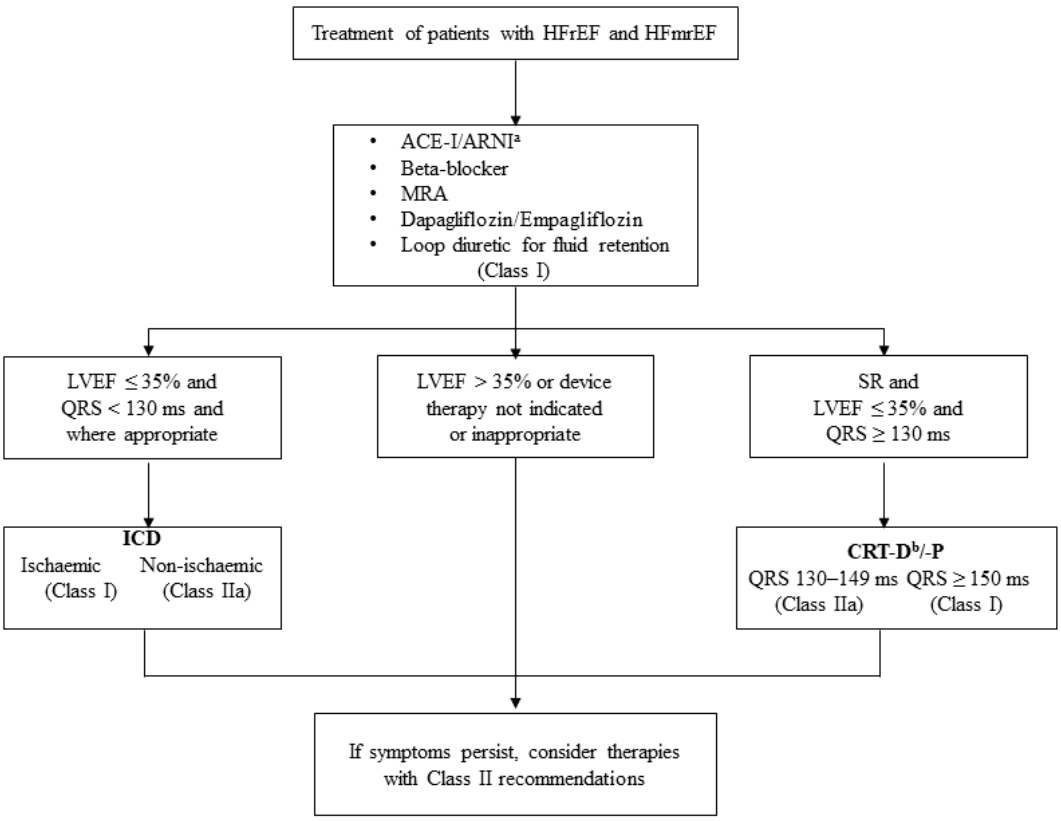

Data Handling and Analysis

The KoboCollect toolbox (v2022.4.4; [30]) will be used to capture data and upload it onto a cloud database that is only accessible to the principal investigator and the data manager. Collated data will be exported into SPSS (*package 2016*; SPSS Inc) for statistical analysis. Tables, bar charts, and pie charts will be used to present the data. For continuous variables, the central tendency and spread measures will be calculated using the mean (SD), and IQR. Categorical variables will be reported as numbers and percentages. Multivariable regression models will be used explore the relationships between variables and rehospitalization and death. We will perform a Kaplan-Meier analysis to estimate the survival and death rate of patients with HF. The Cox regression analysis will determine the relationship between the risk of death in an individual and selected variables and the significance of these variables. Missing values will be handled based on the type and frequency of missing values. A P value <.05 will be considered statistically significant.

Timelines

The table of timelines (Table 2) below summarizes the key activities of the study from the start to the end of the study.

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Table 2. Table of timelines.

	2022	2023												2024	
	December	January	February	March	April	May	June	July	August	September	October	November	December	January-June	June
Training for KBTH and KATH	✓						✓								
Training for other sites								✓			✓				
Sensitization workshops for KBTH and KATH	✓					✓									
Sensitization workshops for other sites								✓			✓				
Enrollment and data collection		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Establishment of HF clinics		✓						✓							
Follow-up				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Preliminary data analysis and reporting										✓					
End of enrollment														✓	
Data analysis									✓	✓	✓	✓	✓	✓	
End of study															✓

Ethical Considerations

Ethical approval has been obtained from the Ethical and Institutional Review Boards of Korle-Bu Teaching Hospital (STC/IRB/000150/2022), Cape Coast Teaching Hospital (CCTHERC/EC/2023/019), Tamale Teaching Hospital (TTH/R&D/SR/229), Ho Teaching Hospital (HTH-REC (30) FC_2023), and Komfo Anokye Teaching Hospital (KATH IRB/AP/166/22). All participants will be informed about the study, its objectives, and the data collection methods. Consent will be obtained from participants who agree to be part of the study and are assured of strict confidentiality and anonymity. Participants will also be informed that participation in the study is entirely voluntary, and all the services they receive at the clinic will continue as usual whether they decide to participate or not. A unique study number will be assigned to each participant, and the collected data will be deidentified. Only the assigned unique number will be used on study documents related to participants. Participants will also be informed that they can withdraw from the study at any time they choose without consequences.

Results

This intervention will generate the necessary information on the etiology of HF, clinical presentations, the diagnostic yield of various tools, and management outcomes. In addition, it will build the necessary capacity and support for HF management in Ghana. As of July 30, 2023, the training of the various health workers in all 9 hospitals has been completed. The KATH and the KBTH acted as supervisory sites and supported the training at 4 and 3 sites, respectively. Preliminary analyses will be conducted by the end of the second quarter of 2024, and results are expected to be publicly available by the middle of 2024.

The test-run of the research and registry instruments and modifications have been completed. Medical equipment (echocardiogram machines and NT-proBNP devices) has been calibrated and distributed to all sites.

Discussion

Overview

HF is one of the leading causes of hospital admissions in developing countries and is predicted to experience the most rapid growth worldwide [2,7,31,32]. This prospective study will answer many clinical questions about HF in Ghana. First, this study will address a notable data scarcity in HF care and research in Ghana by establishing a national HF registry, thus creating a vehicle for the accrual of large, comprehensive, and contemporary data encompassing the sociodemographic, clinical profiles, causes of HF, management of HF, and determinants of outcomes such as mortality and hospitalizations of patients with HF in Ghana. In addition, a national HF registry will also

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provide a good opportunity to evaluate adherence to current guidelines and response to treatment among patients with HF in Ghana.

Clinical registries play a crucial role in gathering real-world data, essential for developing evidence for best clinical practice, measuring outcomes, providing feedback to clinicians, and enhancing the quality of care [1,33]. HF registries, like the Swedish Heart Failure Registry, have played a significant role in advancing knowledge and improving the management of HF. Established in 2000 and implemented nationwide in Sweden by 2003, this registry has yielded valuable research outcomes that have led to notable improvements in the understanding and care of patients with HF and under-treatment detection [1]. The NAtional TUnisian REgistry of Heart Failure (NATURE-HF) contributed valuable data that have the potential to enhance the treatment and overall prognosis of individuals with HF in North Africa [34]. Valuable data were also derived from the Abeokuta Heart Failure Clinical Registry of patients presenting with acute HF in Abeokuta, Nigeria, including acute HF presenting at a relatively younger age, commoner in men, and associated with severe symptoms [35].

While the acquisition of realistic data will address the data gap, this pragmatic study will provide capacity building for the management of HF by enhancing the skills and knowledge of health care providers in diagnosing and treating HF and making diagnostic equipment, including echocardiography, electrocardiograms, and point-of-care NT-proBNP devices, available to participating hospitals. Furthermore, participating institutions' HFMTs and HF clinics will broaden the prospect for specialist HF care and long-term follow-up in their regions.

Although numerous HF guidelines are available to aid in managing patients with HF, their generalizability presents variable challenges, as these guidelines may not be appropriate for managing HF in countries with limited health care resources [19]. Therefore, we anticipate that this study will serve as a significant milestone in establishing a standardized approach to managing HF in Ghana and the wider SSA region.

The study will address a notable void within Ghana's ever-evolving HF care and research domain. The study will generate novel and indispensable data that will improve HF care, serve as a foundation for teaching, develop locally tailored HF guidelines, and establish HF research programs.

Strengths and Limitations of This Study

This pragmatic, prospective, multicenter study will generate the most extensive contemporary data on HF in Ghana. The study will also enhance the knowledge and skills of health personnel in diagnosing and managing HF. The project is also designed to establish HF clinics and provide diagnostic services as part of routine health care services in participating hospitals. This study will describe associations rather than establish causality owing to its observational design.

Acknowledgments

The authors are grateful to the teams at all 9 centers for their dedication and sacrifice. This heart failure intervention is part of the Ghana Heart Initiative. The Ghana Heart Initiative is implemented through German International Cooperation (GIZ) and funded by Bayer.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following completion of the study and publication of the findings of the study.

Authors' Contributions

Conceptualization and development of study was done by AD and IKO. First draft by FRA. All authors reviewed and approved the final manuscript; FRA, EAA, CK, FA, AD, and IKO.

Conflicts of Interest

None declared.

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Abbreviations

AF: atrial fibrillation
CCTH: Cape Coast Teaching Hospital
HF: heart failure
HFmrEF: heart failure with mildly reduced ejection fraction
HFMT: heart failure management team
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HTH: Ho Teaching Hospital
KATH: Komfo Anokye Teaching Hospital
KBTH: Korle-Bu Teaching Hospital
LV: left ventricular
LVEF: left ventricular ejection fraction
NATURE-HF: NAtional TUnisian REgistry of Heart Failure
NNHFMT: national network of heart failure management teams
NT-proBNP: N-terminal pro-brain natriuretic peptide
SR: sinus rhythm
SSA: Sub-Saharan Africa
TTH: Tamale Teaching Hospital

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Protocol

Investigating Rhythmicity in App Usage to Predict Depressive Symptoms: Protocol for Personalized Framework Development and Validation Through a Countrywide Study

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Abstract

Background: Understanding a student's depressive symptoms could facilitate significantly more precise diagnosis and treatment. However, few studies have focused on depressive symptom prediction through unobtrusive systems, and these studies are limited by small sample sizes, low performance, and the requirement for higher resources. In addition, research has not explored whether statistically significant rhythms based on different app usage behavioral markers (eg, app usage sessions) exist that could be useful in finding subtle differences to predict with higher accuracy like the models based on rhythms of physiological data.

Objective: The main objective of this study is to explore whether there exist statistically significant rhythms in resource-insensitive app usage behavioral markers and predict depressive symptoms through these marker-based rhythmic features. Another objective of this study is to understand whether there is a potential link between rhythmic features and depressive symptoms.

Methods: Through a countrywide study, we collected 2952 students' raw app usage behavioral data and responses to the 9 depressive symptoms in the 9-item Patient Health Questionnaire (PHQ-9). The behavioral data were retrieved through our developed app, which was previously used in our pilot studies in Bangladesh on different research problems. To explore whether there is a rhythm based on app usage data, we will conduct a zero-amplitude test. In addition, we will develop a cosinor model for each participant to extract rhythmic parameters (eg, acrophase). In addition, to obtain a comprehensive picture of the rhythms, we will explore nonparametric rhythmic features (eg, interdaily stability). Furthermore, we will conduct regression analysis to understand the association of rhythmic features with depressive symptoms. Finally, we will develop a personalized multitask learning (MTL) framework to predict symptoms through rhythmic features.

Results: After applying inclusion criteria (eg, having app usage data of at least 2 days to explore rhythmicity), we kept the data of 2902 (98.31%) students for analysis, with 24.48 million app usage events, and 7 days' app usage of 2849 (98.17%) students. The students are from all 8 divisions of Bangladesh, both public and private universities (19 different universities and 52 different departments). We are analyzing the data and will publish the findings in a peer-reviewed publication.

Conclusions: Having an in-depth understanding of app usage rhythms and their connection with depressive symptoms through a countrywide study can significantly help health care professionals and researchers better understand depressed students and may create possibilities for using app usage–based rhythms for intervention. In addition, the MTL framework based on app usage rhythmic features may more accurately predict depressive symptoms due to the rhythms' capability to find subtle differences.

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KEYWORDS

depressive symptoms; app usage rhythm; behavioral markers; personalization; multitask learning framework

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Introduction

Background

Need for Identification of Depressive Symptoms

Every 40 seconds, a person commits suicide and there are more than 20 attempts worldwide [1]. Among suicide attempters, major depressive disorder (MDD) is common [2], and people having MDD are at greater risk of suicidality [3]. Despite these facts, there is a significant lack of interventions to mitigate depression, due to which the depression rate is increasing. In fact, it is estimated that depression will rank first as a global burden of disease by 2030 [4]. In addition, due to the COVID-19 pandemic, a significantly higher number of people have MDD [5], and such a negative impact may persist for a prolonged period. In Bangladesh, the depression prevalence is higher than the overall rate in South Asia [6]. Compared to Bangladeshi people of any other professions, the depression rate is higher among university students [7] (eg, 82.4% of students have at least mild depression [8]), which is alarming.

To significantly facilitate early interventions to mitigate depression, there is an urgent need for its early identification [9]. A person is identified as depressed if symptoms (eg, hopelessness) appear for a period, such as most days for a minimum of 14 days [10,11]. However, it is difficult to precisely assess depressive symptoms [12]. In fact, primary care providers fail to identify depression in more than 50% of cases [13,14]. Understanding the depressive symptoms, such as those in the 9-item Patient Health Questionnaire (PHQ-9) [15], of a person in real time can significantly facilitate mental health care professionals to understand the illness more precisely, to identify depression early, and to take steps accordingly for intervention.

Pervasive Health Research in Low- and Middle-Income Countries

Although over 80% of the burden of depression is found in low- and middle-income countries (LMICs) [16], there remains a severe scarcity of mental health care professionals in LMICs. In Bangladesh, there are only 565 psychologists [6], although the population is over 165 million [17], with 1.234 million university students [18]. In these cases, a pervasive technology, such as a smartphone-based monitoring system, which is available to a large number of people in LMICs, can play a significant role [19] In addition, to minimize the barriers to health care facilities in low-resource settings, artificial intelligence (AI)–based mobile apps can be useful [20]. However, almost all the studies that have demonstrated a pervasive technology–based automated system to identify depression have been conducted in the context of high-income countries. For instance, all the studies included in a recent systematic review were from countries other than LMICs [21], which indicates how little pervasive health research has been conducted in the context of LMICs. As a result, the models developed based on participants from high-income countries may not be applicable in LMICs, since the behavior (eg, app usage [22]) varies among countries and various factors, such as socioeconomic status [23] and culture [22], impact behavior.

App Usage Rhythm That May Resemble Biobehavioral Rhythm

Zeitgebers, social and environmental cues, help a person's rhythms synchronize well [24], which can impact their daily activities. Rhythms based on pervasive device–sensed physiological data change depending on external cues, such as light exposure, eating time, and physical activity [24]. Similarly, smartphone usage behavior is linked with factors such as eating behavior [25]. In addition, there is a relation of app usage with alertness, chronotype [26], and physiological data, such as sleep [26-28]. Like physiological data, app usage behavioral markers vary depending on the hour of the day [29-31] and exercise [28]. These facts show app usage behavior may also have a rhythmic pattern with reproducible waveforms similar to the rhythms based on physiological data.

Although a recent study extracted parametric rhythmic feature–dominant periods from smartphone usage data [32], the study was limited by not exploring rhythmic features, such as the acrophase, interdaily stability (IS), intradaily variability (IV), and relative amplitude (RA). In addition, the study explored mere screen usage, without any exploration of more informative features [33], such as entropy data–based features. In the case of other previous app usage data–based studies, researchers used descriptive statistical methods [29-31] to determine whether there is any variation over the day and inferential statistical methods [34,35] to find the difference in terms of aggregated data of the 4 time periods, namely morning, afternoon, evening, and night. These approaches have some limitations. First, there is a lack of statistical evidence to show whether there exists any rhythm that could be resolved with the zero-amplitude test [36,37], which is used to detect rhythm in the field of chronobiology. In addition, the mere analysis in presenting the difference between the aggregated data of morning and evening cannot show whether there is a cycle that can repeat over days. The average data may also miss the microscopic view of data [38]. However, an analysis fitting mathematical models (eg, cosinor model) to time series data can present a microscopic view of the data and inferential statistical estimates of the rhythmic properties [38]. In addition, many informative behavioral markers, such as the dominant period, stability in behavior, and the peak time of oscillations in the rhythm, cannot be extracted from just finding the differences between periods (eg, morning vs night).

Potential of App Usage–Based Rhythms in Identifying Depressive Symptoms in LMICs

In human life, physiological changes reappear in a cyclable waveform [38]. Rhythm features based on physiological data have been explored in both the chronobiology [39] and pervasive health [32] areas. Researchers have found a relation between physiological data–based rhythmic markers and health status [32]. These markers can find out subtle differences that enable marker-based features to predict hospital readmission [40] and to identify loneliness and the depression class [32]. This shows the possibility of improving the performance of the models upon the incorporation of app usage rhythmic features to predict the symptoms of depression. However, previous studies [32,40] have mostly relied on wearables to extract rhythmic features,

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which are costly and may not be affordable [41] for people with a low income. In contrast, smartphones are economically attainable [42], and app usage data are resource insensitive [33]. As a result, app usage data–based systems may be feasible in LMICs.

Predicting Depression and Depressive Symptoms Through an Unobtrusive Method

Classification of the Depressed and Nondepressed

Most existing research based on AI for mental health has worked on classification problems [43]. Researchers have classified depressed and nondepressed individuals by developing personalized models [44] and using contextually filtered features where the rule mining technique was incorporated [45]. Some other studies (eg, [46,47]) have relied on sensing data (eg, GPS data), along with smartphone data call history, to predict depression. Researchers have also leveraged internet usage data [48], location data retrieved through the campus WiFi infrastructure [49,50], and the GPS [50-52]. Recently, some researchers focused on exploring rhythmic features to assess depression. For instance, Yan et al [32] leveraged rhythm-based features to classify depressed and nondepressed participants. However, the classification does not provide precise information about a participant's depressive status, since scores of all the symptoms are aggregated to keep the participant in a particular group (eg, depressed or moderate depression), resulting in a loss of the complexity of the psychological problem of depression.

Predicting Depression Scores

Compared to classification research problems, there is relatively less research on predicting the depression score (eg, PHQ-9 score=11). Studies in the pervasive health area can be broadly categorized into those that have developed models leveraging data based on both smartphones and wearables [53-56]; only smartphones [53,55]; various sensing devices, along with social media [57]; and subjective and smartphone data [58]. There remain mixed findings on whether the smartphone has superior performance than the wearable. Smartphone-sensed data showed higher performance in a previous study [55] when models were evaluated after splitting training and testing data based on time. However, in the same study [55], researchers found smartphones have inferior performance on another evaluation criterion. Regardless of superiority, both wearables and smartphones show promising performance in the automated assessment of depression [53], which can play a role in real-time remote monitoring of depressed individuals [59]. Wearable- and smartphone-sensed behavioral markers, such as call duration [58] and heart rate [60], as well as inferred markers, such as the circadian rhythm [60], have a significant correlation with the depression score, which may explain the fact of enabling the sensed data to predict depression. However, like the classification, in the prediction of depression scores also, there remains the inability to precisely understand depressive symptoms since a person's depression score (eg, 11) can be found in combination with different frequencies of the appearance of different symptoms.

Predicting Symptoms and Multitask Learning

Researchers have conducted a network analysis of depressive symptoms and presented a possible viable target for intervention [61] and central symptoms for possible focused treatments [62]. The relation of ecological momentary assessment of depressive symptoms with the PHQ-9 score [63] and the relation of depressive symptoms with behavioral data [64] have also been investigated in previous studies. Exploring pervasive device–sensed data, researchers have found a link of higher spending duration in students with higher fatigue, which is a depressive symptom [64]. Although there are studies predicting symptoms of other psychological problems, such as schizophrenia [65] and attention-deficit/hyperactivity disorder (ADHD) [66], few studies [67] have predicted the appearance of depressive symptoms. In a previous study [67], authors predicted depressive symptoms through the data of iPhone users and Android users. However, their study has several limitations. First, their models' performance is low in the case of the maximum depressive symptoms; particularly, the specificity score is around 60% or below 60% in many models developed by leveraging smartphone data. Second, they developed a separate model to predict each symptom, which makes the model resource sensitive. Third, they considered each symptom-predicting task as a separate one, which could be improved by leveraging the shareable information among symptoms through the multitask learning (MTL) framework as MTL has superior performance than the single-task learning (STL) technique [53,65]. However, researchers have grouped all the predicting tasks into a single model in previous studies [53,65], which may lower performance since all tasks do not help each other to improve performance [68].

Objective

To overcome the above-mentioned limitations, the main objective of this study is to explore app usage data–based rhythmicity detection and develop and validate an MTL framework leveraging app usage data–based parametric and nonparametric rhythmic parameters through a countrywide study in Bangladesh. Another objective of this study is to explore whether app usage rhythmic features are related to depressive symptoms.

Methods

Ethical Considerations

Our study was approved (reference: 2022/OR-NSU/IRB/0704) by the North South University Institutional Review Board/Ethics Review Committee. While collecting data, we presented the consent form in short in Bangla (native language) and English (Figure 1a), where we provided a summary of the data that we collected. In addition, we provided a consent form in detail (Figure 1b) about different matters, including data safety, privacy, and each data item that we collected. Furthermore, before data collection, we briefly described the research to the participants. All participants provided their consent. After collecting data, we provided an incentive of food tokens equivalent to around US $0.30 to almost all participants. For certain participants (<5%) where it was not feasible to give food

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tokens, we provided an equivalent gift in other forms (e.g., by book diary).

All participants' data are stored in the Google Firebase database, which only 1 of the researchers can access with 2-factor authentication. We did not collect any personal information from the participants, such as name, email, and phone number. In addition, we did not collect the names of the participants' departments and universities so that they would feel more comfortable in providing data. We reported the number of departments and universities based on our aggregated notes.

Figure 1. Screenshot of the data collection tool showing the (a) consent form in short in Bangla and English, (b) consent form in detail, (c) PHQ-9, and (d) app usage data. PHQ-9: 9-item Patient Health Questionnaire.

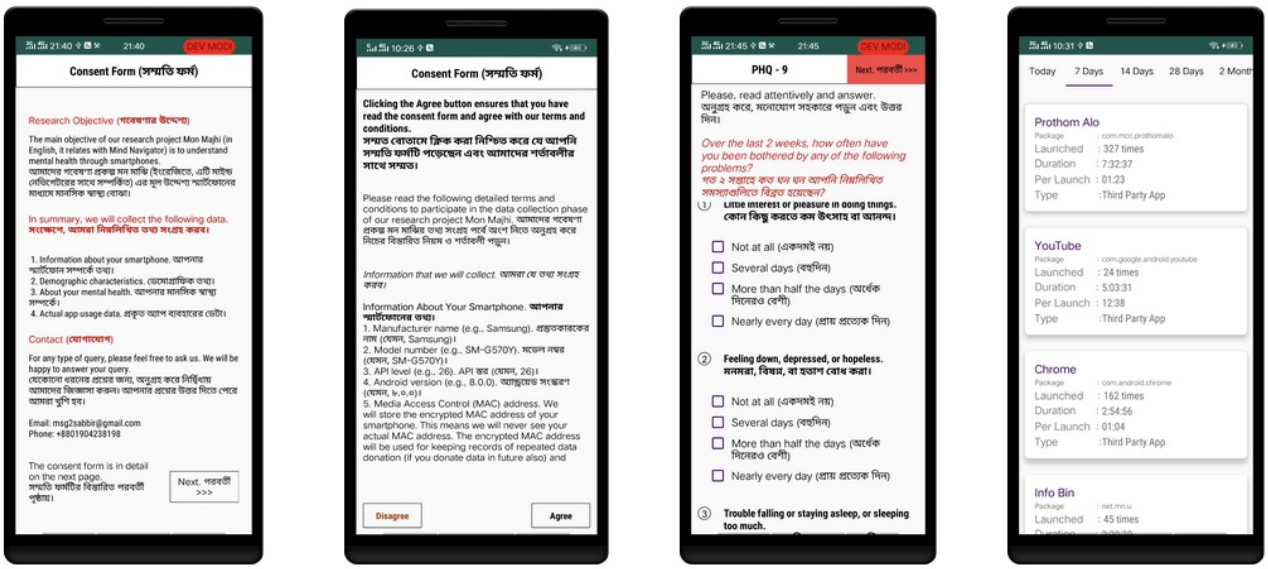

(a) Consent form in short (b)Consent form in detail (c) PHQ-9 scale to collect depressive symptoms' data (d) App usage data

Retrieval of App Usage Behavioral Markers

In this study, we will focus on developing our system in such a way that the users of the system and also health care professionals can be informed about depressive symptoms in real time. For instance, a health care professional, with the user's consent to access information, can be notified if our system's automatic prediction in a day shows that the depressive symptoms can worsen. For this research, we used our previously developed app [69], which can retrieve each participant's past 7 days' foreground and background app usage event data within 1 second once the participant provides consent. The average time required to retrieve app usage events is 307.94 milliseconds (SD 1.1 seconds) [33]. For each app usage event, there are data on the app name, package name, and timestamp of the event, which we will use to extract behavioral markers. The app (Figure 1) was used in our previous studies to explore different research problems, including students' academic results [70-72], depression [33-35,73], and loneliness [74,75], showing the app's reliability and validity.

Sample Size Determination and Data Collection

In Bangladesh, there are around 1.234 million university students [18], and an optimal sample that represents the behavior of this population with a 95% CI and a 5% margin of error is 385 university students, as we found with SurveyMonkey [76], which uses the formula for the finite sample size [77]. Using the same formula, we found that the required sample size to represent the 0.448 million female and 0.786 million male student groups each is 384 [18]. Since the depression rate differs between students of public and private universities in Bangladesh [78], we collected data from both types of universities. In the 0.329 million and 0.902 million students of public and private universities, respectively [18], we found that the required sample size in each case is 384. However, there is no fixed sample size that can ensure the generalizable performance of machine learning (ML) models. Therefore, to develop an impactful model, we tried to maximize the number of participants by conducting a countrywide study. In addition, we tried to maximize the number of students from public universities because the largest number of students study there [18].

We collected data from all 8 divisions of Bangladesh using the multistage convenient sampling method. From each division, we collected data from at least 1 university and multiple departments. We tried to maximize the diversity among the participants because the socioeconomic status and many other demographic characteristics vary by region of a country, which can have an impact on mental health [78] and smartphone usage behavior [79,80].

We collected data from a total of 2952 participants from September 2022 to March 2023. While collecting data, first, through our app [69], the participants responded to questions about demographic characteristics (eg, gender) after providing consent. Next, using the same app, they responded to the items of the PHQ-9 [15] based on their experiences of the past 14 days. After saving the responses to all psychological questions, the app automatically retrieved their app usage data, which may take less than 1 second in almost all cases, as shown in our

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previous estimation [33]. After retrieval, the app saved the app usage data instantly.

Data Preprocessing and Data Set Description

Our app could not retrieve any app usage data from 14 (0.47%) participants' phones. One of the plausible reasons for this problem could be system problems in the phones, as shared by the participants. Several of these participants shared that they do not use the original version of the phones. In addition, for 2 (0.07%) participants, age values were missing, and we did not impute these values, as age information was not required for the primary purpose of the research. Furthermore, data on 82 (2.77%) participants' professions were missing. We imputed the missing professions based on 2 pieces of information: First, in our study, only 2 (0.07%) participants were not students, and we did not reach out to them for data collection; they provided data by installing the app from Google Play Store, which was based on their own interests, indicating a low probability of having a profession other than "student." Second, all 82 (2.77%) participants provided data when we reached the universities for data collection, as we found by matching the study dates and timestamps of when these participants provided data. Thus, we imputed these 82 participants' profession as "student."

Although the participants were required to provide data at least once, we encouraged them to provide data as many times as possible. After excluding the 14 (0.47%) participants for whom our app could not collect any app usage events and the 2 (0.07%) participants who were not students, 2936 (99.46%) participants remained. Of them, 71 (2.42%) provided data at least twice. However, since there were few participants who provided data twice, in this study, we kept only the first time–provided data for the next steps of the analysis.

Since in this study, we will estimate the circadian rhythm, we followed previous studies to find out the minimum number of days required to estimate the circadian rhythm. Studies have suggested to have data of at least 1 day for estimating the circadian rhythm [81]. However, sensed data of 2 days can estimate the circadian rhythm sufficiently [82]. Researchers have also found that rhythmic features extracted based on the data of 2 days can predict more accurately physiological and mental changes [65]. Therefore, inspired by these previous studies, we excluded 34 (1.15%) participants who had app usage data of less than 2 days.

Finally, after excluding 2 nonstudents, 14 students without any app usage data, and 34 students having app usage data of less than 2 days, we were left with 2902 (98.31%) students' app usage data (Figure 2), which will be analyzed in the next steps. In total, there are 24.48 million foreground and background app usage events of 24.84 million minutes. Of the 2902 participants, 2849 (98.17%) have app usage data of 7 days (Figure 3).

Figure 2. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) flowchart.

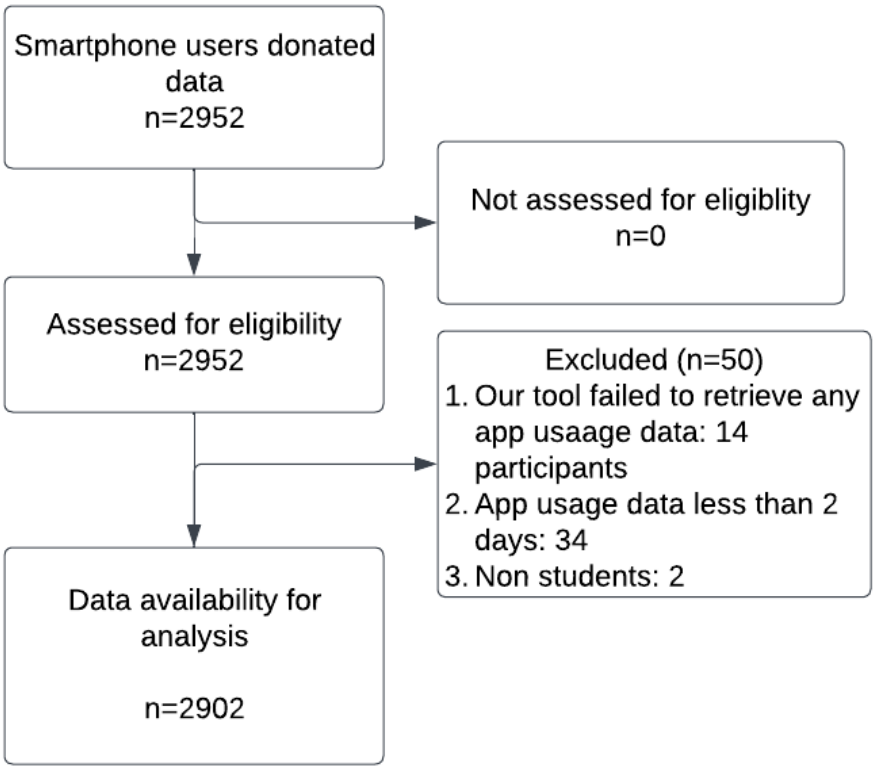

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Figure 3. Number of days' data that each participant has for the final analysis. P: participant.

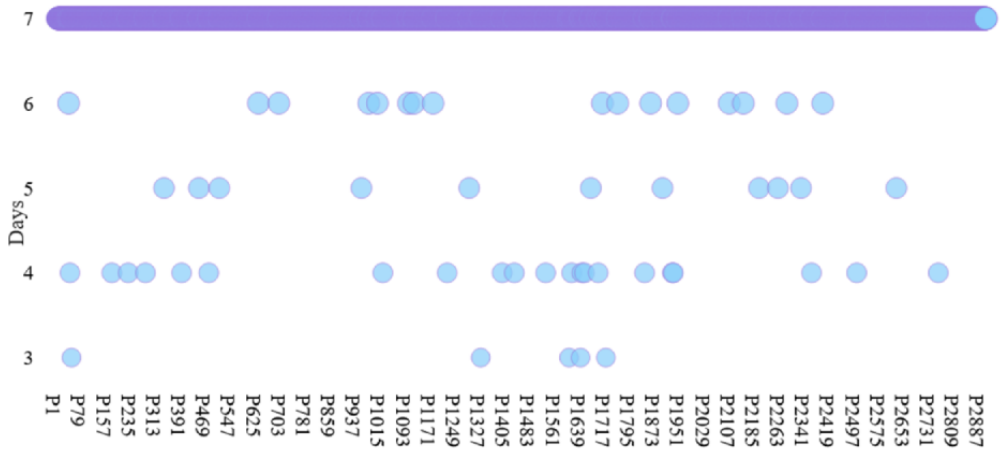

Ground Truth Data to Measure Depressive Symptoms

We used the PHQ-9 (Table 1) [15], which is one of the most commonly used scales to assess depression [21]. In our study, we used the PHQ-9 translated into Bengali [83], which has been validated and is largely used in Bangladesh (eg, [8,78]). The PHQ-9 score of 10 has a sensitivity and specificity of 88% in identifying MDD [15]. Based on this cutoff score, we will categorize the participants as depressed if the PHQ-9 score is at least 10.

In a previous study [67], a person was categorized as having a depressive symptom if that symptom appeared for several days or more. However, we will consider the threshold more than half of the days since the National Institute of Mental Health (NIMH) and the World Health Organization (WHO) define a person as depressed if symptoms appear for a specific time frame, such as most days for a minimum of 14 days [10,11]. In this study, if a participant reports being bothered by a depressive symptom (eg, hopelessness) in the PHQ-9 for more than half of the days or nearly every day of the past 14 days, we will categorize that participant as having that depressive symptom.

Table 1. Depressive symptom for each item of the PHQ-9[a].

Symptom number	Symptom in the PHQ-9
1	Little interest or pleasure in doing things
2	Feeling down, depressed, or hopeless
3	Trouble falling or staying asleep or sleeping too much
4	Feeling tired or having little energy
5	Poor appetite or overeating
6	Feeling bad about yourself or that you are a failure or have let yourself or your family down
7	Trouble concentrating on things, such as reading the newspaper or watching television
8	Moving or speaking so slowly that other people could have noticed or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
9	Thoughts that you would be better off dead or of hurting yourself in some way

[a]PHQ-9: 9-item Patient Health Questionnaire.

Extraction of Behavioral Markers

As we will test the rhythmicity where the time series data are used [36] and explore the rhythmicity of the app usage behavioral markers instead of exploring raw foreground and background app usage events, we will set a time frame of 15 minutes based on which each app usage behavioral marker will be extracted. However, to check the robustness of the findings, we will follow the same process to explore rhythmicity using 2 other time frames as well: 10 minutes and 20 minutes.

In addition to calculating the usage duration, frequency of launching apps, entropy based on duration and entropy based on frequency of launching apps, and app usage sessions [33], we will calculate the following behavioral markers based on which we will extract parametric and nonparametric rhythmic features: relative importance of app categories, personalized top n apps, and cousage of apps.

Relative Importance of App Categories

In pervasive health research, aggregated app usage data (eg, [44-46]) are widely used, where the individual app categories remain unexplored. In our previous studies [33,74], we found that app category–based features are more important than aggregated smartphone usage regardless of category. However, in those studies, features of an app category were extracted independently regardless of the usage behavior of other categories. As a result, the individual category itself may not

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provide higher information for the app categories that are less used but contain distinguishable markers. For instance, if a participant launches social media apps 100 times and health and fitness apps only 10 times, data from the health and fitness category may get lower importance. However, data from the health and fitness category can be more important since depressed students use apps that contain features for smoking prevention and body weight reduction, which may not be used more frequently but may contain enough information to be significantly different from those used by nondepressed students [34]. Hence, we will calculate the term frequency–inverse document frequency (TF-IDF), which is a widely used technique in natural language processing [84] where less frequent terms across documents can get more importance. To adapt TF-IDF in the context of app usage, we will use data from all time frames over all days. In each time frame f, the app usage sessions s will work as the set of documents, and in each session (ie, a document) j, the list of categories of the used apps will act as the words.

Let the set of documents of participant i in f be $\{D_{ij}, D_{ij+1}, \ldots D_{is}\}$, where  , and n represents the number of participants. We will calculate $TF\text{-}IDF_{icj}$ for each app category c based on the participant's data of sessions s.

$$TF\text{-}IDF_{icj} = TF_{icj} \times IDF_{icj},$$

where $TF_{icj} = \log[freq(c) + 1]$, $IDF_{icj} =$ , freq(c) is the number of times app c was launched in session j, df is the number of sessions where c was used, and s represents the total number of sessions in f. After calculating $TF\text{-}IDF_{icj}$ for each session, the mean TF-IDF value will be calculated for each category over the sessions of a time frame. Finally, using that mean value, we will extract the rhythmic features to understand how the relative importance of participant i in using a particular category c varied or remained constant over days and over the periods of a day and whether there was a rhythm in behavioral markers based on the TF-IDF.

To categorize the apps, we will follow relevant previous studies (eg, [30]) and the process in our previous studies [33-35,70,74], where we categorized the apps into more than 20 categories after exploring developers' referred categories in Google Play Store and other app stores and discussing with graduate students of the computer science and engineering (CSE) department.

Personalized Top n Apps

We will calculate entropy based on the usage duration and the frequency of launching the top n apps, which can vary by student. To find the value of n, we will use the probability distribution and plot the probability of using apps on the y axis and the number of apps on the x axis. The point where the curve falls will be considered the threshold (ie, the value of n) to find the top n apps. To find the cutoff value, we will follow a previous study [46] that found cutoff values to exclude the participants having missing values.

Cousage of Apps

A significant portion of app usage consists of switching from one app to another [29]. One plausible reason for such behavior can be changing moods during app usage [85], and the users may do it to seek support, overcome negative emotions, etc. To quantify how participants switch from one app to another, we will calculate the cousage of apps, where the usage of 2 apps will be considered coapp usage if they are used in a single app usage session and also used consecutively. However, in a smartphone, there are many system apps that open automatically to support the function of another app. Users do not need to use those apps intentionally, and as a result, the inclusion of those apps may misrepresent behavior. In addition, to switch from one app to another, the user returns to the home screen of the smartphone, where the launcher app opens automatically. Considering the aforementioned issues, we will exclude these system apps and launcher apps before quantifying the coapp usage.

To find subtle differences in the variation in app usage patterns, we will build a network based on cousage, where each edge will present the cousage of 2 different apps. The weight of the edge will be calculated using point mutual information (PMI).

where $p(A_1, A_2)$ represents the probability of A_1 and A_2 apps to consecutively appear in the same app usage session and $p(A_1)$ and $p(A_2)$ represent the probability of A_1 and A_2 apps, respectively, to appear in that session regardless of consecutiveness. Next, we will calculate the centrality and graph edit distance. The calculation of centrality will help us understand the most influential app in the network that is connected to the maximum number of nodes. The graph edit distance between 2 different sessions of the same time frame will inform whether the behavior differs. Finally, we will use the average data of each session of a time frame to explore the rhythmicity of the centrality and graph edit distance.

Rhythm Analysis and Extraction of Rhythmic Features

The parametric cosinor method is one of the most widely used approaches to find out rhythmic parameters. However, cosinor analysis cannot find out the fragmentation in the rest-activity rhythm [86], which can be detected by extracting nonparametric rhythmic parameters, such as the IS. Therefore, to obtain a comprehensive picture of rhythms, we will conduct both parametric and nonparametric tests and extract the respective rhythmic features, as described later. In this study, to extract rhythms, instead of focusing only on all students' data-based global models, we will also develop individual models and extract the rhythmic parameters for each participant. The main reason is that physiological data–based nonparametric rhythmic [87,88] and parametric rhythmic [89] parameters vary by the characteristics of people, and thus, there may also be a variation in parameters by the individual participant's rhythm that is solely based on app usage data.

Dominant Period

In cosinor analysis, a cosine curve is fitted on the given period (eg, 24 hours) using the least squares method, where the model reduces the difference between observed and estimated values. However, cosinor analysis itself cannot estimate the best-fitting period [90]. Thus, we will empirically investigate through

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periodogram analysis and by setting the periods from 1 to 24. Later, the cosinor model will be developed for each given period (eg, 13 hours). The best-fitting period will be counted as the dominant period where the proportion of explained variance is the maximum.

Rhythm Detection

Cosinor analysis is a parametric method, and hence, we will first test normality [91]. Later, we will process the nonnormally distributed data through log transformation. Next, to find out whether a statistically significant rhythm of a participant exists, we will conduct a zero-amplitude test [36] by setting the significance level to .05. To find out whether an individual participant's rhythm differs from the rhythm based on all participants, we will perform population mean cosinor analysis based on all the participants. In addition, we will develop a cosinor model for each participant and then calculate the average of the cosinor rhythmic parameters [90].

MESOR, Amplitude, and Acrophase

After developing the cosinor model, we will extract the following parametric rhythmic parameters for each participant: midline estimating statistic of rhythm (MESOR), amplitude, and acrophase. MESOR is the rhythm-adjusted mean [36], the amplitude presents the difference between the equilibrium position and the peak point of the rhythm oscillation [92], and the acrophase presents the timing of the high values recurring in each cycle of the rhythm [36]. Since the amplitude can present the strength of the rhythm [93], while comparing the diurnal (12-hour period) and circadian (24-hour period) rhythms to determine which rhythm has more strength, we will compare the amplitude. Moreover, we will compare the coefficient of determination as it presents how well a model fits in a given period.

Interdaily Stability and Intradaily Variability

A person's mental state has a relation with the IS and the IV. For example, patients with bipolar disorder have less IS and higher IV [94]. Similar patterns may be found in the IS and the IV based on app usage data, and we will calculate the IS and the IV, based on a previous study [86] on actimetry.

Here, x_i is the behavioral marker's value at a specific time frame, x_m is the mean value of the same behavioral marker in all time frames, and N is the number of time frames.

Here, x_i is the behavioral marker's average value in that time frame over days and p is the number of time frames per day. The range of the IV value is 0-2 and that of the IS value is 0-1 [95]. The higher the IS, the greater the stability, as the name implies. However, the higher the IV, the higher the fragmentation in the rhythm. If a difference remains, for example, if someone sleeps during the daytime and keeps waking up at nighttime, their IV will be higher [86].

M10, L5, and Relative Amplitude

M10 presents the mean value of the most active consecutive 10 hours and provides information about the diurnal activity. Active persons have a higher M10 [86], and a lower M10 can be associated with exercise reduction [86] and also with a negative mental state [86,96]. L5 presents the mean value of the least active 5 consecutive hours of the day. It is a measure of nocturnal activity, and the higher L5 may represent activity during the rest cycle [86]. After calculating M10 and L5, we will calculate the RA = (M10 – L5)/(M10 + L5). As can be understood from the formula of RA, the RA is actually the normalized difference between M10 and L5. The larger the difference between L5 and M10, the larger the RA. People with psychological problems can have a lower RA [65,86].

Statistical Analysis

To explore whether there is any relation between depressive symptoms and app usage rhythmic features, we will perform binomial logistic regression. As having a variance inflation factor (VIF) of more than 5 can create a biased regression model [97], we will eliminate the variable if the VIF of any variable goes beyond 5.

ML Model Development

Participant Similarity and Development of Personalized Models

Most of the existing models (eg, [33,45,46,74]) to predict depression use training data to predict the outcome regardless of the characteristics of the participant whose class will be predicted. These models may have issues regarding generalizability since all individuals have unique characteristics that may not be captured in one-size-fits-all models (ie, 1 set of training data to predict the depression of all test participants). Indeed, through empirical investigation, it has been found that the personalized model performs better than the one-size-fits-all model [98,99]. The one-size-fits-all or global model is likely to capture the general or the "average" characteristics of the participants for the prediction due to which the model may perform well only on the "average" participants and may not work in the case of the participants whose behavior deviates from the "average" participants [100]. However, the personalized model is trained dynamically for each participant, which can facilitate finding the most relevant set of features to predict the outcome of the test participant [98]. Therefore, a personalized model may perform better in predicting depressive symptoms since each of the depressed students has a unique app usage signature [34] and depressed students have statistically significantly different smartphone usage behaviors than nondepressed students [35], as we found in our previous studies [34,35].

In our app to predict depressive symptoms, we will use each participant i's rhythmic parameters based on each of the app usage behavioral markers of m_i to calculate the cosine similarity with all other participants n – 1.

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Here, B_i and B_j represent the vectors based on the rhythmic parameter sets m_i and m_j of participants i and j, respectively. The cosine similarity s_{ij} will be close to 1 when there is a higher similarity between participants i and j. After finding the similarities between participant i and all other participants, we will use the most similar N participants to train the MTL framework for participant i. The value of N will be decided empirically through a search on the values 200, 250, 300, and 350.

MTL Framework Development and Validation

Although some similar tasks remain, the development of the model through the MTL framework can facilitate improving the performance of the models through information sharing. In addition, if different models are developed for different tasks, then the system can be resource inefficient. In a previous study [65], researchers used MTL to develop systems for predicting the symptoms of schizophrenia. However, in that system, all symptom prediction tasks were considered the same. In reality, all the tasks included in a model do not help one another improve performance [68]. Therefore, we will find the similarities among the symptoms and use similar symptom prediction tasks in a model, while other similar symptom prediction tasks will be in another model. To group the tasks, we will calculate the correlation coefficients among the symptoms. Symptoms that are highly (coefficients>0.7), moderately (0.4≤coefficients≤0.7) [101], and less than moderately correlated or not correlated will be kept in 3 different groups.

While developing the MTL framework, we will use the hard parameter-sharing technique since in this approach, the model can find a common representation to capture all the tasks that can reduce the potential risk of overfitting [102]. Combining multiple loss functions leads to promising performances [103]. In our study, we will use a weighted loss of the hinge and cross-entropy. However, we will not use a fixed weight. Instead, we will tune the weight using the Bayesian search optimization technique, which selects the next parameter based on the performance of the previously selected one.

To validate the framework, we will use the nested cross-validation (CV) method since this approach is found to have a generalizable performance compared to K-fold CV [104]. In the outer loop, we will use the leave-one-out cross-validation (LOOCV) method, and in the inner loop, we will use a 10-fold CV, where in each interaction, 9 folds will be used for tuning the hyperparameters and the remaining 1 fold will be used for validation. We are aware of the fact using the LOOCV will increase the time complexity since there are 2902 participants and we will be developing a personalized model for each of them. However, we chose to use the LOOCV because it will work like the real-world scenario, where the model will predict a single participant's depressive symptoms at a time. In addition, this process will help in personalizing the model, where we will use only those participants in model training who are similar (in terms of app usage behavior without using any information about depressive symptoms) to the student for whom the model will predict the symptoms, as discussed in detail in the *Participant Similarity and Development of Personalized Models* section. During model development, we will maximize the balanced accuracy as it is based on sensitivity and specificity, and having a higher balanced accuracy can lead to higher precision and F_1-score values.

To understand the robustness of the proposed MTL framework, we will compare it with the performance in the following approaches:

- Comparison with STL-based models: We will compare the performance of the proposed personalized MTL framework with that of STL models. This will resemble the approach presented in a previous study [67], where each symptom was considered a single task. To develop the STL model, we will use ML algorithms, such as the random forest (RF), support vector machine (SVM), decision tree (DT) [105], and logistic regression [106], which are widely used in medical informatics, as shown in systematic reviews [105,106].
- Comparison with the nonpersonalized MTL framework: Since we expect that personalization may provide better performance, as discussed in the *MTL Framework Development and Validation* section, we will compare the performance of the personalized MTL framework with that of a nonpersonalized MTL framework, where we will use n – 1 participants' data for training instead of using a personalized subset of data.
- Comparison with the MTL framework without grouping tasks: To understand how grouping tasks based on similarity impact performance, we will compare the performance of the MTL framework with and without grouping tasks.

Results

As mentioned earlier, after applying inclusion criteria, we kept the data of 2902 (98.31%) of 2952 students for analysis, with the data of 24.48 million app usage events, and 7 days' app usage of 2849 (98.17%) students.

Figure 4 shows the findings regarding participants' demographic characteristics. The participants were from the 8 divisions of Bangladesh (Figure 4a). Most participants (n=887, 30.56%) were from the Dhaka division, which also reflects the fact that the majority of university students of Bangladesh reside in this division. The participants' age varied from 18 to 39 years, and 2309 (79.57%) participants were aged 20-23 years (Figure 4b). Of the 2902 participants, 1107 (38.15%) and 1783 (61.44%) were female and male participants, respectively (Figure 4c). There were 2430 (83.74%) and 472 (16.26%) students from public and private universities, respectively. The participants belonged to 19 universities (Figure 4d), including specialized universities, studying the following subjects: agriculture, engineering, and textiles. They also belonged to 52 different departments, including arts (eg, Department of Sculpture), business (eg, Department of Management Studies), engineering (eg, Department of Petroleum & Mining Engineering), science (eg, Department of Botany), textiles (eg, Department of Apparel Engineering), public health, and law faculties.

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In the remaining part of the study, we will work on rhythm detection, rhythmic feature extraction, and MTL framework development. We expect to publish our findings by June 2024.

Figure 4. Participants' demographic characteristics: (a) map of Bangladesh presenting living divisions, (b) age, (c) gender, and (d) number of different institutions.

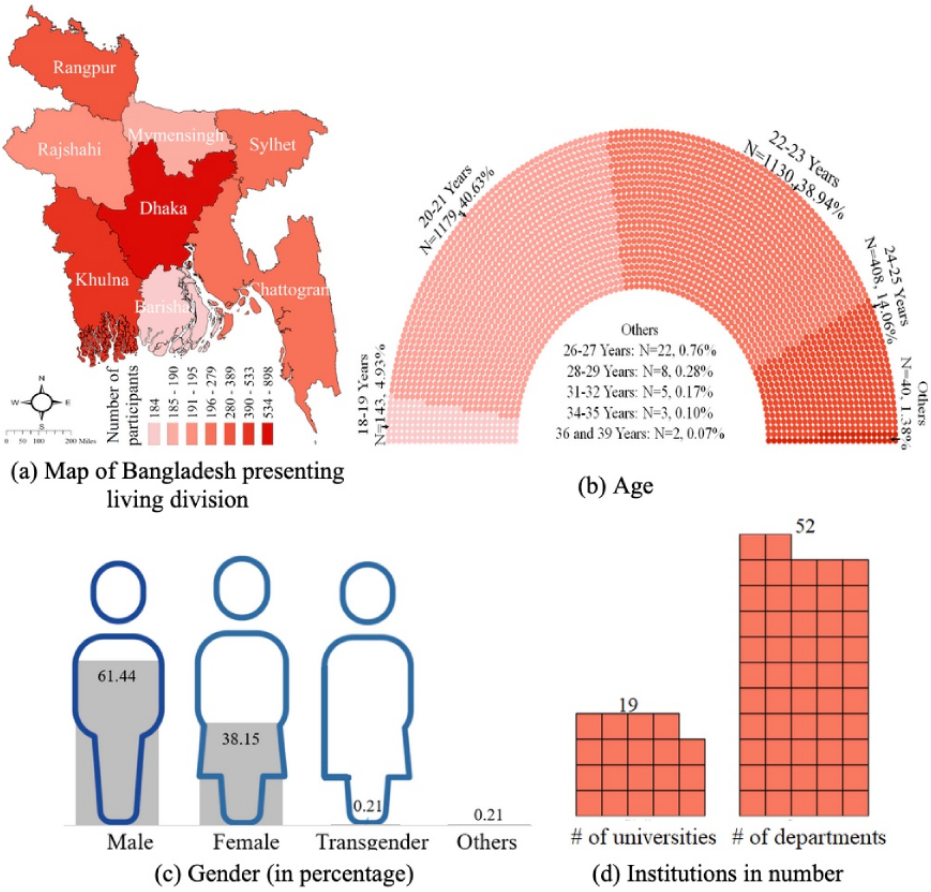

Discussion

Significance

By using the data set constructed through a countrywide study on 2902 students having over 24 million app usage events, we will explore whether there is a statistically significant rhythm based on the different app usage behavioral markers. We hypothesize that app usage behavioral markers, such as the relative importance of an app category, have rhythmic patterns with reproducible waveforms because, like physiological data, the markers vary depending on factors such as the time of day [29-31]. In addition, since rhythmic features based on physiological [39,107] and activity [108] data have potential applications in problems such as determining which participants have a higher risk of disease [107], determining sedentary behavior [39], and finding subtle changes in detecting COVID-19 [107], an in-depth exploration of app usage marker–based rhythms may show an alternative source of data to understand the rhythms in human life. App usage marker–based rhythms have the possibility to be used for different purposes. For example, a statistically significant relation between the rhythmicity of app usage and depressive symptoms can create the possibility of using these rhythmic features for an intervention to mitigate depression.

In addition, by predicting depressive symptoms, our study will extend the findings of previous studies since most studies (details in a recent systematic review [43]) in the pervasive health area have developed classification models (eg, to classify depressed and nondepressed individuals) where the complexity of the psychological problem of depression may be lost. For instance, a participant with a PHQ-9 score of 10 has moderate depression [15], and a score of 10 can result from different combinations of the subscores of the 9 symptoms in the PHQ-9. As a result, by classifying participants into a few groups based on the overall score on a scale, it is not possible to precisely determine the depressive symptoms that bother a student. However, it is important to know since each depressive symptom (eg, symptoms in the PHQ-9 [15]) presents a unique phenomenon (eg, anhedonia, sleep disturbance, suicidal ideation) [109]. Therefore, depending on our proposed personalized MTL framework's performance based on real-time data, the proposed app can contribute to early diagnosis of depressive symptoms and precise understanding of a depressed student, which, in turn, may contribute to mitigating depression prevalence.

Our previous pilot studies in Bangladesh on the relation of app usage with depression [35,73] and loneliness [75], classifying depressed and nondepressed students [33] and with and without loneliness [74], showed promising models solely based on resource-insensitive [33] app usage behavioral markers.

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Incorporating app usage rhythmic features and also the MTL framework by leveraging the similarities among the symptoms' prediction tasks so that tasks do not hurt one another's performance may help researchers and developers in developing more robust models to predict the symptoms of psychological problems solely through app usage data. In addition, our app's reliance on data retrieved from a smartphone within 1 second [33] may also make it feasible in LMICs since smartphones are more affordable [42] compared to wearables [41] that are usually used to obtain physiological data and extract rhythmic features.

Strengths

The median sample size of previous studies that classified or predicted depression was 58, and none of the studies that developed computational models for prediction tasks had a sample size of over 500, as shown in a recent systematic review [21]. However, we constructed a large data set comprising 2902 students. In addition, the participants of our study are from all 8 divisions of Bangladesh, from both public and private universities and 52 different departments. To the best of our knowledge, this is the largest data set containing data on both app usage and depressive symptoms. Considering these facts, our findings based on the proposed methods may be generalizable, may be robust enough to be impactful in the real world, and may contribute significantly to advancing the knowledge in mobile and pervasive health research areas.

To the best of our knowledge, this will be the first study to explore in depth rhythms based on different app usage behavioral markers, which can create an opportunity to find an alternative source of data to understand the rhythms of daily life without depending on physiological data–based rhythms, which are usually retrieved by costly wearables.

In our recent work based on app usage [33], our developed app had higher performance in predicting depression than the existing systems based on app usage as well. Through feature analysis (for details, please see Ref. [33]), we found that our newly explored behavioral markers (eg, ratio of the hamming distance [33]) were more important than the features used in previous studies. That being said, performance varies depending on the behavioral markers used in a model. Hence, the novel behavioral markers (eg, relative importance of app categories, cousage of apps) we presented in this protocol that were not explored in previous pervasive health research have significance. In addition, to predict depressive symptoms, we will develop a personalized MTL framework. Although an MTL framework has been developed in some previous studies (eg, [65]) to predict a person's mental state, our study will add to this knowledge by showing the performance of a personalized MTL framework.

Limitations

Following previous studies [65,81,82], to analyze rhythms, we have included 2902 participants in this study who had app usage data of at least 2 days and most of whom (n=2849, 98.17%) had app usage data of 7 days. Data of more than 7 days will help us better understand the stability of the rhythms, the rhythm disruption over weeks, and its potential effect on depressive symptoms' appearance. However, we believe our study can work as a primary cursor for future studies to further explore app usage rhythms.

Although our study includes over 2900 students from different divisions of Bangladesh, our proposed app may not be generalizable to every student since behavior varies depending on many factors, such as season, region, [22], and socioeconomic status [23]. We recommend future studies to include participants based on more factors that can impact behavior. Moreover, in our study, although we have included participants from all 8 divisions of Bangladesh, we could not include participants from all 64 districts of the 8 divisions. In addition, including more participants from rural areas could have potential to obtain a more reliable picture of the students' behavior, which, in turn, can be useful to develop a better app.

Conclusion

Predicting depressive symptoms accurately could help in better diagnosis of depression and in taking appropriate steps accordingly. However, existing models regarding symptom prediction are limited by various issues, including low performance (eg, specificity is around or below 60% for most symptoms). Our proposed approach to explore rhythmic features from app usage behavioral markers and the development and validation of the MTL framework through our constructed large-scale data set may provide new insights into rhythms and higher performance in predicting depressive symptoms.

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Data Availability

Since app usage data are sensitive, making the data publicly available can raise different data privacy and safety concerns (eg, reidentification of the participants [34]). Thus, we do not plan to upload the data to any public data repositories. However, the data can be accessed by sending a reasonable request to the corresponding author.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CV: cross-validation
IS: interdaily stability
IV: intradaily variability
LMIC: low- and middle-income country
LOOCV: leave-one-out cross-validation
MDD: major depressive disorder
MESOR: midline estimating statistic of rhythm
ML: machine learning
MTL: multitask learning
PHQ-9: 9-item Patient Health Questionnaire
PMI: point mutual information
RA: relative amplitude
STL: single-task learning
TF-IDF: term frequency–inverse document frequency
VIF: variance inflation factor

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Protocol

Lack of Diversity in Research on Females with Ehlers-Danlos Syndromes: Recruitment Protocol for a Quantitative Online Survey

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Abstract

Background: Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders caused by fragile lax collagen. Current EDS research lacks racial and ethnic diversity. The lack of diversity may be associated with the complexities of conducting a large international study on an underdiagnosed condition and a lack of EDS health care providers who diagnose and conduct research outside of the United States and Europe. Social media may be the key to recruiting a large diverse EDS sample. However, studies that have used social media to recruit have not been able to recruit diverse samples.

Objective: This study aims to discuss challenges, strategies, outcomes, and lessons learned from using social media to recruit a large sample of females with EDS.

Methods: Recruitment on social media for a cross-sectional survey examining dyspareunia (painful sexual intercourse) in females was examined. Inclusion criteria were (1) older than 18 years of age, (2) assigned female at birth, and (3) diagnosed with EDS. Recruitment took place on Facebook and Twitter (now X), from June 1 to June 25, 2019.

Results: A total of 1178 females with EDS were recruited from Facebook (n=1174) and X (n=4). On Facebook, participants were recruited via support groups. A total of 166 EDS support groups were identified, 104 permitted the principal investigator to join, 90 approved posting, and the survey was posted in 54 groups. Among them, 30 of the support groups posted in were globally focused and not tied to any specific country or region, 21 were for people in the United States, and 3 were for people outside of the United States. Recruitment materials were posted on X with the hashtag #EDS. A total of 1599 people accessed the survey and 1178 people were eligible and consented. The average age of participants was 38.6 (SD 11.7) years. Participants were predominantly White (n=1063, 93%) and non-Hispanic (n=1046, 92%). Participants were recruited from 29 countries, with 900 (79%) from the United States and 124 (11%) from Great Britain.

Conclusions: Our recruitment method was successful at recruiting a large sample. The sample was predominantly White and from North America and Europe. More research needs to be conducted on how to recruit a diverse sample. Areas to investigate may include connecting with more support groups from outside the United States and Europe, researching which platforms are popular in different countries, and translating study materials into different languages. A larger obstacle to recruiting diverse samples may be the lack of health care providers that diagnose EDS outside the United States and Europe, making the pool of potential participants small. There needs to be more health care providers that diagnose and treat EDS in countries that are predominantly made up of people of color as well as research that specifically focuses on these populations.

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KEYWORDS

Ehlers-Danlos syndrome; hypermobility; social media; recruitment; Facebook; hereditary disease; connective tissue disorders; racial; ethnic; diversity; challenges; strategies; strategy; online; information seeking; cross-sectional survey; dyspareunia; painful sex; United States

Introduction

Overview

Ehlers-Danlos syndromes (EDS) are a group of hereditary connective tissue disorders [1]. The overall prevalence and racial and ethnic breakdowns of EDS are unknown [2]. It is estimated that EDS affects between 1 in 5000 [3] and 1 in 3400 [4] and is thought to be underdiagnosed instead of rare [4,5]. Females are diagnosed at a much higher rate than males with 7 females diagnosed for every 3 males [4]. It is unknown if this is due to the difference in presentation between the 2 sexes or how the condition is passed to offspring [6]. The inability to accurately determine the prevalence of EDS makes it difficult for investigators to recruit large diverse samples for studies, limiting the generalizability of results to participants whose demographics match study samples.

Most EDS studies have been comprised of predominately White samples recruited from the United States and Europe. Recruitment has traditionally been done at clinics or hospitals that treat patients with EDS [7], conferences [8-10], local in-person EDS support groups [11], or big data aggregation of national health records [4,12,13]. These recruitment methods limit the diversity of participants. Recruiting via clinics may limit participation to those who are physically and financially able to travel to the clinics; however, access to clinics is improving with the use of telemedicine. Some studies conducted via hospitals or clinics fail to report race or ethnicity demographics in their results [14-18]. Although national health record studies recruit from a large geographic area, to date they have only been completed in small northern European countries with predominantly White populations [4,12,13]. Extracting data from national health records also limits the types of data that can be analyzed to demographics and health care informatics, lacking metrics not included in patients' charts such as symptom burden and personal experiences. Recruiting via EDS conferences includes only participants who are financially able and healthy enough to travel, excluding those who are of low socioeconomic status and the most ill. Furthermore, health care providers who treat and diagnose EDS and EDS researchers are predominantly located in the United States and Europe [19], which likely decreases the number of people diagnosed outside of these regions and, therefore, the number of people who would be eligible to participate in the research. The Ehlers-Danlos Society is an international nonprofit organization that is involved in raising awareness of EDS as well as supporting EDS research through research grants, patient education conferences, and health care provider symposia. The Ehlers-Danlos Society is based in the United Kingdom and the United States and operates in English, which may be a barrier for non-English speaking health care providers and researchers to participate in research and attend symposia. The Ehlers-Danlos Society is based in the United Kingdom and the United States and operates in English, which may be a barrier for health care providers and researchers in non–English-speaking countries for participating in research and attending symposia. However, the Ehlers-Danlos Society is actively trying to connect with or develop a network of EDS providers and researchers in countries where there are few EDS providers such as Japan [20]. Using social media for recruitment may facilitate the recruitment of diverse samples, increasing the generalizability of results to the global EDS population. However, studies conducted since this study in 2019 had similar results with most participants residing in the United States, Canada, the United Kingdom, and Australia [21-23].

Use of Social Media for EDS Study Recruitment

EDS research has started to use social media for recruitment, but no literature has discussed research methods associated with this approach. A benefit of using social media to recruit is that it can reach a global population in a cost-effective manner [24]. Unable to find care for their symptoms and dismissed by health care providers [25,26], people with EDS often turn to support groups on social media to help them find physicians who diagnose and treat EDS, obtain tips about how to manage symptoms, and feel a sense of belonging [26]. The presence of online EDS support groups allows investigators to access groups of people with EDS. Without these support groups, people with EDS would have been difficult to reach due to the relatively low diagnosis rate. Social media lends itself well to recruiting for sensitive topics, such as medical conditions, because it provides a level of anonymity where individuals may be more comfortable disclosing information than if they had provided information in person [24,27].

Purpose

The purpose of this study is to discuss the challenges, strategies, and outcomes of recruiting people with EDS on social media. We will discuss the protocol used to recruit participants for an online survey examining dyspareunia, pain during sexual intercourse, in people with vaginas who have EDS. The methods for this study in particular were chosen because of the successful recruitment of 1178 participants in 4 weeks, which enabled the research team to identify that vulvodynia occurs in half of females with EDS [28]. For this paper, the term EDS will be used to describe people with hypermobile EDS, hypermobility spectrum disorders, as well as other types of EDS. Not all people who have vaginas identify as female and the use of the terms "female" or "women" to describe all people with vaginas is inaccurate. However, for lack of a better term at this time, we will use the term female to describe people in this study.

Methods

Recruitment

We recruited for an open online survey examining dyspareunia in females who had EDS from June 1 to July 7, 2019. The survey, participant screening, and consent were completed on

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Qualtrics (Qualtrics). Details of the survey design and findings are reported elsewhere [28]. Inclusion criteria were (1) a self-reported diagnosis of EDS or a hypermobility spectrum disorder previously confirmed by a health care provider, (2) assigned to the female sex at birth and not had genital gender reassignment surgery, (3) 18 years of age or older, and (4) able to read English. The IP addresses were monitored to prevent people from participating more than once.

Ethical Considerations

The study was approved by the University of Illinois Chicago institutional review board (IRB; #2019-0219). Informed consent took place on Qualtrics and involved participants reading a consent form and then selecting whether they agreed and wanted to participate or not. The study data collected were anonymous, and no protected health information or personal identifiers were collected. No compensation was provided for participation.

Social Media Platform Choice

There are 3 basic types of social media platforms—text-based, photo or video-based, and private messaging. The social media quick guide (Table 1) outlines the basic functions and features of the most common social media platforms. Text-based platform posts are centered around text, but images and links can be attached. Image-based platform posts are centered around sharing photos or videos that can include text, but the photo or video is the main part of the post. Private messaging platforms are used to communicate privately between users and cannot be used to post information publicly. Text-based platforms such as Facebook (Meta Platforms) and Twitter (now X; Twitter Inc) facilitate discussion. Facebook works especially well for support groups because of the ability to make groups "private." In private groups, members need to be approved by group administrators to join, group content can only be seen by group members, group content is not searchable via search engines such as Google (Alphabet Inc), and members can be banned for breaking rules. Private groups allow members to discuss sensitive topics with some privacy. X uses hashtags to organize public and private posts. Private posts can only be seen by a user's "friends," people they have identified as knowing. X does not have a group function but instead, information can be searched via hashtags (#). For example, if a user searched for #puppies, all posts that included #puppies in the caption would appear. If a post is private, it would only appear in search results for people who have been identified as friends. Keeping posts private is helpful for discussing sensitive topics but eliminates discussion among members who are not "friends."

Facebook and X were selected for recruitment. Facebook was chosen because of the large number of existing EDS support groups. X was used to explore recruitment on social media via a platform that does not allow group formation. Facebook recruitment protocol and results (Figure 1) outline the recruitment protocol and results used for Facebook.

Table 1. Social media platform quick guide and features of common social media platforms.

Features	Facebook	Reddit	X	Instagram	TikTok	Snapchat	WhatsApp	WeChat
Primary purpose								
Text posts	✓	✓	✓					
Image posts				✓				
Video posts					✓			
Private messaging						✓	✓	✓
Available features								
Private posts	✓		✓	✓	✓			
Group formation	✓	✓						
Private group posts	✓							
Posts searchable by topic or hashtags	✓	✓	✓	✓	✓			

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Figure 1. Facebook recruitment protocol and results. EDS: Ehlers-Danlos syndrome; IRB: institutional review board.

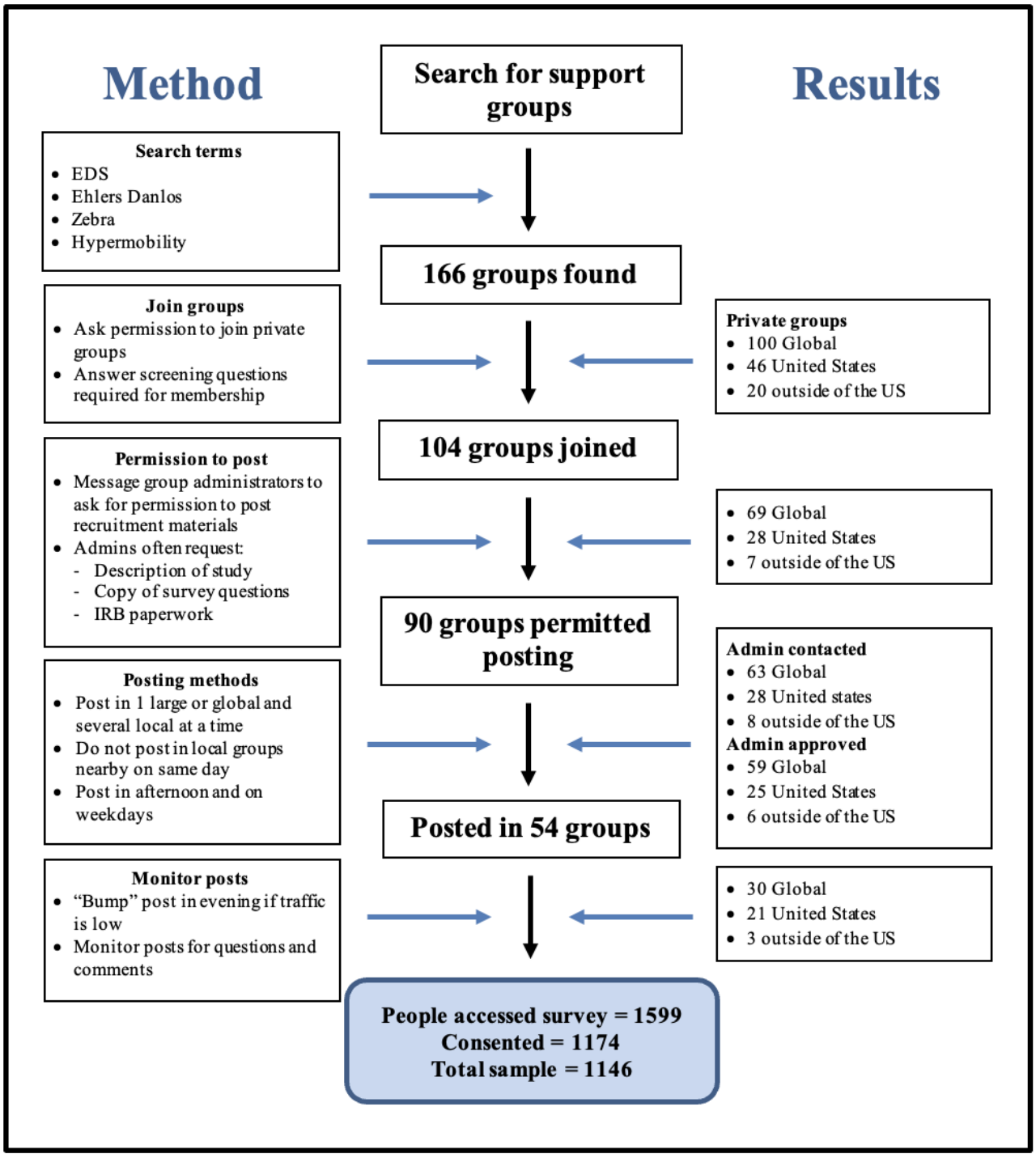

Searching for EDS Support Groups in Facebook

Search terms "Ehlers Danlos," "EDS," "Hypermobility," and "Zebra" were used to search for EDS support groups on Facebook. Zebra was used as a search term because it is the mascot for EDS and other rare diseases. Zebra comes from the phrase taught to medical students that if you hear hoof beats think horse and not zebra, as it is more likely to be a horse. When this concept is applied to patients it can cause doctors to miss rare and underdiagnosed diseases such as EDS [29].

Joining EDS Support Groups on Facebook

All support groups the primary investigator (PI) found were private. The PI requested permission to join the private groups. Private Facebook support groups frequently have users answer questions before granting or denying them membership. Groups often require people to have or know someone who has EDS to join. When requesting to join these groups, the PI disclosed that she was a researcher and would like to join the group for the purpose of recruiting for the study. Once the PI joined a group, the administrators of the group were messaged to ask for permission to post the recruitment materials. Messages included information about the PI and the project, and that the

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project was approved by an IRB. Although groups did not mandate permission before allowing posting, this approach provided transparency about the PI's motives and helped to build trust between the group and the PI.

Posting Recruitment Material on Facebook

Strategies developed based on previous Facebook use were used to try to reach the most participants possible. Recruitment materials were posted in 3 to 4 groups per day, generally 1 large group of over 1000 members and 3 small groups each with less than 1000 members. Groups in the same geographical area, for example, a Michigan support group and a Great Lakes support group were not posted in on the same day due to the likelihood of membership overlap. Posting recruitment materials in all groups that consented at the same time would limit the visibility of the post to people who were on social media at that time and cause users who are in several groups to see the same post in their feed multiple times and potentially cause them to become annoyed. A feed is like a home page that displays posts from a user's friends and groups of which they are a part. Posts are displayed in chronological order with the newest and most active posts appearing at the top. Active posts are posts that have been commented on or liked. You may comment on your own post to help it move up in a feed; this is called bumping. Posting in different groups over several days will increase the time a post is at the top of a feed for users who are in more than 1 group.

Posting Recruitment Material on X

On X, hashtags related to EDS were searched. Recruitment materials were posted with #EDS by an account specifically made for the study. X posts are limited to 280 characters, requiring a shorter study description than Facebook posts. Prior to posting, the PI interacted with and followed other X accounts related to EDS and pain. X accounts were found by searching for accounts that included search terms in their profile or were included in post hashtags. The same search terms used to search for Facebook support groups were used here. This increased the account's presence and boosted the number of users who would see the posts.

Monitoring Recruitment Posts

All posts on Facebook and X were monitored and any questions or comments were addressed quickly. Responding quickly could keep the post at the top of a user's or group's feed and hopefully address the user's question before they left their social media account and lost interest in participating. Once recruitment goals were met, the PI stopped contacting groups for permission to post and stopped posting recruitment materials.

Statistical Analysis

Recruitment data were analyzed from 3 sources—Facebook search results, Facebook group tracking, and survey response data. Excel (Microsoft Corp) was used to track (1) the name of each group, (2) the size of each group, (3) if permission was given to join the group, (4) who was contacted to ask for permission to post in the group, (5) when the person was contacted, (6) if permission was given to post in the group, and (7) when recruitment materials were posted in the group. Stata Software for Statistics (version 15; StataCorp) was used to analyze descriptive statistics of the search results from the Facebook EDS support groups search. Survey response data were exported from Qualtrics to Excel to be cleaned and then to Stata 15 for analysis. For the original study examining dyspareunia, participants missing key data were not included. For this study, all participants who consented were included. Survey response data were used to analyze participant demographics and their traffic. The traffic of participants was analyzed by calculating the number of participants who accessed the survey during the 6-hour time blocks of 4 AM to 9:59 AM, 10 AM to 3:59 PM, 4 PM to 9:59 PM, and 10 PM to 3:39 AM EST.

Results

Facebook Recruitment

The Facebook recruitment protocol and results (Figure 1) provide the number of groups included in each step of the recruitment process. The EDS support groups search yielded 166 EDS Facebook support groups ranging in size from less than 100 to 33,000. Of the 166 groups found, 104 (63%) gave permission for the PI to join. Common questions asked by group administrators when the PI requested permission to join groups included the following: *Why do you want to join the group?*, *Do you or someone you know have EDS?*, *Do you live in XX city (if the group was focused on a specific geographic area)?*, and *Do you agree to follow the rules of the group?* Group rules often included not taking screenshots of group conversations, not disclosing the identity of members to nonmembers, and no soliciting.

Of the 104 groups that gave permission, 90 (86%) gave permission to post the recruitment materials. Three of the groups that did not permit the PI to join offered to post recruitment materials for the PI. The PI was denied access to post in several groups for cisgendered language in the survey and recruitment materials. These groups preferred the use of specific organs instead of the terms "woman" and "female." Of the 90 groups that gave permission to post, 54 (60%) were posted in before recruitment goals were met. Once the recruitment goals were met posting was stopped by the PI.

When analyzing the data, EDS support groups were divided into 3 categories—global (or no specific geographic location specified); United States for users who resided in the United States (eg, Chicago EDS support group); and outside of the United States for users who resided outside of the United States (eg, Sussex, England EDS support group). The categories of United States and outside of the United States were used because of the high prevalence of US groups and the sparseness of groups from other specific countries. Global groups were separated from the US groups and groups outside of the United States because global groups have different focuses than region-specific groups. Groups specific to a geographic location can be used to help members find local health care providers and members are able to meet in person. Global groups are often focused on broad topics such as comorbid conditions associated with EDS. Global groups were larger in size and more prevalent than the other 2 categories, with 100 global groups found compared to 46 US groups and 20 outside of the US groups. Of the 54 groups in which recruitment materials were posted, 30

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(56%) were global groups, 21 (39%) were US groups, and 3 (18%) were outside of the US groups.

User Statistics

There was a total of 110,665 users in the 54 groups posted in; however, this does not take into consideration that users are often members of more than 1 group. The smallest group posted in had 47 members and the largest had 33,170 members. We were unable to calculate a response rate because we were unable to determine how many users saw each post and then accessed the survey. Of the 110,665 people who potentially saw the post, 1599 accessed the survey and 1178 females were eligible, consented, and included in analyses. Of the 1178 consented participants, 1174 were recruited from Facebook and 4 from X. The average age of participants was 38.6 (SD 11.7) years, similar to the average age of participants in big data studies of EDS [4,12,13,30]. Participants were predominantly White (n=1063, 93%), non-Hispanic (n=1046, 92%), and had the most common form of EDS, hypermobile EDS (n=1290,79%) [2]. Participants were recruited from 29 countries with 900 (76%) from the United States and 124 (11%) from Great Britain. The map of the participant's country of residence (Figure 2) shows all the countries from which the participants were recruited. Participant characteristics can be found in the characteristics of the sample (Table 2) [28].

Figure 2. Heat map of countries in which participants reside.

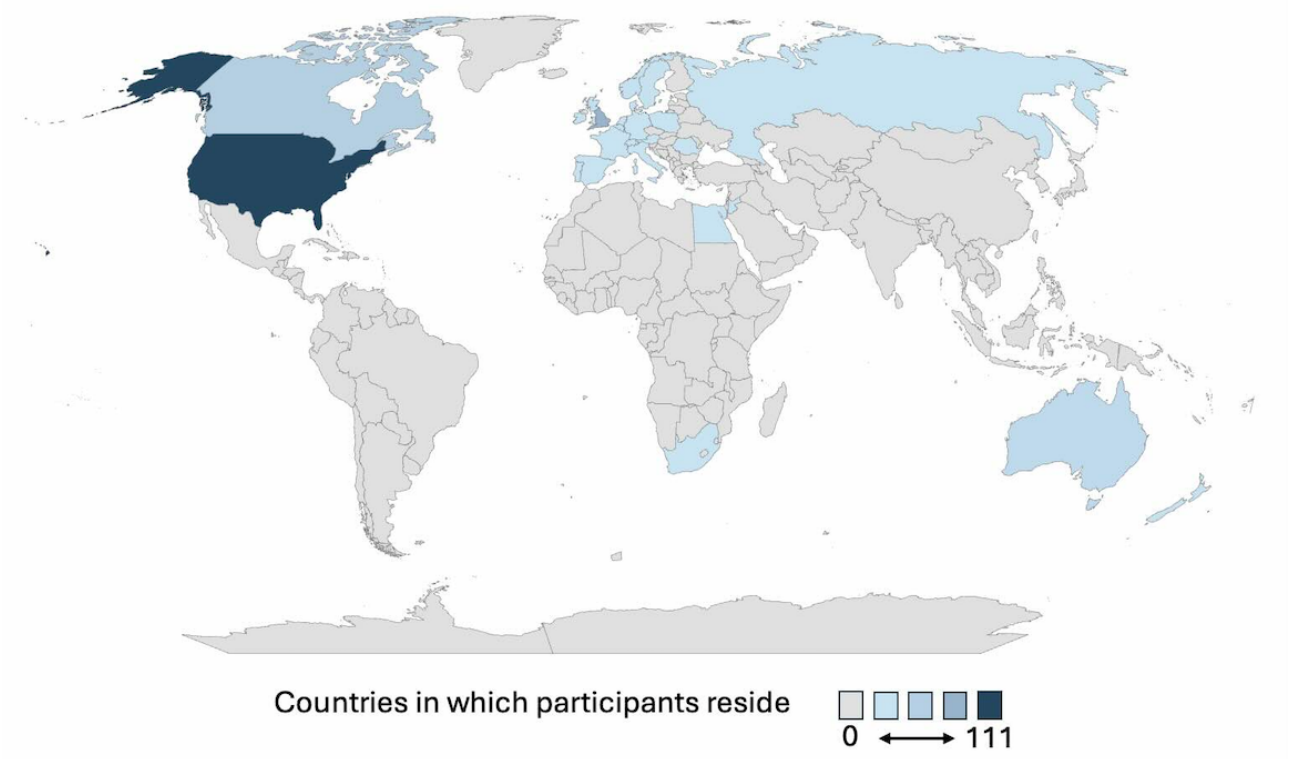

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Table 2. Characteristics of the sample (number of females with Ehlers-Danlos syndromes; N=1178) [17].

Demographics	Values
Age (years; n=1141)	
Mean (SD)	38.6 (11.7)
Range	18-76
Sex, n (%)	
Female	1144 (99.8)
Transgender	2 (0.2)
Race[a], n (%)	
White	1063 (92.8)
Black or African American	12 (1.0)
American Indian or Alaskan Native	17 (1.5)
Asian	11 (1.0)
Native Hawaiian or Pacific Islander	3 (0.3)
Other	47 (4.1)
Ethnicity (n=1138), n (%)	
Hispanic or Latino	41 (3.6)
Not Hispanic or Latino	1046 (91.9)
Unknown or not reported	51 (4.5)
Country of residence, n (%)	
Unites States	900 (78.5)
Great Britain	124 (10.8)
Canada	46 (4.0)
Australia	23 (2.0)
Other	66 (5.7)

[a]Participants selected all races they identified with.

Survey Traffic

To examine when participants from different parts of the world accessed the survey and determine optimal posting times for recruiting participants globally, we analyzed what time participants accessed the survey. What time participant accessed the survey was analyzed by time of day and by day of week for the whole sample (N=1178), those residing in North America (n=971), and those residing outside of North America (n=206). The PI posted recruitment materials at different times during the day and night in hopes of recruiting people in different time zones. The North America and non–North America groupings were used for analysis instead of the country of residence due to data sparseness and overlapping time zones of the countries. The busiest time block for recruitment of participants as a whole (n=465, 39%) and among participants in North America (n=411, 42%) was 4 PM to 9:59 PM. Recruitment was busiest from 10 AM to 3:59 PM for participants outside of North America (n=57, 17%). Recruitment of participants outside of North America was more evenly distributed across all time blocks with about 50 participants per time block. The 4 AM to 9:59 AM time block had the least amount of traffic for the whole group (n=130, 11%), participants from North America (n=87, 9%), and participants from outside of North America (n=43, 4%). Monday was the busiest recruitment day for all groups with 301 (25%) participants from the whole sample, 244 (25%) from North America, and 57 (27%) from outside of North America. Saturday through Tuesday were busier than Wednesday through Friday. The day of the week that participants from North America were recruited differed significantly compared to participants from outside of North America (χ^2_6=34.1; P≤.001).

Discussion

Principal Findings

We were able to recruit a large sample in a short amount of time, highlighting the usefulness of using social media, specifically Facebook EDS support groups and X, for recruitment. Our method of recruiting via Facebook can be used to target populations that have access to the internet and use social media. Support groups on social media provide curated groups of people that would otherwise be difficult to find, facilitating recruitment of large groups of participants for rare and underdiagnosed conditions. However, like other EDS studies that recruited via social media, we were not successful at recruiting a diverse sample with our participants being

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predominantly from the United States and White. Our results do provide greater detail about the countries participants resided in when they accessed the survey, and their races and ethnicities. Many of the large studies conducted in Northern Europe do not provide demographic details such as race and ethnicity. Providing demographic information is key to assessing the diversity of a sample and evaluate generalizability. Demographic information including race and ethnicity should be included in every study's results. Future directions for research to increase diversity in a sample may include investigators connecting with more support groups from outside of the United States and Europe, use of social media platforms that are popular in other countries, and translating study materials into different languages. More fundamental obstacles potentially include the need for more health care providers that diagnose and treat EDS in countries that are predominantly comprised of people of color, and the need to conduct research that targets these populations.

Challenges That Were Successfully Addressed

Some social media platforms are better than others for recruiting participants. Facebook worked well for recruiting because existing EDS support groups had thousands of members. Posting in these groups allowed the PI to reach many people with EDS with each post. When posting in groups on Facebook, it is easy to see how active a group is based on how frequently people are posting in the group and how many comments and likes the posts receive. Posting in groups on Facebook was chosen over platforms where hashtags (#) are used because these platforms do not have existing groups of people with EDS. On platforms where hashtags are used, the visibility of a post for users is influenced by the number of followers users have. Therefore, for a researcher to reach a lot of people with a post they must create a profile, as well as cultivate a following which can take a fair amount of time. It is also difficult to determine which hashtags are most popular and how people are interacting with hashtags. A better way to share a study on platforms that use hashtags, such as TikTok (ByteDance), is to have existing platform users, with a large group of followers, share the study on their social media page, such as EDS nonprofits.

Our recruitment protocol helped to efficiently keep track of where we were in the recruitment process and within each support group. Documenting the name of each group administrator and when they were contacted allowed the PI to quickly determine what chat conversation was associated with each support group because chats are labeled with users' names and not their affiliated support group. It was also difficult to decide what and when support groups should be posted in. Having the size, where each group was located, and if the group had a specific focus helped determine what groups to post in on a given day. Asking for permission to post recruitment materials in groups was the most labor-intensive aspect of recruitment. On Facebook, messages from users who are not your "friend" are sent to a message request folder that is not easily seen. Typically, when using Facebook Messenger, conversations with "friends" are kept in 1 location and users receive a notification when they receive a new message. This does not happen when a user receives a message from someone who is not a friend. When a message is seen by a recipient in Facebook Messenger, their profile picture appears next to the message. To address the challenge of messages going unseen by group administrators, the PI contacted a different group administrator. Administrators of smaller local groups tended to respond to messages more often and more quickly.

Challenges That Still Need to Be Addressed

Recruiting Participants From Diverse Countries of Residence

Efforts to recruit participants quickly may have led to decisions that decreased the diversity of participants. A total of 21 (45%) of the EDS support groups posted in were US support groups. Anecdotally it seemed easier to recruit from small local EDS support groups because they were more active than global groups, determined by users' engagement such as commenting and liking posts. Support groups that were focused on areas outside of the United States were stricter about allowing people from outside their area to join and post, with 6 (30%) of groups outside of the United States permitting posting compared to 59 (59%) of global groups and 25 (54%) of US groups. Establishing relationships with EDS communities in other countries, to gain permission for research recruitment, may lengthen recruitment. Whether or not establishing these relationships would increase diversity in a sample needs to be assessed. A limitation is that the PI only posted in 3 (50%) of the groups outside of the United States that gave permission before stopping recruiting due to meeting recruitment goals. The decision to post in local US groups over groups based in other countries was based in part on the perception that groups outside of the United States received less traffic. Instead of using groups located outside of the United States, due to perceived low activity, larger more active global groups were targeted. However, it is important to consider that even though a group is global, it may have a large percentage of users from the United States. In the future, global groups and groups outside of the United States should both be a priority for recruiting. It may be beneficial to work with local collaborators, researchers, or advocates who are familiar with the local support groups in their respective countries. Furthermore, social media preferences may differ between countries.

Racial and Ethnic Diversity Within the Sample

Definitions of race and ethnicity vary across the world. This study used the race and ethnicity categories from the US National Institutes of Health with an "other" option added. Identifying racial categories that are used globally and less focused on the United States may make it easier to compare demographics from studies conducted in other countries and may be more inclusive. Our sample was predominately White (n=1063, 93%) The racial and ethnic breakdown of EDS is unknown [2]. In a study looking at EDS diagnoses in hospitalized patients in the United States, 1736 of 2007 (86%) participants were White [30]. However, in the United States, race and ethnicity affect access to care, including receiving an EDS diagnosis and having an inpatient hospital admission, which may cause an overestimation of the percentage of people with EDS who are White. Similarly, there is decreased access to the internet in rural and low-income areas in the United States and abroad. This decreased access disproportionately affects minorities within the United States and people of color abroad,

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limiting their participation [31,32]. Big data studies using national health records in predominantly White northern European countries did not report race or ethnicity demographics [4,12,13]. Our high percentage of White participants was likely driven by recruitment from the United States, where structural inequities affect access to care, as well as northern European countries that have predominantly White populations. The lack of access to care and doctors who diagnose EDS outside of North America and Europe [19] likely limits the pool of people from these areas who meet the inclusion criteria of an EDS diagnosis, and therefore, may have impacted the diversity of our study. Similarly, due to the changing terminology for hypermobile EDS and hypermobility spectrum disorders, it is important to include participants with both diagnoses, as a participant's diagnosis may vary based on when or where they were diagnosed, as well as what type of health care provider diagnosed them. There needs to be more health care providers that diagnose and treat EDS in countries that are predominately made up of people of color along with research focused on these specific populations. Research in these groups should be facilitated by members of the EDS community from these groups.

Including LGBTQIA+ Communities

Specific EDS support groups for lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual, people, as well as those who not listed but identify as part of this community, were targeted for recruitment; however, we were not permitted to post in a few groups because of cisgendered language in our recruitment materials and survey. Facebook EDS support groups preferred the use of gender-neutral language based on the specific organs needed to participate rather than the terms "woman" and "female." To ensure the study is in line with the EDS communities' values and inclusive of nonbinary individuals, researchers should include community representatives in the development of their study.

Limitations

As with other EDS research, our sample was predominately White and from the United States. We were limited by the lack of support groups in countries that were not predominately White. In future research, non-US support groups should receive more focus than US-specific groups. The use of social media platforms likely varies between countries. A wider variety of social media platforms should be explored for use.

The use of social media platforms likely varies between countries. A wider variety of social media platforms should be explored in future research. Additionally, participants were recruited for this survey in 2019, since then there have been many changes in social media including Twitter changing to X and the rise of TikTok. However, the lack of diversity in EDS research persists even as recruitment on social media increases. Identifying recruiting obstacles can help develop methods to overcome them for more diverse and inclusive research.

The survey was conducted without verification of participants' EDS diagnosis and, therefore, may have included people who have not been diagnosed with EDS. For more rigorous and valid results, a participant's EDS diagnosis should be verified; however, this may be difficult via social media. Recruiting via social media may work best for studies that are exploring new areas of research and identifying new phenomena that can then be followed up with more rigorous methods.

During recruitment, an IRB amendment was needed. Until the amendment was approved, recruitment was paused. When recruitment was paused, prospective participants were still able to see recruitment posts, and this caused some confusion. To mitigate confusion, we edited the posts to explain recruitment was temporarily paused. We posted again when recruitment resumed. Commenting on the post that recruitment was live again should have brought the post back up to the top of feeds.

Conclusions

Social media is effective and efficient at recruiting people with EDS for research studies. Text-based platforms that have established EDS support groups such as Facebook are well-suited for recruiting. Specific attention should be paid to recruiting people outside of the United States. Considerations for research on recruitment of participants with EDS include (1) working with local researchers and communities where you wish to recruit from, (2) posting during peak social media traffic time in target areas, and (3) increasing diagnoses and care of patients, which will increase awareness of EDS outside of the United States and Europe. Working with researchers, clinicians, and advocates in areas with support groups outside of the United States may help researchers gain permission to post in groups in these regions and provide guidance on where best to recruit people in their area, as well as ensure survey materials are in line with the EDS community's values. Posting during peak traffic for people outside of North America may help recruit a more global sample. There is still little research on people with EDS outside of the United States and Europe. To engage participants outside of these regions, research materials may need to be translated into other languages. A repository of tools used to evaluate written materials related to EDS in many languages would make it easier for researchers to recruit participants who speak different languages, as well as make results easier to compare across studies. A larger issue may be a lack of EDS providers and researchers in countries outside of the United States and Europe. Research needs to be conducted examining the prevalence of EDS in these areas along with increasing awareness of the condition. Recruiting people with EDS in countries where there are few if any health care providers who diagnose and treat EDS will remain a challenge until awareness of EDS grows and care improves.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

EDS: Ehlers-Danlos syndrome
IRB: institutional review board
PI: primary investigator

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Protocol

A Community Mental Health Integrated Disaster Preparedness Intervention for Bushfire Recovery in Rural Australian Communities: Protocol for a Multimethods Feasibility and Acceptability Pilot Study

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Abstract

Background: Natural hazards are increasing in frequency and intensity due to climate change. Many of these natural disasters cannot be prevented; what may be reduced is the extent of the risk and negative impact on people and property. Research indicates that the 2019-2020 bushfires in Australia (also known as the “Black Summer Bushfires”) resulted in significant psychological distress among Australians both directly and indirectly exposed to the fires. Previous intervention research suggests that communities impacted by natural hazards (eg, earthquakes, hurricanes, and floods) can benefit from interventions that integrate mental health and social support components within disaster preparedness frameworks. Research suggests that disaster-affected communities often prefer the support of community leaders, local services, and preexisting relationships over external supports, highlighting that community-based interventions, where knowledge stays within the local community, are highly beneficial. The Community-Based Disaster Mental Health Intervention (CBDMHI) is an evidence-based approach that aims to increase disaster preparedness, resilience, social cohesion, and social support (disaster-related help-seeking), and decrease mental health symptoms, such as depression and anxiety.

Objective: This research aims to gain insight into rural Australian’s recovery needs post natural hazards, and to enhance community resilience in advance of future fires. Specifically, this research aims to adapt the CBDMHI for the rural Australian context and for bushfires and second, to assess the acceptability and feasibility of the adapted CBDMHI in a rural Australian community.

Methods: Phase 1 consists of qualitative interviews (individual or dyads) with members of the target bushfire-affected rural community. Analysis of these data will include identifying themes related to disaster preparedness, social cohesion, and mental health, which will inform the adaptation. An initial consultation phase is a key component of the adaptation process and, therefore, phase 2 will involve additional discussion with key stakeholders and members of the community to further guide adaptation of the CBDMHI to specific community needs, building on phase 1 inputs. Phase 3 includes identifying and training local community leaders in the adapted intervention. Following this, leaders will co-deliver the intervention. The acceptability and feasibility of the adapted CBDMHI within the community will be evaluated by questionnaires and semistructured interviews. Effectiveness will be evaluated by quantifying psychological distress, resilience, community cohesion, psychological preparedness, and help-seeking intentions.

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Results: This study has received institutional review board approval and commenced phase 1 recruitment in October 2022.

Conclusions: The study will identify if the adapted CBDMHI is viable and acceptable within a village in the Northern Tablelands of New South Wales, Australia. These findings will inform future scale-up in the broader rural Australian context. If this intervention is well received, the CBDMHI may be valuable for future disaster recovery and preparedness efforts in rural Australia. These findings may inform future scale-up in the broader rural Australian context.

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KEYWORDS

bushfires; wildfires; rural mental health; natural disasters; mental health; disaster preparedness; natural hazards resilience; community interventions; mixed-methods; pilot study; disaster; preparedness; preparation; natural hazard; psychological distress; resilience; help-seeking

Introduction

Background

Due to climate change, natural hazards are increasing in frequency and intensity in Australia [1-4]. Natural hazards are defined as "threatening events, capable of producing damage to the physical and social space where they take place;" a natural hazard becomes a natural disaster when it has "a major impact on society and/or infrastructure" [5]. The 2019-2020 bushfires followed 3 years of intense drought in southern and eastern Australia and lasted nearly 12 months in some parts of the country. The bushfires burned an estimated 60 million acres, destroyed 6000 buildings (mostly homes), were responsible for the deaths of 462 people (33 fire-related and 426 from smoke inhalation) and contributed to the deaths of an estimated 3 billion animals [6-10]. The loss of land, displacement of people, and related myriad direct and indirect impacts of the 2019-2020 bushfires on millions of Australians were unprecedented [1]. Most communities were ill-equipped to cope with the scale of the fires.

The 2019-2020 bushfires resulted in significant psychological distress for both directly and indirectly exposed Australians [11]. Direct exposure to bushfires includes but is not limited to (1) loss of property, infrastructure, livelihood, and life; (2) impact of smoke inhalation on both physical and mental health; and (3) first-hand exposure to bushfire events. The negative impact of direct exposure on psychological well-being is extensively documented [12]. Indirect exposure to bushfires can occur through watching, listening, or reading news reports; witnessing someone being negatively impacted by bushfires; exposure to bushfire content through social media (eg, Instagram and Facebook); and discussions within the community about bushfire events. The impact of indirect exposure on psychological well-being mimics the experiences of those who are directly exposed [13]. Exposure to natural disasters in general can have long-lasting psychological consequences for individuals and their communities. On an individual level, a third to half of the exposed population can experience transient distress following the catastrophic event and a significant proportion may go on to develop chronic psychological conditions such as posttraumatic stress disorder (PTSD), depression, anxiety disorders, substance use, and suicidality [14-17]. Bushfire-specific research on the Ash Wednesday, Black Saturday, and Black Summer bushfires shows that these disorders and elevated psychological distress can persist for years or even decades, with distress directly proportional to bushfire proximity and severity [18-20]. These psychological consequences can be compounded upon repeated exposure to additional traumatic events or stressful life events [21-23].

The more physically prepared individuals are for natural disasters, the less physical and psychological harm they are likely to experience [24]. Yet, evidence suggests that communities and individuals often do not engage in disaster preparedness, even when sufficient education and resources are provided, and even in areas with past hazard exposure [24-27]. It has been found that individuals overestimate their level of preparedness. For example, a US study using national survey data found that 78% of respondents reported being prepared for disasters, whereas only 45% were actually prepared by objective assessment [28]. Preexisting mental health concerns and mental health consequences of prior disaster exposure may also interfere with disaster preparedness [29,30]. Research has shown that community members with poor mental health are less likely to have either an emergency plan or household disaster supplies [29]. Possible explanations for unpreparedness include cognitive and behavioral avoidances, commonly found in PTSD, and a sense of hopelessness, commonly found in depression, as well as procrastination and denial [30].

It is important to address barriers to disaster preparedness and enhance community resilience. Resilience in relation to natural disasters encompasses 3 common themes, first, the ability to absorb or accommodate the stressor or adverse event; second, the ability to recover and return to healthy levels of functioning (and not necessarily predisaster functioning); third, the ability to learn, adapt, or transform in response to disaster exposure [1,31-35]. The Australian Disaster Resilience Index was created to assess disaster resilience in Australia and it was found that most of the population of Australia lived in areas that were assessed as having "moderate" resilience for natural disasters, with "low" disaster resilience observed primarily in remote areas [1]. Most of the Australian population has a "moderate" ability to prepare for, absorb, and recover from natural disasters, and learn to adapt and problem solve. Natural hazards resulting in disasters have the potential to adversely affect the social cohesion of communities, which in turn, is linked with disaster resilience [31]. For example, disasters can rupture social networks within communities, thereby eroding existing social relationships and undermining social support [14,36]. Research

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also indicates that "cognitive social capital" matters, specifically, that lower levels of trust and a diminished sense of belonging are associated with poor mental health in disaster-affected communities [37]. Reciprocal relationships are important as limited social connections following disaster exposure have been associated with an increased risk of PTSD [38]. Taken together, this body of research underscores the importance of social support and community trust as protective factors associated with mental health in disaster-affected settings. Such factors can enhance or diminish community resilience.

Community-based initiatives that encourage collective involvement in mitigation, preparedness, response, and recovery can build resilience to natural hazards. It is preferable for local community leaders to collaborate with community members in developing local preparedness plans and related initiatives, collectively investing in resilience building [25]. Perhaps not surprisingly, studies suggest that disaster-affected communities often prefer the support of community leaders over that provided by health practitioners or other outsiders [39]. Collective community action associated with preparedness may also help to facilitate social cohesion, in turn having a positive impact on individual and collective well-being [40]. In summary, mental health, social cohesion, and disaster preparedness are important factors to address simultaneously through community-based programs to enhance resilience linked to disaster mitigation, preparedness, response, and recovery [30,40,41].

Community-Based Disaster Mental Health Intervention

The Community-based Disaster Mental Health Intervention (CBDMHI) is an evidence-based approach to building community resilience in the face of natural hazards-related disasters. It has been implemented and evaluated with earthquake, hurricane, and flood-affected communities in Haiti and Nepal [25,30,42-44]. In addition to this initiative, it is in the process of being adapted and further tested in India, Turkey, and Syria for disaster-affected populations. The CBDMHI intervention aims to increase disaster preparedness, resilience, community cohesion, and social support (disaster-related help-seeking) and decrease mental health symptoms, such as depression, anxiety, and PTSD. A 3-day manualized version of the CBDMHI intervention is available in English, Haitian Kreyol, and Nepali. Previous research across 3 studies—2 randomized controlled trials and a matched cluster comparison—with disaster-affected communities in Haiti and Nepal support its effectiveness in increasing preparedness and social cohesion and decreasing mental health symptoms [25,30]. The intervention is specifically designed to be adaptable across contexts, cultures, and specific events. Community members are part of this adaptation process and are trained to cofacilitate the intervention. An initial consultation phase is a key component of this adaptation process.

Study Objectives

This project aims to adapt the CBDMHI for the Australian bushfire context to increase community resilience in the face of ongoing bushfire risk. After adapting to the local context and for fires, the aim is to test the adapted intervention in a small-scale pilot study to assess the feasibility, acceptability, and effectiveness of the intervention in 1 rural community to inform potential scale-up for other disaster-affected communities in Australia.

Methods

Study Design

This research uses a sequential multimethods approach. This research is broken into 3 phases that are outlined in Figure 1. Phase 1 assesses the needs of the community to appropriately adapt the CBDMHI. Phase 1 consists of qualitative interviews (individual or dyads) with self-identifying members of a rural community in New South Wales, Australia, aiming to collect information regarding the community's specific bushfire recovery needs. This process will include identifying themes related to disaster preparedness, social cohesion, and mental health. Phase 2 will involve additional discussion with key members of the community to refine the adaptation of the CBDMHI to specific community needs, building on phase I inputs. Local community leaders will be trained to cofacilitate the intervention in the community, which will be piloted in phase 3 of this study. Intervention acceptability, feasibility, and preliminary effectiveness will be assessed via pre- and postintervention individual mental health and community variables, as well as a 6-week follow-up. Acceptability will also be assessed postintervention.

Phase 1 will focus on community consultation and engagement. Community awareness events will be undertaken in the identified community prior to the commencement of the project, to promote the project and obtain community support (eg, phone calls with individuals in the community, face-to-face meetings in the local café to promote the project, and events with the local fire service). Phase 1 will primarily involve data collection through semistructured interviews with open-ended questions. The interviews will explore the impact of the 2019-2020 bushfires on community cohesion, community resilience, and well-being, as well as intervention preferences and perceived needs. Interviews will also focus on community preparedness for the 2019-2020 bushfires and what measures have been taken since that time to prepare for future fires. Questions will focus on current perceived needs related to the fires (at both the individual and community levels), primary stressors (past and current), and ongoing recovery. The data gathered will be used to inform the adaption of the CBDMHI to the local bushfire context.

In phase 2, the CBDMHI will be adapted to meet specific community needs. Data from phase 1 will be analyzed using inductive thematic analysis at the semantic level. The findings of the qualitative analysis will inform the adaptation of the CBDMHI. Adaptation based on community feedback may include the scenarios and group activities so that they are fire and community-specific; the content covered or focused on in the program (ie, the content will be selected to match stated community needs, for example, based on community feedback, there may be more of a focus on household level preparedness than on assisting extremely vulnerable groups within the community); and the length and timing of the program. The adaptation process may also necessitate additional content being added by clinical experts through the inclusion of additional

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psychoeducation or skills training to meet the community's needs. Phase 2 will also involve additional discussion with key members of the community to further refine the adaptation of the CBDMHI to specific community needs. A local advisory group of community leaders and members will be formed for consultation during the adaptation process. Tailored materials for running the program in the local community will be developed.

Figure 1. Study phases. CBDMHI: Community-Based Disaster Mental Health Intervention.

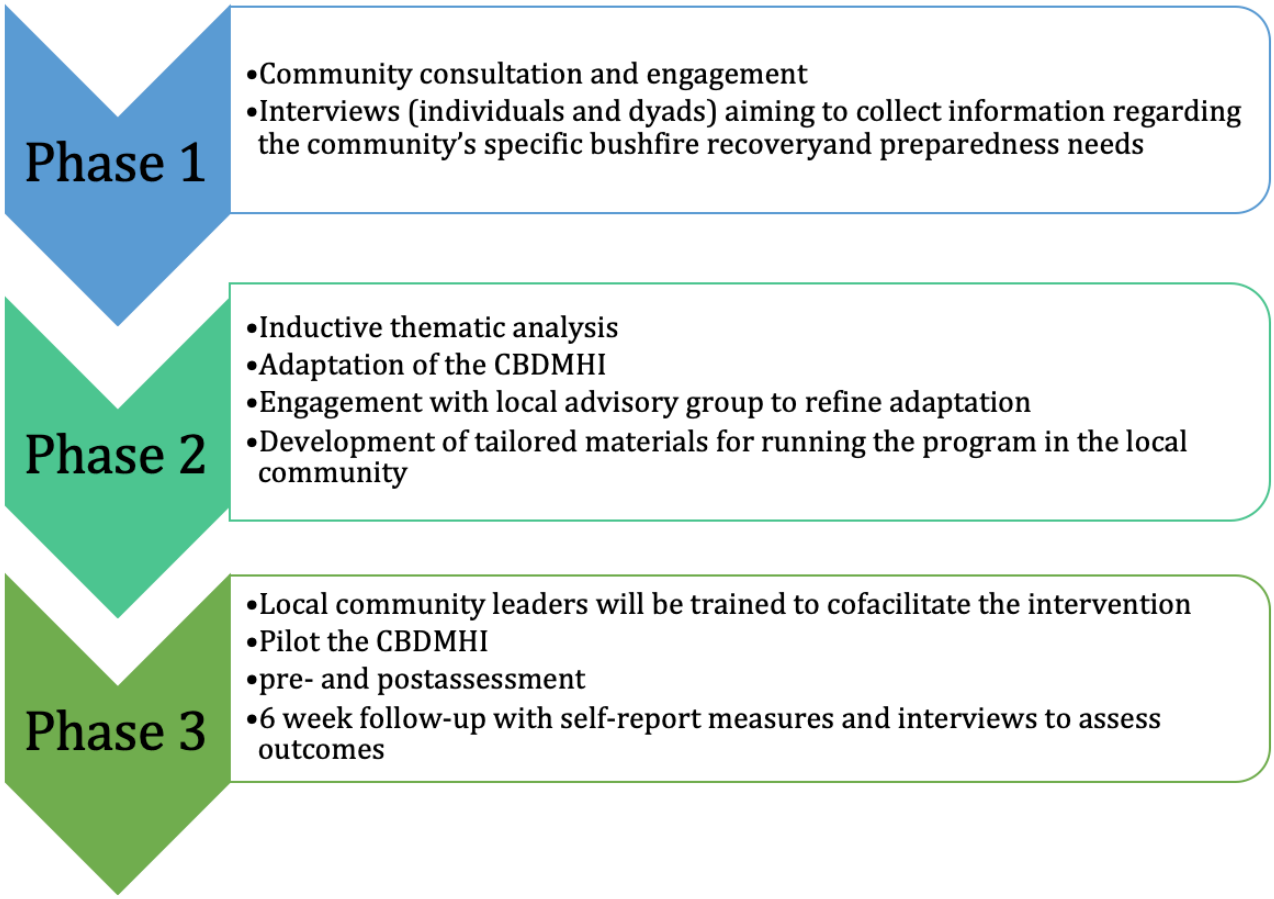

Phase 3 will involve piloting the adapted CBDMHI in the identified rural community. Phase 3 has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) registration (ACTRN12623001023640). As part of this phase, the research team will train local and respected community leaders to administer or co-deliver the adapted CBDMHI. The intervention will consist of facilitated discussion, the space to share personal experiences, the establishment of peer support, the establishment of safety, and learning and practicing coping skills specifically for disaster-related distress. The intervention also provides practical training in disaster preparedness and response techniques that participants can use to support themselves and other community members during future hazards.

Phase 3 of the study will pilot the CBDMHI with residents of the affected community. The pilot intervention will use a pretest and posttest design to assess the acceptability of the intervention, as well as levels of psychological distress, resilience, coping, community cohesion, psychological preparedness, and help-seeking intentions following the intervention. Participants will complete measures before and after the workshop to assess the treatment effectiveness, as well as a 6-week follow-up. Due to the community setting and different availabilities of community members living in rural areas with property and farming obligations, random allocation is unlikely to be possible. Workshop participation and thus treatment implementation will, therefore, be a within-subject design with participants acting as their own controls. Drawing on the results from this study, a framework with Australian bushfire-specific materials will be developed and made available to facilitate broader implementation in the future to support recovery in other fire-affected Australian communities.

Eligibility Criteria

Eligible participants are (1) persons aged 18 years and older, (2) who self-identify as a member of the bushfire-affected community in the Northern Tablelands region of New South Wales, (3) have lived and worked in the community during the fires and continue to reside within the bushfire-affected community, and (4) report having been directly or indirectly impacted by the 2019-2020 bushfires. Direct exposure includes having protected property or livestock; having been evacuated or relocated; experiencing loss of property, family, friends, and livestock; or having served as a firefighter or first responder, including in a volunteer capacity. Indirect exposure includes having heard recounts of the bushfires and their effects on the community secondhand. Ineligible participants are those not fluent in English or individuals who reside outside of the

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recruitment catchment area or are judged by clinicians as under the influence of alcohol or substances or have any other significant impediment to participation.

Proposed Sample

The proposed sample for phase 1 will be determined through informational power [38]. Informational power is based on 5 concepts, aim, specificity, theory, dialogue, and analysis. When informational power is met the sample size will be determined.

The proposed sample for phase 3 is up to 20 participants, which is estimated as more than 15% of the total population of the target community. This target sample size is based on previous adaptations of the CBDMHI that used no more than 20 participants per intervention group [30,42]. This number is also in line with the recommended treatment group size for pilot studies [45].

Recruitment

Phases 1 and 2

Participants will be recruited via advertising within the affected community, including community services, dining venues, and schools. The project will be advertised through partner organizations including the Rural Fire Service (RFS), community groups, and local social media pages, and through community engagement events held with the RFS.

Advertising materials and social media posts will be shareable, permitting recruitment through social contagion and snowball techniques, allowing maximum reach and community representation. The project team will contact individuals who registered their interest by phone and email to confirm eligibility and schedule interviews. Participation will not be incentivized.

Phase 3

This phase is open to any of the phase 1 participants, as well as any other persons residing or working in the catchment area (as per the eligibility criteria). Recruitment will occur through advertising within the target community including through the mentioned partner organizations, community services, community groups, and social media pages, and during local community events.

Intervention

The CBDMHI is a manualized intervention that is culturally adaptable to disaster-affected communities [42]. Prior to the intervention, the research team will select and train local community leaders to deliver the modified CBDMHI. The CBDMHI will be modified in content and length based on the local communities' needs and availability. The main objectives of the CBDMHI are to increase disaster preparedness (physical and psychological), community cohesion, resilience, and social support (disaster-related help-seeking), and decrease mental health symptoms, such as depression, anxiety, and PTSD.

Outcomes

Measures

Participants in phase 3 of this research will complete a range of self-report measures prior to the intervention, at completion of the intervention, as well as a 6-week follow-up to assess durability. Measures will be collected via an anonymous survey completed in person with trained assessors pre- and postintervention and follow-up measures will be emailed along with reply paid envelopes. To link pre- and posttest questionnaire results, participants will be assigned a unique identifier.

Acceptability

Acceptability of the intervention will be measured using Likert-style and open-ended questions. The Likert-style questions will be scored using a 5-point Likert scale ranging from "strongly disagree" to "strongly agree," with higher scores indicating higher acceptability. Open-ended questions (eg, "what did you like about the workshop?") will also be used to measure acceptability. Participants will also be invited to take part in an optional follow-up semistructured interview to assess acceptability and perceived unhelpfulness.

Psychological Distress

Psychological distress will be measured using the Kessler Psychological Distress Scale (K10) [46]. The K10 is a 10-item questionnaire based on questions about anxiety and depressive symptoms that an individual has experienced in the previous 4 weeks. The K10 is based on a 5-point Likert scale, with responses ranging from "none of the time" to "all of the time." The maximum score is 50 (indicating severe distress, likely to have a severe disorder), and the minimum score is 10 (indicating low distress, likely to be well). The K10 has demonstrated favorable discriminant validity and internal consistency [47].

Resilience

Resilience will be assessed through the Brief Resilience Scale (BRS), which aims to assess an individual's ability to bounce back or recover from stress [48]. The BRS is scored on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" and consists of 6 items. Item scores are summed and then divided by 6, so that mean scores range from 0 to 6. Mean scores of 1.00 to 2.99 reflect low resilience, 3.00 to 4.30 reflect normal resilience and 4.31 to 6.00 reflect high resilience. The BRS is a reliable measure of assessing resilience [48].

Social Cohesion

Social cohesion will be measured using items adapted from Sampson et al [49]. The adapted measure consists of 5 questions asking respondents to rate neighborhood's perceived closeness of residents, willingness to help, trust, conflict, and values. The 5 items are each scored on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" [49]. Total scores range from 5 to 25, with higher scores representing a higher sense of community.

Help-Seeking

The help-seeking intention will be measured using 2 adapted items from the CBDMHI developers [30] that ask respondents "Would you be comfortable seeking help from others if you were experiencing sadness, stress or burnout?" and "Would you be comfortable seeking help from others if you needed something to prepare for or in the aftermath of a disaster?" Response options are scored on a 4-point scale ranging from "I would not be comfortable at all" to "I would be very

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comfortable." Total scores range from 2 to 8, with higher scores representing higher help-seeking intention.

Coping

Coping will be measured using an adapted version of the Brief-Coping Orientation to Problems Experienced Inventory (Brief-COPE) [50]. The adapted coping measure consists of 4 questions targeting acceptance, denial, self-distraction, and solution-focused coping. Items are scored on a 5-point Likert scale ranging from "None of the time" to "All of the time." Higher scores represent higher engagement in a given coping style, and are, therefore, evaluated as individual items.

Psychological Preparedness

Psychological preparedness will be measured using the Psychological Preparedness for Disaster Threat Scale (PPDTS) [51]. The PPDTS is a self-report questionnaire that consists of 18 items, each scored on a 4-point Likert scale ranging from "not at all true of me" to "exactly true of me" [51]. Higher scores represent higher perceived psychological preparedness [51].

Planned Data Analysis

Descriptive statistics will be provided for demographic data. Phase 1 community consultation interview data will be analyzed using thematic analysis [52] to explore participants' physical, psychological, social, and environmental needs following the 2019-2020 bushfires. Inductive thematic analysis has been selected for this study as it is a useful qualitative approach for applied research designs [53]. Thematic analysis provides a flexible yet robust, systematic framework for coding data and has been used widely in the health sciences [53]. Data analysis will involve an iterative process including familiarizing oneself with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report [52,54].

One-way repeated measures ANOVAs will be performed for phase 3 outcome measures to identify any changes in pre- and postintervention outcomes, and whether those changes were maintained up to 6 weeks. Multilevel mixed models nested in time may also be used, as these analyses are more robust to missing data and can be used to model change trajectories over time. Where a change in score across time points is identified, the reliable change index will be used to assess the clinical significance of this change to provide further insight into the clinical meaningfulness and use of the program.

Ethical Considerations

Phases 1 and 3 of this study were approved by the University of New England Human Research Ethics Committee (HE22-120 and HE23-083, respectively). Written or recorded informed consent will be obtained from the participants before inclusion in either phase of the study. Study data will be deidentified and any potentially identifiable information will be removed from any published materials to ensure privacy. Participants will be reimbursed for their time through meals and hot drinks being offered during interviews, and through opportunities for participants to win vouchers to local businesses (eg, local café and pub). Study participants are free to withdraw at any time without providing a reason.

Results

Data collection commenced following support from the Black Summer Recovery Grant Scheme. As of January 2023, more than 10% of the identified rural community in the Northern Tablelands has participated in phase 1 interviews. These interviews have been transcribed and a thematic analysis of the data is currently taking place. As of September 2023, a total of 10 rural community members participated in the phase 3 intervention. Follow-up data were collected in November 2023, and the first results are to be submitted for publication in 2024.

Discussion

Overview

The predicted rise in frequency and intensity of extreme weather events underscores the importance of disaster preparation and resilience. Australia has been assessed as currently having a "moderate" level of resilience, with "low" resilience in many rural areas [1], underscoring the critical need for resilience interventions in Australia. Community involvement in recovery positively impacts community resilience, and resilient communities are less vulnerable to the negative effects of natural hazards [32]. The CBDMHI is valuable as it is community-focused and aims to keep the knowledge and skills within the local community. The development of the CBDMHI means that community needs have to be ascertained before the intervention can be adapted, adding to the growing research and literature surrounding natural hazards, preparedness, and mental health in rural Australia. By using community consultation and an advisory group of community members in phases 1 and 3, it is anticipated that acceptability will be high. The local advisory group can also aid in the feasibility of the intervention by ensuring that its design facilitates the participation of community members and reduces barriers to access.

Comparison With Prior Work

Previous research has found that the adapted CBDMHI resulted in increased disaster preparedness (both physical and psychological), community cohesion, social support (disaster-related help-seeking), and resilience and a decrease in psychological distress. Targeting both preparedness and mental health has direct effects on individual and community variables that are also mediated by both mental health training and preparedness training [42]. The CBDMHI will include coping skills and preparedness training to alleviate psychological distress associated with bushfires and to try to increase preparedness for future bushfires. It is hoped that the participants of this pilot study will experience similar benefits to previous communities who have used the CBDMHI. It is hoped that the adapted intervention will decrease psychological distress and increase resilience, coping, community cohesion, psychological preparedness, and help-seeking intentions following the intervention.

Adaptations to the CBDMHI are likely to include bushfire-specific preparedness techniques and be more specific to the Australian context and the cultural makeup of rural communities. If the adapted CBDMHI is feasible and acceptable

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in this rural Australian community, it will provide a framework for other adaptations to disaster- and fire-affected communities within Australia. For instance, the adapted CBDMHI could be tested and evaluated with other communities affected by bushfires. It could also be further adapted and tested with communities affected by major flood events, such as the Northern Rivers region of New South Wales in Australia, which experienced several major floods within the same calendar year (2022) [55].

Limitations

While improvements in target outcomes are likely to increase the community's resilience and preparedness for future disasters, this study is proposed with several limitations. First, the sample size is small and potentially only viable for a pretest and posttest design. In the context of the identified rural Australian community, the intervention may reach 10%-50% of the region's population, with the small village size and sparse population limiting the feasibility of controlled trials or multiple baseline designs. Further, the intervention findings may not generalize to other regions or other natural hazard events. Even if the adapted CBDMHI is effective and feasible, the findings will require replication with other rural communities and those exposed to other hazards. Second, the length of the follow-up on this study is 6 weeks. While this is appropriate to gain insight into whether the effects of the intervention are maintained over time, the research would be strengthened by having longer follow-up times to better assess the durability of the intervention. Finally, document review was not used as complementary data collection. Having document review alongside the interview and quantitative analysis may have provided more insight into resilience and preparedness in Australian communities helped with cross-verification of community experiences and mitigated against selection bias. Future research could consider this option for data collection at study commencement.

Conclusions

This protocol describes a multimethods pilot feasibility study focused on adaptation of a previously successful postdisaster intervention, which has been shown to effectively increase disaster preparedness, reduce psychological distress, and improve social cohesion in affected communities in Haiti and Nepal [25,30]. To date, psychological interventions in the Australian bushfire context have focused on providing low-level psychological support to reduce and prevent the development of psychological disorders (eg, Skills for Life Adjustment and Resilience [SOLAR]) and have been piloted with a small sample in the Victorian community [56]. The proposed study differs in that it will integrate mental health in a standard disaster preparedness training, work in partnership with the RFS, use locally based community trainers, and be delivered in a community-based setting. These differences may allow for a realistically scalable intervention for rural communities that are often the most negatively affected by particularly severe bushfire seasons.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ANZCTR: Australian New Zealand Clinical Trials Registry
Brief-COPE: Brief-Coping Orientation to Problems Experienced Inventory
BRS: Brief Resilience Scale
CBDMHI: Community-Based Disaster Mental Health Intervention
K10: Kessler Psychological Distress Scale
PPDTS: Psychological Preparedness for Disaster Threat Scale
PTSD: post-traumatic stress disorder
RFS: Rural Fire Service
SOLAR: Skills for Life Adjustment and Resilience

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Protocol

Quality of Life in Patients and Their Spouses and Cohabitating Partners in the Year Following a Cancer Biopsy (the Couples Cope Study): Protocol for a Prospective Observational Study

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Abstract

Background: Receiving a diagnosis of cancer is a profound and often very stressful experience. Few studies have prospectively recruited patients prior to receiving a new diagnosis of cancer and included spouses or partners.

Objective: The aim of the Couples Cope Study is to understand the impact of undergoing a diagnostic biopsy and receiving a new cancer diagnosis on quality of life (QoL) in both patients and their spouses or partners, as well as on the quality of their relationship. This protocol paper describes the study design and assesses the feasibility of recruitment and retention.

Methods: Study staff reviewed the schedules of collaborating physicians using specific encounter codes to identify patients scheduled for breast or prostate biopsies. Potential participants were prescreened via the electronic health record and sent a recruitment letter at least 2 to 3 weeks prior to their biopsy procedure. Patients subsequently underwent a phone screening to determine eligibility. Patients who enrolled provided study staff with contact information for their spouses or partners. All consent forms were completed online. Surveys were completed online prior to receiving the biopsy results (baseline), and at 1, 3, 6, and 9 months after the biopsy. Study staff engaged in ongoing, personalized contact with participants and sent assessment completion reminders via phone and email.

Results: A total of 2294 patients undergoing a breast or prostate biopsy were identified and 69% (n=1582) were eligible for phone screening following electronic health record prescreening. Of the 431 patients who underwent phone screening, 75% (n=321) were eligible to participate. Of the eligible patients, 72% (n=231) enrolled and 82% (n=190) of enrolled patients had an accompanying partner or spouse who also enrolled. A total of 77% (34/44) of patients who received a cancer diagnosis and 72% (26/36) of their spouses or partners were retained through 9 months, while 80% (53/66) of patients who received a benign diagnosis and 68% (42/62) of their partners were retained.

Conclusions: Prospective recruitment of patients undergoing diagnostic biopsy and their partners is feasible and requires both strategic collaboration with providers and concerted prescreening and recruitment efforts by study staff. Importantly, this study

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was able to conduct all study activities online without disrupting clinical workflow and without requiring patients and their spouses or partners to come into the laboratory. Consideration should be given to the ratio of biopsies to cancer diagnoses, which can vary significantly by cancer type. Prospective studies are needed and can inform our ability to provide effective support earlier to couples facing a possible cancer diagnosis. Future studies should examine other tumor types that have received less attention in QoL studies, include behavioral and neurobiological assessments beyond self-report measures, and follow couples beyond 9 months in order to examine long-term effects on QoL.

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KEYWORDS

quality of life; cancer; biopsy; couples; dyads; caregiver; patients; patient; cancer biopsy; spouse; spouses; partner; partners; diagnostic; diagnostic procedure; feasibility of recruitment; recruitment; prostate biopsy; breast biopsy; screening; electronic health record; survey; surveys

Introduction

Overview

Receiving a diagnosis of cancer is a profound and often very stressful experience. A new diagnosis of cancer introduces uncertainty and distress as individuals navigate treatment decisions, experience disruptions to social or occupational roles and routines, and undergo arduous treatments such as surgery, radiation, and chemotherapy [1,2]. Individuals who are newly diagnosed with cancer commonly experience decrements in quality of life (QoL) and are at elevated risk for psychological and physical symptoms, including anxiety, depressed mood, fatigue, and pain [1,3,4]. A cancer diagnosis and its subsequent treatment significantly impact not only patients but also their spouses and romantic partners. Spouses or partners are by far the most common informal cancer caregivers, helping patients manage disease symptoms, treatment side effects, and emotional distress [5]. However, caregiving in the cancer context is associated with well-documented risks to psychological and physical health [5-13].

Despite the fact that the impact of cancer extends well beyond the patient, and that patient and caregiver well-being are closely linked and reciprocally influence each other [14-20], few studies incorporate the assessments of spouses or partners or examine how both patients and their spouses or partners report cancer has affected the quality of their relationship. Furthermore, although there is widespread interest in prospective research on QoL following a cancer diagnosis, there is a paucity of non-epidemiological studies that have prospectively recruited patients prior to receiving a new diagnosis of cancer [21-26]. A 1998 study by Northouse et al [27] recruited couples prior to a woman's diagnostic breast biopsy and examined psychosocial adjustment to either a malignant or benign diagnosis at 60-day and 1-year follow-ups. Results demonstrated that couples who received a breast cancer diagnosis reported worse psychosocial adjustment and a greater decrease in marital functioning than couples who received a benign diagnosis. Furthermore, psychosocial adjustment was highly interrelated between women with breast cancer and their spouses. To our knowledge, since this landmark study 25 years ago, no study has prospectively examined trajectories of QoL among both patients and their spouses or partners from prior to a diagnostic biopsy through the year following a malignant or benign diagnosis.

Couples Cope Study

The goal of the Couples Cope Study is to understand the impact of undergoing a diagnostic biopsy and receiving a new cancer diagnosis on QoL in both patients and their spouses or partners, as well as on the quality of their relationship. Using a prospective observational study design and quantitative approaches that model actor-partner effects, we will examine predictors and trajectories of QoL, individual well-being, and relationship quality and functioning among couples who undergo a cancer biopsy. Patients and their spouses or partners will be recruited prior to a breast or prostate biopsy and complete follow-up assessments for 9 months after the biopsy. Comprehensive assessments will include multiple domains of QoL, such as psychosocial adjustment, social well-being, sexual functioning, symptom burden, and physical functioning. Couples will be stratified into 2 groups based on biopsy result (ie, malignant vs benign). The aim of this study is to describe the Couples Cope Study protocol and examine the feasibility of recruitment and retention of patients undergoing diagnostic biopsy and their spouses or partners.

Methods

Overview of Study Design

This is a prospective, nontherapeutic observational study of patients undergoing a diagnostic biopsy for prostate or breast cancer and their spouses or partners. Participants completed a baseline assessment prior to receiving the biopsy result and follow-up assessments at 1, 6, and 9 months after the biopsy, as well as daily diary assessments over a 1-week period at 3 months after the biopsy (Figure 1). Data were collected between April 2018 and November 2020. Study procedures were not altered in response to the COVID-19 pandemic as the study design included only remote contact with participants.

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Figure 1. Participant flow diagram for patients and cohabitating partners or spouses; baseline and 1-, 3-, 6-, and 9-month follow-ups.

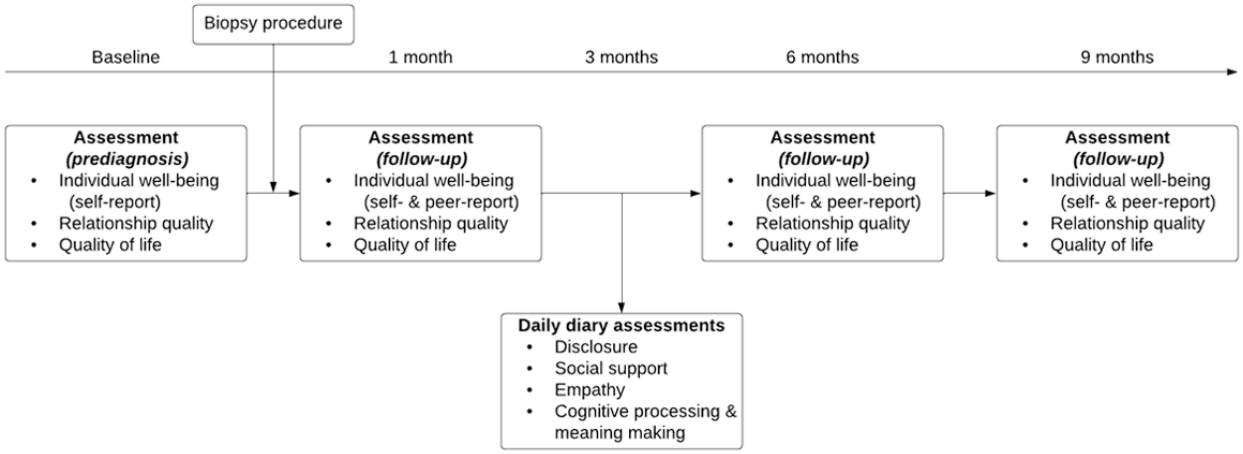

Ethical Considerations

All study procedures were reviewed and approved by the institutional review board at the Northwestern University Feinberg School of Medicine (STU00206691). All participants provided informed consent prior to participation via an electronic consent form. Survey data are stored in encrypted form on Northwestern University Feinberg School of Medicine computers on its corresponding secure, password-protected server. Prior to analysis, data were deidentified and stripped of all relevant personal health information. Participants were compensated US $10 for the baseline assessment, US $20 for each follow-up assessment (3 in total), and US $5 for each daily diary assessment (7 in total), for a possible total of US $105 per participant. The payment was dispensed in the form of a prepaid Visa debit card.

Inclusion and Exclusion Criteria

Patients and their spouses or partners were eligible if they were aged 18 years or older, married or cohabitating, able to speak and read in English, had access to the internet via at least 1 web-enabled device (eg, computer, tablet, or smartphone), and undergoing a diagnostic biopsy for prostate or breast cancer (patients only). Patients were ineligible if they had a previous cancer diagnosis (except nonmelanoma skin cancer like basal cell carcinoma), evidence of distant metastasis (stage IV cancer), inpatient psychiatric treatment in the past 6 months, and were unable to consent.

Recruitment and Enrollment

Authorized study staff reviewed the schedules of collaborating Northwestern Medicine physicians in the Department of Urology and Lynn Sage Comprehensive Breast Center using specific encounter codes to identify patients scheduled for breast or prostate biopsies. The encounter codes used for prescreening via physicians' electronic schedules were (1) "biopsy" for patients with prostate cancer and (2) either "US guided breast biopsy core" or "mamo stereo core ndl bx." Potential participants were prescreened via the electronic health record (EHR) and sent a recruitment letter that introduced the study along with the study flyer at least 2 to 3 weeks prior to their biopsy procedure. Approximately 1 week after receipt of the recruitment letter, study staff called patients to provide additional information about the study and screened patients to assess their eligibility over the phone. Patients who were eligible and enrolled, provided study staff with their own contact information and that of their spouse or partner. If a patient and his, her, or their spouse or partner were determined to be eligible following phone screening, study staff sent each potential participant an email with a link to the online consent form and the baseline assessment. Study staff reviewed the consent form, including all study procedures, with potential participants on the phone in order to ensure understanding and respond to any questions or concerns. Completion of the online consent form allowed participants to proceed to the baseline assessment.

Assessments

Baseline and follow-up study assessments, including variable domains and measures, time points, and sources of data, are described in Multimedia Appendix 1 [28-48]. All surveys were completed online. If patients received a malignant biopsy result (ie, cancer diagnosis), patients and their spouses or partners completed follow-up assessments at 1, 6, and 9 months after the biopsy, as well as daily diary assessments over a 1-week period at 3 months after the biopsy. If patients received a benign biopsy result (ie, no cancer diagnosis) and were among the first 80 couples to enroll in the study, patients and their spouses or partners completed follow-up and daily diary assessments across the same time frame. After the first 80 couples, patients who received a benign biopsy result and their spouses or partners completed only the baseline assessment.

The baseline assessment captured medical and sociodemographic characteristics (eg, age, sex, gender identity, marital status, parental status, race, ethnicity, relationship length, education, and income). EHRs were also reviewed by study staff in order to capture diagnostic biopsy results and, if applicable, cancer stage and cancer treatments (eg, surgical resection, radiation, chemotherapy, and hormone therapy). Both baseline and follow-up assessments included measures of individual well-being (ie, gratitude, empathy, meaning and purpose, attachment style, relatedness, and social support), relationship quality (ie, relationship quality and social constraints), and QoL (ie, depressive symptoms, positive and

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negative affect, life satisfaction, stressful life events, financial toxicity, and sexual functioning). Follow-up questionnaires also included peer reports of specific measures of individual well-being (ie, participants reported their perception of their spouses' or partners' gratitude, empathy, and meaning and purpose). Cancer-specific measures of health-related QoL and symptom burden, intrusive thoughts and avoidance, and supportive care needs were included in follow-up questionnaires only for patients who received a cancer diagnosis. The baseline and follow-up questionnaire batteries were expected to take approximately 30 and 50 minutes to complete, respectively.

Daily diaries assessed dyadic processes (ie, disclosure, social support [general, emotional, informational, instrumental, and cancer-specific], empathy, and cognitive processing and meaning-making) using items adapted from previous studies [49-51]. Daily diary assessments, including variable measures and response options, are described in Table 1. Daily diaries were expected to take 5 minutes or less to complete.

Table 1. Daily diary assessments at 3-month follow-up for patients and cohabitating partners or spouses.

Variable and measure	Response options	Respondents
Disclosure		
"Did you discuss stressful or negative events with your romantic partner today?"	Yes or no	All participants
(If yes) "Was it about your cancer diagnosis/treatment?"	Yes or no	Patients with cancer
(If yes) "Was it about your experience caregiving or your partner's cancer diagnosis?"	Yes or no	Spouses or partners of patients with cancer
Social support		
"How much support did your partner provide today?"	0=none, 1=a little, 2=some, 3=quite a bit, and 4=a lot	All participants
"How much comfort/reassurance did your partner provide?" (emotional support)	0=none, 1=a little, 2=some, 3=quite a bit, and 4=a lot	All participants
"How much advice/information did your partner provide?" (informational support)	0=none, 1=a little, 2=some, 3=quite a bit, and 4=a lot	All participants
"How much help/assistance did your partner provide?" (instrumental support)	0=none, 1=a little, 2=some, 3=quite a bit, and 4=a lot	All participants
"How much did your partner help you cope with your cancer experience or other stressful events today?" (cancer-specific support)	0=none, 1=a little, 2=some, 3=quite a bit, and 4=a lot	Patients with cancer and their spouses or partners
Empathy		
"How empathic or caring was your partner toward you today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	All participants
Cognitive processing and meaning making		
"To what extent did you actively reflect on your cancer experience or stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Patients with cancer
"To what extent did you try to understand or make sense of your cancer experience or stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Patients with cancer
"To what extent did your cancer experience or stressors make you think about what is important and the meaning in your life today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Patients with cancer
"To what extent did you actively reflect on your cancer experience or stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Spouses or partners of patients with cancer
"To what extent did you try to understand or make sense of your cancer experience or stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Spouses or partners of patients with cancer
"To what extent did your cancer experience or stressors make you think about what is important and the meaning in your life today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Spouses or partners of patients with cancer
"To what extent did you actively reflect on your stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Benign biopsy patients and their spouses or partners
"To what extent did you try to understand or make sense of your stressors today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Benign biopsy patients and their spouses or partners
"To what extent did your stressors make you think about what is important and the meaning in your life today?"	0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, and 4=extremely	Benign biopsy patients and their spouses or partners

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Retention Strategies

Strategies to optimize engagement and retention included reminder calls, text messages, and emails prior to upcoming assessments (tailored according to participants' preferences) and providing participants with study contact phone numbers and emails to facilitate communication and accessibility. Flexible questionnaire administration online also eliminated the need for participants to travel to in-person assessments. In addition, our study team sent holiday cards that were personally signed by the principal investigators and lead study coordinator.

Results

As seen in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 2), 2294 patients undergoing a breast or prostate biopsy were identified and prescreened in the EHR. Of those prescreened in the EHR, 69% (n=1582) were eligible for subsequent phone screening and 31% (n=712) were ineligible. Common reasons for patient ineligibility in EHR prescreening included a previous diagnosis of prostate (n=162), breast (n=223), or other (n=149) cancer or not being partnered (n=121). Of the 1582 patients eligible for phone screening, 27% (n=431) underwent phone screening, 13% (n=198) declined phone screening, and 60% (n=953) were unable to be reached. Common reasons for declining phone screening included not being interested in research (n=77), not having time (n=31), and feeling too stressed (n=10). Of the 431 patients who underwent phone screening, 75% (n=321) were eligible to participate and 25% (n=110) were ineligible. Common reasons for patient ineligibility in phone screening included a previous diagnosis of prostate (n=15), breast (n=15), or other (n=18) cancer or not being partnered (n=46). Of the 321 eligible patients, 72% (n=231) enrolled and 82% (n=190) of the enrolled patients had an accompanying spouse or partner who also enrolled.

Figure 2. CONSORT diagram for Couples Cope Study protocol. A prospective, nontherapeutic observational study of patients undergoing a diagnostic biopsy for prostate or breast cancer and their spouses or partners. bx: biopsy; ca.: cancer; CONSORT: Consolidated Standards of Reporting Trials; dx: diagnosis; EHR: electronic health record; hx: history; prev.: previous.

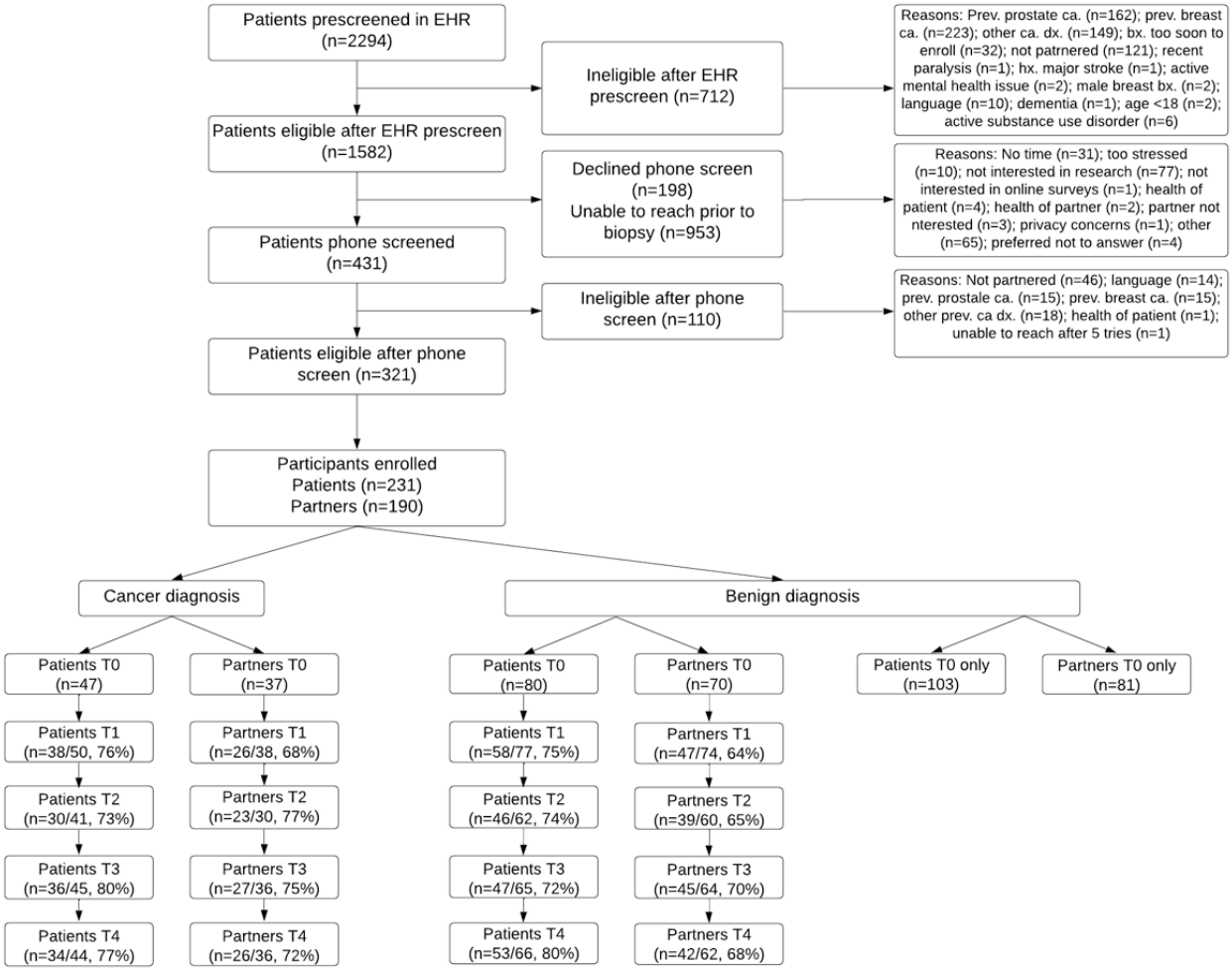

On average, patients who enrolled were 50.4 years old (SD 12.5; min: 20, max: 80) and their spouses or partners were 50.8 years old (SD 11.8; min: 21, max: 85). Patients were primarily non-Hispanic White (81%) with some representation of Asian (9%), Black (7%), multiracial (2%), and Native American (<1%) patients. Additionally, 7% of patients were Hispanic. Similarly, spouses or partners were primarily non-Hispanic White (78%) with some representation of Black (8%), Asian (7%), multiracial (4%), and Native American (<1%) spouses or partners. Additionally, 6% of spouses or partners were Hispanic.

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Approximately 2% of patients and 4% of spouses or partners identified as sexual or gender minorities. More patients underwent breast biopsies (73%) than prostate biopsies (27%). However, 46% of those undergoing a prostate biopsy received a cancer diagnosis, while only 12% of those undergoing a breast biopsy received a cancer diagnosis. A total of 77% (34/44) of patients who received a cancer diagnosis and 72% (26/36) of their spouses or partners were retained throughout the 9-month follow-up assessment, and 80% (53/66) of patients who received a benign diagnosis and 68% (42/62) of their spouses or partners were retained through the 9-month follow-up assessment.

Discussion

Principal Findings

The goal of the Couples Cope Study is to understand the impact of undergoing a diagnostic biopsy and receiving a new cancer diagnosis on QoL in both patients and their spouses or partners, as well as on the quality of their relationship. Our preliminary data demonstrate that prospective recruitment of patients undergoing diagnostic biopsy and their spouses or partners is feasible and requires both strategic collaboration with medical providers and concerted prescreening and recruitment efforts by study staff. The majority of patients who underwent phone screening were eligible to participate (72%) and most patients who were eligible to participate actually enrolled (75%). Furthermore, most patients who enrolled had an accompanying spouse or partner who also enrolled (82%). Retention through the study duration was also generally good and was higher among patients with either a malignant or benign biopsy result (77%-80%) and spouses or partners of patients with cancer (72%) than spouses or partners of patients with a benign biopsy (68%).

Importantly, the design of the Couples Cope Study allowed us to conduct all study activities remotely (either via phone or online) without disrupting clinical workflow and without requiring patients and their spouses or partners to come into the laboratory. Previous studies that have prospectively recruited patients prior to receiving a new diagnosis of cancer have primarily relied on in-clinic recruitment by physicians or medical or research staff [22-26]. These approaches are resource-intensive and can disrupt clinical workflows during sensitive medical appointments. In fact, patients with cancer are more likely to enroll in a research study when they are contacted at home [52]. Given that these factors of convenience influence enrollment, online recruitment and participation in prospective studies may be desirable alternatives to in-person approaches with people faced with a possible cancer diagnosis.

The most resource-intensive aspect of recruitment for this study was the EHR prescreening and outreach for phone screening. Even though most patients were eligible for phone screening after the EHR prescreening (69%) and only a minority of patients actively declined phone screening (13%), stress and the short time frame between scheduling a diagnostic biopsy and the completion of the procedure most likely contributed to our inability to reach a large portion of patients who were eligible for phone screening prior to their biopsy (60%). Furthermore, consideration should be given to the ratio of biopsies to cancer diagnoses, which can vary significantly by cancer type. In our sample, almost half of the patients undergoing a prostate biopsy received a cancer diagnosis, while approximately 1 in 8 patients undergoing a breast biopsy received a cancer diagnosis.

Strengths

The strengths of this study include comprehensive psychosocial assessments that incorporate measures of both distress and symptom burden, as well as protective factors like positive affect and social support. An additional strength is the use of multimodal measurement, including daily diary sampling to examine dyadic processes as predictors or mechanisms of QoL and peer-reported measures of individual well-being to examine observability and convergent validity. Our assessment of relationship quality in both patients and their spouses or partners will allow us to capture each member's perspective and examine correspondence in evaluations of relationship quality. Correspondence (or lack thereof) may provide a unique indicator of relationship dynamics, which may also predict QoL. A prospective design that includes a baseline assessment prior to biopsy allows us to predict QoL based on individual and relational protective and risk factors present prior to a cancer diagnosis and reduce the recall bias inherent in retrospective measures. Furthermore, we include a comparison group of patients who undergo a cancer biopsy but receive a benign result (ie, no cancer diagnosis) and their spouses or partners. Although it is likely that patients with cancer and their spouses or partners will demonstrate greater decrements in QoL than couples in our benign biopsy comparison group, patients who receive a benign biopsy result and their spouses or partners may also experience some impact as a result of the mortality salience related to a "cancer scare."

Limitations

Limitations include primary reliance on clinic-based recruitment in 1 academic medical center in a metropolitan city, which constrains generalizability including racial or ethnic representation. Furthermore, we focused exclusively on patients undergoing breast or prostate biopsies, which are 2 of the most common cancers. Future research should focus on other tumor types that have received less attention in QoL studies. We also recommend that future researchers who are interested in interrogating adaptation to adversity among couples also consider including behavioral and neurobiological assessments in addition to self-report measures. This study included a 9-month follow-up period, which was chosen to feasibly complete recruitment and assessments within the 2-year grant period. Furthermore, in order to retain sufficient resources to enroll and follow as many couples who received a malignant biopsy result as possible, we were not able to longitudinally follow all couples who received a benign biopsy result. Therefore, more prospective studies are needed with follow-up schedules beyond the first year after a biopsy result, specifically among couples who receive benign biopsy results. Finally, although it is important to understand how individual and relational functioning prior to biopsy predicts QoL following a diagnosis, we acknowledge that this assessment time point is not a true baseline of functioning as patients are undergoing

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biopsy as a result of abnormal screening findings and symptomatic presentation (of which they and their spouses or partners are aware).

Conclusions

A cancer diagnosis is a profound and often very stressful experience for both patients and their partners. Spouses and partners are by far the most common informal cancer caregivers, helping patients manage disease symptoms, treatment side effects, and emotional distress. To our knowledge, the Couples Cope Study is the first study to prospectively examine QoL among both patients and their spouses or partners from the moment prior to a diagnostic biopsy through the year following a malignant or benign diagnosis. The results of this study will address a crucial gap in the literature and contribute to our understanding of how individual well-being and relationship quality contribute to QoL outcomes among couples facing cancer and can inform our future efforts to provide effective interventions and support earlier to couples facing a possible cancer diagnosis.

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Data Availability

Data from this study are not publicly available due to ongoing analyses; however, deidentified data from this study will be made available from the corresponding author upon reasonable request (as allowable according to institutional review board standards).

Authors' Contributions

PIM and EOC designed this study and acquired funding alongside FJP, JTM, BY, SMK, SDK, and SCF. JLT led participant recruitment and screening, survey administration, and data management under the supervision of PIM and EOC. PIM, EOC, SMW, JLT, RLN, and HNM developed the initial draft of this study. All authors were involved in the interpretation of findings and participated in the paper preparation and approval.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Baseline and follow-up study assessments.
[DOCX File , 19 KB - resprot_v13i1e52361_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
EHR: electronic health record
QoL: quality of life

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Protocol

Optimizing Response Rates to Examine Health IT Maturity and Nurse Practitioner Care Environments in US Nursing Homes: Mixed Mode Survey Recruitment Protocol

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Abstract

Background: Survey-driven research is a reliable method for large-scale data collection. Investigators incorporating mixed-mode survey designs report benefits for survey research including greater engagement, improved survey access, and higher response rate. Mix-mode survey designs combine 2 or more modes for data collection including web, phone, face-to-face, and mail. Types of mixed-mode survey designs include simultaneous (ie, concurrent), sequential, delayed concurrent, and adaptive. This paper describes a research protocol using mixed-mode survey designs to explore health IT (HIT) maturity and care environments reported by administrators and nurse practitioners (NPs), respectively, in US nursing homes (NHs).

Objective: The aim of this study is to describe a research protocol using mixed-mode survey designs in research using 2 survey tools to explore HIT maturity and NP care environments in US NHs.

Methods: We are conducting a national survey of 1400 NH administrators and NPs. Two data sets (ie, Care Compare and IQVIA) were used to identify eligible facilities at random. The protocol incorporates 2 surveys to explore how HIT maturity (survey 1 collected by administrators) impacts care environments where NPs work (survey 2 collected by NPs). Higher HIT maturity collected by administrators indicates greater IT capabilities, use, and integration in resident care, clinical support, and administrative activities. The NP care environment survey measures relationships, independent practice, resource availability, and visibility. The research team conducted 3 iterative focus groups, including 14 clinicians (NP and NH experts) and recruiters from 2 national survey teams experienced with these populations to achieve consensus on which mixed-mode designs to use. During focus groups we identified the pros and cons of using mixed-mode designs in these settings. We determined that 2 mixed-mode designs with regular follow-up calls (Delayed Concurrent Mode and Sequential Mode) is effective for recruiting NH administrators while a concurrent mixed-mode design is best to recruit NPs.

Results: Participant recruitment for the project began in June 2023. As of April 22, 2024, a total of 98 HIT maturity surveys and 81 NP surveys have been returned. Recruitment of NH administrators and NPs is anticipated through July 2025. About 71% of the HIT maturity surveys have been submitted using the electronic link and 23% were submitted after a QR code was sent to the administrator. Approximately 95% of the NP surveys were returned with electronic survey links.

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Conclusions: Pros of mixed-mode designs for NH research identified by the team were that delayed concurrent, concurrent, and sequential mixed-mode methods of delivering surveys to potential participants save on recruitment time compared to single mode delivery methods. One disadvantage of single-mode strategies is decreased versatility and adaptability to different organizational capabilities (eg, access to email and firewalls), which could reduce response rates.

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KEYWORDS

surveys and questionnaires; survey methods; health care surveys; survey; survey design; mixed-mMode survey; nursing homes; nursing home; clinical informatics research; electronic health records; electronic health record; clinicians; HIT Maturity; Care Environments; United States

Introduction

Background

Survey use in clinical informatics research is ubiquitous. Surveys are often used to collect data and measure phenomena such as knowledge of clinical informatics specialties [1] or the use of electronic health records [2]. Benefits of using surveys include lower costs to conduct research, better population descriptions, flexibility, and dependability of study designs [3]. Surveys are used in many professions and across health care settings, including nursing homes, home health care, and hospitals [4-6]. The expansive use of surveys in clinical informatics research calls for a continued focus on training to improve the ability of researchers to design high-quality surveys, develop effective reporting mechanisms, maximize recruitment strategies, and adapt to recruitment challenges needed to enhance the results. Various modes of survey data collection exist across studies. Literature establishing a theoretical foundation for questionnaire response styles used in surveys when collecting data about public opinion indicate that mode of data collection (eg, mixed-modes) is an important stimulus for response [7]. In this paper, researchers describe a research protocol using mixed-mode survey designs in clinical informatics research using 2 survey tools to explore Health IT (HIT) maturity and nurse practitioner (NP) care environments in US nursing homes (NHs).

In this protocol, HIT maturity is defined in 3 dimensions including HIT capabilities, use, and integration. These HIT maturity dimensions are conceived within NH resident care, clinical support (eg, HIT use in laboratory, pharmacy, and radiology activities), and administrative activities [8]. The HIT maturity survey tool contains 27 content areas and 183 content items [9]. The tool will be used to survey NH administrators. The Nurse Practitioner Nursing Home Organizational Climate Questionnaire (NP-NHOCQ), used to measure NP care environments, contains 5 subscales and 41 items. This tool will be used to survey NPs in NHs. The NP-NHOCQ measures the care environment of NPs in NHs in 5 areas: (1) NP-Physician Relations, (2) NP-Administration Relations, (3) NP-Director of Nursing Relations, (4) Independent Practice and Support, and (5) Professional Visibility.

Mixed-Mode Survey Research

Survey-driven research is known as a reliable data collection method to capture individual perspectives on a large scale. However, there are many challenges related to survey-based data collection, such as low response rates and rising costs of human capital [10]. Previously, researchers have explored the use of mixed-mode survey designs combining methods such as web, phone, face-to-face, and mail administrations. Mixed-mode survey research involves using 2 or more of these modes for data collection [11]. A survey mode is defined as the communication channel used to collect survey data from one or more respondents [11]. Prior research has reported the benefits of mixed-mode surveys such as enhancing engagement [12], mitigating accessibility barriers [13], and increasing response rates [14].

Survey modes can be implemented individually or combined with other modes. A single mode approach deploys only one mode at a time. For example, a researcher may use postal mail services as the only method to contact study participants and collect data. Alternatively, mixed-mode designs use multiple modes to recruit respondents (see Figure 1). For instance, a simultaneous (also known as concurrent) mixed-mode approach allows respondents to choose their preference between multiple modes deployed at the same time. For instance, a researcher may offer study participants a choice to complete a survey using an electronic PDF version of the questionnaire that can be printed, scanned, and faxed back to researchers or an electronic survey link completed via web. Mixed-modes can also use a sequential approach. In this mode, researchers may offer 2 different modes, one mode at a time, with a second mode coming later, after the first. This mode is particularly useful when following up with participants who do not respond (nonrespondents) to provide alternative survey strategies that better suit their workflows. An example of sequential mode may include contacting participants initially via phone call and then, following no initial response, a second contact is made using a QR code that is sent via a mailed letter. Another mixed-mode useful for following up with nonrespondents is called a delayed concurrent mode. In this mode, participants are offered one mode, then nonrespondents are offered a choice between 2 other modes later during follow-up activities. An example of the delayed concurrent mode might include an initial mailed survey. Then when no response is received, potential participants are sent a choice between a face-to-face or a phone interview to complete the survey. Finally, an adaptive mixed-mode design incorporates different sampling units. In the adaptive modes, 2 different samples are each offered a different mode.

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Figure 1. Mixed-mode design strategies (adapted from Schouten et al 2022 [11,15] with permission from Taylor & Francis Group LLC). R: Response; NR: Nonresponse.

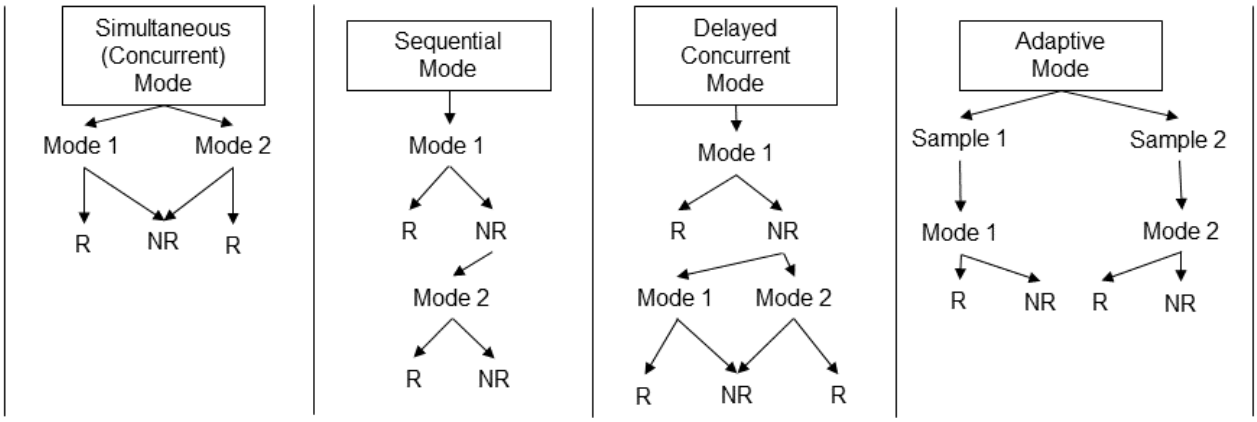

Mixed-mode survey research has long been identified as a means to improve participation in survey recruitment. For instance, a systematic review of 22 articles among nurses provided evidence that recruitment design strategies that include postal and telephone contacts are generally more successful than fax or web-based approaches [16]. In a more recent systematic review of 893 studies, mode of administration was a key factor in successful recruitment. However, in this review, electronic and postal modes of survey data collection were less likely to result in higher response rates [17]. In other research using mixed-modes with clinicians, using a multiple contact protocol generated final response rates 10% points higher than single mode methods [18].

In this paper, we present mixed-mode methods used in a large survey of NHs in the United States. To achieve research goals, we must have a robust and effective recruitment plan. Therefore, we are using an innovative research protocol using mixed-modes to improve NH administrators' and NPs' engagement in survey data collection while increasing the response rates.

Methods

Mixed-Mode Survey Research in Nursing Homes

The US health care system has over 15,600 NHs serving over 1.3 million residents [19]. A growing strategy for improving the outcomes for NH residents is to effectively integrate HIT into care delivery to promote safer care environments for NH residents. HIT integration into NH resident care may improve care environments and by extension, better care quality [20]. Survey-driven research is a reliable method to capture the perspective of individuals about these phenomena on a large scale. Our team is conducting a national survey of NH administrators and NPs, incorporating 2 different survey tools to explore how HIT maturity (survey 1) impacts care environments (survey 2) where NPs work. A specific aim of this research is to provide comprehensive assessments of HIT maturity and NP care environments in NHs nationally. The goal of the National Institute of Aging funded research study (5R01AG080517, principal investigators: GLA and LP) is to assess differences in HIT maturity and care environments in NHs where NPs deliver care to residents with Alzheimer disease and related dementias and examine their impact on hospitalizations and emergency department visits among residents.

Sample

Overview

The sample for this study includes randomly selected NHs including administrators (ie, NH leaders responsible for HIT systems in their organization) and NPs from each NH. Our goal is to recruit participants from 1400 NHs in the United States. We use 2 national sources to identify NHs for this study. The first data source is called NH Compare (or Care Compare), a publicly available national data set containing information about organizational characteristics of US NHs and quality of care [21]. The second data source stems from IQVIA, a company that stores national data about NH location, contact information, and staff including administrators and NPs. In preparation for this proposal, IQVIA provided our team data to identify all US NHs with practicing NPs. According to these data, in 2021, a total of 11,222 unique NPs worked in 5000 NHs for an average of 2.2 NPs/NH. Based on this estimate, we expect to contact 3080 NPs within the 1400 NHs (1400 NHs X 2.2 NPs/NH).

Inclusion and Exclusion Criteria

We use NH Compare files to identify NHs for our study based on 2 specific inclusion criteria. First, we include all NHs located in the United States including Alaska and Hawaii. Second, we include at least 1 NP working in each facility. NPs may include actual employees of a facility or may be employed by an external organization as a consultant for a facility and not directly by the NH. Facilities are not eligible to participate if they meet the following 3 exclusion criteria. First, NHs that do not have an NP employed. Second, NHs with a hospital-based designation as their HIT maturity are likely to be different due to national incentives for HIT adoption in acute care [22,23]. Approximately 6% (n=15,518) of NHs have a health system designation that includes common ownership or joint management [24]. Third, NHs that are designated as a special focus facility (SFF), which indicates any NH with a history of serious quality issues. NHs with an SFF designation are required to be in a program to stimulate quality-of-care improvements [25]. In October 2023, Centers for Medicare & Medicaid Services indicated that approximately 0.5% of US NHs have an SFF designation [25].

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The NH Compare website was downloaded in February 2023 to identify facilities for recruitment. We identified 4163 facilities that matched our criteria. In preliminary work, during 2 prior NH survey studies, we achieved approximately a 45% response rate of surveys returned from administrators. Therefore, for the current protocol, we oversampled by randomly selecting 3000 NHs, which we identified by linking the NH Compare and IQVIA data. We included at least 5 facilities in each state, except for Alaska (2 facilities) and Wyoming (3 facilities) which have few NHs with NPs identified. We will recruit all administrators from these 3000 NHs to complete a HIT maturity survey. For every NH that completes the HIT maturity survey, we will recruit all NPs from those facilities.

Sample Characteristics

After we generated the random sample from the merged files, we compared basic characteristics of NHs between the selected NHs and the rest of the NHs nationally. The following NH characteristics were compared to assure that there was limited bias in sample representation:

1. Bed size (<60 beds, 60-120 beds, and >120 beds)
2. Ownership (for profit vs nonprofit)
3. Location (metropolitan, micropolitan, small town, and rural)
4. Staffing hour
5. Medicare vs Medicaid
6. NH overall rating: (ranging from 1 to 5)

Focus Groups to Assess the Pros and Cons of Mixed-Mode Designs

The research team conducted iterative focus groups that included NPs and survey recruitment experts to discuss the pros and cons of different recruitment strategies. To explore the pros and cons, members of the focus groups assessed recruitment strategies used during 2 prior national studies of long-term care NH sites [26]. The PI and some members of the focus groups lead these national studies that were reviewed. Additionally, members of the focus groups reviewed and discussed potential mixed-mode strategies from the literature to incorporate into this protocol. Schouten [15] mixed-mode survey research helped inform our decisions for our protocol design.

Data Collection

We aim to survey administrators and NPs using 2 survey tools describing HIT maturity and care environments from each discipline, respectively. To prepare the protocol, the research team conducted 3 iterative focus groups with clinicians (NPs and NH experts), recruiters from 2 national survey teams experienced with recruitment in NHs and with NPs, and a statistician to achieve consensus on which mixed-mode designs to incorporate into this research. Our research protocol workflow is illustrated in Figure 2. The following sections include descriptions of the mixed-mode workflows by discipline and the surveys being used in this protocol.

Figure 2. Survey recruitment protocol for hybrid mixed-mode design and data collection workflow NH: Nursing Home, NP: Nurse Practitioner, E-survey: Electronic Survey, QR Code: QR Code Letter Mailed, HIT: Health IT.

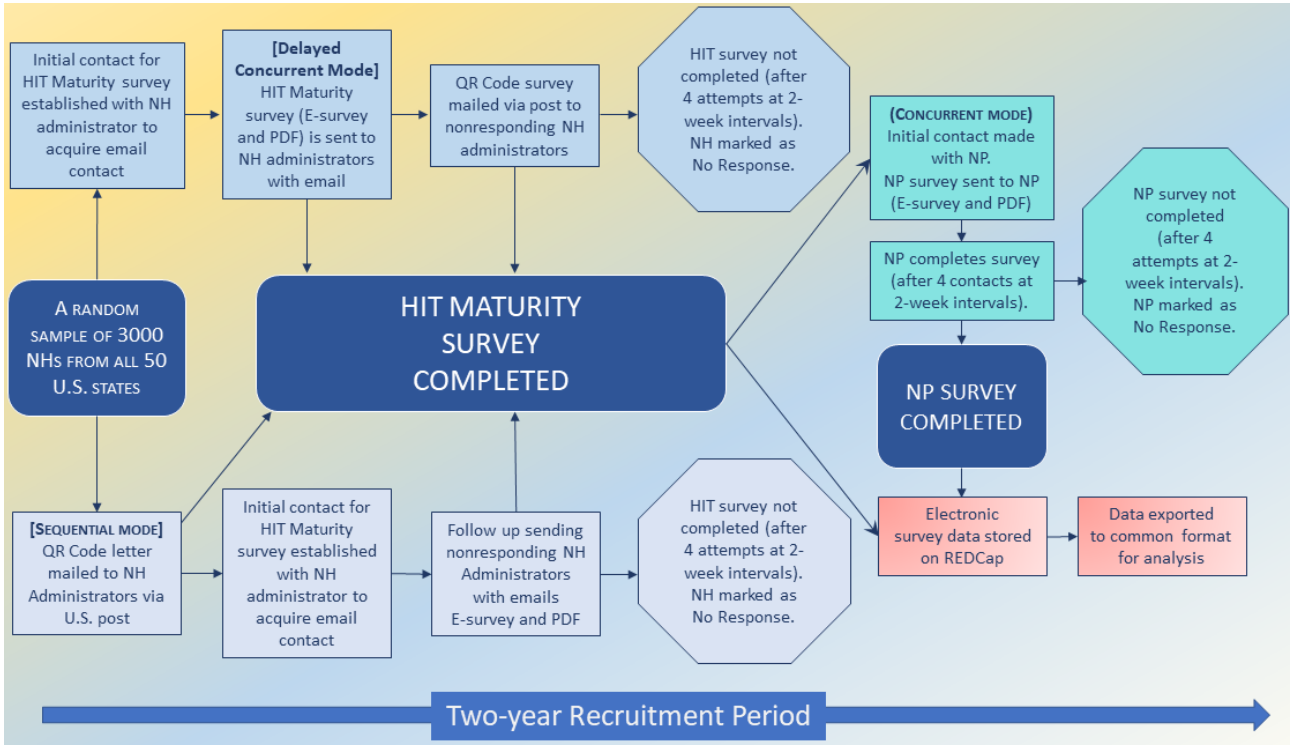

Survey 1: NH Administrator and HIT Maturity

For each randomly selected NH, contact information for NH Administrators has been obtained using IQVIA data set. Our team searched NH websites to confirm contact information of current administrators. During initial contact with each NH administrator (either by phone or a mailed letter), we describe the study's purpose and explain the study. All administrators who are contacted and agreed to participate in the study will be sent a cover letter providing details about the study's purpose, instructions on how to complete the NH HIT maturity survey tool, and descriptions of the benefits and risks of participation.

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We provide a description of the HIT maturity survey for administrators including that the survey measures HIT capabilities, extent of HIT use, and degree of HIT integration in resident care, clinical support, and administrative activities [9]. We incorporate 2 mixed-mode designs when recruiting NH administrators including a Delayed Concurrent Mode and a Sequential Mode with regular follow-up phone contacts to stimulate engagement.

Delayed Concurrent Mode

Our primary mode for this study is a Delayed Concurrent mixed-mode design. In this mode, administrators are offered the choice between multiple modes. During the first contact (conducted by phone), we describe the project and obtain email addresses for administrators who agree to participate. Then, we follow up with administrators by email with an electronic survey link and a PDF simultaneously. This is important because the different choices among electronic surveys and PDFs allow administrators the flexibility to choose a mode that fits their needs. In nonresponse cases, administrators are later offered a different mode including a postal letter with a QR code that includes a URL link to the survey tool that is subsequently sent at a later time.

Sequential Mode

As a secondary option, we incorporate a Sequential Mode for a minimum of 10% of the facilities in each state. In this mode, participants are offered only 1 mode at a time and only part of the nonrespondents are invited for the second mode. The first mode includes mailing a postal letter that describes the study and provides both a QR code and URL link to the survey for the NH administrator. Recruiters make a series of follow-up calls to administrators after the letter is sent. During follow-up calls, emails are confirmed by the recruitment team. In this sequence, administrators who agree to take the survey and have provided their email addresses but have failed to respond with a completed mailed or faxed survey after a minimum of four follow-up calls are offered a second mode. The second mode includes a URL link and a PDF of the survey that is sent to administrators via email.

Survey 2: NPs and Care Environment

Overview

The recruitment team asks administrators to confirm that at least one NP works in their facility (whether employed by the NH or by an external health organization that provides NP services to the facility) and to verify the NP's name and contact information. NP's contact information listed in the IQVIA data is confirmed with administrators to ensure that it is current. Contact information that is not current is updated by the recruitment team in the recruitment database. NHs that do not meet the eligibility criterion (eg, NP left and no new NP hired) are excluded. The research team will incorporate a concurrent mixed-mode design to recruit NPs for the study.

Concurrent Mode

NPs are contacted by email or phone by our recruitment team and are provided with information describing the study, its voluntary nature, and confidentiality per the institutional review board's (IRB's) protocol. NPs are sent links to both an electronic survey and PDF concurrently. We expect some NHs to have more than one NP complete a survey.

Ethical Considerations

The protocol was approved by the IRB (AAAU3845). Ethical issues that were addressed in our IRB protocol included confidentiality and anonymity of privacy to encourage honest responses. Security and accessibility of the data only to authorized research staff. Researchers also created plans for minimizing coercive behaviors during recruitment (eg, applying pressure) by creating systematic follow-up and templates with recruitment language to use during contacts. The research protocol and all procedures were approved by Columbia University IRB (AAAU3845).

Follow-Up and Engagement

Up to 4 follow-up phone calls are conducted at specified 2-week intervals for administrators who have agreed to participate. Administrators and NPs who do not complete surveys are marked as "No Contact." Administrators and NPs who complete a survey receive US $25 compensation in the form of a gift card.

Survey Coding and Cleaning

All survey data collection is conducted through REDCap (Research Electronic Data Capture; Vanderbilt University) a web-based software designed for data collection and management in research studies with emphasis on data security and flexibility [27]. We maintain data about recruitment efforts in REDCap, including number of facilities contacted, persons contacted at each facility, packets or links sent, surveys received, initial cannot reach, contact calls made, follow-up calls made, confirmations received (will complete and not completed), stated completions, and follow-up cannot reach. Recruitment staff, including a project coordinator and 4 research assistants, make recruitment calls and send surveys to NH administrators and NPs.

Data collected via electronic survey are electronically transferred to the REDCap database. Data collected via PDF is manually entered into the REDCap system by our research staff. A meticulous data-cleaning strategy is used before formal statistical analysis to ensure the data quality [28]. We used algorithms to check questionnaires for consistency and validity. For example, graphical exploration through boxplots, histograms, and scatter plots will be used to help with detecting outliers and logically implausible data points. Any identified outlying observations undergo thorough examination to discern between potential data entry errors and genuinely extreme values. Data entry errors are corrected. Any systematic patterns will be scrutinized. Every step of the data cleaning process and associated decisions are documented to ensure transparency.

There is a possibility that some NH administrators or NPs who agree to participate in the study will not fill out an HIT maturity or care environment survey tool completely. We anticipate that there may be some missing data on completed surveys. Based on prior national HIT maturity and NP studies, we have estimated that less than 3% of the data for surveys received was

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missing for both types of surveys. We plan to use all available data in our analyses.

Survey Measures

NH HIT Maturity [8,29] is measured using a total composite score that correspond to 7 HIT maturity stages. The 7 maturity stages range from the lowest HIT Maturity Stage 0—Nonexistent HIT solutions or electronic health records to Stage 6—Use of data by residents and resident representatives to generate clinical data and drive self-management. A higher total HIT maturity score indicates greater IT capabilities, use, and integration in resident care, clinical support (including IT systems in pharmacy, radiology, laboratory), and administrative activities in the NH. The overall standardized Cronbach α for this instrument in past research was 0.86 (high); each dimension or domain achieved a Cronbach α ranging from 0.7 to 0.9 [30].

NP Care Environment is measured by a 44-item Nurse Practitioner Nursing Home Organizational Climate Survey (NP-NHOCS) [31], which asks NPs to rate the work attributes in NHs using a 5-point Likert scale. The NP-NHOCS has five subscales: (1) NP-Physician Relations (7 items)—measures the relationship, communication, and teamwork between NPs and physicians; (2) NP-Administration Relations (11 items)—measures collaboration and communication between NPs and managers; (3) NP-Director of Nursing Relations (8 items)—measures the relationship, communication, and teamwork between NPs and Directors of Nursing; (4) Independent Practice and Support (9 items)—measures resources and support NPs have for their independent practice; and (5) Professional Visibility (9 items)—measures how visible the NP role is in the organization. We first compute NP-level and then NH-level mean scores by aggregating the responses of all NPs in the NHs as recommended [32]. Higher mean scores indicate better care environments. NPs are asked to complete measures of demographics (eg, age, sex, and experience).

Analysis

A number of planned analyses will be performed. In terms of HIT maturity survey, we aim to understand which survey mode (Delayed Concurrent vs Sequential) will maximize NHs' engagement in our research project and which factor(s) influence survey completion method. First, descriptive statistics will be used to summarize the key variables of interest including but not limited to response rates (agreeing to participate or not), completion rates, time taken to complete the survey, and the proportion of electronic surveys received. Chi-square test or Fisher exact test will be used to examine differences in response rates, completion rates, proportion of electronic survey received between the NHs assigned to the Delayed Concurrent Mode and Sequential Mode survey designs. This analysis will determine if one survey mode yields higher response and completion rates compared to the other. Second, if there is sufficient data availability, linear regression models will be used to test whether NH administrators' demographic characteristics (ie, age, sex, race or ethnicity), NH-level characteristics (eg, bed size and staffing hours), and HIT maturity level are associated with the choice of survey completion method (electronic or PDF format).

In terms of NP care environment survey, all NPs will be offered both an electronic survey and a PDF concurrently. The proportion of electronic surveys received among those who respond will be calculated to determine preference for electronic over PDF surveys. If a sufficient number of electronic and PDF surveys are received, linear mixed effects models with NH as random effect will be used to assess whether the choice of survey completion method is associated with NH-level characteristics (eg, HIT maturity score, geographical location, ownership), NP-level characteristics (eg, age, race or ethnicity, years of experience, and job roles), and NP care environment scores, respectively.

Results

The research team conducted 3 iterative focus groups with a total of 14 clinicians including NPs and survey recruitment experts. The following pros and cons were used to determine our recruitment strategies.

Pros of Mixed-Mode Designs

The pros of mixed-mode designs identified by the team during focus groups were that delayed concurrent, concurrent, and sequential mixed-mode approaches can save recruitment time compared to single mode delivery methods. Additionally, effort on the part of recruitment staff is minimized by using mixed-modes. By using mixed survey modes, participants can immediately choose their preferred survey method, potentially enhancing their satisfaction with the survey process. This facilitates engagement that leads to completed surveys and increased response rates. Another pro of the concurrent mode identified was that sending a QR code via the postal service in addition to providing a URL link provides greater selectivity and plasticity in a respondent's choice, which could enhance engagement and responsiveness to surveys. A pro of single mode designs is the potential for quick turnaround times and representative samples for projects with limited resources [33].

Cons of Mixed-Mode Designs

One disadvantage of single mode strategies is that they decrease the versatility and adaptability to different organizational capabilities (eg, access to email and system firewalls), which could reduce response rates. For example, a URL link sent via email might be more difficult for NH administrators and NPs to open due to system firewalls put into place by organizations to meet higher level security standards of HIT systems. We identified another con of a sequential mode; for instance, if a singular mode is offered when initial recruitment is started, the respondent may not engage in the second wave. For example, if respondents are concerned about access to email, they may not engage with us again in further calls if the first mode offered including email is perceived as a barrier to participation. Other cons that were identified related to NH infrastructure and environmental variables. For instance, NPs might have limited access or no workspace available to print a PDF and to complete a survey. Other reported cons of mixed-mode designs (sequential modes [web then telephone]) compared to single mode (telephone only) include higher missing data rates and more focal responses [34].

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After randomization, we rigorously compared selected and nonselected NHs based on key NH level characteristics such as bed size, ownership, location, staffing hours, payer mix, and overall rating. Our analysis did not reveal statistically significant differences in these characteristics (See Table S1 in Multimedia Appendix 1).

The research study was funded in February 2023. Participant recruitment for the project began in June 2023. As of June 3, 2024, a total of 109 HIT maturity surveys and 83 NP surveys have been returned. About 69% of the HIT maturity surveys have been submitted using the electronic link and 27% were submitted after a QR code was sent to the administrator. About 95% of the NP surveys were returned with electronic survey links.

Discussion

Our national study is the first to our knowledge to focus on NH HIT maturity and NP care environments where administrators and NPs work. Although NPs are a predominant provider in NHs [35], no study to date has focused on NP care environments and available resources (eg, technology) to this discipline, leading to limited understanding of how NPs conduct work, and how HIT maturity contributes to an NP's ability to improve care and outcomes for NH residents with serious chronic conditions. Furthermore, a primary objective of this study is to provide evidence of how administrators and NPs codesign technologies that can transform care delivery in NHs. Our team anticipates that using mixed-modes will enhance our ability to work with participants at different stages of HIT maturity, which we believe is in an important factor in how care environments are perceived by employees (eg, NPs) in these settings.

To achieve this goal, we first must be able to maximize engagement in this survey research with strong representation by both NH administrators and NPs from all US states. Second, we must mitigate barriers to NH administrators and NPs accessing surveys so that they can participate. Finally, we must achieve acceptable response rates by generating different modes of support, providing choice and flexible means for NH administrators and NPs to participate in the survey process. In this protocol, we have identified mixed-mode recruitment strategies based on the expert opinion of experienced survey recruitment staff that should enable us to meet our goals and to achieve a representative national sample of NH administrators and NPs.

Limitations

This study may have limitations. In prior work, we have identified great variability in HIT capabilities among many NH's, such as access to external email and connectivity challenges where NH staff work [36]. Depending on the survey mode used during the data collection, this variation may create differences in response rates between facilities. We have incorporated various mixed-mode methods in this research protocol that should allow respondents to choose their preferred method and the ability to complete a survey considering their institutional characteristics. The use of mixed-modes has been shown to improve participation in survey research, thus reducing barriers for less well-resourced NHs (eg, NHs with lower HIT maturity levels). Less resourced NHs are typically those with greater resident ethnic and racial diversity [37], so improving their participation is critical to enhance representation of these communities, which is a benefit of the design.

Conclusions

This research protocol describes a study using 2 survey tools to measure HIT maturity and NP care environments in the US NHs as perceived by administrators and NPs. We have identified the pros and cons of survey recruitment strategies experienced by our team in past work. We reviewed evidence-based recruitment strategies using mixed-modes which are defined in the literature as methods that incorporate the use of 2 or more modes to recruit respondents. In this protocol, we have incorporated a delayed concurrent mode, sequential mode, and a concurrent mode to enhance engagement, mitigate barriers to survey access, and to increase response rates in collecting survey data both from NH administrators and NPs to have robust data for future analysis.

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Authors' Contributions

GLA, LP, YZ, MH, SK, AAN, KW, MBS, AK, TB, and ST contributed to the design, acquisition, interpretation, writing, and revision of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Table.
[DOCX File , 27 KB - resprot_v13i1e56170_app1.docx]

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Abbreviations

HIT: health IT
IRB: institutional review board
NH: nursing home
NP: nursing practitioner
NP-NHOCQ: Nurse Practitioner Nursing Home Organizational Climate Questionnaire
NP-NHOCS: Nurse Practitioner Nursing Home Organizational Climate Survey
REDCap: Research Electronic Data Capture
SFF: special focus facility

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Protocol

Feasibility and Acceptability Study of a Culturally Adapted Web-Based Intervention to Reduce Suicidal Ideation for Syrian Asylum Seekers and Refugees in the United Kingdom: Protocol for a Mixed Methods Study

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Abstract

Background: The war in Syria has displaced over 6.8 million people, more than any other conflict since the Second World War. As a result, Syrian asylum seekers and refugees have experienced several life-changing events, resulting in high rates of anxiety, depression, posttraumatic stress disorder, and suicidal ideation (SI). To address the treatment gap and reduce the burden of help-seeking, a web-based intervention to reduce SI developed for general populations was culturally adapted for and with Syrian asylum seekers and refugees in the United Kingdom. The study revealed the importance of understanding their lived experience with migration and the acculturative process in providing treatment for SI. This study will now assess the feasibility and acceptability of the culturally adapted intervention for this population.

Objective: The first phase of the study will include recruiting participants and delivering the web-based intervention (1) to assess the feasibility of meeting recruitment goals and recruitment rates and (2) to assess the feasibility of outcome measures. The second phase of the study will include one-to-one semistructured interviews (1) to assess the suitability of the culturally adapted intervention in terms of recruitment and adherence rates and barriers and facilitators to engagement and (2) to assess the acceptability of the intervention in terms of its cultural relevance and appropriateness.

Methods: This is a protocol for a single-group, noncontrolled, mixed methods feasibility and acceptability study of a culturally adapted web-based intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom. The study will assess the feasibility of recruitment goals, recruitment rates, adherence rates, and outcome measures using individual participant tracking forms, which will be analyzed quantitatively. The suitability and acceptability of the intervention will be assessed using one-to-one semistructured interviews with 12 participants who completed the intervention, which will be analyzed qualitatively.

Results: Recruitment began in February 2024 and will run until 30 participants are recruited to the study or until the end of July 2024. Thus far, 19 participants have provided informed consent, 16 were eligible and enrolled, and 12 have completed a postintervention interview. No data have been analyzed. The study, including the write-up period, is expected to end in December 2024.

Conclusions: Despite experiencing several stressors related to forced displacement and high rates of mental health issues, access to treatment is still limited for Syrian asylum seekers and refugees in the United Kingdom. To address the treatment gap and reduce the burden of help-seeking, a web-based intervention to reduce SI was culturally adapted in collaboration with Syrian

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asylum seekers and refugees in the United Kingdom. This study will now assess the feasibility and acceptability of the intervention and culturally appropriate recruitment strategies.

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KEYWORDS

cultural adaptation; digital mental health; suicidal ideation; refugee mental health; Syrian refugee; experience-based co-design; mental health; suicide; suicidal; refugee; immigrant; ethnic minority; asylum; user experience; cultural; Syria; Syrian; refugees; feasibility; acceptability; depression; anxiety; posttraumatic stress disorder; United Kingdom; Arabic-speaking

Introduction

Background and Rationale

The Syrian conflict has sparked the largest forced displacement crisis since World War II [1]. Experiences such as bombings, shootings, torture, and involuntary conscription have forced many Syrians to leave behind their homes, jobs, businesses, and extended families to find safety in other cities or abroad [2]. While most of the 6.8 million Syrian refugees living abroad found refuge in neighboring countries, over 1 million have sought asylum in Europe [3]. In the United Kingdom, over 20,000 Syrians were resettled under the Vulnerable Persons Resettlement Scheme [4]. Many more Syrians have sought asylum in the United Kingdom, including 75,615 applications during the year ending in September 2021 [3]. Despite having escaped war, Syrian asylum seekers continue to experience stressors while living in the United Kingdom including, most significantly, a prolonged asylum process [2]. These stressors have resulted in elevated rates of mental health issues including major depressive disorder, posttraumatic stress disorder (PTSD), and suicidality [5]. There is thus an urgent need to improve the understanding and care of mental health issues for Syrian asylum seekers and refugees arriving in the United Kingdom.

Suicidal Ideation

One of the most concerning and least addressed mental health issues for asylum seekers and refugees across Europe is suicidal ideation (SI) and suicidal behavior more broadly [6]. Several studies have shown high rates of SI among asylum seekers and refugees in Sweden, 33.9% [7] and 48% [8]; Switzerland, 42.1% [9] and >30% [10]; and the United Kingdom, 40.9% [11]. Some studies, however, have shown lower rates of suicide attempts among refugees than the Swedish-born population, suggesting variances between asylum seekers and refugees [12]. In fact, a study in Switzerland found that the most frequent reason for referral to emergency psychiatric services among asylum seekers was SI after the rejection of their asylum application [9]. Studies on Bhutanese refugees in the United States have also showed lower rates of SI at 3% [13], 6.2% [14], and 6.7% [15]. However, Meyerhoff and Rohan [15] found a large disparity between their reports of SI, 6.7%, and desire for death, 48.3%, suggesting that culturally inflexible models could mask the real prevalence of SI for different asylum seeker and refugee subgroups. Most importantly, despite their risk for developing mental health issues and SI, refugees and asylum seekers continue to underuse mental health services [16-19].

Cultural Adaptation

Access to treatment for SI among Syrian asylum seekers and refugees in the United Kingdom can be improved with culturally adapted digital mental health interventions [20]. In response to the treatment gap, Beuthin et al [21] culturally adapted a digital intervention to reduce SI with and for Syrian asylum seekers and refugees in the United Kingdom. The study built on Eylem and colleagues' [22] cultural adaptation of van Spijker and colleagues' [23] Leven onder Controle (literally "Living under Control") intervention, a guided 6-week cognitive behavioral therapy–based web-based intervention to reduce SI. The intervention includes 6 modules: thinking about suicide, dealing with thoughts and feelings, thinking about the future, thinking about the self, thinking about others, and repetition and relapse. Several randomized controlled trials (RCTs) have found the intervention to be effective in reducing SI compared to treatment as usual—an information website—for general Dutch (d=0.2) [24] and Belgian populations (d=0.34) [25] but not for Australian populations [26]. The initial cultural adaptation of the intervention for Turkish immigrants in the United Kingdom and the Netherlands was found to be acceptable; however, the study was unable to recruit enough participants for a full RCT [22].

Eylem et al [22] culturally adapted the intervention in line with Bernal and colleagues' [27] framework, which included adapting for cultural metaphors, treatment concepts and goals and the context and methods of the intervention. This framework falls within the school of thought which, based on the universality of emotional expression, asserts that the distinct signs and symptoms of psychopathology are universal. It therefore aims to maintain the integrity of the original intervention as much as possible. However, cultural adaptation based on universal signs and symptoms undermines the more fundamental role of intentions and conventions in meaning making [28]. Conversely, another framework developed by Horrell [29] aims to develop new interventions for different cultural groups. While it is certainly more situated, the framework does not consider the role of acculturation and cultural change. Beuthin et al [21] therefore synthesized these approaches by focusing on shared lived experiences that give rise to (1) core affect, including hedonic valence and physical arousal; and (2) conceptual knowledge [30]. In other words, feeling is perceiving, and perceiving is believing and vice versa [31]. This framework therefore enables researchers to identify resilient core beliefs, which in turn are important in understanding and avoiding identity crises [32] and suicidal behavior [33]. With this

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paradigm in mind, the cultural adaptation process was simplified using experience-based co-design, an action research method for collaboratively improving health care services and interventions [34]. This entailed interviews to understand Syrian asylum seekers' and refugees' cultural conceptualizations, coping-strategies, and help-seeking behavior for mental health and SI in relation to touchpoints, crucial moments that made a difference in their experience, of the migratory process [2]. After a preliminary cultural adaptation of the intervention, Syrian asylum seekers and refugees participated in co-design events to collectively identify and adapt touchpoints of the intervention. A community research panel also helped to maintain the integrity of the intervention and the users' core beliefs at each phase of the cultural adaptation. Importantly, intentions and conventions are not understood as a spectrum, but rather, all communication by definition is intentional but differs in the level to which it adheres to conventions.

Based on the findings of Beuthin et al [2], the main cultural adaptations to the intervention included case examples, coping strategies, and a nondirective approach. Case examples included a wish for death during the post-migration phase, and SI crises during the pre- and peri-migration phases. Notably, a participant who experienced an SI crisis described his thoughts as both SI and a wish for death, potentially highlighting a more salient mechanism of SI for this population. However, while attributing their thoughts to their experiences, they believed that suicide is fundamentally a consequence of diminished sources of support including weak imān (faith), a loss of one's mind, character and soul, and a lack of access to mental health support. Similarly, participants identified their coping strategies as conceptualizing their experiences as ibtilā' (a test) and being hopeful of God's help while engaging in acts of worship, hobbies, walking, volunteering, talking to family and friends, etc. In contrast to the previous feasibility study by Eylem et al [22] that suggested the intervention should be shortened, participants preferred maintaining the integrity of the intervention while providing more explanations about their purpose [2]. Participants were also directly involved in the cultural adaptation process through 3 co-design events, which involved adapting 2 sessions of the intervention each. However, since participants did not use the intervention, this study will now assess its acceptability and suitability by providing it in full to Syrian asylum seekers and refugees in the United Kingdom with SI.

Recruitment

In addition to the cultural adaptation of the intervention, Eylem et al [22] expressed the need to identify culturally appropriate recruitment strategies. Despite advertising their study through public events, newspaper advertisements, television programs, banners on websites, and social media, they were unable to recruit enough participants for a full RCT. They believed that recruitment was hindered by institutional barriers for different Turkish subgroups and therefore recommended task-shifting recruitment to trained lay people from the target population. This was confirmed in a previous study by Beuthin et al [2], which recruited all its participants through cultural brokers via the web. Most charities and nongovernmental organizations (NGOs) contacted in the previous study reported having insufficient capacity to disseminate the study advert. Likewise, participants of the study reported avoiding seeking help via the National Health Service (NHS) due to the long waiting times and fear of having their asylum application rejected. Several Syrian mental health researchers in the United Kingdom confirmed that despite holding events and advertising through mosques, charities, and NGOs, they too only received responses via advertisements in Syrian diaspora Facebook groups. Thus, this study will assess the feasibility of recruiting Syrian asylum seekers and refugees in the United Kingdom with SI from various sources including charities, NGOs, local councils, social media, but most importantly, cultural brokers.

Aims

This study is part of a broader research project aimed at improving the understanding and treatment of SI among Syrian asylum seekers and refugees arriving in the United Kingdom. The study aims to investigate the feasibility and acceptability of a culturally adapted web-based stand-alone intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom.

Objectives

The first phase of the study will include recruiting participants and delivering the digital intervention (1) to assess the feasibility of meeting recruitment goals and recruitment rates and (2) to assess the feasibility of outcome measures. The second phase of the study will include one-to-one semistructured interviews (1) to assess the suitability of the culturally adapted intervention in terms of recruitment and adherence rates as well as barriers and facilitators to engagement and (2) to assess the acceptability of the culturally adapted intervention in terms of its cultural relevance and appropriateness and whether participants were satisfied with their experience.

Methods

Study Design

This is a single-group, noncontrolled, mixed methods feasibility and acceptability study of a culturally adapted web-based intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom. The feasibility and acceptability study will follow the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Guidance for protocols of clinical trials [35] and the CONSORT (Consolidated Standards of Reporting Trials) 2010 extension for randomized pilot and feasibility trials [36].

Expanding on the feasibility study by Eylem et al [22] of the same intervention, the study will assess the feasibility of recruitment methods in meeting recruitment goals. Previously, Eylem et al [22] aimed to conduct a full RCT; however, they were unable to meet their recruitment goal of 286 participants, recruiting instead 85 participants, 30 of whom were found to be eligible, and only 18 provided consent. They therefore recommended task-shifting to trained lay people or cultural brokers to overcome institutional barriers to recruitment.

The feasibility of recruitment goals and recruitment rates will be assessed in accordance with the guidelines for evaluating the feasibility of recruitment in pilot studies of diverse populations

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developed by Stewart et al [37]. Their guidelines include the following eight steps: (1) specifying recruitment goals (target population, desired diversity, and subgroup sample sizes), (2) specifying recruitment processes by stage, (3) establishing a tracking system for each individual (contact tracking form), (4) establishing a tracking database for monitoring processes and results, (5) implementing recruitment processes and monitoring each individual's progress, (6) summarizing recruitment results from the tracking database, (7) calculating and interpreting measures of feasibility, and (8) modifying methods for a larger study if recruitment goals are not met. Their guidelines will be described in more detail in the Data Collection, Management, and Analysis section.

Like the feasibility study by Eylem et al [22], one-to-one semistructured interviews will be conducted with intervention participants to understand the suitability and acceptability of the culturally adapted intervention. This will include identifying the barriers and facilitators to engagement and the cultural appropriateness and relevance of the culturally adapted intervention. Like the initial cultural adaptation process for Syrian asylum seekers and refugees in the United Kingdom, the interviews will involve asking participants to identify touchpoints of the intervention [34]. Research methods will be described in more detail in the Data Collection, Management, and Analysis section.

Participants, Interventions, and Outcomes

Setting

As Syrian asylum seekers and refugees are dispersed across the United Kingdom, all study activities including recruitment, consent, screening for eligibility, intervention, and interviews will be held on the web to lower barriers to participation. However, access to the intervention could still be influenced by barriers and facilitators associated with its institutional affiliations including the University of Oxford, which will be mentioned on all foreword-facing documents, and those who agree to advertise it to their network.

Eligibility Criteria

Inclusion criteria include being a male or female Syrian asylum seeker or refugee in the United Kingdom, aged 18 years and older, and with at least a score of 1 on the Columbia-Suicide Severity Rating Scale (C-SSRS) [38]. Participants also need to be internet literate, have access to a PC or mobile phone with internet, and be willing to provide their email address and the email address of their general practitioner (GP) surgery. Recruitment will take place via the web; and therefore, internet literacy and access also apply. Participants with a score of 4 or above on the C-SSRS, indicating serious SI, will not be eligible to participate. This decision was made to avoid risks of harm to the participants and has thus far not resulted in the exclusion of any participants.

Interventions: Description

After providing informed consent and screening for eligibility, baseline measurements of SI, anxiety, depression, and PTSD will be taken for intervention participants. Participants will then receive the 6-week self-help digital intervention via Qualtrics (Qualtrics International Inc), which consists of the following 6 sessions [22]:

1. Thinking about suicide: The aim of this module is to enable participants to identify the automatic thoughts that give rise to suicidal thoughts in order to gain some control over their thoughts. Specific attention is given to the dichotomous and overgeneralizing nature of the thoughts.
2. Dealing with thoughts and feelings: Participants will learn that they can be resilient in the face of seemingly unbearable feelings. Focus will be given to learning how to tolerate and regulate intense emotions in crisis situations.
3. Thinking about the future: Participants will evaluate their ideas about the future and ask whether they are realistic. Consequently, participants will develop a more realistic view of the future and set new goals.
4. Thinking about the self: Common mistakes in thinking about the self are discussed and challenged. Participants are also taught how to manage suicidality as a long-term vulnerability. Particular attention is given to learning to seek help.
5. Thinking about others: Mistakes in thinking about others will be discussed. Participants will also be provided with information about the effects of suicide for relatives and friends.
6. Repetition and relapse: Several mistakes in thinking and acquired skills are repeated. Attention will also be given to relapse and how to avoid it.

While the intervention was initially intended as a 6-week intervention, it will be provided to participants as a 6-session intervention, which they can complete at their own pace within 6 weeks. Preferably, this involves working on the intervention for 15 minutes daily. If participants fail to submit the session's homework by the end of each week, a further message will be sent asking if they are having any difficulties or if they want to discontinue their participation. If the participant does not reply within a week, they will be contacted again when it is time to assess their SI as part of the study's safety protocol. If they do not respond, it will be assumed that they no longer wish to participate. Likewise, any participant who scores 4 or above on the C-SSRS will be excluded from participation [38]. All participants will be encouraged to seek help from their GP or will be provided information about alternative sources of help during the intervention.

While the goal of the study is to track rather than ensure adherence, strategies for improving adherence were one of the main objectives of the cultural adaptation. Specifically, the electronic case tracking form (eCTF) used to track recruitment goals will be used to track the reasons for ending participation throughout the intervention. Adherence rates, in terms of the number of sessions completed and the amount of time taken to complete them, will be assessed during postintervention interviews and with the platform user analytics.

Outcomes

Primary Outcomes

The primary outcomes of the study include the acceptability and suitability of the intervention to Syrian asylum seekers and

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refugees in the United Kingdom with SI. The acceptability of the intervention to participants will be assessed during interviews in terms of cultural relevance (ie, the familiarity of the therapeutic content to one's cultural background and lived experiences with the migratory process), cultural appropriateness (ie, appropriateness of the therapeutic content in terms of the Syrian cultural context), and whether participants were satisfied with their experience [22].

The suitability of the intervention will be analyzed quantitatively in terms of recruitment and adherence rates. Recruitment rates will be assessed in terms of the percentage of those contacted who met the eligibility criteria and the percentage of those eligible who were enrolled, which should be 70% at each stage. Adherence rates will be assessed in terms of the number of sessions attended, which should be at least 70%, and the time spent completing them. The suitability of the intervention will also be assessed qualitatively in terms of the barriers and facilitators of engagements by way of the case tracking form and postintervention interviews.

Secondary Outcomes

Secondary outcomes include the feasibility of recruitment goals and measurement instruments. Recruitment goals will be tracked in accordance with the guidelines by Stewart et al [37] for diverse populations. This will include using an eCTF to track the sources of potential participants (NGOs, charities, and social media), the number of participants recruited within the set time period (30 in 6 months), sample characteristics (age, gender, ethnicity, and religion), and reasons for loss at each stage (consent, eligibility, enrollment, etc).

The feasibility of measurement instruments will be assessed in terms of the number of people who completed questionnaires, the amount of information missing, which should not exceed 10%, and the time it took to complete them. This will include measuring SI for intervention participants at baseline (T1), after 3 weeks (T2), and post treatment (6 weeks after baseline: T3). Depression, anxiety, and PTSD will also be measured at baseline and post treatment. If possible, all participants who begin the intervention will complete the follow-up assessment at week 6 irrespective of whether they complete the intervention or not. All the data will be recorded on the eCTF. The outcome measures used in the study are as follows:

SI will be measured using the SI subscale of the C-SSRS, which is a 6-item tool used to assess SI [38], which has shown good internal consistency (α=.966) for an Arabic-speaking population [39]. The C-SSRS was chosen due to its compatibility with Syrian's conceptualization of SI as a wish for death. An answer of yes to any of the 6 questions indicates a presence of SI, and a score of 4 and above indicates serious SI.

Anxiety and depression will be measured with the Hospital Anxiety and Depression Scale (HADS) [40,41]. The Arabic version has shown acceptable internal consistency for both the anxiety (α=.73) and depression scale (α=.77) [42]. HADS consists of 14 items, which are scored on a 4-point Likert scale between 0 and 3. The total score range is between 0 and 21, with scores between 0 to 7 indicating normal anxiety or depression, scores between 8 to 10 indicating borderline abnormal anxiety or depression, and scores above 11 indicating abnormal anxiety or depression.

PTSD will be measured with the Arab versions of the Posttraumatic Stress Disorder Checklist for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]; PCL-5), which has shown high (α=.85) internal consistency [43]. The scale consists of 20 self-report items. Each item includes 5 points with scores ranging between 0=not at all and 4=extreme. A total score of 31-35 or higher suggests that a patient may benefit from PTSD treatment.

Participant Timeline

Recruitment will be conducted over a 6-month period starting from February 2024 and ending in July 2024. Recruitment goals will be recorded using the case tracking form up until a final disposition is made. As soon as participants contact OB, they will receive a participant information sheet (PIS) and schedule a time to provide consent. The informed consent process will take 10 minutes via Microsoft Teams, during which the participant will be able to ask questions, and written informed consent can be completed on their behalf. An additional 5 minutes is needed to screen the participant for eligibility. Eligible participants will then complete baseline measures for SI, anxiety, depression, and PTSD, which should take 15 minutes. This entire process should take no longer than 30 minutes. As part of the study's safety protocol, participants will be contacted at week 3 and 6 to assess their level of SI, which should only take 5 minutes. After 6 weeks, a prearranged web-based meeting will be held via Microsoft Teams to take postintervention measures of SI, anxiety, depression, and PTSD, which should require 15 minutes to complete. Intervention participants will also be sent an email to schedule a date for an interview within 1 week of completing the intervention. The interview will be held via Microsoft Teams, which should take 45-60 minutes to complete.

Sample Size

The study aims to recruit 30 male or female Syrian asylum seekers and refugees in the United Kingdom, aged 18 years and older, with at least a score of 1 on the C-SSRS [38]. To assess the acceptability of the intervention, at least 12 eligible participants must be recruited for the intervention and postintervention interviews within 6 months (February to July 2024). This number was chosen to enable data saturation for the acceptability and suitability interview at 7 participants while compensating for expected attrition. Since the target population are minorities in the United Kingdom, recruitment is expected to have a lower yield within the allocated time period. If possible, participants will be stratified for sex (male: n=6 and female: n=6), major ethnic groups (Arab: n=10 and Kurdish: n=2), and age (18-39 years: n=10 and 40 years and older: n=2). The National Center for Complementary and Integrative Health notes that sample sizes should be based on practical considerations, including participant flow, financial constraints, and the number of participants needed to evaluate feasibility goals [44]. For qualitative work, 30 or less participants are enough to reach saturation.

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Recruitment

As mentioned before, Eylem et al [22] were unable to recruit enough participants for an RCT and therefore recommended task-shifting to lay people associated with the target population. Task-shifting recruitment to community-based health workers and volunteers has shown to improve recruitment and access for minority ethnic groups [45,46] and was also suggested to scale up mental health interventions for Syrian refugees in the Middle East and Europe [47]. Thus, participants will be recruited via cultural brokers as well as NGOs, charities, local councils, and social media.

The study will use purposive sampling to recruit participants from various demographic backgrounds including age, gender, religion, ethnicity, and refugee status. All recruitment will be via the web using a study advertisement or email correspondence, which will outline the purpose and development of the intervention. OB will be responsible for all direct communication with participants and external individuals and organizations involved in sharing information about the study. The recruitment process will be recorded using an eCTF in accordance with the 8-step guidelines of Stewart et al [37], which includes tracking the sources of potential participants (NGOs, charities, local councils, and social media), the number of participants recruited within the set time period (60 in 6 months), sample characteristics (age, gender, ethnicity, and religion), and reasons for loss at each stage (consent, eligibility, randomization, waiting list, intervention, and interview). No incentives for participation will be provided other than access to the intervention.

Assignment of Interventions

Since this is an open-label study, aspects such as randomization and blinding procedures were not considered.

Data Collection, Management, and Analysis

Data Collection Plan

Primary Outcomes

In line with the feasibility study by Eylem et al [22] of the same intervention, the acceptability of the intervention to participants will be assessed using one-to-one semistructured interviews in terms of cultural relevance (ie, the familiarity of the therapeutic content to one's cultural background), cultural appropriateness (ie, appropriateness of the therapeutic content in terms of the Syrian cultural context), and whether participants were satisfied with their experience. Like the previous study [2], participants' lived experience with the migratory process will form the basis of discussions on cultural relevance and appropriateness.

As mentioned earlier, the suitability of the intervention will be analyzed quantitatively in terms of recruitment and adherence rates. Data will be collected with case tracking forms throughout the intervention and during interviews at the end of the intervention. Self-reported and user analytics adherence rates will assess the acceptability of these adaptations and the need for further adaptations.

Secondary Outcomes

Recruitment goals will be tracked in accordance with the guidelines of Stewart et al [37] for diverse populations. The use of their guidelines will not only provide structure to the recruitment process but will enable its replication for future studies.

The feasibility of measurement instruments will involve measuring SI for intervention participants at baseline (T1), after 3 weeks (T2), and post treatment (6 weeks after baseline: T3) and depression, anxiety, and PTSD at T1 and T3. Measurements will all be completed during web-based meetings and recorded on the eCTF.

In total, participants will be assessed using 3 outcome measures: C-SSRS [38], the Arabic version of the HADS [40,41], and the Arabic version of the PCL-5 [43]. The C-SSRS was chosen due to its assessment of both SI and a wish for death as well as its good internal consistency (α= .966) for an Arabic-speaking population [39]. The HADS [40,41] was chosen due to its Arabic version showing acceptable internal consistency for both the anxiety (α=.73) and depression scale (α=.77) [42]. In a previous study, Beuthin et al [2] identified stressors with the asylum process as a major concern for Syrian asylum seekers in the United Kingdom, which could be related to anxiety and depression. Finally, the Arabic version of the PCL-5 has shown high (α=.85) internal consistency [43]. Again, in the study by Beuthin et al [2], several Syrian refugees in the United Kingdom reported being diagnosed with PTSD.

Quality Control

All participant data, except for interviews, will be recorded in a separate eCTF, which will be completed in an Excel sheet kept in OneDrive for Business. Data from eCTFs will be added to a joint database for analysis once the participant reaches a final outcome. Interviews will be audio-recorded to ensure accuracy. Once transcribed and translated, the audio recordings will be deleted. At the end of the study, all data will be transferred to the chief investigator.

Training

All members of the research team have completed the National Institute for Health and Care Research Good Clinical Practice course as well as internal university training in research integrity and security and data privacy awareness. All intervention coaches will be fluent Arabic speakers with at least a master degree in health sciences. They will be trained by the DPhil researcher (OB) in the purpose and procedures of each intervention component to help answer participant questions and provide feedback on their homework.

Data Collection Plan: Retention

Participant Retention

To enable retention, obtaining informed consent, eligibility screening, enrollment, and all outcome measures will be completed via Microsoft Teams with the assistance of OB instead of web-based surveys. Participants will be followed throughout the trial, and reasons for nonadherence and withdrawal will be recorded within the eCTF if possible. As

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mentioned earlier, the intervention has been culturally adapted to improve engagement and understanding [2].

Participant Withdrawal

Participants will be informed in the PIS that if they choose to discontinue their participation, information recorded in the eCTF up until discontinuation will be retained. All other data including their contact details and those of their GP surgery, exercises and interview audio recording, and transcriptions and translations will be deleted. Participants who score above the cutoff score (4 and above) on the C-SSRS [39] indicating active SI with some intent to act at T2 (week 3), and T3 (week 6) will be withdrawn. To ensure participation in postintervention interviews, the time and date for the interview will be set with the participant during T2 measurements of SI.

Data Management

Original written informed consent forms and outcome measures completed by OB on behalf of the participant will be scanned, and password-protected copies will be sent to the participant via email. These data as well as eligibility screening and data necessary to stratify the postintervention interviews such as ethnicity, gender, and religion will be entered electronically into individual case tracking forms labeled with a unique participant number and held in OneDrive for Business provided by the university. Data from eCTFs will later be added to a joint database for analysis once the participant reaches a final outcome. Interview participants' audio recordings will be labeled with a unique participant number and stored on OneDrive for Business. They will then be deleted after their transcriptions and translations are uploaded to OneDrive. Participant contact details connected to their unique participant number will be kept in a form on OneDrive for Business throughout their participation and deleted when they reach a final outcome. Access to the uploaded data will only be permitted for the DPhil researcher (OB) and the principal investigator (KB) and upon request to members of the Medical Sciences Interdivisional Research Ethics Committee for the purposes of monitoring and auditing of the research. In accordance with university policy, all nonidentifiable data will be stored for at least 3 years after publication. At the end of the study, OB will transfer all data from university servers to the custodianship of the principal investigator (KB), who will thereon be responsible for data management.

Quantitative Outcomes

Quantitative feasibility outcomes will be reported descriptively. Recruitment rates will be assessed in terms of the percentage of those contacted who met the eligibility criteria and the percentage of those eligible who were enrolled. Adherence is defined in terms of the number of sessions attended and the time spent completing them. Adherence rates will be calculated as the percentage of all participants who adhered to the intervention. Outcome measure completion rates are defined as the percentage of participants who completed the outcomes and the percentage of the outcomes completed. The feasibility of recruitment methods meeting recruitment goals will also be assessed quantitatively in terms of the percentage of participants recruited from different sources (NGOs, charities, social media, and cultural brokers), the number of participants recruited within the set time period, and the sample characteristics (age, gender, ethnicity, and religion).

Qualitative Outcomes

The suitability of the intervention will also be assessed qualitatively in terms of the barriers and facilitators to engagement. This will include participants' reasons for attrition recorded in the eCTF and key touchpoints of their experience with the intervention. Acceptability of the intervention in terms of cultural relevance and appropriateness and participant's overall satisfaction with the intervention will be analyzed thematically. Building on the previous study to culturally adapt the digital intervention, the thematic analysis will be conducted in accordance with the 6 phases outlined by Braun and Clarke [48]. Importantly, Braun and Clarke [48] differentiate between semantic themes revealed through description and latent themes through interpretation. This understanding of language is based on a distinction between semantics and pragmatics, which limits meaning to adherence with conventions. However, since language is a social practice, meaning is more fundamentally the use of conventions [28]. This understanding is especially clear where conventions differ between interlocutors such as in intercultural communication. Therefore, this study will instead extract themes based on the communication of touchpoints of lived experience and the objectives of the study [28]. Internal reliability will be ensured by an iterative review of themes as well as checking for consistency between members of the research team [49]. Irreconcilable differences in interpretations of the data will be solved by preferencing interpretations in line with participants' experiences with the intervention and the objectives of the interviews.

Monitoring

Harms

The intervention was previously found to be safe for general populations in the Netherlands [24], Belgium [25], and Australia [26] and Turkish immigrants in the Netherlands and the United Kingdom [22]. A safety protocol developed in collaboration with and approved by the university ethics department will ensure the safety of participants throughout the study. The safety protocol has an important balance to make between minimizing the risk of adverse events while still ensuring that the intervention is provided to populations that are most likely to use it. As such, Syrian asylum seekers and refugees in the United Kingdom who have serious SI will not be allowed to participate. After providing consent, participants will be assessed for suicidal thoughts using the SI subscale of the C-SSRS [38]. An answer of yes to any of the 6 questions indicates a presence of SI and a score of 4 and above indicates serious SI, specifically, active SI with some intent to act. Participants who answer yes to any of the questions will be encouraged to contact their GP and will be provided with information about alternative sources of help. In addition to measuring SI before receiving the intervention (T1: baseline), SI will be measured again at T2 (week 3) and T3 (week 6). Any increase in SI will be reported to the principal researcher (KB), who will review the circumstances and act according to his judgment. If a participant scores above the cutoff score (4 and above) during the web-based meeting, they will be immediately encouraged to seek help from their GP or

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their GP surgery will be contacted with a generic email already approved by the ethics committee, and they will be withdrawn from the study. Participants will be informed about this procedure in the PIS.

The DPhil researcher (OB) will also report any incidental findings to the principal investigator (KB), who will in turn review the circumstances and act according to his judgment. If further steps are necessary, the matter will be referred to the Multi-Agency Safeguarding Hub, which will be made within 1 working day of first receiving the information from the participant. The Local Area Designated Officer will then advise on the next appropriate steps to take. If any risk of harm is directed toward an adult, a referral will be made to the relevant statutory agency. If there is a risk of immediate harm, the emergency services will be contacted via 999.

Auditing

The Medical Sciences Interdivisional Research Ethics Committee at the University of Oxford will have access to the study data upon request for the purposes of monitoring and auditing of the research.

Ethical Considerations

Ethics approval has been provided for the study by the Central University Research Ethics Committee at the University of Oxford (R89074/RE001). Eligible participants will receive a PIS before meeting via Microsoft Teams to ask questions and provide their informed consent. The PIS will describe, in both Arabic and English, the goals and limitations of the study, its procedures including the intervention and how data will be collected and handled, and any risks to participants. Participants will also be told that they are free to withdraw from participation at any time, for any reason, and without consequence. Since the intervention is web-based, written informed consent will be completed on behalf of the participant. A digital copy will be provided to the participant and kept on university servers for at least 3 years from the time of publication. Access to personal data will be restricted to only authorized individuals. Personal names will be replaced with unique participant numbers on eCTFs and audio recordings and transcriptions of interviews. All audio recordings will be deleted once they have been transcribed, and all original paper copies will be destroyed once transferred to eCTFs. The remaining data will be kept on university servers, OneDrive for Business, for 3 years from the time of first publication in accordance with Oxford University policy. Like the previous study [2], the findings of this study will be disseminated through publication and web-based Syrian asylum seeker and refugee communities. The overall research project will contribute toward OB's dissertation research, which will be held in Oxford University's Bodleian Library and possibly published at a later stage. As per the stipulations of the ethics committee, participants will not be provided any compensation for their involvement in the study.

Results

Recruitment began in February 2024 and will run until 30 participants have been recruited to the study or until the end of July 2024. Thus far, 19 participants have been recruited and provided consent, 16 of whom were eligible, and 12 have completed the postintervention interview. All but one participant were recruited via cultural brokers. The study, including the write-up period, is expected to end in December 2024.

Discussion

Expected Findings

This paper describes the study protocol for the feasibility and acceptability study of a culturally adapted digital SI intervention for Syrian asylum seekers and refugees in the United Kingdom. The intervention was previously culturally adapted in collaboration with Syrian asylum seekers and refugees in the United Kingdom. First, the adaptation process involved conducting interviews to explore their lived experiences with the migratory process; their cultural conceptualizations, coping strategies, and help-seeking behavior for mental health and SI; and their attitudes toward digital mental health. One of the most significant findings of this phase was that a wish for death may not only be less stigmatized but is also a more salient mechanism of SI for this population. More specifically, a wish for death could be related to the acquired capability for suicide dimension in the interpersonal theory of suicide [50]. Moreover, while attributing their thoughts to lived experience, participants believed suicide was fundamentally caused by diminished sources of support such as weak imān (faith), a loss of one's mind, character and soul, and a lack of mental health support. This could suggest that suicide is attributable to a lack of access to one's repetitive sources of support. Second, Syrian asylum seekers and refugees in the United Kingdom collaborated in co-design events to identify and culturally adapt touchpoints of the intervention. The main adaptations to the intervention included translating the intervention to Arabic and adding cultural idioms of distress, case examples of a wish for death and an SI crisis, culturally relevant coping strategies, a nondirective approach that included explanations for each exercise, encouragement, and reminders throughout the intervention. For a more detailed description of the cultural adaptations, see Beuthin et al [2].

Since the participants involved in the cultural adaptation process did not use the intervention and some did not have SI, further research is needed to assess its feasibility and acceptability to users with SI. Thus, this study will consist of two phases: (1) recruiting participants and delivering the digital intervention and (2) one-to-one semistructured interviews. First, participants will be recruited from various sources including cultural brokers via the web, NGOs, and charities to assess the feasibility of meeting recruitment goals and recruitment rates. Second, interviews will be conducted to assess the suitability and acceptability of the culturally adapted intervention. Findings from the study could result in further adaptations to the intervention including those already made as well as inform the design of a future RCT. Two areas that are most likely to require further adaptation are the Arabic translation and content on SI. As English and Arabic belong to very distant language families, it can be challenging to translate in either direction. Likewise, the extent to which Syrian asylum seekers and refugees are willing to approach their thoughts about suicide directly is still

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unknown. The findings of the study may also indicate the need to reduce the number of outcome measures or questions to be asked in a future RCT as well as the amount of contact with researchers.

Limitations

The study has 2 main limitations. First, recruitment strategies will not include recruiting participants via the NHS. However, given the barriers to help-seeking for Syrian asylum seekers and refugees and the current budget of this study, the expected recruitment potential of the NHS does not justify the financial costs. Second, the study will exclude Syrian asylum seekers and refugees with serious suicidal thoughts from participation. While this might be a necessary safety precaution for this study, Syrian asylum seekers and refugees tend toward 2 extremes in relation to SI, either a wish for death or an SI crisis. Thus, in addition to recruiting via cultural brokers, a future RCT or actual implementation of the intervention could include participants with serious SI by recruiting via the NHS.

Conclusions

War in Syria has displaced over 6.8 million people, more than any other conflict since the Second World War [1]. As a result, Syrian asylum seekers and refugees have experienced several life-changing events including the loss of family members, property, and livelihood. These experiences have also negatively impacted their mental health including high rates of anxiety, depression, and PTSD. Syrian asylum seekers and refugees continue to experience stressors in the process of seeking refuge and help for their mental health that could result in SI [2]. However, there is currently only 1 intervention that directly addresses suicidal behavior for asylum seekers and refugees. Thus, towards closing the treatment gap, this study will assess the feasibility and acceptability of a culturally adapted digital intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom. This includes assessing the feasibility of recruitment strategies such as task-shifting to trained lay people within the British Syrian diaspora. Identifying and understanding the touchpoints of experience associated with the intervention could also facilitate a future RCT and local implementation. Finally, this study may also provide insight into the extent to which the culturally adapted intervention can be generalized to Syrian asylum seeker and refugee populations outside of the United Kingdom.

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Data Availability

The data sets generated and analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Authors' Contributions

OB was responsible for conceptualization, methodology, data curation, formal analysis, investigation, project administration, and writing the original draft and reviewing and editing. SS and LMY were responsible for methodology and formal analysis. KB will be responsible for methodology, formal analysis, and supervision.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
C-SSRS: Columbia-Suicide Severity Rating Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
eCTF: electronic case tracking form
GP: general practitioner
HADS: Hospital Anxiety and Depression Scale

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NGO: nongovernmental organization
NHS: National Health Service
PCL-5: Posttraumatic Stress Disorder Checklist for DSM-5
PIS: participant information sheet
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
SI: suicidal ideation
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Parent Education and Counseling (PairEd-C) Intervention to Improve Family-Centered Care: Protocol for a Prospective Acceptability Study Using the Theoretical Framework of Acceptability

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Abstract

Background: Family-centered care (FCC) is an intervention approach based on a respectful relationship between family and health care providers (HCPs) to ensure the health and well-being of children and their families. Although HCPs have a better perception of FCC, the level of its implementation is low. Reasons for low implementation include limited understanding, lack of training, and lack of implementation guidelines and tools to support implementation. Thus, we developed the Parent Education and Counseling (PairEd-C) intervention to improve FCC in pediatric oncology settings and assess its acceptability.

Objective: The objective of this study is to assess the prospective acceptability of the PairEd-C intervention using the theoretical framework of acceptability (TFA) in the pediatric oncology department in a tertiary hospital in Ethiopia.

Methods: The study was conducted using an exploratory qualitative study design. We aimed to recruit 10 to 15 participants for the in-depth interview. The study participants were health service leaders working in child cancer, HCPs, social workers, and parents of children with cancer. The intervention was developed using the integration of the first phase of the Medical Research Council (MRC) framework for developing and testing complex interventions and the behavior change wheel (BCW) framework. The main PairEd-C intervention components align with the intervention functions of education, persuasion, training, environmental restructuring, modeling, and enablement, which were intended to improve FCC in the pediatric oncology unit by providing structured and comprehensive education and counseling of parents of children with cancer. The intervention was implemented by providing training for the health care team, facilitating discussion among HCPs and setting a shared plan, improving the commitment of the health care team, providing education for parents, improving parents' capacity to attend the intervention sessions, arranging discussion among parents of children with cancer, and provision of education and counseling on distress. The HCPs working in the unit received training on the designed intervention. The trained educators and the health care provider delivered the intervention. Data will be analyzed using deductive thematic coding with a framework analysis technique based on the 7 TFA constructs. Atlas ti. version 9 will be used for data analysis.

Results: Funding was acquired in 2017, and ethical clearance for conducting the study was obtained. We conducted the interviews with the study participants from December 2023 to January 2024. As of the acceptance of this protocol (June 2024), 12 study

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participants were interviewed. The data analysis process was started subsequently, and the manuscript will be completed and submitted for publication in early 2025.

Conclusions: This acceptability study is expected to show that the designed intervention is acceptable to study participants, and the findings will be used to improve the intervention before progressing to the next step of our project.

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KEYWORDS

family-centered care; child cancer; theoretical framework of acceptability; education and counseling; acceptability; parent education; family centered; care service; theoretical framework; study protocol; family; health care; well-being; children; implementation; design intervention

Introduction

Family-centered care (FCC) is a respectful relationship between family and health care providers (HCPs) to ensure the health and well-being of children and their families. It recognizes the abilities, customs, cultures, and knowledge that HCPs and families bring to the partnership. In addition to improving the patient's and family's experience with health care, it lowers stress, fosters better communication, lessens conflict, and enhances the health of children with long-term medical disorders. Compared with patients who do not receive FCC, those who receive FCC had improved psychosocial status, communication between family members and health care professionals, and understanding about childhood cancer [1]. Thus, FCC provides care to children and families in which all family members are acknowledged as care recipients and treatment is organized considering the family as a whole [2].

Although HCPs have a better perception of FCC, there are disparities in performance and perceptions of various FCC subdomains [3-9]. Different barriers that hinder the implementation of FCC related to health providers, organizations, and families have been reported. These barriers include limited understanding of FCC principles; communication difficulties; inadequate skills; inconsistent training; and lack of knowledge, skills, time, or tools to support the implementation of FCC [8,10,11]. In addition, a lack of policy and guidelines on FCC, poor infrastructure, poor-quality design, poor intervention content, and the burden on health providers from competing priorities have been reported [12,13]. A shortage of HCPs, a lack of time, and the absence of an FCC system were also identified as barriers [10].

To overcome these challenges and facilitate the intervention of FCC in the pediatric oncology unit, we designed a new intervention based on the local context. To develop this intervention, we identified evidence through a systematic review, explored the relevant and guiding theory for intervention development, conducted baseline studies using mixed methods, and held a series of complex intervention FCC design workshops. Finally, we developed an intervention called Parent Education and Counseling (PairEd-C) to improve the delivery of FCC in the pediatric oncology unit in Ethiopia.

One key aspect of intervention effectiveness is the extent to which the intervention is considered acceptable to those providing and receiving it. Therefore, it is essential to conduct an acceptability study before implementing a new intervention [14]. Sekhon et al [15] defined acceptability as "a multifaceted construct that reflects the extent to which people delivering or receiving a health care intervention consider it appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention." Assessing an intervention's acceptability involves evaluating how well the target population will respond to it and how much of its components suit the needs of the target demographic and organizational setting [14,16,17]. Acceptability studies are important in developing and evaluating complex interventions [18,19]. They help reduce the risk of unsuccessful implementation, reduce distrust, improve adherence to the plan, and increase the likelihood of the intervention's sustainability [14,16,20-23].

Thus, assessing the acceptability of the PairEd-C intervention is particularly important to make all necessary modifications before evaluating the intervention clinically and understanding how best it can be implemented. The aim of this study is, therefore, to explore the prospective acceptability of the PairEd-C intervention among HCPs and parents of children with cancer to optimize further development, evaluation, and, ultimately, its implementation.

Methods

Study Setting and Design

The study was conducted in the pediatric hemato-oncology unit in the Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. This unit is the country's main referral center for child cancer treatment. It provides care delivered by pediatric hemato-oncologists, pediatric hemato-oncology fellows, pediatric residents, oncology nurses, and generic nurses. The unit also has social workers and psychologists. Each year, the unit provides care for about 600 new cases of children with cancer. Cancer treatment in this unit mainly involves chemotherapy, radiotherapy, and surgery.

Study Design

A descriptive, exploratory qualitative study is being used to assess the prospective acceptability of the newly designed PairEd-C intervention using the theoretical framework of acceptability (TFA).

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Participant Recruitment

Since our objective is to assess acceptability from the perspectives of both parents of children with cancer and HCPs, the study participants were the parents of children with cancer and HCPs (physicians, nurses, social workers, and team leaders) working in the unit. In addition, policymakers were interviewed to get their perspectives on the intervention. Parents of children with cancer who visit the pediatric oncology unit and met our inclusion criteria were invited to participate in the in-depth interview. We anticipated recruiting a total of 5 parents of children with cancer. During the selection of parents, maximum variation was maintained by residence, education status, and type of childhood cancer. We planned to include 10 HCPs (physicians, nurses, and psychologists) in the in-depth interviews. During the selection of HCPs, responsibility in the unit, service year at pediatric oncology, working area, and level of education were considered. Saturation determined the final number of study participants.

Theoretical Framework

We adapted the TFA developed by Sekhon et al [15] to guide this study [15]. The TFA is designed explicitly to assess the acceptability of health care interventions from the perspectives of people receiving and delivering interventions. It sets out a theory-informed structure based on participants' cognitive and emotional responses [15]. It consists of 7 conceptually different constructs that capture the following essential acceptability dimensions: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy [15]. See Figure 1. It can be applied before, during, or after an intervention to assess prospective, concurrent, and retrospective acceptability. Since its development in 2017, it has been applied in varied contexts for these purposes [24-27]. It has also been used for structured data analysis [26,28-31], developing questionnaires [32,33], and informing an interview guide development [24,27,32-34]. The TFA can be applied using quantitative, qualitative, or mixed study approaches.

Figure 1. The theoretical framework of acceptability developed by Sekhon and colleagues [15].

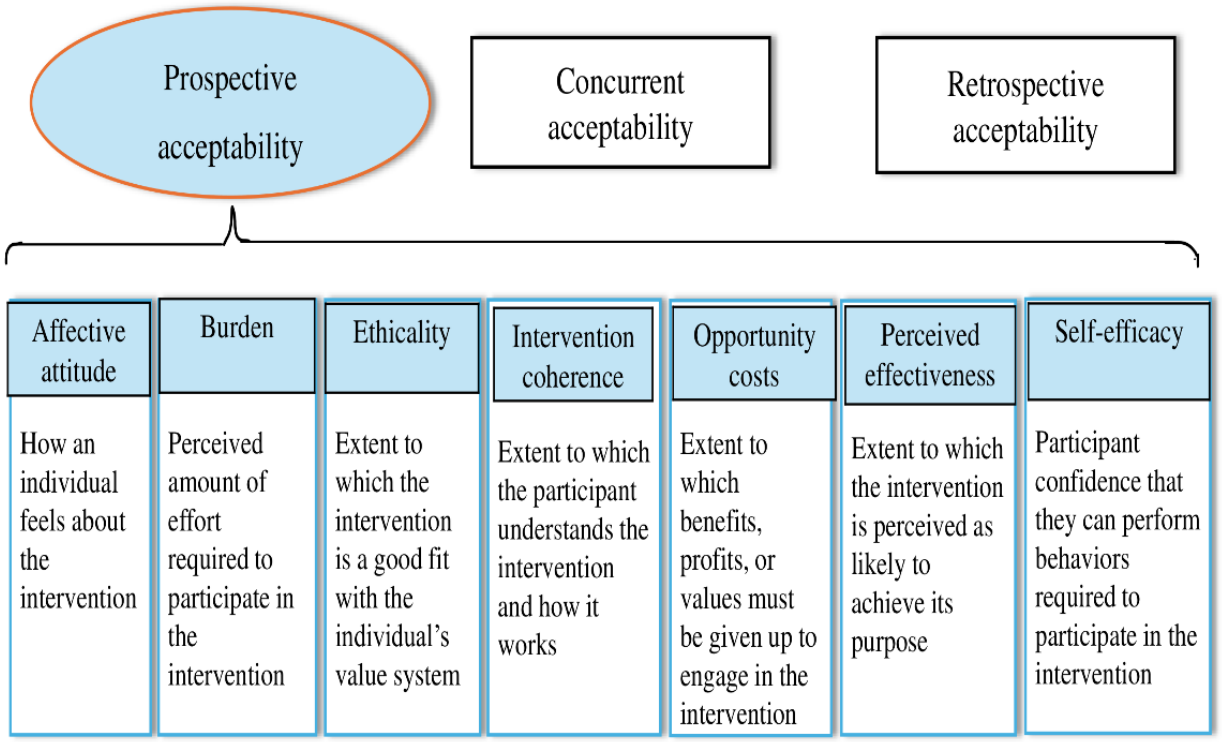

For this study, the TFA is suitable since its concepts are applicable for evaluating an intervention in individual, interpersonal, and community contexts. Similarly, the PairEd-C intervention is planned to be delivered to parents of children with cancer coming from different socioeconomic backgrounds. As a result, to evaluate it, a framework with components that are applicable to assessing how context-specific demands are met by providing a workable and culturally relevant solution must be used. Therefore, we planned to evaluate acceptability as the perception among beneficiaries and intervention implementers. This aids in determining whether the current intervention will be agreeable, palatable, or satisfactory. This will help to obtain more collective feedback about the nature of the PairEd-C intervention from different stakeholders [15,35]. In addition, assessing anticipated acceptability before participation can highlight which aspects of the intervention could be modified to increase acceptability and, thus, participation [15].

The PairEd-C Intervention

The PairEd-C intervention was developed by integrating the Medical Research Council (MRC) [23] and behavior change wheel (BCW) [36] models. These theoretical foundations were used for similarly designed interventions in different setups. The BCW was developed from frameworks of behavior change and includes the behavior system known as COM-B at the center [36]. COM-B includes capability (C), opportunity (O), and motivation (M), which ultimately interact to produce behaviors

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(B) [36]. Parents' behaviors that require modification include their intention to be involved in their child's care, to ask and communicate with HCPs, and communicate with other parents of children with cancer. The BCW includes 9 intervention functions and 7 policy categories that support intervention design [36]. The main PairEd-C intervention components will align with the following intervention functions: education, persuasion, training, environmental restructuring, modeling, and enablement. These intervention functions are intended to improve FCC at the pediatric oncology unit through the provision of structured and comprehensive education and counseling for parents of children with cancer.

The main intervention components are providing training for the health care team, discussion among HCPs and setting a shared plan, improving commitment of the health care team, providing education for parents, improving parents' capacity to attend, monitoring and using the intervention, arranging discussion among parents of children with cancer, and education and counseling on distress. The HCPs will receive training on the designed intervention. The trained HCPs will be responsible for implementing the other components, including providing training to parent-peer educators. The trained educators, with the HCP, will be involved in providing education for parents, facilitating discussion among parents, improving parenting capacity, and providing education and counseling on stress management. The detailed intervention description is presented using the Template for Intervention Description and Replication checklist. See Table 1. Figure 2 presents a logic model developed to link the health care systems context, such as the study setting, resources, intervention activities, theory and assumptions underlying the intervention, and the intervention plan, in a logical order. In addition, Figure 3 shows the implementation flow of the intervention components for the provision of comprehensive, structured education and counseling for parents of children with cancer.

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Table 1. The Template for Intervention Description and Replication checklist [37].

Item number	Item	Item description
1	Brief name	• Family-centered PairEd-C[a] intervention for childhood cancer
2	(Why): Rationale, theory, or goal of the elements essential to the intervention	• The rationale is to improve FCC[b] at the pediatric oncology unit through the provision of structured and comprehensive parental education and counseling. • Improved FCC will improve parents' psychological health conditions. • The intervention is systematically developed based on the MRC[c] framework and the behavior change wheel model.
3	(What materials): Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or training intervention providers.	• Parents will receive education and counseling on general information about cancer, cancer treatment, side effects and management of cancer treatment, providing care for a sick child at home and the hospital, and coping with a child's diagnosis of cancer. • A training manual for parents and HCPs[d] will be provided. • Parents will receive teaching aids at the end of each session.
4	(What procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	• The intervention will be implemented in 4 consecutive phases (Figure 1): phase I: preparation of setups in the pediatric oncology unit; phase II: providing training for HCPs (nurses); phase III: providing training for family peer educators; phase IV: participant selection and provision of parent education and counseling • Parents will be provided with comprehensive information related to childhood cancer through a series of 12 consecutive sessions. • The group discussion will follow information delivery using face-to-face counseling, videos, leaflets, and cartoon dialogs.
5	(Who provided): For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background, and any specific training given.	• All HCPs in the pediatric oncology unit will receive training on the PairEd-C intervention for childhood cancer. • Nurses with an MSc in oncology will be assigned as coordinators and lead the intervention provision. • Other HCPs will help to inform and recruit parents. • The trained parents will facilitate parent group discussions and help as liaisons between parents and HCPs.
6	(How): Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	The intervention will be delivered using multiple approaches: • Face to face: individual counseling and group discussions led by trained parents • Videos, leaflets, and cartoon dialogs to provide information
7	(Where): Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	• The intervention will be conducted at TASH[e] pediatric oncology unit. • Parents of children visiting inpatient and outpatient units will participate in the intervention.
8	(When and how much): Describe the number of times the intervention was delivered and over what period, including the number of sessions; their schedule; and their duration, intensity, or dose.	• The PairEd-C intervention will be delivered every 2 weeks across 28 weeks. • The overall intervention is classified into 12 sessions. • The parents will receive the intervention when they visit the unit for regular child appointments.
9	(Tailoring): If the intervention was planned to be personalized, titrated, or adapted, describe what, why, when, and how.	• The intervention schedule might be modified based on the child's condition and treatment plan. • Parents can also visit the intervention team whenever the need arises. • The topic will be prioritized based on the child's illness, treatment type, and parents' preference. • This will help to address the parents' needs.
10	(Modifications): If the intervention was modified during the course of the study, describe the changes.	• Not applicable. We are currently in the MRC framework's design phase, and this section cannot be described until the study is complete.
11	(How well [planned]): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	• Designed and assessed according to the 5 domains of the NIH[f] Treatment Fidelity Framework

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Item number	Item	Item description
12	(How well [actual]): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	• Not applicable: the intervention is currently in the design phase. • The pilot testing, feasibility, and intervention evaluation will be conducted in the future.

[a]PairEd-C: Parent Education and Counseling.

[b]FCC: family-centered care.

[c]MRC: Medical Research Council.

[d]HCPs: health care providers.

[e]TASH: Tikur Anbessa Specialized Hospital.

[f]NIH: National Institute of Health.

Figure 2. Logic model linking the context of the health care system, resources, and intervention activities [19]. FCC: family-centered care; HCP: health care provider; PairEd-C: Parent Education and Counseling; TASH: Tikur Anbessa Specialized Hospital.

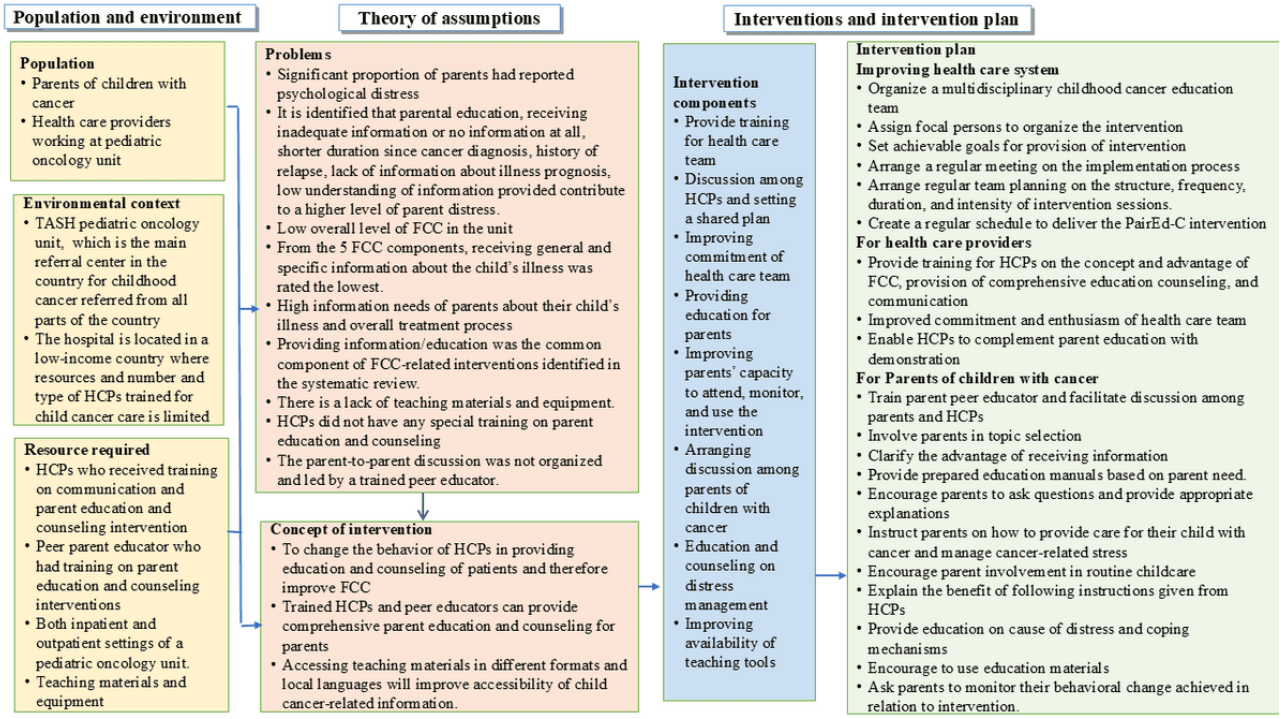

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Figure 3. Flowchart for the implementation of intervention components to provide comprehensive structured education and counseling for parents of children with cancer. HCP: health care provider.

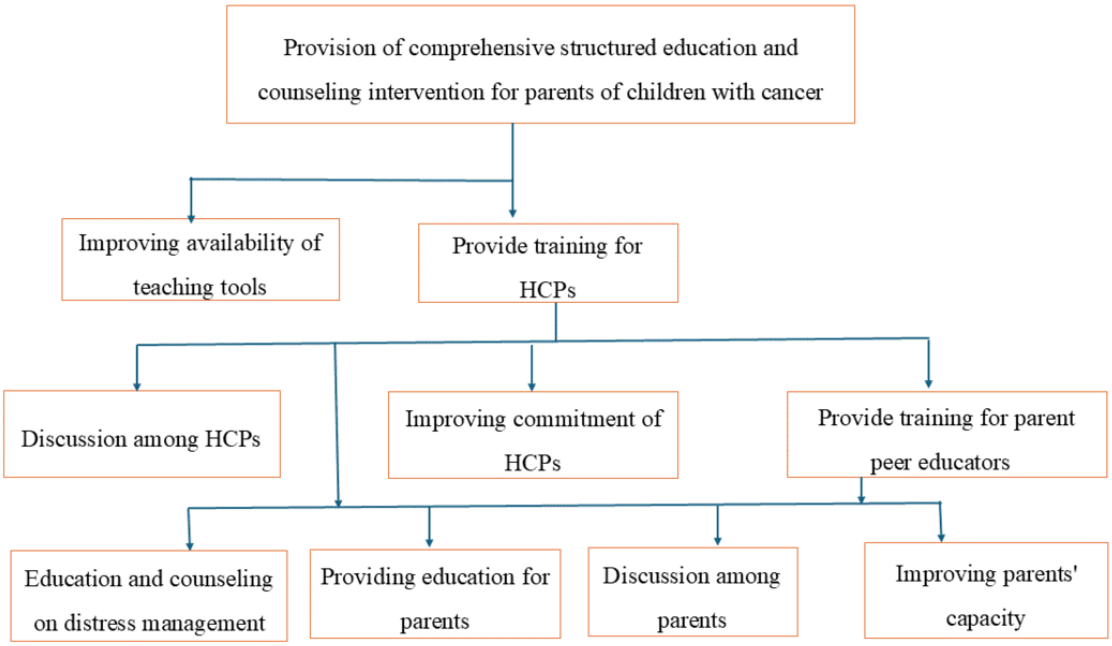

Data Collection

Before data collection, a summarized description of the intervention prepared in the local language, Amharic, was provided to the study participants. The description of the intervention includes the major activities provided in Table 1. In addition, detailed answers were provided for any questions raised by the study participants. Data were collected in an in-depth interview using a semistructured interview guide. The interview guide was developed based on the 7 dimensions of the TFA by Sekhon et al [15] as applied to the designed intervention. See Table 2. We used recommendations from the study by Sekhon et al [38] and similar studies to develop the interview guide [24,34,39]. For instance, "burden" was explored with the question, "How easy or difficult do you think to participate in the parent education or counseling sessions?" The interview guides were pilot tested after they were independently evaluated by 2 researchers with experience in public health and complex behavior change interventions. We used the process of "back coding" to check whether the interview guide aligns with TFA constructs. A draft interview guide with opening and closing questions arranged in a random sequence and a list of the TFA structures was sent to the implementation researchers. They were asked to indicate which TFA construct each question addressed and rate how certain they were of the match on a scale from 1 to 5 (1=not at all sure; 5=sure). This process was used to assess the construct validity and whether the interview guide adequately represented the constructs in the framework [40]. All interviews were digitally recorded using a portable audio recorder and transcribed verbatim.

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Table 2. In-depth interview guide, which was prepared using theoretical framework of acceptability (TFA) definitions to provide guidance for interviewers.

Section	Questions and prompts
Demographic characteristics	
For parents	1. Parent age _____ 2. Child age _____ 3. Family sex _____F_____ 4. Your relationship with the child ____ 5. Your educational status _____ 6. Residence: Urban/Rural _____ 7. Your child's cancer diagnosis ____ 8. Your child's treatment status _____ 9. Your child's type of treatment (chemotherapy, radiotherapy, both, off treatment, other) _____ 10. Time since your child has been ill ___ 11. Time since your child started treatment _____
For health care providers	1. Age _____ 2. Sex _____ 3. Profession _____ 4. Service year _____ 5. Your current position _____ 6. Time since assigned in your current position _____
Introduction	
For parents of children with cancer	• Can you talk me through the family-centered care you received at the pediatrics oncology unit? • How do you explain the attention and the care you received as a parent of a child with cancer? Prompts: Information you received about your child's illness, cancer treatment, and diagnostic procedure? During your stay in hospital or your child is treated in OPD[a]?
For health care providers and health leaders	• Can you talk me through your care in the pediatric oncology unit? • How do you explain the attention and the care you provide for parents of a child with cancer? Prompts: What information do you provide about child illness, cancer treatment, and diagnostic procedures? During their stay in hospital or child treatment in OPD?
Affective attitude: how an individual feels about participating in the intervention	• What are your overall feelings towards the planned intervention (your thoughts or feelings)? Prompts: For parents of children with new diagnoses? For parents of children with treatment follow-up? For a child on a different treatment regimen (chemotherapy/surgery)? For a parent visiting OPD? Admitted child? • How comfortable did you feel receiving/providing the designed intervention?
Burden: related to self-efficacy and focuses on the perceived amount of effort required to participate in the intervention.	• How much effort did it take to participate in the designed intervention? • How easy or difficult do you think it is to participate in the parent education or counseling sessions? What do you think makes the intervention easy or difficult? Prompt: for parents of children with cancer? For health care providers? For other family members?
Ethicality: the extent to which the intervention has a good fit with an individual's value system	• Do you think there are any moral or ethical issues (moral or ethical consequences) related to offering the PairEd-Cb intervention? Prompt: in addressing parents from different sociodemographic backgrounds? Considering inequity in delivering the intervention? • How do you evaluate cultural appropriateness, including the language of the intervention?
Perceived effectiveness: the extent to which the intervention is perceived to have achieved its intended purpose	• Do you think the PairEd-C intervention will be effective for the family of children with cancer? What are the possible outcomes of the interventions? Prompt: Can we help get a better understanding of child illness, treatment, diagnostics, and treatment procedures? In coping with a child's health condition? Improving overall parental and child health conditions? Improving parents' capacity to provide care for their sick child?
Intervention coherence: the extent to which the participant understands the intervention and how it works	• How do you predict the possible clarity (aim [purpose]) of the intervention for parents of children with cancer and/or for health care providers? • How complex will the intervention be for parents of children with cancer and/or for health care providers?

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Section	Questions and prompts
Opportunity cost: the benefits, profits, or values that would be given up engaging in the intervention	
Parents	• What other priorities can the intervention possibly interfere with? Compared to different activities in the hospital, how much do you think this intervention needs priority? Parents priority? Health care providers' priority? • Was there anything that you/health care providers would possibly give up so that you receive the PairEd-C intervention? Prompts: For newly diagnosed? Child on follow-up? Inpatient vs outpatient?
For health care providers	• What other priorities can the intervention possibly interfere with? Parents priority? Health care providers' priority? • Is there anything that you/parents of children with cancer would possibly give up so that you can provide the PairEd-C intervention? Prompts: For newly diagnosed? Child on follow-up? Inpatient vs outpatient?
Self-efficacy: the participant's confidence that they can perform the behavior(s) required to participate in the intervention	
For parents	• How confident are you that you will receive and complete the PairEd-C intervention? • How confident are you using and understanding the education and teaching materials given by the PairEd-C intervention?
For health care providers	• How confident are you delivering the complete PairEd-C intervention?
Closing	• Do you have any comments about the planned intervention? • Is there anything that you think could be done better? • Is there anything else you'd like to tell us? • Any other additional concerns on its acceptability?

[a]OPD: outpatient department.

[b]Pair-Ed-C: Parent Education and Counseling.

Qualitative Data Analysis

Qualitative data analysis will involve both deductive and inductive qualitative content analyses. Deductive thematic coding was used with a framework analysis technique based on the 7 constructs of the TFA [15]. In this phase, the text units were condensed, coded, and labeled using the participants' own words as much as possible. Two independent researchers coded all transcripts, resolving discrepancies through consensus or discussion with a third party. During the coding process, quotes were determined to be generally positive, negative, or neutral toward the designed intervention. Similar codes were merged into key themes and categorized into domains of the TFA where applicable. Themes that did not fit within the constructs and domains of the TFA were also listed as new insights that emerged from the interview. In addition, continuous data analysis was performed following each in-depth interview. A saturation evaluation was conducted, and data collection ceased once data saturation was reached during analysis and no new categories were identified. Atlas.ti version 9 was used for data management. To ensure trustworthiness, we used triangulation, debriefing, and member checking [41]. Triangulation involved cross-verifying data from various sources, including parents, nurses, oncologists, and head nurses.

Ethical Considerations

Ethical clearance was obtained from the Addis Ababa University College of Health Science institutional review board (protocol number 022/22/SPH). Permission was obtained from the TASH pediatric oncology unit. Written informed consent for the interviewee was obtained from each study participant. Participants were assured of their right to withdraw from the interview at any time, and participation in this study or refusal to participate did not affect their ability to access health services or any other services. Names and other personal information were not taken nor recorded. All information is kept confidential.

Dissemination

This study's findings will be published in an open-access journal and via national and international conference presentations.

Results

This acceptability study is expected to show that the designed PairEd-C intervention will be acceptable for both HCPs and parents of children with cancer. In addition, we expect the findings can be used to improve the intervention before progressing to the next step of our project. The study was funded in 2017. We conducted the interviews with the study participants from December 2023 to January 2024. As of the acceptance of this protocol (June 2024), 12 participants, comprising 8 HCPs and 4 families of children with cancer, were interviewed. The manuscript will be completed and submitted for publication in early 2025.

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Discussion

Overview

This study protocol describes the evaluation of the prospective acceptability of a newly designed intervention to improve FCC in the pediatric oncology setting in Ethiopia. A panel of experts in the field of pediatric oncology will modify the designed intervention based on information obtained from baseline surveys, international experiences, and their expertise. Although FCC is highly flexible and can be applied in a multitude of health care settings [42], studies on the design and evaluation of an FCC intervention in low-income countries are scarce. An intervention protocol to implement FCC in pediatric oncology settings is lacking in Ethiopia. Acceptability studies for health care interventions are becoming more widely recognized as a necessary condition [21], and the TFA has been successfully used to explore acceptability in health promotion interventions [28]. Therefore, this prospective acceptability study will establish strong foundational evidence that will play a vital role in the success of the newly developed intervention. In addition, the acceptability study will help to identify factors that would facilitate the acceptability of interventions to improve the designed family-centered education and counseling programs. The findings will also determine the strengths and weaknesses of the proposed intervention. We will also benefit from aligning the intervention with existing child cancer treatment.

Strengths and Limitations

The strength of this study is that we used a widely used framework as guidance. Having an intervention developed based on locally generated information and experts who understand the available setup will facilitate the acceptability of the intervention. Involving health service leaders, HCPs, social workers, and parents of children with cancer will help obtain more comprehensive information about the possible acceptability of the designed intervention. Regarding possible limitations of the study, parents' feedback might be biased due to their anticipation of trying something new. Social desirability bias might be introduced because of the nature of the study's interviews. In addition, the transferability of the findings might be limited due to the purposive nature of participant selection.

Conclusion

The results of this acceptability study will indicate that the designed intervention will be well received and accepted. The feedback obtained from parents, HCPs, and policymakers will be positive for all domains of the TFA. The education and counseling methods designed in the proposed intervention will significantly improve parents' understanding of their children's illness and enhance their capacity to provide care. It will also help fulfill the information needs of parents of children with cancer. In addition, we expect study participants will respond, as the intervention will help reduce parental psychological distress that is caused by their child's diagnosis of cancer. Components of the proposed intervention, such as its detailed nature, inclusion of HCPs, peer educator training, delivery of information using multiple methods, and integrated delivery of the intervention with regular care, will help make it more acceptable among parents and HCPs. The outcome of this study will also help identify possible challenges that might affect the implementation of the study. Furthermore, the findings will help identify potential areas of improvement.

Acknowledgments

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The author(s) attest that there was no use of generative artificial intelligence (AI) technology in the generation of text, figures, or other informational content of this manuscript.

Data Availability

Data sharing does not apply to this protocol, as no data sets have been collected nor analyzed.

Authors' Contributions

LD, AA, EG, AG, ST, and NL conceived, designed, implemented, and supervised the study; conducted the data analysis; reviewed and corrected the manuscript draft; and interpreted the study results. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BCW: behavior change wheel

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FCC: family-centered care
HCP: health care provider
MRC: Medical Research Council
PairEd-C: Parent Education and Counseling
TASH: Tikur Anbessa Specialized Hospital
TFA: theoretical framework of acceptability
TIDieR: Template for Intervention Description and Replication

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Protocol

Predicting the Transition From Depression to Suicidal Ideation Using Facebook Data Among Indian-Bangladeshi Individuals: Protocol for a Cohort Study

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Abstract

Background: Suicide stands as a global public health concern with a pronounced impact, especially in low- and middle-income countries, where it remains largely unnoticed as a significant health concern, leading to delays in diagnosis and intervention. South Asia, in particular, has seen limited development in this area of research, and applying existing models from other regions is challenging due to cost constraints and the region's distinct linguistics and behavior. Social media analysis, notably on platforms such as Facebook (Meta Platforms Inc), offers the potential for detecting major depressive disorder and aiding individuals at risk of suicidal ideation.

Objective: This study primarily focuses on India and Bangladesh, both South Asian countries. It aims to construct a predictive model for suicidal ideation by incorporating unique, unexplored features along with masked content from both public and private Facebook profiles. Moreover, the research aims to fill the existing research gap by addressing the distinct challenges posed by South Asia's unique behavioral patterns, socioeconomic conditions, and linguistic nuances. Ultimately, this research strives to enhance suicide prevention efforts in the region by offering a cost-effective solution.

Methods: This quantitative research study will gather data through a web-based platform. Initially, participants will be asked a few demographic questions and to complete the 9-item Patient Health Questionnaire assessment. Eligible participants who provide consent will receive an email requesting them to upload a ZIP file of their Facebook data. The study will begin by determining whether Facebook is the primary application for the participants based on their active hours and Facebook use duration. Subsequently, the predictive model will incorporate a wide range of previously unexplored variables, including anonymous postings, and textual analysis features, such as captions, biographic information, group membership, preferred pages, interactions with advertisement content, and search history. The model will also analyze the use of emojis and the types of games participants engage with on Facebook.

Results: The study obtained approval from the scientific review committee on October 2, 2023, and subsequently received institutional review committee ethical clearance on December 8, 2023. Our system is anticipated to automatically detect posts related to depression by analyzing the text and use pattern of the individual with the best accuracy possible. Ultimately, our research aims to have practical utility in identifying individuals who may be at risk of depression or in need of mental health support.

Conclusions: This initiative aims to enhance engagement in suicidal ideation medical care in South Asia to improve health outcomes. It is set to be the first study to consider predicting participants' primary social application use before analyzing their content to forecast behavior and mental states. The study holds the potential to revolutionize strategies and offer insights for scalable, accessible interventions while maintaining quality through comprehensive Facebook feature analysis.

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KEYWORDS

human-computer interaction; depression; suicidal ideation; mental health; India; Bangladesh; Facebook; major depressive disorder; MDD; 9-item Patient Health Questionnaire; PHQ-9; natural language processing; NLP; machine learning; ML

Introduction

Background

In Bangladesh and India, low- or middle-income countries (LMICs) of South Asia, the alarmingly high increasing rate of suicides is a dire situation [1]. One of the main reasons for this considerable rate, which is 75.5% [2], is that people going through this condition are not diagnosed early [3]. Stigma and gaps in proper treatment related to such mental health conditions have made this problem more widespread [4]. To help reduce this increasing rate of suicide, an automated and easy-to-access solution is required. This work aims to focus on the early detection of mental health problems in a resource-constrained setting [5].

The conventional approach to diagnosing depression requires patients to complete medical questionnaires and is subjective in nature [4]. Many studies have proven that behavior analysis through social media (SM) is the most convenient and fastest way to make the entire process easier and less time-consuming for patients [3,6-8]. Even by inspecting the behavioral patterns, especially by analyzing the text, it is possible to detect major depressive disorder (MDD) [9]. Studies have proven that identifying posts related to suicide begins with diagnosing depression levels, as suicidal ideation is particularly linked to MDD [10,11]. Numerous studies have shown that individuals with depression are at higher risk of attempting suicide [3]. Systems for detecting suicidal ideation using natural language processing (NLP) and machine learning (ML) on SM data are not fully suitable for LMICs like India and Bangladesh due to different behavioral patterns and socioeconomic conditions [12-14]. For example, texting style and grammar patterns are different [15]. Some sensor-based devices can detect depression [16], but this solution is not apt for this region [17].

In Bangladesh and India, the rising rate of suicides presents a grave concern, and statistics reveal an alarmingly high increase [18], with a significant portion (75.5%) attributed to late diagnosis [19]. The stigma surrounding mental health issues and gaps in appropriate treatment are at the root of this problem [20]. Notably, discussions on mental health problems remain neglected and a taboo in these communities, leading individuals to express their concerns primarily through SM platforms, such as Facebook (Meta Platforms Inc), rather than sharing them directly with others [21]. Moreover, SM continues to play a pivotal role in shaping communication patterns and societal dynamics. Bangladesh ranks among the top 3 countries for Facebook active user growth [22], and similarly, India currently has one of the largest user bases for Facebook, which is >314.6 million [23]. By focusing specifically on Bangladeshi and Indian users' Facebook data [24], the study aims to detect posts related to depression and observe the transition to suicidal ideation. This targeted approach within a specific cultural context will offer unique insights and outcomes, setting it apart from previous research efforts in this domain. Therefore, while building upon existing literature, the study seeks to provide valuable contributions by exploring new dimensions and nuances in the detection and understanding of mental health issues on SM platforms.

We aim to build an automatic system to analyze posts and engagement on SM and predict the person's behavior and mental state. Moreover, we will use the 9-item Patient Health Questionnaire (PHQ-9) as a validated and reliable patient self-report measure to assess depression [25-27]. We will focus on the interaction and participation of people on SM, which will clearly indicate their interest in communicating their tendencies with others, and text pattern analysis, which will show their emotional state. Most studies have analyzed public account data, but we will also analyze some private account data with users' consent. We are focusing on some unexplored and unique variables, such as studying engagement with Facebook games and advertisements, analyzing the content of anonymous posts, and establishing a correlation between them and depressive symptoms. In addition, we focus on analyzing data on people from South Asian countries because very few works have been done targeting this region. Moreover, we will ensure the efficiency and usefulness of the model, which we will assess by examining a group of people. In addition, the model will function as a screening tool and symptom-tracking tool, enabling comprehensive assessments of suicidal thoughts, depression severity, and treatment progress as depicted in the Figure 1 [28].

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Figure 1. Flowchart demonstrating the steps involved in the suicidal ideation identification system using machine learning (ML) and Facebook data. NLP: natural language processing. PHQ-9: 9-item Patient Health Questionnaire.

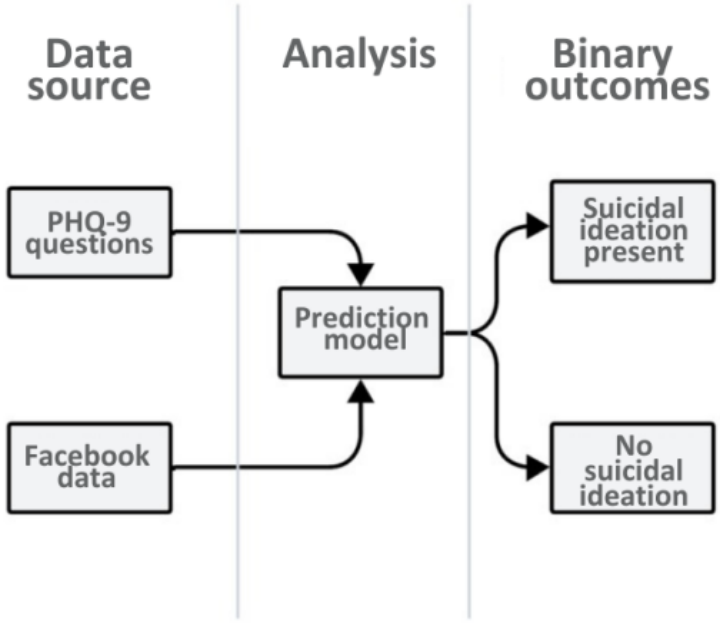

Related Work

Depression and Suicidal Tendency in LMICs

Suicidal ideation, a latent problem, has ranked as the fourth leading cause of death among young adults and adolescents [1]. Close to 800,000 people commit suicide every year [13]. In 2022, Bangladesh reported a total of 446 student suicides [29]. In many LMICs, including India and Bangladesh, suicide rates are alarmingly high, necessitating urgent attention [30]. Depression is a common phenomenon in LMICs due to several factors, including unemployment, poverty, and financial and food crises [31,32]. In LMICs, about one-third of the people commit suicide through the ingestion and inhalation of noxious pesticides; in the Southeast Asian region, 39% of people commit suicide through this method [33,34]. India, in particular, grapples with a substantial number of suicides each year, surpassing 100,000 cases [35]. Notably, suicide ranks as the fourth leading cause of death among young Indians in the 15-29 age group [36]. In Bangladesh, a survey conducted by the Aachol Foundation showed that between January and August 2022, 364 students committed suicide, out of which 194 (53%) were school students and the rest (n=170, 46.7%) were university students [37,38]. Suicide represents a significant social and public health issue that has profound implications for individuals, families, and communities [35]. The causes of suicide are diverse, including professional struggles, social isolation, abuse, family problems, mental disorders, substance addiction, financial challenges, and chronic pain [39]. However, addressing suicide is a complex issue due to various socioeconomic factors prevalent in countries such as India [40] and Bangladesh. Therefore, it is a demanding task to address suicide, which requires multidimensional prevention programs that mirror the multifaceted nature of the issue [4,41].

SM Engagement Analysis

People tend to express their emotional state to others. These days, SM has become the main platform [42] where people express themselves through writing. However, engagement on SM varies because of the mental condition of the individual. Studies have shown that people with clinical depression spend more time on SM than people without clinical depression [10,30,43]. By measuring users' engagement, it is possible to detect their behavioral patterns [44]. To understand behavioral patterns, it is very important to observe emotions such as anger, disgust, fear, happiness, sadness, surprise, shame, and confusion [45]. The observation of the number of daily posts is a fundamental evaluation metric for this project [46], and the details of depressive lexicon analysis will be provided elsewhere. Post segmentation and word representation are 2 approaches that have been used to analyze the results of the depression detection test more effectively. In post segmentation, the sentences are split into words; in word representation, the words are converted into vectors [43]. However, the understanding of how people communicate their feelings through text has not received much attention. After analyzing the premedication and postmedication longitudinal data of a person diagnosed with MDD, it has been clearly stated that the posting pattern has significantly changed the outcome measure, indicating that SM use is affected by a person's mood [47]. Therefore, an efficient strategy for this study is to concentrate on the text features to understand the user's mental state and transform them into a quantifiable shape.

Researchers have investigated whether users' activity and engagement levels right before using Facebook affect how they use it and, if so, then how. They found a noteworthy result from this study: users were affected by the time they spent on SM, and this had a high impact even on their academic performance [48]. However, gathering longitudinal data is a crucial part of this case because these behaviors are entirely dependent on circumstances, which can change very quickly. Modern studies

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have used the internet and social network information to discover links between individual traits and different disorders. As an example, SM sentiments have been used to predict various factors, such as population happiness [49] and even suicide rates [35,50]. Therefore, it is very important to analyze long-term data to mitigate biases and establish a strong relationship between behavior patterns and quantifying methods.

Natural Language Processing

NLP techniques for analyzing Facebook posts encompass a wide range of methods aimed at extracting insights and gaining understanding from text data [51,52]. These techniques include sentiment analysis, which evaluates the emotional tone of posts, enabling the classification of content as positive, negative, or neutral. Named entity recognition identifies and categorizes entities mentioned in posts, such as people, organizations, locations, and dates. Text summarization condenses lengthy posts into shorter, more digestible versions while preserving the main ideas. Topic modeling algorithms, such as latent Dirichlet allocation and nonnegative matrix factorization, uncover underlying themes and patterns within posts, facilitating content organization and categorization [53]. Furthermore, part-of-speech tagging assigns grammatical categories to words, enabling syntactic analysis and the understanding of sentence structures [54]. These NLP techniques empower researchers to gain valuable insights from Facebook posts, ranging from insights into user sentiment and behavior to relevant insights for various applications, such as SM monitoring and user profiling.

Text Pattern Analysis

Earlier studies have demonstrated that users openly express signs of depression on SM platforms such as Facebook [55] and Twitter (X Corp) [56]. In certain scenarios, the shared information provides enough insights for researchers to diagnose a major depressive episode. Most studies that have identified depression through SM data are primarily based on the analysis of text from publicly available data. In a particular study, the analysis of Facebook users' "liked" content unveiled the potential for the precise prediction of diverse traits. Similarly, another investigation revealed that individuals experiencing loneliness are inclined to share more negative content, have fewer friends, and engage in less communication activity on the platform [57]. Valence and arousal, which are the representations of sentiment and intensity, are the 2 most important parameters to examine in any text [58]. Linguistic Inquiry and Word Count (LIWC) is a fully dedicated system for this textual analysis, where it is possible to divide any post into segments and identify the frequently used words, social words, and cognitive processes [59]. Another tool named Natural Language Processing with Java is used to annotate expressions of sentiment and other sociopsychological phenomena using custom lexicons and grammar. It extends the possibilities for the assessment of attitudes expressed in the text beyond sentiment analysis [60]. However, a limitation of these studies is their inability to determine whether the high-frequency words actually indicate suicidal ideation (ie, whether the person has written a post sarcastically).

Methods

Our procedure will consist of several key steps. These are data collection and preparation, feature engineering, model selection, model training, model evaluation, prediction, and model deployment.

Data Collection

Our data collection procedure will have 2 parts. The first one is data collection from Facebook, and the second one is data collection with our website, where we will be asking some questions regarding participants' Facebook use pattern and administering the PHQ-9 to validate our result, which will be predicted using Facebook data.

To streamline the robust and privacy-conscious data collection process for our research, we aim to build a secure web-based system where users can upload their data files [4]. Upon accessing the system, participants would first be directed to a web-based survey where they could provide relevant information and respond to specific questions related to our study. Facebook complies with the General Data Protection Regulation [61] by offering a feature that enables users to download their data, as mandated by the regulation for SM companies. Therefore, following the survey's completion, participants would be guided to download their Facebook data files directly from the Facebook platform. Further, they were instructed to securely upload the data files to our web-based system for conducting a comprehensive and informed analysis of suicidal thoughts.

Privacy is a multidimensional concept that goes beyond a binary value [62]. Therefore, it is essential to respect individuals' autonomy [63] and data control, making it inappropriate to ask users to make their accounts public for research purposes. For individuals facing suicidal thoughts, privacy is crucial [64,65] in fostering a supportive and safe environment, allowing them to seek help without the fear of stigma or reluctance [66,67]. Respecting privacy in research is crucial to upholding ethical standards and protecting participants' personal information [64]. Therefore, we will refrain from asking participants to make their accounts public to uphold the principles of privacy and respect individuals' confidentiality in our research.

While Facebook restricts external entities from accessing its data [68], authorized application programming interfaces (APIs) such as the Facebook Graph API [69] enable the retrieval of publicly available information about Facebook users while adhering to privacy and legal guidelines. However, the API comes with several limitations and concerns [70,71] that can introduce biases into the model for predicting suicidal ideation, affecting the accuracy and effectiveness of the predictions.

Clinical Assessment

To diagonalize and comprehend the severity of depression, we will use the PHQ-9. This questionnaire comprises 9 questions with a scoring range of 0 to 27. The questionnaire categorizes depression into 5 segments: 0 to 4 as minimal, 5 to 9 as mild, 10 to 14 as moderate, 15 to 19 as moderately severe, and 20 to 27 as severe. The ninth item, "Thoughts that you would be better off dead or of hurting yourself in some way," directly indicates

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users' perspective on suicidal thoughts. This assessment is an important point to focus on to understand the shift.

Ethical Considerations

This study has undergone a comprehensive human participant research ethics review and has obtained the necessary approvals. Approval was granted by the scientific review committee from North South University, Dhaka, Bangladesh, on October 2, 2023 (NonCTRG-23-38), followed by institutional review committee ethical clearance on December 8, 2023 (2023/OR-NSU /IRB/1033). Informed consent was diligently obtained from all participants involved in the study, ensuring transparency and ethical integrity. Moreover, stringent measures were implemented to anonymize and deidentify study data, thereby safeguarding the privacy and confidentiality of human participants involved in the research. These ethical considerations underscore our commitment to upholding the highest standards of research integrity and participant welfare throughout the study process.

Participants

The studies investigating the prevalence of suicidal ideation outcomes among adolescents or young adults are dependent on factors such as age, gender, socioeconomic status, and cultural differences in India [72] and Bangladesh [73], as well as factors such as the frequency and intensity of SM use, types of content shared, and the presence of mental health indicators in web-based behavior. Given the complexity of the study and the need for robust statistical analysis, we anticipate determining the sample size based on a power analysis approach and earlier studies conducted in similar settings. We have carefully considered previous research approaches and sample sizes. The study by Patel et al [74] used larger sample sizes, ranging from 1500 to 30,000 participants, allowing for comprehensive analyses and insightful conclusions. Conversely, smaller sample sizes, ranging from 100 to 500 participants, were used in studies such as those by Vornholt and De Choudhury [75] and De Choudhury et al [76], demonstrating the feasibility of conducting impactful research even with fewer participants.

Given the diverse populations and SM use patterns in India and Bangladesh, we have tailored our sample size determination strategy accordingly. While these countries have millions of inhabitants [77,78], the subset that actively engages with SM, particularly Facebook, and is willing to share personal data for research purposes is smaller. In addition, to ensure balanced representation, we will carefully select participants to achieve a proportionate distribution of positive and negative samples once the minimum threshold value is reached. It is worth noting that despite India's larger population, our study anticipates a greater participation rate from Bangladesh due to higher Facebook use. Therefore, we aim to recruit 300 to 1500 participants from Bangladesh and 300 to 700 participants from India. This approach ensures a sufficient sample size to yield meaningful insights while considering the unique demographic and SM landscape of each country.

Text and Behavior Analysis

Overview

We are planning to use NLP techniques to analyze the linguistic patterns and sentiments in user-generated content. We will also identify language indicative of depressive symptoms, negative emotions, and expressions of hopelessness. We will use LIWC and Affective Norms for English Words lexicon categorization for more accurate results in the text analysis [79]. In addition, we will use topic modeling and keyword extraction to identify prevalent themes within the text. These insights are essential for understanding trends, preferences, or concerns within the data set.

Behavior has 2 divisions: post-centric behavior and user-centric behavior. Post-centric behaviors include post time, number of posts, posting frequency, friends, followers, likes, replies, comments, and emoji counts. User-centric behaviors include positive affect, negative affect, activation, dominance, linguistic style, depression lexicon, and antidepressant use. Linguistic style specifically shows the total word count, first-person and third-person pronouns, functional words, assent, negation, etc.

Facebook Game Analysis

According to studies, people who play video games excessively are more likely to experience sadness and social anxiety [80]. Our observation supports this assertion that the number of people playing Facebook games grew dramatically throughout the COVID-19 era [55].

A gaming function on Facebook offers a variety of games that can be played by one person or several people. The accompanying player does not necessarily need to be on the friend list of the user but can be anyone from the Facebook community. A few well-known games are carrom, Bubble Shooter, Uno, Ludo, and chess. People can challenge one another in the game, and if the other person is interested, they can accept the challenge and finish the game. Most likely, these games are web based and can be played directly from a browser without downloading, but some of them also offer an Android version that needs to be downloaded on the phone.

A few factors to consider while analyzing gaming are frequency, duration, genres, single-player versus multiplayer, and in-game behavior.

There are currently no set standards for identifying addictive and nonaddictive players. However, there is a strong relationship among weekly gaming time (WGT), craving, and the problem video game playing (PVP) score. Hard-core or even excessive players (extremely high WGT and PVP scores) as well as nonexcessive players (low WGT and PVP scores) show distinct patterns in their gameplay behavior [56]. It has been established that negative emotional ratings for excessive gamers are higher than for nonexcessive players. In addition, they also have higher "self-devaluation when facing failure" scores. The excessive players displayed higher negative feelings and negative bodily manifestations in terms of both emotions and physical symptoms. This seems to be in line with the idea of addiction, when the action no longer produces happy results but instead causes negative ones. Playing video games over a long period

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might cause a disorder called alexithymia, which impairs the capacity to recognize one's own internal emotions. People's inability to identify particular emotions contributing to their current state of mind might make it worse [81]. Due to the greater focus and cognitive processing required by skill games, these players favor action games over them [82].

Games are categorized based on their intensity level: casual games are simple and easy-to-play games designed for short play sessions, whereas hard-core games are more complex and require a higher level of skill and commitment [50].

Categorizing games according to intensity level, we distinguish between hard-core and casual categories. The hard-core category includes games such as Magic Swap Puzzle, Coin Match, Solitaire, Words With Friends, Quiz Planet, Krunker FRVR, Uno, Chess, and Word Search. In contrast, the casual category comprises games such as Bubble Shooter Pro, Bubble Pop, Basketball FRVR, Ludo Club, Cooking Trendy, Carrom Board, Card Party, Card Wars, Eight Ball Pool, and The Test. This distinction helps in understanding player engagement and preferences based on the intensity of gameplay.

Description Analysis

In the bio section, people generally write about themselves or any famous quote they like or that resembles them. Sometimes, it can be one or multiple lines or even just a word. In the details section, they can add current and previous workplaces, institutions, relationship status, hobbies, and cities they previously lived in and currently live in. People with mental health issues have a tendency not to share their information with everyone. They have a close group of people with whom they feel comfortable sharing information [57]. It is often seen that the bio and details sections of these people remain almost empty or filled with very little information.

Content Analysis

Studies have consistently shown that people are willing to share their depression and medical conditions on various social networking sites [83]. Related studies have investigated language and emotional patterns and successfully assessed new mothers' postpartum behavioral changes from prenatal assessments [84]. These findings highlight the potential of SM as an important indicator in assessing the occurrence of current or future depression.

In our study, we aim to introduce measures that evaluate and characterize users' linguistic styles in posts, comments, and search history, irrespective of whether they are anonymous. An important observation is that users who are depressed post personal content in various groups or pages anonymously. This behavior seems driven by the need for a safe, nonjudgmental space to express emotions and seek support. In addition, depression-related content, such as quotes, internet memes, and music, is prevalent among users. Examples include posts including "sad songs" and "mental illness quotes," along with expressions of feelings of despair and overwhelm, such as "I am so lonely" and "Everything seems too overwhelming and pointless." Understanding such patterns of anonymously shared data on SM platforms can provide valuable insights into predicting the mental health challenges people face. Moreover, analyzing such content and the frequency of posting may be instrumental in identifying depression and the potential areas for targeted interventions and support.

This study also highlighted the untapped opportunity in understanding users' search activity, which holds promising potential for enhancing clinical and public health efforts in suicide risk assessment and prevention. Participants' search themes encompass suicide, help-seeking, mood and anxiety symptoms, and trauma and negative life events [85]. Often, users facing trauma or negative life events search for support resources, coping strategies, and information on seeking professional help. This includes asking questions about outpatient resources, health clinics, and other medically relevant topics, analyzing which helps gain a comprehensive understanding of users' mental health concerns. Further, to enhance the robustness of the predictive model, in this study, we focus on additional insights into users' engagement with relevant resources and communities over Facebook. By integrating a comprehensive list of the user's group memberships, liked pages, and notification messages, we provide a holistic approach to understanding users' mental health, allowing us to develop effective strategies while assessing suicide risk at an early stage.

In this research paper, we will preprocess the text data to ensure their suitability for subsequent model building. Given the unstructured nature of SM data, we will apply customized preprocessing and cleaning techniques. These techniques include removing accented characters; expanding contractions; converting to lowercase; eliminating URLs, symbols, digits, and special characters; fixing word lengthening; applying spelling correction; removing stop words; and performing lemmatization. These steps will aim to standardize the text, reduce dimensionality, improve data quality, and ensure consistent representation in our models. By implementing these preprocessing steps, we will be able to successfully clean and prepare the text data, making them suitable for subsequent analysis and model training [74].

During the data cleaning phase, we will take additional steps to refine the preprocessed text data. These steps will involve removing irrelevant words, empty rows, and outlier rows with high word counts. By eliminating irrelevant words, we will focus on more meaningful features for analysis. The empty rows, which will not contain any useful information, will be dropped to ensure data integrity. At the same time, the outlier rows with high word counts, deviating significantly from the majority, will be removed to optimize model training efficiency. These measures will improve the data set's quality and relevance, preparing it for further analysis and model training.

Further, we will use a vectorizer called Tf-idf Vectorizer to transform our textual data into numerical features suitable for ML algorithms. That vectorizer will can be configured with specific parameters: min_df=50 and max_features=5000. The min_df parameter specifies that a word must appear in at least 50 documents (posts, in our case) to be included in the feature representation. This will help filter out infrequently occurring words that may not contribute significantly to the overall understanding of the data. The max_features parameter sets an

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upper limit on the number of features (words) to be considered. In our case, we will set it to 5000, indicating that only the top 5000 most relevant features (based on their frequency) will be selected for further analysis. This approach will enable us to represent the text data numerically, capturing the importance of different words while reducing the dimensionality of the feature space.

Diurnal Activity

Diurnal activity indicates the activeness of a person on SM both during the daytime and at night. It has been mentioned that individuals who are depressed are most active during the night [6,30,86]. In our study, we will investigate the moods [87] of all people who have written posts on SM. We intend to determine the emotions of a person who is depressed (ie, to visualize whether the person is actually depressed).

Diurnal activity will be calculated using the following formula:

$$XG(d,h) / \sum XG(d,i) \quad \textbf{(1)}$$

where XG (d,h) indicates the average timing of the total number of posts made in hours (h) and days (d), the G in XG indicates the country where the post was made. In addition, h indicates a value from 0 to 23 (ie, an average number of posts is considered up to 11 PM).

Another study indicates a positive relationship between the use of emojis and genders (ie, women use more emojis than men), and the most frequently used emoji was the emoji representing tears of joy, with a use percentage of 22.2% and 18.9% among women and men, respectively. However, to investigate the emoji choices of both genders, a statistical analysis was carried out, named "mutual Information" (MI), which calculates the use of emojis by both men and women [88]:

$$MI(X;Y)e = \sum\sum P(x,y)e \log (P(x,y)e) / (P(x)e \times P(y)e) \quad \textbf{(2)}$$

where X indicates whether the gender (either men or women) uses an emoji. Here, the value of x will be equal to 1 if a user applies emojis, and if the value of x is equal to 0, then the user does not apply emojis. However, Y indicates a user's gender (ie, for men, the value of y will be equal to 1; for women, the value of y will be equal to 1). Here, X is represented as a member of x, and Y is represented as a member of y. In contrast, p(x,y)e indicates the joint probability of X and Y, whereas p(x)e and p(y)e indicate the marginal probability of X and Y [88].

For analyzing the data from Facebook, we will observe the time stamps for negative posts and the types of emojis that are used frequently on posts related depression. We will be focusing on the formulas given earlier, but we will adjust the variables to suit our needs.

For "negative" emotions from posts for "diurnal activity," we will be applying the text2emotion Python function to extract the emotional words used on the posts. However, the text2emotion library shows 5 different emotions, namely happy, sad, angry, surprise, and fear. However, here, we will be dealing with the negative feelings from Facebook posts.

First, our main purpose is to clean the data to make them appropriate for analyzing emotions. For the data cleaning process, we need to follow several steps. For instance, we need to remove the unwanted texts or words from the posts (ie, the words that have low frequency based on term frequency–inverse document frequency), apply various tools of the Natural Language Toolkit for sentiment analysis, and extract the better-preprocessed posts from the previous preprocessed posts. Second, we need to figure out the emotional words from the preprocessed texts and then use them for further visualization of the emotions. Finally, we need to observe the scores of the emotions. The higher the score from 1 of the 5 categories, the more the emotion will belong to that group.

After that, we intend to observe the emojis from the posts to investigate what type of nonverbal attributes a person who is depressed has both during the daytime and nighttime while writing posts on SM. This will help us figure out which emojis a person who is depressed uses repeatedly during the night. Several studies were conducted on emojis [89-92], indicating how they coincide with the linguistic style of a person. For instance, the emojis that are inclined with the negative words from LIWC are "anger," "money," "ingest," "family," "home," and "death" [89].

As mentioned earlier, we will be focusing on the sentiments in the posts and the frequently used emojis by an individual during nighttime. Moreover, we will be considering how the emotions in a person's post and the number of emojis used on a post are correlated with diurnal activity. For that, we will be using the formula for MI, as it consists of both joint probability and marginal probability. "Joint probability" will help investigate the relationship between the emotions in the posts and the number of emojis used, applying a condition, that is, if we work on the sentiments in the posts, then the number of emojis will be kept constant, and vice versa. In contrast, "marginal probability" will help us extract 1 feature at a time (ie, the features will be independent of one another).

There will be a change in the formula for both "diurnal activity" and MI (ie, in the "diurnal activity" formula, the number of posts will be denoted as "Po," and not XG). For MI, instead of "X" and "Y," we will write "Po" and "E," respectively. Here, "Po" will indicate the posts written by an individual during nighttime, and "E" will indicate the types of emojis used by that individual.

The modified formulas for diurnal activity and MI are as follows:

$$(Po(d,h)) / (\sum Po(d,i)) \quad \textbf{(3)}$$

$$MI(Po,E) = \sum\sum P(Po,E)e \log (P(Po,E)e) / (P(Po)e \times P(E)e) \quad \textbf{(4)}$$

To find out the MI, we will consider various combinations for the number of "negative" posts and emojis used by an individual. We will consider the values of both Po and E as binary 1 (ie, Po=1 and E=1) if the posts are "negative" and the emojis are used.

In contrast, we will consider the values of both Po and E as binary 0 (ie, Po=0 and E=0) if the posts are "nonnegative" and no emojis are used in the post.

There are other combinations as well, that is, Po=0 and E=1 if the number of posts is "nonnegative" and emojis are applied in

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the posts, and Po=1 and E=0 if the posts are “negative” and no emojis are used in the posts.

Here, we will eliminate Po=0 and E=1 and Po=0 and E=0, as we will not deal with “nonnegative” posts (ie, Po=0) and “zero emojis” (ie, E=0).

The highest value of MI will indicate both the number of “negative” posts and “emojis” (Po=1 and E=1) used. In contrast, the lowest value will indicate either the number of “nonnegative” posts and “emojis” (Po=0 and E=1) used or the number of “nonnegative” posts and “zero emojis” (Po=0 and E=0).

Advertisement Analysis

Participants revealed a tendency to reduce their SM posts during periods of low moods, with the belief that their SM content might not accurately depict their depressive state. SM platforms such as Facebook use algorithms to direct advertisements to suitable users, leveraging search keywords and previously accessed links. A subset of participants acknowledged the practice of targeted advertising, while a minority reported posting specifically to seek support. In addition, participants acknowledged the existing use of targeted advertising and expressed a preference for its application in mental health care provisioning as opposed to its current use. Individuals experiencing depression tend to conduct searches related to health-related topics, resulting in personalized advertisements that align with their search preferences.

Network Analysis

For measuring the network, we will calculate reciprocity, cluster coefficient, and betweenness centrality. This will help understand the user’s close connections and how frequently they communicate with them. To analyze the post-centric and user-centric behavior in detail, we need to calculate reciprocity, prestige ratio, clustering coefficient, degree centrality, closeness centrality, betweenness centrality, and eigenvector centrality.

In terms of analyzing the network, we will consider “u” as the user whose network property we will analyze. A node indicates a person, and an edge is considered a connection or link. Reciprocity will reflect how often “u” has responded to any message.

The prestige ratio indicates the bidirectional communication of the user. That means after texting back to any message, it tracks the number of times they have participated and the frequency of their interactions.

Mathematically, the reciprocity formula is as follows:

Reciprocity = (number of reciprocated connections) / (total number of connections) **(5)**

To calculate the reciprocity, we have to count the number of connections between pairs of users in a network and determine how many of these connections are reciprocated. A reciprocated connection occurs when 2 nodes have a mutual connection with each other. For example, if user A is connected to user B and user B is also connected to user A, it is considered a reciprocated connection. A higher reciprocity score in network analysis indicates a more tightly connected and interactive network with stronger bidirectional relationships between users.

Clustering coefficient measures how likely it is for the friends or connections of a user to be friends or connected to each other. Basically, it provides a quantifiable measure of how much users tend to form groups or clusters within the network.

For user i, who has ni neighbors, the clustering coefficient Ci is defined as the ratio of ei connected pairs to the number of all possible connections among the ni neighbors:

Ci = 2ei / (ni([ni – 1]) **(6)**

The formula calculates the clustering coefficient by dividing the number of actual connections between the neighbors of the user i (2ei) by the number of possible connections between the neighbors of the user i (ni([ni–1]).

A higher clustering coefficient score in SM analysis signifies a network with well-connected subgroups or clusters, indicating the presence of close relationships and social interactions among users within these groups. A lower clustering coefficient score in social network analysis indicates a network with less local interconnectedness and fewer cohesive groups, suggesting a more diverse and less tightly knit social structure among the nodes.

Closeness centrality annotates how easily “u” can reach other users in a community. To be more specific, it measures how close or directly connected a user is to other users. A high closeness centrality indicates that “u” is closely connected to many other users. A low closeness centrality indicates that “u” is distant from others in the network. It means “u” may need to go through multiple intermediate connections to reach other users.

Closeness centrality, as the name suggests, is an index defined in terms of distance. Length of a (s, r) path represents the number of edges contained in it. We define the (shortest path) distance, dist (s, r) of s, r∈V as the minimum length of any (s, r) path. We reiterate that we consider only connected graphs for now and observe that dist (s, s)=0 for all s ∈ V. The distance matrix D=(dist[s, r])s, r∈V of an undirected graph is symmetrical, so the total distance, dist(v), of a vertex v ∈ V is obtained as either the row or column sum:

(7)

Because of this reversal in ranking, the closeness centrality of a vertex s ∈ V is usually defined as the inverse of the total (or, equivalently, average) distance [49]

(8)

Higher closeness centrality indicates that a user is more central and well connected in the network, while lower closeness centrality suggests that a node is less central and may have less efficient access to other nodes.

Betweenness centrality is a widely used measure that captures a user’s role in allowing information to pass from one part of

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the network to another. It shows the potential of a user in terms of communication:

(9)

The number of shortest paths from a vertex i to a vertex j that goes through a vertex k, denoted sp_{ij} (k), is the maximum number of shortest paths from vertex i to vertex k in the shortest path tree rooted at i and the number of shortest paths from vertex j to vertex k in the shortest path tree rooted at the vertex j [93].

Users with higher betweenness centrality have more control over the flow of communication in the network and act as important mediators or connectors between different parts of the network. In contrast, users with lower betweenness centrality have less influence over the overall communication patterns and may be more localized in their interactions. Betweenness centrality is a measure of a user's importance in facilitating communication, and it provides insights into the user's role in maintaining network connectivity and communication.

ML Modeling

We are planning to train and validate ML models using labeled data, encompassing a balanced number of posts from individuals with diagnosed depression and those without. After that, we will use a combination of features, including sentiment scores, word frequency, and contextual information. We will conduct an extensive analysis using classification models to predict suicidal risk by assembling multiple classification models based on the provided features. The customized models used in the voting classifier will include random forest, decision tree, gradient boosting, XGboost, and k-nearest neighbors.

We will conduct an extensive analysis using various classification models to predict suicide risk using multiple classification models based on the provided features. These models include a voting classifier, random forest classifier, decision tree classifier, gradient boosting classifier, XGBoost classifier, and k-nearest neighbors classifier. Initially, we will split the data set into training and testing sets with a ratio of 7:3. We will use a voting classifier to combine the predictions of 3 naive Bayes classifiers. In addition, we will optimize the performance of the random forest classifier, decision tree classifier, gradient boosting classifier, XGBoost classifier, and k-nearest neighbors classifier by tuning their hyperparameters using techniques such as RandomizedSearchCV. At the same time, we will consider the characteristics of our data set and the nature of the classification task to choose an appropriate model that can effectively capture the patterns and relationships in the text data. Therefore, we will evaluate the performance of each model by calculating training and testing scores. This comprehensive methodology will allow us to identify the most effective model for predicting suicide risk based on the given features.

One of the potential concerns of this study is addressing the data imbalance challenge, particularly regarding the occurrence of suicide. To mitigate this imbalance, we have studied the techniques that were previously implemented in similar settings. Firstly, we will use appropriate data preprocessing techniques, such as oversampling or undersampling methods, based on the collected data to ensure that the predictive model is trained on a balanced data set. In addition, feature selection methods will be used to prioritize the most informative variables related to depression and suicide prediction, thereby minimizing the impact of data skewness on the model's performance. Furthermore, we will consider the use of robust evaluation metrics, such as precision, recall, and F_1-score, which will allow for a comprehensive assessment of the model's predictive capability across different outcome classes, effectively addressing the challenge posed by data imbalance. These approaches would provide valuable insights into addressing data imbalance challenges in predictive modeling studies related to mental health.

Evaluation Metric

Overview

In the process of evaluating our models, we will use various ML metrics that offer critical insights into their performance. These metrics play a pivotal role in determining the accuracy and efficacy of the models. Specifically, we will be focusing on the following metrics [48]: true positive, false negative, true negative, and false positive. These metrics hold significance in assessing the predictive capability of the models in a classification context.

Sensitivity (True Positive Rate or Recall)

This metric measures the ability of the model to correctly identify people who are depressed. It calculates the ratio of true positives (correctly identified people who are depressed) to the sum of true positives and false negatives (people who are depressed incorrectly classified as people who are not depressed).

Specificity (True Negative Rate)

This metric evaluates the proportion of actual negatives (people who are depressed) that are correctly identified as such. It measures the accuracy of identifying healthy individuals who do not have depression.

Precision (Positive Predictive Value)

Precision calculates the fraction of relevant instances (positively labeled) among the predicted instances. It provides an assessment of the accuracy of positive predictions made by the model:

TP / (TP + FP) **(10)**

F1-Score

The F_1-score is a measure that combines precision and sensitivity (or recall) into a single metric. It calculates the harmonic mean of precision and sensitivity and is particularly useful when dealing with imbalanced data:

(2* precision score × recall score) / (precision score + recall score) **(11)**

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Accuracy

Accuracy represents the overall performance of the model, measuring the proportion of correctly classified instances out of the total instances. The error rate, which complements accuracy, quantifies the proportion of misclassified instances:

(TP + TN) / (TP + TN + FP + FN) **(12)**

Evolution

Among the array of standard evaluation metrics, precision, recall, and F_1-score are given more weightage to assess the efficacy of models in accurately classifying depression classes. When assessing early detection algorithms, it is crucial to consider not only the accuracy of decisions but also the associated delays. In line with this, Wang and Mark [48] introduced the early risk detection error metric, which penalizes untimely correct decisions to address this concern. Flatency, introduced in the CLEF eRisk 2021 [59], is an interpretive evaluation metric proposed alongside the early risk detection error metric to enhance interpretability [30]. In addition, known as latency-weighted F_1, flatency combines F_1-score with speed, reflecting both accuracy and efficiency in identifying users' content, particularly emphasizing early and accurate classification. By considering these metrics, we can gain a comprehensive understanding of the performance of our models in terms of their ability to correctly identify individuals who are depressed and individuals who are not depressed. The streamlined flow of the depression identification system is depicted in Figure 2.

Figure 2. Deployment of the suicide ideation prediction model based on the 9-item Patient Health Questionnaire (PHQ-9) and Facebook data examination. ML: machine learning; NLP: natural language processing.

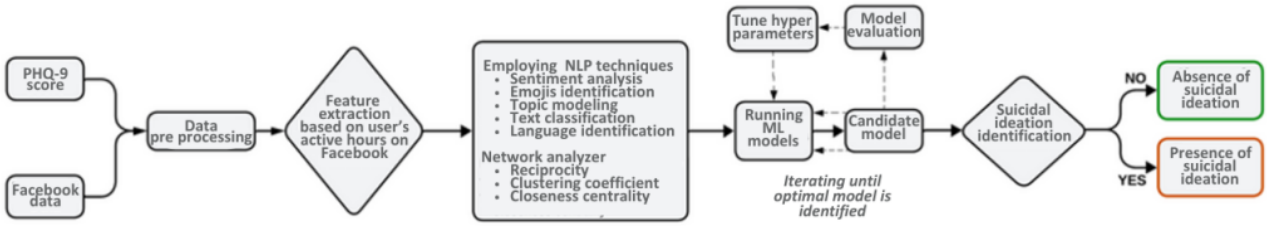

Results

Our system is anticipated to automatically detect posts related to depression by analyzing the text and use pattern of the individual with the best accuracy possible. Ultimately, our research aims to have practical utility in identifying individuals who may be at risk of depression or in need of mental health support.

Simultaneously, by analyzing daily activities on SM, we aim to determine how frequently individuals write "negative" posts on Facebook, as such posts are often associated with depression [94]. Additionally, we will examine the types of emojis that are used repeatedly by these individuals. This will help us identify how often an individual uses emojis while writing a post. Moreover, if a person does not use an emoji, their posts will be detected based on the score of their "negative" emotional words (ie, "sad," "angry," or "fear").

By accurately classifying individuals based on their text analysis, we hope to contribute to the development of early detection systems or interventions that can enhance mental health screening and well-being.

Discussion

Overview

In this study, we will focus on the South Asian region, mainly Bangladesh and India, which is still dealing with economic issues and some problems with regard to basic rights. People from this region do not pay adequate attention to mental health and well-being. Therefore, we aim to build such a solution that will cover most of the gaps regarding all the mentioned facts. Our goal is to establish a procedure that will analyze how a collection of behavioral indicators that appear on SM may be used to forecast postings that are suggestive of depression and, in turn, comprehend widespread suicidal tendencies in populations.

Principal Findings

Our study will begin by administering basic questions to users, followed by a filtering process to select suitable participants for our study. Upon obtaining the Facebook data, our analysis will commence. We will initially determine whether Facebook serves as the primary SM platform for the participants, a crucial factor influencing the accuracy of our predictions. In case it is their main platform, we will focus on their interactions, encompassing messages, posts, comments, and gaming activities. Our analysis will extend to anonymous actions and their engagement with content related to depression.

Conversely, in instances where Facebook is not the predominant medium, judicious focus is shifted to the advertisement analysis model. This model hinges on deciphering users' web-based behavior, scrutinizing their browsing history, visited sites, and thematic inclinations, particularly within realms such as consultancy or support services. For participants who primarily use other platforms, our analysis will shift to evaluating the types of websites they frequent and the content they engage with. This system will work privately to assess the risks associated with anticipated changes in the future while taking into account metrics related to SM activity. We aim to demonstrate a significant correlation among Facebook games, user profile information, and content such as advertisements on mental health as depicted in Textbox 1.

Finally, we will incorporate an assessment of the frequency of their posting, commenting, friend engagement, and previous

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questionnaire responses, thus enhancing the depth and accuracy of our predictive model. Our ultimate prediction will amalgamate these distinct analyses through advanced techniques. Informed by the outcome of these individual models, our predictive synthesis advances, culminating in a definitive assessment of the presence or absence of suicidal ideation.

Textbox 1. Consideration of data variables for suicidal ideation detection based on Facebook activity status.

- If a user is active on Facebook
- 9-item Patient Health Questionnaire (PHQ-9) score
- Facebook games analysis
- Bio analysis
- Post and comment analysis with or without the user's name
- Notification analysis
- Kinds of groups joined and pages liked analysis
- Search history analysis
- Advertisement analysis
- Diurnal activity value
- Network attributes calculation

If a user is not active on Facebook but has created an account

- PHQ-9 score
- Advertisement content analysis

Comparison With Previous Work

Our study will present a novel investigation, first exploring the prevalence of Facebook as the dominant social application, whereas existing studies focused on Twitter, Reddit (Reddit Inc), and Instagram (Meta Platforms Inc) as data sources [95]. We will use a process to collect the data that will not require any extra website or setup to be downloaded or installed on the user's end. This is the reason why we are claiming our process is easy to access. Other existing solutions need some external infrastructure, which makes the data donation process a bit complex for users. Along with all the engagement analysis parameters, including texting patterns, we will also consider some unique parameters such as used emojis, stickers, Facebook games, bio sections, and advertisement suggestions that have a direct connection with users' behavior. People with MDD have noticeable difficulties with their attention span [96]. On this account, we are showing a connection between these parameters and users' behavior. This exploration will provide valuable insights into the emotional state of users.

Limitations

However, this study may have a few limitations and biases that are crucial to consider. First, the recruitment of participants through web-based platforms may introduce selection bias, as individuals who are active on SM may be different from the general population [97]. In addition, reliance on self-reported data, such as responses to demographic questions and mental health assessments, may introduce response and social desirability biases. Participants may underreport sensitive information or provide socially acceptable responses, leading to inaccuracies in the data collected [98]. Moreover, the interpretation of textual data, including language nuances and sentiment analysis, is subject to inherent biases in NLP algorithms [99]. Future research should aim to mitigate these challenges through methodological refinements and validation studies.

Future research directions can include comprehensive validation studies that directly compare the outcomes of our screening method with those of clinical assessments conducted by mental health professionals. This validation process would involve recruiting control groups and conducting direct comparisons to assess the accuracy and reliability of our screening results in identifying individuals with suicidal ideation. This will provide valuable insights into the strengths and limitations of our approach. By establishing the concordance between our screening results and clinical diagnoses, we can enhance the credibility and utility of our screening methodology in real-world settings [100]. Researchers can also conduct a broader exploration of alternative screening methods and interventions based on the screening results. Incorporating additional data sources or using advanced ML techniques could enhance accuracy and efficiency. In addition, developing targeted interventions based on the screening results holds promise for improving mental health outcomes and preventing suicide [101].

Conclusions

The study's timeline unfolds as follows. The data collection, which includes recruiting participants, conducting surveys, and gathering Facebook data, is scheduled to conclude by November 2024. Anticipating the system's ability to accurately detect signs of depression in text and use patterns, we aim to advance early detection systems or interventions, completing the ML model by January 2025. The final results are expected to be available in February 2025.

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By delving into these multifaceted aspects, this study will offer a comprehensive and pioneering approach to the field of mental health. Our approach to predicting depression through SM activity, or the examination, is not intended to replace conventional surveillance systems or laboratory-based depression diagnoses. To maximize the advantages of these approaches and concepts and improve people's quality of life, we believe it is important to highlight the possibilities. This will also encourage discussion and raise awareness of any potential issues that should be resolved on individual and societal levels.

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Conflicts of Interest

None declared.

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Abbreviations

API: application programming interface
LIWC: Linguistic Inquiry and Word Count
LMIC: low- or middle-income country
MDD: major depressive disorder
MI: mutual information
ML: machine learning
NLP: natural language processing
PHQ-9: 9-item Patient Health Questionnaire
PVP: problem video game playing
SM: social media
WGT: weekly gaming time

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Protocol

Strengthening Cause of Death Statistics in Selected Districts of 3 States in India: Protocol for an Uncontrolled, Before-After, Mixed Method Study

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Abstract

Background: Mortality statistics are vital for health policy development, epidemiological research, and health care service planning. A robust surveillance system is essential for obtaining vital information such as cause of death (CoD) information.

Objective: This study aims to develop a comprehensive model to strengthen the CoD information in the selected study sites. The specific objectives are (1) to identify the best practices and challenges in the functioning of the Civil Registration and Vital Statistics (CRVS) system with respect to mortality statistics and CoD information; (2) to develop and implement interventions to strengthen the CoD information; (3) to evaluate the quality improvement of the Medical Certification of Cause of Death (MCCD); and (4) to improve the CoD information at the population level through verbal autopsy for noninstitutional deaths in the selected study sites.

Methods: An uncontrolled, before-after, mixed method study will be conducted in 3 blocks located in the districts of 3 states (Madhya Pradesh, Uttar Pradesh, and Odisha) in India. A baseline assessment to identify the best practices and challenges in the functioning of the CRVS system, along with a quality assessment of the MCCD, will be conducted. An intervention informed by existing literature and the baseline assessment will be developed and implemented in the study sites. The major components of intervention will include a Training of Trainers workshop, orientation of stakeholders in the functioning of the CRVS system, training of physicians and medical officers in the MCCD, and training of community health workers in World Health Organization Verbal Autopsy 2022 instrument. Postintervention evaluation will be carried out to assess the impact made by the intervention on the availability and quality improvement of CoD information in the selected study sites. The outcome will be measured in terms of the quality improvement of the MCCD and the availability of CoD information at population level through verbal autopsy in the selected study sites.

Results: The project has been funded, and regulatory approval has been obtained from the Institutional Ethics Committee. The data collection process began in May 2023. The duration of the study will be for 24 months.

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Conclusions: Our study is expected to provide a valuable contribution toward strengthening CoD information, which could be helpful for policy making and further research. The intervention model will be developed in collaboration with the existing functionaries of the health and CRVS systems in the selected study sites that are engaged in reporting and recording CoD information; this will ensure sustainability and provide lessons for upscaling, with the aim to improve the reporting of CoD information in the country.

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KEYWORDS

cause of death; Medical Certification of Cause of Death; capacity building; Civil Registration and Vital Statistics; training

Introduction

The Civil Registration and Vital Statistics (CRVS) system is the key source of vital statistics [1-4]. It maintains data regarding registered births and deaths, provides death and birth certifications, and publishes vital statistics, which also include cause of death (CoD) information [4]. Additionally, censuses, sample surveys, household surveys, and facility-based service statistics are also used to estimate death rates [5,6]. Information about mortality statistics and ascertaining the CoD are significant components for the formulation of health policies, epidemiological research, health care service planning, and addressing public health emergencies [6-8]. Many of the current health goals—for instance, reducing child and maternal mortality and reducing noncommunicable disease deaths—are aligned with United Nations Sustainable Development Goals [1,7,9,10]. Having effective mortality surveillance systems to monitor the progress toward achieving Sustainable Development Goals is essential [5,8,11].

To strengthen the CRVS system, some efforts have been made at the global and regional levels, such as the *World Health Organization (WHO) CRVS Strategic Implementation Plan 2021-2025* [10], Data for Health initiative by Bloomberg Philanthropies [12,13], and the Africa Programme on Accelerated Improvement of CRVS [12]. In India, the Registration of Births and Death Act was enacted in 1969, which makes it mandatory for citizens of India to register all births, deaths, and stillbirths [14]. According to the annual report on vital statistics of India based on the civil registration system published by the Office of Registrar General of India, the overall level of registration of deaths in India has increased from 7,641,076 in 2019 to 8,115,882 in 2020 [15]. However, only 22.5% of the total registered deaths are medically certified CoD [15,16]. There is a wide variation among the states of India, with Goa (100%) recording the highest number of medically certified deaths and Bihar (3.4%) having the lowest rate [16]. The Medical Certification of Cause of Death (MCCD) scheme is mainly done in a small number of health care facilities concentrated in urban areas of India [16-19].

Further, the majority of teaching hospitals delegate the responsibility for death certificate completion to resident physicians, with only a small number receiving formal training [20-22]. Medical students and resident physicians regularly make mistakes when filling out death certificates, leading to incompleteness and poor quality of CoD information [20,21]. Most of academic medical centers do not provide specific training in the MCCD [18,22,23].

To address the gap in the reporting the mortality statistics, the Sample Registration System under the Registrar General of India regularly conducts verbal autopsy (VA) for noninstitutional deaths. Some studies have shown that VA is a reliable source for noninstitutional deaths [12,24]. There is a significant prospect for VA to complement the MCCD, because in the absence of routine, medically certified CoD information for all deaths, VA has the potential to provide CoD information at the community level [25-29].

Our study presents a novel approach to strengthening CoD information by developing a comprehensive model that includes a baseline assessment of the functioning of the CRVS system, which will enable us to develop appropriate interventions or provide recommendations to have a systematic and efficient approach to improve CoD information [12,30,31]. Additionally, improving the skills and capacities of physicians for certifying CoD [12,18,32-34], along with providing VA training to community health workers and sensitizing key stakeholders to VA, could be helpful in improving the quality and availability of CoD information. Our approach could also be useful for other settings where CRVS systems face challenges in the death registration process and in obtaining CoD information [4,28]. The study aims to develop a comprehensive model to strengthen CoD information in the selected study sites. The objectives are (1) to identify the challenges and best practices in the functioning of the CRVS system with respect to mortality statistics and CoD information; (2) to develop and implement interventions to strengthen CoD information; (3) to evaluate the quality improvement of the MCCD; and (4) to improve CoD information at the population level through VA for noninstitutional deaths in the selected study sites.

Methods

Study Design

An uncontrolled, before-after, mixed method study will be conducted to identify the best practices and challenges in the existing CRVS system with respect to mortality statistics and the generation of CoD information. The intervention will consist of training in the MCCD and VA for health personnel, in addition to designing appropriate interventions or providing recommendations. The outcome will be assessed by evaluating the quality of the MCCD (Form 4; the physician fills out the form to certify the CoD in case of institutional deaths), as well

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as in the availability of CoD information at the population level through VA for noninstitutional deaths in selected study sites.

Study Setting

The study will be conducted in 3 blocks located in the districts of 3 states (Odisha, Madhya Pradesh, and Uttar Pradesh) in India. As shown in Table 1, these states were selected based on the low number of medically certified deaths compared to registered deaths and the presence of a Model Rural Health Research Unit (MRHRU) [16]. MRHRUs are a Government of India initiative that was established with the goal of improving the quality of health care services in rural India. The MRHRUs serve as a hub for translational research that can be extrapolated all throughout the Indian public health care system. They also serve as an interface between researchers, health care providers, and communities.

Table 1. Comparison of total registered deaths with medically certified deaths in the selected states[a].

State	Total registered deaths (in 100,000), n	Total medically certified deaths (in 100,000), n
Odisha	362,982	59,296
Madhya Pradesh	524,454	35,105
Uttar Pradesh	873,419	109,688

[a]Data sourced from the *Report on Medical Certification of Cause of Death* [16].

Study Duration

As depicted in Table 2, the duration of the study will be for 24 months.

Table 2. Gantt chart for the activities planned in the study.

Activities planned	First year				Second year			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preparatory phase (desk review, recruitment of staff, and orientation of staff with the study objectives)	✓	✓						
Pilot-testing of the baseline assessment tool, training of staff, key informant interviews with stakeholders, and development of the implementation plan		✓	✓					
Implementation of interventions, including a Training of Trainers workshop, orientation of stakeholders on the functioning of CRVS[a], training of physicians in MCCD[b], training of community health workers, and sensitization of key stakeholders				✓	✓	✓		
Monitoring, process evaluation, and endline assessment						✓	✓	
Analysis, discussion with stakeholders, and dissemination								✓

[a]CRVS: Civil Registration and Vital Statistics.

[b]MCCD: Medical Certification of Cause of Death.

Sampling

This will be a pilot study primarily focusing on feasibility, proposing a model, and obtaining primary information with respect to the quality and availability of the CoD information in the selected study sites.

Qualitative Data

Keeping in mind the availability of time and resources, a total of 10-15 key informant interviews (KIIs) will be conducted at the district, block, and *panchayat* (village) levels from each study site to gather the relevant information related to mortality statistics and CoD information (Multimedia Appendices 1-2). A list of persons in the study blocks who are knowledgeable and engaged in any way on issues pertaining to recording and generating mortality statistics (registration of deaths and generation of CoD information) will be populated by the research team in consultation with the district health officials. Two separate lists will be generated, one for the key personnel from the community and the another for those who are in official positions and are engaged in the CRVS system. These lists will be used for the selection of the key informants.

Quantitative Data

Considering the feasibility, 10% of the MCCD forms (Form 4) will be randomly selected from all institutional deaths, excluding medicolegal cases, from the selected public health care facility in the study sites for quality assessment; similarly, if available, the quality of VA forms will also be assessed [35-38]. As per the MCCD rapid assessment tool that will be used to assess the quality of the MCCD forms [39], a total of 330-300 MCCD forms (approximately 110-100 MCCD forms each study site) will be chosen for 1 year (April 2022 to March 2023) from the public health care facility.

Data Collection

As per the methods shown in Figure 1, the baseline assessment will include the following.

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Figure 1. Flow chart of the methods. CRVS: Civil Registration and Vital Statistics; KII: key informant interview; MCCD: Medical Certification of Cause of Death; ToT: Training of Trainers; VA: verbal autopsy.

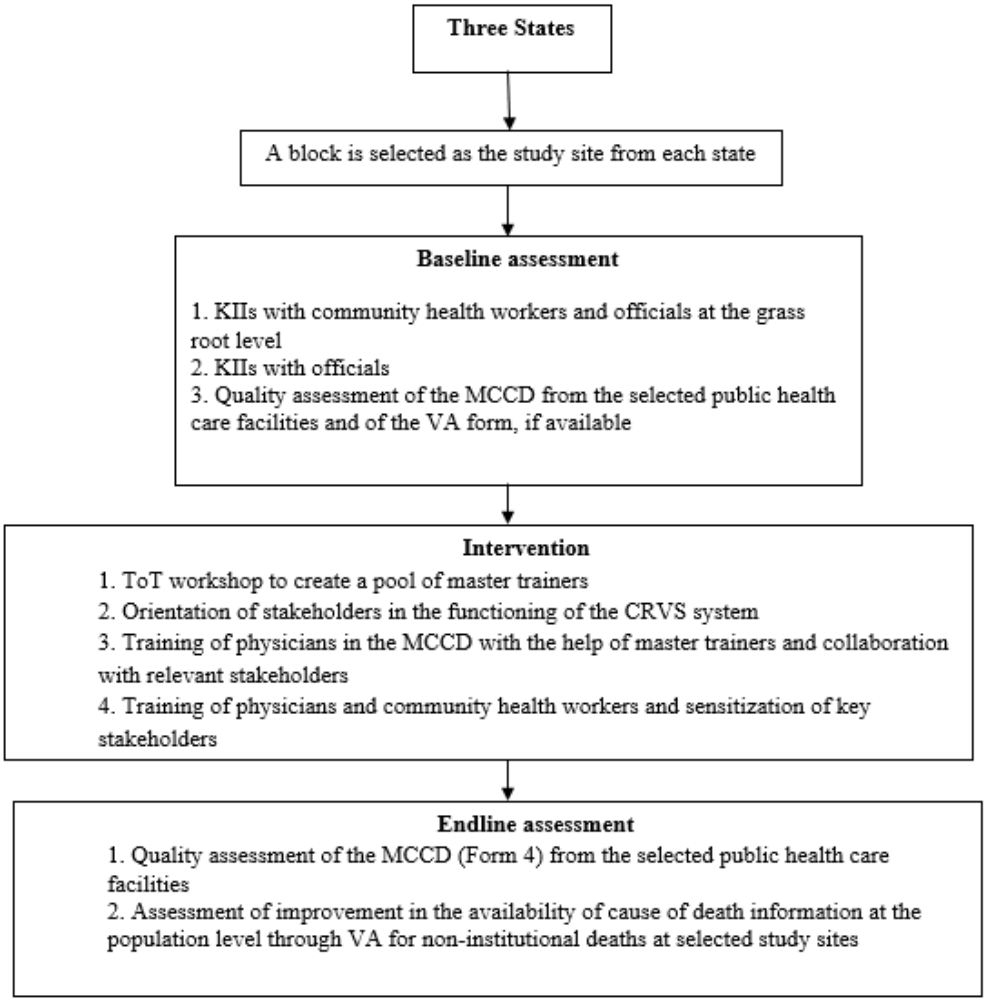

Qualitative Assessment

Following selection from the lists prepared by the research team, an appointment will be sought and those consenting for the interviews will be contacted as per the time given. A total of 10-15 KIIs will be conducted for each study site at the district, block, and *panchayat* levels. Probes will comprise major domains such as practice on death registration, suggestions to improve the death registration, CoD information, and perceptions on public awareness. These will be used to gather the information with respect to mortality statistics and CoD information.

Quantitative Assessment

After obtaining permission from the local health authorities, MCCD forms will be accessed from the selected public health care facility for quality assessment. As per the MCCD rapid assessment tool that will be used to assess the quality of the MCCD forms [39], a total of 330-300 MCCD forms (approximately 110-100 MCCD forms each study site) will be chosen for 1 year (April 2022 to March 2023) from the public health care facility. Physicians trained during the Training of Trainers (ToT) workshop will assess the MCCD forms for quality. Quality assessment for VA will also be conducted, depending on its availability at the selected study site.

Intervention

Intervention activities will include the following strategies.

Baseline Assessment

Baseline assessment will help us to identify the challenges and best practices in the CRVS system with respect to mortality statistics and CoD information, as well as to inform us for the development of appropriate interventions or to provide recommendations. A series of stakeholder orientation meetings will be conducted to inform the baseline results and seek the active engagement of the stakeholders in strengthening the reporting of CoD for noninstitutional deaths.

Training of Physicians on the MCCD

As suggested through existing literature, the training of physicians is crucial for improving the quality and availability of CoD information.

Trainers will be identified at the institutes, MRHRUs, and district and government medical colleges. A ToT workshop will be planned. The agenda for the ToT workshop (physicians and medical officers) on improving medical certification of CoD will be adapted from existing training materials [40-44] and will include topics such as (1) introduction to death reporting forms and its importance (Form 2, Form 3, Form 4, and Form

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4a); (2) guidelines, procedure, and steps for the MCCD through specific reference to diseases; (3) common errors in the MCCD; (4) a brief session on International Classification of Diseases coding; and (5) medical certification of CoD—quality assessment. Each training for physicians and medical officers will last 2 days and will be planned according to the days convenient for them in small batches. The training will be conducted in collaboration with relevant stakeholders and master trainers at each study site.

Training for Health Workers for Conducting VA Using the WHO VA 2022

In parallel, frontline workers such as auxiliary nurse midwifes, community health officers, and physicians will be trained in the WHO VA 2022 instrument for noninstitutional deaths [25,45-47]. Additionally, the sensitization of key stakeholders will be done to make them aware of the significance of VA in improving CoD information.

Outcome Measures

We will use the MCCD rapid assessment tool to evaluate the quality of MCCD forms, for which we have referred to some studies to gain insights into the postintervention assessment [36,39,42,48]. Table 3 provides the variables that will be assessed.

Table 3. Key variables that will be assessed after the intervention.

Category	Variables
General details about the deceased	• Age • Gender
Death certificate details	• Name of the certifier • Trained certifier
Completeness and accuracy	• Multiple cause of death mentioned • Time interval missing from onset to death • Use of abbreviations • Illegible handwriting • Clinically incorrect sequence of events • Incorrect underlying cause

Endline Assessment

Improvement in the Quality of the MCCD

Improvement in the overall quality of the MCCD (Form 4) will be assessed for 6 months from the same public health care facility selected for baseline assessment in each study site. The quality assessment will be done using the MCCD rapid assessment tool [35-37].

Improvement in the Quality of CoD Information

Likewise, improvement in the availability of CoD information at the population level through VA for noninstitutional deaths will be assessed.

Data Management

Qualitative Analysis

Thematic analysis will be conducted to analyze the information collected through KIIs. Themes, categories, and codes will be synthesized to analyze the data.

Quantitative Analysis

All the categorical variables, such as demographic details of the deceased, the name of certifier, time interval missing from onset to death, use of abbreviations, illegible handwriting, etc, will be summarized as frequencies and percentages. The chi-square test will be used to evaluate the improvement in the quality of the MCCD (based on the MCCD rapid assessment tool) before and after the intervention.

Ethical Considerations

The Institutional Ethics Committee of the Indian Council of Medical Research–National Institute for Research in Digital Health and Data Science (erstwhile National Institute of Medical Statistics) has approved the study (NIMS/IEC/03/2022). Participant information sheets (English, Hindi and Oriya) will be developed to communicate the objectives of the study to the stakeholders. Written informed consent will be obtained from the stakeholders before their inclusion in the study. The data collection will start in the first year.

Results

The project has been funded. The data collection process began in May 2023, which will be followed by training of the physicians and community health workers in the MCCD and WHO VA 2022 instrument. The endline assessment is expected to be completed in the initial months of the second year of study duration. The duration of the study will be for 24 months.

Discussion

An uncontrolled, before-after, mixed method study will be conducted in the blocks of 3 states in India. These states were selected based on the low number of medically certified deaths compared to total registered deaths and the presence of MRHRUs. This study aims to develop a comprehensive model to strengthen the CoD information in the selected study sites. The intervention includes a ToT workshop, orientation of stakeholders in the functioning of the CRVS system, training

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of physicians and medical officers in the MCCD, and training of community health workers in the WHO VA 2022 instrument. Postintervention assessment will be conducted to evaluate the impact made by the intervention on the availability and improvement in the quality of CoD information in the selected study sites. The outcome measures will be (1) improvement in the quality of the MCCD forms and (2) improvement in the availability of CoD information at the population level through VA in the selected study sites.

Various strategies have been implemented to improve the CoD information, such as research studies, standard guidelines, training in the MCCD, and use of the VA method. The *WHO CRVS Strategic Implementation Plan 2021-2025* is an initiative to help member states improve the availability of mortality data and certification processes for CoD [10]. The Africa Programme on Accelerated Improvement of CRVS is a regional program to strengthen the CRVS system in the African continent [12]. These initiatives necessitate further efforts to improve the quality and availability of CoD information.

This study focuses on developing appropriate interventions or providing recommendations to address the challenges and understand best practices in the existing CRVS system. KIIs will be conducted to attain this objective. A similar method was used in a study conducted in Zambia by Yokobori et al [31] to assess the CRVS system's performance. This involved conducting a questionnaire based interviews in health facilities.

As a part of intervention, training and capacity building for physicians and medical officers in the MCCD will be conducted at the selected study sites. Myer and Farquhar [20] conducted a similar study, where a 75-minute seminar was conducted as an educational intervention for internal medicine residents on completeness of death certification. Another study was conducted to understand the knowledge, behavior, and attitude of house officers and general practitioners regarding death certification and to ascertain the possibility of developing appropriate intervention in future [22].

Furthermore, this study recognize the importance of involving other stakeholders, such as police officials, *panchayat* leaders, community health workers, etc, that play a crucial in reporting and recording mortality data, especially noninstitutional deaths. To improve the quality and availability of CoD information at the population level through VA, this study will conduct training on the WHO VA 2022 instrument for community health workers along with sensitizing key stakeholders in VA. A study conducted in Thailand by Polprasert et al [26] demonstrated the significance of VA in improving the CoD information, aligning with one of the objectives of this study.

The strengths of the study are as follows: (1) it is one-of-a-kind study where a comprehensive model will be developed to improve the quality and availability of CoD information; (2) it will be a multicenter study that could help us to have a better understanding of the best practices and challenges in the reporting and recording of CoD information; (3) it will involve key stakeholders other than health care professionals in the process of improving CoD information; and (4) the MCCD rapid assessment tool will be used to evaluate the quality of the MCCD before and after the intervention. However, this study may also face some limitations. It does not address the training of mortality coders to accurately code the CoD information provided on the MCCD.

This study is expected to provide a valuable contribution toward strengthening CoD information, which could be helpful for policy making and further research. The intervention model will be developed in collaboration with the existing functionaries of the health and CRVS systems in the selected study sites that are engaged in reporting and recording CoD information; this will ensure sustainability and provide lessons for upscaling, with the aim to improve the reporting of CoD information in the country.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Key informant interview questionnaire for officials.
[DOC File , 46 KB - resprot_v13i1e51493_app1.doc]

Multimedia Appendix 2
Key informant interview questionnaire for frontline workers.
[DOC File , 39 KB - resprot_v13i1e51493_app2.doc]

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Abbreviations

CoD: cause of death
CRVS: Civil Registration and Vital Statistics
KII: key informant interview
MCCD: Medical Certification of Cause of Death
MRHRU: Model Rural Health Research Unit
ToT: Training of Trainers
VA: verbal autopsy
WHO: World Health Organization

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Proposal

Digital Gamification Tool (Let's Control Flu) to Increase Vaccination Coverage Rates: Proposal for Algorithm Development

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Abstract

Background: Influenza represents a critical public health challenge, disproportionately affecting at-risk populations, including older adults and those with chronic conditions, often compounded by socioeconomic factors. Innovative strategies, such as gamification, are essential for augmenting risk communication and community engagement efforts to address this threat.

Objective: This study aims to introduce the "Let's Control Flu" (LCF) tool, a gamified, interactive platform aimed at simulating the impact of various public health policies (PHPs) on influenza vaccination coverage rates and health outcomes. The tool aligns with the World Health Organization's goal of achieving a 75% influenza vaccination rate by 2030, facilitating strategic decision-making to enhance vaccination uptake.

Methods: The LCF tool integrates a selection of 13 PHPs from an initial set proposed in another study, targeting specific population groups to evaluate 7 key health outcomes. A prioritization mechanism accounts for societal resistance and the synergistic effects of PHPs, projecting the potential policy impacts from 2022 to 2031. This methodology enables users to assess how PHPs could influence public health strategies within distinct target groups.

Results: The LCF project began in February 2021 and is scheduled to end in December 2024. The model creation phase and its application to the pilot country, Sweden, took place between May 2021 and May 2023, with subsequent application to other European countries. The pilot phase demonstrated the tool's potential, indicating a promising increase in the national influenza vaccination coverage rate, with uniform improvements across all targeted demographic groups. These initial findings highlight the tool's capacity to model the effects of PHPs on improving vaccination rates and mitigating the health impact of influenza.

Conclusions: By incorporating gamification into the analysis of PHPs, the LCF tool offers an innovative and accessible approach to supporting health decision makers and patient advocacy groups. It enhances the comprehension of policy impacts, promoting more effective influenza prevention and control strategies. This paper underscores the critical need for adaptable and engaging tools in PHP planning and implementation.

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KEYWORDS

influenza; gamification; public health policies; vaccination coverage rates; health promotion

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Introduction

Influenza Epidemiology and Public Health Impact

Influenza is an infectious respiratory disease caused by an airborne virus. There are 4 identified types of influenza viruses, with types A and B being responsible for most of the seasonal influenza epidemics that occur annually [1,2]. The influenza virus can cause mild to severe disease, with risk groups (older people, pregnant women, young children, and individuals with chronic health conditions and autoimmune diseases) being more susceptible to severe forms of the disease [1].

The World Health Organization (WHO) estimates that annual influenza epidemics result in approximately 1 billion infections, 3 to 5 million cases of severe illness, and between 290 and 650,000 deaths [3]. The severity of influenza depends on multiple factors, including the virulence of the virus strain and the level of preexisting immunity in the population [1]. Influenza is also responsible for the worsening of previous health conditions in the individual and has consequences on different domains of individual health [4], such as cardiovascular [5], neurological, renal, respiratory, and diabetic complications.

However, despite the large number of respiratory infections worldwide, it is difficult to estimate the proportion of hospitalizations attributable to influenza across countries or over time [6]. During influenza outbreaks, health systems experience increased demand for services due to an influx of patients seeking medical care. This surge in patient demand can strain health care resources, including hospital beds, medical staff, and supplies [7]. As a result, the pressure on health systems during influenza outbreaks has an impact on access to care for other patients who require medical attention for non–influenza-related conditions, especially those at risk for complications [8].

Another study, published in 2023, which carried out a meta-analysis to improve understanding of the estimates of hospitalizations associated with influenza, concluded that seasonal influenza epidemics result in 3.2 million hospitalizations per year globally [9]. A study that evaluated 10 influenza seasons (between 2008 and 2018) in Portugal to estimate the clinical and economic costs of influenza reported that, on average, hospitalizations due to influenza were 11.6 cases per 100,000 inhabitants [10].

Vaccination for Influenza Prevention

Vaccination against influenza began in the early 1940s, marking a considerable advancement in public health with the introduction of trivalent vaccines [11]. This approach evolved, and in 2012, quadrivalent vaccines were introduced [11], offering broader protection against the influenza virus. The WHO is currently deliberating on the possibility of returning to trivalent vaccines [12], showcasing the ongoing evolution and reassessment of strategies to combat influenza. The effectiveness of the influenza vaccine, which varies between 40% and 60% in the general population, depends on various factors, including patient characteristics such as age and underlying health conditions, as well as the match between the circulating influenza viruses and the seasonal influenza vaccination administered [13].

Recognizing influenza as a considerable global public health challenge, the WHO has advocated for annual influenza vaccination as the most effective measure to combat the influenza. Priority is notably given to older population groups, who face an increased risk of severe influenza disease. However, the effectiveness of influenza vaccinations in these groups is compromised by immune senescence, leading to diminished antibody responses. In response, higher-dose influenza antigen vaccines have been developed, enhancing the immune response and proving to be more effective in preventing influenza infections [14], hospitalizations, and reducing mortality rates [15] compared with standard-dose vaccines.

This targeted approach to vaccination aligns with the WHO's Global Influenza Strategy 2019 to 2030 [16], which recommends a goal of increasing vaccination coverage rates (VCRs) for influenza to 75% by 2030, a goal also echoed by the European Union (EU) in a 2009 Council Recommendation [17]. This 75% target applies especially to older adults, extending as well to other high-risk groups, including persons with chronic conditions and health workers, advocating for comprehensive coverage to mitigate the impact of influenza. Despite concerted efforts, reaching this target has been challenging; as of 2018, influenza vaccination coverage among people aged ≥65 years was <50% in most EU countries, averaging only 39% across these nations and indicating that no country had yet met the 75% coverage target [18].

VCRs are crucially impacted by social inequalities, including financial, cultural, and linguistic barriers [19,20]. Evidence from a broad range of studies highlights this correlation, pointing out a concerning lack of data on VCRs among specific susceptible groups in various countries. The situation is further complicated by the interaction between multimorbidity and social exclusion, creating a vicious cycle where social inequality exacerbates health disparities, thereby deepening social vulnerabilities [21-23]. This interconnection between social determinants and health outcomes underscores the necessity of addressing these challenges holistically to enhance VCRs and strengthen the global response to influenza.

In this context, health management strategies implemented by health and governance authorities, alongside other health decision makers, are pivotal. Public health policies (PHPs) play a key role in managing potential risks by preempting and mitigating their impacts. Vaccination-related PHPs exemplify this approach effectively; by fostering immunity within the community, they not only reduce the likelihood of disease transmission but also ensure that any infections are less severe. This diminishes the demand for hospitalization and decreases mortality risk. Such policies, therefore, are not merely preventive measures but also crucial interventions that address the root causes of health inequities, aiming to break the cycle of multimorbidity and social exclusion by ensuring equitable access to vaccination and health care services.

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Gamification Strategies in Public Health

In the realm of scenario planning and policy development, traditional methodologies have steadily evolved to incorporate advanced technological capabilities, facilitating a more integrated and dynamic approach to learning and assessment. The advent of gamification, defined as the integration of game design elements in nongaming contexts to bolster engagement [24], represents a substantial leap forward in this evolution.

At its core, gamification uses game design elements in nongaming scenarios to augment engagement levels. As delineated in the study by Brangier and Marache-Francisco [25], the gamification design process is anchored in the principles of human-computer interaction, underscoring the importance of user-centric design and interaction. This approach to gamification has gained traction across various sectors, including education, health care, marketing, and human resources, evidencing its versatility and widespread applicability.

However, a substantial fraction of gamification initiatives stumble, primarily due to flawed design strategies. This underscores the criticality of a well-articulated design process, attuned to the nuances of user engagement and interaction dynamics. Moreover, the aspect of measurement emerges as a pivotal consideration in gamification, advocating for a dynamic approach toward redesigning gamified experiences through real-time feedback and user data analytics. However, the adoption of metrics as a quantification tool remains inconsistently applied across gamification frameworks, highlighting an area ripe for further exploration and standardization [24].

The application of gamification in educational contexts, particularly for fostering sustainable behaviors, stands out as a promising approach. Despite existing knowledge gaps, empirical evidence attests to the efficacy of gamification in elevating motivation, engagement, and satisfaction among learners. This enhanced learning environment, in turn, cultivates a fertile ground for the dissemination of sustainability principles and other educational content, demonstrating the transformative potential of gamification as a methodological tool in learning scenarios [26].

These advancements have rendered the simultaneous quantitative and qualitative modeling of policies affecting various facets of the health system and wider society not only feasible but also widely accessible. This confluence of technology and methodology paves the way for an enriched understanding and assessment of policies through sophisticated simulations that blend numerical data with narrative contexts, thereby facilitating a holistic view of potential outcomes and impacts.

Despite this growing interest in the integration of game-like elements into learning scenarios, especially within the health sector, focused design frameworks for health education through gamification remain underdeveloped. This area presents a unique opportunity for pioneering health-specific frameworks that emphasize prototyping, experimentation, measurement, and continuous iteration. Such frameworks are crucial for refining gamification strategies to ensure their effectiveness and relevance in the use of gamification in the health sector [27].

Adopting gamification in PHP decision-making introduces a complex landscape of ethical implications that warrant careful consideration. Despite its potential to enhance public health initiatives by promoting behavior change and increasing engagement being considerable, it also raises concerns regarding data privacy, and informed consent.

Data privacy emerges as a critical concern, as gamification strategies often rely on collecting and analyzing personal health information to personalize interventions and track progress. The ethical management of this data is paramount. According to the study by Mittelstadt et al [28], ensuring data protection and privacy in digital health interventions requires robust encryption methods and transparent data handling policies. Without stringent safeguards, there is a risk of unauthorized access to sensitive information, potentially leading to misuse.

Informed consent is another cornerstone of ethical considerations in gamification. Participants must be fully aware of how their data will be used, the nature of the gamified intervention, and its potential risks and benefits. As Thaler and Sunstein [29] argue in "*Nudge*," while gamification can guide behavior in beneficial ways, it must not manipulate or coerce participants. Ensuring that consent is informed and voluntary preserves autonomy and respects individual decision-making.

Gamification can oversimplify complex policy issues if interpreted verbatim without critical thinking. Especially if used as a game of health policy–related challenges and not a way of rehearsing ideas, there is a risk of reducing nuanced issues to overly simplistic solutions. This oversimplification can lead to misinterpretations and misapplications of policy measures, potentially undermining the effectiveness of interventions and disregarding the intricacies of health outcomes. In addition, given that gamification strategies often use rewards, incentives, and competition to drive behavior, its use in health-related contexts may impact individuals' autonomy and decision-making if it is not framed in critical thinking. Therefore, in the development of this tool, under no circumstances does the individual receive any form of retribution for use or performance.

The "Let's Control Flu" Tool

In the intricate balance between ethical considerations and the exploratory potential of gamification, the "Let's Control Flu" (LCF) tool emerges as a digital, interactive tool designed to support policy decision-making specific to influenza. The LCF tool aims to help enhance VCRs and fulfill the objectives outlined in the WHO's Global Influenza Strategy 2019 to 2030. Rooted in the qualitative framework suggested in the study by Kassianos et al [30], this project seeks to align VCR achievements with the benchmarks established by the WHO and the Council of Europe. The LCF tool demystifies the creation of epidemiological scenarios, eliminating the need for users to possess in-depth knowledge of epidemiological modeling techniques or to engage with complex data sets, such as extensive statistical series. This user-friendly approach facilitates a more accessible and informed decision-making

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process for policy makers striving to combat influenza through increased vaccination uptake.

The LCF tool innovatively applies gamification principles to assist stakeholders in understanding the nuances of different PHPs regarding influenza vaccination. It achieves this by providing a simulated environment where users can experiment with various policy scenarios, thus offering insights into the potential impact on VCRs before their implementation. This simulation enables stakeholders to grasp the intricacies, trade-offs, and consequences of their policy decisions, fostering a deeper understanding and facilitating more informed choices about the PHPs to be adopted and executed. The engaging and interactive presentation of information within the LCF tool simplifies the comprehension of policy impacts, encouraging decisions backed by data-driven insights.

The limitations sector of this paper acknowledges the constraints and challenges faced by the LCF tool. Despite its innovative approach and initial success, the tool's effectiveness and applicability are subject to ongoing evaluation and refinement. Originally piloted in Sweden, the LCF tool's application has proven successful, marking an important first step in its practical use. Following this initial implementation, efforts are underway to broaden the tool's application across 3 additional European countries. This expansion is aimed at enhancing the tool's robustness and increasing its relevance across different geographic contexts, thereby contributing valuable insights to the global effort to improve influenza vaccination coverage through informed policy making.

Methods

Overview

The development of the tool was underpinned by an integrated epidemiological model, encapsulating the burden of influenza disease alongside the predictive impacts of selected PHPs on targeted populations. Initial steps in tool development involved a critical reduction in the number of policies under consideration: on the basis of the foundational work by Kassianos et al [30], the scope was narrowed from 42 to 13 policies, spanning across the 5 pillars identified in their research (Multimedia Appendix 1). This refinement was necessitated by the current state of knowledge, which does not allow for a discrete modeling of the effects attributable to each of the 42 PHPs initially proposed. Consequently, a strategy was used to merge closely related PHPs into coherent bundles, maintaining the original pillar-based categorization to ensure methodological orthogonality.

To ascertain the robustness and reliability of the model, we used a rigorous selection criterion for the scientific literature included in our analysis. Detailed in Textboxes 1 and 2, the inclusion and exclusion criteria were designed to encompass only the most pertinent and high-quality studies. In adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we executed a systematic and comprehensive literature review. The PRISMA flowchart (Figure 1) delineates our methodical approach to the selection of publications, underscoring the scrutiny at each phase of article identification, screening, and inclusion. It is pertinent to note the exclusion of data from 2021 and 2022 to mitigate the confounding effects of the COVID-19 pandemic on the influenza landscape [31].

Textbox 1. Inclusion criteria for scientific works included in the model.

Inclusion criteria

- Only pre-post intervention or controlled studies were included, enabling the effects of the policy to be effectively assessed independently of any background (and potentially not described) policies already in place.
- Studies were included whenever they contained data on one or more of the populations of interest for the model (children, health professionals; pregnant women; older adults, including adults aged ≥65 years and adults aged between 50 and 64 years; and high-risk patients).
- Studies reporting seasonal vaccination uptake were included, as opposed to pandemic influenza vaccination. This restriction was placed to ensure comparability of studies used to inform the model (ie, avoid pooling data for seasonal and pandemic influenza, as the coverage may not be comparable).

Textbox 2. Exclusion criteria for scientific works included in the model.

Exclusion criteria

- Reviews were not included.
- Articles in any other language than English.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of systematic literature review process. TLR: targeted literature review.

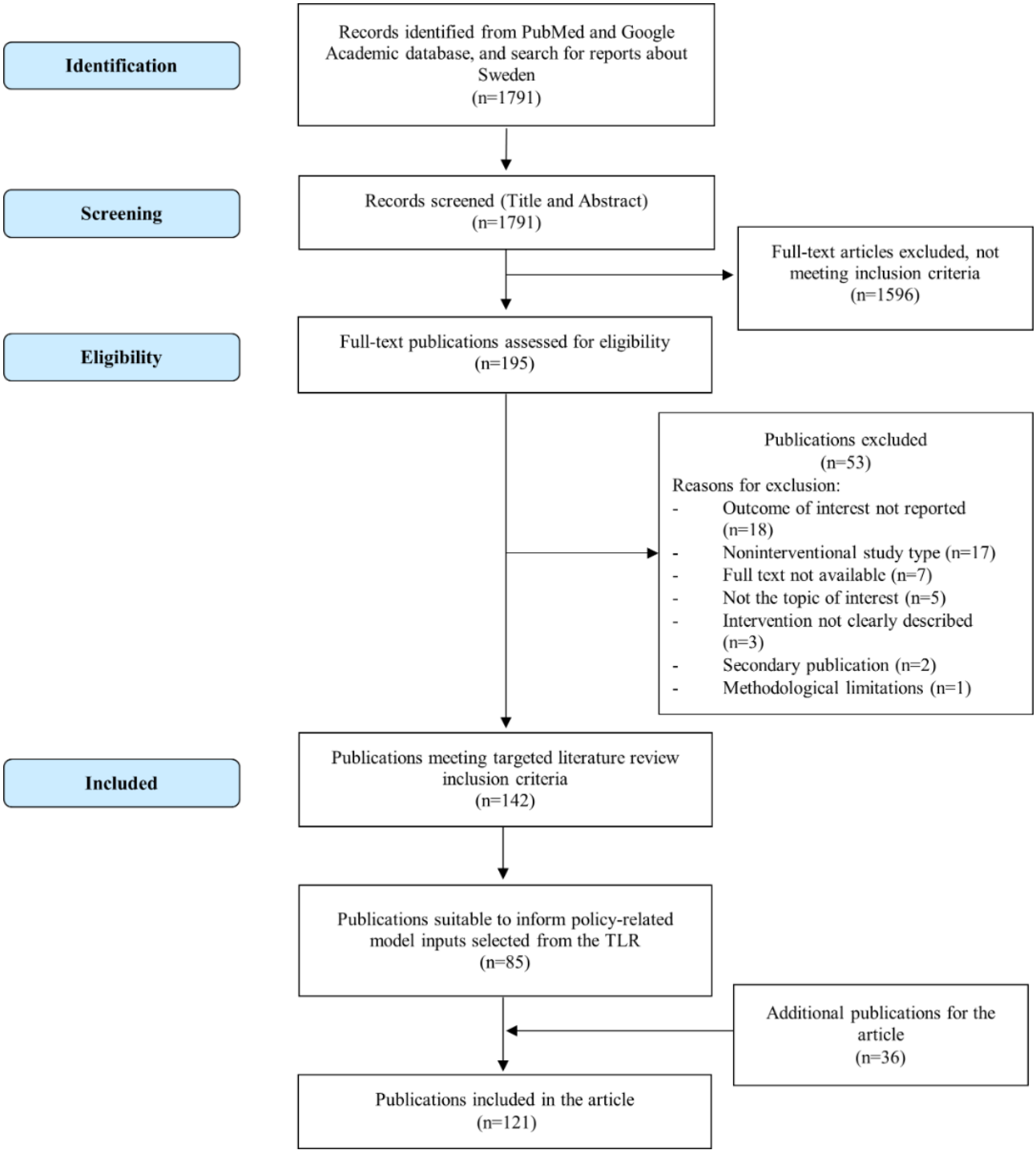

The interventions delineated in the included studies were meticulously aligned with the PHP categories identified in the study by Kassianos et al [30]. To ensure the validity and accuracy of the model construction, a National Advisory Board (NAB) comprising 4 eminent epidemiologists and public health experts from the Swedish health system was constituted. The board's formation was predicated on their prior contributions to scientific literature and health authority reports over the last decade, ensuring their expertise was both relevant and current. The NAB was instrumental in the validation process, meticulously verifying the model-generated values and endorsing the results. This process was crucial, particularly in instances where the scientific literature did not provide ecologically valid data to substantiate the selection of proxies necessary for the tool's development.

Public Health Policies

The set of 13 PHPs incorporated into the LCF model maintained the original categorization into 5 pillars proposed by Kassianos et al [30], each targeting different aspects of public health to enhance vaccination rates and mitigate the health impacts of influenza.

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Pillar 1: Health Authority Accountability and Strengthening the Influenza Program

VCRs targets set at national and regional levels for recommended population: To boost influenza vaccination rates [32], policies set targets at national and regional levels for specific population groups [33]. In Sweden, eg, this policy was implemented nationwide. Strategies programs [34-36] include educating individuals about vaccine benefits, improving vaccine accessibility, and offering incentives for vaccination, all aimed at increasing vaccine uptake.

Funding of influenza vaccinations for all recommended groups: To enhance influenza vaccine access, reduce the burden of disease, and prevent influenza-related deaths, immunization programs [37-41], intervention campaigns, and strategies [32,42-50] can be created. In addition, funds may be allocated to cover the cost of influenza shots for vulnerable groups, such as older adults, children, health care workers, and individuals with underlying health conditions. By doing so, public health officials improve vaccine accessibility and safeguard those with a higher risk of flu complications.

Nationwide regular monitoring of patient VCR at vaccination site and at health care professional (HCP) level by health authorities: Regular tracking of vaccine uptake in designated health facilities such as clinics, hospitals, and pharmacies [51,52] allows for monitoring immunization program effectiveness and identifying areas of improvement. By monitoring immunization coverage rates, public health authorities can use data to enhance programs and achieve desired health outcomes for the population.

HCP VCR as part of performance criteria in hospitals: Boosting vaccine uptake among health care workers and minimizing disease transmission through vaccination. This policy mandates that health worker immunization coverage rates be used as a performance criterion in health care facilities, including hospitals and primary care settings [53]. It encourages health care workers to get vaccinated, prioritizing their well-being and minimizing disease spread among patients, thereby fostering a safer and healthier environment for all.

Sustainable procurement system to ensure appropriate vaccine supply: Ensuring consistent and reliable availability of necessary vaccines for all individuals in need [54], irrespective of their location or financial circumstances. This policy aims to establish a procurement system that effectively manages vaccine acquisition, storage, and distribution to health units, considering cost, quality, and sustainability factors.

Pillar 2: Facilitated Access to Vaccination

Access to multiple vaccination settings: Enhancing vaccine access and reducing barriers to vaccination ensures that individuals can receive vaccines in various locations, including hospitals [48,53,55-57], clinics [36,58], pharmacies [39,59-62], schools [43,52,63-70], and other settings [46,71]. By doing this, public health authorities increase convenience and improve the chances of individuals getting vaccinated.

Call-to-action communications to target groups by multiple stakeholders: This policy targets influenza-related stakeholders, including public health agencies, health professionals, schools, and community organizations. Various methods such as email [69,70,72-74], SMS text messages [75-81], phone calls, health apps, and others [49,82] are used to remind target groups about the importance of vaccination. The objective is to boost vaccine uptake by reminding individuals in target groups of vaccination's significance and encouraging them to get vaccinated [83-86].

HCP pop-up notification or SMS text message to population to vaccinate eligible patients: Health care providers use pop-up notifications or SMS text messages to remind eligible patients of the importance of vaccination and encourage them to get vaccinated [84,85,87-89], thus increasing vaccine uptake.

Pillar 3: HCP Accountability and Engagement

Regular HCP education and training: This policy ensures HCPs, including doctors, nurses, and other professionals, receive ongoing education and updates on new technologies, medical advancements, and changes in vaccination practices [33,34,48,65,77,87-94]. Its objective is to equip HCPs with the necessary knowledge and skills to deliver safe, effective, and high-quality care to patients.

Fair and specific HCP compensation per vaccination: Establishing a system where health professionals receive fair compensation for administering vaccines [95]. This aims to incentivize HCPs to administer vaccines and ensure they are adequately rewarded for their time and efforts. Fair compensation not only supports HCPs but also encourages their dedication to protecting public health.

Mandatory HCP vaccination: Mandating or strongly recommending that health care workers receive specific vaccines as part of their job [35,36,53,96-106]. This policy aims to safeguard public health by minimizing the transmission of communicable diseases in health care settings such as clinics or hospitals, particularly to patients with weakened immune systems. By requiring or strongly recommending vaccination for HCPs, the policy aims to prevent them from being carriers of diseases that could be transmitted to their patients.

Pillar 4: Awareness of the Burden and Severity of the Disease

Coordinated multistakeholder awareness and communication campaigns: This policy promotes immunization through collaboration and coordination among various stakeholders, including government agencies, hospitals and other health organizations [33,34,46,47,52,57,68-71,77,83,86-89,91,97,105,107-110], health professionals [32,41,42,58,65,72,111,112], community organizations, schools, and universities [43,113], as well as the media [105,114]. Its goal is to deliver a cohesive message about the importance of immunization, reaching a wide audience with information on the benefits of immunization and how to access it. By addressing concerns, dispelling misinformation, and creating a supportive environment [115,116], the policy aims to enhance vaccine uptake.

Pillar 5: Belief in Influenza Vaccination Benefits

Positive media coverage of vaccines: The policy promotes a positive approach to vaccine promotion, highlighting the benefits

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of vaccination and countering negative or misleading information. It aims to foster a vaccine-friendly environment by showcasing the safety, efficacy, and importance of vaccines through various media channels, such as news articles, public service announcements, and other media content [41]. The policy's purpose is to boost vaccine uptake by offering accurate information, debunking myths, and empowering the public to make informed decisions about vaccination.

Model Design

The model categorizes the population into 6 age groups—12 to 14, 15 to 34, 35 to 49, 50 to 64, and >65 years—and identifies 5 key target groups: children (aged 0-14 years), older adults (aged >65 years), health professionals, pregnant women, and high-risk patients (aged 15-64 years with ≥1 chronic condition). This segmentation acknowledges the critical challenge of chronic undervaccination in high-risk patients, which poses substantial barriers to achieving optimal health outcomes and protection against influenza and its complications [117].

To assess the impact of PHPs on these target groups, the model simulates 7 health outcomes over a 10-year horizon (2022-2031), including influenza infections averted, hospitalizations averted, influenza-related general practitioner visits averted, workdays lost (productivity impact), influenza-related deaths averted, hospitalizations averted due to cardiovascular complications, and deaths averted due to cardiovascular complications. These outcomes are evaluated both across the total population and within each target group, providing a comprehensive overview of PHP effectiveness in mitigating influenza-related morbidity and mortality.

In the development of the epidemiological model, weights were assigned to each policy across different target groups and specified time frames using a multifaceted approach. This methodology enabled a rigorous, evidence-based evaluation of PHPs' impact on VCRs, accounting for the variability and complexity of policy effects across different demographic and risk groups. It encompassed the following:

1. Policy effects derived from the literature: weights were calculated as weighted averages for each policy and target group based on a comprehensive review of the existing literature. This approach ensures that the model's parameters are grounded in empirical evidence, reflecting the documented effects of PHPs on VCRs.
2. Imputation from similar policies or different target groups: in instances of incomplete data for a specific policy within a target group, weights were imputed based on the relative effects of the most analogous policies available. Alternatively, effects documented for the same policy in different target groups were adjusted and applied, facilitating a coherent extrapolation of policy impacts.
3. Projected increases for subsequent years: for policy effects lacking data beyond the first year, a conservative projection was applied, assuming a 10% increase in the second year and a 20% increase for the third year onward. This assumption is based on the initial year's effect, providing a structured approach to model the temporal dynamics of policy impacts.
4. Integration of expert opinions: insights and recommendations were solicited from the NAB to inform the weighting process, particularly in areas where empirical data were sparse or ambiguous. This inclusion of expert judgment ensures that the model remains adaptable and relevant to current public health contexts, incorporating the nuanced understanding of seasoned professionals in the field.

When policy effects were extrapolated from the literature, the inherent challenges associated with integrating qualitative findings directly into quantitative models led to the necessity of generating temporary proxies to bridge the gap between qualitative insights and the quantitative demands of the model. This process was initiated with comprehensive discussions within the scientific coordination team of the project, after which the proposed proxies underwent a rigorous phase of deliberation and validation by the NAB, ensuring that the proxies accurately reflect the intended policy effects. The final step in this process involved the validation of the proxies by the project's external scientific adviser, who evaluated their suitability and alignment with the model's objectives and the underlying empirical evidence. This layered approach to proxy generation and validation ensured the model's integrity and the reliability of its projections, accommodating instances where direct quantitative data had been lacking.

In scenarios where explicit data concerning the uncertainty of parameters was unavailable, our approach entailed the adjustment of these parameters through the application of suitable statistical distributions, premised on an SE estimated at 10% of the base-case value. This procedure was designed to embed a quantifiable measure of uncertainty into the model, thereby ensuring a broader and more realistic spectrum of potential outcomes.

The model was also designed with a flexible, modular structure, making it easy to update with new scientific findings without having to change its core algorithm. This flexibility is crucial for continually improving the model, allowing regular updates to its parameters and data. The modular design also supports replacing preliminary estimates with actual, up-to-date information, which improves the model's accuracy and relevance as new research becomes available.

Figure 2 showcases the compartmental model designed to elucidate the dynamics among vaccination strategies, influenza transmission, and consequent health outcomes. This model delineates the population into distinct compartments, primarily focusing on the age-stratified cohort of noninfected individuals who are initially unvaccinated. Upon the application of vaccination policies, a transition of these individuals into the vaccinated cohort is anticipated, contingent upon their noninfection status, which predicates the absence of health complications or influenza-induced mortality, thereby facilitating a cyclic annual assessment. In the event of influenza infection, the model accounts for resultant health implications, including hospital admissions, general practitioner consultations, loss in work productivity, and cardiovascular complications, using a formulaic approach that integrates vaccine efficacy and age-specific infection rates. Identical principles extend to the

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unvaccinated population who contract the virus, after which the model delineates 3 potential pathways postinfection: mortality attributable to influenza, mortality from alternate causes, or recovery. The recovery probabilities are quantified through a formula that encapsulates influenza-associated mortality rates across different age groups.

Figure 2. Graphic representation of the model adopted to estimate the effect of the 13 elected public health policies. VCR: vaccination coverage rate.

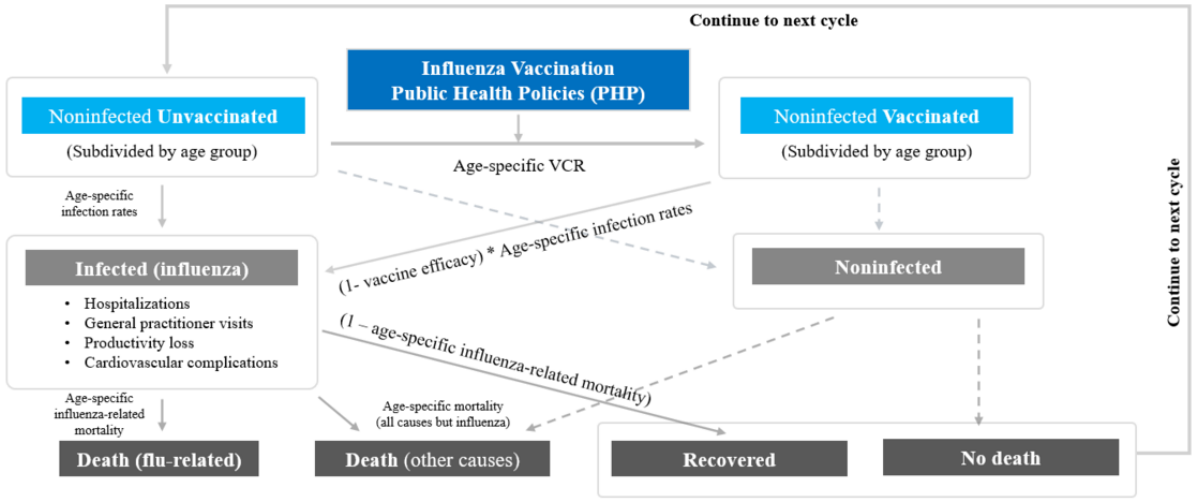

The Operational Functionality of the Tool

The design of this tool prioritized accessibility and user-friendliness, targeting a wide audience that spans HCPs, the public, and patient advocacy groups. By facilitating an interactive platform, it enables users to easily simulate the impact of selecting from the 13 distinct PHPs on various health outcomes within specific target groups, for any year between 2022 and 2031.

Upon the selection of policies, a prioritization mechanism is applied where the weight of each subsequent policy decreases fractionally to reflect its comparative impact on the overall scenario. This methodology underscores the varying significance of individual policies and their synergistic effects when combined. This system also incorporates a realistic element of societal resistance to change, adjusting the cumulative weight of selected PHPs to reflect this factor.

Furthermore, the tool bases its analysis on existing PHPs within a country, recognizing prior efforts and their varying degrees of success. The simulation outcomes represent the scenario of maximum policy efficacy, acknowledging that complete population compliance is an ideal rather than a constant reality due to people's inherent resistance to change. The possibility of achieving perfect policy implementation is speculated for future contexts, suggesting that even in such ideal conditions, there is potential for further enhancement. This could be achieved through the adoption of new communication and educational strategies leveraging emerging technologies, adapting to changing societal contexts, and more effectively engaging target populations.

Ethical Considerations

The LCF project was initiated at the Catholic University of Portugal; was subject to the code of ethics NR/R/1419/2015 at the time; and was later transferred, together with the team, to the NOVA-IMS Faculty of the Universidade Nova de Lisboa, where it was subject to the supervision of its ethics committee, in accordance with the Universidade Nova de Lisboa code of ethics (approval 15464/2014) published on December 19, 2014. Access to data was only granted to published and public material, and there was no access to personal data or any other data that could be used to identify someone.

Democratizing Access and Combating Misinformation

The development of this tool democratizes access to complex epidemiological scenario modeling, allowing users without advanced technical knowledge of PHPs and health impact modeling to explore the potential effects of different health policy scenarios. This capability not only streamlines the decision-making process for health policy but also upholds the principle of technological transparency, ensuring that the underlying mechanisms and assumptions of the tool are clear and understandable.

The dedicated website [118] hosting the LCF tool serves as an educational resource, offering scientifically accurate information about influenza and vaccination in accessible terms. This approach is instrumental in combating misinformation and reducing vaccine hesitancy, thereby supporting global efforts to lessen the impact of seasonal and pandemic influenza [119]. In this context, it is also relevant to acknowledge the differences between vaccine resistance and vaccine hesitancy [120,121], where vaccine resistance often stems from deeply rooted ideological, religious, or philosophical beliefs and, in contrast, vaccine hesitancy is typically driven by fear and doubts, frequently fueled by misinformation or distorted news. Recognizing these differences is crucial for tailoring intervention strategies effectively, as in contexts where vaccine resistance is prevalent due to entrenched beliefs, efforts may need to focus on long-term engagement and education; conversely, in areas where hesitancy predominates, addressing misinformation and

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building trust through transparent communication may prove more effective. Understanding these nuances is essential for optimizing the impact of our approach across diverse populations, as applying this tool in different legal and cultural contexts may face increased inertia from the public.

Results

The LCF project, initiated in February 2021, is projected to conclude in December 2024. The phase focused on model creation and its implementation in the pilot country, Sweden, occurred from May 2021 to May 2023.

The pilot phase of the project was concluded successfully and revealed positive outcomes on the Swedish population. For example, the use of the tool to simulate the comprehensive application of all 13 PHPs across various target populations for the year 2025 provided insightful projections, as the results demonstrate a substantial potential increase in the national influenza VCR, from 18.6% (1,940,964/1,042,283,400) to 28.4% (2,962,903/1,042,294,300). This comprehensive approach revealed increases in VCRs across all specified target populations: older adults experienced a substantial increase to 75% (1,636,707/218,227,600) increase, as well as in high-risk patients who also achieved 75% (825,076/110,010,100), pregnant women's VCR went up to 57.3% (61,894/10,804,700), and health workers saw an increase to 53.1% (276,466/52,085,500). Children VCR went up to 0.8% (15,907/179,057,900) rise, representing an increase of 50% from the baseline value, knowing that high-risk children are vaccinated. Moreover, the anticipated health benefits from this full-scale policy implementation are considerable, including the avoidance of 21,935 influenza infections and 277 hospitalizations. In addition, there would be 5871 fewer physician visits, a reduction of 19,829 workdays lost due to influenza, 38 lives saved from influenza-related deaths, 62 hospitalizations prevented due to cardiovascular complications, and ultimately, 8 fewer deaths from cardiovascular issues related to influenza.

Discussion

Principal Findings

Gamification is an innovative approach that can play a considerable role in improving PHP decision-making. By using gaming mechanics and design, gamification can make complex information and issues more accessible and engaging, leading to a greater understanding of public health challenges, namely for health policy makers who come from outside the professional health sphere and need support tools for their decision-making that provide them with a decision that is best supported by science. Gamification can also create opportunities for active participation and collaboration, allowing individuals to actively shape PHPs and decisions. In addition, gamification can facilitate the collection of real-time data and feedback, providing valuable insights into the impact of PHPs and informing decision-making processes.

By combining play with the need for informed policy decisions, gamification has the potential to positively impact public health and help ensure that policies are both effective and evidence based and also helps to address social determinants of health by engaging disadvantaged communities and increasing their access to health information and resources. Through interactive experiences, gamification can help to break down barriers and increase health literacy, which can lead to better health outcomes. Furthermore, gamification can foster a sense of community and collaboration among individuals, which can help to build a shared understanding of the importance of public health and create a culture of health.

Limitations

In this paper, we delineate several principal limitations inherent to the use of gamification strategies within the realm of predictive modeling. First, we must acknowledge the ethical and methodological implications posed by gamification: these methodologies do not offer precise forecasts of future events but rather serve as heuristic guides. They project potential futures predicated on historical data, presuming all other variables remain constant (ceteris paribus). This deterministic nature inherently restricts the model's ability to predict future impacts with absolute certainty.

Second, the foundation of such modeling lies in data analysis, which encounters substantial challenges regarding the availability and quality of data. This is particularly pronounced at the local level, where the procurement and qualification of data sources, often designed for disparate purposes within complex ecosystems, necessitate the generation of proxy measures. Despite the rigorous and meticulous process of producing and validating these proxies, they introduce inherent risks and uncertainties into the modeling efforts.

Third, we must consider the impact of abrupt contextual shifts that can fundamentally disrupt the health care management landscape, thereby breaching the fundamental principles of modeling. The COVID-19 pandemic serves as a striking example, illustrating how populations initially compliant with national vaccination strategies may suddenly exhibit resistance due to widespread disinformation campaigns. This phenomenon has led to a decline in VCRs for numerous vaccines, culminating in the resurgence of diseases such as polio in locations such as London and New York, a scenario deemed inconceivable a decade ago.

In addition, our model does not account for the influence of other policies that may directly or indirectly affect health outcomes. These include frameworks for occupational health, such as specific recommendations and obligations within various work contexts, as well as the management of health issues within institutions focused on older adult care. Furthermore, the model does not incorporate the integration of health issues into broader economic and policy areas, commonly referred to as Health in All Policies. Despite being endorsed by the EU since 2011, Health in All Policies has seen limited practical implementation. Such policy integration could have a considerable impact on vaccination rates, not only for influenza but also for other vaccines administered throughout an individual's life. Consequently, our model does not capture this dynamic aspect of health management that extends beyond the specific scope of influenza vaccination.

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Given these limitations, we advocate for the periodic reassessment of the modeling framework, recommending an annual (or, ideally, biannual) review. This process is intended to incorporate the latest bibliographic resources and replace proxy measures with evidence-based values. Such a practice not only ensures the model's ongoing refinement but also contributes to the accumulation of evidence necessary for evaluating health impacts in the context of vaccination policy development or modification.

Conclusions

The field of work on increasing VCRs lends itself well to gamification because (1) general trust in vaccines has been deeply shaken by misinformation and fake news during the COVID-19 pandemic, and it is possible to demonstrate the immense advantages that good vaccine coverage provides; (2) in particular, influenza is one of the diseases with the highest pandemic potential, and only through vaccination against the disease will it be possible to mitigate its potential effects; and (3) the entire community, from policy makers, often disconnected from health issues, to the most susceptible citizen, can understand how and where the benefits of influenza vaccination work.

The journey toward improving VCRs globally is not solely a medical challenge but a multifaceted endeavor that requires addressing the underlying social determinants of health. The intertwined relationship between social inequalities and multimorbidity highlights a critical area for intervention. As evidenced, these disparities in social, financial, cultural, and linguistic domains not only hinder equitable access to vaccination but also exacerbate the vulnerability of marginalized communities, thereby impeding the overall effectiveness of influenza vaccination efforts. Therefore, it is imperative that strategies to enhance VCRs also focus on increasing literacy, especially in health-related matters. Empowering individuals with knowledge and understanding of the importance of vaccination can drive more informed decisions, leading to higher uptake rates. In addition, concerted efforts to combat social inequalities are paramount. By creating more inclusive health systems and policies that actively address the barriers faced by disadvantaged groups, a way can be paved for a more equitable distribution of health resources, including vaccines. Ultimately, enhancing health literacy and addressing social inequalities stand as potential catalysts for boosting VCRs, thereby strengthening the global response to influenza and enhancing public health outcomes for all communities.

The design and implementation of the LCF tool have shown promising results in facilitating a broad and user-friendly approach to evaluating PHPs impacts on influenza VCRs and health outcomes. Its capacity to simulate the effects of various PHPs, considering both individual significance and collective synergy, highlights the tool's utility in strategic health planning. Furthermore, the tool's acknowledgment of societal resistance and its foundation on existing PHPs underscore the complexity of health policy efficacy. By offering a platform for dynamic scenario testing, the tool not only assesses current strategies but also identifies opportunities for enhancement, reinforcing the importance of continual innovation and adaptability in public health initiatives. This approach underscores the evolving nature of health strategies and the critical need for responsive, technology-driven solutions to meet public health challenges effectively.

In our interpretation, we see potential for developing the tool in several directions: (1) through its application in other legal and cultural contexts; (2) giving it new capabilities, namely the possibility of cost assessment; (3) adapting the tool to other human vaccination contexts, namely those with low or very low VCRs, as is generally the case with adult vaccination; and (4) developing the gamification capacity used in this context for other public health situations, namely in the prevention of chronic diseases.

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Authors' Contributions

HL and RBL contributed to the conceptualization. HL and CH contributed to data curation, formal analysis, investigation, resources, and software. RBL contributed to funding acquisition. HL contributed to methodology, project administration, and validation. HL and RA contributed to supervision. CH contributed to the visualization. HL, CH, RBL, and RA contributed to writing—original draft. HL, CH, RBL, and RA contributed to writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Public health policies of the "Let's Control Flu" model, organized by Pillar, based on the study by Kassianos et al.
[DOCX File , 17 KB - resprot_v13i1e55613_app1.docx]

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Abbreviations

EU: European Union
HCP: health care professional
LCF: Let’s Control Flu
NAB: National Advisory Board

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PHP: public health policy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
VCR: vaccination coverage rate
WHO: World Health Organization

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Corrigenda and Addenda

Correction: Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study

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(JMIR Res Protoc 2024;13:e57937) doi:10.2196/57937

In "Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study" (JMIR Res Protoc 2024;13:e52946) the authors made one correction.

In the original manuscript, the affiliation of author Francesc López Seguí was listed as follows:

> *Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain*

In the corrected version, it has been changed to read as:

> *Chair in ICT and Health, Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain*

The correction will appear in the online version of the paper on the JMIR Publications website on March 5, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study

Rupa Rubinstein[1,2], MBBCHIR, MSci; Katie Gallagher[3], PhD; John Ho[4], MBBS; Julian Bose[5], BSc; Minesh Khashu[6], MBBS, MD, FRCPCH; Narendra Aladangady[1,2], PhD

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In "Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units With TARGET (Fathers and Partners in Family Integrated Care): Protocol for a Prospective, Multicenter, Multiphase Study" (JMIR Res Protoc 2024;13:e53160), an incorrect title was published.

The title

> *Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units With TARGET (Fathers and Partners in Family Integrated Care): Protocol for a Prospective, Multicenter, Multiphase Study*

has been revised to:

> *Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study*

The reason for this change is that "TARGET" is not defined nor used anywhere in the paper.

The correction will appear in the online version of the paper on the JMIR Publications website on April 3, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Outcomes of Patients With Early and Locally Advanced Lung Cancer: Protocol for the Italian Lung Cancer Observational Study (LUCENT)

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In Outcomes of Patients With Early and Locally Advanced Lung Cancer: Protocol for the Italian Lung Cancer Observational Study (LUCENT)" (JMIR Res Protoc 2024;13:e57183) the authors noted one error.

In the authorship, the following excerpt:

> *Luca Bertolaccini[1], Oriana Ciani[2*], Marco Lucchi[3], Francesco Zaraca[4], Alessandro Bertani[5], Roberto Crisci[6], Lorenzo Spaggiari[1,7]; LUCENT Study Group[8]*
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Proposal

Quality Indicators for Transition from Pediatric to Adult Care for Youth With Chronic Conditions: Proposal for an Online Modified Delphi Study

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Abstract

Background: The transition from pediatric to adult care poses a significant health system–level challenge impeding the delivery of quality health services for youth with chronic health conditions. In Canada and globally, the transition to adult care is regarded as a top priority in adolescent health in need of readily applicable, adaptable, and relevant national metrics to evaluate and benchmark transition success across disease populations and clinical care settings. Unfortunately, existing literature fails to account for the lack of engagement from youth and caregivers in developing indicators, and its applicability across chronic conditions, primary care involvement, and health equity considerations.

Objective: Our proposed study aims to establish a consensus-driven set of quality indicators for the transition to adult care that are universally applicable across physical, developmental, and mental health conditions, clinical care settings, and health jurisdictions.

Methods: Using an integrated knowledge translation (iKT) approach, a panel comprising youth, caregivers, interdisciplinary health care providers, and health system leaders will be established to collaborate with our research team to ensure that the study methodology, materials, and knowledge dissemination are suitable and reflect the perspectives of youth and their families. We will then conduct an iterative 3-round Online Modified Delphi (OMD) study (n=160) to (1) compare and contrast the perspectives of youth, caregivers, health care providers, and health system leaders on quality indicators for transition; and (2) prioritize a key set of quality indicators for transition applicable across disease populations that are the most important, useful, and feasible in the Canadian context. Using the RAND/UCLA Appropriateness Method (RAM) multistage analytic approach, data from each panel and stakeholder group will be examined separately and compared to establish a key set of indicators endorsed by both panels.

Results: The study is funded by the Canadian Institutes of Health Research and Physicians Services Incorporated.

Conclusions: This study will produce quality indicators to evaluate and inform action equitably to improve transition from pediatric to adult care for youth and their families in Canada.

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KEYWORDS

transition to adult care; adolescent health; chronic conditions; quality indicators; consensus; caregivers; adolescent; stakeholder engagement; patient engagement; Delphi

Introduction

Transition from pediatric to adult care services is a challenging and complex process for many youths with chronic physical, developmental, and mental illnesses, and their families [1-3]. Up to 15% of youth in North America are affected by a chronic condition that will require transition to adult care, typically at the age of 18 in Canada [4]. Over 98% of these youth are expected to reach age 20 years and transition to adult health care services [5]. In Canada alone, around 70,000 of these transfers occur every year [6]. These numbers are growing due to advancements in health care which have led to improved survival into adulthood [2]. Chronic conditions make up about 58% of annual total direct health care costs in Canada [7]. In 2016, US $179.6 million was spent on direct health care costs for youth with cirrhosis alone [7]. Additionally, many youths with chronic conditions exhibit poor health outcomes following their transition to the adult health care system (eg, an increase in emergency department visits, hospitalizations, missed appointments, and relapses in disease states) and community services [8-13]. For example, youth living with childhood chronic and complex physical disabilities, specifically cerebral palsy, spina bifida, and acquired brain injuries are expected to be hospitalized once every 6.8 years after transfer, which is 9 times higher than the general population [14].

Significant barriers to successful transition include inconvenient timing during a critical period in adolescent physical and psychosocial development, concurrent life milestones, poor youth and caregiver readiness, inadequate care coordination, underlying differences in pediatric versus adult approaches to care, lack of provider comfort and expertise in managing complex child-onset conditions, limited time and resources for transition navigation, and variation in governance structures and funding models [15]. Accordingly, transition to adult care has been recognized as a priority area in adolescent health care by the Canadian Pediatric Society [16] and highlighted as 1 of 5 domains of need and priority in adolescent health investment in Canada [9]. Significant gaps exist in evaluating and measuring health system performance (ie, the extent to which a health system achieves its goals to improve quality, efficiency, and accessibility) in transition [16]. One major barrier is the absence of universal measures to assess structures, processes, and outcomes in transition care. In practice, there are major inconsistencies in how measurement of transition is approached as there are currently no national Canadian standards informing measurement-based care in transition. A critical step in improving the quality of care delivered for youth with chronic conditions and their families is to develop a systematic approach to measurement in transition through a key set of quality indicators [17]. Quality indicators are defined as robust measures used to evaluate health care delivery, processes, and outcomes to enhance quality of care [17,18] and benchmark performance

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[19,20], informed by key knowledge users. When applied and interpreted carefully, quality indicators could reveal inequities in access, delivery, and outcomes of transition services while highlighting national health system–level practice changes needed to address gaps.

Results of a recent systematic review conducted by our research team identified 169 quality indicators for transition to adult care for youth with diverse chronic conditions; however, significant gaps were found in the process to transition to adult care [21-23]. Notably, the lack of quality indicators focused on equity during the transition period demonstrates that this is an aspect that is neglected in both transition research and the provision of care. Additionally, many studies were limited to physical illnesses (eg, inflammatory bowel disease, sickle cell disease) and excluded mental illnesses and developmental disabilities [24-26]. Consequently, there are no robust quality indicators which can be used in transition across all chronic conditions, hindering our ability to broadly evaluate transition to adult care at a health system level in Canada. While the majority of quality indicators identified in the review were patient-centered metrics, their development rarely involved youth and caregivers [24,25,27]. When included, youth and caregivers were often outnumbered by clinicians, making them less likely to raise their concerns [28]. Previous studies have suggested the priorities of youth with chronic illnesses are different from those of their health care team [29]. Several reviews have concluded that youth want to be involved not only in their own transition planning [30,31] but also in designing and participating in transition research [32]. Engaging youth and caregivers in the design and execution of transition research can increase its relevance for other patients receiving transition services [33]. To prevent the development of poorly actionable quality improvement initiatives and ensure they are meaningful to patients, transition research must be grounded in the unique perspectives and experiences of youth and their caregivers. Building on our previous work [21], this proposed study addresses significant gaps in the literature, particularly the lack of meaningful youth and caregiver engagement in indicator development, applicability across chronic health conditions, community primary care involvement, and health equity considerations.

This study aims to establish a key set of consensus-derived quality indicators for transition to adult care that are applicable across chronic physical, developmental, and mental health conditions, clinical care settings, and health jurisdictions. Following the establishment of an integrated knowledge translation panel, we aim to use an iterative online-modified Delphi study design to (1) compare and contrast the perspectives of youth, caregivers, health care providers, and health system leaders or decision makers on quality indicators for transition; and (2) prioritize a key set of quality indicators for transition applicable across disease populations and care settings in the Canadian context.

Methods

Study Design

Using an integrated knowledge translation (iKT) approach [34], an iKT panel comprising youth, caregivers, interdisciplinary health care providers, and health system leaders will be established at the outset of the project. The iKT panel will collaborate with the research team to ensure that the study methodology and materials are appropriate and youth- and family-centered. We will then conduct a 3-round Online Modified Delphi (OMD) study to prioritize a set of quality indicators for transition across chronic physical, developmental, and mental health conditions that are most important, useful, and feasible for Canadians. Findings will be reported in accordance with the ACcurate COnsensus Reporting Document (ACCORD) reporting guideline [35].

iKT Panel

iKT is defined as a dynamic collaboration between researchers and knowledge users, or those with the authority to enact change, in the synthesis, dissemination, and application of knowledge. An iKT panel with diverse representation will be established and comprise an equal distribution of youth, caregivers, health care providers, and health system leaders in addition to the research team. Panel members will be recruited using the research team's pre-existing relationships with key knowledge users, including leading organizations in child and youth health in Canada. Purposive recruitment will ensure knowledge users with varied backgrounds who can represent transitional care issues that are specific to rural, remote, Francophone, Indigenous, and immigrant communities are included. We will use the best practice activities outlined in the Canadian Institutes of Health Research's (CIHR's) Strategy for Patient-Engagement in Research, in addition to the Ontario Brain Institute (OBI) framework to facilitate engagement with participants and to collaborate [36-38].

The iKT panel will meet on a quarterly basis and be actively engaged throughout the research process. Decision-making processes will occur through active discussion in panel meetings and written feedback. The primary activity of the iKT panel will be to work with the research team to refine the previously identified quality indicators for transition [21] (n=169) to present to the OMD participants minimizing participant burden. Further, the iKT panel will be responsible for finalizing the criteria (eg, importance, usefulness, and feasibility) used to rate quality indicator categories and determining the decision rules for achieving consensus. The panel will also help to inform participant recruitment strategies, consult on the development of supplemental materials for participants in the OMD study (eg, project goals, processes, and timeline), ensure concepts and materials used in the OMD are easily understood and methods used are appropriate for youth and caregivers, and inform the strategies for knowledge dissemination.

OMD Study

Once the quality indicators for transition have been refined, the rating criteria have been finalized, and the decision rules for achieving consensus have been established, we will conduct a 3-round OMD study to prioritize the quality indicators. Each category of quality indicator will be individually rated on the proposed categories of importance and feasibility. These rating scales have been adapted from a previous study aimed at developing quality indicators to evaluate health system performance [39]. The OMD process will follow the RAND

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guidance for conducting Delphi studies and consists of 2 concurrently run panels [40].

The OMD panels will be administered using *ExpertLens*, an online platform for conducting OMD studies developed by RAND, which has been instrumental in advancing consensus-building methodologies. *ExpertLens* has been used previously for quality indicator development in Canada [39,41] and allows for conducting RAND/UCLA Appropriateness panels (a gold standard for developing clinical guidelines and quality indicators) completely online [42]. The RAND/PPMD Patient-Centeredness Method (RPM)—a recently developed approach for engaging patients and caregivers in guideline development—also used the *ExpertLens* platform, which shows the feasibility and benefits of soliciting patient and caregiver input in clinical processes [43,44].

OMD Panels and Participants

We will assemble 2 panels that will be administered concurrently using identical data collection protocols. To maintain balanced panels in all rounds, the 2 panels will be aimed to include equal representations from each expert group [40]. A 2-panel approach ensures methodological robustness and strengthens confidence in our results [40]. Our goal is to recruit approximately 160 participants across the 4 knowledge user groups or "types of experts" (approximately 40 participants per type):

1. Youth (18-24 years old) with any chronic physical, developmental, or mental health condition who are actively navigating or have recently completed their transition to adult care.
2. Caregivers of youth who are currently transitioning or have transitioned to adult care in the last 6 years.
3. Multidisciplinary health care providers from across the continuum of transition, including pediatric physicians, adult physicians, primary care providers, nurses, social workers, mental health professionals, and transition coordinators.
4. Health system leaders such as individuals in child health management or administrative roles, policy makers, decision makers, and community health agency leaders.

Each panel will include 80 participants to increase panel representativeness, engage experts in meaningful online discussions, and explore differences between and within expert groups [45]. Because attrition is common in Delphi panels, we anticipate that about 50-60 participants will complete all OMD rounds in each panel [40].

Similar to recruitment for the iKT panel, we will leverage pre-existing relationships with the Children's Healthcare Canada's (CHC) Health Hub in Transition, the Canadian Paediatric Society (CPS), the Provincial Council for Maternal and Child Health (PCMCH), and other national networks. To minimize the risk of selection bias, we will expand recruitment to community organizations and social media platforms to reach youth and caregivers who may have had an unsuccessful transition or are not connected with a health care team. We may expand our recruitment strategies after consultation with the iKT panel.

Interested participants will be asked to complete a registration survey, provide basic information about them, and suggest quality indicators the panelists should consider. The main selection criteria for OMD participants will include experience with transition care in their respective specialty, navigating transition services, and geographic, practice setting, biological (eg, sex and age), and sociodemographic (eg, gender, race, and ethnicity) diversity. A purposeful recruitment of diverse participant demographics will ensure that an appropriate key set of quality indicators will be developed with equity considerations. Nationally relevant benchmarks require representation from diverse geographical areas (ie, each province and territory, both rural and urban settings), practice settings, and health care organizations [43]. We will use an equity lens to amplify the voices of youth and caregivers that are marginalized, including Black, Indigenous, and LGBTQQIP2SAA (lesbian, gay, bisexual, transgender, queer, questioning, intersex, pansexual, two-spirited, and asexual) individuals, who may have unique experiences with transition. We will aim for at least 25% of participants self-identifying as individuals that are marginalized.

We will review the list of potential participants and identify those who best meet our selection criteria. Selected potential participants will be invited to participate and those who agree will participate in the 3-round OMD. Selected experts from each expert group will be randomly assigned to 1 of the 2 panels, with a goal of achieving balanced panels [46,47]. We will supply participants with preparatory materials that explain the study aims, provide descriptions of candidate quality indicators, and list the rating criteria.

3-Round OMD

Participants in both panels will complete a 3-round OMD process where they will be rating and discussing the candidate quality indicator.

In round 1, expert panelists will be presented with a brief description of each candidate quality indicator category and asked to rate the category on a questionnaire on 2 criteria:

1. Importance: How important is this category of quality indicators in evaluating the transition from pediatric to adult care?
2. Feasibility: How easy is it to obtain this category of quality indicators when evaluating the transition from pediatric to adult care?

Participants will use a 9-point Likert scale (eg, 1=not very important; 9=very important) to rate candidate quality indicators and explain their numeric responses by stating what factors affected their ratings. Participants will be asked to provide recommendations regarding any additions or deletions to the list of candidate quality indicators.

In round 2, participants will see a bar chart for each question demonstrating their responses from round 1 in relation to panel responses. A statement will be displayed for each chart indicating whether agreement between the panel and each of the 4 expert groups was achieved and whether participants considered each quality indicator category to be important and feasible. Further, a comment summary of the major themes

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identified will be provided for low (1-3), uncertain (4-5), and high (7-9) ratings.

Participants will then engage in an online discussion about round 1 results through an asynchronous discussion board. The online discussion boards will be moderated by members of the research team to ensure they remain constructive. A moderator guide developed specifically for *ExpertLens* discussions will be followed [44]. Round 2 discussion data will be used to provide a more nuanced description of knowledge user perspectives and the reasons why expert users agree or disagree with each other.

In round 3, using a questionnaire, participants will have the option to update their round 1 responses according to the feedback and discussions obtained during round 2. Round 3 rating data will be used to determine if there is consensus among diverse experts and prioritize proposed indicators.

Each round will take place over 7-14 days to ensure panelists have ample time to participate and periodic reminders will be sent to maximize participation. The overall time commitment for all 3 rounds will be 3-4 hours in total, with Rounds 1 and 3 taking approximately 1 hour each and round 2 approximately 2 hours. Those completing all 3 rounds will receive compensation for their participation.

Analysis

We will use a previously developed multistage analytic approach to analyzing *ExpertLens* data [28]. We will examine data from each panel and expert group separately and then compare the results to establish a prioritized set of proposed quality indicators using a 3-step approach described below.

First, we will use descriptive statistics (ie, medians and interquartile ranges) to identify how participants within each panel and across the 2 panels viewed each quality indicator category in rounds 1 and 3.

Second, we will use the RAND/UCLA Appropriateness Method (RAM) manual's [47] approach to determine if consensus was reached within each expert group and panel after rounds 1 and 3. *ExpertLens* will automatically do this and display round 1 results to participants in rounds 2 and 3. Round 3 ratings will be used to determine the final study results and address aims. RAM [47] uses the distribution of panel responses to determine if participants agree or disagree with each other and relies on the median value to indicate if the panel's determination is positive, negative, or uncertain.

Third, we will use round 3 data for each indicator category to determine which category is endorsed by each panel. We will identify indicator categories rated highly (median score of 6.5 and above without disagreement) on all rating criteria and automatically include them for further consideration [42].

Finally, we will determine the replicability of the final panel results by calculating a κ coefficient for each indicator category. If the κ statistic is at least moderate (0.41-0.60), we will consider the level of replicability of panel ratings to be acceptable [48]. This threshold is considered conservative. Conducting 2 concurrently run panels will not only help us identify indicators with the highest level of agreement but also increase confidence in our final study results. The final list of endorsed indicator categories will include those rated highly on importance and feasibility by both panels.

To better explain panel and expert group ratings of different indicators, we will analyze participants' explanations of ratings and discussion comments via content analysis [44,47,49]. For each panel separately, we will group all comments for each indicator and rating criterion based on the numeric ratings to which they refer; we will also group all discussion comments by the indicator on which they focus. The coding team will review and code all qualitative comments inductively to identify themes that could be used to explain why a certain quality indicator was considered important, useful, or feasible or if experts have similar perspectives [50]. All coding results will be reviewed by DK to ensure consistency in applying the codebook; AT and other study team members will review coding results to ensure the correct clinical interpretation of comments and appropriateness of conclusions.

Patient and Public Involvement

This study will be heavily influenced by patient and public involvement. Key knowledge users in transition to adult care—youth, caregivers, multidisciplinary health care providers, and health system leaders—will form an iKT panel. This iKT panel will collaborate with the research team to help inform patient facing study materials, recruitment and knowledge dissemination strategies of this research. This is particularly important as the perspectives of youth and caregiver knowledge users are paramount. These youth and caregiver knowledge users will be essential for developing plain language summaries of the research findings that are relevant and accessible to the public.

Ethical Considerations

Ethics approval has been obtained from The Hospital of Sick Children (1000080241). The study has been reviewed and considered to be exempt by the RAND's Human Subjects Protection Committee. Informed consent will be obtained before the start of the OMD study.

Results

Overview

The study is supported by funding from the CIHR through the Transitions in Care (TiC) Team Grant (funding reference number TRC 184533) and Physicians Services Incorporated (PSI; grant number 22-20). A 16-member iKT panel has been established to be actively involved in the preparation for the OMD. Enrollment will begin in September 2024 and the first round of the OMD will commence in October 2024. The study results are expected to be published in late 2026.

Dissemination

We will leverage our partnerships with key knowledge users to promote rapid knowledge mobilization of the key quality indicators, with a primary focus on national-level knowledge dissemination to multiple relevant knowledge users. Our knowledge users have a proven track record of mobilizing knowledge to guide policy decisions and influence clinical practice. We will also engage primary care and community

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leaders through provincial- and national-level workshops, webinars, and media releases on the findings and implications for practice. Many members of the research team are affiliated or situated within pediatric and adult tertiary care and community clinics providing transition support and care to patients. As such, our results will be translated *directly* and *immediately* into these services.

Our study findings will be shared at national and international conferences and published in leading open access journals with youth and caregivers as coauthors. Together with our iKT panel, we will explore the information needs of our youth and families and ensure voices from diverse communities and populations are heard to realize a flexible and clear communication plan. Plain-language summaries with messages that are clear, simple, and individualized for each knowledge user group will be developed to augment the accessibility of the information.

Discussion

Anticipated Findings

Our innovative and equity-focused approach will reveal the differences and similarities in perceptions among youth, caregivers, health care providers, and health system leaders or decision makers on priority quality indicators for transition. The formation of an iKT panel that includes the most important knowledge users, the youth with chronic health conditions and caregivers, will allow the view of youth and caregivers to have significant weight in the study findings.

This study will define a candidate set of quality indicators for transition to adult care that are relevant, feasible to implement, and have the potential to improve the quality of care for Canadian youth and families. This work will respond to the lack of standardized quality indicators for transition from pediatric to adult care in Canada, which has been a major bottleneck toward achieving high quality care for young adults with chronic health conditions.

Implications and Significance

This study will contribute readily applicable, adaptable, and relevant metrics to evaluate and benchmark transition outcomes nationally, addressing 3 major gaps in transition care and research. First, to reflect the needs and priorities of those receiving care, delivering services, and developing health care policies, we will engage with knowledge users involved in the continuum of transition care, including youth (ie, ages 18-24 years), caregivers, health care providers and health system leaders or decision makers. Using an iKT approach, we will appropriately engage and build collaborations with knowledge users throughout the research process [36]. Second, we will ensure demographic and sociocultural diversity among participants [45]. Nationally relevant benchmarks require representation from diverse geographical areas and practice settings [45]. To date, transition research has placed little emphasis on identifying the health system level practices that lead to inequitable transition care and subsequent negative health outcomes [47]. Our strong collaborations with key knowledge ensure that we are well positioned to recruit participants with diverse biological and sociocultural characteristics and lived experiences, including sex, gender, race or ethnicity, immigrant and refugee status, chronic disease, geography, and socioeconomic status [41], helping us to secure representation of diverse transition experiences from marginalized populations. Third, we will also focus on primary care integration. Adolescents with chronic health conditions should engage primary care services to meet their routine health care needs and maintain a continuous patient-provider relationship during the transition period to adult care [46]. An Ontario population–based cohort study by Toulany et al demonstrated youth with severe mental illness receiving no primary care during transition experienced an increased rate of mental health–related hospitalizations in young adulthood [48,49,51]. Despite this, transition research continues to focus on specialist providers [26,47].

Strengths and Limitations

This research study has several notable strengths that contribute to the field of transition care. One strength of the OMD is to define a key of consensus-derived quality indicators that are not only meaningful to youth and families but also useful and applicable for use by health care providers and decision makers. Secondly, the iKT approach will foster collaborations with key knowledge users to ensure the needs and priorities of those receiving care, delivering services, and developing health care policies are reflected throughout the research and dissemination process. Finally, the online approach will allow for a large number of participants with wide geographical distribution and the anonymity of discussions will help promote equal participation without the influence of perceived hierarchy, ensuring that all voices are heard and valued.

This study is not without some potential limitations. While we recognize that internet accessibility may pose a barrier for some potential participants specifically in rural areas, choosing *ExpertLens* will allow greater participation across the country. This platform allows participants to connect to the platform using any basic internet-connected devices, including mobile phones and tablets, addressing some technological barriers that may arise. Using a mixed panel of different expert groups may pose a challenge. To address this issue, all study materials will be written in clear and concise language that is easily comprehensible for both youth and caregivers. Attrition is a potential limitation within a 3-round Delphi as participants may drop out after round 1. To encourage engagement in all 3 rounds, incentives will only be provided at the end.

Conclusions

This study will produce a key set of quality indicators to evaluate and inform action to improve transition from pediatric to adult care for youth and their families equitably in Canada. Determining the most beneficial metrics from the perspectives of various knowledge users, most importantly youth and caregivers, is a fundamental step to identifying areas for improvement in transition, evaluating current processes, benchmarking across jurisdictions, and optimizing health outcomes for youth with chronic conditions into young adulthood.

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Acknowledgments

This project will be completed with the support of Children's Healthcare Canada’s Health Hub in Transition, a national network of experts, to enhance adult care transitions. The hub's mission is to connect youth, parents or caregivers, health care professionals, and health administrators across Canada to create a knowledge mobilization network to share information, ask questions, exchange resources, and bridge the gap between current practices and evidence-based solutions.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AT and SEPM conceptualized the overall study design and methods, wrote the manuscript, and approved the final manuscript as submitted. DK designed the OMD component of the study, drafted the manuscript sections that describe the OMD panels, and critically reviewed the manuscript. SM informed the design of the study engagement approach and coordinated the knowledge user engagement. LS contributed to the design of the study knowledge translation strategies. All authors provided input and guidance on the study design and approved the final manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 193 KB - resprot_v13i1e60860_app1.pdf]

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Abbreviations

ACCORD: ACcurate COnsensus Reporting Document
CHC: Children's Healthcare Canada
CIHR: Canadian Institutes of Health Research’s
CPS: Canadian Paediatric Society
iKT: Integrated Knowledge Translation
LGBTQQIP2SAA: lesbian, gay, bisexual, transgender, queer, questioning, intersex, pansexual, two-spirited, and asexual
OBI: Ontario Brain Institute
OMD: Online Modified Delphi

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PCMCH: Provincial Council for Maternal and Child Health
PSI: Physicians Services Incorporated
RAM: RAND/UCLA Appropriateness Method
RPM: RAND/PPMD Patient-Centeredness Method
TiC: Transitions in Care

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Protocol

Stepped-Care Web-Based Parent Support Following Congenital Heart Disease: Protocol for a Randomized Controlled Trial

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Abstract

Background: Early neurodevelopmental risks, compounded with traumatic medical experiences, contribute to emotional and behavioral challenges in as many as 1 in 2 children with congenital heart disease (CHD). Parents report a strong need for supports; yet, there remains a lack of accessible, evidence-based behavioral interventions available for children with CHD and their families. I-InTERACT-North is a web-based stepped-care mental health program designed to support family well-being and reduce behavioral concerns through positive parenting for children with early medical complexity. In previous pilot studies, the program was effective in increasing positive parenting skills and decreasing child behavior problems, with high parent-reported acceptability. This paper presents the protocol for the first randomized study of stepped-care parent support for families of children with CHD.

Objective: This study will involve a single-site, 2-arm, single-blind randomized controlled trial to evaluate (1) the feasibility and acceptability of a web-based stepped-care parent support program (I-InTERACT-North) and (2) the effectiveness of the program in enhancing positive parenting skills and reducing behavioral concerns among families of children with CHD.

Methods: Families will be randomized (1:1) to either receive treatment or continue with care as usual for 12 months. Randomization will be stratified by child's sex assigned at birth and baseline parent-reported child behavior intensity. Primary outcomes include positive parenting skills and child behavior at baseline, 3 months, 6 months, and 12 months. Secondary outcomes include parental mental health, quality of life, service usage, and feasibility including program reach and adherence. A sample size of 244 families will provide >95% power to detect an effect size of d=0.64. Based on attrition data from pilot studies, a target of 382 families will be enrolled. Parent reports of acceptability, adoption, and suggested adaptability of the program will be examined using cross-case thematic analyses. Primary efficacy analysis will be conducted using an intent-to-treat approach. Generalized estimating equations will be used to examine changes in positive parenting. Child behavior, quality of life, and parent mental health will be tested with repeated-measures analyses. Additional sensitivity and replication analyses will also be carried out.

Results: Recruitment began in February 2024, and recruitment and follow-up will continue until January 2029. We anticipate results in late 2029.

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Conclusions: This study aims to test the effectiveness of I-InTERACT-North web-based stepped-care parent support in improving positive parenting skills and reducing child behavior problems in families of children with CHD compared with a care as usual control group. Results will inform future clinical implementation and expansion of this program among families of children with early medical conditions.

Trial Registration: ClinicalTrials.gov NCT06075251; https://clinicaltrials.gov/study/NCT06075251

International Registered Report Identifier (IRRID): DERR1-10.2196/64216

(JMIR Res Protoc 2024;13:e64216) doi:10.2196/64216

KEYWORDS

congenital heart disease; neurodevelopmental outcomes; web-based mental health care; stepped care; positive parenting; family well-being; mental health; I-InTERACT-North

Introduction

Congenital heart disease (CHD) is the world's leading birth defect, impacting 1% of Canadian children [1,2]. Advances in medical care have significantly enhanced the survival rate post CHD diagnosis; however, children with CHD continue to face greater and persistent challenges in learning, behavior, and socioemotional development than their healthy-born peers [3]. Adverse neurodevelopmental outcomes are influenced by evolving genetic, cardiovascular, and psychosocial risk factors in early childhood [4]. These early risks, compounded with the emotional toll of traumatic medical experiences for children and parents (the word "parent" is used here and throughout this paper to denote the primary caregivers; this may include biological parents, adoptive parents, foster parents, grandparents, family members, or other individuals responsible for childcare), can contribute to the emergence of emotional and behavior problems (eg, noncompliance, acting out) in as many as 1 in 2 children with CHD [5-11]. Yet, a gap remains in the availability of accessible, evidence-based treatments to support the social, emotional, and behavioral needs of children and families affected by CHD [12-14].

When considering factors affecting children's development, parenting and parent-child relationships emerge as potential modifiable determinants of health. Indeed, positive parenting, which includes parental flexibility, responsiveness, constructive parenting, and emotional warmth [15], is a well-established universal protective factor promoting optimal child emotional and behavioral outcomes [16,17]. Several widely used mental health interventions addressing childhood emotional and behavioral problems target positive parenting skills, aiming to strengthen parent-child interactions to improve child behavior [18-20]. Examples include the Incredible Years Parenting Program [21] and the Positive Parenting Program (Triple P [22]). These programs target children identified as at-risk based on socioeconomic factors; however, in recent years, investigators have considered the potential for positive parenting to optimize outcomes among medically at-risk children [23,24]. In our work among children with CHD and their families, parents prioritized mental health support for their children and themselves to empower their parenting skills and confidence. Parents also noted the burdens associated with additional in-person mental health programming, highlighting the need for more accessible web-based services [14].

In response to these identified needs, our team at The Hospital for Sick Children developed the I-InTERACT-North program with and for families of children with CHD by adapting components from the parenting program I-InTERACT (Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury [25]). I-InTERACT was developed at the Cincinnati Children's Hospital Medical Centre by Wade and colleagues [25] and uses in vivo coaching to improve positive parenting skills in a telehealth format. The original I-InTERACT program was shown to improve positive parenting skills and child behavior following pediatric traumatic brain injury (TBI [25,26]). While children with CHD share some underlying vulnerabilities with children with TBI, parents of children with CHD have reflected how their prenatal and neonatal experiences were unique from parents of children with TBI within an initial needs assessment [14]. Specifically, parents described stress beginning prior to or at birth, followed by significant fears and uncertainty during their child's early medical and developmental journey. With this input, the I-InTERACT-North program caters specifically to families of children with congenital and neonatal conditions, including CHD, by providing new information regarding the unique neurodevelopmental and psychosocial impact of these conditions [27]. Likewise, program strategies are tailored to family-specific behavioral concerns, including psychoeducation, coaching, and problem-solving, to address their individual child's needs in the context of their medical and treatment history. Following an initial pilot, which found I-InTERACT-North to be feasible, acceptable, and effective in increasing positive parenting skills and decreasing child behavior problems [28], our group further adapted the program to a novel stepped-care model, as informed by patient-orientated approaches, in which families can access needs-matched incremental supports (ie, an introduction session, an abbreviated program, and a full program [29]). Pilot data from the stepped-care program has demonstrated high acceptability, with strong parent-reported accessibility and adaptability of care to their family's needs. Likewise, pilot data demonstrated the program's success in improving positive parenting skills ($P<.001$; $\eta^2=0.850$) and child behavior problems ($P=.001$; $d=0.390$). Without sacrificing efficacy, stepped-care I-InTERACT-North delivery also improves efficiency and contributes to precision mental health by offering scalable services that are adaptable to the needs of families.

To date, efficacy and feasibility of I-InTERACT-North have not been systematically investigated in children with CHD

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exclusively using a randomized controlled trial (RCT) design. This study aims to test the effectiveness of I-InTERACT-North in improving positive parenting skills and reducing child behavior problems in families of children with CHD compared with care as usual (CAU). This manuscript provides rationale for and information regarding the stepped-care parent support program and describes how intervention effectiveness will be evaluated in families of children with CHD. This study protocol manuscript was developed and submitted before data collection and analyses were completed.

Methods

Study Design

The proposed hybrid type 1 study is a single-site, 2-arm, single-blind RCT designed to simultaneously assess (1) feasibility and acceptability of an RCT of stepped-care web-based parent support (ie, adherence, fidelity, costs, and acceptability) and (2) efficacy of the stepped-care I-InTERACT-North program in improving positive parenting skills and child behavior among families of children with CHD.

Hypothesis 1: based on our pilot data, we hypothesize that the stepped-care program will demonstrate program feasibility (ie, adherence and fidelity, >70%) and high acceptability (ie, based on postintervention program ratings, thematic analysis of feedback, >90%) across CHD families.

Hypothesis 2: we hypothesize that positive parenting skills and child behavior will improve at the end of the treatment among participants in the treatment arm compared to CAU and remain improved compared with CAU at 12 months. We consider positive parenting skills as the primary proximal outcome and child behavior (co–primary outcome) as mediated by improvements in parenting. We also consider secondary outcome changes in parent mental health and family quality of life.

After completion of baseline measures, families will be randomized to receive CAU or active I-InTERACT-North stepped-care treatment. Randomization will be stratified by sex assigned at birth (male, female) and baseline child behavior severity (Eyberg Child Behavior Inventory [ECBI] intensity *t* score above or below cutoff of 60) and executed by a computerized randomization system on REDCap (Research Electronic Data Capture; Vanderbilt University) [30]. Families in both conditions will complete follow-up measures at 3 months, 6 months, and 12 months postbaseline (Figure 1). Families randomized to CAU will receive no direct parent treatment other than clinical care provided in cardiac follow-up (ie, child assessment and consultation), which will be documented accordingly. The CAU families will be offered I-InTERACT-North after completion of their 12-month follow-up measurements. Participants cannot be blinded to their condition, but they will be blinded to primary outcomes and hypotheses. Independent study staff responsible for coding the primary outcomes (ie, positive parenting skills) will be blind to participant allocation, outcomes, and baseline or follow-up status.

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Figure 1. Flowchart of planned study recruitment, retention, and procedures. I-InTERACT: Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury.

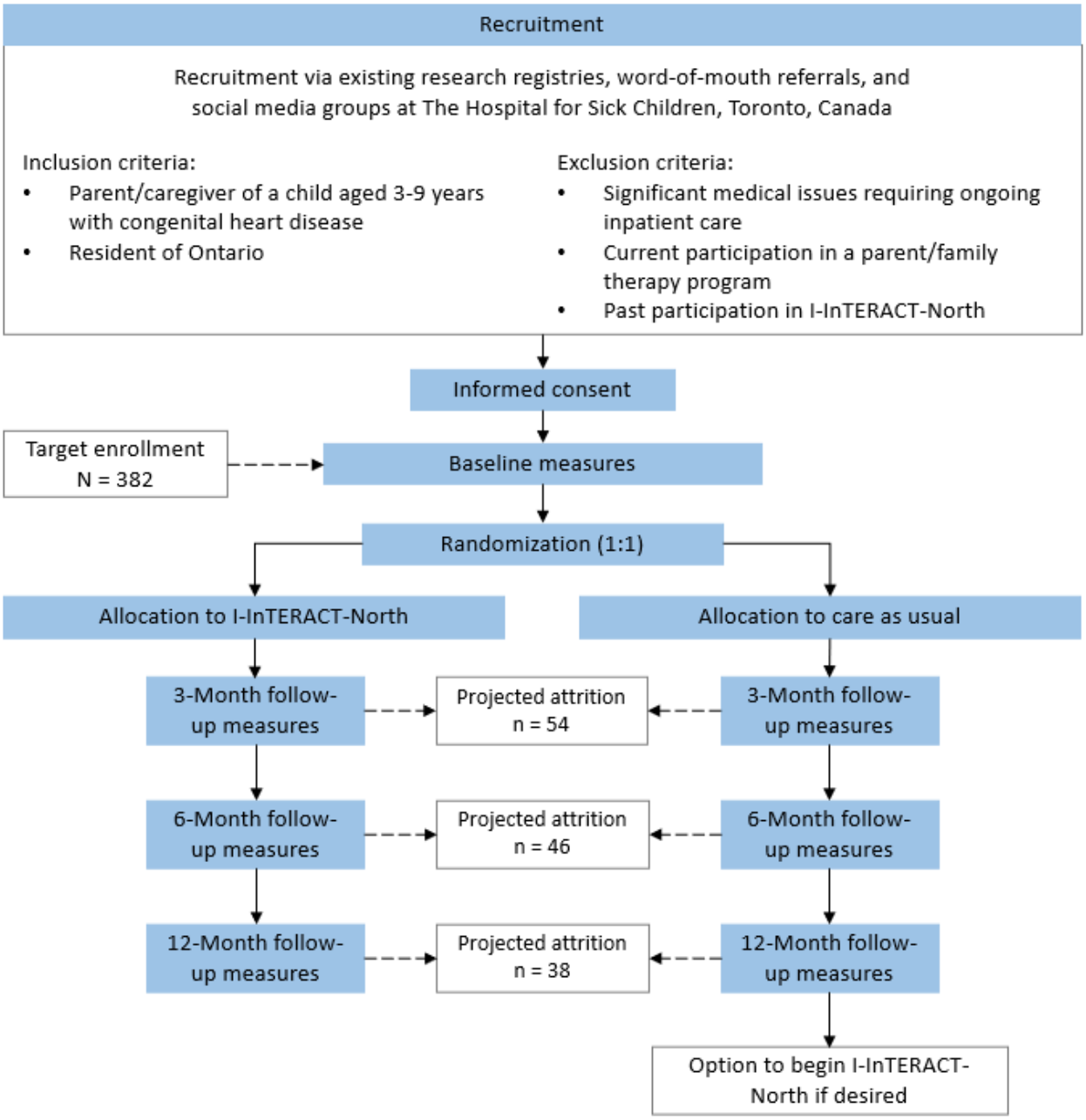

Ethical Considerations

This study was approved by the research ethics board at The Hospital for Sick Children (1000080752). Given that the study participants are parents, all will provide written, informed consent. It is specified that participants can withdraw their consent at any given time in the study upon request. All patient data will be deidentified and stored in secure locations. Families are compensated with a CAD $25 (US $18.47) gift card at each timepoint (ie, baseline, 3 months, 6 months, and 12 months).

Participants

Participants will be recruited from The Hospital for Sick Children in Toronto, Ontario, which is the largest cardiac care center in Canada. Eligible participants must be parents of a child aged 3-9 years (at time of enrollment) with CHD followed at The Hospital for Sick Children. The family must reside in the province of Ontario given professional jurisdiction pertaining to psychological care provision. Exclusion criteria include significant medical issues requiring inpatient care, current participation in a similar family or parent therapy program (eg, Incredible Years Parenting Program [21] and Positive Parenting Program [Triple P] [22]), or previous participation in I-InTERACT-North pilot studies. There are no exclusions based on medical or mental health diagnosis; however, any patients undergoing significant issues requiring inpatient care will be deferred and reapproached at a more appropriate time. To overcome access inclusion criteria, we will provide families in need with tablets based on our Canadian pilot (5%) and Canadian web-based coverage status. Interpreter services are

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also available for recruitment, informed consent, and I-InTERACT-North treatment sessions.

Recruitment

Participants will be recruited through three channels: (1) existing cardiology and neurology research registries at The Hospital for Sick Children (REB #1000051521 and #1000052378) comprising families of children with CHD who have consented to future contact regarding research studies, (2) word-of-mouth recruitment by coinvestigators and collaborators providing clinical care to eligible families, and (3) social media recruitment via Facebook groups moderated by parents for CHD caregivers at The Hospital for Sick Children.

Intervention

I-InTERACT-North is a stepped-care web-based parenting program consisting of 3 tiered steps of increasing therapeutic intensity (Figure 2). In step 1, participants are matched with a therapist for an introductory appointment to review their concerns and goals for the program. Steps 2 and 3 combine web-based therapy sessions with web-based psychoeducational modules that introduce positive parenting skills (eg, labeled praise, reflective responses; Figure 3) as well as child behavior management strategies. Each web-based module concludes with a brief quiz to assess engagement and understanding. Parents complete the web-based modules asynchronously before their web-based therapy appointment, where they review the strategies and engage in active coaching with their therapist while their child is present. Step 2 includes the first 2 therapy sessions and step 3 consists of an additional 5 sessions. Depending on the number of steps completed, as well as scheduling of sessions, I-InTERACT-North may last anywhere from 1 day (ie, 1 single-hour session) up to 7 weeks (for weekly sessions) or 14 weeks (for biweekly sessions).

A collaborative approach to treatment planning (ie, step-up or step-down as outlined by Kennedy et al [31]) is used with families at the end of steps 1 and 2 to decide whether they will proceed with treatment. Step-up indicators include low positive parenting skills as coded from observed parent-child interactions, high child behavior severity, and high in-session ratings of the family's "top problems" [31,32].

Each session follows a manualized therapy protocol to optimize therapist fidelity. All sessions are recorded (with written consent from the participant) and reviewed in supervision. Therapy sessions are delivered via Zoom (Zoom Video Communications, Inc) [33]. All I-InTERACT-North therapists possess masters-level (or higher) education in clinical psychology and come from diverse cultural and language backgrounds. All therapists undergo extensive training and ongoing supervision to ensure program fidelity; this includes a 2-day synchronous training course, 3-6 months of case shadowing, and regular individual and group supervision by a licensed psychologist upon commencing independent program delivery.

Figure 2. Stepped-care model of I-InTERACT-North. I-InTERACT: Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury.

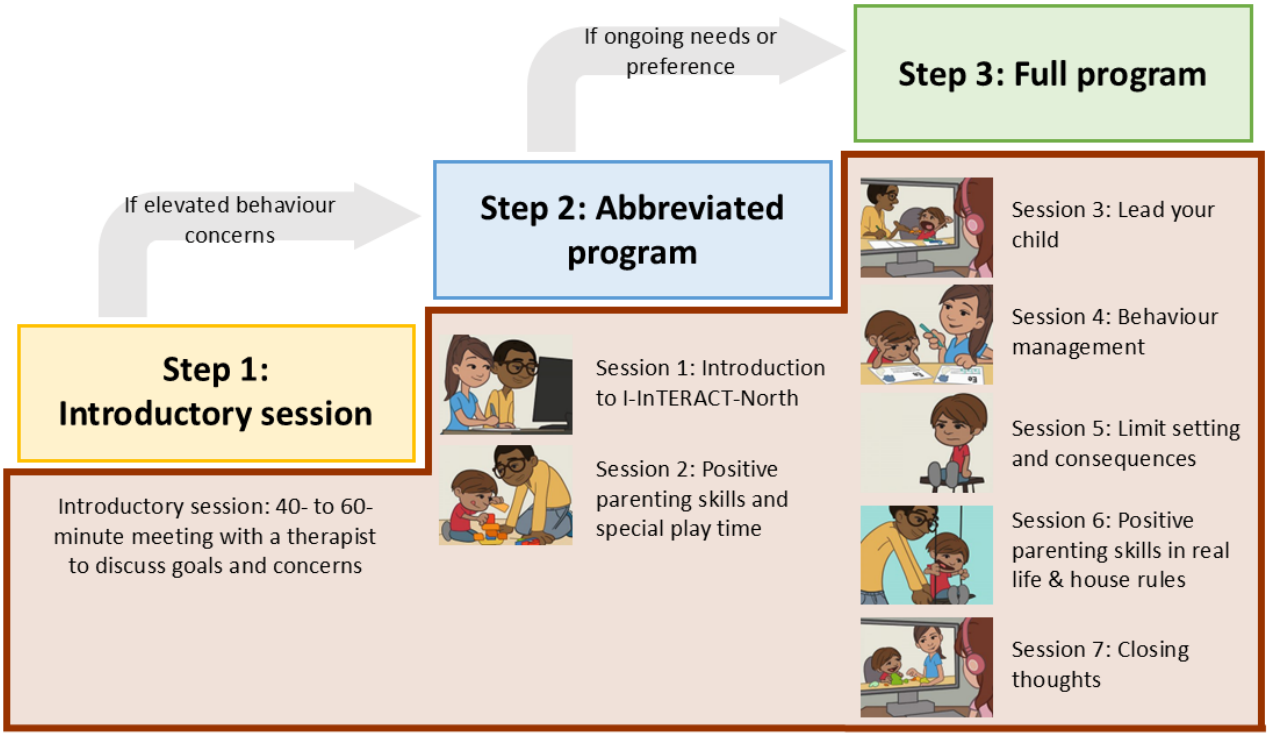

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Figure 3. I-InTERACT-North web-based psychoeducational module. I-InTERACT: Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury.

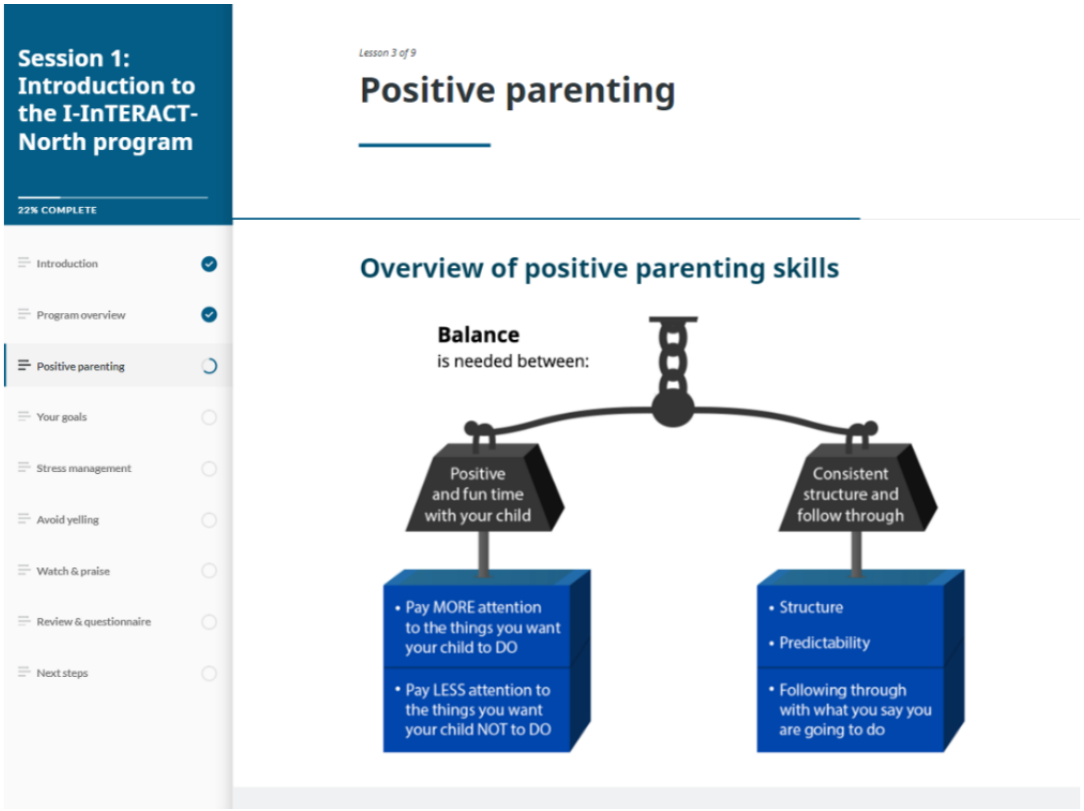

Measures

Overview

Data collected in this RCT include video recordings of parent-child interactions, medical chart extractions, and parent-report questionnaires. All participant-reported measures are completed via REDCap [30] at baseline, 3 months, 6 months, and 12 months (Table 1).

Table 1. Baseline and outcome measures by timepoint.

Measure	Timepoint			
	Baseline	3 Months (± 3 weeks)	6 Months (± 3 weeks)	12 Months (± 3 weeks)
Chart review	✓			
DPICS[a]	✓	✓	✓	✓
ECBI[b]	✓	✓	✓	✓
DASS[c]	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓
CSRI[d]	✓	✓	✓	✓
Parent Acceptability Questionnaire[e]		✓		

[a]DPICS: Dyadic Parent-Child Interaction Coding System.

[b]ECBI: Eyberg Child Behavior Inventory.

[c]DASS: Depression and Anxiety Stress Scale.

[d]CSRI: Client Services Receipt Inventory.

[e]For families randomized to I-InTERACT-North.

Baseline Data

Chart extraction is performed by a research coordinator at baseline. Data collected include the following: CHD type, surgical history, weight and gestational age at birth, current and comorbid medical and mental health diagnoses, presence of pregnancy or delivery complications, seizures, vision problems, hearing problems, motor problems, and cerebral palsy.

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For participants with neonatal magnetic resonance imaging data available, maximal total white matter injury (WMI) volume is documented and will be used for exploratory analyses in this study. WMI volume is calculated based on manual segmentation on the pre- and postoperative magnetic resonance imaging. WMI severity at each time point is categorized with a score of 0-3 (0: none; 1: minimal; 2: moderate; and 3: severe [6]).

Parents will also complete a background questionnaire, which includes questions assessing family history, demographic variables (ie, cultural identity, parents' education, and employment status), and characteristics of the home environment (ie, number of people living in the home, languages spoken in the home).

Primary Outcomes

Feasibility outcomes include program reach and adherence (ie, proportion of eligible families who enroll and complete the study) and program fidelity (assessed with a therapist checklist completed after every session).

Two primary outcomes are evaluated for the second objective: positive parenting skills and child behavior. Positive parenting skills are evaluated using the Dyadic Parent-Child Interaction Coding System (DPICS [34]). One member of a team of 3 coders, blind to condition, will observe a 5-minute recording of parent-child interactions and count the frequency of specific positive parenting skills (eg, labeled praise, behavioral descriptions, commands, questions, etc). In our team's previous studies, interrater reliability coefficients were very high (>0.96 [28,29]). Throughout the RCT, 20% of all videos are double coded to prevent coder drift and coders meet regularly for consensus. In the case that reliability falls below α=.80, the team of coders will convene to reestablish consensus. The second primary outcome, child behavior, is measured with the parent-report ECBI [35]. The ECBI consists of 36 items describing various behavior concerns (eg, noncompliance, emotional regulation), each rated in terms of frequency from 1 (Never) to 7 (Always) as well as whether parents perceive it to be a problem for them (Yes/No). The ECBI yields an intensity score based on frequency of concerns and a problem score representing the number of concerns noted to be problems for the parents. Previous studies have demonstrated good convergent validity of the DPICS and the ECBI for assessing the impact of parenting skills on child behavior [34].

Secondary Outcomes

Parent-reported secondary outcomes include quality of life, parent mental health, service receipt, and treatment acceptability. Quality of life is measured with the EQ-5D-5L ([36]), completed by the parent both for themselves and on behalf of their child. Parent mental health is measured with the Depression and Anxiety Stress Scale—Short Form [37]. Parents will also complete the Client Services Receipt Inventory [38] to report their use of mental health, community rehabilitation, neuropsychology, and educational psychology services. The Client Services Receipt Inventory also includes questions assessing the financial burden of mental health concerns (ie, cost of transportation to and from appointments, medications, alternative childcare, missed work, etc) Finally, for families randomized to I-InTERACT-North, parents will complete a Parent Acceptability Questionnaire at the end of treatment to report their understanding of the structure and purpose of the treatment.

Sample Size and Power Analysis

Based on the size of the research registries available for recruitment and pilot estimates of consent rate (70%), we anticipate that 382 families will consent to participate in the RCT. Using pilot estimates of adherence rate (86%), we anticipate that 328, 282, and 244 families will complete the 3-month, 6-month, and 12-month follow-up measurements, respectively. Samples of 122 participants in each condition at 12 months postbaseline will provide >95% power to detect an effect size of 0.64, which is a medium to large effect size conservatively based on our pilot data. This sample size also achieves a power of 95% for subgroup analyses with subgroups with a split of 50%, which is consistent with or close to that of our pilot data.

Planned Statistical Analysis

A mixed method approach will be taken with quantitative analyses conducted using SPSS Statistics (IBM Corp) [39] and qualitative analyses conducted using NVivo (Lumivero) [40].

Feasibility and Acceptability Analysis

Preliminary descriptive analyses will be used to assess the characteristics of families who participated in the trial, including each program step. Descriptive data will also be computed for adherence, program fidelity, costs, and maintenance. Parent reports of acceptability, adoption, and suggested adaptability of the program by families in the treatment condition, reported in the Parent Acceptability Questionnaire, will be examined qualitatively using cross-case thematic analyses [32,41]. Parent reports and the corresponding case analyses will be used to determine commonalities, differences, and inherent contextual properties that may explain these commonalities and differences across the cases [42]. The results of the case-specific analyses will be entered into a metamatrix to permit thematic analysis across cases. A final thematic table will be created to ensure a coherent, internally consistent, yet distinctive representation of the identified cross-case themes. The essence, scope, and content of the identified themes will be summarized in the final thematic table.

Primary Efficacy Analysis

Primary efficacy analysis will be conducted using an intent-to-treat approach. Generalized estimating equations for longitudinal count-level data having a Poisson distribution will be used to examine changes on the DPICS positive parenting composite. We will account for missing data with the Kenward-Roger degrees of freedom command and using a random intercept with the appropriate covariance structure to allow for unbalanced covariance matrices. The main effect of the program on positive parenting skills will be tested by linear contrast of adjusted DPICS mean change scores from baseline to 3 months between groups. We will also refit the regression model to include stratification variables (sex, baseline behavior intensity) and intervention step as moderators of the effect of treatment. The co–primary outcome of child behavior, as well

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as continuous secondary outcomes of quality of life and parent mental health, will be tested with repeated-measures analyses including condition, stratification variables (ie, sex assigned at birth and baseline child behavior severity), intervention step, and their interactions as fixed effects. Individual subjects as random effects will be adjusted to the data [43,44]. Sensitivity analyses will be carried out to replicate the analyses [29] from the initial adaptation of the I-InTERACT-North program into a stepped-care model for children with neurological risk, examining the preliminary efficacy in changes in positive parenting skills and child behavior based on intervention step. Finally, we will replicate the analyses conducted by Wade and colleagues [25] in the RCT of the original version of I-InTERACT for children with TBI, testing a moderated mediation model using regression-based process modeling to assess the indirect effects of treatment group on child behavior at 12-month follow-up through the change score for positive parenting.

Results

The time period for this study is 5 years, having commenced alongside funding from the Canadian Institutes of Health Research (FRN186222) in February 2023 and research ethics board approval (Figure 4) in August 2023. Hiring and training of I-InTERACT-North therapists spanned April to August 2023, with a total of 13 active therapists as of April 2024. Recruitment began in February 2024. As of September 2024, 24 families have enrolled in the trial, and 55.0% (11/20) families randomized were assigned to the I-InTERACT-North condition. Therapy delivery began in March 2024 and is expected to continue until late 2028. Based on our pilot data and consent rate to date of 65%, we anticipate recruitment to continue through January 2028, with intervention and follow-up concluding in January 2029. An additional 8 months will be allocated toward data analyses and end-of-grant knowledge dissemination including publications in peer-reviewed journals and presentations at international conferences by August 2029.

Integrated knowledge translation will span the 5-year study period, including community partner engagement, family advisory feedback, preparation for knowledge dissemination, multisite collaborations, and preparation for larger-scale multisite grant applications nearing the study end date. To date, knowledge translation has included presentation and discussion with clinical teams in CHD clinics as well as parent and family advisors at SickKids. In February 2024, we consulted with a parent and family advisory council comprising parents and caregivers of children with CHD followed at The Hospital for Sick Children. Members endorsed the strong need for mental health supports, especially in middle childhood as mental health needs become apparent following stressful medical complexities in the early years. Parents also highlighted the lack of accessible mental health programming available, with one parent writing "When my daughter needed this 5 years ago nothing really existed at SickKids. We had to find support in the community which is also really challenging!" Similarly, nurses in the cardiac follow-up clinic at SickKids celebrated the acknowledgment of mental health needs for families and children with CHD and the availability of a free, adaptable, virtual program at SickKids.

Figure 4. Study timeline. CAU: care as usual; I-InTERACT: Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury; REB: research ethics board.

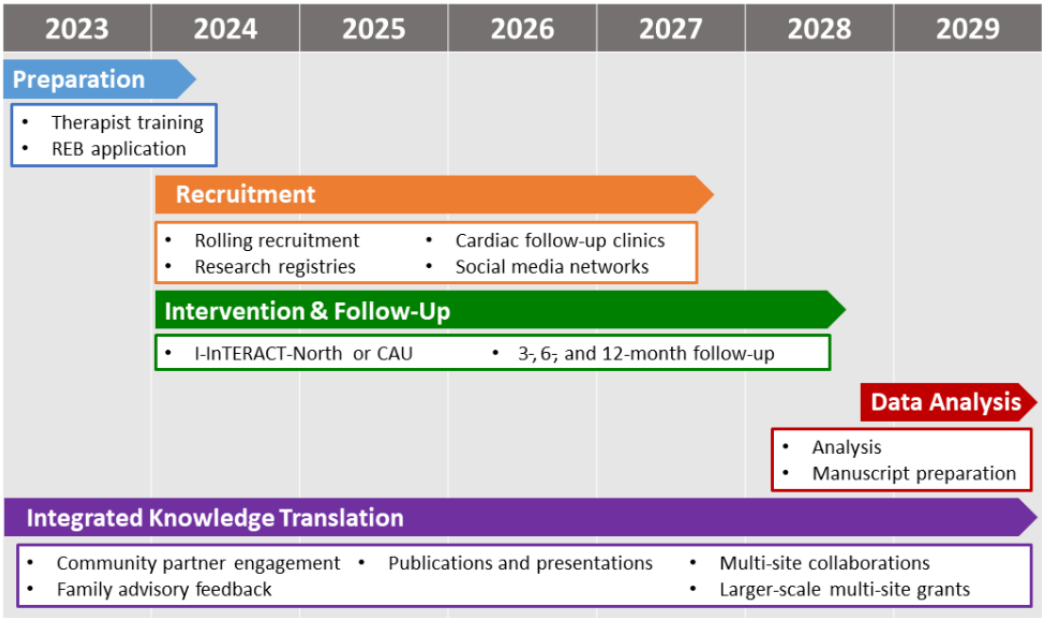

Discussion

Principal Findings

This study protocol presents the rationale and details of a stepped-care web-based support program for parents of children with CHD and describes the trial that will be used to assess the feasibility, acceptability, and efficacy of I-InTERACT-North. To our knowledge, this is the only RCT to examine the efficacy of a virtual positive parenting program among families of children with CHD, contributing to the well-recognized gaps in mental health support in pediatric cardiology follow-up programs. As mortality from CHD has decreased and focus has

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shifted toward addressing developmental and mental health morbidities, the need for intervention programs has become a priority [45], and parents of children with CHD prioritize mental health needs among the most important factors in optimizing their child's and family's well-being [7,8,14,46]. However, existing CHD literature regarding intervention supports has concentrated primarily on early developmental services, psychopharmacological treatment, and the need for academic supports, with limited psychosocial supports available [47]. Thus, the critical need for accessible, evidence-based, and personalized mental health supports, taken together with evidence supporting positive parenting as a modifiable determinant of health and the relationship between psychosocial support and psychological distress among families of children with CHD [48], underlines the need for this trial.

This trial aligns with the Cardiac Neurodevelopmental Outcome Collaborative's clinically informed research agenda to "adapt existing interventions for individuals with CHD" to advance this field of research and elucidate the impact of psychosocial interventions in CHD populations [49]. The hybrid type 1 design was selected purposefully to simultaneously test both intervention efficacy and implementation outcomes, thereby shortening the time needed to study both [50]. The hybrid design is preferred when evidence exists in support of the intervention (as is the case with I-InTERACT-North) and when there is momentum for implementation [50,51]. Examining stepped care also increases potential for improved service delivery and access for at-risk and diverse families traditionally underrepresented in mental health research.

Comparison With Prior Works

Despite significant empirical support for parent management training and behavioral family interventions for children and adolescents with developmental and behavioral challenges [52-55], few studies have specifically targeted CHD populations. The work of Christopher McCusker and his team at The Royal Belfast Hospital for Sick Children, Northern Ireland, has pioneered this work across distinct age groups, with 3 Congenital Heart Disease Intervention Programs (CHIP; ie, CHIP-Infant [56], CHIP-School [57], and CHIP-Family [58]). CHIP-Infant is a 6-session early intervention program that supports infant mental development, feeding, and maternal mental health, with improvements demonstrated 6 months post intervention [56]. CHIP-School and CHIP-Family are designed for school-aged children aged 4-5 and 5-8 years, respectively [57,58]. Both involve single-day parent workshops and follow-up sessions focusing on problem prevention therapy, psychoeducation, and parenting skills. CHIP-School also includes parent observation of their child safely engaging in exercise to demonstrate the child's ability to tolerate physical activity. CHIP-Family offers child-specific cognitive-behavior therapy strategies, light exercise, and activities that promote self-esteem, emotion regulation, and problem-solving. Participation in CHIP-School was associated with improvements in maternal mental health, family functioning, and school attendance 10 months post participation but no significant improvements in child emotional and behavioral concerns. Notably, the CHIP-School study excluded children with neurodevelopmental disorders, limiting generalizability. Similarly, participation in CHIP-Family yielded no significant differences at 6-month follow-up relative to a control group in child emotional and behavioral concerns.

Taken together, the CHIP programs provide preliminary support that parent-centered interventions yield valuable initial gains with respect to parental mental health and family functioning in CHD [56-58]; however, the CHIP programs primarily target parental adjustment to CHD and have a limited focus on positive parenting skills and the parent-child relationship. Similarly, other programs have also targeted the intensive early stress in infancy following CHD diagnosis or treatment for parents. Among parents of children with CHD, Li et al [59] demonstrated significant reduction in parental distress and heightened parental hope for those who underwent a solution-focused brief therapy for parental distress. Likewise, Fleck et al [60] are conducting an RCT to evaluate the efficacy of the REACH intervention for families with infants recovering from surgery for complex CHD. REACH is a home-monitoring program that combines technology and advance practice nurse monitoring to decrease parental stress and improve parental quality of life and infant stability. Although parent-focused interventions may help support early parental coping and adjustment to CHD, they may not extend to later parent-child relationship support. Other psychological intervention research with CHD populations has focused on therapy directed exclusively to children and adolescents, with little to no parental involvement and parent support [61,62].

In reviewing the landscape of the literature to date, the need for evidenced-based and personalized mental health supports for parenting and childhood behavioral problems in CHD is highlighted. Through the proposed RCT, we hope to illustrate the efficacy, feasibility, and acceptability of a novel web-based stepped-care program in improving positive parenting skills and child behavior among families of children with CHD. This trial represents the first examination of a positive parenting intervention program designed with and for families of children with CHD. Embedded within a well-established cardiac follow-up program at The Hospital for Sick Children, we have the unique opportunity to leverage a large, prospective cohort of children with a history of CHD. These children and families have longitudinal neurodevelopmental and neuroimaging data collected since birth. If the effects of the intervention are positive, as we hypothesize given previous pilot trials, this study can contribute toward widespread implementation and expansion. This implementation can span nationally and globally across various CHD cohorts, while leading the way in elucidating key mechanisms of change in treating emotional and behavioral challenges in children with CHD. As such, this study can inform the application of this program to support families of children with other early medical conditions.

Limitations

Several limitations will be taken into consideration with respect to this clinical trial. This is a single-site study that reflects findings specific to The Hospital for Sick Children, the Toronto, Ontario, context, and a public health care system. Recruitment and intervention materials are currently available only in English, thus limiting access and generalizability to

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non–English-speaking families. However, several therapists are bilingual or multilingual (English and French) and interpreter services are available for recruitment, informed consent discussions, and web-based coaching sessions. Likewise, we provide families in need with tablets and web-based sticks as necessary to ensure that web-based coverage status does not pose a barrier to participation. Although the stepped-care treatment model offers increased customization and precision in our intervention approach to optimally address families' needs, it may be challenging to elucidate differences in outcomes between those who receive exclusively an introductory appointment relative to the CAU group. It may also be difficult to control the effects of concurrent intervention services (eg, psychotherapy, rehabilitation) in evaluating the efficacy of I-InTERACT-North; however, service receipt will be explored as a secondary objective to ascertain valuable insight into additional mental health supports sought by families.

Conclusions

There is a lack of accessible, evidence-based behavioral interventions available for CHD children and families. This web-based, stepped-care mental health program was designed to support family well-being and reduce behavioral concerns through positive parenting and psychoeducation regarding CHD. In implementing this research protocol, we expect to provide evidence for the program's effectiveness in increasing positive parenting skills and decreasing child behavior problems in families of children with CHD, while also demonstrating high parent-reported acceptability. This study can provide evidence to support future widespread clinical implementation and expansion. Likewise, our findings can help elucidate mechanisms of change in treating emotional and behavioral challenges in children with CHD. Overall, the clinical and research implications derived from this study can support the mental health and well-being of children and families who experience CHD and advance the field of psychological interventions in this population more broadly.

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Data Availability

The data sets generated during or analyzed during this study will be made available upon study completion by reasonable request to the corresponding author.

Authors' Contributions

MT and BCB contributed to the project administration, writing—original draft and writing—review, and editing of this manuscript. BFA, SHA-Y, VC, AD, ND, TG, DO-A, SW, and SM contributed to the investigation, funding acquisition, and writing—review and editing. TSW contributed the conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-review report by Project Grant/Subvention Projet - Committee / Comité: Social & Developmental Aspects of Children's & Youth's Health/Aspects sociaux et développementaux de la santé de l'enfant et de l'adolescent - Canadian Institutes of Health Research/Instituts de recherche en santé du Canada (CIHR/IRSC) (Canada).

[PDF File (Adobe PDF File), 34 KB - resprot_v13i1e64216_app1.pdf]

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Abbreviations

CAU: care as usual
CHD: congenital heart disease
CHIP: Congenital Heart Disease Intervention Programs
DPICS: Dyadic Parent-child Interaction Coding System
ECBI: Eyberg Child Behavior Inventory
I-InTERACT: Internet-based Interacting Together Everyday Recovery from Traumatic Brain Injury
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
TBI: traumatic brain injury
WMI: white matter injury

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Proposal

Early In-Bed Cycle Ergometry With Critically Ill, Mechanically Ventilated Patients: Statistical Analysis Plan for CYCLE (Critical Care Cycling to Improve Lower Extremity Strength), an International, Multicenter, Randomized Clinical Trial

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Abstract

Background: Survivors of critical illness are at risk of developing physical dysfunction following intensive care unit (ICU) discharge. ICU-based rehabilitation interventions, such as early in-bed cycle ergometry, may improve patients' short-term physical function.

Objective: Before unblinding and trial database lock, we describe a prespecified statistical analysis plan (SAP) for the CYCLE (Critical Care Cycling to Improve Lower Extremity Strength) randomized controlled trial (RCT).

Methods: CYCLE is a 360-patient, international, multicenter, open-label, parallel-group RCT (1:1 ratio) with blinded primary outcome assessment at 3 days post-ICU discharge. The principal investigator and statisticians of CYCLE prepared this SAP with approval from the steering committee and coinvestigators. The SAP defines the primary and secondary outcomes (including adverse events) and describes the planned primary, secondary, and subgroup analyses. The primary outcome of the CYCLE trial is the Physical Function Intensive Care Unit Test-scored (PFIT-s) at 3 days post-ICU discharge. The PFIT-s is a reliable and valid performance-based measure. We plan to use a frequentist statistical framework for all analyses. We will conduct a linear regression to evaluate the primary outcome, incorporating randomization as an independent variable and adjusting for age (≥65 years versus <65 years) and center. The regression results will be reported as mean differences in PFIT-s scores with corresponding 95% CIs and P values. We consider a 1-point difference in PFIT-s score to be clinically important. Additionally, we plan to conduct 3 subgroup analyses: age (≥65 years versus <65 years), frailty (Baseline Clinical Frailty Scale ≥5 versus <5), and sex (male versus female).

Results: CYCLE was funded in 2017, and enrollment was completed in May 2023. Data analyses are complete, and the first results were submitted for publication in 2024.

Conclusions: We developed and present an SAP for the CYCLE RCT and will adhere to it for all analyses. This study will add to the growing body of evidence evaluating the efficacy and safety of ICU-based rehabilitation interventions.

Trial Registration: ClinicalTrials.gov NCT03471247; https://clinicaltrials.gov/ct2/show/NCT03471247 and NCT02377830; https://clinicaltrials.gov/ct2/show/NCT02377830

International Registered Report Identifier (IRRID): RR1-10.2196/54451

(JMIR Res Protoc 2024;13:e54451) doi:10.2196/54451

KEYWORDS

rehabilitation; mechanical ventilation; cycle ergometry; critical illness; exercise therapy; recovery of function

Introduction

Background and Rationale

Survivors of critical illness are at risk of developing physical dysfunction that can last for 5-8 years after discharge from the intensive care unit (ICU) [1,2]. Muscle atrophy can occur rapidly during critical illness, particularly in the leg muscles, which are most vulnerable to weakness due to immobility in the ICU [3]. Quadriceps size can decrease by approximately 18% during a 10-day ICU stay, with the most significant reduction occurring within the first 3 days of admission [4]. At the 1-year follow-up, approximately 35% of ICU survivors had a below-normal 6-minute walk distance, and around 50% had not returned to work [5]. Before the pandemic, the demand for ICU services in Canada was projected to increase by 40% between 2011 and 2026. Based on a 75% survival rate [6] and a conservative estimate of a 50% post-ICU disability rate, national health care utilization costs for ICU survivors 5 years after hospitalization are estimated to exceed CAD $1.6 (US $1.18) billion [7].

Physical rehabilitation initiated in the ICU can improve patients' functional outcomes at hospital discharge [8,9]. In a randomized trial, critically ill patients who were randomized to in-bed cycling starting 2 weeks after ICU admission had a greater 6-minute walk distance at hospital discharge compared with those receiving routine physiotherapy alone [8]. In-bed cycling initiated earlier in a patient's ICU stay is safe [10-12] and feasible [13], but its efficacy on patients' physical function is unknown. To address this, we planned a randomized trial comparing early in-bed cycling and usual physiotherapy versus

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usual physiotherapy alone. We report this statistical analysis plan (SAP) in accordance with the guidelines for the content of SAPs in clinical trials [14].

Objectives

The primary objective of the CYCLE (Critical Care Cycling to Improve Lower Extremity Strength) randomized controlled trial (RCT) is to determine the efficacy of early in-bed cycling (initiated within 4 days of starting invasive mechanical ventilation) combined with usual physiotherapy versus usual physiotherapy alone on patients' physical function at 3 days post-ICU discharge. We hypothesize that patients receiving in-bed cycling combined with usual physiotherapy will have better physical function at 3 days post-ICU discharge compared with those receiving usual physiotherapy alone.

Methods

Design

CYCLE is a 360-patient, international, multicenter, open-label, parallel-group randomized trial (1:1 ratio) with blinded primary outcome assessment at 3 days post-ICU discharge. Assessors are blinded to treatment group allocation. The study includes patients from a 46-patient internal pilot (NCT02377830).

Ethics Approval

CYCLE is approved by the Research Ethics Boards of all participating centers and by Clinical Trials Ontario (Project 1345).

Sites

The trial involves 17 sites across Canada, Australia, and the United States. Sites were selected through established research networks and chosen based on their interest and capacity to conduct the trial. Each site has obtained local ethics approval.

Eligibility

The inclusion and exclusion criteria are detailed in Textbox 1.

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Textbox 1. Trial inclusion and exclusion criteria [15].

1. Inclusion criteria

- Adults (≥18 years)
- Within the first 4 days of mechanical ventilation
- Expected additional 2 days intensive care unit (ICU) stay
- Within the first 7 days of ICU admission
- Could ambulate independently before hospital admission (with or without a gait aid)

2. Exclusion Criteria

- Acute condition impairing patients' ability to cycle (eg, leg fracture)
- Acute proven or suspected neuromuscular weakness affecting the legs (eg, stroke or Guillain-Barré syndrome)
- Traumatic brain injury
- Inability to follow commands in the local language before ICU admission
- Severe cognitive impairment before ICU admission
- Temporary pacemaker (internal or external)
- Pregnant (or suspected pregnancy)
- Expected hospital mortality >90%
- Body habitus unable to fit the bike (eg, leg amputation, morbid obesity)
- Specific surgical exclusion as stipulated by the surgical or ICU team
- Palliative goals of care
- Able to march on the spot at the time of screening
- Persistent therapy exemptions in the first 4 days of mechanical ventilation:
  - Increase in vasopressor/inotrope within the last 2 hours
  - Active myocardial ischemia or unstable/uncontrolled arrhythmia, as determined by the ICU team
  - Mean arterial pressure <60 mmHg or >110 mmHg, or as deemed appropriate by the treating team within the last 2 hours
  - Heart rate <40 bpm or >140 bpm within the last 2 hours
  - Persistent oxygen saturation (SpO_2) <88% or as determined by the treating team within the last 2 hours
  - Neuromuscular blocker within the last 4 hours
  - Severe agitation (Richmond Agitation and Sedation Scale >2 [or equivalent] [16]) within the last 2 hours
  - Uncontrolled pain
  - Change in goals to palliative care
  - Team perception that in-bed cycling or physiotherapy is not appropriate for other new reasons (eg, acute peritonitis, new incision/wound, known/suspected muscle inflammation such as rhabdomyolysis)

3. Eligible, nonrandomized exclusion criteria

- Enrolled previously in the CYCLE (Critical Care Cycling to Improve Lower Extremity Strength) randomized controlled trial or related study
- Patient unable to give consent and no substitute decision maker (SDM) identified
- Patient or SDM declines consent
- ICU physician declines patient or SDM to be approached
- Other, specified by attending team

Randomization

Randomization occurred after informed consent was obtained. Allocation was concealed, and a central randomization process was used. We used a web-based, comprehensive, and secure randomization service [17]. After obtaining consent, the site research coordinator logged into the website, registered the patient, and received the randomized assignment, ensuring allocation concealment. Patients were stratified by center and age (≥65 years vs <65 years).

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Intervention and Comparator

Intervention (Cycling + Usual Physiotherapy)

Patients randomized to cycling received 30 minutes per day of in-bed cycling, in addition to usual physiotherapy interventions, 5 days per week, during their ICU stay. Cycling continued for a maximum of 28 days or until the patient could march in place for 2 consecutive days, whichever came first.

Comparison (Usual Physiotherapy)

Patients randomized to usual physiotherapy received interventions according to current institutional practice. Depending on the patient's alertness and medical stability, usual physiotherapy included activities to maintain or increase limb range of motion and strength, in- and out-of-bed mobility, ambulation, and assistance with optimizing airway clearance and respiratory function [9,18-20].

Outcomes

Primary Outcome

The primary outcome for this study was the Physical Function Intensive Care Unit Test-scored (PFIT-s), measured at 3 days post-ICU discharge [21,22]. The PFIT-s includes 4 items (arm strength, leg strength, ability to stand, and step cadence), each scored from 0 to 3, summed to a maximum of 12 points, and then transformed to a total score of 10 (Table 1) [21]. Higher scores represent a better function. The PFIT-s was developed for an ICU population and includes functional items commonly performed during physical rehabilitation sessions. Unlike the 6-minute Walk Test, which is challenging to administer during ICU awakening as few patients can walk, the PFIT-s can be measured serially over time [23]. Psychometric studies of the PFIT-s identified a minimal clinically important difference of 1.0 points [21,24]. We chose the PFIT-s because we anticipated that all ICU patients could complete at least part of the assessment, even if they could not stand (eg, arm or leg strength), thereby reducing the risk of floor effects.

The PFIT-s is reliable and valid in critically ill patients, demonstrating strong psychometric properties (reliability range 0.996-1.00 [22]; convergent validity with the 6-minute Walk Test and muscle strength [21]). We selected 3 days post-ICU discharge because it is close to the intervention period and prior studies have documented variable delivery of rehabilitation post-ICU [25], which could influence later evaluations. Tables 2-4 describe the preplanned primary outcome, subgroup, and sensitivity analyses.

Table 1. PFIT-s[a] scoring (adapted from Denehy et al [21]).

PFIT-s component	PFIT-s component value score			
	0	1	2	3
Shoulder strength	MRC[b] grade 0, 1, or 2	MRC grade 3	MRC grade 4	MRC grade 5
Knee strength	MRC grade 0, 1, or 2	MRC grade 3	MRC grade 4	MRC grade 5
Sit-to-stand assistance	Unable	Assist of 2 people	Assist of 1 person	No assistance
Step cadence	Unable	>0 to 49	50 to <80	>80

[a]PFIT-s: Physical Function Intensive Care Unit Test-scored.

[b]MRC: Medical Research Council strength grade (0-5).

Table 2. Description of primary outcome measure and analysis.

	Description of outcome	Measurement timing	Analysis
Physical Function Intensive Care Unit Test-scored	Based on 4 patient activities: arm strength, leg strength, ability to stand, and step cadences. Total scores range from 0 to 10 with higher scores meaning better function.	3 days after intensive care unit discharge	Linear regression, adjusted for age and clinical site

Table 3. Subgroup analyses.

Objective	Hypothesis	Analysis
To determine if age modifies the effect of cycling plus usual physiotherapy versus usual physiotherapy alone on the primary outcome.	Cycling will be more effective in older patients than in younger patients.	Linear regression adjusted for age and clinical site, which also includes a term for the interaction between age (≥65 years versus <65 years) and randomized allocation.
To determine if baseline clinical frailty modifies the effect of cycling plus usual physiotherapy versus usual physiotherapy alone on the primary outcome.	Cycling will be more effective in patients with baseline frailty than in patients without baseline frailty.	Linear regression adjusted for age and clinical site, which also includes the main effect of frailty (≥5 versus <5) and a term for the interaction between frailty and randomized allocation.
To determine if sex modifies the effect of cycling plus usual physiotherapy versus usual physiotherapy alone on the primary outcome.	Cycling will be more effective in male than in female patients.	Linear regression adjusted for age and clinical site, which also includes the main effect of sex and a term for the interaction between sex and randomized allocation.

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Table 4. Sensitivity analyses.

Objective	Hypothesis	Analysis
To account for ICU[a] mortality on the primary outcome.	Accounting for mortality will not change the effect of cycling on the primary outcome.	Linear regression, adjusted for age and clinical site. All patients will be included. Those who died before 3 days post-ICU discharge will be assigned a PFIT-s[b] score of 0.
To determine the effect of cycling plus usual physiotherapy versus usual physiotherapy alone including only a blinded assessment of the primary outcome.	Including only patients with a blinded assessment of the primary outcome will not change the effect of cycling on the primary outcome.	Linear regression, adjusted for age and clinical site. Only patients with blinded PFIT-s assessments will be included.
To determine the effect of cycling plus usual physiotherapy versus usual physiotherapy alone under maximal protocol conditions.	Cycling will more greatly be associated with increased function in patients with higher protocol adherence.	Linear regression, adjusted for age and clinical site. Only patients who received the randomized intervention or had a temporary exemption on ≥80% of planned intervention days will be included.
To determine the effect of cycling plus usual physiotherapy versus usual physiotherapy alone in those patients with a completed assessment of the primary outcome.	Including only patients with a complete assessment of the primary outcome will not change the effect of cycling on the primary outcome.	Linear regression adjusted for age and clinical site. Only patients with a total score for the PFIT-s at 3 days post-ICU discharge will be included.
To determine if the cycling effect is affected by the center, we will conduct an analysis adjusting for age only.	Excluding adjustment for clinical sites will not change the estimated effect of cycling on the primary outcome.	Repeat the primary linear regression adjusted for age only (ie, exclude clinical site).

[a]ICU: intensive care unit.

[b]PFIT-s: Physical Function Intensive Care Unit Test-scored.

Secondary Outcomes

Secondary outcomes include performance-based measures, patient-reported outcomes, and those collected by chart review. Performance-based measures include muscle strength (Medical Research Council Sum Score) [26,27] and function (30-second Sit-to-Stand Test [28,29] and 2-minute Walk Test [30]). The 30-second Sit-to-Stand Test and 2-minute Walk Test are reliable in critically ill or frail older adult populations and also have age- and sex-matched norms [29,30]. Patient-reported measures included the Patient-Reported Functional Scale for ICU [31,32], critical care–related psychological distress using the Intensive Care Psychological Assessment Tool [33,34], health-related quality of life using the EuroQoL (EQ-5D-5L) [35-37], and the Hospital Anxiety and Depression Scale [38]. We also collected data on frailty (Clinical Frailty Scale) [39], Katz activities of daily living scale [40], duration of mechanical ventilation, length of stay (ICU and hospital), mortality at multiple time points (ICU, hospital, and 90-day postrandomization), and changes in living location at hospital discharge from baseline. Because of funding limitations, 90-day postrandomization outcomes were restricted to patients enrolled after March 7, 2018. Table 5 outlines our preplanned secondary outcome analyses and their timing.

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Table 5. Description of secondary outcome measures and analyses.

Outcome	Description of outcome	Measurement timing	Analysis
Physical Function Intensive Care Unit Test [21,22]	Patients complete 4 activities: arm strength, leg strength, ability to stand, and step cadences. Total scores range from 0 to 10 with higher scores representing better function. The PFIT-s[a] has strong psychometric properties (reliability range 0.996-1.00; convergent validity with the 6-minute walk distance and muscle strength) [21,22].	ICU[b] awakening, ICU discharge, and hospital discharge	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Medical Research Council Sum Score [41,42]	Standardized physical examination of 6 muscle groups (3 upper and 3 lower), using a 6-point scale (0=no contraction; 5=contraction sustained against maximal resistance), summed to a total score. Total scores range from 0 to 60 with higher scores representing more strength. The MRC[c] Sum Score has excellent interrater reliability (ICC[d] 0.98, 95% CI 0.95-1.00) [26].	ICU awakening, ICU discharge, 3 days after ICU discharge, and hospital discharge	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
ICU-Acquired Weakness - Medical Research Council Sum Score, categorized as <48 versus ≥48 [41,42]	Standardized physical examination of 6 muscle groups (3 upper and 3 lower), using a 6-point scale (0=no contraction; 5=contraction sustained against maximal resistance), summed to a total score. Total scores range from 0 to 60 with higher scores representing more strength.	ICU awakening, ICU discharge, 3 days after ICU discharge, and hospital discharge	Includes survivors at each time point. Separate logistic regressions for each time point, adjusted for age.
30-second Sit-to-Stand Test [28,43]	Patients complete as many full sit-to-stand repetitions as possible within 30 seconds. Higher scores represent better strength. The 30-second Sit-to-Stand Test has good interrater reliability with critically ill patients (ICC 0.85, 95% CI 0.76-0.90) [44].	ICU awakening, ICU discharge, 3 days after ICU discharge, and hospital discharge	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
2-minute Walk Test [30,45]	Patients walk as far as possible over 2 minutes. Higher scores represent better endurance. The 2-minute Walk Test has good interrater reliability with critically ill patients (ICC 0.78, 95% CI 0.66-0.87) [44].	ICU discharge, 3 days after ICU discharge, and hospital discharge	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Intensive Care Psychological Assessment [33]	Patients answer 10 questions related to psychological distress in the ICU using a 3-point scale (0=no; 1=yes, a bit; and 2=yes, a lot), summed to a total score. Total scores range from 0 to 20, with higher scores representing more distress. The Intensive Care Psychological Assessment has good test-retest reliability (r=0.8) and concurrent validity with other measures of anxiety and depression [33].	Following the ICU awakening assessment	Includes survivors. Linear regression, adjusted for age.
Patient-reported functional score for ICU [46]	Patients answer 6 questions about their current perception of function, using an 11-point scale (0=unable to the perform activity; 10=able to the perform activity at the same level as before ICU admission), summed to a total score. Total scores range from 0 to 60, with higher scores representing better function. The patient-reported functional score for ICU has excellent interrater reliability (ICC 0.91, 95% CI 0.76-0.97) [46].	ICU discharge, hospital discharge, and 90 days postrandomization	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Euro-QOL 5D-5L Index [37]	Patients answer 5 questions about their current perception of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, scored according to a prescribed algorithm. Higher scores represent better perceptions of health.	ICU discharge, hospital discharge, and 90 days postrandomization	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Euro-QOL Visual Analogue Scale [37]	Patients rate their overall health on a 100-point visual analog scale (0=worst health; 100=best health).	ICU discharge, hospital discharge, and 90 days postrandomization	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Katz Activities of Daily Living scale [40]	The patient's ability to complete 6 tasks: bathing, dressing, toileting, feeding, continence, and bed mobility. A rater assesses whether the patient is dependent or independent according to prespecified criteria. Total scores range from 0 to 6, with higher scores representing better function.	ICU discharge and hospital discharge	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.

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Outcome	Description of outcome	Measurement timing	Analysis
Clinical Frailty Scale [39]	Frailty includes a reduction in physical reserve and loss of function across multiple body systems. The clinical frailty scale is a 9-point scale, with higher scores representing more frailty. The Clinical Frailty Scale is reliable by chart review conducted by ICU research coordinators, occupational therapists, and geriatric residents [47].	Hospital discharge and 90 days postrandomization	Includes survivors at each time point. Separate linear regressions for each time point, adjusted for age.
Hospital Anxiety and Depression Scale [38]	Patients answer 14 questions on a 4-point scale (7 related to anxiety and 7 related to depression); higher scores (maximum 21 points) represent worse anxiety or depression.	90 days postrandomization	Includes survivors. Linear regression, adjusted for age.
Duration of mechanical ventilation	Days of invasive mechanical ventilation via endotracheal tube or tracheostomy	ICU discharge	Linear regression, adjusted for age
ICU length of stay	Days in ICU	ICU discharge	Linear regression, adjusted for age
Hospital length of stay	Days in hospital	Hospital discharge	Linear regression, adjusted for age
Mortality	Death	ICU discharge, hospital discharge, and 90 days postrandomization	Separate Cox proportional hazards models for each time point, adjusted for age
Hospital discharge location	Same or better living location at hospital discharge from baseline	Hospital discharge	Includes survivors. Logistic regression, adjusted for age

[a]ICU: intensive care unit.

[b]MRC: Medical Research Council.

[c]PFIT-s: Physical Function Intensive Care Unit Test-scored.

[d]ICC: intraclass coefficient.

Adverse Events

We collected data on the following adverse events if they occurred during or immediately after in-bed cycling or usual physiotherapy interventions, were attributed by the clinical team to the randomized intervention, and resulted in clinical deterioration of the patient's status [8,12,48-50]: concern for myocardial ischemia or suspected new unstable/uncontrolled arrhythmia; sustained symptomatic bradycardia (<40 bpm) or tachycardia (>140 bpm); sustained hypertension (mean arterial pressure >120 mmHg); sustained oxygen desaturation below baseline (typically <90% or 88%); marked ventilator dyssynchrony; bleeding at the femoral catheter site; and new bruising at the femoral catheter site. Serious adverse events included unplanned extubation, cardiac arrest, or falls to the knees during usual physiotherapy activities.

Sample Size

Our sample size of 360 patients was determined to detect a 1.0-point mean difference [51] between the cycling + usual physiotherapy group and the usual physiotherapy group for the PFIT-s measured at 3 days after ICU discharge [21,22]. Previous psychometric studies of the PFIT-s identified the minimal clinically important difference as 1.0 point [21,24]. Logistic regression analysis of patients enrolled in the TryCYCLE [12] and the CYCLE pilot randomized study [13] found that each 1.0-point increase in PFIT-s at ICU discharge (indicating better function) was associated with a 40% reduction in the composite outcome of death, readmission to ICU, or requiring paid assistance for activities of daily living at hospital discharge [51]. Based on an SD of 2.5 points at ICU discharge [12,52], a 1.0-point difference between groups [21,24,51], and 90% power (α=.05), we estimated the need to randomize and analyze 266 patients (133 per group). Based on data from 66 patients enrolled in the CYCLE Pilot RCT, we anticipated approximately 35% total attrition (25% ICU mortality, 1% mortality in the first 3 days post-ICU discharge, 5% missed primary outcome assessments at 3 days post-ICU, and 5% unblinded). Therefore, we recruited a total of 360 patients.

Framework

This trial was designed as a superiority trial, hypothesizing that patients receiving in-bed cycling combined with usual physiotherapy early in their ICU stay will have better physical function at 3 days post-ICU discharge compared with those receiving usual physiotherapy alone.

Statistical Analysis

Interim Analysis

We conducted a blinded interim analysis of the first 180 patients enrolled (half of the sample size) to assess benefits and harms, including serious adverse events. We adhered to conservative statistical guidelines for data monitoring based on the modified Haybittle-Peto rule [53]. The Data Monitoring Committee recommended continuing the trial on September 29, 2020, based on this interim analysis. To maintain the overall type-I error rate (ie, α), we evaluated the primary endpoint using a fixed conservative α of .001 for the interim analyses and plan to use α of .05 for the final analysis.

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Timing of Final Analysis

The first publication of the trial results will focus on comparing the cycling + usual physiotherapy group with the usual physiotherapy group once every patient has reached 90 days postrandomization and data on vital status at hospital discharge have been received. Longer-term endpoints for the economic evaluation will be reported in a separate publication. This document will outline only the analyses included in the primary CYCLE manuscript.

Timing of Outcome Assessments

Table S1 in Multimedia Appendix 1 outlines the schedule of study procedures with 5 time points for outcome assessments.The ICU awakening time point was based on the physiotherapist's assessment of the patient's ability to consistently follow 3 out of 5 verbal commands [42]. A patient's discharge might be delayed for reasons unrelated to their readiness for discharge (eg, unavailability of hospital beds in the transfer ward). Therefore, ICU discharge measures were recorded either when the patient was discharged from the ICU or when a discharge order was written, whichever occurred first. The 3-day post-ICU time point was scheduled for 3 days after the patient's physical discharge from the ICU. The hospital discharge time point was recorded when a discharge order was written for the patient for the index admission, including transfer to an alternative level of care. The 90-day time point was scheduled for 90 days after randomization.

Other Principles

All statistical tests will be 2-sided and performed at a 5% significance level. We will report 2-sided 95% CIs and conduct all analyses using SAS version 9.4. Our final RCT report will adhere to (1) the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement for reporting parallel group randomized trials (Multimedia Appendix 2) [54]; (2) the Extension for Reporting Trials of Nonpharmacologic Treatments [55]; (3) the Guidelines for Reporting Outcomes in Trial Reports, The CONSORT-Outcomes 2022 Extension [56]; and (4) the CONSORT 2024 Statement [57].

Trial Profile

We will report the total number of patients screened, including those meeting all inclusion criteria and those with exclusion criteria, based on screening logs from participating sites. For eligible patients, we will provide reasons for non-enrollment. Patient withdrawals and losses to follow-up will be documented in our CONSORT diagram (Figure 1).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) patient flow diagram.

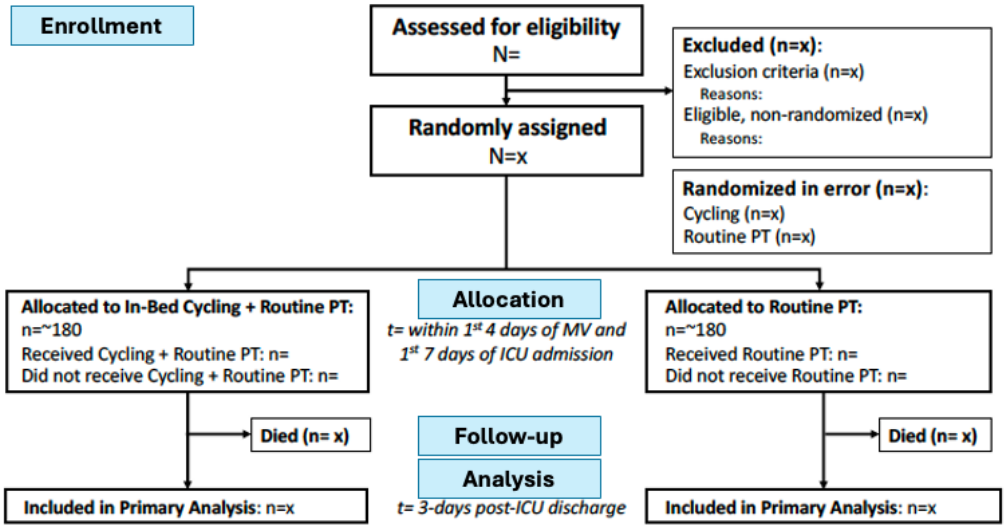

Protocol Adherence

The following definitions are used in this study.

"Study days" included all days in the ICU from the day of randomization to 28 days postrandomization.

We did not plan for the randomized intervention to occur under the following circumstances:

- on days when a patient was randomized after normal physiotherapist working hours;
- on days when a patient was transferred out of the ICU before 12:00 pm;
- on weekends or statutory holidays;
- for patients randomized to in-bed cycling, if they had marched on the spot for 2 consecutive days and continued marching or had higher mobility for the remainder of their ICU stay; and
- on days when a patient did not meet the criteria to receive usual physiotherapy, based on institutional policies for the delivery of usual care.

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The remaining days were designated as "Planned intervention days." On weekdays (ie, nonholiday Monday through Friday), physiotherapists reviewed study patients for 1 or more of the following "Temporary exemptions" before offering the randomized intervention:

- increase in vasopressor/inotrope within the last 2 hours;
- active myocardial ischemia or unstable/uncontrolled arrhythmia, as determined by the ICU team;
- mean arterial pressure <60 mmHg or >110 mmHg, or as deemed appropriate by the treating team within the last 2 hours;
- heart rate <40 bpm or >140 bpm within the last 2 hours;
- persistent oxygen saturation (SpO_2 <88% or as determined by the treating team within the last 2 hours;
- receipt of neuromuscular blocker within the last 4 hours;
- severe agitation (Richmond Agitation and Sedation Scale >2 [or equivalent] [16]) within the last 2 hours;
- uncontrolled pain;
- change in goals to palliative care; and
- team perception that in-bed cycling or therapy was not appropriate for other new reasons (eg, acute peritonitis, new incision/wound, known/suspected rhabdomyolysis).

If the patient had no "temporary exemptions," we proceeded with offering the randomized intervention.

Each "planned intervention day" without a "temporary exemption" was considered an "eligible day." An eligible day where the patient did not receive the randomized intervention was classified as a "missed opportunity." Missed opportunities may have occurred due to the following:

- patient factors (eg, patient unavailable due to a test or declined intervention);
- therapist factors (eg, therapist unavailable due to vacation or illness); and
- equipment factors for patients in the cycling arm (eg, malfunction of the cycle ergometer).

We define percent adherence as the ratio of days on which patients received the randomized intervention or had a temporary exemption (numerator) to all planned intervention days, including days with the randomized intervention, temporary exemptions, and missed opportunities (denominator). Descriptive statistics on percent protocol fidelity will be reported for the cohort, broken down by randomization group.

Major Protocol Deviation

If a patient randomized to usual physiotherapy alone received cycling, this was considered a major protocol deviation.

Analysis Populations

Patient Inclusion and Outcome Analysis

We will include all eligible randomized patients (ie, excluding postrandomization exclusions representing noneligible patients) according to the treatment they were randomized to receive. Analyses of the primary outcome will be restricted to patients who survived to 3 days post-ICU discharge, as specified in our original protocol and sample size calculation [15]. Analyses of the PFIT-s at other time points (ICU awakening, ICU discharge, and hospital discharge) and all performance-based (strength and function) and patient-reported (eg, quality of life) outcomes will be restricted to patients who survived to the respective time point. We will include only patients discharged alive from the hospital in the analysis of hospital discharge location. The analyses of the duration of mechanical ventilation, ICU and hospital length of stay, and mortality will include all enrolled patients.

Analysis of the Primary Outcome

To determine if there is a difference in PFIT-s score at 3 days after ICU discharge between the cycling + usual physiotherapy and usual physiotherapy groups, we will conduct a linear regression analysis with randomization group (cycling + usual physiotherapy vs usual physiotherapy) as the independent variable [58]. We will adjust for age (≥65 years vs <65 years) and clinical site, as these were used as randomization stratification variables. We will report the results of the regression analysis as the mean difference in PFIT-s scores with corresponding 95% CIs and *P* values. Although the goal was to have all outcome assessors remain blinded to treatment allocation, this was not always feasible. To maximize the use of available data, we will include all PFIT-s measures at 3 days postrandomization, regardless of the blinding status of the outcome assessor, and will report the proportion of assessments conducted by blinded assessors.

To account for incomplete component data in the PFIT-s at 3 days post-ICU, we will concurrently consider data from the PFIT-s, 30-second Sit-to-Stand, and 2-minute Walk tests. We will evaluate all PFIT-s data components at 3 days post-ICU discharge. We will identify patients with any incomplete physical function data and review the scores for all 4 components of the PFIT-s (ie, shoulder flexion, knee extension, level of assistance required for sit-to-stand, and step cadence). In the PFIT-s, a score of "0" indicates a lack of physical ability to complete the measure. Therefore, if a patient attempts an item and is unsuccessful, the item receives a score of "0", which accurately reflects their performance (Tables 1). Further details are provided in Tables S2 and S3 in Multimedia Appendix 1. Table 2 describes the primary outcome analysis.

Subgroup Analyses

We will conduct 3 exploratory a priori subgroup analyses to investigate potential treatment effect modification for the primary outcome.

- age ≥65 years versus <65 years;
- baseline clinical frailty ≥5 versus <5; and
- male versus female.

In separate linear regression models for each of the 3 subgroup analyses, we will include randomized treatment allocation, the subgroup variable, and the interaction between the subgroup variable and randomized treatment allocation as independent variables. These analyses will be adjusted for age and center. We hypothesize that the treatment effect will be greater for older patients compared with younger patients [59], greater in patients with frailty compared with those without [59], and greater in males compared with females [60,61]. For statistical significance in the subgroup analyses, we will use an α of .10 for the

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interaction term. We will assess the credibility of any statistically significant subgroup effect using the method described by Schandelmaier et al [62]. These data will be reported in a forest plot.

Sensitivity Analyses

To assess the robustness of the findings, we will conduct 5 sensitivity analyses for the primary outcome. All sensitivity analyses will be adjusted for age and center, unless specified:

- To account for ICU mortality on the primary outcome, we will include all patients who died before 3 days post-ICU discharge, assigning a PFIT-s score of 0 for these patients.
- We will conduct a linear regression analysis that includes only PFIT-s assessments performed by assessors blinded to treatment allocation.
- We will analyze data from patients who adhered to the protocol on ≥80% of planned ICU days. Adherence is defined as either receiving the randomized intervention or having a temporary exemption.
- We will investigate the effect of missing data by conducting a complete case analysis, including only patients with a total PFIT-s score at 3 days post-ICU discharge.
- To determine if the cycling effect is influenced by the center, we will conduct an analysis adjusting for age only.

See Table 4 for further details.

Analyses of Secondary Outcomes

For each continuous secondary outcome, we will conduct a linear regression analysis [58]. We will conduct secondary outcome analyses adjusting for age (≥65 years versus <65 years) only. To avoid the risk of overfitting, we will not adjust for center when analyzing our secondary outcomes. We will report the results of the linear regressions as mean differences with corresponding 95% CIs. If needed to normalize the data, we will perform the linear regression on the log-transformed outcome [58]. If the data are still skewed, we will perform nonparametric analyses. As secondary analyses are underpowered and therefore hypothesis-generating, we will not present *P* values. In Multimedia Appendix 1, we describe the scoring algorithm to account for incomplete data in the 30-second Sit-to-Stand and 2-minute Walk tests based on a patient's observed function.

We will analyze time to ICU, hospital, and 90-day mortality using Cox proportional hazards regression analysis [63]. We will report hazard ratios and corresponding 95% CIs [63]. All other binary outcomes will be analyzed using logistic regression analysis, reporting odds ratios with corresponding 95% CIs [58]. We will check the assumptions of the different regression analyses by examining residuals and using other relevant methods. Table 5 describes secondary outcomes analyses.

Adverse Events

For the safety analysis, we will only include the days on which the patients received the randomized intervention (ie, days at risk of a safety event associated with rehabilitation activities). We will report the frequency and percentage of patients with severe and serious adverse events, by group. We will also report the frequency and percentage of randomized intervention days with severe and serious adverse events, by group.

Missing Data

We will use multiple imputations to account for missing data in performance-based and patient-reported outcomes [64-66]. In the Cox proportional hazards analyses for ICU and hospital mortality outcomes, we will censor patients with incomplete follow-up at the time of last contact.

Tables and Figures

We will summarize categorical data as counts and percentages. We will summarize continuous data as means, SDs, or median and IQR, if data are nonnormally distributed. For baseline variables, we will not conduct tests of statistical significance between randomized groups; rather, we will note the clinical importance of any imbalance between groups. We will report subgroup analyses in a forest plot.

Document History

Version 1.0 of the SAP was finalized on January 9, 2024. It was uploaded to clinicaltrials.gov on January 24, 2024.

Results

CYCLE was funded in 2017, and enrollment was completed in May 2023. Data analyses are complete, and the first results were submitted for publication in 2024.

Discussion

SAP-Specific Strengths and Limitations

The CYCLE RCT is the largest trial of in-bed cycling for critically ill, mechanically ventilated adults, to date. Strengths and limitations related to the design of the CYCLE RCT and the intervention of in-bed cycling have been discussed previously in the published protocol [15]. Briefly, we describe the strengths and limitations specific to this SAP.

A key strength of this SAP is the use of published guidelines to guide our reporting [14]. In addition, we selected outcome measures for the CYCLE RCT that have been validated in the ICU population and have strong psychometric properties. For our primary outcome, the PFIT-s, patients can complete parts of the outcome even if they are deconditioned (ie, cannot stand), limiting floor effects and maximizing the number of outcome assessments. We conducted a preplanned interim analysis once we reached half of our enrollment target, preventing the continuation of the trial with identified harm or benefit.

Our SAP also has important limitations. Given the number and types of outcome measures, we anticipate missing or incomplete data or both. Therefore, in this SAP we have specified the use of multiple imputations to account for these missing data. In addition, given the number of secondary outcomes, multiplicity is a concern. As a result, any significant findings from secondary outcomes will be exploratory rather than confirmatory.

This SAP complements the protocol paper [15] and was publicly available before data analysis (NCT03471247). We will adhere to it for all analyses, enhancing the rigor of our trial. The

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CYCLE RCT will add to the growing body of evidence evaluating the efficacy and safety of ICU-based rehabilitation interventions.

Acknowledgments

We are grateful to our study participants, research coordinators, research assistants, physiotherapists, and outcomes assessors who contributed to this study. We acknowledge the contributions of CYCLE Methods Center personnel to the coordination and conduct of this study, including Alexander Molloy, Geoff Strong, Abby Hurd, Ashley Sawyer, Marilyn Swinton, Jennifer Hoogenes, Lisa Buckingham, and Quazi Ibrahim.

Data Availability

The data sets generated during or analyzed during this study are not publicly available because we did not receive participant consent for open sharing. Data will be available from the corresponding author on reasonable request 1 year after publication of the main manuscript.

Funding and Registration

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Use of Generative Artificial Intelligence

Generative Artificial Intelligence was not used in this document.

Conflicts of Interest

Restorative Therapies (Baltimore, MD) provided 4 RT-300 supine cycle ergometers at Ottawa Civic Hospital, London Health Sciences (Victoria site), Duke University Medical Center, and the University of Maryland, Baltimore for this research. The funding sources and equipment manufacturer had no role in the design of this randomized trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Multimedia Appendix 1
Summary assessments and scoring algorithm.
[PDF File (Adobe PDF File), 103 KB - resprot_v13i1e54451_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[DOCX File , 26 KB - resprot_v13i1e54451_app2.docx]

Multimedia Appendix 3
Peer Review Report - Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 945 KB - resprot_v13i1e54451_app3.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CYCLE: Critical Care Cycling to Improve Lower Extremity Strength
ICU: intensive care unit
MRC: Medical Research Council
PFIT-s: Physical Function Intensive Care Unit Test-scored
RCT: randomized controlled trial
SAP: statistical analysis plan
SDM: substitute decision maker
SpO2: oxygen saturation

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Protocol

Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis: Protocol for a Phase 1 Clinical Trial to Determine Safety and Identify Side Effects

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Abstract

Background: Chronic abdominal pain is the hallmark symptom of chronic pancreatitis (CP), with 50% to 80% of patients seeking medical attention for pain control. Although several management options are available, outcomes are often disappointing, and opioids remain a mainstay of therapy. Opioid-induced hyperalgesia is a phenomenon resulting in dose escalation, which may occur partly because of the effects of opioids on voltage-gated sodium channels associated with pain. Preclinical observations demonstrate that the combination of an opioid and the antiseizure drug lacosamide diminishes opioid-induced hyperalgesia and improves pain control.

Objective: In this phase 1 trial, we aim to determine the safety, tolerability, and dose-limiting toxicity of adding lacosamide to opioids for the treatment of painful CP and assess the feasibility of performance of a pilot study of adding lacosamide to opioid therapy in patients with CP. As an exploratory aim, we will assess the efficacy of adding lacosamide to opioid therapy in patients with painful CP.

Methods: Using the Bayesian optimal interval design, we will conduct a dose-escalation trial of adding lacosamide to opioid therapy in patients with painful CP enrolled in cohorts of size 3. The initial dose will be 50 mg taken orally twice a day, followed by incremental increases to a maximum dose of 400 mg/day, with lacosamide administered for 7 days at each dose level. Adverse events will be documented according to Common Terminology Criteria for Adverse Events (version 5.0).

Results: As of December 2023, we have currently enrolled 6 participants. The minimum number of participants to be enrolled is 12 with a maximum of 24. We expect to publish the results by March 2025.

Conclusions: This trial will test the feasibility of the study design and provide reassurance regarding the tolerability and safety of opioids in treating painful CP. It is anticipated that lacosamide will prove to be safe and well tolerated, supporting a subsequent phase 2 trial assessing the efficacy of lacosamide+opioid therapy in patients with painful CP, and that lacosamide combined with opiates will lower the opioid dose necessary for pain relief and improve the safety profile of opioid use in treating painful CP.

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International Registered Report Identifier (IRRID): PRR1-10.2196/50513

(JMIR Res Protoc 2024;13:e50513) doi:10.2196/50513

KEYWORDS

abdominal pain; opioid-induced hyperalgesia; pain; abdomen; protocol; toxicity; toxic; lacosamide; pancreas; pancreatitis; opioid

Introduction

Background

Chronic pancreatitis (CP) is a syndrome characterized by inflammation and progressive architectural destruction of the pancreas. This may result in pancreatic fibrosis with concomitant loss of exocrine and endocrine function, regardless of etiology. The most common symptom of CP is debilitating abdominal pain, which may be constant or flare intermittently. The health care and socioeconomic consequences of CP may be substantial. Notably, painful disease exacerbations often prompt medical evaluation. Patients with constant pain often require daily analgesics for pain relief; further, they may experience disability, subsequent loss of productivity, and frequent need for hospitalization [1].

The treatment of abdominal pain is idiosyncratic and typically based on the skill set of the provider or the resources available at an individual institution. The management of pain in patients with CP has traditionally been based on the assumption that all symptoms have a structural basis. However, in a recent review, it was noted that central sensitization and psychological and social factors are now recognized to potentially contribute to chronic pain, supporting the expansion of therapeutic approaches to include nonstructural behavioral interventions [2]. Although the authors recommended avoidance of chronic opioid use in this patient population, opioids remain a mainstay of therapy at many centers in the United States. However, opioid use may present serious risks, including overdose and opioid use disorder. From 1999 to 2014, >165,000 people died of overdose related to opioid pain medication in the United States [3]. In addition, opioid monotherapy is often insufficient for the management of chronic pain of any etiology. Notably, the single-agent maximum-tolerated dose (MTD) of these drugs may reduce pain by only 25% to 40%, owing to incomplete efficacy, dose-limiting adverse effects, or both. The side effects of opioids, including marked detrimental effects on respiratory, gastrointestinal, and cardiovascular functions, may limit the use of opioid analgesia. In 2016, the Centers for Disease Control and Prevention published a guideline for prescribing opioids for chronic pain, noting that nonpharmacological and nonopioid pharmacological therapies are preferred for chronic pain [4]. If opioids are used, they should be combined with nonpharmacological therapy and nonopioid pharmacological therapy, if possible. Therefore, to minimize side effects, clinicians should prescribe the lowest effective opioid dose. Successful development of an opioid-minimizing strategy would provide clinicians with a new tool to lower the prescribed opioid doses. Studies addressing the efficacy of alternative methods for pain management are necessary. We propose an innovative study and intervention that focuses on the safety and tolerability of a novel combination of narcotic and nonnarcotic approach to pain experienced by patients with CP.

Adjuvant drugs, including antidepressants and anticonvulsants, are often used in combination with opiates for the treatment of pain with modest outcomes. One rather pronounced adverse off-target effect of opioids is an increasing sensitivity to noxious stimuli, even evolving a painful response to previously nonnoxious stimuli (allodynia). This condition is clinically known as opioid-induced hyperalgesia (OIH) [5,6]. The underlying pathophysiology of OIH is complex and may be mediated by central [7-9] or peripheral [10] pathways. An intervention targeted against 1 or more of these mechanisms may potentially limit OIH and lead to improved pain control in patients requiring opioids. On the basis of preclinical published data [11], preliminary studies presented subsequently, and clinical observations [12], we hypothesize that therapeutic targeting of the sodium channel NaV1.7 will improve opioid efficacy for controlling pain in patients with CP. Voltage-gated sodium channels (NaVs) play a key role in the initiation and propagation of action potentials in electrically excitable nociceptive neurons. Specific NaVs in these neurons can be activated by nonclassical opioid receptors [11,13]. This activation and augmentation of NaV-dependent pain sensing appears to counter a few classical opioid effects [14-16]. Therefore, neuronal activation of NaV1.7 could be one of the mechanisms that limit opioid effectiveness [11,13,15,16]. The activation of these channels can be blocked with an existing class of Food and Drug Administration (FDA)–approved antiepileptic seizure drugs that modulate NaVs [11,17-20]. The recent identification of neurobiological mechanisms associated with NaV1.7 and opioid efficacy provide the innovative rationale for this combinatorial opioid adjuvant therapy. The basic drug mechanism is that nonclassical opioid receptors function to increase the NaV1.7 current in nociceptive sensory neurons, leading to drug-induced pain, or OIH. The combination of an opioid and specific antiseizure drugs such as carbamazepine, oxcarbazepine, or lacosamide effectively diminishes the opioid-induced NaV1.7 current [11,13,15]. These preclinical observations in several neuropathic pain-induced injury models lay the foundation for changing the management of chronic pain from empirical symptom control to personalized targeting of specific mechanisms responsible for pain.

Lacosamide is a first-in-class FDA-approved modified amino acid antiepileptic drug that targets NaV1.7. It was approved by the FDA after phase 3 trials as adjunctive and monotherapy in adults with refractory partial epileptic seizures [21]. The mechanism of action of lacosamide is thought to be that it enhances the slow inactivation of NaV1.7 without affecting its fast inactivation [17-20]. Lower concentrations of this drug may also bind to fast-inactivated states in a manner similar to other

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antiseizure agents but with slower kinetics of binding and unbinding [20]. Therefore, this means that lacosamide only affects neurons that are depolarized or active for long periods, which is typical of neurons not only at the focus of epilepsy but also central to active pain states. We chose lacosamide as our study drug over other sodium channel inhibitors because it has a favorable side effect profile. Carbamazepine use as an adjunct to opioids is limited by its adverse effects; therefore, the reduced side effect profile of lacosamide may make it a better choice for chronic pain management [22]. In addition, carbamazepine is a well-known inducer of hepatic drug metabolism and therefore may result in a variety of drug interactions that might compromise the efficacy and safety of ongoing therapies. Lacosamide, on the other hand, has minimal interaction with hepatic cytochrome P450 drug-metabolizing enzymes [23]. Lacosamide is a *CYP2C19 substrate* [24]. The drug has a negligible first-pass effect, with a bioavailability of approximately 100%. The maximum lacosamide plasma concentrations occur approximately 1 to 4 hours after oral administration, and the pharmacokinetics of lacosamide are dose proportional. Food intake does not affect its absorption. Notably, *CYP2D6* is responsible for the metabolism of most of the commonly prescribed opiate medications, including codeine, tramadol, hydrocodone, and oxycodone [25]. Furthermore, the *CYP3A4* system regulates the excretion of fentanyl, methadone, and buprenorphine. However, patients receiving methadone will be excluded from participation in Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis (STTEPP), as this is a μ-opioid agonist and acts as an antagonist of the N-methyl-D-aspartate (NMDA) receptor [26].

Several studies have evaluated lacosamide as a monotherapy for clinical pain conditions such as fibromyalgia and painful diabetic peripheral neuropathy. Although all studies claimed that lacosamide reduced neuropathic pain and was well tolerated, the outcomes were generally inconclusive and provided only marginal benefits [27-31]. Notably, however, all these studies excluded patients who required opioids for pain control. One clinical case report suggested that chemotherapy-induced painful peripheral neuropathy uncontrolled by opioids alone is accompanied by a dramatic reduction in pain when lacosamide was added to opioid therapy [12]. This provides clinical evidence supporting our rationale for the use of lacosamide in combination with opioids to treat neuron-based symptoms. Therefore, we propose to evaluate lacosamide in conjunction with opioids, which is where evidence consistently shows a benefit. Evidence regarding the effect of lacosamide on NMDA receptor has been shown by its ability to prevent seizures and death in NMDA-induced convulsion test paradigms in mice [32].

Objectives

In this protocol, we will evaluate the safety, tolerability, and dose-limiting toxicity (DLT) of the combination of lacosamide and opioid therapy in patients with CP, as well as the feasibility of the performance of this phase 1 pilot study. The MTD will be determined. Lacosamide, an anticonvulsant that is safe and well tolerated in patients with epileptic seizures, may potentially lower the opioid dose necessary for adequate pain relief in patients with CP. The positive outcomes of this pilot study will then support proceeding with a phase 2 efficacy trial assessing the ability of opioid adjuvants to alleviate abdominal pain in this difficult patient population. In addition, we believe that this combination therapy will serve to significantly enhance the safety profile of opioid use in these patients.

Methods

Study Organization

The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) has been tasked by the National Institutes of Health (NIH) with the comprehensive clinical, epidemiological, and biological characterization of patients with CP to develop treatments and gain insight into the pathophysiology of CP and its sequelae, including chronic pain, pancreatic exocrine and endocrine insufficiency, and diabetes pancreatic cancer association [33]. All participating clinical centers in the STTEPP trial are CPDPC members and are contributing to a longitudinal cohort study called *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) [34], the first prospective cohort study of pancreatitis in the United States. STTEPP was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; R01DK132709) in April 2022 as a multi-institutional prospective ancillary study within the CPDPC. MD Anderson Cancer Center, University of Texas, will serve as the data coordinating center for STTEPP, and the Institutional Review Board (IRB) at MD Anderson will serve as the single-center IRB for this study. The goal of this clinical research study is to determine whether adding the antiseizure medication lacosamide to opioid pain medications will help in managing chronic, ongoing abdominal pain symptoms caused by CP. The safety of this drug combination will also be studied. This is an investigational study.

Lacosamide

Lacosamide is a Schedule V controlled substance approved by the FDA for the management of seizure disorders. A controlled substance is a drug or other substance that is tightly controlled by the government, because it may be abused or cause addiction. All controlled substances in the United States are classified into 5 schedules. Schedule V drugs, including lacosamide, have the lowest potential for misuse and addiction compared with those in other schedules. Although it has been used off-label to treat pain resulting from nervous system damage, this medication is not FDA approved for the management of abdominal pain. Currently, it is being used to treat abdominal pain for research only. There may or may not be benefits for participants in this study. The participant will be closely followed by a study coordinator and site investigator during participation. Although the actual drug therapy will only last for 7 days, the participant may experience improved control of their abdominal pain symptoms during the study. Future patients may also benefit from what is learned in this study.

Ethical Considerations

This study protocol was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board (IRB

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ID 2021-1197). Informed consent was obtained from all participants or their legal guardians. All methods were performed in accordance with relevant guidelines and regulations.

Participation is completely voluntary. Before choosing to participate in this study, participants should discuss any concerns they may have with the study team, including side effects, potential expenses, and time commitment. The participant can read the full list of potential side effects in the *Possible Risks* section of the consent form.

The participant may choose not to take part in this study, and they do not have to participate. They may withdraw from the study at any time. The participant has the right to choose whether to participate in this research study. They may decide to stop participating in the study once they have started. Leaving the study early will not result in any loss of benefits that they already have. Instead of participating in this study, they may choose to continue with their current medications and plan of care.

Study Details

Who Is Eligible to Take Part in the Study?

Patients with ongoing chronic abdominal pain related to CP, even with opioid pain medication treatment, were asked to participate in the study.

How Many Participants Are Expected to Take Part in the Study?

Approximately 24 participants will participate in this multicenter study from approximately 5 institutions. Up to 10 participants will be enrolled at Indiana University.

How Long Will the Participation Be? How Long Will It Take to Complete the Study?

If the patient decides to take part in this study, they will complete a screening visit in person to determine if they qualify for enrollment. This visit will take approximately 30 to 60 minutes. After the screening visit, participation will involve an in-person visit that will last 60 minutes. The participant will be asked to take the study medication (provided at no cost) for the 7 days of participating in the study. The participant will also keep a medication diary to confirm when and how they take the study medications and their pain medications. The final study visit will be an in-person follow-up visit on day 8, lasting approximately 60 minutes. The study team will collect medical history and clinical information, draw blood samples, and ask the patient to complete the visit questionnaires as well as medication diaries of all pain medications they take, including the study medication. The research data will be maintained indefinitely.

What Will Be Done to the Patient If They Agree To Be a Research Subject?

If a patient wants to participate in the study, they will be asked to sign the consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization before starting any study procedures. If they agree to participate in the study, the study team will collect several items on the days of their study visits.

Screening Visit

The screening visit will be completed in person and is expected to last 30 to 60 minutes. The protocol for the screening visit has been described in Textbox 1.

Textbox 1. Protocol for screening visit.

- The participant will be asked about the medicines they have used or are now taking, including all prescriptions and nonprescription medications.
- They will also be asked to provide demographic information (eg, age and ethnicity).
- They will have blood (approximately 7 teaspoons) collected for routine safety tests. These blood tests are important to determine whether they are eligible to participate in the study and to monitor for possible side effects of the study drug. They should fast (ie, eat nothing and drink only water) for at least 8 hours before this blood investigation.
- If the patient can become pregnant, they will undergo a urine pregnancy test. To participate in this study, they must not be pregnant.
- The patient will have an electrocardiogram test performed to measure the electrical function of their heart.
- They will be asked to complete 4 questionnaires related to pain and how it affects their daily life.
- They will be given a medication diary to track the medications they take for pain.
- The study team will review their medical records to confirm eligibility to continue in the study.

Enrollment Visit

The enrollment visit will be completed in person on day 0 and is expected to last for 60 minutes. The protocol for enrollment visit day and the treatment days 1 to 7 is described in Textbox 2.

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Textbox 2. Protocol for enrollment visit and treatment days.

Enrollment visit day 0

- The patient will be asked if they have any health problems other than chronic pancreatitis and what medical or surgical procedures they have undergone in the past.
- They will be asked to complete 4 questionnaires related to their pain and how it affects their daily life.
- They will be asked about any health problems they may be experiencing.
- They will be asked what medications they are taking, including all prescription and nonprescription medications.
- Patients' vital signs (eg, heart rate, blood pressure, and temperature), height, and weight will be recorded.
- They will have a physical examination.
- If they can become pregnant, they will have a urine pregnancy test.
- Patients will be given a 7-day supply of the study drug and medication diaries to document all medications taken for pain.

Treatment days 1 to 7

- The lacosamide tablets can be stored at room temperature. Patients will take lacosamide by mouth, 2 times a day, approximately 12 hours apart. They will be asked to try and take the tablets at the same time on each of the 7 days of the study. The tablets may be consumed with or without food. Patients will be asked to swallow the tablets whole with a glass of water or any other liquid of their choice and not chew them.
- Patients will be asked to complete daily medication diaries for all medications taken for pain, including the study drug.

Follow-Up Visit

The first follow-up visit will be completed in person on day 8 and is expected to last for 60 minutes. Subsequently, a follow-up visit will be conducted via telephone on day 21. The protocol for these follow-up visits in described in Textbox 3.

Textbox 3. Protocol for follow-up visits.

Follow-up visit on day 8

- Patients will be asked to complete 4 questionnaires related to pain and how it affects their daily life.
- They will be asked about any health problems they may be experiencing.
- They will be asked what medications they have taken, including all prescriptions and nonprescription medications from the enrollment visit day 0.
- Their vital signs will be recorded.
- They will have a physical examination.
- Blood (approximately 7 teaspoons) will be collected for routine safety investigations. They will need to fast before the blood is collected.
- They will have an electrocardiogram test performed to measure the electrical function of their heart.
- They will return any leftover study drug doses to this visit, in the original bottles.

Follow-up on day 21: phone visit

- Patients will be asked about any health problems they may be experiencing.
- They will be asked what medications they have taken, including all prescriptions and nonprescription medications, from the follow-up visit on day 8.

Risks Associated With the Study

Risks of Receiving the Study Drug

There are risks to participating in any research study. One risk is that the study drug does not relieve the abdominal pain. There is a risk of side effects or feeling bad during this study. Side effects vary from person to person. Everyone participating in this study will be carefully monitored for side effects. It is important that the patients tell the study physician about any side effects that they have during this study, even if they do not think it is related to the study drug. The side effects may range from mild to severe. Study physicians and the company that makes the study drug cannot know all the side effects that may occur, and there may be unknown side effects.

Lacosamide Side Effects

Lacosamide intake can result in common, occasional, or rare but serious side effects.

- *Common* side effects (occurring in >20% of the patients):
  - Dizziness

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- *Occasional* side effects (occurring in 3%-20% of the patients):
  - Headache, fatigue, sleepiness, skin wound, nausea, vomiting, diarrhea, bruising, tremors, loss of coordination, difficulty in walking, double vision, blurry vision, eye twitching, and injection site pain

- *Rare but serious* side effects (occurring in fewer than 3% of patients):
  - Irregular or slow heartbeat, fainting, fever, difficulty in forming words or speaking, abnormal brain function (eg, affecting balance and coordination), mental status change (eg, memory loss and impaired thinking), suicidal thoughts or behavior, hallucinations (ie, seeing or hearing things that are absent), liver damage because inflammation, abnormal sensation (eg, pins and needles), walking or balance problems (eg, possible falling), and life-threatening allergic reactions (eg, difficulty breathing, low blood pressure, and organ failure)

- Lacosamide may rarely cause low blood cell counts (red or white blood cells).
  - A low red blood cell count (anemia) may cause difficulty in breathing or fatigue. The patient may require a blood transfusion.
  - A low white blood cell count increases the risk of infection (eg, pneumonia or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty in breathing.

In other studies of lacosamide, stopping the drug suddenly did not lead to unpleasant physical symptoms. As a Schedule V controlled substance, lacosamide has a very low potential for abuse. No restrictions on activities need to be followed when taking this drug. However, should the patient have a side effect or feel bad during this study, they should call the study physician. The study physician's telephone number is on the front page of the consent form. They should also call the physician if they have a side effect that makes them visit the hospital during the study.

Other Risks

Collecting blood for investigations may cause pain, bleeding, and bruising. The patient may faint and develop an infection with redness and irritation of the vein at the site of blood collection. Frequent blood collection may cause anemia (low red blood cell count), which may necessitate blood transfusions. Undergoing an electrocardiogram (EKG) may cause discomfort while lying on the examination table, and the tape on the EKG pads may cause skin irritation.

The questionnaires may contain questions that are sensitive in nature. They may refuse to answer any question that may make them feel uncomfortable. If the patient has concerns about completing the questionnaire, they are encouraged to contact their physician or the study chair.

The arm cuff used in measuring blood pressure may feel tight or slightly uncomfortable for a short time, and during the measurement, their hand or arm may experience numbness.

Certificate of Confidentiality

This study is covered by a Certificate of Confidentiality (CoC) from the NIH. With this CoC, the researchers may not disclose or use information that may identify the patient in any federal, state, or local civil; criminal; administrative; legislative; or other action, suit, or proceeding or be used as evidence, for example, if there is a court subpoena, unless the patient has consented for this use. Information protected by this CoC cannot be disclosed to anyone else who is not connected with the research, except if there is a federal, state, or local law that requires disclosure (eg, reporting child abuse or communicable diseases but not for federal, state, or local civil; criminal; administrative; legislative; or other proceedings).

The CoC cannot be used to refuse a request for information, for auditing or program evaluation purposes, from personnel of the United States federal or state government agencies sponsoring the project. A CoC does not prevent the patient from voluntarily releasing information about themselves or their involvement in this research. If the patient wants their research information to be released to an insurer, medical care provider, or any other person not connected to the research, they must provide consent to allow the researchers to release it. The CoC will not be used to prevent disclosure for any purpose you have consented.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so the patient should not become pregnant, breastfeed a baby, or father a child while in this study. They must use birth control during the study if they are sexually active.

- Male patients should tell the physician right away if their partner becomes pregnant or suspects pregnancy.
- If female patients are pregnant, they will not be enrolled in this study. If they become pregnant or suspect pregnancy, they must tell their physician immediately. Pregnancy will result in exclusion from this study.

Risk of Possible Loss of Confidentiality

Every effort will be made to keep patients' personal information confidential; however, we cannot guarantee absolute confidentiality. No information that could identify the patient will be shared in the publication of this study. Patients' personal information may be shared outside the research study if required by law and with individuals or organizations that oversee the conduct of research studies, and these individuals or organizations may not be held to the same legal privacy standards as physicians and hospitals.

There are some types of sharing the CoC does not apply to. The CoC does not stop reporting required by federal, state, or local laws, such as reporting of child or elder abuse, some communicable diseases, and threats to harm oneself or others. The CoC does not stop a government agency who is funding research from checking records or evaluating programs. The CoC also does not prevent their information from being used

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for other research when allowed by federal regulations. The CoC also does not stop sharing of information required by the FDA.

Researchers may release information about the patient when they say that it is okay. For example, the patient may still give them permission to release information to insurers, medical providers, or others not connected to the research.

Costs and Compensation

Will Participants or Their Insurers Be Billed for Any Costs of the Study? If so, Which and What Happens if Insurance Does Not Cover the Costs?

The study will pay for the study drug, blood collection, ECGs, physical examinations, and data collection associated with the research study and for the investigations that are performed for research purposes only.

What Happens if the Patient is Hurt or Became Sick as a Result of the Study?

The researchers have taken steps to minimize the known or expected risks. However, they may still experience problems or side effects, even when the researchers are cautious to avoid them. If the patient believes that they have been harmed, they should notify the researchers listed in Section 6 of the consent form. The team at Indiana University Hospital will provide first aid or emergency care. The cost of this first aid or emergency care may be billed to the patient's insurance company. Additional medical care will be provided if the injury is determined to be caused by the research. If they sign the form, they do not give up their right to seek additional compensation if they are harmed because of being in this study.

Of note, it is important that the patients tell the researchers about any injuries, side effects, or other problems that they experience during this study. They may also need to tell their regular physicians. Furthermore, it is the patient's responsibility to determine the extent of their health care coverage. There are no other monetary compensation programs in place for such injuries. They will not be reimbursed for expenses or compensated financially by MD Anderson or the NIH and NIDDK for this injury. They may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries.

Are Patients Paid or Given Anything for Being in the Study?

The patient will be paid US $50 at the completion of enrollment visit day 0 and US $100 at the completion of follow-up visit day 8; both payments will be in the form of gift cards.

Patient Eligibility

Relevant to STTEPP, PROCEED study participants are divided into subcohorts to distinguish the natural history of different disease presentations at the time of admission into the cohort [34]. In STTEPP, we will leverage the resources of the CPDPC by approaching participants already enrolled in PROCEED. This approach will facilitate timely accrual, as these participants have demonstrated an interest in research and willingness to participate in CPDPC studies. Although all participants must meet the criteria for diagnosis of suspected or definite CP as per PROCEED definitions [34], study enrollment will not be limited to participants participating in PROCEED. The STTEPP inclusion and exclusion criteria are listed in Textboxes 4 and 5, respectively.

Textbox 4. Inclusion criteria.

1. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization for release of personal health information
2. Age ≥18 years at the time of informed consent
3. Suspected (YELLOW 2 or 3) or definite (RED) diagnosis of chronic pancreatitis, as per the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer's *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) study definition with ongoing symptoms of abdominal pain
4. Patients must be maintained on an opioid (except methadone or suboxone) for 4 weeks before enrollment for the treatment of abdominal pain related to pancreatitis, with a daily morphine equivalent dose of 20 mg to 120 mg.
5. Ongoing symptoms of abdominal pain even with opioid use (Visual Analog Score and Brief Pain Inventory average score ≥4, at enrollment)
6. Eastern Cooperative Oncology Group performance status of 0 to 2 (Oken et al [35])
7. Ability to swallow and tolerate oral tablets
8. Females of childbearing potential must have a negative pregnancy test
9. The following laboratory parameters must be met: white blood cell count ≥3.0 K/mm^3, absolute neutrophil count ≥1.5 K/mm^3, hemoglobin ≥9 g/100 ml, platelets ≥75 K/mm^3, creatinine ≤1.5 mg/100 mL, bilirubin ≤1.5 x upper limit of normal (ULN), aspartate transaminase ≤3 ULN, alanine transaminase ≤3 ULN; normal PR interval on baseline 12-lead electrocardiogram.

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Textbox 5. Exclusion criteria.

1. Participants with indeterminate chronic pancreatitis (YELLOW 1) as per *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) criteria
2. Treatment with any investigational agent within 30 days before registration or concurrent participation in a clinical trial which involves another investigational agent
3. Rapidly escalating pain that requires parenteral (eg, intravenous or intramuscular) opioid therapy within 30 days of enrollment
4. Known hypersensitivity or allergic reaction to lacosamide, carbamazepine, or oxcarbazepine
5. Pregnant or breastfeeding
6. Diagnosis of epilepsy or a patient who is currently taking antiepileptic drugs
7. Abdominal surgery or pain intervention (eg, endoscopic retrograde cholangiopancreatography with sphincterotomy or stent or stone removal and celiac plexus block) within 90 days of enrollment.
8. Hospitalization for pancreatitis exacerbation or pain management within 90 days of enrollment
9. Patient who currently takes Suboxone or methadone.
10. Other factors which might explain the patient's ongoing symptoms, at the discretion of the enrolling physician.
11. History of autoimmune or traumatic pancreatitis or sentinel attack of acute necrotizing pancreatitis which results in suspected disconnected duct syndrome.
12. Primary pancreatic tumors, pancreatic ductal adenocarcinoma, suspected cystic neoplasm (>1 cm in size or main duct involvement), neuroendocrine tumors, and other uncommon tumors
13. Pancreatic metastasis from other malignancies
14. History of solid organ transplant and HIV or AIDS
15. Known isolated pancreatic exocrine insufficiency (eg, without any eligible inclusion criteria)
16. No medical or psychiatric illnesses or ongoing substance abuse that, in the investigator's opinion, would compromise participant's ability to tolerate study interventions or participate in follow-up.

Objectives and End Point

Our primary objectives are to (1) evaluate the safety, tolerability, and DLT of lacosamide in combination with opioids in patients with CP and (2) assess the feasibility of the performance of a pilot study of adding lacosamide to opioid therapy in patients with CP. As a secondary, exploratory objective, we will assess the efficacy of adding lacosamide to opioid therapy for the treatment of abdominal pain because of CP. The safety end point includes toxicity and DLT of the combination of lacosamide and opioids, defined as grade 3 or 4 toxicities, according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Tolerability will be assessed by compliance with the intervention. The participants will be evaluated for completing the 7-day trial. The percentage of participants taking 100%, 75%, 50%, and <50% of the study tablets will be recorded. The feasibility end point will include the recruitment rate (ie, the proportion of eligible patients who agree to participate) and the dropout rate, including a qualitative assessment of barriers to retention. The efficacy end point will be assessed using the Visual Analog Score; Brief Pain Inventory, short form, average score; and the Comprehensive Pain Assessment Tool, short form [36] total score. A 50% decrease in pain scores from baseline at study completion will be deemed clinically meaningful. In addition, opioid use will be evaluated, with a decrease of 25% in pain scores from baseline at study completion, identified as clinically significant.

Investigational Plan, Intervention, and Treatment Regimen

We will conduct a dose-escalation trial of lacosamide added to opioid therapy in patients with chronic abdominal pain owing to CP. Participants who meet all the inclusion criteria and none of the exclusion criteria will be included in this dose-finding study. We will use the Bayesian optimal interval (BOIN) [37,38] design to determine the MTD. The BOIN design received a fit-for-purpose designation from the FDA as a drug development tool [39]. The BOIN design is implemented in a simple manner similar to the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics compared to those with more complex model-based designs, such as the continual reassessment method [40]. The target DLT rate for MTD is 0.3, and the maximum sample size is 24. We will enroll and treat patients in cohorts of size 3. The initial dose will be 50 mg taken orally twice a day (100 mg/day), followed by an incremental increase of 100 mg/day in 2 divided doses. The maximum daily dose of lacosamide will be 400 mg/day. The duration of lacosamide administration will be 7 days at each dose level. This target DLT rate and dose-escalation schedule were chosen based on previous trials that had suggested the efficacy and tolerability of comparable doses of lacosamide when used to treat partial seizures and painful diabetic neuropathy. Follow-up laboratory parameters (as obtained at study entry) will be obtained on day 8 (with a 3-day window) after therapy is completed. The trial design is illustrated in Figure 1 and is described as follows:

1. Patients in the first cohort are treated at dose level 1.

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2. To assign a dose to the next cohort of patients, dose escalation or de-escalation will be performed according to the rules displayed in Table 1.
3. Repeat step 2 until the maximum sample size of 24 is reached or stop the trial if the number of patients treated at the current dose reaches 15.

In the BOIN design, the number of DLT is the number of patients with at least 1 DLT. When none of the actions (ie, escalation, de-escalation, or elimination) is triggered, the current dose remains unchanged for the next cohort of patients. "N/A" means that a dose cannot be eliminated before treating 3 evaluable patients. After the trial is completed, we will select the MTD based on isotonic regression [38]. This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program [41]. Notably, each cohort of 3 patients will consist of 3 new patients. Therefore, dose escalation or de-escalation is interpatient (or, more precisely, intercohort), not intrapatient in nature.

Considering the low disease prevalence of CP, including referral bias at academic centers, we chose to avoid the use of eligibility criteria that would narrow the potential recruitment pool. In this phase 1 trial, in which safety, tolerability, and feasibility are the primary outcomes of interest, we propose including all patients with suspected or definitive CP if the above inclusion and exclusion criteria are met. Similarly, although there may be potential variability in patients because of the etiology, duration of CP, or other features of the disease, it is impractical to impose more stringent eligibility criteria during this early phase of the investigation. Doing so would substantially deplete the recruitment pool for this orphan disease and would not be feasible or scientifically justified.

Figure 1. Bayesian optimal interval (BOIN) schema. The BOIN schema is a model-assisted dose-finding design that can be used to determine the maximum-tolerated dose (MTD) of a study drug based on safety or the optimal biological dose (OBD) based on safety and efficacy. DLT: dose-limiting toxicity.

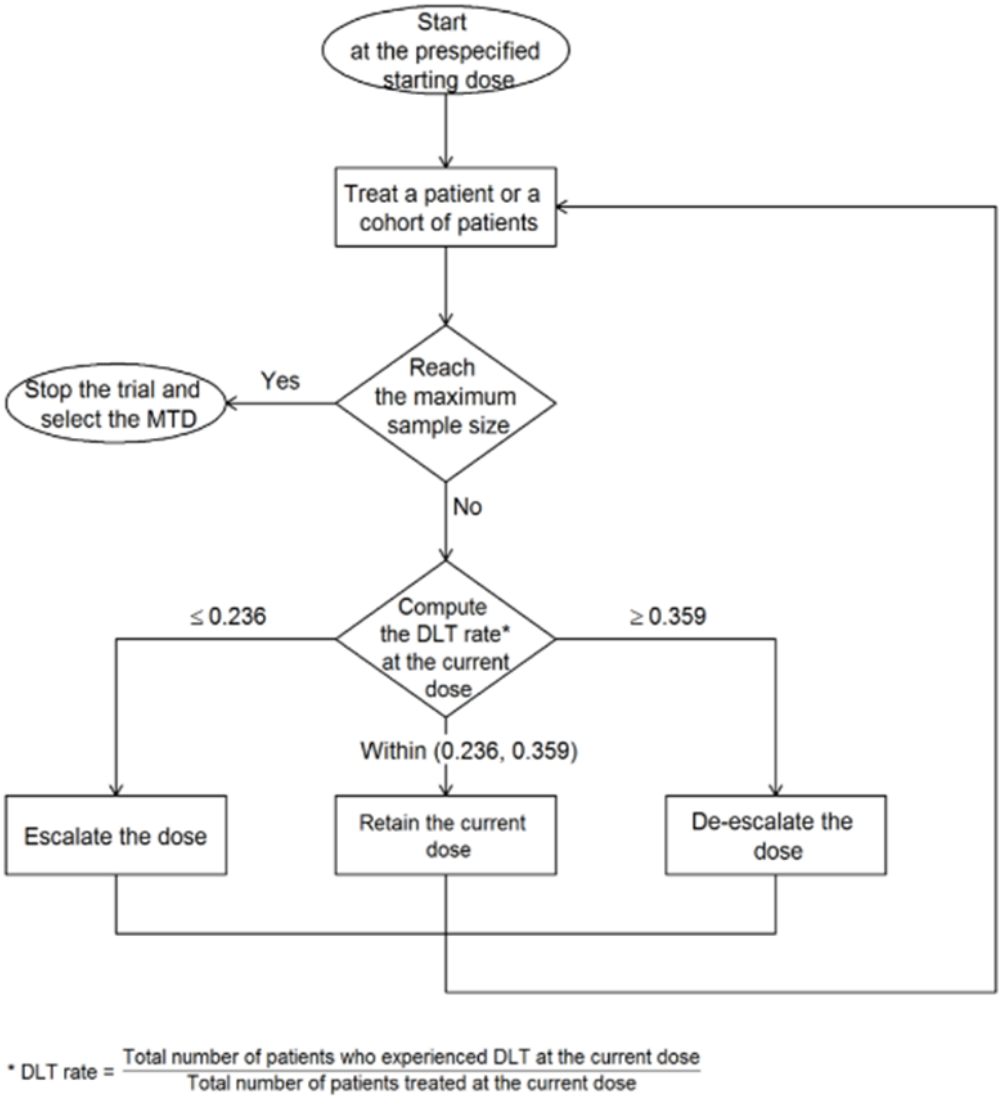

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Table 1. Dose-escalation or de-escalation rule for the Bayesian optimal interval design.

Actions	The number of patients treated at the current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if the number of DLT[a] is ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3
De-escalate if the number of DLT is ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if the number of DLT is ≥	N/A[b]	N/A	3	3	4	4	5	5	5	6	6	7	7	8	8

[a]DLT: dose-limiting toxicity.

[b]N/A: not applicable.

Drug Dispensing and Compliance

In this phase 1 trial, all enrolled participants will receive the active drug lacosamide. There is no placebo group, and there is no blinding to the treatment or dose received. Following the initial drug purchase, the investigational drug service at each participating institution will purchase additional disbursements on an as-needed basis, depending on patient recruitment. Participants will be provided with drug diaries, which will be reviewed for compliance at the end of the study at the final in-person visit. Patients who miss a dose (defined as beyond 2 hours of the patient's typical drug administration time) will not be instructed to take it later on the same day. Patients will be informed not to take missed doses on the subsequent day (ie, the patient should not take more than the prescribed daily dose).

Study Visits

A screening visit for eligibility in person or via telephone will occur at 7 to 30 days prior to enrollment. There will be 2 in-person study visits. During study visit 1 on day 0, baseline study assessments and questionnaires will be completed in person. Drug treatment days will then occur from days 1 to 7. During study visit 2 on day 8 (with a 3-day window), following completion of the 7-day drug treatment period, participants will have a face-to-face clinic visit, where similar assessments and questionnaires will be completed, as per the study calendar (Table 2). Participants will return all unused drugs during this visit for disposal and to monitor compliance.

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Table 2. Study calendar.

	Screening visit, from 7 to 30 days	Enrollment visit, day 0	Treatment days 1-7	Follow-up visit, day 8 (+3-day window)
Required assessments				
Informed consent	✓			
Medical history[a]		✓		
Height and weight		✓		
Physical examination		✓		✓
Vital signs		✓		✓
ECOG[b] performance status	✓	✓		✓
EKG[c]	✓			✓
Blood chemistries[d]	✓			✓
Hemoglobin, absolute neutrophil count, and platelets	✓			✓
Urine pregnancy	✓	✓		
Medication assessment[e]	✓	✓		✓
Adverse event assessment		✓		✓
Questionnaires				
Physician questionnaire		✓		
Study coordinator questionnaire		✓		✓
Patient questionnaire (VAS[f], BPI[g], PROMIS[h], and COMPAT[i])	✓	✓		✓
Medication diary	✓	✓		✓

[a]Medical history and establishment of suspected or definite chronic pancreatitis diagnosis may occur at any time before trial entry.

[b]ECOG: Eastern Cooperative Oncology Group.

[c]EKG: electrocardiogram.

[d]Will include at a minimum: electrolytes, glucose, blood urea nitrogen, creatinine and creatinine clearance, calcium, and hepatic function panel.

[e]Will include detailed use of rescue pain medications and opioids use.

[f]VAS: Visual Analog Score.

[g]BPI: Brief Pain Inventory.

[h]PROMIS: Patient-Reported Outcomes Measurement Information System.

[i]COMPAT: Comprehensive Pain Assessment Tool for Chronic Pancreatitis.

Study Measurements

A site gastroenterologist will review the complete medical history, including medications (particularly opioid use), Eastern Cooperative Oncology Group performance status, physical examination (including vital signs, height, and weight), EKG, and laboratory test results. A site research nurse will collect up to 35 mL of fasting blood using standard protocols. Given the safety or risk protocol of lacosamide and to satisfy inclusion and exclusion criteria, the blood specimens are considered routine safety laboratories and will include electrolytes, glucose, blood urea nitrogen, creatinine, creatinine clearance, calcium, and a hepatic function panel.

The patient, nurse coordinator, and physician case report forms (CRFs) will be completed before study entry. This will be based on a similar CRF currently used in PROCEED. Completion of these forms before enrollment will allow confirmation that the patient is eligible for the study. We will obtain approval from the single-center IRB to share data between protocols with the patients' consent. An additional CRF will be completed by the nurse coordinator in collaboration with the site-specific principal investigator at the follow-up study visit, documenting all side effects noted during the drug treatment phase according to Common Terminology Criteria for Adverse Events (version 5.0).

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Safety or Risk Issues

Lacosamide is a Schedule V medication available in tablet, oral solution, and injectable forms. In this study, only the tablet form will be used, and this is available in 50 mg, 100 mg, 150 mg, and 200 mg dosages. For simplicity in drug ordering and distribution, only 50 mg tablets will be used. Lacosamide is FDA approved as monotherapy or adjunctive therapy for partial-onset seizures, with a maximal recommended oral total daily dose of 400 mg, administered in 2 divided doses.

Summary of Known Potential Risks With Study Medication

Side Effects

A complete list of reported side effects from lacosamide trials and postmarketing experience can be found in the medication insert and Amneal Pharmaceuticals website [42]. The common side effects of lacosamide at doses in the range of 200 mg to 400 mg include dizziness (25%), ataxia (6%), fatigue, nausea, diplopia, headache, or tremor (12%-17%). Severe side effects such as cardiac rhythm or conduction abnormalities (first-degree arteriovenous block and atrial fibrillation or flutter, 0.5%) and suicidal ideation or behavior (0.2%) are rare. Case reports have been published regarding episodes of syncope and hypersensitivity reactions.

Prior and Concomitant Medications or Procedures

Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken before and during the trial and any dose or dose regimen changes that occur during the trial will be recorded in the source documents and case report form. Owing to the potential drug-to-drug interaction with other CYP3A4 or CYP2C9 inhibitors that may interfere with lacosamide levels, patients taking medications that may interfere with lacosamide metabolism will be monitored carefully. Furthermore, patients taking medications that affect cardiac conduction (eg, sodium channel blockers, β-blockers, and calcium channel blockers), including those that prolong the PR interval, will be carefully observed. We will obtain an EKG before beginning drug therapy and at the end of treatment**.**

The study principal investigators serve as the medical monitors for this trial, overseeing all aspects of the trial, including management of source documentation, adverse event collection, adverse events and protocol deviation reporting, interaction with the Data and Safety Monitoring Board (DSMB), and the creation of corrective and preventive action plans, when necessary. The DSMB will meet to review the study conduct and data relating to safety and efficacy to ensure the continued scientific validity and merit of the study. Following recruitment of the first study participant, summaries will be submitted monthly and reviewed quarterly by the DSMB and will follow the established CPDPC protocols.

Statistical Plan and Analysis

A sample size of 24 was determined and calibrated based on the simulation such that the phase 1 trial has reasonable accuracy (>60% probability) to correctly identify the MTD across a set of practically plausible scenarios. We will use descriptive statistics to summarize the demographic and clinical characteristics of the patients. Safety data will be tabulated by the grade and type of toxicity using descriptive statistics, including mean, SD, and 95% CI. The reduction in pain scores will be summarized by the dose using the mean and 95% CI. As an exploratory analysis, *t* test (2-sided) or Wilcoxon rank-sum test will be used to compare the reduction in pain scores between the doses. The recruitment and dropout rates will be calculated for all patients and by dose and used to determine the feasibility of the treatment. Although the data generated will not have a comparator group (ie, no placebo), these will be helpful in understanding the variability of responses in patients with suspected or definite CP, which in turn will be useful for sample size calculation for a follow-up trial.

Results

As of December 2023, we have currently enrolled 6 participants. The minimum number of participants to be enrolled is 12 with a maximum of 24. We expect to publish the results by March 2025.

Discussion

The management of abdominal pain in patients with CP remains a significant challenge, and innovative approaches to pain management are urgently needed. By potentially limiting OIH, lacosamide may improve pain control in patients requiring opioids. There are no data evaluating the use of lacosamide in patients with CP; this was the impetus of the STTEPP trial. Achieving recruitment goals is a priority. We acknowledge that patients may be unwilling to participate in a dose-finding trial with a low likelihood of long-term therapeutic benefit. Those patients who do note a benefit, however, may choose to be considered for our planned phase 2 trial. The 5 participating centers include experienced researchers, who have led clinical trials in this challenging patient population. In addition, all are members of the CPDPC and participate in PROCEED [38]. This brings substantial synergy to this study because the infrastructure for recruitment and follow-up of study participants is already in place at these institutions. We do not require the study entry to be limited to patients enrolled in PROCEED, to avoid limiting the recruitment pool. However, placing our initial focus on patients participating in PROCEED, particularly those who have demonstrated compliance and return for their follow-up visits, will identify motivated patients who are familiar with the study protocols and the importance of research. The short-term nature of this study should facilitate compliance. Because the safety data of combination therapy with lacosamide and opioids are unknown in patients with CP, this phase 1 trial is necessary. We initially considered the conventional 3+3 design for this study protocol, which suffers several limitations, such as low accuracy in identifying and estimating the MTD and the tendency of underdosing patients. Therefore, we adopted a novel phase 1 trial design (ie, the BOIN design) that allows better statistical learning of the dose-toxicity curve and more reliable identification of the MTD [37].

This study will provide new knowledge regarding the safety, toxicity, and DLT of lacosamide in patients with CP. It is

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anticipated that lacosamide will prove to be safe and well tolerated. The results of this pilot study will then support proceeding with a phase 2 trial of assessing the efficacy of lacosamide added to opioid therapy to alleviate abdominal pain caused by CP. We will demonstrate that these pilot trials, in which long-term therapeutic benefits are unlikely, are feasible in this challenging population. This knowledge will facilitate future clinical trials on CP, providing data regarding patient engagement and recruitment that will better inform trial design. Future clinical trials may indicate that a combination of lacosamide and an opioid will achieve better analgesia at lower doses of each drug than either as a single agent.

Acknowledgments

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Data Availability

Deidentified patient data may be shared with investigators from other institutions for ancillary studies upon request. Requests should be made to the study principal investigator.

Authors' Contributions

ELF and FAW wrote the main manuscript and prepared figures and tables. JJE, YY, DY, DLC, SSV, WP, SYH, and VP reviewed and approved this manuscript.

Conflicts of Interest

DY is a consultant for Pfizer, Inc. and gives research support to AbbVie Pharmaceuticals. SSV has received royalty payments for chapters in *UpToDate* on pancreatitis and received travel and honorarium for the *Orlando Health* scientific meeting in December 2023.

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Abbreviations

BOIN: Bayesian optimal interval
CoC: Certificate of Confidentiality
CP: chronic pancreatitis
CPDPC: Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer
CRF: case report form
DLT: dose-limiting toxicity
DSMB: Data and Safety Monitoring Board
EKG: electrocardiogram
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
MTD: maximum-tolerated dose
NaVs: voltage-gated sodium channels
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIH: National Institutes of Health
NMDA: N-methyl-D-aspartate
OIH: opioid-induced hyperalgesia
PROCEED: Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies
STTEPP: Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis

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Protocol

Benefits, Harms, and Stakeholder Perspectives Regarding Opioid Therapy for Pain in Individuals With Metastatic Cancer: Protocol for a Descriptive Cohort Study

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Abstract

Background: Opioids are a key component of pain management among patients with metastatic cancer pain. However, the evidence base available to guide opioid-related decision-making in individuals with advanced cancer is limited. Patients with advanced cancer or cancer that is unlikely to be cured frequently experience pain. Opioids are a key component of pain management among patients with metastatic cancer pain. Many individuals with advanced cancer are now living long enough to experience opioid-related harm. Emerging evidence from chronic noncancer pain literature suggests that longer-term opioid therapy may have limited benefits for pain and function, and opioid-related harms are also a major concern. However, whether these benefits and harms of opioids apply to patients with cancer-related pain is unknown.

Objective: This manuscript outlines the protocol for the "Opioid Therapy for Pain in Individuals With Metastatic Cancer: The Benefits, Harms, and Stakeholder Perspectives (BEST) Study." The study aims to better understand opioid decision-making in patients with advanced cancer, along with opioid benefits and harms, through prospective examination of patients' pain experiences and opioid side effects and understanding the decision-making by patients, care partners, and clinicians.

Methods: This is a multicenter, prospective cohort study that aims to enroll 630 patients with advanced cancer, 20 care partners, and 20 clinicians (670 total participants). Patient participants must have an advanced solid cancer diagnosis, defined by the American Cancer Society as cancer that is unlikely to be cured. We will recruit patient participants within 12 weeks after diagnosis so that we can understand opioid benefits, harms, and perspectives on opioid decision-making throughout the course of their advanced cancer (up to 2 years). We will also specifically elicit information regarding long-term opioid use (ie, opioids for ≥90 consecutive days) and exclude patients on long-term opioid therapy before an advanced cancer diagnosis. Lived-experience perspectives related to opioid use in those with advanced cancer will be captured by qualitative interviews with a subset of patients,

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clinicians, and care partners. Our data collection will be grounded in a behavioral decision research approach that will allow us to develop future interventions to inform opioid-related decision-making for patients with metastatic cancer.

Results: Data collection began in October 2022 and is anticipated to end by November 2024.

Conclusions: Upon successful execution of our study protocol, we anticipate the development of a comprehensive evidence base on opioid therapy in individuals with advanced cancer guided by the behavioral decision research framework. The information gained from this study will be used to guide interventions to facilitate opioid decisions among patients, clinicians, and care partners. Given the limited evidence base about opioid therapy in people with cancer, we envision this study will have significant real-world implications for cancer-related pain management and opioid-related clinical decision-making.

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KEYWORDS

cancer; cancer-related pain; neoplasm-related pain; opioid analgesics; opioids; pain

Introduction

Patients with advanced cancer or cancer that is unlikely to be cured frequently experience pain [1,2]. Although the overall prevalence of pain and pain severity related to cancer appear to be decreasing, 40% of patients with cancer experienced pain during and up to 3 months after cancer treatment [1,3,4]. When stratified by cancer severity, patients with more advanced disease have higher rates of pain: up to 66%, compared to 39% for patients with localized or curative disease [4]. Although patients with any cancer can experience pain, those with breast, lung, head, and neck cancer experience pain most often [5]. Under- and untreated pain in individuals with cancer is associated with a variety of adverse health consequences, including functional limitations (eg, inability to work), suboptimal health behaviors (eg, reduced physical activity), emotional distress, social isolation, high health care use (eg, emergency department and inpatient admissions), and earlier death [6-9].

Opioids are a key component of pain management among patients with metastatic cancer pain [10]. Although rates of opioid prescribing in advanced cancer have not been well described, people with advanced cancer are prescribed long-term opioid therapy (ie, opioid prescription for at least 90 consecutive days) more often than people with limited-stage disease (66% vs 40%) [11]. A recent study using data from the National Survey on Drug Use and Health found that approximately half of cancer survivors with a recent diagnosis (within 12 months of the National Survey on Drug Use and Health survey) were prescribed an opioid during that year (54%) [12]. National guidelines from the American Society of Clinical Oncology [10] and the National Comprehensive Cancer Network [13] support opioids as a cornerstone of pain management for individuals with advanced cancer, suggesting that the benefits of opioid use outweigh the harms for this patient group.

However, many individuals with advanced cancer are now living long enough to experience opioid-related harm. Indeed, some advanced cancers are considered chronic diseases as patients are surviving longer due to improvements in cancer treatments [14]. For example, the median survival of individuals with metastatic breast cancer in a large national cohort of patients with breast cancer in France was 37 months [15], which has increased steadily over the previous decades [16]. Approximately one-third of individuals with metastatic breast cancer [17] or metastatic prostate cancer [18] survive for at least 5 years. This presents a complex clinical context for treating cancer-related pain with opioids, increasing the need to balance opioid-related benefits and harms.

Emerging evidence from the chronic noncancer pain literature suggests longer-term opioid therapy may have limited benefits for pain and function. For example, a recent meta-analysis of randomized controlled trials of opioids versus placebo for chronic (>3 month) “noncancer” pain observed a small improvement in pain of 0.69 (95% CI 0.56-0.82) on a scale of 0-10 that was less than the prespecified minimum clinically important difference of 1 [19]. Other systematic reviews and meta-analyses have yielded similar findings, including a lack of functional improvement with opioid therapy over placebo [20,21]. Analogous data do not yet exist for patients with advanced cancer; given the unique features of cancer pain and the commonly concurrent noncancer pain experienced by patients with cancer, it is important to better understand pain and pain management in persons with advanced cancer.

Opioid-related harms are also a major concern among people prescribed opioids. In one meta-analysis of 26 studies, 23% of participants decided to discontinue opioids due to side effects (eg, nausea and dizziness) [22]. In the general population, long-term opioid therapy is also associated with more serious harms; 21% to 29% develop opioid misuse, and 8% to 12% may progress to an opioid use disorder. Although more rare, opioid overdoses can occur (256 per 100,000 person-years among people recently prescribed opioids vs 36 per 100,000 years among those not prescribed opioids) [23,24]. In studies of noncancer pain, opioid-related harms are consistently related to both ingestion of high-dose opioids (ie, >90 mg morphine equivalents) and coprescription of sedating medications (benzodiazepines and gabapentin) [25-28]. People with cancer are more likely to be represented in the high-dose opioid groups and frequently experience polypharmacy [29,30]. However, whether these benefits and harms of opioids apply to patients with cancer-related pain is unknown.

This manuscript describes the study protocol for “Opioid Therapy for Pain in Individuals With Metastatic Cancer: The Benefits, Harms, and Stakeholder Perspectives (BEST) Study.”

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The study aims to better understand opioid decision-making in patients with advanced cancer, along with opioid benefits and harms, through prospective examination of patients' pain experiences and opioid side effects and understanding the decision-making by patients, care partners, and clinicians.

Methods

Study Design

This is a multicenter, prospective cohort study that aims to enroll 630 patients with advanced cancer, 20 care partners, and 20 clinicians (670 total participants). The data collection is underway at 4 clinical sites. Site selection considered geographic diversity (Northeast, mid-Atlantic, West, and Southeast), the balance of urban versus rural patients, sufficient patient volume to reach the enrollment goal, and the ability to recruit based on previous success in cancer studies. Given well-established health disparities in cancer pain and its treatment, we selected sites that demonstrated a track record of successful recruitment of Black and Hispanic patient participants [31]. None of the chosen sites have opioid stewardship committees or programs, which could have the unintended consequence of limiting opioid prescribing [32]. Additionally, we conducted a comprehensive review of state opioid laws in preparation for the study [33], with most states specifying blanket cancer exemption for any opioid limitation, such as dose or limited day supply.

Participants

Patient participants must have an advanced solid cancer diagnosis, defined by the American Cancer Society as cancer that is unlikely to be cured [2]. An advanced cancer diagnosis can include patients who have distant metastases or a recurrence. Patient participants must be their own decision maker as determined by the electronic medical record (EMR) and enroll within 12 weeks of their advanced cancer diagnosis date. The research team will confirm an advanced cancer diagnosis using medical record documentation of pathology results or radiology and oncology documentation. We will recruit patient participants early after diagnosis so that we can understand opioid benefits, harms, and perspectives on opioid decision-making throughout the course of their advanced cancer (up to 2 years). Lived-experience perspectives related to opioid use in those with advanced cancer will be captured by qualitative interviews with a subset of enrolled patients, clinicians, and care partners.

We will specifically elicit information regarding long-term opioid use (ie, opioids for ≥90 consecutive days) and exclude patients on long-term opioid therapy before an advanced cancer diagnosis. Consistent with previous studies, we confirm opioid use in the medical record and will ask patient participants, "Did you take a strong prescription pain medication known as an opioid or narcotic for at least 90 days in a row during the past year? Examples of opioids include oxycodone, hydrocodone, hydromorphone, morphine, fentanyl, buprenorphine, methadone, and combination products such as oxycodone/acetaminophen." This question is consistent with other commonly used research definitions of long-term or chronic opioid therapy [34,35]. Notably, this long-term opioid use definition also excludes individuals who are receiving methadone or buprenorphine/naloxone (suboxone) for the treatment of opioid use disorder, as the potential benefits and harms of opioid therapy in this population are unique and merit separate investigation [36]. This will allow us to understand the benefits, risk factors for harm, and perspectives on opioid decision-making when a patient with newly diagnosed advanced cancer begins an opioid or continues a newly initiated opioid.

From the larger cohort, we will recruit 40 patient participants with advanced cancer—20 who are prescribed opioids at the time of enrollment and 20 who are not. From that sample of 40 patients, we will aim to obtain consent from care partners of at least 20 patients and clinicians of at least 20 patients.

We will exclude individuals younger than 18 years of age, prisoners, pregnant people, and patients currently enrolled in hospice at the time of recruitment from the study. Patient participants do not need to report pain at the time of diagnosis since pain can occur at any point in the cancer trajectory. By including patient participants without pain at the time of diagnosis of metastatic disease, the study has the added benefit of describing the natural history of pain in patients with metastatic cancer for 2 years after diagnosis, filling an existing literature gap [3]. Patients who meet advanced cancer eligibility criteria will be recruited irrespective of their predicted prognosis, due to the inherent challenges of predicting prognosis [37,38].

For qualitative interviews, care partner participants must be a spouse, partner, child, relative, or friend who helps the patient with activities of daily living and health care needs at home, consistent with the National Cancer Institute definition of family caregivers [39]. Clinician participants will be physicians or advanced practice clinicians caring for a patient participant who has opioid prescribing authority and is willing to participate in a qualitative interview.

Theoretical Framework

Our data collection will be grounded in a behavioral decision research (BDR) approach [40] that will allow us to develop future interventions to inform opioid-related decision-making for patients with metastatic cancer. Opioid-related decision-making refers to decisions to initiate opioids or continue opioids over time. The BDR approach consists of 2 components. The first is the characterization of a "normative decision model," which describes the information distilled from existing scientific evidence that experts in the field believe that decision makers (patients, care partners, and clinicians) need to know to be able to make an informed decision. The second is a lay "mental model" of the decision, or what interested parties (ie, patients and care partners) already know and how they currently make their decisions. The normative decision model is a well-established approach for medical decision-making [41], including the development of opioid guidelines [42,43]. Consistent with previous studies, the lay decision model solicits perspectives on what patients, care partners, and clinicians consider foundational knowledge and how they make their decisions [44]. Interventions to support optimal decision-making can bridge the gap between the normative model and the contextual reality of how individuals are currently making those choices. Figure 1 provides the BDR framework-based approach mapped to the study aims.

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Figure 1. Study aims mapped to behavioral decision-making model element.

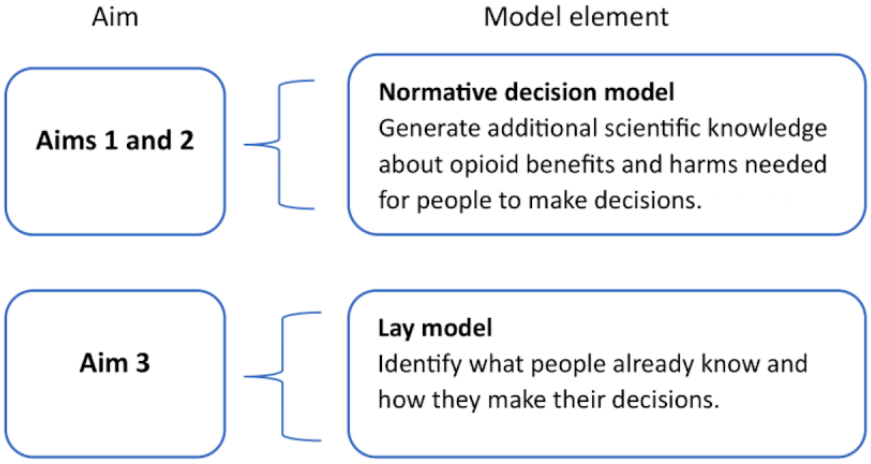

Specific Aims

Using the BDR framework, the objective of this study is to create evidence to guide opioid prescribing in patients with advanced cancer.

The study's aims are as follows:

- Aim 1: To investigate the relationship between opioid therapy and opioid-related benefits.
- Hypothesis 1a: Prescribed opioids will be associated with decreased pain severity and pain interference (coprimary outcomes).
- Aim 2: To investigate risk factors for opioid-related harms.
- Hypothesis 2a: Certain coprescribed medications will be associated with an increased risk of opioid side effects (eg, benzodiazepines and somnolence).
- Hypothesis 2b: Younger age, history of substance use disorder, and history of mood disorders will be associated with a greater risk of opioid misuse and use disorder.
- Aim 3: To understand patient, care partners, and clinician perspectives on opioid-related decision-making.

Study Procedures

Recruitment

Potential patient participants will be identified using EMRs; *International Classification of Diseases, Tenth Revision* diagnosis codes; direct clinician referral; and referral from informational handouts in patient-facing platforms (eg, clinic rooms and chemotherapy teach-back packets). Study sites will develop reports to generate lists of potentially eligible patient participants in accordance with all rules of the HIPAA (Health Insurance Portability and Accountability Act), preparatory to the research exception [45]. The research coordinator will review listed patients' EMRs to verify eligibility following institution-specific procedures for contacting potential patient participants in clinic, over the telephone, or through letters. After receiving permission using one of the methods described above, trained research staff at each site will contact potential patient participants in-clinic or over the telephone to confirm eligibility. Subsequently, research staff will obtain consent, and data will be collected using Research Electronic Data Capture (REDCap; Vanderbilt University), a free and secure web-based application to capture research data [46].

Assessments

Once patients have consented and enrolled in the study, data collection will include patient-reported outcomes (PROs), chart reviews, and interviews. Table 1 provides an overview of the study procedures and time frame.

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Table 1. Schedule of research activities.

Study stage	Screening and enrollment	Follow-up			
	Within 12 weeks of the date of diagnosis	Weekly after baseline	Monthly after baseline	Quarterly after baseline	Semiannually after baseline
Prescreening	✓				
Consent, screening, and contact information	✓				
Demographics and medical history	✓				
Baseline and demographics	✓				
Weekly 3-questions pain assessment: pain severity and inference		✓			
Monthly PRO[a] assessment: mood, substance use, symptoms, and opioid misuse (Carey 2-year index)			✓		
Chart reviews: substance use, opioid misuse, and opioid overdose				✓	
Patient calls and chart review: Opioid prescription or dose, benzodiazepine prescription, over or under consumption of opioids					✓
TAPS[b]: substance use and opioid use disorder				✓	
Patient participants, care partners, and clinician interviews				✓	

[a]PRO: patient-reported outcome.

[b]TAPS: Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool.

Study staff will confirm patient demographics and cancer type from the medical record. Sites will use a chart abstraction tool to gather medication-related data every 6 months. Opioid dose will also be assessed through self-report by reading back the dose and instructions on the opioid bottle and confirmed in the EMR. Patient participants will consent to receiving a phone call from the study staff for pill counts during the latter part of the month of their prescriptions every 3 months.

Patient participants will complete baseline assessments and PROs electronically using REDCap, over the phone, or during clinic visits through a tablet by the study staff. If patient participants are unable to complete PROs, care partners will be permitted to complete the PRO assessments on behalf of the patient participants. We acknowledge that based on systematic reviews in oncology, there may be differences in patient-proxy reports, with proxies having a more negative view of the patient's well-being [47].

The outcome measure for pain will be the Pain, Enjoyment, and General Activity (PEG) scale, a 3-item commonly reliable and validated measure used in oncology populations that asks about pain severity, pain interference in enjoyment of life, and pain interference in general well-being [48-50]. The PEG meets the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations and has a 7-day recall period [51]. The PEG will be collected weekly to provide longitudinal impact on pain severity, pain interference, and whether opioids precede any change in pain.

Additional monthly PROs will include information on mood (Functional Assessment of Cancer Therapy-General Well-Being Subscale); comorbidities (Self-Administered Comorbidity Questionnaire); functioning (Carey index); and if prescribed opioids, information on opioid misuse (Patient-Reported Outcomes Measurement Information System), opioid side effects (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events), and substance use (Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool) [52-56]. These measures were selected because of their favorable psychometrics in the study population, brevity, and similar recall periods. This patient-participant burden is similar to other studies among patients with metastatic cancer [57].

For Aim 3, we will conduct one-on-one interviews with patients, their care partners, and clinicians with the goal of better understanding opioid-related decision-making. These interviews will occur every 3 months for 2 years or until death. The rationale for this frequency is that it strikes a balance between interviewing people often enough for them to remember aspects of opioid decision-making since the last interview but not so often as to ask about opioid-related decisions more frequently than those decisions occur or cause undue participant burden.

Analytic Plan

Aim 1: Data Analysis

This analysis will draw from all patient participants, regardless of whether they are prescribed opioids, so we can compare those who are with those who are not prescribed opioids. We will estimate differences in pain severity and interference between patients treated with opioids versus patients not treated with opioids using linear mixed-effects models, which will allow us to (1) account for repeated measures over time for each patient and (2) adjust for potential confounders. In the linear mixed-effects models, the dependent variables will be based on

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the PEG: pain severity (first question is a continuous 0-10 value) and pain interference (mean of 3 PEG items) at each time point. Current opioid prescription, baseline pain severity or interference, and other confounders (ie, factors statistically associated with the exposure and outcome) will be included as fixed effects, while the subject will be included as a random effect.

Power Calculation for Aim 1

Power calculations were performed by simulation to allow a range of parameters to vary in all scenarios. Unlike a randomized trial, in this study we will not have control over the ratio of patients allocated to the 2 comparison groups (eg, there will not be precisely a 1:1 ratio of patients prescribed opioids vs patients not prescribed opioids for comparison). Scenarios were considered where the proportion of patients prescribed opioids was allowed to vary from 30% up to 70%, all assuming a mean baseline PEG of 6 in the patients not prescribed opioids, a reduction in the PEG of 1 point for patients that are prescribed opioids, and a common standard deviation in PEG scores of 2 points [51]. All scenarios considered had at least 90% power to detect a difference of 1 point between groups with a total sample size of 630 patients (allowing for 30%-70% of the population to be prescribe opioids, meaning that with a range of 189 up to 441 patients prescribed opioids during the study period, there is ample power to detect differences between groups). All scenarios had at least 99% power to detect a 2-point difference on the PEG. We acknowledge that up to 40% of patients may drop out during the study due to the morbidity and mortality of patients in palliative care [58]. Data up until the point of attrition will be included in the analysis, and this has also been accounted for in our calculations.

Missing Data for Aim 1

In general, linear mixed-effects models provide unbiased estimates when the data are assumed to be missing at random, meaning that the likelihood of a missing value is not related to the values of the outcome data (in this case, the assumption that missing values for pain are not related to the severity of the patient's pain). The setting of this study will have two basic missingness problems: (1) data that are missing while the patient still lives, either because the survey could not be completed or the patient did not wish to complete the pain instrument; and (2) pain data that are missing because the patient is deceased. The missing at random assumption can never be fully confirmed, so we will perform three sensitivity analyses to see how our results vary under different approaches to handling the missing pain values: (1) multiple imputations; (2) imputing the worst pain value for patients that fail to complete the pain instrument for any reason (including death before the scheduled assessment); and (3) imputing the worst pain value for patients that fail to complete the pain instrument, but omitting patients that have died. It should be noted that in this patient population, death is an expected outcome and not necessarily a negative outcome with respect to end-of-life suffering and pain management.

Aim 2a: Data Analysis

To test our hypothesis that coprescribed medications will be associated with an increased risk of opioid side effects (eg, benzodiazepines and somnolence), we will include only study patient participants who are prescribed opioids. Linear mixed-effects models will be used to assess the relationships between selected risk factors and the corresponding suspected opioid side effects. Each side effect is scored on the respective weekly or monthly assessments. Analyses will be conducted to examine the relationship between coprescribed medications and each of the respective opioid side effects (constipation, nausea, dry mouth, and somnolence) as well as targeted relationships specifically of interest for individual exposures or side effects combinations, including (1) coprescription of other constipating medications and constipation, (2) coprescription of other constipating medications and nausea, (3) coprescription of anticholinergic medications and dry mouth, and (4) coprescription of benzodiazepines with somnolence. We will also examine the association between which opioid is prescribed (ie, morphine vs oxycodone) and each of the same respective opioid side effects (constipation, nausea, dry mouth, and somnolence). The use of linear mixed-effects models will provide estimates of the effect of each risk factor of interest on each of the respective side effects while also allowing the inclusion of longitudinal measurements from patient participants.

Power Calculation for Aim 2a

With an overall sample size of 630, we anticipate approximately 50% (315/630) of the study sample to be prescribed opioids, leaving 315 patient participants available for the analyses pertinent to this hypothesis. We examined a range of scenarios allowing anywhere from 10% to 30% of the eligible participants to have each exposure, performing power analyses to detect a 0.5-point difference in means for each side effect on the 1-5 scale (assuming a SD of 1 point). Power is about 65% if the exposure is rare (10% of patients prescribed opioids) but increases to 87% if the exposure is present in 20% of patients prescribed opioids and 93% if exposure is present in 30% of patients prescribed opioids. Again, we account for up to 40% attrition during the study. Note that patient participants will contribute data until they drop out, and this data will be included in the analysis.

Aim 2: Data Analysis to Test Hypothesis 2b

To test our hypothesis that younger age, history of substance use disorder, and history of mood disorders will be associated with a greater risk of opioid misuse and use disorder, we will perform multivariable Cox regression analyses to assess the respective risk factors of interest. We will use a single prespecified model that includes age, history of substance use disorder, and history of mood disorders using baseline PRO data and chart review.

Power Calculation for Aim 2b

With a total sample size of 630 patients recruited in Aim 1, the power calculation for this subaim assumed a scenario where approximately 50% (315/630) of the patients are prescribed opioids, leaving 315 patients available for this aim. We anticipate opioid misuse will occur in 20% to 30% of patients.

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For a rarer event such as opioid use disorder, which is estimated to occur in approximately 10% of the patients, a sample size of 315 patients will be sufficient to support a model with 5 candidate predictor variables.

Missing Data for Aim 2

Unlike Aim 1, missing data should not affect analyses in this aim. The development of opioid-related complications will also be considered an event if it is known to occur and otherwise assumed not to occur during the period patients are under observation.

Aim 3: Data Analysis

The purpose of Aim 3 is to identify what patients, care partners, and clinicians already know and how they make opioid-related decisions to develop the lay model of the BDR. To determine decisional influences, the BDR framework uses the "mental models approach" to elicit these views [59]. To create the BDR framework lay model, we will structure the patient and care partner interviews by focusing on (1) what they already know about opioids, (2) how they make decisions, (3) examining whether this is consistent with or contrary to the normative model of evaluating risks and harms, and (4) how they think decisions around opioid use should ideally be made. The interviews begin with general questions and then become more specific, asking about each topic from the expert model. We will structure the clinician interviews by focusing on (1) their assessment of the patient's pain; (2) approaches to best treating it, including opioids; and (3) their decision-making around opioid prescribing. We will also evaluate whether different patient, care partner, and clinician perspectives are consistent with or contrary to one another.

For the semistructured interviews (40 participants with metastatic cancer from our larger cohort, 20 who are prescribed opioids at the time of enrollment, and 20 who are not), we aim to understand perspectives on deciding to initiate or continue opioid therapy or not. This sample size is based on evidence that suggests thematic saturation is achieved at 8-16 interviews; since we expect up to 40% attrition, this approach will ensure we have at least 20 participants [60]. We will purposively sample [61] to ensure diversity on race, site, and baseline PEG value; we will also recruit some individuals who have a history of a substance use disorder and are therefore at particularly high risk for negative consequences when prescribed opioids.

Similarly, we will recruit patient participants' care partners and clinicians. We will aim for at least 10 people who have care partners who consent to the group prescribed opioids at enrollment and 10 care partners of patient participants who have been prescribed opioids at enrollment. This approach will ensure that we have enough care partners to provide adequate perspective but not severely bias our sample by only allowing the enrollment of individuals who have care partners willing and able to enroll in this study. As described above, we will also purposefully sample 25% of patient participants who do not have care partners so that these perspectives are represented. Interviewing patients and their care partners s and clinicians will allow for triangulation of findings. Additionally, following patients, care partners, and clinicians longitudinally will allow for a detailed understanding of how decision-making changes over the course of metastatic cancer, allow participants to reflect on what they would have liked to know earlier based on what they know now, and provide real-time data on actual decisions (eg, initiation or discontinuation of opioids) on which participants can be asked to comment. Given the challenges inherent in engaging clinicians, we will aim for 15-minute focused interviews.

Trained qualitative researchers will collect and analyze the qualitative data. Interviews will be conducted remotely (through phone or Zoom [Zoom Video Communications], according to the interviewee's preference), and interview recordings will be transcribed verbatim (with details that might identify the interviewee redacted). Coding the data will require a hybrid deductive-inductive approach. A prespecified set of codes will be identified from the normative model. The presence and absence of these codes (eg, the accuracy of knowledge about the relationship between opioids and addiction) will be used to document the consistency between the normative model and stakeholder perspectives. In addition, we will take an inductive analytical approach to identify emergent values and beliefs that are not present in the normative models. Codes will be developed through open coding of the transcripts to determine topics and themes that emerged in the interview transcripts with input on topics or themes that the study team anticipates being relevant, resulting in simultaneously inductive and deductive development of the codebook. A draft codebook including detailed code definitions will be discussed with the study team to ensure that codes reflect both the data as they are emerging as well as relevant topical themes that are important to the team. Codes will be thoroughly checked to determine that definitions are distinct enough to reduce ambiguity in the coding process.

About 25% of the transcripts will be coded by 2 independent, trained qualitative coders to ensure quality and consistency in coding. Coding will then be compared for the purposes of calculating Cohen kappa inter-coder reliability scores [62]. Any coding discrepancies identified during this comparison will be adjudicated by the coders until full agreement on coding is achieved. The finalized coding on these transcripts will be recorded in a single ATLAS.ti file, following which the primary coder will complete the coding of the remaining transcripts according to the codebook and through the adjudication process and discussion by the study team with content and methodologic expertise. This process allows for consistency and quality across transcripts. Once coding is complete and uploaded to ATLAS.ti with quotes associated with codes, we will thematically analyze and determine the relative frequencies of various codes and the most salient themes. The resulting thematic analysis will be discussed with the entire investigator team to use the findings to build lay models of patient, care partner, or clinician decision-making around opioid use for patients with metastatic cancer.

Ethical Considerations

This study has been reviewed and approved by the University of Pittsburgh Institutional Review Board (STUDY20090231), which serves as the institutional review board of record for all research locations. Informed consent is obtained by trained

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research staff members at each site. The study was granted a waiver of HIPAA authorization to identify participants who meet study inclusion criteria. The study was granted a waiver to document informed consent for the qualitative interviews conducted in Aim 3. Verbal consent will still be obtained by interviewers before commencing the interview.

Study data will be identifiable while the study is ongoing, as there are many contact points with participants. All study data are segregated by research site, so recruitment team members only have access to the data for participants they have enrolled. The University of Pittsburgh team has access to all study records as the team conducts follow-up assessments. All results that will be published in this study in the future will be done in an aggregate, deidentified manner.

We will reimburse patient participants US $10 for the baseline questionnaire, US $2 per weekly questionnaire, and US $10 per monthly questionnaire (up to US $394 if all questionnaires are completed over the 2 years). Patient participants who complete at least 80% of questionnaires during each year of follow-up will be eligible for an annual bonus payment of US $20. This results in US $434 of total possible compensation for Aims 1 and 2. For Aim 3, patients and care partners will be reimbursed US $30 per interview. Clinicians will not be compensated.

Results

This study was peer-reviewed and funded by the National Institute of Nursing Research in September 2021. Recruitment began in October 2022; we anticipate completing recruitment by November 2024. Follow-up assessments will end by November 2026, at which time we can finalize our data analysis.

Discussion

This paper presents the study protocol for the benefits, harms, and stakeholder perspectives regarding opioid therapy for pain in individuals with metastatic cancers .The study also uses PRO measures, qualitative data collection, and repeated assessments to ascertain how decision-making differs throughout the cancer trajectory, including at the end of life. The protocol is innovative because it addresses the research gap on the benefits and harms of opioids in metastatic cancer in a novel way. This includes our prospective design in patients recently diagnosed with advanced cancer, the collection of data from multiple perspectives (patients, clinicians, and care partners), and the inclusion of a well-known decision-making framework that can facilitate the design of future interventions.

There are several potential challenges or limitations to the research protocol. The first is likely challenges of retention and recruitment that are expected in longitudinal studies, especially in individuals with cancer and serious illnesses. Second, there is a potential for low enrollment or a high rate of missing data due to death, illness, dropout, or participant burden. We have attempted to account for these anticipated issues by having backup recruitment sites and conservative sample size estimates. Third, opioid prescribing is an evolving area of clinical practice and subject to federal and state oversight. It is possible that local and state regulations or institutional policies will change during the study period, resulting in a decrease in opioid prescribing and recruitment issues. Last, prospective investigation of adverse effects such as overdose or opioid-related mortality may be difficult to capture because these events are relatively rare.

At the end of the study, we anticipate the development of a comprehensive evidence base on opioid therapy in individuals with advanced cancer, guided by the BDR framework. The information gained from this study will be used to guide interventions to facilitate opioid decisions among patients, clinicians, and care partners. Given the limited evidence base about opioid therapy in people with cancer, we envision this study will have significant real-world implications for cancer-related pain management and opioid-related clinical decision-making.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Institute of Nursing Research.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e54953_app1.pdf]

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Abbreviations

BDR: behavioral decision research

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BEST: Benefits, Harms, and Stakeholder Perspectives
EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act
REDCap: Research Electronic Data Capture
PRO: patient-reported outcome
PEG: Pain, Enjoyment, and General Activity

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Protocol

Leveraging Parents and Peer Recovery Supports to Increase Recovery Capital in Emerging Adults With Polysubstance Use: Protocol for a Feasibility, Acceptability, and Appropriateness Study of Launch

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Abstract

Background: Emerging adults (aged 18-26 years) are the most at-risk yet underserved age group among people with substance use disorder, especially rural emerging adults, and polysubstance use is common. Recovery capital is lower among emerging adults than older adults, and evidence-based treatments are typically unavailable or not developmentally tailored, especially in rural areas. Both supportive parents (or parental figures) and peer recovery support services (PRSS) can be leveraged to better support these emerging adults. Previous research indicates parents can be engaged to deliver contingency management (CM), an extensively researched evidence-based intervention for substance use.

Objective: This protocol describes a funded pilot of *Launch*, a novel, scalable service package that pairs web-based coaching for parents to deliver CM for emerging adults (CM-EA) at home and in-person PRSS with educational and vocational goal setting. Specifically, this protocol describes feasibility, acceptability, and appropriateness testing (implementation-related outcomes) and steps taken to prepare for a future large-scale trial of *Launch.*

Methods: Upon the recruitment of 48 emerging adult and parent pairs from sites serving primarily rural clients, participants will be randomized into 1 of 3 conditions for this randomized controlled trial: virtual parent coaching to deliver CM-EA, in-person PRSS for emerging adults, or both sets of services. Emerging adult eligibility includes polysubstance use, a substance use disorder, and availability of a consenting parent. Emerging adults will be interviewed at baseline and 6 months about substance use, quality of life, recovery capital, parental relationship, and *Launch* implementation-related outcomes (6-month follow-up only). Parents, peer workers delivering PRSS, and parent CM-EA coaches will be interviewed about implementation-related outcomes at the end of the study period. Peer workers and CM-EA coaches will be asked to complete checklists of services delivered after each session. Finally, payers and providers will be interviewed for additional insights into *Launch* implementation and to identify key outcomes of *Launch*. Data analysis for emerging adult outcomes will be primarily descriptive, but parent CM-EA training adherence will be assessed using nested mixed-effects regression models of repeated measures.

Results: *Launch* is currently ongoing, with funding received in August 2023, and is expected to end in September 2025, with data analysis and results in December 2026. Participants are expected to begin enrolling in June 2024.

Conclusions: While this pilot is limited by the small sample size and restriction to emerging adults with an involved parent, this is mitigated by the study's strengths and is appropriate for the pilot stage. *Launch* uses an innovative combination of existing strategies to generate better outcomes for emerging adults while remaining scalable. This pilot will provide insights into the feasibility and acceptability of *Launch* from the perspectives of service recipients, providers, and payers to inform a larger-scale effectiveness trial.

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KEYWORDS

peer recovery support services; contingency management; emerging adults; rural

Introduction

Background

Substance use (SU) among emerging adults (aged 18-26 years) is one of the worst public health problems in the United States. Emerging adults are 3 times more likely to report SU compared to adolescents or older adults [1,2]. An estimated 12.4 million emerging adults in the United States used illicit drugs in 2020, and 4.8 million met the criteria for SU disorder [2]. During the opioid epidemic, emerging adults were the age group with the largest uptick in opioid misuse [3]. This is especially challenging for people in rural communities, who initiate opioid misuse at earlier ages [4] and have higher rates of opioid-related deaths than their urban counterparts [5]. That said, polysubstance use (poly-SU) represents the norm for emerging adults regardless of rural or urban residence, with nearly 100% of emerging adults with SU problems reporting use of multiple drugs [6-8]. Not surprisingly, high levels of SU can have life-altering costs, including impaired academic or career performance, development of chronic physical and mental health conditions, sexually transmitted diseases, unintended pregnancies, and death, with poly-SU being an additional risk factor for negative outcomes [9-13]. In that context, effective services are clearly needed to target poly-SU in emerging adults to prevent these devasting outcomes, particularly in rural areas.

Recovery capital is also much lower for emerging adults compared to older adults [14,15]. Recovery capital is the internal and external resources that can be mobilized to promote or sustain SU recovery [16-25]. Recovery capital is acutely pertinent for emerging adults as this developmental phase is known for substantial instability and change in the very domains that recovery capital encompasses [26]. Among other things, emerging adults may be moving to independent housing, solidifying vocational identities, developing adult relationships, and undergoing final executive functioning maturation, which are often unique milestones happening concurrently during this life stage as compared to adolescents (aged 12-18 years) and more mature adults (aged ≥26 years) [26-28]. Thus, it is logical that emerging adults would have deficits in recovery capital. Given that recovery capital in emerging adults can be critical to preventing long-term SU problems [29,30], effectively targeting poly-SU requires carefully considered adaptation based on emerging adults' specific developmental needs.

Unfortunately, existing services fall short in addressing the needs of emerging adults with poly-SU. Of the 4.8 million emerging adults in 2020 who met the criteria for SU disorders, only 4% reported receiving treatment [31], in line with nationwide shortfalls in SU services [32]. For rural emerging adults, treatment gaps are even more striking, with most rural towns having a small tax base and, thus, reduced funds for behavioral health [33] and a weak infrastructure for poly-SU services [34]. Long distances, travel times, and inadequate public transportation in rural areas significantly impact receipt of health care, with a 5% lower likelihood of receiving care for every additional kilometer of distance to care and 1.6 to 2.3 times lower likelihood of receiving care if a person lacks a driver's license in rural areas [35]. Often, federally qualified health centers are the only source of rural health care, but the vast majority offer no behavioral health services, including for SU [36]. When services are available for SU in either rural or urban settings, they are rarely evidence based [37,38] and rarely focus on poly-SU, the most common presentation for emerging adults. Furthermore, emerging adults are the least likely to engage with services, with 70% of emerging adults in outpatient treatment attending ≤3 sessions and emerging adults being more likely to drop out of treatment than mature adults [39,40]. There are varied reasons for low service engagement, but one prominent issue cited by experts is that existing services cater to adolescents or older adults and ignore the unique developmental needs of emerging adults described previously (eg, changes in brain development, housing, education or vocational roles, and relationships with caregivers and romantic partners) [41].

Clearly, more developmentally appropriate and engaging services are needed for emerging adults with poly-SU, particularly in rural communities. This National Institute on Drug Abuse–funded pilot study (grant R34DA057639) initiates research that aims to fill this service gap via an innovative adaptation of existing interventions and service delivery strategies called *Launch* that leverages (1) parents of emerging adults and (2) peer recovery support services (PRSS) while ensuring that services are equitable and scalable. Parents and PRSS were selected as key points of emerging adult engagement after feedback from national community boards created by the Justice and Emerging Adult Populations Initiative (grant R24DA051950), which consists of both emerging adults in SU disorder recovery and payers and providers of SU services (current membership for those willing to disclose identifying information [42]). It also aligns with developmental transitions and needs of emerging adults, especially related to building effective recovery capital.

According to the US census, 47% of emerging adults resided with their parents in 2019, and this proportion increased to 52% during the COVID-19 pandemic [43]. A national survey showed that emerging adults prefer to reach out to parents when they need help with a problem, voicing less certainty about the help provided by formal supports [44]; thus, incorporating supportive family members into services may promote recovery success [45,46]. Indeed, previous work has proposed that teaching parents contingency management (CM) principles may improve

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SU outcomes for their emerging adult children [47]. A large meta-analysis also indicated that treatments involving family members regularly outperform individually based treatments for SU and related problems [48]. Still, parents are rarely invited to participate in emerging adult SU services beyond covering costs and transportation, similar to findings for emerging adult mental health services [49]. Our research addresses this neglected parent resource via a service that leverages direct parent involvement but in a way that can address poly-SU.

Peer workers are a trained and certified workforce that has lived experience with SU and delivers PRSS, which includes direct social support, resource linkages, and connecting clients to a broader recovery community [50-53]. The Substance Abuse and Mental Health Services Administration strongly backs the use of peer workers across behavioral health conditions, with a special focus on emerging adults [54], and PRSS is increasingly becoming a billable service [55]. Reviews of the literature indicate that PRSS significantly improve SU and other outcomes (eg, recidivism and treatment retention) [52,56-58], although the active ingredients of PRSS are not currently known [59]. Typical PRSS may be enough to decrease poly-SU and increase recovery capital for emerging adults, but it may be that targeted work toward emerging adult vocational and educational goals is necessary to effectively engage emerging adults and build key elements of recovery capital. Hence, *Launch* will incorporate specialized training for peer workers in vocational and educational skill building to increase recovery capital in domains important to emerging adults. Notably, PRSS have proliferated across the United States, including in rural communities [60].

Launch is a service model that will incorporate both parents and specially trained peer workers to target reducing poly-SU in emerging adults. Within the parent component, *Launch* will include web-based paraprofessional coaches teaching parents how to deliver CM for emerging adults to their own emerging adult children using a protocol built on a rigorous body of previous research that we and others have conducted to validate a CM model specifically for emerging adults. Importantly, CM is one of the most well-established interventions for SU [61], including opioid use, stimulant use, and poly-SU [62-65]. CM studies specifically with emerging adults have yielded positive results [66-68]. A systematic review even found that CM for emerging adults had 8-week retention rates as high as 70% [69]. The research team recently completed a study (grant R01DA041434-03S1) in which off-site paraprofessionals were trained to deliver CM to emerging adults while engaging parents to be supportive in various aspects of CM. Therefore, we believe that it is feasible for parents to be coached to deliver CM for emerging adults (CM-EA) to target their emerging adults' poly-SU, which could be particularly valuable in underresourced rural areas lacking traditional service access. This pilot study allows us to adapt our training to do so.

Objectives

We developed *Launch* for feasible delivery in both rural and urban communities by combining (1) virtual parent coaching and (2) connections with peer workers. It is informed by a unique convergence of factors, including community-based participatory research results (ie, involvement of affected community members in the development of the project [70,71]), developmental theory about emerging adulthood and SU [26], decades of research conducted by our team (and others) on effective SU interventions for poly-SU, and the fact that half of emerging adults still reside with their parents [43]. As described previously, extensive collaboration with national community boards directed our focus on parent and peer supports as key leverage points for emerging adults. We adapted the services provided in *Launch* to meet emerging adults' unique developmental needs during this "in-between" life stage fraught with instability, stress, self-exploration, and experimentation [26]. Thus, the objectives of this pilot of *Launch* are to adapt and evaluate the *Launch* parent coach and peer worker training protocols and adherence tools (aim 1); assess the feasibility and acceptability of (a) a virtual study protocol for recruiting, randomizing, assessing, and retaining parents and emerging adults and (b) *Launch* components (aim 2); and determine from payers and providers the data needed for future funding and delivery of *Launch* (aim 3).

Methods

Overview

This pilot study will assess the feasibility and acceptability of *Launch*, an innovative service package for poly-SU in emerging adults that can be scaled up for rural communities. Consistent with the appropriateness of a pilot study, this study will examine objectives rather than formal hypotheses. In particular, this study will accomplish the following activities: (1) adapting and developing peer worker training protocols and adherence tools, (2) gathering pilot data on a small sample of the population to test the acceptability and feasibility of *Launch*, and (3) gathering information from payers and providers in preparation for a larger effectiveness trial of *Launch*. This study uses a mixed methods and multi-informant assessment design involving collection of both qualitative and quantitative data [72]. A total of 48 emerging adults with poly-SU problems and their parents will be primarily recruited from sites that provide services to clients living in rural areas. The emerging adults will be randomized to one of three conditions: (1) virtual parent CM-EA coach for parents only, (2) in-person PRSS plus vocational or educational skill building for emerging adults only, or (3) a combination of virtual parent CM-EA coaching for parents *and* in-person PRSS plus vocational or educational skill building for emerging adults. Payers and providers of recovery services will be recruited for qualitative interviews.

Ethical Considerations

This protocol was reviewed by the Chestnut Health Systems Institutional Review Board (study 1177-0723) and approved on March 7, 2024. The Institutional Review Board–approved informed consent documents that will be reviewed with each category of participants have been included with this protocol in Multimedia Appendix 1. All qualitative data will be deidentified at the time of transcription, and original recordings will be destroyed. All participants will be assigned a unique identifier, and identifying information linked to those unique identifiers will be stored separately on a secure server. Emerging

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adult participants will receive US $50 for each assessment, 1 administered at baseline and 1 administered at the 6-month follow-up; US $20 for a final qualitative interview; and US $5 per mail-in urinalysis completed (2 requested: 1 at baseline and 1 at the 6-month follow-up). Parent participants will be compensated with US $20 for a 6-month assessment and US $20 for a qualitative interview. Peer workers providing PRSS to emerging adults will have the option to receive a US $100 stipend per emerging adult participant per month to offset any activity or travel costs.

Participants

The sample for the study will include 48 emerging adults with poly-SU problems and a supportive parent for each emerging adult (n=48 parents paired with the 48 emerging adults) recruited from rural areas. Inclusion criteria for emerging adults are as follows: emerging adults aged 18 to 26 years who report (1) any misuse of opioids or stimulants and at least one other substance in the same week during the past 30 days; (2) at least 1 SU disorder reported by the emerging adult as assessed via the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) Checklist* [73]; and (3) a supportive parent willing to be virtually coached to deliver CM-EA. Participating "parents" can include any supportive adult who is in a financially supportive caregiving role for the emerging adult and has the desire and ability to implement the CM-EA program. Only emerging adults who present with unstable conditions requiring intensive treatment will be excluded from the sample (eg, active suicidal or homicidal intentions or requests for medically supervised detoxification services). Families will be recruited using referrals from community partners that serve rural clients, email outreach, flyers, print advertisements, and word-of-mouth referrals. Community partners will obtain verbal permission to refer potential participants to research staff. Within 72 hours of referral (self-referral or from a community partner), the research team will contact the emerging adult and parent by phone to explain the research and schedule a virtual appointment to review the consent forms for both the emerging adult and parent as well as baseline measures for the emerging adult participant.

Additional participant categories that will not be recipients of an intervention but who will directly inform the feasibility- and acceptability-related outcomes of the study include peer workers delivering *Launch* PRSS to emerging adult participants and a virtual CM-EA parent coach supporting parents. Payers and providers will also give feedback on the feasibility and acceptability of *Launch* and will inform the selection of key outcomes of interest (including cost-related outcomes) for the future large-scale study of *Launch*. For this study, payers and providers are defined as people working for organizations that may be responsible for funding services such as *Launch* whether via insurance or through grants (payers), individuals involved in the direct provision of services that could include services such as *Launch* (providers), or those involved in the administration or supervision of either payers or providers. We will use a multistage I (ie, funnel approach) purposeful sampling strategy [74] to ensure variation in payer or provider types while also targeting those with expertise on services for emerging adults with SU.

Intervention

CM-EA Coaching

Parents in either CM-EA condition (parent CM-EA component only or parent CM-EA plus in-person PRSS for the emerging adults) will be virtually coached to deliver CM-EA by an at least Bachelor's-level paraprofessional via web-based videoconferencing. Weekly CM-EA coaching sessions are expected to last 20 to 40 minutes each. This service was developed by the research team and collaborators. Strategies are well specified, and multiple tools (session checklists and worksheets) facilitate CM-EA delivery. CM-EA draws from CM approaches that target poly-SU in adults and teenagers. CM-EA is grounded in a family-based CM model that uses both behavior modification and cognitive behavioral strategies. CM has garnered tremendous support in the SU treatment field, and our team has modified and examined CM specifically for emerging adults. All components involve a support person, which in *Launch* is a parent (see the aforementioned definition of "parent"). After introducing CM-EA, a contingency contract is developed (described in the following paragraph) that provides emerging adults with rewards for negative drug screens and completion of developmentally appropriate goals that build recovery capital (eg, submitting job applications and opening a bank account), along with disincentives for positive screens or engaging in inappropriate behaviors (eg, using the parent's car without permission). Concurrently, parents are taught to conduct random urine drug screens (instant). In addition, parents are trained to complete functional analyses that identify the emerging adult's poly-SU triggers. Triggers are targeted via self-management planning and drug refusal skill training tailored to each emerging adult. Before ending, plans will be made with the family to sustain recovery and improvements in other behaviors.

The contingency contract in CM-EA follows a specified protocol. First, with guidance from the parent coach, the parent will generate a menu of rewards with their emerging adult that can effectively compete with the emerging adult's poly-SU. The coach helps ensure that there is a balance between natural incentives and tangible items. Rewards are monetary (eg, gift cards) and nonmonetary (eg, privileges) items that the emerging adult determines as desirable. Prizes are sorted (based on cost or desirability) into small, medium, large, and jumbo. Our team has experience creating effective, tailored reward menus for families from various financial backgrounds. CM-EA uses a "fishbowl" technique [65]. When drug screens are negative for the targeted substances, emerging adults have the opportunity to draw from colored "chips" in a "fishbowl" (cloth bag; Figure 1), with different colors indicating different levels of prizes. There is escalating reinforcement such that the number of draws increases with maintained abstinence from targeted substances (eg, on the eighth consecutive negative screen, the emerging adult makes 8 draws). A positive drug screen on the targeted substances resets draws to 1. Emerging adults can also earn coupons, which can be used toward earning extra draws for completing clearly defined behaviors advancing their vocational or educational or other developmentally appropriate goals (eg, writing a resume). Consistent with behavioral principles, contingencies are provided as temporally close to the behavior

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as possible. These procedures have been used with success by the research team. This method was chosen to enhance the sustainability of CM-EA within home-based and rural settings. For example, the fishbowl method is much less expensive and reduces the need for frequent purchase of rewards [75]. This method was also viewed favorably by providers delivering CM-EA in our recently completed pilot study for emerging adults on probation (grant R01DA041434-03S1).

Figure 1. Contingency management for emerging adults "fishbowl."

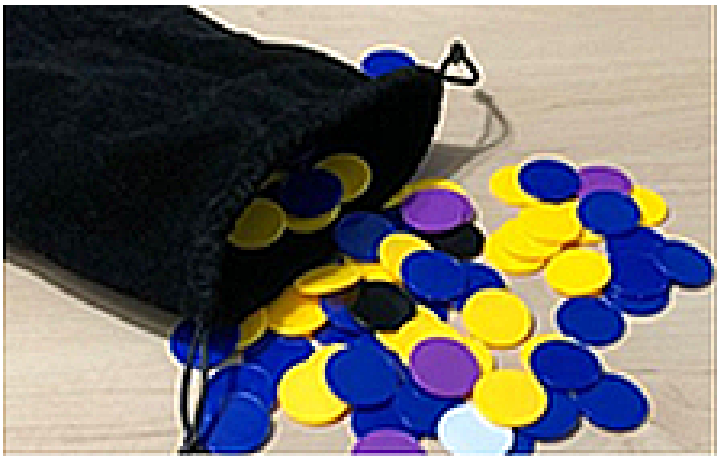

PRSS Condition

Overview

For approximately 1 hour per week, each emerging adult assigned to either of the 2 PRSS conditions (in-person PRSS only or in-person PRSS with the parent CM-EA component) will work with a state-certified peer worker. Depending on agency protocols, peer workers will have the option to be provided a US $100 stipend per month per emerging adult to engage in recreational activities (as is typical in community mentoring programs). Peer workers will deliver standard services common to their certification, which begin by identifying clients' needs in key domains (eg, transportation, employment, and school or General Educational Development enrollment). After needs are identified, the peer workers address them through informational resources and community linkages. In addition, peer workers regularly engage in substance-free recreational activities with clients, during which they offer advice, hope, and empowerment to encourage steps toward recovery from SU. When desired, peer workers also link clients to a broader recovery peer community, often via facilitation of social events (eg, game night, frisbee golf, and potluck dinner) with individuals with similar SU reduction goals. In addition, peer workers will be provided materials and encouraged to spend time during their weekly meetings dedicated to increasing recovery capital via skill building related to vocational or educational advancement.

Peer Worker Training and Supervision

Peer workers will be trained by the research team to use the workbook *Targeting Employment for Emerging Adults: A Toolkit for Mental Health Providers* [76]. The workbook was developed and examined in previous research and provides a resource for providers to support emerging adult skill building [76]. It targets both educational and vocational training or attainment—the inclusion of both is vital to working with emerging adults. This workbook was selected for the proposed project because of its (1) specific focus on emerging adults, (2) portability and ease of use, (3) structure, and (4) ability to personalize to a given emerging adult. The workbook covers a range of topics relevant to vocational or educational skills. There is a combination of instructions for providers, informational handouts for emerging adults, and worksheets to support progress. While it was designed for an outpatient mental health setting, it can be easily used in other settings, and the training has been developed with input from individuals with lived experience in SU recovery (grant K23DA048161). Peer workers will receive supervision from the research team at least twice a month that may include reviewing adherence tools adapted as part of the project.

Protocol

Aim 1: Adaptation of Training Protocols

Overview

Members of our team have trained various providers (clinicians, probation officers, and students) in different versions of CM (including CM-EA) and other SU services over the past 15 years. As a result, we have established multifaceted training protocols to train and support diverse providers to deliver SU services with high adherence. To ensure that the materials fit the scope of the current project, we will adapt our training protocols to allow for virtual training and support of *Launch* for both the parent coach and peer workers.

A parent coach will train the parents to deliver CM-EA. However, for training the parent coach, a web-based CM-EA training support system will be used [77]. Developed by coinvestigator AJS with support from principal investigator TKD and modified from previous web-based CM training systems, it includes modules corresponding to each CM-EA component. Within each module, sections describe CM steps, give troubleshooting tips, and provide sample scripts and video examples. Each module can be completed in 1 to 2 web-based sessions depending on the activities involved (eg, some sessions include homework), and it takes the average user <8 hours to complete all modules. The website's navigation guides users

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through the modules, and a passing score of 80% is required on a multiple-choice test to access the next module. Trainees failing to pass a test are able to rereview the module or access support from a CM-EA expert and can take the posttests to achieve a passing score. Furthermore, the team will adapt written training materials and develop a 3-day virtual CM-EA training for the parent coach, which will include *Launch* services review, role-playing, and other active training exercises that the team has successfully used across numerous research studies involving CM.

Similar web-based training protocols will be adapted with input from individuals with lived experience with SU recovery for peer workers to deliver the in-person emerging adult PRSS components. These are more straightforward because peer workers will already be trained and certified.

Adaptation of Adherence Instruments

The research team has developed adherence measurement tools for the delivery of CM-EA led by coinvestigator JEC as part of other related projects. The original tools were developed using methods from the Standards for Educational and Psychological Testing and Item Response Theory–based methods defined by Wilson [78]. However, the existing tools will need to be reviewed and adapted.

First, our existing observational tool for measuring CM-EA adherence among clinicians and paraprofessionals working with emerging adults will be adapted to measure CM-EA adherence among coaches working with parents. Coaches will audio record all CM-EA coaching sessions to facilitate our assessment of their adherence. Coaches will also complete a modified session checklist where they report the CM-EA skills that the parent reported implementing at home in their coaching session. Second, our observational vocational or educational skill-building adherence tool developed in a previous project (grant K23DA04861) will be reviewed to ensure that it remains relevant to this project. A self-report adherence measure will be adapted from the same project (grant K23DA04861) to capture PRSS interactions that occur when audio recording is not optimal (eg, during recreational activities such as playing basketball or frisbee). The peer workers will complete a self-report measure of adherence for every emerging adult interaction and audio record sessions as appropriate. The participating parent coach and peer workers will be asked to provide feedback on these forms as part of their qualitative interviews.

Members of the research team will code the coach and PRSS session tapes and train an additional coder in using the adapted adherence instruments to obtain observational ratings on whether the different *Launch* components were delivered with adherence. Training for coders will begin with review of the coding tools and group practice ratings. Next, coders will independently rate session tapes and review for consensus. From this process, the coding instrument and manual will be refined as needed. This process will continue until coder ratings achieve acceptable consistency (≥80% agreement). As feasibility is a major aim of this pilot project, all submitted tapes will be coded. Booster trainings will monitor and address coder drift identified through discrepancies in double coding. The steps for developing this observational coding system and training coders follow procedures that the investigators have used numerous times for adherence measurement [79] and have been a focus of a project led by coinvestigator JEC (grant MH097000). These adherence tools will also be used during supervision to monitor adherence to each protocol and provide feedback or booster trainings.

Aim 2

After recruitment, interested participants will meet with a research team member to complete informed consent. Then, emerging adults will complete an approximately 1-hour virtual baseline interview. On the basis of the experience of the research team, 1-hour assessments rarely present a significant response burden, but the research team will use breaks to attenuate circumstances that threaten the validity of the assessments. A stratified permuted block randomization design [80] will be used to randomize the families to one of three treatment conditions: (1) web-based CM-EA parent coaching only, (2) in-person PRSS for the emerging adult only, or (3) both web-based CM-EA parent coaching and in-person PRSS for the emerging adult. Families will receive *Launch* services for approximately 5 months. All activities with the parents will be web-based, assessments with emerging adults will be web-based, and PRSS sessions with the emerging adults will be in person. The parent coach and peer workers will track session attendance. At 6 months after the baseline, emerging adults will complete a virtual, 1-hour follow-up assessment, and parents will complete an approximately 1-hour qualitative interview (see the *Measures* section) that will also include a limited number of brief quantitative questionnaires. At the end of their participation in the project, the parent coach and peer workers will complete an approximately 1-hour qualitative interview about *Launch* services (see the *Measures* section).

Aim 3

We plan to conduct a series of interviews with approximately 10 pertinent payers or providers of recovery services to ensure that we have a complete list of data to be collected in a follow-up large-scale trial. The research team will use access to their national community boards as part of other funded work (grant R24DA051950) and community partners to interview administrators of provider agencies of SU recovery services as well as representatives from insurance providers or behavioral health care systems. An explicit goal of these interviews will be gathering information on types of evidence needed to promote future funding of a service package such as *Launch* or the components within *Launch*. Information gathered from these interviews will allow us to include appropriate measures in the resulting large-scale study as well as help inform a future economic evaluation aim. At the completion of the interviews with payers or providers, we will have a list of key outcomes to include in the follow-up large-scale study proposal informed by those who will be funding and providing the services in the future.

Measures

Emerging Adult Measures

Primary outcomes for emerging adults include the emerging adults' perceptions of *Launch* acceptability, appropriateness,

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and feasibility; the emerging adults' satisfaction with *Launch* services; and a qualitative interview. Emerging adult perceptions of implementation-related outcomes will be measured using the 3 implementation outcome measures validated in the study by Weiner et al [81]: the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and Feasibility of Intervention Measure, which together total 12 items scored on a Likert-type scale taking respondents approximately 4 minutes to complete. This combined measure has demonstrated good internal consistency (Cronbach α=0.87 to 0.89) and test-retest reliability (0.73 to 0.88) [81]. Satisfaction with *Launch* services will be measured using the 8-item Client Satisfaction Questionnaire (CSQ-8) [82], adapted to reflect receipt of *Launch* services. The CSQ-8 is an 8-item measure using a 4-point Likert-type scale, with higher scores indicating greater satisfaction, and takes approximately 3 minutes to complete [82]. Finally, the emerging adult qualitative interview (approximately 30 to 60 minutes) will delve deeper into emerging adult perceptions of the acceptability, appropriateness, and feasibility of *Launch* as well as the research protocol and ask emerging adults to describe the impact of receiving *Launch* services and any impacts (positive or negative) on the parent–emerging adult relationship. All primary outcomes for emerging adults will be measured at the end of the study period (6 months after baseline).

Secondary outcomes for emerging adults include the emerging adults' relationships with their peer workers if receiving PRSS, the emerging adults' relationship with their parents, SU, emerging adult PRSS session attendance (for those randomized to this condition), quality of life, nonstudy medical service use, self-efficacy, recovery capital, history of medications, and research values. Emerging adults' relationships with their peer workers and their parents will be measured using adapted versions of the short form of the Dual-Role Relationship Inventory [83], a validated measure that assesses whether provider-client relationships are perceived as firm, fair, and caring by participants; consists of 9 items scored on a 7-point Likert-type scale ranging from *never* (1) to *always* (7); and takes approximately 3 minutes to complete. SU among emerging adult participants will be measured at baseline and at follow-up using self-reported measures only. The *DSM-V* Substance Use Checklist [73] measures past–12-month SU as a *yes* or *no* response to 8 substance categories—alcohol, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, or anxiolytics, stimulants, and an "other" category—but does not ask about frequency. For each substance type, 11 yes or no items measure *DSM-V* SU disorder symptom endorsement, and each question set takes approximately 2 minutes to complete (ie, if an emerging adult endorses 2 substances, then the total *DSM-V* checklist time will be approximately 4 minutes). Endorsing ≥2 symptom items qualifies as an SU disorder for that specific substance, with 2 to 3 symptoms constituting a mild SU disorder, 4 or 5 symptoms constituting a moderate SU disorder, and ≥6 symptoms endorsed constituting a severe SU disorder. A second SU measure from the Global Appraisal of Individual Needs [84] and the Justice Community Opioid Innovation Network (JCOIN) Core Measures [85] will be used to ask about frequency (number of days) of using different substances in the past 30 days as well as number of abstinent days, past–30-day overdose or receipt of naloxone, and symptoms of SU disorder. The Global Appraisal of Individual Needs SU measure consists of 53 closed-ended items and 1 open-text item and takes approximately 10 minutes to complete. Finally, the Polysubstance Assessment Tool [86,87] will be used to assess poly-SU in the past 30 days and main motivation for use. This measure uses branching logic, consists of 2 ranking items and 6 closed-ended items (checklists of substances used and combinations of use), and takes approximately 5 minutes to complete. PRSS session attendance will be tracked by the peer worker. Quality of life will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS)–29+2 Profile version 2.1 [88], a 31-item measure of quality of life across 7 domains: physical function, anxiety, depression, fatigue, sleep disturbance, social participation, pain interference, pain intensity, and cognitive function. The 31 items are multiple choice and scored on a 5-point Likert-type scale for all items except for a 10-point general pain level ranking item and take approximately 10 minutes to complete. Importantly, the PROMIS-29+2 Profile version 2.1 can be used with a scoring method called PROMIS-Preference (PROPr) to calculate a utility weight, which is key to economic evaluation methods such as cost-effectiveness analysis, thereby ensuring that a future large-scale study of *Launch* can integrate an economic evaluation aim. This version of the PROMIS is used as part of the JCOIN Core Measures [85], as is the measure of nonstudy medical service use.

Self-efficacy will be measured using the Brief Abstinence Self-Efficacy Scale [89] at baseline and the 6-month follow-up. The Brief Abstinence Self-Efficacy Scale consists of 11 items scored on a 5-point Likert-type scale [89] and takes approximately 4 minutes to complete. Recovery capital will be measured using an emerging adult–specific measure under development by members of the study team and collaborators at baseline and the 6-month follow-up. The emerging adult recovery capital measure uses 49 items scored on a 4-point Likert-type scale, with higher values meaning higher recovery capital, and also includes 3 preliminary short-answer questions, totaling 52 items and approximately 17 minutes to complete. Medication history will also be drawn from the JCOIN Core Measures and ask about current medication use only as well as lifetime prescription of a medical marijuana card and will be asked at both baseline and follow-up. The medication history measure consists of 5 items and takes approximately 2 minutes to complete. The Emerging Adult Research Values Exercise [90] was developed by members of the study team and collaborators and will be administered at the end of the baseline interview only. The emerging adult will be asked about why they were willing to participate in the research, choosing from as many of the possible response options available as they wish to select. Response options include reasons such as "to get the study incentives" and "to help other people like me." Participants can then choose their top 3 reasons from among the reasons they selected. As the final step of the research values exercise, the emerging adult will be asked how likely they are to meet with the research team for follow-up and whether the researchers can do anything to increase that likelihood.

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Demographics will also be collected at baseline, with some items that are changeable (eg, housing, employment, or educational status) repeated at the 6-month follow-up. The demographics measure used has been adapted from Brown [91] and is from the JCOIN Core Measures [85], with updated demographic response options from the Justice and Emerging Adult Populations Initiative's resource on using destigmatizing language [92]. The final demographic instrument consists of 33 items and takes approximately 6 minutes to complete.

Parent Measures

The CM-EA coach will track parent session attendance. All parent-reported measures will be collected at the 6-month follow-up. At that time, parents will complete a demographic interview similar to the one completed by the emerging adults as well as a parent version of the CSQ-8 [82] and the 3 implementation measures [81]. Finally, parents will also be engaged in a qualitative interview delving further into the acceptability, appropriateness, and feasibility of *Launch* services and the research protocol; the impact of CM-EA coaching and PRSS on parents and their emerging adult children; and any impacts on the parent-child relationship.

Recruitment and Retention Measures

The research team will track all potential participant research contacts of those interested in participating in the pilot project and will track all assessment completion statuses.

Peer Worker and Parent CM-EA Coach Measures

Peer workers delivering PRSS and the parent CM-EA coach will complete checklists of services delivered after each session and will engage in a follow-up qualitative interview at the end of their participation in the project. The peer workers will complete a checklist after each session to indicate which topics they covered with their emerging adult client. The CM-EA parent coach will complete a checklist after each session with each parent noting each CM-EA skill that the parent indicated using since the last time they met with the coach. Qualitative interviews with both types of participants will delve deeper into implementation-related concepts, perceived or actual impacts on emerging adults or parents, and other suggestions for service improvement.

Payers and Providers

Finally, payer and provider participants will engage in qualitative individual interviews throughout the study. Payers and providers will be asked about what kinds of participant-level outcomes or economic-related information they would want to know about as the result of a future large-scale study. They will also be asked to help inform the selection of appropriate comparators for the cost-effectiveness analysis as well as the selection of willingness-to-pay thresholds. Analysis procedures for all qualitative data are described in the following subsection.

Analysis Plan

Aim 1

Aim 1 includes 2 groups of analyses. The first group is a preliminary psychometric evaluation of the adapted instruments measuring the adherence of (1) coaches training parents in the use of CM-EA and (2) standard PRSS plus vocational or educational skill building. The number of families is modest, but each will have numerous repeated measurements. The second group of analyses will determine whether coaches can train parents to deliver CM-EA and whether peer workers can deliver the combined services (ie, PRSS plus vocational or educational skill building). All data will be nested, with repeated measurements (level 1) nested within families (level 2), but the actual number of measurements will vary for each family and type of adherence. Nesting will be addressed using mixed-effects regression models. To evaluate parent training, the model will include a linear time term, which will estimate the initial level of coach adherence and test for change over time, and this will be interpreted relative to theory-based standards for acceptable training. To evaluate the delivery of PRSS plus vocational or educational skill building services, the same type of model will be performed. Combined, the results will determine whether the proposed protocols lead to the expected levels of adherence for coaches as well as peer workers, and low adherence scores will be investigated during the proposed qualitative interviews.

Aim 2: Feasibility of Launch Recruitment, Assessment, and Retention

Overview

The feasibility of recruitment will be evaluated by comparing the proportion of families recruited to the target rate of 75%, as well as comparison to demographics of families who decline participation after completing screening (eg, emerging adult biological sex, race, and ethnicity). The feasibility of the assessment design and retention of parents and their emerging adult children will be evaluated using a 2-level multivariate and repeated measures model, with completion status at repeated assessment occasions (level 1; two assessments per family) nested within families (level 2; 48 families). The model estimates the overall log-odds of assessment completion, and subsequent models will test for differences by condition (parent CM-EA only vs standard PRSS plus vocational or educational skill building vs combined services), demographics (eg, emerging adult biological sex), and emerging adult poly-SU profile.

Feasibility of Launch Components

To assess the feasibility of parents' abilities to deliver CM-EA to their emerging adult children, a parent coach session checklist will be developed. The checklist will be completed at the end of each session. Here, the parent coach will report on what CM-EA components the parents reported attempting since the last session (eg, creating a reward menu with the emerging adult, providing rewards, or discussing self-management plans for poly-SU triggers).

The statistical analyses will focus on parents' delivery of CM-EA components to their emerging adult children. The models will be formulated as described for aim 1, with repeated measurements of parent adherence to CM-EA (level 1) nested within families (level 2) [93]. An initial unconditional model will be used to estimate the proportion of variance in CM-EA delivery that is attributable to sessions and parents. This will be followed by a model to estimate the initial level and rate of

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change in CM-EA adherence. Of note, if the initial measurement models indicate that scoring should occur for the course of *Launch* (ie, at the level of parents) rather than session by session, the descriptive parent-level average scores will be evaluated relative to predefined thresholds for acceptable delivery of CM-EA components. The adherence models will be used to determine whether parent coaching of CM-EA leads to actual implementation of CM-EA in the participating families' households. Any trends observed in the data will be incorporated into the qualitative interviews detailed in the following sections (eg, select CM-EA components not being implemented at high levels).

Acceptability of Launch Components

Descriptive data analyses will assess the average number of sessions attended, cancelled, no-showed, and rescheduled for parents with the parent coach and for emerging adults with PRSS. Similarly, data analyses will assess the average and item-level client satisfaction ratings of parents and emerging adults with *Launch* services. The attendance and CSQ-8 scores will be used to determine the acceptability of *Launch* services. Themes from the qualitative interviews will aid in the interpretation of the quantitative data.

Secondary Outcomes

While we will not have sufficient power to perform any statistical analyses of secondary outcomes (eg, SU and self-efficacy), descriptive statistics of all emerging adult secondary outcomes will be reported to aid in power analyses for a future large-scale study of *Launch*.

Qualitative Data Analysis

All interviews will be digitally taped and then transcribed verbatim and deidentified. The deidentified transcripts will then be uploaded to the most updated version of Dedoose (SocioCultural Research Consultants) [94] for qualitative analyses using inductive coding [95]. One member of the research team will perform an initial round of open coding of the transcripts, followed by coding common themes that emerge across transcripts using axial and pattern coding [95]. This coding pattern will then be reviewed by 1 to 2 other research team members to iteratively interpret the coded data. Finally, research team members involved in coding will review a summary of the qualitative findings to reach a consensus on their accuracy. These findings will be used to further adapt and improve the *Launch* service package via an iterative process from the perspectives of the parent coach, peer workers, and participating emerging adults and parents.

Aim 3

The payer and provider interviews are less open ended than the interviews of other participants; thus, some responses will produce lists rather than thematic findings (eg, lists of potential outcomes of interest). However, when appropriate, the qualitative methods described for aim 2 will be used to analyze the interview data with payers and providers.

Sample Size and Power Considerations

Because this study is *developmental work*, the sample size (n=48 families) was driven by appropriateness for pilot study objectives rather than by statistical power computations for formal hypothesis testing [96,97]. Pilot studies play an important role in providing information for the planning and justification of future large-scale trials (eg, for feasibility of service protocols and refinement of recruitment and assessment strategies) [98]. The sample size conforms to guidelines for pilot studies (n≥12 per group) [99,100] and provides representativeness of a diversity of participant characteristics for examining feasibility, data collection procedures, and *Launch* service acceptability. However, this pilot will inform power analyses and sample size planning for a subsequent larger effectiveness trial. Because of this, it is important for the measurement and research design to support accurate estimates of the focal model parameters—thus, there are important considerations regarding the precision of estimated effects. For the measurement models proposed, the sample is sufficient for stable and precise estimates of family and item parameters and SEs. Specifically, sample sizes in the range of 16 to 36 are sufficient for 95% confidence that the estimated person or item calibrations are stable within –1 logit to +1 logit [101]. It is also worth noting that this estimate is conservative because repeated measurements of adherence will provide additional data for evaluating the psychometric performance of the proposed instruments. For the proposed mixed-effects regression models, the sample of 48 families is sufficient for accurate estimates of the focal model parameters, in particular fixed-effects estimates for between-group differences and change over time [102]. Although variance components could be prone to bias, this information is less important for planning the subsequent larger trial as the power estimates can straightforwardly penalize for a range of nesting effects.

For the qualitative interviews with payers and providers of recovery support services, the estimated 10-participant sample size falls within the parameters of 6 to 12 interviews to determine saturation and variability [103]. The credibility of the results will be promoted by ensuring that the investigators have the required knowledge and skills to perform their roles of interviewing and coding, requiring the interviewer to maintain field notes that will be stored with the data, including a peer review process of coding, and using a semistructured interview guide that includes prompts that allow for elaboration of answers and the chance to ask for more information as needed, allowing for both focus and adjustability during interviews [104]. Transferability of the qualitative results will be promoted by using purposeful sampling and reaching data saturation, when no new codes are identified in the transcripts and the research team agrees that theoretical saturation has been reached through the discussion of coding and identifying any variation in key concepts [16].

Results

We are currently engaging recovery community organizations as potential recruitment sites for emerging adult and parent participants, as well as for participating peer workers to take the vocational or educational toolkit training and deliver *Launch* services. We have also engaged a parent coach and initiated training. This project was funded (grant R34DA057639) in August 2023 and is currently expected to end in September

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2025. We anticipate publication of the results of this study in late 2026. Participants are expected to begin enrolling in June 2024.

Discussion

Expected Findings

We anticipate that the *Launch* research protocol and both services (virtual CM-EA parent coaching and peer workers specially trained in vocational or educational goal setting) will be reported as acceptable, appropriate, and feasible and that feedback for improving the research and service models will be qualitatively provided, which will be incorporated into a future larger-scale study, leading to further reports of acceptability, appropriateness, and feasibility in follow-up projects. Results from this project will be disseminated via peer-reviewed manuscripts and presentations at professional conferences as well as to interested research participants. In addition, data from this study will be stored in the Helping to End Addiction Long-Term Data Repository after the completion of analyses as required by the funding agency for further investigation.

A strength of *Launch* is that it is explicitly tailored for the state of recovery capital with which emerging adults present, and this pilot allows for a preliminary exploration of *Launch*'s acceptability for targeting emerging adults' recovery capital domains [14,29,105-108]. *Launch* leverages existing resources in rural areas—parents and peer workers—and examines whether CM-EA can be delivered virtually to parents and by paraprofessional coaches versus clinicians who are in short supply in rural communities [109]. Formative research on CM has involved delivery by paraprofessionals, and this approach has been deemed both feasible and efficacious [65]. The use of peer workers had a similar motivation as they are also paraprofessionals and a local workforce found in most regions of the United States [110].

Limitations

This is a relatively small pilot study with only 48 emerging adult participants and their parents; therefore, there will be known limitations with generalizability and other restrictions evident with small sample sizes. However, given that this is a study focused on assessing the feasibility, acceptability, and appropriateness of research and service protocols in preparation for a future large-scale study of *Launch* effectiveness, the size is appropriate to meet those goals.

A second limitation is in the selection bias introduced by the requirement of having a "parent" involved. Although this study allows for a loose definition of *parent* and can include any parental figure offering financial support to the emerging adult even if not related to them, we recognize that many emerging adults with SU disorder will not have such a figure in their lives. Given the challenges to interpersonal relationships that SU disorder can present, we recognize that *Launch* will only benefit a subset of emerging adults who have maintained some connection with a parent figure, but this remains a substantial segment of the population in need.

Conclusions

In summary, emerging adults with SU problems nearly always present with poly-SU and are an underserved population who (1) make up a large share of those seen in community-based care, (2) are at the highest risk of adverse outcomes, and (3) produce the most significant societal costs. At the same time, little high-quality research has been conducted with this group, especially interventions that attend to emerging adults' developmental needs and can be delivered in rural communities. *Launch* uses an innovative combination of existing strategies to generate better outcomes for these emerging adults while still being highly scalable. Of importance, rather than taking a one-size-fits-all approach, *Launch* is fundamentally personalized to the unique needs of each emerging adult. For example, the incentives for reduced SU and behavioral interventions used in CM for emerging adults are tailored to each client and family's individual circumstances and SU profile. In addition, supports provided by peer workers are naturally matched to the types of help that each emerging adult requests. Furthermore, we have taken careful steps to ensure that *Launch* is amenable to widespread delivery, especially in rural areas through the use of web-based coaching and leveraging both parents and paraprofessional coaches rather than clinicians. A virtual platform eliminates the need for families to travel to clinic sites, particularly relevant for individuals in remote rural and frontier areas. Delivery of CM-EA by paraprofessionals also minimizes costs, making uptake more feasible in lower-resourced settings. Thus, their key role within *Launch* seems ready-made for national scalability. Finally, this pilot project engages funders of poly-SU services to ensure that what we pursue in a follow-up large-scale study provides the data necessary to drive decision-making and uptake.

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Data Availability

The deidentified data sets for participant attendance, client satisfaction, and emerging adult outcomes generated during and analyzed during this study will be available in the Helping to End Addiction Long-Term Data Repository after the completion of analyses.

Conflicts of Interest

AJS is a co-owner of Arena Evidence-Based Programs, which provides web-based training and quality assurance for contingency management. There is a management plan in place to ensure that this conflict does not jeopardize the objectivity of this research. She will not collect or analyze data for this study. No other authors have any conflicts to report.

Multimedia Appendix 1
Consent forms for all participant categories.
[PDF File (Adobe PDF File), 244 KB - resprot_v13i1e60671_app1.pdf]

Multimedia Appendix 2
Peer-review report by the National Institute on Drug Abuse Special Emphasis Panel (NIDA) - HEAL Initiative: Understanding Polysubstance Use and Improving Service Delivery to Address Polysubstance Use (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 252 KB - resprot_v13i1e60671_app2.pdf]

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Abbreviations

CM: contingency management
CM-EA: contingency management for emerging adults
CSQ-8: 8-item Client Satisfaction Questionnaire
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
JCOIN: Justice Community Opioid Innovation Network
poly-SU: polysubstance use
PROMIS: Patient-Reported Outcomes Measurement Information System
PRSS: peer recovery support services
SU: substance use

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Proposal

Development and Evaluation of a Web-Based Platform for Personalized Educational and Professional Assistance for Dementia Caregivers: Proposal for a Mixed Methods Study

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Abstract

Background: Alzheimer disease (AD) and AD-related dementia are prevalent concerns for aging populations. With a growing older adult population living in the United States, the number of people living with dementia is expected to grow, posing significant challenges for informal caregivers. The mental and physical burdens associated with caregiving highlight the importance of developing novel and effective resources to support caregivers. However, technology solutions designed to address their needs often face low adoption rates due to usability issues and a lack of contextual relevance. This study focuses on developing a web-based platform providing financial and legal planning information and education for dementia caregivers and evaluating the platform's usability and adoptability.

Objective: The goal of this project is to create a web-based platform that connects caregivers with personalized and easily accessible resources. This project involves industrial, academic, and community partners and focuses on two primary aims: (1) developing a digital platform using a Dementia Care Personalization Algorithm and assessing feasibility in a pilot group of caregivers, and (2) evaluating the acceptability and usability of the digital platform across different racial or ethnic populations. This work will aid in the development of technology-based interventions to reduce caregiver burden.

Methods: The phase I study follows an iterative Design Thinking approach, involving at least 25 dementia caregivers as a user feedback panel to assess the platform's functionality, aesthetics, information, and overall quality using the adapted Mobile Application Rating Scale. Phase II is a usability study with 300 dementia caregivers in Texas (100 African American, 100 Hispanic or Latinx, and 100 non-Hispanic White). Participants will use the digital platform for about 4 weeks and evaluate its usefulness and ease of use through the Technology Acceptance Survey.

Results: The study received funding from the National Institute on Aging on September 3, 2021. Ethical approval for phase I was obtained from the Texas A&M University Institutional Review Board on December 8, 2021, with data collection starting on January 1, 2022, and concluding on May 31, 2022. Phase I results were published on September 5, 2023, and April 17, 2024, respectively. On June 21, 2023, ethical approval for human subjects for phase II was granted, and participant recruitment began on July 1, 2023.

Conclusions: Upon completing these aims, we expect to deliver a widely accessible digital platform tailored to assist dementia caregivers with financial and legal challenges by connecting them to personalized, contextually relevant information and resources

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in Texas. If successful, we plan to work with caregiving organizations to scale and sustain the platform, addressing the needs of the growing population living with dementia.

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KEYWORDS

Alzheimer disease; dementia caregivers; digital platform; financial planning; legal planning; usability study; evaluation; older adults; caregiver support

Introduction

Background

Currently, 6.7 million Americans live with Alzheimer disease (AD) and AD-related dementia, a progressive and debilitating neurocognitive disease that leads to loss of memory, motor function, and other psychological symptoms [1]. With the growing aging population in the United States, the number of people living with dementia is projected to grow exponentially to 13.8 million by 2060 [1]. These trends indicate a growing public health crisis that requires multifaceted interventions. People living with dementia are primarily cared for by informal caregivers, typically spouses and adult children [2,3], with as many as 16 million Americans currently serving in this role [4]. These informal caregivers of people living with dementia often have a higher risk of developing depression, anxiety, social isolation, and physical problems due to the chronic stress and diverse burdens associated with caregiving [5,6]. In recent years, dementia caregivers are estimated to provide more than 18 billion hours annually with an estimated economic value of US $346 billion for their care services [1], and this informal care cost is projected to increase to US $2.2 trillion in 2060 [7].

A large part of the informal caregiver burden is related to various responsibilities in caregiving for people living with dementia, including management of the care recipient's financial, legal, and estate-related challenges [6,8]. Without adequate support, caregivers often struggle to find or use proper resources, making even simple tasks burdensome. Furthermore, these primary family caregivers often must balance the challenges of caregiving with other personal responsibilities, such as employment and family obligations [8,9]. Considering the significant financial burden associated with caregiving, role strain is further exacerbated when caregiving requires a full-time commitment. Six out of 10 family caregivers of people with dementia have reported significant work impacts ranging from reduction of work hours to early retirement due to their caregiving obligations, which disrupts their wages and employment and depletes their savings [6,10]. The varied progressive nature of dementia further compounds the complexity of care for people with dementia, increasing the psychological, physical, and financial factors of the caregiving burden [1,11].

The variation in caregiver burdens related to sociodemographic characteristics contributes to greater complications. Burdens are often exacerbated in ethnic and minority populations, who generally have higher rates of dementia but lower access to caregiving services and information [12,13]. In addition, ethnic minorities can experience complications when communicating with care professionals due to cultural or linguistic barriers [13]. These barriers can disproportionately affect nonnative English speakers, increasing the informal caregiver burden due to the greater experienced inaccessibility in support systems within the American health care system. Unique stressors have also been demonstrated in gender or sexual minority caregivers, further emphasizing the diversity of caregiving experiences and challenges within the United States [14]. Literature has shown that considering unique barriers or challenges in diverse demographics when developing support interventions increases their effectiveness in reducing caregiver burden [15].

Technological Interventions and Artificial Intelligence–Driven Digital Health

There are many professional caregiver assistance organizations that provide services to informal caregivers, including aging care law, financial services, respite care, in-home care, older adults living, and medical services [16]. Digital interventions present a promising tool for assisting caregivers in identifying relevant professional caregiver assistance organizations services. A myriad of digital interventions have been developed to aid caregivers of people with dementia in identifying these services, ranging from web-based training, educational forums, caregiving support groups, and videoconferencing [17-19]. However, the adoption rate of these technologies remains low outside of pilot studies. This low adoption rate can be attributed to factors such as poor usability and accessibility, information complexity, funding limitations, and lack of contextualized relevance [8,20-24]. This issue is especially pronounced among minority populations, such as African American and Hispanic or Latinx caregivers, where cultural differences and caregiving challenges are often not considered in the development and evaluation of technology-based interventions [25].

Factors influencing the implementation and adoption of technology-based interventions by informal caregivers include the expected or perceived value by users, the features of the technology, the characteristics of the caregivers, and the condition of dementia [26]. According to the Technology Acceptance Model (TAM), perceived usefulness and ease of use are the 2 most important factors in determining how likely users are to adopt or reject new technologies [27]. The features of developed technologies, such as physical appearance, simplicity, and usability, are crucial for caregiver adoption [26]. In addition, the continued adaptation of technology over time, as dementia progresses and as caregiving needs evolve, is noted as important [26]. Family caregivers come from various racial and ethnic groups, generations, occupations, financial situations,

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and educational and cultural backgrounds [6], and their characteristics and specialized care needs are widely mentioned as influencing factors for technology adoption [26].

Artificial intelligence (AI) can offer various benefits to developing interventions that help caregivers better understand and use information in real time, leading to a more personalized and effective decision-making process [28]. AI has the potential to improve perceived usefulness and ease of use by personalizing and simplifying complex information. For instance, AI-driven applications can often offer user-friendly interfaces and navigation, reducing the learning curve for caregivers who may not be technologically savvy and enhancing user experience. Moreover, AI can be used to create and deliver personalized dementia care suggestions, meeting the evolving needs of people with dementia and their caregivers [29].

Development of a Caregiving Support Platform

While there is increasing interest in technology interventions for dementia caregiving, limited literature has explored their effectiveness outside of research settings. Early involvement of caregivers, as emphasized in community participatory research and dissemination and implementation science, can enhance intervention adoptability and sustainability [18,30-32]. Our study seeks to address the paucity of research by exploring the efficacy of delivering caregiving resources and services in a technology-driven setting that considers individualized and cultural issues, in order to provide personalized, relevant, timely interventions to caregivers of people living with dementia.

To address this gap, our team developed a website-based platform designed to provide personalized caregiver support, including identification of caregiving resources related to older adults living arrangements, financial services, and legal services, as well as education related to dementia management and caregiving. In our web-based care planning tool, the Olera.care platform, we use our Dementia Care Personalization Algorithm (DCPA) based on logic decision trees and geolocation to provide caregivers of people living with dementia with a tailored guide on the aging care, older adults living, financial, and legal aspects of dementia caregiving (Olera.care). Studies have shown that such caregiving assistance is particularly effective in reducing caregiver burden [8]. To provide a technological intervention that would reduce the caregiving burden and address the needs of caregivers of people living with dementia, we developed a study with 2 phases centered in a community-engaged approach [33,34].

In further development cycles, various AI elements will be incorporated into our digital platform to take advantage of the rapidly advancing technology to increase acceptance and adoption. These AI elements include large language models (LLMs), a novel class of AI, and personalized care planning agents specialized in social assistance functions and resource connection. LLMs are a type of AI program that can recognize and interpret vast amounts of human language, texts, and data. Fine-tuning of LLMs through aging care domain-specific training can vastly improve algorithm accuracy and provide the most up-to-date information that is relevant for each user, enabling caregivers to navigate and use preexisting resources and information databases more effectively. The LLM's capacity is particularly valuable in navigating the complexity of dementia caregiving information, especially for individuals unfamiliar with financial and legal terminology, those unfamiliar with terminology related to aging services, or those who are uncertain about their specific needs. In addition, personalized care planning agents, capable of perceiving information and making decisions, can be integrated to guide users through various resources and instructions for navigating websites, significantly improving the user interface and user experience. These agents can be optimized using machine learning, specifically through reinforcement learning from human feedback that leverages domain expertise to train the AI to output more contextually relevant responses.

Evaluation Metrics and Framework

There are several metrics to evaluate the usability, ease of use, and acceptance of health care technological interventions, including the Mobile Application Rating Scale (MARS) and the TAM [35-37]. The MARS evaluates a digital product based on the functionality, design, information quality, engagement, and subjective quality of digital applications using a 5-point Likert scale survey [35]. The TAM evaluates the acceptability of a technology primarily based on its perceived usefulness and perceived ease of use among users [36,37]. Perceived usefulness refers to the degree to which a person believes that using a particular system can allow them to work more quickly, fulfill its intended purpose, increase productivity, enhance effectiveness, and make the job easier, with responses ranging from "strongly disagree" to "strongly agree" [38]. Similarly, perceived ease of use indicates the degree to which a person believes that the system is easy to learn, controllable, clear and understandable, flexible, easy to become skillful, and easy to use [38]. According to the TAM, perceived usefulness and ease of use are critical factors influencing the adoption or rejection of new technologies, and it has been used to determine the likelihood of dementia caregivers adopting digital technology interventions [39]; therefore, it is particularly suited for this evaluation study.

Study Objectives

This study has 2 phases to develop, evaluate, and refine the Olera.care web-based platform. Phase I aims to develop the Olera.care platform, identify the caregiving challenges and needs of informal caregivers, and pilot-test the performance of the platform among a group of dementia caregivers. Phase II aims to understand the perceived usefulness and ease of use of the Olera.care platform among 3 different sociodemographic groups of informal caregivers of people living with dementia: African American, Hispanic or Latinx, and non-Hispanic White American.

Methods

Study Overview

The study consists of 2 phases of platform development and evaluation (Textbox 1). Phase I of the study involves identifying caregiving challenges and needs, developing the Olera.care web-based platform, and pilot-testing the usability of the platform in a group of dementia caregivers. Phase II aims to

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evaluate the Olera.care platform among 3 of the largest racial and ethnic groups in Texas and iteratively develop the Olera.care platform. Human subjects research was critiqued by the National Institutes of Health reviewers with key comments (Multimedia Appendix 1) addressed including clarifying risks and benefits for human participants in informed consents, along with privacy protection protocols.

Textbox 1. Study overview

Phase I: Platform development and pilot test

Development of platform (Build Stage)

- Task 1: Compile care resources and educational materials
- Task 2: Build a logic decision tree for personalized recommendations
- Task 3: Design user questionnaire to collect user characteristics and develop prototypes
- Task 4: Develop a web-based application

Pilot testing of the platform in caregivers (n=30)

- Qualitative research: Identify caregiving challenges and needs for the platform using one-on-one interviews with caregivers
- Quantitative research: Collect user characteristics and preliminarily evaluate the platform using modified Mobile Application Rating Scale

Phase II: Iterative platform development and evaluation

Iterative development of the platform

- Expand care resources database outside of Texas
- Update educational materials of Alzheimer disease and Alzheimer disease–related dementia
- Integrate phase I feedback to platform features

Usability study across different racial or ethnic groups (n=300)

- Develop a comprehensive evaluation survey using the technology acceptance model
- Enroll and instruct caregivers to complete tasks:
  1. Generate a personalized caregiving checklist
  2. Identify and save 3 relevant resources to “favorite” list
  3. Register for “recommendation of the Day” and complete technology acceptance survey (TAS)
  4. Four-week interaction with the platform followed by a second completion of the TAS
- Evaluate perceived usefulness and ease of use of the platform across caregiver characteristics

Platform Development

The development of the platform (Olera.care) adopts a build-measure-learn framework to prioritize the needs and preferences of caregivers for people living with dementia, using the Design Thinking product design methodology [40]. This iterative development process consists of three major steps: (1) prototypes will be developed to address preidentified user needs [Build Stage], (2) product usability will be tested [Measure Stage], and (3) key lessons will be identified for changes in next product iteration [Learn Stage]. The platform uses user feedback and a self-improving DCPA to provide caregivers with tailored educational information on the legal, financial, and estate planning aspects of dementia caregiving, as well as details on relevant local care and support options. DCPA considers care recipients’ stage of disease, financial circumstances, and care preferences to create unique recommendations. As a result, when the platform is in use, information is presented in a personalized and user-friendly manner that enhances the experience of caregivers when searching online for Alzheimer disease and AD-related dementia (AD/ADRD) support and reduces time spent sorting through general search engine results. We are improving the DCPA algorithm by leveraging LLMs and personalized AI agents. These AI agents will enhance our ability to provide real-time support, guidance, and information to caregivers to find dementia care services. By learning from caregivers’ interactions with Olera.care, these AI agents will continuously improve in delivering personalized and contextually relevant assistance.

The platform is developed to be a free web-based service to assist caregivers in connecting them with educational and professional assistance. The educational materials (Figures 1 and 2) are created in collaboration with subject matter experts from local Area Agencies on Aging and Texas A&M University Center for Community Health and Aging. In addition, the National Institute on Aging, the American Association of Retired Persons, and the Texas Alzheimer’s Research and Care Consortium offer detailed informational materials on the legal and financial considerations for our targeted caregiver groups, which we frequently reference. Information on local care (ie, non–medical home care, assisted living, and nursing home)

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options (Figure 3) is gathered from public knowledge bases such as websites of Medicare and the websites of local Area Agencies on Aging (eg, Brazos Valley Area Agency on Aging, Harris County Area Agency on Aging, and Area Agency on Aging of the Capital Area). The primary objective of this step is to compile a comprehensive library of information on the functional, legal, financial, and estate planning aspects of AD/ADRD caregiving, along with a detailed list of care facilities in Texas.

The educational content gathered was organized after compilation. This process involved dividing the information into clear, manageable segments and classifying each segment into one of three categories: (1) legal, financial, or other services; (2) home care; and (3) senior communities. Once categorized, a logical decision tree was created to match each piece of information with specific combinations of caregiver characteristics provided by the user. The algorithm for this process was developed using Python (Python Software Foundation) due to its straightforward syntax, extensive open-source libraries, and capability for efficient data manipulation [41]. In the final website-based application, caregiver characteristics will serve as input criteria, including factors such as the dementia stage of the care recipient, the caregiver's knowledge and skills, the availability of external resources, the care recipient's insurance status, financial capacity for care, and family support presence. These criteria will be collected when users create their accounts for the first time, determining the personalized information and recommendations from each of the 3 categories that will be presented to the caregiver. The logic decision tree was ultimately converted into a user-friendly website-based platform for caregivers to access customized educational materials (eg, videos, articles) and relevant care options (eg, at-home care, older adults living arrangements, paying for care options, caregiver support). Google's Firebase is employed for backend programming to enable seamless data synchronization, user authentication, and secure data management. The front-end user interface is built using Google's Flutter software development kit, facilitating cross-platform development for Android, iOS, and web applications from a single codebase. This approach streamlines the development process and reduces long-term maintenance costs.

Figure 1. Video educational materials on the Olera.care platform.

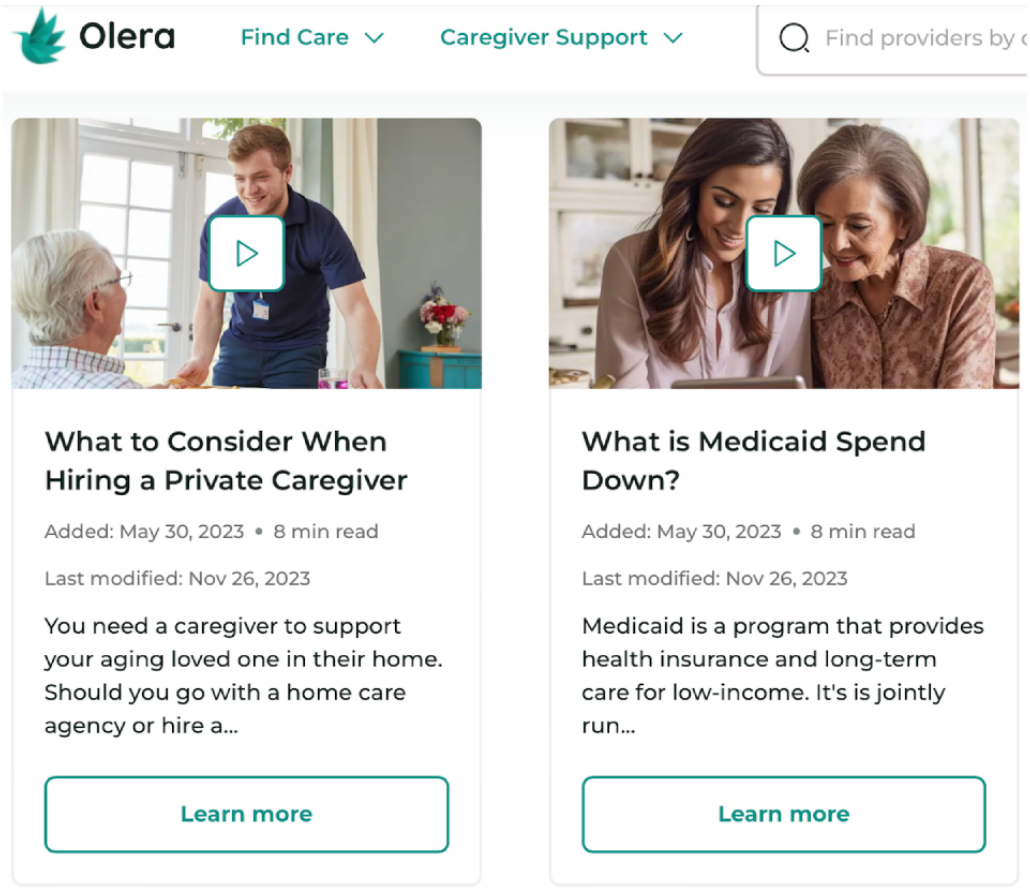

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Figure 2. Article educational materials on the Olera.care platform.

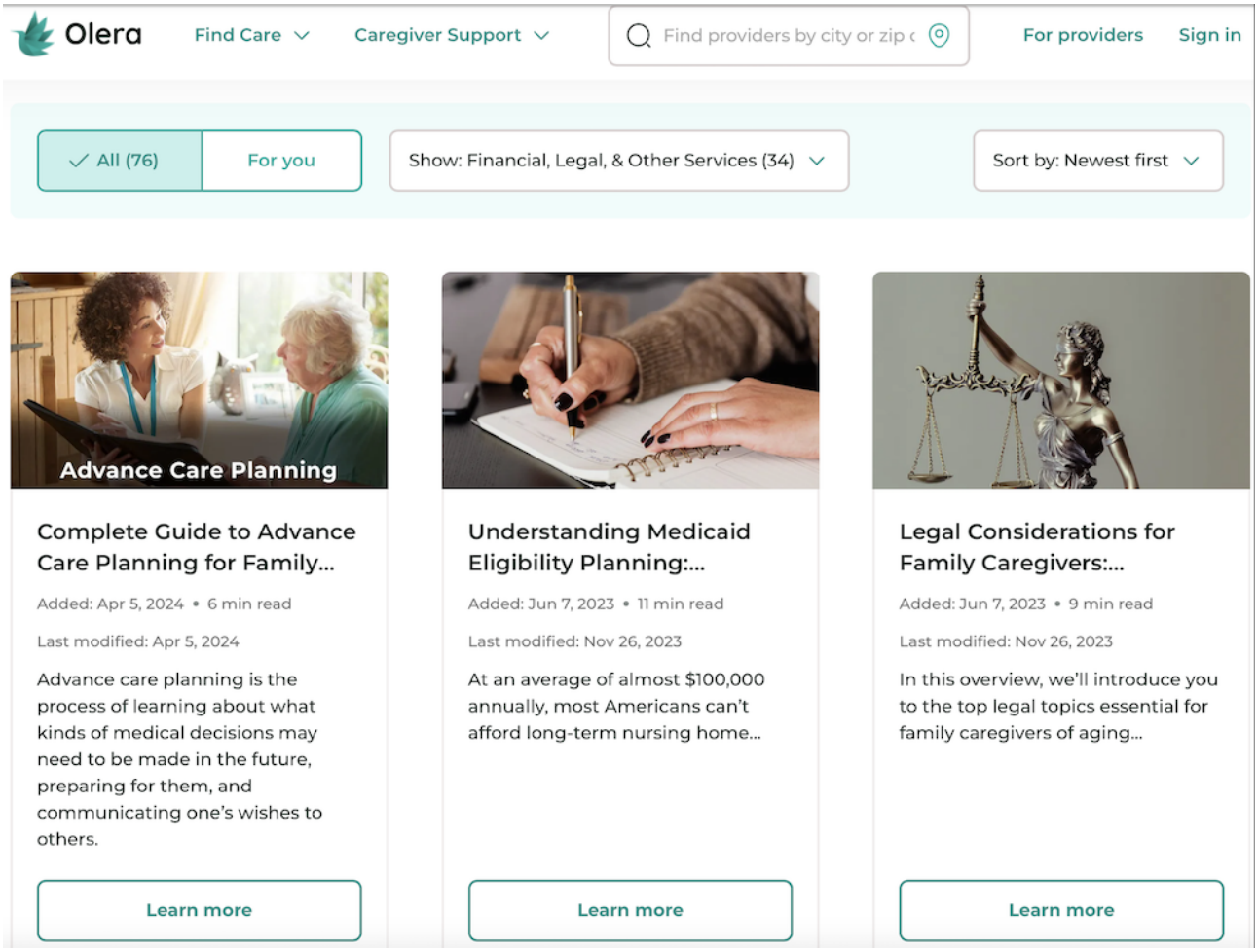

Figure 3. Information on local care on the Olera.care platform.

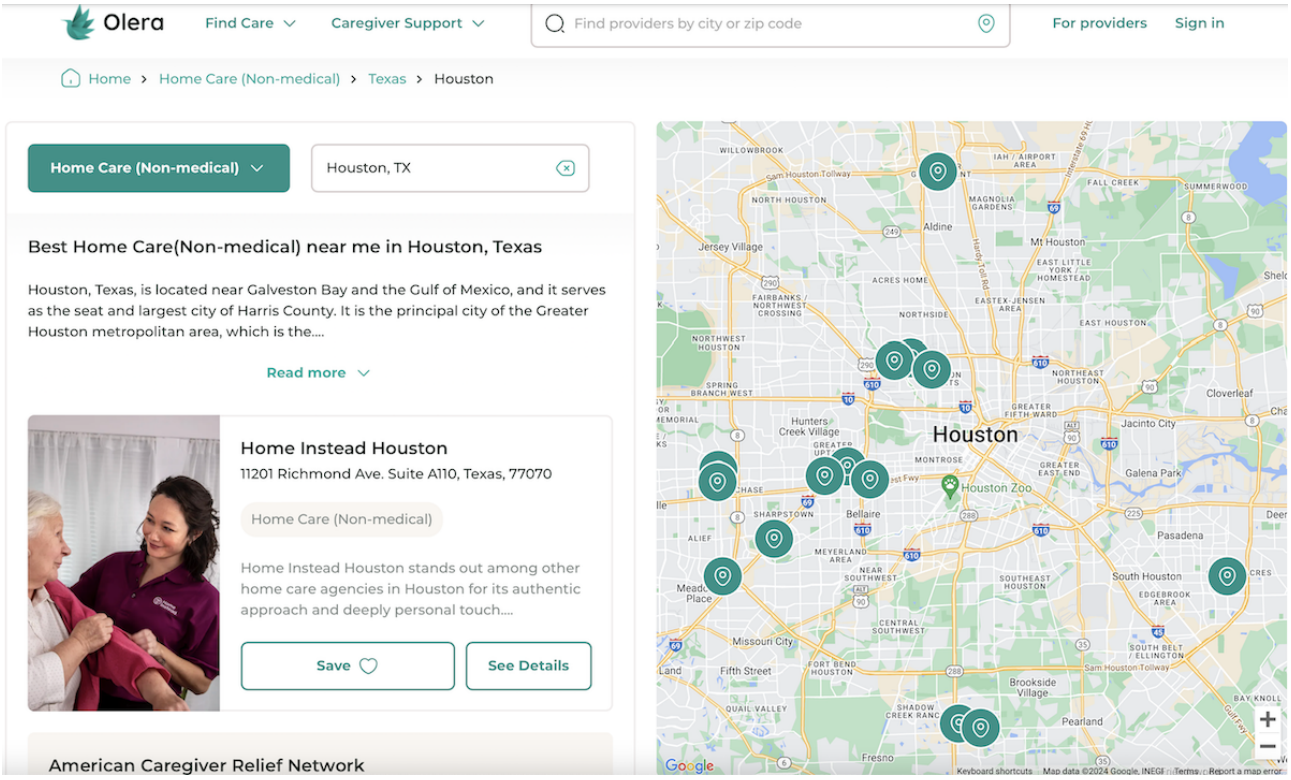

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Phase I: Mixed Methods Study—Needs Assessment and Pilot Testing

The phase I study is designed in a sequential mixed methods approach to understand the caregiving challenges and needs of caregivers and assess the platform's usability with a pilot panel of AD/ADRD caregivers. The mixed-methodological design aims to enhance the depth and richness of data interpretation. The qualitative research serves as a need assessment, providing comprehensive information on the caregiving needs and expectations for the digital platform. Subsequently, the quantitative research evaluates the platform's usability and usefulness for caregiving and identifies areas for platform enhancements.

The qualitative part involves semistructured interviews with caregivers, focusing on financial and legal challenges related to caregiving, unmet needs in financial management and legal planning, and expectations for a caregiving support platform. These interviews are recorded and transcribed for qualitative data analysis using thematic analysis in a framework approach [42]. Participants were also invited to complete a survey including questions about sociodemographic and caregiving characteristics, as well as questions on the usage and preferences for older adult care services.

A panel of dementia caregivers was invited to test the prototype web-based application by performing specific tasks, such as searching for financial and legal information. The study team is responsible for monitoring task completion, recording the status and time taken, and taking observation notes. After the prototype test, participants are invited to complete a usability survey to rate the perceived usefulness, ease of use, and overall rating of the web-based platform in supporting their caregiving needs. The usability of the platform was assessed using a modified MARS, which evaluates functionality, design, information quality, and engagement on a 5-point Likert scale [35]. The development goal is a MARS score of 3.6 or higher [43] among the pilot group of caregivers. The collected information will enable the development team to learn from the user feedback and plan for continuous product enhancement.

Phase II: Usability Evaluation Study Among Diverse Racial and Ethnic Groups

The phase II study is a usability study that evaluates the acceptance of the platform among the 3 largest racial and ethnic groups in Texas (Black or African American, Hispanic or Latinx, and non-Hispanic Whites) from a diverse socioeconomic spectrum. Participants who are interested in the study will complete a short interest form consisting of 4 questions to provide contact information. Participants will then be contacted to complete an intake form via Qualtrics consisting of eligibility screening questions; an informed consent form; questions on their demographic, socioeconomic, and caregiving characteristics; and an assessment of care receipt's dementia stage using a validated 8-item screening instrument, the Ascertain Dementia-8 [44]. Next, eligible participants can select either to explore the platform and complete the rest of the study on their own for greater flexibility or to schedule a guided session with 1 of the study staff over Zoom (Zoom Video Communications, Inc). With instructions from the study staff, participants will create an account on the Olera.care platform and generate a personalized caregiver checklist based on their needs by answering a few questions. After setting up their account, participants will explore and use the platform for 4 weeks. At the end of the 4 weeks, participants are invited to provide feedback by filling out an evaluation survey of the platform, the Technology Acceptance Survey, which was developed based on the TAM, a well-established framework for assessing the perceived usefulness and ease of use of information technologies [38,45].

Participant Eligibility and Recruitment

To be eligible for phase I, participants must meet the following criteria: (1) be the primary unpaid caregiver for a person living with dementia, (2) provide a minimum of 10 hours of care per week to a person living with dementia who has not been institutionalized, (3) be an adult child, spouse, or family member of the person living with dementia, (4) have concerns about or perceive the need for additional information on financial management and legal planning for caregiving in Texas, and (5) have access to a smartphone or computer with internet connectivity. Paid formal caregivers will be excluded from this study. For the phase II study, the study participants must meet an additional criterion: be of Caucasian, African American, or Latino or Hispanic descent. Study participants are recruited in collaboration with the Center for Community Health and Aging at Texas A&M University and the Brazos Valley Area Agency on Aging. Web-based advertisements, emails, in-person presentations, and network recruitments are used to recruit participants. Potential participants will be invited to complete an eligibility assessment survey, and eligible participants will be invited to enroll in the study.

Ethical Considerations

Human subject research approval (institutional review board [IRB] number: IRB2021-0943 D) was obtained from the Institutional Review Board at Texas A&M University, with phase I study approved on December 8, 2021, and phase II study approved on June 21, 2023. Electronic informed consents are obtained from study participants before study activities. Participants' personal identifying information (eg, names, emails, phone numbers) was used solely for contacting purposes. We protected participants' privacy and confidentiality by limiting access to IRB-approved team members, separating identifying information from deidentified study data, encrypting study information on Microsoft OneDrive, and deleting identifying information upon project completion. Participants in phase I received a US $25 e-gift card for completing both interviews and surveys, and phase II participants will receive up to US $50 e-gift card for completing the study.

Sample Size Calculations

The phase 2 research hypothesis is that there will be a difference in the perceived usefulness and ease of use between different racial and ethnic groups. For the sample size calculation, we assumed a minimum power of 80% and a type I error rate of 5%. Due to the limited research on the influence of racial or ethnic factors on caregiving technology acceptance, we estimated the necessary sample size across a range of effect

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sizes (f^2=0.02-0.35). Our analysis model will adjust for caregivers' sociodemographic characteristics, caregiving duration, and the dementia stage of the care recipient. Depending on the effect sizes, the required sample size varies from approximately 40 to 550 participants [46]. Previous studies have shown low retention rates among informal caregivers for individuals with AD/ADRD, around 50% [47,48], and even lower retention rates among Hispanic or Latinx caregivers [47]. By following recommended recruitment and retention strategies and drawing on the recruitment experience of Texas A&M Center for Community Health and Aging in various community and clinical projects, we estimate that a minimum total sample size of 300 for enrollment surveys (100 per group) with 150 for conclusion surveys (50 per group) is necessary. This minimum sample size of 150 caregivers is feasible and can detect a small effect size of 0.09.

Data Analysis

For phase I data, thematic analysis of qualitative interview transcript data was conducted using the framework method [42,49]. The framework method consists of several essential steps: transcribing interviews, familiarizing oneself with the interview material, coding, developing an analytical framework, applying this framework, charting data into the framework matrix, and interpreting the data [42]. In addition, descriptive analyses of quantitative survey responses will be conducted to describe the sociodemographic and caregiving characteristics of the participants, their usage and preference for care services, and their evaluations of the platform's functionality, design, information quality, and engagement.

For phase II survey data, descriptive statistics (mean and SD or frequency and percentage) will be used to describe the characteristics of study participants and their perceived usefulness and ease of use of Olera.care digital platform. First, using the Technology Acceptance Survey data, separate multivariable regression models will be used to examine any differences in each key outcome (perceived usefulness and ease of use of Olera digital platform) by racial or ethnic characteristics and socioeconomic status (eg, education and income level). The regression model will be adjusted for known factors that influence technology adoption (eg, age, sex, and care recipients' dementia stage).

Results

Overview

The study received funding from the National Institute on Aging on September 3, 2021. Ethical approval for phase I was obtained from the Texas A&M University Institutional Review Board on December 8, 2021, with data collection starting on January 1, 2022, and concluding on May 31, 2022. Phase I results were published on September 5, 2023, and April 17, 2024, respectively. On June 21, 2023, ethical approval for human subjects for phase II was granted, and participant recruitment began on July 1, 2023, and is anticipated to end by December 31, 2024. We expect to publish our phase II results by June 30, 2025. The Olera.care platform has seen promising growth since its official launch in 2023, now with more than 350 daily logins and a steady increase in organic traffic from August 6, 2023, to June 1, 2024 (Multimedia Appendix 2). In addition, our Facebook "Health Aging Community" has more than 11,000 followers by June 1, 2024. The goal is to expedite this organic growth of our website and social media platforms in a way that requires no paid advertisements and is sustained only by quality content on the website attracting visitors (organic traffic). Our goal is to reach more than 30,000 caregivers daily by June 30, 2027. This will be achieved through continued investment in quality content, strategic partnerships, and community engagement.

Platform Description and Functionality

The primary function of the Olera.care platform is to provide personalized recommendations for learning materials, including articles and videos, tailored to caregivers' specific needs. The platform also offers recommended listings of local service providers across various domains such as legal and financial advisors (eg, older adults law attorneys, certified financial planners), home care providers, senior living options, and public support services such as Meals on Wheels and Area Agencies on Aging. This personalized approach aims to simplify the web-based research process for caregivers, providing a guided experience akin to expert advice.

Key features of the Olera.care (Figure 4) include the following:

1. *Personalized recommendations*: the DCPA customizes content based on the care recipient's disease stage, financial circumstances, and care preferences. This ensures that caregivers receive relevant, contextually appropriate information and resources.
2. *Educational materials*: The platform hosts a comprehensive library of educational content created in collaboration with experts from various organizations, including the National Institute on Aging, the American Association of Retired Persons, and the Alzheimer's Association.
3. *Service provider listings*: Caregivers can access a curated list of local care options, including non–medical home care, assisted living, and nursing homes, gathered from reliable public sources.
4. *User-friendly interface*: developed using Ruby on Rails web application framework for a seamless cross-platform experience, the platform ensures ease of use across different devices.

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Figure 4. Key features of the Olera.care platform. AARP: American Association of Retired Persons; NIA: National Institute on Aging.

Marketing and User Growth Strategy

Since its launch, the Olera platform has focused on building organic traffic through several key strategies:

Community Building

The "Healthy Aging Community," a web-based space hosted on Facebook, for seniors and caregivers, has become a significant marketing channel, with more than 11,000 registered members. This community fosters engagement and word-of-mouth promotion, driving new users to the platform.

Content Marketing and Search Engine Optimization

The platform's Educational Material and Caregiver Resource repository features more than 20,000 indexed pages of high-quality content (Multimedia Appendix 3). This content attracts organic traffic from users searching for relevant caregiving information, supported by digital public relations efforts and outreach to journalists, bloggers, and podcast hosts.

Strategic Partnerships:

Collaborations with organizations such as the Alzheimer's Association and Texas A&M Center for Community Health and Aging have expanded the platform's reach. These partnerships are crucial for user growth, with plans to engage more caregivers through connections with local Area Agencies on Aging and older adult centers.

Promotion to Service Providers

Marketing efforts also target service providers in the older adult care industry. Promotions for new providers and participation in industry conferences help build a robust network of providers on the platform. When families like a provider, a lead can be generated for that organization when we forward their contact information. Weekly leads are directly related to the volume of organic visits we get from caregivers using the platform (Multimedia Appendix 4).

Study Progress by June 30, 2024

Phase I study data collection started on January 1, 2022, and ended on May 31, 2022. For participants, 822 respondents filled out prescreening surveys and 150 (18.2%) of them were qualified. Approximately 20% (30/150) of the eligible respondents participated in the in-depth interviews and completed the survey. The preliminary results of the phase I study were disseminated in a few regional or national conferences (ie, 2024 annual meeting of American Academy of Health Behavior; 2024 Texas Alzheimer's Research and Care Consortium Symposium; 2023 Healthy Aging and Dementia Research Symposium; and 2023 annual meeting of American Association for Geriatric Psychiatry), and formal results were published on September 5, 2023 [8] and April 17, 2024 [50].

Phase II study commenced on July 1, 2023, and we aim to complete recruitment and data collection by the end of December 31, 2024, and conduct analysis and report our phase II evaluation results by June 30, 2025. By thoroughly evaluating the Olera.care digital platform across diverse sociodemographic groups, we aim to ensure that the platform is both effective and user-friendly for a broad audience. This evaluation will provide critical insights into the specific needs and preferences of different caregiver populations, enabling us to tailor the platform more precisely.

Discussion

Principal Findings

This study presents an iterative approach to developing, refining, and evaluating a novel caregiver assistive technology. Current literature regarding the efficacy and acceptance of predeveloped caregiver interventions, while able to provide context regarding caregiver needs and future directions, often overlooks user feedback during the developmental phase. Using a build-measure-learn approach, the development of the Olera.care platform incorporates caregiver opinions and thoughts throughout the process. In the phase I study, we used a mixed methods approach to obtain comprehensive feedback in both qualitative and quantitative measures and examine the quality of the developed platform using the validated MARS tool. In the phase II study, we evaluated the acceptance of the technology among 3 major racial and ethnic groups using the TAM framework. This enables a comparison of measurements in perceived ease of use and usefulness, similar to another study that used the TAM framework to evaluate the acceptability of a care coordination platform [51].

A significant difference between our product and recently developed caregiver platforms is the multifaceted nature of the Olera.care platform. While many caregiving assistive

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technologies aim to decrease caregiver burden and strain, they mainly focus on only 1 or 2 aspects of the caregiving experience, thus limiting their use. For example, while the end goal is the same, these technologies often target specific aspects such as caregiver management [51-54], clinical reasoning [55], caregiver education and training [56,57], or caregiver mental well-being [58]. Olera.care platform serves functions in all 4 of the identified components and thus is able to serve as a simplified hub, capable of assisting caregivers in all needed aspects. For these reasons, Olera.care is a more rounded and comprehensive intervention than existing platforms.

Strengths and Limitations

One of the key strengths of the study is the build-measure-learn process. This iterative approach ensures that caregiver feedback is incorporated throughout the development phase, leading to a more user-centric design. By continuously refining the platform based on user input, the Olera.care platform is better tailored to meet the actual needs and preferences of caregivers, enhancing its usability and effectiveness. Another significant strength is the mixed methods approach in phase I, which allows for the collection of both comprehensive qualitative data on caregiving needs and expectations, as well as quantitative measures of usability and usefulness using the validated tool, MARS. The majority of similar studies have evaluated the acceptance of an intervention using only qualitative measures as opposed to quantitative [52,53,55]. Other studies have demonstrated the use of a mixed methods approach and MARS in broadening the caregiver perspective [54,56,59,60]. While app quality can be assessed in a multitude of ways, it is important to consider the MARS during developmental testing to prevent poor quality, especially considering that the average caregiving app was found to be “of [minimal] acceptable quality” that is “likely to be insufficient to meet care partner needs” [61]. Furthermore, this study stands out by investigating the acceptance of the technology among diverse ethnic and racial groups of caregivers in phase II. It is important to note the necessity of a diverse study population, considering the aforementioned burden disparities in racial and ethnic groups. Limitations in similar studies often arise from a lack of generalizability and consideration of a broadly representative sample [56,57]. Often, the unintentional focus on non-Hispanic White populations materializes in a lack of culturally tailored interventions [62]. This study will help bridge this gap by focusing on the needs and feedback across racial or ethnic populations.

The study has several limitations typical to research in this field of study. Recruiting racially and ethnically diverse caregiver participants, specifically from the 3 largest groups in Texas: non-Hispanic White, Hispanic or Latinx, and African American individuals requires intense efforts. Despite significant efforts to collaborate with communities and local agencies for recruitment, achieving a truly representative sample remained challenging. In addition, we were unable to include other racial or ethnic groups such as Asian American, Pacific Islander, Indian American, and Multiracial American. This omission is noteworthy as it potentially excludes populations that could offer important insights. However, the decision to focus on the 3 major groups was based on examining differences across these groups and considering the feasibility of recruiting caregivers in Texas. In addition, while our sample was racially diverse, it may not have been socioeconomically diverse and representative of all residents in Texas and the United States. Therefore, it is important to compare our participants’ characteristics with Texas caregiver profiles and national caregiver profiles to determine the representativeness of our recruited sample. Despite measuring household income levels and self-reported financial situations, unmeasured factors may influence the acceptance and perceived usefulness of the platform. For instance, health literacy and technology literacy can significantly impact the access and use of web-based caregiving resources [63,64]. Another limitation is the lack of longitudinal testing to observe changes in perceived usefulness over time. This gap means we are unable to assess how perceived acceptance and ease of use might evolve as caregivers continue to use the platform and their caregiving responsibilities evolve. Longitudinal studies are essential to understanding the sustained impact and usability of interventions over time. This underscores the need for a longitudinal study design and a more comprehensive assessment of caregiver characteristics in our future studies. By addressing these limitations in future research, we can gain a deeper understanding of the long-term effectiveness and broad applicability of the platform across various demographic and socioeconomic groups.

Conclusions

This 2-phase study focuses on caregiver-based iterative development and evaluation of the quality and usability of the platform among caregivers. The development of our platform incorporates the needs and opinions of end users throughout the entire process to ensure the creation of an effective product. The platform is rigorously assessed regarding overall app quality and acceptability using validated tools in a pilot group and across diverse caregivers, respectively. The phase I results demonstrate that digital platforms, especially those offering personalized and comprehensive support, hold significant promise for supporting family caregivers of people living with dementia. By the end of the study, we expect to deliver a highly accessible digital platform designed to assist dementia caregivers in managing financial and legal challenges by linking them to personalized and contextually relevant information and resources in Texas. If the Olera.care platform demonstrates the usefulness and ease of use, we plan to collaborate with caregiving organizations to expand it nationally, addressing the needs of the growing population of dementia caregivers.

Acknowledgments

The authors express their gratitude for the support by the Center for Community Health and Aging at Texas A&M University and community partners. They are also thankful to all the study participants. This research was funded by the National Institute on Aging Small Business Innovation Research program (contract 1R44AG074116-01, Solicitation AG21-025). The findings and

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conclusions expressed in this study are those of the authors and do not necessarily reflect the views of the National Institute on Aging.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to protection of study participants' privacy, but de-identified data sets are available from the corresponding author on reasonable request.

Authors' Contributions

TF, LD, SL, and MGO contributed to the original proposal submitted to the National Institute on Aging. LD, QF, MNH, LF, and TF contributed to this manuscript's first draft writing. SL and MGO contributed to supervision. All authors contributed to the critical revision of the manuscript.

Conflicts of Interest

TF and LD are executives and owners of Olera, Inc.

Multimedia Appendix 1
NIH peer review summary statement for original proposal.
[PDF File (Adobe PDF File), 113 KB - resprot_v13i1e64127_app1.pdf]

Multimedia Appendix 2
Number of visitors who found Olera.care website from free traffic of search engines by June 1, 2024.
[PNG File , 109 KB - resprot_v13i1e64127_app2.png]

Multimedia Appendix 3
Number of pages indexed by Google by June 1, 2024.
[PNG File , 141 KB - resprot_v13i1e64127_app3.png]

Multimedia Appendix 4
Number of client requests by June 1, 2024.
[PNG File , 92 KB - resprot_v13i1e64127_app4.png]

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Abbreviations

AD: Alzheimer disease
AD/ADRD: Alzheimer disease and Alzheimer disease–related dementia
AI: artificial intelligence
DCPA: Dementia Care Personalization Algorithm
IRB: institutional review board
LLM: large language model
MARS: Mobile Application Rating Scale
TAM: Technology Acceptance Model

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Proposal

Assessment of Sexual Violence Risk Perception in Men Who Have Sex With Men: Proposal for the Development and Validation of "G-Date"

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Abstract

Background: Sexual violence (SV) is a significant problem for sexual minorities, including men who have sex with men (MSM). The limited research suggests SV is associated with a host of syndemic conditions. These factors tend to cluster and interact to worsen one another. Unfortunately, while much work has been conducted to examine these factors in heterosexual women, there is a lack of research examining MSM, especially their SV risk perception. Further, MSM are active users of dating and sexual networking (DSN) mobile apps, and this technology has demonstrated usefulness for creating safe spaces for MSM to meet and engage partners. However, mounting data demonstrate that DSN app use is associated with an increased risk for SV, especially given the higher likelihood of using alcohol and other drugs before sex. By contrast, some researchers have demonstrated that DSN technology can be harnessed as a prevention tool for HIV; unfortunately, no such work has progressed regarding SV.

Objective: This study aims to (1) use qualitative and quantitative methods to tailor an existing laboratory paradigm of SV risk perception in women for MSM using a DSN mobile app framework and (2) subject this novel paradigm to a rigorous validation study to confirm its usefulness in predicting SV, with the potential for use in future prevention endeavors.

Methods: To tailor the paradigm for MSM, a team of computer scientists created an initial DSN app (G-Date) and incorporated ongoing feedback about the usability, feasibility, and realism of this tool from a representative sample of MSM. We used focus groups and interviews to assist in the development of G-Date, including by identifying relevant stimuli, developing the cover story, and establishing the appropriate study language. To confirm the paradigm's usefulness, we are conducting an experimental study with web-based and face-to-face participants to determine the content, concurrent, and predictive validities of G-Date. We will evaluate whether certain correlates of SV informed by syndemics and minority stress theories (eg, history of SV and alcohol and drug use) affect the ability of MSM to detect SV risk within G-Date and how paradigm engagement influences behavior in actual DSN app use contexts.

Results: This study received funding from the National Institute on Alcohol Abuse and Alcoholism on September 10, 2020, and ethics approval on October 19, 2020, and we began app development for aim 1 immediately thereafter. We began data collection for the aim 2 validation study in December 2022. Initial results from the validation study are expected to be available after December 2025.

Conclusions: We hope that G-Date will enhance our understanding of factors associated with SV risk and serve as a useful step in creating prevention programs for this susceptible population.

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KEYWORDS

sexual violence; risk perception; laboratory analog; dating and sexual networking apps; men who have sex with men

Introduction

Background

Sexual violence (SV) includes any nonconsensual oral, anal, or vaginal contact or penetration in which the perpetrator uses force, intimidation, coercion, or other means (eg, purposeful intoxication) to impose sexual contact [1]. SV is an umbrella term that encompasses a variety of experiences (eg, sexual assault and rape) between strangers, relatives, acquaintances, or intimate partners [2]. National surveys indicate lifetime prevalence rates of approximately 20% for penetrative SV and 44% for nonpenetrative SV in women and 2% for penetrative SV and 23% for nonpenetrative SV in men [3-5]. While much of the literature focuses on heterosexual individuals, SV is more prevalent among sexual minorities, including men who have sex with men (MSM) [6-8]. Estimates of lifetime exposure to SV vary considerably according to definitions and samples, with between 26% and 67% of MSM reporting such experiences [9]. Further, intimate partner violence (IPV), which often includes or is associated with SV [10,11], is also highly prevalent among MSM, with rates of IPV exposure ≥33% [12]. Finally, alcohol use by the SV survivor, perpetrator, or both is a common risk factor noted across studies [13].

The prevalence of exposure to SV among MSM is not surprising, given that sexual minority men experience a clustering of challenging conditions. Syndemics theory posits that negative social conditions cluster and interact to worsen one another [14,15]. In fact, SV is associated with a range of other syndemic conditions, including substance use, mental health disorders, IPV, sexual compulsivity, sexual risk behavior, and HIV transmission [7,16-22]. Likely a common basis for many psychosocial syndemic conditions in MSM [23], minority stress theory posits that the expectations for, experiences of, and internalization of discrimination and prejudice contribute to health disparities and outcomes [23-26], including SV [9,27]. In fact, minority stress is consistently associated with a variety of syndemic conditions, such as alcohol and other drug use [28,29] and SV or IPV [13,18]. Taken together, these theories suggest that a variety of constructs might be associated with SV risk; therefore, these factors will be used as mechanisms to validate the proposed laboratory paradigm.

Dating and Sexual Networking Mobile App Use Among MSM

In addition to heightened susceptibility to SV and its clustering with other syndemic conditions, MSM also frequently participate in dating and sexual networking (DSN) via mobile apps and other web-based venues [30,31]. Research indicates high rates of sexual risk behavior, more partners among internet and DSN app users [32,33], and a higher likelihood of using alcohol or other drugs before sex [33,34], thus highlighting the potential for exposure to SV with men met via DSN apps. While the prevalence of SV by partners met via DSN apps is unknown, research, media, and law enforcement reports suggest it may be common [35]. One study found that 9.3% of women and 11.4% of men reported SV with someone they met on a dating site or mobile app [36]. Research across gender and sexual orientation groups indicates a higher risk of past-year SV among those who use dating apps than among those who do not, although studies have not examined exposure to SV by partners specifically met via dating apps [37,38]. Similarly, a survey of DSN app–using MSM found that 11% reported lifetime experience of sexual IPV [39], although not necessarily perpetrated by DSN app–using men. Finally, a recent study of violence related to DSN use in MSM found that 33% reported some exposure to physical violence or SV by someone they met on a DSN app. Moreover, nearly 48% noted other MSM they know who have experienced physical violence or SV by someone they met on a DSN app [40].

Despite limited prevalence data, DSN app–met partners pose a risk for exposure to SV for several reasons: the anonymity inherent in web-based spaces, meeting in private locations, a lack of disclosure of whereabouts to others for privacy reasons or stigma avoidance, the potential for perpetrators to target and access potential targets, disinhibition regarding sharing personal details in web-based spaces, and heightened expectations for sex [37]. It is also common for MSM to use apps while under the influence of alcohol or drugs, and many individuals use substances when they meet in person [6,37]. Further, MSM are concerned for their physical or sexual safety when seeking and meeting partners in web-based venues [41]. DSN app use represents a unique opportunity for MSM to detect risk factors for SV, screen potential partners, and control their interactions [42]. MSM engage in sexual preference and risk negotiations in web-based spaces [43,44]. When MSM use alcohol or drugs while vetting potential partners, their ability to detect risk may also be impaired. Because MSM use DSN apps to make sexual decisions and negotiate risk, additional research is needed to understand the information that guides their decisions about sexual activity with partners met through DSN apps.

Identifying Risk Factors for SV Perpetration Among MSM

While little is known about SV risk perception and negotiation in DSN environments, the literature has identified specific risk factors among men. Specifically, for this project, we focused on problematic alcohol and drug use, antisociality, and the internalization of homophobia. First, alcohol and drugs are common in dating and sexual encounters with DSN app–met partners [45]. Among MSM, alcohol and drug use in general, and in sexual situations specifically, predicts SV perpetration [46-49]. As such, alcohol and drug use cues may help identify potential partners more likely to perpetrate SV.

Second, among heterosexual men, signs of antisociality, such as controlling behaviors [50], low levels of agreeableness [51], and hypermasculinity (and perhaps also a preference for these characteristics in potential partners), predict SV perpetration [52]. Among heterosexual men, masculine discrepancy stress, where men perceive they do not meet traditional standards of masculinity, is associated with IPV perpetration [53], sexual

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risk behavior, and alcohol and drug use [54], all of which are risk factors for SV perpetration. Third, and unique to MSM, minority stressors, such as internalized homophobia, or anticipating sexual orientation prejudice or discrimination correlates with perpetration [55]. That said, it is important to note that while such factors may increase risk for exposure to SV or affect one's decision-making and risk perception, it is never a person's fault for experiencing SV.

Existing Measures of SV Risk Perception

In general, researchers examining SV risk perception have studied heterosexual dyads and relied on vignettes. For example, the potential perpetrator in a vignette may use alcohol or attempt to isolate a potential target, and participants indicate the point when they would begin to feel uncomfortable and when they report wanting to leave the situation [56,57]. Failing to report discomfort during the reading of a vignette and delayed exit are conceptualized as poor SV risk perception. For example, participants can be presented with a description of a first date and asked to rate the level of risk associated with several cues described in the date, such as a man paying for the date, alcohol intoxication, and making sexual comments [58,59]. This methodology has been expanded to include audio or video vignettes depicting an interpersonal situation in which participants are asked to project themselves and predict how they would respond [60,61]. Researchers then determine whether participants identify the threats and remove themselves from the hypothetical situation. The longer participants take to indicate that the man should stop his sexual advances, the higher the response latency and the poorer the SV risk perception.

Although SV risk cues can range from being ambiguous to blatant, most vignette scenarios portray clear cues and focus on high-risk situations. Further, many risk perception paradigms adhere to a third-person perspective; therefore, the risk may not be immediate to the participant, and their appraisals remain hypothetical. These measures may lack ecological validity: assumptions of how one *might* act may not accurately reflect one's *actual* behaviors when confronted with the same situation in reality. Therefore, stronger tests of risk perception entail the examination of decision-making in an actual interpersonal interaction [59]. For example, in a paradigm, female participants engaged in a social interaction with a male confederate in a bar laboratory [62]. The researchers examined the impact of sexually ambiguous cues on participants' nonverbal behaviors and perceptions of the confederate.

Given the limitations of existing risk perception paradigms and the paucity of measures that use a web-based medium, members of our team developed a paradigm (ie, EduDate) to examine SV risk perception in college women [63]. This novel web-based speed-dating paradigm assesses threat appraisals and behavioral reactions to SV risk. It provides an opportunity to study dispositional and environmental factors that influence the perception of clear and ambiguous risk cues. Naturally, the use of laboratory analog methods is limited by the nature of perpetration and by the need to engage in ethical and responsible research methods [64]. While the ultimate goal is to reduce SV, researchers are appropriately limited in their ability to mimic such behavior and examine the decision-making process of a potential target. As a laboratory method, there is a high degree of experimental control for EduDate, which provides strong internal validity. EduDate also approximates a real-world experience, which strengthens ecological validity. EduDate incorporates behaviors consistent with the literature about perpetrators and mimics situations where women respond to potential SV in real time.

EduDate was modeled in appearance and functionality after web-based dating services accessible via a computer rather than through a mobile app. Participating women are told the study involves "beta testing online speed-dating software." Participants initially view a profile of a bogus dating candidate with whom they will be having a speed date and then rate the candidate across characteristics typical of speed dating (ie, physical attractiveness, social status, and likelihood to date). Next, each participant "interacts" with the candidate through a rigged chat-based speed date involving predetermined questions and responses. Once participants provide an answer to a question, they view the bogus dating candidate's response, which presumably had been typed at the same time. The candidate's responses become increasingly indicative of potential SV perpetration by the inclusion of risk cues empirically established for male-on-female SV. Risk perception is measured by the number of risk cues a participant tolerates, which represents behavioral response, and changes in the participant ratings from before to after the interaction with the dating candidate, which measures the threat appraisal [63]. There is evidence for the usefulness of EduDate to study SV risk perception, which supports adapting the paradigm to investigate SV risk perception in DSN app environments among MSM. However, potential differences in the risk factors for MSM compared to those for heterosexual women necessitate an empirically driven approach to ensure the stimuli used in the paradigm are tailored for MSM. In addition, the surge of technology, including the use of mobile apps, necessitates an infrastructure update to this laboratory-based tool.

This Study

A total of 2 primary aims guide this study. Our first aim was to develop a rigged DSN app (ie, G-Date) that allows for the investigation of SV risk perception in MSM. Our work on the first aim included three objectives: (1) the production of an app whose appearance and functionality mimic those of contemporary real-time DSN apps used by MSM while actually being a predetermined and rigged system in which we could embed SV cues and assess participant engagement with these cues; (2) the development of stimulus materials to embed into the app; and (3) the refinement of the stimulus materials and app through an iterative process to ensure its appearance, functionality, and data collection capabilities were adequate for the purposes of the study. The EduDate paradigm (previously validated with heterosexual women) served as a foundation for designing this new paradigm.

Our second aim (which is in progress) is to validate the G-Date paradigm as a measure of SV risk perception in MSM. We will evaluate G-Date's content validity by having participants undergo 2 speed dates on the app: one with a dating partner who displays SV risk cues and another with a dating partner

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who does not display SV risk cues. Next, we will compare participant engagement with, and ratings of, the risky versus the safe dating partners. We hypothesize that participants will end the speed date with the risky dating partner sooner than that with the safe partner and will rate the risky partner more negatively after the date. Per syndemics theory and the processes outlined in minority stress theory, we will evaluate G-Date's concurrent validity by examining the extent to which participants' existing risk factors for exposure to SV (eg, SV history and drug or alcohol use) predict their engagement with the risky versus the safe dating partners. We hypothesize that the length of participants' speed date with the risky partner and their ratings of the risky candidate after the date will be predicted by syndemic and minority stress factors associated with SV. Finally, we will evaluate the predictive validity of G-Date by examining the extent to which participants' engagement with the risky and safe dating partners predicts SV rates at 9-month follow-up. We hypothesize that the length of participants' speed date with the risky partner and their ratings of the risky partner after the date will predict subsequent SV.

Methods

Ethical Considerations

This study received initial ethics approval from the Rowan University Institutional Review Board on October 19, 2020 (PRO-2020-25) and has continuously been approved since that time. All participants provide informed consent before engaging in the study and are able to opt out of the study for any reason. All data are deidentified using a 4-character code to match responses to the questionaries with the data stored in the app. All participants were paid US $40 for engaging in focus groups and interviews, US$30 for participation in part 1 of the validation study, and US $20 for part 2 of the validation study at 9-month follow up.

Research Design Overview

Aims 1 and 2

The 2 aims of this research involve several points of qualitative and quantitative data collection. As presented in Figure S1 of Multimedia Appendix 1 [65-86], qualitative and quantitative designs were used to develop and refine the cover story; app procedures and functionality; and app materials, including photos and the question and answer (Q&A) scripts. We then used this information to finalize the app and research materials for use in aim 2.

The first aim of this project entailed the production of the G-Date app and protocol, creation of the stimulus materials to embed into the app, and subsequent refinement of both the stimulus materials and app to ensure their adequacy for the study. The production of the G-Date app and protocol involved working with an app development team led by a computer scientist and staffed by computer science graduate students. The team worked to make G-Date appear to be a contemporary DSN app geared for speed dating for MSM. We also wanted G-Date to be developed in such a way that other researchers could easily modify components of the app's content and functionality for follow-up work in this area. G-Date uses a software platform similar to popular dating apps; therefore, its functionality and appearance would be familiar to those with even casual prior exposure to dating apps (Figure S2 in the Multimedia Appendix 1). The app was built to be compatible with iOS (Apple, Inc) devices (eg, iPad, iPhone, and MacBook). The protocol as experienced by the user involves four components: (1) profile setup, (2) the review of potential partners, (3) Q&A speed date, and (4) partner comparison (Textbox 1).

The creation of the stimulus materials involved the development of the (1) script for the Q&A speed date and (2) dating partner photos.

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Textbox 1. Protocol components as experienced by users.

Profile setup

Access to the app requires a username and password provided by the research team. Once logged into the app, participants set up their own profile, which involves (1) taking and uploading a headshot with the G-Date logo in the background; (2) providing information about themselves, such as that commonly found on dating apps for men who have sex with men (MSM), including age, relationship status, position (eg, top, bottom, or versatile), and community (eg, bear or jock); (3) providing information about the kind of person they are seeking (eg, age range, relationship status, position, and community); and (4) answering questions about their personality.

Review of potential partners

After the completion of their profile, participants view photos of 60 prospective dating partners who ostensibly meet their desired characteristics. The photos are headshots of men in the participant's preferred age range, who vary in ethnic background, and who were rated as attractive in the pilot work (refer to the Dating Partner Photos section for more information on photos). Embedded into each photo is a thumbs-up and thumbs-down icon. If participants give a thumbs-down to a photo of a potential partner, they move on to the next photo. If participants give a thumbs-up to a photo, a starred rating scale appears on the screen, and participants are asked to rate the attractiveness of the potential partner on a 5-star scale before moving to the next photo. After viewing all 60 photos, participants are informed they have been matched with several partners and will get an opportunity to participate in 2 speed dates.

Question and answer (Q&A) speed date

Speed dates proceed in a structured and predetermined manner. Speed date partners are selected by the app based on the highest starred ratings that participants provide to the photos viewed in the aforementioned review of potential partners. Before commencing a speed date, participants rate the partner's physical attractiveness and personality and their interest in meeting their partner in person. Each speed date is then conducted using "G-Date's patent pending Q&A system," in which the participant and their partner respond to questions designed to maximize the assessment of a partner's compatibility. During the Q&A date, a question appears on the screen (eg, "Based solely on your last date, what would that person say about you?"), and participants have 90 seconds to text their response to the question. After time elapses, participants see their response delivered to their partner and receive their partner's response to the same question, which presumably had been typed at the same time. After the third Q&A, participants can end or continue the speed date, and they are given the opportunity to end or continue the speed date after each subsequent Q&A. In the speed date with the safe partner, none of the partner's Q&A responses contain risk cues. In the speed date with the risky partner, the first 2 responses to the Q&As do not contain risk cues, but the third and all subsequent responses do; therefore, every participant is exposed to at least 1 risky response from the risky partner and given the opportunity to end the speed date afterward. If participants remain on the risky date, every subsequent response contains a risk cue. After the 12th Q&A, the speed date is automatically terminated. After each speed date, participants rate their partner on the same 3 attractiveness and interest scales as they had before the speed date.

Partner comparison

After the completion of both speed dates, participants are presented with side-by-side photos of their speed date partners and asked to rate each of them on a series of dimensions: vibe, interpersonal style, personality, feeling about their sexual identity, respect of sexual boundaries, and alcohol or drug issues.

Script for the Q&A Speed Date

Initial stimuli for the Q&A in the speed date embedded within the app were developed based on the existing literature about SV in MSM, as well as feedback from our consultants with expertise in SV among MSM. One set of stimuli was developed for the risky dating partner and contained SV risk cues, while a second set was developed for the safe dating partner and contained no risk cues. A total of 53 potential Q&As were then developed after extensive discussion with the primary research team and consultants to clarify whether the language would be appropriate for young MSM and contains a realistic degree of risk and safety. Responses containing risk cues included descriptions of the loss of control over alcohol or drug use, antisociality (eg, low empathy, narcissism, and aggression), and internalized homophobia, all empirically documented constructs associated with perpetration. For example, in response to the question, "In a sentence or two, what do you like most about being in a relationship?" the risky partner responds as follows: "tbh the best part is having a guy around who knows it's his job to drain my balls every day."

With regard to the safe dating partner, we developed a set of stimuli that contained no risk cues. For example, for the question, "What's one of the best ways for you to get to know a new partner?" the safe partner responds as follows: "It can be a lot of diff things but I think when they share something they are passionate about like a playlist or a favorite movie it can tell you a lot about them."

Next, using Prolific (Prolific Academic Ltd), a nationally recruited sample of 102 MSM evaluated all proposed Q&As. Participants were told, "Imagine that you are using a speed-dating app to connect men with other men. Please read the following answers provided by a potential partner to questions about themselves, then rate their answers."

For each Q&A, participants evaluated (1) how realistic it would be that a man provided this answer on a gay speed-dating app (on a scale of 0 [less realistic] to 10 [more realistic]); (2) how likable the person who potentially wrote the answer is (on a scale of –3 [not at all likable] to +3 [extremely likable]); and (3) how likely the person who wrote the answer would be to engage in verbal, physical, and alcohol or drug-facilitated SV (on a scale of –3 [not at all likely] to +3 [extremely likely]). Participants were also asked whether the person who wrote the response would have (1) substance abuse issues (they have an alcohol or drug problem or cannot seem to control their alcohol or drug use; (2) internalized homonegativity (self-hate; someone is uncomfortable being gay); (3) toxic personality (being narcissistic, lacking empathy, or controlling and intimidating); (4) other negative traits; and (5) none of the above.

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Responses were included in the final set of Q&As only if the mean realism score was greater than the midpoint of 5. Moreover, for the risky date, all Q&As included ≥1 of the SV types (ie, verbal, physical, and alcohol or drug-facilitated SV) with mean scores in the positive range and the identification of one of the primary perpetration risk constructs (ie, substance use issues, internalized homonegativity, and toxic personality) across participants. For the safe date, all Q&As included only SV types with mean scores in the negative range and no indication of any perpetration risk constructs. The final Q&A responses included in the risky date were rated significantly higher in terms of the likelihood of engaging in all 3 types of SV compared to the Q&A responses included in the safe date. Taken together, these data led to the development of the aforementioned 2 unique dates: risky and safe.

Dating Partner Photos

We relied on artificial intelligence (AI) to initially create 139 racial and ethnically diverse headshots of men who would appear to be in their late teens to late twenties to serve as bogus dating partners. One of our primary reasons for choosing AI rather than actual photos stemmed from ethical concerns about using the photos of people whose physical appearance may be judged negatively and associated with the inappropriate behavior of the risky partner in the Q&A date. All photos were evaluated by the same nationally recruited sample of 102 MSM to provide impressions (on a scale of 0 [less] to 10 [more]) of physical attractiveness, interest in dating, and interest in having sex, as well as perceived age, race, ethnicity, community (eg, bear or muscle guy next door), and sexual position (eg, top, bottom, or versatile). It is important to note that due to the large number of photos and Q&As under review, each participant saw only a subset of photos presented in random order.

Visualization of the photo data revealed a broad range of responses across all items. Further, our app development team suggested we limit the potential options for speed date matching to reduce the potentially unnecessary advanced algorithm work. To this end, we decided to split our potential dates into 2 age groups based on perceived age in pilot testing: 18 to 23 years and 24 to 29 years. We also wanted the potential dates to represent a range of attractiveness and to be racially and ethnically diverse to provide a wide range of options for each participant. Therefore, anyone with mean ratings on attractiveness, interest in meeting, and interest in sex <3.67 was removed from consideration. We next removed any photos with participant comments that noted “distortions” that might suggest these were AI-developed images or any photos identified as too similar to another photo (in actuality, all photos have some degree of similarity based on the generative AI algorithms used). We then chose photos of different racial and ethnic groups that were representative of the demographics of the region where the study took place (eg, 65% White) based on the majority ratings by participants that fit typical categories and omitted any photos that demonstrated low scores on attractiveness and interest scales or higher average age group. This led to a final list of 96 photos for use in the app. However, given our interest in maximizing the number of headshots available for participants to choose from (similar to real-world app use), we included 60 photos for each of the age categories. To this end, of the 96 photos, any photo with a mean age of ≤27.29 years was included in the 18- to 23-year category (n=60, 62.5%), and any photo with a mean age of ≥25.82 was included in the 24- to 29-year category (n=60, 62.5%). This decision led to 12 photos that overlapped in both categories. In consultation with our app development team, we also noted the need to include a group of photos that would represent a “both” category for those participants who noted no preference for age group. Therefore, we included the same 12 overlapping photos and a random selection of 24 of the 60 photos from each of the age categories to form a “no preference” category (n=60, 62.5%). Taken together, this led to 3 groups of 60 photos, and all participants with a preference for partners aged 18 to 23 years, 24 to 29 years, or either saw the same 60 photos, respectively.

To refine the stimulus materials and app, we obtained qualitative feedback from MSM. We sought participants aged 18 to 30 years to best target a high-risk group in terms of exposure to SV. Potential participants were screened using a web-based survey for eligibility before engagement in the study based on the following criteria: (1) being aged between 18 and 30 years, (2) gender identification as a man, (3) sexual contact with a man in the previous 12 months, and (4) having used a DSN app in the last 12 months. The web-based focus groups and interviews lasted approximately 1.5 to 2 hours, and participants were paid US $40 for their time. We conducted 3 focus groups and 2 interviews for a total of 14 participants using an iterative process wherein ongoing data analysis and app development informed subsequent interviews. All discussions were audio recorded and transcribed by the research team and uploaded into Dedoose (Sociocultural Research Consultants LLC) for analysis. Participants had a mean age of 23.5 (SD 1.5) years. Half of the participants self-identified as Black (7/14, 50%), while the others self-identified as White (2/14, 14%) or chose not to report their race or ethnicity (5/14, 36%).

Initial participants were asked to provide perceptions of what constitutes cues in an app that a person or an environment is of high risk (signs that indicate a person will become sexually violent or an environment poses danger) and of low risk (signs that indicate a person or an environment has limited risk). Subsequent, participants were presented with the prototype version of G-Date and asked to provide feedback on (1) the app’s realism; (2) the quality of the stimulus materials, including the bogus candidate profile photos and Q&As; and (3) the feasibility of the cover story. In addition to guided discussion, a self-administered questionnaire was used to gather feedback. Throughout this iterative process, there were ongoing modifications of G-Date by the app developer team to incorporate further feedback about the stimulus materials and app usability.

The second (and ongoing) part of this study examines the content, concurrent, and predictive validities of the G-Date paradigm. Given minority stress and the syndemic situation of MSM, we are assessing the following SV risk factors and their relationship to participant behavior in G-Date: (1) historical exposure to SV, (2) alcohol and drug use or abuse, (3) dating and sexual behaviors, (4) psychological symptoms, and (5) minority stress indicators. G-Date also affords the opportunity to examine 2 related but distinct indices of risk perception:

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behavioral response (the number of responses tolerated from the bogus dating partner) and threat appraisal or identification (changes in the perception of the bogus dating partner). For content validity, participants' level of risk perception will be assessed relative to their interaction with the risky versus safe partners. For concurrent validity, participants' level of risk perception during their interaction with the risky partner will be assessed in association with their endorsement of the aforementioned risk factors for SV. For predictive validity, participants' level of risk perception during their interaction with the risky partner will be assessed in association with their exposure to SV at the 9-month follow-up.

Participant Recruitment and Eligibility

Potential participants are being recruited via advertisements on social media platforms and at in-person locations (eg, lesbian, gay, bisexual, and transgender [LGBT] centers and college campuses). Participant eligibility criteria include the following: (1) being aged 18 to 30 years, (2) gender identification as a man, (3) sexual contact with a man in the previous 12 months, and (4) DSN app use in the last 12 months. Any individual who participated in aim 1 is excluded, given their knowledge that G-Date is a simulation. The completion of the G-Date protocol takes approximately 1.5 hours, and participants are paid US $30 for their time.

Procedure

Data collection occurs within physical laboratory spaces using iPads or over a video-call platform using participants' iPhones, iPads, or Apple laptops. Participants are told that the experimenter is "part of a team of consultants contracted to beta test a prototype of a new speed-dating app called G-Date, for men who have sex with men." Experimenters explain that they seek to evaluate "the best speed date questions" and want participants' feedback from their dates that are limited to answering a set of predetermined questions. Participants are provided with a username and password so that they can log into G-Date and engage the paradigm. This entails creating a profile and reviewing photos of potential dating partners (as described in Textbox 1).

After being exposed to photos of 60 potential dating partners, participants are told that based on their preferences and profiles, they can have 2 dates, due to the "limited number of users available in the beta-testing phase." Participants then begin the first of the 2 dates. Each participant has 1 risky dating partner (risky condition) and 1 safe dating partner (safe condition), as described in the Script for the Q&A Speed Date section. The order of the conditions is randomized. After the G-Date paradigm, participants are asked to complete a battery of questionnaires on Qualtrics (Qualtrics International Inc), which includes a demographic form, and a comprehensive battery of personality and behavioral measures targeting syndemic and minority stress-related factors that have been theoretically or empirically linked with SV (Multimedia Appendix 1). Upon the completion of the questionnaires, participants are debriefed, compensated, and thanked for their participation. To evaluate the predictive validity of the paradigm, participants will be contacted 9 months after their initial visit to the laboratory and asked to retake the battery of questionnaires they originally completed with reference to the time period since their initial study completion.

Data Analytic Plan for Aim 2

Before testing our hypotheses, adherence to distributional assumptions will be examined. When the assumptions of linear models are untenable, we will use transformations, nonparametric procedures, or generalized linear models. The family of generalized linear models will be determined based on the distribution of the data, although it will likely be either a Poisson or a negative binomial model. Missing data will be handled via multiple imputation [87], and results will be reported after considering both findings obtained through listwise deletion and multiple imputation. To evaluate the validity of G-Date, we have 3 hypotheses that map onto 3 different types of statistical models.

Our first set of hypotheses addresses the content validity and premise of the G-Date paradigm, that is, that participants will perceive and respond to the risky date differently than the safe date. Hypothesis 1 is that participants will engage in fewer Q&As with the risky date than with the safe date. Hypothesis 2 is that there will be larger pre to post evaluation declines in attractiveness and desirability for the risky date than for the safe date. To evaluate these hypotheses, we will conduct paired 1-tailed *t* tests. If the normality assumption is untenable, we will use the Wilcoxon signed rank test or transform the data.

Our second set of hypotheses aims to address the concurrent validity of the G-Date paradigm by evaluating whether participants who engage longer in the Q&A date and more positively evaluate the risky date are rated higher in the various syndemic and minority stress-related characteristics associated with exposure to SV. Hypothesis 3 is that the number of Q&As participants engage in with the risky date will correlate with and be predicted by participants' historical exposure to SV, alcohol and drug use or abuse, risky sexual behaviors, psychological symptoms, and minority stress. Hypothesis 4 is that the extent of the pre- to postdate questionnaire declines will correlate with and be predicted by participants' historical exposure to SV, alcohol and drug use or abuse, risky sexual behaviors, psychological symptoms, and minority stress. For some of these variables (eg, history of exposure to SV), we expect many individuals to endorse a lack of experience. Therefore, standard linear models (which assume normality) will not be appropriate. Rather, a Poisson generalized linear model, a negative binomial model, or a zero-inflated model will better match the distribution of the data. To determine which distribution family is appropriate, we will conduct likelihood ratio tests, supplemented with Akaike information criterion and Bayesian information criterion comparisons, as well as residual analyses.

The third set of hypotheses will evaluate the predictive validity of the G-Date paradigm. Participants who engage longer in the Q&As and more positively evaluate the risky date should be at a higher risk for future SV exposure while accounting for historical SV exposure. Hypothesis 5 is that the number of Q&As participants engage in with the risky date will correlate with and predict 9-month exposure to SV. Hypothesis 6 is that the extent of the pre- to postdate questionnaire declines will

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correlate with and predict 9-month exposure to SV. As in the previous hypotheses, many of these variables are expected to follow a nonstandard (ie, nonnormal) distribution. The results of hypotheses 3 and 4 will inform the selection of both the type of model for hypotheses 5 and 6 and priors for the parameters in a Bayesian analysis.

Given that the targeted sample size (n=325) is only slightly more than the estimated sample size required to detect statistical significance via a priori power analyses (n=275), a Bayesian analysis will increase the chances of the sample size being adequate. The prior distribution for the Bayesian analysis will be estimated from the relationship between history of exposure to SV and risk perception. Provided the relationship between history of exposure to SV and risk perception yields similar parameters to the relationship between 9-month exposure to SV and risk perception, the Bayesian results will yield more precise estimates than traditional (likelihood or frequentist-based) procedures. However, given the unfamiliarity most users have with Bayesian analysis, we will perform the analysis in three ways: (1) using traditional (likelihood or frequentist-based) statistical procedures; (2) using Bayesian analysis with priors obtained from the relationship between past exposure to SV and risk perception; and (3) using a Bayesian analysis using "uninformative" priors, which are prior estimates of the parameter that will heavily weight the data in estimating the parameters, rather than the user-specified priors. The results from these 3 models will serve as a sensitivity analysis; they will be presented side-by-side in an effort to maximize transparency and highlight differences (if any) in the scientific conclusions reached as a function of the models' assumptions. In addition, it is expected that some individuals will drop out before the completion of the study. As mentioned previously, all the available data will be used to generate a multiple imputation model to impute the missing values. The results from each imputation will be averaged using imputation rules proposed by Rubin [87], and these aggregated results will be presented alongside the more common method of listwise deletion.

Results

Funding for this project began on September 10, 2020. Development of the G-Date app commenced in October 2020. Enrollment of participants for aim 2 commenced in December 2022. As of May 2024, a total of 245 participants have completed the protocol. Participant recruitment is expected to continue through August 2024, and data collection is expected to be completed in May 2025 to allow for a 9-month follow-up. Final results of the project are expected to be submitted for publication in December 2025.

Discussion

Principal Findings

Findings from the study will test G-Date's content, concurrent, and predictive validities. With respect to content validity, we anticipate that participants will rate the risky partner more negatively and terminate the Q&A date with the risky partner sooner than that with the safe partner. With respect to concurrent validity, we anticipate that syndemic and minority stress-related factors such as prior exposure to SV and substance use will impact participants' ratings and termination of the risky versus safe dates such that greater syndemic and minority stress will be associated with impairments in risk perception. Finally, with respect to predictive validity, we anticipate that participants' risk perception during G-Date will predict exposure to SV at the 9-month follow-up.

Comparison With Prior Work

Our prior work in SV risk perception used a web-based speed-dating paradigm (EduDate) designed for a desktop or laptop computer reflecting the technology of the era in which it was developed. G-Date represents an advance in that it is designed as a mobile app and mimics contemporary DSN apps used by MSM. Further, the stimuli of the EduDate paradigm were developed for use with heterosexual women, while the content of G-Date was developed specifically for use with MSM, an understudied but high-risk population for exposure to SV.

Strengths

This proposal has several methodological strengths. G-Date is built on a software platform similar to that of popular dating apps; therefore, its appearance and general functionality from setting up a profile to swiping and rating photos of potential partners can be easily understood and used by participants with even casual prior experience with DSN apps. The risk cues embedded into the risky date are derived from the empirical literature, while the language and context in which the cues are presented in the Q&A date were vetted and shaped by discussions with consultants and focus groups and found in pilot testing to be realistic and indicative of risky content. The use of AI to generate photos allowed for a diverse range of attractive headshots of men from varied ethnic backgrounds without the ethical concerns of using actual photos, in which case, the appearance of the men in the photos would be judged and the simulated behavior of the men in the Q&A date could be expected to be seen negatively. Finally, we embedded manipulation and suspiciousness checks that will allow for the flagging of data from participants who did not attend to the risk cues or who did not believe the cover story for the protocol.

Limitations

There are a number of methodological and practical challenges involved in the undertaking of this project. First, a methodological issue common to laboratory analogs is external validity. Participants may behave differently on G-Date from how they might ordinarily behave when using a DSN app in the community. While G-Date stimuli were pilot-tested for validity, there may be different contextual factors related to participation in the study (eg, beta testing an app for compensation and the presence of an experimenter) that influence participants to behave with heightened or reduced caution. A second related external validity concern is the generalizability of the participants' risky behavior in G-Date to risky decision-making during real-world in-person dates or hookups. It is possible that participants who engage in more risk in G-Date are, in fact, more cautious when it comes to meeting a new web-based acquaintance in person. We hope to

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be able to address these potential limitations through the 9-month follow-up with participants, when we will assess their subsequent DSN behavior, exposure to SV, and substance abuse, among other risk variables. A third potential limitation could be a lack of SV experiences reported by participants both initially and at the 9-month follow-up. This would reduce our ability to explore G-Date's predictive and concurrent validities. A possible remedy for this problem would be to increase the number of participants and identify a more "at-risk" sample, such as specific subgroups of MSM. A related predictive validity concern is extensive attrition at the 9-month follow-up. To this end, we plan to periodically remind participants about the 9-month follow-up and to provide a monetary incentive at the 9-month follow-up.

Future Directions

Upon the successful validation of G-Date, we anticipate using the refined paradigm on an ongoing basis to elucidate the range and relative strength of risk factors that can inform SV prevention endeavors, especially the study of risk detection under the effects of alcohol intoxication. For example, we anticipate embedding G-Date into an alcohol administration protocol to parse the unique influence of intoxication, as well as the nexus of intoxication and other relevant alcohol or drug use factors. We also believe G-Date can be used within prevention programs. First, because G-Date will serve as a validated measure of risk perception, it can be used as a tool to measure the success of relevant intervention programs. For example, G-Date behaviors could be evaluated both before and after the intervention, and a successful program would demonstrate an increase in participant risk perception over time. Second, G-Date might be used as a stand-alone mechanism for prevention programming. For example, the paradigm could be used to educate participants about navigating sexual risk and communication in DSN app environments. Therefore, participants engaging in G-Date could be reinforced for decisions that could protect them from SV and educated about decisions that could increase the risk for SV in real time.

Conclusions

This project aims to (1) design a new laboratory paradigm in the form of a DSN app called G-Date that can be used to investigate SV risk perception in MSM and (2) evaluate G-Date's content, concurrent, and predictive validities by examining the relationship between participant engagement in the app with risky and safe dating partners and their status on a battery of syndemic and minority stress-related factors. The findings have the potential to provide a new methodological tool for basic and applied researchers and advance the understanding of crucial factors related to SV risk perception in MSM.

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Data Availability

The data sets generated during this study will be available in the NIMH Data Archive (NDA) repository [88].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of measures administered to participants.
[DOCX File , 763 KB - resprot_v13i1e57600_app1.docx]

Multimedia Appendix 2
Peer-review reports from the Health Disparities and Equity Promotion (HDEP) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 138 KB - resprot_v13i1e57600_app2.pdf]

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Abbreviations

AI: artificial intelligence
DSN: dating and sexual networking
IPV: intimate partner violence
LGBT: lesbian, gay, bisexual, and transgender
MSM: men who have sex with men
Q&A: question and answer
SV: sexual violence

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Protocol

Novel Machine Learning HIV Intervention for Sexual and Gender Minority Young People Who Have Sex With Men (uTECH): Protocol for a Randomized Comparison Trial

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Abstract

Background: Sexual and gender minority (SGM) young people are disproportionately affected by HIV in the United States, and substance use is a major driver of new infections. People who use web-based venues to meet sex partners are more likely to report substance use, sexual risk behaviors, and sexually transmitted infections. To our knowledge, no machine learning (ML) interventions have been developed that use web-based and digital technologies to inform and personalize HIV and substance use prevention efforts for SGM young people.

Objective: This study aims to test the acceptability, appropriateness, and feasibility of the uTECH intervention, a SMS text messaging intervention using an ML algorithm to promote HIV prevention and substance use harm reduction among SGM people aged 18 to 29 years who have sex with men. This intervention will be compared to the Young Men's Health Project (YMHP) alone, an existing Centers for Disease Control and Prevention best evidence intervention for young SGM people, which consists of 4 motivational interviewing–based counseling sessions. The YMHP condition will receive YMHP sessions and will be compared to the uTECH+YMHP condition, which includes YMHP sessions as well as uTECH SMS text messages.

Methods: In a study funded by the National Institutes of Health, we will recruit and enroll SGM participants (aged 18-29 years) in the United States (N=330) to participate in a 12-month, 2-arm randomized comparison trial. All participants will receive 4 counseling sessions conducted over Zoom (Zoom Video Communications, Inc) with a master's-level social worker. Participants in the uTECH+YMHP condition will receive curated SMS text messages informed by an ML algorithm that seek to promote HIV and substance use risk reduction strategies as well as undergoing YMHP counseling. We hypothesize that the uTECH+YMHP intervention will be considered acceptable, appropriate, and feasible to most participants. We also hypothesize that participants in the combined condition will experience enhanced and more durable reductions in substance use and sexual risk behaviors compared to participants receiving YMHP alone. Appropriate statistical methods, models, and procedures will be selected to evaluate primary hypotheses and behavioral health outcomes in both intervention conditions using an $\alpha<.05$ significance level, including comparison tests, tests of fixed effects, and growth curve modeling.

Results: This study was funded in August 2019. As of June 2024, all participants have been enrolled. Data analysis has commenced, and expected results will be published in the fall of 2025.

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Conclusions: This study aims to develop and test the acceptability, appropriateness, and feasibility of uTECH, a novel approach to reduce HIV risk and substance use among SGM young adults.

Trial Registration: ClinicalTrials.gov NCT04710901; https://clinicaltrials.gov/study/NCT04710901

International Registered Report Identifier (IRRID): DERR1-10.2196/58448

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KEYWORDS

HIV; mobile health; mHealth; text messaging; machine learning; mobile app; sexual and gender minority; Young Men's Health Project; YMHP; motivational interviewing; substance use; harm reduction; mobile phone

Introduction

Background

Sexual and gender minority (SGM) young adults are disproportionately affected by HIV in the United States, and substance use is a major driver of new infections. Among men who have sex with men (MSM) in the United States, the lifetime risk of receiving an HIV diagnosis is 1 in 6, compared to 1 in 524 among heterosexual men [1]. According to the 2022 Centers for Disease Control and Prevention (CDC) *HIV Diagnoses, Deaths, and Prevalence* report, approximately 70% of new HIV diagnoses were attributable to male-to-male sexual contact [2]. Young MSM are at particularly high risk for HIV and sexually transmitted infections (STIs). The CDC in the same report found that young people aged 13 to 34 years accounted for approximately half of all new HIV diagnoses in the United States in 2022. Transgender women in the United States have also been found to be at an increased risk for HIV [3]. A 2021 CDC report found that 4 in 10 transgender women surveyed in 7 major US cities are living with HIV [4]. While transgender women made up the large majority of new HIV diagnoses within transgender and gender nonbinary populations at 87%, HIV incidence among all these identities substantially rose between 2018 and 2022, with a staggering 136% rise in diagnoses among gender nonbinary persons, 33% in transgender men, and 24% in transgender women [2].

In the United States, evidence suggests that substance use is associated with condomless anal sex and increased numbers of sexual partners [5-9], both of which may increase one's risk of HIV infection. MSM have been shown to be 3 to 4 times more likely to report substance use compared to the general population [10-12]. HIV infection among transgender women has also been associated with polysubstance use and sexual risk behaviors [13]. Compared to the populations of cisgender men and transgender women, little has been established in existing literature that examines the effects of sexual risk and substance use behaviors contributing to HIV and STIs in transgender men and gender nonbinary individuals. Our work uses the definition of *transgender* as individuals whose gender identity differs from their assigned sex at birth [14] and *gender nonbinary* as an umbrella term for individuals whose gender identity is neither man nor woman, encompassing a variety of experiences including but not limited to identification with multiple genders, no gender, or a gender that changes over time [15].

Lesbian, gay, and bisexual adults in the United States are approximately twice as likely to use web-based dating sites and apps compared to their heterosexual counterparts [16]. People who use web-based venues to meet sexual partners are more likely to report substance use, sexual risk behaviors, and STIs [17-19]. Geosocial networking apps, such as Grindr (Grindr, Inc) and Tinder (Match Group, Inc), use GPS to facilitate more efficient dating and networking with others based on proximity, which in turn may increase the likelihood of STI acquisition in specific geographical areas [20]. Research has also indicated that some MSM, transgender women, and gender nonbinary people use digital technologies to search for and intentionally use illicit drugs before or during sex to sustain, enhance, disinhibit, or facilitate the sexual experience, which may contribute to increased risk of HIV and other STIs through substance-induced disinhibition and increased length of sexual sessions [21,22].

Although web-based and social media data have been used by researchers in interdisciplinary fields for a range of health-related applications [23-25], to our knowledge, no interventions have been developed that use machine learning (ML) to inform HIV prevention and substance use harm reduction efforts for both MSM and other SGM populations. Previous research suggests the feasibility of applying social media and web-based data mining as a public health surveillance strategy [26-29]. ML, a branch of computer science that uses statistical and optimization tools to "learn" patterns and trends from large quantities of data, can be used to identify or predict new patterns or trends [30]. This approach has been used to detect and predict other health-related outcomes, such as preterm births [31], health care monitoring of patients with chronic illnesses [32], and suicide prevention [33]. On an individual level, insights gleaned from web-based and social media use patterns can inform cost-effective, scalable interventions that are highly personalized and delivered via technology (ie, tailored messaging and outreach from health workers).

The use of web-based and social media data mining and ML approaches within SGM populations for HIV prevention and substance use harm reduction has important implications for public health. Our team previously developed and tested a social media data mining program that correctly identified HIV risk and amphetamine and methamphetamine use using only social media data [34]. This system was refined and tested for this intervention trial.

There are few "best" rated evidence-based risk reduction interventions (EBRRIs) in the CDC Compendium of Prevention Research Synthesis for young adult, HIV-negative MSM. To our knowledge, there is currently 1 "best" rated EBRRI for

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young transgender women [35] and no "best" rated EBRRIs for other SGM populations, such as transgender men and gender nonbinary people. One of the few "best" rated EBRRIs for young gay and bisexual men is the Young Men's Health Project (YMHP), which is a manualized 4-session intervention that uses motivational interviewing (MI) and problem-solving skills to provide personalized feedback for reducing risk behaviors and promoting HIV prevention skills such as using HIV pre-exposure prophylaxis (PrEP) [36]. It is also the only intervention to show significant effects in reducing both condomless anal sex and substance use. YMHP has also been effectively used in remote delivery [37]. The YMHP intervention component, MI, is a proven approach in HIV or STI prevention for many populations [38,39]. However, few research studies have tested the effectiveness of MI for risk reduction with other SGM people, including transgender women, transgender men, and gender nonbinary young people [40,41].

This Study

We hypothesize that the uTECH+YMHP intervention will be considered acceptable, appropriate, and feasible by most participants. Furthermore, we hypothesize that participants receiving the combined uTECH+YMHP intervention will show greater and more sustained reductions in substance use and sexual risk behaviors compared to those receiving the YMHP intervention alone. Specifically, we anticipate that the integration of ML-informed SMS text messages will enhance the efficacy of YMHP counseling methods by providing personalized, timely, and contextually relevant support, ultimately leading to improved health outcomes in this sample of SGM young adults.

Methods

Overview

This protocol was created following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines (Multimedia Appendix 1) [42]. The proposed study is a randomized comparison trial to evaluate the acceptability, appropriateness, and feasibility of uTECH, which is a text-based risk reduction intervention that leverages a data mining and ML algorithm to provide personalized prevention messaging to users. uTECH will be compared to an existing best-evidence MI intervention (YMHP). Participants will be randomly assigned to one of two conditions: (1) uTECH+YMHP (trial intervention+existing intervention) or (2) YMHP only (existing intervention only). Those in the uTECH+YMHP condition will receive 4 YMHP sessions with a trained master's-level social worker and tailored SMS text messages. Those in the YMHP arm will only receive 4 YMHP sessions. Participants in both conditions will either contribute location-tracking and keylogger smartphone data through an app called "eWellness" (version 1.0.24) or provide data downloads from their most-used, web-based dating and social media accounts. These data will be used to inform and prime the ML algorithm that will be used to make predictions and generate tailored SMS text messages for the uTECH+YMHP condition. The overarching goal of this study is to evaluate the acceptability, appropriateness, and feasibility of uTECH in conjunction with YMHP (condition 1) compared to YMHP alone (condition 2). This study was registered with ClinicalTrials.gov under NCT04710901.

Target Population

This study aims to recruit 330 participants. Half (n=165, 50%) of the participants will be randomized to receive uTECH+YMHP (condition 1), and the remaining half (n=165, 50%) will be randomly assigned to receive YMHP only (condition 2).

To be eligible for the study, participants must be aged 18 to 29 years, identify as SGM, have had anal or oral sex with a man (defined by the participant's interpretation) in the past 3 months, have used substances (such as alcohol, marijuana, amyl nitrate [poppers], methamphetamines, heroin, cocaine, and ecstasy) in the past 3 months, have had sex while using substances in the past 3 months, have a negative or unknown HIV status, and have used a dating app to meet sexual or substance use partners in the past 3 months. Participants must also own a smartphone, reside in the United States, be willing to participate in a 12-month study, and be able to provide informed consent. Participants that use an Android smartphone as their primary device must consent to install the eWellness app on their phone to remotely collect keystroke and geolocation data throughout the duration of the study. Participants who use an iOS (Apple Inc) smartphone must provide the study team with at least 1 set of data from both their primary dating app and their most-used social media account every 6 months. Failing to meet all the stated criteria would disqualify individuals from enrollment in the study. Exclusion criteria were conceived to build upon existing literature for HIV prevention in SGM populations while also expanding gender criteria to be inclusive of transgender and gender nonbinary individuals who have sex with men. Our study population aims to capture the identities of young adult users of queer-centered dating apps and websites such as Grindr, Scruff (Perry Street Software, Inc), and Sniffies (Sniffies, LLC) who may be at heightened risk of HIV and STI transmission [17-19], particularly in the context of substance use [5-9].

eWellness App Development

The mobile app, eWellness, was developed during phase 1 of this study and uses the AWARE framework [43], which is an open-source context instrumentation that uses smartphone sensor instruments to infer, log, and share mobile information for application developers and researchers. The AWARE framework has been used in numerous earlier eHealth studies, for example, to predict depression and anxiety [44,45], progression of Parkinson disease [46], or alcohol use events [47]. We developed eWellness using the AWARE framework and dashboard to record keylogging data (data entered into the user's preferred smartphone keyboard), which are remotely downloaded to secure databases daily. eWellness is also enhanced with a user-friendly interface that provides several "tabs" of information, including a study timeline and incentive chart; a brief survey; and an interactive Google-based map of nearby HIV and STI testing locations, risk reduction supportive services, needle exchanges, and other harm reduction and substance use treatment services.

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The data collected through the eWellness app are used to refine and "teach" the ML algorithm to make predictions that can be used to inform the uTECH intervention. During the 12-month design process, we developed a working version of the app and added additional features as they were developed. We recruited SGM people (n=20) aged >18 years who used Android phones and used websites and apps to seek sexual or substance use partners. These phase-1 participants downloaded the app, which collected data that were used by the study team to further refine the ML algorithm.

Throughout the 12-month study, we also conducted semistructured interviews with the participants to obtain feedback and preferences on possible app functions. Interviewers followed a questionnaire developed by the principal investigator and research staff. Data from these phase-1 interviews were analyzed using rapid qualitative analysis [48], and insights were used to refine and finalize the app in preparation for phase 2.

During phase 2, the eWellness app will be installed by participants who use Android smartphones. Once installed, the app will collect data continuously for 12 months. The app collects the following data: keystrokes (letters and numbers that the user types into their smartphone keyboard), the time and date of information that is typed into the keyboard, the name of the app used when typing in an app, and geolocation. The app does not collect the following data: any data that are not typed directly into the smartphone keyboard, photos or camera data, accelerometer data, video, drop-down menu selections, barometer, audio or microphone data, battery data, text-to-speech data, Bluetooth data, address book contacts, gyroscope data, screen time tracking data, gravity sensor data, incoming SMS text messages, magnetometer data, phone logs, proximity sensor data, installation logs, scheduler data, network sensor availability, temperature data, rotation sensor data, Wi-Fi data, telephony data, or time zone data.

Social Networking App Downloads

Participants who use iOS smartphones will be asked to provide social networking app account downloads from their most frequently used web-based dating apps, such as Grindr or Tinder, and social media accounts, such as Twitter or X (X Corp), Instagram (Meta Platforms, Inc), Reddit (Reddit, Inc), and Facebook (Meta Platforms, Inc), to send to the research team. The data requests will occur at baseline and at 6-month and 12-month follow-up interviews. The exact data request process varies for each app but generally involves the user going into the app settings and requesting a data download that will be sent to the participant's email address. The participant then downloads their data and emails the files to an encrypted email address managed by the research team.

Data requests may include but are not limited to text-based content of social media posts, profile information, chats and messages they send to others, like or viewing history, advertisement history, and background activity (such as time spent on the app, geolocation, and account settings).

YMHP Intervention

The YMHP intervention consists of four 1-hour counseling sessions that use MI as a collaborative, goal-oriented approach of communication to discuss how participants manage sexual health and substance use in their daily lives. The goal of the YMHP counseling sessions is to explore these issues while supporting participants in making informed decisions for their health [36]. The sessions will be conducted by doctoral students trained in YMHP, holding master's degrees in social work, and supervised by a licensed clinical social worker.

There is a wealth of evidence demonstrating the effectiveness of MI for behavioral change [49]. MI is rooted in the principles of engaging, focusing, evoking, and planning. The practice and implementation of MI use deep listening skills, effective reflections, and strategies for responding to resistance. Engaging involves building rapport and creating a sense of alliance through approaching participants with an attitude of curiosity, compassion, and understanding. Focusing involves exploring the participant's view of their situation and selecting a target behavior for change. Although the main target behaviors are sexual health and substance use, understanding the participant's priorities and goals is essential. Evoking is the act of finding out the participant's own reasons for change and brainstorming how to reach those goals. Evoking can be achieved using open-ended questions and the Ask-Tell-Ask method [50]. Planning involves the creation of a course of action and the anticipation of obstacles. The transition into the planning stage should only be done when the participant is ready and willing to do so.

For this study, YMHP will be tailored and used with young adults across the SGM spectrum and will include gay and bisexual men as well as transgender women, transgender men, and gender nonbinary individuals who have sex with men, reflecting our study population.

The uTECH Intervention

Participants randomized to receive the uTECH intervention (uTECH+YMHP) will receive SMS text messages that use the Information-Motivation-Behavior Skills (IMB) model [51] to improve substance use harm reduction and promote safer sex practices. The IMB model was developed to use information, motivation, and behavioral skills to promote HIV-related behavior change, positing that when groups at risk for HIV are well informed, motivated to act on their knowledge, and have the necessary behavioral skills to seek out and initiate change, they will successfully overcome obstacles to make behavior change. The IMB model is effective in enhancing protective health behaviors such as adherence to interventions or reduction of risk behaviors with people living with HIV or AIDS [52-54] and people who use substances [55-57].

Staff will follow the IMB framework to generate content for the SMS text messages, a process that will be informed by an extensive review of public health messaging, scientific literature, and validated survey instruments tailored for specific subgroups that will be recruited for this study. The groups include people who inject drugs, people who do not inject drugs, people who are on PrEP, people who are not on PrEP, transgender and nonbinary people who are on PrEP, and transgender and nonbinary people who are not on PrEP. Each participant will be assigned to 1 of the above subgroups based on their answers in their baseline interview. The SMS text messages will be sent

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to participants using Twilio (version 8.0.0; Twilio Inc) [58], a web-based communications service that can be programmed to send and receive SMS text messages. Approximately 2 SMS text messages will be scheduled per week, so that each participant will receive 100 text messages over the course of 12 months.

To obtain feedback, participants will be asked to respond to each SMS text message. Participants will be compensated US $1 per SMS text message to which they reply. Each SMS text message also includes an opt-out option to comply with cell carrier antispam policies. The feedback from participants will also be used to enhance the ML algorithm in preparation for fully automated SMS text message generation and assignment (Table 1).

Table 1. Text message content examples from the uTECH intervention using the Information-Motivation-Behavior Skills (IMB) model.

	PrEP[a] initiation	PrEP adherence	Sexual risk reduction	Substance use harm reduction
Information	"PrEP reduces the risk of getting HIV from sex by approximately 99%—if taken on an ongoing basis before sex and continued after sex. It is also called Truvada or Descovy."	"Did you know? The Food and Drug Administration approved injectable PrEP, which is an option for people who are tired of taking a pill every day. It is an injection given every 2 months. Find out more at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention."	"If you had unprotected sex, you can take PEP (postexposure prophylaxis) up to 72 hours after possible exposure to prevent HIV. Watch a video to learn more: https://www.youtube.com/watch?v=Yu82TFo6j94&featu"	"Here is a tip for staying hydrated while drinking: drink 1 glass of water for every alcoholic beverage you have. This is known as the 1-for-1 rule and may help moderate your drinking and lessen the chance of a hangover."
Motivation	"Did you know that studies show taking PrEP lowers HIV-related anxiety? Are you less anxious about HIV when you are on PrEP?"	"Did you know that studies show taking PrEP lowers HIV-related anxiety? Are you less anxious about getting HIV when you are on PrEP?"	"Nervous about getting STI[b] testing? It is safer to get tested and know the results. Here is how others overcame their concerns about STI testing: https://www.youtube.com/watch?v=rN5d_XQKRxg."	"If you ever inject with a friend, you could consider doing so at a SIS[c]. SIS refers to places where people who use injectable, but illegal, opioids such as heroin can do so without fear of overdose, prosecution, or spreading disease. You can try looking up sites in your area to find them or contact a member of the research team for assistance."
Behavior	"Reply with the number of the statement that applies to you: 1. I have talked to a medical provider about getting PrEP but have not yet started taking it. 2. I have already talked to a medical provider about getting PrEP and have begun taking it. 3. I have not talked to a medical provider about getting PrEP and have not taken it yet."	"Reply with the number of the statement that applies to you: Have you at any point considered stopping PrEP? 1. No, I am happy with PrEP and expect to continue taking it. 2. No, I am neither happy nor unhappy with PrEP, it just does not seem like an option to stop PrEP use. 3. Yes, but I changed my mind and expect to continue taking it. 4. Yes, and I did stop use for a period of time. Since then, I have resumed and plan to continue taking it. 5. Yes, and I am planning on discontinuing use soon."	"Reply with the number of the statement that applies to you: 1. In the past month, I have gotten tested for HIV or ≥1 STIs. 2. In the past month, I have not gotten tested, but I have booked an appointment or set a date to get tested in the near future. 3. In the past month, I have not gotten tested and currently do not have an appointment or plan to do so."	"Reply with the number of the statement that applies to you: Have you ever trusted someone to supervise you (or trip-sit) as you inject for safety purposes? 1. Yes, always. 2. Yes, but only once or a few times. 3. Yes, but I would not do it again. 4. No, but I would like to in the future. 5. No, I do not feel comfortable being supervised."

[a]PrEP: pre-exposure prophylaxis.

[b]STI: sexually transmitted infection.

[c]SIS: safe injection site.

Recruitment

Web-Based Outreach

Participants will be recruited through web-based outreach methods including targeted advertising on social media sites (ie, Meta, Grindr, Craigslist [Craigslist Inc], and Reddit), with a focus on Facebook Pages and Groups, or forums that may attract SGM individuals who use substances. The research team will also contact community organizations and prominent users with high follower counts to broaden recruitment efforts on social media sites such as OnlyFans (OnlyFans Ltd) and Instagram.

In-Person Outreach

The research team will distribute recruitment materials such as business cards, flyers, and palm cards at events that may attract SGM individuals who use substances; sexual health clinics; lesbian, gay, bisexual, transgender, and queer centers; substance use treatment centers; nonprofit organizations; and retail businesses. Staff will reach out to community-based

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organizations and retail businesses by phone and email, offering to mail recruitment materials to display at their locations to broaden recruitment nationwide.

Referral Program

Both participants and nonparticipants will be given the opportunity to refer others to the study and receive compensation for their referrals. Those interested in the referral program will be given information about the study, a sample message to send to others for referral purposes, and a link to sign up as a referrer so that the study staff can compensate them. Participants will be offered the opportunity to receive physical recruitment materials by mail (flyers and palm cards) to refer people within their social networks. Referrers will receive US $20 sent to their payment method of choice (Venmo [PayPal Holdings Inc], Cashapp [Block Inc], Paypal [PayPal Holdings Inc], or Amazon [Amazon Inc] e-gift card) for every person referred into the study that completes their baseline appointment (up to 5 people total).

Enrollment Process

Screening

All participants will first complete a web-based screener survey on Qualtrics (Qualtrics International Inc), a web-based survey platform [59]. The screener will provide information about the study and ask the participant questions to determine eligibility and their willingness to provide keystroke and geolocation data (Android users) or social media data (iOS users). If the potential participant meets initial eligibility criteria, the survey will use branching logic to show additional screens for the individual to provide contact information, including email address and phone number.

Research staff will review screener responses daily and closely examine responses to check for fraudulent or false eligibility. Qualtrics collects users' geolocation information and IP addresses, which will be used to input into a third-party fraud-checking website, such as Scamalytics [60]. The information we receive from Qualtrics will be checked using such websites to determine whether their phone number is a voice-over IP (or noncellular, internet) number or whether their IP address has been blacklisted for fraudulent activity or uses virtual private network, which would enable non-US users to bypass geolocation-based restrictions. "Eligible" screened participants who use a voice-over IP or virtual private network or come from an IP address with high fraudulent activity will be coded as "fraud" and will not be contacted by study staff.

Those who submit screeners that appear legitimate and who are eligible according to study criteria will be contacted by research staff via phone call, email, or SMS text message to schedule an onboarding. Participants will be provided a link to Calendly [61], a web-based calendar scheduling service, to pick a time for their onboarding session and will receive automated reminders for their appointments once booked. All appointments will take place over the Zoom videoconferencing platform. The interviewer will confirm that the participant will be in a safe and private setting to talk about confidential information for the duration of the call before beginning the session.

Randomization

All eligible participants will have their information entered into a password-protected and encrypted database that is only accessible by Health Insurance Portability and Accountability Act–certified and institutional review board–approved research staff. Alongside contact information, all participants will be assigned a participant ID number and computer-generated randomized assignment to 1 of 2 intervention groups: uTECH+YMHP or YMHP only. This randomization will be done before onboarding so that the onboarding study staff will know which type of onboarding will be required.

Onboarding Procedures

Preparing for the Session

Before the participant joins their onboarding Zoom call, the interviewer will review the crisis management protocol, open up the appropriate forms for the participant's mobile device (iOS or Android), and review the participant tracking sheet to ensure that they have the participant's information from the screener. The interviewer will join the Zoom virtual conference room 5 to 10 minutes in advance of the participant and will have their camera on for the duration of the call. The participant will not be required to have their camera on. When the participant joins the Zoom call, the interviewer will confirm with the participant that they have 60 to 90 minutes available for the appointment and confirm that the participant is in a safe and private setting.

Consenting (All Participants)

The interviewer will open the appropriate consent form for the participant's phone type (Android or iOS) and study condition (uTECH+YMHP or YMHP only), which is a survey hosted on Qualtrics, and share their screen on Zoom so that the participant can view it simultaneously. The interviewer will remind the participant that they will receive a copy of the document via email at the end of the call. The interviewer will input the participant ID at the top of the page and review study details while regularly asking the participant if they have any questions. The consent form includes a detailed explanation of all study requirements and how their data will be protected. At the end of the consent form, the interviewer will ask if the participant consents to the study. If affirmative, the interviewer will check the box for "I agree to participate in the study," provide their initials on the survey, and submit the consent survey. If the participant does not consent, then the interviewer will check the box for "I decline to participate in the study," provide their initials on the document, submit the survey, thank the participant for their time, and end the call. The consent process will take approximately 25 minutes. If the participant consents to participate, then the onboarding session will continue.

Installation of the eWellness App (Android Users Only)

Participants who use Android smartphones will receive step-by-step instructions on how to install the eWellness app (version 1.0.24, released January 2023) on their primary smartphone, where it will remain active and collect data for 12 months. The interviewer will send the participant a short link that they can type in their Android internet browser and download the app. The interviewer will guide the participant

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through the app download and setup process and troubleshoot any technical issues that may arise. If the interviewer or the participant runs into technical difficulties that cannot be resolved at the time of the interview, the interviewer will continue onto the baseline survey and make a note that they will have to complete the app download within a week's time after consulting with the research team. If the app is compatible with the device and successfully downloads, the interviewer will continue to guide the participant in completing the in-app Wellness Survey. This process will take approximately 15 minutes.

Wellness Survey (iOS Users Only)

The Wellness Survey is a Qualtrics survey version of the in-app Wellness Survey that Android users complete. The participant receives a link to this survey through SMS text message, and the interviewer will instruct the participant to complete this short survey. This process will take approximately 5 minutes.

PrEP Verification (All Participants)

If the participant endorses current PrEP use, the interviewer will ask the participant to upload a photo of their prescription bottle to the eWellness app, which is routed to a Qualtrics survey that is encrypted with Transport Layer Security for all transmitted data. Participants may also choose to block or cover any personal information they do not wish to share with researchers. This process will take approximately 5 minutes.

Social Networking App Download Requests (iOS Users Only)

Participants who use iOS smartphones will receive step-by-step instructions on how to request social networking app downloads from their most frequently used web-based dating apps (such as Grindr or Tinder) and social media accounts (such as Twitter or X, Instagram, Reddit, and Facebook) to send to the research team. The study staff will describe the process specific to each dating app or social media app and either email the instructions to the participant or walk the participant through the process during the Zoom meeting. The participant will then need to download their data and email the files to an encrypted email address managed by the research team. This process will take approximately 10 minutes.

Baseline Interview (All Participants)

The interviewer will share their screen to display the baseline survey, which is hosted on the Qualtrics platform, and includes a series of questions about demographics, intimate partner history, sexual health, substance use, intimate partner violence, vaccine hesitancy, effects of COVID-19, and eHealth mobile app tracking and notification preferences. The survey also asks the participants for their preferred payment information. After all questions have been answered, the interviewer will stop sharing their screen and submit the baseline survey. This process will take approximately 30 minutes.

YMHP Scheduling (All Participants)

The interviewer will schedule the participant with their first YMHP session through Calendly, a scheduling website, with an interventionist who is not the baseline interviewer. The participant's first session will be scheduled approximately 1 week after the onboarding and baseline survey (week 1). The interventionist and the participant will receive a calendar invite reminder for this session. Subsequent sessions are scheduled between the interventionist and the participant and will take place in week 2, month 1, and month 2 after onboarding. The scheduling process will take approximately 5 minutes.

Closing Out the Onboarding (All Participants)

The interviewer will open the "Locator form" to document the participants' preferred forms of contact, their phone type, and how they heard about the study. The interviewer will remind the participant of the follow-up surveys at 3, 6, 9, and 12 months; their first YMHP session (if applicable); and when to expect payment (approximately 3-5 business days after each data collection point or YMHP session). This process will take approximately 10 minutes.

Postonboarding Activities (All Participants)

Immediately after ending the onboarding session with the participant, the interviewer will download the materials completed by the participant and upload them to a secure, password-protected cloud-based database (such as Box). Afterward, to ensure confidentiality, the interviewer will delete all materials from their computer. The interviewer will also update the participant's information in a tracking database and send a thank you email to the participant, which will include a copy of the study's consent form and the University of California, Los Angeles (UCLA) Office of Human Research Protection Program participant bill of rights [62], which details protections for participants within the consent and participation process. This process will take approximately 30 minutes.

STI or HIV Testing (All Participants)

Participants will be offered the option of sending STI or HIV test results to the study team at their baseline and 6-month appointment dates. While testing is optional, those who do elect to send results will be compensated US $30 at both points (for a total of US $60) for providing test results for HIV, syphilis, chlamydia, and gonorrhea. Participants will be instructed to send their results in the form of a scanned document, screenshot, or PDF to an encrypted email managed by the study team. All identifying information in the file containing results will be redacted by the research team before being saved in the study's password-protected, encrypted, cloud-based database. When test results are received, participants will be reminded of their compensation and encouraged to reach out to research staff or their YMHP interventionist if they would like further information or resources.

If requested, participants will be provided HIV, syphilis, gonorrhea, or chlamydia prevention and treatment resources. They will also be asked if they have a health care provider who they could contact for treatment. If they do not, they will be offered a list of sexual health clinics or providers in their area. In addition, participants will be offered a partner notification service to anonymously notify recent sexual partners of a possible STI exposure.

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YMHP Sessions (All Participants)

Overview

YMHP intervention sessions will be held over Zoom, a videoconferencing platform. Session 1 will take place during week 1 (following onboarding), session 2 during week 2, session 3 during month 1, and session 4 during month 2 (Figure 1). All sessions will be audio recorded for intervention fidelity and ongoing intervention training and clinical support. No video or participant names will be captured for the recording. Participants will be asked to change their Zoom name to their participant ID before recording.

Figure 1. uTECH participation overview flowchart. STI: sexually transmitted infection; YMHP: Young Men's Health Project.

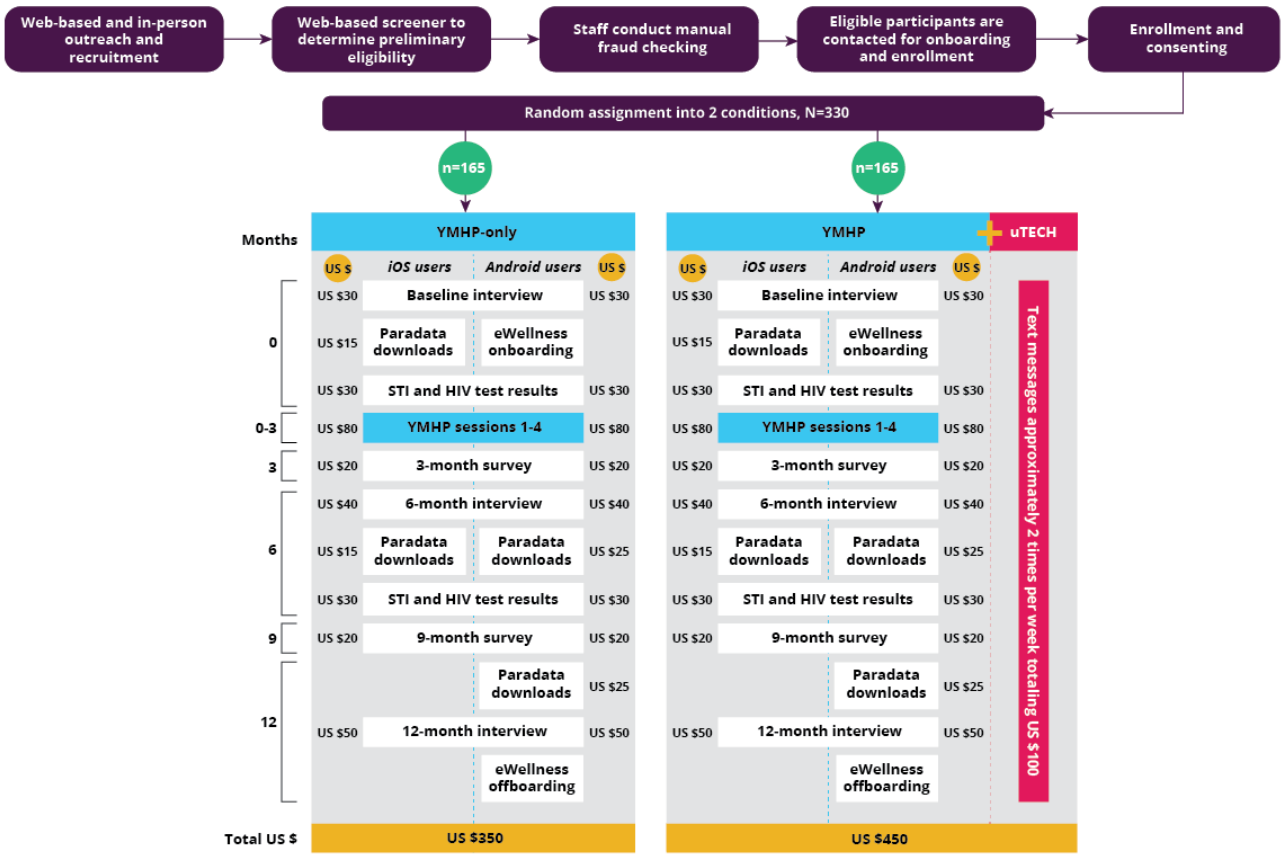

Session 1: Engagement, Focusing, and Evoking on the First Target Behavior (Sexual Health or Substance Use)

The interventionist will remind the participant about the YMHP structure and limits of confidentiality. The interventionist will engage in a priorities card sorting activity to identify participant's 3 main values, which will guide future motivational enhancement and begin to elicit the participant's view of their first target behavior. After identifying whether they will first tackle sexual health or substance use, the interventionist will assess the participant's readiness for change, discuss a plan for moving forward, and consider goals. At the end of the session, the interventionist will offer a closing summary and schedule the next session for the following week.

Session 2: Second Target Behavior; Continue Focusing and Evoking

The second session will begin with an opening statement to highlight any change talk [50] or goal that was mentioned in the previous session. This session will center primarily on introducing the second target behavior and collaborating on setting the session agenda with the participant. The interventionist will briefly revisit the previous session's topic and check for any changes or recent events since they last met. Next, they will ask permission to address the second target behavior, all the while using strategies for eliciting change talk and managing discord. Finally, the interventionist will offer a closing summary at the end of the session, highlighting change talk and any steps taken toward change, and schedule the third session during month 1.

Session 3: Change Plan

This session will begin by highlighting and integrating change talk on both target behaviors and any ideas or goals the participant has articulated around these behaviors. This will be done collaboratively to set the agenda for the session together. The interventionist will ask permission to discuss collaborating on a change plan together based on the participant's progress over the last 2 weeks on both goals. Through evoking the participant's ideas about change, the interventionist will reinforce their self-efficacy for taking steps toward change and offer suggestions on how to adhere to their plan. The interventionist will elicit feedback on a change plan that reflects the participant's goals, priorities, and readiness to change while anticipating and planning for barriers that may arise in the future. At the end of the session, the interventionist will offer a closing summary highlighting change talk, briefly reiterating the basic

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plan, and reminding them that the next session will be focused on moving ahead independently.

Session 4: Consolidating Commitment; Relapse Prevention or Termination

The final YMHP session will open with the interventionist summarizing the plan developed previously, collaborating on the session agenda based on the participant's goal updates, and reiterating that this will be the last YMHP session. The participant will discuss how the plan has gone, and the interventionist will manage discord as appropriate while affirming the participant for any steps moving forward. The interventionist will evoke the participant's ideas about how to adapt the plan in the future should problems arise and develop a backup plan as appropriate. The session will end with a progress summary of the last 4 sessions and a space to reflect on the process of termination with the participant.

Automated SMS Text Messages (uTECH+YMHP Participants)

Participants assigned to the uTECH+YMHP intervention will receive approximately 2 SMS text messages per week that provide resources promoting sexual wellness and substance use harm reduction. Participants are assigned to specific subgroups based on their answers to the baseline interview to ensure that SMS text messages are tailored. Participants are compensated US $1 per SMS text message to which they respond, and this amount is disbursed at 4 time points corresponding to their 3-, 6-, 9-, and 12-month assessments.

Incentives

Incentives vary according to intervention and phone type (Figure 1). Participants assigned to the YMHP-only condition will receive US $350, and participants assigned to the uTECH+YMHP condition will receive US $450, including responses to all uTECH messages. The payments for baseline (US $30), 6-month (US $40), and 12-month (Android: US $50; iOS: US $55) interviews are escalated to promote retention in the study. Participants will be paid for each study activity to encourage engagement.

Discharge From the Study

Participants will be discharged from the study after they complete their 12-month assessment and offboarding. At their final interview, Android-using participants will receive instructions on how to uninstall the eWellness app from their phone. The study team will also discontinue sending automated SMS text messages to uTECH+YMHP participants.

Ethical Considerations

The research and ethics presented in this study were reviewed and approved by the South Campus institutional review board of the UCLA (#22-000009). The research has also been granted a Certificate of Confidentiality from the National Institutes of Health (CC-OD-22-3555), which deems identifiable information gathered in the course of research not admissible as evidence in any legal processes. Additional terms were provided to ensure confidentiality for the participants. These terms included protection for all study-related data obtained by all uTECH study staff, which includes employees, students, interventionists, and other professionals staffing the project. All participant data will be deidentified and accessible only to staff who completed training in Health Insurance Portability and Accountability Act guidelines and human participants research ethics.

Technical concerns related to data privacy were considered throughout the app development process, which occurred during phase 1 of this project. In collaboration with the UCLA Information Technology and UCLA Compliance departments, considerations related to data storage and data in transit were considered, including the institution's legal and ethical duties related to the handling of personally identifiable information. Procedures and protocols were established in collaboration with the UCLA Technology Development Group and the UCLA Departments of Computer Science and Engineering.

To enroll in the study, participants would have to review and consent to a study consent form detailing all activities associated with study participation; potential risks and benefits to participation; incentives; and privacy or confidentiality protections granted by the National Institutes of Health Certificate of Confidentiality, UCLA Office of Human Research Protection Program, and study investigators. Participants will be informed during the consenting process that all payments will be made via e-gift card disbursement with a breakdown of all payments totaling the amount of US $350 or US $450 depending on the study group assignment and phone type.

Primary Outcomes

The primary outcomes that the study will measure are the acceptability, appropriateness, and feasibility of the implementation for uTECH+YMHP and YMHP-only conditions. These primary outcomes will be assessed through surveys conducted at 3-, 6-, 9-, and 12-month time points. The study will measure how outcomes differ between uTECH+YMHP and YMHP-only conditions.

Secondary Outcomes

The overall framework of this study recognizes that substance use and sexual risk behaviors are primary drivers of HIV and other STIs, which will be assessed through self-reported data on sexual risk, substance use, and self-reported HIV and STI diagnosis, verified through independent medical chart review when submitted by participants. Intimate partner violence, stigma, sociodemographic factors, and use of web-based venues for sex or drug seeking are potential risk factors for HIV and other STIs [63-66]. PrEP use, vaccination, and condom use are potential health protective behaviors. For all participants, we posit that YMHP can also help participants make positive changes toward their self-defined substance use and sexual health goals. For participants in the uTECH+YMHP condition, uTECH can improve participants' skills and motivation to make behavioral changes to improve their health, which may lessen their risk of acquiring HIV and other STIs. In addition, we posit that in this combined condition, positive behavior changes may be more sustainable and durable compared to receiving YMHP without uTECH.

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Assessment Measures (Baseline and 3-, 6-, 9-, and 12-Month Time Points)

This study will include 3 types of assessment: interviews, web-based surveys, and HIV risk assessments. Interviews (approximately 30 min to 1 h) will be completed at baseline and at 6-month and 12-month time points. Self-completed web-based surveys (approximately 15-30 min) will be completed at 3-month and 9-month time points. HIV risk assessment surveys (approximately 5 min) will be completed at all 5 time points (Table 2).

Table 2. Primary and secondary outcomes of the study.

Outcomes	Measures	Variables
Primary		
Acceptability, appropriateness, and feasibility of uTECH SMS text messages	Adapted from AIM[a], IAM[b], and FIM[c] [65]	5-item Likert scale
Acceptability, appropriateness, and feasibility of Young Men's Health Project	Adapted from AIM, IAM, and FIM [65]	5-item Likert scale
Secondary		
Sociodemographic	Multiple items	Nominal
Sexual risk behavior	Multiple items	Nominal, continuous, and dichotomous
Intimate partner violence	Intimate partner violence among gay and bisexual men scale [67]	Ordinal
PrEP[d] and PEP[e] use	Self-reported PrEP or PEP use history	Nominal, continuous; dichotomous, and 6-item Likert scale
STDs[f]	Self-reported STD diagnosis history	Nominal, integer, dichotomous, and interval
PrEP stigma	PrEP Stigma Scale [68]	5-item Likert scale
Substance use	The Alcohol, Smoking, and Substance Involvement Screening Test [69]	Nominal, dichotomous, and yes or no for specific substances
COVID-19	Self-reported COVID-19 diagnosis; how COVID-19 has impacted sexual behavior	Dichotomous and qualitative
Mpox (monkeypox)	Vaccination status, history of mpox diagnosis and exposure, perceived risk, and stigma	Dichotomous, nominal, interval, and 5-item Likert scale
Vaccine confidence	Vaccine Confidence Index [70]	5-item Likert scale
Vaccination history	Self-reported vaccination status for hepatitis A, hepatitis B, human papillomavirus, meningococcal B, meningococcal A, C, W, or Y, and COVID-19	Dichotomous and yes or no for specific vaccines
Seeking sex or drugs on social networks	Websites, chat rooms, message boards, and apps used to meet partners for sex or partying	Nominal
eWellness app features	Types of features (ie, notifications and device functions) and frequency or time of day of notifications that participant would be comfortable with	Nominal, 6-item Likert scale, and dichotomous
HIV risk assessment	Men who have sex with men risk index [71] and people who inject drug (injection drug user) risk index [72]	Nominal and ordinal

[a]AIM: Acceptability of Intervention Measure.

[b]IAM: Intervention Appropriateness Measure.

[c]FIM: Feasibility of Intervention Measure.

[d]PrEP: pre-exposure prophylaxis.

[e]PEP: postexposure prophylaxis.

[f]STD: sexually transmitted disease.

Expected Timeline

Development of the initial version of eWellness was completed in October 2020, and enrollment for the trial started soon after. The eWellness app continued to undergo refinement and development until phase 2 began in November 2021. Enrollment will continue until the target sample size is reached, with 12 months of study engagement per participant. We expect to complete data collection 12 months after the last participant has been enrolled in the study, that is, by June 2024, and plan the dissemination of results subsequently.

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Statistical Analyses

Statistical methods, models, and procedures will be selected according to the research hypotheses being tested and the types of measures involved. We will set $\alpha<.05$ as the level for statistical significance but will use appropriate corrections for multiple comparisons (eg, Bonferroni and Hochberg correction [73]) to ensure that the actual overall effective type 1 error remains at an $\alpha=.05$ level for the tests to be conducted. The frequency and patterns of missing data will be carefully evaluated. To avoid potential bias resulting from missing data, imputation (eg, hot deck or multiple imputation [74]) will be conducted, and statistical significance tests and modeling will be conducted with and without the imputed values. The findings from these analyses will be compared, and any differences will be evaluated. Potential nonlinear relationships between continuous predictors (eg, participants' age) and outcomes (eg, acceptability, appropriateness, and feasibility of uTECH and YMHP) will be evaluated through spline functions (eg, cubic spline).

Planned Analytic Approach

Primary outcomes for the study include the acceptability, appropriateness, and feasibility of each intervention condition. In addition, we will examine behavioral health outcomes (sexual risk and protective behaviors and substance use) in both intervention conditions. Tests of fixed effects for estimates of time-specific differences will be performed using appropriate contrasts. Trend changes and their significance will be analyzed, driven by variance components (random effects). We will use growth curve modeling [75] to examine the effects of treatment on outcomes. Growth curve factors also account for the covariation of follow-up observations within participants. Data from 3-, 6-, 9-, and 12-month follow-up assessments will be modeled using latent growth factors using R statistical software [76] (version 4.4.0; R Foundation for Statistical Computing). Because the first nonbaseline time point in the latent growth curve will be the 3-month follow-up, significant differences in the intercept factor would indicate significant postintervention effects. Significant differences in slope factors would indicate that the groups follow different trajectories. When this is noted, potential group differences at each follow-up assessment will be evaluated by varying the location of the referent time point.

Missing Data

We will impute any missing values, based on the characteristics of the data and the assumptions of the final analyses, such as using multiple imputation if data are missing at random [77]. While analyses of treatment effects are questions of differences after the intervention, baseline data will be used to inform and supplement analyses. For example, baseline data will be used to evaluate whether randomization successfully equated groups on demographic variables and other covariates of theoretical significance. We will use baseline data to evaluate correlates of differential attrition, if observed. If randomization fails or attrition produces group differences, models will use baseline data to control for covariates that are nonorthogonal with treatment condition. We will use growth mixture modeling techniques, including latent class growth curve modeling, to evaluate any meaningful patterns in outcome variable responses across time. We will examine whether treatment condition is associated with outcome response pattern.

Mediation and Moderation

For outcomes where statistically significant differences in acceptability, appropriateness, and feasibility are observed (ie, significant regression coefficients for the treatment variable associated with the participant-level intercept or slope growth factors), post hoc analysis will examine the roles of substance use and technology use as potential mediators. A primary assumption is that uTECH will be associated with improvement in awareness of how technology influences engagement in HIV risk and substance use behavior [78-80]. For each mediator, validated substance use and technology reports will be entered into the model. Like the approach described for primary outcomes, we will specify latent growth curve factors for the hypothesized mediators to understand the covariation of observations within individuals across time. Subsequently, we will examine whether initial differences in the mediators or changes in the mediators over time account for associations between the outcome variable and the treatment conditions. We will use strategies for assessing time-varying mediators that permit regression coefficients of the outcome on the mediator to vary over time. Where appropriate, we will examine the utility of applying these techniques. We will use parameter constraint approaches [81] to assess the statistical significance of indirect pathways. Bootstrapping [82] tests of mediation cannot be conducted with latent variable mediators and nonnormal exogenous variables. When appropriate, we will use alternative approaches such as Bayesian structural equation modeling and Monte Carlo simulation methods in the presence of nonnormality and complex latent variable structures [83]. Participant-level reports of substance use and technology use will be entered into the models, and we will examine whether initial levels of substance use and technology use (or changes in these variables over time) moderate the association between primary outcome variables and treatment condition by examining the significance of interaction terms between growth factors.

Sample Size Calculation and Power Analysis

For the power calculation, we used 1 primary outcome, acceptability. We used a balanced repeated measures design [84] with pretreatment baseline measurements. Using a logistic regression generalized linear mixed model [85], we allowed an individual's 5 measurements (baseline and 3-, 6-, 9-, and 12-month) for acceptability to be correlated via an autoregressive-1 structure. With an initial sample size of 330 (to account for 95% retention), an autocorrelation of 0.1, and a baseline effectiveness of 85%, we aimed to detect a minimum time-averaged difference of 9% in acceptability between any 2 conditions, maintaining 80% power and an a priori α level of .05. This calculation was based on pairwise comparisons between uTECH+YMHP versus YMHP-only conditions. If the autocorrelation [86] between measures within the same individual was as high as 0.5, the sample size was adjusted to detect a minimum difference of 11% between the 2 conditions. A 9% to 11% difference between the 2 conditions is considered statistically significant, given the existing evidence supporting

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YMHP and the relative cost-effectiveness and ease of delivery of the uTECH intervention. The ability to demonstrate a small increase in the acceptability of uTECH over YMHP will support the widespread implementation of uTECH in future efficacy trials.

Results

This study was funded in August 2019. Between August 2019 and June 2024, we have enrolled 424 participants on a rolling basis. Approximately 71% (301/424) of the study participants have completed 12 months of participation. Data collection concluded in June 2024. Data analysis is currently under way, and expected results will be published in the fall of 2025.

Discussion

Anticipated Findings

As mentioned in the *Results* section, at the time of writing this manuscript, the study was fully enrolled (N=424), which meets and exceeds the enrollment objective of 330 participants to account for attrition. Data analysis activities to evaluate the stated study hypotheses are currently underway.

uTECH is a response to changing internet or social media habits and aims to leverage ML-enhanced technology for personalized and automated HIV prevention and substance use harm reduction. Websites and social media use recommendation algorithms to personalize nearly every aspect of our web-based lives, from what news we see to what products we want to buy. All internet users already interact with websites and social media that use ML algorithms to predict and personalize content for their users based on their individual preferences, purchases, and habits. To do this, ML requires an enormous amount of personal data to make accurate and meaningful predictions. The widespread use of recommendation algorithms in social media and websites has also changed how people use the internet, and algorithm-mediated personalized content is not only widely accepted but is also increasingly preferred by people, especially young adults [87], for consuming media and content. According to a consumer research survey, the vast majority of users are willing to share personal data in exchange for better, more relevant, and curated digital experiences [88].

There are potential challenges to the success of uTECH's implementation trial. First, it uses convenience sampling techniques to recruit the target population, which limits the generalizability of the results. In addition, even if recruitment efforts enable us to successfully meet our planned enrollment target, participant data could still fall short of what is needed for ML or for adequate statistical power to detect the effects of intervention conditions on outcomes. For example, numerous technical issues could impact data collection. The eWellness app requires additional battery power as it runs in the background of mobile phones. Certain phone models may automatically turn off data collection to optimize battery use. Participants could also turn off the eWellness app themselves and forget or be unable to turn it back on.

For iOS users, we rely on the availability of third-party data, which may sometimes be unavailable. For example, during leadership changes at Twitter, mass system outages occurred, which impacted the ability of some participants to download their data. Some data downloads (eg, from Grindr) take an unknown amount of time to become available to access and are sometimes a greater burden for participants because it requires the participant to log in to access and download their data and then send them to our secure, encrypted email. This process takes some time, and the access could expire if participants miss their email notification from the third-party system. Despite incentives, many participants may not complete all data collection activities, resulting in missing data. Among these, missing SMS text message feedback may impact adaptive ML and thus reduce the personalization and relevance of the SMS text messages participants receive.

This research will contribute as an implementation science demonstration project on the acceptability, appropriateness, and feasibility of an intervention that delivers a moderate to high level of relevance and personalization that requires fewer direct contact hours and has the potential to reach a far greater number of participants than structured, multisession interventions or in-person interventions. In a less-resourced environment or as public funding becomes more constrained, high-impact interventions that require less staffing may be a more efficient option compared to traditional HIV and substance use intervention paradigms. In addition, this work can potentially be adapted for other public health promotion efforts, including chronic disease management, HIV care adherence, and vaccination promotion.

Conclusions

The primary objective of this study is to evaluate the acceptability, appropriateness, and feasibility of uTECH, a text message–based risk reduction intervention that leverages an ML and data mining algorithm to provide personalized prevention messaging to SGM participants. To our knowledge, this is the first study to use ML and digital technologies to provide tailored sexual and substance use harm reduction for these populations. The results of this implementation trial will offer insights for future research within this field, contributing to developments that can reduce HIV risk and substance use. Outcomes and summaries of this implementation trial will be presented, and recommendations for future research will be suggested if any knowledge gaps are identified. The potential findings of this implementation trial will be reported in academic papers, which will be submitted to peer-reviewed journals and presented at national and international conferences.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available due to the sensitive nature of the data but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 120 KB - resprot_v13i1e58448_app1.doc]

Multimedia Appendix 2
Peer-review report from the National Institute on Drug Abuse Special Emphasis Panel - National Institute on Drug Abuse (NIDA).
[PDF File (Adobe PDF File), 176 KB - resprot_v13i1e58448_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
EBRRI: evidence-based risk reduction intervention
IMB: Information-Motivation-Behavior Skills
MI: motivational interviewing
ML: machine learning
MSM: men who have sex with men
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
SGM: sexual and gender minority
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STI: sexually transmitted infection
UCLA: University of California, Los Angeles
YMHP: Young Men's Health Project

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Protocol

A Microfinance Intervention With or Without Peer Support to Improve Mental Health Among Transgender and Nonbinary Adults (the Creating Access to Resources and Economic Support Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Transgender and nonbinary (TNB) people experience economic and psychosocial inequities that make them more likely to be subject to financial and mental health harms exacerbated by the COVID-19 pandemic. Sustainable, multilevel interventions are needed to address these harms. The onset of the COVID-19 pandemic galvanized many TNB-led organizations to provide emergency financial and peer support for TNB people negatively impacted by the pandemic. However, the efficacy of these interventions has not been evaluated. The Creating Access to Resources and Economic Support (CARES) study seeks to assess the efficacy of feasible, acceptable, and community-derived interventions to reduce economic and psychological harms experienced by transgender people in the wake of the COVID-19 pandemic.

Objective: The study aims to (1) compare the efficacy of microgrants with peer mentoring with that of microgrants without peer mentoring in reducing psychological distress, (2) examine mechanisms by which microgrants with or without peer mentoring may impact psychological distress, and (3) explore participants' intervention experiences and perceived efficacy.

Methods: We will enroll 360 TNB adults into an embedded, mixed methods, 3-arm, and 12-month randomized controlled trial. Participants will be randomized 1:1:1 to arm A (enhanced usual care), which will receive a single microgrant plus monthly financial literacy education, arm B (extended microgrants), which will receive enhanced usual care plus monthly microgrants, or arm C (peer mentoring), which will receive extended microgrants combined with peer mentoring. All intervention arms last for 6 months, and participants complete semiannual, web-based surveys at 0, 6, and 12 months as well as brief process measures at 3 and 6 months. A subset of 36 participants, 12 (33%) per arm, will complete longitudinal in-depth interviews at 3 and 9 months.

Results: Full recruitment began on January 8, 2024, and, as of July 26, 2024, a total of 138 participants have enrolled. Recruitment is expected to be completed no later than March 31, 2025, and the final study visit will take place in March 2026.

Conclusions: This national, web-based study will demonstrate whether an intervention tailored to reduce material hardship and improve peer support among TNB adults will reduce psychological distress. Its equitable, community-academic partnership will ensure the rapid dissemination of study findings.

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Trial Registration: ClinicalTrials.gov NCT05971160; https://clinicaltrials.gov/study/NCT05971160
International Registered Report Identifier (IRRID): DERR1-10.2196/63656

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KEYWORDS

clinical trial; depression; anxiety; peer support; minority stress; cash transfer; COVID-19

Introduction

Financial and Mental Health Inequities

The COVID-19 pandemic has had devastating impacts on transgender and nonbinary (TNB) people. TNB people are a National Institutes of Health–designated health disparity population [1] who experience economic and psychosocial disadvantages that make them particularly vulnerable to pandemic-related harms [2]. Baseline data from an observational cohort of >1500 transgender women indicated elevated prepandemic levels of poverty (46% vs 11%), food insecurity (48% vs 11%), and survival sex work (21% vs 1%) compared with the general US population [2]. Participants also reported high levels of psychological distress (27%), traumatic stress symptoms (41%), and suicidal ideation (28%), all of which can be exacerbated by pandemic-related stress [2]. Another prepandemic study of 850 transgender men also identified high levels of psychological distress (20%), hazardous alcohol use (59%), and polysubstance use (20%) [3]. These prepandemic vulnerabilities are consistent with a nationally representative sample of TNB adults in which 48% were living in poverty and 42% had a history of prior suicide attempts [4].

A national poll of 7000 adults conducted after the onset of the COVID-19 pandemic found that twice as many TNB people became unemployed and 5 times as many TNB people received a pay cut due to the pandemic compared with the general population [5]. A later poll found that TNB people were 125% more likely to have reduced work hours since states reopened after the COVID-19 lockdowns expired [6]. A longitudinal study of 208 TNB people found significant increases in psychological distress, depression, and anxiety after the pandemic onset compared with before the pandemic [7]. A mixed methods study of Latina transgender women found a significant decline in mental health, with the psychological health in the “likely to be well” range falling from 93% (prepandemic) to 50% (after pandemic onset) [8]. Qualitative findings indicated that much of this psychological distress was related to pandemic-induced material hardship [8]. In summary, TNB people experienced financial and psychological inequities before the pandemic and were highly vulnerable to long-term negative economic and mental health consequences of the COVID-19 pandemic.

Pandemic-induced material hardship has been associated with poor mental health globally [9]. At the national level, economic recession has been associated with psychological distress [10]. At the neighborhood level, poverty has been associated with depression and anxiety [11]. At the individual level, material hardship (eg, difficulty paying utility bills, rent, or mortgage or fear of running out of food) has been associated with poor mental health [12,13] and the worsening of existing mental health conditions [14] independent of other measures of socioeconomic status. Material hardship increases exposure to stressors (eg, inability to pay for basic needs) and stressful events (eg, eviction) while also hindering the ability to cope with stress [15,16]. A recent cross-sectional study of 849 transgender people using structural equation modeling found that socioeconomic loss partially mediated the relationship between pandemic-related societal changes (eg, social isolation) and poor mental health [17].

Microfinance Interventions

Microgrants (also called cash transfers) provide a small monetary amount to individuals or families, which they do not have to repay. They can be considered structural interventions because they alter the economic conditions within which health outcomes are produced or reproduced [18]. Cash transfers have been extensively studied in large-scale cluster randomized trials in low- and middle-income countries [19-21] where positive effects on mental health were found [21-24]. A randomized trial with unhoused individuals in Vancouver found that cash transfer recipients accessed stable housing more quickly than controls and increased spending on food, clothing, and rent while reducing spending on alcohol and drugs [25].

Of the 2 major cash transfer programs in the United States, namely the Alaskan National Petroleum Reserve Impact Grant Program [26] and the North Carolina Eastern Band of Cherokee casino grants [27], only the Cherokee program has been evaluated. Several studies have demonstrated positive mental health effects of the Cherokee program [27,28]. While these data provide an important premise for the psychological benefits of cash transfers in the United States, these programs provide ongoing, long-term, and annual revenue generated from business enterprises and do not address whether short-term, targeted microgrants, provided incrementally over several months, can mitigate the long-term negative mental health effects of a pandemic crisis such as the COVID-19 pandemic. Data are needed not only to understand whether short-term microgrants are effective in improving TNB mental health inequities exacerbated by the pandemic but also to assess the mechanisms that may account for their effects.

Peer Support Interventions

Social distancing and isolation, the key aspects of the COVID-19 pandemic response, have been linked to poor mental health [29]. A longitudinal study of 208 TNB adults found that the loss of transgender-specific support during the pandemic was associated with greater intrapandemic psychological distress [7]. Social support and community connection are known to facilitate mental health recovery after crises [30]. Studies conducted before the pandemic indicate that social support via transgender

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community connectedness can reduce suicidal ideation, anxiety, and depression and buffer the mental health effects of stressors among transgender people [31-34]. These data suggest that supportive transgender community connection (ie, peer support) may reduce the psychological distress associated with the pandemic.

Peer mentoring is a form of peer support in which a trained peer promotes skill building in a mentee [35]. Evidence suggests that peer support alone is unlikely to improve mental health in the context of economic challenges [36]. Combining peer mentoring with microgrants may be more beneficial for mental health than providing microgrants alone. However, studies of combined financial and peer support interventions are limited, and none have examined psychological outcomes [37-39]. Given the lasting multilevel harms caused by the COVID-19 pandemic and the associated economic downturn, combining an intervention that directly addresses material hardship (structural) with one that provides peer mentoring support (interpersonal) may be the most effective.

Community Leadership and Engagement

The COVID-19 pandemic galvanized transgender-led organizations, such as the National Black Trans Advocacy Coalition (BTAC), to provide support for impacted TNB people [40]. BTAC provides peer mentoring as well as referrals and support for health, housing, and employment for TNB people. During the early phase of the COVID-19 pandemic, BTAC provided TNB applicants with a onetime US $125 microgrant. They awarded >1200 microgrants and reached >5000 TNB people with health, housing, or employment referrals and peer support [40]. However, the efficacy of these community-led social and structural interventions has not been evaluated. Strong community-academic partnerships with organizations such as BTAC can ensure that community-derived, relevant, feasible, acceptable, and effective interventions are identified and translated into sustainable change.

Theoretical Framework

The Gender Minority Stress and Resilience (GMSR) model [41] describes the way interventions are expected to act via multiple levels of the National Institute on Minority Health and Health Disparities Research Framework [42] to mitigate lasting pandemic-induced harms. Briefly, the GMSR model posits that TNB people experience a combination of general (eg, material hardship) and minority (eg, stigma) stressors. The excess minority stressors combined with general stressors, experienced regardless of gender identity, lead to mental health inequities. The model posits that transgender community connectedness will mitigate minority stress and improve mental health. The Creating Access to Resources and Economic Support (CARES) study (Figure 1) will test whether addressing a general structural-level stressor (material hardship) alone or in combination with social support (ie, peer mentoring to increase transgender community connection) at the interpersonal level will improve mental health and COVID-19 risk reduction behaviors without intervening directly on minority stressors [43].

The CARES study seeks to assess the efficacy of microgrants with or without peer support to reduce economic and psychological harms experienced by TNB people in the wake of the COVID-19 pandemic. The CARES study builds on TNB community–led interventions, leverages the expertise of an existing TNB community advisory board (CAB), and extends ongoing community-academic partnerships with BTAC. This paper outlines the protocol for the CARES study.

Figure 1. A theoretical model for the effects of the COVID-19 pandemic on material hardship and psychological distress among transgender and nonbinary people who experience minority stress.

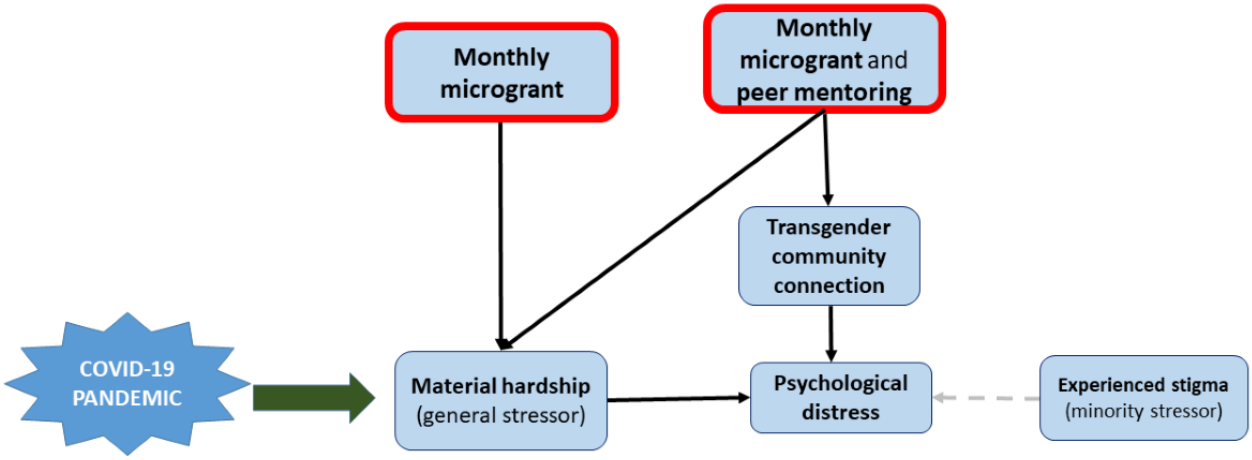

Study Aims and Hypotheses

The CARES study has 3 aims and 3 hypotheses (Textbox 1).

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Textbox 1. The Creating Access to Resources and Economic Support (CARES) study aims and hypotheses.

Aims and hypotheses

- Aim 1 is to compare the efficacy of monthly microgrants, with or without peer mentoring, to reduce psychological distress among transgender and gender nonbinary (TNB) adults, relative to the receipt of a single microgrant. This includes hypothesis 1, that the receipt of monthly microgrants, with or without peer mentoring, will significantly reduce psychological distress scores compared with the receipt of a single microgrant, and exploratory hypothesis 1.1, that the receipt of monthly microgrants with peer mentoring will significantly reduce psychological distress scores compared with the receipt of monthly microgrants without peer mentoring.
- Aim 2 is to examine mechanisms by which monthly microgrants, with or without peer mentoring, impact psychological distress among TNB adults. This includes hypothesis 2, that material hardship will mediate relationships between the receipt of monthly microgrants and psychological distress scores, and hypothesis 3, that transgender community connectedness will mediate relationships between the receipt of monthly microgrants with peer mentoring and psychological distress scores.
- Aim 3 is to qualitatively explore intervention experiences and perceived efficacy with TNB adults.

Methods

Trial Design

This study uses an embedded mixed method design for a 3-armed, randomized controlled trial with 360 transgender adults. Participants are randomized to 1 of 3 arms: arm A (enhanced usual care), which includes monthly financial education videos for 6 months and a single microgrant of US $150 at baseline; arm B (the extended microgrant arm), which includes enhanced usual care components with the addition of monthly microgrants of US $150 for a total of US $900 over the course of 6 months; or arm C (the peer mentoring arm), which includes the extended microgrant arm components with the addition of a structured peer mentoring intervention for a total of 6 months. All study procedures are self-administered over the web or interviewer administered over the telephone, as described in the Study Procedures section (Figure 2).

Potential participants complete an interest form that is reviewed by the participant engagement coordinator (PEC) to exclude bots. Once the interest form is reviewed and approved by the PEC, the participant is sent an individualized link to a web-based prescreening form. Participants deemed eligible based on the prescreening form are then scheduled for final eligibility screening by telephone. Eligible individuals take part in informed consent procedures. Individuals who provide informed consent are then stratified by gender identity to ensure balance across gender groups (transgender man, transgender woman, and gender nonbinary) and then randomized to 1 of the 3 study arms (Table 1). Once the randomized participant completes the baseline survey, they are considered fully enrolled.

Thirty-minute survey questionnaires are conducted at 0, 6, and 12 months. The 6-month survey will assess changes in outcome measures from baseline to the end of the intervention. The 12-month survey will assess for changes in outcomes since the intervention ended. Participants will also complete brief (3-5 minutes) process measures at 3 and 6 months that assess how microgrant funds were spent, participation in peer mentoring sessions, and engagement with financial education videos. During the course of the intervention, a research assistant makes monthly outreach calls to confirm identity and contact information for sending microgrants and study incentives. A subset of 36 participants will be invited to complete in-depth interviews (IDIs) in the middle of the intervention (3 months) and after the intervention (9 months) to explore changes in experiences and perceptions during and after the assigned intervention. Participants will be purposively selected for interviews using maximum variation sampling by gender identity, racial identity, and geography.

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Figure 2. Diagram of study flow for the Creating Access to Resources and Economic Support (CARES) study.

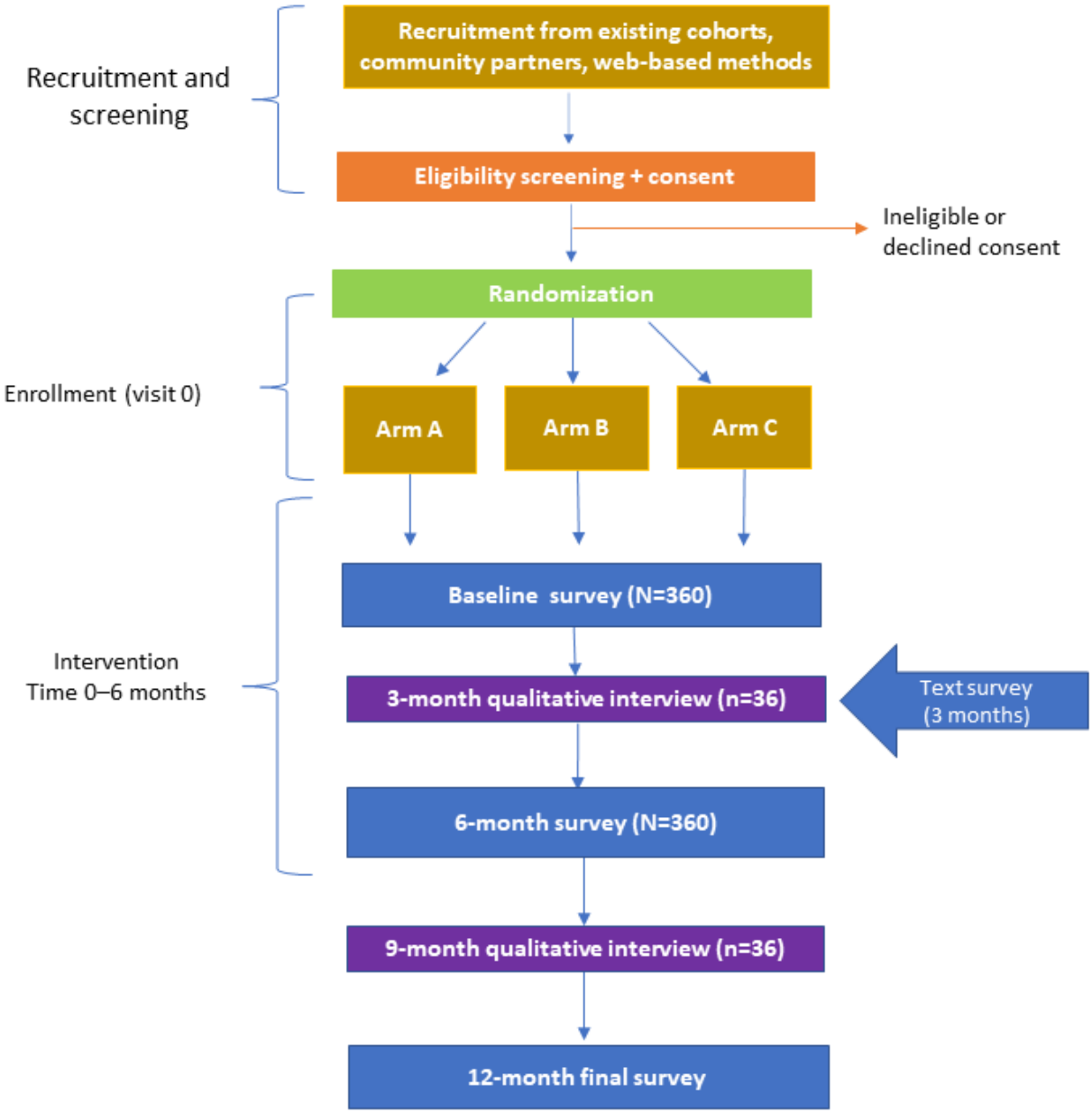

Table 1. Overview of the study arms and planned sample sizes (N=360).

Intervention for each study arm[a]	Peer mentoring	Monthly microgrant	Sample size, n (%)
Arm A: enhanced usual care (a single US $150 microgrant)	No	No	120 (33.3)
Arm B: extended microgrant (monthly US $150 microgrant × 6 months)	No	Yes	120 (33.3)
Arm C: peer mentoring (monthly US $150 microgrants × 6 months + peer mentoring)	Yes	Yes	120 (33.3)

[a]All study participants will receive brief financial education videos each month for 6 months.

Ethical Considerations

This study has received ethics approval from the Duke University Medical Center Institutional Review Board (IRB; Pro00113319). The Duke IRB serves as the IRB of record for all partner institutions in this collaborative study. Before enrollment, all participants complete a detailed informed consent process, including an explanation of their ability to opt out of participation and a consent quiz to ensure the understanding of study procedures. All participants electronically sign a written informed consent document. This protocol was registered in ClinicalTrials.gov (NCT05971160) on July 24, 2023.

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Data are collected using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based platform designed for health research. The website maintains stringent levels of encryption specifically designed to meet and exceed research standards for Internet security as well as IRB standards for the protection of research participants and electronic records. Servers are protected by high-end firewall systems and uses transport layer security (TLS) encryption for all transmitted data. Participant identifiers are stored separately from survey data; and only deidentified datasets are downloaded onto the secure cloud service, OneDrive, for analyses.

Participants are compensated US $50 for completion of the baseline and 6-month survey, respectively. They receive $10 for completion of the 3-month process measures; and $70 for competing the final 12-month survey. Participants who complete IDIs are compensated $50 for each interview.

Eligibility Criteria

Study participants must meet the following self-reported eligibility criteria: (1) age ≥18 years,; (2) gender identity different from the sex assigned on the original birth certificate (inclusive of TNB people); (3) ability to provide informed consent in English; (4) access to a mobile phone and email; (5) a score >0 on the material hardship index, which indicates exposure to at least 1 material hardship; and (6) willingness and ability to provide some form of photo ID at enrollment.

Sample Sizes

Quantitative Sample

Statistical power was estimated using the mean and SD from the Leading Innovation in Trans Equity (LITE) study, a longitudinal study with 1273 transfeminine individuals [44]. In this sample, the mean score on the 6-item Kessler Psychological Distress Scale (K6) was 10.67 (SD 5.68). When stratified by food insecurity (a type of material hardship), the difference in mean K6 scores between participants experiencing food insecurity and participants not experiencing food insecurity was 20%. Therefore, we considered a ≥20% improvement in either the extended microgrant or the peer mentoring arm compared to the enhanced usual care arm at 6 months as a clinically meaningful effect size.

Assuming a baseline mean for the K6 of 12.15 (SD 5.83) for all 3 groups, no change in the enhanced usual care arm, a 20% improvement over time in either intervention group (mean 9.72 at 6 months), and an α of .05, power to detect a significant group-by-time interaction is 0.89 with 110 (33.3%) individuals per group (n=330), 0.92 with 120 (33.3%) individuals per group (n=360), and 0.94 with 130 (33.3%) individuals per group (n=390). On the basis of the power analysis, we selected a final sample size of 360, with 120 (33.3%) individuals per group. With this sample size, we will retain sufficient power (0.82) even if we observe a 17% difference. We plan to recruit 400 individuals to allow for a 10% attrition rate over the course of the study. However, a sample size as small as 320 (20% attrition) will still provide statistical power that exceeds 80%.

Qualitative Sample

Sample sizes for qualitative research aim to include enough participants to reach the point at which no new, relevant information is gleaned from continued data collection, a concept known as saturation [45]. Studies indicate that saturation often occurs within the first 12 interviews, although early themes can be identified with as few as 6 interviews [46,47]. To facilitate reaching saturation within each arm, we will conduct IDIs with 12 participants per arm (n=36).

Study Procedures

Recruitment

A growing body of research indicates that digital research studies that recruit through web-based and social media advertisements are highly susceptible to fraudulent participation by bots or enrollment by ineligible participants seeking study compensation [48,49]. Financial compensation for study participation has been found to increase the risk of participant deception about study eligibility [50]. However, failure to compensate participants for the burden of research engagement can be considered unethical [51,52]. Given that our study intervention includes microgrant payments, it would be impossible to enroll participants without providing them with money. Therefore, to reduce the potential for fraudulent enrollment, the study team has implemented a tailored recruitment strategy as well as several evidence-based screening strategies [49,53-57] to ensure enrollment only by eligible participants.

The study team leverages community partnerships and existing web-based observational cohorts of TNB adults for recruitment. BTAC, which is based in Texas and has reached >5000 TNB people with services, has taken a leadership role in recruiting potential participants through their extensive community networks. In addition, the study team has developed a database of numerous transgender-led and transgender-focused community organizations across the country, whom we are contacting to share information about the study (Figure 3). If we are unable to reach recruitment goals through these community-engaged strategies, participants in recent and ongoing TNB-focused studies led by our study team, for example, the LITE study (N>1200) and the LEGACY study (N=2011), who have consented to be contacted for future research will be invited to participate in this study [44,58].

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Figure 3. Strategy for community-engaged study recruitment with community-based organizations (CBOs).

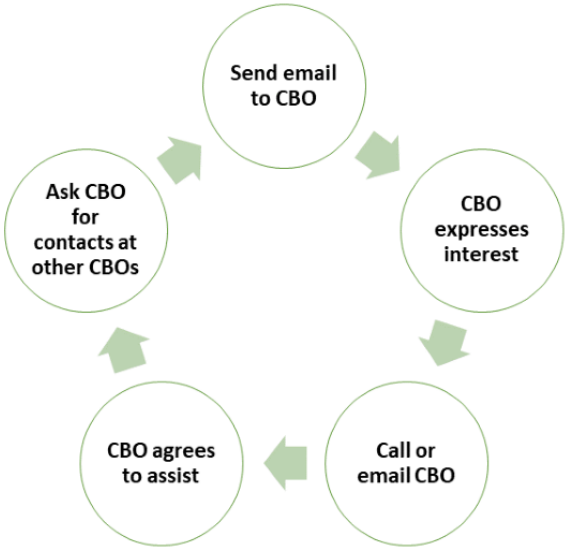

Screening and Enrollment

Interested potential participants are directed to the CARES study web page for further information and to complete an interest form. The PEC reviews the email address from the interest forms as well as the encrypted IP address for any indication of fraud and then sends a personalized link to the prescreener, which asks questions to assess eligibility for the study, as well as collects a phone number, an email address, and best times for contact. Participants who are prescreened as eligible receive an email informing them that study staff will call or text them to schedule a telephone appointment for enrollment. They are also offered the opportunity to book a specific time using a calendar link. At the scheduled appointment time, the PEC calls to complete the final eligibility screening and conducts the informed consent process. Eligible participants who consent to enroll are randomized to one of the study arms using stratified randomization by gender identity (transgender men, transgender women, and gender nonbinary) to facilitate assessment for gender differences. Once randomized, participants are sent a link to the baseline survey. Participants are considered fully enrolled once the baseline survey is complete.

Retention

Upon enrollment, participants are asked to provide extensive contact information, including phone numbers, email addresses, and contact person and number in case study staff are unable to reach them. A dedicated staff member will call participants each month to confirm or update their contact information and will also confirm their identity using date of birth to ensure microgrant payments are being sent to the enrolled individual. The study database has been programmed to automatically send an email and text to each participant when they are due for data collection. Study staff follow up with telephone calls to participants who do not complete the survey within 10 to 15 days after the automated message is sent. We have hired study staff from the TNB community to foster cultural competence and optimize acceptability to participants. We anticipate a 90% retention rate over the 12-month study based on our experience retaining 90% of participants over 12 months in the LITE study.

Quantitative Data Collection

All participants complete a 30-minute self-administered web-based survey at baseline and every 6 months for a total of 3 full surveys over the course of 12 months. To reduce bias associated with literacy and technology challenges, interviewer-administered surveys will be offered to all participants at enrollment. We have successfully used this approach for our COVID-19 testing study of >2000 TNB adults across the United States. Study participants will also complete a brief (≤10 minutes) SMS text message survey with only process measures (eg, number of financial education videos viewed, number of peer mentoring sessions attended, and how microgrant funds were spent) at 3 months. These process measures will also be incorporated into the 6-month survey.

A summary of key study measures and their reported internal consistency assessed by Cronbach α, where available, are presented in Table 2. To facilitate data sharing and population comparisons, primary outcome and potential mediator measures are drawn from the PhenX Toolkit Social Determinants of Health [59] and Mental Health Collections and the National Institutes of Health Public Health Emergency and Disaster Research Response [60]. The primary mental health outcome measure is the K6, a 6-item Likert scale of psychological distress [61]. K6 is a validated, brief, and self-report instrument that is low burden for investigators and participants [62]. It can easily be self-administered via the internet and has performed well in prior studies with TNB people [63-65]. The summary scale score ranges from 0 to 24, with scores ≥5 consistent with moderate distress [66] and scores ≥13 consistent with significant distress [61]. Higher scores on the K6 have been associated with an increased risk of all-cause mortality [67]. Reductions in K6 scores have correlated with reductions in symptoms of anxiety and depression [68].

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Table 2. Key study measures.

Construct	Instrument	Variable type	Source	Cronbach α
Mental and behavioral health				
Psychological distress	Kessler 6	Primary outcome	Kessler et al [69], 2002	0.83 [68]
Substance use disorder	10-item Drug Abuse Screening Test	Exploratory outcome	Yudko et al [70], 2007	0.94
Economic hardship				
Material hardship	Material hardship index	Potential mediator	Oulette et al [71], 2004	Not applicable
Social support				
Peer social support	Transgender community connectedness	Potential mediator	Testa et al [41], 2015	0.90
Discrimination				
Gender-related discrimination	Gender Minority Stress and Resilience	Potential confounder	Testa et al [41], 2015	0.90
Intersectional discrimination	Intersectional Discrimination Index–Major	Potential confounder	Scheim and Bauer [72], 2019	0.72

The primary economic hardship measure is a 7-item material hardship index used in the Coronavirus Health and Impact Survey V0.2 [73]. This index from the Disaster Research Response has been recommended by the US Department of Health and Human Services and included in the federal Survey of Income and Program Participation by the US Census Bureau [71,74]. The primary social support measure is the validated transgender community connectedness scale, a 5-item subscale of the GMSR measure [41].

While extant data indicate microgrants do not increase substance use [25], we have included the 10-item Drug Abuse Screening Test as a validated screening tool to assess any changes in substance use over the course of the study [75]. None of the CARES study interventions are hypothesized to affect experiences of discrimination. However, experiences of discrimination (eg, employment discrimination) may be associated with economic hardship as well as with mental health; therefore, we have included discrimination measures as potential confounders. Gender-related discrimination is a 5-item subscale of the GMSR measure [41] included to assess experiences related to TNB identity; and the Intersectional Discrimination Index-Major is a 13-item subscale of the Intersectional Discrimination Index [72] included to assess experiences related to any aspect of the participants' identity.

Qualitative Data Collection

Qualitative research is the most appropriate for eliciting detailed accounts of participant experiences and the perceived efficacy of the interventions. The open-ended nature of IDIs provides the opportunity to more deeply explore issues relevant to the study aims [76]. Prior studies have demonstrated how embedding qualitative data collection within a randomized trial enriches the understanding of how and why the interventions work or do not work [77,78]. Longitudinal interviews are an important means by which to study how participants experience, interpret, and respond to their assigned intervention over time.

We will conduct one-on-one IDIs at months 3 and 9 to capture intraintervention and postintervention experiences and perspectives. Interviews will take place using a Health Insurance Portability and Accountability Act–compliant videoconference platform. Our team has successfully collected qualitative data remotely using this method [79]. We will use stratified sampling [80] to select participants who vary by gender identity within each study arm. We will seek variability by race, age, and geography. Each IDI will last approximately 1 hour with an interviewer who has been trained in qualitative research methods and has experience conducting research with TNB people.

A topical guide will structure the interview. Open-ended questions, followed by prompts, as needed, will be used to elicit participant narratives. The initial IDIs will begin by exploring the participants' lives, stressors, and coping strategies. The interviewer will then guide the discussion toward participants' experiences of the intervention (eg, how they spend the microgrants and how they relate with their peer mentor) and how they perceive their financial situation and mental health to have changed or not have changed since the intervention began (ie, interim perceived efficacy). Follow-up IDIs will explore how their financial situation and mental health have changed since the intervention ended and discuss their retrospective reflections on the intervention. This qualitative longitudinal design will also enable the study team to clarify any unclear or incomplete responses in the prior IDI in follow-up interviews. All interviews will be digitally audio recorded and transcribed verbatim by a professional transcription company. Interviewers will write field notes and narrative summaries after each interview that will supplement the transcripts. During biweekly meetings, the study team will review field notes, transcripts, and summaries; discuss emerging themes; and revise interviewing and coding strategies, as appropriate.

Interventions

Comparison Intervention: Enhanced Usual Care for All Study Arms

Enhanced usual care interventions include a single microgrant of US $150 provided via virtual or physical Mastercard (Mastercard Inc). In addition, each participant will receive a link to 1 financial education video lasting 5 to 10 minutes each

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month for 6 months. Prior research identified financial education as an important need for TNB people [81,82]. Providing financial education to every participant in all arms will allow the study team to distinguish the effects of financial education (offered to everyone) from the effects of peer mentoring (offered in only 1 arm). Each video (Table 3) is based on content from a financial literacy intervention developed specifically for TNB adults by members of our research team (NCT04275310).

Table 3. Financial education video topics and knowledge objectives by the month of intervention.

Topic	Title	Knowledge objective
1	Protecting Yourself & Your Money	Identify and avoid predatory loans, financial abuse, and coercion
2	Income Generation	Identify job opportunities and considerations for the gig economy
3	Banking	Select and open a bank account
4	Budgeting	Develop a personal budget to meet goals
5	Credit and Loans	Build and maintain good credit
6	Transgender Financial Advisor	Navigate financial systems as a transgender person

Experimental Intervention: Extended Microgrants for Arms B and C

Participants in arms B and C will receive US $150 per month for 6 months, totaling US $900, via a virtual or physical Mastercard, as outlined for enhanced usual care. During each month of the intervention, participants will receive a phone call from the study team and will be required to respond to verify their date of birth and contact information. After verification, funds will be added to the participants' accounts. Date of birth verification will be the only condition required for subsequent microgrant funds. The study team disburses funds monthly for 6 months in the intervention arms to be consistent with the frequency and duration of interventions in prior research and to align with what would be the most sustainable after the study.

In the absence of prior US data on microgrants, the study team explored existing data to determine the amount for each microgrant. The median annual income of LITE participants was less than the federal poverty level at the time (US $12,760 for an individual). Therefore, a microgrant of US $150 represents 15% of their monthly income. This is approximately the proportion of income that the average US household spends on food. Because food insecurity is an important element of material hardship, a US $150 microgrant is sufficient to reduce this aspect of material hardship [83].

The research team also considered clinical relevance, ethics, and sustainability. In many US settings, US $150 in a given month may financially support travel expenses (eg, bus, subway, rideshare, and fuel costs) to access employment, mental health, and other social services. The US $150 amount may financially support gender-affirming purchases, such as hormones, that can reduce psychological distress [84]. From an ethical standpoint, US $150 was chosen to be substantive enough for economic impact without being so high as to be coercive. Finally, community partners determined US $150 to be sustainable and scalable by community-based organizations in the United States, as noted by BTAC and demonstrated by the longevity of the Trans Lifeline microgrants program, which has distributed >US $1 million since 2018 [85].

Experimental Intervention: Peer Mentoring for Arm C Only

In addition to the interventions mentioned earlier, participants randomized to arm C are assigned a peer mentor who matches their gender identity (transgender man, transgender woman, or gender nonbinary). Gender matching has been found to be important to rapport building in mentoring relationships [86,87]. Peer mentoring interventions are forms of peer support that have been shown to improve mental health [88-90]. Published peer mentoring interventions vary widely in the content, structure, duration, and frequency of interactions [35,91,92]. A variety of approaches to mentoring can be effective [93-95], and telephone-delivered peer support is feasible and acceptable [96]. However, while multiple studies have tested transgender peer navigation strategies for engagement in health care [97-99], the study team found no published individual (vs group) peer mentoring interventions for mental health for TNB adults. The Healthy Divas curriculum (described in the subsequent paragraph) was selected for the CARES study because it was designed specifically for transgender people. It has been successfully implemented and found to be feasible, acceptable, and readily adaptable to diverse settings [100].

The CARES peer mentoring intervention was adapted from the Healthy Divas curriculum [101], designed for transgender women, and uses key elements of BTAC's Akanni peer support program [102]. Healthy Divas is a manualized evidence-informed peer mentoring intervention developed by study consultant Dr Jae Sevelius and implemented at HIV care sites across the United States [100]. Based on the gender affirmation [103,104] and health empowerment [105] frameworks, the intervention improved transgender women's HIV medication adherence through 6 sessions of strength-based peer mentoring. Guided by the 8 step method involving (1) assessment of priorities, (2) decisions on adapting, (3) administration of intervention, (4) production of adapted version, (5) topical experts, (6) integration of feedback from topical experts, (7) training staff to implement, and (8) testing the adapted intervention, ie, ADAPT-ITT [106], the CARES team, BTAC leadership, and Dr Sevelius completed a full-day workshop to adapt Healthy Divas for use with TNB people of any gender and HIV status and to focus on participant-selected goal setting. The adapted intervention was manualized by the

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CARES project coordinator and reviewed by the adaptation workshop participants, as well as TNB community leaders. Revisions were made based on this feedback before pilot-testing with the existing CAB, which has provided our research team with input on TNB-focused studies for several years. After pilot-testing with the CAB, the manual was finalized and used to develop training materials for peer mentors. The final peer mentoring intervention guides the participant in setting achievable goals and building their capacity to reach the goals they have selected. Each peer mentoring session addresses a specific topic (Textbox 2).

BTAC recruited, interviewed, and hired an experienced full-time peer mentor supervisor as well as 3 part-time peer mentors. The peer mentor supervisor completed the CARES peer mentoring intervention training and participated in the training of peer mentors. In addition to training on the content of the intervention and the logistics of implementation, mentor training also included skill building, such as active listening, boundary setting, and self-care [107]. Peer mentors passed the intervention competency assessment, including mock sessions, before being matched with arm C participants. The peer mentor supervisor meets with the peer mentors on a monthly basis for supervision and will make himself available throughout the study period to support the peers. In addition, mentors have access to one-on-one mental health support sessions with a nonbinary professional counselor hired by the CARES study team, as well as vouchers for a limited number of free telehealth psychotherapy sessions. Mentors meet biweekly one-on-one with their assigned participant by telephone or secure video to complete each of the 6 manualized peer mentoring sessions. Peer mentors also meet weekly with the PEC and study coordinator to troubleshoot any logistical issues that arise.

Fidelity to the peer mentorship curriculum is assessed through routine tracking of the number, duration, and content of peer interactions by the peer supervisor. In addition, participants in arm C will complete brief fidelity surveys at 3 and 6 months. All mentors have been provided with a national resource list to link mentees to supportive services as needed. Mentors track all referrals made and assess whether the participant used the referrals provided.

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Textbox 2. Content of each Creating Access Resources and Economic Support (CARES) study peer mentoring session.

Session 1

- Introductions and expectation setting
- Identify vision for future
- Introduction to goal setting
- Amplify gender affirming experience

Session 2

- Review vision for future
- Set attainable goals
- Identify personal strengths
- Amplify gender affirming experience

Session 3

- Review goals
- Discuss impact of stigma
- Strategize distress reduction strategies
- Amplify gender affirming experience

Session 4

- Review goals
- Identify impact of stigma
- Identify current self-care strategies
- Identify sources of support
- Set self-care goals
- Amplify gender affirming experience

Session 5

- Review goals
- Identify success and challenges
- Problem solve barriers to goals
- Identify additional resources
- Amplify gender affirming experience

Session 6

- Review goals
- Identify progress
- Revisit vision
- Set future goals
- Visualize achieving goals

Data Analysis

Quantitative Data

Overview

Quantitative data analyses will be conducted using Stata (Stata Corp) and R (R Foundation). The distribution of all variables will be examined for outliers and to determine whether they meet the assumptions of the planned analyses. The pattern of missing data will be explored, including testing for differences in baseline variables between those with and those without missing data. Variables related to missingness will be included in the main analyses, which should yield valid inferences [108]. In the rare event of >10% missing data, we will use multiple imputation. In addition, we will conduct a series of sensitivity analyses to evaluate the robustness of conclusions with respect

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to departures from missing at random assumption by comparing the magnitude of the primary effect between analyses using complete data only to analyses using multiple imputation. ANOVA will be used to test whether randomization achieved balance in the baseline participant characteristics across the 3 arms. Variables in which the groups differ will be included as covariates in the main analyses. We will specify 2-sided tests and a .05 significance level. In subsequent subsections, we outline data analysis plans by study aim.

Aim 1

To test the efficacy of the interventions (hypothesis 1), generalized estimating equations will be used with time (baseline and 6 months), group (A, B, and C), and the group-by-time interaction included in the model. A Gaussian model will be used to examine the K6 scale. A significant group-by-time interaction would signify that the change over time differed between the 3 intervention arms. Significant group-by-time interactions will be graphed, and simple main effects will be estimated. In addition, we will examine the maintenance of the effects from 6 to 12 months using linear regression. This outcome will be the change in K6 from 6 to 12 months. Group assignments (A, B, and C) will be the main independent variable. The baseline value of the outcome will also be included in the model as a covariate. This will allow us to test whether the effect of each intervention is sustained over time in comparison to enhanced usual care. In exploratory analyses, we will repeat this set of analyses for the 10-item Drug Abuse Screening Test to examine whether the change over time in substance use differs between the 3 groups. Exploratory analyses to examine the heterogeneity of treatment effects will repeat the above-mentioned analyses stratified by race, gender, sex assigned at birth, stigma scores, and other relevant covariates. The effect sizes will be compared across the levels of each stratum to determine whether intervention effectiveness varies across groups. We will also explore whether efficacy varies by geographic location and compare the relative effectiveness of arms (A and B).

Aim 2

We will examine the mechanisms by which the interventions work using structural equation modeling. Variables in the model will include a change from baseline to 6 months in the mediators (Material Hardship Index and Transgender Community Connectedness Scale) and a change from baseline to 6 months in the K6 outcome as well as group assignment (Figure 4). Structural equation modeling provides tests of the direct and indirect paths from the independent variable to the dependent variables. Of interest will be the significance tests of the indirect paths from intervention assignment through material hardship to psychological distress (hypothesis 2) and through community connectedness to psychological distress (hypothesis 2). We will examine the goodness of fit of the overall model (model chi-square, adjusted goodness of fit, comparative fit index, and standardized root mean square error of approximation).

Figure 4. A structural equation model to be tested for aim 2.

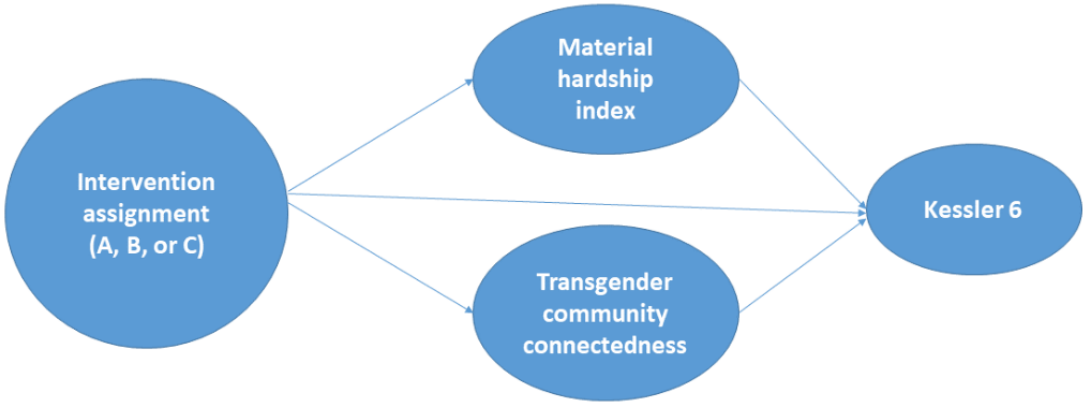

Qualitative Data

Coding

Analysts will first compare the transcript to the digital audio recording to identify and correct any transcription errors. Then, transcripts, reflexive notes, and narrative summaries for each interview will be imported into qualitative data analysis software, such as ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), to facilitate analysis. Analysis will begin with an open coding phase in which data will be read iteratively to generate analytic memos and tentative codes [109]. Open coding will be followed by systematic coding by 2 coders to ensure reliability [110].

Aim 3 Analysis

To take full advantage of the longitudinal nature of the data, we will apply multiple analytic approaches to the constant comparison technique [111]. We will review the narrative summaries for each participant over time to look for change within the individual. We will read across the transcripts for each period to look for themes unique to the midintervention and postintervention periods. Finally, we will read and compare all data across study arms. Analytical memos will be used to track the analytic process and describe themes that emerge. While it is not feasible for coders to be masked to the study arm, initial open coding will take place without attention to intervention assignment. Once coding is complete, we will use advanced visualization features of qualitative data management software to map out any differences in code density by study arm. Findings will be structured to best summarize participants'

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experiences of material hardship and mental health as well as their perception of their assigned intervention and its efficacy. We will assess variation by race, gender, and geography.

Data Integration

Embedding is a type of integration that occurs when different types of data and analyses are linked at multiple points in the study and is particularly useful in intervention trials [112]. In the CARES study, qualitative data will be linked at the randomization phase when participants will be sampled from within each arm after randomization. During the intervention (month 3), qualitative data will facilitate the identification of contextual factors that could influence the trial results while also providing detailed information about the nature of the participants' experience by the study arm. Qualitative data collected after the intervention (month 9) will facilitate the identification of changes that might be necessary for the widespread implementation of the intervention. In short, integration will help explain outcomes, improve future iterations of the intervention, and understand mediators and moderators [113]. CARES qualitative and quantitative data will also be integrated at the end of the study using result-based convergent synthesis [114]. This integration method involves analyzing qualitative and quantitative data separately and then merging results during a final synthesis [115]. Results will be merged using joint display [116], in which the interview themes will provide context for the survey results. The qualitative code density (frequency of each code) will be displayed by the study arm. Visualization will facilitate the identification of similarities and differences in participant experiences across study arms. Process data will be integrated into the joint display to visually assess any relationships among microgrant expenditures (eg, food and emergency savings fund), dose and content of the intervention (eg, peer contacts and referrals made and utilized), experience of the intervention (eg, perceived efficacy), and effect of the intervention on outcomes of interest.

Results

Participant recruitment for the CARES study began as a "soft launch" in November 2023, when we asked our community partners to invite a few participants to screen for the study. In total, 3 participants were enrolled during the soft launch phase to ensure that study processes worked as intended before opening for full recruitment. Lessons from the implementation of this soft launch led to streamlining the enrollment process by implementing a participant self-booking option for scheduling screening and consent appointments. Full recruitment began on January 8, 2024, and, as of July 26, 2025, 138 participants have enrolled. Recruitment is expected to be completed no later than March 31, 2025, and the final study visit will take place in March 2026.

Discussion

Principal Findings

We hypothesize that the CARES study will demonstrate that monthly microgrants, with or without peer mentoring, will reduce psychological distress among TNB adults. Further, we anticipate that reductions in material hardship and an increased sense of connection with the transgender community will mediate these effects. We expect qualitative results to support the perceived feasibility and benefits of both microgrants and peer mentoring. This study will fill an important gap in the literature because studies on short-term microgrants in the United States are rare [117-119]. We found neither prior studies that combine microgrants with peer support nor those that aim to use financial interventions to improve the psychological well-being of TNB adults [120].

Strengths and Limitations

The CARES study has multiple strengths. Study findings will provide important data on the efficacy of 2 community-derived, structural, and psychosocial interventions to improve mental health among TNB people in the United States and potentially mitigate some of the psychosocial harms of the COVID-19 pandemic. The community-academic partnership between BTAC, a national transgender-led organization, and a leading research university throughout the research process will ensure that rigorous data will flow directly to the community in real time. Study findings will provide useful data for BTAC and other community organizations to guide investments of their limited resources toward evidence-based programs. Findings will also have relevance for policy makers and researchers who seek to address economic vulnerability and mental health among TNB adults.

The CARES study responds to the calls for researchers to address multilevel drivers of health disparities [121] by implementing interventions that operate at the structural (economic) and interpersonal (peer mentoring) levels. In addition, this study advances the science behind minority stress theories by testing whether stigma-driven health inequities can be mitigated without intervening specifically on identity-based stigma.

However, the study has several limitations. While the team has multiple measures in place to prevent fraudulent enrollment, it is possible that people who are not TNB will misrepresent themselves to enroll in the study. To reduce this possibility, we are carefully recruiting through transgender-specific organizations, rather than through a broader approach. There is also the potential for differential attrition in the enhanced usual care arm that may lead to attrition bias. Our staff will conduct monthly check-ins for participants in this arm to enhance retention, and we are closely monitoring attrition by the study arm.

Future Directions

The research team plans wide dissemination of study findings across policy (eg, white papers), academic (eg, scientific conferences), and community (eg, town halls) spaces to ensure results can inform future health equity approaches. Ideally, future research will build on this study's findings to develop, refine, and test community-derived interventions to enhance TNB well-being.

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Data Availability

The data sets generated during this study will be available from the corresponding author upon reasonable request 1 year after the completion of data collection.

Authors' Contributions

TCP contributed to conceptualization, funding acquisition, resources, methodology, supervision, writing the original draft, and manuscript review and editing. CB contributed to conceptualization, project administration, investigation, and manuscript review and editing. AH contributed to data curation and manuscript review and editing. ALW contributed to investigation, software access, and manuscript review and editing. SLR contributed to investigation and manuscript review and editing. LJM-W contributed to investigation, methodology, and manuscript review and editing. WK contributed to project administration and manuscript review and editing. NP contributed to investigation, methodology, and manuscript review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Health Promotion in Communities (HPC) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 115 KB - resprot_v13i1e63656_app1.pdf]

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Abbreviations

BTAC: National Black Trans Advocacy Coalition
CAB: community advisory board
CARES: Creating Access to Resources and Economic Support
GMSR: Gender Minority Stress and Resilience
IDI: in-depth interview
IRB: institutional review board
K6: 6-item Kessler Psychological Distress Scale
LITE: Leading Innovation in Trans Equity
PEC: participant engagement coordinator
TNB: transgender and nonbinary

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Protocol

Stimulation Therapy to Induce Mothers: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: More than 1 million women have their labor induced in the United States each year, and synthetic oxytocin infusion is the most common method used. However, compared to spontaneous labor, medical induction is resource intensive, has increased obstetric risks, and is associated with less successful breastfeeding. In contrast to the endogenous oxytocin hormone, which is released in a pulsatile fashion in the brain, synthetic oxytocin is continuously infused intravenously, resulting in important limitations related to efficacy, safety, and cost. Akin to spontaneous labor contractions, infant suckling of the breast nipple is known to stimulate the pulsatile release of endogenous oxytocin from the posterior pituitary gland. Nipple stimulation therapy via an electric breast pump similarly stimulates endogenous oxytocin release and may be a favorable inpatient method for patients undergoing labor induction.

Objective: This study aims to examine whether inpatient nipple stimulation therapy is an efficacious labor induction method that increases the likelihood of spontaneous vaginal delivery and sustained breastfeeding and determine whether it is a cost-effective approach.

Methods: This is a multicenter, pragmatic, open-label, parallel-group randomized controlled trial of nulliparous patients with singleton gestations ≥36 weeks undergoing labor induction. This trial compares inpatient nipple stimulation therapy via an electric breast pump versus immediate synthetic oxytocin infusion without nipple stimulation. This trial including 988 nulliparas will provide adequate statistical power to detect clinically meaningful differences in delivery mode and breast milk as the sole source of nutrition for newborns at hospital discharge or 72 hours after birth.

Results: The project received pilot funding in 2021 and full funding in 2023. Enrollment for this study began in November 2021 at a single site, and as of May 2024, recruitment is underway at 3 study sites. It is anticipated that enrollment will be completed by late 2026.

Conclusions: Successful completion of this trial will provide rigorous data to determine whether inpatient nipple stimulation therapy with an electric breast pump can improve the way we induce labor and positively impact breastfeeding success and early infant nutrition through lactation.

Trial Registration: ClinicalTrials.gov NCT05079841; https://clinicaltrials.gov/study/NCT05079841

International Registered Report Identifier (IRRID): DERR1-10.2196/63463

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KEYWORDS

nipple stimulation; nipple stimulation therapy; breast pump; labor induction; oxytocin; lactation

Introduction

Background

Of the approximately 4 million births in the United States each year, >1 million women have their labor medically induced in the hospital [1]. Synthetic oxytocin infusion is the most common method used currently to induce labor [2]. At the molecular level, synthetic oxytocin is identical to endogenous oxytocin [3] and is therefore effective at stimulating uterine contractions [2-4]. However, synthetic oxytocin has important shortcomings. First, it is designated as a "high alert" medication [5] and requires strict oversight by the medical team for safety concerns [6-8], which is resource intensive. Second, unlike endogenous oxytocin, which is released in a pulsatile fashion, synthetic oxytocin is infused continuously, which can induce downregulation of oxytocin receptors in myometrial muscle and result in reduced efficacy [9]. Third, compared to spontaneous labor, induced labor is associated with increased risks of operative delivery, postpartum hemorrhage, and other obstetric complications, especially when oxytocin use is prolonged [10,11]. Fourth, synthetic oxytocin is infused into the peripheral circulation and minimally penetrates the blood-brain barrier [12], which precludes it from mimicking the other physiological benefits of endogenous oxytocin [13].

In contrast to synthetic oxytocin, breast nipple stimulation therapy induces a physiological process by stimulating the pulsatile release of the endogenous oxytocin hormone from the pituitary gland. Pulsatile stimulation of oxytocin [14] mimics physiological labor, which could prove nipple stimulation to be a more efficacious method of labor induction compared to continuous infusion of synthetic oxytocin. More efficient labor typically results in improved obstetric outcomes, including an increased likelihood of a spontaneous vaginal delivery. In addition, just as infant suckling of the breast nipple triggers postpartum lactation by inducing the milk ejection reflex [15], our pilot feasibility study found that nipple stimulation therapy via an electric breast pump results in early colostrum production and milk letdown during labor in many women, including nulliparas [16].

Breastfeeding has many known short- and long-term benefits, yet early discontinuation is common [17]. Breastfeeding protects against gastroenteritis, lower respiratory infection, and other infectious diseases in infancy [18-22]. Sustained breastfeeding promotes the infant's sensory and cognitive development [23] and protects the infant from chronic diseases [20,24]. Furthermore, a history of lactation is associated with reduced maternal risks of type 2 diabetes and breast and ovarian cancers [24]. No breastfeeding or early cessation is associated with increased risks for postpartum anxiety and depression [24-26]. Given these benefits, the World Health Organization [27], the Centers for Disease Control and Prevention [28], and the American Academy of Pediatrics [29] recommend exclusive breastfeeding without any supplementary formula or water from birth until 6 months of age. However, based on US data from the Centers for Disease Control and Prevention, although 84% of infants started breastfeeding, 20% were supplemented with formula within 2 days of age, and only 25% were exclusively breastfed at 6 months as recommended [17]. Maternal perception of insufficient milk supply (PIMS) and infant weight loss are the most common reasons reported for early breastfeeding cessation [30-32]. While almost all newborns lose weight after birth due to diuresis and low enteral intake [33], it is more pronounced in those who exclusively breastfeed [33-36]. The trajectory of newborn weight loss becomes the basis for multiple clinical decisions, including the timing of hospital discharge, the need for lactation support or supplementation, and the timing and type of newborn follow-up [37,38]. A poor weight trajectory can be especially detrimental to maternal confidence [39,40], and low breastfeeding confidence in the first week post partum predicts early cessation [41,42].

Therefore, this multicenter clinical trial aims to test the central hypothesis that intrapartum nipple stimulation therapy via an electric breast pump will positively alter childbirth and early postpartum experience by increasing the likelihood of spontaneous vaginal delivery and exclusive and sustained postpartum lactation. Furthermore, studies have shown that strategies that increase the likelihood of vaginal delivery can have significant impact on public health and cost [43]. In addition, increasing breastfeeding rates would reduce reliance on infant formula and potentially reduce health care use during the early newborn period. The potential economic and public health impacts of our intervention on the success of breastfeeding and subsequent maternal and infant health are also substantial [44,45], and therefore, we also aim to examine the cost-effectiveness of this intervention.

Aims and Hypotheses

The Stimulation Therapy to Induce Mothers (STIM) trial was designed to pursue 3 aims. First, we aim to compare the effect of inpatient nipple stimulation therapy via an electric breast pump versus synthetic oxytocin infusion without nipple stimulation (comparator) on the delivery method. We hypothesize that those randomly assigned to nipple stimulation therapy will be more likely to achieve spontaneous vaginal delivery and have fewer labor-related complications compared to those in the comparator group. Second, we aim to compare the effect of inpatient nipple stimulation therapy via an electric breast pump versus synthetic oxytocin infusion without nipple stimulation (comparator) on postpartum lactation. We hypothesize that those randomly assigned to nipple stimulation therapy during labor will be more likely to use breastfeeding as the sole source of nutrition (BSSN) at hospital discharge, which will be associated with improved maternal perception of milk supply, less severe newborn weight loss, and sustained breastfeeding for the recommended 6 months. Third, we aim to examine the cost-effectiveness of inpatient nipple stimulation therapy via an electric breast pump in comparison to synthetic oxytocin infusion without nipple stimulation (comparator). By examining the cost of care and health-related quality of life, we hypothesize that administering nipple stimulation therapy during

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labor will be more cost-effective than the comparator after considering their overall impact on labor and delivery, breastfeeding, and early infant nutrition and care in the first 6 months.

Methods

Overview and Study Design

STIM is a multicenter, pragmatic, open-label, parallel-group randomized controlled trial of nulliparas to compare the effectiveness of inpatient nipple stimulation therapy with or without adjunctive synthetic oxytocin (intervention) versus immediate synthetic oxytocin infusion without nipple stimulation (comparator) during labor induction. Randomly allocating participants to different interventions minimizes selection bias and results in groups that are comparable with regard to important confounding variables, both measured and unmeasured. A pragmatic trial design was selected so that study findings, if positive, can be directly applied and disseminated quickly and widely in the "real world." We will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines wherever appropriate in the conduct and reporting of this trial [46]. The use of broad eligibility criteria, the simplicity and low cost of the study intervention, and the multicenter design with patient diversity increase generalizability and promote direct application of the findings.

Ethical Considerations

This study is approved by the Yale University Institutional Review Board (IRB), which serves as the single IRB (approval 2000031338). The study is approved by the Weill Cornell Medicine IRB (23-05026095) and Northwestern University IRB (STU00219048) with reliance agreements to the Yale University IRB. The study was registered in Clinicaltrials.gov (NCT05079841) before the initiation of the study. All study participants are required to sign a written informed consent form in English or Spanish to participate in study activities before their enrollment. All participants, regardless of study group, are compensated up to $50 USD ($10 USD at each of the 5 survey study points) for completion of study surveys. In addition, all participants randomized to the nipple stimulation therapy group receive a hands-free pumping bra (valued at $30 USD) and all participants randomized to the comparator group receive a pack of diapers (also valued at $30 USD). the patient study data are all collected by trained certified staff on REDCap, a secure data software. All data will be de-identified at the analysis phase.

Study Setting and Population

There are 3 planned recruiting sites for the STIM trial: Yale New Haven Hospital (YNHH) in New Haven, Connecticut; the Alexandra Cohen Hospital for Women and Newborns at NewYork-Presbyterian Hospital (NYP)—Weill Cornell Medicine in New York, New York; and the Prentice Women's Hospital at Northwestern Memorial Hospital (NMH) in Chicago, Illinois.

Eligible participants are identified among patients admitted to the labor and delivery units for planned delivery at each recruiting site. We are using broad inclusion criteria to ensure the generalizability of our results. In brief, eligible patients are nulliparas with singleton gestations at ≥36 weeks 0 days, aged ≥18 years, and who are planned to undergo labor induction with synthetic oxytocin. Exclusion criteria are limited to conditions for which nipple stimulation, synthetic oxytocin, or labor attempt are contraindicated or the fetus is thought to be at higher risk for admission to the neonatal intensive care unit after birth. More specific eligibility criteria are listed in Textbox 1.

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Textbox 1. Eligibility criteria of the Stimulation Therapy to Induce Mothers trial.

Inclusion criteria

- Age ≥18 years
- Nulliparous
- Live singleton gestation ≥36 weeks
- Intact or ruptured membranes (if amniotic membranes ruptured, <3 contractions per 10-minute period, averaged over 30 minutes regardless of cervical examination)
- Able to give informed consent
- Able to understand and speak English or Spanish

Exclusion criteria

- Presence of tachysystole, recurrent variable or late fetal decelerations, or fetal bradycardia within 30 minutes before enrollment
- Nonvertex-presenting fetus at enrollment
- Planned for cesarean delivery or contraindication to labor by institutional policy (eg, active genital herpes infection, placenta previa, vasa previa, and history of cavity-entering myomectomy)
- HIV infection
- History of mastectomy or contraindication to nipple stimulation
- Known allergic reactions to components of the electric breast pump or to synthetic oxytocin intravenous solution
- Significantly impaired consciousness or executive function (eg, intubated or sedated)
- Fetus suspected to be at an increased risk for neonatal intensive care (eg, major fetal anomaly, which is defined as a prenatally diagnosed anomaly anticipated to require neonatal intensive care unit admission; alloimmunization; and severe fetal growth restriction, defined as prenatally suspected estimated fetal weight less than the third percentile or abnormal umbilical artery Doppler assessment showing absent or reversed flow in diastole)

Study Interventions

Overview

The active arm (study intervention) in this trial is intrapartum nipple stimulation therapy via an electric breast pump (with or without adjunctive synthetic oxytocin). The control arm (current standard management) is immediate synthetic oxytocin infusion without nipple stimulation therapy as the comparator. Continuous fetal cardiotocography will be required in both treatment groups.

Active Arm: Nipple Stimulation Therapy via an Electric Breast Pump

Nipple stimulation therapy will be initiated in lieu of starting with synthetic oxytocin. There is no maximum length of time for which nipple stimulation can be continued if it is tolerated by the participant and her fetus. The study intervention requires a minimum of 2 hours of nipple stimulation therapy without synthetic oxytocin use to be considered valid. The 2-hour threshold was chosen because our preliminary data showed that it took a median of 69 (IQR 21-80) minutes for participants undergoing nipple stimulation therapy to have an “adequate” contraction pattern (defined as at least 3 contractions in a 10-minute period, averaged over >30 minutes) [16]. After at least 2 hours (excluding breaks) of nipple stimulation therapy, synthetic oxytocin infusion may be initiated as part of a step-up treatment strategy if desired by the participant or by their primary obstetric clinician. Synthetic oxytocin infusion can be initiated as an adjunct to continued nipple stimulation therapy or can be used as a replacement. In such cases, synthetic oxytocin will be infused according to each study site’s hospital protocol. If synthetic oxytocin infusion is initiated <2 hours (excluding breaks) of attempting nipple stimulation therapy, this will be considered a crossover. The time spent performing nipple stimulation therapy will be recorded in two ways using methods of data collection that were validated in the pilot feasibility study [16]: (1) participants or their labor support person or persons will complete a study “diary” to record start and stop times, mark unilateral or bilateral nipple stimulation, and record suction settings; and (2) per hospital protocol at all study sites, the labor nurse assesses the patient and reviews the fetal cardiotocography every 15 to 30 minutes and records the method of labor induction (ie, nipple stimulation, synthetic oxytocin, or both) as well as their interpretation of the fetal cardiotocography in the electronic medical record (EMR). In addition, the labor nurse documents the start and stop times of any labor induction agent (ie, nipple stimulation, synthetic oxytocin, etc) in the EMR as per hospital protocol.

Participants randomized to the active arm will be provided with a hospital-grade electric breast pump (Medela Symphony at YNHH and NYP and Ameda Platinum at NMH), its accessories, as well as a hands-free pumping bra and will receive a tutorial from their labor nurse. Additional support will be available from the hospital lactation consultants at all study sites. Both electric pump types use technology that mimics an infant’s natural sucking rhythm with 2 distinct phases: the stimulation phase to emulate the initial light but fast sucking to start milk flowing, followed by the expression phase that emulates slower deep suck to bring out more milk faster. Nipple stimulation will be initiated on a single breast until uterine contractions are elicited

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and are occurring at least every 3 minutes by patient report or based on the tocodynamometer. If stimulation of either breast does not result in the desired contraction pattern after 30 minutes, stimulation of bilateral breasts will be attempted. Therapy will be performed continuously with the pump suction set to the pressure (measured in mm Hg) most tolerated by the participant and can be self-adjusted by the participant. Similar to how synthetic oxytocin is infused and titrated, nipple stimulation therapy will be "titrated" based on the fetal cardiotocography. If there are >5 contractions in 10 minutes, the pump suction setting will be reduced or turned off until the contraction pattern is in the desired range to avoid tachysystole. If uterine contractions start to occur less than every 3 minutes by patient report or based on the tocodynamometer, the pump suction setting will be increased or turned back on (if it had been turned off) until the desired contraction pattern is obtained again. The pump can be temporarily turned off or the suction settings can be temporarily decreased per patient request even if the contraction pattern is in the desired range; however, it is not recommended for >15 minutes at a time.

Comparator Arm: Immediate Synthetic Oxytocin Infusion Without Nipple Stimulation Therapy

Participants randomized to the control arm will receive immediate synthetic oxytocin infusion, which is administered and dosed according to each study site's protocol. All recruiting sites will use an oxytocin dosing protocol with an initial and incremental dose rate increase of 2 mU/min. Premixed oxytocin intravenous solutions are infused via a programmed smart pump. Dosage may be increased every 15 to 40 minutes depending on the hospital site. The oxytocin maximum infusion dose rate differs at each study site per hospital policy: 20 mU/min at YNHH and 40 mU/min at NYP and NMH. Rate changes or discontinuation of oxytocin administration are based on the assessment of the following factors: fetal status, contraction status, and maternal coping. Per protocol at all study sites, the labor nurse assesses the patient and reviews the fetal cardiotocography every 15 to 30 minutes and records the method of labor induction (ie, synthetic oxytocin) as well as their interpretation of the fetal cardiotocography in the EMR. In addition, the labor nurse documents the start and end times of any labor induction agent (ie, synthetic oxytocin) in the EMR as per hospital protocol. If nipple stimulation is performed at any time, this will be considered a crossover.

Additional Study Procedures

For participants assigned to nipple stimulation therapy, those who express colostrum or breast milk during the stimulation process can collect and store it for postnatal feeding. Supplies for safe collection and storage are provided. All participants, regardless of group assignment, are asked to report their pain score before and 1 hour after the start of the intervention using the visual analog scale (VAS) [47]. In addition, all participants, regardless of group assignment, are asked to complete electronic surveys at 5 different study timepoints: at the time of enrollment, 1 to 3 days post partum, 2 weeks post partum, 4 to 12 weeks post partum, and 6 months post partum (Table 1). Surveys are administered using the REDCap (Research Electronic Data Capture; Vanderbilt University) survey tool, and weblinks and QR codes are provided to participants via email or SMS text message (whichever the participant prefers). Paper versions and survey administration via phone call are also available if requested.

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Table 1. Schema of participant procedures as part of enrollment and study outcomes.

Participant procedure	At study enrollment (inpatient)	Labor and birth (inpatient)	Postpartum days 1-3 (inpatient)	Postpartum week 2 (follow-up)	Postpartum weeks 4-8 (follow-up)	Postpartum month 6 (follow-up)
Baseline procedures	✓					
Sign medical release forms for participant and soon-to-be newborn	✓					
IFI[a] survey	✓					
EQ-5D survey	✓					
Aim 1: delivery mode		✓				
Intrapartum nipple stimulation diary (study intervention group only)		✓				
Primary outcome: spontaneous vaginal delivery		✓				
Secondary (exploratory) outcomes: time to delivery, cesarean, OVD[b], intraamniotic infection or PP[c] endometritis, and PPH[d]		✓				
Aim 2: lactation		✓	✓	✓	✓	✓
Primary outcome: breastfeeding as the sole source of infant nutrition			✓			
Secondary outcomes:			✓			
Survey about intrapartum milk letdown and colostrum collection			✓			
Maximal newborn weight loss			✓			
PIMS[e] survey				✓		
MBFES[f] survey					✓	
Breastfeeding continuation survey						✓
Aim 3: cost analysis	✓	✓	✓	✓	✓	✓
Income and education level questions	✓					
Employment status and return to work	✓				✓	✓
Delivery hospitalization encounter cost (participant)		✓				
Birth hospitalization encounter cost (infant)		✓				
EQ-5D survey			✓	✓	✓	✓
EQ-TIPS survey			✓	✓	✓	✓
Infant feeding method			✓	✓	✓	✓
Breast pump use				✓	✓	✓
Workplace absenteeism and presenteeism						✓
Household productivity loss						✓

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Participant procedure	At study enrollment (inpatient)	Labor and birth (inpatient)	Postpartum days 1-3 (inpatient)	Postpartum week 2 (follow-up)	Postpartum weeks 4-8 (follow-up)	Postpartum month 6 (follow-up)
Postpartum medical care after hospital discharge (participant)						✓
Postnatal medical care after hospital discharge (infant)						✓
Travel to and from postpartum care office (participant)						✓
Travel to and from pediatrician's office (infant)						✓

[a]IFI: infant feeding intention.

[b]OVD: operative vaginal delivery.

[c]PP: postpartum.

[d]PPH: postpartum hemorrhage.

[e]PIMS: perception of insufficient milk supply.

[f]MBFES: maternal breastfeeding evaluation sale.

Recruitment, Assignment, and Allocation

All patients who are scheduled for labor induction or are admitted to the hospital's labor and birth unit to undergo labor induction are screened for study eligibility by a trained member of the investigative team. With the assent of their primary obstetric clinician, patients meeting eligibility criteria are approached for potential recruitment. The study is explained in detail, and all questions will be answered before signing written informed consent to participate in the study. Patients can be consented before completion of cervical ripening (if cervical ripening is needed) but will not be randomized until the medical team confirms that the patient is ready to start oxytocin and therefore eligible for randomization.

At each study site, enrolled participants are randomly assigned in a 1:1 ratio to both study groups. A web-based randomization sequence was prepared by an independent statistician using blocks of variable sizes, stratified by study site and amniotic membrane status (intact vs ruptured). The advantage of this method is that it provides a good probability of balance, and future assignments are unpredictable. A participant's group assignment is obtained only after the participant is confirmed to continue to meet inclusion criteria, and a study number is entered and locked in using REDCap. Although blinding of participants and their obstetric teams would be ideal, blinding is clearly not possible in this trial. We will minimize systematic bias by applying the same standard procedures for other labor and management strategies between groups at each study site. Furthermore, the group assignment of participants will not be considered by the study staff collecting maternal and neonatal outcomes. Importantly, the main outcomes of spontaneous vaginal delivery and exclusive breastfeeding at hospital discharge are objective measures.

Study Outcomes

The primary outcome (aim 1) is spontaneous vaginal delivery, defined as delivery without the use of forceps, vacuum, or cesarean, as it is the most desirable obstetric outcome for laboring women. Compared to a cesarean delivery, spontaneous vaginal delivery is associated with lower maternal and neonatal morbidity, including hemorrhage, wound infection, endometritis, and prolonged hospitalization [48]. Furthermore, once a primary cesarean is performed, the risk of delivery by cesarean for future pregnancies is significantly increased [49], further escalating maternal morbidity. Although operative vaginal delivery (ie, forceps or vacuum) is associated with lower maternal morbidity compared to cesarean delivery, it carries higher risks for maternal pelvic floor and neonatal injury than spontaneous vaginal delivery [50]. Secondary outcomes (aim 1) include time to delivery among those who achieve spontaneous vaginal delivery, cesarean delivery, operative vaginal delivery, intraamniotic infection or postpartum endometritis, and postpartum hemorrhage. Labor agentry [51], birthing experience satisfaction [52,53], and depression scale [54] scores will also be examined.

The main outcome for aim 2 is BSSN at the time of postpartum discharge from the delivery hospitalization or within the first 72 hours after birth. This time point is chosen because it is most likely to be causally linked to the study intervention, avoids the risk of attrition bias, and predicts the likelihood of sustained breastfeeding for the recommended 6 months post partum [55]. BSSN is defined as the infant receiving breast milk without any supplementary formula or water within the first 72 hours of life. The infant feeding method (breast milk only, mixed feeding that includes both breast milk and infant formula, or infant formula only) is standardly documented in the EMR at least daily until the day of birth hospitalization discharge, and these data will be abstracted from the EMR by trained study staff. The baseline strength of breastfeeding intention will be assessed using a validated infant feeding intentions scale [56,57] at the time of trial enrollment. The total score of the 5-question Infant Feeding Intentions scale ranges from 0 (very strong intention not to breastfeed at all) to 16 (very strong intentions to provide breast milk as the sole source of milk for the first 6 months). Secondary outcomes (aim 2) include maximal percent newborn weight loss within the first 72 hours of life, patient-reported PIMS in early lactation, patient-reported satisfaction with

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breastfeeding, and the rate of sustained breastfeeding for the recommended 6 months post partum. These secondary outcomes are chosen to explore potential reasons if, as we hypothesize, there are differences seen in BSSN or sustained breastfeeding. Maximal percent newborn weight loss is defined as the difference between birth weight and the lowest weight recorded subsequently up to 72 hours of age during the birth hospitalization, calculated as a percentage of the birth weight, as is typically done daily in clinical practice. It is standard hospital practice at all study sites to regularly weigh each newborn during their birth hospitalization. Infants are weighed naked using a digital scale, and the weight is expressed in kilograms. At all study sites, newborns are weighed at birth and then at least daily until the day of discharge. The second weight measured after birth is usually performed after at least 6 hours after birth. Weighing is typically discontinued if the newborn regains his or her birth weight before discharge. Infant birth weights are recorded in a standardized fashion in specific EMR flow sheets at all study sites. The date and time of each weight are recorded, which allows the calculation of precise age at the time of weight. Patient-reported PIMS will be assessed using the validated PIMS survey [58]. The 14-question PIMS uses a Likert scale for each statement, and all responses are grouped into positive (consistent with a perception of adequate milk supply) and negative (consistent with PIMS) responses. Patient-reported satisfaction with breastfeeding will be assessed using the validated Maternal Breastfeeding Evaluation Scale (MBFES) [59,60]. The total score of the 30-question MBFES ranges from 30 to 150, with higher scores reflecting greater satisfaction, indicating a positive evaluation of the breastfeeding experience. To assess continuation of breastfeeding at 6 months post partum, participants are asked via a survey whether they are exclusively breastfeeding, mixed feeding with breast milk and formula, or exclusively formula feeding.

Outcomes assessed in aim 3 include the following: (1) cost of relevant care and (2) health-related quality of life. Both outcomes will be measured for the mother-infant pair. Cost of care will include direct medical cost, direct nonmedical cost, and indirect cost. The direct medical cost will encompass hospital facility costs and provider professional fees associated with relevant care (maternal labor and delivery hospitalization, newborn's initial birth hospitalization, maternal postpartum care, and infant's postnatal pediatric visits). Direct nonmedical cost will account for breast pump use at home, infant formula use, and transportation to relevant care. Indirect cost (ie, maternal productivity loss) will measure participants' work loss in the postpartum period based on income and employment survey questions. As the project will span multiple years, we will adjust all cost estimates for inflation using the Consumer Price Index (CPI) to reflect a constant-year US dollar [61]. Health-related quality of life for participants will be measured by the EQ-5D instrument [62]. EQ-5D is a validated instrument for measuring and valuing health. It includes a descriptive system assessing 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), along with a VAS (EQ VAS) assessing overall health ranging from worst to best imaginable health. Response to each dimension includes 5 severity levels (no, slight, moderate, severe, or extreme problems). Participants' response to the 5 dimensions of the EQ-5D descriptive system will be converted to a utility score using a validated US population–based algorithm [63]. Utility score ranges from 0 to 1, with 0 referring to a health state equivalent to death and 1 equivalent to perfect health. EQ-5D is a recommended and widely used instrument for measuring utility scores in clinical trials and in maternal health research [64,65]. For infants, the South Africa (English) EQ-TIPS paper proxy 1 questionnaire (previously known as Toddler and Infant Health-Related Quality of Life [66]) is completed by participants (as proxy reporters for their infants). This questionnaire has been shown to be valid and reliable for use in very young children [66]. It contains a 6-dimension descriptive system (movement, play, pain, social interaction, communication, and eating) with 3 severity levels (no, some, or a lot of problems), along with a VAS assessing an infant's overall health. As an algorithm for calculating utility scores based on the EQ-TIPS descriptive system is not available yet, we anticipate using a linearly transformed VAS score to approximate a utility score on a 0 to 1 scale.

Data Collection and Management

Labor course and outcome data of randomized participants and their newborns are collected by study staff through direct interview and chart review of the EMR. Data are collected on standardized forms in REDCap, an established, secure, web-based capture and management tool developed at Vanderbilt University and supported by the Yale Center for Clinical Investigation, on which nearly all responses are precoded.

All participants will be assessed for aims 1 and 2 and their secondary outcomes. Maternal follow-up will occur until 6 months post partum. We expect that all participants will be included for the coprimary outcomes as all study sites provide maternity and newborn care with the highest levels designated by each respective state (Connecticut, New York, and Illinois), and early out-of-hospital transfers are not expected. Aim 3 will include all participants and newborns with complete cost data, with regular follow-up for up to 6 months.

Data on cost of care will be collected from multiple sources. First, accounting databases are available at all study sites and use advanced platforms that allow for the extraction of detailed data on hospital facility costs. Physician professional fee data will also be extracted for services provided by physicians and other practitioners. If these data are not accurately available, relevant fee schedules from the Centers for Medicare and Medicaid Services [67] will be used alternatively. Hospital facility costs and physician professional fees will be determined for the delivery hospitalization encounters of the participants and the birth hospitalization encounters of their newborns. As hospital-grade electric breast pumps are multiuser pumps, its cost for each participant will be allocated based on duration of use and the expected total life span of the pump. Second, the cost of medical care after hospital discharge will be based on a roster of outpatient visits, emergency department visits, and rehospitalizations for both participants and their newborns. Third, participants are asked to complete surveys to report personal income; education level; employment status and return to work; workplace absenteeism, presenteeism and household

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productivity loss; infant formula use; and breast pump use at home. Fourth, travel costs for the care of participants and their newborns will be estimated based on round trip miles between the home zip code and the zip codes of the postpartum care office and the pediatrician's office.

Sample Size and Power

The sample size for the trial is based on the primary outcome of spontaneous vaginal delivery for aim 1 (Table 2). All sample size and power estimates are based on 2-tailed tests. This is important because we will be powered to detect both increases and decreases in outcomes with intrapartum nipple stimulation therapy (intervention) versus immediate synthetic oxytocin infusion without nipple stimulation (comparator). The expected rate of spontaneous vaginal delivery in the setting of immediate synthetic oxytocin infusion without nipple stimulation used for the sample size estimation is based on averaged institutional data from the 3 study sites: (62%+66%+70%)/3=66%. Accounting for a 5% attrition rate, we estimate that a total of 988 participants (494 in the nipple stimulation therapy group and 494 in the immediate synthetic oxytocin infusion without nipple stimulation group) will be sufficient to detect a minimum of 9.8% absolute difference (estimated 75.8% with nipple stimulation therapy vs 66% in the comparator group) in spontaneous vaginal delivery with 90% power (2-sided α=.05). Of note, 80% statistical power would be needed to detect a minimum absolute difference of 8.6% (74.6% vs 66%).

Table 2. Sample size estimation for primary outcome.

Detectable absolute difference (%)	Anticipated with nipple stimulation therapy (%)	Total sample size across 2 study groups for 90% power, N
9.4	79	988
9.6	78	988
9.7	77	988
9.8	76	988
9.9	75	988
10.0	74	988
10.1	73	988
10.1	72	988

At first glance, the anticipated minimum of approximately 10% absolute increase in the spontaneous vaginal delivery rate in our proposed trial appears modest. On the contrary, because the potential public health impact is large, this effect size is significant. It is estimated that 40% of the 1 million women who undergo inpatient labor induction each year in the United States are nulliparas. Therefore, a minimum of approximately 10% increase in spontaneous vaginal delivery corresponds to 40,000 more spontaneous vaginal deliveries and 40,000 fewer operative and cesarean deliveries each year. Avoiding 40,000 operative or cesarean deliveries each year will have a substantial impact on overall morbidity and health care resource use in the United States and can have broad implications beyond the United States.

The sample size of 988 for the primary outcome will be sufficient to detect a 9.4% or 10.8% absolute difference in BSSN at the time of delivery and hospitalization postpartum discharge with 80% power and 90% power, respectively (2-sided test, α=.05). This represents the difference between an expected BSSN rate of 45.5% in the setting of synthetic oxytocin infusion without nipple stimulation (average rate at the 3 study sites based on institutional data: 44%+50%+42.5%/3=45.5%) and 54.9% (with 80% power) or 56.3% (with 90% power) with nipple stimulation therapy.

Assuming a 15% attrition rate at 2 weeks post partum (the time frame for our primary cost-effectiveness analysis in aim 3), the sample size of 988 will have 90% power for detecting a standardized effect size of 0.224 (0.194 for 80% power) for the between-group difference in cost and difference in quality-adjusted life year (QALY; 2-sided test, α=.05). This is considered a small effect size based on conventional criteria; hence, if we observe an even larger effect size, we should be sufficiently powered [68].

Data Analysis Plan

Overview

Analyses will follow the intention-to-treat principle in which participants will be analyzed in the group to which they were randomized, regardless of whether they received the assigned intervention. Descriptive statistics will characterize the group of individuals recruited and investigate the comparability of the 2 study groups at baseline. Formal statistical testing will be limited to select baseline characteristics considered to be prognostic factors for the primary outcome, including hospital admission BMI, primary indication for labor induction, Bishop score at randomization, and birth weight. Categorical variables will be compared between trial groups by using the chi-square or Fisher exact tests as appropriate, and continuous variables will be compared using Student *t* tests (2-tailed) or Wilcoxon rank sum tests as appropriate. Distributions of continuous variables will be assessed by visual inspection of histograms.

The primary outcome (spontaneous vaginal delivery) and other categorical secondary outcomes will be compared between trial groups using the chi-square or Fisher exact tests as appropriate. The estimates of the relative risk and 95% CIs associated with the primary and secondary outcomes will be calculated using the Agresti and Coull method. The time to event regression analyses for labor length (regardless of delivery mode) and labor

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length censored for cesarean will be evaluated by Kaplan-Meier estimates and plots and tested with the log-rank test, whereas Cox proportional hazards analysis will be used in adjusted analyses accounting for Bishop scores at study entry (proportionality assumption will be checked graphically with ln[-lnSurvival] plots), and results summarized using hazard ratios and 95% CI. A sensitivity analysis will be performed using the induction method that the patient actually received (per-protocol analysis) to determine whether crossovers influenced the results. The distribution of maximal percent newborn weight loss is not expected to follow a normal distribution in the population, so we plan to use Wilcoxon rank sum tests to compare the distribution of the maximal percent weight loss between treatment groups and summarize the results as medians (25th and 75th percentiles) and bootstrapped 95% CIs. Similarly, the distributions of the PIMS survey scores and MBFES survey scores are not expected to follow normal distributions in the population, so we will use Wilcoxon rank sum tests to compare the distribution of the MBFES scores between treatment groups and summarize the results using the group medians (25th and 75th percentiles) and bootstrapped 95% CIs.

Adjusted Analyses

We will conduct additional analyses as needed to obtain adjusted assessments of treatment effectiveness, accounting for baseline patient characteristics (covariates). The objectives of these analyses are to estimate the influence of covariates on the outcome and to use covariates to improve the estimated difference between treatment groups. The Poisson regression model (link=log) with robust SEs stratified by the study site will be used to identify and estimate the effect of multiple prognostic factors on the probability of spontaneous vaginal delivery and other categorical outcomes, with results summarized as adjusted risk ratios. For continuous secondary outcomes such as maximal newborn weight loss and PIMS and MBFES survey scores, quantile regression, for example, modeling the 50th percentile, will be considered to adjust for prognostic factors.

Planned Subgroup Analyses

The following prespecified subgroup analyses will be conducted: (1) study site, (2) amniotic membrane status (intact vs ruptured) at enrollment, (3) presence versus absence of maternal diabetes (inclusive of pregestational and gestational diabetes), (4) insurance type (commercial vs public insurance), (5) maternal race (non-Hispanic Black vs non-Hispanic White vs other), and (6) obesity (obese vs nonobese). In separate models, each of these subgroup variables will be included as an additional covariate in the models for outcomes of interest, plus their interaction with the treatment variable, followed by stratified analyses (by each of the above variables) of the effect of treatment on each outcome of interest.

Cost-Effectiveness Analyses

Cost analyses will follow recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine [69]. We will use both a societal perspective (include all costs and health effects regardless of who incurs such costs or effects) and the health care sector perspective (only include direct medical cost) to best inform decision-making. Costs will be categorized by phase or type of care (labor and delivery, newborn hospitalization, postnatal care, etc) and then aggregated to calculate the total cost for each participant-infant pair. Effectiveness of the intervention will be assessed using QALY. QALY is calculated by weighting the duration of life years in each health state by its corresponding utility score. We will use utility score at the various assessment timepoints and use an area under the curve approach to calculate QALY [70]. QALY of each participant and her infant will be summed. Our primary analysis will examine costs and health effects up to 2 weeks post partum (the period when the intervention is most influential on the outcomes and less likely to be confounded by other factors occurring post partum). To capture potential longer-term impact, we will conduct a secondary analysis extending the period to 6 months post partum. Because the analytical time frame for a given participant is <1 year, we will not discount cost or QALY [69]. In addition, although EQ-5D has been demonstrated to adequately capture differences in women's quality of life between cesarean delivery and spontaneous vaginal delivery [65], there is some concern that the 5 dimensions of the EQ-5D descriptive system may not be very sensitive to other pertinent outcomes of labor induction [71]. Therefore, we will perform a sensitivity analysis using participants' EQ VAS rating as a utility score (with linear transformation to a 0 to 1 scale), which presumably captures a participant's perceive overall health regardless of dimensions.

To estimate the difference in cost and difference in effectiveness between the intervention and comparator groups, we will use a generalized linear model with log link and gamma distribution for cost (given skewness in cost data) and identity link and normal distribution for QALY. The unit of analysis will be each participant-infant pair. Explanatory variable will be an indicator for intervention (vs comparator) group. All analyses will follow the intention-to-treat principle. As randomization will be stratified by study site and amniotic membrane status, we will test if they are associated with cost or QALY and then decide whether to include them as covariates in analysis [72]. Cost-effectiveness will be evaluated by calculating the incremental cost-effectiveness ratio (ICER), defined as $\Delta C/\Delta E$ where ΔC denotes the estimated difference in cost between the intervention and comparator groups and ΔE reflects the estimated difference in QALY between the 2 groups. ICER informs the additional cost associated with the intervention for each additional QALY gained. We will use nonparametric bootstrap resampling to estimate 95% CI of ICER and produce a cost-effectiveness plane and cost-effectiveness acceptability curve. In special situations where the intervention leads to significantly lower cost and higher QALY, the intervention is considered the dominating strategy. We will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the findings [73].

Results

The project received pilot funding in 2021 and full funding in 2023 (Multimedia Appendix 1). Enrollment for this study began at YNHH in November 2021, NYP in April 2024, and NMH

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in May 2024. As of June 2024, a total of 320 participants have been enrolled. We anticipate to complete enrollment by late 2026, and we expect to submit the initial results for publication by 2027.

Discussion

Anticipated Findings

Our central hypothesis is that intrapartum nipple stimulation therapy via an electric breast pump will positively alter the childbirth and early postpartum experience by increasing the likelihood of spontaneous vaginal delivery and exclusive and sustained lactation. This hypothesis is based on the synthesis of our prior work [16] and others' published work [74-79].

Comparison to Prior Work

Prior studies have shown that nipple stimulation therapy induces uterine contractions [74-78] and increases endogenous oxytocin levels [79], supporting our hypothesis that it will prove to be an efficient labor induction method. Furthermore, nipple stimulation has the added benefit of inducing the milk ejection reflex [80,81]. Our prior work [16] showed that nipple stimulation therapy with an electric breast pump is feasible to perform during labor, that patients are interested in trying this induction method and protocol adherence is high, and that most patients had early colostrum production and milk letdown during labor. By studying, refining, and operationalizing the study intervention through our preliminary work [16], we are well positioned to successfully conduct an adequately powered large clinical trial.

Strengths and Limitations

With our robust and rigorous experimental design, this multicenter clinical trial will amplify and expand on prior research in several important ways. First, this trial is testing inpatient nipple stimulation therapy in a well-defined study population at multiple study sites, which will optimize external validity and promote generalizability. Prior randomized studies included both nulliparas and multiparas [76,82] or did not consider parity [77]. This is a severe limitation given well-known differences in labor patterns, childbirth outcomes, and familiarity with breastfeeding based on parity. Our feasibility study [16] piloted the intervention in both groups and found that nulliparas were similarly willing and able to perform nipple stimulation therapy during labor. Therefore, nulliparas were chosen as the population of interest for this study because they are at greater risk for failed labor induction and early breastfeeding discontinuation compared to multiparas and, therefore, anticipated to reap the most potential benefit from the study aims. This trial also seeks to overcome the limited validity of prior studies in which eligibility criteria were poorly defined [77] or too restrictive [82]. We will use eligibility criteria that are appropriately inclusive to maximize study recruitment and enhance generalizability but are also well defined to minimize confounding factors and safeguard against harm.

Second, this trial is adequately powered to assess for clinically significant differences in 2 key outcomes. Three prior published randomized studies [76,77,82] comparing nipple stimulation versus synthetic oxytocin infusion were severely limited by small sample sizes (62 to 92 participants), and none of them examined postpartum breastfeeding. The planned sample size of 988 women will be adequately powered to detect clinically important differences in spontaneous vaginal delivery, a desirable labor outcome, and the rate of infants receiving breast milk as their sole source of nutrition at hospital discharge, a desirable postpartum outcome.

Third, this trial investigates whether inpatient nipple stimulation therapy improves lactation outcomes and comprehensively explores potential reasons such as maternal perception of milk supply and severity of early newborn weight loss. One randomized trial [83] examined nipple stimulation via breast pump versus synthetic oxytocin in the third stage of labor (ie, after birth of the newborn but before delivery of the placenta). They found that women who performed nipple stimulation were more likely to initiate breastfeeding in the first 24 hours after birth but did not examine whether breastfeeding was sustained past the first 24 hours. Alternatively, antenatal breast milk expression before labor has also been studied as a method to promote breastfeeding and prevent complications such as hypoglycemia for newborns at increased risk (eg, those born to diabetic mothers) [80]. However, the association between antenatal breast milk expression and endogenous oxytocin release has raised concerns about the possible induction of premature labor. If true, a strategy that induces breast milk expression hours before birth, like ours, may prove to be the ideal intervention.

Fourth, we will investigate the potential economic implications of this innovative study intervention. With the large number of births each year, identifying cost-effective obstetric interventions can have substantial public health and financial benefits. Inpatient nipple stimulation therapy is expected to be of low cost. Our rigorous collection and assessments of cost data along with participants' and infants' health-related quality of life will contribute important information to inform the cost-effectiveness of this novel intervention.

There are potential limitations that we continue to work to overcome. First, as with any prospective study, recruitment can be a challenge due to clinical volume fluctuation or low consent rates. With the recent addition of 2 recruiting sites (NYP and NMH) and the addition of more research staff to recruit during off-hours, we expect to readily achieve our planned sample size. Second, there is risk of crossover for participants in the study intervention group if synthetic oxytocin is initiated before completing 2 hours of nipple stimulation. In our feasibility study [16], the mean duration of nipple stimulation therapy was 208 (SD 28) minutes, or 3.5 hours, and attrition rate in the nipple stimulation group was only 5%, which is already captured in our sample size calculation. In addition, sensitivity analysis will be performed to address potential crossover. Participants in the intervention group can receive synthetic oxytocin as adjunctive therapy after 2 hours of nipple stimulation therapy without being considered a crossover. Even if synthetic oxytocin is used adjunctively to nipple stimulation, this is not considered a failure of treatment because these 2 treatments likely work synergistically, and intrapartum nipple stimulation can still have other benefits aside from uterine contractions. Furthermore, this

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is not likely to increase type I error, but in fact, it can skew our inference toward the null hypothesis or to the superiority of synthetic oxytocin infusion without nipple stimulation (comparator) because attempting nipple stimulation therapy would have only prolonged or complicated the labor induction process in cases in which it was unsuccessful. In a sensitivity analysis, we will obtain risk ratios by further recategorizing our intervention by accounting the time to initiation of synthetic oxytocin as adjunctive therapy after at least 2 hours of nipple stimulation therapy. Third, nipple stimulation therapy is controlled by the participant, which will likely prove to be a major benefit of the therapy. However, measurement of the therapy relies somewhat on patient participation as they are asked to complete a standardized diary to track what they are doing. In our feasibility study [16], the diary completion rate was >90%. In addition, per hospital protocol at all study sites, the labor nurses document the start and end times of any labor induction agent in the EMR. Therefore, measurement of adherence to study intervention protocol is expected to be reliable. Fourth, survey completion rates in our feasibility study [16] were high; however, a higher than anticipated loss to follow-up is possible. While this will not impact our primary outcomes, incomplete data would affect secondary outcomes. Multiple strategies are in place, such as reminder SMS text messages and follow-up phone calls to participants, to minimize missing data.

Conclusions

The expected outcome of this clinical trial is that nipple stimulation therapy with an electric breast pump during labor will increase the likelihood of spontaneous vaginal birth and improve breastfeeding success and early newborn hydration and nutrition, thereby decreasing health care costs. With >1 million US women having their labor medically induced every year, successful completion of this randomized trial will help address the need to improve induction methods and may offer an opportunity to positively impact the childbirth and postpartum experience.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request. We are committed to the open and timely dissemination of all research outcomes through the development of repositories and databases, posting data on open websites, presentations, and publications as soon as feasible after peer review. Research data will be made publicly available through open websites, presentations, and peer-reviewed publications, with any embargo periods not exceeding 1 year. We will document our methods and sources for developing and modifying any questionnaires used for the trial that may enhance data sharing in the future. In the process of data sharing, several approaches may be considered to protect privacy of the data, including release of only part of the data, altering the data in ways that will not compromise analyses, requiring outside researchers to adhere to strict confidentiality requirements, or providing access to the data through a controlled data enclave. We will assure the confidentiality of all human participants' data and will adhere to all Health Insurance Portability and Accountability Act rules by deidentifying data as appropriate to ensure compliance with human participant confidentiality requirements. To ensure patient protection, the following procedures will be established to deidentify the data before research data sets are released: patient ID (the unique identifier for each patient consisting of a computer assigned number) will be removed, variables with low frequencies for some values that might be used to identify individual participants will be recoded and grouped into categories (eg, maternal age >40 years), and racial or ethnic groups will be collapsed if there are few individuals in certain groups or cells. The data will be evaluated to ensure the risk of reidentification is very small. We will ensure that the policies for use of the released database are followed. Before releasing the data set, an authorized individual from the institution must sign a data use agreement requiring that the database is for the use of the investigators only and cannot be copied or distributed, participant confidentiality must be maintained by not seeking or facilitating mechanisms leading to identification of individual participants, and the research investigator must show evidence of IRB or human participants review committee approval.

Authors' Contributions

DT contributed to writing the original draft, investigation, and visualization. VS contributed to conceptualization, data curation, methodology, resources, validation, and reviewing and editing the draft. ST contributed to conceptualization, methodology, and reviewing and editing the draft. XX contributed to conceptualization, data curation, methodology, and reviewing and editing the

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draft. MM participated in investigation, project administration, resource acquisition, supervision, and reviewing and editing the draft. BS contributed to investigation, project administration, supervision, and reviewing and editing the draft. SM contributed to data curation, validation, and reviewing and editing the draft. ES contributed to investigation, project administration, and reviewing and editing the draft. AA contributed to investigation and reviewing and editing the draft. JL contributed to investigation, project administration, resource acquisition, supervision, and reviewing and editing the draft. MS contributed to conceptualization, funding acquisition, investigation, methodology, project administration, resource acquisition, supervision, visualization, and preparing the original draft.

Conflicts of Interest

XX has received honoraria from the American Association of Gynecologic Laparoscopists (AAGL).

Multimedia Appendix 1
Peer review report from the Pregnancy and Neonatology Study Section - Endocrinology, Metabolism, Nutrition and Reproductive Sciences Integrated Review Group - Center for Scientific Review.
[PDF File (Adobe PDF File), 91 KB - resprot_v13i1e63463_app1.pdf]

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Abbreviations

BSSN: breastfeeding as the sole source of nutrition
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CONSORT: Consolidated Standards of Reporting Trials
EMR: electronic medical record
ICER: incremental cost-effectiveness ratio
IRB: institutional review board
MBFES: Maternal Breastfeeding Evaluation Scale
NMH: Northwestern Memorial Hospital
NYP: NewYork-Presbyterian Hospital
PIMS: perception of insufficient milk supply
QALY: quality-adjusted life year
REDCap: Research Electronic Data Capture
STIM: Stimulation Therapy to Induce Mothers
VAS: visual analog scale
YNHH: Yale New Haven Hospital

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Protocol

Feasibility and Acceptability of a Motivational Interviewing–Based Telehealth Intervention for Bacterial Sexually Transmitted Infection Screening: Protocol for a Sequential Explanatory Mixed Methods Study

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Abstract

Background: Gay, bisexual, and other men who have sex with men living with HIV (GBMSM-LWH) in the United States bear a heavy burden of bacterial sexually transmitted infections (STIs). Timely diagnosis and treatment are key to prevention. Only a few studies have combined home specimen self-collection for bacterial STI screening with live audio and video (AV) conferencing. None have focused on GBMSM-LWH or incorporated motivational interviewing (MI), a client-centered, strengths-based counseling approach that seeks to support individuals to create positive behavioral change.

Objective: Our study seeks to investigate the feasibility and acceptability of an MI-based telehealth intervention that integrates home specimen self-collection from different anatomical sites of possible exposure and MI delivered via live AV conferencing to engage sexually active GBMSM-LWH in bacterial STI screening.

Methods: Participants are being recruited from across the United States via advertising on mobile dating apps and social networking sites and via peer referral. Phase 1 involves piloting the delivery of an innovative telehealth intervention for bacterial STI screening to 75 GBMSM-LWH. Our intervention includes three components: (1) a pretest live AV conferencing session involving an MI-guided discussion to elicit awareness of bacterial STIs; fill any knowledge gaps; bolster the perceived importance of regularly testing for gonorrhea, chlamydia, and syphilis; and build self-efficacy for specimen self-collection; (2) home self-collection and return via mail of a urine sample (for gonorrhea and chlamydia testing), a throat swab (for gonorrhea and chlamydia testing), a rectal swab (for gonorrhea and chlamydia testing), and a finger-stick blood sample (for syphilis testing); and (3) a posttest live AV conferencing session involving an MI-guided discussion to prepare participants for receiving test results and formulate personalized action plans for seeking treatment (if warranted) and repeat testing. Descriptive statistics and progression ratios will be calculated, and potential variations in our intervention's feasibility and acceptability will be numerically summarized and graphically visualized. Phase 2 involves elucidating attitudes, facilitators, and barriers related to engaging in each intervention component via semistructured in-depth interviews with a purposive subsample of 20 participants who complete progressively smaller subsets of the pretest session, specimen return for bacterial STI testing, and the posttest session. Thematic analysis will be used to identify, analyze, and report patterns in the data. Quantitative and qualitative data will be integrated at the design, methods, interpretation, and reporting levels.

Results: Study procedures were approved by the Institutional Review Board at the University of Michigan in September 2023. Participant recruitment began in April 2024.

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Conclusions: Our study will advance multiple goals of the STI National Strategic Plan for the United States for 2021 to 2025, specifically those pertaining to preventing new STIs; accelerating progress in STI research, technology, and innovation; and reducing STI-related health disparities.

Trial Registration: ClinicalTrials.gov NCT06100250; https://www.clinicaltrials.gov/study/NCT06100250

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KEYWORDS

HIV; sexually transmitted infections; gonorrhea; chlamydia; syphilis; telehealth; motivational interviewing; self-testing; sexual health; sexual and gender minorities; mobile phone

Introduction

Background

Gay, bisexual, and other men who have sex with men living with HIV (GBMSM-LWH) in the United States bear a heavy burden of bacterial sexually transmitted infections (STIs), such as gonorrhea, chlamydia, and syphilis. National surveillance data from the Centers for Disease Control and Prevention (CDC) indicate that among GBMSM-LWH who presented for HIV medical care in 2022, gonorrhea positivity was greater than and chlamydia positivity was similar to those in GBMSM without HIV or of unknown serostatus [1]. In addition, a higher proportion of GBMSM-LWH were diagnosed with primary or secondary syphilis compared to GBMSM without HIV or of unknown serostatus [1]. Left undiagnosed and untreated, bacterial STIs may lead to serious health complications, such as epididymitis, orchitis, prostatitis, seminal vesiculitis, and proctitis [2-4]. Inflammatory and ulcerative STIs can also facilitate the onward sexual transmission of HIV in the presence of inadequate viral suppression [5-9]. For example, new syphilis infections can increase HIV viral loads and decrease CD4 cell counts, and syphilitic ulcers can aid the passage of HIV [9]. These observations underscore the importance of diagnosing and treating bacterial STIs among GBMSM-LWH in a timely manner.

It is recommended that sexually active GBMSM-LWH be tested for gonorrhea, chlamydia, and syphilis at least annually or more frequently (eg, every 3 to 6 months) if risk behaviors persist or if they or their sex partners have multiple partners [10]. However, bacterial STI screening rates among GBMSM-LWH in the United States are currently suboptimal [11-13]. Gonorrhea and chlamydia infections at pharyngeal and rectal sites are often asymptomatic and are frequently missed [14-16]. Computer-assisted telephone interviews conducted in 2022 with clinics in 6 high-incidence states found that only 57.5% (432/751) offered extraurethral gonorrhea or chlamydia testing, 74.5% (322/432) of which did not offer tests unless their clients requested tests or reported symptoms [17]. Provider-related barriers to offering testing include limited time, the fear of appearing judgmental, discomfort around discussing sexual risk behaviors, and uncertainty about current screening guidelines [18,19]. Patient-related barriers include low risk perceptions of acquiring bacterial STIs, being unaware of the importance of triple-site gonorrhea and chlamydia testing, the fear of stigmatization by providers, and concerns about privacy and confidentiality [20-22]. Therefore, novel approaches are needed to reduce the impediments to bacterial STI screening experienced by GBMSM-LWH.

Home specimen self-collection has increasingly been used to test for bacterial STIs in studies conducted with diverse populations [23-30]. Self-collected specimens for bacterial STI screening have been shown to be as valid and reliable as those collected by a clinician [31-35]. Telehealth has also demonstrated promise in managing mental health [36-38] and increasing antiretroviral therapy (ART) adherence in people living with HIV [39-43]. Only a few studies have combined home specimen self-collection with live audio and video (AV) conferencing, all of which excluded people living with HIV [28-30]. None have focused on GBMSM-LWH or incorporated motivational interviewing (MI), a client-centered, strengths-based counseling approach that seeks to support individuals to create positive behavioral change [44]. Brief (eg, 30-45 minutes) in-person MI sessions have proven effective in reducing sexual risk behaviors, substance use, and ART nonadherence in people living with HIV [45-47]. Integrating home specimen self-collection from different anatomical sites of possible exposure with MI delivered via live AV conferencing might offer a unique solution to engage GBMSM-LWH in bacterial STI screening. MI-guided discussions have the potential to increase a participant's knowledge of bacterial STIs when key knowledge gaps exist, enhance their intrinsic motivation to protect themselves and their sex partners, build their self-efficacy for specimen self-collection, and mitigate their barriers to seeking treatment (if warranted) and repeat testing.

Objectives

To investigate the feasibility and acceptability of an MI-based telehealth intervention to engage GBMSM-LWH in bacterial STI screening, we are conducting a sequential explanatory mixed methods study titled Zenyth. Our intervention includes three components: (1) a pretest live AV conferencing session involving an MI-guided discussion to elicit awareness of bacterial STIs; fill any knowledge gaps; bolster the perceived importance of regularly testing for gonorrhea, chlamydia, and syphilis; and build self-efficacy for specimen self-collection; (2) home self-collection and return via mail of a urine sample (for gonorrhea and chlamydia testing), a throat swab (for gonorrhea and chlamydia testing), a rectal swab (for gonorrhea and chlamydia testing), and a finger-stick blood sample (for syphilis testing); and (3) a posttest live AV conferencing session involving an MI-guided discussion to prepare participants for

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receiving test results and formulate personalized action plans for seeking treatment (if warranted) and repeat testing. The purpose of this manuscript is to describe the protocol for our study. Our study meets the definition of a National Institutes of Health clinical trial and has been registered in ClinicalTrials.gov (NCT06100250).

Methods

Study Overview

Our sequential explanatory mixed methods study includes a quantitative strand (phase 1) followed by a qualitative strand (phase 2). Phase 1 involves piloting the delivery of an innovative telehealth intervention for bacterial STI screening to 75 GBMSM-LWH in the United States, including a pretest MI-guided live AV conferencing session; home self-collection and return of specimens for gonorrhea, chlamydia, and syphilis testing; and a posttest MI-guided live AV conferencing session. For pilot studies, sample sizes between 25 and 150 have been recommended to examine the practicality of the methods to be used in a subsequent larger study [48,49]. Phase 2 involves elucidating attitudes, facilitators, and barriers related to engaging in each intervention component via semistructured in-depth interviews with a purposive subsample of 20 participants who complete progressively smaller subsets of the pretest session, specimen return for bacterial STI testing, and the posttest session. For in-depth interviews, sample sizes between 10 and 30 have been recommended to reach information power and thematic saturation [50,51].

Theoretical Foundation

Our intervention is guided by the constructs of the information-motivation-behavioral (IMB) skills model of Fisher et al [52]. The model theorizes that information about a behavior (ie, knowledge), motivation to perform the behavior (based on attitudes and social norms), and behavioral skills (ie, self-efficacy and action planning) act collectively to influence the behavior. The extent to which GBMSM-LWH are informed of the importance of regularly screening for gonorrhea, chlamydia, and syphilis; are motivated to act on their knowledge; and have the behavioral skills to self-collect specimens or seek testing could influence their engagement in bacterial STI screening. MI is consistent with the IMB skills model, and MI-guided discussions have the potential to increase a participant's knowledge of bacterial STIs when key knowledge gaps exist, enhance their intrinsic motivation to protect themselves and their sex partners, build their self-efficacy for specimen self-collection, and mitigate their barriers to seeking treatment (if warranted) and repeat testing. Our choice of measures in the baseline and satisfaction surveys for phase 1 has also been guided by the IMB model. In addition, the theoretical framework of acceptability of health interventions proposed by Sekhon et al [53] has been used to develop the semistructured in-depth interview guide for phase 2.

Ethical Considerations

Study procedures outlined in this manuscript have been reviewed and approved by the Institutional Review Board at the University of Michigan (HUM00240181) and have been deemed to pose no more than minimal risk to participants.

Participant Recruitment

Given the common use of social media by GBMSM to find sex partners [54-56], our primary recruitment strategy involves advertising on mobile dating apps (eg, Grindr [Grindr Inc] and Adam4Adam [A4A Network Inc]) and social networking sites (eg, Facebook [Meta Platforms, Inc] and Instagram [Meta Platforms, Inc]). Our goal is to enroll 75 GBMSM-LWH from across the United States to receive the intervention, with approximately 20 (27%) Hispanic participants, 25 (33%) non-Hispanic Black participants, 25 (33%) non-Hispanic White participants, and 5 (7%) participants of other races or ethnicities, mirroring the current racial and ethnic distribution of GBMSM-LWH in the United States [57]. Our advertisements include the study's logo; the University of Michigan's logo; images of racially and ethnically diverse men holding hands, cuddling, or kissing; and call-to-action text.

Individuals who click on the advertisements are directed to our study's landing page programmed in Qualtrics (Qualtrics International, Inc), which provides a brief overview of the intervention. Those who are not interested can exit by closing their browser. Those who are interested can click on a link to the informed consent form that includes a detailed description of all study activities, including completing an eligibility screener; providing contact information to receive study communications and a specimen self-collection box if eligible; completing a baseline survey, each intervention component, and a satisfaction survey in phase 1; and participating in an in-depth interview in phase 2 if selected. Individuals have the option to download a copy of the informed consent form for their records. As they are using their own computers, tablets, or smartphones, informed consent is obtained by them clicking on "I understand what this research study is about, and my questions so far have been answered. I agree to participate in this study" or "I do not wish to participate in this research study." The consent response, date, and IP address are recorded in Qualtrics. Those who do not consent are directed to a terminal page with a link to the CDC's website with information and resources on STIs.

Individuals who consent proceed to an eligibility screener that assesses whether they (1) identify as a man (regardless of sex assigned at birth); (2) reside in a US state or territory; (3) will be physically located in a US state or territory when completing study activities; (4) are aged ≥18 years; (5) are of legal age to provide consent for research participation in their US state or territory of residence; (6) have been diagnosed with HIV; (7) have had any kind of condomless sex with ≥2 men in the past year; (8) are willing to provide their contact information (full name, email address, mobile phone number, and mailing address); (9) are able to participate in live AV conferencing sessions using an internet-connected device; and (10) are willing to receive a box that contains kits to self-collect a urine sample, a throat swab, a rectal swab, and a blood sample for bacterial STI testing. Those who do not meet the criteria are directed to a terminal page with a link to the CDC's website with information and resources on STIs.

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Individuals who meet the criteria proceed to a contact information form that asks them to provide their full name, email address, and mobile phone number to receive study communications and their mailing address to receive a specimen self-collection box. Those who do not provide their contact information are directed to a terminal page with a link to the CDC's website with information and resources on STIs. Those who provide their contact information are informed that a study team member will reach out to verify their full name, email address, mobile phone number, and mailing address. Those who do not provide valid contact information are excluded from further consideration.

Given the reliance on social networks as sources of support by GBMSM, particularly those living with HIV [58-60], our secondary recruitment strategy involves peer referral. Individuals are requested to share the link to our study's landing page with anyone in their social network who they believe might be interested in participating. The link is provided at the end of the contact information form and on the terminal page. To minimize the potential for fraudulent activity, we use a Completely Automated Public Turing test to tell Computers and Humans Apart (CAPTCHA) challenge, exclude multiple submissions from the same IP address, and review IP addresses to ensure that they are located within the United States.

Phase 1 Procedures

Baseline Survey

Individuals whose contact information has been verified are assigned a randomly generated participant identification number and sent a link to the baseline survey programmed in Qualtrics that includes questions on the following: (1) sociodemographic characteristics (eg, age, race, ethnicity, educational level, employment status, income level, and relationship status); (2) bacterial STI–related knowledge (using a 22-item scale to assess knowledge of gonorrhea, chlamydia, and syphilis [61]); (3) awareness and use of home STI tests and commercial telehealth services (using binary measures of whether one has heard of and used home STI tests sold on the web by companies and commercial telehealth services that offer STI treatment); (4) attitudes around safer sex (using a 13-item subscale from the Sexual Risks Scale [62]); (5) perceived risk of bacterial STIs (using a risk perception ruler ranging from 1 [extremely unlikely] to 10 [extremely likely] to assess the perceived likelihood of contracting a bacterial STI in the next 12 months [61]); (6) safer sex self-efficacy (using a 7-item scale to assess confidence in practicing safer sex [63]); (7) specimen self-collection self-efficacy (using 5-point Likert items to assess the perceived ease of self-collecting each type of specimen); (8) history of HIV testing and management, including the timing of the first positive HIV test, the location of the test, the receipt of HIV medical care, ART use, HIV viral load, and CD4 count [64-66]; (9) history of bacterial STI testing and management, including the frequency of testing for gonorrhea, chlamydia, and syphilis; the timing of the latest tests; the location of the latest tests; the types of specimens provided; test results; and the receipt of treatment; (10) relationship and partner characteristics, including relationship duration and type; partner's HIV status and use of ART or pre-exposure prophylaxis; and partner's history of testing for gonorrhea, chlamydia, and syphilis; (11) sexual behaviors, including engagement in oral, anal, and vaginal or frontal sex in the past 12 months and condom use; and (12) history of tobacco use, alcohol use, prescription medication misuse, and other substance use [67].

The baseline survey takes approximately 30 minutes to complete, and it allows participants to skip questions or indicate that they prefer not to answer a question. If participants do not complete the baseline survey within 1 week, reminders are sent at regular intervals over the next 7 weeks. Those who do not complete the baseline survey by the end of 8 weeks are not contacted any further (unless they request an extension). Those who complete the baseline survey receive an Amazon e-gift card (Amazon.com, Inc) worth US $40 and are considered "fully enrolled" participants (ie, participants who proceed to receive the intervention).

Intervention Component 1: Pretest MI-Guided Live AV Conferencing Session

Once participants complete the baseline survey, they are contacted to schedule a 30-minute pretest session to be conducted over Zoom (Zoom Video Communications, Inc) with an interventionist trained in MI and on the transmission, prevention, and treatment of bacterial STIs. Time slots are offered in all US time zones and are flexible to meet their individual circumstances. If participants do not schedule a session within 1 week, reminders are sent at regular intervals over the next 7 weeks. Once a time is confirmed, participants are sent a password-protected Zoom link. They are advised to join the session from a private location and are offered the option to reschedule if the original time no longer works or if they anticipate being in a situation where their privacy may be compromised.

Pretest sessions are conducted from a private location, and participants have the option to switch off their own video (ie, use only audio from their end) if they prefer. Sessions are audio recorded using a digital voice recorder to allow for the continuous monitoring of intervention fidelity. No audio or video is recorded in Zoom. The session begins with a conversation to initiate a collaborative partnership and build rapport (MI process: engaging). Next, the interventionist elicits participants' awareness of the epidemiology and transmission of bacterial STIs among GBMSM-LWH, provides new information to fill any knowledge gaps or address misconceptions around triple-site gonorrhea and chlamydia or syphilis testing, and elicits reactions to this new information. Open-ended questioning and reflective listening are used to gain a better understanding of participants' perspectives on their own sexual risk and protective behaviors (MI process: focusing). Subsequently, the interventionist explores the participant's history of bacterial STI testing, their motivations for testing or reasons for not testing, and their perceived benefits and challenges of regular testing (MI process: evoking). To build self-efficacy for specimen self-collection, the interventionist displays the contents of the specimen self-collection box, reviews step-by-step instructions for self-collecting each type of specimen, and addresses any questions or concerns.

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Participants who express an intent to test with their own provider or at a clinic are encouraged to pursue that route. The session ends by summarizing and affirming the participants' strengths and goals with respect to protecting their own and their partners' sexual health and discussing their plans to test for gonorrhea, chlamydia, and syphilis over the next month (MI process: planning).

Participants who do not schedule or attend the pretest session by the end of 8 weeks are deemed not interested in this intervention component (unless they reschedule). Those who complete the session proceed to the next intervention component. Although participants who express an intent to test with their own provider or at a clinic are encouraged to pursue that route, they still proceed to the next intervention component (ie, they are shipped a specimen self-collection box) upon completing the pretest session unless they choose to withdraw from the study.

Intervention Component 2: Home Self-Collection and Return of Specimens

Once participants complete the pretest session, they are shipped a box in plain, unmarked packaging that contains kits to self-collect a urine sample, a throat swab, a rectal swab, and a finger-stick blood sample. Boxes are assembled using specimen self-collection kits supplied by the Clinical Virology Research Laboratory at Emory University and shipped using United Parcel Service. The shipment and return statuses of boxes are tracked by a study team member on a regular basis. Each component of the box is described in Textbox 1.

Textbox 1. Description of the box components.

Components and description

1. General information sheet: this sheet provides participants with a brief description of the box contents and information on how to package and deliver their self-collected specimens to the Clinical Virology Research Laboratory (CVRL) at Emory University. It also instructs participants not to include any sort of personally identifiable information in the laboratory requisition form.
2. Urine sample self-collection kit: this kit includes materials for participants to self-collect a urine sample of 3 milliliters (which is <1 teaspoon of urine). These materials include a collection cup, a transfer pipette, and a transport tube containing a buffer solution. The transport tube is affixed with a unique specimen identification number to document gonorrhea and chlamydia test results. The kit also includes written instructions with color images and a QR code that leads to video instructions.
3. Throat swab self-collection kit: this kit includes materials for participants to self-collect a throat swab. These materials include a sterile specimen collection swab and a transport tube containing a buffer solution. The transport tube is affixed with a unique specimen identification number to document gonorrhea and chlamydia test results. The kit also includes written instructions with color images and a QR code that leads to video instructions.
4. Rectal swab self-collection kit: this kit includes materials for participants to self-collect a rectal swab. These materials include a sterile specimen collection swab, 2 lubricant packets, and a transport tube containing a buffer solution. The transport tube is affixed with a unique specimen identification number to document gonorrhea and chlamydia test results. The kit also includes written instructions with color images and a QR code that leads to video instructions.
5. Finger-stick blood sample self-collection kit: this kit includes materials for participants to self-collect a finger-stick blood sample of 500 microliters (which is equivalent to 10 drops of blood). These materials include an alcohol wipe, 2 safety lancets, 2 gauze pads, 2 bandages, and a transport tube containing a buffer solution. The transport tube is affixed with a unique specimen identification number to document syphilis test results. The kit also includes written instructions with color images and a QR code that leads to video instructions.
6. Plastic biohazard bag: this bag is used by participants to enclose the transport tubes containing their self-collected specimens.
7. Laboratory requisition form: this form is used by participants to write down the date on which they self-collected their specimens and the unique specimen identification numbers affixed to the transport tubes.
8. Prepaid shipping box with a category B sticker: this cardboard box affixed with a prepaid United Parcel Service shipping label is used by participants to deliver their self-collected specimens and the completed laboratory requisition form to the CVRL at Emory University.

Participants are requested to self-collect their specimens, enclose the transport tubes in the plastic biohazard bag, complete the laboratory requisition form, place the bag and the form in the prepaid shipping box, and return the box to the Clinical Virology Research Laboratory at Emory University. Specimen return is voluntary, and participants can choose to return all, some, or none of the 4 specimens. However, if no specimens have been received within 3 weeks of box delivery, reminders are sent at regular intervals over the next 5 weeks. Urine samples, throat swabs, and rectal swabs are screened for gonorrhea and chlamydia, and finger-stick blood samples are screened for syphilis. Laboratory personnel can connect the participants' test results to only the unique specimen identification numbers affixed to the different transport tubes. They do not have access to either the participants' identification numbers or the participants' contact information (full name, email address, mobile phone number, and mailing address). Gonorrhea, chlamydia, and syphilis test results are shared with us via a secure Dropbox folder.

Participants who do not deliver any specimens by the end of 8 weeks are deemed not interested in this intervention component (unless they request an extension). Those who deliver some or all specimens proceed to the next intervention component.

Intervention Component 3: Posttest MI-Guided Live AV Conferencing Session

Once we receive participants' test results, they are contacted to schedule a 30-minute posttest session to be conducted over Zoom with the same interventionist who conducted the pretest session. Time slots are offered in all US time zones and are

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flexible to meet their individual circumstances. If participants do not schedule a session within 1 week, reminders are sent at regular intervals over the next 7 weeks. Once a time is confirmed, participants will be sent a password-protected Zoom link. They are advised to join the session from a private location and are offered the option to reschedule if the original time no longer works or if they anticipate being in a situation where their privacy may be compromised.

Posttest sessions are conducted from a private location, and participants have the option to switch off their own video (ie, use only audio from their end) if they prefer. Sessions are audio recorded using a digital voice recorder to allow for the continuous monitoring of intervention fidelity. No audio or video is recorded in Zoom. The session incorporates the 4 MI processes of engaging, focusing, evoking, and planning. It begins with a conversation to initiate a collaborative partnership and build rapport. The interventionist discusses the meaning of negative and positive bacterial STI test results and assesses participants' emotional responses to each possible outcome using open-ended questioning and reflective listening. Test results are delivered by screen sharing the laboratory test result form. For participants receiving negative gonorrhea, chlamydia, and syphilis test results, the interventionist uses affirmations to acknowledge their engagement in protective behaviors and jointly formulates a plan to prevent the acquisition of bacterial STIs. For participants receiving a positive gonorrhea, chlamydia, or syphilis test result, the interventionist offers emotional support, discusses the benefits of timely antibiotic treatment, and jointly formulates a linkage to a care plan. Barriers to accessing treatment (eg, the lack of insurance, limited personal transportation, and reluctance to visit one's own provider) are elicited, and the interventionist works with participants to find practical solutions. For example, if someone lacks insurance, screen sharing is used to give information on local STI clinics that provide free or low-cost services identified using site locators on the CDC and Planned Parenthood websites. If someone has limited personal transportation, the interventionist assists in creating a commute plan that uses public transportation options. If someone is reluctant to visit their own provider, the interventionist assists in finding other STI clinics or identifying commercial telehealth services that offer STI treatment (eg, GoodMDs, PlushHealth, and CallonDoc). Participants are encouraged to notify their sex partners of their positive test results so that those individuals can seek testing. Open-ended questioning and reflective listening are used to engage them in a discussion on sexual risk reduction. Next, the elicit-provide-elicit approach is used to find out what participants already know about the current national recommendations for bacterial STI testing among GBMSM-LWH and to fill any knowledge gaps or address misconceptions around the recommended frequency of testing. The interventionist also explores whether and how home STI tests sold on the web by companies (eg, NURX, myLAB Box, and LetsGetChecked) might fit into the participants' testing routines. The session ends by reviewing the participants' personalized action plans formulated based on their test results and summarizing and affirming their strengths and goals with respect to reducing sexual risk behaviors and regularly testing for bacterial STIs. After the session, a copy of the laboratory test result form is shared with participants via a secure Dropbox folder that is accessible only to them and the study team members. The folder also includes a supplemental information sheet on using site locators on the CDC and Planned Parenthood websites to identify local STI clinics to seek treatment (if warranted) and repeat testing. The link to the folder expires after 4 weeks, following which the folder is deleted.

For participants receiving a positive gonorrhea, chlamydia, or syphilis test result, a study team member reviews their state and local statutory reporting requirements and procedures and makes up to 3 attempts to notify the relevant public health authorities. This notification may result in participants being contacted for follow-up and possible contact tracing. A study team member also follows up via phone at 2 weeks and 4 weeks to attempt to determine participants' treatment statuses. During each of these interactions, the study team member completes a case report form programmed in Qualtrics, documenting whether the participant has initiated treatment, completed treatment, has not yet initiated treatment but has made an appointment with a provider, or has not yet made an appointment with a provider. Those who have not yet made an appointment with a provider are encouraged to do so as soon as possible and offered additional assistance.

Participants who do not schedule or attend the posttest session by the end of 8 weeks are deemed not interested in this intervention component (unless they reschedule). However, a copy of the laboratory test result form and the supplemental information sheet on using site locators to identify local STI clinics is shared with these participants via a secure Dropbox folder that is accessible only to them and the study team members. The link to the folder expires after 4 weeks, following which the folder is deleted.

Satisfaction Survey

Upon the completion of intervention delivery, each fully enrolled participant (regardless of their level of engagement in the pretest session, specimen return for bacterial STI testing, and the posttest session) is sent a link to the satisfaction survey programmed in Qualtrics that includes questions on the following: (1) pretest live AV conferencing session experience (using a 4-item subscale from the Telehealth Usability Questionnaire on the quality of interaction with the interventionist [68]; the 12-item Counselor Rating Form short version to assess perceptions of the interventionist [69]; and 5-point Likert items to assess the satisfaction with, willingness to repeat, and likelihood of recommending the session); (2) urine sample self-collection experience (using 5-point Likert items to assess the experience with, willingness to repeat, and likelihood of recommending self-collection [70]); (3) throat swab self-collection experience (using 5-point Likert items to assess the experience with, willingness to repeat, and likelihood of recommending self-collection [70]); (4) rectal swab self-collection experience (using 5-point Likert items to assess the experience with, willingness to repeat, and likelihood of recommending self-collection [70]); (5) finger-stick blood sample self-collection experience (using 5-point Likert items to assess the experience with, willingness to repeat, and likelihood of recommending self-collection [70]); (6) specimen

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packaging and return experience (using 5-point Likert items to assess the experience with packaging and delivering specimens); (7) posttest live AV conferencing session experience (using a 4-item subscale from the Telehealth Usability Questionnaire on the quality of interaction with the interventionist [68]; the 12-item Counselor Rating Form short version to assess perceptions of the interventionist [69]; and 5-point Likert items to assess the satisfaction with, willingness to repeat, and likelihood of recommending the session); (8) bacterial STI–related knowledge (using a 22-item scale to assess knowledge of gonorrhea, chlamydia, and syphilis [61] for comparison with the baseline survey responses); and (9) the likelihood of testing for bacterial STIs in the future (using 5-point Likert items to assess the likelihood of testing for bacterial STIs at least annually and likelihood of using home STI tests sold on the web by companies).

The satisfaction survey takes approximately 15 minutes to complete, and it allows participants to skip questions or indicate that they prefer not to answer a question. If participants do not complete the satisfaction survey within 1 week, reminders are sent at regular intervals over the next 7 weeks. Those who do not complete the satisfaction survey by the end of 8 weeks are not contacted any further (unless they request an extension). Those who complete the satisfaction survey receive an Amazon e-gift card worth US $20.

Phase 2 Procedures

To gain a deeper understanding of attitudes, facilitators, and barriers related to engaging in each component of the intervention, we will conduct in-depth interviews with a subsample of 20 participants. Purposive sampling will be used to select a mix of participants who complete progressively smaller subsets of the pretest session, specimen return for bacterial STI testing, and the posttest session [71].

Participants will be contacted to schedule a 1-hour interview with a study team member to be conducted over Zoom or phone (depending on their preference). Time slots will be offered in all US time zones and will be flexible to meet their individual circumstances. If participants do not schedule an interview within 1 week, reminders will be sent at regular intervals over the next 7 weeks. Participants who prefer being interviewed over Zoom will be sent a password-protected Zoom link. They will be advised to join the interview from a private location and be offered the option to reschedule if the original time no longer works or if they anticipate being in a situation where their privacy may be compromised.

Interviews will be conducted from a private location, and participants on Zoom will have the option to switch off their own video (ie, use only audio from their end) if they prefer. Interviews will be audio recorded using a digital voice recorder to allow for verbatim transcription for future analyses. No audio or video will be recorded in Zoom. During the interview, the study team member will ask participants open-ended questions using a semistructured in-depth interview guide. Informed by the theoretical framework of acceptability of health interventions [53], the interviews will focus on a range of participants' experiences, including factors influencing their attendance (eg, discussing specimen self-collection procedures and receiving bacterial STI test results) or nonattendance (eg, concerns about session length and scheduling conflicts) of the pretest or posttest session and reasons for delivering specimens (eg, confirm bacterial STI status and limited access to testing) or choosing not to deliver specimens (eg, lack of confidence and preference for clinic-based testing).

Participants who do not schedule or attend the interview by the end of 8 weeks will be deemed not interested (unless they reschedule). Those who attend the interview will receive an Amazon e-gift card worth US $40.

Study Outcomes

Primary Outcomes

The feasibility of our intervention will be assessed by documenting the following: (1) the number of participants who schedule a pretest session, (2) the number of participants who join the pretest session within 30 minutes of the start time, (3) the number of participants who deliver each type of specimen within 6 weeks of box delivery, (4) the number of participants who provide specimens of adequate quality for laboratory testing, (5) the number of participants who schedule a posttest session, and (6) the number of participants who join the posttest session within 30 minutes of the start time. Data on these outcomes will be extracted from the participants' study records.

The acceptability of our intervention will be assessed by documenting the following: (1) overall intervention satisfaction, (2) interventionist perceptions, (3) usability of the pretest and posttest sessions, (4) willingness to repeat the intervention, and (5) likelihood of recommending the intervention to friends or sex partners. Data on these outcomes will be summarized using participants' responses on the satisfaction survey. Further details are presented in Textbox 2.

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Textbox 2. Description of the primary outcomes to assess the acceptability of the intervention.

Overall intervention satisfaction

- Participants' satisfaction with the pretest session, urine sample self-collection, throat swab self-collection, rectal swab self-collection, finger-stick blood sample self-collection, and the posttest session will be assessed using six 5-point Likert items included in the satisfaction survey [70]. Response values will be summed to obtain a total score ranging from 6 to 30, with higher scores indicating greater overall intervention satisfaction.

Interventionist perceptions

- Participants' perceptions of the interventionist conducting the pretest and posttest sessions will be assessed using two 12-item Counselor Rating Form short versions included in the satisfaction survey [69]. Response values will be summed to obtain a total score ranging from 24 to 168, with higher scores indicating more positive interventionist perceptions.

Usability of the pretest and posttest sessions

- Participants' usability of the pretest and posttest sessions will be assessed using two 4-item subscales from the Telehealth Usability Questionnaire on the quality of interactions with the interventionist during each session included in the satisfaction survey [68]. Response values will be summed to obtain a total score ranging from 8 to 56, with higher scores indicating greater usability of the pretest and posttest sessions.

Willingness to repeat the intervention

- Participants' willingness to repeat the pretest session, urine sample self-collection, throat swab self-collection, rectal swab self-collection, finger-stick blood sample self-collection, and the posttest session will be assessed using six 5-point Likert items included in the satisfaction survey [70]. Response values will be summed to obtain a total score ranging from 6 to 30, with higher scores indicating greater willingness to repeat the intervention.

Likelihood of recommending the intervention to friends or sex partners

- Participants' likelihood of recommending the pretest session, urine sample self-collection, throat swab self-collection, rectal swab self-collection, finger-stick blood sample self-collection, and the posttest session to friends or sex partners will be assessed using six 5-point Likert items included in the satisfaction survey [70]. Response values will be summed to obtain a total score ranging from 6 to 30, with higher scores indicating a greater likelihood of recommending the intervention to friends or sex partners.

Secondary Outcomes

The potential impact of our intervention on IMB skills model constructs will be assessed by documenting the following: (1) improvement in bacterial STI–related knowledge, (2) likelihood of testing for bacterial STIs at least annually, and (3) improvement in self-efficacy for specimen self-collection. Data on these outcomes will be summarized using participants' responses on the baseline and satisfaction surveys. Further details are presented in Textbox 3.

Textbox 3. Description of the secondary outcomes to assess the potential impact of the intervention on information-motivation-behavioral skills model constructs.

Improvement in bacterial sexually transmitted infection (STI)–related knowledge

- Potential increases in participants' knowledge of gonorrhea, chlamydia, and syphilis will be assessed by comparing responses to the same set of 22 items included in the baseline and satisfaction surveys [61]. Response values will be summed to obtain separate total scores ranging from 0 to 22, with higher scores indicating greater STI-related knowledge.

Likelihood of testing for bacterial STIs at least annually

- Participants' likelihood of testing for bacterial STIs at least annually will be assessed using a single 5-point Likert item included in the satisfaction survey. Response values will range from 1 to 5, with higher values indicating a greater likelihood of testing for bacterial STIs at least annually.

Improvement in self-efficacy for specimen self-collection

- Potential increases in participants' self-efficacy for urine sample self-collection, throat swab self-collection, rectal swab self-collection, and finger-stick blood sample self-collection will be assessed by comparing responses to similar sets of four 5-point Likert items included in the baseline and satisfaction surveys. Response values will be summed to obtain separate total scores ranging from 4 to 20, with higher scores indicating greater self-efficacy for specimen self-collection.

The prevalence of bacterial STIs and receipt of treatment will be assessed by documenting the following: (1) the number of participants who test negative or positive for gonorrhea, chlamydia, and syphilis in our test using our specimen self-collection kits, in a test with their own provider, or in a test at a clinic and (2) the number of participants who initiate treatment with their own provider, at a clinic, or via commercial telehealth services within 1 week of receiving a positive test result. Data on these outcomes will be extracted from the participants' study records.

Analytic Plan

Descriptive statistics (eg, means, medians, and ranges for continuous variables and counts and proportions for categorical

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variables) and progression ratios (ie, proportions of participants who sequentially progress through different intervention components) will be calculated using software for quantitative data analysis (eg, SAS [IBM Corp]). As our study is inherently exploratory, we do not plan on using probability-based statistical inference techniques in line with current best practices [72,73]. Instead, potential variations in our intervention's feasibility and acceptability across selected participant characteristics and their potential impacts on IMB skills model constructs will be numerically summarized and graphically visualized (eg, using side-by-side boxplots and scatter plots), as recommended for exploratory data [74].

In-depth interview transcripts will be imported into software for qualitative data analysis (eg, Dedoose [Socio Cultural Research Consultants, LLC]). Thematic analysis will be used to identify, analyze, and report patterns in the qualitative data [75,76]. This approach is being chosen because it allows for flexibility within both postpositivist and constructivist paradigms, which is consistent with mixed methods research [77]. We will follow the six stages of thematic analysis proposed by Braun and Clarke [77]: (1) becoming familiar with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) writing up the results. The trustworthiness and authenticity of the qualitative analysis will be enhanced through multiple mechanisms, including double coding a subset of transcripts independently, conducting regular meetings among the study team members to discuss and resolve discrepancies, and maintaining documentation for auditing purposes.

Integration at the design level will be achieved by our use of a sequential explanatory mixed methods design wherein we will first collect quantitative data on the feasibility and acceptability of our intervention and then collect qualitative data on attitudes, facilitators, and barriers related to engaging in different intervention components. Integration at the methods level will be achieved via (1) connecting (ie, when one form of data links to the other form through the sampling frame), as we will select a purposive subsample of 20 (27%) participants for the qualitative phase from 75 participants in the quantitative phase, and (2) building (ie, when results from the first phase inform data collection in the second phase), as we will use information on participants' level of engagement in different intervention components to guide our in-depth interviews. Integration at the interpretation level will be achieved through a comparison of our quantitative findings (ie, potential variations in our intervention's feasibility and acceptability across selected participant characteristics) with our qualitative findings (ie, themes describing attitudes, facilitators, and barriers related to engaging in each intervention component) Integration at the reporting level will be achieved by representing comparisons through combined written descriptions of the quantitative and qualitative data (eg, statistics by themes) and visual representations (eg, joint displays). Results from our study will be contextualized by and compared to the existing literature on home specimen self-collection and telehealth-delivered MI in other sexual and gender minority populations in the United States.

Results

Our study was funded by the National Institutes of Health in February 2023 and was approved by the Institutional Review Board at the University of Michigan in September 2023. Participant recruitment began in April 2024.

Discussion

Principal Findings

Our study is unique with respect to combining home specimen self-collection and return for gonorrhea, chlamydia, and syphilis testing with MI-guided discussions over live AV conferencing, a novel combination that has not yet been explored in GBMSM-LWH. Thus far, most MI-based interventions for people living with HIV have been delivered in person [45-47,78-80], and few have prioritized GBMSM [45-47]. Our pretest sessions focus on eliciting awareness of bacterial STIs; filling any knowledge gaps; bolstering the perceived importance of regularly testing for gonorrhea, chlamydia, and syphilis; and improving self-efficacy for specimen self-collection. Our posttest sessions focus on preparing participants to receive test results and formulating personalized action plans for seeking treatment (if warranted) and repeat testing. Our findings will help fill a void in existing knowledge on the feasibility and acceptability of using a synchronous telehealth modality to deliver MI for engaging sexually active GBMSM-LWH in bacterial STI screening.

Strengths and Limitations

Combining quantitative and qualitative approaches offers several advantages, such as complementing each other's strengths and weaknesses, reducing biases, and allowing for the triangulation and contextualization of results [81,82]. Our use of a sequential explanatory mixed methods design will provide a more nuanced understanding of which intervention components might benefit from enhancements to suit the varying needs of GBMSM-LWH in the United States. Recruiting participants via advertising on mobile dating apps and social networking sites can limit generalizability [83], but prior research indicates that GBMSM recruited via the web have a similar prevalence of HIV, bacterial STIs, and screening [84] and a higher engagement in sexual risk behaviors [85,86] compared to those recruited via time-location sampling. We recognize practical issues such as low survey response rates, scheduling conflicts for the pretest and posttest sessions, and the potential for the nondelivery of specimen self-collection boxes due to incorrect mailing addresses, but these have not been problematic in our previous studies among people without HIV that involved similar procedures [28-30,87-89]. If we face challenges in scheduling a posttest session, we will ensure the accessibility of bacterial STI test results in a timely manner via a secure Dropbox folder. Although it might be difficult to re-engage participants who completed only a subset of the 3 intervention components (in phase 1) for in-depth interviews (in phase 2), we hope the incentive being offered for their time will help circumvent this obstacle while being noncoercive. Finally, we acknowledge that assessing the adequacy of specimens for laboratory testing is dependent upon their return.

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Dissemination Plan

Our study's findings will be disseminated through publications in peer-reviewed journals, presentations at academic conferences, and posts on social media.

Conclusions

Our study will advance multiple goals of the STI National Strategic Plan for the United States for 2021 to 2025, specifically those pertaining to preventing new STIs; accelerating progress in STI research, technology, and innovation; and reducing STI-related health disparities [90]. Our findings will guide refinements to our intervention before the assessment of its potential impact on improving gonorrhea, chlamydia, and syphilis screening rates among GBMSM-LWH in a future full-scale clinical trial.

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Data Availability

Data sharing is not applicable to this manuscript, as no data sets have been generated or analyzed at this stage of the study. Once analyses related to the study's objectives have been completed, the data sets will be available from the corresponding author upon reasonable request.

Authors' Contributions

AS and EEB wrote the original draft of this manuscript. SB reviewed and edited the original draft. All authors contributed to and approved the final draft of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report: clinical management in general care settings study section, health care return and methodologies integrated review group, Center for Scientific Review, National Institutes of Health.
[PDF File (Adobe PDF File), 146 KB - resprot_v13i1e64433_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
AV: audio and video
CAPTCHA: Completely Automated Public Turing test to tell Computers and Humans Apart
CDC: Centers for Disease Control and Prevention
GBMSM-LWH: gay, bisexual, and other men who have sex with men living with HIV
IMB: information-motivation-behavioral

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MI: motivational interviewing
STI: sexually transmitted infection

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Protocol

Using Systems Engineering and Implementation Science to Design an Implementation Package for Preoperative Comprehensive Geriatric Assessment Among Older Adults Having Major Abdominal Surgery: Protocol for a 3-Phase Study

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Abstract

Background: Older Americans, a growing segment of the population, have an increasing need for surgical services, and they experience a disproportionate burden of postoperative complications compared to their younger counterparts. A preoperative comprehensive geriatric assessment (pCGA) is recommended to reduce risk and improve surgical care delivery for this population, which has been identified as vulnerable. The pCGA optimizes multiple chronic conditions and factors commonly overlooked in routine preoperative planning, including physical function, polypharmacy, nutrition, cognition, mental health, and social and environmental support. The pCGA has been shown to decrease postoperative morbidity, mortality, and length of stay in a variety of surgical specialties. Although national guidelines recommend the use of the pCGA, a paucity of strategic guidance for implementation limits its uptake to a few academic medical centers. By applying implementation science and human factors engineering methods, this study will provide the necessary evidence to optimize the implementation of the pCGA in a variety of health care settings.

Objective: The purpose of this paper is to describe the study protocol to design an adaptable, user-centered pCGA implementation package for use among older adults before major abdominal surgery.

Methods: This protocol uses systems engineering methods to develop, tailor, and pilot-test a user-centered pCGA implementation package, which can be adapted to community-based hospitals in preparation for a multisite implementation trial. The protocol is based upon the National Institutes of Health Stage Model for Behavioral Intervention Development and aligns with the goal to develop behavioral interventions with an eye to real-world implementation. In phase 1, we will use observation and interviews to map the pCGA process and identify system-based barriers and facilitators to its use among older adults undergoing major abdominal surgery. In phase 2, we will apply user-centered design methods, engaging health care providers, patients, and caregivers to co-design a pCGA implementation package. This package will be applicable to a diverse population of older patients undergoing major abdominal surgery at a large academic hospital and an affiliate community site. In phase 3, we will pilot-test and refine the pCGA implementation package in preparation for a future randomized controlled implementation-effectiveness trial. We anticipate that this study will take approximately 60 months (April 2023-March 2028).

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Results: This study protocol will generate (1) a detailed process map of the pCGA; (2) an adaptable, user-centered pCGA implementation package ready for feasibility testing in a pilot trial; and (3) preliminary pilot data on the implementation and effectiveness of the package. We anticipate that these data will serve as the basis for future multisite hybrid implementation-effectiveness clinical trials of the pCGA in older adults undergoing major abdominal surgery.

Conclusions: The expected results of this study will contribute to improving perioperative care processes for older adults before major abdominal surgery.

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KEYWORDS

systems engineering; participatory design; user-centered design; implementation science; surgery; aging research; randomized controlled trial

Introduction

Background

Each year, approximately 4.5 million older adults undergo major surgery [1]. On average, 25% of these older adults develop postoperative complications, costing the health care system approximately US $8000 to US $13,000 per complication [2] and an average of US $20,000 to US $30,000 for the postoperative hospitalization [3-6]. Unfortunately, the risk of complications doubles with preoperative functional decline, frailty, or cognitive impairment [7-14], which are risk factors that are rarely measured. A preoperative comprehensive geriatric assessment (pCGA) is a multicomponent intervention evaluating and optimizing multiple chronic conditions and factors commonly overlooked in routine preoperative planning, including physical function, polypharmacy, nutrition, cognition, mental health, and social and environmental support [15]. Major abdominal surgery carries unique risks, disrupting the core muscles with often-delayed functional recovery [16-21], cognitive decline [17,20,22-24], and disproportionately high morbidity and mortality [7,25-28]. When implemented properly, the pCGA improves outcomes for patients undergoing abdominal surgery, reducing postoperative complications by 40% and length of stay by 2 days [29,30].

Experts and best practice guidelines recommend a pCGA for all older patients undergoing major surgery [15,31-33]. In prior work with the American College of Surgeons, an expert consensus conference of >50 stakeholder organizations generated national standards for the surgical care of older adults through the Geriatric Surgery Verification Program [34,35]. These standards include conducting a pCGA for older surgical patients. Defining the standards is a critical first step; however, this work is incomplete without generalizable implementation strategies applicable to real-world settings. A lack of evidence on how best to implement the pCGA in a variety of health systems has limited patient access to this intervention [36]. The few implementation studies that exist demonstrate challenges due to contextual factors (eg, misaligned incentives) and low fidelity to the intervention [36,37]. As a result, few programs use the pCGA for older surgical patients, and reach is limited to patients receiving care at large academic medical centers with significant resources. Thus, there is a critical need for novel, evidence-based strategies to promote the successful implementation of this intervention in a variety of health care settings. To address this gap, this study seeks to answer the research question “What implementation strategies will improve provider use (adoption) and patient access (reach) to the pCGA, while preserving effectiveness (fidelity) in academic and community medical settings?”

Objectives

The overall objective of this study is to use implementation science and systems engineering methods to tailor and pilot-test a user-centered pCGA implementation package that can be adapted to community-based hospitals for future multisite implementation-effectiveness trials. Therefore, we aim to (1) map the pCGA process and identify system-based barriers and facilitators to its use among older adults undergoing major abdominal surgery, (2) co-design a pCGA implementation package applicable to a diverse population of older patients undergoing major abdominal surgery at a large academic hospital and an affiliate community site, and (3) test and refine the pCGA implementation package in preparation for a future randomized controlled implementation-effectiveness trial. We hypothesize that systems engineering methods of process mapping and co-design can successfully be applied to the pCGA (aims 1 and 2) and that a rigorous user-centered pCGA implementation package will improve surgical care processes (reach and adoption, which are the primary implementation outcomes) and patient outcomes (length of stay, which is the primary effectiveness outcome) for older adults undergoing major abdominal surgery.

Methods

Design and Conceptual Framework

This study will apply implementation science and human factors engineering principles to optimize the delivery of an existing, effective intervention—the pCGA—and generate an adaptable implementation package for future work. Through process mapping, supplemented with observation and interviews, we will identify opportunities for system redesign that will improve pCGA delivery (phase 1) and use participatory design with patients, caregivers, and health care providers to develop a user-centered implementation package (phase 2) that is adaptable to academic and community settings. Subsequently, we will pilot-test the implementation package (phase 3) using the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [38], generating preliminary data in

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preparation for a larger randomized controlled implementation-effectiveness trial. This work aligns with the National Institutes of Health (NIH) Stage Model [39] for intervention development, considering implementation early in development (stage IA) and recognizing that the development and evaluation of complex interventions may not be linear.

The pCGA (Table 1) is based on a model by McDonald et al [29] that has demonstrated decreased length of stay, readmission rates, and discharge to nonhome destination for patients undergoing abdominal surgery. To improve outcomes, the pCGA must be implemented with fidelity to key elements [15]. Treatment fidelity, particularly for complex behavioral interventions, is conceptualized as consistency in the content of the intervention, the quality of intervention delivery by health care professionals, and the receipt and adherence by patients [40]. The content of the pCGA requires a multidomain assessment [41,42]; however, equally important are the presence and quality of a follow-up plan to optimize identified deficits, as well as patient adherence to this plan. The pCGA often generates recommended tasks for the patient (exercises and nutritional shakes) and provider (medication changes) or identifies additional preoperative workup to be performed (imaging or physiological testing). Many studies on pCGA fall short by using it primarily as a risk stratification tool without a plan or sufficient time to address modifiable factors [43-45]. In addition to the aforementioned study by McDonald et al [29], studies from the United Kingdom have demonstrated that the pCGA, performed in multidisciplinary settings with a plan to address deficits, reduces postoperative length of stay and complications [30,46]. These studies have led to national and international guidelines that recommend a pCGA for older adults before major surgery [15,31-33].

Systems engineering methods improve health care delivery and outcomes by tailoring the fit of the intervention to the local context. A seminal report from the Institute of Medicine and the National Academy of Engineering outlines the unique methods and tools by which systems engineering can transform the quality and delivery of health care [47]. We will use a human factors engineering model: the systems engineering initiative for patient safety (SEIPS) model [48]. It builds on the structure-process-outcome model developed by Donabedian [49] by providing a detailed and expanded structure of the interacting components (ie, the work system)—people (or teams), tasks, tools and technology, organizational factors (eg, policies and teamwork), physical environment (clinic location), and external environment—that influence health care processes and outcomes. SEIPS has been extensively and successfully applied to health care delivery [50-58], including work to improve care transitions for older adults [59-64]. We will use SEIPS 2.0 [65], which expanded the original model [48] to acknowledge that patients and families perform work within the health care process and that their internal environment (ie, patient home) plays a role within the system (Figure 1).

Table 1. Preoperative comprehensive geriatric assessment.

Domain	Assessment	Staff performing the assessment	Example output
Polypharmacy	• Medication reconciliation • Identification of high-risk Beers criteria medications • Anticholinergic cognitive burden score	Pharmacist	Medication changes made directly or referred to PCP[a]
Medical comorbidities	• History and physical examination, including cardiac risk assessment with revised cardiac risk index	Geriatrician	Additional testing ordered; specialist referral placed
Physical function	• Mobility testing (eg, Timed Up and Go Test) • Lawton Independent Activities of Daily Living scale, activities of daily living, and home support and resources	Medical assistant and social worker	Home exercises prescribed or preoperative physical therapy referral (“prehabilitation”)
Cognition	• Delirium risk assessment (eg, Montreal Cognitive Assessment)	Social worker	Memory clinic referral
Mood	• Depression screen (eg, Patient Health Questionnaire-9)	Medical assistant	Medication or specialist referral
Nutrition	• Nutritional status (eg, Mini Nutritional Assessment–Short Form) and BMI	Medical assistant	Nutritional supplementation
Goals of care	• Discussion and documentation of acceptable outcomes and code status • Assist patient with documenting health care power of attorney	Geriatrician	DNR[b] status established and communicated to surgeon

[a]PCP: primary care provider.

[b]DNR: do-not-resuscitate.

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Figure 1. Preliminary systems engineering initiative for patient safety model 2.0 depicting the preoperative comprehensive geriatric assessment process. CVA: cerebrovascular accident; VTE: venous thromboembolism.

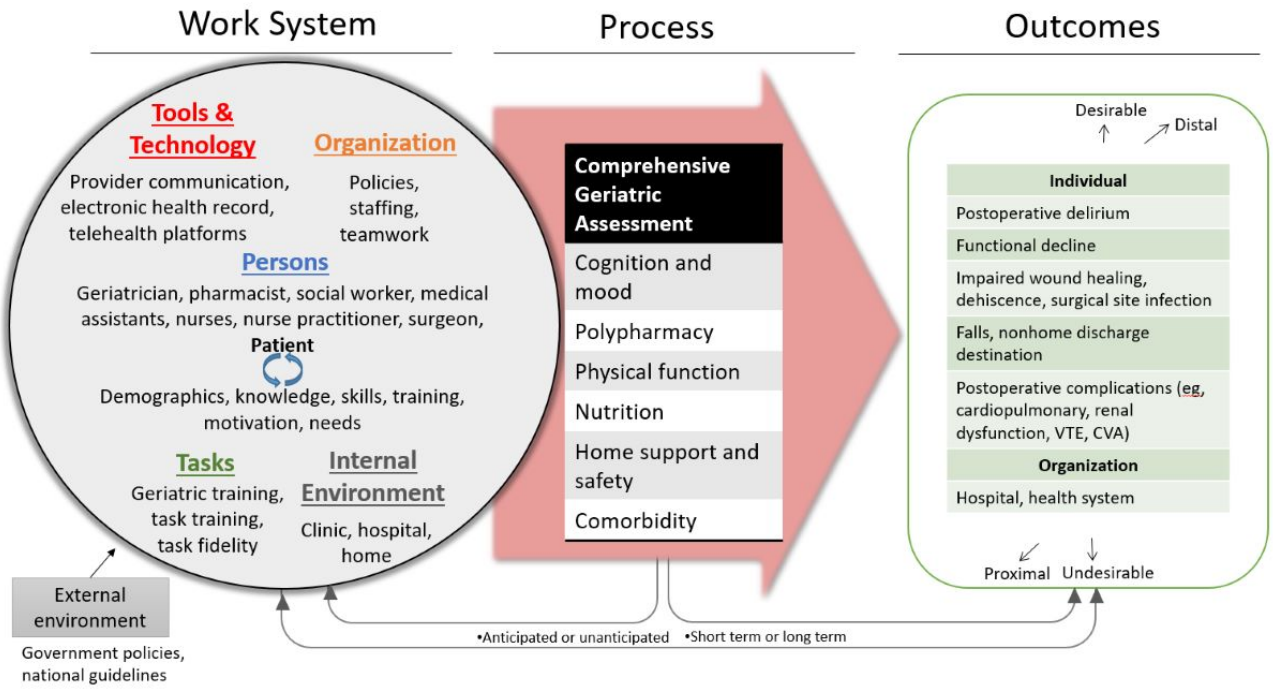

The study was registered at ClinicalTrials.gov in accordance with NIH policies and regulations (phases 1 and 2 [observational phases]: NCT06184919; phase 3 [pilot trial]: NCT06184724).

Ethical Considerations

The study will be conducted in 3 phases. Each phase will be reviewed separately by the institutional review board (IRB) of the University of Wisconsin–Madison. Phase 1 of the study was approved by the IRB on January 19, 2023 (2022-1516). All participants provide informed consent for both observations and interviews. To protect privacy and confidentiality, all data are deidentified. Compensation is provided in the form of gift cards. Participants receive US $20 for participating in observations and US $20 for a 45-minute qualitative interview. Health care staff receive US $45 for a 90-minute focus group. Surgeons receive US $50 for a 45-minute interview. Phase 2 of the study was approved by the IRB on March 1, 2024 (2024-0044). All participants provide informed consent. To protect privacy and confidentiality, all data are deidentified. Compensation is provided in the form of gift cards. Patient and caregiver participants receive US $50 per 90-minute session. Health care professionals receive US $100 per 90-minute session. Phase 3 study activities will be initiated after receiving approval from the IRB. All participants will be required to provide informed consent. To protect privacy and confidentiality, all data will be deidentified. Compensation will be provided in the form of gift cards. Participants will receive US $5 per completed survey.

Phase 1: Process Mapping

Study Design

We will perform process mapping [66,67] via direct clinical observation of the pCGA visit, qualitative interviews with patients, and a focus group with staff, using SEIPS as a framework [60,67,68]. Process mapping is a fundamental systems engineering approach based upon the recognition that work, as it is performed in real-world settings, is not always consistent with its expected or prescribed form. We expect that phase 1 will catalog components of the SEIPS-based work system (traditional process map), and we will supplement the map by identifying barriers and facilitators to each step.

Participants

Patients and Caregivers

Eligible participants are patients aged ≥85 years or those aged ≥65 years with multiple comorbid conditions (>2), diagnosed or suspected cognitive impairment, diagnosed or suspected functional impairment, or poor nutrition (documented weight loss of 10% within a year). Inclusion criteria are older adults for whom the surgeon recommends an operative intervention and who intend to undergo the elective major abdominal surgery. Exclusion criteria are non-English speakers (because we do not have the resources for translation) or the absence of a caregiver for those without decisional capacity. On the basis of prior literature [68], we will enroll 20 older adults and their caregivers, if present, for observation and interviews. We will use purposive sampling to recruit at least 2 patients each for groups traditionally underrepresented in medical research by race, ethnicity, socioeconomic status, and rural or urban backgrounds [69]. Research staff will screen patients for eligibility. Clinic staff will approach participants to assess interest, and research staff will obtain informed consent.

Health Care Professionals and Staff

All health care professionals working in the preoperative geriatric clinic (n=10) who are responsible for performing the tasks of the pCGA will be approached and consented for direct observation and focus groups to provide feedback on the pCGA

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process map. Additional staff (n=5) engaged in the clinic (administrative leads and schedulers) will be invited to participate. We will invite referring surgeons (n=10) for one-on-one interviews, with the plan to recruit additional participants as informed by thematic saturation during the ongoing analysis. We will purposively select surgeons, men as well as women, to represent a range of surgical specialties. Recruitment will occur by email for health care professionals.

Predicted pCGA Process Map

The pCGA clinic is conducted after the initial surgical consultation and before the surgical operation. A predicted map of the existing process is outlined in Figure 2. The patient consults with a surgeon who recommends an operative intervention and places a referral for the pCGA clinic. The pCGA is conducted at 2 locations and provides web-based options for patients traveling from a distance. The pCGA results include recommendations for patient-level tasks (exercises and nutritional shakes), provider tasks (medication changes), or additional preoperative evaluation.

Figure 2. Predicted process map of patient journey through the preoperative comprehensive geriatric assessment (pCGA). Each point along the process will be evaluated using the systems engineering initiative for patient safety to identify key work tasks and associated barriers. Research activities are noted in blue italics.

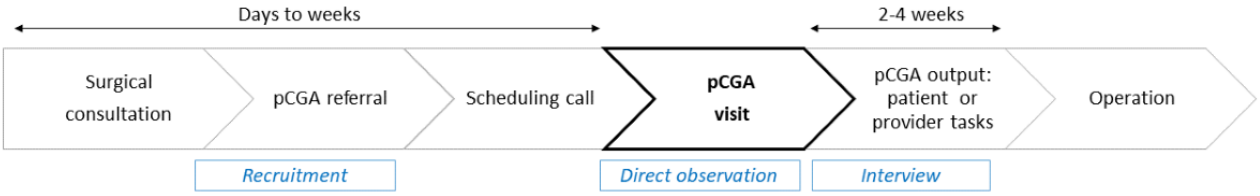

Data Collection

Direct Observation

We will embed a trained research assistant at the clinic and use direct observation guided by a fidelity checklist to document the events of the pCGA and take notes on the process. We will follow the patient from initial check-in through the completion of the visit, providing a detailed and direct account of the patient's journey [66]. The observers will use a standardized template to document the persons, tasks, tools and technology, environment, and organizational factors according to the SEIPS model. Observer notes will be supplemented with an audio recording of the patient-physician interaction.

Interviews

We will interview patients and caregivers 2 weeks after the pCGA visit. Research staff trained in qualitative methods will conduct the interviews using a semistructured interview guide to elicit feedback on the predicted process map (Figure 2). The interview probes will assess barriers, facilitators, motivation, and adherence to patient work tasks, as well as reflections on the process of scheduling, attending, and participating in the pCGA. We will conduct interviews using a virtual platform. The interviewer will ask the patient to visually show on screen the home environment and ask probing questions to gain a more in-depth understanding of how tasks are performed. We expect each interview to last 45 minutes. We will interview surgeons using semistructured guides to elicit feedback on the process map and any barriers or facilitators according to the SEIPS model. The interview will provide an understanding of perceived barriers and facilitators to the adoption of the pCGA and explore how the surgeons' separate workflow fits into the proposed process map. Surgeon interviews are expected to last 45 minutes.

Focus Groups

Qualitative research staff will engage pCGA health care professionals and staff (n=10) in a focus group after completing direct observations. Focus groups naturally foster within-group interactions, allowing us to gain additional insight into the accuracy of the process map from multiple perspectives. A semistructured guide based on the SEIPS model will elicit feedback on the process map, clarifying its accuracy as a representation of the tasks and procedures performed and identifying system-level barriers and facilitators at each step. The focus group will be audio recorded and is expected to last 90 minutes.

Data Analysis

Qualitative Analysis

The interview and focus group audio recordings will be transcribed and analyzed using a deductive strategy [70,71] and the SEIPS framework to develop the coding taxonomy, with a focus on identifying barriers and facilitators within each SEIPS category for each step. Our analysis will use triangulation, comparing observed data points from the pCGA visit to those from the patient interviews. The transcripts will be coded independently by 3 researchers, followed by a joint discussion to explore disagreement and achieve consensus. We will use qualitative analysis software NVivo 14 (Lumivero) to catalog coded data.

Process Mapping

The aforementioned qualitative analysis and direct observations will be used to adapt the SEIPS-based process map [68]. We will supplement the map with a table, cataloging individual tasks in rows, numbered in reference to the map, with columns listing the persons, environment, and tools and technology, as well as the barriers and facilitators to the completion of each task.

Phase 2: Participatory Design

Study Design

In phase 2, we will apply user-centered participatory design methods to adapt the process map (phase 1) into an implementation package, consisting of a set of implementation

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strategies, to address barriers and enhance facilitators at each step. Participatory design [72] is a systems engineering method where researchers and participants work together to design the workflow of an intervention. Co-design sessions will be conducted in parallel at a large quaternary academic medical center and an affiliated community-based hospital. There will be 2 groups (design teams) of patients and caregivers and health care professionals per location (a total of 4 groups).

Participants

Overview

Each design team will consist of 7 participants. As participatory design aims for solution convergence, having an odd number of participants facilitates tie-breaking within groups. The small number of stakeholders in each group, as opposed to 14 in 1 group, allows all stakeholders to provide their input and facilitates critical evaluation.

Patients and Caregivers

Older adults are eligible after having completed the pCGA, followed by major abdominal surgery and subsequent recovery. We will approach patients and caregivers at each location (academic hospital and community-based hospital) with the goal to enroll 7 of them for participation. Patients and their caregivers will be approached at the follow-up surgical visit, which is conducted at 14 days postoperatively. Of note, older adults with Alzheimer disease or related dementias will be included if they provide assent and are accompanied by a caregiver who also consents and participates alongside them. We will use purposeful sampling to recruit at least 1 patient or caregiver from underrepresented groups by race, ethnicity, socioeconomic status, and rural or urban backgrounds [69]. We intend to oversample to ensure that perspectives from patients identified as vulnerable are heard.

Health Care Professionals

Eligible health care professionals will include surgeons performing major abdominal surgery whose patients may benefit from pCGA and health care professionals who conduct or could potentially conduct elements of the pCGA. For the academic medical center, this will involve the same set of health care professional participants as in phase 1. These include geriatricians, primary care providers, advanced practice providers, social workers, medical assistants, pharmacists, and physical therapists. We will also invite the participation of additional ancillary staff, such as administrative leads, schedulers, and tech support.

Data Collection

We will conduct 5 co-design videoconference sessions with each group over 6 months, with a gap of 2 to 3 weeks between each session (Textbox 1; during the periods between the sessions, input from the alternate design team will be synthesized for presentation to the next team and an analysis performed of prior session content). In session 1, we will present the process map generated in phase 1 and a prototype of the current pCGA implementation package. Researchers will facilitate the discussion, maintaining respectful debate among design team members as they identify process changes that will promote the implementation of the pCGA package. The facilitators will focus on solution convergence from session to session. Each design team will participate in sessions independently; however, we will summarize the output from each session and present it to the alternate design team for comment. Each session is expected to last 90 minutes. Sessions will be conducted virtually to promote participation and retention and audio recorded for qualitative analysis. Co-design sessions will be conducted separately for the academic hospital and the community-based hospital.

Textbox 1. Outline of the participatory co-design sessions.

Sessions and content for preoperative comprehensive geriatric assessment (pCGA) implementation redesign

1. Methods introduction, process map review, initial implementation package design
2. Refinement of inputs (eg, referrals)
3. Refinement of pCGA system workflows (eg, telephone calls)
4. Refinement of pCGA output and feedback mechanisms
5. Finalizing implementation package, rollout planning

Data Analysis

Qualitative data analysis of the design sessions will be performed using the rapid identification of themes from audio recordings method [73] to facilitate rapid iterative refinement of the implementation package between sessions. After each session, the research team will analyze audio recordings directly without transcription, identifying key themes, an initial codebook, and preliminary analysis of codes. We will synthesize these findings with outputs from the design session, such as sketches, case scenarios, ratings, research team observation notes, and stakeholder notes. This allows early identification of key themes after each session that can then be provided back to stakeholders in the subsequent session. Data analysis will focus on identifying implementation strategies to mitigate perceived barriers or strengthen known facilitators (Textbox 2). We will investigate novel solutions as well as known implementation strategies, such as the 73 discrete strategies delineated in the Expert Recommendations for Implementing Change [74,75].

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Textbox 2. Examples of potential implementation strategies based on the systems engineering initiative for patient safety (SEIPS) categories to improve reach and adoption while maintaining fidelity.

SEIPS categories and possible strategies

- People: dedicated referral coordinator (or registered nurse) within surgical clinics
- Organization: clear parameters for referral and script for telephone triage
- Tools: telehealth for remote patients, educational handouts, and order sets
- Tasks: automate recommendations to primary care or referring provider
- Environment: travel vouchers for patients with limited transport

Phase 3: Pilot Trial of the pCGA Implementation Package

Study Design

We will conduct a pretest-posttest pilot study of the implementation package over 10 months, conducted at the clinic level at 2 busy academic medical center surgical subspecialty clinics performing major abdominal surgery (selecting one that does not routinely refer for pCGA in addition to one that does routinely refer). We will collect baseline prepilot data via retrospective chart abstraction from the year before the intervention. After an implementation rollout period of 2 months, postintervention data will be collected over 10 months. Specifically, we will assess outcomes according to the RE-AIM framework [38], using chart abstraction for patient-level data and simple self-reported surveys for the health care professionals. We hypothesize that a user-designed implementation package will improve the reach and adoption of the pCGA compared to the historic baseline.

Participants

Patients

Older adults presenting to surgical clinics will be screened for eligibility criteria by study staff. Eligible participants are patients aged ≥85 years or those aged ≥65 years with multiple comorbid conditions (>2), diagnosed or suspected cognitive impairment, diagnosed or suspected functional impairment, or poor nutrition (documented weight loss of 10% within a year). The inclusion criterion is eligible older adults planning to undergo elective major abdominal surgery. Exclusion criteria are non-English speakers (because we lack resources for translation) or the absence of a caregiver for those without decisional capacity.

Health Care Professionals

Consistent with implementation research, health care professionals using the pCGA implementation package are considered study participants [76]. As participants from among the health care professionals who participated in the co-design will be recruited for the pilot trial, they will be familiar with the intervention. Surgeons referring patients from the 2 clinics (n=12) and health care professionals engaged at the pCGA clinic (n=10) will be asked to participate in the pilot.

Recruitment and Enrollment

Clinic staff will approach potential participants to determine interest, and a study team member will then share study details and obtain consent. At baseline, 40 patients per year are seen for pCGA. We expect to enroll 20 patients over the pilot period. All patient data for the pilot will be obtained via chart abstraction. The study will be subject to IRB approval.

Intervention

The pCGA implementation package (generated via phase 2) will include a set of implementation strategies [74,75] and an explicit stepwise plan defining the people, tasks, tools or technology, relevant organizational factors, and physical or virtual environment [65] for the pCGA. The implementation package will target systems-level processes to promote pCGA administration before surgery (eg, automating referrals in the electronic medical record, improving patient education materials, or increasing telehealth opportunities).

Data Collection and Variables

We will obtain quantitative data from two sources: (1) chart abstraction for patients and (2) self-reported survey instruments for health care professionals.

Chart Abstraction

Trained research assistants will prospectively abstract and enter data into a deidentified database on a secure server using a data dictionary. We will conduct random audits for interrater reliability according to best practices for retrospective chart review [77]. Patient-level characteristics will include demographics (age, sex, height, weight, zip code, race, and ethnicity), comorbidities (diabetes, chronic corticosteroid use, cancer diagnosis, congestive heart failure, chronic obstructive pulmonary disease, bleeding disorders or anticoagulant use, and renal insufficiency and dialysis). Clinical data from the pCGA will include polypharmacy (anticholinergic burden score [78] and Beers criteria medications [79]), physical function (Timed Up and Go Test [80], Lawton Independent Activities of Daily Living scale [81], and activities of daily living [82]), cognition (Montreal Cognitive Assessment [83]), mood (Patient Health Questionnaire-9 [84]), nutrition (Mini Nutritional Assessment–Short Form [85] and BMI), multiple chronic conditions (Charlson comorbidity index [86,87] and revised cardiac risk index [88]), documentation of code status, completion of health care power of attorney forms, and recommendations for additional tests or referrals (eg, physical therapy). Clinical data from the surgical hospitalization will include the date of surgery, procedure performed, postoperative complications (pneumonia, myocardial infarction, surgical site infection, sepsis, urinary tract infection, venous thromboembolism, renal failure, readmission, and unplanned reoperation), postoperative delirium, the date of discharge,

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discharge destination, readmission within 30 days, and death. We will abstract postoperative delirium using a validated method [89-91].

Outcomes

The primary outcomes of this pilot trial will be reach and adoption, assessed using the RE-AIM framework [38] (Table 2). Reach refers to the percentage and characteristics of older adults receiving the pCGA intervention, while adoption accounts for those health systems and health care professionals who refer patients for, or deliver, the pCGA [38,92]. Of note, implementation in the RE-AIM framework refers to fidelity, or the extent to which an intervention is delivered as intended. We will expand the implementation domain to include measures of fidelity, as defined by NIH Best Practices [40], as well as feasibility, acceptability, and appropriateness according to the taxonomy of implementation outcomes developed by Proctor et al [93]. The primary effectiveness outcome will be postoperative length of stay, which is an easily measured, continuous outcome variable commonly used in the surgical literature on pCGA [29]. We will collect exploratory measures to inform the selection of effectiveness outcomes for a future implementation-effectiveness trial. These exploratory outcome measures will include (1) a composite of death or postoperative complication events; and (2) data points relevant to the pCGA, including a cognitive outcome (postoperative delirium), functional outcome (discharge destination to home, rehabilitation, or skilled nursing), nutritional outcome (discharge diet, albumin level, and weight at discharge), and polypharmacy (Beers criteria discharge medications [79], anticholinergic burden score [78], and number of opioid pain pills prescribed at discharge).

Table 2. The reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) domains and associated outcome measures.

Domain	Definition	Measurement
Reach	The percentage and characteristics of older patients who receive pCGA[a] before abdominal surgery	• Referred ÷ potentially eligible patients • Comparison of referred ÷ eligible patients by age, sex, race, ethnicity, BMI, and zip code • Target reach: >50% referral of eligible pCGA patients per clinic
Effectiveness	The improvement in clinical outcomes from pCGA receipt	• Primary: postoperative length of stay • Secondary: 30-day morbidity and mortality (refer to Chart Abstraction section)
Adoption	Surgeon intent, decision, and action to refer eligible patients for pCGA	• Percentage of surgeons referring ÷ total surgeons in the pilot clinic • Target adoption: >75% of surgeons achieving >50% referrals
Implementation: fidelity	Multifaceted outcome that includes (1) treatment *dose* or amount of intervention delivered, (2) quality or content of intervention delivered by health care professionals, and (3) treatment receipt and enactment by patients (NIH[b] Best Practices) [40]	• (1 and 2) Percentage of completed pCGA components, as abstracted from the medical record at pCGA visit • (3) Completion of pCGA recommendations, as abstracted from the medical record at the time of surgery • Target fidelity: >90% of pCGA components completed
Implementation: feasibility[c]	Perceived ease of use of pCGA implementation package	• Feasibility of intervention measure (4-item survey) [94]
Implementation: acceptability[c]	Satisfaction with the pCGA implementation package	• Acceptability of implementation measure (4-item survey) [94]
Implementation: appropriateness[c]	Fit and relevance of pCGA implementation package	• Intervention appropriateness measure (4-item survey) [94]
Maintenance	The extent to which pCGA use is sustained over the pilot period	• Trends in reach, adoption, and implementation outcomes will be evaluated at 6 months and 12 months

[a]pCGA: preoperative comprehensive geriatric assessment.

[b]NIH: National Institutes of Health.

[c]The feasibility, acceptability, and appropriateness of the pCGA implementation package will be assessed via surveys administered to health care professionals (eg, surgeons, geriatricians, advanced practice providers, nurses, medical assistants, technicians, and staff).

Self-Report Surveys

We will administer surveys to health care professionals (surgeons and pCGA staff) at 6 and 12 months into the pilot to assess the feasibility, acceptability, and appropriateness of the implementation package. We will contact health care professionals via email to complete the survey electronically; however, recognizing the demands of clinical schedules, a research assistant will make paper copies of the survey available for completion during clinic hours. We will use a previously validated survey instrument to measure implementation outcomes, specifically the acceptability, appropriateness, and

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feasibility of the intervention [94]. The self-report survey includes 4 items for each domain (12 items in total) and is estimated to take ≤15 minutes to complete (approximately 5 min/domain). Psychometric assessments of the instrument have demonstrated high validity (Cronbach α values ranging from 0.85 to 0.91) and high reliability (test-retest values ranging from 0.73 to 0.88). The items are scored on a 5-point scale. For each 4-item domain, the score can be calculated by averaging the responses. While cutoff scores have not been established, higher scores indicate greater acceptability, appropriateness, or feasibility.

Data Analysis

The aim of the pilot is to maximize reach and adoption while maintaining implementation fidelity before a full-scale implementation-effectiveness hybrid trial is conducted. The limited sample size will restrict our ability to evaluate differences in effectiveness outcomes such as mortality or morbidity; however, more proximal effectiveness estimates will be explored by abstracting short-term clinical outcomes (eg, medication changes at discharge). We will use exploratory measures to establish some preliminary point estimates for event rates and CIs within our sample for the purpose of planning a future study. As such, formal power calculations are not applicable to this pilot study. Recruitment data will inform the calculation of the reach, adoption, and maintenance outcomes. We will explore all RE-AIM outcomes for differences across underrepresented groups [69] (rural vs urban as determined by zip code, racial majority vs minority groups, men vs women vs other gender identities, and Hispanic vs non-Hispanic ethnicity). All data will be entered into Stata software (StataCorp LLC) for analysis. Data will be evaluated for accuracy and missingness. Descriptive univariate and bivariate analyses will be conducted, including chi-square tests for categorical data and 2-tailed *t* tests or Mann-Whitney *U* tests for continuous data as appropriate, with a cutoff of $P<.05$ for statistical significance.

Results

Overview

We anticipate that this study will take approximately 60 months to complete, from study start-up procedures to the completion of the pilot trial. The 3 phases will take place between June 2023 and March 2028. We expect the results outlined in the following subsections. The study was funded in April 2023. Phase 1 officially started in May 2023 with the first enrollment June 2023. Data collection were completed in February 2024; however, recruitment was extended specifically for vulnerable populations such as underrepresented minority groups. Phase 1 remains open as of August 2024. This action was made due to low recruitment of underrepresented minority groups in an effort to honor the NIH commitment to diversity, equity, inclusion and accessibility. Phase 2 of the study was initiated in May 2024 and remains ongoing in August 2024.

Phase 1

The results of this phase will include a detailed process map and the corresponding barriers and facilitators as a starting point for system redesign to improve the implementation of the pCGA, specifically expanding reach while maintaining fidelity.

Phase 2

The results of the participatory co-design sessions at the academic medical center are expected to converge upon an adaptable pCGA implementation package, ready for feasibility and pilot testing (stage IB of the NIH Stage Model). Stakeholder design sessions at the community-based hospital will serve as a template for user-centered implementation of the pCGA at a future date. The results of co-design at the community-based hospital will provide a starting point for understanding the potential generalizability of the implementation package and the extent to which adaptation may be needed to begin implementation at new sites.

Phase 3

The pilot trial will test the pCGA implementation package using a pretest-posttest design at 2 surgical clinics enrolling 20 patients in the preimplementation period and 40 in the postimplementation period. Using the RE-AIM framework [38] we will measure reach, effectiveness, adoption, implementation, and maintenance. We aim to improve reach and maintain fidelity. Exploratory analyses will assess differences across traditionally underrepresented groups [69] (rural vs urban, racial majority vs minority groups, men vs women vs other gender identities, and Hispanic vs non-Hispanic ethnicity). We hypothesize that reach will increase while maintaining fidelity in the postimplementation phase of the pilot.

Dissemination

The findings from each phase of the study will be disseminated following best practices throughout the conduct of this research. We will publish peer-reviewed manuscripts and present findings at professional conferences for each phase of the study. The results will be posted to ClinicalTrials.gov within 12 months of study completion.

Discussion

Anticipated Principal Findings

This study will apply both implementation science and human factors engineering methods aiming to generate the following main findings for each phase of the study: (1) detailed process map for the pCGA, (2) a co-designed implementation package to improve the use of the pCGA among older patients having major abdominal surgery, and (3) preliminary data to support a future implementation-effectiveness trial. In addition to the aforementioned expected output, the study will allow us to explore our hypothesis that systems engineering methods of process mapping and co-design can successfully be applied to the pCGA in surgical care (aims 1 and 2) and that a rigorous user-centered pCGA implementation package will improve surgical care processes (reach and adoption, which are the primary implementation outcomes) and patient outcomes (length of stay, which is the primary effectiveness outcome) for older adults undergoing major abdominal surgery.

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Comparison to Prior Work

The findings will be interpreted in the context of prior literature. There are few studies addressing pCGA implementation challenges. Implementation science can provide insight into the heterogeneity of the literature on the pCGA. Poor implementation of the pCGA contributes to variable effectiveness among older adults undergoing abdominal surgery. Two randomized controlled trials involving patients undergoing abdominal surgery have been conducted; however, both were underpowered, with significant variability in the fidelity to, and the implementation of, the pCGA [95,96]. Hempenius et al [95] randomized a heterogeneous group of 260 patients with cancer undergoing minor, intermediate, or major operations (eg, abdominal surgery) to usual care or an in-hospital "geriatric liaison" service conducting pCGA tests 24 hours before the operation. The authors found a 34% relative reduction in postoperative delirium, but it was not significant due to an underpowered sample size and a lower-than-expected rate of delirium [95]. The effect of the intervention was likely reduced because the "liaison" model leaves inadequate time to reduce risks, and minor procedures carry very low complication rates with lower postoperative delirium rates. Ommundsen et al [96] randomized a population of patients with frailty with colorectal cancer to receive outpatient pCGA versus usual care, finding no significant difference in the primary outcome of severe surgical complications [96]. This study was limited by the lack of a multidisciplinary team supporting the intervention, inadequate preoperative time to implement pCGA recommendations, unclear patient adherence to recommendations, and an inability to reach the necessary sample size. This resulted in an underpowered study and a weak intervention with poor fidelity.

Strengths

By applying an implementation focus, this study will define system-level strategies to maintain fidelity while improving implementation, thereby elevating the quality of evidence in examining the effectiveness of the pCGA. We expect that this study will facilitate a paradigm shift toward rigorous implementation-effectiveness [97] work to enhance perioperative care for older patients undergoing surgery. Our line of research is innovative because it aims to refine the implementation of an existing intervention, engaging an affiliate community-based hospital in user-centered design, to expand the reach of the pCGA to patients in a variety of settings. Our methods are also innovative, applying human factors engineering methods and the SEIPS model to a new field: the use of the pCGA among older patients having major abdominal surgery.

Limitations

We anticipate that there will be limitations and potential challenges in conducting this study. Recruitment and retention will be addressed by incentivizing participation (gift cards) and recruiting at least 10% more participants than required. As user-centered design sessions will require continuity, we will conduct team-building exercises to promote investment in the process and provide sufficiently generous incentives to retain participants. Smaller design teams are often more effective, and we will accept 2 dropouts per group. Patient and caregiver access to technology may limit participation in video-based assessments in phases 1 and 2; however, we believe that this challenge can be overcome because these methods have successfully been applied over the course of the COVID-19 pandemic. Alternative strategies such as in-person attendance of interviews and design sessions also risk potential limitations or exclusion of those with poor access to transportation. We recognize that the process map within the academic medical center may not be generalizable to the community-based hospital. It is possible that the pCGA implementation package cannot be successfully adapted to the community-based hospital. In this case, user-centered design will allow us to explore the pCGA components that will be most valuable to the health care professionals and patients at the community-based hospital. This may require a shift toward intervention adaption, evaluating a pared-down, community-specific pCGA intervention. The implementation package and pilot test in phase 3 will focus on system-level changes; however, we anticipate identifying individual-level barriers and facilitators to implementation (primary care provider follow-through or patient barriers to performing exercises). The role of individual behavior in fidelity to the intervention cannot be ignored and may serve as an area for future research. We plan to track these findings; however, interventions to alter individual behavior are beyond the scope of this system-level investigation.

Future Directions

This study will produce preliminary data on which to build a future implementation-effectiveness trial. Upon successful adaptation of the implementation package, we anticipate performing a step-wedge randomized controlled trial to implement the pCGA at multiple sites. The anticipated type II hybrid implementation-effectiveness trial will equally weigh implementation and effectiveness outcomes. It will track both short-term (30-day) and longer-term (90- and 120-day) outcomes, including morbidity and mortality, and, as noted in the *Outcomes* section, will include outcomes across the pCGA domains (cognition, function, nutrition, polypharmacy, mood, and quality of life). If successful, the adaptable pCGA implementation package will provide an actionable strategy for hospitals seeking to improve surgical care for older adults. With an effective intervention and a well-tested implementation strategy, future work will focus on scalability and dissemination. By engaging an affiliate community-based hospital in user-centered design, this research will develop implementation strategies by which to expand the reach of the pCGA. We will explore the differential receipt and experience of the pCGA across diverse populations, consistent with the NIH commitment [98] to diversity, equity, and inclusion, including the study of health equity. Throughout the study, we will engage and elicit the voices of patients and caregivers traditionally underrepresented in medical research [69] according to race, ethnicity, socioeconomic status, and rural or urban backgrounds. In addition to hybrid implementation-effectiveness trials, future directions will focus on adaptation to new populations, dissemination strategies, and the scalability of the intervention.

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Dissemination Plans

We anticipate that surgeons and hospitals participating in statewide quality improvement collaboratives, such as the Surgical Collaborative of Wisconsin, may be interested in interventions that aim to improve surgical care for older adults. Larger national initiatives, such as the American College of Surgeons Geriatric Surgery Verification Program [99], require the performance of a pCGA. If successful, the pCGA implementation package may serve as a valuable resource and provide an actionable strategy for hospitals in these or similar programs. Our ability to provide an effective intervention with a well-tested implementation strategy will open the possibility of regional or national dissemination.

Conclusions

Upon completion, the study will produce a comprehensive and rigorously evaluated pCGA implementation package as well as feasibility data to support a multisite hybrid implementation-effectiveness clinical trial. This study will advance the field, improving the quality of implementation data on the pCGA, providing replicable implementation strategies for the pCGA, and integrating human factors methods into perioperative science. It will further our overall goal to improve surgical care for older adults through transdisciplinary research that promotes the implementation and dissemination of effective, evidence-based, patient-oriented interventions.

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Data Availability

The data sets generated and analyzed during this study will be available in deidentified form after study completion from the corresponding author on reasonable request.

Authors' Contributions

JRB was responsible for conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft, and reviewing and editing subsequent drafts. MLS, NEW, JEM, and MNS were responsible for conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, validation, visualization, and reviewing and editing subsequent drafts.

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
NIH: National Institutes of Health
pCGA: preoperative comprehensive geriatric assessment
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
SEIPS: systems engineering initiative for patient safety

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Protocol

Testing a Conceptual Model of Early Adversity, Neural Function, and Psychopathology: Protocol for a Retrospective Observational Cohort Study

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Abstract

Background: Early adversity, broadly defined as a set of negative exposures during childhood, is extremely common and increases risk for psychopathology across the life span. Previous research suggests that separate dimensions of adversity increase risk through developmental plasticity mechanisms shaping unique neurobiological pathways. Specifically, research suggests that deprivation is associated with deficits in higher order cognition, while threat is associated with atypicality in fear learning and emotion dysregulation. However, most of this research has been conducted in adolescent and adult samples, long after exposure to adversity occurs and far from periods of peak developmental plasticity.

Objective: The Wellness Health and Life Experiences (WHALE) study examines the neurobiological and behavioral mechanisms by which deprivation, threat, and unpredictability increase risk for psychopathology in early childhood (age 4-7 years) directly following periods of peak developmental plasticity. The objective of this study is to describe the study rationale and aims, the research design and procedures, and the analytical plan to test the study hypotheses.

Methods: This is a retrospective cohort study that examines associations between exposure to deprivation and threat and their hypothesized neurobiological mechanisms, how these neurobiological mechanisms link early adversity and psychopathology, and associations between unpredictability, reward learning, and psychopathology. The sample was a convenience sample of children (aged 4-7 years) and their families, identified through flyers, email blasts to listserves, school-based advertising, and involvement in community events. Data were collected during a home visit, a subsequent laboratory visit, and a final neuroimaging visit. Planned analyses include linear regression, path analyses, and functional magnetic resonance imaging analyses to explore the role of neural function in the association between early adversity and psychopathology.

Results: Participants (N=301) have been recruited into the study, and data collection has commenced. The expected results will be available in 2024.

Conclusions: The findings of this study will help elucidate the neurobiological mechanisms by which early adversity increases risk for psychopathology in early childhood. This study represents the earliest test of an influential theory of biological embedding of early adversity.

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KEYWORDS

early adversity; psychopathology; neurodevelopment; adverse childhood events; child development

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Introduction

Background

Exposure to early adversity (EA) is extremely common in the population, with one-half of children in the United States experiencing some form of EA [1-3]. Moreover, EA profoundly increases risk for novel onset of internalizing and externalizing psychopathology [1,2], making it a central public health concern. Childhood psychopathology is associated with increased risk for psychopathology later in life [4], and these disorders cause economic burden to public health systems (eg, estimated annual costs of US $43.2 billion) [5]. However, current efforts in this direction are stymied by a lack of understanding of the pathways through which EA increases risk for psychopathology [6].

Progress in identifying these pathways has been limited by several critical barriers, including a lack of focus on neurodevelopmental mechanisms linking EA exposure to psychopathology. Understanding neurodevelopmental mechanisms is of import because psychopathology is an equifinal outcome for numerous forms of adversity, whereas neurobiology is likely to be more specifically impacted by different forms of EA. Second, to date, most work examining the impact of adversity on neurobiology has been conducted in adolescent or adult samples, long after EA exposure and often after the onset of psychopathology. This focus on adolescents and adults limits how research findings can be used for early preventive interventions and confounds psychopathology with adversity exposure in identifying neurobiological pathways. In the study presented here, we focus on neural mechanisms linking EA to symptoms of psychopathology in early childhood.

Aims and Hypotheses of the Wellness Health and Life Experiences Study

The primary aim of this study is to differentiate pathways linking distinct dimensions of EA to psychopathology by testing a novel conceptual framework: the dimensional model of adversity and psychopathology (DMAP) [2]. The DMAP draws on basic neuroscience principles from animal models, existing developmental data, and preliminary findings from our own laboratory [2-5,7,8]. This framework differentiates between deprivation (absence of expected cognitive learning experiences) and threat (presence of atypical traumatic learning experiences) as distinct dimensions of EA and makes predictions about their distinct effects on structural and functional brain development. The DMAP proposes that experiences of deprivation primarily influence the development of cognitive control systems, including the structure and function of the frontoparietal network, while experiences of threat primarily influence the development of negative valence systems, including the structure and function of the amygdala and medial prefrontal cortex. In this study, we additionally propose testing the impact of unpredictability (inconsistent caregiver response) on neurodevelopment and psychopathology. We expect unpredictability to have distinct and specific effects on positive valence systems, including ventral striatal function and reward learning. This study stands to contribute meaningfully to our understanding of how specific dimensions of environmental experience influence neural development to increase risk for psychopathology, addressing objectives 1 and 2 of the National Institute of Mental Health Strategic Plan.

Before this application, earlier work focused on linking single types of adversity, such as poverty, abuse, and neglect, to specific mechanistic pathways. These models of individual adversities ignore clustering of risk exposure. Associations of one form of adversity with an outcome without measuring other forms of adversity may lead to misidentification of risk pathways [9-11]. Other prior approaches used a cumulative risk approach where associations between the number of adversities of any kind with developmental outcomes were measured [1-3]. In this model all forms of adversity are grouped together and considered to have similar, equal, and additive effects on development. The most commonly proposed neurobiological mechanism for the cumulative risk model is allostatic load and disruptions in physiological stress response systems [12]. Proposing a single stress pathway is problematic as it ignores numerous other developmental mechanisms through which early experience shapes brain development. For example, poverty is associated with a broad range of child development outcomes, not only because of alterations to stress physiology but also because of differences in access to formal and informal learning opportunities (eg, access to educational resources and variety of experiences) [13]. The proposed research moves beyond the approach of collapsing across diverse experiences of adversity to one that aims to distill these complex exposures into their core underlying dimensions of experience [6]. Exposure to deprivation and threat often co-occur; however, we have accumulating evidence from our laboratories and independent replication by others [14], indicating that it is possible to observe independent effects of deprivation and threat. Importantly, we do not expect these to be the only 2 dimensions of adversity. In this proposal we include a third dimension: unpredictability.

The Wellness Health and Life Experiences (WHALE) study addresses 3 specific aims. Aim 1 addresses the selective associations between deprivation, threat, cognitive control, and fear learning. Two sets of hypotheses are proposed for aim 1. The first is that experiences of deprivation (lack of cognitive enrichment and decreased complexity of linguistic input) will be negatively associated with cognitive control, reduced cortical thickness in lateral prefrontal cortex, and reduced activation in lateral prefrontal cortex during executive function. Second, threat (experiences of interpersonal violence) will be associated with altered fear acquisition and extinction learning, reduced medial prefrontal cortex thickness, and heightened amygdala activation during emotion regulation. Aim 2 examines the distinct neurobiological pathways through which deprivation and threat predict psychopathology. A total of 2 sets of hypotheses are proposed for aim 2. We hypothesize that alterations to cognitive control and frontoparietal network structure and function will mediate the association of early childhood deprivation and psychopathology across internalizing and externalizing dimensions. In addition, we predict that altered fear learning and altered structure and function of the amygdala and medial prefrontal cortex will mediate the association of threat with psychopathology. Finally, aim 3, an exploratory aim, assesses the association of unpredictability with altered associative learning of reward and psychopathology. We

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hypothesize that decreased predictability of the family environment (inconsistent and low contingency of caregiver responses, instability of the family and physical environment, and family chaos) will predict blunted reward learning and ventral striatal activation. Finally, we predict that disrupted reward learning and underlying neural circuitry will mediate the association of unpredictability with psychopathology.

Methods

Sample

Power Analyses

We used functional magnetic resonance imaging (fMRI)–based power analysis implemented in the fMRIpower software package 2007 version [15] in MATLAB [16]. Power calculations were for activation in the medial prefrontal cortex (equivalent to a region of interest analysis with $P<.05$) extracted from a study conducted in our laboratory of a cognitive control task that included children as young as 5 years to estimate the size of our effect. This analysis indicated that a sample of n=45 would achieve 80% power to detect an expected medium effect size of 0.45 in the medial prefrontal cortex. Our total projected sample was >200 participants, which achieves power of >85% to detect a medium effect.

Power for the mediation analyses was examined using Monte Carlo simulations in MPlus 6.1 [17-19]. Data were simulated for a population based on estimated parameters, and a model was estimated for multiple samples drawn from that population. Power was derived based on the proportion of replications in which the null hypothesis (ie, that a given parameter is 0) is correctly rejected when it is false. We estimated power in 1000 replications to detect effects based on our estimated sample size of 200 using minimum detectable effect sizes. For path models predicting indirect effects of threat and deprivation on psychopathology via neural function (aim 2), we will have power (with a sample of 200) to detect indirect effects as small as a×b=0.067.

Recruitment Strategy

The sample was a convenience sample identified through flyers, email blasts to listserves, school-based advertising, and involvement in community events. The first 20 participating families were recruited into the study without regards to subsequent selection criteria and were only required to live within 1 hour of Chapel Hill, North Carolina, and to have a child aged between 4 and 7 years. Following these early participants, interested families who provided their contact information were called and a phone screen was conducted. This phone screen identified participants likely to experience EA based on identity variables related to structural inequality, self-disclosed family violence, or self-disclosed previous involvement with child protective services. Extensive prior research suggests that structural inequality related to race and class increases risk of experiencing childhood adversities, including deprivation and threat [20,21]. The screening questionnaire first asked if either caregiver had less than a high-school education or had a minoritized ethnic or racial identity. If caregivers answered positively, they were recruited into the study, if not, they answered a short series of questions about family violence or child protective services involvement. If they reported either involvement in child protective services or family violence exposure, they were recruited into the study. If they did not endorse low caregiver education, minoritized identity, family violence, or child protective services involvement, they were not recruited into the study. Prospective participants who did not meet inclusion criteria completed screening questionnaires only. Due to the "funnel" nature of the screen, not all participants were asked all screen questions (ie, once the family "screened in," the questionnaire was terminated). Consequently, all information about family violence in the study is from subsequent study visits and not the screener form. Our recruitment strategy resulted in a diverse sample with respect to race, ethnicity, and caregiver education, and is enriched for exposure to EA, including interpersonal violence and neglect. Before participation in any study visit, some participants were screened out if the primary caregiver and child did not endorse speaking and reading English well enough to provide informed consent. Additional exclusion criteria included major medical conditions which would compromise study involvement, neurological illness, pervasive developmental disorders, or substantial prenatal substance exposure. Child participants were not included in the magnetic resonance imaging (MRI) visit if their caregiver reported the presence of MRI contraindications or history of concussion. Given the extensive nature of these criteria, some were ascertained after inclusion in initial study visits. Our final cohort (N=301) includes every caregiver participant who consented to study participation following initial phone screen regardless of if they met subsequent exclusion criteria or refused to participate following consent.

Design and Procedures

Study Overview

The study consisted of 3 visits. A total of 275 (91.4%) of 301 participants participated in at least 1 study visit, 234 (77.7%) of 301 participated in 2 study visits, and 217 (72.1%) of 301 participated in 3 study visits. The same primary caregiver participated in all 3 visits, except in cases where legal custody changed between visits. Between visit 1 and 2, there was on average 3.63 (SD 4.66) months; between visit 2 and visit 3, there was on average 4.41 (SD 4.87) months. At each visit, 1 research assistant (RA) worked with the primary caregiver (caregiver RA) and another with the child (child RA). See Multimedia Appendix 1 for an overview of every measure and task included in the study.

Visit 1

Visit 1 took place in the participant's home or current place of residence and lasted approximately 2.5 hours. We began with a tour of the family's home with careful attention to the home and neighborhood environment. The child RA obtained verbal assent from the child, after which the research staff conducted interviews and tasks with the family. The caregiver RA completed interviews assessing the child's MRI contraindications and exposure to enriched learning experiences with the child's primary caregiver. Next, caregivers completed web-based questionnaires using Qualtrics, which assessed

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developmental milestones, prenatal exposure to substances, sleep hygiene, life events, and collateral contacts for longitudinal follow-up. Finally, the caregiver RA took 2 photos each of the primary caregiver and a secondary caregiver for task stimuli at visits 2 and 3. These photos were headshots taken against a neutral background in which caregivers were asked to make neutral and smiling faces. The caregiver RA compensated the family and scheduled the second study visit. The child RA began by giving the child a prize bag and building rapport. The child RA administered a series of behavioral tasks assessing executive function and reward learning to the child. For every game the child played, they received a prize, and all children were given their prizes regardless of their performance. In most cases, the caregivers and children completed their tasks in separate spaces from each other. When not possible to administer study tasks in separate spaces for caregivers and children, caregivers were instructed to not interfere with their children's task performance.

Visit 2

Visit 2 was conducted in laboratory facilities on the University of North Carolina campus and was 6 hours long, including a half hour lunch break. Upon the family's arrival, the child RA completed verbal assent with the child in their caregiver's presence. The caregiver RA began the day with a general overview and reminders about confidentiality, and then completed interviews and surveys with caregivers. During visit 2, caregivers completed questionnaires about child behavior, symptoms of psychopathology, family functioning, and discipline practices in the home. Meanwhile, the child RA started the day with an introduction to prizes and built rapport with the child. Children completed tasks that assessed executive function, fear learning, and reward learning. They additionally completed an electroencephalogram (EEG) recording. EEG recording was accomplished using a 128-channel Sensor Net system. The net is composed of an elastic tension structure forming a geodesic tessellation of the head surface containing carbon fiber electrodes embedded in pedestal sponges. At each vertex, there is a sensor pedestal housing a silver/silver chloride–coated, carbon-filled plastic electrode and sponge containing saline electrolyte. Before fitting the Sensor Net over the scalp, the sponges are soaked in electrolyte solution (6 mL KCL per liter of distilled water) to facilitate electrical contact between the scalp and the relevant electrode. The data were amplified, filtered (bandpass 0.1-100.0 Hz), and sampled at an effective rate of 250 Hz. Before recording, measurements of channel gains and zeros were taken to provide an accurate scaling factor for display of waveform data and so that baseline correction can be performed. The participant's head was measured and marked to ensure accurate placement, and the net is then placed over the scalp. All RAs collecting EEG data were trained by the study's principal investigator (MS), an expert on EEG data collection and analysis. In the middle of the visit, the caregiver and child were reunited to complete video-recorded parent-child interaction (PCI) tasks [22]. The PCI tasks included 3 interactive tasks, lasting 10 minutes each, during which the caregiver and child played with toys, completed puzzles, and read a book. The child RA provided verbal instructions before each task. Families were permitted to speak in the primary language spoken at home across each task. After this, families were typically given their lunch break for 30 minutes.

After lunch, the caregiver RA and the child RA instructed the child to refrain from drinking or eating to prepare for saliva collection. The child participant completed a resting-state and task-based EEG recordings. Next, the child RA completed a 3-part saliva collection; 1 sample was taken immediately after EEG. Next, children participated in a finger prick task where a single finger prick was performed to obtain up to 5 blood spots. Children participated with their caregiver and an RA they had not previously interacted with, as these semistructured tasks were developed to measure how parents support children's emotion regulation (see below), and we wanted to avoid children using the child RA as support. Saliva was collected before the finger prick task, 20 minutes after finger prick, and 40 minutes afterward. Finally, a mock scan was completed to prepare the child for visit 3.

Visit 3

Visit 3 of the WHALE study was conducted at the University of North Carolina Biomedical Research Imaging Center in Chapel Hill, United States. This visit included an MRI comprising structural (ie, magnetization-prepared rapid gradient echo [MPRAGE]), diffusion tensor imaging, and functional sequences on a 3T Siemens Prisma scanner. Upon arrival, the child RA obtained verbal assent from the child in their caregiver's presence. Children underwent training for 3 tasks that they would later complete in the scanner, including an executive function task, a reward anticipation and receipt task, and an emotion regulation task. Families were reminded of MRI procedures. At the visit, caregivers completed a series of questionnaires assessing their own and their child's emotion regulation, executive function, and the caregivers' history of exposure to adversity. While being trained, the child selected prizes that they would win for completing these tasks during the MRI scan to serve as motivation. After task training, both RAs accompanied the caregiver and child to the MRI suite.

At the MRI suite, the caregiver helped the child change into MRI-safe scrubs, after which the MRI technician reviewed the completed MRI safety screening form with the caregiver. The child and caregiver were separately asked about potential MRI-unsafe materials inside the child's body. During MRI scan, children were given earplugs and noise-canceling headphones, cushions around their head, a sheet, and a weighted blanket to ensure comfort during the scan and limit movement. The child RA stayed with the child in the scan room throughout the scan to communicate with them and respond to any child concerns. After completing MPRAGE and 1 task, each child came out of the scanner for a break and a snack. We used AAScout for slice positioning to ensure that children can get in and out of the scanner multiple times, allowing better data collection. After returning to the scanner, they completed the remaining 2 tasks and diffusion tensor imaging sequence. Before and after every acquisition, the caregiver RA communicated with the child through an intercom system embedded in the child's noise-canceling headphones, to remind the child to stay still and assess their ability to continue through the study. The child was told that if they remained still enough during the entirety

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of the scan session, they would receive a big prize which they had selected before entering the scanner. After each scan, the caregiver RA communicated progress toward this goal.

The emotion-regulation task included images of children expressing emotional distress or in potentially dangerous situations (eg, being physically threatened by an adult). Following completion of this task, the child RA completed a debrief with the child to assure them that all people in the pictures were "playing-pretend" for the pictures. Next, the child RA completed 2 interviews with the child to assess their experiences of neglect and interpersonal violence in a separate space from the caregiver. If abuse or neglect were suspected based on the child's endorsements, the RAs consulted with a staff clinical psychologist or the study principal investigator to evaluate if mandatory reporting thresholds were met and gather relevant information for appropriate child protection agencies. All participating caregivers were offered a consultation with a clinical psychologist following their child's visit to understand how they had performed on standardized tests and interviews.

Neuroimaging Protocol With Young Children

At the end of visit 2, the child completed a mock MRI scan to prepare them for their final study visit. The child RA first introduced the child to the mock scan using a picture book that described the MRI machine, its function, and the importance of staying still. The child RA played scanner sounds for the child and showed the child the earplugs and headphones. This was a way to help the child acclimate to the sounds making them as normal as everyday items, such as a telephone ringing or a truck's horn. The child then sat on the bed of the mock MRI machine and looked inside of the mock scan to see the screen they would watch their movie on. The child RA helped the child insert the earplugs into their ears, placed the headphones over their ears, and the child was asked to lie down and remain as still as possible while they watched a video for about 5 minutes. If the child expressed discomfort or asked to stop anytime during the process, the child RA would respond accordingly. For children who were fearful of the scan, extra steps were taken to assess whether the child was willing and able to try again. For children who were willing to try again, they completed the mock scan loading procedure again.

During visit 3, the child was asked to pick out prizes they would want to win after playing games. The child completed a practice round and then completed the test of the inhibitory control task. Once the game was completed, the child received their prize and were told that they would play a similar game. They were also informed that they would only be practicing this version of the game because the real game (test) would be played later in the scanner. The child then chose the prize they would like to win after completing the task in the MRI. Behavioral notes were recorded by the RA on the child's hand use, performance, and prize selection. If the child exhibited a lack of understanding of the game rules, the RA would correct them and allow them to practice again. The next task, a reward sensitivity task, was introduced to the child. The child chose another small prize they would want to win for this game. The final task training was an emotion regulation task. Before completion of this training, caregivers were shown pictures of the training and test stimuli that the child would see so they could specifically consent to their child being shown this mildly negative content. If a caregiver preferred for their child to not see select images, those images were removed from training and test (caregivers could also opt out of this game). Once the child completed emotion regulation task training, they chose a medium-sized prize to win for once they completed the game in the scanner and began to practice the task.

After completion of all task training, the child was told about the special game buttons they would use in the scan to play their games. Then, the child was given a sheet with Disney movies and asked to pick a movie that they would like to watch during the MPRAGE scan. They also picked out a snack for their snack break and a small prize for watching their movie. Finally, the child was reminded about the importance of staying still in the scanner and introduced to "staying still points." The child was informed that throughout the scan they could win points for staying still to win a large prize. If they won enough points by staying still throughout the scan, they could go home with the large prize they selected. In addition, the child was reminded that the child RA would be standing next to them during the duration of the scan while another team member (caregiver RA) would be talking to them through their headphones. The child RA also informed the child that to help them win their "staying still points," they would put their hand on the child's leg to remind them to stay still if they were moving. The children were given all the prizes they selected during this training phase, regardless of task performance or actual movement in the scanner.

Once all prizes were selected and instructions were given to the child, the child met their caregiver at the MRI suite. The research staff provided the caregiver with scrubs to help their child change, and their pediatric MRI screening form was overviewed again with the caregiver by the MRI technician. The child's height and weight were measured by staff and reported to the technician. The child then entered the scan room with the child RA. The child RA and MRI tech walked the child through all the materials mimicking their mock scan for a sense of familiarity. In addition, the child RA showed the child their scan buttons and instructed them on how to use them. The headphone volume was tested before putting them over the child's ears, and the child was introduced to the voice of caregiver RA at the scan console and asked to respond verbally to them.

Measures

Early Adversity

Caregivers and children reported on adverse experiences involving deprivation, threat, and unpredictability using self-report measures and interviews. Continuous composite scores representing the severity of deprivation, threat, and unpredictability will be calculated by summing sample-standardized scores from the self-report and observational measures and by creating count scores reflecting the number of different exposures to deprivation, threat, and unpredictability. Deprivation will be operationalized as exposure to neglect and low social and cognitive stimulation. Exposure to neglect is reported by caregivers on the neglect subscale of

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the Conflict Tactics Scale (CTS) parent-child version [23], Juvenile Victimization Questionnaire [24], and exposure to physical, supervisory, and cognitive neglect reported by children on the Multidimensional Neglectful Behavior Scale [25]. Exposure to low cognitive stimulation was observed in the Home Observation Measurement of the Environment [26], reported by caregivers on the StimQ [27], and reported by children on the Multidimensional Neglectful Behavior Scale. In addition, indexes of caregiver use of complex language will be measured during the book reading PCI and included in some measures of deprivation pending factor analytic and other clustering approaches to dimension development.

Threat will be operationalized as exposure to physical abuse, sexual abuse, domestic violence, community violence, and other interpersonal violence. These exposures were reported by caregivers on the CTS parent-child version, CTS 2nd edition [28], Juvenile Victimization Questionnaire, University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index [29], the Life Events Scale for Children [30], and the School Safety Questionnaire [31], and by children on the Violence Exposure Scale for Children-Revised [32]. Corporal punishment and endorsements of harsh punishment were additionally observed or reported by caregivers on the Home Observation Measurement of the Environment instrument.

Unpredictability will be operationalized as exposure to lack of consistent responding, instability of the family and physical environment, and disorganization reported by caregivers on the Family Life Project Chaos Scale [33], the Confusion, Hubub, and Order Scale [34], the US Department of Agriculture Food Insecurity Scale [35], the Family Routines Inventory [36], and the Questionnaire of Unpredictability in Childhood [37]. In addition, observations of entropy in caregiver behavior from the PCI tasks will be incorporated [38] into indexes of unpredictability pending factor analysis and other clustering approaches to dimension development.

Childhood Psychopathology

Child psychopathology was assessed using the Mini-International Neuropsychiatric Interview for Children and Adolescents and caregiver report on the Child Behavior Checklist [39-42].

Study questionnaires and interviews were administered to caregivers using Qualtrics [43] across the multiple study visits and took around 10 hours to complete in total. Moreover, all of these questionnaires and surveys have been validated and used in multiple studies exploring the impact of childhood adversity on child development, including various studies from our group [44-47]. For information about each individual measure's validity and reliability please review its citation.

Fear Learning Task

The task involves 3 phases: habituation, learning, and extinction, and it is based on previous work studying fear learning in young children and work in adults examining fear learning to images of close friends [44,48-51]. On a computer screen, 4 different images, 2 of caregivers and 2 of strangers, were shown one at a time, 4 times each to the child (preacquisition). Then, the images were shown again and 2 of the pictures (caregiver and stranger) were paired with an aversive 95 dB noise, which was counterbalanced across participants (conditioning). The conditioning phase involves 6 to 10 trials of each face. The alarm noise rings for 2 stimuli (caregiver and stranger) but not for the other 2 stimuli (secondary caregiver and stranger). Finally, the pictures (caregiver or stranger) were shown one at a time again with no noises for 6 to 10 trials each (extinction). Children rated how much they fear or like each picture at the end of each phase. Children were informed that they can discontinue the task at any time. Skin conductance and heart rate were collected continuously throughout the task using MindWare Technologies. To measure skin conductance, 2 electrodes were attached to the index and middle finger of the child's nondominant hand after the fingers were cleaned with rubbing alcohol. To measure continuous echocardiogram, we used MindWare Technologies BioLab acquisition software at 500 Hz. Two electrodes were attached to the participant's collar bone and rib cage. Electrode attachment was always done in the presence of 2 RAs using electrodes designed for use with small children.

Parent-Child Observed Emotion Regulation

The researcher collected blood spot samples from the child, and then later from the caregiver, by pricking a finger with a pressure-activated lancet. For this procedure, the researcher set up the materials (eg, lancet, blood spot collection paper, alcohol wipe, gauze, and Band-Aids) and then verbally described the finger prick to the caregiver and child. Each child was first instructed to shake their hand toward the floor. The researcher then gently massaged the finger, cleaned the puncture site with an alcohol wipe, pricked the finger with the pressure-activated lancet, and held the child's finger to place 2 to 5 drops of blood on the collection paper. After obtaining the samples, the researcher cleaned up the materials and left the space, while the caregiver was asked to place a Band-Aid around the child's finger. Throughout the finger prick procedure, caregivers were welcome to speak and interact with their child and reposition themselves or their child (eg, taking child in lap) however they wished. No instructions were provided to caregivers on how to respond to their child.

The finger prick also served as the context for the coding of caregiver- and child-directed behaviors using a novel coding scheme based on existing schemes [22,52,53]. The full finger prick blood collection procedure was video recorded, with cameras placed in a location that captured both caregiver and child. Children's emotion regulation, caregivers' sensitivity, caregivers' hostility, and the dyad's level of engagement were coded from the video-recordings on scales of 1 to 5. Child distress was rated on a scale of 1 to 5 every 30 seconds of the video. Furthermore, the presence or absence of children's engagement in specific behaviors (eg, positive expressions, distraction, and avoidance), caregivers' initiation of strategies to regulate the child (eg, distraction, calming techniques, and emotion word use), and dyadic behavioral mimicry were also coded every 30 seconds. The full finger-prick procedure from the start to end times of coding ranged from 2 minutes and 30 seconds to >5 minutes, depending on both the speed of the researcher and child's level of discomfort. Videos where caregivers and children had instances of speaking in languages

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other than English (eg, Spanish, Mandarin, and Russian) were translated by multilingual RAs on the study team before coding. Each video was coded by at least 2 individuals on the team to maintain reliability and increase coding accuracy.

Structural MRI and fMRI

Imaging acquisition was performed on a Siemens 3T Prisma scanner with a 32-channel head coil. T1-weighted MPRAGE were acquired for anatomical coregistration with fMRI and for analysis of cortical thickness, surface area, subcortical volume, and T1/T2*-weighted mapping (repetition time=2500 ms, echo time=2.88 ms, flip angle=8°, field of view=256 mm^2, 176 slices, in-plane voxel size=1 mm^3). For task blood-oxygenation–level dependent signal is acquired using a gradient-echo T2*-weighted echo-planar imaging (EPI) sequence. Seventy-two 2 mm slices are acquired positioned parallel to the anterior commissure-posterior commissure line. Imaging parameters are repetition time=0.8 seconds, echo time=37 ms, flip angle=52°, bandwidth=2300, echo spacing=0.58 ms, filed of view=104×104, and interleaved slice acquisition, multiband acceleration factor is set to 8. We used FIRMM software to monitor movement in a moment-to-moment fashion, allowing us to give real time feedback to participants and adjust scanning appropriately. We use AAScout to position slices on the long axis of the brain. AAScout was run before acquiring data at the beginning of the scan, following the break for a snack, and anytime a substantial movement occurred. All slice acquisition for EPI scans came from the AAScout. Using this autoalign procedure limited our ability to place slices on the AC-PC line but it allowed us to acquire EPI scans across runs and after the child exited and entered the scanner using identical slice placement on the child's brain.

T1-weighted scans will be used to calculate cortical thickness and gray matter volumes using FreeSurfer. Automatic image segmentation is used to identify subcortical gray matter structures. Next, gray and white matter, and gray matter and cerebrospinal fluid boundaries are constructed, and the cortex is parcellated based on the structure of gyri and sulci. The results will be manually inspected and edited. These procedures have demonstrated good test-retest reliability across scanner manufacturers and field strengths, and cortical thickness measures have been validated against manual measurement [54]. Preprocessing and statistical analysis will be performed using fMRI data preprocessing pipeline [55] and Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) [56] to capitalize on the relative strengths of different statistical packages. Preprocessing will include spatial realignment, slice-time correction (4D reconstruction), and spatial smoothing. Outliers (frame wise displacement <0.9 mm for task, <0.2 mm for rest), motion regressors and their derivatives (6 rigid body parameters), cerebrospinal fluid, and white matter signal will be included in person-level models. After estimating the person-level models, contrast images will be normalized into standard anatomical space using an appropriate atlas. FSL will be used to construct generalized linear models at the level of the run, which will be combined using FLAME to the level of the person and group.

Executive Function fMRI Task

We assessed executive function using the conditioned appetitive response inhibition task. A total of 1 version of this task is commonly used in early childhood [57] and another in middle childhood, adolescence, and adulthood [58-61]. Performance and neural recruitment in this task has been linked with transdiagnostic risk for psychopathology [61]. In the training period of the conditioned appetitive response inhibition task (outside the scanner), participants are rewarded for pressing a button when they see a specific stimulus. In the scanner participants perform a go-no go task where 30% of the stimuli are "no go" and 70% are "go" stimuli. Within the "no go" stimuli, half are the stimulus which was rewarded during training and half are a previously seen but not rewarded stimulus. This task was administered in 2 runs lasting about 5 minutes each.

Reward fMRI Task

For the reward task, participants see a question mark and are asked to guess what is "behind" the question mark by pressing a button. After responding, participants receive feedback: either gold coins for guessing correctly or gold coins with an "X" through them for guessing incorrectly. The feedback is predetermined and randomly assigned such that half of responses will be "correct," and thus, the child will receive a reward, and the other half will be "incorrect," and the child will garner a loss. Children were shown before each trial if it was a high value (win US $1.00, lose US $0.50) or a low value (win US $0.20, lose US $0.10) trial [62]. Although wins and losses were reported as monetary amounts on each trial, the child was told that they would not receive money but instead earned a prize.

Emotion Regulation fMRI Task

We assessed emotion reactivity and regulation using a novel task developed for this study, which is a variant of a commonly used older-child and adult cognitive-reappraisal task [63,64]. This novel task is optimized for use in early childhood. In older child and adult cognitive-reappraisal tasks, participants are told to use reappraisal strategies, or stories, to distance themselves from negative stimuli. In the novel early childhood version, participants are *told* reappraisal stories by an adult instead of coming up with these stories on their own, which mimics strategies regularly used by caregivers to help children regulate their emotions. Versions of this task have been used previously in EEG studies [63,65].

Analytic Plan

Associations between EA and task performance will be assessed using linear regression. All analyses will include controls for age, sex, cognitive ability, and aspects of family environment not directly related to deprivation and threat, such as caregiver education. Differences in cortical thickness as a function of deprivation, threat, and unpredictability will be examined using surface-based analysis tools in Free Surfer, correcting for multiple comparisons using false discovery rate. To examine the influence of deprivation, we will estimate regressions to test for linear associations between deprivation exposure and cortical thickness.

fMRI data analysis will be conducted in FSL. Stimulus onset regressors will be convolved with a canonical hemodynamic

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response function in all tasks. The general linear model will be estimated in individual space, and nuisance regressors will be included for motion parameters and outliers. Individual-level regression coefficients will be submitted to group-level random effects models, and linear regression parameters will be estimated to examine activation as a function of deprivation and threat. Cluster-wise false positive rates of $P<.05$ corrected for multiple comparisons will be applied. Finally, to determine whether the impact of deprivation threat, or unpredictability on neural structure and function are pathways linking EA to psychopathology, we will test a multiple mediation model.

Ethical Considerations

This study has institutional review board approval from The University of North Carolina at Chapel Hill (study 16-1278). Informed consent was obtained from all individual participants included in the study. Participants received US $280 in total across the 3 study visits for their time and effort. Participating children earned prizes by completing study tasks. In addition, families were reimbursed for transportation costs associated with attending study visits.

Results

Overview

The WHALE study is funded by the National Institute of Mental Health (R01MH115004; see grant review provided in Multimedia Appendix 2). The study began data collection in November 2018 and continued through May 2024. Recruitment for this study has concluded, and data collection is ongoing. Study results will be available in 2024.

Sample

Participants (N=301; 49% male) were enrolled in the study when they were aged between 4 years 0 months and 7 years 3 months. Average age at first visit was 5.69 (SD 0.83) years. Our sample is racially and ethnically diverse with 36.8% (111/301) self-identified as Black or African American, 15.2% (46/301) as other or mixed race, 6.9% (21/301) Asian, 0.9% (3/301) American Indian or Pacific Islander, 11.9% (36/301) Hispanic or Latino, and 36.8% (111/301) non-Hispanic White. Of the total participants who enrolled in the study, 26 (8.6%) did not participate in any study visits. Data collection occurred between November 2018 and May 2024; study attrition was primarily due to disruption in the operation of the laboratory during the COVID-19 pandemic.

Early Adversity

The sample has substantial strengths. First, we have multi-informant assessment of exposure to adversity, and multimodal assessments of executive function and emotion dysregulation, including caregiver report, child task performance, and neural function. Second, we recruited participants based primarily on indexes of structural inequality. Consistent with evidence supporting a strong association between structural inequality and adverse childhood experiences, participating families reported a range of deprivation and threat experiences (Multimedia Appendix 3).

In addition, this sampling strategy more accurately reflects the range of profiles that emerge from exposure to adversity, which can be obscured when sampling is predicated on the outcome (eg, psychopathology) [66]. Finally, this sample was recruited during the peak age for likely exposure to adversity in the home. Evidence from epidemiological literature indicates that the early childhood period carries the greatest risk for exposure to maltreatment [67,68] and corporal punishment [69], and it is a period of maximal brain, cognitive, and emotional development [70]. Assessing neural function in this age range is rare. Here we have excellent measurement of cognitive, emotional, and neural functioning during this early period, and thus, the opportunity to observe the impact of adversity on child development.

Discussion

Principal Findings

The WHALE study is one of the first studies to explore the differential impact of deprivation, threat, and unpredictability on neural function and risk for psychopathology. Recruitment is complete with a sample of 301 participants, and our sampling strategy was successful in recruiting an ethnic and racially diverse sample. Moreover, in a subsample of participants (n=270), we observe a wide range of deprivation and threat experiences. These distributions are similar to prior research aiming to differentiate the effects of dimensions of adversity on neurodevelopment in prior samples [42,69], and will allow us to capture the unique effects of experience on development. As this is an ongoing study, no formal testing of the project's hypotheses has been conducted yet.

Previous research documents the differential effects of deprivation and threat on psychopathology through distinct neurobiological mechanisms in adolescence [71-73]. However, no study has evaluated these associations in early childhood, despite consistent evidence that early exposure to adversity is associated with differences in neurodevelopment during this period [44,47]. To the best of our knowledge, the WHALE study is one of the first cohort studies exploring the differential effects of deprivation, threat, and unpredictability on neurobiological mechanisms that increase risk for psychopathology. The 3 primary aims of the study were to examine (1) the associations between deprivation, threat, cognitive control, and fear learning, (2) the association between deprivation and threat with psychopathology through its hypothesized neural mechanisms, and (3) the associations between unpredictability, reward learning, and psychopathology. The results of this study will provide unique insights into the neurobiological mechanisms by which EA increase risk for psychopathology.

Limitations and Future Directions

One of the key limitations in this study is its cross-sectional design, thus future research should aim to explore the role of EA on neurodevelopmental outcomes longitudinally. These designs are important as they allow to establish directionality in observed effects. Another limitation includes the exclusion of other dimensions of EA that could have similar or differential effects on child development, such as parental loss [74]. Thus, future studies should aim to have a holistic assessment of

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children's environments that can capture other dimensions of adversity. Our results will elucidate the effects separate dimensions of EA on child neurodevelopment.

Conclusions

This protocol describes a study aiming to explore the roles of deprivation, threat, and unpredictability on neurodevelopment. We were successful at enrolling 301 children and their families into the study, and obtaining measurement on children's exposure to EA, neural function, and psychopathology. The results from this study could inform future intervention and prevention strategies to aid children exposed to EA.

Acknowledgments

Publication authorship order will be based on the relative scientific contributions of the investigators and key personnel. All raw data generated in this project will be publicly available through the National Institute of Mental Health Data Archive Research facilities.

The authors would like to thank the participants and their families for their time and effort in being part of this study.

Data Availability

The data sets generated from this study are not publicly available because of ongoing data collection efforts.

Authors' Contributions

M Sheridan is the principal investigator of this project. NM wrote the first draft of the paper with the assistance of MT, LL, ZP, SB, M Shipkova, MR, LM, SF, AM, KM, and M Sheridan. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of study measures.
[DOCX File , 26 KB - resprot_v13i1e59636_app1.docx]

Multimedia Appendix 2
Peer-review report from the Child Psychopathology and Developmental Disabilities Study Section (CPDD) - Biobehavioral and Behavioral Processes Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 128 KB - resprot_v13i1e59636_app2.pdf]

Multimedia Appendix 3
Histograms of deprivation and threat composite scores in a subsample of participants (n=270). The number of subdomains endorsed for physical neglect, insufficient supervision, insufficient resources, cognitive deprivation, and physical environment (0-5) are shown for deprivation. The number of subdomains endorsed for physical abuse, peer and community violence, sexual abuse, domestic violence, emotional abuse, and other threatening experiences (0-6) are shown for threat.
[PNG File , 59 KB - resprot_v13i1e59636_app3.png]

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Abbreviations

CTS: Conflict Tactics Scale
DMAP: dimensional model of adversity and psychopathology
EA: early adversity
EEG: electroencephalogram
fMRI: functional magnetic resonance imaging
FSL: Functional Magnetic Resonance Imaging of the Brain Software Library
MPRAGE: magnetization-prepared rapid gradient echo
MRI: magnetic resonance imaging
PCI: parent-child interaction
RA: research assistant
WHALE: Wellness Health and Life Experiences

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Proposal

Prescribing Trends and Associated Outcomes of Antiepileptic Drugs and Other Psychotropic Medications in US Nursing Homes: Proposal for a Mixed Methods Investigation

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Abstract

Background: Pilot data suggest that off-label, unmonitored antiepileptic drug prescribing for behavioral and psychological symptoms of dementia is increasing, replacing other psychotropic medications targeted by purposeful reduction efforts. This trend accelerated during the COVID-19 pandemic. Although adverse outcomes related to this trend remain unknown, preliminary results hint that harms may be increasing and concentrated in vulnerable populations.

Objective: Using a mixed methods approach including both a retrospective secondary data analysis and a national clinician survey, this study aims to describe appropriate and potentially inappropriate antiepileptic and other psychoactive drug prescribing in US nursing homes (NHs), characteristics and patient-oriented outcomes associated with this prescribing, and how these phenomena may be changing under the combined stressors of the COVID-19 pandemic and the pressure of reduction initiatives.

Methods: To accomplish the objective, resident-level, mixed-effects regression models and interrupted time-series analyses will draw on cohort elements linked at an individual level from the Centers for Medicare and Medicaid Services' (CMS) Minimum Data Set, Medicare Part D, Medicare Provider Analysis and Review, and Outpatient and Public Use Files. Quarterly cohorts of NH residents (2009-2021) will incorporate individual-level data, including demographics; health status; disease variables; psychotropic medication claims; comprehensive NH health outcomes; hospital and emergency department adverse events; and NH details, including staffing resources and COVID-19 statistics. To help explain and validate findings, we will conduct a national qualitative survey of NH prescribers regarding their knowledge and beliefs surrounding changing approaches to dementia care and associated outcomes.

Results: Funding was obtained in September 2022. Institutional review board exemption approval was obtained in January 2023. The CMS Data Use Agreement was submitted in May 2023 and signed in March 2024. Data access was obtained in June 2024. Cohort creation is anticipated by January 2025, with crosswalks finalized by July 2025. The first survey was fielded in October 2023 and published in July 2024. The second survey was fielded in March 2024. The results are in review as of July 2024. Iterative survey cycles will continue biannually until December 2026. Multidisciplinary dissemination of survey analysis

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results began in July 2023, and dissemination of secondary data findings is anticipated to begin January 2025. These processes are ongoing, with investigation to wrap up by June 2027.

Conclusions: This study will detail appropriate and inappropriate antiepileptic drug use and related outcomes in NHs and describe disparities in long-stay subpopulations treated or not treated with psychotropics. It will delineate the impact of the pandemic in combination with national policies on dementia management and outcomes. We believe this mixed methods approach, including processes that link multiple CMS data sets at an individual level and survey-relevant stakeholders, can be replicated and applied to evaluate a variety of patient-oriented questions in diverse clinical populations.

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KEYWORDS

Alzheimer disease; dementia; antiepileptic drug; antiseizure medication; antipsychotic; National Partnership; nursing home; mood stabilizer; COVID-19

Introduction

Background

Despite safety concerns and limited evidence of efficacy, antipsychotics have been highly used to treat behavioral and psychological symptoms of dementia (BPSD), particularly in nursing home residents [1,2]. Due to their risk profile and high prevalence of use, antipsychotics have also been singled out for medication reduction efforts. The Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), patient advocacy groups, and others have taken significant steps to curb inappropriate antipsychotic use in vulnerable older adults [3-5]. In 2012, the CMS debuted the *National Partnership to Improve Dementia Care in Nursing Homes*, an initiative that included targeted efforts to reduce antipsychotic use among nursing home residents with Alzheimer disease (AD) or AD-related dementias (ADRD) [1]. Subsequently, the percentage of long-stay residents who receive antipsychotic medication has been measured and graded as a long-stay quality measure in the Minimum Data Set (MDS) [6].

Since the National Partnership, antipsychotic use in nursing homes has decreased substantially [7-9]. However, this and other regulatory efforts to curb antipsychotic use have resulted in unintended outcomes, including increased prescribing of alternative, potentially high-risk agents [10]. For example, data suggest increased use of mood-stabilizing antiepileptic drugs (AEDs), which are not monitored by the CMS or assessed using a quality measure [11-15]. All AEDs have the potential for severe side effects, particularly for older adults, and several mood-stabilizing AEDs carry *black box* warnings for use in older patients [16-18]. Exactly how AEDs are prescribed in US nursing homes is unknown, as, unlike other psychotropics, a detailed national assessment has not been reported for almost 20 years [19-25]. In 2018, Maust et al [12] described the prevalence of psychotropic classes in nursing homes from 2009 to 2014 and reported a decline in long-stay prescribing of all classes of psychotropics except mood-stabilizing AEDs, which accelerated after the 2012 National Partnership debut. Other studies support this finding of increased mood-stabilizing AED use in nursing homes, with the greatest increases seen in residents without seizure epilepsy [11,12,14,15,23,26-33]. In addition to the unintended prescription shift in response to the National Partnership's initiative, analysis of Virginia claims data suggests that the pandemic is driving a second increase in AED prescribing, leading to a profound effect on dementia care and nursing home outcomes [14,15,31-34]. As AEDs are the one class of psychotropic medications not mandatorily reported in the MDS, prescribing changes would go undetected by the CMS and other stakeholders in dementia care.

With the goal of increasing understanding regarding the use of all psychoactive medications in nursing homes, we began a mixed methods investigation deploying both quantitative and qualitative approaches to describe how and why AEDs and other psychotropics are used in nursing homes; the characteristics and outcomes associated with their use; and how their use may be changing as the COVID-19 pandemic stresses long-stay facilities, unmasking existing deficiencies and gaps in care. Guided by quality improvement frameworks, we hypothesize that, as antipsychotics and anxiolytics are used less in nursing homes, prescribing of mood-stabilizing AEDs as unmonitored alternatives has increased. To test this general hypothesis, we will be guided by the study aims outlined in the following sections.

Specific Aims

Aim 1

Overview

The first aim is to evaluate the prevalence; use trends; and associated patient, facility, and regional characteristics of AEDs and other psychotropics prescribed to nursing home residents, including those with AD and ADRD.

Subaim 1a

The first subaim of aim 1 is to measure the quarterly prevalence of individual AEDs used in nursing homes (2009-2021) and investigate changes in prevalence trends before and during the COVID-19 pandemic and surrounding the introduction of the National Partnership among all long-stay residents, focusing on those with AD and ADRD.

Subaim 1b

The second subaim of aim 1 is to evaluate appropriate and potentially inappropriate AED prescribing, including for AD and ADRD (2009-2021), and investigate changes surrounding the pandemic and the National Partnership's debut.

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Subaim 1c

The third subaim of aim 1 is to compare the patient (demographic, medical, and cognitive) characteristics, facility elements, and regional variables of US nursing home residents prescribed or not prescribed AEDs in 2021.

Hypothesis 1

The potentially inappropriate long-stay use of mood-stabilizing AEDs for AD and ADRD is increasing as other psychotropic drugs are used less, a trend that accelerated during the COVID-19 pandemic, with vulnerable populations from less resourced facilities being at greatest risk of unsafe prescribing.

Aim 2

Overview

The second aim is to evaluate the association between adverse health events and individual AED and other psychotropic prescribing (2009-2021) for all indications, including AD and ADRD, and investigate changes surrounding the COVID-19 pandemic and the National Partnership's debut, adjusting for patient, facility, and regional variables.

Subaim 2a

The first subaim of aim 2 is to evaluate the association between individual AED prescribing and adverse health events, including detrimental nursing home outcomes (ie, falls; decreases in cognitive, functional, mood, and behavior scores; hospice or palliative needs; and death), hospitalizations, and emergency department (ED) visits.

Subaim 2b

The second subaim of aim 2 is to compare the patient characteristics (including AD and ADRD), facility elements, and regional variables of nursing home residents with and without adverse prescribing complications.

Subaim 2c

The third subaim is to investigate trends in the quarterly rates of adverse health events, including detrimental long-stay outcomes, ED visits, and hospitalizations of residents (concentrating on AD and ADRD) prescribed or not prescribed AEDs (2009-2021), focusing on prevalence changes surrounding the pandemic and the National Partnership's debut.

Hypothesis 2

Adverse prescribing complications are associated with individual AED use, which increased during the COVID-19 pandemic, and are more common among residents who have AD or ADRD and are frail, Black and African American or Hispanic, and from facilities and regions with fewer resources.

Aim 3

Overview

The third aim is to develop and implement a survey based on the theory of planned behavior to assess the knowledge, attitudes, and beliefs of US long-stay prescribers regarding their current and evolving approaches to managing AD and ADRD and other dementias, with an emphasis on outcomes and the impact of policies and the pandemic.

Hypothesis 3

National data from purposefully sampled nursing home clinicians can affirm the validity of all study findings, support the understanding of mechanisms underlying prescribing patterns, and elaborate on prescribing outcomes while identifying critical opportunities to mitigate disparities and improve AD and ADRD care and safety.

Clinical Implications

This study will address clinically meaningful evidence gaps directly relevant to clinical guidelines and policies and is consequential to all stakeholders in dementia care, including residents, providers, specialty groups, payers, patient advocates, and policy makers. If pharmacological approaches to BPSD management rapidly evolved during the pandemic, with risky and ineffective—but unreported—medications being used more, then harms could increase with no clinical or safety benefit, jeopardizing the health and safety of all nursing home residents, especially vulnerable ones. We know very little about outcomes or adverse health events associated with this changing approach to dementia care. Our proposed study will close this existing knowledge gap by providing a clearer picture of all long-stay pharmacological approaches to noncognitive dementia symptoms, the health outcomes associated with these varying approaches, and how such management and consequent outcomes are changing under the pressure of pandemic stressors and targeted medication reduction efforts.

Methods

Overview

We propose a mixed methods approach including both a retrospective secondary data analysis and a national survey to describe appropriate and potentially inappropriate antiepileptic and other psychoactive drug prescribing in US nursing homes, characteristics and patient-oriented outcomes associated with this prescribing, and how these phenomena may be changing under the combined stressors of the COVID-19 pandemic and the pressure of reduction initiatives.

Secondary Data Analysis

Data Sources and Data Management

We will create a combined data set linking elements extracted from multiple CMS files that will collectively allow for a quarterly assessment of the use rate of individual AEDs and other psychotropic medications in US long-stay facilities over a 12-year study period as well as the nursing home, ED, and hospital adverse outcomes associated with their use while controlling for important demographic, health, regional, and facility variables. This period will encompass the 3 years before and 9 years after the National Partnership's 2012 debut, as well as the 10 years leading up to and the first 2 years of the COVID-19 pandemic. Thus, trends in prescribing and outcomes associated with prescribing will be assessed with an emphasis on evaluation for change surrounding 2 primary inflection points: the March 2012 debut of the National Partnership and the January 2020 commencement of the COVID-19 pandemic [35-44].

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This study includes data elements extracted from 5 sources: the CMS MDS, the Medicare Part D Drug Event File, the Medicare Provider Analysis and Review (MedPAR), and 2 CMS public files. The CMS *Long-Term CareMDS 3.0* is a systematic assessment of the health of nursing home residents performed at admission, annually, and—for a subset of items—quarterly or when the resident has a change in health status [6,35,38,45]. The MDS will be used to define the study cohorts by identifying all US long-stay residents during the period of January 2009 to December 2021 and contains patient identifiers and demographic and regional variables, as well as a wealth of quarterly data on medication use (not including AEDs); chronic health conditions; and updated cognitive, psycho-behavioral, functional, and prognostic outcome data.

The *Medicare Part D Drug Event File* provides prescription fill information, including drug name, National Drug Codes, date of dispensing, days' supply, and dosage for all beneficiary medications paid for under the Medicare Part D Prescription Drug Program. AED prescription fill information for 2009 to 2021 will be extracted [39,46].

The *Provider Information Public File* available at data.cms.gov [47] provides quarterly quality data for all long-stay facilities, including the quality metrics that inform the CMS's 5-star facility rating and that are available for public review [11]. These data can be accessed at the Nursing Home Compare data archive beginning from July 2013 [36]. Variables to be extracted include facility variables such as ownership type and size, various facility ratings, and staffing details.

For facility COVID-19–related data, we will use the CMS's *COVID-19 Public File* [42]. This file, sourced from the Centers for Disease Control and Prevention National Healthcare Safety Network system Long-term Care Facility COVID-19 Module, includes weekly data elements (first reported on May 17, 2020, but entered retroactively up to January 1, 2020) describing facility COVID-19 status, facility capacity, and staffing or personal protective equipment adequacy.

Finally, for hospital and ED data, we will incorporate individual-level results from the *MedPAR* and *Outpatient Research Identifiable File* (RIF). The MedPAR file was specifically created by the CMS for the study of inpatient hospital care and contains claims for all Medicare Part A inpatient stays [40]. MedPAR Medicare Advantage claims are incomplete (with no data available from 2009 to 2014), and consequently, only patients insured with Medicare Fee-For-Service will be included in all portions of the analysis. However, we will request Medicare Advantage inpatient and outpatient data for the years that are available (2015-2021), and we will incorporate these findings into the analysis where possible. The Outpatient file includes Fee-For-Service claims associated with outpatient hospital care. This includes all claims submitted by institutional outpatient providers, including outpatient hospital care. Using MedPAR and Outpatient RIFs, we will identify ED visits, hospitalizations, hospitalization diagnoses (including COVID-19), length of stay, and hospitalization costs. Beneficiary identifiers (namely BENE_ID) extracted from the MDS will be used as crosswalks to link MDS, MedPAR, Outpatient, and Medicare Part D files at an individual level. The MDS–Part D link has been negotiated successfully by multiple other investigators with matching errors of 4% to <1% [48,49]. The MDS-MedPAR link is more challenging as it requires both a BENE_ID file match and a temporal match where MDS Part A transition dates are linked with MedPAR data for that same period. For this link, a match rate approaching 90% is expected [50,51]. Identifying ED visit claims is more straightforward as no MDS transition is involved and is accomplished simply by searching for a MedPAR or Outpatient ED charge amount of >0 for that quarter. National Provider Identifiers will serve as crosswalks between individual-level data from the MDS, Part D, MedPAR, and Outpatient files and the facility-level data from the 2 facility files. Data will be compiled in the CMS's Virtual Research Data Center (VRDC) and accessed via a Data Use Agreement (DUA) with the CMS [41]. The CMS's VRDC is a virtual research environment that allows access to CMS data in a more secure, timely, and affordable manner [41]. All person-level health information will remain in the virtual data center for analysis, a virtual workspace that meets all CMS safety and security requirements. Only deidentified data downloads are eligible.

Final Cohort Construction

Long-stay residents with >100-day stays at a nursing home facility will be identified from the CMS MDS (2.0 for 2009-2010 and 3.0 for 2010-2021). The timing and location of stay will be confirmed based on a previously validated residential history file algorithm [43]. Cohorts will be limited to residents with continuous Fee-For-Service or Medicare Advantage plans as well as continuous Part D coverage over that quarter and those who are aged >21 years [44]. Research Data Assistance Center enrollment files will allow us to determine beneficiaries' continuous enrollment. Nursing home residents who are discharged before the end of the quarterly study period will be excluded starting from the quarter in which discharge occurred. Residents with discharges for acute hospitalizations followed by facility re-entry on the same record will not be excluded. A total of 48 quarterly cohorts comprising all nursing home residents will be identified for the 12-year period of January 2009 to December 2021. Quarterly analysis is ideal as this is how MDS data are collected and organized.

Data Linkage and Data Collection

Once cohorts are created, the following information will be extracted from the MDS: resident and facility identifiers, demographic data, regional data (using facility identifier and geolocation), and resident-specific health variables that are mandatorily reported by nursing home facilities to the MDS. Beneficiary identifiers will be used as crosswalks to query Part D claims for at least one fill of an AED prescription in that quarter, and medication use will be assessed and organized at a quarterly level [46]. Claim date and days of supply will allow drug use to be attributed to all appropriate quarters (for example, a 2-week fill in a quarter's last week will count for both quarters). AEDs will be identified by name (generic and brand) as well as by National Drug Codes (9, 10, and 11) from Part D claims and further mapped to the appropriate drug using drug databases such as Multum. Lithium and dextromethorphan or quinidine (Nuedexta) use will also be evaluated as they affect

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mood. All other psychotropic medications, including antipsychotics, anxiolytics, antidepressants, and sedative-hypnotics, will be similarly queried from Part D and at a class level from the MDS and reported as MDS, Part D, and MDS–Part D. Comparing data from different classes and sources will serve a function in quality control. Similarly, as some AEDs are prescribed for pain, opiates will be analogously assessed.

To add expanded facility data to our growing cohort, we will incorporate data from 2 publicly available long-stay facility files. The first is CMS's Provider Information file that collates all the quarterly facility quality data that inform the CMS's 5-star facility ratings [52]. Variables to be extracted include ownership type (for profit and not for profit), facility size, star rating, and staffing rating, as well as aide, licensed professional nurse, registered nurse, and therapist staffing hours. All staffing hours will be adjusted per resident day and also resident case-mix index. For COVID-19–related facility data, we will use the COVID-19 Public File [42]. This public file comprises data reported by nursing homes to the Centers for Disease Control and Prevention National Healthcare Safety Network system Long-term Care Facility COVID-19 Module. This data set includes weekly data elements (first reported on May 17, 2020, but entered retroactively up to January 1, 2020) describing facility COVID-19 status and facility capacity as well as staffing, supplies, and personal protective equipment adequacy. Monthly and weekly data from the Provider Information and COVID-19 Public Files will be summed or averaged to correspond with quarterly cohort data. Where weeks or months do not match quarters, data will be proportionately divided.

Finally, for hospital and ED outcomes, we will incorporate data at an individual level from MedPAR and Outpatient RIFs. Hospitalization dates reported in section A of the MDS will be linked with inpatient data extracted from MedPAR for that same period. Hospital data to be extracted from MedPAR include hospital admission and discharge date, principal diagnosis codes, death, and hospital costs. In addition, admission diagnoses can be used to identify both "potentially avoidable" and "medication-related" hospitalizations using previously validated algorithms. Both protocols were developed by expert panels and include detailed International Classification of Diseases, 9th and 10th Revision, codes [53-57]. Thus, "potentially avoidable" hospitalizations, "medication-related" hospitalizations, and hospitalizations overall can be compared between cohorts treated or not treated with a psychotropic and across medication types. ED data to be extracted from MedPAR and Outpatient files include ED charge amount and ED-related revenue center codes to determine the ED visit rate between the aforementioned cohorts.

Survey Assessment

Overview

The *Psychotropic Prescribing in Nursing Homes* (PPIN) survey goals are to confirm and validate the findings of aims 1 and 2 while adding context, detail, meaning, and clarity to their results. We will survey a purposive national sample of nursing home psychotropic prescribers regarding their use of all psychotropics with an emphasis on the impact of reduction efforts and the pandemic on their current and historic prescribing practices. This will be accomplished by (1) drawing on an existing multidisciplinary team experienced in national clinician surveys and mixed methods analyses of long-stay issues, (2) using existing pilot study data to inform initial survey development, and (3) using the theory of planned behavior to guide design and analysis [58-61].

Conceptual Framework

Construction and analysis of the PPIN survey is based on the theory of planned behavior by Azjen [60]. The theory of planned behavior outlines the relationship among beliefs, attitudes, norms, and human behavior; is a well-supported model for examining human behavior; and has been effectively applied specifically to surveys on health care–related decisions [60-63].

Survey Content

Due to the unprecedented turbulence in long-term care, survey construction will follow an adaptive sequential exploratory design process. Accordingly, the PPIN survey will include 6 survey cycles over a 36-month period to allow for flexibility in exploring relevant themes and issues perhaps currently unforeseen. While the initial survey will be grounded in existing literature and our own pilot data, each iterative version will be informed by retrospective and emergent data, including early data generated by aims 1 and 2 [15,31]. Early survey results may also provide direction to the ongoing investigations of aims 1 and 2. Given the ongoing and unprecedented period of dynamic stress in long-term care related to the COVID-19 pandemic, assuming transformation over the survey period is both reasonable and potentially clinically meaningful. For the same reason, it would not be appropriate to develop all survey instruments before the start of the study—the ideal survey today will likely be obsolete by the time of fielding. The PPIN surveys will include 4 key components: "Core" questions, "Flash" questions, demographic questions, and open-ended comments. Core questions will consistently assess issues surrounding the decision to prescribe or not prescribe psychotropic medications, including AEDs, in nursing homes, with a focus on prescribing for dementia symptoms. We will specifically explore the impact of reduction measures and the COVID-19 pandemic on management approaches and outcomes. This will include questions detailing factors that encourage or discourage the use of medications and encourage or discourage the use of nonpharmacologic therapy (NPT) for psychiatric symptoms. "Flash" questions are so named for the way in which they mimic flash mobs—sudden, impactful, meaningful, and then gone. The flash questions will allow the research team to be adaptive and iterative through the survey process, providing the opportunity to explore new or unanticipated issues, including data deficiency. Every cycle will allow participants at least one opportunity for comments with open-ended questions, at times expanding to longer open opportunities. These responses will inform future flash questions. While flash questions will vary each cycle, thematic consistency still allows for longitudinal qualitative analysis. Finally, all surveys will include demographic questions about the prescriber and prescriber location to allow for subanalyses of findings.

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Survey Development and Sampling Frame

This survey will be designed to minimize respondent burden, asking only the most relevant pieces of information each cycle, with a goal of a 4- to 5-minute response time. We will spend the first year after funding finalizing a pilot survey informed by initial quantitative findings. Initial questions and response options will be developed from our published and unpublished previous work and relevant literature [15,31]. Pilot questions will be tested using cognitive interviews, an approach that this team has used successfully in past studies [64,65]. Once the initial survey has thus been generated, we will field our first survey cycle at the 12-month mark to obtain a baseline. This means that our baseline survey will be unbiased by the preliminary results of aims 1 and 2 but would be timely in informing the ongoing evaluations of aims 1 and 2. A total of 6 biannual survey cycles will continue over a 36-month sampling frame. We anticipate preliminary data from aims 1 and 2 to become available by 18 months. Survey content will be updated each cycle based on previous surveys and early data from aims 1 and 2. The survey advisory committee—a multidisciplinary subgroup of the research team primarily dedicated to the successful completion of aim 3—will vet questions for each cycle, iterating proposed response options and scales and modifying survey focus. The goal will be to improve clarity with each cycle while allowing for the potential to explore unexpected new avenues or add granular detail to an area deserving further clarification. The committee, survey respondents, and survey partners will all have the opportunity to submit potential new questions. The final survey is selected by the advisory committee. This stakeholder-engaged process is based on lessons learned from previous National Institutes of Health– and Agency For Healthcare Research and Quality–funded studies conducted by our investigative team [65-70]. This iterative approach will be of value over this dynamic period in health care in which the perfect survey instrument for today could well be incomplete tomorrow.

Participant Recruitment and Survey Distribution

Participants will be licensed nursing home clinicians who prescribe psychotropic medications, including advanced practice clinicians and physicians. Our goal is a sample of >500 participants per cycle, purposefully selected to reflect what is known about the national long-stay psychotropic prescriber population. Given that the intent of this investigation is not to create knowledge or test hypotheses but rather to confirm and validate the findings of aims 1 and 2 while outlining the forces and influences driving them, an exact representative sample is not required; a purposive sample will be sufficient to accomplish our aims [71]. By *purposive*, we mean a sample that is deliberately recruited to reflect the little that is known about the regional, demographic, and professional characteristics of the national long-stay prescribing population. We will accomplish this by collaborating with partner professional organizations whose membership are known to prescribe psychotropics in nursing homes in a direct emailing campaign [44,72,73]. Data will be collected using SurveyMonkey. Partnering organizations will receive "partner emails" that include priority requests from our research team (eg, a need to increase participation among minority groups and rural areas) and easy-to-use social media information to enable quick sharing of the survey link via organization-driven social media. These organizations may choose to share the SurveyMonkey survey link with their membership via email or advertise the SurveyMonkey survey link to membership on their social media platforms. Alphanumeric codes embedded in the survey link will allow our team to track a longitudinal cohort while maintaining the anonymity of participants at the point of data collection.

Survey Responses

Our understanding of exactly who prescribes psychotropics in US nursing homes is imperfect [25,73-76]. We estimate the total number to exceed 100,000 clinicians, with most being internists, family physicians, and nurse practitioners and a minority being psychiatrists, neurologists, and physician assistants. On the basis of our recent and ongoing experience collaborating with professional organizations on electronic clinician surveys, we anticipate an initial survey distribution to 10,000 clinicians. Our historical survey response rate from clinicians when recruiting in partnership with professional organizations has been approximately 5% [65,68,69]. Thus, we anticipate a sample of >500 participants for each cycle. We accomplished our published response rates by "advertising" our survey with links on social media, including postings by partner organizations on partner organization websites and the use of the modified Dillman method [77]. We are successfully using near-identical methodology for surveying clinicians in an ongoing Agency For Healthcare Research and Quality R01–funded investigation, and lessons learned will inform this investigation [65-67,78] However, while 2 years of data collection and 35,000 web-based surveys received engenders confidence in this methodology, we acknowledge a unique practice environment during the pandemic where it may be prudent to anticipate response rates lower than in the past, so we have budgeted for the possibility of purchasing email information for long-term care prescribers from commercial vendors. These data will be purposefully selected based on regional, demographic, and educational clinician characteristics. We have a proven track record with this approach, and while it is more labor intensive and expensive, we have reached response rates approaching 30% and are comfortable with methodology including protocols to protect participant anonymity [79].

Outcomes

Aim 1

The primary outcome of aim 1 will be quarterly use rates of each AED and other psychotropics in the general study population for the entirety of our study period. A secondary outcome will be quarterly use rates of individual AEDs among specific subsets of long-stay residents. AED prescribing within these subsets can then be compared. Subsets of long-stay residents will be those with and without dementia, seizure epilepsy, psychiatric illness, and neuropathic pain. A final subset will be those with and without an appropriate diagnosis to support the specific AED prescribed. As Medicare Part D does not link prescriptions to their indication, we will approximate the appropriateness of prescribing by identifying the presence or absence of FDA-approved diagnoses in the MDS data of the recipient to support the specific AED used. If an approved

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diagnosis for a given AED exists, that prescription will be approximated as appropriate. However, if no approved diagnosis exists, that prescription will be approximated as inappropriate. For all analyses, the rate numerator will be the number of individuals within a cohort filling at least one psychotropic prescription during that quarter. The rate denominator will be the quarterly cohort, or subcohort, of all long-stay residents meeting the inclusion criteria.

Aim 2

The primary outcome of aim 2 will be the quarterly rate of adverse health events among long-stay residents prescribed or not prescribed individual AEDs and other psychotropics. Adverse health events to be evaluated include several adverse nursing home outcomes as well as ED and hospital outcomes. Rate numerators will be the relevant nursing home outcome reported for that quarter or the presence of an ED or hospital event at any time during that quarter. Rate denominators will be the quarterly cohort of long-stay residents receiving the pertinent AED or other psychotropic at any time during that quarter versus those not receiving it. In the analyses for both aims, we will control for demographic and regional variables and functional, health, and disease markers, as well as facility data, including ownership, performance scores, staffing, and COVID-19–related information.

Aim 3

The primary outcomes of aim 3 will be diverse. First, they will serve to affirm and validate the results of aims 1 and 2 while informing the extractions and analyses of the secondary data assessment. In addition, survey results should clarify which drugs are used or not used for dementia symptoms and why. They should outline impacts of policy efforts on prescribing and prescribing outcomes and present the impact of the COVID-19 pandemic on prescribing and prescribing outcomes. Results will also contrast management by prescriber, facility, and regional variables. Finally, they should delineate barriers to the use of nondrug therapies for dementia symptoms.

Statistical Analysis

Subaim 1a

The 2021 prevalence of individual AEDs and other individual psychotropic medications in US nursing homes will be estimated and compared by geographic regions using a mixed-effects logistic regression model with a 4-level fixed-effects quarterly time indicator and both patient-level and nursing home–level random effects to account for within-subject dependence and the nesting of patients within nursing homes. Differences in the trends of AED prevalence over the 12-year period from 2009 to 2021 will be investigated using a patient-level interrupted time-series analysis [80]. AED and other psychotropic medication prevalence will be modeled individually as binary outcomes (prescribed in a particular quarter or not) against a continuous time trend (both linear and quadratic), indicators for (1) pre– and post–National Partnership and (2) pre– and post–COVID-19 period, and an interaction between time trend and period (significant indicator or interaction effects are indicative of differential trends between periods) [80]. A model will be used to identify temporal changes: one occurring before or after March 2012, reflecting potential reactions to the National Partnership guidance change, and the second occurring before or after January 2020, reflecting potential changes due to COVID-19. This model will also account for within-patient repeated measures through an auto-regressive correlation structure as residents are continuously enrolled and prescriptions are assessed evenly (quarterly) in the study databases. A facility-level random effect to account for nesting of patients within nursing homes will also be included. While we hypothesize 2 primary inflection points (the National Partnership and COVID-19), due to the potential for other impact points, we will conduct sensitivity analyses looking for secular trends in our data to identify the possibility of other policy inflection points.

Subaim 1b

To compare the 2021 prevalence of individual AEDs between subsets of nursing home residents with and without a diagnosis approximated as appropriate, we will expand on the logistic regression model described in the *Subaim 1a* section to include only the long-stay subset. The odds of AED prevalence (and their 95% CI) will be estimated in each of the 4 quarters in 2021. Trends of quarterly AED prevalence from 2009 to 2021 will be compared between subsets of nursing home residents with and without a diagnosis approximated as appropriate by extending the interrupted time-series model described for subaim 1a to include interactions between time and each of these terms modeled using a binary indicator [81].

Subaim 1c

Resident (demographic, medical, and functional) characteristics, facility elements (resources and ownership status), and regional variables will be compared between those US nursing home residents prescribed individual AEDs or other psychotropics at any point in 2021 and those who were not prescribed such drugs using linear and generalized linear mixed-effects models, including fixed effects for quarter (4 levels), AED prescription indicator (yes or no), an interaction term, and both patient-level and site-level random effects.

Subaim 2a

The association between individual AED and other psychotropic prescribing and adverse health events, including nursing home outcomes, hospitalizations, and ED visits, in 2021 will be assessed using multiple linear or logistic mixed-effects models controlling for resident, facility, and regional variables. Fixed effects in these models will include binary prescription indicators, a 4-level quarter indicator, their interaction, and control variables. Patient-level and site-level random effects will be included to account for within-patient dependence and the nesting of patients within nursing homes, respectively.

Subaim 2b

Resident (demographic, medical, and functional) characteristics, facility elements (resources and ownership status), and regional variables will be compared between those US nursing home residents with adverse prescribing complications from AEDs and other psychotropics in 2021 and those who were prescribed such drugs without adverse prescribing complications using linear and generalized linear mixed-effects models, including

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fixed effects for quarter (4 levels), an adverse event indicator (yes or no), an interaction term, and both patient-level and site-level random effects.

Subaim 2c

Differences in the quarterly prevalence of adverse health events (including detrimental long-stay outcomes, ED visits, and hospitalizations) among nursing home residents prescribed or not prescribed AEDs or other psychotropics over the 12-year period of 2009 to 2021 will be determined using interrupted time-series models (similar to those described for subaims 1a and 1b), with the binary adverse health event measure included as the longitudinal outcome modeled against a binary AED prescription indicator, continuous time trends, and their interaction; within-resident dependence will again be modeled using a first-order auto-regressive structure, and a site-level random effect will be included to account for patient nesting within nursing homes.

Aim 3

Quantitative and qualitative analyses are first conducted separately and then combined. Structured data will be described using summary statistics (means and SDs for numerical responses and frequencies and proportions for categorical responses). Univariate statistical tests (1- and 2-tailed *t* tests, ANOVAs, and chi-square tests) will be used to assess whether the observed changes are due to chance variation or are likely to be real. Subgroup analyses will be performed comparing outcomes by provider type; facility variables; and regional variables, including social determinants of health for that location. A dedicated division of the research team will read through open-text comments for each survey cycle to identify main content areas. This, combined with elements of the theory of planned behavior and our previous research, will be used to create an a priori codebook to guide a template-based analysis [60]. Analysis will incorporate both template-based and emergent coding techniques. We will follow a protocol-driven approach to analysis that involves 3 steps. The first step involves group reading of the data to refine a priori codes, identify emergent codes, and reach agreement on code definition. Second, independent test coding is performed to probe the operational limits of the codebook and the ability of coders to apply codes reliably and consistently. Finally, independent coding combined with scheduled merges of coded data and monthly team coding huddles allow for early detection of threats to intercoder reliability [82]. Once coded, the team identifies themes within the data. All free-response qualitative data will be managed using ATLAS.ti (ATLAS.ti Scientific Software Development GmbH) [83].

Sample Size Determination

Our study's power to detect effect differences in AED prescribing trends over time assumes 1,406,220 nursing home residents in the United States; that nearly 14% and 38% of nursing home residents are diagnosed with epilepsy or dementia, respectively; and that 4.5% of nursing home residents are prescribed mood-stabilizing AEDs [7,33,44,84]. Assuming a quarterly AED prevalence near 4.5% with 1.4 million nursing home residents will allow for a margin of error of <0.1% (subaim 1a). On the basis of these quarterly estimates over 12 years (48 total estimates), we will have 80% power to detect differences in the rates of change in AED prevalence between periods as small as 0.52%, which is similar to the decrease in rates of psychotropic or memory medications observed in the literature. Similar power and detectability can be expected for the comparative analyses in subaims 1b, 1c, 2a, 2b, and 2c. For aim 3, quantitative analyses include a comparative time study evaluating changes over the 36-month sampling window. We hypothesize that the differences observed for most clinician outcomes will fall in the large effect size category. Still, with estimated sample sizes of 1000 clinicians per period, our sample sizes are sufficiently large to detect even small effect sizes [85]. For analyses of outcomes, a planned sample size of 1000 residents in each comparison time has 90% power to detect a standardized effect size of 0.14 with a significance level of 0.05 [86]. For quantitative outcomes, an effect size of 0.14 would be considered very small as defined by the Cohen *d* statistic [85]. Samples of 500 clinicians per period would also enable the detection of a comparable small difference in outcomes between periods. While the clinician cross-sectional samples can be expected to be independent samples, they may contain some overlap, thus introducing auto-correlation. To address this, our approach to significance testing between periods will be to conduct ordinary least squares statistics (eg, *t* test and ANOVA) and then modify the SEs afterward [87]. Subgroup analyses will be based on at least a 20% sample of the total, and a sample of 200 clinicians will have 80% power to detect a standardized effect size of 0.2 at a 0.05 level of significance. Thus, even for the subgroup analyses, we will have adequate statistical power to detect small effect size differences [85].

Ethical Considerations

Only deidentified aggregate data were available to the research team, and no participant received compensation. This study has been approved by the Virginia Commonwealth University (VCU) Institutional Review Board (IRB; HM20025382) and poses minimal risk to participants. The risks include breaches of confidentiality and privacy. Due to the retrospective nature, the protocol qualified for exemption and Health Insurance Portability and Accountability Act authorization. Consequently, the VCU ethics committee on the IRB waived the need for written informed consent from all participants or their legal guardians. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Overview

Funding for this 60-month project was obtained in September 2022. The project mobilized with a pre–data extraction phase. The entire research team assembled for at least monthly meetings to evaluate goals and prepare for future project activities. The first critical task was to acquire IRB exemption approval. IRB approval was obtained in January 2023 (IRB HM20025382). In parallel to the IRB application, we developed our DUA with the CMS. Our proposal was submitted in May 2023. This went through 2 rounds of comments as well as an

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internal institutional review. The DUA (RSCH-2024-70173) was signed in March 2024.

Secondary Data Analysis

In our DUA, we applied for regular researcher access to the Chronic Conditions Warehouse in the VRDC [41]. Access was obtained in July 2024. The VRDC facilitates more rapid and convenient access to our data sets of interest within a CMS-approved secure virtual workspace, which eliminates many of the logistical challenges of ensuring the safety and security of resident personal health information [36,41,88]. There are many sequential steps to preparing a DUA and obtaining VRDC access. The team obtained access to the VRDC 14 months after our DUA was first submitted. It took 9 months to develop our DUA, a process that included obtaining IRB approval.

We purchased 2 years' worth of access to the VRDC using an Interagency Agreement Number assigned in October 2023. This 2-year period began in July 2024 at the start of year 3 of the investigation. The critical milestone for the first half of year 3 will be building our quarterly sample cohorts in the secure VRDC environment using patient-level data from the MDS [89]. The next critical milestone will be linking these MDS cohorts with pharmacy claims data from the Part D Drug Event File as well as ED and hospital data from MedPAR and Outpatient files [39,46]. Facility-level facility data, including COVID-19 statistics from CMS public files, will enrich the cohorts further [42,72]. Beneficiary identifiers will be used for patient-level data crosswalks. Constructing our multisource cohorts within the VRDC will be an intensive 12-month process. We anticipate that cohorts will be created and the linkage with Part D data will be completed by December 2024, the halfway point of year 3. The full data set will take an additional 6 months to complete.

Our cohorts will include all available data. MDS data are easily accessible beginning from 2011. Files are continually updated but may lag real time by as much as 12 months [38,39]. Notwithstanding, in 2024, we should have access to data up to 2023. Evaluating data for completeness and accuracy will be an ongoing task while we have VRDC access in years 3 and 4. Queries will be revised and resubmitted if necessary with technical support from Research Data Assistance Center personnel. Early analysis of team research questions will occur within the secure virtual environment of the VRDC beginning in the second quarter of year 3. Deidentified data extracted from the VRDC and eligible for formal analysis are anticipated to be available to the full team by the third quarter of year 3. These extractions will continue until our VRDC access expires at the end of year 4. The final 18 months of the investigation will focus on analysis of data and dissemination.

Survey Assessment

Parallel to our CMS data request, we initiated the qualitative portion of our evaluation: the development, validation, distribution, and analysis of a series of questionnaires surveying the perspectives of long-term care facility psychotropic prescribers. The intent of this survey series will be to confirm and validate our quantitative findings while outlining the forces driving these outcomes, with an emphasis on policies and the impact of the ongoing COVID-19 pandemic. Our protocol calls for us to debut a new and iterative survey every 6 months for a 36-month sampling window (running from years 2 to 4) as part of a sequential exploratory design. Iterative survey content will be informed by early results of our CMS data request. Conversely, our data request may be modified by early survey results and feedback from early dissemination.

The first 12 months of the investigation were spent developing and validating the initial survey instrument. The first survey was fielded in October 2023; the second survey was fielded in March 2024. We anticipate that the third survey will debut in September 2024. Survey cycles will continue roughly every 6 months for a total of 6 cycles to be completed at the end of year 4. The first survey focused on indications for gabapentin prescribing and clinician beliefs and perspectives regarding gabapentin increases. The second survey emphasized the relative frequency of identified indications and the role of gabapentin deprescribing. The third survey will concentrate on issues related to long-stay valproate use; the fourth survey will focus on lamotrigine and carbamazepine derivatives. Early mixed methods analysis began immediately after the first survey cycle. These will continue throughout the survey window. Our timeline's overlapping data collection, analysis, and dissemination or feedback seeking reflects the iterative nature of our methods. Analysis and the first stages of dissemination began well before the project's midpoint. Formal survey analyses were initiated as soon as the first survey results became available in year 2. Analysis will be ongoing until the end of the 5-year study. Multimodal and multidisciplinary dissemination and knowledge translation was introduced in year 2 as well and, similarly, will also continue throughout the study period. The results of our first survey were published in July 2024 [90]. We anticipate publication of findings of the second survey before the end of the year 2024.

Discussion

Expected Findings

While federally mandated reporting of antipsychotics, anxiolytics, antidepressants, and sedative-hypnotics to the MDS has helped clarify the use of most psychoactive medications in nursing homes, a clinically meaningful knowledge gap still exists regarding the long-stay use of unmonitored mood-stabilizing AEDs [91]. Over the last 10 years, our team has looked extensively at issues related to the treatment of BPSD in Virginia nursing homes through projects funded both by our home institution (VCU) and the Virginia Center on Aging [13-15,31-34,92]. In Virginia, nursing home providers have increased their prescribing of mood-stabilizing AEDs as they have decreased their use of antipsychotics, benzodiazepines, and other monitored psychotropics. Long-stay antiepileptic prescribing is increasing even though long-stay reporting of the diagnosis of seizure epilepsy is decreasing [13-15,31-33,93]. Similar to what has been described in European nursing homes, the increases in mood-stabilizing AED use is concentrated in the long-stay subgroup of residents with dementia and without a diagnosis of epilepsy [26]. In fact, more mood-stabilizing

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antiepileptics are now prescribed to the subset of Virginia nursing home residents without a diagnosis of seizure epilepsy than antipsychotics are prescribed to the entire nursing home population [13].

Significant differences also exist in AED prescribing for residents with epilepsy compared with those without. Mood-stabilizing AEDs dominate prescribing for residents without an epilepsy diagnosis, whereas non–mood-stabilizing AEDs are the preferred therapy for residents with epilepsy [13,15,90]. Also relevant, since 2012, Virginia nursing home providers have increased use of the exclusionary diagnoses (primarily schizophrenia) that allow for antipsychotic prescribing without mandatory reporting to CMS quality measures via the MDS, likely inflating apparent reductions in inappropriate antipsychotic use [32,33]. We believe that this diagnostic trend represents another unintended consequence of reduction initiatives.

The variance between long-stay facilities in the top and bottom quintiles for mood stabilizer prescribing in Virginia is also significant. Facilities in the top quintile for mood stabilizer use in Virginia had significantly more male and African American residents and were more likely to be privately owned. Facilities in the bottom quintile for mood stabilizer use had vastly better scores for social determinants of health, including higher health opportunity indexes with superior health opportunity, economic opportunity, consumer opportunity, environmental, and wellness disparity rankings [34]. Similarly to all risky medications, prescribing of mood-stabilizing AEDs is more common in vulnerable populations. In Virginia, both antipsychotic and antiepileptic mood stabilizer prescribing is more common in male African American individuals [13,34]. Parallel qualitative assessment from our mixed methods pilots added supporting context as long-stay prescribers were frank that sensitivity to CMS reporting and treatment guidelines emphasizing antipsychotic deprescribing influenced both documentation and management choices [15,31,92].

We are only just beginning to see all the impacts of the COVID-19 pandemic play out in measurable nursing home outcomes. We already know that adverse health events such as potentially avoidable hospitalizations are associated with breakdowns in communication and care processes as well as with shortages in staffing and resources [53]. We know that facilities have struggled to provide adequate staffing during the pandemic for many reasons. Anecdotally, resident loneliness and negative mood symptoms spiked dramatically as the pandemic stressed facilities already underpowered to manage BPSD using NPT. In Virginia, we have seen significant deterioration in MDS measures for functional independence; an increased need for activities of daily living support; worsening of detrimental behavioral symptoms; declining mood scores; and escalated prescribing of all psychoactive classes, predominantly an acceleration of the trend toward unmonitored AEDs [93].

This proposal addresses specific and clinically meaningful evidence gaps directly relevant to clinical guidelines and policies and deeply consequential to all stakeholders in dementia care, including residents, providers, specialty groups, payers, patient advocates, and policy makers. If pharmacological approaches to BPSD management rapidly evolved during the COVID-19 pandemic, with risky and ineffective—but unreported—medications being used more as medications mandatorily reported to the CMS are used less, then harms could be increasing with no clinical or safety benefit, jeopardizing the health and safety of all nursing home residents but of vulnerable populations most of all. In addition, we know almost nothing about outcomes or adverse health events associated with this changing approach to dementia care. Our proposed study will close this existing knowledge gap by providing a clearer picture of all long-stay pharmacological approaches to noncognitive dementia symptoms, the health outcomes associated with these varying approaches, and how such management and consequent outcomes are changing under the pressure of pandemic stressors and targeted medication reduction efforts.

Strengths and Limitations

This study is not without limitations. While the comprehensiveness of our sample, which includes Medicare or Medicaid residents from all US states, is an asset, our sample is limited to include only those with continuous Fee-For-Service, Medicare Advantage, and Part D coverage. This means that residents with a Part D alternative or without a drug plan will be excluded. However, the coverage of nursing home residents is more stable than that of noninstitutionalized populations, and we know that our study will include the vast majority of long-stay residents [94]. We also view our long 12-year study period as a strength and, given our complex models, we are minimizing the potential for overfitting by using the maximal number of time points available from the MDS (48). While our study will assess for the presence of FDA-approved indications for specific drugs, a step toward approximating the appropriateness of medication use, we acknowledge that FDA-approved indications comprise only a fraction of reasonable prescribing. Unfortunately, we do not believe that guidelines are congruent enough that we could easily add guideline-driven indications to this investigation. This study will identify and describe meaningful trends in long-stay prescribing and outcomes. Still, we acknowledge that many potential confounders exist that impact management approaches, and definitive explanations of the root cause of these trends will need to be addressed in future evaluations. We will perform sensitivity analyses to evaluate secular trends in our data. In addition, our proposed survey will add nuance and context that can help explain the trends that we discover. Coping with data inconsistencies when linking data sets is always a challenge. However, we are comfortable with methods that have resulted in matching errors of <1% to 4% [48,49]. Finally, although the effort and resources required for a representative national survey would be excessive to realize aim 3, we can still accomplish a purposive sample that can approximate what is known about the long-stay prescriber population and is sufficient to provide a meaningful understanding of the forces behind prescribing decisions [95,96].

Conclusions, Dissemination, and Future Directions

Drugs with unproven efficacy and concerning risk profiles continue to be overused for BPSD, although purposeful

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reduction efforts are curbing antipsychotic and anxiolytic prescribing. However, pilot data suggest that, while use of these targeted drugs is decreasing, off-label prescribing of antiepileptics is increasing. Unlike antipsychotics, anxiolytics, and other psychotropic medications used for BPSD, antiepileptic use in nursing homes is not mandatorily reported to the CMS via the MDS, and even basic national prevalence data about their long-stay use are lacking. Moreover, nothing is known about potentially adverse health outcomes related to these prescribing changes. If pharmacological approaches to BPSD management are evolving, with medications not reported to the CMS being used more and medications reported to the CMS being used less—all with completely unknown patient-oriented outcomes—this has an impact on clinical guidelines and policies and direct relevance to all stakeholders in dementia care, including residents, providers, specialty groups, payers, patient advocates, and policy makers. This study will detail the use of all psychotropics and the outcomes associated with their use and evaluate changes and trends in prescribing and in outcomes with an emphasis on the impact of policies and the COVID-19 pandemic.

We view a complete detailing of all pharmacological approaches to BPSD as a critical first step to optimizing dementia care in nursing homes. Describing the patient-oriented outcomes associated with all such prescribing is an equally important step 2. Closing these knowledge gaps and providing all stakeholders with a clearer perspective is crucial to informing ongoing policies, guidelines, and improvement measures. Reaching multiple stakeholder groups will be facilitated by our multidisciplinary team as dissemination will in turn also be multidisciplinary, with geriatric nurses, nurse practitioners, anthropologists, epidemiologists, primary care and long-term care physicians, pharmacists, public health, and social workers all represented. The dissemination process will involve sharing our data with all our diverse partner organizations. Our team has detailed experience with the traditional formats of dissemination, including social media, blogs, commentaries, and peer-reviewed publications and conference presentations. We view this project as an essential stepping stone in an ongoing line of inquiry. Our overarching goal is to improve dementia care by ensuring that, if drugs are needed, the right medications are used at the right dose, at the right time, and as a last resort. Related to that, identifying and deconstructing barriers to NPT for BPSD as well as providing clinicians and families with more precise, helpful, and evidence-based BPSD decision tools are ongoing team goals.

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Data Availability

Data sharing is not applicable to this article as no data have been collected and the data set has not yet been generated or analyzed. Once data becomes available, the data sets generated during and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

JDW contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, draft writing, and review and editing. JWK contributed to conceptualization, data curation, funding acquisition, investigation, methodology, validation, draft writing, and review and editing. NB contributed to investigation, methodology, supervision, validation, and review and editing. LW contributed to investigation, methodology, supervision, validation, and review and editing. DQ contributed to investigation, methodology, supervision, validation, and review and editing. RTS contributed to investigation, methodology, software, supervision, validation, and review and editing. SP contributed to software, methodology, data curation, and review and editing. YKC contributed to software, methodology, data curation, and review and editing. SR contributed to conceptualization, investigation, draft writing, and review and editing. CW contributed to conceptualization, investigation, draft writing, data curation, and review and editing. KMW contributed to conceptualization, investigation, methodology, validation, draft writing, and review and editing. AK contributed to conceptualization, funding acquisition, investigation, methodology, validation, draft writing, and review and editing. RE contributed to conceptualization, funding acquisition, investigation, methodology, validation, draft writing, and review and editing. EE contributed to data curation, investigation, and review and editing. YHF contributed to data curation, investigation, and review and editing. CE contributed to review and editing. AF contributed to data curation, investigation, methodology, software, and validation. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADRD: Alzheimer disease–related dementias
AED: antiepileptic drug
BPSD: behavioral and psychological symptoms of dementia
CMS: Centers for Medicare and Medicaid Services
DUA: Data Use Agreement
ED: emergency department
FDA: Food and Drug Administration
IRB: Institutional Review Board
MDS: Minimum Data Set
MedPAR: Medicare Provider Analysis and Review
NH: nursing home
NPT: nonpharmacologic therapy
PPIN: Psychotropic Prescribing in Nursing Homes
RIF: Research Identifiable File
VCU: Virginia Commonwealth University
VRDC: Virtual Research Data Center

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Protocol

Neural Conversational Agent for Weight Loss Counseling: Protocol for an Implementation and Feasibility Study

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Abstract

Background: Obesity is a common, serious and costly chronic disease. Current clinical practice guidelines recommend that providers augment the longitudinal care of people living with obesity with consistent support for the development of self-efficacy and motivation to modify their lifestyle behaviors. Lifestyle behavior change aligns with the goals of motivational interviewing (MI), a client-centered yet directive counseling modality. However, training health care providers to be proficient in MI is expensive and time-consuming, resulting in a lack of trained counselors and limiting the widespread adoption of MI in clinical practice. Artificial intelligence (AI) counselors accessible via the internet can help circumvent these barriers.

Objective: The primary objective is to explore the feasibility of conducting unscripted MI-consistent counseling using Neural Agent for Obesity Motivational Interviewing (NAOMI), a large language model (LLM)–based web app for weight loss counseling. The secondary objectives are to test the acceptability and usability of NAOMI's counseling and examine its ability to shift motivational precursors in a sample of patients with overweight and obesity recruited from primary care clinics.

Methods: NAOMI will be developed based on recent advances in deep learning in four stages. In stages 1 and 2, NAOMI will be implemented using an open-source foundation LLM and (1) few-shot learning based on a prompt with task-specific instructions and (2) domain adaptation strategy based on fine-tuning LLM using a large corpus of general psychotherapy and MI treatment transcripts. In stages 3 and 4, we will refine the best of these 2 approaches. Each NAOMI version will be evaluated using a mixed methods approach in which 10 adults (18-65 years) meeting the criteria for overweight or obesity ($25.0 \geq BMI \leq 39.9$) interact with NAOMI and provide feedback. NAOMI's fidelity to the MI framework will be assessed using the Motivational Interviewing Treatment Integrity scale. Participants' general perceptions of AI conversational agents and NAOMI specifically will be assessed via Pre- and Post-Interaction Questionnaires. Motivational precursors, such as participants' confidence, importance, and readiness for changing lifestyle behaviors (eg, diet and activity), will be measured before and after the interaction, and 1 week later. A qualitative analysis of changes in the measures of perceptions of AI agents and counselors and motivational precursors will be performed. Participants will rate NAOMI's usability and empathic skills post interaction via questionnaire-based assessments along with providing feedback about their experience with NAOMI via a qualitative interview.

Results: NAOMI (version 1.0) has been developed. Participant recruitment will commence in September 2024. Data collection activities are expected to conclude in May 2025.

Conclusions: If proven effective, LLM-based counseling agents can become a cost-effective approach for addressing the obesity epidemic at a public health level. They can also have a broad, transformative impact on the delivery of MI and other psychotherapeutic treatment modalities extending their reach and broadening access.

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KEYWORDS

conversational agents; artificial intelligence; behavior change; weight loss; obesity; motivational interviewing; web-based application; deep learning; transformers; large language models; feasibility study

Introduction

Background

Obesity, defined as having a BMI exceeding 30 kg/m^2 is a complex chronic disease, in which abnormal or excess adiposity (ie, body fat) impairs health [1]. It is a common, serious, and costly disease. A recent nationally representative survey [2] found that nearly 1 in 3 (30.7%) US adults are overweight (have a BMI in the range of 25-29.9 kg/m^2), more than 2 in 5 (42.4%) are obese, and about 1 in 11 (9.2%) have severe obesity (BMI exceeding 39.9 kg/m^2). Obesity is strongly correlated with increased morbidity and mortality [3], reduced lifespan [1], and an increased risk of metabolic, cardiovascular, musculoskeletal, and psychiatric diseases and conditions [4]. Individuals with obesity incur significantly higher medical costs than individuals without obesity, both overall and for most major categories of health expenditures [5]. The annual cost of adult obesity in the US including direct costs of treating obesity-related diseases and conditions, lost wages, short-/long-term disability, and lost productivity is estimated to exceed US $200 billion [6]. Additionally, people with obesity experience pervasive weight bias and stigma, which further contribute to increased morbidity and mortality [7]. Despite significant attention and funding [8-10], obesity rates in both adults and youth in the United States and worldwide continue to increase [11-13], which poses a significant public health problem.

The most common cause of obesity is a chronic caloric imbalance [14] attributed to lifestyle factors, such as diet and physical activity [15]. Depending on severity, the treatment options for obesity range from psychological interventions and lifestyle modification to pharmacotherapy and surgery. Current clinical practice guidelines [1] suggest incorporating multicomponent psychological interventions combining behavior modification (goal setting, self-monitoring, and problem-solving), cognitive reframing, and value-based strategies to alter diet and activity levels into all obesity treatment plans. Moreover, health care providers are advised to augment longitudinal care of people living with obesity with consistent messaging to support the development of self-efficacy (confidence in one's abilities to enact behavior changes) and intrinsic motivation (desire to engage in behavior changes for reasons of personal interest or satisfaction) for lifestyle modifications supporting weight loss. Such messaging aligns with motivational interviewing (MI) [16,17], a client-centered, yet directive counseling modality aiming to enhance self-efficacy and intrinsic motivation toward behavior change [18,19]. Originally developed to address addiction [20], alcohol [21-23], and substance abuse [24,25], MI has a growing evidence base for health behavior change [26], including smoking cessation [27], HIV medication adherence [28], as well as the treatment of depression, anxiety, and other mental health conditions [29-35].

The widespread adoption of MI into primary care faces 2 major barriers. First, training health care providers to be proficient in MI is expensive and time-consuming [36] and the typical training approaches have a modest, diminishing effect on MI fidelity [37,38]. This often results in modest outcomes (anthropometric changes in the case of obesity [39]). Second, there is a shortage of qualified mental and behavioral health counselors [40]. Artificial intelligence (AI) counselors that are accessible via the internet to deliver MI-based weight loss counseling can help mitigate these barriers as well as extend the reach and broaden access to weight loss counseling beyond primary care. Accessible 24/7 in any location, these counselors can provide in-the-moment support during times of high need (eg, social situations). They can complement human counselors in the health care delivery continuum by delivering weight loss interventions to patients with mild- and early-stage obesity, supporting in-person counseling between visits, and via preventive interventions to patients at risk for developing obesity. This approach has the potential to conserve costly therapeutic resources for those with more severe obesity and less responsive to treatment. Another option is to leverage AI counselors as part of a hybrid strategy to boost motivation before initiating more intensive in-person weight loss interventions.

Although automated counselors in the form of embodied agents [41-45], health coaches [46,47], and patient advisors [48,49] featuring animated human-like characters with emulated speech, gaze, posture, and gestures are visually appealing, their ability to engage the patients in a natural dialog is severely limited due to their reliance on scripted interactions, in which patients must choose from a set of actions (eg, responses, requests, and questions) predefined for each situation anticipated during an intervention. The responses of these counselors are also either completely predefined or templatized, which further constrains patient interaction and limits the scope and effectiveness of behavioral and mental health interventions involving free-form communication [50], such as MI counseling [16,51].

Recent advances in deep learning [52], including the emergence of the Transformer architecture [53] and large language models (LLMs) [54], which excel at question answering, text generation, and summarization, have enabled AI-based conversational agents to engage in nontemplatized, unscripted, human-like dialogue. These advances have paved the way for testing the feasibility of using deep learning–based conversational AI agents to deliver free-form (ie, unscripted) MI-style weight loss counseling. However, no studies of fully automated deep learning–based generative AI counselors have been reported in the literature.

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Goals of This Study

The main objectives of this study are 2-fold. The primary objective is to explore the feasibility of conducting unscripted weight loss MI with a fully automated LLM-based AI counselor by developing Neural Agent for Obesity Motivational Interviewing (NAOMI), a Web app for MI-style weight loss counseling. The secondary objectives are to test the acceptability and usability of NAOMI's counseling and examine its ability to shift motivational precursors in a sample of overweight and obese patients recruited from primary health clinics.

Because this is a feasibility study involving a single interaction with NAOMI, it is not expected that participants will experience anthropometric changes. Participants will be advised to continue their current weight loss interventions (if any) and those who wish to engage in a weight loss intervention will be encouraged to contact their primary care provider for a referral to a weight loss treatment.

Prior Work

Overview

This study builds on recent advances across 3 research areas: dialog systems, Transformer-based neural architectures and LLMs; conversational agents for mental health care; and natural language processing methods for annotating MI session transcripts. Below we provide a detailed overview of prior work in each area.

Dialog Systems, Transformers, and LLMs

General-purpose dialog systems are traditionally categorized [55] into goal-oriented [56] and non–goal-oriented [57]. Non–goal-oriented dialogue systems, commonly referred to as chatbots, try to maintain a human-like "small talk" or casual conversation without any specific goal and for as long as possible. Goal-oriented dialog systems, on the other hand, explicitly incorporate a supervision signal, such as progress towards completion of a certain task (eg, reserving a table at a restaurant). This type of dialog system structures human-computer communication as a sequence of distinct dialog states, with each dialog state defined in terms of values of discrete variables (ie, slots, such as location, time, party size, and type of cuisine for restaurant reservations). Goal-oriented dialog systems (eg, intelligent assistants) are also typically integrated with automated schedulers or databases and maintain a conversation with their users until all the information necessary to accomplish a task has been collected. Conversational agents for behavioral counseling fall into the category of specialized dialog systems. They are different from general-purpose dialog systems and other conversational agents in health and medical care [58], since they need to effectively use a variety of counselor communication skills at appropriate moments during a loosely structured and time-limited interaction with users.

The advent of the Transformer [53], an encoder-decoder neural architecture with a multihead attention mechanism, has revolutionized machine learning, including natural language processing and dialog systems. Neural models based on the Transformer architecture are typically pretrained on large human-written textual corpora consisting of tokens (words, punctuation marks, emojis, etc) to minimize the error on several computational tasks, most commonly to predict a token given a sequence of tokens (the context). The Transformer gave rise to 3 types of neural architectures. Architectures of the first type, which include Bidirectional Encoder Representations from Transformers [59] and its variants [60-63], use only the encoder stack of the Transformer and are typically used in a transfer learning scenario to create dense representations of text for a particular downstream natural language processing task. Specifically, they are pretrained on a large textual corpus using the token prediction and next-sentence classification objectives and fine-tuned on a much smaller corpus for a specific downstream task, such as text classification. The architectures of the second type, which include BART [64] and T5 [65], use the encoder and decoder stacks of the Transformer and are typically used for text summarization. Models of the third type, which include foundation LLMs [54], such as GPT [66], ChatGPT [67], PaLM [68], and LLaMa [69], use only the decoder stack of the Transformer architecture. Rather than being specialized architectures developed for a particular task or for creating representations that can be fine-tuned for a certain task, foundation LLMs are trained to attain general-purpose cognitive capabilities and help users accomplish many different tasks. Such LLMs are typically used in zero-shot or few-shot learning scenarios when they are provided with a textual prompt describing a problem optionally accompanied by several examples of inputs and solutions [70].

In the context of health care, the Bidirectional Encoder Representations from Transformers architecture trained on clinical notes was shown to accurately predict patients' readmission, in-hospital mortality, comorbidity index, length of stay, and insurance denial [71]. Other studies [72,73] found that foundation LLMs possess significant medical knowledge and can write medical notes based on transcripts of physician-provider encounters, solve problems from board examination with accuracy similar to or surpassing human physicians (with the highest scores in psychiatry), or interactively provide a "curbside consult" given a clinical case summary. Foundation and other Transformer-based LLMs can also be used in dialog systems to generate system responses given the context of prior interactions with users. Due to the central role language and conversation play in the description, manifestation, and treatment of mental health disorders, LLMs hold marked potential for mental health care and psychiatry [74]. Neural architectures (including the Transformer-based ones) have been previously adapted to generate specific counselor language, such as empathy (statements of support and understanding of the client's experiences and emotions) [75-77] and reflections (repetitions or rephrasing of the client's prior statements) [78,79]. Partner [80], a system combining reinforcement learning and GPT-2, was proposed and evaluated for empathic rewriting of responses in online mental health support platforms.

Conversational Agents for Mental Health Care

The use of conversational agents [58] and LLMs [81] in health care, including mental health care and psychiatry [82], is increasing in frequency. Recent systematic reviews [83-85] established that conversational agents have been tested in the

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delivery of mental health services, most commonly focused on providing support during psychological distress (such as dealing with stress, depression, anxiety, or posttraumatic stress disorder), health behavior counseling and promoting psychological well-being, with cognitive behavioral therapy most frequently used as psychotherapeutic modality. The vast majority of existing conversational agents for mental health care, promoting psychological well-being, and health behavior counseling are rule- or retrieval-based [86]. Consequently, such agents require a substantial amount of manual input in the form of dialog scripts, action rules, and agent response databases. By directing conversations through a set of predefined or templatized responses, such agents are prone to unnatural, impersonal, or repetitive communication, which reduces their clinical effectiveness [86]. For example, Bonobot [87], a nonneural text messaging conversational agent for MI on stress management, uses predefined session scripts and templates triggered by the keywords in patient utterances to generate responses. It is built on top of ELIZA [88], a system developed more than half a century ago to mimic a Rogerian psychotherapist by persistently rephrasing patient statements and asking questions. Woebot (Woebot Health), [89] a mobile phone app for mood tracking and delivering cognitive behavior therapy, permits only constrained user input (eg, a set of utterances predefined for each dialog situation) and responds with predefined counselor phrases. Lark [90], a mobile health coach, responds to users' specific input, such as food and beverage consumption, weight, or sleep duration, with predefined content (eg, praise or educational material). Embodied conversational agents [91] focus on the visual modality of automated behavioral health interventions, restricting user input in a scripted dialog to selecting predefined answers to the agent's templatized questions [41,44,45,92,93].

While neural conversational agents have been previously developed to simulate patients for training human counselors [94], we are unaware of any previously published research on fully automated neural generative (ie, using neural architectures to generate from scratch rather than retrieve predefined responses) conversational agents for MI-style counseling. Therefore, whether it is feasible to use such agents for delivering free-form MI interventions remains an open research question. The recent paper by Brown et al [95], reporting the results of an iterative study of an MI agent for smoking cessation is the closest prior work to this study. However, the agent evaluated in this study is significantly simpler and only generates reflections of the users' responses in a scripted dialog consisting of just 5 predefined open-ended questions.

Natural Language Processing Methods for MI Session Transcripts

Previously proposed machine and deep learning methods for the analysis of MI session transcripts fall into 2 categories: methods for identification and characterization of counselor communication behaviors and methods for session-level analysis and prediction.

Identification and Characterization of Counselor Communication Behaviors

The methods in this category include machine [96-98] and deep learning [97-101] binary classifiers to identify counselor communication behaviors, such as expressions of empathy [102,103] and multiclass classifiers [96-98,100,101,104] to identify specific or a range of counselor or client communication behaviors. Such classifiers are primarily used for auto-coding MI transcripts, a common first step in a retrospective analysis of MI session transcripts to identify effective and ineffective counselor communication patterns. Other prior work in this category focused on identifying acoustic [102] and contextual [103] markers of empathy, extracting linguistic patterns associated with specific counselor communication behaviors [105], predicting counselor [105] or client [100] communication behaviors, and automated scoring of human MI counselor reflections [106].

Session-Level Analysis and Prediction

The methods in this category take MI session transcripts manually or automatically annotated with behavior codes as input to predict the likelihood of eliciting target patient language [107] and identify effective counselor communication strategies [108]. Other methods in this category include a method to discover the discourse structure in email-based MI sessions [109] and a method to discover linguistic differences between high-quality and low-quality MI sessions [110].

Study Hypotheses

This study will explore the following hypotheses: (1) NAOMI will achieve at least intermediate MI fidelity based on Motivational Interviewing Treatment Integrity (MITI) coding scheme [111] (see the Statistical Analysis subsection of the Methods section for more details); (2) At least 80% of the last cohort of study participants will find NAOMI acceptable and usable; specifically, they will like using NAOMI, be comfortable discussing their weight with it, find their interaction with it pleasant, its guidance helpful, and want to use it again (see the Measures subsection of the Methods section for more details); (3) Interaction with NAOMI will result in positive shifts in all motivational precursors (see the Qualitative Analysis subsection of the Methods section for more details).

Methods

In this section, we provide the details of the overall study design, recruitment activities, and measures that will be used to assess the acceptability and usability of NAOMI and explore change in motivational precursors.

Overview

The design and implementation of this research protocol have three main strengths: (1) a strong multidisciplinary team consisting of computer scientists and behavioral health researchers with specific expertise in social work, clinical psychology, intervention development, and health equity; (2) partnerships with primary care clinics interested in providing evidence-based care and eliminating health disparities; and (3) the methods and techniques feasibility tested in this project can,

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in principle, be adapted to a wide spectrum of psychotherapeutic interventions.

Study Design

Overview

We are planning 4 stages of NAOMI's development and validation with each stage following an explanatory mixed methods design [112]. The results of stages 1 and 2 will inform development activities in the remaining stages. Study participants will complete an in-person or online study visit and a follow-up survey 1 week later.

Study Visit

Participants will complete an in-person study visit using a tablet computer. If a study visit takes place online, the participants will complete the visit on a device of their choice using Zoom. The structure of the study visit is detailed in Textbox 1.

Textbox 1. Structure of a study visit.

Prior to the commencement of study visit activities, study staff will provide and review a copy of the study information sheet with eligible and interested patients and allow prospective participants to ask any questions. Prospective participants will be informed that by proceeding with study activities, they are consenting to participate in the study, however, their participation is completely voluntary and can stop at any time. Upon verbal acknowledgment from the prospective participant, study activities will proceed as follows:

1. Study participants will complete the Participant Information Form and the Pre-Interaction Questionnaire (described below).
2. Participants will then interact with Neural Agent for Obesity Motivational Interviewing (NAOMI) using a tablet computer (with a detachable keyboard) for at least 10 minutes but no more than 1 hour.
3. Participants will complete the Post-Interaction Questionnaire, Usability Questionnaire, and the Consultation and Relational Empathy Measure (described below).
4. Participants will complete a Semi-Structured Qualitative Interview to share their impressions of NAOMI and suggestions for its improvement.

Follow-Up

One week after the study visit, participants will be sent a link to the online Follow-Up Questionnaire (described below).

Measures

The study measures described below will be administered online using Qualtrics.

Participant Information Form

The study investigators developed this form to collect demographic information including the participant's age, sex, gender identity, racial/ethnic background, marital status, education, employment status, income levels, and perceptions of their weight and food security. Completing this form should take no more than 10 minutes.

Pre-Interaction Questionnaire

This 15-question instrument includes 12 five-point Likert-scale questions adapted from the Psychometric Analysis of the Perceptions of Computerized Therapy Questionnaire-Patient version (PCTQ-P) [113]. The PCTQ-P is a validated measure grounded in the diffusion of innovations theory [114] previously shown to be effective at predicting successful dissemination of evidence-based mental health interventions [115]. The goal of these questions is to assess the participants' degree of exposure to and perceptions of AI conversational agents in general, including the detection of any presuppositions and biases towards AI, their attitude about AI counselors, preference for AI over human counselors, and belief in the ability of AI counselors to facilitate weight loss. The questions about participants' attitudes toward AI counselors, preference for AI over human counselors, and beliefs in the ability of AI counselors to facilitate weight loss are also assessed post-interaction. The Pre-Interaction Questionnaire also includes 3 weight loss motivational assessments, in which the participants are asked to rate their confidence, importance, and readiness to change their weight-related lifestyle behaviors using a ruler ranging from 1 to 10, where 1 indicates "not at all" and 10 indicates "very much" [21]. These assessments are repeated in the Post-Interaction and Follow-Up Questionnaires. Completing this questionnaire should take no more than 15 minutes.

Post-Interaction Questionnaire

This instrument includes 16 five-point Likert-scale questions adapted from PCTQ-P and the confidence, importance, and readiness rulers assessed in the Pre-Interaction and Follow-Up Questionnaires. Completing this questionnaire should take no more than 15 minutes.

Usability Questionnaire

This instrument includes 15 five-point Likert-scale questions from the Telehealth Usability Questionnaire [116], a validated measure that combines the questions from popular traditional computer technology questionnaires, such as the Technology Acceptance Model [117] and the IBM Post-Study System Usability Questionnaire [118]. The Telehealth Usability Questionnaire was adapted for this study to assess perceptions of NAOMI's usability, such as usefulness, ease of use, reliability, and satisfaction. Completing this questionnaire should take no more than 15 minutes.

Consultation and Relational Empathy Measure

The 10-question validated Consultation and Relational Empathy (CARE) measure [119] was adopted by the investigators to assess NAOMI's empathic skills. Answers are converted to a numeric summary score on a 0-100 scale allowing the investigators to directly compare NAOMI's empathic skills with those of human or other AI counselors. Completing this measure should take no more than 10 minutes.

Follow-Up Questionnaire

This instrument includes the confidence, importance, and readiness rulers assessed in the Pre- and Post-Interaction

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Questionnaires. Completing this questionnaire should take no more than 5 minutes.

Semi-Structured Qualitative Interview

Research staff will use a semi-structured interview guide composed of 13 questions to query participants' prior experience with other conversational agents or AI counselors and to gather feedback on their interaction with NAOMI, including the usefulness of NAOMI's advice, quality of its counseling, and suggestions for improving NAOMI. The qualitative interview should take no more than 45 minutes.

Recruitment

Setting

We will recruit participants from the primary care clinics in Detroit, Michigan, and the greater Metropolitan Detroit area that are part of the MetroNet primary care practice-based research network [120]. Developed in 2001 with federal funding, MetroNet is a collaborative effort of the Wayne State University's Department of Family Medicine and Public Health Sciences, its affiliated family medicine residency programs, and 10 community-based primary care practices serving the diverse population of approximately 50,000 patients from Metropolitan Detroit (≈60% identifying as African American, 30% White, 5% Arab/Chaldean, and 5% Hispanics).

Inclusion Criteria and Target Sample Size

To be included in this study, patients must be (1) English-speaking, (2) aged 18 years 0 months to 65 years 0 months, and (3) meet criteria for overweight or obesity (BMI 25.0-39.9) as documented by their treating physician. The exclusion criteria are in line with other similar studies [121]: (1) comorbid conditions that might compromise data integrity or the patient's ability to autonomously interact with NAOMI (eg, severe autism, schizophrenia, or other psychotic disorders), (2) patients whose elevated weight is secondary to another medical condition (eg, Prader-Willi), and (3) women who are pregnant. Following literature recommendations for sample size in feasibility studies [122,123], we are planning to recruit 50 (12-13 per each of the 4 study cycles to account for possible attrition between the study visit and a follow-up survey) participants to ultimately have 40 participants (10 per cycle), who will have completed both the study visit and a follow-up survey.

Procedures

MetroNet primary care clinics will be sent an introductory email describing this study and inviting them to serve as recruitment partners. Emails will be followed up by the study staff, who will make phone calls to assess interest and discuss the project in more detail. Clinics that agree to partner will be asked to identify a staff member to liaise with the study team in the recruitment of study participants from their clinical population. Patients eligible for participation in this study will be identified through a review of the participating clinics' medical charts either by clinic or authorized study staff and recruited using 2 approaches.

In the first approach, clinicians will briefly introduce the study to eligible patients at the end of their in-person clinic visit. If a patient is interested in learning more about the study, they will either sign a Release of Contact Information Form to be forwarded to the study staff for follow-up or, if study staff are available in the clinic, they will meet with the patient to discuss the study and their interest in participating.

In the second approach, all potentially eligible patients identified via chart review will be mailed a letter of introduction explaining the purpose of the study and offering the opportunity to opt out of further contact. The study staff will follow up with the patients who do not opt out to present the details of the study, assess their interest in participating, and schedule interested patients for their study visit.

System Versions and Training

We will develop and evaluate NAOMI in 4 stages. To determine the general direction for developing NAOMI, in stages 1 and 2, it will be implemented using an open-source foundation LLM and (1) using few-shot learning based on a prompt with task-specific instructions and examples of key counselor communication behaviors, and (2) using a domain adaptation strategy based on 1555 transcripts of psychotherapy sessions and 205 transcripts of MI sessions gathered in our previously funded studies to fine-tune the LLM with communication patterns and the language of MI counseling. In stages 3 and 4, we will refine the best approach.

Data Analysis

We will use a combination of statistical, qualitative, and thematic approaches to analyze the data collected during this study.

Statistical Analysis

NAOMI's adherence to the core principles of MI will be assessed using the MITI coding scheme [111], a standard instrument for assessing MI fidelity. Two trained MITI coders (the primary and secondary) will code NAOMI's utterances in the transcripts of its interactions with the study participants with MITI codes. The primary coder will code all transcripts with the second coder co-coding randomly selected 25% of transcripts to assess interrater agreement using the Krippendorff α statistic [124]. The quantitative assessment of NAOMI's counseling skills based on the MITI-coded transcripts has 2 components: global scores and behavior counts. The global scores aim to characterize the overall quality of patient-counselor interaction and include 4 dimensions (Cultivating Change Talk, Softening Sustain Talk, Partnership, and Empathy). Behavior counts are evaluated by tallying instances of specific counselor behaviors, which can be grouped into 5 broad categories: questions, reflections, MI adherent behavior, MI nonadherent behavior, and neutral behaviors. The global scores and behavior counts will then be used to assess the level of NAOMI's counseling skills according to the MITI manual.

Qualitative Analysis

Due to the small sample size, only qualitative analysis of changes in the measures of perceptions of AI agents and counselors (administered in the Pre- and Post-Interaction Questionnaires) and motivational precursors (administered in

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Pre-, Post-Interaction, and Follow-Up Questionnaires) will be performed.

Thematic Analysis

Framework matrix analysis [125], an efficient, systematic approach to thematic analysis that begins with the construction of a matrix based on content areas derived from the interview guide, will be used to analyze transcribed qualitative interviews. Two coders will independently code the interviews by "charting" a summary of feedback into the matrix. Coders will meet to review and compare their matrices, resolve discrepancies, and develop a final coded-to-consensus matrix. Coders then identify emergent themes to summarize users' experience with NAOMI and suggestions for intervention modification.

Ethical Considerations

This research protocol was reviewed and approved by the institutional review board of Wayne State University (protocol IRB-23-01-5404), as amended, on May 25, 2024. After completing the study visit, the participants will be compensated with a US $75 Amazon gift card. A US $15 Amazon gift card will be provided to the participants after completing the Follow-Up Questionnaire. The data set for fine-tuning the LLM underlying NAOMI is fully deidentified. Transcripts of participants' interactions with NAOMI will be modified by the study staff after the interaction to remove any identifying information. Audio and video data collected during qualitative interviews will be transcribed and deidentified. After transcription has been completed and the integrity of the data confirmed, the audio and video files will be destroyed. All survey data will be collected using a unique research identification number, which will also be used as a link to the participant's survey data and to label the data derived from the participant's interaction with NAOMI. The linkage between the research identification number and the participant's identity will be maintained in a password-protected file stored on a secure server.

Results

The first version of NAOMI has been developed. The investigative team also developed a website for the study visit, which will allow only study participants to access NAOMI, automatically guide the participants through the steps of the study visit detailed in Textbox 1, keep track of their progress, and allow them to complete the study visit only once. Participant recruitment will commence in September 2024. Data collection activities are expected to conclude in May 2025.

Discussion

Study Hypotheses

This study explores the hypotheses that NAOMI, an LLM-based AI counselor, can conduct unscripted weight loss MI sessions achieving: (1) at least intermediate MI fidelity; (2) 80% user satisfaction, and (3) positively shifting motivational precursors. LLM-based counselors have the potential to address the following limitations of scripted counselors.

First, LLMs can generate fluid, diverse, and knowledgeable AI agent responses that take into account previous interactions in a conversational session. Diversity (mixing informational statements, questions, reflections, and affirmations) and contextual relevance of counselor responses are integral parts of MI. Receiving short, generic, or repetitive replies from scripted and retrieval-based conversational agents for mental health care in response to deeply personal questions has been identified as one of the primary reasons for patient dissatisfaction in prior qualitative studies [87].

Second, LLMs possess human-level capabilities for generating fluent and coherent content. They recognize fine nuances of language and can be taught the concepts of style and tone. They can also pay close attention to patient language and communicate emotions and empathy. Understanding and paying attention to the nuances of patient language is necessary to generate engaging and contextually relevant responses.

Third, due to the open and loosely structured nature of MI counseling sessions, it is infeasible to capture all possible session contexts and scenarios with a finite set of rules, patterns, scripts, or dialog states. As part of this study, we will explore the feasibility of training LLMs to conduct MI counseling sessions by using context-appropriate provider communication skills to elicit target patient language and respond to client resistance.

Limitations, Risks, and Mitigation Strategies

At the same time, LLMs (and consequently conversational agents based on them) have several known limitations and risks. First, LLMs are trained on large human-authored textual corpora and thus can learn the biases and stereotypes expressed in these corpora. Training corpora may also make a conversational agent personalized to the users in a specific region or belonging to a particular culture or demographic group and thus less relatable and effective for other users. To mitigate this risk, the LLM underlying NAOMI will be fine-tuned on a large and diverse corpus of psychotherapy and MI counseling session transcripts.

The "black box" nature of LLMs is another source of potential risk since it translates into minimal control over what and understanding of how LLM-based conversational agents generate their responses. LLMs are also known to be prone to "hallucinations" [126], that is, generating outputs that are fluent and plausible, yet factually incorrect. The lack of interpretability and controllability is, however, common to many machine learning models and scientific understanding of the mechanism by which LLMs generate their output is still in its infancy [127]. The risk of NAOMI generating inappropriate or factually incorrect content will be mitigated by a study team member observing NAOMI's interaction with every study participant and intervening should the interaction go awry.

Since study participants in each recruitment wave are not randomized to different conditions, our results may also be subject to cohort effects. Once NAOMI is fully developed and validated, we will address these limitations by conducting a randomized controlled trial testing NAOMI's efficacy.

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Conclusions

This study aims to explore the feasibility of developing NAOMI, an LLM-based Web app for fully automated MI-style weight loss counseling. If proven effective, LLM-based counseling agents have the potential to become a cost-effective approach for addressing the obesity epidemic at a public health level. They can also have a broad, transformative effect on the delivery of MI and other psychotherapeutic modalities helping to mitigate the key barriers to their widespread adoption and enabling just-in-time and on-demand counseling anywhere. Upon successful completion of this study, we will measure NAOMI's efficacy in improving motivational precursors and actual lifestyle behaviors in a randomized clinical trial.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

AK designed the research methodology and wrote the original draft of the manuscript. All authors participated in study conceptualization, funding acquisition, and manuscript review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
NIH peer-review report.
[PDF File (Adobe PDF File), 152 KB - resprot_v13i1e60361_app1.pdf]

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Abbreviations

AI: artificial intelligence
CARE: Consultation and Relational Empathy
LLM: large language model
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity
NAOMI: Neural Agent for Obesity Motivational Interviewing
PCTQ-P: Perceptions of Computerized Therapy Questionnaire-Patient

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Protocol

Examining the Impact of Simultaneous Alcohol and Cannabis Use on Alcohol Consumption and Consequences: Protocol for an Observational Ambulatory Assessment Study in Young Adults

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Abstract

Background: There is significant conflicting evidence as to how using cannabis while drinking alcohol (ie, simultaneous alcohol and cannabis use) impacts alcohol volume consumed, patterns of drinking, and alcohol-related consequences. The impact of simultaneous use on drinking outcomes may be influenced by several within-person (eg, contextual) and between-person (individual) factors.

Objective: This study was designed to examine naturalistic patterns of alcohol and cannabis use to understand how simultaneous use may impact drinking outcomes. The primary aims were to understand the following: (1) if simultaneous use is associated with increased alcohol consumption and riskier patterns of drinking, (2) if simultaneous use leads to increased alcohol consequences, and (3) how contextual circumstances moderate the impact of simultaneous use on consumption and consequences.

Methods: Data collection involves a 28-day ambulatory assessment protocol in which a sample of non–treatment-seeking young adults who report simultaneous use of alcohol and cannabis complete ecological momentary assessments (random, event-contingent, and time-contingent surveys) of alcohol and cannabis use, contexts, motives, and consequences on their personal smartphones while continuously wearing an alcohol biosensor bracelet. Participants also complete a baseline assessment, brief internet-based check-in on day 14, and a final session on day 28. Community-based recruitment strategies (eg, social media and flyers) were used to enroll 95 participants to obtain a target sample of 80, accounting for attrition.

Results: Recruitment and data collection began in May 2021 and continued through June 2024. Initial results for primary aims are expected in October 2024. As of March 2024, the project had recruited 118 eligible participants, of whom 94 (79.7%) completed the study, exceeding initial projections for the study time frame. Remaining recruitment will provide the capacity to probe cross-level interactions that were not initially statistically powered. Strengths of the project include rigorous data collection, good retention and compliance rates, faster-than-expected enrollment procedures, use of a novel alcohol biosensor, and successful adaptation of recruitment and data collection procedures during the COVID-19 pandemic.

Conclusions: This is the first investigation to assess the key momentary predictors and outcomes of simultaneous use as well as self-reported and objective (via alcohol biosensor) measures of alcohol consumption and patterns. The results of this study will inform prevention efforts and studies of individuals who use cannabis who are engaged in alcohol treatment.

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KEYWORDS

ecological momentary assessment; alcohol; cannabis; consequences; transdermal alcohol biosensors; ambulatory assessment; mobile phone

Introduction

Overview

Alcohol and cannabis use are among the most commonly used substances in the United States. Rates of using both substances are particularly high among young adults [1], who also report the highest rates of simultaneous alcohol and cannabis use (ie, using alcohol and cannabis at the same time so that the effects overlap) [2]. Young adults (ie, aged 18-26 years) are the only age group for whom rates of cannabis use increased following the legalization of cannabis [3]. Co-use of alcohol and cannabis (ie, use of both substances but not necessarily so that the effects overlap), and particularly simultaneous use (ie, use of both alcohol and cannabis so that the effects overlap [4]), are associated with increased risky behaviors and negative consequences, including driving under the influence, alcohol-related injuries, and other legal, academic, interpersonal, physical, and mental health problems relative to alcohol or cannabis use only [1,5-9]. Despite the increased risks associated with co-use, findings as to whether or not cannabis use leads to momentary increases in alcohol consumption or consequences remain mixed [10], and our understanding of how co-use confers susceptibility to alcohol problems remains poorly understood. It is critical to understand the impact of cannabis use on alcohol use and its consequences, as alcohol use is the third-leading cause of preventable death in the United States [11,12], and alcohol misuse cost US $249 billion in 2010 [13] and contributed to 5.1% of the global burden of disease and injury [14]. Globally, alcohol misuse was the leading risk factor for death and disability among those aged between 15 and 49 years in 2016 [15]. The present work was designed to use ambulatory assessment (AA) methods to closely examine the momentary impact of simultaneous use on alcohol consumption, patterns, and consequences, as well as the social and contextual factors that may moderate those effects.

Simultaneous Alcohol and Cannabis Use

Laboratory work examining the acute effects of simultaneous use suggests that cannabis enhances the subjective effects of alcohol [16-18], increases motivation to drink alcohol [19,20], and leads to synergistic cognitive impairment [21-23] relative to when alcohol is used alone. Although these studies provide ideally controlled conditions for examining the acute effects of combined cannabis and alcohol, they are less ideally suited to examine complex contextual factors (eg, location, activity, and social context) and naturalistic patterns of consumption. Observational studies of simultaneous use in which participants self-report their patterns of alcohol and cannabis use yield a naturalistic observation of cannabis' impact on alcohol outcomes. In particular, the use of repeated measurement, including the Timeline Followback (TLFB; calendar-assisted method using anchoring dates to gather substance use estimates at the day level) [24], and AA methods, including ecological momentary assessment (EMA), are increasingly used to measure fine-grained patterns and correlates of co-use at the event level [25]. Initial research suggests simultaneous use is associated with higher levels of alcohol and cannabis consumption relative to when either substance is used alone [26-29]. However, competing findings exist in an observational study of primarily college students who provided 14 days of daily diary entries suggesting no increased risk of consumption [30]. With regards to alcohol-related consequences, there is a body of literature suggesting a higher risk of consequences on simultaneous or co-use days relative to alcohol-only days (refer to the review by Lee et al [31]). Despite these significant findings, several studies found no significant association between simultaneous use and consequences, especially when alcohol or cannabis quantity is controlled [27,32-34].

These conflicting results about the effects of simultaneous use have given way to 2 competing theories, namely whether cannabis acts as a substitute (ie, replacing the effects of alcohol, resulting in decreased use) or a complement (ie, used to enhance the effects of alcohol, resulting in increased use) [10,35,36]. The extant empirical literature provides compelling evidence for both substitution and complementary effects, in addition to nuanced findings based on population and mechanisms, including patterns (eg, order of use in a day) and contexts (eg, social settings) of use. These seemingly conflicting findings highlight that simultaneous use is at times complementary and at other times reflects substitution patterns (ie, within-person effects). There is a need for additional research examining fine-grained details of simultaneous use events, including mechanisms and contexts of simultaneous use, to isolate the conditions in which simultaneous use may lead to increased consumption and consequences.

Proposed Mechanisms of the Impact of Simultaneous Use on Alcohol Outcomes

Overview

Incentive-sensitization theory posits that addiction results from the foundational characteristics of *drug liking* and *drug wanting* [37]. Expansion of this theory suggests that incentive sensitization, paired with loss of inhibitory control, (ie, disinhibition) leads to increased motivation to use substances [38,39]. We can test whether this theory applies to how simultaneous use events confer risk for increased alcohol consumption by examining whether simultaneous use indeed leads to increased motivation or craving, subjective effects, and reduced disinhibition, and, in turn, increased alcohol consumption and consequences. Each of these proposed mechanisms can be assessed with AA methods and are discussed in more detail subsequently (refer to Figures 1 and 2 and the Aim 1 section).

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Figure 1. Aim 1: proposed mechanisms of the association between simultaneous use and alcohol consumption. TAC: transdermal alcohol concentration.

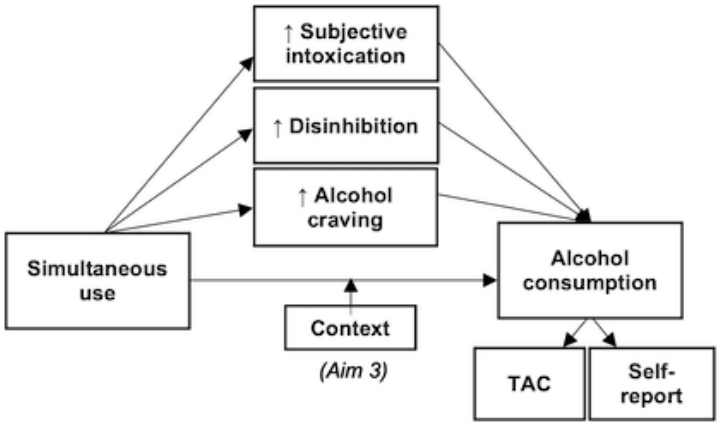

Intoxication

There is mixed evidence regarding the impact of simultaneous use on subjective intoxication in naturalistic settings, with some studies suggesting increased subjective intoxication during co-use occasions relative to alcohol-only occasions [4] and other studies failing to find these effects [30]. While conflicting findings exist among the limited AA studies, participants consistently report increased intoxication during simultaneous use occasions, often referred to as "cross-fading" [40,41], and laboratory work under controlled conditions suggests synergistic effects of a single low dose of alcohol with a low dose of cannabis compared to an alcohol-only dose [16,42-44]. Individuals may engage in simultaneous use to enhance these experiences of positive subjective intoxication through increased alcohol consumption. Alternately, alcohol may alleviate negative affect states or reduce feelings of anxiety or physiological arousal experienced at higher levels of intoxication from delta-9 tetrahydrocannabinol (THC; the primary psychoactive cannabinoid in cannabis) [45]. Importantly, increased intoxication associated with higher rates of alcohol consumption is a robust predictor of risk for experiencing alcohol consequences [4,46-49], and may explain the link between simultaneous use and alcohol consequences, such as drinking more than intended, experiencing nausea or vomiting, or neglecting responsibilities (refer to Figure 2 and the Aim 2 section).

Figure 2. Aim 2: proposed mechanisms of the association between simultaneous use and alcohol consequences.

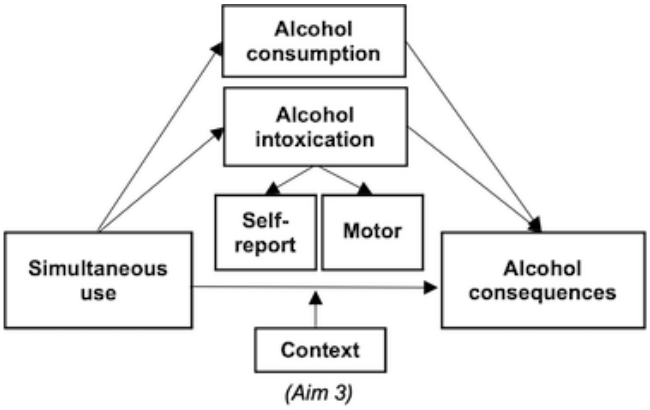

Disinhibition

There is evidence that simultaneous use, compared to either substance alone, increases disinhibition (the ability to suppress an automatic behavioral or cognitive response), a core component of executive functioning [50]. Laboratory studies suggest that both cannabis [51-53] and alcohol [54-57] acutely impair inhibitory control (one indicator of disinhibition). In line with this, research and theory suggest that one's ability to moderate alcohol consumption is lower when inhibitory control is impaired [58,59]; this alcohol-induced impairment in inhibitory control increases ad libitum alcohol consumption [60]. Thus, simultaneous use could increase disinhibition, resulting in increases in alcohol use compared to nonsimultaneous use situations. This possibility has not been well studied in real time.

Craving

Cannabis and alcohol use both activate the endocannabinoid system [61] and, in turn, the approach motivation system [62], thereby increasing the tendency to approach rewarding stimuli (eg, alcohol) [63]. As alcohol and cannabis are commonly paired and known to increase the pleasurable effects of both drugs [16,64], simultaneous use may trigger an alcohol craving. Craving increases after exposure to alcohol cues and initiation [65-67], but only 1 laboratory study examined the effects of simultaneous use, finding an increase in "drug wanting" [67]. Active THC (vs placebo) alone has been shown to lower alcohol craving in a laboratory study [68], but no

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studies have examined the effect of simultaneous use on alcohol craving in the natural environment. AA methods are ideal for examining the direct effects of simultaneous use on the proposed mechanisms, as they can be assessed during the simultaneous use events.

Social Context in Simultaneous Use

Another critical consideration for understanding how simultaneous use affects alcohol outcomes is social contexts (eg, the number of people present and the percent of people who are drinking), which are consistent predictors of a higher level of alcohol consumption [69-71]. Research on the context of alcohol consumption suggests that individual differences in motivation to drink predict drinking in certain contexts, but that social context is a consistent motivator for heavy drinking [72,73]. A recent EMA study of college students revealed that a majority of cannabis use episodes involved being with others and found a positive association between using cannabis with others and the amount of time spent using it [74], suggesting using in social contexts may lead to higher levels of cannabis consumption as well. Recent work has also examined social contexts of simultaneous use episodes, revealing that among young adults, social events in private settings with a high percentage of people who are intoxicated resulted in an increased likelihood of simultaneous use [75], and among adolescents in social contexts with a greater number of underage individuals drinking was associated with an increased likelihood of simultaneous use [46]. In daily or EMA data, social contexts were significantly associated with simultaneous use occasions (relative to alcohol or cannabis only) among college students [76] and young adult populations [77]. In qualitative work, young adults and adolescents suggest that they consider physical, social, and situational contextual factors when engaging in simultaneous use and that social characteristics are associated with simultaneous use [78,79]. Despite the converging evidence of the importance of social contexts for simultaneous use, no studies to date have examined whether context moderates the association between simultaneous use and alcohol consumption or consequences (refer to Figures 1 and 2 and the Aim 3 section).

AA of Simultaneous Use

AA methods include passive data collection (eg, wearable biosensors) and EMAs; they are ideal for studying substance use behavior and consequences as they allow for the assessment and control of contextual and social factors integral to substance use behaviors [25], as well as timing and direct effects as they naturally occur [80,81]. AA also allows for the assessment of intoxication and impairment from self-administered doses of alcohol and cannabis and with higher concentrations of THC than cannabis available for laboratory research. Recent advancements in AA also afford the opportunity to objectively assess substance use impairment via behavioral and cognitive tasks in the natural environment [82], expanding our ability to test these mechanisms in real time as they occur.

Transdermal alcohol biosensors provide a minimally invasive, objective, and passive method for continuously assessing alcohol consumption in the natural environment via transdermal alcohol concentration (TAC), a measurement derived from the small fraction (approximately 1%) of consumed alcohol excreted through the skin [83]. TAC sensors show robust correlations with breath alcohol sensors in the laboratory [84-86] and provide an objective, fine-grained indicator of alcohol use and specific high-risk patterns (eg, rate of consumption) and are stable indicators of within-person variability [87,88], allowing for the examination of time-varying factors (eg, cannabis use or context) on patterns of consumption. The 3 characteristics of drinking events that can be derived from TAC data and are of particular interest to our study aims are absorption rate (a function of physiological absorption rate and behavioral factors, such as drinking pace and stomach contents), peak TAC (a proxy for maximum blood alcohol concentration or a marker of peak intoxication), and area under the curve (including time and TAC values as an approximation of volume of alcohol consumed) [84,88]. TAC data mitigates the sole reliance on subjective self-report while reducing participant burden and circumventing issues with lower compliance with AA at higher drinking rates [89]. Taken together, pairing EMA with alcohol biosensors minimizes recall bias, maximizes external validity, and enhances the ability to more precisely model the influence of proximal factors linked with alcohol outcomes in the natural environment [90].

Study Aims and Hypotheses

This protocol aims to examine mechanisms by which simultaneous use leads to alcohol consumption and consequences using naturalistic data collection. In addition to traditional self-report EMA methods (eg, assessing self-report craving and subjective impairment), the study will leverage technological advances in AA to assess motor impairment (gait and balance) and disinhibition (inhibitory control) with app-based behavioral tasks in a participant's natural environment, as well as alcohol biosensors to passively and objectively measure patterns of alcohol consumption. This is the first study to directly examine the mechanisms by which simultaneous use leads to increased alcohol consumption and its consequences in the natural environment. Further, it is the first study to use transdermal alcohol biosensors and behavioral measures to assess objective impairment during simultaneous use events in the natural environment. The specific aims and hypotheses presented in Textbox 1 will be examined.

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Textbox 1. Study aims.

Aim 1

Prospectively examine whether simultaneous use (vs alcohol only) is associated with increased alcohol consumption at the event level, as measured objectively and via self-report.

Aim 1a

Evaluate mechanisms by which simultaneous use may be associated with increased alcohol consumption. We hypothesize that simultaneous use will be associated with (1) increased disinhibition, (2) increased subjective intoxication, and (3) increased alcohol craving, and in turn increased alcohol consumption (self-report).

Aim 1b

Examine whether simultaneous use is associated with high-risk patterns of alcohol use (eg, increased rate of consumption), as measured objectively (transdermal alcohol concentration [TAC]).

Aim 2

Prospectively examine whether simultaneous use is associated with increased alcohol consequences at the daily level.

Aim 2a

Evaluate mechanisms that may explain the association between simultaneous use and alcohol-related consequences. We hypothesize that simultaneous use will result in increased alcohol intoxication, as measured by (1) motor impairment (gait and balance) and (2) subjective impairment, leading to a greater number of alcohol consequences.

Aim 2b

Examine whether simultaneous use leads to increased alcohol consequences via increased alcohol consumption, as measured objectively (TAC).

Aim 3

Examine event-level contextual moderators of the association between simultaneous use and alcohol consumption and consequences. We hypothesize that simultaneous use in social contexts (eg, locations where there are others drinking) relative to nonsocial contexts will result in (1) increased alcohol consumption and (2) more alcohol-related consequences.

Methods

Design Overview

Young adult participants (aged 18-30 years) complete a baseline session, 28 consecutive days of AA, including daily EMA and continuous wear of the BACTrack Skyn transdermal alcohol biosensor bracelet, and 2 internet-based videoconference sessions during the AA period (a midpoint check-in at 14 days and a final session at 28 days). Data collection assesses the characteristics of alcohol and cannabis use events, in addition to hypothesized mechanisms and moderators of the association between simultaneous use events and alcohol outcomes (consumption and consequences).

Ethical Considerations

The human participants ethics review was completed and approved by the university institutional review board (IRB#1911002571). All participants completed informed consent, where all aspects of the study protocol were reviewed by a research assistant and knowledge checks were completed before a participant consented. All study data are deidentified. Monetary compensation (described in the Compensation section) was provided and deemed to be commensurate with time to complete study procedures.

Participants

Up to 150 young adult participants will be recruited to achieve a final sample of 115 participants (accounting for up to 20% attrition) who complete the full study. Eligibility criteria include the following: (1) aged 18 to 30 years; (2) ability to read and speak English; (3) drink alcohol on average twice per week (or 16 times) and drink heavily (>5 drinks for men and >4 drinks for women per occasion) on average once per week (or 8 times) over the last 60 days; 4) and use cannabis on average of at least once weekly (or 8 times) for the past 60 days; 5) report recent (at least once in the past 30 days) simultaneous alcohol and cannabis use (defined as using both alcohol and cannabis at the same time so that their effects overlap); 6) no recent use (past 30 days) of substances other than alcohol, cannabis, or tobacco; 7) not currently in or seeking treatment for cannabis or alcohol use; 8) not experiencing suicidal ideation (ie, current intent) or symptoms of psychosis or mania in the past 30 days; 9) own a smartphone; 10) live within a 10-mile radius of study location site or willing to drive within this radius to pick up study materials; 11) not color-blind; and 12) not currently working overnight (ie, third shift).

Procedures

Recruitment and Screening

Advertisements targeting individuals who use alcohol and cannabis include print and web-based media, social media, flyers, and handouts posted in the local community, as well as "snowball" recruitment [91] (ie, participant referrals). Participants who respond to advertisements complete a web-based screener, followed by a telephone screener to assess initial eligibility. Following initial remote screening, participants are scheduled for an internet-based videoconference session in which they complete informed consent, followed by the Structured Clinical Interview for DSM-5 Research Version (SCID 5-RV) [92] interview to rule out those with current psychosis, mania, or suicidal intent and a TLFB [24] interview to confirm eligibility on past 60-day alcohol, cannabis, and other

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substance use. Eligible participants complete a demographic and substance use history questionnaire and are scheduled for the baseline orientation session. Figure 3 depicts the study flow.

Figure 3. Study flow. EMA: ecological momentary assessment; RA: research assistant.

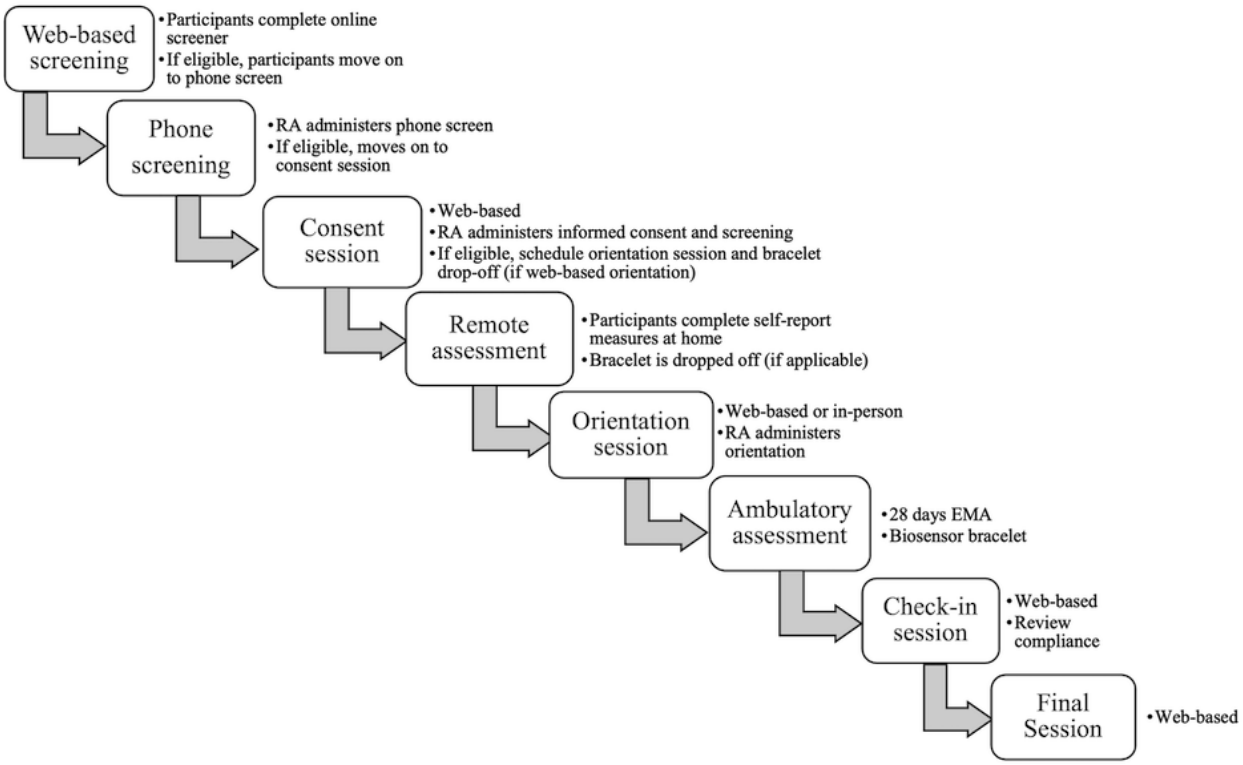

Baseline Orientation Session

The baseline orientation occurs in person or via videoconference. The decision to conduct the session in person or via Zoom videoconference (Zoom Video Communications, Inc) depends on participant preference and the status of university policies around the COVID-19 pandemic. If via Zoom, research staff deliver the Skyn biosensor to the participant in advance of the orientation session. Before the session (regardless of whether it occurs in person or virtually), participants complete a web-based assessment consisting of questionnaires to assess various mental health, personality, and substance use constructs (Multimedia Appendix 1 [93-109] shows a full list of non-EMA self-report measures). During the orientation session, participants train in the use of the survey app (TigerAware; TigerAware LLC [110]), including how and when to initiate surveys, answer different survey types, estimate standard drink and cannabis quantity reporting, and when to reach out to staff during data collection. They are trained on the use of the Skyn biosensor for AA data collection, including when and how to sync and charge the bracelet and when to remove it (eg, to avoid water damage). They also receive study-related handouts detailing reminders of the study protocol, Skyn biosensor operating procedures, and personalized standard alcohol and cannabis quantity estimates.

The AA

The EMAs

Immediately following the baseline orientation session, participants begin the AA data collection phase, which consists of using their personal smartphones to answer daily surveys (EMA) and wearing the Skyn biosensor in daily life. The EMA protocol (Multimedia Appendix 1 for full EMA survey details) will instruct participants to self-initiate event-contingent surveys when they begin drinking alcohol or using cannabis (this is termed a *start survey*) and when they finish drinking or using cannabis (a *finish survey*) during each day of the AA data collection period. Participants are instructed to complete a finish survey if they are done using cannabis or drinking but forgot to initiate the start survey. Follow-up surveys at 30, 60, 90, and 120 minutes are pushed after the initiation of a start survey to capture additional use, intoxication, affect, craving, and contextual changes. Follow-up surveys assess hypothesized mechanisms (disinhibition, subjective intoxication, and craving) and social context moderators (refer to the Data Analysis section for more details).

In addition to event-contingent surveys, participants receive signal-contingent surveys (ie, random prompts) to capture substance use periods that were not self-initiated and social contexts during nonuse moments. Random prompts occur once within each 3-hour block during the afternoon, evening, and night (block 1: 3 PM-6 PM, block 2: 6 PM-9 PM, and block 3: 9 PM-12 AM). Prompts for these random surveys are not sent

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if they would occur during the follow-up period of a start survey. When substance use is reported on a random survey, follow-up surveys identical to those following the start surveys are prompted.

Finally, a time-contingent *morning survey* is available to be self-initiated every morning and prompted by 2 reminders (9 AM and 11 AM). Morning surveys assess the prior days' alcohol and cannabis use, alcohol and cannabis-related consequences, other substance use, reasons for nonuse, and intentions for use in the present day. All surveys are designed to be short (<3 minutes), and participants may suspend prompts at any time to avoid interrupting their sleep or tasks (eg, employment or education activities).

Passive Alcohol Consumption Assessment

The Skyn biosensor is worn continuously on the nondominant wrist of each participant to passively collect TAC during the AA data collection period (Figure 4). The app used to transmit data collected via Bluetooth from the Skyn biosensor is not supported on Android (Google LLC) devices; therefore, study iPhones (Apple Inc) are provided for syncing the Skyn biosensor only (no data or cell service required) for participants who own Android phones; study-provided phones are not used for EMA data collection. Participants are instructed to open the Skyn app and sync the app once a day, which they are compensated to complete (Tables 1 and 2). Participants are also instructed to wear the bracelet at all times but are told that it is not waterproof, so to only remove it when charging, swimming, showering, or doing any other activities where the bracelet may be submerged in water. The charging protocol varies based on the bracelet version. In September 2021, BACTrack Skyn released a new bracelet, which has a prolonged battery life (average of 13 days), relative to the previous version (48-72 hours). The protocol for charging instructions is adapted to these versions. It is emphasized during orientation to wear the bracelet while drinking and overnight, as drinking often occurs in the evening hours, and removing the bracelet before full metabolization of alcohol consumption would result in missing data. Therefore, we suggest participants that they charge the bracelet while bathing to reduce the number of removals. Participants are instructed to avoid exposure to alcohol-based products (eg, using hand sanitizer) when possible, as this can cause a temporary elevation in TAC (this does not resemble a consumed alcohol episode but is troublesome during data cleaning and should be minimized).

Figure 4. BACTrack Skyn bracelet.

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Table 1. Compliance schedule.

Reimbursement for sessions	Compensation (US $)
Orientation session	30
Remote baseline assessment	25
Check-in session	15
Final session	15
Completion bonus	50

Table 2. Weekly reimbursement for daily surveys[a].

	Week 1 compensation (US $)	Week 2 compensation (US $)	Week 3 compensation (US $)	Week 4 compensation (US $)
Reimbursement for daily surveys				
<25% completion	5	5	5	5
25%-49% completion	10	10	15	15
50%-74% completion	25	25	30	30
75%-89% completion	35	35	45	45
>90% completion	40	40	50	50
Reimbursement for biosensor bracelet wearing				
Full compliance (US $5 per day)	0-35	0-35	0-35	0-35

[a]Total possible compliance is US $450.

Check-in and Final Sessions

Participants complete an internet-based check-in session via Zoom videoconference after 2 weeks of AA data collection to review compliance and allow for troubleshooting of any technical aspects of the study. Finally, participants complete a final session via Zoom after coordinating the bracelet return with research staff. In the final session, research staff review the final compensation earned and administer a brief interview to receive feedback on the protocol. The interview requests general feedback on the study protocol, comfort of wearing the bracelet, the usability of the TigerAware app, and study compensation.

Compensation

Participant compensation is outlined in Table 2. Compliance will be maximized in the AA study phase by compensating participants by increasing dollar amounts based on compliance rates each week. Compliance is also incentivized for wearing the Skyn biosensor bracelet with a maximum of US $35 per week (US $5 per day for keeping the bracelet charged and synced). Payments are made on reloadable debit cards. Payments for orientation completion are given directly after those sessions, while total payments are given at study completion or at the time of withdrawal (prorated).

Measures

Remote Baseline Assessments

Before the orientation session, participants complete a battery of self-report measures assessing various mental health, personality, and substance use constructs using a web-based Qualtrics survey (version May 2021; Qualtrics) at home (Multimedia Appendix 1 for the full list of self-report measures). This battery is expected to take approximately 1 hour to complete.

Baseline Demographics and Substance Use History

This survey assesses demographic information (eg, sex at birth, gender, race, and ethnicity) and substance use history information (eg, age at first alcohol and cannabis use and history of use of substances other than alcohol and cannabis). In addition, a subset of items from the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory [111] are included. The survey takes approximately 15 minutes to complete during the recruitment and screening session and was completed using a web-based Qualtrics survey by the participant. Full scoring information is not described here, as a subset of items were included in this study; however, this information is provided in the original citation for the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory [111].

The TLFB

The TLFB [24] is a calendar-assisted interview administered by a research assistant to assess recent daily substance use. It uses a calendar to assist participants in remembering substance use, with cues for personal events and dates to enhance accurate recall. The TLFB will be used to assess past 60-day alcohol (number of drinks), cannabis, tobacco, and other substance use to confirm eligibility and characterize substance use patterns. It has been found to be reliable and valid in a variety of prior studies with various substances and populations [112-115] and

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takes approximately 10 to 30 minutes to complete, depending on the substance use patterns of the participant who is being interviewed.

The SCID 5-RV

The SCID 5-RV [92] semistructured interview administered by research staff includes a screening tool that is used to assess current symptoms of psychosis and mania. The SCID 5-RV screening tool for mania and psychosis takes approximately 10 minutes to complete and is scored based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for each diagnosis. It has shown strong clinical validity and intrarater and test-retest reliability [116].

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 [117] is a self-report measure administered by the participant of current depressive symptoms, including suicidal ideation, and is used to screen for current suicidal intent. The Patient Health Questionnaire-9 is administered using a web-based Qualtrics survey and takes approximately 5 minutes to complete. It has shown strong reliability and validity as a self-report screening tool for major depressive disorder [118].

EMA Survey Items

Key constructs are assessed in EMA through event-contingent (begin- and end-use alcohol and cannabis surveys [ie, start and finish], follow-ups, morning) and signal-contingent (random) surveys using TigerAware [110] software. Each construct assessed is included in Table 3, and exact items are included in Multimedia Appendix 1. Measures were selected based on hypothesized associations with the primary dependent variables of alcohol consumption and consequences. Start and finish surveys are always available and begin with an assessment of whether the participant is reporting alcohol or cannabis use (or both) and continue to additional constructs as relevant (Multimedia Appendix 1). In addition, participants are instructed to complete a "hand sanitizer/alcohol-based product" survey anytime they encounter these products, which will simply ask them to enter the time they come in contact with the product. A modified version of the Stroop [119] task and a Gait and Balance task developed by Apple ResearchKit (Apple, Inc) [120] are included in the 30- and 60-minute Follow-up surveys to assess disinhibition and motor impairment, respectively. The Stroop task asks participants to select the first letter of the name of the color that is presented (eg, b for blue), where the color of the text is displayed in the opposing color for a proportion of the trials. The Gait and Balance task instructs participants to place their phones in their pockets and walk in a straight line for 20 steps.

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Table 3. Ecological momentary assessment constructs assessed.

Construct	Delivery	Example item
Alcohol use	ST[a], ED[b], FU[c], RM[d], and MR[e]	Have you had any alcohol since your last report?
Alcohol type	ED and MR	What type of alcoholic drinks did you have?
Alcohol start time	ST, RM, and MR	Confirm the time you started drinking.
Alcohol end time	ED and MR	What time did you finish drinking?
Alcohol quantity	ST, ED, FU, RM, and MR	How many total standard drinks did you have?
Subjective intoxication	ST, FU, ED, and RM	Rate how drunk/high you feel.
Cannabis type	ST, FU, ED, and MR	Are you using flower (i.e., plant, bud)?
Cannabis quantity	ST, FU, ED, and MR	How much flower (i.e., plant, bud) are you using?
Cannabis start time	ST, RM, and MR	Confirm the time you started using flower.
Cannabis end time	ED and MR	What time did you finish using flower yesterday?
Cannabis reasons	ST and RM	Please select the reason(s) you are using cannabis.
Cannabis mode	ED and MR	Which of the following modes did you use with flower?
Context: location	ST, RM, and FU	Where are you?
Context: activity	ST, RM, and FU	What are you doing?
Context: social	ST, RM, and FU	Are you by yourself or with others?
Context: social relationship	ST, RM, and FU	Who are you with?
Context: social use	ST, RM, and FU	Are the people (person) you are with drinking alcohol?
Nicotine use	ST and MR	Are you using any of the following nicotine products?
Craving	ST, FU, RM, ED, and MR	How strong is your urge to drink alcohol right now?
Affect	ST and ED	How much have you felt upset in the past 15 minutes?
Impulsivity	ST	I did something without really thinking it through.
Disinhibition (Stroop task)	FU[f]	Multimedia Appendix 1
Motor intoxication (gait task)	FU[g]	Multimedia Appendix 1
Alcohol or cannabis consequences	MR	Did you experience any of the following yesterday as a result of your alcohol use?
Alcohol or cannabis intentions	MR	Do you plan to drink alcohol today?
Intoxication intentions	MR	How high do you plan to get today?
Nonuse reasons	MR	Please select the reasons you did not use cannabis yesterday.
Other substance use	MR	Did you use substances other than alcohol or cannabis yesterday?

[a]ST: event-contingent begin alcohol or cannabis use or start survey.

[b]ED: event-contingent end alcohol or cannabis use or finish survey.

[c]FU: event-contingent follow-up survey.

[d]RM: signal-contingent random survey.

[e]MR: event-contingent morning report.

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[f]Administered in the first follow-up only.

[g]Administerd in the second follow-up only.

BACTrack Skyn Alcohol Biosensor

The Skyn biosensor uses fuel cell–based sensors to continuously measure TAC, body temperature, and movement in 20-second intervals. TAC data will be used to assess the daily peak TAC and rate of consumption as reflected in the rate of absorption (refer to the Analytic Plan section). Data are synced via Bluetooth on the Skyn iOS–based app by the participant, and a single CSV file is downloaded at the completion of participation. Research staff also perform daily data tracking on the BACTrack web-based portal to check for participant compliance with the syncing and charging protocol and reach out to participants if any missing data are observed.

Data Analysis Plan

Data Cleaning and Aggregation

An event-level data set will be created to examine aims 1 and 2, and a day-level data set will be created to test aim 3 hypotheses. Event rows will be derived from (1) initiation of start surveys paired with corresponding Follow-up and finish surveys, (2) random surveys and corresponding follow-up surveys (when substance use is reported), and (3) "orphan" finish surveys where participants complete a finish survey but there is no corresponding start or random survey where substance use is reported or there is another preceding finish survey. Finish surveys will be paired with start or random surveys with substance use if they are submitted 6 hours apart. A social day (6 AM-6 AM) will be used to aggregate event-level data and morning surveys for a day-level data set. Each row in the day-level data set will encompass data from the morning survey and an aggregate of relevant event-level variables.

Simultaneous use events will be defined by a self-report of alcohol and cannabis use at any point in the initial survey (start or random surveys) and associated follow-up or finish surveys. Drinking events from the Skyn biosensor will be identified and processed using the TASMAC 2.0 survey software [121]. Timestamps will be used to associate and merge TAC data with drinking events. Events with no self-reported drinking or cannabis-only use with unreported (ie, missing) drinking that are indicted from TAC data will be flagged and removed from analyses when self-reported data are necessary for analyses. Social context will be defined as events where others are around or being around others who are drinking alcohol ("Are the people (person) you are with drinking alcohol?").

All variables will be examined descriptively and checked for assumptions of normality [122]; significantly skewed variables will be transformed or modeled appropriately. Analyses will be conducted to examine whether missing data, specifically on dependent variables, are associated with baseline characteristics (eg, demographics and alcohol use disorder). Sensitivity analyses will determine if findings are consistent in cases with significant missingness [123]. Full information maximum likelihood (FIML) estimation [124] will be used for data missing at random. FIML allows for the handling of missing data without compromising the power of large, intensive longitudinal data. After checking for missing data assumptions, FIML [125] or sequential modeling will be used in multilevel models to impute missing data using packages such as *mdmb* [126].

Aim 1: Examine the Impact of Simultaneous Use on Alcohol Consumption

To determine if simultaneous use leads to increased alcohol consumption, data from alcohol-only and simultaneous use events (from both event- and signal-contingent surveys) will be analyzed. In addition, 2-level linear mixed effects (LMEs) [127] will be used and will include aggregated measures of level 1 (L1) predictors (random intercepts for individuals) at level 2 to control for the effect of individual-level predictors (eg, simultaneous use), allowing for the interpretation of other L1 predictors on outcomes as purely within-person associations (eg, impact of simultaneous use on total alcohol consumption). Aim 1 models will control for subject-level covariates at level 2 (sex, age, race, and ethnicity) and time-varying covariates at L1 (time lag of cannabis use for simultaneous events, tobacco, day of the week, and other substance use). Aim 1a will use mediation to examine the effects of hypothesized mechanisms (increased disinhibition, subjective intoxication, and craving measured in follow-up surveys) between simultaneous use (vs alcohol-only use) and alcohol consumption, measured via self-report (total number of drinks consumed). Aim 1b will use LME to test the association between simultaneous (vs alcohol-only) events and drinking rate (measured via TAC absorption rate). Peak TAC will be calculated as the highest TAC recorded within an episode, area under the curve will be calculated as the sum of the area of trapezoids under the TAC curve, and absorption rate is calculated as peak TAC divided by time from the last 0 reading to peak TAC [84,87,88].

Aim 2: Examine the Impact of Simultaneous Use on Alcohol Consequences

To examine whether simultaneous use is associated with increased alcohol consequences, LMEs will again be used with day-level aggregate data where consequences are assessed in the morning survey and simultaneous use is defined as the incidence of simultaneous use in any event data from the prior day. The same subject- and time-varying covariates will be included as in aim 1 models. Mediation in LME will again be used to test the effects of hypothesized mechanisms: motor impairment (ie, gait or balance data) and subjective impairment (self-report) measured from follow-up surveys (2a) and total alcohol consumption measured via TAC (2b) between simultaneous use and alcohol consequences.

Aim 3: Examine Contextual Moderators of the Association Between Simultaneous Use and Alcohol Consumption and Consequences

To test whether social context moderates the impact of simultaneous use on increased consumption and consequences, an interaction of social context (from self-report event and signal-contingent surveys) and type of substance use episode (simultaneous vs alcohol only) will be included as predictors

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on total alcohol consumption and consequence models, as defined earlier.

Results

This protocol was funded in September 2019 and received institutional review board approval in January 2020. A modified protocol to accommodate COVID-19–related disruptions in research, including a fully remote protocol, was approved in April 2021, and the first participant was enrolled in May 2021. Initial recruitment goals for the project [128] aimed to enroll 95 participants to obtain a target sample of 80, accounting for attrition. However, at the time of this submission, 118 eligible participants have been enrolled, of whom 94 (79.7%) have completed the full protocol. Of the 20 who did not complete the protocol, 12 (60%) withdrew before participating in the AA, and 8 (40%) withdrew during participation. Given the successful recruitment rate and remaining funding timeline, recruitment is ongoing at the time of this submission and is intended to continue until up to 115 total participants complete the protocol. These additional participants will allow for the probing of cross-level interactions that were underpowered based on the initial budget and recruitment projections in the funding proposal (eg, moderation of simultaneous use effects by frequency of cannabis use [129]). Data collection is expected to end by June 2024, and initial results for primary aims are expected in October 2024.

Discussion

Overview

This paper describes a protocol aimed at understanding the impact of simultaneous alcohol and cannabis use on alcohol consumption and consequences among nontreatment-seeking young adults in the natural environment. Given the high prevalence of simultaneous use among young adults [1-3] and its association with high-risk behaviors and alcohol-related consequences among those who use both substances [5-9], this investigation has a critical public health impact on young adults. Furthermore, although simultaneous use has been linked to alcohol-related risks, there is conflicting evidence as to the momentary impact of cannabis use on drinking [10,35]. This study is the first naturalistic observational study that will comprehensively examine the mechanisms whereby simultaneous alcohol and cannabis use may confer alcohol-related risks in the moment and across contexts. With the use of EMA and alcohol biosensors, this protocol will objectively identify how self-reported cannabis impacts patterns of drinking (eg, rate of consumption). Furthermore, the assessment of alcohol and cannabis use behaviors in the moment, while young adults are in their natural drinking environment, will allow for the direct measurement of the critical risk mechanisms under study, specifically craving, subjective intoxication, motor impairment, disinhibition, and contextual influence.

Study Implications

The comprehensive study of these substance use patterns, and the identification of key hypothesized mechanisms are critical to informing prevention and intervention efforts. In particular, this work will inform the next wave of technology-assisted treatment and intervention research, such as just-in-time adaptive interventions [130-133] and digital interventions [134]. There has been significant interest in this approach, specifically in the use of mobile apps to reduce alcohol use [135] and several effective trials; however, no work yet has tested interventions for simultaneous use behaviors in young adults. To do this important prevention and intervention work, it is critical to understand the specific risk mechanisms of simultaneous use on alcohol outcomes. This study will elucidate these mechanisms and clarify the competing literature (ie, substitution vs complementary theories) on the momentary impact of simultaneous use on alcohol outcomes to inform these intervention approaches.

This study will also pave the way for additional work aimed at integrating alcohol biosensor assessment within intensive longitudinal research protocols using EMA as well as for preventive interventions. While this is not the first study to use wrist-worn biosensors in naturalistic data collection [136,137], this is the first to align the use of additional substances within drinking events to understand how co-use may impact drinking patterns, such as the rate of consumption. This work will not only elucidate the impact of cannabis use on drinking topography in naturalistic settings, thereby clarifying the role of simultaneous use in risky alcohol consumption patterns, but also establish the feasibility of complex polysubstance use assessment methods across levels of data analysis. This research has the potential to lead to important health policy recommendations, such as regulations on the proximity of retail cannabis and alcohol placement and the distribution of products that include both alcohol and cannabis.

Limitations

Several limitations of the present protocol are worth identifying. First, while it is critical to understand the etiology of simultaneous use in nontreatment samples to inform prevention and developmental models of addiction, the implications of this study are limited to nontreatment-seeking young adults. Given that treatment status has been identified as a potential critical between-person moderator in the study of simultaneous use and the impact on alcohol outcomes [10], future work will be necessary to extend these findings to those with severe alcohol use disorder or who are seeking treatment for alcohol use. Second, recent use of substances other than nicotine or tobacco is an exclusion criterion in this protocol. This exclusion criterion was necessary due to the limited resources of this funding mechanism that prohibits recruiting a sample large enough to power for variability from additional substance use that may greatly impact alcohol consumption patterns. Although it will be controlled for in the current analyses, future work that includes individuals who use a variety of additional substances is needed to understand the full range of polysubstance use and its impact on alcohol consumption and its consequences. Finally, given that there is no validated objective method for assessing cannabis use in naturalistic data collection, this study is limited to the self-report of cannabis use in the context of an objective assessment of alcohol consumption. The objective measurement of both alcohol and cannabis use would further validate a

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rigorous approach to studying patterns of simultaneous use in the natural environment.

Conclusions

This protocol describes the most comprehensive observational study to date of the impact of simultaneous alcohol and cannabis use on alcohol consumption and consequences in the natural environment among young adults. Data collected at the moment through self-report and passive alcohol sensing with a transdermal alcohol biosensor will elucidate competing theories as to how cannabis use while drinking impacts patterns of alcohol consumption and associated consequences. The study will also identify within- and between-person mechanisms and moderators of these key associations, such as subjective and objective measures of intoxication, via assessment during substance use events. Results will inform key prevention and intervention efforts to reduce the negative impact of simultaneous use among young adults who use alcohol and cannabis frequently and set the groundwork for future work aiming to use these methods in expanded populations.

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Data Availability

All data, including acknowledgment of missing data, will be made available at study completion at the preregistration site [128].

Authors' Contributions

RLG contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, and writing the original draft. JM, NPB, KMJ, SL-K, and RM Jr contributed to supervision, conceptualization, writing, reviewing, and editing the manuscript. TJT contributed to supervision, conceptualization, writing, reviewing, and editing the manuscript, and software. MEF contributed to data curation, methodology, project administration, writing, reviewing, and editing the manuscript.

Conflicts of Interest

TJT is a co-founder of TigerAware LLC which developed the software described in this study. He receives no compensation or royalties for the use of the software.

Multimedia Appendix 1
This includes all measures administered at the remote assessment, as well as the full battery of ecological momentary assessment survey items.
[DOCX File , 143 KB - resprot_v13i1e58685_app1.docx]

Multimedia Appendix 2
Peer-review reports from AA-2 - Epidemiology, Prevention and Behavior Research Review Subcommittee - National Institute on Alcohol Abuse and Alcoholism Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 163 KB - resprot_v13i1e58685_app2.pdf]

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Abbreviations

AA: ambulatory assessment
EMA: ecological momentary assessment
FIML: full information maximum likelihood
L1: level 1

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LME: linear mixed effect
SCID 5-RV: Structured Clinical Interview for DSM-5 Research Version
TAC: transdermal alcohol concentration
THC: delta-9 tetrahydrocannabinol
TLFB: Timeline Followback

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Protocol

Intervention for the Management of Neuropsychiatric Symptoms to Reduce Caregiver Stress: Protocol for the Mindful and Self-Compassion Care Intervention for Caregivers of Persons Living With Dementia

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Abstract

Background: Stress related to Alzheimer disease and related dementias (ADRD) is common, particularly among those who care for persons with challenging behaviors and personality or mood changes. Mindfulness and self-compassion programs are efficacious for managing stress. The skills of mindfulness and self-compassion, however, must be integrated with behavioral management skills in order to effectively improve caregiver stress.

Objective: In this study, we aimed to describe the development of the Mindful and Self-Compassionate Care (MASC) program, the first program that combines mindfulness and self-compassion with behavioral management skills to decrease caregiver stress, and its evaluation in the Supporting Our Caregivers in ADRD Learning (SOCIAL) study.

Methods: Using the National Institutes of Health (NIH) stage model, we describe 3 phases of work encompassing NIH Stages 1A and 1B. In phase 1, we conducted 5 focus groups (N=28) of stressed individuals caring for persons with ADRD and challenging behaviors. Rapid data analysis informed the development of a 6-week online intervention. Phase 2 (NIH stage 1A) includes an open pilot (N>10) with optional exit interviews. Phase 3 (NIH stage 1B) is a feasibility randomized controlled trial of the intervention versus the Health Education Program control. Primary outcomes focus on feasibility with secondary outcomes encompassing acceptability, credibility, fidelity, and signals of preliminary efficacy. Phase 1 follows traditional recommendations for qualitative analyses (at the point of thematic saturation) which was achieved after 5 focus groups (N=28). For the phase 2 open pilot, up to 12 participants will be recruited. For the phase 3 feasibility study, recruitment of 80 caregivers will allow the assessment of feasibility benchmarks. Data for phase 1 included 5 focus groups. In phases 2 and 3, data collection will occur through REDCap (Research Electronic Data Capture; Vanderbilt University) surveys and an optional qualitative exit interview. Analyses will include hybrid inductive-deductive analyses for qualitative data and assessment of changes in our intervention targets and outcomes using *t* tests and correlation analyses.

Results: In phase 1, caregivers reported interest in a brief, online stress management program. Participants held misconceptions about mindfulness and self-compassion, but after detailed explanation thoughts, these skills could be helpful when directly linked to implementation during caregiving routines. Phases 2 and 3 will be completed by the end of 2025.

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Conclusions: We describe the protocol for the Supporting Our Caregivers in ADRD Learning study, as well as the development and feasibility testing of the Mindful and Self-Compassionate Care intervention. Future work will include a fully powered efficacy-effectiveness randomized controlled trial.

Trial Registration: ClinicalTrials NCT05847153; https://clinicaltrials.gov/study/NCT05847153; and ClinicalTrials.gov NCT06276023; https://clinicaltrials.gov/study/NCT06276023

International Registered Report Identifier (IRRID): DERR1-10.2196/58356

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KEYWORDS

mindfulness; caregiver; self-compassion; ADRD; Alzheimer's disease and related dementias; mental health

Introduction

More than 6 million people live with dementia in the United States and this number is projected to more than double by 2050 [1]. Characterized by a loss of cognitive functioning due to an irreversible loss of neurons (can be caused by many different diseases), dementia encompasses Alzheimer disease, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia [2].

The cost of dementia impacts health care systems, individuals, and society in general. According to the Alzheimer's Association, in 2024, the total costs of care will reach US $360 billion, with US $91 billion borne from out-of-pocket spending. These costs do not account for informal caregiving by relatives, friends, or neighbors who are unpaid for their services [3]. Indeed, in 2023, it is estimated that over 11 million unpaid caregivers provided over 18.4 billion hours of care for people living with Alzheimer disease and related dementias (ADRD) [3].

The extent of care provided by caregivers often results in a great deal of psychological, physical, emotional, and functional stress with 40% of caregivers citing a level of stress that interferes with their ability to care for themselves and their loved ones [1,4,5]. Despite their critical role in supporting people with ADRD, caregivers are often described as "hidden patients" whose health care needs often go underrecognized and undertreated [6]. A growing body of literature suggests that caregivers are at risk for decreased quality of life, increased depression as well as negative health outcomes [1,3]. Most caregivers lack effective nonpharmacological interventions to manage the stress associated with caregiving and their care recipient's behavioral and mood symptoms. For instance, individuals living with ADRD may present with challenging behaviors such as aggression, agitation, and apathy [7,8]. Such behaviors have been associated with heightened emotional distress (eg, symptoms of depression and anxiety), decreased well-being, and increased risk for morbidity and mortality in both caregivers and care recipients [3,4].

Addressing a caregiver's stress has the potential to mitigate risk for the exacerbation of the caregiver's chronic health problems and to improve emotional and health outcomes for people living with ADRD [4,5]. Preliminary data [8] indicate ADRD caregivers desire real-time guidance and support to learn about emotional regulation, self-compassion, and behavioral management skills that can help them navigate stress related to their care-recipients' challenging and developing needs.

Many of the current caregiver support programs do not fully meet the psychological and social needs of stressed caregivers for 3 main reasons. First, support groups may not teach evidence-based behavioral management skills that caregivers report they need to manage the challenging behaviors of people living with dementia successfully. Second, behavioral management skills interventions, while available, often do not teach emotional regulation skills, which are necessary to foster the caregiver's ability to manage their care recipient's behaviors. Third, though mindfulness and self-compassion interventions are theoretically based, effective solutions for managing stress and distress among caregivers have rarely been applied to managing common challenging behaviors experienced by care recipients [9,10].

To address the need for a feasible, acceptable, effective, and scalable stress management program to reduce the stress of ADRD caregivers, we created the Supporting Our Caregivers in ADRD Learning (SOCIAL) study which aimed to identify and manage stressful situations that arise for caregivers. We hypothesize that learning and practicing skills with mindfulness and self-compassion will decrease loneliness, increase the quality of relationships, and increase caregiver's self-efficacy when managing challenging patient behavioral symptoms.

Methods

Conceptual Model

Our conceptual model (Figure 1) draws from principles and skills from Kabat Zinn's Mindfulness-Based Stress Reduction program [11], Kristin Neff's Mindful Self-Compassion program [12], and Laura Gitlin's caregiver guide to managing challenging behaviors [13]. Our multicomponent program incorporates (1) Mindfulness-Based Stress Reduction program's mindfulness skills (observe, describe, mindful action, nonjudgement, and nonreactivity) to support emotional regulation during challenging dementia behaviors; (2) Christine Neff's compassion and self-compassion skills (self-kindness and common humanity) to encourage caregivers to be kind to themselves and encourage connection with their care recipients and others; and (3) Laura Gitlin's behavioral management strategies to navigate patient behavioral symptoms. Psychoeducation and group-based practice will provide an opportunity to learn how to integrate skills into the daily caregiver role. The Mindful and Self-Compassionate Care (MASC) program's mechanistic

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targets are hypothesized to act synergistically, leading to reduced stress, symptoms of depression, and anxiety, and improved well-being (Figure 1).

This paper describes preliminary qualitative input from 28 caregivers in 5 focus group interviews (phase 1) used to guide the MASC intervention's development. We describe the design of the open pilot (phase 2) and the feasibility randomized controlled trial (RCT; phase 3). Ultimately, we aim to provide a framework for increasing access to evidence-based psychoeducation interventions for caregivers of people with ADRD.

Figure 1. Mindful and Self-Compassionate Care program intervention model. MASC: Mindful and Self-Compassionate Care.

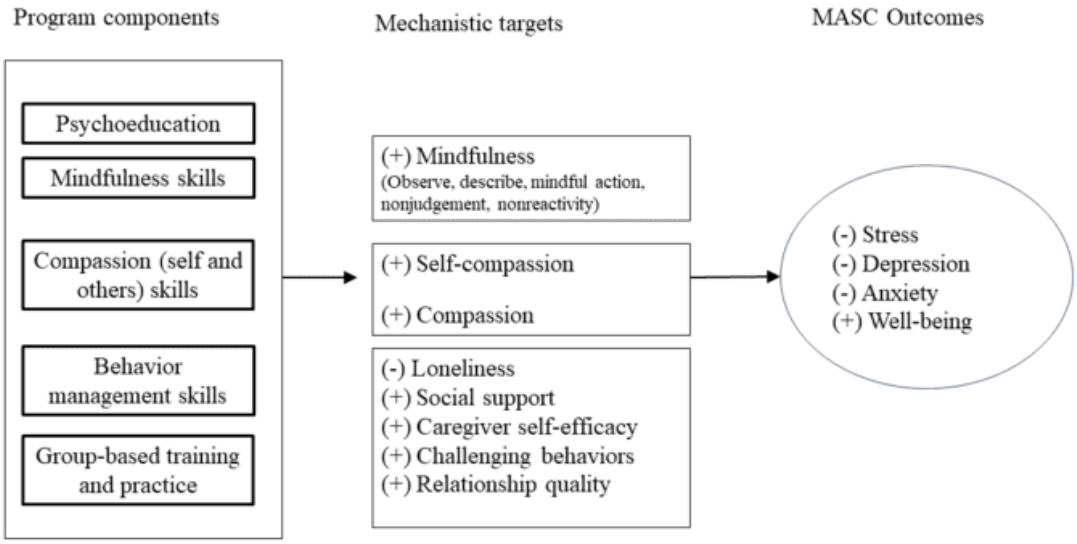

Study Design

This study consists of 3 phases, that are a qualitative phase, an open pilot phase, and a feasibility RCT (Figure 2 [14]).

Figure 2. Mindful and Self-Compassionate Care Program intervention development, optimization, and testing following the National Institute of Health stage model and Science of Behavior Change principles [14]. ADRD: Alzheimer's Disease and Related Dementias; HEP: Health Education Program; MASC: Mindful and Self-Compassionate Care; RCT: randomized controlled trial.

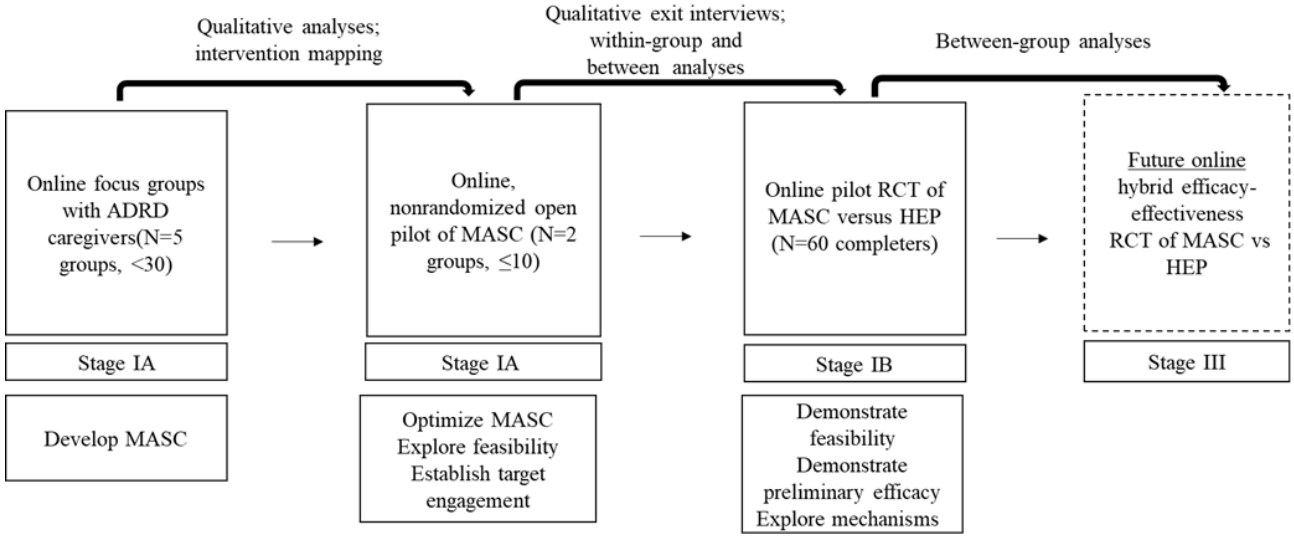

Ethical Considerations

The study has been reviewed and approved (phase 1 protocol 2022P002037, phase 2 protocol 2023P001130, and phase 3 protocol 2023P003628) by the Massachusetts General Brigham institutional review board. Eligible participants will engage in an informed consent discussion with the research assistant surrounding study procedures, expectations, potential risks and benefits of participation, and contact information for further questions. They will also be informed that participation at every stage is voluntary, and they can withdraw from the study at any time. To protect against privacy risks, all participants will be assigned a unique study ID to keep their identity confidential. In addition, all data will be collected and stored within the Massachusetts General Brigham secured REDCap (Research Electronic Data Capture; Vanderbilt University). Compensation

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varies depending on the stage of the study; up to US $50 (phase 1), up to US $60 (phase 2), and up to US $120 (phase 3).

Setting and Participants

Participants for all phases of the study will be English-speaking adults (aged 18 years or older) who identified as informal caregivers to individuals with ADRD. Participants must live with and have provided more than 4 hours of direct unpaid care per day in the past 6 months. In addition, caregivers must endorse stress (Perceived Stress Scale [PSS]–4 [15] score ≥6) and self-report that they managed one or more behavioral symptoms in the past month as defined by the Neuropsychiatric Inventory Questionnaire [16]. Caregivers were excluded if the care recipient had a recent change in psychiatric medications, had used a mindfulness app or any meditation for more than 60 minutes per week in the past 6 months, or were participating in another clinical trial for caregivers. All focus groups and interventions were conducted through a secure online platform.

Recruitment, Screening, and Enrollment

Caregivers were recruited from local sources, including the Dementia Care Collaborative program at Massachusetts General Hospital, the Massachusetts Alzheimer's Disease Research Center, the Massachusetts General Brigham research posting site, nationally, through the National Alliance of Caregiving and ADRD caregiver-specific social media pages (ie, Facebook [Meta], Instagram [Meta], and Twitter [rebranded as X]). All recruitment efforts were documented in REDCap (version 14.0.27) to solidify the recruitment plan for subsequent phases of the study.

Phase 1: Focus Groups

A total of five 60-minute qualitative focus groups were conducted with caregivers through secure live videoconferencing to elicit feedback on proposed content, skills, and logistics (length and duration of sessions, online vs in person). Participants responded to prompts surrounding caregiver needs, proposed program content, and structure as well as barriers and facilitators to participation. Focus groups included modeling of mindfulness and self-compassion skills as well as discussions on a case-based scenario to gauge interest in and reactions to tailoring the program content. Focus groups were recorded and transcribed [17]. Participants were also given the opportunity to complete an optional exit survey comprised of the outcome measurement tools being used in phases 2 and 3. In total, 24 caregivers completed the exit survey and 21 caregivers provided additional written feedbacks.

Data Coding and Analysis

Rapid data analysis (RDA) guided immediate refinement of the intervention, based on the Framework Method [18,19]. Analysis comprised of 3 researchers (SMS, AT, and XXX) coding data into superordinate themes and subthemes using hybrid deductive-inductive analysis [20]. Our RDA template was organized into certain domains, such as population-specific caregiver experiences, program content, and barriers and facilitators for program implementation. The completed RDA template was reviewed by the study team and entered into a matrix of responses which informed manual and procedural adaptations before the open pilot. The matrix was organized in a hybrid inductive-deductive manner based on a combination of the domains from the RDA template and the information that emerged from qualitative focus groups that was most useful in guiding program adaptations.

Formal qualitative analyses and in-depth synthesis of the qualitative data are forthcoming. Thematic analyses will be supported by NVivo 12 (Lumivero). A codebook will be developed using a hybrid deductive-inductive approach wherein codes are created based on a priori categorizations using the Framework method [21]. A second revision will create additional codes based on novel content identified directly from the data and through the analysis process. Furthermore, 2 trained research assistants will code the transcripts under the guidance of the investigative team. Discrepancies between coders will be discussed until a consensus is reached.

Phase 2 and 3: Open Pilot of Mindful and Self-Compassionate Care (Phase 2) and RCT of SOCIAL

Phase 2 and 3 Study Design

The open pilot (phase 2) of MASC will be comprised of a 6-session open pilot delivered through live video to ADRD caregivers who meet eligibility criteria (Figure 1). MASC will be delivered by a trained clinical social worker to 2 groups of 6-10 caregivers. Caregivers complete a questionnaire packet focused on mental well-being as well as questions about their experiences as caregivers for someone living with dementia. Participants will participate in a weekly, 60-minute, online group training session for 6 weeks followed by an exit interview. The open pilot will be used to refine the intervention and the manual used in the phase 3 feasibility RCT of MASC versus a Health Education Program (HEP; the SOCIAL Study).

Setting and Participants of Phases 2 and 3: Recruitment, Screening, and Enrollment

Initial recruitment, screening, and enrollment procedures will be identical to those described for the focus groups. Potential participants recruited nationally will indicate their interest by completing the REDCap screener using the QR code on the flyer or by emailing the research assistants. Research assistants will reach out to eligible caregivers and engage in a discussion that includes an explanation of study procedures, potential risks and benefits of participation, and contact information. All eligible and available caregivers will be emailed a link to the baseline questionnaire in REDCap and offered assistance with questionnaire completion. Caregivers who provide consent but are unavailable to participate in the next available group will be placed on a waitlist for the next group cohort. Assigned participants will have the opportunity to attend a Zoom practice session with the research assistant to problem-solve any technical challenges.

Phase 2 and 3 Mindful and Self-Compassionate Care Intervention Content

Participants receive the 6-week MASC intervention including the manual, web resources, and live intervention. Session content is detailed in Table 1. Broadly, each session will include psychoeducation on each program skill, skill practice, strategies

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to incorporate the skill into the caregiver experience, and strategies for sustained practice. Participants will attend the session using a tablet or computer and will be encouraged to use the video feature to interact "face-to-face" during each video session. Participants will complete weekly "homework" consisting of skills practice audio exercises that allow them to continue to engage with the skills that they are learning outside of the sessions.

Table 1. Mindful and Self-Compassionate Care program content.

Session	MASC[a] topic	Content and skills
1	Getting to know your stress response	Psychoeducation on stress response and sources of stress. Overview of program goals, skills and conceptual model, and goal settings.
2	Introduction to mindfulness	Benefits of mindfulness and meditation for managing caregiver stress. Incorporation of mindfulness into caregiving tasks and daily life.
3	The skill of compassion and managing challenging behaviors	Identifying sources of support and self-care. Incorporation of compassion into caregiving tasks and daily life. Introduction to challenging behaviors.
4	The skill of self-compassion while caregiving	Integrating mindfulness and self-compassion with behavioral management skills.
5	Communication skills	Reframing challenging behaviors as a form of communication as the brain degenerates. Anticipating and problem-solving communication and behavior challenges.
6	Putting it all together	Program review and strategies for continued practice (skills practice; continuing to work on individual goals).

[a]MASC: Mindful and Self-Compassionate Care.

Phase 2 and 3 Treatment Fidelity

Adherence checklists will ensure all components of the intervention are delivered in compliance with the study protocol. Clinicians write session summaries to capture session content and any issues that arise regarding individual concerns and progress. Sessions will be recorded, and independent reviewers will review 20% of the sessions to assess for fidelity [22]. Feedback will be provided in weekly supervision, led by one of the study's principal investigators (A-MV). Participants who miss a session will be offered one-on-one make-up sessions. Home practice will be tracked through daily, 1-question yes or no surveys asking about whether they have engaged in the home practice that day sent by REDCap emails. These procedures follow the NIH (National Institutes of Health) Science of Behavior Change recommendations and have been used by the multiple principal investigators of this study in prior clinical trials [14].

Phase 2 and 3 Primary Outcomes

The primary outcomes for the open pilot (phase 2) and the RCT (phase 3) include feasibility of recruitment, assessments, and quantitative measures, credibility, accessibility, and fidelity (Table 2). Our secondary outcomes (Table 3) will explore indicators of the preliminary efficacy of the same quantitative measures. The feasibility of recruitment and retention will be assessed using proportions. Satisfaction and credibility will be assessed with proportions of scores over the midpoint of the Client Satisfaction and Credibility and Expectancy questionnaires [23,24].

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Table 2. Phase 2 and 3 primary outcome benchmark definitions.

Measure	Brief description
Feasibility of recruitment	Assessed by the proportion of caregivers who were eligible to enroll, proportion of caregivers recruited from each recruitment source, and the proportion of racial and ethnic minorities recruited and enrolled across the entire sample.
Feasibility of randomization	Assessed by the proportion of randomized caregivers that completed the posttest.
Feasibility of assessment measures	Assessed by the proportion of participants with less than 25% of their questionnaires missing.
Adherence to treatment	Assessed by the proportion of randomized caregivers that attended at least 4 of the 6 sessions for both the intervention (MASC[a]) and control group (HEP[b]).
Therapist fidelity	Assessed by therapist's ability to deliver the content of each session (through therapist-completed adherence checklists) and therapist fidelity (through cotherapist's review of recorded sessions).
Credibility and expectancy	Assessed with the Credibility and Expectancy Questionnaire (CEQ) [23] which captures participants' perceptions on whether treatment will work after learning about the study.
Satisfaction with the program	Assessed by the proportion of participants that score above the Client Satisfaction Questionnaire (CSQ-3) [24] midpoint which assesses caregivers' satisfactions with the intervention.
Patients' perception of improvement	Assessed by the proportion of caregivers that report improvement in stress, depression, anxiety, and well-being [25].
Adherence to home practice	Assessed by the proportion of caregivers that have completed more than 50% daily home practice exercises (assessed by REDCap[c]).

[a]MASC: Mindful and Self-Compassionate Care.

[b]HEP: Health Education Program.

[c]REDCap: Research Electronic Data Capture.

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Table 3. Phase 2 and 3 secondary outcome measures.

Measure	Administration time frame	Brief description
Symptoms of depression	Baseline, postintervention, and follow-up	The Center for Epidemiological Studies-Depression Scale (CES-D) [26] is a 20-item scale widely used with ADRD[a] caregivers to assess depression.
Mindfulness	Baseline, postintervention, and follow-up	The Applied Mindfulness Process Scale (AMPS) [27] is a 15-item scale that assesses caregivers' ability to apply mindfulness to everyday challenges.
Perceived stress	Baseline, postintervention, and follow-up	The Perceived Stress Scale (PSS-10) [28] assesses perceived stress using a 5-point Likert scale.
Symptoms of anxiety	Baseline, postintervention, and follow-up	The State Trait Anxiety Inventory (STAI) [29] form Y (20 items) assesses anxiety symptoms in response to stressful situations. State Trait Anxiety Inventory has been successfully used with ADRD caregivers.
Self-compassion	Baseline, postintervention, and follow-up	The Self-Compassion Scale-Short Form (SCS-SF) [30] has 12 items that assess self-kindness.
Compassion	Baseline, postintervention, and follow-up	The Compassion Scale (CS) [31] has 16 items assessing common humanity, kindness toward others and ability to understand the suffering or challenges of others.
Distress due to challenging behaviors	Baseline, postintervention, and follow-up	The Neuropsychiatric Inventory Caregiver Distress Scale (NPI-Q) [16] has 12 items assessing distress associated with behaviors of patient's suffering from dementia.
Caregiver self-efficacy	Baseline, postintervention, and follow-up	The Revised Scale for Caregiver Self-Efficacy (RSCSE) [32] (8 items) assesses domains of self-efficacy including obtaining respite, responding to disruptive patient behaviors, and controlling upsetting thoughts.
Well-being	Baseline, postintervention, and follow-up	The World Health Organization-Five Well-Being Index (WHO-5) [33] has 5 items assessing emotional well-being.
Loneliness	Baseline, postintervention, and follow-up	The University of California Los Angeles 3-item loneliness scale [34] assesses relational connectedness, social connectedness, and self-perceived isolation.
Social support	Baseline, postintervention, and follow-up	The Interpersonal Support Evaluation List short form (ISEL) [35] has 12 items assessing appraisal, belonging, and tangible social support.
Relationship quality	Baseline, postintervention, and follow-up	The Dyadic Relationship Scale (DRS) [36] has 11 items that assess negative and positive interactions between caregivers and their care recipient.

[a]ADRD: Alzheimer disease and related dementias.

Secondary outcomes include stress [28], depression [26], anxiety [29], and well-being [33] through the mechanistic targets of mindfulness [27], caregiver self-efficacy [32], social support [35], loneliness [34], compassion for self and others [30,31], behavioral symptom management [16], and relationship quality [36]. Participants will complete assessments within 1 week of starting the first session and will provide feedback at the end of session 6 and at 3 months. Study assessments are presented in Table 3. The self-reported measures and assessment domains align with the purpose of the study and with recommendations for feasibility trials. The measures are reliable and valid for dementia caregivers [37,38].

Phase 2 Data Analysis

The feasibility of recruitment and retention will be assessed using proportions defined in Table 2. Satisfaction and credibility will be assessed with proportions of scores over the midpoint of the Client Satisfaction [24] and Credibility and Expectancy [23] questionnaires. Qualitative data from exit interviews will be analyzed using procedures outlined in phase 1. Given the exploratory nature of this open pilot, we do not anticipate statistical significance [39]. Pre- and postchanges in intervention targets and outcomes will be analyzed using *t* tests and explore correlations between change scores in targets and outcomes in the pre- and post–follow-up surveys.

All outcomes will report 95% CIs consistent with recommendations for pilot trials [40]. Procedures, content, and measures will be revised based on quantitative and qualitative data.

Phase 2 Open Pilot Intervention Refinement

The MASC intervention will be refined based on overall findings of feasibility, acceptability, credibility, fidelity, preliminary efficacy outcomes, and 30-minute exit interviews from study participants.

Phase 3 Health Education Program

Phase 3 SOCIAL study will include a 6-session HEP comparator which will mimic the dose, format, and duration of MASC. The topics of each session will contain dementia-related educational information adapted from the National Alliance of Caregiving. HEP will include topics of (1) the stress of caregiving, (2) sleep

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hygiene, (3) physical activity as a dementia caregiver, (4) nutrition, (5) developing healthy eating habits, and (6) a review of program content and postprogram plans. HEP will not teach any of the mindfulness, self-compassion, and behavioral management skills that are hypothesized to be responsible for improvements in the mechanistic targets and through them, improvements in outcomes.

Phase 3 Randomization Strategy

A 2:1 MASC:HEP randomization will be prepared by an unmasked statistician using REDCap to create permuted blocks stratified by gender. To maintain blinding and masking, the programs will be labeled as SOCIAL 1 (MASC) and SOCIAL 2 (HEP). Both MASC and HEP groups will be run by an experienced clinical social worker trained in the intervention and the HEP and will work from updated facilitator manuals. The same social worker will run the intervention and comparison groups to control for nonspecific factors.

Phase 3 Analysis

The RCT will follow the same general analysis plan as the phase 2 open pilot with expansion to include the feasibility of randomization. Required benchmarks are depicted in Table 4. We will report benchmarks for both MASC and the HEP, consistent with recommendations for stage 1B trials [14]. We estimate between-group differences in change from baseline in intervention targets and outcomes to posttest and 3 months as proof of concept. Variance components and effect sizes will be estimated for each outcome [41]. The study will not be powered for stringent inferential testing of efficacy unless an overwhelming benefit is observed from the MASC program. The variance estimates from repeated-measures analysis of data on PSS-10 scores in tandem with the minimal clinically significant difference will guide the design and power calculations for the future hybrid efficacy-effectiveness trial [42]. We will compute the effect sizes of changes in these scores along with 95% CIs. Analyses will be repeated for all targets and outcomes. For example, proofs of concept or preliminary efficacy will be demonstrated if decrease in stress (PSS-10) in the intervention group from baseline to posttest is greater than in the educational control and the 95% CI includes the minimal clinically significant difference. We chose this benchmark because PSS-10 will be the primary outcome in the future R01. If the benchmark is not met, revisions will be required before conducting a fully powered RCT. The correlation of changes will be assessed in the mechanistic targets (mindfulness, caregiver self-efficacy, social support, loneliness, compassion, self-compassion, behavioral symptom management, and relationship quality) with changes in the outcomes (stress, depression, anxiety, and well-being). We hypothesize that the intervention (targeting mindfulness, self-efficacy, coping, social support, and interpersonal bonds) is a mechanism for effecting change in outcomes. Outcomes will be assessed post intervention and at 3 months.

Table 4. Phase 3 outcome benchmarks.

Measure	Brief description
Feasibility of recruitment	≥70% of caregivers who are eligible will enroll; ≥38% of caregivers are from racial and ethnic minorities.
Feasibility of randomization	≥70% of caregivers randomized will complete the posttest.
Feasibility of assessment measures	≥70% of caregivers will have less than 25% missing questionnaires.
Adherence to treatment	≥70% of randomized caregivers will attend at least 4 (out of 6) sessions for both MASC[a] and HEP[b].
Therapist fidelity	≥75% fidelity (checklists and audio recordings) for ≥70% caregivers.
Credibility and Expectancy Score	≥70% of caregivers with score over the scale midpoint.
Client Satisfaction Score	≥70% of caregivers with score over the scale midpoint.
Patients' perceptions of improvement	≥70% of caregivers report improvement in stress, depression, anxiety, and well-being.
Adherence to home practice	≥70% of caregivers will complete more than 50% daily home practice exercises (assessed through REDCap[c]).

[a]MASC: Mindful and Self-Compassionate Care.

[b]HEP: Health Education Program.

[c]REDCap: Research Electronic Data Capture.

Results

Caregiver Experiences

Phase 1 is complete. Findings from our rapid data analysis include confirmation from care providers that caregiving was rewarding but also difficult. Caregivers spoke of difficulties associated with the emotional toll, that were linked to (1) their emotions (sadness and grief) prompted by seeing their care recipient decline mentally and physically or (2) the impact of the difficulty in managing the rapidly changing emotions or moods of their care recipients. Caregivers affirmed the challenges of caregiving for a person with ADRD, including navigating behavioral symptoms and their impact on daily activities, such as bathing, taking medications, and going to doctors' appointments. Caregivers primarily cited using music and touch as ways they addressed challenging behaviors and expressed that they would like to learn more skills to use in the moment.

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Feedback on Skills

Many caregivers were unfamiliar with the concept of mindfulness and had not used it before. After being introduced to the concept of mindfulness and its benefits, they felt that mindfulness would help them manage caregiving stress. After being guided through a short mindfulness exercise they reported that this skill would be feasible to learn and implement. When caregivers were presented with the concept of self-compassion, many had misconceptions about it and its applicability to caregiving. When provided with information about the meaning of self-compassion, they were unsure if it was possible to be both self-compassionate and tend to their duties as a caregiver—but noted a willingness to try. Caregivers expressed interest in learning practical strategies to manage the neuropsychiatric symptoms of their care recipient and affirmed the rationale for using mindfulness and self-compassion to regulate their emotions.

Delivery and Format

Participants provided feedback on the delivery and format of the group offering suggestions to support their learning and engagement in the program content. Caregivers suggested that audio recordings would be beneficial for ensuring the active practice of the skills independently. They had mixed feelings about the assignment of homework to reinforce skills. The caregivers overwhelmingly expressed a desire for a 1-hour online format.

Discussion

Anticipated Findings

This paper describes the process of developing, optimizing, and testing a clinical intervention for stressed caregivers through psychoeducation and skills training in mindfulness, self-compassion, and management of behavioral symptoms of dementia. The aim of this intervention is to fill the gap in nonpharmacological interventions to meet the psychological and practical needs of stressed caregivers of persons with ADRD with challenging behaviors and personalities.

Findings from the rapid data analysis guided the development of the intervention and the group format to meet the needs expressed by dementia caregivers and prevent factors that could hinder caregivers' sustained participations. For example, MASC's development incorporated facilitators to caregiver's participation through the addition of an online delivery of program content, length, and duration with 6 sessions lasting for 60 minutes. Feedback on the program format guide indicated the need to offer the program online at flexible times that work best for most caregivers.

To date, most caregiver support groups are either unstructured or focused on strategies to address communication or behavioral symptom strategies [5]. Lack of attention to the psychological needs of the caregiver in many of these interventions may contribute to their modest ability to reduce caregiver stress and behavioral symptoms. Fostering self-regulation skills and strategies as outlined in the MASC intervention may augment caregivers' abilities to navigate the array of challenges faced in caring for someone with dementia and reduce their stress at the same time. Given the difficulties grasping mindfulness and self-compassion concepts, MASC directly addresses these barriers by delivering simple lay language and easy to engage exercises linked with ADRD caregiving challenges. Content specifically addresses common challenging behaviors and associated stressors for both the caregiver and the care recipient.

Conclusion

MASC's skills grounded in mindfulness, self-compassion, and behavioral management aim to address stress, depression, loneliness, and anxiety. Similarly, content was developed to improve well-being through caregiver self-efficacy, social support, mindfulness, self-compassion, compassion, and improved relationship quality. We hypothesize that the combination of evidence-based mindfulness and self-compassion skills with behavioral management skills within a multi-component program will increase intervention potency and efficiently support caregivers of people with ADRD. By reducing stress in caregivers of people with ADRD and evaluating this intervention with a rigorously designed control condition, the proposed work has the potential to improve caregivers' well-being and elucidate the mechanisms most relevant for improving caregiver outcomes.

Acknowledgments

We are grateful for the input of our study participants in guiding the development of the intervention. This research study is funded by the National Institute on Aging (1R01AG078204).

Data Availability

The data sets generated during and/or analyzed during this study are not publicly available until they have been deposited at the National Archive of Computerized Data on Aging, located within the Inter-university Consortium for Political and Social Research, and funded by the National Institute on Aging, but are available from the corresponding author on reasonable request.

Authors' Contributions

A-MV and CSR were responsible for the development, procurement of funding, conduct, and oversight of the Mindful and Self-Compassionate Care (MASC) program, and supervision of this manuscript completion. AT was responsible for recruitment and data analysis. DT assisted with facilitating the focus groups as well as completing the rapid qualitative analysis. SMS and

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AT conducted a qualitative analysis of the focus groups transcripts for phase 1. AO was responsible for leading and facilitating groups and for supporting the write-up of this manuscript. NG-S and SRA were responsible for supporting the write-up of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Institute on Aging (NIA) Special Emphasis Panel - Dementia Care (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 111 KB - resprot_v13i1e58356_app1.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
HEP: Health Education Program
NIH: National Institute of Health
MASC: Mindful and Self-Compassionate Care

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PSS: Perceived Stress Scale
RCT: randomized controlled trial
RDA: rapid data analysis
REDCap: Research Electronic Data Capture
SOCIAL: Supporting Our Caregivers in ADRD Learning

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Protocol

Intervention Development for Tailored Education for Aging and Cognitive Health (TEACH) for Dementia Prevention in Midlife Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: A total of 12 modifiable risk factors account for 40% of dementia cases globally, yet population adherence to health behaviors associated with these factors is low. Midlife is a critical window for dementia prevention, as brain pathology often begins to accumulate years or decades before the onset of symptoms. Although multidomain behavioral interventions have been efficacious in reducing the risk of cognitive decline, adherence is low. Intrapersonal factors, such as health beliefs, are known mediators of the relationship between knowledge and health behavior.

Objective: In keeping with stage I of the National Institutes of Health (NIH) Stage Model for Behavioral Intervention Development, this study will use mixed methods to (1) develop an enhanced health education intervention, including an explanatory method for communicating information about dementia risk and personal health beliefs, and (2) conduct a pilot randomized controlled trial (n=20 per intervention arm) over 8 weeks to assess the feasibility of delivering the enhanced intervention versus basic health education alone.

Methods: Phase 1 will involve focus groups and individual qualitative interviews. Focus groups will be analyzed using (1) a descriptive framework matrix analysis and (2) interpretive data review by the research team. Individual qualitative interviews will be coded using applied thematic analysis using a phenomenographic approach. Phase 2 will involve a pilot randomized controlled trial. Proximal outcomes (measured at baseline, 4 weeks, and 8 weeks) include the perceived threat of Alzheimer disease, dementia awareness, and self-efficacy.

Results: This project was funded in August 2022. Data collection began in 2023 and is projected to be completed in 2025.

Conclusions: Study findings will reveal the feasibility of delivering an 8-week multidomain health education intervention for primary prevention of dementia in midlife and will provide preliminary evidence of mechanisms of change.

Trial Registration: ClinicalTrials.gov NCT05599425; https://clinicaltrials.gov/study/NCT05599425

International Registered Report Identifier (IRRID): DERR1-10.2196/60395

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KEYWORDS

health behavior change; dementia prevention; Alzheimer disease; multidomain health intervention; intervention development; dementia

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Introduction

Background and Problem

By 2060, an estimated 13.8 million people in the United States will be living with Alzheimer disease (AD), the most common form of dementia, with health care and long-term care costs exceeding US $1 trillion annually [1]. While the US Food and Drug Administration (FDA) has approved the first disease-modifying therapies for AD, these are currently only indicated for patients in the symptomatic phases of the disease and remain costly. Primary prevention efforts are critical to achieving reductions in risk for dementia.

The 2020 report of the Lancet Commission on dementia prevention described 12 modifiable risk factors that account for 40% of dementia cases worldwide (including AD and related dementias [ADRD])—depressed mood, diabetes, early life education, excessive alcohol consumption, hearing impairment, hypertension, obesity, physical inactivity, smoking, social isolation, toxin exposure (particularly air pollution), and traumatic brain injury [2]. Many of these factors confer particular risk in midlife, when cerebrovascular changes, AD neuropathology, and related pathologies begin to accumulate in the brain [3]. Thus, targeting prevention efforts to adults in midlife or early late life is likely to confer maximal benefit [4].

Unfortunately, population adherence to health behaviors for dementia prevention is low among midlife adults. In 2014, only 28.4% of Americans aged 45 to 64 years met federal guidelines for aerobic exercise and 17.6% met guidelines for both aerobic and muscle-strengthening activity [5]. Adherence to healthy diet recommendations is also poor, with only 23.5% of Americans eating the recommended 5 servings of fruits and vegetables daily and more than 70% exceeding dietary guidelines for sodium, saturated fat, and added sugars [6]. Modification of these health behaviors through multidomain lifestyle intervention may promote positive cognitive and brain health outcomes. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a multidomain invention that included physical activity, nutritional guidance, cognitive training, and management of vascular risk factors [7]. After 2 years of intervention, participants in the active treatment condition showed a 25% larger improvement in composite cognitive measures and a lower risk of cognitive decline compared to the control condition [8]. This has led to large, multisite replication studies in the United States (Alzheimer's Association US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk [US POINTER] [9]) and worldwide, though results from these trials are not yet available. Similarly, the Systematic Multi-Domain Alzheimer Risk Reduction Trial (SMARRT) trial demonstrated that individual health coaching and nurse visits modestly improved cognition and health indices associated with dementia risk in older adults at elevated risk for dementia compared to a health education control [10].

Despite promising results of single- and multidomain intervention trials [11-13], adherence to these interventions remains problematic even with intensive individualized coaching. For example, only 19% of participants adhered to all components of the FINGER intervention (defined as attending at least 66% of sessions within each component) [14]. As expected, participants with higher adherence showed the greatest cognitive benefits of the intervention [15]. Adherence is likely to be even lower for less intensive interventions and over longer follow-up intervals. Thus, although research has identified critical components of health behavior interventions for dementia prevention, new approaches are needed to sustain health behavior change over years to decades.

Theoretical Approach

Numerous theoretical models describe mechanisms of health behavior change. One of the oldest is the Health Belief Model (HBM) [16], which states that personal health beliefs including perceived threat of disease, perceived benefits and barriers, and self-efficacy are mediators of health behavior change. These health beliefs, as well as cues to action, motivate health behavior change. The HBM has rarely been applied to dementia directly. In 1 recent study surveying Chinese adults about knowledge of dementia prevention and current health behaviors [17], perceived benefits, cues to action, and self-efficacy played a partial mediating role between knowledge and health behavior, supporting the use of the HBM in the context of dementia prevention.

We propose a working model in which individual health beliefs are moderated by constructs identified by the Science of Behavior Change Research Network [18], namely, one’s degree of dementia risk, future time perspective, reward sensitivity, and executive control moderate health beliefs, that determine the likelihood of making a health behavior change (Figure 1). By educating patients about HBM and these personal health belief factors, we hypothesize that there will be increased engagement in behaviors known to prevent dementia. The goal of this study is to use this theoretical orientation to develop a novel, personalized educational program for primary prevention of ADRD in midlife adults—Tailored Education for Aging and Cognitive Health (TEACH).

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Figure 1. Theoretical model adapted from the Health Belief Model. Constructs shown in green reflect domains assessed via empirically validated measures from the Science of Behavior Change Research Network. ADRD: Alzheimer disease and related dementias; TEACH: Tailored Education for Aging and Cognitive Health.

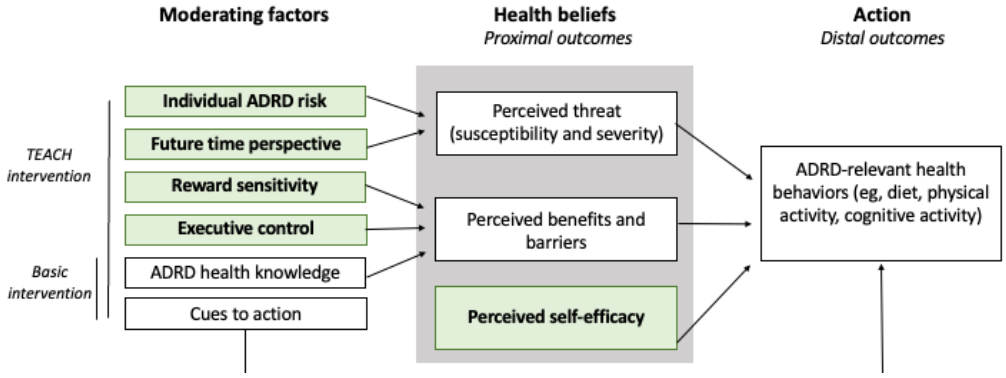

Study Objectives and Design Overview

As a National Institutes of Health (NIH) stage I behavioral intervention development study, the primary objectives are to establish feasibility and preliminary estimates of the efficacy of the TEACH intervention. The objectives of this study are (1) to use qualitative methods to develop an enhanced health education intervention, including an explanatory method for communicating information about personal health beliefs, and (2) to conduct a pilot randomized controlled trial (RCT; n=20 per intervention arm) over 8 weeks to assess the feasibility and preliminary efficacy of the enhanced health education intervention versus basic health education alone on ADRD risk perception, self-efficacy, and knowledge about dementia risk. To establish the feasibility of measurement for future distal outcomes, we will collect pre- and posttreatment body weight, blood pressure measurement, hemoglobin A_{1c} (HbA_{1c}) and lipid panel, and physical activity or sleep quality measured by a wearable activity monitor.

Methods

Study Setting and Recruitment

Project TEACH will take place at Rhode Island Hospital, a primary teaching hospital of the Alpert Medical School of Brown University in Providence, Rhode Island. Participants will be recruited from the Rhode Island Alzheimer's Disease Prevention Registry and the greater Rhode Island community. All study procedures have been reviewed and approved by the institutional review board (IRB) at Lifespan, Rhode Island Hospital's parent organization. All study-related information will be stored securely at the study site and in password-protected databases. The RCT is registered at ClinicalTrials.gov (NCT05599425). Any modifications to the protocol that could impact the conduct of the study, potential benefit to the participant, or participant safety profile will be agreed upon by all study investigators and approved by the Lifespan IRB prior to implementation. Administrative changes to the protocol, including minor corrections or clarifications, will be documented in a memorandum and in records of the protocol version.

Ethical Considerations

The study protocol has been approved by the Lifespan IRB 3 (IRB00000482) under protocol (1895972). All participants will be screened for inclusion and exclusion criteria by phone, and eligible participants will provide written, informed consent before participating in assessment and intervention procedures.

Participants

Inclusion criteria were adapted from the US POINTER study, a multidomain lifestyle intervention clinical trial for AD [9]. Inclusion criteria include (1) age 45-69 years, (2) normal cognition (Minnesota Cognitive Acuity scale >52 [19]), (3) proficiency in written and spoken English, and (4) at least 2 dementia risk factors that include BMI >24.9, systolic blood pressure >100 mm Hg, low-density lipoprotein (LDL) cholesterol >115 mg/dL, (4) HbA_{1c} >5.6%, (5) at least 1 apolipoprotein E ε4 allele, and first-degree relative with AD. Exclusion criteria include (1) a history of serious mental illness (ie, schizophrenia and bipolar disorder); (2) a history of major neurologic or neurodevelopmental disorder that affects cognitive performance (eg, stroke, epilepsy, and intellectual disability); (3) current alcohol or drug use disorder based on self-report; and (4) current enrollment in an AD prevention clinical trial.

Measures

Empirically validated measures were selected from the Science of Behavior Change Research Network to assess specific health belief constructs (Table 1). These measures were administered to a group of 177 adults aged 50 years and older to establish normative data to inform interpretation within our target population [20]. Modifiable dementia risk factors will be assessed using the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI), a self-report inventory that assesses dementia risk across multiple domains and has been validated in middle-aged and older adult cohorts [21]. All measures will be administered electronically via REDCap (Research Electronic Data Capture; Vanderbilt University) survey or computerized paradigm administered via e-Prime [22]. Data will be deidentified. Data integrity will be enforced through range checks, consistency checks, and referential data rules.

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Table 1. Health belief assessment.

Health belief domain and measure	Method	Description	Time
Perceived susceptibility			
Future Time Perspective Scale [23]	10-item self-report	Perception of the future as time-limited	5 minutes
ANU[a] Alzheimer's Disease Risk Index [21]	45-item self-report	AD[b] risk assessment including demographics, medical history, physical activity, cognitive activity, social engagement, diet, and toxic exposure	20 minutes
Perceived benefits and barriers			
Monetary Choice Task [24]	27-item self-report	Reward sensitivity or delay discounting; tendency to discount future rewards (ie, preference for small rewards received sooner vs larger rewards received later)	5 minutes
Deferment of Gratification Scale [25]	12-item self-report	Reward sensitivity; ability to defer gratification versus pursue immediate rewards	5 minutes
Consideration of Future Consequences Scale [26]	12-item self-report	Reward sensitivity; tendency to guide behavior based on short versus long-term consequences	5 minutes
Parametric Go-No Go Task [27]	Computer	Executive control; response inhibition	7 minutes
Attentional Network Test [28]	Computer	Executive control; conflict monitoring	20 minutes
Self-efficacy			
Generalized Self-Efficacy Scale [29]	10-item self-report	Belief in one's own abilities	5 minutes

[a]ANU: Australian National University.

[b]AD: Alzheimer disease.

Phase 1: Protocol Development

Objective

The first phase of the study is to develop an enhanced health education intervention using qualitative methods. The intervention adapts an existing 24-session program (2 sessions per week for 12 weeks) that was designed to educate participants about major modifiable risk factors for dementia. The basic intervention was originally designed for patients diagnosed with mild cognitive impairment or mild dementia. It is designed to increase knowledge of AD risk factors but does not include tailored content about personal health beliefs that affect health behaviors [19]. We have adapted the basic intervention for a cognitively unimpaired population in middle age or early late life by aligning the content with the modifiable dementia risk factors included in the 2020 Lancet Commission report [2] and ensuring recommendations are appropriate for the target age group rather than the older patients with mild cognitive impairment or dementia for whom the intervention was originally designed.

The TEACH intervention will include the same didactic content as the basic health education intervention. However, a major focus of the intervention will be a discussion of their health belief profiles and how their behavioral tendencies affect engagement in and maintenance of specific health behaviors. Sessions will include a discussion of perceived risk for ADRD, perceived benefits of behavior change to mitigate ADRD risk, troubleshooting barriers to action, making specific action plans, and implementing natural reward systems to bolster self-efficacy.

Focus Groups

Structure of the Focus Groups

We will first conduct focus groups (4-5 groups of 6-8 participants) to develop content, educational strategies, and delivery methods for communicating about modifiable ADRD risk factors and the HBM and personal health beliefs. During each focus group, we will present images conveying ADRD risk factors and the HBM and individual health belief factors that affect willingness to engage in behavior change. We will present a hypothetical person's profile across the ADRD risk spectrum and health belief measures described, rather than participants' personal health information.

We will use purposive sampling to include diverse participants based on sex, education, and race or ethnicity. Each group will take place in a private location at Rhode Island Hospital. Sessions will be digitally recorded and professionally transcribed. A research assistant will be present in the group to take notes and record nonverbal communication and participant interactions that could be missed by using the audio recording only. We plan to have 4-5 groups of 6-8 participants, but additional groups will be added as needed to reach data saturation (ie, when no new information emerges from the group discussion). The focus groups will last approximately 1 hour and will follow a discussion guide, including probes to explore and seek clarification. The groups will be attended by 2 study investigators; 1 will serve as the facilitator who will provide an overview of the group discussion and present questions and follow-up probes.

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Qualitative Analysis

Focus groups will be analyzed using (1) a descriptive framework matrix analysis and (2) interpretive data review by the research team [30]. A framework matrix is a process for qualitative data reduction commonly used in health services research [31,32]. This approach is particularly appropriate because we require an aggregated descriptive summary of participant responses to the images, risk factors, and health beliefs reviewed in the focus groups in order to design intervention material. One rater will chart the data into a matrix by summarizing participant comments on each of the major focus group questions. A meta-summary of all individual responses will also be included in the framework matrix. All summaries will be reviewed by the research team, who will dedicate several meetings to discussing and interpreting the data. Decisions and notes from the discussion will be tracked. This 2-step process includes descriptive and interpretive transdisciplinary review by 3 clinical psychologists and a medical anthropologist. Analysis will identify the clarity of messages, alternative ways of summarizing and displaying information, and preferences for explanatory images. This will be used to refine the explanatory framework for disclosing dementia risk and personalized health belief information. Images and language used to describe the health belief constructs will be developed from the thematic analysis of the focus groups. For example, we may visually present data in images or graphs that show the relative magnitude of personal health belief traits based on individuals' performance on the assessment measures.

Individual Qualitative Interviews

Structure of the Qualitative Interviews

We will test the explanatory framework for communicating about personal health beliefs by conducting qualitative interviews with 10-12 individuals. Participants will complete the health belief assessments. Their personalized data will be scored and presented to them in a 30-minute individual session. A trained facilitator will complete a semistructured interview with standardized questions and follow-up probes. This interview will use a phenomenographic approach, a well-accepted qualitative research method to study variations in how people learn and understand concepts in educational and health care settings [33,34]. Phenomenography examines 2 components of learning—referential and structural [35]. The referential aspect is the global meaning of the construct being conceptualized. The structural aspect is the specific combination of features (eg, images and words or phrases) being deployed.

Questions will be constructed to allow participants to reflect on their experience and will emphasize the relationship between the participant and the presented material (ie, phenomenon). The interview will include questions about acceptability (eg, "What is your reaction to your personalized health belief profile?"), appropriateness (eg, "Explain your understanding of the presented information"), and applicability ("How does this information apply to you and your health?").

Qualitative Analysis

Interviews will be coded using applied thematic analysis [36]. Interview transcripts will be coded by 2 team members (a clinical psychologist and medical anthropologist) who will together discuss interview passage interpretations and apply codes attending to both the referential and structural phenomenographic meaning. Agreed-upon codes will be entered into NVivo software (version 12; Lumivero) for analysis [37]. Descriptive data summaries will be written along with interpretive qualitative memos that identify phenomenographic meaning-making by participants as they respond to intervention content and their personalized data scores [30]. Summaries and memos will be used to identify the overall preference for the presentation of data about ADRD risk. Based on these analyses, intervention content and images will be modified to ensure participant understanding, generate relevant explanations, and simplify content as needed.

Risks of Disclosing Personal Health Information

There is potential for disclosure of ADRD risk factors and personal health beliefs to induce distress, though risk factor disclosure has previously been demonstrated to be safe and well-tolerated by most older adults [38-40]. To mitigate risk, personalized ADRD risk and health belief information will be presented by a licensed psychologist. Immediately following the health belief disclosure, participants will complete the Perceived Stress Scale (PSS) [41] and Patient Health Questionnaire-9 item (PHQ-9) [42]. Participants will receive a follow-up phone call to readminister these measures after 2 weeks.

If any participant scores >13 on the PSS (indicating moderate distress) or >4 on the PHQ-9 (indicating possible depression), the Columbia Suicide Severity Rating Scale (C-SSRS [43]) will be administered by a trained research assistant to assess suicidal ideation and intent. Should the participant endorse active suicidal ideation with a plan or intent to act, or endorse suicidal behavior (eg, a suicide or self-harm attempt or preparatory acts), the research assistant will immediately contact 1 of the study investigators (both licensed clinical psychologists) to conduct a more thorough risk assessment and make appropriate referrals for mental health treatment.

Phase 2: Pilot RCT

Objective

The second phase of the study is to conduct a pilot parallel-group, 2-arm RCT with 1:1 allocation to assess the feasibility and preliminary efficacy of the TEACH intervention compared to basic health education alone.

Approach

Procedures

A total of 40 participants will complete the baseline assessment of personal health belief factors described above (Table 1). Participants will be randomly assigned to the basic health education intervention or the TEACH intervention with a 1:1 allocation using a computer-generated randomization schedule. Due to the nature of the intervention, neither participants nor course instructors can be blinded to allocation. However, participants will be blind to study hypotheses and which intervention is considered active.

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Each intervention will be conducted via a Health Insurance Portability and Accountability Act (HIPAA)-compliant videoconference platform. The intervention will be delivered twice weekly for 8 weeks (see Table 2 for class topics). The intervention will begin within 2 weeks of baseline assessments. We will recruit at least 4 participants (3 in each treatment arm) into each group, with an intended group size of 6-8. Intervention content is designed to be modular, with each session focusing on a different modifiable ADRD risk factor.

Table 2. Intervention class topic list.

Session	Topic
1	Physical activity (aerobic)
2	Sleep
3	Nutrition
4	Substance use (alcohol, tobacco, and cannabis)
5	Physical activity (resistance training, and mind or body practice)
6	Cognitive activity
7	Diabetes
8	Social relationships
9	Hypertension
10	Stress management and positive thinking
11	Obesity
12	Depression, anxiety, and mental health
13	Traumatic brain injury
14	Medications and supplements (including medication side effects)
15	Hearing loss
16	Air pollution and toxin exposure

Prior to beginning the intervention, participants will meet individually with the instructor for their assigned condition for a 30-minute introductory session. For participants in the basic health education treatment arm, this will include reviewing information about their personal health history and orienting them to what to expect from classes. For participants in the TEACH intervention arm, this will include education about their personal dementia risk based on their health history and responses to the ANU-ADRI, as well as their health belief factors using materials developed in phase 1.

Attendance will be taken at each session and participants will be given a schedule to track their progress and to record homework or home practice. Participants who miss a session will be contacted by email or telephone to review the missed session policy and to be encouraged to attend. Posttreatment assessments will be completed within 2 weeks of the last class and will include a measure of treatment credibility and expectancy for each arm of the trial [44].

Treatment Fidelity and Adherence

Participants will be blind to which treatment arm they have been assigned. All intervention classes will be video recorded. These will be reviewed by a member of the study team for treatment adherence and protocol deviations using existing monitoring protocols from our prior study of the basic health education intervention [19]. Any protocol deviations will be directly addressed and remediated.

Outcomes

Feasibility Benchmarks

A primary goal of Phase 2 is to establish the feasibility of delivering the TEACH intervention. As part of the posttreatment assessment, participants will complete 7-point Likert scales assessing the understandability, satisfaction, and perceived relevance of course material. We have established the feasibility benchmarks and they are (1) attendance—participants attend at least 75% of classes (12 of 16), (2) understandability—80% of participants agree or strongly agree that the material was understandable, (3) satisfaction—80% of participants agree or strongly agree that the program was satisfying, and (4) relevance—80% of participants agree or strongly agree that the material was relevant to their personal situation.

Proximal Outcome Measures

The pilot RCT is designed to estimate the preliminary efficacy of the intervention on proximal outcome measures. These will be assessed at baseline, 4 weeks, and 8 weeks (study end point). Proximal outcome measures include (1) the Perceived Threat of AD Scale [45], a 7-item Likert-type scale assessing perceived likelihood, concern, and consequences of ADRD; (2) the Dementia Awareness Questionnaire [46], a measure of knowledge of modifiable ADRD risk factors and the Generalized Self-Efficacy Questionnaire [29], which measures self-beliefs to cope with demanding situations. The 10-item PSS and PHQ-9 will also be administered at these timepoints to minimize the risk of adverse events related to personal ADRD risk and health

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belief information disclosure. The procedures described will be used to ensure the safety of participants who endorse clinically significant distress or depressive symptoms.

Distal Outcome Measures

This pilot RCT is powered to detect changes in proximal outcome measures. We will also administer some measures pre- and posttreatment to establish the feasibility of assessment and they are (1) weight measurement; (2) blood pressure measurement; (3) venipuncture for HbA_{1c} and lipid panel (total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides); (4) 14-item Mediterranean Diet Assessment Tool [47]; (5) Community Healthy Activities Model Program for Seniors (CHAMPS) Activities Questionnaire for Older Adults [47]; and (6) 25-item Florida Cognitive Activities Scale [48]. Participants will also be provided a wearable activity monitor (Fitbit [Google]) to assess physical health (eg, steps per day and heart rate variability) and sleep quality. All distal outcome measures will be considered preliminary and used to inform the design of a future, fully-powered RCT.

Power and Data Analysis

We estimate attrition at 10% based on our previous study investigating the basic health education intervention. Power was derived based on 3 proximal outcome measures that are likely intercorrelated (assumed 0.5 correlation). Assuming 10% attrition, a sample size of 36 could detect a medium effect (d=0.5) with a power of 0.80 and α=.05.

All participants, regardless of adherence or attrition, will be included in the primary intention-to-treat analysis. Primary analyses will use generalized linear mixed models to compare pre- and posttreatment change in proximal outcome measures by treatment arm. We will use *t* tests to assess group differences in feasibility benchmarks (attendance, understandability, satisfaction, and relevance) by treatment arm. Secondary analyses will examine the relationship between treatment dose (defined as class attendance) and proximal outcome measures. Given that this is a stage I pilot study, all inferential statistical results will be considered preliminary and used to assess the feasibility of the TEACH intervention. Distal outcomes will not be formally analyzed but will be used to determine the feasibility of assessment for future studies.

Results

This project was funded in August 2022. Data collection is ongoing, with 26 individuals enrolled to participate in focus groups and 11 enrolled to complete individual interviews (phase 1) by the submission of this study in May 2024. Enrollment into the RCT (phase 2) is anticipated to begin in 2024, with completion of enrollment and data analysis anticipated in 2025.

Discussion

The goal of this study is to develop a personalized, multidomain behavioral intervention to promote long-term maintenance of health behaviors for primary prevention of ADRD in midlife and establish the feasibility of delivering this type of intervention. Despite a robust body of evidence describing modifiable health behaviors that could reduce the global dementia burden by 40% [2], multidomain behavioral interventions for the primary prevention of dementia have been hampered by poor adherence [14,15]. This study uses behavioral science to educate individuals about the intrapersonal factors that promote and maintain health behavior change (ie, understanding why we behave the way we do in addition to educating people about what behaviors are optimal). We hypothesize that this personalized approach will result in higher treatment adherence and greater efficacy of a multidomain health education intervention.

Very little research to date has used personalized intervention to promote health behavior change specifically for primary prevention of dementia. One of the challenges in dementia prevention is that individuals must maintain health-promoting behaviors like dietary changes and exercise for years to avert or delay an adverse outcome (dementia) that is perhaps decades away. Thus, effective interventions must focus on the maintenance of health behavior change over the long term. One recently completed trial, the SMARRT intervention, used motivational interviewing to assess participants' values and motivators to reduce Alzheimer risk and help them adopt specific, achievable risk-reduction steps [10,49]. Participants in the active intervention showed greater improvements in cognition, dementia risk factors, and quality of life. However, the SMARRT trial enrolled participants aged 70 to 89 years, whereas our intervention is designed to target midlife adults aged 40-69 years. Additionally, the TEACH intervention adopts the HBM and will specifically educate people about intrapersonal processes that may promote health behavior.

This stage I intervention development project aims to use a mixed methods approach to refine a multidomain behavioral health intervention for primary prevention of dementia in midlife and early late life (age 45-69 years). The first phase of the project will use qualitative methods, including focus groups and individual interviews, to develop the personalized health education intervention (TEACH). This will include the development of an explanatory method for communicating information about personal health beliefs that is perceived to be acceptable, appropriate, and applicable to participants. The second phase of the project includes a pilot RCT to examine the feasibility and preliminary efficacy of the TEACH intervention compared to basic health education on personal dementia risk perception, dementia knowledge, and self-efficacy. If successful, this study will contribute new knowledge about personalized health education for primary prevention of dementia and a framework for educating individuals about intrapersonal processes that may be barriers or facilitators of health behavior change. Results will be used to inform intervention development and design a fully powered RCT to determine the efficacy of the TEACH intervention versus basic health education alone.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

JDD and LEK conceived the study and are primary grant holders. GT provided expertise with health education for dementia prevention. RKR provided expertise with qualitative methods. All authors assisted with study design and implementation. All authors approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Social Psychology, Personality and Interpersonal Processes (SPIP) Study Section - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 100 KB - resprot_v13i1e60395_app1.pdf]

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Abbreviations

AD: Alzheimer disease
ADRD: Alzheimer disease and related dementias
ANU-ADRI: Australian National University Alzheimer's Disease Risk Index
CHAMPS: Community Healthy Activities Model Program for Seniors
C-SSRS: Columbia Suicide Severity Rating Scale
FDA: US Food and Drug Administration
FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
HbA1c: hemoglobin A1c
HBM: Health Belief Model
HDL: high-density lipoprotein
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LDL: low-density lipoprotein
NIH: National Institutes of Health
PHQ-9: Patient Health Questionnaire-9 item
PSS: Perceived Stress Scale
REDCap: Research Electronic Data Capture
SMARRT: Systematic Multi-Domain Alzheimer Risk Reduction Trial
TEACH: Tailored Education for Aging and Cognitive Health
US POINTER: Alzheimer's Association US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk

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Protocol

Structural Influences on Methamphetamine Use Among Black Sexual Minority Men (HISTORY Study): Protocol for a Longitudinal Cohort Study

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Abstract

Background: Sexual minority men are disproportionately affected by methamphetamine use, with recent studies suggesting an increase in use specifically among Black sexual minority men. Black sexual minority men face unique structural barriers to achieving optimal health. Given its harmful effects, and in light of existing health disparities, an increase in methamphetamine use among Black sexual minority men poses a significant public health concern.

Objective: The Health Impacts and Struggles to Overcome the Racial Discrimination of Yesterday (HISTORY) study is investigating the potential impacts of exposure to the census tract–level structural racism and discrimination (SRD) on methamphetamine use among Black sexual minority men in Atlanta, Georgia, and will identify intervention targets to improve prevention and treatment of methamphetamine use in this population.

Methods: This study uses a mixed methods and multilevel design over a 5-year period and incorporates participatory approaches. Individual-level quantitative data will be collected from a community-based cohort of Black sexual minority men (N=300) via periodic assessment surveys, ecological momentary assessments, and medical record abstractions. Census tract–level measures of SRD will be constructed using publicly available administrative data. Qualitative data collection will include longitudinal, repeated in-depth interviews with a subset (n=40) of study participants. Finally, using a participatory group model–building process, we will build on our qualitative and quantitative data to generate causal maps of SRD and methamphetamine use among Black sexual minority men, which in turn will be translated into actionable recommendations for structural intervention.

Results: Enrollment in the HISTORY study commenced in March 2023 and is anticipated to be completed by November 2024.

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Conclusions: The HISTORY study will serve as a crucial background upon which future structural interventions can be built, to mitigate the effects of methamphetamine use and SRD among Black sexual minority men.

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KEYWORDS

substance use; methamphetamine; social determinants; racism; discrimination; homonegativity; LGBT; mixed methods

Introduction

Background

Methamphetamine use is increasingly common in the United States. Among the total US population of individuals aged 12 years and older, 1% (or 2.7 million people) reported past-year methamphetamine use in 2022, 66.7% (or 1.8 million) of whom met the criteria for methamphetamine use disorder [1]. These represent the highest rates in an upward trend in past-year methamphetamine use and methamphetamine use disorder, according to the annual National Survey on Drug Use and Health [2]. Sexual minority men are disproportionately affected by methamphetamine use; most recent national surveillance data report rates of methamphetamine use up to 4 times higher among sexual minority men compared to their heterosexual counterparts [3]. Black sexual minority men had historically lower rates of methamphetamine use compared to their White counterparts [4-9]; however, emerging data suggest a changing trend. A 2021 study demonstrated an overall increase in past-year methamphetamine use among Black sexual minority men in New York City from 6.5% in 2004 to 11.3% in 2017, with a concomitant overall decrease in use among White sexual minority men from 17% to 6.2% over the same time frame [5]. A similar trend was demonstrated in Washington, District of Columbia, in 2017 [6], with additional supporting data from qualitative studies and lay publications [10-13].

Methamphetamine is a highly addictive synthetic stimulant drug [14,15] associated with adverse health consequences including, but not limited to, cardiovascular system dysfunction, neurotoxicity, dental decay, mental health comorbidities, polydrug use, fatal overdose, increased sexual risk, HIV and sexually transmitted infection transmission, and decreased health care (including HIV care) engagement [8,15-26]. Methamphetamine use is also associated with social harms including homelessness, food insecurity, exposure to violence, and criminal justice involvement [27-32]. Given the detrimental impacts of methamphetamine use alone, as well as its potential to exacerbate existing health inequities, increasing methamphetamine use among Black sexual minority men constitutes a major public health concern for which effective interventions are urgently needed but sorely lacking.

Research has primarily focused on individual-level determinants of methamphetamine use including social networking, incarceration history, and various forms of victimization (like intimate partner violence and childhood sexual abuse) [4,33-39]. Similarly, interventions have generally focused on individual behavioral change [40-44]. A few interventions have included cultural considerations for Black sexual minority men, focusing on intrapsychic processes and individual-level behavior change to impact methamphetamine use and sexual health [44,45]. While these are critically important, they have not fully addressed structural barriers that contribute to methamphetamine use or explore the intersecting social positions occupied by Black sexual minority men and the resultant synergistic manifestations of structural racism and discrimination (SRD) to which they are uniquely exposed, related to both racial and sexual minoritized status [46-48].

While HIV-related inequities are the most well-studied health concern impacting Black sexual minority men, studies have notably demonstrated that disparities in HIV incidence are not driven by differences in individual-level sexual risk behaviors but are driven in part by differential health care access and concentrated poverty resulting from SRD in the health, housing, and economic sectors [49-52]. While research on SRD is central to understanding the health of Black sexual minority men, such research remains sparse, particularly with respect to health outcomes beyond HIV and sexual health [53].

Study Setting and Historical Context

Atlanta, Georgia, often referred to as the “de facto capital of the South” [54], provides a unique combination of supportive and detrimental environmental features for Black sexual minority men. In the Southern United States, Atlanta has a substantial population of Black sexual minority men, due in part to the migration of Black sexual minority men seeking economic opportunity and freedom of sexual expression [55,56]. However, Atlanta remains impacted by the legacy of legal racial segregation and Jim Crow policies that followed the abolition of slavery [57,58]. In particular, Black sexual minority men in Atlanta remain vulnerable to multiple forms of SRD, including persistent housing discrimination, increased gentrification, residential segregation based on race or income, and structural homonegativity [10,56,59,60].

Risk Environment Framework and SRD

Prior exploratory qualitative work identified housing instability and inadequate access to health and social services as potential pathways through which various forms of SRD may increase the risk for methamphetamine use and its sequelae among Black sexual minority men in Atlanta, Georgia [10]. Grounded in the risk environment framework [61-65], we posit that 4 intersecting forms of SRD in the macro-level risk environment (housing discrimination; gentrification; racial and income residential segregation; and discriminatory lesbian, gay, bisexual, transgender [LGBT] community climate) influence the meso-level problems of housing instability and inadequate service access, ultimately leading to the health outcome of

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consequent methamphetamine use among Black sexual minority men (Figure 1).

Figure 1. Risk environment framework conceptual model. LGBT: lesbian, gay, bisexual, transgender.

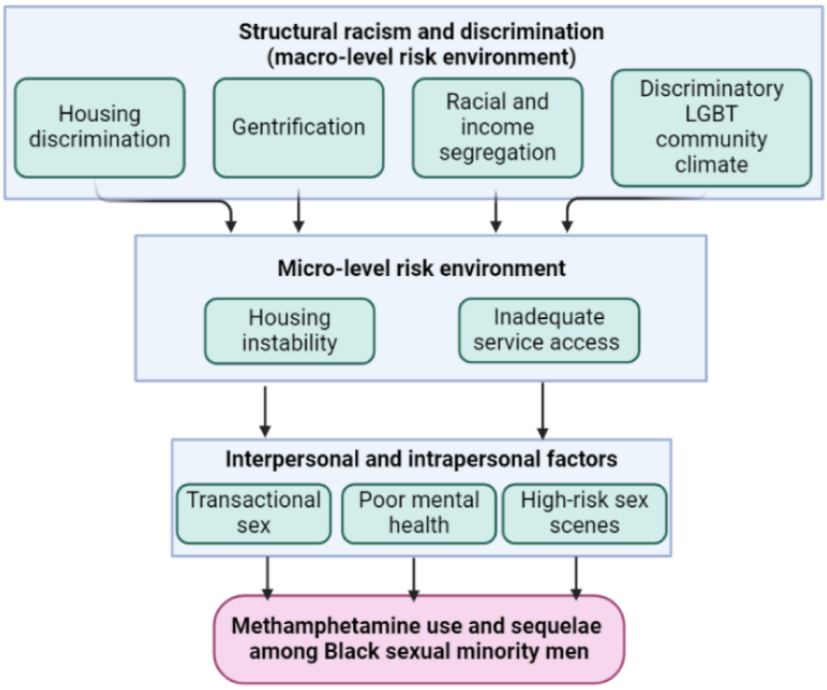

Study Objectives

The overall goals of this study are to (1) identify structural intervention targets to improve the prevention and treatment of methamphetamine use among Black sexual minority men, and (2) generate knowledge that will inform the design of multilevel, culturally congruent structural approaches for the prevention of methamphetamine use and its associated harms among Black sexual minority men. We seek to address these objectives through three specific aims: (1) to examine the impacts of census tract–level SRD measures on housing instability, service access, and methamphetamine use among Black sexual minority men in Atlanta; (2) to elicit narratives of methamphetamine use, housing instability, service access, and SRD; and (3) to examine systems of structural influence and develop qualitative causal maps linking various forms of SRD, service access, housing, and methamphetamine use. This paper will describe the methods that will be used to achieve these aims.

Methods

Study Overview and Design

Overview

This study uses a convergent, parallel mixed methods design set over a 5-year period (Figure 2), using multiple forms of qualitative and quantitative data via an integrative approach, whereby preliminary quantitative data will inform sampling and interview guide content for in-depth interviews (IDIs), and qualitative data will inform consideration of additional concepts and constructs to surveil via quantitative data collection. Qualitative data analysis will also inform the selection of covariates, potential modifiers, and interpretation of the impact of unmeasured confounders in quantitative analysis. Data sources for the 3 phases of the study (corresponding to our 3 study objectives) are described as follows.

Figure 2. Convergent parallel mixed methods study design. SRD: structural racism and discrimination.

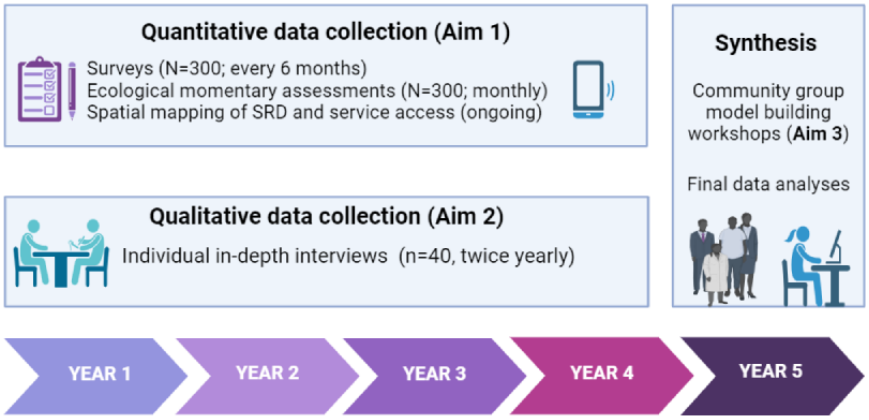

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Examining the Impacts of Census Tract–Level SRD Measures on Housing Instability, Service Access, and Methamphetamine Use Among Black Sexual Minority Men in Atlanta

We are in the process of recruiting a community-based cohort of Black sexual minority men in Atlanta (N=300), each of whom will be followed for 2 years. Data collection includes (1) self-administered, web-based electronic surveys every 6 months to measure methamphetamine use (alone or in combination with other drugs), residential location, housing instability, mental health indicators, and other covariates; (2) monthly brief assessments of supplementary methamphetamine use and location data via ecological momentary assessment (EMA) methods; (3) abstraction of HIV prevention and treatment-related clinical data from electronic medical records; and (4) census tract–level geolocation of four measures of SRD (housing discrimination, gentrification, racial and income segregation, discriminatory LGBT community climate) and measurement of spatial accessibility of Black sexual minority men to supportive services (substance use treatment and harm reduction services).

Participant Eligibility

Participants are being screened for eligibility via a self-administered or in-person, web-based survey. Eligibility criteria for enrollment are self-reported (1) Black race, including multiracial identities; (2) male gender identity; (3) identification as gay, bisexual, or any history of consensual sex with men; (4) aged 18-44 years; and (5) current residence within the 5-county Atlanta metropolitan area (Cobb, Clayton, DeKalb, Fulton, and Gwinnett counties).

Participant Recruitment

Overview

Specific strategies for Black sexual minority men recruitment include (1) community-based organization (CBO) recruitment, based on preexisting partnerships with CBOs located in various parts of the Atlanta metropolitan area; (2) web-based recruitment on apps and websites shown to be effective for recruitment of sexual minority men for research [66]; (3) venue-based recruitment, targeting events catering to sexual minority men around Atlanta; (4) clinic-based recruitment at the Grady Ponce De Leon Center, a large HIV clinic serving the entire Atlanta metropolitan area; and (5) research-based recruitment, using lists of patients recruited from previous studies who have expressed interest in being contacted for future studies. We cross-reference lists of potential participants obtained from the various sources mentioned earlier and eliminate duplicates to ensure that individuals are not contacted multiple times.

Eliciting Narratives of Methamphetamine Use, Housing Instability, Service Access, and SRD

Via a purposive sampling strategy based on baseline survey data, we are inviting 40 cohort participants to participate in a longitudinal substudy of serial qualitative IDIs conducted every 6-12 months. We will stratify recruitment for this substudy on methamphetamine use to result in 20 participants who use meth, and 20 participants who do not. We will also aim to present diverse perspectives with respect to age range, housing status, and exposure to our 4 SRD measures. We anticipate this sample size will be adequate for thematic saturation [67], breadth and depth of data, and allow for comparative analyses.

Group Model–Building Workshop and Development of Causal Maps

In the final year of the study, we will conduct a participatory group model–building workshop with up to 25 participants comprising a mix of four types of community stakeholders: (1) community activists and organizers; (2) CBO staff and leaders; (3) health care and social service providers; and (4) public health and local housing officials. In recruiting participants for this workshop, we will seek diverse representation in terms of age, occupation, experience, and educational background. The workshop will involve a participatory, iterative process that engages stakeholders in creating qualitative causal maps, also known as causal loop diagrams, of the interconnected relationships between SRD, mobility, and methamphetamine use.

Measures and Procedures

Outcomes and Covariates (Including Micro-Level Risk Environment)

Our primary outcome is methamphetamine use. Guided by the World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test [68], we will combine measures of periods (eg, ever, past year, past 30 days) and frequencies of methamphetamine use to create meth-related risk categories (low-, medium-, or high-risk use). Secondary outcomes will include other drug use, mental health comorbidities, and sexual risk behavior (eg, multiple sexual partners or condomless sex). The micro-level risk environment will be assessed through questions about housing status, perceived neighborhood characteristics, and residential location. Effect modifiers will include additional risk and resilience factors: transactional sex, use of geosocial networking apps, active coping (John Henryism [69]), social support, health care and social service use, and experiences with interpersonal discrimination. Details of these measures are shown in Table 1.

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Table 1. Individual-level measurement priorities (longitudinal electronic survey domains).

Outcome and construct	Measures
Primary outcome	
Methamphetamine use	NIDA[a]-modified ASSIST[b] [68], DAST[c] [70], additional structured questions (frequency and administration routes)
Secondary outcomes (sequelae of methamphetamine use)	
Other substance use (eg, cocaine, opioids)	NIDA-modified ASSIST, DAST, structured questions (ever, past 6 months, past 30-day, frequency, and administration routes)
Depression	Center for Epidemiologic Studies Depression Scale [71]
Anxiety	Generalized Anxiety Disorder-7 Scale [72]
Stress and trauma	PTSD[d] Checklist-Civilian [72]
General well-being	General Well-Being Scale [73]
HIV risk behavior	Items adapted from HIV Prevention Trials Networks 061 protocol
Covariates, mediators, moderators (micro-level risk environment, inter- or intrapersonal factors, and resilience factors)	
Housing stability (mediator)	Moves in last 6 months, items from Recession and Recovery Study [74]
Eviction	Series of items used by Desmond et al [75-77]
Housing conditions	Questions informed by the Department of Housing and Urban Development
Need for affordable housing	Questions informed by the Picture of Subsidized Households [78]
Interpersonal discrimination	Everyday discrimination scale [79] Internalized homonegativity inventory [80]
John Henryism	John Henryism Active Coping Scale [69]
Social support	Multidimensional scale of personal social support [81]
HIV prevention or care behaviors	HIV care continuum metrics [82], PrEP[e] use [83]
Mental health care use	Selected items from the National Survey of American Life [84]
Drug treatment use	Selected items from the National Survey of Drug Use and Health
Mode of transportation	Single item: What is the most common way that you get around the city?
Perceived neighborhood characteristics	Neighborhood social control scale, neighborhood social cohesion scale, and neighborhood violence scale [85]
Transactional sex	Items from Bauermeister et al [86] and Stevens et al [87]
Geosocial network app use	Items from Duncan et al [88]
Sociodemographics	
Age	Single item: What is your date of birth (baseline only)
Ethnicity	US Census categories (at baseline only)
Poverty	Material resources scale [89], income, source of income
Food insecurity	US Department of Agriculture measure of food insecurity [90]
Education	Single item: What is your highest level of completed education?
Rent or mortgage payment cost	Single item: What is your current monthly rent or mortgage payment?
Household size	Single item: How many other people live in your home?

[a]NIDA: National Institute on Drug Abuse.

[b]ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test.

[c]DAST: drug abuse screening test.

[d]PTSD: posttraumatic stress disorder.

[e]PrEP: preexposure prophylaxis.

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Census Tract–Level Measures of SRD

To measure the macro-level risk environment, we will develop census tract–level proxies for at least 4 constructs of SRD (housing discrimination, gentrification, residential racial and income segregation, and discriminatory LGBT community climate) and potential place-based mediators of the relationships of SRD to methamphetamine use (eg, spatial access to behavioral health and harm reduction services). To develop these measures or proxies, we will extract data from publicly available datasets that include but are not limited to the US Census Bureau's American Community Survey, US Department of Agriculture Labor Statistics, the Substance Abuse and Mental Health Services Administration, National Survey of Substance Abuse Treatment Services, and AIDSVu. Examples of census tract–level measures of consideration are shown in Table 2, with references to our own or others' prior research and descriptions of potential means of operationalization of these variables.

Table 2. Examples of potential census tract-level measures of structural racism and discrimination and service access.

Construct (exposure, mediator)	Potential data source(s)	Example(s) of prior use
Housing discrimination (exposure)	Housing Mortgage Disclosure Act database (Federal Reserve Board)	Gee [91], Linton et al [92]
Gentrification (exposure)	Geolytics Neighborhood Change Database; American Community Survey	Linton et al [93], Corrigan et al [60]
Residential racial segregation (exposure)	US Census American Community Survey	Linton et al [92], Krieger et al [94]
Residential racial and income segregation (exposure)	US Census American Community Survey	Krieger et al [94]
LGBT[a] community climate (exposure)	American Community Survey, USDA[b] Labor Statistics	Oswald et al [95]
Spatial access to substance abuse treatment programs (mediator)	SAMHSA[c] N-SSATS[d]	Cooper et al [62,96]
Spatial access to harm reduction services (mediator)	AIDSVu	Cooper et al [62,96]

[a]LGBT: lesbian, gay, bisexual, transgender.

[b]USDA: US Department of Agriculture.

[c]SAMHSA: Substance Abuse and Mental Health Services Administration.

[d]N-SSATS: National Survey of Substance Abuse Treatment Services.

EMA Surveys

EMA is a smartphone-based data collection tool that can actively capture substance use behaviors and social exposures while also passively collecting location data using GPS tracking [97,98]. Because we expect high participant mobility, we are using monthly EMA check-in surveys to track locations more frequently than semiannual web-based electronic surveys. The brief (approximately 5 minutes) EMA surveys collect data on methamphetamine use, provide opportunities to update contact information, and encourage retention in the study (through frequent, brief, and incentivized engagement). Surveys will be administered monthly over the 2-year duration of the study via a smartphone-based app that will be downloaded to the participants' phones at the baseline assessment. The EMA app is provided through LifeData, an established Health Insurance Portability and Accountability Act (HIPAA)–compliant software company.

Retention Plan

At enrollment, participants will fill out a locator form to document preferences with regard to modes of contact, as well as alternate contacts. To maintain participant engagement for the duration of the study, research staff will send out survey reminders, schedule interviews, troubleshoot participant challenges as appropriate, and mail care packages to participants periodically. We will also periodically check in with participants via an automated text messaging service. Monthly EMA surveys will serve as additional opportunities for engagement; if participants miss an EMA survey, we will contact them to determine individualized strategies to enhance follow-up. Given the criminalization of methamphetamine use, we will scan arrest records and mugshots if needed, as done in our previous research [99-101].

Qualitative Interviews

All IDI participants will complete a life-line interview facilitated by a semistructured guide at baseline and then IDIs every 6 months afterward. The life-line interview method is useful for collecting autobiographical data of participants across their life span [102]. Via the life-line interview method, we will obtain information about participants' insights and experiences with the following domains of our conceptual model (Figure 1): (1) the four forms of SRD; (2) housing; (3) service use and accessibility; (4) interpersonal and intrapersonal factors; and (5) methamphetamine use and sequelae. The baseline life-line interview will also explore participants' backgrounds, migration histories, and formative experiences. Follow-up IDIs will explore the same domains examined at baseline, using an iterative process guided by responses to the baseline life-line interview, as well as choropleth maps generated from preliminary data.

All interviews will be conducted by experienced study staff trained in qualitative techniques and cultural humility, many of

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whom are Black and sexual minority men. All IDIs will be digitally recorded, deidentified, and transcribed verbatim.

Group Model–Building Workshop

This approach is rooted in community-based system dynamics, a participatory method for involving community stakeholders in understanding and changing systems [103,104]. The design of the workshop will be led by the core modeling team, which will include a subset of members from the research team and community partners. Through a group model–building workshop, we will enable the co-creation of qualitative causal maps that facilitate the visualization of interconnected factors in a complex system and elicit stakeholders' insights and recommendations to implement systems-level change [104]. We will facilitate the workshop centered around the question, "What barriers and facilitators affect the prevention and treatment of methamphetamine use among Black sexual minority men in Atlanta?" Predetermined, adaptable exercises, or scripts used in previous research [105] will form the basis for workshop activities. Proposed scripts are depicted in Table 3; these will be refined and adapted with our partners and study team prior to implementation. We will use these workshop products to develop community- and research-derived recommendations for community-level action in Atlanta.

Table 3. Proposed workshop activities (adapted from Mui et al [105], which is published under Creative Commons Attribution 4.0 International License [106]).

Script	Functions	Activity details	Outputs
1. Setting the stage	Establish the purpose, processes, and ground rules of the workshop	Complete this activity in small groups, then altogether	List of guidelines and priorities
2. Behavior over time graphs	Generate multiple factors as potential drivers of methamphetamine use among Black sexual minority men	Work in pairs, then join a larger group discussion	Candidate factors for causal loop diagrams
3. Dots	Sort through possible choices and select the most important factors related to methamphetamine use among Black sexual minority men	Each participant places up to four sticker dots next to the graphs that they deem to be the highest priority	Prioritized factors
4. Connection circles	Introduce the concepts of causal connections and feedback relationships in a system	Factors identified in scripts (2) and (3) used to develop connection circles, first in small groups and then all together	One connection circle per group
5. Causal loop diagrams	Synthesize multiple perspectives of methamphetamine use and reveal new insights	Connections identified in script (4) expanded upon by including feedback loops and identification of sub-systems	One causal loop diagram per group
6. Action ideas	Identify and prioritize action ideas along a matrix of low-high feasibility and low-high impact	First in small groups, and then in larger group	Prioritized list of potential structural interventions

Throughout the workshop, research assistants will take notes on large flip charts to record concerns and recommendations voiced during the collaborative feedback process. Flipchart pages will become primary data sources. Workshops will also be audio recorded and transcribed for further review. Field notes (with both observational and interpretive elements) will be taken by research assistants observing the workshop sessions. At the end of the workshop, the study team will develop combined reflection notes based on these conversations.

Community-Engaged Research Approach

All of the data collection described above will be informed by extensive, ongoing community engagement. We collaborate closely with CBOs that work closely with Black sexual minority men who use or are at risk for using methamphetamine across the Atlanta metropolitan area. Our CBO partnerships enable us to recruit from geographically diverse areas of Atlanta and refer participants to those organizations for support services where indicated. We have also convened an active community advisory board (CAB) of Black sexual minority men, who were recruited primarily through referrals from community partners and selected with the goal of representing Black sexual minority men across a range of social backgrounds. Our CAB meets weekly: activities include reviewing instruments, developing recruitment strategies, and capacity building. Finally, we consult periodically with an expert advisory panel comprised of leading scholar activists in Atlanta's Black gay community; they provide input at each stage and will facilitate community dissemination of results and translation of our research to practice.

Data Analysis

Quantitative Data Analysis

Preliminary Analysis

Across each visit, we will assess the distribution of methamphetamine use, secondary outcomes, and demographic and behavioral characteristics among participants. We will also assess the distribution of participants across census tracts and summarize exposure to census tract–level measures of SRD and spatial access to services. Geolocations of participants across census tracts and census tract–level information will be mapped in ArcGIS (Esri) or R (R Foundation of Statistical Computing) to assess the spatial distribution of participants, census tract–level measures of SRD and other constructs, and access to health care services over time.

Based on the results of pilot spatial analyses of segregation and gentrification in Atlanta and other cities [60,93], we will explore the correlation among housing discrimination, residential segregation and gentrification, LGBT community climate, as well as other census tract–level and spatial access measures in our proposed analyses. If necessary, we will use data reduction

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techniques including principal component analysis, or we will construct an outcome-predicting census tract score [107], to characterize census tract–level exposures for each year of follow-up.

Multilevel and Longitudinal Analyses

We will use random effects models to estimate the longitudinal associations of census tract–level exposure to measures of SRD with methamphetamine use and secondary outcomes. We will adjust for time-dependent and time-independent covariates to describe changes in the population mean given changes in covariates, while accounting for within-census tract nonindependence of observations. Analyses will include random intercepts for census tracts. The distribution and link function of the model will be determined based on the preliminary investigation of the distributions of the measures of methamphetamine use and secondary outcomes. To establish temporality, census tract–level exposure to SRD and covariates will be lagged at least 1 visit, and the suitability of alternative lagging strategies will also be explored. Cross-classification will be used to address any movement of participants across census tracts over time.

Mediation Analyses

Adopting the counterfactual approach to mediation [108,109], we will decompose the total association of forms of SRD with methamphetamine use and secondary outcomes into natural direct and indirect effects via primary mediators, housing instability, and health care service access. We will follow the formal mediation analysis procedure by Lange et al [110], which allows for simultaneous examination of multiple mediators, flexible outcome, and mediator specification (binary and categorical; continuous scales and indices will be categorized based on quantiles). The intuition behind the approach is that the analysis is conducted on a weighted pseudopopulation, in which exposure-outcome and mediator-outcome relationships are unconfounded through the application of inverse probability weights. In this study, the hypothesized paths (informed by the literature; to be refined through empirical analysis) that we wish to test are shown in Figure 1.

Addressing Missing Data

Data for individual participants may be missing due to loss to follow-up or other reasons, and missingness, if not properly evaluated and addressed, may bias study findings. We will examine whether missingness is associated with observed data using standard methods [111-113]. If we do identify predictors of missingness (ie, data are clearly not missing completely at random), we will conduct a second set of outcome analyses using multiple imputations. As missing data may have different distributions, we will impute using chained equations [114]. We would produce multiple imputed datasets, run outcome analyses on all sets, and derive point and SE estimates for treatment effects and other parameters from the distribution of estimates from the outcome analyses with imputed datasets.

EMA Analysis

EMA data will supplement and validate location and substance use data from electronic surveys. This will enable us to take participant mobility between census tracks into consideration when conducting our analyses. Similarly, EMA substance use data that do not match electronic survey responses will prompt us to contact the respondent for clarification or conduct sensitivity analyses without these data. We will also conduct exploratory analyses focused on EMA data, to more fully describe mobility in the cohort and to further explore associations between location and methamphetamine use. Similar to other studies examining longitudinal EMA data [115,116], we will use time-varying effect modeling to examine associations between time-varying, location-related variables (eg, residing in gentrification hotspots) with time-varying methamphetamine use behaviors. Given this flexibility, and that we expect methamphetamine use to switch states (eg, recent use vs none) over time, momentary relationships between location and methamphetamine use can be captured and smoothed over time to produce effect estimates.

Qualitative Data Analysis

Qualitative data collection and analysis will be ongoing and iterative. After completion of baseline IDIs, the qualitative analysis team will read all transcripts and establish a codebook comprised of a list of preliminary a priori and emergent codes. Transcripts will be reread to create pattern codes that connect concepts. Analysts will then code all transcripts in pairs, meeting regularly to discuss findings and emerging themes. Analytic activities will be discussed as a team during dedicated meetings, and discrepancies in coding or interpretation will be resolved through consensus. Consistent patterns in meaning, concepts, and themes across interviews will be identified. Comparative analyses will clarify differences that may exist between subgroups of participants (eg, those in highly gentrified vs nongentrified areas). Findings will be reviewed regularly with expert advisory panel and CAB to strengthen representation and transactional validity. Emergent findings from IDIs at a given time may inform changes to guides used in subsequent IDIs.

Our team-based qualitative analysis approach will use an interpretive phenomenological framework [117] to establish experiential commonality among Black sexual minority men with regard to the phenomena of methamphetamine use, gentrification, discriminatory community climate, and housing instability while analyzing emerging patterns, themes, and categories in the data. This approach will allow us to learn about culturally circumscribed behaviors, language, and roles among Black sexual minority men, including individual and shared experiences and meanings related to methamphetamine use, housing, and the various forms of SRD. We will conduct comparative analyses between groups based on methamphetamine use (comparing those who use to those who do not), in order to explore both unique and shared experiences. We will also use aspects of deductive analysis through the creation of a priori codes representing macro- and micro-level constructs within our risk environment model (Figures 1 and 2), as informed by similar previous research (Tables 1 and 2).

Group Model–Building Workshop

The main product of the workshop will be a qualitative causal loop diagram (example shown in Figure 3) depicting the system of factors influencing the prevention and treatment of

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methamphetamine use among Black sexual minority men in Atlanta, and an accompanying prioritized list of action recommendations. Through an iterative process, the core modeling team will synthesize outputs from the workshop, using Vensim PLE, supplemented by written notes documenting workshop discussions. The core modeling team will also identify key systems insights, including themes and feedback loops. The causal loop diagram will be presented back to participants in a follow-up workshop as a form of member checking, along with preliminary findings from the surveys and interviews. Additional insights will be incorporated into a final causal loop diagram, which will be used to highlight potential points of structural intervention in the system with low-high feasibility and with high or low impact.

Figure 3. Sample causal loop diagram.

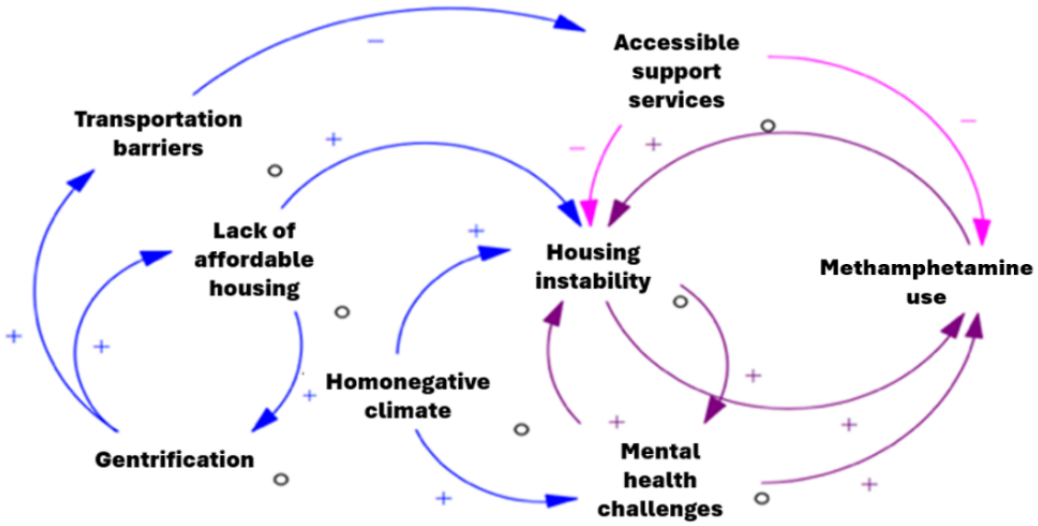

Ethical Considerations

Approval was obtained from the Emory Institutional Review Board (STUDY00004193) and the Grady Health System Research Oversight Committee, with an agreement for reliance from the Johns Hopkins University institutional review board. As appropriate, modifications or additions to the study will be reviewed as an addendum to the initial protocol. For the purposes of participant recruitment, the study was granted a partial waiver of HIPAA authorization. Written informed consent will be obtained from all participants at the time of enrollment. Participants will be asked for HIPAA authorization for medical record abstraction during the consent discussion at the time of enrollment. Consent forms will be administered in English. Participants will be compensated with US $50 for each completed REDCap (Research Electronic Data Capture; Vanderbilt University) survey and an additional US $10 for each completed monthly brief assessment. Those who participate in the qualitative substudy will receive an additional US $50 per qualitative interview. Participants who opt not to finish the study will be compensated for the surveys or interviews they completed. Data obtained from each participant will be stored confidentially and will only be accessible to authorized research personnel. A unique study identifier will be issued to each enrolled participant and linked to each data entry over the study duration. During future dissemination of study findings, all data will be presented in an aggregate and deidentified format.

Results

Participant recruitment and data collection commenced in March 2023. As of August 9, 2024, a total of 279 participants had been recruited, with 40 total IDIs completed. Recruitment and data collection are anticipated to be completed by November 2024, with a target of 300 total participants and 40 qualitative substudy participants.

Discussion

Expected Findings

The increasing rate of methamphetamine use among Black sexual minority men constitutes a growing manifestation of deep social and health inequities to which this group is uniquely susceptible. The HISTORY project uses an innovative approach aimed at describing this growing problem of methamphetamine use among Black sexual minority men in Atlanta in relation to the spatial distribution of measures of SRD. Upon completion of our aims, we will be able to define potential relationships between SRD and risk for methamphetamine use. Mediation analyses and our qualitative data will allow us to further explore mechanisms linking SRD variables with individual-level methamphetamine use.

Strengths and Limitations

This multilevel and participatory study, including its qualitative modeling approach, will leverage the experiential knowledge of various stakeholders, proving crucial in the design of specifically tailored interventions for the prevention and treatment of methamphetamine use disorder and its harmful effects among Black sexual minority men. The qualitative approach will further ensure meaningful community engagement by preserving the narratives of participants and key community informants. Despite these strengths, our study also has notable potential limitations. There is a potential for study enrollment

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to influence key socioeconomic variables, by providing support via the study team and community partner organizations, and also due to financial incentives for participation. There are also likely challenges in retaining the cohort longitudinally. Finally, there may be limited variability in the policy environment given the single-city design. However, given the important questions posed and answered, rigorous and transferable methodology, and wide-reaching results, we anticipate that this study will be used as a basis for further research on locoregional, national, and international scales.

Future Directions

Beyond what the study will offer for future scientific inquiry, we hope that it will inform the development of programs and policies to improve support for Black sexual minority men who might be at risk for meth-related harms. Future studies could also include quantitative simulation studies based on causal relationships found in our study and exploration of similar themes across different US cities and regions.

Dissemination Plan

The group model–building workshops will inherently serve as opportunities for dissemination of our qualitative and quantitative findings, as they will bring together community stakeholders to share findings and discuss implications and next steps. Further dissemination of our study results will include presentations at both scientific and program-focused conferences, publication of papers in academic journals, and community-focused presentations to share interim and final results.

Acknowledgments

The authors would like to acknowledge our community partner organizations, community advisory board, and most of all our current and future research participants.

This research is supported by the National Institutes of Health, under grant R01 DA056235 from the National Institute on Drug Abuse, and the Emory Center for AIDS Research (P30 AI050409).

Data Availability

The datasets generated and analyzed during this study will be available upon request from the corresponding author after the completion of our study aims.

Authors' Contributions

SCOO wrote the initial draft of the manuscript, SLL, DPH, CS, JCS, and SAH conceptualized the project, SLL and SAH acquired funding, SLL, BWW, YM, NDC, DPH, and SAH designed the methodology, ANJ, MB, MOR, SD, and KD are conducting participant interviews and maintaining the data. All authors reviewed drafts and approved the submitted final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Institute on Minority Health and Health Disparities Special Emphasis Panel - Impact of Structural Racism and Discrimination on Minority Health and Health Disparities - National Institute on Minority Health and Health Disparities (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 326 KB - resprot_v13i1e63761_app1.pdf]

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Abbreviations

CAB: community advisory board
CBO: community-based organization
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
HISTORY: Health Impacts and Struggles to Overcome the Racial Discrimination of Yesterday
IDI: in-depth interview
LGBT: lesbian, gay, bisexual, transgender

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REDCap: Research Electronic Data Capture
SRD: structural racism and discrimination

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Proposal

Neighborhoods, Networks, and HIV Care Among Men Who Have Sex With Men: Proposal for a Longitudinal Study

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Abstract

Background: The majority of people living with HIV in the United States are men who have sex with men (MSM), with race- and ethnicity-based disparities in HIV rates and care continuum. In order to uncover the neighborhood- and network-involved pathways that produce HIV care outcome disparities, systematic, theory-based investigation of the specific and intersecting neighborhood and social network characteristics that relate to the HIV care continuum must be engaged.

Objective: Using socioecological and intersectional conceptual frameworks, we aim to identify individual-, neighborhood-, and network-level characteristics associated with HIV care continuum outcomes (viral suppression, retention in care, and antiretroviral adherence) among MSM living with HIV in New York City.

Methods: In the longitudinal cohort study, we assess 3 neighborhoods of potential influence (residential, social, and health care access activity spaces) using Google Earth. We investigate the influence of neighborhood composition (eg, concentrated poverty and racial segregation) and four neighborhood-level characteristics domains: (1) community violence, physical disorder, and social disorganization (eg, crime rates and housing vacancy); (2) alcohol and other drug use; (3) social norms (eg, homophobia and HIV stigma); and (4) community resources (eg, social services and public transit access). We test theoretical pathways of influence, including stress or coping, stigma or resilience, and access to resources, across the different neighborhoods in which MSM live, socialize, and receive HIV care. At each visit, we locate each participant's reported activity spaces (ie, neighborhoods of potential influence) and collect individual-level data on relevant covariates (including perceptions of or exposure to neighborhoods) and social network inventory data on the composition, social support, and perceived social norms. The outcomes are HIV viral suppression, retention in care, and antiretroviral adherence. These data are combined with an existing, extensive geospatial database of relevant area characteristics. Spatial analysis and multilevel modeling are used to test the main theory-driven hypotheses and capture independent neighborhood-level and network-level effects and changes over time.

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Results: The study began enrollment in March 2019 and concluded visits in December 2023, with a total of 327 participants enrolled. The median age was 44.1 (SD 11.5) years. Almost all participants self-identified as cisgender men (n=313, 98.1%) and as gay, homosexual, or bisexual (n=301, 94.4%). Overall, 192 (60.1%) participants identified as non-Hispanic Black, and 81 (25.3%) identified as Hispanic. Most (n=201, 63%) reported at least occasional difficulty in meeting basic needs (eg, rent and food) in the past 6 months. The mean number of years living with HIV was 15.4 (SD 10.1).

Conclusions: This study will have direct implications for the design of multilevel interventions, addressing factors at the neighborhood, network, and individual levels. Results may inform urban planning and program design to improve HIV care outcomes for MSM, particularly for Black and Latino MSM living in urban areas.

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KEYWORDS

neighborhoods; social networks; HIV care outcomes; men who have sex with men; living with HIV; activity spaces

Introduction

In order to successfully implement treatment, as well as prevention, as a national strategy to end the HIV epidemic in the United States, it is crucial to address and bridge gaps in the HIV care continuum. The vast majority of people living with HIV in the United States are men who have sex with men (MSM). Among MSM, there are marked race- and ethnicity-based disparities in HIV infection rates and engagement and retention in HIV care. Compared with White MSM, Black and Hispanic or Latino (henceforth, Latino) MSM living with HIV are less likely to be on antiretroviral therapy (ART), adhere to ART, and achieve viral suppression [1-12]. Despite the long-standing focus on individual-level drivers, disparities in HIV acquisition and care engagement and retention among Black and Latino MSM are influenced by factors that are often beyond the individual such as the social determinants of health (SDH) [13]. The SDH can shape environments and behaviors that increase vulnerability to HIV acquisition and negatively affect HIV outcomes (eg, viral suppression, morbidity, and mortality rates). Yet the role of the SDH on HIV outcomes is not widely studied; thus, the mechanisms of action are not well understood.

Research on neighborhood factors and the care continuum suggests that poverty and racial segregation, as well as access to transit and distance to pharmacies and medical care, are associated with HIV care–related outcomes [14-19]. Similarly, social network-level factors, such as high levels of social support and HIV serostatus disclosure to social network members, are associated with improved HIV care outcomes [15,20-25]. Network and neighborhood characteristics are reciprocally related, with age composition, concentrated poverty, and racial segregation differentially fostering advantages and disadvantages for networks and residents alongside individual-level characteristics, such as socioeconomic status [26-28]. Still, additional research is needed to elucidate the pathways through which networks and neighborhoods foster racial and ethnic disparities in HIV care outcomes. The results of such analyses will provide an empirical basis for interventions and policies to fill gaps in the care continuum among Black and Latino MSM. To reach that goal, a systematic, theory-based investigation of the specific and intersecting neighborhood and network characteristics that relate to retention in care, ART adherence, and viral suppression must be used.

In this longitudinal study, which was recently completed with data analysis ongoing, we enrolled MSM living with HIV in New York City to complete study visits every 6 months, up to either 12 (post–COVID-19 cohort) or 36 (pre–COVID-19 cohort) months, to determine whether and how neighborhood and network characteristics influence their HIV care. Using socioecological and intersectional stigma and discrimination conceptual frameworks, we aim to examine neighborhood- and network-level characteristics that influence different aspects of the HIV care continuum among MSM living with HIV in New York City in a longitudinal study. We focus on 3 reported activity spaces (ie, potential neighborhoods of influence)—where MSM reside (home neighborhood), where they socialize and spend the most time (social neighborhood), and where they access their HIV medical care (health facility access neighborhood). We investigate the influence of four neighborhood-level characteristic domains: (1) community violence, physical disorder, and social disorganization (eg, interpersonal crime rates, concentrated poverty, and racial segregation); (2) neighborhood alcohol and other drug (AOD) use-associated factors (eg, alcohol outlets); (3) neighborhood-level social norms (eg, homophobia, HIV stigma, racial discrimination, and health norms); and (4) community resources (eg, HIV prevention services, social services, public transit access, and greenspace) and how these play out in the different neighborhoods in which MSM live, socialize, and receive HIV care.

Methods

Study Design

The Neighborhoods, Networks and HIV Care among Men Who Have Sex with Men (NNHIV) study is a longitudinal cohort study that examines neighborhood and social network factors that influence HIV care outcomes (retention in care, ART adherence, and viral suppression) using spatial analysis and multilevel modeling among MSM living with HIV in New York City. The study investigates the influence of neighborhood composition and 4 neighborhood-level domains, testing theoretical pathways of influence across the different

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neighborhoods in which MSM live, socialize, and receive HIV care.

Ethical Considerations

This study has been reviewed and approved by the New York Blood Center institutional review board (1066143). Written informed consent was obtained for participants 18 years of age and older who took part in the longitudinal study; an assent process was in place for any participants aged 16-17 years along with the use of a minor advocate. Participants received US $100 for their time and travel at the baseline visit and at each follow-up visit.

Eligibility Criteria

Eligibility criteria included (1) reporting male sex at birth, (2) self-report being HIV-positive (including being newly diagnosed with acute HIV infection), (3) engaging in anal sex with a man in the past 6 months, (4) at least 16 years of age, (5) reside within the 5 New York City boroughs, (6) able to read and respond in English, and (7) provide written informed consent (or assent if between 16 and 18 years of age, not inclusive of 18 years). Only cisgender men were included in this study. We excluded other populations, including cisgender and transgender women, because the study specifically seeks to understand the influence of neighborhoods and networks on HIV care outcomes among MSM living with HIV, and therefore, would not be optimally designed to capture the unique needs and barriers impacting women.

Sample Size

Sample size, power, and effect size considerations focused on longitudinal logistic regression models with neighborhood-, network-, and individual-level variables included as covariates. We aimed to enroll at least 40% who self-identify as Black, non-Hispanic and 30% who self-identify as Hispanic or Latino. Effect size calculations were performed assuming a minimum of 40% (n=220) of Black, non-Hispanic MSM and 30% (n=165) Latino MSM. Fixing type I error rate at 0.05, a sample size of 550 MSM, within-person correlation of 0.5, statistical power of at least 80%, and 10% attrition (loss to follow-up), minimum effect sizes (in terms of odds ratios) for detecting any difference in neighborhood and network effects on HIV care outcomes over the 5-visit, 24-month period range from 1.14 to 1.23. The proposed sample size of 550 MSM was later modified to 327 given the challenges of recruitment experienced during the COVID-19 pandemic.

Recruitment

We enrolled a total of 327 MSM. Initially, convenience sampling for recruitment was used to recruit participants, which included in-person recruitment at venues including bars clubs, gay pride events, and HIV clinics and service organizations, internet-based ad placements (eg, Craigslist [Craigslist Inc], geospatial dating applications such as Grindr [Grindr Inc]), and referrals from enrolled participants (maximum 3 referrals per participant). Later, the recruitment strategy was revised to use a modified, venue-based, time-space sampling methodology, to ensure a diverse sample to increase generalizability. For in-person and internet-based recruitment, the sampling frame of venues included a range of neighborhoods across the 5 New York City boroughs (from traditionally considered gay enclaves to those with a less visible gay presence, from places where known HIV-infected individuals frequent to lesser-known areas) and a range of venues within neighborhoods, such as bars, clubs, HIV clinics and service organizations, gay pride events, and street locations. Each month, a sample of 8 to 16 locations and day-time periods were randomly selected.

Participants who enrolled and completed a study visit were provided with referral cards (either in person, via email, or text) in which they could refer their friends to the study, a maximum 3 referrals for US $10 for each referral who successfully screened for the study and enrolled into the study (maximum US $30 for total 3 referrals); this referral system was later amended with a limit of 1 referral per participant to reduce referral bias. For internet and mobile app–based recruitment, banner ads were placed on select websites and social media apps, including Facebook (Meta Platforms), Craigslist, Instagram (Meta Platforms), and Grindr.

Participants were asked to complete a brief internet-based eligibility screener if they indicated interest in participating in the study. Potentially eligible (based on the results of the screener) participants were asked to provide contact information to schedule their study visit. At the time their study visit appointment was scheduled, the participant was asked to bring in a copy of their prior HIV diagnosis report to the visit, if available.

Study enrollment began in March 2019 and was paused in March 2020 with an enrollment of 213 participants prior to the COVID-19 pandemic lockdown in New York City (henceforth “pre-lockdown cohort”). As a result, recruitment and enrollment into the study was paused from March 2020 to August 2021. Follow-up visits for the 213 participants in the pre-lockdown cohort used a hybrid visit model initially during the beginning of the pandemic (remote and in-person procedures), followed by a transition back to all in-person visits; follow-up visits were extended from month 24 to month 36 for a longer follow-up period for the pre-lockdown cohort. The study reopened for enrollment in August 2021 with 114 participants enrolled (“post-lockdown cohort”) before enrollment finally closed in November 2022. The post-lockdown cohort participants were followed to month 12, with the last visits completed in December 2023. A total of 327 participants enrolled in the longitudinal study.

Study Visit Procedures

Baseline Visit Study Procedures

Study visits took place at our research site in Manhattan. After written informed consent (assent for those aged 16-17 years), participants underwent a rapid HIV antibody test (Orasure Oraquick ADVANCE Rapid HIV-1/2 Antibody) to confirm their self-reported HIV status if they did not bring a copy of their prior HIV diagnosis report. Participants were also asked to bring their ART medications for a pill count by staff and to sign a medical release form, with medical provider office visit notes obtained to confirm attendance and missed visits. They also had blood collection, which was sent to a local laboratory for HIV viral load and CD4 T lymphocyte (CD4 T cell) count

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testing. Test results were provided to participants, and referrals for HIV medical care and risk reduction counseling were provided and documented, as needed. The study visit ended for those who did not provide an HIV status report or whose HIV status was not confirmed.

Participants were then asked to identify their home, social, and health facility access neighborhoods by a trained research counselor using a neighborhood locator questionnaire and a desktop version of Google Earth. First, the interviewer asked for the name of their home neighborhood based on a drop-down menu of all 343 New York City neighborhoods. The interviewer then assisted participants in using Google Earth to "drop a pin" at the closest intersection near their home (home neighborhood), with the latitude and longitude coordinates of the pin drop recorded. Data on the perceived activity spaces (geographical neighborhoods) were collected with the question "When you think about your home neighborhood, what area do you usually think of?" with response categories "the block you live on, the area within (5 blocks/10 blocks/larger than 10 blocks) around the place you live." This process was repeated for the neighborhood where they most often hang out or spend the most time (social neighborhood), and where they most often went for their HIV medical care in the prior 6 months, as well as the pharmacy where they get your HIV medications filled in the last 6 months (health facility access neighborhoods).

Participants then completed an egocentric social network inventory (SNI) which provides network-level covariate data. The inventory was administered by a trained research counselor, who entered participant responses into a computer-based program (EgoWeb 2.0 for Windows). For the social network inventory, participants were asked to name persons, using a name generator, whom they could rely on for support in the domains of (1) companionship—who do you get together with to spend time talking, relaxing, or hanging out with?; (2) confidant—who do you talk to about very personal and private things?; (3) financial—who would you ask to lend you US $100 if you needed it?; (4) housing—who would provide you with housing or a place to stay a few days or more if you needed it?; (5) medical—who would go to a medical appointment, such as to an HIV provider or mental health provider, with you?; and (6) medication adherence—who encourages you to take your HIV medications regularly or who you could talk to about problems with taking your HIV medications? In order to construct a comprehensive network composition of the participants, there were no restrictions on the number of network members named. The attributes that were asked about each social network member are (1) demographics (eg, age, gender, and race or ethnicity); (2) social member relationship type (sex partner, friend, family member, coworker, etc); (3) HIV status and HIV serostatus disclosure; (4) home borough and proximity (live within 20 blocks of ego); (5) communication, including duration of relationship, frequency and content of communication, distance, conflicts, and support; (6) perceived behavioral and attitudinal norms including norms for AOD use, ART adherence, medical care follow-up, HIV serostatus disclosure, and medical mistrust; (7) whether ART drugs are shared or sold to or bought from network member; and (8) whether the person knows other members of the social network. In addition, the participants provided information about social support from each named social network member, adapted from the Inventory of Socially Supportive Behaviors [29], consisting of 19 items grouped into 3 sub-domains to assess cognitive guidance (9 items, eg, [network member] suggested some action that you should take), emotional support (5 items, eg, [network member] expressed interest and concern in your well-being), and tangible assistance (4 items, eg, [network member] gave you over US $50).

Next, participants completed the computer-assisted survey instrument (CASI) questionnaire, with the first part of the CASI involving ART use and pill count completed with study staff and then the rest of the CASI completed alone in private with staff assisting as needed. The CASI included measures that tap into common (eg, depression, anxiety, and substance use perceived patient-provider interaction) and network and neighborhood-level factors that may also be related to HIV care outcomes (eg, perceived racism in health care, homophobia and HIV stigma, empowerment, and coping, racial or ethnic and gay community attachment and acculturation; Table 1).

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Table 1. Independent variables.

Measure	Variables (measures)
Sociodemographics	
Demographics	Age, socioeconomic status (SES; income, education, and employment housing or food insecurity), housing status, public assistance, place of birth, primary and secondary languages, marital or live-in status, current living situation, and arrest or incarceration history
Health status or health care	
Medical history	Year of HIV diagnosis, transmission risk, Centers for Disease Control and Prevention (CDC) stage of HIV disease, non-HIV medical comorbidities, ART[a] adherence self-efficacy (refers to a person's confidence to carry out behaviors related to adhering to treatment plans, HIV Treatment Adherence Self-Efficacy Scale [HIV-ASES] [30]), adherence motivation [31], perception of quality of HIV care [32], health literacy [33,34]. Availability of and access to ART adherence support, HIV care coordination or medical case management, and outreach programs with health care facility or provider [35,36], availability of and access to pillboxes or reminders or calendars from pharmacy or HIV medical provider [37]. History of diversion of ART drugs, and if so, in which neighborhoods [38-40]. Medical mistrust based on the HIV Conspiracy Beliefs Scale [41,42]
Health care and perceived racism in health care	Health insurance coverage and type of care, usual place of care, access to HIV care [43], number and type of HIV medical providers, reasons for change in providers, type of HIV medical care setting (academic, clinic, community-based organization, etc), and access to and usual pharmacy (retail vs independent vs mail order). Perceived racist treatment from health care providers (doctors' offices and hospitals): 4-item instrument [44,45]
Perceived patient-provider interaction	Perceived quality of patient-provider interaction is based on 15 items from reactions assessments on the following domains: perceived quality of information, perceived level of difficulties of communication, and perceived affection and respect [46,47]
Sexual history	
Sexual behaviors	Number of male, female, and transgender partners in the last 6 months, partner type (primary, casual, etc), partner concurrency, frequency of vaginal, anal sex with, or without condoms and with or without alcohol and other drug use in the last 6 months, HIV serostatus of partner, and HIV serostatus disclosure to or by partner
Substance use	
Alcohol and drug use	Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [48], adapted for 6 months intervals
Psychological and psychosocial	
Psychological distress and depression	Depression: Patient Health Questionnaire (PHQ-9) [49], anxiety: Generalized Anxiety Disorder (GAD-7), how often in last 30 days they felt nervous, restless or fidgety, worthless [50], occurrence of traumatic life events and post-traumatic stress disorder [51], and stressful life events in last 6 months [50]
Racial discrimination and stigma	Social stress and social discrimination (every day unfair treatment) [50], schedule of racist events: an 18-item scale that measures subjective experiences of racism across multiple domains (employment, education, housing, etc) [52]
Homophobia and HIV stigma	Experiences of homophobia: scale capturing experiences with homophobia as children and adults [53]; Internalized homophobia scale [54] based on (1) public identification about being gay, (2) stigma associated with being considered unattractive in the gay world and stigma associated with being gay outside the gay world, (3) social comfort with other gay men, and (4) moral and religious acceptability of being gay. Internalized HIV stigma [55], anticipated HIV stigma from friends or family, and neighbors or community and health care workers [56]
Empowerment	Adaptation of Rogers and colleagues' scale [57] assessing empowerment among mental health consumers
Fatalism	External locus of control of health (God Locus of Health Control Scale (GLHC) scale) [58], 6-item scale that measures belief that God is in control of health and health conditions (eg, "God is directly responsible for my HIV getting better or worse")
Machismo	Traditional Machismo and Caballerismo Scale [59,60]
Coping	Brief Coping Orientation to Problems Experienced Inventory (brief-COPE) [61]: 28-item measure of positive and negative (avoidant) coping responses to life problems
Racial or ethnic and gay community attachment and acculturation	Multigroup Ethnic identity Scale: 21-item scale that measures 4 sub-domains: positive ethnic attitudes and sense of belonging, ethnic identity of achievement, ethnic behaviors and practices, and other-group orientation 5-item scale assessing attachment to "a gay community" [62]; 12-item scale assessing attachment to the gay community in NYC[b] [63]; 5-item scale assessing attachment to "a gay community" [62]; 12-item scale assessing attachment to the gay community in NYC [63]; and acculturation [64]

[a]ART: antiretroviral therapy.

[b]NYC: New York City.

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Follow-Up Study Visit Procedures

Every 6 months for up to 12 months (post–COVID-19 lockdown cohort, after August 2021) or 36 months (pre–COVID-19 lockdown cohort with participants enrolled prior to the onset of the COVID-19 pandemic in New York City in March 2020, which caused the city to go on pause or lockdown), participants completed the neighborhood locator questionnaire using Google Earth, SNI, and CASI questionnaire similar to those completed at the baseline visit; they underwent CD4 T cell and HIV viral load testing that were sent to a local laboratory. To assess network turnover, the SNI collected information on any new social network members from the prior 6 months and on any persons named previously who were no longer part of the networks. Medical records review and pill count were performed. Participants were reimbursed US $100 at each follow-up visit.

If participants were unable to come to the study site for their follow-up visit (for various reasons, including during lockdown in New York City during the COVID-19 pandemic), they were provided with the option of completing part of the follow-up visit remotely. For this remote visit, they were contacted by staff by secure videoconference or phone and completed surveys remotely on a computer via secure links. Participants then made an appointment with study staff to come into the site in person within 2 weeks for HIV viral load and CD4 T cell count testing.

Study Retention

At the baseline visit, extensive locator information was obtained using a locator form, including the participant's address and phone number. We also collected names, telephone numbers, and addresses of at least 2 secondary contacts, with an emphasis on stable relatives both within and outside of New York City, which allowed us to maintain contact with residentially mobile or marginally housed individuals. We asked the participant for specific instructions on how to leave messages to protect confidentiality. Retention efforts for the longitudinal study included reminders in between study visits, use of contacts, telephone reminders prior to follow-up visits, texts, and emails. If a participant missed a visit, the retention protocol was initiated by study staff, which included letters sent to participants' homes and reaching out to the listed secondary contacts on the locator form.

Statistical Analysis

Measures

The primary biological outcome is viral suppression (HIV viral load <20 copies per mL based on testing). Secondary outcome measures include retention in care (ie, >1 visit with an HIV medical provider in the last year) and retention in continuous care (ie, >2 visits at least 3 months apart with an HIV medical provider in the last year) as reported by CASI and confirmed by medical records review. ART adherence is based on the AIDS Clinical Trials Group (ACTG) [31] 4-question adherence instrument as reported by CASI and confirmed by pill count. Participants are categorized as adherent if they report taking ≥85% of the dispensed dosage. The geospatial database, which characterizes the demographic and socioeconomic conditions of the neighborhoods, provides data for the four neighborhood characteristic domains of interest that are (1) community violence, physical disorder, and social disorganization; (2) neighborhood AOD use-associated factors; (3) neighborhood-level social norms; and (4) community resources.

The geospatial database, which characterizes the demographic and socioeconomic conditions of the neighborhoods, provides data for the four neighborhood characteristic domains of interest that are (1) community violence, physical disorder, and social disorganization; (2) neighborhood AOD use-associated factors; (3) neighborhood-level social norms; and (4) community resources.

Table 1 lists the independent variables that are collected by CASI. Data on the participants' perceptions of neighborhoods were obtained by CASI (Table 2) while Table 3 lists neighborhood characteristics based on archival data. As there are no area-level indicators available for some measures, select constructs from Table 2 will be aggregated up to the area level to create neighborhood-level variables used in the analyses, similar to prior work [65-67].

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Table 2. Neighborhood characteristics assessed by participants.

Measure	Definitions
Exposure to neighborhoods	Level of exposure to both residential and other neighborhoods, including length of residence, who lives with them, assigned housing, how much time they spend in their neighborhoods, and how much time they spend in other neighborhoods [68,69]
Social ties	Number of friends or relatives respondents have in the neighborhood and the frequency with which the respondents see friends and relatives based on Sampson's assessment of social ties [70]
Social cohesion and trust	Perceptions of connectedness and trust in their community [71-73]
Social or neighborhood involvement	Degree to which respondent is involved in local community or other groups (eg, local neighborhood groups or block associations), degree to which respondents interact with their neighbors will be assessed, using a sociability measure [71]
Perceived disorder, safety, and community violence	Perceived social disorder and physical decay based on Ross and Mirowsky [74]; Screen for Adolescent Violence Exposure (SAVE): 32-item self-report measure to assess frequency and type of violence [75]
Neighborhood integration, sense of community, and identification with neighborhood	Neighborhood integration will be measured using Perkin's Sense of Community Scale [76]. 12-item 3D Strength of Identification Scale assesses self-reported feeling of identification with residential neighborhood [77]
Drug market presence	Presence of open air drug markets, street corner sales, corner store or bodega sales and known residence-based sales will be assessed directly using adaptation of previous assessments [78]
Social norms: drug use, sexual behaviors, violence, HIV medical care, and general health	Questions modified from the National Survey on Drug Use and Health [79] to measure behavioral and attitudinal norms around drug use and violence. Perceptions of neighborhood social norms concerning multiple partners, safer sexual behaviors, condom use, receiving HIV medical care, and general health
Social norms: neighborhood homophobia and HIV stigma or discrimination	Brief 6-item scale assesses experiences of and responses to race and sexual orientation–based discrimination in different domains [80], HIV stigma will be assessed using Earnshaw's HIV stigma framework [56]

Table 3. Neighborhood characteristics from archival data.

Dimension	Data
Community violence, physical disorder, and social disorganization	
Crime or social disorder	Crime risk index (overall crime, personal crime, murder, rape, robbery, assault, property crime, burglary, larceny, and motor vehicle theft); acceptably clean streets and sidewalks; and domestic and gender-based violence and hate crimes
Built environment	Housing vacancy and Area Deprivation Index (ADI)
Sociodemographics	Sex ratio, race or ethnicity, immigration status, linguistic isolation (families in which all members ≥14 years have at least some difficulty speaking English) [81-83], poverty, unemployed, on public assistance, proportion living in the same house for the previous 5 years, proportion of owner-occupiers, and same sex household
Neighborhood AOD[a] use-related factors	
Alcohol outlets	Alcohol outlets (National Establishment Time Series [NETS] [84] database)
Community resources	
Community-based organizations, food pantries, and prevention services	InfoShare listing of all nonprofits, services, and public assistance
Health care facilities and pharmacies	NETS database [85] include hospitals, health clinics, community-based care facilities, and so forth; pharmacies or drug stores
Public transport access	Minimum distance to subway or bus and fewer bus stops
Parks	Percent of tract covered by park and park cleanliness
HIV-related data	
HIV prevalence, incidence, and related data	HIV prevalence, new diagnoses, pre-exposure prophylaxis (PrEP), testing, linkage to care, late diagnoses, receipt of care, viral suppression, and mortality [86]

[a]AOD: alcohol and other drug.

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Data Analysis 1: Clustering and Spatial Trends in HIV Care Outcomes

First, we will use spatial analysis to characterize clustering and spatial trends in HIV care outcomes (retention in care, ART adherence, and viral suppression) among MSM living with HIV in the study. Mapping the data distributions of outcomes will provide visual appraisals and display potential spatial variations. We will measure and compare distances between home, social, and health facility access locations and the extent to which there is neighborhood overlapping. We will quantify patterns and relationships describing spatial variation at both the smaller scale (spatial clustering) and larger scale (spatial trends), and examine the association of sociodemographic covariates such as race or ethnicity, socioeconomic status, and neighborhood exposure with spatial clustering of the HIV care outcomes. Results will provide important insights into how social and spatial environments impact the outcomes and help inform our other regression analyses by providing baseline information on trends and variability that will be incorporated in the covariates in the regression models, both at the individual and neighborhood levels.

Data Analysis 2: Baseline Associations Between Exposure to Neighborhoods and HIV Care Outcomes

Second, we will conduct baseline analyses to assess associations between exposures to neighborhoods of potential influence (home, social, and health facility access) separately for each of the HIV care outcomes using logistic regression models. Univariate logistic regressions will be computed for the full set of independent variables describing the neighborhood of potential influence to assess the effect and contribution of each variable separately. Variables significant at the $P<.10$ level will be considered for multivariate analysis and longitudinal analyses to examine HIV care outcomes by race or ethnicity among MSM living with HIV in relationship to longitudinal changes in (1) exposure to neighborhoods of potential influence (home, social, and health facility access); (2) neighborhood characteristics in four conceptual domains (community violence, physical disorder, or social disorganization; neighborhood AOD use-associated factors; neighborhood-level social norms; and community resources); and (3) social networks.

Data Analysis 3: Associations in Changes Over Time Exposure to Neighborhoods and Social Networks and HIV Care Outcomes

We will use multilevel modeling to assess associations among changes over time in exposure to the 4 neighborhood characteristic domains and changes in social networks with HIV care outcomes.

Results

The study was initially funded in August 2017, with additional multiyear funding in April 2019. The study began enrollment in March 2019 and concluded visits in December 2023, with a total of 327 participants enrolled (213 in the pre–COVID-19 pandemic lockdown cohort and 114 in the post–COVID-19 pandemic lockdown cohort). The study paused enrollment from March 2020 to August 2021 as a result of the COVID-19 pandemic, with the resumption of enrollment in August 2021 to November 2022. The participants in the prelockdown cohort completed study visits up to 36 months, while those in the postlockdown cohort completed visits up to 12 months. Results are planned for publication in the spring of 2025.

Baseline sociodemographic characteristics for 319 participants with available data are described in Table 4, with 205 participants in the prelockdown cohort and 114 in the postlockdown cohort. The median age was 44.1 (SD 11.5) years. Almost all the participants self-identified as cisgender men (n=313, 98.1%) and as gay, homosexual, or bisexual (n=301, 94.4%). Overall, 192 (60.1%) participants identified as non-Hispanic Black, 81 (25.4%) as Hispanic, 32 (10.0%) as non-Hispanic White, and 14 (4.4%) as other. More than half had any college education (n=175, 54.8%), while 216 (67.7%) reported an annual household income of US $20,000 or less and 280 (87.8%) had Medicare, Medicaid, or New York State AIDS Drug Assistance Program (ADAP) insurance coverage. Most (n=201, 63%) reported at least occasional difficulty in meeting basic needs (eg, rent and food) in the past 6 months. The mean number of years living with HIV was 15.4 (SD 10.1).

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Table 4. Baseline sociodemographic characteristics of NNHIV[a] study cohort.

	Total (N=319)	Prelockdown cohort (n=205)	Postlockdown cohort (n=114)
Age (years), mean (SD)	44.1 (11.5)	43.5 (11.6)	45.2 (11.4)
Male, n (%)	313 (98.1)	205 (100.0)	108 (94.7)
Gender identity, n (%)			
Straight or heterosexual	3 (0.9)	3 (1.5)	0 (0.0)
Gay, homosexual, or bisexual	301 (94.4)	192 (93.7)	109 (95.6)
Other	15 (4.7)	10 (4.8)	5 (4.4)
Race or ethnicity, n (%)			
Non-Hispanic Black	192 (60.2)	140 (68.3)	52 (45.6)
Hispanic	81 (25.4)	44 (21.5)	37 (32.5)
Non-Hispanic White	32 (10.0)	12 (5.9)	20 (17.5)
Other	14 (4.4)	9 (4.4)	5 (4.4)
Education level, n (%)			
No high school diploma	58 (18.2)	50 (24.4)	8 (7.0)
Completed high school	86 (27.0)	59 (28.8)	27 (23.7)
Some college or 2-year degree	103 (32.3)	64 (31.2)	39 (34.2)
College or higher	72 (22.6)	32 (15.6)	40 (35.1)
Annual personal income of US $20,000 or less	216 (67.7)	170 (82.9)	46 (40.4)
Health insurance, n (%)			
Private	24 (7.5)	6 (2.9)	18 (15.8)
Medicare, Medicaid, or ADAP[b]	280 (87.8)	189 (92.2)	91 (79.8)
Do not know or prefer not to answer	15 (4.7)	10 (4.9)	5 (4.4)
Unstable housing	29 (9.1)	24 (11.7)	5 (7.0)
Not enough money for basic needs (eg, rent and food) in the past 6 months	201 (63.0)	140 (68.3)	61 (53.5)
Years since HIV diagnosis			
Mean (SD)	15.4 (10.1)	15.3 (10.2)	15.8 (9.9)
Value, n	298	192	106

[a]NNHIV: Neighborhoods, Networks and HIV Care among Men Who Have Sex with Men.

[b]ADAP: AIDS Drug Assistance Program.

Discussion

Principal Findings

Significant racial or ethnic disparities in HIV care–related outcomes among MSM in the United States motivate us to understand whether and how neighborhood and network characteristics act and interact to influence these outcomes. This study has several innovative features. First, neighborhoods and networks are rarely static and the HIV care continuum is a dynamic process in which individuals with HIV move on and off steps of the continuum. Given the limited data available on neighborhood and network dynamics among MSM living with HIV, this study's longitudinal design examines changes in exposure to neighborhoods and social networks over time and determines how these influence HIV care outcomes, elucidating the potentially unique mechanisms by which they impact the HIV care continuum for MSM living with HIV by race or ethnicity. This design positions the study team to capture differential exposure to neighborhood and network characteristics and effects of national health policy changes, including changes to local, state, and federal health and social policy that may occur over time.

Second, we focus on identifying how individual-level factors mediate the impact of neighborhood-level factors, enabling us both to identify malleable characteristics that are amenable to traditional individual-level intervention and area-level factors, which, if modified, may have important positive effects on a range of health outcomes among MSM living with HIV. In addition, we investigate multiple neighborhood contexts for MSM living with HIV in the urban environment, rather than

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only their residential neighborhoods, which has been the focus (and a key limitation) of the majority of neighborhood research. We use innovative spatial analysis methods that will address limitations inherent in prior neighborhood-level research. We use Google Earth to identify the location and scale of multiple neighborhoods that are potentially important to the MSM. We collect neighborhood boundaries that are defined and characterized by the participants, which will reflect their own local, small-area definitions of the size of influential space in these contexts. Furthermore, the incorporation of subjective (perceptions) and objective measures of neighborhoods is innovative and has been not used in prior research examining the disparity in HIV care outcomes among MSM.

One area of focus of our analysis is HIV stigma, which has been associated with significant negative health and social outcomes among people with HIV [87,88]. HIV stigma influences the HIV care cascade by reducing access to testing [89,90] and medical treatment [91,92]. It also reduces the uptake of biomedical prevention technologies, critical tools to interrupt HIV transmission [89-95]. There is limited data on how community-level HIV stigma influences HIV care-related outcomes. In this study, we will examine the impact of individual-level intersectional stigma (internalized, experienced, and perceived community) at various levels on HIV care outcomes and will evaluate these relations over time.

A second area of focus is on stress and coping. According to stress theory, stressful life events give rise to coping responses, which can be adaptive or maladaptive. When a coping response is adaptive and effective, the impact of the stressor is mitigated; when the response either does not exist or is maladaptive, the stressor has a negative effect on the individual [96,97]. Neighborhood environmental conditions, such as concentrated poverty, racial segregation, physical disorder, and violence, increase the likelihood of experiencing stressors. Physical disorders (eg, vacant buildings) can lead to stressful experiences, such as crimes and assault, as they provide spaces and cover for illegal activity (eg, drug trade) [98-102], increasing general arousal or anxiety, and consequent negative immune function. There is literature on community violence and adverse health outcomes [103-105]. We will examine the impact of neighborhood-level concentrated poverty, racial segregation, and physical disorder on stressful life events and subsequent HIV care outcomes. We will examine whether they are mediated by individual-level psychological distress and moderated by coping mechanisms, with maladaptive ones (ie, AOD use) mediating adverse neighborhood effects and positive ones (ie, positive coping skills) buffering them.

A more nuanced understanding of the mechanisms by which neighborhood and network-level factors influence the HIV care continuum steps among MSM will guide the development of urban planning policies and multilevel, neighborhood and network-level interventions to augment individual and patient provider-level interventions to improve outcomes. Neighborhood and network factors are often examined separately in research studies, and this study aims to evaluate both factors using multilevel modeling. Specific interventions can be tailored to subpopulation groups focusing on malleable characteristics that specifically influence HIV care outcomes for that group. For example, high-poverty neighborhoods with numerous health and HIV-related resources that also have high levels of HIV stigma and homophobia may be associated with inconsistent care receipt inside of that neighborhood and, subsequently, low levels of ART adherence for MSM, especially among those with high internalized stigma and social networks that offer less support. In contrast, for care receipt outside the neighborhood, network and individual-level poverty may be more important to care outcomes than local resources or neighborhood stigma. Our planned analyses will identify sets of neighborhood and network-level characteristics that constitute the varying contexts where access to care and engagement are optimized. Results will also identify how individual-level factors interact with these contexts.

Such results could inform the design of care engagement interventions for MSM who receive HIV care inside and outside their neighborhoods. Determining if the association between neighborhood resources and HIV care outcomes is modified by transit access and the neighborhood type (eg, home vs social) could inform future siting of resources for urban MSM living with HIV in underserved areas. Identifying the effects of exposure duration to stressful neighborhoods, through analysis of MSM who move, and network-level influences could inform our understanding of where to site housing for MSM living with HIV and who might benefit from moving to a different neighborhood. Social network–based interventions can be tailored to promote HIV serostatus disclosure, ART adherence, and retention in care within social networks through peer leaders to leverage their influence over HIV care-associated social norms within networks, taking into account how neighborhood-level factors condition network influences. Most importantly, the level of detail and longitudinal nature of the study addresses concerns around one-size-fits-all approaches, even at the neighborhood and network levels, such as generic antistigma media campaigns and crime reduction efforts.

The COVID-19 pandemic caused by the SARS-CoV-2 virus that emerged in New York City in March 2020 was associated with high levels of morbidity and mortality, especially among those who are immunocompromised and have underlying comorbidities, including HIV [106]. Our study had to pause enrollment from March 2020 to August 2021, with the resumption of enrollment in August 2021 to November 2022. This will allow us to conduct additional analysis on the effect of the COVID-19 pandemic on the mental health, substance use, and general well-being of MSM living with HIV in New York City, as well as its effect on how neighborhood and social network factors influence HIV care outcomes pre- and post-pandemic.

Conclusions

In summary, the study uses an innovative approach combining geospatial mapping of neighborhoods with multilevel modeling, spatial statistics, and an extensive geospatial database. It will have direct implications for the design of multilevel interventions, addressing factors at the neighborhood, network, and individual levels, to improve HIV care outcomes for MSM, particularly for Black and Latino MSM. This study will have direct implications for the design of neighborhood- and

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network-level interventions and urban planning to improve the HIV care outcomes for MSM, particularly for Black and Latino MSM.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HVT and VAF performed the conceptualization. HVT, VAF, MW, VN, AR, FC, CW, and MRD contributed to the data curation. HVT, VN, VAF, JD, EG, FC, CW, and MRD performed the formal analysis. HVT and VAF contributed to the funding acquisition. HVT, VAF, MW, MB, JB, PG, LN, JS, and GY did the investigation. HVT, VAF, VN, JD, EG, AR, FC, and CL contributed to the methodology. HVT, VAF, and MW contributed to the project administration. VN and FC helped with the software. HVT, VAF, VN, AR, and FC helped with the resources. HVT, VAF, and MW performed the supervision. VN, FC, CW, and MRD did the validation. VN, FC, CW, and MRD did the visualization. HVT and VAF contributed to writing—original draft. HVT, VAF, JD, EG, MW, FC, MRD, CW, and CL contributed to writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Population and Public Health Approaches to HIV/AIDS Study Section (PPAH) - AIDS and Related Research Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 133 KB - resprot_v13i1e64358_app1.pdf]

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Abbreviations

ACTG: AIDS Clinical Trials Group
ADAP: New York State AIDS Drug Assistance Program
AOD: alcohol and other drug
ART: antiretroviral therapy
CASI: computer-assisted survey instrument
CD4 T cell: CD4 T lymphocyte
MSM: men who have sex with men
NNHIV: Neighborhoods, Networks and HIV Care among Men Who Have Sex with Men
SDH: social determinants of health
SNI: social network inventory

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Protocol

The Young Adult Centered Healthforce Training (YACHT) Program to Increase HIV Testing and Pre-Exposure Prophylaxis Referrals Among Young Sexual Minority Men in Florida: Protocol for a Type 2 Implementation-Effectiveness Hybrid Trial With a Stepped Wedge Design

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Abstract

Background: There is a high incidence of HIV among young sexual minority men in Florida. Many are unaware of their status due to low testing rates. Counseling, testing, and referral (CTR) services are essential for diagnosis and prevention of HIV and are integral to the Ending the HIV Epidemic (EHE) strategic plan. However, efforts to increase CTR among young sexual minority men have not been successful.

Objective: The Young Adult Centered Healthforce Training (YACHT) program promotes developmentally sensitive, culturally appropriate, and evidence-based CTR services for young sexual minority men. This study tests whether the YACHT program increases HIV testing among young sexual minority men and fidelity to evidence-based CTR among testing providers.

Methods: Agencies in Florida EHE counties that tested at least 24 young sexual minority men aged 18 to 29 years in 2021 will be invited to participate. The sites (N=42) will be randomized in blocks of 6 to participate in the YACHT program, following a stepped wedge design. Through YACHT, all sites will receive visits from mystery shoppers (MSs), who are trained to evaluate HIV testing services and complete postvisit quality monitoring assessments. Sites will be offered the opportunity to review their MS feedback and to receive tailored motivational interviewing training and evidence-based technical assistance to address areas of need identified through MS assessments. The study will evaluate whether YACHT leads to increased HIV testing by comparing numbers of young sexual minority men testing for HIV before versus after YACHT's implementation. The Exploration, Preparation, Implementation and Sustainment framework will help understand the barriers to and facilitators of the program's implementation and sustainment.

Results: YACHT was funded in August 2022. Data collection began in June 2023. As of June 2024, 194 MS visits have taken place at 42 sites; 4 (67%) sites from the first block and 1 (33%) site from the second block have engaged with the study. At baseline, sites exhibited the lowest competencies in relationship context, counseling sessions, and safer sex education and the highest competency in privacy and confidentiality. Data collection will continue through May 2027, with results published by the end of 2027.

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Conclusions: To address the high incidence of HIV among young sexual minority men in Florida, YACHT aims to support testing sites with tailored motivational interviewing training and technical assistance to address needs identified by MS assessments. The program seeks to improve delivery of evidence-based CTR services, thereby increasing HIV testing, counseling, and pre-exposure prophylaxis referrals and reducing HIV incidence among this population.

Trial Registration: ClinicalTrials.gov NCT06015581; https://classic.clinicaltrials.gov/ct2/show/NCT06015581

International Registered Report Identifier (IRRID): DERR1-10.2196/63191

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KEYWORDS

sexual minority men; youth; HIV prevention; tailored motivational interviewing; technical assistance

Introduction

Background

In Florida, as in many other areas of the United States, young sexual minority men, particularly those of color, bear a disproportionate burden of HIV infection [1,2]. HIV counseling, testing, and referral (CTR) services have long served as the gateway to prevention and care and are critical to reducing the impact of HIV among young sexual minority men. CTR services offers opportunities to address the "diagnose" and "prevent" pillars of the Ending the HIV Epidemic (EHE) plan through evidence-based practices (EBPs) such as risk reduction counseling (RRC), referral to pre-exposure prophylaxis (PrEP), early detection of HIV infection, and linkage to care. Despite concerted efforts at promoting uptake of HIV testing, only half of all young people living with HIV know their infection status [3]. Compared with other age groups, young sexual minority men are more likely to report never having undergone an HIV test [4] and are less likely to link and adhere to HIV treatment or biomedical prevention, including PrEP [5]. Reducing the devastating impact of HIV infection on young sexual minority men necessitates increasing access and uptake of CTR services among this heavily impacted population.

The HIV HealthForce is at the center of the EHE strategic plan and has been historically responsible for providing CTR services including HIV testing, discussing risk practices, encouraging risk reduction and repeat testing, identifying and addressing other psychosocial needs, linking to HIV care, and more recently, facilitating PrEP referrals. However, studies suggest that the HIV HealthForce is not adequately equipped to provide developmentally sensitive and culturally appropriate CTR services to young sexual minority men. In a recent assessment of CTR agencies by mystery shopper (MSs) to rate the services provided [6], young sexual minority men noted deficiencies in the testing providers' competencies while working with sexual minorities, which led them to feel uncomfortable during their visits. Testing providers at about half of the CTR agencies visited by MSs missed opportunities for prevention by not providing EBPs such as counseling or PrEP referrals. Without developmentally and culturally responsive CTR services, outreach to increase testing uptake is less likely to be successful [7], young sexual minority men are unlikely to return for repeat tests [8], and the counseling and referral attempts are more likely to fail [9].

Mystery Shopping Can Be an Effective Client-Centered Tool for Developing Targeted Workforce Development Plans to Improve CTR Services at Individual Sites

Mystery shopping [8,10] is an action-oriented strategy whereby organizations can understand their performance across a systematically obtained set of service indicators, as rated by the client base they intend to serve. MS data could be used to improve the quality of CTR services and establish a foundation from which to develop individualized workforce development (WD) plans that are tailored to the unique needs of each CTR site. Our team developed an MS assessment for CTR services driven by young sexual minority men and tested the measurement approach in 46 HIV and sexually transmitted infection (STI) testing clinics in the Detroit metropolitan area. We subsequently replicated the measurement approaches in Atlanta, Philadelphia, and Houston in Adolescent Trials Network (ATN) Protocol 139 [11].

For these studies, young sexual minority men from local communities served as MSs. They were trained to use a psychometrically sound quality assurance instrument to examine clinics' environmental characteristics, compliance with federal and state EBPs, and delivery of developmentally and culturally competent CTR services. The MS sought services and completed the instrument immediately after completing the visit. A confidential 5-page report that documented site performance in comparison with other county agencies was provided to the agency directors. The directors expressed unanimous, positive support for how these reports helped advance their agency mission. However, beyond audit and feedback loops, quality management (QM) strategies must offer concrete WD strategies (eg, technical assistance [TA] and consultation) to help agencies address and monitor their improvement. Thus, an implementation package for the Young Adult Centered Healthforce Training (YACHT) program that includes MS and tailored motivational interviewing (TMI) WD strategies may be useful to improve CTR services for young sexual minority men in Florida.

TMI Is a Promising Approach for Improving Testing Provider Competence in Delivering Evidence-Based CTR Services for Young Sexual Minority Men

There are several EBPs that should be standard as part of CTR services to young sexual minority men. These include counseling to encourage condom use and repeat testing, making referrals to PrEP services delivered from a motivational interviewing (MI) foundation to ensure collaboration, and providing

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nonjudgment and autonomy support to promote behavior change [12-19]. MI is a person-centered communication approach designed to elicit and strengthen motivation to change. This approach is particularly well suited for adolescents and young adults [20]. An additional benefit is that MI is flexible and thus, can be tailored to different contexts and geographic settings [7,21-25].

During the previous 2 decades, our team has conducted several studies to developmentally and culturally tailor MI with theory-driven training protocols resulting in an implementation package called TMI. The goal of TMI is to improve testing provider–patient communication across the youth HIV prevention and care cascades [7,21,26,27]. We have successfully used TMI in CTR settings [10]. The tailoring process was systematic and adolescent- and young adult–focused, and it used a variety of strategies. For the developmental tailoring, we analyzed recordings of real-world interactions with adolescents and young adults that happened during multidisciplinary clinic visits [7,23] and were guided by a seminal MI text focused on adolescents and young adults [20]. We culturally tailored MI through a series of communication science studies to specify testing provider behaviors most associated with the use of motivational language in ethnic minority populations [7,23,28]. To address stigma, we focused on incorporating more activities geared toward improving testing providers' communication skills to demonstrate acceptance and support autonomy of patients [29,30]. There is evidence that increasing testing provider competence in these types of communication skills can reduce the manifestation of multiple and intersectional stigmas in the health care setting [31,32]. To further enrich TMI, we included activities to promote cultural humility [29]. Studies have shown that TMI can improve testing [7], linkage [33], retention [21], and viral suppression [21,27] in population samples comprised primarily of young sexual minority men of color.

However, delivering TMI with fidelity is not easy, and the MI literature suggests that workshops alone are not sufficient to improve testing provider competence; additional training activities are needed [34-37]. In our previous study of care providers for adolescents with HIV from different disciplines across 10 clinics in the United States (ATN 146), only 7% care providers scored in the intermediate or advanced TMI competence range, as assessed using a standardized assessment of simulated patient interactions [38]. This was despite the care providers reporting having received some prior MI training. To address this need, as part of our TMI implementation studies, we developed and tested a series of WD strategies to increase care provider competence in delivering TMI. These strategies include an introductory workshop, coaching and feedback sessions, standardized patient interactions, and performance-based coaching sessions [39]. Our studies suggest that these WD strategies were useful in enhancing care provider confidence and 100% adherence to all the strategies was not necessary [40].

Completing these WD strategies requires dedicated effort, and care providers in our studies cited time, funding, and competing demands as barriers to completing the strategies [40]. Innovative approaches, such as MSs, that identify improvement areas in the delivery of developmentally and culturally appropriate CTR services to young sexual minority men could be used to tailor the trainings and reduce the time burden. Linking MS methods with TMI WD strategies to enhance care provider–client communication could be a winning combination for improving CTR service delivery to young sexual minority men.

Exploration-Preparation-Implementation-Sustainment Framework Offers a Rigorous Approach to Guide Implementation Strategies to Improve Health Force Fidelity to EBPs for Diagnosing and Preventing HIV Among Young Sexual Minority Men

Implementation science (IS) includes the study of strategies to adopt and integrate EBPs within specific settings to improve service quality and effectiveness. IS methods improve upon the historical approaches to studying structural interventions in several ways. IS provides theoretical frameworks to guide implementation strategy planning and to specify the assessment of barriers to and facilitators of success. The Exploration, Preparation, Implementation and Sustainment (EPIS) framework specifies 4 phases of the implementation process and delineates inner organizational and outer system variables that reflect the complex context in which interventions are implemented and scaled. The framework provides a reproducible mixed methods measurement approach. Our team has adapted the EPIS framework for IS studies in youth-focused HIV settings (ATN 153) [41,42]. Specifically, we developed an EPIS-based mixed methods framework for understanding youth HIV implementation contexts, and we have used this framework to organize implementation phases [37]. IS also offers new methods for rigorously testing such strategies, including hybrid trials and stepped wedge designs, which we leveraged in our previous studies. Finally, IS specifies QM and WD strategies to promote the uptake and fidelity of EBPs [43].

Florida-Wide Initiative to Improve CTR Services to Young Sexual Minority Men Is Both Significant and Timely

With 7 EHE jurisdictions located in the state [44], Florida continues to battle a severe HIV crisis. For example, Miami, Orlando, and Jacksonville are consistently ranked among the top 10 US cities for new HIV diagnoses. Miami's HIV incidence is 3 times more than that of the United States overall [1]. Although HIV rates are declining nationwide, 17 of Florida's counties saw an increase in new diagnoses of HIV from 2018 to 2019, and approximately 76% were among racial and ethnic minorities (38% Black, 36% Hispanic and Latinx, and 2% American Indian, Asian, and mixed race) compared with 24% of the White population [45].

Florida has a large and ethnically diverse population, with almost half the population being people of color. It is also a state marked by great urban and rural contrasts and large disparities in wealth, health, age, and opportunities. Furthermore, the Florida Department of Health (FDOH) has an established and well-functioning HIV surveillance system and a strong track-record of public-academic partnerships.

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YACHT Implementation Package May Improve CTR Services to Young Sexual Minority Men

The YACHT implementation package follows the EPIS model to deliver MS feedback reports, TA in problem-solving identified areas of need, and TMI training to improve cultural humility and developmental appropriateness of HIV-testing services. We have partnered with FDOH to launch a state-wide initiative to test the YACHT implementation package. Through this collaboration, we are approved to access state surveillance databases as sources for pragmatic outcomes (number of HIV tests conducted among young sexual minority men). This state-wide testing of the YACHT implementation package paves the way for wide-scale sustainability and public health impact that can be documented with state-level HIV surveillance. This initiative could be a model for other state-wide implementation projects.

Goal

In this manuscript, we present the protocol to test the effectiveness of the YACHT implementation package to improve the fidelity to the "diagnose" and "prevent" EBPs in CTR sites in Florida's 7 EHE jurisdictions (Multimedia Appendix 1). Guided by the EPIS framework, we will examine both effectiveness (number of HIV tests conducted among young sexual minority men) and implementation (EBP fidelity) outcomes. After intervention implementation, a second randomization will be conducted to test whether the implementation of ongoing QM strategies (MS feedback reports) serves as a sustainment strategy. Our study also contains a qualitative component based on the EPIS framework to further understand the context of implementation and sustainment (sequential explanatory mixed methods) [46].

Methods

Study Design

The YACHT program will be tested using a type 2 implementation-effectiveness hybrid trial with a stepped wedge cluster randomization (Figure 1). The trial comprises variable preimplementation phases (quarterly MS visits), a 12-month implementation phase (MS feedback along with TMI WD strategies and recommendations for improvement), and variable sustainment phase. For the stepped wedge, agencies will be randomly assigned to blocks. The number of assessments will be consistent across blocks, but baseline and sustainment windows will vary by block. The preimplementation phase will provide baseline data over a specified period before the implementation package is delivered. The preimplementation phase for block 1 will last for 12 months, whereas the preimplementation phase for block 7 (last block) will last for 30 months. Subsequently, each block will transition from preimplementation to implementation delivery at a 3-month interval. The implementation phase will last for 12 months and will be delivered to all the agencies within each block. MS visits will continue quarterly to inform implementation. At the end of the 12-month implementation period, the agencies will transition to the sustainment phase. Agencies within each block will be rerandomized to groups marked for either ongoing QM (MS feedback) or no further feedback (observation only). The length of the sustainment phase for block 1 will be of 24 months; for block 7, the sustainment phase will be of 6 months. We will conduct qualitative interviews with clinics' testing providers and staff after the completion of the implementation and the sustainment phases using a sequential explanatory mixed methods approach. Implementation facilitators at each study site will collect written informed consent from the testing providers and staff before the interviews. Our logic model will guide the interview process (Textbox 1). The study will evaluate whether the YACHT program leads to an increase in HIV testing by comparing the number of young sexual minority men who test for HIV postimplementation versus preimplementation (primary effectiveness outcome). In addition, we will evaluate program implementation based on MS assessments of fidelity to developmentally and culturally responsive evidence-based CTR practices (implementation outcomes).

The study will use a multicomponent implementation strategy based on the EPIS framework (Figure 2). MS assessments will be used for quality monitoring, and WD strategies will include TMI training and evidence-based TA at HIV-testing sites. All testing sites in Florida EHE counties that tested at least 24 young sexual minority men aged between 18 and 29 years in 2021 will be invited to participate. Participating sites (N=42) will be randomized to receive the YACHT program in 7 blocks of 6, following a stepped wedge design (Textbox 1). They will receive TMI training for RRC and PrEP referrals and evidence-based TA for their identified areas of need, based on MS feedback. Finally, we will use the EPIS framework to understand the barriers to and facilitators of program implementation and sustainment.

This study design will accommodate real-world constraints and provide strong evidence for evaluating the research aims. It is carefully configured to optimize statistical power and will afford numerous and increasingly well-known benefits, including 2 comparisons for assessing the effect of the implementation package (ie, including inter- and intracluster comparisons for assessing the effect of the implementation package), evaluation and control of outer context factors, substantial rigor and power relative to quasi-experimental alternatives, and superior feasibility and power relative to alternative randomized designs. Institutional review board approval from the Florida State University was obtained on December 12, 2022.

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Figure 1. Stepped wedge study design. M: month; MS: mystery shopper; QM: quality management.

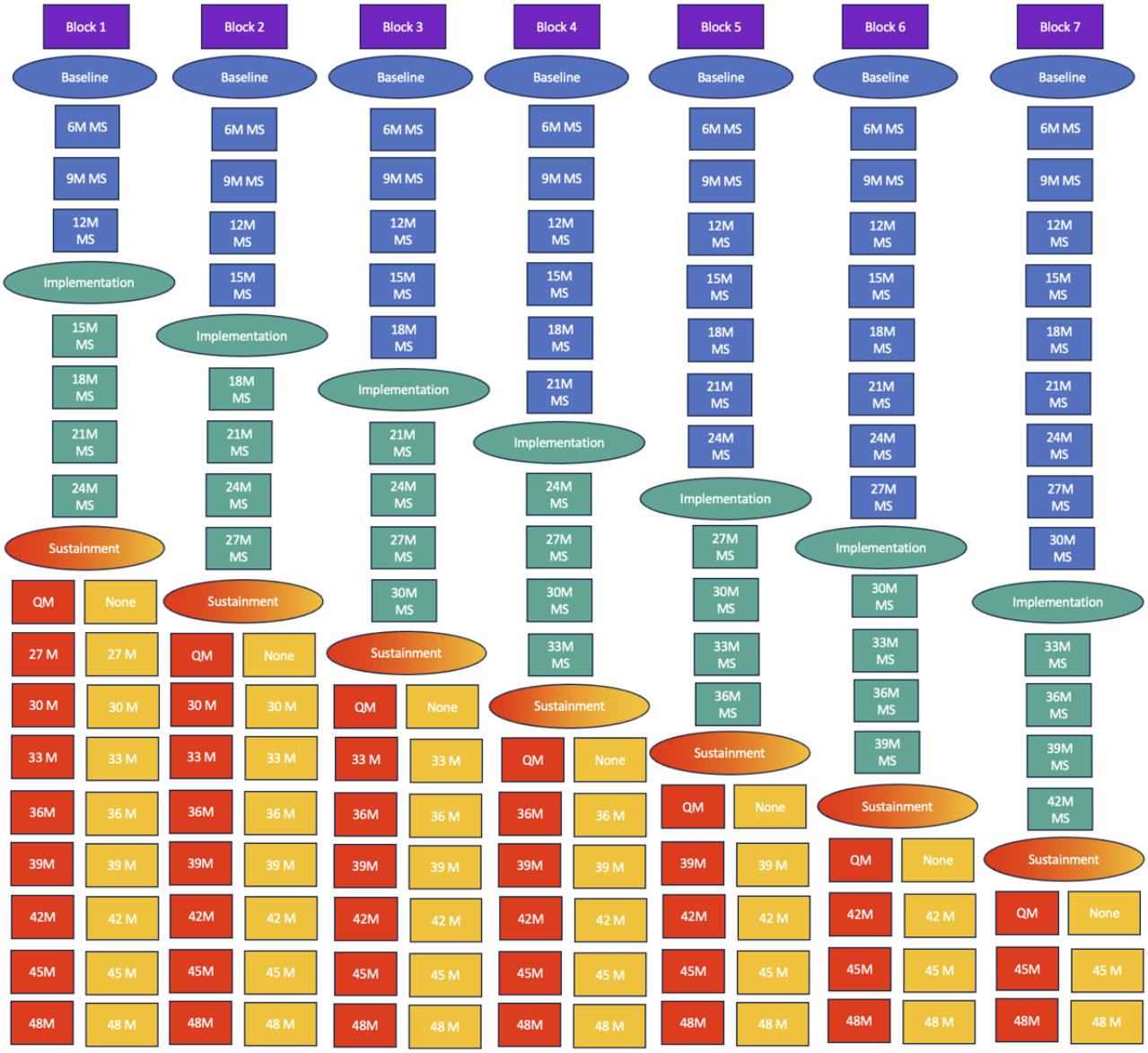

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Textbox 1. Logic model.

Determinants

- Innovation
  - Mystery shopper (MS) assessments and feedback shared with HIV testing sites
  - Technical assistance and tailored motivational interviewing (TMI) offered to HIV testing sites
- Outer setting
  - Ending the HIV Epidemic national initiative
  - High HIV incidence among young sexual minority men in the state of Florida
  - Florida Department of Health support for program
  - Accountability and performance tied to funding
- Inner setting
  - HIV testing already occurring at sites
  - Culture at sites supports client centeredness in HIV testing and counseling
  - Leadership is committed to staff development and data-driven practices
  - Site incentives provide resources to support implementing the innovation
- Individuals
  - High-level leaders, including research and clinical operations managers, engaged in exploration to identify need
  - Mid-level leaders, such as HIV testing directors, engaged in preparation to discuss capability
  - Implementation team members, such as HIV testing staff, engaged in implementation to support opportunity and motivation
- Process
  - MSs will identify potential needs at each site
  - Implementation facilitators (IFs) will share the needs assessment and collect information about priorities, preferences and context at testing sites
  - IFs will engage mid-level leaders to plan strategies for implementation of innovation and adapt as needed
  - Implementation team will together to carry out steps identified during the preparation phase
  - IFs will assess barriers and facilitators to implementation to inform adaptation

Strategies

- Develop and implement tools for quality monitoring (MS)
- Audit and provide feedback
- Organize implementation team meetings: assess for readiness and identify barriers and facilitators
- Conduct ongoing training (TMI)
- Provide local technical assistance
- Provide ongoing consultation
- Provide financial incentives

Mechanisms

- Training testing providers/staff
  - Increase cultural competence when working with young sexual minority men
  - Promote skills in having sex-positive and inclusive conversations with young sexual minority men
  - Increase knowledge of pre-exposure prophylaxis (PrEP) guidelines and referrals
  - Strengthen motivation to discuss, refer, and link to PrEP
  - Reduce stigma and promote equity during testing encounter

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- Improvement of clinic procedures
  - Destigmatize client environment
  - Increase buy-in from staff on the value of PrEP
  - Ensure adequate resources are available for clients who are young sexual minority men
  - Take ownership of PrEP as a community response
  - Create feedback loops to support accountability

Outcomes

- Implementation: improved MS scores in LGBTQ visibility, medical form inclusivity, clinic environment, privacy and confidentiality, PrEP information and dialogue, relationship context, participant counseling, safer sex education, perceived testing provider competency, testing provider interactions, cultural humility, and client centeredness
- Clinical/patient: increase number of young sexual minority men tested for HIV; increase number of young sexual minority men with PrEP referrals

Figure 2. Young Adult Centered Healthforce Training (YACHT) Implementation Package by Exploration, Preparation, Implementation and Sustainment (EPIS) framework. FDOH: Florida Department of Health; MS: mystery shopper; QM: quality management; TA: technical assistance.

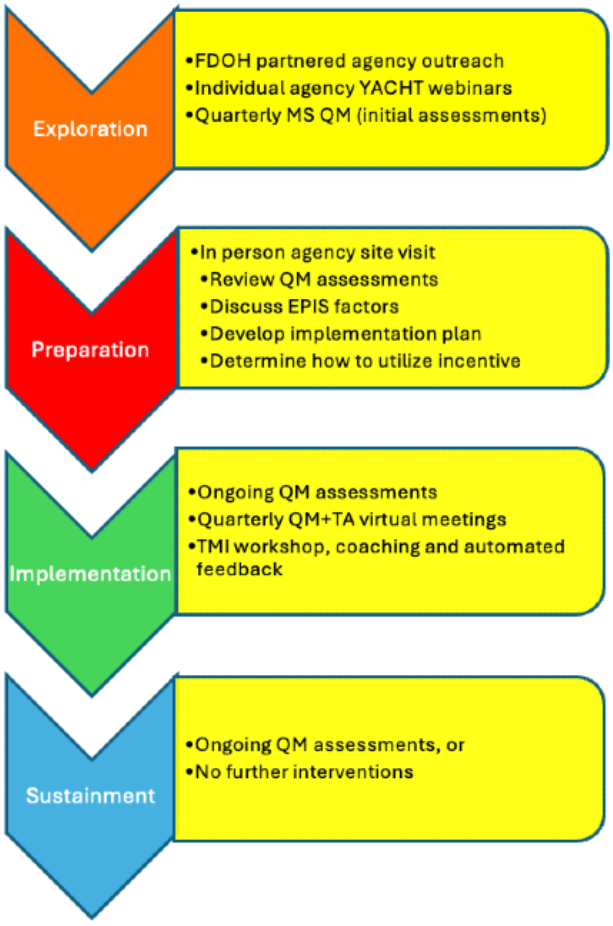

Ethical Considerations

This protocol was reviewed and approved by the institutional review board at the Florida State University on December 12, 2022 (study ID STUDY00003373). All participants who will be interviewed for this study will review and sign an informed consent form.

All study data will be deidentified. Reports of MS findings regarding individual study sites will only be reported aggregately outside of sharing the reports with site staff for quality monitoring purposes.

Study sites that opt to develop an implementation plan and collaborate with the study facilitator for ongoing quality monitoring and TA will be offered a US $3000 token of appreciation for their participation in the study. Study staff who

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complete a 4-session tailored MI training will receive continuing education credits. Finally, participants who are interviewed for the study will receive a US $25 gift card per interview, with a maximum compensation of US $50.

Eligibility

Consistent with the partnering requirements of the funding opportunity announcement, we will be targeting all FDOH-contracted or direct service agencies (N=42) across all 7 EHE counties of Florida that meet the following eligibility criteria: (1) provide HIV CTR services and (2) have tested at least 24 young sexual minority men in 2021. FDOH has agreed to the participation of these 42 agencies. Given that a few agencies may cease operations or may be either unable or unwilling to adopt the implementation strategies, we conservatively estimate that we will need 36 agencies that have tested at least 24 young sexual minority men within each cluster.

Hiring and Training of MSs

We will hire and train 4 to 6 MSs per region (north Florida, central Florida, and south Florida) to conduct QM assessments throughout the study period. We will use both active (eg, directly approaching young sexual minority men) and passive strategies (eg, posting advertisements on social media) to identify HIV-negative young sexual minority men (aged 18-29 years) who are interested in serving as MSs. We will also promote the opportunity via advertisements on various platforms. These platforms include lesbian, gay, bisexual, and transgender (LGBT) listservs; college listservs; HIV and AIDS community-based organizations; and local coffee shops and bars. In addition, we will use social media platforms and dating apps such as Jack'd (Perry Street Software), Facebook (Meta Software), Instagram (Meta Software), LinkedIn (Microsoft), and Idealist (Free Software Foundation).

MSs will participate in a training session that will follow the procedures we used in our previous studies [11]. Specifically, MSs will receive a structured 2-hour training session on the fundamentals of HIV or STI transmission, the guidelines and protocols surrounding HIV or STI testing and PrEP eligibility, and state-specific HIV guidelines and policies. MSs will also be trained to complete the assessment tool to optimize standardized data collection across agencies.

We will underscore the importance of being well versed in their rights and procedures, and increase skills on how to respond to worst-case scenarios (eg, how to turn down any unwanted procedures), were they ever to occur. MSs will be instructed to be honest about their sexual behaviors during their visits. For an HIV-positive test result, MSs will alert the study staff who will provide referrals for care, if needed.

MSs will be randomly assigned to each study site to avoid selection bias. The team will create a calendar for MSs to know their schedule of clinic visits. MSs will be instructed to report that they do not have income or health insurance and do not possess any proof of identification. By doing so, we will ascertain whether these are potential barriers to testing at a given location and document the lowest possible fees that may be charged to a young sexual minority man.

MS Site Assessment Measure

MSs will complete a web-based agency checklist and qualitative debrief with study staff to summarize their impressions of the following: (1) how they felt about the agency, (2) interaction with the counselors and testing providers, (3) anything notable that occurred in the course of the visit (be it positive or negative), and (4) any other information deemed pertinent to the experience. Assessment training will include a discussion on the definition, understanding, and measurement of each mystery shopping domain (Table 1). The 11 mystery shopping domains include 9 that were previously used to assess HIV-testing sites in our previous studies along with 2 new domains focused on cultural humility and MI based on validated scales [47,48].

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Table 1. Mystery shopping site assessment domains.

Domains	Items assessed	Interpersonal or environmental factor
Medical form inclusivity	Clinic used LGBT[a]-inclusive language on forms	Environmental
Clinic environment	Friendliness, sensitivity, use of affirming language by staff, lack of judgment, and comfort of waiting room	Interpersonal and environmental
Privacy and confidentiality	Patient info kept confidential by office staff and testing provider, privacy in waiting room, and confidentiality explained	Interpersonal and environmental
PrEP[b] information and dialogue	Presence of PrEP information and whether testing provider shared info about PrEP as a prevention strategy	Interpersonal and environmental
Relationship context	Testing provider asked about sexual orientation, relationship status, sexual activity, and experiences with intimate partner violence	Interpersonal and environmental
RRC[c]	Testing provider explored motivation for testing, offered to help set safer sex goals and action steps, and presented risk reduction options	Interpersonal
Safer sex education	Testing provider helped me to identify condom and lube that work for me and made sure I know how to use them, and discussed PrEP as prevention strategy	Interpersonal and environmental
Testing provider knowledge	Testing provider was knowledgeable about HIV and STIs[d] and LGBT health issues	Interpersonal and environmental
Testing provider interactions	Testing provider made me feel comfortable, was not judgmental about my sexual activity or partners, did not pressure me to adopt risk reduction options	Interpersonal
Cultural humility	Testing provider was knowledgeable, understanding, or curious about my cultural background, or made assumptions about my cultural experiences	Interpersonal
Client-centeredness	Clinic staff took a collaborative stance when discussing making healthy changes, supported my autonomy, helped me recognize need for change and feel confident in my ability without acting as an authority	Interpersonal

[a]LGBT: lesbian, gay, bisexual, and transgender.

[b]PrEP: pre-exposure prophylaxis.

[c]RRC: risk reduction counseling.

[d]STI: sexually transmitted infection.

YACHT Implementation Package Specification

Overview

During the exploration phase, we will present at state-wide meetings and conferences to inform agencies state-wide about the initiative in collaboration with FDOH. Every quarter, each study site will receive 2 MS visits. We will use time-space sampling to ensure that varying days (weekdays vs weekends, when applicable) and times (eg, morning vs afternoon or evening) are selected for visits, thereby maximizing the chance of meeting different counselors at each agency. The exploration phase will end with virtual meetings of individual agencies with regional facilitators to orient HIV-testing directors to the program, address any initial concerns, and increase engagement with the planned implementation strategies. These meetings will aim to create an engaging, interactive environment to probe knowledge and utility of MSs for HIV-testing programs. Regional facilitators will describe the MS assessment and approaches using TMI and TA, ending the session with an overview of the study and scheduling an in-person visit for the preparation phase.

The preparation phase will occur 2 months before the implementation phase and will consist of an in-person meeting with the executive director and the leads of testing and prevention services. We will provide personalized feedback using the MS assessment findings that address environmental and interpersonal factors. We will elicit their views regarding the findings, focusing on the aspects they would like to improve. We will also suggest strategies for change and assist them with planning an intervention appropriate for their agency. To address environmental factors, we will lead agency directors in a problem-solving exercise to brainstorm ideas and develop a plan to address the components they select. To address the interpersonal factors, we will discuss how TMI may be used to improve testing provider–client interactions and discuss challenges and opportunities for improving CTR services. In collaboration with the agency, we will compile a list of staff to engage in the intervention. Consequently, the YACHT program will be adapted to each agency's needs and culture.

The implementation phase (12 months) will consist of quarterly 1-hour QM meetings in which we will review data regarding adherence to the implementation plan (eg, staff attendance at TMI training) as well as the most recent MS assessments, iteratively revising the implementation plan as needed. TA tailored to the areas of need identified during the preparation phase will be offered throughout the implementation period. We will use a facilitated problem-solving approach consisting of the following 4 steps: (1) define and analyze the problem, (2) generate new ideas, (3) analyze potential solutions, and (4) implement and evaluate the plan. In addition, to build testing

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provider's interpersonal counseling skills, we will offer TMI options as follows:

Initial TMI Workshop

This workshop is theoretically grounded in behavior modification and behavioral skills training developed by Bandura [49] and Miltenberger [50] as well as research in education on cooperative learning environments [51,52]. Originally designed as a 2-day in-person training, we will deliver TMI workshop virtually via structured web-based modules followed by two 3-hour interactive modules on Zoom with cooperative learning activities, video examples, and behavioral skills acquisition steps (modeling, verbal and behavioral rehearsal, and feedback). We have further adapted these TMI modules to ensure delivery from a foundation of cultural humility [53] and antiracism [54], emphasizing how learners engage in a lifelong process of self-reflection and self-critique, challenge power dynamics, commit to understanding and respecting different points of view, and engage with others authentically and from a place of learning. Discussion sessions will focus on moving from not racist to antiracist while concepts of cultural humility with video examples will be interwoven throughout training. Participants will practice how to use TMI skills to demonstrate cultural humility in language with video demonstrations.

Coded Standard Patient Interactions With Automated Feedback

After participating in the workshop, testing providers will complete a 15- to 20-minute long standard patient interaction by phone. TMI coaches will code the interactions with the Motivational Interviewing Coach Rating Scale (MI-CRS) [47,55]. The MI-CRS consists of 12 items rated on a 4-point scale (beginner, novice, intermediate, and advanced) representing essential MI components such as a collaborative stance, autonomy support, open questions to elicit motivational language (ie, change talk), reflections of change talk, affirmations, cultural humility, and summaries. Testing providers will receive an autogenerated report based on scores with recommendations for practice activities and links to short videos of skill demonstration, including newly developed cultural humility videos, based on the lowest scoring items. These scores will guide the group coaching (discussed next) and will also be repeated at 6 months to provide further feedback.

Group Coaching

Standardized 1-hour virtual coaching sessions (up to 4 per agency) will include a brief interaction to elicit motivation for TMI implementation and then, behavioral skills acquisition based on the lowest ratings received on the most recent MI-CRS and MS assessments. The coaching of each skill will follow the skills acquisition steps of modeling, verbal and behavioral rehearsal, and feedback.

In the sustainment phase, agencies will be randomized to either continue receiving written feedback from the quarterly MS assessments or no additional feedback. Agencies will not have any contact with the TMI coaches during this period; however, agencies may continue to seek TA from FDOH as standard of care.

EPIS Fidelity Procedures

In the exploration phase, MSs will complete the site assessments. We will also have site communication logs in which the facilitator for each study site will document contact with sites, including e-mails, phone calls, and meeting notes. In the preparation phase, each site will have a personalized feedback report based on the MS assessments, and we will continue to document contact in the site communication logs. We will also have a checklist of completed steps and of potential facilitators of and barriers to engagement in implementation. Finally, we will develop and document an implementation plan for each site. In the implementation phase, we will document (1) review of new MS data and any agency data regarding testing, (2) review of adherence to implementation plan, (3) provision of TA to overcome barriers and enable facilitators, (4) revision of implementation plan, and (5) development of sustainment plan at the last QM meeting. Furthermore, 1 TMI group coaching session per block will be randomly selected and coded by the study's principal investigator for content and TMI consistency with the MI-CRS. Finally, agency directors, supervisors, and staff will be interviewed to determine barriers to and facilitators of YACHT fidelity. In the sustainment phase, agencies will be referred to health departments for ongoing TA and another round of interviews will be conducted at the end of the phase with the same staff to identify the barriers to and facilitators of sustaining EBPs.

Quantitative Measures and Data Analysis

Data are nested, which will be addressed using mixed-effects regression models. The key feature is that a minimum of 36 (out of 42 recruited) agencies are nested within the 7 counties. We will explore the use of random intercept at the county level. With only 7 counties, our model may run into convergence and estimation issue. In such a situation, we will include appropriate fixed-effects indicators in our model. We will request FDOH data on the number of HIV tests administered in quarterly intervals during all 3 phases (preintervention, intervention, and sustainment).

Primary Effectiveness Outcome

The primary outcome is the number of tests completed by young sexual minority men (aged 18-29 years), as reported in aggregate at the agency and county levels. We expect that the YACHT package will improve the number of HIV tests administered to young sexual minority men at each agency. As an exploratory outcome, FDOH has recently begun tracking PrEP uptake. Both the testing and PrEP data are reported in a standardized fashion to FDOH. Data will be aggregated within agencies and will be requested biannually. We have budgeted for staff at FDOH to manage data and deliver it in analyzable format. Data will be managed into quarterly windows to correspond to the data collection intervals in the stepped wedge design.

Analytic Strategy

We will use descriptive and graphical approaches to describe demographic characteristics, evaluate distributional properties, and identify outliers. The primary outcome of this study is the number or rate of HIV tests among young sexual minority men at each of the 42 FDOH-contracted CTR agencies in the 7

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Florida EHE counties. The secondary outcome of this study is the mean score changes across MS domains at each of the FDOH-contracted CTR agencies. We will use generalized linear mixed models to evaluate our outcomes under the intention-to-treat analysis framework. Specifically, we will explore the use of the mixed-effects negative binomial model or the mixed-effects Poisson regression model for estimating risk ratio between the treatment and control arms for the testing data, and a mixed-effects model with a normal distribution for the MS data. Time will be included in the model as continuous exposure. Our models will evaluate the difference between the intervention and control arms, adjusting for calendar time and exposure time, which is recommended by Nickless et al [56] to reduce bias in stepped wedge cluster randomized trials. To account for correlation between multiple tests conducted within each agency and heterogeneity between agencies, we will include an agency-specific random effect term. We will also explore the inclusion of a higher order quadratic term for time for better model fit. Akaike information criteria and Bayesian information criteria will inform final model selection. We will calculate the intervention effect after 3, 6, 9, and 12 months of exposure and the time-averaged intervention effect. We will report 95% CI and corresponding *P* values for our parameter estimates. At the conclusion of the 1-year intervention period, agencies will be randomized to continuous quality improvement versus control groups to evaluate sustainment over time. The sustainment period will be 24 months for agencies that receive intervention during the first step and 6 months for agencies that receive intervention during the last step. We will again use mixed-effects regression models to evaluate the difference between continuous quality improvement versus control groups over time.

We will conduct sensitivity analysis to evaluate a per-protocol effect of the intervention on the number of HIV tests administered to young sexual minority men. We will extend our generalized linear mixed models framework to examine the presence of mediation and moderation effects in our models. Specifically, we will examine whether there is a moderating relationship between agencies using our implementation strategies (eg, TMI coaching attendance, number of TA sessions requested, prospective improvements in domains assessed by MSs) and changes in the number of HIV tests administered to young sexual minority men over time.

Attrition and Missing Data

The analyses will follow an intention-to-treat approach, with observations retained in the randomly allocated cluster and phase independently of participation in the experimental interventions. Highly successful tracking and retention protocols will minimize missing data. However, some data will inevitably be missing, and multiple methods will be used to evaluate assumptions and guide the analyses: (1) for a small proportion of missing data with evidence of missing at random, the data will be analyzed using the estimation procedures described above; (2) for a nontrivial amount of missing data and evidence of missing at random, multiple imputation for repeated measurements will be used to generate complete data; and (3) for a nonrandom missing data mechanism, pattern mixture models will be used to identify and control the effect of the nonrandom mechanism.

Primary Implementation Outcomes

Using the pre-established MS domains in Table 1, we will compute an overall agency score using the pooled scores from the 2 MS visits conducted each quarter. Pooled scores will be presented to reduce potential selection bias and confounding based on whether the same or a different testing provider interacted with the shoppers at either agency visit, and to account for the variability across shoppers. We will also create domain subscores using our psychometrically tested subscales for (1) LGBT visibility, (2) medical form inclusivity, (3) perceived clinic environment, (4) privacy and confidentiality, (5) relationship context, (6) RRC, (7) safer sex education, (8) PrEP information and referral, (9) perceived testing provider competency, and 10) patient–testing provider interactions. For ease of interpretability across domains, we will normalize the pooled average scores into percentiles.

Secondary Implementation Outcomes

Secondary Aim 1: To Assess the Effect of Continuous Quality Improvement (Ongoing MS Feedback) in Sustaining the Primary Outcomes

The data structure is identical to that described for the primary effectiveness outcome. To evaluate the outcomes in the sustainment period, including the number of tests administered to young sexual minority men and MS scores, a dichotomous indicator will be added at the agency level to differentiate agencies randomized to continued MS feedback from those randomized to no further intervention. In the model detailed for the primary effectiveness outcome, cross-level interactions will be specified between this condition indicator and the level-2 sustainment phase indicator, along with the level-1 growth term for the sustainment phase. This will test the extent to which changes in outcomes during the sustainment phase differ for agencies receiving ongoing MS feedback versus the control arm. Likewise, the model can be simplified to test for a difference in the average level of MS scores and young sexual minority men tested rather than change over time during this phase.

Secondary Aim 2: To Use Mixed Methods Based on the EPIS Framework to Understand Barriers to and Facilitators of Successful Implementation and Sustainment of Youth-Specific EBPs

Up to 5 testing providers per agency will be interviewed immediately after the Implementation and Sustainment periods using the EPIS-based HIV interviews developed in preliminary studies. Accordingly, the interviews (45-60 min) will focus on the inner and outer context factors influencing the implementation of RRC, PrEP referral, and TMI; utility of and adherence to the YACHT strategies; and bridging and innovation factors to consider for future scalability and sustainment. We will use rapid content analysis as recommended to produce actionable information for planners and decision makers [56,57] by first summarizing individual interviews using a rapid feedback template of EPIS constructs and then consolidating the summaries by the main EPIS factors. Next, we will adapt

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the innovation profile approach [58] originally developed for classroom research. This approach results in a multidimensional rubric to classify where an organization is in the process of developing its capacity to engage in a particular set of activities; in this case, it is the integration of EBPs into routine service provision. The dimensions and subdimensions of the matrix we develop, as well as descriptions of the behavioral indicators of exemplary, intermediate, emerging, and low capacity to integrate EBPs will be derived from aggregating the data produced during content analysis at the agency level. These data will be integrated with the quantitative fidelity and the outcomes data using a sequential explanatory design where qualitative findings are used to help explain variability in fidelity and outcomes [59].

Results

The study was funded on August 4, 2022. A simple randomization scheme was generated using SAS (version 9.4; SAS Institute) to assign agencies to receive feedback versus no feedback during the sustainment phase on April 18, 2023. MS visits were initiated on June 1, 2023. As of June 2024, 194 MS visits have taken place at 42 sites. In addition, 4 sites from the first block and 1 site from the second block have engaged with the study. At baseline assessment, sites exhibited the lowest competencies in relationship context, counseling session, and safer sex education, and the highest competency in the privacy and confidentiality domain.

The exploration phase is projected to last from June 1, 2023, to March 31, 2024 (10 months), for block 1 and until September 30, 2025, for block 7 (28 months), with the other blocks staggered every 3 months. The preparation phase for block 1 started on April 1, 2024, and is projected to take up to 2 months for each block. The implementation phase will last for 1 year and started on June 1, 2024, for block 1 and will begin on December 1, 2025, for block 7, with other blocks staggered every 3 months. Finally, the sustainment phase will start on June 1, 2025, for block 1 and last for 2 years. For block 7, it will start on December 1, 2026, and continue for 6 months. Data collection will be completed by May 31, 2027.

Discussion

Principal Findings

We hypothesize that the YACHT implementation package will contribute to increasing the number of HIV tests conducted among young sexual minority men and improving the developmentally and culturally responsive delivery of EBPs by participating sites in Florida's 7 EHE jurisdictions. An important innovation of our proposed approach is using the services of MSs who are young sexual minority men to identify areas of strength and improvement in the delivery of CTR services for young sexual minority men at participating sites. The proposed design guided by the EPIS framework, a type 2 implementation-effectiveness hybrid trial with a stepped wedge cluster randomization, will allow us to examine both effectiveness outcomes (number of HIV tests on young sexual minority men) and implementation outcomes (EBP fidelity). The second randomization conducted after intervention implementation will test whether the delivery of ongoing QM (MS feedback reports) serves as a sustainment strategy. The qualitative component will advance our understanding of the context of implementation and sustainment.

MS visits started on June 1, 2023. We have learned that recruitment of MSs is challenging and often requires more resources than originally allocated. Recruitment via dating apps such as Jack'd has been most successful but requires an advertising budget that is more extensive than simply posting on social media or posting flyers in local universities and cafes. Interest in serving as an MS varies by geographic location. Scheduling and MS retention can be demanding and often requires extensive efforts from research assistants. The current compensation structure for MSs merits further examination. Most MSs are neither university employees nor study participants but consultants. We pay them on a per visit basis as has been done in previous work with young sexual minority men [53]. However, timeliness of the payment per University processes prevents immediate payment upon visit completion, which may also deter engagement of MSs.

We have some preliminary evidence that garnering participation of some CTR sites may be problematic, even though we have the full support of the FDOH. In February 2023, directors of the CTR sites in the EHE jurisdictions were sent an opt out letter describing the study and giving them the opportunity to opt out of the MS visits. Although a small percent of sites opted out after the initial mailing, a few sites opted out after our follow-up calls and others did not return our calls. As a result, we have ramped-up our site engagement efforts by conducting outreach to both FDOH and county HIV and AIDS prevention coordinators to promote the study and to verify contact information for site directors. We are currently contacting sites in the first 3 blocks through an exploration engagement email, with plans to follow-up over phone if no response is received. To date, we have engaged 8 sites in exploration visits and 3 sites in preparation visits. By emphasizing our plan to share MS data and to provide site incentives (eg, continuing education units for staff that complete the full TMI training and a US $3000 incentive for each site that elects to participate and develop an implementation plan), we hope to continue to garner interest in the study as it is beneficial for the testing agencies.

Limitations, Foreseeable Challenges, and Potential Solutions

Staff turnover is a threat to any health force training. All trainings will be recorded so that the recorded trainings along with our TMI video examples will allow new testing providers to join the program even if they miss the original workshop. In addition, TMI webinar trainings will be offered on a rolling basis for all agencies. In addition, each agency's implementation plan will be clearly documented and we will ensure they have a copy they can refer to and share with new staff. Another potential challenge is that agencies may close or lose funding and drop out of the study. We have included all 42 eligible agencies to reduce bias, but power calculations suggest that the study may be completed with as few as 30 agencies. In addition, the political context in Florida is currently challenging for HIV-testing sites that target young sexual minority men because

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images and language that explicitly support LGBT youth are banned. As a result, the evaluation and discussion of developmental and cultural aspects of CTR for young sexual minority men must be tailored to be both acceptable and clear, without penalizing sites for political factors they cannot control. Finally, MSs are likely to turn over, but we have budgeted for additional outreach and training time for new shoppers.

Conclusions

Improving the CTR service delivery to young sexual minority men has the potential to reduce the impact of HIV on this underserved, at-risk group of young people. Our study provides an innovative strategy for identifying areas of strengths and improvement and an implementation package to address these needs. If successful, the MS visits coupled with the YACHT implementation package will provide a scalable model to improve CTR services that could be adapted for other underserved populations.

Acknowledgments

This study was funded by the National Institute of Mental Health (NIMH). The NIMH did not play a role in the study design.

Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

SN, MIF, and JAB contributed to study design, conceptualization, and funding acquisition. RG, MIF, and SN drafted the manuscript. JAB, SA, and WL contributed to the sections on mystery shoppers. ICB, AC, SG, and JM reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Funded peer review.
[PDF File (Adobe PDF File), 137 KB - resprot_v13i1e63191_app1.pdf]

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Abbreviations

ATN: Adolescent Trials Network
CTR: counseling, testing, and referral
EBP: evidence-based practice
EHE: Ending the HIV Epidemic
EPIS: Exploration, Preparation, Implementation and Sustainment
FDOH: Florida Department of Health
IS: implementation science
LGBT: lesbian, gay, bisexual, and transgender
MI: motivational interviewing
MI-CRS: Motivational Interviewing Coach Rating Scale
MS: mystery shopper
PrEP: pre-exposure prophylaxis
QM: quality management
RRC: risk reduction counseling
STI: sexually transmitted infection
TA: technical assistance
TMI: tailored motivational interviewing
WD: workforce development
YACHT: Young Adult Centered Healthforce Training

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Protocol

Impact of Changes in Criminal-Legal Practices During the COVID-19 Pandemic on the HIV Risk Behaviors of Women Who Use Drugs: Protocol for a Multimethods Qualitative Study

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Abstract

Background: HIV risk behavior in women who use drugs is related to myriad psychosocial issues, including incarceration. The experience of incarceration elevates women's HIV risk by disrupting social networks, housing, employment, and access to health care. During the COVID-19 pandemic, changes in criminal-legal practices resulted in decreased incarceration, especially among women. These changes may have largely altered HIV risk among women who use drugs, depending on their access to care in the community.

Objective: This study seeks to build knowledge about the impact of shifts in criminal-legal practices during the COVID-19 pandemic on HIV risk behaviors of justice-involved women who use drugs.

Methods: Qualitative methods are used to gather and analyze women's narratives about their life experiences before and during the COVID-19 pandemic, with a focus on individual and structural determinants of HIV risk behaviors. Thirty formerly incarcerated women with a history of substance use are being recruited through collaboration with community partners. Each participant completes a sociodemographic survey and two interviews. The first interview uses a life history instrument that invites participants to reflect on key turning points in their lives. The second interview uses a calendar approach to gather information about participants' lives during the first year of the COVID-19 pandemic (March 2020-March 2021). The interviews (1 hour each) are audio-recorded and transcribed for analysis. Rapid Qualitative Inquiry and thematic analysis are being used to manage, organize, and interpret the data. The study team will collaborate with a subset of participants to develop digital stories about their COVID-19 experiences, a process that allows for member-checking and triangulation. Findings will be disseminated to program and policy makers in academic venues, community settings, and social service agencies.

Results: To date, 10 women's data have been collected. In total, two themes have been identified in this preliminary data: (1)the chaos and instability of participants' lives increased during the COVID-19 pandemic: participants reported a wide range of psychosocial and health problems and limited engagement with social service systems. Interaction with criminal-legal systems was rife with uncertainty; participants described living in a state of limbo, which was extremely stressful. (2) When asked to describe a "turning point" in their lives, many participants attributed their substance use to the traumatic loss of a child due to death, incarceration, or termination of parental rights. During the COVID-19 pandemic, participants' struggles to cope with these unresolved experiences of grief and loss were intensified by the widespread death and dying of the pandemic.

Conclusions: Preliminary findings suggest that HIV risk factors increased for participants during the COVID-19 pandemic and invite further investment in community-based harm reduction programs, especially housing, that support women who use drugs. Interventions that address experiences of maternal grief and loss may reduce women's substance use.

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KEYWORDS

HIV; corrections; women; substance use; COVID-19; criminal-legal systems; carceral; qualitative; SARS-Cov-2; coronavirus; pandemic; drug; women who use drugs; psychosocial; HIV risk; health care; qualitative method; socio-demographic; audio-recorded; thematic analysis

Introduction

Background

In 2019, a total of 6400 women were diagnosed with HIV in the United States, representing 18% of the country's new infections [1]. About half of these new infections were among African American women [2]. Women who use illicit drugs are also disproportionately impacted by HIV: 16% of newly diagnosed women in 2019 attributed the transmission to injection drug use and women who use drugs are more likely to report high-risk sexual behavior [2-6].

The ability of women who use drugs to reduce their HIV risk (ie, negotiate condoms, reduce their number of sexual partners, use sterile syringes, and access pre-exposure prophylaxis) is mediated by a constellation of factors related to the individual and structural determinants of human behavior [6]. This project focuses on one of these myriad factors, incarceration, because women who use drugs, especially women of color who use drugs, are disproportionately ensnared in carceral systems. There are approximately 170,000 women incarcerated in the United States, a number that has increased 7-fold since 1980 [7]. Compared with white women, the rate of incarceration is 1.7 times higher for Black women and 1.3 times higher for Latinas [7]. Most incarcerated women meet the criteria for a substance use disorder, and report using drugs in the 30 days before their arrest [8,9]. Women are primarily convicted of nonviolent drug-related, property, or public order crimes [10].

Research has documented how incarceration elevates HIV risk by disrupting housing, employment, relationships, and access to health care, including substance use treatment programs [11-18]. These findings recommend services that can be provided during and after incarceration to recover from carceral disruptions and trauma [19-23]. However, resources are limited for the thousands of women who are released each year [24]. Furthermore, consensus around the detrimental impacts of incarceration on HIV risk has failed to articulate if and how community-based services could address individual and community harm, including HIV risk, in the absence of criminal-legal sanctions.

Research has documented the perception among criminal-legal professionals, service providers, and even women who use drugs that prison is the only place that can provide women in crisis with safe refuge [25,26]. Indeed, incarceration may temporarily decrease harm, including HIV risk, for women who use drugs by interrupting drug use, unprotected sexual behavior, interpersonal violence, homelessness, and hunger. That some women describe prison to be "the safest place I have ever lived," despite the abundant research that documents the trauma and stress of incarceration, speaks to the profound danger and vulnerability experienced by marginalized women who use drugs in the United States [25]. Efforts to decrease the use of incarceration as a response to illicit behavior among women who use drugs must develop community-based alternatives to incarceration that can protect and support women who are actively using or experiencing serious mental health episodes [27].

Currently, the term "alternatives to incarceration" is used to describe community-based criminal-legal responses, that is, probation, mandated treatment, drug court. The largest alternative to incarceration is probation, a legal mechanism that sentences people convicted of crime to community supervision, allowing them to stay in the community provided they adhere to the stipulations of their supervision. There are about 700,000 women on probation in the United States [28]. An assessment of this population's needs and HIV risk has found that "compared to those with no CJ [criminal justice] involvement…women who had been on probation or parole in the past year had higher adjusted odds of homelessness, physical assault, sexual assault, illegal income and injection drug use in the past 6 months" [29]. These findings suggest that probation is not effective in reducing women's HIV risk behavior. Furthermore, probation often leads to incarceration: 29% of prison admissions in 2019 were for violation of community supervision rules [30], further elevating this group's HIV risk, as previously noted [11-18].

COVID-19 Pandemic: a Natural Experiment in Criminal-Legal Reform

Short-term changes in criminal-legal policies during the COVID-19 pandemic created a natural experiment about the impact of criminal-legal, social service, and community-based alternatives to incarceration on the HIV risk of women who use drugs. In 2020, many states sought to prevent the transmission of COVID-19 by decreasing the number of people detained in carceral institutions [30-32]. Connecticut led the nation in this decarceration response, reducing its prison population by 26%, the largest drop of any state [32]. The number of people at Connecticut's correctional institution for women decreased by 43% between March 01, 2020, and March 01, 2021, from 883 to 502 women [33]. While some women were released early, this decrease in prison population was primarily related to changes in policing, prosecution, and judicial procedures that slowed entry into the state's correctional facilities [31,32]; more specifically, there was a large decrease in the number of women held in pretrial detention and serving sentences of less than a year for minor nonviolent charges (eg, violation of probation, drug sales or possession, sex work, larceny) [33]. Drug-related behaviors that would have resulted in incarceration before the COVID-19 pandemic were largely overlooked during this time.

The impact of these changes in criminal-legal practices during the COVID-19 pandemic on the HIV risk behaviors of women who use drugs is not known. Nascent research suggests that access to community-based programs varied, creating disparate experiences. For example, to promote social distancing, methadone clinics implemented systems of "take home" doses

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for all clients and eliminated the requirement for psychosocial groups [34]. Lifting rules which required clients to come in person each day to receive methadone and participate in groups may have facilitated access to the medication for some, while jeopardizing the recovery of those who relied on program structure and group support. Similarly, housing stability increased for some unhoused people who were offered long-term stays in local hotels to reduce loitering and sleeping in public areas and to allow people with COVID-19 infection to quarantine [35,36]. However, these isolated accommodations may have had some detrimental outcomes, for example, reduced sense of community belonging and social connection [35-38]. Overdose trends suggest that the COVID-19 era was dangerous for people who use drugs, especially non-Hispanic Blacks. The number of fatal overdoses in Connecticut increased by 14.3% during 2020 [39]. Qualitative data from women who use drugs about their lived experiences during the COVID-19 pandemic can help build knowledge about what happened during the pandemic and how the shifting service environment shaped their HIV risk.

Methods

Overview

This community-engaged research project uses multiple qualitative methods to explore the lived experience of justice-involved women who use drugs (n=30) to answer the research question: what was the impact of COVID-19–related shifts in criminal-legal practices in CT on the HIV risk behaviors of justice-involved women who use drugs? Study methods include life history interviews, calendar interviews, and digital storytelling. The team-based approach to data collection, analysis, and dissemination reflects the project's commitment to undergraduate mentorship and training and brings an intentionality to each step of the research that slows down the process and allows for deep contemplation of the data.

Conceptual Framework

Figure 1 illustrates this project's conceptual framework. During the COVID-19 pandemic, social distancing mandates decreased the use of incarceration in Connecticut to avoid crowding inside carceral institutions. These mandates also impacted community-based social services. Some community programs expanded to provide emergency support, while others contracted to protect the health of clients and staff [40]. Given that incarceration is negatively associated with HIV protective factors, the limited detention of women who use drugs during COVID-19 pandemic may have reduced their HIV risk. However, for women who use drugs in the community who are experiencing acute addiction, mental health, and socioeconomic crises, HIV risk would only be reduced if they were willing and able to access psychosocial services, housing, health care, and other needed supports [41]. The dramatic decrease in the incarceration of women in Connecticut during COVID-19 pandemic offers an opportunity to explore this conceptual framework by building knowledge about what happened to justice-involved women who use drugs when they were not incarcerated.

Figure 1. Conceptual framework. PrEP: pre-exposure prophylaxis.

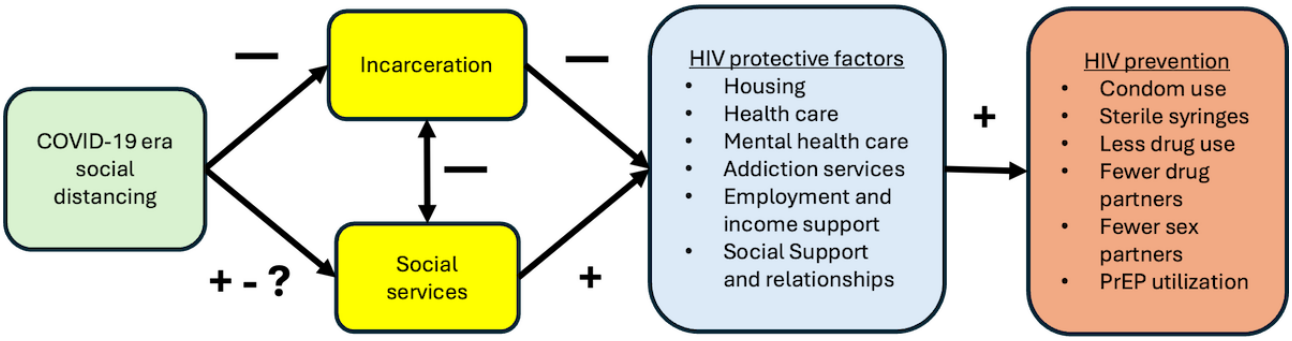

Study Funding and Team

This study is funded by an R15 grant from the National Institutes of Health's National Institute on Drug Abuse (NIH/NIDA 1R15DA056285; Principal Investigator [PI]: ABS) (Multimedia Appendix 1). The R15 mechanism has a dual mission to build health knowledge and create research opportunities for undergraduates studying at institutions that have not been major recipients of NIH funding [42]. From this, the study team, which began meeting in June 2022, is comprised primarily of undergraduate students. Led by the PI, who is a member of the university's social work faculty, the team consists of 5 to 7 student research assistants (RAs) and a part-time graduate assistant. In addition, three community practitioners, who are alumnae of the university's social work program and have expertise related to substance use, criminal-legal systems, trauma, and HIV, serve as project consultants. The team is primarily cisgender women and nonbinary people and includes women with lived experiences of substance use and incarceration. Over half of the study team are Black and Latinx.

Participant Recruitment

Participant recruitment began by engaging with women who use drugs and the service providers who support this population. Since the beginning of the project, the research team has been visiting with local service providers, volunteering with community-based agencies, and attending local re-entry roundtable and HIV planning meetings. These experiences have allowed research staff to spend time with justice-involved and formerly incarcerated women who use drugs, become familiar with local organizations that support justice-involved women, and notice and reflect upon their own positionality. In June 2023, after a year of this community engagement, the team began to recruit participants using stratified convenience

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sampling. The goal is to recruit up to 30 people who (1) have been incarcerated at the York Correctional Institution (CI) in Connecticut at least 3 times before March 2020, and (2) report a history of drug use (ie, have received in-patient or out-patient drug treatment, experienced overdose, or were incarcerated or placed on probation for a drug-related crime). The exact number of people who enroll in the study will depend upon when saturation is achieved (ie, interviews do not introduce new information or themes to the project) [43]. Research has found that saturation is generally reached with 12-17 individual qualitative interviews [43,44]. The diversity of this population and their lived experiences suggests the sample size at which this project reaches saturation may be slightly higher than average [44].

York CI is the only carceral facility designated for women in the State of Connecticut. It is a consolidated facility that serves both jail and prison functions, incarcerating people for pretrial detention and short- and long-term sentences. While most of the people detained in this facility are cisgender women, the population may also include nonbinary people, transgender men, and transgender women. This study has no eligibility criteria related to gender identity: anyone with a history of drug use who was incarcerated at York CI at least 3 times before the COVID-19 pandemic is eligible to participate. The sample will be stratified by race, oversampling Black and Latina women, who are disproportionately impacted by HIV, to construct a sample that is 50% Black, 30% Latina, and 20% White. This recruitment plan has been developed and implemented in collaboration with community consultants.

Recruitment flyers have been distributed to local service agencies that work with formerly incarcerated people in New Haven, Connecticut. Potential participants can express interest by contacting the study team by telephone or by scanning the QR code on the recruitment flyer to complete an online interest form. Snowball sampling, wherein participants share information about the study with their friends and colleagues, has also been encouraged. Study team members use a screening tool to determine the eligibility of all potential participants who contact the study. This 11-item survey can be administered by phone or in person. All eligibility information about individual histories of incarceration and drug use is based on self-report data. Contact information is collected from eligible participants. This information includes first names, telephone numbers, and email addresses (if any), and the option to provide the name of a professional support person who the study team could contact if phone and email are not working. This contact information is recorded in a password-protected Excel (Microsoft Corp) spreadsheet that is not linked in any way to the study data and is used only to communicate with participants about scheduling data collection appointments.

Data Collection

After establishing a participants' eligibility, staff explain that the project requires three consecutive appointments as well as the option to participate in a digital storytelling project. If an individual wants to participate, a first appointment is set, usually for the following day. At this first appointment, informed consent is administered. During this process, staff emphasize that participation is voluntary, and participants can withdraw from the study at any time and decline to answer any question. The consent process and all data collection are conducted in a private office at a centrally located social service agency that provides housing, employment support, and case management to justice-involved people. This location is well known by the community and easy to access by public transportation.

All data collection is conducted by two team members, using "joint interviewing" [45]. Each RA will participate in four interviews. During the first two of these interviews, the PI conducts the interviews with the undergraduate RA serving as an observer and note-taker. During the next two interviews, the RA will conduct the interviews with the PI serving as an observer and note-taker. This graduated system of support builds RAs' research capacity by offering mentorship, feedback, and practice. It also strengthens the project to have more than one person conducting the interviews, allowing multiple perspectives and experiences to shape the data.

The study includes three data collection points: the sociodemographic survey, life-history interview, and COVID-19 calendar interview. These data collection points each take 30-90 minutes to complete and are conducted on separate days. To compensate for their time and expenses, participants are compensated US $20 at the survey meeting and US $40 for each interview. In addition, participants have the option to participate in a digital storytelling project after completing the survey and interviews.

The sociodemographic survey, which was built in Qualtrics (Silver Lake) and includes 141 close-ended questions, is administered using an iPad immediately after consent is administered. Participants can complete the survey on their own or can choose a staff-administered survey option. The survey takes about 10 minutes to complete when self-administered and 20 minutes when staff administered. The survey questions ask about demographics, family, housing, employment, health, criminal-legal experiences, and substance use and treatment.

Individual life history interviews use a semistructured instrument to understand women's lives before the COVID-19 pandemic [46]. These 90-minute interviews begin by asking participants to identify key "turning points" in their lives [47]. They are then invited to describe these critical periods. Follow-up questions ask participants to discuss the psychosocial contexts (family, education, employment, housing, and social services) of these moments with a focus on criminal-legal, drug use, and sexual histories. Data from these life history interviews establish women's baseline behaviors before the COVID-19 pandemic. The interview is intentionally strengths-based and designed to build rapport between the participants and study team [48,49].

The calendar interview focuses on participants' lives during the first year of the COVID-19 pandemic (March 2020-March 2021). Using calendar techniques, specific information is gathered about participants' socioeconomic circumstances, with a focus on criminal-legal experiences and HIV risk and protective factors [50]. The interview begins by asking participants to review a 20-21 calendar, noting anchoring dates from their own lives and the US calendar that spark memories about this period [51]. Next, study staff ask a series of specific

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prompts about their lived experience during this time, with a focus on HIV protective factors, sexual behavior, and drug use.

Digital Storytelling and Member Checking

At the end of the calendar interview, staff ask participants if they want to create a digital story related to their life during the COVID-19 pandemic. Guided by Lambert's Digital Storytelling Cookbook, the study team will run a series of individual digital storytelling sessions with interested participants [52]. The storytelling process will take 4 to 6 sessions to complete, and participants will be compensated US $20 per session for time and expenses. The PI and one RA, who have both completed StoryCenter's Digital Storytelling training, will teach the study team, including the community consultants, how to facilitate these sessions [53]. Digital stories are a tool that allows people to share moments in their lives through short, 3- to 4-minute, narrated videos [54]. Participants' digital stories will provide another data point to triangulate narratives collected in the COVID-19 calendar interviews. The process is also an opportunity for member-checking, an activity that builds the trustworthiness of qualitative data. Finally, with participants' permission, digital storytelling can be a mechanism for dissemination and community engagement.

The first digital storytelling session will be dedicated to member checking, a process that builds the trustworthiness of qualitative study findings by gathering participant feedback and comments on analyzed study data [55]. Participants will be given a copy of their transcribed interviews and a summary of preliminary findings and quotes that exemplify each finding. Members of the study team will discuss the findings, consider if the data align with their memories, and invite participants to comment on anything they would like to change or add [55]. This member checking has 2 purposes: (1) participants' feedback will inform and validate the ongoing data analysis process; (2) the process will refresh participants' memories about the COVID-19 era in preparation for the digital storytelling process. In subsequent sessions, the team will guide participants to write a short story and produce a short video using still photos. Participants may choose to build upon a narrative in the calendar interviews or pick another moment in time. Digital storytelling tasks will include imagining, writing, planning, video instruction and editing, sharing, and reflecting [52,54].

Data Analysis

Data analysis will be conducted in two rounds. First, data collection will pause after every block of 5 interviews to conduct Rapid Qualitative Inquiry (RQI). Second, after all data have been collected and transcribed, thematic analysis of the interview data will be conducted.

Rapid Qualitative Inquiry

RQI is a method of data collection, management, and analysis that centers the knowledge of impacted community [56]. RQI is defined as: "intensive, team-based qualitative inquiry with (a) a focus on the insider's or emic perspective, (b) using multiple sources and triangulation, and (c) using iterative data analysis and additional data collection to quickly develop a preliminary understanding of a situation" [57]. RQI processes concentrate the data in a way that allows for a rapid analysis without compromising rigor or trustworthiness. This express treatment of the study data will allow for prompt feedback for social service and state agencies about the impact of the COVID-19 era on women's HIV risk in order to inform prevention services. Given the rapid evolving nature of the COVID-19 pandemic, and the possibility of other viral outbreaks, this technique offers a way to give immediate knowledge and information to relevant agencies. This approach will also allow the student RAs to practice using a data analysis tool that aligns with social work's need for swift, pragmatic, and accurate understandings of program outcomes.

As part of the RQI process, data are collected in "scheduled blocks," a strategy that sets intentional pauses in data collection for the team to review data and consider possible conclusions and what changes, if any, should be made in subsequent interviews [58]. After each set of 5 interviews, the entire team will meet to discuss this set of interviews, for a total of 6 data collection blocks [59]. Presentation of the interview data at team block meetings will begin the analysis process and allow for early identification of central themes and patterns that can inform subsequent interviews. In preparation for these block meetings, the audio from each interview will be transcribed using Rev, an online transcription service. Next, each transcription will be reviewed and edited by the RA who participated in the interview. During this review process, all identifying information, including names and specific locations, will be removed from the text. The RA will then create a summary of the interview that will be shared with the team and presented at the block meeting [56]. The summary will provide a sociodemographic description of the participant and her reported HIV risk behaviors (individual and structural) and criminal-legal experiences. The goal is to create "intensive team interaction" among the study team throughout the data collection and analysis process [60]. A matrix will be developed by the team, based on discussion at the meetings, that summarizes participants' pre–COVID-19 experiences.

Thematic Analysis

Thematic analysis is an iterative process that uses a "family of methods" to summarize and interpret participants' narratives [61]. The study team will begin its thematic analysis with a series of steps that develops a summary of the topics that are explored and explicated in the data. At the same time, team members will simultaneously engage in a reflective analysis and interpretation of the data that identifies and articulates deeper meanings and ideas within the participants' narratives.

Topic Summary

After the interviews have been conducted and transcribed, the transcripts will be uploaded into Dedoose (SocioCultural Research Consultants), a qualitative data management application for thematic analysis [62]. To begin this analysis, the team members will use the thematic analysis steps set forth by Braun and Clarke [63]. While Braun and Clarke [64] caution against following these steps like a "baking recipe" (ie, a set of procedures to be followed), the topic summaries that the team creates with this analysis will offer a valuable orientation to data analysis for the team's novice undergraduate RAs. In addition, these summaries will offer a description of women's

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lived experiences during the COVID-19 pandemic related to drug use, sexual behavior, housing, food security, and access to health and social services that can begin to inform social work practice. The first step in this process is to become familiar with the data. Because the team conducted the interviews and reviewed and summarized the data during the RQI process, they will already be acquainted with the interview data. The next step is to generate an initial set of codes (or, in this case, topics), based on the project's research questions, and team notes and summaries about the content of the data. This scheme of initial codes, which are likely to have a positivist slant, will then be piloted in Dedoose, with each team members coding one transcript. After this initial application, the team will meet to review, edit, and further define each category. The team will then return to the dataset to code the remaining interviews; each interview will be independently coded by two people. Once the data have been coded, the team can develop findings by extracting and analyzing data that have been coded at one or more themes.

Reflective Analysis

While the team is coding to create topic summaries, they will also be invited to engage in reflective thematic analysis [65]. The PI will be reading the narratives in an interpretive manner with the goal of identifying latent meaning. As a social worker with two decades of experience working with justice-impacted individuals on issues related to HIV prevention, the PI has a personal and professional framework through which she will interpret and derive meaning from the data. This reflective analysis is a subjective practice that will be informed by input from colleagues. Discussion with the full research team, including undergraduate RA and community consultants, will help to curate and refine these interpretations. Student RAs who can reach the "depth of engagement" [66] that is required to conceptualize the data in this nonpositivist manner may also contribute reflective analysis of the data. The level of analysis that is available to these new scholars, who are juggling myriad personal, professional and academic responsibilities, is an empirical question that this collaboration can begin to answer.

Trustworthiness and Credibility

Several processes are being taken to ensure the trustworthiness and credibility of these qualitative data. One, team members will engage in deliberate reflection to recognize and examine their positionality through open researcher-participant interaction, peer debriefings, and reflexive journaling [67]. Weekly meetings create space for peer dialogue and critical thinking while participation in community forums brings RAs in close contact with women who use drugs and creates opportunity for them to explore their own ideas about and reactions to criminal-legal, addiction, and HIV-related topics. Two, the study's data collection, analysis, and reporting steps are designed to promote the rigor of study findings. By engaging a diverse team in all aspects of the project from development of study instruments to data collection, the validity of the study is boosted [67]. Sampling techniques and goals are designed to establish broad representation and scope. Oversampling populations most impacted by HIV promotes the usefulness of data. A team approach on data collection and analysis encourages group and individual reflection about research-participant interactions and transparency [56]. The calendar and DST techniques encourage the creation of thick descriptions with rich details as specific moments in time are explicated. During the data analysis process, efforts will be made to remain open to the possibility of conflicting or contrasting narratives that run counter to overall themes [67]. Specific findings that can inform actionable next steps and be applied to other contexts will be advanced.

Efforts will also be made to bolster the credibility of this study [68]. First, the PI and the study consultants have been engaged with communities impacted by criminal-legal systems and HIV for decades. These relationships have established a track record that strengthens the project's credibility. In addition, the university with which the PI, community consultants, and student RAs are affiliated is a public, regional university of access with strong reputable ties throughout the community. Precise record keeping of the study's confidential dataset will allow study narratives to be available to other researchers who want to work with or examine the data.

Ethical Considerations

The protocol was reviewed and deemed exempt by the Southern Connecticut State University institutional review board (protocol #670). Informed consent is administered to all interview participants. During this process, it is emphasized that participants are volunteers and can decline to answer any questions or end the interview at any time. Specific permission to audiotape the interview is requested and each participant is invited to select their own pseudonym. During the transcription process, all identifying information (ie, names, dates, and locations) are removed. To protect participants' confidentiality, consent is obtained verbally because writing the participants' names on the consent form would create the only record of their name in the study files.

Results

Overview

Ten cisgender women have completed the survey and both interviews. Participants identify as Black (n=5), Latina (n=4), and White (n=1). Their average age is 40 (range 27-56) years. Data collection will be completed by December 2024, with analysis and dissemination continuing through 2025. Analysis from the first "scheduled blocks" have resulted in 2 preliminary findings. These preliminary findings suggest that the circumstances of women who use drugs deteriorated during the COVID-19 pandemic, and that services that might reduce HIV risk behaviors were not accessed.

Instability

The chaos and instability of participants' lives increased during the COVID-19 pandemic. Most experienced homelessness and were unable to access COVID-19–related housing programs or were evicted from these programs after short stays. Participants reported that social isolation and pandemic-related fear increased their anxiety, depression, and substance use. Sources of income included minimum-wage employment, primarily at fast food outlets, and illicit hustles, including sex work and larceny. Use

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of social services was low; food pantries and mobile syringe services were the most frequented programs. Several women were arrested during the COVID-19 pandemic and were either sentenced to probation or released with a "promise to appear" in court at a future time for adjudication. The uncertainty of being placed on probation with unclear stipulations and awaiting future court dates fueled a sense of hopelessness that increased substance use. Women reported that they frequently had limited to no cell phone access, which hindered their ability to maintain communication with judicial and social service systems. These findings suggest that community services failed to protect and support women who use drugs who were experiencing acute mental health and substance use crises during the COVID-19 pandemic.

Grief and Loss

When asked to describe a "turning point" in their lives, most of the women talked about the traumatic loss of a child. Participants' experiences of loss included the death of a child to illness or accident, the long-term incarceration of a child, and the permanent, sudden removal of one or more children by the state's child protection agency. None of the participants had ever received any kind of psychosocial services related to their maternal grief and loss. Left alone to cope with these experiences, many women reported using substances and engaging in self-harm behaviors. While none of the participants reported losing a close family member or friend to COVID-19 infection, bearing witness to the widespread death and dying of the pandemic activated their own unresolved grief and surfaced a range of complicated emotions that they were unprepared to manage. This finding informs knowledge about the etiology of substance use and invites further research and program development related to mothers' grief related to the loss of a child. In addition, this data is an opportunity to better understand how noncustodial mothers employ narratives of grief and loss to perform and assert their identity as "good mothers" in a socioinstitutional environment that has consistently denied or contested this claim.

Discussion

Summary

This project investigates the lived experiences of women who use drugs during the COVID-19 pandemic, when the use of incarceration decreased, and asks: What happens when she is not incarcerated? Given that incarceration is understood as a structural determinant of women's HIV risk, one hypothesis is that the HIV risk of women who use drugs may have decreased when they remained in the community with their sexual and drug using networks intact. Alternatively, HIV risk may have increased due to social isolation, stress, and reduced access to community-based services, including substance use and mental health treatment. Similarly, postponement of criminal-legal adjudication or punishment may have offered respite from prison life or could have been experienced as a time of uncertainty and limbo that elevated women's anxiety and risk behavior. This qualitative study uses multiple methods to better understand how COVID-19 era shifts in criminal-legal practices impacted the HIV risk behaviors of justice-involved women who use drugs.

Preliminary Findings

Preliminary analysis suggests that changes in the criminal-legal system during the COVID-19 pandemic had a detrimental impact on the lives of justice-involved women who use drugs. Participants reported limited access to criminal-legal and social service resources during the COVID-19 pandemic, including community supervision. As a result, women experienced homelessness, hunger, and mental health challenges which fueled increases in substance use. Women's previous experiences of grief and loss were activated by COVID-19–related death and dying. In addition to these preliminary findings, there were isolated stories that invite further exploration. For example, narratives from women who sold sex during the COVID-19 pandemic described the complications of simultaneously negotiating COVID-19 and HIV safety. Women who were arrested for larceny and released with a "promise to appear" at an unknown future date, used what they perceived to be the inevitability to their future incarceration, and lack of any viable alternatives, to justify further law-breaking and substance use.

Future interviews may offer additional data on the evolving definitions of risk in the context of sex work. Some women reported renting rooms from strangers whom they met in the community, circumstances that could lead to disputes, violence, sexual assault, and arrest. The nuances of this unregulated rental market may be another area of potential discovery in this project. The digital storytelling process, which has not yet begun, will also offer new perspectives and insights into women's lived experiences.

Strengths and Limitations

This protocol has several strengths and limitations. First, because all the data will be collected from people living in one northeastern state in the United States, the findings may not be transferable to other communities. Responses to COVID-19 by criminal-legal and social service systems varied across the country. Still, while what happened in this one state may be different than what happened elsewhere, the study will be helpful to researchers and community-based service providers in other regions by suggesting areas of vulnerability that require attention and theorizing about the meanings women ascribe to social policy and administrative actions. Second, the depth and breadth of the findings may be inhibited by the fact that the research team is comprised primarily of undergraduate students with little to no research experience. The pace of the program is shaped by its dual aims: (1) to train new scholars and (2) to build knowledge about complex social phenomenon. At the same time, the team's composition is a strength. This team of first-time researchers brings novel ideas and enthusiasm that disrupt entrenched practices and knowledge that can inhibit the production of new postulations. Third, the retrospective design of this inquiry raises questions about the accuracy of participants' memories. Especially if people were engaging in heavy substance use, it can be difficult to recall what transpired during the first year of the COVID-19 pandemic. Given this time lapse, the qualitative design of the study is a strength. This

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postpositivist methodology recognizes that there are many truths and values storytelling for its ability to produce meaning. In this sense, the most pressing question is, "Why is this story being told?" not "Is this story an accurate description of past events?"

Dissemination and Future Directions

Dissemination of study findings will take many forms. First, topic summaries will invite conversation with social workers, criminal-legal professionals, and other service providers about what happened during the COVID-19 pandemic and how the community might respond differently to future crises. Two, reflective analysis offers insights into the lives of women who use drugs and narratives that they tell themselves and others about who they are. This nuanced understanding of women's meaning making and identity that can inform clinical practice and program development. Three, findings will contribute to academic discussions in journals and conferences about engaging undergraduates in research, criminal-legal systems, substance use, and HIV prevention. The focus on women who use drugs and women's HIV risk in all these dissemination efforts contributes to ongoing efforts to center women's lives in dialogue about criminal-legal systems, substance use and HIV prevention that tends to focus on men.

Taken together, the multiple methods in this project will build understanding about the lives of women who use drugs during the first year of the COVID-19 pandemic. Findings may inform efforts to reduce reliance on carceral systems by building more community-based programs that to protect and support for vulnerable women.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available for reasons of participant confidentiality but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Report page documenting grant funding.
[PDF File (Adobe PDF File), 261 KB - resprot_v13i1e58285_app1.pdf]

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Abbreviations

CI: Correctional Institution
NIH/NIDA: National Institutes of Health's National Institute on Drug Abuse
PI: principal investigator
RA: research assistant
RQI: Rapid Qualitative Inquiry

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Protocol

Designing, Developing, and Testing a Chatbot for Parents and Caregivers of Children and Young People With Rheumatological Conditions (the IMPACT Study): Protocol for a Co-Designed Proof-of-Concept Study

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Abstract

Background: Pediatric rheumatology is a term that encompasses over 80 conditions affecting different organs and systems. Children and young people with rheumatological chronic conditions are known to have high levels of mental health problems and therefore are at risk of poor health outcomes. Clinical psychologists can help children and young people manage the daily difficulties of living with one of these conditions; however, there are insufficient pediatric psychologists in the United Kingdom. We urgently need to consider other ways of providing early, essential support to improve their current well-being. One way of doing this is to empower parents and caregivers to have more of the answers that their children and young people need to support them further between their hospital appointments.

Objective: The objective of this co-designed proof-of-concept study is to design, develop, and test a chatbot intervention to support parents and caregivers of children and young people with rheumatological conditions.

Methods: This study will explore the needs and views of children and young people with rheumatological conditions, their siblings, parents, and caregivers, as well as health care professionals working in pediatric rheumatology. We will ask approximately 100 participants in focus groups where they think the gaps are in current clinical care and what ideas they have for improving upon them. Creative experience-based co-design workshops will then decide upon top priorities to develop further while informing the appearance, functionality, and practical delivery of a chatbot intervention. Upon completion of a minimum viable product, approximately 100 parents and caregivers will user-test the chatbot intervention in an iterative sprint methodology to determine its worth as a mechanism for support for parents.

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Results: A total of 73 children, young people, parents, caregivers, and health care professionals have so far been enrolled in the study, which began in November 2023. The anticipated completion date of the study is April 2026. The data analysis is expected to be completed in January 2026, with the results being published in April 2026.

Conclusions: This study will provide evidence on the accessibility, acceptability, and usability of a chatbot intervention for parents and caregivers of children and young people with rheumatological conditions. If proven useful, it could lead to a future efficacy trial of one of the first chatbot interventions to provide targeted and user-suggested support for parents and caregivers of children with chronic health conditions in health care services. This study is unique in that it will detail the needs and wants of children, young people, siblings, parents, and caregivers to improve the current support given to families living with pediatric rheumatological conditions. It will be conducted across the whole of the United Kingdom for all pediatric rheumatological conditions at all stages of the disease trajectory.

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KEYWORDS

caregivers; chatbot; paediatric rheumatology; parents and caregivers; parents/carers; pediatric; proof-of-concept; quality of life; rheumatology

Introduction

Background

Pediatric rheumatological illnesses are chronic inflammatory conditions that affect the musculoskeletal system [1,2]. While some are rare, juvenile idiopathic arthritis (JIA), the most common rheumatological disease of childhood, currently affects 10,000 children and young people in the United Kingdom [3]. JIA occurs as frequently as juvenile diabetes mellitus and 10 times more frequently than acute lymphoblastic leukemia [4]. Children and young people with rheumatological conditions are well known to experience a high psychological burden, with decreased quality of life, increased pain and disease activity, physical disabilities, school absenteeism, suboptimal medication adherence, and transition challenges [1,5]. Up to two-thirds of young people continue with active disease into adulthood [6,7], with visible and invisible symptoms causing marked psychological ramifications. High levels of mental health comorbidity and consequent risk for adverse health outcomes are common in children and young people with rheumatological conditions [1,8]. The British Society of Paediatric and Adolescent Rheumatology (BSPAR) Standards of Care (2010) include the recommendation that a pediatric clinical psychologist should be part of the core multidisciplinary team [9]. However, a 2021 survey of 15 high-volume pediatric rheumatology UK centers highlighted that 7 centers failed to achieve this [10]. In 2019, the British Society of Rheumatology's (BSR) pediatric and adolescent state of play report [11] highlighted poor access to psychology expertise and recommended increased psychology provision. Early identification of children and young people who are struggling is known to improve outcomes, but current systems fall short of providing adequate emotional and mental health support to those with rheumatological conditions [12].

A review examining the impact of living with a child with a long-term health condition revealed that parents perceive that they are not always supported in their quest for information, and their ultimate responsibility for their child's health can be overwhelming [13]. Parents and caregivers described that when information is not available from health care professionals, they are compelled to search for it elsewhere [14] and feel the need to "take charge," becoming advocates for their child through "tenacious information seeking" [15]. Patient and Public Involvement and Engagement (PPIE) activities revealed that available parental support is currently inequitably distributed and accessed. Charity access is inconsistent, with awareness dependent on clinical teams, other parents, or "internet searching." Education support offered at "family weekends" is limited by geography and capacity. Social media closed groups are only available to those who know about them, and due to the unregulated content, parents were skeptical about the levels of support received.

Rheumatologists and nurse specialists in the United Kingdom identified a lack of clinic time as one of the biggest limitations to asking about emotional and mental health support in appointments, followed by the absence of resources when concerns are raised [10]. While clinic time is limited, waiting lists are too long, and an increase in the number of psychologists is awaited, upskilling parents has the potential to improve their child's psychological well-being and prevent the need for later mental health interventions. The James Lind Alliance also supports this in its 10 identified priority areas for mental health in children and young people, specifically: what methods can parents and caregivers use to identify that their child's mental health is deteriorating and what are the most effective early intervention strategies for supporting them to improve mental resilience [16]. In 2023, 5 UK pediatric rheumatology charities were so worried about mental health that they collaborated to develop and deliver a survey to understand the scale of the problem. The results from this work showed that out of 291 parents and caregivers completing the survey, 218 (82%) parents and caregivers reported their child's diagnosis as impacting their own mental health. It also highlighted that 60% of children and young people have needed mental health support since diagnosis (had help, are undergoing help, or are on a waiting list), and in relation to condition specific difficulties, 81% needed help with needle phobia, 80% are reluctant to take their rheumatology medicines, and 78% are struggling with side effects from medications [17].

At the time of this study application, chatbots were being used as a means of providing useful information in a variety of

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settings [18]. Chatbots are typically cloud-based programs that require internet-connected devices, and users interact with them in a number of ways, including through text and voice. In particular, chatbots such as Vincent have proven to be useful to enhance mental health [19], iHelper provides guided self-assessment for stress, anxiety, depression, and self-esteem, and Woebot is a text-based conversational agent providing 2-weeks of self-help, proven to significantly reduce depression [20]. Chatbots are beginning to be used in National Health Service (NHS) services, such as "Ask Olli" for parents at Alderhey [21] and "Oriel Assistant" for patients and staff at Moorfields [22], and evidence showed that most internet users would be receptive to using health chatbots [23]. Since the funding for the study was awarded, chatbot interest has progressed rapidly with the launch of commercially available chatbots. Chatbots potential in health care is also growing, with research progressing in this area. For example, ChatGPT and GPT-4 already show promise in translating radiology reports into plain language for families [24]. The exact deliverable for this study, however, is still work in progress and will be decided by the co-design group, taking into account issues such as digital poverty, scalability, advantages and disadvantages of platforms, data security, and outcome measures.

The "Interventions to improve Mental health supPort in families with children And young people with Chronic rheumaTological conditions" (IMPACT) proof-of-concept study aims to design, develop, and test a chatbot intervention for parents and caregivers of children and young people with rheumatic conditions. It is hoped that by empowering parents and caregivers, we will strengthen the support around children and young people, prevent anxieties and uncertainties from escalating, and improve other aspects of pediatric rheumatological care, such as adherence to therapies. This intervention is not to replace human contact but to be an adjunct when human contact is limited, for example, between appointments and while on holiday.

Study Setup

The research team is led by the principal investigator (PL), who is a senior pediatric rheumatology nurse, and the research facilitator (KK), who has a psychology degree and background in pediatric rheumatology research. This study proposal was submitted for a personal postdoctoral National Institute for Health and Social Care Research (NIHR) Advanced Clinical Academic Fellowship (ACAF; NIHR 302864), awarded in 2023 to PL, the first and currently (at the time of writing) only ACAF award given to a nurse in the United Kingdom. The study timeline is from April 2023 to April 2026.

Patient and Public Involvement and Engagement

A strong and engaged UK-wide steering group of children, young people, parents, caregivers, and health professionals is pivotal to the success of this study. The group is composed of 4 children and young people, 4 parents and caregivers, and 3 health care professionals (a clinical psychologist in pediatric rheumatology, a senior pediatric nurse working in rheumatology research, and a clinical informatics expert). The working group currently includes over 30 children and young people, parents and caregivers, health professionals, and key charity stakeholders who have all been involved in the study proposal since idea conception.

PPIE activities began over 2 years ago and helped shape this study. Initially, children, young people, parents, caregivers, and health professionals were asked whether they needed more support in living with a chronic pediatric rheumatological condition. As conversations proved there was a need to increase support to improve psychosocial well-being, discussions moved over time to consider what this may look like. Initially, the intervention was expected to be tailored toward children and young people; however, as conversations continued, parents and caregivers were open about their need for further support for themselves. A digital intervention was suggested that could help to better prepare their child through their "firsts" (first joint injection, first blood test, or first scan), know the right questions to ask in appointments, know how to have conversations with school, know how to encourage medication adherence, know how to talk about distorted body image due to corticosteroid therapy, know how to encourage home exercises, and know how to identify red flags in their child's mental health and where to go for help. During brainstorming activities, the idea of a "chatbot" was presented by a parent and unanimously selected as a potential targeted intervention. Parents and caregivers particularly liked the anonymity of chatbots and their constant availability.

Regular meetings, both web-based and face-to-face, have ensured key decisions have been agreed upon as a group, for example. whether 2 participants from the same family could be included in the focus groups. Key documentation has been reviewed by both the steering and working groups, and they will continue to be involved from the beginning to the end of the study. The methodology used for this study ensures that the study is directed by children, young people, parents, and caregivers, ultimately for children, young people, parents, and caregivers.

Methods

Methodological Underpinnings

This research study uses experience-based co-design (EBCD) methodology to guide the project, underpinned by the Medical Research Council (MRC)-NIHR Complex Intervention Research Framework [25]. EBCD is a form of participatory research that combines user-centered design and learning theory and is delivered through a 6-stage collaborative process (Textbox 1) [26,27]. These stages will be embedded throughout the study, maximizing the potential to use creativity and ideation to generate wide-ranging ideas and maximize opportunities for innovation, as recommended in the recently updated research framework [25].

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Textbox 1. The 6 stages of experience-based co-design (EBCD).

Stage:

- Project set-up
- Staff experiences
- Patient and caregiver experience
- Feedback and co-design
- Co-design teams
- Celebration event

A "trigger film" (short film) is integral to the EBCD methodology and highlights "touch points," which elicit shared reflections. For this study, the focus groups and planned exercises during the workshops will be video recorded, then edited to produce the trigger film. This film is useful to understand some of the key decisions made throughout the study and can be a useful aid for dissemination. Using the EBCD methodology is compliant with the NIHR Participant in Research Experience survey, which recommends that "technology provided to participants should be tested for reliability and ease of use and co-designed with the intended users" [28].

Aim

This proof-of-concept study aims to design, develop, and test a chatbot intervention to provide enhanced support compared to current clinical practice that is accessible, acceptable, and usable for parents and caregivers.

Inclusion and Exclusion Criteria

Children and young people aged 8 years or older with a rheumatological condition diagnosed before the age of 17 years and their siblings will be invited to join focus groups. Parents and caregivers of those with rheumatological conditions will also be invited to parent-specific focus groups. Health professionals who care for pediatric and adolescent rheumatological patients will also be invited to join health care–specific focus groups. Those without rheumatological conditions as a child or young person, siblings, or parents of these will not be included. Members of our steering group are also excluded from participating as research participants in the focus groups, although they are welcomed as facilitators.

Designing EBCD Focus Groups

The "core elements" of the revised MRC-NIHR Framework [25] state that it is imperative to understand key uncertainties, consider the context, and engage stakeholders. Therefore, the aim is to understand, from the perspective of children, young people, siblings, parents, caregivers, and health professionals, what support they think would be useful and whether they think this could be delivered within a chatbot intervention. Focus groups will be used to yield rich qualitative data from a range of individuals from across the United Kingdom. A minimum of 8 focus groups are planned, with approximately 6-12 participants in each group. The parent and caregiver groups will outnumber the child or young person, sibling, and health care professional groups as the intervention is ultimately for parents and caregivers. However, we are also interested in asking participants with rheumatic conditions what they would have found helpful for their parents or caregivers to know, asking siblings for their perspectives, and asking health professionals to discuss where they see more support being offered. Groups will be undertaken remotely or face-to-face, depending on the requests of the majority of participants (in line with NIHR PPIE survey findings) [29].

Parents and caregivers, siblings, children, and young people will be recruited using consecutive sampling. Participants will learn about the study through study advertisement flyers in clinical settings or by being given a flyer. Ethical approval has been granted for local pediatric and adolescent rheumatology centers to display and distribute flyers, and in conjunction with pediatric rheumatology charity social media channels and email lists, this should increase the opportunities for inclusivity across all 4 nations of the United Kingdom. A study-specific website has been developed that encourages interested children, young people, or parents and caregivers to contact the study team to find out more, or if they are unable to access technology, their local team can contact the IMPACT research team on their behalf. Language-specific study documentation and interviews will be offered for those for whom English is not their first language. Staff will be recruited by seeing the study flyers and contacting the study team. A sampling matrix will ensure representation from professional groups and centers.

Consent will be sought for audio and visual recording, the former to guide data analysis, while the video recording will form the trigger film. Thematic analysis [30] will be conducted by 2 members of the research team and discussed with the steering group to identify themes critical to shaping chatbot development using NVivo (QSR International). The final themes will help develop the chatbot.

Developing EBCD Workshops

The working group will meet in 2 face-to-face workshops to discuss the themes and help identify the core components of the chatbot intervention. The workshops will use personas and scenarios developed from the focus group discussion to help inform the chatbot development process. Such creative and participatory methods will allow the shared experiences of the members of the working group to shape the intervention development process. The workshop will be video recorded as recommended in the EBCD methodology, with excerpts of the film used later in the trigger film.

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Over the last few years, as chatbot technology has developed at an alarming rate, with large language models now leading the way, their popularity has increased [31]. While it is not possible to be specific regarding the content of the chatbot until the focus groups have been completed and analyzed, a content management system will be developed to inform the chatbot development. It is anticipated that the chatbot may include such functions as (1) frequently asked questions, (2) rheumatology-specific information, (3) information about managing "firsts," (4) parental red-flag identification and signposting, and (5) persuasive argument roleplay. Using agile principles, the exact technologies and approaches used may change as the team learns more about the user requirements. Development of the chatbot will occur within existing recommendations such as the National Institute for Health and Care Excellence Evidence Standards Framework for Digital Health Technologies [32], NHS Digital guidance for cloud security [33], and the Department of Health guidelines for "Putting data, digital, and tech at the heart of transforming the NHS" [34].

User Testing the Agile Sprint Methodology

Chatbots can potentially lead to frustration, anger, dissatisfaction, and, at worst, disengagement with the technology if not designed and developed with key stakeholders [35,36]. This is not a new technology; however, using it for this purpose for parents and caregivers of children and young people with rheumatological conditions is new. Therefore, the crucial step before a larger study must be to determine accessibility, acceptability, and usability through user testing.

User testing will occur through an iterative methodology with short product development cycles and the deployment of the prototype to groups of parents and caregivers. This will ensure user feedback directs incremental iterative software development. This process of "agile development" runs in a cycle of design, develop, test, and refine (termed a "sprint"). Every 3-month cycle, we will user-test, analyze, and develop. At least 25 parents and caregivers will be recruited for each cycle, which is anticipated to be up to 4 cycles in total. While the majority of participants will be naïve to each cycle, some may be invited back to 'test' new modifications in the next cycle. Parents and caregivers will be requested to use the chatbot on a number of occasions for a defined frequency of time.

Eligible parents and caregivers will be those of a child or young person who was diagnosed while being aged 17 years or younger with a chronic pediatric rheumatological condition and who agrees to complete the user metrics throughout the testing period. Flyers in local hospitals will again advertise this part of the study to parents and caregivers, who will then contact the study team for further information. If families are identified as those who do not have access to technology, individual conversations will occur to investigate whether a device may be loaned. All parents and caregivers will be sent an information pack and must provide written consent. Of note, the chatbot technology can integrate "Google Translate," and as such, families who do not have English as a first language will be able to participate.

Usability outcome measures and qualitative experiences will be sought in order to understand the acceptability of the chatbot for progression to a future study. Outcome measure selection will be informed by exploring what success would look like for families. These may include such measures as (1) attrition of participants; (2) engagement and duration of conversations; (3) user satisfaction measures, such as the System Usability Scale (SUS) [37,38], the User Experience Questionnaire (UEQ) [37], and the Net Promoter Score (NPS) [39,40]; and (4) semistructured interviews with the final group of "sprint" participants.

Ethical Considerations

The study will be conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. Ethical approval from the Health Research Authority has been received for the study (approval received on August 31, 2023, from the Yorkshire & The Humber–Leeds West Research Ethics Committee, IRAS ID: 329476. REC Reference:23/YH/0172). All participants are asked to provide informed written consent or assent (for those aged 16 years or younger, paired with parental or caregiver's consent) before being enrolled in the study. Consent and assent are requested to audio and video record the focus groups and workshops to enable data analysis and the production of the trigger film, while also requesting to use anonymized quotes and pictures of physical creations in dissemination.

Results

The study is ongoing. As of February 28, 2024, we have enrolled 73 children, young people, parents, caregivers, and health professionals in 12 focus groups so far. We have had over 280 children, young people, siblings, parents, and caregivers reach out to be included in focus groups, and therefore an ethics amendment has been sought to increase our recruitment target. This huge interest validates the need for the study, and already interesting ideas are emerging. Preliminary results will be published from the focus groups by the end of 2024 and from the user testing by the beginning of 2026.

Discussion

The rheumatological conditions of childhood affect the whole family. Children and young people have been shown to suffer with their emotional and mental health as they cope with the implications of a chronic health condition. Parents, caregivers, and siblings of the child have also been shown to experience difficulties as they navigate the new normal family lifestyle and the implications of the health condition on their own lives. Parents and caregivers report that for conditions such as JIA, there is a wealth of information available on the internet; however, it is not always clear how robust and trustworthy this information is, while for rarer pediatric rheumatological conditions, there is much less available information, and searching for what little there is can be upsetting and often futile. Providing information and support in the style of a chatbot has many advantages, including physician-ratified and endorsed information, anonymity, being accessible throughout the day and night, and the ability to integrate new novel functions, such

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as the ability to practice difficult conversations with the chatbot enacting as their child or young person. Therefore, the aim of this study is to investigate whether a chatbot intervention could provide additional support to families between appointments without the need for human resources.

If the chatbot proves to be a success, then such an intervention may be useful in other diseases and with other populations. If the chatbot shows that parents and caregivers do not find it useful and its function is limited, this is useful learning in the current rapidly advancing technological climate, and further intervention and development may be commissioned. If the intervention is deemed acceptable, then to draw conclusions regarding the effectiveness of the intervention, a further study would be required. Discussions will begin early to scope out options for embedding the chatbot into NHS services in order to enhance the transition from research to service delivery following further assessment. Links to research outputs will be made available on the IMPACT study website [41].

This study has several limitations; primarily, as a proof-of-concept study, it will be difficult to generalize the findings. Coping with a chronic health condition varies on a daily basis depending on disease severity, treatments and their side effects, social support, and daily mood fluctuations. Therefore, the chatbot may prove useful to families for the short duration of this study, but as there is no external control group, analyzing all variables and drawing sound conclusions could be challenging. Also, due to the technological nature of a chatbot intervention, families who do not have easy access to technology may be disadvantaged; however, we are in the process of scoping local technology resources, which can be loaned out if required. We also set a lower age limit (aged 8 years or older) for child participation. This was to be mindful that the questions we are asking children about what else they would have liked support with would be difficult for most children aged 8 years or younger to answer. However, we are aware that in some instances, parents and caregivers feel their younger child may have liked the opportunity to take part.

We believe this study can have significant future applications and implications, such as learning from family perspectives on how we can improve upon current rheumatological clinical care, providing a responsive and tailored intervention to help support families better, and an understanding of how such technology could be embedded into the wider health care system. This is particularly relevant in today's current climate of limited staffing resources and an interest in delivering care differently. This study also offers an insight into how a chatbot could be used for families who live at a distance from their health care site, thus offering advantages over face-to-face support appointments and providing a resource for families, which may in turn lessen the need to contact the local team for support and thus free up valuable resources. The interest in the study so far, at over 280 families who have reached out in just over three months, over double the planned recruitment for the focus groups, is clear evidence that we need to do more to listen to, engage with, and support families further.

Acknowledgments

The authors would like to thank the children, young people, parents, and caregivers who formed the working group and have been pivotal in getting this study started. We would also like to thank all of the pediatric rheumatology charities who have also supported this work from inception to the present day (particularly Children's Chronic Arthritis Association, Versus Arthritis, National Rheumatoid Arthritis Society, Scottish Network for Arthritis in Children, Lupus UK, and Myositis UK) and all of the rheumatological teams across the United Kingdom for their support so far. We would also like to thank Professor Endacott (National Institute for Health and Social Care Research [NIHR] Director of Nursing and Midwifery) for supporting the fellowship application and this study.

PL (ACAF reference number 302864) is funded by Health Education England/NIHR for this research project. The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care.

Data Availability

The anonymized data sets analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

PL, KK, AK, ALS, RS, GR, and NJS participated in the design, conception, and revision of this study. KK undertook the design and revision. PL substantially contributed to the conception and design of the protocol and its write-up. PL, KK, LRW, AK, ALS, RS, GR, and NJS have approved the submitted version, agreed to be personally accountable for their own contributions, and ensured that any accuracy and integrity issues that may arise in the future will be appropriately investigated and resolved. The IMPACT Steering Group contributed to the design and conception of the study, reviewed the manuscript, and approved the submitted version. The steering group comprises Eire Byrne, Natalia Kasaru, Morgan Pawlett, Cameron Papantoniou, Emily Earle, Nathanael Bourns, Rachel Pulfree-Blythe, Eunice Kasaru, Emma Piepenstock, Gemma Molyneux and Heather Rostron. Further information is available elsewhere [41].

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Conflicts of Interest

PL is currently receiving a personal fellowship award from the NIHR fellowship for nonmedical health care professionals (ACAF reference number 302864), and as Patient and Public Involvement and Engagement (PPIE) co-lead for the NIHR Great Ormond Street Hospital for Children NHS Foundation Trust and Biomedical Research Centre (GOSH BRC), she receives some salary support from the NIHR Biomedical Research Centre at GOSH. PL is also a Senior Center Affiliate at The Centre for Adolescent Rheumatology Versus Arthritis at UCL University College London (UCL), University College London Hospital NHS Foundation Trust (UCLH), and GOSH, which is supported by Versus Arthritis (21593). LRW's contribution was underpinned by grants from the Medical Research Council (MRC; MR/R013926/1), Versus Arthritis (22084, 21593), and Great Ormond Street Hospital Children's Charity (VS0518). AK's contribution is supported by a Canada Research Chair in Mental Health and Chronic Disease of Childhood. ALS is supported by an NIHR Clinician Scientist Award (CS-2018-18-ST2-005). This work is supported by the NIHR GOSH Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health.

Multimedia Appendix 1
Reviewer comments.
[PDF File (Adobe PDF File), 1300 KB - resprot_v13i1e57238_app1.pdf]

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Abbreviations

ACAF: Advanced Clinical Academic Fellowship
BSPAR: British Society of Paediatric and Adolescent Rheumatology
BSR: British Society of Rheumatology
EBCD: experience-based co-design
IMPACT: Interventions to improve Mental health supPort in families with children And young people with Chronic rheumaTological conditions
JIA: juvenile idiopathic arthritis
MRC: Medical Research Council
NHS: National Health Service
NIHR: National Institute for Health and Social Care Research
NPS: Net Promoter Score
PPIE: Patient and Public Involvement and Engagement
SUS: System Usability Scale
UEQ: User Experience Questionnaire

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Protocol

Developing and Evaluating a Data-Driven and Systems Approach to Health Promotion Among Vocational Students: Protocol for the Data Health Study

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Abstract

Background: Vocational school students exhibit significant risk behaviors in terms of poor diet, frequent use of nicotine products, inadequate fruit and vegetable intake, low levels of physical activity, and poor mental health. This makes vocational students vulnerable to the development of noncommunicable diseases. Therefore, effective health promotion programs targeting vocational students are required.

Objective: The Danish study “Data-driven and Systems Approach to Health Promotion Among Vocational Students” (Data Health) aims to develop, implement, and evaluate a systems approach to support vocational schools, municipalities, and local communities in implementing locally relevant health promotion actions among and for vocational students. This paper describes the Data Health program and how implementation and preliminary effectiveness will be evaluated.

Methods: The Data Health program offers an iterative 5-step process to develop changes in the systems that shape health behavior and well-being among vocational students. The program will be implemented and evaluated in 8 Danish vocational schools in 4 municipalities. The implementation of the process and actions will be explored using a systems-based evaluation design that assesses contextual differences and the mechanisms through which the program leads to changes in the systems. Preliminary effectiveness at the individual level (students’ self-reported health behavior and well-being) and organizational level (school organizational readiness reported by school staff) will be assessed using a quasi-experimental design, and cross-sectional data will be collected at all 8 schools simultaneously 4 times during the 2-year study period.

Results: This study was launched in 2021, and data collection is expected to be completed in June 2024. The first results are expected to be submitted for publication in January 2024.

Conclusions: We expect that the Data Health study will make significant contributions to complex intervention research by contributing to the paucity of research studies that have used systems approaches in school settings. The study will also provide evidence of successful elements for systems change and effectiveness to determine whether a national scale-up can be recommended.

Trial Registration: ClinicalTrials.gov NCT05308459; https://clinicaltrials.gov/study/NCT05308459

International Registered Report Identifier (IRRID): DERR1-10.2196/52571

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(JMIR Res Protoc 2024;13:e52571) doi:10.2196/52571

KEYWORDS

health promotion; health behavior; well-being; organizational readiness; cocreation; causal loop diagram; systems thinking; systems-based evaluation; vocational schools; youth

Introduction

Social Inequalities in Health

Globally, 71% of all deaths are due to noncommunicable diseases (NCDs), and more comprehensive preventive strategies are needed to reduce NCD mortality worldwide [1]. Social gradients exist in NCD risks (tobacco use, physical inactivity, unhealthy diet, and harmful use of alcohol) and NCD-related premature deaths. Populations with higher educational attainment have better health than those in lower socioeconomic groups [2]. Most students attending vocational schools come from low-income families [3,4], and an ordinary vocational degree is defined as "shortened school education." This makes vocational students vulnerable for NCDs, and already as students, they report a high prevalence of tobacco smoking, inadequate fruit and vegetable consumption, physical inactivity, and obesity [5]. For example, in Denmark, 39% of vocational students are overweight (BMI >25 kg/m^2) compared with 14% of high school students, and this prevalence among vocational students is increasing (2014: 30%; 2019: 39%) [6,7]. Despite this, students in vocational education are an often overlooked but important group to target for health promotion to reduce health inequalities [5].

The Complexity of Health Behavior

The application of health promotion can strengthen the capability of individuals to take action and build the capacity of groups, communities, or organizations to act collectively to exert control over the determinants of health [8]. The determinants of health are complex and influenced by underlying dynamic factors at multiple levels (ie, individual, intrapersonal, organizational, environmental, neighborhood, and structural) [9,10]. Evidence suggests that chancing organizational structures and processes and strengthening relationships between organizations are more likely to maintain healthy behavior among individuals than programs that target individual behavior change only [11]. In addition, multicomponent approaches (a combination of structures, processes, and individual behavior changes) for health promotion are more effective than single-component programs [12,13].

A challenge for health promotion is the "voltage drop" that has been identified when effective programs are scaled up across contexts (eg, schools of different sizes), as different contexts lead to different outcomes [14,15]. Vocational students' health behaviors and well-being vary across educational tracks (technical, business, agriculture and food services, social and health services) and regions [7], requiring the use of local data to identify intervention opportunities and priorities. Data-driven programs that use relevant local data to strengthen intervention design are emerging in health promotion research. These programs explicitly consider local conditions as a means of increasing the strength and relevance of the interventions implemented [16,17].

Approaches to Health Promotion in Schools

Schools are important settings that influence health behaviors [18]. In the Danish vocational school reform in 2015, vocational schools were mandated to engage in health promotion to increase students' healthy behavior and well-being and reduce dropout [19]. There is little evidence on how to support vocational schools to implement effective and sustainable health promotion. Vocational schools have struggled to implement and integrate health promotion into their core business [20], so more knowledge is needed about what approaches are feasible, effective, and sustainable in this setting. In Denmark, the smallest administrative unit, the municipalities, are responsible for health promotion among all citizens within their jurisdiction [21]. This places the 92 Danish municipalities as central to vocational school health promotion, but many schools and their students often cross municipal boundaries, making the responsibility for vocational school health promotion unclear and therefore less of a priority in many Danish municipalities [21]. However, previous research shows that municipalities are keen to work with health promotion at vocational schools but often lack a framework for these activities [22].

The World Health Organization's Health Promoting Schools (HPS) principles [23] state that efforts to improve health should go beyond individual behavior change to consider local contexts, organizational and policy changes (eg, from educating individuals to choosing alternative foods to changing the foods available), or a combination of these [14]. In addition, the HPS principles argue that involving the surrounding community and key community leaders will create a more sustainable environment that can support the maintenance of healthy behavior changes among students [24]. Systems thinking has emerged as a method for understanding and changing the drivers of complex health behavior challenges [10,25]. A systems perspective considers a broad approach that engages different groups of participants to contribute to the design, implementation, and evaluation of actions that disrupt current systems and normalize change [10,26]. Identifying and activating modifiable parts of systems (ie, leverage points) is essential to change structures, goals, and beliefs in the systems and thus achieve sustainable health behavior change [27]. Engaging key stakeholders in coordinated efforts [28] has been conducted in recent attempts to apply systems approaches within health promotion (eg, obesity [17,29-31], reducing dietary inequalities [32] and physical inactivity [33], and tobacco control [34]). In combination, HPS approaches and systems thinking provide a set of methods and perspectives that could be effective and sustainable for school health promotion [35].

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Objectives

The Data-Driven and Systems Approach to Health Promotion Among Vocational Students (Data Health) study aims to develop, implement, and evaluate a systems approach informed by local data to support vocational schools, municipalities, and local communities in implementing locally relevant health promotion actions among and for vocational students. This protocol describes the Data Health program and how its implementation and preliminary effectiveness will be evaluated at 8 vocational schools across 4 municipalities in Denmark to determine if national scale-up can be recommended.

Methods

The Vocational School Setting

Vocational education in Denmark prepares students for specific occupations and is divided into four main educational tracks: (1) technical (eg, electrician), (2) business (eg, office assistant), (3) agriculture and food service (eg, farmer or chef), and (4) social and health service (eg, health care assistant). Vocational education alternates between school-based training and workplace-based training, with approximately one-third of the time spent in school [36]. Some schools are multisited and have student populations greater than 6000, whereas other schools are located at a single address with a student population of no more than 100. Almost two-thirds of students are men (64.7%), but the gender distribution varied according to educational track; for example, the proportion of men is 89.3% in technical education but only 12.3% in social and health service education [37]. The average age of students is 24 years; some students enroll directly from primary school (aged 15-17 years), whereas others begin later in adult life (39.8% is aged >25 years) [37].

Recruitment

We will use a purposive sampling strategy. A total of 8 vocational schools will be recruited based on the region (Capital Region of Denmark and Region Zealand) and educational track (technical, business, agriculture and food service, and social and health service) to include one vocational school from each educational track in both regions. Simultaneously, the municipalities where the vocational schools are geographically located will be recruited. The enrolled schools and municipalities will be responsible for recruiting community actors with support from the research team, if needed. The role and responsibilities of the actors in the community is described in steps 3 and 4 of the program. In this case, “community actors” refers to individuals, organizations, or companies, both local and national, who can provide resources and social support for the implementation of actions for change.

Content of the Data Health Program

Development

The Data Health program offers an iterative 5-step process (Figure 1) for developing change in the systems to shape vocational students’ health behavior and well-being, combining best practices in health promotion research, including methods from systems science [10,38], data-driven approaches [16,39], and the World Health Organization’s HPS principles [23]. The program was developed by a health promotion research group piloted and formatively evaluated in 1 vocational school and 1 municipality from June 2021 to June 2022. The formative evaluation included observations and interviews and surveys of key participants from both school and municipality. Weekly meetings were held between the evaluator (AS) and the research team to discuss the experiences, barriers, and enablers of implementation. During the formative evaluation, suggestions for program changes were made by exploring the municipality and vocational school environmental contexts and how the program would fit or function within these settings. The research team adjusted and incorporated changes to the program steps throughout the pilot test.

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Figure 1. The 5 steps of the Data Health program.

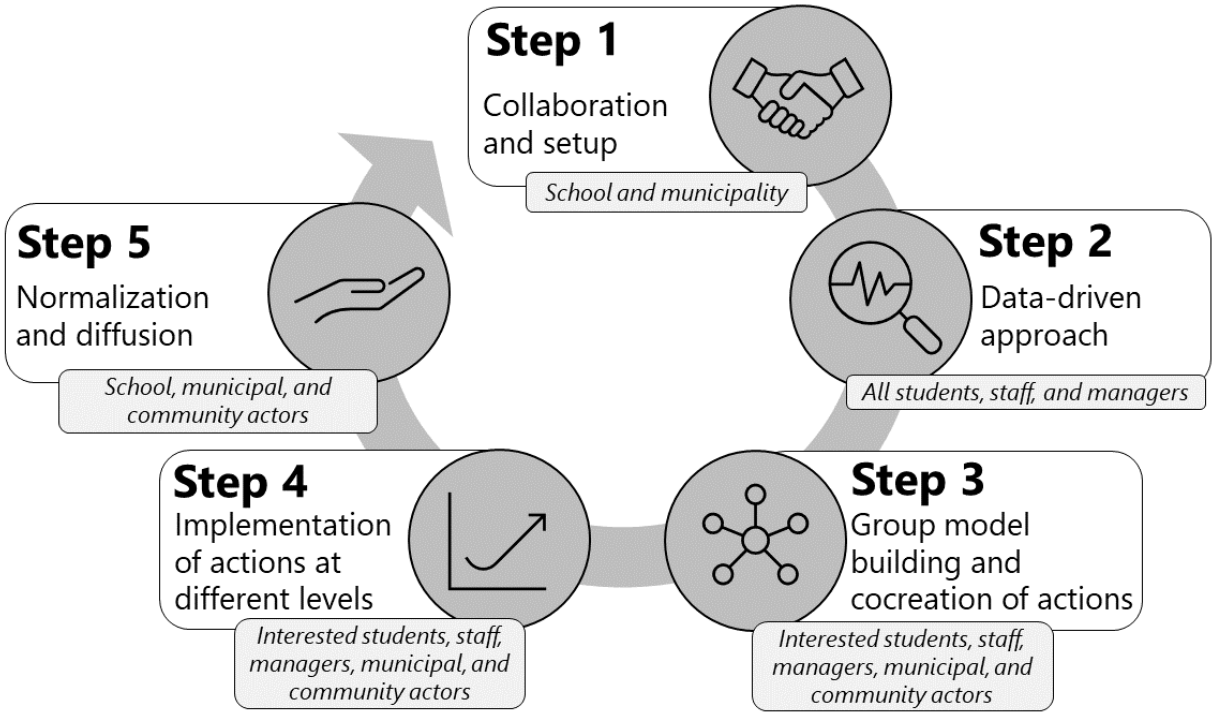

The research team will be responsible for the implementation of steps 1 to 3 of the program but will concurrently build the capacity, motivation, and commitment of the school and municipal program coordinators to be responsible for the implementation of actions and to promote the normalization of the program (steps 4-5).

Step 1: Collaboration and Setup

The Data Health program will begin with the establishment of a formal collaboration agreement between management representatives from the vocational school, the municipality, and the research team. Both the school and the municipality will appoint 1 or 2 staff members as school and municipal program coordinators, respectively. One month of salary will be provided to each school program coordinator (€4000; a currency exchange rate of €1=US $1.09 is applicable) to support program implementation. The roles and responsibilities of the different partners will be clarified and negotiated. Once the collaboration and commitment at the management level has been secured, information about the program will be disseminated by the school management to all staff and students. Dissemination activities include information by email and a kick-off meeting for staff, whereas dissemination for students includes customized posters and flyers distributed in common areas of the school. On the basis of the learnings from the pilot study, we have enhanced the dissemination strategy for the program to boost program visibility at the schools and comprehension among both staff and students.

Step 2: Data-Driven Approach

Local survey data on students' health behaviors and well-being will be collected and analyzed by the research team (see the description of individual outcomes in research question [RQ] 5). To stimulate motivation and interest, the data will be returned to the school and municipality within few weeks in the form of a local health profile. The local health profile covers modifiable health risk factors among vocational students, for example, nicotine use, unhealthy eating habits, physical inactivity, and poor mental health [7]. A simplified version of the health profile will be presented by the research team and the municipal program coordinator at separate meetings for school managers and staff and for students to share and increase their knowledge about health promotion, stimulate discussions and reflections about the results, and promote engagement and motivation for change. On the basis of the data presentations and discussions, the staff and students will be asked to complete a short questionnaire to select the health issue they are most motivated to address. During the pilot, we explored how best to select the specific health issue to be addressed in the remaining steps of the program and who should make this decision. The conclusion was that it is a school management decision, but schools are strongly encouraged to include the perspectives of staff, students, the municipality, and data from the local health profile in the process. To increase the prospect of becoming an iterative model, the local health survey has been designed to match an existing municipal-based health profile system [40] that the school-municipal collaboration can sign up after the research team has withdrawn the program.

Step 3: Group Model Building and Cocreation of Actions

Group Model Building (GMB) is a participatory method from systems science to facilitate a shared understanding of the structures and relationships that shape the system through the creation of causal loop diagrams (CLDs) [38,41]. A CLD helps to build a shared understanding among participants of the cause and effect relationships within a given system and to identify and agree on relevant and important areas for change [41]. In previous community research, this approach has been shown to improve the understanding of the problem, develop consensus

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on actions for change among a diverse group of participants, and increase participants' social network [41,42].

GMB is a central part of the Data Health program, as we aim to involve and engage a wide range of participants in developing a CLD and identifying locally adapted actions for change. In this program, the GMB process consists of 3 sessions (GMB1-3), as proposed and applied by an Australian research group at the Institute for Health Transformation, Deakin University [43]. The Data Health research team was trained in the GMB process by this group and then adapted the process and methods to a vocational school setting and vocational students, primarily based on the approaches and results of the pilot test.

In GMB1-2, participants will cocreate a CLD [44] to gain a shared understanding of the perceived causes and drivers of the health issue selected in step 2, for example, poor mental health or physical inactivity. Participants will also identify existing initiatives or programs in the school or community that could have an impact on perceived causes and drivers. GMB1-2 will involve 5 to 10 students, 5 to 10 school staff members, the school and municipal program coordinators, and school management. The school program coordinator will recruit a diverse group of motivated students and staff based on gender, age, and education. The Systems Thinking in Community Knowledge Exchange computer software [45] will be used during this process. At the end of GMB2, participants will identify several community actors who are considered relevant or necessary for the identification and implementation of actions across the school, community, or municipality. These community actors, representing different organizations, sectors and areas of expertise, will then be invited to GMB3 via phone calls. Together with the participants from GMB1-2 and other interested students and staff members, this wider group of participants will identify leverage points in the CLD and prioritize actions to change the system. Within systems thinking, actions can range from minor actions to major actions [27,41]. Minor actions often aim to solve a single issue and can often be implemented quickly with low resource costs (eg, single events), whereas major actions can aim to change paradigms in the way individuals or organizations think and behave and are often more difficult and costly to implement (eg, changes in an organization's goals and beliefs) [27]. The principle in systems thinking is that minor actions can stimulate major actions [27,41].

Participants will identify existing actions or codevelop new actions to change specific elements of the system or the entire system. Actions for further implementation will be selected based on feasibility and expected impact. As a result of GMB3, "action groups" of community actors, staff, and students will be formed, based on motivation, to plan and implement one or more specific actions.

Step 4: Implementation of Actions at Different Levels

In the months following GMB3, the action groups will plan and implement actions for changing the system, assisted by the school and municipal program coordinators. Examples of actions at different levels can be found in the description of program evaluation (implementation of actions [RQ2]). To support the coordinators and action groups, a guide to the development and implementation process has been adapted from previous work [38]. In addition, the Data Health study has reserved funds for each school (€1350) to support the implementation of actions or involvement of community actors to run implementation.

Step 5: Normalization and Diffusion

The school and municipal program coordinators will be responsible for the continuation of the program, and the resources available for this will depend on the priorities of these organizations. The research team will organize meetings between relevant community actors and managers from the school and municipality to encourage the initiated collaborations to remain formalized beyond the program. At these meetings, we will develop a strategy for the continuation of the actions already initiated and a plan for new data collection and development of new local actions. Most municipalities in Denmark have a questionnaire tool [40] for data collection to support the municipalities' work with health behavior and well-being among children and youth. The municipalities will be encouraged to use the tool for future data collection at the program school, as well as at other vocational schools within the municipality.

To increase and maintain momentum for health promotion practices among vocational students, all school and municipal program coordinators and relevant community actors will connect across study sites every 4 months in a community of practice (CoP), initiated by the research team. The CoP is a forum for sharing experiences and learnings on effective strategies for health promotion and collaboration across study sites but will eventually be open to other schools and municipalities interested in implementing the Data Health program.

If all 5 steps are completed as intended, we expect various elements of the Data Health program to be sustained, including the actions implemented, the collaborations initiated, and the organizational practices and motivation to repeat the monitoring to evaluate changes and develop new actions.

Program Evaluation

Research Questions

In total, 5 RQs will comprise the evaluation of the Data Health program:

- RQ1 (process evaluation—steps 2 and 3 of the program): To what extent is the data-driven approach and the GMB process implemented as intended, and what seem to be the most important mechanisms of change and contextual factors?
- RQ2 (implementation of actions—step 4 of the program): What characterizes the planned and initiated actions and what are the unintended consequences related to implementation? Who is involved in the planning and implementation?
- RQ3 (program normalization—step 1 and 5 of the program): What are the opportunities, barriers, and needs for the collaboratives and program to be sustained and normalized?

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- RQ4 (organizational outcomes): Does the program stimulate organizational changes in schools to work in a more health-promoting direction?
- RQ5 (individual outcomes): Does the program contribute to improvement in health behaviors and well-being among vocational students?

Study Design

To evaluate the implementation of the program, related actions, and systems impact (RQ1-3), we will use a systems-based evaluation design that seeks to understand how the program and the systems adapt to each other [10,46]. Evaluation using a systems perspective needs to adapt as the program unfolds by examining emergent outcomes that result from the interactions of participants [10,46], and it involves examining relationships, interactions, and patterns rather than individual outcomes and static "snapshots" [46,47]. The systems-based evaluation design aims to gain an in-depth understanding of the system as a whole without a "control system." However, it is not possible to include every part of a dynamic system; therefore, it is necessary to define systems boundaries to determine what is considered relevant in terms of what and where to evaluate [46,48]. The starting point for defining the boundaries is the identified primary health issue that each of the 8 program schools has chosen to target. All organizations and interventions relevant to the targeted problem will be considered as part of the system. In terms of system factors, we will focus on modifiable social and physical environmental factors rather than psychological or genetic factors.

We will examine preliminary effectiveness (see descriptions of organizational outcomes [RQ4] and individual outcomes [RQ5]) at the organizational level (ie, school organizational readiness) and at the individual level (ie, students' health behavior and well-being) using a quasi-experimental design with a nonrandomized clustered stepped-wedge strategy. The 8 program schools will be enrolled in 2 steps, matched by educational track (one school from each main track) and geographic location (2 schools from 2 Danish regions). The matched clusters will be assigned to early start (January 2022) or late start (6 months later). This design allows for a sequential roll-out of the program and allows us to control for differences between study sites (vertical control) and secular trends (horizontal control) during the study period [49]. Organizational- and individual-level data will be collected simultaneously at all 8 schools 4 times during the 2-year study period at baseline and at 3 follow-up points (T1, T2, and T3; Figure 2). As systems change takes time to diffuse into individual behavior changes [31], the research team will in due course seek opportunities and funding for longer-term data collection (ie, a 5- and 10-year follow-up).

Figure 2. Study design and timeline of the data collection for the effectiveness evaluation. GMB: Group Model Building.

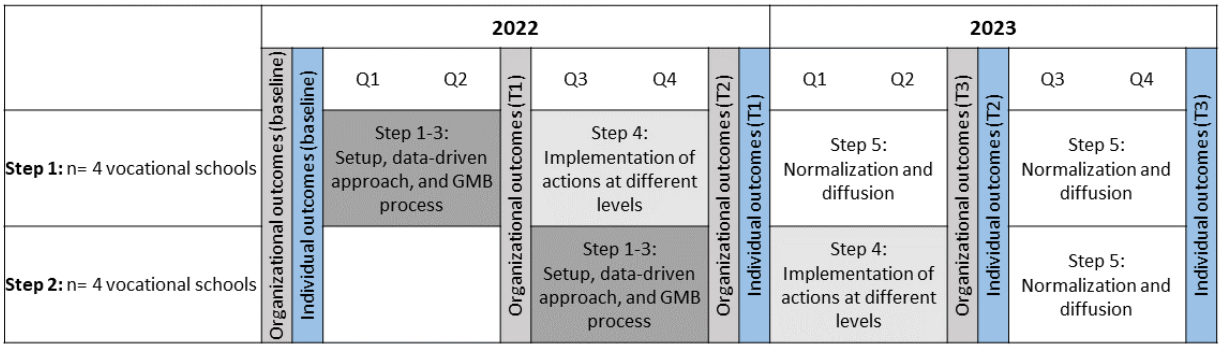

Program Theory

A program theory explains how a program is expected to work and under what conditions [10]. The Data Health program theory (Multimedia Appendix 1) is captured in a series of "if-then" statements and is based on key findings from the pilot test, published literature reporting trial results or theoretical abstractions [8,16,27,50-53], and the research group's experiences and previous research in the field [20,54-57]. Mechanisms of change are the hypothesized causal links between the program components and identified outcomes, triggered within the contexts in which the program is implemented [10]. In total, we hypothesize 6 mechanisms of change as plausible causal links between the data-driven approach and the GMB process and outcomes; these are indicated by mechanisms connected to steps 2 and 3 in Figure 3. To understand the interactions among context, program components, mechanisms, and outcomes; the research group visualized the initial program theory as a systems map, illustrated in Figure 3. The map summarizes our proposed model of how program components are expected to lead to systems change and outcomes. The connecting arrows show how changes in one part of the system are expected to generate changes in other parts of the system. The Data Health program theory and system map will continually be refined and revised as part of the evaluation process.

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Figure 3. The Data Health system map.

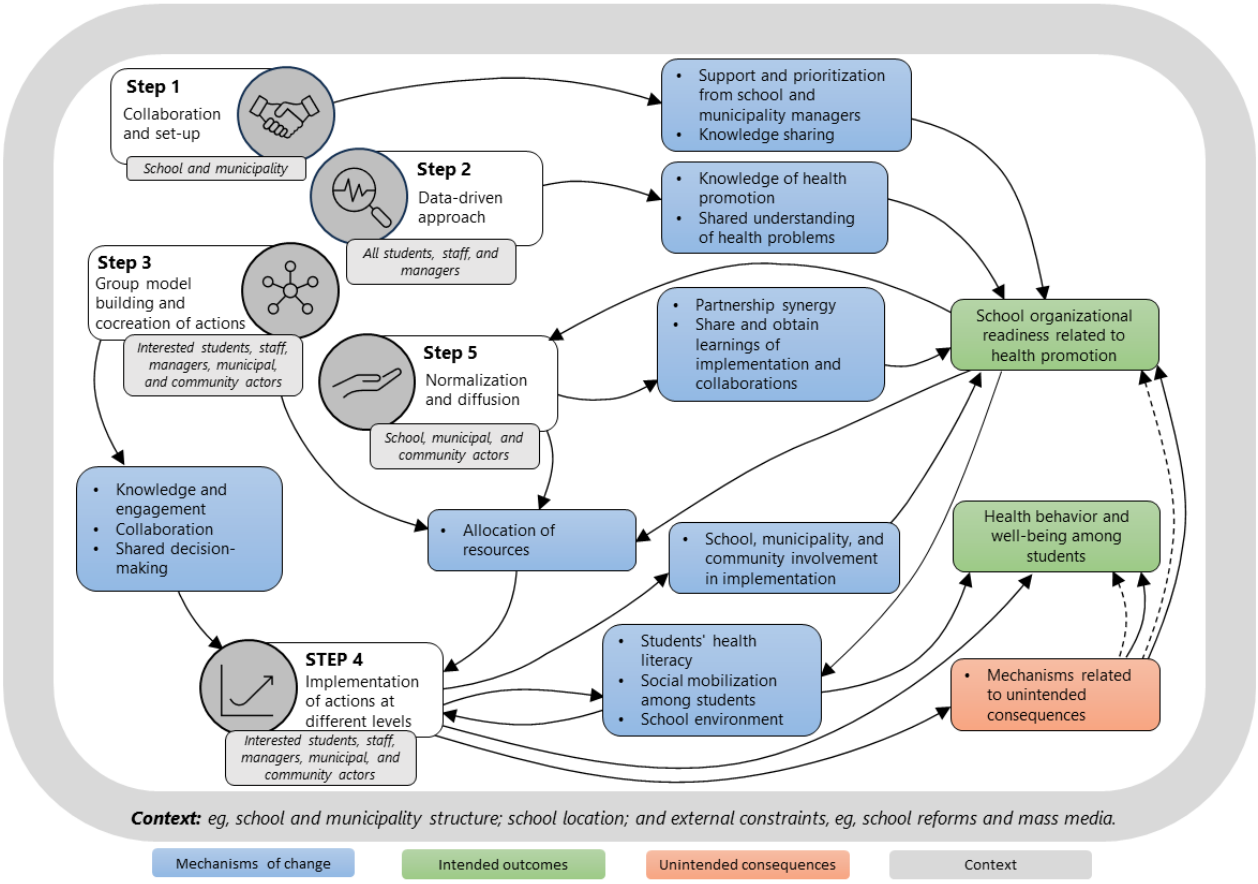

Process Evaluation (RQ1)

In the process evaluation [58], we will examine whether the data-driven approach and the GMB process (steps 2 and 3 of the program) are being implemented as intended, the associated contextual factors and the mechanisms of change.

Both quantitative and qualitative methods will be used to collect data for the process evaluation (Table 1). Following the Medical Research Council guidelines [58], 5 process evaluation components will be assessed: recruitment, reach, fidelity, dose delivered, and dose received. In addition, we will examine whether the 6 hypothesized mechanisms of change are activated and the extent to which these mechanisms are modified through their interaction with contextual factors. However, we will remain open to other emerging mechanisms.

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Table 1. Items, methods, instruments, and frameworks used in evaluation of implementation (research questions 1-3).

Component and items of interest	Methods and data	Applied evaluation instruments and frameworks
Process evaluation—steps 2 and 3 of the program		
Context information		
Examples: • School type • School size • School location • School and municipal structure	• Semistructured interviews with the principal school managers and the municipal program coordinators (after GMB[a]3) • Facts obtained through school and municipality websites	• Medical Research Council guidance [58]
Implementation		
What is delivered: • Recruitment • Reach • Fidelity • Dose • Adaptations	• Registration of participants during meetings and GMB sessions • Exit surveys to all participants (after data presentation meetings, GMB2 and GMB3), semistructured interviews with the school program coordinators (after GMB2) and the principal managers (after GMB3)	• Medical Research Council guidance [58] • COMPACT Stakeholder-driven Community Diffusion Survey [59]
Mechanisms of change		
• Knowledge of health promotion • Shared understanding of health issues • Motivation and engagement • Collaboration • Shared decision-making • Resource allocation • Other emerging mechanisms	• Exit surveys to all participants (after data presentation meetings, GMB2 and GMB3), semistructured interviews with the school program coordinators (after GMB2) and the principal managers (after GMB3)	• Medical Research Council guidance [58] • COMPACT Stakeholder-driven community diffusion survey [59]
Implementation of actions—step 4 of the program		
Actions		
• Number of actions initiated • Primary variable of influence • Action level (beliefs, goals structures, events)	• Semistructured interviews with the school and municipal program coordinators quarterly	• The Systems Thinking in Community Knowledge Exchange computer software [45] • Action Scale Model [27]
Involvement		
• Number of involved participants • Level of involvement in preparation, execution, and implementation of the developed actions	• Semistructured interviews with the school and municipal program coordinators quarterly	• The involvement matrix [53]
Unintended consequences		
• Rippling effects and potential positive and negative unintended consequences of the actions implemented	• The community of practice network will be involved in a process (meetings or workshops) of identifying the rippling effects	• Ripple effect mapping [60]
Program normalization—steps 1 and 5 of the program		
Maintenance of collaboratives		
• Potentials, barriers and needs • Partnership synergy	• Notes from the meetings for program maintenance (6 months after GMB3) • Semistructured interviews with the school manager (after GMB3) and the municipal program coordinator managers (6 months after GMB3)	• Partnership synergy [51]
Program normalization		
• Coherence • Cognitive participation • Collective action • Reflexive monitoring	• Semistructured interviews with the school manager (after GMB3) and the municipal program coordinator managers (6 months after GMB3)	• Normalization process theory framework [61]

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[a]GMB: Group Model Building.

Qualitative and quantitative data will be interpreted separately and combined. Quantitative data will be analyzed descriptively, whereas qualitative interviews will be recorded, transcribed, and thematically analyzed in NVivo (Lumivero) [60].

Implementation of Actions (RQ2)

Actions initiated by the school, municipal, or community actors and the consequences of these actions are a direct indicator of systems change. The number of actions initiated and the primary factors in the locally developed CLD that are influenced will be tracked and visually added to the CLD. The Action Scale Model [27] will be used to determine whether the actions address one of four hierarchical levels to change the functioning of the system in the anticipated direction: (1) beliefs (eg, the school creates a local action group as health promotion champions), (2) goals (eg, the school sets new goals for health promotion), (3) structures (eg, school and municipal staff receive training on the complexity of health), and (4) events (eg, a single sport event at schools) [27]. The hierarchical structure suggests that changing beliefs and goals will not only have a greater systemic impact but also be more costly and time consuming than implementing single events [27]. We will also examine which participants (ie, students, school staff and management, municipal staff, and community actors) are involved in the planning and implementation of the actions and how and to what extent they are involved. The involvement levels of the participant groups will be interpreted using the involvement matrix [53].

All actions and involvement will be tracked on a quarterly basis for up to 2 years after GMB3 through semistructured interviews with the school and municipal program coordinators and involved community actors to enable interpretation of the level of system change and engagement across participant groups over time (Table 1).

In addition, an adapted version of "ripple effect mapping" [62] will be used to understand the rippling-initiated actions, effects, and potential positive and negative unintended consequences of the actions implemented. The CoP will be involved in a process to explore and visualize unintended consequences.

Program Normalization (RQ3)

We will explore the opportunities, barriers, and what is needed to integrate the collaboratives and the program into normalized practice (steps 1 and 5 of the program).

The school-municipality collaboration and program normalization will be explored through interviews with school and municipal program coordinators (Table 1). Interview guides inspired by the Partnership Synergy framework [51] will be developed to explore the functioning of the collaborations and the potential for maintenance, and the normalization process theory [61] will be used as a framework for understanding program normalization. In addition, carefully written notes will be taken from the program maintenance meetings, which will be completed as part of step 5 of the program.

Interviews will be recorded and transcribed, and all data will be analyzed thematically in NVivo [60] to understand opportunities, barriers, and needs related to sustaining collaborations and normalizing the program. Finally, we will develop recommendations for the implementation of systems approaches for sustainable health promotion in vocational schools.

Organizational Outcomes (RQ4)

School organizational readiness to address health promotion is selected as a primary organizational outcome. We will apply the "organizational readiness framework" [50] to track change over time. Organizational readiness refers to the extent to which an organization is willing and able to implement change, and the elements in the framework have previously been shown to be related to implementation success [63]. School organizational readiness will be assessed by questionnaires administered to all school staff, supplemented by semistructured interviews with the principal managers at the schools (Table 2).

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Table 2. Items, methods, instruments, and frameworks used in evaluation of effectiveness (research questions 4 and 5).

Component and items of interest	Methods and data	Applied evaluation instruments and frameworks
System outcomes		
Organizational readiness		

• Baseline and change in the following:
  • Organizational motivation
  • General capacity
  • Health promotion capacity
	• Questionnaire to staff members (4 times in total)
	• Semistructured interviews with principal managers (after GMB[a]3)
		• Organizational readiness [50]

Individual outcomes		
Health behavior		

• Baseline and changes in the following:
  • Mental health and well-being
  • Physical activity
  • Food intake
  • Nicotine use
  • Alcohol use
	• Questionnaire to all students (4 times in total)	• WHO-5[b] [64] and SGPALS[c] [65]
		• Validated measures from the Danish National Health Survey and the Health Behaviour in School-aged Children study [66]

Health promotion outcomes		

• Baseline and changes in the following:
  • Health literacy
  • Knowledge relevant to the problem of interest
  • Self-empowerment
  • Self-confidence
  • Self-efficacy
  • Behavioral intentions
  • Motivation
  • Social network and interaction
  • Social connectedness
  • Student autonomy
	• Questionnaire to all students (4 times in total)	• HLQ[d] [67]; HLSAC[e] [68] validated measures from the Danish National Health Survey and the Health Behaviour in School-aged Children study [66]

[a]GMB: Group Model Building.

[b]WHO-5: World Health Organization (Five) Well-Being Index.

[c]SGPALS: Saltin-Grimby Physical Activity Level Scale.

[d]HLQ: Health Literacy Questionnaire.

[e]HLSAC: Health Literacy for School-Aged Children.

The questionnaire instrument will adapt and refine existing and tested items [20,69] across 3 dimensions and 10 subdimensions: motivation (relative advantage, compatibility, complexity, and priority), general capacity (culture, climate, and staff capacity), and program-specific capacity (knowledge, skills, and abilities). We will use exploratory and confirmatory factor analyses to initially validate the instrument and assess its internal consistency and convergent validity. The questionnaire will be distributed electronically via email in SurveyXact [70] to all school staff (eg, teachers, counselors, and administrators), and repeated data will be collected 4 times during the study period (Figure 2). Changes in school organizational readiness will be assessed primarily using linear mixed modeling, adjusting for clustering, with school as a random effect and time as a fixed effect.

Interviews with school leaders will contribute to a deeper understanding of how the support and priorities of the school management can stimulate or hinder the school's readiness and willingness to change. The interviews will be recorded, transcribed, and analyzed thematically according to the dimensions and subdimensions of organizational readiness.

To generate a comprehensive understanding of school organizational readiness, a convergent parallel mixed methods design will be used in the analyses [71]. Quantitative and qualitative data will be analyzed independently and then compared, related, and interpreted.

Individual Outcomes (RQ5)

We will explore the indications of effectiveness at the individual level through changes in students' health behaviors and well-being. Items to assess health behavior will primarily consist of validated measures and items used in other national health profile studies in Denmark (Table 2). The research team will preidentify one primary and one secondary outcome indicator item for each targeted health area (ie, dietary behavior, physical activity, alcohol consumption, marijuana and drug use, and well-being). The primary indicator will be an item assessing students' health behavior during school time, and the secondary

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indicator will be an item assessing health behavior during leisure time or overall.

Following Bauman and Nutbeam [8], we will assess both health behavior and health promotion outcomes to understand the complexity of health behavior. While health behavior outcomes are expressed in terms of changes in, for example, levels of physical activity or mental well-being, health promotion outcomes are personal, social, and environmental factors that are a means of improving people's ability to change behavior [8]. Therefore, health promotion outcomes are considered intermediate to health behavior (see Table 2 for examples).

The questionnaire data will be collected 4 times (Figure 2). Regardless of the specific health issue each school chooses to address, all students will receive the same questionnaire to identify potential intended and unintended consequences on other health promotion outcomes or behaviors, as suggested in a complex systems sense [46,72]. Electronic questionnaires in SurveyXact [70] will be distributed during school hours by the research team, who will be present in the classrooms so that students can ask questions as they complete the questionnaire. The estimated student population of the 8 program schools is approximately 2000 and, based on previous experience with this procedure [54], we expect that 90% of the students present in class will complete the questionnaire at each of the 4 data collection points. Informed consent will be obtained from all students and can be withdrawn at any time.

Most analyses will be based on cross-sectional data and descriptive in nature, interpreting the mean differences between the intervention and control groups. However, the analyses will also include linear mixed models with time and selected covariates (eg, gender, age, ethnicity, and socioeconomic status) as fixed effects and school as a random effect. It is important to note that the total time of 2 years to assess individual outcomes may be too short to provide conclusive evidence at this level.

Ethical Considerations

The study has been referred to the Capital Region of Denmark's legal center for personal data handling (journal number: P-2021-327). The study will be conducted without approval from the Committees on Health Research Ethics for the Capital Region of Denmark (journal number: 22012766), as this is not required for social health science in Denmark [73]. Participation in research related to the study is voluntary and requires written informed consent from all participants. Consent may be withdrawn at any time. Questionnaire data, key files, audio files, and transcripts of interviews and observations will be stored in a secure folder on the corporate network in accordance with the requirements of the Capital Region of Denmark and European General Data Protection Regulation. Only the principal investigator and those with permission from the principal investigator will have access to data. None of the authors have any financial or competing interests.

Results

This study was launched in 2021, and data collection is expected to be completed in June 2024. The first results will be submitted for publication in January 2024. The results of this research will be disseminated through national and international conferences, peer-reviewed journals, reports, and web-based sources. In addition, key findings will be disseminated through the CoP and other national practice network meetings with stakeholders and policy representatives.

Discussion

Overview

The Data Health study is the first to apply a systems approach to the implementation and evaluation of health promotion programs among vocational school students. The program comprises 5 steps aimed at establishing strong collaborations, building local capacity, identifying leverage points, and generating and implementing collective actions for systems change to improve health and well-being among vocational students. The program will be accompanied by a systems-based evaluation to support the sustainability of program implementation and to determine the scalability of the program. Guided by the Medical Research Council guidance, the evaluation will assess implementation outcomes, contextual differences, and the mechanisms through which the program leads to changes in systems, school organizational readiness, and health behavior and well-being.

Strengths and Limitations

Program Implementation

The steps of the Data Health program are based on systems and health promotion theory, previous health promotion evidence, and formative evaluation at a pilot site. This study has the potential to improve the health behavior and well-being of vocational students and reduce social inequalities in health. The use of systems approaches in communities to address childhood obesity has shown promising results [31,74]. However, adaptation to disadvantaged educational settings may be challenging. One possible challenge is to engage students who are only in school for short periods between workplace-based training. As workplaces are likely to be located across municipalities, it may be difficult to engage students in the GMB process and implementation of actions during workplace training. If possible, we will try to involve the local workplaces in creating collective actions in GMB3 to involve the students, even if they are not physically at the school.

In most health promotion programs, resources often run out before the desired changes in individuals or systems are normalized [75]. The sustainability of actions for system change has been demonstrated in communities, with actions continuing to be implemented years after the reduction in research support [76]. On the basis of locally relevant data and existing capacities and resources, we will test whether the program steps can be successfully sustained. However, sustainable and long-term partnerships between schools, communities, and municipalities can be challenging owing to organizational changes or staff turnover. To address this issue, we will seek to engage and motivate commitment at the management level. In addition, the CoP will serve as an informal capacity building and will expectantly keep the organization as the drivers for systems

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change. If the steps in the program prove to be sustainable and effective, the CoP can be used to disseminate knowledge about methods and approaches to other schools and municipalities interested in implementing the Data Health program.

Program Evaluation

This study involves a complex program evaluation. The processes and steps within the Data Health program are systematic but flexible in the sense that the study sites themselves choose the targeted health issue, actions, and process for normalization. The complexity of a systems approach does not allow for a fully randomized controlled trial with a single set of quantitative outcomes [26]. Therefore, we will use a systems-based and quasi-experimental design to test the preliminary effectiveness of the program at an individual and organizational level. We will use mixed methods to account for the complexity and contextual variation. The comprehensive evaluation design of program implementation and outcomes—combining many data sources from different perspectives—will generate new knowledge that can be used in similar or different contexts at the national and international levels.

To our knowledge, few studies have reported on the implementation of systems approaches and sustainment of actions over time [43,77], particularly using GMB as a participatory method. Understanding the use of GMB in a school setting will provide important information for researchers and practitioners regarding enablers and barriers to this approach.

The systems-based evaluation design provides an opportunity to test new system-level evaluation methodologies, such as the Action Scale Model [27], measuring change within complex adaptive systems. There are many uncertainties in studying changes in complex systems, as complex systems are dynamic [26]. Therefore, we recognize that capturing systems change might not be fully comprehensive. To accommodate this, we set systems boundaries to determine what is relevant to capture and will be used to guide the evaluation.

In parallel, we will assess preliminary indications on individual-level outcomes, assessing the effectiveness on students' health behavior and well-being because of systems change. A limitation of this study is that most of the student data will be cross-sectional because of the vocational school structure. The research team will explore the possibility of tracking individuals' educational attainment, employment status, and health registers (compiled by Statistics Denmark [78]) 5 or 10 years postprogram implementation.

This study will test a systems change approach in vocational schools and whether such an approach is suitable for adaptation and scale-up. If this study is shown to be sustainable and effective, the established CoP will support implementation at scale.

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Authors' Contributions

CDK, LWR, ALB, and CH conceived the overarching program. AS was responsible for the pilot test and the formative evaluation of the study. CH designed the research design of the study and wrote the main manuscript. RDH, ALB, RFK, AB, and CDK contributed to the research design and writing of the manuscript. LWR, AS, and SA contributed to writing the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Data Health program theory.
[PDF File (Adobe PDF File), 114 KB - resprot_v13i1e52571_app1.pdf]

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Abbreviations

CLD: causal loop diagram
CoP: community of practice
GMB: Group Model Building
HPS: health promoting school
NCD: noncommunicable disease
RQ: research question

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Protocol

Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial

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Abstract

Background: Endovascular thrombectomy (ET), combined with intravenous thrombolysis if possible, is an effective treatment option for patients with stroke who have confirmed anterior large vessel occlusion (aLVO). However, ET is mainly limited to comprehensive stroke centers (CSCs), resulting in a lack of ET capacity in remote, sparsely populated areas. Most stroke networks use the "Drip and Ship" or "Mothership" strategy, resulting in either delayed ET or intravenous thrombolysis, respectively.

Objective: This study protocol introduces the *Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette* (LESTOR) strategy, developed to optimize the preclinical part of the stroke chain of survival to improve the clinical outcome of patients with suspected aLVO stroke. This involves refining the dispatch strategy for identifying patients with acute aLVO stroke using a phone-based aLVO query. This includes dispatching emergency physicians and emergency medical services (EMS) to urban emergency sites, as well as dispatching helicopter EMS to remote areas. If a highly suspected aLVO is identified after a standardized aLVO score evaluation during a structured examination at the emergency scene, prompt transport to a CSC should be prioritized.

Methods: The LESTOR study is a controlled, nonrandomized study implementing the LESTOR strategy, with a stepped-wedge, cluster trial design in 6 districts in southwest Germany. In an interprofessional, iterative approach, an aLVO query or dispatch protocol intended for use by dispatchers, followed by a coordinated aLVO examination score for use by EMS, is being developed, evaluated, and pretested in a simulation study. After the training of all participating health care professionals with the corresponding final aLVO query, the LESTOR strategy is being implemented stepwise. Patients otherwise receive usual stroke care in both the control and intervention groups. The primary outcome is the modified Rankin Scale at 90 days in patients with stroke receiving endovascular treatment. We will use a generalized linear mixed model for data analysis. This study is accompanied by a cost-effectiveness analysis and a qualitative process evaluation.

Results: This paper describes and discusses the protocol for this controlled, nonrandomized LESTOR study. Enrollment was completed in June 2023. Data analysis is ongoing and the first results are expected to be submitted for publication in 2024. The project started in April 2020 and will end in February 2024.

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Conclusions: We expect that the intervention will improve the clinical outcome of patients with aLVO stroke, especially outside the catchment areas of CSCs. The results of the accompanying process evaluation and the cost-effectiveness analysis will provide further insights into the implementation process and allow for a better interpretation of the results.

Trial Registration: German Clinical Trials Register DRKS00022152; https://drks.de/search/de/trial/DRKS00022152

International Registered Report Identifier (IRRID): DERR1-10.2196/51683

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KEYWORDS

large vessel occlusion; emergency medical dispatch; lay first responder; emergency call; thrombectomy; stroke; thrombolysis; triage; anterior large vessel occlusion; endovascular thrombectomy; intravenous thrombolysis; modified ranking scale

Introduction

Background

Clinical outcomes of patients with acute ischemic stroke due to the occlusion of the proximal large intracranial arteries (large vessel occlusion [LVO]) remain poor when treated with intravenous thrombolysis (IVT) alone [1]. In recent years, the treatment of patients with acute LVO stroke with endovascular thrombectomy (ET), combined with IVT if possible, has been shown to produce tremendous clinical improvement [2].

In contrast to the widespread access to IVT (usually accessible at any type of stroke center—primary stroke centers [PSCs] or comprehensive stroke centers [CSCs]) in German, ET is mainly limited to CSCs due to the need for technological resources and specialized interventional physicians. This leads to a shortage of ET capacities in remote, sparsely populated areas.

Several strategies exist for the management of patients with suspected LVO in geographic areas not primarily served by a CSC, none of which are superior in terms of stroke outcome [3-6]. Currently, most stroke networks use the “Drip and Ship” (DS) or the “Mothership” (MS) strategy. According to the DS strategy, all patients with acute stroke are transferred to the nearest—in nonurban areas, mostly primary—stroke center to receive IVT if appropriate. Only if imaging indicates LVO and the patient is a candidate for thrombectomy would subsequent transfer to a CSC be initiated.

Following the MS strategy, patients with acute stroke are evaluated on scene with a stroke severity score to assess for possible LVO. Patients with a high probability of LVO stroke bypass the PSC and are transferred directly to the CSC, where both IVT and—in case of proven LVO—ET can be performed. Both the DS and MS strategies present advantages and disadvantages. The DS strategy assumes faster administration of IVT, but IVT is delayed due to the time delay in organizing and performing the transfer to the CSC [7]. On the other hand, the direct transfer to a CSC (MS strategy) results in faster initiation of ET but at the expense of delayed or even denied IVT administration due to longer ground transport times.

Since air rescue is the main means of transport for longer distances (>50 km) in the stroke network in southwest Baden-Wuerttemberg (including sparsely populated areas of the Black Forest region), optimizing the transport allocation process could shorten preclinical times in this region and comparable areas. Data from air rescue missions in Germany showed that parallel dispatch of emergency medical services (EMS) and helicopter emergency medical services (HEMS) resulted in equal arrival times of EMS and HEMS at the emergency site, shortest on-scene time, and reduced transport time to the most appropriate hospital [8]. Hence, to optimize prehospital logistics in the event of an LVO stroke, parallel dispatching of EMS and HEMS would require the identification of patients with possible LVO stroke by dispatchers in the emergency control centers (ECCs). Dispatchers already use simple stroke screening algorithms such as the “Face Arm Speech Time” (FAST) scale [9] as the basis for standardized protocol-based stroke detection in medical emergency calls. However, these simple stroke scales (relying on 1 single stroke symptom only) might be insufficient for reliable LVO detection. Lately, many publications have underlined the high value of cortical signs, such as aphasia and neglect, in combination with hemiparesis, to predict the presence of anterior LVO (aLVO), defined as emergent occlusion of the intracranial carotid artery, the tandem intracranial carotid artery, or the middle cerebral artery (M1 or proximal M2 segment) [10-12]. A recent study consistently showed that the reporting lay first responders mentioned aphasia and conjugate eye deviation (as a symptom of neglect syndrome) during emergency calls for patients with aLVO stroke [13]. It may therefore be possible to develop a stroke query specifically designed for the interaction between dispatchers and the reporting lay first responders to detect cortical signs in patients with aLVO stroke in emergency calls (“aLVO query”).

Considering the requirements and disadvantages of the DS and MS strategies, this study’s authors developed the new *Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette* (LESTOR) strategy. The aim is to optimize the dispatching strategy after the identification of patients with acute stroke with a high probability of aLVO stroke at the dispatcher level by using an aLVO query adapted to the dispatchers’ needs. This includes the dispatch of emergency physicians (EPs) in addition to EMS personnel for urban emergency sites and the parallel dispatch of an air ambulance for nonurban emergency sites for longer distances. A highly qualified EP with the most suitable rescue transport equipment arrives at the scene as quickly as possible for a structured assessment of aLVO probability by applying a standardized aLVO score. If a high suspicion of aLVO persists on-site, transport to a CSC can take place as quickly as possible.

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With this strategy, this study's authors want to eliminate the disadvantage of the delayed application of IVT in the MS strategy by enabling an early IVT administration comparable to the DS strategy with the help of the fastest possible transport, even to regions far from the CSC, while maintaining the possibility of rapid access to the MS strategy on ET.

Objective

The LESTOR study aims to investigate whether the implementation of an aLVO query at the dispatcher level with subsequent optimization of dispatch (ie, LESTOR strategy) and a structured assessment at the emergency site improves the clinical outcomes of patients with aLVO stroke. We also compare the health-economic metrics of our approach to established allocation strategies.

Intervention

Development and First Evaluation of the aLVO Query for Dispatchers

To identify patients with aLVO during telephone contact with emergency services, we intend to query the combination of hemiparesis with cortical deficits. Cortical signs (such as aphasia, neglect, and gaze deviation) in combination with hemiparesis predict the presence of aLVO with high sensitivity and specificity [10]. The Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST) examination steps apply these fundamentals. The combination of right-sided arm paresis and aphasia or left-sided arm paresis with gaze deviation or neglect, respectively, showed high accuracy for aLVO detection in a prospective validation in EMS [14]. An advantage of the ACT-FAST algorithm is that the examination steps are adjusted to the paretic side, resulting in fewer examination steps compared to undirected scores.

The examination steps for cortical signs and the ACT-FAST algorithm serve as the starting point for the development of the aLVO query for dispatchers. This study's authors focused on adapting the wording of the examination instructions to be comprehensible for the reporting lay first responder during the telephone query and upon collection of the results by the dispatcher on the telephone. The interprofessional development with the dispatchers of the ECCs is decisive since dispatchers are experienced in recognizing serious conditions such as cardiac arrest over the telephone. Given many years of practice in telephone resuscitation, they already have expertise in dealing with complex medical situations and communicating with laypeople who are adapted to these exceptional situations [15].

Through a multistep iteration process, this study's authors constructed an aLVO query for dispatchers aimed at identifying cortical stroke deficits (Figure 1). Stroke experts of this study's team prepared a first proposal based on previously published results [10,16]. Dispatchers (n=6) from the ECC in Freiburg and this study's team adjusted the wording in a consensus meeting about the specific requirements of the emergency call. We then evaluated this second proposal in a simulation study. Simulated patients simulated stroke symptoms with or without aLVO symptoms under controlled conditions. Further, 50 members of the public (potential lay first responders) were confronted with the simulated patients in a randomized block sequence. To ensure blinding, lay first responders simulating the emergency calls were positioned out of sight of dispatchers in another room. The dispatcher conducting the aLVO query with the lay first responder via telephone determined whether the simulated patient presented symptoms suspicious of an aLVO stroke. We recorded these encounters and analyzed this setting with the first participants, which served as a pilot test to check the procedure's comprehensibility and feasibility. Subsequently, this study's team optimized the questions' wording, if necessary. This study's authors then tested this third proposal with the remaining individuals (N=45).

By comparing the dispatcher's decision with the simulated symptoms, this study's team can determine the correct identification. We consider the aLVO query for dispatchers as sufficient if sensitivity and specificity reach at least the values that are achieved with other comparable aLVO screening scores [17] (ie, sensitivity ≥0.75 and specificity ≥0.70). Statistical case number calculations show that assuming this effect, 32 cases would be required to demonstrate significance. We therefore planned conservatively with 45 study participants (considering possible dropouts). If this study's authors do not achieve the abovementioned aims, they will further adapt the aLVO query through more in-depth instructions.

After the simulation study, this study's authors developed the fourth proposal of the aLVO query, which they finally discussed again with dispatchers. The dispatchers and this study's team approved a final version of the aLVO query for dispatchers. By using this complex, multistage procedure, we are striving for the best possible combination of test quality criteria, practical feasibility, and a high level of acceptance during the implementation phase.

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Figure 1. Multistage procedure in the development of the aLVO-dispatch protocol. aLVO: anterior large vessel occlusion.

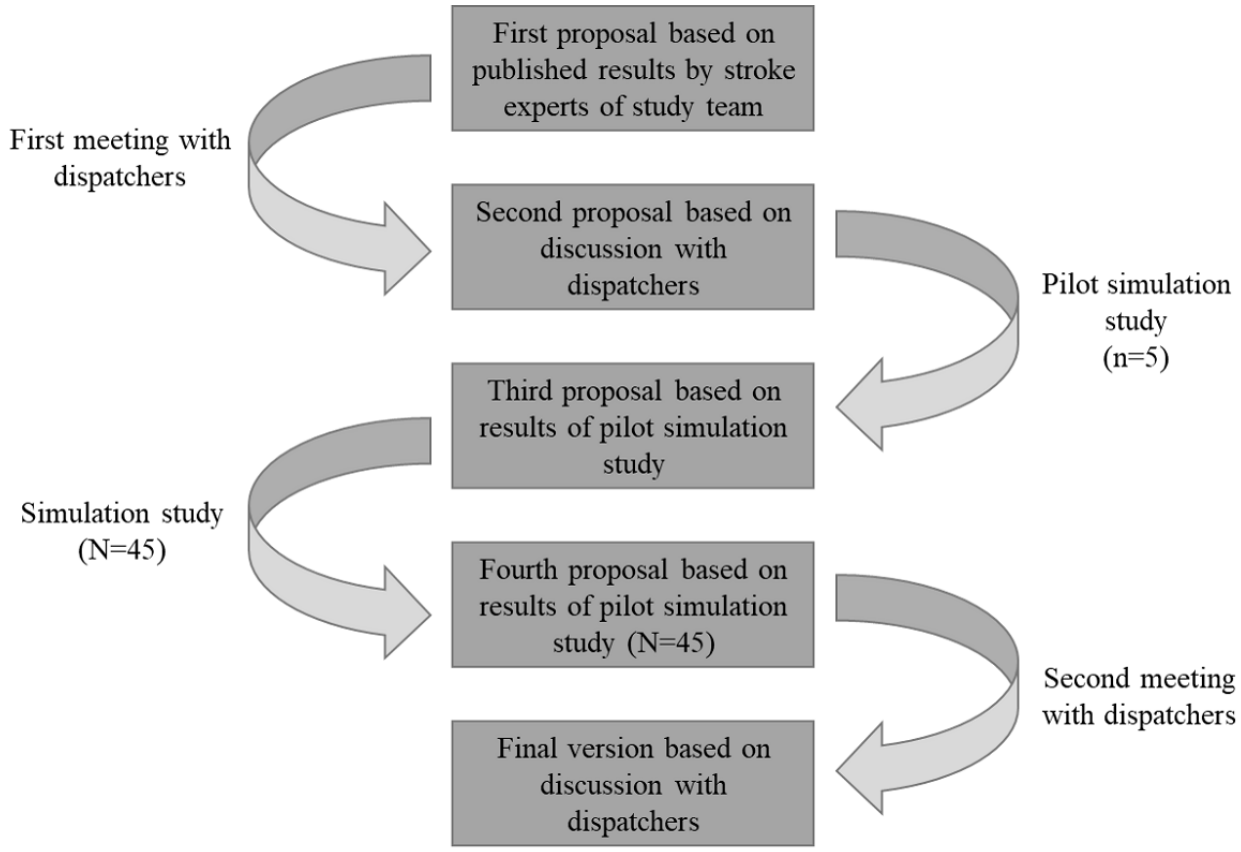

Development of the aLVO-Dispatch Protocol and Integration in the Stroke Detection Protocols in the ECC

We aim at establishing an aLVO-dispatch protocol that queries for eligibility for thrombectomy if the aLVO query is positive. Therefore, the aLVO-dispatch protocol consists of the final aLVO query, which, if aLVO is suspected, is expanded to include a query on the patient's previous state of health and the time window in which the stroke symptoms occurred. The aLVO-dispatch protocol is "LESTOR positive" at the ECC level only, if aLVO is suspected in patients who are not bedridden within the 24-hour window.

All the participating ECCs use electronic dispatch systems with protocol-based dispatching programs. For stroke detection in general, the FAST algorithm is used in all participating ECCs, followed by the immediate dispatch of EMS. We maintain this procedure and implement our aLVO-dispatch protocol directly after completing the first dispatch. Immediately afterward, the dispatcher carries out the aLVO query. If the aLVO-dispatch protocol results in "LESTOR positive," the dispatchers check whether they can optimize the dispatching strategy: within the catchment areas of the CSC, a ground-based EP is dispatched in addition to EMS; outside the catchment area of the CSC, a physician-staffed helicopter is dispatched in parallel. Both protocol-based dispatching programs (FAST and aLVO query) are not mandatory, as the dispatcher can dispatch for unambiguous cases, bypassing the structured dispatching programs to perform faster dispatching.

Development of the aLVO Query for EMS or HEMS

Since EPs and EMS or HEMS need to confirm the aLVO stroke suspicion established by the dispatchers after arrival on the scene, an analogous 2-step procedure is implemented as a secondary survey on scene. In the first step, they apply the FAST scale. If it is positive, they examine cortical symptoms indicative of an aLVO stroke. To enable a comparison between the results of the ECC and EMS or EP or HEMS, as well as to establish a "common" and concerted language at the ECC and EMS or HEMS interface, we closely adapted the examination steps of the aLVO query used in the ECC to the use in EMS or EP or HEMS ("LESTOR Score").

Development of Seminars for Training or Implementation

General Structure of the Seminars

Since the intervention involves neurological examination steps of the patient with stroke that were not previously carried out by the dispatchers or the EMS, EP, or HEMS personnel, this study's authors developed training seminars for all professionals involved in the project. We used didactically carefully designed units for knowledge transfer, including interactive, case-based examples. The didactic training concept builds on principles of the "adult learning theory" (eg, linking to everyday needs and teaching problem-oriented approaches) [18]. Experienced stroke physicians who are part of our study team taught stroke symptoms, recanalizing therapies, and existing referral concepts (DS and MS) with their potential barriers. This study's team then introduced the LESTOR strategy as a new referral concept assessed in this study. aLVO detection, the prerequisite of this

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strategy, is visualized with the use of video samples demonstrating simulated patients with hemiparesis and the corresponding cortical symptoms. The stroke experts also taught practical applications of the examination steps and their interpretation, including pitfalls. Due to the COVID-19 pandemic, all the training was held digitally using videoconferencing software. To enable discussions, time slots for discussions were planned at 3 predetermined time points within each seminar.

Adaptions of Seminars for Dispatcher Training

Due to limited practical familiarity with strokes, adjustments for dispatchers included a more detailed description of stroke symptoms, therapies, and referral concepts. Adapted to the dispatchers' workplace situation, we taught the content and application of the aLVO query additionally with a recorded simulated emergency call. To optimize training success, small groups of 4 dispatchers were taught in 4-hour sessions, resulting in 6 to 10 training seminars for each ECC.

Adaptions of Seminars for EMS or HEMS Personnel and EP Training

In the 2-hour seminars for EMS or HEMS personnel and EPs, we introduced the "LESTOR Score" that complements the examination of patients with FAST-positive stroke at the emergency site. To this end, the specifically designed LESTOR app offers additional teaching of the examination steps and algorithm support (see below). Special focus lies on the allocation and prenotification process for patient who are LESTOR positive s.

Supporting Materials

LESTOR App

This study's team has developed a freely available mobile app intended to support the implementation and penetration of the "LESTOR Score" in the EMS or HEMS and for EPs. The main aim of the app is to consolidate knowledge through e-learning modules (eg, instructions, illustrations, and explanatory videos).

Further Materials

Professionals participating in this study can access training and study content digitally to repeat content and train new personnel in the LESTOR approach, including pocket cards and handouts for EPs and EMS or HEMS personnel.

Intervention Implementation

The intervention consists of (1) the implementation of the aLVO-dispatch protocol for suspected stroke at the ECC level, (2) the adjustment of the dispatch in case of a positive aLVO query result, (3) the structured aLVO reassessment on-scene, and (4) the referral strategy of patients with stroke depending on the aLVO probability.

First, after accomplishing stroke dispatch following a positive FAST score, the aLVO-dispatch protocol is started automatically in the ECC, resulting in either "LESTOR negative" (with no further action) or "LESTOR positive" results.

Second, a "LESTOR positive" result of the aLVO-dispatch protocol necessitates a review of the dispatch made: inside the catchment areas of the 2 CSCs, a ground-based EP is dispatched in addition to EMS, whereas outside the catchment area of the 2 CSCs, HEMS is dispatched in parallel.

Third, on the scene, in case of a FAST-positive stroke, EMS, HEMS, or EPs repeat the aLVO query, by applying the aLVO query customized for their situation ("LESTOR Score"), supported by the mobile app or the pocket card.

Finally, the referral strategy of patients with stroke depends on the result of the LESTOR Score on the scene, time window, and preexisting severe impairment due to another disease.

Patients who are "LESTOR positive" without severe impairment due to another disease, and where the duration of symptoms is <24 hours, are transported to the next CSC: via ground-based dispatch when inside the catchment areas of the CSCs, and via air-based dispatch when outside the catchment area of the 2 CSCs. All other patients with stroke are transported to the nearest stroke unit, regardless of whether they are a PSC or CSC.

Methods

Overview

The LESTOR study comprises various process stages and an accompanying process evaluation. We prospectively registered the trial for the World Health Organization Universal Trial Number and in the German Clinical Trials Register (DRKS00022152) on October 19, 2020.

Study Design

This study's authors performed a controlled, nonrandomized study, introducing the LESTOR strategy with a nonrandomized, stepped wedge, cluster trial design in 6 districts (ie, clusters) in Baden Wuerttemberg in southwest Germany (Figure 2).

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Figure 2. Stepped wedge, cluster trial design of the LESTOR study in 6 districts. LESTOR: Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette.

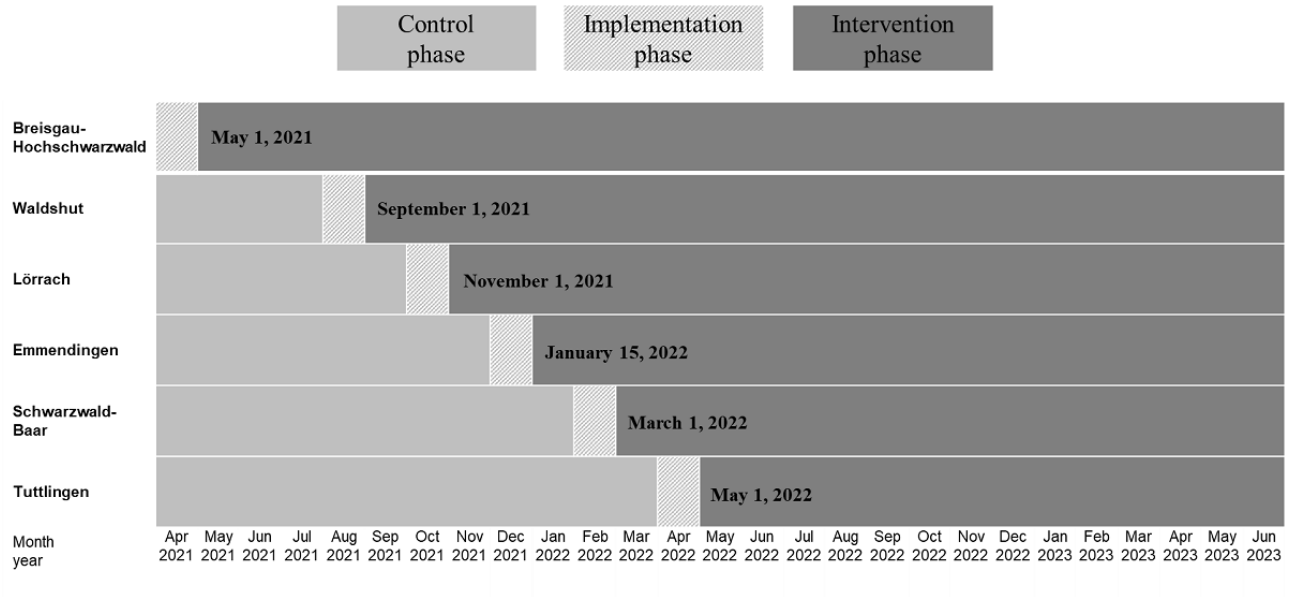

Each cluster includes 1 ECC. Ground emergency medical ambulances are nearly equally distributed across the districts. All 6 districts are supported by 3 air rescue facilities. Further, 6 PSCs and 2 CSCs provide stroke service. The research team sequentially assigns the clusters to the intervention at intervals of 2 to 3 months in an unblinded manner (Figure 2).

This study's team implemented the multicomponent LESTOR approach simultaneously for each cluster's ECC, EMS personnel, EPs, and stroke units. Since HEMS were involved in the intervention from the beginning, this study's authors introduced the LESTOR approach to the 3 air rescue facilities before the implementation of the first cluster.

Each cluster passed through the following phases:

Phase 1 was the control phase (preintervention baseline phase, 3-15 months). During phase 1, ECCs carried out the emergency call and stroke dispatch by local standards: they used the FAST scale for stroke detection, followed by the immediate dispatch of EMS (with additional EP dispatch depending on local conditions). EMS personnel and EPs also used the FAST scale for stroke detection at the scene. The standard allocation for stroke patients was the nearest stroke unit (regardless of whether it is a PSC or CSC). Allocation to CSCs outside their catchment area was based on an individual decision by the EMS or EP to contact the CSC and requires CSC approval. If a helicopter was considered to be the most suitable means of transport on-site, a sequential additional request for the helicopter must be made.

Phase 2 was the implementation phase, when all the professionals involved in acute stroke patient care in a cluster participated in seminars (see above) paralleling the technical implementation of the aLVO query.

Phase 3 was the intervention phase (14-26 months), which follows the intervention's implementation as described above.

Patient Recruitment

In total, 6 districts in Baden Wuerttemberg in southwest Germany participated in the LESTOR study (Breisgau-Hochschwarzwald, Loerrach, Emmendingen, Schwarzwald-Baar, Tuttlingen, and Waldshut) including 6 ECCs; the EMS and EPs of all districts; 3 air rescue facilities; and all the stroke centers of the 6 districts: 2 CSCs (Freiburg im Breisgau and Villingen-Schwenningen) and 6 PSCs—5 of them having a telestroke connection. The maximum distances to CSCs in this study's area were about 120 km by ground and about 80 km by air, while the distances to PSCs were mostly less than 30 km by ground. The distribution of stroke units was specified by the Ministry of Social Affairs in Baden Wuerttemberg, Germany [19].

The 6 districts cover a population of about 1.4 million people living on almost 6000 square kilometers; population density in this area is 233 per square kilometer on average, with the minimum in the district Waldshut (151.4 per square km) and the maximum in the district of Loerrach (283.7 per square km) [20]. According to the Organisation for Economic Co-Operation and Development "Urban-rural classification for NUTS 3 regions" [21], all 6 districts are classified as intermediate regions (rural population between 20% and 50% of the total population). As a regional peculiarity, 5 out of 6 districts have a share of the sparsely populated Black Forest with areas that are difficult to access.

Each district had 1 ECC, operated by the aid organization "Red Cross" and the state administration of each district. EMS was provided in the vast majority by the aid organizations "Deutsches Rotes Kreuz (Red Cross)" and "Malteser," while EPs were organized by the hospitals assuring EP coverage within each district. EMS and EPs were organized at the district level. All 6 districts were supported by 3 air rescue facilities (the German *Deutsche Rettungsflugwacht e. V. Luftrettung*, the Swiss *Rettungsflugwacht Garde Aérienne*, and the Swiss Alpine Air

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Ambulance) with 5 helicopters during the day and 4 helicopters at night.

Inclusion and Exclusion Criteria

Inclusion Criteria

Eligible for inclusion were patients aged older than 18 years presenting stroke symptoms that can be treated within 24 hours of the initial symptoms' onset.

Exclusion Criteria

Exclusion criteria were preexisting severe impairment due to another disease (corresponding to level 5 of the modified Rankin Scale [mRS]: "Severe disability; Bedridden, incontinent, requires constant nursing assistance") [22-24], patients in a coma (National Institutes of Health Stroke Scale [25] item of consciousness>2), patients with an unstable clinical status who required emergent life support care, patients hospitalized with acute stroke and suspected aLVO, and patients unlikely to be available for the 90-day follow-up (eg, no fixed home address or visitor from overseas).

Primary and Secondary Outcomes

Primary Outcome

The primary outcome was the mRS score at 90 days in patients with ischemic stroke who received ET. The mRS measures the degree of disability after a stroke with a score ranging from 0 to 6 (0=no deficit; 1=minor deficit without limitations; 2=deficit with limitations; 3=dependence, but independent walking possible; 4=dependence, independent walking no longer possible; 5=being bedridden; and 6=death) [22-24]. The primary outcome was assessed by a structured telephone interview conducted by a central assessor blinded to group allocation.

Secondary Outcomes

Prespecified secondary outcomes were the dichotomization of the mRS (day 90) into scores of 0-2 and 3-6 and the time from emergency call to hospital admission.

Control Variables

Control variables were age, sex, pre-mRS score, and severity of stroke (National Institutes of Health Stroke Scale) [25] at hospital admission.

Data Collection

This study's team asked each participating ECC to share their aLVO-query results with the research team along with time metrics. This study's authors also collected deidentified case data from the 2 ECCs receiving endovascular treatment in a database. A study staff member blinded to group allocation requested the 7-point (0-6) mRS by telephone from patients with stroke receiving endovascular treatment or their guardians 90 days after stroke (unblinded treatment and blinded end point assessment). For the health economic evaluation, this study's authors asked the medical controlling department of the University Medical Centre of Freiburg.

Health Economic Evaluation

This study's team will analyze the costs associated with hospitalization and the intervention for all the patients. Data will be provided by the medical controlling department of the University Medical Centre. This study's authors will also perform a cost-effectiveness analysis, whereby the primary end point (mRS) is related to the total costs.

Power Considerations

A power analysis showed that testing for the statistically significant superiority of the intervention over the control group required far more cases (N=664) than available in the target region during this study's period. This study's authors, therefore, conducted a controlled feasibility study to explore achievable effects and practicability under routine care conditions. This study's team will explore the clinical significance of the intervention effects and refrain from testing for the statistical superiority of the intervention over the control group.

Statistical Analysis

We will use a generalized linear mixed model following the basic model proposed by Hussey and Hughes [26], including the 6 districts as clusters. This study's team will extend the model as proposed by Hemming et al [27] and Li et al [28] to control for the secular trend to avoid potential bias. We will therefore stratify the sample by the 2 stroke centers and add a fixed effect for the secular trend stratified by each of these 2 hospitals, taking into account the control variables. We will assume the same treatment effect in both strata but will exploratively test this assumption by extending the model with an interaction term.

As studies have shown that it is advantageous to examine the full-scale range of mRS—rather than dichotomizing it—this study's authors will account for the ordinal scaling of the mRS [29].

We will conduct exploratory subgroup analyses for cases within and outside of the catchment areas of the 2 CSCs and consider the dichotomous mRS because a favorable clinical outcome is defined as mRS≤2 similar to Goyal et al [2]. In addition, the area under the curve for different mRS cutoff values will be calculated in an exploratory sensitivity analysis.

Missing Values

We will use multiple imputations [30], assuming that the data are missing at random, and perform a full case analysis as a sensitivity analysis for the imputed model.

Process Evaluation

The process evaluation will consist of semistructured, guideline-based individual telephone interviews conducted by trained researchers to assess the implementation process at 2 points in time (in the middle of and at the end of the intervention phase). This study's authors will interview representatives of the ECC, EMS and HEMS personnel, EPs, and first responders. A study nurse will recruit lay first responders of patients receiving ET at the University Hospital of Freiburg to participate in interviews. Key topics for the interviews with medical professionals will be the feasibility of implementation, accessibility, acceptability, appropriateness, fidelity, penetration, and sustainability of the intervention. This study's authors will ask lay first responders about the emergency and personal stress, and the instructions given during the emergency call. Further,

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2 independent researchers will use Kuckartz's [31] multistage qualitative content analysis to analyze transcribed data using MAXQDA (VERBI Software GmbH) software.

The results of the first interview round will provide input for a midintervention workshop for all participating medical professionals involved in this study. The workshop aims to discuss the experience and data gained to improve the intervention. The results of the second interview round may help to optimize the intervention for future implementations and projects.

Ethical Considerations

This study's authors did not expect any disadvantages for patients when applying the aLVO query. Even if the aLVO assessment failed and aLVO-positive cases were missed, patients received standard care.

By the local ethics committee, this study's team had established a waiver of consent approach, as a high proportion of patients with stroke with aLVO experienced severe neurological sequelae and had diminished capacity to consent. Moreover, acute psychological distress occurred in approximately 30% of cases during the acute phase, and obtaining consent from relatives, legal guardians, or health care proxies was only possible in a small proportion of cases without causing undue additional psychosocial stress for the representatives [32]. The researchers inform patients using an invitation about a telephone call, which addresses the patient's further neurological course at 90 days after stroke.

For the process evaluation, the interview partners will be informed, in written and verbal form, about this study and must have agreed to the procedure. Project participation will be voluntary and consent can be revoked at any time.

Ethical approval for this study was obtained from the Ethics Committee at the University of Freiburg (416/20; August 10, 2020). The project started in April 2020 and will end in February 2024. All procedures were performed in accordance both with the ethical standards of the institutional or national research committee, and the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. This study protocol adheres to the recommended SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

Results

The development phase of this study was completed and the successful integration of the LESTOR strategy into the daily work was in place before patient enrollment. This study was conducted between April 2020 and February 2024, with final data collected by June 2023 and final analyses and results anticipated by mid-2024.

Discussion

Relevance

More than 7 years after the establishment of ET as the standard therapy for aLVO stroke, the best prehospital care and strategy for patients with aLVO stroke, particularly outside the catchment areas of CSCs, remains unclear.

This study aims to evaluate a new strategy, targeting the essential steps of the prehospital section of the stroke chain of survival. The detection of aLVO stroke in the emergency call enables optimization of the dispatch process in terms of human expertise as well as for means of rescue. Involving the lay first responder in the clinical examination of cortical signs for aLVO detection over the telephone represents a major challenge, which this study's authors aim to address with their multistage, interprofessional development process for the aLVO query in the ECC. Re-establishing the aLVO suspicion by EMS, HEMS, or EPs necessitates the introduction of a structured aLVO examination, which the stroke study team closely adapted to the examination steps of the aLVO query used in the ECC ("LESTOR Score"). The LESTOR strategy might enable a delay-free transport to the CSC and could therefore overcome the disadvantage of the MS strategy and still provide an equally fast initiation to thrombolysis as the DS strategy by maintaining the faster access to ET.

As this new strategy does not require any additional human or material resources, other than training time for all the parties involved, it may be easy to implement in comparable regions. The extensive accompanying process evaluation and the health economic evaluation should help to identify determinants of the implementation and thus optimize the transferability.

Limitations

The project faces several challenges. The pieces of training need to reach many dispatchers, EMS and HEMS personnel, and EPs in all 6 districts. Due to the COVID-19 pandemic, the pieces of training were delivered digitally with videoconferencing software. While this enables more flexibility in terms of participation, it may reduce interactions and learning compared to face-to-face sessions. Despite the extensive development of the query, certain known problems with the detection of a stroke in an emergency call cannot be solved, for instance, the misjudgment of strokes as falls or misclassification of aphasia as confusion or reduced vigilance. Moreover, not all callers may be able to understand and perform the instructions for the aLVO query due to stress during the emergency situation or language barriers. Although this study's team plans the trial in an area with 1.4 million inhabitants, the expected number of patients with aLVO stroke during this study's phase is likely to be too small to assess the statistical superiority of the intervention and could therefore be addressed in future trials.

Conclusion

The LESTOR study aims to optimize prehospital care for patients with aLVO stroke with a focus on reducing inequality in aLVO stroke care within and outside of CSC catchment areas. The proposed LESTOR strategy addresses the earliest possible detection of aLVO symptoms in patients suspected of having a stroke, by using the results of the LESTOR query in the emergency call to guide dispatch decisions. This may enable optimization of the dispatch in terms of human expertise as well as for means of rescue and, in case of aLVO suspicion, create the conditions for a fast and direct transport to the CSC,

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including the immediate use of air rescue for longer distances to the CSC. The results of the accompanying process evaluation and the cost-effectiveness analysis will provide further insights into the implementation process and allow for a better interpretation of the results.

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Data Availability

Data sharing is not applicable to this work as no data sets were generated or analyzed.

Authors' Contributions

NW, DR, FS, and JB wrote this paper with support from EF-G, SM, MLH, and UB. EF-G, FS, and JB conceived and designed this study and supervised this project. All authors reviewed the final paper. Generative AI was not used in any part of this paper's writing process.

Conflicts of Interest

None declared.

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Abbreviations

ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment
aLVO: anterior large vessel occlusion

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CSC: comprehensive stroke center
DS: Drip and Ship
ECC: emergency control center
EMS: emergency medical services
EP: emergency physician
ET: endovascular thrombectomy
FAST: Face Arm Speech Time
HEMS: helicopter emergency medical services
IVT: intravenous thrombolysis
LESTOR: Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette
LVO: large vessel occlusion
mRS: modified Rankin Scale
MS: Mothership
PSC: primary stroke center
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Codevelopment and Deployment of a System for the Telemonitoring of Activities of Daily Living Among Older Adults Receiving Home Care Services: Protocol for an Action Design Research Study

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Abstract

Background: Telemonitoring of activities of daily living (ADLs) offers significant potential for gaining a deeper insight into the home care needs of older adults experiencing cognitive decline, particularly those living alone. In 2016, our team and a health care institution in Montreal, Quebec, Canada, sought to test this technology to enhance the support provided by home care clinical teams for older adults residing alone and facing cognitive deficits. The Support for Seniors' Autonomy program (SAPA [Soutien à l'autonomie des personnes âgées]) project was initiated within this context, embracing an innovative research approach that combines action research and design science.

Objective: This paper presents the research protocol for the SAPA project, with the aim of facilitating the replication of similar initiatives in the future. The primary objectives of the SAPA project were to (1) codevelop an ADL telemonitoring system aligned with the requirements of key stakeholders, (2) deploy the system in a real clinical environment to identify specific use cases, and (3) identify factors conducive to its sustained use in a real-world setting. Given the context of the SAPA project, the adoption of an action design research (ADR) approach was deemed crucial. ADR is a framework for crafting practical solutions to intricate problems encountered in a specific organizational context.

Methods: This project consisted of 2 cycles of development (alpha and beta) that involved cyclical repetitions of stages 2 and 3 to develop a telemonitoring system for ADLs. Stakeholders, such as health care managers, clinicians, older adults, and their families, were included in each codevelopment cycle. Qualitative and quantitative data were collected throughout this project.

Results: The first iterative cycle, the alpha cycle, took place from early 2016 to mid 2018. The first prototype of an ADL telemonitoring system was deployed in the homes of 4 individuals receiving home care services through a public health institution.

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The prototype was used to collect data about care recipients' ADL routines. Clinicians used the data to support their home care intervention plan, and the results are presented here. The prototype was successfully deployed and perceived as useful, although obstacles were encountered. Similarly, a second codevelopment cycle (beta cycle) took place in 3 public health institutions from late 2018 to late 2022. The telemonitoring system was installed in 31 care recipients' homes, and detailed results will be presented in future papers.

Conclusions: To our knowledge, this is the first reported ADR project in ADL telemonitoring research that includes 2 iterative cycles of codevelopment and deployment embedded in the real-world clinical settings of a public health system. We discuss the artifacts, generalization of learning, and dissemination generated by this protocol in the hope of providing a concrete and replicable example of research partnerships in the field of digital health in cognitive aging.

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KEYWORDS

action design research; protocol; activities of daily living; older adults; cognitive deficits; telemonitoring; public health care system; home care services

Introduction

Background

In Canada, it is estimated that 2 million people, or 5.4% of the total population, are active users of publicly funded home care services, with more than half of them being aged ≥65 years [1,2]. Home care is considered a priority by the Canadian government and its provincial counterparts [3]. In the province of Quebec, a predominantly French-speaking province in Eastern Canada, the Ministry of Health and Social Services has promoted aging in place since 2003 through a policy known as "Home Support: Always the Option of Choice" ("Chez soi: Le premier choix") [4]. Despite this policy, 40% of older adults in Quebec living with disabilities report unmet home care needs [2], which has been attributed to factors such as the lack of funding, difficulties in recruiting and retaining home care staff, and the increase in care needs in an aging population [5,6]. These challenges, exacerbated by the COVID-19 pandemic, have led to urgent calls in Canada as well as in other countries to better support home care [6,7].

The presence of cognitive deficits is an important risk factor for the loss of functional autonomy [8,9] and is associated with important needs for home care support services [6]. Older adults with cognitive decline, such as those diagnosed with Alzheimer disease, are progressively dependent on others for both instrumental and basic activities of daily living (ADLs), which increases the stress and burden on caregivers (families and relatives) and social and health care services [8,9]. Everyday memory losses and difficulties identifying and recognizing their own limitations affect the ability to recall and report on events, including how they manage their ADLs [10,11]. These individuals may also put themselves at risk by engaging in behaviors that are dangerous to their health and safety, in particular when they live alone (eg, falls, kitchen fires, and medication noncompliance) [12].

Therefore, progressive cognitive decline and its impact on ADLs limit the ability of health and social services to rely on these patients to better understand their home care service needs. This uncertainty can significantly affect intervention plans and resource management [13,14]. On the one hand, this may lead to the costs of some care recipients' needs not being covered by public care services because of a lack of supporting evidence; on the other hand, some services may be offered although they are unnecessary because of clinicians' need to create contingencies to address potential risks [15,16].

In this context, we propose that a key strategy to better understand the needs of older adults with cognitive decline and optimize available human and financial resources lies in the use of digital health technologies, in particular telemonitoring of instrumental and basic ADLs—hereafter referred to as *ADL telemonitoring*.

Telemonitoring of ADLs

ADL telemonitoring is a form of remote monitoring and, as such, a component of telehealth. It is generally used to acquire proxy information about several factors or outcomes relevant to the home care support of older adults, such as functional independence, cognitive state, mobility, risk of falls, and urinary tract infections [13,14,17,18]. The information is based on data collected via several sensors, such as wearables, ambient sensors (eg, motion detectors and contact sensors), radiofrequency identification, and GPS [19]. The resulting profile of the person is based on information collected regarding their behavior in the home over the course of one or several days, such as entering and leaving a room, opening and closing kitchen cupboards, home entrances and exits, and the use of small electrical appliances. Various algorithms can be used to recognize and classify ADLs, including hidden Markov models, linear discriminant analysis, support vector machines, artificial neural networks, and adaptive network fuzzy inference system [20].

ADL telemonitoring can be used in the context of naturalistic scenario-based assessments in which participants are invited to a research laboratory apartment designed to simulate real-life situations. There, participants are usually asked to perform several scripted ADLs, such as cooking a meal, cleaning the apartment, or booking a reservation [21-24].

ADL telemonitoring can also be used in the context of real-life assessments in which participants are asked to continue their daily routine while sensors are installed directly in their homes to collect data on sleeping habits, meal preparation, hygiene,

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mobility in the home, periods outside the home, and so on [25,26]. Over time, deviations from previous patterns can be detected and used to assess the ability of an older adult to live independently in the community and detect potential future critical situations [27-30].

Thus, ADL telemonitoring holds great promise to facilitate better understanding of the needs of older adults with cognitive decline, in particular those living alone, in terms of ADL functioning and home care service requirements. Indeed, research in the area of ADL telemonitoring has been expanding over the last 20 years. In a recent umbrella review, Tannou et al [31] identified over 191 experiments in the field and 17 reviews published to date. Despite this dynamism, there is still little available evidence on the effectiveness of ADL telemonitoring and strategies for integrating it successfully into health care systems [31]. Most studies have reported data on prototypes, but very few large-scale deployment studies have been conducted. Therefore, there is a pressing need for more in-depth studies on this subject.

Context and Aim

In 2016, the authors were approached by a health institution in the city of Montreal, Quebec, Canada, more specifically by the director of the *Support for Seniors' Autonomy* program (*Soutien à l'Autonomie des Personnes Âgée*s in French; SAPA). SAPA programs aim to support older adults and meet their physical, psychological, and gerontopsychiatric needs both in the community and during hospital stays. The director was searching for innovative ways to support home care clinical teams to better address the needs of older adults with cognitive deficits who live alone. The directorate was also looking for solutions to optimize the use of limited human and financial resources to offer the right service at the right moment. Our team and the top management team decided to engage in a joint research project on ADL telemonitoring, which became the "SAPA Project." The global objectives of the SAPA project were to (1) codevelop an ADL telemonitoring system that addresses the needs of all key stakeholders, (2) deploy the system in a real-world clinical setting and identify the specific use cases, and (3) identify factors that could contribute to ensuring its long-term use in a real-world setting. To foster the project's success, we engaged with all key stakeholders involved in public home care services for older adults with cognitive deficits. We considered that, to ensure the optimal use and adoption of technologies by the health care community, it would be crucial to identify existing solutions or create novel solutions that address the specific needs of all key stakeholders, including the care recipients themselves [32]. To do so, stakeholders had to be involved in every step of the project to align their needs with the technology [33].

Considering the context of the SAPA project, the use of an action design research (ADR) approach was identified as crucial. ADR provides a framework for developing practical solutions to complex problems encountered in a specific organizational setting. It is an iterative process that involves collaborations among researchers, practitioners, and stakeholders in designing [34], deploying, and evaluating interventions that improve the outcomes of a particular problem or issue [35]. This four-stage research process includes (1) problem formulation; (2) building, intervention, and evaluation; (3) reflection and learning; and (4) formalization of learning. ADR proposes the use of multiple cycles of development leading to cyclical repetitions of stages 2 and 3. Carried out in collaboration with the stakeholders (codevelopment process), these cycles allow for the refinement of the technology and related interventions to be implemented subsequently in a real-world setting. The SAPA project underwent 2 iterative technological design cycles entitled "alpha" and "beta." The alpha cycle took place from early 2016 to mid 2018, and the beta cycle took place from late 2018 to late 2022.

A key feature of the SAPA project was its novel methodological approach. In this paper, we present the SAPA research protocol and its various codevelopment and deployment phases for the 2 cycles of ADR. To our knowledge, this represents the first detailed publication of a methodological framework in this field of research. Taking the initiative to share a research design makes it possible to be more transparent about the methodologies used as well as provide an in-depth explanation of the process so that it can be reproduced in the future. It also provides a description of a concrete example of research partnerships in the field of digital health in cognitive aging.

In the following sections, we will present each cycle and stage of the project, which involve multiple research methods as recommended by action research methodologists [36]. Specific methodological details are presented in Multimedia Appendix 1. Figure 1 [35,37] presents an overview of the project's timeline and key elements of each cycle and stage.

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Figure 1. Summary of action design research protocol (based on the studies by Sein et al and Schacht et al). ADL: activity of daily living; CLSC: local community services center; NEARS-Hub: Innovative Easy Assistance System–Hub; NEARS-SAPA: Innovative Easy Assistance System–Support for Seniors' Autonomy program; POC: proof of concept.

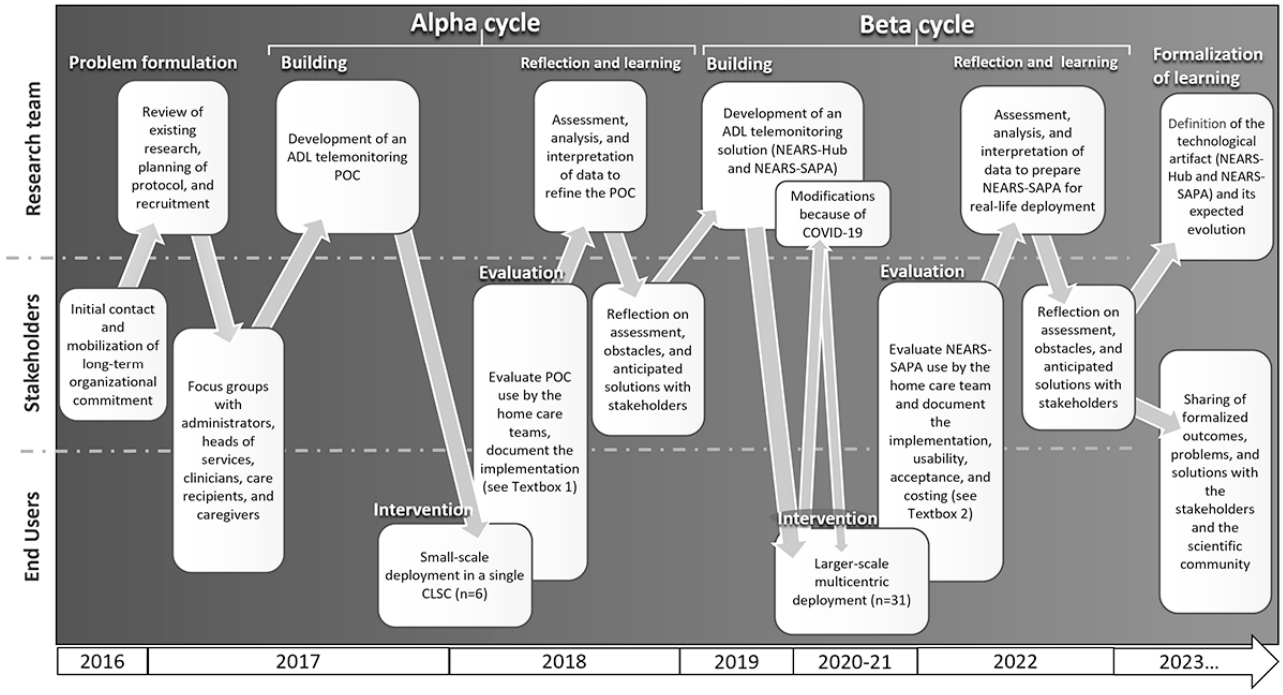

Note: Stakeholder refers to home care services directorates, administrators, and heads of services. End-users refers to clinicians, care recipient, and caregivers of home care services.

Alpha Cycle

Methods

Background

The SAPA project aimed to provide an in-depth understanding of the potential of ADL telemonitoring in the specific context of the Canadian public health care system, particularly in the province of Quebec. This province has an estimated population of 8.3 million residing in 18 administrative areas referred to as health regions. For a given health region, all public health and social services institutions are networked into integrated health and social services centers (CISSSs [*Centre intégré de santé et de services sociaux*]) or integrated university health and social services centers (CIUSSSs [*Centre intégré universitaire de santé et de services sociaux*]) when located in an area where a university offers an undergraduate medical training program or has an institute in the social services field. These administrative entities are responsible for delivering care and services to the population of an assigned territory via hospitals, residential and long-term care establishments, rehabilitation centers, child and youth protection centers, and local community service centers (CLSC [*Centre local de services communautaires*]). CLSCs offer frontline health and social services, including home care, through dedicated programs.

The alpha cycle of the SAPA project was conducted within the clinical services of the CLSC of one CIUSSS in the city of Montreal referred here as CIUSSS 1.

Problem Formulation

The alpha cycle started with a problem formulation stage aimed at conceptualizing the research problem, securing long-term organizational commitment, and clarifying roles and responsibilities with stakeholders. This stage combined theoretical and experiential knowledge informed by real-life practices [35]. As previously mentioned, the initial problem (ie, the need to support home care clinical teams in meeting the needs of older adults with cognitive difficulties living alone in the community) was brought to the research team by the health institution.

To arrive at a mutual understanding of the problem and prioritize potential technological solutions at the start of the project in late 2016, a descriptive qualitative method was followed [38]. More specifically, individual interviews and focus groups were conducted with key stakeholders (administrators, heads of services, clinicians, older adults, and caregivers; n=23 in total) of 1 specific sector covered by a CLSC of CIUSSS 1 (for more details, see Multimedia Appendix 1, section 1, as well as the study by Couture et al [34]). This sector was chosen by the head administrator as the most appropriate site for project deployment. Participants were questioned about the leverages of and obstacles to the home care of older adults and technology use within this context. At that time, neither the researchers nor the clinical team had a specific technology in mind to address the problem. However, to support the reflection process, several technological solutions were presented to the clinical teams. These included assistive devices and monitoring technologies such as smart home sensors, smart calendars, pill distributors, serious games, and stove safety devices.

One of the main findings was that administrators and clinicians thought that monitoring technologies could help them obtain more objective and reliable information to support their decision-making process to develop an adapted intervention plan with the care recipients [34,39]. More precisely, they

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wanted a technology to support their assessment and management of the risks involved in maintaining care recipients at home as long as possible. A second finding was that stakeholders insisted on avoiding the use of cameras or microphones to preserve intimacy and confidentiality [34,39]. They also wanted to avoid wearable technologies as older adults with cognitive deficits would likely forget to wear them. Finally, it was mentioned that an unobtrusive technology requiring little involvement on the part of the older adults would most likely be successfully implemented.

Considering these expectations, ADL telemonitoring seemed to be the most promising technology to fully address the needs expressed by all. At the time of the study, there was no such system available on the market and ready to be deployed in a home care setting. Therefore, we resolved to design a system specifically for this research project based on our previous work [13,24,40-43]. With the stakeholders' approval of the project scope and vision, we secured a long-term organizational commitment as well as funding for the subsequent phases.

Building, Intervention, and Evaluation

Overview

In the second stage of ADR, the initial design of the technological artifact is generated using the problem framing adopted in the first stage [35]. The building, intervention, and evaluation phase, which is an iterative process conducted in the target environment, involves building the technological artifact, intervening in the organization, and evaluating the outcomes. The product of this stage is the design of the artifact.

At this point in the alpha cycle, the overall target and goal of knowledge generation was to design and create an ADL telemonitoring system to support clinicians' decision-making process related to risk management. As is often the case in IT-dominant artifact creation, we opted to develop a proof of concept (POC) that could be quickly developed and tested in the homes of a small sample of older adults receiving home care services (ie, alpha cycle). POC versions are formative and can help validate several anticipated and unanticipated outcomes of technology use and deployment [35]. Early designs serve as lightweight interventions in a limited organizational context.

Building

For the POC, we used a lightweight sensor infrastructure comprising 4 nonintrusive, low-cost, wireless devices similar to the one deployed in the study by Caroux et al [44]. With their consent, sensors were deployed in each participating patient's home: passive infrared sensors, magnetic contact sensors, smart electric switches, and water sensors. Sensors were paired with an Internet of Things device, the VeraPlus Z-Wave Home Controller, which served as the data collection point (ie, a controller). Sensors were positioned in each home so as to capture data on ADLs, including sleeping, cooking, showering, and leaving the home (Figure 2). Multimedia Appendix 1, section 2, provides more details on each sensor's role.

Figure 2. Example of sensor placement in the home. PIR: passive infrared.

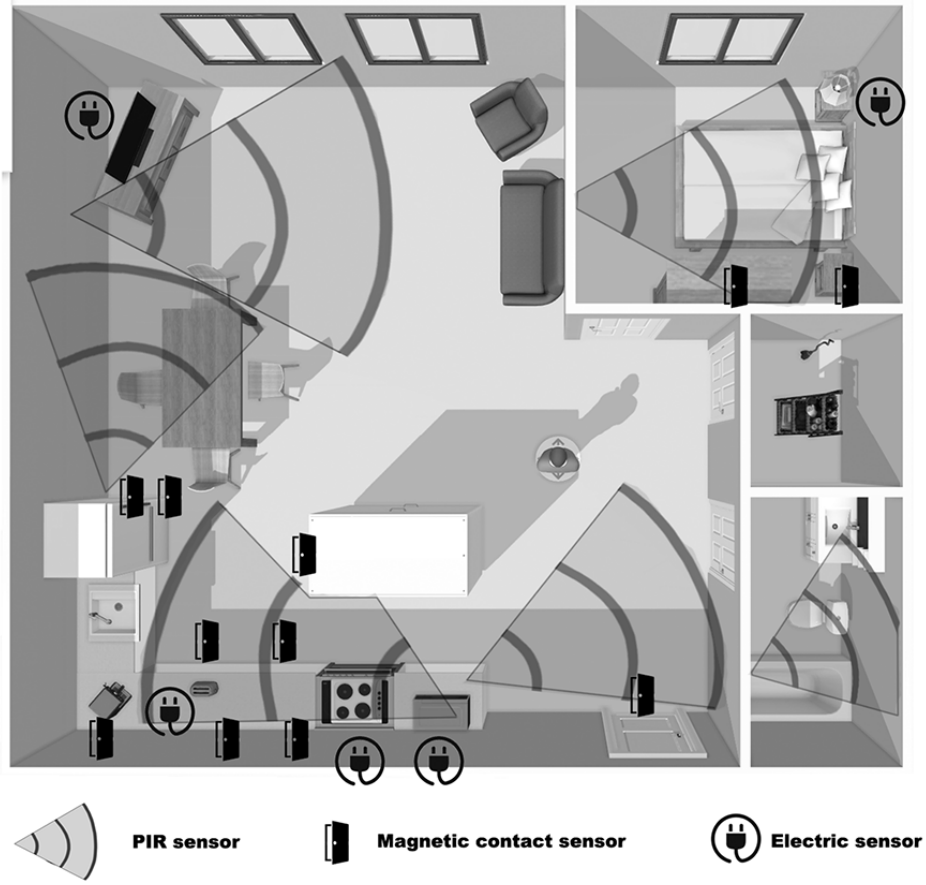

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Algorithms using an inference system and finite state machine computation models were developed to monitor ADLs such as sleep, periods outside the home, cooking, hygiene, and general activity levels in the home (for more details, see the study by Lussier et al [45]). From these algorithms, it was possible to relay graphical information about the daily habits of the individual to clinicians to support their decision-making process. The information was summarized on a 3-page PDF report sent directly to the clinicians.

Intervention

In the intervention phase, the POC needs to be used firsthand by practitioners from the real-life setting for which it is designed. This participatory process provides opportunities for end users to influence and guide the design.

In early 2017, the POC was presented to clinicians and managers in team meetings in the identified testing sector. Clinicians were invited to identify older home care recipients for whom they thought ADL telemonitoring would be useful. Clinicians who wished to participate filled out a request form about their needs and the care recipient they identified. Complex cases were discussed with the research team to ensure that the needs of the clinician were within the scope of ADL telemonitoring. Recruitment procedures are detailed in Multimedia Appendix 1, section 3.

Evaluation

Overview

The general objective of the alpha cycle was to document the feasibility of using ADL telemonitoring in real-life settings and quickly iterate the POC. More specifically, the objectives pursued were to (1) describe the characteristics of the participants and their demands for telemonitoring, (2) describe the use and impact of the POC by the home care teams, and (3) document the facilitators of and barriers to POC use.

To achieve these objectives, a mixed embedded single-case study design was used [46]. Case studies are relevant when the research question requires a comprehensive description of a social phenomenon [46], as is the case here in studying the perspectives of different stakeholders on the feasibility of using technology. The single case was the home care division of CIUSSS 1. The 6 subunits consisted of care recipients (n=6); their clinicians (n=8; 2 were replaced during the project) from home care services; and, when possible, a family caregiver (n=2; Figure 3). These subunits made it possible to shed light on the personalized trajectories of each care recipient as well as the intended and actual use of the system in relation to these trajectories. Multimedia Appendix 1, section 6, provides more details on the subunits and data analysis methods. A mix of quantitative and qualitative data was collected. Textbox 1 provides an overview of the data collection process in the alpha cycle.

Figure 3. Diagram of embedded case study.

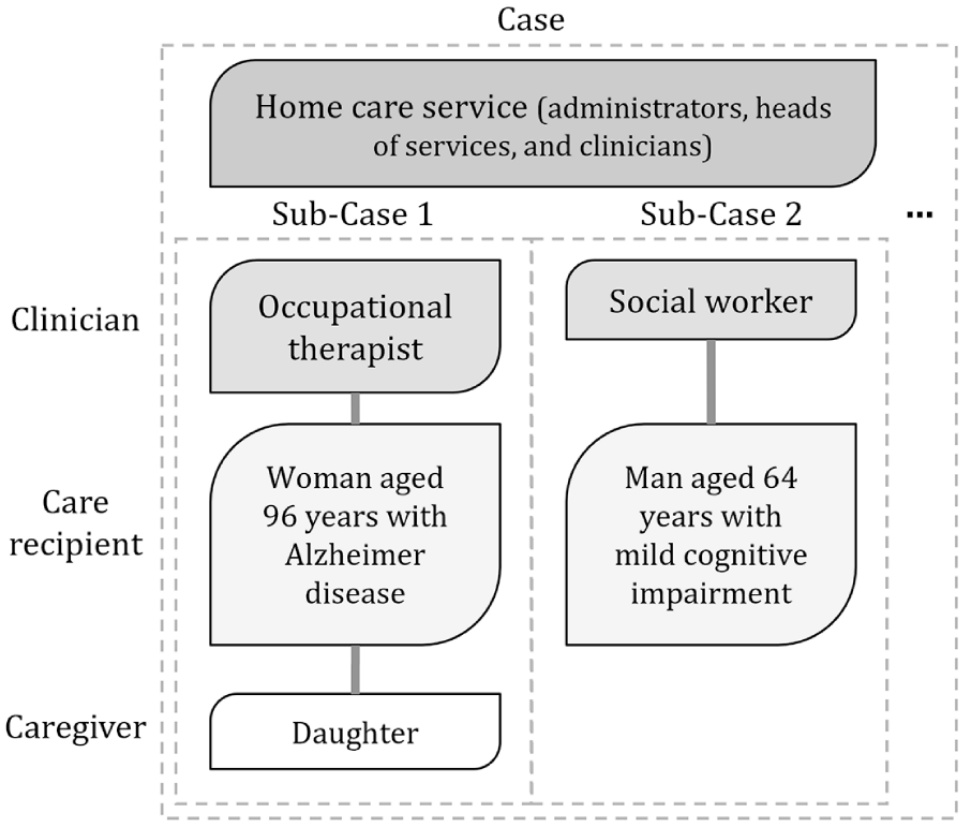

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Textbox 1. Overview of the alpha cycle data collection, sample, measurements, and variables in the evaluation stage.

Telemonitoring request form filled out by clinicians and with follow-up questions via phone interviews

- Facilitators of and barriers to home care of care recipients
- Demands for telehealth technology

Characteristics of clinicians (n=8) and care recipients (n=6)

- For clinicians: profession
- For care recipients only: age, sex, years of schooling, Mini-Mental State Examination, Montreal Cognitive Assessment, Multiclientele Assessment Tool, Functional Autonomy Measurement System profile, metadata on the home care service received, cognitive evaluation (Rey Auditory Verbal Learning Test; Mini-Geriatric Depression Scale; and Delis-Kaplan Executive Function System Trail Making test, Stroop test, and Tower Test), and Instrumental Activity Profile

Initial individual interviews with care recipients (n=6) and caregivers (n=2)

- Facilitators of and barriers to home care of care recipients
- Anticipated leverages of and obstacles regarding telemonitoring deployment in home care

Total of 3 follow-up focus groups with clinicians after proof of concept installations (n=8)

- Observed facilitators of and barriers to telemonitoring deployment
- Use case, impacts, and general satisfaction regarding deployment

Postdeployment focus groups with administrators (n=2), heads of services (n=5), and clinicians (n=8)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

Characteristics of Participants and Demands for ADL Telemonitoring

With the care recipients' consent, their medical history was extracted, including cognitive screening scores as well as needs for home care support, sociodemographic information, and the quantity of home care services required. Metadata were also extracted from the medical records about each service provided by the health network for each care recipient (ie, type of act and its time and duration). Finally, to obtain a more in-depth cognitive profile of each care recipient, a cognitive evaluation, as well as an evaluation of ADL performance, was completed by a research assistant. Multimedia Appendix 1, section 6, provides more details.

Clinicians who identified a care recipient and wished to participate filled out a request form detailing their demands for telemonitoring, the reasons that led them to request remote monitoring for this care recipient, and which ADL they would like to obtain more information about via telemonitoring. Through interviews, they were also asked about facilitators of and barriers to home care for this specific care recipient. After receiving the form, a research assistant called the clinician to provide any further details or clarifications as needed.

Use and Benefits of ADL Telemonitoring

During the follow-up focus groups, clinicians were asked how telemonitoring was used, for which ADL, and how it influenced their decision-making process regarding the recipients' care plan. They were also asked about their satisfaction, whether it was relevant to continue telemonitoring for each care recipient, and why.

Finally, during postdeployment focus groups, administrators, heads of services, and clinicians were asked about their general satisfaction with telemonitoring as well as the benefits it had for clinical practice.

Facilitators of and Barriers to ADL Telemonitoring Deployment

During the initial interviews, care recipients and caregivers were asked whether they foresaw any barriers to and facilitators of the deployment of the ADL telemonitoring system. In addition, to document their perceived needs, they were asked to describe ADLs that were difficult for them to perform, the current help they received, and their unmet care support needs.

In follow-up focus groups, clinicians were asked about the facilitators and obstacles they encountered during deployment.

During postdeployment focus groups, participating clinicians and managers were asked about elements that could promote or hinder deployment of the ADL telemonitoring system in their organization as well as their thoughts regarding the sustainability of this type of system.

Finally, throughout the study, data on several additional factors to be considered were collected: occurrence of adverse events; clinician turnover; reason for care recipient's withdrawal, relocation, or hospitalization; or cause of death.

Ethical Considerations

The alpha cycle was approved by the Centre de recherche de l'Institut universitaire de gériatrie de Montréal research ethics board (CER VN 16-17-22). All participants (ie, care recipients, clinicians, caregivers, and managers) provided informed and

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written consent before taking part in the data collection process. Information that could potentially identify participants was securely stored in a locked storage unit or protected by passwords. Whenever possible, data were deidentified through codification. Participants did not receive any monetary compensation.

Results

Overview

The *Reflection and learning* stage of ADR mirror a conventional *Results* section, entailing the analyses and interpretation of the data collected during the evaluation phase. The alpha cycle aimed to develop and deploy the POC in a real-life context as well as quickly reveal anticipated and unanticipated outcomes regarding technology use and deployment. In the following sections, we synthesize the outcomes for each of the 3 objectives. Multimedia Appendix 1, section 5, provides more details on the outcomes.

Characteristics of Participants and Demands for ADL Telemonitoring

The system was deployed in the homes of 4 care recipients with severe cognitive deficits. They all lived alone, and half (2/4, 50%) had family caregivers. Participating clinicians included 3 occupational therapists, 3 nurses, and 2 social workers.

During these interviews, social and health care professionals expressed the need for monitoring data to support their clinical decision-making process. More precisely, they wanted access to technology that could help assess and manage the risks involved in maintaining care recipients at home. In other words, their aim was to gain a better understanding of how care recipients were functioning in their homes. This information would support their intervention plan and help determine which services should be put in place.

Use and Benefits of ADL Telemonitoring

The evaluation stage revealed that the ADL telemonitoring system was used by clinicians to collect additional and reliable data about the home care recipient's ADL routine (for more details, see the study by Lussier et al [15]). In accordance with the demands for ADL telemonitoring, this technology made it possible to gain a better understanding of how care recipients were functioning in their homes, providing an objective measure that complemented other subjective clinical evaluations. More precisely, it was used to confirm or refute hypotheses before developing a comprehensive intervention plan. It was also used to facilitate discussions with the older adults and their families based on consensual information

Overall, clinicians described the monitoring technology as a useful tool for allocating home care services that corresponded to the needs of care recipients and optimizing their autonomy and safety [15].

Facilitators of and Barriers to ADL Telemonitoring Deployment

Overall, the alpha cycle presented several encouraging results regarding the POC's perceived usefulness and reported satisfaction, as well as the feasibility of its deployment in SAPA teams operating in the field [39]. Although the prototype was successfully deployed in 4 care recipients' homes, several obstacles were encountered. In total, 3 main obstacles were identified: the characteristics of some participants, burdensome evaluation protocol, and maturity level of the POC.

First, the technology used for the prototype was suboptimal for some care recipients' profiles. More specifically, a concern was expressed that sensors would exacerbate symptoms of a paranoid personality disorder with invasive thoughts, and consequently, this care recipient was not included in further testing. In addition, the usefulness of the sensors for care recipients presenting important mobility challenges was questioned. For instance, these care recipients performed very few ADLs by themselves and moved around their units in a wheelchair—which decreased monitoring efficiency and accuracy.

Second, the alpha cycle protocol allowed us to better understand the population followed by the CLSC and refine the protocol for evaluating care recipients' characteristics. In fact, our original protocol was too long, formal, and confronting for many care recipients, increasing the risk of a refusal to participate in the study or withdrawal. Thus, it was decided that formal evaluations with care recipients would be reduced as much as possible in subsequent cycles.

Overall, the feedback showed that the prototype was not ready for wider deployment—the installation took too long, data processing was too slow, output analysis was complex and time-consuming, and it was mostly done by hand, among other issues. Finally, despite the lack of real danger, it was decided that water sensors were to be avoided in the future as they were the only type of sensor that generated anxiety in almost all care recipients because of their concerns regarding having wires near water.

Beta Cycle

Methods

Building, Intervention, and Evaluation

Overview

Following the alpha cycle stage and deployment of the POC, CIUSSS 1 was interested in participating in a second cycle of development with a wider deployment. In addition, during the alpha cycle, 2 other institutions from the Greater Montreal area (CIUSSS 2 and CISSS 3) manifested their interest in using the ADL telemonitoring system, and researchers from our team met with managers and clinicians from these institutions. They identified the needs and challenges of home care for older adults with cognitive deficits that were very similar to those encountered by CIUSSS 1. As such, the beta cycle was conducted with CIUSSS 1, CIUSSS 2, and CISSS 3 without repeating the problem formulation stage. Furthermore, a second problem formulation stage was deemed nonrelevant as the alpha cycle results did not indicate a need to refine our understanding of the context.

The general goals of the beta cycle were to further improve the ADL telemonitoring system based on experience gathered during

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the POC and deploy this newer version on a wider scale to further document specific use cases and factors that could contribute to ensuring its long-term use in a real-world setting. As the COVID-19 pandemic occurred as deployment for the beta cycle was just starting, many adjustments to the research protocol and monitoring system had to be made. These are summarized in the following sections and detailed in Multimedia Appendix 1, section 6.

Building

Between 2018 and 2019, a blitz of technological developments was undertaken to develop an edge computing based on a distributed architecture that offers more flexibility for integrating new technologies with high performance in data ingestion than the POC developed in the alpha cycle. Details of the system optimization can be found in Multimedia Appendix 1, section 7.

Organized into software modules, the system centralizes data encryption, storage, computation, communication, and system robustness on a single low-power, low-cost computing device. This framework, called the Innovative Easy Assistance System (NEARS)–Hub, integrates nonintrusive sensors in the smart home [47].

Several features were added to build on the alpha cycle learning and address limitations. First, the deployment of sensors was optimized, which not only simplified the installation but also minimized the technicians' presence in the patients' homes. The latter was a particular source of concern for both clinicians and care recipients.

Second, to facilitate rapid data collection, the VeraPlus Z-Wave Home Controller was replaced with a Raspberry Pi 3 linked with a USB Z-Wave controller, offering several options for local data preprocessing and a number of other improvements, such as the automation of collection, maintenance, and data processing; local data storage; and automation of local backups to compensate for service interruptions.

Third, 2 additional types of sensors were integrated into the ecosystem: a heavy-appliance smart electric switch to monitor oven use and pressure mattress sensors that could be added to the bed or couch.

Fourth, a major achievement was compliance with the safety and confidentiality standards required by the Quebec Ministry of Health and Social Services.

Fifth, a web-based user interface supporting advanced data visualization and comparison tools, called NEARS-SAPA, was designed for clinicians, enabling them to monitor (1) 5 significant ADLs (ie, sleep, eating, mobility, activity, and hygiene), (2) relevant object use (eg, fridge, television, and coffee maker), and (3) room occupancy. As a result, the platform provided a broad overview of the ADLs performed by each care recipient as well as some specific information regarding each ADL (eg, the care recipient's sleeping schedule). To compensate for both the inability of research staff to train clinicians because of the pandemic and clinicians' increased workload, the research team simplified reporting, sending a data summary electronically in PDF highlighting the trends and changes in ADLs for each care recipient every 2 months.

Finally, to reduce in-person home visits related to fixing technical problems, a modular and component-based IT infrastructure was built into the NEARS-Hub to solve as many maintenance issues as possible remotely.

Intervention

Strategies based on the alpha cycle were put in place to improve deployment (see Multimedia Appendix 1, section 8, for details). With the involvement of managers from each health institution, it was decided that the project and its opportunities would be presented during regularly scheduled meetings of each targeted profession. Coordinators from different professional teams were asked to promote the project to their colleagues. Although it was not considered an exclusion criterion, clinicians were alerted to poor acceptance and possible adverse outcomes of ADL telemonitoring in individuals with paranoid disorders and extensive mobility challenges.

Evaluation

Overview

For the beta cycle, the objectives were as follows: (1) to describe the characteristics of the participants and their demands for telemonitoring, (2) to describe the use and benefits of the ADL telemonitoring system on a larger scale, (3) to document facilitators of and barriers to its deployment, (4) to evaluate the usability and acceptance of the system, and (5) to estimate the costs related to system deployment and use. To respect COVID-19 sanitary guidelines, interviews and evaluations were conducted through telephone.

Textbox 2 provides an overview of the data collection process used during this cycle. Details can also be found in Multimedia Appendix 1, section 9.

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Textbox 2. Overview of the beta cycle data collection, sample, measurements, and variables in the evaluation stage.

Telemonitoring request form filled out by clinicians, with follow-up questions via phone interview

- Facilitators of and barriers to home care of care recipients
- Demands for telehealth technology

Characteristics of clinicians (n=31), care recipients (n=31), and caregivers (n=9)

- For all: demographics
- For care recipients only: Mini-Mental State Examination, Montreal Cognitive Assessment, Multiclientele Assessment Tool, and Functional Autonomy Measurement System profile

Before deployment—individual interviews with clinicians (n=31), care recipients (n=8), and caregivers (n=9)

- Facilitators of and barriers to home care of care recipient
- Anticipated leverages of and obstacles to telemonitoring deployment in home care
- Demands for telehealth technology

During deployment—follow-up individual interviews with clinicians (n=31) every 4 months

- Observed facilitators of and barriers to telemonitoring deployment
- Use case, impacts, and general satisfaction regarding telemonitoring

Questionnaires for clinicians (n=23)

- 10 in-house questions on use
- 7 questions from the System Usability Scale on usability
- 11 questions from the technology acceptance model–2 on acceptance

Questionnaires for care recipients (n=23)

- 3 in-house questions on telemonitoring perceived usefulness
- 8 in-house questions on telemonitoring acceptance

After deployment—focus groups with clinicians (n=8)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

After deployment—individual interviews with administrators (n=2)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

Estimate of direct, indirect, and intangible costs related to telemonitoring

- Material costs
- Time invested
- Adverse outcomes reported

Characteristics of Participants and Demands for ADL Telemonitoring

For subunit characteristics, we used the same measurements as for the alpha cycle but dropped the cognitive and functional evaluations because of sanitary constraints and adverse reactions reported by clinicians and caregivers from the alpha cycle. For clinicians, age, sex, profession, affiliation, and years of experience in home care services were collected (self-reported). As in the alpha cycle, clinicians who identified a care recipient and wished to participate filled out a request form detailing their demands for ADL telemonitoring. An initial individual interview with the clinician was added before NEARS-SAPA reports were sent to them. This interview was specifically aimed at identifying the demands, facilitators of, and barriers to home care for this specific care recipient.

Use and Impact of ADL Telemonitoring

Qualitative data were similar to those collected in the alpha cycle (Textbox 2), with slight modifications in terms of time points and type of data collection: (1) follow-up focus group interviews with clinicians were replaced with individual

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interviews held every 4 months with clinicians following the installation of the sensors and (2) follow-up focus group interviews with administrators and managers were replaced with individual interviews at the end of the cycle.

In addition, after the first follow-up interview, 10 in-house questions specifically related to the ADL telemonitoring system and reported uses were sent to clinicians in the form of a web survey. Finally, 3 in-house questions were administered orally to care recipients regarding their perceptions of the usefulness of the telemonitoring system.

Facilitators of and Barriers to ADL Telemonitoring Deployment

Qualitative data were collected following procedures similar to those in the alpha cycle (Textbox 2), with the same slight modifications as those mentioned previously in terms of time points and type of data collection.

Usability and Acceptance of ADL Telemonitoring

Usability is defined as the effectiveness, efficiency, and satisfaction with which specified users achieve specified goals in particular technological environments [48]. Several measures were added to evaluate the usability of the system. During the initial interview, clinicians were asked whether they foresaw any facilitators of and obstacles to their intended use of the ADL telemonitoring system. During follow-up interviews, they were asked whether there were any barriers to and facilitators of their actual use of the telemonitoring system. A web survey comprising 7 questions from the System Usability Scale [49] was also sent to clinicians. The System Usability Scale is a reliable tool for measuring such usability, and the questions centered on the ADL telemonitoring system and reports. The survey also comprised an 11-question form built from the *perceived usefulness* and *ease of use* sections of the technology acceptance model–2 questionnaire [50]. The technology acceptance model–2 is an information systems theory that maps how users come to accept and use a technology.

To evaluate care recipients' and caregivers' level of acceptance of the presence of the sensors in their homes, they were asked to respond to an oral questionnaire composed of 8 questions developed by the research team.

Cost Estimation of ADL Telemonitoring

We collected metadata on each service provided to care recipients by the CIUSSS and CISSS and recorded them in Intégration CLSC. Intégration CLSC is a provincial ministry database containing personal information and providing data on service requests, users, and interventions concerning services delivered. The database is used to describe frontline services to ensure the quality and efficiency of health and social services. For this study, we examined the monthly count of services received by the care recipients within the time frame of 6 months preceding and 6 months following clinician access to ADL telemonitoring.

Throughout this project, we aimed to document the cost of implementing ADL telemonitoring in the public health care system by totaling direct, indirect, and intangible costs [51,52]. To do so, we documented the material costs (eg, number of devices used, lost material, server maintenance cost, software, licenses, material for fixtures, repairs and maintenance, internet services, and database and server maintenance). We also estimated the time invested by technicians and clinicians over the study period (eg, time for recruitment, needs analyses, installation, training, and technical support). This estimate was validated by the technicians and clinicians during group interviews in the postdeployment phase. The time invested was translated to cost using the common hourly rates for technicians and clinicians. Time dedicated exclusively to research purposes (eg, interviews about the usability of the system) was not included in the deployment costs.

Ethical Considerations

The beta cycle was approved by the Centre de recherche de l'Institut universitaire de gériatrie de Montréal research ethics board, mandated to be the evaluating committee in a multicenter procedure (CER VN 17-18-10). The same protocols and considerations as those in the alpha cycle were followed.

Results

Results corresponds to the *Reflection and learning* stage of ADR. Data collection ended in late 2022. In total, the NEARS-SAPA was installed in 31 care recipients' homes, and 34 clinicians were involved in the beta cycle. Data analyses for the beta cycle are nearing completion, and the results specific to each subobjective will be shared in the future. Three manuscripts currently being written and are expected to be published in 2024-2025.

Discussion

Expected Findings

The aging population and increasing demand for ADL support faced by social and health care services in many countries call for the deployment of innovative solutions to better meet the needs of older adults with cognitive deficits. In close collaboration with 3 public health care institutions in the province of Quebec, we conducted a study designed to arrive at an in-depth understanding of the potential of ADL telemonitoring to support older adults with cognitive decline in the context of a public health care system. More specifically, the objectives of the project were to (1) codevelop an ADL telemonitoring system that addresses the needs of all key stakeholders involved in home care services for older adults with cognitive deficits, including the older adults and their caregivers; (2) deploy ADL telemonitoring in the Quebec public health care system and identify the specific use cases; and (3) identify factors that could contribute to ensuring its long-term use in a real-world setting (ie, participants' characteristics, demands, and use of telemonitoring; facilitators of and obstacles to its deployment; usability and acceptance; and estimated cost of the system). To achieve these objectives, we opted for an innovative research approach with ADR and engaged with all stakeholders involved in home care services throughout 2 iterative cycles of system codevelopment.

The publication of our protocol was part of the completion of the formalization of learning stage, the last ADR stage, comprising the identification of artifacts, generalization of

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learning, and dissemination. These 3 components will be addressed in this section.

Identification of Artifacts

In this paper, we report the ADR protocol for the SAPA project and its related artifacts. As a form of ADR result, an artifact encompasses tangible or intangible elements, including objects, documents, processes, or outcomes, shaped by the ADR processes. These artifacts serve as tangible proof of the actions taken and the resulting benefits in the research context. The SAPA project has given rise to IT artifacts such as NEARS-SAPA (a web-based user interface supporting advanced data visualization and comparison tools) and NEARS-Hub (an Internet of Things infrastructure model) [47]. In addition, scientific and clinical artifacts such as the outcomes of the alpha cycle have been published in the form of case studies [15,45]. From data gathered within the beta cycle, our objective is to generate more artifacts, such as presenting comprehensive documentation and analyses of use cases along with factors supporting or limiting the deployment of the ADL telemonitoring system. This endeavor aims to contribute valuable scientific insights into the clinicians' decision-making processes and deployment strategies that will further support the adoption and integration of ADL telemonitoring in real-life home care contexts.

Generalization of Learning

This protocol paper also provides a thorough presentation of the entire project and its intricate phases. It illustrates how ADR principles could apply to the field of ADL telemonitoring, enabling stakeholders to be actively involved in developing technology that is useful, acceptable, and deployable in real-life environments. To our knowledge, a comprehensive ADR protocol spanning 2 cycles of development has not been published so far in the fields of smart environments and ADL telemonitoring. This is surprising as ADR offers a promising framework for developing practical technological solutions to complex problems, such as in health care services [35,37]. In this context, we present the detailed ADR protocol of this project as an outcome or artifact, enabling its replication in similar projects in the future and the generalization of our results.

Furthermore, the SAPA project and ADR protocol are innovative as they include and report the steps involved when ADL telemonitoring is deployed in real life. A recent umbrella review conducted by our team [31] revealed that few real-world deployment studies have been undertaken in the field of smart environments thus far. As an emerging area of research, published studies have primarily focused on the development and conceptualization of technological components, with only a limited number involving small-scale testing in a laboratory context. Consequently, there are limited published data on the deployment strategies required to integrate smart environments into the health care system or community [31], and our project was designed to fill this gap.

To our knowledge, we are the first to have codeveloped and deployed a system in iterative cycles of collaboration with all stakeholders involved in home care support in the context of a public social and health care system. Coconstruction and collaboration are at the heart of ADR principles. Other studies have reported the deployment of similar solutions, but the development or deployment were not carried out using a coconstruction approach in partnership with a health care system and did not consider how stakeholders wish to integrate telemonitoring information into their practice [14,49,53,54]. It has been shown that the codevelopment of technological solutions with all stakeholders and users is an important factor in ensuring that the deployment of sustainable technological solutions proceeds smoothly and leads to their long-term adoption [55]. Our protocol, centered on co-design, use cases, and deployment factors, is parallel to another recently published protocol reporting a clinical trial to document the effectiveness of an ADL telemonitoring platform via a quasi-experimental study [56]. In that study, more than 73 older adults will receive an active and assisted living–based multiservice assistance platform called HomeAssist. The platform includes ADL telemonitoring but also many applications designed for the older adults themselves to help them engage in their daily and social activities. Although the HomeAssist project has not yet been deployed in the home care services context at the time of publication, this type of project is key to advancing the field of ADL telemonitoring, for which very little rigorous experimental data exist thus far [31]. As for ADR procedures, this study illustrates how to realize various cycles of coconstruction and codeployment of a technology in close collaboration with stakeholders.

Although the SAPA project is innovative in terms of its vision and methodology, it operates on a relatively small scale. Therefore, it will be important to conduct larger-scale studies in the future. As a next step, we intend to conduct an evaluative study to determine the benefits of ADL telemonitoring. These benefits could include, for instance, effectiveness in terms of clinician productivity and work, older adults' functional independence, use of other health services, and changes in the living environment, as well as benefits for the institutions in terms of cost-effectiveness [56]. To engage in these types of larger-scale evaluations, we recommend that research teams in the field of ADL telemonitoring rely on recognized models or frameworks of technology implementation and adoption that are well established in the digital health field. For example, the nonadoption, abandonment, scale-up, spread, and sustainability framework by Greenhalgh and Abimbola [55] enables anticipation of the challenges that may arise during the implementation of an eHealth system in a particular environment. As another example, the Clinical Adoption Framework [56] considers the micro-, meso-, and macrodimensions that influence the long-term adoption and sustainability of technological solutions. The use of such frameworks will ensure rigorous development of ADL telemonitoring supported by sophisticated data.

Dissemination

Finally, in terms of dissemination, initial findings from the beta cycle were shared with the participating program managers, heads of services, and clinicians from the CISSS and CIUSSS. Ultimately, the comprehensive results and assessments will be shared with the scientific community, providers of home care services for older adults, managers, and policy makers. There

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has been discussion about progressing toward a third cycle of development. The primary objective of such a cycle would be to make NEARS-SAPA fully independent of the research team. Currently, the technology relies on support, supervision, and knowledge transfer from the research team for optimal functionality, posing a significant barrier to broader implementation—including integration into clinical processes—and cost-effectiveness.

Conclusions

This paper reports the protocol for the SAPA project, which used an ADR framework to codevelop and deploy an ADL telemonitoring system in the Canadian public social and health care system. Through 2 ADR iterative cycles, the SAPA project made it possible to consider all stakeholders' needs, expectations, and perceptions in the final telemonitoring strategies proposed as well as the imperatives related to the deployment of such solutions in real test environments. Future studies could follow this protocol and further develop some methodological aspects.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of specific methodological details for problem formulation, building, intervention, evaluation, and reflection and learning phase for both cycles.
[DOCX File , 54 KB - resprot_v13i1e52284_app1.docx]

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Abbreviations

ADL: activity of daily living
ADR: action design research
CISSS: centre intégré de santé et de services sociaux (integrated health and social services center)
CIUSSS: centre intégré universitaire de santé et de services sociaux (integrated university health and social services center)
CLSC: centre local de services communautaires (local community service center)
NEARS: Innovative Easy Assistance System
POC: proof of concept
SAPA: Soutien à l'autonomie des personnes âgées (Support for Seniors' Autonomy program)

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Protocol

Designing Implementation Strategies for the Inclusion of Lesbian, Gay, Bisexual, Transgender, Intersex, Queer, and Allied and Key Populations' Content in Undergraduate Nursing Curricula in KwaZulu-Natal, South Africa: Protocol for a Multimethods Research Project

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Abstract

Background: Lesbian, gay, bisexual, transgender, intersex, queer, and allied (LGBTQIA+) individuals encounter challenges with access and engagement with health services. Studies have reported that LGBTQIA+ individuals experience stigma, discrimination, and health workers' microaggression when accessing health care. Compelling evidence suggests that the LGBTQIA+ community faces disproportionate rates of HIV infection, mental health disorders, substance abuse, and other noncommunicable diseases. The South African National Strategic Plan for HIV or AIDS, tuberculosis, and sexually transmitted infections, 2023-2028 recognizes the need for providing affirming LGBTQIA+ health care as part of the country's HIV or AIDS response strategy. However, current anecdotal evidence suggests paucity of LGBTQIA+ and key populations' health content in the undergraduate health science curricula in South Africa. Moreover, literature reveals a general lack of health worker training regarding the health needs of LGBTQIA+ persons and other key populations such as sex workers, people who inject drugs, and men who have sex with men.

Objective: This study aimed to describe the design of a project that aims at facilitating the inclusion of health content related to the LGBTQIA+ community and other key populations in the undergraduate nursing curricula of KwaZulu-Natal, South Africa.

Methods: A multimethods design encompassing collection of primary and secondary data using multiple qualitative designs and quantitative approaches will be used to generate evidence that will inform the co-design, testing, and scale-up of strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. Data will be collected using a combination of convenience, purposive, and snowball sampling techniques from LGBTQIA+ persons; academic staff; undergraduate nursing students; and other key populations. Primary data will be collected

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through individual in-depth interviews, focus groups discussions, and surveys guided by semistructured and structured data collection tools. Data collection and analysis will be an iterative process guided by the respective research design to be adopted. The continuous quality improvement process to be adopted during data gathering and analysis will ensure contextual relevance and sustainability of the resultant co-designed strategies that are to be scaled up as part of the overarching objective of this study.

Results: The proposed study is designed in response to recent contextual empirical evidence highlighting the multiplicity of health challenges experienced by LGBTQIA+ individuals and key populations in relation to health service delivery and access to health care. The potential findings of the study may be appropriate for contributing to the education of nurses as one of the means to ameliorate these problems. Data collection is anticipated to commence in June 2024.

Conclusions: This research has potential implications for nursing education in South Africa and worldwide as it addresses up-to-date problems in the nursing discipline as it pertains to undergraduate students' preparedness for addressing the unique needs and challenges of the LGBTQIA+ community and other key populations.

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KEYWORDS

lesbian, gay, bisexual, transgender, intersex, queer, and allied; LGBTQIA+; key populations; nursing curricula; health science education; South Africa; undergraduate; nursing; lesbian, gay, bisexual, and transgender; LGBT; legislation; health care; unmet; barrier; stigma; discrimination; threats; co-design

Introduction

Background

South Africa is one of the most progressive African nations when it comes to legislation protecting the human rights of individuals who identify as lesbian, gay, bisexual, transgender, queer, intersex, and allied (LGBTQIA+) [1]. Despite institutionalized rights, evidence suggests that the LGBTQIA+ community continues to encounter stigma, discrimination, and threats to their personal well-being [2-4]. Studies examining the experiences of gender and sexual minorities reveal that the LGBTQIA+ community often faces neglect, harassment, and substandard treatment from health care providers when seeking medical care [5,6]. Moreover, studies report that the LGBTQIA+ community faces several systemic and structural barriers that hinder access to various forms of basic public services including health care, resulting in unmet health needs [7,8]. The obstacles to health care access stem from structural and systemic issues, including insufficient physical resources tailored to the unique needs of this population, stigmatizing attitudes among health care personnel, and a shortage of skilled professionals capable of providing affirming care tailored to their needs [9-11]. Furthermore, literature suggests that the LGBTQIA+ community faces disproportionate rates of HIV or AIDS and tuberculosis infection [12]. Moreover, they are at higher risk for mental health disorders, substance abuse, and long-term sequelae resulting from untreated communicable and noncommunicable disease due to barriers hindering access to health care [10,13,14].

The current reported state of health service delivery as it pertains to the LGBTQIA+ community threatens local and global health policy reforms in terms of universal health coverage and the Sustainable Development Goals. It has been argued that the poor training of health care workers regarding the health needs of this community and the limited provision of appropriate health care may account for challenges faced by the LGBTQIA+ community when accessing health services in South Africa [8,9,11,15]. Although literature on the inclusion of LGBTQIA+ health content in the curricula of health science programs in sub-Saharan Africa, including South Africa, is limited, it suggests that there is little, to no, formal theoretical and clinical training provided to undergraduate health science students [16,17]. It is further suggested that, in instances where content is included, it is often among medical disciplines with no systematic structure, which results in inadequate mastery of essential clinical skills and the knowledge required to enable students to learn how to address the health needs of the LGBTQIA+ community [16,18]. The findings of a curriculum mapping exercise to determine LGBTQIA+ health–related content, pedagogical assessment, and methodology at a selected university in South Africa revealed that the gaps in the inclusion of LGBTQIA+ health content in the curriculum were only evaluated once throughout the duration of the course, with no follow-up, long-term assessment to determine knowledge retention, assess improvement of attitudes, or measure increased levels of comfort. Moreover, the teaching styles adopted did not allow for an awareness and reflection of students' perceptions in a manner that challenges their biases toward the LGBTQIA+ community [16]. The reported inconsistencies in the curriculum may impact the preparedness of health science graduates for a health system that requires that universal, quality care be provided for all, irrespective of gender identity and sexual orientation. In addition, they may account for the reported challenges experienced by LGBTQIA+ persons in relation to access and quality of health services provided. This subsequently necessitates training interventions to be directed at preservice and in-service health care workers to address the current health service delivery disparities faced by the LGBTQIA+ community [19,20].

The South African health system, which is based on a primary health care approach to service delivery, is nurse led, as nurses constitute the majority workforce [21]. The literature reviewed on the training and inclusion of LGBTQIA+ health needs and care has revealed gaps in relation to how such training is provided. Current evidence suggests poor preparation of South African health care workers to address the health needs of this

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community [7,8]. This may in turn contribute to unmet health needs and the possibility of poor public health outcomes for South Africa, especially in light of the current incidence and prevalence of communicable and noncommunicable diseases.

The South African National Strategic Plan (NSP) for HIV or AIDS, tuberculosis, and sexually transmitted infections (STIs), 2023-2028 necessitates targeted interventions to be directed toward key populations and LGBTQIA+ persons to achieve HIV or AIDS epidemic control, in line with the Joint United Nations Programme on HIV or AIDS 95-95-95 strategy [22,23]. An essential part of achieving this goal thus consists of facilitating access to quality health care to meet the needs of LGBTQIA+ persons and other key populations. Thus, there is a need to facilitate the inclusion of LGBTQIA+ health content in the undergraduate nursing curricula to ensure that preservice nurses are adequately prepared to address the health needs and challenges of these individuals in line with the principles of universal health coverage and the Sustainable Development Goals [24,25].

The proposed research will thus be conducted to facilitate the inclusion of LGBTQIA+ and key populations' health content in the undergraduate nursing curricula of higher education institutions in KwaZulu-Natal, South Africa. In this regard, 4 higher education institutions, namely, the University of KwaZulu-Natal, the Durban University of Technology, the University of Zululand, and the KwaZulu-Natal College of Nursing, will form part of the project, as these institutions offer undergraduate nursing programs producing nurses who predominantly serve the KwaZulu-Natal province of South Africa. The proposed study findings have implications for nursing and health science education, and the findings may inform knowledge and skills transfer for the inclusion of LGBTQIA+ and key populations' health content into the curriculum for all undergraduate nurses in South Africa and could extend to broader health science disciplines at higher education institutions in KwaZulu-Natal and throughout the country. In addition, the study findings have implications for future research in this area and for broader public health issues related to provision of health services for the LGBTQIA+ persons and other key populations. For the purpose of this study, other key populations refer to sex workers, drug users, and men who have sex with men (MSM), as identified in the South African NSP for HIV or AIDS, tuberculosis, and STIs, 2023-2028.

Aim

This study aims to design implementation strategies for the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa.

Objectives

The following sections outline the research objectives and corresponding research questions:

1. To analyze the health needs and practices of service provision for the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa
2. To explore the existing practices regarding the inclusion of LGBTQIA+ and key populations health content in the curricula of undergraduate nursing programs in KwaZulu-Natal, South Africa
3. To co-design, test, and evaluate relevant approaches to facilitate the inclusion of LGBTQIA+ and key populations health content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa
4. To spread and scale-up the use of co-designed evidence-based strategies for the inclusion of LGBTQIA+ and key populations health content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa

Research Questions

In relation to objective 1:

1a. What is the current practice of health service provision for the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa?

1b. What are the health needs of the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa?

In relation to objective 2:

2a. What is the current available health content on the LGBTQIA+ community and other key populations in the curricula of undergraduate nursing programs in KwaZulu-Natal, South Africa?

2b. What are various academics' and students' experiences, understanding, and perceptions regarding the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa?

In relation to objective 3:

3a. What strategies can be codeveloped to facilitate the inclusion of health content on LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa?

3b. What are the reported outcomes of testing the codeveloped strategies to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa?

In relation to objective 4:

4a. What are the recommended approaches to facilitate spread and scale-up of codeveloped strategies to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa?

Methods

Study Setting

The study will be conducted within the KwaZulu-Natal province of South Africa, and 4 higher education institutions, namely, the University of KwaZulu-Natal, the Durban University of Technology, the University of Zululand, and the KwaZulu-Natal

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College of Nursing, will be the sites for data collection. These higher education institutions each presently have an annual size intake of 50 students per year and collectively produce between 120 and 170 new nurse graduates annually. The institutions also have a complement of academic staff with varying qualifications ranging from junior degrees to PhDs, with job functions aligned to respective qualifications as per the national higher education policy and regulations stipulated by the professional body.

Overarching Design

The study will use a multimethods design, encompassing quantitative and qualitative approaches to collect data from various categories of participants to address the objectives of the research study. The multimethods design allows multiple approaches to data collection, which address the different research objectives and research questions that are related to the broad objectives of the research project. Moreover, the design will also allow concurrent triangulation of data, which will inform the process of co-designing strategies to facilitate the inclusion of health content related to the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal. The study will thus incorporate multiple research designs to execute the research process. The data that will be generated through the research process will inform the design, testing, and implementation of a relevant strategy to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal using the process of continuous quality improvement (CQI), as recommended by the Institute of Health Improvement [26]. The collection of data with concurrent data analysis will be an iterative process comprising data triangulation, collation, and collaborative strategy design. The study will thus be conducted in three phases that will entail (1) formative phase, (2) co-design and testing, and (3) spread and scale-up. Table 1 provides an overview of the proposed research methodology and research process to be followed for execution of this study, as informed by the 3 phases of the study. All phases of this study are yet to be carried out and will thus commence in 2024. Before this stage of the project, informal activities were conducted through undocumented sensitivity training sessions. These sessions were initiated in response to contextual anecdotal evidence influenced by the study findings, and they were primarily led by 1 of the principal investigators involved in the study [9,15]. Other work relates to the exploration of nursing students' knowledge attitudes and perceptions regarding the health needs of sexual and gender minority individuals in KwaZulu-Natal, South Africa [27].

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Table 1. Summary of methodology and study execution.

Research questions	Design	Population	Sampling and data collection processes
Phase 1: formative phase			
Objective 1: to analyze the health needs and practices of service provision for the LGBTQIA+[a] community and other key populations in KZN[b], South Africa			
1a. What is the current practice of health service provision for the LGBTQIA+ community and other key populations in KZN, South Africa?	• Scoping review using the framework Arksey and O'Malley [28] • Empirical study: qualitative descriptive phenomenological case study	• Published and gray literature, including related studies, policies, and guidelines • Health care workers, that is, nurses, physicians, clinical associates, and policy makers	• Population, intervention, context, and outcomes framework to identify relevant literature • Purposive sampling of health care workers and key informants and a combination of focus group discussions and in-depth interviews to collect data
1b. What are the health needs of the LGBTQIA+ community and other key populations in KZN, South Africa?	• Exploratory qualitative descriptive study	• LGBTQIA+ individuals and other key populations (men who have sex with men, sex workers, and people who inject drugs)	• Purposive adjusted snowball sampling to identify relevant participants and individual interviews and focus group discussions to collect data
Objective 1.1: to explore the existing practices regarding the inclusion of LGBTQIA+ and key populations health content in the curricula of undergraduate nursing programs in KZN, South Africa			
1.1a. What is the current available health content on the LGBTQIA+ community and other key populations in the curricula of undergraduate nursing programs in KZN, South Africa?	• Retrospective document analysis	• Teaching and learning documents including, but not limited to, relevant teaching, learning and assessment policies, study guides, module descriptors, course contents, and examination papers	• A modified curriculum audit tool will be used to assess documents with a review period of 12 months before commencement of data collection
1.1b. What are various academics' and students' experiences, understanding, and perceptions regarding the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KZN, South Africa?	• A qualitative phenomenographic study	• Various categories of academic staff and undergraduate nursing students at all levels of study in the selected higher education institutions	• Purposive sapling will be used to collect data using focus group discussions
Phase 2: co-design and testing			
Objective 2: to co-design, test, and evaluate relevant approaches to facilitate the inclusion of LGBTQIA+ and key populations health content in the undergraduate nursing curricula in KZN, South Africa			
2a. What strategies can be codeveloped to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KZN, South Africa?	• Consensus methodology using nominal group technique underpinned by the continuous quality improvement process (Plan-Do-Study-Act)	• All participants identified in phase 1 of the study (LGBTQIA+ individuals, academics, nursing students, health care workers, policy makers, and core research team)	• Purposive sampling of participants identified in phase 1 of the study and focus group discussions to gather data.

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Research questions	Design	Population	Sampling and data collection processes
2b. What are the reported short-term outcomes of testing the codeveloped strategies to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KZN, South Africa?	• Exploratory qualitative descriptive study and quantitative descriptive cross-sectional survey	• Academic staff and nursing students in various levels where co-designed interventions will be tested	• Purposive sampling will be used to collect data from all participants, and a combination of focus group discussions and individual in-depth interviews will be used to gather qualitative data from participants. Quantitative data will be collected using a tested knowledge, attitude, perception, and awareness survey to assess the short-term outcomes of testing the co-designed strategies for facilitating inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KZN, South Africa
Phase 3: spread and scale-up			
Objective 3: to spread and scale-up the use of co-designed evidence-based strategies for the inclusion of LGBTQIA+ and key populations health content in the undergraduate nursing curricula in KZN, South Africa			
3a. What are the recommended approaches to facilitate spread and scale-up of codeveloped strategies to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KZN, South Africa?	• Data triangulation method	• Data collected from phase 1 and 2 and academic staff in the selected higher education institutions	• The core research team will use data informed by phase 1 and phase 2 of the study to develop a relevant approach to scale-up co-designed strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KZN, South Africa
3b. What are the reported outcomes of scaling-up the codeveloped strategies to facilitate the inclusion of health content on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KZN, South Africa?	• Exploratory qualitative descriptive study and quantitative descriptive cross-sectional survey	• Academic staff and nursing students in various levels where co-designed interventions will be tested	• Purposive sampling will be used to collect data from all participants, and a combination of focus group discussions and individual in-depth interviews will be used to gather qualitative data from participants. Quantitative data will be collected using a tested knowledge, attitude, perception, and awareness survey to assess the large-scale outcomes of scaling-up the co-designed strategies for facilitating inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KZN, South Africa

[a]LGBTQIA+: lesbian, gay, bisexual, transgender, intersex, queer, and allied.

[b]KZN: KwaZulu-Natal.

Phase 1: Formative Phase

Overview

This phase serves to facilitate the situational analysis related to the broad objective of the research project. In phase 1, primary and secondary data will be collected to generate evidence on the health needs and practices of health service provision for the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa. This phase will also entail execution of research processes to generate data on the existing

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LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. This phase will thus address the research objectives 1 and 2 together with the related research questions of each objective.

Design

During the formative phase (phase 1), primary and secondary data will be collected concurrently, analyzed, and triangulated to inform research processes that will unfold in phase 2 of this study. Multiple research designs will be used to gain comprehensive and holistic data that will contribute to evidence that will inform the design of implementation strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. Thus, the research designs to be used for phase 1 of this study are as follows: (1) scoping review, (2) exploratory descriptive qualitative study design, (3) descriptive phenomenological case study design, (4) document review through a curriculum mapping exercise, and a (5) qualitative phenomenographic study design. These research designs will collectively inform the execution of the research process that will address objectives 1 and 2 of this proposed study.

To attain information on the health needs and practices of health service provision for the LGBTQIA+ community and other key populations, a systematic scoping review guided by the methodological framework by Arksey and O'Malley [28] will be conducted. An empirical research study will also be conducted using an exploratory qualitative descriptive design to gain a more in-depth understanding of the health needs of LGBTQIA+ individuals and other key populations. A descriptive phenomenological case study will subsequently be conducted to explore various stakeholder experiences regarding service provision for the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa. The results of this empirical study along with the findings of the scoping review will be integrated with other data that will be generated to inform the health content on the LGBTQIA+ population and key populations that should be included in the undergraduate nursing curricula in KwaZulu-Natal.

A curriculum mapping exercise will also be conducted to review and determine the current content that is available on the LGBTQIA+ community and other key populations in the undergraduate nursing programs in KwaZulu-Natal. A qualitative phenomenographic study design will be used to explore the qualitative differences in the experiences, understanding, and perceptions of various academics and students regarding the inclusion of content related to the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa.

Sampling and Recruitment

As a combination of primary and secondary data will be collected during phase 1 of the project, varying recruitment and data collection processes will be conducted. The secondary data that will be collected in this study will comprise document review of existing research including peer-reviewed and gray literature on the practices of health service provision and health needs of the LGBTQIA+ community and other key populations in KwaZulu-Natal, South Africa. The collection of secondary data will also include a curriculum review exercise that will entail mapping of the existing content that is included on the LGBTQIA+ community and other key populations in the undergraduate nursing curricula at higher education institutions in KwaZulu-Natal, South Africa. In this regard, document review of learning materials; study guides; module descriptors; and relevant institutional teaching, learning, and assessment policies will be performed for all undergraduate nursing programs in the selected institutions identified for data collection.

As part of the empirical study related to the health needs of the LGBTQIA+ population and other key populations in KwaZulu-Natal, South Africa, data will be collected from a purposive sample of individuals from the LGBTQIA+ community and other key populations, namely, MSM, transgender persons, sex workers, and people who inject drugs. To recruit participants for this study, a purposive adjusted snowball sampling technique will be used. Initial recruitment of participants will be facilitated through the mediated access as informed by key informants that are acquainted to the research team. Identification of participants will thus begin purposively, wherein the researchers will identify relevant participants from the LGBTQIA+ community and those that belong to other key populations (namely, sex workers, MSM, etc) from their individual network of acquaintances, which will include peers, family members, community networks, and other spheres of influence. Mediated access to relevant participants will also be facilitated through professional research networks and other related organizations of influence. As the researchers broadly have diverse networks of influence by virtue of differences in geographical location and professional position of influence, a diversity in the participants is expected, which may thus minimize researcher biases.

To explore stakeholders' experiences regarding service provision for the LGBTQIA+ community and other key populations, purposive sampling of key informants, including health care workers, policy makers, key populations, and the people identifying as LGBTQIA+, will be conducted. Policy makers will be recruited from district and provincial department of health offices. Health care workers will be recruited from primary health facilities within various health districts within the KwaZulu-Natal Department of Health and will include nurse managers, primary health care nurses, enrolled nurses, and nursing assistants. Recruitment of these participants will also be facilitated through relevant line managers and heads of establishment within the various levels of the health system. In this regard, written letters of information will be circulated electronically to provide information of the nature of the study and proposed data collection approaches. Following approval and confirmation by relevant managers, the participants will be contacted through the respective reporting lines, and arrangements will be made to facilitate data collection based on their reported convenience in terms of date, time, and preferred mode of data collection (whether web-based or face to face).

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For sampling related to the empirical study of the experiences, understanding, and perceptions of various academics and students regarding the inclusion of content of the LGBTQIA+ community and other key populations, convenience sampling techniques will be used to identify undergraduate nursing students and academic staff in various levels of study. Participants will be approached through academic leaders and relevant level coordinators and lecturers. Recruitment of students will thus take place while students are on campus at the various higher education institutions. Written communication will be providing to the relevant head of department and thereafter disseminated to the various subject lecturers. Arrangements will subsequently be made to collect data from the students based on their availability, as informed by the various heads of department of the undergraduate nursing programs and the relevant lecturers. Students will thus be conveniently approached after attending lecturers, and information about the nature of the study will be provided, and those granting consent will be taken to private offices within the institutions where individual in-depth interviews and focus group discussion sessions will be conducted based on the number of students who consent to participate as convenient sampling processes unfold.

Data Collection Processes

All primary data will be collected following the appropriate informed consent processes; data will be collected at settings that are most convenient to participants. A combination of individual in-depth interviews and focus group discussions will be conducted. Web-based and face-to-face methods of data collection will be adopted based on the convenience of participants. The web-based data collection methods will be facilitated through Zoom Video Communications, Inc, Microsoft, WhatsApp Inc, and telephonic interviews, as informed by participant's convenience. All qualitative data will be collected until saturation is reached, and data analysis will be guided by the qualitative design adopted. The individual in-depth interviews and focus group discussions to be held will be guided by a self-developed interview schedule that is aligned to the respective objectives of this study. Typically, all the semistructured interview guides will comprise 2 sections, namely, participant demographics and guiding interview questions related to the various objectives of the study. All interviews are anticipated to be conducted for approximately 35 to 60 minutes to obtain depth of qualitative data.

The secondary data collection processes will be conducted using the relevant methodological framework and data extraction tools aligned to the objective of the study. For the scoping review component, a self-developed data extraction tool including fields such as author, year of publication, summary of methodology, key findings, recommendation, and limitations will be used to chart the data related to the health needs and practices of service provision of the LGBTQIA+ community and key populations. In this regard, 2 different review processes will be followed culminating in 2 scoping review documents. The curriculum mapping exercise to review the existing content of LGBTQIA+ and key populations will be conducted using a self-developed curriculum review audit tool that assesses the type of content delivered, teaching styles, assessment methods adopted, and learning outcomes associated with the content.

Phase 2: Co-Design and Testing

During this phase, primary and secondary data generated from phase 1 of this study will be consolidated following application of the relevant data analysis and triangulation processes. The consolidated data will be presented as emerging themes and possible recommendations to inform the design, testing, and implementation of strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. To operationalize the process of co-designing related to the phase 2 of this study, participants recruited as participants during phase 1 of the study will be contacted to facilitate member checking of triangulated data and emerging results from the data analysis process. The participants will be recruited directly by the researchers of the study using information obtained from phase 1 of the study. Workshop sessions will subsequently be set up to facilitate the co-design of strategies to facilitate the inclusion of LGBTQIA+ and key populations content using data collected from phase 1 through nominal group technique to facilitate consensus. Implementation and testing of co-designed strategies will be facilitated through the CQI process. The Plan-Do-Study-Act cycle embedded within the CQI process will be used to iteratively define, test, and refine the appropriate strategies that may lead to successful implementation of appropriate strategies that will facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula on the basis of contextual relevance and feasibility. Sustained stakeholder engagement through a series of workshops, engagements, and consensus building sessions will be a key feature of this phase and will serve to ensure co-designed strategies that are relevant for the contextual dynamics of higher education and health service delivery responsiveness within the KwaZulu-Natal context. The precise intervention strategy that will be co-designed for testing is presently not known; however, it is anticipated that the strategy to be developed will be informed by primary and secondary data that will be generated in this study. Moreover, the strategy to be codeveloped will also inform the content to be included; approach to inclusion; assessment strategies; and other approaches related to teaching, learning, and assessment. The anticipated outputs of this phase may thus be teaching content, learning aids, teaching guidelines, and related policy briefs and publications. A crucial aspect of this study's implementation will involve engaging multiple stakeholders, including members of the LGBTQIA+ community and other key populations. This will ensure that the strategies and content to be included in the curricula are informed by the needs of individuals that the students will eventually have to cater to upon completion of their studies. This may thus facilitate contextualized learning to ensure that nursing students who graduate are able to address the health needs of the LGBTQIA+ community and key populations in KwaZulu-Natal, South Africa.

Phase 3: Spread and Scale-Up

This phase will be informed by the outcomes of the small-scale testing of strategies that will be co-designed during phase 2 of this study. The outcomes of the testing process will be informed by the CQI process that will be adopted during phase 2. During

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the spread and scale-up, co-designed strategies will be rolled out at a large scale in the undergraduate nursing programs of the selected higher education institutions in KwaZulu-Natal. In this regard, key stakeholders from the undergraduate nursing programs of the selected institutions will be identified as informed by participants included in the phases 1 and 2 of the study. The relevant gatekeeper processes will be followed, and large-scale adoption of the strategies designed in phase 2 will be scaled up based on the outcomes of the testing process and unique contextual factors affecting teaching and learning at different higher education institutions. The precise format of scale-up remains unknown and will depend on the outcomes of phase 2 of the study, which, in turn, is dependent on the findings of phase 1. However, the anticipated scaling up of the co-designed strategy is expected to inform both the content to be included in nursing curricula and the practices necessary to facilitate their inclusion. The spread and scale-up process will also be monitored through CQI processes that entail routine data collection related to students' and academic staff's experiences of the spread and scale-up process. Behavior and attitude change assessment will also be embedded within the scale-up process as part of CQI; this will be facilitated through the administration of quantitative survey tools to students and academic staff on attitudes, perceptions, and awareness regarding key contents related to the LGBTQIA+ community and key populations in KwaZulu-Natal, South Africa. The long-term sustainability of the project and emerging outcomes will be ensured by the development of policy briefs and recommendations for teaching, learning, and assessment that advocate for co-designed content and strategies to be embedded within mainstream curriculum and pedagogical practices based on the contextual dynamics of the specific higher education institutions. In addition, the inclusion of various categories of academic staff from various higher education institutions as part of co-design, testing, and implementation also serves as one of the means of ensuring long-term sustainability.

Data Analysis

Qualitative Data Analysis

The primary qualitative data collected in this study will be analyzed based on the design adopted per objective of the study. All qualitative data collected will be analyzed following verbatim transcription of all interviews that will be conducted by the researchers and contracted research assistants. In line with primary data collection processes, data collected using the exploratory qualitative design will be analyzed inductively through content analysis, as recommended by Cresswell [29]. The analysis of the data will thus include (1) verbatim transcription of all audio-recorded interviews, (2) writing of field notes with subsequent reading for comparison with audio-recorded data to ensure accuracy, (3) repeated reading of transcriptions to attain familiarity with contents and formulate meaning units, (4) selection of informative components of the data, (5) repetition of previous steps to ensure valuable information is not missed, (6) grouping of similar topics together, and (7) formulation of relevant themes and subthemes.

For the descriptive phenomenological case study design, data collected will be analyzed as recommended in the steps of phenomenological data analysis by Colaizzai [30], as cited in the study by Nxumalo et al [31]. The steps to be followed are as follows: (1) repeated reading of transcripts to gain a general sense of its contents; (2) extraction of substantial statements in line with the relevant objective; (3) formulation of meanings from the significant statements derived; (4) sorting of formulated meanings into categories, clusters of themes, and themes; (5) integration of findings into an exhaustive description of the phenomenon being investigated; (6) description of the fundamental structure of the phenomenon; and (7) member checking to validate the descriptive results.

Data collected through the phenomenographic study design will be an iterative process following steps guided by Sjöström and Dahlgren [32]. The first step will entail the familiarization, where transcripts are read several times to become familiar with their contents. The second step will involve a more focused reading to deduce differences and similarities in the transcripts. In the third step, the researchers will identify the key elements in the answers. During the condensation step, only the meaningful and relevant aspects of the transcript will be extrapolated. The fourth step will involve preliminary grouping, with the focus on identifying and classifying similar responses into preliminary groups. These preliminary groups will be reviewed to ascertain whether any other groups convey the same meaning under different headings. This will be followed by a preliminary comparison of categories. Following confirmation, categories were named to highlight their significance. In the final step, the hope is to discover the outcome space based on their internal relationships and the qualitatively unique ways of understanding, conceiving, and experiencing the phenomena. Analysis of secondary data from the curriculum reviews and scoping reviews will be conducted thematically using steps recommended by Braun and Clarke [33]. The secondary data will thus be presented narratively following thematic analysis.

Quantitative Data Analysis

The quantitative data collected as part of the CQI process of phase 3 of the study will be analyzed using descriptive statistics and inferential analysis. To facilitate this process, the data collected from Google Forms will be imported into an Excel spreadsheet (Microsoft Corp) in preparation for analysis, which will be conducted using SPSS (IBM Corp). The demographic profile data will be converted into categorical data, and the remaining sections will be converted into statistical data for interpretation. The categorical variables will be analyzed descriptively as counts and percentage frequencies. To determine the association between categorical variables, the chi-square test will be used. When the distribution of the cross-tabulations contains an expected value of <5, the Fischer exact test will be applied.

Trustworthiness and Rigor

Techniques to ensure dependability, credibility, confirmability, and transferability in this study will include triangulation and member checking. Individual in-depth interviews recorded using an audiotape will ensure credibility and confirmability of the data. Transcribing the data accurately and using appropriate data analysis methods informed by the research design will ensure the dependability of the process. The iterative data

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collection and concurrent analysis approaches to be adopted will also facilitate credibility and confirmability. Data analysis will be done by experts in qualitative research methods to ensure reliability of findings. Moreover, member checking will also be done to facilitate confirmability. To facilitate member checking, copies of transcriptions with emerging preliminary analyses of the data will be provided electronically to all participants to ascertain whether the transcripts and analyzed data reflect participants' responses and personal interpretation of the data. Moreover, during the workshop sessions to be held in phase 2 in line with the CQI processes, the analyzed data will be presented for participants to provide input as part of ensuring that the analyzed data presented resonate with the participants' personal interpretations and intended meaning they wished to convey during the qualitative interviews. All details related to the design and execution of the study are documented to facilitate transferability of the findings that are to emerge. For the quantitative data, the internal consistency of a set of items will be assessed using Cronbach α and the item-rest correlation. Inferential statistical analysis tests will be conducted at a 5% level of significance.

Ethical Considerations

Ethics approval has been obtained from the Biomedical Research Ethics Committee at the University of KwaZulu-Natal (BREC/00002917/2021). Gatekeeper permission to conduct the study has been obtained from all selected higher education institutions where data will be collected. Written and verbal informed consent will be obtained from all participants before data collection. Ethical principles of autonomy, confidentiality, anonymity, and the right to withdraw will be observed. To ensure autonomy and right to withdraw from the study, informed consent will be obtained from all participants before data collection, and a written information sheet will be provided to all participants clarifying the nature of the study, in addition to the verbal information that will be provided. Informed consent will be obtained verbally from all participants, and they will be given the option to provide voluntary consent and opt out of the study at any time without any form of penalty. Confidentiality and anonymity will be ensured during the data collection processes by conducting individual interviews and focus groups at private venues that are not accessible to the general public; moreover, special precautions will be taken to avoid collecting personal information such as names, addresses, and phone numbers during the recording of interviews. Unique participant codes will be assigned to ensure anonymity during data storage. The data will be kept in a password-protected folder on 1 researcher's laptop, accessible only to the research team. In the process of disseminating data, no personal information or data revealing participant identity will be included. This applies to all written outputs such as manuscripts and reports that may result from the data collection process.

Results

The proposed project is informed by the findings of recent contextual studies related to health service provision for the LGBTQIA+ community and key populations in KwaZulu-Natal, South Africa. The findings of these studies have revealed gaps in the training and preparedness of health science graduates to address the unique needs of these individuals in the South African context. Moreover, the South African NSP for HIV or AIDS, tuberculosis and STIs, 2023-2028 necessitates targeted interventions and health care be provided to the LGBTQIA+ community and key populations as part of the HIV or AIDS response strategy. These interventions must be rooted in holistic and comprehensive person-centered care. The aforementioned factors thus necessitate capacity to be created within existing undergraduate health science programs to enable preservice health care providers to be adequately prepared to attend to the unique health needs of the population. As current empirical evidence reveals gaps in the training of health science graduates in this regard, it is necessary that research be conducted to inform co-design of relevant strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. Data collection is anticipated to commence in June 2024.

In the context of the proposed study, strategies to facilitate the inclusion of health content related to the LGBTQIA+ community and key populations relate to the design and implementation of relevant course content and other relevant teaching, learning, and assessment materials that may support existing curriculum and pedagogical factors. The precise format of strategies and content that is to be developed remains unknown due to the varying contextual dynamics of higher education institutions and diverse health landscape of South Africa. Nonetheless, the codevelopment and implementation process will be underpinned by recommended best practice related to teaching, learning, and assessment practices, particularly in relation to teaching content related to sexual and gender minority groups. In this context, the plan is to systematically integrate strategies and content into the curriculum. This integration will be designed to encourage values clarification, challenging students' personal biases. Ultimately, this approach aims to address the current issues of stigma and discrimination experienced by LGBTQIA+ persons and other key populations. It is also envisaged that the training methodology and content will foster a culture of empathy and respect among students, thus enabling them to be able to render affirming health care.

Discussion

Anticipated Findings

This protocol paper describes the design of an evidence-informed project aimed at facilitating the inclusion of health content related to the LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. A multimethods design encompassing collection of primary and secondary data using multiple qualitative design methods and quantitative approaches will be used to generate data that will be triangulated and integrated to inform the co-design, testing, and scale-up of strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. Engaging multiple stakeholders and anchoring the process in CQI will ensure the contextual relevance and sustainability of the project outcomes. This

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includes the spread and scale-up of the co-designed strategies. As informed by the recommendations of previous contextual and international literature, the undoubted severity of the health-related problems of the LGBTQIA+ community and other key populations and the importance of different types of intersectional discrimination against LGBTQIA+ persons, the appropriateness of high-quality education of nurses emerges as a possible means to ameliorate these problems. On the contrary, existing literature alludes to the lack of training of undergraduate nursing students regarding the unique health needs of the LGBTQIA+ population and other key populations with potential consequences of unmet health needs, which may contribute to poor health outcomes for these individuals [34].

The potential for mortality and morbidity associated with untreated communicable and noncommunicable diseases due to challenges in accessing health care among these individuals has significant public health implications. The training of preservice nurses is thus a crucial step toward addressing the reported challenges experienced by the LGBTQIA+ population and other key populations. In this regard, a holistic understanding of the different factors operating in the complex social processes involved in the health care problems of the LGBTQIA+ community may also be important to facilitate a better understanding of these problems and therefore form the basis for appropriate strategies to be designed and implemented. In relation to training of preservice nurses, this information may form the basis upon which content to inform health service provision is designed and implemented. The proposed study uses a multimethods design to elicit data using a multiphase data collection processes through multistakeholder engagement to co-design contextually relevant strategies to facilitate the inclusion of LGBTQIA+ and key populations content in the undergraduate nursing curricula in KwaZulu-Natal.

Implications

The expected outcomes of this research have implications for nursing education and scholars in South Africa and globally. It tackles current issues within the nursing discipline, particularly regarding undergraduate students' readiness to address the specific needs and challenges of the LGBTQIA+ community and other key populations. In the South African context, this study has potential implications for informing preservice nurses training on health care provision for the LGBTQIA+ persons and other key populations, as documented in the South African NSP for HIV or AIDS, tuberculosis and STIs, 2023-2028. In addition, the findings of this study have potential implications for all undergraduate nursing programs in the country and may inform knowledge transfer for other health science disciplines that do not have this content formally embedded in their curricula.

Limitations

The execution of this project will be limited to undergraduate nursing programs in KwaZulu-Natal, South Africa, which may not necessarily be reflective of all undergraduate nursing programs in the country. Moreover, as the study will be limited to undergraduate nursing programs, the findings may not be entirely applicable to other health science programs. Nonetheless, the findings may provide foundational information to guide the co-design of similar strategies in other health science disciplines and undergraduate nursing programs in South Africa.

Conclusions

This paper describes the design of a multimethods research project aimed at facilitating the inclusion of LGBTQIA+ community and other key populations in the undergraduate nursing curricula in KwaZulu-Natal, South Africa. This project is informed by the findings of previous contextual studies that have revealed challenges faced by the LGBTQIA+ community when accessing health care. Furthermore, evidence indicates that South African health care workers lack training to address LGBTQIA+ health issues both before and during their service. The proposed study findings may thus contribute to addressing this gap and may serve as a means of ameliorating the health challenges faced by LGBTQIA+ persons. The use of the multimethods design and multiple stakeholder engagement including students, academics, members of the LGBTQIA+ community, and other key populations serves as a means of ensuring that contextually relevant strategies are designed. The CQI process to be adopted as part of the co-design and testing phase will serve to ensure relevance of the strategies to be co-designed. The quantitative and qualitative evaluation processes to be adopted will ensure that outcomes of the project are measured in terms of knowledge, attitudes, and perceptions.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

CQI: continuous quality improvement
LGBTQIA+: lesbian, gay, bisexual, transgender, intersex, queer, and allied
MSM: men who have sex with men
NSP: National Strategic Plan
STI: sexually transmitted infection

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Protocol

The Durban University of Technology Faculty of Health Sciences Decentralized Clinical Training Project: Protocol for an Implementation Study in KwaZulu-Natal, South Africa

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Abstract

Background: The Durban University of Technology (DUT) Faculty of Health Sciences (FHS) in KwaZulu-Natal, South Africa, is embarking on a project to implement a Decentralized Clinical Training Program (DCTP). The DUT FHS DCTP project is being conducted in response to the growing demands of students requiring clinical service placements as part of work-integrated learning. The project is also geared toward responding to existing gaps in current practices related to the implementation of a DCTP, which has mainly been through traditional universities providing training to medical, optometry, occupational therapy, and physiotherapy students. In South Africa, a DCTP is yet to be implemented within the context of a university of technology; it is yet to be implemented within health science faculties that offer undergraduate health science programs in mainstream biomedicine and alternative and complementary disciplines.

Objective: We aim to design, pilot, and establish an effective DCTP at the DUT FHS in KwaZulu-Natal, South Africa.

Methods: Participatory action research comprising various designs—namely, appreciative inquiry, qualitative case study design, phenomenography, and descriptive qualitative study design—will be used to conduct the study. Data will be collected using individual interviews, focus group discussions, nominal group technique, consensus methodology, and narrative inquiry. Study participants will include various internal and external stakeholders of the DUT, namely, academic staff; students; key informants from universities currently using successfully established DCTPs; academic support staff; staff working in human resources, finance, procurement, and accounting; and experts in other disciplines such as engineering and information systems. Overall, 4 undergraduate health science programs—namely, Radiography, Medical Orthotics and Prosthetics, Clinical Technology, and Emergency Medical Care and Rescue—will be part of the project's pilot phase. Findings from the project's pilot phase will be used to inform scale-up in the other undergraduate programs in the DUT FHS. The project is being implemented as part of the university's strategic objective of devising innovative curricula and pedagogical practices to improve the mastery, skill set, and competence of health science graduates.

Results: The study has currently commenced with the situational analysis, consisting of engagement with external stakeholders implementing DCTPs. The data to be generated from the completion of the situational analysis are anticipated to be published in 2024.

Conclusions: This project is envisioned to facilitate collaboration among the universities of technology, traditional universities, Ministry of Health, and private sector for clinical placement of undergraduate health science students in health establishments that are away from the university, thereby exposing them to real-life experiences related to health care. This will facilitate authentic

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learning experiences that will contribute to improved competencies of graduates in relation to the health needs of society and the multiple realities of the South African health system.

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KEYWORDS

decentralized clinical training programs; curriculum; clinical education; health science education; university of technology; pedagogy; transformative education; teaching; higher education; South Africa

Introduction

Background

Decentralized Clinical Training Programs (DCTPs) refer to learning platforms adopted in health science education, which facilitate theoretical and clinical learning in remote decentralized health facilities that are often some distance away from traditional academic teaching health establishments [1]. Traditional DCTPs have predominantly been implemented with medical students through the use of community-based primary health care facilities, community health centers, and district hospitals [2-4]. Facilitating successful implementation of DCTP for health science education requires a geographical shift in terms of clinical placement facilities used for work-integrated learning of students. Moreover, a curriculum and pedagogical shift from the traditional teaching approach is necessary to maximize the benefits of this strategy [5]. Initial implementation of DCTP in low- to middle-income countries such as South Africa predominantly involves a geographical shift; however, developments in recent years have resulted in universities adopting both a geographical and pedagogical shift due to the many potential benefits of such a change. By facilitating the pedagogical shift, higher education institutions implementing DCTP have realigned health science curricula to place a strong emphasis on the primary health care approach [6,7]. Thus, this serves to align health science education practices with the current evolving nexus of higher education and the changing landscape of health service delivery necessitated by developments in global and regional health policies [8,9].

DCTPs are considered to be transformative approaches to health science education adopted by higher education institutions, in response to the growing demand for clinical service placement owing to the increasing number of students being registered for medical and health disciplines [10,11]. Studies further suggest that the benefits of DCTPs include fostering a sense of social accountability through clinical placement of students in community-based settings and rural health facilities [12]. This process also exposes undergraduate students to the multiple realities of the health systems and the varying social determinants of health. Training students through DCTP produces successful graduates who are more fit for purpose in terms of community needs and the regional landscape of health service delivery [13].

Studies conducted on existing implementation models of DCTPs, particularly in South Africa, have suggested that this approach to health science education has predominantly been implemented in traditional universities. In recent years, students taught through DCTPs have been expanded beyond medicine to include undergraduate students in the multidisciplinary biomedical system of health care, which encompasses nursing, occupational therapy, physiotherapy, and optometry, to name a few. Anecdotal evidence regarding students' experiences of and perspectives about DCTPs indicates overall positive learning experiences reported by students who are taught using this approach [14,15]. Moreover, students have perceived education through DCTPs as strengthening their responsiveness, preparedness, and relevance as graduates. Similar studies about educators' experiences of DCTPs have also reported positive perspectives regarding the value of teaching and learning using this platform [16]. Additional studies regarding the perspectives about DCTPs have also been elicited from other stakeholders such as service providers and public health service managers. A study to explore public health sector optometrists' perspectives regarding a DCTP in KwaZulu-Natal, South Africa, revealed that while the DCTP was generally supported by the optometrists, challenges were reported in relation to the resources required for comprehensive optometric assessments. Despite the challenges cited, the study highlighted the DCTP as an important strategy for improving eye care service capacity in KwaZulu-Natal, South Africa [17].

In South Africa, health services are rendered through a re-engineered primary health care approach using the district health system as a vehicle to drive primary health care services [18,19]. Moreover, the newly adopted National Health Insurance (NHI) bill serves to further propel the agenda of universal health coverage, consistent with the sustainable development goals. The current NHI bill makes provision for public and private health sector collaborations to ensure optimum service delivery for all, irrespective of socioeconomic status. Thus, this change in health policy reform requires health care workers who are adequately prepared in terms of the various aspects of the health system. Therefore, the nature of teaching and learning using DCTPs is instrumental in facilitating the realization of this prepared state using health science education [20]. Moreover, the globalization of health care calls for the adoption of such innovative approaches in curriculum and pedagogy so that graduates are equipped to deal with the multitude of health demands arising from policy and health practice changes.

The benefits of DCTPs as an adaptive methodology for teaching and learning within health sciences cannot be overemphasized. Thus, there is increasing advocacy for the adoption of DCTPs in health science education; moreover, there is growing evidence regarding the models to facilitate the implementation of DCTPs, particularly within the South African higher education institutions offering medical and related health qualifications

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that form a part of mainstream biomedicine. Despite growing evidence in support for DCTPs from various categories of stakeholders—namely, students, health educationists, and global policy development experts—gaps persist in the practice of implementing DCTPs in higher education institutions in South Africa. Moreover, the full complement of health science disciplines has yet to implement this teaching approach at higher education institutions.

In South Africa, DCTP implementation is currently limited to certain traditional universities that have implemented DCTPs in specified health science disciplines such as medicine, occupational therapy, optometry, and physiotherapy [12,21]. Universities of technology (UoTs) are yet to implement DCTPs within health science disciplines offered within such institutions. Principally, UoTs are a new classification of technikons that previously offered diploma qualifications while harnessing technological advancement and partnerships with society and industry to solve community problems [22]. UoTs differ from traditional universities in that their primary focus is vocational and technical education while responding to a social responsibility of promoting access, redress, and equity. UoTs are driven by market forces and entrepreneurialism, whereas traditional universities' purpose is motivated by ideation and liberalism [23]. In the context of implementing a DCTP within a UoT, which will be a first in South African higher education history, the key areas of differences will be the overarching objective of producing graduates who are responsive to the health needs of the communities and society in the South African region. This will be facilitated through the learning that will allow health science students to be exposed to diverse, real-life, health-related experiences and challenges in their natural context. Another key difference will be the exposure to diverse health conditions and scenarios during the clinical placement that is not limited to a specific type of health setting. In this regard, students will be placed in health facilities that encompass the broad range of spheres within the national health system. Students' clinical exposure will encompass private and public health facilities across all levels, commencing from community-based health care to regional-level or tertiary-level health services. The envisaged partnership among the UoTs, traditional universities, private health sector, and public health sector will be facilitated through strategic high-level engagement with relevant authorities and will be operationalized through a documented memorandum of understanding among the institutions.

Considering the gap in practice and the reported benefits of DCTPs in terms of health science graduates' competencies and preparedness for the work environment, the Durban University of Technology (DUT) seeks to design, pilot, and evaluate a model to facilitate the successful establishment of a DCTP within the dimensions of contextual factors influencing teaching and learning at a UoT. In their position paper about the implementation of a DCTP at a UoT, the institution seeks to use a pilot of selected health disciplines to inform the design, piloting, and establishment of a DCTP, which will eventually be rolled out to the Faculty of Health Sciences (FHS), based on the outcomes of the pilot phase of this project [24]. While the implementation of a DCTP within the UoT will be a first in South African higher education practices, many challenges are anticipated in relation to piloting and implementation. These challenges relate to the availability of resources such as financial capital, human resources, and physical infrastructure. Other anticipated challenges relate to student and staff perceptions and existing challenges that are associated with clinical practice in remote areas, particularly those that are underresourced. Therefore, the UoT plans to establish collaborations with existing universities that are implementing DCTPs and engage with various categories of stakeholders' prior piloting and implementation and scale-up of the project. An iterative process of data generation facilitated by multistakeholder engagement will be performed throughout all phases of the project as part of monitoring and evaluation to ensure success of the project at all stages.

The DUT currently consists of 6 faculties, which include the FHS. The FHS offers undergraduate and postgraduate qualifications in health sciences that lead to the professional development of graduates as health professionals in different fields of health sciences. The faculty currently has the following academic departments: Biomedical and Clinical Technology, Community Health Studies, Chiropractic, Dental Sciences, Emergency Medical Care and Rescue, Medical Orthotics and Prosthetics, Nursing, Radiography, Homoeopathy, and Somatology. The faculty offers a range of courses within these departments, which lead to the development of health professionals for mainstream and alternative health care. For the purpose of design and testing, the undergraduate academic departments that will form a part of the pilot are Radiography, Emergency Medical Care and Rescue, Clinical Technology, and Medical Orthotics and Prosthetics. While the envisaged methodology is discussed further in this paper, the execution of the project remains relatively subject to change, given the diversity of the courses included in the pilot and the nature of teaching and learning within a UoT. Nonetheless, the project will be valuable, as the institution's FHS will be the first UoT to pilot and implement a DCTP within the context of health science education, which encompasses biomedical and alternative health care disciplines. The findings of the proposed project have implications for research, education, and practice related to DCTPs, both from a broad higher education perspective and within contextual factors related to UoTs.

Aim

We aim to design, pilot, evaluate, and establish an effective DCTP at a selected UoT in KwaZulu-Natal, South Africa.

Objectives

This study has the following objectives:

1. To critically analyze the current practice of implementing a DCTP at selected higher education institutions in South Africa
2. To explore stakeholders' perceptions regarding the range of factors to be considered to design, pilot, and establish a successful DCTP at a selected UoT in KwaZulu-Natal, South Africa

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3. To design, pilot, and establish systems to aid the implementation of a DCTP at a selected UoT in KwaZulu-Natal, South Africa
4. To propose a relevant model for the successful establishment of a DCTP at a selected UoT in KwaZulu-Natal, South Africa

Research Questions

Following is the research question in relation to objective 1:

1. What is the current practice of implementing DCTPs at selected higher education institutions in South Africa?

Following are the research questions in relation to objective 2:

1. What are the stakeholders' perceptions regarding the range of factors to be considered in designing, piloting, evaluating, and establishing a successful DCTP at a selected UoT in KwaZulu-Natal, South Africa?
2. What are the stakeholders' perceptions about the range of infrastructure, pedagogy, curriculum, and human resources factors that are related to the successful establishment of DCTP at a selected UoT in KwaZulu-Natal, South Africa?

Following are the research questions in relation to objective 3:

1. What approach or model can be designed or adopted to pilot, evaluate, and establish a successful DCTP at a selected UoT in KwaZulu-Natal, South Africa?
2. What are the range of IT systems required to be designed, piloted, and established to support the successful testing, evaluation, and establishment of a DCTP at a selected UoT in KwaZulu-Natal, South Africa?
3. What are the range of human resource and financial systems required to be designed, piloted, and established to support the successful testing, evaluation, and establishment of a DCTP at a selected UoT in KwaZulu-Natal, South Africa?
4. What are the range of infrastructure systems that need to be designed, piloted, and established to support the successful testing, evaluation, and establishment of DCTP at a selected UoT in KwaZulu-Natal, South Africa?
5. What are the curriculum and pedagogical systems required to be designed, piloted, and established to support the successful testing, evaluation, and establishment of a DCTP at a selected UoT in KwaZulu-Natal, South Africa?
6. What are the stakeholders' experiences, understanding, and perceptions regarding the design, testing, and establishment of a DCTP at a selected UoT in KwaZulu-Natal, South Africa?

Following is the research question in relation to objective 4:

1. What intervention model may be proposed to establish a successful DCTP at a selected UoT in KwaZulu-Natal, South Africa?

Context of the Study

The study will be conducted within the KwaZulu-Natal province of South Africa. The DUT will be one of the primary data collection sites because this is where the DCTP will be designed, piloted, and evaluated for successful establishment. This design process will be informed by a multistakeholder engagement process, which includes consultation with individuals who are internal and those who are external to the UoT. As the University of KwaZulu-Natal (UKZN) has already successfully established several decentralized clinical platforms in KwaZulu-Natal, the university and personnel affiliated to these platforms will be key informants in this project. Thus, the DUT plans to formalize a partnership with the UKZN for the purpose of executing this project.

Theoretical and Conceptual Underpinnings

Theories of health science education practice and concepts related to DCTP implementation as identified by the literature will be refined and operationalized to guide this study. Moreover, existing policies related to curriculum and pedagogy, as governed by the UoT's strategic objectives, guidelines, and related polices, will form a part of the conceptual map to guide the study. The conceptual framework and theories to be used are in the process of being refined and have been used to develop the research objectives and questions. These will subsequently guide the inquiry process of this study.

Methods

Overview

A multimethod design encompassing quantitative and qualitative research approaches, using different research designs underpinned by participatory action research, will be used to conduct the study. This design will allow for the use of multiple forms of quantitative and qualitative approaches to collect data from various sources through different forms of data collection (surveys, individual in-depth interviews, focus group discussions, consensus-building sessions, and implementation science processes). The multimethod design will be underpinned by participatory action research because the broad aim of the study relates to intervention design, testing, and evaluation. The study will be executed in various phases, namely, (1) situational analysis; (2) empirical phase (piloting and preliminary testing); (3) evaluation and refining; and (4) establishment and continuous monitoring, as underpinned by the abovementioned design. The phases of execution for the proposed project are discussed in the following sections.

Phase 1: Situational Analysis

Objective

The purpose of the inquiry phase is to develop a conceptual framework and understanding to guide the process of developing, piloting, evaluating, and establishing an effective DCTP at a selected UoT in KwaZulu-Natal, South Africa. Then, the conceptual model will inform the development of a logic model with a set of activities to operationalize key elements in the conceptual framework that is focused upon the broader aim of piloting and implementing the DCTP. The inquiry phase will also comprise high-level engagement with key informants to determine the primary factors for consideration when piloting, implementing, and evaluating the DCTP at the selected UoT. Thus, the following methods and related approaches will be included in phase 1.

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Step 1: Desktop Review

This step will encompass the review of existing literature and research about the models and reported experiences of implementing DCTPs in higher education institutions, with the review of best practices, international perspectives, and evidence from low- to middle-income countries. The review will be conducted using systematic scoping, narrative review, and integrative methods. The desktop review will also include a review of relevant policies and guidelines related to teaching and learning, higher education practices, and related phenomena.

Step 2: Stakeholder Engagement and Benchmarking

This step will be underpinned by participatory action research design, wherein various categories of key informants will be consulted to conceptualize the strategy of designing, piloting, and implementing DCTPs. In this step, engagement sessions will be facilitated through workshop sessions to obtain buy-in from executive-level stakeholders, with training and evaluation embedded within each session. A combination of focus group discussions and individual in-depth interviews will be used to collect data during the stakeholder engagement sessions. On the basis of the emerging findings from individual interviews and focus group discussions, consensus methodology will be used to triangulate the data that will respond to key questions of the research project and inform the emerging phases of the project. For this purpose, a combination of qualitative research designs will be used, namely, descriptive qualitative design, case study design, and appreciative inquiry, as part of the participatory action research design. The stakeholder engagement workshop sessions will also be designed using appreciative inquiry to stimulate discussion around the key factors to be considered during the design, pilot, implementation, and evaluation of a DCTP, with emphasis on the context of the selected UoT. Thus, this stakeholder engagement will comprise (1) university's academic executive management with representation from health sciences and envisioned collaborating faculties, such as engineering, accounting, and information systems; (2) key informants from universities with existing DCTPs, namely, the UKZN and Stellenbosch University; (3) external stakeholders from public sector and private sector health organizations with experiences of hosting DCTPs in their health establishments; (4) senior members of the student representative council for the FHS; and (5) heads of the academic departments identified for the pilot phase of the DCTP. Collectively, the stakeholders will provide valuable insights about the methods and approaches that will inform the piloting and establishment of a DCTP within the context of a UoT, particularly because such an initiative is novel within the context of the South African higher education sector. There is evidence suggesting that the implementation of a DCTP requires consideration of numerous factors including curriculum and pedagogy and various forms of resources including human, infrastructural, and financial resources, all of which have an impact on the sustainability of this transformative learning approach [1]. In the context of the DUT FHS, the existing practices and related sustainability elements are a product of collaborative engagement with various stakeholders from both the academic and nonacademic sector that ensure availability, scalability, and maintenance of the necessary faculty and university systems and processes that are required for teaching and learning. Thus, the combination of stakeholders is crucial for providing foundational insights about the practices and establishment of processes that will help in successfully piloting and establishing a DCTP beyond the pilot and initial implementation at the DUT FHS.

Step 3: Act and Observe

Following the stakeholder engagement workshops, a situational analysis of the university regarding the resources available, infrastructure, curriculum, teaching and learning, and pedagogical needs will be conducted, encompassing a multidisciplinary and multistakeholder involvement, whereas a narrative reporting process will be used to document findings, possible avenues of opportunity, recommendations and identification of possible communities, and organizations and health establishments that will be included as sites where decentralized clinical training will be provided. The stakeholders identified in step 2 will also be included in this phase, which will extend to the clinical placement facilities that will be identified as potential sites for the DCTP at the selected UoT.

Step 4: Reflection

This step will entail a consolidation of data obtained from steps 1 to 3 to inform the development of a conceptual framework to guide the development, pilot, evaluation, and establishment of the DCTP. In this step, the data generated for consolidation will be triangulated using a combination of theoretical models related to higher education pedagogy; teaching and learning practice frameworks; quality norms and standards related to teaching, learning, and assessment practices; and theories of program planning and implementation in health science education.

Step 5: Revised Plan

On the basis of the conceptual framework and policy documents emanating from step 4, strategic and operational systems related to the pilot phase of the DCTP will be formulated, with guidelines and operating procedures and standards to govern the teaching and learning practices, finance, procurement, and related operational activities essential for the pilot phase of the project.

Phase 2: Empirical Phase

This phase will encompass a research and implementation science process, which will include the collection of primary data using multiple research designs and approaches to data collection. The multiple research designs will include qualitative case study design, descriptive qualitative design, phenomenography, narrative inquiry, and appreciative inquiry. The combination of individual interviews and focus group discussions will be used to collect data from participants through self-developed semistructured interview guides and open-ended questions. The design and implementation of interventions, systems, and processes for the piloting and implementation of the DCTP within the DUT FHS will be an integral part of this phase. Through ongoing consultation with relevant participants and stakeholders, the design, development, and establishment of the necessary infrastructure, human resources, pedagogical systems, financial systems, and related sustainability systems will be facilitated. Technological innovation for teaching and learning through biomedical engineering systems, telemedicine,

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and eHealth will also be a part of this phase, and the outcomes of this phase will be evaluated through the exploration of students and stakeholders' experiences of using such technological applications in the context of teaching and learning within the DCTP at the DUT.

Phase 3: Evaluation and Refining

Overview

This phase will encompass an implementation science research approach underpinned by action research and other research designs to facilitate the testing and evaluation of the DCTP within the selected pilot academic programs—namely, Clinical Technology, Radiography, and Emergency Medical Care—at the selected UoT in KwaZulu-Natal, South Africa. This phase will also entail primary data collection from stakeholders in relation to the outcomes of piloting the DCTP at the selected UoT and the assessment of established systems and processes to support the pilot phase of the DCTP as part of the testing and evaluation phase of the project. A combination of evaluation frameworks will be triangulated to guide the evaluation process using empirical research and implementation science approaches. These frameworks include models related to continuous quality improvement consistent with participatory action research and other impact evaluation frameworks.

Evaluation Framework

The Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) framework will be used to guide the evaluation of the pilot phase of the DCTP and its establishment at the selected UoT for primary data collection (Figure 1). The RE-AIM framework has been used in various contexts, ranging from clinical interventions to community programs, corporate settings, and multiple project phases from planning to implementation and summative evaluations [25]. The RE-AIM planning and evaluation framework is a tool for implementation and can be applied to assist in estimating the public impact of programs and interventions. Thus, it provides a structure to systematically evaluate program impact. It entails an explicit focus on issues relating to the design, dissemination, and implementation process of programs that can facilitate or impede success in achieving broad and equitable population-based impact. The framework also allows the use of both quantitative and qualitative methods to understand why and how the results were obtained for different RE-AIM dimensions. Thus, it will allow for the triangulation of different data sources and methods, which will both enhance the validity of the evaluation and allow for a better description of the generative mechanisms of the program. Multiple stakeholders will be included in data collection, drawing from qualitative and quantitative methods, using primary and secondary data. Accordingly, the evaluation will be conducted using nonsequential mixed methods, with equal importance attributed to the respective quantitative and qualitative components.

Figure 1. Elements of the Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) framework.

Application of the RE-AIM Evaluation Framework

The RE-AIM evaluation framework was selected to guide the evaluation process as it allows for comprehensive data collection using participatory mixed methods approaches to provide information about project outcomes. The envisaged multipronged approaches to facilitate piloting, implementation, and long-term sustainability of the DCTP at the DUT FHS will be placed within this framework. The elements of the RE-AIM framework, namely, (1) reach (2) effectiveness, (3) adoption, (4) implementation, and (5) maintenance, will be used as informed by their original theoretical definitions (Figure 1) to

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guide the formulation of questions that will be a part of the quantitative and qualitative data collection tools that will be used to generate routine data about the outcomes of DCTP based on the overarching objectives of this research project. The data generated from the evaluation process will inform interventions to ensure continuous quality improvement of the project to maintain the sustainability of the project. The precise questions that will be formulated as part of this process are yet to be developed; however, they relate to the outcomes of the project in terms of original intent; consistency; and standards of implementation, effectiveness, and long-term sustainability as aligned to the research objectives and elements of the framework.

Phase 4: Establishment and Continuous Monitoring

This phase will encompass the implementation of the DCTP throughout all departments in the FHS, as informed by the collective results of phases 1 to 3 of the study. Primary data will be collected empirically from all identified stakeholders who would have been participants since phase 1 of the study. Quantitative and qualitative approaches will be used to collect data during this process regarding the outcomes of implementing DCTP as informed by various lived experiences, perceptions, and understanding of the phenomenon. Observational data will also be collected by conducting continuous assessments of the implementation processes in relation to specified standards, as guided by the conceptual and theoretical underpinnings informing the study. The quantitative and qualitative data will be triangulated by other sources of routine data as informed by the university and faculty standards and guidelines. This will subsequently inform practices related to continuous quality improvement and monitoring and evaluation. In addition, routine data about academic success indicators such as pass rates, graduation rates, and throughput rates will be collected. Consultative engagements will be facilitated with various industry personnel to determine the skills and graduate attributes of students who are trained through the DUT FHS DCTP project. This will be performed as part of the pilot, initial implementation phase and continuous monitoring during the eventual scale-up of the project.

Data Analysis

Qualitative Data

Data analysis involves a systematic application of a process or processes for managing and organizing qualitative data, which brings order, structure, and meaning to the mass of data collected. Qualitative data analysis is an active process, whereby the researcher must carefully and deliberately scrutinize data that they have collected, often reading data repeatedly until meaning or deeper understanding of the data is obtained [26]. Analysis of qualitative data involves categorizing data into segments, with symbols or abbreviations used to classify words or phrases. This is known as coding [27,28]. In qualitative research studies, data analysis is performed concurrently with data collection and is conducted throughout the study [27]. Qualitative analysis techniques use words rather than numbers as a basis, and this strategy is contextual in nature. Analytical reasoning skills are required when conducting content analysis. In this study, data will be analyzed using the Tesch method of data analysis for qualitative research [28]. The steps in the Tesch method of data analysis include the following:

- Reading through all the transcripts carefully to obtain a sense of their content
- Picking 1 transcript randomly; going through it and asking oneself, “what is it about?”; and thinking about the underlying meaning of the interview
- Noting down thoughts in the margin
- Repeating this process with all the transcripts and making a list of all topics, and clustering similar topics together into columns, which consist of themes and subthemes
- Taking this list of topics and going back to the transcripts; abbreviating the topics as codes next to the appropriate segments of the text; and observing the organization of data to check whether new codes emerge

Quantitative Data

The data collected will be evaluated and analyzed using descriptive and inferential statistical methods in consultation with a statistician, using SPSS (version 26.0; IBM Corp). Descriptive statistical analysis for categorical data and continuous data will be presented as frequencies, percentages, and ranges. The descriptive statistics will be summarized in graphs and charts.

All electronic data will be stored in password-protected files, and hard-copy data will be stored in a locked cupboard that only the researcher has access to. Once the mandatory 5-year period after the study has passed, all electronic files will be deleted and all hard-copy data will be shredded.

Reliability and Validity

A pilot study will be conducted to test the feasibility of the survey questionnaire that will be developed as part of the quantitative data collection tools for the study. A statistician will be consulted to calculate the estimated study sample size for the quantitative data to be collected during the study, and logistic regression analysis will be used to ensure the reliability of the quantitative data.

Trustworthiness

Trustworthiness of the study will be operationalized through several methods to ensure rigor and robustness of the qualitative data that will be collected. Consistent with a social constructivist paradigm, the researcher will strive for the triangulation of data to ensure that multiple perspectives are captured. The researcher will accomplish data source triangulation by collecting data from various categories of stakeholders using multiple qualitative designs and data collection processes. Data method triangulation will be achieved by using different methods to collect data, namely, focus groups, semistructured interviews, and document review. Additional strategies will include peer debriefing and true member checking. To operationalize peer debriefing, the researcher will review the codes and themes with the study’s coinvestigators, which will allow for reflexivity and ensure that all the data are included. True member checking will entail summarizing the key points at the end of the focus groups and interviews and asking participants to verify the accuracy of the data. These strategies will ensure the credibility

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of the data. Dependability of the data will be achieved using an audit trail. The researcher will keep field notes from the participant interviews.

Ethical Considerations

The basic principles of the Declaration of Helsinki will be adhered to throughout this research process. These include basic principles of respect, the right to self-determination, and the right to make informed decisions. All participants will sign an informed consent form after reading about the procedure of the study, indicating their willingness to participate in the study. The consent form highlights the benefits and risks of the study and requests permission to use audio recording in cases where interviews will be used to collect data. The right to withdraw at any stage of the research process will also be emphasized to participants. Beneficence will be ensured by supporting the well-being of participants during the study process. The study has received provisional ethical approval from the Durban University of Technology's Institutional Research Ethics Committee. Gatekeeper permission will be sought to access participants from the selected UoT and external universities identified for data collection. Moreover, gatekeeper permission will be obtained from the KwaZulu-Natal Department of Health, respective health facilities, and private sector health establishments that will be identified for data collection. Informed consent from individual participants will also be obtained before data collection.

Results

The study has currently commenced with the situational analysis, consisting of engagement with external stakeholders implementing DCTPs. In this regard, engagement meetings have been held with the UKZN and Stellenbosch University. The situational analysis is to proceed with other stakeholders and will encompass formal data collection processes once full ethical approval has been obtained from the DUT. The data to be generated from completion of the situational analysis are anticipated to be published in 2024. The project will also be piloted and implemented in collaboration with the UKZN, a traditional university that has successfully implemented a DCTP and will provide valuable insights in terms of lessons and approaches that can be adopted by the DUT FHS. It is also envisaged that undergraduate students within the DUT FHS from the 4 selected departments will be placed in remote clinical facilities where the UKZN also places its students to facilitate interprofessional education. Moreover, students from the various departments at the DUT FHS will be placed collectively in locations where they do not share facilities with students from universities that are already implementing DCTP.

Discussion

Anticipated Findings

The DUT FHS functions with operational guidance underpinned by the institution's ENVISION 2030 strategy and is guided by the evolving landscape of higher education, which is governed by local and international guidelines and best practices. The envisaged implementation of the DCTP at the UoT is in response to the existing gaps in implementation of DCTP at higher education institutions in South Africa. These gaps relate to the type of undergraduate health science students who are currently predominately trained through DCTPs, type of higher education institutions, and clinical placement facilities that are used for the practice of DCTPs. Studies suggest that training through DCTPs has largely been through traditional universities that offer mainstream biomedical health science disciplines in the field of medicine, nursing, optometry, occupational therapy, and physiotherapy. Health science disciplines such as medical orthotics and prosthetics, emergency medical care and rescue, radiography, dentistry, and dietetics and complementary health science disciplines remain neglected.

Literature also reveals that clinical placement facilities have largely been from the public health sector, with the use of community-based centers, primary health care facilities, and district hospitals as decentralized sites for learning. This is thus a gap in practice as the South African health system comprises public and private health care. In the context of the current implementation models of DCTPs, the use of remote private health facilities has not been reported in practice. The aforementioned gaps in existing practices of DCTPs and the nature of the UoT, in terms of teaching, learning, and assessment practices that differ from a traditional university, prompted this study. Moreover, the growing demand for clinical service placement, due to the increasing admissions of undergraduate health science students within the faculty, also necessitates the addition of new clinical placement facilities owing to a growing demand for such services in urban areas. Through the DUT FHS DCTP project, the growing demand for clinical service placement will be addressed through partnership with the ministry of health and private sector to increase the number of accredited health establishments that will allow for clinical service placement for students as part of their work-integrated learning and teaching practice of DCTPs. In this regard, an increasing number of distant health facilities will be sought through collaboration and cooperation with relevant authorities of these health establishments.

The reported benefits of DCTPs relate to the training outcomes of graduates regarding the mastery and skills required for the job as a health professional. In this regard, it is hoped that graduates within the UoT's FHS will be better prepared for the current demands of the health system by virtue of the benefits of DCTPs in relation to learning experiences. This subsequently aligns with the university's strategic objectives of producing creative, innovative, and adaptive graduates who will be able to make changes that lead to positive outcomes in the country and region. The DUT FHS remains anchored to its ENVISION 2030 strategy, which is founded upon four strategic perspectives, namely, (1) stewardship, (2) systems and processes, (3) sustainability, and (4) society, with the overarching vision of creativity, innovation, entrepreneurship, and production of adaptive graduates as outlined in the university's statement of intent [29]. As DCTPs will facilitate authentic learning experiences through exposure to the real-world life experiences in varying clinical placement facilities, it will allow for the development of innovative and adaptive graduates as outlined in the university and faculty's strategic objectives.

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The changing landscape of service delivery caused by policy changes related to the globalization of health and the adoption of the principles of universal health coverage also require health science graduates who are responsive to local needs within a global view of health. As the DCTP creates learning opportunities that expose students to multiple realities of the health system, the implementation of the DCTP will contribute to producing more fit-for-purpose graduates who are able to better respond to the diverse health needs of communities based on varying geographic and sociocultural contexts. This will be realized through clinical placement of students in diverse health care facilities that are located away from the university, thereby allowing for exposure to real-life experiences that form a part of the learning process. Therefore, this contributes to the knowledge and skill set required for health graduates to provide optimal health care services based on the needs of communities. Thus, the DCTP contributes to improved competencies and skill set of graduates in this manner. The exposure to different health establishments that are distant from the university, encompassing private and public health facilities, will reveal the differences in health systems' functioning and establishment and will enhance learning by virtue of the inherent diversity, thus contributing to adaptive graduates who are more informed about the varying complexities of the South African national health system that is underpinned by the principles of universal health coverage.

Another major gap identified in the current practice of DCTPs is the lack of integration between private sector and public sector health facilities during the training of students. The new NHI policy will require graduates who will be able to adapt easily to the demands of both private and public sectors, as an integral part of the policy involves partnership with the private sector to facilitate optimum standards of health service delivery for all. Thus, the design, piloting, evaluation, and establishment of the DCTP at the DUT will include the element of collaboration between the private and public sectors. The outcomes of this collaboration will include improved skill sets for health science graduates, and they will be exposed to the dynamics of the private and public health sectors as clinical placement will be conducted in health establishments in the private and public health sectors. This may contribute to more well-rounded health professionals in terms of the operational functioning of the health systems in the 2 sectors. Moreover, students will be exposed to more diverse clinical health situations, which will form part of their learning process.

Partnership with the KwaZulu-Natal Department of Health, the private sector, and the UKZN are foundational elements for the successful implementation of this project. The collaboration between these entities is novel, due to the distinct differences in organizational structure and strategic mandate. The differences in primary purpose, policy orientation, and operations among the DUT, UKZN, private health sector, and public health sector is one of the many key factors that are anticipated to pose as challenges to the successful scale-up and establishment of the DCTP at the DUT FHS. These organizational differences may hinder the teaching practices that may be adopted to facilitate learning for undergraduate health science students and may contribute to unforeseen interruptions that may have implications for implementation of the project. Ongoing engagement and communication with all stakeholders at various levels within the 4 establishments is planned as one of the key strategies for mitigating the possible challenges that may arise. The development of an institutional DCTP steering committee with representatives from all 4 establishments is also planned as an approach for mitigating the anticipated challenges. The collaboration among the DUT, UKZN, private sector, and public sector will also be formalized through a documented, joint memorandum of agreement, which will be signed by all the relevant parties for legal and ethical purposes and for mitigating the reported and anticipated challenges. Despite the distinct differences and anticipated challenges of such a partnership, this collaboration will generate new insights about how institutions with historically diverse philosophies can cooperate with each other for the purpose of transforming health science education, fostering interprofessional and collaborative practice, and improving health service delivery.

Currently, no formal collaboration exists among the UoT, UKZN, Department of Health, and the private sector; however, due to the availability of existing data about the implementation of a DCTP at UKZN, the possibility of a successful rollout with a UoT is a notion that is not farfetched. Formal guidelines to operationalize the processes and guide the execution of the project are currently unavailable and are thus necessary in light of the unique dimensions within which the project will be implemented. Thus, the following recommendations provide foundational principles for operationalizing the DCTP at the DUT and will guide the project's execution:

- *Ongoing multilevel stakeholder engagement and collaboration*: This will allow the generation of comprehensive primary data to inform findings related to the research process, which will ultimately be holistically integrated into data that will inform the operationalization of the DCTP during the pilot, implementation, and eventual scale-up.
- *Resource allocation*: For the piloting, implementation, and scale-up of the project to be achieved, financial, human, and physical resources will have to be provided. The allocation of financial resources is most critical as it will ensure that the necessary infrastructure, personnel, and processes are instituted to enable the success of the project.
- *Relevant policy and system review, development, and realignment*: As one of the foundational elements of this project is collaboration with different stakeholders and entities, the review of existing policies and guidelines governing the organization's operational process will be necessary to ensure the seamless integration of the DUT with the identified partner organizations.
- *Curriculum review and realignment*: Existing practices related to teaching and learning within the undergraduate health science programs at the DUT FHS will have to be reviewed, and findings of the review process will inform the realignment of the curriculum to match the dynamics within the clinical placement facilities, thereby producing graduates who are adaptive and responsive to the health needs of the communities and society, as informed by

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experiences that are encountered in the decentralized clinical placement facilities.

- *Continuous professional development and mentorship*: Academic and other relevant stakeholders within the FHS and DUT should receive training, mentorship, and support regarding the recommended teaching, learning, and assessment practices to be adopted within the context of a DCTP. This should be aligned with the relevant institutional policy and appropriate local and international best practices. This may facilitate buy-in from the stakeholders who will be responsible for implementation, thereby ensuring the success of the project.
- *Availability of monitoring, evaluation, and continuous quality assurance processes*: This may be in the form of ≥1 tool such as guidelines, standard operating procedures, audit tools, monitoring and evaluation framework, and routine data collection instruments that monitor the progress of the project at pilot, implementation, and scale-up phases to ensure its success in terms of the overarching objectives. Facilitating ongoing scholarship related to DCTP implementation within a UoT and its operational process will be an integral part of the broad project and the monitoring and evaluation process to ensure continuous quality improvement as supported by empirical evidence.
- *Facilitating technological innovation*: A key aspect of implementation of the DCTP within the DUT FHS is technological innovation for teaching and learning, which will have to be embedded within the teaching practices. In this regard, IT systems, infrastructure, and applications will have to be developed, sourced, and continuously updated to ensure compliance with innovative teaching practices. Therefore, an integral part of the implementation process is the development of systems rooted in biomedical engineering, telemedicine, and eHealth technologies.

The adoption of recommended foundational principles for the operationalization and execution of the DUT FHS DCTP project has implications for pilot, scale-up, and sustainability of the project beyond implementation. Moreover, the long-term sustainability of the project will be ensured through the development of a clear road map for the DCTP that provides short-term, intermediate, and long-term guidance for the execution of the project. The project is integrated into the DUT FHS long-term strategic and operational plans as a flagship initiative. This ensures the availability of financial, human, and physical resources necessary for the sustainability of the project beyond its pilot and initial implementation phases. The FHS strategic operational plan with the embedded DCTP project will subsequently form a part of the institutional strategic plan, thus further ensuring long-term sustainability.

Conclusions

It is envisioned that the DUT FHS DCTP project will facilitate collaboration among the UoTs, traditional universities, Ministry of Health, and private sector for clinical placement of undergraduate health science students in health establishments that are away from the university, thereby exposing them to real-life experiences related to health care. This will facilitate authentic learning experiences that will contribute to improved competencies of graduates in relation to the health needs of the society and the multiple realities of the South African health system.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

DCTP: Decentralized Clinical Training Program
DUT: Durban University of Technology
FHS: Faculty of Health Sciences
NHI: National Health Insurance
RE-AIM: Reach, Efficacy, Adoption, Implementation, and Maintenance
UKZN: University of KwaZulu-Natal
UoT: university of technology

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Protocol

Defining and Risk-Stratifying Immunosuppression (the DESTINIES Study): Protocol for an Electronic Delphi Study

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Abstract

Background: Globally, there are marked inconsistencies in how immunosuppression is characterized and subdivided into clinical risk groups. This is detrimental to the precision and comparability of disease surveillance efforts—which has negative implications for the care of those who are immunosuppressed and their health outcomes. This was particularly apparent during the COVID-19 pandemic; despite collective motivation to protect these patients, conflicting clinical definitions created international rifts in how those who were immunosuppressed were monitored and managed during this period. We propose that international clinical consensus be built around the conditions that lead to immunosuppression and their gradations of severity concerning COVID-19. Such information can then be formalized into a digital phenotype to enhance disease surveillance and provide much-needed intelligence on risk-prioritizing these patients.

Objective: We aim to demonstrate how electronic Delphi objectives, methodology, and statistical approaches will help address this lack of consensus internationally and deliver a COVID-19 risk-stratified phenotype for "adult immunosuppression."

Methods: Leveraging existing evidence for heterogeneous COVID-19 outcomes in adults who are immunosuppressed, this work will recruit over 50 world-leading clinical, research, or policy experts in the area of immunology or clinical risk prioritization. After 2 rounds of clinical consensus building and 1 round of concluding debate, these panelists will confirm the medical conditions that should be classed as immunosuppressed and their differential vulnerability to COVID-19. Consensus statements on the time and dose dependencies of these risks will also be presented. This work will be conducted iteratively, with opportunities for panelists to ask clarifying questions between rounds and provide ongoing feedback to improve questionnaire items. Statistical analysis will focus on levels of agreement between responses.

Results: This protocol outlines a robust method for improving consensus on the definition and meaningful subdivision of adult immunosuppression concerning COVID-19. Panelist recruitment took place between April and May of 2024; the target set for over 50 panelists was achieved. The study launched at the end of May and data collection is projected to end in July 2024.

Conclusions: This protocol, if fully implemented, will deliver a universally acceptable, clinically relevant, and electronic health record–compatible phenotype for adult immunosuppression. As well as having immediate value for COVID-19 resource prioritization, this exercise and its output hold prospective value for clinical decision-making across all diseases that disproportionately affect those who are immunosuppressed.

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KEYWORDS

immunosuppressed; immunocompromised; COVID; vaccines; COVID-19; surveillance; phenotype; adult; immunosuppression; clinical risk; disease surveillance; clinical consensus; eDelphi; immunosuppressed patient; immunosuppressed patients; study design; Delphi; methods; methodology; statistic; statistics; statistical; consensus; immune; immunity; immunology; immunological

Introduction

At present, there is no clinical consensus around the conditions and medications that confer immunosuppressed status upon an individual [1]. This population scales from 2% [2] to over 10% [3] of the general population dependent on the definition applied, most notably when individuals with diabetes, malnourishment, or older age are incorporated [3]. This disagreement on what constitutes immunosuppression extends to how best to subdivide this heterogeneous population: out of the binary [4], continuum [5], and hierarchical [6] approaches available, there is currently no gold standard [7]. This inconsistency undermines ambitions for targeted care and disease surveillance as aggregate-level analysis dominates, and subtrends lose visibility [7].

Despite this, it is well known that patients who are immunosuppressed experience worse infection outcomes [8] and, in some cases, respond poorly to vaccination [9]. Meanwhile, there has been no concerted effort to differentiate vaccine side effects within those who are immunosuppressed [10]. Without a clinically meaningful and electronic health record–compatible means of identifying and subdividing adults who are immunosuppressed, it will not be possible to improve this poor resolution in vaccine benefit-risk profiling in this population. Clinical guidelines around vaccine dosing, scheduling, and boosting as well as policies on the targeted distribution of antivirals or passive forms of immunization (eg, monoclonal antibodies and convalescent plasma) fare poorly as a result [7].

This study aims to obtain clinical consensus on a risk-stratified phenotype of adult "immunosuppression" to be implemented within UK health databases as standard. The use of COVID-19 as our reference condition is justified by pandemic gains to the immunosuppressed literature base [11]. While findings of differential vulnerability for COVID-19 among adults who are immunosuppressed may not be fully generalizable to alternative infections or even pediatric patients, the specificity of COVID-19 immunosuppressed literature—inclusive of infection outcomes among extremely rare or complex diseases—enables comparisons across all conditions and medications cited by the *UK Immunisation Against Infectious Disease* manual (Green Book [12], Multimedia Appendix 1).

Methods

Study Design

The objective of this protocol is to demonstrate how the electronic Delphi (eDelphi) [13] study design will be used to surface a definitive and risk-stratified phenotype for adult immunosuppression based on vulnerability to COVID-19. This process will see panelists seek to align on the conditions to be included in the said definition, their respective levels of risk for severe COVID-19 outcomes and key risk dependencies (eg, time treated, diagnosed, or in remissions and dosage of medication received). Consensus will be determined by whether over ≥75% of panelists agree on definition contents and risk relationships. A range of consensus statements will also be presented and evaluated by this same ≥75% consensus target. These statements will assess panelist agreement on the heterogeneity of patients who are immunosuppressed and their COVID-19 infection outcomes as well as the accuracy of the draft phenotypes (multilevel and high- vs low-risk categorized) that will be presented between eDelphi rounds. The >75% consensus level is not arbitrary but is based on the systematic review of Delphi consensus definitions by Diamond and colleagues [14]; here, across a random sample of 100 successful Delphi investigations, 75% was the median threshold to establish consensus.

The Delphi technique aims to build consensus on prespecified topics by soliciting the opinions, testimonies, or judgments of experts (Delphi panelists) with successive, anonymized questionnaires [13]. This method is especially valuable for generating insight and informing decision-making on complex, sensitive, emerging, or underresearched subject matters [15]. Its anonymized nature reduces demand characteristics or the influence of dominant personalities that can skew results in unblinded exercises [16]. Delphi questionnaires are improved upon by embedding opportunities for panelist feedback between consensus-building rounds. The amount and type of questions presented, as well as the time available to reach consensus, determines the number of rounds attempted in each study.

The eDelphi method hosts these investigations entirely online. This widens the pool for recruitment as geographical limitations are removed. Data management advantages and time and cost savings have also made the eDelphi method more attractive than in-person and paper-based alternatives [17].

Although neither Delphi nor eDelphi studies are supported by unambiguous methodological guidelines, the present protocol has cross-referenced Conducting and Reporting Delphi Studies guidance [18] and recommendations from systematic reviews into successful Delphi execution [14]. Its publication is intended to maximize study quality and transparency.

Ethical Considerations

This study will be coordinated by the Clinical Informatics and Health Outcomes Research Group at the Nuffield Department of Primary Care Health Sciences, University of Oxford. Separate ethical approval was sought for this work but deemed unnecessary after review by both the University's dedicated Research Governance Ethics and Assurance Team and the Joint Research Office Study Classification Group. It was determined that all activities fell under "pre-research," "priority setting," or "survey"; as such, these would not be subject to the Department of Health's UK Policy Framework for Health and Social Care Research [19] and would not be subject to sponsorship or research ethics review. This decision was

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corroborated when cross-referenced with the Health Research Authority's dedicated review algorithm [20], attendant leaflet (*Defining Research* [21]), and Health Care Quality Improvement Partnership *Guide for Clinical Audit, Research and Service Review* [22].

Study Management

A steering group comprised of senior staff members, a primary investigator, statistical supervisors, external research collaborators, and a patient champion who is immunosuppressed will contribute to the design and implementation of this study protocol, provide ongoing advice while the study is active, and assist in the interpretation, write-up, and dissemination of study results.

As illustrated in Figure 1, this study will involve a preparation period (to provide panelists with their consent form and preread materials), 2 rounds of consensus building, and a concluding discussion group to field final comments, points of clarification, confirmation, dissent, and feedback from panelists. Subject to successful recruitment, this study will run between May and July 2024. Panelists will be given 2 weeks to complete each round. To prevent attrition, reminders will be sent via email to nonresponders on days 6, 10, and 12. As per recruitment, telephone calls will be made on day 10 to encourage form submission; this will only occur when this information is listed publicly or has been provided by panelists who consent to it being used for this purpose.

Figure 1. Schematic of the DESTINIES study timeline. DESTINIES: electronic Delphi Study to Define and Risk-Stratify Immunosuppression.

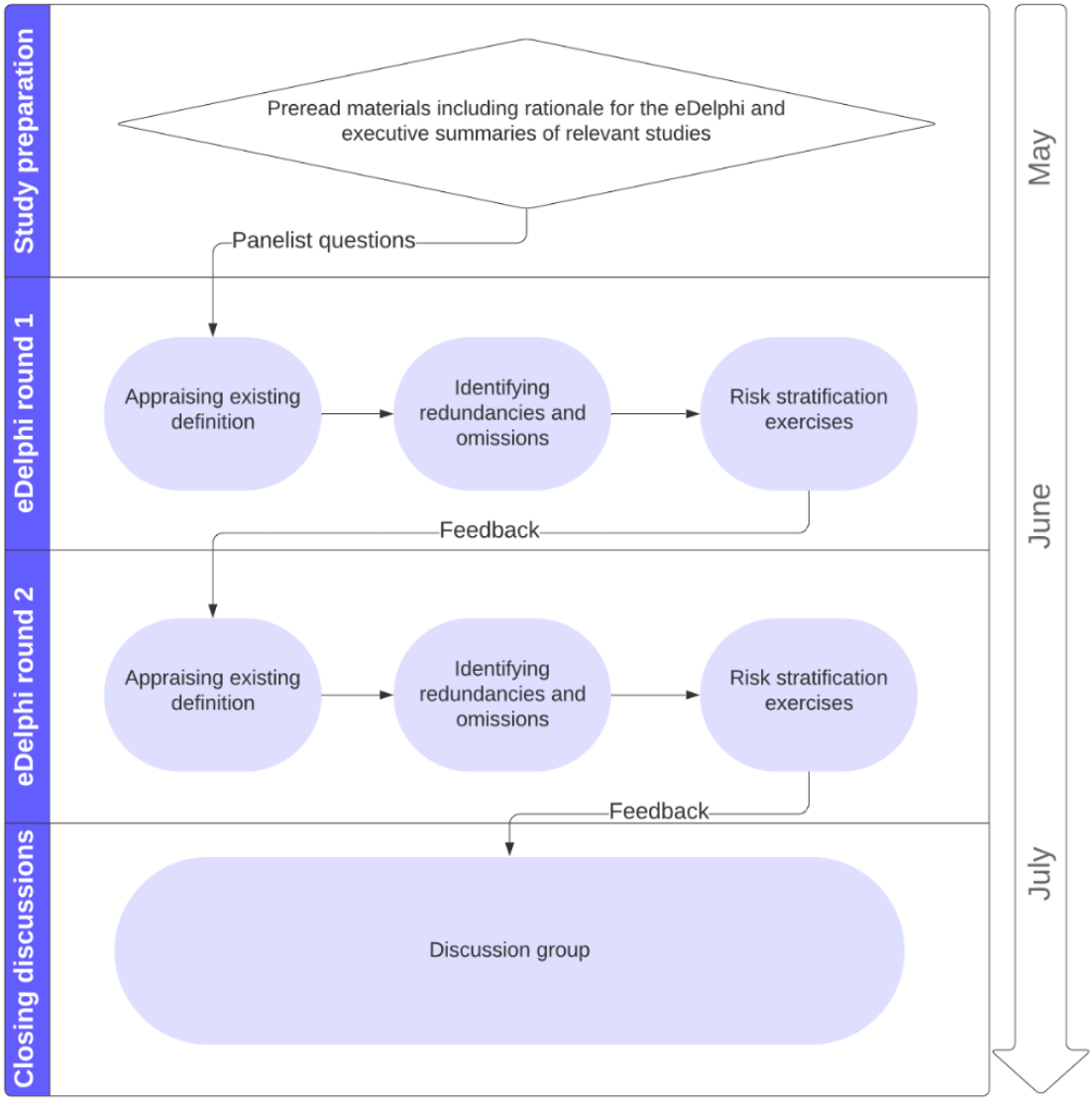

Recruitment

No sample size calculation is required for the eDelphi methodology; however, at least 50 specialists will make up the international eDelphi panel. This is intended to ensure that generalist and condition-specific experts are equally well-represented and to maximize the global footprint of this work. panelists will not be paid for their participation but are made aware that due attribution will be given to any outputs of this work should they be willing to be named.

Panelists will be recruited based on their affiliation with the following:

- World Health Organization Global Advisory Committee on Vaccine Safety

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- Coalition for Epidemic Preparedness Innovations Scientific Advisory Committee
- The Global Immunocompromised Health Coalition
- The European Alliance of Associations for Rheumatology
- European Medicines Agency's Vaccines Working Party
- Joint Committee on Vaccination and Immunization
- COVID-19 Neutralizing Monoclonal Antibodies (nMABs) and Antivirals Access Independent Advisory Group
- UK Scientific Advisory Group for Emergencies
- Independent Scientific Advisory Group for Emergencies
- Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
- Food and Drug Administration Vaccine Advisory Panel
- The Nuffield Department of Primary Care Health Sciences
- The Nuffield Department of Medicine

Beyond this, inclusion will be dependent upon the credentials of prospective panelists—clinical, academic, or policymaking experience in vaccinology or immunology is essential. Willingness to use Google Forms to submit survey responses is desirable, but not essential. Paper-based versions of each eDelphi round will be provided for those either uncomfortable or unable to use this platform. Prospective panelists will be excluded, however, if they are unable to commit to the full study duration or their expertise is entirely pediatric.

Invitations to participate will be sent via email and managed by the primary investigator. When publically available, the primary investigator will follow up with invitations by telephone. The email invitation will outline the aims of this study, participation details, the level of commitment expected, and the inclusion and exclusion criteria specified. To maximize recruitment, those contacted will also have the opportunity to signpost figures in their network that adhere to the inclusion and exclusion specified.

Those who accept to participate will be allocated random identification numbers. Panelists will not be known to one another until the end of data collection. Preread materials will also be distributed. In this, panelists will be provided with a panelist information sheet, a brief rationale of this study, executive summaries of relevant steering group research outputs, and a consent form. Executive summaries include a systematic review of differential vulnerability to COVID-19 [23], a phenotyping methodology paper (publication imminent), and real-world evidence for differential vaccine response and COVID infection outcomes (observational cohort trial T cells, antibodies, and vaccine efficacy in SARS-CoV-2 [24] and investigation of COVID-19 risk among populations who are immunocompromised [25] studies, respectively). Consenting panelists will be asked to sign and return their consent forms to researchers and retain a copy for their records.

Panelists will be encouraged to ask investigators any clarifying questions on the preread materials or study design before the first round begins. The panelist information sheet will also be presented before each active eDelphi round to remind panelists of study objectives and their rights to withdraw.

Panelists who fail to respond to an eDelphi round after three consecutive email reminders will be defined as withdrawn. Panelists can also make their own requests to withdraw, however, data collected up to that point of participation cannot be erased. To assess potential attrition bias, the number, percentage, and characteristics of withdrawn panelists will be reported and compared to those who continue to participate. A withdrawal rate greater than one-third would be considered an unacceptable loss to follow-up. In this instance, this study would be discontinued and recruitment reopened.

Questionnaire Design

The stated objectives of this study require that consensus be built around the definition of adult immunosuppression and digital phenotypes based on observed vulnerability to severe COVID-19 outcomes. This involves establishing and risk-stratifying constituent conditions and determining their dependencies (eg, time, dose).

To assess this, panelists will be presented with the complete list of conditions that, per the UK criteria for immunosuppression (Green Book chapter 14a [12], Multimedia Appendix 1), would lead to immunosuppressed status among adults. This resource has been selected on account of its expansiveness, its influence over vaccine allocation in the United Kingdom during this study's period and its continuity with the systematic literature review included in preread materials. Leveraging their professional experiences and their understanding of preread findings, panelists will be asked to assess the appropriateness of each condition for inclusion in a definition of immunosuppression and to then evaluate their respective risk levels concerning COVID-19. The latter questions will be presented via Likert scale and binary "higher risk immunosuppressed" versus "lower risk immunosuppressed" options. Once this is completed, panelists will repeat this exercise for immunosuppressed conditions that are absent from the United Kingdom definition but are cited in comparable international resources (Immunisation Guidelines for Ireland [26], the Canadian Immunization Guide [27], the Australian Immunisation Handbook [28], the New Zealand Immunisation Handbook [29], US Yellow Book [30], US Pink Book [31] among others). Finally, consensus statements on how drug management, time since diagnosis or last treatment, duration of treatment, and duration of remission may modify vulnerability to COVID-19 will be presented via Likert agreement scale; these will be followed by more generalized consensus statements on the challenges associated with defining, treating, and protecting patients who are immunosuppressed from disease.

Collectively, these exercises will enable researchers to identify redundancies and omissions in the United Kingdom's working criteria for immunosuppression and their respective vulnerabilities to severe COVID-19 outcomes; this data will then inform the construction of a risk-stratified phenotype of the patient spectrum that will be evaluated in the second eDelphi round and refined via the final discussion group. Although panelists will not be able to skip any questions presented, they will be able to indicate uncertainties in their answers. Optional feedback forms, again hosted on Google Forms, will be distributed via email between consensus-building rounds to clarify or refine questionnaire items if needed. Panelists will also be provided with a summary of results for each round to inform their subsequent responses and the concluding debate.

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Areas of agreement and disagreement will be discussed during the final discussion group.

Data Protection

All study members will endeavor to protect eDelphi panel rights to privacy and informed consent, including adhering to the Data Protection Act, 1998 [32]. Each round will only collect the minimum required information for study purposes; panelists will not be known to each other. The primary investigator, however, will be required to know the panelists' details for administrative purposes. Panelist data, including consent forms, completed surveys, and discussion audio files and transcripts, will be retained for 18 months before being destroyed.

eDelphi questionnaire rounds will be conducted on Google Forms. Google Forms' functionalities include customizable questionnaire items, 1-time completion, advanced security measures (eg, data encryption, privacy protections, malware protections), real-time data insights, and automated Excel (Microsoft) spreadsheet generation and download. Paper-based copies of this questionnaire will be distributed to any panelist who declares discomfort using this platform, however. All panelists will be made aware of the importance of not sharing any sensitive or identifying information about patients in free text questionnaire items.

The final discussion groups will be hosted remotely on Zoom (Zoom Video Communications, Inc). Further, 3 discussion groups will be organized in total, breaking panelists into 3 groups based on time zone. Additionally, 4 time slots will be offered for each group. The time slot that receives the most votes will be taken forward. Panelists who are unable to attend any time slot offered will be connected to a Google Forms containing all items that will be discussed. This will ensure all panelists have been provided with the opportunity to contribute to final data collection. Panelists who can attend their final discussion group will be asked to turn their cameras off and not identify themselves by name at any point over the course of the discussion. Attendees will be reminded that discussions are recorded.

Only this study's steering group will have access to study data. Computer-based information will be held securely and password-protected as per the standard. All data will be stored on a secure web server, Oxford Royal College of General Practitioners Clinical Informatics Digital Hub [33], hosted by the Nuffield Department of Primary Care Health Sciences. Access will be restricted by user identifiers, passwords, and multifactor authentication. Electronic data will be backed up every 24 hours to both local and remote media in an encrypted format.

Panelists will be offering their expertise within their capacity as a clinical, research, or policy professional. Panelists who consent to be named will be listed as coauthors in all study outputs; those who wish to remain anonymous will be acknowledged as part of the electronic Delphi Study to Define and Risk-Stratify Immunosuppression (DESTINIES) Consortium, where only professional affiliation will be listed. Study results will be made available to the public as well as relevant policy makers and academic institutions. Oversight from the European Alliance of Associations for Rheumatology People with Arthritis/Rheumatism across the Europe community will ensure that study results are available in a patient-accessible format.

Results

Aggregated results of panelist response rate, level of agreement for each measure, and condition risk ranking will be calculated with R (version 4.3.1; Posit). As per Diamond and colleagues [14], consensus is reached when ≥75% of panelists agree on each item disputed. The analysis will be quality assured by the statistical supervision available within this study's steering group. Areas of consensus and continued dissent will be content analyzed (inductive) and quantified and visualized via distributions of panel results. Panelist recruitment took place between April and May of 2024; the target set for over 50 panelists was achieved. The study launched at the end of May and data collection is projected to end in July 2024.

Discussion

Principal Findings

This protocol describes the research design and intended methodology for an eDelphi study to build consensus around the definition and risk stratification of immunosuppression in adults in the context of COVID-19. This work is a response to urgent calls to improve the precision of immunosuppressed disease surveillance [9]—something that is impossible without first establishing a universally accepted, clinically meaningful, and health record–compatible means of subdividing this diverse risk group. If fully executed, this protocol will achieve just this.

This study will be unique in its ability for panelists to leverage authors' literature reviews and real-world evidence for differential immunosuppressed COVID-19 outcomes as preread materials. Likewise, the research group conducting this work has a global network of collaborators to call upon as panelists, including national and international health agencies and their respective vaccine advisory groups. Given the global implications of this work, we intend to secure a cross-continental panel with the highest possible caliber of panelists.

However, we anticipate that it will be difficult to achieve consensus on all questionnaire items at the level specified. The sheer scale and complexity of immunosuppression as a clinical risk group invites debate and likely ongoing disagreement. We predict that there may be discrepancies between the risks reported by condition-specific and condition-general panelists, for example. Condition-specific experts may report disproportionate vulnerability among their own patients. Likewise, geographical differences between panelists are likely to affect consensus. Those from less economically developed contexts may report elevated risks than those from contexts where medical provision is more assured. That said, there is a great advantage to capturing ongoing areas of dissent between international experts. Doing so will only improve the rigor of this investigation and the nuance of study insights and outputs that result.

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Acknowledgments

ML is the principal author of this paper, responsible for the study conception, design, and write-up of this protocol. ML will act as the principal investigator mentioned within. LL, IM, JO-M, and RH proofed this work, providing suggested edits and commentary. The remaining authors are part of the steering group the protocol cites. No separate funding has been received for this study.

Conflicts of Interest

The student stipend of ML is paid for by the Medical Research Council (MRC) and EMIS Health under the MRC Industrial-CASE Studentship. SdL has received funding for vaccine related research from AstraZeneca, GSK, Moderna, MSD, Pfizer, Sanofi, and Seqirus. He has been a member of advisory boards for AstraZeneca, GSK, Sanofi, and Seqirus with any funding paid to his University.

Multimedia Appendix 1
Definition of immunosuppression in adult populations as per Green Book chapter 14a criteria.
[DOCX File , 316 KB - resprot_v13i1e56271_app1.docx]

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Abbreviations

DESTINIES: Delphi Study to Define and Risk-Stratify Immunosuppression
eDelphi: electronic Delphi

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Protocol

Canadian Armed Forces Veterans' Perspectives on the Effects of Exposure to Children in Armed Conflict During Military Service: Protocol for a Qualitative Study

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Abstract

Background: The mental health of military personnel has garnered increased attention over the last few decades; however, the impacts of perpetuating, observing, or failing to prevent acts that transgress deeply held moral standards, referred to as moral injuries, are less understood, particularly in relation to encounters with children during deployment. This paper describes a multiphased research protocol that centers around the lived experiences of Canadian Armed Forces (CAF) Veterans to understand how encounters with children during military deployments impact the well-being and mental health of military personnel.

Objective: This study has four objectives: (1) highlight the lived experiences of CAF Veterans who encountered children during military deployments; (2) improve understanding of the nature of experiences that military personnel faced that related to observing or engaging with children during military service; (3) improve understanding of the mental health impacts of encountering children during military service; and (4) use participatory action research (PAR) to develop recommendations for improving preparation, training, and support for military personnel deployed to contexts where encounters with children are likely.

Methods: The research project has 2 main phases where phase 1 includes qualitative interviews with CAF Veterans who encountered children during military deployments and phase 2 uses PAR to actively engage Canadian Veterans with lived experiences of encountering children during military deployments, as well as health professionals and researchers to identify recommendations to better address the mental health effects of these encounters.

Results: As of January 26, 2024, a total of 55 participants and research partners have participated in the 2 phases of the research project. A total of 16 CAF Veterans participated in phase 1 (qualitative interviews), and 39 CAF Veterans, health professionals, and researchers participated in phase 2 (PAR). The results for phase 1 have been finalized and are accepted for publication. Data collection and analysis are ongoing for phase 2.

Conclusions: Prioritizing and valuing the experiences of CAF Veterans has deepened our understanding of the intricate nature and impacts of potentially morally injurious events involving children during military deployments. Together with health professionals and researchers, the PAR approach empowers CAF Veterans to articulate important recommendations for developing and improving training and mental health support. This support is crucial not only during the deployment cycle but also throughout the military career, helping lessen the effects of moral injury among military personnel.

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KEYWORDS

moral injury; mental health; Canadian Armed Forces Veterans; children; deployments; conflicts; military culture; trauma-informed research; people-centered research; participatory action research

Introduction

Background

Research on the traumatic impacts of armed conflict and the resulting mental health consequences to military personnel has largely focused on experiences of being wounded, coming under fire, and witnessing comrades being killed or injured. In addition to these harms, military health research has accumulated evidence over the last decade pointing to the deleterious impacts that may be exerted by perpetuating, observing, or failing to prevent acts that transgress deeply held moral standards, referred to as moral injury [1,2]. International deployments increasingly involve exposure to complexities less common in previous conflict eras, including engagement with unmarked enemy combatants, suicide bombings, and encounters with children. Importantly, while deployment-related encounters with children are associated with mental health and other consequences in military personnel [3], and have been conceptualized as potentially morally injurious events (PMIEs; ie, events that can lead to mental health impacts due to a violation of moral beliefs or values) [4,5], the effects of such encounters remain largely understudied. For example, approximately 58% of the 33,500 Canadian military personnel deployed in North Atlantic Treaty Organization (NATO) operations in Afghanistan experienced PMIEs, with 43% of these individuals endorsing having experienced PMIEs involving women and children [6]. Despite the prevalence of such encounters, a recent systematic review revealed that no study has yet been conducted and peer-reviewed that focuses explicitly on the nature and impacts of deployment-related encounters with children [3]. Given that the use and recruitment of children in armed conflict are rising [7], and that PMIEs are associated with a host of mental health difficulties (eg, posttraumatic stress disorder [PTSD] and suicidality) among military personnel and Veterans [1,8,9], a concerted effort to understand the nature and effects of deployment-related encounters with children is necessary to advance policy, prevention, and intervention efforts aimed at supporting the mental wellness of military personnel and Veterans.

Children and Armed Conflict

A total of 68% of children globally live in conflict-affected countries and over 460 million children, or 1 in 6, live in a conflict zone [10]. The number and nature of conflicts are rising and changing, often taking place in densely populated areas where civilians live. Consequently, armed conflict is increasingly and disproportionately impacting children, disrupting all aspects of their lives from health to education to peace and security. According to the latest Children and Armed Conflict report from the Special Representative of the United Nations Secretary General [11], over 24,000 grave violations were committed against children in 2022. Based on the increasing number of conflicts occurring, all projections point to an unprecedented number of grave violations committed against children in 2023.

Peace support operations are rapidly changing due to the increasingly complex security climate. Changes include the context of operations, the splintering of armed groups, rising intercommunal violence, and the increased engagement of children in conflict-related activities [10-12]. While the use of children in armed violence is not new, the strategic use of children in contemporary armed violence brings new dimensions to peace operations, particularly due to the emerging forms of recruitment and use of children in conflict and the rise of terrorism [12-14]. For the purpose of this research project, as per the Paris Principles [15], “child soldiers” or children recruited and used in armed violence are defined as:

> *any person below 18 years of age who is or who has been recruited or used by an armed force or armed group in any capacity, including but not limited to children, boys and girls, used as fighters, cooks, porters, spies or for sexual purposes. It does not only refer to a child who is taking or has taken a direct part in hostilities.*

The changing security landscape, including the increase in children’s engagement, may put military personnel at greater risk for moral injury and other impacts [5]. For example, changing tactics, such as the increased use of girls in combat operations, may lead to unexpected encounters that violate previously held assumptions about the involvement of children in armed conflict. Despite these emerging dilemmas, little research has focused on the impacts of deployment-related encounters with children.

Mental Health and Military Deployments

Military organizations remain inadequately prepared to deal with the complex psychological and operational requirements of service members deployed in conflict zones where children are recruited and used [5,16]. As such, military personnel are increasingly at risk for serious psychological sequelae due to exposure to these situations, which in many ways are representative of prevailing conceptualizations of PMIEs [4,5,16]. Consequences of PMIE exposure are serious, as research has demonstrated consistent associations with PTSD, depression, anxiety, and most concerningly suicidality [1,9]. Furthermore, studies have shown that exposure to and direct involvement in PMIEs is associated with PTSD symptom severity, even after controlling for exposure to combat (eg, receiving enemy fire and going on patrols) [17,18], showcasing that distinct qualities of deployment events can have particular impacts on mental health.

Encounters with children may have particularly devastating mental health implications for military personnel who hold deeply engrained individual, cultural, and religious understandings of children as innocent souls [19]. Violations

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of such views, for example, through perceived failure to protect children or witnessing children being harmed, may, therefore, elicit appraisals of the self or the world that leave a "stain" on the individual's perceptions of their own and others' moral worth [20], potentially contributing to the development or exacerbation of mental health problems, including moral injury [2]. While it is likely that individual beliefs and perceptions play a role in this process, it has also been suggested that morally challenging deployment experiences involving children represent violations of core binding moral foundations [5], adaptive characteristics inherent to humans that promote our evolutionary survival through adherence to values such as respect, purity or sanctity, and in-group loyalty [21]. Such values inherently involve the protection of vulnerable persons, including children. In this way, the moral quality of encounters with children on deployment may further burden military personnel who may already be at risk for several mental health challenges related to military service such as PTSD, major depression disorder, generalized anxiety disorder, and suicidality [22].

While symptomology may present similarly to PTSD, moral injury is unique in that feelings of shame, guilt, worthlessness, and changes in moral attitudes, including perceived institutional betrayal, are central to the etiology and maintenance of distress arising from PMIEs [23-29]. Several studies conducted thus far appear to corroborate the notion that PTSD and moral injury are distinct, showing, for example, that symptom patterns can be statistically differentiated [30] and that neural mechanisms can be distinguished when recalling traumatic compared with potentially morally injurious memories [20]. Despite advances in how we understand the impacts of specific deployment experiences [31], attention to deployment-related encounters with children is still glaringly missing from research. While there is accumulating evidence highlighting the detrimental impact of child soldiering on the children themselves [32-36], to date there is little evidence centered around people's lived experiences documenting the effects of witnessing or interacting with children engaged in armed violence on the well-being and mental health of military personnel [3].

Considering the moral complexities of military deployments can vary widely from one region to the next, there is a need to better understand the multifaceted nature of encounters with children on deployment. For instance, a recent review by Ein et al [3] on encounters with children and their effects on military personnel demonstrated a wide range of experiences as well as consequences. Encountering children on deployment can elicit not only psychosocial and health consequences, but operational consequences as well, such as hesitation to engage with children recruited and used as soldiers. Importantly, no mechanisms are currently in place that seek to systematically document or evaluate the impact of deployment-related encounters with children, obscuring our understanding of their prevalence and consequences.

Action-oriented lived experience research is greatly needed to guide ways to better prevent and address the mental health effects of these encounters. Ein et al [3] observed that most policies and training related to encountering children on deployment are perceived by military personnel as inadequate if such policies and training exist at all. To our knowledge, there are no studies that have facilitated the collaboration of researchers and community members, including people with lived experience of encountering children during military deployments, in steering the development of recommendations for addressing the effects of deployment-related encounters with children.

In response to these important knowledge gaps, our research program provides foundational knowledge on the nature and the impact of encounters with children on deployment, as well as participatory action research (PAR) to inform future efforts to develop and implement effective policy, training, and intervention aimed at supporting the well-being of military personnel and Veterans.

Methods

Overview

As described below, our overall methodological approach involves centering the perspectives and lived experiences of Canadian Armed Forces (CAF) Veterans through two phases, that are (1) qualitative interviews to understand people's lived experiences of the nature and the impacts of encounters with children during military deployments and (2) PAR to empower participants in articulating recommendations for changing predeployment, deployment, and postdeployment training and supports focused on mitigating the impacts of encountering children on deployment.

Collaborative Approach

This study is a multiphase collaboration between the Dallaire Institute for Children, Peace and Security, the Centre for Addiction and Mental Health (CAMH), the MacDonald Franklin Operational Stress Injury Research Centre at Lawson Health Research Institute, Mount Saint Vincent University, the Canadian Institute for Military and Veteran Health Research (CIMVHR), as well as the Royal Military College of Canada. The project involves monthly team meetings with all partners to ensure that our rich multidisciplinary perspectives inform the design, data collection, analysis, and knowledge dissemination processes. The unique collaboration of mental health professionals, academic researchers, Veterans, and humanitarian practitioners, has enabled opportunities to explore this research from an interdisciplinary framework and to apply this research to multiple fields, including health, security studies, and children, peace, and security.

Goals and Objectives

The overarching goal of this collaboration is to improve the collective understanding of the nature and impact of encountering children in armed conflict, and particularly children recruited and used in armed violence, on military personnel's mental health and develop robust recommendations for preventing and addressing the effects of these encounters. Improved understanding is also needed to enhance operational effectiveness, including strengthening protections for military personnel and the children they seek to protect. This research project is the first of its kind to explore these important questions. The project team aims to identify opportunities to improve training, policy, and support to ensure military

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institutions and personnel are prepared to operate in complex conflict environments that increasingly include children.

The objectives of this study are, therefore, to (1) highlight the lived experiences of Canadian Veterans who encountered children during military deployments; (2) improve understanding of the nature of experiences that military personnel face related to observing or engaging with children during military service; (3) improve understanding of the mental health impacts of encountering children during military service; and (4) identify priority areas of action to improve preparation, training, and support for military personnel deployed to contexts where encounters with children are likely. This study is generating rich qualitative data on the nature and impacts of encountering children in armed conflict.

Phase 1: Qualitative Interviews

Overview

Phase 1 of this research involved eliciting the perspectives and lived experiences of CAF Veterans through in-depth qualitative, semistructured open-ended interviews. This approach was used to uncover rich insights regarding the poorly understood phenomenon of encountering children during military deployments.

Participants and Recruitment

The participants include CAF Veterans who had direct experiences (eg, exposed to, witnessed, or engaged) with children, particularly children recruited and used in armed violence, during military deployments or operations. Participants had to be 18 years of age or older and live in Canada. The team aimed to interview about 20 participants, of whom at least 10 were women, and at least 6 of whom were Francophone.

Participants were recruited using advertisements outlining the study and providing study contact information, which were circulated among stakeholder institutions in Canada for distribution to their membership (eg, Veteran Trainers to Eradicate the Use of Child Soldiers, Dallaire Institute for Children, Peace, and Security, and the CIMVHR). Additionally, we distributed the advertisement on social media (eg, Facebook [Meta Platforms, Inc] and Twitter [Twitter Inc]). English and French versions of the advertisement were distributed. English advertisements instructed prospective participants to contact the project coordinator by telephone or email. The Project coordinator confirmed eligibility and provided an overview of the study. Additionally, permission to contact the participant through email and Webex (Cisco), the secure network used by CAMH, was obtained at this point. For those who elected to take part in the study, the project coordinator scheduled an interview. The French language advertisement directed individuals interested in participating to contact the French interviewer, who conducted the screening and consent procedures described above and conducted the interview in French.

Procedure

Research team members from the MacDonald Franklin Operational Stress Injury Research Centre and CAMH conducted the interviews due to their trauma-informed and counseling expertise, qualitative research experience, or their extensive knowledge and experience related to children and armed conflict. A trauma-informed approach was central to the interview process and included strategies such as collecting participant contact information and emergency contact information from participants prior to the interview, well-being checks throughout the interview process, prior arrangements with mental health providers in advance of the interviews to ensure availability of support if required, and provision of a list of available mental health resources for the participants.

Before the interview, the participant's consent was obtained using Webex and an eConsent platform provided using Research Electronic Data Capture (REDCap). After the interview, participants were asked demographic questions. The responses to these demographic questions were entered by the interviewer directly into REDCap and were linked to individual interview data using a unique identification number assigned to the participant. Aggregate questionnaire responses are used only for descriptive information about the sample.

During the semistructured interviews, participants were asked about the nature of experiences they had faced related to observing or engaging with children during their military service. Aligning with the most current understanding of the domains of the impact of moral injury, participants were also asked about the impact of these experiences with domains of exploration, including (1) alterations in self-perception (eg, changes in identity and confusion about whether there is a moral code); (2) psychological impact of alterations in moral thinking (eg, changes in moralism, appraisal of others, and rumination); (3) relational impacts (eg, lack of interest or investment in social relationships, change in interactions with children, loss of belonging, and social isolation); (4) emotional aftermath (eg, shame, guilt, and anger); and (5) spirituality (eg, loss of life purpose and loss of spiritual or religious beliefs).

We also aimed to explore whether these experiences and the effects of these experiences differed for men and women, as well as what kinds of training and support they felt were needed for military personnel who may be deployed to regions where child soldiers operate.

Interviews lasted approximately 60 minutes. Participants were provided a CAD $50 (US $36.60) gift card as remuneration, and the gift card was delivered to the participant by the project coordinator by email or mail, per the participant's wishes.

Interviews were audio-recorded using Webex's recording feature. The interviewer took field notes during the interview to elaborate on the content of the interview, such as nonverbal cues. Raw audio files and transcripts are stored on the CAMH server, separately from other documents containing personally identifiable information, to prevent identifying participants. All data were deidentified, with numeric identifiers used in place of names. Pseudonyms were used in place of names, where applicable. Upon completion of the interviews, all materials were transferred to the project coordinator, and the interviewers' access to the audio files and the REDCap eConsent forms was removed. For participants who did not wish to be contacted in the future, emails and contact information were destroyed by the project coordinator once all interviews were completed.

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Contact information for all other participants is saved on the CAMH server.

Analyses

Transcribed interviews were analyzed using Braun and Clarke's [37] 6-stage approach to thematic analysis to identify themes within the interview data. The process involves familiarization and initial coding, organizing codes into potential themes, summarizing data relevant to each theme, reviewing, verifying, defining, and then naming each theme. NVivo software (version 12; Lumivero, 2017) was used to manage the data. Interviews were coded by several authors independently, including the interviewers and members of the research team. The research team met regularly to review coded excerpts and to resolve any discrepancies through group consensus.

Coding was done in an ongoing manner as interviews occurred. A codebook was created to capture evident themes. As new themes were identified throughout the study, the codebook was refined, and previously coded interviews were reanalyzed using the updated codebook. This iterative approach allowed the subsequent interviews to be tailored around unanticipated themes identified during analysis. This ensured that the lived experiences of the participants were captured and validated appropriately. Member-checking was done where coders were unsure of or needed further clarification on themes. Upon completion of the analysis, a qualitative synthesis was developed to describe in detail the thematic contents of the interview data.

Phase 2: PAR

Overview

The second phase of the research involved PAR. PAR is a qualitative research methodology that actively engages the community in all aspects of the research, incorporating the perspectives and lived experiences of participants in meaningful ways [38,39]. It is considered a category of action research [40], which involves the systematic collection and analysis of information to identify real and salient issues, act on those issues, and make social change. In PAR, researchers and community members collaborate to explore a problem and identify priorities for action through a cyclical and responsive process of research, reflection, action, evaluation, and modification [41]. Using this research-to-action approach, study participants, who are people with lived experience of encountering children during military deployments, particularly children recruited and used in armed violence, steer the development of recommendations, rather than being passive research subjects.

The PAR approach involves iterative cycles of reflection, data collection, and action. Each phase of the PAR project organically builds on previous cycles, with strong involvement of, and direction from, an interdisciplinary team of key stakeholders. As working relationships develop within the research team, information and perspectives are shared, questions emerge, plans are formed for how best to address those questions, more data are gathered, the team collaborates in analyzing and interpreting the data, and more questions emerge. Figure 1 summarizes the iterative process by which the PAR project is unfolding.

Figure 1. PAR project stages. PAR: participatory action research.

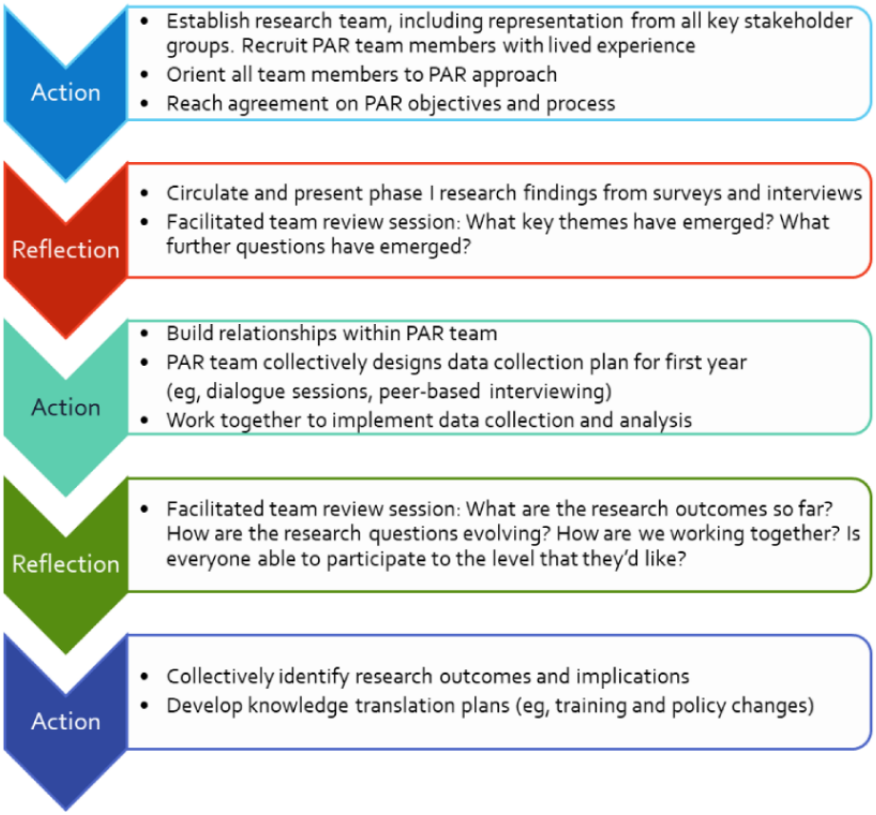

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Participants and Recruitment

Phase 2 of the research project includes CAF Veterans as well as health professionals and researchers from varied disciplines including health, peace and security, and child and youth study. The aim of the initial phase of the PAR project was to recruit approximately 5-10 Veterans, including at least 2 women. Participants could be located anywhere in Canada, speak either official language, and are military Veterans who have self-identified lived experiences with trauma or moral injury and encountered children during deployment, particularly children recruited and used in armed violence.

Participants were recruited through posters distributed among stakeholder institutions in Canada (eg, Veteran Trainers to Eradicate the Use of Child Soldiers, Dallaire Institute for Children, Peace and Security, and the CIMVHR) for distribution to their membership, including through social media (eg, Facebook, Twitter, and Instagram [Meta Platforms]). The posters instructed interested individuals to contact the PAR coordinator by email or telephone. The research team also followed up with participants from phase 1 who agreed to be contacted for future phases of the study, as per the previous protocol approved by Dalhousie (#2021-5723 and #2022-6163), CAMH (#2021-045 and #2022-078), Mount Saint Vincent (#2022-015 and #2022-048), Lawson (#11430 and #12699), and Western (#120351 and #121499) Research Ethics Boards. Please see Figure 2 below for an explanation of the PAR team composition.

Figure 2. PAR team composition. PAR: participatory action research.

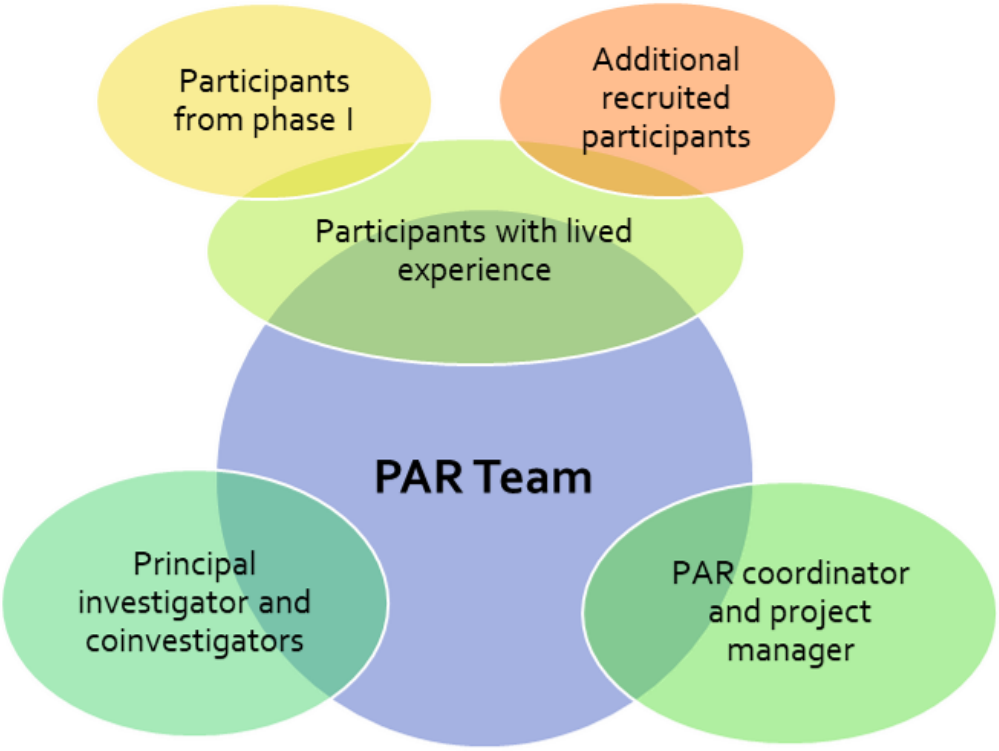

PAR Process

Overview

The first stage of the PAR project involved the collaborative interpretation of initial phase 1 findings with the full PAR team, including people with lived experience. The PAR team has so far engaged in a series of 6 participatory analysis workshops that involved sharing findings from the phase 1 interviews and information created in previous workshops through an iterative process of questioning, data generation, and interpretation. In this first stage of the PAR project, the PAR team reviewed phase 1 findings. Note that the PAR research team was presented with general findings from phase 1 that had been anonymized and compiled thematically. Next, they engaged in a discussion to answer interpretive questions that are, (1) how do the phase 1 study findings resonate (or not) with your own perspective, expertise, or experience encountering children during deployment?; (2) what questions do the phase 1 findings leave for us to further explore in relation to moral injury?; (3) who should we engage in addressing these questions, and how do we engage them in ways that feel safe and productive?; and (4) what are the implications of these findings in terms of providing preparatory training and support services for military personnel?

The PAR project's data collection does not involve traditional research instruments, but rather the interpretive discussion emerged through a series of participatory analysis workshops (the first workshop agenda is detailed in Multimedia Appendix 1). At the time of writing, the PAR process has unfolded over a series of 6 workshops that included CAF Veterans, researchers,

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and health service providers. These workshops were spread over 16 months and were 2 hours to 2 days in duration.

The first workshop was in October 2022 and the most recent sixth workshop was held in January 2024. Additional workshops continue to be organized based on the guidance and recommendations of the Veteran participants. Below is a synopsis of the focus for each workshop so far.

- Workshop 1 (October 2022, in-person): introductions, share overall objectives or goals, share key findings from phase 1, discuss implications of findings in terms of providing preparatory training and support services for military personnel who have encountered children in combat situations, and identify other stakeholders who should be engaged in these services
- Workshop 2 (January 2023): Review of workshop 1 findings, gap analysis of predeployment training for CAF personnel, gap analysis of policies to guide CAF personnel in how to prepare for encounters with children during deployment, and gap analysis of supports for CAF personnel after they have experienced encounters with children during deployment
- Workshop 3 (February 2023): Review of workshop 2 findings; discussion of the health effects of encountering children during deployments to inform policy, practice, and supports; identify circles of support pre-, during, and postdeployment; and discussion of best practices for support services
- Workshop 4 (March 2023): Review of workshop 3 findings, identify key messages and recommendations emerging from phases 1 and 2, and knowledge dissemination ideas
- Workshop 5 (July 2023, in-person): review of workshop 4 findings, discussion of concepts of childhood and military culture from the perspectives of Veterans and health professionals, and explore strategies for the improvement of care relating to moral injury, particularly in relation to the health effects of encountering children during deployment
- Workshop 6 (January 2024, in-person): Review of findings from phases 1 and 2 with only women PAR team members to explore findings and propose possible actions from a gender-responsive perspective

In PAR processes, the data collection and data analysis are integrated into each exercise, rather than as separate steps. The collaborative interpretation process occurs within each participatory analysis workshop using techniques such as (1) free list and pile sort of key messages emerging from phase 1 to categorize and prioritize emergent themes; (2) stakeholder identification and mapping of stakeholders' level of influence and degree to which they are affected; (3) arts-based elicitation of themes and implications; and (4) mapping implications for prevention, preparation, and intervention, based on criteria of impact and feasibility.

In keeping with the PAR methodology, all findings are shared with the participants to seek their feedback and input on the accuracy and appropriateness of representation. This process involves a series of collaborative editing and adjusting to ensure the whole PAR team is satisfied with the final themes and knowledge products. A lay summary of the PAR study results with no identifying information will be prepared and made publicly available.

Ethical Considerations

For both research phases, ethical approval was obtained from each primary collaborating site, including Dalhousie University (for the Dallaire Institute for Children, Peace, and Security); the CAMH; the University of Western Ontario (for the Lawson Health Research Institute and the MacDonald Franklin Operational Stress Injury Research Centre); and Mount Saint Vincent University (approval numbers are listed in the *Participants and Recruitment* subsection of the *Phase 2: PAR* section). Strict protocols are in place for sharing data between institutions. Cross-site data sharing agreements were drawn up outlining protocols for data governance and data sharing, which all parties are adhering to closely.

Phase 1

Strict adherence to institutional ethical standards and protocols is being maintained. For one-to-one interviews in phase 1, we used Webex, a secure videoconferencing software. Participants were informed of best practices for maintaining privacy and confidentiality in research settings and were notified of the additional risks associated with research using online platforms (ie, email and Webex). Before beginning the research session, the interviewer ensured the participant's space was private to avoid disruption and breaches of confidentiality. Participants were advised that the session would be audio-recorded. A link to the Webex session was provided to the participant through email. Only invited participants who signed the consent form were permitted to access the meeting.

A trauma-informed approach was used throughout the interview process due to the sensitive and potentially distressing nature of the subject matter discussed during interviews. Before the interview, participants were provided contact information for emergency clinical mental health support and other support and information. At the start of the session, the interviewer obtained an emergency phone number, a secondary phone number, and the participant's address in case the need arose to confirm the safety of the participant. And finally, during the interview, the interviewer assessed the safety of the participant on an ongoing basis, and if deemed necessary, was prepared to terminate the interview early and provide options for available mental health support to the participant. Having clinically trained interviewers was a significant asset to this project, allowing both interviewees and other research team members to feel comfortable that the well-being of participants was being prioritized.

To address the potential for vicarious trauma that may be incurred by the interviewer, the research team held debrief sessions with the interviewer and offered space and time for the interviewer to reflect on the interview experience. A trained psychologist who is a member of the team was also available in the event of any psychological distress exhibited by the interviewer.

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Phase 2

Participants with lived experience were provided with a copy of a research concept form (RCF) through email by the PAR coordinator. The contents of the RCF were discussed with the PAR team members after they had time to review the RCF, including a review of the purpose and nature of the project, privacy, confidentiality, the participant's rights, and the right to withdraw from the study at any time without giving a reason. Participants were reassured that whether they participate or complete the full study will not affect any treatment needs that they might have at the CAMH, or hospitals affiliated with the Lawson Health Research Institute, now or in the future. Participants were given the opportunity to ask questions about the project and after the consent discussion, prospective participants were sent a link to the eConsent. Participants were told that some data (eg, collected anonymously or as part of a group discussion) may not be identified as belonging to the participant and cannot be destroyed.

Before the first workshop, all PAR members were asked to review and sign an ethics commitment form focusing on maintaining the confidentiality of the group members (Multimedia Appendix 2). Additionally, during our first workshop, participants were invited to develop community norms, that is, the group's agreements regarding confidentiality, respectful, and inclusive discussion. As in focus group research, participants are asked to respect the privacy and confidence of all other participants and agree not to disclose any personal information shared during the meetings or workshops. These expectations are also outlined in the RCF. Names of people with lived experience will not appear in any publications or reports about this research unless approved by the participants.

Finally, all participants were provided with a list of services in the event they needed information or support related to mental health and trauma. For their safety, participants were asked for an emergency contact number, alternate phone number, and address before they participated in virtual or in-person PAR activities. Participants were advised that they could opt out of any PAR activities should they feel uncomfortable, and that if the research team is concerned for their immediate safety, the research team may contact them, their emergency contact, or emergency responders to follow-up. Importantly, our PAR team included a trained psychologist, who was present during all data collection and analysis and is available to discreetly offer support during or after any signs of distress among the PAR team.

Special Consideration for Military Personnel: Phases 1 and 2

All Veteran participants were advised not to divulge operationally sensitive information during their interviews or PAR workshops to avoid contravention of the Security of Information Act. Participants were instructed to relate only the types of encounters with children and the impact they had on them. All participants were reminded not to disclose information related to operational details, including (1) identity of key national or allied commanders, leaders, units, interpreters, insurgents, other special operations entities; (2) dates, time, locations of special operations; (3) linking code words and operations to high-level security clearance access; (4) targeting Boards—decision processes or parameters; (5) specific rules of engagement; (6) intelligence gathering methodology and sources; (7) weapon and sensor capabilities and limitations of any platform (land, sea, and air); (8) manning and employment of special operations units; (9) operational and tactical plans and procedures; (9) personal identity of enemy killed in action or taken prisoner of war; (10) covert activities and collection methods to gain intelligence and operational advantage; (11) identify encryption and cryptographic systems—vulnerabilities or limitations; (12) electronic warfare capabilities and signal analysis; (13) research and technical development initiatives regarding future operations; (14) platform capabilities and employment—numbers, manning, and operational limitations; and (15) Government of Canada or CAF Strategic Defence and Security Plans.

If information was inadvertently mentioned during the interview, the interviewer was instructed to redact that information from the audio recording before it was saved to the CAMH server or recorded during the PAR group discussions. Fortunately, all participants have abided by these instructions. To date, no participant has made an inadvertent statement that would compromise national security.

Timeline

Research Ethics Board approval for phase 1 was secured in June 2021 and participant recruitment and data collection occurred between November 2021 and June 2023. Findings from phase 1 are expected to be published in 2024. Research Ethics Board approval for phase 2 was secured in July 2022 and continues to evolve. Participant recruitment and data collection for phase 2 began in the fall of 2022 and remains ongoing.

Results

As of January 26, 2024, a total of 55 participants and research partners have participated in the 2 phases of the research project. A total of 16 Canadian Veterans participated in phase 1 (qualitative interviews) and 39 Canadian Veterans, health professionals, and researchers participated in phase 2 (PAR). The research results stemming from phases 1 and 2 point to the complexities and significance of the impacts of encountering children during military deployments. Six key themes have been identified that include, (1) the types of encounters with children during deployment vary and include experiences of heightened ambiguity with children in conflict contexts; (2) the contextual factors, including the mission framework, the deployed environment, and personal contexts, shape the impact of encounters; (3) how military personnel appraise encounters with children influences the impact; (4) the impacts of encounters with children vary in intensity and scope and are part of a larger stressor of deployment; (5) various coping strategies are used to manage such impacts during and after deployments; and (6) formal and informal support following encounters with children is likely to mitigate mental health impacts. The preliminary findings also point to the possibilities for enhancing preparatory training, care, and support at all phases of military deployment for those who face these potentially morally injurious experiences. The results for phase 1 have been finalized and are

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accepted for publication. Data collection and analysis are ongoing for phase 2.

Discussion

Prioritizing and valuing the experiences of CAF Veterans has resulted in an increased understanding of the complexities of the nature and impacts of PMIEs involving children during military deployments. The qualitative study with Canadian Veterans (phase 1) generated new knowledge in relation to the interconnections between military mental health, deployment experiences, and observing or engaging with children during military service, an overlooked area within military mental health research. Additionally, the PAR approach (phase 2) empowered Canadian Veterans to articulate important recommendations for changing predeployment, deployment, and postdeployment training and support to reduce moral injury among military personnel. While the overall analysis of the 2 phases is ongoing, we acknowledge that expanding the number and diverse identities of the participants, particularly in relation to gender and race, will be an important future research plan to ensure an intersectional analysis is applied to the complexities of the impacts of encountering children during international deployments. We encourage researchers to conduct similar research within other peace support–contributing states to continue building our collective knowledge of the connections between PMIEs, such as encountering children, and mental health to inform better prevention and intervention programming.

From a research design perspective, this novel, multilayered, qualitative, trauma-informed, Veteran-centered, and action-oriented project has resulted in key learnings related to the development of research protocols, implementation, analysis, and knowledge dissemination in Veteran mental health. Human-centered and trauma-informed principles guided the design of both phases of the study and were strengthened by a collective commitment among the research team to prioritize care and respect within our learning environment. The trauma-informed design and multidisciplinary team were key strengths contributing to the creation of meaningful, respectful, and care-centered research processes that prioritized the well-being of participants and the research team. The iterative process of collecting and analyzing in-depth qualitative data (phase 1), then validating and deepening the analysis through PAR methods (phase 2), has produced a robust set of findings, as well as recommendations for real-world policy and program implications. The participants expressed appreciation for and positive benefits from their engagement in the PAR processes, building a sense of solidarity, productivity, and empowerment. Moreover, the colearning and participatory action approach taken with multidisciplinary team members, including Canadian Veterans, served to propel key knowledge mobilization activities to address mental health challenges among military personnel and substantiate future research directions to be investigated from the perspectives of our various disciplines, highlighting the impact that integrative teams can produce.

Acknowledgments

The engagement of Canadian Armed Forces (CAF) Veterans, who are motivated to enhance protection for children in armed conflict, and the personnel who will be deployed to complex operations where engagements with children are likely is key to our collective learning. We extend a sincere and heartfelt thank you to the CAF Veterans who continue to demonstrate integrity and a lasting commitment to the protection of children and those who serve. Special thanks to Sharon Bernards, Centre for Addiction and Mental Health (CAMH) Research Methods Specialist, for assisting with the planning and development of the phase 1 research protocol and coordination of phase 1 data collection. This project is funded by generous support from the Waverly Foundation, the CAMH Foundation, and the Veteran Affairs Canada Well-Being Fund.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to the sensitive nature of this research and the ethical commitments to study participants.

Authors' Contributions

CBA, AN, and SW managed funding acquisition. CBA, KH, and SW handled project administration. CBA, KH, AN, and SW performed supervision. CBA, SB, SAH, AN, and SW performed study conception and design. CBA, SAH, AN, SP, and SW contributed to methodology. CBA, SB, SAH, SP, and KR performed formal analysis. CBA, SB, SAH, AN, SP, KR, and SW handled writing, reviewing, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participatory action research workshop 1 agenda.
[DOCX File , 211 KB - resprot_v13i1e57146_app1.docx]

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Multimedia Appendix 2
Ethics commitment form.
[DOCX File , 344 KB - resprot_v13i1e57146_app2.docx]

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Abbreviations

CAF: Canadian Armed Forces
CAMH: Centre for Addiction and Mental Health
CIMVHR: Canadian Institute for Military and Veteran Health Research
NATO: North Atlantic Treaty Organization
PAR: participatory action research
PMIE: potentially morally injurious event
PTSD: posttraumatic stress disorder
RCF: research concept form
REDCap: Research Electronic Data Capture

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Protocol

Rationale, Design, and Baseline Characteristics of Participants in the Health@NUS mHealth Augmented Cohort Study Examining Student-to-Work Life Transition: Protocol for a Prospective Cohort Study

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Abstract

Background: Integration of mobile health data collection methods into cohort studies enables the collection of intensive longitudinal information, which gives deeper insights into individuals' health and lifestyle behavioral patterns over time, as compared to traditional cohort methods with less frequent data collection. These findings can then fill the gaps that remain in understanding how various lifestyle behaviors interact as students graduate from university and seek employment (student-to-work life transition), where the inability to adapt quickly to a changing environment greatly affects the mental well-being of young adults.

Objective: This paper aims to provide an overview of the study methodology and baseline characteristics of participants in Health@NUS, a longitudinal study leveraging mobile health to examine the trajectories of health behaviors, physical health, and well-being, and their diverse determinants, for young adults during the student-to-work life transition.

Methods: University students were recruited between August 2020 and June 2022 in Singapore. Participants would complete biometric assessments and questionnaires at 3 time points (baseline, 12-, and 24-month follow-up visits) and use a Fitbit smartwatch and smartphone app to continuously collect physical activity, sedentary behavior, sleep, and dietary data over the 2 years. Additionally, up to 12 two-week-long bursts of app-based ecological momentary surveys capturing lifestyle behaviors and well-being would be sent out among the 3 time points.

Results: Interested participants (n=1556) were screened for eligibility, and 776 participants were enrolled in the study between August 2020 and June 2022. Participants were mostly female (441/776, 56.8%), of Chinese ethnicity (741/776, 92%), undergraduate students (759/776, 97.8%), and had a mean BMI of 21.9 (SD 3.3) kg/m^2, and a mean age of 22.7 (SD 1.7) years. A substantial

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proportion were overweight (202/776, 26.1%) or obese (42/776, 5.4%), had indicated poor mental well-being (World Health Organization-5 Well-Being Index ≤50; 291/776, 37.7%), or were at higher risk for psychological distress (Kessler Psychological Distress Scale ≥13; 109/776, 14.1%).

Conclusions: The findings from this study will provide detailed insights into the determinants and trajectories of health behaviors, health, and well-being during the student-to-work life transition experienced by young adults.

Trial Registration: ClinicalTrials.gov NCT05154227; https://clinicaltrials.gov/study/NCT05154227

International Registered Report Identifier (IRRID): DERR1-10.2196/56749

(JMIR Res Protoc 2024;13:e56749) doi:10.2196/56749

KEYWORDS

wearable; wearables; movement behaviors; university students; mHealth; cohort study; data collection; well-being; young adults; health behaviors; physical health; Singapore; biometric assessment; questionnaire; Fitbit; smartwatch; smartphone app; app; application; sleep; dietary data; diet; dietary; psychological distress; distress; mobile phone

Introduction

Noncommunicable diseases, such as cardiovascular diseases and type 2 diabetes, accounted for 74% of deaths globally [1] and contributed to 80% of Singapore's total disease burden in 2019 [2], as leading causes of mortality [3,4]. The prevalence of people with chronic mental health conditions (eg, mood disorders and anxiety disorders) is also rising [5,6]. During the COVID-19 pandemic, 1 in 3 Singaporean youths aged 11 to 18 years reported symptoms associated with poorer mental health [7], and adults aged 18 to 34 years reported the highest proportion of mental health conditions [8]. Lifelong mental health conditions often begin in adolescence [9,10], emphasizing the importance of supporting the mental health of young adults [11].

The transitionary period from university to working life brings about numerous changes for young adults, such as increased work and financial responsibilities, alongside psychological developments as they adapt to new stressors [12-14]. Changes during the transitionary period are reported to have psychological impacts such as increasing stress levels or worsening mental health in young adults [15-17]. In response, some young adults may engage in health-promoting lifestyle behaviors, such as exercise [18] and healthy eating [19], to manage their stress, which may, in turn, improve their psychological, physical, and mental well-being [20]. In contrast, some young adults may engage in health-compromising behaviors, such as poor-quality diet, lower physical activity, or increased screen time [21-25], to manage their stress. Engaging in health-promoting behaviors (eg, healthy eating, exercise, and having adequate sleep) and refraining from risky behaviors (eg, binge drinking and smoking) is essential for preventing physical and mental illness in later life [26]. Additionally, health behaviors are often shaped in early adulthood and can persist throughout later life [11,23].

Despite the knowledge that health behaviors adopted in adolescence persist throughout adult life and influence health and well-being, gaps remain in understanding how environmental factors (eg, physical and social environment) influence changes in health and lifestyle behaviors during adolescence and early adulthood [27]. The complex and dynamic interplay between health behaviors often result in a synergistic effect on well-being [22]. For example, university students with poor mental well-being were more likely to consume sugar-sweetened beverages, consume alcohol, and smoke [28], and subsequentially are at an increased risk of chronic diseases in later adulthood [28,29]. As such, a rigorous understanding of health behaviors, their determinants, the interplay between multiple health behaviors, and the trajectories of health behaviors over time would deepen our understanding of their impact on the health and well-being of young adults [30]. Much of our current understanding comes from longitudinal studies using conventional data collection methods (eg, surveys, interviews, and telephone calls) that are vulnerable to recall biases and do not capture health behaviors, and the complex and dynamic interactions between them, in real-time, real-life settings [31-33].

Integration of mobile health (mHealth) data collection methods (eg, smartphones, wearable devices, and accelerometers) into cohort studies may allow the convenient collection of richer and more ecologically valid data [34], enabling deeper insights into individuals' health and lifestyle behavioral patterns over time. mHealth allows continuous data collection throughout the day [33], capturing contextual information on health behaviors, as these occur in real time [35,36].

This paper aims to provide an overview of the study methodology and baseline characteristics of participants in Health@NUS, a longitudinal study leveraging mHealth to examine the trajectories in health behaviors, body weight, well-being, and their diverse determinants, for young adults during the student-to-work life transition.

Methods

Study Design and Setting

Health@NUS is a prospective cohort study conducted by researchers at the National University of Singapore (NUS) in partnership with the Singapore Government's Health Promotion Board (HPB). Reporting of this study protocol follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [37].

Health@NUS follows participants longitudinally over a 2-year period during university and transition to early working life. The study uses mHealth data collection methods, including a

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Fitbit smartwatch and the Health Insights SG (hiSG) mobile app developed by HPB, which collect data continuously over the 2-year period. Objective biometric measurements and questionnaires are collected at the 3 time points (baseline, 12-, and 24-month follow-up visits) with additional app-based ecological momentary surveys pushed out between the time points. Upon enrollment, participants also indicate whether they consent to be contacted for further follow-up assessments beyond the 2-year study period.

In addition to providing informed consent to join the study, participants were required to pay an SGD 20 (US $14.50) deposit to receive the Fitbit smartwatch (Versa Lite), which is refundable upon completion of the study. Participants were also required to setup a Direct Debit Authorization prior to approval to make a deduction from their bank account with HPB for SGD 248 (US $183) to recover the cost of the smartwatch should they lose it or withdraw from the study partway through.

Participants and Recruitment

Participants were recruited between August 2020 and June 2022 via emails, internal student communication systems, and word-of-mouth. Data collection was expected to be completed by June 2024.

To be eligible, participants had to be (1) a full-time undergraduate or graduate university student, (2) a resident of Singapore, (3) aged between 18 and 26 years, and (4) own a smartphone with a Singapore registered mobile number and an iOS or Android operating system compatible with both the Fitbit app and hiSG mobile app. Students were excluded from participating if they (1) were pregnant at the point of recruitment, (2) traveled overseas for more than 6 weeks at a time, (3) were not willing to make an upfront deposit of SGD 20 (US $14), or (4) were not willing to set up a Direct Debit Authorization with HPB.

Initially, between October 2020 and April 2021, only students who were between 1 and 3 semesters away from graduating were recruited. However, recruitment challenges were faced due to Singapore's strict safety management measures during the COVID-19 pandemic; thus, this selection criterion was removed after April 2021. Students completed their digital registration, which included initial eligibility screening. Participants who were screened as eligible were invited to visit the study site to provide written informed consent and baseline biometric measurements (Figure 1). All study visits at baseline and 12- and 24-month follow-ups are conducted at the health screening site at NUS.

Figure 1. Participant flow diagram. DDA: Direct Debit Authorization; NUS: National University of Singapore.

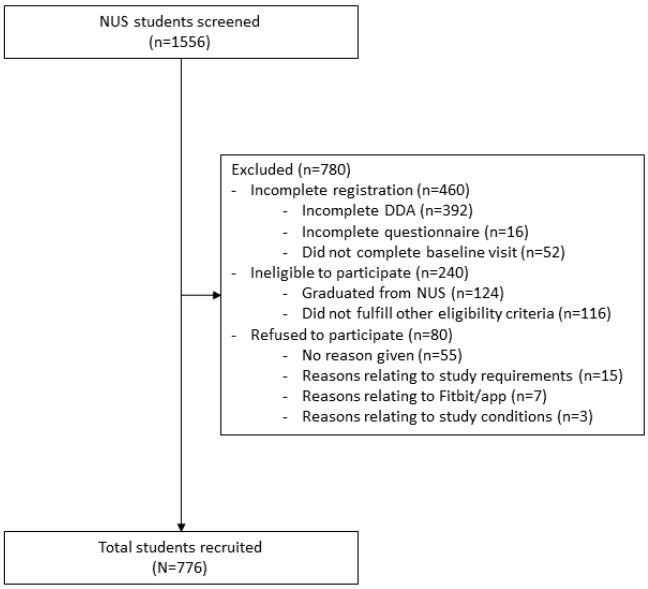

Data Collection

Biometric measurements, including height, weight, blood pressure, waist circumference, and resting heart rate, were conducted by trained staff using standardized protocols [38]. In addition, participants were issued a Fitbit smartwatch at baseline and were required to self-administer a web-based questionnaire on diet, physical activity, and other lifestyle factors and their underlying determinants at baseline, and the 12- and 24-month follow-up visits (Figure 2). Full details of the baseline questionnaire are presented in Table S1 in Multimedia Appendix 1 [38-79].

Repeated 2-week bursts of ecological momentary assessment (EMA) surveys were sent between the 3 main data collection time points (baseline, 12 months, and 24 months) via the hiSG app. Adapted from another ongoing study in Singapore [80], the EMA surveys contain questions relating to physical activity, diet, sleep, well-being, affect and physical feeling, behavioral cognitions (intentions and self-efficacy), cigarette smoking, alcohol consumption, and screen use (Table S2 and Figure S1 in Multimedia Appendix 1). Participants received an electronic voucher for completing the baseline assessments (SGD 5, US $3.50), each follow-up visit (worth SGD 50, US $36), and each of the EMA surveys was rewarded through Healthpoints (SGD 7, US $5).

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Figure 2. Timeline of assessments. Bars represent the continuous collection of data. Dots represent specific periods of data collection. EMA: ecological momentary assessment.

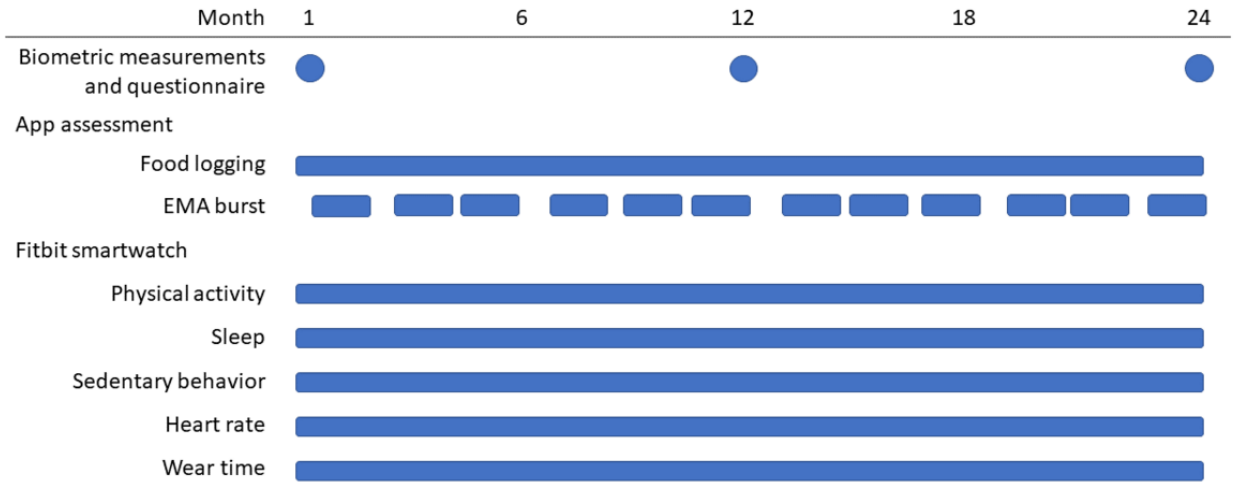

Fitbit Wear Time and hiSG App Logging Requirements

During the 2-year period, participants were asked to fulfill minimum data logging requirements relating to (1) wear time (awake and sleep) and (2) food logging (Table 1). Participants receive Healthpoints (150 Healthpoints=SGD 1, US $0.7) for completing the minimum study requirements across the 2-year study duration. The rewards would commensurate the level and duration of participation in the study and participants will receive milestone rewards of approximately SGD 80 (US $58) worth of Healthpoints (Figure S2A in Multimedia Appendix 1). Accumulated Healthpoints can be exchanged for electronic vouchers within the hiSG mobile app. Monthly reminders are sent via SMS text messages and emails to participants who do not fulfill the minimum logging requirements. Additionally, study participants are allowed to keep their Fitbit smartwatch at the end of the 2-year study period.

Table 1. Summary of minimum data logging requirements for waking wear time, sleep time, and food logging.

Activity and frequency	Minimum duration
Wearing a smartwatch during waking hours	
Monthly	At least 8 hours a day, for at least 5 weekdays and 2 weekend days
Wearing a smartwatch to sleep	
Monthly	At least 1 weekday (Sunday to Thursday nights) and 1 weekend (Friday to Saturday nights)
Food diary: quarterly (timeline) according to the cycles	
1 (January 1-March 31)	All food and beverages consumed at least on 2 weekdays and 1 weekend day
2 (April 1-June 30)	All food and beverages consumed at least on 2 weekdays and 1 weekend day
3 (July 1-September 30)	All food and beverages consumed at least on 2 weekdays and 1 weekend day
4 (October 1-December 31)	All food and beverages consumed at least on 2 weekdays and 1 weekend day

Ethical Considerations

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the National Health Care Group Domain Specific Review Board (Ref: 2019/00285, Singapore) and registered at ClinicalTrials.gov (NCT05154227). Written informed consent to participate in the study was obtained from all participants prior to data collection. Participants were offered SGD 120 (US $87) worth of Healthpoints for fulfilling the minimum data logging requirements, and up to SGD 425 (US $312) worth of Healthpoints were offered for additional wear time, sleep time, food logging, and survey data provided.

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Data Sources or Measurements or Outcomes

Web-Based Questionnaires

Table S1 in Multimedia Appendix 1 summarizes the variables collected from the self-administered questionnaires administered at 3 time points (baseline, 12-, and 24-month follow-up visits). The questionnaire collects sociodemographic information and assesses lifestyle behaviors and related factors. The questionnaire is administered via REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data tools hosted at the NUS [81,82].

The collected sociodemographic data include age, ethnicity, sex, marital status, housing type, household income, current enrolled course of study, and year of study. Physical activity including time spent in different domains (active transport, occupational, leisure, and household) and sedentary behavior (including passive transport) were assessed using the modified version from the Singapore Prospective Study Program [38-40] validated for the local context. Screen time use across different devices was assessed using a modified version of the Adult Sedentary Behavior Questionnaire [41,42]. Items from the Pittsburgh Sleep Quality Index [43] assess sleep quality and quantity [43]. Dietary information comprises daily intake of key food groups (eg, fruits, vegetables, and whole grains) [44] assessed using standard serving sizes for each food item [83], alcohol consumption [38,40], dietary practices [44,45] (eg, type of fat or oil used for cooking, and type of milk or sweeteners consumed), and habitual eating behaviors [45-47].

Potential determinants of movement behaviors and diet are also assessed including cognitive determinants (eg, behavioral perceptions [48,49], self-efficacy [48,50,51], attitudes [51], intentions [52], plans [52], knowledge, personality [9,53], self-control [54], habit strength [55], and mental health and wellness [56-58]) and social determinants [48,51,59]. Assessment of the physical environment was adapted via the Physical Activity Neighborhood Environment Scale [60,61] and Food Environment Assessment in Singapore Tool. Mental health and wellness were assessed using the WHO (World Health Organization)-5 Well-Being Index (WHO-5) [58] and Kessler Psychological Distress Scale (K6) [56,57]. WHO-5 assesses positive well-being, where a cutoff score of less than or equal to 50 indicates reduced well-being [58]. K6 assesses psychological distress, where a cutoff score of greater than or equal to 13 indicates increased mental distress [56,57]. Questions on important events, including COVID-19 and the transition to working life, were added to the 12- and 24-month follow-up questionnaire.

Biometric Measurements

Height was measured using a portable stadiometer (Seca 213) without footwear and head positioned on the "Frankfurt" plane. The stadiometer headpiece was lowered and pressed firmly against the crown of the participant's head. Height in meters was recorded to 3 decimal places. Weight was measured using an electronic scale (Seca 703) once participants removed all objects from their pockets, and recorded them to 2 decimal places in kilograms. According to the BMI classifications for the Asian population [4,84], overweight is defined as having a BMI between 23.0 and 27.4 kg/m^2, while obesity is defined as having a BMI equal to or greater than 27.5 kg/m^2. Waist circumference was measured using a standard measuring tape at the midpoint between the last rib and iliac crest during light expiration and recorded in centimeters to 1 decimal place.

Resting heart rate and blood pressure measurements were both taken twice using the Dinamap machine (Dinamap Carescape V100, General Electric), and the average of the readings was calculated. Participants were instructed to sit on a chair with their feet flat on the ground and their arms resting on a firm surface. The measurement was repeated 5 to 15 seconds after the cuff was fully deflated. Blood pressure was measured on the left arm unless contraindicated for blood pressure measurements.

Fitbit Smartwatch

At the baseline visit, participants set up their Fitbit smartwatch (Versa Lite) and their hiSG mobile app account. The Fitbit smartwatch passively collects data on physical activity such as step count, time spent active, calories burnt, heart rate, sedentary time, type of physical activity performed, and sleep. Participants were allowed to configure the Fitbit app for use on either their dominant or nondominant wrist. The data collected by the smartwatch are then synced with the Fitbit app, and subsequently transferred into the hiSG mobile app.

Smartphone-Based Assessments

The hiSG mobile app collects information on lifestyle behaviors, well-being, and their determinants through EMA surveys and dietary information through a food and beverage diary. hiSG monitors whether participants meet the minimum wear time and food logging study requirements, and participants can track whether these requirements are fulfilled within the app ("Progress," Figure S2A in Multimedia Appendix 1). The "Healthpoints" tab of hiSG enables participants to view their accumulated Healthpoints and to exchange them for electronic vouchers (Figure S2B, Multimedia Appendix 1). Participants self-report their food and beverage intake via one of two methods: (1) text search for the food item consumed or (2) taking a photograph of the food item in the mobile app. The app then provides search results from which participants are required to select the closest matching food item from a local Singapore food database of items. Participants also indicate the portion size in household measures (such as cups or bowls) or grams and the approximate time that they ate the food by selecting one of the following time windows: midnight to 5 AM, 5 AM to 11 AM, 11 AM to 2 PM, 2 PM to 5 PM, 5 PM to 9 PM, or 9 PM to midnight. Figure S2C in Multimedia Appendix 1 shows an example of food and drink logging completed through the text search using the example of "kaya and butter toast" (a popular food item in Singapore). After each food item is logged, participants can click on the "see daily summary" tab to view a summary of foods and beverages logged for the day.

The 2-week bursts of EMA surveys commenced from April 2021 onward. Participants receive multiple bursts (lasting 1-2 weeks each) of EMA surveys each year, covering different phases of the academic calendar (instructional, examination,

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and vacation). Participants receive text messages and 2 in-app notification reminders to encourage them to respond to the EMA surveys. EMA surveys are spaced throughout the day, and participants have 45 minutes to answer each survey. The details of the EMA question constructs, response options, item source, and frequency of questions can be found in Figure S1 and Table S2 in Multimedia Appendix 1. Presented EMA content will be used in bursts 1 through 8 to cover the first year of follow-up. Subsequent EMA bursts will be adapted to cover a wider range of topics.

Sample Size and Statistical Analysis

The study initially aimed to recruit 1300 students to account for attrition over the 2-year follow-up period and to achieve a target sample size of 1000. However, due to the challenges associated with recruitment during the COVID-19 pandemic, the original recruitment target was not met and 776 participants were recruited.

The sample size of 776 allows the detection of a small exposure effect (f^2=0.02) on a continuous outcome when performing a multiple linear regression that accounts for 9 confounders at a significance level of 5% with more than 80% power [85,86]. The sample size of 776 also allows the detection of an odds ratio of 1.85 when performing a multiple logistic regression where 25% of the binary exposure's variability is explained by the other predictors in the model, the probability of an outcome is between 0.2 and 0.7 among the unexposed, and the prevalence of being exposed is between 0.3 and 0.7 at a significance level of 5% with power at 80% or more [87]. The sample size (N=776) is larger than the number of participants recruited in previous EMA studies on youth [88-90].

Demographic data were analyzed descriptively. As the health and lifestyle behavior of university students are influenced by gender [91-93], comparisons of means between male and female participants were made via 2-tailed *t* test, and comparisons of medians between males and female participants were made via the Mann-Whitney *U* test. For categorical variables, differences between males and female participants were assessed by the chi-square test or the Fisher exact test for variables with small cell counts.

Results

Participant Flow

Interested participants (n=1556) were screened for eligibility prior to joining the study. We excluded 780 participants due to incomplete registration forms (n=460), ineligibility (n=240), and refusal to participate (n=80), as shown in Figure 2. A total of 776 participants were enrolled in the study.

Participant Demographics

Of the 776 participants, 4 participants had incomplete baseline questionnaire data. The mean age of participants is 22.70 (SD 1.7) years. Participants are mostly female (441/776, 56.8%), Chinese ethnicity (714/776, 92%), undergraduate students (759/776, 97.8%), and not married (773/776, 99.6%). Half of the students (403/776, 51.9%) were in year 4 or year 5 of their undergraduate degree and were expected to transition into their working life during the study period. More details on participant demographics are presented in Table 2.

Table 3 shows anthropometric and lifestyle characteristics stratified by sex. Participants had a mean BMI of 21.9 (SD 3.3) kg/m^2. Based on Asian classifications for BMI [84], 26.1% (202/773) were classified as being overweight (BMI ≥23 and <27.5 kg/m^2) and 5.43% (42/773) were classified as being obese (BMI≥27.5 kg/m^2). Participants had a mean systolic blood pressure of 113.7 (SD 11.42) mm Hg and a mean diastolic blood pressure of 64.76 (SD 7.94) mm Hg.

Most participants were nonsmokers (746/772, 96.6%), and more male participants (16/334, 4%) reported as being current or ex-smoker as compared to female participants (4/438, 1%). For dietary intake, the median intake of standard servings per day is reported in Table 3. Participants consumed 2.86 (IQR 1.71-4.64) servings of fruits and vegetables per day. Furthermore, participants reported consuming 1.53 (IQR 0.89-2.75) servings of refined grains as compared to 0.39 (IQR 0.08-1.00) servings of whole grains per day. For seafood, red meat, and poultry, participants consumed 0.71 (IQR 0.36-1.00) servings of poultry, 0.44 (IQR 0.23-0.86) servings of red meat, and 0.37 (IQR 0.20-0.64) servings of seafood per day. Only a small percentage of participants reported binge drinking (54/759, 7%).

For movement behaviors, participants engaged in an average of 0.78 (SD 0.76) hours per day in moderate to vigorous physical activity (MVPA), 10.87 (SD 3.60) hours of sedentary time, 13.39 (SD 4.22) hours of screen time, and 6.84 (SD 1.08) hours of sleep. For mental well-being, 37.7% (291/772) of the participants had poor mental well-being (WHO-5 score ≤50), and 14.1% (109/772) of the participants were at higher risk for psychological distress (K6≥13).

Significant differences between male and female participants (P<.05) were observed for all anthropometric measures (eg, height, weight, BMI, blood pressure, waist circumference, and average resting heart rate). Female participants were more likely to be underweight and had a higher resting heart rate, while male participants were more likely to be overweight. Significant differences between males and female participants were observed only in a few lifestyle behaviors such as consumption of refined grains and red meat, time spent in MVPA, and mental well-being and psychological distress (Table 3). Male participants consumed more refined grains and red meat and spent more time engaging in MVPA than female participants. A larger proportion of females reported poor mental well-being and psychological distress, as compared to male participants.

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Table 2. Demographics of participants at baseline.

Characteristics	Total (N=776)	Male (n=335)	Female (n=441)
Age (years), mean (SD)	22.70 (1.7)	23.58 (1.6)	22.20 (1.4)
Ethnicity, n (%)			
Chinese	714 (92)	305 (91)	409 (92.7)
Malay	20 (2.6)	10 (3)	10 (2.3)
Indian	24 (3.1)	13 (3.9)	11 (2.5)
Others	18 (2.3)	7 (2.1)	11 (2.5)
Student type, n (%)			
Undergraduate	759 (97.8)	328 (97.9)	431 (97.7)
Postgraduate	17 (2.2)	7 (2.1)	10 (2.3)
Faculty of study, n (%)			
Science	204 (26.3)	69 (20.6)	135 (30.6)
Medicine, nursing, and dentistry	149 (19.2)	53 (6.8)	96 (12.4)
Engineering	130 (16.8)	93 (27.8)	37 (8.4)
Arts and social sciences	108 (13.9)	32 (9.6)	76 (17.2)
Business and accountancy	73 (9.4)	34 (10.2)	39 (8.8)
Design and environment	55 (7.1)	21 (6.3)	34 (7.7)
Computing	37 (4.8)	24 (7.2)	13 (3)
Others	20 (2.6)	9 (2.7)	11 (1.4)
Level of study, n (%)			
Year 1	134 (17.3)	70 (20.9)	64 (14.5)
Year 2	64 (8.1)	26 (7.8)	38 (8.6)
Year 3	175 (22.5)	68 (20.3)	107 (24.3)
Year 4	347 (44.7)	150 (44.8)	197 (44.7)
Year 5	56 (7.2)	21 (6.3)	35 (7.9)
Residence, n (%)[b]			
On campus	112 (14.5)	50 (15)	62 (15)
Off campus	661 (85.5)	284 (85)	377 (85.9)
Marital status, n (%)			
Never married	773 (99.6)	332 (99.4)	440 (99.8)
Currently married	3 (0.4)	2 (0.6)	1 (0.2)
Monthly family[a] income (SGD, 1 SGD=US $1.38), n (%)[b]			
<$2000	69 (8.9)	36 (10.8)	33 (7.5)
$2000-$3999	112 (14.5)	44 (13.1)	68 (15.4)
$4000-$5999	108 (14)	50 (14.9)	58 (13.2)
$6000-$9999	122 (15.8)	68 (20.3)	54 (12.2)
>$10,000	156 (20.2)	60 (17.9)	96 (21.8)
Refuse to answer or do not know	206 (27.8)	56 (16.7)	130 (29.5)

[a]Monthly family income refers to the income received by all family members (eg, parents).

[b]Missings residence (n=3), and monthly family income (n=3).

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Table 3. Anthropometric measures and lifestyle profiles of participants at baseline (n=773).

Characteristics	Total	Male (n=335)	Female (n=441)	*P* value
Anthropometric measures (n=773[a]), mean (SD)				<.001
Height (m)	1.66 (0.09)	1.73 (0.06)	1.60 (0.06)	
Weight (kg)	60.67 (11.91)	68.66 (10.44)	54.63 (9.07)	
BMI (kg/m^2)	21.91 (3.29)	22.88 (3.26)	21.20 (3.11)	
BMI category (kg/m^2; n=773[a]), n (%)				<.001
Underweight (<18.5)	91 (11.8)	15 (4.5)	76 (17.3)	
Normal (18.5-<23)	438 (56.7)	172 (51.7)	266 (60. 5)	
Overweight (23-<27.5)	202 (26.1)	121 (36.3)	81 (18.4)	
Obese (≥27.5)	42 (5.4)	25 (7.5)	17 (3.9)	
Waist circumference (cm; n=773[a]), mean (SD)	73.09 (8.6)	77.46 (8)	69.78 (7.4)	<.001
Blood pressure (mm Hg; n=767[a]), mean (SD)				<.001
Systolic	113.68 (11.42)	120.76 (9.61)	108.33 (9.65)	
Diastolic	64.76 (7.94)	67.17 (7.50)	62.93 (7.78)	
Average resting heart rate	71.59 (11.55)	69.28 (11.55)	73.35 (11.56)	
Lifestyle behaviors				
Cigarette smoking status (n=772[a]), n (%)				.003
Never smoker	746 (96.6)	313 (93.7)	433 (98.9)	
Ex-smoker	9 (1.2)	7 (2.1)	2 (0.5)	
Current smoker	11 (1.4)	9 (2.7)	2 (0.5)	
Refuse to answer	6 (0.8)	5 (1.5)	1 (0.2)	
Dietary intake (servings per day; n=773[a]), median (IQR)				
Refined grains	1.53 (0.89-2.75)	1.87 (1.16-2.97)	1.38 (0.80-2.57)	<.001
Whole grains	0.39 (0.08-1.00)	0.42 (0.08-1.00)	0.39 (0.08-0.91)	.44
Seafood	0.37 (0.20-0.64)	0.43 (0.21-0.80)	0.32 (0.19-0.58)	.003
Red meat	0.44 (0.23-0.86)	0.71 (0.36-1.07)	0.44 (0.17-0.71)	<.001
Poultry	0.71 (0.36-1.00)	0.71 (0.36-1.00)	0.71 (0.36-0.71)	<.001
Fruits and vegetables	2.86 (1.71-4.64)	3.02 (1.79-4.64)	2.72 (1.68-4.61)	.25
Sugar-sweetened beverage	0.08 (0.03-0.14)	0.08 (0.03-0.14)	0.08 (0.03-0.14)	.89
Binge drinking[b] (n=759[a]), n (%)	54 (7.1)	27 (8.3)	27 (6.2)	.26
Movement behavior, mean (SD)				
Time spent in MVPA[c] (hours/day; n=773[a])	0.78 (0.76)	0.96 (0.78)	0.65 (0.71)	<.001
Total sedentary time (hours/day; n=772[a])	10.87 (3.60)	10.82 (3.63)	10.91 (3.58)	.73
Total screen time (hours/day; n=772[a])	13.39 (4.22)	13.40 (4.17)	13.39 (4.27)	.89
Sleep duration (hours; n=771[a])	6.84 (1.08)	6.78 (0.99)	6.89 (1.13)	.15
Mental well-being (n=772[a]), n (%)				
K6[d] score ≥13	109 (14.1)	35 (10.5)	74 (16.9)	.02
WHO-5[e] score ≤50	291 (37.7)	110 (32.9)	181 (41.3)	.02

[a]Incomplete baseline questionnaire data.

[b]Binge drinking is defined as consuming 5 or more servings of alcohol for males, or 4 or more servings of alcohol for females in a single drinking session in the past month.

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[c]MVPA: moderate to vigorous physical activity.

[d]K6: Kessler Psychological Distress Scale.

[e]WHO-5: World Health Organization–5 Well-Being Index.

Discussion

Principal Findings

Health@NUS is the first longitudinal study of its kind to explore the interrelationships and associations among health behaviors, health, and well-being of young adults as they transition from university and into their working lives. In addition to traditional assessments used in cohort studies (self-report surveys and physical examination), Health@NUS uses mHealth technologies for continuous and repeated assessments of health behaviors and related contextual information at a level of granularity that has not previously been possible [36]. These data will provide important insights into the determinants and trajectories of health behaviors, health, well-being and related contextual information, and the dynamic and synergistic interrelationships between them.

With an increasing number of young adults graduating from universities in Singapore [94] and across the world, more young adults are subjected to this transitionary period between university and working life [6]. Understanding young adults' health behaviors, health, and well-being during this vulnerable period in their lives, how they change, and what influences these changes has important implications for the promotion of population health. The early results from Health@NUS baseline assessments provide insights into indicators of physical health (eg, BMI, waist circumference, and blood pressure) among university students in Singapore. For instance, participants of Health@NUS reported an average BMI of 21.91 kg/m^2, and the prevalence of obesity (5.43%) was substantially lower than among all Singapore residents aged 18 to 29 years (13.1%) [4]. This may be in part due to the low age of the study population, even though most weight gain occurs between the ages of 18 and 29 years in Singapore [95]. The proportion of underweight female participants (n=91, 17.3%) was greater than Singapore residents (10%) [4], which is an underrecognized public health problem prevalent among young female participants [96]. Further research is warranted to investigate this issue. In addition, the average waist circumference for both male (77.46 cm) and female (69.78 cm) participants was lower than the cutoffs for abdominal obesity in Asian populations [4,97]. Moreover, the prevalence of smoking (11/772, 1.4%) and binge drinking (54/759, 7.1%) among participants of Health@NUS was very low compared to Singapore residents aged 18 to 29 years who reported a prevalence of smoking and binge drinking of 8.3% and 15.6%, respectively [98]. The prevalence of smoking and binge drinking in this study population was also low in comparison to other studies among university students in Singapore and globally [99-102].

In contrast, baseline data on movement behaviors and diet present a less favorable outlook of the student population. While physical activity levels and sleep duration appear low, time spent being sedentary and using screen devices is high. This is in contrast to the physical activity levels observed among Singapore residents aged 18 to 29 years, who were reported to be most likely to engage in regular exercise [4,98]. Compared to Singapore residents aged 18 to 29 years (76.3%), our findings suggest that fewer students (n=555, 72.7%) met the minimum recommendations of at least 150 minutes per week of MVPA as defined by the World Health Organization guidelines [4,103,104]. This was particularly obvious among female students, for whom the proportion meeting recommendations was markedly lower than among their male counterparts. Furthermore, time spent in sedentary behavior among Health@NUS participants was greater than in other studies in Singapore, which reported an average of 5 to 6 hours per day [105,106]. Low levels of physical activity and large amounts of time spent in sedentary behavior by Health@NUS participants may in part be attributable to the fact that university students spent the longest time per week globally studying [107]. With regard to the consumption of whole grains, fruits, and vegetables, the situation also appears suboptimal compared to the "My Healthy Plate" dietary recommendations from the HPB for Singapore residents [108]. On average, students did not meet the recommended daily 5 to 7 servings of whole grains, and daily 4 servings of fruits and vegetables [109]. The daily consumption of sugar-sweetened beverages on the other hand was exceptionally low as compared to Singapore residents [110,111], where sugar-sweetened beverages accounted for 52% of dietary sugar intake [111]. These findings warrant further investigation based on Health@NUS's extensive diet logging and EMA data to better understand dietary patterns of university students in Singapore.

The high prevalence of poor mental well-being (291/772, 37.7%) and psychological distress (109/772, 14.1%) observed in this study population of young adults is of great concern. Our findings from the WHO-5 scores suggest that university students in Singapore have poorer mental well-being as compared to other countries such as Germany [112], New Zealand [113], Hong Kong [114], the United Kingdom [115], and the United States [116]. According to national studies in Singapore, poor mental well-being is most prevalent in young adults aged 18 to 29 years residing in Singapore [4,8], and the proportion of young adults with poor mental well-being has been gradually rising in recent years [4,8,98]. In comparison to the Singapore Mental Health Study 2016, Singapore residents aged between 18 and 34 years reported the highest prevalence of lifetime- and 12-month mental disorders at 21.6% and 11.9%, respectively [8]. Furthermore, the prevalence of poor mental well-being in Singapore prior to and during the COVID-19 pandemic was found to be 8.4% and 8.7%, which is lower than reported in Health@NUS [117,118]. As most mental illnesses (eg, anxiety and depression) [6] emerge during adolescence or early adulthood [9,119,120], the delay in help-seeking by affected individuals could have long-lasting emotional and social impacts on their adulthood [119,121]. Greater levels of stress experienced by students in university increase their vulnerability toward mental health conditions (eg, depression), substance abuse (eg, alcohol abuse), and chronic health conditions (eg,

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obesity) [6] in later adulthood without proper coping mechanisms. As modifiable lifestyle behaviors (eg, physical activity, diet, and sleep) are associated with positive mental well-being [122], it is important for Health@NUS to explore the underlying determinants of students' health behaviors during the transition period from university to working life. To this end, data collected from Health@NUS will be used to inform the design of future interventions to promote healthy behaviors and the health and well-being of students during these formative years and beyond. Given recent attention on the poor mental health and well-being of young people in Singapore [4,5,7,8,119,121], 1 of 4 priorities will also be to use the detailed data from Health@NUS to understand trajectories of well-being and psychological distress, as well as their related contextual factors over time, and to identify potential intervention strategies to promote well-being among the student population in Singapore.

Health@NUS will provide unprecedented information on health behaviors, health, and well-being, and related contextual information. We have recruited a large sample and followed these students for 2 years, over their time at university and as they transition into their postgraduation working life. Combining assessments used in traditional cohort studies (self-reported questionnaires and biometric assessments), as well as repeated and continuous data collection via smartwatches and smartphones will provide detailed longitudinal data. Importantly, much of the data collected required minimal inputs from participants (ie, data from the smartwatch and smartphone), and we captured these data in real time and as participants were going about their daily lives, which enhances the ecological validity of our findings. A potential limitation of presented results relates to the self-reported lifestyle behaviors (eg, dietary intake, cigarette smoking, alcohol consumption, and physical activity). Future analysis of data collected via smartwatches, food logging, and EMA will help to overcome this limitation to some extent. Additionally, there could be a possibility of selection bias as health-conscious and motivated students were more likely to join the study. Disruptions stemming from the COVID-19 pandemic might have affected the job opportunities of university students seeking employment, thus intensifying their stress levels during the challenging transition from study to work. This will have implications on the generalizability of our findings to the wider university student population in Singapore and emphasizes the need for further research in the post–COVID-19 era.

Conclusions

To our knowledge, Health@NUS is a novel prospective cohort study that augments information collected from traditional questionnaires and on-site health screening, with mHealth technologies to capture intensive longitudinal data on individual characteristics, lifestyle behaviors, health, and well-being among young adults during their transition from university to working life in real life [34,35]. Health behaviors shaped in early adulthood often persist into adulthood [11,23] and can have negative implications for health and well-being. A deeper understanding of how health behaviors cluster or interact and of the influence of individual and ecological determinants is essential to developing effective health promotion strategies for young adults in Singapore. Furthermore, the findings from this study will provide insights into the mental health of students during the potentially stressful transition from university to work life.

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Data Availability

The data sets used or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KC, RMVD, and FMR conceived the study, and all authors contributed to the study design. AL, JC, and XHC acquired the data. XHC drafted the manuscript with critical revisions from SME and FMR, except for the statistical analysis performed by CMJLG. All authors critically reviewed the final version of the manuscript.

Conflicts of Interest

AL, JC, DK, and KC are current employees at the Singapore Health Promotion Board.

Multimedia Appendix 1
Supplementary tables and figures.
[DOCX File , 530 KB - resprot_v13i1e56749_app1.docx]

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Abbreviations

EMA: ecological momentary assessment
hiSG: Health Insights SG
HPB: Health Promotion Board
K6: Kessler Psychological Distress Scale
mHealth: mobile health
MVPA: moderate to vigorous physical activity
NUS: National University of Singapore
REDCap: Research Electronic Data Capture
STROBE: Strengthening the Reporting of Observational studies in Epidemiology
WHO-5: World Health Organization–5 Well-Being Index

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Protocol

Evaluating the Preliminary Effectiveness of the Person-Centered Care Assessment Tool (PCC-AT) in Zambian Health Facilities: Protocol for a Mixed Methods Cross-Sectional Study

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Abstract

Background: Person-centered care (PCC) within HIV treatment services has demonstrated potential to overcome inequities in HIV service access while improving treatment outcomes. Despite PCC being widely considered a best practice, no consensus exists on its assessment and measurement. This study in Zambia builds upon previous research that informed development of a framework for PCC and a PCC assessment tool (PCC-AT).

Objective: This mixed methods study aims to examine the preliminary effectiveness of the PCC-AT through assessing the association between client HIV service delivery indicators and facility PCC-AT scores. We hypothesize that facilities with higher PCC-AT scores will demonstrate more favorable HIV treatment continuity, viral load (VL) coverage, and viral suppression in comparison to those of facilities with lower PCC-AT scores.

Methods: We will implement the PCC-AT at 30 randomly selected health facilities in the Copperbelt and Central provinces of Zambia. For each study facility, data will be gathered from 3 sources: (1) PCC-AT scores, (2) PCC-AT action plans, and (3) facility characteristics, along with service delivery data. Quantitative analysis, using STATA, will include descriptive statistics on the PCC-AT results stratified by facility characteristics. Cross-tabulations and/or regression analysis will be used to determine associations between scores and treatment continuity, VL coverage, and/or viral suppression. Qualitative data will be collected via action planning, with detailed notes collected and recorded into an action plan template. Descriptive coding and emerging themes will be analyzed with NVivo software.

Results: As of May 2024, we enrolled 29 facilities in the study and data analysis from the key informant interviews is currently underway. Results are expected to be published by September 2024.

Conclusions: Assessment and measurement of PCC within HIV treatment settings is a novel approach that offers HIV treatment practitioners the opportunity to examine their services and identify actions to improve PCC performance. Study results and the PCC-AT will be broadly disseminated for use among all project sites in Zambia as well as other HIV treatment programs, in addition to making the PCC-AT publicly available to global HIV practitioners.

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KEYWORDS

person-centered care; HIV; action plans; preliminary; person-centered care assessment tool; PCC-AT; assessment tool; Zambia; health facility; exploratory study; HIV treatment; inequities; framework; practitioners; health services

Introduction

Background

Given that the HIV epidemic in Zambia is largely concentrated among women and key population members who are highly marginalized, person-centered care (PCC) is perceived as a priority to advance outcomes for people living with HIV [1-4]. The World Health Organization [5] describes a person-centered framework as one in which:

> *all people have equal access to quality health services that are co-produced in a way that meets their life course needs and respects their preferences, are coordinated across the continuum of care and are comprehensive, safe, effective, timely, efficient, and acceptable and all carers are motivated, skilled and operate in a supportive environment.*

From a health systems perspective, PCC can improve job satisfaction, reduce overall costs, and increase efficiencies and resilience [6]. From a client perspective, PCC models are increasingly recognized as critical to overcome inequities in health service access while increasing participation in quality and responsive care, improving health literacy and self-care, and increasing satisfaction with care [7,8].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that the potential benefits of PCC for clients extend to improved clinical outcomes [7]. A study in South Africa demonstrated that person-centered approaches such as 3-month community-based differentiated antiretroviral treatment (ART) service delivery resulted in improved client retention over the standard of care [9]. In Uganda, monthly support groups for adolescents and parents/caregivers, telephone appointment reminders, and notification of missed visits contributed to increased retention in care [10]. In Zimbabwe, community adolescent treatment supporters provided monthly support and ART refill groups for adolescents, cofacilitated caregiver workshops, provided individual health education and counseling, sent SMS text message reminders and check-ins, provided home visits, and referred and linked adolescents to care, leading to significant increases in ART initiation, viral suppression, and ART adherence [11,12]. In Mozambique, a combination intervention approach including SMS text message appointment reminders and individualized health messages contributed to improved linkage to care [13].

In Zambia, 89% of HIV-positive adults (aged 15+ years) are aware of their status, 97% of adults diagnosed with HIV report being on ART, and 96% of those on ART are virally suppressed [4]. At 11.7%, the HIV prevalence has been steadily declining from a high of 14% in 2000 [14]. However, progress in this regard is not universal. The national HIV prevalence rate is estimated to be 49% among female sex workers [14], 22% among transgender people, 21% among men who have sex with men, 15% among people who inject drugs, and 14%-27% among people who are incarcerated [1]. Although adolescents and young people (aged 15-24 years) represent 20% of the total population of Zambia, they account for 40% of all new infections [15], and the HIV prevalence among adolescent girls and young women is double that of adolescent boys and young men [16]. Among these key and priority populations, elevated HIV risk is associated with multiple determinants, including criminalization, stigma and discrimination, harmful gender norms, and limited access to acceptable health services. To advance progress for the most vulnerable populations, person-centered HIV treatment service delivery models that are tailored to the needs and expectations of diverse populations offer an important opportunity to help overcome service access, uptake, and continuity challenges.

Despite PCC being widely considered a best practice in serving both the needs of recipients of care and the goals of reaching epidemic control more broadly, no consensus exists on how to assess and measure the construct. This study conducted in Zambia will build upon previous evidence collected by the study team, including (1) a systematic literature review, which further defined the construct of PCC and led to a proposed framework that informed the PCC assessment tool (PCC-AT) [17]; and (2) a PCC-AT content validity, score consistency and reliability, and feasibility study conducted in Ghana [18].

The PCC-AT is an Excel-based tool that measures health facility staff perspectives on PCC service delivery within HIV treatment settings. Implementation of the PCC-AT requires in-depth discussions among health facility staff to assign a score using a benchmarking approach (eg, simple yes/no or mostly/partly/none responses) for each of the 55 performance expectations linked to 3 domains and 12 subdomains (see Figure 1). Similar to other tools that are widely used to measure the organizational and technical performance of implementing partners, the PCC-AT includes dropdown menus and formulas to calculate composite scores from multiple tabs. The PCC-AT culminates in an “action planning” process, a template for which is embedded within the tool itself, to design tailored interventions and improvements based on PCC-AT scores.

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Figure 1. Domains and subdomains of the person-centered care assessment tool.

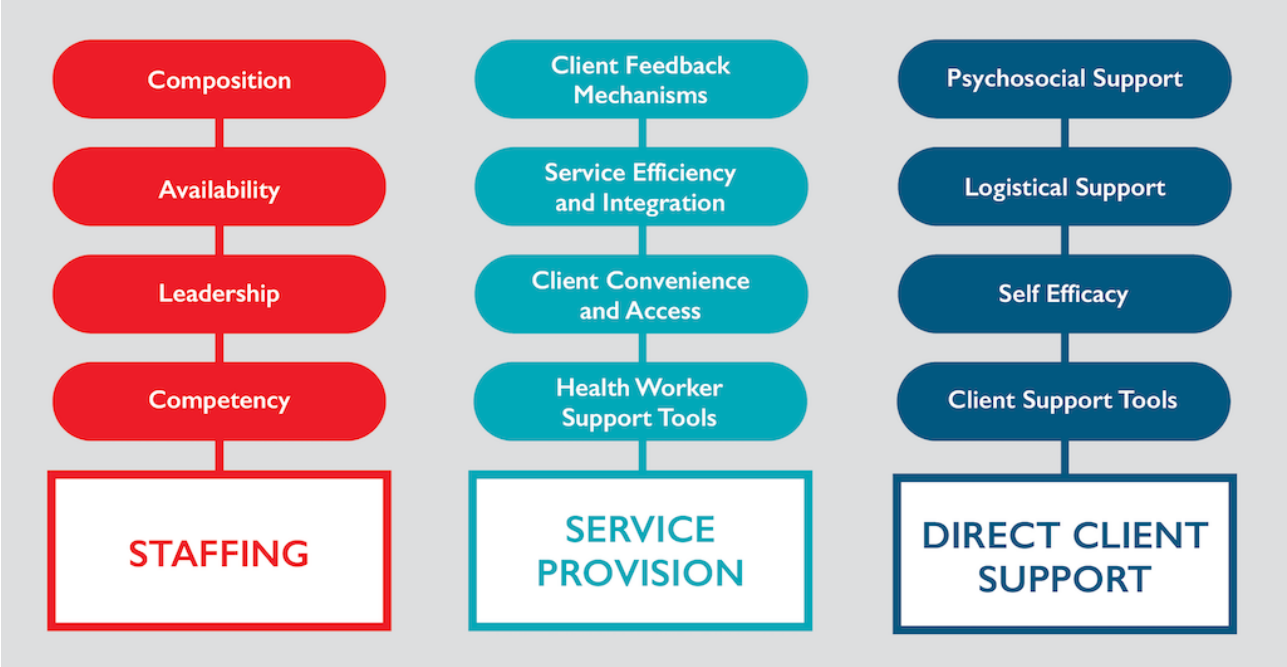

Objectives and Study Questions

This study seeks to examine the correlation between PCC-AT scores with HIV service delivery indicators, including treatment continuity, viral load (VL) coverage, and viral suppression, at 30 randomly selected health facilities in the Copperbelt and Central provinces of Zambia. This study also seeks to identify the types of PCC-strengthening activities that health facility staff identify as priorities based on PCC-AT scores. Specifically, we aim to answer the following research questions: (1) Do facilities with higher PCC-AT scores demonstrate higher performance of HIV service delivery indicators in comparison to facilities with lower PCC-AT scores? and (2) What common and unique themes emerge from PCC action planning in facilities with high PCC-AT scores compared with facilities with low PCC-AT scores? We hypothesize that facilities with higher PCC-AT scores will demonstrate more favorable HIV treatment continuity, VL coverage, and viral suppression in comparison to those of facilities with lower PCC-AT scores.

Methods

Study Design

This research is based on a mixed methods, cross-sectional study design, and will be guided by a vulnerable and marginalized populations approach [19] under a health equity lens [20].

Site Selection and Study Setting

The study will be carried out at USAID DISCOVER-Health project sites (N=66) in the Copperbelt and Central provinces, which are public, primary-level facilities. Sites will be considered eligible for inclusion if the health facility (1) provides direct HIV treatment services and (2) expresses interest in scaling PCC to strengthen services. Prisons associated with health facilities are excluded from randomization (n=9) due to differences in how services are delivered at such sites. The 57 eligible health facilities are spread across urban, periurban, and rural locations; hence, the study's sample frame is based on a proportionate stratification method to stratify the health facilities by rural, periurban, and urban locations. All sites are considered primary sites. Using a random-number generator in Excel, 30 health facilities were selected as data collection sites from the sampling frame to ensure that selected clinics have a proportionate representation of urban, periurban, and rural facilities to more precisely reflect the range of facility characteristics in the overall sample frame. As needed, alternate facilities will be selected from the randomly ranked stratum lists in ascending order (see Multimedia Appendix 1).

Participants

At each randomly selected health facility, 5-10 English-speaking health facility staff members, based on availability, will be selected to participate in the PCC-AT on the day of data collection. Inclusion criteria for participants include at least 1 year of employment or volunteering at the study health facility and direct provision of or knowledge related to HIV treatment services (eg, ART providers, nurses, lab technicians, counselors, pharmacists [or the equivalent], data managers, and community group liaisons). Where there are more than 7 eligible staff members, participation of staff based on a gender balance and experience will be encouraged. Exclusion criteria for participation in the PCC-AT study include any staff who have worked or volunteered at the study facility for less than 1 year and any staff member whose job description does not include direct HIV treatment service delivery or knowledge of how services are delivered.

Study Procedure

PCC-AT Implementation

PCC-AT implementation at the health facilities will be conducted by full-time English-speaking project staff members, divided into 6 data collection teams with each team composed

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of 3 data collectors. All data collectors will undergo a 2-day training led by the PCC-AT developers, consisting of a general introduction on the purpose and nature of the study, along with instruction on obtaining informed consent, interviewing and facilitation techniques, data storage, and practice implementing the PCC-AT.

Each data collection team will designate a lead facilitator responsible for introducing the study, collecting informed consent forms, and facilitating the PCC-AT process with the health facility team through a guided discussion. The lead facilitator will guide PCC-AT implementation in a neutral manner so that health facility staff assess their own strengths and weaknesses. The assessment process is intended to promote information sharing, a healthy internal dialogue, and consensus building by including a range of staff who will discuss institutional abilities, systems, procedures, and policies in various domains that influence PCC. The goal is to arrive at a consensus for the 55 performance expectations across each of the 12 subdomains of the PCC-AT.

Action Planning

Once the scoring is complete, each PCC-AT implementation will culminate in an action-planning process. The lead facilitator will (1) guide health facility staff to identify low scores on the PCC-AT; (2) lead an examination of the performance expectations to identify why the facility had a low score; and (3) facilitate a discussion so that health facility staff identify potential solutions, rank the potential solutions in order of their ability to be implemented by the staff, and identify the priority activities and a timeline for action. The remaining study team members will take detailed notes that document the discussion on an action planning template to capture the full universe of potential activities and the rationale behind activity selection. It is anticipated that PCC-AT implementation, including action planning, will require approximately 2 hours, taking place in the afternoon when patient flow is light in a private room located within each health facility.

Service Delivery Data Collection

Following PCC-AT implementation, the study team will select key indicators within the last 3 months (April 1 to June 30, 2023) from each of the 30 selected health facilities, in alignment with the timing of the PCC-AT study activities. This study will use the monitoring, evaluation, and reporting guideline of the President's Emergency Plan for AIDS Relief version 2.6 definitions and calculations [21] for each indicator of interest, including (1) continuity of treatment, (2) VL coverage, and (3) viral suppression.

Continuity of treatment is a proxy measure of the overall gain or loss in patients compared to the expected number of patients on treatment, which is calculated by tracking the number of adults and children currently receiving ART (TX_CURR) over time to measure the ongoing scale-up and uptake of ART and continuity of treatment in ART programs.

VL coverage is a comparison of the number of patients on ART with a VL result documented in the medical or laboratory records/laboratory information system (LIS) within the past 12 months (viral suppression indicator denominator) with the result for TX_CURR from 6 months earlier.

Viral suppression reflects the percentage of patients on ART with a suppressed VL result (<1000 copies/mL) documented in the medical or laboratory records/LIS within the past 12 months as the numerator and the total number of patients on ART with a VL result documented in the medical or laboratory records/LIS within the past 12 months as the denominator. This indicator monitors the proportion of documented VL results from adult and pediatric ART patients who have been on ART for at least 3 months (or according to national guidelines) with a suppressed VL result (<1000 copies/mL). This allows ART programs to monitor the individual and overall programmatic response to ART as measured by virologic suppression.

Data Analysis

Overall Analysis Plan

Data analysis will include all 3 sources, (1) the PCC-AT composite score page, (2) PCC-AT action plan template, and (3) descriptive facility statistics (eg, client population size, urban/periurban/rural location, and province), as well as the service delivery data for these 3 key indicators.

Quantitative Data

We will investigate if a correlation exists between the 3 key indicators of interest, including treatment continuity, VL coverage, and viral suppression, and PCC-AT domain/subdomain scores using STATA or similar software. Analysis will include descriptive statistics (mean, median, range) on the PCC-AT results by domain and subdomain while stratifying by facility characteristics. In addition, cross-tabulations and/or regression analysis will be performed to determine if there are any associations between scores and treatment continuity, VL coverage, and/or viral suppression.

Qualitative Analysis

Qualitative data from the action planning template will be separately analyzed using the detailed notes in the template. These notes will be analyzed via NVivo or similar software. Axial and open coding of the action plan text will allow for deconstruction of the text and uncovering of emergent themes, concepts, issues, and ideas. Action plans will be coded separately by 2 members of the study team according to the framework and compared to ensure interrater reliability.

Materials

In addition to the PCC-AT, materials will include the study information sheet and consent form (Multimedia Appendix 2) and the PCC-AT action planning template (Multimedia Appendix 3). All PCC-AT activities will be recorded and take place in English.

Ethical Considerations

The study received ethical approval from the Zambia National Health Research Authority (reference number 4150-2023) and was determined to be exempt from human subjects' oversight by the JSI Institutional Review Board (23-36E). Facilitators will be trained in informed consent and confidentiality principles and protocols. All study participants will be asked if they are

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interested in participating in the study. Study participants will be presented with a study information sheet and a consent form in English, which they will be asked to sign if they agree to participate in the study. The consent form explicitly states that participation is voluntary. In-kind provisions (ie, water, snacks, lunch) will be provided depending on the length of each session. There will be no monetary compensation for participation. Refusal to participate will have no bearing on health providers' work assignment in the future or payments for health work. Participants may choose to stop at any point during the interview or discussion with no penalty or bearing on their employment status. Only the study team will have access to data. Participant confidentiality will be protected throughout study procedures, including (1) excluding the names of participants on all data collection materials; (2) storing data in a secure place; (3) developing codes during qualitative data analysis so that any potential identifiers (eg, staff positions) are not associated with the data; and (4) maintaining strict adherence to the principles of voluntary participation, confidentiality, anonymity, and protection of human subjects as guaranteed by the consent form (Multimedia Appendix 2).

Results

Data collection in Zambia took place in July and August 2023 and data analysis was performed in September-November 2023. One manuscript related to this work has been published [18]. As of May 2024, we enrolled 29 facilities in the study and data analysis from the key informant interviews is currently underway. All results are expected to be published by September 2024.

Discussion

This study in Zambia seeks to understand associations between PCC-AT scores and HIV clinical outcomes, contributing to the overall evidence base on the importance of a person-centered approach to delivering HIV care. Specifically, the data from this study will increase the existing evidence on how to measure, evaluate, and implement PCC at the primary health care level in the Zambian context. PCC has demonstrated potential to contribute to health equity for vulnerable and/or marginalized populations [22]. Given that the HIV epidemic in Zambia is largely concentrated among vulnerable and marginalized populations, PCC is a critical measure to overcome HIV service access limitations and to advance health outcomes [4,23].

A potential limitation of this study is the high performance of the majority of health facilities included in the sample frame for each of the indicators of interest. Given that the majority of clients are retained on treatment, have recent VLs (within the past 12 months), and have achieved viral suppression, it will be challenging to detect differences in service delivery indicators between groups with high and low PCC-AT scores. In addition, the PCC-AT has not yet been validated; results from this study will provide information on initial effectiveness, which will guide priorities for a future validation study. The PCC-AT also does not measure external factors that may influence scores and external generalizability is limited, although the clinic randomization process improves our ability to generalize results to other Zambian HIV treatment facilities.

These study results will inform any required refinements to the PCC-AT so that it more effectively measures PCC as identified through treatment continuity, VL coverage, and viral suppression. Assessment and measurement of PCC within HIV treatment settings is an approach that can offer HIV treatment practitioners the opportunity to critically examine their services, identify actions to improve PCC performance, and ultimately improve HIV treatment outcomes for vulnerable populations. Given the role that PCC has demonstrated to contribute to improving HIV treatment outcomes [24,25] and the potential for the PCC-AT to contribute to strengthened person-centered HIV treatment services, the study team anticipates publishing study findings in 2024 and presenting the findings at the International Conference on AIDS and STIs in Africa, which may include a training session for global health professionals in use of the tool.

After data are analyzed and if positive results emerge, it is anticipated that the PCC-AT will be broadly disseminated for use among all 173 DISCOVER-Health health facilities in Zambia as well as other HIV treatment programs in Ghana supported by this study team. This tool and process may improve PCC, and could be a valuable, strengths-based person-centered tool for the global HIV community with the aim of strengthening HIV treatment outcomes for all people.

Authors' Contributions

JP, APN, and JMM were responsible for study conceptualization, and writing, review, and editing of the manuscript. JP was responsible for project administration. MD wrote the original draft of the manuscript. AC and CMM were responsible for methodology, and writing, review, and editing of the manuscript. ND and MS contributed to the methodology.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Randomly identified study facilities and alternate sites.
[DOCX File , 20 KB - resprot_v13i1e54129_app1.docx]

Multimedia Appendix 2

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Participant and consent forms.
[DOCX File , 16 KB - resprot_v13i1e54129_app2.docx]

Multimedia Appendix 3
Action plan template.
[DOCX File , 10 KB - resprot_v13i1e54129_app3.docx]

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Abbreviations

ART: antiretroviral treatment
LIS: laboratory information system
PCC: person-centered care
PCC-AT: person-centered care assessment tool
TX_CURR: number of adults and children currently receiving antiretroviral treatment
UNAIDS: The Joint United Nations Programme on HIV/AIDS
VL: viral load

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Protocol

Capitalizing on Community Groups to Improve Women's Resilience to Maternal and Child Health Challenges: Protocol for a Human-Centered Design Study in Tanzania

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Abstract

Background: Maternal and neonatal deaths remain a major public health issue worldwide. Income Generation Associations (IGAs) could form a critical entry point to addressing poverty-related contributors. However, there have been limited practical interventions to leverage the power of IGAs in addressing the challenges associated with maternal care and childcare.

Objective: This study aims to co-design an intervention package with women in IGAs to improve their readiness and resilience to address maternal and child health (MCH) challenges using a human-centered design approach.

Methods: The study will use a qualitative descriptive design with purposefully selected women in IGAs and key MCH stakeholders in the Shinyanga and Arusha Regions of Tanzania. A 4-step adaptation of the human-centered design process will be used involving (1) mapping of IGAs and exploring their activities, level of women's engagement, and MCH challenges faced; (2) co-designing of the intervention package to address identified MCH challenges or needs considering the perceived acceptability, feasibility, and sustainability; (3) validation of the emerging intervention package through gathering insights of women in IGAs who did not take part in initial steps; and (4) refinement of the intervention package with MCH stakeholders based on the validation findings.

Results: The participants, procedures, and findings of each co-design step will be presented. More specifically, MCH challenges facing women in IGAs, a list of potential solutions proposed, and the emerging prototype will be presented. As of August 2024, we have completed the co-design of the intervention package and are preparing validation. The findings from the validation of the emerging prototype with a new group of women in IGAs and its refinement through multistakeholder engagement will be presented. A final co-designed intervention package with the potential to improve women's resilience and readiness to handle MCH challenges will be generated.

Conclusions: The emerging intervention package will be discussed given relevant literature on the topic. We believe that subsequent testing and refinement of the package could form the basis for scaling up to broader settings and that the package could then be promoted as one of the key strategies in addressing MCH challenges facing women in low- and middle-income countries.

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KEYWORDS

maternal and child health; maternal and child deaths; human-centered design; income generating associations; sub-Saharan Africa; Tanzania; community groups; community; capitalizing; resilience; maternal deaths; neonatal deaths; mortality; co-design

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Introduction

Despite massive improvements in recent years, maternal and child health (MCH) care remains a significant global public health problem. According to the World Health Organization (WHO), 5.2 million children aged younger than 5 years and 295,000 mothers die each year, with low- and middle-income countries accounting for most of these deaths [1,2]. In sub-Saharan Africa (SSA), several countries still face higher maternal mortality rates (MMR) which are persistently above the sustainable development goal target of below 70 deaths per 100,000 live births by 2030 [3,4]. Therefore, most SSA countries are far from achieving the Sustainable Development Goals for maternal mortality [5].

In Tanzania, MMR has continued to be alarming despite some improvements. The Tanzania Demographic and Health Survey and Malaria Indicator Survey have been indicating a fluctuation in MMR. For instance, a decrease from 578 to 454 per 100,000 live births in 2005 and 2010 respectively, followed by a rise to 524 per 100,000 live births in 2017 [6]. Tanzania Demographic and Health Survey and Malaria Indicator Survey reports of 2022 indicate that the neonatal mortality rate has remained steady at 25/1000 live births since the 2015-2016 survey [7]. Amid these fluctuations, the country recently documented an MMR of 362 deaths per 100,000 live births, and an under-5 mortality rate (U5MR) of 56 deaths per 1000 live births [8,9]. Evidence indicates that most of these deaths could have been averted if women had access to high-quality MCH services including expert delivery assistance and postnatal care [10,11]. Therefore, massive efforts are still needed to address the MCH challenges more broadly.

Several community and individual factors significantly influence MCH outcomes, including socioeconomic status, cultural beliefs and practices, health literacy, and social support [12]. These factors collectively contribute to persistently high MMR and U5MR in many regions worldwide [10-12]. Most importantly, socioeconomic status plays a critical role in shaping MCH outcomes. Women and families with lower incomes often encounter formidable barriers to accessing essential health care services. Limited financial resources can impede women's ability to obtain timely and adequate prenatal care, skilled birth attendance, and postnatal care [12,13]. Consequently, women from economically disadvantaged backgrounds face heightened risks of complications during pregnancy and childbirth, including maternal mortality, preterm birth, and low birth weight [13]. Moreover, negative cultural beliefs and practices prevalent among women of low socioeconomic status also exert significant influence on MCH outcomes by shaping health-seeking behaviors. In economically disadvantaged communities, entrenched norms and taboos may discourage women from attending antenatal visits or using modern contraceptives [14]. This reluctance contributes to higher rates of unintended pregnancies, unsafe abortions, and childbirth complications, exacerbating poor MCH outcomes. Furthermore, inadequate health literacy, often prevalent among mothers and families with low socioeconomic status, further compounds these challenges. A limited understanding of the importance of MCH services and preventive health care practices hinders appropriate care-seeking behaviors [14,15]. Insufficient knowledge about nutrition, immunization, and child development increases the likelihood of suboptimal care and missed opportunities for early interventions, thereby elevating maternal and child morbidity and mortality rates [15]. Additionally, inadequate social support networks among women of low socioeconomic status amplify the difficulties faced in accessing and using MCH services. A lack of emotional, informational, or practical support heightens stress levels during pregnancy and postpartum periods, negatively impacting maternal mental health and overall well-being [15]. Addressing socioeconomic determinants of health is crucial for improving MCH outcomes globally. Effective interventions must prioritize enhancing economic opportunities for women with low socioeconomic status, promoting culturally sensitive health care practices, improving health literacy, and bolstering social support networks. These efforts are essential to ensure equitable access to quality MCH services and to mitigate disparities in MCH outcomes across diverse populations.

The WHO in 2017 developed a framework for raising the standard of MCH care with an emphasis on the need for a holistic approach that addresses health systems, community, and individual factors impacting MCH care [16,17]. A key aspect of this framework is the need for the promotion of community engagement and empowerment as an effective strategy for reducing deaths in MCH care [16,18]. In what appears as partly embracing the WHO framework, Tanzania has taken notable steps to improve MCH service quality and use. At the macro level, the government developed and implemented the 2016-2020 Maternal and Newborn Health Road Map and the 2021-2026 health sector strategic plan, both of which focused on addressing infrastructure and resource limitations, improving health care provider training, and increasing access to essential medicines and supplies [17,19]. At the micro level, the country has implemented the MCH scorecard supported by ALMA2030 and the *Mama na Mtoto* program involving training, mentorship, facility upgrading, and support to health care providers [20,21]. In collaboration with some development partners, the country implemented a community health worker program involving training and deployment of community members to provide basic health care services in their communities, including MCH [22]. Other notable efforts included the m-mama intervention coimplemented by Vodacom Mobile Company, which connects pregnant women in emergency care in rural regions [23].

A major problem with the current interventions for reducing MMR and U5MR in Tanzania is the inadequate engagement of the end users (community members) in the design and implementation and their evaluation. There has been a tendency to adopt a top-down approach in developing MCH interventions posing a risk of not effectively addressing the needs and priorities of local communities. Evidence indicates that community engagement is a key driver of the success of many health care interventions [24,25]. Community engagement is crucial in addressing the deficiencies of MCH care as it helps identify and address the unique needs and challenges of each community [26,27]. Engagement of community members in

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MCH intervention design, implementation, and evaluation cannot be successful if women are excluded.

Women play an important role in families; therefore, MCH is central to their health. However, they indeed hold less or no power and most decisions on MCH care with financial implications are often fully controlled by men, particularly in low-income countries [28,29]. Nevertheless, socioeconomic transformations are occurring both globally and in SSA where women are becoming more and more supported politically. For example, women are increasingly coming together in Income Generation Associations (IGAs) that are widely supported as one of the efforts to uplift their economy [30]. Tanzania, for example, has a large number of women's groups including Village Community Banks (VICOBAs), farmers' groups, and self-help groups. VICOBAs for instance, operate as a form of microfinance institutions, providing small loans and other financial services to their members for self-income generation [31,32]. The VICOBAs are frequently found by women and are intended to economically empower them.

Since poverty is among the key drivers of poor MCH outcomes, VICOBA and other women IGAs that focus on uplifting socioeconomic status could form an important entry point for cushioning poor women toward unfavorable income-related MCH outcomes [33]. The potential contribution of IGAs in improving MCH outcomes has been previously documented [31]. Consequently, the implementation of participatory interventions with women IGAs has been considered an effective strategy for improving MCH outcomes in low-resource settings [31]. However, such evidence is not well established in Tanzania. More specifically, there have been limited MCH interventions leveraging on the power of women IGAs in addressing income-related drivers of poor MCH outcomes in Tanzania. To partly bridge this scholarly and practical gap, we propose a human-centered design (HCD) study to jointly co-design a package of interventions for enhancing women's resilience and readiness to respond to MCH needs or challenges. HCD is an innovative approach to problem-solving that leverages insights from the end users of new products, services, and experiences to develop best-fit solutions that are rapidly prototyped and iteratively refined [34]. HCD is thought to provide more community satisfaction as well as greater efficiency and cooperation in the process of developing and implementing public health interventions [34]. In addition, compared to conventional problem-solving techniques in the fields of health care and public health, HCD may lead to interventions that are more effective and long-lasting [34]. We seek to engage women from IGA groups in the design and evaluation of interventions alongside the research team and MCH stakeholders. An emerging intervention package through the HCD process is expected to be widely accepted among women and feasible in local contexts in improving their resilience and readiness (income, knowledge, skills, decision-making, engagement, and advocacy) toward addressing MCH challenges. Through testing of the intervention package, if deemed feasible, it could be scaled up to broader settings and promoted as one of the key strategies in addressing MCH challenges facing women in low- and middle-income countries. Therefore, this study aims to co-design an intervention package with women in IGAs to improve their readiness and resilience to address MCH challenges using the HCD approach.

Methods

Study Design

The study will use qualitative descriptive design using a 4-step adaptation of the HCD approach as an investigative framework (Figure 1). The use of qualitative descriptive design within the HCD process is aimed at answering the (1) design problem: how can women use IGAs (eg, VICOBA) to improve their resilience and readiness to address MCH challenges? (2) Research question: what are the major challenges facing IGA's that hinder them from being used to support and help women overcome the MCH challenges? (3) Design question: what is the best intervention package (prototype) co-developed by women in IGAs and stakeholders to address these challenges considering the perceived feasibility, sustainability, and acceptability? The use of a qualitative descriptive approach is also because we aim to develop a deep understanding and describe the challenges and experiences of women in IGA's (VICOBA). This approach enables a holistic examination of the topic, ensuring that social, cultural, and individual influences are considered and ultimately facilitating the development of targeted intervention using the HCD process.

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Figure 1. The study's implementation framework. IGA: Income Generation Association.

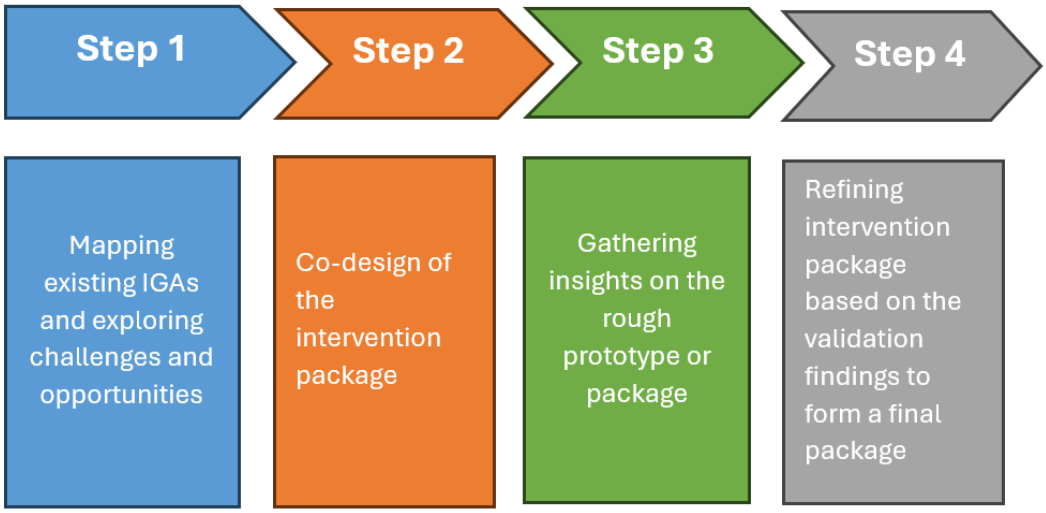

Study Setting

The proposed implementation sites for this study are the Shinyanga and Arusha regions in Tanzania. On the one hand, Shinyanga is a region located in the lake Zone forming what used to be Sukuma land. Shinyanga is described in depth by Isangula et al [35]. In a nutshell, the area is predominantly characterized by rural occupancy. The decision to use Shinyanga as a study site was made due to the necessity to draw on the rural experience of Sukuma women, who have less decision-making authority than males, poor MCH indicators, the prevalence of medical pluralism, and the ability to leverage already-existing SONAM networks. Due to its rich IGA groupings, Shinyanga MC was specifically chosen for the research inside the Shinyanga Region. On the other hand, Arusha is home to various ethnic groups, including the Maasai people. The Maasai society is a patriarchal community where men hold the most decision-making power. Given that women in patriarchal communities often have limited access to resources, decision-making power, and social networks, existing community groups can be an essential tool to improve their resilience and readiness to respond to MCH challenges. Within Arusha, Arumeru District is purposefully selected because it has a mix of urban and rural communities, which presents an opportunity to study and explore both urban and rural experiences at the same time.

Study Population, Sample Size, and Sampling

Step 1: Mapping and Community-Driven Discovery Inquiry

This study's team mapped existing women IGAs in this study's settings to understand their activities and the level of women's engagement. This was followed by a qualitative inquiry with the purpose of identifying IGA's challenges that hinder them from enhancing women's resilience and readiness toward MCH challenges using a semistructured interview guide. This facilitated the development of an understanding of the local context and the needs of the target population. About 3 focus group discussions (FGDs; in each site) with 6-8 purposefully selected women in IGAs (6 FGDs in total), and 5 key informant interviews (KIIs; in each site) with purposefully selected municipal IGA coordinators and community development officers were conducted (10 KIIs in total). Participants were recruited through IGA coordinators and community development officers. All interviews were conducted at a convenient location confirmed with the respondents in advance to enable them to identify an alternate location if required. Upon arrival, research assistants provided detailed information on this study, obtained informed consent, and engaged respondents for approximately 45 to 60 minutes in a semistructured audio-taped discussion. Data were managed and analyzed thematically using NVivo (Lumivero) software and informed the next step.

Step 2: Consultative Co-Design Meetings

Few IGAs' members, IGA coordinators, and community development officers who participated in FGDs and KIIs were purposefully selected to participate in the co-design meetings. The purpose was to co-design an intervention package aimed at addressing the IGA's challenges identified in step 1 with a focus on building the resilience and readiness of women toward MCH challenges. A transdisciplinary team of purposefully selected 30 participants (15 women in IGAs and 5 IGA coordinators, 5 community development officers, and 5 other relevant stakeholders) convened for 2 consecutive days. The activities involved (1) a synthesis session to evaluate and validate the qualitative findings from step 1 and share perspectives, experiences, and insights to build a deeper comprehension of the challenges of IGA's within Arusha and Shinyanga; (2) an ideation session to develop ideas of the potential solutions; and (3) prototyping and co-creation solutions to generate the initial (rough) prototype models and components essential to its testing (features, modalities, responsible person, etc). Participants were divided into 3 groups and rated all the proposed solutions on a scale of 0 to 10 for perceived acceptability, feasibility, and sustainability. Commutative scores were computed using Excel (Microsoft Corp) and a moderated discussion was held for the participants to reach a consensus on the top-scoring solutions that formed a rough prototype package. The emerging prototype will guide step 3 of the HCD process.

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Step 3: Validation and Insight Gathering Inquiry

This step will involve gathering the opinions of women who were not involved in the earlier steps of HCD. The purpose is to gather their insights on the rough prototype considering areas for improvement. We will conduct 3 FGDs with purposefully selected women in IGAs at each site with a focus on separate communities within the selected districts. Women will be recruited through community development officers who are responsible for IGA activities. The FGDs will be conducted at a convenient location confirmed with the respondents in advance to enable them to identify an alternate location if required. Upon arrival, research assistants will provide detailed information on this study, obtain informed consent, and engage respondents for approximately 45 to 60 minutes in a semistructured audio-taped discussion. At the end of the FGDs, participants will also be engaged in rating of the components of the rough prototype from a score of 0 to 10 considering the perceived acceptability, feasibility, and sustainability. FGD data will be managed and analyzed thematically using NVivo software and rating data will be managed and analyzed with Excel. The findings will inform us of the next step.

Step 4: Refinement and Adaptation Meeting

The research team will invite 20 MCH stakeholders within Aga Khan University for a 1-day consultative workshop to review the validation findings, refine the intervention package, and form a final package that could be subjected to definitive trials upon securing external grants.

Data Management and Analysis

Data will be collected by 2 trained research assistants at each site with diplomas in medicine and community development. Data transcription and translation will occur simultaneously by research assistants followed by validation by the coprincipal investigators and the principal investigator. To promote participant anonymity, each interviewee will be assigned a pseudonym, and the transcripts of the interviews will be deidentified. The analytical process will involve a deductive thematic analysis approach [36]. To begin, the research team will collectively review the research questions and, through a consensus-based approach, identify and select various thematic categories. This will lead to the development of an analytical matrix comprising the primary themes and their associated subthemes. Individual transcripts and relevant content representing participants' responses will then be uploaded into the NVivo (version 12) software for deductive coding. The research team will collaboratively assess any codes that do not align with the predetermined subthemes and themes, removing them if both subjective and objective evaluations indicate that they do not significantly contribute to this study's objectives. Finally, the research findings will be synthesized into a comprehensive research report by exporting the coded NVivo data into Word (Microsoft Corp), facilitating an interpretative analysis.

Ethical Considerations

The study has received ethical clearance from the Aga Khan University Ethics Review Committee and was granted a certificate (AKU/2023/08/fb/06/05). Further, this study received approval from the President's Office–Regional Authority and Local Government and local approvals from the regional medical officers and regional community development officers of Shinyanga and Arusha. We have secured letters of introduction from these entities that will be shared with local community leaders and health care facilities. Before participation, all participants will be asked to provide written consent, which will ensure that this study is conducted ethically. Additionally, the researchers will make sure that there are no repercussions for participants who decide to quit this study at any stage. Limited risks are anticipated because this study does not expose community members or other MCH stakeholders directly or indirectly to any diagnostic activity or treatment. Before analysis, data will be cleaned and potentially identifying information removed. All responses will be kept private as a precaution, and data analysis and reporting will be performed at aggregated levels throughout the Shinyanga and Arusha regions. The collected information will only be used for this research.

Results

Participants Demographics

The first section of the results will summarize the participant demographics for each research site considering every HCD step. Participants' gender, age, primary occupations, marital status, and years of engagement in IGA activities are some of the demographics that will be presented in a tabular form.

Findings From Community-Driven Discovery Inquiry

The findings from FGDs with women in IGAs and KIIs with stakeholders will be triangulated. Key themes and subthemes related to the challenges faced by women in IGAs and opportunities for addressing them will be examined. Heuristic categorization of themes, subthemes, and relevant categories will be made to ensure a comprehensive presentation of key issues that guided subsequent HCD steps. A focus will be results related to women's experiences of IGAs including how IGAs operate, perceived benefits, drivers of their desires to join IGAs, challenges facing IGAs, barriers that hinder them from being used to support women overcome MCH challenges, and how women in IGAs respond to these challenges. Findings from health care workers still focus on how they use IGAs to support women in achieving positive MCH outcomes. The findings will be supported by selected participants' quotes. This section will conclude with how the findings served as a stepping stone for the subsequent HCD steps.

Findings From the Consultative Meetings

Consultative meetings form a critical step of the co-design process [37]. Participants' reflections on the findings of community-driven inquiries and suggested refinements as part of the synthesis meetings will be examined. A final categorization of challenges facing IGAs after refinements and reflections will be summarized. Then, a critical analysis and a list of all ideas for the potential solutions to address the identified challenges proposed during an ideation session will be presented. Finally, the findings of prototype and cocreation sessions will be examined. More specifically, rating scores from

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each participant group for all the potential ideas and cumulative scores will be arranged from the highest to the lowest. The interventions selected to form "a rough prototype model" will be highlighted. The rough prototype may include up to 3 or more interventions with the highest scores. We will use descriptions, tables, figures, and participant quotes for a comprehensive presentation of the findings. It is important to note that, as of August 2024, we have completed the co-design of the intervention package and are preparing validation.

Findings From the Validation Inquiry

Validation of the rough prototype forms a critical aspect of the co-design process. Ideally, validation could have involved practical testing of the rough prototype in a live setting. However, due to limited resources, we chose to gather insights into women in IGAs who were not included in the initial HCD steps. The findings from FGDs will be synthesized, categorized, and presented. Insights about the features appealing to participants, potential benefits, and modifications or key considerations to improve the implementation success of the rough prototype model will be considered. Individual and summative rating scores of the prototype will be examined and presented in a tabular form. Likewise, the findings will be supported with relevant quotes from the participants.

Findings From Prototype Refinements or Adaptation Model

The findings from the discussions between the research team and MCH stakeholders will form the key components of the HCD process. A summary of the discussions regarding the validation of the rough prototype and key considerations for the final prototype generation will be developed. The refinements, adaptations, and the final prototype will be presented. The presentation will be accompanied by the figure presenting the final prototype and relevant participants' quotes.

Dissemination Plan

Pertinent to the development of a final prototype, the dissemination plan has been devised. The findings of this study will be disseminated through institutional forums (with Aga Khan University) such as university depositories, research meetings, and journal clubs. The summary of the findings in terms of presentations and technical briefs will also be disseminated through national, regional, and district forums to encourage local adoption. We envision disseminating the findings to the international scientific communities through publication in high-impact journals and conference presentations.

Discussion

Principal Findings

This study is designed to co-design an intervention package for equipping women in IGAs with essential capabilities to deal with MCH challenges using an iterative process of HCD. The key findings of this inquiry are expected to be 4-fold. First, the finding from the community-driven inquiry with a focus on the potential impacts of IGAs on MCH, women's engagement practices and challenges hindering IGAs from being used as an entry point to prepare women members to address MCH challenges. The findings will be discussed given previous studies that have examined women's engagement in IGAs and the potential contribution of IGAs on women, children, and family health [27-33]. Further, the implications of women's engagement in IGAs on MCH, opportunities for improvements, and barriers that require novel approaches for addressing them will be discussed given previous studies with an emphasis on how HCD forms a promising entry point.

Second are the findings from the co-design sessions with a focus on an emerging rough prototype proposed to address identified challenges. The emerging prototype will be compared with previous interventions for addressing women's MCH challenges [10-12,17,19-23]. A critical comparison of the potential strengths, weaknesses, opportunities, and threats of the emerging prototype given the previous interventions to improve women's readiness to handle MCH challenges will be made. We should note that the data management and analysis for this stage are currently in progress.

Third, are the findings from the validation inquiry with a focus on the methodological approach (insight gathering) and adaptations needed to improve the effectiveness of the rough prototype. This step is pivotal to the co-design process. A comparison of our approach (insight gathering) and validation approaches used in previous studies will be made [35,38]. Likewise, the quality of findings of validation through insight gathering in our study will be viewed through the lens of those emerging from previous studies applying similar or different approaches. A methodological question to be answered during the discussion is whether the findings generated through insight gathering suffice amid concerns of limited resources for live rough prototype testing. The section will conclude with how the insights gathered shaped the rough prototype and considerations for future studies on using this strategy when financial resources are limited.

Fourth and finally, are the findings from refinement and adaptation meetings with MCH stakeholders forming the final prototype. Again, a comparison of the methodological approach for the refinement stage used in previous studies will be made. Most importantly, the considerations made by MCH stakeholders to arrive at the final prototype and the refinements made will be discussed and compared with previous literature on interventions for addressing income-related MCH challenges.

Limitations

To the best of our knowledge, this is the first study to examine the potential value of IGAs in addressing MCH challenges by using the HCD approach, however, it is not without limitations. The first limitation is that some HCD steps used in this study are not similar to the conventional steps described in previous literature [34,35,37,38]. However, this is a recognition of the growing emphasis that HCD need not be prescriptive, rather, steps should be adapted based on expertise, resources, participants, and contexts [38]. Second, we only used VICOBA as exemplars of IGAs, however, we acknowledge the existence of a wide range of IGA groups that could be leveraged to improve women's readiness to address MCH challenges. While our findings form the basis of exploring this avenue, future

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inquiries may seek to engage women in groups other than VICOBA. Third and final, while we largely refer to and focus on "women in IGAs," we acknowledge the role of male partners in MCH care. Exploring male engagement in IGA and whether such engagement could improve women's readiness and resilience is not a primary focus of this study. However, attempts will be made to draw on men's perspectives about women's participation in IGA and the potential contribution to addressing MCH issues, particularly during co-design sessions which are expected to engage male participants.

Conclusions and Future Recommendations

The HCD approach is an innovative and iterative approach to advance global health and holds a promising opportunity for addressing MCH challenges through the engagement of women in the co-design of effective, sustainable, and acceptable interventions. The study presents an opportunity to apply the HCD approach in designing interventions for addressing income-related barriers to MCH care among women capitalizing on their engagement in IGAs. By actively involving women from IGAs and key stakeholders, we aim to develop an intervention package that not only empowers women economically but also equips them with the resilience and readiness to address MCH barriers effectively. The results of this study have the potential to inform future MCH interventions in low-resource settings and contribute to the global efforts to reduce MMR and U5MR.

Acknowledgments

The authors acknowledge the financial support from Aga Khan University. We also extend our thanks to the Regional medical officers, Regional Development officers, Municipal medical officers, and municipal development officers of Arusha and Shinyanga for their support during the implementation of this project.

Data Availability

Our HCD intervention package findings will be shared in future publications, ensuring data transparency. However, for ethical reasons and to protect participant privacy, some details may not be disclosed. Additional data requests can be made through the corresponding author [KGI] at the Aga Khan University.

Conflicts of Interest

None declared.

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Abbreviations

FGD: focus group discussion
HCD: human-centered design
IGA: Income Generation Association
MCH: Maternal and Child Health
MMR: maternal mortality rate
SSA: sub-Saharan Africa
U5MR: under-5 mortality rate
VICOBA: Village Community Bank
WHO: World Health Organization

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Protocol

Virtual Hospitals and Patient Experience: Protocol for a Mixed Methods Observational Study

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Abstract

Background: Virtual care is increasingly incorporated within routine health care settings to improve patient experience and access to care. A patient's experience encompasses all the interactions an individual has with the health care system. This includes a greater emphasis on actively involving carers in the decisions and activities surrounding a patient's health care.

Objective: This study aimed to investigate the variety of health care delivery challenges encountered in a virtual hospital and explore potential ways to improve the patient experience.

Methods: Focusing on acute respiratory, this protocol outlines a mixed methods study exploring the patient experience of a virtual hospital in Australia, Royal Prince Alfred Virtual Hospital (rpavirtual). We will use an exploratory mixed methods approach comprising of secondary data analysis, observations, interviews, and co-design focus groups. Participants will include patients, their carers, and health care workers who are involved in the acute respiratory virtual hospital model of care. Together, the data will be triangulated to explore views and experiences of using this model of care, as well as co-designing recommendations for further improvement.

Results: Findings from this study will identify current barriers and facilitators to implementing virtual care, such as work-as-done versus work-as-imagined, equity of care, the role of carers, and patient safety during virtual care. As of August 2024, a total of 25 participants have been interviewed.

Conclusions: This protocol outlines a mixed methods case study on the acute respiratory model of care from Australia's first virtual hospital, rpavirtual. This study will collect the experiences of patients, carers, and health care workers to co-design a series of recommendations to improve the patient experience.

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KEYWORDS

virtual care; patient experience; virtual hospital; mixed method; co-design; barriers; facilitators; virtual services

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Introduction

Overview

Virtual health care has expanded across the globe in the wake of the COVID-19 pandemic and has been incorporated into routine health care settings to provide unparalleled access to care [1,2]. However, the push to adopt virtual services has yet to address the challenges and barriers that have risen during their implementation. This protocol outlines a study to clarify and address challenges to virtual services using patient experience as our benchmark. The context of this study will be the Royal Prince Alfred Virtual Hospital (rpavirtual) acute respiratory model of care. rpavirtual is a virtual hospital located in Sydney Local Health District (SLHD), Australia. The goal of this study is to understand the challenges that influence patient experience and co-design recommendations to improve models of virtual care. This study uses an exploratory mixed methods approach of secondary data analysis, observations, interviews, and co-design focus groups.

The rpavirtual acute respiratory model of care offers virtual health care for patients with mild to moderate respiratory illness which can include community-acquired pneumonia, COVID-19, Asthma, or exacerbation of other chronic lung diseases. Suitable patients are referred through the emergency department or their community general practitioner. These patients are provided with a supply of medication and the rpavirtual wearables pack (which contains an oximeter, thermometer, and patient information documentation). The model of care includes 24/7 nursing support, daily virtual medical reviews by phone or video call, 24/7 email messaging, and other care or monitoring tasks as required. Upon discharge, patients are referred to allied health clinicians as required.

Background

Virtual hospitals have been implemented globally, such as in the United Kingdom, the United States, Australia, Germany, India, Canada, and Saudi Arabia [3-8]. Virtual hospitals aim to deliver hospital-level care remotely through video conferencing, remote monitoring, digital platforms, and linking hospital services with community health care [1,2]. One of the first virtual hospitals was the Atuline Virtual Hospital, which was registered in the European Union in 2001 and was established by a Finnish company to offer online medical consultations and e-prescriptions [5]. In the United States, the Mercy Hospital Virtual Care Centre has been operating in St. Louis, Missouri since 2015, providing rural patients with access to health care providers and specialists (eg, neurologists, intensive care unit clinicians, and stroke care specialists) [8]. In February 2020, the SLHD launched rpavirtual, the first Australian virtual hospital [9]. The aim of rpavirtual is to support patient flow in the district's acute hospitals by delivering more care in the community, reduce avoidable emergency department presentations, lower hospital admissions, minimize length of stay, enhance the patient experience of care, and inform the broader adoption of virtual health care in the district. In March 2020, rpavirtual had to quickly pivot its focus and respond to the increasing demand for health care services in the COVID-19 pandemic [3].

There is increasing motivation to incorporate hybrid models of care following the COVID-19 pandemic. Notable successes were identified in certain medical specialties such as internal medicine, psychiatry, preventative medicine, surgery, neurology, dermatology, pediatrics, and infectious diseases [10,11]. In addition, a range of visit types was reported to be appropriate for virtual care, such as chronic condition management, rehabilitation, dermatological concerns, mental health support, maternity and parenting services, or matters where there is a pre-established patient-provider relationship (eg, prescription reviews, established diagnoses, or a lack of complex physical examinations) [10,12,13]. Reported findings, pre– and post–COVID-19 pandemic, also indicate that access to virtual care can reduce the burden on in-person resources, assist patients in avoiding transmissible diseases, and empower patients to take a more active role in their own health care [1,2,14]. These benefits should translate to positive patient safety outcomes, reduced hospitalizations, early discharge, and promotion of greater linkages with primary care services [15].

Patient experience is a broad dimension of patient care that describes the quality of interactions patients have with the health care system, health care workers, services, carers, and virtual care technologies [16]. This is an important dimension for virtual models of care as it indicates the ongoing acceptance and trust a patient has in their health care and the likelihood of successful performance in the long run [7-11]. To improve patient experience, patients and carers need to be actively involved in the decisions surrounding their health care both with individual care and health care service design [17,18]. In this study, authors analyze patient experience with a broad lens to be able to assess patient's preferences and acceptability of interactions with virtual care services, technology, the virtual hospital, health care workers, and carers [1,2]. This metric has become more pressing with the changing environment of health care in Australia. Initial studies report higher levels of patient satisfaction and a willingness to use virtual care again in the future in comparison with earlier virtual care studies pre–COVID-19 pandemic [19]. For example, the study by Manski-Nankervis et al [20] reported that 94% (469/499) of participants found telehealth as an acceptable way to receive health care services in a primary care setting and 97% (485/499) of participants responded that they were comfortable using telehealth technologies.

Despite the great strides made in virtual hospital development, there are still barriers to effectively integrating virtual care within routine health care settings [21-29]. Many challenges identified often stem from the patient experience, such as digital literacy [29], technological difficulties [21-23], unintended burdens on patients [24-26], unintended impact on their carers [25,26], patient safety concerns [29], and questions on privacy and how to ensure confidentiality [22].

There have been studies that have proposed methods of addressing barriers and challenges of video consultations following the COVID-19 pandemic [30,31]. However, few studies have examined the patient experience of virtual hospitals or investigated whether patients are appropriately supported during virtual care [22,26,28]. To explore this area, this study includes the perspectives of health care workers and carers with

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the aim of understanding their contribution to the patient experience. To summarize, we will investigate patient, carer, and health care worker experiences, identify the challenges of virtual care, and co-design recommendations to improve the patient experience of rpavirtual's acute respiratory model of care.

Aim

This study aims to understand and improve the patient experience of the rpavirtual acute respiratory model of care.

Objectives

First, identify the current patient experience of rpavirtual's acute respiratory model of care using secondary data and primary observations.

Second, identify the challenges that currently influence the patient experience during virtual care by observing and interviewing a range of stakeholder groups. This includes patients, carers, and health care workers.

Third, co-design a concise, practical, and realistic list of recommendations to mitigate any challenges from engaging with rpavirtual to improve the patient experience of the acute respiratory model of care.

Methods

Study Setting

The setting of the study will be a virtual hospital based in Sydney, Australia (rpavirtual). This is the first Australian virtual hospital [9], located in the SLHD. The SLHD is an area of Sydney that contains 5 hospitals, 4 large community health centers, and 12,000 staff members and is responsible for the health of over 700,000 individuals [32]. The rpavirtual acute respiratory model of care provides patients with acute respiratory illnesses with at-home medical devices (eg, pulse oximeter and digital thermometer) to enable remote monitoring and access to hospital support in the home [4,9].

Study Design

This study will use an exploratory mixed methods approach to explore patient experience using virtual care. The structure will comprise of four stages, that are (1) analyzing existing patient data, (2) observing virtual consultations, (3) interviewing participants, and (4) holding focus groups (Figure 1).

Figure 1. Study process diagram. PREMs: patient-reported experience measures.

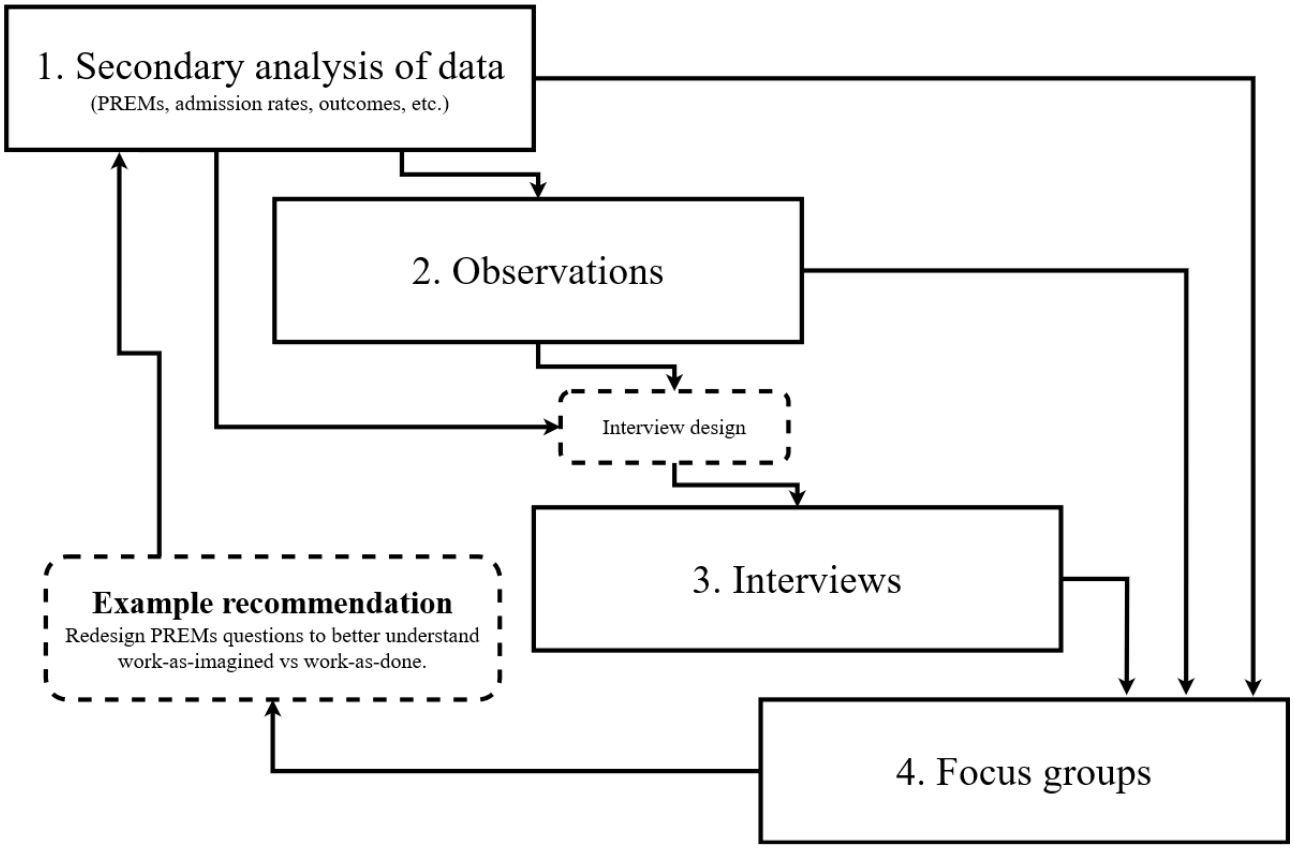

Considering the innovative nature and relative novelty of virtual hospitals, we designed a comprehensive method, drawing on existing approaches to investigate new phenomena [33,34], explore complex systems [35], and gain a holistic understanding of an event or interaction [36]. The aim is to produce a practical list of recommendations for improvement founded on action-based evidence [37].

Research activities of secondary analysis of routinely collected data, observations, and interview activities shall run simultaneously (ie, insights from different stages may inform other activities simultaneously). The interviews shall follow a semistructured design to adapt to insights from other research stages while upholding participant anonymization. Microsoft Teams will be used to transcribe observation recordings and

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interviews with participants. The accuracy of the transcription is checked by authors KW and AL.

Stage 1: Secondary Data Analysis

The initial stage of this research study is the analysis of secondary data collected from standard hospital procedures as part of the acute respiratory model of care. This is the preliminary stage of the mixed methods design to understand complex systems through a quantitative foundation [35]. The data used for analysis will include patient-reported experience measures (PREMs), readmission rates, length of stay, mortality, and adverse outcomes. Descriptive statistical analysis on patient demographics and patient experience will be conducted, using deidentified electronic medical records (eMRs) and anonymized PREMs data sets. PREMs survey responses will be tested using standard statistical tests (including but not limited to factor analysis) to identify potential relationships between participant groups and their responses. This data will also be used to inform the study design of prospective data collection approaches (observations, interviews, and focus groups), and in triangulation of data analysis with the other research activities.

Stage 2: Consultation Observations

The second stage involves observations of current practices in the acute respiratory model of care at rpavirtual. This is the first qualitative stage of the mixed methods design with the aim of understanding the current process of providing virtual care [36]. The observations will take place in virtual consultations with patients. The audio and video will be recorded using external audio devices or Microsoft Teams and field notes will be created.

Content analysis and other qualitative data analysis approaches will be used to understand the patient experience of rpavirtual (eg, thematic analysis, conversation analysis, and linguistic ethnography). The type and range of data analysis approaches will be subject to the sample size and variances of observations we are able to obtain during the data collection of the research study. We will explore how information is communicated between clinician, patient, and carer (eg, how patients and carers notify clinicians of results collected from patient-facing digital devices such as an oximeter during virtual consultations). Quantitative descriptive statistical tests will also be used to compare consultations with each other and the literature (eg, length of consultation and frequency of mentioning use of patient-facing digital devices during consultation). This data will also be used in triangulation with the other research activities.

Stage 3: Interviews

The third stage is a series of interviews with individuals involved in the acute respiratory model of care. This includes health care workers, patients, and their carers. The aim of this stage is to explore known challenges identified from the perspectives of health care workers, patients, and carers [38]. The interviews will last from 30 to 40 minutes. Video and audio will be recorded using an external audio device and Microsoft Teams and transcribed verbatim. Unknown challenges will be identified and analyzed using an inductive approach, where we will collect patient experience perspectives through interviews and narratively analyze the data to make sense of the individual participants' responses. The qualitative methods of constant comparison and axial coding shall be used to identify the relationships and themes between responses, comparing similarities and differences between responses to sort the data [39]. Then, we will explore any issues unraveled to improve the patient experience. Individual biases will be addressed by triangulating different sources of data (ie, deidentified routinely collected data from rpavirtual, observations made by researchers, and interview self-reported data by research participants). Using multiple methods and sources help counteract biases inherent in any single approach, leading to more objective conclusions. Multiple researchers will be involved in the data coding and analysis stages to reduce the impact of individual biases.

Stage 4: Co-Design Focus Groups

The fourth and final stage of this research is a series of focus groups. Focus groups are a useful method to explore the experiences, attitudes, and challenges of different stakeholder groups [40]. They achieve this by emphasizing group interaction and fostering group discussion of ideas [41]. We will follow the co-design framework of Boyd et al [42], which used patient journey mapping, experience-based surveys, and co-design workshops to improve the patient experience. We have also included the modification suggested by Yeates et al [43] of including a refinement stage [43]. We will undertake a collaborative approach, conducting a series of focus group workshops to delve deeper into developing solutions to barriers and challenges identified.

Preliminary findings from the previous stages of the study will be explored in the focus groups. We will intentionally involve participant groups in designing solutions and recommendations through a participatory approach. We will gather feedback, synthesize feedback into insights using a thematic and comparative analysis, and develop solutions and recommendations based on that feedback.

The aim here is to co-design concise and realistic recommendations to improve the patient experience. Each participant group (health care workers, patients, and carers) will have a focus group to discuss potential challenges they have encountered. A final focus group, using a combination of individuals from different participant groups, will synthesize the key points from the previous groups. All focus groups will range from 50 to 60 minutes. Audio will be recorded and transcribed verbatim.

Participants

A total of 3 participant groups have been identified in this study. First, health care workers—any worker involved in the virtual care of patients under the acute respiratory model of care at rpavirtual. This includes medical doctors, nurses, technical support staff, and allied health staff. Second, patients—any individual who received treatment for an acute respiratory illness. Third, carers—individuals who provide support and care for a patient who has received care under the acute respiratory model of care at the virtual hospital. These could be formal (ie, someone employed to provide a professional carer service such as a paid nurse) or informal relationships (ie,

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someone not employed to provide carer support such as a family member).

Participant numbers have yet to be determined as it is limited to patients admitted to the acute respiratory model of care. The goal of a qualitative study is to reach saturation of knowledge, where relevant, as well as methodology-specific indicators for validity [44]. The saturation of knowledge is based on the level of information gained and triangulated from all research activities, including observations, interviews, focus groups, and PREM survey open-ended responses [45]. In a mixed methods study using qualitative interviews and observations, we shall recruit participants until we reach data saturation, which is often around 5 to 15 participants according to qualitative studies in similar areas [46,47]. Considering the various participant groups, informed by general guides from previous studies, the aim will be for 5 or more individuals from each participant group (health care workers, patients, and carers) but researchers will aim for as many as possible from each group until we reach data saturation [48].

Participant Recruitment

Potential participants will be identified by rpavirtual. Patients will first be asked by their health care worker if they are interested in possibly participating, and if they consent, the research team will share the recruitment material. Patients will be encouraged to ask their carers to participate in the research study, to which if they consent, the REDCap (Research Electronic Data Capture; Vanderbilt University) e-consent form will be forwarded to those patients and carers. The research team does not have access to patient records of the rpavirtual. To motivate patients and carers, a financial gratuity will be offered. Any patient or carers who participate in an interview will receive a gift card of AUD $40 (US $26.71) and if they participate in a focus group will receive a further AUD $60 (US $40.06). A currency exchange rate of AUD $1=US $0.67 is applicable as of September 3, 2024. Financial gratuity will not be offered for observations to reduce potential Hawthorne effect and subject bias. Patients' clinical care will not be impacted by their choice to participate (or not) in consultation observations. Health care worker staff members will be recruited through internally shared promotional videos, internal education sessions and presentations, and word of mouth.

Consent Process

In addition to obtaining written consent or e-consent, participants will be asked for verbal consent before involvement in any observation, interview, and focus group activity. Consent will be requested at multiple stages and at each stage the participant will be reminded that they can withdraw their consent and exit the study at any time. They will also be informed that withdrawing from the study will have no impact on their employment, the health care provided to them, or their relationship with the research team and the universities conducting the study. Participants will have the option to consent to each individual research activity (eg, observations, interviews, and focus groups). Only currently admitted patients may be included in the consultation observations. Current or discharged patients may be included in interviews and focus groups. Email and SMS reminders will be sent to participants (up to 2 times over 2-4 weeks). Consenting discharged patients may participate in interviews and focus group activities. In the scenario when e-consent cannot be elicited before a consultation, verbal consent from all parties may be elicited during the consultation and before recording the consultation. The research team will continue to elicit e-consent from all parties involved after the consultation recording. Therefore, discharged patients may complete an e-consent form for the research team getting access to their consultation recordings, which were collected and recorded with their verbal consent while being admitted. If there is no response after following up, researchers will assume that the individual does not wish to participate and will cease follow-up contact.

Step 1: Identification of Potential Participants

The research team at Macquarie University (MQ) will provide study material, the participant information consent form, and advertisement material to rpavirtual to be disseminated to potential participating health care workers, patients, and carers of consenting health care workers, seeking permission for MQ researchers to contact them. MQ researchers will then initiate contact with the potential participant using their preferred contact mechanism, or at their next interaction with the participating virtual hospital clinician.

Step 2: First Contact With Potential Participant

Initial contact may occur in the following ways: participant reaches out to MQ researchers for more information, MQ researcher contacts potential participants through their preferred contact channel after they have consented to their health care worker, or during their virtual consultation session to explain the study and elicit their informed consent (written and verbal) after the patients have expressed interest through their health care workers.

Step 3: Further Information Given

Potential participants will be provided the participant information packet and REDCap e-consent form through SMS or email or web link. Once the study promotion material is disseminated, the contact point will be MQ researchers. Potential participants are to be provided an opportunity to ask questions about the study either by email, telephone, or face-to-face before signing a consent form.

Step 4: Return of Consent Forms

Participant returns signed REDCap e-consent form. If no response, researchers will follow up with the participant (up to 2 times over 2-4 weeks). In the scenario when e-consent was not elicited before recording a consultation, the research team will continue to elicit e-consent from all parties involved after the consultation recording before gaining access to conduct analysis. If no response after following up, researchers will assume the individual does not wish to participate and cease follow-up contact.

Privacy and Data Security

Electronic consent forms will be stored on REDCap using the SLHD license. Electronic consent forms will be securely archived in the study REDCap project. Hard copies of written consent forms will be securely stored at rpavirtual Research and

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Evaluation Hub in a locked filing cabinet only accessible to the research team.

We will use the following methods to protect the data collected. Access restrictions (physical key lock and passwords), deidentification (anonymized data), and storing on institutional networks at rpavirtual and MQ. Deidentified eMR and anonymized PREMs data will be stored securely in MQ Microsoft Teams and deleted 5 years after analysis is completed. External audio devices and Microsoft Teams will be used to record observations, interviews, and focus groups. Personal mobile devices will not be used for audio recording or video recording. Only investigators in the research team have access to the data collected.

A custom-made software was developed in-house to blur the faces of individuals appearing in consultation videos, ensuring the privacy of participants before analysis.

Ethical Considerations

Human Participants Ethics Review Approvals or Exemptions

This research involves humans, medical records, patient information, observations of public behaviors, or secondary data analyses. This study adheres to appropriate ethical review and approvals, as per institutional guidelines. Ethical approval for this project was obtained from the Macquarie University Human Research Ethics Committee for Medical Sciences (reference 520231595552727) and the Sydney Local Health District Ethics Review Committee (Royal Prince Alfred Hospital Zone; reference 2023/ETH01269). The project has been approved and supported by the rpavirtual Research Steering Committee.

Informed Consent

Participants of this research study are provided the opportunity for informed consent. Participants are to be provided the ability to withdraw from the study up until the point of the data being deidentified for analysis. For secondary analyses of routinely collected data (ie, PREMs), original consent was obtained by rpavirtual with the original consent covering secondary analysis without additional consent.

Privacy and Confidentiality

Primary data collected (ie, interviews, focus groups, observations, and eMR data) will be stored and analyzed in a deidentified format. Secondary data collected from routinely collected data (ie, PREMs) will be collected, stored, and analyzed in a deidentified and anonymized format.

Compensation Details

Any patient or carers who participate in an interview will receive a gift card of AUD $40 (US $26.71) and if they participate in a focus group will receive a further AUD $60 (US $40.06). Health care workers will not receive any financial gratuity for participating in this research study.

Results

The project has started recruitment of participants for observations and interviews. As of August 2024, over 25 participants have been interviewed. All recorded consultations, field notes, interviews, and focus groups will be recorded and transcribed verbatim. The software NVivo (Lumivero) will be used to manage transcripts and analysis. Triangulation [38], content [49], and thematic analysis will be used to identify commonalities. The analysis of our study shall potentially investigate any or all of the barriers and challenges identified, and the known or unknown solutions from the perspectives of patients, their carers, or health care workers. Open coding will also be used to identify any additional themes not previously uncovered [36]. The context and associated factors of the consultation will be analyzed through linguistic ethnography. Each aspect of patient experience shall be triangulated to provide a comprehensive analysis. We anticipate results to (1) narrate patients experiences with rpavirtual services, the role of patients' carers, and their interactions with virtual care services; (2) list and detail known challenges, unknown challenges, successes, and types of patient interactions with virtual care; and (3) create realistic and comprehensive solutions to the challenges identified to improve upon the narrated patient experiences with rpavirtual services.

Discussion

Principal Findings

This paper outlines an ongoing study investigating patient experiences of using rpavirtual's virtual hospital services in the acute respiratory model of care, aiming to identify the types of challenges and propose solutions. By using a mixed methods approach of observations, interviews, focus groups, and analysis of routinely collected data, we will provide a comprehensive analysis of the current patient experience and challenges. Our exploratory approach aims to map patients' journeys, providing case studies of interactions that result in positive patient experiences or may benefit from further support, involving patients' carers and health care workers. By triangulating insights from these perspectives, we aim to uncover both realized and unrealized challenges, contributing important insights to the current literature, and facilitating the co-design of impactful solutions. The findings of this research will be disseminated to metropolitan, national, and international audiences through publication in peer-reviewed journals and presentations at scientific conferences.

Strength and Limitations

This study's strength lies in its mixed method approach (routinely collected PREMs, observations, interviews, and focus groups) with multiple stakeholders (patients, carers, and health care workers) to investigate the patient experience of a virtual hospital. Existing methods of collecting patient experience information (eg, PREMs data) do not consider the perspectives of health care workers or carers. Using a multi-method, staged approach ensures we are capturing a comprehensive picture of patient experience from different perspectives. Furthermore, our research team includes a combination of academics with

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expertise in health informatics, mixed methods, clinical science, and the involvement of practicing clinicians (nurses and medical doctors) and key staff from the virtual hospital. The diverse, multidisciplinary research team ensures our research investigations are inclusive and relevant and that findings can be directly applied to improve current practices.

This study does not include clinical and medical data of patients. This level of access is not required to understand the patient experience. The risks of such access are outweighed by the benefits generated for the participant; thus, only basic deidentified administrative data of a patient's admission in the virtual hospital is included in our analysis.

Conclusion

The findings from this study will contribute significantly to the limited research on patient experiences with virtual hospital services, adding new perspectives by using multiple methods and participant groups. The integration of quantitative and qualitative methods will allow the identification and in-depth analysis of realized and unrealized challenges patients, their carers, and health care workers face. We anticipate that insights from this study will guide the development of targeted solutions to address unmet needs and challenges, facilitating the co-design of practical and meaningful solutions to enhance patient experiences in this health care setting.

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Authors' Contributions

Study conception was contributed by AYSL, OH, SS, and SW. Study design was managed by all authors. First draft of manuscript was written by TMJ, KW, and AYSL. Manuscript revision and approval were performed by all authors. The authors TMJ and KW contributed equally for this paper and request to be treated as co–first authors.

Conflicts of Interest

None declared.

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Abbreviations

eMR: electronic medical record
MQ: Macquarie University
PREM: patient-reported experience measure
REDCap: Research Electronic Data Capture
rpavirtual: Royal Prince Alfred Virtual Hospital (a hospital in Sydney, Australia. Part of the SLHD)
SLHD: Sydney Local Health District (a collection of health services and hospitals run by the Australian Government in Sydney, Australia)

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Protocol

Fostering Shared Decision-Making Between Patients and Health Care Professionals in Clinical Practice Guidelines: Protocol for a Project to Develop and Test a Tool for Guideline Developers

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Abstract

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Background: Clinical practice guidelines (CPGs) are designed to assist health care professionals in medical decision-making, but they often lack effective integration of shared decision-making (SDM) principles to reflect patient values and preferences, particularly in the context of preference-sensitive CPG recommendations. To address this shortcoming and foster SDM through CPGs, the integration of patient decision aids (PDAs) into CPGs has been proposed as an important strategy. However, methods for systematically identifying and prioritizing CPG recommendations relevant to SDM and related decision support tools are currently lacking.

Objective: The aim of the project is to develop (1) a tool for systematically identifying and prioritizing CPG recommendations for which SDM is considered particularly relevant and (2) a platform for PDAs to support practical SDM implementation.

Methods: The project consists of 6 work packages (WPs). It is embedded in the German health care context but has an international focus. In WP 1, we will conduct a scoping review in bibliographic databases and gray literature sources to identify methods used to foster SDM via PDAs in the context of CPGs. In WP 2, we will conduct semistructured interviews with CPG experts to better understand the concepts of preference sensitivity and identify strategies for fostering SDM through CPGs. WP 3, a modified Delphi study including surveys and focus groups with SDM experts, aims to define and operationalize preference sensitivity. Based on the results of the Delphi study, we will develop a methodology for prioritizing key questions in CPGs. In WP 4, the tool will be developed. A list of relevant items to identify CPG recommendations for which SDM is most relevant will be created, tested, and iteratively refined, accompanied by the development of a user manual. In WP 5, a platform for creating and digitizing German-language PDAs will be developed to support the practical application of SDM during clinical encounters. WP 6 will conclude the project by testing the tool with newly developed and revised CPGs.

Results: The Brandenburg Medical School Ethics Committee approved the project (165122023-ANF). An international multidisciplinary advisory board is involved to guide the tool development on CPGs and SDM. Patient partners are involved throughout the project, considering the essential role of the patient perspective in SDM. As of February 20, 2024, we are currently assessing literature references to determine eligibility for inclusion in the scoping review (WP 1). We expect the project to be completed by December 31, 2026.

Conclusions: The tool will enable CPG developers to systematically incorporate aspects of SDM into CPG development, thereby providing guideline-based support for the patient-practitioner interaction. Together, the tool for CPGs and the platform for PDAs will create a systematic link between CPGs, SDM, and PDAs, which may facilitate SDM in clinical practice.

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KEYWORDS

shared decision-making; practice guidelines as topic; decision support techniques; support; decision-making; decisions; tool; testing tool; protocol; medical decision-making; patient decision aid; decision aid; tool development

Introduction

Background

Clinical practice guidelines (CPGs) are systematically developed statements that provide evidence-based recommendations for decision-making by health care professionals and patients regarding appropriate care for particular health problems [1,2]. However, CPG recommendations should be contextualized to a patient's personal circumstances, making it essential to apply a person-centered CPG approach [3,4]. Therefore, CPGs aim to support medical decision-making that considers the values and preferences of patients [4].

Shared decision-making (SDM) is an established procedure that supports patients and health care professionals in making joint decisions on health issues [5,6]. To reach a shared decision, discussing the possible options and supporting the patient to become aware of their individual preferences are essential SDM steps to be considered in practice [6,7].

SDM is desired by patients and expected from health care professionals when implementing CPG recommendations [8]. However, initial studies indicate that in their current form, CPGs are only suitable to a very limited extent for supporting health care professionals in engaging in SDM [9-11]. Additionally, data from implementation research and health care professionals' practical experience with CPGs indicate that guideline-associated barriers impede the implementation of SDM in clinical practice: First, there commonly exists a risk that health care professionals misunderstand CPG recommendations as strict instructions to follow in any case, regardless of patient preferences [4,12]. A survey among health care professionals revealed that they perceive stronger and weaker recommendations as equally binding [13]. Second, depending on the health care system mode, the development of guideline-based quality indicators and the resulting nonfinancial and financial incentives for a health care facility (eg, certification and remuneration) can contribute to health care professionals following a recommendation rather than discussing the available treatment options with patients [4,14]. In particular, this applies to possible legal consequences such as malpractice claims [15]. From the perspective of SDM researchers, CPGs have been repeatedly criticized for hindering rather than promoting person-centered decision-making [4,11,16,17].

To overcome these barriers, it is necessary to integrate tools and use a variety of strategies, which enable SDM through CPGs and facilitate the implementation of SDM in clinical practice

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[4,5]. Therefore, it is important to first identify the CPG recommendations that are particularly relevant to SDM [4,7,18]. Evidence suggests that SDM is appropriate when faced with preference-sensitive options, where the choice of option depends largely on the individual preferences of the patient [4,5,7]. Preference-sensitive decisions are typically decisions in which there exist multiple options, but either the value that patients place on the associated benefits and harms differ or the available options are relatively balanced in terms of their benefits and harms [4,7]. Regarding the Grading of Recommendations, Assessment, Development and Evaluation methodology, conditional recommendations imply discussion of benefits and harms with patients [19]. However, it must be emphasized that the degree of preference sensitivity does not necessarily depend on the certainty of evidence.

When faced with such preference-sensitive decisions, decision support tools can be used to facilitate decision-making [4,18]. Decision support tools include, for instance, patient versions of CPGs, decision trees, and patient decision aids (PDAs) [4]. However, of these tools, particularly PDAs used during clinical encounters have the purpose of enabling SDM [4]. PDAs are available in various formats, such as booklets, leaflets, videos, or web-based resources [20]. In this project, we focus on PDAs that meet least the following elements [21-25]: (1) they provide evidence-based information about available treatment options, including their potential benefits and harms, to a specific patient target group and (2) they aim to facilitate decision-making and encourage SDM by empowering patients to explore their values and preferences regarding the available options.

PDAs cover different types of decisions (eg, prevention, diagnosis, and treatment) and are available for many different conditions and health problems (both acute and chronic) [22,25].

By establishing a more robust link between CPGs and PDAs, it is possible to translate general CPG recommendations into personalized recommendations for SDM processes more effectively [4,16]. Overall, there is consensus that PDAs can be a vehicle by which CPGs and SDM can be linked [4,26].

In addition, there is high-quality evidence that PDAs as a tool for SDM can improve patient-relevant outcomes [20,27]. However, research indicates that despite the proven benefits of high-quality PDAs, they are not being used enough in practice likely due to inadequate resources for continuous updating or because of health care professionals' reluctance to accept them when not having been involved in their development [28-30]. In contrast, studies show that health care professionals consider brief, guideline-based PDAs to be valuable for practice [12,31].

At expert workshops hosted by the German Network for Evidence-Based Medicine (EbM-Network; on September 1, 2022, as part of the EbM Congress) and the Guidelines International Network (GIN; on September 24, 2022, as part of the GIN Conference) [32], national and international CPG developers unanimously formulated a high need for a tool that could aid in the structured prioritization of CPG recommendations according to their relevance for SDM as well as for a repository or database for guideline-based PDAs. Currently, there are no tools available for the systematic identification and prioritization of CPG recommendations with high SDM relevance [4].

Objectives

We aim to develop a tool that will enable CPG developers to systematically identify and prioritize CPG recommendations for which SDM is considered particularly relevant. The tool for CPGs will be generic and can be used regardless of the underlying condition or health problem. In parallel, we aim to develop a platform for PDAs. While we focus on German CPGs for practical reasons, the project has a clear international focus and aims to inform CPG development worldwide.

Methods

Overview

The project, titled Development and testing of a tool to foster shared decision-making in clinical practice guidelines [Entwicklung und Testung eines Instruments zum Einbezug von Shared Decision-Making in Leitlinien; acronym EDELL], is funded by the German Innovation Fund and affiliated with the Brandenburg Medical School Theodor Fontane in cooperation with 3 consortium partners, including the German Agency for Quality in Medicine, Clinical Guideline Services GmbH, and SHARE TO CARE Patient-Centered Care GmbH. The guidelines working group of the German EbM-Network supports the project as a cooperation partner.

Study Design

The project comprises 6 work packages (WPs) and will run over 3 years (Q4 2023 to Q4 2026; Figure 1). WPs 1 to 3 serve as preparation for developing and testing the tool afterward in WPs 4 and 6. WP 5 runs parallel to the other WPs by developing a platform for PDAs to complement the tool.

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Figure 1. Overview of the project course. API: application programming interface; CPG: clinical practice guideline; PDA: patient decision aid; Q: quarter; SDM: shared decision-making.

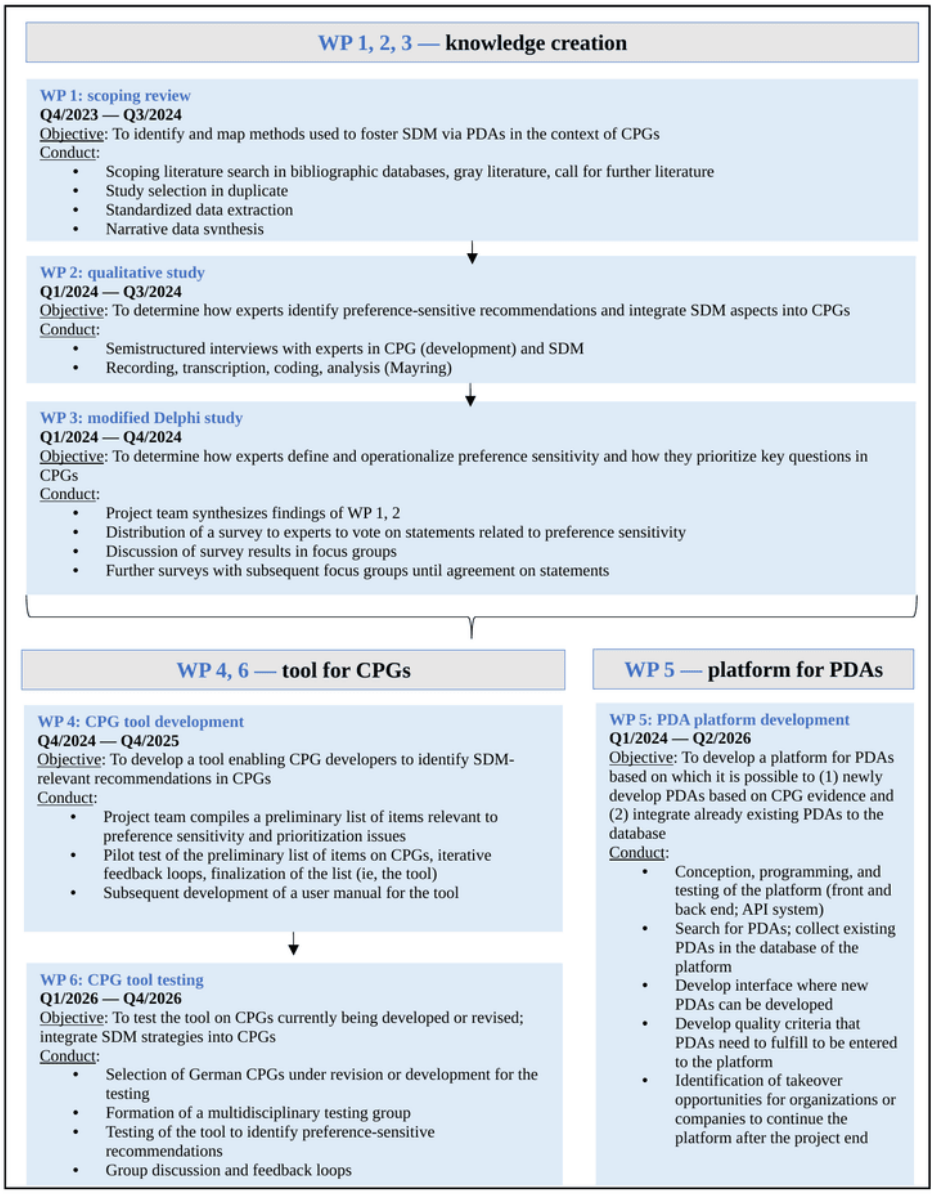

In WP 1, we aim to summarize the methods currently used to foster SDM via PDAs in the context of CPGs. In WP 2, we will conduct interviews with international experts to determine how preference-sensitive recommendations can be identified and how SDM can be successfully implemented in CPGs. In WP 3, a modified Delphi study with SDM experts will be conducted, aiming to define and operationalize preference sensitivity and develop a methodology for prioritizing key questions in CPGs. WP 4 will concern the actual development of the tool by generating items that are relevant for the identification of SDM-relevant recommendations. Subsequent evaluation of the tool's first version will follow. In WP 5, our aim is to develop a digital platform that will provide (1) a toolkit for the development of PDAs and (2) a database for German language PDAs. Finally, in WP 6, practical testing of the tool within selected CPGs will follow.

WP 1: To Identify and Map Methods Used to Foster SDM Through PDAs in the Context of CPGs—A Scoping Review

Objective, Literature Search, and Eligibility Criteria

In WP 1, we will conduct a scoping review, which adheres to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews) [33] and follows the updated methodological guidance for the conduct of scoping reviews proposed by the JBI (formerly Joanna Briggs Institute) [34].

To provide an overview of methods to foster SDM via PDAs in the CPG development process, we will use the GIN Public Toolkit—Patient and Public Involvement in Guidelines as a starting point [4]. To account for the progress after the publication of the GIN Public Toolkit, we will update the current state of knowledge by conducting a scoping review in relevant scientific databases (PubMed and Embase; see Multimedia

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Appendix 1 for full search strategy). To account for research-relevant information that is not formally published [35], we will additionally search in Google and Google Scholar. The search will be restricted to studies published since 2000, as the link between CPGs and PDAs is relatively new [3,4]. References will be eligible for inclusion if they meet all the following criteria: they are published from the year 2000 onward, provide information about the methodology of developing and integrating PDAs in the context of CPGs, are available in German or English, and have full texts available. The exclusion will apply to studies not focusing on PDAs but on other patient-directed knowledge tools, such as the patient version of CPGs.

As part of the scoping review, handbooks, method manuals, and other documents of international CPG organizations that are known for providing patient-directed knowledge tools [36] (see Multimedia Appendix 2 for a list of organizations) will be sought via their websites. To obtain additional information on methods for the development and integration of PDAs in the context of CPGs, we will contact experts via the earlier-mentioned CPG organizations [36] and via GIN. Ideally, this will help to identify CPGs that have already systematically integrated PDAs, as the applied methods for doing so cannot be easily identified using other research techniques. After removing potential duplicates, 2 reviewers (LF and LVS) will independently screen all identified literature based on title and abstract for eligibility. They will independently continue with a full-text screening of references found to be eligible at the title and abstract screening stage. A list with the reasons for excluding full texts will be compiled, while disagreements will be resolved through discussion and by contacting a third reviewer (DP) for advice.

Data Collection and Analysis

One reviewer (LF) will extract findings into standardized tables, which the second reviewer (LVS) will double-check. The extraction tables will contain categories of general study and method manual characteristics, such as title, publication year, authors, and their corresponding CPG organization. Additionally, information concerning the methods for developing and integrating PDAs in the context of CPGs will be extracted. Disagreements will be again resolved through discussion, and consensus will be reached by the judgment of a third reviewer (DP). The generated information will be narratively synthesized.

WP 2: To Determine How Experts Identify Preference-Sensitive CPG Recommendations and Integrate SDM Strategies Into CPGs—A Qualitative Study

Objective

In WP 2, we aim to explore experts' perspectives on the identification of preference-sensitive CPG recommendations and the successful integration of SDM strategies into CPGs by conducting a qualitative study via semistructured interviews. We will use COREQ (Consolidated Criteria for Reporting Qualitative Research) for planning and reporting [37].

Sampling

For recruitment, we will develop a sample plan to ensure that relevant experts of national and international CPG organizations are adequately presented (ie, selective sampling). By contacting the 17 CPG organizations mentioned earlier [36] and potential other identified relevant organizations, we will continue to recruit experts until we reach data saturation. However, we expect that 10-15 experts will be sufficient to reach data saturation. Their expertise concerns the areas of CPGs, PDAs, and SDM. For example, experts can be either methodologists or health care professionals involved in CPG development.

Interview Guide

The consortium and all collaborators will conceptualize an interview guide before the interview. The developed interview guide will be piloted in the first interviews and adapted if necessary. The guide will include preformulated open questions related to the project topic but will focus in particular on questions concerning (1) What is meant by preference sensitivity? and (2) How can SDM be successfully integrated into CPGs? All interviewees will receive the interview guide in advance.

Data Collection and Analysis

The interviews will be conducted by telephone or videoconference and digitally recorded. The interviewer will take notes during or immediately after the interview. Conducted interviews will be transcribed, coded, and analyzed using MAXQDA analysis software (standard version 18.2.4; Verbi GmbH). The interviews will be analyzed using qualitative content analysis according to Mayring [38]. A category system will be developed deductively based on the core themes or questions. Further subcategories may be developed inductively. Category building will be discussed within the research team.

WP 3: To Determine How Experts Define and Operationalize Preference Sensitivity and How They Prioritize Key Questions in CPGs—Modified Delphi Study

Objective

WP 3 will start with a workshop to synthesize the results of WP 1 and preliminary results of WP 2, based on which a multistage Delphi study including Delphi focus groups will be conducted. As there has been limited research in the area of preference sensitivity and prioritization of CPG questions with regard to the provision of PDAs, WP 3 aims (1) to provide a clear and generic definition of preference sensitivity and (2) to identify clear criteria for prioritizing CPG recommendations where PDAs may be required. To systematically develop statements on the topics of preference sensitivity and prioritization of CPG questions regarding the provision of PDAs, all members of the core team and the patient partners of the project will participate in the workshop. The subsequent modified Delphi study will be based on the internationally proven RAND/UCLA Appropriateness Method [39]. We will use ACCORD (Accurate Consensus Reporting Document) for reporting [40].

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Sampling

Expert panelists will be recruited through GIN and the International Shared Decision Making Society and invited by email to participate in the Delphi study. We will select the panelists on the basis of their expertise while ensuring representation of relevant perspectives (ie, selective sampling of CPG or SDM methodologists and health care professionals). The Delphi survey rounds will each consist of 20-30 participants, approximately half of whom will actively participate in the Delphi focus groups.

Delphi Process

Based on the workshop conducted in advance, statements on the topic of preference sensitivity will be developed and put to vote. Before distributing the survey to the panelists, the developed statements will be pilot-tested by the Brandenburg Medical School Theodor Fontane and consortium partners to ensure clarity, usability, and functionality. As a first step in the Delphi study, a group of national SDM experts will evaluate and, if necessary, expand criteria that are considered appropriate for SDM. In the second step, international panelists will be asked to consider and vote on the inclusion of statements in web-based Delphi rounds in order to achieve a high level of agreement. Voting will take place on a scale from 1=no agreement to 8=full agreement. To specify the statements for the second Delphi round and the Delphi focus group discussion, a free-text option will be offered for each item. For a statement to be accepted, 75% (n=15-23) of the participants must agree with the statement, defined as a value of 5 or higher. Participants in the Delphi rounds will be sent the respective preliminary results and asked for feedback. As the number of Delphi rounds is difficult to estimate a priori, we will flexibly adapt the number of rounds needed to reach an agreement for statements put to vote. However, most Delphi studies reach agreement within 2 or 3 rounds, which is also assumed to be the case here. A new vote will be taken in each round.

In addition to the written feedback, the Delphi focus group will be held via videoconference. The purpose of the focus group is to reach an agreement on statements that were not agreed upon in the previous survey rounds. With an agenda, background information, consent form, and survey results provided in advance, participants will discuss the statements before a verbal summary and final vote. The results of this Delphi focus group will be recorded and incorporated into the methods to be developed.

WP 4: To Develop a Valid and Reliable Tool Enabling CPG Developers to Identify SDM-Relevant Recommendations in CPGs—Item Generation, User Manual, and Testing

Objective

The findings from the previous WPs will form the basis for the development of the tool to identify recommendations in CPGs that are most relevant to SDM. The methodology for developing the tool is based on the methods from the AGREE II (Appraisal of Guidelines for Research and Evaluation II) portfolio [41]. The process that we will follow, as described below, is geared on the development of the AGREE-REX (Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence) [42,43]. A small working group (consisting of the project partners) will compile a preliminary list of initially relevant items, which will mainly be derived from the results of WPs 1-3. Subsequently, the list will be revised and reduced in terms of focus and objectives as well as potential overlaps between items. At the same time, a user manual will be produced, presenting the items with background, rationale, and explanation.

Items

Items will reflect relevant aspects of preference sensitivity as identified in WPs 1, 2, and 3 as well as aspects of prioritization such as relevance of the clinical decision, burden of disease or treatment, and others. Items will be assessed using a Likert scale. An overall score may be calculated by summing up the individual scores. The use of weighing different items will be assessed by the development team. The higher the total score, the greater the need to provide SDM support for the respective recommendation. The possibility to generate a total score will facilitate the use and interpretation of the tool for subsequent application.

Prioritization

The number of PDAs developed or integrated into a CPG will depend highly on the resources available. The tool will reflect this by providing the possibility to prioritize those recommendations for which decision support seems most needed. Whether a cut-off value or a ranking according to total scores is more helpful will have to be considered.

Testing

The items on the list (ie, the preliminary tool), including the user manual, will be tested on 5 completed CPGs within the working group and then revised. We will ensure that the selected CPGs cover a broad spectrum of (1) conditions and (2) areas of application (diagnosis, prevention, and treatment).

The tool will be applicable to all recommendations of a CPG, regardless of the grade of recommendation. However, it may be discussed whether strong negative recommendations, probably recommendations for emergency settings, are worth rating, given that the addressed intervention is no sensible alternative (no benefit but relevant harm) or the urgency to act does not allow for SDM. The resulting version of the tool will be circulated among the project partners. They will be asked to provide feedback with regard to clarity, completeness, relevance, and user-friendliness. This includes both the items and the overall structure. The group will use the feedback received to revise the tool. This version will then be circulated to the project partners to test the tool against 2 CPGs and provide feedback, which will be followed by another revision and refinement loop. The project partners will finalize the items in a concluding workshop.

WP 5: To Develop a Platform for PDAs

Objective

A key strategy to promote SDM in CPGs is to attach or link PDAs to SDM-relevant recommendations so that health care professionals can directly find the PDA and use it as support

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for the SDM process when their patient is facing a medical decision. In addition, there is currently no platform in Germany that (1) collects already existing PDAs, (2) makes them easy to find, (3) systematically compiles them, and (4) facilitates the creation of machine-readable PDAs through a user-friendly web-based editor. Taken together, we recognized the need to develop a platform for PDAs. With this platform, it will be possible to develop PDAs semiautomatically and to digitize as many of the existing formats of German-language PDAs as possible in a database in order to make them ubiquitously available via an interface for other applications (eg, hospital or physician information systems). The aim is to create a valuable possibility, in particular for those who create CPGs, to link existing PDAs and create new PDAs on key issues with little effort from the evidence syntheses that have been done in advance as part of the CPG work. WP 5 is of central importance for the project, as the development of the tool for CPGs alone misses the point of care practice. Without such a platform, the CPG tool would be able to identify and prioritize the recommendations for which SDM seems most relevant in the CPG development process, but the bridge to support the practical SDM process between health care professionals and patients would be missing. The platform also corresponds with the idea that all CPGs should be digitized so that PDAs can ultimately be better integrated or linked with CPGs and thus be more readily available at the point of care. An example of such a platform is PADA (formerly Collaborative Platform for Authors of Healthcare Decision Aids), which can be used to create new PDAs [44]. However, our target database aims to take another step forward by integrating already available PDAs, which may also differ in their formats, into the database.

Platform Development

To this end, a data structure is being developed that can be used to map the majority of existing PDA formats and make them digitally available. As a central function, the database will allow PDAs to be linked to each other and to external resources, for example, to the respective recommendation in the CPG and vice versa, when possible.

Three forms of presentation for PDAs are planned for the first version of the platform: (1) digital user-friendly option overviews, (2) multistage and partially digital user-friendly PDAs, and (3) option for information based exclusively on a sequence of texts, tables, and graphics.

To fill the database, known authors of PDAs will be contacted and invited to enter their PDAs in the German language. Additionally, a simultaneous search will be conducted in bibliographic databases such as PubMed and Embase, complemented by a Google search. A selection of PDAs identified in this way will be entered into the database when agreed by the PDA authors. The PDAs will be selected according to quality criteria defined during the project phase.

For the specific implementation of important functions, such as import, maintenance, linking of literature sources, data structures for study results or effect measures, and word export, previous knowledge of the consortium partners can be used. The platform should allow registered authors to independently enter PDAs into the system. For this purpose, a back end will be developed that includes a team-based user administration, an input system for PDAs in the 3 modes described earlier, as well as a release workflow for the PDAs and a versioning system for tracking changes. A literature management system for citing literature references in the PDA and a glossary function are also planned.

The front end with the interface for searching and retrieving PDAs should include a simple and comprehensive search with filter options using keywords and metadata (eg, subject area, year, and publisher). Users of the platform should be able to rate and review the PDAs (nonpublic). Possible improvements in presentation and completeness can be suggested by automated feedback mechanisms aimed at continuously evaluating and improving the quality of PDAs. The interface will be developed in a responsive design, making it possible to be displayed on mobile devices, tablets, and PCs. In addition, it should be possible to export the PDA as a PDF and other formats.

The system should provide an interface (application programming interface), through which third-party systems can access the system and retrieve PDAs. For example, integration into hospital information systems, decision support systems, or similar would be possible. The interface should have an authentication mechanism and allow access to the PDA and its metadata in a structured form.

To meet the needs of CPG developers and patients, they will be involved in the planning and subsequent test phase. To ensure the continuation of the platform after the end of the funding phase, it is intended to evaluate possibilities for further development and continued operation. A viable concept for this will be developed during the funding phase. In our view, possible institutions that could be interested in the continuation of such a platform include the EbM-Network, the German Network for Health Literacy, and the Association of the Scientific Medical Societies (AWMF), in addition to their digitization strategy.

Platform Quality Criteria

For the integration of PDAs into the platform, inclusion criteria, in terms of minimum requirements, will be developed in advance and applied to the identified PDAs. The Good Practice Health Information of the EBM-Network [45] and the International Patient Decision Aid Standards criteria [46], among others, will be used to develop the quality criteria.

WP 6: To Test the Tool on CPGs Currently Being Developed or Revised

Objective

The last WP will serve to test the tool on approximately 12-15 German CPGs. Applying the tool in practice will allow to gain insights into its handling and application. At the same time, the actual integration of PDAs to CPG recommendations identified by the tool as sensitive to individual preferences will be realized.

Selection of Suitable CPGs

For pragmatic reasons, the selected CPGs should be close to completion in order to test the developed tool. It is a prerequisite that the CPG group is currently working on the CPG, but at the

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same time, new or updated CPG recommendations have already been established so that individual recommendations or entire CPG chapters can already be used. Given the increasing number of living guidelines [47], this selection process seems realistic and has the advantage of not having to wait for the entire CPG to be finalized or updated. We will consider S3 CPGs (which represent the highest level of a systematic approach in the CPG development process according to the AWMF) registered in the AWMF registry or CPGs under revision, including the National Program for Disease Management Guidelines (NDMG) and CPGs of the German Guideline Program in Oncology (GGPO). For this purpose, an overview of these CPGs will be obtained from the AWMF registry and sorted by planned publication date (or alternatively expiry date of the CPG to be updated). In this way, the CPG organizations that are closest to finalizing the respective CPG will be contacted first. The relevant CPG organizations will be contacted consecutively but in such a way that at least 3 CPGs of the NDMG and GGPO will be included. Pragmatic aspects, such as the willingness to participate in the testing of the tool, will be particularly important in the selection process. The number of CPG recommendations included in the testing will vary from chapter to chapter, both within and across the CPGs. Approximately 30 recommendations per CPG should be included in the test. To achieve the planned number of recommendations for testing the tool, we may also decide to use several chapters of a CPG.

Testing Phase

Similar to the development of quality indicators [48] or patient versions of CPGs [49] during the initial CPG development process, a small multidisciplinary team will be formed for each CPG, on which the tool will be tested. For this purpose, in addition to the person responsible for the respective CPG chapter (ie, CPG methodologist and health care professional), the involvement of patients and patient partners is planned. Patients or patient partners who are already involved in the CPG development will be contacted first. Otherwise, alternatives will be sought through patient organizations. The team will be completed by a person involved in the development of the tool (ie, one member of our project team) and an SDM expert. At the beginning of the testing phase, the latter 2 group members will present the SDM concept and the developed tool to the multidisciplinary team. Using the tool, the multidisciplinary team approaches a CPG that is being revised or newly developed and screens all CPG recommendations. This means that the tool will be applied to every single recommendation. Ratings will be given by health care professionals and patients. These ratings will be used to prioritize preference-sensitive recommendations. The SDM expert and a member of our project team will support the rest of the team in gathering continuous feedback with the intention of refining the tool during the application phase, if necessary. Each test group will provide (1) verbal feedback directly during the testing phase and (2) written feedback via a questionnaire after the testing phase.

In a final workshop, the findings and experiences will be reflected upon with representatives of the NDMG, GGPO, and AWMF. The aim of the workshop (or several workshops, if necessary) is to implement the tool in the respective manuals of the CPG organizations, taking into account their digitization strategies.

Ethical Considerations

For the qualitative studies (ie, WPs 2 and 3), ethics approval was given by the Brandenburg Medical School on January 29, 2024 (165122023-ANF). We will obtain informed consent from all participants prior to conducting these WPs, and participants will have the opportunity to opt out at any point in time without giving reasons. Data are deidentified and cannot be traced back to individuals. Participants in WPs 2 and 3 will not receive any compensation; patient partners in the project will receive an honorarium to compensate for the time they devote to the project. We will conduct our research in accordance with the Declaration of Helsinki, respect the General Data Protection Regulation and findability, accessibility, interoperability, and reusability principles for data management [50]. Ethics approval is not required for the other WPs, as we will not be collecting personal data. In WP 1, the scoping review involves secondary research based on already published material, whereas WPs 4, 5, and 6 focus on technical development and testing processes that will be directly overseen by our project team. The findings from each WP of the project will be published in peer-reviewed journals and presented at scientific conferences. Results will also be made available early in prepublication repositories.

Results

The project has started on December 1, 2023, and is ongoing. To ensure that the patient perspective is taken into account, patient partners are involved throughout the project and provide input for each WP. For example, patient partners will be consulted when compiling the list of items as part of the tool development in WP 4 or when setting up and designing the platform for PDAs in WP 5. As the project has international relevance, an international advisory board is convened. The members of the advisory board are internationally recognized experts in the field of CPGs and SDM. As of February 20, 2024, we are currently assessing literature references to determine eligibility for inclusion in the scoping review (WP 1). Upon completion of WP 1 and WP 2, we expect to provide key methodological considerations that will enable the linked development of CPGs and guideline-based PDAs. At the end of WP 3, a methods paper on the definition and operationalization of preference sensitivity and the prioritization of CPG key questions for PDAs will form the basis for the subsequent WP 4. Once developed in WP 4 and tested in WP 6, the tool for CPGs will provide a methodologically valid identification of CPG recommendations for which SDM appears to be particularly relevant during the CPG development process. The platform for PDAs (WP 5) translates the objective of supporting SDM into practice by providing tools to support joint decision-making between patients and health care professionals. The PDAs on the platform can also be used to link to the recommendations in the CPG that the tool has identified as most relevant for SDM. We expect all parts of the project to be completed by December 31, 2026.

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Discussion

Main Findings

This protocol outlines a multistage project aimed at developing a tool for CPGs to systematically identify and prioritize CPG recommendations for which SDM is particularly relevant. It describes the parallel creation of a platform for PDAs to support the application of SDM in clinical practice. It outlines how both the tool for CPGs and the platform for PDAs can work together to foster SDM between patients and health care professionals.

The Project in Context

To our knowledge, this is the first project to provide a tool for CPG developers to systematically consider SDM during CPG development. The tool addresses the issue that current CPGs often do not adequately facilitate deviations from recommendations when appropriate [9]. By using the tool, CPG recommendations that are particularly sensitive to individual patient preferences can be highlighted, helping health care professionals apply CPGs correctly and practice SDM. The outputs of each WP will be able to support both evidence-based and person-centered care [51,52].

Drawing on the proven effectiveness of PDAs [22], we anticipate that the platform for PDAs has the potential to improve decision-making by providing a digital toolkit for the development of guideline-based PDAs while serving as a central repository for high-quality PDAs at the same time. This project is in line with international efforts to support a person-centered approach to CPGs [53] as well as efforts to use digital support for the development of CPGs and PDAs (eg, computable guidelines [54] and MAGICapp [55]). In the broader health care context, this project represents one of several strategies needed to strengthen SDM in practice [27].

Implications During and After the Project Phase

Although the aim is to develop a generic tool, we recognize that during the development process, it may become apparent that the tool needs to be adapted or modified due to the wide range of conditions or health problems addressed in CPGs. We will test the tool during the ongoing update or creation of CPGs. This will have the advantage that the tool can be tested directly in practice but will be accompanied by the difficulty that CPG development groups will be confronted with an increased workload. While the tool will only be developed and tested on CPGs in the project phase, we anticipate that these efforts will also lead to the integration of PDAs into patient versions of CPGs.

Input from an international advisory board that collaborates across countries to advise on the development of the tool will ensure an international perspective on CPGs and SDM. Once translated, the tool for CPGs will also be available in multiple languages. We plan to keep updating, maintaining, and disseminating the tool after this project. Further quantitative validation will also be helpful. With regard to PDAs, more research appears to be needed on issues such as “Which type or format of PDA is most effective (for which patient group)?” “When to best use it?” and “What is its impact, depending on the type of decision, condition, and other patient-related factors (such as socioeconomic factors and health literacy)?”

Limitations

Within the project, each WP has some limitations. These will be discussed further in the publication of each WP. In WP 1, limited resources may prevent the identification of all relevant documents, as we cannot search all international CPG organization websites. In WPs 2 and 3, a selective sample may not fully reflect all health care contexts and stakeholder perspectives, although we will mitigate this through careful recruitment at the international level. In WPs 4 and 6, we will develop and test the tool for CPGs primarily in the context of German CPGs. However, CPG recommendations may differ depending on the geographical context [56], and cultural influences may contribute to a different operationalization of preference sensitivity [57-59]. To overcome this shortcoming, the international project advisory board will be consulted for its expertise in all phases of the project. Similarly, the platform for PDAs (WP 5) will be limited to German-language PDAs for pragmatic reasons.

Conclusions

This project will produce a generic tool to promote SDM as part of the CPG development process, with the potential to improve the quality of health care by enabling CPG developers to systematically incorporate aspects of SDM into CPGs. This will offer users, particularly health care professionals, guideline-based support for the patient-clinician interaction. The platform for PDAs will systematically link PDAs to SDM-relevant CPG recommendations, thereby facilitating the use of PDAs in practice. In the long term, this project intends to raise awareness among international CPG organizations to make SDM and related tools an integral part of CPGs and to foster international collaboration to improve SDM practices worldwide.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

DP, CS, FS, TK, and TL wrote the first draft of the manuscript and contributed to the conceptualization of the study design. LF revised the manuscript. DP contributed to drafting the manuscript and supervised the process. All authors discussed and edited the final manuscript.

Conflicts of Interest

FS is a partner of SHARE TO CARE. Patientenzentrierte Versorgung GmbH. AH is employed by the National Institute for Health and Care Excellence. SL is the co-editor-in-cheif of *JMIR Diabetes*. No other relevant conflicts of interest are declared.

Multimedia Appendix 1
Search strategies for bibliographic databases.
[DOCX File , 15 KB - resprot_v13i1e57611_app1.docx]

Multimedia Appendix 2
List of clinical practice guideline organizations searched.
[DOCX File , 15 KB - resprot_v13i1e57611_app2.docx]

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Abbreviations

ACCORD: Accurate Consensus Reporting Document
AGREE II: Appraisal of Guidelines for Research and Evaluation II
AGREE-REX: Appraisal of Guidelines for Research and Evaluation-Recommendation Excellence
AWMF: Association of the Scientific Medical Societies
COREQ: Consolidated Criteria for Reporting Qualitative Research
CPG: clinical practice guideline
EbM-Network: German Network for Evidence-Based Medicine
GGPO: German Guideline Program in Oncology
GIN: Guidelines International Network
NDMG: National Program for Disease Management Guidelines
PDA: patient decision aid
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
SDM: shared decision-making
WP: work package

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Protocol

Real-Time Triage, Position, and Documentation (TriPoD) During Medical Response to Major Incidents: Protocol for an Action Research Study

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Abstract

Background: There is a need to address the implementation of technological innovation into emergency medical services to facilitate and improve information exchange between prehospital emergency care providers, command centers, and hospitals during major incidents to enable better allocation of resources and minimize loss of life. At present, there is a lack of technology supporting real-time information sharing in managing major incidents to optimize the use of resources available.

Objective: The aim of this protocol is to develop, design, and evaluate information technology innovations for use in medical response to major incidents.

Methods: This study has a qualitative action research design. This research approach is suitable for developing and changing practice in health care settings since it is cyclical in nature and involves development, evaluation, redevelopment, and replanning. The qualitative data collection will include workshops, structured meetings, semistructured interviews, questionnaires, observations, and focus group interviews. This study assesses the use of a digital solution for real-time information sharing by involving 3 groups of indented users: prehospital emergency care personnel, hospital personnel, and designated duty officers with experience and specific knowledge in managing major incidents. This study will explore end users' experiences and needs, and a digital solution for prehospital and hospital settings will be developed in collaboration with technology producers.

Results: The trial implementation and evaluation phase for this study is from April 2024 to May 2026. Interviews and questionnaires with end users were conducted during the planning phase. We have performed observations in connection with 2 major exercises in April 2024 and November 2024. The outcome of this analysis will form the basis for the design and development of a new information technology system. We aim to complete the observations in training sessions and exercises (phase 3) by September 2025, followed by modification of the technology solutions tested (phase 4) before dissemination in a scientific journal.

Conclusions: This protocol includes several methods for data collection that will form the basis for the design and development process of a digital solution for real-time information sharing to support efficient management in major incidents based on the experiences and requirements of end users. The findings from this study will contribute to the limited research on users' perspectives and the development of digital solutions for real-time information during major incidents.

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KEYWORDS

action research; decision support technique; information technology; medical response; major incident; management

Introduction

Information technology plays an important role in the improvement of information exchange during a medical response to a major incident (MI) or disaster [1-6]. However, effective information sharing and transfer between the field and command centers continues to remain a problem [7-9]. The greatest challenge in a high patient surge setting is the coordinated management of limited resources to optimize patient care and save lives [2,7,10-12]. The medical response to an MI is the action taken immediately following the incident to reallocate available resources; mobilize additional resources; and triage, treat, and allocate patients to hospitals for definitive care [13]. In this paper, an MI is defined as "a situation in which available resources are insufficient for the immediate need of medical care" [13].

Inadequate or incorrect flow of information on the resources required and the number of patients involved and their injuries has a negative impact on the management of MIs and disasters. This has been highlighted in several systematic reviews, reports, and inquiries [14-16]. Resource management and logistics problems after an MI are often identified as caused by communication failure and not by the lack of medical resources [17,18]. Resource allocation is based on decisions made at the scene of the incident, at the hospital, and at regional and national command centers. Decision-making under extreme stress is very demanding. In a study by Hugelius et al [19], prehospital emergency care personnel in the emergency medical services (EMS) experienced radio communication to be less supportive than expected in a noisy and chaotic environment.

There is widespread interest in information and communication technologies for the transfer of data in an emergency setting [5,7,8,11,20,21], and many believe that technology has the potential to vastly improve the medical response to MIs [2,4,8,11,18,21,22]. Information technology has been tested in various command situations [1,11], including EMS [11,21,23], at the hospital [11,24-28], in pediatric care [29], and in a military context [30]. Even if information technology has advanced in recent times, there are still barriers to going from a project stage to an operational implementation phase [31]. One challenge or barrier described by Zhang et al [7] relates to the limited ability of prehospital emergency care personnel to communicate when dealing with critically injured patients in the field, as their foremost function is to perform hands-on examinations and treatments on patients. Given the extreme workload in a stressful environment, the prehospital emergency care personnel's ability to use handheld devices for communication has been perceived as a hindrance to the user [32].

In 2004, Chan et al [11] proposed the use of wireless technology in MIs to track patients, report patient numbers, triage status, and allocate resources by automatic sharing of information between devices. Haverkort et al [25] argue that patient tracking and tracing systems should cover both prehospital and hospital care and that performance of triage, registration, documentation, and tracing functions should be given equal importance.

Prehospital emergency care personnel still rely on radio communications and verbal reports to share and transfer information of the amount of injured and triage category (eg, red, yellow, green, black, possibly blue) from the scene of the incident. This has resulted in delayed and incomplete transfer of information both at the scene of the incident and after admission to hospital [6,7,11,16,25]. Breakdown in communication is often cited as a challenge that information technology can address. A systematic review of patient tracking technologies by Dobson et al [29] identified a lack of studies that were methodologically strong. Furthermore, most studies focus on adopting techniques with little attention paid to reliability and usability, that is, intended users' perceived usefulness and ease of use [5,7,32,33]. Evidence-based practice must be defined to decrease the risk of poor outcomes [34]. However, according to Zhang et al [7], Chan et al [11], Lee et al [31], and Waterman et al [35], research into the practical implementation of innovations in a complex environment is no easy task. For implementation to be successful and for it to improve the quality of medical response, users must be ready and eager to adopt new technology. Providing real-time data is an area where new technology can excel in MI management [11]. The limitation of information sharing during MIs leads to insufficient communication and common operating pictures at command centers that hinder management decision-making [7]. Chan et al [11] highlight the need for developing support for managing an MI. However, there remains a gap in knowledge regarding the collaborative design and development of supportive technologies with end users as well as their practical application. Therefore, to address the need for improved communication and to make the users eager to adopt new technology, our project aims to co-develop a real-time communication and information system with collaboration with prehospital emergency care professionals, stakeholders, and MI managers. By actively involving users, we aim to create a solution that meets operational needs and facilitates implementation in a complex environment.

A real-time communication and information system for Triage, Position, and Documentation (TriPoD) will be developed, designed, and evaluated in collaboration with intended users. Specifically, the project will develop a seamless, automated information system to support the real-time transfer of data to all health care management levels. The system will include electronic triage tags, mobile devices, a web portal, and patient-tracking devices covering prehospital and in-hospital settings. A key feature of the study project is automatic information transmission through the usage of electronic tags (each tag has a unique ID and is attached to each patient) from the scene of the incident to the hospital and within the hospital, which will provide timely and accurate information visualized on data screens at command centers at different management levels. TriPoD will also permit re-evaluation in real-time to be made, as triage is a dynamic process. At the user level, the

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systems developed must be easy and intuitive to use and not interfere with the user's ability to perform optimally [11]. This is why the viewpoints of the intended users will be addressed using cyclic action research [36], where iterative design is an essential part of the methodological approach. Action research focuses on generating knowledge, facilitating action, implementation, and evaluation of context-specific solutions [37]. Therefore, the aim of this study protocol is to develop, design, and evaluate information technology innovations for use in medical response to MIs.

Methods

Study Background

This study adopts an action research approach [36], which is a cyclic study design and involves development, evaluation, redevelopment, and replanning. Action research is a suitable method for developing and changing practice in the health care setting [37]. Action research aims to improve practice by involving those directly affected by it in the research process [38] and can be defined as "research strategies that address real world problems in a participatory, collaborative, and cyclical way to produce knowledge and action" [39]. In the subsequent studies, involvement and collaboration will be performed with intended users to identify and solve the most important issues regarding information exchange in the medical response to MIs. By collaborating with the intended users, the researchers' team will receive information about the current practices and thereby understand what is required to be changed for the better. According to Dinsmore et al [40], the strength of action research is the researcher's capability to identify and create solutions to practical problems by using different methods such as focus groups interviews and observations. In addition, the design advocates that the action of the researcher is to be a part of the research process where the act itself is used as a tool to generate essential knowledge and then to develop and change the system [41]. In this context, part of the researcher's task is to identify and listen to intended users to develop a real-time communication and information system that will facilitate management decision-making during an MI. The following research questions will form the basis of the action research:

1. How do we create interoperable robust technology for medical management at different command levels during an MI?
2. How will we capture and share information in chaotic and stressful situations?
3. How should informatics and technology solutions be designed to fit different levels of management in the medical response to MIs?
4. How can information be easily shared between medical teams and command centers to provide a real-time accurate overview, and how should they act based on this information?

The research process is cyclic, where planning, action, observation, and reflection are repeated until a satisfactory result is achieved. The working group in this study consists of academicians, health care professionals from EMS, hospitals, designated duty officers, and information technology producers.

Study Setting

This study will be conducted from April 2024 to May 2026 in Region Stockholm, which is the largest health care provider in Sweden with 6 emergency hospitals, 3 pediatric emergency departments, 10 local emergency clinics, and 9 minor hospitals. Region Stockholm includes Stockholm County with 26 primary municipalities and a population of 2.4 million inhabitants (>20% of the total Swedish population). In terms of area, Stockholm County is one of the smaller counties in Sweden (approximately 6500 square kilometers).

In Sweden, there are 3 command levels in the event of an MI: national, regional (strategic), and local. The local level includes prehospital and hospital management. The EMS is a pool of regional resources, including agencies, health care providers, personnel, equipment, and facilities, under the command of the regional authority. This study protocol focuses on ambulance and hospital care. In Sweden, the first ambulance personnel will adopt the position of the prehospital incident commander in case of an MI. This position has the mandate to lead and organize the prehospital medical response, distributing prehospital resources and working together with relevant partners such as police and firefighters on-site [19].

The planned studies will involve one of the 6 emergency hospitals serving approximately 420,000 inhabitants. Regardless of levels, all command centers deal with the mobilization and allocation of resources according to expected requirements. Higher levels have the authority to increase the framework of resources available. Effective response requires accurate and timely information from the field to the hospital and within the hospital. In this study protocol and in the subsequent planned studies, the term command will be used to cover both prehospital and hospital MI management. Medical management at each level comprises the incident commander and the chief medical officer.

Participants

The overall aim has been predetermined and defined by the research team. Data collection started in April 2024 and is ongoing. Intended users are actively involved in the development, design, and evaluation of the technology system developed for information sharing and transfer of real-time data. The Stockholm County EMS organization is involved in the project, and e-triage, patient-tracking, and trace systems will be tested and evaluated in both prehospital and hospital settings. The recruitment of the participants will be strategic and purposive, including personnel with specific knowledge, experience, and wishes related to information technology. A total of 3 participant groups will be included in this study: prehospital emergency care personnel, hospital personnel (including physicians, nurses, and administrators), and designated duty officers. Qualitative studies have no optimal sample size since they depend on the purpose of the study and the richness of data [42]. However, since this study is based on homogenous groups, the sample size will be smaller, and the participants will be recruited until information power is reached. The need for specific experiences and expertise among participants is crucial in our studies and limits the number of participants that can be and need to be included. However,

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information power will be assessed throughout the research process by using preliminary analyses as recommended by Malterud et al [43].

Study Design

This project is designed to stimulate reflection among users through discussion and feedback. Action research is an iterative process that depends on a continuous dialogue between the research team, information technology producers, and intended users [39]. The selected cyclic process comprises 4 iterative phases described by Kemmis et al [36]: (1) planning, (2) action, (3) observation, and (4) reflection (Figure 1). Each phase uses mixed methods to explore end user experiences, communication challenges, and attitudes to new technology.

Figure 1. The action research spiral.

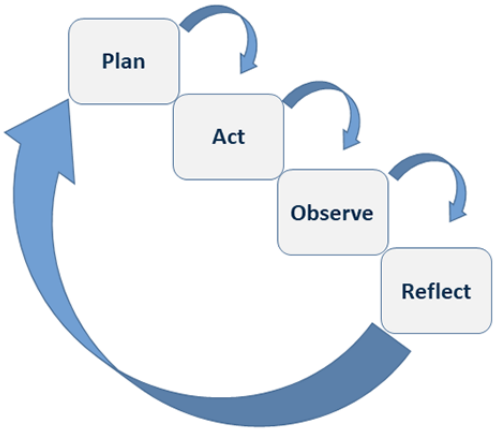

Phase 1: Planning

The starting point has been structured meetings and workshops with different health care professionals, stakeholders, researchers, senior lecturers in EMS, and technology producers (n=10-12) to define the problems to be investigated. Furthermore, previous research has been reviewed to gain an overview and understanding of which real-time communication and information systems have been tested or used. This was done, as changing systems and work processes are one of the fundamental challenges to the digitalization of services in health care. To obtain insight into the current communication methods, the needs and impact of new technology in response to MIs, and the desired way forward presented among prehospital emergency care personnel (n=18), we used questionnaires and interviews for collecting data. Findings have been used to plan for the development of technical and user-friendly aspects of TriPoD. During the planning phase, interviews will also be conducted with 5-10 duty officers and hospital personnel to understand and explore known communication challenges from their perspective when working in the management function during an MI. The interviews will be digitally recorded and transcribed verbatim. Data will be analyzed using content analysis as described by Elo and Kyngäs [44], and to reduce bias, the data analysis will involve multiple researchers. After problem identification and the outcome from the content analysis, a technological innovation for use in the medical response to an MI will be developed and designed, and this will become the starting point for reflection and problem-solving according to action research. This will form the basis of the analysis and will be reflected in the project results.

Phase 2: Action

The basic idea of action research is to create participation, dialogue, and reflection in the development and design process as well as to capture user reactions to the innovation technology such as ease of use, utility, and efficiency. In this phase, the developed technical prototypes will be pilot tested in prehospital and hospital settings, and user feedback will be used to take new ideas forward in the technical development process. The specific topic for this data collection is to obtain deeper knowledge from the pilot tests on how to further improve the design of the digital system. Based on the findings from the tests, an assumption is that the users' opinions and reflections can be applied to the development process of TriPoD. This phase of data collection involves field observations during exercises and has been practiced in 1 exercise with figurants concerning the management of an MI. A qualitative observational design with nonparticipant observers stationed at the incident site at a regional command center and at a hospital command center was used in the early summer of 2024. Observers systematically compared standard procedures and management with TriPoD and made field notes during the test. Trying new ideas and assessing how they function in practice is important in the cyclic process of action research enabling users and project partners to find solutions. A reference group of 8-10 indented users has been established during spring 2024. This is an important phase where users are encouraged to suggest possible changes themselves. In the literature, this phase is described as increasing the likelihood of solution sustainability [37]. It can also enrich the understanding of the specific settings in which the new system will be used.

Phase 3: Observation

In this phase, the research team will observe and evaluate the performance and outcomes from phase 2. The TriPoD system must be intuitive and user-friendly, given the stressful and potentially hazardous environments in which it is used. Phase 3 involves observations of current practice and includes (1) creation of test situations in prehospital and hospital settings to simulate real-time patient flow and tracking, (2) assessment of the solutions developed, and (3) creation of exercises where

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users test and evaluate the TriPoD system under realistic conditions.

The research team shall, during pilot tests and exercises, investigate the attitudes, motivations, rules, and organizational issues surrounding interoperability and information sharing at all levels of MI management. Observations at training sessions and exercises will be performed, followed by focus group interviews. These will include 5-6 duty officers, 5-6 prehospital emergency care personnel with experience in prehospital MI management, and 5-6 hospital personnel with experience of in-hospital organization and management of an MI. All transcribed interviews and focus group interviews will be analyzed using systematic text condensation according to Malterud [45], guided by the COREQ (consolidated criteria for reporting qualitative research) checklist developed by Tong et al [46]. Malterud [45] describes 4 stages in the analysis process: (1) the text is read to capture themes, (2) the code units of meaning are extracted, (3) these are condensed into core content, and finally, (4) the findings are summarized. One researcher will be responsible and initiate the analysis, while the whole analysis process will be followed up by the research team to ensure trustworthiness. Questionnaires will be used to gain reflections of 10-15 emergency department physicians and nurses on real-time integrated information systems and the use of patient tags in the hospital setting.

Phase 4: Reflection

Reflections will be conducted at both individual and group levels. An important component of action research is reflection, where users' ideas lead to modification of the technology solutions tested. Based on the results, the working group (n=10-12 health care professionals and technology producers) shall decide what to do next and modify the system prior to a new round of application and reassessment before implementation (Figure 1). Evaluation will focus on the end users' opinion on TriPoD whether the technique meets the needs and expectations and will feature qualitative methods. A series of focus groups will be performed to solve the challenges and barriers identified during tests. These will include 5-6 duty officers, 5-6 prehospital emergency care personnel with experience of prehospital MI management, and 5-6 hospital personnel with expertise in hospital organization and management of an MI. Data will be analyzed using content analyses as described by Elo and Kyngäs [44]. The recruitment will be strategic to include participants with specific knowledge and experiences. The specific topic for this data collection is to keep the good changes, add new ones, and then begin the action research process again. This will continue until the working group is satisfied that the study objectives have been met. The outcomes of the cyclic process will be documented. In this action research study, a variety of data collection methods will be used [35,37,38,47], as displayed in Table 1.

Table 1. Description of the methods in the study process.

Phases	Methods	Sample size
Phase 1: planning	• Workshops and structured meetings • Literature review • Semistructured interviews and questionnaires	• 10-12 health care professionals and technology producers • 8 PECa personnel, 5-10 duty officers, and hospital personnel
Phase 2: action	• Workshops • Pilot tests/observations/field notes • Reference group involvement	• 10-12 health care professionals and technology producers • Prehospital and hospital settings • 8-10 intended users
Phase 3: observation	• Workshops and structured meetings • Exercises/observations/field notes • Focus group interviews • Questionnaires	• 10-12 health care professionals and technology producers • Command levels (regional/local) • 5-6 duty officers, 5-6 PEC personnel, and 5-6 hospital personnel • 10-15 emergency department personnel
Phase 4: reflection	• Structured meetings • Focus group interviews • Reference group involvement • Evaluation and analysis of total data material	• 10-12 health care professionals and technology producers • 5-6 duty officers, 5-6 PEC personnel, and 5-6 hospital personnel • 8-10 intended users

[a]PEC: prehospital emergency care.

These methods will be used to collect data prior to and during the development of technology and after the evaluation of the information technology developed. The intention is that the working group and intended users should come to a common understanding of how to solve real-life problems that do not have clear or obvious solutions during the developing process. Topics/questions to be covered are current practices, experiences in MI management, conventional methods versus new technologies, information needs, attitudes and expectations, real-time data transfer, interoperability, perceived feasibility and usefulness, perceived ease of use, and quality and safety issues.

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Data Analysis

As this study will have several data sources (workshops, focus group interviews, questionnaires, observations), it will provide a holistic perspective and limit the risk of bias when relying on limited data sources. The information obtained should have high scientific value and facilitate assessment of the system studied. The iterative approach enables discussions and analyses during ongoing data collection.

Ethics Approval

This study has been approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten [EPM] 2023-04615-01; October 20, 2023), and in accordance with the guidelines of EPM, the research team will obtain informed written consent from the study participants. Participation is voluntary and may be withdrawn without consequences. Furthermore, confidentiality regarding interviews and observation data is guaranteed, and data will be stored securely.

Results

The trial implementation and evaluation phase for this study is from April 2024 to May 2026. Based on meetings, interviews, and questionnaires in the planning phase, an early prototype has been developed. The findings from questionnaires in phase 1 gave valuable insights into users' needs and wishes concerning communication and information sharing during an MI. Results from the full-scale exercise with figurants in phase 2 revealed that command centers received real-time updates on the patient count, triage, and position faster than traditional standard procedures of sharing information during an MI. Data transmitted through the web portal were updated each time a new patient was scanned by the prehospital emergency care personnel, allowing for continuous real-time monitoring and decision-making at command centers. Both prehospital emergency care personnel and the management personnel working at command centers observed TriPoD's effectiveness and usability, despite minor delays when prehospital personnel on some cases failed in the efforts to consistently scan injured patients. We have performed observations in connection with 2 major exercises in April 2024 and November 2024. Final analyses of the observations will be reported. The outcome of the qualitative content analysis will form the basis for the design and development of the new information technology system. We aim to complete the observations in training sessions and exercises (phase 3) by September 2025, followed by modification of the technology solutions tested (phase 4) before dissemination in a scientific journal.

Discussion

Principal Findings

The main findings from this action study report will form the basis for the design and development process based on the experiences and requirements of end users. The main contribution of this study will be to assess the ways users work and to get their opinions on the functionality and usability of electronic devices. Different opinions are likely to arise on how information sharing can benefit from the implementation of a new technology, and this will enrich the project. However, it is not unusual that electronic devices are not used due to portability and usability issues [7]. If the device is impractical, it can significantly impact how successfully it is adopted in clinical practice and impede the implementation phase [5]. Despite decades of effort to create efficient information-sharing systems for communication between prehospital emergency care personnel, inefficiencies still persist [7]. Effective and timely exchange of information between command centers is crucial in the medical response to MIs and disasters [1-6], and any innovation in this field must be practical, user-friendly, and feasible [7]—not just the simple adoption of a new technique [33]. In a study by Reddick [5] on how communication technologies affect our readiness for MIs, results showed that technology is effective in emergency management, especially during the response phase.

Comparison to Prior Work

TriPoD gives real-time information to command centers, supporting situational awareness by continuous update from the incident scene during transport and upon arrival at the hospital. TriPoD applies commercial technology and available information technology services in an innovative way. Although similar projects may be in progress, to our knowledge, no recommended system has been fully implemented at the time of this study.

Strengths and Limitations

The strength of the methodology chosen is that it improves and changes practice by directly involving the intended users [38]. All methods used will be reported together with their justification so that other researchers can confirm the reliability of the study. However, it is challenging to replicate action research studies due to the context dependency, and the design offers explanatory theories that can be falsified. In addition, the research team consists of academicians from the field of emergency and disaster medicine, but there are no cocreating end users involved in the research process, and this can be considered as a limitation, as their perspectives will not be included in the research process. This approach requires trust between researchers, the working group, and the users involved in the development process of TriPoD and that all understand the value of rigor in research. Action research also has limitations since it usually involves very specific investigations, often within organizations, and findings can be considered to only apply to that setting. Although action research encourages the transferability of project outcomes, the generalizability of the findings is limited to context similarity [39]. The researchers are aware that the structure and quality of EMS can vary based on local, regional, national, and international context and resources. However, triage, delivery of emergency care, and transport to appropriate facilities are essential components of emergency care worldwide and enable the transferability of project outcomes to EMS in similar contexts.

Dissemination Plan

Findings from this study plan will be disseminated through multiple channels to reach diverse audiences. Findings will be presented at national and international scientific conferences to

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engage with experts and practitioners in the field. Additionally, results will be published in peer-reviewed journals to ensure rigorous academic dissemination. We will also produce public scientific publications to make findings accessible to a broader audience, including practitioners and policy makers. To further enhance visibility, we will share the key results and updates on social media platforms, targeting both academic and professional communities. This strategy aims to increase the impact of our research by reaching relevant stakeholders.

Future Directions

Locating patients can become complicated if multiple hospitals and adjacent regions are involved in an MI. After the implementation of TriPoD, a hypothesis is that the system can be further developed to support the reunification of family members. Furthermore, TriPoD is intended to increase civil-military synergies in the event of MI management.

Conclusions

The result from the action research will highlight the ways intended users work, their opinions, and wishes to ensure high usability when developing and designing new technology in complex environments. Although the literature confirms the promising benefits of information technology, the opinions and needs of end users have yet to be addressed. Results will also support the practical implementation of new technology.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

MR and VL planned the study design, study protocol, and the development of the data collection methods. MR wrote the manuscript and applied for ethics approval. VL contributed to drafting and revision of the manuscript. TK commented on the manuscript draft. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

COREQ: consolidated criteria for reporting qualitative research
EMS: emergency medical services
EPM: Etikprövningsmyndigheten
MI: major incident
TriPoD: Triage, Position, and Documentation

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Corrigenda and Addenda

Correction: Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS)- Protocol for a Pilot Randomized Controlled Trial

Philip Kreniske[1], PhD; Olive Imelda Namuyaba[2], BA; Robert Kasumba[3], MS; Phionah Namatovu[2,3], MPH; Fred Ssewamala[2,3], PhD; Gina Wingood[4], SCD; Ying Wei[5], PhD; Michele L Ybarra[6], PhD; Charlotte Oloya[7], LLB, LLM; Costella Tindyebwa[7], MA; Christina Ntulo[8], MA; Vincent Mujune[7], MPH; Larry W Chang[9], MPH, MD; Claude A Mellins[10], PhD; John S Santelli[11], MPH, MD

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In "Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS): Protocol for a Pilot Randomized Controlled Trial" (JMIR Res Protoc 2023;12:e49352), the authors noted two errors:

The affiliation of author Claude A Mellins was:

> *Community Health and Social Sciences Department, Graduate School of Public Health and Health Policy, City University of New York, New York, NY, United States*

It has been revised to:

> *HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute and Columbia University, New York, NY, United States*

The affiliation of authors Charlotte Oloya, Costella Tindyebwa and Vincent Mujune was:

> *Malachite Center for Mental Health, Kampala, Uganda*

It has been revised to:

> *StrongMinds Uganda, Kampala, Uganda*

The correction will appear in the online version of the paper on the JMIR Publications website on January 8, 2024, together with the publication of this correction notice. Because this was

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made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial

Marianna Masiero[1,2], PhD; Gea Elena Spada[2], MSc; Virginia Sanchini[1], PhD; Elisabetta Munzone[3], MD; Ricardo Pietrobon[4], PhD; Lucas Teixeira[4], MSc; Mirtha Valencia[4], MSc; Aline Machiavelli[4], MSc; Elisa Fragale[2], MSc; Massimo Pezzolato[1,2], MSc; Gabriella Pravettoni[1,2], PhD

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In "A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 12(1); e48852) the authors noted one error.

In the Acknowledgments, the last sentences appeared as follows:

> *The 8-item Morisky Medication Adherence Scale content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAS, LLC. The property/identifier issue/registration date/categories are as follows: US registration 5,837,273 August 20, 2019, Trade/Service Mark; US registration TX-8-285-390 June 12, 2016, Copyright; and US registration TX-8-632-533 September 21, 2018, copyright.*
>
> *This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).*

This has been changed to appear as follows:

> *The MMAS-8 Scale, content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAR, LLC., www.moriskyscale.com.*
>
> *This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).*

The correction will appear in the online version of the paper on the JMIR Publications website on January 15, 2024 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study

Bryony Waters[1], BSc, MSc; Martin Orrell[1], BMedSci, MBBS, PhD; Orii McDermott[1], ARCM, BA, MMT, PhD

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Related Article:

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(JMIR Res Protoc 2024;13:e56085) doi:10.2196/56085

In “The Development of a UK Culturally Adapted Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study” (JMIR Res Protoc 2023; 12(1):e43408) the authors made some modifications.

1. The title “The Development of a UK Culturally Adapted Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study” has been revised to:

> *The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study*

2. *PAMI-United Kingdom* was revised to *PAMI-Modified*, with all subsequent mentions in the paper being changed from *PAMI-UK* to *PAMI-M*.

3. In Table 1, all instances of the word *Dutch* were revised to *Danish*, as the language of the intervention is Danish.

4. Also in Table 1, the phrases in the title and footnote *PAMI-DK* and *PAMI-DK- Person Attuned Musical Interaction Danish Version* have been replaced by *PAMI* and *PAMI-Person Attuned Musical Interactions*, respectively.

5. In the Corresponding Author's address, *Truiumph Road* was corrected to *Triumph Road*.

6. Some sentences were revised to add the words *modified*, *modification* or *modifying* where necessary, as follows:

In the Abstract, in the section Background, “...a team of researchers in the United Kingdom have culturally adapted the tool.” has been edited to:

> *...a team of researchers in the United Kingdom have modified and culturally adapted the tool.*

In the Abstract, in the section Objective, “This study aims to investigate the appropriateness of the adapted UK manual for UK care homes and to explore...” has been edited to:

> *This study aims to investigate the appropriateness of the adapted and modified manual for UK care homes and to explore...*

In the Abstract, in the section Conclusions, “This study will be the first to investigate the culturally adapted UK PAMI” has been edited to:

> *This study will be the first to investigate the modified version of PAMI.*

In Background, in the section Person Attuned Musical Interactions Manual, “a UK version of PAMI was developed by a team of researchers at the University of Nottingham” has been edited to:

> *A modified version of PAMI was developed by a team of researchers at the University of Nottingham.*

In Background, in the section Person Attuned Musical Interactions Manual, “The first author’s thesis reports the manual development process and the differences between the Danish and UK version of PAMI” has been edited to:

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> *The first author's thesis reports the manual development process and the differences between the Danish and Modified version of PAMI.*

In Methods, under the section Training Session, "BW was the researcher who developed the translated PAMI manual as part of her PhD" has been edited to:

> *BW was the researcher who developed the modified PAMI manual as part of her PhD.*

In Methods, under the section Intervention Development, "...the research team liaised with the Danish PAMI team to ensure that any adaptation remained consistent with the PAMI ethos" has been edited to:

> *...the research team liaised with the Danish PAMI team to ensure that any adaptation and modification remained consistent with the PAMI ethos.*

In Discussion, under the section Anticipated Findings, "This study will be the first to investigate the culturally adapted PAMI. Therefore, the data collected in phases 1 and 2 will provide feedback on the appropriateness of the manual for staff..." has been edited to:

> *This study will be the first to investigate the modified PAMI-M. Therefore, the data collected in phases 1 and 2 will provide feedback on the appropriateness of the modified manual for care staff...*

In Discussion, under the section Anticipated Findings, "This study will investigate whether the UK-adapted version of PAMI can benefit residents,..." has been edited to:

> *This study will investigate whether the modified version of PAMI can benefit residents,...*

In Conclusions, the phrase "The study will be the first to investigate the culturally adapted UK PAMI" has been edited to

> *The study will be the first to investigate the modified PAMI.*

In Conclusions, "...and explore participants' experience of using PAMI" has been edited to:

> *...and explore participants' experience of using a modified version of PAMI.*

In the Caption of Figure 2, "PAMI: Person Attuned Musical Interactions" has been edited to:

> *PAMI-M: Person Attuned Musical Interactions-Modified.*

In the caption of Figure 3, the phrase "The manual development process for culturally translating and adapting the Danish Person Attuned Musical Interactions (PAMI) intervention for UK care homes. PAMI-DK: Person Attuned Musical Interactions Danish version; PAMI-UK: Person Attuned Musical Interactions United Kingdom" has been edited to:

> *The manual development process for culturally translating and modifying the Person Attuned Musical Interactions (PAMI) intervention for UK care homes. PAMI: Person Attuned Musical Interactions.*

In the caption of Table 1, "The changes between the Danish and UK Person Attuned Musical Interactions (PAMI)" has been edited to:

> *The changes between the Danish and Modified Person Attuned Musical Interactions (PAMI).*

The correction will appear in the online version of the paper on the JMIR Publications website on January 26, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study

Yakubu Ibrahim[1,2*], BMLS, MSc; Nurul Iftida Basri[1*], MBChB, DrObGyn; Norshariza Nordin[3*], BSc, MSc, PhD; Amilia Afzan Mohd Jamil[1*], MOG, MD

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In "Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study (JMIR Res Protoc 2024;13:e53722) the authors noted one error.

The author list was originally:

Yakubu Ibrahim[1,2]; Nurul Iftida[1]; Norshariza Nordin[3]; Amilia Afzan Mohd Jamil[1]

and has been changed to:

Yakubu Ibrahim[1,2]; Nurul Iftida Basri[1]; Norshariza Nordin[3]; Amilia Afzan Mohd Jamil[1]

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Corrigenda and Addenda

Correction: Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial

Nicole Wimmesberger[1*], MSc; Diana Rau[1*], MSc; Florian Schuchardt[2*], MD; Simone Meier[2], MD; Matthias L Herrmann[2], MD; Ulrike Bergmann[2]; Erik Farin-Glattacker[1*], Prof Dr; Jochen Brich[2*], MD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e51683

(JMIR Res Protoc 2024;13:e58180) doi:10.2196/58180

In "Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial" (JMIR Res Protoc 2024;13:e51683) the authors noted the following error.

In the originally published manuscript, the following authors' degrees were incorrectly listed as:

Florian Schuchardt, PhD

Simone Meier, PhD

Matthias L Herrmann, PhD

Jochen Brich, PD Dr

This has been corrected to:

Florian Schuchardt, MD

Simone Meier, MD

Matthias L Herrmann, MD

Jochen Brich, MD

The correction will appear in the online version of the paper on the JMIR Publications website on April 16, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 08.03.24; this is a non–peer-reviewed article;accepted 13.03.24; published 16.04.24.

Please cite as:
Wimmesberger N, Rau D, Schuchardt F, Meier S, Herrmann ML, Bergmann U, Farin-Glattacker E, Brich J
Correction: Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial
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Corrigenda and Addenda

Correction: Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial

Lydia A Shrier[1,2], MPH, MD; Madison M O'Connell[1], MPH; Alessandra Torres[3], MPH; Laura P Shone[3,4], MSW, DrPH; Alexander G Fiks[5], MD, MSCE; Julia A Plumb[1], BS; Jessica L Maturo[1], BA; Nicholas H McCaskill[1], BA; Donna Harris[3], MA; Pamela J Burke[1,6], RN, PhD, PPCNP-BC; Thatcher Felt[7], DO; Marie Lynd Murphy[8], MD; Lon Sherritt[9], MPH; Sion Kim Harris[1,2], RN, PhD, CPH

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e55039/

(JMIR Res Protoc 2024;13:e59383) doi:10.2196/59383

In "Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial" (JMIR Res Protoc 2024;13:e55039) the authors noted some errors.

The following sentence:

> *The AAP PROS network consists of 67,000 pediatrician members whose guiding mission is to foster and conduct national collaborative practice-based research for improving child health.*

Has been changed to:

> *The AAP PROS network consists of pediatrician members whose guiding mission is to improve the health of children and enhance primary care practice by conducting and fostering national collaborative practice-based research.*

The author Laura P Shone's affiliation:

> *Primary Care Research, American Academy of Pediatrics, Itasca, IL, United States*

Has been corrected to include:

> *Shone Sciences, DBA, Lowville, NY, United States (current); Primary Care Research, American Academy of Pediatrics, Itasca, IL, United States (former)*

Additionally, the following sentence was added to the "Acknowledgments" section:

> *Laura P Shone was affiliated with the American Academy of Pediatrics at the time of protocol development and is affiliated with Shone Sciences, DBA at the time of publication.*

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The correction will appear in the online version of the paper on the JMIR Publications website on May 8, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 10.04.24; this is a non–peer-reviewed article;accepted 12.04.24; published 08.05.24.

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Shrier LA, O'Connell MM, Torres A, Shone LP, Fiks AG, Plumb JA, Maturo JL, McCaskill NH, Harris D, Burke PJ, Felt T, Murphy ML, Sherritt L, Harris SK
Correction: Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial
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Corrigenda and Addenda

Correction: A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study

Alla Melman[1*], BAppSci, MSc; Min Jiat Teng[1,2*], BAppSci, MHSM; Danielle M Coombs[1], BAppSci, PhD; Qiang Li[3], MSc; Laurent Billot[3], MSc, MRes; Thomas Lung[3,4], MSc, PhD; Eileen Rogan[5], MBBS, MHSM, PhD; Mona Marabani[5], MBBS; Owen Hutchings[2], MBBS; Chris G Maher[1], BAppSci, DMedSc, PhD; Gustavo C Machado[1], BPhty, PhD; Back@Home Investigators[6]

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e50146

(JMIR Res Protoc 2024;13:e60298) doi:10.2196/60298

In "A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study" (JMIR Res Protoc 2024;13:e50146) the authors noted the following errors.

In the originally published article, the group author Back@Home Investigators was omitted from the authorship list. Furthermore, the equal contribution note was erroneously assigned to all authors when it should have only been assigned to the first two authors, Alla Melman and Min Jiat Teng.

The authorship list was originally published as:

> *Alla Melman*, Min Jiat Teng*, Danielle M Coombs*, Qiang Li*, Laurent Billot*, Thomas Lung*, Eileen Rogan*, Mona Marabani*, Owen Hutchings*, Chris G Maher*, Gustavo C Machado**
>
> **all authors contributed equally*

This has been changed to:

> *Alla Melman*, Min Jiat Teng*, Danielle M Coombs, Qiang Li, Laurent Billot, Thomas Lung, Eileen Rogan, Mona Marabani, Owen Hutchings, Chris G Maher, Gustavo C Machado, Back@Home Investigators*
>
> **these authors contributed equally*

Then, the *Acknowledgments* section was originally published as follows:

> *This study has received a Hospitals Contribution Fund (HCF) Research Grant: Optimizing outcomes for patients with back pain by preventing hospital admission (Aus $315,000 [US $207,500]), HCF Health Services Research Grant, HCF Research Foundation. We would like to thank the Back@Home collaborators (Bethan Richards, Ananthila Anandacoomarasamy, Kirsten McCaffery, Miranda Shaw, Cassandra Dearing, Ian Harris, Rachelle Buchbinder, Chris Needs, James Edwards, Narcyz Ghinea, Michael Dinh, Dane Chalkley, and Rachael*

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Dodd) for their assistance with the project planning and governance.

This has been changed to

This study has received a Hospitals Contribution Fund (HCF) Research Grant: Optimizing outcomes for patients with back pain by preventing hospital admission (Aus $315,000 [US $207,500]), HCF Health Services Research Grant, HCF Research Foundation.

The Back@Home Investigators are: Alla Melman, Danielle M Coombs, Qiang Li, Laurent Billot, Bethan Richards, Eileen Rogan, Ananthila Anandacoomarasamy, Owen Hutchings, Min Jiat Teng, Kirsten McCaffery, Mona Marabani, Miranda Shaw, Cassandra Dearing, Ian Harris, Rachelle Buchbinder, Chris Needs, James Edwards, Narcyz Ghinea, Michael Dinh, Dane Chalkley, Rachael Dodd, Chris G Maher, Gustavo C Machado.

The correction will appear in the online version of the paper on the JMIR Publications website on May 16, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 07.05.24; this is a non–peer-reviewed article;accepted 07.05.24; published 16.05.24.

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Melman A, Teng MJ, Coombs DM, Li Q, Billot L, Lung T, Rogan E, Marabani M, Hutchings O, Maher CG, Machado GC, Back@Home Investigators
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©Alla Melman, Min Jiat Teng, Danielle M Coombs, Qiang Li, Laurent Billot, Thomas Lung, Eileen Rogan, Mona Marabani, Owen Hutchings, Chris G Maher, Gustavo C Machado, Back@Home Investigators. Originally published in JMIR Research Protocols (https://www.researchprotocols.org), 16.05.2024. This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on https://www.researchprotocols.org, as well as this copyright and license information must be included.

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Corrigenda and Addenda

Correction: Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study

Anandi N Sheth[1,2], MSc, MD; Dazon Dixon Diallo[3], MPH, DHL; Celeste Ellison[4], MPH; Deja L Er[1], MPH; Adaora Ntukogu[5], BA; Kelli A Komro[4,6], MA, MPH, PhD; Jessica M Sales[4], MA, PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e56293

(JMIR Res Protoc 2024;13:e63249) doi:10.2196/63249

In "Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study" (JMIR Res Protoc 2024;13:e56293) an error was noted:

In the *Acknowledgments* section, the funding source number was incorrectly listed as R01MH121962. It has been revised to:

This study is funded by the National Institutes of Health (NIH; R01MH128045).

The correction will appear in the online version of the paper on the JMIR Publications website on June 21, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study

Sara Russo[1], BSc, MSc; Rosario Caruso[2,3], MSc, PhD; Gianluca Conte[2], MSc, PhD; Arianna Magon[2], MSc, PhD; Ida Vangone[1,4], BSc, MSc; Barbara Bascapè[5], BSc, MSc; Giulia Maga[1], BSc, MSc; Malgorzata Pasek[6], BSc, MSc; Cristina Arrigoni[7], MSc

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Related Article:

Correction of: http://researchprotocols.org/2024/1/e51084

(JMIR Res Protoc 2024;13:e60392) doi:10.2196/60392

In “Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study” (JMIR Res Protoc 2024;13:e51084) the authors noted two errors.

In the originally published manuscript, an error was noted in author affiliation 2:

> *Health Professions Researchand Development Unit, Istituto di Ricerca e cura a carattere scientifico Policlinico San Donato, San Donato Milanese, Italy*

Which has been corrected to the following:

> *Health Professions Research and Development Unit, IRCCS Policlinico San Donato, San Donato Milanese, Italy*

The academic degrees for author Ida Vangone were originally published as "BCS, MSc". This has been corrected to "BSc, MSc".

The correction will appear in the online version of the paper on the JMIR Publications website on June 21, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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JMIR Res Protoc 2024;13:e60392
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Corrigenda and Addenda

Correction: Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial

Heena Akbar[1,2], MPH, PhD; Madison Contor[3], BSc; Winnie Niumata[4], RN; Debra Anderson[5], PhD; Danielle Gallegos[2], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e55435

(JMIR Res Protoc 2024;13:e65322) doi:10.2196/65322

In "Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial" (JMIR Res Protoc 2024;13:e55435) the authors made three additions.

A section of text has been added to the "Acknowledgements" that reads as follows:

> *The MMAS-8 Scale (U.S. Copyright Registration No. TX0008632533), content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAR, LLC., www.moriskyscale.com*

Additionally, two citations will be added after Reference 28 in the second paragraph of the "Objectives" section which appeared as:

> *The secondary objective is to determine whether, compared with control participants, the intervention group achieves changes to bring body composition measurements closer to the recommended healthy range for specific cultural groups (eg, BMI ≤30 kg/m^2 and waist circumference <80 cm based on World Health Organization criteria) and improved diabetes self-care scores on diet, physical activity, routine health checks, and medication adherence assessed using the validated Summary of Diabetes Self-Care Activities scale [23,25-31].*

This will now be changed to read as:

> *The secondary objective is to determine whether, compared with control participants, the intervention group achieves changes to bring body composition measurements closer to the recommended healthy range for specific cultural groups (eg, BMI ≤30 kg/m^2 and waist circumference <80 cm based on World Health Organization criteria) and improved diabetes self-care scores on diet, physical activity, routine health checks, and medication adherence assessed using the validated Summary of Diabetes Self-Care Activities scale [23,25-33].*

The references added are as follows, with all subsequent references reordered accordingly:

> *29. Berlowitz DR, Foy CG, Kazis LE, Bolin L, Conroy LB, Fitzpatrick P, et al. for the SPRINT Study Research Group. Impact of Intensive Blood Pressure Therapy on Patient-Reported Outcomes: Outcomes*

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Results from the SPRINT Study. N Engl J Med 2017; 377:733-44.

30. Bress AP, Bellows BK, King J, Hess R, Beddhu S, Zhang Z, et al, for the SPRINT Research Group and the SPRINT Economics and Health Related Quality of Life Subcommittee. Cost- Effectiveness of Intensive versus Standard Blood Pressure Control. N Engl J Med 2017; 377:745-55.

The correction will appear in the online version of the paper on the JMIR Publications website on August 26, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics

Gerald J Jerome[1,2], PhD; Lawrence J Appel[2,3], MD, MPH; Linda Bunyard[2], MS; Arlene T Dalcin[2], MS; Nowella Durkin[2]; Jeanne B Charleston[3], PhD; Norma F Kanarek[4,5], PhD; Michael A Carducci[5], MD; Nae-Yuh Wang[2,3,6], MS, PhD; Hsin-Chieh Yeh[2,3,5], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e54126

(JMIR Res Protoc 2024;13:e63678) doi:10.2196/63678

In “Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics” (JMIR Res Protoc. 2024 Jun 12:13:e54126), the authors noted one error.

In the originally published article, Figure 1 included additional information regarding the follow-up time points rather than focussing on baseline data. The originally published figure is available in Multimedia Appendix 1. Figure 1 has been corrected as follows:

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Figure 1. Flow of study participants.

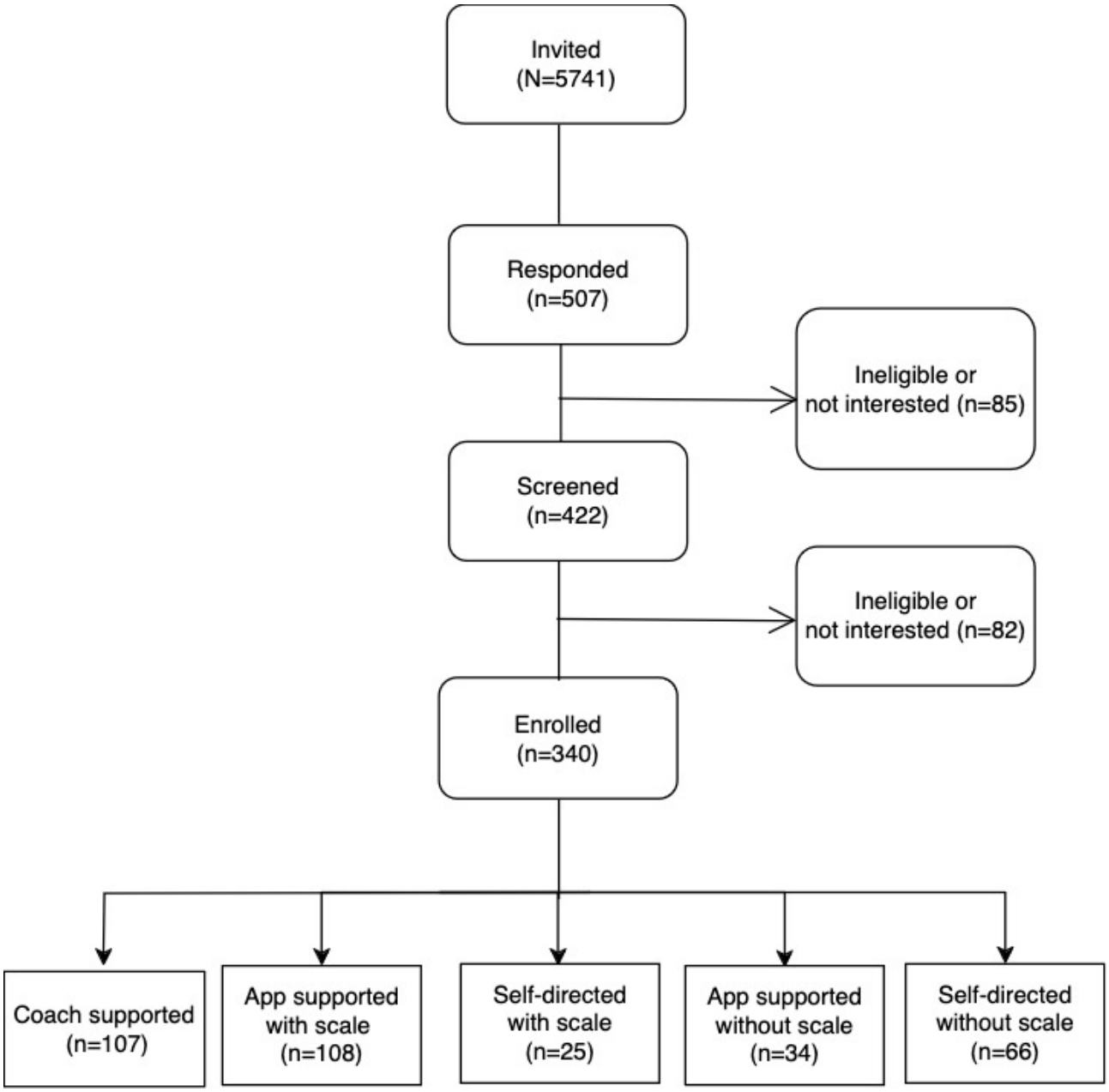

The correction will appear in the online version of the paper on the JMIR Publications website on October 7, 2024 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Multimedia Appendix 1
Original version of Figure 1.
[PNG File , 75 KB - resprot_v13i1e63678_app1.png]

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Correction: Behavioral Weight Loss Programs for Cancer Survivors Throughout Maryland: Protocol for a Pragmatic Trial and Participant Characteristics
JMIR Res Protoc 2024;13:e63678
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Corrigenda and Addenda

Correction: Using Digital Media to Improve Adolescent Resilience and Prevent Mental Health Problems: Protocol for a Scoping Review

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Related Article:

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In “Using Digital Media to Improve Adolescent Resilience and Prevent Mental Health Problems: Protocol for a Scoping Review” (JMIR Res Protoc 2024;13:e58681) the authors made one addition.

The following affiliation was added for the first author:

> *Doctoral Program in Public Health, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia*

This will be labelled as "affiliation 2", with all the subsequent affiliations being renumbered accordingly.

The correction will appear in the online version of the paper on the JMIR Publications website on December 5, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study

Debbie de Graaf[1], MSc; Nienke M de Vries[1], PhD; Tessa van de Zande[1], MSc; Janneke J P Schimmel[1], MSc; Sooyoon Shin[2], PhD; Nathan Kowahl[2], MSc; Poulami Barman[2], MSc; Ritu Kapur[1,2], PhD; William J Marks Jr[2], MD, MS; Alex van 't Hul[3], PhD; Bastiaan R Bloem[1], MD, PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e55452

(JMIR Res Protoc 2024;13:e68647) doi:10.2196/68647

In “Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study” (JMIR Res Protoc 2024 May 7:13:e55452) the authors noticed one error:

The last author's name was listed as:

Bastiaan Bloem

This has been changed to the following:

Bastiaan R Bloem

The correction will appear in the online version of the paper on the JMIR Publications website on December 09, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Model for Doctor of Nursing Practice Projects Based on Cross-Fertilization Between Improvement and Implementation Sciences: Protocol for Quality Improvement and Program Evaluation Studies

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Abstract

Background: Hundreds of nursing professionals graduate each year from Doctor of Nursing Practice (DNP) programs, entrusted with roles as practice scholars and leaders. Graduates are tasked to lead multidisciplinary knowledge implementation projects to improve safety, quality, and key performance metrics. Nevertheless, there is a continued lack of agreement and faculty dissatisfaction with the format, focus, and results of the DNP graduation projects. The use of a wide range of models and methodologies from different sciences for knowledge implementation introduces challenges to DNP students; affects the scientific rigor of the projects; and results in the overuse, superficial use, or misuse of the models. Quality improvement (QI) and program evaluation studies are substantial investments that may lead to waste and even harm if not well conducted. Traditional QI methodologies, commonly used in DNP projects, were found to be uncertain in improving health care outcomes. The complexity of health care systems calls for cross-fertilization between improvement and implementation sciences to improve health care outcomes.

Objective: This study describes the development, implementation, and evaluation of a hybrid model for QI and program evaluation studies to guide scholarship in the DNP program.

Methods: The hybrid model was based on cross-fertilization between improvement and implementation sciences. The model adapted the Getting to Outcome (GTO) and Knowledge to Action (KTA) models as the overarching process models for knowledge implementation. Within each phase of the GTO and KTA models, expected barriers and facilitators for the implementation and adoption of innovation were identified based on the CFIR (Consolidated Framework for Implementation Research). Accordingly, strategies to facilitate the implementation and adoption of innovations were identified based on a refined list of implementation strategies and QI tools. The choice of these models was based on the top 5 criteria for selecting implementation science theories and frameworks. Seven DNP students used the hybrid model to conduct QI projects. Students evaluated their experiences by responding to a Qualtrics survey.

Results: The hybrid model encouraged a comprehensive systematic way of thinking, provided tools essential to implementation success, emphasized the need for adaptability in implementation, maintained rigor in QI, and guided the sustainability of change initiatives. Some of the challenges faced by students included finding reliable and valid measures, attaining and maintaining staff buy-in, and competing organizational priorities.

Conclusions: Cross-fertilization between improvement and implementation sciences provided a roadmap and systematic thinking for successful QI projects in the DNP program. The integration of the CFIR with the GTO or KTA process models, enforced by

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the use of evidence-based implementation strategies and QI tools, reflected the complexity of health care systems and emphasized the need for adaptability in implementation.

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KEYWORDS

quality improvement; implementation; Doctor of Nursing Practice; model; methodology; Nursing; Doctor of Nursing; hybrid approach; implementation sciences; scholarship; scholars; Nursing Practice Program; nursing program

Introduction

The Doctor of Nursing Practice (DNP) is the entry-to-practice degree for advanced practice registered nurses and focuses on improving health care outcomes, system practices, and health policy through knowledge implementation [1,2]. According to the American Association of Colleges of Nursing, there were 426 DNP programs in the 50 US states and the District of Columbia, in addition to 70 programs in the planning stage, in 2022 [3]. The number of students enrolled in DNP programs increased from 40,834 to 41,021 from 2021 to 2022 [3]. A core requirement for the degree is the design, implementation, and evaluation of a DNP project [4]. The exponential growth in the number of DNP programs is accompanied by a large inconsistency in the format and focus of the DNP projects [5,6]. To provide clarity, the American Association of Colleges of Nursing recommended that projects focus on knowledge implementation by introducing a change to improve health care outcomes and to have a system focus [2]. Despite these recommendations, a study that included 90 DNP program directors revealed the continued lack of agreement with the format and focus of the DNP projects and reported dissatisfaction of 87% of faculty with the DNP projects [7]. To this end, this study aims to describe a model for designing, implementing, evaluating, and sustaining DNP projects.

At a public university in the Southwest of the United States, our School of Nursing requires DNP projects that are quality improvement (QI) or program evaluation focused. Students over the past 10 years used different theories, models, and methodologies to guide the design, implementation, and evaluation of their projects. Although a difference exists between "models" and "frameworks," these terms will be used interchangeably in this paper. The theories, models, and methodologies used by students include (1) evidence-based practice (EBP) models (eg, Iowa Model and Academic Center for Evidence-Based Practice [ACE] Star Model), (2) implementation science models (eg, Promoting Action on Research Implementation in Health Services [PARiHS] Framework, Knowledge to Action [KTA] Framework, and the Consolidated Framework for Implementation Research [CFIR]), (3) program evaluation models (eg, Logic Models and Getting to Outcomes [GTO] Model), (4) improvement models (eg, Donabedian, Kotter, and Lewin Models), (5) QI methodologies (eg, Plan, Do, Study, Act [PDSA] and Six Sigma—Define, Measure, Analyze, Improve, and Control [DMAIC]), and (7) midrange change theories (eg, Rogers' Diffusion of Innovation).

The use of a wide range of theories, models, and methodologies from different sciences for knowledge implementation and uptake and the absence of criteria to guide that selection introduced challenges to our students in all phases of the project; affected the scientific rigor of the projects; and resulted in the overuse, superficial use, and misuse of the models [8]. This was manifested by several poor practices including a mismatch between the intended use of the guiding model and the complexity of the clinical problem at hand; the selection of inappropriate or least appropriate theory or model to guide the intended change; the selection of multiple (more than 3) models and theories without identifying how the relationship between them supports the different phases of the project; superficial use of the theory or model (ie, selective use of phases, dimensions, or criteria, and the elimination of critical components of a model or a theory); inaccurate representation and application of the dimensions; the lack of using a process model to guide the implementation of a change; and most importantly, the lack of integrating the theory or model into all phases of implementing a change (ie, the theory was mentioned in the planning phase but never used in the implementation, evaluation, or sustainability phases).

The lack of understanding of the intended purposes of these sciences and the interchangeable use of terminologies further complicate the situation. Multimedia Appendix 1 [9-17] provides the definitions of these sciences and associated terminologies. Other terms related to knowledge implementation were well-defined by Graham et al [18]. As shown in Multimedia Appendix 1, the goal of these sciences is to improve health by "producing" or "implementing" knowledge to improve the structure, processes, and outcomes of health care systems [9-17]. For example, implementation science, translation 1 science, and translation 3 science focus on the research, with the goal of "producing and generalizing" new knowledge. QI and EBP, on the other hand, focus on improvement and aim at "applying or implementing" the best available knowledge. Program evaluation is a scientific methodology that aims at either producing or implementing knowledge based on the approach used to conduct the evaluation (ie, research vs QI). On the other hand, most of the models used to guide the conduct of implementation science, QI or improvement science, program evaluation, translation 2 science, and EBP share similar theoretical underpinnings (eg, system theories, change theories, and cognitive theories).

The complexity of health care systems calls for a system-thinking approach to QI. System thinking examines the interrelatedness and interdependence among the system's components to understand the system's behavior and design interventions to improve outcomes. A recent systematic review found the effectiveness of continuous QI methodology for

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improving health care outcomes to be uncertain. The uncertainty was related to the complexity of health care systems, in addition to poor application of the methodology [19]. In the same vein, a recent systematic review challenged the legitimacy of PDSA-based QI projects in specifying and achieving predefined improvement aims, highlighted the poor and inconsistent application of the methodology, and called for a theoretical rationale to support the conduct of the methodology and interpretation of the results [20]. Similarly, and to better improve the quality of care, Leeman et al [21] and Check et al [22] called for cross-fertilization between improvement (or QI) and implementation sciences. Implementation science extensively studies best implementation strategies for knowledge implementation and uptake, provides process and determinant models for successful implementation, and focuses on the complexity of the system's components in implementation. QI or improvement science provides useful tools to assess the need for the local context, measures outcomes, and adapt available knowledge at the local level.

The availability of many theories and models for knowledge implementation, the challenges faced by our DNP students in model selection and application, the need for a system thinking approach in QI, the shortcomings of continuous QI and PDSA methodologies in improving health outcomes, and the fact that there is no one best theory to guide all types of projects support the need for cross-fertilization and a hybrid approach in theory and model application between QI and implementation sciences. To this end, this paper describes a hybrid approach to QI in DNP projects by integrating GTO and KTA with the CFIR model and complementing that with the refined list of implementation strategies from Powell et al [23]. A hybrid approach between the different sciences is warranted to deepen our understanding of the interrelated, interdependent contextual factors and the complexity of health care systems, processes, and medical conditions.

The study-specific aims are to (1) describe the development, implementation, and evaluation of a hybrid model between improvement and implementation sciences to guide QI and program evaluation studies in the DNP programs and (2) explore the value of the model and challenges faced in all phases of the DNP projects (planning, implementation, evaluation, and sustainability).

Methods

Overview

The methods section describes the hybrid model and its components; the criteria for selecting GTO, KTA, and the CFIR as process and determinant models; the need to adapt existing models; piloting the hybrid model; and the data analysis plan.

Development of the Hybrid Model

Faculty and the DNP curriculum committee at our School of Nursing recognized the necessity for a standardized and rigorous approach to DNP scholarly projects. This awareness sparked discussions within committee meetings regarding the most effective models to guide DNP projects. The first author of this study (AS) led a task force to develop a comprehensive "DNP Project Guide." The guide encompassed various elements such as the purpose of the DNP program; the focus of the DNP projects; settings of the DNP projects; project format; knowledge dissemination approaches; project timeline; interprofessional collaboration; responsibilities and qualifications of the DNP project committee members; DNP project phases; and a cross-map of DNP project courses, project phases, and milestones. Expanding on this groundwork, the first author (AS) led the development of a new model for DNP scholarly projects and solicited input on its different aspects in subsequent faculty meetings.

Description of the Hybrid Model

The challenges faced by our DNP students in model selection and application call for (1) a "process model" to guide all phases of the DNP project, (2) a "determinant model" to focus attention on the complexity of health care systems, and (3) the application of context- and evidence-based implementation strategies to enhance knowledge uptake and sustainability. Drawing from our expertise in implementation science, QI, and program evaluation, along with input from faculty, a decision was made to use GTO as the overarching process model and the CFIR as the determinant model. KTA was also used as another process model due to its wide adoption in implementation science. These models were complemented by the refined list of implementation strategies and other QI tools from Powell et al [23], as described further below. The choice of these models was based on the top 5 criteria for selecting implementation science theories and frameworks [8]. The criteria include empirical support, application to wide settings or populations, explanatory power, description of a change process, and analytical level (ie, individual, organizational, and system).

In terms of empirical support and application to wide settings or population criteria, the CFIR is the most cited determinant model in implementation science [24], KTA is a widely used process model in implementation science [25], and GTO is a widely used program evaluation model [26]. In terms of explanatory power and description of the change process criteria, the selected models focus on the process of implementation and implementation barriers and facilitators during the full scope of innovation or knowledge implementation, that is, before, during, and after implementation. Regarding the analytic-level criterion, the models consider all levels of implementation for successful adoption. Adoption of innovation occurs at the external, organizational, innovation, and individual levels. Considering the full scope of implementation and the multiple levels of adoption should (1) facilitate engaging the right stakeholders in the implementation process, (2) promote the uptake and ownership of the innovation, (3) build key dimensions of organizational capacities to initiate and sustain a change, (4) foster inter- and intraorganizational collaboration, and therefore (5) provide STEEEP (Safe, Timely, Effective, Efficient, Equitable, and Patient-Centered) care.

The hybrid model consisted of "adapted" versions (described below) of GTO or KTA models as the overarching process model for knowledge implementation. Within each phase of the GTO and KTA models, the expected barriers and facilitators for the implementation and adoption of innovation (ie, best

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evidence) were identified based on the CFIR—a determinant model. Accordingly, the implementation strategies to facilitate the implementation and adoption of innovation were identified based on the refined list of implementation strategies and QI tools from Powell et al [23]. Multimedia Appendix 2 [18] illustrates the integration of the CFIR constructs and implementation strategies into each phase of the "adapted" GTO and KTA models.

CFIR Model Overview

The CFIR model is a guide to systematically identify and assess barriers and facilitators to a new program and innovation implementation. The model was guided by studies across 13 fields of research and the analysis of 18 theories and models from different disciplines [27]. It includes 39 constructs that can influence implementation success. These are clustered into 5 domains: intervention characteristics, inner setting, outer setting, individuals' characteristics, and implementation process. These constructs can aid or hurt evidence-based program implementation, depending on their manifestation in organizations. Studies using the CFIR have identified the relationships between different constructs and implementation effectiveness [28,29]. Further, GTO studies have explicitly used the CFIR. In a comparison of community-based sites attempting to implement a drug prevention program with and without GTO, GTO sites had significantly higher average ratings than non-GTO sites for 2 constructs from the CFIR process domain: planning and reflecting and evaluating [30]. In addition, GTO sites had higher ratings of program fidelity, despite having worse CFIR ratings on the culture and available resources constructs. These findings suggest that strong planning, evaluation, and reflection—improved with a process model such as GTO—can aid implementation despite a less desirable implementation climate and further support the need for integrating a process model and a determinant model in QI and program evaluation studies.

GTO Model and the Need for Adaptation

The GTO is a 10-phase action-oriented model for planning, implementing, evaluating, and sustaining innovations and programs. The original phases include (1) needs and resources assessment, (2) goals and desired outcomes, (3) best practices, (4) fit, (5) capacities, (6) planning, (7) process evaluation, (8) outcome evaluation, (9) continuous QI, and (10) sustainability [31].

In our hybrid model (Multimedia Appendix 2), the GTO model was adapted in 5 ways to better guide the implementation of DNP projects (Multimedia Appendix 2). First, "fit" and "capacities" phases were combined and expanded to "fitness and absorptive capacities." Unlike "capacity," absorptive capacity reflects the "dynamic capability of the organization pertaining to knowledge creation and utilization that enhances a firm's ability to gain and sustain a competitive advantage" [32]. Absorptive capacity entails 4 multilevels or dimensions of organizational learning and capabilities, which are knowledge acquisition, assimilation, transformation, and exploitation [32]. An organization's absorptive capacity is critical to its innovative capabilities; is a function of the organization's prior related knowledge; and is influenced by all technical, behavioral, and cultural aspects of the organization [32,33]. Accordingly, the "fitness" phase in the GTO model—the match between the innovation and the organization or user or patient population—is embedded into the organizational absorptive capacity. We decided to keep the term "fitness" in the phase name to remind users of the adapted model to examine fitness at multiple levels (ie, organization, end user, and patient population). According to Cox et al [34], organizational capacity revolves around organizational culture and communication, which in turn are linked to 6 capacity dimensions of leadership, strategy, structure or governance, skills, human capital, and accountability. Effective communication and supportive culture are essential to successful implementation and fundamental for the organization to achieve high performance.

Second, an "implementation" phase was added as part of the cyclic phases after the "planning" phase to move the process to "evaluation." This adaptation is congruent with the action-oriented nature of the GTO model. The third adaptation of the GTO model was clarifying that "process evaluation" means "evaluation of the implementation process." The purpose of this change was to eliminate any confusion between "implementation process evaluation" and the evaluation of "process measures." Although there is some overlap between the 2, "evaluating the implementation process" focuses on 6 main measures of implementation fidelity (the degree to which the innovation was implemented as prescribed in the original protocol), penetration, appropriateness, actual adoption, cost, and sustainability of the innovation [35]. On the other hand, a process measure focuses on the workflow and operations performed to achieve the main outcome metrics. The Institute for Healthcare Improvement identified 3 types of metrics in QI: outcome measures, process measures, and balance measures [36]. The outcome metrics are reflected by the goal of the project. Balance measures track the unintended consequences, if any, resulting from implementing a change or innovations. For example, in implementing a clinical practice guideline (CPG) for cancer screening, an outcome measure would be the cancer screening rate, the process measures might be adherence to CPG use and wait time for a patient to obtain a screening appointment, and a balance measure might be the accuracy of the screening results. Similarly, in implementing a provider in triage model in an emergency department, an outcome measure could be the percentage of patients who left without being seen, process measures could be "door to provider time" and nurse and clinician satisfaction with the provider in triage model, and a balance measure could be "left without treatment" and patient satisfaction with emergency department services. In these 2 examples, it is worth noting that "adherence to CPG use" and "nurse satisfaction" (process measures) could also serve as a proxy for "actual adoption" (adherence to CPG use) and "appropriateness" (clinician satisfaction), which are implementation-related measures. On the other hand, not all process measures reflect implementation-related measures. For example, "time to obtain a screening appointment" and "door to provider time" in the examples above are not 2 of the 6 implementation-related measures.

Fourth, we also changed "outcome evaluation" to "evaluation of measures" to reflect the complexity of measures in QI (ie,

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process, balance, and outcomes). Fifth, we combined the "continuous improvement" and "sustainability" phases because continuous QI is a sustainability indicator and a central element of sustainable development [37]. Changes and continuous improvements need to be sustained to achieve their values to consumers of care.

KTA Model and the Need for Adaptation

KTA consists of two interdependent, interrelated phases of (1) knowledge creation that is surrounded by (2) an action cycle [18]. Knowledge creation produces guidance and tools to inform practice, while the action cycle is action oriented to select and implement the best available knowledge to improve practice (ie, the focus of QI). Since improvement science involves the "implementation" of the best available knowledge, the use of KTA to guide QI projects is limited to the action cycle. The KTA framework is based on 31 planned action theories about the process of change [25]. Studies using the KTA model have demonstrated the dynamic, nonlinear aspect of knowledge translation and implementation [25]. However, recent scope reviews that used KTA in behavioral change in rehabilitation and educational interventions for the management of sleep disorders supported the complexity of knowledge implementation and recognized the need to (1) complement the KTA model with determinant models to better assess barriers to implementation and influence implementation outcomes and (2) guide the selection of implementation strategies [38,39]. Along the same line, our hybrid model supports the need for a determinant model (ie, the CFIR) to complement a process model (ie, KTA or GTO) and the need for a refined list of context- and evidence-based implementation and QI strategies to improve implementation fidelity, that is, the list of implementation strategies from Powell et al [23].

A great similarity exists between the original phases of KTA and GTO models (Multimedia Appendix 3). Both models address knowledge implementation starting by identifying the opportunity for improvement (problem) through sustainability. Similar to GTO, KTA was adapted in our hybrid model to better guide the implementation of DNP projects as a process model (Multimedia Appendices 1 and 2). The adaptation (Multimedia Appendix 3) includes (1) adding a "Goals and Desired Outcomes" phase, (2) adding a "Planning" phase, (3) changing "monitor Knowledge use" to "Evaluation of implementation" to capture other crucial aspects of the implementation process, (4) changing "Evaluate outcomes" phase to "Evaluation of Measures" to reflect the complexity of measures in QI, and (5) changing "Sustain knowledge use" to "Sustainability" to emphasize the fact that sustainability is not limited to knowledge "use" but includes sustaining all measures (process, outcome, and balance).

Multimedia Appendix 2 presents the GTO and KTA models with the adapted phases and emphasizes the dynamic nature of QI and program evaluation studies, that is, the need to complete some phases concurrently, adapt subsequent phases based on earlier phases and preliminary results, and the need to adapt and revisit earlier phases.

Integrating CFIR, Implementation Strategies, and QI Tools Into the Adapted Process Models

Multimedia Appendix 2 demonstrates the most important constructs to be considered in each phase of implementation in QI and program evaluation studies based on our expertise in improvement and implementation sciences and program evaluation. Researchers can adapt the list of constructs to fit the needs of the study based on the context of implementation [27]. Our selection of the constructs, and consequently implementation strategies and QI tools, in each phase of the implementation process was also guided by research findings related to core context dimensions in implementation science [40]; heterogeneity in implementation outcomes and dimensions of implementation weaknesses [41]; the relationship among organizational culture, capacity, and communication [34]; stages of knowledge use [42,43]; and strategies for aligning QI science and implementation science [21].

Piloting the Hybrid Model

Students enrolled in the DNP program typically choose models to guide their QI projects based on their familiarity with a model, its previous application in similar studies and clinical contexts, or recommendations from their DNP project mentor. Those without prior exposure to the chosen QI guiding model typically grasp its application with the support of their mentor during the phases of designing, implementing, and evaluating their DNP projects. In this study, none of the involved students had prior experience with KTA, GTO, or the CFIR. The first author (AS) of this study served as the primary mentor for 7 DNP students and with support from a comentor guided students through integrating and applying the hybrid model.

The hybrid model was piloted by 7 DNP students: 5 in the post–Bachelor of Nursing–to-DNP track (BSN-DNP) and 2 in the post–Master of Nursing Science–to-DNP track (MSN-DNP). The 2 tracks have the same program objectives, outcomes, and standards for the DNP project. The only difference concerning the project is the time for completion. Students in the BSN-DNP track complete their projects in 3 semesters, while students in the MSN-DNP track complete their projects in 2 semesters.

The hybrid model was described to all students in the first DNP project course. Students in the BSN-DNP track incorporated GTO as the overarching process model, while students in the MSN-DNP track used KTA. All students used the CFIR as the determinant model, Powell et al [23] refined list of implementation strategies, and different QI tools. The latter included tools such as a swim lane workflow analysis, fishbone analysis, Gantt charts for project management, and control charts of trended data for the main outcome variable before, during, and after implementation. Students were familiar with these tools due to prior application in previous courses. Another required tool that guided project implementation was the TIDieR (template for intervention description and replication) checklist [44]. The primary DNP project mentor (AS, the first author of this study) and the comentor (Amanda Bridges) met with the students monthly to help them apply the hybrid model, monitor progress, maintain rigor and sustainability, and help identify and solve implementation barriers early in the process.

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GTO offers a range of tools to facilitate its application. The list of tools is available on the model's website. It is important to note that some of these tools were adapted to fit the nature of QI studies, while others were supplemented with more detailed tools in implementation science (eg, TIDieR). For example, students used a Literature Analysis Table that focused on different available interventions or innovations used to improve the primary project outcome. In addition to the conventional analysis of the literature (covering study design, sample, setting, etc), the analysis focused on the features of each innovation, necessary implementation resources, implementation results, factors contributed to implementation sustainability, and lessons learned.

Model Evaluation

The model was evaluated by students using a Qualtrics survey distributed to students via a link at the end of their DNP projects. All students successfully completed their projects in a variety of inpatient and outpatient settings and thus were eligible to participate in evaluating the hybrid model. The survey included two questions soliciting feedback on (1) the value of the hybrid model in project design, implementation, evaluation, and sustainability and (2) the main challenges faced in all phases of the DNP project. Students received 3 reminders to improve the response rate.

Ethical Considerations

The study was approved by the institutional review board of the University of Texas Health Science Center at San Antonio (IRB; protocol 20210487) as a "non-regulated QI educational project." After the IRB approval, the Qualtrics survey was sent to all students who participated in the pilot. The IRB granted a waiver of consent for educational research. An information sheet was presented at the beginning of the survey with details about the value of responding to the survey, anonymity of responses to maximize objectivity, and confidentiality of the data. Voluntary participation was emphasized in the information letter. Compensation was not offered for participation.

Data Analysis

The 4-stage content analysis methodology by Bengtsson [45] was used to categorize narrative data into themes. To maintain, the transparency, quality, and trustworthiness of the analysis, 2 researchers (AS and Ana Vera) performed the analysis separately and met to discuss the findings and reach a consensus. In the decontextualization phase (stage 1), the 2 researchers read the answers provided by students thoroughly to identify meaning units and generate codes. In the recontextualization stage (stage 2), the researchers went back to the original text to ensure they comprehensively captured all ideas and meanings and revisited the unused text for consideration to be included. In the categorization stage (stage 3), the meaning units were condensed to categories or themes without losing the meaning of the content. In the compilation stage (stage 4), quotes were extracted to support the main themes. As the survey responses were anonymous, we refrained from conducting an "informants check," which involves verifying the alignment between respondents' submitted answers and identified themes or meaning units. However, to mitigate this limitation and to improve the confirmability of the findings, the second researcher (Ana Vera) was a colleague with content analysis expertise who was not involved in the study.

Results

All students designed and implemented projects with QI focus, and none of the projects involved program evaluation. All students (N=7) responded to the survey. Multimedia Appendix 4 presents the themes that represent the value of the hybrid model and challenges reported by students in project design, implementation, and evaluation. The themes are presented in descending order of significance, determined by the quantity of student feedback received for each theme. As per students' feedback, the primary strengths of the hybrid model revolved around its capacity to offer a holistic systematic approach to thinking and the necessary tools for effectively communicating project progress and ensuring implementation fidelity. The model helped students in recognizing how various aspects of implementation are interconnected and supported the complex nature of health care systems and knowledge implementation. The model also maintained rigor in QI, presented a roadmap for a successful project, and empowered the institutionalization of innovation for sustainability. Not surprisingly, the model emphasized the need for adaptability in implementation as it reflected the complexity inherent in health care systems.

Despite these benefits, challenges are inevitable in improvement and implementation endeavors. The challenges reported by students include finding reliable and valid measures, establishing and maintaining staff buy-in, timely access to data, and ensuring the project remains an organizational priority given other competing priorities and organizational changes. Other challenges were related to managing the literature review and selecting the right balance measures.

Discussion

Principal Findings

The need for a theoretical basis for knowledge implementation and uptake has been well supported in the literature [40]. Yet, the availability of a mountain of models and theories for knowledge uptake introduces a burden on researchers and practitioners to choose from [46] and results in a "haphazard selection" or a selection that is "driven by convenience or prior exposure" [8]. Selecting the most appropriate model is crucial to provide systemic thinking for project success; enrich the scientific underpinnings of improvement and implementation endeavors; and minimize "the black box of implementation" and challenges in initiating, implementing, evaluating, and sustaining a change [35]. QI and program evaluation projects are substantial investments that may lead to waste and even harm if not well conducted. The complexity of health care calls for a cross-fertilization between improvement and implementation sciences. This paper presented an improvement-implementation hybrid model to guide scholarship in QI and program evaluation studies.

The hybrid model was successfully implemented to guide QI projects in different inpatient and outpatient settings. The hybrid

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model provided a roadmap for rigorous and sustainable QI projects and was crucial to implementation success. Faculty who attended the final presentations of DNP projects using the hybrid model praised the systematic methodology for improving health care outcomes and reinforcing the projects' rigor.

Establishing and maintaining staff buy-in was one of the challenges reported by some students during project implementation. Examples of strategies students implemented to overcome this challenge include the use of project champions, securing leadership support, working on a project that is an organizational priority, creating a sense of urgency to the need of the project, communicating milestones and project progress, conducting rigorous training programs with sufficient support resources for innovation use, and engaging users in every step of the project. However, despite these evidence-backed strategies, sustaining staff enthusiasm and support proved challenging due to competing priorities, notably in projects within acute care settings that experienced significant structural changes, such as transitioning to COVID-19–designated units. Additionally, change in unit directors was a factor in delaying some projects and also impacted staff buy-in. The support of unit directors and charge nurses is essential to project success. These leaders usually act as implementation champions and support students in navigating the system.

Most of the other challenges reported by students in project design, implementation, and evaluation were not related to the hybrid model. For example, managing the literature review and selecting the most appropriate balance measures were expected because of the learning curve to attain these skills in graduate studies. In each DNP project, students complete a comprehensive literature search to identify the best available knowledge and innovations that have been implemented in similar settings to improve the main outcome measure. "Having a manageable set of studies to analyze and synthesize," as reported by students, is a function of selecting the best search terminologies and filters or limits. Similarly, the challenges faced by some students in finding instruments for their process measures (eg, "nurse competence in nasogastric tube care") were not model related. Students had to create these measures based on policies and procedures recommended by professional organizations and test the instruments for face validity before using them in their projects. Nurse competence is a prerequisite to the appropriate use of innovation in these projects. Appropriate use, in turn, reflects "actual adoption"—an implementation-related measure. The lack of sufficient valid and reliable measures for the 6 implementation-related outcomes is well reported in the literature [47-49]. Part of this challenge was related to the fact that the selected process measures are specific to the project. These challenges were acknowledged in the limitation section of the DNP projects.

It is worth noting that following the successful outcomes of this trial project, the DNP curriculum committee and faculty opted to formally incorporate the hybrid model into the DNP program. This structured approach aims to ensure consistent and standardized use of the model across all phases of future DNP projects.

Future Considerations

The substantial diversity in the methodological approaches and rigor of DNP projects across various DNP programs presents significant challenges for faculty, students, and health care organizations. In this study, we aimed to deliberately use well-established, empirically tested, and common models; furnish a structured path for systematic QI planning and implementation; and improve the rigor of QI endeavors. Establishing a standardized and rigorous approach is crucial to prevent any waste associated with unsustainable QI projects, minimize the need for deimplementation, and ultimately improve health care outcomes.

For successful implementation, the hybrid model should be integrated into the DNP curriculum. The frameworks, methodologies, and tools used in the hybrid model (Multimedia Appendix 2) may guide DNP education and curriculum revision. Educators in the DNP program can incorporate many strategies and models in their courses to equip students with sufficient knowledge to design and implement rigorous QI projects. These may include, but are not limited to, team science and team development, best practices and models for stockholders' engagement, best practices and models for optimizing organizational absorptive capacities and capabilities, best practices in sustainability and sustainability models, data visualization in QI, and quality metrics (ie, balance, process, and outcome metrics). The integration of improvement and implementation sciences in 1 model may also advance project dissemination using multiple venues (eg, journals that target implementation science and journals that target improvement science).

Widespread adoption of the hybrid model also necessitates dialogue with clinical partners regarding the value of the model. The hybrid model may allow clinicians and change leaders to consider the full scope of implementation, build key dimensions of organizational absorptive capacity in practice, foster inter- and intraorganizational collaboration, and therefore provide a STEEEP care. However, and based on our experience, some clinical partners are accustomed to specific QI approaches (eg, PDSA, continuous QI, and DMAIC) and expect DNP students to demonstrate these approaches in their proposed projects before endorsing project implementation in their settings.

Equally important is the development of a cadre of faculty capable of guiding students in applying improvement and implementation science principles. Schools of nursing should empower faculty with improvement and implementation science competencies, foster an environment conducive to knowledge sharing among faculty members (eg, faculty huddles), and establish a network of faculty engaged in interdisciplinary QI collaborations. This holistic approach aims to bridge the gap between theoretical understanding and the practical application of QI and implementation science, ensuring that QI initiatives are methodologically sound when implemented in health care settings.

By developing the hybrid model, our intention was not to confine the use of other implementation science models. Model selection in QI and implementation science should be supported by a strong rationale that establishes model relevancy to the

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study objectives; pragmatic applicability and fitness to the context, clinical problem, and patient population; model creditability through expert consensus and supporting literature; and other important criteria [8]. Justification for model selection is pivotal to ensure a purposeful and methodologically sound approach, thereby strengthening the credibility of QI and implementation science studies.

Limitations

The hybrid model was created to guide DNP students in QI and program evaluation projects. The model was used by 7 students to pilot its feasibility. All students' projects focused on QI, and none of the projects was program evaluation. Although the model provided many benefits and guided the implementation of rigorous projects, the use of the model by a larger number of students is essential to generalize its use as a guide to all DNP projects that focus on QI and to assess its value in program evaluation studies. While we have not formally sought faculty feedback on the newly developed model, all faculty members acknowledge the necessity of a hybrid improvement-implementation approach in DNP projects. The wide use of the hybrid model in the future will require an assessment of faculty experience regarding the model's value in QI for broader applicability. Future studies should incorporate interviews, alongside surveys, to seek faculty and students' input.

Conclusions

Knowledge implementation and uptake are essential yet complex aspects of health sciences to improve health care and systems outcomes. Improvement endeavors require a hybrid model that integrates improvement and implementation sciences. The integration of the CFIR model with the GTO or KTA process models accompanied by the use of evidence-based implementation strategies and QI tools provided a roadmap and systemic thinking for successful QI projects. The hybrid model can be applied to different inpatient and outpatient settings.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to presenting the data as quotes in Multimedia Appendix 4 but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions of terms.
[DOCX File , 16 KB - resprot_v13i1e54213_app1.docx]

Multimedia Appendix 2
A hybrid model for quality improvement (QI) and program evaluation studies.
[DOCX File , 70 KB - resprot_v13i1e54213_app2.docx]

Multimedia Appendix 3
Adaptation of Getting to Outcome (GTO) and Knowledge-to-Action (KTA) models.
[DOCX File , 15 KB - resprot_v13i1e54213_app3.docx]

Multimedia Appendix 4
Value of the hybrid model and challenges in project design, implementation, evaluation, and sustainability.
[DOCX File , 17 KB - resprot_v13i1e54213_app4.docx]

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Abbreviations

ACE: Academic Center for Evidence-Based Practice
BSN-DNP: post–Bachelor of Nursing–to–Doctor of Nursing Practice
CFIR: Consolidated Framework for Implementation Research
CPG: clinical practice guideline
DMAIC: Define, Measure, Analyze, Improve, and Control
DNP: Doctor of Nursing Practice
EBP: evidence-based practice
GTO: Getting to Outcome
IRB: institutional review board
KTA: Knowledge to Action
MSN-DNP: post–Master of Nursing Science–to–Doctor of Nursing Practice
PARiHS: Promoting Action on Research Implementation in Health Services
PDSA: Plan, Do, Study, Act
QI: quality improvement
STEEEP: Safe, Timely, Effective, Efficient, Equitable, and Patient-Centered
TIDieR: template for intervention description and replication checklist

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Protocol

Understanding Employee Voice Behavior Through the Use of Digital Voice Channel in Long-Term Care: Protocol for an Embedded Multiple-Case Study

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Abstract

Background: Specific challenges in the health care sector, such as hierarchical structures, shortages of nursing staff, and high turnover of nursing staff, can be addressed by a change process of organizational culture into shared governance. Data from business organizations show that the use of digital voice channels provides employee voice. This approach makes concrete the opportunity for employees to raise their voices by answering surveys and making comments in an anonymous forum, which subsequently positively influences staff turnover and sick leave. Since there is no clear understanding of how a digital voice channel can be used in long-term care to address employee voice, a research gap has been identified.

Objective: The purpose of ADVICE (Understanding Employee Voice Behavior; the acronym for this study) is to understand how the use of a digital voice channel performs in long-term care (residential long-term care and home care facilities). The aim of this study is to understand how the digital voice channel can support staff in making their voices heard and to see what managers need to use the voice channel to change the work environment.

Methods: An embedded multiple-case study will be used to explore the experiences of 2 health care providers who have already implemented a digital voice channel. ADVICE is organized into two main phases: (1) a scoping review and (2) an embedded multiple-case study. For this purpose, focus group interviews with employees, discursive-dialogical interviews with managers, meeting protocols, and data from the digital voice channel will be analyzed. First, all units of analysis from every embedded unit will be separately analyzed and then comprehensively analyzed to obtain a case vignette from every embedded unit (within-analysis). In the second stage, the analyzed data from the embedded units will be compared with each other in a comparative analysis (cross-analysis).

Results: The results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and, consequently, create a better work environment. Data collection began in August 2023, and from a current perspective, the first results are expected in summer 2024.

Conclusions: In summary, the results may help to better understand the use of a digital voice channel in the health care sector and its transformative potential for leadership. At the organizational level, research can help to improve the attractiveness of the workplace by understanding how to give employees a voice.

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KEYWORDS

digital voice channel; employee participation; employee voice; health care provider; home care facilities; long-term care; nursing home

Introduction

Overview

The International Council of Nurses points out that there is a need to reduce the dropout rate in nursing and promote the loyalty of employees to their health care provider [1]. Data from the Austrian Work Climate Index that are related to working conditions in the nursing professions describe that 65% of nurses intend to leave their current position, and 15% have plans to change their profession [2]. Furthermore, according to the NORDCARE report on working conditions in long-term care in Austria [3], the working conditions perceived by nurses have declined in recent years. As justifications, the respondents noted the increase in work demands, staff shortages, and lack of time for caring activities. A low level of autonomy, especially among nurses, is highlighted by the collected data. Nursing assistants and home assistants state that they feel left alone with the responsibility for people in need of care. The NORDCARE report [3] findings are corroborated by data from the Austrian Work Climate Index [2], indicating that 44% of employees lack or have inadequate chances to participate in work activities, which may negatively impact on-job satisfaction.

Background

To promote high-quality, person-centered care in the context of challenges related to nursing turnover as well as the different needs and requirements of different generations, health care providers need to invest in creating a productive work environment [4]. To sustainably change the culture in an organization, the interplay of transformational leadership, shared governance, and action processes is needed [5]. In particular, transformational leadership is presented as a leadership style that is action-oriented and enables development and change through shared governance. Shared governance is seen as a management approach in the sense of enabling all stakeholders and employees to have a voice in decision-making processes [5,6].

Recommendations to implement a change process in organizations using transformational leadership and shared governance are supported by the positive impact of the Pathway to Excellence in Long-Term Care (PTE-LTC) program. This is a special Magnet Recognition Program of the American Nurses Credentialing Center for long-term care. The PTE-LTC program is based on 6 pathway standards: professional development, shared decision-making, leadership, well-being, quality, and safety. The goal is to empower and give frontline staff a voice, promote staff participation in improving outcomes, create a sustained culture, strengthen interprofessional collaboration, and ensure the well-being of employees [7]. Key differences between the Magnet Recognition Program and the PTE-LTC program are that the PTE-LTC program includes a person-centered model of care and unlicensed assistive personnel such as nurse assistants [7]. Research indicates that the focus in health care organizations on a better work environment and higher engagement in shared governance decreases rehospitalization and lowers nurse burnout and job dissatisfaction levels [8-10]. A systematic review shows that certified magnet hospitals, compared with nonmagnet hospitals, have higher job satisfaction levels, less burnout, lower turnover, lower rates of nurse shortages, higher quality of care, and better patient outcomes [11].

The “Relationship-Centered Team Nursing Model for Care Delivery in Nursing Homes” is a nursing care delivery model that attempts to address workforce challenges in long-term care. The model describes 4 assumptions. The first is to skillfully manage a multilevel team with a focus on care coordination and communication; the second is to empower and develop staff and delegate appropriately and responsibly; the third is the requisite preparation of nursing staff to deliver person-centered care; and the fourth is nursing leadership. In conclusion, the model addresses an evidence-based approach, clear communication, and staff empowerment [4]. Clear communication means, according to Siegel et al [4], open, clear, and timely communication between staff, residents, their families, and the involved structures.

The PTE-LTC program and the “Relationship-Centered Team Nursing Model for Care Delivery in Nursing Homes” emphasize the importance of empowering frontline staff so that in practice they can have a participatory voice that aims to influence decisions, communicate ideas, communicate residents’ needs and requirements, and initiate change [4,7]. This participatory element of workplace democracy is known as employee voice. Employee voice refers to all organizational structures, mechanisms, or practices in which employees participate and try to influence their work and the performance of their organization [12,13]. The term employee voice has a long tradition in organizational research and is variously defined in the literature [14]. A summary by Dundon et al [15] describes the concept of employee voice in terms of four characteristics: (1) addressing dissatisfaction, opinions, or suggestions; (2) expressing a collective organizational culture; (3) managing decision-making processes; and (4) demonstrating a cooperative relationship between management and employees in an organization [15]. Elizabeth Wolfe Morrison, a professor of management and organization at the Stern School of Business, New York University, defines employee voice as “informal and discretionary communication of ideas, suggestions, concerns, problems, or opinions about work-related issues, with the intent to bring about improvement or change” [14].

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The literature on employee voice addresses promotive and prohibitive factors of voice, such as how supervisors respond to that behavior and the effects that voice has. For example, Holland et al [16] and Kee et al [17] show that mechanisms that address the voice of employees can reduce burnout, promote employee well-being [16], and influence organization development through structures that employees are encouraged to explore and give feedback [17]. However, according to Morrison [14], there is a need to consider how informal employee voice behavior is affected by formal opportunities and channels for voicing, both individually and collectively.

Recent developments in digital and communication technology have opened new opportunities to address employee voice [18-20]. For example, the social and economic scientist and sociologist Ellmer and Reichel [19] describe the possibility of a company mirror or digital voice channel. This digital communications technology enables voice by allowing employees to periodically report their work satisfaction through minisurveys and make anonymous comments in miniforums. Ellmer and Reichel [19] show in their case study that employees are encouraged to speak up and discouraged from an affordance perspective. In this context, the affordance perspective refers to the definitions of Gibson [21] and Norman [22] and means analyzing the possibilities for action that an artifact offers to an actor, as well as the constraints. The possibilities that an artifact can support or hinder a person in achieving a goal. These results indicate that the interplay of material and social aspects, that is, the characteristics of the voice channel and the responses of the management embedded in the respective organizational context, lead to employees perceiving the channel as either promoting or restricting speech. This further leads to whether employees feel encouraged or discouraged to speak up or not speak up [19]. In summary, a digital voice channel can have a positive impact on the identification and attachment of the employees with the company, leading to a reduction in turnover and sick leave, which depends on job satisfaction [16], perception of autonomy, the influence of organizational context [23], and the perception of safety [24] and dependencies [19]. These results indicate that a digital voice channel is not sufficient on its own; it must be seen as a part of an overall approach to shared governance [19].

Based on these findings, due to the increasing challenges related to nursing turnover and the different needs and requirements of different generations, new measures are needed to meet the increasing demand for nurses to ensure high-quality, person-centered care.

To date, the use of a digital voice channel in the health care sector has received little attention. Improvements in the health care structure, IT, organization, and legislation are needed to ensure that health care is error-free, efficient, and effective. The Health & Care Expert Council recommends investing in the promotion of digital health literacy, that is, empowering people to deal competently with the digitalization of health care [25]. Available data indicate that in the health care sector, it can be difficult for employees to have a voice due to hierarchical structures [17,26]. For example, Kee et al [17] research how nursing assistants can develop voice behavior that transcends hierarchical levels. The study results show that by training in personal reflection as well as individual coaching, nursing assistants are able to influence organizational structures and initiate change. As a result, it is necessary to understand the wider context of social processes in an organization to address the voice of employees. For example, to know that psychological safety and commitment-based safety management have an impact on whether nurses are willing to raise concerns and be aware that psychological safety is a social-cognitive variable that varies between individuals within the same work context [27-29]. Research also exists regarding the content and structure of simulation training on speaking up in health care organizations [30,31]. It should be noted that the evidence on simulation training has mainly focused on inpatient and emergency settings, operating theaters, and intensive care units and not on long-term care. Martin et al [32] suggest that relying solely on formal channels may discourage some individuals from speaking up, hence the importance of complementing with informal methods. It is recommended to use a combination of both to encourage a greater variety of voices to be heard. Further studies have examined the implementation of a new role called “guardian” to promote voice in the organization. The research indicates that this role should not only focus on formal acts of voice such as support and advice. Instead, a relationship role between the guardian and colleagues is needed, as well as a well-defined role between the existing channels for voice [33]. As Jones et al [34] and O’Donovan and McAuliffe [35] noted, it is unlikely to find a 1-size-fits-all approach to creating a culture where health care professionals can raise their voice. In summary, it must be mentioned that in the health sector, the term employee voice is not used consistently. The existing literature on the use of voice in health care focuses on the use of voice in the context of patient safety and error reporting. In summary, the current review by Lainidi et al [36] points to the lack of a comprehensive theory of employee well-being and communication in the health care sector, which leads to heterogeneous mechanisms and an unclear understanding of the phenomenon of employee voice in health care. Lainidi et al [36] argue that understanding the concepts of voice and silence from both organizational and employee perspectives is crucial, as is the need for different solutions for different contexts. This means that individual approaches and evaluations are needed to gain a deeper understanding of employee voice, especially in the long-term care sector.

In their systematic review, Mair et al [37] note that the published literature focuses on organizational aspects yet neglects the broader social framework that needs to be considered when introducing new technologies. More recently, Krick et al [38] have recommended more evaluations of digital technologies in a real-life setting. It is not about what is technically possible; rather, it is about how new digital technologies in the daily routine can be designed to consider staff needs and preferences [20,39]. Ong et al [40] address this research gap and analyze the implementation of a digital patient feedback system using normalization process theory (NPT) from May and Finch [41] and May et al [42]. NPT is a middle-range theory that provides a sociological framework to understand social processes. The theory was developed to understand how a practice becomes or does not become routinely embedded in social contexts. A total of 4 key components of the theory are of relevance: coherence,

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cognitive participation, collective action, and reflexive monitoring. These 4 components define the process of normalization. Coherence refers to the fact that the practice is an ensemble of beliefs, behaviors, and acts that are defined by a set of ideas about its meaning, uses, utility, and socially defined and organized competencies. The nature of embedding depends on the work that defines and organizes a practice as a cognitive and behavioral ensemble and requires that actors collectively invest meaning in it. Cognitive participation means that normalization depends on the work that defines and organizes the actors involved in a practice. Collective action includes the chain of interactions, that is, a place of mental and material work that deals with organizing and enacting a practice. Reflexive monitoring means the continuous formal and informal evaluation of the patterns of collective action and their outcomes by all participants [41,42]. Collectively, NPT provides an appropriate conceptual framework to understand issues relating to routinization of new technology [37,43]; it will therefore be used in the ADVICE (Understanding Employee Voice Behavior; the acronym for this study) study as the theoretical lens.

This study will fill a gap in knowledge because it aims to understand how staff and managers use a digital voice channel in the social context of health care providers who offer long-term care services, to subsequently understand how employee voice behavior is affected by the digital voice channel, and to explore what opportunities arise for the employees and for the organization through a digital voice channel. The digital voice channel is a browser-based software-as-a-service system that organizations can purchase on a subscription basis. The founders of the digital channel provider aim to empower employees to actively participate in the improvement and decision-making processes in their workplace by giving them the opportunity to (1) periodically report on their job satisfaction through minisurveys and (2) post anonymous comments in a miniforum. On the user interface, a dashboard with a graph shows the progression of a sentiment metric over time, allowing analysis of current and past sentiment levels in the organization. The sentiment metric is based on responses to anonymous minisurveys covering 6 categories: well-being, health, collaboration, potential development, work activity, and organizational culture. The standard pool of questions can be supplemented by various additional pools. Employees can select from a Likert scale ranging from 1 to 7 (1=does not apply at all to 7=completely true). To gather votes, a link to minisurveys (ranging from 3 to 10 questions) is sent to all employees through email at specified intervals (weekly or monthly), depending on the organization's preference. Managers are alerted when new votes or anonymous comments are available. This information, combined with the dashboard, can be used to identify and act on trends and dynamics in the team early on, allowing decisions to be made based on this information.

Aim of This Study

The aims of the study are to investigate the phenomenon of the digital voice channel in a real-life context and to explore opportunities and capture experiences to enable a systematic and professional approach in the future. This means that it is about generating new knowledge to make the new techniques usable and normalized in long-term care. The overall question is as follows: How does the use of a digital voice channel support opportunities to affect employee voice behavior in long-term care?

For the planned scoping review, the following question is relevant: Which opportunities are mentioned in the literature to address employee voice in health care providers?

For the embedded multiple-case study, further questions are relevant:

What are the experiences in long-term care with the use of a digital voice channel? How is the normalization process described in long-term care, and how do they differ?

Methods

Overview

To answer the research questions, an embedded multiple-case study will be chosen. Case studies can be used to analyze a phenomenon from multiple perspectives in a real-life context [44] to gain a deeper understanding [45]. The case study approach is especially appropriate when there is little understanding of a phenomenon in a certain context [44]. According to Yin [44], case study research is described by 5 components: questions, propositions, cases, data collection, and data analysis. Propositions in ADVICE will result from the scoping review and from NPT. The contexts are 2 health care providers that have already implemented a digital voice channel. These 2 long-term care providers describe the context in which several residential long-term care and home care facilities (cases) operate. Both providers use the same digital voice channel.

To analyze the social processes related to the use of a digital voice channel in health care providers, multiple data sources are necessary to create dense descriptions [44,46]. For this purpose, focus group interviews with employees, discursive-dialogical interviews [47] with managers (plus field notes), meeting protocols, and data from the digital voice channel will be analyzed (units of analysis). The qualitative data and comments in the survey will be analyzed by a deductive-inductive content analysis approach developed by Schreier [48]. Data from the digital voice channel include response rates and frequency of the mentioned topics. These quantitative data are displayed in the digital voice channel and provided by the health care provider. In summary, a phenomenon (digital voice channel) will be analyzed in a real context (2 health care providers) to achieve a deeper understanding of how a digital voice channel becomes a daily routine, that is, normalized [49]. It should be noted that the case definition or units of analysis, as well as other aspects of the research design in a case study, may be revised during data collection [50].

ADVICE is organized into two main phases: (1) the completion of a scoping review and (2) the conduction of an embedded multiple-case study, as shown in Figure 1.

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Figure 1. Overview of the research phases of the ADVICE (Understanding Employee Voice Behavior) study.

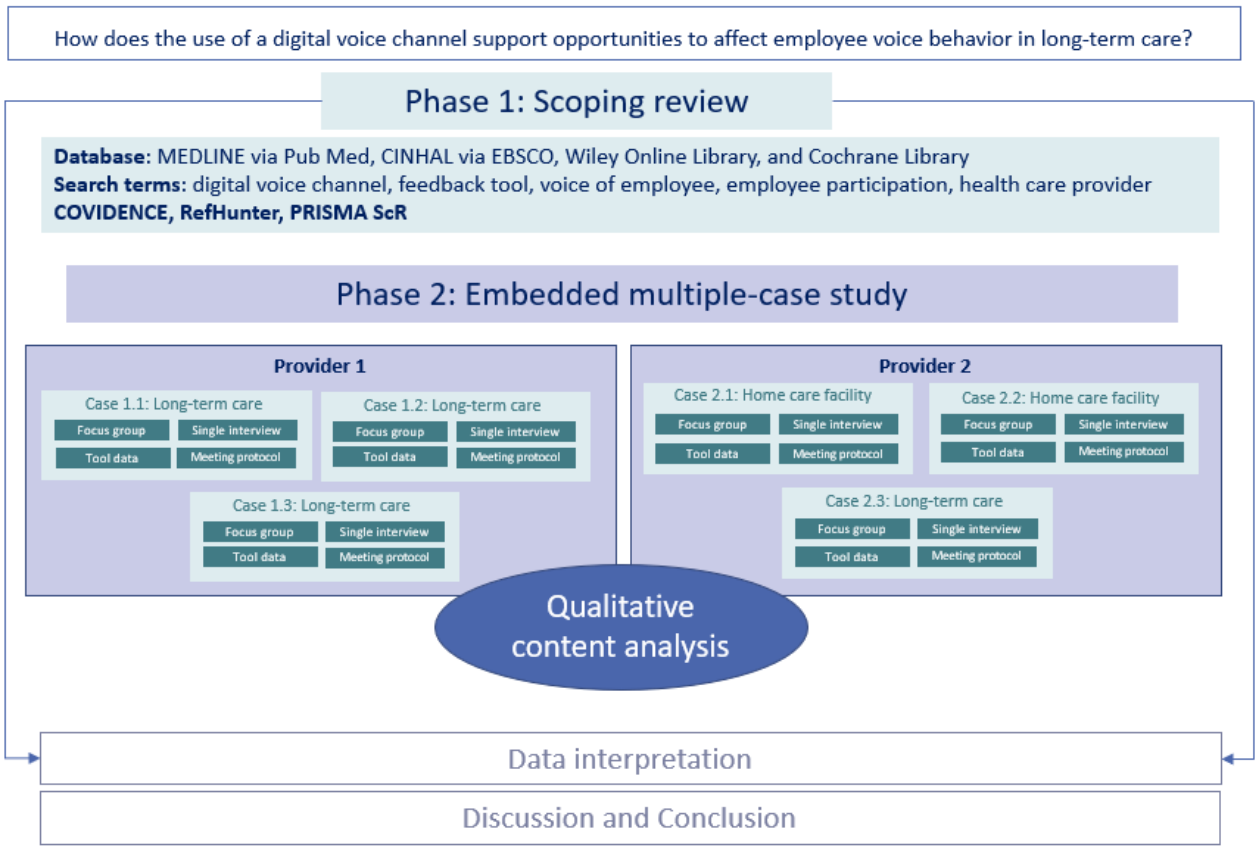

Phase 1: Scoping Review

The scoping review [51] aims to provide an overview of the literature on employee voice in health care providers and the use of opportunities or interventions such as voice channels, assessments, tools, feedback instruments, feedback training, or meetings to promote having a voice in the organization. To develop the search components, the question is integrated into the PICO (population, interest, and context) schema for qualitative studies [52], as shown in Textbox 1. The scoping review will be conducted using the PRISMA ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [53].

Textbox 1. PICO schema.

P: population

- Health care provider

I: interest

- Opportunities like digital voice channel

Co: context

- Employee voice

The search process took place in the period ranging from September 2022 to April 2023 in the MEDLINE through PubMed, CINHAL through EBSCO, Embase, Wiley Online Library, and Cochrane Library databases. Furthermore, the reference lists of relevant results will be screened and identified through Google Scholar. The following search terms will be used for the search: digital voice channel, feedback tool, company mirror, feedback, assessment, tool, voice of employee, employee participation, health care provider, long-term care, and home care facilities. Furthermore, the search terms and their synonyms will be linked to search strings using Boolean operators dependent on the databases, as well as MeSH (Medical Subject Headings) terms. After a sensitive search, the research team will consult with each other and adapt the search string. To support the search, the researchers will use the manual for literature search in specialized databases, namely, RefHunter [54]. The inclusion and exclusion criteria shown in Textbox 2 have been derived from the objective and research questions. There will be no restrictions regarding the currency of the literature included.

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Textbox 2. Inclusion and exclusion criteria for scoping review.

Inclusion criteria

- Health care provider, residential long-term care, and home care facilities
- Digital voice channel, digital feedback tools, feedback tools, evaluation, assessment, and tools
- Employee voice, employee participation, and team learning
- Qualitative and quantitative studies (all scientific studies)
- English and German

Exclusion criteria

- Other settings similar to business areas
- Summaries and discussions
- Other languages

Covidence is a software for managing and simplifying reviews. The program Covidence supports the review process after the removal of duplicates and enables the screening of the literature by 2 reviewers independently [55]. Specifically, the titles and abstracts will be reviewed against the inclusion and exclusion criteria to identify appropriate studies. In the next step, the full texts of the relevant studies will also be reviewed by 2 reviewers independently. Any disagreements about the eligibility of a study will be resolved by discussion in the research group. For data extraction, a standardized data extraction form will be developed. The form will be tested with the first 3 results and discussed in the research group. The items included in the description of each article will be selected following the Template for Intervention Description and Replication (TIDieR) [56] and Criteria for Reporting and Evaluation of Complex Interventions (CReDECI 2) in health care [57]. Based on the iterative character of the scoping review, all changes will be documented in the protocol [51]. The results of the scoping review will be used to develop propositions and the interview guide used in phase 2 of the ADVICE study.

Phase 2: Embedded Multiple-Case Study

Overview

Based on the results of the scoping review, this research phase aims to go into the field and immerse itself in the day-to-day work of the cases to understand the social processes that involve the promotion of employee voice. A detailed description of the components of Yin's [44] case study research design follows.

Casing

As shown in Figure 1, the ADVICE sample includes 6 different cases that are situated in 2 different contexts (providers 1 and 2). After Sandelowski [50], the cases for a case study are made, not found, through an iterative and theoretical process called casing. The boundary of the cases can be determined by the phenomenon of the use of the digital voice channel and the same scope of long-term care (content boundary). In these cases, the temporal boundary refers to the time of digital voice channel implementation. Starting with the time of implementation in provider 1, (2020) and provider 2 (2021), the end time describes the end of the data collection from the current point of view (2024) [44].

Provider 1 is a health care provider with approximately 1000 employees in different residential long-term care facilities in Austria. A digital voice channel has been used there since 2020. From the current perspective, this health care provider is defined by 3 cases through 3 long-term care facilities.

Provider 2 is a health care provider of several residential long-term care and home care facilities with approximately 5000 employees in Austria. The health care provider has been using a digital voice channel in a pilot phase in a few facilities since 2021. From the recent perspective, this health care provider is defined by 3 cases, namely, 1 residential long-term care and 2 home care facilities. In this case, a long-term residential care facility is an institution where people who need care can live or stay for a period of time under the responsibility of professional health care workers. Home care facilities provide professional care to patients in their own homes. The research team is aware of the different settings (residential long-term care and home care facilities) in the embedded units, which represents a limitation. The use of the different samplings can be argued by the fact that the focus of the analysis is the use of a digital voice channel, as well as employee voice behavior, in long-term care providers. Thus, it is not about the setting of health care providers per se; rather, the commonality is the same setting of long-term care, the same digital voice channel, and therefore, the same organizational culture with different characteristics. Additionally, based on the different settings, additional data, such as individual characteristics of the specific areas and differences, can be generated. The concrete number of employees and number of beds in the embedded units cannot yet be described, as the recruitment phase is only just beginning.

Data Collection

Overview

Based on the recommendation of Yin [44], data collection will take place using multiple sources of evidence. Consequently, data will be collected in the form of focus group interviews, discursive-dialogical interviews [47], meeting protocols, and data from the digital voice channel (anonymous survey data and free comments). During the whole research process, field notes and written memos concerning methodological, personal, and case-related issues will be taken by the first author [58].

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These different data are, according to Yin [44], the embedded units of analysis.

Specifically, data from the digital voice channel will be searched concerning the key mechanism of reflexive monitoring drawn from NPT [41,42], for example, how benefits or problems with the digital voice channel are identified or measured.

The Interviews

The interviews will include managers, nurses, and social care professionals in each case. Based on the Austrian Nursing Practice Act, nurses are defined as registered nurses with a diploma and a bachelor's degree (full-time training, 3 years), nursing specialist assistants (full-time training, 2 years), and nursing assistants (full-time training, 1 year). In addition to nurses, social care professionals also work in residential long-term care and home care facilities. There are 3 levels of qualification based on the Social Care Profession Act (home assistant, social care workers, and certified social care workers). Home assistant complete 200 hours of theoretical course and 200 hours of practical training. Social care workers complete a 1200-hour theoretical course and 1200 hours of practical training. Certified social care workers have an 1800-hour theoretical course and 1800 hours of practical training.

It should also be noted that medical care in residential long-term care in Austria varies greatly according to the laws of the individual federal states. In most facilities, it is provided by general practitioners. This means that general practitioners are not employed by the health care provider; they provide medical care by visiting their patients. For example, it is possible for nurses in residential long-term care facilities to have different general practitioners to contact because residents bring their own general practitioners with them. This applies to other health care professionals like physiotherapy, occupational therapy, and speech and language therapy. In summary, this indicates that physicians and health care professionals are not employed in the health care providers and therefore are not using the digital voice channel.

In addition, managers in different positions will be interviewed. The inclusion and exclusion criteria used for the interview participants are summarized in Textbox 3.

The interviews will focus on the following key NPT mechanisms*:* coherence, cognitive participation, and collective action [41]. In the context of ADVICE, coherence means asking about sense-making both as an individual component and as a team component. For example, do the participants see a sense in the use of the digital voice channel or not? Do they see a benefit for themselves and for the team? Cognitive participation includes topics aiming to understand the initiation, promotion, and legitimation of participation. Social norms and formal or informal rules in the team play a role in this key mechanism. For example, are facilitators involved in which role they either have or do not have, and is there a collective commitment in the digital voice channel or not? The collective action mechanism refers to all measures taken to use the digital voice channel. Examples include competencies for workability, such as knowledge work, which is necessary to build trust, and digital competencies [41,59].

Textbox 3. Inclusion and exclusion criteria for interviews.

Inclusion criteria

- Women, men, and diverse
- Nurse (registered nurse, nursing specialist assistant, and nursing assistant)
- Home assistant, social care workers, and certified social care workers
- Manger (nursing director, nursing manager, department manager, deputy manager, head of nursing department, and head of nursing unit or nursing home)
- Employed for at least 6 months in 1 of the 2 health care providers that uses a digital voice channel
- German or English

Exclusion criteria

- Employees who do not work in 1 of the 2 health care providers or who are retired nurses or nursing students
- Employed for less than 6 months in 1 of the 2 health care providers that uses a digital voice channel
- Other languages

During the focus group interviews, nurses will have the opportunity to discuss the use of the digital voice channel. The aim here is to obtain a picture of what nurses need to be able to give a voice and the impact of the voice channel on their voice behavior. Focus group interviews will be conducted with nurses who work in one of the cases of provider 1 or 2 and do not have a management position. Approximately 6 focus groups will be conducted, each with at least 5-6 individuals in each group. Heterogeneity will be considered in the recruitment process. With attention to the professional qualification mix, every professional nursing group will be represented. The focus group interviews will be moderated by the first author with the help of an interview guide based on the results of the scoping review and NPT.

The single interviews will be conducted by the first author in a dialog-discursive interview form based on the interview guide and on the results of the focus group interviews. The reason for choosing dialog-discursive interviews with the help of a semistandardized interview guide is that interviews are

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conducted openly on the one hand, while on the other hand, targeted exploratory questions can be asked regarding specific topics. A semistandardized interview guide is intended to be of assistance, whereby the order of the questions, as well as their wording, are flexibly adapted to the interview situation [47]. The semistandardized interview guide will be developed based on the research results of the scoping review and NPT [41,42] using the SPSS principle, according to Helfferich [60]. The number of interviews is based on the fact that at least 1 interview will be conducted at each management level, for approximately 14 interviews in total. It should be mentioned that the data collection will be determined by an iterative approach. Participants will be recruited by the first author through written information as well as through participation in staff meetings to get to know each other directly. Participation will be strictly voluntary. The providers and work councils (employee representation in the health care provider) will provide informed consent before the data collection step.

All interviews will be recorded using a voice recorder. The transcriptions will be performed by the first author, and after the transcriptions, the audio files will be deleted. The transcription of the interviews will follow the content-semantic transcription process word-for-word. Statements in dialect will be, if possible, translated word-for-word into standard German [61]. Before transcription, the interviews will be stripped of any identifiers so that the participants remain anonymous. Table 1 below shows the coding rules used as an example.

Table 1. Exemplary coding rules transcription.

Health care providers and embedded units	Interview	Code
Provider 1		
Case 1.1: long-term care	Focus group interview 1	P1CL1.1F1
Case 1.2: long-term care	Single interview 2	P1CL1.2S2
Provider 2		
Case 2.1: home care facility	Single interview 4	P2CH2.1S4

Data From the Digital Voice Channel

Relevant for ADVICE are the response rate, the frequency of topics mentioned, reactions or responses to comments, and, above all, the consistency of the topics mentioned in the interviews. Furthermore, the digital voice channel data ought to corroborate interview statements, for example, indicating infrequent usage of the free comment fields or the absence of any response. It is important to note that this is an iterative process, using different data to get deeper and deeper in understanding the case.

Data Analysis

The principle of data analysis in the case study ADVICE follows the rule of playing with the data and searching for promising patterns, insights, or concepts [44]. Therefore, first, before data analysis, all qualitative and quantitative data will be transferred into MAXQDA Analytics pro software (version 22.2.1; Udo Kuckartz, VERBI software GmbH), where they will be analyzed. Data collection and analysis will be conducted partially in parallel because the case study is an iterative process. The data analysis will be carried out in 2 stages based on the analysis of the individual cases within-case analysis and a subsequent cross-case analysis**,** as shown in Figure 2.

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Figure 2. Data analysis.

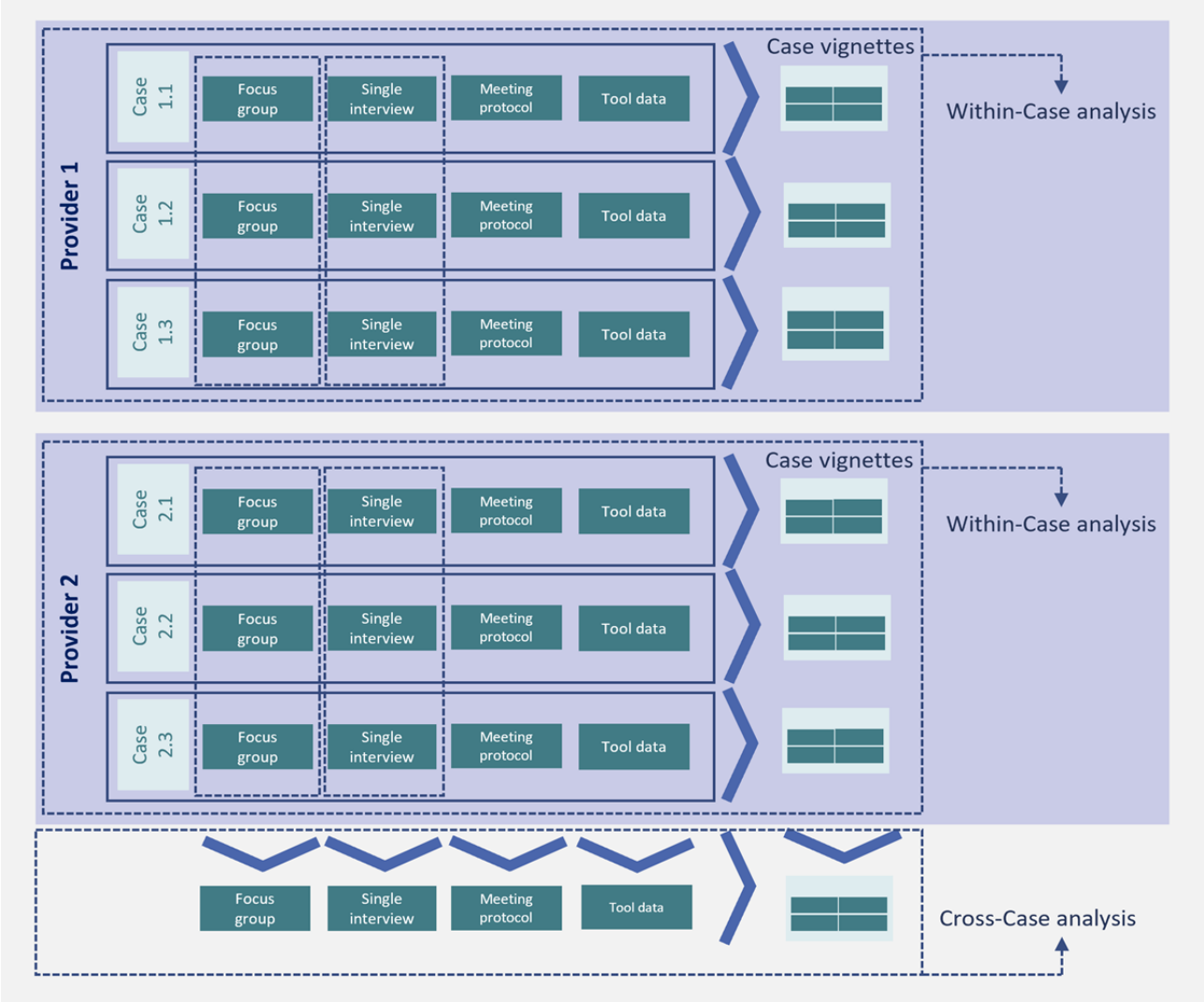

First, in the *within-case analysis*, the individual cases will be analyzed as independent units, and patterns and peculiarities will be identified. The aim is to obtain an in-depth understanding of the specificities of each case. Therefore, all data from every embedded unit will be comprehensively analyzed. For this step, every unit of analysis (focus group interviews, single interviews, protocols, and data from the digital voice channel) will be repeatedly read and reread by the first author. In this iterative process, first, all focus group interviews will be analyzed in light of these results, and the first author will pursue further data collection within the single interviews. Before the interviews are conducted, the interview guide will be updated based on the results from the focus group interviews. Then, all single interviews from every embedded unit will be interpreted. Afterward, a case description will be written for each case with the results of the interviews (plus data from the digital voice channel). This within-analysis is oriented toward qualitative content analysis with regard to Schreier [48].

Based on the research questions, the first author will derive the categories based on the body of knowledge and then further add to or expand on the inductive codes. To be specific, after the first author has determined the deductive category system based on the theoretical framework, all coding units and context units will be determined in consultation with the research team (ie, sample coding). The category system will then be additionally extended by inductive codes. For example, further categories will be formed that are not represented by the coding guide but are relevant to the understanding of the case. Inductive coding will be performed by the first author and selectively verified with other researchers. In summary, a qualitative content analysis with a theoretical deductive framework will be conducted, that is, a deductive-inductive content analysis [48].

In the subsequent second stage of the cross-case analysis, the analyzed data from the embedded units will be compared with each other in a comparative analysis, and possible distortions caused by individual cases will be identified. The results of the within-analysis will provide content for the case vignettes and serve as a basis for the cross-analysis [44]. In this analysis step, the stacking comparable strategy will be used. This strategy includes case-oriented and variable-oriented cross-case analysis strategies. Each case is analyzed with a standard set of variables (based on the results of the within-analysis). After each case is understood in itself (the results will be the case vignettes), a matrix will be used to analyze each case in depth. From this, patterns and differences will be deduced. The case vignettes will include a case study report title, case description summary

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based on the within-case analysis, analyst view, context information, issues, and uniqueness, among others [45,58]. The goal is to understand how the use of the digital voice channel addresses employee voice not only in every embedded single case but also on a meta-level in long-term care. The presentation of the results will follow the format (graphic, matrix, or networks) proposed by Miles et al [58].

Ethical Considerations

All participants will receive overall information about the study and be able to agree to participate and to fill out the informed consent form before the interview. Participation will only take place if the written consent form has been signed by the interviewee. The data will be processed in accordance with the data protection legislation in force, pursuant to the GDPR. The personal data collected (age, sex, professional activity, etc) are processed exclusively in an anonymous form and saved separately from the audio data (such as statements made in interviews).

Ethics approval for the empirical parts of the project was given by the ethics committee of Witten/Herdecke University (S230/2022). The ethics vote was submitted under an expedited procedure in accordance with the rules of procedure of the Ethics Committee of the University of Witten/Herdecke, as it does not raise any difficult ethical or legal issues. Furthermore, no review was requested.

Results

The results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and consequently create a better work environment.

The recruitment of the cases from the health care providers took place in consultation with the management and human resources managers. The decision was based, particularly in health care provider 2, on which facilities are already working with the digital voice channel. The recruitment for the focus group interviews and the single interviews began in June 2023.

Data collection began in August 2023, and from a current perspective, the first results are expected in summer 2024.

Discussion

Summary

To retain nurses in a health care organization, it is essential that they have a voice and that their views are heard. Reports from nurses working in the Austrian long-term care sector suggest that working conditions need to be addressed [2,3]. The international PTE-LTC program addresses these challenges. Specifically, this program focuses on empowering nurses, giving them a voice to actively participate in improving outcomes for residents [7]. Employee voice is 1 way of involving employees. It means that employees are able to influence work-related decisions through their feedback [12-15].

The current literature shows that employee voice has a positive impact on reducing burnout, promoting job satisfaction [16], and managing change [11,17]. It is important to note that most of the available data on employee voice in health care focuses on 1 aspect of employee voice, namely speaking up regarding patient safety and managing errors [34-36]. This leads to an unclear understanding of the phenomenon of employee voice in health care [36]. Lainidi et al [36] argue that individual approaches and evaluations are needed to gain a deeper understanding of employee voice, especially in different settings. Recent developments in digital and communication technology have opened new opportunities to address employee voice, for example, as a company mirror or digital voice channel [18-20]. Analyses show that a digital voice channel can have a positive impact on employee identification and commitment to the organization [16]. However, it depends on the organizational culture [16,23,24]. In summary, the research gap is the understanding of employee voice in a specific setting, namely long-term care, and the analysis of the use of a digital voice channel. The NPL [41,42] is used in ADVICE to better understand how the social context influences how the digital voice channel gets used to address employee voice.

We assume that the results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and, consequently, create a better work environment. Furthermore, we aim to understand how managers deal with the data from the digital voice channel, whether they use the data, and how they respond to trends and comments in the tool. In summary, the results may help to understand how employee voice behavior is affected by the digital voice channel and to identify what opportunities arise for the employees and for the organization through a digital voice channel.

Strengths and Limitations

We are aware of the different settings, and we try to develop a case understanding of individual cases through our within-case analysis and gain a deeper understanding of employee voice in health care providers by analyzing their similarities and differences. The authors therefore also refer to the NORDCARE report [3], which includes both residential long-term care and mobile care under the term long-term care.

The strength of the method proposed herein lies in the fact that the case study approach addresses the individual experiences of every employee and is oriented to the social processes in the daily routine to understand the use of a new approach to communication (digital voice channel) [44]. These are precisely the aspects that are addressed in the calls for future research on the use of new digital technologies [20,38,39] and employee voice [36]. Potential challenges can be encouraging employees to participate in interviews since these will take up working time, which is very limited due to staff shortages. This challenge can be addressed by attempting to allow the interviews to be completed during duty hours during the recruitment process in consultation with the health care providers. It must be mentioned that the generalizability of case studies is limited based on the high level of specificity and the small number of cases [62]. Furthermore, there is a possibility that, due to the way in which the scope of the data integration of the qualitative and

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quantitative data will evolve over the course of the work, the case study will also become a mixed methods case study. This may result from the fact that more attention per individual case and subcase is needed in the data integration process that will occur between the qualitative and quantitative research steps [45]. Both interview bias and selection bias must be considered. Interviewer bias is addressed through constant reflection by the research team. The selection of the health care providers is based on the fact that they are the only ones in Austria who use this digital voice channel. The choice of cases is made by the health care provider themselves. Finally, to avoid conflicts of interest, it must be mentioned that the case selection process is undertaken by the company that provides the digital voice channels. It should be noted that the company is not involved in the research process, and moreover, the name of the company is not explicitly mentioned to avoid conflicts of interest.

Importance of This Study

ADVICE also attempts to address the recommendations of Lainidi et al [36] to consider organizational and employee perspectives to better understand the concepts of voice and silence in a specific context (long-term care). Of course, individual case specifics are considered in the case descriptions, but the main focus is on the digital voice channel used in residential long-term care and home care facilities. At the organizational level, research can help to improve the attractiveness of the workplace by understanding how to give employees a voice.

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Data Availability

Data sharing is not applicable as this is a protocol paper where no data sets were generated or analyzed.

Authors' Contributions

All authors made significant contributions to the research protocol, contributed to editing, and approved the final version of the manuscript. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript. DeepL Write (free version; DeepL SE) was only used for spelling and grammar correction.

Conflicts of Interest

None declared.

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Abbreviations

ADVICE: Understanding Employee Voice Behavior (acronym for the study)
CReDECI 2: Criteria for Reporting and Evaluation of Complex Interventions
MeSH: Medical Subject Headings
NPT: normalization process theory
PICO: population, interest, and context
PRISMA ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PTE-LTP: Pathway to Excellence in Long Term Care
TIDieR: Template for Intervention Description and Replication

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Protocol

Understanding the Acceptability of Broadly Neutralizing Antibodies for HIV Prevention Among At-Risk Populations and Feasibility Considerations for Product Introduction in India: Protocol for a Qualitative Study

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Abstract

Background: Acceptability and preference research play a crucial role in the design, evaluation, and implementation of any new prevention product in any geographical setting. They also play a critical role in the development of clinical guidelines and policies. A wide range of acceptability studies have been conducted in diverse general and key populations for various new HIV prevention products worldwide. As clinical development strategies are being developed for clinical studies of broadly neutralizing antibodies (bNAbs) as potential HIV prevention products, appropriately tailoring them to address the type of HIV epidemic at hand would be critical for efficient uptake within in-country public health systems and decrease adoption and adherence challenges. Accomplishing this will require comprehensive acceptability and feasibility studies to inform multisectoral efforts that increase access to these products and national policies supportive of access to health care for those in most need. Thus, it is both opportune and important to undertake focused efforts toward informing product development strategies.

Objective: This study aims to understand preferences for product attributes and key behavioral factors influencing adoption and uptake of bNAb prevention products among end-users including female sex workers, men who have sex with men, transgender women, people who inject drugs, and adolescent girls and young women in India and understand the key health system and programmatic perspectives toward the introduction of bNAb prevention products from health service providers and policy makers in India.

Methods: A multisite study will be conducted in Delhi, Mumbai, and Chennai to capture the differences in perspectives among diverse end-users and key informants across the country. The study will use a multimethods design using focus group discussions, in-depth interviews, simulated behavioral experiments, and key informant interviews. A total of 30 focus group discussions, 45 in-depth interviews, 15 simulated behavioral experiments sessions, and 15 key informant interviews will be conducted across 3 sites.

Results: The data collected and analyzed will enable insights on which specific product attributes matter the most to the populations and why some attributes are less preferred; contextual drivers of preferences and choices at individual, interpersonal, social, and structural levels; and relative positioning of bNAb products among other potential HIV prevention products. Insights

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from the health service providers and policy makers will provide a critical understanding of the need perception of the potential product in the existing product landscape and what additional efforts and resources are required for potential introduction, delivery, and uptake of the bNAb products in the Indian context.

Conclusions: Insights generated from the abovementioned objectives will represent perspectives of populations of interest across geographies in India, will provide an overview of the acceptability of bNAb products and the feasibility of their introduction in this region, and will inform product development strategies.

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KEYWORDS

HIV; key populations; acceptability; feasibility; product attributes; end-user preferences; broadly neutralizing antibodies; simulated behavioral experiments; qualitative study

Introduction

HIV Prevention Product Landscape

HIV/AIDS has been one of the most devastating epidemics in human history. Since the official recognition of *AIDS* in the early 1980s, a total of 77 million people have been infected globally and approximately half of them have succumbed to the disease. Although effective and affordable antiretroviral (ARV) treatment has transformed HIV from a *death sentence* to a chronic, manageable disease, people with HIV have shorter life expectancy than those without the virus. New infections continue to fuel the epidemic while disproportionately affecting low- and middle-income countries. India has the third largest HIV epidemic in the world, with 2.1 million people currently living with HIV, and the sixth highest incidence with 88,000 new infections per year [1]. In addition, the high variability and ever-changing face of the virus along with the persistent marginalization and stigmatization of populations most at risk remain critical challenges in controlling the spread of HIV infection [2].

Current HIV prevention strategies include a range of behavioral and biomedical interventions, including behavior change campaigns, promotion of consistent use of male and female condoms, use of clean needles and syringes, opioid substitution therapy (eg, buprenorphine), voluntary male medical circumcision, and biomedical tools such as the use of ARV medication as preexposure prophylaxis (PrEP), and the treatment of people living with HIV to reduce viral load to undetectable levels and prevent onward transmission (treatment as prevention). There are several new HIV prevention products in the pipeline that have the potential to reduce the spread of HIV infection, including next-generation ARVs, especially long-acting ARVs [3], intravaginal (dapivirine) ring [4], preventive vaccines, and broadly neutralizing monoclonal antibodies (bNAbs) [5-11]. Multiple studies have highlighted that a single product will not be preferred by all end- users under all circumstances [12,13] because there is a constant evolution in the life journeys, social contexts, and product attributes. Thus, different products may be preferred by end-users at different times. Introduction of a new product does not necessarily mean that the importance or relevance of existing products has been replaced. It is important to identify the unique value of novel interventions and understand end-user perspectives to highlight their value addition to the current prevention landscape. There is a need to create a toolbox and choice sets that will cater to the unique needs of end-users [14]. bNAbs are antibodies that can potentially be used to fight against multiple strains of HIV and are poised to have advantages over other preventive drugs such as the ability to target and act against a broad spectrum of viral strains, longer half-life and hence less frequent dosage, no risk of development of resistance to ARVs used for treatment, and comparatively safe with rare cases of adverse side effects [11,15-19]. More than 200 different bNAbs targeting HIV have been isolated to date, varying significantly in their coverage of global HIV isolates (breadth) as well as the amount required to neutralize the virus (potency). bNAbs have been proven to be safe for humans and can work effectively in preventing HIV infection. The antibody-mediated prevention trial found that an antibody called VRC01 could prevent HIV infection with specific HIV strains when administered every 8 weeks to adults [20]. In addition, combinations of bNAbs engineered with extended half-lives and increased potency are also being developed and tested in trials to ensure lower dosage and lesser frequency that would make the end product accessible and affordable. The World Health Organization (WHO) has also recently published the preferred product characteristics for monoclonal antibodies for HIV prevention [21], and it highlights that based on the needs of various target populations, the antibodies should have longer lasting duration of protection, have minimal side effects, and be delivered as injections, among others. In India, most of the abovementioned prevention options have not yet been rolled out as a part of the national policy, and hence, there is a need to understand the acceptability for bNAbs and their preference vis-à-vis other potential options.

Acceptability and Feasibility Studies for bNAbs

Value of Acceptability and Feasibility Studies

Acceptability and preference research play a crucial role in the design, evaluation, and implementation of any new product in any geographical setting. They also play a critical role in the development of clinical guidelines and policies [22]. A wide range of acceptability studies have been conducted in diverse general and key populations for HIV prevention products including women, adolescent boys and girls, men who have sex with men (MSM), female sex workers (FSWs), people who inject drugs (PWID), and transgender women (TGW) [23-26]. These studies have focused on prevention products such as oral and injectable PrEP, vaginal and rectal microbicides, vaginal

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rings, and future HIV vaccines [22,26-29]. The main drivers of prevention product adoption and uptake include product effectiveness, cost, absence of side effects, and multipurpose protection against sexually transmitted diseases and pregnancy [30]. Acceptability studies have shown that emotional and intuitive decision-making for a product choice is also driven by factors such as sexual satisfaction, dimensions of trust, self-efficacy, and sociocultural environments [26,31]. There is evidence for differential preference for prevention products among different populations. For example, in South Africa, FSWs preferred injectable products over oral PrEP and microbicide gel, adolescents preferred a potential HIV vaccine and expressed dislike for a vaginal ring, and MSM preferred rectal microbicides [24,25]. Relative importance of specific product attributes also varied across target populations. For example, the route of PrEP administration was found to be the most important attribute for prospective end-users in Peru, Ukraine, India, and Botswana; FSWs in Kenya; and young women in South Africa [32], whereas the PrEP dispensing site was the most important attribute for participants from Uganda and MSM in South Africa and the second most important attribute for FSWs in Ukraine [32].

There are several standard qualitative methods for assessing the acceptability of an intervention for the target population and setting. Two common methods are focus group discussions (FGDs) and in-depth interviews (IDIs). Moderated FGDs allow for understanding of group dynamics including similarities and differences and allow to probe further on particular topics as they come up in the discussion. This type of interaction generally results in a deeper understanding of the forces in a community that may impede or facilitate the implementation of effective interventions. IDIs are conducted in a one-on-one setting with members of the target communities. They allow for deeper probing to understand more details, have nuanced understanding of sensitive topics, and have an opportunity to monitor changes in tone and body language, which is also an important factor in eliciting key responses.

For the successful development and adoption of any product, it is critical that perspectives from all service providers including health care professionals and community "gatekeepers" are taken into account in the development process [33,34]. Thus, there is a need to gather evidence from diverse populations and multitude of related stakeholders across geographies in India and focus on understanding their perspectives on potential new products such as bNAbs and preferences of different product attributes. These are often conducted through key informant interviews (KIIs).

In India, acceptability and feasibility studies have been conducted for various microbicides and PrEP [35-42]. These studies have been scattered over time and have been restricted to a few geographical locations and key populations. Thus, there is a need to gather evidence from diverse populations and multitude of related stakeholders across geographies in India and also focus on perspectives with respect to the potential new product—bNAbs.

Behavioral Science for Contextualized Understanding of End-User Decision-Making

Apart from the aforementioned methods, there are other qualitative research methods that are necessary to complement some of the emerging insights from the potential end-users. It has often been observed that studies conducted to explore preferences for hypothetical products or willingness to participate in hypothetical trials have shown differences in the stated preferences and intentions versus the eventual decisions and observed behavior of end-users [43-45]. In Kenya, an observational cohort study reported a 90% willingness to participate in future trials; however, during actual trial recruitment, only 30% were willing to actually enroll [44]. In a real-time scenario, end-users may be presented with multiple contextual trade-offs as well as nonconscious factors that may influence their decision-making, and hence, stated versus revealed preferences may be different [45]. It has also been reported that hypothetical choice experiments with end-users provide relatively satisfactory predictive results for positive choices, but they are less effective for predicting negative choices [43]. Thus, to premeditate and elicit the "say-do" gap, one of the useful methods deployed by behavioral scientists is to identify and analyze shortcuts known as heuristics in action, which take off the cognitive load of decision-making and help anticipate and explain potential avenues for gaps between the stated intention and action [46,47].

The cognitive process marking the final behaviors exhibited and decisions made by prospective end-users may be a mix of conscious and nonconscious factors and, hence, cannot always be brought out through in-person discussions alone. Therefore, the application of behavioral science in a simulated context has been found to be extremely beneficial for deciphering the key drivers of decisions and behaviors. In such a situation, the participants in a study do not just have to talk about their past or future decisions but have to actively make a decision in real time in a simulated environment. This provides researchers with a better understanding of the decision pathways of prospective end-users as well as potential aspects of say-do gaps to inform the design and development of products. Toward this, Ethnolab is a behavioral research methodology that often uses a Conundrum game [48] to deploy scenarios based on the preliminary qualitative research findings in a simulated environment and observe user choices in real time. The method has been used in several sociobehavioral and acceptability studies for health programs and interventions, including voluntary male medical circumcision decision-making in Zimbabwe and Zambia [48]; understanding HIV prevention for adolescent girls and young women (AGYW) in South Africa [49]; and estimating the impact of nonconscious drivers of human behavior among pregnant women and mothers of infants as well as with frontline workers on reproductive, maternal, newborn, and child health outcomes in Uttar Pradesh [50].

Population of Interest

As noted previously, India has the third largest HIV epidemic in the world, with 2.1 million people living with HIV, and the sixth highest number of new infections at 88,000 per year [2]. Therefore, ensuring the acceptability and feasibility of any new

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potential HIV prevention product in the regional Indian context and needs is critical. The HIV epidemic in India is concentrated among key populations such as FSWs, MSM, PWID, and TGW. The average national prevalences from the government studies range from 1% to 6% (PWID: 6.3%, TGW: 3.1%, MSM: 2.7%, and FSWs: 1.6%) with high interstate variations [51], and access to HIV prevention and treatment services for these populations remain hindered by sociobehavioral and structural barriers including multilayered stigma, discrimination, and marginalization [52,53]. In addition to epidemiological and behavioral diversity across regions and key populations, the rapidly evolving nature of the epidemic as well as changes in risk behaviors owing to the rise in the use of new communication technologies also necessitate systematic and structured inquiry into the health system and end-user contexts and preferences impacting the eventual adoption and uptake of new HIV prevention products such as bNAbs. In addition, although there has been a steady decline in HIV prevalence in India over the last decade, the decline among men has been significantly more rapid than that among women [54]. Similarly, significant gender-based gaps persist in knowledge on HIV prevention among young people (aged 15-24 years); although 75% of the women had heard of HIV (as compared with 89% of men), only 43% of the women in the country knew where to get tested for HIV, and of them, only 14% were ever tested and received results [54]. In addition, the prevalence of intimate partner violence among women of reproductive age (15-49 years) remains high at 22% [54]. Thus, in addition to key populations, it also becomes important to understand the perspectives of AGYW to cover diverse viewpoints and preferences for HIV prevention products, specifically bNAbs.

Study Objectives

The study objectives are as follows:

1. To understand preferences for product attributes and key behavioral factors influencing the adoption and uptake of bNAb prevention products among end-users including FSW, MSM, TGW, PWID, and AGYW populations in India
2. To understand key health system and programmatic perspectives toward the introduction of bNAb prevention products from health service providers and policy makers in India

Methods

Study Population and Sites

The study populations include potential end-user populations such as FSWs, MSM, TGW, PWID, and AGYW and key stakeholders such as health service providers (including frontline health care workers, community-based organization [CBO] or nongovernmental organization [NGO] representatives, and lead community representatives) and policy makers (including national, state, and district level officials or program managers).

The multisite study will be conducted in Delhi, Mumbai, and Chennai regions to ensure coverage of perceptions from North, West, and South India, including differences in perspectives among diverse end-users and stakeholders. These sites also have very high HIV prevalence among the study populations [51].

Conceptual Framework

Conceptual Framework for Acceptability

Acceptability may be defined as the extent to which people delivering or receiving a health care intervention consider it to be appropriate based on anticipated or experienced cognitive and emotional responses to the intervention [55]. Several theoretical frameworks are available for understanding acceptability of new HIV prevention products or technologies [41,42,55-57] at the individual and community levels. A recent systematic review proposed a model of acceptability of health interventions, the Theoretical Framework of Acceptability (TFA) [55]. According to TFA, intention to use a health intervention is determined by seven factors: (1) perceived effectiveness, (2) intervention coherence, (3) affective attitudes, (4) burden, (5) ethicality, (6) self-efficacy, and (7) opportunity costs. It was chosen to adapt the TFA to guide exploration of acceptability of bNAbs in this study as it can readily incorporate individual- and community-level influences on attitudes and behavior. The study design was also informed by the conceptual framework developed by Mensch et al [56] to incorporate the various factors operating at individual, interpersonal, community, and structural levels in influencing a person's product-related attitudes and perceptions. In addition to adopting aspects from the social-ecological model, the framework emphasizes the role of actual product-related factors, including product attributes, which also play a role in defining an individual's preferences [56]. Thus, guided by these frameworks, an adapted conceptual framework was used to design this study. In this adaptation, the constructs were embedded within three domains (Figure 1) [55,56]:

1. Product factors: those related to the potential product characteristics (formulation, device, site of administration, dosage, frequency of administration, and side effects) and delivery characteristics (place of delivery, privacy and confidentiality, and coadministration)
2. Intrinsic factors: those related to a person's individual traits and not influenced by external factors. These include a person's those related to a person's individual traits and not influenced by external factors. These include a person's *perceived benefit* of the product (coherence, relevance, effectiveness as well as relative positioning, and advantage of the product among other options), *perceived burden* in using the product (cognitive burden—complexity of dosage and time; emotional burden—fear, anxiety, and discreteness; physical burden—pain, side effects, and impact on sex; and financial burden—cost, travel, and opportunity loss), and *self-efficacy* (skills and capability, confidence, and adherence)
3. Extrinsic factors: those related to external influences including *interpersonal influences* (peer, partner, and family attitude) and *social/structural influences* (social perceptions—stigma and discrimination, cultural norms, and structural or environmental factors).

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Figure 1. Conceptual framework for acceptability (adapted from the Theoretical Framework of Acceptability and the conceptual framework for product acceptability).

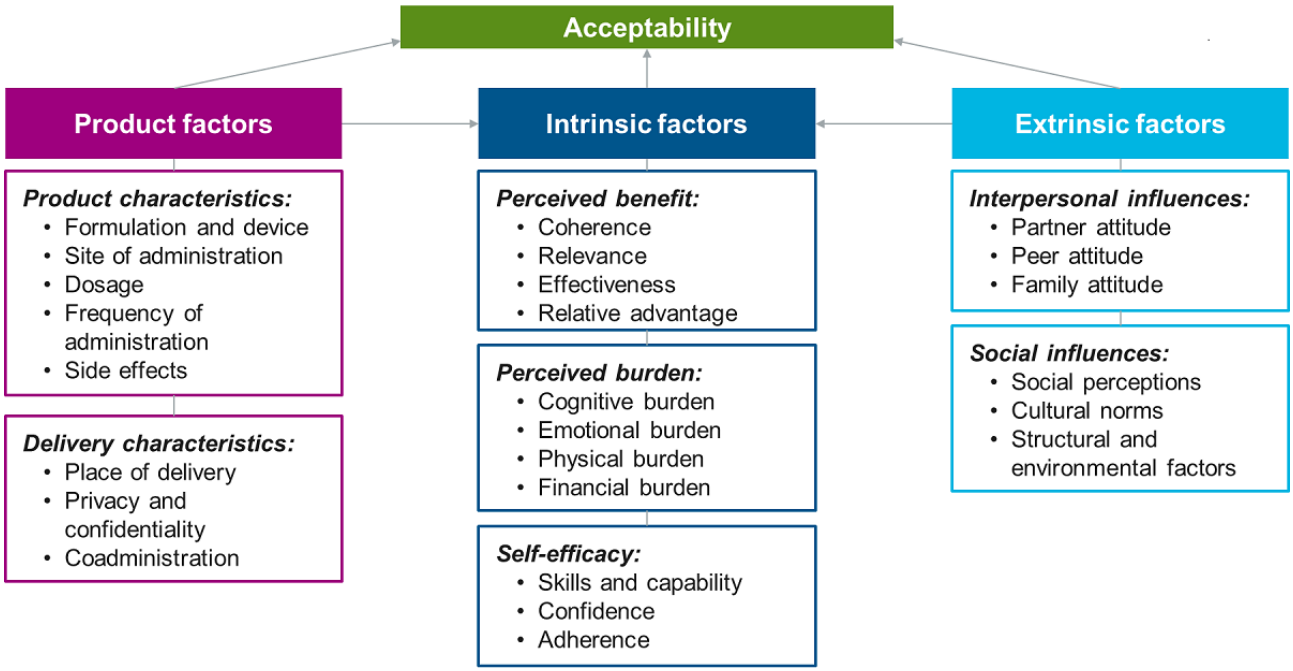

Conceptual Framework for Feasibility

There are multiple factors at the health systems and programmatic levels that service providers such as frontline health care providers, policy makers, and program managers at national, state, and district levels would consider as key issues that are needed for introduction and uptake of bNAbs as HIV prevention products in the future. Thus, complementing the study's conceptual framework for acceptability, which will be used among the end-users, there is a need to have a conceptual framework to assess the feasibility. For this purpose, the framework shown in Figure 2 [58] was adapted from the WHO Framework on Health Systems, which was also used by the WHO for reviewing the impact of new vaccine introduction on immunization and health systems. The broad themes include the following:

1. Contextual alignment: This will enable an understanding of the need perception of the current product, its social and cultural acceptability, the outreach mechanisms that will be needed, and whether there is any risk compensation because of the introduction of this new product.
2. Program integration: This is toward understanding delivery strategies, venues, and time points; possibility of integration with already existing services; additional programmatic costs required; and alignment with the existing policy environment in India.
3. Health care workforce: This will explore the availability of adequate human resources—their distribution and workload, existing technical capacity and additional training needs, and incentives and supportive supervision required to successfully implement the introduction of a potential new product.
4. Integrated supply chain: This will be toward assessing the health systems' readiness in terms of robust stock management, cold chain availability, and biomedical waste management.

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Figure 2. Framework for the assessment of feasibility of introduction of potential broadly neutralizing antibody products for HIV prevention (adapted from a study by World Health Organization).

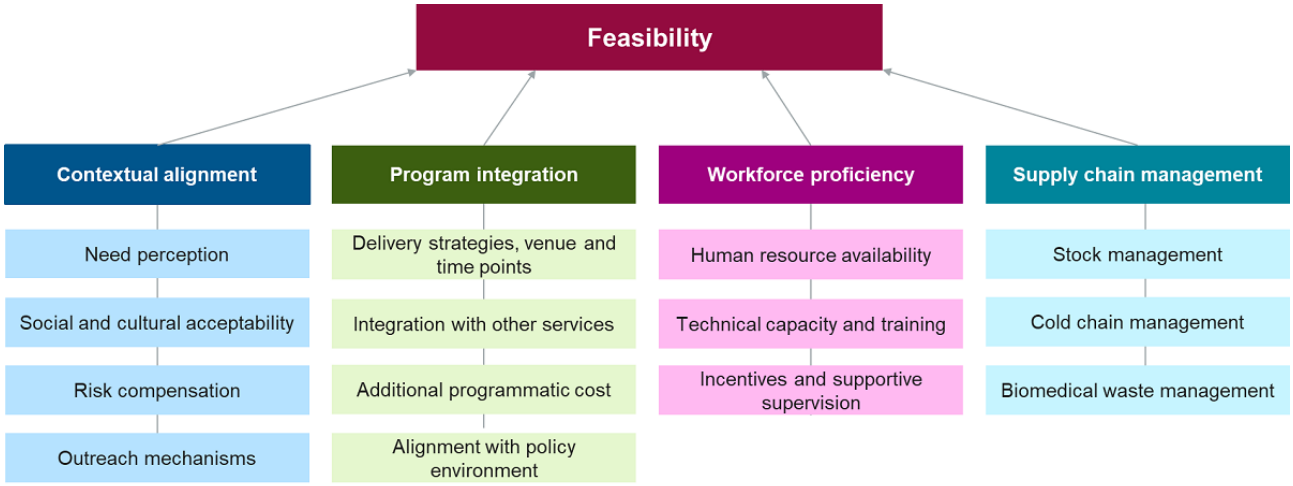

Study Design

Data Collection Methods

Overview

To understand preferences with regard to product attributes and key behavioral factors influencing the adoption and uptake of bNAb prevention products, this study will use a multimethods design [59] to provide a holistic approach based on complementarity and corroboration [60] by including the following qualitative methods:

- FGDs
- IDIs
- Simulated behavioral experiments (SBE)
- KIIs.

Data Collection Through FGDs

FGDs will be conducted among various groups such as FSWs, MSM, PWID, TGW, and AGYW. These discussions aim to understand the preferences and aspirations of prospective end-users regarding characteristics of HIV prevention products. In addition, the research seeks to uncover the key factors influencing their decision-making process including influential individuals and other contextual factors. Furthermore, the aim is to correlate these insights with what motivates or dissuades them from favoring specific HIV prevention options over others. This will be conducted in a small group of 7 to 8 participants. The end-users will also be asked about specific delivery preferences that would guide their adoption of and adherence to novel HIV biomedical prevention tools. FGDs allow the members of the group to collectively brainstorm on the issues, choices, drivers, and solutions, sometimes called a "synergistic group effect" [61]. This also allows for assessing participant behavior in a group setting wherein not only the individual respondent's views are deliberated on, but the voices of the community as a whole are also accounted for.

Data Collection Through IDIs

IDIs will be conducted with additional participants from all the target populations through one-to-one discussions and will cover aspects similar to the FGDs. However, these will provide an opportunity to gather deeper insights as the interviewer can probe more, note the changes in respondent's tone and body language, and also have views that are not influenced by group dynamics or social desirability [62].

Data Collection Through SBEs

SBEs will be conducted in small groups of 5 to 6 end-users to delve deeper into the causative factors of decision-making and potential avenues for intention-action gaps by using interdisciplinary concepts from behavioral economics and decision science. SBEs will use the insights generated from the FGDs and IDIs to construct a range of decision scenarios that end-users could face in deciding their preferences for a potential prevention product. SBEs will then use a game-based research technique (Ethnolab) to understand the context, emotions, and decision levers that influence decision-making based on these scenarios. Ethnolab is designed to minimize the impact of biases in decision-making, such as fear of value judgment, social desirability, and expectation of higher self-control in the future, which make respondents claim behaviors that may not play out in real life, thereby giving rise to "say-do" gaps [48]. Ethnolab would allow participants to not only discuss preferred attributes but also make real-time decisions revealing their preferences through multiple test scenarios. One of the critical objectives is to decipher the patterns of preference exhibited by different respondents across divergent contexts. Therefore, Ethnolab will help to identify the following:

- Past experiences that have led to decision-making criteria, values, norms, or beliefs that influence health behaviors and product preference
- Present goals around health management, relationship management, and life management and how they influence attribute selection
- Factors that could lead to preference reversal.

Data Collection Through KIIs

In addition, to better understand the environmental, market, programmatic, and policy contexts at the national, state, and local levels, along with decision-making factors and pathways informing HIV policy, KIIs will be conducted with policy makers and health service providers to understand their

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perspectives on drivers for the adoption and uptake of health innovations. Efforts will also be directed toward seeking their input on implementation and access issues as well as health systems challenges on non–cold chain versus cold chain product requirements and other parameters related to effective delivery and adoption of biomedical interventions to prevent HIV.

Sample Selection

The following sample selection criteria will be followed for the abovementioned methods.

End-Users

The inclusion criteria for the various target groups are:

- Inclusion criteria for MSM, TGW, PWID, and FSWs in the FGDs and IDIs were as follows: Aged at least 18 years, self-identifies as MSM, TGW, PWID, or FSW, and willing to provide informed consent.
- Inclusion criteria for AGYW in the FGD and IDIs were as follows: Aged 18 to 24 years and willing to provide informed consent. According to the Joint United Nations Programme on HIV and AIDS definition, AGYW fall into the age group of 15 to 24 years [63]. However, given the ethical considerations with respect to minor adolescent girls (15-17 y) in the Indian context and keeping in mind their relatively lower exposure to HIV prevention services, it was decided that for the purpose of this study, only adolescent girls aged 18 to 19 years and adult young women aged 20 to 24 years will be included. Efforts will be made during data collection and data analysis to ensure that perspectives from participants aged 18 to 19 years and those aged 20 to 24 years are disaggregated to bring out the unique highlights from these populations.
- For FGDs, diverse typologies and subgroups of MSM (kothis [feminine/primarily receptive role], panthis [masculine and primarily insertive role] , double-deckers or versatile, gay, and bisexual men), FSWs (brothel or bar based, street based, internet or social media based, and home based), TGW (gharana based and nongharana and those in sex work and those who are not), PWID (who use different types of injectable drugs), and AGYW across the age group (adolescents aged 18-19 years and young women aged 20-24 years) will be recruited.
- To explore diverse perspectives, maximum variation purposive sampling [64] will be used to recruit individuals from diverse backgrounds such as engaging in sex work; being from lower and middle class; and being single, living with male or female partners, heterosexually married, and representative of male and female PWID groups.

Key Informants

For KIIs, the inclusion criteria will be as follows:

- Key informants should be aged >18 years, ≥5 years of experience as a community leader or ≥3 years of working experience with population of interest or as a part of the HIV program, and willing to provide informed consent.
- Key informants will include information-rich individuals who have worked with key populations or have some experience of working with AGYW or in the field of HIV. These may include health service providers (physicians, counselors, nurses, CBO or NGO representatives, and community leaders) and policy makers (program managers and district or state or national level officials).

Sample Size

A total of 30 FGDs (2 FGDs per end-user group per site; for 5 end-user groups across 3 sites) and 45 IDIs (3 IDIs per end-user group per site; for 5 end-user groups across 3 sites) will be conducted in Delhi, Mumbai, and Chennai to investigate factors at individual, interpersonal, and sociostructural levels that facilitate or impede the acceptability of bNAbs among susceptible communities in India.

The SBE will mirror the sampling frame and the broad respondent profiles from the FGDs and IDIs. Keeping in mind that Ethnolab elicits the most useful insights in small and intimate settings, the sample would include 6 participants for each end-user group (distinct and different from the participants in the FGD or IDIs) across each site. Thus, the total sample size would be 90. Each instance of Ethnolab will have 6 respondents, and a total of 20 Ethnolab-based SBEs will be conducted across all 3 sites.

In addition, 5 KIIs will be conducted with health care service providers and policy makers in each region, amounting to a total of 15 KIIs. Thus, the total sample size of the qualitative component of the study is expected to be approximately 300 (FGD: 30×8=240, IDI=45, and KII=15).

Implementing Partners

The implementing partners for the study are YR Gaitonde Centre for AIDS Research and Education (YRGCARE), Centre for Sexuality and Health Research and Policy (C-SHaRP), and The Humsafar Trust (HST), who will be responsible for conducting the FGDs, IDIs, and KIIs. The designing of the Ethnolab game–based data collection method will be done by Final Mile and IAVI. Final Mile, in working with other study partners (YRGCARE, C-SHaRP, and HST), will be responsible for the implementation and conduct of the SBE sessions across all study sites.

Data Collection

Overview

Data from FGDs, IDIs, and KIIs will be collected using semistructured interview topic guides. Trained research staff will conduct the FGDs, IDIs, and KIIs. The research staff will receive additional training specific to the content of this study and research ethics. SBEs will be conducted by partner consultants and will also include a round of initial meetings with the other study clinical research center partners to ensure alignment with the findings from the FGDs and IDIs.

Lines of Enquiry for FGDs and IDIs

For the FGDs and IDIs among end-users, the following broad areas will be covered in the lines of inquiry:

1. Preference elicitation questions: Under this process, the group will be asked about individual product attributes and their preference for different features under that attribute. The process will aim to understand which attributes matter most to the populations and the preferences for different

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subgroups under that population to gain an overall community-level perspective. Efforts will also be made to understand the reasons for these preferred options. This section would also cover the individual, interpersonal, and social concerns that might drive end-user decision-making.

2. Relative desirability of predetermined product profiles (attribute bundles): As a next step, participants within each focus group will be presented with 4 product profiles comprising 5 to 6 attributes in different combinations (bundles) through a mixture of visual methods and information, education, and communication tools. These are modeled after various HIV prevention products, including the current bNAb product under investigation. Participants will be requested to choose their "most/least preferred" profiles, rank the remaining 2, and explain the reasons behind their choice. In addition to enabling a deeper understanding of preferences and trade-offs, this would also aid in understanding the most critical attributes informing decision-making on product use among prospective end-users.

The topic guide will be translated into native languages (Hindi, Tamil, Telugu, or Marathi), back-translated into English, and then revised in the original language. All discussions will be audio-recorded, transcribed, and translated. They will be deidentified before proceeding for further data analysis. Each FGD and each IDI will span over 60 to 90 minutes.

Data Collection Process for SBE

The SBE sessions will consist of three parts:

1. *Ethnolab Conundrum game*: The Conundrum game will expose participants to multiple scenarios, each ending with a decision conundrum having different possible outcomes. Each scenario will simulate the real-world context of participants by representing a protagonist of the same age, gender, and socioeconomic level in a relevant health-related situation. The scenarios will be constructed using preliminary insights generated from the FGDs and IDIs, with decision points informed by heuristics and behavior science principles. The research is gamified: participants will be asked to respond quickly in real time and choose the option they think will coincide with most respondents in the group and will win points if it does. The game will thus generate responses representative of mental models, emotions, and biases rather than deliberate and rational analysis [48]. Preference reversal will be tested through tweaks in the context simulation and the framing of attributes.
2. *Ideal product profile exercise*: The participants will go through a series of prompts to design the ideal prevention product suited to their needs. This activity will be an adapted version of the product profile ranking exercise used in the first round of qualitative research. It will be designed to give participants an expanded choice set to clearly articulate their trade-offs and allow for tracing certain preference reversal patterns. This will enable an overall high engagement and easy and detailed discussion on product attributes.
3. *Group conversations*: Once the games are over, participants will be split into multiple groups of dyads and triads for group conversations (where scenarios and reactions are still fresh in their minds) regarding the experience, decisions, and preferences in the game [50]. The conversations on the scenarios provide opportunities for improved contextualization of the responses, understanding emotions and other causative factors behind preferences, and tracing decision pathways.

The data generated from the games, along with the ensuing conversations, will help elicit behavioral insights and identify intrinsic drivers and extrinsic factors influencing the preferences and decisions of prospective end-users. The Ethnolab play will last for approximately 60 minutes, and the subsequent group discussions will last for 45 minutes. The overall activity will not exceed 2 hours. The session will involve engaging games to maintain a playful environment, and adequate breaks will also be incorporated to ensure that the time of engagement does not become burdensome for the participants.

Lines of Enquiry for KIIs

Semistructured interview guides will consist of 10 to 12 open-ended questions and scripted probes. The interview guides will be translated into native languages (Hindi, Tamil, or Marathi), back-translated into English, and then revised in the original language. Key informants for each study population will be asked questions for the need perception of a prevention product, preference and importance of product attributes, social and cultural acceptability, risk compensation, health systems readiness, and alignment with the policy environment in India. Each KII will be conducted for approximately 90 minutes.

Data Analysis and Validation

Analysis

The qualitative approach will use triangulation to strengthen and ensure the accuracy of data [65]. According to Denzin and Lincoln [66], triangulation is a process in which several methods are used in the study and might be used in four basic ways: (1) data triangulation, (2) methods triangulation, (3) theory triangulation, and (4) researcher triangulation. In this study, data triangulation, methods triangulation, and researcher triangulation will be used. All transcripts will be redacted (to remove any personally identifying information that might inadvertently have been recorded) and uploaded into NVivo (Lumivero) or Dedoose (University of California). First, a line-by-line review of the transcripts will be performed, and first-level codes will be identified to create a common a priori codebook (based on the adapted conceptual or theoretical framework and topic guides). All codes will be then entered and tagged to associated chunks of text. Texts corresponding to each of the first-level codes will be coded by at least 2 independent analysts and reviewed by senior investigators. Explanatory or theoretical or etic (researcher generated) codes will be arrived at using a constant comparative method [67].

The SBE results will be analyzed using the cognitive and emotional appraisal framework [68] as a base. Appraisal theories are componential theories that view an emotional episode as involving changes in a number of organismic subsystems and

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components. The components could include an appraisal, a motivational, a somatic, and a motor component. The framework will be used to generate the codebook and will then feed into the 4 major categories of context, emotions, mental models, and decision levers. This will be done along with the ranking of preferences drawn from the experiential game data. The SBEs will be analyzed to gain an in-depth understanding of (1) preference construction and (2) preference reversal.

Validation

Data source triangulation and researcher triangulation will enhance the reliability and trustworthiness of the findings [69]. Thus, study implementation and data analysis will also incorporate researcher reflexivity and researcher triangulation by maintaining "quicknotes" (a brief summary of every interview or focus group by the interviewers or moderators that will be shared with the analysts and investigators for feedback), writing memos, and engaging in peer debriefing to maintain ongoing awareness of our social location and how it may influence the research process and interpretation. A maximum of 2 interviewers or moderators will be used for every population of interest to ensure that there is minimum bias in the way questions are asked or follow-up probes are used.

Data Security for Storage and Transmission

Names or other personal identifiers will not be collected from the participants. Only the investigators and key research staff at the participating research sites will have access to the transcripts or translated text and digital recordings. As soon as an interview is completed, the audio file will be transferred from the digital recorder to password-protected computers. Subsequently, the file will be deleted from the digital recorder. The transcriptionist and translator will sign a confidentiality pledge stating that they will not reveal any information from the interviews to anyone else. The digital copies of transcripts and translated text will also be stored on password-protected computers.

Only this study's research staff at the participating research site will have access to the audio files, transcripts, and translated text. All digital recordings will be redacted, and any personal identifying information will be removed. Digital recordings will be deleted after 1 year (the 1-year delay is to ensure that there are no gaps in the transcripts). Redacted transcripts will be maintained for 2 years and then destroyed. Informed consent forms will be separately stored and will include signs, initials, or "X" marks rather than names. Unique identification codes will be assigned to all individual records, including digital recordings and transcripts. Hard copies of the data and related documents will be stored in a secure location in locked cabinets in the offices of study and will be accessed only by the research staff.

Ethical Considerations

Institutional Review Board Review and Approvals

The study was presented to the institutional review boards (IRBs) of all 3 implementing partners (HST, C-SHaRP, and YRGCARE), and all comments received were adequately addressed in the protocol. The approved protocol (HST-IRB-50-01/2021; C-SHaRP/0007327/220; YRGCARE-359) will be implemented for data collection and analysis.

Informed Consent Process

Participants for IDIs, KIIs, FGDs, and SBEs will be presented with an information sheet that outlines the scope of the study and a consent form that provides options to sign or put initials or put an "X" mark. This approach has been accepted by the IRB for other previous studies. Given the potentially low literacy levels of some participants, the research assistants will offer to read and explain the information sheet and consent form to the participants. As part of the informed consent process, all potential participants will be informed that their decision to participate or not in interviews or games will not affect the services they currently receive or may receive in the future from their respective community agencies.

Compensation

Participants in the FGDs, IDIs, and SBEs will receive an honorarium of INR 500 (US $6.25) for participating in the study. This amount is based on input from the community advisory boards of the study partners in India. This covers the costs incurred for roundtrip transportation. If the focus group or IDI participants elect to withdraw from the study during data collection, they will still receive compensation. Key informants will receive INR 1500 (US $18.75) (wherever applicable), and this is proposed from previous learning wherein key informants reported loss of wages owing to their participation and suggested that an honorarium should be instituted for KIIs to minimize such experiences. All interviews will be conducted in person, and honorariums will be in cash.

Privacy and Confidentiality Protection of Participants and Do-No-Harm Measures

Overview

Being a qualitative study, with no biological samples collection, there is no medical risk to a research participant of this study. The study also does not pose any financial risk to the participants. However, participants' confidentiality could be compromised through engagement in the study, and participants might feel uncomfortable answering questions about sexual behaviors. Recognizing these possibilities, some mitigation measures that will be adopted are as follows:

1. Unique identity number and no names: No participant names will be collected. Participants will be asked to mark only their initials or put an "X" mark on the consent form. Participants will be identified only by a unique numerical identifier. Individuals will be instructed not to use their surnames but to use a nickname or pseudonym. In addition, all transcripts will be anonymized so that any identifying information that is inadvertently mentioned will be removed from the written transcript.
2. Training for research interviewers or FGD moderators: Interviewers or moderators will be well trained in research ethics and interviewing techniques. They will be trained to be sensitive to the needs of the participants to stop, rest, skip particular questions, or discontinue their involvement

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in the study at any time. Interviewers will be clearly instructed that participants are allowed not to answer any question and continue with the interview or to stop the interview at any time. In addition, research interviewers and field research staff will be trained in research ethics and confidentiality and will all be required to sign confidentiality agreements.

3. Explicit information on potential social risks to participants of focus groups: For focus groups, social risks include unwanted disclosure of one's sexual orientation or sexual behaviors and facing possible stigma or discrimination if a member of the larger community discovered the participant's orientation or drug use or sex work status. Furthermore, confidentiality will be maintained by holding interviews and focus groups at discreet locations that many of the participants already frequently visit (eg, local CBO or NGO office). In addition, facilitators and interviewers will be trained in research ethics and there is already a list of transcribers or translators who possess sufficient experience in transcribing research interviews. They are also well versed in the significance of upholding confidentiality and anonymity.
4. Transcription and translation of FGD, IDI, KII, and behavioral experiments: Professional transcribers will be hired for the transcription or translation of audio-recorded interviews (FGDs, IDIs, KIIs, and behavioral experiment discussions). There already exists a list of transcribers or translators with adequate experience in transcribing research interviews and who know about the importance of maintaining confidentiality and anonymity. They (new or experienced) will be oriented about the importance of maintaining the confidentiality of the audio files and transcripts and will be asked to keep all the research information confidential by not discussing or sharing the content of the interviews in any form or format with anyone other than the designated research contact persons. The transcriber or translator will be asked to sign a confidentiality pledge before transcription or translation.

Do-No-Harm Measures

In addition to the mentioned measures, all study staff will be trained in guidelines and policies related to human participant research ethics to ensure no unintended harm to the participants. This will be applicable for all participants, keeping in mind their vulnerabilities, but especially noteworthy for engagement with adolescent populations. The study teams will adhere to the National Youth Policy and also be trained in the guidelines stated by the Rashtriya Kishore Swasthya Karyakram [70].

Plan for Reporting Unanticipated Problems or Study Deviations

The study investigators will report unanticipated problems and study deviations to the local IRB. Such events will also be communicated to International AIDS Vaccine Initiative for further review or escalation, if required. Minor problems and protocol deviations, if any, (which pose no risk to participants or others) will be reported in the annual protocol continuing review.

COVID-19–Related Guidelines

All study data collection–related activities will be conducted by adhering to the state or national guidelines in view of COVID-19.

Possible Benefits to Participants

There are no direct benefits to participants for taking part in this study. However, the participants will be better informed about the various HIV prevention options currently available across the globe and the options under development. The study has the potential to benefit the society and the participant's communities if the data collected are found effective and are adopted in routine service delivery or for further informing bNAb research.

Results

The study is being implemented across 3 sites in India among 5 different populations and key informants. The data collection will be followed by data analysis workshops to enable standardization of analysis across all sites and partners. Extensive analysis based on the analytical frameworks will lead to the expected outcomes of the study.

Discussion

Principal Findings

The study will provide critical insights into factors driving the end-user decision-making with regard to prevention product choices and assess the acceptability of bNAbs in the Indian context. It will also help understand the health system and programmatic factors that would influence product introduction and uptake among target populations in India. The specific anticipated outcomes from the study can be highlighted as follows:

1. *Product preferences*: Insights from the FGDs, IDIs, and SBEs will aid in identifying specific product attributes that matter the most to the end-users and why some attributes have less preference. Within each attribute, it will be possible to identify the options that the respondents feel are more significant to their individual context. Insights will also be generated on end-user preferences that are stable across all contexts and preferences that are dynamic and may vary with changing circumstances. Finally, it will also be possible to outline the acceptability and unique value proposition of bNAb products in the Indian context.
2. *Behavioral factors*: Another outcome of the study will be identification of the most relevant target populations in India for HIV bNAb products and user segmentation of the target population based on key behavioral determinants, including an interplay between user profiles and preferences. The study will also help understand the contextual drivers of preferences and choices at individual, interpersonal, social, and structural levels and aid in delineating the key decision levers and pathways that lead to a preference or reversal of the same. These decision levers could be understood in the form of norms, values, goals, mental models, and emotions and would be critical

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to decipher to understand acceptability of a product. In addition, often, the stated preferences are different from the observed choices when they are simulated through real-life situations. Thus, the gamified components will also provide a chance to highlight the say-do gap to inform product development.

3. *Health systems and programmatic readiness*: Insights from the health service providers and policy makers will provide a critical understanding of the needs perception of the potential product in the existing product landscape, understanding of the cultural and social acceptability, and risk compensation. Their views will also provide critical insights into the additional efforts and resources required for potential introduction, delivery, and implementation of bNAb products in the Indian context. This will include program integration perspectives and other structural factors such as workforce availability and supply chain integration. The study will also enable an understanding of the existing policy landscape and alignment of the potential product with the same toward informing the feasibility of introduction.

Insights generated from all the abovementioned outcome domains will represent perspectives of populations of interest across geographies in India and will be collated into management presentations to provide an overview of the acceptability and feasibility of bNAb products in this region toward informing product development strategies.

Limitations of the Study

We anticipate some limitations. First, being a qualitative study, an inherent limitation of the study is that the findings may not be generalizable (in a statistical sense) as purposive sampling, a nonprobability sampling widely used in qualitative research, was used. However, we will try to ensure diversity when recruiting potential participants from various study subgroups, that is, by using maximum variation or diversity sampling, a type of purposive sampling. Such a strategy, along with a detailed description of the settings and participant characteristics, will increase the chances of the transferability of the findings to similar contexts and populations. Second, the study is being implemented by 3 study partners in different settings. Although all interviewers used standardized data collection tools and underwent common trainings, personal differences in interviewing styles may result in varied elicitation of responses from end-users. We will try to reduce this bias by having periodic debriefing sessions with the research team, especially data collectors, which will help the team to reflect on how one's values and beliefs might influence the way we ask questions in the interviews or FGDs or in arriving at inferences when analyzing the data [71].

Conclusions

With the evolution in the HIV prevention research field and the expansion of the prevention toolbox, end-users have a wide spectrum of choices. It is important for product developers to understand the drivers of these choices to clearly articulate the unique value proposition of each product to define their positioning in the choice spectrum. It is also critical to generate timely evidence on target populations, facilitators and barriers of use, relative importance of products, and communication needs to facilitate, plan, and enable policy decisions for the introduction of newer products. Thus, this study will aid in generating insights that will be critical for product developers and policy makers.

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Data Availability

The data sets generated during the study will be used to analyze the final findings from the study. The analyzed data sets will be available in the main manuscript that will be published highlighting the findings from this study. For data sharing, national policies applicable to Indian research data [72] will be adhered to.

Conflicts of Interest

Some of the authors (JM, SuH, PA, SM, MK) are affiliated with the International AIDS Vaccine Initiative, which is a not-for-profit organization that is involved in the development of broadly neutralizing antibodies. All other authors declare no other conflicts of interest.

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Abbreviations

AGYW: adolescent girls and young women
ARV: antiretroviral
bNAb: broadly neutralizing antibody
CBO: community-based organization
C-SHaRP: Centre for Sexuality and Health Research and Policy
FGD: focus group discussion
FSW: female sex worker
HST: Humsafar Trust
IDI: in-depth interview
IRB: institutional review board
KII: key informant interview
MSM: men who have sex with men
NGO: nongovernmental organization
PrEP: preexposure prophylaxis
PWID: people who inject drugs
SBE: simulated behavioral experiment
TFA: Theoretical Framework of Acceptability
TGW: transgender women
WHO: World Health Organization
YRGCARE: YR Gaitonde Centre for AIDS Research and Education

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Protocol

Lifestyle Medicine Implementation in 8 Health Systems: Protocol for a Multiple Case Study Investigation

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Abstract

Background: Lifestyle medicine (LM) is the use of therapeutic lifestyle changes (including a whole-food, plant-predominant eating pattern; regular physical activity; restorative sleep; stress management; avoidance of risky substances; and positive social connection) to prevent and treat chronic illness. Despite growing evidence, LM is still not widely implemented in health care settings. Potential challenges to LM implementation include lack of clinician training, staffing concerns, and misalignment of LM services with fee-for-service reimbursement, but the full range of factors facilitating or obstructing its implementation and long-term success are not yet understood. To learn important lessons for success and failure, it is crucial to understand the experiences of different LM programs.

Objective: This study aims to describe in depth the protocol used to identify barriers and facilitators impacting the implementation of LM in health systems.

Methods: The study team comprises team members at the American College of Lifestyle Medicine (ACLM), including staff and researchers with expertise in public health, LM, and qualitative research. We recruited health systems that were members of the ACLM Health Systems Council. From among 15 self-nominating health systems, we selected 7 to represent a diversity of geographic location, type, size, expertise, funding, patients, and LM services. Partway through the study, we recruited 1 additional contrasting health system to serve as a negative case. For each case, we conducted in-depth interviews, document reviews, site visits (limited due to the COVID-19 pandemic), and study team debriefs. Interviews lasted 45-90 minutes and followed a semistructured interview guide, loosely based on the Consolidated Framework for Implementation Research (CFIR) model. We are constructing detailed case narrative reports for each health system that are subsequently used in cross-case analyses to develop a contextually rich and detailed understanding of various predetermined and emergent topics. Cross-case analyses will draw on a variety of methodologies, including in-depth case familiarization, inductive or deductive coding, and thematic analysis, to identify cross-cutting themes.

Results: The study team has completed data collection for all 8 participating health systems, including 68 interviews and 1 site visit. We are currently drafting descriptive case narratives, which will be disseminated to participating health systems for member checking and shared broadly as applied vignettes. We are also conducting cross-case analyses to identify critical facilitators and barriers, explore clinician training strategies to facilitate LM implementation, and develop an explanatory model connecting practitioner adoption of LM and experiences of burnout.

Conclusions: This protocol paper offers real-world insights into research methods and practices to identify barriers and facilitators to the implementation of LM in health systems. Findings can advise LM implementation across various health system contexts. Methodological limitations and lessons learned can guide the execution of other studies with similar methodologies.

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KEYWORDS

healthy lifestyle; implementation science; lifestyle medicine; multiple case study; noncommunicable diseases; prevention; qualitative methods

Introduction

Cardiovascular disease, diabetes, and other chronic illnesses (including mood disorders) continue to be the leading causes of morbidity and mortality in the United States [1,2]. An estimated US $4.1 trillion is spent annually on health care for individuals with chronic physical and mental health conditions [2]. Poor health behaviors, such as a less healthy diet, physical inactivity, and substance use, exacerbate these conditions and cost the United States an estimated US $1.3 trillion per year [3]. An estimated 75%-90% of chronic illnesses could be prevented by lifestyle modification [4].

Lifestyle medicine (LM) is a "medical specialty that uses therapeutic lifestyle interventions as a primary modality" to prevent, treat, and reverse chronic conditions [5]. This "evidence-based, whole-person, prescriptive lifestyle change" is built around 6 pillars: a whole-food, plant-predominant eating pattern; regular physical activity; restorative sleep; stress management; avoidance of risky substances; and positive social connection [5]. These innovative and comprehensive approaches, especially those related to diet, have been shown to promote healthy weight, decrease the risk of type 2 diabetes, reduce cardiovascular risk factors, and improve quality of life [6-15]. Experts estimate US $116 billion could be saved annually through modest changes in health behavior and care delivery that result in improved treatment rates, increased physical activity, reduced smoking, and reduced obesity [16].

Interest in LM is growing, as evidenced by the rising membership of the American College of Lifestyle Medicine (ACLM), which increased by approximately 300% between 2018 and 2021 [17]. In 2017, the American Medical Association House of Delegates emphasized the importance of LM treatment by passing a resolution supporting providers to prescribe healthy lifestyle behaviors [18]. Despite these advances, adoption in clinical practice is slow [12,13,19-21], and additional research is needed to better understand the barriers and facilitators to implement this approach in health care settings [20].

The Consolidated Framework for Implementation Research (CFIR) is commonly referenced in the implementation science field to characterize factors that can influence the successful implementation of health services [22]. It includes 5 domains: intervention, inner setting, outer setting, individuals involved, and the implementation process. About 13% of the estimated 625 health systems across the United States are members of the ACLM Health Systems Council and are at varying stages of LM implementation [23,24]. Commonly, the inner setting of LM takes place within primary care and the general internal medicine environment, as well as medical specialties such as diabetes and oncology. Implementation processes and strategies can often extend across disciplines, such as the case with the modification of electronic medical records to prompt behavioral screening and referrals. Systematic implementation of LM faces various challenges, including inadequate leadership support and clinician training in the inner setting and patient preferences and reimbursement complexities in the outer setting [19,20,22,25]. A 2019 survey of ACLM members assessed respondents' current practice of LM, including reimbursement, quality measures, and patient outcomes [26]. In reviewing findings (published elsewhere), ACLM leadership and consultants determined that greater critical richness and additional details could be achieved through a qualitative examination of a subset of US health care systems with LM programs.

ACLM's mission calls for additional high-quality research, education, and advocacy to continue building evidence that LM should be more comprehensively implemented by US health care systems [27]. However, the current literature lacks documentation of the most effective implementation strategies to support LM practice. To address this gap, we are conducting a multi–health system case study to understand the factors that led to the development, growth, and maintenance of successful LM programs within health systems. Specific aims of *Lifestyle Medicine Integration in Health Systems: A Case Study Project* include: (1) examining in-depth 8 LM programs and constructing a detailed case narrative report for each system; (2) identifying factors influencing the initiation and growth of LM practices; and (3) describing common facilitators and barriers across health systems to the continued implementation of LM.

This paper outlines the study protocol, including case selection, data analysis, and dissemination of research findings. It will aid in interpreting study findings and advise the research execution of other studies that incorporate similar methodologies across various settings.

Methods

Overview

In response to a gap in the rich understanding of barriers and facilitators to implementing LM in health systems, the research team selected a qualitative research approach investigating multiple health systems as individual case studies. This multiple case study approach incorporates insights from multiple instances of the phenomenon of interest [28,29].

This paper describes the 8 steps used to conduct this research, as outlined in Table 1. At the time of this writing, steps 1-5 have been completed and steps 6-8 are in progress.

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Table 1. Protocol steps for the Lifestyle Medicine Integration in Health Systems study.

Step	Activity	Status[a]
1	Formation of the study team	Complete
2	Selection of methods	Complete
3	Recruitment and training of the study team	Complete
4	Case study nomination and selection	Complete
5	Iterative data collection	Complete
6	Iterative preparation of case study narratives	In progress
7	Preparation of cross-case reports	In progress
8	Dissemination of findings	In progress

[a]As of February 1, 2024.

Step 1: Formation of Study Team (Completed)

The study team comprises team members at ACLM staff and researchers with expertise in public health, LM (including behavior change), and qualitative research. As the national medical professional organization representing physicians and other health professionals practicing LM, ACLM is uniquely positioned to form and coordinate this study team. In addition to representing individual practitioners, ACLM also coordinates a network of health systems, the Health Systems Council (HSC). This group comprises integrated health systems around the United States committed to growing their LM service offerings and sharing their experiences and learnings with other council members [24]. In July 2021, the study team initiated regular (weekly or biweekly) meetings to discuss research aims and methods. The study team has continued to meet throughout the duration of the project.

Step 2: Selection of Methods (Completed)

Through discussion at regular meetings and review of qualitative literature, the study team identified the methods that would be used for this project. We selected a qualitative case study approach, embracing constructivist epistemology (the belief that there is no one truth and that findings are created by the interaction between the patients or informants and the observer or data collector) [30]. Case studies are a qualitative methodology that facilitates the exploration of a specific topic through the development of complex narratives, promoting rich insights from multiple sources within single and multiple cases [28,31,32]. Although findings are heavily influenced by contextual factors, the cross-case reports (described later) provide insights that can be transferred to other settings. This need for transferability suggests a multiple case (rather than single-case) design would be appropriate for the identified research questions [32].

We selected case studies to allow for contextual diversity and triangulation, or the gathering of evidence from multiple data sources, to yield convergent findings [28,33]. To facilitate triangulation, the study methodologies included data collection from multiple stakeholders and source types (in-depth interviews, document review, survey responses, and direct observation). Further, document review allows for the gathering of evidence by interviewers ahead of interviews and reduces the burden on informants [32]. We selected in-depth interviews instead of focus groups to allow for triangulation from different perspectives (both individual experiences and professional roles) and reduce social desirability bias and fear of disclosure among informants [34]. Finally, direct observation (in the form of in-person site visits) yields insights that interviewees may have accidentally omitted due to their own familiarity with their particular context.

Step 3: Recruitment and Training of Study Team (Completed)

The study team is coled by the principal investigator (MCK) and a senior investigator with expertise in qualitative research and case study methods (JG). Additional expert advisors representing ACLM (TAH and KLS) and academic institutions (MLA, SMS, ND, and MMR) offer critical insights and guidance to protocol development and implementation. All data collection was completed by researchers who are external to ACLM, apart from 2 students who were previously involved as members of ACLM. ACLM staff advise on study design or implementation, participate in team meetings, and are part of the iterative review process, but do not conduct data collection.

There were 8 data collectors, who primarily comprised graduate-level students trained in the fields of public health and medicine. Data collectors were hired as research assistants and recruited through study team networks. All data collectors completed data collection training designed and delivered by the academic consultant. The training included general principles of qualitative research, qualitative interviewing techniques, and a review of the study protocol.

Step 4: Case Study Nomination and Selection (Completed)

Multiple case studies are recommended to contain 4-10 cases to achieve sufficient variability while providing a manageable amount of transferrable insights [28]. Stake [28] identifies 3 criteria that should be present when selecting cases: (1) the case must be relevant to the quintain (or phenomenon of interest, which is LM implementation); (2) the cases must provide contextual diversity; and (3) the cases must allow researchers to observe and explore complexities and contexts.

We followed a purposive sampling approach that leveraged the preexisting ACLM HSC network, which is uniquely positioned

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to access health systems with LM programs. From March 21-April 1, 2022, recruitment emails were disseminated through ACLM HSC email communications. During the recruitment period, 15 health systems were self-nominated by an employee representative from each interested health system. The self-nomination form captured data on the health system's geographic location, patient demographics, payer types, LM practitioners, programs available, and the estimated reach of the LM program.

Table 2 includes selected self-reported data for the participating health systems and describes geographic location by census-based US regions to preserve health system anonymity [35]. Data reported through the nomination form were not corroborated and should be interpreted conservatively. One health system (site code H) did not complete the nomination form and was recruited through a different mechanism, described below.

Table 2. Summary of self-reported characteristics of participating health systems.

Site code	Region	Level of focus[a]	Reach[b]
A	South	Subspecialty	Small
B	West	Specialty	Large
C	Midwest	Subspecialty	Medium
D	West	Specialty	Medium
E	South	Specialty	Medium
F	Midwest	Subspecialty	Small
G	West	Specialty	Large
H	South	—[c]	—

[a]"Specialty" indicates lifestyle medicine is a stand-alone area of treatment programming; "subspecialty" indicates lifestyle medicine is an adjunct approach embedded in other treatment specialties.

[b]Reported estimated number of patients receiving care at the time of nomination, where "large" is >5000, "medium" is 1000-5000, and "small" is <1000.

[c]Not available.

Study team members reviewed all self-nomination forms and came to a consensus through discussion about which cases to include to achieve contextual diversity, including variability in program size, age, geographic location, payer model, and population served. We selected 4 instrumental cases that were generally representative of the "typical" nominees seen but varied in the aforementioned characteristics [28]. We also selected 2 intrinsic cases that offered a unique context due to their stage (either very early or relatively mature in development), size, and extent of LM practice integration [28]. Selected cases were invited to confirm participation through a health system representative authority.

Partway through case recruitment and data collection, the study team determined that a contrasting case was needed to demonstrate the experiences of a health system that had initiated and then aborted an LM program. The study team agreed that this perspective would yield unique insights about implementation barriers to LM. This iterative approach is an accepted multiple case study procedure, through which redesign can emerge partway through case selection [32]. Original recruitment strategies did not satisfy this need, and the study team used an additional recruitment strategy that built upon individual communications rather than wide-reaching HSC communications channels. One case (site code H) was recruited using this approach and varied slightly in the data collection methods described below.

Step 5: Iterative Data Collection (Completed)

Overview

Each participating health system was assigned a single data collector as a site lead, whose responsibilities included coordinating data collection and drafting the case narrative. The site lead managed a team of 1-2 other data collectors, who conducted individual interviews with different members of the health system's LM team. Overall, 4 types of data were collected: in-depth interviews, site visits, existing documents, and study team notes.

In-Depth Interviews

The study team conducted at least 6-8 in-depth interviews with individuals identified in each participating health system. Health system liaisons were asked to identify employees who were integral to the implementation of the LM programming. They were provided a list of potential types of roles sought for interviews and asked to prioritize individuals who served as health system leaders or administrators (including billing professionals) and physicians. Other health care professionals delivering LM were also requested and included nurse practitioners, registered dietitians, behavioral health specialists, health coaches, exercise physiologists, physical therapists, kinesiologists, and mental health professionals. Only in the instance of the contrasting case were former employees also invited to participate in interviews.

Interviews lasted 45-90 minutes and were conducted through video call (typically), telephone (rarely), or in-person (rarely). When using video call, interviewees had the option of

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participating with their camera on (typically) or off (rarely). Interviews were open-ended and exploratory and followed a semistructured interview guide designed to achieve the study aims and allow for adaptability based on the interviewee or health system context. The interview guide was iteratively designed by study team members and loosely structured on the CFIR model [22]. Minor updates to the interview guide were made as emergent topics were identified.

In alignment with the CFIR, interviewees were asked about the inner (structural characteristics, culture, and available resources) and outer (patient population, billing, or payer practices) settings of their health system in addition to individual factors (their specific role and the roles of others) [22]. They were also asked to describe their understanding of the intervention (LM), how it differs from other types of medicine within their setting, and how it was adapted for their specific setting. The interview also included questions about barriers, facilitators, and processes related to program launch and growth. Interviewers were trained to probe topics particularly relevant to the interviewee or health system context. If warranted, the interviewer requested a follow-up interview with an interviewee. These follow-up interviews were intended to answer specific questions, provide missing details, or explore a topic not previously discussed. The most recent version of the interview guide at the time of publication is available in Multimedia Appendix 1.

The 2 study team members assigned to each participating health system were responsible for participating in each associated interview, either as a primary interviewer or as an interview reviewer, which involves reviewing the transcript. Interviews were recorded using the video meeting software (Zoom; Zoom Video Communications [36]) or a recording device (or sometimes both for redundancy) and stored in a secure location on the cloud. Recordings were transcribed using the Microsoft One Drive (Microsoft Corporation) transcription and then manually reviewed and edited for accuracy by study team members. Additionally, interviewers documented emerging themes or other contextual factors following each interview.

Document Review

Interviews were supplemented by the review of available health system documentation. The study team collected and reviewed publicly available annual reports, websites, program promotional materials, strategic plans, and relevant community health needs assessments. Interviewees were asked about additional materials they thought were relevant to the interview themes, and such materials (which may include organizational charts, internal planning documents, and patient education materials) were also reviewed. The study team maintained a database of all reviewed documents to aid in identifying additional documents for review. Interviewers referenced documents if and as needed when reflecting on and taking notes about past interviews, preparing for upcoming interviews, and sharing updates during study team discussions. For example, if an interviewee mentions an LM program that is referenced by multiple names, the interviewer can reference the health system website and patient recruitment materials to confirm the official name of the program. Additionally, documents are referenced during the preparation of the case study narratives and cross-case analysis to corroborate findings, fill in missing details, and provide illustrative examples. For example, if a health system reported promoting referrals by sending email communications to physicians, the language from the communication may be included in the case study narrative as an example of that recruitment strategy.

Site Visits

An in-person site visit occurred for 1 site and included unstructured observations of the settings and conversations with health system employees, which mirrored themes included in the in-depth interview guide. Photos from the site visit (including patient waiting areas, exam rooms, dining and exercise facilities, offices, and other available areas) are referenced in the qualitative data analysis. Otherwise, site visits were not conducted. This decision was made due to the restrictions of the COVID-19 pandemic.

Weekly Study Team Discussions and Iterative Review (Currently in Progress)

Following the principle of emergent design [37], the study team meets 2-4 times per month to debrief from interviews and discuss emerging themes. During team meetings, data collectors report on themes from recent interviews, and the study team discusses how findings enhance the understanding of health system LM implementation and identifies areas to probe further in future interviews. This is also when the study team discusses similarities and differences among health systems and determines the need for potential changes to the study protocol, case selection, interview guide, case narrative outline, and cross-case analysis. Additionally, study team members report on current events and publications that are relevant to research aims. Meeting recordings and minutes are available for study team members to reference during data analysis.

Step 6: Preparation of Case Study Narratives (Currently in Progress)

In collective case study analysis, it is prudent to conduct individual analysis initially (described below) and follow with cross-case analysis (described in step 7) [38]. Through an iterative and collaborative process, the study team developed a case report format that is followed for the preparation of each case narrative to facilitate intercase comparison. This requires that case narratives open with a presentation of objective data, including name, location, size, payer model, etc. The following sections align with the overall study aims and include potential barriers and facilitators to initiation and sustainment. After completing 2 of the case study narratives, the study team decided to add 2 additional sections focused on clinician training and provider burnout to capture emergent themes. All case reports will follow the same report template (the original 2 case study narratives were revised to align with the updated structure) but vary in length and subtopics covered specific to each health system. The case narrative template is included in Multimedia Appendix 2.

The site's lead data collector is primarily responsible for writing the case study narrative. Other study team members review and comment on case narrative drafts until a consensus is reached. As appropriate and necessary, study team members may conduct

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additional follow-up interviews or share versions of the case narratives with interviewees (with individual identifiers removed) to facilitate member checking. Additionally, 1 team member is responsible for reviewing all reports for consistency in form, content, and style.

Step 7: Cross-Case Analysis (Currently in Progress)

Following the completion of case study narratives, the study team completes cross-case analyses focused on topics of interest. Specific analysis topics are not yet final but will likely include billing, care delivery models, clinician training, leadership support, buy-in, intervention content, workplace culture, and burnout. Each cross-case analysis will yield a manuscript to be submitted for peer-reviewed publication. Because the cross-case analyses are not yet complete, the following methods offer a high-level overview of the procedures planned for each analysis report.

Some cross-case analyses will follow the multiple case study methodology reported by Stake [28], which includes the following steps: (1) plan the cross-case analysis and identify themes relevant to research questions; (2) become familiar with individual cases; (3) assess case utility for each cross-case theme; and (4) sort and merge findings relevant to themes. In the Stake [28] approach, a series of interactive worksheets are completed to identify emergent themes, guide analysts through their review of case narratives, and plan and execute a cross-case report. This case study analysis methodology was selected as it preserves contextual information to a large degree. Other cross-case analyses may leverage a coding approach, which uses search queries to identify relevant segments of transcripts or documents and then applies an inductive coding schema to the resulting data.

Step 8: Dissemination of Findings (Currently in Progress)

The study team plans to disseminate a series of manuscripts. This paper offers an overview of the methods conducted and planned for data collection, analysis, and reporting. We also plan to disseminate shortened, deidentified versions of the case study narratives to serve as vignettes for consideration by other practitioners. Additional papers will provide insights for each of the cross-case analyses by comparing and contrasting specific findings for each case study site and highlighting common practices seen in instrumental cases and unusual situations seen in intrinsic cases [28]. These can advise on the implementation and integration of LM programs into health systems that can be applied in other settings to initiate or scale current LM offerings.

Additionally, we plan to share deidentified case narratives with the respective participating health systems. This serves the dual purpose of (1) facilitating member checking and (2) offering the benefit of an external perspective to participating health systems.

Ethical Considerations

The University of New England's institutional review board (IRB) reviewed the study protocol and determined it was exempt from IRB review and oversight (project number 1221-21). Before the interview, all participating individuals completed a written informed consent, which included an overview of the study purpose, a request for participation, a description of privacy protection efforts, and a review of potential risks and benefits. Participants were not compensated for their time.

Results

At the time of this writing (February 1, 2024), the study team has completed all the interviews at 8 health systems. The team interviewed 63 individuals, 5 of whom participated in a follow-up interview, resulting in 68 total interviews. Every site included an interview with at least 1 administrator and physician. Across all sites, interviews were conducted with 25 health system leaders or administrators; 16 physicians; 7 registered dietitians; 6 behavioral health specialists or health coaches; 4 nurse practitioners; 2 exercise physiologists, physical therapists, or kinesiologists; 2 mental health professionals; and 1 individual with an unclassified role.

The study team has completed initial drafts of all 8 case study narratives and is abridging and deidentifying them for member checking and broader dissemination. Cross-case analysis is underway to identify critical facilitators and barriers, explore clinician training strategies to facilitate LM implementation and develop an explanatory model connecting practitioner adoption of LM and experiences of burnout. Additional analyses may investigate how billing strategies, care delivery models, leadership support or buy-in, and intervention content can impact LM implementation in health systems.

Discussion

Overview

This research is the first multiple case study examining facilitators and barriers to LM implementation in health system settings. It will address a gap in the literature by providing insight into the barriers and facilitators to adopting LM practice in health systems. Below is a discussion of limitations, strengths, and opportunities for further research.

Limitations

ACLM serves as the primary funder for this work, potentially introducing a pro-LM bias. To reduce the influence of this bias, the study team was intentionally designed to be diverse and include experts who are external to ACLM and thus not biased in the same way that ACLM affiliates are. Additionally, all methodological and analysis decisions are made during study team meetings, which include multiple perspectives, including 1 senior advisor, in addition to ACLM.

In some cases, the study team was challenged to identify interviewees who comprehensively represented the breadth of LM activities in a single health system. This is partly due to the size and complexity of participating health systems. Individual interviewees were identified by 1 or 2 liaisons at each health system and sometimes did not include groups or types of individuals who would have offered valuable insights. For example, 1 site provided names of individuals who were involved in implementing one specific LM program but were

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not familiar with the LM residency program that was offered by a different unit of the health system. This resulted in in-depth data about the specific LM program but fewer insights into the LM residency offerings. Additionally, some health systems were unable to allow nonexempt employees to participate in in-depth interviews because the study was not compensating interviewees for their participation. This resulted in an overrepresentation of leadership and an underrepresentation of front-line workers and intervention delivery personnel. To address these challenges, the study team circled back to health system liaisons to request interviews with additional individuals whose perspectives were not initially included, although the requests were not always met. Data collection methods did not directly include patients or community members, resulting in a gap in these perspectives. Interviewees were asked to speak about the experiences of these individuals, but future research should also investigate these perspectives, specifically.

Finally, site visits and in-person interviews were limited due to restrictions associated with the COVID-19 pandemic. We were only able to conduct 1 site visit, which was conducted in person. To adapt, we revised our methods to prioritize internet-based interviews. Through this process, we learned that internet-based interviews facilitated easier scheduling and access to individuals and often yielded high-quality interviews that were thought to be comparable to in-person interviews. Considering the added logistical benefits, the study team determined the internet-based interview approach to be preferable to in-person site visits. No interviews were conducted in person.

Strengths

This multiple case study methodology and our iterative team-based approach are strengths of this research. By preserving the context of each case, researchers can gain a rich understanding of the many factors impacting the phenomenon of interest [28,31]. Although the selection of ACLM HSC members allows for insights into the experiences of early adopters, the findings may not be translatable to relatively more nascent programs. Throughout the early stages of case selection, our team reviewed health system components to ensure variability in program maturation. We intentionally selected health systems with more recently established LM programs and also sought out and recruited a contrasting case that had initiated and then greatly reduced LM programming. However, the study would have been further strengthened by the inclusion of additional negative cases. The heterogeneity of participating health systems will contribute to the transportability of the study findings. Future research should investigate if and how barriers and facilitators are different among health systems that are not currently aligned with LM.

A strength of this study is that the cases and analyses take place at the health system level, allowing a more comprehensive perspective that incorporates all CFIR domains [22]. Health systems are complex systems of hospitals, clinics, and individuals connected through joint ownership or management [38]. Within these systems are varying cultures (“individuals involved” domain), policies, and processes (“inner setting” domain), which can impact practices (“process domain”). Examination at the health system organization level offers insights into the macrolevel factors (“inner” and “outer setting” domains) that impact LM implementation. Gaining permission to work with such large and complex organizations can be challenging, however, and in some instances, investigation was delayed and even prohibited due to the inability or unwillingness of health system leadership to provide permission for participation. Some health system leaders expressed confidentiality concerns, noting that patient perspectives of the organization and their practices were a critical consideration.

Conclusions

This protocol paper offers real-world examples of research methodologies used to gather data on a series of health systems. Additionally, the study findings will yield practical insights into strategies to effectively implement LM in health systems. Health system leaders and administrators can draw on these findings to establish and grow their own LM programs and integrate LM practices into existing services. Expanded access to LM treatment may result in improved morbidity and mortality outcomes related to chronic diseases [1,6,12].

Acknowledgments

The authors would like to thank the participating health systems and staff for their support of this project, as well as American College of Lifestyle Medicine employees, including Kaitlyn Pauly, who advised on this work.

Data Availability

The data presented in this study cannot be shared due to privacy concerns and the inability to adequately secure the identity of the participants.

Authors' Contributions

MCK and JG are co–principal investigators. MLA, JG, MCK, and SMS contributed to the methodology. MLA was involved in writing and preparing the original draft of the manuscript. MLA, ND, JG, TAH, MCK, MMR, KLS, SMS, and BW contributed to the writing, reviewing, and editing of the manuscript. MCK and SMS were responsible for project administration. MCK was responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

MCK, TAH, and KLS are employed by the American College of Lifestyle Medicine. The other coauthors receive consulting payments from the American College of Lifestyle Medicine.

Multimedia Appendix 1
In-depth interview guide.
[DOCX File , 42 KB - resprot_v13i1e51562_app1.docx]

Multimedia Appendix 2
Case study narrative outline.
[DOCX File , 37 KB - resprot_v13i1e51562_app2.docx]

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Abbreviations

ACLM: American College of Lifestyle Medicine
CFIR: Consolidated Framework For Implementation Research
HSC: Health Systems Council
IRB: institutional review board
LM: lifestyle medicine

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Protocol

Target Product Profile for a Machine Learning–Automated Retinal Imaging Analysis Software for Use in English Diabetic Eye Screening: Protocol for a Mixed Methods Study

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Abstract

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Background: Diabetic eye screening (DES) represents a significant opportunity for the application of machine learning (ML) technologies, which may improve clinical and service outcomes. However, successful integration of ML into DES requires careful product development, evaluation, and implementation. Target product profiles (TPPs) summarize the requirements necessary for successful implementation so these can guide product development and evaluation.

Objective: This study aims to produce a TPP for an ML-automated retinal imaging analysis software (ML-ARIAS) system for use in DES in England.

Methods: This work will consist of 3 phases. Phase 1 will establish the characteristics to be addressed in the TPP. A list of candidate characteristics will be generated from the following sources: an overview of systematic reviews of diagnostic test TPPs; a systematic review of digital health TPPs; and the National Institute for Health and Care Excellence's Evidence Standards Framework for Digital Health Technologies. The list of characteristics will be refined and validated by a study advisory group (SAG) made up of representatives from key stakeholders in DES. This includes people with diabetes; health care professionals; health care managers and leaders; and regulators and policy makers. In phase 2, specifications for these characteristics will be drafted following a series of semistructured interviews with participants from these stakeholder groups. Data collected from these interviews will be analyzed using the shortlist of characteristics as a framework, after which specifications will be drafted to create a draft TPP. Following approval by the SAG, in phase 3, the draft will enter an internet-based Delphi consensus study with participants sought from the groups previously identified, as well as ML-ARIAS developers, to ensure feasibility. Participants will be invited to score characteristic and specification pairs on a scale from "definitely exclude" to "definitely include," and suggest edits. The document will be iterated between rounds based on participants' feedback. Feedback on the draft document will be sought from a group of ML-ARIAS developers before its final contents are agreed upon in an in-person consensus meeting. At this meeting, representatives from the stakeholder groups previously identified (minus ML-ARIAS developers, to avoid bias) will be presented with the Delphi results and feedback of the user group and asked to agree on the final contents by vote.

Results: Phase 1 was completed in November 2023. Phase 2 is underway and expected to finish in March 2024. Phase 3 is expected to be complete in July 2024.

Conclusions: The multistakeholder development of a TPP for an ML-ARIAS for use in DES in England will help developers produce tools that serve the needs of patients, health care providers, and their staff. The TPP development process will also provide methods and a template to produce similar documents in other disease areas.

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KEYWORDS

artificial intelligence; design; developers; diabetes mellitus; diabetic eye screening; diabetic retinopathy; diabetic; DM; England; eye screening; imaging analysis software; implementation; machine learning; retinal imaging; study protocol; target product profile

Introduction

Diabetic Eye Screening and Its Delivery in the United Kingdom

Diabetic eye screening (DES) aims to prevent vision loss from diabetic retinopathy (DR), a sight-threatening microvascular complication of diabetes [1]. In the United Kingdom, people with diabetes aged 12 years or older undergo yearly fundus photography with images interpreted by human graders to detect and assess the severity of DR. This allows detection of DR in its early asymptomatic stages, facilitating early referral to hospital eye services where treatment is more effective [2,3]. DES is associated with improved clinical [4] and economic [5] outcomes and a reduction in blindness from DR since its introduction in 2003 [6]. However, DES is both labor and resource intensive [7], and costs are expected to increase with a projected rise in diabetes prevalence [8]. In the United Kingdom, grading is undertaken by experienced professionals in a quality-assured and controlled multilevel system [9] with a high sensitivity for sight-threatening diseases [10]. However, grading represents a significant cost despite the fact that the majority of people with diabetes have no evidence of DR or only mild disease [11] and are at low risk of visual loss in the near term [12].

Automated Retinal Imaging Analysis Software

DES grading is considered a promising use case for automation, and indeed, DES in Scotland has used automated retinal imaging analysis software (ARIAS) since 2012 [13,14]. This software uses "symbolic" artificial intelligence (AI) with grading "rules" programmed by humans [15] and is used in a primary grader role. The Scottish "autograder" has demonstrated a sensitivity of 90.5% (95% CI 89.3%-91.6%) and specificity of 67.4% (95% CI 66%-68.8%) for referable disease or ungradable images [13], with 50% of images it graded in 2018 requiring no further human review [16]. It is, however, unable to process the optic disc–centered images acquired in screening protocols elsewhere in the United Kingdom and has not been adopted outside Scotland [17].

Subsequent advances in AI, most notably in machine learning (ML), where AI "learns" patterns from data it is presented as opposed to being programmed by humans, have given rise to a newer generation of machine learning–automated retinal imaging analysis software (ML-ARIAS). These have demonstrated better performance than symbolic tools on

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routinely collected UK screening images, including disc-centered photos. Heydon et al [18] found ML-ARIAS was able to achieve sensitivity and specificity of 95.7% (95% CI 94.8%-96.5%) and 54% (95% CI 53.4%-54.5%), respectively, for referable disease or ungradable images in a large sample taken from routine screening in 3 UK programs. A health technology assessment has also estimated that ML-ARIAS in a triage or primary grader role could be cost-effective and cost-saving compared to purely manual grading [17]. Consequently, there have been calls for ML-ARIAS's adoption into DES in the United Kingdom [19].

Bridging the Implementation Gap

In response to these calls, the UK National Screening Committee (NSC), an independent scientific advisory group that advises UK governments on screening programs, commissioned a review to ascertain whether ARIAS should be more widely adopted in 2021 [19]. While the review found evidence suggesting ML-ARIAS to be safe, accurate, and cost-effective, it also highlighted evidence gaps that prevented a recommendation for their use. The review highlighted that the acceptability of ML-ARIAS with patients and health care professionals was unknown, as was their real-world performance post implementation, recognizing that this may be affected by a range of clinical and technical factors. While research to address these evidence gaps is currently ongoing [20], the review's conclusions reflect an awareness in the wider field of health care AI that evidence of good diagnostic accuracy cannot predict the impact tools will have post deployment. This awareness contributes toward a growing "implementation gap" [21,22] or "chasm" [23] in health care AI, with increasing numbers of tools failing to be adopted into clinical use following promising research. This situation has a number of negative consequences, such as significant opportunity cost, with tools' development requiring significant public [24] or private investment [25], as well as a failure for patients, health care professionals, or systems to realize the benefits tools may offer for a lack of appropriate evidence generation.

A similar situation has existed in the pharmaceutical and medical device industries for decades. Despite significant investment in research and development, few biomarkers, drugs, or devices are ever adopted into routine clinical care, often failing to achieve regulatory approval or demonstrate sufficient clinical or economic benefits to health care providers [26,27]. To combat this situation, pharmaceutical companies began to outline the characteristics necessary for a successful product in the earliest stages of development, summarizing these in "target product profiles" (TPPs). These documents often incorporate considerations essential to successful clinical use but not covered in traditional research, such as interaction with existing care pathways and resource constraints. TPPs are used to guide research development as part of a broader "quality by design" approach that has been encouraged by regulatory agencies [28,29] and widely adopted in industry with notable successes [30,31]. TPPs have since been used by governments [32], health care providers [33], and nonprofit organizations [34] for drugs [35,36] and medical devices [37], particularly in the context of infectious diseases [38,39] and the developing world [40,41].

Aim

This study aims to produce a TPP for an ML-ARIAS for use in English DES (E-DES), enabling the development of ML tools that match the needs of people with diabetes, health care professionals, regulators, and providers. This work will focus on the English context, as variations in the commissioning and organization of DES between UK nations may affect the stakeholders needed as well as the TPP's final contents. However, we hope this work will be valuable for screening programs in other nations in the United Kingdom and beyond.

Objectives

The objectives of this study are to (1) identify which characteristics should be addressed in a TPP for an ML-ARIAS (this will be achieved through an overview of systematic reviews of TPPs, a systematic review of digital health TPPs, and by extracting standard's from the National Institute of Health and Care Excellence's (NICE) Evidence Standards Framework for Digital Health Technologies (ESF); (2) draft specifications for an ML-ARIAS TPP through semistructured interviews with members of key stakeholder groups; and (3) validate the contents of a TPP for an ML-ARIAS through a modified Delphi consensus study.

Methods

Ethical Considerations

Ethical approval for this study has been granted by the University of Birmingham Institutional Research Board (ERN_2023-0620). The study will be undertaken in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent will be sought from participants. The interviews and consensus meeting will be recorded and transcribed, with participants given the opportunity to opt out with deletion of their responses up to a week after their interview or meeting date, after which their responses will be anonymized and therefore no longer attributable to them. Recordings of the interview and consensus meeting will be deleted following transcription, with the anonymized transcripts stored on secure institutional research servers for up to 10 years. Delphi participants will be informed that their responses are anonymized and therefore cannot be deleted following submission. Contact details they provide in order to be able to participate in the consensus meeting will be stored on secure servers until the end of the study, after which they will be deleted.

People with diabetes participating in the study advisory group (SAG) and consensus meeting will have their travel costs reimbursed as well as their time reviewing documents or attending meetings at £25 (US $31.57) per hour in line with National Institute for Health and Care Research (NIHR) guidance [42,43].

Identifying Key Stakeholder Groups

The successful use of ML-ARIAS in E-DES will require the approval, collaboration, and consent of a diverse range of stakeholder groups. To ensure our TPP is both comprehensive

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and authoritative it is therefore important to incorporate the knowledge and opinions of all these groups in its development.

A recent qualitative systematic review on stakeholder perspectives of clinical AI implementation identified the following key stakeholder groups influencing implementation: patients, carers, and the public; health care professionals; health care managers and leaders; regulators and policy makers; and developers [44]. Mapped to our use case and context, these broad stakeholder groups can be further divided as follows: people with diabetes, carers, and the public; E-DES technicians and graders, as well as ophthalmologists (health care professionals); managers of E-DES services provided by either the NHS or independent providers (health care managers and leaders); the Medicines and Healthcare Products Regulatory Agency (MHRA), NICE, the Care Quality Commission (CQC), and NSC (regulators and policy makers); and ML-ARIAS developers. Our study will aim to encompass the opinions of all these groups as outlined below.

Study Delivery and Oversight

Study Management Group

A study management group (SMG) led by the chief investigator AKD will be responsible for the design and delivery of the study.

Recruitment

SMG members will be recruited from the host institution to facilitate ease of communication and regular meetings.

Sampling

The SMG will include experts in the relevant clinical, scientific, and methodological domains, project management support, and a person with diabetes.

Study Advisory Group

The SMG will be supported by a SAG, which will bring additional breadth of expertise from a range of key stakeholder groups. The SAG will provide critical feedback and advice throughout the project in quarterly project review meetings and at specific junctures outlined in the protocol and ad hoc.

Recruitment

SAG recruitment strategies will be tailored to individual stakeholder groups. People with diabetes will be recruited through diabetes charities. Clinical and methodological experts with previous experience developing TPPs will be identified through their publications in the field. Representatives of relevant regulatory and policy bodies will be recruited through their organizations (NSC, MHRA, NICE, and CQC).

Sampling

The SAG will aim to recruit at least 2 representatives from each of the broad stakeholder groups previously identified, with the exception of ML-ARIAS developers, omitted to avoid bias arising from conflict of interest. Experts in TPP development and health economics will also be invited to the SAG to add a greater breadth of expertise.

User Group

A TPP user group (UG) consisting of ML-ARIAS developers will be assembled to provide feedback on the TPP as outlined below to ensure feasibility is factored into the development process.

Sampling

The UG will consist of only ML-ARIAS developers.

Recruitment

Developers with ML-ARIAS approved by British, European, Australian, or US medical device regulators will be invited to participate, along with those with technologies included in the UK NSC's 2021 review.

Phase 1: Literature Reviews to Establish the Scope of an ML-ARIAS TPP

See Figure 1 for an overview of the ML-ARIAS TPP development process.

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Figure 1. Diagram of the machine learning–automated retinal imaging analysis software (ML-ARIAS) target product profile (TPP) development process. AI: artificial intelligence; NICE: National Institute for Health and Care Excellence; SAG: study advisory group.

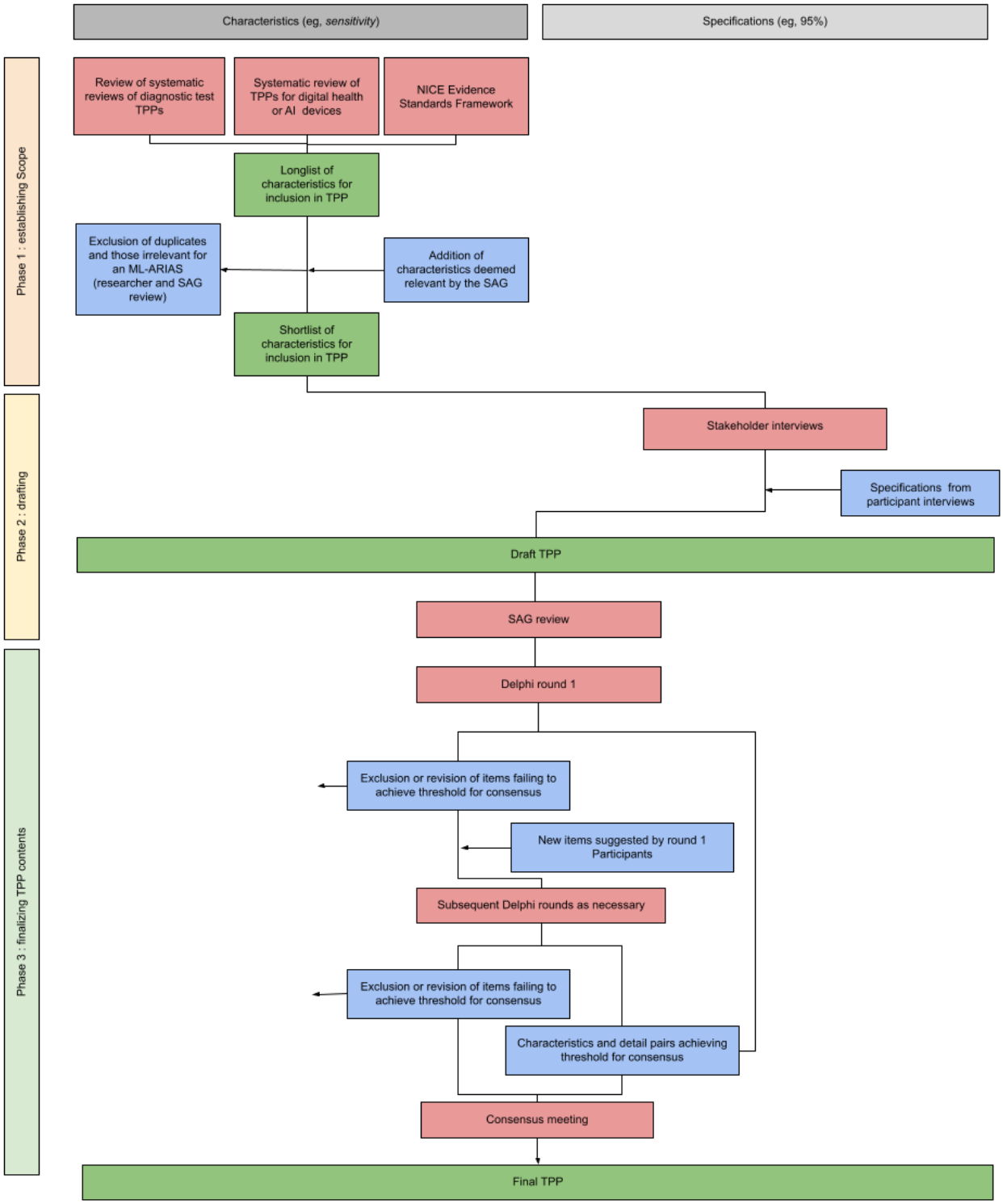

Rationale

This phase will seek to establish what characteristics a TPP for an ML-ARIAS should address in order to be both relevant and comprehensive. A long list of potential characteristics for inclusion in an ML-ARIAS TPP will be generated through 2 reviews. These will be built on the work of Cocco et al [45], who published a list of all characteristics previously reported in diagnostic test TPPs in a 2020 systematic review.

Overview of Systematic Reviews of Target Product Profiles for Diagnostic Tests

This will seek to identify all systematic reviews of diagnostic test TPPs with the aim of extracting the characteristics reported in each review or the TPPs they capture. Based on a scoping search, we anticipate this review will include the systematic review by Cocco et al [45] and any new resources published since.

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Systematic Review of TPPs for Digital Health Tools

As Cocco et al's [45] review did not include any TPPs for digital health tools, our long list of potential characteristics may therefore omit characteristics unique to these tests. The purpose of this review is to identify all TPPs published for digital health tools (including AI) and extract the characteristics they report. This will include TPPs for therapeutic as well as diagnostic devices.

Multimedia Appendix 1 includes MEDLINE search strategies for both reviews, developed in consultation with an information specialist and using validated search filters where possible [45-47]. Strategies for other bibliographic databases will be adapted from these, as will a web search strategy using a systematic method previously reported [48]. The 2 reviewers (TM and JH) will perform a title and abstract screening, then a full-text review to assess eligibility. Disagreements will be arbitrated by the senior investigator (AKD).

Generating AI-Specific Characteristics from NICE's Evidence Standards Framework for Digital Health Technologies

Rationale

As scoping searches for digital health TPPs have returned very few TPPs for AI and specifically ML tools, relying on the above reviews alone to determine the scope of our TPP may risk omitting characteristics unique to these devices and essential for their successful deployment. To generate AI-specific characteristics, we will therefore adapt standards from NICE's ESF for digital health technologies, a gold standard tool designed to evaluate digital health technologies for UK commissioning decisions. This was revised in 2022 to encompass AI devices, with the new AI standards being generated through a multistakeholder Delphi consensus process [49,50]. The 2 reviewers (TM and JH) will review the ESF, extracting relevant standards, with disagreements resolved by discussion or arbitration by the senior investigator (AKD). The extracted standards will be adapted into characteristics and added to the long list from the earlier reviews.

Shortlisting Characteristics for Inclusion in a Draft TPP

The list of candidate characteristics will be reviewed by the SMG to remove any irrelevant to the use case or proposed technology and consolidate the remainder, removing any duplicates. Disagreements between SMG members will be resolved through discussion and arbitration by the senior investigator (AKD) if necessary.

The remaining characteristics will then be mapped to the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework [51], a tool outlining the interacting complexity of factors at the policy, organizational, and practice level that may influence the successful implementation of digital health technology [52]. The NASSS will help group the characteristics into broader themes and help identify factors affecting successful implementation that they do not cover.

The included characteristics will then be presented to the SAG, along with those excluded and the NASSS domains not covered by the shortlist. SAG members will be asked to identify any characteristics incorrectly excluded and approve a final shortlist of characteristics for subsequent research phases through discussion or vote.

Phase 2: Drafting the TPP

Scoping Interviews

A TPP typically includes a table of characteristics and their specifications. Characteristics might include "target population" with "people with diabetes aged 12 years or older" as its associated specification. The drafting of specifications for each of the characteristics shortlisted in phase 1 will be informed by semistructured interviews with participants from each key stakeholder group previously identified. The final output of phase 2 will be a full draft TPP for entry into a modified Delphi consensus study in phase 3.

Sampling

Purposive sampling will initially be used with the aim of interviewing at least 1 individual from all the stakeholder groups relevant to the use case previously identified, with the exception of ML-ARIAS developers. As the interviews progress, theoretical sampling will be used to better explore areas of disagreement or characteristics that have not been addressed in previous interviews. Snowball sampling will also be used, with participants invited to suggest potential interviewees. An approximate target of 20 participants has been set; however, the scale of recruitment will be refined by the SMG as the interviews progress.

Recruitment

People with diabetes will be recruited through diabetes charities and offered compensation for their time in accordance with NIHR guidelines [42,43]. Clinical and methodological experts, as well as industry representatives with previous knowledge or experience of AI in DES or TPPs, will be identified through their publications in the field. Representatives of relevant regulatory and policy bodies will be recruited by contacting their organizations (NSC, MHRA, and NICE). It is anticipated that members of the SAG will facilitate the recruitment of key stakeholders in their respective stakeholder groups.

Data Collection

Ahead of the interviews, participants will be sent information in plain English on E-DES, AI, and TPPs.

The interviews will be conducted over video teleconferencing software (Zoom; Zoom Video Communications, Inc). Interview participants will initially be asked to provide demographic data, including stakeholder groups, location, age, sex, gender, and ethnicity. A preprepared topic guide informed by the shortlist of characteristics produced in phase 1 will be developed and used to encourage a free-flowing conversation between interviewer and interviewee focused on the latter's opinions, priorities, and concerns regarding the adoption of ML-ARIAS in E-DES. The topic guide will be iterated as the interviews progress to ensure all implementation considerations are covered and adapted to different stakeholder groups to facilitate meaningful participation.

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All the interviews will be conducted by 2 clinicians (TM and JH) with previous training and experience in qualitative interviewing. They will present themselves as researchers during the interviews so as not to introduce bias to the data collected [53]; however, as their status may become apparent during the interview and can be discovered on the internet, they will use reflective journaling to identify and mitigate against any effects this may have on data collection [54]. Both interviewers will take field notes during and after the interviews to provide context for the data analysis.

Data Analysis

All the interviews will be digitally recorded and transcribed verbatim. Data analysis will begin after the first interview and proceed in parallel with the remainder. One researcher (TM) will code the interview transcripts using qualitative analysis software (NVivo, Lumivero). The coded data will then be mapped to the shortlist of characteristics produced from phase 1, using this as a framework to aid analysis [55].

The data collected will be reviewed throughout the collection period by the SMG to identify and manage biases in sampling, data collection, analysis, and interpretation. The data will be used to iterate the topic guide, recruitment, and sampling strategies to allow the exploration of problematic issues, divergent views between or within stakeholder groups, and implementation considerations not previously explored.

On completion of the data analysis, the SMG will draft characteristics' specifications based on the analyzed data. An initial draft TPP will be presented to the SAG for review and approval before entry into phase 3.

Phase 3: Finalizing the TPP

Internet-Based Delphi Consensus Rounds

The draft TPP will be entered into an internet-based Delphi study using purpose-made software (Qualtrics XM; Qualtrics). The contents and form of the Delphi survey will be coproduced by the SMG and SAG with the close involvement of both groups' patient representatives. It will also be piloted to ensure it is broadly comprehensible and accessible.

At the start of each Delphi round, participants will be presented with information in plain English on E-DES, AI, and TPPs. In subsequent rounds after round 1, participants will also be provided with a report of the previous round (see Data Analysis section below). Each round will remain open for a minimum of 2-4 weeks, and it is expected that at least 2 rounds will be conducted. Extensions to rounds' time frames and further rounds may be considered in consultation with the SAG.

Sampling

In line with similar studies successfully conducted in other contexts [56-58], we aim to recruit more than 100 respondents overall, with at least 10 from each broader stakeholder group previously outlined, including ML-ARIAS developers. Completed returns will be monitored by the stakeholder group, and further measures taken targeted at individual groups to boost recruitment if necessary. These may include targeted email or newsletter reminders.

Recruitment

People with diabetes will be recruited by asking diabetes charities to disseminate a link to the Delphi survey among their members. Similarly, the British Association of Retinal Screeners will be asked to disseminate a link among their members to recruit DES professionals. The SMG and SAG will be asked to disseminate a survey link to their wider networks to recruit regulators, clinicians, and academics. ARIAS developers with technologies previously identified by the UK NSC's Rapid Review will be invited to participate, as will those receiving funding from the NHS AI Health and Care Award.

Data Collection

Participants will be asked which stakeholder groups they belong to, their geographic location, age, sex, gender, and ethnicity. In each round, participants will be asked to score each characteristic and specification on a Likert scale ranging from 1 to 5, with 1 being "definitely exclude" and 5 being "definitely include." Recognizing that some stakeholder groups may not have the expertise to confidently score characteristic and specification pairs in some areas, participants will be given the option to omit pairs or identify other stakeholder groups they would be comfortable making this decision on their behalf. Free-text boxes will be provided to comment on characteristic and specification pairs or suggest edits. Another box at the end of the survey will provide an opportunity for participants to suggest entirely new characteristic and specification pairs.

Data Analysis

After each round, the responses will be aggregated and analyzed. A report will be produced summarizing response rates and characteristic and specification pairs scores descriptively, with scores broken down by subgroup. Free-text responses will be imported into qualitative analysis software and coded.

Consensus will be defined as >70% of respondents scoring a characteristic and specification pair 4-5 and <15% 1 in any stakeholder group. Characteristic and specification pairs exceeding this threshold will exit the survey process and proceed to the consensus meeting for discussion. Those not meeting this threshold will be revised by the SMG, taking into account their scores in previous rounds by different stakeholder groups and their coded free-text responses. The revised characteristic and specification pairs will then enter subsequent rounds, along with any new items suggested by participants in the previous round.

Consensus Meeting

The Delphi results will be reviewed, and the final TPP contents will be agreed upon at an in-person consensus meeting.

Before the consensus meeting, feedback will be sought from members of the UG. This feedback, along with the Delphi round results broken down by stakeholder group, will be sent to consensus meeting participants ahead of the meeting.

The consensus meeting itself will be led by an experienced facilitator. At the meeting, participants will be presented with each characteristic and specification pair in turn, and an opportunity will be provided for discussion and edits. The Delphi round results broken down by stakeholder group as well as the UG's feedback on the characteristic and specification

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pairs will be made available to aid discussion. Meeting participants will be asked to vote on the inclusion of each characteristic and specification pair, with a supermajority of >70% among voting participants needed for inclusion in the final TPP. An abstention will be permitted.

Recruitment

Participants in the Delphi study will be asked whether they wish to be considered for participation. Meeting attendees will be agreed upon with the SAG and invited to the meeting by email.

Sampling

Purposive sampling will be used to ensure there are at least 2 members from all the key stakeholder groups previously identified, with the exception of ML-ARIAS developers, to avoid conflicts of interest. Travel expenses will be offered to all attendees.

Results

This project has received funding from the NIHR Birmingham Biomedical Research Centre since February 2022 and an NIHR incubator grant for regulatory science awarded to the University Hospitals Birmingham NHS Foundation Trust in June 2023.

Both the SMG and SAG have been assembled and have convened their first meetings. Phase 1 began in April 2023; database searches were performed in May 2023 and the phase was completed in November 2023. Phase 2 began in November 2023 and is expected to be completed in March 2024. As of March 2024, 21 interviews have been performed. Phase 3 is expected to begin in April 2024 and be completed in July 2024. The final TPP and its methods will be submitted to a peer-reviewed journal for publication and reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) criteria [59].

Discussion

Benefits of Establishing a TPP for an ML-ARIAS for Use in E-DES

ML-ARIAS offer an innovative approach for E-DES to meet rising demand and improve clinical, economic, or service outcomes. However, there is a risk that any or all of these could be negatively impacted by the introduction of an ML-ARIAS due to failures to design, evaluate, or deploy such tools appropriately. For example, placing an ML-ARIAS designed to be highly sensitive but poorly specific as a primary grader may necessitate additional decision arbitration in the screening service, or risk increasing unnecessary referrals to hospital eye services. Either eventuality may significantly reduce (or even negate) any cost benefits, or negatively impact the experience of people with diabetes or E-DES professionals. Alternatively, an ML-ARIAS's economic value could be significantly reduced by any requirement to update existing IT infrastructure, making it economically unviable.

While it is impossible to forecast all such potential pitfalls, some are predictable and could be avoided by outlining the NHS' requirements with regard to an ML-ARIAS within a TPP. This can then be used to guide product development and evaluation. Depending on who is involved in TPP development, these documents can also reflect the priorities of all stakeholder groups, including those often neglected in traditional procurement processes, such as patients and delivery staff.

The knowledge of what should go into a TPP for an ML-ARIAS likely already exists, albeit spread over members of different stakeholder groups and sometimes not formally recorded. Where desired characteristics are not clearly understood, for example, when trade-offs exist between competing priorities, our proposed consensus methodology provides a means to better establish requirements or areas where future research is needed.

Given that product requirements can be hard to identify, it is unsurprising that innovation frequently aligns poorly with the actual needs of health care professionals, health services, and their users. Creating a TPP to gather this knowledge in a concise format can accelerate the development of products that meet these stakeholders' needs at a cost much less than that of late-stage product failures or unsuccessful deployments. As well as improving developers' efficiency in product development or testing, other stakeholders stand to gain from TPPs' development. Knowing the essential characteristics of a tool, commissioners can make more assured commissioning decisions, drawing on the collective knowledge of all stakeholders contributing to the TPP. In an ML-ARIAS context, people with diabetes will also have a unique opportunity to influence product design and implementation strategies, increasing the likelihood that tools are acceptable to them and good DES uptake is maintained.

Comparison to Previous Work

To our knowledge, this project represents the first public use of TPPs for an AI health care technology. Our final TPP and the learning accrued through its development will provide a strong basis for the development of TPPs for other disease areas. As no best practice currently exists on TPP development [45], we will use a 3-phase multistakeholder-modified Delphi-consensus method similar to that used to develop reporting guidelines [56,60], core outcome sets [57,61] and previous TPPs [35,40,62]. This method aims to foster values such as inclusivity, patient empowerment, and consensus, and we intend to transfer these values into best practices in a new field.

Limitations

This project has a number of potential risks that we have sought to mitigate, most notably a failure to recruit and retain participants in the Delphi process, the omission of critical characteristics, and a failure to adequately represent and balance the needs of stakeholder groups.

With regard to securing good recruitment and retention for the Delphi process, we have secured the strong engagement of all relevant stakeholder groups with representatives of each on the SAG. Their involvement in the design of the Delphi survey aims to ensure it is broadly acceptable and achievable by all, as well as mitigate against a significant "drop-off" between Delphi rounds, a common issue that can introduce bias. To further mitigate this, we will also monitor returns collectively and at a

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stakeholder group level during each round, allowing interventions such as reminders, further engagement activities, or the extension of round durations, if necessary.

The risk of omitting an essential characteristic in our TPP is increased as this will be the first developed for an AI diagnostic test, and characteristics cannot simply be copied from those previously published in the field. Additionally, some characteristics may only be identified and prioritized by single stakeholder groups. It is therefore important that the TPP development process provide sufficient opportunity for these novel or underappreciated characteristics to be identified. To do this, our reviews will specifically target resources in the field of digital and AI health care to establish which characteristics to report, and our method will provide opportunities for members of all stakeholder groups to put forward additional requirements at multiple stages.

There is also the risk that our methods may generate characteristics that put undue emphasis on the priorities of 1 stakeholder group over another. One may hypothesize that a developer might wish to set TPP requirements at a low, easily achievable level that would be unacceptable to patients and health service providers on the grounds of safety or quality. Conversely, patients and health professionals may have an unrealistic idea of what is possible and argue for TPP requirements to be set near or at perfection (eg, "must not miss any cases"). Our TPP development process seeks to both surface and balance competing priorities to produce a common, achievable target where possible, including being open regarding which stakeholder groups hold different views, potential conflicts of interest, and the actual consequences of decisions and compromises. To ensure that the requirements of the TPP remain achievable, ML-ARIAS developers will be invited to participate in the internet-based Delphi rounds as well as the UG, feedback from which will be presented at the meeting where the final TPP will be agreed. Bidirectional thresholds will also be used in the Delphi phase, such that characteristic and specification pairs must have a minimum level of support as well as a maximum level of dissent allowed to progress, increasing the likelihood that these are achievable as well as acceptable to all.

Conclusions

In developing a TPP for an ML-ARIAS, we will for the first time bring patients, health care professionals, commissioners, methodologists, clinical AI experts, and developers together to provide a target for AI developers to work toward. It is our aim that this will increase the likelihood of the development of ML-ARIAS that are fit-for-purpose for the NHS, improve screening outcomes and of benefit all stakeholders. In addition, we hope that this first public use of TPPs in health care AI and our open sharing of our methods will enable others to develop TPPs for a range of unmet needs, providing clarity to developers and accelerating innovation toward products that will be welcomed by patients and providers alike.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during this study.

Conflicts of Interest

CM acts as the national professional advisor for patient safety at the Care Quality Commission. RGW is a member of the UK National Screening Committee and a nonexecutive director of Moorfields Eye Hospital. FG is employed by NICE and the Department of Health and Social Care in England.

Multimedia Appendix 1
Review search strategies.
[DOCX File , 19 KB - resprot_v13i1e50568_app1.docx]

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Abbreviations

AI: artificial intelligence
ARIAS: automated retinal imaging analysis software
COREQ: Consolidated Criteria for Reporting Qualitative Research
CQC: Care Quality Commission
DES: diabetic eye screening
DR: diabetic retinopathy
E-DES: English diabetic eye screening
ESF: Evidence Standards Framework
MHRA: Medicines and Healthcare Products Regulatory Agency
ML: machine learning
ML-ARIAS: machine learning–automated retinal imaging analysis software
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health and Care Research
NSC: National Screening Committee
SAG: study advisory group
SMG: study management group
TPP: target product profile
UG: user group

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Protocol

How a National Organization Works in Partnership With People Who Have Lived Experience in Mental Health Improvement Programs: Protocol for an Exploratory Case Study

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Abstract

Background: This is a research proposal for a case study to explore how a national organization works in partnership with people with lived experience in national mental health improvement programs. Quality improvement is considered a key solution to addressing challenges within health care, and in Scotland, there are significant efforts to use quality improvement as a means of improving health and social care delivery. In 2016, Healthcare Improvement Scotland (HIS) established the improvement hub, whose purpose is to lead national improvement programs that use a range of approaches to support teams and services. Working in partnership with people with lived experience is recognized as a key component of such improvement work. There is, however, little understanding of how this is manifested in practice in national organizations. To address gaps in evidence and strengthen a consistent approach, a greater understanding is required to improve partnership working.

Objective: The aim of this study is to better understand how a national organization works in partnership with people who have lived experience with improvement programs in mental health services, exploring people's experiences of partnership working in a national organization. An exploratory case study approach will be used to address the research questions in relation to the Personality Disorder (PD) Improvement Programme: (1) How is partnership working described in the PD Improvement Programme? (2) How is partnership working manifested in practice in the PD Improvement Programme? and (3) What factors influence partnership working in the PD Improvement Programme?

Methods: An exploratory case study approach will be used in relation to the PD Improvement Programme, led by HIS. This research will explore how partnership working with people with lived experience is described and manifested in practice, outlining factors influencing partnership working. Data will be gathered from various qualitative sources, and analysis will deepen an understanding of partnership working.

Results: This study is part of a clinical doctorate program at the University of Stirling and is unfunded. Data collection was completed in October 2023; analysis is expected to be completed and results will be published in January 2025.

Conclusions: This study will produce new knowledge on ways of working with people with lived experience and will have practical implications for all improvement-focused interventions. Although the main focus of the study is on national improvement programs, it is anticipated that this study will contribute to the understanding of how all national public service organizations work in partnership with people with lived experience of mental health care.

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KEYWORDS

partnership; engagement; case study; mental health; improvement; national program; quality improvement

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Introduction

Overview

The need to improve quality in mental health (MH) care is widely recognized, in response to both long-standing problems and more contemporary pressures [1,2]. For several years, quality improvement (QI) has been considered a key solution to many health care challenges, supporting the design and delivery of services. Over the last decade, there has been a significant effort to use QI within health care settings, including the introduction of national organizations to lead improvement programs.

There are several national organizations in Scotland with an improvement focus, including the Centre for Sustainable Delivery, the Health and Social Care Alliance Scotland, the Improvement Service, and Healthcare Improvement Scotland (HIS). In 2016, HIS established the improvement hub (ihub), whose purpose is to enable health and care systems to apply improvement methodologies to the design and implementation of changes that deliver sustainable improvements in the health and well-being outcomes of people in Scotland [3]. The ihub within HIS is uniquely placed with a focus on improvement support for those delivering health and social care across Scotland, including MH services.

Work within the ihub is delivered through improvement programs that use a range of theories and techniques to support teams and services through an improvement journey. National improvement programs have an important role to play in health care. However, there are challenges within centrally led programs that require sensitive understanding and management [4]. The development of improvement programs recognizes growing evidence that the impact of QI in health care is mixed and of poor quality [5], and there is a need to reconceptualize improvement efforts in response to the evidence base [6]. In order to address some concerns within the literature, the ihub has outlined a broad approach to improvement that forms the basis of their improvement programs. The core components of improvement programs within the ihub are described in the framework for planned improvement (Figure 1 [3]), which outlines the stages of improvement work. In the Framework for Planned Improvement, the initial focus is on understanding the system and designing, implementing, and evaluating changes, with people with lived experience at the center of this work. People with lived experience include people who have lived or living experience, their families, caregivers, and supporters. Improvement programs then aim to embed and sustain successful change within practice and spread the learning to other areas. Underpinning the framework is the recognition of the importance of the relational aspect of change and the use of technical QI approaches, including the model for improvement.

Figure 1. Components of improvement programmes, adapted from Healthcare Improvement Scotland's Framework for Planned Improvement.

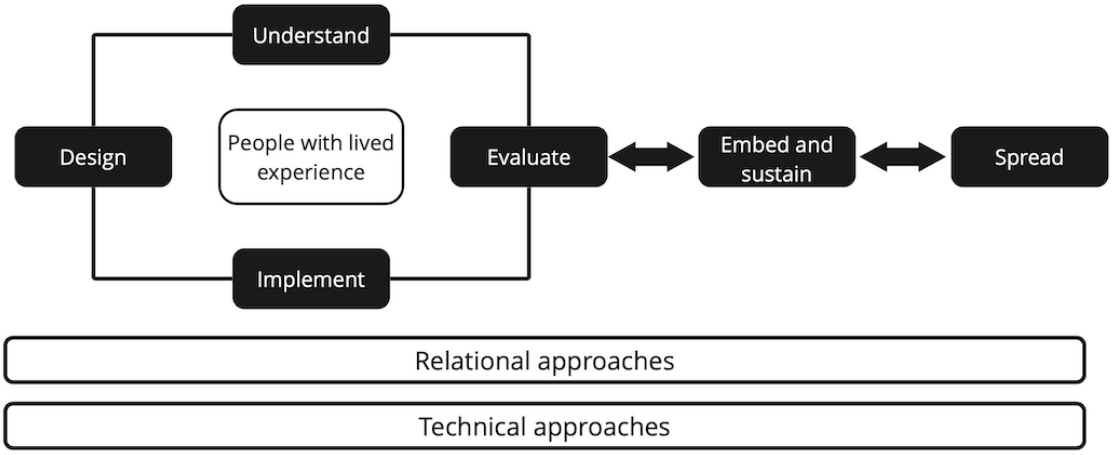

A key principle to improvement is working in partnership with others in the system, including other agencies, people with lived experience, and frontline staff. In Scotland, a seminal paper by Christie [7] recommended that there should be a stronger partnership working with people and communities in the design and delivery of services they use, including those involved in health care improvement. There is a growing evidence base supporting the need to work with people with lived experience in health care improvement. People with lived experience have a key role to play in understanding problems and identifying solutions to ensure change delivers outcomes that make a difference to patients [8]. Working with people with lived experience in improvement initiatives can strengthen and enrich the organizational agenda for improvement in health care [9] and should be seen as a core component of all improvement programs. Within MH services, people with lived experience should be able to participate in the development of policies to improve MH systems [10] and should therefore be involved in health care improvement initiatives. Working with people with lived experience should be based on authentic, interdependent partnership work [6], which will improve the quality and value of services.

Despite the recognition that working with people with lived experience is central to improvement-focused work, there are a number of challenges and a lack of critical examination of partnership working within the health care improvement literature [11]. There is a lack of understanding of the phenomenon of partnership working, including the mechanisms of partnership working, organizational features supporting partnership working (eg, leadership), and the impact and outcomes achieved from working with people with lived experience [11,12]. There is also little understanding in the

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literature of how working with people with lived experience is manifested in practice in national organizations [13].

This research will explore how a national organization works in partnership with people with lived experience in a MH improvement program. This research will focus on one improvement program—the Personality Disorder (PD) Improvement Programme within HIS' ihub. The PD Improvement Programme is a commissioned piece of work funded by the Scottish Government to understand the current service provision in Scotland for people with a diagnosis of PD and identify the key opportunities for improvement. This research will use a case study approach to explore how partnership working is planned, conceptualized, and manifested in practice within the PD Improvement Programme.

Objectives

The aim of this study is to better understand how a national organization works in partnership with people who have lived experience with improvement programs in MH services, exploring people's experiences of partnership working in a national organization. An exploratory case study approach will be used to address the research questions in relation to the PD Improvement Programme:

1. How is partnership working described in the PD Improvement Programme?
2. How is partnership working manifested in practice in the PD Improvement Programme?
3. What factors influence partnership working in the PD Improvement Programme?

This research will consist of 2 phases. The first phase will address the first 2 research questions through document analysis and observations of meetings within the early stages of the PD Improvement Programme. Semistructured interviews will be carried out in the second phase of this research to explore participants' experiences of partnership working, addressing the third research question.

Benefits of This Research

It is anticipated that the findings of this research will contribute to an understanding of partnership working in national organizations and will be used to identify a framework for partnership working so that partnership working can be improved across the organization and other national organizations.

Methods

Overview

In order to address the research aim, it is appropriate to use case study methodology. A case study approach is appropriate when the focus of the study is on how and why questions; the behavior of participants will not be changed; the context is relevant to the phenomenon studied; and when there are unclear boundaries between phenomenon and context [14]. Partnership working sits within the wider context, and case study methodology is well placed to understand relationships between context and intervention [15], with partnership working conceptualized as the intervention in this research. A case study approach will enable a holistic exploration of the complex social processes and mechanisms underpinning partnership working within QI [16]. Data will be collected from a wide range of qualitative sources, including document data, participant observations, and semistructured interviews.

Case Study Design

The DESCARTE model [17] will be used in this research to inform the design, conduct, and reporting of the case study. There are 3 stages to this model: the situation of the research and the researcher, determining the components of the case study design, and data analysis.

Situation of the Research and the Researcher

In designing case study research, it has been recommended that the researcher state explicitly their informing philosophical approach, situation of "Self" within the research, and any ethical considerations to outline the position of research and the researcher [17].

The lead researcher is currently working as part of the improvement team within HIS and therefore will be considered an insider researcher. Although this position may support access to naturalistic data and respondents, there is a risk that there may be conflict between the researcher and participants who have professional relationships, and a risk that respondents may change their behavior or responses due to this relationship [18]. This will increase the risk of bias within the research, and strategies should be used throughout the different stages of the research process to reduce these risks [19]. For this study, strategies will include planning the interview process, using research diaries, reflection, and ongoing monitoring with the supervisory team. The lead researcher will also work closely with a public partner at key stages of this research. Public partners are volunteers who HIS trains and supports to provide a public perspective to their work, and a public partner with lived experience of mental illness will be involved at several stages of this research.

Components of the Case Study

Although case study research can have a level of creativity and flexibility—where the researcher may choose epistemologies and theories suited to their preferences and the nature of the inquiry, clear descriptions of paradigms, theories, and methods should be provided to demonstrate rigor [20]. These will be described to outline the main components of the case study.

Binding the Case

First, it is important to identify what the case will be and set clear parameters or boundaries to ensure the study has a clear and reasonable scope—a process referred to as binding [21]. The parameters of this study will be determined by definition and context; for this research, the case will consist of the PD Improvement Programme within HIS. Early involvement of people with lived experience in the conceptual stages of improvement work has been highlighted to ensure meaningful involvement with influence and impact [22]. The PD Improvement Programme is the first commissioned work for HIS to improve the understanding of the context of service provision for people with a diagnosis of PD across Scotland.

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The program will include working with people with lived experience and frontline staff working in clinical roles. The commission is from the Scottish Government and will run between June 2021 and March 2023. This case study will follow the PD Improvement Programme during the current stage of the program: creating the conditions and understanding the system. This stage will involve establishing the program and working practices for working in partnership during the PD Improvement Programme. The parameter for this case is to explore working in partnership with people with lived experience and will not include exploration of wider partnerships working in this program.

Type of Case Study

Exploratory case studies can be used to explore situations in which the intervention being researched does not have a clear, single set of outcomes [21]. Given the diversity within QI and the complexity of partnership work, an exploratory approach is considered appropriate.

Design

In phase 1 of this case study, data will be collected from organizational documents, followed by nonparticipant observations of key program meetings. This data will help explore how partnership working is described, defined, and manifested in practice. This will be followed in phase 2 by semistructured interviews with key participants to explore their experiences of partnership working in the program.

Phase 1: Document Data

In the first phase of data collection, analysis of organizational documents will be used to provide an understanding of plans, infrastructure, and frameworks used to support partnerships working with people with lived experience. It is anticipated that documents may include commission agreements, planning papers, minutes of key meetings, presentations or diagrams describing the program infrastructure, and partnerships working in the program. Further documents relevant to the study may emerge and will be included as appropriate. Access to these documents will be through the program lead within HIS.

As there is no agreed definition of partnership working, documents will be analyzed for any description of partnership, which may include terms such as involvement, participation, engagement, and empowerment. The content of documents will be analyzed, including the document, author, date, description of partnership working, and any actions taken or recommendations. Meetings with the public partner will be agreed upon to discuss the data analysis and the identification of themes at each stage of the data analysis.

Themes developed from the document review will be included in the structure of observations and used to develop the interview proforma in the following phases of the research.

Phase 1: Nonparticipant Observations

Following document analysis, nonparticipant observations of PD Improvement Programme meetings will be used to gather data on how partnership working with people with lived experience in the program is manifested in practice. Meetings observed will be chosen based on a purposive sample, and there will be between 3 and 6 observations completed. The portfolio lead will be asked to provide a list of all meetings taking place in the early stages of the program, which is likely to be within the first 6-9 months of the program. A sample of meetings most likely to demonstrate partnership working in practice [23] will be selected to be observed, such as planning meetings and advisory group meetings. The meetings will be chosen by the researcher to address any potential bias and ensure the appropriate independence of the research.

A framework for partnership working will be used to guide observations (Textbox 1 [24]). This model describes 4 key dimensions of partnership: process, actors (identity and position), decisions, and power relationships. Although the use of this framework provides some structure to the observations, a form of semistructured observation will be adopted to allow for some naturalistic observations [23] and include themes identified in the document analysis.

Nonparticipant observation will allow observation of the environment, language, nonverbal data, and interaction in partnership. General context will be noted for each observation, including location, time, duration, meeting roles, and purpose of the event or meeting.

There is a possibility that the presence of a researcher will increase the risk bias by changing the behavior of participants, and strategies will be used to reduce this risk. Strategies will include giving a clear explanation of the plan for observation and being aware of the position of the researcher to be as unobtrusive as possible [25]. Observations will be primarily descriptive and will provide the basis for the interpretation of data obtained by semistructured interviews in the final stage of data collection. Meetings will be held with the public partner to discuss themes developed at this stage of data collection and to agree on the format of semistructured interviews in phase 2.

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Textbox 1. Framework for partnership working observation guide used in an exploratory case study, adapted from Carpentier.

Dimension of partnership working and observation guide

- Process
  - How is partnership working planned for and what preparations are in place to support partnership working?
  - How many events or meetings involve people with lived experience?
  - Who is involved in setting the agenda and context for meetings?
- Actors: identity and position
  - Who attends meetings?
  - What are people's positions within the organization or program?
- Decisions
  - How are decisions in the program made?
  - How are people with lived experience involved in decision-making in the program?
- Power relationships
  - Who contributes to the event or meeting?
  - What is the response to people with lived experience's contribution?
  - What efforts are made to support contributions from people with lived experience?

Phase 2: Semistructured Interviews

The final stage of data gathering will be semistructured interviews with participants from the PD Improvement Programme, including people across disciplines and people with lived experience. Interviews will be used to gain an understanding of participants' experiences and perceptions of partnership working with people with lived experience. A schedule for interviews will be prepared based on themes developed from the document review and observations. The interview proforma will be developed with people with lived experience working as a public partner in HIS to ensure questions are relevant and likely to receive meaningful responses [22]. All interviews will follow the schedule developed as an aide memoire; however, it is important to allow flexibility to adapt to each participant's response to allow exploration of emerging and reported experiences [26]. Interviews will be held at a location agreed upon the researcher and participant and may be face-to-face, remote through Teams (Microsoft Corporation), or by telephone. All interviews will be recorded and transcribed.

The population within this case will include a purposive sample of staff and people with lived experience who are involved in and contribute to the work of the PD Improvement Programme. It is anticipated that this will be between 6 and 8 interviews. Participants will include clinical and improvement staff working directly on the PD Improvement Programme operating at different levels of the organization and people with lived experience working with the PD Improvement Programme. This should ensure diversity within the perspectives gained from the interviews.

Recruitment Strategy and Informed Consent

Participants will be recruited through the PD Improvement Programme and will include a purposive sample of people involved in the program based on their role. All people involved in the program will be offered the opportunity to participate in this study and will be asked to sign a consent form and return it to the researcher at the start of each stage of the research.

There will be a process of ongoing consent for each phase of this research. In phase 1, each participant in the meetings observed will be asked to consent to the observation and recording during selected meetings and consent to being contacted for an interview at the second phase of research if appropriate. This will ensure each participant has a full understanding of the research, their role within it, the benefits and risks, and their right to withdraw from the research. Each participant's consent will be documented in a written form they will be invited to sign before the meeting. Consent will be reviewed at the start of the meeting as a process of ongoing informed consent. If there are participants in the meeting who do not consent, their contribution to the meeting will be omitted during transcription. For meetings held online, participants who do not consent will be offered the chance to turn their camera off during the meeting and use the chat box for contributions if required. This may affect the understanding of the wider context of discussions, and therefore, efforts will be made to observe meetings with full consent.

In phase 2, people will be asked to consent to participate in semistructured interviews. Consent will be documented for each participant; they will be asked to sign a written consent form, and consent will be confirmed verbally at the start of each interview. Once consent is documented, the researcher will select a purposive sample of people who will participate in interviews based on their role in the program. All people who have given consent will be contacted to discuss the next steps, and interviews will be arranged with participants to ensure they take place at a suitable time and setting.

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Data Analysis

Data analysis will organize, find patterns, and elicit themes in the data to help deepen an understanding of partnership working within the national PD Improvement Programme. There are various mechanisms for quality assurance within this research, including the use of a reflexive field diary, discussions with supervisors, and member checking where participants can check transcriptions following observations and interviews. During analysis, there will also be regular meetings with a public partner working in HIS to review and discuss themes to check emerging findings and the researcher's interpretation, as a form of participant validation to improve scientific rigor. A framework for data analysis is outlined in Table 1 [27].

In order to develop convergent evidence, the structure outlined in Figure 2 will be applied to data analysis.

Effective organization of data will be important to this case study to enable the tracking of data sources, notes, documents, narratives, and other data [14]. NVivo (version 12; QSR International) will be used to support the management of data and to assist within and across case study analysis, appropriate to case study research [27]. Data collection and analysis will occur concurrently, as is practiced in qualitative studies [14].

Table 1. Thematic data analysis plan for an exploratory case study adapted from Houghton et al.

Stage of data analysis	Analysis strategy	Application for this research
Comprehending	Broad coding	This stage will analyze data to generate and develop codes. In this stage, enough data will be gathered to write a detailed, coherent, and rich description of partnership working.
Synthesizing	Pattern coding memoing	This stage will review codes identified at the broad coding stage and identify patterns within the data. Memos will provide summaries of key information for each theme, which will be used in further development of propositions of the data.
Theorizing	Distilling and ordering and testing executive summary statements	Relationships between categories of data will be examined, building a more integrated understanding of partnership working from all perspectives and data sources.
Recontextualizing	Developing propositions	Concepts identified will be synthesized to consider how the understanding of partnership working may be applied in different settings.

Figure 2. Data analysis plan for thematic analysis in an exploratory case study.

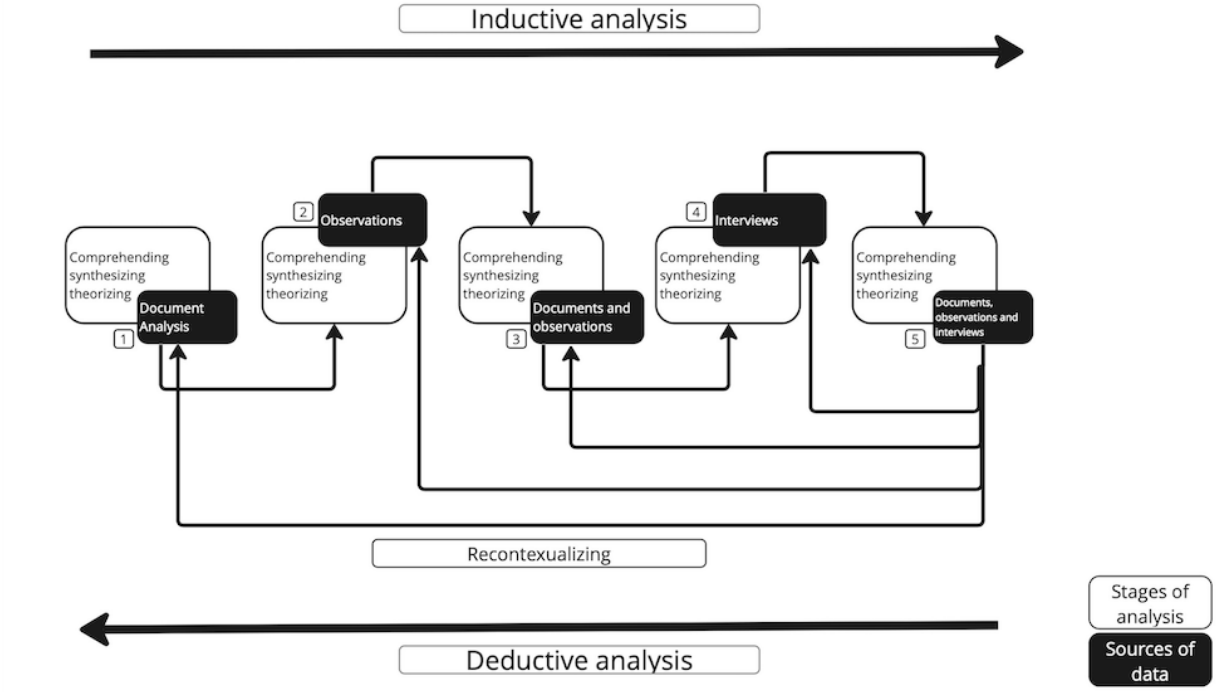

Patient Involvement

The objective of this research is to deepen an understanding of how national improvement programs work in partnership with people with lived experience. This focus was developed through a review of current literature and organizational objectives [28] and has been highlighted by people with lived experience who have worked with HIS in other national MH improvement programs [29].

Patient involvement has been central to the development and design of this research, and a public partner has been involved in the design and will be involved in the analysis of this research. In phase 1, this included involvement in the review and analysis of themes as a form of participant validation to improve scientific rigor [30]. The public partner advised on the burden of intervention for people with lived experience in this study and has been involved in the design of phase 2, including the

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design of interviews, the development of the distress response policy, and advising on participant recruitment. The public partner will continue to be involved during the data analysis of phase 2, reviewing and discussing themes developed at this phase, and will be invited to advise on plans for dissemination of the study results to participants and linked communities.

Ethical Considerations

Ethical approval has been granted from HIS' research oversight group, the University of Stirling Research Ethics Committee, and the Integrated Research Application System through the Queen Square Research Ethics Committee (for phase 1; 318323) and the Black Country Research Ethics Committee (for phase 2; 309926). This study is part of a clinical doctorate program at the University of Stirling and is unfunded.

Results

Data collection was completed in October 2023; analysis is expected to be completed and results published in January 2025.

Discussion

This study will produce new knowledge on ways of working with people with lived experience and will have practical implications for all improvement focused interventions. Though the main focus of the study is on national improvement programs, it is anticipated that this study will contribute to the understanding of how all national public service organizations work in partnership with people with lived experience of MH care. The anticipated time for completion and write-up is 24 months. Information will be shared with key stakeholders on the progress of this research, including HIS and the University of Stirling, and opportunities for presentation of this research will be sought. These may include QI conferences and communities—including the Q Community (The Health Foundation), MH organization events, and NHS Scotland events. The findings will be completed with a thesis submitted to the University of Stirling and will be reported in an appropriate journal, such as *BMJ Open Quality* or the *Journal for Healthcare Quality*.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CR is a student in the clinical doctorate program at the University of Stirling. CH is the lead supervisor and researcher. AS is the supervisor for this research. Both supervisors contributed to the design of the research protocol, advising on analysis, and developing the manuscript for this research. GJ is the public partner advising on the design, analysis, and dissemination of this research.

Conflicts of Interest

None declared.

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Abbreviations

HIS: Healthcare Improvement Scotland
ihub: improvement hub
MH: mental health
PD: personality disorder
QI: quality improvement

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Protocol

Preimplementation Evaluation of a Self-Directed Care Program in a Veterans Health Administration Regional Network: Protocol for a Mixed Methods Study

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Abstract

Background: The Veteran-Directed Care (VDC) program serves to assist veterans at risk of long-term institutional care to remain at home by providing funding to hire veteran-selected caregivers. VDC is operated through partnerships between Department of Veterans Affairs (VA) Medical Centers (VAMCs) and third-party Aging and Disability Network Agency providers.

Objective: We aim to identify facilitators, barriers, and adaptations in VDC implementation across 7 VAMCs in 1 region: Veterans Integrated Service Network (VISN) 8, which covers Florida, South Georgia, Puerto Rico, and the US Virgin Islands. We also attempted to understand leadership and stakeholder perspectives on VDC programs' reach and implementation and identify veterans served by VISN 8's VDC programs and describe their home- and community-based service use. Finally, we want to compare veterans served by VDC programs in VISN 8 to the veterans served in VDC programs across the VA. This information is intended to be used to identify strategies and propose recommendations to guide VDC program expansion in VISN 8.

Methods: The mixed methods study design encompasses electronically delivered surveys, semistructured interviews, and administrative data. It is guided by the Consolidated Framework for Implementation Research (CFIR version 2.0). Participants included the staff of VAMCs and partnering aging and disability network agencies across VISN 8, leadership at these VAMCs and VISN 8, veterans enrolled in VDC, and veterans who declined VDC enrollment and their caregivers. We interviewed selected VAMC site leaders in social work, Geriatrics and Extended Care, and the Caregiver Support Program. Each interviewee will be asked to complete a preinterview survey that includes information about their personal characteristics, experiences with the VDC program, and perceptions of program aspects according to the CFIR (version 2.0) framework. Participants will complete a semistructured interview that covers constructs relevant to the respondent and facilitators, barriers, and adaptations in VDC implementation at their site.

Results: We will calculate descriptive statistics including means, SDs, and percentages for survey responses. Facilitators, barriers, number of patients enrolled, and staffing will also be presented. Interviews will be analyzed using rapid qualitative

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techniques guided by CFIR domains and constructs. Findings from VISN 8 will be collated to identify strategies for VDC expansion. We will use administrative data to describe veterans served by the programs in VISN 8.

Conclusions: The VA has prioritized VDC rollout nationwide and this study will inform these expansion efforts. The findings from this study will provide information about the experiences of the staff, leadership, veterans, and caregivers in the VDC program and identify program facilitators and barriers. These results may be used to improve program delivery, facilitate growth within VISN 8, and inform new program establishment at other sites nationwide as the VDC program expands.

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KEYWORDS

long-term institutional care; self-directed care; veteran directed care; veteran; veterans; institutional care; long term care; mixed-methods; caregivers; caregiver; United States; nursing home; homecare; community-based; home-based; unmet; pre-implementation; barriers; barrier; facilitators; facilitator; quantitative data

Introduction

Due to exposures during their service, veterans are at increased risk for a variety of health conditions, such as mental disorders such as depression and posttraumatic stress disorder which are notably higher than in the civilian population [1-3]. Additionally, higher frailty is also found among veterans with more severe wartime exposures [1-3]. Moreover, an estimated 7% of veterans are living with Alzheimer disease and Alzheimer disease–related dementias. Many veterans who need assistance with multiple daily activities such as eating, bathing, and dressing, or have severe cognitive impairment, may need care in institutional settings such as nursing homes [4,5]. However, most older adults prefer to age in their own homes rather than in institutional settings [6]. Institutional care is also costly [7-9]. In fiscal year (FY) 2018, the Department of Veterans Affairs (VA) spent US $6.1 billion on institutional care, a 21% increase compared to 2014 [9]. By 2037, these costs are projected to double [9]. As the number of veterans at risk for long-term institutional care (LTIC) increases, the VA Geriatrics and Extended Care (GEC) has focused on expanding the home- and community-based services (HCBS) available to veterans [10].

The VA's Veteran-Directed Care (VDC) is one such HCBS program, which was established as a partnership between the VA and the US Department of Health and Human Services Administration for Community Living in 2008 [11]. The goal of this collaboration was to help veterans with disabilities of all ages and their families receive needed services in their own homes and communities. The program operates as a self-directed program that empowers veterans at risk of LTIC to choose their own long-term care providers and services [12]. In the VDC program veterans and their caregivers have direct control over the goods and services they receive; they can hire their own workers, including family or friends, to provide homemakers, and home health aide services focused on delivering personal care services in the home. Patients who meet eligibility requirements, which include a clinical assessment of their needs to establish the level of care needed and approval of an appropriate budget, undergo referral and enrollment in VDC. These steps are collaboratively completed by the VA staff and VDC Providers such as Area Agency on Aging, Aging & Disability Resource Centers, Centers for Independent Living, and State Units on Aging. The VDC providers assist the veterans in fulfilling their employer responsibilities. Both VA and VDC providers subsequently review and approve all program expenditures and regularly evaluate the veteran's health and well-being. The management of the budget is done by third-party Financial Management Services (FMS) staff, who receive a monthly fee for these administrative duties, which also include processing payroll and taxes.

Previous research has suggested that similar self-directed services are associated with fewer unmet long-term care needs, improved patient satisfaction, and lower risk of adverse outcomes, including injuries, compared to other HCBS [13]. VDC enrollees have similar hospitalization rates and costs compared to users of other VA-purchased HCBS, despite VDC enrollees being more medically complex. Compared to other HCBS enrollees, VDC enrollees were more likely to receive aid and attendance benefits, to have a spinal cord injury, and to have higher health care costs [12-17]. VDC enrollees were less likely to have a VA-paid nursing home admission compared to veterans using other personal care services paid for by VA [14]. In addition, there were fewer potentially avoidable acute care admissions and emergency department visits among rural veterans enrolled in VDC (but not among urban VDC enrollees) [14]. Moreover, there is qualitative evidence that the VDC program is acceptable, and satisfaction among enrolled veterans is high with participants expressing that it has given them purpose and meaning [18]. Given current workforce shortages in the health care sector and especially in rural areas, the ability to hire family members and neighbors as paid caregivers through self-directed services may be a particularly effective way to surmount access challenges for veterans [19].

VDC is currently available at 70 of the 171 Veteran Affairs Medical Centers (VAMCs) and served approximately 7232 veterans in FY 2023, a nearly 15% increase from FY 2022. As a solution to meet its priority of allowing veterans to age in place if that is their preference, the VA has committed to expanding VDC to all VA facilities by the end of FY 2024 [20]. However, there is limited understanding of factors that affect VDC expansion and program-level needs to increase enrollment.

The objective of this pre-expansion implementation evaluation is to understand the factors that affect VDC program implementation and growth in current sites in Veteran Integrated Service Network (VISN) 8, to inform implementation in new

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sites. This study focused on 7 VDC programs within a single VISN. In the VA Healthcare System, VISNs include multiple VAMCs and Community-Based Outpatient Clinics and represent an important unit for oversight and service delivery [21]. VISN 8 cares for veterans in 7 VAMCs across Florida, Puerto Rico, and South Georgia and serves about 10% (n=619,840) of veterans aged older than 65 years receiving VA care in the country.

The primary aim of this project is to evaluate the VDC program implementation in VISN 8 with the following objectives: (1) describe the variability in VDC program organization and delivery across VISN 8, (2) identify barriers and facilitators faced by existing VDC programs in VISN 8, (3) understand leadership and stakeholder perspectives on VDC programs' reach and implementation, (4) compare VDC programs in VISN 8 to national in terms of veterans served and GEC service use, and (5) use the information from aims 1-4 to identify strategies and make recommendations to guide VDC program expansion.

In this paper, we describe this study's objectives and methods of this pre-expansion implementation evaluation.

Methods

Project Site

The VA Sunshine Healthcare Network is the nation's largest system of VA hospitals and clinics serving a population of more than 1.5 million veterans in a vast area of 64,153 square miles spread across 79 counties in Florida, South Georgia, Puerto Rico, and the US Virgin Islands [22]. VISN 8 serves a substantial proportion of older veterans; in FY 2020, veterans aged 65 years or older comprised a little over 50% of the entire veteran population served in Florida [23]. Every VAMC in VISN 8 has an operational VDC program. The 7 VAMCs of interest for this study are located in Bay Pines, Gainesville, Miami, Orlando, Tampa, and West Palm Beach (Florida), and San Juan (Puerto Rico). The catchment areas for these VAMCs also cover a portion of Southern Georgia (Gainesville VAMC) and the US Virgin Islands (San Juan VAMC).

Conceptual Framework—Consolidated Framework for Implementation Research

We used the Consolidated Framework for Implementation Research (CFIR) to guide our evaluation plan, data collection, and analysis [24]. CFIR is a well-known determinate framework used throughout the VA and health services research to identify and describe variables influencing implementation. CFIR is an appropriate framework for providing a grounded understanding of the barriers and facilitators to the expansion and implementation of VDC programs across multiple contexts by various stakeholders. The updated CFIR 2.0 framework provides a comprehensive classification consisting of 48 constructs and 19 subconstructs over 5 domains: innovation, outer setting, inner setting, individual characteristics, and implementation process [25]. We identified potentially relevant CFIR constructs to assess the key determinants impacting the VDC program's operations, as well as the dynamics of organizational structure, implementation support, and other relevant domains. We then used these identified constructs to develop quantitative and qualitative data collection instruments and to guide analysis. Not all CFIR domains were represented in all the instruments (Table 1). This is consistent with other work using CFIR. Our iterative review process included project team discussions, consultation with a VA VDC staff member, and feedback from operational partners and another VA research team with expertise in VDC.

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Table 1. CFIR (version 2.0)a domains and constructs represented in data collection by the study population.

Construct	VA[a] leadership	VA staff	VDC[b] providers (AAA[c] and ADNAs[d])	A_1, enrolled veterans	B_1, enrolled veterans' caregivers	C_1, enrolled veterans' employees	A_2, unenrolled veterans	B_2, unenrolled veterans' caregivers	C_2, unenrolled veterans' employees
Innovation									
Relative advantage		✓	✓	✓	✓	✓	✓	✓	✓
Evidence base		✓	✓						
Adaptability	✓	✓	✓						
Complexity		✓	✓	✓	✓	✓	✓	✓	✓
Outer setting									
Partnerships and connections		✓		✓	✓	✓	✓	✓	✓
Policy and laws	✓								
Local conditions	✓			✓	✓	✓	✓	✓	✓
Inner setting									
Access to knowledge and information		✓	✓	✓	✓	✓	✓	✓	✓
Work infrastructure	✓	✓	✓						
Relative priority		✓					✓	✓	✓
Relational connections		✓	✓	✓	✓	✓	✓	✓	✓
Available resources		✓	✓	✓	✓	✓	✓	✓	✓
Structural characteristics	✓	✓	✓	✓	✓	✓			
Mission alignment	✓		✓						
Information technology infrastructure		✓	✓	✓	✓	✓			
Individuals									
High-level leaders		✓	✓						
Implementation facilitators	✓	✓	✓	✓	✓	✓			
Innovation recipients			✓	✓	✓	✓			
Implementation process									
Assessing needs		✓	✓	✓	✓	✓	✓	✓	✓
Assessing context	✓			✓	✓	✓	✓	✓	✓
Reflecting and evaluating	✓	✓	✓	✓	✓	✓			
Adapting		✓							
Tailoring strategies		✓	✓						
Engaging		✓	✓	✓	✓	✓	✓	✓	✓
Antecedent assessments									
Implementation climate		✓	✓	✓	✓	✓	✓	✓	✓
Appropriateness	✓								
Implementation outcomes									
Anticipated implementation outcomes	✓			✓	✓	✓			

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[a]VA: Veterans Affairs.

[b]VDC: Veteran-Directed Care.

[c]AAA: Area Agency on Aging.

[d]ADNA: Aging and Disability Network Agency.

Study Period

This 3-year evaluation will use concurrent mixed methods to collect CFIR-based data about VDC implementation in VISN 8 in FYs 2022-2024 [26].

Data Collection Procedures

We have conceptualized this project occurring in 5 phases (Table 2), beginning with interviews of VA and Aging and Disability Network Agency (ADNA) staff (phase 1), followed by VISN and facility leadership (phase 2). In phase 3, existing administrative data will be used to describe the VDC participants in VISN 8 and nationally and compare results in VISN 8 to national VDC results. Phase 4 will involve interviews with veterans and caregivers who have been referred to or enrolled in VDC. In phase 5, we will integrate information from phases 1-4 to identify strategies and make recommendations to guide VDC program expansion. Both primary and secondary data will be used in this project. Primary data will be gathered through (1) VA and ADNA staff surveys, (2) VA and ADNA staff interviews, (3) VISN leadership interviews, (4) VAMC GEC leadership interviews, (5) veteran and caregiver surveys, and (6) veteran and caregiver interviews. See Multimedia Appendices 1-6 for all interview guides being used as primary data collection materials. We will use secondary data from VA administrative data sources about VDC, which appear in the Veterans' Health Administration Corporate Data Warehouse, and the Geriatrics and Extended Care Data and Analysis Center (GECDAC) data files [27]. The GECDAC collects and analyzes population-based data about GEC programs and services, providing evidence-based information to facilitate continuous quality improvement [27]. We will collect data from participants from both the inner setting (VA program staff and leadership) and the outer setting (ADNA and FMS staff, and veterans and caregivers).

Table 2. Data collection methods, purpose, and results.

Phase	Participant group	Data collection methods	Purpose	Results or summary reports
1	VA[a] and ADNA[b] VDC[c] staff	• Surveys • Semistructured interviews	• Gauge knowledge base, staff experiences and perceptions, and program operation	• Report on variability in VDC program organization and delivery
2	VISN 8[d] and VAMC[e] leadership	• Semistructured interviews	• Gain insight into leadership support, priorities, and funding	• Factors impacting VDC programs' reach and implementation, and organizational facilitators and barriers
3	GECDAC[f] VDC data	• Secondary administrative data from different VA sources	• Data regarding veterans served and the use of HCBS[g]	• Quantitative description and comparison of VISN 8 to national VDC programs on access and HCBS use
4	Veterans and caregivers	• Semistructured interviews • Surveys	• Learn from the lived experiences of enrolled and unenrolled veterans' and their caregivers. Detailed needs, social determinants, and service use data	• Factors affecting VDC enrollment decision, and satisfaction with enrollment processes • Health, function, quality of life, unmet needs, other HCBS program use, and socioeconomic status
5	Research team	• Integration of findings from aims 1-4	• Use the information from aims 1-4 to identify strategies to make recommendations to guide VDC program expansion	• Final report on the project summarizing data from all stakeholders to inform VDC expansion

[a]VA: Veterans Affairs.

[b]ADNA: Aging and Disability Network Agency.

[c]VDC: Veteran-Directed Care.

[d]VISN: Veteran Integrated Service Network.

[e]VAMC: Veterans Affairs medical centers.

[f]GECDAC: Geriatrics and Extended Care Data and Analysis Center.

[g]HCBS: home- and community-based services.

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Quantitative Methods

Surveys

We have developed VDC and ADNA staff surveys and interview guides based on CFIR constructs to collect information on VDC program design, administration, and staffing. The survey and interview questions were informed by previous VDC work and are adapted from the Organizational Readiness to Change Assessment developed by Sperber et al [28] and Helfrich et al [29]. The survey and interview guides were reviewed by a VA VDC coordinator at 1 VISN 8 site and by national experts in VDC and other VA HCBS. We created distinct surveys for VA and ADNA staff that covered similar topics but addressed their unique roles and responsibilities (see Multimedia Appendices 1-6).

VA staff surveys include questions about VDC program staffing, enrollment criteria, program size, referral sources, program goals and tracking, the ADNA partners, and the use of an external financial management system. We collect information about the respondents' professional and work experience, including how long they have worked with veterans, in VDC, and other HCBS programs. We ask respondents to rate a variety of VDC program aspects including referral and enrollment processes; workflow, communication, relationships, and payments between the VA and ADNA; VDC quality; and the overall program operation and delivery. The rating scale includes "excellent," "very good," "good," "fair," and "poor" response options. We ask what respondents would need at their site to be well-equipped for a hypothetical 25% increase in VDC enrollment, providing them with some options such as more staff; more streamlined referral and enrollment processes; more funding or quicker reimbursements, etc, and space for up to 3 additional items the respondent may enter. Response options for this question include "yes," "no," and "not sure." We will field the final surveys via Qualtrics, and participants will be emailed an invitation message explaining the purpose of the project along with a link to the survey.

In the interview with veterans and caregivers, we will ask about the need for VDC service, factors affecting VDC enrollment decisions, and perceptions of the VDC program's enrollment process and quality. We will also invite veterans and caregivers to complete a survey that asks about their health, quality of life, function, unmet needs, and other HCBS program use, using the Home Excellence Research and Outcomes Center to Advance, Redefine and Evaluate Non-Institutional Caregiving surveys fielded by the Elizabeth Dole Center of Excellence for Veteran and Caregiver Research [30].

Administrative Data

We will explore veteran demographics and health characteristics, along with the use of other VA HCBS designed to support veterans with disabilities or long-term health care needs [30,31]. Veteran demographics and health characteristics will be retrieved from the Geriatrics and Extended Care Data & Analysis Center Core Files (GCF) [32]. The GCF is a data set that includes information on all veterans who used the VA in an FY. The GCF combines information from many VA and non-VA data sources, capturing health care use, costs, risk factors, and outcomes for each veteran. A new GCF file is created each FY, and we will use the GCF FY file that matches the FY of a veteran's VDC enrollment date when compiling demographic and health characteristic information. Variables will include veteran age, gender, marital status, race, ethnicity, VA enrollment priority group, rurality of veteran's residence, diagnosed health conditions, Minnesota case-mix level, predicted LTIC risk score, Care Assessment Need score, Nosos score, and JEN Frailty Index score [33-35]. We will extract data on chronic conditions including but not limited to dementia, cancer, stroke, diabetes, chronic obstructive pulmonary disease, paraplegia, congestive heart failure, chronic kidney disease (CKD), and spinal cord injury. These diagnoses' indicators will be identified by using hierarchical condition category (HCC) Version 24-Community variables applied to combined VA and Medicare data. A veteran will be considered to have dementia if HCC indicators HCC51 (dementia with complication) or HCC52 (dementia without complication) are flagged. Similarly, cancer will be indicated if HCC8 (metastatic cancer and acute leukemia), HCC9 (lung and other severe cancers), HCC10 (lymphoma and other cancers), HCC11 (colorectal, bladder, and other cancers), or HCC12 (breast, prostate, and other cancers and tumors) are flagged. Congestive heart failure is indicated if MCVA_V24_HCC85 (congestive heart failure) is flagged, and CKD is indicated if MCVA_V24_HCC136 (CKD, stage 5), MCVA_V24_HCC137 (CKD, severe, stage 4), or MCVA_V24_HCC138 (CKD moderate, stage 3) are flagged.

Health care use data will be retrieved using the GECDAC Residential History File (RHF). The RHF uses data from VA, Medicare, Medicaid, and nursing home resident assessments to provide a daily summary of an individual's health service use and location of care [36]. Using the RHF, we will extract data from all inpatient visits, emergency department visits, inpatient rehabilitation, VA or non-VA nursing homes, or home health care use 180 days before and 180 days post the VDC enrollment date.

Qualitative Methods

Interviews

We have developed interview guides based on the CFIR constructs discussed below and as shown in Table 1. The interview guides are tailored for each type of participant (ie, VA staff, ADNA staff, VAMC GEC leadership, VISN leadership, enrolled veterans, caregivers of enrolled veterans, unenrolled veterans, and caregivers of unenrolled veterans). Interviews will focus on site and program-specific contexts and the facilitators and barriers to VDC program implementation and administration. We will request verbal consent from all participants before the interviews.

VA and ADNA staff interviews will cover 6 CFIR domains [24]. Survey responses will be reviewed and incorporated into our interview templates to allow the interviewer to inquire about specific ratings or information from the interviewee's responses. The questions will ask about roles and responsibilities, enrollment and referral procedures, expansion barriers and facilitators, adaptations or best practices, local leadership support, available and needed resources, and their personal anecdotes about the VDC program.

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VISN 8 administration and leadership interviews will include 7 CFIR domains. The questions will ask about their roles in overseeing program operations, comparisons to other noninstitutional care services, experiences with program expansion and initiation, and the most impactful aspects of VDC when advocating for medical center support.

Veteran and caregiver interviews will include 7 CFIR domains. The questions will ask about their experiences with the recruitment and referral processes, factors they considered when choosing (or not choosing) VDC, how the program has helped or hindered receiving care, and how VDC delivery could be improved.

Procedures for all interviews are similar. Interviews will be semistructured and conducted by at least two qualitatively trained project staff, including 1 facilitator and 1 dedicated notetaker. In the event 2 project staff are unable to attend due to scheduling conflicts, 1 facilitator will conduct the interview and the notetaker will watch the recorded interview to develop notes. Interviews will last about an hour, with leadership interviews lasting about 30 minutes, and will be conducted via Teams (Microsoft Corp). Veteran and caregiver interviews may be conducted by telephone as needed based on available technology access. Interview participants will be asked for their permission to record and transcribe the conversation; transcriptions will be created using Microsoft Teams' built-in transcription function and edited by project staff using the audio recording for reference. Detailed notes will be taken, reviewed for completeness against transcripts, and then finalized.

Participant Recruitment

We will identify participants by their relationship to each of the 7 VISN 8 VDC programs. Each VDC program has a designated VDC program coordinator who oversees their local program; we will therefore recruit 7 VDC coordinator participants. The project will be presented in a VISN 8 call to all the VDC coordinators by the VISN 8 GEC manager to stress the importance of the project. Following that, the 7 VA VDC coordinators will be invited to participate via email, with follow-up in a week, with up to 3 invitations. These VA VDC coordinators will be asked to provide contact information for the ADNA staff with whom they work, and we will invite these 7 ADNA staff to participate. ADNA representatives will be recruited via email consistent with the VA coordinator protocol. We will interview the GEC leads at all VAMCs, and VISN leads from GEC and the Caregiver Support Program.

We will ask VDC coordinators at each VAMC to contact veterans who are eligible for interviews and ask their permission to share their contact information with our team. The eligibility requirements for these patients include their having undergone referral processes of VDC but include both those who decided to enroll as well as those who did not enroll. We will invite them to participate and schedule interviews, with the intended aim of interviewing a dyad of a veteran and their caregiver that is enrolled and unenrolled from each of the 7 sites, for a total of 14 interviews. We will ask veterans for their caregiver's contact information if they have one and invite them to participate.

Ethical Considerations

This evaluation was determined to be a quality improvement project by the VA Miami Research and Development Service and received an exemption from a full institutional review board review. Therefore, formal informed consent is not required. However, participants will be made aware of the interview process, their rights to stop the interview at any time; how evaluators plan to use the data being collected; and of the measures and processes that will be followed to ensure confidentiality.

All data will be collected with the permission of the participant. Interview notes, transcripts, and matrix analysis will be stored in a secure folder behind the Veterans' Health Administration firewall. The folder will only be accessible to approved team members.

Data Analysis

Quantitative Survey Data

Both survey and administrative data will be analyzed by calculating frequencies for categorical variables or means, SDs, medians, and IQRs for continuous variables. Responses to open-ended questions will be synthesized into key summary points. We aim to characterize the veterans served by VDC at each site in VISN 8 and to identify any potential differences, recognizing that the underlying veteran populations across the state may vary by many of the demographic and health characteristics that will be evaluated.

We will compare responses between groups of interest using chi-square tests for categorical responses and *t* tests (1-tailed) for continuous responses and consider any *P* value less than .10 to indicate a statistical difference. Given the small number of responses and our focus on learning about and describing VDC-related needs and experiences, we will not rely heavily on formal statistical tests.

Quantitative GECDAC Data Analysis

We will summarize VDC "participants" health care service use, including HCBS, inpatient visits, emergency department visits, inpatient rehabilitation, VA or non-VA nursing home, or home health care, 180 days pre- and post-VDC enrollment date in periods of 30 days in the first 3 months and then the most distant quarter 91-180 days before or post VDC enrollment, and compare these to national VDC data.

Qualitative Data Analysis

Qualitative data from semistructured preimplementation interviews will be analyzed using rapid qualitative techniques guided by CFIR domains and constructs [37-41]. Interview notes and Teams transcriptions eliminate the need for traditional transcription processes and specialized qualitative analysis software. A structured interview summary template will be created based on each of the interview guides. Interview notes will be divided among team members and summary points will be derived for each interview. These summary notes will be compared across at least two qualitative team members and will be refined and finalized. Summary points will then be entered in individual rows of a Excel (Microsoft Corp) spreadsheet. Qualitative analysts will review summary notes and identify

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key concepts, which will be added to the matrix as column headers. Summary note entries will then be coded at the intersection of the row and column. Team members will review codes for discrepancies and develop consensus by adding new codes or splitting summary notes. These codes will be used to develop themes within the CFIR constructs. These themes will then be reviewed and discussed with the full analytic team during weekly meetings and analysis memos will be drafted to document relevant findings.

Results

The current status of this project is ongoing through the end of FY 2024 (September 2024), with recruitment of participants and data collection having begun in October 2022. Data collection and data analyses are both ongoing; as of April 2024, we have recruited 7 VDC coordinators, 15 ADNA representatives, 1 FMS representative, and 10 pairs of veterans and caregivers who have been referred to VDC in the past.

We will calculate descriptive statistics including means, SDs, and percentages for survey responses. Facilitators, barriers, number of patients enrolled, and staffing will also be presented. Interviews will be analyzed using rapid qualitative techniques guided by CFIR domains and constructs. Findings from VISN 8 will be collated to identify strategies for VDC expansion. We will use administrative data to describe veterans served by the programs in VISN 8.

Discussion

Principal Findings

The possibility of making VDC available to veterans nationwide depends on identifying barriers and facilitators to VDC implementation and expansion. Given that veterans prefer not to be in institutional settings, there is a palpable interest in expanding care options to include VDC for these patients. This evaluation will fill a critical gap in the literature related to VDC implementation in existing programs across the VA health care network.

Our proposed evaluation has several strengths. Our project uses a mixed methods approach with quantitative data using both surveys and administrative data, and qualitative data using interviews. Moreover, data will be gathered not only through the engagement of VDC staff and leadership at multiple organizational levels, both within VA and their partnering community agencies, but also directly from veterans and caregivers on how VDC, in its current iteration, addresses their needs. This study will strengthen our understanding of the barriers and facilitators impacting VDC-eligible veterans and examine the factors that influence veterans to choose VDC or elect to use other HCBS.

Potential weaknesses of this study include that these practices can be unique to the VA ecosystem. Moreover, it is only studying 1 VISN alone in the VA, a VISN that has a higher proportion of older veterans than other VA regions, thus potentially affecting the availability of services. Therefore, these results may not be generalizable to non-VA self-directed programs, nor to other VA regions. We also anticipate challenges associated with recruitment, especially for veterans who chose not to enroll in VDC.

This examination is particularly timely as President Biden required the VA to expand VDC to all VAMCs by the end of FY 2025 via Executive Order 14095—“Increasing Access to High-Quality Care and Supporting Caregivers” [42]. Our results will guide not only VDC programs wishing to expand their VDC patient roster but for those VAMCs newly implementing VDC services for the first time. Our long-term aim is to use this work to inform best practices, and policy decisions for VDC.

Acknowledgments

This work was supported in part by funding from the VISN 8 and the Miami VA Geriatric Research Education and Clinical Center (GRECC). Portions of this work were presented as a poster at the 15th Annual Conference on the Science of Dissemination and Implementation in Health, cohosted by the National Institutes of Health and AcademyHealth, on December 12, 2022, and as a paper presentation at the Gerontological Society of America annual meeting on November 8, 2023.

Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) coordinator interview guide.
[DOCX File , 38 KB - resprot_v13i1e57341_app1.docx]

Multimedia Appendix 2
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) community providers interview guide.

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[DOCX File , 23 KB - resprot_v13i1e57341_app2.docx]

Multimedia Appendix 3
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) financial management services interview guide.
[DOCX File , 34 KB - resprot_v13i1e57341_app3.docx]

Multimedia Appendix 4
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) leadership interview guide (financial year 2022 Q1-Q3).
[DOCX File , 25 KB - resprot_v13i1e57341_app4.docx]

Multimedia Appendix 5
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) enrolled veterans and caregivers interview guide.
[DOCX File , 28 KB - resprot_v13i1e57341_app5.docx]

Multimedia Appendix 6
Veterans Integrated Service Network (VISN) 8 Veteran-Directed Care (VDC) nonenrolled veterans and caregivers interview guide.
[DOCX File , 26 KB - resprot_v13i1e57341_app6.docx]

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Abbreviations

ADNA: Aging and Disability Network Agency
CFIR: Consolidated Framework for Implementation Research
CKD: chronic kidney disease
FMS: Financial Management Service
FY: fiscal year
GCF: Geriatrics and Extended Care Data & Analysis Center Core Files
GEC: Geriatrics and Extended Care
GECDAC: Geriatrics and Extended Care Data and Analysis Center
HCBS: home- and community-based services
HCC: hierarchical condition category
LTIC: long-term institutional care
RHF: Residential History File
VA: Veterans Affairs
VAMC: Veteran Affairs Medical Center
VDC: Veteran-Directed Care
VISN: Veterans Integrated Service Network

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Protocol

Long-Term Post–COVID-19 Health and Psychosocial Effects and Coping Resources Among Survivors of Severe and Critical COVID-19 in Central and Eastern Europe: Protocol for an International Qualitative Study

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Abstract

Background: There is a strong need to determine pandemic and postpandemic challenges and effects at the individual, family, community, and societal levels. Post–COVID-19 health and psychosocial effects have long-lasting impacts on the physical and mental health and quality of life of a large proportion of survivors, especially survivors of severe and critical COVID-19, extending beyond the end of the pandemic. While research has mostly focused on the negative short- and long-term effects of COVID-19, few studies have examined the positive effects of the pandemic, such as posttraumatic growth. It is essential to study both negative and positive long-term post–COVID-19 effects and to acknowledge the role of the resources available to the individual to cope with stress and trauma. This knowledge is especially needed in understudied regions hit hard by the pandemic, such as the region of Central and Eastern Europe. A qualitative approach could provide unique insights into the subjective perspectives of survivors on their experiences with severe COVID-19 disease and its lingering impact on their lives.

Objective: The aim of the study is to qualitatively explore the experiences of adult survivors of severe or critical COVID-19 throughout the acute and postacute period in 5 Central and Eastern European countries (Bulgaria, Slovakia, Croatia, Romania, and Poland); gain insight into negative (post–COVID-19 condition and quality of life) and positive (posttraumatic growth) long-term post–COVID effects; and understand the role of survivors' personal, social, and other coping resources and local sociocultural context and epidemic-related situations.

Methods: This is a qualitative thematic analysis study with an experiential reflexive perspective and inductive orientation. The analytical approach involves 2-stage data analysis: national analyses in stage 1 and international analysis in stage 2. Data are collected from adult survivors of severe and critical COVID-19 through in-depth semistructured interviews conducted in the period after hospital discharge.

Results: As of the publication of this paper, data collection is complete. The total international sample includes 151 survivors of severe and critical COVID-19: Bulgaria (n=33, 21.8%), Slovakia (n=30, 19.9%), Croatia (n=30, 19.9%), Romania (n=30, 19.9%), and Poland (n=28, 18.5%). National-level qualitative thematic analysis is currently underway, and several papers based on national results have been published. Cross-national analysis has started in 2024. The results will be submitted for publication in the third and fourth quarters of 2024.

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Conclusions: This research emphasizes the importance of a deeper understanding of the ongoing health and psychosocial challenges survivors face and what helps them cope with these challenges and, in some cases, thrive. It has implications for informing holistic care and improving the health and psychosocial outcomes of survivors of COVID-19 and will be crucial for evaluating the overall impact and multifaceted implications of the pandemic and for informing future pandemic preparedness.

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KEYWORDS

COVID-19 survivors; severe COVID-19; COVID-19 hospitalization; long-term COVID-19 effects; post–COVID-19 condition; posttraumatic growth; coping resources; qualitative; international; Central and Eastern Europe

Introduction

Long-Term Negative Health and Psychosocial Effects of COVID-19

The COVID-19 pandemic has become a major health crisis across the world. The new SARS-CoV-2 virus has caused over 774 million confirmed cases and over 7 million deaths globally [1]. As the pandemic progressed, in addition to the acute disease, a prolonged form has been identified, known as post–COVID-19 condition (or long COVID, post–COVID-19 syndrome, and postacute sequelae of SARS-CoV-2 infection [PASC]), with a global estimated prevalence of 43% [2]. The condition is characterized by long-term symptoms and complications that continue or develop after acute COVID-19. The World Health Organization (WHO) defines the post–COVID-19 condition as occurring usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness and generally have an impact on everyday functioning. Symptoms may also fluctuate or relapse over time [3]. Clinical guidelines in the United Kingdom and the United States define the prolonged form of COVID-19 as symptoms ongoing for 4 weeks or more [4,5]. A variety of long-term, patient-reported symptoms have been identified in adult survivors of COVID-19, with over 200 different symptoms reported across 10 organ systems [6]. Commonly reported symptoms include fatigue, shortness of breath, brain fog (concentration problems, cognitive dysfunction), headache, dizziness, weakness, postexertional malaise, depression, hair loss, loss or change in taste and/or smell, gastrointestinal symptoms, cough, nausea and vomiting, sweating, palpitations, intermittent fever, chest pain/discomfort, joint pain, body aches, sleep disturbance, memory loss, hearing loss or tinnitus, anxiety, posttraumatic stress, reduced pulmonary capacity, skin rash, and allergic reactions [6-10]. More severe post–COVID-19 condition has been associated with worse well-being and quality of life, worse perceived overall health [11], difficulties in performing daily tasks [6,8,9,11], reduced ability to work [6,12], and social and family life impairment [12]. Post–COVID-19 symptoms (most commonly fatigue) and lower quality of life have been found in both hospitalized and nonhospitalized survivors of COVID-19 at follow-up 2 years after symptom onset, although in significantly lower proportions compared to the 6-month follow-up [13,14].

A number of risk factors for post–COVID-19 condition have been identified, with disease severity being a major factor. COVID-19 severity levels have been defined in clinical guidelines by the World Health Organization [15,16] and the National Institutes of Health, United States [17], as nonsevere and severe COVID-19. Nonsevere COVID-19 includes asymptomatic or presymptomatic infection [17], mild illness (symptoms of COVID-19, but without viral pneumonia or hypoxia [15,16]), and moderate illness (clinical signs of pneumonia but no signs of severe pneumonia, including oxygen saturation [SpO_2]≥90% [15,16] or SpO_2≥94% on room air [17]). Severe COVID-19 is defined by clinical signs of pneumonia (fever, cough, and dyspnea) plus one of the following: oxygen saturation <90% on room air; severe pneumonia; signs of severe respiratory distress [16] or by SpO_2<94% on room air, arterial oxygen pressure [PaO_2]/fraction of inspired oxygen [FiO_2]<300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50% [17]; it requires hospitalization and oxygen therapy. Critical COVID-19 is defined by acute respiratory distress syndrome, sepsis, septic shock, or other conditions that require mechanical ventilation (invasive or non-invasive) or vasopressor therapy [16] or respiratory failure, septic shock, and/or multiple organ dysfunction [17]; it requires intensive care unit (ICU) treatment. Severe COVID-19 disease and hospitalization have been considered as key risk factors for post–COVID-19 condition across studies [8,18-20]. Any person infected with SARS-CoV-2 can experience long-term postacute COVID-19 effects, but the proportions are significantly higher among patients admitted to hospital with severe and critical COVID-19 disease. The global estimated prevalence of post–COVID-19 condition is 34% in nonhospitalized patients and 54% in hospitalized patients [2]. A systematic review and meta-analysis estimated the prevalence of any post–COVID-19 condition symptom at 50.6% among cohorts recruited in a community setting; 66.5% among cohorts recruited in a hospital setting; and 73.8% among cohorts recruited in the ICU setting [8]. A systematic review found that studies including more hospitalized participants or more patients in ICU tended to report higher prevalence estimates: 0% to 67% in studies with 10% hospitalized participants, and 5% to 93% in studies in which all participants were hospitalized; 34.9% in studies with <5% of their samples admitted to ICU, and 48.8% in studies in which 10% or more of the sample were admitted to ICU [18]. Among hospitalized patients, those who had been more severely ill during their hospital stay had more severely impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, depression or anxiety, and fatigue or muscle weakness [19]. After 2 years of symptom onset, the physical health and health-related quality of life of hospitalized survivors of

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COVID-19 were still poorer than those of the control population [13].

Other risk factors for post–COVID-19 condition are older age [2,10,11,18], female gender [2,10-13,19,20], preexisting chronic diseases (diabetes, hypertension, cardiovascular disease, respiratory disease, liver disease, kidney disease, and immunological disorder or allergy) [2,12,18,20], obesity [2,11,12,18], and nonvaccination status prior to infection [20].

Long-Term Positive Psychosocial Effects of COVID-19

While medical and public health experts and the scientific community have mostly focused on the negative short- and long-term effects of COVID-19, few studies have examined the positive effects of the COVID-19 pandemic. Alongside the preponderant negative effects, positive psychological and social outcomes have been identified, including positive changes in the lives of adolescents as a whole and in the domains of mental health and well-being and improved family relationships [21-23]; positive effects in the lives of adults related to more family time, work flexibility, and calmer life [24]; and posttraumatic growth [25-32]. Posttraumatic growth is a positive psychological outcome occurring as a result of struggling with highly challenging life circumstances and traumatic experiences, which can be found in survivors of serious diseases [33]. Experiencing the pandemic and the severe COVID-19 disease can challenge the adaptive resources of individuals, and "life-changing" psychological shifts in thinking and relating to the world and the self can arise, contributing to a deeply meaningful personal process of change in the posttraumatic growth domains of appreciation of life; relating to others; personal strength; new possibilities; and spiritual, existential, or philosophical change [33]. Indeed, aspects of posttraumatic growth in relation to the experience of the COVID-19 pandemic have been identified in the general population [25] and in persons infected with SARS-CoV-2 with various levels of disease severity and place of treatment [25-30], including hospitalized survivors of severe or critical COVID-19 [27,28,31,32]. Higher levels of posttraumatic growth have been associated with a higher severity of COVID-19 acute disease [27]. COVID-19–related posttraumatic growth has been found to coexist with negative psychological trauma-related outcomes such as anxiety, depression [27,31], and posttraumatic stress disorder [25-28,31].

The coping resources available to individuals have an important role in the ability to cope with trauma and bring about positive change. Coping resources are personal, social, or other resources for managing stress and coping with adversity, which interact with coping processes [34,35]. Personal resources found to be associated with higher levels of COVID-19–induced posttraumatic growth included optimism, self-compassion, self-transcendence, religiosity/spirituality, purpose in life, agreeableness, self-efficacy, sense of coherence [25], self-esteem [25,28], and resilience [25,26]. Social support has been proven to be a significant protective factor for the development of posttraumatic growth among the general population and survivors of COVID-19 [25-30,32], with family and friends being the most important source of social support [25,30]. Financial safety has been negatively associated with posttraumatic growth [29]. In a qualitative study of females with post–COVID-19 condition, coping with the disease involved individual resources (cognitive, emotional, and spiritual), social resources (social support from family, friends, coworkers, and web-based support groups), and health systems resources (guidance and treatment by counselors and medical professionals), and insufficient financial resources have been identified as a main challenge [36].

The Impact of the COVID-19 Pandemic on Central and Eastern Europe

Europe has been the epicenter of the pandemic several times in the period 2020-2022 and has reported the largest cumulative number of COVID-19 cases among WHO regions [1]. The countries in Central and Eastern Europe have been among the most heavily affected, which has been associated with death rates and excess mortality among the highest in the world, alongside very low vaccination rates. As of January 2024, the cumulative total reported COVID-19 deaths per 100,000 population were 556 in Bulgaria (second in the world), 460 in Croatia (seventh in the world), 389 in Slovakia (12th in the world), and 355 in Romania (15th in the world) [1]. In Europe, the countries most affected by excess mortality during the second wave (autumn to winter 2020) have been in Central and Eastern Europe (Czechia, Slovakia, Bulgaria, and Poland). In the spring of 2021, the highest mortality rates were recorded in Bulgaria (period average 168% and period maximum 202%), Romania (period average 163% and period maximum 230%), and Slovakia (period average 153% and period maximum 193%) [37]. Peaks in COVID-19 hospitalizations as high as 20,529 patients in Romania on October 26, 2021, and 10,355 patients in Bulgaria on April 11, 2021, were registered [38]. The number of patients with COVID-19 in ICUs per million reached 117,81 in Bulgaria (April 18, 2021), 112,17 in Slovakia (February 27, 2021), and 96,75 in Romania (November 7, 2021) [39]. Bulgaria, Romania, Slovakia, and Croatia have the lowest percentage of the total population vaccinated with at least 1 dose of a COVID-19 vaccine in the European Union—30% in Bulgaria, 42% in Romania, 52% in Slovakia, and 57% in Croatia [1].

In light of the repercussions of COVID-19, there is a strong need to determine pandemic and postpandemic challenges and effects at the individual, family, community, and societal levels. To advance this field, this study focuses on post–COVID-19 health and psychosocial effects, which have long-lasting impacts on the physical and mental health and quality of life of a large proportion of survivors extending beyond the end of the COVID-19 pandemic. This research complements the existing literature by examining both the negative (post–COVID-19 condition) and positive (posttraumatic growth) health and psychosocial long-term post–COVID-19 effects, their interrelationships, and their associations with the resources available to the individual to cope with stress and trauma. The study brings to the knowledge of the impact of the pandemic in the understudied region of Central and Eastern Europe, characterized by death rates and excess mortality among the highest in the world alongside very low vaccination rates associated with mistrust in vaccine benefits; mistrust of government, medical system, and medical staff; and mistrust

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in information from official sources [40-42]. The limited qualitative evidence regarding the outlined research topics is addressed by this study by adopting a qualitative approach that will deepen our understanding of the subjective experiences of survivors and provide valuable insights into personal meanings and the ways in which they are shaped by the specific sociocultural context and local epidemic-related situations in the studied Central and Eastern European countries. To our knowledge, this is the first study to qualitatively examine and cross-nationally compare the experiences of survivors of severe and critical COVID-19 throughout the acute and postacute period.

Objectives

The aim of the study is to qualitatively explore the experiences of adult survivors of severe or critical COVID-19 throughout the acute and postacute period in 5 Central and Eastern European countries: Bulgaria, Slovakia, Croatia, Romania, and Poland. The study objectives are as follows: (1) to gain insight into the negative long-term post–COVID-19 effects experienced by survivors—post–COVID-19 condition (physical and mental health symptoms, cognitive symptoms, and posttraumatic stress) and its impact on quality of life (diminished functional ability, difficulties in social functioning, etc); (2) to gain insight into the experienced positive long-term post–COVID-19 effects—posttraumatic growth; (3) to understand the role of survivors' coping resources, including personal (eg, self-efficacy, resilience, hope, optimism), social (eg, social support), and other (eg, financial) coping resources; and (4) to understand the role of the local sociocultural context and the local epidemic-related situations in the participating countries.

Methods

Study Design

This research is designed as an international qualitative study, adhering to the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines.

Theoretical Framework

The general theoretical framework of the study is the biopsychosocial model of health and illness [43], which conceptualizes our understanding of the COVID-19 disease as a result of the interaction of biological, psychological, and social factors.

The study follows the methodological orientation of qualitative thematic analysis [44-46] and the approach of reflexive thematic analysis [46], emphasizing the subjectivity of research and the researcher's active role in coding and theme generation. Themes are produced by the researcher(s) through systematic analytical engagement with the dataset and through personal positioning and metatheoretical perspectives. We adopt an experiential reflexive thematic analysis perspective focusing on participants' experiences and sense-making. The study has an inductive orientation, which is understood as "grounded" in data, considering that pure induction is impossible and data analysis is always underpinned by theoretical assumptions [46].

Our analytical approach includes a 2-stage data analysis. In stage 1, thematic analysis of each national dataset will be conducted and a national thematic map for each country's data will be produced, allowing for a meaningful discussion of findings and their implications for policy and practice at the national level. In stage 2, the national analyses will be collated and an international thematic map will be produced, allowing for highlighting cross-national differences, underlying epidemic-related and sociocultural factors, and drawing conclusions about the region of Central and Eastern Europe.

Study Site

This international study is conducted in 5 countries in Central and Eastern Europe: Bulgaria, Slovakia, Croatia, Romania, and Poland. The sampling frame used across countries comprises lists of discharged patients with severe or critical COVID-19 who have given their consent to be contacted, including lists from major public and private hospitals, rehabilitation centers, and recreational facilities that have treated patients with COVID-19 in the respective country, as well as from individual health care practitioners and lists created by the national research teams based on their private contacts, faculty, and students.

Study Duration

The study duration is 3 years (January 2022 to December 2024). Initially, the study started with 4 participating countries (Bulgaria, Slovakia, Croatia, Romania), and Poland was associated with the study at a later stage (in November 2022).

Research Team and Reflexivity

The implementing partners who are responsible for conducting the study in the 5 countries are the Department of Psychology, Institute for Population and Human Studies at the Bulgarian Academy of Sciences (Sofia, Bulgaria); the Centre of Social and Psychological Sciences, Slovak Academy of Sciences (Bratislava, Slovakia); the Department of Psychology, Faculty of Humanities and Social Sciences, University of Zagreb (Zagreb, Croatia); the Department of Psychology, Babes-Bolyai University (Cluj-Napoca, Romania); and the Faculty of Health Science, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń (Bydgoszcz, Poland). The members of the national research teams are psychologists holding academic positions in the above-listed institutions and PhD students in psychology. All researchers involved in data collection received training in qualitative data collection according to a standardized training protocol developed specifically for the study.

Participant Selection

Participants are selected through purposive sampling and snowball sampling. The purposive sampling strategy aims to achieve maximum variation and capture a wide range of perspectives and experiences. Participants' characteristics of interest include gender, age, country of residence, city of residence, need for ICU treatment, length of postdischarge period, and chronic diseases.

In this study, severe and critical COVID-19 disease is defined in accordance with WHO and National Institutes of Health clinical guidelines and their clinical classifications of COVID-19

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severity [15-17], using the clinical judgment of the patient's condition as requiring hospitalization (severe COVID-19 disease) or ICU care (critical COVID-19 disease) according to WHO guidance as the main criterion. Participants have been enrolled based on self-reported severe or critical COVID-19 disease.

The eligibility criteria for participation in the study include the following inclusion and exclusion criteria:

- Inclusion criteria: aged 18 years or older; tested positive for SARS-CoV-2; has had evidence of pneumonia; has been hospitalized (for severe COVID-19) or has been hospitalized and admitted to the ICU (for critical COVID-19); a resident of Bulgaria, Slovakia, Croatia, Romania, or Poland; and provided consent to participate in the study
- Exclusion criteria: treated for severe COVID-19 in a country other than the country of residence, member of the family of a participant, or unwillingness to comply with the study protocol

The national research teams approach participants in several different ways. Eligible participants who have given their consent are approached through the health care system, including hospitals, rehabilitation centers, recreational facilities for recovering from severe COVID-19, and individual health care practitioners. A group of participants is recruited through private contacts of the research team members and faculty and students in the participating research institutions. Another group is approached through advertisements on social media. The snowball technique is also used, and participants have been asked to invite other survivors of severe and critical COVID-19 to participate in the study. The participants are contacted via telephone or email.

Sample Size

The sample size of this study has been determined based on the suggestion of Braun and Clarke [47] that qualitative studies of experiences and influencing factors using interviews and a thematic analysis approach require a sample size of 15-30 participants in order to convincingly demonstrate patterns across the dataset while retaining a focus on individual experiences. The sample size is guided also by the concept of information power in qualitative interview studies [48], which considers that a broader study aim, a study supported by limited theoretical perspectives, and a cross-case analysis require a larger sample size. Based on the adequacy of the sample size for stage 1 thematic analysis, the target sample size has been decided to include 30 participants in each participating country.

Setting

Across countries, participants are sampled from public and private hospitals, rehabilitation centers, recreational facilities, and individual health care practitioners' practices, as well as from research and higher education institutions accessible to the researchers. Additionally, some participants are sampled from the general population after responding to invitations to participate in the study posted on social media or promoted by the researchers and their contacts. Data are collected through in-depth, semistructured interviews, conducted one on one by the members of the national research teams in person, through videoconferencing or by telephone. The in-person interviews are conducted in counseling rooms or at the premises of the research institutions.

Data Collection

The research methodology and study documentation have been developed in English and then translated into the national languages of the participating countries: Bulgarian, Slovak, Croatian, Romanian, and Polish. The method for qualitative data collection is in-depth, semistructured interviews, conducted after hospital discharge. The first 4 conducted interviews in each country serve as a pilot study for testing the study instrument and procedures. Based on the pilot study, revisions to the methodology have been made.

Instruments include a specifically designed for the study semistructured questionnaire (interview guide; Multimedia Appendix 1) and a sociodemographic questionnaire, which have been prepared based on a literature review. The topics in the semistructured questionnaire follow the experiences of survivors throughout the trajectory of the disease, from preinfection COVID-19 attitudes to first symptoms, hospitalization, recovery, and postdischarge adjustment. The interview guide covers various aspects such as vaccination attitudes and decision-making; illness experience; aggravating of existing chronic conditions; difficulties with access to testing, treatment, and hospitalization; hospitalization experience; communication with medical personnel; coping resources and coping strategies; social support; postdischarge experiences; impaired quality of life; and posttraumatic growth. The sociodemographic questionnaire collects data on gender, age, country of residence, city of residence, ethnicity, marital status, having children, educational level, profession/occupation, length of hospitalization, ICU treatment, length of postdischarge period, and chronic diseases.

The duration of the interviews depends on the natural flow of the conversation, with each participant being given sufficient time to fully share their experiences. To ensure accurate and complete data representation, an audio recording of the conversation is made after receiving permission from the participant. In the case of videoconferencing, only the audio recording of the meeting is used.

Ethical Considerations

Ethics approval for the study has been obtained from the Ethical Committee of the Institute for Population and Human Studies—Bulgarian Academy of Sciences (ethical approval number PD-2-140/15.08.2022).

Participants give their informed consent about their voluntary participation in the study. They are provided with the opportunity to withdraw their consent and terminate their participation at any time. An information sheet is part of the ethical documentation along with the informed consent form. It provides information about the study and explains the procedure, voluntary participation, the right to withdraw from the study, anonymity and confidentiality of participant information, potential benefits and risks associated with study participation, and the use of collected data only for scientific purposes.

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Collected qualitative data are anonymized, with all potentially identifying information removed. Demographic information and participant-identifying data are organized in separate files. Demographic information and qualitative data are analyzed and reported in aggregate form only.

Participants receive no compensation for their participation in the study.

Data Analysis

The audiotaped interviews are transcribed verbatim using the automated transcription package of the NVivo software (Lumivero) for qualitative data analysis, which supports transcription in the national languages of the partners. The transcriptions are then checked by the researchers for accuracy and are corrected where needed.

Data are analyzed through reflexive thematic analysis [44-46]. The analytic process involves searching for meanings and patterns in the data, generating codes, grouping codes into themes, and producing a thematic map—a complete conceptualization of the patterns in the data and the connections between them. The 6-phase process includes familiarizing with the data; generating initial codes; generating initial themes; reviewing potential themes; defining and naming themes; and producing the report. A total of 2-4 researchers code and compare the data in the different countries. The analysis is assisted by NVivo software for qualitative data analysis.

Data analysis is conducted in 2 stages. Stage 1 includes thematic analysis at the national level conducted by the national research teams on their national dataset in their national language. Stage 2 includes the translation of the national thematic maps into English and the integration of the national-level results of the 5 participating countries. The process will involve discussions of data and results between the national teams.

Results

Recruitment and Data Collection

Recruitment of participants and qualitative data collection (pilot study) started at the end of August 2022 for the main participating countries. Poland joined the study as an associate partner at a later stage (at the end of November 2022) and started recruiting participants and collecting data in January 2023.

As of the publication of this paper, data collection is complete in all countries. The total international sample includes 151 survivors of severe and critical COVID-19 in the 5 Central and Eastern European countries: Bulgaria (n=33, 21.8%), Slovakia (n=30, 19.9%), Croatia (n=30, 19.9%), Romania (n=30, 19.9%), and Poland (n=28, 18.5%). In Poland, the sample includes fewer than 30 participants, as 4 participants have withdrawn their consent to participate in the study.

Data Analysis and Expected Results

Transcription is complete in all countries. National-level qualitative thematic analysis is currently underway. The Slovak [49] and Romanian [50,51] teams have published research articles based on the analysis of their national datasets, presenting findings on posttraumatic growth and vaccine decision-making. Cross-national analysis has started in 2024. The results will be submitted for publication in the third and fourth quarters of 2024.

Discussion

Principal Findings

The study aims to gain a deeper understanding of the experiences of survivors of severe and critical COVID-19 throughout the acute and postacute period in 5 Central and Eastern European countries: Bulgaria, Slovakia, Croatia, Romania, and Poland. The results of the research will be presented in national thematic maps of the experiences of people who survived severe COVID-19 and in an international thematic map delineating the experiences of survivors in the region of Central and Eastern Europe. Thematic maps will visually represent the interconnected themes identified in the analysis and improve our understanding of the complex relationships between illness experience, negative and positive long-term health and psychosocial post–COVID-19 effects such as the post–COVID-19 condition, impaired quality of life, and posttraumatic growth, influencing factors such as coping resources and processes, and the specific sociocultural context and local epidemic-related situations that shape the experiences and impact the health outcomes of survivors of COVID-19.

Published results based on the analysis of Slovak [49] and Romanian [51] data provide insight into experiences of posttraumatic growth that have occurred through a reassessment of priorities and changed life perspective and appreciation of life itself and loved ones, and are built on effective coping strategies, self-care, inner strengths (such as optimism, determination, fighting difficulties attitude), and gratitude, highlighting pathways through which health adversities have induced enduring positive changes across cognitive, emotional, behavioral, and relational domains. Findings on survivors' perspectives on vaccination from Romania [50] increase our understanding of vaccine decision-making, underscoring severe illness as a factor for vaccine acceptance and vaccine adverse reactions as a factor for hesitancy, and the role of influences from trustworthy relationships and general disbelief and conspiracy theories in the decision-making process.

Ongoing research will shed further light and advance scientific knowledge on the acute and prolonged forms and physical and mental health symptoms of the coronavirus disease, the emergence and coexistence of positive psychological outcomes in the aftermath of psychological trauma and functional impairment, the multifaceted subjective experiences of patients, the diverse mobilized coping resources during the fight with severe COVID-19, survivors' needs for psychosocial support through the recovery process, and the impacts of the specific sociocultural contexts in the Central and Eastern European region. Based on the results, we will make recommendations that can inform the development of socioculturally appropriate tailored approaches to providing health and psychosocial support for coping with the post-COVID-19 condition and associated difficulties in different life domains, and the implementation of interventions to facilitate posttraumatic growth.

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Limitations

The study limitations could include the possibility of sampling bias, as individuals having multiple pronounced long-term post–COVID-19 symptoms may be more likely to participate due to relating to the study and wanting to share their experiences. On the other hand, individuals with higher levels of post–COVID-19 trauma and posttraumatic stress disorder may be less likely to participate due to experiencing retraumatization while recalling painful experiences. This could potentially lead to overrepresentation and underrepresentation of specific groups and bias within the study's findings. Self-selection bias is possible to arise due to using recruitment strategies such as advertisements about the study on social media. To minimize selection biases, a purposive sampling approach aiming at maximum variability and specific inclusion and exclusion criteria are implemented. Participants are recruited through diverse recruitment methods, and data are collected on their motivations for participation and nonparticipation. Collecting data on preillness and illness experiences in the postacute period postulates the retrospective nature of the study and the possibility for recall bias. A strategy to mitigate this bias is to achieve diverse lengths of the postdischarge period, ranging from participants who have been recently released from hospital to participants who have been infected and treated during the first and second waves of the COVID-19 pandemic.

Conclusions

This study protocol outlines an international qualitative investigation into the experiences of survivors of severe and critical COVID-19 of acute illness and long-term negative and positive post–COVID-19 health and psychosocial effects in the understudied region of Central and Eastern Europe. It emphasizes the importance of a deeper understanding of the ongoing health and psychosocial challenges survivors face and what helps them cope with these challenges and, in some cases, thrive. The results will add knowledge that can inform health care practice in hospitals and rehabilitation services, informal caregiving, and provision of psychological support to survivors of COVID-19 and ultimately improve the health and psychosocial outcomes of adult survivors of COVID-19. In the aftermath of a global pandemic, this research will be crucial for evaluating its overall impact and multifaceted implications and for informing future pandemic preparedness.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to the nature of the research containing potentially identifying and sensitive patient information but are available from the corresponding author on reasonable request.

Authors' Contributions

AAK, in collaboration with ALK, PH, and AB, is responsible for the overall conception and design of the study, funding acquisition, development of the study methodology, project administration, and supervision. All authors are involved in resourcing, data curation, investigation, and formal analysis. The writing of original draft is undertaken by AAK. All authors have contributed to the review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 19 KB - resprot_v13i1e57596_app1.docx]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
FiO2: fraction of inspired oxygen
ICU: intensive care unit
PaO2: arterial oxygen pressure
PASC: postacute sequelae of SARS-CoV-2 infection
SpO2: oxygen saturation
WHO: World Health Organization

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Protocol

Mapping Respiratory Health Digital Interventions in South and Southeast Asia: Protocol for a Scoping Review

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Abstract

Background: The last 2 decades have been a time of exponential growth and maturation for digital health, while the global burden of respiratory disease continues to grow worldwide. Leveraging digital health interventions (DHIs) to manage and mitigate respiratory disease and its adverse health effects presents itself as an obvious path forward.

Objective: We aimed to understand the current digital landscape and enabling environment around respiratory health to reduce costs, avoid duplication, and understand the comprehensiveness of DHIs.

Methods: This study will follow a scoping review methodology as outlined by Arksey and O'Malley, the Joanna Briggs Institute, and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. MEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library, Web of Science, PakiMedNet, and MyMedR databases will be searched along with key websites, repositories, and gray literature databases. The terms "respiratory health," "digital health," "South Asia," and "Southeast Asia," as well as related terms will be searched. The results will be screened for duplicates and then against the inclusion and exclusion criteria. For the studies included, data will be extracted, collated, and analyzed.

Results: The scoping review was started in July 2023 and will be finalized by February 2024. Results will be presented following the World Health Organization's classification of DHIs to categorize interventions in a standardized format and the mobile health evidence reporting and assessment checklist to report on the effectiveness of interventions. Further exposition of the evidence extracted will be presented through narrative synthesis.

Conclusions: As DHIs continue to proliferate, the need to understand the current landscape becomes more pertinent. In this scoping review, we will seek to more clearly understand what digital health tools and technologies are being used in the current landscape of digital health in South and Southeast Asia for respiratory health and to what extent they are addressing the respiratory health needs of the region. The results will inform recommendations on digital health tools for respiratory health in South and Southeast Asia will help funders and implementers of DHIs leverage existing technologies and accelerate innovations that address documented gaps in the studied countries.

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KEYWORDS

digital health; respiratory health; Asia; scoping review; landscape mapping; digital health intervention; digital health environment; mobile health; mHealth

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Introduction

Digital health and care refer to the use of information communication technologies, commonly known as digital health interventions (DHIs), by health and care professionals, patients, carers, or health managers to manage illnesses and wellness [1-4]. The last 2 decades have been a time of exponential growth and maturation for digital health [4] due to the promises of improved health for all and personal health empowerment [5]. Concurrently, the global burden of respiratory disease continues to grow worldwide, with infectious and noncommunicable respiratory diseases being among the top 10 medical conditions (out of 369 diseases and injuries measured) in terms of years of life lost due to premature death and years lived with a disability (measured by disability-adjusted life years) [6,7]. This increased burden of respiratory disease is more acutely felt in Asia, where mortality rates are higher and public awareness and government engagement are lower than in other regions of the world [8,9]. Leveraging DHIs to manage and mitigate respiratory disease and its adverse health effects presents itself as an obvious path forward. However, the first step to harnessing the power of digital health must be understanding the current digital landscape and enabling the environment to reduce costs, avoid duplication, and increase the efficiency, accessibility, and sustainability of such interventions [10-13].

The National Institute for Health Research (NIHR)–funded Global Health Research Unit on Respiratory Health (RESPIRE) is a collaboration between several Asian organizations and universities in Bangladesh, Bhutan, India, Malaysia, Pakistan, Indonesia, and Sri Lanka and the University of Edinburgh in Scotland, United Kingdom [9,14,15]. RESPIRE aims to achieve the following:

> *develop into a world-leading Unit that will: (i) map and collate continuing and emerging respiratory challenges; (ii) prioritise existing evidence-based interventions that have the potential to be adapted to reduce mortality and morbidity in low- and middle-income countries (LMICs); (iii) support local adaptation and tailoring of interventions for deployment in low-resource environments and catalyse developmental work in areas of unmet need; (iv) support local implementation efforts and evaluation of programmes of work; and (v) identify the best delivery mechanisms for long-term delivery and scaling-up.*

This is done through 4 different translational platforms, of which 1 platform focuses on Digital Health and Innovation and aims to provide holistic support to partner countries on the design, funding, deployment, and sustainability of new and existing digital health interventions for respiratory health. This scoping review will contribute to advancing the aims and work of Digital Health and Innovations.

Understanding the current landscape of DHIs that target respiratory diseases will (1) uncover existing gaps, (2) highlight potential opportunities, (3) suggest research and program priorities most needed in the field of digital health to address current respiratory health diseases in South and Southeast Asia, and (4) further advance RESPIRE's overall aims. Therefore, we aim to undertake a scoping review to map respiratory disease DHIs in South and Southeast Asia to identify existing technologies, opportunities, and gaps, and to put forward pertinent recommendations from the insights gained.

Methods

Scoping Review Methodology

The scoping review methodology, as outlined by Arksey and O'Malley and the Joanna Briggs Institute (JBI) [16,17], is an appropriate approach for mapping DHIs. Scoping reviews allow flexibility when exploring the diverse and heterogenous field of digital health, are appropriate when using different sources of data (eg, peer-reviewed journals, gray literature, and expert opinions), and permit inclusion and exclusion criteria to be iteratively refined as more evidence is uncovered [16-19]. Additionally, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [20] will be followed to ensure adherence to methodological standards.

Identifying the Research Question

This scoping review will seek to answer the following research questions:

1. What digital health tools and technologies are being used in South and Southeast Asia for respiratory health?
2. How are these addressing (or not) the respiratory health needs of the region?
3. What recommendations can be made from the literature?

Identifying Relevant Studies

To identify relevant literature, academic databases will be searched along with key websites, repositories, and gray literature databases that may contain relevant information for our scoping review. Textbox 1 shows the proposed databases.

The search strategy has been initially drafted for MEDLINE in the Ovid platform (Textbox 2) and will be adapted for the remaining databases. The search strategy has been iteratively developed and refined by the authors' input and the librarian at the University of Edinburgh. The terms "respiratory health," "digital health," "South Asia," and "Southeast Asia," as well as all relevant variations of these terms have been included in the search strategy to gather as much pertinent literature and information as possible.

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Textbox 1. Proposed database and key websites.

Databases

- MEDLINE
- Embase
- CINAHL
- PsycINFO
- Cochrane Library
- Web of Science
- PakMediNet
- MyMedR

Other sources

- ProQuest Thesis and Dissertations
- Digital Health Atlas
- Global Digital Health Index
- Digital Square's Map and Match
- United Nations Children's Emergency Fund's Mapping of Digital Health Tools and Technologies
- World Health Organization's Global Index Medicus

Textbox 2. Search strategy.

Search terms

1. occupational diseases/ or Asthma/ or Air Pollution/ or Respiratory Tract Diseases/ or Occupational Exposure/ or Air Pollutants/ or Tuberculosis/ or Tuberculosis, Pulmonary/ or "Tobacco Use"/ or Tobacco/ or "Tobacco Use Cessation"/ or "Tobacco Use Cessation Devices"/ or Pulmonary Disease, Chronic Obstructive/ or Pneumonia/ or COVID-19/
2. (respiratory health or tuberculosis or tobacco or pneumonia).mp
3. 1 or 2
4. telemedicine/ or telehealth/ or artificial intelligence/ or machine learning/ or medical informatics/ or electronic health records/ or mobile applications/ or exp Informatics/
5. (artificial intelligence or digital health or e-health or ehealth or m-health or mhealth or (digital adj2 (health or solution* or system*)) or (health adj2 (electronic or record* or tele*)) or ict4d or (information adj5 development) or machine learning or mobile health or telecare or telehealth or telemedicine or tele-health or teleconsultation or tele-consultation or tele-care or tele-medicine or (tele adj1 (medicine or care or health or consultation)) or ((virtual* or remote*) adj4 (visit* or consult* or meet* or appoint* or communicat*)) or (Health* adj4 tech*) or e-portal* or eportal* or (Patient* adj2 portal*) or (medical adj2 informatic*)).mp.
6. 4 or 5
7. Asia/ or Asia, Southern/ or Asia, Southeastern/
8. (Asia or Brunei Darussalam or Cambodia or Indonesia or Lao People's Democratic Republic or Malaysia or Myanmar or Philippines or Singapore or Thailand or Timor-Leste or Viet Nam or Vietnam or Afghanistan or Bangladesh or Bhutan or India or Iran or Islamic Republic of Iran or Maldives or Nepal or Pakistan or Sri Lanka).mp
9. 7 or 8
10. 3, 6, and 9

Study Selection

Exclusion and inclusion criteria have been developed according to the domains of population, concept, context, and type of evidence, suggested by the JBI [17,18]. Additionally, an "other variables" category has been created to include year, language, and format criteria (Table 1). The regions of South and Southeast Asia include 19 countries as established by the United Nations Statistics Division [21]. These 2 regions have been chosen because they contain all the RESPIRE2 countries. Multicountry studies containing countries from the selected regions and other regions of the world will be included in the initial screening and only excluded if they do not provide the data of interest separate for each country. Only studies in English and those published in the last 10 years (since 2013) will be included to keep the scope of this review within manageable boundaries.

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Table 1. Inclusion and exclusion criteria.

Domain	Inclusion criteria	Exclusion criteria
Population	• Any population	• N/A[a]
Concept	• Technological interventions for respiratory health that fall under any of the categories of the World Health Organization's classification of digital health interventions • Respiratory health includes respiratory infections, noncommunicable respiratory diseases, and preventable risk factors for respiratory conditions, as defined by RESPIRE[b]	• Other nontechnological interventions used for respiratory health • Not a respiratory health focus
Context	• South and Southeast Asia	• The rest of the world
Types of evidence sources	• Any study design	• Books • Abstracts only • Posters • Protocols
Other variables	• Published in English • Studies or data published in the last 10 years (2013-2023) • Full article or data are available digitally	• Published in any other language • Studies or data published before 2013 • Full article or data are not available digitally

[a]N/A: not applicable.

[b]RESPIRE: The National Institute for Health Research–funded Global Health Research Unit on Respiratory Health.

For information found in a scientific study format, Covidence software [22] will be used to eliminate duplicates and carry out screening and extraction. After deduplication, title, abstract, and full-text screening will be done by 2 authors according to the inclusion and exclusion criteria. Discrepancies will be first addressed by consensus between those 2 authors. If there is a lack of consensus, a third reviewer will decide.

For all other types of information or data found from searches, manual screening by 1 reviewer will happen first. Relevant data will be entered into a spreadsheet, and a second reviewer will assess it. Discrepancies will first be addressed between both reviewers, and if there is no consensus, a third reviewer will make the final decision. We will not contact authors directly to further understand whether a study should be included since it would most likely significantly lengthen the timeline for this scoping review.

Scoping reviews use secondary data and do not require ethics approval under RESPIRE rules. However, the authors will adhere to the highest ethical standards when carrying out the review. This protocol establishes a transparent and reproducible study design, which limits the potential for personal bias [23].

Charting the Data

After selection, relevant data will be extracted to a spreadsheet using Covidence. The extraction form will be first piloted in 3-5 studies to assess if it is fit for purpose as recommended by the JBI. Data selected from a nonscientific study format will be entered into the extraction spreadsheet as accurately as possible. However, it is acknowledged that not all fields may contain relevant information, and some fields may need to be modified (eg, data from the Digital Health Atlas will have a "source of information" field instead of an "author" field).

When 2 or more articles refer to the same overall study, those articles will be grouped as one before data extraction.

Collating, Summarizing, and Reporting the Results

After data analysis, the data will be collated and analyzed as follows:

- Quantitative data (ie, the number of studies, type of study, and year) will be presented.
- Qualitative data will be presented following the World Health Organization's classification of digital health interventions [24] to categorize interventions in a standardized format and the mobile health evidence reporting and assessment checklist [25] to report on the comprehensiveness of the interventions.
- Narrative synthesis will be used to answer the research questions and to present further data extracted.

Consultation

Consultation with stakeholders will be ongoing throughout the scoping review process. We will disseminate early findings among partners so that they can provide feedback on findings and that feedback can be incorporated into the discussion.

Results

This scoping review was started in July 2023 and will be finalized by February 2024. Preliminary findings will be shared with stakeholders and a final write-up of the scoping review is projected to be finalized by the end of March 2024. To date, 10,469 studies have been screened. The screening of abstracts is underway.

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Discussion

Expected Outcomes

Through this scoping review, we will seek to better understand what digital health tools and technologies are being used in South and Southeast Asia for respiratory health and to what extent they are addressing the respiratory health needs of the region. The results will inform recommendations on digital health tools for respiratory health in South and Southeast Asia and will help funders and implementers of DHIs leverage existing technologies and accelerate innovations that address documented gaps in the studied countries. The results of this review will be limited by the fact that only studies in English and studies published in the last 10 years will be included. This review will enhance the knowledge of digital health tools and technologies in the region, which is paramount before undertaking any new initiative, as it helps prevent redundant work and investment by building on existing systems and lessons learned.

Conclusions

As DHIs, in general and in respiratory health in particular, continue to proliferate, the need to understand the current landscape becomes more pertinent. Through this scoping review, we will systematically map out DHIs, which serves as the required first step in any well-informed and thought-out design and deployment of DHIs.

Acknowledgments

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Generative artificial intelligence was not used at any time during the research and writing of this protocol.

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Data Availability

The data resulting from this scoping review will be made available as supplementary materials at the time of publication.

Authors' Contributions

JE and LE conceptualized the idea. LE drafted the manuscript and search strategy. JE, MF, AA, and ZA provided feedback on the draft.

Conflicts of Interest

AA is a shareholder of a digital health company in Malaysia (UMCH Technology Sdn Bhd).

Multimedia Appendix 1
Peer-review reports from the National Institute for Health and Care Research (NIHR).
[PDF File (Adobe PDF File), 741 KB - resprot_v13i1e52517_app1.pdf]

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Abbreviations

DHI: digital health intervention
JBI: Joanna Briggs Institute
NIHR: National Institute for Health Research
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
RESPIRE: National Institute for Health Research–funded Global Health Research Unit on Respiratory Health

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Protocol

Homestay Hosting Dynamics and Refugee Well-Being: Protocol for a Scoping Review

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Abstract

Background: The process of refugee resettlement and integration into new communities is a complex and multifaceted challenge, not only for the refugees themselves but also for the host families involved in homestay housing arrangements. While these homestay arrangements are designed to facilitate smoother transitions and enhance the well-being of refugees, the nuanced dynamics of these interactions and their overall impact on both refugees and their host families remain underexplored. Understanding the experiences of refugees and their host families is vital for effective refugee settlement, integration, and well-being. However, the intricacies of homestay refugee hosting, their interactions with host families, and the impact on their well-being are still unclear and ambiguous.

Objective: The aim of this scoping review is to examine the breadth of literature on the experiences of refugees living in homestay arrangements with their host families. This review seeks to understand how these dynamics influence refugee well-being, including their integration, social connections, and mental health. Additionally, this scoping review aims to synthesize existing literature on homestay hosting dynamics, focusing on the experiences of refugees and their host families, to identify gaps in knowledge and suggest areas for future research.

Methods: This scoping review follows Joanna Briggs Institute methodology and will search databases such as CINAHL, SOCIndex, MEDLINE through EBSCO; APA PsycInfo, Scopus through OVID; and Web of Science Core Collection, ProQuest Dissertations, and Theses, and SciELO Citation Index, focusing on literature from 2011 onward, in English, in relation to refugee groups in different host countries, including all types of literature. Literature will be screened by 2 independent reviewers, with disagreements resolved by consensus or a third reviewer. A custom data extraction tool will be created by the research team.

Results: The results will be organized in tables or diagrams, accompanied by a narrative overview, emphasizing the main synthesized findings related to the dynamics of homestay hosting with host families and refugee well-being. No critical appraisal will be conducted. This scoping review is expected to identify research gaps that will inform the development of homestay refugee hosting models, policies, and practices. It will also offer insights into best practices and policy recommendations to improve homestay hosting programs, ultimately contributing to more effective refugee settlement and integration strategies.

Conclusions: Understanding the intricate dynamics of homestay hosting arrangements is crucial for developing policies and programs that support the well-being of refugees and the families that host them. This scoping review will shed light on the current knowledge landscape, identify research gaps, and suggest ways to enhance the homestay hosting experience for all parties involved. Through this work, we aim to contribute to the development of more inclusive, supportive, and effective approaches to refugee hosting, resettlement, and integration.

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KEYWORDS

cohabitation; homestay; hospitality; host family; host-guest relationship; refugee; well-being

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Introduction

Overview

The global displacement of refugees amounted to 35.3 million individuals, with a majority comprising female individuals [1]. However, as the number of individuals seeking refuge in host countries grows, the housing needs of such people beckon resolution. One prosperous solution that has arisen from housing needs is refugee hosting [2]. Within the purview of refugee studies, the term "hosting" signifies the established societies or communities that undertake the resettlement of refugees [3]. Hosting communities are often credited with the expectation to foster welcoming and accepting environments for refugee women and their families to settle after escaping conflict [4].

Families seeking support may be placed, by publicly or privately funded organizations, into the homes of host families. Such homes are volunteered by willing families or individuals, many of whom are refugees or immigrants [4]. Hosting communities and their members often play a crucial role in extending hospitality and support to refugee women and their families to facilitate integration [5]. This culture of hospitality is also observed at the individual level notably within urban communities, where there is a rising trend of individuals and families hosting refugees in their private residences [6]. The role of these host families typically involves temporarily sharing their homes and resources with newly arrived refugees, all with the aim of enhancing the settlement process [6]. However, the use of the terms "host" and "hosting" illustrates a host-guest relationship, positioning refugees within the domain of the hosts. This conveys an underlying power imbalance between the hosts and the refugees [4,7]. This dynamic can also cultivate certain expectations imposed on refugees, dictating their behavior according to the host's perceived standards of being worthy of hospitality [7]. For example, in a study by Monforte et al [7], exploring the responsibility of hosting, private hosts expressed emotional connection and mutual affection as a jointly shared responsibility with refugees, placing expectations on refugees to reciprocate. When refugees did not meet their expectations due to language barriers or unwillingness to discuss their past, hosts' perception of the refugee's value altered [7].

The expectation of the refugee to be a "good guest" highlights the conditional nature of private hosting, therefore requiring refugees to prove they are deserving of being hosted [4,5,7]. When refugees do not match the expectations or ideas of hosts, this can create an uncomfortable environment for refugees [5]. Furthermore, hosting arrangements and expectations can limit refugees' control over their surroundings, as they are essentially guests in someone else's domain [4,6,7]. This lack of control over their living situation can potentially hinder their ability to rebuild their lives autonomously, trigger power differences, and add an extra layer of vulnerability [8,9]. This power difference is even more pronounced for refugee women due to the intersection of gender-related disparities [10]. In addition, refugees' lack of host country citizenship further positions them as guests and makes them vulnerable to various abuses of power [11]. Viewing refugees women as mere guests within host homes and communities increases their social and economic vulnerabilities, especially without sufficient system-level policies and safeguards in place to protect their welfare [12].

Dağtaş [13] argues that refugee lived experience is heavily influenced by the host country's political conditions and social welfare policies (for refugees). In addition, current literature has revealed that hosting frameworks have created a racialized discourse of nonbelonging [14]. Furthermore, reviews of the literature on current homestay or family hosting practices and regulations for refugee groups highlight an enormous gap [6]. Although communities and host families play an immense role in refugee settlement, refugee well-being relies heavily on standards being shaped by inclusive and informed social welfare policies and practices [15]. Host families and the communities in which refugees are hosted are pivotal in their successful settlement and success [7,15]. They may provide crucial aid to refugees, including more tangible forms of support, such as housing or financial aid, in addition to more abstract forms of assistance, such as cultural orientation, emotional support, and social comfort [7]. However, as generally unregulated social groups, the success of such support provided to refugees can vary largely based on cultural competency, empathetic disposition and understanding, and the attitudes and perspectives of communities and host families [4,15]. For a meaningful exploration of the hosting practices and dynamics implemented by the host families, it is imperative to understand the discourse these practices bring forth and their implications on refugees' well-being.

A preliminary search of the literature through review registries (Open Science Framework and Joanna Briggs Institute (JBI) Evidence Synthesis) was conducted. No current or in-progress scoping reviews on this topic were identified. Existing reviews do not study the specific relationship between refugees and host families; reviews on the topic of refugee integration, in general, tend to be focused on a particular geography in terms of the host country or on a particular subset of refugees (eg, by gender, host country, or accommodations practices). The aim of this scoping review is to explore the experiences of refugees with their host families and understand the dynamics of homestay hosting on refugee well-being. A scoping review is an appropriate method to gather, organize, and chart the evidence [16] related to refugees living with host families. It aims to pinpoint variances and parallels in homestay hosting approaches and practices, enhancing our comprehension of their effects on refugee well-being. This review is intended to inform future research that could guide evolving practices or models for refugee hosting.

Review Question

What is known from the existing literature about the experiences of refugees with homestay hosting?

Methods

Overview

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping review [16] and the PRISMA-ScR (Preferred Reporting Items for Systematic and Meta-Analyses extension for Scoping Reviews) [16,17]. The

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protocol of this review has been registered with the Open Science Framework [18].

Eligibility Criteria

Participants

This review will consider studies involving participants who identify as refugees, displaced persons, or asylum seekers. There will be no restrictions based on age or gender.

Concept

This review will consider literature that pertains to refugee hosting experience, hosting practices, homestay, host-guest relationship, cohabitation, and refugee well-being.

Context

This review will consider literature specific to refugee accommodation, hosting family, and homestay hosting practices in different host countries and different geographical settings.

Types of Sources

This review will consider all types of study designs. Database searches will not be limited to a particular evidence source type. Primary research articles, review articles, editorials, theses, dissertations, reports, publications after 2011, and other gray literature in English will be included. This scoping review will also include theses and conference proceedings. Opinion papers will also be considered for inclusion in this scoping review, depending on the focus and context.

Search Strategy

In collaboration with a research librarian, the search strategy was built using some seed articles supplied to the librarian by the lead researcher as well as an initial search of several databases using basic terms. The search strategy, encompassing all identified keywords and index terms, will be tailored to suit each database and information source included. These searches were built up and used to develop a full search strategy for CINAHL (Multimedia Appendix 1). For other interfaces, the search will be modified as per the accepted Booleans, etc. The final scoping review will include all searches as appendices. The search strategy was also peer-reviewed by a fellow librarian using the PRESS Peer Review Strategy [19]. Studies published in English since 2011 will be included. The reference list of all included sources will be screened for additional studies. The databases to be searched include CINAHL, SOCIndex, MEDLINE, and Academic Search Complete through the EBSCO interface; APA PsycInfo and Scopus through the OVID interface; and Web of Science Core Collection, ProQuest Dissertations and Theses, SciELO Citation Index, and ProQuest through the Web of Science interface. As no source filters will be used, gray literature on these databases, such as conference proceedings and theses, will also be captured.

Study Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 21; Clarivate) and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management of the Assessment and Review of Information (SUMARI) for the unified management, assessment, and review of information [20]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of papers in full text that do not meet the inclusion criteria will be recorded and reported in an appendix to the full review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic and Meta-Analyses) flow diagram [16,17].

Data Extraction

Data will be extracted from studies included in the review by 2 independent reviewers using a data extraction tool developed by the reviewers based on content relevant to the review question (Multimedia Appendix 2). The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review question. The initial data extraction tool will undergo adjustments and updates as needed throughout the data extraction phase from each selected source of evidence. These changes will be thoroughly documented in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. We will reach out to the authors for further details or clarifications when necessary. Should we encounter missing, unclear, or ambiguous data crucial for our analysis, we will contact the respective authors.

Results

To address this scoping review's objective of identifying, collating, and mapping the evidence about the term homestay hosting in relation to refugee groups with their host families in different host countries, we will undertake a comprehensive and thorough analytical process. This will involve synthesizing information from the selected studies into a cohesive framework. The key outcomes of this process will be systematically documented in a detailed table, which will encapsulate the diverse definitions, interpretations, and implementations of "homestay hosting" encountered in the literature (Multimedia Appendix 3). This will serve as a crucial reference point, offering a consolidated view of how "homestay hosting" is understood and applied by different researchers and practitioners in the field. Beyond merely summarizing these findings, the review will extend its analysis to include the development of diagrams. These visual aids, to be included in Multimedia Appendix 4 are designed to visually represent the relationships and connections between the various elements of refugee homestay hosting.

The diagramming effort aims to clarify how the specific aspects of homestay hosting interact with the broader concept of family hosting and with each other. This visual mapping will not only make the complex interrelations more accessible but also highlight potential areas for further research or intervention.

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Complementing the tables and diagrams, a narrative summary will be provided to weave together the review's findings in a coherent format. This narrative will contextualize the evidence within the scope of the review's objectives, offering insights into how the concept of homestay hosting contributes to our understanding of refugee support mechanisms. It will explore the implications of the findings for policy, practice, and future research, particularly emphasizing the nuances of refugee experiences in homestay settings and the roles of host families. Through this multifaceted approach—combining tabular summaries, visual diagrams, and narrative synthesis—the scoping review will offer a comprehensive and nuanced exploration of refugee homestay hosting, thereby enriching the discourse on refugee accommodation and support strategies.

Discussion

Overview

This scoping review will shed light on the intricate relationship between homestay hosting environments and refugee well-being, offering new perspectives on how these arrangements affect refugees' lives. By dissecting the dynamics within homestay settings, our analysis will bring to the forefront the multifaceted ways in which these hosting arrangements influence refugee well-being. Such insights are invaluable for policy makers and practitioners tasked with crafting and executing refugee hosting programs and models, providing them with a deeper understanding of the elements that contribute to successful refugees' integration and support. Our findings will highlight critical areas ripe for further exploration, suggesting that while this review lays the groundwork, it also underscores the necessity for more focused research. Detailed investigations, particularly longitudinal studies, could elucidate the evolving nature of refugee well-being within homestay contexts, offering a clearer picture of long-term outcomes. Similarly, comparative analyses of various hosting models could reveal best practices, guiding the development of more effective and supportive hosting frameworks. While this scoping review opens the door to a better understanding of the complex interplay between homestay hosting and refugee well-being, it also highlights the critical need for ongoing research. Future studies, armed with the foundational knowledge provided by this review, have the potential to further dissect and enhance the nuances of the homestay-refugee relationship. Such research is crucial for refining hosting practices and policies, aiming for a more empathetic and effective approach to supporting refugees worldwide, ultimately contributing to their well-being and successful integration into host communities.

Implications

The implications of our review extend beyond academic discourse, offering actionable insights for policy makers, practitioners, and researchers alike. By advocating for tailored support mechanisms, clear policy guidelines, and further research into the long-term effects of homestay arrangements, this review sets the stage for future studies that can build on our findings. Ultimately, we hope that our work will pave the way for more empathetic, effective, and sustainable refugee support practices worldwide, ensuring that both refugees and their host families can thrive together in their shared communities.

Limitations

This review protocol is not without limitations. One significant constraint is the scope of the literature reviewed, which may not encompass all existing studies on homestay hosting and refugee well-being due to language and publication date restrictions. Additionally, the inherent nature of scoping reviews to broadly map a field of study implies that the depth of analysis on specific topics might be limited and there will be no quality assessment of the selected resources. This limitation points to the necessity for targeted, in-depth studies that can build on the preliminary insights offered here. Furthermore, the diversity of homestay arrangements and refugee experiences across different cultural and geographical contexts may not be fully captured, highlighting the need for context-specific research to fully understand the nuances of homestay hosting and its impact on refugee well-being.

Conclusion

This scoping review will highlight the complex relationship between homestay hosting and refugee well-being, revealing both the potential and challenges of such arrangements. By examining the current state of research, the multifaceted nature of these hosting arrangements and their effects on both refugees and their host families will be illuminated. Our findings can highlight the critical need for policies and practices that are deeply informed by an understanding of these intricate dynamics to support the well-being of refugees and their hosts effectively. Understanding the intricate dynamics of homestay hosting arrangements is crucial for developing policies and programs that support the well-being of refugees and the families that host them. This review will shed light on the current knowledge landscape, identifying research gaps and suggesting ways to enhance the homestay hosting experience for all parties involved. This review's findings will inform the development of more inclusive, supportive, and effective approaches to refugee hosting, resettlement, and integration. To the best of our knowledge, this review represents the inaugural scoping review designed to explore the dynamic of homestay hosting and refugee well-being and the benefits such exploration brings to inform the development of refugee hosting models and practices.

Acknowledgments

We would like to thank all authors who contributed to this protocol. Their expertise, unique insights, and commitment have been crucial in shaping and enriching this work. Each author's distinct knowledge and dedication have significantly enhanced the quality and depth of our discussion. We are grateful for their valuable contributions and the collaborative effort that made this

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protocol both informative and comprehensive. We affirm that ChatGPT was used solely for the purpose of language enhancement in the preparation of this protocol. It did not generate content for the study protocol, contribute to ideation, or provide any statements or references used herein. ChatGPT is not listed as an author, and its use was strictly limited to linguistic improvements. We adhered to all applicable artificial intelligence–related policies, regulations, and best practices in the use of this tool, ensuring that its application was in compliance with ethical standards for academic publication.

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Data Availability

This review protocol's supporting data are shared in the manuscript appendices, enhancing transparency and understanding. These appendices include the search strategy, data extraction tool or instrument, table of key findings, and term map diagram, offering insights into our methodology, data analysis, findings, and conceptual framework. For further details or clarifications, readers are encouraged to contact the corresponding author.

Declaration

AAH, YMY, K Metersky, and SG are registered nurses and researchers deeply committed to issues of equity and social justice in practice and inquiry and situate themselves as immigrants working to support the health and well-being of refugee groups. The work of this scoping review represents a continuation of a program of research dedicated to supporting meaningful hosting, settlement, and integration of refugee groups as a fundamental aspect of promoting and protecting their health and well-being.

Authors' Contributions

AAH contributed to the conceptualization of the review topic. K Mahsud contributed to developing and running the search strategies. AAH, YMY, K Metersky, and SG contributed to developing the review methods and criteria, providing feedback for the search strategies, and drafting and critically reviewing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v13i1e56242_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 13 KB - resprot_v13i1e56242_app2.docx]

Multimedia Appendix 3
Table of key findings.
[DOCX File , 12 KB - resprot_v13i1e56242_app3.docx]

Multimedia Appendix 4
Term map diagram.
[DOCX File , 69 KB - resprot_v13i1e56242_app4.docx]

Multimedia Appendix 5
Peer-review report from the Social Sciences and Humanities Research Council (SSHRC).
[PDF File (Adobe PDF File), 21 KB - resprot_v13i1e56242_app5.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic and Meta-Analyses extension for Scoping Reviews
SUMARI: System for the Unified Management of the Assessment and Review of Information

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Protocol

Monitoring and Evaluation of Dementia-Friendly Neighborhoods Using a Walkshed Approach: Protocol for a Scoping Review

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Abstract

Background: The number of people in society living with dementia is growing. In Canada, most people who live with dementia live at home, often in a neighborhood setting. Neighborhood environments can be a source of independence, social engagement, and well-being. They can also contain barriers that limit physical activity, social engagement, and well-being. A dementia-friendly neighborhood includes assets that support persons living with dementia and their caregivers in multiple life domains, including those that support walking within the neighborhood environment.

Objective: The objectives for this scoping review are twofold. First, focusing on walkshed analysis, we aim to extend scholarly understandings of methodological practices used in the monitoring and evaluation of dementia-friendly neighborhoods. Second, we aim to provide clear and practical guidance for those working in planning, design, and public health fields to assess the neighborhood context in support of evidence-based action to improve the lives of persons living with dementia.

Methods: The study design follows Arksey and O'Malley's scoping review framework and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. We will conduct a search of peer-reviewed studies in 6 electronic databases to identify the use of Geographic Information System analysis to measure the walkshed of persons living with dementia in a community setting. As age is a primary risk factor associated with dementia, we will also include studies that focus more broadly on community-dwelling older adults aged 65 years and older. Data will be extracted, analyzed, and represented according to 3 domains. This includes study details, walkshed analysis methods, and criteria and indicators used to measure dementia-friendly neighborhoods.

Results: The results of the study and the submission of a manuscript for peer review are expected in June 2024. The results of the review are expected to contribute to an understanding of methods for monitoring and evaluating dementia-friendly neighborhoods. Expected findings will include a detailed breakdown of current parameters and routines used to conduct walkshed analysis. Findings will also convey criteria that can be operationalized in a Geographic Information System as indicators to assess barriers and facilitators to walking in a neighborhood setting.

Conclusions: As far as we are aware, the proposed scoping review will be the first to provide comprehensive methodological or technical guidance for conducting walkshed analysis specific to persons living with dementia. Both the scalability and objective nature of walkshed analysis are likely to be of direct interest to public health practitioners, planners, and allied professionals. Clearly documenting methods used in walkshed analysis can spur increased collaboration across these disciplines to enable an evidence-informed approach to improving neighborhood environments for persons living with dementia.

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KEYWORDS

dementia-friendly; neighborhood; persons living with dementia; walkability; walkshed

Introduction

Overview

Walkshed analysis identifies the extent of the community environment surrounding a central location that is accessible at a scale where walking is a competitive mode of mobility [1]. Once a walkshed is delineated in a Geographic Information System (GIS), criteria and indicators can identify barriers and enablers to walking [2]. Walkshed analysis is relevant to planning and public-health partnerships that seek to support persons living with dementia. More than 55 million people are currently living with dementia across the world. The global prevalence of dementia is projected to continue to rise by approximately 10 million new cases per year [3]. In Canada, most people experiencing dementia live at home. As of 2016, around 69% of those aged 80 years or younger were living outside of the long-term care system [4]. As an umbrella term, dementia captures the experience of progressive cognitive decline. It can impact an individual's mood, behavior, and actions, including the performance of key activities of daily living [5]. There are many types of dementia, including Alzheimer dementia, vascular dementia, frontotemporal dementia, lewy body dementia, mixed dementia, and young-onset dementia. Alzheimer disease is the most common cause, contributing to 60% to 70% of cases of dementia [6].

Literature on dementia-friendly communities (and neighborhoods) takes a relational view [7,8]. This view acknowledges that well-being is conditioned by interrelated aspects of a person's social, built, and ecological surroundings [8-10]. Accordingly, scholars identify dementia-friendly environments as the arrangement of supportive assets into a community fabric that promotes meaningful societal engagement for persons living with dementia and their caregivers [11]. This includes the complex social relations that persons living with dementia experience in a community setting, making the physical neighborhood part of a relational and moral context [12,13].

Scholarship on dementia-friendly communities and neighborhoods stems from calls to better support persons who are living with dementia outside of an institutional setting [11]. These calls reflect the fact that scholars have long viewed neighborhoods as a central relational context shaping individual behavior and life quality [14]. As early as the turn of the 20th century, ideas about neighborhood planning in North America drew on sociological concepts such as Charles H Cooley's primary group. The primary group and similar concepts asserted that the neighborhood was the main setting for the social relations that informed one's perspectives and ideals [15].

A long fascination with neighborhood environments helps explain the growing effort to understand how the neighborhood can enable or hinder self-determination for persons living with dementia. This includes aspects of identity development and one's ability to shape life balance [10,12,16]. Remaining close to the home, or aging in place, is also "closely intertwined with (a person's) sense of self and identity" [17]. By contrast, moving away from familiar areas can have negative effects on persons living with dementia [18]. To remain active and engaged within their environments while aging in place, persons living with dementia need special considerations and support in their neighborhoods [17].

The influence of the built environment on a sense of community and one's place therein remains up for debate in an increasingly mobile and digital society [19,20]. At the same time, there is a convincing body of evidence demonstrating that planning and design can impact behavior. The extent to which a neighborhood setting encourages or discourages important social and health behaviors such as walking is a particular focus for planning-health partnerships [21-23]. There is also a growing body of evidence illustrating that walking outdoors boosts quality of life for those living with dementia, contributing to improved mood, quality of sleep, and sense of freedom [17,24,25].

Urban planning scholar Lawrence Frank significantly advanced the conception and measurement of walkability. He describes walkability as the extent to which an environment's social and physical characteristics promote walking as a competitive and desirable form of mobility [26,27]. Recent work has extended the idea of walkability to a more encompassing notion of "active living environments." Active living environments are defined as "the emergent natural, built, and social properties of neighborhoods that promote physical activity and health and allow for equitable access to health-enhancing resources" [28].

Scholars have used a wide variety of methods to study walkability and its relation to walking behavior. These include phenomenological interviews [29], cross-sectional community surveys [30], observational techniques [31], surveys [32,33], photovoice [34,35], and in-situ walking interviews [12]. Scholars have also deployed criteria and indicators that enable monitoring and evaluation of the social, built, and ecological environments that make up a city [36]. In some cases, criteria and indicators are operationalized using a geospatial approach that assesses barriers and facilitators to walking in a small area (eg, 1 km) surrounding a central location such as a residence. This approach is often referred to as walkshed analysis.

In North America, walkability is now well researched within urban settings in the context of the "general population." By comparison, factors that shape walkability for members of equity-deserving groups, particularly persons living with dementia, are comparatively understudied. There is a need to better document (1) what walkability criteria and indicators are relevant to the lived experience of persons living with dementia, (2) how methods are operationalized to examine barriers and facilitators using a walkshed approach, and (3) where barriers and facilitators of walkability for persons living with dementia

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may align or conflict with those of other populations. Given these needs, the objectives for this scoping review are twofold:

1. Focusing on walkshed analysis, extend scholarly understandings of methodological practices used in the monitoring and evaluation of dementia-friendly neighborhoods.
2. Provide clear and practical guidance for those working in planning, design, and public health fields to assess the neighborhood context in support of evidence-based action to improve the lives of persons living with dementia.

To achieve the preceding objectives, this scoping review will address the following research question: What dimensions, criteria, and indicators can be recognized within the academic literature for measuring neighborhood walkability for persons living with dementia based on a walkshed methodology?

Existing Reviews

This protocol was informed by an initial review of existing peer-reviewed literature. The purpose of this review was to identify possible knowledge syntheses on the use of walkshed methodology to document barriers and facilitators faced by persons living with dementia. Table 1 summarizes key aspects of 6 related knowledge syntheses. All but 1 of the identified studies were published within the past 5 years [36]. A total of 2 of the studies directly focused on persons living with dementia. Other studies focused on dementia risk factors among older adults (see Table 1).

Table 1. Summary of comparable existing knowledge syntheses as they relate to the proposed scoping review.

Reference	Title	Objective	Population focus	Addresses aspects of walkshed methods	Addresses objective criteria
Akinci et al [21], 2022	How different are objective operationalizations of walkability for older adults compared to the general population? a systematic review	Summarize and compare methods used to operationalize objective walkability for older adults and the general population	Older adults or general population	Yes	Yes
Cerin et al [36], 2017	The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis	Identify correlates of neighborhood physical features and active travel in older adults and quantify the strength of associations	Older adults	No	Yes
Sturge et al [37], 2021	Features of the social and built environment that contribute to the well-being of persons with dementia who live at home: a scoping review	Summarize evidence from qualitative studies about how social and built environment features influence well-being for persons living with dementia	Persons living with dementia	No	Yes
Gan et al [25], 2022	Dementia-friendly neighbourhood and the built environment: a scoping review	Synthesize knowledge and support policy direction related to dementia-friendly neighborhood environments and attendant psychosocial outcomes	Persons living with dementia	No	Yes
Peters et al [2], 2020	Measuring the association of objective and perceived neighborhood environment with physical activity in older adults: challenges and implications from a systematic review	Assess the correlates of neighborhood characteristics and physical activity in older adults to provide a body of evidence to support neighborhood environmental interventions	Older adults	Yes	Yes
Chen et al [38], 2022	Neighbourhood-built environment associated with cognition and dementia risk among older adults: a systematic literature review	Assess the state of current knowledge on the links between neighborhood environments and cognitive health in older adults	Older adults at risk of dementia	No	Yes

Gan and colleagues [25] reviewed 29 studies and documented methodologies ranging from applications of virtual reality to measurements of statistical association. No use of walkshed methods was reported. The authors also assessed the psychosocial outcomes of outdoor use (eg, increased social agency, anxiety, and promotion of personhood) and built environment characteristics that facilitate use and participation (eg, land use diversity, presence of landmarks, and irregular street grids).

By contrast, Sturge and colleagues [37] focused solely on qualitative studies exploring how social and built environments contribute to the well-being of persons living with dementia at home. Under a theme examining "connection to society and supportive relationships," the authors review 4 key areas of support. These include contact with friends and family, social networks afforded by formal events and professional services, connections available across a host of neighborhood settings (eg, pubs and cafés), and the mixed reactions persons living with dementia can experience when disclosing their diagnosis. A second theme titled "interaction with natural environments and public space" examines supports (eg, parks and sounds of children playing) and barriers (eg, complex street environments and noise from traffic).

Both Peters and colleagues [2] and Akinci and colleagues [21] review (respectively) aspects of walkshed methodology in the context of older adults or older adults and the general public. Neither focused specifically on persons living with dementia. Peters and colleagues [2] distinguish between subjective and

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objective measures and discuss the use of accelerometers, GIS, and field-based audit approaches. They document key aspects related to the use of walkshed methods with older adults. Elements include operational definitions of a neighborhood, walking times or distances used to define a walkshed, and neighborhood attributes associated with walking and other physical activity. Akinci and colleagues [21] similarly report on GIS-based methods for spatial analysis. They report on walkshed buffer types and sizes and 167 different walkability variables across 24 studies of older adults.

The identified 6 studies are each related to the aim of this proposed scoping review. None directly cover the realm we seek to document. In 4 cases, the studies do not review objective walkshed methods. The remaining 2 cases do not focus on persons living with dementia.

Methods

Study Eligibility

The primary objective of this study is to report on research relevant to the use of walkshed methodology. We are specifically interested in walkshed analysis which involves the monitoring and evaluation of barriers and facilitators to walking in a neighborhood setting. Eligible studies will include those that reveal details about how to define a walkshed in a manner that is appropriate to the walking experience of persons living with dementia (eg, walking distance used to define a walkshed). We anticipate that this group of studies may largely involve quantitative, GIS-based case studies. Studies that document criteria and indicators that can be used to identify and track barriers to and facilitators of walking will also be included. We anticipate that the methodologies of these studies will be more diverse, including qualitative, quantitative, mixed methods and review articles.

We will include publications from any date in our initial pool. This may influence the variability of results, such as key definitions. A start date is not included because we anticipate that there will be a limited number of available studies related to walkshed analysis for our focus population. An open-ended start date may also allow us to identify when walkshed analysis emerged in various literatures.

We will not limit eligibility by geographic scope and will include studies from any country or region. Studies from a diverse range of geographic settings will also be eligible. This will include various community environments (eg, urban, suburban, exurban, and rural), but we anticipate that urban and suburban settings will predominate. Due to the composition of the team, eligibility will be limited to studies available in English. Our primary goal is the transfer of knowledge about rigorous methodological techniques within and beyond the academic sphere. As such, only peer-reviewed journal articles will be eligible. For additional details on study inclusion or exclusion, see Textbox 1.

Textbox 1. Summary of the inclusion and exclusion process and the criteria (framed as prompts) used to exclude studies.

Review level

- Level 1: title, abstract, and keyword review
  - Does the study include a focus on geographic areas within a community setting?
  - Does the study include a focus on outdoor spaces?
  - Does the study include a focus on people's use of the community environment by walking or other forms of non-motorized mobility?
- Level 2: full text article review
  - Did the study collect and analyze primary or secondary data following a structured methodological approach?
  - Does the study identify measurable criteria and indicators related to walkability or report on the use of walkshed methods?
  - Does the study specifically focus on environmental use by persons living with dementia or older adults?

Population and Setting

This review will be guided by Arskey and O'Malley's [39] 6-step scoping review process. It will include studies that involve participants recognized to be living with dementia or mild cognitive impairment and who reside in a community setting. Studies that focus on persons living in congregate care-based facilities such as assisted living homes and long-term care homes will be excluded. We expect to find few published studies that explicitly focus on this population in the context of operational aspects of walkshed methodology. As age is the primary risk factor associated with dementia, we will also include studies that focus more broadly on community-dwelling older adults aged 65 years and older [6]. We will track differences in existing evidence between these population groups.

Search Strategy

Our search strategy was developed by a project manager with experience conducting scoping reviews. It involved consultation with a research librarian and the broader research team. The latter consultation involved a workshop that iteratively identified, tested, and respecified search domains and terms. Our search strategy includes a combination of subject headings and title or abstract-focused keyword searching (Textbox 2). These strategies target the intersection of an activity or policy domain (walking), an environmental setting domain (outdoor neighborhood setting), and a population focus domain (persons living with dementia and older adults). We will apply search

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strings to 6 electronic databases known to publish high-quality research around our focus domains (PubMed, Medline, CINAHL, APA PsycINFO, Business Source, and Web of Science). Endnote will be used to manage citations, and DistillerSR (DistilerSR Inc) and Excel (Microsoft Corporation) will be used to manage the inclusion, data extraction, and charting stages of this review.

Textbox 2. Domain areas and search terms to be used in search strings for database searches.

Domain areas and search terms

- Activity or policy - walking, walkshed, walkability, walk, wayfinding, way finding, indicator, criteria, dimension, requirement, experience, audit, measure
- Environmental setting - footpath, greenspace, green space, population density, rural population, neighbourhood characteristics, city planning, communit*, neighbo*rhood*, built environment, urban design*, urban planning, town planning, city planning, building densit*, social densit*, population densit*
- Population focus - dementia, alzheimer*, aged

Article Selection Process

After removing duplicate sources from our initial study pool using DistillerSR, we will use DistillerSR to complete screening at 2 levels. At level 1, we will assess the title, abstract, and keywords of each potential source. This assessment will include 2 independent reviewers using the level 1 inclusion criteria in Textbox 1. Studies will be excluded if both reviewers definitively identify relevant content and answer no to any of the criteria prompts. Studies will be moved to level 2 screening if a prompt cannot be answered definitively. To promote consistency at level 2 article screening, 2 reviewers will assess the full text of all remaining sources. Studies will only be included if reviewers can definitively answer yes to all inclusion prompts. We will address discrepancies at each level at a team meeting that involves a reassessment of the source and a consensus decision made by the team.

Data Charting and Representation

Data charting and representation will follow 2 interrelated steps outlined by Arksey and O'Malley [39]. Common practices in scoping review methodology and existing knowledge syntheses documented above informed the creation of the data charting schema listed below. Using this schema, we will develop a data matrix in Excel. This matrix will organize data and allow for the analysis of key items of information. Following guidance from Levac and colleagues [40], we will review and iteratively update the initial schema shown in Table 2 as the final study pool is examined. A total of 2 reviewers will extract data for a subset of papers (n=5). They will compare and update the schema as they reflect on processes and outcomes. Final data extraction will be completed by a single reviewer.

Table 2. Initial data charting schema for creation of data charting matrix.

Study details	Walkshed methods	Criteria and indicators
Title	Definition of walkability	Measurement domains reported
Lead author	GIS[a] operationalization of walkshed	Measurement criteria reported
Year of publication	Distance or time parameter	Criteria used with persons living with dementia
Journal name	Data sources and types	Criteria used with older adults
Journal discipline (if applicable)	GIS routines (if reported)	Measurement indicators reported
Country of lead author's institution	Population focus	GIS based indicators
Study method	N/A[b]	Data sources for indicator calculation
N/A	N/A	Method for indicator measurement or representation

[a]GIS: Geographic Information System.

[b]N/A: not applicable.

Beyond tracking the breadth (eg, diversity of methods) and location (eg, countries of origin) of literature, descriptive numerical summaries will examine 2 key topics. First, we will document the tools, data, and parameters used to define a walkshed. The review will make a contribution to the existing literature by documenting implementation approaches specific to the context of persons living with dementia. We will also compare these approaches to those used in studies of an older adult population. Second, we will chart criteria and indicators used to measure aspects of dementia-friendly neighborhood and community environments. By documenting indicators that scholars have operationalized using GIS-based analyses, we will make a key contribution to the transfer of the methodology.

The final scoping review will use descriptive results (eg, diversity of methods) represented using a combination of summary tables and figures (eg, Sankey diagrams). Limited textual information will support these visual elements. We will represent comparative results related to criteria and indicators as a larger data matrix. This matrix will visualize how

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researchers have operationalized indicators in GIS for the 2 populations of interest. A longer textual description will contextualize these results. Finally, using thematic analysis, we will convey synthesized themes that capture nuance lacking in the descriptive and comparative results [41-43]. We expect to highlight considerations for the use of walkshed methodology not yet documented in recent studies focused on older adults [2,21]. We also expect to identify where criteria used to assess walkability for persons living with dementia and older adults converge and diverge. The risk of bias will not be assessed. This is consistent with the broad nature of our review question and the norms identified in the development of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [44,45].

Results

The results of the study and the submission of a manuscript for peer review are expected in June 2024.

Discussion

Overview

Scholars from the fields of planning, public health, urban design, gerontology, and architecture have produced a wealth of evidence and guidance related to walkability. Branching out from the "general population," studies increasingly focus on targeted population groups. These foci better recognize the social, cultural, and demographic barriers and enablers to walking that shape one's experience of the neighborhood. The proposed scoping review will synthesize the growing evidence base with specific reference to persons living with dementia. By including relevant studies focused on an older adult population, the review will also identify where current best practice for monitoring and evaluation diverges and converges for these populations. Expected findings include a detailed breakdown of current parameters and routines used to conduct walkshed analysis. Findings will also convey criteria that can be operationalized in GIS as indicators to assess barriers and facilitators to walking in a neighborhood setting.

Studies already identified here have documented monitoring and evaluation methods relevant to walkability for persons living with dementia. Methods include interviews, community survey techniques, and field audits of the neighborhood environment. Our planned focus on GIS-based walkshed analysis will further document a highly scalable monitoring and evaluation tool and technique.

Limitations

The final scoping review will be subject to limitations, despite following accepted methodological practice [39,40]. First, as a scoping review, there will not be a quality assessment of studies, which presents a risk of bias. Second, only English studies will be included, which will overemphasize evidence and practice from western countries. Third, we expect that the use of walkshed analysis for persons living with dementia will be an offshoot of techniques and literature focused on older adults. There may therefore be limited literature specific to persons living with dementia. To mitigate the risk of making assumptions about the transfer of methodological guidance from one population to another, we will explicitly track and compare findings across groups.

Conclusions

As far as we are aware, the proposed scoping review will be the first to provide comprehensive methodological or technical guidance for conducting walkshed analysis specific to persons living with dementia. There are 3 target audiences for this scoping review. These include applied academic researchers in the field of public health, applied academic researchers in the fields of urban planning and design, and evidence-based practitioners across these fields. Scholars identify neighborhood environments as an upstream source of barriers and enablers that shape walking behavior and associated health and well-being cobenefits [12,17,25]. Understanding the individual and population health impacts of neighborhood environments requires the expertise of health researchers and practitioners. Understanding how neighborhood environments came to be and how to reshape them through land-use and built-form interventions requires the expertise of planners and designers. By clearly documenting methods used in walkshed analysis, our goal is to spur increased collaboration across these disciplines to enable an evidence-informed approach to improving neighborhood environments for persons living with dementia.

Acknowledgments

The authors would like to thank the DemSCAPE team for their efforts.

Data Availability

The data generated and analyzed during this study will include content extracted from published, peer-reviewed journal articles. Full details about parameters, data sets, and Geographic Information System routines used in walkshed analysis, as well as a full list of associated indicators, will be reported in the scoping review publication. Additional data generated and analyzed during the study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

GIS: Geographic Information System
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Overview of Retention Strategies for Medical Doctors in Low- and Middle-Income Countries and Their Effectiveness: Protocol for a Scoping Review

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Abstract

Background: The global shortage and maldistribution of health care workers, especially medical doctors, pose a significant threat to achieving the United Nations' sustainable development goal 3 of ensuring well-being and healthy lives for all. Low- and middle-income countries (LMICs) are disproportionately affected by this crisis, with a high rate of brain drain from rural to urban areas, as well as to high-income countries. Various retention strategies have been implemented in different settings and organizations. However, their effectiveness remains underexplored, particularly in LMICs.

Objective: We aim to review the available retention strategies for medical doctors in LMICs and to determine the effectiveness of the various strategies. This review aims to compile relevant research findings on this issue to generate a thorough summary of all the retention strategies practiced in LMICs and, more importantly, to provide the current state of evidence of the effectiveness of these strategies in retaining medical doctors in countries with limited resources and high disease burden.

Methods: The structured framework given by Arksey and O'Malley will serve as the basis for conducting this scoping review. A comprehensive search strategy will be conducted across 4 electronic databases (PubMed, EBSCOHost, Scopus, and ScienceDirect). A systematic approach following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be executed to search, screen, review, and extract data from studies that meet predefined inclusion criteria. Data encompassing bibliographical information, study location, retention strategies, influencing factors, and outcomes (effectiveness) will be obtained from the selected studies using standardized data extraction. Endnote and Microsoft Excel will be used for reference management and removal of duplicate studies. A narrative synthesis will be performed after categorizing and analyzing all the extracted data to identify recurrent themes.

Results: This ongoing review will generate a comprehensive compilation of retention strategies implemented in LMICs to prevent brain drain among medical doctors. Data extraction is currently in progress, and completion is expected by early 2024. Themes regarding the types of strategies, influencing factors, and outcomes will be synthesized. The findings will highlight effective retention strategies, gaps, and challenges in implementation for the benefits of future research. By identifying common barriers and facilitators, this review will provide insights into enhancing the policies and initiatives for doctor retention in LMICs.

Conclusions: This scoping review explores the retention strategies practiced in LMICs and attempts to identify effective strategies from existing research. By evaluating the barriers and challenges that influence the effectiveness of these strategies, policymakers and health care leaders can strive to obtain balanced and optimal health human resources in their respective organizations and countries.

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KEYWORDS

health care workforce; retention strategies; medical doctors; low-income and middle-income countries; scoping review

Introduction

Overview

Optimal functioning of the health care system relies heavily on the quantity and quality of health care workers (HCWs). The ability to enhance health service coverage and ensure that everyone in the population has access to the highest possible level of health relies on the availability, accessibility, acceptability, and quality of the health care workforce [1]. However, in recent years, a critical global challenge has emerged: a crisis characterized by a shortage and maldistribution of HCWs including doctors, nurses, and other professionals. This crisis poses a significant threat to achieving the United Nations Sustainable Development Goal 3 (promoting well-being and ensuring healthy lives for people of all ages) [2]. Nowhere is the impact of this challenge more acute than in low- and middle-income countries (LMICs), where limited financial and human resources compound the challenge of providing essential health care services. LMICs represent various nations in a diverse economic spectrum, encompassing low-income, lower-middle-income, and upper-middle-income countries. On the basis of the World Bank classification [3], low-income economies are defined as those with a gross national income (GNI) per capita of ≤US $1135 in 2022; lower middle-income economies are those with a GNI per capita between US $1136 and US $4465; upper middle-income economies are those with a GNI per capita between US $4466 and US $13,845. In contrast, high-income economies are those with a GNI per capita of ≥US $13,846. Remarkably, this classification encompasses 137 countries, constituting 63% of all nations worldwide [4].

The World Health Organization projected that by 2030, countries, predominantly LMICs, will face a substantial deficit of approximately 18 million health workers [5]. This significant shortage will greatly hamper the capacity to deliver vital health care services to those populations in most significant need. Simultaneously, countries with varied levels of socioeconomic development encounter different challenges in health human resource planning related to employment, deployment, and retention of their workforce [6]. Medical doctors are vital to the health care system because of their expertise, care, and impact. They play a crucial role in ensuring optimal health care delivery within health care institutions [7]. However, many parts of the world are grappling with a shortage of doctors, which stems from various factors such as emigration, imbalanced distribution between rural and urban areas, and shifts in population demographics [5]. There is a global shortage of approximately 2.8 million doctors [5], with LMICs bearing the brunt of this burden [8]. This scarcity is further exacerbated by the phenomenon of brain drain, with doctors from LMICs emigrating to high-income countries (HICs) due to better job offers and career progress. In some HICs, foreign-trained physicians sometimes amount to one-fifth of the total number of doctors in the workforce [9]. The movement of doctors from lower-to higher-income settings has resulted in substantial economic consequences, not solely due to the transfer of human capital, but more importantly, indirect impacts, such as increased morbidity and mortality associated with the loss of doctors [10].

Apart from brain drain to other countries, there is also a high rate of doctors' resignations from the public health care system to join the more lucrative private sector, especially in countries with dual health care financing systems. Job dissatisfaction, including unsatisfactory work environment (lack of facilities, inflexible working hours, poor career progression, lack of professional autonomy, and ineffective management style) and unfavorable service conditions (poor salaries and funding, duplication of activities), are closely associated with high mobility, especially from the public to private sectors [11-13]. The phenomenon of HCWs resigning poses a significant obstacle to the advancement of the health care system in any given country, making it a topic of widespread concern [14]. The increasing number of resignations among HCWs, particularly in the Asia Pacific region, has been reported as the greatest threat to the development and sustainability of a resilient health care system in a recent study [15]. Despite efforts to increase supply and retain them, the workforce is still struggling to meet public health demands, as demonstrated in Spain and Brazil [16]. The same issue was also reported in India, where the vacancy rates were nearly 21% and 42% for medical officers and specialists at health centers, respectively [17].

Addressing the global health workforce crisis requires comprehensive strategies at both national and international levels. Retaining HCWs is a challenge in almost every country, be it HICs such as Canada, Australia, and Scotland or LMICs in Africa and Asia, especially in rural and remote areas [18,19]. Retention encompasses the duration between the initial engagement with a service and the eventual separation or departure from that service. It serves as a metric to gauge the length of time an individual stays within the service [20]. Retention strategies in the context of doctors encompass a range of interventions designed to attract and keep doctors in particular settings, such as remote or rural areas, with a specific focus on LMICs [21-23]. These strategies are aimed at mitigating doctor shortages and ensuring equitable health care access for underserved populations. Policy makers and health care managers must comprehend the factors that influence doctor retention and formulate targeted measures to address these factors [24,25]. Effective retention strategies contribute to the

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stability and continuity of health care delivery, especially in regions with limited accessibility [21,23].

The significance of retention strategies lies in their capacity to yield various benefits, including cost savings, employee engagement, productivity, knowledge retention, competitive advantage, and organizational stability [26]. Addressing doctor shortages requires tailoring retention strategies to the unique challenges and requirements of health care professionals in each country. This is particularly critical in LMICs, where health care systems often contend with fragility, staffing shortages, limited resources, and a higher disease burden [27-29]. Furthermore, these countries grapple with brain drain challenges, issues of health care accessibility, weakened political will, and unstable governmental systems [30-33].

There are many known impediments to the retention of doctors, the most common being unfavorable working conditions, limited opportunities for career advancement, nonappealing financial incentive structures, unsupportive community environments, and the restriction of financial resources [34,35]. Other barriers include inadequate living standards, excessive workloads, insufficient equipment, lack of opportunities for skill enhancement and private practice, and unfair promotion practices [36]. In addition, stress, burnout, and insufficient work-life balance also play a role in doctors' decision to leave [37]. Strategies aimed at addressing these barriers have been proposed and implemented at various levels and organizations, such as providing career development plans, ensuring minimum financial incentives, establishing avenues for private practice, enhancing work conditions, providing opportunities for skill improvement, and implementing transparent and equitable promotion systems.

Objective of Conducting the Scoping Review

Numerous publications have discussed the factors influencing the retention of doctors in LMICs [38-41], providing suggestions for various strategies and initiatives. However, there is limited research evaluating and summarizing the effectiveness of these strategies, particularly in LMICs. Therefore, the objective of this scoping review is to identify and delineate the available retention strategies for medical doctors in LMICs and to determine the effectiveness of these strategies.

To determine if prior research has addressed the same subject, we performed an initial exploratory literature review. Our search revealed the absence of existing or ongoing systematic reviews and scoping reviews related to our specific topic. McClain et al [42] primarily explored retention strategies and barriers concerning nurses, while Noya et al [43] concentrated on the rural and remote medical workforce, and Verma et al [22] focused on primary care doctors in general.

Conversely, our review aims to synthesize research evidence to generate an all-encompassing perspective on the effectiveness of retention strategies for doctors in LMICs. This synthesis will identify gaps in existing literature, pinpointing areas that require additional investigation within the context of doctor retention in resource-constrained countries with high disease burden. Our inclusive methodology considers a broad spectrum of studies and settings and delivers a comprehensive evaluation of these strategies.

Methods

Ethical Considerations

As the methodology for this scoping review solely entails reviewing and collecting data from existing literature without involving human participants, ethical clearance was waived by the Medical Research and Review Committee Malaysia.

Protocol Design

Overview

For this scoping review, we will use the methodological framework introduced by Arksey and O'Malley [44], who structured the review process into 5 stages. In addition, we enhanced the quality and rigor of our review based on the guidelines from the Joanna Briggs Institute Manual [45]. We will also incorporate the recommendations provided by Levac et al [46] to ensure consistency in assessing the studies during this scoping review. Transparent reporting will be ensured by using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [47]. We describe the protocol for this scoping review in five stages:

1. Formulating research questions
2. Identifying relevant studies
3. Selecting eligible studies
4. Charting the data
5. Collating, summarizing, and reporting the results

Stage 1: Formulating Research Questions

Following the recommendations given by Levac et al [46], we set our objective to explore strategies or interventions available for retaining doctors within health care institutions in LMICs and to identify effective measures to prevent doctor attrition. Therefore, we formulated two specific research questions for this review:

1. What are the retention strategies currently being implemented for doctors in LMICs?
2. Which strategies have been identified and evaluated as effective in retaining doctors in LMICs?

Stage 2: Identifying Relevant Studies

A meticulous search strategy plays a vital role in ensuring the inclusion of pertinent studies in scoping reviews. The research team has developed a comprehensive search strategy that encompasses various keywords and their synonyms related to the topic of interest. We selected search terms based on the research questions, including terms such as "retention," "retain," "maintain," "doctor," "physician," and "general practitioner." These terms has been used both individually and in combination following the iterative process inherent in the scoping review methodology.

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The final search string, adhering to Boolean logic, takes the following form: *(retention OR retain OR intention to leave OR intention to stay OR motivation to stay OR willingness to work) AND (doctor OR physician OR specialist OR general practitioner OR medical practitioner) AND (low- and middle-income countries OR LMIC)*. This meticulously designed search string aimed to gather all pertinent materials aligned with the objectives of this scoping review.

Various types of documents were screened during this stage, including journal articles, documents, or regulatory reviews, sourced from each of the 4 databases: PubMed, EBSCOHost, Scopus, and ScienceDirect. These databases were selected for their relevance to health and human resource services. During the screening process, if the available information in the title and abstract is insufficient to make an informed decision, the articles will be included for full-text screening. Adhering to the standard approach for conducting scoping reviews, we will not conduct quality appraisal of the included studies. An example of a preliminary MEDLINE (PubMed) search strategy is presented in Textbox 1.

Textbox 1. Example of MEDLINE (PubMed) search strategy.

- (retention[Title/Abstract] OR retain[Title/Abstract] OR intention to stay[Title/Abstract] OR intention to leave[Title/Abstract] OR motivation to stay[Title/Abstract] OR willingness to work[Title/Abstract]) AND (doctor*[Title/Abstract] OR physician*[Title/Abstract] OR specialist*[Title/Abstract] OR general practitioner*[Title/Abstract] OR general physician*[Title/Abstract] OR medical practitioner*[Title/Abstract]) AND (low- and middle-income country[Title/Abstract] OR low- and middle-income countries[Title/Abstract] OR low-income country[Title/Abstract] OR low-income countries[Title/Abstract] OR lower middle-income country[Title/Abstract] OR lower middle-income countries[Title/Abstract] OR upper middle-income country[Title/Abstract] OR upper middle-income countries[Title/Abstract] OR Afghanistan[Title/Abstract] OR Albania[Title/Abstract] OR Algeria[Title/Abstract] OR American Samoa[Title/Abstract] OR Angola[Title/Abstract] OR Armenia[Title/Abstract] OR Azerbaijan[Title/Abstract] OR 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Stage 3: Selecting Eligible Studies

The review process begins with the team convening to discuss decisions related to study inclusion and exclusion based on the principles of transparency, reproducibility, and rigor. This practice further advances a systematic and unbiased approach throughout the review process. The inclusion and exclusion criteria are presented in Textbox 2. We chose to focus primarily on studies published in English language due to their global prevalence, ensuring a comprehensive analysis, increased accessibility, and reduced language-related biases due to limited translation resources. Furthermore, the focus on studies published in English language streamlines the accessibility and application of research findings, making them readily available and applicable to a broader audience.

To maintain the scientific rigor of this review, we made a deliberate choice to exclude gray literature from our review, such as dissertations, essays, consensus, reports, theses, and government documents. However, while gray literature may provide valuable insights that supplement traditional academic

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literature [48], it presents challenges in terms of systematic search and quality verification [49].

Following the PRISMA-ScR guidelines [47], the first step begins with identifying articles from various databases. Duplicates and irrelevant studies will then be removed. Abstracts or full texts will be evaluated based on predetermined inclusion and exclusion criteria to determine eligible studies. This screening process involves careful examination of both the retrieved search results and their reference lists. To ensure the most relevant search results, we will refine the literature search throughout the review process. At least 2 investigators will independently assess the eligibility of publications by reviewing their titles and abstracts. Publications deemed relevant to this scoping review are obtained in full text and reviewed against the same inclusion criteria.

In cases of disagreement during publication selection, both reviewers will revisit the full-text articles to reach a consensus. If consensus cannot be reached, an impartial third reviewer will be consulted to resolve the disagreement. Consistent meetings and discussions at different stages of the article review process are essential to maintain alignment, address challenges, refine search strategies, ensure consistency, and foster a collaborative and efficient approach. The scoping review will record and report reasons for excluding sources of evidence in the full text that do not meet the inclusion criteria. The reporting of the review will incorporate a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1), which visually presents the screening and selection process [50].

Textbox 2. Inclusion and exclusion criteria of the study selection process.

Inclusion criteria

- Publication year: January 2013 to February 2023
- Language in publication: English
- Research location: low- and middle-income countries (LMICs)
- Target population: medical doctors
- Types of documents: journal articles, documents, or regulatory reviews with proper references

Exclusion criteria

- Publication year: before January 2013 and after February 2023
- Language in publication: other languages
- Research location: other than LMICs
- Target population: other health care professionals
- Types of documents: dissertations, essays, consensus, government documents, reports, and theses that do not have any proper references

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the scoping review process.

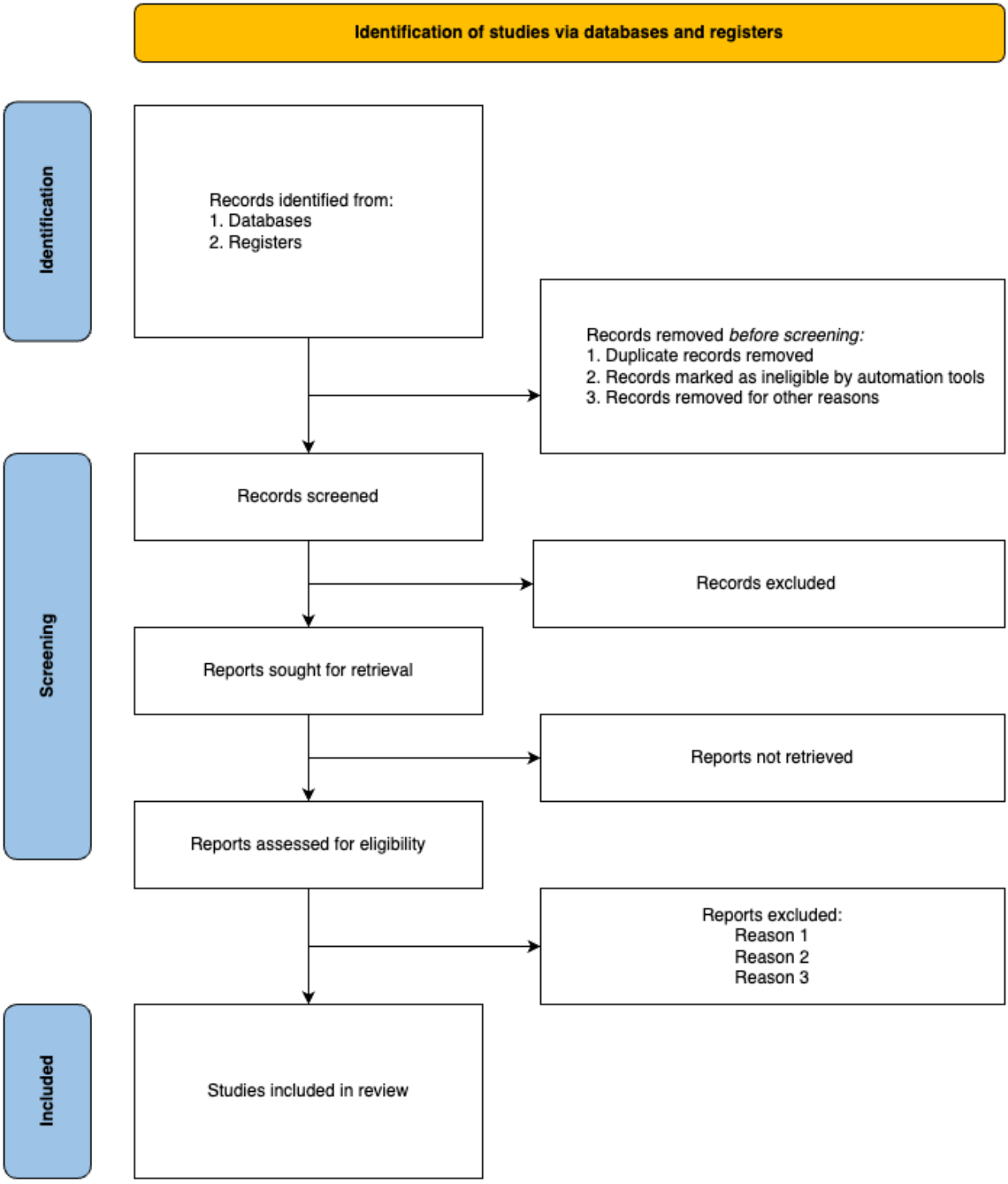

Stage 4: Charting the Data

The data extracted from the full-text articles will be organized into a data extraction table using Microsoft Excel (Microsoft Corporation). The data table will be structured to accommodate the characteristics of the data. The aim of charting the data is to create a descriptive summary of the results to address the objectives of the scoping review and to answer the research questions. This process facilitates the categorization of information before proceeding with further tabulation. For reference, Textbox 3 presents the categories corresponding to each characteristic in the data extraction table. In an iterative process, investigators will continually gather data and keep the data extraction table up-to-date. If significant data are found in records initially not designated for extraction, the data extraction form will be revised, and these additional data will be retrieved from the records already reviewed.

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Textbox 3. Preliminary data extraction table.

Basic characteristics and description

- Bibliographical data
  - First author and year of publication of the article
- Article title
  - A succinct description of the content of the article
- Country
  - Name of the low- and middle-income countries
- Aims or purpose of the study
  - Expresses the intention or aspiration of the research
- Type of study
  - Study design or methodology
  - Which type of study was conducted?
- Study population
  - Physician—specialty or department
  - Number of people involved
  - Inclusion and exclusion criteria of the study
  - Demographic characteristics
  - Other characteristics
- Study location
  - Location characteristics (urban, rural, or remote or hospital or district, state, or area)
  - Institution (name)
- Factors influencing retention
  - Financial or career and professional or working conditions, personal, cultural, or living conditions factors
- Retention strategy
  - Strategy type or focus (education and regulatory or ii. monetary compensation or iii. management, and environment and social support)
  - Strategy name
  - Strategy characteristics, content, and description
  - Strategy implementation (levels, duration, and date)
- Outcomes measure
  - Description of the result (effective or successful to retain)
  - How were the turnover and results assessed?
- Barriers and challenges
  - Barriers and challenges in implementing the strategies
- Study limitations
  - Weaknesses within the research design that may influence the outcomes and conclusions of the research

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Stage 5: Collating, Summarizing, and Reporting the Results

The primary goal of the scoping review is to present the narrative findings of existing literature through an analytical framework or thematic construction, without the requirement to assess the quality or significance of each study. We will use a traditional integrative review approach to compile all the identified materials. Our objective is to identify recurring themes across research and synthesize data from the selected studies. Using these themes as guidelines, we will create a literature map and present it in the form of a table, summarizing the publications and their respective characteristics.

The results of the scoping review will be organized into tables that categorize the characteristics of each publication. Accompanying these results will be narrative summaries that describe how each result relates to our research questions, including any unexpected or particularly notable findings. We will also address any gaps observed in the literature, research needs, and implications for practice. Subsequently, the outcomes of this review will be shared with relevant stakeholders, and their expertise and perspectives will be incorporated.

Results

This review will provide a comprehensive mapping of existing research and literature pertaining to the retention of medical doctors in LMICs to enhance the understanding of the complex dynamics of doctor retention. It will also assess the current knowledge and pinpoint any gaps in the literature, focusing on factors influencing doctor retention and effective retention strategies such as financial incentives, working conditions, career advancement opportunities, and personal motivations.

Furthermore, this review can offer insights into best practices and approaches for retaining doctors in LMICs to guide policy makers and health care administrators who struggle with retention challenges. They can customize the best policy recommendations based on specific needs and obstacles in local settings to improve doctor retention rates in their respective organizations and governments.

The review was initiated in May 2023, and the research protocol was finalized in July 2023. We registered the review with the Malaysian National Medical Research Register (NMRR ID-23-01994-OGW). The search, which was concluded in August 2023, yielded 9141 articles. The PRISMA flow diagram will be used to illustrate the flow of the literature search in this review [50]. The results will be presented using charts and tables, supplemented by a narrative description. Any existing literature gaps will be identified, and the significance of our findings will be emphasized in the subsequent discussion section. The review is expected to be concluded in January 2024, with the outcomes published in a journal for wider dissemination.

Discussion

Overview

Adequate investment in health care capacity is imperative to move toward the United Nations' sustainable development goals, specifically goal 3 (ensuring good health and well-being) and goal 10 (reducing inequalities), and to achieve various global development objectives, with a robust health care workforce being the top priority. Therefore, establishing a comprehensive plan that encompasses effective retention strategies to complement medical education reforms is vital to cultivating a health care environment that is equitable and resilient at both regional and global levels. Our focus on retention strategies for medical doctors is driven by their unique challenges and critical roles in health care. Doctors hold central positions in health care delivery, not only providing medical expertise but also taking a leadership role in influencing critical patient care decision-making, and their turnover can have significant negative impacts on patient care and quality of health care services [51]. Furthermore, doctors are the most affected by the brain drain crisis, especially in LMICs, leading to a significant financial burden and experience loss. Therefore, prioritizing doctor retention is vital for mitigating brain drain, reducing productivity and financial loss, and sustaining effective health care service delivery.

The shortage of doctors in LMICs represents a pressing concern that demands immediate attention and concerted efforts on a global scale, in view of its significant impact on public health. This predicament has a direct adverse effect on the health and welfare of populations residing in LMICs, as doctor shortages can impede access to crucial medical services, ultimately resulting in preventable illnesses and higher mortality rates. Moreover, cross-border brain drain exacerbates existing health care inequalities both within and between countries. Persistent disparities in the accessibility of health care services, if they continue to exist, will disproportionately affect rural and underserved areas with limited resources, thereby perpetuating social and economic inequalities and impeding advancements toward achieving universal health care coverage.

Expected Outcomes

This scoping review will present a comprehensive overview of retention strategies that have been proposed, practiced, and evaluated in LMICs as a response to overcome the challenges faced in retaining medical doctors and preventing brain drain. These strategies may encompass a wide array of approaches, including financial incentives, opportunities for professional development, initiatives to promote work-life balance, and support for career advancement. Moreover, the focus on LMICs may shed light on distinct regional or country-specific challenges and variations in customized strategies. It may also highlight the varied effectiveness of different strategies, depending on the contextual factors at play. It is unlikely to be a one-size-fits-all solution, as certain strategies may exhibit promising outcomes in bolstering medical doctor retention, while others may demonstrate limited impact depending on the local settings.

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In short, this review will present common barriers and facilitators that significantly influence the successful implementation of retention strategies for doctors in LMICs. By exploring the challenges encountered during strategy implementation, we also aim to offer a more comprehensive and nuanced understanding of the factors influencing the effectiveness of doctor retention strategies in LMICs. This, in turn, can contribute to improving the retention of medical doctors in LMICs, aligning with the Sustainable Development Goal 3 goal of promoting well-being and ensuring healthy lives for everyone. Comprehension of these elements has the potential to aid policy makers and health care administrators in developing more relevant interventions and prioritizing effective strategies.

Since it is likely that different contexts play a critical role in the outcomes of various retention strategies, we will also attempt to address this connection in our review. Certain strategies, if proven successful, can also be modified and embedded within a broader health care ecosystem to benefit a wider group of health care professionals. Common factors contributing to brain drain among HCWs include financial rewards, career development, hospital infrastructure, political issues, and family issues [52]. While we focus on the dynamics surrounding medical doctors and the customized retention approach for them in this review, as the challenges faced by doctors may be unique and differ significantly from those of other groups, the comparison and extrapolation of various retention strategies for different health care professionals is a worthy topic for future research or review.

Review Limitations

This review has several limitations that deserve further discussion. First, the language restriction used in the search strategy may have unintentionally excluded relevant studies published in languages other than English. This is a significant concern because many LMICs have diverse linguistic landscapes with numerous languages. The decision to focus primarily on English was necessitated by practical considerations, such as the broader availability and accessibility of English-language research. Furthermore, we believe that the exclusion of non–English-language studies would minimize language-related biases in the review process, given the limited access to translation resources in our setting.

Another limitation of this review is the exclusion of gray literature. This decision is influenced by the difficulties associated with accessing gray literature, which encompasses issues of limited availability, inconsistent indexing, variable accessibility, and challenges in assessing the quality and reliability of information. By excluding gray literature, there is a risk of missing important findings and diverse perspectives not found in peer-reviewed academic sources. Nevertheless, although gray literature can offer valuable insights as a complement to conventional academic literature [48], it introduces difficulties in systematic retrieval and quality assessment [49], thus making it difficult to maintain the scientific rigor of this review.

In addition, this review is likely to include studies with different levels of methodological rigor and quality, and this could potentially affect the overall reliability of its conclusions and may introduce heterogeneity into our analysis. Moreover, this review aims to provide a comprehensive overview of existing literature regarding effective retention strategies for doctors in LMICs; thus, the analysis results are likely to be less in depth compared with systematic reviews that follow a more rigorous and narrowly focused methodology. Nonetheless, this broad approach is valuable for summarizing the diversity of strategies and findings in the field of doctor retention in LMICs, allowing for a holistic understanding of the subject.

Conclusions

This scoping review is fundamental in providing a better understanding of the practical implications of various retention strategies for doctors in LMICs and in drawing valuable lessons from effective strategies in existing literature. Furthermore, by highlighting emerging trends and identifying implementation challenges within LMICs, this review will pave the way for more precisely targeted policies and interventions to strengthen doctor retention in the most needed regions. It also offers valuable guidance to policy makers and health care administrators by showcasing best practices with positive outcomes, thereby refining their approach to addressing attrition and brain drain.

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Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed in this review.

Conflicts of Interest

None declared.

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Abbreviations

GNI: gross national income
HCW: health care worker
HICs: high-income countries
LMICs: low- and middle-income countries
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Virtual Reality for Developing Patient-Facing Communication Skills in Medical and Graduate Education: Protocol for a Scoping Review

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Abstract

Background: Clinician-patient communication is an integral component in providing quality medical care. However, research on clinician-patient communication has shown overall patient discontent with provider communication skills. While virtual reality (VR) is readily used for procedural-based learning in medical education, its potential for teaching patient-facing communication skills remains unexplored. This scoping review aims to evaluate the effectiveness and feasibility of VR applications used for patient-facing communication skills development in medical education.

Objective: The primary objective is to synthesize and evaluate the effectiveness of available VR tools and applications used for patient-facing communication skills development in medical education. The secondary objectives are to (1) assess the feasibility of adapting VR applications to develop patient-facing communication skills in medical education and (2) provide an overview of the challenges associated with adapting VR applications to develop patient-facing communication skills in medical education.

Methods: A total of 4 electronic databases (ERIC, Embase, PubMed, and MEDLINE) were searched for primary peer-reviewed articles published through April 11, 2023. Articles evaluating the implementation of non-, semi-, and fully immersive VR training for patient- or caregiver-facing communication skills training provided to graduate, medical, or other allied health care professions students were included. Studies that assessed augmented reality, mixed reality, artificial intelligence, or VR for non–communication-based training were excluded. Study selection will include a title, abstract, and full-text screening by 4 authors. Data from eligible studies will be extracted and entered into a database and presented in tabular format. Findings will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for scoping reviews.

Results: As of April 11, 2023, the search strategy has been confirmed and the search has been completed. We are currently at the title and abstract screening stage. Once complete, the articles will undergo full-text screening according to eligibility criteria as described in the methods.

Conclusions: The findings of this review will inform the development of a graduate-level clinical skills research course within the Institute of Medical Science graduate department at the University of Toronto. It is also expected that these findings will be of interest to other health care–specific faculties inside and beyond our institution. Further, our scoping review will summarize the limited field of literature on VR use in medical communications training and identify areas for future inquiry.

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KEYWORDS

communication; medical education; patient-facing; scoping review; technology; virtual reality

Introduction

Effective communication skills are crucial for health care professionals to establish trust and build rapport with their patients, facilitate shared decision-making, and deliver high-quality care. Poor communication between clinicians and patients has been associated with decreased health care quality, increased human and economic cost of care, disenrollment from health care plans, poor adherence to recommended treatments, and propensity to sue for medical malpractice [1-4]. Accordingly, American medical colleges [5] and Canadian medical schools [6] have stated that clinician-patient communication is an integral component of quality medical care and highlighted the need for formal training programs at the undergraduate, postgraduate, and continuing education levels. However, research on clinician-patient communication has shown overall patient discontent even when clinicians indicate their own communication to be good or excellent [7]. Although there has been increasing emphasis placed on communication skills training in most health care curricula, significant challenges remain in their implementation and evaluation. These training approaches are often limited in time, resources, personnel, contextualization, unclear frameworks, and teaching strategies [8]. Incorporating educational tools that promote and develop patient-focused communication skills is imperative for the delivery of comprehensive care by health care professionals.

Virtual reality (VR) has emerged as a promising tool that addresses the challenges associated with limited access to health care institutions, personnel, contextualization, and feedback to evaluate frameworks and teaching outcomes. VR is defined as an educational tool that uses computer technology to generate a 3D image or environment with which a user can interact in a seemingly real or physical manner [9]. Presently, VR has been mainly used for training in procedural skills, typically for surgical training, but has been expanding to other applications as well [10]. There are currently 3 main categories of VR: nonimmersive, semi-immersive, and fully immersive. Nonimmersive VR is typically a screen-based display that is connected to handheld mechanical or haptic units [11]. Nonimmersive VR is commonly used to develop technical psychomotor skills, such as those needed in endoscopic surgery [12]. In semi-immersive VR, users use a VR headset and dedicated controllers to interact with a 3D VR, usually spanning 180° [13]. The addition of body sensors provides a fully immersive experience in which a user is placed entirely in a virtual environment, and their awareness of the real world is disconnected [9]. Semi- and fully immersive VR is particularly useful for teaching appropriate responses to stressful scenarios such as mass casualties, emergency surgical procedures, and cardiopulmonary resuscitation [14,15].

VR offers a simulated environment for diverse applications that enable learners to practice various skills with patients and caregivers in a safe and controlled setting without relying on health care facilities or personnel [10]. For example, Izard et al [16] demonstrated the effective use of VR in teaching surgical trainees detailed practical knowledge about surgical procedures. Another study by Birrenbach et al [17] leveraged VR during the COVID-19 pandemic to explore the short- and long-term effectiveness of VR simulation versus traditional learning methods for training health care professionals in hand disinfection, nasopharyngeal swab-taking, and donning or doffing of personal protective equipment [17]. VR technology can also provide learners with immediate feedback on their communication skills, tangible learning outcomes for educators, and allow for the repeated practice of challenging scenarios that may not be possible in real-life clinical settings [11,12]. Zackoff et al [14] used VR to train medical students in managing respiratory distress. The participants reported the VR environment as equal or superior to the perceived effectiveness of other training modalities such as standardized patients and high-fidelity mannequins. The learners also perceived VR as equally effective to standardized patients for communication training [14].

While less researched compared to technical medical skills, the rapid progression of technology has expanded the possibilities of using VR as a training tool targeting communication skills. Immersive first-person VR was found to be successful in teaching effective health dialogues and communication skills. For example, clinicians and postgraduate medical residents who used VR were more confident in and more capable of communicating difficult medical information to patients [18]. Furthermore, undergraduate research students who were trained with VR were better prepared for real-world patient interactions that involved obtaining consent [19]. Overall, VR was able to improve the dialogue performance of students with little to no previous communication training, with students posttraining being able to respond to patient questions in a more accurate and timely manner [19]. In another study, VR allowed participants to replay their experiences to help them recognize and analyze their interactions and emotions to help inform their future communications with patients [20]. Altogether, VR delivers immersion and realism, reflecting real-world scenarios that increase empathetic communication with patients [21-23]. Despite the strong evidence presented in these studies, there is still a lack of consensus on the most effective VR tools and applications for patient-facing communication skills development in medical or health care professional education (referred to as “medical education” hereafter).

Effective communication skills are crucial for health care professionals to deliver high-quality care and establish positive patient-clinician relationships, ultimately improving patient outcomes. The use of VR technology for communication skills training in medical education has the potential to provide learners with a safe and controlled environment to practice challenging scenarios and receive immediate feedback on their

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communication skills. The majority of VR participants agreed that the technology was reflective of real life, strongly suggesting VR as a capable educational tool [21,23]. VR was also a highly rated learning experience and preferred over standard didactic lectures [24,25]. However, the applications of VR for communication skills development in health care professionals remain limited. This scoping review aims to synthesize and evaluate the available evidence on the effectiveness of VR tools and applications for patient-facing communication skills development in medical education and inform educators and health care professionals on the potential benefits and limitations of this technology.

Methods

Approach

To inform our objectives, we will conduct a scoping review following the methodology described by Arksey and O'Malley [26] and Levac and colleagues [27]. As our research aims to describe the application of an emerging tool (VR) in medical education and we intend on applying the findings of the scoping review to the development of a new clinical research skills course, a scoping review is an appropriate approach. While similar in rigor to systematic reviews, a scoping review allows for a preliminary assessment of the size of existing evidence to inform future directions for research priorities by identifying knowledge gaps, usually in an area of ongoing research and knowledge synthesis [28,29].

The scoping review approach encompasses the following six stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) engaging in knowledge translation and stakeholder discussions. We will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [30].

Stage 1: Identifying the Research Question

The objective of this scoping review is to outline and assess the available VR tools and applications used for patient-facing communication skills development within the context of medical education. To meet this objective, we have developed the following research questions:

1. How is VR implemented in a medical education setting to develop patient-facing communication skills?
2. Is VR an effective tool to develop patient-facing communication skills in a medical education context?
3. Is adapting VR tools to develop patient-facing communication skills in medical education feasible?
4. What are the challenges associated with adapting VR tools and applications to develop patient-facing communication skills in medical education?

Stage 2: Identifying Relevant Studies

To inform our study selection, we developed an operational definition of VR, communication, and medical education students.

Operational Definition of VR

We defined VR as a computer-based tool that generates a 3D image or environment that allows the participant to look about and navigate within a seemingly real or physical world [21,31,32]. Key attributes of VR in our definition included the use of (1) 3D imaging, (2) the ability to actively interact with the virtual environment, and (3) visual and auditory feedback that allows the user to feel immersed in the virtual environment [33]. In order to capture the full breadth of VR, our operational definition included nonimmersive (eg, screen-based VR simulators), semi-immersive (ie, immersive VR without physical movement), and fully immersive VR (usually using head-mounted displays and hand-held equipment) [31].

Operational Definition of Communication

We define communication as effectively engaging in conversation and exchanging information with patients, caregivers, or decision-makers regarding a medical condition in simple, clear, and plain language. Within the context of trainees in a medical education setting, effective communication skills include, but are not limited to (1) obtaining informed consent to perform a procedure; (2) engaging in difficult conversations (eg, breaking bad news); (3) collecting personal, sensitive, and confidential patient information in an ethical manner; (4) listening attentively to patient or caregiver concerns to assess the patient's health and condition; (5) maintaining professional relationships with patients and caregivers; and (6) validating and addressing patient or caregiver emotions and concerns [34,35].

Operational Definition of Medical Education Students

For our scoping review, we identified medical education students as any student in a medical or health care profession field. These students included but were not limited to, graduate, medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students that are required to interact directly with patient populations in the delivery of their care and would thus benefit in communications training in their work. All students and trainees that may be included in the circle of care, either directly or indirectly, that communicated with patients were included in our definition of medical education students.

Search Strategy

In collaboration with a health sciences research librarian at the University of Toronto, a member of our team (MS) developed the search strategy to locate published and unpublished studies on PubMed, ERIC, Embase, and MEDLINE databases on April 11, 2023. The search was limited to data that were published from January 2000 to April 2023.

The search strategy explores specific search terms within subject headings, titles, abstracts, and keywords (Textbox 1). The search strategy, including all identified keywords and index terms, was adapted for each database to account for appropriate MeSH (Medical Subject Headings) terms. Textbox 1 shows the search strategy used for each database, with concepts combined with Boolean operators AND and OR. Further potentially relevant studies will be identified by conducting a search of the

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references of included articles and relevant systematic reviews and meta-analyses.

Textbox 1. The search strategy used to obtain studies.

1. computer simulation/ or augmented reality/ or virtual reality/
2. computer-assisted instruction/ or simulation training/ or high fidelity simulation training/ or patient simulation/
3. ((virtual or mixed or augment*) adj3 (realit* or simulation*)).tw,kf.
4. (simulation* adj3 (train or trained or training* or patient* or instruction*)).tw,kf.
5. ((computer* or computational) adj3 (model* or simulation* or assisted instruction)).tw,kf.
6. 1 or 2 or 3 or 4 or 5
7. (class* or postsecondary or educat* or instruct*).tw,kf.
8. 6 and 7
9. ((clinic* or patient or medic* or communicat*) adj2 (skill* or interact* or instruct*)).tw,kf.
10. 8 and 9

Stage 3: Study Selection

Overview

The study selection phase will include the following two screening phases: (1) title and abstract screening and (2) full-text screening. First, 4 authors (NK, KGL, TM, and MS) will screen the titles and abstracts of all eligible studies identified through searching the electronic databases for relevance according to the inclusion and exclusion criteria outlined in Textbox 2. Each title and abstract will be screened by 2 of 4 authors (NK, KGL, TM, and MS), and in order for an article to move past the first screening phase, it must be accepted for inclusion by 2 authors. Disagreements will be resolved through a discussion among at least 3 of the following 4 authors: NK, KGL, TM, and MS. Second, these 4 authors (NK, KGL, TM, and MS) will download and review the full text of all articles passing the first screening phase. Similar to the first screening phase, each article will be reviewed by 2 of 4 authors (NK, KGL, TM, and MS), and in order for an article to move past this screening phase, it must also be accepted for inclusion by 2 authors. Disagreements will be resolved through a discussion among all authors. Screening and study selection will be conducted using the Covidence reference management system.

Textbox 2. Study inclusion and exclusion criteria used during screening.

Inclusion criteria

- Published in a peer-reviewed journal in the English language.
- Participants are graduate medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students receiving patient-facing communication skills training.
- Study evaluates the implementation of nonimmersive, semi-immersive, or fully immersive virtual reality training for patient- or caregiver-facing communication skills training.
- Study reports (quantitatively or qualitatively) the learning outcomes of students, the teaching outcomes of educators, or educators' and learners' perspectives on virtual reality content and delivery.
- Published after 2000.

Exclusion criteria

- Commentaries, editorial notes, systematic reviews, meta-analyses, opinion articles, protocols, dissertations, or book chapters.
- Studies using any form of virtual reality for non–communication-based clinical skills (eg, surgical planning and therapeutic or treatment applications).
- Studies using augmented reality, mixed reality, artificial intelligence, or robotics.
- Studies using manikins for simulation training.

Inclusion Criteria

Only articles published in the English language will be considered for this scoping review. Only articles that are peer-reviewed will be considered in order to ensure that the quality of the articles reviewed is of the highest standard. Articles published only after the year 2000 will be included, as the use of technology in education only became more widespread in the early 2000s. Although most of the literature on VR in medical education was published after 2010, there are relevant articles that were published between 2000 and 2009, as 3 of the 9 studies included in the systematic review by Rourke [36] were published between 2000 and 2009. Similarly, 2 other systematic reviews [37,38] included studies published between

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2000 and 2009. We adhered to the PICO framework to define the populations, interventions, comparisons, outcomes, and study designs eligible for our review. Studies were included if they met the following criteria: studies including undergraduate, graduate, medical students, medical residents, and any health care professional (ie, population); studies assessing either asynchronous or synchronous VR training methodologies specifically designed for the cultivation of clinical skills in medical education (ie, intervention); studies may or may not comprise of a control group of learners who do not receive VR training (ie, comparison); and studies that assess either the learning outcomes, feasibility, efficacy, and impact of the VR technology in relation to clinical skills teaching methodologies (ie, outcomes).

Exclusion Criteria

We aim to further develop a clinical research skills graduate-level course focused on patient-facing communication skills. Therefore, we excluded articles that outline the utility of VR for non–communication-based clinical skills, such as studies using VR to teach surgical procedures, other field-specific medical interventions, combining and administering pharmacotherapy, pain management, and other noncommunication skills or practices. We additionally excluded commentaries, editorials, other reviews and meta-analyses, opinion articles, protocols, dissertations, conference abstracts, and book chapters. Studies in a language other than English were excluded, in addition to studies using non-VR tools to teach clinical communication skills, such as manikins, CD-ROMs, or roleplaying actors. As our aim is to inform the development of a graduate-level clinical research skills course using VR, we restricted our search to only capture VR applications and excluded other forms of experiences, including augmented reality (AR) and mixed reality (MR). While VR allows the user to be fully immersed in the virtual environment, AR and MR supplement and integrate VR with the user's reality [39,40]. As our course intends to use technology to simulate patient-facing scenarios to teach medical communications skills to students, AR and MR were not considered due to the low fidelity of these technologies. Textbox 2 presents a comprehensive overview of our review's inclusion and exclusion criteria.

Stage 4: Charting the Data

Data from studies meeting the inclusion criteria will be extracted and entered into a database created by the study team. Proposed data fields for extraction include: bibliographic information (ie, author, year of publication, and study's PubMed ID), location of publication, reported time frame, type of study, participant population (ie, student field of study, student year of study, and affiliated institution), description of the VR tool (eg, nonimmersive, semi-immersive, and fully immersive), technology used to deliver the VR (eg, computer screen and head-mounted device), reported student experience (eg, satisfaction and ease of use), developer and instructor experience (eg, lessons learned), reported barriers and facilitators to the use of VR (if available), and communication-related outcomes. This developed database will be revised upon piloting the data extraction of 25 articles to ensure that the data relevant to the aforementioned aims are satisfied.

Stage 5: Collating, Summarizing, and Reporting Results

The aim of our scoping review is to synthesize the evidence describing the effectiveness and impact of and lessons learned in the feasibility and implementation of VR applications and tools used for patient-facing communication skills. Accordingly, we will use a narrative-qualitative approach to synthesis. Descriptive data about the included studies (ie, location of study, type of study, and participant population) will be reported. Collated data pertaining to effectiveness, impact, lessons learned, and facilitators and barriers to implementation and use of VR will be organized into key themes, then presented through narratives and tables. The results of the search will be included in the final scoping review and presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. Data will be charted using a structured form and narratively summarized. Additionally, we will identify and report gaps in the available literature. Lastly, the review's findings will be considered within a broader context of research, practice, and educational design implications.

Stage 6: Stakeholder Discussions

The findings from this scoping review will help modify the clinical research skills graduate course that is being developed by the authors for the Institute of Medical Science (IMS) graduate program. The findings will be shared with the IMS Curriculum Committee, and the recommendations from this committee will be reviewed to further develop the course, which will undergo the governance process at the University of Toronto. The IMS would like to offer this course to students from different clinical departments in the future, and having this review include participants who are graduate medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students will help inform course development.

Ethical Considerations

No protocol was registered, and research ethics approval was not sought as all data are publicly available.

Results

As of April 11, 2023, the search strategy has been confirmed, and the search has been completed. After removing duplicates, our search identified 4141 studies eligible for title and abstract screening. Of these studies, 89 were included for full-text screening. Currently, 4 authors (NK, TM, KGL, and MS) are completing the full-text screening. We anticipate that full-text screening will be completed by February 2024. Following this stage, the results of the review will be tabulated, visualized, and summarized descriptively. The target date for manuscript submission is June 2024.

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Discussion

Principal Results

VR is emerging as a promising educational tool in medical education that can address the challenges associated with limited resources, cost, and the provision of immediate feedback. This scoping review aims to synthesize and assess the effectiveness of available VR tools and applications to teach patient-facing communication skills in medical education. In addition, this review will assess the feasibility of implementing VR applications and provide an overview of the challenges and lessons learned in VR application implementation and use in medical education.

Implications and Conclusions

Immediately, the findings of this review will inform the development of a graduate-level VR-based clinical skills research course within the IMS at the University of Toronto, but it is expected that these findings will be of interest to other health care–specific departments within and beyond our institution and will guide future research questions. For example, VR use in medical education has largely focused on technical skills in, for example, anatomy or surgery to date [41,42], with limited literature on VR use in medical communications or professional skills training [10]. Nevertheless, of the scarce literature available on communications and professional skills training in medical education, VR has been shown to foster the development of various competencies, including interprofessional collaboration [43,44], empathy and compassion [45,46], and confidence [47]. Moreover, given the significance of communication as a crucial skill in various medical education specialties, our scoping review holds relevance for educational settings across all medical specialties wherein clinicians and researchers engage with patients and caregivers. Therefore, our scoping review will contribute to this growing field by summarizing the limited field of literature on VR use in medical communications training, informing educators and health care professionals of the potential benefits and limitations of this technology, and identifying areas for future inquiry.

Limitations

Our proposed protocol has potential methodological limitations and limitations related to the current use of VR in medical education. We restricted our search to only include VR applications and excluded AR or MR applications; therefore, our review is not equipped to draw any conclusions regarding AR or MR use in medical communication skills training. Moreover, we only included studies reported in the English language, and therefore we may potentially not entirely capture findings reported in other languages. Additionally, we recognize the current technological and accessibility limitations in the utility of VR within medical education. For example, implementing VR applications requires costly resources, including specialized hardware of high quality and the expertise of trained personnel, which could present technological barriers and create disparities in accessing the technology among academic institutions [48]. From a pedagogical perspective, previous authors have outlined limitations, including decreased face-to-face communication, the need for robust and adequate evaluation procedures that assess real-life skills, and the importance of more research establishing VR as an effective education for clinical and communication skills [49]. However, a comprehensive overview of the limitations of VR is beyond the scope of this protocol and has been the focus of other reviews [48,49].

Conflicts of Interest

None declared.

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Abbreviations

AR: augmented reality
IMS: Institute of Medical Science
MeSH: Medical Subject Headings
MR: mixed reality
PICO: populations, interventions, comparisons, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review
VR: virtual reality

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Protocol

Interactive Narrative–Based Digital Health Interventions for Vaccine Communication: Protocol for a Scoping Review

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Abstract

Background: Interactive narrative–based digital health interventions hold promise for effectively addressing the complex determinants of vaccine hesitancy and promoting effective communication across a wide range of settings and vaccine types. Synthesizing evidence related to the implementation and evaluation of these interventions could offer valuable perspectives for shaping future strategies in vaccine communication. Prior systematic and scoping reviews have examined narrative-based vaccine communication interventions but not the inclusion of interactivity in such interventions.

Objective: The overall objective of the scoping review is to summarize the evidence on the use of interactive narrative–based digital health interventions for vaccine communication. Specific research questions focus on describing the use of interactive narrative–based digital health interventions (RQ1), describing evaluations of the impact of interactive narrative–based digital health interventions on promoting vaccine uptake (RQ2), and factors associated with their implementation (RQ3).

Methods: A detailed search string will be used to search the following databases for records that are relevant to the review questions: PubMed, Embase, Scopus, Web of Science, CINAHL, and PsycINFO. Two reviewers will independently screen the titles and abstracts of identified records against the predefined eligibility criteria. Subsequently, eligible records will undergo comprehensive full-text screening by 2 independent reviewers to assess their relevance to review questions. A data charting tool will be developed and used to extract relevant information from the included articles. The extracted information will be analyzed following the review questions and presented as a narrative summary. Tabular or graphical representations will be used to display review findings, as relevant.

Results: Public health informationists were consulted to develop the detailed search strategy. The final search string comprised terms related to narrative communication, digital health, and vaccines. The search string was customized to each proposed publication database and implemented on April 18, 2023. A total of 4474 unique records were identified using the search strategy and imported into the Covidence (Veritas Health Innovation Ltd) review management software for title and abstract screening. Title and abstract screening of identified records are ongoing as of December 29, 2023.

Conclusions: To our knowledge, this will be the first scoping review to investigate the features of interactive narrative–based digital health interventions and their role in vaccine communication. The goal of this study is to provide a comprehensive overview of the current research landscape and identify prevailing gaps in knowledge. The findings will provide insights for future research and development of novel applications of interactive narrative–based digital health vaccine communication interventions.

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KEYWORDS

narrative; storytelling; digital health; social media; interactive; vaccine; vaccination; vaccine hesitancy; vaccine communication

Introduction

Background

Vaccinations prevent more than 20 infectious diseases and avert 4-5 million deaths across the lifespan globally each year [1]. Yet, global progress on vaccinations has stalled in the last decade because of factors associated with vaccine complacency, convenience, or confidence [2]. These factors can result in vaccine hesitancy, a state of decisional ambivalence that manifests as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" [2]. Vaccine hesitancy is blamed for backslides in vaccination coverage in high-income countries (eg, in Europe and the Americas), where issues with vaccine availability are less of a factor in suboptimal vaccine uptake [3]. Even in non–high-income settings, vaccine hesitancy may be present because of vaccination service interruptions and barriers to vaccine access [4]. The World Health Organization Strategic Advisory Group of Experts on Immunization noted that "vaccine hesitancy is complex and context-specific, varying with time, population, geographical location, and vaccine type" [2]. Passive or sloganized approaches frequently used by vaccination programs are insufficient to address the complexity and variability of the factors underlying vaccine hesitancy [5]. In a systematic review, Jarrett et al [6] found that dialogue-based communication strategies such as those leveraging mass media, social mobilization, and community influencers were effective in addressing vaccine hesitancy, whereas passive strategies such as those using posters and websites had a lower impact. One way to incorporate dialogue-based content may be through the use of narratives. The growth in the use of narratives for vaccine communication in recent years presents an opportunity to further study and innovate on its use to support vaccination uptake.

Narratives are ubiquitous in human society and have been used for persuasive health communication for decades [7,8]. Narrative-based communication strategies may be effective for understanding and addressing the complex determinants of vaccine hesitancy and enabling dialogue-based vaccine communication across varied settings and types of vaccines. The proliferation of digital technologies such as mobile phones has led to rapid and widespread sharing of health-related narratives via digital media (eg, social media platforms). These digital modalities of information communication may permit new ways for individuals to interact with narratives. For instance, interactive narrative–based digital health interventions, such as choose-your-own-adventure games, may offer individuals the chance to make decisions for their characters, influencing the unfolding of divergent paths and outcomes of their journeys [9]. Such interventions show a promising approach to storytelling by fostering self-efficacy that could be leveraged for vaccination promotion [10].

While prior systematic and scoping reviews have examined narrative-based communication for health [11,12], or specifically vaccines [13], the interactivity of narrative-based digital health interventions was not the focus. A synthesis of ways in which interactive narrative–based digital health interventions have been used for vaccine communication can facilitate the development and adaptation of novel applications to support vaccination. The goal of this scoping review is to summarize the evidence on the use of interactive narrative–based digital health interventions for vaccine communication.

Concepts Included in This Review

Overview

The 4 key concepts included in this review are narrative communication, digital health, interactivity, and vaccine communication.

Narrative Communication

For the purposes of this review, we follow Hinyard and Kreuter [7] definition of narratives as: "any cohesive and coherent story with an identifiable beginning, middle, and end that provides information about scene, characters, and conflict; raises unanswered questions or unresolved conflict; and provides resolution."

Narratives may be presented in different ways (eg, entertainment education, case histories, and testimonials) or delivered through different modalities (eg, social media, comics, and plays) [7,8]. The content of narratives may include "official stories that are constructed to tell an innocuous version of events or the position of a group, invented stories that are made up or fictional, firsthand experiential stories, secondhand stories (ie, retelling of someone else's story), and culturally common stories that are generalized and pervasive in a cultural context" [7,14]. For this review, we are interested in describing all elements of narratives used in vaccine communication, including the use of characters, settings, plots, points of view, features, and themes.

Digital Health

Digital health is defined as "the use of information and communications technology in support of health and health-related fields" [15]. The phrase digital health encompasses computer-based (electronic health or "eHealth") and mobile phone–based approaches for communicating health information and delivering health services. It also includes newer information and communication technology domains such as artificial intelligence [15]. Individuals may leverage digital technologies to cultivate social connections and access medical advice, including information on vaccines [10,16]. For this review, we are interested in describing all elements of digital health interventions that deliver narratives on vaccines, including the types of devices, modalities, and specific digital strategies as defined in the World Health Organization classification of digital health interventions [17].

Interactivity

For the purpose of this review, we define the term "interactive" as the active engagement of individuals with the narrative via digital health, aiming to raise awareness, empower behavior

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change, and ultimately lead to improved vaccination outcomes. Interactivity in narrative-based digital health interventions may allow individuals to make sense of stories related to vaccines and vaccination. Interactivity may take various forms depending on the specific narrative, digital medium, or platform being used. For instance, interactive narratives may transcend the boundaries of passive information consumption, empowering individuals to actively shape the narrative's trajectory through decision-making processes (eg, games for health) [9], or individuals may respond to actions and outcomes of the narrative's characters (eg, via likes or comments on posts), or feature in the narratives themselves (eg, as avatars). For this review, we are interested in describing ways in which interaction with narratives has been incorporated via digital health in vaccination communication interventions.

Vaccine Communication

For this review, we describe vaccine communication very broadly as any communication related to vaccines. The purpose of the communication could vary (eg, for mass communication to promote new vaccines, provider-patient communication, to reduce misinformation, counter vaccine hesitancy, or train health workers). Communication about vaccines can involve a wide range of mechanisms including improving knowledge or awareness, shaping attitudes and beliefs, and so forth. We are interested in describing different vaccine communication use cases where interactive narrative–based digital health interventions have been used. We will include all vaccine types and populations targeted for communication. The communication process will be examined for 5 key components: sender, channel, message, receiver, and feedback [18].

Description of the Intervention

We are interested in any digital health interventions that incorporate narratives and interactivity for vaccine communication. We are interested in all types of narrative communication including games for health, entertainment education, storytelling, testimonials, and case histories. The entities delivering the narratives (ie, the messengers) may be formally trained (eg, doctors, public health experts, and researchers), laypersons (eg, community health workers, and peers), organizations, or health systems. The recipients may be persons receiving information on vaccinations or persons providing vaccination services.

The narrative vaccination communication process can take place entirely through a digital medium or via hybrid approaches that have at least 1 digital health component. For instance, in a hybrid approach, a provider may use a digital health aid to communicate vaccination narratives (eg, a narrative vaccination video on a tablet device) but follow up with a discussion (ie, interaction) about the video.

Research Objectives

This scoping review aims to answer the following specific research questions (RQs):

RQ1: How have interactive narrative–based digital health interventions been used for vaccine communication?

RQ2: How have interactive narrative–based digital health interventions been evaluated for promoting vaccine uptake?

RQ3: What implementation factors are associated with the use of interactive narrative–based digital health interventions for vaccine communication?

Methods

Overview

The methods of this scoping review are reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist (Multimedia Appendix 1) [19].

Inclusion Criteria

Due to the hierarchical nature of the research questions, all included articles need to fulfill the inclusion criteria for RQ1. Within this subset of research articles, a subset of articles will also satisfy the inclusion criteria for RQ2 and RQ3.

RQ1: How have interactive narrative–based digital health interventions been used for vaccine communication?

- Studies encompassing any form of vaccine communication irrespective of vaccine type. We will consider studies incorporating vaccine communication alongside other interventions (eg, nutrition)
- Studies using narrative communication where the target audience can engage with the narrative
- Studies where the narrative is delivered via digital health devices (eg, via mobile phones and tablets) and modalities (eg, SMS text messages, applications, and games for health), including hybrid approaches where at least 1 component is delivered digitally
- Studies published as original research articles, presenting empirical findings obtained from data collection efforts.

RQ2: How have interactive narrative–based digital health interventions been evaluated for promoting vaccine uptake?

- Studies that meet the criteria for RQ1
- Studies that have been evaluated for vaccine uptake (eg, whether individuals received a vaccination or not after exposure to the narrative intervention) or vaccination intention.

RQ3: What implementation factors are associated with the use of narrative-based digital health interventions for vaccine communication?

- Studies meeting the criteria for RQ1
- Studies reporting implementation factors (ie, barriers and facilitators) related to the implementation of interactive narrative–based digital health interventions for vaccine communication
- Studies reporting implementation outcomes (eg, feasibility, acceptability, adoption, cost, reach, usability, and sustainability) derived from the evaluation of interactive narrative–based digital health interventions for vaccine communication.

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Exclusion Criteria

We will exclude (1) publications classified as gray literature, protocols, trial registries, editorials, opinion pieces, and systematic and scoping reviews (ie, not an original research article); (2) original research articles for which full text are not available; (3) studies published in languages other than English for which certified translations in English are not available from the original source; (4) for RQ2, studies solely reporting intermediate outcomes related to vaccination knowledge, attitudes, or beliefs without data on vaccination intention or uptake; and (5) for RQ3 specifically, studies lacking empirical data on implementation factors or outcomes.

Search Strategy and Data Extraction

Two public health informationists (ER and HR) were consulted to develop the search strategy. A detailed search string was formulated in PubMed (Textbox 1) using a combination of MeSH (Medical Subject Headings) terms and relevant keywords to cover the domains of narratives, digital health, and vaccine communication.

The following other databases were searched using customized versions of the search string presented in Textbox 1: PubMed, Embase, Scopus, Web of Science, CINAHL, and PsycINFO. Studies that were published since 2010 will be included in the review due to the proliferation of digital storytelling as a tool for health care delivery around that time [20]. The research articles will be limited to English only. Screening and data extraction will be conducted using Covidence review management software as follows:

- Titles and abstracts will be independently reviewed by 2 researchers and records will be sorted as included or excluded for the next stage of review based on consensus voting. Full-text screening of included abstracts and titles will be completed by 2 reviewers, and a similar consensus voting approach will be followed. A third independent researcher will be consulted if the reviewers do not reach a consensus, and the majority vote will apply.
- We will develop and implement a data extraction template in Covidence based on the inclusion criteria, research objective, and RQs. Characteristics of the studies (eg, date, author, research question, and study findings) will be documented using the template by 2 researchers for each included study.

During the data extraction process (Textbox 2), we will focus on gathering the following information from included studies.

Textbox 1. Search string used for identifying relevant records in PubMed.

((“Narration”[Mesh] or Communication[Mesh]) or (narrat*[tw] or storytell*[tw] or story-tell*[tw] or “story telling”[tw] or storyline*[tw] or story[tw] or stories[tw] or conversation*[tw] or testimoni*[tw])) AND ((“Social Media”[Mesh] or “Mobile Applications”[Mesh] or “Smartphone”[Mesh] or “Telemedicine”[Mesh] or “Artificial Intelligence”[Mesh] or “Digital Technology”[Mesh] or “Computers”[Mesh]) or (digital[tw] or app[tw] or apps[tw] or “social media”[tw] or twitter[tw] or facebook[tw] or tiktok[tw] or instagram[tw] or Weibo[tw] or youtube[tw] or telegram[tw] or Whatsapp[tw] or Tumblr[tw] or Pinterest[tw] or snapchat[tw] or wechat[tw] or reddit[tw] or myspace[tw] or computer*[tw] or smartphone*[tw] or chat[tw] or blog*[tw] or game[tw] or gaming[tw] or games[tw] or gamification[tw] or weblog*[tw] or online[tw] or web-based[tw] or electronic[tw] or ehealth[tw] or e-health[tw] or “electronic health”[tw] or mhealth[tw] or m-health[tw] or “mobile health”[tw] or “artificial intelligence”[tw] or ai[tw] or “machine learning”[tw] or “deep learning”[tw] or chatbot[tw] or “chat bot”[tw] or chatgpt[tw])) AND ((“Vaccines”[Mesh] or “Vaccination”[Mesh]) or (vaccin*[tw] or immuniz*[tw] or immunis*[tw] or anti-vax*[tw] or antivax*[tw] or “anti vax”[tw] or anti-vaccin*[tw])) AND (English[Filter]

Textbox 2. Proposed elements of data extraction by review question.

Study information: In a table of included studies, we will summarize study dates, publication information, study setting, participants, study designs, and objectives.

RQ1: We will summarize different elements involved in narrative communication across a range of contexts. Our analysis will include how individuals engage with interactive digital health interventions or modalities, examining the various modes of interaction and their impact on the overall narrative experience. The outcome of the narratives, examining factors such as their congruence with individuals’ personal values, their memorability, perceived realism, and other relevant elements will be described. Theories and frameworks used in the included studies such as Schank and Berman categorization of narratives (official, invented, first-hand experiential, second-hand, and culturally common), or other pertinent theoretical frameworks will be analyzed [14]. Furthermore, we will provide insights into the available evidence by vaccine type, whether the emphasis is solely on vaccination, and whether the vaccines are integrated with other health interventions.

RQ2: All elements described for RQ1, and evidence of impact on the uptake of vaccines, specifically examining whether individuals were vaccinated or not after being exposed to interactive narrative-based digital health interventions for vaccine communication. We will also review studies that have evaluated vaccination intention, which relates to individuals’ expressed willingness or plans to get vaccinated.

RQ3: We will include all elements described in RQ1, along with the implementation outcomes related to the use of narrative-based digital health interventions for vaccine communication. These implementation outcomes include outcomes such as acceptability, adoption, cost, reach, usability, sustainability, and others. Additionally, we aim to identify studies that report on the barriers and facilitators associated with implementing interactive narrative-based digital health interventions for vaccine communication. By examining these factors, we seek to gain a comprehensive understanding of the feasibility and implementation of utilizing such interventions for vaccine communication efforts.

Data Analysis

Review findings will be communicated through a PRISMA (Preferred Reporting Items for Systematic Reviews) flowchart, tables, figures containing descriptive statistics, and narrative summaries corresponding to our research questions. Research findings will be published in a peer-reviewed academic journal and presented in scientific conference presentations in the forthcoming months.

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Ethical Considerations

Since the review used published journal articles exclusively, an ethical board review board was not necessary to conduct this review.

Results

The detailed search string was implemented in the proposed databases searching for publications from inception until April 18, 2023. The search results (n=6836 records) were imported into EndNote Software (version 20; Clarivate) for the removal of duplicate records, and deduplicated records (n=4676) were uploaded to Covidence review management software for eligibility screening. Title and abstract screening is ongoing as of December 29, 2023. We anticipate the scoping review findings to be published in 2024.

Discussion

Principal Findings

Prior systematic and scoping reviews in the realm of vaccine communication have evaluated various interventions such as behavioral nudges [13] and dialogue-based communication interventions [21]. However, none of these reviews have specifically evaluated the effects of interactive narrative–based digital health interventions for vaccine communication. This scoping review aims to identify and synthesize relevant studies that describe interactive narrative–based digital health interventions tailored specifically for vaccine communication. Our primary goal is to synthesize empirical evidence on the ways these interventions are used, implemented, and evaluated and highlight gaps to inform future research and implementation.

Implications for Research and Practice

The study findings may help researchers and public health practitioners understand how interactive narrative–based digital health interventions have been used to promote vaccinations and add context or perspective that may be missing from traditional messaging campaigns [2,5]. The findings from the scoping review may guide the future development of interactive narrative–based digital health interventions for vaccine communication and identify interventions for further evidence synthesis. Additionally, the review may highlight implementation outcomes linked to these interventions or successful components within them. Through a comprehensive synthesis of existing literature, the review may reveal effective strategies, challenges, and gaps in previously developed interventions. Furthermore, the review has the potential to stimulate new research questions or hypotheses aimed at addressing these gaps, thereby contributing to the dynamic landscape of vaccine communication.

Narratives are often exploited in the spread of vaccine misinformation. While the proliferation of digital devices such as mobile phones and tablets has enabled widespread reach of information through communication channels such as social media, they have also helped the spread of misinformation, thereby affecting the public's confidence around vaccination [22]. Hence, review findings may also inform the use of interactive digital health interventions to combat vaccine misinformation.

Strengths and Limitations

The strength of our study lies in its inclusive research approach, encompassing all populations, vaccine types, narratives, and digital health interventions, potentially capturing a diverse array of use cases for interactive narrative–based digital health interventions. However, several potential limitations exist with our approach. First, our reliance on peer-reviewed journal articles might lead us to overlook relevant interventions described in the gray literature. Second, our search strategy does not include the term "interaction," which necessitates researchers' interpretation of interactivity during title and abstract screening. Finally, this being a scoping review, we do not plan to appraise the studies for risk of bias, and our conclusions may have limitations as we are not accounting for potential biases in the included studies.

Conclusions

In this scoping review, we will summarize the use of interactive narrative–based digital health interventions for vaccine communication. To our knowledge, this study will be the first to investigate the interactive features of these interventions and their impact on vaccine communication. Our study aims to illuminate the prevailing gaps in knowledge and provide an overview of the present research landscape. Furthermore, review findings may provide insights for public health practitioners and researchers, laying the groundwork for future studies and applications using interactive narratives for vaccine communication. Review findings may also be of relevance to vaccine communication researchers and global vaccination programs, enabling them to consider novel applications of interactive narrative–based digital health interventions in future initiatives for vaccine communication.

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Conflicts of Interest

None declared.

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Multimedia Appendix 1
Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
[PDF File (Adobe PDF File), 94 KB - resprot_v13i1e51137_app1.pdf]

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Abbreviations

MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RQ: research question

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Protocol

Simultaneous Cardiopulmonary Exercise Testing and Echocardiography for Investigation of Cardiopulmonary Dysfunction in Outpatients: Protocol for a Scoping Review

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Abstract

Background: Cardiopulmonary dysfunction is a complex process with a broad range of etiologies. Investigations performed either at rest or those that only assess the function of a single organ (heart or lungs) are often insufficient. A simultaneous cardiopulmonary exercise test with stress echocardiography is a new approach to assessing cardiopulmonary dysfunction as it provides anatomical and functional imaging simultaneously while under increasing stress. To date, the application of cardiopulmonary exercise test-stress echocardiography (CPET-SE) has been broad and without structure, and its effect on patient outcomes is unclear.

Objective: The objective of this scoping review is to explore and analyze the evidence regarding the role of simultaneous CPET-SE in investigating cardiopulmonary dysfunction in outpatients. It will include any published study in which adult (older than or equal to 18 years of age) patients have completed a CPET-SE for the investigation of cardiopulmonary dysfunction.

Methods: This review will follow the Arksey and O'Malley framework, supported by the Joanna Briggs Institute methodology for scoping reviews. It will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. Data sources will include MEDLINE, Scopus, Embase, and Cochrane (including reviews, trials, and protocols) electronic databases, with no date range defined. The search will be limited to the English language with no restrictions regarding pathology. Secondary references of the included sources will also be assessed by a hand search for suitability. A 2-person title-abstract screen and data charting process will be used. Independent experts will be used for consultation including an academic librarian and clinicians. The Covidence software will be used for article screening.

Results: This scoping review will provide a unified and detailed description of the applications of CPET-SE in investigating cardiopulmonary dysfunction. This will provide a platform for future research harnessing this investigatory method. The results will be presented in both tabular and graphical formats to ensure clarity. The results of this scoping review will be submitted to a relevant peer-reviewed academic journal for publication.

Conclusions: The CPET-SE is a powerful tool for investigating cardiopulmonary dysfunction but remains in its infancy with a patchwork approach to indications, data reporting, and interpretation. This scoping review will unify the literature and provide a platform for future researchers and the development of a comprehensive application guideline.

Trial Registration: Open Science Framework; https://osf.io/98r3e

International Registered Report Identifier (IRRID): PRR1-10.2196/52076

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KEYWORDS

cardiopulmonary; echocardiography; exercise; cardiopulmonary exercise test

Introduction

Cardiopulmonary dysfunction is the loss of the normal bidirectional functional relationship that exists between the heart and the lungs [1,2]. It can range in severity from subclinical (and only manifesting under stress) to fatal, with a timeline that can be acute, chronic, or acute on chronic. Cardiopulmonary dysfunction can be the consequence of single-organ (heart or lung) disease, systemic disease (eg, sepsis) [3,4], or iatrogenic (eg, medications or mechanical ventilation) [5,6].

The investigation of cardiopulmonary dysfunction requires an assessment of the complex heart-lung relationship. The 2 primary interfaces where these organs interact are the right heart-pulmonary circulation relationship (often referred to as "coupling") and the alveolus-pulmonary capillary relationship [7]. Coupling denotes the relationship between the pulsatile pump of the right ventricle and its opposing arterial vascular load (ie, pulmonary arterial circulation) [8]. As one component of this relationship changes (eg, the increase in arterial stiffness seen in aging due to loss of vessel elasticity) [9], the other responds (eg, with ventricular remodeling) to maintain normal coupling, giving optimal cardiac mechanics and cardiopulmonary efficiency at rest [10].

The alveolus-pulmonary capillary relationship has pressure as its currency. In the healthy upright lung, the majority of ventilation and perfusion occurs at the lung base, where both the pulmonary arterial and pulmonary venous pressures exceed the alveolar gas pressure (West zone 3) [11]. This facilitates constant blood flow past the alveolus giving uninterrupted gas exchange—in normal physiological conditions the alveolar pressure does not affect blood flow through the pulmonary circulation [11,12]. Lung hyperinflation can cause compression of the alveolar vessels leading to raised pulmonary vascular pressures, an increase in pulmonary blood transit time, myocardial hypoperfusion, and biventricular systolic dysfunction [13-16]. If there is concurrent right heart dysfunction, there may also be reduced pulmonary vascular blood flow, further worsening this process [15]. Patients with airway disease have a predilection for progressive (dynamic) hyperinflation during exercise, a condition characterized by increasing end-expiratory lung volume. This increase in volume within the fixed thoracic cage leads to an increase in the intra-alveolar pressure, with higher degrees of dynamic hyperinflation related to a poorer cardiac output during the activity [17].

In the outpatient setting, the investigation of cardiopulmonary dysfunction often involves a series of single-organ assessment tools such as computed tomography imaging of the lung, complex lung function testing, and transthoracic echocardiography. These single-organ, static investigations provide little insight into cardiopulmonary performance when under physiological (eg, exercise) or pathological (eg, sepsis) stress [18,19]. Current commonly used functional testing modalities such as stress echocardiography can provide additional information and have a role in the investigation of specific conditions in patients with the appropriate pretest probability—for example, assessing for coronary artery disease in patients with anginal symptoms [5]. However, this test is not capable of assessing the intricacies of cardiopulmonary dysfunction. A cardiopulmonary exercise test (CPET) provides integrative information about cardiac, respiratory, and metabolic responses to exercise and is considered the gold standard in the integrative assessment of cardiorespiratory function [20]. Peak oxygen consumption (VO2peak) measured by CPET is the key measure of cardiopulmonary fitness [21], has a stronger relationship with all-cause mortality than many common chronic diseases [22], and can be improved with low-burden lifestyle interventions [23]. Despite this, CPET also has limitations, most notably that it provides no anatomical information about cardiac function under an increasing workload. As a result, conditions with significant prognostic implications including exercise-induced pulmonary hypertension [24] or exercise-induced diastolic function [25] may go unnoticed.

Recently the combination of cardiopulmonary exercise test-stress echocardiography (CPET-SE) has been used to explore cardiopulmonary dysfunction. Studies have explored the role of CPET-SE in exploring conditions such as dyspnea [26], heart failure [27,28], contractile reserve [29], and left atrial dysfunction [30]. While the application is broad, the indications for this test combination remain undefined, and there is no consensus regarding the optimal protocol for the exercise and imaging components. Similarly, any additional prognostic benefits over traditional testing are undefined.

Given the complexity involved in investigating cardiopulmonary dysfunction, the breadth of applications for CPET-SE, and the lack of standardization for the test, we propose a scoping review to assess the literature surrounding the use of CPET-SE in investigating cardiopulmonary dysfunction in the outpatient setting. This will include an exploration of its impact on shaping the diagnostic and management processes of cardiopulmonary dysfunction. This scoping review will provide shape to the literature regarding this combined testing modality and provide an evidence base for future research.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified.

Methods

Overview

This scoping review will be conducted in accordance with the JBI methodology for scoping reviews [31], based on earlier work from Arksey and O'Malley [32]. It will follow the process of (1) identifying the research question; (2) identifying the

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relevant studies; (3) defining criteria for study inclusion; (4) data charting; (5) collation, summarizing, and reporting of results; and (6) peer feedback [29]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [33] checklist will be followed.

Identification of the Research Question

The primary question of this scoping review is "What is the role of simultaneous cardiopulmonary exercise testing and echocardiography in investigating adult outpatients with symptoms of cardiopulmonary dysfunction?" Associated subquestions for this review are "What are the primary pathologies in which simultaneous cardiopulmonary exercise testing and echocardiography has been used?" and "Is there any evidence that CPET-SE provides additional diagnostic benefit over traditional testing?"

Identification of the Relevant Studies

Overview

The Population, Concept, Context (PCC) framework was used to scaffold the main components of the research question.

Population, Concept, and Context

Population and concept have been combined in this scoping review as they are interlinked, that is, it is inclusive of all patients undergoing this particular combined investigatory modality.

All studies involving patients aged 18 years or older with either known cardiopulmonary disease or symptoms suggestive of cardiopulmonary dysfunction who underwent a simultaneous transthoracic echocardiogram and CPET will be included. There will be no limitations regarding specific disease states or symptom burden.

To best capture the potential breadth of the literature, all studies involving simultaneous echocardiography and cardiopulmonary exercise testing will be included. The minimum data set required for the CPET is continuous gas exchange data, continuous cardiac monitoring, and either a stationary bike or treadmill ergometer. This is in line with accepted clinical practice [34].

The outcomes of interest are the range of contexts in which the combined investigation technique has been applied and the overall assessment of its use in providing clinically relevant information.

Sources

This scoping review will consider the following study designs: randomized and nonrandomized controlled trials, observational studies (retrospective and prospective), and descriptive studies including case series and reports. Systematic reviews that meet the inclusion criteria will also be included.

A hand search of all studies included in the final review will be performed to identify additional literature that may not have been uncovered in the initial database search. Published abstracts and conference proceedings will be considered if they meet the inclusion criteria. Consideration will also be given to grey literature (including expert opinion pieces) if they contain sufficient detail to meet the inclusion criteria. Such data will be identified through discussion with an existing local and international network of experts in the field.

Study or Source of Evidence Selection

All identified citations will be collated via the online software Covidence [35]. EndNote (version 20.3; Clarivate Analytics) will be used as the reference management software. The title and abstract screening will be performed by 2 independent reviewers to determine relevance and suitability using the inclusion criteria.

Studies identified as relevant will undergo full-text assessment by 2 independent reviewers. Appropriate studies will undergo data extraction. Studies deemed inappropriate will have the rationale for such recorded and reported in the scoping review.

Disagreements at either title-abstract or full-text screening will be resolved through the use of a third independent reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [33].

Study Inclusion Criteria

The search strategy will be constructed with assistance from an experienced academic librarian. An initial limited search of MEDLINE and Scopus was performed to identify relevant keywords from titles and abstracts. These index terms were used to develop the complete search strategy for MEDLINE, Scopus, Embase, and the Cochrane Library (including reviews, protocols, and trials; see Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The search strategy deliberately does not reference inpatient or outpatient to ensure that the search results have an appropriate breadth. Only studies published in English will be included. No date restrictions are in place, that is, the databases will be searched from inception to the search date.

Data Charting

Data extraction will be performed by 2 independent reviewers using a customized data extraction tool based on the JBI template [31] (see Multimedia Appendix 2 for the draft data extraction tool). This tool will be piloted using the first 10% of the included full-text studies. After this period the tool will be reevaluated and modified as appropriate to ensure collection of all relevant data. If necessary, this modified (final) data extraction tool will be used for all included full-text studies including the cohort used in the pilot.

Any disagreements with the data charting process will be resolved through discussion, or where necessary, by a third independent reviewer. Where there is missing data, the authors of the original manuscripts will be contacted for additional data or clarification. A critical appraisal of the articles included in the full-text analysis will not be performed.

Result in Collation, Summary, and Reporting

The PRISMA-ScR [33] checklist will be used to guide collation and reporting. The extracted data will be presented predominately in tabular format, in line with the data extraction tool and the review questions of this scoping review (Multimedia

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Appendix 3). It is expected that some data (specifically diagnostic categories and symptom burden) will also be presented diagrammatically to aid clarity. A narrative summary will accompany the tabulated results and will describe how the results relate to the objective and research questions of this scoping review.

Validation, Consultation, and Feedback

Local experts on echocardiography, cardiopulmonary disease, and exercise testing not involved in the authorship of this protocol will be consulted at specific points in this process, including during stages 3 and 5. An academic librarian will be used during stage 2 to ensure the search is thorough and relevant.

Ethical Considerations

Ethics approval has not been sought for this review as data are being collected from published literature.

Results

This scoping review is expected to yield results by late 2023 or early 2024. These results will be presented within the local hospital network by the authorship group to inform current clinical practice and provide an evidence base for future studies using this combined modality. The results of this scoping review will also be presented in article format and submitted for publication in a relevant peer-reviewed journal.

Discussion

Principal Findings

We seek to explore the application and outcomes of a combination of CPET-SE in clinical practice. To the best of our knowledge, this is the first exploratory review on this subject and will be a comprehensive description of the literature.

Advanced functional testing (including CPET) provides data that are more representative of an individual's ability to tolerate a stressor (eg, surgery) or it can induce the symptom (eg, exercise intolerance) of a patient while simultaneously capturing a comprehensive data set for thorough investigation. Combining this with real-time imaging such as echocardiography adds another layer of information [26,27]. Individually there are international guidelines for these tests [20,36,37], but how to best combine them is not clear.

There are significant potential advantages with the CPET-SE; however, the literature appears heterogeneous across testing or acquisition protocols and inconsistent in reporting results making interpretation challenging for clinicians. This scoping review can serve as part of the groundwork required for future guidelines regarding simultaneous CPET-SE.

Strengths of this protocol include the use of a structured, multi-database literature search with few constraints; the use of an established scoping review framework; and the use of independent expert consultation throughout the process.

Limitations

There are 2 primary limitations to this scoping review. The first is the risk of missing relevant studies in the search steps. Multiple databases relevant to medical literature are being included, and the search terms include both whole words and conventional acronyms for CPET, there is a risk that there are additional acronyms or abbreviations used internationally that are unknown to the authors of the scoping review and therefore the literature may be missed. Limiting search results to articles published in English is the second limitation.

Conclusions

The role of exercise testing in clinical practice is expanding, and with this expansion comes novel testing regimens such as CPET-SE. By providing a summary of the application of combined CPET and echocardiography in current practice we will have the base from which a unified, comprehensive, and standardized testing approach can be proposed including indications, testing procedures, and reporting protocols. This will benefit clinicians (by providing an evidence base on which they can structure their testing), researchers (by giving a degree of data homogeneity and allowing more rigorous statistical analysis), and ultimately patients.

Acknowledgments

The authors acknowledge the University of Sydney library staff (Tess Aitken) for their assistance in search planning and preparation. The authors acknowledge the Nepean and Blue Mountains Local Health District, and Nepean Hospital for their support of the project.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 13 KB - resprot_v13i1e52076_app1.docx]

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Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 15 KB - resprot_v13i1e52076_app2.docx]

Multimedia Appendix 3
Data presentation instrument.
[DOCX File , 14 KB - resprot_v13i1e52076_app3.docx]

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Abbreviations

CPET: cardiopulmonary exercise test
CPET-SE: cardiopulmonary exercise test-stress echocardiography
JBI: Joanna Briggs Institute
PCC: Population, Concept, Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Ethical and Quality of Care-Related Challenges of Digital Health Twins in Older Care Settings: Protocol for a Scoping Review

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Abstract

Background: Digital health twins (DHTs) have been evolving with their diverse applications in medicine, specifically in older care settings, with the increasing demands of older adults. DHTs have already contributed to improving the quality of dementia and trauma care, cardiac treatment, and health care services for older individuals. Despite its many benefits, the optimum implementation of DHTs has faced several challenges associated with ethical issues, quality of care, management and leadership, and design considerations in older care settings. Since the need for such care is continuously rising and there is evident potential for DHTs to meet those needs, this review aims to map key concepts to address the gaps in the research knowledge to improve DHT implementation.

Objective: The review aims to compile and synthesize the best available evidence regarding the problems encountered by older adults and care providers associated with the application of DHTs. The synthesis will collate the evidence of the issues associated with quality of care, the ethical implications of DHTs, and the strategies undertaken to overcome those challenges in older care settings.

Methods: The review will follow the Joanna Briggs Institute (JBI) methodology. The published studies will be searched through CINAHL, MEDLINE, JBI, and Web of Science, and the unpublished studies through Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. Studies published in English from 2002 will be considered. This review will include studies of older individuals (aged 65 years or older) undergoing care delivery associated with DHTs and their respective care providers. The concept will include the application of the technology, and the context will involve studies based on the older care setting. A broad scope of evidence, including quantitative, qualitative, text and opinion studies, will be considered. A total of 2 independent reviewers will screen the titles and abstracts and then review the full text. Data will be extracted from the included studies using a data extraction tool developed for this study.

Results: The results will be presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews) flow diagram. A draft charting table will be developed as a data extraction tool. The results will be presented as a “map” of the data in a logical, diagrammatic, or tabular form in a descriptive format.

Conclusions: The evidence synthesis is expected to uncover the shreds of evidence required to address the ethical and care quality-related challenges associated with applying DHTs. A synthesis of various strategies used to overcome identified challenges will provide more prospects for adopting them elsewhere and create a resource allocation model for older individuals.

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KEYWORDS

accessibility; data security; effectiveness; equality; health equity; patient safety; right to privacy; social care

Introduction

Overview

Digital health twins (DHTs), defined as digital representations (digital twins) of patients (physical twins), are an emerging technology aimed at meeting some of the above challenges. DHTs are generated from multimodal patient data, population data, and real-time updates on patient and environmental variables [1]. The field of a digital twin, particularly in health care, has been evolving by using machine learning data aggregated from various patients through modeling the conditions and attributes of a particular patient [2].

The application of digital twins in health and medicine is diverse; for example, DHTs have been used in intensive care units for critical care [3], treatment of patients with trauma [4], and cardiac treatment [5]. Precision health or personalized care for primary prevention with DHTs for older adults has emerged to address the need to mitigate these significant resources and reinforcements. This can allow for collecting data that enables more individually tailored interventions, both to promote and prevent, diagnose, and treat—interventions with greater precision [6].

Moreover, digital twins have widely been used in older care settings, for example, care homes [7] or for older individuals in different settings, such as hospitals [8]. The evidence suggests that the application of DHTs in dementia is broad, such as detecting the signs of dementia [8], assessing the risks associated with Alzheimer disease–related dementia [9], and supporting better dementia care [10]. DHTs have also been found to improve health care services for older individuals by providing real-time supervision and accurate crisis warning [11] and to improve the efficiency and accessibility of medical services for older individuals [12].

With the increase in life expectancy, older adults are growing in the United Kingdom and around the world and are expected to live longer with multiple disabilities and diseases [13]. Around 19% of the population in the United Kingdom is aged 65 years or older, many of whom require health and social care services to enable them to live longer and have a better quality of life [14]. This number is expected to grow by a further 77% (from 1.4 million to 2.4 million) for older adults by 2040 [15]. While this demographic shift makes older adults the major users of health and care resources [16], it places an unprecedented strain on the workforce of the social care sector [17].

Health and social care for older adults is a complex sociotechnical system that undergoes continuous change [18]. Over the last 3 decades, quality of care has progressively been on the agenda because the care delivery can itself harm patients [19,20], either by providing less than optimal care [21] or by things going wrong with its delivery [22,23]. Whenever a new technology or technological innovation is introduced to improve the quality of care, such as efficiency and effectiveness, new and often unforeseen issues emerge that require attention and awareness [18,21,24]. Thus, new challenges arise continuously, which need resetting priorities for other dimensions of quality of care [18], such as patient safety [25] and health equity [26]. This new technology, that is, the implementation of DHT, is no exception, which can even cause technical [27], ethical [26,27], legal [27,28], and societal challenges [27].

The challenges associated with management and leadership include a lack of discussions, cooperation, negotiations, and agreement among various health and social care providers while new routines are being adopted [6,29]. Design considerations concerning big data-related problems involve data visualization, data availability and accessibility, data integration and interoperability into clinical workflow [10], and privacy and security across the entire system [6,10]. Issues involving the quality of care in terms of DHT implementation are safety, equity, and appropriateness [10,26,28]. Some of the ethical challenges regarding the application of DHTs include autonomy, informed consent, the right to privacy, and surveillance health care [26].

The UK Government's Plan for Tech and Digital Economy desires an expansion of the United Kingdom's existing expertise in deep foundational technologies, including digital twins and artificial intelligence [30]. This has been supported by the Government's Plan for Digital Health and Social Care to expedite technology adoption [31], while the UK Research and Innovation (UKRI) inaugurated a funding scheme to establish a multidisciplinary research community in digital twinning [32]. The UKRI's initiative focuses on addressing aspects of ethics, human interaction, environmental sustainability and security, and resilience [32], while NHS (National Health Service) England emphasizes the digital transformation of adult social care—the need for personalized care [33].

In order to shape this review, we will focus on older individuals and consider the following dimensions for the quality of care: safety, equity, effectiveness, and accessibility. Conducting a scoping review for the care of older adults is the most ideal and reliable approach to illuminate the current issues associated with DHTs. There is a need for mapping the key concepts to address questions beyond those associated with the experience and effectiveness of this intervention due to DHT's evolving applications in older care settings [34]. Our proposed review is in line with the vision of the NHS and the UKRI to understand the challenges faced by health and social care professionals, older adults, and their relatives concerning DHT used in personalized care for older adults. Therefore, the review results can readily be accepted, with more prospects of being adopted elsewhere and meeting today's societal challenges—creating a model for gathering individualized data, disease prevention, monitoring, and resource allocation for older adults.

A preliminary search of Campbell systematic reviews, the Cochrane Database of Systematic Reviews, PROSPERO

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(International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted; however, no current or underway systematic reviews or scoping reviews on the topic were identified.

Aim and Review Questions

The primary purpose of this scoping review is to compile and synthesize the best available evidence regarding the challenges of DHT encountered in older care settings. This review is believed to uncover the shreds of evidence that will require diligent attention to address the ethical challenges and the challenges concerning the quality of care associated with the application of DHT. Moreover, this study will identify the strategies that have been used to overcome those challenges in older care settings. Therefore, there is a need for new knowledge through evidence synthesis using existing knowledge to be put to good use.

Specifically, the review questions are as follows:

1. What problems are faced by older individuals (their family and relatives) and health and social care providers associated with the application of DHTs in older care settings?
2. What are the documented issues related to the quality of care for older adults, such as safety, equity, effectiveness, and accessibility, concerning DHTs?
3. What are the ethical challenges concerning the application of DHTs in older care settings?
4. What strategies have been evaluated and implemented in older care settings that address the challenges associated with DHTs?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [35].

Search Strategy

Databases will be searched for both published and unpublished studies. The approach to searching for studies for a scoping review will follow the standard 3-step method (Table 1). The first step will be an initial limited search of a selection of relevant databases, followed by an analysis of text words in the title and abstract and the index terms used to describe the article. The search for published studies will include a 2-way search strategy. One is to search the journal and reference databases, such as CINAHL, MEDLINE, JBI, and Web of Science. Another is to search article-based (journal) databases, such as the ACM digital library, IEEE Xplore, and BMJ Journals. The search for unpublished studies will include Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. A second search using all identified keywords and index terms will then be undertaken across all included databases. Additional search strategies, that is, citation search—specific researcher or article (eg, gold-standard article), and chain search—review reference list of the systematically selected articles will be included to complement the search for published and unpublished papers. Studies, such as reviews (systematic, scoping, and umbrella) and letters to editors, will be excluded. Any studies that lack ethical concerns will also be excluded. Studies published in English will be considered. Studies published from 2002 (when the concept of “digital twin” was first coined by Dr Michael in 2002) [36] onward will be considered for inclusion in this review.

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Table 1. Search strategy on databases.

Participant, concept, and context scheme	#	Search string	Hits on MEDLINE (July 18)	Hits on CINAHL (July 18), n	Hits on APA PsycInfo (July 18), n	Hits on Web of Science (July 18), n	Hits on Scopus (July 19), n	Hits on WorldCat (July 20), n	Hits on JBI[a] (July 20), n
Digital health twin in older care settings	1	"digital health twin*" OR "digital twin*" OR "digital phenotype" OR "digital shadow" OR "virtual patient*" OR "personalised health model*" OR "digital patient model" OR "in silico patient*"	6,404,833	639	2982	11,763	17,051	36,108	2
Digital health twin in older care settings	2	older OR aged OR elderly OR senior* OR elder OR "old person*" OR "older person*" OR "old people" OR "older adult*" OR "older people" OR geriatric*	2457	1,251,839	829,113	5,690,683	6,817,585	31,208,688	1773
	3	# 1 AND #2	204	46	21	449	327	1682	0
Health care setting	4	health* OR hospital* OR care* OR caring OR nursing OR treatment OR aid OR management OR therapy	18,297,577	5,152,991	2,786,771	21,428,220	23,457,440	5180	2837
Combined	5	#3 AND #4	189	43	19	308	250	1384	0
Filters	6	#3 + English, from 2002 onward (exc meeting abstract, editorial material and book chapters.	197	45	21	428	309	8	0
Filters	7	#5 + English, from 2002 onward (exc meeting abstract, editorial material and book chapters.	184	43	19	300	237	4	0

[a]JBI: Joanna Briggs Institute.

Eligibility Criteria

Overview

This scoping review will include the following PCC mnemonics—population, concept, and context. These mnemonics will be used as a guide (not a policy); therefore, the inclusion criteria of this systematic review will include a detailed description of types of participants, concepts, and context, as well as search strategies, data extraction, charting, analysis, and presenting the results. The eligibility criteria are listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Review articles
- Conference paper
- Gray literature
- Early access
- English
- Studies involving older individuals associated with a digital health twin (DHT), regardless of gender, age, ethnicity, socioeconomic status, disorders, or disability.
- Studies that include paid or unpaid carers, whether they are family members or friends.
- Studies that include care providers involved in older care settings and DHTs, whether they are licensed or unlicensed.
- Studies that evaluate and discuss the process and application of DHTs involving caregivers, older individuals, or family, friends, or relatives.
- Studies from 2002 through 2023.
- Studies that specifically evaluate and discuss the process and application of DHTs in settings such as geriatric wards of primary health care, hospitals or clinics, nursing homes, care homes, and home care facilities for older individuals.

Exclusion criteria

- Meeting abstracts
- Editorial materials
- Book chapters
- All other languages
- Studies that do not involve older individuals or care providers associated with DHTs in older care settings.
- Studies that do not focus on the application of DHTs or are not directly related to older care settings.
- Studies from 2001 and earlier.
- Studies not in the context of older care settings.
- Studies where DHTs are not used.

Participants

This review will include studies of older individuals (aged 65 years or older) undergoing care delivery associated with DHTs, irrespective of gender and diversity, including age, ethnicity, socioeconomic status, disorders, and disability. Studies that focus on caregivers (family and friends—paid or unpaid) and care providers (licensed or unlicensed) involved in the care of older adults in relation to DHTs will also be included.

Concept

In this scoping review, the key concept is the process and application of DHTs. Studies that evaluate the application of DHTs involving older care providers, older individuals, family, friends, or relatives will be considered.

Context

The systematic review will consider studies that are based in the older care settings associated with DHTs, such as geriatric wards of primary health care, hospitals or clinics, old-age homes, nursing homes, care homes, and home care facilities for older individuals.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies, for inclusion.

Qualitative studies that focus on qualitative data, including but not limited to designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research, will also be considered.

Text and opinion papers regarding the benefits and challenges of DHT and strategies to overcome the challenges posed by DHTs will also be considered as a scoping review that includes a broad scope of evidence.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 20; Clarivate Analytics),

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and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment and Review of Information [37]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer or reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [38].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 or more independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions.

A draft charting table will be developed as a data extraction tool. The charting table will be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer or reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Results

The results will be presented as a “map” of the data extracted from the included papers in a logical, diagrammatic, or tabular (as necessary) form and in a descriptive format that aligns with the objective and scope of the review. Some critical information that the charting table will include is (but is not limited to): year of publication, country of origin for the study, aims, study population and sample size, methodology or methods, type of intervention or comparator, duration of the intervention, and type of outcomes and how they were measured (if applicable). A clear explanation for each category will be provided, accompanied by a narrative summary describing how the results relate to the review objective and questions.

This scoping review protocol was first developed by the principal author as part of a postdoctoral fellowship at Linnaeus University in February 2022. Later, the protocol was refined and continued as part of research development at the University of Bradford by the lead author, who has been undertaking a full search since July 2023. We expect the analysis to be completed by January 2024 and the final scoping review manuscript to be submitted by April 2024.

Discussion

Overview

The world’s population is getting older—aging brings with it complicated and multiple challenges such as poorer mobility, balance, sight or hearing, dementia, diabetes, and an increased risk of injuries [39]. With the trend of increasing older adults, it is estimated that almost 1 in 6 adults must work in care by 2038 to meet the demand for older adults in home care alone. This is a hard target to meet, given the current shortfalls in the workforce available in social care sectors, which became more apparent during the COVID-19 pandemic [17]. Not to mention the lack of incentive in many countries to take such jobs. Since technology is seen as a means to address the shortage of care workers by health and social care policy makers [13], we believe that DHTs have the capability of addressing the demand for the care of older adults and compensating for the shortage of care workers.

A recent rapid literature review of studies of DHT for managing health care systems identified 17 studies, concluding that DHT can contribute to safety management, information management, health management and well-being promotion, and health care operational control [40]. With appropriate implementation, DHT helps treat patients as virtualized standalone assets [41], improve patient treatment and diagnostics [6], and improve the quality of life overall [42].

The current concept of DHT is diverse as it is still a new and emerging domain, particularly in older care settings [7-10,34], with the aim of improving the quality of care by increasing efficiency [43]. New definitions, concepts, and dimensions in regard to DHT may be identified in this review that may have the potential to help in furthering the design, development, implementation, and evaluation process of DHT. We believe that the evidence synthesis will help us design a larger implementation project, that is, assembling unique and existing technologies to create a new digital twin platform for older care settings.

Since DHTs are expensive and sometimes may not be readily available to older adults to a large extent [44], this study will assess the different circumstances and needs of older adults. This study will ensure appropriate resources and solutions are allocated to needy individuals, covering aspects of equity, and closing the gap in health inequality. The benefits of DHT will help us understand informed decision-making in older care settings.

Limitations

The findings of the review need to be treated with caution since our search is restricted in terms of language and publication period. To overcome these limitations, a comprehensive strategy, that is, a standard 3-step method, will be followed, such as the inclusion of gray literature, which may provide additional insights into the review findings. There may also be a possibility pertaining to the findings in terms of the limited number of included studies, which may further add a layer of bias to the

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selected studies. The evidence-based practice center methods guide proposed by the Agency for Healthcare Research and Quality will be followed to minimize the risk of bias in individual studies [45].

To ensure the systematic scoping review generates generalizable findings, discussions with older adults, their relatives, and the relevant public will be held to support the interpretation of the findings and dissemination of the review.

Conclusions

No current or ongoing systematic reviews or scoping reviews on the topic were identified. This review will uncover the shreds of evidence requiring diligent attention to address the ethical challenges and the challenges concerning the quality of care associated with the application of DHT. Additionally, this study will identify the strategies that have been used to overcome those identified challenges in older care settings, providing more prospects for adopting them elsewhere and creating a model of resource allocation for older individuals.

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Data Availability

All data generated during this study will be included in the original review article (and its supplementary information files).

Conflicts of Interest

None declared.

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Abbreviations

DHT: digital health twin
JBI: Joanna Briggs Institute
NHS: National Health Service
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews
UKRI: UK Research and Innovation

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Protocol

Professional-Facing Digital Health Solutions for the Care of Patients With Chronic Pain: Protocol for a Systematic Scoping Review

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Abstract

Background: Chronic pain is a highly prevalent condition and one of the most common reasons why people seek health care. As a result, chronic pain has a significant personal and economic burden. The COVID-19 pandemic has aggravated the situation for patients with chronic pain through increased risk factors (eg, anxiety or depression) as well as decreased access to health care. Digital health solutions to support people with chronic pain are becoming increasingly popular. Most of the research has focused on patient-facing digital health solutions, although it is clear that the involvement of health and care professionals is crucial in chronic pain care. Certainly, digital health solutions intended for the use of health and care professionals in the care of patients with chronic pain (ie, professional facing) exist, for example, for clinical decision support; however, no review has investigated the studies reporting these interventions.

Objective: The overall aim of this scoping review is to identify the available professional-facing digital health solutions for the purpose of chronic pain management. The objectives of this review are to investigate the components, target populations, and user settings of the available professional-facing digital solutions; health and care professionals' perspectives on using digital health solutions (if reported); the methods in which the digital health solutions are developed; and the outcomes of using professional-facing digital health solutions.

Methods: Databases including MEDLINE, Embase, CINAHL, PsycInfo, and Inspec will be searched for studies reporting professional-facing digital health solutions for chronic pain care, using a comprehensive search strategy developed for each of the specific databases. A total of 2 independent reviewers will screen the titles and abstracts for review inclusion and then conduct full-text screening. Any conflicts in study inclusion will be resolved by a third reviewer at each stage of the screening process. Following data extraction and quality assessment, a qualitative content analysis of the results will be conducted. This review will identify the available professional-facing digital health solutions for chronic pain management. The results of this review are likely to be heterogeneous in terms of content (ie, the digital solutions will serve a variety of purposes, settings, target populations, etc) and methods (ie, experimental and nonexperimental designs).

Results: The review is expected to finish in March 2024 and published in the summer of 2024.

Conclusions: This protocol outlines the need for a scoping review to identify professional-facing digital health solutions for the management of chronic pain. Results from this review will contribute to the growing field of research into the utility of digital health for chronic pain management.

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KEYWORDS

burden; chronic pain; clinician; digital health solution; digital health; digital solutions; eHealth; healthcare professional; mHealth; pain management; patient-facing; risk factor

Introduction

Overview

Chronic pain is a highly prevalent condition, estimated to be affecting 20% to 30% of people worldwide [1,2]. Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" [2]. Although there is some debate on the length of time an individual must experience pain for it to transition from "acute" to "chronic," the *International Classification of Diseases, 11th Revision* defines chronic pain as pain lasting ≥3 months [3]. Chronic pain can also be further categorized into primary (no evident cause); secondary (as a result of an underlying condition); or in some cases, both [4,5].

Various approaches to chronic pain treatment exist, including pharmacological interventions (ie, analgesic medication from paracetamol to opioids) and nonpharmacological interventions (eg, physical therapy and psychological therapy such as cognitive behavioral therapy) [6]. The treatment of chronic pain can be extremely complex; mismanagement can lead to significant issues, for example, opioid dependency [7]. Working toward providing appropriate and effective treatment for patients with chronic pain is crucial to reducing the issues surrounding the mismanagement of chronic pain.

Pain is one of the most common reasons why people seek health care [1]. Due to the prevalence of the condition and its consequent impact on health care, chronic pain has a significant economic burden [1,8] with the estimated costs to the economy reaching billions in the United Kingdom [9,10] and other countries within Europe [11]. Furthermore, during the COVID-19 pandemic, health care resources were diverted from chronic pain management toward more emergency, COVID-19–related conditions [12]. The pandemic has exacerbated the challenges that patients with chronic pain may face; for example, social isolation and lockdown have led to reduced access to health care as well as increased anxiety or depression and reduced mobility, all of which are factors that may aggravate chronic pain symptoms [13-15]. Certainly, the pandemic has led to a reconsideration of traditional health care methods and has highlighted the importance of being flexible with novel methods of health care delivery [13,16]. There is a clear need for new innovations in chronic pain management [17] as a result of its economic burden, which has been further aggravated by the issues presented by the pandemic.

Digital health solutions may provide a unique opportunity to mitigate these challenges to chronic pain management cost-effectively [8,12]. There has been a recent rise in the number of digital solutions available for chronic pain management [14], such as applications for patient self-management [18] and digitally delivered physical therapy [19]. There is variation in the nomenclature of "digital health," with definitions continuing to evolve [20]. Although there is no universally accepted definition for "digital health," digital health refers to all digital, electronic, and computer technologies to improve health [21]; it is used synonymously with "eHealth" in much of the literature [21]. Indeed, terms such as "digital health," "eHealth," "mobile health (mHealth)," and "telemedicine or telehealth" have been used interchangeably [21]. The components of digital health are broad and may include mobile apps (mHealth), web applications, wearable technology, artificial intelligence, analytics, and telemedicine [20]. Digital solutions within health care provide many benefits, specifically to chronic pain management; they offer access to remote care and reduce the impact in some areas of health care service provision, for example, staff shortages and lack of resources [22]. It may also help in reducing waiting lists for care [23]. Now more than ever, this is important due to the challenges that health care systems face.

Previous reviews have focused on digital solutions for chronic pain [24-26] and for specific chronic pain conditions such as osteoarthritis and lower back pain [22,27]. Such reviews have focused particularly on the effect of digital solutions on patient outcomes, with many of the included interventions being patient-facing for the purpose of self-management. The results of these reviews show that digital solutions have a positive impact on patients with chronic pain, on outcomes such as pain intensity, quality of life, coping skills, and adherence to exercise [22,24-27].

There has been an emphasis on health and care professional involvement and contact as an important facilitator in the adoption of digital health solutions, as collaboration with key stakeholders and end-user groups is essential for the development of sustainable and usable systems [28]. Despite this, many digital solutions are developed and implemented without the involvement of health and care professionals [27]. Much of the literature also highlights the importance of multidisciplinary professional involvement in general chronic pain care [2,29,30]. Primary care clinicians are particularly essential in the process of chronic pain management [5,30]. Chronic pain management must go beyond self-management alone (through purely patient-facing solutions) and also involve multidisciplinary health and care professionals [2,5,29,30].

Previous studies on the perspectives of health and care professionals have also highlighted the potential of digital solutions as a useful tool for health and care professionals, that is, for education, patient-follow ups, etc [23]. Digital solutions targeting education for professionals may be particularly useful for chronic pain management, as negative attitudes and a lack of clinician knowledge are significant barriers to chronic pain care [31]. National guidelines state that it is essential for health and care professionals to have the best possible resources and support to manage patients with chronic pain [5], which could be facilitated by digital health solutions. Indeed, there are existing professional-facing digital solutions for the management of chronic pain, such as clinical decision support tools [32]. It is clear that there is a utility to digital health solutions for health

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and care professionals (ie, to provide education and other resources that adhere to guidelines for care) and that such applications exist; however, to our knowledge, no previous reviews have investigated the available professional-facing digital solutions for chronic pain.

Thus, the objective of this scoping review is to investigate the professional-facing digital solutions available for the management of chronic pain conditions.

Review Question

This scoping review aims to answer the question: What research-based digital health solutions, specifically designed for the use of health and care professionals, are available for the management of chronic pain?

Therefore, the objectives of this scoping review are to investigate the following:

1. The components of existing professional-facing digital solutions for the management of chronic pain: (1) what are the user features, (2) what data do they collect, (3) are they integrated into larger systems or stand-alone (eg, within a system involving a patient-facing application), (4) security or privacy considerations, (5) target populations, and (6) settings (eg, pharmacy, hospital, or multisite adoption)
2. The frameworks and methods with which the digital solutions were designed and developed.
3. The outcomes measured and the effectiveness of the digital solutions, that is, implementation success and clinical effectiveness
4. Health and care professionals' perceptions of the usability and usefulness of digital solutions in the management of chronic pain (if reported)

Methods

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews [33] and will be reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [34].

Eligibility Criteria

The population, concept, and context (PCC) will be used to guide the assessment of studies for review inclusion.

Inclusion Criteria

Population

Studies will be included if the reported digital health solutions' intended user demographic is health and care professionals directly involved in the care of patients (aged 18 years or older) with chronic pain. "Health and care professional" will refer to any professional who provides a health and care service, including, but not limited to, nurses, pharmacists, general practitioners, physiotherapists, other therapists, psychologists, and social care professionals. There will be no restrictions on the type of health and care profession of the participants.

Concept

The concept of interest for this review is digital health solutions (including, but not limited to, eHealth, mHealth, telehealth, web-based interventions, etc) intended to assist health and care professionals in the diagnosis and management of chronic pain. Any chronic pain-specific digital health solutions that are specifically designed for the end user to be health and care professionals will be considered in this review; therefore, the included solutions are likely to be heterogeneous in aim, user features, and functionality. This may include those intended for clinical decision support, education, remote patient monitoring, etc. Solutions may include mobile apps, web-based applications, or any other tools provided digitally.

Digital health solutions for the management of all types of chronic pain conditions will be considered, including chronic primary pain (eg, fibromyalgia, complex regional pain syndrome, and chronic primary headache), chronic secondary pain (eg, osteoarthritis and chronic pain secondary to cancer), or both [4,5]. Digital health solutions must be chronic pain specific, that is, for the management of a diagnosed chronic pain condition, with pain defined as "chronic" and lasting 3 or more months.

Context

There will be no restrictions on the context of this review. Contexts may include research and clinical settings, that is, any environment in which health and care professionals may be involved in the management of patients with chronic pain. Settings will likely include primary, secondary, and tertiary care settings (eg, pharmacies, general practitioners, and hospitals) and community settings (eg, residential facilities and the patient's home).

Exclusion Criteria

Studies reporting digital health solutions intended for use by patients only (eg, for self-management purposes) without a professional-facing component will be excluded. Studies will also be excluded if the digital health solution is not specifically intended for the management of a chronic pain condition (eg, studies reporting communication between health care professionals and patients through telephone or videoconferencing [Zoom, Zoom Video Communications; Microsoft Teams, Microsoft Corporation; etc] only, without specific digital chronic pain support, or studies reporting management of chronic pain using a digital health solution designed for general health care, that is, electronic health records). Digital health solutions will not be considered if they support the care of acute or nonchronic pain, for example, nonspecific low back pain. Studies reporting digital health solutions for nonadult patients (<18 years old) with chronic pain will also be excluded. Other exclusion criteria include gray literature and studies not written in the English language.

Types of Sources

This scoping review will consider all types of study designs. This may include experimental studies on the effectiveness of professional-facing digital solutions for the management of chronic pain (eg, randomized controlled trials, before and after sequential design, etc) or nonexperimental studies on the

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development of digital solutions (eg, qualitative studies involving interviews). If only the abstract is available for a relevant study, the author will be contacted for further study information.

Search Strategy

A comprehensive search strategy will be developed using subject headings specific to databases MEDLINE, Embase, CINAHL, PsycInfo, and Inspec (Multimedia Appendix 1). The search strategy will comprise three categories relevant to the PCC inclusion criteria: terms relating to (1) chronic pain (concept of interest), (2) digital health (concept of interest), and (3) health and care professionals (population). There will be no terms in the search strategy limiting the context, as there will be no restrictions on setting. Search terms used for chronic pain will be developed using terms used in the National Institute for Health and Care Excellence guidelines for the management of chronic pain [4]. Keywords and index terms from previous relevant literature will be used to form search terms for all categories within the search strategy. The search strategies will be reviewed by an academic librarian to gain assistance on database-specific guidelines and to ensure the searches capture as many papers fitting the eligibility criteria as possible. Backward-citation searches will also be conducted by reviewing the references of the included studies for relevant articles. Researchers and experts in the field will be contacted to inquire about studies that fit the inclusion criteria.

Study or Source of Evidence Selection

Following the search and after removing duplicates, titles and abstracts will be screened by 2 independent reviewers against the inclusion criteria, with any disagreements resolved through discussion with a third independent reviewer. Full texts of potential studies fitting the inclusion criteria will then be reviewed again, in detail, by 2 independent reviewers. Reasons for exclusion will be recorded at the full-text reviewing stage and reported in the scoping review. Any disagreements that may arise at this stage will be resolved through discussion with a third independent reviewer. Screening and full-text review will be conducted on Covidence (Veritas Health Innovation Ltd).

Data Extraction

Data will be extracted from the studies fitting the inclusion criteria by 2 independent reviewers using a data extraction tool developed for the purpose of this review (Multimedia Appendix 2). The data extraction tool will be developed from the Template for Intervention Description and Replication checklist [35], which focuses on the digital solution components, that is, the rationale of the intervention, user features, procedures, etc. Additional information specific to the review aims will also be collected, for example, participant demographic information and perspectives of health and care professional users (if reported). Data extraction will first be piloted by the 2 reviewers by extracting the data from 10% of the studies fitting the inclusion criteria together through discussion.

As the included studies are likely to be diverse in design (due to no restrictions being imposed on the type of source), quality assessment will be conducted using Quality Assessment for Diverse Studies [36]. Although it is not essential to conduct a quality assessment in a scoping review [33], ascertaining the overall quality of the studies included in this review will be beneficial, as the literature suggests research in digital health for chronic pain is of low quality [37].

Data Analysis and Presentation

This scoping review will aim to conduct a qualitative content analysis of the results, that is, code the features of the digital health solutions used by the included studies into overall categories using NVivo (Lumivero, QSR International). If the results of the review are too heterogeneous for this, a narrative synthesis of the features of the digital health tools will be conducted. No analyses will be conducted to ascertain the overall effectiveness of professional-facing digital health solutions (as this is out of the scope of a scoping review). However, we will report the effectiveness of the individual digital health solutions as reported by each of the included studies in a narrative summary.

Expected Results

This scoping review will identify the available professional-facing digital health solutions for the management of chronic pain, their components, user settings, and target populations; professionals' perspectives on the use of digital health solutions; the methods in which the professional-facing digital health solutions are developed (ie, co-design framework used); and the outcomes of professional-facing digital health solutions. It is expected that the included studies will report on a variety of professional-facing digital health solutions. This may include systems for clinical decision support, symptom management, patient follow up, and educational tools. The outcomes of individual professional-facing digital solutions are also expected to be varied; they will likely have differing measures of effectiveness.

The types of studies fitting the inclusion criteria will most likely be heterogeneous in their methodology, as no restrictions have been imposed on design. Some included studies may report the early stages of developing the professional-facing digital solution (eg, nonexperimental studies such as those using interviews, surveys, and focus groups), while others may report on the effectiveness of the professional-facing digital solution (eg, experimental studies like randomized controlled trials). It is difficult to predict the quality assessment of these studies, at this stage.

The qualitative content analysis of the results will help to answer the review questions, that is, what are the user features, what data do they collect, are they integrated into larger systems or stand-alone, and what are their target population and user settings? If the included studies report on health and care professionals' perspectives, for example, through interviews or surveys, qualitative analysis will also provide information on the health and care professionals' perspectives on using professional-facing digital solutions.

Results

The scoping review is expected to be finished by March 2024 and the first search will be implemented in July 2023. The

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results of the scoping review are expected to be published by the summer of 2024.

Discussion

Overview

To the best of our knowledge, this will be the first scoping review of professional-facing digital health solutions for the management of chronic pain. As we move further into a more digital age, there is a growing need for research into digital health and chronic pain care. This has been further emphasized by the challenges to care presented by the pandemic.

This scoping review will provide a foundation for further research into digital health solutions to make chronic pain care more efficient and innovative, from a health and care professional perspective. Results from this review will contribute to knowledge on the available professional-facing digital health solutions (including their components, user settings, target populations, development, and the perspectives of professionals on the use of such systems), as well as the gaps in the research on digital health solutions targeted toward health and care professionals (for example, areas of care that are not covered). As this is a scoping review, no conclusions can be drawn on the overall effectiveness of the professional-facing digital solutions, only the outcomes of the individual digital solutions as reported by the included studies.

We intend to conduct a qualitative content analysis to synthesize the results of this review. However, it is difficult to ascertain the method by which the included studies will report their findings (most likely extremely heterogeneous, given the broad inclusion criteria). Therefore, it may only be possible to conduct a narrative synthesis of the features of the professional-facing digital health solutions for chronic pain management. Either method of synthesizing the results of this review will produce valuable information on practices in chronic pain care and contribute knowledge to the field of digital health research.

Patient-Facing Versus Professional-Facing Digital Health Solutions for Chronic Pain Management

Although previous reviews have not focused on digital health solutions intended for use by health and care professionals, the literature supports the effectiveness of digital health solutions for the management of chronic pain. Recent systematic reviews suggest that mHealth interventions for chronic pain have a positive effect on patient outcomes (eg, pain intensity, quality of life, and functional ability) [25,26]. However, the literature also suggests that the quality of studies on digital health solutions for chronic pain is subpar, with Moreno-Ligero and colleagues [25] reporting “medium” quality for the majority of their included studies. This further highlights the need for a quality assessment to be conducted in this scoping review, to ascertain the quality of the studies on professional-facing digital solutions for chronic pain management.

Similarly, previous studies reporting on health and care professionals’ perspectives have focused on patient-facing digital health solutions for chronic pain management, that is, self-management interventions. Varsi and colleagues [23] emphasized the need for a comprehensive treatment approach to chronic pain care of which digital health solutions could provide if factors such as health care provider involvement, timely support, and follow up are also considered. Professional-facing digital health solutions may be one of the ways in which the latter factors could be incorporated into a more comprehensive system for managing chronic pain. Additionally, health and care professional involvement is required, not only in the use of digital health solutions but also in their development; many studies reporting digital health solutions for chronic pain management were designed without stakeholder involvement [23] and developed without using co-design methods or any form of user evaluation. This is also particularly essential for professional-facing digital health solutions and will be addressed in this review.

Strengths and Limitations

A significant strength of this scoping review is the systematic method of conducting the searches. A specialized academic librarian will aid in the development of comprehensive and individualized search strategies (Multimedia Appendix 1). Search terms will be formulated using specific subject headings for each database (eg, Medical Subject Headings for MEDLINE) as well as keywords taken from previous similar reviews. Search terms to describe chronic pain will be developed from terms used in the National Institute for Health and Care Excellence guidelines for the management of chronic pain [4]. A total of 2 blinded reviewers will independently complete all steps of the reviewing process, and a third reviewer will resolve any disagreements. Due to this systematic process, this review is likely to include most of the relevant studies that fit the inclusion criteria. Furthermore, this scoping review will follow the Joanna Briggs Institute scoping review manual as well as the PRISMA-ScR checklist.

The findings of this review will be limited to those published in the English language; therefore, there is a possibility that some professional-facing digital health solutions developed and reported in non-English–speaking countries will be missed by this review. It is important to consider that, as guidelines for chronic pain care and digital health differ between countries, jurisdiction of development and implementation may be a significant factor in the type of digital health solutions reported in this review. Furthermore, as some digital health solutions are developed commercially and do not have an academic foundation, the search of academic databases (without a market review, eg, app store search) may not have captured all professional-facing digital health solutions for chronic pain management. However, the quality of digital health solutions is largely dependent on their scientific foundation, which is facilitated by academic development, and nonevidence-based professional digital health solutions are not likely to be useful or realistically implemented in clinical chronic pain care settings. In order to find all available digital health solutions, it would be useful to communicate with health and care professionals currently involved in chronic pain care. Future studies may benefit from conducting interviews with health and care professionals to ascertain what digital health solutions are currently implemented in clinical settings and the benefits or

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drawbacks of such systems in the care of patients with chronic pain.

Conclusion

This protocol outlines the need for a scoping review to identify professional-facing digital health solutions for the management of chronic pain. The results of this review will highlight the available digital health solutions available for health and care professionals to use specifically for chronic pain care and provide information regarding the system's components, user settings, specific target populations, and development. This scoping review will be systematically conducted to ensure most of the relevant literature is included; however, some professional-facing digital health solutions may be missed if they are developed commercially (without academic publication) or not reported in the English language. Findings from this review will contribute to the ever-growing field of digital health research and provide further information on how digital health can improve chronic pain care.

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Data Availability

Data sharing is not applicable to this article as it is a protocol and no data sets have been generated or analyzed yet.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies.
[DOCX File , 24 KB - resprot_v13i1e51311_app1.docx]

Multimedia Appendix 2
Data extraction template.
[DOCX File , 26 KB - resprot_v13i1e51311_app2.docx]

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Abbreviations

mHealth: mobile health
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Data Visualization Support for Tumor Boards and Clinical Oncology: Protocol for a Scoping Review

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Abstract

Background: Complex and expanding data sets in clinical oncology applications require flexible and interactive visualization of patient data to provide the maximum amount of information to physicians and other medical practitioners. Interdisciplinary tumor conferences in particular profit from customized tools to integrate, link, and visualize relevant data from all professions involved.

Objective: The scoping review proposed in this protocol aims to identify and present currently available data visualization tools for tumor boards and related areas. The objective of the review will be to provide not only an overview of digital tools currently used in tumor board settings, but also the data included, the respective visualization solutions, and their integration into hospital processes.

Methods: The planned scoping review process is based on the Arksey and O'Malley scoping study framework. The following electronic databases will be searched for articles published in English: PubMed, Web of Knowledge, and SCOPUS. Eligible articles will first undergo a deduplication step, followed by the screening of titles and abstracts. Second, a full-text screening will be used to reach the final decision about article selection. At least 2 reviewers will independently screen titles, abstracts, and full-text reports. Conflicting inclusion decisions will be resolved by a third reviewer. The remaining literature will be analyzed using a data extraction template proposed in this protocol. The template includes a variety of meta information as well as specific questions aiming to answer the research question: "What are the key features of data visualization solutions used in molecular and organ tumor boards, and how are these elements integrated and used within the clinical setting?" The findings will be compiled, charted, and presented as specified in the scoping study framework. Data for included tools may be supplemented with additional manual literature searches. The entire review process will be documented in alignment with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart.

Results: The results of this scoping review will be reported per the expanded PRISMA-ScR guidelines. A preliminary search using PubMed, Web of Knowledge, and Scopus resulted in 1320 articles after deduplication that will be included in the further review process. We expect the results to be published during the second quarter of 2024.

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Conclusions: Visualization is a key process in leveraging a data set's potentially available information and enabling its use in an interdisciplinary setting. The scoping review described in this protocol aims to present the status quo of visualization solutions for tumor board and clinical oncology applications and their integration into hospital processes.

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KEYWORDS

clinical oncology; tumor board; cancer conference; multidisciplinary; visualization; software; tool; scoping review; tumor; malignant; benign; data sets; oncology; interactive visualization; data; patient; patients; physicians; medical practitioners; medical practitioner; conference

Introduction

Multidisciplinary team interventions, and especially tumor boards (or multidisciplinary cancer conferences [MCCs]) have been shown to significantly improve the quality of cancer care [1-3]. Complex, multimodal, and ever-growing data sets in multidisciplinary settings present special challenges when it comes to data visualization [4]. These data sets can include anything from demographic information and laboratory results to tumor imaging, pharmacotherapeutic timelines, and genomics data, providing limitless opportunities for aggregation and joint visualization. The need for digital support and customized visualization solutions becomes especially apparent when discussing the time constraints often found in clinical oncology settings. Available time frames for treatment decisions might range between 10 and 20 minutes per patient [5], highlighting the importance of aggregated and annotated data to enable participating health care professionals to include all relevant information in the decision-making process. However, even without taking limited time into account, the growing complexity of patient data makes it difficult to fully understand a patient's health status without the support of visualization, even more so when multiple points of data on the patient journey are available [6,7]. While tools for the visualization of multimodal data in the described settings exist [8-10], there is no current overview of actively used and established visualization tools and their key differences, especially on an international level.

The rise of molecular tumor boards (MTBs) has been an additional driving factor in the development of digital support applications for interdisciplinary settings and the incorporation of multimodal data. Combining ordinary clinical information with the complexity of genomics data required special tooling to enable oncologists to make fully informed treatment decisions and limit the time necessary for the MTBs' preparation [11,12]. Virtual MTBs and rising numbers of outpatient referrals lead to a heterogeneous pool of tumor board participants and increase the need for intuitive visualization. Complex patient journeys have to be presented in a condensed and clear manner, sometimes crossing language barriers, without prior knowledge of the patient or their history [12,13]. This led to the emergence of software solutions such as cBioPortal (Memorial Sloan Kettering Cancer Center) [14-16], The Cancer Core Europe Molecular Tumor Board Portal [17], and AMBAR [18], offering complex visualization of genomic variants found in cancer samples.

Additionally, knowledge bases such as OncoKB [19] or CIViC [20] have been created, providing access to annotations with aggregated and structured information on available targeted therapies. The usage of these established tools not only supports the preparation and execution of MTBs but also increases the consistency of therapy recommendations between molecular tumor conferences, even for patients with rare cancers and mutation patterns [21]. Research indicates that differing processes and tools may lead to inconsistent therapy recommendations [22].

To enable the visualization of data for the preparation and execution of MCCs, patient and supplementary data must be made available to the tools used. This is challenging as the availability of interfaces or APIs for the import of data sets can vary greatly and is often only possible through the use of proprietary data formats, which may require the development of extract, transform, and load processes to automate data import and export [23]. Additionally, data privacy regulations and ethical concerns may limit the usage of external services. Several German initiatives and consortiums (eg, Medical Informatic Initiative [24], Bavarian Center for Cancer Research [25], and German Network for Personalized Medicine [26]) are working on standardized data sets and processes related to the cancer patient journey in German hospitals. This includes software extensions for established tools such as cBioPortal, for example, covering the documentation and visualization of therapy decisions in MTBs [27,28].

In summary, there is an increasing need for additional visualization in the context of tumor board settings to leverage the full potential of growing data sets for patient care and therapy decisions. Integrating these software solutions into clinical processes is a challenging task, requiring data from a variety of sources to be readily available to facilitate their use in the preparation and execution of tumor boards. With this in mind, the objective of the proposed scoping review is to identify available software support for MCCs described in scientific literature, gather key aspects of applied visualization strategies as well as their integration into existing processes, and present them in a comprehensive overview.

Methods

Design

For conducting this scoping review study, we will use the scoping study framework of Arksey and O'Malley [29] as a methodological blueprint for this review.

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Arksey and O'Malley describe a five-stage model for scoping study design: (1) identification of the research questions; (2) identification of relevant studies; (3) study selection; (4) data extraction and charting; and (5) collating, summarizing, and reporting the results. Any subsequent deviations of the final report from the scoping review protocol will be highlighted and explained in the scoping review report.

Stage 1: Identification of the Research Questions

While there has been a continuous development of digital support tools for clinical oncology settings over the last few years, currently no structured overview of the visualization tools and techniques used in these applications exists. The core research question driving the scoping review was proposed based on these circumstances, and further developed through multiple iterations of discussion in the research team:

> *Research question: What are the key features of data visualization solutions used in molecular and organ tumor boards, and how are these elements integrated and used within the clinical setting?*

Starting from this overarching research question, specific questions we wanted to answer while extracting data from relevant literature were developed. These were used at a later step to design the data extraction template. They were the following: (1) What data visualization solution is being used? (2) What kind of data are being visualized? (3) How do they visualize the available data? (4) How are these elements integrated and used within the clinical setting? (5) How accessible are the solutions? (6) Are the solutions already being used in hospitals? (7) Have the proposed or implemented solutions been evaluated?

Stage 2: Identification of Relevant Studies

Core Concepts and Keywords

To find relevant studies and gain an insight into the search domain an initial manual literature search was executed. In total, 19 key papers were identified and used to extract concepts for the development of a search strategy. All in all, we were able to identify 3 core concepts that relevant literature would have to encompass. First, tumor boards or similar settings as the target domain. Second, software or some other form of digitalized support. Lastly, the described mode of support delivered by the software, for example, visualization, usage as a decision support system, or personalized medicine.

In the following process, these concepts were used to define keywords for the development of individual search strategies for the chosen databases (Textbox 1). The initial manual literature search showed that relevant literature can be found in a variety of different contexts. Supporting applications for tumor boards may be described in publications covering the development of those tools, their integration into hospital processes, evaluations of their efficacy, or even as a sidenote in the medical literature. As such some of the keywords may seem out of scope at first glance but lead to the inclusion of additional relevant results. MTBs present one of the driving institutions for the development of multimodal and interactive visualization solutions for clinical oncology settings and as such provide a variety of keywords to the search strategy.

Textbox 1. Concepts and corresponding keywords.

Target domain

- Tumor board, tumor conference, molecular tumor board, mutation database, and cancer genomics.

Software

- Virtual, digital, software, tool, platform, and portal.

Mode of support

- Visualization, interactive, preparation, usability, clinical decision support system, personalized medicine, and precision medicine.

Query Construction

Using the defined concepts and corresponding keywords, search strategies for the different databases were built. The general strategy for this process was connecting concepts through "AND" operators, while keywords were connected by "OR" operators. The search was limited to title and abstract where possible since this proved to consistently recall key literature and articles of interest while greatly reducing the amount of out-of-scope search results. The queries were adapted to the specific database needs, for example, the usage of Medical Subject Heading Terms for PubMed. The resulting queries were tested on their recall of key literature and accuracy. They underwent an iterative optimization process based on their performance and in a last step were validated by a librarian. The proposed queries can be found in Multimedia Appendix 1. All future deviations will be documented and discussed in the final publication.

Stage 3: Study Selection

Inclusion and Exclusion Criteria

Only articles published in English during the last 10 years will be included. Since our initial search showed a very broad range of target literature types, we decided not to use further inclusion or exclusion criteria to include all potentially relevant articles.

Selection Process

All literature found by applying the search strategies to PubMed [30], Web of Knowledge [31], and SCOPUS [32] will be exported into a compatible format and uploaded to Rayyan (Rayyan) [33], which will be used for the 2-step study selection process. In the first step, title-abstract screening will be

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performed to quickly exclude out-of-scope literature, reducing the workload for the full-text screening stage. Each paper will be screened by at least 2 reviewers. An additional reviewer will solve conflicting inclusion decisions. During the second screening phase, full-text screening will be performed to exclude results that will not assist in answering the research question described in Stage 1. To increase consistency, criteria for the inclusion and exclusion of literature during the screening process will be supplied to all participating researchers and discussed in a meeting before the start of the screening. The study selection process will be documented using Rayyan. The results of this process will be compiled into a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [34] flowchart.

Stage 4: Data Extraction and Charting

All selected literature will be searched for metadata and information relevant to answering the proposed research question. For a standardized approach between reviewing parties, a data extraction template (Table 1) was developed, encompassing all required metadata, as well as specifics regarding each aspect of the overarching research question. The data extraction template was designed in a close fashion to templates from similar review projects [35,36] as their authors were consulted during the development process of this protocol. Potential modifications to the template will be documented, properly highlighted, and discussed in the final publication.

Table 1. The data extraction tool template.

Data and item	Description
Metadata	
Title[a]	Title
Citation details[a]	Author (first), journal, and DOI
Year of publication[a]	Year of publication
Publication type[a]	Type of publication
Institute[a]	Corresponding institute
Funding source	Funding source of the publication
Objective[a]	Publication objective
Methods[a]	Short description of the methodology used
Summary result[a]	Short description of the results
Conclusion	Short description of the conclusion
Keywords	Keywords
Citations	List of articles citing this paper
Results related to the research question	
What data visualization solutions are being used?	Name and description of the applications or tools that are being used
What kind of data are being visualized?	List and description of the data that is being visualized. Name and a short description of the corresponding standardized or harmonized data set if applicable
How do they visualize the available data?	List and description of the modes of visualization applied, including interactive features such as filtering or customization
How are these elements integrated and used within the clinical setting?	Description of the integration into the clinical setting if available, covering the process integration as well as software interfaces and capabilities for the documentation of tumor boards, if available
How accessible are the solutions?	Accessibility of the software, for example, open source or commercial product, and licensing information
Are the solutions already being used in hospitals?	List of hospitals that are already using the software
Has there been a methodical evaluation of the proposed or implemented solution?	Description of the evaluation methodology and the corresponding results, if available

[a]Mandatory field.

Stage 5: Collating, Summarizing, and Reporting the Results

After data extraction and charting, the results will be analyzed in a 2-step process per Arksey and O'Malley's framework [29]. First, the findings will be analyzed numerically, comparing the extent, nature, and distribution of the literature found. Following that we will prepare a thematic overview on visualization solutions for tumor boards and clinical oncology. The visualized data per tool, as well as the respective visualization strategies

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used and remaining elements of the data extraction template, will be charted and appropriate graphics will be created. The findings will be presented following the PRISMA-ScR reporting guidelines [34].

Ethical Considerations

Since our review will not involve human participants, this study does not require ethics approval.

Results

The scoping review started with a tentative search beginning in September 2023 leading to 2057 results with a suspected 1227 duplicates. In the next step titles and abstracts will be iteratively screened by reviewers to decide on the paper's inclusion in the further review process (see stage 3). This will be based on the criteria described in the Methods section. Included articles will be analyzed by applying the appended data extraction tool (see stage 4). This step is expected to be finished by December 2023. Lastly, the results will be summarized and compiled (see stage 5) up until the beginning of 2024. We expect them to be published during the second quarter of 2024.

Discussion

We designed a scoping review, aiming to present the current state of software support for clinical oncology settings, focusing on visualization solutions used in MCCs and their integration into hospital processes. The initial search, executed using the methods and queries described in this protocol, was able to show that a significant amount of potentially relevant literature can be found in the selected electronic databases. By asserting that manually identified key papers are included in the results, we are confident that the results produced by the search queries include the target domains.

However, a potential limitation of the completeness of the scoping review might be its focus on scientific literature. While tumor boards are often actively part of research projects and publicize their findings including used software solutions, commercial visualization tools and supporting software are being used as well. These might present new and interesting approaches but would not be necessarily found during a literature search. However, limited access to these applications would make their analysis difficult, and closed-source solutions often present limited possibilities for extensions and follow-up work. Additionally, available literature on supporting software might focus on features apart from visualization and offer limited insight into the questions posed. We aim to mitigate this by supplementing the findings through additional manual searches for included software.

We expect the scoping review's findings to show the current state of data visualization in clinical oncology settings. By comparing these results with the data most commonly available in the context of tumor boards and upcoming data sets we aim to anticipate visualization needs and provide starting points for more focused requirement analysis. Lastly, we hope to inform the future development of flexible visualization solutions for expanding oncology data sets.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed search queries for PubMed, Web of Knowledge, and SCOPUS.
[DOCX File , 14 KB - resprot_v13i1e53627_app1.docx]

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Abbreviations

MCC: multidisciplinary cancer conference
MTB: molecular tumor board
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Innovative Solutions for Patients Who Undergo Craniectomy: Protocol for a Scoping Review

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Abstract

Background: Decompressive craniectomy (DC) is a widely used procedure to alleviate high intracranial pressure. Multidisciplinary teams have designed and implemented external medical prototypes to improve patient life quality and avoid complications following DC in patients awaiting cranioplasty (CP), including 3D printing and plaster prototypes when available.

Objective: This scoping review aims to understand the extent and type of evidence about innovative external prototypes for patients who undergo DC while awaiting CP.

Methods: This scoping review will use the Joanna Briggs Institute methodology for scoping reviews. This scoping review will include noninvasive medical devices for adult patients who undergo DC while waiting for CP. The search strategy will be implemented in MEDLINE, Embase, Web of Science, Scielo, Scopus, and the World Health Organization (WHO) Global Health Index Medicus. Patent documents were also allocated in Espacenet, Google Patents, and the World Intellectual Property Organization (WIPO) database.

Results: This scoping review is not subject to ethical approval as there will be no involvement of patients. The dissemination plan includes publishing the review findings in a peer-reviewed journal and presenting results at conferences that engage the most pertinent stakeholders in innovation and neurosurgery.

Conclusions: This scoping review will serve as a baseline to provide evidence for multidisciplinary teams currently designing these noninvasive innovations to reduce the risk of associated complications after DC, hoping that more cost-effective models can be implemented, especially in low- and middle-income countries.

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KEYWORDS

cranioplasty; decompressive craniectomy; global neurosurgery; intellectual property; stroke; traumatic brain injury; innovative; innovative solutions; craniectomy; increased intracranial pressure; intracranial pressure; prototypes; medical devices; middle-income countries; low-income countries; noninvasive

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Introduction

Traumatic brain injuries (TBIs) remain a significant global health challenge affecting more than 69 million people annually [1]. The incidence of TBIs in low- and middle-income countries is disproportionate, 3 times greater than in high-income countries [1]. Severe forms of TBI (5.58 million people each year or 73 cases per 100,000 people) and other critical pathologies such as strokes and brain tumors often require a life-saving neurosurgical procedure called decompressive craniectomy (DC) [1]. DC is an essential surgical procedure that alleviates intracranial pressure, which consists of removing a section of the skull to avoid inward brain constriction due to brain parenchyma and cranial rigidity [2]. However, this intervention leaves patients vulnerable and at risk of neurological impairment, further traumas, and self-esteem difficulties while waiting for cranioplasty (CP) [3].

The overall complication rate after DC has been reported to be as high as 50% [3]. These complications include (1) the syndrome of the trephined, in which the atmospheric pressure compresses the brain parenchyma and the neurological status of the patient deteriorates after the removal of a skull bone flap, in 13% of patients who undergo DC; (2) hemorrhage, in 58%; (3) external herniation, in 25%; (4) wound complications (such as ulceration or necrosis) or surgical site infection, in up to 9%; (5) cerebral spinal fluid leakage, in 6.3%; and (6) increased risk of severe injuries from falling, among others [4-6].

A critical challenge post-DC patients face is the need for protective measures for the craniectomy site. A study described that at least 88.9% of patients have reported needing a device to prevent contact with the craniectomy site [7]. In response to this challenge, external protective devices have emerged as a potential solution to replicate the protective effects of CP and minimize postoperative complications.

Nowadays, technological innovation in medicine drives care improvements, surgical techniques, and preventative medicine. This is especially true in neurosurgery, as shown by neurostimulation in functional neurosurgery, microneurosurgery, and the merging of computed tomography and magnetic resonance imaging intraoperatively, always possible because of the multidisciplinary teams [7,8]. The global medical device industry is highly competitive, with many countries contributing to its development and growth worldwide. Interdisciplinary teams have designed and implemented external medical prototypes in response to the need to improve patient's quality of life and avoid complications following DC in patients awaiting CP, including 3D printing and plaster prototypes, when available. Therefore, the objective of this scoping review is to develop a better understanding of available innovations in technology for patients with DC who are awaiting CP worldwide.

Methods

Overview

The proposed scoping review will use and follow the Joanna Briggs Institute methodology for scoping reviews [9]. The proposed methodology is presented in Figure 1.

Figure 1. Summary of the search strategy process. WHO: World Health Organization; WIPO: World Intellectual Property Organization.

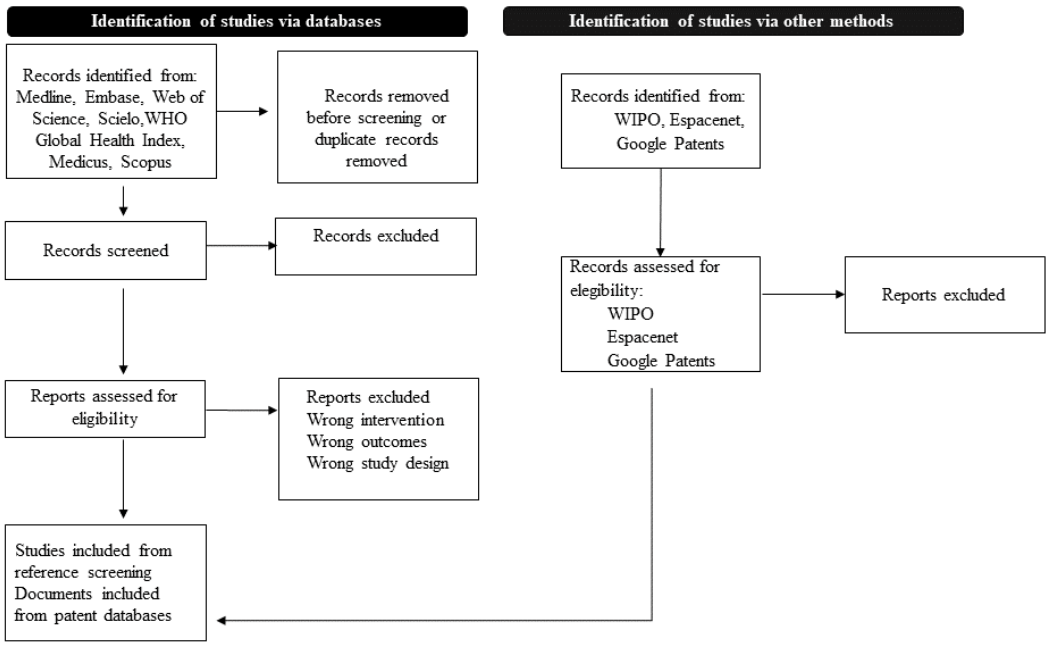

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Review Question

What is the current landscape of external medical devices replicating the effects of CP worldwide?

Eligibility Criteria

Participants

This scoping review will include prototypes for adult patients who undergo DC while waiting for CP.

Concept

External medical devices that replicate the effects of CP.

Context

This scoping review will not exclude documents based on geographic areas as it is intended to identify and locate where they have been designed and implemented.

Types of Sources

This scoping review will consider experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. Consideration will be given to the inclusion of analytical observational studies, which may include prospective and retrospective cohort studies, case-control, or analytical cross-sectional studies. This review will consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies that focus on qualitative data will also be included, but are not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research.

In addition, systematic reviews that meet the inclusion criteria will also be considered, depending on the research question. Text and opinion papers will also be considered for inclusion in this scoping review. Worldwide patents will be allocated in the central databases Espacenet, Google Patents, and World Intellectual Property Organization (WIPO).

Search Strategy

The search strategy will be carried out by an experienced librarian (IK) to locate both published and unpublished documents. An initial limited search of MEDLINE was undertaken to identify studies on the topic. The text words in the titles and abstracts of relevant studies and the index terms used to describe the studies were used to develop a complete search strategy for PubMed, Scopus, Web of Science, Scielo (see Multimedia Appendix 1), and the World Health Organization (WHO) international database. Patents will also be allocated in Espacenet, Google Patents, and WIPO. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies. Studies published in any language will be included, and translation services will be used if necessary. No time limit has been established.

Study or Source of Evidence Selection

All identified citations will be collated and uploaded to EndNoteX9 (Clarivate Analytics) after the search. The citations will then be imported into Covidence software (Veritas Health Innovation) for screening. A total of 2 independent researchers will examine titles and abstracts for inclusion. The full text of selected studies will be retrieved and assessed. Full-text studies that do not meet the inclusion criteria will be excluded, and the reasons for exclusion will be provided in the final scoping review. Any disagreements between the researchers during either title and abstract screening or full-text screening will be resolved through discussion or with a third reviewer. All included studies will undergo a process of data extraction using a standardized data extraction tool. The final study will report the search results in complete and present using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.

Data Extraction

Data will be extracted from papers and patent documents included in the scoping review by 2 or more independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the participants, concept, context, study methods, and critical findings relevant to the review questions.

A draft extraction is provided in Multimedia Appendix 2. It will be modified as necessary while extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any reviewer disagreements will be resolved through discussion or with additional reviewers. If appropriate, authors of studies could be contacted to request missing or other data, where required.

Data Analysis and Presentation

The extracted data will be presented in tabular form and as a narrative summary that aligns with the aim of this scoping review. The table will report (1) the distribution of medical devices by countries of origin or study design, (2) functional claims or features, (3) implementation strategies, (4) patient outcomes, (5) costs, and (6) strengths and weaknesses. This table may be further refined at the review stage. Graphical representations may be used, including bar charts, line charts, pie charts, and diagrams. A narrative summary will accompany the tabulated or charted results and describe how the results relate to the review's objectives.

Ethical Considerations

No ethics approval will be required, as this review is based on already published data and does not involve interaction with human participants.

Results

The research for this systematic review commenced in February 2023, and we expect to publish the findings in 2024. The plan for dissemination, however, is to publish the review results in a peer-reviewed journal and present findings at high-level conferences that engage the most pertinent stakeholders involved in innovation and neurosurgery.

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Discussion

Cumulatively, 6838 studies were identified from the database searches and 1652 from patent searches, after which 64 scientific papers and 4 patent documents were left for full-text review. Of these, 9 documents met the inclusion criteria and will be used in the final synthesis. Three categories of study design were identified: case reports (n=6), cohort studies (n=1), and exploratory clinical trials (n=1). One of the documents was not a scientific report and was categorized as a patent document. The complete data analysis and discussion will be published in an indexed journal once it is finished in an indexed journal upon completion.

This protocol has been rigorously developed and explicitly designed to illustrate and summarize the evidence regarding innovative external devices for patients with DC awaiting CP worldwide. This scoping review will serve as a baseline to provide evidence for multidisciplinary teams currently designing these noninvasive innovations to reduce the risk of associated complications after DC, hoping that more cost-effective models can be implemented, especially in middle-income and low-income countries. The principal limitation of this and any scoping review is the quality of the included studies leaving the included literature with a higher risk of bias.

Although most of these devices were developed in middle- and high-income countries, they serve as a starting point for implementation and future development in lower-income countries where no current solutions exist.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LLF, DG, and IK designed the review. LLF and DG refined the review design. All authors were involved in subsequent draft study reviews and updates and approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pubmed and Scopus Search strategy.
[DOCX File , 16 KB - resprot_v13i1e50647_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 32 KB - resprot_v13i1e50647_app2.docx]

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Abbreviations

CP: cranioplasty
DC: decompressive craniectomy
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
TBI: traumatic brain injury
WHO: World Health Organization
WIPO: World Intellectual Property Organization

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Protocol

Characteristics of Occupational Therapy Interventions to Promote Healthy Aging: Protocol for a Scoping Review

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Abstract

Background: Healthy aging is a pressing public health priority. Focusing on what people do every day may be a meaningful approach to lifestyle change, suggesting a need for occupation therapy interventions to promote healthy aging. A preliminary database search was conducted, and no current or underway systematic or scoping reviews on the topic were identified. Developing an overview of studies of occupational therapy interventions to promote healthy aging is a necessary first step to understanding the existing knowledge and increasing the impact of future interventions. This scoping review will build on previously conducted reviews.

Objective: This scoping review will identify the following: (1) what occupational therapy interventions exist for promoting healthy aging in community-dwelling adults? and (2) what are the intervention characteristics, their evaluated outcome, and the impact observed?

Methods: This protocol was reviewed by 2 occupational therapists as part of a patient and public involvement consultation. The review will consider all studies and publications of occupational therapy focused on promoting healthy aging in community-dwelling adults who are aged 18 years and older. Databases to be searched are AMED, CINAHL, Cochrane Library, Embase, JBI EBP database, MEDLINE, OAlster, PsycINFO, PsycArticles, ProQuest Dissertations & Theses, ProQuest nursing and allied health source, PubMed, and Science Direct. Studies published in any language will be included. Titles and abstracts will be screened against the inclusion criteria using Covidence (Veritas Health Innovation). Potentially relevant studies will be retrieved in full and assessed against the inclusion criteria. No date limiters will be used. Study selection will be completed by 2 independent reviewers. Data will be extracted using a data extraction tool, including descriptive characteristics of the participants including age, sex, and socioeconomic status. Data will be charted using the TIDieR (Template for Intervention Description and Replication) checklist in alignment with the review objectives. The scoping review will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) statement.

Results: The research began in October 2023, and the results are expected to be published in 2024.

Conclusions: This scoping review will produce valuable information about occupation-based interventions to promote healthy aging to support the development of an occupational therapy intervention.

Trial Registration: Open Science Framework 5k36d; https://osf.io/5k36d/

International Registered Report Identifier (IRRID): DERR1-10.2196/55198

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KEYWORDS

healthy aging; interventions; occupational therapy; public health; scoping review; intervention; aging; lifestyle change; aging population; well-being; occupation-based approach; occupational therapists; older people

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Introduction

Overview

The proportion of older people in society will double to 22% between 2015 and 2050 [1]. To this end, the United Nations has instituted a *decade of healthy aging 2021-2030* aimed at promoting healthy aging and addressing the challenges associated with an aging population across the life course [2]. This means active aging and healthy lifestyles have become priorities for public health internationally [3]. Healthy aging is "the process of developing and maintaining the functional ability that enables well-being in older age" [4]. It comprises the intrinsic capacity of the individual—their physical and mental capacities, environmental characteristics, and the interactions between them [2]. It is not necessary to be completely free from illness or disability to achieve healthy aging [2]. A meaningful life, such as a life filled with worthwhile activities [5] or being able to remain living in the community, may help promote successful and healthy aging [6]. This suggests an occupation-based approach centered on what people do every day could be a key to unlocking the 5 pillars to aging well, namely, healthy eating, hydration, exercise, social connections, and cognitive health [7]. Occupational therapists provide opportunities for individuals to engage in activities and live how they wish at every stage of life, and this may offer a meaningful approach to healthy aging [8]. It has been suggested that "The occupational therapy profession has an essential role to play in healthy aging that includes enabling participation" [9].

Occupational therapists already work in this field and occupation-based health promotion interventions exist [10]. However, some of the existing reviews are no longer current; for example, Gustafsson et al [11], Arbesman and Mosley [12], and Stav et al [13] have not been updated. A review of older people's lived experience of occupation and well-being, based on 3 studies of moderate quality, suggests there is a relationship between well-being and occupation for older people. This is shaped by 2 factors: "first, variation and independence in undertaking activities; second, having a choice between the occupations and a structure of activities that make up daily life. The two factors are influenced by a balance between having activities alone and with others." [14]. A review of economic evaluations of occupational therapy for people with cognitive or functional decline, or both, found that evidence was scarce, with few comprehensive high-quality economic evaluations having been conducted, but those that have been conducted suggest the interventions are effective and have economic benefits [15].

The literature focuses on older people, rather than other points in the life span, despite the life course approach endorsed by the United Nations' *decade of healthy aging 2021-2030* [2]. Nonetheless, the population of older adults has been variously defined as 60 years old [13], over 65 years of age or older [9], or 80 years of age or older [12]. Interventions have targeted people living in nursing homes [16], Australian residential aged care facilities [17], and community-dwelling older people [10,17,18]. The focus has tended to be on secondary prevention, within the context of disease management, rather than primary prevention with community-dwelling adults [10]. No study was identified that delineated the characteristics of the interventions reviewed, which is a necessary first step to understanding the existing knowledge and supporting the design, evaluation, and impact of future interventions [19]. Intervention development should be explicit about the content of the intervention, its theoretical foundation, and the context in which the intervention is delivered [11]. Therefore, to further understand how occupational therapy can contribute to promoting healthy aging, it is important to understand the interventions available, their characteristics, and the impact observed [20].

A scoping review is a first step toward identifying what occupational therapy interventions exist to promote healthy aging for community-dwelling adults. A preliminary search of Cochrane Library, figshare, JBI Evidence Synthesis MEDLINE, Open Science Framework, PROSPERO, and PubMed was conducted. The search identified 11 recent reviews. While the reviews identified had a bearing on the topic, most were not specifically about the topic. A total of 7 of the 11 reviews were about discrete topics, that is, older adults' occupations in heatwaves [21], joy among older people [22], quality of life [16,23], e-tools for transportation planning [24], occupational therapy in residential aged care [17], and instruments to support occupational therapy practice [9]. A review by Kim et al [18] focused on daily functioning and included occupational therapy, but its focus was on activities of daily living and instrumental activities of daily living rather than the broader concept of healthy aging. A scoping review by Mehrotra et al [20] about healthy aging and occupational therapy in South Asian countries was potentially replicable for a wider population, but the full report is not available and the authors of the protocol have not responded to requests for the full report. The rapid review by Owusu-Addo et al [25] was about implementation approaches rather than interventions. Occupational therapy was included in the review of the theory-based specification of nonpharmacological treatments in aging and dementia by Sikkes et al [26], but it did not cover specific interventions and its focus was dementia—secondary prevention—rather than healthy aging more generally. This means that no existing or contemporary review was identified, but these reviews provide valuable insights into how to conduct a review in this field. For example, keywords for searching should include productive aging [10], aging well, healthy aging, positive aging, and successful aging [20]. Thus, a scoping review will be conducted to provide an overview of occupational therapy in relation to promoting healthy aging and discover gaps in knowledge. This will provide up-to-date evidence about occupational therapy interventions to promote healthy aging and its characteristics [19].

Review Questions

This scoping review will identify the following: (1) what occupational therapy interventions exist for promoting healthy aging in community-dwelling adults? and (2) what are the intervention characteristics, their evaluated outcome, and the impact observed?

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Methods

Study Design

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [27]. This scoping review protocol is registered on the Open Science Framework [28] and will be reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [29]. This scoping review protocol will be conducted using the JBI guidelines for scoping reviews to ensure a systematic methodology that can be replicated and reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [30].

Eligibility Criteria

Participants

This review will consider studies of occupational therapy focused on promoting healthy aging in adults living in the community—community-dwelling—aged 18 years or older. This may include adults living in their own homes or a care setting. Studies will be excluded if they focus on children.

Concept

The concept being mapped in this scoping review will be occupational therapy interventions to promote healthy aging in the context of the life course approach. The life course approach acknowledges that health and well-being are influenced by social, economic, and environmental factors throughout a person's life, as well as personal characteristics [31]. The terms active aging and healthy aging, although subtlety different, are often used interchangeably, that is, active aging refers to "optimizing opportunities for health, participation and security in order to enhance the quality of life as people age" [32], and healthy aging is defined as "developing and maintaining the functional ability that enables well-being in older age" [4], where functional ability includes people's ability to meet their basic needs to ensure an adequate standard of living, learning, growing and making decisions, being mobile, building and maintaining relationships, and contributing to society [2]. Therefore, this scoping review will consider studies with interventions that focus on active aging or healthy aging as part of health promotion, that is, primary prevention. Studies will be excluded if they address secondary prevention, that is, interventions that focus on the early stages of disease, such as fall prevention for older adults following a fall, or tertiary prevention, that is, interventions during the symptomatic phase of a disease to minimize disability and maximize quality of life, such as foot care for people living with diabetes.

The word "occupation," in the context of occupational therapy, refers to the everyday activities that humans engage in as part of their daily routine to occupy time, providing purpose and meaning to their lives [33,34]. Occupations are the activities people want to do, need to do, or are expected to do [34]. Examples of these meaningful activities can include social interaction with peers, cooking, different forms of exercise, and working [35]. Occupation-based interventions aim to enhance the performance of an individual when undertaking meaningful activities of daily living by increasing their social and community interaction [36]. Occupation-focused interventions encapsulate the rapid improvement of an individual's performance through compensatory methods by implementing adaptive measures to be tailored to their current performance level [37]. Interventions are implemented to increase the performance of the individual in the desired or necessary tasks [38].

Context

This review will consider studies from any setting, in any country. As a global perspective will be considered, it means no limit on language will be made in the search strategy. This will ensure valuable insights are not lost because they were published in a language other than English [39]. As no language limits will be imposed, relevant papers that are not published in the English language will be translated using Google Translate. Jackson et al [40] have revisited the work by Balk et al [41], who recommended that Google Translate can be used with caution because Google has updated its translation engine. Jackson et al [40] concluded that it is a viable, accurate tool for translating non-English language trials for the purpose of conducting systematic reviews, which is why we will use it for our review. We appreciate that a scoping review is more narrative based than a systematic review; therefore, if we have access to a native speaker, the translation will be checked by them. If it is not possible to verify the translation, this will be reported within the review report. The number and sources of non-English language literature will be reported in the review report.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs, including case studies, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies will also be considered that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. In addition, systematic reviews that meet the inclusion criteria will also be considered depending on the research question. Text and opinion papers will also be considered for inclusion in this scoping review.

Review Team

The review is being conducted by a team comprised of an academic (KB) and 3 postgraduate researchers (JCHS, NJL, and ERRM).

Patient and Public Involvement

The scoping review protocol has been reviewed by 2 occupational therapists working in the field of healthy aging or with older people.

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Search Strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of AMED, CINAHL, Cochrane Library, MEDLINE PsycINFO, and PubMed was undertaken to identify if a review of this topic has previously been conducted. The text words contained in the titles and abstracts of relevant studies, and the index terms used to describe the studies were used to develop a full search strategy for AMED, CINAHL, Cochrane Library, Embase, JBI EBP database, MEDLINE, OAlster, PsycINFO, PsycArticles, ProQuest nursing and allied health source, ProQuest Dissertations & Theses, PubMed, and Science Direct (see Multimedia Appendix 1 for an example search strategy). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies. The searches will be conducted by KB, NJL, JCHS, and ERRM. No date or language limiters will be used.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into Covidence [42] and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details imported into Covidence [42]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of sources of evidence that do not meet the inclusion criteria during full-text screening will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with additional reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [30].

Data Extraction

A draft extraction form is provided (see Multimedia Appendix 2). The draft data extraction tool may be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with additional reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Ethical Considerations

As this scoping review covers reviewing and extracting data from publicly available materials, this study does not require ethics approval.

Data Analysis

The TIDieR (Template for Intervention Description and Replication) checklist will be used in this review to ensure completeness in the reporting of the characteristics of interventions [43]. The extracted data will be charted in tabular form using the TIDieR checklist. The charted results will be accompanied by a narrative summary and will describe the relationship between the result and the review's objectives and questions. The results will be presented in accordance with the TIDieR format and the main conceptual categories used in the extraction too, as well as gaps in the existing literature. These results will be presented in relation to the question of this scoping review. The narrative will be guided by the Patterns, Advances, Gaps, Evidence for practice and Research recommendations (PAGER) framework [44]—a structured approach to the analysis and reporting of scoping reviews.

Results

The research began in October 2023, and the results are expected to be published in 2024.

Discussion

Findings

This scoping review will produce a map of the current body of research about occupational therapy interventions to promote healthy aging among community-dwelling adults. As far as we know, this is the first scoping review that maps the occupational therapy interventions that exist to promote healthy aging for community-dwelling adults, the intervention characteristics, and their evaluated outcome and impact that is not limited to any country. Similar to any review, there exist limitations when conducting a scoping review. Although a rigorous identification and inclusion strategy has been delineated, there is still a risk that some valuable information, which could have enhanced our comprehension, might be inadvertently excluded. This is particularly prevalent in the case of grey literature, which may not always come up in academic searches. As the aim and nature of a scoping review are to explore the breadth of a topic to see what has been done, but not the depth, the reviewers are not able to evaluate the quality of the studies that are incorporated within the scoping review. Although scoping reviews can be helpful in generating hypotheses and identifying research gaps, they may not offer the same degree of thoroughness or meticulousness as a systematic review that involves a more rigorous and comprehensive methodology for data collection and analysis and, consequently, may offer a higher level of evidence than scoping reviews [45]. A methodological appraisal of the included studies will not be performed. It is important to note that the limitations and results presented in the suggested review may not be all-encompassing or investigated beyond the peer-review stage of the published paper.

Conclusions

The review authors will use the findings of this scoping review to support the development of a manualized occupational therapy intervention [46] to promote healthy aging within the EmpowerAge program being developed at Glasgow Caledonian University.

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Acknowledgments

The authors would like to thank Laura Hall and Rowena Harrison for their contribution to the development of this protocol.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during protocol development.

Authors' Contributions

The design of the protocol was conducted by KB. The drafting of the study was done by KB, JCHS, NJL, and ERRM. All authors approved the final study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 30 KB - resprot_v13i1e55198_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 33 KB - resprot_v13i1e55198_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PAGER: Patterns, Advances, Gaps, Evidence for practice and Research recommendations
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
TIDieR: Template for Intervention Description and Replication

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Protocol

Analysis of Self-Care Activities in Type 2 Diabetes in Brazil: Protocol for a Scoping Review

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Abstract

Background: Diabetes mellitus is a chronic disease that is growing worldwide. It is estimated that 15.7 million people aged between 20 and 79 years live with diabetes in Brazil, and the majority of cases are type 2 diabetes (T2D). To successfully manage diabetes, the patient needs to develop self-care activities. However, there is limited understanding of what self-care activities are performed by people with T2D in Brazil.

Objective: This study aims to identify and map studies that evaluate self-care activities in T2D in Brazil.

Methods: This is a scoping review protocol structured according to the methodological guidelines of the Joanna Briggs Institute. Six databases and gray literature were used. The process of searching, identifying, and evaluating the papers was carried out by 2 independent reviewers, guided by the assumptions established by the Joanna Briggs Institute. We sought to answer the following guiding question: How are self-care activities for people with T2D evaluated in Brazil? We included papers and publications in any language, from public and private domains, and with different methodological approaches.

Results: Initial database searches produced a total of 681 results. These papers will be critically analyzed, and relevant information will be extracted. Quantitative and qualitative results of the papers reviewed will be presented to respond to the study's objective. We intend to publish the scoping review in the first half of 2024.

Conclusions: The protocol for this scoping review will evaluate the main self-care activities carried out by adults and older people with T2D in Brazil. The results may help identify knowledge gaps and contribute to future research and diabetes education interventions.

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KEYWORDS

type 2 diabetes mellitus; self-care; self-care activities; Brazil; diabetes mellitus; T2D; chronic disease; self-care activity; aging; ageing; methodological guidelines; knowledge; gaps; diabetes education; hyperglycemia; insulin resistance; health education

Introduction

Diabetes mellitus (DM) is a significant and growing health problem worldwide. In 2021, the International Diabetes Federation estimated that 8.8% (537 million) of the world's population aged 20 to 79 years had diabetes. If current trends persist, the number of people with diabetes is projected to exceed 783 million by 2045. Brazil ranks sixth in the number of cases, with 15.7 million people diagnosed in the 20-79 years age group, which is projected to increase to 23.2 million cases in 2045 [1].

DM can be classified into 4 main types, based on its etiology: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational DM,

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and other types of diabetes. T2D is the most prevalent form, accounting for approximately 90% to 95% of diabetes cases worldwide [2].

The causes of T2D are still poorly understood, but there is a strong link with excess weight, obesity, lack of physical activity, aging, ethnicity, and family history. T2D has an insidious onset and is characterized by insulin resistance, partial deficiency of insulin secretion by pancreatic β cells, and changes in incretin secretion [2,3].

There is evidence that T2D can be prevented or delayed [1]. However, the patient often remains undiagnosed with T2D for several years. T2D occurs when hyperglycemia is the result of insulin resistance that has been established gradually over many years until diagnosis [1,2]. In this case, the person does not present the classic signs of diabetes, such as dehydration or involuntary weight loss, and the diagnosis comes with acute or chronic complications of diabetes [2].

Diabetes complications are categorized as microvascular and macrovascular disorders. Thus, diabetes and its complications can lead to disability and constitute one of the main causes of early mortality in most countries [1,4].

For satisfactory management of diabetes and effective adjustment in lifestyle, it is necessary to develop self-care activities, which include adherence to a healthy diet, regular physical activity, blood glucose monitoring, foot care, medication use, and smoking cessation [5].

Self-care is defined as the ability of individuals, their families, and the community to promote and maintain their health, prevent disease, and manage their illness and disability with or without the support of a health professional [6].

The Association of Diabetes Care & Education Specialists (ADCES) emphasizes that diabetes self-care can be effective through 7 important behaviors (ADCES7 self-care behaviors [7]): (1) ensuring variety and balance between quality, quantity, and food safety (healthy eating)—fresh or minimally processed foods should be prioritized and thus form the basis of the diet, and ultraprocessed foods should be avoided; (2) engaging in physical activity and regular training with aerobic and resistance exercises (being active); (3) blood glucose monitoring, using reagent strips and glucometers or glucose monitoring with interstitial glucose sensors (controlling blood glucose values); (4) understanding and managing the use of medications at the correct times every day, according to medical prescription (taking medication); (5) being prepared to face unexpected complications, such as hyperglycemia or hypoglycemia, resulting from an error in carbohydrate counting, physical activity, use of alcoholic beverages, excess medication, or change in medication schedule (solving problems); (6) practicing behaviors that prevent or minimize chronic complications and adverse outcomes related to diabetes (reducing risks)—examples of these behaviors include making positive lifestyle changes and participating in a diabetes education program, and it is recommended to be up to date with laboratory and complementary tests (glycated hemoglobin, cholesterol levels, assessment of renal function, and fundus examination), clinical assessment, and emotional aspects; and (7) developing personalized strategies to face daily stress and know how to act in special situations such as travel, parties, and intercurrent illnesses (eg, infections and other clinical situations that impact blood glucose, etc). Seeking information and alternatives to adapt to different situations, thus benefiting glycemic control and self-efficacy, favors patients to face the challenges of diabetes (adapting healthily) [7].

There is vast scientific literature on diabetes and many self-care–related studies. However, to the best of our knowledge, no previous attempt to establish an analysis of different self-care activities in T2D focused on Brazilians. Thus, this protocol will guide a scoping review to identify and map studies evaluating self-care activities in T2D in Brazil. Scoping reviews are considered a type of literature review that maps and identifies the nature and extent of relevant evidence in a given field of research. It also seeks to identify gaps in evidence, clarify key concepts, and report on the types of evidence that address and inform practice in a thematic area [8].

This protocol will guide a scoping review to identify and map studies that evaluate self-care activities in T2D in Brazil.

Methods

Scoping Review

To maintain rigor, the scoping review methodology used for this protocol will be that of the *Joanna Briggs Institute (JBI) Reviewer's Manual 2020* [9], which establishes five steps: (1) identification of research question; (2) identification of relevant studies; (3) selection of studies; (4) data analysis; and (5) grouping, synthesis, and presentation of data. The authors also followed the recommendations of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews), according to the JBI Manual [9].

This study also followed all procedures standard to systematic reviews (search tests during elaboration of the protocol, data collection, data extraction, synthesis, analysis, and discussion of results and conclusions), as recommended by Cochrane (*Cochrane Handbook for Systematic Reviews of Interventions* [10]). A preliminary search of the PROSPERO Cochrane Database of Systematic Reviews and JBI Evidence Synthesis was performed. No existing or ongoing scoping reviews or systematic reviews were identified on this topic.

After completing the scoping review, the results will be submitted for publication in a peer-reviewed scientific journal. The research project for this scoping review protocol was previously registered in the Open Science Framework [11].

Stage 1: Identifying the Research Question

The first step comprises the elaboration of a research question. This review followed the *Population*, *Concept*, and *Context* strategy for a scoping review [9]. The following were defined: people diagnosed with T2D (*Population*); actions or strategies to evaluate self-care, self-management, or self-efficacy of people with T2D (*Concept*); and studies developed in Brazil (*Context*). Thus, the guiding question of this study is as follows: How are self-care activities for people with T2D evaluated in Brazil?

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Stage 2: Identifying Relevant Studies

We performed a database search: (1) MEDLINE, (2) Web of Science - Core Collection, (3) Scopus, (4) Embase, (5) LILACS, and (6) SCIELO. In addition, a search was carried out for unpublished and possibly eligible studies in the gray literature, retrieved from 3 sources: the Brazilian Digital Library of Theses and Dissertations, Google Scholar (limited to the first 10 pages, in order of relevance), and the website of the Brazilian Diabetes Society. For the search strategy, terms were extracted from recognized thesauruses in the health area: Health Sciences Descriptors, Medical Subject Headings, and Embase Subject Headings. Thus, it started with the following terms: type 2 DM, self-management, self-efficacy, self-care, and Brazil. In order to broaden the search and better direct the findings, synonymous terms and the Boolean operators OR and AND were used according to the needs of each database (Multimedia Appendix 1).

As eligibility criteria, we included (1) Brazilian studies that were conducted with people diagnosed with T2D, older than 18 years, of both genders, and with or without comorbidities; (2) studies that focus on self-care activities for people with T2D; (3) studies that describe the evaluation process of these activities; and (4) studies that evaluate 2 or more self-care activities. The time frame used was the period from 2011 to 2023. The year 2011 is marked by the elaboration of the Strategic Action Plan for Combating Chronic Noncommunicable Diseases in Brazil 2011-2022 [12] and the Model of Attention to Chronic Conditions [13]. Original studies, dissertations, and theses were considered without language restriction, with quantitative, qualitative, or mixed design. Duplicate studies; studies on T1D, gestational diabetes, or prediabetes; studies that associate T2D with other types of diabetes; research protocols; editorials; reviews; letters; and Brazilian studies carried out in partnership with other countries were excluded.

Stage 3: Study Selection

The identified literature was exported to the Mendeley reference manager (Elsevier), via the web version, to remove duplicates. It was then imported into the Rayyan (Qatar Computing Research Institute) systematic review management software, online version [14], for screening and selection of studies. The studies were selected independently by 2 previously trained researchers from the team, and a third researcher resolved conflicts in the absence of consensus. All identified studies' titles and abstracts were evaluated based on the established inclusion and exclusion criteria. After the assessment of a study's pertinence to the review question, it was selected for reading in full for later data extraction. Its references were analyzed in search of additional studies. This stage was developed based on the recommendations of the international guide PRISMA-ScR, with the presentation of a flowchart on the process of the search and selection of studies, quantitative results of each database, included or excluded studies, and the total number of works selected for evaluation and synthesis [15].

Stage 4: Charting the Data

For the data extraction, a standardized data extraction tool was created in a Microsoft Office Excel Online spreadsheet, developed by the reviewers, and tested for this study in a pilot test based on the JBI tool [9] to characterize the studies. The instrument was independently used by 2 researchers to capture information to describe the extent and nature of the studies (authorship, year of publication, study typology, objectives primary results, and authors' recommendations). Information was also collected, such as characteristics of the population, specific self-care activities (general food, specific food, physical activity, blood glucose monitoring, foot care, medication use, and smoking), and identification of diabetes self-care behaviors. If there was any disagreement between the data extracted by the 2 reviewers, it was resolved by dialogue between both reviewers or, if necessary, with a third reviewer. The studies were coded with letters and numbers following a logical sequence. Tables S1-3 in Multimedia Appendix 2 [7,16] are examples of the data extraction tools created for this study.

Stage 5: Collating, Summarizing, and Reporting the Data

Qualitative data will be analyzed using the Bardin content analysis technique [17] and descriptively by 2 authors and validated by the entire research team. As for quantitative data, Table S1 in Multimedia Appendix 2 will verify which self-care activities were carried out in each study and classify each activity as favorable or unfavorable. Table S3 in Multimedia Appendix 2 will verify which of the 7 self-care behaviors are addressed in the studies. The results will be presented in tables, graphs, and images, along with the construction of narratives to clarify the information and discuss it in light of relevant and updated literature. The scoping review will record and report reasons for excluding sources of evidence in the full text that do not meet the inclusion criteria. The review report will incorporate a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1), visually presenting the screening and selection process.

The assessment of methodological quality and risk of bias is optional [8] and will not be performed in our study.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the scoping review process.

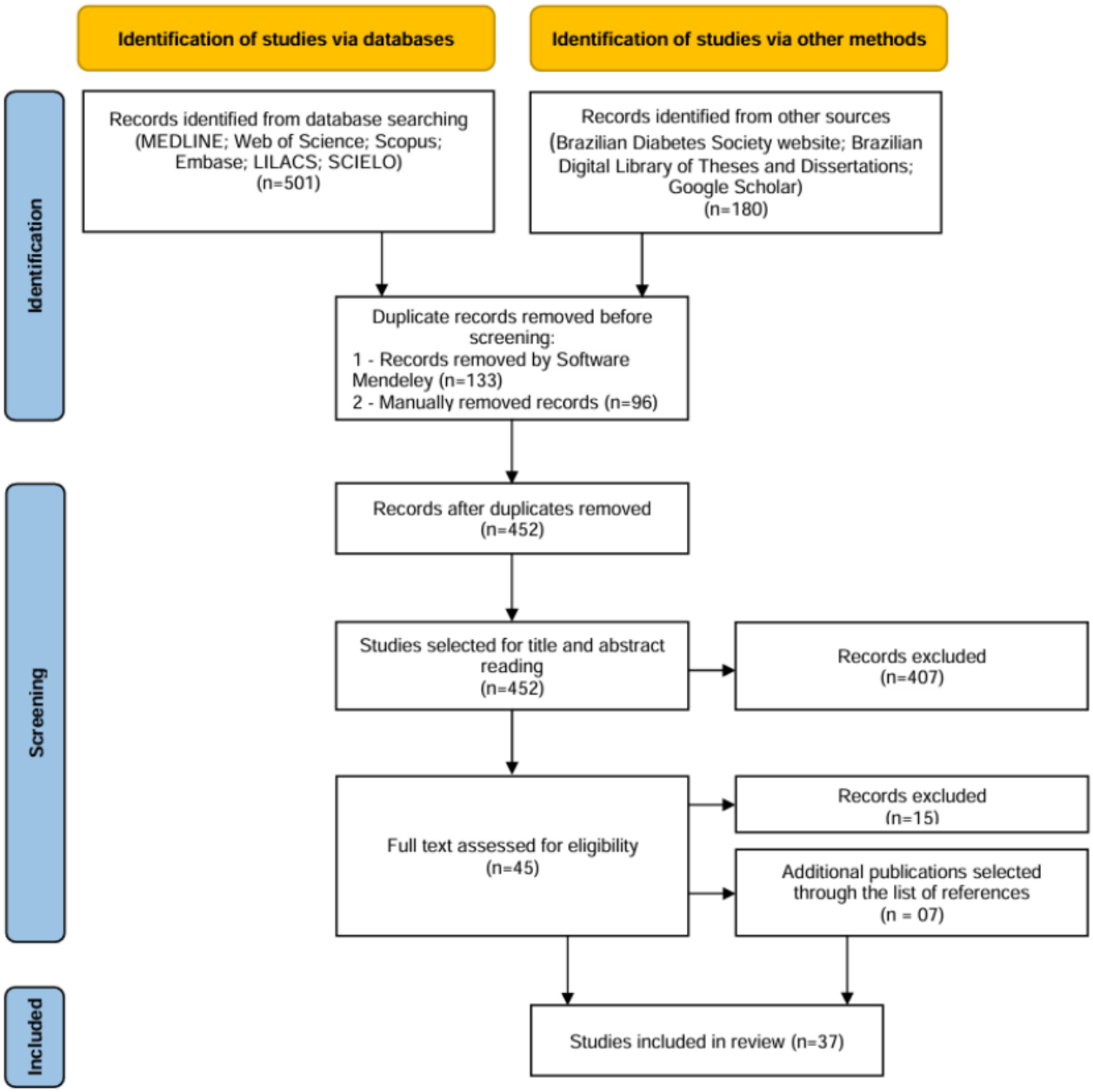

Ethical Considerations

This scoping review does not require ethical approval from the institutional review board.

Results

In August 2023, our initial database searches identified 681 papers. Duplicates were removed, and screening of extracted titles and abstracts resulted in 37 papers. A critical evaluation analysis of the collected papers was carried out to extract relevant information. The screening was carried out in September 2023. Similarities and differences contained in various data from the papers are being analyzed and compared between September and November 2023. We estimate the publication of the scoping review will be in the first half of 2024.

Discussion

Principal Findings

Reviews that focus on self-care for adults and older people with T2D have been specific to educational interventions for self-care. To the best of our knowledge, this will be the first scoping review to understand how self-care activities carried out by people with T2D in Brazil are evaluated.

This scoping review will identify gaps in the literature and provide information on future research needs related to self-care assessment and its relationship to the 7 ADCES self-care behaviors [7] of adults and older adults with diabetes.

The method of this scoping review complies with the JBI recommendations [9] and the most recent guidelines for using the PRISMA-ScR tool [15], adapted for the study context. One of the benefits of using PRISMA is that it makes it possible to

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guide the writing of the research so that it reflects the investigative activities that will be carried out without losing details, in addition to guaranteeing methodological rigor [18]. Another advantage of a scoping review is the possibility of obtaining an overview of the scientific evidence about a given phenomenon in a structured, systematized, impartial, and transparent way [8].

The results of the scoping review will be discussed thoroughly based on the research question and will be discussed with the evidence reported in the literature on the research topic. We believe that our results will support the development of guidelines, thereby overcoming identified challenges and revealing new opportunities for assessing self-care behaviors in diabetes.

Limitations

This scoping review will follow well-established methods, yet limitations will exist. First, most of the studies included are cross-sectional, which does not allow for long-term conclusions. Second, the noninclusion of texts published in other indexing databases and the choice to select studies only on the first 10 pages of Google Scholar may result in omitting potentially relevant research.

Conclusions

This review will map and compare how the main self-care activities carried out by people with T2D in Brazil are evaluated. Our study will help identify existing knowledge gaps and how research on the topic is conducted. This knowledge will enable researchers and health care professionals to understand self-care activities in T2D better. Consequently, the results of our scoping review may contribute to future research and health education programs focusing on T2D.

Acknowledgments

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Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

The study was designed by MMT, ES, and EAE. MMT and ES contributed to data collection. MMT wrote the manuscript, and ES and EAE contributed to the final draft of the manuscript. All authors approved the final article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy outlining concepts and alternative search terms.
[PDF File (Adobe PDF File), 116 KB - resprot_v13i1e49105_app1.pdf]

Multimedia Appendix 2
Information about the following instruments: Data extraction instrument; Measurement of each self-care activity seven days a week; and Diabetes self-care behaviors.
[PDF File (Adobe PDF File), 302 KB - resprot_v13i1e49105_app2.pdf]

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Abbreviations

ADCES: Association of Diabetes Care & Education Specialists
DM: diabetes mellitus
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
T1D: type 1 diabetes
T2D: type 2 diabetes

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Protocol

Definitions and Measurements for Atypical Presentations at Risk for Diagnostic Errors in Internal Medicine: Protocol for a Scoping Review

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Abstract

Background: Atypical presentations have been increasingly recognized as a significant contributing factor to diagnostic errors in internal medicine. However, research to address associations between atypical presentations and diagnostic errors has not been evaluated due to the lack of widely applicable definitions and criteria for what is considered an atypical presentation.

Objective: The aim of the study is to describe how atypical presentations are defined and measured in studies of diagnostic errors in internal medicine and use this new information to develop new criteria to identify atypical presentations at high risk for diagnostic errors.

Methods: This study will follow an established framework for conducting scoping reviews. Inclusion criteria are developed according to the participants, concept, and context framework. This review will consider studies that fulfill all of the following criteria: include adult patients (participants); explore the association between atypical presentations and diagnostic errors using any definition, criteria, or measurement to identify atypical presentations and diagnostic errors (concept); and focus on internal medicine (context). Regarding the type of sources, this scoping review will consider quantitative, qualitative, and mixed methods study designs; systematic reviews; and opinion papers for inclusion. Case reports, case series, and conference abstracts will be excluded. The data will be extracted through MEDLINE, Web of Science, CINAHL, Embase, Cochrane Library, and Google Scholar searches. No limits will be applied to language, and papers indexed from database inception to December 31, 2023, will be included. Two independent reviewers (YH and RK) will conduct study selection and data extraction. The data extracted will include specific details about the patient characteristics (eg, age, sex, and disease), the definitions and measuring methods for atypical presentations and diagnostic errors, clinical settings (eg, department and outpatient or inpatient), type of evidence source, and the association between atypical presentations and diagnostic errors relevant to the review question. The extracted data will be presented in tabular format with descriptive statistics, allowing us to identify the key components or types of atypical presentations and develop new criteria to identify atypical presentations for future studies of diagnostic errors. Developing the new criteria will follow guidance for a basic qualitative content analysis with an inductive approach.

Results: As of January 2024, a literature search through multiple databases is ongoing. We will complete this study by December 2024.

Conclusions: This scoping review aims to provide rigorous evidence to develop new criteria to identify atypical presentations at high risk for diagnostic errors in internal medicine. Such criteria could facilitate the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine.

Trial Registration: Open Science Framework; www.osf.io/27d5m

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KEYWORDS

atypical presentations; diagnostic errors; internal medicine; scoping review protocol; atypical presentation; high risk; data extraction; descriptive statistics; criteria; qualitative; content analysis; inductive approach; clinical informatics; clinical decision support

Introduction

Diagnostic errors, defined as "the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient" [1], is an important concern in improving patient safety and diagnostic excellence. According to a recent report, approximately 0.8 million people may become permanently disabled or die annually due to diagnostic errors in the United States [2]. While diagnostic errors can occur across care settings, internal medicine is one of the highest-risk care settings for diagnostic errors [3,4]. Internal medicine physicians, as well as surgery and emergency medicine physicians, also frequently confront malpractice claims related to diagnostic errors [5,6]. Internal medicine covers a broad spectrum of complaints and diseases, which can contribute to higher diagnostic uncertainty in patients presenting to internal medicine with undiagnosed conditions [3,7]. Therefore, more complex and difficult diagnostic decisions are required in internal medicine, which can result in higher susceptibility to diagnostic errors [3].

Diagnostic errors are usually related to multifactorial causes such as system-related errors; cognitive errors; and patient factors, including challenging disease presentations [8-10]. To date, while many studies have been conducted to address major system-related and cognitive errors using common measurements, patient factors, including challenging disease presentations, have not been investigated as much. However, among challenging disease presentations, atypical presentations have been increasingly recognized for their significant impact on diagnostic errors [11-15]. Atypical presentations are described as "a shortage of prototypical features that are most frequently encountered in patients with the disease, features encountered in advanced presentations of the disease or simply features of the disease commonly listed in medical textbooks" [16], which can make diagnosis more challenging and distract the diagnostic process. Indeed, atypical presentations were reported to be associated with a higher prevalence of diagnostic errors compared to typical presentations [12-14], and a pilot systematic review of case reports of diagnostic errors suggested that higher numbers of contributing factors were detected in the cases with atypical presentations compared to the cases without atypical presentations [15]. Moreover, a previous study showed that the prevalence of diagnostic errors in patients with atypical presentations of stroke was smaller when cared for by health care providers who are familiar with atypical presentations of stroke [17]. Although the results cannot be easily generalized to other conditions, developing strategies to prevent progression from an atypical presentation to diagnostic error seems to be a promising approach to improving patient safety [11,12].

Atypical presentations seem to be especially an important issue for diagnostic errors in internal medicine: first, atypical presentations may be commonly observed (up to approximately 30%) in the internal medicine department [13]; second, internal medicine physicians consider atypical presentations to be the most important contributor to diagnostic errors in their clinical practice [18]; and third, atypical presentations can be an important contributing factor to a higher prevalence of diagnostic errors in internal medicine [10,13]. Therefore, a comprehensive understanding of the association between atypical presentations and diagnostic errors is required. Knowledge gaps in this area persist possibly due to the lack of consensus on the definition and measurement of atypical presentations and because a comprehensive conceptual model to understand how atypical presentations progress to diagnostic errors is still lacking.

A scoping review is more appropriate than a systematic review when the review aims to identify knowledge gaps, scope a body of literature, and clarify concepts. A scoping review is also more appropriate than a narrative review when clarification around a concept or theory is required [19]. From this perspective, a scoping review is more ideally suited to determine the body of literature on atypical presentation and diagnostic errors and identify any gaps in knowledge [20]. Moreover, without a universal definition for atypical presentations, future studies about diagnostic errors may have systematic biases by excluding patients with atypical presentations at high risk for missed diagnostic opportunities [21]. Therefore, this scoping review will also facilitate future studies by developing practical criteria and measurements for atypical presentations.

Throughout this scoping review, the key terms such as diagnostic errors, atypical presentations, and internal medicine are defined as follows:

- Diagnostic errors—defined as the failure to (1) establish an accurate and timely explanation of the patient's health problems or (2) communicate that explanation to the patient [1], which also include delayed, wrong, and missed diagnosis [10].
- Atypical presentations—defined as patient demographics (eg, age, sex, and race); symptoms and signs; test results; or clinical course, including the response to treatment, deviated from the prototypical patterns for the final diagnosis.
- Internal medicine—defined as a medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults.

To develop a new definition and useful criteria to identify atypical presentations that are at high risk of diagnostic errors,

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this scoping review aims to identify and present the available information regarding the definitions and measurements for atypical presentations in the evidence sources about diagnostic errors in internal medicine.

The primary review question is "What definitions and measurements have been used to identify atypical presentations in the studies investigating diagnostic errors in adult patients in internal medicine?" The subquestions are "What specific diseases have been targeted by the studies investigating the association between atypical presentations and diagnostic errors in adult patients in internal medicine?" and "What specific types of atypical presentations have been reported as relevant to diagnostic errors in adult patients in internal medicine?"

Methods

Study Design

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews [22,23] and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [24].

Inclusion Criteria

Participants

This review will consider studies that include adult patients. We will exclude studies that focus on children.

Concept

This review will consider studies that explore the association between atypical presentations and diagnostic errors (using any clear definition or criteria or measurement to identify atypical presentations and diagnostic errors). We will exclude studies that investigate only atypical presentations or diagnostic errors.

Context

This review will consider studies that focus on the setting of internal medicine.

Types of Sources

This scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. In addition, systematic reviews and text and opinion papers will be considered for inclusion in the proposed scoping review. Case reports, case series, and conference abstracts will be excluded.

Search Strategy

The search strategy will aim to locate both published and unpublished primary studies, reviews, and text and opinion papers. An initial limited search of MEDLINE (PubMed) and Science Citation Index Expanded (Web of Science) was undertaken to identify papers on the topic. The text words contained in the titles and abstracts of relevant papers, and the index terms used to describe the papers, were used to develop a full search strategy for MEDLINE (PubMed; Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference lists of papers included in the review will be screened for additional papers. Papers published in all languages will be included. Papers indexed from database inception to December 31, 2023, will be included. The databases to be searched include MEDLINE (PubMed), Science Citation Index Expanded (Web of Science), CINAHL, Embase, Google Scholar, and Cochrane Library. Sources of unpublished studies and gray literature to be searched include medRxiv.

Study or Source of Evidence Selection

Following the search, all identified records will be collated and uploaded into Covidence (Covidence), and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 independent reviewers (YH and RK) for assessment against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full, and their citation details imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers (YH and RK). Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer (MY). Interrater reliability will be monitored and reported. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [25].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers (YH and RK) using a data extraction tool developed by the reviewers. The data extracted will include specific details about the patient characteristics (eg, age, sex, and disease), the definitions and measuring methods for atypical presentations and diagnostic errors, clinical settings (eg, department and outpatient or inpatient), type of evidence source, and the association between atypical presentations and diagnostic errors relevant to the review question. A draft extraction tool is provided in Table 1. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (MY). Authors of papers will be contacted to request missing or additional data, where required.

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Table 1. Data extraction instrument for the scoping review. The scoping review will include published or unpublished studies indexed in databases until December 2023; the scoping review will include quantitative, qualitative, and mixed methods study designs; systematic reviews; and opinion papers. The target population is adult patients cared for in internal medicine settings without restriction on disease, location, or time frame.

	Data extraction
Evidence source information	
Author	✓
Year	✓
Country	✓
Aim	✓
Study type or source	✓
Population	
Participants	✓
Age (years)	✓
Sex	✓
Target disease	✓
Context	
Setting	✓
Concept	
Details of the definitions and measurements to identify atypical presentations	✓
Details of the definitions and measurements to identify diagnostic errors	✓
Description or statistical results about the association between atypical presentations and diagnostic errors	✓
Details of the characteristics related to atypical presentations	✓

Data Analysis and Presentation

The extracted data will be presented in tabular format with descriptive statistics, and from this, the key components or types of atypical presentations—the purpose of this scoping review—will be identified to develop new criteria to identify atypical presentations for future studies of diagnostic errors. Developing the new criteria will follow the Joanna Briggs Institute guidance for a basic qualitative content analysis approach (following an inductive approach) [26]. In addition, we will classify the sources of evidence into 2 categories: disease-specific or generic studies to identify diseases and settings where the current evidence is lacking. Finally, we will list the specific types of atypical presentations highly associated with diagnostic errors.

Results

As of January 2024, a literature search through multiple databases is ongoing. We will complete this study by December 2024.

Discussion

Expected Findings

This scoping review aims to identify and present the available information regarding the definitions and measurements for atypical presentations to inform a new definition and criteria to identify atypical presentations at high risk of diagnostic errors. To maximize the quality of this scoping review, we will follow the updated scoping review guidelines, use multiple databases, and develop search strategies in consultation with experienced and skilled librarians. In addition, our review group includes expertise in diagnostic error research and has experience in developing new theories and concepts related to the diagnostic process. This scoping review aims to provide a rigorous evidence summary to describe how atypical presentations have been defined and measured in prior literature and use these findings to develop new criteria to identify atypical presentations at high risk for diagnostic errors. Findings will also inform the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine.

Comparison With Prior Work

In a systematic review focused on diagnostic errors in primary care, Kostopoulou et al [16] defined atypical presentations as “a shortage of prototypical features that are most frequently encountered in patients with the disease, features encountered in advanced presentations of the disease or simply features of the disease commonly listed in medical textbooks”; however, this definition has not been applied in subsequent research investigating the association between atypical presentations and diagnostic errors due to several limitations. For instance, the difficulty in defining the gold standard classic textbook disease descriptions may be one of the possible reasons that the definition has not been used. Current studies use disease-specific criteria for atypical presentations to detect and measure atypical presentations at high risk of diagnostic errors [12]. However, such an approach also has limitations: understanding of certain

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atypical presentation features of a disease evolves over time, and these features might not stand the test of time. An example of this is the loss of taste, which was recognized as an atypical symptom of COVID-19 during the early stages of the pandemic; however, as we learn more about the disease, the loss of taste is no more considered atypical for COVID-19. This scoping review will clarify the gaps and complexity in each disease's diagnostic criteria to diagnose atypical presentations and suggest a more refined approach that accounts for the limitations of prior definitions. The implications of our findings will be significant, indicating the potential for improving diagnostic processes and diagnostic accuracy by applying our new criteria.

Limitations

This scoping review will have several limitations. First, this scoping review will not include studies outside of internal medicine, and findings may not generalize to specialties outside of internal medicine. Furthermore, the evolving nature of diagnostic criteria and practices in internal medicine necessitates ongoing revision and validation of our proposed definitions and criteria. Second, although we will search for unpublished studies and gray literature, we may overlook some, potentially bringing bias to our understanding and conclusions. Third, confirmation bias can distort the findings in this scoping review because each study related to diagnostic errors may have overlooked atypical presentations. However, the upcoming new criteria from this scoping review can be expected to increase sensitivity to detect atypical presentations and reduce confirmation bias in future studies. Fourth, defining "atypical presentation" itself may present challenges, as evidenced by the difficulty in clearly distinguishing between concepts such as atypical presentations, phenotype, and nonspecific symptoms, as well as the challenge in defining the degree of atypicality and the boundary between typical and atypical. However, this is precisely the reason this research needs to be done because these issues need further clarification. Definitions and distinctions of these concepts will become clearer as a result of this exploration.

Conclusions

This scoping review can provide a rigorous evidence summary to describe how atypical presentations have thus far been defined and measured and help develop new criteria to identify atypical presentations at high risk for diagnostic errors in internal medicine. Developing the new criteria is expected to facilitate the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine. Additionally, such criteria can reduce the systematic selection biases in future diagnostic error studies that evaluate patients with atypical presentations. Review findings will highlight the need for further research to validate and refine these criteria, aiming to improve diagnostic processes and outcomes for patients with atypical presentations.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

YH conceptualized the study and conducted an initial limited search; YH wrote the draft and RK, MY, TS, and HS provided critical revisions to it; all authors contributed to the final revision of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v13i1e56933_app1.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Telehealth Evaluation in the United States: Protocol for a Scoping Review

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Abstract

Background: The rapid expansion of telehealth services, driven by the COVID-19 pandemic, necessitates systematic evaluation to guarantee the quality, effectiveness, and cost-effectiveness of telehealth services and programs in the United States. While numerous evaluation frameworks have emerged, crafted by various stakeholders, their comprehensiveness is limited, and the overall state of telehealth evaluation remains unclear.

Objective: The overarching goal of this scoping review is to create a comprehensive overview of telehealth evaluation, incorporating perspectives from multiple stakeholder categories. Specifically, we aim to (1) map the existing landscape of telehealth evaluation, (2) identify key concepts for evaluation, (3) synthesize existing evaluation frameworks, and (4) identify measurements and assessments considered in the United States.

Methods: We will conduct this scoping review in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). This scoping review will consider documents, including reviews, reports, and white papers, published since January 1, 2019. It will focus on evaluation frameworks and associated measurements of telehealth services and programs in the US health care system, developed by telehealth stakeholders, professional organizations, and authoritative sources, excluding those developed by individual researchers, to collect data that reflect the collective expertise and consensus of experts within the respective professional group.

Results: The data extracted from selected documents will be synthesized using tools such as tables and figures. Visual aids like Venn diagrams will be used to illustrate the relationships between the evaluation frameworks from various sources. A narrative summary will be crafted to further describe how the results align with the review objectives, facilitating a comprehensive overview of the findings. This scoping review is expected to conclude by August 2024.

Conclusions: By addressing critical gaps in telehealth evaluation, this scoping review protocol lays the foundation for a comprehensive and multistakeholder assessment of telehealth services and programs. Its findings will inform policy makers,

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health care providers, researchers, and other stakeholders in advancing the quality, effectiveness, and cost-effectiveness of telehealth in the US health care system.

Trial Registration: OSF Registries osf.io/aytus; https://osf.io/aytus

International Registered Report Identifier (IRRID): DERR1-10.2196/55209

(JMIR Res Protoc 2024;13:e55209) doi:10.2196/55209

KEYWORDS

cost; effectiveness; evaluation; framework; healthcare delivery; measurement; quality; scoping review; telehealth; United States

Introduction

Overview

Telehealth has witnessed a remarkable transformation in recent years, propelled by the COVID-19 pandemic, which has greatly accelerated its adoption and expansion. The imperative for social distancing and the need to minimize in-person contact have made telehealth a pivotal tool at the forefront of health care delivery, helping to ensure accessibility and continuity of health care. This transformation has been further facilitated by significant expansions in telehealth service coverage, as well as regulatory requirements for telehealth visits, by the Centers for Medicare and Medicaid Services (CMS) and other payers, enhancing accessibility and affordability for patients across the nation [1-5].

The rapid expansion of telehealth services underscores the necessity for comprehensive guidance and evaluation of telehealth programs to guarantee the quality and effectiveness of health care delivery. The World Health Organization (WHO) has published a series of operational guidelines and evaluation frameworks to facilitate its global strategy on digital health development [6-9].

Recognizing the importance of maintaining service quality in practice, professional groups and telehealth stakeholders across the United States have actively contributed to the development of clinical guidelines. For instance, the American Telemedicine Association (ATA) published practice guidelines to enhance the technical quality and reliability of telemental health services for children and adolescents [10]. The ATA's practice guidelines for ocular telehealth-diabetic retinopathy were updated to their third edition in 2020 to incorporate new evidence and technologies [11]. Furthermore, the American Heart Association (AHA) has advocated using remote patient monitoring technologies to improve cardiovascular disease outcomes [12], highlighting the ever-expanding role of telehealth in quality health care. The American Nurses Association (ANA) updated its core principles on telehealth in 2019 to provide guidance for health care professionals in delivering quality care using health technologies [13]. Similarly, the National Association of Social Workers (NASW) published guidance on legal considerations for telemental health, promoting adherence to state and federal practice guidelines and payer contract agreements among social workers [14].

Concurrently, in response to the rapidly evolving landscape of telehealth services, researchers, professional groups, and organizations have crafted telehealth evaluation frameworks. These frameworks have been designed to guide and facilitate the assessment of specific dimensions of telehealth programs. For example, Zhang et al [15] designed a framework to guide the development and evaluation of sustainable telehealth programs. Curfman et al [16] developed an economic framework focusing on measuring the value of pediatric telehealth. Moreover, a consortium of experts from the Kaiser Permanente (KP) Institute for Health Policy, AcademyHealth, the ATA, and the Physician Insurers Association of America (PIAA) collaborated on a telehealth research and policy framework, facilitating the assessment of health services and the quality of health care [17]. During the COVID-19 pandemic, the National Quality Forum (NQF) updated its telehealth measurement development framework, initially created in 2017, through an environmental scan conducted in 2021 [18-20].

Despite the wealth of telehealth evaluation frameworks available, several critical questions remain unanswered. First, the rapidly evolving state of telehealth programs, along with the emergence of innovative telehealth tools, has underscored the pressing need for a comprehensive grasp of the essential concepts that should be considered in their evaluation. For instance, the growing use of artificial intelligence in clinical assessments and the application of virtual reality among pediatric patients with autism spectrum disorder have garnered broad attention [21,22]. It is imperative to acquire a broader evaluation framework that accommodates these emerging technologies and provides a comprehensive understanding of integrating state-of-the-art technologies on telehealth platforms. As such, a scoping review that systematically identifies what telehealth services and programs are evaluated and how they are assessed is needed.

Additionally, while numerous frameworks have been proposed, many of them have been developed primarily from a narrow perspective or to address a specific need, potentially limiting their broader applicability and the comprehensiveness of the evaluation. For example, the framework developed by Zhang et al [15] focused on the sustainability of single telehealth programs, encompassing domains of program implementation, clinical effectiveness, and economic analysis. In contrast, the framework developed by KP, AcademyHealth, the ATA, and the PIAA considered five domains, including (1) policy context, (2) payment policy, (3) delivery, (4) modality, and (5) outcomes [17]. In the case of the NQF telehealth measurement development framework, it emphasizes assessing the impact of telehealth on health care system readiness and health outcomes in rural areas, spanning across another five domains: (1) access to care and technology; (2) costs, business model, and logistics; (3) experience; (4) effectiveness; and (5) equity [15,18,19]. Given the diverse array of telehealth stakeholders in the United

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States, including patients, providers, hospitals, payers, professional associations, federal agencies, policy makers, and legislators, it is necessary to consider the perspectives of multiple stakeholders and comprehensively evaluate telehealth services and programs.

Moreover, the measurements and assessments associated with telehealth evaluation domains and frameworks remain unclear, raising questions about how to effectively gauge the impact and outcomes of telehealth services and programs. While the frameworks developed by the WHO, Zhang et al [15], and NQF outline the measurements to be considered, this clarity is absent in the frameworks developed by KP, AcademyHealth, the ATA, and the PIAA [6-9,17,18].

Objective and Review Question

The broad objective of this scoping review is to answer the question of what is known about telehealth services and program evaluation in the United States. Specifically, this scoping review will be conducted to (1) map the existing landscape of telehealth evaluation, (2) identify key concepts for evaluation, (3) synthesize existing frameworks, and (4) identify measurements and assessments that have been considered.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, the Open Science Framework, and JBI Evidence Synthesis was conducted, and no current or in-progress scoping reviews or systematic reviews on the topic were identified.

Methods

Study Design

The scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [23-25].

Protocol and Registration

The protocol for this scoping review is registered on the Open Science Framework (osf.io/aytus) [26]. The scoping review is expected to be completed in 6 months.

Eligibility Criteria

The eligibility for this scoping review is elaborated following the Population, Concept, and Context (PCC) framework.

Participants

This scoping review will consider a range of document types, including reviews, reports, and white papers, specifically related to telehealth evaluation frameworks and associated measurements. The evaluation frameworks to be included will focus on telehealth services and programs used for the provision of health services through well-established modalities, such as store-and-forward telemedicine, remote monitoring, real-time counseling, audio and video conferencing, and videotelephony, as well as emerging innovations integrated with telehealth platforms, such as virtual realities and artificial intelligence [27]. We will exclude manuscripts with data analyses only, case studies, project intervention reports (including scale-up and scale-down studies), and commentaries.

Concept

This review will examine concepts pertaining to the evaluation frameworks of telehealth services and programs. The concepts to be examined will encompass existing evaluation frameworks and associated measurements developed by telehealth stakeholders, professional organizations, and authoritative sources, excluding those developed by individual researchers. This approach will allow us to collect data that reflect the collective expertise and consensus of experts within the respective professional group. The aim is to create a comprehensive overview of telehealth evaluation, incorporating perspectives from multiple stakeholder categories, including but not limited to public and private payers, providers, and policy makers.

Context

This review will consider documents published in English for various health care settings, for example, primary care, specialty care, and rural health care for adult and pediatric patients. Considering the diversity of the contexts of telehealth services and programs across different health care systems and the unique nature of the US health care system, publications reporting on evaluation frameworks developed for regions that do not include the United States will be excluded. Documents published by worldwide health organizations will be included, given their relevance and influence in US health care.

Search Strategy

As many evaluation frameworks are likely to be published on stakeholders' websites, we will source data from peer-reviewed journals and gray literature, such as reports, white papers, policy documents, and guidelines.

The search strategy will aim to locate published reviews, reports, and white papers. An initial PubMed search was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for PubMed (Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference lists of all included studies will be screened for additional titles. The databases to be searched include PubMed (US National Library of Medicine), Health Technology Assessments (International Network of Agencies for Health Technology Assessment), and Web of Science Core Collection (Clarivate Analytics). The websites of telehealth stakeholders, professional organizations, and authoritative sources mentioned in the included articles will be screened for additional documents.

Documents published from January 1, 2019, to the present will be considered for inclusion. While we recognize the relevance of earlier publications, the rapid expansion of telehealth, particularly accelerated by the COVID-19 pandemic, has led to significant changes in telehealth services and programs. During and after the pandemic, not only did the volume of telehealth

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services increase, but there was also a diversification in the types of modalities considered under the telehealth umbrella. For example, before the pandemic, audio-only interactions were not widely regarded as telehealth, and various modalities like e-consults and e-visits were not as commonly used as they are now. Therefore, the inclusion of documents published from January 1, 2019 onward will allow us to focus on the most recent and relevant telehealth service and program evaluations.

Source of Evidence Selection

Following the search, all identified records will be collated and uploaded into EndNote (V21; Clarivate Analytics), with duplicates removed. A total of 2 reviewers will independently screen titles and abstracts against the inclusion criteria. Following a pilot test, titles and abstracts will then be screened by 2 independent reviewers for assessment against the inclusion criteria for the review. All screening will be completed through Rayyan, a web-based tool for evidence synthesis projects [28]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of full-text documents that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [29].

Data Extraction

Data will be extracted from documents selected for inclusion in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers based on the JBI data extraction template for scoping review [24]. The data extracted will include specific details about the PCC methods and key findings relevant to the review question. A draft extraction tool is provided in Multimedia Appendix 2. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included document. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion.

Results

Reviewers will synthesize data across selected documents using tools such as tables and figures. Frequency counts of domains and measurements considered in frameworks and guidelines will be presented when applicable to highlight key patterns. Visual aids like Venn diagrams will be used to illustrate the relationships between the evaluation frameworks from various sources. Additionally, a narrative summary will be crafted to further describe how the results align with the review objectives, facilitating a comprehensive overview of the findings. This scoping review is expected to conclude by August 2024.

Discussion

Implications

In light of the rapid expansion of telehealth services, this scoping review seeks to address critical gaps in the current understanding of telehealth evaluation. The urgency of this endeavor is underscored by the need to ensure the quality, effectiveness, and cost-effectiveness of telehealth programs, with their increasing significance to the US health care system.

This scoping review will be the first to synthesize existing evidence of telehealth services and program evaluation in the United States and to facilitate the future development of telehealth in the postpandemic era. It will provide insights into the evaluation of state-of-the-art technology integration into telehealth.

In addition, the synthesized evaluation concepts and frameworks crafted by multiple telehealth stakeholders will guide the development of a multistakeholder evaluation framework that allows the comprehensive assessment of telehealth services and programs. Specifically, a multistakeholder framework will offer an inclusive and adaptable approach to telehealth evaluation, making it relevant and valuable to a wide range of users. By accommodating the diversity of telehealth initiatives, technologies, and objectives that exist within the US health care system, it will provide flexibility for stakeholders to tailor their evaluations for specific needs and objectives. In the evolving landscape of telehealth, where innovations and changes occur regularly, new technologies, practices, and policies would also be considered in the multistakeholder framework. The consideration of measurements and assessments will further illuminate the path toward actionable telehealth evaluation by providing more context and details.

Limitations

While we aim to conduct a comprehensive scoping review, some limitations should be considered. First, to ensure the comprehensiveness and relevance of this study's findings, we only consider frameworks developed for regions that encompass the United States. For instance, frameworks from organizations like the WHO are considered if they pertain to the US context. However, given the unique and complex nature of the US health care system, the results from this scoping review might not be directly applicable to other countries. In addition, given that the scoping review aims to provide a comprehensive overview of telehealth evaluation from a multistakeholder perspective, the scoping review will exclude documents carried out by individual researchers. Therefore, when evaluating local telehealth programs, it is advisable to include specific local considerations in addition to the results of this scoping review.

Conclusions

This scoping review will serve as a critical initial step in advancing the understanding of telehealth evaluation, given the current role of telehealth in the US health care system. Its findings will inform policy makers, health care providers, researchers, and other stakeholders involved in the rapidly evolving field of telehealth. By addressing these fundamental questions, this protocol lays the foundation for the scoping

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review for comprehensive telehealth evaluation and future telehealth advancement.

Acknowledgments

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Authors' Contributions

YZ, YYL, LSL, JCR, EGH, and JMS undertook the conceptualization and methodology of this study. YZ drafted the initial version of the manuscript, with all authors contributing to the investigation and subsequent review and editing. YZ and EGH managed the resources for the study, while YZ and SC handled project administration. SC secured the funding for the project. SC and JMS provided additional supervision.

Conflicts of Interest

LSL is an employee of ConcertAI. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Search strategy.
[DOCX File , 21 KB - resprot_v13i1e55209_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 22 KB - resprot_v13i1e55209_app2.docx]

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Abbreviations

AHA: American Heart Association
ANA: American Nurses Association
ATA: American Telemedicine Association
CMS: Centers for Medicare and Medicaid Services
JBI: Joanna Briggs Institute
KP: Kaiser Permanente Institute for Health Policy
NASW: National Association of Social Workers
NQF: National Quality Forum
PCC: Population, Concept, and Context
PIAA: Physician Insurers Association of America
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Digital Health Interventions in Older Adult Populations Living With Chronic Disease in High-Income Countries: Protocol for a Scoping Review

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Abstract

Background: Globally, around 80% percent of adults aged 65 years or older are living with at least 1 chronic disease, and 68% percent have 2 or more chronic diseases. Older adults living with chronic diseases require greater health care services, but these health care services are not always easily accessible. Furthermore, the COVID-19 pandemic has resulted in unprecedented changes in the provision of health care services for older adults. During the COVID-19 pandemic, digital health interventions for chronic disease management were developed out of necessity, but the evidence regarding these and developed interventions is lacking.

Objective: In this scoping review, we aim to identify available digital health interventions such as emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms for chronic disease management for older adults in high-income countries.

Methods: We will follow the Arksey and O'Malley framework to conduct the scoping review. Our full search strategy was developed following a preliminary search on MEDLINE. We will include studies where older adults are at least 65 years of age, living with at least 1 chronic disease (eg, cancer, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes), and residing in high-income countries. Digital health interventions will be broadly defined to include emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms.

Results: This scoping review is currently ongoing. As of March 2023, our full search strategy has resulted in a total of 9901 records. We completed the screening of titles and abstracts and obtained 442 abstracts for full-text review. We are aiming to complete our full-text review in October 2024, data extraction in November 2024, and data synthesis in December 2024.

Conclusions: This scoping review will generate evidence that will contribute to the further development of digital health interventions for future chronic disease management among older adults in high-income countries. More evidence-based research is needed to better understand the feasibility and limitations associated with the use of digital health interventions for this population. These evidence-based findings can then be disseminated to decision-makers and policy makers in other high-income countries.

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KEYWORDS

chronic disease; high-income countries; digital health; interventions; older adults; quality of life

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Introduction

Globally, according to the World Health Organization (WHO), 41 million people die from chronic diseases each year [1]. Four chronic diseases, including cancer, cardiovascular diseases, chronic respiratory diseases, and diabetes, are responsible for over 80% of all premature mortality worldwide [1]. Chronic disease outcomes are worse for older adults compared to their younger counterparts [2]. For instance, according to the US Centers for Disease Control and Prevention (CDC), around 85% of older adults in the United States endure at least 1 chronic disease and approximately 60% have at least 2 chronic diseases [3,4]. In Canada, approximately 70% of people aged at least 65 years are living with at least 1 of 10 common chronic diseases [4]. Life expectancy continues to increase, especially in high-income countries [5], and, given that age increases the risk of developing chronic diseases [6], the prevalence of chronic disease is also expected to grow. Thus, it is crucial to identify potential strategies for older adults with chronic diseases in high-income countries. Furthermore, while older adults living with chronic diseases require a greater amount of health care services, these health care services are not always easily accessible for this population [7].

The COVID-19 pandemic has had and continues to have a detrimental impact on the global health systems [8]. During the initial stages of the COVID-19 pandemic, older adults were often unable to access health care services due to public health mandates [9]. In the later stages of the COVID-19 pandemic, access to health care services was still limited due to lengthened waitlists and increased staff shortages [10]. Older adults living with chronic diseases and their caregivers experienced increased levels of stress and worse chronic disease outcomes due to this lack of access [11,12]. It is therefore essential that alternatives to in-person interventions be developed to ensure accessible health care services during public health emergencies such as the COVID-19 pandemic.

Amid the emergent COVID-19 pandemic, digital health interventions such as telehealth and app-based health care were developed in response to limitations to in-person interventions [13]. There are few evidence-based guidelines on digital health intervention for chronic disease management. Thus, this review is essential to identify available digital health interventions to manage chronic diseases among older adults. So, the primary aim of this scoping review is to identify available digital health interventions for chronic disease management among older adults in high-income countries. The secondary aim of this scoping review will be to identify potential outcomes associated with these digital health interventions such as early diagnosis, increasing health literacy for chronic disease management, or improving quality of life. Findings from this scoping review will further support the development and evaluation of future digital health interventions.

Methods

Overview

The 6 steps of the Arksey and O'Malley [14] framework will be used to conduct a scoping review to investigate digital health interventions to manage chronic disease among older adults in high-income countries. Given the possibility of a high risk of bias when conducting reviews [15], we will include a quality assessment as an additional step in our scoping review as recommended by Levac et al [16]. Thus, the scoping review will be completed in the 7 steps illustrated in Figure 1.

Figure 1. Arksey and O'Malley's methodological framework with the additional step of quality assurance.

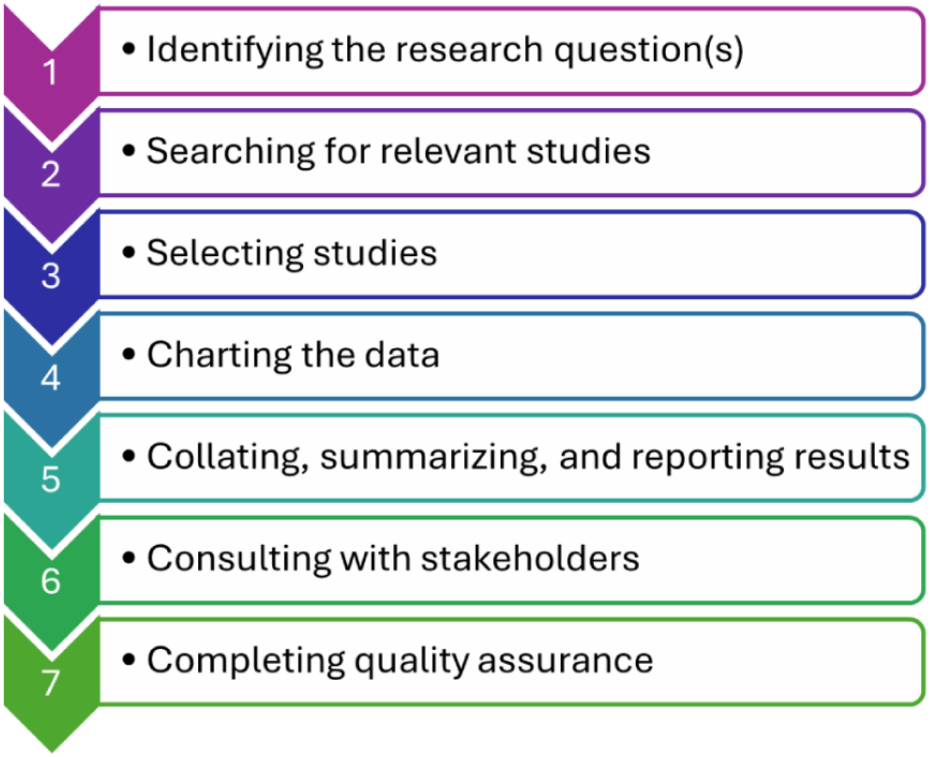

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Step 1: Identifying the Research Questions

For this scoping review, the research questions that have been identified are as follows: What are the digital health interventions aimed at improving outcomes associated with chronic disease management for older adults? (2) With regards to the identified digital health interventions, what are the associated outcomes (such as early diagnosis, prevention, or treatment for chronic disease or increasing health literacy on chronic disease management) for (1) older adults, (2) their caregivers, and (3) the health system?

Step 2: Searching for Relevant Studies

A preliminary search was conducted in the Cochrane Database of Systematic Reviews, Joanna Briggs Institute (JBI) Evidence Synthesis, Open Science Framework, and International Prospective Register of Systematic Reviews (PROSPERO) to identify other similar scoping reviews. Following this preliminary search, the full search strategy was conducted by an academic librarian. An initial MEDLINE search was undertaken in February 2023 to identify papers on the topic by focusing on the concepts of older adults, caregivers, the health care system, digital interventions, and chronic disease. The text words contained in the titles and abstracts of relevant papers, as well as the index terms used to describe the papers were used to develop a full search strategy for Ovid MEDLINE(R) and In-Process, In-Data-Review and Other Non-Indexed Citations and Daily (1946-2023; Multimedia Appendix 1). Papers published in any language from database inception to the present were included. The search strategy, including all identified text words and index terms, was translated to CINAHL Plus (Ebsco; 1966-2023), JBI EBP Database (Ovid; 2012-2023), PsycINFO (Ovid; 1806-2023), and Web of Science (1966-2023) by the academic librarian that can be accessed upon request. Finally, using similar text words and index terms, sources of grey literature searched included Google Advanced, Grey Literature Report, and ProQuest Dissertations & Theses: Global (1861-2022). The full search strategy was undertaken on April 3, 2023.

Step 3: Selecting Studies

Following a pilot test, titles and abstracts of studies including methodology of randomized controlled trials, nonrandomized controlled trials, pre-post studies, interrupted time-series studies, prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies will be imported into Covidence (Veritas Health Innovation). The titles and abstract will be screened by 2 independent reviewers for assessment against the inclusion criteria for the scoping review as outlined below for full-text review. The selected papers will be downloaded for full-text review in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer.

Inclusion Criteria

Population

The population of interest includes adults who are aged at least 65 years and living with chronic disease. For a study to be included in this review, at least 50% of the sample must be aged at least 65 years or the mean age of the sample needs to be at least 65 years. Chronic diseases considered eligible for this review include cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes. Finally, studies will be included if they are with populations residing in 1 of the selected countries with a high or very high Human Development Index [17]—Australia, Canada, and the United States.

Interventions

Studies examining digital health interventions for chronic disease management will be included. Digital health interventions will be broadly defined to include emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms. Chronic disease management will be defined as the management of at least one of the following chronic diseases: cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes.

Comparisons

Studies with comparisons to digital health interventions (such as placebo or health service delivery as usual) or without comparison (no comparative intervention), will be considered.

Outcomes

Following the initial screening of papers, we have identified a few potential outcomes such as studies that include outcomes related to physical health (eg, blood pressure and blood sugars) and mental health (eg, anxiety and depression) assessed with validated tools or approaches will be considered for this scoping review. Improvements in health education or health literacy as well as quality of life will also be considered as appropriate. However, we are open to adding other outcomes following full-text review after iterative discussion with research team members.

Exclusion Criteria

The exclusion criteria for this study are (1) studies published in a form other than a peer-reviewed journal paper; (2) studies written in a language other than English; (3) studies with less than 50% of the sample aged at least 65 years or the mean age of the sample less than 65 years; (4) studies focused solely on chronic diseases other than cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes; (5) studies published in a country other than Australia, Canada, or the United States; and (6) studies examining health interventions that are not digital (eg, in-person counseling) or digital interventions that are not focused on health (eg, general time management skills).

Step 4: Charting the Data

Data will be extracted from studies included in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers. Any disagreements that arise between the reviewers will be resolved through discussion or

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with a third reviewer. The data extracted will include the following details: authors, year of publication, objectives, type of study, population, intervention, comparisons, and outcomes. Where required, authors of papers will be contacted to request missing or additional data. A draft of our data extraction tool is provided (Multimedia Appendix 2). The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review.

Step 5: Collating, Summarizing, and Reporting the Results

The results will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [18,19]. When summarizing, we will list the type and format of interventions included in eligible studies. We will also organize similar outcomes together to determine the direction of outcomes included in the interventions. We will use descriptive numerical summary analysis for the results. The data will be mapped and presented in tabular format to make it easier to answer our research questions. A narrative summary will accompany the results and will describe how the results relate to the research questions.

Step 6: Consultation With Stakeholders

For this step, we will consult with researchers from high-income countries with expertise in older adults, chronic disease management, and digital interventions to provide any relevant studies aligned with our research questions. We will also consult with a group of patient partners living with chronic disease to validate the study findings.

Step 7: Quality Assessment

We will assess the quality of the studies included in this scoping review using JBI's Critical Appraisal Checklist for Systematic Reviews and Research Syntheses [20]. Prior to critical appraisal, 2 independent reviewers will meet to determine the criteria for indicating a "yes," "no," "unclear," or "not applicable" response in the context of this scoping review for each of the 11 items. For items that are deemed "unclear," authors of the reviews will be contacted to request missing or additional data for clarification. Each study will be ranked according to findings from the critical appraisal as low quality (ie, "yes" for 0%-33% of critical appraisal items with a "yes" or "no"), medium quality (ie, "yes" for 34%-66% of critical appraisal items with a "yes" or "no"), and high quality (ie, "yes" for 67%-100% of critical appraisal items with a "yes" or "no"). The results of critical appraisal will be reported in a critical appraisal table.

Results

Screening of titles and abstracts has been completed. The full-text review is expected to be complete by the end of October 2024, followed by data extraction in November 2024, and data synthesis in December 2024. We will disseminate the findings of the scoping review at the national and international scientific conference proceedings and by publishing the paper in a peer-reviewed journal.

Discussion

Principal Findings

With our rapidly aging population, digital health interventions may play a crucial role, especially for the management of chronic diseases among older adults. To our knowledge, our research will be one of the first that will highlight the available digital health interventions for the management of chronic disease which leads to major issues such as disability and interruption in the activities of daily living among older adults [7]. This scoping review will provide a comprehensive synthesis of existing digital interventions that will contribute to designing a feasible intervention model that can be customized by communities that need to manage chronic disease and improve the quality of life among older adults.

Though we will conduct a comprehensive scoping review, there may be some limitations that we will not be able to address. In this scoping review, we will only include peer-reviewed journal papers, so we may miss and exclude some of the evidence-based unpublished data from our findings. Another important limitation is that papers written in a language other than English will be excluded from our scoping review. Thus, additional research focusing on the available unpublished data findings and non-English papers would be helpful for generating evidence to gather available digital health interventions for chronic disease management.

The findings of the scoping review will assist researchers in the further establishment of digital health interventions for chronic disease management among older adults. More evidence-based research is crucial to understanding the potential barriers and enablers of digital health for older adults and, especially, older adults with chronic diseases.

Conclusions

Digital health interventions have become a prevalent form of health care services since the COVID-19 pandemic, but more evidence-based research is needed to assess the outcomes associated with digital health interventions. Findings from this scoping review will provide an overview of empirical evidence regarding digital health interventions and provide a stepping stone for the development and evaluation of future digital health interventions for older adults living with chronic disease.

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Authors' Contributions

All authors contributed to the paper writing, revision, and identifying the search strategy. NLG and MNA conceptualized the study. CB formulated and modified the search strategy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Database and search strategy.
[DOCX File , 16 KB - resprot_v13i1e49130_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOC File , 25 KB - resprot_v13i1e49130_app2.doc]

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Abbreviations

CDC: US Centers for Disease Control and Prevention
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
WHO: World Health Organization

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Protocol

Holistic Person-Centered Care in Radiotherapy: Protocol for a Scoping Review

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Abstract

Background: Several types of health care professionals are responsible for the care of patients with cancer throughout their engagement with the health care system. One such type is the radiotherapist. The radiotherapist not only administers treatment but is also directly involved with the patient during treatment. Despite this direct contact with the patient, the narrative tends to focus more on technical tasks than the actual patient. This task-focused interaction is often due to the highly sophisticated equipment and complex radiotherapy treatment processes involved. This often results in not meeting the psychosocial needs of the patient, and patients have acknowledged noncompliance and delayed treatment as a result.

Objective: The scoping review aims to explore, chart, and map the available literature on holistic person-centered care in radiotherapy and to identify and present key concepts, definitions, methodologies, knowledge gaps, and evidence related to holistic person-centered care in radiotherapy.

Methods: This protocol was developed using previously described methodological frameworks for scoping studies. The review will include both peer-reviewed and gray literature regarding holistic, person-centered care in radiotherapy. A comprehensive search strategy has been developed for MEDLINE (Ovid), which will be translated into the other included databases: Scopus, CINAHL (EBSCO), MEDLINE (PubMed), Embase (Elsevier), Cochrane Library, and the Directory of Open Access Journals. Gray literature searching will include Google (Google Books and Google Scholar), ProQuest, the WorldWideScience website, the OpenGrey website, and various university dissertation and thesis repositories. The title and abstract screening, full-text review, and relevant data extraction will be performed independently by all 3 reviewers using the Covidence (Veritas Health Innovation) software, which will also be used to guide the resolution of conflicts. Sources selected will be imported into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH) for analysis, which will consist of content analysis, narrative analysis, and descriptive synthesis. Results will be presented using narrative, diagrammatic, and tabular formats.

Results: The review is expected to identify research gaps that will inform current and future holistic, person-centered care in radiotherapy. The review commenced in November 2023, and the formal literature search was completed by the end of February 2024. Final results are expected to be published in a peer-reviewed journal by 2025.

Conclusions: The findings of this review are expected to provide a wide variety of strategies aimed at providing holistic, person-centered care in radiotherapy, as well as to identify some gaps in the literature. These findings will be used to inform future studies aimed at designing, developing, evaluating, and implementing strategies toward improved holistic, person-centered care in radiotherapy.

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KEYWORDS

cancer patient; cancer; cancer care; holistic care; person-centered care; person-centered; radiologist; radiology; radiotherapist; radiotherapy; scoping review; holistic care

Introduction

Radiotherapy, also referred to as radiation therapy, is a treatment modality that uses high-energy radiation or radioactive substances to destroy cancer cells or prevent their growth [1]. The clinical usefulness of ionizing radiation was discovered after the discovery of X-rays and has since developed into a medical specialty. Ionizing radiation damages the genetic material of cancer cells, blocking the cells' ability to proliferate, thus destroying the cancer cells [2]. Radiotherapy has become a highly cost-effective, leading modality in cancer treatment, as it can be used as a primary form of treatment or in combination with other modalities for curative or palliative purposes within cancer treatment [3]. Radiotherapy has an approximate 40% cure rate when used as a single modality of treatment compared to only 11% achieved by chemotherapy when used as a single modality of treatment [4]. Chemoradiotherapy use has experienced substantial growth and is now established as the standard treatment for various types of tumors, such as cervical, non–small cell lung cancer, and bladder cancer, as elaborated in this discussion. It provides considerable advantages in patient survival and local disease control while not significantly increasing long-term toxicities [5]. Radiotherapy is considered a conservative form of treatment with reduced adverse effects, unlike other treatments such as surgery, which can have mutilating and other long-term adverse effects, thus maintaining a good quality of life [6].

Evidence-based practice shows that more than 50% of patients with cancer will undergo a course of radiotherapy as part of their treatment, and despite this, patients appear to lack knowledge of the importance of radiotherapy treatment and its effects [7,8]. Negative perceptions toward receiving radiotherapy treatment have been expressed, as some patients with cancer consider it to be a form of poison, while others fear the effects of radiation as they believe it would cause another cancer, thus delaying seeking care [6,9]. Despite the vast improvement in radiotherapy technology, in addition to dealing with treatment-related toxicities [10], many patients also experience emotional challenges such as fear, anger, depression, stress, and anxiety [7,11]. Almost a third of patients with cancer acknowledge not having their psychosocial needs taken care of during treatment, resulting in a decrease in compliance, delayed treatment, and a decrease in quality of life, thus negatively impacting tumor control [7,12,13]. These perceptions, therefore, present an urgent need for a person-centered care approach to enhance the experience and well-being of the patient with cancer [14]. A person-centered care approach considers the needs and preferences of patients and thus allows patients to be actively involved in any treatment and decision-making [15]. Although patients with cancer come across many health professionals along their journey, radiotherapists have a key role in the experience of the patient with cancer as they find themselves in direct contact with the patient throughout the course of their radiotherapy treatment [12,16].

Radiotherapists are experts in the technical and clinical planning and delivery of radiotherapy treatment. They are equally responsible for providing care and support, monitoring and managing treatment-related toxicities, and coordinating supportive care, which can be last up to 6 weeks [8]. This places the radiotherapist in a unique position to engage with patients concerning their diagnosis and treatment [16,17]. However, despite the radiotherapist's direct contact with the patient, the narrative tends to focus more on technical tasks and other barriers, often at the cost of important psychosocial needs not being met [18]. Radiotherapists' disregard for patient care has also been influenced by the stressful nature of the workplace environment and the time pressures they face [17]. Nonetheless, the consequences of providing support in the form of empathy, compassion, and reassurance must be understood by radiotherapists, as it can result in alleviating their patients' anxiety and fear before the treatment [19]. Empathy is of particular importance in cancer delivery, as patients acknowledge having greater satisfaction and self-awareness when treated with empathy [20,21]. The length of time that a patient with cancer spends interacting with a radiotherapist has been shown to have a considerable impact on their overall experience [17]. Radiotherapists' daily direct contact with patients with cancer, therefore, not only enables them to prioritize their unique needs and values but also allows them to be involved in their care, creating a person-centered approach to treatment.

Radiotherapists can facilitate person-centered care by ensuring patients have their undivided attention [22]. This process can be initiated by building a rapport with each patient, communicating effectively, answering their questions, discussing their preferences, listening actively, addressing their physical and emotional needs, providing them with dignity, and collaborating with other health care professionals to ensure the patient's needs are met. Patients stated that they felt more included and positive about their radiotherapy treatment when these aspects were addressed [8,17,22]. Person-centered care is also considered to be synonymous with "wholism," or, as some may prefer, "holism." Holistic care considers the body, mind, soul, and spirit as interrelated and acknowledges the whole experience [23]. Holistic, person-centered care is, therefore, becoming increasingly important in cancer treatment, including radiotherapy [24]. Holistic care in radiotherapy allows for a personalized approach to patient care, which includes addressing the physical, emotional, social, and spiritual needs of the patient, empowering the patient, and promoting healing and well-being, thus improving the overall quality of life of the patient.

There is a paucity of literature related to holistic, person-centered care in radiotherapy. A search of the Open Science Framework, the Cochrane Database of Systematic Reviews, and Johanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no published or in progress scoping or

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systematic reviews were identified relating to holistic person-centered care in radiotherapy.

The proposed scoping review will explore, map, and summarize the nature, range, and extent of published literature available that relates to holistic person-centered care in radiotherapy. Identified sources will be described in terms of population, purpose, and setting, as well as theoretical underpinnings, outcome measures, and key findings. The proposed scoping review will assist in identifying common practices, knowledge gaps in the literature, and potential areas for future research and development.

Methods

Protocol Design

The proposed scoping review was developed using the methodological framework for scoping reviews developed by Arksey and O'Malley [25] and incorporates the updated frameworks suggested by Levac et al [26] and Peters et al [27], as well as the updated JBI methodology for scoping reviews [28]. The "population, concept, and context" (PCC) framework will guide the review, which will follow the following stages: (1) identification of the review question or questions and (2) identification of relevant studies. This will assist with the development of specific inclusion criteria to facilitate a comprehensive search of the literature. A comprehensive search for relevant studies will then be conducted, followed by the screening of those studies. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) will guide the reporting process [29].

Step 1: Identification of the Review Question or Questions

The research questions that will guide this scoping review are as follows: (1) What sources are available that relate to holistic, patient-centered care in radiotherapy? (2) What types of studies have been conducted on holistic, patient-centered care in radiotherapy? (3) In what settings have these studies been conducted? (4) What health care professionals and patients have been included in the studies? (5) What has the key approach been to the studies? (6) What theories have underpinned the studies? and (7) Were there any identified measures or outcomes from the studies?

Step 2: Identification of Relevant Studies

A comprehensive search strategy has been developed by the 3 members of the research team and an experienced librarian and information specialist. An exploratory search in MEDLINE (PubMed) and CINAHL (EBSCO) was performed to identify relevant articles on the topic (Multimedia Appendix 1). Once the scoping review commences, identified keywords in the titles and abstracts of articles related to the review question will be used to complement the search strategy, thus allowing for a more comprehensive search. The search strategy will also be adapted as required by scrutinizing the reference lists of articles that meet the inclusion criteria to find additional papers. Literature published in English and studies that can be translated will be considered. The search will commence in August 2023 and will not have a date limit to ensure that all studies that meet the inclusion criteria are considered. Once the search for each database has been completed, the results will be imported into Covidence (Veritas Health Innovation) for storage, organization, removal of duplicates, screening, and mapping of the data [30].

Step 3: Selection of Studies for Inclusion

The preliminary inclusion criteria will be defined using the PCC format. Details for each aspect of this format are described in the following sections.

Population

The population for this scoping review will be radiotherapists and patients involved in radiotherapy. Given that the scoping review aims to explore holistic person-centered care in radiotherapy, there will be no limitations placed relating to cancer or radiotherapy type, duration of treatment, or final outcome, nor will there be age, geographical, or time-based limitations placed on sources.

Concept

This review will consider studies that focus on person-centered care within radiotherapy to identify key concepts, definitions, methodologies used, existing models of care, and knowledge gaps in the literature. Any studies that included an intervention to improve person-centered care in radiotherapy and sources of evidence that informed practice will also be included.

Context

The scoping review will consider literature that is relevant to the radiotherapy context. The review will include the experiences of patients receiving radiotherapy treatment and evidence on the role of radiotherapists in providing any form of care or support to patients with cancer during radiotherapy treatment. in both private and public settings.

Types of Sources

In view of the fact that patient-centered care has been and is still a key issue in health care, the scoping review will aim to explore and integrate qualitative, quantitative, and mixed methods research data concerning person-centered care. Literature will be sourced from databases that will include Scopus, CINAHL (EBSCO), PubMed, the Education Resources Information Centre, the Cochrane Library, Sabinet, and the Directory of Open Access Journals. Any systematic reviews that meet the inclusion criteria will also be taken into account. Secondary sources that will be used in the search include Google (Google Books and Scholar), ProQuest, the WorldWideScience website, the OpenGrey website, and various university dissertations and thesis repositories.

Study Selection

Studies identified in the initial database search will be collated and then transferred into Covidence, which allows for duplicates to be removed and for appropriate studies to be sorted and selected based on the inclusion criteria [30]. The first stage, which involves the screening of titles and abstracts, will be performed independently by all 3 members of the research team, who will vote in Covidence to determine primary inclusion. Any disagreements will be resolved through discussion among

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the team members, and in the event of an impasse, the decision will be by majority vote. The second stage of article selection will involve the downloading of identified sources from the first stage and then a screening of these articles in Covidence. Full-text sources that do not meet the inclusion criteria will be recorded, and reasons for exclusion will be reported in the scoping review. Any disagreements between the research team members at any stage of the selection process will be resolved through discussion. The PRISMA-ScR checklist and flow diagram will be used to report and present in full the results of the search and study inclusion selection in the final scoping review [28,29].

Step 4: Charting and Extraction of the Data

The extraction tool will be developed by the research team (Multimedia Appendices 2 and 3) in accordance with the JBI methodology for scoping reviews [29] and will be piloted in Excel (Microsoft Corporation) for relevance and ease of use. With the aid of an extraction tool, data will be independently extracted from the selected studies by the 3 members of the research team. Covidence has the advantage that changes can be made to the data extraction form at any time, even while extraction is in progress [30]. The data extracted will include study-specific details regarding article title, authors, geographic area, journal or other source, year of publication, aim or purpose, study population and sample size, context, methodology, intervention, outcomes, and key findings related to the scoping review questions. Data must be compared, and a consensus must be reached before the data can be exported. After completing the literature search and collecting all related evidence regarding person-centered care in radiotherapy, the next step will be to chart the data. This step involves synthesizing and interpreting the data, which allows key issues and themes to be highlighted. Sources will be imported into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), and thematic analysis will be used to identify themes that will then be summarized and discussed in relation to the study aims and objectives [31]. The identified codes and themes will be used to map the different aspects of person-centered care in radiotherapy as well as any evidence gaps. Should any missing data be noted in the data extraction table, it will be noted as “missing.” The data will be collated from ATLAS.ti and presented in a narrative summary and table format.

Step 5: Collation, Synthesis, and Reporting of the Results

The results will allow the researchers to better understand the delivery of holistic, person-centered care in radiotherapy. In addition, the role of the radiotherapist will be analyzed, as will what is required of them to enhance this phenomenon. The results may also raise awareness of important issues in the radiotherapy profession that should be included in the education of future radiotherapists. The results will be reported in accordance with the PRISMA-ScR reporting guidelines.

Results

The scoping review commenced in November 2023, and the formal literature search was completed by the end of February 2024. We are currently in the process of screening articles. A preliminary search of the literature was conducted using the Scopus database in November 2023, revealing 37,345 results using the initial search terms. We intend to publish the manuscript in an appropriate, peer-reviewed, and open-access health care journal to describe our findings and conclusions to the academic audience in 2025.

Discussion

Overview

There are several aspects related to patient-centered care within radiotherapy where gaps exist, but these are not well described. This scoping review intends to provide an overview of the current knowledge related to patient-centered care in radiotherapy, the effects that patient-centered care in radiotherapy has on both patients and radiotherapists, and to highlight existing gaps in the literature. The use of gray literature may also supplement the search to find pertinent information that cannot be found in the databases. Finally, this strategy will provide an important lens for understanding the value of delivering holistic, person-centered care in radiotherapy. The scoping review method complies with the JBI recommendations [28] and will use the most recent reporting guidelines [29] to ensure that a comprehensive process that can be tracked is used.

The findings will assist radiotherapists and radiotherapy departments, as well as educational institutions, in identifying elements that are vital for the delivery of holistic, person-centered care in radiotherapy. The study may also determine the need for additional curriculum content or additional courses for radiotherapists to fulfill their role as holistic care providers.

Limitations

The scoping review has some limitations. First, the search terms are variable due to the differing terminology used to describe radiotherapy and patients with cancer. Also, the research team will only consider sources available in English, meaning that sources not written in English will be missed, limiting generalizability. The quality of the studies included will not be evaluated for quality or methodological rigor; however, this is acceptable within the context of a scoping review and the aims of this review.

Conclusion

The scoping review will assist in providing information that will be indispensable in the development of a conceptual framework to guide holistic, person-centered care in radiotherapy. The results will be disseminated at a national radiotherapy conference, including publishing a paper in a radiotherapy journal. This scoping review strategy hopes to address a gap in the literature and create awareness for radiotherapists about the importance of delivering holistic, person-centered care.

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The review will contribute to the completion of a doctoral degree from the Faculty of Health Sciences, University of Johannesburg, for the author FB.

Authors' Contributions

All authors contributed to the manuscript. AWM led the development of the methods and search strings. FB and KH contributed to the contextualization of the protocol and reviewed the Methods section. AWM is the primary supervisor, and KH is the co-supervisor of FB.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms and results from an initial search conducted in Scopus.
[DOCX File , 155 KB - resprot_v13i1e51338_app1.docx]

Multimedia Appendix 2
JBI template source of evidence details, characteristics, and results extraction instrument.
[DOCX File , 154 KB - resprot_v13i1e51338_app2.docx]

Multimedia Appendix 3
Data extraction sheet developed by researchers for data extraction.
[DOCX File , 154 KB - resprot_v13i1e51338_app3.docx]

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Abbreviations

JBI: Johanna Briggs Institute

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PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Exploring the Use and Implications of AI in Sexual and Reproductive Health and Rights: Protocol for a Scoping Review

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Abstract

Background: Artificial intelligence (AI) has emerged as a transformative force across the health sector and has garnered significant attention within sexual and reproductive health and rights (SRHR) due to polarizing views on its opportunities to advance care and the heightened risks and implications it brings to people's well-being and bodily autonomy. As the fields of AI and SRHR evolve, clarity is needed to bridge our understanding of how AI is being used within this historically politicized health area and raise visibility on the critical issues that can facilitate its responsible and meaningful use.

Objective: This paper presents the protocol for a scoping review to synthesize empirical studies that focus on the intersection of AI and SRHR. The review aims to identify the characteristics of AI systems and tools applied within SRHR, regarding health domains, intended purpose, target users, AI data life cycle, and evidence on benefits and harms.

Methods: The scoping review follows the standard methodology developed by Arksey and O'Malley. We will search the following electronic databases: MEDLINE (PubMed), Scopus, Web of Science, and CINAHL. Inclusion criteria comprise the use of AI systems and tools in sexual and reproductive health and clear methodology describing either quantitative or qualitative approaches, including program descriptions. Studies will be excluded if they focus entirely on digital interventions that do not explicitly use AI systems and tools, are about robotics or nonhuman subjects, or are commentaries. We will not exclude articles based on geographic location, language, or publication date. The study will present the uses of AI across sexual and reproductive health domains, the intended purpose of the AI system and tools, and maturity within the AI life cycle. Outcome measures will be reported on the effect, accuracy, acceptability, resource use, and feasibility of studies that have deployed and evaluated AI systems and tools. Ethical and legal considerations, as well as findings from qualitative studies, will be synthesized through a narrative thematic analysis. We will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) format for the publication of the findings.

Results: The database searches resulted in 12,793 records when the searches were conducted in October 2023. Screening is underway, and the analysis is expected to be completed by July 2024.

Conclusions: The findings will provide key insights on usage patterns and evidence on the use of AI in SRHR, as well as convey key ethical, safety, and legal considerations. The outcomes of this scoping review are contributing to a technical brief developed by the World Health Organization and will guide future research and practice in this highly charged area of work.

Trial Registration: OSF Registries osf.io/ma4d9; https://osf.io/ma4d9

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KEYWORDS

artificial intelligence; AI; sexual health; reproductive health; maternal health; gender; machine learning; natural language processing; review; systematic documentation; protocol; scoping review; electronic database; technical consultation; intervention; methodology; qualitative; World Health Organization; WHO; decision-making

Introduction

Artificial intelligence (AI) refers to the development of algorithms, processes, machines, and computer programs capable of performing automated tasks, without the programming of each step explicitly by a human [1,2]. Advances in computing processing combined with the amassing of data through digital tools, particularly with increases in the penetration of mobile devices, have propelled the field of AI within health [3-6]. AI includes approaches such as machine learning, in which statistical and mathematical modeling techniques are used to define and analyze data. This can also be applied through natural language processing to analyze text-based data and signal processing for audio, images, and videos [6,7]. The use of AI varies across health fields, with radiology and pathology being the dominant areas where machine learning has been leveraged to optimize the processing of large volumes of medical imaging data [6,7]. Recent advancements in AI, particularly generative AI and large language models, have expanded the ability to address a diverse set of health needs.

The field of sexual and reproductive health encompasses health domains, such as family planning and fertility care, maternal health, sexually transmitted infections (STIs), safe abortion care, sexual health and well-being, and gender-based violence [8,9]. It is underpinned by broader principles of bodily autonomy, human rights, women's empowerment, and gender equality, encapsulated as sexual and reproductive health and rights (SRHR) [10]. Considering the perceived sensitivity and often politicization of these health topics beyond the influence of technology, the use of AI in SRHR is an emerging area with both great potential and justifiable concerns. Individuals' desires for anonymity in seeking sexual and reproductive health services positions AI systems and tools, such as conversational agents, as critical conduits for expanding access to information and care [11-13]. Furthermore, shortfalls in human resources and the need for targeted health interventions, such as in the areas of maternal health care and management of STIs, serve as key issues that have the potential to be addressed through the predictive capabilities offered by AI [14]. In addition, the use of AI to power "software as a medical device" [15] presents an opportunity to leapfrog access to diagnostic devices, such as ultrasounds [16] and blood pressure equipment [17]. This has also been seen with the emergence of contraceptive and fertility software applications [18,19], which are increasingly securing regulatory approvals from national authorities [20,21].

The convergence of AI in SRHR also presents heightened risks and implications. This is especially evident as the use of underlying health data raises concerns about infringements on women's health and bodily autonomy, as well as the potential misuse of this technology for surveillance of populations in vulnerable situations. Furthermore, existing challenges in digital health implementation [22], including biases, limited inclusivity, and gender disparities, could be exacerbated with the introduction of AI [6,23-25]. As such, the intersection of AI and SRHR raises nuanced implications and warrants close examination of the current landscape to highlight the evidence base and document the ethical, regulatory, and human rights considerations. This scoping review will build on the general literature of AI in health and focus specifically on how AI is being used within SRHR, including evidence on effect and related considerations to inform a comprehensive understanding of the state of the field.

Methods

Overview

We will conduct a scoping review using the established methodological framework of Arksey and O'Malley [26] that includes (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting the results. Considering this is an emerging area of research, we will also include a stakeholder consultation to inform the discussion. We will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) format for the publication of the findings [27].

Stage 1: Identifying Research Questions

This scoping review aims to explore the range of ways in which AI is being applied in SRHR and synthesize the key considerations to ensure its effective, safe, and ethical use. The research questions for this review include the following:

- Patterns and characteristics of use: How are AI systems and tools being applied to SRHR, in terms of health domains, intended purpose (eg, screening, counseling, forecasting), target users, and AI data life cycle?
- Evidence on harms and benefits: What are the effect, acceptability, feasibility, resource use, and implications on gender, equity, and rights of AI systems and tools used in SRHR?
- Ethical, legal, and safety implications: What are the ethical, legal, and safety considerations specific to the use of AI systems and tools in SRHR?

Stage 2: Identifying Relevant Studies

To identify relevant studies for inclusion, we will search the following electronic databases: MEDLINE (PubMed), Scopus, Web of Science, and CINAHL. In addition, we will use citation searching from relevant articles to identify sources that may not have been retrieved in our original search.

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The search strategy will be a combination of constructs related to AI and SRHR. An overview of search terms is presented in Multimedia Appendix 1. We will leverage search strategies and Medical Subject Headings (MeSH) terms used in other scoping reviews focused on AI in health care [28-32]. Considering this is an emerging topic, we will not set a start date for the search.

Stage 3: Study Selection

We will conduct a 2-step abstract and title screening following the eligibility criteria in Textbox 1. We will use Covidence, a standard web-based screening and extraction tool, to manage the screening process.

We will not exclude manuscripts based on geographic location, language, or publication date. Commentaries, opinions, and editorials that do not have an underlying empirical basis will be excluded to adjust for potential subjectivity and bias. In addition to using Covidence, we will search the citations of included studies to identify relevant articles that may have been overlooked in our initial search.

All references will be collated into a single reference manager (EndNote), where duplicate entries will be removed. Articles will be screened independently by 2 coauthors. Identified discrepancies will be resolved through discussion, and, if needed, escalated to a coauthor for arbitration.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Studies reporting on artificial intelligence (AI) applications to aspects of sexual and reproductive health and rights
- Clearly described methodology; we will include quantitative studies, qualitative studies, and program evaluations and descriptions

Exclusion criteria

- Focus exclusively on digital interventions (eg, traditional text messaging or targeted client communication) that do not explicitly use AI systems and tools
- Focus on health care robotics or nonhuman studies
- Commentaries, opinion pieces, and editorials

Stage 4: Charting the Data

We will develop a data extraction sheet to standardize the retrieval of information in alignment with the research questions (Table 1). The data extraction form will be developed by adapting common themes from other scoping reviews on AI [31,33], as well as reviewing requirements from digital health reporting checklists [34,35], information on the intervention, including how AI was applied to SRHR, the specific SRHR domains of interest, population, geographic coverage, implementation challenges, outcomes, and ethical and legal considerations.

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Table 1. Categories for data extraction.

Category	Illustrative information to be extracted	Relevant research questions
Article information	• Article title • Author(s) • Year • Country • Setting or context (facility, community, home or self, research) • Aim or objectives • Study design or methodology	• Patterns of use
SRHR[a] health domain	• To be selected from a predefined list of common SRHR areas and expanded on accordingly • Examples include family planning or contraception counseling and provision, fertility care, safe abortion, sexually transmitted infections, antenatal care, post-natal care, etc	• Patterns of use
Targeted population	• Will be selected from a predefined list and expanded accordingly. Examples include health workers, health system managers, individuals or health service users	• Patterns of use
Intended purpose of AI[b]	The intended purposes for using AI: • Health information, education, and promotion • Screening and diagnostics • Clinical care and management • Personal health monitoring • Forecasting health trends • Health systems management • Research and drug development	• Patterns of use
AI life cycle	Stages of AI development and evaluation [36]: • Data creation • Data acquisition • Model development • Model evaluation • Model deployment	• Patterns of use
Algorithm development and models	• Predictive or generative models • Documentation of algorithm development and training process • Presence of regulatory approval	• Patterns of use
Outcomes and findings	• Outcomes based on the Evidence to Decision framework [37], which includes effect, accuracy, acceptability, feasibility, equity, resource considerations, gender, equity, and rights • Key themes and findings • Implementation challenges • Lessons learned • Unintended consequences, risks, and implications • Approaches used to mitigate unintended consequences	• Evidence on harms and benefits
Implications	• Legal implications • Ethical implications	• Ethical and legal implications

[a]SRHR: sexual and reproductive health and rights.

[b]AI: artificial intelligence.

Stage 5: Collating, Summarizing, and Reporting the Results

We will collate and summarize information from the data extraction sheets. The results will present the general patterns of use of AI in SRHR, including the specific health domains for which AI is being applied, the intended purpose of the AI system and tools, and maturity within the AI life cycle. We will use established frameworks, including the continuum of care and SRHR conceptual model for categorizing health domains [8,9] and the AI life cycle to map the maturity of AI systems and tools in use [36].

To assess evidence on harms and benefits, studies will first be tagged based on their AI life cycle [36] to distinguish between interventions that are in the early stages of model development and validation versus those that have been implemented and evaluated. We will extract outcomes on the subset of studies identified as being in the model deployment and evaluation phases of the AI life cycle [36]. The type of outcome data to be extracted will be guided by the domains of the Evidence to

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Decision framework, including accuracy, effect, acceptability, feasibility, resource use, and gender equity and rights [37]. Where possible, we will pool findings across similar outcome measures and present a summary of findings on outcomes related to accuracy and effect. We will conduct a thematic analysis on ethical, legal, and safety considerations, as well as on findings from qualitative studies.

Results

The database searches described above resulted in 12,793 records when the searches were conducted in October 2023. Screening is underway, and the analysis is expected to be completed by July 2024.

Discussion

Building on the broader literature on AI and health, findings from this review will provide fundamental insights into the usage patterns, implications, and evidence related to AI in SRHR, as well as highlight key considerations and risks. A key strength of this review is the composition of a multidisciplinary authorship team to ensure both the technological and SRHR perspectives are appropriately reflected. Moreover, this scoping review serves as a foundational resource to inform a technical brief developed by the World Health Organization [38] and to guide future research and practice. One limitation of this review is its focus on empirical studies, in which insights from the gray literature and AI consumer products may be overlooked if they are not reflected in the peer-reviewed literature. However, due to the high number of records in the search, we believe this scoping review can reliably provide a comprehensive overview of usage patterns and key implications.

The intersection of AI and SRHR has been fraught with concerns, particularly related to infringements on women's reproductive health choices and the exacerbation of gender biases and inequity [39]. Meanwhile, technological advances hold great promise for overcoming longstanding challenges in access to and provision of SRHR services. This systematic analysis of AI in SRHR seeks to facilitate clarity and nuanced discussion in this highly charged field and direct efforts toward responsibly and meaningfully harnessing of AI to address SRHR needs and the broader goals of universal health coverage.

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Data Availability

Access to the Covidence database can be made available after the publication of findings by emailing srhhrp@who.int and through a mutually signed agreement.

Authors' Contributions

TT developed the protocol and manuscript with input from YZ, DS, SA, SP, and LS. All authors have made substantial intellectual contributions in developing the manuscript and have reviewed and approved it for submission and publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 30 KB - resprot_v13i1e53888_app1.docx]

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Abbreviations

AI: artificial intelligence
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
MeSH: Medical Subject Headings
SRHR: sexual and reproductive health and rights
STI: sexually transmitted infection

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Protocol

The Conceptualization and Measurement of Research Impact in Primary Health Care: Protocol for a Rapid Scoping Review

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Abstract

Background: The generation of research evidence and knowledge in primary health care (PHC) is crucial for informing the development and implementation of interventions and innovations and driving health policy, health service improvements, and potential societal changes. PHC research has broad effects on patients, practices, services, population health, community, and policy formulation. The in-depth exploration of the definition and measures of research impact within PHC is essential for broadening our understanding of research impact in the discipline and how it compares to other health services research.

Objective: The objectives of the study are (1) to understand the conceptualizations and measures of research impact within the realm of PHC and (2) to identify methodological frameworks for evaluation and research impact and the benefits and challenges of using these approaches. The forthcoming review seeks to guide future research endeavors and enhance methodologies used in assessing research impact within PHC.

Methods: The protocol outlines the rapid review and environmental scan approach that will be used to explore research impact in PHC and will be guided by established frameworks such as the Canadian Academy of Health Sciences Impact Framework and the Canadian Health Services and Policy Research Alliance. The rapid review follows scoping review guidelines (PRISMA-ScR; Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews). The environmental scan will be done by consulting with professional organizations, academic institutions, information science, and PHC experts. The search strategy will involve multiple databases, citation and forward citation searching, and manual searches of gray literature databases, think tank websites, and relevant catalogs. We will include gray and scientific literature focusing explicitly on research impact in PHC from high-income countries using the World Bank classification. Publications published in English from 1978 will be considered. The collected papers will undergo a 2-stage independent review process based on predetermined inclusion criteria. The research team will extract data from selected studies based on the research questions and the CRISP (Consensus

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Reporting Items for Studies in Primary Care) protocol statement. The team will discuss the extracted data, enabling the identification and categorization of key themes regarding research impact conceptualization and measurement in PHC. The narrative synthesis will evolve iteratively based on the identified literature.

Results: The results of this study are expected at the end of 2024.

Conclusions: The forthcoming review will explore the conceptualization and measurement of research impact in PHC. The synthesis will offer crucial insights that will guide subsequent research, emphasizing the need for a standardized approach that incorporates diverse perspectives to comprehensively gauge the true impact of PHC research. Furthermore, trends and gaps in current methodologies will set the stage for future studies aimed at enhancing our understanding and measurement of research impact in PHC.

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KEYWORDS

research impact; primary health care; measurement; definition; concept; development; implementation; health policy; policy; health service; rapid review; review; research; policies; societal; productivity; literature database

Introduction

High-performing primary health care (PHC) is recognized as the cornerstone of robust health care systems [1,2]. High-income countries often possess robust health care systems with well-established PHC organizations and research institutions, making them pivotal in shaping global health policies and practices [3,4]. High-quality research identifying what is needed to strengthen the performance of PHC organizations and their integration with each other and the broader health system is essential to inform the sustainable development of health care [5]. A PHC orientation to health service research strives to understand the influence of health's socioeconomic, physical, biological, and cultural determinants within the relevant broader political, sociohistorical, and economic contexts. PHC services can improve health and health services delivery, which could result in improved individual, community, and population health outcomes.

The need for PHC research to determine the efficacy of treatment and test theories and develop new models of care has been documented [6]. PHC encompasses primary care, disease prevention, health promotion, population health, and community development within a holistic framework to provide essential community-focused health care [7,8]. We operationalize "PHC research" to refer to studies that investigate a broad range of topics related to preventive care, health promotion, diagnosis, treatment, ongoing management of common illnesses and chronic conditions, and the social determinants of health within the context of PHC settings [9].

There are several conceptual frameworks and approaches that have been developed for research impact assessment [10]. In Canada, the Canadian Academy of Health Sciences (CAHS) Impact Framework has been adapted to examine the impact of investments in health research. The CAHS Impact Framework uses 5 impact categories: advancing knowledge, capacity building, informing decision-making, health impacts, and socioeconomic impacts and provides a menu of nearly 70 indicators that map onto these domains [11]. In 2018, the Canadian Health Services and Policy Research Alliance (CHSaPRA) was developed by the Canadian health research community based on CAHS to guide the assessment of the impact of research on decision-making [12].

Despite the development of these frameworks, little is known about how research impact is conceptualized in PHC [13]. Globally, PHC research is a small proportion of research output [14]. While existing reviews address research impact within the health care and health service research context [15,16], these reviews are not tailored to consider the unique functions of PHC. As noted by the Council of Academic Family Medicine, PHC research is unique since it involves the delivery of care to patients across the care life cycle, which includes disease prevention, health promotion, and chronic care management [17-20]. It also provides evidence that is unique for the organization and delivery of care, evaluation of innovations, translation of research into practice, and participatory action and community-based approaches [17]. Due to the broader effects of research on patients, practices, services, population health, community, and policy formulation, a dedicated review in PHC is essential to broaden our understanding of research impact, including nuances of how it may or may not be different than other health services research. To establish directions to evolve definitions of research productivity in the context of PHC, funders, academic institutions, researchers, and the public need a better understanding of "research impact" in PHC.

Several scoping reviews, such as those conducted by Murphy et al [21] on measurement in rural PHC, Noorihekmat et al [22] on performance measurement frameworks in public health and primary care systems, and Akl et al [23] on faculty productivity in academic medical centers, have explored aspects of research productivity and measurement within health care. However, to the best of our knowledge, there is no existing review that has offered a focused exploration of the specific conceptualizations and measures of research impact within the context of PHC. Such a review would offer a unique and detailed analysis that aims to elucidate the nuances and intricacies of research productivity, thereby contributing a distinct perspective to the existing literature.

This review protocol aims to fill a gap in knowledge by examining the scientific literature on research impact in the context of PHC. Drawing from established frameworks like the

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CAHS Impact Framework [24] and CHSaPRA [25], we will aim to (1) elucidate the various conceptualizations of research impact within the context of PHC and (2) identify measures of research impact used in the PHC literature by PHC researchers. The study will contribute to understanding and identifying trends in how the impact is understood and measured, highlighting existing gaps or areas needing further investigation within this domain. The findings of the study will be leveraged to inform a future study that will explore the perspectives of patients, citizens, community groups representing equity-deserving groups, PHC leaders, researchers, and policy makers on the definition and measurement of research impact in PHC.

Methods

Study Design

A rapid scoping review [26] and environmental scan [27] will be conducted. A rapid scoping review methodology is suitable for this investigation, as it allows for a comprehensive but expedited exploration of the existing literature surrounding research impact within PHC. Given the breadth of the topic and the need to capture a wide array of literature quickly, the rapid scoping review methodology aligns with the urgency to understand conceptualizations and measurements of research impact in PHC [26]. This approach permits the incorporation of diverse study designs, including gray literature and various publication types, facilitating a thorough investigation of research impact concepts within a condensed timeframe [26]. However, the rapid review will be informed by existing guidelines for scoping reviews [28] and the Arksey and O'Malley [29] methodological steps (stages 1 to 5 described below), aiming for standardized execution and reporting and enhancing the credibility of the findings. Scoping reviews aim to map fundamental concepts in a research area, define key terms, and delineate conceptual limits, making it suitable for our purposes [29,30]. The CRISP (Consensus Reporting Items for Studies in Primary Care) statement proposed by Sturgiss et al [31] will be used for the comprehensive extraction and reporting in PHC research to enable the analysis of practices and policies across a diverse range of countries and territories.

Similar to a rapid review, an environmental scan is often used by institutions to collect information [27]. An environmental scan is a systematic approach to gathering and analyzing information from various sources beyond traditional academic literature, including publicly available data, unpublished reports, and consultations with experts [32]. It aims to comprehensively identify relevant information, trends, and developments within a specific field or context [32]. Researchers can also use an environmental scan to identify current and potential research needs and trends to enhance decision-making [27]. While there are various methodologies and sources for collecting and analyzing information for an environmental scan [32], our environmental scan will be conducted by identifying professional organizations, academic institutions, and experts in the fields of information science and PHC to begin our search.

We will adhere the reporting of our review to the PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews) reporting guidelines [33], as there are currently no existing guidelines for rapid reviews. The study will be conducted in 2024 with results anticipated by the end of the year. The research team is comprised of PHC researchers (clinicians, PhD trained) or leaders in the field.

Stage 1: Identifying the Research Questions

We intend to address the following research questions: (1) How is research impact conceptualized in PHC? (2) How is research impact measured in PHC? (3) What methodological or conceptual frameworks are used to evaluate PHC research impact? What are the benefits and challenges of assessing PHC research impact?

Stage 2: Identifying Relevant Studies

We will work with an information specialist to develop a search strategy for the following academic databases: PsycINFO, MEDLINE, Embase, and CINAHL Plus. These databases were intentionally selected for their inclusion of PHC literature and thus are likely to capture relevant scholarly material. The strategy will initially be applied in MEDLINE before being adapted for other databases. We will also search for literature in Google Scholar to "the wide range of resources including papers from academic journals, conference papers, theses, and dissertations" [34]. The peer-reviewed search strategy will also be used in Google Scholar. A citation search of the reference lists of selected papers will be conducted to ensure that a wider scope of papers is included. Forward citation searching will also be done for literature that cites eligible studies included in the review [35]. Scopus, Web of Science, and Google Scholar will be used for forward citation tracking to ensure a comprehensive search.

To ensure a comprehensive review of relevant sources and databases, relevant gray literature databases, catalogs, and search engines (eg, Google, OpenGrey, and TripPro) will be hand searched across high-income countries. White papers will also be explored through health care–focused think-tank websites. We will also contact librarians in the field of PHC and information specialists through several mailing lists (including Canadian Medical Libraries and expert searching through the College of Family Physicians of Canada) to ask for further studies or gray literature. We define gray literature as "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers" [36].

An environmental scan of institutes and initiatives that follow their strategic funding to understand research impacts, such as the Canadian Institute for Health Research's Community-Based Primary Health Care reports and the SPOR Evidence Alliance [37] will also be conducted. We also aim to examine metrics used by funding agencies within jurisdictions. We will contact each one individually for any published or unpublished evaluations of these PHC activities and ask for any other organizations or experts, who may help us to find as many materials as possible.

The search strategies for the databases were devised in collaboration with the 2 information specialists (Multimedia Appendix 1). Before the literature search and screening process,

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reviewers will receive training from the principal investigator (MA) to ensure a foundational grasp of the field's background and the review's objectives.

Stage 3: Study Selection

Two research assistants (one of whom is KMK) will perform all searches in the databases, citation searching, as well as the environmental scan. Findings from all databases will be amalgamated and imported into Covidence (Veritas Health Innovation) for streamlined documentation and management of studies throughout the review process [38]. Additionally, any duplicate publications will be eliminated.

For the gray literature and environmental scan, the research assistants will independently conduct searches across the sources. The research assistants will document the sources and databases accessed for gray literature, specifying the search terms, strategies, and any limitations applied. Any date range, filters, and criteria used to identify relevant gray literature sources will be noted. The research assistants will document the results obtained, including the number of documents retrieved, and provide a clear account of any exclusions made along with justifications. During frequent team meetings, the research team will discuss how duplicates were managed. This documentation should ensure transparency and reproducibility, allowing others to follow and validate the search methodology [39,40]. Gray literature will be organized and managed in a structured Microsoft Excel (Microsoft Corp) spreadsheet. Microsoft Excel will also be used to organize details of the environmental scan, such as the institute or initiative names, contact information, links to relevant reports or evaluations, dates of contact, and any additional notes or follow-up actions required.

We will include gray and scientific literature of any study design that (1) have an explicit focus on the research impact, (2) explicitly focus on PHC research, and (3) are published from a high-income country (defined as per the World Bank classification [41], ie, Andorra, Antigua and Barbuda, Aruba, Australia, Austria, Bahamas, Bahrain, Barbados, Belgium, Bermuda, British Virgin Islands, Brunei Darussalam, Canada, Cayman Islands, Channel Islands, Chile, Croatia, Curaçao, Cyprus, Czech Republic, Denmark, Estonia, Faroe Islands, Finland, France, French Polynesia, Germany, Gibraltar, Greece, Greenland, Guam, Hong Kong SAR China, Hungary, Iceland, Ireland, Isle of Man, Israel, Italy, Japan, Republic of Korea, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Macao SAR China, Malta, Monaco, Nauru, Netherlands, New Caledonia, New Zealand, Northern Mariana Islands, Norway, Oman, Palau, Poland, Portugal, Puerto Rico, Qatar, San Marino, Saudi Arabia, Seychelles, Singapore, Sint Maarten (Dutch part), Slovakia, Slovenia, Spain, St Kitts and Nevis, St Martin (French part), Sweden, Switzerland, Taiwan China, Trinidad and Tobago, Turks and Caicos Islands, the United Kingdom, United Arab Emirates, Uruguay, the United States, and Virgin Islands (United States).

We define an "explicit focus on the research impact" as studies or papers where the primary or significant emphasis is placed on evaluating, measuring, or discussing the effects, outcomes, influence, or implications of research activities or interventions in the field of PHC or by PHC providers. This includes studies using both formal methodological frameworks, such as the CAHS Impact Framework, and ad hoc approaches using single or limited metrics. This could involve investigations into the tangible outcomes or effects of research endeavors such as changes in health care practices, policy implications, patient outcomes, health system improvements, or societal impacts resulting from PHC research initiatives [42]. Additionally, studies proposing frameworks for evaluating PHC research impact, regardless of whether they are empirically trialed or piloted, are considered, recognizing the value of theoretical advancements in this domain. However, studies predominantly focused on assessing the impact of health care interventions themselves, rather than the research process or outcomes, are excluded to ensure a manageable scope and relevance to the review objectives.

Limiting inclusion to studies published from high-income countries aligns with the rapid nature of this review while ensuring a focus on PHC research that reflects contexts, systems, and health care settings that share similar socioeconomic and health care infrastructure characteristics.

Only literature from 1978 (signing of the Alma-Ata Declaration [43]) to the present day and published in English will be considered. Research conducted within this timeframe ensures relevance to contemporary PHC practices and current understanding but also allows for the inclusion of recent advancements, methodologies, and perspectives in the field. Setting a specific timeframe and language criteria can help manage the volume of literature to be reviewed, which is key in a rapid review [26,44].

The results from all databases will be imported into EndNote (Clarivate Analytics), and all duplicates will be removed [45]. The unique papers will then be added to Covidence software to help facilitate screening, study selection, and extraction [38]. After generating a list of papers from our search strategy, we will engage in a 2-stage screening process with at least 1 independent reviewer at each stage. In the first stage, 2 trained, independent reviewers will screen papers for suitability based on their titles and abstracts in duplicate. We will report on the calculation of interrater reliability using Cohen κ coefficient [46] to assess the consistency of screening decisions between reviewers and ensure the reliability of the study selection process. A third reviewer will review 25% of the excluded papers to ensure no papers were inadvertently excluded. If there is ambiguity on whether specific papers fit the scope of this protocol, the principal investigator (MA) will be consulted. In the second stage, single reviewer (KMK) will conduct full-text reviews of the potentially eligible studies using the inclusion criteria aforementioned [47]. Again, a third reviewer will review 25% of the excluded papers to ensure no papers were inadvertently excluded. Throughout the process, disagreements between reviewers regarding the inclusion or exclusion of papers will be resolved via discussion with the principal investigator (MA), who will advise the reviewers of the outcome (ie, include or exclude). Given the iterative nature of scoping reviews, the inclusion and exclusion criteria will be refined (eg, added specificity), if needed, after increased familiarity with the data.

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The comprehensive outcomes of both the searches (ie, databases and gray literature, including the environmental scan) and the study inclusion procedure will be thoroughly detailed in the final report of the review. These will be articulated using a PRISMA-ScR flow diagram, ensuring a clear and structured presentation of the search process and the selection of studies for the review [33].

Stage 4: Charting the Data

The research team will develop initial charting variables based on the research questions and the CRISP statement [48]. The preliminary variables that will be extracted from the studies will include (1) authors, (2) year, (3) country where the study was conducted or country of first author's affiliation, (4) journal, (5) methodology of paper (including whether a framework or ad hoc approach is used for measuring impact), (6) definition or conceptualization of impact (including how the impact is measured), (7) notice of research team's primary care experience and collaboration, (8) description of the study participants and populations in the context of primary care, (9) description of the primary care team, (10) description of the conditions under study in the context of primary care outcome measures (primary and secondary), (11) units of analysis, (12) findings, and (13) recommendations or discussion (eg, gaps, challenges or barriers, recommendations, and evidence-based or best practices).

Two team members will independently chart the first 5 papers that meet our inclusion criteria and refine the definitions for the variables or charting categories if necessary. The research team will discuss the extracted data. If consensus is reached, 1 researcher (KMK) will extract data from the remaining papers. If consensus is not reached, the 2 individuals will continue to extract 1 paper in duplicate until consensus is reached. All discrepancies between reviewers will be addressed through discussion and by involving additional individuals. The charted data will be organized and presented in a Microsoft Excel spreadsheet.

Stage 5: Collating, Summarizing, and Reporting the Results

To achieve our aims, we will adopt 3 distinct strategies for reporting and presentation. Initially, the research team will use a PRISMA-ScR checklist to ensure systematic reporting of our methods and screening processes [33]. Additionally, the charted data will be reviewed, synthesized, and analyzed through a numerical summary analysis that will include an overview of study characteristics and help to identify predominant conceptualizations and measurement frameworks used for research impact in PHC [29]. A directed content analysis will be carried out on the extracted data [49]. This method entails identifying specific concepts, definitions, methodological approaches, recommendations, benefits, and challenges associated with research impact in PHC. A coding framework will be developed based on established theories and frameworks relevant to PHC research impact, ensuring that the analysis remains focused and aligned with the study objectives. Each piece of extracted data will be systematically coded according to predefined categories, allowing for consistent and structured analysis. Through the directed content analysis, key themes extracted from the selected papers will be categorized, summarized, and presented using a narrative synthesis [47] that describes how research impact is conceptualized and measured in PHC. This analysis will also encompass definitions of research impacts, methodological techniques to measure research impact, and recommendations for improving PHC research impact and identify benefits or challenges of measurements of research impact in the context of PHC.

Finally, the synthesis will address strengths, study limitations, existing knowledge gaps, and potential avenues for future research pertinent to research impact in the realm of PHC. This is aligned with the goals of scoping reviews, which aims to comprehensively outline the scope and characteristics of existing literature [29]. However, as consistent with the scoping review methodology, we anticipate that the narrative synthesis will be an iterative process and dependent on the literature found [47].

Results

The results of this study are expected in December 2024. The dissemination of findings from this rapid scoping review on the conceptualization and measurement of research impact in PHC will ensure that the insights generated are shared with relevant stakeholders and contribute to informed decision-making and further research efforts.

The findings of this scoping review will be disseminated through various channels to reach a wide audience. A paper detailing the methodology, findings, and implications of the rapid review and environmental scan will be submitted to a relevant peer-reviewed journal in the field of PHC, family medicine, health services research, or impact assessment (eg, *Journal of Primary Care & Community Health*, *BMC Family Practice*, *Health Services Research*, *Journal of Health Services Research & Policy*, and *The Annals of Family Medicine*). A concise and accessible policy brief summarizing the key findings and their implications for policy makers, stakeholders, and PHC leaders will be developed and distributed through appropriate channels (eg, College of Family Physicians of Canada, Canadian Institute for Health Information, Canadian Foundation for Healthcare Improvement, Canadian Institutes of Health Research, Canadian Primary Care Sentinel Surveillance Network, and Canadian Primary Care Research Network). The research team will present the findings at relevant academic conferences, seminars, and workshops attended by researchers, practitioners, and policy makers in the fields of PHC and health services research (eg, North American Primary Care Research Group, Canadian Association of Health Services and Policy Research, Society for Academic Primary Care, and International Conference on Primary Health Care). Collaboration with existing networks and initiatives in PHC research and impact assessment will be sought to integrate the findings into ongoing discussions and efforts. The dissemination materials will be tailored to the needs and interests of different stakeholders. For example, academic publications will provide detailed methodology and findings for researchers, while policy briefs will focus on practical implications for decision makers. We will also create 1-page infographics for patient and public communities (eg, National Association of Community Health Centers). Presentations and

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webinars will be customized to engage different audiences effectively.

Discussion

Preliminary Findings

The preliminary findings from this study have yet to be compiled and analyzed as the review is ongoing. The forthcoming rapid review and environmental scan on research impact in PHC will help to elucidate conceptualizations and measurement methodologies of impact, shaping the understanding of research impact within this domain. By rigorously and systematically reviewing a breadth of literature sources, this study aspires to unravel the diverse perspectives and approaches used to gauge the impact of research activities in PHC. This review will be able to discern trends, illuminate potential gaps, and outline areas necessitating further exploration or refinement in the assessment of research impact. Such delineations are envisioned to inform future research, policy considerations, and practice innovations in medicine and academia, ultimately contributing to the continuous enhancement of PHC services and policies in PHC settings.

Limitations

The methodology and methods outlined for the scoping review and environmental scan present several potential limitations. First, the selection process might carry biases due to restrictions such as language and publication date, possibly excluding valuable insights from diverse settings or languages. We acknowledge that relying solely on the World Bank's classification system for high-income countries may oversimplify the diversity of socioeconomic and health care infrastructure characteristics among nations and may not consider the varied health care contexts, systems, and priorities among high-income countries that could in turn influence research impact.

Additionally, researcher biases might influence study interpretation or selection, potentially affecting the review's credibility. Second, while the rapid review approach aids efficiency, it may compromise a comprehensive understanding of nuanced concepts related to research impact in PHC. Third, accessing relevant unpublished materials in gray literature might pose challenges, potentially affecting the credibility or reliability of findings.

Conclusions

This protocol outlines a rapid scoping review and environmental scan for exploring research impact in PHC, which will provide critical insights for advancing PHC systems. Recognizing PHC's pivotal role in health care, this study underscores the need for comprehensive research to bolster PHC organizations' performance and integration within broader health systems. Drawing from established frameworks such as CAHS and CHSaPRA, the forthcoming review will examine how research impact is conceptualized and measured in PHC, addressing an existing gap in knowledge. Emphasizing the scarcity of recent reviews specifically focused on this domain, this upcoming study pioneers a comprehensive analysis, shedding light on the nuances of research impact. By delineating varied conceptualizations of research impact and measures used in PHC, this review charts a pathway for future research, potentially refining measurement methodologies and informing decision-making for stakeholders in the PHC landscape.

While findings are pending, the study aspires to inform future research endeavors, policy formulations, and practice enhancements in the realm of PHC, which has a pivotal role within health care systems both provincially and federally, for example, Indigenous people living on reserve and people living in prisons.

Data Availability

The data sets generated and analyzed during this study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 26 KB - resprot_v13i1e55860_app1.docx]

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Abbreviations

CAHS: Canadian Academy of Health Sciences

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CHSaPRA: Canadian Health Services and Policy Research Alliance
CRISP: Consensus Reporting Items for Studies in Primary Care
PHC: primary health care
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews

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Protocol

Natural Language Processing for Work-Related Stress Detection Among Health Professionals: Protocol for a Scoping Review

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Abstract

Background: There is an urgent need worldwide for qualified health professionals. High attrition rates among health professionals, combined with a predicted rise in life expectancy, further emphasize the need for additional health professionals. Work-related stress is a major concern among health professionals, affecting both the well-being of health professionals and the quality of patient care.

Objective: This scoping review aims to identify processes and methods for the automatic detection of work-related stress among health professionals using natural language processing (NLP) and text mining techniques.

Methods: This review follows Joanna Briggs Institute Methodology and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The inclusion criteria for this scoping review encompass studies involving health professionals using NLP for work-related stress detection while excluding studies involving other professions or children. The review focuses on various aspects, including NLP applications for stress detection, criteria for stress identification, technical aspects of NLP, and implications of stress detection through NLP. Studies within health care settings using diverse NLP techniques are considered, including experimental and observational designs, aiming to provide a comprehensive understanding of NLP's role in detecting stress among health professionals. Studies published in English, German, or French from 2013 to present will be considered. The databases to be searched include MEDLINE (via PubMed), CINAHL, PubMed, Cochrane, ACM Digital Library, and IEEE Xplore. Sources of unpublished studies and gray literature to be searched will include ProQuest Dissertations & Theses and OpenGrey. Two reviewers will independently retrieve full-text studies and extract data. The collected data will be organized in tables, graphs, and a qualitative narrative summary. This review will use tables and graphs to present data on studies' distribution by year, country, activity field, and research methods. Results synthesis involves identifying, grouping, and categorizing. The final scoping review will include a narrative written report detailing the search and study selection process, a visual representation using a PRISMA-ScR flow diagram, and a discussion of implications for practice and research.

Results: We anticipate the outcomes will be presented in a systematic scoping review by June 2024.

Conclusions: This review fills a literature gap by identifying automated work-related stress detection among health professionals using NLP and text mining, providing insights on an innovative approach, and identifying research needs for further systematic reviews. Despite promising outcomes, acknowledging limitations in the reviewed studies, including methodological constraints, sample biases, and potential oversight, is crucial to refining methodologies and advancing automatic stress detection among health professionals.

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KEYWORDS

health professionals; natural language processing; text-mining; work-related stress; healthcare; occupational well-being; automatic detection; scoping review protocol; methodology; synthesis

Introduction

Worldwide health care systems are in urgent need of qualified health professionals. The global demand–driven shortage of health professionals is expected to exceed 14 million by the year 2030 [1]. There are many reasons for the shortage, such as the aging of society, the increase in medical and technological treatment options, and the high workload on health care staff [2-4]. The pandemic has put additional strain on an already tense situation. During the initial phase of the pandemic in March 2020, health professional shortages increased by 62% [5], and over 80% of nurses experienced psychological distress [6]. The already high contemplation of quitting one's job increased due to the pandemic by up to 20.3% [7].

During the COVID-19 pandemic, health professionals have faced increased pressure, including heavy workloads, job-related stress, physical and mental health risks, and even instances of violence and harassment [8]. Furthermore, high stress levels and understaffing at the workplace are associated with negative impacts on patient safety and the quality of care [9]. Workplace dissatisfaction and psychological stress significantly increase the risk of mental health issues, such as burnout [10]. As a result, many health professionals leave the profession within the first 5 years after graduation [10]. To reduce the turnover rate of health professionals, it is crucial to reduce workplace stressors and improve working conditions [9]. However, the implementation of international or national measures requires adequate monitoring of the situation, especially regarding working conditions [1].

In this context, the early detection of work-related stress becomes particularly relevant. Previous research in this area has primarily relied on studies that collected self-reported data from health professionals through surveys [11]. However, the response rate in these study designs is decreasing and a further decline is expected [12]. Conducting instant monitoring is time-consuming, which underscores the benefits of automatic stress detection [13].

In recent decades, there has been continuous innovative development in the field of information technology, with these milestones contributing to the advancement of e-health care in terms of quality, continuity, and efficiency [14]. An example of this progress is the use of sensors that can capture physiological data, including the use of smartphones and wearable sensors, which allow the detection of biomarkers to measure stress. These sensors not only have the capacity to identify stress but also accurately categorize and differentiate various emotions [15]. A systematic review examined the use of wrist-worn wearables for the identification of stress levels. The results show that the development of such devices with physiological and chemical sensors is possible but challenging [16]. Another systematic review aimed to investigate and summarize the literature on physiological responses to acute stress, revealing a focus on retrospective assessment, with a notable gap in methodological approaches suitable for health care. The findings emphasize the need for future research to leverage sensor technology for real-time evaluation of acute stress in health professionals [17].

A promising application area that has made significant progress involves the use of natural language processing (NLP) and text mining techniques for recognizing clinical information in unstructured free-text documents and transforming it into structured data [18]. NLP, a technique within the broader field of artificial intelligence, has rapidly evolved in the past 2 decades with the increasing proliferation of computer technology. NLP is now used daily by every smartphone user and has significantly contributed to the development of speech translation, personal digital assistants, and voice-controlled home automation systems [19]. The primary goal of NLP is to view text or speech input or output not only as a sequence of characters, sentences, phrases, or paragraphs but rather as a complex syntactic and phonological data structure [20].

NLP is an algorithmic tool that identifies and manages texts, similar to text mining. Text mining involves various techniques for characterizing and converting texts. Within text mining, NLP methods are applied based on syntactic or semantic processing algorithms to analyze text data [21]. Text mining is a part of NLP. We will use the term "NLP," which includes text mining. NLP techniques have been applied in various health care areas for decision-making processes, including mental health and oncology [22,23]. One study investigated the use of NLP to analyze social media posts for inferring mental states and creating personalized mental health interventions, fostering a connection between mental health, human-computer interaction, and NLP fields [22]. Another study used NLP as a tool for enhancing evidence-based oncological research and improving cancer care quality [23].

NLP was also used for stress detection among patients. A study examines the automated assessment of patient self-narratives for signs of posttraumatic stress disorder (PTSD) using NLP [24]. The authors use NLP techniques to identify patterns in patients' texts. The key results show that automated analysis of patient texts holds promise in recognizing potential indicators of PTSD. This approach could be efficient for the early detection and diagnosis of PTSD, especially in large volumes of patient narratives [24]. NLP could also be used as an opportunity to transform mental health conversation and help early intervention for depression [25]. It is indicated to detect stress and mental disorders in an early stage [25]. However, the use of NLP extends not only to the detection of stress in patients but also to the field of health professionals. Under these promising conditions, the extent to which NLP can be used to identify workplace stress among health professionals needs to be clarified.

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The main goal of this scoping review is to identify processes and methods for the automatic detection of work-related stress among health professionals using NLP and text mining. By examining these innovative approaches, the authors aim to contribute to the improvement of health and well-being among health professionals.

The review question includes the following: Which processes and methods for automatic work-related stress detection using NLP among health professionals have been identified in the scientific literature?

Methods

Overview

This scoping review has not been registered on any public platform. A preliminary search was conducted in the PROSPERO, MEDLINE, and Cochrane databases for systematic reviews and Joanna Briggs Institute Evidence Synthesis. No existing or ongoing scoping or systematic review on this topic could be identified. The proposed scoping review will follow the Joanna Briggs Institute methodology for scoping reviews [26]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist will also be applied [27].

Participants

This scoping review will consider studies that include health professionals and focus on automatically detecting work-related stress using NLP. Other professions and children are excluded.

Concept

This scoping review examines the detection of work-related stress among health professionals through NLP. The investigation covers different aspects related to this topic. Initially, it focuses on the scope of NLP applications for stress detection. This involves using NLP methods and techniques to analyze text data produced by health professionals to identify signs of work-related stress.

Another crucial aspect involves the features and criteria for stress detection, encompassing the definition of text features and criteria that could indicate the presence of stress. These may include specific linguistic patterns, keywords, or other linguistic indicators.

Within the scope of this review, the technical aspects of NLP approaches are also examined, encompassing the various NLP methods and techniques that can be used for stress detection in health professionals. These methods include machine learning, sentiment analysis, text mining, and data mining.

Last, the review illuminates the results and implications of this automatic stress detection through NLP, including potential enhancements in identifying stressed health professionals, facilitating the implementation of stress management measures, promoting a better understanding of stress factors in health care, and the potential improvement in patient care through efficient stress management.

These concepts serve as a foundation for the identification of relevant studies and research works that deal with the automatic detection of work-related stress among health professionals using NLP techniques.

Context

This review will encompass studies focusing on the application of NLP in the health care domain. It will encompass investigations conducted in diverse environments, including hospitals, clinics, and health care facilities, where NLP techniques are used to automatically detect work-related stress among health professionals. Emphasis will be placed on the use of textual data generated by health professionals to identify stress patterns and enhance the mental health and well-being of the workforce. This context extends across various health care sectors and settings, where the implementation of NLP for stress detection holds the potential for positive impacts on working conditions and patient care.

Types of Sources

This review paper considers various types of study designs in the field of NLP. This includes experimental studies such as randomized controlled trials, cluster-randomized trials, pre- and posttest designs, and qualitative studies that investigate the effects of NLP techniques on stress detection in health professionals. Analytical observational studies, including prospective and retrospective cohort studies as well as case-control studies, are also included to analyze potential associations between the use of NLP and stress among health professionals. Descriptive observational studies, such as case series, individual case reports, and descriptive cross-sectional studies, provide insights into the application of NLP for stress detection in real health care settings. Furthermore, observational studies are considered to monitor the behavior of health professionals in dealing with NLP systems and document their impact on stress. Last, expert opinions and evaluations from professionals in the field of NLP and health care are incorporated to obtain best practices and recommendations. The inclusion of these various types of sources allows for a comprehensive understanding of the application of NLP for stress detection in health professionals and to gain relevant insights from different perspectives.

Search Strategy

The search strategy was developed to capture both published and unpublished studies. This process commenced with defining the objectives and establishing inclusion and exclusion criteria. Subsequently, the PICO (population, intervention, control, and outcomes) framework was constructed, suitable databases were identified, and search components and keywords were defined. Initially, a preliminary limited search was conducted in PubMed and CINAHL (via EBSCOhost) to gain an overview of the available results. Based on these findings, the search strategy was further refined.

A second search will be conducted using the adapted keywords across all relevant databases. A detailed search strategy conducted on October 5, 2023, for PubMed is extensively described in Table 1. The reference list of all included sources of evidence will be screened for additional studies.

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Papers in English, German, and French were included to encompass a broad range of literature sources. Studies published from 2013 to the present were included to ensure that current literature is integrated into the analysis. This timeframe was justified by a significant increase in the number of publications, particularly after 2012 [28].

Table 1. Preliminary search on PubMed.

Search number	Query	Records retrieved
1	(((((((((caregiver) OR (nurse)) OR (allied health personnel)) OR (physician)) OR (health personnel)) OR (medical professional)) OR (clinician)) OR (medical practitioner)) OR (health providers)) OR (health professional)	2,930,096
2	((NLP[a]) OR (natural language processing)) OR (text mining)	51,668
3	((((((((((work-related stress) OR (job-related stress)) OR (occupational stress)) OR (workplace stress)) OR (work stress)) OR (job stress)) OR (occupational pressure)) OR (work-induced stress)) OR (professional stress)) OR (work-related strain)) OR (job-related tension)	165,798
4	#1 AND #2 AND #3	70
5	Limited to English, German, French, and abstract available	68

[a]NLP: natural language processing.

Information Sources

The databases to be searched include MEDLINE (via PubMed), CINAHL (EBSCOhost), PubMed, Cochrane, ACM Digital Library, and IEEE Xplore. In addition to the mentioned databases, sources for unpublished studies and gray literature will also be searched, including ProQuest Dissertations & Theses and OpenGrey. This comprehensive search strategy was developed to ensure the inclusion of a wide range of relevant studies and information for the research.

Study Selection and Extraction

Following the search, all identified citations will be collated and uploaded into Zotero (version 6.0.27; Roy Rosenzweig Center for History and New Media), and the duplicates will be removed. Titles and abstracts are then screened for assessment by 2 independent reviewers, following the inclusion criteria. Two reviewers will independently extract data from each eligible paper. Papers are retrieved and evaluated in detail based on the inclusion criteria. Full texts that do not meet the inclusion criteria are excluded, and the reasons for exclusion are provided in an appendix in the review's final report. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer or reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [27].

Data will be extracted from papers included in the scoping review by 2 or more independent reviewers using a data extraction tool developed by the reviewers. The descriptive data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review question, along with the evidence levels [29] of the respective studies. A draft of the data collection instrument is provided in Textbox 1. It is modified and revised from each included paper during the data collection process. Modifications are detailed as part of the full review. Authors of the papers are contacted to request for missing or additional data if necessary.

Textbox 1. The data to be extracted.

- Authors
- Year
- Title
- Countries
- Context or setting
- Participants
- Purpose or objective
- Research methods
- Natural language processing methods and techniques for stress detection
- Features and criteria for stress detection
- Evidence level

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Data Analysis

The extracted data will be presented in tables or graphs, depending on the objectives and scope of this review. The tables and graphs will report on the distribution of studies by publication year or timeframe, countries of origin, fields of activity, and research methods used. The research methods used will be extracted to depict the range of available evidence, including both quantitative and qualitative aspects on the subject. Descriptive qualitative data synthesis of text data from the studies involves the following 3 steps: identifying results, grouping results, and categorizing groups. A narrative summary accompanies the tables or graphically represented results using a PRISMA-ScR flow diagram and describes how the findings relate to the review's objectives and questions. The results are discussed in terms of their implications for practice and research.

Results

We anticipate that the final outcomes will be presented in a systematic scoping review by June 2024.

Discussion

Principal Findings

The main findings of this scoping review will present several key aspects regarding the automatic detection of work-related stress among health professionals using NLP and text mining techniques. This scoping review could successfully identify a range of processes and methods for the automatic detection of work-related stress among health professionals using NLP and text mining techniques. Analysis of the literature will reveal various approaches used in detecting stress, including machine learning algorithms, sentiment analysis, and text mining methodologies. The findings will underscore the potential of NLP and text mining in revolutionizing stress detection methods within health care settings. By improving advanced technological tools, health care institutions could potentially integrate these approaches into their systems to streamline stress monitoring processes and enhance the well-being of health professionals. The discussion further clarifies the implications of these findings for both practice and research domains, emphasizing the importance of adopting innovative strategies to moderate workplace stress among health professionals.

Comparison With Prior Work

Comparisons to existing literature highlight the novelty and significance of using NLP and text mining for stress detection in health professionals. Traditionally, stress detection relied on self-reported data, often gathered through surveys, resulting in diminishing response rates [11,12]. Immediate monitoring proves to be time-consuming, underscoring the advantages of automated stress detection [13]. This scoping review demonstrates the feasibility and benefits of automated stress detection methods. Furthermore, the scoping review explores how these findings align with and contribute to the broader field of literature on stress management and occupational health within health care settings.

Limitations

Despite the promising outcomes, it is crucial to recognize the limitations present in the reviewed studies. These limitations may include methodological constraints, sample biases, and technological challenges associated with NLP and text mining applications. While the authors attempt to search for unpublished studies and gray literature, it is essential to acknowledge the possibility of oversight, which could introduce bias to the authors' comprehension and conclusions. Furthermore, limiting our scope to studies from the past decade may lead to a time bias, potentially excluding relevant information from earlier literature. However, concerning the recent advances in NLP in the last years and an exponential increase in publications on that topic, we expect to identify the most relevant publications. Additionally, including only English, French, and German studies may introduce a language bias, potentially overlooking relevant research published in other languages. Future research can refine methodologies and advance automatic stress detection among health professionals by addressing these limitations.

Conclusions

This scoping review fills a significant gap in the existing literature by identifying automated methods for detecting work-related stress among health professionals using NLP and text mining. The study's outcomes may offer valuable insights into the potential applications of these technologies in health care settings, emphasizing the importance of proactive stress management strategies. Moreover, the review highlights the potential for future research and underscores the need for ongoing investigation into the efficacy and implementation of NLP-based interventions.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in the final scoping review publication and its supplementary information files.

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Authors' Contributions

JSB drafted the scoping review protocol with support from CG and MCS. CI, SBS, and TJM provided revisions and a critical review of the paper. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

NLP: natural language processing
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PICO: population, intervention, control, and outcomes
PTSD: posttraumatic stress disorder

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Protocol

National Public Health Dashboards: Protocol for a Scoping Review

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Abstract

Background: The COVID-19 pandemic highlighted the importance of robust public health data systems and the potential utility of data dashboards for ensuring access to critical public health data for diverse groups of stakeholders and decision makers. As dashboards are becoming ubiquitous, it is imperative to consider how they may be best integrated with public health data systems and the decision-making routines of diverse audiences. However, additional progress on the continued development, improvement, and sustainability of these tools requires the integration and synthesis of a largely fragmented scholarship regarding the purpose, design principles and features, successful implementation, and decision-making supports provided by effective public health data dashboards across diverse users and applications.

Objective: This scoping review aims to provide a descriptive and thematic overview of national public health data dashboards including their purpose, intended audiences, health topics, design elements, impact, and underlying mechanisms of use and usefulness of these tools in decision-making processes. It seeks to identify gaps in the current literature on the topic and provide the first-of-its-kind systematic treatment of actionability as a critical design element of public health data dashboards.

Methods: The scoping review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The review considers English-language, peer-reviewed journal papers, conference proceedings, book chapters, and reports that describe the design, implementation, and evaluation of a public health dashboard published between 2000 and 2023. The search strategy covers scholarly databases (CINAHL, PubMed, Medline, and Web of Science) and gray literature sources and uses snowballing techniques. An iterative process of testing for and improving intercoder reliability was implemented to ensure that coders are properly trained to screen documents according to the inclusion criteria prior to beginning the full review of relevant papers.

Results: The search process initially identified 2544 documents, including papers located via databases, gray literature searching, and snowballing. Following the removal of duplicate documents (n=1416), nonrelevant items (n=839), and items classified as literature reviews and background information (n=73), 216 documents met the inclusion criteria: US case studies (n=90) and non-US case studies (n=126). Data extraction will focus on key variables, including public health data characteristics; dashboard design elements and functionalities; intended users, usability, logistics, and operation; and indicators of usefulness and impact reported.

Conclusions: The scoping review will analyze the goals, design, use, usefulness, and impact of public health data dashboards. The review will also inform the continued development and improvement of these tools by analyzing and synthesizing current practices and lessons emerging from the literature on the topic and proposing a theory-grounded and evidence-informed framework for designing, implementing, and evaluating public health data dashboards.

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KEYWORDS

dashboard; scoping review; public health; design; development; implementation; evaluation; user need; protocol; data dashboards; audiences; audience; systematic treatment; public health data dashboards; PRISMA-ScR; snowballing techniques; gray literature sources; evidence-informed framework; framework; COVID-19; pandemic

Introduction

Background

The disjointed public health response to the COVID-19 pandemic highlighted the critical importance of having robust public health data systems in place and the potential utility of data dashboards for ensuring timely and unrestricted access to critical public health data. Data dashboards have been used extensively in the pandemic, collating real-time public health data, including confirmed cases, deaths, and testing figures, to keep the public informed and support policymakers in refining interventions [1,2]. The growing availability of data visualization platforms and tools, coupled with the ubiquitous use of dashboards to chronicle different aspects of the COVID-19 pandemic, increased the appeal of data dashboards to a wide and diverse range of decision makers including public health leaders and professionals, health care providers, community leaders, policymakers, and advocates [3,4]. Data dashboards are frequently touted as cost-effective means to share and access public health and other types of publicly available data because they integrate and transform complex data into intuitive information displays, afford immediate availability and near-universal access of multiple and diverse groups of users to data, and allow users to explore data on their own to answer questions that are important to them [5-8]. They are also increasingly recognized for their democratizing potential, both in terms of making data available to a wider and more diverse range of audiences and ensuring that diverse stakeholders, particularly those who are less privileged and are most likely to be impacted by how data are interpreted and used in decision-making, have the power and opportunity to shape what and how data are used in this context, thus reframing how we think about health disparities and social determinants of health [9].

As public health data dashboards are poised to become more ubiquitous, it is imperative to proactively consider how they may be best integrated with data systems and decision-making routines of diverse audiences to advance sound, equitable, and sustainable public health policies and practices [3,10]. Getting there likely requires additional investments in the continued development, improvement, and sustainability of these tools, but progress in this direction is currently impeded by considerable fragmentation in the academic literature regarding the purpose (why) and intended audiences (who) of public health data dashboards, the design philosophy and features (what) that enable informed and consistent use of these tools across user populations and decision-making contexts, the causal mechanisms (how) that link use of public health data dashboards to users' decisions and actions, and the factors (conditions, circumstances, and support mechanisms) that explain variations in use and usefulness of these tools across users and applications [3,8,10,11]. A systematic review and synthesis of the extant literature on this topic that is focused on closing these gaps can therefore be extremely valuable for developing a theory-grounded and evidence-informed framework to guide the design, implementation, and evaluation of effective public health data dashboards.

Aims and Prior Work

This scoping review will provide a descriptive and thematic overview of the purpose; intended audiences; health topics; design elements and characteristics; evidence of the impact of national public health data dashboards; and the processes used for development, implementation, and evaluation. Previous reviews of the literature on this topic have focused on identifying and evaluating key design features of public health data dashboards, but most were limited to a specific health topic, such as COVID-19 [2,12], food and nutrition systems [13], infectious diseases [14], and environmental hazards [15], or were limited in focus to specific design features such as data visualization design [16] or usability and usefulness [4]. By comparison, the planned scoping review will be much broader and comprehensive in terms of the scope of health topics and applications considered, but also in terms of considering different potential goals of data dashboards (eg, alert, educate, and persuade), theories of action (or how dashboards are presumed or expected to work), and outcomes of use (including impact indicators)—and comparing these across different settings and intended audiences.

In addition, this scoping review is poised to provide the first-of-its-kind systematic treatment of actionability as a critical design element of public health data dashboards. Stimulated by disjointed public health response to the COVID-19 pandemic, there has been a growing interest in the question of what makes public health data dashboards actionable, that is, ensuring they provide an optimal match for both purpose and use of data in support of decisions that lead to sound and equitable public health policies and practices [17]. Yet, actionability, as applied to public health data dashboards, is not yet fully defined or sufficiently operationalized to inform the design and implementation of such tools. Ivanković et al [18], for example, defined data dashboard actionability according to 7 features: (1) knowing and clearly stating the desired consumers of the information, (2) selecting and presenting appropriate indicators, (3) clearly stating the sources of data and methods used to generate indicators, (4) demonstrating variation over time and linking changes to public health interventions, (5) providing as high a spatial resolution as possible to enable consumers to evaluate local risk, (6) disaggregating data to population subgroups to further enable evaluation of risk, and (7) providing narrative information to enhance interpretation of the data by the consumer. This type of user-centered conception understands actionability as a function of both usability and degree of match between data and users' information needs is intuitive but may not be adequate or sufficient to assess the actionability of dashboards intended for a general audience [19]. Other scholars in this space considered a design-centered conception of

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actionability [20]. In their view, to be actionable, dashboards must prompt or trigger users to act on data by being integrated, via behavioral design, into users' data use practices or routines such as assessing performance on tasks or progress on goals. Finally, some advocate for a decision-centered conception of actionability, whereby data dashboards are considered actionable to the extent they provide data, analyses, and forecasts (eg, predictive analytics) that allow decision makers to make an informed choice among alternatives [19,21,22]. All 3 conceptions appear to be relevant to the definition and operationalization of actionability as a key design feature of public health data dashboard and the scoping review will be instrumental both in terms of more fully explicating actionability based on the integration of existing conceptions, as well as identifying additional potential dimensions that may be used to this end.

Accordingly, the key research questions that will be addressed by this study are as follows: (1) What is the current landscape of national public health data dashboards? Who creates them, for what purpose, with what data, and for whom? (2) What processes and frameworks are used for the development, implementation, and evaluation of national public health data dashboards? What are common metrics or indicators for assessing use and impact? (3) What design approaches, principles, and features are most frequently incorporated in national public health data dashboards? How may they be associated with the actionability of these tools?

Methods

Study Design

Given the aims of this study and the considerable diversity in research questions and methodologies used across disciplines and fields to study public health data dashboards, a scoping review of the literature is a sound choice. A scoping review is a type of evidence synthesis that aims to identify and map relevant scholarship that meets predetermined inclusion criteria regarding the topic, field, context, concept, or issue under review [23]. Like other types of systematic reviews, rigorous scoping reviews are based on well-defined methodological guidance and reporting standards that include a priori protocol, eligibility criteria, and a comprehensive search strategy. Accordingly, this study will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews), which is the most up-to-date and advanced approach for conducting and reporting scoping reviews [24].

Selection Criteria and Search Strategy

For the purposes of this scoping review, we define the "public health data dashboard" as a publicly accessible, web-based, and regularly updated information management and data visualization tool that displays and tracks certain public health indicators, metrics, and data points that can support decisions regarding population health. This definition is inclusive of a broad range of population health-relevant data such as vital statistics, epidemiological surveillance, aggregated measures of access and use of health services, community health indicators, and health information ecology (eg, data that tracks the spread of misinformation about a health topic), but excludes the use of data dashboards in clinical and health care organizations (eg, data used to track or benchmark internal performance or practices), as well as dashboards incorporated into patient portals.

Accordingly, the target population of this scoping review consists of all English-language, full-text, peer-reviewed journal papers, conference proceedings, book chapters, and reports that describe the design, implementation, and evaluation of a public health dashboard published between 2000 and 2023. Whereas the rapid advancements in dashboard technology in recent years may warrant a greater focus on more recent research, adopting a broader historical perspective can be useful for determining what, if anything, changed over time regarding the design philosophies and theories of action guiding the development and implementation of these tools. For the same reason, no geographical location, health focus, or methodological orientation–based restrictions will be imposed as selection criteria. Research reports involving data dashboards that do not use national data sources (eg, regional, state, or county level) are beyond the scope of the current review as prior research suggests that published case studies of these types of dashboards are not comparable given considerable variations in the resources available to develop and maintain data dashboards, availability and quality of data, and intended audiences [25]. However, we recognize that such case studies can contribute valuable insights regarding the actionability of public health data dashboards despite being underrepresented in the current literature on the topic [3]. Accordingly, we plan to compare and contextualize the findings of this scoping review against the findings and conclusions of several recent studies that systematically assessed key design and use elements of state-level data dashboards [25-27]. In addition, the next phase of this project, which involves the mapping and analysis of publicly accessible national and state-level US public health data dashboards, was intentionally designed to produce a more systematic and complete account of similarities and differences among public health data dashboards across levels.

Our search procedure is designed to minimize potential errors in our search strategies that negatively affect the quality and validity of this scoping review [28]. First, in collaboration with a research librarian, we searched both the Medical Subject Headings database and keywords listed in recently (2019 and onward) published journal papers on the topic of public health data dashboards to identify the most relevant keywords and terms for searching for relevant publications that meet our inclusion criteria. In the next step, we followed an established procedure [29] to experiment with different combinations of databases and search queries to optimize the recall (sensitivity) and precision (specificity) of our search strategy. Given the aims of this scoping review, we opted for a search strategy that maximizes coverage, that is, will increase the likelihood of identifying all or as many as possible relevant resources. Hence, the reviewer needs to select a search system that provides the best coverage of the chosen search topic. Accordingly, we searched CINAHL, PubMed, Medline, and Web of Science databases in June 2023 for published research reports using the search query ([“dashboard” OR “data dashboard” OR “Information visualization” OR “data visualization”] AND

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["public health" OR "population health"]). These databases were selected because they were identified, via rigorous testing, as providing optimal coverage of research published across a broad range of disciplines and fields [30]. In our testing, this combination of databases and search queries increased recall but resulted in a precision level of about 25%, providing a rough estimate of the expected number of relevant documents returned by the search. We conducted supplementary searches of gray literature using the same search query to search OpenGrey for additional documents that met all selection criteria.

Study Selection

All papers retrieved by the search across the 4 databases were imported into and initially reviewed using Zotero (Corporation for Digital Scholarship), a free and open-source reference management software to manage bibliographic data. After duplicate records were identified and duplicates removed, the remaining pool of documents was manually screened by members of the research team for relevance. All coders (n=5) first received training on the task and then were provided with a random sample of 45 records to screen for relevance by applying the selection criteria. Agreement among coders was assessed using Krippendorff α [31], and the test result was significantly lower (α=0.37) than the acceptable standard (α=0.70). Coders then received additional training on the task of screening items for relevance and then independently coded a fresh set of 25 randomly selected items. An intercoder agreement was reassessed and reached an acceptable standard (α=0.78), allowing coders to proceed with the task, with any potential ambiguity regarding relevance resolved via a full team review.

Data Charting

A preliminary list of data elements for charting is presented in Textbox 1, but an iterative process will be used to identify additional elements for data extraction and analysis as the study progresses and based on inputs received from the project's expert advisory group (composed of national data dashboard creators). A standardized data extraction form will be developed and pilot-tested by following the same procedure described above for validating the screening and selection procedure including tests of intercoder agreement. Once a high level of agreement is achieved, coders will proceed to extract the data from all documents included in this scoping review. Any confusion or disagreement regarding data extraction will be resolved by discussion among research team members.

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Textbox 1. List of data extraction elements.

Study identifiers

- Metadata (title, authors, journal, year of publication, and keywords)
- Study type (eg, descriptive, exploratory, and explanatory)
- Research methodology
- Study focus (eg, development, implementation, and evaluation)
- Geographic location (country)

Data characteristics

- Data sources
- Health topics
- Type of data (eg, epidemiological, health services, and behavioral)
- Populations represented in the data
- Indicators or metrics selected for visualizations
- Data level of granularity (eg, national, state, county, and city)

Dashboard design characteristics

- Stated goals or purposes of the dashboard (eg, tracking or monitoring)
- Design philosophy cited (eg, user-friendly, functional, and co-design)
- Design process (eg, iterative and collaborative)
- Dashboard features (eg, customization and search functionalities)
- Data visualization tools (eg, maps, graphs, and tables)

Users and usability

- Intended audiences
- Public access (open, restricted/limited, requires registration)
- Dissemination channels (eg, social media, news outlets, email, and listserv)
- Reported use- or usability-related barriers or challenges

Logistics or operation

- Ownership or hosting
- Source of funding
- Software tools (commercial and open source)
- Data updating and quality assurance protocols
- Technical support (eg, user manuals, training, and customer service option)

Performance and usefulness or impact evaluation

- Evaluation methodology
- Use or usability indicators captured (eg, website analytics and user ratings)
- Impact indicators or other evidence of impact
- Explanations given for observed effects or impact (or lack of)

Data Collection, Curation, and Analysis

Data extraction and collection will be performed using a web-based survey tool (Qualtrics; Silver Lake Technology Management, LLC) as, in our experience, this method improves workflow and reduces recording errors compared with alternative methods (eg, entering data in a spreadsheet). The data file generated will be cleaned and then converted to an SPSS (IBM Corp) file for data analyses (mainly frequency counts and cross-tabulation of variables). This scoping review will follow the PRISMA-ScR checklist [24] for reporting methods and outcomes.

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Results

In June 2023, electronic database searches for relevant papers were completed using the search procedure outlined above. After the removal of duplicate results, the remaining records were screened manually by members of the research team following the procedure outlined above. The PRISMA flow diagram (Figure 1) summarizes the process and outcomes of the screening process. As shown, a total of 2529 documents (peer-reviewed journal papers, conference proceedings, and book chapters) were initially retrieved. An automated Zotero plugin was initially used to remove duplicate records (n=1385), leaving 1144 records. A manual quality control screening identified additional duplicate records (primarily preprint and published versions of the same work), leaving 1113 records. Following the addition of "grey literature" sources (n=10) and additional papers that were identified through our snowballing review of sources cited in other related literature reviews (n=5) [2,4,12,32], the corpus included 1128 documents. Of these, a total of 289 documents (or 25.6% of all documents screened) met the study's selection criteria and were retained for analysis. This percentage is consistent with the estimate of precision we produced (25%) based on our initial experimentation and testing of our search strategy. These documents can be divided into three general categories of research studies: (1) US case studies of national public health data dashboard (n=90), (2) non-US case studies of national public health data dashboards (n=127), and (3) reviews of the literature and other background information items such as expert evaluations of dashboard design elements that are not specific to a particular data dashboard (n=73), which are therefore excluded (but will be consulted for comparing and contextualizing the scoping review findings), leaving a total of 216 case studies included in the review. We will conduct an initial round of review to determine whether and how differences across case studies may influence the validity and reliability of the findings and the conclusion drawn from this scoping review before deciding on the final pool of papers to be coded and analyzed. We aim to finish the coding and analysis of papers and draft the final report by mid-2024. Findings will be summarized narratively (with the addition of summary tables and graphs) and organized around the research questions motivating the review. The final report will be submitted for publication along with the completed PRISMA-ScR reporting checklist.

Figure 1. Flow diagram of paper screening and selection process [33].

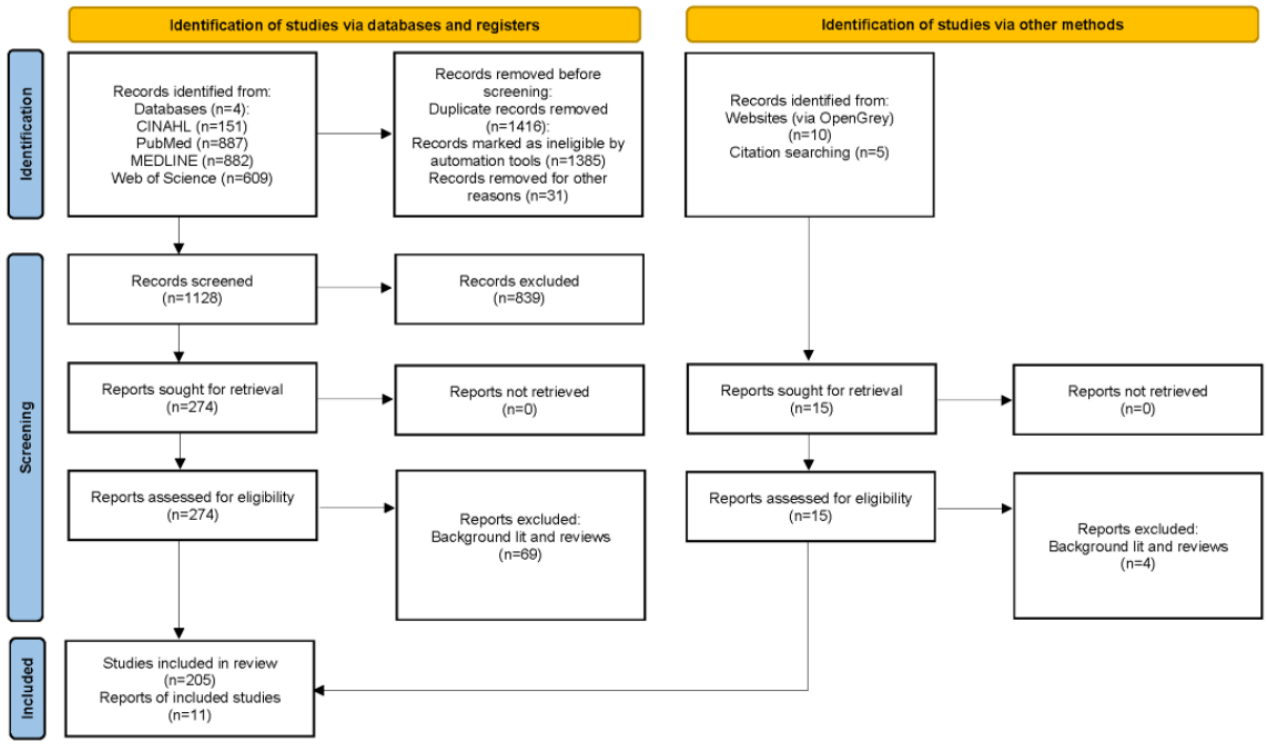

Discussion

Principal Findings

As public health data dashboards are poised to become more ubiquitous, it is imperative to proactively consider how they may be best designed to leverage public health data systems and meet the information needs of diverse audiences to support sound decisions regarding equitable and sustainable public health policies and practices [3,10]. However, the scientific literature available to inform such efforts is considerably fragmented, lacking a standard, coherent focus regarding the goals, design, use, usefulness, and impact of these tools, as well as regarding factors (ie, conditions, circumstances, and support mechanisms) that explain variations in their use and usefulness across users and applications [3,8,10,11]. We intended to use the findings of this scoping review to inform the development of a theory-grounded and evidence-informed framework for guiding the design, implementation, and evaluation of effective public health data dashboards. In addition, the review will produce evidence that can be used for identifying important gaps and deficiencies, but possibly also best practices, in current

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practices that can enhance the efficient and effective use of these tools moving forward.

Limitations

The scoping review methodology used in this study has several limitations. First, whereas we took multiple steps to ensure the rigor of our literature search and screening strategy, it is still reasonable to assume that some relevant studies are overlooked. However, by opting for a procedure designed to maximize coverage at the expense of precision, we are potentially able to mitigate this limitation. Second, because the studies included in the review vary considerably in the type and depth of the information provided, data extraction and analysis may not be sufficiently robust to support sound conclusions and recommendations based on findings. We will take care to qualify any conclusions or recommendations accordingly and to reflect critically on the state of research on this topic. Third, it is possible for potential bias in findings and conclusions to creep in because studies that considered a particular type of data dashboard are disproportionately represented in the literature on the topic, for example, studies of COVID-19 data dashboards [4]. If this is the case, we will make sure to minimize bias by clustering dashboards of the same type (including multiple studies of the same data dashboard) and analyzing them separately. Fourth, limiting the scope of the review to national public health data dashboards may result in potentially missing valuable insights that can be drawn from case studies of regional, state, and county-level data dashboards. However, such insights may be gleaned from recently published work that systematically collected and analyzed such case studies [25-27] and will also emerge from the next phase of this research project (mapping and analysis of the national and state-level public health data dashboards ecosystem in the United States).

Conclusions

Public health data dashboards have significant potential to ensure timely and unrestricted access to critical public health data that can inform decisions made by a wide range of stakeholders and decision-makers. This scoping review will inform the continued development and improvement of these tools by analyzing and synthesizing current practices and lessons emerging from the literature on the topic and proposing a theory-grounded and evidence-informed framework for designing, implementing, and evaluating public health data dashboards.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Application of Machine Learning in Multimorbidity Research: Protocol for a Scoping Review

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Abstract

Background: Multimorbidity, defined as the coexistence of multiple chronic conditions, poses significant challenges to health care systems on a global scale. It is associated with increased mortality, reduced quality of life, and increased health care costs. The burden of multimorbidity is expected to worsen if no effective intervention is taken. Machine learning has the potential to assist in addressing these challenges since it offers advanced analysis and decision-making capabilities, such as disease prediction, treatment development, and clinical strategies.

Objective: This paper represents the protocol of a scoping review that aims to identify and explore the current literature concerning the use of machine learning for patients with multimorbidity. More precisely, the objective is to recognize various machine learning models, the patient groups involved, features considered, types of input data, the maturity of the machine learning algorithms, and the outcomes from these machine learning models.

Methods: The scoping review will be based on the guidelines of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews). Five databases (PubMed, Embase, IEEE, Web of Science, and Scopus) are chosen to conduct a literature search. Two reviewers will independently screen the titles, abstracts, and full texts of identified studies based on predefined eligibility criteria. Covidence (Veritas Health Innovation Ltd) will be used as a tool for managing and screening papers. Only studies that examine more than 1 chronic disease or individuals with a single chronic condition at risk of developing another will be included in the scoping review. Data from the included studies will be collected using Microsoft Excel (Microsoft Corp). The focus of the data extraction will be on bibliographical information, objectives, study populations, types of input data, types of algorithm, performance, maturity of the algorithms, and outcome.

Results: The screening process will be presented in a PRISMA-ScR flow diagram. The findings of the scoping review will be conveyed through a narrative synthesis. Additionally, data extracted from the studies will be presented in more comprehensive formats, such as charts or tables. The results will be presented in a forthcoming scoping review, which will be published in a peer-reviewed journal.

Conclusions: To our knowledge, this may be the first scoping review to investigate the use of machine learning in multimorbidity research. The goal of the scoping review is to summarize the field of literature on machine learning in patients with multiple chronic conditions, highlight different approaches, and potentially discover research gaps. The results will offer insights for future research within this field, contributing to developments that can enhance patient outcomes.

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KEYWORDS

multimorbidity; multiple long-term conditions; machine learning; artificial intelligence; scoping review; protocol; chronic conditions; health care system; health care

Introduction

Background

According to the World Health Organization, multimorbidity is characterized as the coexistence of 2 or more chronic conditions in a single individual. These chronic conditions are often long-term health conditions that require complex and ongoing care [1]. Chronic diseases include both mental and physical health conditions [2]. In the context of multimorbidity, no single chronic condition is necessarily more central than the others, as this could result in designating one condition as the index condition, where a more appropriate term would be comorbidity [2-4].

On a global scale, approximately one-third of adults, and over half of all adults with any chronic condition, already experience multimorbidity [5]. The occurrence of multimorbidity increases with age [5-7], with projections showing a doubling of individuals aged 60 years and older globally before 2050; the number of persons with multimorbidity is also expected to rise dramatically [5,8].

In Denmark, a report from 1 of the 5 regions responsible for delivering health care (Region Zealand) concludes that in 2022, there were approximately 1.2 million people with multimorbidity in Denmark, which corresponds to 26% of the population [9]. This number is expected to increase by 1.4% annually to 1.5 million in 2050 if no efforts are made to improve the population's health [9].

Multimorbidity is linked to an increased likelihood of premature death [10,11]. This risk escalates with both the quantity of conditions and the particular combinations of chronic diseases [10,11]. Multimorbidity also lowers quality of life, which gets worse as you have more chronic diseases [11-14]. It disproportionately affects individuals with low socioeconomic status, contributing to increased health inequality [5,15-17], and is also associated with more mental symptoms and a greater perception of fragmented care [10,11]. Multimorbidity is also responsible for higher health care expenditure due to longer hospital stays and larger medication consumption [12,18].

There exist several risk factors associated with the development of multimorbidity including sociodemographic factors (eg, age, household income, and education) [5,14], biomedical risks (eg, overweight, high blood pressure, high cholesterol, and genetic predispositions), and health behaviors (eg, physical inactivity, poor nutrition, smoking, and alcohol consumption) [19,20]. Additionally, certain chronic conditions may share common risk factors, or one disease may be a risk factor for another [21].

However, in contrast to patients with single diseases, there is a complex relationship between risk factors and multimorbidity [22]. For example, according to a report from the Australian government [23], there is a correlation between the number of chronic conditions a person has and the likelihood of having multiple risk factors [23].

Nonetheless, without the information regarding the duration of an individual's exposure to risk factors and the onset of their chronic condition, attributing their chronic conditions solely to the number of risk factors is not possible. This is due to the onset of some chronic conditions possibly motivating people to change their behavior for the better. For instance, when a person is diagnosed with chronic obstructive pulmonary disease (COPD), it may inspire them to quit smoking and thereby reduce the risk of exacerbating COPD and cancer. In contrast, a person diagnosed with COPD will not be motivated to engage in physical activity, which would then increase the risk of, for example, diabetes [19-21].

As a result of the complexity of the risk factors, clinical decisions for patients with multimorbidity are a complicated and challenging task since the health care system is primarily designed to manage patients with a single disease [24].

Understanding the patterns and factors associated with multimorbidity, particularly the modifiable factors, can help contribute to the prevention and treatment of multiple chronic diseases [24,25]. Predictive analytics, such as machine learning, has the potential to solve these kinds of problems [26]. It enables more advanced analysis, automation, and recognition of unidentified patterns [27]. Machine learning enables systems to learn and improve from experience without explicit programming. It involves the process of fitting one or more statistical models to a given data set that contains both explanatory variables and an outcome variable. The models provide coefficients that quantify the relationship between the explanatory variables and the outcome. These model coefficients are applied to predict the same outcome with the same explanatory variables but on new, unseen data. The model's ability to predict the outcome depends on its capacity to recognize and apply statistical patterns found in the data while it is being trained [27,28].

In health care, machine learning has demonstrated improvements in various tasks, including drug discovery [29], histopathological diagnosis [30], brain magnetic resonance imaging segmentation [31], and disease prediction using electronic health records [32,33]. In the context of machine learning for multimorbidity, there are numerous options and choices when developing an algorithm that are relevant. Combinations of disease groups have the potential to uncover new mechanisms of diseases, develop treatments, develop multidisease clinical strategies, meet the patient's needs, and manage polypharmacy [34,35]. For instance, Prados-Torres et al [36] have identified 3 common multimorbidity clusters: cardiovascular and metabolic diseases, mental health problems, and musculoskeletal disorders.

Different outcomes have also been addressed in the literature, such as predicting a new disease for patients with multimorbidity [25,37,38], identifying factors for multimorbidity [39,40], predicting rehospitalization [41], and developing a multimorbidity frailty index [42]. Furthermore, a variety of different machine learning models have been used, for example,

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logistic regression [37,39,40], random forest [25,41,42], neural network [37,40], and network model [38]. It is also evident that a wide range of features have been applied in developing these machine learning algorithms. These features include sociodemographic data [25,41,42], electronic health record data [39,41], self-reported data [40], and medical data [38,39,42], among others.

The literature indicates ongoing research and a growing interest in the field of multimorbidity. However, the type and amount of evidence remain unclear as well as potential gaps in the literature [25]. Therefore, a scoping review was chosen to identify and map available evidence within this field.

Review Objective

The objective of this scoping review is to explore the existing literature regarding the use of machine learning in the context of multimorbidity. Specifically, it seeks to identify the machine learning models that have been used, the patient groups that have been the focus in various studies, the features, types of input data, the maturity of the algorithms, and outcomes that have been in focus. In doing so, any potential gaps in research or knowledge can be identified.

Methods

Ethical Considerations

Ethics approval is not required, as this scoping review does not involve primary data collection from human participants.

Study Design

The development of this protocol has followed the guidelines from Joanna Briggs Institute [43]. The conduct and reporting of this scoping review will follow the guidelines of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [44]. Furthermore, the review will follow the methodological framework for scoping reviews outlined by Peters et al [45], which provides guidance in the development and execution of a scoping review.

Search Strategy

Overview

To identify appropriate search terms, keywords, and index terms, a preliminary search will be conducted. The initial search will identify text words that can be applied in the subsequent systematic search. The search strategy will be adjusted to the requirements of each database and will include a range of related terms, synonyms, acronyms, and spellings. Furthermore, various search functions, such as thesaurus, Boolean operators, truncation, phrase searching, and free-text searching, will be applied to optimize the searches. The searches will be done in the databases PubMed, Embase, IEEE, Web of Science, and Scopus.

After conducting the searches, all studies that meet the inclusion criteria will be compiled and imported into Covidence (Veritas Health Innovation Ltd), which is a reference management software. Here, duplicate entries are eliminated. The eligibility of titles and abstracts will be screened by one reviewer under the supervision of another reviewer. Subsequently, full text will be individually evaluated by the 2 reviewers. Any discrepancies will be resolved through discussion or involvement of a third reviewer. The exclusion of full-text studies and the reason for exclusion will be reported in the final scoping review. The results of the search will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and fully reported in the final scoping review. As recommended by Joanna Briggs Institute, this scoping review will apply the PCC (participants, concept, context) framework.

Participants

The scoping review will consider studies that involve patients with multiple chronic conditions. Since multimorbidity and comorbidity have been applied interchangeably in the literature, both terms will be included. There are no restrictions on the types of diseases included, as long as they meet the criteria for chronic diseases, which are characterized by lasting for a prolonged period and often progressing over time. Research that focuses on individuals with at least 2 chronic diseases or studies that examine individuals with a single chronic disease at risk of developing another will be considered in this study.

Concept

This scoping review will consider studies that evaluate machine learning models applied on a population diagnosed with multimorbidity. This includes supervised learning methods, such as logistic regression, support vector machine, decision tree, random forest, or neural network.

Context

This scoping review will consider studies concerning either on the diagnosis, treatment, monitoring, or prediction of diseases in patients with multimorbidity.

Inclusion and Exclusion Criteria

Studies that examine patients with more than 1 chronic disease or individuals with a single chronic disease who are prone to developing another will be included in this study. A chronic disease is defined as a long-term health condition that necessitates complex and continuous medical care, which either can be mental or physical health conditions [1].

Due to the interchangeable use of the 2 terms multimorbidity and comorbidity in the literature, both terms will be considered in this study. Additionally, only studies using supervised learning algorithms will be considered. Supervised learning algorithms are trained on labeled data, allowing them to learn from examples with known input-output pairs.

This scoping review will consider all study types and aims to find published and unpublished studies. Furthermore, studies with full text and free full text will be included, since there is an interest in looking at their process, such as input data, methods, model, and outcome. Full-text studies published in all languages will be considered, provided there is an abstract available in English, French, Spanish, or German.

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Results

To ensure all relevant results are extracted from the identified studies, a template based on Aromataris et al [46] with extraction fields is adapted to suit our specific requirements. These can be seen in Textbox 1. For managing and screening references, Covidence will be used. For data extraction, Microsoft Excel (Microsoft Corp) will be applied. Data will be extracted by 2 reviewers, including information about the study population, method, medical application, and outcome.

Textbox 1. Overview of extraction fields for data retrieval from the identified studies. Inspired from Joanna Briggs Institute methodology guidance for scoping reviews [46].

Extraction fields

- Authors
- Publication year
- Source of origin or country of origin
- Objective
- Study population or type of patient with multimorbidity and sample size
- Medical application
- Type of input data
- Type of algorithm
- Maturity of the algorithm
- Performance
- Validation of algorithm
- Outcomes
- Key findings that relate to review question

The data that have been extracted from the included studies will be presented in either tabular or diagrammatic format, depending on what is most suitable. These will also be supported by narrative descriptions. The key findings that relate to the review question will be analyzed thematically. Any emerging themes and subthemes will be depicted in a diagrammatic or alternative visual format that is appropriate.

Discussion

Principal Findings

Multimorbidity is a global challenge for the health care system since it is associated with increased mortality, reduced quality of life, and increased health care costs. With the increasing prevalence, the problem is only growing. Machine learning has the potential to address these challenges, as these methods can understand the patterns and factors associated with multimorbidity. This scoping review aims to explore and synthesize the current literature addressing the use of machine learning in the context of patients with multimorbidity.

Following the definition of a scoping study established by Arksey and O'Malley [47], this scoping review serves 2 primary objectives. It aims to compile and communicate research findings to policy makers, practitioners, and consumers. Besides that, it will also pinpoint any existing research gaps within the literature [47]. The available literature indicates ongoing research into the application of machine learning within the context of multimorbidity. Unfortunately, there is uncertainty regarding the type and quantity of evidence as well as potential knowledge gaps. To our knowledge, this may be the first scoping review in this field to uncover this.

The insights gained from this scoping review can be valuable for both researchers and health care practitioners. For researchers, understanding the current landscape of machine learning methods can provide a foundation for future studies by stimulating new research questions and help to identify research gaps. Health care practitioners can gather awareness of the current state of machine learning use in multimorbidity research. Overall, the findings from this scoping review can contribute to more precise interventions, ultimately improving patient outcomes.

Limitations

Nevertheless, the scoping review may have some limitations regarding the search strategy. The scoping review follows the PCC framework, where including the last block (context) may potentially constrain the search outcomes. A potential solution is only to use the first 2 blocks (participants and concept), although this approach may introduce more noise into the search results. However, this might not pose an issue, as the last block (context) is comprehensive due to the included search words within the block.

A particular challenge in this field is the interchangeable use of the terms "multimorbidity" and "comorbidity" in the literature. To address this issue, the participant search block in the PCC framework contains synonyms for both terms. This ensures the retrieval of relevant studies and accounts for potential variations in terminology across the literature. Besides that, it also captures a broader spectrum of research related to patients with multiple

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chronic conditions. A disadvantage of this approach is the potential for more noise and irrelevant results.

Whether there is a need for quality assessment of the included studies can be discussed. Typically, this is not done in a scoping review, as the objective is to provide an overview of the evidence rather than a critically appraised and synthesized response to a specific question [48-50]. On the other hand, using tools such as the Prediction Model Risk of Bias Assessment, which is designed for systematic reviews, could provide insights into the quality of prediction models [51]. Being aware of this, this study will follow the typical approach for conducting scoping reviews, and thereby not conduct a quality appraisal of the included studies.

Conclusions

The primary objective of this scoping review is to investigate the existing literature on machine learning in patients with multiple chronic conditions and potentially highlight research gaps. To our knowledge, this scoping review marks the initial exploration into the application of machine learning in multimorbidity research.

The outcome of the searches will be presented following the PRISMA-ScR checklist and flow diagram, which will provide a comprehensive overview of the search process, including the number of identified studies, duplicates removed, screened studies, excluded studies, and studies included in the review. A conclusive summary based on the results of the scoping review will be presented, and recommendations for future research will be suggested if any possible knowledge gaps are identified. The potential findings of the scoping review will be reported in an academic paper, which will be submitted to a peer-reviewed journal and presented at a national conference.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

COPD: chronic obstructive pulmonary disease
PCC: participants, concept, context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Identifying Existing Guidelines, Frameworks, Checklists, and Recommendations for Implementing Patient-Reported Outcome Measures: Protocol for a Scoping Review

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Abstract

Background: Implementing patient-reported outcome measures (PROMs) to measure and evaluate health outcomes is increasing worldwide. Along with this emerging trend, it is important to identify which guidelines, frameworks, checklists, and recommendations exist, and if and how they have been used in implementing PROMs, especially in clinical quality registries (CQRs).

Objective: This review aims to identify existing publications, as well as publications that discuss the application of actual guidelines, frameworks, checklists, and recommendations on PROMs' implementation for various purposes such as clinical trials, clinical practice, and CQRs. In addition, the identified publications will be used to guide the development of a new guideline for PROMs' implementation in CQRs, which is the aim of the broader project.

Methods: A literature search of the databases MEDLINE, Embase, CINAHL, PsycINFO, and Cochrane Central Register of Controlled Trials will be conducted since the inception of the databases, in addition to using Google Scholar and gray literature to identify literature for the scoping review. Predefined inclusion and exclusion criteria will be used for all phases of screening. Existing publications of guidelines, frameworks, checklists, recommendations, and publications discussing the application of those methodologies for implementing PROMs in clinical trials, clinical practice, and CQRs will be included in the final review. Data relating to bibliographic information, aim, the purpose of PROMs use (clinical trial, practice, or registries), name of guideline, framework, checklist and recommendations, the rationale for development, and their purpose and implications will be extracted. Additionally, for publications of actual methodologies, aspects or domains of PROMs' implementation will be extracted. A narrative synthesis of included publications will be conducted.

Results: The electronic database searches were completed in March 2024. Title and abstract screening, full-text screening, and data extraction will be completed in May 2024. The review is expected to be completed by the end of August 2024.

Conclusions: The findings of this scoping review will provide evidence on any existing methodologies and tools for PROMs' implementation in clinical trials, clinical practice, and CQRs. It is anticipated that the publications will help us guide the development of a new guideline for PROMs' implementation in CQRs.

Trial Registration: PROSPERO CRD42022366085; https://tinyurl.com/bdesk98x

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KEYWORDS

patient-reported outcome measures; patient-reported outcomes; quality of life; clinical quality registry; guidelines; frameworks; recommendations; scoping review; patient perspectives; patient perspective; patient-reported outcome; patient-reported; clinical setting; clinical registry; registry; systematic review

Introduction

Patient-reported outcome measures (PROMs) are standardized, validated questionnaires that seek to ascertain patients' views on their physical and mental well-being [1]. Traditionally, PROMs were developed for use in research, to assess treatment effectiveness in clinical trials, and were later adopted by clinicians to enhance their clinical management of patients [2,3]. PROMs are increasingly accepted to measure outcomes of an intervention from the patient's point of view in various health care and research settings including clinical practice, clinical trials, and clinical quality registries (CQRs) [1,4,5].

PROMs are routinely used in clinical trials to assess the impact of treatment from the patient's perspective, especially in disease-specific areas such as oncology and cardiovascular disease [6,7]. For instance, the Australian government supports a Quality of Life Office that collaborates with 13 National Cancer Clinical Trial Groups to include PROs in investigator-initiated oncology trials such as breast cancer trials [6,8]. A review of the Australian New Zealand Clinical Trials Registry indicated that of 13,666 trials registered from 2005 to 2017 in the registry, 6168 (45%) included a PROM [9].

PROMs in clinical trials are important for decision-making among the stakeholders involved, especially in medical device-related trials to measure adverse events and other negative outcomes to assess the safety of a medical device [10]. Evidence indicates that in Western European nations such as the United Kingdom and Germany, the use of PROMs in medical device studies is increasing [11]. The European Medicines Agency also has a guideline on the use of patient-reported outcomes (PROs) in evaluating anticancer medical products [12].

In countries such as Australia, there are national-level initiatives, such as the National Safety and Quality Health Service standards, that encourage the involvement of patients in planning, delivering, monitoring, and evaluating health care [13]. The use of PROMs in clinical practice has increased over the years as a collection of PROs "ensures the patient's values and expectations are present in all aspects of care ensuring management remains patient-centred" [14,15]. For instance, organizations such as the International Consortium for Health Outcomes Measurements drive the use of PROMs in clinical practice [16]. At the patient level, PROMs may be used for screening, monitoring, promoting patient-centered care, and facilitating better communication between the patient and the provider. At a higher level, PROMs may be used to facilitate system health care planning and assess the quality of health care delivery over time [17,18].

CQRs systematically monitor the quality of health care within specific clinical domains by routinely collecting, analyzing, and reporting health-related information to their numerous stakeholders [13]. CQRs have expanded in the last decade to monitor clinical outcomes and facilitate evidence-based clinical practice in most developed countries [5,19,20]. Many registries also capture PROs on the expectations and impact of treatment from patients to provide benchmark reports for quality improvement within clinical settings [21].

PROMs captured in clinical practice, clinical trials, and CQRs can contribute to understanding variation in health care, efficacy, and safety of interventions and potentially improve health care provision. Implementation of these measures, however, is complex, and requires a thorough consideration of various aspects such as selecting the appropriate PROM, determining the mode and method of administration, ensuring good quality data are captured and high response rates are achieved, and analysis and reporting of the data [22]. Along with the increase in the use of PROMs, it is important to ensure that guidelines, frameworks, checklists, and recommendations for implementing PROMs, addressing various aspects of PROMs' implementation, exist to aid successful PROs collection.

The findings of this scoping review will help us identify which guidelines, frameworks, checklists, and recommendations exist and if and how they have been applied in PROMs' implementation in clinical trials, clinical practice, and CQRs. In addition, the publications identified will help us create a preliminary set of recommendations that can be used when developing a new guideline for PROMs' implementation in CQRs.

Methods

Information Sources and Search Strategy

A comprehensive literature search will be performed using a search strategy developed by a medical librarian (LR). The search will be performed using both MeSH (Medical Subject Headings) terms and free text including PROMs AND ("clinical trials" OR "clinical practice" OR "clinical quality registry"). The detailed search is provided in Multimedia Appendix 1.

The review will include MEDLINE, Embase, CINAHL, PsycINFO, and Cochrane Central Register of Controlled Trials databases. The publications will be limited to those in the English language. All publications from database searches will be exported to Covidence (Veritas Health Innovation) [23], a software that assists the paper screening, database extraction, and cooperation among multiple assessors, and duplicates will be removed for screening.

The protocol for this scoping review has been developed according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guideline or checklist [24].

Selection and Screening Process

Two independent researchers (RTJ and RR) will conduct title and abstract screening of all records including publications of

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guidelines, frameworks, checklists, recommendations, conference abstracts, opinion pieces, websites, media articles, and presentations identified in the initial search to determine eligibility. The eligibility will be determined according to the inclusion and exclusion criteria described below. The last phase will include 3 researchers (RTJ, RR, and ADM) independently reviewing full-text papers to determine eligibility for the review. Any conflicts will be resolved through discussion and consensus.

Inclusion Criteria

Publications describing the implementation of PROMs in any clinical setting for various purposes including clinical trials, clinical practice, and CQRs will be included in the final review. The included publications must describe the conception, development, or application of the guidelines, frameworks, checklists, and recommendations for implementing PROMs. PROMs' implementation will include all aspects from selecting the appropriate PROM, integrating it into practice, collection of the data, analysis, and reporting. Qualitative, quantitative, and mixed methods studies will be included. Government and clinical registry reports and gray literature including guidelines, frameworks, checklists, and recommendations documents and websites will also be included.

Exclusion Criteria

Non-English publications and any unpublished papers, dissertations, conference proceedings, and meeting abstracts will be excluded.

Data Extraction

Data extraction will be independently performed by the 3 reviewers (RTJ, RR, and ADM), and any discrepancies in the data will be resolved through discussion and consensus with the senior author. Evidence will be synthesized based on the information presented in Textbox 1.

Textbox 1. Data extraction items of included publications.

Bibliographic information

- Author, year, and country of publication
- Title

Publications of guidelines, framework, checklists, and recommendations

- Name of the guideline, framework, checklist, and recommendations
- Purpose of patient-reported outcome measures (PROMs) use (ie, clinical trial, practice, or registry)
- Aspects or domains of PROMs' implementation addressed by the guideline, framework, checklist, and recommendations (ie, selection of the tool, administration, data collection, analysis, and reporting)

Publications discussing the use and application of guidelines, framework, checklists, and recommendations

- Brief aims of the study
- Purpose of PROMs use (ie, clinical trial, practice, or registry)
- Condition (disease)
- Name of the guideline, framework, checklist, and recommendations
- Rationale for development and purpose of the guideline, framework, checklist, or recommendations (ie, development and implementation of PROMs including selection of the tool, administration, data collection, analysis, and reporting)
- Implications of applying the guideline, framework, checklist, and recommendations for PROMs implementation (ie, changes in clinical practice, improving outcomes, and response rates)

Data Management

The search will be carried out in the databases mentioned in the Methods section under "Information Sources and Search Strategy" and then loaded into EndNote X8 software (Clarivate) [25], a management software for references that allows the identified references to be organized into different electronic databases. All results will be inserted in a single EndNote folder and duplicated publications will be identified and removed using EndNote X8 [25]. After duplicate removal of publications, the research results will be loaded onto Covidence [23].

Data Analysis

A narrative synthesis of the data will be conducted using tables and texts in this scoping review. A table with a summary of study characteristics from the data extracted will be presented. This will indicate existing guidelines, frameworks, checklists, and recommendations for implementing PROMs in any clinical setting, their purpose, and the implications. For the analysis, data will be grouped according to the purpose of PROMs use (ie, clinical trials, clinical practice, or CQRs). The narrative synthesis will be conducted by summarizing and explaining the extracted data from Textbox 1. This will include discussing the rationale for the development and implications of existing guidelines, frameworks, checklists, and recommendations for different purposes. The need for an appropriate guideline in CQRs will be discussed as well.

Ethical Considerations

Ethical approval is not required for this scoping review because all the data included in the review has been published and is

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publicly available. This review did not include the collection of data from human participants.

Results

The review was registered in PROSPERO on October 21, 2022 (CRD42022366085). Electronic database searches have been completed in March 2024, title and abstract screening, full-text screening, as well as data extraction will be completed in May 2024. As of May 2024, a total of 4905 records have been identified, 177 articles have been assessed for eligibility and 56 studies have been selected for data extraction. The study is expected to be completed by the end of August 2024.

Discussion

Principal Findings

The proposed scoping review aims to identify any existing guidelines, frameworks, checklists, and recommendations in clinical trials, practice, and registries. We anticipate that the findings will also guide the development of a new guideline for PROMs' implementation in CQRs.

This review will be the first part of a broader project to develop a guideline for PROMs' implementation in CQRs. The findings will help us identify existing guidelines, frameworks, checklists, and recommendations and various aspects of the PROMs' implementation they address. These may include PROMs' selection, administration, collection, analysis, and reporting. Furthermore, the review will provide evidence of how the guidelines, frameworks, checklists, and recommendations have been developed and their implications (including barriers and enablers) when used in PROMs' implementation in clinical trials, clinical practice, and CQRs. From these findings, we will be able to create a set of preliminary recommendations that can be used as the foundation to guide the development of a new guideline for PROMs' implementation in CQRs.

In addition to clinical trials and practices, clinical registries also use PROMs, especially for reporting and benchmarking purposes [1]. The significance of PROMs' data from CQRs is that they can be collected from a large population and outcomes can be monitored over a long time. Additionally, the collection of PROMs in CQRs has many implications. These include improving patient outcomes, improving quality of care, improving response rates, minimizing the cost and resource burden, and providing benchmarks for participating health services. Despite these benefits, no standard guideline, framework, checklist, and recommendations exist for the implementation of PROMs in CQRs.

Having a standard guideline, framework, checklist, and recommendations to collect patients' perspectives appropriately will be useful for CQRs in many different ways. For instance, long-term monitoring of a patient's condition through PROMs helps clinicians understand the status of a patient's health during a disease or treatment [22]. This can facilitate patient-clinician communication and support making informed decisions regarding treatment options based on the patient's opinion. However, these opinions will only be useful if they are collected, analyzed, and reported in a useful manner. Hence, a standard guideline outlining the steps to implement PROMs will ensure that patient perspectives are captured successfully.

Thus, by using the findings from this review as the foundation, followed by a consensus study, validation, and testing studies, our ultimate aim is to develop a guideline for PROMs' implementation in CQRs worldwide.

Limitations

There is potential for heterogeneity in the papers included in this review. Also, the reproducibility of the study might be limited.

Conclusions

Implementation of PROMs is complex and requires a thorough consideration of various aspects such as selecting the most appropriate PROM, determining mode and method of administration, ensuring good quality data are captured and high response rates are achieved, and analysis and reporting of the data. This review findings will help identify existing guidelines, frameworks, checklists, and recommendations in clinical trials, clinical practice, and CQRs. The findings will also guide the development of a new guideline for PROMs' implementation in CQRs.

Acknowledgments

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Authors' Contributions

RR conceived the study and provided oversight to the project. Each author contributed to conceptualizing this project, creating the search strategy, refining the inclusion and exclusion criteria, and producing this paper. RTJ registered the protocol with PROSPERO and drafted the first draft. RR, ADM, SA, and LR were involved in the data collection, extraction, and data analysis. Constructive feedback was provided by all authors, which was incorporated into the final version of the paper. All authors read and approved the final copy of the protocol.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Search strategy of the Ovid MEDLINE database.
[DOCX File , 16 KB - resprot_v13i1e52572_app1.docx]

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Abbreviations

CQR: clinical quality registry
MeSH: Medical Subject Headings
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRO: patient reported outcome
PROM: patient-reported outcome measure

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Protocol

The Use of Metabolomes in Risk Stratification of Heart Failure Patients: Protocol for a Scoping Review

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Abstract

Background: Heart failure (HF) is a significant health problem that is often associated with major morbidity and mortality. Metabolic abnormalities occur in HF and may be used to identify individuals at risk of developing the condition. Furthermore, these metabolic changes may play a role in the pathogenesis and progression of HF. Despite this knowledge, the utility of metabolic changes in diagnosis, management, prognosis, and therapy for patients with chronic HF has not been systematically reviewed.

Objective: This scoping review aims to systematically appraise the literature on metabolic changes in patients with HF, describe the role of these changes in pathogenesis, progression, and care, and identify knowledge gaps to inform future research.

Methods: This review will be conducted using a strategy based on previous reports, the *JBI Manual for Evidence Synthesis*, and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines. A comprehensive search of electronic databases (Medline, EBSCOhost, Scopus, and Web of Science) will be conducted using keywords related to HF, myocardial failure, metabolomes, metabonomics, and analytical chemistry techniques. The search will include original peer-reviewed research papers (clinical studies conducted on humans and systematic reviews with or without a meta-analysis) published between January 2010 and September 2023. Studies that include patients with HF younger than 18 years or those not published in English will be excluded. Two authors (UGA and MB) will screen the titles and abstracts independently and perform a full-text screen of the relevant and eligible papers. Relevant data will be extracted and synthesized, and a third author or group will be consulted to resolve discrepancies.

Results: This scoping review will span from January 2010 to September 2023, and the results will be published in a peer-reviewed, open-access journal as a scoping review in 2024. The presentation of the findings will use the PRISMA-ScR flow diagram and descriptive and narrative formats, including tables and graphical displays, to provide a comprehensive overview of the extracted data.

Conclusions: This review aims to collect and analyze the available evidence on metabolic changes in patients with HF, aiming to enhance our current understanding of this topic. Additionally, this review will identify the most commonly used and suitable sample, analytical method, and specific metabolomes to facilitate standardization, reproducibility of results, and application in the diagnosis, treatment, and risk stratification of patients with HF. Finally, it is hoped that this review's outcomes will inspire further research into the metabolomes of patients with HF in low- and middle-income countries.

Trial Registration: Open Science Framework; https://osf.io/sp6xj

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International Registered Report Identifier (IRRID): DERR1-10.2196/53905

(JMIR Res Protoc 2024;13:e53905) doi:10.2196/53905

KEYWORDS

metabolomes; metabolomics; heart failure; risk stratification; morbidity; mortality; metabolic abnormality; scoping review protocol; electronic database

Introduction

Heart failure (HF) is a heterogeneous disease with increasing prevalence and incidence owing to advances in cardiac care and increasing life span [1]. Despite advances in the care of patients with HF, rehospitalization and death rates remain high, especially in those with advanced disease and associated comorbidities [2,3]. The estimated readmission rate at 30 days is 25%, and the 5-year survival rate is 50%, which is as poor as some common cancers [3,4]. Therefore, a knowledge gap remains, and further studies are needed to identify better ways to risk-stratify these patients. HF is a multisystemic disease associated with metabolic abnormalities including inadequate energy (glucose and fatty acids) handling, anabolic-catabolic imbalance, and urea cycle dysfunction [5,6]. Understanding the critical role of metabolic dysfunction in HF has opened a conceptual gap between cardiac metabolism and HF, particularly in the era of precision medicine.

Metabolomics has emerged as a tool for measuring intermediates or metabolomes in various biological samples including plasma, urine, saliva, and tissues [7-9]. Metabolic profiling assesses endogenous and environmental factors, such as dietary intake and physical activity, and integrates genomic, transcriptomic, and proteomic variation. Hence, metabolomes are biomarkers that can be used to identify individuals at risk of developing HF diagnosis and prognostication in patients with HF [10,11]. In a study by Cheng et al [12], metabolomes complemented other cardiac biomarkers in the stratification of patients with acute decompensated HF. Metabolomes correlated better with rehospitalization and all cause death than B-type natriuretic peptide (areas under the curve 0.85 and 0.74, respectively; hazard ratio 3.08; $P<.001$) [12].

Although the use of metabolomes as a stand-alone biomarker or as a component of a multi-marker strategy is challenged partly by the need for more research, scoping reviews may help overcome this by pulling all shreds of evidence into 1 piece. Scoping reviews are used in cases where the literature on a particular topic is limited, and therefore, not harmonized, and they help identify knowledge gaps [13,14]. Further, scoping reviews do not criticize or appraise the existing literature.

The objectives of this scoping review are to systematically appraise the existing literature on the metabolic changes that occur in patients with HF, the platforms for analyzing them, and to describe the knowledge gap to inform future targeted research that will help optimize their usefulness in patients with HF.

Methods

Scoping Review Framework

This scoping review will be carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) statement [15] and the methods proposed in the updated *JBI Manual for Scoping Reviews* [16,17].

The methodology of this scoping review will include the following stages proposed by the Joanna Briggs Institute (JBI) in developing a protocol and conducting a review, namely (1) identifying the specific research questions, (2) identifying information sources and search strategies, (3) selecting sources of evidence, (4) selecting data items and extracting them, (5) charting the evidence, (6) synthesizing results, and (7) conducting an ethics review and dissemination [16,17]. The PRISMA-ScR method will guide the synthesis and reporting of the existing evidence in the research area in this review. Any subsequent modification will be highlighted in the final publication.

Research Questions

The scoping review eligibility will be based on the following research questions: (1) What energy sources are available for a healthy heart under normal physiological conditions? (2) What metabolic changes occur in patients with HF? (3) Which analytic modalities are available for metabolomics profiling? (4) What are the roles of metabolomes in the diagnosis, treatment, and risk stratification of patients with HF?

Identifying the Specific Research Question or Eligibility Criteria

We will adopt the population, concept, and context framework to define the eligibility criteria and direct the search strategy [15].

Inclusion Criteria

Population

The review will include studies in patients with HF from any etiology who are 18 years and older, including ischaemic and nonischaemic causes, either in an inpatient or outpatient setting. We will exclude studies in patients with HF who are younger than 18 years.

Concept

The concept of interest is the use of metabolomes in managing patients with HF. The role of metabolomes in patients with HF is being studied and has been found to help diagnose, assess response to therapy, and predict prognosis. Of late, omics technology, including metabolomes, has opened an avenue to

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explore other biomarkers for HF management. This scoping review aims to assess the metabolomes in individuals with HF and the alterations noted in the systemic circulation, and by extension, the myocardium during the diseased state. Furthermore, the analytical methods used to assay metabolomes will be explored and included. This review will not critique the methods of analysis but describe what was used in estimating various metabolomes. We will exclude papers that include patients younger than 18 years.

Context

This scoping review will include papers or studies that describe metabolome use in managing patients with HF. Studies from all parts of the world will be included.

The specific questions that will guide the search, charting, and reporting of the relevant literature and inform the use of the metabolomes include the following: What energy sources are available for a healthy heart under normal physiological conditions? What metabolic changes occur in patients with HF? Which analytic modalities are available for metabolomics profiling? and What are the roles of metabolomes in the diagnosis, treatment, and risk stratification of patients with HF?

Information Sources and Search Strategies

An experienced medical librarian will be consulted to assist in developing the framework for the search strategy [18] and will follow the 3-step process recommended by the JBI [17]. The search will aim to identify both published and unpublished reviews and studies. The steps are as follows.

First, a preliminary search of PubMed (Medline) will be conducted using the index terms and text words contained in the title and abstract to describe the paper. The initial keywords used included: [Heart Failure OR myocardial failure] AND [metabolomes] AND [metabonomic *] AND [Analytical Chemistry Technique].

Second, all the identified keywords, index terms, Boolean terms (ie, “AND“ ‘AND,“, ’ OR‘ ‘OR, ' ‘OR” NOT,’ ‘NOT'), and a combination of the appropriate medical subject headings terms that describe the papers will be searched in the following databases: PubMed (Medline), EBSCOhost, Scopus, and Web of Science from January 2010 to September 2023 (Textbox 1). We chose January 1, 2010, as the starting date since metabolomic literature became much more robust, and older papers may not be relevant now.

Last, the authors will manually search the reference lists of all relevant sources to obtain additional studies. A gray literature search of conference proceedings, dissertations, and thesis reports will be conducted manually using the study keywords through Google Scholar in the World Health Organization Library and Open Grey. Only studies published in English will be considered for inclusion in this scoping review, as the author’s team is proficient in English.

Textbox 1. Key concepts of the search strategy.

Heart failure

- “heart failure” [MeSH terms] OR Cardiac Failure [text word]) AND (“heart failure” [MeSH terms] OR Heart Decompensation [text word]) AND “heart failure” [MeSH terms] AND “heart failure” [MeSH terms] AND “heart failure” [MeSH terms] AND (“heart failure” [MeSH terms] OR Right-Sided Heart Failure [text word]) AND (“heart failure” [MeSH terms] OR Right Sided Heart Failure [text word]) AND (“heart failure” [MeSH terms] OR Myocardial Failure [text word]) AND (“heart failure” [MeSH terms] OR Congestive Heart Failure [text word]) AND “heart failure” [MeSH terms] AND “heart failure” [MeSH terms] AND “heart failure” [MeSH terms] AND (“heart failure” [MeSH terms] OR Left-Sided Heart Failure [text word]) AND (“heart failure” [MeSH terms] OR Left Sided Heart Failure [text word]

Metabolomes

- “metabolome” [MeSH terms] OR Metabolomes [text word]) OR (“metabolome” [MeSH terms] OR Metabolic Profile [text word]) OR (“metabolome” [MeSH terms] OR Metabolic Profiles [text word]) OR Profile [All Fields] OR (“metabolome” [MeSH terms] OR Metabolic Profiles [text word]) OR Metabolic [All Fields]

Mass spectrometry

- “mass spectrometry” [MeSH terms] OR Mass spectrometry [text word]) OR (“tandem mass spectrometry” [MeSH terms] OR Tandem mass Spectrometry [text word]) OR (“gas chromatography-mass spectrometry” [MeSH terms] OR Gas Chromatography-Mass Spectrometry [text word]

Nuclear magnetic resonance spectroscopy

- “magnetic resonance spectroscopy” [MeSH terms] OR Nuclear Magnetic resonance spectroscopy [text word]

Selection of Sources of Evidence

The sources of evidence will be developed and selected based on the eligibility criteria that will ensure that specific information relating to the research questions is included in the scoping review (Textbox 2).

The screening of identified studies for the scoping review shall consist of a title and abstract screening to identify eligible publications and full-text screening to choose papers based on the study’s inclusion and exclusion criteria. The search results will be exported into EndNote version 20, and the reference management system and duplicates will be removed. The authors (UGA and MB) will independently search the title and abstract of all studies for assessment against the inclusion criteria for the scoping review. The potentially relevant sources will be fully retrieved including their citation details. We (UGA and MB) will critically assess the full text of the selected citations

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against the inclusion criteria. The team will note the reasons for excluding full texts and report in the scoping review. Discrepancies in the study selection will be resolved by a team member (DM, MM, or NT) or by consensus. The authors will undergo in-house training on how to extract before the complete screening of relevant full-text papers. Intra and interobserver reliability will be assessed using Cohen κ coefficient (X) statistics [19].

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Study design: all study types (observational, cross-sectional, retrospective, prospective, quantitative, and qualitative designs)
- Publication: original, peer-reviewed publications between January 1, 2010, and September 30, 2023, in English
- Study location: all health care settings, no location restrictions
- Study participants: patients with heart failure (HF) 18 years and older
- Studies of cohorts of patients with HF using metabolomes with emphasis on pathophysiology, diagnosis, treatment, and follow-up

Exclusion criteria

- Papers like case series and conference abstracts
- Papers that assessed metabolomes without addressing their usefulness in the diagnosis and follow-up of patients with HF
- Papers that included patients with HF younger than 18 years

Data Extraction

Two authors (UGA and MB) will independently extract data that fit the inclusion criteria from the included studies in the scoping review using the Microsoft Excel form developed by the reviewers (Textbox 3). The data to be extracted includes the paper characteristics (first author, journal, year of publication, study design, study objectives [aims], country of origin); the population characteristics (number of participants, mean age or median with IQR, percentage of males, and diagnosis); the concepts (samples, analytical methods, metabolomes, primary findings, and comments); and the contexts (inpatient or outpatient, globally).

The Microsoft Excel form shall be reviewed, pretested, and modified as necessary by the authors during the data extraction in an iterative process. The reasons for change will be outlined and presented as an appendix for the review. Any discrepancies will be resolved through discussion or by any of these reviewers (DM, MM, and NT).

Textbox 3. Extraction instrument depicting the details of the included studies.

Paper characteristics or context

- First author, journal, year of publication, and country of origin
- Study design
- Study aims
- Inpatient or outpatient

Population characteristics

- Population, N
- Mean age, median with IQR, percentage male

Concept

- Sample type
- Analytical method
- Metabolomes assessed
- Summary of findings

Charting the Evidence

The authors will present the characteristics of each of the included studies in a tabular form. We will compare the charted data to ensure uniformity and inconsistencies resolved by arbitration. If additional categories emerge during data extraction, they will be noted and discussed during meetings, and the charting will be amended accordingly. The authors will not perform the bias assessment because it is a scoping review. This modality is in keeping with the recommendations of the PRISMA-ScR [3,15].

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Synthesis of Results

The details of the study selection process will be shown using a flowchart (PRISMA-ScR) of the databases searched, included, and excluded through the steps of a scoping review [18]. For this scoping review, the potential eligible papers will be counted, charted, synthesized, and summarized using descriptive statistics. In some cases, figures and images will be provided to enhance clarity. Since scoping reviews aggregate and summarize available evidence, there will be no critical appraisal of the quality of included papers. The patient and the public will not be involved in developing the protocol.

Ethics Approval

This scoping review protocol is part of a research work and has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (M220519).

Results

The results from the scoping review will be presented in a narrative form. The PRISMA-ScR flow diagram will be used to depict the study selection process, the number of papers initially identified and included, and the reason for exclusion. In addition, the charted details, including the title, year of publication, country, study design, characteristics of study participants, study objectives, sample, and analytical methods, will be presented in diagrams or tabular format. The result of this scoping review will be disseminated at conferences, and the paper will be published toward the end of the second quarter of 2024.

Discussion

Principal Findings

The discussion section will address various questions that inform the scoping review process. One such is how the heart uses various substrates in health and disease to generate energy in the form of adenosine triphosphate and the various analytical methods used to analyze metabolomes. We will discuss how the heart switches from using the preferred fatty acids to other substrates. We will itemize the papers studied on each substrate during the study period. Analyzing substrate used by the heart in health and disease and finding pathways commonly affected in HF phenotypes will inform future research directions. Furthermore, we will explore the patients with HF studied in the included studies, discuss the knowledge gaps, and the implications for future research efforts. The scoping review will synthesize the evidence from the included papers on the usefulness of metabolomes in the diagnosis, treatment, risk-stratification, and prognosis of patients with HF, with particular attention to the assumptions and limitations. We will, however, not undertake the formal risk of bias evaluation. This information may provide valuable insights into the current state of the literature and highlight areas where improvements may be needed and hope to stimulate further research into metabolomes of HF patients in low- and middle-income countries.

Limitations

A potential limitation of this scoping review could be the inability to access the full text of some of the included papers; hence, the contents of such references cannot be synthesized. However, efforts will be made to contact the authors of these papers to get those texts or elements relevant to the review. The strength of this scoping review is its ability to examine the state of science and subsequently identify knowledge gaps and directions for future research.

Conclusions

The prevalence of HF is increasing despite the continued development of several diagnostic and treatment modalities; it is, therefore, imperative to search for biomarkers that will better characterize patients with HF and ensure targeted therapy. The European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF implored clinicians to search for other more specific biomarkers, and hence this scoping review will help synthesize available literature on the use of metabolomes in patients with HF, identify the knowledge gaps, and recommend future research.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study (protocol) and the scoping review are available from the corresponding author on reasonable request.

Authors' Contributions

UGA conceived and formulated the scoping review objectives; UGA and MB wrote the search strategy and charted the data; DM, MM, and NT contributed to the conception of the study, designed, and edited the protocol; and MM and NT supervised the work. All the authors contributed significantly to this work and approved the final version for publication.

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Conflicts of Interest

NT is a cardiologist and has received consultation fees from Acino Health Care Group, AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Elly Lilly, Janssen Pharmaceutica, Novartis Pharmaceuticals, Novo Nordisk,Organon, Pfizer, Sanofi, Phillips, Servier, Takeda, and Merck. He has also received educational and travel grants from Medtronic, Biotronik, Boston Scientific and Vertice Health Care Group.

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Abbreviations

HF: heart failure
JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews

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Protocol

Exploring the Distribution of 3D-Printed Simulator Designs Using Open-Source Databases to Facilitate Simulation-Based Learning Through a University and Nonprofit Collaboration: Protocol for a Scoping Review

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Abstract

Background: Advancements in technology have enhanced education, training, and application in health care. However, limitations are present surrounding the accessibility and use of simulation technology (eg, simulators) for health profession education. Improving the accessibility of technology developed in university-based research centers by nonprofit organizations (NPOs; eg, hospitals) has the potential to benefit the health of populations worldwide. One example of such technology is 3D-printed simulators.

Objective: This scoping review aims to identify how the use of open-source databases for the distribution of simulator designs used for 3D printing can promote credible solutions for health care training while minimizing the risks of commercialization of designs for profit.

Methods: This scoping review will follow the Arksey and O'Malley methodological framework and the Joanna Briggs Institute guidance for scoping reviews. Ovid MEDLINE, CINAHL, Web of Science, and PsycINFO will be searched with an applied time frame of 2012 to 2022. Additionally, gray literature will be searched along with reference list searching. Papers that explore the use of open-source databases in academic settings and the health care sector for the distribution of simulator designs will be included. A 2-step screening process will be administered to titles and abstracts, then full texts, to establish paper eligibility. Screening and data extraction of the papers will be completed by 2 reviewers (MS and SS) for quality assurance. The scoping review will report information on the facilitation of distributing 3D-printed simulator designs through open-source databases.

Results: The results of this review will identify gaps in forming partnerships with NPOs and university-based research centers to share simulator designs. The scoping review will be initiated in December 2024.

Conclusions: The information collected will be relevant and useful for stakeholders such as health care providers, researchers, and NPOs for the purpose of overcoming the gaps in research regarding the use and distribution of simulation technology. The scoping review has not been conducted yet. Therefore, there are currently no findings to report on.

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KEYWORDS

simulation; three-dimensional printing; health professions education; database; simulator; simulator design; health care provider training; simulation-based education; simulation technology; open-source; databases; simulation-based learning; e-Learning; scoping review; technology; 3D printed simulators; design; 3D printing; 3D; health care training; university-based; research centers; gaps

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Introduction

Simulation-based education (SBE) is a rapidly growing field that requires sufficient training and expertise from health care providers who play essential roles in delivering safe and adequate care to patients [1]. Integrating health care provider training in various fields of health care facilitates advancements in technology and improves the performance of health care providers to strengthen both experiential and educational practices [1]. For decades, advancements in technology, such as the introduction of medical printing and digital technology, have promoted effective education, training, and application in health care [2]. To optimize the use of technology for adequate practice and services in health care, simulation techniques have been studied to explore the potential benefits of using 3D-printed simulators to train health care providers and the subsequent benefits on patient health and safety [3]. This education-based training method tests the technical, nontechnical, and clinical skills that are critical for health care providers to apply during patient-provider interactions [3]. Enhancing the accessibility of technology developed in university-based research centers and nonprofit organizations (NPOs) by targeting the barriers that limit the evolution of modern innovations has the potential to benefit the health of many communities worldwide [2]. Most importantly, it reflects the importance of bridging the gap between theory and application in health care and educational settings as simulation has the potential to limit medical errors [3].

SBE is an educational strategy that is used to improve training and assessment for health care providers [4]. SBE offers hands-on experience by enforcing interactions with simulators to mimic real-world scenarios to develop the expertise of health care providers and improve the quality of care that patients receive [4]. SBE in health care is emerging as a crucial educational modality as it enables learners to improve their proficiency through experiential learning using 3D-printed simulators [3]. It provides the replication of a real task without impairing the time and safety of patients [4]. The purpose of 3D-printed simulators is to supplement, not replace, existing technologies to evolve the understanding of SBE in health care [5]. In addition to educational objectives, 3D-printed simulator designs can be used for implants, prosthetics, tissue or organ modeling, therapeutic testing, and also have the potential to help patients when attempting to understand their health condition by using visual models [5].

The development of effectively designed simulation technology strengthens practices associated with training and education through the use of adequate resources in university-based research centers and NPOs [6]. Currently, there is discussion surrounding the execution of SBE from small- to large-scale interventions to be used globally [7]. However, to optimize the sustainability of simulation technology, investments in training and expertise must be targeted [7]. The consistent use of SBE creates positive patient outcomes as it increases health care professionals' confidence in real-world situations [6]. Despite the acknowledgment of experiential learning, limited information was found on targeting the barriers surrounding training and expertise to support the use of simulation techniques. The lack of research on recognizing credible solutions for health care training and experiential learning regarding patient care through simulation techniques limit the potential of transferring theory into practice [8]. For example, it was found that students of entry-level surgical technology have no experience in the operating room, making it beneficial for health systems and schools to incorporate SBE into their curriculum to allow students to have hands-on experience and an opportunity to practice before interacting with patients [7]. It is fundamental that high-quality training for health care providers is available in both low- and high-income environments to strengthen the use of SBE globally [8]. The implementation of simulation technology relies predominantly on the capacity and availability of resources to support the expansion of SBE. The cost of acquiring resources is one of the main limitations of this intervention, posing conflict with stakeholder interactions due to the expenses of SBE [6]. Although organizations are beginning to incorporate 3D printing for health care purposes, it is found that industries are not moving fast enough to supply instruments and resources to stimulate its universal use [6]. To administer this, consistent assessment of resources required for SBE, including determining what is necessary to expand the use of simulation technology, the cost of distributing resources, and identifying what resources are available, will benefit stakeholders from university-based research centers and NPOs [8].

Despite the benefits regarding the use of simulator designs in health care, the lack of implementing the optimal use and distribution of digital designs limit the evolution of 3D-printed augmented SBE globally [9]. The use of databases as an open-source network to store data and information enables the management and collaboration of simulator designs through varying repositories [10]. Databases have the potential to facilitate the process of sharing designs to improve health care training by making designs accessible to varying institutions such as university-based research centers, hospitals, and other NPOs. While 3D-printable object databases that are readily available to the public are beneficial in introducing and contributing to designs, limitations are present in terms of the distribution of the simulators due to cost, accessibility, space, time, and expertise [10]. Forming a partnership between appropriate stakeholders can support institutions that do not have the design expertise to produce their own simulator designs. Appropriate administration for the use of simulator designs by different institutions needs to be examined to optimize and strengthen the use of the simulators.

The ability to share designs of 3D-printed simulators on different platforms benefits the use of these designs primarily by regions that experience challenges in developing a stronger workforce capacity to improve the delivery of health care services. Given that there are several open-source repositories, guidelines must be met to understand the purpose and use of these databases by varying institutions to protect the intellectual property (IP) of designs [10]. Building partnerships among university-based research centers, hospitals, and NPOs may enhance the distribution of 3D-printed simulator designs using databases that are accessible across many institutions [9]. However, it requires critical attention to how these designs can be freely

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used by other organizations while also protecting them from being commercialized for profit. The need to modify IP laws to constant changes in technology is an important measure that must be recognized for the security and accountability of designs published on software systems [10]. The protection of repositories requires recognition surrounding the verification and identification of the initial rights holder of the designs and frameworks published on databases [10]. Currently, limited research has been conducted on the use of databases and repositories across academic institutions to share designs and their use in multi-institutional partnerships. The objective of this scoping review is to examine the current scope of literature regarding the use of databases and repositories to store and manage simulator designs among academic institutions, hospitals, and NPOs.

Methods

Protocol Design

Overview

For this scoping review, the Arksey and O'Malley [11] methodological framework will be used and will follow the five stages of conduct: (1) determining the research question, (2) identifying relevant literature, (3) selecting studies, (4) charting data, and (5) reviewing, synthesizing, and reporting the results. The scoping review will follow the Joanna Briggs Institute guidelines for conducting a scoping review [12], as well as the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist (Multimedia Appendix 1 [13]) [12].

Stage 1: Identifying the Research Question

The purpose of this scoping review is to explore the current literature on the distribution of 3D-printed simulator designs through open-source databases and determine how to implement the sharing of designs among academic institutions, hospitals, and NPOs while preventing the commercialization of designs for profit. The research question developed based on this purpose and in consultation with the research team is: what is the nature and breadth of research examining the use of databases and repositories to store, manage, and distribute 3D-printed simulator designs among academic institutions, hospitals, and NPOs? Preliminary searches indicate that sufficient research has not been conducted on the use of databases across various institutions and between organizations. Barriers exist in protecting the external use and commercialization of designs, resulting in the limitation of using databases to share 3D-printed simulator designs. The objectives of this scoping review are to (1) identify which open-source databases can be used to build partnerships with stakeholders to address the facilitation of SBE and (2) determine how to protect IP shared using open-source databases from being commercialized.

Stage 2: Identifying Relevant Studies

The published literature databases that will be searched for this scoping review are Ovid MEDLINE, Web of Science, Elsevier ScienceDirect, and IEEE Xplore. Free-text codes and database-specific subject headings will be used to create the search strategy using concepts from the research question. The keywords that were extracted from the research question include "simulation," "educational institute," "database," "healthcare," "3D-printed models." Synonyms of these keywords will also be used in the search strategy. A search strategy has been drafted on Ovid MEDLINE and is viewable in Multimedia Appendix 2. The search will involve the selection of papers based on specific criteria, such as the publication year of the paper and the paper language, to limit the searches and establish applicable information relevant to the research question.

Gray literature databases will be used to search for papers, as these may provide information on studies that are limited in published literature databases. The gray literature databases that will be searched include OpenGrey, Grey Matters, Google Scholar, and Google. The reference list of relevant papers selected for the study will also be manually searched to find additional papers relevant to the research question. Due to the current demand for SBE in health care throughout the most recent decade, a time frame of 10 years, from 2012 to 2022, will be placed on the search to enable results of papers with the latest findings on the distribution of simulation techniques using databases. In addition, the search will also be confined to papers published in the English language. The search strategy has been developed in consultation with a health science librarian as recommended by the Peer Review of Electronic Search Strategies guidelines [14].

Stage 3: Study Selection

A 2-step screening process will be conducted to refine the selected papers. First, titles and abstracts will be screened to identify the purpose and relevance of the publications, with papers that do not fall within the inclusion criteria being removed from the review. Second, a full-text screening will be conducted on the selected publications from the first step by applying the same inclusion criteria to select papers for the review. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to summarize the screening process. The selection of papers will involve applying precise inclusion and exclusion criteria to each publication to identify applicable papers relevant to the research question and explore papers with information on the suggested limitations. To be included in the review, papers must address the usage of simulation education in health care, discuss the use of a database or digital repository, discuss the barriers that restrict the distribution of 3D-printed simulator designs, focus on postsecondary education and incorporate university-based research centers and NPOs.

Papers will be excluded if they were published before the year 2012, are not in the English language, or focus on kindergarten to grade school education.

Stage 4: Charting the Data

Elements of the selected papers that will be extracted are details of the author, publication year, country of publication, the purpose of the study, the study design, details of participants, sentences describing IP, and key information that addresses the research question (the database used and purpose of using the database).

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Stage 5: Collating, Summarizing, and Reporting the Results

The results on the use of simulation technology in health care and education regarding the facilitation in distributing 3D-printed simulator designs through open-source databases will be reported in the scoping review. Information regarding the sharing of designs between NPOs while preventing the commercialization of designs for profit will also be identified. The reported information will be organized and presented in tables and graphs where necessary and will include both qualitative and quantitative data with information summarized descriptively in the text. The findings from the papers that address the distribution of 3D-printed simulator designs as well as the barriers will be synthesized and grouped into specific themes. Subthemes will be created using information from papers that is applicable to the research gap and distribution process.

Quality Assurance

Endnote 20 (Clarivate Analytics) is a referencing management program that will be used to manage duplicate checking. EPPI-Reviewer software (EPPI Centre), used to screen, analyze, and select papers, will be used to extract and chart the data [15]. References from Endnote 20 will be imported into EPPI-Reviewer where screening and selection of papers, analysis, and reporting will be managed. To screen and chart the data, 2 reviewers will participate in the process to maximize the validity of the results. The 2 reviewers will contribute to the screening and selection of papers individually based on relevant titles and abstracts from the search results while referring to the eligibility criteria. The reviewers will discuss their findings for a subset of papers and make changes to the eligibility criteria as required with a third reviewer settling any disagreements between the primary 2 reviewers. The first reviewer will then screen the remaining references and discuss any concerns with the second reviewer. Following the screening of papers, the first reviewer will extract data from 100% of the studies, and the second reviewer will extract data from 2 random samples of 5% each from the selected studies. This will be done to ensure adequate charting quality.

Ethical Considerations

This scoping review will identify the current use of open-source databases in academic settings and the health care sector and build upon the importance of collaborating with partners for the distribution of simulator designs to promote solutions in health care and education. The results of this scoping review will provide an understanding of the gaps in existing literature surrounding the distribution of 3D-printed simulator designs. In addition, the results of this review will demonstrate the potential barriers in establishing partnerships with NPOs and university-based research centers to share designs globally. The information collected will be relevant and useful for stakeholders such as health care providers, researchers, and NPOs for the purpose of overcoming the gaps in research regarding the use and distribution of simulation technology. The results of this scoping review will be submitted to an academic peer-reviewed journal for publication. Ethical approval is not required for this scoping review as the data are gathered from publications that are in the public domain.

Results

The scoping review will be initiated in December 2024. The results on the implementation of simulation technology in health care and education regarding the use and distribution of 3D-printed simulator designs through open-source databases will be reported in the scoping review. Based on prior experience in a research laboratory at the Ontario Tech University, Oshawa, Ontario, Canada, partnerships were formed with organizations to share and distribute 3D-printed simulator designs using open-source databases. Due to the challenges in sharing these resources through the database, it was determined that more research needs to be conducted on this topic.

Discussion

This scoping review will explore the current literature on the distribution of 3D-printed simulator designs through open-source databases to facilitate the sharing of designs among academic institutions, hospitals, and NPOs. The findings from this scoping review will provide an understanding of the limitations of the existing literature regarding the distribution of 3D-printed simulator designs and identify the potential barriers in establishing partnerships with NPOs and university-based research centers to share designs globally. The findings will be used to create robust partnerships with stakeholders to ensure the delivery of SBE is effective, reliable, and accessible in educational environments. This will increase the sharing of designs while building connections with organizations to address the implementation of SBE and identify the gaps in research surrounding potential solutions in health care and education.

The scoping review has not been conducted yet. Therefore, there are currently no findings regarding the distribution of 3D-printed simulator designs to report on. However, it is expected that the scoping review will help identify the barriers surrounding how to acquire resources to support the distribution of simulation technology. The scoping review will be the first to explore current literature to determine how to facilitate the distribution of simulation technology between partners such as NPOs and university-based research centers using open-source databases. Papers will be selected from 4 published literature databases and 3 gray literature databases. Preliminary searches indicate there is a lack of findings regarding the distribution of simulator designs, limiting information on the implications and comparisons to existing literature. There is also limited information on databases that are used to share 3D-printed simulator designs, which is important in order to determine how the designs can be used by potential stakeholders and expand the use of simulation technology within organizations. The inadequacy of literature that is available on databases makes it challenging to address the research question. Because the nature of the project aims to understand the breadth of research in this area, the selected papers from the scoping review will not undergo a critical appraisal process.

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The findings of the scoping review will help integrate advancements in the delivery, use, and expansion of SBE. This will not only assist in building partnerships with stakeholders to investigate the planning and delivery of SBE but will also guide how to protect IP shared using open-source databases. Determining the necessary approach and resources to expand the use of simulation technology will benefit stakeholders from university-based research centers and NPOs, facilitating the distribution of simulator designs.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Review) checklist.
[DOCX File , 86 KB - resprot_v13i1e53167_app1.docx]

Multimedia Appendix 2
Draft search strategy for Ovid MEDLINE.
[DOCX File , 11 KB - resprot_v13i1e53167_app2.docx]

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Abbreviations

IP: intellectual property
NPO: nonprofit organization
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Review
SBE: simulation-based education

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Protocol

Impact of Responsible AI on the Occurrence and Resolution of Ethical Issues: Protocol for a Scoping Review

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Abstract

Background: Responsible artificial intelligence (RAI) emphasizes the use of ethical frameworks implementing accountability, responsibility, and transparency to address concerns in the deployment and use of artificial intelligence (AI) technologies, including privacy, autonomy, self-determination, bias, and transparency. Standards are under development to guide the support and implementation of AI given these considerations.

Objective: The purpose of this review is to provide an overview of current research evidence and knowledge gaps regarding the implementation of RAI principles and the occurrence and resolution of ethical issues within AI systems.

Methods: A scoping review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines was proposed. PubMed, ERIC, Scopus, IEEE Xplore, EBSCO, Web of Science, ACM Digital Library, and ProQuest (Arts and Humanities) will be systematically searched for articles published since 2013 that examine RAI principles and ethical concerns within AI. Eligibility assessment will be conducted independently and coded data will be analyzed along themes and stratified across discipline-specific literature.

Results: The results will be included in the full scoping review, which is expected to start in June 2024 and completed for the submission of publication by the end of 2024.

Conclusions: This scoping review will summarize the state of evidence and provide an overview of its impact, as well as strengths, weaknesses, and gaps in research implementing RAI principles. The review may also reveal discipline-specific concerns, priorities, and proposed solutions to the concerns. It will thereby identify priority areas that should be the focus of future regulatory options available, connecting theoretical aspects of ethical requirements for principles with practical solutions.

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KEYWORDS

artificial intelligence; AI; responsible artificial intelligence; RAI; ethical artificial intelligence; trustworthy artificial intelligence; explainable artificial intelligence; XAI; digital ethics

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Introduction

Background

The development of artificial intelligence (AI) is expanding across industries and its implementation has created ethical apprehensions, centered on the responsible creation and use of AI systems. Various guidelines, regulations, and frameworks have emerged with the goal of delivering responsible application and progression of AI [1]. The notable increase in instances of ethical harm has been caused by the misuse of technology (eg, voter manipulation, facial recognition surveillance, and unauthorized mass data collection) or by design flaws in the technology itself (eg, bias in recidivism, loan rejection, and medical misdiagnosis) [2]. Other ethical concerns include the transparent and equitable usage of data, safeguarding data privacy across platforms and systems, ensuring data availability and quality, endorsing data integration for interoperability, and addressing intellectual property concerns [1]. Responsible AI (RAI) promotes the adoption of ethical frameworks and the incorporation of RAI's 3 main pillars of accountability (ie, the need to explain and validate decisions), responsibility (ie, users interpreting results and identifying errors), and transparency (ie, the need to describe, examine, and duplicate mechanisms) to foster moral responsibility in emerging technology [3].

Rationale

AI ethics is an emerging field that falls within the broader domain of digital ethics and addresses concerns arising from the development and implementation of new digital technologies [4]. Due to AI's transformative potential, the discourse of guiding values and principles for its development and implementation highlights the need for resolving concerns for AI for data privacy, accountability, and inadvertently fostering bias. Governance against unregulated uses, privacy violations, and algorithm biases requires resilience for security and the preparation for potential attacks. By delivering and maintaining accessibility, safety, accuracy, and fairness, these challenges can be addressed through standardized RAI principles that involve ethical consideration and stakeholder participation [4-8].

The collaboration among diverse stakeholders in developing RAI principles and policies demonstrates the potential for developing robust ethical guidance. RAI principles could have a tangible impact on reducing both the frequency and intensity of ethical issues that arise in various contexts. The implementation of RAI principles exerts a positive influence on the overall ethical landscape, leading to a discernible decrease in the occurrence of ethical dilemmas and mitigating the severity of those that do emerge. The adoption of RAI principles could foster a more accountable AI ecosystem with heightened attention to conducting responsible research and innovation [8].

Recent literature advocates for continued efforts to adhere to RAI principles as a means of fostering a more ethical and trustworthy AI landscape and suggests the incorporation of RAI principles as a vital safeguard, not only in curbing the frequency of ethical issues but also in minimizing their impact. Academia, government, and corporate institutions have published guidelines aimed at fostering the responsible development and deployment of AI technology, encompassing beneficence, nonmaleficence, autonomy, justice or fairness, and accountability, as crucial considerations in ensuring RAI practices [2,9,10]. Various entities, both public and private, offer diverse RAI frameworks, contributing to democratization but lacking consensus and standardization in ethical values. Practical support for AI practitioners is limited, with few frameworks covering all phases of the software development life cycle (SDLC), which ensures the completion of all functionalities, user requirements, objectives, and end goals when creating, planning, and maintaining the development of a software project. The SDLC enhances the overall quality of software programs and the software development process and establishes a structured approach that comprises 7 distinct stages of planning, requirement gathering and analysis, design, coding, testing, deployment, and maintenance [8]. Theoretical frameworks are currently deficient in practical assistance encompassing all SDLC phases in developing, testing, and deploying RAI applications, including practical validation techniques for theoretical principles, as well as supporting stakeholders during the implementation and auditing phases. The synthesis of positive effects of RAI mitigation strategies through the application of RAI principles for minimizing ethical harm and the lack of standardization reveal the shortcomings of complete, uniform, and user-friendly RAI frameworks in current literature. Research value can be added that supports stakeholders across the entire SDLC and is accessible to different stakeholders (both technical and nontechnical), is streamlined, and expedites the adoption of RAI practices [8]. There is a need for both an update and an overview of effective and standardized RAI frameworks to reveal the current state of RAI principles driving positive change and mitigating ethical risks [2,9-14].

Given the evidence of the feasible effectiveness of RAI mitigation strategies for ethical issues in a broader sense, it is necessary to develop a comprehensive and multidisciplinary approach throughout the AI pipeline by embracing a practical and cohesive approach to RAI implementation [14-21]. Current literature on RAI primarily focuses on ethical principles like transparency and fairness but lacks detailed guidance on their practical implementation across the AI development lifecycle [19]. The main gap in the literature lies in transitioning from dynamic and changing theoretical frameworks to actionable strategies for embedding ethical principles in real-world AI applications [19].

Aim and Research Questions

This scoping review will offer an overview and summarize the state of the field of ethical issues inherent to AI systems, linked RAI practices, their strengths and weaknesses, the studies evaluating them, and gaps in the literature. This will help to inform directions of the present ethical issues and current practices to reduce the occurrence and resolve them through RAI principles (Table 1). This study aims to assess the impact of RAI principles on resolving ethical challenges inherent to AI systems. This review will be based on our research question: How does the use of RAI practices and ethical frameworks impact the occurrence and resolution of ethical issues within AI systems?

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Table 1. Types of ethical issues and responding RAI[a] principles [2].

Ethical issue (categorized)	Description	Linked RAI code (categorized)
Bias or discrimination	AI[b] systems can exhibit bias and discriminate against individuals or groups based on factors such as race, gender, or socioeconomic status. This can lead to unfair treatment and perpetuate existing inequalities	Principle of fairness and nondiscrimination: ensuring that AI systems do not exhibit bias or discriminate against individuals or groups based on protected characteristics
Lack of transparency and explainability	AI systems often operate as black boxes, hindering understanding of their decision-making process and raising concerns about biases and errors	Principle of XAI[c]: techniques such as interpretable machine learning, model explanations, and rule-based systems are used to provide insights into how AI systems arrive at their decisions, increasing transparency
Privacy and data protection	AI systems rely on personal data, necessitating safeguards and measures to address privacy breaches and unauthorized use	Principle of privacy: using privacy-enhancing technologies, anonymization techniques, data minimization practices, and secure data handling protocols to protect individuals' privacy rights and prevent unauthorized access or misuse of personal data
Accountability and responsibility	AI systems can have unintended consequences and significant socioeconomic impacts, requiring comprehensive assessments and proactive measures to mitigate risks and address socioeconomic effects	Principle of auditing: conducting rigorous risk assessments, including ethical impact assessments, can help identify and mitigate potential risks and unintended consequences of AI systems. This may involve using frameworks such as the AI Ethics Impact Assessment Tool kit and involving multidisciplinary teams to evaluate the societal, environmental, and economic implications of AI applications

[a]RAI: responsible artificial intelligence.

[b]AI: artificial intelligence.

[c]XAI: explainable artificial intelligence.

Methods

Overview of the Study Design

Scoping reviews represent a specialized form of literature review that focuses on charting available literature across a wide-ranging subject area. Scoping reviews are well-suited for outlining present research pinpointing essential insights and areas of understanding that warrant deeper investigation [22]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) and Population, Intervention, Comparator, Outcome, and Studies (PICOS) framework were used to build the search strategy (Textbox 1) and provide a methodological framework for the scoping review.

Textbox 1. Population, intervention, comparator, outcome, and studies (PICOS) framework.

Population

Organizations developing artificial intelligence (AI) systems.

Intervention

Implementation of ethical frameworks and responsible artificial intelligence (RAI) principles in practice.

Comparator

Not applicable.

Outcomes

The focus is to examine the impact of RAI principles on ethical issues in AI systems. Secondary goals involve assessing the strengths, weaknesses, benefits, and limitations of current RAI principles in resolving ethical concerns.

Study types

Qualitative, quantitative, and mixed methods studies and literature that present any form of RAI principles for the implementation and resolution of ethical concerns in AI systems are eligible for inclusion. Protocols, reviews, abstracts, and meta-analyses older than 10 years were excluded from this review.

Search Strategy

The review will search 8 databases, including, PubMed, CORE, Scopus, IEEE Xplore, EBSCO, Web of Science, the ACM Digital Library, and ProQuest (Arts and Humanities). Based on a preliminary review of the literature, Medical Subject Headings (MeSH) terms and keywords were identified and grouped into 4 categories. They will be put together in the following way when searching the databases: RAI (MeSH OR Keywords) AND Ethical Issues (MeSH OR Keywords; Table 2).

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Table 2. Search terms.

Category	MeSH[a]	Keywords (in title or abstract)
Ethical issues within AI[b]	Ethical challenges in artificial intelligence	"Artificial Intelligence" OR "ethical challenges in AI" OR "ethical issues in AI" OR "Machine Learning" OR "AI governance"
RAI[c]	Responsible AI OR machine learning OR deep learning	"Responsible AI" OR "RAI principles" OR "supervised deep learning" OR "RAI" OR "supervised machine learning" OR "trustworthy AI" OR "Explainable AI" OR "XAI"
Ethical frameworks	AI ethics OR AI governance	"AI ethics" OR "ethical AI principles" OR "moral frameworks in AI" OR "ethical frameworks in AI"
RAI management	Responsible AI management	"Ethical intervention" OR "Responsible AI Management" OR "RAI management"

[a]MeSH: Medical Subject Headings.

[b]AI: artificial intelligence.

[c]RAI: responsible AI.

Inclusion Criteria

All literature and research proposing RAI principles will be included and studies presenting theoretical impact and suggestions of ethical frameworks will be identified and analyzed independently as well. Interventions aimed at mitigating ethical issues will be included given that they support all main pillars of RAI principles; no comparator is required, and all study types will be eligible for inclusion.

Exclusion Criteria

Studies that do not evaluate RAI principles or responses to ethical issues within the development and use of AI systems such as protocols, reviews, and abstracts will be excluded. Studies that are not published in the English language and studies published before 2013 will not be eligible for inclusion. Considering the rapid technological advancements and the evolving consideration of AI ethics and RAI, expectations in literature older than 10 years may not provide the current insights and information required for a relevant analysis in this field [9].

Screening and Article Selection

Article references will be stored, and duplicates will be removed using the citation management software EndNote X9 (Clarivate). The EndNote X9 search function will also be used to conduct an initial screening of the references based on keywords from the search strategy. The remaining titles and abstracts will be screened, and a full-text review will be conducted by the author (SB) to determine final eligibility.

Data Extraction

Data will be extracted from included studies into a predeveloped charting list, highlighting the data that will be in focus for this scoping review (see Textbox 2).

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Textbox 2. Full data charting list.

Title
Title of publication
Author
Full name of first author
Year
Year of publication
Country
The country in which the study is conducted
Quality or quantity
Whether the study entails qualitative, quantitative, or mixed methods research. Added “other” category that may fall outside of categories
Aims or purpose
Stated aims and objectives the research seeks to meet
Source of evidence
Whether the study is primary or secondary research, evidence synthesis, conference abstract, discussion article, etc
Study design
Description of methods and activities
Type of artificial intelligence (AI)–based technology
Notes on specific AI systems, that is, machine learning (ML), deep neural network (DNN), clinical decision support system (CDSS), and AI augmentation
Ethical issues
Inconclusive evidence, inscrutable evidence, misguided evidence, unfair outcomes, transformative effects, traceability, unjustified actions, and opacity
Responsible artificial intelligence (RAI) principles
Respect for human autonomy, prevention of harm, fairness, explicability, and patient privacy
Level of impact (high, medium, and low)
Data on evidence of the impact of RAI principles on the resolution of ethical issues
Probability (high, medium, and low)
Data on the expected likelihood of successful mitigation
Benefits of RAI principles
Notes on the benefits of RAI principles
Limitations of RAI principles and their impact
Notes on the theoretical and practical restrictions of RAI guidelines including affected impact
Strengths and limitations of RAI principles
Notes on the strengths and weaknesses of the use of RAI principles

Data Analysis and Synthesis

A descriptive analysis will be used given the expected large variety of study types. A meta-analysis will be attempted based on the outcome measures of the impact and influence of RAI principles on the occurrence and resolution of ethical issues, which may also indicate the primary outcome of the meta-analysis. The meta-analysis will aggregate findings on how RAI principles impact ethical issue management in AI systems, focusing on effectiveness metrics and stakeholder perceptions. Once all data were extracted, we would assess the feasibility of a meta-analysis. Given the expected variety of outcomes, a quantitative meta-analysis is unlikely to be possible, but we will synthesize findings of the differential impacts of various RAI principles on diverse ethical concerns and applications. There is a possibility that this may not be feasible due to the expected heterogeneity of studies. The extracted data will be summarized in a narrative synthesis to bring together findings relating to implementation challenges and successes of RAI principles, their influence on policy making, and trends in ethical AI research. This approach aims to provide insights into the operationalization of RAI principles and highlight areas for future research.

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Results

The results will be included in the full systematic review, which is expected to start in June 2024 and be completed for the submission of publication by the end of 2024.

Discussion

Expected Findings

This scoping review will provide an overview of the state of the literature regarding the influence of RAI principles on the resolution of ethical issues within AI systems. This section will use the data extracted from studies to explore the conclusions that can be drawn, the limitations of the scoping review, and key areas for future research. Special focus will be placed on relevant stakeholders involved in the ethical AI ecosystem, and studies investigating interventions for RAI development will be summarized and discussed in a subsection. A summary of the current principles, their strengths and weaknesses, and the studies evaluating them will help to inform the development of functional RAI frameworks for mitigating ethical issues for the progress of AI development and use.

Strengths and Limitations

A key strengths of the proposed study is its use of the PRISMA-ScR guidelines to ensure transparent and replicable reporting of the review and its interdisciplinary approach. By including data across different disciplines, the review will be able to develop a nuanced understanding of RAI principles and their implementation in various contexts. We expect this to lead to a comprehensive, cross-disciplinary dialog that enriches the AI community's perspective on ethical considerations.

The limitations of the scoping review will be discussed in detail in the full review; key limitations are expected to include the scope and the use of only 1 main reviewer. Although the broad scope is a strength in that the findings will not be limited to a specific discipline, including a broad scope will increase the difficulty of synthesizing various findings and determining lessons that are generalizable. It also means that, although we have selected a variety of databases to obtain good coverage of the literature for the search, there is a possibility of missing relevant studies meeting our inclusion criteria. Another limitation is that the literature search, screening, and data analysis will be executed by only 1 reviewer, which has an increased risk of overlooking relevant research and potential biases due to the lack of diverse perspectives and independent verification mechanisms. It is not expected to be possible for a second reviewer to conduct an independent screening due to time and resource constraints, although this will be reassessed when conducting the review. Additionally, the research team does not have proficiency in other languages, which will hinder our capability to review any literature beyond data sets available in English.

Future Directions and Dissemination

Future research could build upon findings from this review by conducting in-depth analyses to identify the gaps in ethical AI frameworks, particularly focusing on stakeholder engagement and interventions for RAI development. Additionally, there is a need for longitudinal studies to assess the effectiveness of emerging principles and interventions in mitigating ethical issues throughout the lifecycle of AI systems. The dissemination plan for this paper will involve publishing the findings in a peer-reviewed journal dedicated to computer sciences, social sciences, philosophy, and ethics. A concise policy brief will be drafted for review to inform and guide regulatory frameworks, ensuring accessibility to legislative audiences. The dissemination will leverage digital platforms, including academic social networks and research repositories, to maximize reach and impact across various sectors.

Conclusions

This scoping review is expected to provide a vital synthesis of research on RAI principles and guidance for efforts to chart a course for the balanced development of AI systems, where innovation is matched with ethical integrity. The scoping review's findings will likely prompt the development of more nuanced ethical frameworks for AI, influencing both emerging technologies and policy making by highlighting the importance of aligning AI innovation with ethical responsibility. Future research may focus on creating adaptive, real-time monitoring tools to continuously evaluate and guide the ethical implementation of AI as technologies and societal norms evolve.

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Data Availability

The authors confirm that the data supporting the findings of this study are available within the paper and appendices (Multimedia Appendices 1 and 2).

Authors' Contributions

The review protocol was conceived and supervised by MM-I and EM. SB drafted the protocol including the research question, use of the population, intervention, comparator, outcome, and studies (PICOS) framework, and the search strategy. All authors contributed revisions.

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Conflicts of Interest

EM is the editor-in-chief of *JMIRx Med*. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Search strings.
[DOCX File , 15 KB - resprot_v13i1e52349_app1.docx]

Multimedia Appendix 2
Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
[DOCX File , 25 KB - resprot_v13i1e52349_app2.docx]

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Abbreviations

AI: artificial intelligence
MeSH: Medical Subject Headings
PICOS: population, intervention, comparator, outcome, and studies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
RAI: responsible artificial intelligence
SDLC: software development life cycle

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Protocol

Centering Digital Health Equity During Technology Innovation: Protocol for a Comprehensive Scoping Review of Evidence-Based Tools and Approaches

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Abstract

Background: In the rush to develop health technologies for the COVID-19 pandemic, the unintended consequence of digital health inequity or the inability of priority communities to access, use, and receive equal benefits from digital health technologies was not well examined.

Objective: This scoping review will examine tools and approaches that can be used during digital technology innovation to improve equitable inclusion of priority communities in the development of digital health technologies. The results from this study will provide actionable insights for professionals in health care, health informatics, digital health, and technology development to proactively center equity during innovation.

Methods: Based on the Arksey and O'Malley framework, this scoping review will consider priority communities' equitable involvement in digital technology innovation. Bibliographic databases in health, medicine, computing, and information sciences will be searched. Retrieved citations will be double screened against the inclusion and exclusion criteria using Covidence (Veritas Health Innovation). Data will be charted using a tailored extraction tool and mapped to a digital health innovation pathway defined by the Centre for eHealth Research roadmap for eHealth technologies. An accompanying narrative synthesis will describe the outcomes in relation to the review's objectives.

Results: This scoping review is currently in progress. The search of databases and other sources returned a total of 4868 records. After the initial screening of titles and abstracts, 426 studies are undergoing dual full-text review. We are aiming to complete the full-text review stage by May 30, 2024, data extraction in October 2024, and subsequent synthesis in December 2024. Funding was received on October 1, 2023, from the Centre for Health Equity Incubator Grant Scheme, University of Melbourne, Australia.

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Conclusions: This paper will identify and recommend a series of validated tools and approaches that can be used by health care stakeholders and IT developers to produce equitable digital health technology across the Centre for eHealth Research roadmap. Identified evidence gaps, possible implications, and further research will be discussed.

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KEYWORDS

digital health technology; eHealth; mHealth; health informatics; equity; inclusion; participatory design; universal design; Validitron; digital health; cost; technology; technology innovation; innovation; evidence-based tools; evidence-based; tools; digital innovation; cost-effective; accessibility; digital inequity; digital health equity

Introduction

The United Nations' Sustainable Development Goals champion a healthful future by ensuring no one is left behind [1]. Achieving health and wellness equity remains a paramount challenge for global health systems [2]. Digital health technologies (DHTs)—encompassing telehealth, electronic health records, mobile devices and apps, wearables, and artificial intelligence (AI)—present a promising solution. Evidence indicates that DHTs are cost-effective for enhancing health outcomes across populations; elevating care quality and convenience; and addressing service accessibility, availability, and capacity concerns [2]. While DHT adoption has increased gradually over the last decade, the COVID-19 pandemic accelerated its integration worldwide across health care, research, government, and industry [3]. However, this digital shift poses a risk to priority communities who may miss out on the technologies and their benefits [4]. Priority communities refer to those who require intentional support due to a history of oppressive policy choices and marginalization. This may be defined by socioeconomic status, race, ethnicity, disability, gender, or other demographic factors. The use of the term "priority community" emphasizes a strengths-based approach that focuses on the need for health system investment to promote equity, ensuring the community is prioritized by that system rather than being made vulnerable by it [5].

Regrettably, priority communities experience "digital exclusion," or the inability to access digital technologies, and "digital inequity," which prevents them from effectively engaging with digital technologies to manage their health [6-8]. Evidence shows that priority communities may not have equal access to the underlying technologies that support DHTs, such as mobile phones, computers, and internet services [9-14]. Moreover, communities with culturally or linguistically diverse backgrounds are less likely to have access to culturally appropriate DHTs [15,16]. This was a prominent experience during the COVID-19 pandemic response and vaccination rollout over 2020-2022 [17,18] and demonstrates a need for cultural considerations in health messaging and technologies. Further, priority communities may have concerns about data privacy and lack trust in the digital products and health care systems that provide them [4,13]. In parallel, they are also considered to be underserved by the health system [19], have a greater prevalence of chronic conditions, and experience worse health outcomes [20]. Indeed, they already experience a multitude of factors causing disadvantage, often set against structural barriers like ageism, sexism, racism, and homophobia [21,22]. Thus, digital exclusion and inequity cannot be another mechanism to leave priority communities behind [5].

Poorly designed DHTs that are developed using inaccurate, biased, or incomplete data sets can also worsen health outcomes for priority communities and can further entrench inequities [4,8]. For example, the lack of diverse racial representation during the development of AI health algorithms may introduce negative biases resulting in preferential treatment to some racial groups over others [23]. Data poverty, or a lack of data in low- and middle-income countries, is also a major barrier to the equitable adoption of DHTs with data gaps underrepresenting some populations [22,24]. To counter these disparities, a proactive strategy to center equity is needed by professionals working across health care, health informatics, digital health, and technology development [6-8].

Digital health equity is often defined as equitable access to digital health care and equitable outcomes from digital health care [25], but we argue equity can also be enacted through priority community involvement in the pathway of digital technology innovation. These stages include project contextual inquiry, value specification, design, operationalization, and summative evaluation [26]. When digital health equity is considered along the Centre for eHealth Research (CeHres) roadmap, digital exclusion and inequity may be reduced, and DHTs can even mitigate the preexisting disparity experienced by priority communities [22]. To achieve these outcomes, priority communities must be proactively considered and included throughout the development process [4,27-29].

The factors that drive digital health equity are a growing discourse. Frameworks evolving from health equity typically describe individual, social, and structural factors, or the Digital Determinants of Health. These factors occur on multiple levels affecting equity across the individual, interpersonal, community, and society settings [25,30,31]. Although frameworks and theories are useful guides, it is only through the application of this knowledge to technology innovation and in health care services that an effect on equitable outcomes can be achieved [22,32]. Additionally, the measurement and validation of equity outcomes are topics of debate. A recent systematic review assessing analytical frameworks and economic evaluations of DHTs suggested a lack of equity assessment across multiple assessment domains [33]. Similarly, a rapid review of technologies to address digital health equity found that "limited data are available on the effectiveness of these initiatives in

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reducing health inequities" [34]. These studies highlight the need to approach equity from an evidence-informed perspective.

To date, a systematically executed review that addresses evidence-based tools and approaches to translate digital health equity appears to be lacking. Hence, this review will chart tools and approaches used during digital health innovation to promote equitable inclusion of priority communities and then identify the gaps at each stage of the CeHRes roadmap [26]. This review builds on previous research identifying inequities and factors that result in the uneven use of DHTs [35] and is distinguished from other scholarly works only covering the design phase in the digital health innovation pathway [36]. Where possible, ideas to explain the identified evidence gaps and the implications of these issues for professionals working across health care, health informatics, digital health, and technology development will arise. Further research will also be identified. Hence, this review will answer the following questions: (1) What tools and approaches are used when involving priority communities in the development of DHTs? (2) Where are these tools and approaches located along the CeHRes roadmap? (3) How is the acceptability of these tools and approaches described by the priority community or measured by researchers?

Methods

Participants

Eligible publications will consider priority communities, which may be defined by location (eg, rurality), socioeconomic status, race, ethnicity, disability, older population, gender, children, culture, or other demographic factors.

Concept

All papers that include approaches or tools for improving digital health equity, defined as equitable inclusion in the development of DHTs [6], will be eligible.

Context

This scoping review will consider DHT used by priority communities to manage health or access health care services. As articulated by the National Institute for Health and Care Excellence (UK), DHTs include "standalone software and apps that are used to improve health outcomes or to improve how the health and care system runs." [37] These can include (1) regulated medical devices classed as software as a medical device; (2) software and apps designed to help people to manage their own health and well-being; (3) software that is designed to help the health and care system to run more efficiently or to help staff manage their time, staffing, or resources; and (4) apps or software designed to work alongside a medical device.

To improve the feasibility of the review, traditional imaging that has been transformed into digital imaging and data-driven technologies (blockchain and AI-based algorithms) will be excluded as these are not routinely used in health care services.

The review will consider project contextual inquiry, value specification, design, operationalization, and summative evaluation. Given digital health inequities affect priority communities across high-income and low- and middle-income countries, studies from all countries will be eligible for inclusion in the review.

Types of Studies

The review will include quantitative studies of experimental and quasi-experimental designs, including peer-reviewed journal articles, relevant to the research question, which meet the inclusion and quality criteria as eligible for inclusion. Study types such as randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies will be eligible. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. Descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies will also be eligible for inclusion.

Qualitative studies including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research will also be considered.

Literature reviews will not be included; however, their bibliographies will be hand searched to identify relevant studies. Commentary papers that do not generate empirical evidence will not be eligible. Preprints and theses will also be excluded.

Ethical Considerations

This work is a literature review of previously published analyses. The University of Melbourne's Office of Research and Integrity advised that it did not meet the criteria for requiring human ethics review (personal communication, May 17, 2024).

Review Strategy

This review will be based on the Arksey and O'Malley [38] framework for scoping reviews [39] and will be informed by contemporary guidance from the Joanna Briggs Institute [40]. The 6-stage framework includes identifying research questions; identifying relevant studies; study selection; charting the data; summarizing and reporting the results; and a consultation exercise with groups who are targeted by digital health equity initiatives.

Inclusion and exclusion criteria will be iteratively refined to answer the research question as the scoping review progresses. A 2-stage (title or abstract and full article) screening process will be conducted to choose eligible studies for final inclusion. A standardized data extraction tool will be used to extract and chart the data. Included studies will be analyzed using a qualitative analysis approach summarizing the findings.

Search Strategy

The search strategy will aim to locate published studies. An initial limited search of MEDLINE and ACM Digital Library was undertaken to identify articles on the topic, from both the health and IT literature. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for the targeted databases (listed in Multimedia Appendix 1). The search strategy, including all identified keywords and index

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terms, was adapted for each included database or information source. The reference lists of all included sources of evidence will be screened for additional studies. A search is also being conducted for forward citations of key publications identified in this process.

Inclusion and Exclusion Criteria

Eligible sources for this scoping review will be peer-reviewed papers that report on a tool or approach that has been implemented to promote equitable inclusion during technology innovation. We will include studies published in the English language after 2010. Items in other languages will be included if they include an English abstract that clearly reports the required data. The authors of relevant studies will also be contacted where necessary for study details. Items for which full text is not available will be excluded.

Evidence Selection

Following the search, all identified citations will be collated and uploaded into Covidence (Veritas Health Innovation) for the removal of duplicates and management of the subsequent stages of the review screening and data extraction processes [41]. After the pilot screening test of 10% of the citations, 1 reviewer will screen the items in the title or abstract stage, against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. The reasons for the exclusion of sources of evidence at the full-text stage that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram [42].

Data Extraction

Data will be extracted from papers by 2 independent reviewers using a data extraction tool developed for the project and piloted by authors across multiple fields of research (Textbox 1). The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions and mapped to the digital innovation pathway through the CeHRes roadmap for the development of eHealth technologies [26].

Textbox 1. Data extraction form.

- Authors
- Year of publication
- Country of study
- Aim of the research
- Methodology (study design, interventions, description, and analysis techniques)
- Population
- Concept
- Context
- Low-, middle-, or high-income country
- Identified barriers to achieving digital health equity
- Identified facilitators for achieving digital health equity
- Tool description
- Use of theory to inform paper or tool development (if available)
- Stakeholder (eg, patients, end users, and priority communities) involvement in the tool co-design
- Results
- Authors' recommendations
- Relevant stage of the Centre for eHealth Research roadmap

Data Analysis and Presentation

Data will be deductively mapped to the CeHRes roadmap for the development of eHealth technologies [26]. The roadmap includes 5 stages; however, some technologies may be distributed across multiple stages, and emergent stages may also be discovered:

1. Contextual inquiry—this stage involves gathering information from intended users and relevant stakeholders about the nature of the problem and potential solutions.
2. Value specification—this stage involves determining and ranking the social, economic, medical, and behavioral values of key stakeholders. From this process, the most favorable solutions are identified, as well as the user and organizational requirements to achieve them.

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3. Design—this stage involves developing prototypes that align with the values and user requirements.
4. Operationalization—this stage involves the implementation of the technology into practice. Operationalization may include enabling activities, training, education, and deploying the technology into practice.
5. Summative evaluation—this stage refers to the actual uptake of the technology in practice and its clinical, organizational, and behavioral impacts.

A narrative summary will accompany the data map to describe how the results relate to the review objectives and research question.

Results

Screening of records retrieved from databases and other sources has reached the full-text stage and is expected to be complete by the end of May 2024. Data extraction (mapping to the CeHRes roadmap stages) and synthesis are scheduled between June and December 2024. Following a planned exposure of the review's findings to our panel of stakeholders including consumers and digital health innovation experts, we will disseminate the final review findings in a peer-reviewed journal publication and presentations at relevant conferences.

Discussion

Principal Findings

Noting the apparent absence of an overarching review of evidence-based tools and methods to translate digital health equity in all stages of digital health innovation, our scoping review will identify these tools and methods and map them to stages in the CeHRes roadmap (contextual inquiry, value specification, design, operationalization, and summative evaluation). Our work is aimed at synthesizing how priority communities initiate or are brought into the development and evaluation of DHTs and how they describe the tool's acceptability. We will also note how researchers measure the acceptability of the tools or approaches used.

Limitations

We may encounter limitations in the published literature that prevent us from building a factual account of the range of methods or tools that have been trialed with priority groups. In particular, there might be an absence of reports of negative initiatives or tools that failed to achieve equity outcomes, since positive study results are more likely to be published [43]. We acknowledge that excluding non-English language studies may bias the outcomes we are able to include. Additional research using material in data repositories and non-English studies could remedy these issues.

Conclusions

The scoping review will identify tools and approaches that have been validated for use by health care technology developers to enable equitable digital innovations. Where gaps are detected in either the available evidence or in their span across the 5 stages of the CeHRes roadmap, these will be highlighted, and their possible implications will be proposed. The work described in this protocol supports the methodological development of the Digital Health Validitron, a collaborative and interdisciplinary research group that assists digital health innovators from health care, academia, and industry to accelerate the creation of evidence that proves the real-world value of their ideas and products.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 31 KB - resprot_v13i1e53855_app1.docx]

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Abbreviations

AI: artificial intelligence
CeHRes: Centre for eHealth Research
DHT: digital health technology
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review

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Protocol

In Silico Approaches to Polyherbal Synergy: Protocol for a Scoping Review

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Abstract

Background: According to the World Health Organization, more than 80% of the world's population relies on traditional medicine. Traditional medicine is typically based on the use of single herbal drugs or polyherbal formulations (PHFs) to manage diseases. However, the probable mode of action of these formulations is not well studied or documented. Over the past few decades, computational methods have been used to study the molecular mechanism of phytochemicals in single herbal drugs. However, the in silico methods applied to study PHFs remain unclear.

Objective: The aim of this protocol is to develop a search strategy for a scoping review to map the in silico approaches applied in understanding the activity of PHFs used as traditional medicines worldwide.

Methods: The scoping review will be conducted based on the methodology developed by Arksey and O'Malley and the recommendations of the Joanna Briggs Institute (JBI). A set of predetermined keywords will be used to identify the relevant studies from five databases: PubMed, Embase, Science Direct, Web of Science, and Google Scholar. Two independent reviewers will conduct the search to yield a list of relevant studies based on the inclusion and exclusion criteria. Mendeley version 1.19.8 will be used to remove duplicate citations, and title and abstract screening will be performed with Rayyan software. The JBI System for the Unified Management, Assessment, and Review of Information tool will be used for data extraction. The scoping review will be reported based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

Results: Based on the core areas of the scoping review, a 3-step search strategy was developed. The initial search produced 3865 studies. After applying filters, 875 studies were short-listed for further review. Keywords were further refined to yield more relevant studies on the topic.

Conclusions: The findings are expected to determine the extent of the knowledge gap in the applications of computational methods in PHFs for any traditional medicine across the world. The study can provide answers to open research questions related to the phytochemical identification of PHFs, criteria for target identification, strategies applied for in silico studies, software used, and challenges in adopting in silico methods for understanding the mechanisms of action of PHFs. This study can thus provide a better understanding of the application and types of in silico methods for investigating PHFs.

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KEYWORDS

polyherbal formulation; Ayurveda system; Ayurveda; Ayurvedic medicine; Ayurvedic treatment; herbal; herbal drug; pharmacodynamic; pharmacology; computer-aided drug design; in silico methodology; scoping review

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Introduction

Herbal medicine plays a significant role in treatment in various traditional medical systems worldwide [1-5]. Among such traditional medicine systems, Ayurveda has been a cornerstone of health care for a significant portion of the Indian population for centuries [6]. Despite its long-standing use, the scientific community's acceptance of Ayurveda as an evidence-based health system remains tempered due to the lack of evidence-based data regarding the mode of action of Ayurvedic formulations.

Over the last 3 decades, substantial effort has been made to assess the effectiveness of Ayurvedic formulations. Traditional pharmacology tools, including in vivo and in vitro models, have been the most common means used for evaluating the preclinical efficacy of these formulations [7]. However, a persistent issue has been the lack of a detailed explanation regarding how these compounds work within the framework of modern science. This poses a challenge in establishing a robust scientific evidence base for Ayurveda. Thus, further efforts are needed to address the critical question of how Ayurvedic formulations work to justify their widespread use in health care.

There has been a notable shift toward the development and application of computational and in silico methods in pharmacological research [8]. These techniques have increasingly been used for formulating and testing various hypotheses related to a drug's mode of action. In particular, in silico screening has emerged as a powerful tool for predicting a drug's potential mechanism of action and its impact on specific target proteins of the human body. Thus, in silico studies that can identify lead compounds in polyherbal formulations (PHFs) and subsequently predict the molecular mechanism of action hold immense promise in the domain of Ayurvedic drug development.

To date, in silico approaches in understanding traditional medicine have mainly focused on single herbs. Although individual herbs contain hundreds of diverse phytochemicals, when combined to form PHFs, some of the original phytochemicals may be lost. In addition, the manufacturing process of a PHF may introduce new phytochemicals, resulting in a complex and dynamic mixture of metabolites [9]. This complexity necessitates a distinct approach in understanding the pharmacological properties of PHFs.

Although established methods are available for conducting in silico studies on individual herbs, little is known about strategies for in silico studies on PHFs. Therefore, the aim of this scoping review is to identify and chart the diverse in silico approaches that are currently being explored to understand the mechanism of action of PHFs, which can further help to identify the existing knowledge gaps in this area to target efforts for future research directions.

A preliminary search of MEDLINE, Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis database yielded no ongoing or completed scoping reviews on this specific topic. Apart from Ayurveda, other traditional medicine systems also depend on PHFs for the management of diseases. Considering the primary focus on PHFs, our search scope will extend to other traditional systems of medicine, ensuring a comprehensive understanding of the potential applications of in silico techniques in studying PHFs across different medical systems.

Methods

Study Design and Registration

This scoping review protocol was developed according to the framework proposed by Arksey and O'Malley [10] and complies with the recommendations of the JBI for elaborating scoping reviews [11]. A similar study from Brazil on in silico approaches in drug repurposing served as a guide in formulating this scoping review protocol [12]. This protocol has been registered with Open Science Framework [13] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline [14].

Objectives and Search Strategy

The following questions were established to guide the review and literature search strategy: (1) How are the phytochemicals of PHFs identified? (2) What are the criteria for target identification? (3) Which in silico strategies are used in PHFs? (4) What is the methodology used in in silico studies of PHFs? (5) What are the challenges in adapting in silico studies in PHFs? (6) How are the results interpreted in the purview of the mode of action of PHFs? (7) How successful are these methods in proving the findings of in silico studies using other experimental methods?

A detailed 3-step search strategy will be developed by comparing the search terms and the related Medical Subject Heading (MeSH) terms. Using the developed search strategy in PubMed as a base, the search will further extend to the Embase, Science Direct, Web of Science, and Google Scholar databases to identify relevant articles on the topic. The search strategy will combine all identified keywords, MeSH terms, their relevant synonyms, and the Boolean operators "AND" and "OR." The following three concept clusters were included: (1) polyherbal formulation, (2) in silico approach, and (3) mechanism of drug action.

Study Selection

Inclusion Criteria

Peer-reviewed research articles published from January 2021 to December 2023 that incorporated in silico strategies in PHFs will be included. The rationale for this date range is to ensure that we capture the most current and relevant research findings related to in silico studies in PHFs, as the field of in silico research is continuously evolving. Studies published in any language will be included. Moreover, no limitations will be placed with respect to the system of medicine. In this regard, in silico studies related to PHFs used in any system of traditional medicine will be eligible for inclusion in the scoping review, including, but not limited to, Ayurveda.

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Exclusion Criteria

Studies will be excluded if they meet the following criteria*:* in silico studies focusing solely on single drugs; studies in which only network pharmacology is employed (single drugs and PHFs); and reviews (mini, narrative, scoping, and systematic reviews), editorials, commentaries, letters, opinions, and grey literature.

Study/Source of Evidence Selection

After completion of the search, all identified articles will be collected and organized using Mendeley software version 1.19.8. Any duplicate citations will be removed at this stage [15]. The titles and abstracts will then be subjected to screening by two or more independent reviewers using Rayyan software [16] in line with the predetermined inclusion criteria for the review.

Sources that are found to be potentially relevant will undergo a comprehensive review, and the citation details will be integrated into the JBI System for the Unified Management, Assessment, and Review of Information (SUMARI) for full-text assessment. Two or more independent reviewers will evaluate the selected citations against the preestablished inclusion criteria [17]. Any sources of evidence assessed at the full-text stage that do not meet the inclusion criteria will be clearly documented and the reasons for exclusion will be reported in the scoping review. Any disagreements among the reviewers at any stage of the selection process will be addressed through discussion or by involving additional reviewers for resolution.

The results of the search and the entire study inclusion process will be presented in full in the final scoping review. A PRISMA-ScR flow diagram will be included in the report to provide an overview of the selection process and outcomes.

Data Extraction

Data will be extracted from articles included in the scoping review by two or more independent reviewers using the JBI SUMARI data extraction tool. This scoping review intends to yield a descriptive summary of the results.

The components listed in Textbox 1 will be considered while extracting the data. A data extraction pilot will be performed with 5 selected studies. The insights gained from the pilot study will be used to modify the draft data extraction tool as necessary during the process of extracting data from each included study. Any modifications will be detailed in the final scoping review. In the case of missing data or additional data, the authors of the papers will be contacted.

Textbox 1. Components of data to be extracted from the selected studies for the scoping review.

- Title
- Date of publication
- Authors
- Country
- Study objectives
- Study design
- Name of the polyherbal formulation (PHF)
- Phytochemical analysis of the PHF
- In silico method implemented
- Limitations/challenges of the study
- Study outcome
- Proof of findings (supported by in vitro/in vivo experiments)

Collating, Summarizing, and Reporting the Results

The data gleaned from the included studies will be presented in a descriptive format. This will involve a summary of the key findings, methodological approaches, and study characteristics. To facilitate understanding and enhance the clarity of the data collected, tables and graphs will be used. The results will be charted to provide an organized overview of the findings from the included studies. This charting process will categorize the data according to the components of data extraction listed in Textbox 1. Findings will be dissected and discussed explicitly in relation to the predefined questions of the scoping review. The scoping review will adhere to the PRISMA-ScR guidelines to ensure a rigorous and transparent reporting process.

Results

An initial search was performed on the PubMed database using the keywords and strategy outlined in Table 1. The initial search yielded 3865 studies. After applying filters such as full-text availability, articles published in English, and those published between January 2021 and December 2023, 875 studies were obtained. As the study progressed, the search strategy was changed. The Boolean term “NOT” was removed and additional keywords were included.

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Table 1. Initial search strategy for the scoping review performed in PubMed in December 2023.

Step	Search strategy	Yielded studies
1	((((((polyherbal formulation) OR (Traditional formulations)) OR (Traditional Medicine)) AND (in silico)) OR (molecular docking)) OR (Molecular dynamic)) AND (mechanism Drug Action))	3865
2	Filters: text availability: Full Text	1867
3	Filters: Published between January 2021 to present date	878
4	Filters: Language: English	875

Discussion

The findings of this scoping review are expected to address the specific review questions and identify knowledge gaps related to the methods used for the phytochemical identification of PHFs, determine the criteria for target selection, and propose evidence-backed methods for conducting in silico studies on PHFs.

This scoping review will be the first of its kind in providing a comprehensive understanding of the potential applications of in silico techniques in studying PHFs across different traditional medicine systems. The findings will also be interpreted in a manner that can facilitate evaluating the effectiveness of these methods for gaining a better understanding of the mechanism of drug action.

In silico approaches have proven to be significant in identifying novel drug candidates and repurposing existing drugs [12,18,19]. These studies have also been instrumental in shedding light on the likely mechanisms of action of single herbal drugs [20]. However, the in silico strategies used to study PHFs are not well understood. Several methods appear to be used to conduct in silico studies on PHFs [21,22]. This scoping review can thus help to identify the most effective in silico methods in this context and can further help to guide the design of future in silico studies on various types of PHFs used in traditional medicine.

The scoping review is limited by its reliance on in silico studies, which can offer valuable preliminary insights but may not fully capture the complex interactions and bioavailability of compounds within PHFs when administered in vivo. Additionally, this review might encounter limitations due to the variability of methodologies and the quality of reporting across in silico studies, potentially affecting the consistency and comparability of findings related to the efficacy and safety of PHFs.

The future scope and perspectives of this field that can be informed by this scoping review are depicted in Figure 1. The results of in silico studies can be further validated through preclinical and clinical studies. Multiomics strategies such as genomics and metabolomics can also be applied. The review seeks to provide an overview of the progress made in employing in silico techniques to decipher the mechanisms underlying the efficacy of PHFs, thereby contributing to our understanding of this critical aspect of traditional medicine.

Figure 1. Future perspectives of scoping reviews of in silico studies related to polyherbal formulations (PHFs).

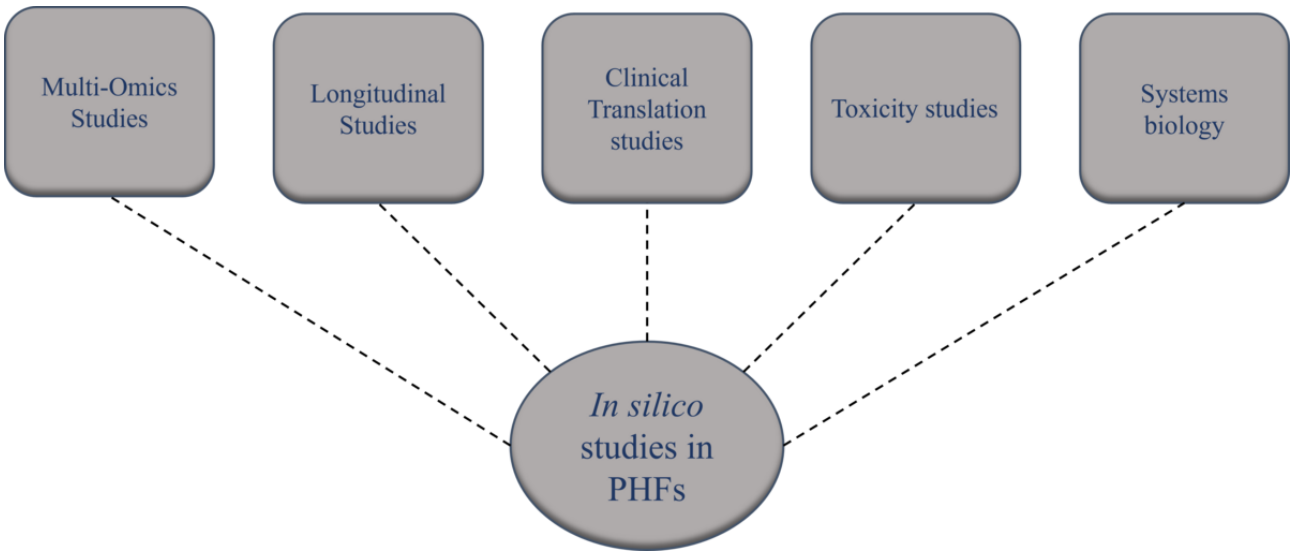

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Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subject Heading
PHF: polyherbal formulation
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SUMARI: System for the Unified Management, Assessment, and Review of Information

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Protocol

Social Factors Associated With Nutrition Risk in Community-Dwelling Older Adults in High-Income Countries: Protocol for a Scoping Review

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Abstract

Background: In high-income countries (HICs), between 65% and 70% of community-dwelling adults aged 65 and older are at high nutrition risk. Nutrition risk is the risk of poor dietary intake and nutritional status. Consequences of high nutrition risk include frailty, hospitalization, death, and reduced quality of life. Social factors (such as social support and commensality) are known to influence eating behavior in later life; however, to the authors' knowledge, no reviews have been conducted examining how these social factors are associated with nutrition risk specifically.

Objective: The objective of this scoping review is to understand the extent and type of evidence concerning the relationship between social factors and nutrition risk among community-dwelling older adults in HICs and to identify social interventions that address nutrition risk in community-dwelling older adults in HICs.

Methods: This review will follow the scoping review methodology as outlined by the JBI Manual for Evidence Synthesis and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. The search will include MEDLINE (Ovid), CINAHL, PsycINFO, and Web of Science. There will be no date limits placed on the search. However, only resources available in English will be included. EndNote (Clarivate Analytics) and Covidence (Veritas Health Innovation Ltd) will be used for reference management and removal of duplicate studies. Articles will be screened, and data will be extracted by at least 2 independent reviewers using Covidence. Data to be extracted will include study characteristics (country, methods, aims, design, and dates), participant characteristics (population description, inclusion and exclusion criteria, recruitment method, total number of participants, and demographics), how nutrition risk was measured (including the tool used to measure nutrition risk), social factors or interventions examined (including how these were measured or determined), the relationship between nutrition risk and the social factors examined, and the details of social interventions designed to address nutrition risk.

Results: The scoping review was started in October 2023 and will be finalized by August 2024. The findings will describe the social factors commonly examined in the nutrition risk literature, the relationship between these social factors and nutrition risk, the social factors that have an impact on nutrition risk, and social interventions designed to address nutrition risk. The results of the extracted data will be presented in the form of a narrative summary with accompanying tables.

Conclusions: Given the high prevalence of nutrition risk in community-dwelling older adults in HICs and the negative consequences of nutrition risk, it is essential to understand the social factors associated with nutrition risk. The results of the review are anticipated to aid in identifying individuals who should be screened proactively for nutrition risk and inform programs, policies, and interventions designed to reduce the prevalence of nutrition risk.

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KEYWORDS

community; malnutrition risk; nutrition risk; older adults; social factors; geriatric; geriatrics; malnutrition; community-dwelling; older adult; elderly; HIC; high-income countries; diet; dietary intake; nutritional status; Canada; nutritional risk; social; intervention; public health; community-based intervention; health promotion

Introduction

In high-income countries (HICs), between 65% and 70% of community-dwelling adults aged 65 years and older are at high nutrition risk [1]. In Canada, one-third of community-dwelling adults aged 60 and older are at increased nutrition risk [2,3]. While there is no universally agreed-upon definition of nutrition risk, 1 common definition is the risk of poor dietary intake and nutritional status [3,4]. Nutrition risk occurs when there are factors present that negatively affect food intake [5], and can lead to malnutrition if its causes are not addressed [3].

Many measures or instruments, commonly referred to as tools, are available to measure and screen for nutrition risk and malnutrition risk in community-dwelling older adults, such as Seniors in the Community Risk Evaluation for Eating and Nutrition and the Mini Nutritional Assessment [6]. Nutrition risk and malnutrition risk lie on a continuum between nutritional health and malnutrition [3]. Malnutrition is a clinical condition that occurs when there is unintentional weight loss, low body mass index, or reduced muscle mass, along with reduced food intake, reduced assimilation of food and nutrients, chronic disease, or inflammation related to acute disease or injury [7]. Malnutrition risk exists in clinical settings when individuals have 1 or more of these indicators [8]. In contrast, nutrition risk occurs earlier in the process. Nutrition risk "represents the determinants and risk factors that place an individual at risk for poor food intake and if not interrupted, can lead to malnutrition" [8]. However, in the literature, the terms nutrition risk and malnutrition risk are often used interchangeably, with nutrition risk sometimes referred to as early-stage malnutrition risk [9]. The following figure, adapted from Keller [8], illustrates the relationship between food intake, nutrition risk, and malnutrition (Figure 1).

Figure 1. The conceptual relationship between nutrition risk and malnutrition, adapted from Keller [8] with permission from Heather H Keller.

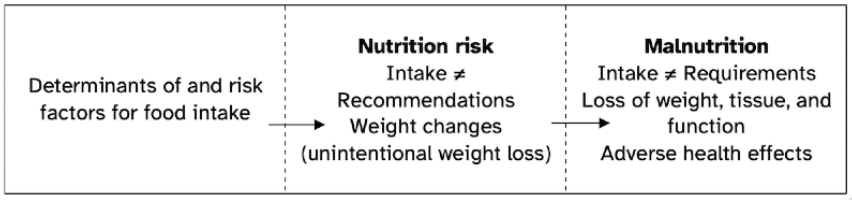

Individuals who are at nutrition risk are more likely to be hospitalized and have an increased risk of mortality, even when health status, health behaviors, and socioeconomic factors are considered [10,11]. Nutrition risk is also associated with early institutionalization [12], frailty [13], and poor quality of life [14,15].

Many social factors are associated with nutrition risk in older adults in the literature [16,17]. These include, but are not limited to, social network type (restricted, diverse, family-focused, friend-focused, etc), living arrangement (alone or with others), social support (emotional, informational, tangible, and affectionate support), social engagement (engagement in social activities with others), and social participation (participation in community activities) [3,17-19]. It is well-established that eating with others improves dietary intake and reduces nutrition risk [16], whereas eating alone is associated with high nutrition risk [16,20]. In many studies, social isolation is a significant factor leading to increased nutrition risk [3,11]. Social relationships may decrease nutrition risk by encouraging compliance with dietary norms [16], while eating with others may provide "social cues for when and what to eat" [16]. An individual's social support system may also encourage healthy behaviors, such as consuming adequate amounts of nutrient-rich foods [21]. Studies have found that social support helps reduce nutrition risk [17], whereas low levels of social support are associated with increased nutrition risk [22]. Individuals with higher levels of social support may have greater assistance with food-related activities, such as meal preparation and grocery shopping [16]. Social interventions, such as congregate meal programs, have also been shown to improve nutrition risk scores in older adults. Despite the research showing that social factors are associated with nutrition risk, reviews in this area have not specifically focused on nutrition risk, but rather on eating behavior [16], dietary intake [23], food choice [24], or nutrition screening [25]. Although related to these concepts, nutrition risk is different, describing the presence of risk factors and determinants of food intake such as poor appetite, food insecurity, and low dietary intake [14,26].

To advance research on how social factors are associated with nutrition risk, it is essential to synthesize the available evidence. A scoping review was chosen as it is an appropriate method to understand and summarize the extent and type of evidence available [27]. It is important to understand the social factors associated with nutrition risk so that individuals who should be screened proactively for nutrition risk can be identified, and programs and policies designed to reduce the prevalence of nutrition risk can be appropriately developed and implemented. Understanding what types of social interventions have been

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shown to reduce the prevalence of nutrition risk can also help inform such policy and program development.

This review aims to examine the social factors associated with nutrition risk in community-dwelling older adults in HICs and to identify social interventions designed to address nutrition risk in community-dwelling older adults in HICs. A preliminary search was conducted in October 2023 to identify any existing systemic or scoping reviews on this topic. Searching PROSPERO, MEDLINE (Ovid), the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis identified no current or in-progress scoping reviews or systematic reviews on the topic. There have been reviews examining adjacent topics, for example, the social influences on eating behavior in later life [16], factors influencing food choice in older adults [24], and determinants of dietary intake in older people [23] although none of these have specifically examined the relationship between nutrition risk and social factors or examined social interventions designed to address nutrition risk.

The results of this scoping review will provide researchers and clinicians with knowledge of the social factors associated with nutrition risk in community-dwelling older adults in HICs. Identifying the social factors associated with nutrition risk can help inform future research into nutrition risk and guide program and policy development. Promising social interventions that can improve nutrition risk may also be identified. Additionally, the results of this review may help identify groups of individuals who should be screened for nutrition risk.

Methods

Scoping Review Methodology

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [28] and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) [29].

Research Questions

The research questions for this scoping review are as follows: (1) What social factors (including, but not limited to, social networks, social engagement, social support, and social participation) are associated with nutrition risk or malnutrition risk among community-dwelling adults aged 60 years and older living in HICs? (2) What social interventions improve nutrition risk or malnutrition risk in community-dwelling adults aged 60 years and older living in HICs?

Search Strategy

The search strategy was developed with the assistance of a university research librarian and will be conducted electronically. The search will aim to locate both published and unpublished studies and reviews. An initial limited search of MEDLINE and CINAHL was undertaken to identify articles on the topic. The initial search terms included “malnutrition,” “nutrition risk,” “older adults,” “social factors,” “social support,” “social engagement,” “social participation,” “social influence,” and “social networks.” The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE, CINAHL, PsycINFO, and Web of Science. A sample search strategy for MEDLINE is available in Table 1.

Table 1. Sample search strategy for a scoping review examining social factors and nutrition risk in community-dwelling older adults in high-income countries; results of a search of MEDLINE on October 10, 2023.

Search	Query	Records retrieved, n
#1	exp Malnutrition/ or exp Nutritional Status/ or nutrition risk.mp.	167,909
#2	undernutrition.mp.	8345
#3	poor dietary intake.mp.	227
#4	poor nutrition.mp. or exp Diet/	305,502
#5	1 or 2 or 3 or 4:	453,221
#6	exp Aged/ or exp Aging/ or older adults.mp.	3,506,670
#7	seniors.mp.	8211
#8	elderly.mp.	277,535
#9	6 or 7 or 8:	3,574,189
#10	social factors.mp. or exp Social Factors/	11,115
#11	social support.mp. or exp Social Support/	98,186
#12	social engagement.mp. or exp Social Participation/	4565
#13	social influence.mp. or exp Social Behavior/	276,421
#14	social networks.mp. or exp Social Networking/	14,147
#15	10 or 11 or 12 or 13 or 14:	383,726
#16	5 and 9 and 15:	874

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The search strategy, including all identified keywords and index terms, will be adapted for each included database or information source. The reference lists of articles included in the review will be screened for additional studies. Only studies in the English language will be included, as there are limits to language proficiency within the research team. No date restrictions will be applied when conducting searches. As recommended by a research librarian, sources of unpublished studies or gray literature will be searched, including preprint servers such as medRxiv, ProQuest dissertations and theses, Open Grey, and Google Scholar. Both social factors associated with nutrition risk and social interventions designed to address nutrition risk will be searched for in the gray literature.

Study Selection

Overview

Inclusion and exclusion criteria have been developed according to the domains of participants, concept, context, and types of evidence sources, as recommended in the JBI Manual for Evidence Synthesis [28]. The inclusion and exclusion criteria (Textbox 1) are described in detail.

Textbox 1. Inclusion and exclusion criteria for screening sources of evidence for a scoping review examining social factors and nutrition risk in community-dwelling older adults in high-income countries.

Inclusion criteria

- Older adults (60 years of age and older)
- Community-dwelling
- High-income countries
- Social factors including social support, social engagement, social participation, social isolation, social inclusion, commensality (eating with others), and loneliness
- Social interventions such as congregate meals programs, group nutrition education programs, etc
- Nutrition risk, malnutrition risk, and risk of malnutrition

Exclusion criteria

- Age groups other than older adults (unless information for older adults available separately)
- Long-term care, care homes, hospital, institutionalized, and assisted living
- Low- or middle-income countries
- No social factors in relation to nutrition risk
- Not a social intervention
- Other nutritional factors such as risk of overnutrition, disease-related malnutrition, diet quality, diet patterns, nutrition risk in specific diseases (ie, diabetes, heart disease, kidney disease, dementia, cancer, and COVID-19)

Inclusion Criteria

Participants

This review will consider studies that include community-dwelling adults aged 60 years and older in HICs. The minimum participant age of 60 years is consistent with the United Nations' definition of older persons [30,31]. Studies that include other age groups but present the results of adults aged 60 years and older as a subgroup will be included, whereas studies that do not separate this age group will not be included, as the causes of nutrition risk may differ in younger age groups. Similarly, studies that examine disease-related nutrition risk and malnutrition risk will be excluded from this review, as specific diseases affect nutrition risk and malnutrition risk in different ways.

This review will be restricted to HICs, given that there is a paucity of literature examining nutrition status specifically in older adults living in low- and middle-income countries (LMICs) [32], and that the causes of nutrition risk are likely different in LMICs compared with HICs [33]. In LMICs, food insecurity and rapid urbanization are the major contributors to malnutrition in older adults [32], and access to sufficient health care and welfare may not be adequate [34]. Moreover, adherence to the use of validated malnutrition risk screening and assessment tools is low in LMICs, rendering the prevalence of nutrition risk among older adults in these settings largely unquantified [32].

Concept

This review will consider studies that explore nutrition risk and malnutrition risk, in the community. While there is no universally agreed-upon definition of nutrition risk or malnutrition risk, 1 common definition is the risk of poor dietary intake and nutritional status that places an individual at risk of developing malnutrition if action is not taken to improve dietary intake [3,4]. Nutrition risk occurs when there are factors present that negatively affect food intake or nutrient metabolism [5].

Context

This review will consider studies that examine social factors and social interventions. Social factors include, but are not limited to, social support, social networks, social engagement, and social participation. Social networks are "the web of social relationships that surround an individual and the characteristics of those ties" [35]. Social participation refers to participation

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in activities with friends and family or the community [36], whereas social engagement emphasizes meaningful engagement and desire for social change [37]. Social support includes "the functions that individuals in a person's social network perform" [36]. The term "social factors" can be said to encompass these concepts.

Types of Evidence Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials that examine how social factors or social interventions affect nutrition risk, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion.

Qualitative studies will also be considered, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. In addition, systematic reviews, rapid reviews, and narrative reviews will be considered for inclusion in the proposed scoping review. Papers that are conference abstracts or letters to the editor will not be considered for inclusion in this scoping review.

Gray literature consisting of dissertations, theses, reports, or unpublished papers that examine how social factors affect nutrition risk or that describe social interventions designed to address nutrition risk will also be considered for inclusion.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote 21 and duplicates will be removed. Citations will then be uploaded to Covidence. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their full texts will be imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with additional reviewers. The results of the search and the study inclusion process will completely be reported in the final scoping review and presented in the PRISMA-ScR flow diagram [29].

Data Extraction

Data will be extracted from sources of evidence included in the scoping review by 2 independent reviewers, using an adaptation of the Covidence data extraction tool as shown in Textbox 2. The extraction tool is based on the JBI guidelines for data extraction and the default Covidence extraction tool. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions (social factors associated with nutrition risk). Data will be extracted verbatim from the included sources.

The data extraction tool will be further modified and revised, if necessary, during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion, or with an additional reviewer. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

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Textbox 2. Data extraction instrument for a scoping review examining social factors associated with nutrition risk in community-dwelling older adults in high-income countries.

General information

- Title
- Authors
- Journal
- Year
- Country

Study characteristics

- Study aims
- Study design
- Study methods
- Dates (start date, end date, and length of follow-up period for longitudinal studies)
- Study funding sources
- Possible conflicts of interest for study authors

Participants

- Population description
- Inclusion criteria for study
- Exclusion criteria for study
- Recruitment methods
- Total number of participants
- Baseline population characteristics

Main findings

- Nutrition risk, malnutrition risk measure, or tool
  - SCREEN-3 (Seniors in the Community Risk Evaluation for Eating and Nutrition-3)
  - SCREEN-8 (Seniors in the Community Risk Evaluation for Eating and Nutrition-8, formerly SCREEN II AB)
  - SCREEN-14 (Seniors in the Community Risk Evaluation for Eating and Nutrition-14, formerly SCREEN II)
  - SCREEN/SCREEN I (Seniors in the Community Risk Evaluation for Eating and Nutrition/Seniors in the Community Risk Evaluation for Eating and Nutrition I)
  - MNA (Mini Nutritional Assessment)
  - MNA-SF (Mini Nutritional Assessment-Short Form)
  - SGA (Subjective Global Assessment)
  - DETERMINE (Determine your health checklist)
  - SNAQ (Short Nutritional Assessment Questionnaire)
  - MUST (Malnutrition Universal Screening Tool)
  - Other (describe)
- Social factors included
  - Social support
  - Social influence
  - Social participation
  - Commensality (eating with others)
  - Living situation (alone or with others)
  - Social networks or social network types

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- Social capital
- Social standing
- Social isolation
- Loneliness
- Other (describe)

- Measures of social factors (social factor and how it was measured)
- Found a relationship between social factors and malnutrition and nutrition risk (yes, no, or other)
- Description of the relationship between social factors and malnutrition and nutrition risk

Additional information for intervention studies

- Description of intervention
- Time points (number and time between time points)
- Outcomes at different time points

Additional information for trials

- Description of control group
- Comparison of intervention group to control group

Data Analysis and Presentation

Social factors associated with nutrition risk or malnutrition risk will be reported in the scoping review, as will any social interventions that affect nutrition risk or malnutrition risk. Data will be analyzed to identify the common social factors that have been examined in conjunction with nutrition risk and to identify which social factors and interventions have been found to affect nutrition risk. Similarities and differences between findings will be noted; for example, differences in the tools used to measure nutrition risk, differences in how the various social factors were measured, and whether a social factor was consistently associated with nutrition risk across all (or the majority of) studies. Data from studies included in this review will be presented as a narrative summary with the use of tables. The tables will be used to highlight central concepts described in the narrative summary.

Results

The scoping review was started in October 2023 and will be finalized by August 2024. As of May 28, 2024, a total of 5064 studies have been identified through database searches and imported for title and abstract screening, and 293 duplicates have been removed (266 duplicates identified by Covidence and 27 duplicates identified manually). Title and abstract screening has been completed, resulting in 235 full-text studies ready to be assessed for eligibility. The results of this scoping review will provide a comprehensive understanding of the social factors associated with nutrition risk in community-dwelling older adults in HICs.

Discussion

Expected Outcomes

This scoping review will identify which social factors have been examined concerning nutrition risk in the literature and which social factors have been shown to impact nutrition risk. It will also identify any social interventions that have successfully reduced the prevalence of nutrition risk. The results of the review are anticipated to aid in identifying individuals who should be screened proactively for nutrition risk by identifying the social factors associated with increased risk. If the literature shows that certain social factors are consistently associated with increased nutrition risk, then screening programs can target individuals who reflect those social factors, for example, individuals with low levels of social support [17,22], low levels of social participation [3,17], or those who are socially isolated [3,11,22,38].

The results of this review will also inform programs and policies designed to reduce the prevalence of nutrition risk and help guide the development of interventions aimed at reducing nutrition risk through the identification of interventions that have affected nutrition risk and social factors that impact nutrition risk.

Gaps in the literature exploring social factors associated with nutrition risk will also be identified by noting which social factors have not been well-studied in the literature. This will help inform future research into nutrition risk and social factors.

Strengths and Limitations

A strength of this scoping review is the use of the JBI methodology for scoping reviews [28], and the PRISMA-ScR [29]. All screening and data extraction will be completed by at least 2 reviewers, out of whom at least 1 is a registered dietitian with experience in working with older adults in the community.

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Any disagreements between the reviewers will be resolved through discussion or by a third reviewer.

Due to many different tools that can be used to measure nutrition risk in community-dwelling older adults and due to the many ways that social factors can be measured, it is anticipated that there will be significant heterogeneity between studies. This information will be captured in the data extraction tool and will be discussed in the scoping review.

Conclusions

With the high prevalence of nutrition risk in community-dwelling older adults in HICs and the negative consequences of nutrition risk, it is essential to understand the social factors associated with nutrition risk. The Canadian Malnutrition Task Force has identified that research into the root causes of nutrition risk in community-dwelling older adults is a priority [39], and this scoping review will help to identify the potential social factors that may be the root causes of nutrition risk among this demographic.

Conflicts of Interest

None declared.

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Abbreviations

HIC: high-income country
LMIC: low- and middle-income country
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Effects of Sound Interventions on the Mental Stress Response in Adults: Protocol for a Scoping Review

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Abstract

Background: Sound therapy methods have seen a surge in popularity, with a predominant focus on music among all types of sound stimulation. There is substantial evidence documenting the integrative impact of music therapy on psycho-emotional and physiological outcomes, rendering it beneficial for addressing stress-related conditions such as pain syndromes, depression, and anxiety. Despite these advancements, the therapeutic aspects of sound, as well as the mechanisms underlying its efficacy, remain incompletely understood. Existing research on music as a holistic cultural phenomenon often overlooks crucial aspects of sound therapy mechanisms, particularly those related to speech acoustics or the so-called “music of speech.”

Objective: This study aims to provide an overview of empirical research on sound interventions to elucidate the mechanism underlying their positive effects. Specifically, we will focus on identifying therapeutic factors and mechanisms of change associated with sound interventions. Our analysis will compare the most prevalent types of sound interventions reported in clinical studies and experiments. Moreover, we will explore the therapeutic effects of sound beyond music, encompassing natural human speech and intermediate forms such as traditional poetry performances.

Methods: This review adheres to the methodological guidance of the Joanna Briggs Institute and follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist for reporting review studies, which is adapted from the Arksey and O’Malley framework. Our search strategy encompasses PubMed, Web of Science, Scopus, and PsycINFO or EBSCOhost, covering literature from 1990 to the present. Among the different study types, randomized controlled trials, clinical trials, laboratory experiments, and field experiments were included.

Results: Data collection began in October 2022. We found a total of 2027 items. Our initial search uncovered an asymmetry in the distribution of studies, with a larger number focused on music therapy compared with those exploring prosody in spoken interventions such as guided meditation or hypnosis. We extracted and selected papers using Rayyan software (Rayyan) and identified 41 eligible papers after title and abstract screening. The completion of the scoping review is anticipated by October 2024, with key steps comprising the analysis of findings by May 2024, drafting and revising the study by July 2024, and submitting the paper for publication in October 2024.

Conclusions: In the next step, we will conduct a quality evaluation of the papers and then chart and group the therapeutic factors extracted from them. This process aims to unveil conceptual gaps in existing studies. Gray literature sources, such as Google Scholar, ClinicalTrials.gov, nonindexed conferences, and reference list searches of retrieved studies, will be added to our search strategy to increase the number of relevant papers that we cover.

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KEYWORDS

mental stress; anxiety; sound therapy; music therapy; voice-guided relaxation; voice-guided meditation; prosody; paralanguage; expressive sounds; psychoacoustics

Introduction

Background

The mental stress response exerts a profound influence at various levels in both the brain and the body. At the neural level, the amygdala (often referred to as "the emotional center") plays a pivotal role by triggering rapid reactions to potential threats. The prefrontal cortex, responsible for rational decision-making, is also impacted. Additionally, the hypothalamus-pituitary-adrenal axis becomes activated, prompting the release of stress hormones such as cortisol, which affects bodily functions. Physiologically, the cardiovascular system responds by increasing heart rate and constricting blood vessels, redirecting blood flow to vital organs. These combined effects in the brain and body demonstrate the intricate interconnectedness of the stress response, underscoring its significance in shaping human behavior and health outcomes.

In the classical definition, stress is seen as a universal response to disrupted homeostasis [1]. From the point of view of the autonomic nervous system, we have 2 opposite reactions. One reaction is the stress response, which is accompanied by the arousal of the sympathetic nervous system, and a fight-or-flight response, which could lead to mydriasis, increased heart rate and force contraction, vasoconstriction, bronchodilation, glycogenolysis, gluconeogenesis, lipolysis, sweating, decreased motility of the digestive system, secretion of the epinephrine and cortisol from the adrenal medulla, and relaxation of the bladder wall. Opposing this reaction are the relaxation response, the activation of the parasympathetic nervous system, and the rest-and-digest response (which involves miosis, bronchoconstriction, increased activity of the digestive system, and contraction of the bladder walls) [2]. Chronic distress can worsen the quality of life, impair performance, lead to mental health problems, and aggravate bodily illnesses.

Ample evidence documented sound therapy's integrative impact on the psycho-emotional and physiological outcomes, which makes it helpful for treating stress-related conditions such as pain syndromes, depression, and anxiety [3-6]. Sound therapy techniques have become widespread over the past decades, mainly focusing on music among other types of sound stimulation.

There is also evidence suggesting that a similar effect can be exerted by poetry therapy [7-9]. Similar features in the processing of speech and music are also evident at the level of brain activity. For example, in a study by Maess et al [10], it was shown that the Broca area, traditionally associated with language, is also involved in the processing of musical syntax. However, a comprehensive list of sound components that hold the potential for therapeutic influence remains ambiguously defined. There is a blind spot in understanding sound, such as speech therapeutic intervention and the impact of the spoken word.

In the case of speech, there are 8 paralinguistic features: pitch, tempo, loudness, resonance, timbre, intonation range, syllabic duration, and rhythm [11]. Despite this variety of features, studies on paralinguistic characteristics are scarce. The investigation of the effects of speech acoustics on changing mind-body conditions is just beginning. It is still unclear which combination of acoustic features (eg, prosody, pitch, loudness, and timbre) might work more effectively. We do not know whether there are individual differences in sound perception and, if so, whether they depend on cultural context, personal experience, characteristics of the listener's nervous system, etc. We do not know whether a positive effect of sound is necessarily associated with subjective pleasure during listening, or whether there are conditions under which intervention would be beneficial regardless of subjective emotional preference. We plan to complete a scoping review of laboratory experiments, clinical trials, and randomized controlled trials to elucidate this field and investigate the capacity of sound stimulation to manage mental and physiological stress.

The main research question we intend to answer through this review is "what are the therapeutic factors of sound in the case of reducing mental stress and stress-related conditions in human adults?" For example, it might be rhythm, emotional prosody, environmental context of presentation of sound stimuli, individual preferences, or something else. Secondary research objectives will be to clarify body responses (physiological effects measured by biomedical technologies and devices) as well as subjective experiences (psychological effects measured by surveys and questionaries) associated with sound interventions.

We will incorporate investigations that delve into the responses of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system as indicators of stress, supplemented by self-reported data and introspective surveys as markers of emotional stress. Our primary result of interest will be the neural mechanisms underpinning the therapeutic influence of sound. Beyond this, we are also interested in a comparison of delivery methods and sound sample choices for understanding the "active components" of sound in the therapeutic process.

Novelty of This Work

There are reviews of music therapy and the effects of music, but there are currently no reviews that include a "polymodal" approach. This is particularly true of the therapeutic value of the human voice, the acoustic effects of which can be masked by the content of speech. The novelty of our review lies in a conceptually new perspective on sound interventions.

Methods

Overview

This section describes our protocol design, selection criteria, data extraction, and analytic methods.

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Protocol Design

In this study, we will follow the Joanna Briggs Institute Updated Methodological Guidance for the Conduct of Scoping Review [12]. It outlines the main steps to follow when conducting work using the evidence synthesis approach.

Inclusion Criteria

To be selected for inclusion in our review, research articles must meet the following criteria.

Participants

Human adults are often exposed to diverse stress conditions that will be represented in a paper by the following keywords: stress-related abnormalities, anxiety, depression, stressful life conditions, personal crises, emergency, grief, loss, deprivation, burnout, occupational hazard, experimental stress, stress reduction, stress coping, relaxation skills, emotional flexibility, and mindfulness. These are associated with mental stress and can occur both inside the clinic and with healthy people, including artificial experimental stress.

This research excludes the outcomes within which health conditions can be treated with sound therapy but are not primarily caused by mental stress. However, they may be related to it because of difficult social conditions or disability. Meanwhile, the main malfunction can be found in a different area. For instance, this review does not consider the outcomes related to the pain syndromes or psychiatric disabilities (eg, bipolar disorder and schizophrenia). As for the other excluded outcomes, the work does not review Alzheimer or Parkinson disease, age-related cognitive changes, autism spectrum disorders, tinnitus, and hyperacusis.

Regarding excluded populations, our work does not take studies on animals, participants younger than 18 years of age, and participants with hearing disabilities into consideration.

Concept

The concept of the research is to study the sound intervention healing factors and provide an explanation of how and why a sound intervention works. All types of passive sound interventions, such as listening to instrumental music, poetry, human voices, nature sounds, etc, will be included. Our work will also clarify the conceptual basis that guides researchers in choosing one or the other sound sample for intervention, and why the authors consider some sound samples to be more effective than others.

As for kinds of sound intervention, various types of therapy (sound, music, poetry, and acoustic stimulation in hypnosis) are regarded, with sound intervention, guided relaxation, and guided meditation. Moreover, the study will consider issues with voice-guided imagery, affective prosody, expressive sounds, delivering emotions by music and voice, and voice-guided mental health.

Context

Regarding the context of the research, it incorporates the potential positive or harmful influence of sound in the areas of media, arts, and therapeutic and cultural practices. The study will remain in the psychophysiological context, which involves tracking instrumentally measurable body responses and subjective experiences. It will clarify the effectiveness of sound therapy as quantified by stress markers such as salivary cortisol, heart rate variability, electrodermal activity, neuroimaging markers, or other validated measures.

Considering the study types, the work will include not only randomized controlled trials and clinical trials but also laboratory and field experiments. We have deliberately limited the range of studies to controlled trials, clinical trials, and laboratory and field experiments to use more rigorous scientific information, as the field of sound therapy is often subject to a wide range of biases and speculations, which is currently beyond our research interest. All publications are in the English language. Although it is not recommended by the Joanna Briggs Institute Updated Methodological Guidance for the Conduct of Scoping Reviews to apply language restrictions, we do not currently have the resources for relevant translations from multiple languages. Even though automatic translators are available, they produce translations of different quality for different languages, which may misrepresent the results.

Considering the search strategy, we will use PubMed, Web of Science, Scopus, and PsycINFO or EBSCOhost databases. Since the neurobiology of music and sound therapy emerged as a separate field in the 1990s, the search strategy covers research from 1990 to the present day**.** We will also consider gray literature sources such as Google Scholar, ClinicalTrials.gov, nonindexed conferences, and searching the reference lists of retrieved studies.

Evidence Screening, Selection, and Data Extraction

A clinical psychologist, MS, leads all aspects of the review, including literature search, extraction, screening, and data analysis. IS assists with the literature search and extraction and performs independent screening. Disagreements are resolved through discussion and consensus with other research team members, ZL and IP.

The complete string for the search strategy used across all identified medical databases (PubMed, Web of Science, Scopus, and PsycINFO or EBSCOhost) is formulated as follows: “(stress or anxiety or relax*) and (“sound therapy” or “music therapy” or “guided relaxation” or “guided meditation” or hypno* or ASMR or MBSR) and (prosody or song or poetry or voice or paralinguistics or paralanguage) NOT (children or infants or animal or teen).”

A 2-step process is used to select studies. First, we will screen citation titles, abstracts, and keywords and classify each citation as “include,” “exclude,” “unclear,” or “duplicate.” Next, full-text reports for “include” and “unclear” citations are read, with a final decision made about inclusion or exclusion. Reference management is performed in Rayyan. After the screening, we will construct a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension) flow diagram [13] showing citations and full-text reports reviewed, included, and excluded. Data extraction, qualitative analysis, and data charting will then take place.

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Data Analysis and Synthesis

We will combine a descriptive analysis guided by the questions given at the beginning of this protocol and a thematic analysis that induces themes from the papers. Two reviewers will conduct independent data extraction from the full-text papers at this stage. Key data will be structured and placed in tables according to predetermined templates.

Two tables for primary data extraction will contain detailed information about each included study, as well as the relevant key findings regarding the review questions for original papers. The first table will serve as a summary of basic information and will include the sections mentioned in Textbox 1.

The second table will detail the "intervention" and "key findings" sections. We will elaborate 2 aspects of "intervention." First, we will detail the parameters of the sound samples that the authors considered significant components of the intervention (pitch, tempo, rhythm, emotional tone, prosody, etc). Second, it is essential to provide details about the context of sound presentation, which can encompass a broad spectrum of factors, ranging from considering the individual features and preferences of the research participants to cultural context. For the "key findings" section, we are interested in detailing how mental stress was defined, and precisely which psychological and physiological markers were measured to track changes in the state of the participants. These may include autonomic responses such as heart rate variability or electrodermal activity, biochemical responses, brain activity measurements, behavioral responses, results from psychological questionnaires, and others.

After systematically describing the therapeutic aspects of sound in the presented papers, we will proceed with charting and categorizing. Based on the tables, we will review the effectiveness data of sound interventions, rank sound types according to their popularity of use, and identify gaps in research concerning potentially promising but infrequently used sound impact categories. We will also track which components of stress states (bodily responses, behavioral responses, subjective experiences, etc) are most sensitive to sound interventions. Furthermore, we will explore which varieties of clinical stress–related issues are most successfully addressed through sound therapy.

We will not conduct quality appraisal (risk of bias assessment) in this scoping review, which is consistent with the framework proposed by Arksey and O'Malley, as well as the Joanna Briggs Institute Methodological Guidance for Scoping Reviews [12].

Textbox 1. Sections for the summary table.

Sections

- First author (year): indicating the first author and publication year.
- Sampling: the country where the study was conducted, sample size, and population type (nurses, students, patients from a specific clinic, etc).
- Study type: randomized controlled trial, clinical trial, laboratory experiment, etc.
- Intervention (sound type): the type of sound stimulation as described in the article (music, voice, nature sounds, etc).
- Target or conditions: the target condition or issue that the sound stimulation aims to impact (different mental stress types or stress-related clinical conditions such as anxiety, burnout, etc).
- Key findings: the primary findings of the study, such as clinical outcomes, body-mind responses, effectiveness, etc.

Results

This section presents preliminary results that include searches of the main bases that do not consider the analysis of gray sources. According to the search strategy, we generated a search query that was used in 4 databases. Using the operator "and" we combined 3 fields. The first field consists of mental stress, stress related, or the opposite. The second field consists of interventions, in which sound plays a significant role. We included not only interventions based on sound explicitly but also those in which sound is not the central focus, such as speech instruction or performance. The third field consists of the terms related to the voice and the paralinguistic (intonation and acoustic) component. By combining the search fields in this way, we expect to identify a blind spot in the study of sound therapy, namely those papers that appeal to the therapeutic components of sound in natural speech, along the same lines as many music studies do.

The initial query was structured such that the "and" operator combined groups of factors, such as findings, intervention, and specification of studies related to acoustic characteristics of oral speech, and the "not" operator excluded an irrelevant portion of the population.

Running this query on PubMed generated 1467 results. Interestingly, including only "music therapy" in the "intervention" section generated 1370 results. However, when all other types of sound intervention except "music therapy" were included, only 191 results were returned. This illustrates a significant emphasis on research related to music and a lack of studies for other sound types. It is important to note that for therapies such as directed meditation, hypnosis, or other formal practices associated with oral speech, studies focusing on the conceptual and semantic aspects of the intervention are widely presented in these studies. Even so, they fall outside the scope of our review.

Within the focus of our work, it is crucial to highlight the paralinguistic component, which is invariably present in any oral speech interaction. For that purpose, we added a group of factors, related to the acoustic characteristics of voice, to our search query.

Searching all the databases identified 2027 papers. After removing duplicates, 1924 papers remained. We performed an

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initial screening of those papers using Rayyan software. We first eliminated inappropriate papers by unambiguous, incontrovertible attributes such as year of publication, paper language, and study design. We then screened by title and abstract using the predefined legibility criteria outlined in the methodology section of this study. After abstract screening, we identified 41 eligible papers. As of October 2023, we are in the full-text analysis phase. Results have been organized according to the PRISMA flowchart format [13] (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

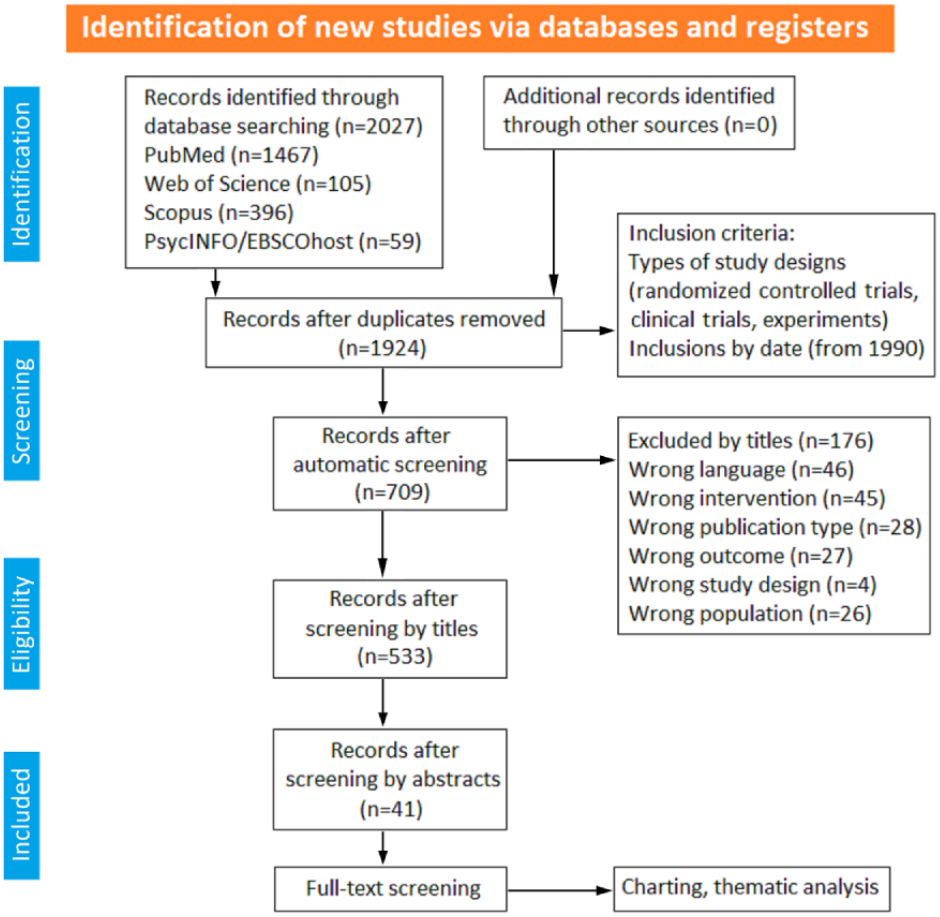

Discussion

Principal Findings

The anticipated main finding of this study would be a comprehensive overview of empirical research on sound interventions, aiming to elucidate the mechanisms underlying their positive effects. The focus lies on identifying therapeutic factors and mechanisms of change associated with various sound interventions, including but not limited to music therapy.

A preliminary search with various query options shows a lack of research beyond music therapies. In methods using natural speech, such as poetry therapy, guided imagination, and guided meditation, the acoustic component is masked by the semantic component (the part of the intervention that can be separated from the vocal expression and conveyed as text). We suggest grouping the therapeutic factors of sound as a potential way to overcome these blind spots (Figure 2).

Stimuli for sound intervention can be described at different levels of generality: starting with basic characteristics, such as frequency (pitch) and amplitude (volume), and then moving on to more complex processing levels, such as tempo, rhythm, and melody (the sound patterns that can be determined through analysis of spectro-acoustic characteristics) [11]. These parameters can be defined for any stimulus, whether it is music, speech, or a nature sound. We can then define the emotional-expressive component, in terms of basic emotions (calm, sad, joyful, ecstatic, etc), which remains a common characteristic for speech and music (modern programs for identifying emotions in voice and music use similar emotion classifications [14]) Thus, we see that dividing sound stimulation into the categories of “music”, “speech”, and “natural sounds” is a very high level of generalization that may hide some basic common features.

We noticed that many articles focus on higher-level attributes, for example, distinguishing groups of participants who listen to “nature sounds” versus “music,” without specifying which particular music and nature sounds were chosen. For example, the murmuring of a stream, the rumbling of a rockfall, the chirping of birds, and the screams of fighting cats can all be considered sounds of nature. These examples can provoke a wide range of emotional responses in a listener. Conversely, some sound examples are difficult to define unambiguously. An example might be a vocal expression in opera singing, modern electronic music, or traditional rituals and folklore

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performances. In some borderline cases, if the listener does not initially know the situational context, then it is difficult to determine whether a sound is speech, music, or from nature.

Following this observation, we consider situational, personal, and cultural contexts in our analysis. After a preliminary review of papers on abstracts, we found several papers focusing on factors such as personal preferences or freedom of selecting sound samples at the intervention time.

A cluster of papers also suggests country-centric interventions, such as traditional music or poetry, implicitly recognizing the importance of cultural context [15]. Often, both the authors and participants in these experiments hail from the country of origin of the music or poetry used in therapeutic sound interventions. However, only a few studies consider that the therapeutic effect may stem from the sound itself and cultural learning. In the latter case, such interventions may be more effective for native listeners. In our review, we aim to focus on these papers to explore the correlation of therapeutic factors of different levels.

Figure 2. Field of study and research gap.

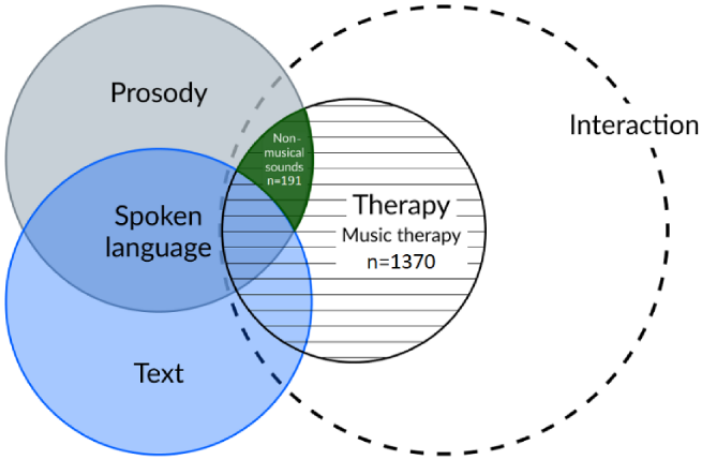

Limitations

Although the aim of the study is to elucidate the mechanisms underlying sound interventions, we may encounter an incomplete understanding of the mechanisms due to the lack of scientific consensus regarding strict definitions in this field. Considering its complexity and multifaceted nature, it may be more appropriate to conclude existing research approaches rather than the very mechanisms of sound therapy. Even a surface review at the level of abstracts shows us the fragmentation and ambiguity of the categorization used by the authors to compare different types of sounds. The range of characteristic analyses extends from the physical features (comparing sound effects of different frequencies), or grouping by context (live presence vs records and free choice of intervention vs predetermination), to categorization by abstract, culturally specific concepts (comparing the effectiveness of sounds by country of origin). Although the study mentions a comprehensive search strategy, it is possible that some trials were missed due to limitations in the search terms or databases used. In addition, this study focuses on the literature in English, which hides from us data published in other languages. This imposes some limitations on the understanding of global research on this topic.

Conclusions

As an expected result of this study, we are going to identify different approaches and concepts underlying sound interventions. The comparison of different sound interventions could reveal specific strengths and weaknesses of each approach in addressing various psycho-emotional and physiological conditions. This could lead to more targeted recommendations for sound therapy apps. Moreover, by exploring the therapeutic effects of natural speech and poetry, the study might uncover additional benefits and potential apps of these sound forms beyond traditional music therapy. Also, we are going to categorize identified therapeutic factors based on their specific characteristics, such as acoustic properties, emotional associations, or cognitive engagement. The study might identify specific sound elements or combinations that are most effective for mental stress treatment leading to more targeted sound therapy protocols. Including gray literature sources could reveal valuable insights and potentially identify novel sound interventions or therapeutic apps not yet documented in mainstream research.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Authors' Contributions

MS performed conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, and writing (original draft). ZL contributed to conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, and writing (review and editing). IP conducted supervision, validation, and writing (review and editing). IS handled data curation, investigation, validation, visualization, and writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Nursing Regulation Literature in Canada: Protocol for a Scoping Review

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Abstract

Background: Significant reforms are occurring in health practitioner regulation across Canada. Within the nursing profession, growing workforce challenges and health system demands have accelerated the pace of changes to nursing regulation policies and practices. There is significant political investment to modernize and harmonize nursing regulation across Canada, and evidence is needed to guide regulatory decision-making. To better understand the current state of scholarship and the gaps that exist, a comprehensive understanding of the available literature informing nursing regulation in Canada is first warranted.

Objective: The objective of this scoping review is to examine the nature, extent, and range of literature focused on nursing regulation in Canada.

Methods: The review will be conducted in accordance with the Joanna Briggs Institute guidelines for scoping reviews. We will search electronic databases, including Ovid MEDLINE, Ovid EMBASE, CINAHL, Scopus, and Web of Science Core Collection. We will also search for grey literature using the websites of Canadian nursing regulatory bodies, nursing organizations, and other leading Canadian regulatory organizations. No limitations will be placed on the year of publication. The review will include papers that explore nursing regulation in Canada, including topics such as education program accreditation or approval, licensure, standards of practice and code of conduct/ethics development and enforcement, continuing competence, discipline and conduct, regulatory models, governance, and reform. We will extract data using a predeveloped tool. Data will be analyzed using descriptive statistics and conventional content analysis.

Results: A preliminary search in Ovid MEDLINE was undertaken on December 7, 2023, and a full search was conducted in 5 academic databases on March 15, 2024. Findings will be presented using evidence tables and a narrative summary. Reporting will follow the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. This scoping review is expected to be completed in early 2025.

Conclusions: The results will be disseminated through conference presentations and a publication in a peer-reviewed journal. The findings will provide a comprehensive overview of the state of nursing regulation literature across Canada and inform the development of a focused research agenda.

Trial Registration: Open Science Framework osf.io/3qk8t; https://osf.io/bm7jv

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KEYWORDS

professional regulation; health profession regulation; nursing workforce; licensure; continuing competence; standards of practice; professional conduct; regulatory reform; nursing; Canada; health practitioner; nursing regulation; literature; practitioner regulation

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Introduction

Background

The primary goal of health practitioner regulation is to protect the public by ensuring the delivery of safe, competent, and ethical care [1]. While regulatory schemes differ across jurisdictional contexts, in general, health practitioner regulation across North America involves several core functions such as providing oversight on education programs, maintaining a public register of practitioners, developing and enforcing standards of practice and codes of conduct, and managing unprofessional conduct [2-5]. Health practitioner regulation plays a critical role in managing risk and reducing potential harm to the public. While regulatory bodies have historically focused their work at the individual practitioner level, scholars and regulatory experts increasingly recognize that regulation does not occur in a vacuum. Improving health practitioner regulatory systems also strongly contributes to health workforce planning and broader health system goals such as universal health coverage [4,6]. To improve health practitioner regulation, there is a need to better understand the breadth and depth of the evidence available to guide decision-making; identify knowledge gaps that exist; and examine the impacts and outcomes of regulation on practitioners, patients, and health systems.

Large-scale reviews conducted on the topic of health practitioner regulation provide a useful understanding of the current state of literature within a global context. For example, Browne et al [7] used a rapid evidence assessment to examine the international literature on health care and professional regulation. They found that the literature focuses on a variety of topics, including how regulators address harm prevention and patient safety, processes for addressing unprofessional conduct and complaints, ways that regulatory bodies address the quality of education and training, work related to the maintenance of registers, the development and impact of regulatory guidance, and the relationships between regulators and stakeholders. A recent large-scale international integrative review conducted by Leslie et al [4] explored the available evidence on the design, delivery, and effectiveness of health practitioner regulation to inform policy decisions. This review included many academic and grey literature sources and mapped the existing literature using a modified Donabedian framework that includes structures, processes, and outcomes.

Despite this body of scholarship, an overarching conclusion was that health practitioner regulation is a relatively underdeveloped field of academic study. Specifically, the existing evidence is diffuse, largely descriptive, and insufficient to support strong conclusions about the impact of different regulatory approaches, policies, and practices on patient safety, health workforce, and health system outcomes. Another important area of consideration is context, as regulatory schemes that work in one jurisdiction may not necessarily work in another given varied social, political, economic, and historical factors. As a result, more specific knowledge syntheses on health practitioner regulation at the profession or country level may be of particular use to guide decision-making and inform the development of policy and research agendas.

Our scan of Canadian nursing regulators' websites illustrates that key priorities include the modernization of governance structures, amalgamation of regulatory bodies, separation of professional associations and regulatory bodies, alignment of principles of "right-touch regulation," reduction of barriers to enable the integration of internationally educated nurses, and shifts in policy to enable the introduction of technology such as virtual care. In 2021, the National Council of State Boards of Nursing convened regulatory experts, including leaders of Canadian regulatory bodies, to create a global research agenda of nursing regulation. Stakeholders identified several research areas of interest, including labor mobility, regulation and governance, education, practice, continuing competency, discipline, and telehealth [8]. Although these priorities provide a blueprint for future research, there is first a need to fully understand the breadth and depth of available literature focused on nursing regulation in Canada.

A preliminary search on Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis database identified no current or in-progress systematic reviews or scoping reviews on this topic. Gaining a comprehensive understanding of the available evidence is critical for identifying knowledge gaps so that Canadian nursing stakeholders can invest their time and resources strategically to engage in high-impact research and knowledge development. To fill this gap, we chose to conduct a scoping review as our focus is on mapping the existing literature and providing an overview of evidence, concepts, and studies within the field of nursing regulation in Canada [9,10]. This protocol has been developed using the reporting guidelines in the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols) as they apply to scoping reviews [11] (see Multimedia Appendix 1).

Objectives and Review Questions

The overarching objective of this scoping review is to explore the breadth and depth of literature on nursing regulation in Canada. The research questions guiding our review are:

1. What is the nature, extent, and range of available scholarship informing nursing regulation within the Canadian context?
2. How does the extant scholarship align with emerging health practitioner regulation trends and what are the knowledge gaps that exist?

Methods

Design

We will conduct this scoping review in accordance with the JBI methodology for scoping reviews [12], drawing on Arksey and O'Malley's [13] initial framework, which has been further enhanced by Levac et al [14] and Peters et al [15]. Our review will be organized into the following 6 stages: (1) identifying the research question and aligning it with the review objectives; (2) identifying relevant studies using inclusion and exclusion criteria that are aligned with the research objective and questions; (3) selecting relevant studies using a planned approach to evidence searching, selection, data extraction, and

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the presentation of evidence; (4) using both descriptive statistics and qualitative content analysis to chart the data; (5) consulting subject matter experts in regulation through professional networks; and (6) collating, summarizing, and reporting the evidence.

Eligibility Criteria

Population

The population of interest includes Canadian nurses of all designations, including registered nurses, licensed practical nurses, registered psychiatric nurses, registered practical nurses (in Ontario), and nurse practitioners. Papers that discuss nursing regulation but focus more broadly on other regulated health professions (with no disaggregated data) will also be included to ensure the wide range of evidence and scholarship is captured.

Concept

The key concept of interest is professional regulation. We draw on the broad definition of professional regulation offered by Benton et al [2] (p. 307), where nursing regulation is defined as:

> *all those legitimate, appropriate and sustained means whereby order, identity, consistency, control and accountability are brought to practitioners through legally enforced, professional and/or voluntary action resulting in enhanced protection of the public, efficient and effective trans-jurisdictional movement, and the ongoing re-alignment of professional practice to patient and societal needs.*

We will include papers that focus on any of the core functions of regulation, including education program accreditation or approval, registration and licensure, standards of practice and code of conduct/ethics development and enforcement, continuing competence, and discipline and conduct, as well as papers regarding topics such as regulatory models, governance, trade and mobility agreements, and reform.

Context

The review will include all relevant literature on nursing regulation within Canada. We chose to focus on this country as the purpose of the review is to inform the development of a research agenda to strengthen professional nursing regulation in Canada.

Types of Sources

We will consider quantitative, mixed methods, and qualitative studies. Quantitative studies may include experimental and quasiexperimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies; analytical observational studies, including prospective and retrospective cohort studies; case-control studies; analytical cross-sectional studies; and descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies. Qualitative studies may include but are not limited to designs such as phenomenology, grounded theory, ethnography, qualitative description, interpretive description, action research, and feminist research. Systematic reviews will be excluded; however, reference lists will be screened for relevant studies. Discussion papers, commentaries, and opinion papers will also be considered for inclusion if they provide substantive exploration, examination, or critique of nursing regulation in Canada. We will search for grey literature such as policy documents and reports from the websites of Canadian organizations relevant to nursing regulation. Theses will be included given the potential for in-depth exploration of nursing regulatory issues. Books and unavailable articles will be excluded. See Multimedia Appendix 2 for the detailed inclusion and exclusion criteria.

Search Strategy

Our search strategy aims to locate both published and unpublished studies. A professional research librarian was consulted throughout the development of the search strategy. An initial limited search of Ovid MEDLINE was undertaken to identify articles on our review topic (see Multimedia Appendix 3). The search strategy, including all identified keywords and index terms, was adapted for each included database or information source. The databases searched include Ovid MEDLINE, Ovid EMBASE, CINAHL, Scopus, and Web of Science Core Collection (see Multimedia Appendix 4). We will screen the reference lists of all included articles to identify additional papers. Given our focus on identifying the nature, extent, and range of scholarship focused on nursing regulation in Canada, we will not place any limitations on the date of publication. Non-English papers will be excluded due to resource constraints. We will search for grey literature using the websites of Canadian nursing regulatory bodies, the Canadian Nurses Association, the Canadian Association of Schools of Nursing, the Canadian Nurses Protective Society, the Canadian Network of Agencies of Regulation, and newsletters and legal updates from law firms focused on professional regulation in Canada. Further, we will search the first 200 citations from Google Scholar.

Study/Source of Evidence Selection

Following the search, we will collate and upload all identified citations into Covidence, a review management software system [16], and remove duplicates. We chose to use Covidence for this purpose as it enables collaboration among multiple reviewers. Following a pilot test using 10% of the studies, titles and abstracts will be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full text. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for excluding sources during full-text review will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved by a third reviewer. Citations of included studies will be uploaded into Zotero, a reference manager software program. The results of the search and the selection process will be reported in full in the final scoping review, guided by the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Review) checklist [17].

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Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include the year of publication, type of publication, focus and or/aim of the paper, nursing designation, jurisdiction (eg, international, national, provincial, territorial), and key findings/concepts. We will group the focus or aim of each paper using the core regulatory functions of education program and accreditation, registration or licensure, standards of practice or code of ethics, continuing competence, discipline, and conduct. Given significant changes within the health professions regulatory landscape in Canada and the likelihood of scholarship on this topic, we will also group papers under categories such as governance, reform, regulatory models, and trade and mobility agreements. A draft extraction form is provided in Multimedia Appendix 5. The draft data extraction tool will be modified and revised as necessary during data extraction. We will pilot the extraction form using 10% of the included articles and resolve any discrepancies through discussion. Modifications from the protocol will be detailed in the scoping review. If appropriate and when required, authors of papers will be contacted to request missing or additional data. Critical appraisal of individual sources of evidence will not be completed as this is generally not required for scoping reviews.

Data Analysis

We will organize results using evidence tables to ensure the data are presented in a clear and structured format. We will use descriptive statistics to illustrate frequency counts and percentages for data such as year of publication, type of publication, areas of focus, type of nursing designations discussed, and jurisdictions of focus. Conventional content analysis will be used to identify and map the key purpose, aims, findings, and concepts within the included papers. Conventional content analysis [18] is an appropriate analytical method as it enables the development of broader categories based on coded data. A narrative summary will accompany the evidence tables and describe how the results relate to the review objective and questions. To ensure the overall reporting quality of this scoping review, reporting will follow the PRISMA-ScR guidelines. All retrieved records from the search strategy, included and excluded records from primary and secondary screening, and records retrieved from other sources will be reported using an adapted PRISMA flow diagram to enhance the reproducibility of this scoping review.

Results

This review was registered with the Open Science Framework on January 8, 2024. A preliminary search in Ovid MEDLINE was undertaken on December 7, 2023. After confirming the search terms, the medical librarian (JYK) performed a full search on March 15, 2024, in the Ovid MEDLINE, Ovid EMBASE, CINAHL, Scopus, and Web of Science Core Collection databases. A total of 1850 records were retrieved and when all duplicates were removed, 951 unique results remained for the initial title and abstract screening. We anticipate completing the scoping review in early 2025.

Discussion

Projected Significance and Contributions

Health practitioner regulation across Canada is changing rapidly, with legislative reforms occurring in several provinces giving rise to new regulatory and governance schemes. Notably, in British Columbia, the enactment of the Health Professions and Occupations Act in 2022—one of the most significant regulatory reforms in Canada's history—paved the way for a new regulatory scheme for health practitioner regulation within the province [19]. These changes have already influenced regulatory reform in other Canadian jurisdictions such as Nova Scotia, with Bill 323, An Act to Provide a Common Legislative Foundation for Regulated Health Professions [20]. Nursing regulation in particular has been thrust into the spotlight since the COVID-19 pandemic [21]. With the combination of vexing issues such as increasing public and government mistrust, labor market challenges, the introduction of new ways of working, and the explosion of digital technologies, nursing regulators continue to face pressures to modernize and reform their regulatory approaches to ensure they are fit for purpose and responsive to today's health system needs. The appointment of a federal chief nursing officer and growing political interest and investment in reforming nursing regulation [22] are strong determinants for continued change.

To our knowledge, this is the first scoping review that will examine the state of Canadian nursing regulation literature. We anticipate that the amount of evidence available to support regulatory decision-making will be relatively low. Given historical and contemporary health system trends and issues, we hypothesize that the majority of the literature will be focused on licensure and registration policies and practices for both Canadian and internationally educated nurses. Further, we anticipate that the majority of the literature will be situated in provinces with a larger population and nursing workforce. Having a comprehensive understanding of the existing body of work will provide a meaningful foundation to create a research agenda to inform the advancement of nursing regulation across Canada. We plan to disseminate our findings to our existing network of nursing regulation leaders through forums such as the Canadian Nurse Regulator Collaborative, conference presentations, and a peer-reviewed manuscript.

Strengths and Limitations

Given the purpose of the scoping review, the quality of the literature will not be assessed. Further, due to significant reforms across Canada and ongoing changes to regulators' websites, it may not be possible to capture all the relevant grey literature that has been produced. However, our comprehensive search strategy will provide a fulsome understanding of the nature, extent, and range of literature to identify research gaps and inform future areas of inquiry that can strengthen regulatory decision-making.

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Authors' Contributions

PC conceived the idea for this scoping review and developed the research questions, objectives, and inclusion criteria. PC, KL, and JYK contributed to the creation of the search strategy. PC and KL contributed to drafting and editing of the scoping review protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols) checklist.
[PDF File (Adobe PDF File), 128 KB - resprot_v13i1e56163_app1.pdf]

Multimedia Appendix 2
Inclusion/exclusion screening form.
[PDF File (Adobe PDF File), 40 KB - resprot_v13i1e56163_app2.pdf]

Multimedia Appendix 3
Ovid MEDLINE search strategy.
[PDF File (Adobe PDF File), 37 KB - resprot_v13i1e56163_app3.pdf]

Multimedia Appendix 4
Full search strategies.
[PDF File (Adobe PDF File), 77 KB - resprot_v13i1e56163_app4.pdf]

Multimedia Appendix 5
Data extraction instrument.
[PDF File (Adobe PDF File), 32 KB - resprot_v13i1e56163_app5.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols

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Protocol

Correlates of Mild Behavioral Impairment in Older Adults: Protocol for a Scoping Review

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Abstract

Background: Understanding mild behavioral impairment, a relatively recent notion in neuropsychological studies, provides significant insights into early behavioral indicators of cognitive decline and predicts the onset of dementia in older adults. Although the importance of understanding mild behavioral impairment is acknowledged, comprehensive reviews of its correlates with older adults are limited.

Objective: This scoping review aims to identify the impact of mild behavioral impairment on health outcomes in older adults and the factors associated with mild behavioral impairment.

Methods: The review will adhere to the Joanna Briggs Institute's methodological principles for scoping reviews. We will include studies focusing mainly on mild behavioral impairment in older adults, with the literature on this topic being limited to the period from 2003 to the present. Other clinical diagnoses, such as cognitive impairment, Parkinson disease, and multiple sclerosis, will not be included. We will use databases including PubMed (MEDLINE), CINAHL, Web of Science, Embase, PsycINFO, Cochrane, and Scopus for relevant articles published in English. Both gray literature and peer-reviewed articles will be considered during screening. Three independent reviewers will extract data using a predefined data extraction tool. Extracted data will be presented using tables, figures, and a narrative summary aligned with review questions, accompanied by an analysis of study characteristics and categorization of mild behavioral impairment correlates.

Results: The results will be presented as a descriptive summary, structured according to the associated factors related to mild behavioral impairment, and the health outcomes. Additionally, the data on study characteristics will be presented in tabular format. An exploratory search was conducted in July 2023 to establish a comprehensive search strategy, and iterative refinements to the scoping review protocol and formalization of methods were completed. A follow-up search is planned for May 2024, with the aim of submitting the findings for publication in peer-reviewed journals.

Conclusions: To our knowledge, this would be the first study to map the literature on the health-related factors and outcomes of mild behavioral impairment. The findings will support the development of interventions to prevent the occurrence of mild behavioral impairment and mitigate the negative outcomes of mild behavioral impairment.

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KEYWORDS

mild behavioral impairment; older adults; mild cognitive impairment; subjective cognitive decline; behavioral symptoms; scoping review; protocol; elderly; behavioral impairment; cognitive; cognitive decline; scoping review protocol; older adult; neuropsychological; impairment; behavioral; behavior

Introduction

As population aging continues to become an irreversible global trend, the prevalence of dementia is also expected to increase rapidly. The global prevalence of dementia in older adults is projected to double every 20 years, reaching 58 million in 2020, an anticipated 82 million in 2030, and 150 million in 2050 [1]. The financial cost of dementia was already substantial at US $ 818 billion in 2015 [2]. However, the recent COVID-19 pandemic has amplified the escalating costs of dementia care [3]. The economic impact of dementia extends beyond direct medical and social service expenses, such as treatment, medication, and social welfare, and encompasses indirect costs borne by caregivers and family members of older adults with dementia [4,5]. Caregivers often experience long-term stress, depression, anxiety, burnout, and physical health problems, which can limit their participation in economic activities, thereby amplifying the significant economic burden associated with dementia care [6,7]. The escalating health care burden presents a global social challenge that impacts not only the affected individuals but also families and communities, underscoring the urgent need for comprehensive strategies to address this pressing issue [8].

Although no cure for dementia currently exists, several studies have suggested that preventive interventions in the preclinical and prodromal stages can delay its onset and improve cognitive function by targeting modifiable risk factors [6,9]. The preclinical stage represents individuals who, despite not showing overt clinical signs of cognitive decline, have underlying dementia pathology. Meanwhile, those in the prodromal stage display evidence of clinical decline, demonstrated by subtle changes in cognition and short-term memory loss [10,11]. These stages have become focal points of recent research. Typically, the progression starts with normal cognition, transition into subjective cognitive decline (SCD)—a decrease in cognitive ability that is subjectively perceived compared to prior normal status but irrelevant to objective cognitive test results [12]—and eventually evolves into mild cognitive impairment (MCI), a condition characterized by a noticeable decline in cognitive abilities that does not interfere with daily functioning but increases the risk of Alzheimer disease or other types of dementia [13-15]. This transitional state of MCI poses a relatively high risk of progression to dementia, with some studies highlighting an estimated annual progression rate of approximately 10% [15-18]. However, not all cases of MCI inevitably progress to dementia [19]. The rate of return to normal cognition from MCI varies across studies, but one meta-analysis reports that approximately 24% of individuals with MCI revert to objectively normal cognition [20].

Recently, mild behavioral impairment (MBI), a neuropsychological syndrome that typically emerges later in life and can manifest across the entire predementia spectrum, has been introduced as a precursor to cognitive decline and dementia [21]. Prior to the development and implementation of preventive and supportive interventions for at-risk populations, it is essential to thoroughly understand MBI and its related factors that can influence multidimensional aspects of health in older adults.

According to the latest diagnostic guidelines published by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment, MBI is characterized by behavioral and personality changes persisting for at least 6 months from the initial onset [22]. These changes, including reduced motivation, impaired emotional regulation, deficiency in impulse control, and inappropriate social behavior, minimally impact interpersonal relationships and workplace performance [23]. Evidence suggests that older adults with SCD who experience MBI are more likely to develop dementia [23]. Moreover, when MBI is accompanied by functional deterioration in daily life, it can serve as a neuropsychiatric symptom and prognostic marker of dementia [21,24]. Therefore, exploring the health outcomes of MBI has significant implications for dementia prevention and prediction of its progression.

Since the diagnostic criteria for MBI were first introduced in 2003 [25,26], MBI has been studied over the past two decades as a predictor and prognostic marker of cognitive impairment and dementia [23,27]. During this period, significant strides were made toward the conceptual understanding of MBI and the development of tailored diagnostic tools offering consistent and reliable means of assessing MBI, such as the Neuropsychiatric Inventory Questionnaire (NPI-Q) and the MBI Checklist [28-30]. The MBI Checklist was validated in comparison with the NPI-Q [31]. Furthermore, diverse methodologies have been employed in MBI research, including family interviews [32], neuropsychological tests [33], and imaging and cerebrospinal fluid diagnostic tests to identify MBI [34]. Several studies have also scrutinized differences in MBI manifestations according to sociodemographic characteristics [30,35] and have examined correlations between biomarkers [36], specific diseases, and MBI [37] as well as the impact of MBI on the progression from MCI to dementia [33,38].

However, as MBI is a relatively recent neurobehavioral concept, the literature lacks a comprehensive review addressing the correlates of MBI in older adults, apart from one meta-analysis on pathological and genetic relationships with MBI prevalence [39]. Given the potential insights into predicting and preventing dementia and assessing the risk of transition to this condition, a thorough review of the physiological, psychological, and social factors associated with the development and progression of MBI, as well as their influence on the relationship between MBI and other health outcomes, is crucial. Therefore, this scoping review aims to provide an overview of MBI and its correlates among older adults. Mapping evidence of factors correlated with MBI will guide the development of targeted preventative and supportive interventions for at-risk populations, laying the

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groundwork for interventions to promote preventive measures and improve self-management. This will also provide valuable insights for health care providers, enabling them to facilitate awareness and early detection of MBI. This, in turn, can lead to improved patient care and health outcomes. Furthermore, it underscores the importance of addressing behavioral symptoms later in life, and it advocates for targeted patient-centered clinical intervention and nursing care for older adults. The specific research questions are as follows:

1. What are the health outcomes associated with MBI in older adults?
2. What are the identified factors associated with MBI in older adults, and how have they been reported to be related to MBI?
3. What are the research trends in MBI, and what are the limitations and knowledge gaps in the existing studies?

Methods

Study Design

To identify the impact of MBI on health outcomes in older adults and factors associated with MBI, we seek to conduct a scoping review, which is the most suitable method for mapping evidence on this topic. This review follows the Joanna Briggs Institute's methodology for scoping reviews [40] and reports the results according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [41]. An exploratory search took place in July 2023 to construct the full search strategy, yielding preliminary results. An update is scheduled for May 2024.

Ethical Considerations

As this is a review of published and gray literature, ethical approval from a human research committee is not required.

Search Methods

Sources of Evidence

This review will consider observational (including prospective and retrospective cohort studies, analytical cross-sectional studies, and case-control studies), experimental (including randomized and nonrandomized controlled trials), and qualitative studies for inclusion. We will include papers published in English from 2003 to date. Given that most previous research on MBI has been conducted in English, prioritizing English-language publications ensures consistency in terminology, which is critical for the search strategy and inclusion criteria and allows for interpreting and summarizing the impact of MBI on health outcomes accurately in accordance with international standards. Additionally, restricting the review to English-language publications minimizes the risk of variability and potential bias, allowing little impact on the overall integrity and conclusions of the review [42,43]. Books, editorials, commentaries, and letters will be excluded. However, we will include gray literature sources, such as reports, working papers, policy literature, government documents, and newsletters for a more comprehensive review.

Search Strategy

The search strategy will adhere to the PRISMA-ScR checklist [41]. Joanna Briggs Institute's 3-step search strategy will be followed to ensure a comprehensive search. First, we will search MEDLINE and CINAHL to identify keywords and indexing terms in the titles and abstracts of potential articles that will be included in the review. This initial search will inform the development of the final search strategy. Second, these identified keywords and indexing terms will be used to search all the included databases. In other words, terms from the titles and abstracts of relevant articles, along with the indexing terms used to describe these articles, will be used to develop a comprehensive search strategy for multiple databases, specifically PubMed (MEDLINE), CINAHL, Web of Science, Embase, PsycINFO, Cochrane, and Scopus. After establishing a search formula using the appropriate subject words and consistent keywords in each database, the search formulae will be reviewed by a professional librarian at the university's medical library. Tables S1–S7 in Multimedia Appendix 1 present the search strategy for each database. Third, after conducting the search using the previous strategies, we will analyze the bibliographies of the studies selected after the final search to identify relevant papers that may not be captured during the initial search. Our search strategy encompasses peer-reviewed published literature as well as gray literature, including doctoral dissertations to ensure comprehensive coverage.

Information Sources

The following databases will be searched: PubMed (MEDLINE), CINAHL, Web of Science, Embase, PsycINFO, Cochrane, and Scopus. During the search process, we may discover other potentially useful information sources and terms that will be incorporated into the review. To ensure completeness, we will contact the original authors of the studies to further clarify this information, if necessary. As scoping reviews primarily aim to map evidence rather than synthesize findings, we will not evaluate the methodological quality of the included sources of evidence.

Inclusion and Exclusion Criteria

Population or Participants

This scoping review will include studies on older adults in the preclinical or prodromal stages of the dementia continuum, encompassing normal stages of SCD or MCI. Due to varying age thresholds for older adults in different studies, our review will adopt a broad approach, incorporating all studies that classify their population as "older adults" based on each study's criteria. The term "older" refers to a specific group of adults who are chronologically older within the larger population of adults. The term has been broadly defined to include all studies that focus on recruiting older adults based on their criteria, such as being 60 years and older. Furthermore, the definition of older adults varies among countries, as diverse age standards exist for defining this population, according to the World Health Organization [44]. The diagnostic criteria for SCD and MCI adhere to the criteria established in each study.

Considering the challenges of identifying early SCD without solid empirical data, our search criteria will also encompass

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older adults who have not obtained a definitive diagnosis. This means including those diagnosed with normal cognition at the time of the study, essentially expanding our focus to include individuals on the threshold of cognitive decline. Studies on older individuals with other clinical diagnoses that can result in cognitive decline as one of its symptoms, such as dementia, Parkinson disease, or multiple sclerosis, will be excluded. However, to enhance the comprehensiveness of our review, we will include studies that conducted supplementary analyses, wherein patients with dementia were subsequently excluded, despite their initial inclusion within the subject groups.

Concept

MBI is the key concept in this review. We will include literature published from 2003 onwards, as the diagnostic criteria for MBI were first presented in 2003 in an academic journal [25,26].

Context

To thoroughly investigate the research questions related to MBI, there will be no restrictions on the study contexts or settings. A wide range of contexts will be considered eligible, including acute care, long-term care, and community-based environments.

Study Selection

All identified citations will be collated and uploaded to EndNote 20 (Clarivate Analytics), and the duplicates will be removed following the search. The titles and abstracts will be screened by 3 independent reviewers to assess the inclusion criteria. Prior to embarking on source selection, pilot testing for the title and abstract screening will be undertaken to refine the inclusion/exclusion criteria and validate the reviewers' screening process using a randomly selected sample of 50 titles and abstracts. Thereafter, the full texts of potentially relevant sources will be retrieved. The full texts of the selected articles will be assessed in detail against the inclusion criteria by 3 independent reviewers. This review will report the reasons for excluding sources that fail to meet the predetermined inclusion criteria. Any disagreements between the reviewers during any stage of the selection process will be resolved by involving an additional reviewer or through discussion. The final scoping review will include a comprehensive report on the search results and the process of study inclusion, along with a presentation of the findings using a flowchart based on PRISMA-ScR [41].

Data Extraction

Three independent reviewers will utilize the data extraction tool, as presented in Multimedia Appendix 2. The extracted data will encompass specific participant details, concepts, contexts, study methods, and the main findings relevant to the review questions. The preliminary data extraction tool will be adjusted and refined throughout the data extraction process for each source, as required. These modifications will be documented in the final review. In the event of any discrepancies between the reviewers, we will resolve them through discussion or by consulting an additional reviewer. If necessary, the authors of the selected studies will be contacted to obtain any missing or supplementary data.

Data Synthesis

The extracted data will be presented using tables and figures to address the review questions. Tables will be constructed to illustrate the classification of MBI correlates, with comprehensive descriptions of health outcomes (research question 1), related factors (research question 2), and critical assessment of research limitations (research question 3). Additionally, a narrative summary will discuss how the results correspond to the objectives and questions of the review. During the discussion of results, we will analyze the characteristics of the selected studies and categorize MBI correlates according to their subgroups. The methods for presenting the results may be further refined during the review process, with details provided in the final review.

Results

An exploratory search was conducted in July 2023, and a comprehensive search strategy was formulated based on the preliminary results. We reviewed studies on MCI and SCD in older adults in the exploratory search and recognized the difficulty in detecting early SCD without substantial empirical data in individuals diagnosed with normal cognition at the study's inception. Therefore, as noted in the *Methods* section, we broadened our review scope to include studies of older adults across the spectrum from normal cognition to MCI, refining our search strategy with a librarian's assistance. Iterative refinements to the scoping review protocol and formalization of methods were completed. A subsequent search is scheduled for May 2024, with the objective of submitting the results for publication in peer-reviewed journals.

Discussion

Expected Findings

This study introduces a protocol outlining a scoping review designed to address specific research questions regarding the correlates of MBI. The main findings of the review will identify key physiological, psychological, and social factors associated with MBI in older adults. Previous research has largely focused on the prevalence or individual domains of MBI, but this review will fill a significant gap in the literature, providing a broader understanding of how various factors contribute to MBI and the diverse ways MBI can impact health outcomes; to the best of our knowledge, such a review has not yet been conducted.

Strengths and Limitations

Our review will provide a timely and valuable contribution, encompassing evidence from various fields and methodological approaches and focusing on the physiological, psychological, and social factors associated with MBI in older adults. Understanding these factors and their influence on the relationship between MBI and health outcomes is crucial for proposing preventive measures and improving self-management strategies for person-centered intervention. This review will also contribute to the development of targeted preventive and supportive interventions aimed at alleviating the influence of MBI on health outcomes in older adults. Since this review will comprehensively map the correlates of MBI rather than

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measuring effectiveness, it will not perform a quality appraisal. Additionally, since non-English literature will not be included, some relevant studies may be missed which will reduce the generalizability of the findings. However, to increase the identification of eligible studies, we selected seven databases, including databases for gray literature, and developed appropriate search strategies.

Conclusions

This study will provide significant insights into the health-related factors and outcomes of MBI. Finally, it will lay the groundwork for policy development, fostering a broader social understanding of MBI, which can be a crucial focal point for future interventions targeting the at-risk group for dementia. Our knowledge dissemination strategy will employ various approaches, including peer-reviewed journals, webinars, and conference presentations. Collaborating with national research networks will extend our reach and inform policy, practice, and research. Recognizing the necessity for detailed dissemination plans, we will enhance our strategy by outlining specific channels to share our findings with academic communities, policy makers, and practitioners.

Acknowledgments

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Authors' Contributions

BK, SY, and IJ contributed to the study concept and design; all authors contributed to the methodology, drafted the manuscript, and participated in the manuscript revision; they all read and approved the final manuscript. Subsequently, the final manuscript underwent a comprehensive review and received unanimous approval from all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 30 KB - resprot_v13i1e60009_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 16 KB - resprot_v13i1e60009_app2.docx]

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Abbreviations

MBI: mild behavioral impairment
MCI: mild cognitive impairment
NPI-Q: Neuropsychiatric Inventory Questionnaire
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SCD: subjective cognitive decline

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Protocol

Socioemotional Skills in the Teaching-Learning Process Mediated by Medium- and High-Fidelity Clinical Simulation in Nursing Students: Protocol for a Scoping Review

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Abstract

Background: In nursing education, contact with real scenarios implies the design of favorable experiences to develop prioritization, reasoning, critical thinking, and management skills that support future practice. In the context of the teaching-learning process, simulation emerges as a support strategy, but its use and management require the knowledge and appropriation of teachers. Clinical simulation during education promotes growth in technical skills and aptitudes such as critical thinking, emotional management, organization, delegation, and teamwork. The culmination positively impacts the student, reflecting on their confidence, security, and adaptability to unexpected or unknown situations and risks.

Objective: The aim of this scoping review is to determine the socioemotional skills described during the teaching-learning process mediated by medium- and high-fidelity clinical simulation in nursing students.

Methods: The main concepts and limits of the research area will be determined according to the 5 phases of a scoping review proposed by Arksey and O'Malley. Research articles and postgraduate theses published between 2010 and 2023 in English and Spanish will be considered. Dissertation-type documents, book chapters, editorials, abstracts, and articles focused on clinical simulation among nursing professionals will be excluded. The articles will be retrieved from databases available at the Universidad Cooperativa de Colombia, along with CINAHL, Scielo, and PubMed. The search strategy will be based on the Population-Concept-Context framework. Article selection will be carried out by 2 independent evaluators who will review titles and abstracts in stage 1 and the full text in stage 2. A database of retrieved articles will be built with the variables of interest. A qualitative thematic analysis will be conducted by 5 independent reviewers to provide an overview of the literature, focusing on identifying similarities and contrasts between studies and contributions related to the aspects of social skills described in nursing students.

Results: The investigation has not yet started. The findings aim to focus on variables within the academic environment that, when correlated with the clinical simulation experience, may determine student learning. The working hypothesis is that students who experience greater satisfaction or possess better communication skills also demonstrate superior performance during high-fidelity simulation activities. The most relevant results will be contrasted considering the stated objective and knowledge gaps. Key aspects will also be compared with other reviews addressing related topics such as communication, self-efficacy, and self-confidence. Skills described by other authors that were not considered in the initial literature review will also be mentioned.

Conclusions: Educational institutions are responsible for including learning experiences in controlled environments such as medium- and high-fidelity simulation to ensure the acquisition of technical capabilities and additional socioemotional skills. Recognizing and managing emotions is necessary to provide adequate care for users of health care services and for the increased effectiveness of professionals.

Trial Registration: Open Science Framework p4ays; https://osf.io/p4ays

International Registered Report Identifier (IRRID): PRR1-10.2196/56436

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(JMIR Res Protoc 2024;13:e56436) doi:10.2196/56436

KEYWORDS

social skills; nursing students; high-fidelity simulation training

Introduction

In the context of the teaching-learning process, simulation emerges as a support strategy; however, the use and management of simulators require the knowledge and appropriation of teachers [1]. Simulation is how a trained teacher creates scenarios to promote autonomous, collaborative learning along with critical and reflective thinking [2]. In turn, the mediator can formulate professional skills that respond to the needs of the context [3]. A requirement for this type of simulation is that teachers are trained in a pedagogical strategy for practice in the development of a model of enhancing competencies and clinical judgment in nursing [4].

Medium- and high-fidelity simulation has been used in nursing education. These scenarios reflect environments such as a hospital room, surgery room, or intensive care unit. Typically, a life-sized mannequin is used, which is connected to a computer system that simulates physiological variables such as vital signs, heart sounds, and respiratory sounds. The proposed cases can vary in complexity and aim for students to experience a situation similar to reality and acquire appropriate technical skills [5].

The implementation of this methodology among nursing students is supported by the use of technology for the training of facts and concepts, critical thinking, decision-making, and reasoning skills, which is then used to assess the progress of skills competencies and care interventions [6]. In this way, safe environments are generated that enable caring for a patient in a real situation, thus developing autonomous learning. Therefore, the main purpose of clinical simulation is to learn from significant experiences that allow building knowledge, representing a teaching-learning strategy that reflects the clinical practice environment, and finally offers the opportunity for evaluation of the training [7].

In nursing education, contact with real scenarios necessitates the design of favorable experiences to develop prioritization, reasoning, critical thinking, and management skills that support future practice [8]. Clinical simulation during education promotes technical skills and aptitudes, critical thinking, emotional management, organization, delegation, and teamwork, which has a positive impact on the student, reflecting on confidence, security, reaction to unexpected or unknown situations, and risk [9,10].

Barra and Calisto-Alegría [11] mentioned that simulation favors procedural skills through practice and repetition. They identified anxiety and shortcomings in the inputs, recommending methodological and didactic aspects in curricular proposals [11]. In addition, establishing socioemotional competencies of future nursing professionals will influence the quality of care, along with academic and effective performance via training, and improvement through clinical simulation is a favorable methodology for learning and evaluating socioemotional skills [12].

Understanding the patterns of communication in simulated situations in education is relevant as it generates trust in the clinical environment, which can in turn increase the efficiency of education in the processes of interaction with peers and patients [13].

Similarly, it is important to highlight the empathy that is required in nursing care, which is an art and the ethical center of the act of caring. The nurse is not exclusively limited to operational tasks, as nursing requires the establishment of interpersonal relationships with patients; therefore, communication and empathy are complementary to the knowledge and procedural skills necessary for an optimal condition of care. Through deliberate practice in simulation, one can effectively promote and improve the effectiveness of communication skills as well as the empathy and self-efficacy of students [14-16].

The aim of this study is to help identify the response patterns of teaching and learning methods or strategies. These patterns are manifested as emotional effects of students in a clinical simulation environment, which can cause tension, anxiety, and stress in students when facing nursing practices [17]. Toward this end, we will perform a scoping review to determine the socioemotional skills described during the teaching-learning process mediated by medium- and high-fidelity clinical simulation among nursing students.

Methods

Study Design and Registration

A scoping review will be carried out, which involves establishing the main concepts and their limits of a given area of research interest [18]. This study considers publications on the teaching-learning process for nursing in clinical simulation, high- and medium-fidelity simulation guides, and drug administration processes. The 5 phases proposed by Arksey and O'Malley [19] will be followed to carry out the review: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting results.

This study represents the largest such investigation conducted as of January 2023 when the protocol was registered on the Open Science Framework under the identifier p4ays.

Eligibility Criteria

Full-text articles published on the central theme of the study, including postgraduate theses, studies using different quantitative methodologies, mixed methods studies, and systematic reviews, will be eligible for inclusion in the review. Articles published from 2010 to 2024 involving nursing student populations will be considered eligible. In addition, articles written in English and Spanish are considered. Dissertation-type documents, book chapters, editorials, abstracts, and articles focused on clinical simulation in nursing professionals will be excluded.

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Information Sources

The databases available at the Universidad Cooperativa de Colombia (OVID Medicina y Enfermería, Science Direct, Sage Journals, Proquest Psychology Database, Proquest Social Science Database, Proquest UK & Ireland Database, Psycarticles, Redalyc, and Dialnet) and databases such as CINAHL, Scielo, and PubMed will be searched for relevant articles.

Search Strategy

The Population (or Participants)-Concept-Context framework recommended by the Joanna Briggs Institute [19] will be followed to identify the main concepts to orient the search strategy, which are summarized in Textbox 1.

Textbox 1. Population-Concept-Context framework of the study.

Population

Nursing students

Concept

The personal set of abilities required to successfully interact and communicate with others, both verbally and nonverbally through gestures, body language, and personal appearance

Context

The teaching-learning process mediated by medium- and high-fidelity clinical simulation

To achieve standardization of search terms, the article's keywords will be selected from the Descritores em Ciências da Saúde (DeCS) website for the descriptors in Spanish [20] and from Medical Subject Headings (MeSH) for the descriptors in English [21], which are presented in Table 1.

Table 1. Standardized search terms.

Spanish terms	English terms	Definition
Enseñanza mediante simulación de alta fidelidad	High-fidelity simulation training	A controlled learning environment that closely represents reality
Estudiantes de enfermería (synonyms: alumnos de enfermería, estudiante de enfermería)	Nursing students (synonyms: pupil nurses, pupil nurse)	Individuals enrolled in a school of nursing or a formal educational program leading to a degree in nursing
Entrenamiento simulado	Simulation training (synonym: interactive learning)	A highly customized interactive medium or program that allows individuals to learn and practice real-world activities in an accurate, realistic, safe, and secure environment
Modelos educacionales comunicación en salud	Educational model (synonyms: instructional models, instructional model, educational model)	Theoretical models that propose methods of learning or teaching as a basis or adjunct to changes in attitude or behavior. These educational interventions are usually applied in the fields of health and patient education but are not restricted to patient care
Comunicación en salud (synonyms: información y comunicación en salud, información y comunicación en la salud)	Health communication (synonym: health communications)	The transfer of information from experts in the medical and public health fields to patients and the public; the study and use of communication strategies to inform and influence individual and community decisions that enhance health
Habilidades sociales (synonym: habilidades socioemocionales)	Social skill (synonyms: social skills, social abilities, social ability, interpersonal skills, interpersonal skill, social competence)	The personal set of abilities required to successfully interact and communicate with others, both verbally and nonverbally through gestures, body language, and personal appearance

Selection of Sources of Evidence

The search will begin in the databases available in the university library and then the literature review will be expanded to other open access databases. The compilation will be carried out in two stages.

The first stage involves title and abstract selection, which will be carried out by 2 reviewers independently considering the inclusion exclusion criteria. In this first stage, the selected keywords will be put to the test to verify that the articles that respond to the proposed theme are adequately recovered with these terms.

In the second stage, the full text of the articles selected in the first phase will be read by 2 reviewers independently and then the results obtained will be contrasted. Any disagreement between the 2 reviewers will be resolved by a third reviewer.

Data Charting Process

The extracted data will be organized in a Microsoft Excel spreadsheet, including the following aspects: title, bibliographic source, objective of the study, country of origin, type of study, design, evaluated social skills, simulation scenario, and level of the students.

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Subsequently, a qualitative thematic analysis will be performed by 5 independent reviewers to offer an overview of the literature with the aim of identifying similarities, contrasts among authors, and contributions in the aspects of social skills described in nursing students. Because this is a scoping review, it will encompass many types of evidence and therefore it is not considered pertinent to apply bias control to the sources of information or the results of individual studies [22].

Synthesis of Results

The characteristics of the selected articles related to socioemotional skills mediated by clinical simulation as part of the teaching-learning process for nursing education will be described in detail. The data will be presented using summary tables and grouped figures.

Ethical Considerations

In accordance with current international regulations [23,24], this project does not require approval from an ethics committee, as the research does not involve the collection of new data from humans, does not present any risks to participants, and is based on the analysis of secondary data from previously published research.

Results

Selection of Sources of Evidence

The article selection process will be summarized using a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart [22], as shown in Figure 1.

Figure 1. Example PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart for study inclusion.

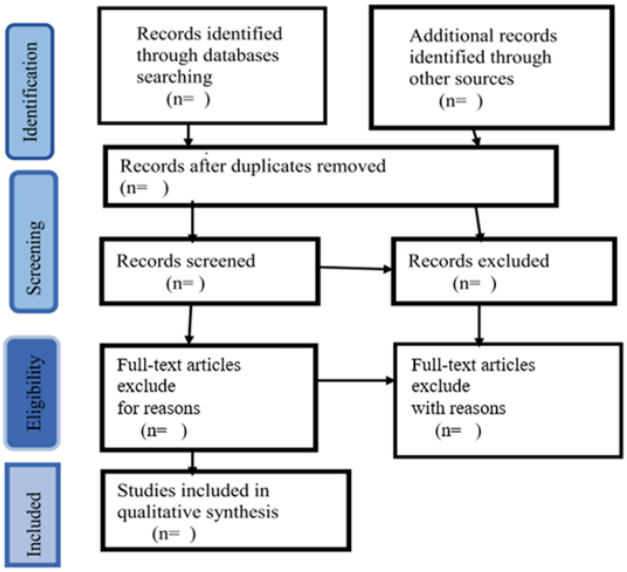

Characteristics of Sources of Evidence

A table will be developed to summarize the main characteristics of the selected articles for the research objective, including the country where the study was conducted, design, and identified communication skills. The findings of this scoping review aim to focus on variables within the academic environment that, when related with the clinical simulation experience, may determine the outcomes of student learning. The working hypothesis posited is that students who experience greater satisfaction or possess better communication skills will also demonstrate superior performance during high-fidelity simulation activities.

Synthesis of Results

We will use a narrative approach for data extraction, including descriptions of author characteristics, year of publication, study design, objective, sample size, country, level of education, type of clinical simulation, and categorization by themes. The purpose is to consolidate knowledge about the study phenomenon. Toward this end, the 5 reviewers will apply criteria for critical reading to evaluate the evidence [25]. In case of any disagreement regarding theme categorization, resolution will be achieved through consensus among the reviewers.

Discussion

Summary of Evidence

Medium- and high-fidelity clinical simulation is a learning tool for technical capabilities and generates response patterns in students that can influence the acquisition of the socioemotional skills necessary for the adequate performance of nursing students in the real environment [26]. Social skills influence the academic and clinical performance of the student in training, complementing preparation for real-world scenarios.

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We predict identifying a relationship between exposure to clinical simulation and the improvement of skills such as communication, self-confidence, and problem-solving, along with an increase in satisfaction perception.

The most relevant results will be contrasted considering the stated objective and knowledge gaps. Key aspects will also be compared with other reviews addressing related topics such as communication, self-efficacy, and self-confidence. Skills described by other authors that were not considered in the initial literature review will also be mentioned.

Limitations

Limitations related to the omission of gray literature or documents written in languages other than Spanish and English will be discussed, and recommendations for conducting future research will be proposed.

The main limitation is the lack of evaluation of the quality of the articles that will be selected; however, Arskey and O'Malley [18] specify that a scoping review does not aim to assess the quality of the evidence but rather to answer the research question. Additionally, there are limited studies on medium- and high-fidelity clinical simulation in nursing students available to date.

Conclusions

In accordance with the findings, the most significant results will be outlined. Providing adequate nursing care involves knowledge of equipment, advanced health care practices, and advanced technical capabilities. Educational institutions are responsible for including learning experiences in controlled environments such as medium- and high-fidelity simulation to ensure the acquisition of technical capabilities as well as socioemotional skills. Recognizing and managing emotions is necessary to provide adequate care for users of health care services and for the increased effectiveness of professionals.

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Authors' Contributions

All authors participated in the initial idea of the project, protocol design, and search strategy. MLVO, ELJ, and LMCR drafted the protocol. All authors contributed to the review, correction, and approval of the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DeCS: Descriptores en Ciencias de la Salud
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Surgical Residents' Perception of Feedback on Their Education: Protocol for a Scoping Review

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Abstract

Background: Feedback is an essential tool for learning and improving performance in any sphere of education, including training of resident physicians. The learner's perception of the feedback they receive is extremely relevant to their learning progress, which must aim at providing qualified care for patients. Studies pertinent to the matter differ substantially with respect to methodology, population, context, and objective, which makes it even more difficult to achieve a clear understanding of the topic. A scoping review on this theme will unequivocally enhance and organize what is already known.

Objective: The aim of this study is to identify and map out data from studies that report surgical residents' perception of the feedback received during their education.

Methods: The review will consider studies on the feedback perception of resident physicians of any surgical specialty and age group, attending any year of residency, regardless of the type of feedback given and the way the perceptions were measured. Primary studies published in English, Spanish, and Portuguese since 2017 will be considered. The search will be carried out in 6 databases and reference lists will also be searched for additional studies. Duplicates will be removed, and 2 independent reviewers will screen the selected studies' titles, abstracts, and full texts. Data extraction will be performed through a tool developed by the researchers. Descriptive statistics and qualitative analysis (content analysis) will be used to analyze the data. A summary of the results will be presented in the form of diagrams, narratives, and tables.

Results: The findings of this scoping review were submitted to an indexed journal in July 2024, currently awaiting reviewer approval. The search was executed on March 15, 2024, and resulted in 588 articles. After the exclusion of the duplicate articles and those that did not meet the eligibility criteria as well as the inclusion of articles through a manual search, 13 articles were included in the review.

Conclusions: Conducting a scoping review is the best way to map what is known about a subject. By focusing on the feedback perception more than the feedback itself, the results of this study will surely contribute to gaining a deeper understanding of how to proceed to enhance internal feedback and surgical residents' learning progress.

Trial Registration: Open Science Framework yexb; https://osf.io/yexkb.

International Registered Report Identifier (IRRID): PRR1-10.2196/56727

(JMIR Res Protoc 2024;13:e56727) doi:10.2196/56727

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KEYWORDS

medical education; occupational training; surgical residents; feedback; perception

Introduction

Background

Feedback is the delivery of information based on direct observation [1] that must always generate an action in the learner [2]. Feedback constitutes specific information about the comparison between learners' performance or knowledge regarding a task and the desired standard, with the objective of learners seeking to improve their performance and reduce the distance between the ideal and the real [3]. In other words, feedback is a process in which learners acquire knowledge about their performance and use it to improve the quality of their work or learning strategies [4].

Thus, feedback is an essential tool for learning and improving performance in any sphere of education, especially in medical education and surgery [5-8]. Although the mechanism is not fully known, feedback represents an important part of the resident physician's training [9], which focuses on the goal of providing qualified care for patients [1,10]. For this reason, the delivery of feedback to residents continues to be an important area of study in medical teaching [5,11].

There are different ways of giving feedback to learners: orally, in writing, through simulation, by videotaping learners, using audience response systems, and via computer-based and patient feedback tools, among others [6,11-13]. Likewise, many methodologies concerning the delivery of feedback have been described, including a feedback sandwich, Pendleton, Pendleton Plus, learning conversation, in groups, among peers, multisource feedback, and self-feedback [7,14-16]. However, independent of the approach, all modes of feedback must focus on the following 3 learning domains: cognitive, psychomotor, and affective [17].

The large number of methodologies in this field reflects the former paradigm related to feedback, where the key research question was "How can we develop the best feedback?" Accordingly, studies in this field traditionally focused on the quality of the information to be transmitted, how to transmit such information, and what would be the best moment to transmit the information [10]. However, the paradigm has since changed, with the crucial question to answer shifting to "How do learners become attentive to feedback and use the information they receive more effectively?" [18]. Thus, the priority has become the progress achieved in learning and the learner's engagement in the process enabled by the feedback, which is encompassed by the term "feedforward" [16]. Recent studies on the subject have largely focused on this path [2,7,10,15,19].

Therefore, how the feedback is perceived and the reaction it generates in the learner is as important (or even more important) as the methodology that is used, the moment when it is given, or the information that is provided. Studies have shown that medical students and residents consider that the amount of feedback they receive is insufficient [11,12,20]. Furthermore, they often have a different perception of the feedback received compared to that of the person delivering the feedback [3,9,18,19], although some studies have shown that residents and teachers can share similar opinions concerning the qualities of effective feedback [10]. Feedback is considered effective when it can generate results and promote positive and desirable development [3]. Some factors that reportedly influence the perception of feedback include the teacher's credibility in the opinion of the learner, who is responsible for giving feedback when the teams are multidisciplinary, the manner and the environment in which feedback is given, the teacher's educational beliefs, the learner's individual experiences, the learner's level of expectation and motivation, and the relationship between feedback and the reflection it generates in the learner [5,7,11,15,21,22].

In opposition to active (or external) feedback, in which the teacher has a primordial role in the learning process, the reflection that the feedback generates in the learner (or internal feedback) enables the learner to go through stages of the competence awareness theory [23], developing a metacognitive learning process, a step that is inseparable from the intentional learning process [3]. That is, the learner's perception of the feedback they receive is extremely relevant to their learning progress. Moreover, the incorporation of metacognitive aspects in the learning process equips the student with skills to become a lifelong learner [24].

Prior Work

Surgical residents recognize that feedback provides useful suggestions for future improvement, and the lack of feedback can cause frustration [25] or affect self-confidence [26]. They prefer to receive feedback during or immediately after a case, in a face-to-face manner, and value the feedback much more when received within 1 week of the event [27]. However, both resident and staff surgeons agree that postoperative feedback is given far less often than needed [28]. Moreover, surgical residents desire better feedback during residency to grow and develop as leaders [29].

Nevertheless, the studies pertinent to this topic differ substantially with respect to methodology, population, context, and objective, which makes it even more difficult to achieve a clear understanding of the issue. Among all knowledge synthesis methodologies, scoping reviews are considered to be the best way to present a broad overview of evidence in heterogeneous scenarios, summarizing and promoting better comprehension of a field [30-32]. In addition, despite the relevance of the theme, in a preliminary search, few scoping reviews were found on this topic. Although all of these scoping reviews focused on surgery residents' training in some manner [33-35], none focused on their feedback perception during and after their training. Therefore, it is evident that a scoping review on this theme would have an unequivocal contribution to the understanding and enhancement of surgical residents' learning progress.

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Study Aim

The aim of this scoping review is to identify and map out data from studies that report surgical residents' perception of the feedback received during their education, analyze these themes, determine knowledge gaps, and disseminate the research findings.

Methods

Design

This scoping review will be carried out rigorously and transparently using the first 5 stages of the structure proposed by Arksey and O'Malley's [36]: (1) identify the research question; (2) identify relevant studies; (3) select studies; (4) map out the data; and (5) collate, summarize, and report the results. As this is an emerging field, more studies on the theme will likely be finalized. Although the 6th stage of Arksey and O'Malley's [36] structure (consulting) will not be completed in this review, the results of the review can inform this stage in a future study. This structure is congruent with the Joanna Briggs Institute's (JBI) scoping review methodology [32].

Research Question

The research question was elaborated according to the objective of the review and through the Population, Concept, Context model, with the population including resident physicians of any surgical specialty under the concept of feedback perception in the context of surgical education. Therefore, the following research question was established: "What is known about surgical residents' perception of feedback in their training?"

Inclusion Criteria

The main eligibility criteria to include articles in the study are those including a population comprising resident physicians of any surgical specialty and age group who were attending any year of residency. Studies assessing the target population's perception of feedback will be included, regardless of the type of feedback given and the way the perceptions were measured. Eligible studies will be those related to the teaching of the population in question, focusing on surgical education in any country. The following types of articles will be included in the review: studies with qualitative and quantitative approaches, primary studies, systematic reviews, meta-analyses and/or meta-syntheses, books, and guidelines published in indexed sources.

Exclusion Criteria

Any studies not meeting the eligibility criteria, not published in indexed sources; and publications of opinions, consensuses, retractions, editorials, websites, and advertisements published in the media will be excluded from the review.

Search Strategy

The search strategy will be determined by a librarian who is a specialist in digital search strategies based on the following descriptors: formative feedback, hospital medical staff, teaching, general surgery, and perception, with their corresponding terms in the Portuguese and Spanish languages, encompassing the period from 2017 to the search date. For the combination of descriptors, the Boolean operators "AND," "OR," and "NOT" will be considered. The full search strategy that will be used is detailed in Multimedia Appendix 1.

We will consult the databases of journals indexed in Medline, Directory of Open Access Journals, Directory of Open Access Scholarly Resources, Academic Search Premier, BioMed Central Open Access, and Wiley-Blackwell, using the descriptors and/or synonyms according to *Descritores em Ciências da Saúde* (Health Science Descriptors) and Medical Subject Headings for each item of the strategy. These databases were selected because they are comprehensive and have broad coverage of publications in the area of health. The choice of databases will depend on the research question.

Study/Source of Evidence Selection

Duplicate articles will be excluded manually. For the remaining articles, titles and abstracts will be analyzed by 2 independent reviewers to select those that meet the inclusion criteria. Articles that do not meet the eligibility criteria described above will be excluded. In case of divergence, a third reviewer will be consulted and will give the final opinion about the relevance of the article for answering the main research question. Additional sources can be included in the review after a manual search performed by the reviewers, as long as they meet the eligibility criteria, are important to complete the study, and have not already been identified by the search strategy.

To align the inclusion criteria among the reviewers, the titles and abstracts of 25 random articles will be analyzed by 3 researchers. Disagreements regarding the inclusion or exclusion of the articles will be discussed until a consensus is reached.

The complete texts of the selected articles will be evaluated by the main researcher (CDdSC) based on the inclusion criteria. The reasons for the exclusion of articles that have undergone full-text review will be registered and reported in the scoping review report. Any disagreement that emerges among the researchers at any stage of the selection process will be solved through discussion or the addition of other researchers. A PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram [36-39] will be used to present, in full, the results of the process of search and inclusion of studies in the scoping review.

Data Extraction

After article selection, the main researcher (CDdSC) will create a form for data extraction, which will be filled in after reading of the full text of the article. The extracted data will include specific details about participants, concept, context, and methods of study, as well as key information related to the research question, such as the method and model of feedback delivery, the strategy used, the study population's perceptions, and impact of these perceptions on surgical resident education, when such information is available.

A draft of the data extraction form is provided in Textbox 1. This form can be modified and revised as the need arises during the process of data extraction from each included source. The modifications will be described in the scoping review. If

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appropriate, the authors of the articles will be contacted and asked about missing or complementary data when necessary.

Textbox 1. Data extraction instrument developed by the researchers.

Publication details

- Journal
- Year
- Title
- Author
- Country
- Type of study

Inclusion/exclusion criteria

- Participants
- Concept
- Context
- Reason for exclusion

Findings

- Method of feedback
- Model of feedback
- Resident's perception
- Impact

Analysis of the Evidence

The data will be analyzed in light of the study's objectives. Quantitative and qualitative analyses will be performed through calculation of descriptive statistics (eg, absolute and percentage frequencies) and content analysis, respectively [40]. Basic data coding will be used for the qualitative analyses, if necessary, depending on the findings. The results will be presented graphically and in the form of tables. This information will be enriched by a descriptive text that will clearly show how the results are related to the research question.

Results

The findings of this scoping review were submitted to an indexed journal in July 2024, currently awaiting reviewer approval. The search was executed on March 15, 2024, and resulted in 588 articles. After the exclusion of the duplicate articles and those that did not meet the eligibility criteria as well as the inclusion of articles through a manual search, 13 articles were included in the review.

Discussion

Projected Significance

This protocol was designed according to the first 5 stages of Arksey and O'Malley's [36] structure and is congruent with the JBI methodology. Conducting a scoping review is the best way to map what is known about surgical residents' perception of the feedback received during their education, which can further help to analyze related concepts and determine gaps in the published literature about this subject. Studies in this field have largely focused on the quality of the information to be transmitted, how to transmit such information, and what would be the best moment to do so. However, recent studies on the subject have revealed a shift in priority toward understanding the progress achieved in learning and the learner's engagement in the process enabled by the feedback.

For example, understanding residents' perceptions of the feedback received according to the method and model used to provide the feedback could help educators reconsider how to effectively reach their educational objectives in surgery education. As part of knowledge translation [41], such understanding could even result in the proposal of modifications to the medical curriculum and its development, which could be the topic of future research.

Limitations

This protocol has an important limitation. The search strategy was established using terms in Portuguese, Spanish, and English, which surely excludes articles published in different languages and cultures. Moreover, it is known that feedback concepts and practices differ according to the culture and environment [42]. Thus, the findings of this scoping review may not depict the perception of feedback worldwide.

Conclusions

Feedback is an essential tool for learning and improving performance in any sphere of education. Although its mechanism is not fully known, the delivery of feedback to residents continues to be an important area of study in medical teaching.

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Despite the relevance of the theme, the methodologies, populations, and contexts of the few studies available that are pertinent to the matter differ markedly from one another, and a scoping review on this topic would unequivocally enhance and organize what is already known. In addition, by focusing on the feedback perception more than the feedback itself, the results of this scoping review will contribute to gaining a better understanding of how to proceed to enhance internal feedback and residents' learning progress.

Acknowledgments

We are grateful to Zélia Cristina Regis, librarian of the Faculty of Medicine of São José do Rio Preto, Brazil, for her collaboration in designing the search strategy.

Authors' Contributions

CDdSC is the main researcher, who was responsible for the protocol conceptualization, data curation, investigation, formal analyses, writing of the original draft, review and editing of the manuscript, and project administration. GGS contributed to investigation and data curation. ERdS, AMRPVTdCE, ACdSC, TMdS, WHdC, HC, ARdAL, VMSB, TSGB, and AHO contributed to the writing, review, and editing of the manuscript. JCA contributed to the protocol conceptualization, formal analyses; manuscript writing, review, and editing; and supervision. All authors contributed to manuscript review and approval of the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full search strategy.
[DOCX File , 18 KB - resprot_v13i1e56727_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Identifications of Similarity Metrics for Patients With Cancer: Protocol for a Scoping Review

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Abstract

Background: Understanding the similarities of patients with cancer is essential to advancing personalized medicine, improving patient outcomes, and developing more effective and individualized treatments. It enables researchers to discover important patterns, biomarkers, and treatment strategies that can have a significant impact on cancer research and oncology. In addition, the identification of previously successfully treated patients supports oncologists in making treatment decisions for a new patient who is clinically or molecularly similar to the previous patient.

Objective: The planned review aims to systematically summarize, map, and describe existing evidence to understand how patient similarity is defined and used in cancer research and clinical care.

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Methods: To systematically identify relevant studies and to ensure reproducibility and transparency of the review process, a comprehensive literature search will be conducted in several bibliographic databases, including Web of Science, PubMed, LIVIVIVO, and MEDLINE, covering the period from 1998 to February 2024. After the initial duplicate deletion phase, a study selection phase will be applied using Rayyan, which consists of 3 distinct steps: title and abstract screening, disagreement resolution, and full-text screening. To ensure the integrity and quality of the selection process, each of these steps is preceded by a pilot testing phase. This methodological process will culminate in the presentation of the final research results in a structured form according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart. The protocol has been registered in the *Journal of Medical Internet Research*.

Results: This protocol outlines the methodologies used in conducting the scoping review. A search of the specified electronic databases and after removing duplicates resulted in 1183 unique records. As of March 2024, the review process has moved to the full-text evaluation phase. At this stage, data extraction will be conducted using a pretested chart template.

Conclusions: The scoping review protocol, centered on these main concepts, aims to systematically map the available evidence on patient similarity among patients with cancer. By defining the types of data sources, approaches, and methods used in the field, and aligning these with the research questions, the review will provide a foundation for future research and clinical application in personalized cancer care. This protocol will guide the literature search, data extraction, and synthesis of findings to achieve the review's objectives.

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KEYWORDS

patient similarity; cancer research; patient similarity applications; precision medicine; cancer similarity metrics; scoping review protocol

Introduction

Background

Rapid advances in precision medicine have revolutionized cancer research, opening new opportunities to develop an unprecedented, new, personalized view of each patient. The concept of precision medicine is seemingly simple; similar patients with similar characteristics share similar outcomes. By identifying important patient characteristics and traits, the search for similar patients contributes to the pursuit of precision medicine that may determine clinical outcomes through more precise targeting of treatment by genetic, biomarker, phenotypic, or psychosocial characteristics that differentiate a given patient from others with similar clinical presentations [1-4]. The ever-increasing volume and availability of health-related data is currently challenging the broad definitions of patient groups set out in the clinical practice guidelines. Defining a similarity measure that can handle the high-dimensional space of patient data is an essential step to enable the stratification of patients into clinically meaningful subgroups [4-6]. The complex interaction between personalized patient treatment and the application of aggregate data underlines the fundamental understanding of modern oncology, which is based on the main principle that each patient has a deeply individual nature of their illness, and each case is special [7-9]. However, there is a parallel paradigm that demonstrates the essential role of applying existing data in improving the understanding of the individuality of cancer and optimizing the approach to personalized treatments. It suggests that a deep understanding of each patient's unique characteristics and subsequent selection of therapeutic strategies can be greatly improved by identifying similarities between patients with cancer. This approach indicates that the most effective individualized treatment strategies do not develop independently but instead result from comprehensive comparison and analysis of aggregate patient data [10,11].

Patient similarity is a topic of significant interest and research in various areas of precision medicine, including cancer research. Some studies have explored the concept of patient similarity across different dimensions, such as genomics, clinical characteristics, treatment responses, and outcomes [1,5,12,13].

Despite the extensive interest in this area, there is currently no systematic approach to clarify precisely what is understood by the concept of "patient similarity" in cancer research [6]. While individual studies may use various methodologies and metrics to assess patient similarity, there is a lack of consensus on combined approaches and definitions [4,6,9]. This creates an opportunity for further research to explore and define patient similarity more comprehensively.

In addition, the definition and evaluation of common similarity metrics in cancer research that involves careful evaluation of both quantitative and qualitative factors need to be systemized. These metrics can serve as a powerful method for furthering the understanding of cancer and improving personalized patient care [6,9]. Faced with all these research gaps, we want to conduct a scoping review.

Aim and Research Questions

The goal of our planned research is to collect and describe the existing knowledge that could help in defining and exploring how patient similarity is determined in cancer research and care. The scoping review addresses the following research questions, outlined in Textbox 1.

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Textbox 1. Research questions.

Main research question:

- What is understood by the concept of "patient similarity" in cancer research?

Secondary questions:

- What types of data sources are used to identify similarities between patients with cancer?
  - Molecular genetic data
  - Clinical data
  - Therapies or treatment
  - Histological data
- What different approaches and methods are used to identify and analyze similarities between patients with cancer and what clinical relevance they have?
- Which types of cancer have been the most frequently researched when it comes to finding similarities between patients?
- What challenges and limitations have been observed in the existing literature when identifying similarities between patients with cancer?

To the best of our knowledge, no scoping review has addressed the research questions proposed by this review.

Methods

Overview

To ensure a transparent review process, our methodology will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist and the Joanna Briggs Institute Reviewer's Manual on scoping reviews [14,15]. The methodological process of conducting a scoping review will be iterative. Given this, it is expected that there may be some deviations from the originally developed a priori protocol, as a natural part of the iterative process, to refine and improve the review as it progresses. To ensure transparency in the conduct of the review, any deviations from the original protocol will be explicitly documented and reflected in the final paper of the review.

Main Concepts and Keywords

To guide the literature search, ensure the relevance of included studies, and improve the efficiency of the planned review process, 3 basic concepts and corresponding keywords were defined, which are graphically represented in Figure 1. Based on the main goals and research questions of this review, 3 basic concepts with corresponding keywords were selected (Figure 1), and peer review was sought from experts in the field to validate the keyword selection. These keywords guided the literature search, ensured the relevance of included studies, and improved the efficiency of the planned review process. The first concept is "Cancer patient similarities." It focuses on understanding and summarizing the various dimensions in which patients with cancer can be similar. The main keywords are "patient similarity," "similarities of cancer patients," and "cancer similarity metrics." All these terms are broad and encompass any research comparing various aspects of patients, such as molecular genetic features, clinical features, treatment outcomes, survival rates, and applications used to investigate these similarities. The second concept is "Types of data sources to identify similarities between cancer patients." The keywords in this category expand on the first category by providing detailed perspectives that define cancer similarity metrics. These are essential for identifying studies that explore similarities from different views, such as common prognostic biomarkers, protein-protein interaction pathways, gene expression analysis, and cancer gene profiling. The third concept is "Approaches & methods to identify and analyze similarities," with the overarching keyword being "patient similarity applications." This category aims to identify potential methods, technologies, and algorithms that can be applied in cancer research regarding patient similarities.

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Figure 1. Main concepts of planned scoping review and corresponding keywords.

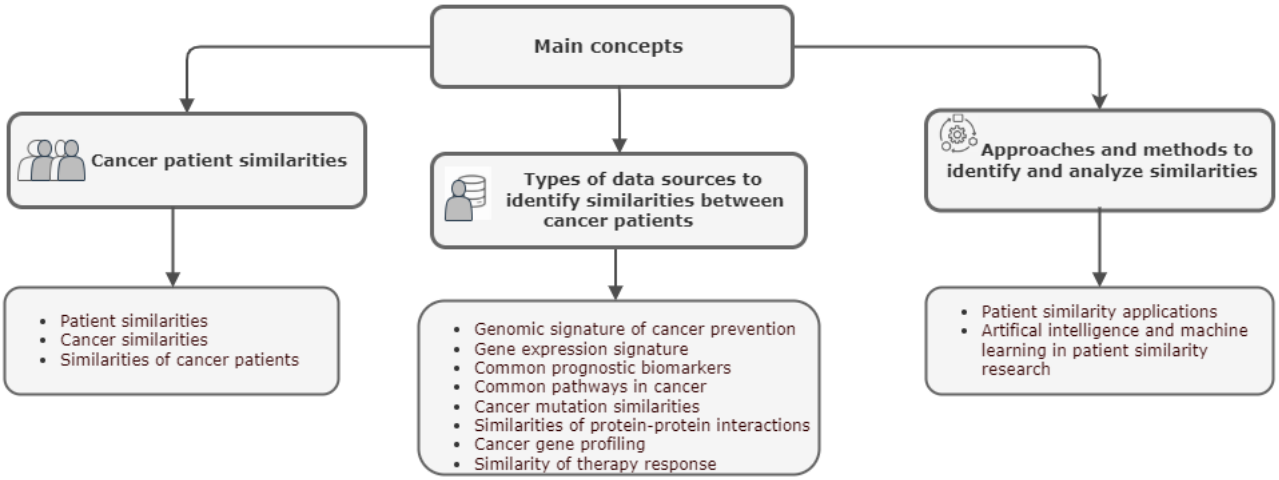

Eligibility Criteria: Inclusion and Exclusion

Even though our primary goal is to cover a wide range of studies to ensure broad coverage of studies on similarities to patients with cancer, we adhere to minimum exclusion criteria to maintain the quality and relevance of included studies. Pilot testing of eligibility criteria was performed on a sample of studies. Based on the findings, inclusion and exclusion criteria were refined to ensure robustness and effectiveness in capturing relevant studies. For selecting pertinent studies for planned scoping review, we have established the following inclusion and exclusion criteria, outlined in Textbox 2.

Textbox 2. Eligibility criteria.

Inclusion criteria

- Type of study: All types of studies providing substantial evidence or data relevant to cancer patient similarities.
- Population: Studies focusing on patients with cancer of all ages, genders, and ethnicities with different diagnoses.
- Publications: Studies published within the last 25 years.
- Language: Studies published in English or German. (We chose English and German as the primary languages since they are the working languages of our team. This decision aims to facilitate better internal discussion and ensure the quality of results.)

Exclusion criteria

- Type of study:
  - Publications not addressing the aspects of similarity of patients with cancer as defined in objectives.
  - Bachelor's and master's theses, as well as unpublished papers.
- Population: Studies focusing on noncancer conditions or animal studies.
- Publications: Studies published more than 25 years ago.
- Language: Studies published in other languages.

Types of Evidence

To identify potentially relevant studies and to ensure reproducibility and transparency of the planned review process, the following bibliographic databases were searched for literature coverage from 1998 to February 2024: Web of Science, PubMed, LIVIVO, and MEDLINE. These databases were chosen for their comprehensive coverage of the biomedical and health care literature, ensuring a thorough review of studies regarding similarities of patients with cancer over 25 years. This approach ensures reproducibility and transparency of the review, facilitating detailed analysis of existing evidence and identification of research gaps in the field [14,16].

Search Strategy

As a result of the numerous discussions, the team developed a search strategy with 3 important steps that are keyword search, snowball system, and manual search. In the planned systematic review, keyword searching will serve as the primary method for identifying relevant studies. This approach involves the use of carefully selected keywords and keyword combinations defined using a nesting approach involving Boolean operators and field tags to provide precision (more information in Multimedia Appendix 1). Initially, the search will be conducted in the Web of Science database, and after that, the search queries will be refined and adapted for subsequent use in other chosen databases to identify relevant information on the research topic effectively. To reduce irrelevant findings in our research and

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to make it more exact [17,18], we integrated the Medical Subject Headings (MeSH) option (MeSH=neoplasms) with keyword searches. This was directly applied in Ovid MEDLINE and PubMed. However, we did not apply it in the Web of Science, which uses its unique indexing system [19]. To uncover literature that may have been missed after the initial keyword search, a "snowballing" method was applied [20,21]. This involved reviewing the references of the searched papers to identify additional studies not covered in the initial database search. In addition to the keywords and snowballing searches, a manual search will be conducted. This will involve manually scanning relevant journals, conference proceedings, and other literature sources to identify studies that are not indexed in mainstream databases or published in less accessible formats. Applying this triangular search strategy to the main concepts identified in Figure 1 will provide a robust review of the existing literature and will allow the fullest possible range of studies to be integrated to identify potential similarities between patients with cancer. The search options used in the individual databases are optimized to the strengths and specific functions of each platform to maximize the effectiveness and comprehensiveness of the literature selection.

Data Extraction

Following the search, all identified references will be collected and uploaded to the reference management software package, EndNote (version 20.2.1, Clarivate Plc), where duplicates will be removed. Subsequently, we will use a selection process by our multidisciplinary team as proposed by Guar et al [22] and Schwenker et al [23], using Rayyan, a web-based software designed to facilitate the process of conducting various types of reviews [24]. The study selection process will consist of 3 stages: title-abstract screening, disagreement resolution, and finally, full-text screening, outlined in Textbox 3. To ensure the quality of the overall study selection process, pilot testing will precede each step, and the following calibrated forms will be applied. The final results will be represented using the PRISMA-ScR flowchart [14].

Textbox 3. Stages of the study selection process.

Stage 1: Title-abstract screening

In this first step, we will screen titles and abstracts to quickly filter out publications that are not relevant to our research questions. This step will significantly reduce the volume of work required in the subsequent full-text review phase. To ensure objectivity, at least 2 reviewers in blind mode will screen each paper. A total of 11 reviewers participated in the title-abstract screening process.

Stage 2: Disagreement resolution

Discrepancies during data extraction will be resolved based on the decision of an additional reviewer, as suggested by von Elm et al [15]. Each reviewer will extract data independently. In case of disagreements, the independent reviewer will be consulted to make the final decision. All discrepancies and their resolutions will be documented for transparency.

Stage 3: Full-text screening

After the primary selection, we will conduct a full-text review of the remaining papers to further refine our selection based on specific inclusion and exclusion criteria directly related to our research questions. A total of 9 independent reviewers will be involved at this stage, as well as in the data extraction process.

Management of Data Charting

From all publications that will be included in the research after the full-text screening stage, data will be extracted. The data extraction process is manual, performed by our team using a predefined template to ensure systematic and accurate data capture. By using a predefined data extraction template, we can systematically capture all relevant information from each study, maintaining consistency and minimizing errors. Pilot testing of the template was conducted to ensure robustness and accuracy. The final draft extraction form is provided in Table 1.

This template is designed with several sections to capture essential information from the studies; "Metadata" includes general information about the publication, and "Research findings" summarizes the main findings from each paper, specific to the research questions and objectives of the planned scoping review. The process of data charting, as in the case of the selection of sources of evidence, will start with a calibration step, which will help us prevent errors and ensure high interrater agreement [14].

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Table 1. Data extraction table for the scoping review.

Item	Description	Keypoints
Metadata[a]		
Title	Title	__[b]
Details	Author (first), journal, DOI[c]	—
Year of publication	YYYY	—
Publication type	Type of publication	—
Institute	Corresponding institute	—
Objective	The main objective of the publication	—
Methods	Summary of the proposed methodological approach	—
Results	Short description of the results	—
Conclusion	Summarizing the main points and findings	—
Keywords	Main keywords of the publication	—
Research findings		
Main research question		
What is understood by the concept of "patient similarity" in cancer research?	Key definition of "patient similarity" in the context of the publication.	• Explanation of how the study defines patient similarity in the context of cancer research. This can include genetic, clinical, histological treatment-related similarities, or view from methodological approaches. • Determining the aspects of patient similarity that this publication focused on.
Secondary questions		
What types of patient data are used to identify similarities?	Short description of the data (molecular genetics, clinical, histologic, and treatment-related) used to define patient similarity.	• Categorization of the types of patient data used to identify similarities.
What different approaches and methods are used to identify and analyze similarities between patients with cancer and what clinical relevance they have?	The approaches and methods used to analyze and identify similarities (eg, software, tools, and algorithms). Information on how these findings contribute to personalized medicine.	• Typification of the tools used to identify similarities. • Clinical relevance of the methods and suitability for practical application.
Which types of cancer have been the most frequently researched when it comes to finding similarities between patients?	A list of cancer types that can be related as a basis for identifying similar cancer metrics.	• Identification of cancer types associated with the patient similarities in this study.
What challenges and limitations have been observed in the existing literature when identifying similarities between patients with cancer?	List of potential limitations and challenges.	• Determination of the limits, future challenges, and unexplored areas in this field of research.

[a]Mandatory field.

[b]Not applicable.

[c]DOI: digital object identifier.

Summarizing and Presenting Results

To comprehensively answer the main research question and related secondary questions, our findings will be summarized and presented using a structured approach to ensure clarity, consistency, and alignment with overarching objectives. Detailed narrative synthesis and descriptive analysis will provide the basis for summarizing and presenting the findings of the studies [14,24,25], included in the review, focusing on how "patient similarity" is conceptualized and operationalized within cancer research. This process will summarize key findings and thematic categories and establish links between approaches to "cancer patient similarity" across studies. Additional graphical and tabular forms will be used to visualize and systematically present the collected data. For this purpose, we are planning to include flowcharts representing the study selection process, diagrams, and bar charts illustrating the intersection of different types of data sources or showing the frequency of studies of different cancer types.

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Ethical Considerations

There was no requirement for ethical approval because only literature was being evaluated.

Results

The review protocol, which outlines the methodology for the review, began with a database search, identifying 1183 unique papers after the removal of duplicates. As the review advanced to full-text screening by March 2024, the selection process led to 67% (797/1183) of the papers being excluded and 13% (151/1183) of papers being earmarked for conflict resolution. Consequently, 20% (235/1183) of selected papers, which significantly contribute to the analysis of the review and align with the research questions and objectives, were initially considered for inclusion. This number rose to 22% (258/1183) after resolving conflicts. Currently, a full-text analysis is underway using a pretested chart template to ensure that each selected study contributes to the comprehensive understanding the review aims to establish.

Discussion

Our planned scoping review will offer insights into how the concept of patient similarity in patients with cancer has been defined and interpreted thus far. In addition, the review aims to provide an overview of the methods used to identify similarities and differences among patients with cancer. It will also specify the types of data used in these methods. Furthermore, it will provide an overview of the types of cancer addressed in the studies we cover. However, the scoping review of similarity measures for patients with cancer may face limitations, including the possibility of missing specific study details due to its broad coverage, variability in study design, diversity of data sources, and possible publication bias. In addition, rapid advances in the field and subjectivity in study selection may affect the comprehensiveness and accuracy of the review. Despite these limitations, it is important to note that the advantages and benefits of conducting such studies far outweigh the possible disadvantages, offering valuable insights into personalized cancer treatment strategies. First, it facilitates a more nuanced understanding of cancer's biological diversity, recognizing that while each case is unique, there are often underlying similarities that can guide treatment [5]. In addition, the benefits of studying patient similarities also include the potential for more effective and targeted therapies, improving prognostic models, and discovering new approaches. Finally, identifying indicators of similarity supports ongoing treatment by allowing one to act more efficiently and effectively, armed with knowledge drawn from a broader data set [11,26]. Our review will examine the scope, range, and nature of similarity studies of patients with cancer. It will highlight key findings, identify research gaps, and explore new methods for assessing patient similarity. It will also suggest future directions for research. These directions may include patient-centered approaches by incorporating patient-reported outcomes and experiences into the definition of similarity measures. Thereby, we aim to ensure the relevance and applicability of findings in clinical practice. This is of special importance when the focus is on rare cancers, which are often underrepresented in studies. To understand if and how similarities can be identified and used in these cases, we will also consider longitudinal studies exploring patient similarities and their impact on treatment outcomes.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed search queries for Web of Science, PubMed, LIVIVO, and MEDLINE.
[DOCX File , 18 KB - resprot_v13i1e58705_app1.docx]

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Abbreviations

MeSH: Medical Subject Headings

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Challenges and Facilitation Approaches for the Participatory Design of AI-Based Clinical Decision Support Systems: Protocol for a Scoping Review

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Abstract

Background: In the last few years, there has been an increasing interest in the development of artificial intelligence (AI)–based clinical decision support systems (CDSS). However, there are barriers to the successful implementation of such systems in practice, including the lack of acceptance of these systems. Participatory approaches aim to involve future users in designing applications such as CDSS to be more acceptable, feasible, and fundamentally more relevant for practice. The development of technologies based on AI, however, challenges the process of user involvement and related methods.

Objective: The aim of this review is to summarize and present the main approaches, methods, practices, and specific challenges for participatory research and development of AI-based decision support systems involving clinicians.

Methods: This scoping review will follow the Joanna Briggs Institute approach to scoping reviews. The search for eligible studies was conducted in the databases MEDLINE via PubMed; ACM Digital Library; Cumulative Index to Nursing and Allied Health; and PsycInfo. The following search filters, adapted to each database, were used: Period January 01, 2012, to October 31, 2023, English and German studies only, abstract available. The scoping review will include studies that involve the development, piloting, implementation, and evaluation of AI-based CDSS (hybrid and data-driven AI approaches). Clinical staff must be involved in a participatory manner. Data retrieval will be accompanied by a manual gray literature search. Potential publications will then be exported into reference management software, and duplicates will be removed. Afterward, the obtained set of papers will be transferred into a systematic review management tool. All publications will be screened, extracted, and analyzed: title and abstract screening will be carried out by 2 independent reviewers. Disagreements will be resolved by involving a third reviewer. Data will be extracted using a data extraction tool prepared for the study.

Results: This scoping review protocol was registered on March 11, 2023, at the Open Science Framework. The full-text screening had already started at that time. Of the 3,118 studies screened by title and abstract, 31 were included in the full-text screening. Data collection and analysis as well as manuscript preparation are planned for the second and third quarter of 2024. The manuscript should be submitted towards the end of 2024.

Conclusions: This review will describe the current state of knowledge on participatory development of AI-based decision support systems. The aim is to identify knowledge gaps and provide research impetus. It also aims to provide relevant information for policy makers and practitioners.

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KEYWORDS

artificial intelligence; AI; participation; participatory design; co-creation; clinical decision support system; CDSS; decision support; challenges; clinical staff; scoping review

Introduction

Background

Clinical decision support systems (CDSS) play an important role in health care by providing evidence-based guidance and recommendations to clinical staff. Typical use cases include medication management, disease diagnosis and management, treatment planning, risk assessment, and workflow optimization. The use of these systems aims to increase the accuracy and effectiveness of clinical staff [1,2].

The increasing digital transformation of health care means that more and more health care data is available in digital form, which means that artificial intelligence (AI) applications are also becoming more relevant in this area. More and more AI applications are being developed in health care. In clinical practice, AI has a wide range of potential applications, including disease diagnosis, treatment selection, and patient monitoring [3]. AI-based CDSS is essential in this context.

Although studies have shown that CDSS can reduce medical errors and improve outcomes, they have also shown that CDSS are not being used to their full potential [4-10]. It can be assumed that the challenges of non–AI-based CDSS also apply to AI-based CDSS. Further challenges arise with respect to AI-based CDSS [11]: pointed out in the viewpoint is that the use of deep learning and other analytic methods brings additional challenges. These methods generate insights in ways that are not directly traceable, meaning that clinical staff cannot apply the same validation as with traditional clinical decision support tools. As a result of this lack of transparency, trust in the AI system may decrease [11,12].

Another challenge is integration into workflows [13,14]. When developing AI-based technologies for clinical use, it is crucial to consider existing workflows in both the design and development phases. This will ensure that the technology can be used effectively and make a positive contribution to patient care. Consideration of workflows and the needs of clinical staff will ensure the successful integration of AI technologies into everyday clinical practice. Poor integration processes can have a negative impact on uptake and adoption, as illustrated by a case study on the implementation of a CDSS [14]. For successful integration, it is essential that clinical staff develop the skills to interpret the results appropriately. This “black box” nature of AI described by [11] and the lack of transparency of the basis for decision making can make practical implementation difficult and may also be a factor in low user adoption [11,15].

The notion of the user’s acceptance of new technologies is derived from the Theory of Reasoned Action [16]. According to various technology acceptance models (TAMs; eg, TAM and UTAUT [Unified Theory of Acceptance and Use of Technology]) based on this theory, acceptance encompasses both the intention to use technology and its influence on actual use behavior [4,17,18]. For researching clinicians’ acceptance of CDSS these models serve as a foundation [19-22].

Acceptance of CDSSs is crucial for their successful use. Involving users at an early stage can improve the acceptance and use of information technology by taking into account their needs, preferences, and experiences. This can help to optimize the user experience and increase the effectiveness of the technologies [15,17].

Involving future users is possible through participatory research approaches. Such approaches aim to plan and carry out research processes with people who investigate their social world and meaningful actions as lifeworld-situated living and working practices that are to be improved by developing appropriate innovations [23]. In addition, a participatory approach may also help to avoid problems that arise when transferring the AI-based CDSS to new patient populations for instance due to overfitting of training data or lack of generalizability [24]. This problem can be counteracted by involving expert knowledge from practice, for instance by reviewing the operationalization of health care–related concepts, feature selection, and data quality.

The stage of participation can be determined using the Wright et al [25] stage model. This model consists of 9 stages and is divided into four areas: (1) nonparticipation (stages 12), (2) preparticipation (stages 3-5), (3) participation (stages 6-8), and (4) beyond participation (stage 9). It is also used to determine the stage of participation in the studies reviewed. In order to be able to categorize the studies, particular attention should be paid to the methodological description of the studies. The second version of the GRIPP (Guidance for Reporting Involvement of Patients and Public), a tool to improve the reporting of patient and public involvement in research, shows in its fourth section of the long-form reporting checklist on the methodology of the work (design, people involved, stages of involvement, and level or type of involvement) the relevant aspects for describing the involvement of groups of people [26]. The content can also be transferred to other stakeholder groups (not only patient and public involvement). An alternative to the Wright et al [25] stage model and GRIPP 2 could have been the participatory ergonomics framework, which focuses on the active involvement of participants, particularly workers, in ergonomic interventions to improve work conditions and processes [27]. However, the Wright model and GRIPP 2 were selected because of their established use in health care, their broad applicability, their transferability to different stakeholder groups, and their alignment with the objectives of this review.

According to a recent review, clinical professionals (future users) are already involved in the development of AI-based CDSS, but only in about 30% of cases. The focus is on the creation of predictive CDSS specifications or the evaluation of system implementations. However, clinical experts are less likely to be involved in the development phases to check clinical validity, select model features, process data, or act as a gold standard [28].

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Nevertheless, the development of AI applications poses challenges to participatory methods: A precondition for carrying out participatory methods on the topic of AI is that the participants have a basic understanding of AI. Furthermore, implementing design ideas is difficult, as a realistic prototype is often hard to realize. In addition, evaluating the results is only possible to a limited extent. Much has to be done via simulations or imagination because it often requires a long testing period. Another difficulty is often the lack of comprehensibility of the AI decisions for the user [29].

Although clinical staff are already involved in the research and technology development process of AI-based CDSS, no overarching overview has been identified that summarizes and presents the main approaches, methods, and practices for participatory research and technology development of AI-based CDSS for clinical staff. Hence, this gap of knowledge should be addressed by this scoping review.

A preliminary search of MEDLINE was conducted, and no current or ongoing systematic reviews or scoping reviews on the topic were identified.

Objectives and Research Questions

The objective of the review is to provide an overview and systematization of participatory approaches of various disciplines for developing, piloting, implementing, and evaluating AI-based information systems in a clinical setting.

The following research questions will be addressed:

1. Perspectives on the underlying clinical problem: Are the different perspectives on underlying clinical problems (eg, by nurses, doctors, and other health care workers) addressed by any particular CDSS included in the design of the CDSS?
2. Participation as a process: Which participatory approaches are used to develop, pilot, and evaluate AI-based CDSS in health care?
3. Participation in technical aspects of CDSS design: In which ways are participatory methods specifically supporting the development of AI components of CDSS and their performance?
4. Participation for ethical, legal, and social implications: Which ethical, legal, and social implications have been identified in existing projects for participatory development, piloting, implementation, and evaluation processes targeting clinical staff?

Methods

Design

We are going to conduct one scoping review. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) is used as a basic tool [30] in combination with the Joanna Briggs Institute (JBI) approach to scoping reviews. This approach ensures that the scoping review is transparent, reproducible, and methodologically sound [31].

Search Strategy and Terms

Information Sources

To identify relevant papers, we have chosen various databases that encompass publications from the fields of biomedical science and health science, computer science and information technology, psychology, and nursing and allied health. The following electronic databases will be included as information sources: MEDLINE via PubMed, ACM Digital Library, Cumulative Index to Nursing and Allied Health, and PsycInfo. Additionally, we will supplement this research with the snowball technique [32] and the screening of websites (eg, Google Scholar and DAHTA). These information sources were chosen since they encompass a wide range of research fields considered appropriate to address the objectives of this review. The databases provide the most comprehensive coverage of relevant studies examining the participatory design and development of AI-based technologies in health care, particularly CDSS.

Search Strategy

The above sources will be searched using combinations of relevant search terms we developed and tested for sensitivity before performing the scoping review. We used an iterative approach to develop the search strategy. First, we identified search terms used in previous studies and reviews related to participatory research and AI-based CDSS for clinical staff (particularly relevant: [33-37]). Then, we conducted an initial search in MEDLINE (via PubMed) and Cumulative Index to Nursing and Allied Health after analyzing text words (title and abstract) and indexed terms, as suggested by the Joanna Briggs Institute methodology for systematic scoping reviews [31,38]. Based on these results, we used the search terms in all databases. Afterward, we will check the references for all included contributions. If relevant, we will contact the authors. We will contact the authors if a publication is inaccessible or further information is required. Other reasons for contacting authors might include clarifying any ambiguous or unclear data presented in their publication, requesting additional data that may not have been included in the original publication, or seeking permission to use specific figures, tables, or other content.

Multimedia Appendix 1 demonstrates the search strategy for MEDLINE (via PubMed). The research began in 2012, the year in which the use of deep neural networks in image processing marked a breakthrough in the field of deep learning [39]. The terms will be adapted to the basic search particulars (eg, wildcards [*]and truncations) of each electronic database.

In order to describe the inclusion criteria precisely, we rely on the Population, Concept, and Context scheme [31,38]. Textbox 1 shows the most important criteria according to the Population, Concept, and Context scheme.

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Textbox 1. Population, Concept, and Context criteria used in the scoping review.

Population

Clinical staff (medical doctors, nurses,...)

Concept

Participation/participatory design/Co-creation/co-design.

Context

Development, piloting, implementation, and evaluation of artificial intelligence–based clinical decision support systems (hybrid and data-driven artificial intelligence approaches).

Types of sources

Primary research—All study types (eg, qualitative, quantitative, mixed methods) will be included. Systematic reviews and meta-analyses will be used for manual searches in the reference lists to identify further primary studies.

Papers that provide information on at least 1 research question should be included. More specific inclusion and exclusion criteria are provided below for each review.

Eligibility Criteria

The inclusion and exclusion criteria that were applied to the studies are shown in Textbox 2.

Textbox 2. Inclusion and exclusion criteria applied in the scoping review.

Inclusion criteria

Target group: Clinical staff.

Involvement: Participation in the development, design, piloting, and evaluation of artificial intelligence–based information systems.

Related approaches: Other related approaches, research and design strategies, or concepts often used interchangeably with participation and co-creation, such as co-design.

Type of research: Primary research using different methods (eg, qualitative, quantitative, and mixed methods)

Language of publications: English or German.

Exclusion criteria

Participation: No evidence of a participatory research element.

Target group: No relation to clinical staff.

Thematic focus: Does not refer to artificial intelligence–based clinical decision support systems.

Study Selection

The retrieved references will be checked for duplicates and transmitted to Covidence (software for managing and streamlining reviews, operated by Veritas Health Innovation Ltd) [40] for the screening steps. We will use Zotero (a free and open-source literature management program) [41] as a bibliographic tool. Two independent reviewers (TR and PG) will screen all titles and abstracts separately for inclusion or exclusion. Disagreements will be solved by including a third reviewer. Afterward, the same procedure will be applied to the full-text screening, which is carried out by 3 independent reviewers (TR, PG, and CH). Reasons for excluding a study will be assessed in each of these steps. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [30].

Data Extraction

A data charting form has been developed jointly by the authors to identify the variables to be extracted. The 2 reviewers will chart the data independently, discuss the results, and continually update the data charting form in an iterative process, with changes detailed in the scoping review. Any reviewer disagreements will be resolved by discussion or with additional reviewers. Where appropriate, authors of papers will be contacted to request missing or additional data as required. A draft extraction form is provided (Multimedia Appendix 2). Data on the participation process is also extracted to assess the stage of participation.

Data Analysis and Presentation

Data Analysis and presentation will follow the recommendations of the Joanna Briggs Institute scoping review methodology group [42]. First, the extracted data will be presented in a logical and descriptive way (diagrams and tables), guided by the objectives and questions of the scoping review. Additional relevant data items may be identified during the data extraction process. If additional items are extracted that were not prespecified in the review protocol, this will be made clear in the final report together with a rationale as to why it occurred. The extracted data will be summarized in a narrative synthesis to bring together findings relating to challenges and facilitators for participatory design processes. Given the breadth of scoping review questions, the analysis will also use qualitative content analysis. In order to identify and structure relevant aspects of the research questions, the analysis will follow an inductive approach. Following an open coding process, a coding

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framework will be developed and reviewed by all authors. This approach aims to provide insights into participatory design and research practice for AI-based CDSS and highlight areas for future research.

Results

This review protocol was submitted to the Open Science Framework on March 11, 2024. The full-text screening had already started at that time. Of the 3,118 studies screened by title and abstract, 31 were included in the full-text screening. Data collection and analysis as well as manuscript preparation are planned for the second and third quarter of 2024. The manuscript should be submitted towards the end of 2024.

Discussion

Principal Results

The main objective of this study is to identify, clarify, and map key approaches, methods, and procedures for participatory research and technology development of AI-based CDSS in the context of clinical staff. It will also analyze, synthesize, and develop existing approaches, concepts, and conceptualizations. The insights gained from this process will serve as a basis for designing, developing, and testing participatory processes specifically designed for clinical staff. Various stakeholders can use the results to design, develop, and review participatory processes that address the development of an AI-based CDSS for clinical staff.

Limitations

Scoping reviews have limitations, particularly in that they focus on the collection and synthesis of data and do not assess the strength of evidence or the risk of bias in the research. Therefore, further research is needed to assess and analyze the quality of existing studies on the participatory development of AI-based decision support systems. It should be noted that only papers written in English or German were considered, which meant that potentially relevant studies in other languages could not be included. Furthermore, despite the comprehensive inclusion criteria, some relevant sources of information may not be included.

Conclusions

Up to now, no review of this scope and objective has been identified. Hence, this review will be the first to address this specific knowledge gap targeting clinical staff. Additionally, one aim of this review is to identify further research and knowledge gaps and to give hints where further reviews would be helpful.

Acknowledgments

The work on this review is part of the KIDELIR-Project (Hybrid AI delirium prediction system to reduce the burden on caregivers), funded by the Federal Ministry of Education and Research (BMBF) in Germany. The aim of the KIDELIR project is to develop hybrid AI models for predicting delirium in a hospital setting and supporting reflective care decisions with the close involvement of care professionals.

Authors' Contributions

TR and PG conceptualized the study as a scoping review. CK and PK provided oversight for scoping review protocol development. TR drafted the protocol. PG, CK, and PK helped to review and edit the protocol. TR, SM, and PG drafted the search strategy and ran the search on electronic databases. All authors read and approved the final protocol. TR and PG carried out the title and abstract screening. Ambiguous cases were discussed and jointly decided with CK and PK. TR, PG, and CH conduct the full-text screening.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 22 KB - resprot_v13i1e58185_app1.docx]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 19 KB - resprot_v13i1e58185_app2.docx]

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Abbreviations

AI: artificial intelligence
CDSS: clinical decision support system
GRIPP: Guidance for Reporting Involvement of Patients and Public
JBI: Joanna Briggs Institute
PRISMA-ScR: referred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
TAM: technology acceptance model
UTAUT: Unified Theory of Acceptance and Use of Technology

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Protocol

Self-Management Systems for Patients and Clinicians in Parkinson Care: Protocol for an Integrated Scoping Review, Product Search, and Evaluation

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Abstract

Background: Parkinson disease (PD) poses emotional and financial challenges to patients, families, caregivers, and health care systems. Self-management systems show promise in empowering people with PD and enabling more control over their treatment. The collaborative nature of PD care requires communication between patients and health care professionals. While past reviews explored self-management systems in PD diagnosis and symptom management with a focus on patient portals, there is limited research addressing the interconnectivity of systems catering to the needs of both patients and clinicians. A system's acceptability and usability for clinicians are pivotal for enabling comprehensive data collection and supporting clinical decision-making, which can enhance patient care and treatment outcomes.

Objective: This review study aims to assess PD self-management systems that include a clinician portal and to determine which features enhance acceptability and usability for clinicians. The primary aim is to assess evidence of clinicians' acceptability and usability of self-management systems with a focus on the integration of systems into clinical workflows, data collection points, monitoring, clinical decision-making support, and extended education and training.

Methods: The review will entail 3 separate stages: a literature review following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, a product search, and an evaluation of the level of evidence for the identified products. For the first stage, 5 databases will be searched: PubMed, CINAHL, Scopus, ACM digital library, and IEEE Xplore. Studies eligible for inclusion will be qualitative, quantitative, and mixed methods studies examining patients' and clinician's perceptions of the acceptability and usability of digital health interventions, synthesized by a narrative qualitative analysis. A web search in the iOS Apple App Store and Android Google Play Store will identify currently available tools; the level of evidence for these will then be assessed using the Oxford Centre for Evidence-Based Medicine guidelines.

Results: Literature search and screening began soon after submission of the protocol, and the review is expected to be completed by end of September 2024.

Conclusions: This review will examine currently available self-management systems in PD care, focusing on their acceptability and usability. This is significant because there is limited research addressing the integration of clinicians into these systems. The findings from this study may provide critical knowledge and insight to help inform future research and will contribute to the design of self-management systems that promote collaborative efforts in PD care.

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KEYWORDS

Parkinson's disease; digital health; self-management; health care systems; self-care; Parkinson; mobile health; mHeath; evaluation; acceptability; usability; decision-making support; database; qualitative; quantitative; mixed method; perception

Introduction

Parkinson disease (PD) is a complex and progressive neurological condition with no current cure. It represents the second most common neurodegenerative disorder worldwide [1], with a 30% rise in prevalence and incidence between 2018 and 2030 [2,3]. Clinicians in PD care often have limited data due to infrequent patient contact, constraining their ability to fully inform treatment decisions [4]. The diversity of symptoms experienced by people with PD means that care management is complex. Optimizing symptom management requires an understanding of current symptoms and trends, necessitating thorough communication between patients and clinicians [4,5]. Positive relationships between patients and clinicians can enhance patient trust, medication adherence, and the patients' active engagement in care, with potential benefits in mitigating health care disparities, fostering interdisciplinary collaboration, and ultimately enhancing patient outcomes [6,7]. Given the strain on health care resources and the limited regular clinical contacts, digital technologies have the potential to help patients self-manage symptoms and provide accurate records of symptoms for clinical review. Despite the availability of such systems, there is limited understanding of how they are adopted, accepted, and used within clinical contexts.

Despite advancements in digital health, many systems still fall short in effectively compiling information for clinician use at the point of care and facilitating seamless care communication [6]. Systems that combine patient self-reporting with clinician management can improve data collection and communication, leading to more efficient care, better decision-making, and ultimately enhanced patient outcomes through more timely and personalized interventions [6], [7]. Previous research has extensively examined engagement with and impact of digital tools in PD care, focusing on self-management methods to enhance physical and cognitive aspects for patients [8-18]. A comprehensive understanding of the acceptance and usability by health care professionals (HCPs) is lacking, leaving room for more inclusive research in PD care [19-28]. There is a need to understand what systems are currently available, how they integrate self-management techniques, and how clinical elements and clinicians are integrated [29-35]. This knowledge gap is particularly crucial to address, as improving clinician engagement with digital tools can lead to more effective and tailored patient care strategies.

This study aims to fill this gap by examining the state of the literature on clinician perspectives of PD self-management systems and the state of clinician-focused features in existing self-management systems. The review will summarize available systems and evidence of their acceptability and usability of self-management systems, while the product evaluation will identify active digital applications, tools, and services (eg, apps, websites, portals, and wearable devices) that support self-management for people with PD to explore what types of technologies are used, which self-management techniques are applied, and how clinicians are integrated.

Methods

Design

This review is structured in 3 distinct stages, each contributing to building a comprehensive overview and understanding of the landscape of self-management systems for PD. We will perform a scoping review by leveraging bibliographic databases, search and select eligible systems on the Apple App store and Google Play store, and evaluate the level of their evidence. Identified self-management systems will be evaluated using the Oxford Centre for Evidence-Based Medicine (OCEBM) guidelines following adherence to established eligibility criteria. Separate analyses will be conducted for the scoping review and product evaluation, as they will extract different types of data, but findings from each will be synthesized in the discussion. The design concludes with a narrative synthesis to summarize study findings and product evaluation results, incorporating study methods, key findings, and outcomes. All review stages are summarized in Table 1.

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Table 1. Review stages.

Review stage	Data collection method	Analysis method
Stage 1: a scoping review	Search bibliographic databases (PubMed, CINAHL, Scopus, ACM Digital Library, and IEEE Xplore) using PRISMA-ScR[a] and PICOS[b] frameworks	Narrative synthesis to identify key themes and gaps
Stage 2: product search	Search Apple App Store and Google Play Store using relevant keywords	Evaluation of system characteristics and user feedback
Stage 3: data analysis	Extract data from the literature review and product search	Adapt OCEBM[c] guidelines for system classification and narrative synthesis

[a]PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

[b]PICOS: Population, Intervention, Comparator, Outcome, and Studies.

[c]OCEBM: Oxford Centre for Evidence-Based Medicine.

Search Strategy

Stage 1: Scoping Review

Search

The first stage of the research involves the exploration of existing literature through 5 bibliographic databases: PubMed, CINAHL, Scopus, ACM Digital Library, and IEEE Xplore. The search strategy is designed to identify studies using qualitative, quantitative, and mixed method approaches that investigate HCPs' perspectives on the acceptability and usability of self-management systems. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; Multimedia Appendix 1) and Population, Intervention, Comparator, Outcome, and Studies (PICOS) frameworks were used to structure the protocol for the review strategy (Table 2) [35]. The PICOS framework was used to outline key themes that shaped the search strategy (Table 3), with themes relating to the population (HCPs), intervention (PD and self-management interventions), and outcomes (evaluation).

The scoping review will be used to systematically chart and synthesize data to identify key themes and gaps in the existing literature, thereby providing a comprehensive overview of this research results and studies to build the foundation for subsequent stages of this research, ensuring that relevant aspects are actual and addressed. The database search will be performed in August 2024 using PubMed (MeSH [Medical Subject Headings] terms), CINAHL (abstract), Scopus (title and abstract), ACM digital library (full text), and IEEE Xplore (full text). A preliminary exploration of identified relevant terms based on the PICOS framework was used to develop the search strategy (Multimedia Appendix 2). The search strategy will include a set of keywords relating to digital self-management tools and their user-friendliness and user acceptance. Keywords were derived from MeSH related to the subject and used as search terms (Table 3).

Table 2. PICOS[a] framework [35].

PICOS	Detail
Population	• Health care professionals treating patients
Intervention	• Digital interventions for self-management for people with PD[b], for example, telehealth, exergaming, websites, smart homes, mobile apps, web-based systems, and wearable devices, which offer a clinician portal or similar which may enable clinical use (eg, e-record integration, messaging features, remote monitoring, or treatment decision support)
Comparator	• None
Outcomes	• Primary outcome: clinician usability and acceptability of digital interventions for self-management in PD care • Secondary outcomes: factors that might impact the usability of these systems including regulatory requirements, training protocols, and any other elements that may influence the overall user experience for both people with PD and clinicians
Study types	• Qualitative and quantitative studies, for example, case-control studies, case series, longitudinal studies, cohort studies, or RCTs[c]

[a]PICOS: Population, Intervention, Comparator, Outcome, and Studies.

[b]PD: Parkinson disease.

[c]RCTs: randomized controlled trials.

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Table 3. MeSH[a] terms and keywords used for literature search.

Category	MeSH terms	Keywords (in title and abstract)
Parkinson disease	Parkinson disease OR parkinsonian disorders	"Parkinson's disease" OR parkinson OR parkinson's OR "parkinson disease"
Health care professional	Physicians OR health personnel	"Healthcare professional" OR "healthcare personnel" OR clinician OR practitioner OR doctor OR nurse OR "care professional"
Self-management intervention	Electronic OR technology OR data collection OR internet-based intervention OR digital health OR telemedicine OR computing methodologies OR software OR wearable electronic devices OR self-help devices OR rehabilitation OR computer-user training	"Digital intervention" OR technology OR system OR portal OR remote OR home-based OR database management system OR internet-mediated therapy OR remote consultation OR personal health services
Evaluation	Quality of health care OR health care evaluation mechanism OR program evaluation OR attitude OR behaviour OR acceptance process OR acceptance processes OR treatment adherence and compliance OR communication methods, total OR security measures OR educational measurement OR time management OR efficiency, organizational	Evaluation OR attitude OR user experience OR acceptability OR usability OR impact OR acceptance OR compliance OR conformity OR efficiency

[a]MeSH: Medical Subject Headings.

Eligibility

Studies eligible for inclusion are papers that analyze self-management systems for people with PD and their HCP, embed clinical measures, or focus on clinical evidence of acceptability and usability. A comprehensive definition of self-management interventions was used to enable the collection of various intervention types. Any digital form of intervention, whether websites or mobile apps, are considered for inclusion if the system's intention includes enhancing any aspect of patient self-management in PD. Inclusion criteria for literature encompass published studies at any given time, including randomized controlled trials, cohort studies, and case-control studies. There will be no limit of the publication date as this review aims to have a full overview of available self-management systems for patients with PD.

Studies that do not review or analyze self-management intervention for PD will be excluded as well as editorials, perspective articles, conference papers, and protocols. Literature that is not published in English will be excluded as the research team does not have the necessary resources to assess these.

Screening and Selection of Studies

The selection of studies will be determined by a review of study titles and abstracts in the indexed databases to assess their relevance to the use of digital self-management systems for PD. Selected references will be managed, and duplicates will be eliminated using the citation management software EndNote X21 (Clarivate). The initial screening of these references, based on search strategy keywords, will be conducted through EndNote X21's search function. A total of 2 authors will screen the title and abstract of each record and will either include or exclude using the eligibility criteria previously described. Once the title and abstract screening is completed, selected records will be obtained for full-text screening. Full-text screening will be undertaken following the eligibility criteria. The stages of the scoping review process and selection of records will be presented using the PRISMA-ScR flowchart [35]. The data extraction and analysis process for this scoping review are described in stage 3.

Stage 2: Product Search

Search

The second stage includes the search and selection of digital interventions currently available in app stores. The process will be executed by searching the Apple App store and Google Play store using relevant keywords to identify and assess digital interventions. The keywords "Parkinson" and "Parkinson's Disease" will be searched separately on both app stores; all results from each search will be extracted, the lists will be combined, and duplicates will be removed before screening. This stage is designed to encompass a diverse range of self-management tools available that are specific to PD or of potential relevance for patients managing specific symptoms caused by PD. This stage aims to respect the dynamic nature of the systems available for clinicians, ensuring the inclusion of real-world offerings to facilitate a holistic analysis of practical implications for available digital solutions.

Eligibility

Any digital self-management intervention, such as websites, web portals, mobile apps, or wearable devices, will be considered eligible if it primarily focuses on providing self-management services for individuals diagnosed with PD. The system will be designed to operate as a stand-alone product, eliminating the need for the combination of multiple devices. This was chosen to account for operational or financial consequences for the patient in acquiring the system. The system may adopt a paid subscription model, feature in-app purchases, or be offered free of charge to users. Systems included for review must be available in the Apple App store or Google Play store and accessible in English and in the United Kingdom. Eligible apps are any systems for the use of PD self-management. Detailed eligibility criteria are presented in Textbox 1.

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Textbox 1. Eligibility criteria for systems on app stores included in the study.

- Inclusion criteria
  - Systems available on the UK Apple App store or UK Google Play store
  - Systems available in English
  - Systems intended for the self-management of Parkinson disease
- Exclusion criteria
  - Systems not available on the UK Apple App store or UK Google Play store
  - Systems not available in English
  - Systems not yet released for public use or access

Screening and Selection of Self-Management Systems

All self-management systems found in the scoping review or product searches will be documented in a Microsoft Excel file, and duplicate entries will be removed. Systems meeting the criteria will be accessed and purchased, if necessary, and downloaded to either the MacOS system or iOS or Android devices. Any systems that, upon closer inspection, do not meet the inclusion criteria will be excluded. In case of disagreements between the reviewers, these will be discussed and, if required, resolved by a third reviewer.

Stage 3: Data Analysis

Data Extraction

Following completion of the screening process and deduplication using EndNote 21 software, eligible studies will be transferred to a Microsoft Excel spreadsheet for further data extraction (Textbox 2). Any modifications to the data extraction items will be recorded contemporaneously and reported in the final review.

Textbox 2. Full data charting list.

- Literature: system description
  - Name
  - Year of launch
  - Technology domain (eg, internet of things [IoT], mobile app, or website)
  - Costs
  - Evaluation method
  - Type of self-management intervention
  - Description of self-management intervention
- Product evaluation: system characteristics
  - Intervention outcome or intention
  - Possibility of data exchange (clinician-patient)
  - Peer collaboration (clinician-clinician)
  - Feedback mechanism
  - Possibility of uploading eHealth records
  - (Real-time) remote monitoring
  - Alerts and notifications
  - Training support
  - Appointment scheduling
  - Integration of wearables

Data Analysis

Data extracted from the studies included in the literature review will be analyzed and synthesized narratively. The criteria used to assess the systems found through literature and product searches will be adapted from the OCEBM guidelines [7]. In this categorization, systems will be classified based on the strength of their evidence, ranging from case reports to randomized controlled trial methodology. We will characterize

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self-management systems described in these reports based on different types of technology, such as mobile apps, websites, web portals, telehealth, digital communication platforms, digital solutions for data management, wearable devices, and web-based training systems. The analytical narrative synthesis of the reviewed literature will examine what self-management techniques are used within the systems and how clinicians are incorporated, investigating if their perspectives are solicited and the degree to which such feedback influences the design and evolution of these digital tools. Systems will be summarized focusing on clinical and operational intention to identify key trends and outcome measures will be examined. The results of this will be tabulated to facilitate visualization of identified systems and their characteristics and elaborated in the discussion of the review. Following the summarization of the findings from the literature review and system selection, the final stage will be a synthesis of qualitative findings from eligible studies combined with information derived from the system search and system descriptions or reviews on the app stores. By categorizing systems based on the technology domain and examining the qualitative data about user experiences, stage 3 aims to synthesize information found; this will enabling a deeper understanding of digital self-management solutions for patients and clinicians in relation to the type and features of the technology, to ensure that the systems not only serve patients but also include integral components in the clinical workflow, thus fostering an efficient and collaborative care environment. The synthesis of qualitative insights with system evaluations will reveal how well current tools support this vital relationship, guiding the development of future solutions to better meet the needs of both patients and HCPs.

Ethical Considerations

There are no ethical considerations for the first stage (scoping review), as this will only examine previously published data. For the stage-2 production evaluation, we will be evaluating intervention features and will not have access to any patient data. The privacy of any user data accessed from app store reviews will be protected through anonymization in the data extraction process.

Results

Literature search and screening began soon after submission of the protocol, and the review is expected to be completed by end of September 2024.

Discussion

This review will examine currently available self-management systems within PD care with a particular focus on their acceptability and usability. The review will adopt a 3-stage approach, involving a scoping review, product search, and evidence of evaluation across various databases.

In the scoping review, there is also a potential publication bias, as the narrative synthesis may rely on published literature that predominantly reports positive outcomes, potentially overlooking negative or inconclusive results. In addition, selection bias could arise from the criteria used to assess and include systems, potentially favoring certain types of technology or studies with more rigorous methodologies. Finally, reporting bias might affect the qualitative synthesis, as the perspectives of clinicians and users reported in app store reviews or system descriptions may not fully capture the range of experiences, particularly those of individuals who did not engage with the tools or had negative experiences. To mitigate these biases, we will include a comprehensive range of studies, apply rigorous inclusion criteria, and seek diverse sources of qualitative data to ensure a balanced and representative analysis. Potential biases in data selection and interpretation may arise from the single-reviewer methodology, which is due to time and resource constraints.

Choosing only the Apple App store and Google Play store can be limiting, especially for health-related apps, as it may exclude specialized or region-specific app stores that offer unique or locally relevant health solutions. In addition, some innovative or niche health apps might only be available on alternative platforms like the Amazon App store, Samsung Galaxy Store, or F-Droid, potentially overlooking valuable resources for comprehensive health management.

The scope of the study will include an examination of the presence and extent of clinician-focused evaluations in existing research but will not deeply synthesize factors affecting clinicians' acceptability and usability. This is a gap in the literature, but it is not within the scope of this review due to resource and logistical limitations, and the purpose of the scoping review is to provide an overview of the literature. Understanding how to best support clinician adoption and use will be an important factor in the implementation of such systems and a good target for further research.

Despite the limitations, the review is expected to contribute to the literature by addressing a gap in research on the acceptability and usability of self-management systems for clinicians. It will provide a comprehensive summary of self-management systems adopting different types of technology used in PD care and differentiate between patient-centered and clinician-centric tools, aiming to offer recommendations that can inform future system designs.

Acknowledgments

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Authors' Contributions

The review protocol was conceived and supervised by MMI and EM. Clinical feedback was provided by CC. SB drafted the protocol, including the research question, Population, Intervention, Comparator, Outcome, and Studies (PICOS), and search strategy. All authors contributed revisions.

Conflicts of Interest

EM is the Editor-in-Chief of *JMIRx Med*. CC has received advisory, consulting or lecture fees from AbbVie, Bial, Mission Therapeutics, MODAG and Roche, and research funding from Parkinson's UK, Edmond J Safra Foundation, National Institute of Health and Care Research and Cure Parkinson's.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic review and Meta-Analysis Extension for Scoping Reviews) 2015 checklist.
[DOCX File , 20 KB - resprot_v13i1e58845_app1.docx]

Multimedia Appendix 2
Search strings of sample search.
[DOCX File , 16 KB - resprot_v13i1e58845_app2.docx]

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Abbreviations

HCP: health care professional
OCEBM: Oxford Centre for Evidence-Based Medicine
PD: Parkinson disease
PICOS: Population, Intervention, Comparator, Outcome, and Studies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

The Impact of Digital Technology on the Physical Health of Older Workers: Protocol for a Scoping Review

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Abstract

Background: Digital technologies have penetrated most workplaces. However, it is unclear how such digital technologies affect the physical health of older workers.

Objective: This scoping review aims to examine and summarize the evidence from scientific literature concerning the impact of digital technology on the physical health of older workers.

Methods: This scoping review will be conducted following recommendations outlined by Levac et al and will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines for reporting. Peer-reviewed papers written in English will be searched in the following databases: MEDLINE, Cochrane, ProQuest, Web of Science, Scopus, APA PsycInfo, and ERIH PLUS. The web-based systematic review platform Covidence will be used to create a data extraction template. It will cover the following items: study and participant characteristics, health measures, digital tool characteristics and usage, and research findings. Following the Population, Concept, and Context (PCC) framework, our review will focus on studies involving older workers aged 50 years or older, any form of digital technology (including teleworking and the use of digital tools at work), and how digital technologies affect physical health (such as vision loss, musculoskeletal disorders, and migraines). Studies that focus only on mental health will be excluded. Study selection based on title and abstract screening (first stage), full-text review (second stage), and data extraction (third stage) will be performed by a group of researchers, whereby each paper will be reviewed by at least 2 people. Any conflict regarding the inclusion or exclusion of a study and the data extraction will be resolved by discussion between the researchers who evaluated the papers; a third researcher will be involved if consensus is not reached.

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Results: A preliminary search of MEDLINE, Epistemonikos, Cochrane, PROSPERO, and JBI Evidence Synthesis was conducted, and no current or ongoing systematic reviews or scoping reviews on the topic were identified. The results of the study are expected in April 2025.

Conclusions: Our scoping review will seek to provide an overview of the available evidence and identify research gaps regarding the effect of digital technology and the use of digital tools in the work environment on the physical health of older workers.

International Registered Report Identifier (IRRID): PRR1-10.2196/59900

(JMIR Res Protoc 2024;13:e59900) doi:10.2196/59900

KEYWORDS

digital tools; digital technology; digitalization; physical health; mobility; vision loss; musculoskeletal disorders; migraine; older workers; older population; aging; scoping review; mobile phone

Introduction

Aging is a multifaceted process characterized by extensive intra- and interindividual differences, often conceptualized within theoretical frameworks as a dynamic balance between physiological advantages and limitations. Connected with this view, physical health has been described succinctly as "soundness of body" [1] and can be defined as a "dynamic state, the process of preserving and developing its biological, physiological and mental functions, optimal work capacity and social activity with the maximum life expectancy" [2], has been a major concern not only in the context of general aging but also aging in the workplace, especially with the extension of the working life and retirement age [3]. Physical health for older workers goes beyond maintaining the ability to perform job-related tasks effectively and includes prevention and management of age-related conditions, and ensuring overall well-being. Indeed, significant physiological changes have effects on the capabilities of older workers. These involve sensory function, muscle function, cardiovascular and respiratory function, neurological function, and immune response [4]. Nonetheless, despite the inevitable age-related physiological decline, a significant proportion of older workers demonstrate adaptation abilities, facilitating the maintenance of work performance [5].

As the global workforce ages and digital technologies increasingly penetrate the occupational landscape (through practices such as working from home, blended work, teleworking, and the use of digital apps), understanding the impact of digital technology on the physical health of older workers has emerged as a critical area of research. According to the latest European Union data from 2020, the share of older workers aged 55 years and older in the total number of employees increased from 12% to 20% between 2004 and 2019 [6]. At the same time, 21.6% of employees older than 55 years of age reported more than 2 work-related physical health problems [7].

With the global advancement of digital technology, especially in recent decades, the labor market and traditional work processes have undergone significant changes. New job roles and work conditions have emerged, introducing new physical and psychological requirements [8] that come with advantages and disadvantages. For instance, digital tools offer flexible arrangements such as working from home and diminish reliance on physically demanding tasks, thereby lowering the risk of musculoskeletal injuries, but only if workstations are ergonomically prepared, and regular breaks are taken [9]. However, the digitalization of work also introduces a spectrum of challenges that can adversely affect the physical health of older workers, including prolonged screen exposure leading to eye strain and headaches and extended periods of sitting without any physical activity, thereby increasing the risk of cardiovascular diseases and stress induced by the expectation of constant connectivity, which might lead to spinal, postural and other types of muscular disorders [9-11]. Furthermore, the inability to cope with technological innovation is a health risk that affects the work ability of older workers. Hence, providing continuous training or regular monitoring of biometric and physical health information [12,13], maintaining physical fitness, managing chronic diseases, and adapting workplaces are recommended to improve the safety and health of older workers and to support their productivity. Likewise, digital health coaching programs also assist older employees in maintaining health during the transition to retirement, potentially influencing physical health [14].

Against the aging of the workforce and the digital transition of the work environment, despite some emerging research and reviews in recent years focusing on understanding the psychological consequences of the digitalization of workplaces in terms of techno-stress [15,16], burnout, and mental strain [12,17,18], as well as on digital technologies for health and disease management [7,13,14,19-24], to the best of our knowledge, there is no existing systematic or scoping review that focuses on how older workers are affected physically by the digitalization of their tasks and workplaces. In this regard, this scoping review protocol aims to address the existing research gap in understanding the current scientific literature that examines various physical health consequences (positive or negative) of digitalizing work environments among older workers.

Methods

Guidance Frameworks

Based on the first methodological framework for conducting scoping reviews by Arksey and O'Malley, this scoping review will be conducted following the recommendations outlined by Levac et al [25] to guarantee a systematic and coherent process. Levac et al advocate proceeding by describing the following

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stages: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting and collating the data, and (5) summarizing and reporting the results. To report our findings, we will also adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines for reporting [26]. The PRISMA-ScR checklist for the scoping review will be reported in an appendix, and the PRISMA-ScR checklist for this protocol can be found in Multimedia Appendix 1.

Protocol and Registration

This protocol was written before we performed the full electronic literature search (we searched for existing scoping reviews and pilot-tested different search terms; more details below). After the peer-review process the study was registered at the Open Science Framework [27].

Stage I: Identifying the Research Question

We posed the research question: How do digital technologies in the workplace affect the physical health of older workers? As there are many ways in which digital technology can affect an older worker's health (from vision loss to musculoskeletal disorders), there are many types (from working online from home to the use of robotics in a car assembly line); we also have the following subquestions: (1) What are the most common physical health issues that older workers have to manage as a result of digital technologies in the workplace? (2) What industries most affect older workers' health as a result of the use of digital technology?

Based on our research questions, we defined the Population, Concepts, and Context (PCC) criteria of interest to clarify the focus of the scoping study and establish an effective search strategy (see also [25]; Textbox 1): To summarize the main points reflecting the PCC criteria: regarding the population, our review will focus on studies involving older workers aged 50 years or older.

The concept of interest is the implicit (eg, working from home) or explicit (eg, software systems, communication platforms, document management systems, lighting control systems, and automated and robotic systems) use of any type of digital technology within the work environment to execute job-related tasks. In terms of context, we are specifically interested in examining how digital technologies impact physical health issues such as vision loss, musculoskeletal disorders, migraines, and cardiovascular diseases. Studies focusing solely on mental health impacts will be excluded from this review.

Textbox 1. Definitions of the inclusion criteria regarding Population, Concepts, and Context in the scoping review.

Population: older workers

- Older workers include study participants employed at the moment of the study.
- Study participants must be aged 50 years or older. When only age ranges are analyzed, the age of 50 should be included in the youngest age category (eg, 45-54). While ongoing debates exist regarding what age defines older workers [28], we have opted to include individuals 50 or older. This decision is based on the increasing presence of this cohort in the labor market, their likelihood of remaining in the workforce longer than previous generations, and the need to recognize the diversity within this demographic group. People in their 50s may have varying career trajectories, skill sets, and motivations for remaining in the workforce. By defining older workers as those aged 50 years and older, organizations can more effectively cater to the unique needs and experiences of this diverse and increasing group of older individuals in the labor market.
- If age is treated as a continuous variable rather than analyzed as categories, the sample also has to have participants aged 50 years or older; that is, younger ages are only permitted if older ages are also represented in the study.

Concept: digital technologies

- Digital technologies refer to data manipulation, storage, transmission, and processing in binary data [29]. It allows for the interaction with stored data using electronic devices (eg, computers and microprocessors). Digital data can be stored in various digital storage media (eg, hard drives, solid-state drives, memory cards, and cloud storage). Furthermore, digital technology also enables the transmission of data over digital communication networks (eg, the internet, local area networks, and wireless networks).
- Digital technologies are defined as any type of digital tool or device used in the context of (creative) production, that is, studies or study results that look at the effect of digital technologies not related to work (eg, for health management) are excluded.
- Digital technologies include the use of computers at home for work (eg, teleworking) as well as more recent digital technologies (eg, apps), but only if they are used for work purposes.
- Studies will be excluded if working from home does not involve digital tools (eg, only landlines are used).

Context: physical health

- Any physical health outcome is accepted.
- Mental health outcomes are excluded unless mentioned in combination with a physical health outcome.
- Studies will be excluded if the health outcome is not associated with an effect of the use of digital technologies in the work sphere.

Stage II: Identifying Relevant Studies

We follow the JBI Manual for Evidence Synthesis [30] for our search strategy. For the protocol, the databases PubMed (Multimedia Appendix 2), PROSPERO, and JBI Evidence Synthesis were searched on April 15, 2024. Still, no current or underway systematic reviews or scoping reviews were identified (the 4 results shown are not related to the topic of our interest).

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For the scoping review, we will search for peer-reviewed studies in the following databases: MEDLINE, Cochrane, ProQuest, Web of Science, Scopus, APA PsycINFO, and ERIH PLUS. The web-based systematic review platform Covidence will be used to import the references and remove duplicates. The search terms to be used are: (physical adj (health* OR condition* OR issue* OR impairment* OR fitness OR wellbeing OR (well adj being) OR integrit* OR state* OR stress) OR disease* OR vision OR mobility OR obes* OR overweight OR "Body Mass Index") AND (digital OR app* OR web OR internet OR tech* OR (social adj media) OR chat OR online* OR cyber OR virtual OR computerized OR computerised OR electronic OR ICT) AND ((old* or elder* or ageing or ageing or senior*) adj1 (work* OR employee* OR profession* OR labor OR labour OR colleague* OR staff* OR cowork* OR personnel)).

In constructing our search strategy, we used the asterisk "*" symbol as an end-of-root-word-truncation mark and the Boolean operator "OR" to encompass a broad range of related physical health conditions, digital technologies, and terms referring to older workers. In addition, we used the adjacency operators "adj" and "adj1" to ensure that closely related terms appearing contiguously in the literature are captured, thereby enhancing the specificity of our search results and enabling a comprehensive inclusion of relevant studies.

A preliminary search conducted on April 18 and 19, 2024, for MEDLINE, Cochrane, and Epistemonikos provided 299, 260, and 5 references, respectively, before deduplication (more details in Multimedia Appendix 3).

In our final search, we will restrict our search to papers written in English and exclude any gray literature.

Stage III: Study Selection and Eligibility Criteria

Once the references (excluding duplicates) are imported onto the Covidence platform, the first phase of the study selection will be the title and abstract screening. This is then followed by the full-text review to select the relevant studies for the main and secondary research questions of our scoping review. Finally, during the last phase, a data extraction template will be created in Covidence and used to facilitate the extraction of relevant information from the previously selected studies. This template will encompass items on participant demographics (age and gender), type of worker (occupation or employment branch), the specific digital technology examined and amount of usage, physical health outcome variables, and fundamental research findings derived from the selected studies.

Given the sheer number of papers likely to be retrieved during the first phase, most, if not all, co-authors will be involved in the selection process during each phase, whereby each paper will be revised by 2 people. Furthermore, when Covidence detects a conflict regarding the inclusion or exclusion of a study, this is then resolved by a third person.

In addition, regular online meetings will be held with the whole team to discuss any issues during the different study selection phases.

The eligibility for a study to be included will be based on the PCC and other criteria shown in Textbox 2. Note that there are no inclusion or exclusion criteria regarding the year of publication or the country of study. The former is because no previous scoping review on the precise topic has yet been published in a peer-reviewed journal, while any exclusion of territories would have to be justified.

Textbox 2. Eligibility criteria for the scoping review.

Inclusion criteria

- Population: older workers (50+ included in study)
- Concept: digital technologies related to work
- Context: physical health outcomes
- Setting: nonclinical and in the work sphere
- Study type: original studies with any design or data type (quantitative and qualitative)
- Publication status: published in a peer-reviewed journal
- Publication language: English
- Full-text available

Exclusion criteria

- Population: younger workers (50+ not included in the study)
- Concept: digital technologies not related to work (eg, for health management)
- Context: nonphysical health outcomes (eg, mental health)
- Setting: clinical and not in the work sphere
- Study type: other study types (eg, protocols, narrative reviews, or systematic reviews)
- Publication status: published without peer review, dissertations, books, conference papers, letters, and editorials
- Publication language: written in a language other than English
- Full-text not available

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Stage IV: Charting the Data

The information from each selected publication, obtained from the final data extraction phase, will be summarized in a table. The main outcomes of interest are provided in Item 11 of the PRISMA-ScR checklist (see Multimedia Appendix 1).

Stage V: Collating, Summarizing, and Reporting Results

In accordance with the recommendations outlined by Levac et al [25], the fifth stage of our methodology consists of 3 distinct steps: (1) analyzing research findings, encompassing both descriptive numerical summary analysis and qualitative thematic analysis; (2) evaluating the research findings to extract outcomes aligned with the research question, which are then reported narratively; and (3) interpreting and discussing the findings in relation to additional research questions, practical applications, and policy implications.

In addition to narrative reporting, tables will be used to provide a structured overview of the key findings. The PRISMA-ScR [26] guidelines will be adhered to ensure systematic reporting of the results.

In addition, we will assess the quality of studies using the Mixed Methods Appraisal Tool [31], whereby any discrepancies will be resolved through consensus between the reviewers.

Results

We devised a comprehensive search strategy to identify papers on physical health issues associated with the use of digital technologies in the workplace. The outcomes of our inquiry will be disseminated through a scoping review. Consequently, the selection process for publication will be delineated using flowcharts, while the data extracted from our research will be organized in tables and expounded upon in a narrative summary. Subsequently, the summarized findings will endeavor to address the research question, “How do digital technologies in the workplace affect the physical health of older workers?” and the following subquestions: (1) what are the most common physical health issues that older workers have to manage as a result of using digital technologies at the workplace; and (2) what industries most affect older workers’ physical health as a result of applying digital technologies?

Discussion

Preliminary Findings

The scoping review outlined in this protocol will lay the groundwork for a comprehensive research initiative examining the impact of digital technologies on the health of older workers. Building upon the proposed work in the scoping review, there is potential to harness innovative technological solutions and evaluations to promote enhanced well-being and productivity among older workers in various work settings. Furthermore, we anticipate that the results of this scoping review will provide methodological insights and direction for exploring the integration of adaptive features for digital technology in the context of older workers. The findings from the scoping review will be shared through peer-reviewed scientific journals and conference presentations, contributing to the advancement of knowledge in this crucial area.

Limitations

Our selection criteria restrict the inclusion of papers presenting empirical evidence published in English, potentially biasing the study pool toward research from Western countries as well as the physical health effects of digital technology used. Therefore, readers should exercise caution when interpreting the findings, considering the varying quality and applicability of the included studies.

The term “digital technology” was chosen as the subject heading for its relevance to our research scope. In developing our search strategy, we worked closely with an information specialist to pilot test a variety of terms, both subject headings and text words, aiming for comprehensive coverage. Subject headings are part of a controlled vocabulary that helps standardize the indexing of studies, while text words can vary greatly depending on the author’s choice of language. This variability in text word usage may affect the inclusiveness of the search results. For instance, authors may use different terminology to describe similar concepts, or a term might have different connotations in different regions. Despite a thorough approach and expert consultations, we must acknowledge the possibility of not capturing all pertinent studies due to the dynamic nature of terminology in this rapidly evolving field.

Comparison With Previous Work

Our scoping review focuses on identifying digital technologies that impact the physical health of older workers and discerning which job types are most influenced by the integration of these technologies. The integration of digital technologies into the workplace offers potential benefits by automating physically demanding tasks and optimizing work processes, which could potentially reduce physical strain on older workers [32,33]. However, despite the frequent use of technologies like smartphones, laptops, and tablets among older individuals, comprehensive studies exploring the direct links between digital work environments and physical health outcomes among older workers are scarce.

Previous scoping and systematic reviews have predominantly examined the mental impacts of digital technology at work, such as those on mental health outcomes listed in Table 1. The focus was largely on psychotherapeutic interventions using digital tools, with an emerging interest in technologies such as extended reality. A comprehensive overview of the effectiveness of digital and technological interventions in mental health and well-being is provided by De Witte et al [34]. Similarly, Seberini et al [35] reviewed the impact of information and communication technologies (ICT) on older workers, particularly focusing on strategies to reduce the digital divide and technostress, and found how the rapid adoption of digital tools during the COVID-19 pandemic increased technostress among older workers as well as feelings of marginalization among older adults with a lack of technological skills, which also impacted their mental and physical health. Li [36], on the other hand, highlights how digital technologies were effectively used to address mental health issues among older workers during

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the COVID-19 pandemic, providing support through various web-based and mobile-based platforms. Overall, the reviews collectively suggest that while digital technologies hold significant potential for improving mental health outcomes in workplace settings, they also discussed the dual nature of digital technology in workplaces, where it can either exacerbate stress and mental health issues or be a tool for promoting well-being.

While there is extensive research on digital work's mental health impacts, our review focuses on the less explored physical health implications for older workers. Substantial causal evidence regarding how digital technologies affect their physical health is notably scarce.

Therefore, the anticipated outcomes of our scoping review are expected to elucidate dimensions considered pertinent to health promotion and disease prevention, particularly in supporting and maintaining the physical health of the aging workforce. This review will underscore the significance of mitigating occupational health risks, emphasizing the crucial influence of various factors, including physical, ergonomic, and psychosocial elements, on work-related health outcomes.

Table 1. Selected systematic reviews on digital technologies for older people's mental health.

Review citation	Population age (older people, years)	Digital technologies	Health outcomes
Li [36]	>50	eHealth and remote support	Reduction in depression, stress, and anxiety
De Witte et al [34]	50-55	Workplace digital interventions	Workability and health maintenance
Seberini et al [35]	≥60	Information and communication technologies	Technostress

Conclusions

This scoping review will be the first to offer a comprehensive overview of physical health effects resulting from the use of digital technologies in the workplace. The findings of this scoping review will serve as foundational knowledge for understanding the impact of digitalization on the health and well-being of older workers, informing future research directions and potential interventions aimed at promoting the health of this demographic in evolving work environments.

Acknowledgments

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Authors' Contributions

JJAS conceptualized the study. JJAS and CMT developed the methodology. Besides the Research Librarian, JJAS, DAG, and YG also performed preliminary searches of article databases. All authors contributed to the first draft and critically reviewed and revised the submitted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 147 KB - resprot_v13i1e59900_app1.pdf]

Multimedia Appendix 2
Search results of scoping reviews of the effect of digitalization on the physical health of older workers (no relevant hits).
[PDF File (Adobe PDF File), 444 KB - resprot_v13i1e59900_app2.pdf]

Multimedia Appendix 3
Pilot test 1 of search terms of studies on the effect of digitalization on the physical health of older workers using Cochrane, Medline and Epistemonikos.
[PDF File (Adobe PDF File), 183 KB - resprot_v13i1e59900_app3.pdf]

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Abbreviations

ICT: information and communication technologies
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Factors Influencing Primary Care Access for Common Mental Health Conditions Among Adults in West Africa: Protocol for a Scoping Review

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Abstract

Background: Mental health conditions are expressed in various ways in different people, and access to health care for these conditions is affected by individual factors, health care provider factors, and contextual factors. These factors may be enablers or barriers to accessing primary care for mental health conditions. Studies have reported a gap in treatment for mental health conditions in many countries in West Africa due to barriers along the access pathway. However, to the best of our knowledge, there is yet to be a review of the factors influencing access to primary care for common mental health conditions among adults in West Africa.

Objective: Our scoping review will explore the factors influencing access to primary care for common mental health conditions among adults aged 18 years and older in West Africa from 2002 to 2024.

Methods: Our review will follow the approach to scoping reviews developed by Arksey and O'Malley in 2005. This approach has five stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. We will search electronic databases (PubMed, Embase, PsycINFO, Cairn.info, and Google Scholar), source gray literature from relevant websites (the World Health Organization and country-specific websites), and manually explore reference lists of relevant studies to identify eligible records. Pairs of independent authors (NYA-B, RNBA, VR, or DS) will screen the titles, abstracts, and full texts of studies based on predefined eligibility criteria. We will use a data extraction tool adopted from the *JBI Manual for Evidence Synthesis* to chart the data. Deductive, thematic analysis will be used to categorize factors influencing access to mental health care under predetermined themes. New themes derived from the literature will also be charted.

Results: Database searches were conducted between February 1, 2024, and February 12, 2024. As of July 2024, the review report is being drafted, and it will be disseminated through publication in a peer-reviewed journal.

Conclusions: The results of the review will inform decision-making on policies, programs, and their implementation in West Africa to improve primary care access for mental health care.

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KEYWORDS

scoping review; mental health; noncommunicable disease; primary care; access; barriers; enablers

Introduction

Background

Mental health is defined as "a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community. It is an integral component of health and well-being, and is more than the absence of a mental disorder" [1]. It comprises an intricate range of mental health states, and not simply the absence of a defined mental disorder. Mental health conditions are expressed in various ways in different people and are affected by numerous individual and environmental factors [1]. Some common mental health conditions include depression, anxiety disorders, bipolar disorder, and schizophrenia [1].

The global figures on mental health conditions are staggering. In 2019, it was estimated that 970 million people were living with a mental condition, 82% of whom were living in a low- or middle-income country (LMIC) [2]. In that same year, 301 million people were said to be living with anxiety disorders, while 280 million people had depressive disorders globally [2]. Furthermore, mental disorders are the foremost cause of years lived with disability (YLDs), contributing to 1 in 6 YLDs worldwide [2]. In 2019, 5.6% of YLDs were attributable to depression alone [2]. A scoping review of population-based epidemiological studies in Africa conducted in 2020 revealed that the prevalence of mental disorders ranged from 3.3% to 9.8% for mood disorders, 5.7% to 15.8% for anxiety disorders, and 3.7% to 13.3% for substance use disorders [3].

Apart from the alarmingly high prevalence of various mental disorders, an emerging area of concern is the link between these disorders and noncommunicable diseases (NCDs) such as hypertension and diabetes. Reviews and meta-analyses have established a connection between mental disorders and cardiovascular diseases [4,5]. Primary studies conducted in LMICs have confirmed a similar association between mental disorders and NCDs [6-8]. A study conducted by Nkporbu et al [9] in Nigeria to determine the pattern and prevalence of psychiatric comorbidity among patients with hypertension revealed that almost two-thirds of the 232 participants had coexisting mental disease, most commonly depression, followed by anxiety disorders. These findings are consistent with that of a similar study by Keskin and Bilge [8] in a primary care setting in Ankara, Turkey, which found that about half of the patients with hypertension and diabetes in their study had mental health disorders, the most frequent of which were mood disorders.

Common mental disorders are a collection of illnesses characterized by depression, anxiety, and the experience of unexplained bodily symptoms [10]. On the other hand, mood disorders are psychiatric conditions characterized by prolonged and marked emotional disturbance [11]. While persons living with NCDs are at risk of some mental disorders, mood disorders are their most commonly encountered mental disorders [8,9]. For instance, depressive illnesses are frequent among patients with diabetes [6]. People with chronic NCDs may experience depression due to challenges with managing their condition [12]. The World Health Organization (WHO) recommends a protocol for managing mental conditions in primary care settings. This means that people with physical conditions (including NCDs) need to be screened for mental disorders (by appropriate history taking and mental state examination where needed) and offered the required psychosocial (psychoeducation, counseling, promotion of function, and psychological treatment) or pharmacological intervention as indicated [13].

The WHO defines primary care as "a model of care that supports first-contact, accessible, continuous, comprehensive and coordinated person-focused care" [14]. In health care, access can be defined as "the opportunity to have healthcare needs fulfilled" [15]. Despite the prevalence of mental health conditions and the emphasis on access to primary care, the West African subregion has responded slowly to the burden of these disorders. Mental health policies and legislation in most West African countries are either obsolete or have major pitfalls, budgetary allocation for mental health is insufficient, and mental health services are mostly limited to large facilities that are poorly distributed geographically, thereby impeding access [16]. In addition, some people believe mental illnesses are caused by evil spirits [17]. Consequently, in West Africa, patients seek primary care at allopathic facilities as well as from alternative health providers such as herbal medicine practitioners [16]. All these avenues of first-contact care provide primary care for mental health conditions.

Providing timely and accessible care for mental health conditions requires the efficient integration of mental health care into existing primary care systems [18]. This ensures that people with mental illnesses are provided with care within their community that is adapted to fit their context [19]. However, in many West African countries, this is not the case. For instance, in Ghana, although there have been efforts to provide adequate mental health care at the primary care level, it has been fraught with challenges with personnel, policy implementation, and funding; as such, persons with mental illnesses have to travel long distances to specialized hospitals to receive care [20]. The situation is similar in countries such as Liberia, Sierra Leone, and the Gambia, where mental health care provision at the primary care level is almost nonexistent [16]. Also, in Nigeria, most people with mental health challenges do not have access to care in their communities. Instead, they have to resort to the few overburdened psychiatric facilities for care, regardless of illness severity [21].

As a result, mental health care provision in West Africa is largely pluralistic, characterized by a complex, uncoordinated system of allopathic, traditional, complementary, and alternative medicine providers [22-26]. In Burkina Faso, most patients seen at formal mental health care facilities will have already visited a traditional medicine practitioner for some form of treatment [22]. Similarly, in Ghana, Nigeria, and Liberia, it is common for service users to seek mental health care from traditional

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healers, faith healers, and other alternative medicine providers before eventually resorting to formal mental health care [24-26]. Rather than benefiting from the collaborative effort of different types of mental health service providers, people with mental health challenges in West Africa experience delays in receiving adequate primary health care due to a lack of an efficient coordination system [26].

Factors influencing primary health care access for common mental health conditions can be broadly categorized as factors that act as barriers to access and factors that act as enablers to access. Factors we identified in the literature that can act as barriers to primary care access for common mental health conditions include the stigmatization of mental health service users [20,27-36]. Also, a lack of knowledge of mental health on the part of patients and the absence of capacity-strengthening programs for service providers hinder effective primary care for mental disorders [20,27,32,33,36-38]. Furthermore, individual experiences of mental health services such as the perceived ineffectiveness of some medications and unpleasant side effects could serve as barriers [39]. As in other LMICs, costs of care, including medication and transportation, also hinder people from seeking mental health care in West Africa [17,20,30-32,34,40,41]. This represents a significant burden to the families of service users [20].

A study in Liberia by Herman et al [41] revealed that some service users and their families do not seek help because they live too far from health facilities. Some persons in Nigeria also report prolonged waiting times at mental health facilities [32]. In many West African countries, mental health services are centralized despite the existence of decentralization and integration policies [28,42]. Moreover, there are many bottlenecks with the referral systems, aggravated by the lack of application of policies on task-shifting —the process of delegating tasks from specialized health workers to other health workers—in mental health care delivery [40,43,44]. Also, primary health care facilities frequently run out of essential medications for treating mental health disorders [34,40,45]. This is usually reported simultaneously with the poor state of psychiatric facilities, hindering quality mental health care provision [40,45]. Different studies also identify poor human resource management as a major hindering factor. There are not enough mental health workers [34,40,45]. The few available also need further training to improve their service delivery.

Factors that act as enablers of access to primary mental health care identified in the literature are, first, support services for persons with mental health conditions [20]. Such services are predominantly provided by the families of those affected [20]. Religious organizations, neighbors, and friends also provide support in certain areas [20]. For example, in the 5 northernmost administrative regions of Ghana, there are self-help groups that provide social and financial support to service users and caregivers [46]. Second, the existence of mental health laws is an enabling factor [45]. In some instances, such as in the Gambia, there is mental health legislation in place, although it is not backed by law [36]. Finally, although its implementation has been met with some challenges, studies have shown that task-shifting enhances the provision of quality mental health care delivery [28,43,47].

Rationale

Despite the need and importance to inform policy and program decision-making for the selection, design, and implementation of interventions to address and improve mental health in West Africa, we did not find a systematic review of these enablers and barriers or factors that influence primary health care access for mental health in West Africa. A scoping review of population-based epidemiological studies of mental disorders in Africa was conducted [3], but it was a prevalence study that did not address the factors that influence access to primary care for these conditions. An integrative review of enablers and barriers to accessing mental health services was limited to Ghana [20], 1 of the 15 countries of the Economic Community of West African States (ECOWAS). Similar reviews were not available for the remaining countries of ECOWAS. A systematic review of the literature on factors influencing primary mental health care access will also help to identify gaps in the literature, which will necessitate further research to inform policy and program decision-making. However, it was uncertain from our initial literature review whether the breadth and depth of the literature available across the 15 West African countries that made up ECOWAS at the time of the review was adequate for a classical systematic review. We therefore chose to start with a scoping review. Scoping reviews are a form of systematic review that is particularly useful in situations of uncertainties about the breadth and depth of the literature. They enable systematic mapping of the available evidence and are particularly suitable for identifying knowledge gaps and the main sources of evidence on a concept in these situations of uncertainty about the evidence base [48].

Objectives

The main objective of this review is to identify factors influencing access to primary care for common mental health conditions (depression, bipolar disorders, schizophrenia, anxiety disorders, stress disorders, and substance use disorders) in adults aged 18 years and older in West Africa from 2002 to 2024.

The specific objectives, all related to access to primary care for common mental health conditions among adults aged 18 years and older in West Africa from 2002 to 2024, are as follows: (1) to identify patient-level factors that affect and how they affect access to care; (2) to identify primary health care facility–level factors that affect and how they affect access to care; (3) to identify specific contextual factors (societal beliefs, norms, and practices) that affect and how they affect access to care; and (4) to synthesize implications for co-design with stakeholders in interventions for primary mental health care, identify gaps in the literature, and suggest areas for further research into primary care for common mental health conditions among adults aged 18 years and older in West Africa from 2002 to 2024.

Conceptual Framework for Enablers and Barriers to Primary Care Access for Mental Health

We adapted a conceptual framework to guide our exploration and analysis of factors influencing access to primary care for mental health, drawing on the work of Levesque et al [15] and the concept of context from the framework of context described by Leichter [49].

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The framework (Figure 1) categorizes and explores factors (or enablers and barriers) that influence access to primary care for mental health, further categorized into factors that operate at the level of individual perspectives and the level of the primary health care facility. Enablers and barriers influencing access to care related to the primary health care facility include (1) approachability, (2) acceptability, (3) availability and accommodation, (4) affordability, and (5) appropriateness of services. Enablers and barriers influencing access to care related to the individual include (1) perceptions of care, (2) care-seeking behavior, (3) reaching and obtaining health care, (4) health care payment, and (5) health care engagement.

The framework also includes specific contextual factors that influence access to primary care for mental health conditions. We defined contextual factors as those elements outside individuals but within their environment that interact with the individual and influence their approach to seeking and using health care services [50]. Thus, although Leichter [49] subdivided contextual factors into situational, structural, cultural, and environmental factors, we only focused on the cultural factors to meet our third specific objective. These contextual factors include sociocultural and socioeconomic factors such as social norms, cultural beliefs, traditions, and income levels [50]. These sociocultural and socioeconomic enablers and barriers act as background factors in the society of the individual and primary health care facility that shape other enablers and barriers to accessing primary care for mental health.

Individuals' access to primary care for mental health will depend on their perceptions of care, their care-seeking behavior, their ability to reach a primary care facility, and their capacity to pay for and engage with the available services. Access will also depend on how approachable the primary care facility is, how well the individual accepts the mode of service delivery, the services available, how affordable they are, and how appropriate they are for attending to mental health. These factors are all affected by social constructs of mental health such as the beliefs, norms, traditions, and income levels of that specific society. Therefore, primary care access for common mental health conditions among adults in West Africa is affected by interactions between enablers and barriers to access at the individual and primary health care facility level, and these interactions take place within a background of, and are shaped by, specific contextual factors.

Figure 1. Conceptual framework for access to primary care.

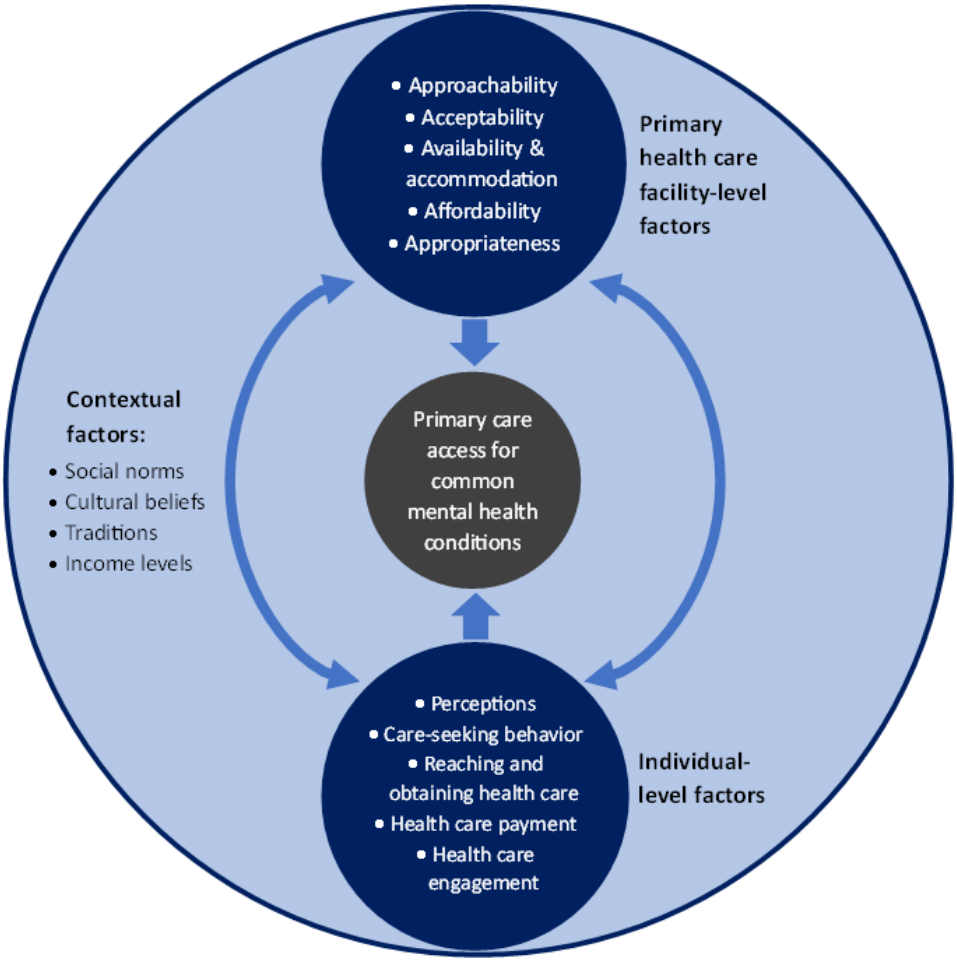

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Methods

Protocol Design

Our review will follow the approach developed by Arksey and O'Malley [51] in 2005. Their seminal work in scoping reviews was, in many respects, a foundation for further initiatives to bring some standardization to the structure of scoping reviews. As they suggested, we will follow these five stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. We will not assess the risk of bias or quality of the studies included, as this scoping review seeks to present an overview of the information available on the research topic.

Identifying the Research Question

The research question was developed based on the gaps identified from the initial literature review and in consultation with a team of researchers with expertise in the field. Following an iterative process, the main research question we seek to answer is as follows: "What factors influence access to primary care for common mental health conditions in adults aged 18 years and older in West Africa?"

As defined earlier, common mental conditions are a collection of disorders characterized by depression, anxiety, and the experience of unexplained bodily symptoms [10]. The mental conditions of interest to our review are depression, bipolar disorders, schizophrenia, anxiety disorders, stress disorders, and substance use disorders.

Identifying Relevant Studies

Eligibility Criteria

We will focus on studies published between January 1, 2002, and January 31, 2024, and will use the participants, concept, context, and type of study (PCCS) framework to identify studies that are eligible for our review.

Participants

Studies in which participants are adults aged 18 years or older who have a mental disorder will be considered. These patients should be those who seek primary care at various facilities. Studies that report the perspective of other stakeholders, such as health care workers (including allopathic and alternative medicine providers), policy makers, and caregivers (relatives and support workers) of these patients, will be included. We will use the definition of primary care stated in the Background section of this paper. Studies conducted in adults and children in which the data for participants aged 18 years or older cannot be extracted separately will be excluded. Studies conducted on pregnant women will also be excluded.

Concept

We are interested in studies reporting factors influencing primary care of common mental health conditions in adults. These could either be individual characteristics or behaviors such as income, livelihood, or gender; they could also emanate from environmental and contextual influences such as societal beliefs, norms, and practices. The mental health conditions we will consider include depression, bipolar disorders, schizophrenia, anxiety disorders, stress disorders, and substance use disorders in the study participants.

Context

The included studies had to be conducted in 1 or more countries in West Africa. The 15 countries that belonged to ECOWAS over the period covered by this study were Benin, Burkina Faso, Cabo Verde, Cote d'Ivoire, the Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, and Togo. Studies conducted in settings that include West African countries and other countries in which the data for the West African countries cannot be extracted separately will be excluded.

Type of Study

Primary studies, whether experimental or nonexperimental and descriptive or analytical, will be considered for our scoping review. Systematic and scoping reviews that meet other inclusion criteria will also be considered. Unpublished studies and gray literature reporting data that answer our research question will also be included. On the other hand, case studies, case reports, and anecdotal evidence from gray literature will be excluded.

Conducting the Search

The search will include studies conducted from January 1, 2002, to January 31, 2024. The start date was chosen because that was when the WHO, through the Mental Health Gap Action Programme (mhGAP) [52], spearheaded a concerted effort to address the global burden of mental health conditions, with particular attention paid to LMICs. Under this initiative, the WHO, through partnerships with member states, outlined a comprehensive strategy to strengthen the capacity of governments to reduce the risk and burden of mental health conditions [52]. Our search will be restricted to English and French, the official languages of most countries in West Africa. The databases we will search will include PubMed, Embase, PsycINFO, Cairn.info, and Google Scholar. Key concepts from our research question and alternative terms (Table 1) will be used to develop a full search strategy. The search strategy for PubMed is provided in Multimedia Appendix 1. This search strategy will then be adapted for each database. The coauthors will search the databases with the help of an information scientist. The bibliographies of studies included in the initial search will be manually explored for additional papers. The search results will then be exported to Rayyan, a web-based screening tool, which will be used to screen the titles and abstracts. Records that are in French will be translated with the help of a bilingual secretary and translation software (DeepL Translate; DeepL SE).

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Table 1. Key concepts and alternative terms.

Concepts	Terms
Mental health condition	common mental disorder; mental disorder; mental illness; stress; stress disorder; anxiety; anxiety disorder; generalized anxiety disorder; depression; recurrent depression; major depression; major depressive illness; depressive illness; depressive disorder; mood disorder; substance abuse; substance use disorder; bipolar disorder; schizophrenia
Hypertension	high blood pressure; raised blood pressure; increased blood pressure; hypertensive disease; hypertensives; hypertensive patients
Diabetes	diabetes mellitus; high blood glucose; high plasma glucose; raised blood glucose; increased blood glucose; diabetics; diabetic patients
Influence	barrier; hindrance; hinder; obstacle; difficult*; obstruct; prevent; limit*; restrain*; inhibit; enable*; facilitat*; support; opportunit*; aid; ease; promot*; help
West Africa	Benin; Burkina Faso; Cape Verde; Cabo Verde; Cote d'Ivoire; Gambia; Ghana; Guinea; Guinea-Bissau; Ivory Coast; Liberia; Mali; Niger; Nigeria; Sierra Leone; Senegal; Togo
Primary care	health education; patient counseling; psychotherapy; exercise; cognitive behavioural therapy; behavioural therapy; stress therapy; selective serotonin reuptake inhibitors; SSRIs; tricyclic antidepressants; TCAs; antidepressants; anxiolytics; rehabilitation; primary care; primary healthcare; health services; healthcare

Study Selection

Rayyan will be used to handle the results, remove duplicates, and screen the records. Pairs of reviewers (NYA-B, RNBA, VR, or DS) will independently screen the titles and abstracts of the studies. We will then select the studies that are relevant to our topic. After this, we will retrieve and read the full text of the selected studies. Studies that meet the inclusion criteria described above will be selected for final analysis. In our final report, we will document the reasons for excluding any study. The operationalization of our eligibility criteria will be tested beforehand, using a random sample of 5 of the retrieved studies. This will be done by the pairs of independent reviewers to ensure reliability. A third reviewer will settle any disagreements following this process. The results of the entire search strategy and study selection process will be illustrated in the final report using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [53] flow diagram, shown in Figure 2. Zotero (Corporation for Digital Scholarship), a reference management tool, will be used to add citations and a list of references in the final report.

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Figure 2. PRISMA flow diagram.

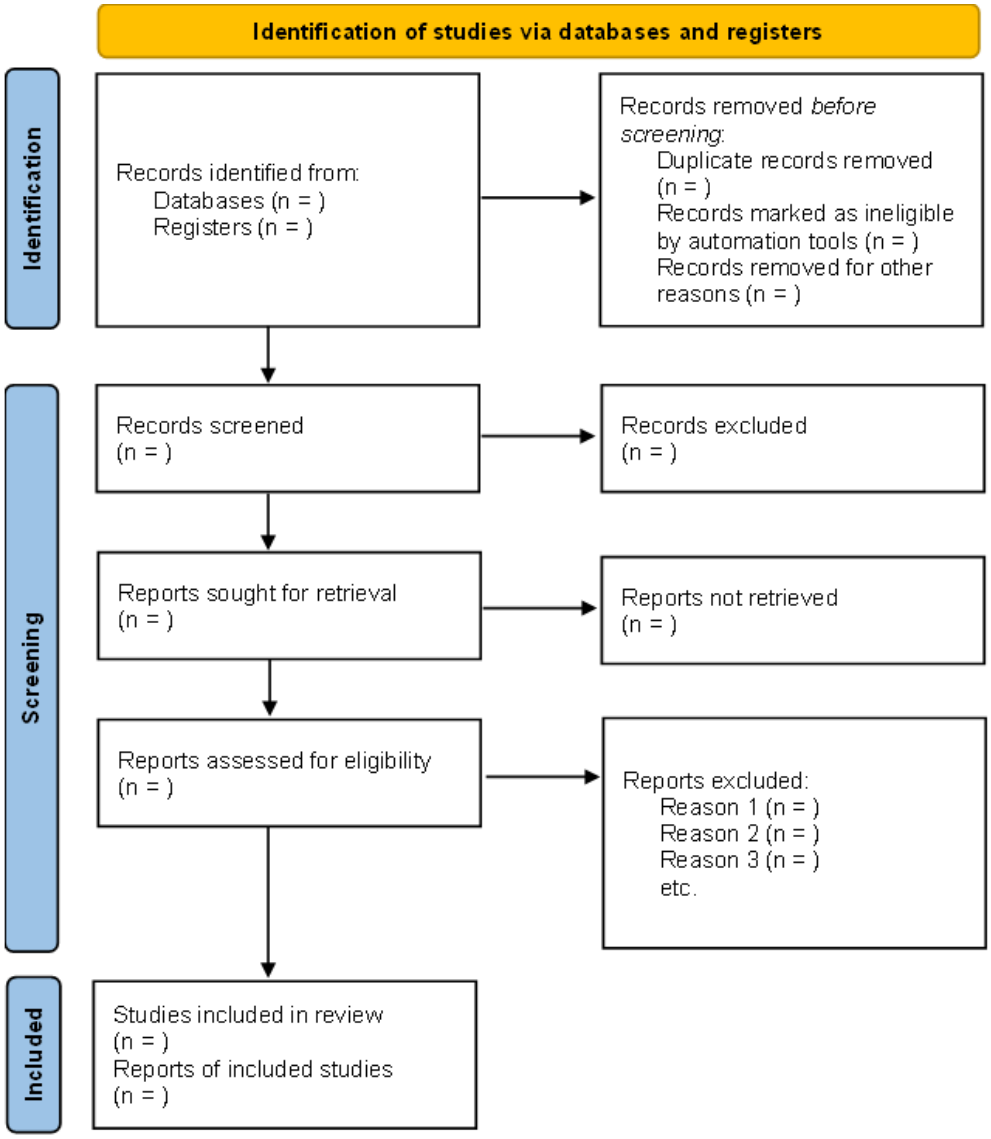

Charting the Data

The data will be charted using Microsoft Excel spreadsheets. A draft data extraction tool adopted from the *JBI Manual for Evidence Synthesis* [54] will be used (Figure 3). The data to be extracted will include publication details (author, year of publication, title, country, and language), study characteristics (objectives; characteristics of the study population and participants; sample characteristics, including sample size and sampling method; study design; and type of evidence source, whether it is a review, primary study, or website), the context, the key findings, and comments such as strengths or weaknesses of the study. The key findings will include the results of the study as well as information related to the objectives of our review. Pairs of independent reviewers will pilot the tool on a sample of 5 studies to assess validity. Where necessary, modifications will be made to the tool and documented in the final review. A third independent reviewer will settle any disagreements. We will contact the authors for more information and clarification concerning missing data.

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Figure 3. Draft data extraction tool.

Publication Details	Key Findings			Comments
Author(s): Year: Title: Country: Language:	**Patient-level factors** Perceptions Care-seeking behavior Reaching health care Health care payment Health care engagement	**Enablers**	**Barriers**	
Study Characteristics Objectives: Study population: Study participants: Study design: Setting:	**Primary health care facility-level factors** Approachability Acceptability Availability and accommodation Affordability Appropriateness	**Enablers**	**Barriers**	
Sample size: Sampling method: Data collection method: Data analysis: Type of evidence source:	**Contextual factors:** Social norms Cultural beliefs Traditions Income levels	**Enablers**	**Barriers**	

Collating, Summarizing, and Reporting the Results

The extracted data will be summarized and presented narratively according to the framework for access to primary care described earlier. Based on this, the following themes determined a priori will be used to categorize the influencing factors: perceptions; care-seeking behavior; reaching and obtaining health care; health care payment; health care engagement; approachability, acceptability, availability and accommodation, affordability, and appropriateness; and social norms, cultural beliefs, traditions, and income levels. Under each theme, the factors will be identified as enablers or barriers to primary care access. The level at which these factors act, be it patient level, primary health care facility level, or contextual (beliefs, norms, and practices), will also be presented. Additionally, new themes derived from the literature will be organized as subthemes under the predefined domains in the framework. Themes that do not fit under any of the predefined domains will be added as new

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main themes. The various themes and subthemes will be illustrated using appropriate diagrams and tables. Subgroup comparisons will be done where relevant. Subgroups may include gender, age groups, social status, and other relevant subgroups identified in the studies. Inconsistencies and gaps in the literature will also be identified, with recommendations made for further research to fill those gaps.

Results

Database searches were conducted between February 1, 2024, and February 12, 2024. After screening, 28 papers were included in the final analysis. As of July 2024, the review report was being drafted and will be disseminated through publication in a peer-reviewed journal.

Discussion

Principal Findings

This study will gather available evidence on the enablers and barriers to accessing primary care for common mental health conditions in West Africa. Findings will be related to perceptions, care-seeking behavior, reaching and obtaining health care, health care payment, and health care engagement of the individual. Findings will also include approachability, accessibility, availability and accommodation, affordability, and appropriateness of primary health care services for mental health. Our review is likely to discover that these enablers and barriers to access are influenced by the sociocultural and economic contexts of West African countries within which people with mental illnesses seek care.

The proposed review is a part of the first phase of the Stop-NCD project, which aims to improve the health and well-being of populations in West Africa by developing the capacity for high-quality research to inform improved prevention, diagnosis, and treatment of interconnected NCDs (hypertension, diabetes, and coexisting mental disorders). The project also seeks to understand mental health disorders in relation to people with hypertension and diabetes. This is the reason for our decision to include the interconnection among mental health conditions, hypertension, and diabetes in our search strategy, though it is not part of the main objectives for our review.

Comparison to Prior Work

As mentioned earlier, to the best of our knowledge this is the first review of the factors influencing primary care access for mental health conditions among adults in West Africa. However, similar studies have been conducted in Southeast Asia, as well as in Australia and other high-income countries [55-57]. In these reviews, self-awareness, resources and information, affordability, accessibility, patient-centered care, use of technology, mental health literacy, culturally sensitive practice, and gender were reported as factors that influence access to mental health care among adults in these regions [55-57]. In our review report, our study findings will be compared to these findings and the results of other identified studies.

Strengths

To the best of our knowledge, this will be the first scoping review to map the factors that influence primary care for mental conditions in adults in West Africa. Furthermore, our review protocol follows the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines [58]. Also, the review will use a comprehensive search strategy for eligible studies that will include 5 electronic databases, key websites for gray literature, and reference lists of pertinent studies.

Limitation

We perceive a potential challenge in accessing eligible papers reported in French. However, we believe that using the services of a bilingual secretary and using DeepL to assist us with translation will help us overcome this challenge.

Future Directions

Considering the similarities in the socioeconomic and political climate among most countries in sub-Saharan Africa, the findings from our review, though focused on West Africa, will be useful to various actors in other countries in sub-Saharan Africa who seek to answer a similar question. The findings from our review will also highlight specific areas where further research is needed.

Conclusions

Exploring the barriers and enablers to accessing primary care for common mental health conditions is essential to shape policies to address the pressing need for quality and accessible mental health care in this subregion.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Authors' Contributions

NYA-B conceptualized the study and drafted the protocol under the supervision of IAA and SO. NYA-B, IAA, and TM formulated the research questions. NYA-B, RNBA, TM, AM, SO, EA, VR, DS, and IAA contributed to developing and editing the background and methodology of the protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for PubMed.
[DOCX File , 16 KB - resprot_v13i1e58890_app1.docx]

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Abbreviations

ECOWAS: Economic Community of West African States
LMIC: low- or middle-income country
NCD: noncommunicable disease
PCCS: participants, concept, context, and type of study
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews And Meta-Analyses Extension for Scoping Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO: World Health Organization
YLD: year lived with disability

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Protocol

Investigating Data Diversity and Model Robustness of AI Applications in Palliative Care and Hospice: Protocol for Scoping Review

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Abstract

Background: Artificial intelligence (AI) has become a pivotal element in health care, leading to significant advancements across various medical domains, including palliative care and hospice services. These services focus on improving the quality of life for patients with life-limiting illnesses, and AI's ability to process complex datasets can enhance decision-making and personalize care in these sensitive settings. However, incorporating AI into palliative and hospice care requires careful examination to ensure it reflects the multifaceted nature of these settings.

Objective: This scoping review aims to systematically map the landscape of AI in palliative care and hospice settings, focusing on the data diversity and model robustness. The goal is to understand AI's role, its clinical integration, and the transparency of its development, ultimately providing a foundation for developing AI applications that adhere to established ethical guidelines and principles.

Methods: Our scoping review involves six stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consulting with stakeholders. Searches were conducted across databases including MEDLINE through PubMed, Embase.com, IEEE Xplore, ClinicalTrials.gov,

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and Web of Science Core Collection, covering studies from the inception of each database up to November 1, 2023. We used a comprehensive set of search terms to capture relevant studies, and non-English records were excluded if their abstracts were not in English. Data extraction will follow a systematic approach, and stakeholder consultations will refine the findings.

Results: The electronic database searches conducted in November 2023 resulted in 4614 studies. After removing duplicates, 330 studies were selected for full-text review to determine their eligibility based on predefined criteria. The extracted data will be organized into a table to aid in crafting a narrative summary. The review is expected to be completed by May 2025.

Conclusions: This scoping review will advance the understanding of AI in palliative care and hospice, focusing on data diversity and model robustness. It will identify gaps and guide future research, contributing to the development of ethically responsible and effective AI applications in these settings.

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KEYWORDS

palliative care; artificial intelligence; ethical frameworks; AI; data diversity; model robustness; decision support; clinical settings; end-of-life care; hospice environments; hospice; methodology; thematic analysis; dissemination

Introduction

Background

Artificial Intelligence (AI) has become a pivotal element in health care at large, leading to significant advancements across various medical domains, including palliative care and hospice services [1,2]. Palliative care and hospice services focus on improving the quality of life for patients with life-limiting illnesses: palliative care provides relief from the symptoms and stress of serious illness, while hospice care offers comfort for patients in the final stages of a terminal illness. AI's ability to process complex datasets can enhance decision-making and personalize care in these sensitive settings. Recent studies have demonstrated the potential of AI to improve patient outcomes in palliative care by predicting symptom trajectories, optimizing pain management, and identifying patients who may benefit from hospice services [1,2]. For instance, AI models can analyze electronic health records to detect patterns that may indicate a decline in a patient's condition, allowing for timely interventions [3].

Despite its potential, incorporating AI into palliative and hospice care requires careful examination to ensure it reflects the multifaceted nature of these settings. AI models must be robust enough to withstand the complexities of palliative care environments. Moreover, the robustness of AI models must be scrutinized to withstand the complex dynamics of palliative care environments. There is growing advocacy for ethical AI applications that can sensitively meet the unique needs of patients receiving palliative care, such as personalized care plans and real-time monitoring for complex symptom management while safeguarding against the amplification of existing biases within health care data [3-5]. As such, there is a pressing need to evaluate the representativeness and robustness of AI in these settings critically.

A few reviews have explored the application of AI in palliative and hospice care, but these reviews often focus on specific types of diseases or the general benefits of AI applications without delving into detailed aspects of model performance, bias, or robustness [1,2,6].

This gap highlights the need for a comprehensive review that critically examines these important factors in the context of palliative and hospice care. This review aims to address this gap by systematically mapping the landscape of AI applications in palliative care and hospice settings, focusing on the diversity of data in AI models and their robustness in clinical integration. By expanding the literature and including recent studies and key papers on AI applications in palliative care and hospice, we aim to provide a comprehensive overview that will guide future research and contribute to the development of effective and ethically responsible AI applications in these sensitive settings.

Goals of the Review

Our scoping review aims to systematically map the landscape of AI in palliative care and hospice settings by focusing on the diversity of data in AI models and the robustness of the models. We seek to understand AI's role, the extent of its clinical integration, and the transparency of its development. We believe this comprehensive overview will provide the foundation for developing AI applications that adhere to established ethical guidelines and principles, ensuring fairness, transparency, and accountability.

Methods

Design

Overview

Our scoping review was guided by Arksey and O'Malley's [7] framework and Joanna Briggs' manual for scoping reviews [8], which consists of six main stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consulting with stakeholders to validate findings and enhance the comprehensiveness of the review. This scoping review has been registered in the Open Science Framework (OSF) database [9]. For reporting, we will use PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Statements) for our searches and PRISMA-ScR (PRISMA-Extension for Scoping Reviews) for the review itself [10].

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Stage 1: Identifying the Research Question

The interdisciplinary research team, including experts in palliative care, informatics, data science, and public health, initiated the scoping review with an informal prescreening of literature from MEDLINE through PubMed and various gray literature sources. With the guidance of an information specialist in scoping reviews, keywords were identified and used to navigate the research terrain. Contributions from the team, reflecting their diverse fields of expertise, along with the analysis of 5 key papers and 5 previous reviews, shaped the development of broad research questions. Through discussion, the team generated the research questions stated below.

Primary Research Questions

1. Research question 1: use in hospice and palliative care: in what ways are AI used to identify patients for hospice and palliative care or to measure or improve the care quality for patients receiving hospice and palliative care?
2. Research question 2: data diversity: in the development of AI models for palliative and hospice care, what strategies are used to incorporate diverse demographic and clinical profiles? In addition, which methodologies ensure the representativeness of the datasets used?
3. Research question 3: model robustness: what frameworks and best practice guidelines inform the development of AI models within palliative and hospice care?
4. Research question 4: bias assessment: how is bias detection and mitigation systematically integrated and what ethical guidelines are in place?

Secondary Research Questions

1. Research question 5: applications and outcomes: what specific tasks and outcomes are targeted by AI technologies in palliative care and hospice settings?
2. Research question 6: research trajectory: what are the emergent directions and identified literature gaps in AI for palliative and hospice care?

Stage 2: Identifying Relevant Studies

Peer-Reviewed Literature

The databases MEDLINE through PubMed, Embase.com, IEEE Xplore, ClinicalTrials.gov, and Web of Science Core Collection were used to search for peer-reviewed literature. These searches were developed by an information specialist. Our search strategy included studies from the inception of each database up to November 1, 2023. This approach was taken to ensure comprehensive coverage and to capture the full breadth of relevant literature on AI applications in palliative care and hospice settings. Non-English records were excluded from further processing if their abstracts were not in English. The search terms and queries, detailed in Multimedia Appendix 1, along with the inclusion and exclusion criteria outlined in Textbox 1, were formulated after reviewing relevant publications and consulting with coauthors and information specialists.

Specifically, terms relating to “advanced disease” were not included in the search strategy. After thorough discussion, it was concluded that including “advanced disease” is too diffuse a term and could lead to an overwhelming and unmanageable volume of data, complicating the review process. In a similar vein, terms related to clinical decision support (CDS) were also intentionally excluded from our search strategy. This exclusion was based on the finding that a substantial number of CDS methods do not integrate AI technologies. However, this does not mean CDS studies are excluded. Any CDS studies using AI technologies will be identified through our AI-related search terms. Our primary focus was on AI techniques rather than specific names of tools. By emphasizing AI techniques, our goal was to ensure that our review concentrated on the fundamental role of AI in palliative care and hospice settings. We believe that this strategy will enable us to focus on the integration and use of AI as a distinct technological paradigm in these areas, as opposed to a broader examination of CDS tools, many of which may not use AI technologies.

Our research will encompass studies conducted across various international health systems. This inclusive approach is chosen to capture a diverse range of health care practices and methodologies globally, which are vital for providing a comprehensive understanding and guiding future clinical quality improvements and research in the field of palliative and hospice care.

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Textbox 1. Inclusion and exclusion criteria for the scoping review.

Phenomenon of interest

- Artificial intelligence applications in palliative care and hospice

Inclusion criteria

- Study type:
  - Observational studies (cohort, case-control, and cross-sectional)
  - Experimental studies (randomized controlled trials, nonrandomized, and experimental)
  - Other study designs: (qualitative, case series, diagnostic test accuracy, clinical prediction rule, and economic evaluations)
  - Gray literature: conference papers and PhD theses
- Population type:
  - Patients aged 18 and older: those with severe life-limiting illness, and patients who are already enrolled in palliative care or hospice settings
  - Studies that reported recruiting both adults and children will be included only if the results were stratified by age group
- Artificial intelligence model criteria: the study must either:
  - Propose or use an artificial intelligence model that uses a training set to learn its model parameters, or
  - Implement a pre-established artificial intelligence model, focusing on deployment and practical application in the field
- Setting:
  - All care settings (ie, inpatient and outpatient) within palliative and hospice care
- Other:
  - Available electronically in full text
  - Articles in English
  - Studies must explicitly state their aim to identify patients for hospice and palliative care or to measure or improve the care quality for patients receiving hospice and palliative care.

Exclusion criteria

- Study type:
  - Conference abstracts with no full text
  - Case studies, editorials, reports, and reviews
  - Books and book chapters
  - Letters to editors and perspectives
- Other
  - Any study not directly targeting palliative care, as determined by the absence of specific search terms (Multimedia Appendix 1). Studies mentioning these groups only as a subgroup or solely using the term “Inoperable or Incurable” without explicit reference to palliative care will also be excluded.
  - Studies that solely used traditional, rule-based algorithms without any artificial intelligence components

Gray Literature

In our research on AI applications in palliative care and hospice, we used Web of Science to identify both peer-reviewed and gray literature. Conference abstracts and proceedings were located through Embase.com and Web of Science. Theses and dissertations were collected through ProQuest Theses & Dissertations Global. Preprints from platforms like ArXiv were excluded as they can be withdrawn or significantly revised after initial posting, affecting the stability and reliability of the information. In addition, excluding these preprints avoids duplication, as many are eventually published in peer-reviewed journals.

All peer-reviewed and gray literature results will be downloaded into EndNote X20 (Clarivate Analytics) and imported into the web-based systematic review software (version 2.0; Covidence) for review. The expert authors’ committee (RP, AW, KG, and DK) will also be asked to identify other potentially relevant peer-reviewed and gray literature materials not identified through previous search strategies (ie, “hand-searched” articles).

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Duplicates will be removed using EndNote and Covidence software to ensure a clean and accurate dataset for review. Covidence software will also be used for screening to facilitate blinding and streamline the review process.

Stage 3: Study Selection

A screening guide developed by the reviewers (SB and SF) will be used to determine if the inclusion and exclusion criteria have been met (Textbox 1). Feedback will be obtained from the coauthors (KG and DK) and palliative care experts (RP, AW, CL, KL, and TQ) while developing the screening guide. The 4 reviewers (SB, SF, IK, and CD) will then independently pilot-test this guide on the first 100 abstracts. The first 100 abstracts were selected using the "most relevant articles" option provided by Covidence software. Agreement rates will be evaluated after the initial 15 and again after 100 abstracts, with discussions to follow and adjustments to the inclusion or exclusion criteria made as necessary. Any discrepancies in study selection will be resolved through consensus. To ensure the appropriateness of the selections, an example of both an included and an excluded article will be presented to the project team. Subsequently, all remaining articles will be independently screened by at least 2 reviewers using the guide, focusing on titles and abstracts for their relevance to "artificial intelligence," "palliative care and hospice," and the general inclusion criteria. The reviewers will meet at the beginning, middle, and end of the screening process to discuss any challenges and ensure consistent application of the criteria.

After this initial phase, the full texts of articles that pass the initial screening will be reviewed at least by 2 independent reviewers to assess their relevance to the primary research questions of the study. If disagreements among reviewers cannot be resolved through discussion, the principal investigator (SB) will make the final decisions. Regular check-in meetings will be scheduled to discuss results and resolve any discrepancies, ensuring a comprehensive and systematic approach to study selection. Reasons for the exclusion of full-text papers will be recorded using the PRISMA 2020 flow diagram.

Stage 4: Charting the Data

We will design a data charting form in Covidence, specifically structured to accommodate each primary research question. These questions are a combination of those from the Minimum Information for Clinical Artificial Intelligence Modeling (MI-CLAIM) checklist [11] and additional ones formulated by our authorship team. We chose MI-CLAIM due to its comprehensive coverage and practicality for our scoping review. AI-related studies benefit from several reporting guidelines, thanks to pioneering efforts by the SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence) [12,13] and CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) [12] extensions committees. Similarly, for review studies, the PRISMA-AI Steering Committee is developing an AI-specific implementation of PRISMA guidelines, which will be used in future studies to further standardize AI research reporting [14].

This form's sample layout is depicted in Textbox 2. To validate these forms for both academic and gray literature, our reviewers (SB and CD) will initially chart data from 10 included sources independently. Following this pilot phase, once interrater reliability is confirmed, these forms will then be made available to all team members for use. For a portion, specifically 20%, of the included academic and gray literature sources, the data extraction will be verified by a second reviewer. Recognizing that data charting is a dynamic process, it is anticipated that the team might modify aspects of the forms to ensure they accurately reflect the findings of the included articles. After achieving consistency and finalizing the pilot-tested forms, data from each included full-text article will be charted by 1 member of the research team.

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Textbox 2. Data that will be charted.

- **Article information**
  - Title
  - Author
  - Year
- **Study context**
  - The clinical problem in which the model will be used is clearly detailed in the paper (the questions are derived from the Minimum Information for Clinical Artificial Intelligence Modeling checklist; yes or no)
  - Study design: eg, randomized controlled trial, cross-sectional, and qualitative
  - Clinical condition or disease: eg, coronary artery disease, chronic obstructive pulmonary disease, and Alzheimer disease
  - Clinical setting: eg, hospice, inpatient hospice, and outpatient palliative clinic
- **Data**
  - The origin of the data is described, and the original format is detailed in the paper (the questions are derived from the Minimum Information for Clinical Artificial Intelligence Modeling checklist; yes or no)
  - Data Source: eg, electronic health records, publicly available data, and study-specific data; if MIMIC (Medical Information Mart for Intensive Care), specify "MIMIC"
  - Data modality: eg, images, audio recordings, and multimodal
  - Data volume: text entry for number of records and patients
  - The characteristics of the cohorts (training and test sets) are detailed in the text (the questions are derived from the Minimum Information for Clinical Artificial Intelligence Modeling checklist; yes or no). If yes, then (1) age range (min-max), (2) gender distribution (female percentage), (3) race distribution (White percentage), (4) ethnicity distribution (Hispanic percentage), (5) does the article report socioeconomic status as demographic information of the study population? (yes or no), and (6) does the article report insurance as demographic information of the study population? (yes or no)
  - The cohorts (training and test sets) are shown to be representative of real-world clinical settings (the questions are derived from the Minimum Information for Clinical Artificial Intelligence Modeling checklist; yes or no). If yes then, what strategies or frameworks are reported to ensure the dataset's representativeness and heterogeneity in the artificial intelligence study? (text entry)
- **Artificial intelligence**
  - Artificial intelligence outcome: eg, survival, disease risk, and metastasis
  - Have any specific design, development, or evaluation frameworks or guidelines been used in the artificial intelligence technology's lifecycle? If yes, please provide details (yes or no; text entry)
  - Reported accuracy: text entry for the highest metric, prioritize F_1-score and area under the curve (AUC)
  - Evaluation: eg, in silico (proof of concept), offline (silent and shadow), safety and utility, small-scale (early live clinical), safety and effectiveness, large-scale (comparative perspective), and postmarket surveillance
- **Bias identification and attribution**
  - Has a biased evaluation been conducted or referenced within the study? (yes or no). If yes then, what methods, if any, have been proposed or implemented to address identified biases? (text entry)
  - A discussion of the reliability and robustness of the model as the underlying data distribution shifts (eg, changes in patient demographics, treatment guidelines, or health care protocols over time) is included (the questions are derived from the Minimum Information for Clinical Artificial Intelligence Modeling checklist; yes or no)
- **Other**
  - Data publicly available: yes or no
  - Model open source: yes or no
  - Ethical approval mentioned: yes or no
  - Informed consent mentioned: yes or no
  - Funding source: who funded the research or development of the artificial intelligence model? Or any report of conflict of interest (text entry)

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Stage 5: Collating, Summarizing, and Reporting the Results

Data charting will be the initial step in summarizing our research findings. In this process, we will meticulously record key information for each study, such as the article title, author or authors, year of publication, and the study's objectives. Recognizing the practices in other AI reviews, we will also document technology-specific details, including the model's task, output, its development stage, the data sources used, and the methods used for evaluation.

To effectively synthesize the findings from multiple studies on AI applications in palliative care and hospice settings, we will use a framework analysis approach. This method involves systematically categorizing and organizing data according to predefined themes. Initially, we will familiarize ourselves with the data by reading and rereading the studies, noting key findings. A thematic framework will be developed based on our research objectives, including themes such as the model's task, output, development stage, data sources, and evaluation methods. We will then index the data according to this framework, systematically coding and categorizing relevant information. Charts or matrices will be created to organize the indexed data, allowing us to map out patterns and explore relationships between themes. Through iterative discussions, we will review and refine the framework and charts, ensuring the robustness of our analysis. This approach will provide a comprehensive understanding of AI applications in palliative care and hospice, highlighting commonalities, differences, and research gaps to guide future developments in this field.

Depending on the nature of the results obtained, we may also create visual representations to aid in clearer communication and understanding of the data. These visuals can include charts or graphs, providing an accessible way to grasp complex patterns and insights derived from the research. This multifaceted approach to data charting and analysis is aimed at producing a comprehensive and nuanced understanding of AI applications in palliative care and hospice settings.

Stage 6: Consultation

To incorporate wider perspectives, we will share the preliminary summary of our findings with teams of authors through video calls and emails to assess the alignment of identified themes with their expertise and to highlight any missing themes. Structured presentations and discussions will follow with the senior authorship team, comprising palliative care physicians and researchers, and health services and organizational behavior experts, to explore future research directions. Feedback from these sessions will be systematically reviewed and integrated into the analysis, refining the themes and ensuring comprehensive coverage. A final round of consultation will review the refined themes and overall findings to ensure consensus. The integration of consultation feedback will be documented, highlighting its influence on the final analysis and presentation of results.

Ethical Considerations

Ethical approval was not required because only literature will be evaluated without accessing identifiable source data.

Results

In November 2023, our electronic database searches resulted in 4614 studies. After the removal of 1124 duplicates, we selected 330 studies for full-text review to determine their eligibility and inclusion in our scoping review based on predefined criteria. Following this review, we will finalize the set of studies for data extraction. The extracted data will be methodically organized into a table to aid in crafting a narrative summary. Our primary method of presenting these findings will be through a scoping review publication. The entire process, encompassing the screening of titles and abstracts, charting of data, and subsequent stages of the scoping review, is projected to be completed by May 2025. This timeline also includes the execution of dissemination activities, such as a symposium and a briefing paper.

Discussion

Principal Findings

The findings of this review are set to significantly advance our understanding of AI in palliative care and hospice, with a particular emphasis on the challenges of data diversity and model robustness. A notable concern is the prevalence of data diversity issues and biases within AI models in these settings. Despite these challenges, there seems to be a lack of uniformly applied, robust frameworks to address them effectively, raising concerns about potential disparities in the effectiveness and equity of AI applications in palliative and hospice care. This underscores the urgent need for more stringent ethical and operational frameworks.

A key strength of our review lies in its interdisciplinary nature, offering insights into the use of AI in palliative and hospice care from societal, legal, ethical, and technical perspectives. Our methodology, grounded in a scoping review framework and encompassing interdisciplinary databases, is thorough. The diverse team of researchers involved in this study will analyze and interpret findings, which are expected to stimulate further discussions and guide future research, particularly focusing on AI applications for vulnerable adults requiring palliative and hospice care.

Limitations

One limitation of our study is its exclusion of non-AI (rule-based) algorithms, narrowing our focus to AI-driven technologies and omitting insights from traditional systems in palliative and hospice care. This could limit our understanding of the full technological evolution in these fields. However, the current trend towards AI-driven models justifies this focus, as it reflects the growing importance and anticipated future dominance of AI in health care. Another limitation of our study is the inclusion of only English-language literature, which may lead to the omission of relevant non-English studies, potentially introducing language bias and limiting the comprehensiveness of our review. In our upcoming full-text review, we will document the number of non-English records identified and screened. For non-English records with abstracts in English, we will assess their relevance and note those not further

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processed despite their relevance at the title and abstract screening stage to address potential biases introduced by excluding non-English evidence. We also acknowledge the potential limitation of not identifying all possible search terms and synonyms for palliative care. Despite our comprehensive search strategy, some relevant studies may have been missed. Future research should refine and expand search terms for more exhaustive coverage.

Conclusions

In light of the increased awareness of bias in AI, we anticipate that newer studies will more comprehensively address data representativeness and diversity, likely showcasing a commitment to ethical AI practices in health care. To our best knowledge, this is the first scoping review to explore the data diversity and robustness of AI models specifically in palliative care and hospice settings. Our protocol outlines not just our search strategy but also the detailed process for synthesizing literature in this clinical domain catering to a vulnerable population. Through this review, we aim to provide valuable insights, guide future research, and contribute to the development of ethically responsible and effective AI applications in palliative care and hospice environments.

Acknowledgments

The content does not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

Authors' Contributions

Every author has contributed intellectually to the conceptualization of the protocol. SB was responsible for drafting the manuscript. All authors have participated in editing and reviewing and have given their approval for the manuscript to be submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Keywords and search strategies.
[DOCX File , 26 KB - resprot_v13i1e56353_app1.docx]

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Abbreviations

AI: artificial intelligence
CDI: clinical decision support
CONSORT-AI: Consolidated Standards of Reporting Trials–Artificial Intelligence
MI-CLAIM: Minimum Information for Clinical Artificial Intelligence Modeling
OSF: Open Science Framework
PRISMA-AI: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Artificial Intelligence
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Statement
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SPIRIT-AI: Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence

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Protocol

Learning Styles of Medical Students, Surgical Residents, Medical Staff, and General Surgery Teachers When Learning Surgery: Protocol for a Scoping Review

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Abstract

Background: Learning styles are biological and developmental configurations of personal characteristics that make the same teaching method effective for some and ineffective for others. Studies support a relationship between learning style and career choices in medicine, resulting in learning style patterns being observed in different residency programs, including in general surgery, from medical school to the last stages of training. The methodologies, populations, and contexts of the few studies pertinent to the matter are very different from one another, and a scoping review on this theme will enhance and organize what is already known.

Objective: The goal of this study is to identify and map out data from studies on the learning styles of medical students, surgical residents, medical staff, and surgical teachers.

Methods: The review will consider studies on the learning styles of medical students in a clinical cycle or internship, surgical residents with no restriction on year of residency, medical staff in general surgery, or general surgery's medical faculty. Primary studies published in English, with no specific time frame, will be considered. The search will be carried out in four databases, and reference lists will be searched for additional studies. Duplicates will be removed, and two independent reviewers will screen the titles, abstracts, and full texts of the selected studies. Data collection will be performed using a tool developed by the researchers. A results summary will be presented with figures, narratives, and tables. A quantitative and qualitative analysis will be carried out and further results will be shared.

Results: The search was funded on September 25, 2023. Data collection was performed in the two following months. Of the 213 articles found, 135 were excluded due to duplication. The remaining 78 articles will have their titles and abstracts analyzed by three of the researchers independently to select those that meet the eligibility criteria. This data is expected to be published in the first semester of 2025.

Conclusions: Conducting a scoping review is the best way to map what is known about a subject. Understanding how students, residents, staff, and even teachers prefer to learn surgery is key to staying up to date and knowing how to best educate those pursuing a surgical career.

Trial Registration: Open Science Framework 75ku4; https://osf.io/75ku4

International Registered Report Identifier (IRRID): DERR1-10.2196/57229

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(JMIR Res Protoc 2024;13:e57229) doi:10.2196/57229

KEYWORDS

general surgery; medical staff; students; medical faculty; medical student; surgery; surgical resident; internship; clinician; teaching method; residency program; residency; training; leaning style; health care education; Kolb; Kolbs model; experiential learning; Felder and Silverman

Introduction

The concept of learning styles first developed at the beginning of 1960 with an increased interest in the individual [1]. According to Dunn [2], everyone has a peculiar learning style, like a signature, so tailoring teaching to different learning styles may help improve results in education.

In the current literature, there are different models to determine learning styles, especially in health care education: Kolb's model, Felder and Silverman's model, and Gregorc's model. Whether learning styles are fixed or flexible and to what extent learning styles can be determined by the context is still being debated today [3].

Kolb [4] describes learning as a process where knowledge is transformed through experience and says that acknowledgment is the combination of appropriation and the transformation of experience. The theory is a holistic model called "experiential learning" and emphasizes the central role experience plays, differing it from other theories [5]. Kolb's [4] scheme hypothesizes that the learner has a concrete experience that he reflects on. Through reflection, it is possible to formulate abstract concepts and make appropriate generalizations, and then consolidate the understanding by testing the implications of the knowledge in new situations, providing a concrete experience, and the cycle continues. Learners with different learning preferences will have different strengths and weaknesses in the quadrants of the (Kolb) cycle [4]. Based on that, he created the Learning Style Inventory to determine and assess different learning styles [6].

Felder and Silverman [7] created the Index of Learning Survey, which was initially for engineering education but is also valid among medical students. The Index of Learning Survey classifies individuals into four fields: preferred information observation (sensory or intuitive; visual or verbal), active versus reflective information processing, and sequential versus global progression for understanding information [8].

In medical education, it is particularly important to remember that some programs count on learners who have already completed a university degree, and in others, the students have only completed secondary school. Medical education includes postgraduate students and those who are continuing professional development. Each of them will have variable individual constraints, experiences, and preferences [9].

Perry [10] noted that students change their learning approach as they progress over their college years. Students often begin with a "duality" approach, with a clear view between right and wrong, and move toward "multiplicity," where they recognize that context is important and that there are various valuable sources of knowledge and experience.

Knowledge is the main domain of medical education, but the outcome depends strongly on other domains such as attitude, lifelong learning, empathy, communication, ethics, and professionalism. The clinical environment is challenging for both the student and the teacher, without even mentioning the patient. It is vital to use different learning theories to promote effective learning [9].

Contemporary surgical trainees come from diverse educational, cultural, ethnic, and gender backgrounds [11], and are pressured to develop skills not only as medical experts but also as professionals, scholars, health advocates, managers, collaborators, and communicators [12].

Educating surgeons is an ancient tradition that has existed since the development of surgery [13], and for centuries, surgical residency curricula have been guided primarily by tradition. The apprenticeship model has been one of the essential components of surgical training. It generally involves three steps: assisting at operations, performing operations with expert assistance, and operating without assistance. In modern times, however, there are more complex procedures, performed more regularly and in safer manners, demanding even more prepared professionals [14].

Modern surgical education has been revolutionized by exponents such as Halsted. The historical model of apprenticeship was transformed into the current organized system that we call residency [11].

This scoping review aims to identify and map out data from studies that report the learning styles of medical students, surgical residents, medical staff, and general surgery teachers while learning surgery.

Methods

Overview

The proposed scoping review will be carried out according to Arksey and O'Malley's [15] structure using the first 5 stages: (1) identify the research question; (2) identify relevant studies; (3) select studies; (4) map out the data; and (5) collate, summarize, and report the results. Since this is preliminary research, more studies on the theme will likely be included. Although the sixth stage of Arksey and O'Malley's structure (consulting) will not be completed in this review, our results can inform this stage in a future study. This structure is also congruent with the Joanna Briggs Institute's (JBI) scoping review methodology [16].

Research Question

The research question was elaborated on according to the objective of the review and through the PCC (Population, Concept, Context) model:

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- Population: general surgery residents, general surgery, medical students
- Concept: learning style
- Context: surgical education

Therefore, the following research question was proposed. How do learning styles characterize medical students, surgical residents, medical staff, and general surgery teachers while learning surgery?

Inclusion Criteria

After a discussion involving the researchers, the eligibility criteria were defined.

- Participants: Studies with medical students in the clinical cycle or an internship, surgical residents with no restriction on year of residency, medical staff in general surgery, or general surgery's medical faculty.
- Concept: The included studies approached "learning styles" of the target population regardless of the chosen instrument to define it.
- Context: The eligible studies were those related to the teaching of the population in question, focusing on surgical education in any country.

Types of Sources

The following were included in the review: studies with qualitative and quantitative approaches, primary studies, systematic reviews, meta-analyses or meta-syntheses, books, and guidelines published in indexed sources.

Exclusion Criteria

The review excludes the publications of opinions, consensus, retractions, editorials, websites, and advertisements published in the media. Other exclusion criteria are not being published in indexed sources and gray literature. Publications made in other languages than English were excluded due to translation barriers. Studies that did not focus on learning styles were excluded, as well as those outside medical education in a surgical environment.

The inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Article type

Inclusion criteria

- Qualitative approaches
- Quantitative approaches
- Primary studies
- Systematic reviews
- Meta-analyses or syntheses
- Books published in indexed sources
- Guidelines published in indexed sources

Exclusion criteria

- Opinions
- Consensus
- Retractions
- Editorials
- Websites
- Advertisements
- Gray literature

Language

Inclusion criteria

- English

Exclusion criteria

- Other languages

Research Strategy

The search strategy was performed on September 25, 2023, by a librarian who is a digital search strategy expert using 3 descriptors: learning, style, and surgery. There was no time frame restriction in the search. After the research question was created, the keywords were used to identify articles referring to the topic, namely "learning style" and "surgery." For the combination of descriptors, the Boolean operators "AND" and

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"OR" were considered. Words were reduced to their root to include variations in writing and broaden the search scope.

The Embase, SCOPUS, Web of Science, and PubMed databases were searched using the descriptors and their synonyms, according to Medical Subject Headings (MeSH), to every strategy term. These databases were selected because they are comprehensive and have a broad coverage of health publications. Articles found in the database searches were tabulated in an Excel Ink 2021 (Microsoft Corporation) spreadsheet.

Study and Source of Evidence Selection

Of the 213 articles found, 135 were excluded due to duplication. The remaining 78 articles will had their titles and abstracts analyzed by three of the researchers independently to select those that meet the eligibility criteria. Articles that do not mention the eligibility criteria described above will be excluded. In case of divergence, a fourth researcher will be consulted and will give the final opinion about the relevance of the study in answering the research question. Additional sources can be included in the review after a manual search is performed by the researchers if they meet the eligibility criteria, are important to complete the study, and have not been identified by the search strategy.

To align the eligibility criteria among the researchers, the title and abstract of 25 random articles were analyzed by three of the researchers. There was 100% agreement concerning the inclusion and exclusion of the articles. Disagreements regarding the inclusion or exclusion of the articles were discussed until a consensus was reached.

The complete texts of the selected articles will be evaluated by the main researcher based on the eligibility criteria. The reasons for the exclusion of articles that are fully read will be registered and reported in the scoping review. Any disagreement that emerges among the researchers at any stage of the selection process will be solved through discussion or the addition of other researchers. A PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram [16] will be used to present the search results and the studies included in the scoping review.

Data Extraction

After article selection, a form for data extraction will be used to extract data from the full articles. The extracted data will include specific details, shown in Textbox 2. It can be modified and revised as needed during data extraction. The modifications will be described in the scoping review. Any disagreement that emerges among the researchers will be solved through discussion or inclusion of additional researchers. If appropriate, the articles' authors will be contacted and asked about missing or complementary data when necessary.

Textbox 2. Data extracted from studies.

Identification of the article

- Journal
- Year
- Title
- Author
- Country
- Type of study

Eligibility/exclusion criteria

- Participants
- Concept
- Context
- Exclusion

Details of the article

- Learning theory
- Learning style instrument
- Impact

Registration

The present protocol was registered in the Open Science Framework database [17].

Data Analysis and Presentation

The results will be analyzed considering the study's objectives and will be presented graphically or in the form of tables. This information will be enriched by a descriptive text that will show, as clearly as possible, how the results are related to the research question. All the researchers will participate in this stage.

Results

The search was funded on September 25, 2023. Data collection was performed in the two following months. Of the 213 articles

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found, 135 were excluded due to duplication. The remaining 78 articles had their titles and abstracts analyzed by three of the researchers independently to select those that meet the eligibility criteria. The pool of literature found corresponds to 78 articles that discuss learning styles in surgical environments, from university to faculty. This data is expected to be published in the first semester of 2025.

Discussion

Expected Findings

This scoping review aims to map out data from studies that report on the learning styles of medical students, surgical residents, medical staff, and general surgery teachers while learning surgery. We seek to compare results across time, countries, and learning theories presented in the existing literature.

Conducting a scoping review will provide an overview of learning styles in a surgical educational environment and determine gaps in the published literature about this subject. By looking at the teaching-learning process in surgery, we can better understand and guide future medical education.

From the students to the teachers, new pathways to surgical education can be developed and, ultimately, provide better care for patients undergoing surgery.

Comparison With Prior Work

Previous studies have supported the relationship between learning style and career choice in medicine, resulting in learning style patterns being observed in distinct residency programs, including general surgery, from medical school to the last stages of training. Based on Kolb's Learning Style Inventory, students classified as accommodating and diverging frequently chose surgery as their career choice, whereas those with a convergent learning style chose internal medicine and those who were assimilators chose academic medicine [18].

However, despite the theme's relevance, in a preliminary search in the MEDLINE, Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis databases, no scoping reviews were found. Moreover, the methodologies, populations, and contexts of the few pertinent studies are different from one another, and a scoping review on this theme would enhance and organize what is already known.

Limitations

The main limitation of this protocol is the fact that only English articles were searched, which diminishes the results in terms of language and culture, considering that surgical residency uses different models and resources throughout the world.

Conclusions

There are several ways to address adult education, with multiple theories, which can superpose, and multiple ways of evaluating learning according to the chosen theory. In health care, several specificities make the process even more complex, since there are a lot of abilities and competencies faced in a short period. Medical science is evolving faster all the time, adding challenges to the education and preparation of professionals.

Surgery education requires developing skills and training in high-risk procedures. How to deal with the students, residents, and surgical staffs' education, while taking into account their necessities, the new ways of teaching and sharing knowledge, and the speed of scientific knowledge, is key. Knowing a bit more about how these populations learn is vital to providing good education and, ultimately, good care.

Acknowledgments

We acknowledge LVCN, who was ready to collaborate on the search strategy, even through hard times.

Data Availability

The data concerning the total papers and the inclusion of papers is available for further analysis in Multimedia Appendix 1.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Studies found in search.
[XLSX File (Microsoft Excel File), 188 KB - resprot_v13i1e57229_app1.xlsx]

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PCC: Population, Concept, Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Methodology for Measuring Intraoperative Blood Loss: Protocol for a Scoping Review

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Abstract

Background: At present, there is no standardized method for measuring intraoperative blood loss. Rather, the current data on existing methods is very broad and opaque. In many cases, blood loss during surgery is estimated visually by the surgeon. However, it is known that this type of method is very prone to error. Therefore, better standardized methods are needed.

Objective: This study aims to conduct a scoping review to present the currently available methods for measuring intraoperative blood loss. This should help to capture the current status and map and summarize the available evidence for measuring blood loss to identify any gaps.

Methods: We will use a state-of-the-art methodological framework. The databases PubMed (MEDLINE) and Cochrane Library will be searched using a search strategy based on the PICO (Population, Intervention, Comparator, and Outcome) scheme. The search period will be limited to January 01, 2012, to December 31, 2023, and our search will be restricted to clinical trials or clinical studies, randomized controlled trials, and observational studies (in line with PubMed definition of study types). Only publications in English and German will be considered. The intention is to identify clinical studies that define “blood loss” as a target criterion or as a primary or secondary end point. EndNote (version 20.6; Clarivate) will be used for the screening process. The data will be collected and analyzed using Microsoft Excel (version 16.77.1).

Results: The included studies will be listed in a database, and the following basic data will be extracted: title, year of publication, country, language, study type, surgical specialty, and type of procedure. The number of participants will be listed and the distribution of the participants will be documented in terms of gender and age. The following results are extracted: the type of measurement method used to measure blood loss in this study and whether the parameter “blood loss” was recorded as a primary or secondary outcome.

Conclusions: Currently, there is no comparable review, resulting in ambiguous data regarding the prevailing measurement methods for intraoperative blood loss. The aim of this study is to provide a comprehensive overview—from methods of measurement to various formulae for calculating blood loss—and to establish a status quo. This could then serve as a foundation for further studies.

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KEYWORDS

intraoperative blood loss; estimation of blood loss; intraoperative monitoring; surgery; surgical care; postoperative care; quality improvement

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Introduction

Every year, around 313 million operations are performed worldwide [1]. Intraoperative blood loss plays a very important role in the outcome of the patient in terms of perioperative morbidity and mortality [2]. There is currently no standardized method for recording, measuring, or estimating blood loss.

A common method, for example, is visual estimation using collection containers, abdominal drapes, and blood on the floor. The addition of irrigation fluid often leads to incorrect estimates of the amount lost, which can result in overestimates and underestimates by a factor of 2-3. Even longer professional experience did not provide any advantages in terms of a more accurate estimate [3]. Thus, the inaccuracies of the visual method and the consequences of misjudgment are well known. Nevertheless, visual estimation continues to persist due to the low effort and low costs involved [4].

To counteract this inaccuracy, newer methods have been developed, such as photometry [5]. However, this method is still largely unfamiliar to hospitals and medical staff [4]. Mathematical formulas for calculating blood loss are also available, some of which have been modified over the years or established from scratch [5,6]. Examples include the Gross equation [7], the Nadler formula [8], and the Meraculi equation [9]. For example, the Gross formula calculates blood loss by multiplying the patient's blood volume by the initial hematocrit minus the minimum hematocrit divided by the average of the 2 latter values. The patient's blood volume can either be estimated or determined using the Nadler formula. Meraculi's formula also calculates the blood loss using the patient's blood volume multiplied by the initial, respectively postoperative hematocrit. The first value is then subtracted from the latter. However, the formula takes into account transfusions, which are added. The reason is that the formula was initially described for a better transfusion strategy during operations.

Currently, the situation of the existing measurement methods and formulas has become very opaque, especially with regard to newly developed methods. However, the precise determination of blood loss forms the basis for improving surgical management and patient care, as well as the comparability of different surgeons, centers, surgical methods, and patient populations.

The aim of this scoping review is to provide an exploratory overview of the extent to which the methodology has been used in clinical studies (randomized controlled trials and others) with the end point or target criterion "intraoperative blood loss." This is intended to record the current status and map the available evidence, but without going into the individual measurement methods in an evaluative manner. Our study, in contrast to those currently available, is intended to cover all specialties. This makes it possible to capture and classify the broad spectrum of surgery and surgical procedures. It summarizes the available evidence base for measuring blood loss in order to identify any gaps and can serve as a starting point for further studies.

Methods

The scoping review will follow the methodological framework published by Arksey and O'Malley [10] and the further development and refinement of the methods by Levac et al [11]. This framework goes a long way to ensuring the quality of scoping reviews and promoting robustness and validity. For reporting, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be used [12].

The primary purpose of a scoping review is to explore a complex and multilayered topic that has not yet been comprehensively investigated and, if necessary, to fundamentally categorize it in order to gain an initial overview as representative as possible of the data situation. Therefore, the intention is not to cover the entire available literature but predominantly to create a comprehensive foundation sample. In this context, the research question is designed to be as open as possible and the identification of relevant results will be determined iteratively. This is based on the fact that with increasing familiarity with the data situation, better knowledge of the unexplored topic area is gained, and the search strategy should be reflected upon and critically adapted to the newly acquired knowledge as necessary [10]. The process guarantees, on the one hand, that the subject area is comprehensively presented or categorized for the first time and, on the other hand, that the boundaries of the research environment are clearly articulated [11].

PubMed was chosen as the primary database. The search is also extended to the Cochrane Library database. This is another international library that comprises 3 scientific databases: the Cochrane Database of Systematic Reviews (CDSR, Cochrane Reviews), Cochrane Clinical Answers (CCAs), and Cochrane Central Register of Controlled Trials (CENTRAL, Trials). In our scoping review, we will rely on the latter, and all trials will be included in it, even those from the various original sources of publication (MEDLINE through PubMed, Embase, CINAHL, ClinicalTrials.gov, and ICTRP). We will not use a third database, as a very large number of studies could already be found in an initial search. We justify this by stating that we cover the 2 most important databases and that a systematized search that includes all possible literature is not the main objective of the scoping review.

We have decided to limit the time period to the last 11 years, as the topic of methods for measuring intraoperative blood loss is very diverse and complex, and there is a large number of existing studies. In this way, our scoping review will be able to cover the methods currently in use and answer the key questions on the data situation in order to initiate more specific studies if necessary. Therefore, studies published from January 01, 2012 to December 31, 2023, will be included.

We will only include studies in English or German because English is the standard language in research and thus encompasses the majority of studies, and German is spoken by all authors of this scoping review.

Our search will be limited to clinical trials or clinical studies, randomized controlled trials, and observational studies (in line

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with PubMed's definition of study types). This restricts our scope to primary research and excludes secondary research such as reviews. In addition, case reports, commentaries, or letters will be excluded, as these only meet the research standards to a limited extent.

Only studies that include humans as study participants will be considered. Therefore, studies in which experiments were conducted on animals will be excluded.

Search Strategy

In order to pursue the research question, a search strategy was developed using the PICO scheme (Population, Intervention, Comparator, and Outcome). We will proceed as follows.

First, the databases will be studied using this standardized search. Multimedia Appendix 1 shows the search strategy that will be used in PubMed (MEDLINE). The same search strategy will be used for the Cochrane Library, which can be found in Multimedia Appendix 2.

Second, the bibliographies of the included studies will be manually searched for further suitable studies. The abstracts will be read independently by 2 authors and will be evaluated with regard to the inclusion and exclusion criteria. Differences of opinion between the authors will be settled by mutual agreement. If no agreement can be reached, a third reviewer will evaluate the study and decide on inclusion or exclusion. The decision-making process in the literature search and the selection of studies will be supplemented by a flow chart in the final report (more details in Multimedia Appendix 3). During the selection process, the studies will be extracted separately by the 2 authors and will be collected in a separate database.

For the screening process, the software Endnote (version 20.6; Clarivate) will be used.

The inclusion and exclusion criteria are summarized in Table 1.

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Database	• PubMed • Cochrane Library	—[a]
Study type	• Randomized controlled trial • Clinical study, Clinical trial • Observational study	• Reviews • Case reports • Case series with less than 5 patients • Commentaries • Letters
Study population	• Humans	• Animals

Reported outcomes	• Primary outcome:
	  • Measurement method for intraoperative blood loss
	• Secondary outcomes:
	  • Measurement method unknown (study that measures blood loss but does not specify a method)
	  • "Blood loss" as a primary or secondary outcome
		—

Language	• English • German	• Other language

[a]Not available.

Data Extraction

The included studies will be listed in a database using Microsoft Excel (version 16.77.1), and the following basic data will be extracted: Title, year of publication, country, and language. The number of participants will be listed, and the distribution of the participants will be documented in terms of gender and age. For better evaluation and comparability, we will divide the age into groups: infants (up to the age of 3 years), children (ages 4-12 years), adolescents (ages 13-18 years), young adults (ages 19-30 years), adults (ages 31-60 years), older adults aged 61-80 years, and older adults aged ≥81 years.

Finally, the following data will be extracted: study type, surgical specialty, type of surgery, measurement method, and "blood loss" as a primary or secondary outcome.

A preselection will be made for the respective points provided in Textbox 1.

In the event that a study does not differentiate outcomes directly into primary and secondary end points, the outcomes are all considered "primary" and will be included in our scoping review, too.

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Textbox 1. Preselection criteria.

- Study type:
  - Intervention study
    - Randomized controlled trial
    - Controlled clinical trial
  - Observational study (case-control study and cohort study)
    - Prospective
    - Retrospective
- Surgical specialty:
  - Vascular surgery
  - Trauma surgery and orthopedics
  - Thoracic surgery
  - Visceral surgery
  - Plastic surgery
  - Pediatric surgery
  - Cardiac surgery
  - Ear, nose, and throat surgery
  - Neurosurgery
  - Gynecology
  - Urology
  - Oral and maxillofacial surgery
  - Eye surgery
  - Endocrine surgery
  - Spinal surgery
  - Multidisciplinary interventions
  - Emergency general surgery
- Type of procedure: Name of the operation, eg “Appendectomy.”
- Measurement method:
  - Visually estimated or bleeding scores (specify the score)
  - Measured using measurement data (specify the method used)
  - Calculated using a formula (specify the formula used)
  - Unknown
- Blood loss as an outcome or parameter:
  - Primary outcome
  - Secondary outcome
  - Not defined as an outcome, but one of the target criteria of the study

Results

The results will be collected in a database and will be presented in tabular form or diagrams using Microsoft Excel (version 16.77.1). For a better overview, the data will be grouped according to the type of method (measurement methods, estimation methods, and calculation methods). Reviewing the studies has been started. Evaluation and analysis of the data is planned to be finished in 2025.

Discussion

The data summary facilitates the comparison of evaluation methods and the identification of dependencies. It allows for

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an assessment of the methods in terms of their precision and required effort. In addition, it will help to uncover patterns, such as the prevalence of certain methods in various surgical specialties. Questions can be explored, like whether there is a link between the complexity or accuracy of a method and the time of publication or the quality of the study (eg, randomized vs observational studies). These aspects, among others, present opportunities for comparison.

Up to now, there has been no comparable review. An existing study has investigated methods for quantifying blood loss in orthopedic trauma [13]. In the field of obstetrics, 3 studies have been published on estimating blood loss: 2 literature reviews [14,15] and 1 systematic review [16]. There is also a systematic review highlighting the strengths and weaknesses of currently used measurement methods [5], which only included studies that examined the accuracy of blood loss quantification techniques in vivo and in vitro.

Currently, the measurement of intraoperative blood loss lacks clarity due to the absence of standardized methods. A variety of methods are used in practice, often with personal modifications. This inconsistency extends to the formulas used for calculating blood loss. Such variability could pose challenges for our scoping review, particularly in categorizing the methods used in different studies. In addition, there is a potential for bias if multiple studies fail to detail their measurement methods. To mitigate this issue, we plan to include these studies in our collection and consider this factor in our analysis.

Overall, this approach offers the opportunity to identify existing gaps and propose ideas for standardization.

Acknowledgments

Generative artificial intelligence was not used in any part of the manuscript creation process.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[DOCX File , 15 KB - resprot_v13i1e58022_app1.docx]

Multimedia Appendix 2
Search strategy Cochrane Library.
[DOCX File , 14 KB - resprot_v13i1e58022_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram.
[DOCX File , 39 KB - resprot_v13i1e58022_app3.docx]

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Abbreviations

CCAs: Cochrane Clinical Answers
CDSR: Cochrane Database of Systematic Reviews
PICO: Population, Intervention, Comparator, and Outcome
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Using Digital Media to Improve Adolescent Resilience and Prevent Mental Health Problems: Protocol for a Scoping Review

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Abstract

Background: Global databases show a high prevalence of mental health problems among adolescents (13.5% among those aged 10-14 years and 14.65% for those aged 15-19 years). Successful coping depends on risk and protective factors and how their interaction influences resilience. Higher resilience has been shown to correlate with fewer mental health problems. Digital mental health interventions may help address these problems.

Objective: This protocol serves as a framework for planning a scoping review to map the types of digital communication media and their effectiveness in increasing resilience in youths.

Methods: The Joanna Briggs Institute guidelines will be used: defining the research questions; identifying relevant studies; study selection (we will select articles based on titles and abstracts); charting the data; collating, summarizing, and reporting the results; and consultation. The synthesis will focus on the type of digital media used to increase adolescent resilience skills and the impact they have on adolescent resilience skills. Quantitative and qualitative analyses will be conducted.

Results: The study selection based on keywords was completed in December 2023, the study screening and review were completed in February 2024, and the results manuscript is currently being prepared. This scoping review protocol was funded by the Center for Higher Education Funding and the Indonesia Endowment Fund for Education.

Conclusions: The results of the study will provide a comprehensive overview of commonly used digital media types and their effectiveness in increasing youth resilience. Thus, the results of this scoping review protocol can serve as foundational evidence in deciding further research or interventions. This study may also be used as a guideline for mapping and identifying the type and impact of communication media used to increase adolescents' resilience skills.

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KEYWORDS

adolescents; digital media; mental health; resilience; scoping review

Introduction

Background

Positive mental health is the desired outcome of health promotion interventions [1]. Preventive and promotive mental health interventions have been shown to be feasible and effective in many age groups and settings [2]. Promoting adolescent mental health is the most effective and proactive technique to prevent mental illness and disability now and in the future [3]. Mental health problems with varying symptoms are characterized by abnormal thoughts, perceptions, emotions, behaviors, and relationships with others [4].

Adolescents are vulnerable to mental health problems due to puberty, body, and hormonal changes; changes in their social environment; and changes in the brain and mind. Mental illnesses such as depression, anxiety, eating disorders, substance use disorders, and psychosis appear for the first time before the age of 24 years [5]. Global databases show that the prevalence of adolescent mental health problems is as much as 13.5% for those aged 10-14 years and 14.65% for those aged 15-19 years [6]. Adolescent mental health problems emerge due to many factors, including social determinants such as parent or family condition, peer group, socioeconomic status, and community and local services [7].

Being able to deal with problems depends on the associated risks and protections. The interaction between risk and protection affects resilience [8]. Resilience is an individual's ability to function in adversity or stress. Adolescents with high resilience can face life difficulties more easily as they become adults [9], and high adolescent resilience has been shown to be related to fewer mental health problems [10]. Resilience refers to successfully adapting to stress and an individual's ability to maintain or regain homeostasis despite experiencing adverse life events [11].

The use of media to build adolescents' health literacy is one method used to increase youth resilience, and activities online can contribute to youths' resilience. Thus, social work interventions can harness online media to help promote resilience [12]. Digital interventions have been shown to improve resilience [13,14], maintain emotional regulation [15,16], and help users self-monitor [17]. Adolescents can build resilience by practicing making safe decisions when faced with risks, helping them construct supportive connections [18]. Additionally, adolescents who are more resilient offline are also more resilient online [12]. Bad mental health events may have an impact on the future of children and teenagers younger than 18 years. The mental health of children and adolescents is the foundation for their mental health as adults [10].

Digital technology has been linked to many positive outcomes related to information, peer support, professional online support, and more informal benefits, such as distraction and social connection [12]. Digital mental health interventions electronically deliver information, support, and therapy to treat, alleviate, or manage symptoms of mental health conditions [19]. Digital mental health interventions have been proven to be beneficial for addressing mental health problems [20].

With digital interventions, technological barriers, cost-effectiveness, and technical challenges exist, including fragmented and unsustainable systems, lack of clear standards, unreliable available data, and infrastructure and capacity gaps [21]. Challenges specific to digital health interventions include user involvement, user suitability, and the accuracy of the digital intervention [22]. Despite these challenges, media can still contribute to the treatment and prevention of mental health problems, including by helping build resilience to improve adolescents' abilities to prevent mental health issues. This systematic review will address the following:

- Map the impact of digital communication media on increasing adolescents' resilience
- Map the types and features of digital communication media that increase resilience in the adolescent population

This protocol will use evidence-based methods for the mapping of the types of digital mental health interventions.

Objectives

A protocol describes details, provides a clear understanding of the authors' research questions, and ensures transparency and reproducibility. Protocols allow systematic reviewers to plan carefully and thereby anticipate potential problems; allow reviewers to explicitly document what is planned before they start their review, enabling others to compare the protocol and the completed review, replicate review methods if desired, and judge the validity of the planned methods; and prevent arbitrary decision-making about study selection and data extraction [23]. A protocol for a scoping review makes the research objectives, methods, reporting, and process more transparent. Protocols help researchers set clear goals for reflection, predict possible obstacles and anticipate them, evaluate the success of the process and the results of the review, and prevent duplication of other research [24]. Protocols provide transparency to the process, help manage the review, minimize bias (a risk of bias assessment will not be performed in this scoping review), and list references to digital health interventions for other researchers to review. This protocol aims to guide and manage a scoping review (research objectives, methods, study selection, extraction, and reporting) for identifying the types, effectiveness, and benefits of digital communication media used to intervene in youth resilience.

Methods

Overview

This review will follow the Joanna Briggs Institute (JBI) guidelines for scoping reviews [25,26]. Additionally, Arksey and O'Malley [27] have outlined the following six steps for

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scoping reviews: (1) defining the research questions; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist will also be used. Searching the literature, refining the search strategy, assessing articles for inclusion, and collecting pertinent data will be done iteratively.

Protocol Registration and Report Information

A PRISMA checklist is provided in Multimedia Appendix 1. The checklist is an effective tool for guiding the reporting of scoping studies [28,29]. This protocol was registered on the Open Science Framework (3CNRT) [30] on July 7, 2023.

Research Questions

The following research questions were proposed:

1. What are the characteristics of digital mental health interventions being carried out to prevent adolescent mental health problems?
2. What type of content is being used for digital mental health interventions to prevent adolescent mental health problems?
3. Does digital communication media affect the resilience abilities of adolescents and reduce mental health problems?

Eligibility Criteria

The research questions previously mentioned and the eligibility criteria were developed using the Population, Intervention, Comparator, Outcomes (PICO) framework (Multimedia Appendix 2). Researchers use PICO to identify the key concepts of a scoping review, develop appropriate search terms to describe the problem, and determine inclusion and exclusion criteria.

Population

The population in this study are adolescents (also known as youth, young people, teenagers); adolescent, based on the World Health Organization definition, refers to the phase of life between childhood and adulthood, from ages 10 to 19 years [31]. Sawyer et al [32] described adolescents as people aged 10-24 years. This review will include all studies reporting on adolescents aged 10-24 years who are registered as students.

Intervention

This review will include interventions that use communication media for digital health. Digital health refers to the development and adoption of modern information and communication technology systems to help various health system stakeholders interact and make informed decisions about their health, the health of others, and the health system [33]. Digital interventions for health promotion or risk prevention can be distributed through mobile devices (eg, smartphones and tablets), computer- and web-based programs, social media apps, telemonitoring devices (eg, external sensors or smartwatches), and games [34]. Digital media includes the internet, social media, and mobile tools, while nondigital media includes television, print, radio, etc [35]. In this scoping review, the articles can include all intervention-related digital communication or digital media (websites, mobile apps, chat rooms, the internet, social media, and other digital media).

Comparator

Comparators or comparisons refer to groups that were compared to the intervention group [36]. The comparison can be to another treatment or intervention or no treatment at all [37]. In this scoping review, articles will be included if the comparator or comparison does not use digital or nondigital media (eg, television, radio, or printed media such as leaflets, posters, and brochures).

Outcomes

Outcome refers to the measure of interest or the study's target end points that are objectively defined. There may be only primary outcome measures or additional and secondary outcome measures [38]. In this scoping review, the articles must include the outcome of resilience (coping mechanism, coping stress, positive mental health) and well-being on mental health (stress, anxiety, depression, eating disorder, bipolar disorder, posttraumatic stress disorder, schizophrenia, and suicide).

Identifying Relevant Studies

Stage 2 of the review includes two steps. The first step is to identify all scoping reviews that are relevant and were published by August 2023. The search was conducted on the Cochrane and Scopus databases with an unlimited time period. A total of 6 scoping reviews were found related to digital mental health and adolescents [39-44]. However, these 6 reviews were more focused on anxiety in adults, implementing digital health interventions for people experiencing homelessness or youths who dropped out of school, and developing digital health interventions for native aboriginal people. No scoping review focused on the effectiveness of digital mental health for increasing resilience in adolescents. The second step is to identify randomized controlled trials on digital mental health interventions used to boost resilience and prevent adolescent mental health problems.

Search Strategy

Studies will be identified by conducting a literature review, establishing a search strategy, and searching for peer-reviewed articles and gray literature. The screening will start with the title, followed by the abstract and full text of selected studies. Studies published between 2000 and 2023 will be included. The search strategy and inclusion and exclusion criteria have been established and approved.

A search for relevant studies will be done in a structured manner using four databases: ProQuest, Scopus, Cochrane Library (CENTRAL), and *JMIR Mental Health*. Gray literature will be searched for through GreyNet International. We will also hand search for articles by selecting appropriate references from the articles eligible for analysis and other relevant publications. All search results and the screening process will be exported to Rayyan's free online systematic review management software. Articles that match the inclusion criteria will be included (Multimedia Appendix 3). The authors will use Medical Subject Headings (MeSH) to search databases using keywords related to mental health, resilience, youth, digital, communication, and

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media (Multimedia Appendix 4). The PRESS (Peer Review of Electronic Search Strategies) guideline developed in 2015 has six steps: translation; Boolean and proximity operators; subject headings; text word searching; spelling, syntax, and line number; and limits and filters [45]. In addition, the PICO elements will be used as a guide for screening and identifying studies.

Study Selection

The study search results obtained in stage 2 will be exported to Rayyan for data management (removing duplicates and referencing) [46,47]. The screening of titles, abstracts, and full texts will be conducted by three independent reviewers based on the inclusion and exclusion criteria. Studies that meet the inclusion criteria will be included in the full-text screening. Otherwise, they will be excluded, with the reasons for exclusion presented in the final report. Three independent reviewers will conduct the data extraction. The final results will be presented in the form of a PRISMA diagram [28]. Disagreements or discrepancies that arise will be resolved by discussion or consensus.

Charting (Extracting) the Data

Data Extraction

This study used three reviewers for data extraction to determine and discuss eligible articles. Reviewers will sift through the same data and discuss the results of the screening of the titles, abstracts, and full texts; if there is easy access to the full text; and the key PICO elements. The reviewer team will resolve any disagreements by using the judgment of the third reviewer. Three experienced verifiers will verify the search results. An Excel (Microsoft Corporation) sheet will be created to extract essential information from the selected studies (Multimedia Appendix 5).

Data Synthesis

The synthesis will follow the JBI guidelines. This synthesis focuses on the type of media used to intervene in adolescent resilience skills and the impact the media had on adolescent resilience skills. The quantitative analysis will be presented descriptively with frequency distribution tables and statistical summaries of the article characteristics. The synthesis will use evidence source details and characteristics (citation details, country, context, and participants). The synthesis will also detail the results extracted from the sources (in relation to the scoping review's concept) concerning the type of media and its impact. Researchers will read the selected articles and develop themes based on the main results. Themes will be created by determining the type of digital media used (game, website/internet based, mobile app, or computer based) and the media's effectiveness or impact (effective or noneffective), determined by P values <.05 or <.001 depending on the statistical method used in the eligible manuscript. Themes will be developed while analyzing the results of the eligible articles. Two other researchers will validate the results of the thematic analysis. If there are differences, they will be discussed and resolved together. Each article will be categorized based on the research location, methodology, and participant demographics.

Collating, Summarizing, and Reporting the Results

The eligible references from the scoping review will be exported into Mendeley (the list of databases will be exported in RIS format with full-text references). A PRISMA flowchart will be used to visualize the sequence of the literature screening process for eligible articles for analysis. A literature map will then be used to match and categorize the relevant references. Later, a descriptive analysis and tabulation will be used to make a narrative summarization.

Consultation

Discussion between consultants and the research team will review and refine preliminary findings, aiming to reach a consensus. A psychiatrist will be consulted when additional data or information is needed. Follow-up discussions will be done for further clarifications. Additionally, consultations will be done to improve the results' accuracy and provide additional information and meaning [28].

Ethical Considerations

There will be no involvement of humans, animals, patients, or the public in this review. This review will synthesize data from peer-reviewed studies that have been published. Thus, no ethical approval was required.

Results

The selection of studies based on keywords was completed in December 2023. Meanwhile, study screening and study review were completed in February 2024, and preparation of the scoping review's results manuscript is currently underway. The scoping review is expected to be completed by the end of November 2024. This paper will describe the following findings: research selection, research characteristics (percentages based on the total eligible manuscripts), description of digital health, synthesis of results (type of media, content of media, targeting accessibility, and the effectiveness or the effect and impact of the intervention related to adolescent mental health), and evaluation, including strengths, limitations, and recommendations for research. This scoping review is supported by the Ministry of Education as funding for a scholarship program (Indonesian Educator Scholarship), which was awarded for 2022-2025. Funders were not involved in the development of the protocol.

Discussion

Previous studies have shown that technology can help improve the resilience capabilities of youths aged 10-19 years [12]. Digital technologies can impact multiple areas of development for adolescents in an increasingly digital world, including engendering positive outcomes in terms of the brain, cognition, social-emotional development, and mental health [48]. The role of digital health in mitigating risk and increasing resilience has been extensively studied [13]. Digitalization has impacted the ability of supply chains to mitigate disruption and build resilience [49]. Digital technology was also shown to enhance resilience during the COVID-19 pandemic [50]. During the pandemic, five things were found to strengthen resilience when

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using digital technology, namely, distributed training, local expertise, regional autonomy and ownership, local infrastructure, and platform design infrastructure including in the form of digital information [51]. Digital platforms can also increase individual resilience for overcoming mental health problems [52].

This protocol acts as an effective preplan, providing clarity to the study's flow and considering how to communicate the outcome data to the reader [53]. All scoping reviews must begin with a well-defined topic and a carefully developed and detailed protocol, guiding the conduct and reporting of the review while providing transparency and minimizing reporting bias [54]. Protocols are highly recommended before beginning a scoping review [55].

Some challenges may arise in this study. First, few articles might be found on the topic, considering that research in digital mental health and resilience is still not widely studied. To mitigate this, we have added a registered database, gray literature, and hand searching to our review. Second, there may be too few randomized controlled trials on digital health interventions to increase resilience. To mitigate this, we will include all types of experiments. Third, if the initial screening finds a vast number of articles, the keywords may be too broad. To mitigate this, we will use specific keywords. Fourth, studies on mental health outcomes related to chronic illness, situations during the pandemic, and other disease problems outside of mental health may emerge. Therefore, keywords need to be specified, and the initial screening stage (abstract selection) needs to be stringent [56].

The results of the study will provide a complete picture of the types of digital media that are used for increasing youth resilience and their effectiveness. Media has been shown to influence adolescent resilience abilities [57], so the integration of digital media in interventions may help decrease adolescent mental health problems [58]. Thus, the results of this scoping review can be used as a basis for evidence in determining further research or interventions. This scoping review only focuses on digital communication media.

Our dissemination plan includes presentations at conferences and for relevant stakeholders, and publication in a peer-reviewed journal. One limitation of this study is that improving resilience skills is influenced by other factors such as the environment, social support, social skills, and socioeconomic status. Including these variables would allow for further analysis.

This scoping review will provide a comprehensive overview of the existing literature on the use of communication media for improving resilience skills in adolescents.

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Authors' Contributions

RDR designed and wrote the manuscript. FSTD, DS, and RV provided advice and reviewed the manuscript. HM, RD, and RV helped write and proofread the manuscript, and will review the screening process selection on Rayyan. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[PDF File (Adobe PDF File), 125 KB - resprot_v13i1e58681_app1.pdf]

Multimedia Appendix 2
Population, Intervention, Comparator, Outcomes (PICO) framework.
[PDF File (Adobe PDF File), 45 KB - resprot_v13i1e58681_app2.pdf]

Multimedia Appendix 3
Inclusion and exclusion criteria.
[PDF File (Adobe PDF File), 48 KB - resprot_v13i1e58681_app3.pdf]

Multimedia Appendix 4
Searching strategy.

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[PDF File (Adobe PDF File), 77 KB - resprot_v13i1e58681_app4.pdf]

Multimedia Appendix 5
Data extraction variables.
[PDF File (Adobe PDF File), 49 KB - resprot_v13i1e58681_app5.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PICO: Population, Intervention, Comparator, Outcomes
PRESS: Peer Review of Electronic Search Strategies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Coproduction in Social Prescribing Initiatives: Protocol for a Scoping Review

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Abstract

Background: Social prescribing (SP) takes a holistic approach to health by linking clients from clinical settings to community programs to address their nonmedical needs. The emerging evidence base for SP demonstrates variability in the design and implementation of different SP initiatives. To effectively address these needs, coproduction among clients, communities, stakeholders, and policy makers is important for tailoring SP initiatives for optimal uptake.

Objective: This study aims to explore the role of coproduction in SP initiatives. The research question is as follows: How and for what purpose has coproduction been incorporated across a range of SP initiatives for different clients?

Methods: A review of international literature will be conducted following the JBI guidelines for scoping reviews. We will search multiple databases including Scopus, MEDLINE, and the PAIS Index, as well as gray literature, from 2000 to 2023. The primary studies included will describe a nonmedical need for clients, a nonmedical SP program or initiative, coproduction of the SP program, and any follow-up. Review articles and commentaries will be excluded. Titles, abstracts, and full-text articles will be screened, and data will be extracted by at least 2 research team members using Covidence and a pilot-tested extraction template. Clients with lived experience will also participate in the research process. Findings will be descriptively summarized and thematically synthesized to answer the research question.

Results: The project was funded in 2023, and the results are expected to be submitted for publication in early 2025.

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Conclusions: Descriptions of what coproduction is meant to accomplish may differ from theoretical aspirations. Continued understanding of how coproduction has been designed and executed across varied international SP models is important for framing engagement in practice for future SP arrangements and their evaluation. We anticipate this review will guide clients, communities, stakeholders, and policy makers in further developing SP practice within health care systems.

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KEYWORDS

social prescribing; coproduction; codevelopment; policy; social prescription; nonmedical need; social need; clinical setting; community programs; policy; health care system; pilot-tested; user involvement; health education

Introduction

Background

The World Health Organization (WHO) defines social determinants of health (SDOH) as the conditions in which people are "born, grow up, live, work and age, and the systems put in place to deal with illness" [1]. The WHO estimates that 30% to 55% of individual health outcomes are accounted for by SDOH, and many outside factors affecting SDOH can strongly influence health equity, both positively and negatively [2]. SDOH include education, food security, housing, social inclusivity, and nondiscrimination [1]. Although health care providers are aware of and acknowledge the influence of SDOH on overall health and well-being, education and resources supporting their abilities to effectively address these needs are often limited [3-6].

The United Kingdom was among the first countries to develop a national long-term plan in addressing health inequities related to SDOH [7]. They have had success in doing this through their National Health Service *Long Term Plan* by linking patients from primary care to nonmedical resources and support through their communities, termed social prescribing (SP). SP allows health care providers to enable patients to connect to personalized, nonclinical supports and services in their community. It also empowers patients to have an active role in coproducing, along with their health care team, individualized prescriptions for improving their overall health and well-being through existing social resources. SP is a first step in helping to decrease the effect of social inequities [7-11]. Other countries have since implemented and invested funding and resources into SP initiatives [7,12]. Although the terminology differs worldwide, there are currently 17 countries around the world that have developed and implemented SP initiatives. In addition, an international SP network was formed in 2015 [7].

Research has shown that SP can improve social connectedness and belonging by helping people develop social support networks within individual communities, resulting in improved self-confidence, self-esteem, and empowerment [13,14]. SP enables individuals to actively address challenging, personal, nonmedical needs, which can lead to improvements in long-term health outcomes, such as better management of mental health conditions like anxiety and depression [9,10,15,16].

Although worldwide evidence on SP initiatives is promising, the literature remains inconsistent, with most studies consisting of small-scale evaluations with poor study design and reporting [9]. Since SP was first described in the 1990s, the discourse around it has continuously evolved, but there is still no universal service model [7]. A service model would describe how health care providers, social workers, community organizations, and other stakeholders collaborate to connect individuals with nonclinical supports and services. Previous literature has described a need for consistent frameworks across SP programs and evaluations, although varying definitions and program structures present challenges. On the individual level, SP initiatives can also vary in terms of client population, the activities and stakeholders involved, duration of support provided to clients, and the resources required to address the intended social needs [7,13,17]. Understanding the various facets underpinning SP initiatives is important for achieving collective scalability, widespread adoption, and sustainable impact at both the individual and health systems level, ultimately aiming to mitigate health inequities.

What This Scoping Review Will Contribute

Emerging evidence from 1 UK region identified public-service user involvement as a key factor in the successful delivery of a SP scheme [17]. Clients' adherence to the program was maximized when they co-designed their social prescriptions through detailed assessment of their needs and preferences while considering potential access barriers. The involvement of local communities as coproducers and designers was also noted to be important in the development of place-based services within the region [17]. A recent systematic review of SP interventions that utilized a coproduction approach to improve well-being identified 8 relevant articles [9]. The review found that such engagement resulted in effective and efficient SP interventions and improved well-being outcomes [9].

Coproduction involves working with stakeholders to implement a solution that has been agreed upon for a specific problem or established need. It emphasizes the allocation of resources and assets within these set boundaries to achieve improved outcomes [18]. Continued understanding of how coproduction has been designed and executed across varied international SP models is important for framing engagement in practice for future SP arrangements and their evaluation. As previous research and systematic reviews have indicated, there is a need to better understand the mechanisms, or "black box," behind coproduction processes across various SP models [9].

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The objective of this scoping review is to explore the role of coproduction in SP initiatives. Empirically based descriptions of what coproduction is meant to accomplish may differ from theoretical aspirations. The findings from this review could provide further guidance for evaluating SP initiatives, ultimately leading to improved services, better client outcomes, and a reduction in health inequities through the global development of SP programs [19].

Methods

Design

This scoping review will adhere to the guidance provided by JBI and follow updated recommendations for this methodology [19,20]. The development and quality of this protocol were informed by the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [21]. The review's conduct and reporting will align with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist as recommended by JBI [22]. Both the PRISMA-P and PRISMA-ScR provide a framework that ensures rigorous reporting of the review process and results. This scoping review will involve the following prescribed processes: (1) creating the research question; (2) developing the search strategy; (3) screening, selecting, and appraising studies; (4) extracting data; and (5) analyzing and reporting data. The protocol has been registered with the Open Science Framework Registries (B8U4Z) [23].

Creating the Research Question

The research question and overall approach were developed in collaboration with the larger research team, which includes members with lived experience and expertise in SP and coproduction. The approach also incorporates scoping review methodology and draws on the Population, Intervention, Comparison, Outcomes framework as outlined in PRISMA-P, although no comparison group was included.

The scoping review research question is as follows: How and for what purpose has coproduction been incorporated (outcome) across a range of SP initiatives (intervention) for different clients (population)? The term "client" refers to individuals and communities.

Search Strategy Development

The search strategy will be refined in collaboration with the research team, including those with professional expertise and experience in developing search strategies for a scoping review. The search will include OVID MEDLINE, Scopus, and the PAIS Index using a variety of keywords developed from concepts related to coproduction and SP. A pilot search on Scopus was conducted to aid the development of a comprehensive search strategy, including subject headings and search terms. The final strategy for identifying published literature will include database-specific subject headings and keywords. Additionally, we will review the reference lists of included studies and relevant review articles to identify potentially relevant studies. While we considered hand-searching, we determined it unnecessary since scholars in the emerging field of SP have not yet published extensively in key research journals. The search will not be limited by language or study design but will focus on literature from 2000 to 2023, as preliminary research indicated that the concept of SP is relatively new, with reports of SP programs appearing in the early 2000s [22,24]. Multimedia Appendix 1 presents the search string developed in consultation with an information specialist.

Evidence Screening, Selection, and Appraisal

We will include studies describing an SP program or initiative incorporating coproduction in its approach. For the purposes of this scoping review, SP is defined as "a means for trusted individuals in clinical and community settings to identify that a person has non-medical, health-related social needs and to subsequently connect them to non-clinical supports and services within the community by co-producing a social prescription—a non-medical prescription, to improve health and well-being and to strengthen community connections" (p. 9) [3]. The term "trusted individual" refers to service providers who may not be health care professionals but are trusted within the community by those they serve; these individuals, also known as identifiers, are considered part of SP programs [3]. The required conditions for SP outlined by Muhl et al [3] were rigorously developed with input from the international SP community, including researchers and other stakeholders, using a Delphi approach. These conditions are as follows: SP is "a holistic, person-centred, and community-based approach to health and well-being that satisfies Condition 1 and either Condition 2 or Conditions 3 and 4:

- Condition 1: Identifier identifies that person has non-medical, health-related social needs (e.g., issues with housing, food, employment, income, social support)
- Condition 2: Identifier connects person to non-clinical supports and services within the community by co-producing a non-medical prescription
- Condition 3: Identifier refers person to connector
- Condition 4: Connector connects person to non-clinical supports and services within the community by co-producing a non-medical prescription" [3].

A connecter, also part of the SP program, is responsible for linking the person to community resources. This role may be filled by the same person as the identifier or by someone else. The connector is sometimes referred to as the link worker. Muhl et al [3] also developed a Common Understanding of Social Prescribing Conceptual Framework, which outlines that the connector follows up with the person and reports back to the identifier.

Based on our research question and the specified conditions, we will select articles that (1) were published between 2000 and 2023; (2) are peer-reviewed primary research, including qualitative, quantitative, or mixed methodology studies; (3) include information on the client and/or community in the coproduction of the SP initiative (population); (4) describe an SP initiative, including the identification of a nonmedical needs for the client (intervention); (5) describe an SP initiative with follow-up, such as feedback, to the SP identifier or connector regarding the client (intervention); and (6) describe the client

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and/or community engagement process in the coproduction of the SP initiative (outcome). We will also search for gray literature, including resources disseminated by international SP initiatives, which may encompass local program evaluations and/or review articles commissioned by the initiatives. We will examine the reference lists of these resources for additional relevant studies.

Results from the database and gray literature searches will be exported to and managed through Covidence (Veritas Health Innovation), a web-based collaboration platform that streamlines the production of systematic and other literature reviews [25]. After removing duplicates, the screening process will involve 2 rounds: an initial screening of titles and abstracts, followed by a full-text review. A pilot test with randomly selected articles will be conducted by at least 4 research team members to clarify the inclusion/exclusion criteria and ensure consistent screening. Through repeated iterations and discussions, we will reach a common understanding of the study concepts. Subsequently, 2 raters will review all articles for eligibility. Eligible articles will proceed to the second round of screening. Any conflicts in determining article eligibility will be resolved by a third reviewer. The second round will involve a detailed, full-text screening against our eligibility criteria. Reviewers will document the reason for excluding articles based on these criteria [25]. We will not conduct a quality or risk assessment of the articles, as this is not typically part of the scoping review methodology [22].

Data Extraction

The team will use the *JBI Manual* data extraction guidance to develop our data extraction template. We anticipate recording the following characteristics from each article: (1) title, (2) author, (3) year of publication, (4) country involved, (5) type of literature, (6) purpose/goal/aim of the article, (7) study methodology, and (8) health care setting. In addition to these metadata characteristics, we will extract information about the SP initiative, including the clients involved, their nonmedical needs, the role of the connector or link worker, the nature of the social prescription, and follow-up with the initiator. We will also collect data on the coproduction process at both the community and client levels to understand the reasons for and methods of engagement.

A pilot extraction process will be conducted to refine the template. Three team members will participate in the extraction process. Each article will be initially extracted by 1 researcher and subsequently reviewed by others to ensure consistency. The team will meet regularly to discuss their extractions and ensure alignment.

Data Analysis and Reporting

The metadata of the included studies will be summarized with descriptive statistics. Qualitative content analysis will be employed to synthesize data about the SP initiative and how coproduction was utilized [26]. The reporting of this scoping review will follow the PRISMA-ScR checklist recommended by JBI [22].

Client Involvement

Two coresearchers with lived experience, who are members of Canadian Institute for Social Prescribing Patient Advisory Committee, will be involved in the scoping review process. They are expected to contribute to 1 or more of the following activities: discussing and reflecting on study findings during research team meetings, supporting the development of our gray literature strategy, and assisting in the creation of a lay summary. The coresearchers will be offered an honorarium consistent with the Canadian Institute for Social Prescribing's guidelines.

Ethical Considerations

This scoping review involves a secondary analysis of primary research studies and gray literature on coproduction in SP initiatives; therefore, institutional research ethics approval is not required.

Results

The project was funded in 2023, and the results are expected to be submitted for publication in early 2025.

Discussion

Expected Findings

This scoping review will serve as a foundation for a larger research study aimed at further evaluating and understanding the importance of coproduction and SP as they become increasingly common practices across Canada. Both traditional and nontraditional dissemination strategies will be employed to broaden the reach of the review's findings.

Coproduction approaches, which can lead to more engaging, usable, relevant, and effective programs, are gaining momentum [27,28]. Through meaningful and reciprocal engagement, coproduction can support shared responsibility and ownership of programs and interventions [27]. There is mounting evidence that using coproduction to design SP initiatives is beneficial, but there is limited consistency in understanding how this has been accomplished. The proposed scoping review will synthesize the evidence on the role of the client or community in coproducing SP initiatives. This review will identify where current practices related to coproduction for SP diverge and converge.

Limitations

Challenges are anticipated in the search process due to inconsistencies in terminology related to SP. For example, articles describing SP initiatives from different countries may use varied language. While our research team, including experts in the field, will strive to compile a comprehensive list of search terms to encompass all iterations of SP in the literature, it is possible that some SP terms may be overlooked and relevant articles may be missed.

Conclusions

The existing literature lacks a comprehensive understanding of coproduction in SP initiatives, which is important for leveraging community and client expertise in developing this integrated care model. This scoping review aims to address the knowledge

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gap regarding the role of coproduction in SP initiatives. We anticipate the findings will guide clients, communities, stakeholders, and policy makers in further developing SP practices and coproduction options within health care systems.

Acknowledgments

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Authors' Contributions

All authors contributed to the design and content of the study protocol. MD and TT contributed equally to the writing of the initial draft of the protocol and are coprincipal authors. EZ contributed to the writing of the initial draft of the protocol. AK contributed critical comments, supervised the writing, did final revisions to the protocol, and is the corresponding and senior responsible author. All authors provided important comments on drafts and have approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for OVID MEDLINE.
[DOCX File , 16 KB - resprot_v13i1e57062_app1.docx]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SDOH: social determinants of health
SP: social prescribing
WHO: World Health Organization

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Protocol

Development of Leadership Skills in Medical Education: Protocol for a Scoping Review

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Abstract

Background: Leadership is recognized as an essential competency in health care and science, being central for professionals to face health challenges. Few physicians feel prepared to serve as leaders in the health care environment, and few receive training in the leadership skills needed to be successful. Teaching leadership skills together with extensive, longitudinal, clinical education in an authentic and nurturing environment can effectively develop students for leadership in medicine. Studies on the subject still do not show the best way to implement it in medical education, and an updated review is necessary.

Objective: The aim of this study is to identify the types of available evidence on the teaching of leadership skills in undergraduate courses in the health area, analyze them, determine knowledge gaps, and disseminate the research results.

Methods: This is a scoping review that will consider studies on leadership skills in medical and health undergraduate courses. Primary studies published in English, Spanish, and Portuguese since 2019 will be considered. The search will be performed in 8 databases, and reference lists will be searched for additional studies. Duplicates will be removed, and 2 independent reviewers will examine the titles, abstracts, and full texts of the selected studies. Data extraction will be performed using a tool developed by the researchers.

Results: The scoping review is currently in progress. The preliminary database search has been completed, yielding a total of 1213 articles across multiple databases. The next stages, including deduplication, title and abstract screening, and full-text review, are scheduled to be completed by December 2024. Data extraction and analysis are expected to be finalized by March 2025, with the final report anticipated to be ready for submission by June 2025.

Conclusions: This scoping review on leadership in the medical curriculum can significantly contribute to the literature by organizing and synthesizing the available evidence on teaching leadership skills in undergraduate courses in the health area. Furthermore, by analyzing evidence and identifying knowledge gaps, the study can provide valuable insights to develop more efficient and comprehensive medical education programs, thus preparing students to take on leadership roles in the complex environment of health care.

Trial Registration: Open Science Framework YEXKB; https://osf.io/yexkb

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KEYWORDS

leadership skills; medical education; undergraduate curriculum; health care management; professional development; scoping review protocol

Introduction

Leadership is recognized as an essential competency in health care and science [1], being fundamental for professionals to face important health challenges. For this reason, the preparation of health professionals for leadership roles and responsibilities has become increasingly important [2]. Effective leadership through ethical decision-making, communication, teamwork, and flexibility are necessary skills during health crises, having been given greater prominence after the stress inflicted on our health system by the COVID-19 pandemic [3].

There are now more discussions about leadership in medical education. Thus, "medical leadership and management" describe the involvement of physicians in the leadership and management of individual patient care and the departments, organizations, and systems where they work [4]. Therefore, the future of medical leadership and management development has great potential to improve patient care. However, it must be longitudinally integrated throughout physicians' careers. Furthermore, the development of undergraduate courses is a critical step in increasing awareness, creating professional identity, and thus helping physicians in training to recognize and understand their broader responsibility to the system and patients [4].

The existing gap due to the absence of leadership education leads to the question of whether students develop skills to handle and resolve conflicts, learn to share leadership, prepare others to help and replace them, assume mutual responsibility, and discuss their actions [5]. Informal leadership preparation coupled with extensive, longitudinal, clinical education in an authentic and nurturing environment can effectively develop students for leadership in medicine [6]. Medical knowledge alone is insufficient to provide excellent medical care [7].

In the health care system, leadership has never been more crucial. In low- and middle-income countries, the lack of management capacity leads to frequent failures in initiatives to improve health care, even with clinical knowledge and public health. Some barriers to implementing full leadership development are present at all career levels [8]. Thus, this scoping review aims to fill the following gaps: difficulty in introducing specific programs of leadership training into the medical school curriculum; the existence of curricula filled with other priority topics; and how leaders' performance should be evaluated during the medical course [9].

Leadership development in medical education is crucial for several reasons:

1. Holistic preparation: The inclusion of leadership in the curriculum helps provide a more holistic and realistic preparation for professional practice and development [3,10,11].
2. Quality of care: Effective leadership is fundamental to generating high-quality care for patients and improving their safety through a collective leadership style [12].
3. Evolving needs: There is an urgent need to adapt current medical curricula, implementing leadership teaching to meet evolving health care needs [1,10,12].
4. Global perspective: It is not known whether medical schools globally promote leadership education and what is the best way to implement it. Therefore, this project is justified to examine leadership education in medical curricula worldwide [4,7,8,12].

Despite the growing effort for physician leadership education to begin earlier and continue throughout their careers [5] and evidence that leadership training must be longitudinally integrated throughout the clinician's career [12], it is not known whether medical schools globally promote leadership education and what is the best way to implement it. A scoping review can provide a comprehensive, detailed, and unbiased view of this subject. Therefore, a scoping review will be used to address the different perspectives and evidence [4,7,8,12]. The results of this study should allow for a more deep and informed understanding of leadership teaching in medical courses.

Although the benefits of physician leadership are well established according to the *Harvard Business Review* [10], few physicians feel prepared to act as leaders in the complex environment of health care and/or receive training for the leadership skills needed to be successful. Therefore, acquiring leadership should not be different from acquiring the necessary knowledge to become a competent physician [3].

However, studies on the subject greatly differ in methodology, population, context, and objective, making their clear understanding even more difficult. Among all methodologies of knowledge synthesis, scoping reviews are the best way to present a broad view of evidence in heterogeneous scenarios, summarizing and promoting a better understanding [11]. Furthermore, a preliminary search showed that few scoping reviews were found despite the relevance of the topic. How to evaluate leaders' performance during medical school is also a major gap. In medical school, leaders' performance appears to be a set of skills different from academic performance, although both types of knowledge can be taught and developed [9]. Therefore, a scoping review on this topic will allow for a more deep and informed understanding of teaching leadership in medical education.

The objective of this scoping review protocol is to identify the types of evidence available on the teaching of leadership skills in undergraduate courses in the health area globally, analyze them, and determine gaps of knowledge.

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Methods

Overview

The literature search process was conducted using various search databases and strategies in English, Portuguese, and Spanish. Databases included ROAD, MEDLINE, DOAJ, PubMed, Science Direct, Scopus, and Web of Science for the searches in English. For searches in Portuguese, SCIELO was used, whereas for searches in Spanish, SCIELO was also used along with Latindex.

Table 1 summarizes the key components of the search strategy, including the search terms, filters, use of quotations, combination of terms, and an example of an exact search string used in PubMed.

Similar search strings were used for other databases, adapted to their specific syntax and controlled vocabulary.

The search strategy consisted of combining key terms related to students in the health area, health care leadership competencies, and skills. For searches in English, the terms "Students, Health Occupations" and "Health Leadership, Competencies," along with the synonyms "Aptitude," "Abilities," and their variations, were used. Figure 1 shows the concepts explained in this review.

The research question was formulated in line with the review objective using the mnemonic conceptual model Population, Concept, and Context (PCC): "What is the literature overview regarding leadership skills that can be cultivated during the training of students in the health area?"

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Table 1. Key components of the search strategy.

Search strategy component	Details

Search terms and keywords	• English:
	  • "Students, Health Occupations"
	  • "Health Leadership, Competencies"
	  • "Aptitude"
	  • "Abilities"
	  • "Aptitudes"
	  • "Ability"
	• Portuguese:
	  • "Estudantes de Ciências da Saúde"
	  • "Competência de Liderança em Saúde"
	  • "Aptidão"
	  • "Habilidade"
	  • "Habilidade Pessoal"
	• Spanish:
	  • "Estudiantes del Área de la Salud"
	  • "Competencia de Liderazgo en Salud"
	  • "Aptitud"

Filters and limits	• Date range: Studies published since 2019 • Languages: English, Spanish, and Portuguese • Publication types: Primary studies, systematic reviews, meta-analyses, meta-syntheses, books, and guidelines published in indexed sources
Use of quotations	• Quotation marks were used around specific phrases to ensure exact phrase matching, as shown in the search strategies

Combination of search terms	• English:
	  • ("Students, Health Occupations") AND ("Health Leadership, Competencies") AND ("Aptitude" OR "abilities" OR "Aptitudes" OR "Ability")
	• Portuguese:
	  • ("Estudantes de Ciências da Saúde") AND ("Competência de Liderança em Saúde") AND ("Aptidão" OR "Habilidade" OR "Habilidade Pessoal")
	• Spanish:
	  • ("Estudiantes del Área de la Salud") AND ("Competencia de Liderazgo en Salud") AND ("Aptitud")

Exact search string	• PubMed: • ("Students, Health Occupations"[MeSH[a] Terms] OR "Students, Health Occupations"[Title/Abstract]) AND ("Health Leadership"[MeSH Terms] OR "Health Leadership"[Title/Abstract] OR "Competencies"[Title/Abstract]) AND ("Aptitude"[MeSH Terms] OR "Aptitude"[Title/Abstract] OR "abilities"[Title/Abstract] OR "Aptitudes"[Title/Abstract] OR "Ability"[Title/Abstract]) AND ("2019/01/01"[Date - Publication] : "3000"[Date - Publication])

[a]MeSH: Medical Subject Headings.

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Figure 1. Concepts explained in this review.

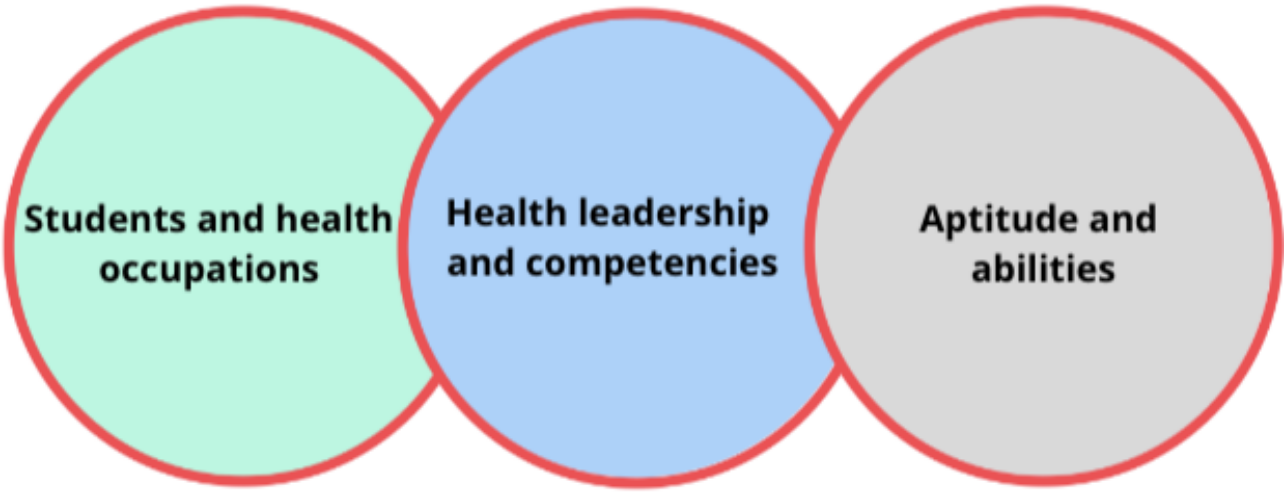

Inclusion Criteria

For inclusion in this review, studies whose target population was students in the health area will be considered, specifically those addressing leadership skills, regardless of the types of teaching and methodology used to train students.

- Population: Studies whose population consists of medical students and any age groups attending any year of health education will be included.
- Concept: Studies that mentioned "leadership development in medical curricula" will be included, regardless of the type of leadership behaviors and the way the perceptions were measured.
- Context: Eligible studies will be those related to teaching leadership in the health area in any educational context worldwide, regardless of the country of origin of the study.

Types of Sources

Studies with qualitative and quantitative approaches will be included in the review, including primary studies, systematic reviews, meta-analyses, and/or meta-syntheses, as well as books and guidelines published in indexed sources. For inclusion in this review, opinion, consensus, retraction, editorials, websites, and media advertisement publications will not be considered.

Exclusion Criteria

The following exclusion criteria will be considered: not meeting the eligibility criteria; not being published in indexed sources; and being publications of opinions, consensuses, retractions, editorials, websites, and advertisements published in the media.

Search Strategy

In searches in Portuguese, the corresponding terms were the used: "Health Sciences Students"; "Health Leadership Competence"; and "Aptitude," "Ability," and their variations. For searches in Spanish, the terms "Estudiantes del Area de la Salud," "Competencia de Liderazgo en Salud," and "Apitud" were used (Table 2).

Table 2. Search strategy structure.

Category	Details
Subject 1 in Portuguese (DeCS[a])	"Estudantes de Ciências da Saúde"
Subject 1 in English (MeSH[b])	"Students, Health Occupations"
Subject 1 in Spanish (DeCS)	"Estudiantes del Área de la Salud"
Subject 2 in Portuguese (DeCS)	"Competência de Liderança em Saúde"
Subject 2 in English (MeSH)	"Health Leadership, Competencies"
Subject 2 in Spanish (DeCS)	"Competencia de Liderazgo en Salud"
Subject 3 in Portuguese (DeCS)	"Aptidão" OR "Habilidade" OR "Habilidade Pessoal"
Subject 3 in English (MeSH)	"Aptitude" OR "abilities" OR "Aptitudes" OR "Ability"
Subject 3 in Spanish (DeCS)	"Aptitud"

[a]DeCS: *Descritores em Ciências da Saúde* (Descriptors in Health Sciences).

[b]MeSH: Medical Subject Headings.

After the question was prepared, the keywords that managed to capture articles referring to the theme of this research were identified: "Knowledge Translation [Title] OR Translational Medical Research [Title/Abstract]." The search was performed using descriptors and/or their synonyms, according to the *Descritores em Ciências da Saúde* (DeCS; Descriptors in Health

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Sciences) and Medical Subject Headings (MeSH) for each strategy item. To combine descriptors, the AND, OR, and NOT Boolean terms were used.

This diversity of databases and search strategies provided a broad coverage of the available literature, contributing to the comprehensiveness and relevance of the review.

Study or Source of Evidence Selection

To select studies that meet the inclusion criteria, duplicate articles will initially be removed from the analysis process. Then, 2 researchers will independently analyze the titles and abstracts of the remaining articles using the previously established eligibility criteria. If a disagreement between them occurs regarding the inclusion of a study at this stage, the final decision will be made by a third researcher, who will be consulted to resolve the divergence and determine the relevance of the article to the research question. Additionally, a manual search for relevant sources not captured in the initial search strategy may complement the review, as long as they meet the eligibility criteria and significantly contribute to the conclusion of the study.

Next, the main researcher will evaluate the full texts of the previously selected articles, ensuring that they are aligned with the inclusion criteria. The reasons for excluding any studies after full-text reading will be appropriately documented and presented in the context of the scoping review. At any stage of the selection process, any disagreements that may arise between members of the research team will be resolved either through a consensual discussion or with the intervention of additional researchers to reach a consensus if necessary.

The study selection process will be reported using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to ensure transparency and reproducibility.

Data Extraction

After the article selection phase, the main researcher will prepare a form for data extraction, which will be completed after a thorough analysis of each selected article. The data to be extracted will cover specific information related to the PCC and methodology of the study, in addition to relevant data for the research question such as method and model of leadership teaching adopted, strategies used, perceptions of the studied population, and identified impact. The initial draft of the form is presented in Multimedia Appendix 1 and can be adapted and improved as necessary during the extraction of data from each bibliographic source included in the scoping review. Any adjustments made will be duly documented in the revision scope. Furthermore, the article authors will be contacted to clarify missing information when applicable or obtain additional data to ensure the integrity and accuracy of data analysis. The data extraction indicators are presented in Table 3.

Table 3. Data extraction indicators developed by the researchers.

Category	Indicator
Publication details	• Journal • Year • Title • Authors • Country • Type of study
Inclusion or exclusion criteria	• Population • Concept • Context • Reason for exclusion
Findings	• Leadership teaching method • Leadership teaching model • Student perception • Impact

Analysis of the Evidence

The analysis of the results will be conducted following the objectives established in this scoping review. As is typical for scoping reviews, we will provide a narrative synthesis of the findings, mapping the available evidence on leadership development in medical education. Descriptive statistics such as absolute frequencies and percentages will be used to summarize characteristics of publications (journal, year, title, authors, country, and type of study). However, unlike a systematic review, we will not conduct in-depth quantitative analyses or assess the quality of individual studies. We will use a qualitative content analysis approach to explore and categorize findings related to the method and model of teaching leadership, student perception, and identified impact. This analysis will focus on identifying patterns and themes across the included studies, rather than synthesizing effectiveness data as would be done in a systematic review. Data will be presented in figures and tables, complemented by a narrative synthesis to describe the relationship of the results to the research question. This approach aligns with the purpose of a scoping review, which is to map the available evidence and identify knowledge gaps, rather than to answer a specific clinical question or assess the quality of evidence as in a systematic review. The results will be reported following the PRISMA-ScR (PRISMA Extension

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for Scoping Reviews) guidelines to ensure transparency and reproducibility of our scoping review process.

The complete search strategies used for each database are provided in Multimedia Appendix 2.

Results

The scoping review is currently in progress. The preliminary database search has been completed, yielding a total of 1213 articles across multiple databases. The next stages, including deduplication, title and abstract screening, and full-text review, are scheduled to be completed by December 2024. Data extraction and analysis are expected to be finalized by March 2025, with the final report anticipated to be ready for submission by June 2025.

Discussion

Expected Findings

The recognized needs for effective succession planning and leadership training are well established, with a current shortage of emerging leaders assuming leadership roles [5,13,14]. Effective leaders require support and guidance from the organizations where they were educated and trained, and where they work [15]. Leadership as a learned skill is gaining momentum as a fundamental curriculum item in medical education. Leadership development, assessment, and feedback are essential throughout the education and training of health professionals. Aspiring and current leaders can be identified, trained, and assessed through formal leadership development programs and organizational supportive cultures. This requires the incorporation of programs for leadership training, opportunities for leadership practice, and promotion of professional networks within and outside the organization. Mentoring in health education is recognized and important, and it offers a means to further enhance leadership and engagement in the workforce [16,17].

Leadership is composed of a set of practices and skills that can be learned and can be developed by reading literature articles and participating in leadership courses [17]. Moreover, investment in the social capital of organizations, promoting interprofessional learning and communication in the workplace, and collaboration between organizations help develop leadership. The development of leadership skills is a lifelong process [18,19]. Resources and opportunities should be considered to help develop leadership skills through activities such as reading about leadership theories, attending leadership training workshops, engaging in mentoring programs, attending small-group seminars on leadership development, and accepting more responsibilities when necessary or when opportunities arise [20].

Effective leadership does not necessarily require an academic title. It can manifest itself in daily work and collaboration with other professionals in education and health systems, such as teaching, administration, research, and clinical practice [3]. Leadership functions include the important concepts of managing personal and professional practices, prioritizing tasks, time management, and effective delegation [21].

Research indicates that while students consider leadership an essential competency due to the responsibilities inherent to the medical profession, professors may not see the need to separately consider leadership as an essential competency due to the implicit training provided by the curriculum. However, both students and professors identify rigorous curricula as barriers to implementing leadership training. Students also highlight the feasibility of leadership training as a challenge, especially in clinical settings. However, the lack of recognition seems to be the most influential obstacle [22-24].

Qualities such as emotional intelligence, confidence, and humility can be taught during medical courses along with skills in teamwork, communication, and management. As a result, medical institutions have introduced explicit leadership curricula and integrated leadership training into their programs to meet these needs [25].

The consistent themes behind the implementation of curricula and explicit leadership structures in medical schools emphasize the intention to actively embody and pursue leadership skills and competencies that can be naturally observed and taught. Integrating training with these principles in mind would be much more effective against the obstacles posed by overloaded curricula and would increase recognition or at least reduce disinterest in leadership training [26].

Implementing changes based on a curriculum model would be beneficial, as it is described as one of the most comprehensive models for leadership education. However, incorporating leadership as a core objective and constructing or adapting a conceptual framework for medical curricula similar to the examples mentioned above, while considering student perceptions, would be prudent. Incorporating such training would be more effective if done through experiential learning, although additional small-group sessions and classroom-based interactive seminars could also be used [27].

Finally, the methods used in residency training to develop leadership can be extended to medical schools. Providing formative feedback on leadership skills can be effective in improving leadership skills. Ultimately, training must be integrated and aligned with education rather than separated and isolated from clinical instruction. Curriculum planners must be flexible and engage with medical professionals to emphasize the importance of such a competency [28].

Limitations

The limitation of this research is the possible incompleteness or bias of the available data sources, although an extensive search was conducted in several databases. Although the inclusion and exclusion criteria have been carefully defined, omission or nonidentification of some relevant studies during the search is possible. Due to the comprehensive nature of the scoping review, it may also not allow for a detailed analysis of each study, thus limiting the depth of assessment of the available evidence.

To mitigate these limitations, we will implement the following strategies:

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1. Collaborate with an experienced librarian to refine our search strategy, ensuring comprehensive coverage across databases
2. Include gray literature sources such as conference proceedings and organizational reports to capture non–peer-reviewed but relevant information
3. Conduct hand-searching of reference lists from the included studies and relevant systematic reviews
4. Consult with experts in medical education and leadership to identify key studies that may have been overlooked
5. Maintain transparent reporting of all methodological decisions and processes

Another significant limitation is the lack of clarity on how leaders' performance should be evaluated during medical school. To address this gap, our review will specifically focus on identifying and synthesizing information about evaluation methods, including but not limited to the following:

- Multisource feedback mechanisms
- Objective Structured Leadership Examinations
- Leadership portfolios
- Longitudinal assessment approaches
- Self-assessment tools
- Project-based assessments

For a more comprehensive and precise understanding, it is important to recognize that the interpretation of the results of this review must consider these possible limitations and be complemented by other sources of evidence when necessary. We will explicitly discuss these limitations in our final report and suggest areas for future research to address remaining gaps in knowledge.

These revisions address the potential biases and limitations of the study, as well as the gap in understanding how to evaluate leadership performance in medical education.

Conclusions

In this research protocol, a scoping review on the development of leadership skills in medical education was outlined, recognizing the fundamental importance of leadership in clinical practice and health sciences. The proposed review aims to address the existing gap in the literature on the implementation of leadership education in health care colleges by highlighting the need to prepare students to assume leadership roles in the complex environment of health care. The preliminary results show a wide range of articles, pointing out the relevance and urgency of this topic. This review offers valuable insights to develop more comprehensive and effective educational programs, empowering students to lead interdisciplinary teams and promote positive change in the health system.

Furthermore, the inclusion of leadership in the medical courses curriculum can provide more holistic and realistic preparation for future health care professionals, equipping them with the necessary skills to provide high-quality care to patients and face emerging challenges in the health area. This scoping review will not only contribute to the literature but will also have a practical and tangible impact on students professional training and development, thus promoting significant advances in medical practice and education.

Acknowledgments

We give thanks to Zélia Cristina Regis, librarian of the School of Medicine of São José do Rio Preto, Brazil, for her collaboration in designing the search strategy. This study will not receive any funding.

Data Availability

All data generated or analyzed during this scoping review will be included in the published article and its supplementary files. The complete list of included studies, along with their extracted data, will be made available as a supplementary file upon publication. The search strategies for each database are provided in Multimedia Appendix 2. Any additional data related to this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Structuring search performance.
[DOCX File , 14 KB - resprot_v13i1e62810_app1.docx]

Multimedia Appendix 2
Detailed search strategies for each database used in the scoping review.
[DOCX File , 13 KB - resprot_v13i1e62810_app2.docx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 16 KB - resprot_v13i1e62810_app3.docx]

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Abbreviations

DeCS: Descritores em Ciências da Saúde (Descriptors in Health Sciences)
MeSH: Medical Subject Headings
PCC: Population, Concept, and Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Current State of Connected Sensor Technologies Used During Rehabilitation Care: Protocol for a Scoping Review

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Abstract

Background: Connected sensor technologies can capture raw data and analyze them using advanced statistical methods such as machine learning or artificial intelligence to generate interpretable behavioral or physiological outcomes. Previous research conducted on connected sensor technologies has focused on design, development, and validation. Published review studies have either summarized general technological solutions to address specific behaviors such as physical activity or focused on remote monitoring solutions in specific patient populations.

Objective: This study aimed to map research that focused on using connected sensor technologies to augment rehabilitation services by informing care decisions.

Methods: The Population, Concept, and Context framework will be used to define inclusion criteria. Relevant articles published between 2008 to the present will be included if (1) the study enrolled adults (population), (2) the intervention used at least one connected sensor technology and involved data transfer to a clinician so that the data could be used to inform the intervention (concept), and (3) the intervention was within the scope of rehabilitation (context). An initial search strategy will be built in Embase; peer reviewed; and then translated to Ovid MEDLINE ALL, Web of Science Core Collection, and CINAHL. Duplicates will be removed prior to screening articles for inclusion. Two independent reviewers will screen articles in 2 stages: title/abstract and full text. Discrepancies will be resolved through group discussion. Data from eligible articles relevant to population, concept, and context will be extracted. Descriptive statistics will be used to report findings, and relevant outcomes will include the type and frequency of connected sensor used and method of data sharing. Additional details will be narratively summarized and displayed in tables and figures. Key partners will review results to enhance interpretation and trustworthiness.

Results: We conducted initial searches to refine the search strategy in February 2024. The results of this scoping review are expected in October 2024.

Conclusions: Results from the scoping review will identify critical areas of inquiry to advance the field of technology-augmented rehabilitation. Results will also support the development of a longitudinal model to support long-term health outcomes.

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KEYWORDS

connected sensor technology; digital health; rehabilitation; rehabilitation care; remote monitoring; telehealth; mHealth; mobile health; wearables; wearable technology

Introduction

Connected sensor technologies are defined as "technology products that process data captured by mobile sensors using algorithms to generate measures of behavioral and/or physiological function" [1,2]. Examples include medical technologies such as ingestibles (smart pills) and dermal patches, along with direct-to-consumer wearables that include activity trackers, heart rate monitors, and smart clothing. Consumer wearables have grown in popularity and ownership over the past decade for a variety of reasons. A 2016 market research survey reported that consumers were motivated to buy wearable technologies to support health, and consumers noted benefits of wearables that include enhancing accountability, improving exercise habits, and becoming more efficient at home and work [3]. These motivations for ownership have stayed consistent over the years. In fact, the American College of Sports Medicine annual survey for fitness trends predicted wearable technology to be the top trend in fitness in the United States for 2024—a trend that has been in the number one spot for 7 of the previous 9 years [4]. This survey also highlighted a new trend for 2024—data-driven training technology—that was defined as using real-time data output such as heart rate to guide workouts [4].

In addition to consumer uptake, health care systems and providers are beginning to adopt connected sensor technologies. A driving factor for health system uptake is the need to deliver health care services to more people at lower costs due to an aging population with high rates of noncommunicable diseases [5]. One approach to reduce costs while promoting better health is through the reallocation of funds to preventative services such as primary care [6] and lifestyle modification programs such as those that promote physical activity. Common limitations of these programs, however, are that maintenance beyond 1 year has not been established [7] and cost-effectiveness is unclear [8]. Alternatively, funds could be used to support remote monitoring programs that use connected sensor technologies with the goal of preventing unnecessary health care utilization. In theory, earlier detection of health deterioration or nonadherence, such as in patients with chronic obstructive pulmonary disease or heart failure, would prompt early, at-home intervention, thus reducing emergency department visits and hospitalizations. While evidence to support such mitigation is mixed [9], one study found that increased adherence was associated with a reduced risk of subsequent hospitalization and death [10], suggesting that a remote monitoring approach may be beneficial for some patients.

Despite increasing popularity among consumers and health care systems, the role of connected sensor technologies in rehabilitation remains unclear. Potential benefits of using patient data from sensor technologies include deeper insights on treatment effectiveness, health behaviors, and symptom patterns [11-13]. However, there may also be negative effects to using such data. Both patients and providers recognize that consumer-grade devices may report inaccurate data [11,12], and they have concerns about data privacy, how to manage and use collected data, and what specific data should be shared [11-13]. Malalignment of patient and provider expectations may contribute to tensions within the therapeutic relationship [14].

As such, there is a need to evaluate how connected sensor technologies can be used effectively to enhance rehabilitation services. The use of connected sensor technologies in rehabilitation practice is relatively new, and much remains unknown given the complexity of available sensor types and heterogeneous patient populations. Most prior studies have focused on the development and validation of connected sensor technologies [15-17] and the infrastructure necessary to support data sharing and cloud computing [18,19]. Previous reviews have focused broadly on technological solutions to address specific behavior interventions such as weight loss [20], while others have focused on tools capable of assessment and remote monitoring of specific patient populations—those with cardiac disease [21], pulmonary disease [22], neurological disorder [23], and cancer [24]. To our knowledge, no review has focused on the use of connected sensor technologies to inform rehabilitation interventions. Such a review would identify the breadth of research, identify knowledge gaps, and elucidate directions for future study while providing clinicians with case examples of how to implement connected sensor technologies into rehabilitation practice.

The aim of this scoping review is to discover and map research that focuses on using connected sensor technologies to augment rehabilitation services by informing care decisions. The general research question guiding this aim is as follows: What is known from existing literature about the remote use of connected sensor technologies integrated into rehabilitation care to monitor patient status and inform care decisions?

Methods

Overview

The scoping review will be conducted in accordance with the JBI methodology for scoping reviews [25,26] and reported in line with PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [27]. We will also follow the 6-stage framework for a scoping review proposed by Arksey and O'Malley [28].

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Stage 1: Identifying the Review Questions

The first stage in the scoping review as outlined by Arksey and O'Malley [28] is to identify specific questions to help guide the search strategy and answer the general question posed above. Thus, we developed the following specific questions:

1. How have researchers studied the use of connected sensor technologies in rehabilitation (eg, what types of studies) as part of a feedback loop between patients and providers?
2. Within the context of rehabilitation care, what types of connected sensor technologies have been used, how were they used, and what types of patient-generated health data were collected?
3. With what patient populations have these connected sensor technologies been used and what has been found?
4. Have researchers explored various partner experiences and perspectives of using connected sensor technologies in rehabilitation, and if so, which partner groups are represented?
5. Based on the scope of research in this area, what are the general limitations and research gaps?

In addition to these questions, we set specific parameters around the research of interest such that each study needed to include (1) a connected sensor technology; (2) data transfer from the patient to the clinician; and (3) use of the data by the clinician to inform the rehabilitation intervention.

Stage 2: Identifying Relevant Studies

Based on recommendations from JBI, we used the Population, Concept, and Context (PCC) framework to develop initial search terms [26]. These keywords and synonyms will be used to iteratively develop a robust search strategy.

Population

The population for the scoping review will be limited to adults (aged ≥18 years). If a study includes both children and adults, the study may be included if data can be separated between the age groups. If data cannot be separated, then the study will be excluded. We will include all patient populations (those with cardiac disease, pulmonary disease, etc). We made this decision because we anticipate that connected sensor technologies used during rehabilitation could be applicable to patient populations other than those studied.

Concept

The concept involves studies that include (1) at least one connected sensor technology product that collects patient data; (2) data transfer from the product and patient to the clinician; and (3) use of the data by the clinician to inform the intervention. We used the definition provided in *The Playbook* [1], which defines a connected sensor technology as "products [that] process data captured by mobile sensors using algorithms to generate measures of behavioral and/or physiological function" (p. 79). A connected sensor technology was further defined as one that is capable of electronic transfer; thus, early activity trackers that used an accelerometer to collect step data such as a pedometer would be out of scope for this review as they were not connected technologies. Table 1 shows the different sensor types that will be considered for this review. It is also important to note that multiple sensor types may be combined in one product. Thus, terms such as connected sensor, remote monitoring, accelerometer, Bluetooth, inertial measurement unit, actigraphy, biomedical technology, remote sensing technology, haptic technology, digital technology, and wearable electronic devices will be considered for the search strategy. To capture the concept of data transfer, we will consider terms such as electronic health record integration, cloud, and dashboard. Because the final concept—use of data by the clinician—is difficult to capture using search terms, we will identify this component during full text review.

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Table 1. Connected sensory technology types[a] and examples.

Sensor types	Definition	Example product (manufacturer)
Accelerometer	Senses change in person's (or object's) linear velocity	• CentrePoint Insight Watch (ActiGraph)[b] • Vivoactive 5 (Garmin)[b]
Gyroscope[c]	Senses change in angular velocity	• Apple Watch Series 9 (Apple)[b]
Magnetometer	Measures angles relative to the Earth's magnetic field	• MetaMotion C (Mbientla)[d]
Pressure sensor	Measures external pressure	• Blue Chip Pressure Mapping Mattress Sensor (Blue Chip Medical) • Sensoria Mat Wheelchair Cushion (Sensoria) • OpenGO Insoles (Moticon)
IMU[e]	Contains multiple sensors to measure motion in 3 axes; to accomplish this, IMUs include accelerometers, gyroscopes, magnetometers, and pressure sensors	• Opal V2R (Clario) • Xsens Awinda (Movella) • MetaMotion C (Mbientla)[d]
Biomedical sensor	Measures physiological and biological metrics within the human body (heart rate, oxygen saturation, blood glucose, temperature, etc)	• Omron Complete 2-in-1 Upper Arm Blood Pressure Monitor and 1-Leak EKG Monitor (Omron)
Temperature sensor	Senses heat and detect changes in temperature	• SmartMat (Podimetrics)
Passive infrared sensor	Measures infrared light to detect motion	• DomoCare home monitoring system (DomoSafety SA)

[a]This table does not include an exhaustive list of sensor types but rather includes more common examples used in health care.

[b]The CentrePoint Insight Watch, Vivoactive, and Apple Watch also contain a temperature sensor; the Vivoactive and Apple Watch also have biomedical sensors; the Apple Watch uses both an accelerometer and a gyroscope.

[c]Gyroscope and accelerometer are often used concurrently in products.

[d]The MetaMotion C system is an inertial measurement unit that contains a magnetometer in addition to an accelerometer and gyroscope.

[e]IMU: inertial measurement unit.

Context

The context will include rehabilitation- and exercise-related studies. As such, the search terms will include rehabilitation, physical therapy, physiotherapy, telehealth, telerehabilitation, digital medicine, and digital health. There will be no other restrictions on the context.

Understanding the context is important to interpret what may be possible in different settings. For example, the Veterans Health Administration (VHA) has been and continues to be a leader in deploying technology solutions for health care. The VHA Telehealth Services program office was established over 20 years ago [29] and has developed necessary infrastructure to support rehabilitation practices that leverage remote patient monitoring to inform care decisions. In contrast, other health care systems may have inadequate infrastructure, which is a significant barrier to organizational implementation of connected sensor technology–augmented services.

Search Strategy and Information Sources

A comprehensive literature search was designed and performed by a medical librarian (CP) in February 2024 for the concepts of wearable sensors, rehabilitation, and medical health data. The search was built in Embase and translated to additional databases. Prior to translation, the Embase search strategy was peer-reviewed by a medical librarian following the PRESS (Peer Review of Electronic Search Strategies) guidelines [30]. Relevant publications will be identified by searching the following databases with a combination of standardized index terms and keywords: Ovid MEDLINE ALL (from 1946 to February 22, 2024), Embase (via Elsevier, from 1947 to the present), Web of Science Core Collection (via Thomson Reuters, including Science Citation Index Expanded, from 1974 to the present, and Social Sciences Citation Index, from 1974 to the present), and CINAHL (via EBSCOhost, from 1981 to the present). When possible, the searches will be limited to adult studies, with the publication types of conference abstracts and reviews excluded, and the publication date will be limited to range from 2008 to the present. Multimedia Appendix 1 provides the complete list of database search strategies.

Data Management

Following the search, all results will be exported to EndNote 21 (Clarivate Analytics), and duplicates will be initially removed using this reference management software. Results will then be uploaded to Covidence systematic review software (Veritas Health Innovation) for final duplicate removal, screening, and data extraction.

Stage 3: Article Selection and Eligibility Criteria

This scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. While reviews,

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editorials, and other opinion papers will be excluded, we will manually search such manuscripts for relevant articles. Inclusion and exclusion criteria are summarized in Table 2 according to the PCC framework.

Studies will be screened for inclusion in 2 stages, and each study will be screened by 2 independent reviewers during both stages. The first stage will involve screening of titles and abstracts; if there are no clear exclusion criteria, the study will advance to the second stage of screening, which is the full-text review. Full-text articles will be retrieved through the University of Colorado library and associated resources, through the Department of Veterans Affairs library, and by contacting corresponding authors. If the full text cannot be found through reasonable means, then the article will be excluded from the review. All inclusion criteria must be met during the full-text review for inclusion in the results, and specifically, each of the 3 steps relevant to the concept domain of the PCC framework must be present (Figure 1). If there are discrepancies at either screening stage, the articles will be discussed as a team. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [31].

Table 2. Inclusion and exclusion criteria.

Domain	Inclusion	Exclusion
Population	• Adults (aged ≥18 years)	• Sample aged <18 years • Does not involve human subjects (animals, etc)
Concept	• Connected sensor technology product used in the study either as the primary or secondary technology (eg, secondary to virtual reality intervention) • Collects patient data primarily through passive means • Data transfer from the participant's connected sensor technology to a clinician • The clinician uses the data to inform an intervention	• Study not related to an intervention (observational, validation, or reliability study; review; opinion; etc.) • No data transfer or data transfer requires ongoing active input from the participant (eg, paper or electronic diary) • The data are not used to inform the intervention (eg, accelerometry data collected only for study outcome)
Context	• Intervention is relevant to rehabilitation (exercise, physical activity, symptom management, etc)	• Intervention is not relevant to rehabilitation (eg, medication adherence)
Other	• —[a]	• Full text not available in English

[a]Not applicable.

Figure 1. Depiction of the inclusion criteria as defined by the concept domain of the Population, Concept, and Context (PCC) framework.

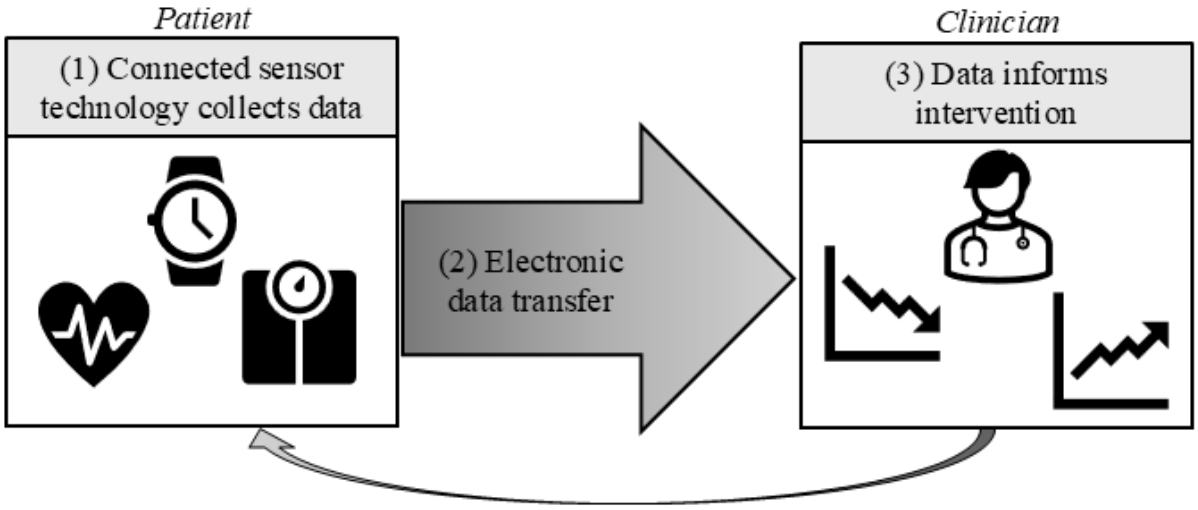

Stage 4: Data Extraction and Charting

We will pilot a custom data extraction table within Covidence and/or Excel (Microsoft) before starting formal data extraction. Data extraction will include article characteristics (eg, authors, title, journal, and year of publication), study characteristics (study design, country where study was conducted, aim or aims, population studied, etc), and data pertinent to the scoping review questions. As we are interested in describing what is known about connected sensor technologies integrated into rehabilitation interventions, we will extract technology and data characteristics (eg, type of connected sensor technology, name and manufacturer, prior validation, and type of data collected from the connected sensor technology). In addition, we will describe the method(s) used for data transfer and how the data were used to inform the intervention. The data extraction table will be updated as we become more familiar with the literature and identify salient data to answer the research questions. Further details of planned data extraction are in Table 3.

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Primary data extraction will be completed by MRR and checked by a second member of the team for completeness. Any discrepancies that arise will be discussed as a team for resolution. Authors of papers will be contacted when needed to request missing or additional data. Modifications to data extraction will be detailed in the full scoping review.

Table 3. Data extraction plan.

Category	Data extracted
Population	• Sample size • Participant demographics (sex, age, etc) • Population diagnoses (chronic obstructive pulmonary disease, congestive heart failure, Parkinson disease, etc)
Concept	• Type of sensor technology • Type of data collected from sensor technology (heart rate, step count, sleep duration, etc) • Method of data collection • Data transfer methods • Compatibility (platform and operating system) • How sensor technology was used • Prior validation • Method of validation (if applicable) • Co-occurring digital health technologies (eg, artificial intelligence)
Context	• Health care system • Type of health care setting (hospital, clinic, home, etc) • Type of rehabilitation (physical therapy, occupational therapy, etc) • Country

Stage 5: Data Synthesis

The scope of the literature will be described using counts (n), percentages, means, medians, and measures of variance as appropriate. For example, we will describe the number and type (randomized controlled trial, quasi-experimental, etc) of studies that have been conducted. We will also describe the number of connected sensory technologies studied by category (accelerometer, magnetometer, etc) and the populations in which the products were studied (those musculoskeletal or neurological disorders, healthy adults, etc). These results will be presented in figures and tables. A narrative approach will be used to describe how connected sensor technologies were used during rehabilitation interventions and to summarize any qualitative data that may be included in the review.

Stage 6: Partner Engagement

Once results are synthesized, we will present them to various partner groups including patients and rehabilitation clinicians. Partner feedback will be incorporated into the results and discussion to afford a broader presentation and interpretation of the findings of the scoping review. We anticipate that partner input will help identify areas that have been understudied or not studied, situate the results in the context of priorities of various partner groups, and identify salient future directions for research.

Results

We conducted initial searches to refine the search strategy in February 2024. Through this process, we added a date requirement to include studies from 2008 to the present. We aim to complete the scoping review through data synthesis (stage 5) by October 2024, followed by partner engagement (stage 6) before dissemination in a scientific journal.

Discussion

Principal Findings

The findings from this scoping review will identify how connected sensor technologies have been integrated into rehabilitation care and with which populations. We suspect that many of the interventions using connected sensor technologies will focus on behavior change and that the most common type of connected sensor technology will be consumer activity monitors. We also anticipate that connected sensor technologies will be commonly applied to cardiac and pulmonary rehabilitation programs, because these programs are well established [32-34] and much work has been done to evaluate the effectiveness of telehealth delivery for these programs [32,35,36].

Comparison to Prior Work

Previous reviews have evaluated similar concepts to the ones described in this manuscript. For example, Wei and Wu [37] conducted a review of preclinical studies that evaluated the ability of sensors to assess, recognize, and classify human movements in patient populations. Similarly, Kim et al [38] reviewed the use of sensors for upper-extremity assessment and intervention in a population with stroke. Only 5 of the reviewed studies used the sensor data to assist with an intervention, but none of the technologies used in the studies transferred data. As a result, the clinician was not actively involved in using the sensor data to inform treatments. Another review focused on the use of wearable technologies in oncology populations and found 10 studies that used wearables to effect health outcomes [39]; however, there were no details about the interventions and how or if sensor data were used by the clinician. The review described in this protocol will address these limitations.

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Strengths and Limitations

The scoping review protocol has strengths that will improve the reliability of its findings. First, a strength of this review is the use of established and rigorous methodology [25,26,28]. Second, we are a diverse team with different research backgrounds and interests in technological applications; this diversity will enhance the findings by accounting for various perspectives. Additionally, we will use step 6 (partner engagement) of the Arksey and O'Malley [28] framework, which will improve the interpretation, communication, and dissemination of the findings.

The scoping review also has limitations. First, there is a lack of standard language to describe the data transfer process and how sensor data are used by a clinician; therefore, our search may miss articles that use terms not captured in our search strategy. This limitation also highlights the need for future work to generate consensus for such terminology. Another limitation is that the search strategy may miss eligible articles in which a connected sensor technology was used but was secondary to a different health technology (eg, virtual reality intervention that included connected sensor technologies). Similarly, our search may miss technologies that were studied privately or went directly to consumer markets.

Dissemination Plan

Findings from this scoping review will be disseminated through various communication channels. First, we will share our findings with partners through presentations and discussions. Then, formal findings will be disseminated in peer-reviewed journals, presented at scientific conferences, and shared on social medial platforms such as LinkedIn.

Conclusion

We designed this scoping review to help map how connected sensor technologies have been studied to augment rehabilitation interventions. Results from the scoping review will identify the current state of this research while highlighting critical areas of inquiry to advance this field. Results will also support the development of a longitudinal care model to prioritize long-term health outcomes.

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Data Availability

Data sharing is not applicable to this protocol as no datasets were generated or analyzed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 34 KB - resprot_v13i1e60496_app1.docx]

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Abbreviations

PCC: Population, Concept, and Context
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
VHA: Veterans Health Administration

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Protocol

Misinformation About Climate Change and Related Environmental Events on Social Media: Protocol for a Scoping Review

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Abstract

Background: Climate change and related environmental events represent major global challenges and are often accompanied by the spread of misinformation on social media. According to previous reviews, the dissemination of this misinformation on various social media platforms requires deeper exploration. Moreover, the findings reported applied mainly to the context of the United States, limiting the possibility of extending the results to other settings.

Objective: This study aims to assess the current state of knowledge about misinformation concerning climate change and related environmental events that are circulating on social media. More specifically, we will explore past and current themes, actors, and sources, and the dissemination of this misinformation within the Canadian context.

Methods: This scoping review protocol follows the methodological approach developed by Arksey and O'Malley and advanced by Levac, complemented by the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist and the best practice guidance for the development of scoping review protocols. Following the identification of the research questions and assisted by a specialized librarian, we developed search strategies for selected bibliographic databases (MEDLINE, Embase, Web of Science, and GreenFILE) and for gray literature (Google and pertinent databases) searches. Bibliographic and gray literature will be searched to identify relevant publications. In total, 2 members of our team will use the review software Covidence (Veritas Health Innovation) to independently select publications to include in the review. Publications specifically addressing our research questions, peer-reviewed, evidence-based, and published from January 1, 2000, in the full-text version in English or French will be included. Data will be extracted from the included publications to chart, among other items, the years of publication, geographic areas, themes, actors, and sources of the climate change–related misinformation and conclusions reported. Our team will then synthesize the extracted data to articulate the current state of knowledge relating to our research inquiries.

Results: The research questions were identified in January 2024. The search strategies were developed from January to March 2024 for MEDLINE, Embase, and Web of Science and in July 2024 for GreenFILE and gray literature. MEDLINE, Embase, and Web of Science searches were launched on March 26, 2024. The first of 2 rounds of selection of publications identified through these databases was achieved in April 2024.

Conclusions: This protocol will enable us to identify the evolution of themes, actors, and sources of misinformation regarding climate change and related environmental events on social media, including the latest platforms, and to potentially identify a context particular to Canada. As misinformation is known to undermine actions and public support in the fight against climate change, we intend to facilitate the targeting of efforts to combat misinformation related to climate change in an up-to-date and contextualized manner.

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KEYWORDS

misinformation; disinformation; infodemiology; infoveillance; climate change; global warming; greenhouse effect; social media; online social network; environmental health; public support; global challenges; Google; health policy

Introduction

Background

Climate change has constituted a major global challenge for several decades [1]. The observed environmental events associated with climate change include global warming, deglaciation, rising sea levels, and increased concentrations of gases leading to the greenhouse effect [1], as well as extreme weather events and natural disasters, such as intense heat waves, forest fires, drought, storms, and floods [2]. Thus, adapting to climate change requires swift modifications of both individual and collective behaviors. However, despite the urgency we face, governmental actions are hindered by, among other factors, disinformation and misinformation [3]. Indeed, disinformation and misinformation create confusion within the population, foster skepticism toward scientific knowledge [4,5] and undermine public support for climate change mitigation policies [6].

Communications regarding climate change are known to be prone to misinformation and disinformation [7]. While misinformation is defined as erroneous information disseminated with no intention to mislead or cause harm, disinformation, which includes fake news and conspiracy theories, is spread with malicious intent [8]. Since the distinction between disinformation and misinformation lies in the intention to deceive, which remains difficult to prove, this article opts to use the term "misinformation" uniformly regardless of whether there is intent to mislead. Terms specific to misinformation related to climate change are also used [8,9]; these include climate skepticism, which refers to views in opposition to the scientific consensus or opposing action to prevent climate change [10], and climate denial, which refers to "misinformation that rejects mainstream climate science" [11].

When unreliable information enters discourse, social media platforms are frequently implicated. Social media are known to provide "fertile ground" for misinformation dissemination [12]. According to studies, misinformation about climate change and related environmental events has circulated through social media, including Twitter (now known as X; X Holdings Corp) [10,13-17], YouTube (Google) [15,18], Facebook (Meta Platforms Inc) [15] and various blogs [11]. By consulting social media, people are thus, inadvertently or through research, exposed to misinformation related to climate change [7,10,11,19]. In addition, the structural, interactive, and social features of social media facilitate and accelerate public polarization [9,11,12] and may reinforce controversy [19,20] surrounding climate change issues. Numerous studies on misinformation about climate change and related environmental events circulating on social media have been conducted [9,11,15,17,19,21,22]. These studies have explored types of climate change denial [22], actors who have propagated misinformation [21], sources of misinformation [9,11,15,21], climate change perceptions [17], or related political ideologies [19].

Several knowledge gaps were identified by previous reviews [9,21]. A "comprehensive review of the academic literature on social media communication on climate change" was published by Pearce et al [21] in 2018. This review highlighted the fact that studies exploring climate change-related communication on newer social media platforms such as Instagram (Meta Platforms Inc) and LinkedIn (Microsoft Corp) should be conducted. An overview was published by Treen et al [9] in 2020, discussing "online misinformation and how it relates to climate change." This publication identified a lack of knowledge regarding the dissemination of climate change misinformation on social media, calling for future study of this phenomenon. Conducting a more recent review will allow for the highlighting of changes over time in trends tied to the dissemination on social media of misinformation about climate change and related environmental events.

Also, studies on misinformation about climate change and related environmental events circulating on social media reference mainly United States of America contexts [9], which limits the possibility of extending the results to other settings, such as the Canadian context. In fact, the social and geopolitical background [23,24], the French and English Canadian culture [25], as well as the stance on climate change [26] apparent in Canada represent a particular context for the dissemination of climate change–related misinformation.

Review Objectives

The main objective of this review is to assess the current state of knowledge about misinformation regarding climate change and related environmental events disseminated through social media.

The subobjectives of this review are to (1) report on the themes, actors, and sources of misinformation concerning climate change and related environmental events disseminated on social media, (2) evaluate how this dissemination of misinformation has evolved over time, and (3) assess whether a particular context surrounding this dissemination of misinformation prevails in Canada.

Considering the breadth of topics covered by our research objectives and subobjectives, we opted to conduct a scoping review, which allows us to effectively map the concepts underlying an area of research as well as the main sources and types of data available [27].

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Methods

Approach

This scoping review will follow the methodological approach developed by Arksey and O'Malley [27] and advanced by Levac et al [28]. This approach entails the following 5 steps: (1) identification of the research question; (2) identification of relevant studies; (3) selection of relevant and reliable studies; (4) charting the data from the included studies; and (5) collating, summarizing, and reporting the findings.

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [29] and the best practice guidance and reporting items for the development of scoping review protocols [30] were also used to develop this protocol.

Identification of the Research Questions

By conducting this exploratory review, we aim to answer the following research questions: (1) What is the current state of knowledge about misinformation related to climate change and related environmental events circulating on social media? More specifically, (2) What are the themes, actors, and sources of misinformation about climate change and related environmental events disseminated on social media? (3) How has the dissemination of this misinformation evolved over time? (4) Is there a context particular to Canada, especially given the French and English Canadian background, surrounding the spread of misinformation about climate change and related environmental events through social media?

Identification of Relevant Studies

Bibliographic Database Search

The literature search strategy was developed iteratively in collaboration with a specialized librarian (EB). First, 4 bibliographic databases relevant to our review topics were selected: MEDLINE (Ovid), Embase (Ovid), Web of Science, and GreenFILE. Free-text keywords were then identified through the databases for each of the 3 concepts covered by our research questions, misinformation, climate change and related environmental events, and social media (Table 1). In addition, controlled vocabulary search terms (thesaurus terms used by electronic bibliographic databases) were specified, as used by the MEDLINE, Embase, and GreenFILE search tools (Table 2). Search strategies specific to each database were defined (Multimedia Appendix 1).

Table 1. Concept associated free-text keywords identified for databases searches.

Concept	Free-text keywords[a] (MEDLINE, Embase, Web of Science, and GreenFILE)
Climate change and related environmental events	((climate OR climatic) AND (change*, warming, issue*, vulnerabilit*, emergenc*, action*, crisis, disaster*, variabilit*, science, scientist*, modification*, topic*)), global warming, earth warming, greenhouse effect*, greenhouse gas*, drought*, flood*, hot temperature*, deglaciation, desertification, natural disaster*, heat wave*, hurricane*, tornado*, typhoon*, wildfire*, wild fire*, storm*, cyclone*, sea level* rise, ((extreme) AND (cold, weather, heat, temperature)), temperature* rising
Misinformation	disinform*, misinform*, dis inform*, mis inform*, malinfor*, mal infor*, infodem*, infobesit*, rumor*, rumour*, hoax*, fallac*, conspirac*, myth*, gossip*, propaganda, skeptic*, sceptic*, infoxication, veracity, polariz*, polaris*, controvers*, denial*, dessent*, contest*, deny, denier*, ((inaccurate, false, fake, poor quality, low quality, misleading, distorted) AND (information*, news, communication*))
Social media	((social, digital, onlin*) AND (media*, information*, network)), ((cyber, electronic, internet, onlin*, virtual, web*) AND (chat*, communit*, communicat*, conversat*, discussion, forum*, group*, messag*, network*, posts, posted, posting, share, shared, sharing, social)), blog, web 2.0, web 2.0s, webcast, streaming, podcast*, facebook, youtube, twitter, X, instagram, linkedin, linked in, flickr, pinterest, tiktok or tik tok, whatsapp, snapchat, reddit, telegram, wechat, hashtag*, hash tag*, tweet*, myspace, facetime, vlog*, influencer*, media* expos*

[a]Asterisks indicates various terminations are included.

Table 2. Concept associated controlled vocabulary search terms identified for bibliographic databases searches.

Concept	Databases' controlled vocabulary search terms	
	MEDLINE	Embase
Climate change and related environmental events	Climate change, greenhouse effect, greenhouse gases, droughts, floods, cyclonic storms, sea level rise, and extreme weather	Climate change, greenhouse effect, greenhouse gas, drought, flooding, storms, sea level rise, hurricanes, heat waves, and extreme weather
Misinformation	Misinformation, disinformation, and information dissemination	Misinformation, disinformation, and information dissemination
Social media	Social media, blogging, communications media, and online social networking	Social media, blogging, mass medium, and online social network

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Gray Literature Search

To complement the bibliographic database searches, we also developed a gray literature search strategy in collaboration with a specialized librarian (EB). In applying this strategy, we will consult Google, the Overton database, as well as dissertations and theses repositories. Using free-text keywords identified for the bibliographic database search strategies (Table 1), we will search through Google for textbooks, books, dissertations, and theses or reports covering our 3 research concepts in a combined manner. The first 100 Google search results will be screened for relevant publications. We will also seek reports related to our research concepts throughout the Overton database, which gathers policy documentation produced by or for policy makers from over 188 countries. These documents derive from governmental sources (government agencies, federal and provincial institutions), intergovernmental organizations (United Nations, World Health Organization, Organisation for Economic Co-operation and Development, and the European Union), think tanks and nongovernmental organizations (foundations, institutes and professional associations). Directories of international and national (Canada) institutional repositories will be screened for relevant dissertations and theses released by universities and other research institutions.

Gray literature searches will be documented in a Microsoft Excel spreadsheet, which will tabulate the following information for each search: date of search, source searched, terms or expressions used in search, number of results found, number of results retained, and comments. The relevance of publications from gray literature will be assessed using a simplified checklist itemizing authority, accuracy, coverage, objectivity, date, and significance.

Reference lists of relevant publications from bibliographic databases or gray literature could also be examined for additional references.

Selection of Relevant and Reliable Studies

First, publications identified by the bibliographic database and gray literature searches will be imported into the bibliographic management software EndNote (Clarivate). Then, they will be exported to the Covidence platform (Veritas Health Innovation) to remove duplicates and facilitate the selection of publications to include in our review. Selection will be based on our defined inclusion and exclusion criteria (Textbox 1). The selection of publications will be piloted on a subset of potentially relevant sources and thereafter carried out independently by 2 members of the research team. Disagreements between the 2 reviewers will be settled by consensus, consulting a third research team member if necessary. The publication type filters of the Embase (Ovid) and Web of Science databases will be used to extract relevant publications.

Textbox 1. Criteria for including or excluding publications in the review.

Inclusion criteria

- Covers misinformation about climate change and related environmental events disseminated on social media
- Provides author's name
- Provides publication date
- Published on or after January 1, 2000
- Available in full-text version
- Published in English or French
- Publication types: peer-reviewed original article, systematic literature review, meta-analysis, scoping literature review, textbook, book, dissertation, thesis, or report

Exclusion criteria

- Publication types: opinion piece, media article, written or video commentary, editorial, press release, speeches, letter to the editor, conference proceeding, or data paper

A first selection round, based on publication titles and available abstracts, will be carried out. Published work covering misinformation related to climate change and related environmental events disseminated by social media will be included in order to answer our research questions. Publications addressing misinformation about issues other than climate change and related environmental events or disseminated through sources other than social media will be excluded, as not specifically related to our research questions.

A second selection round, based on the full text of publications, will define which publications are ultimately to be assessed. Publications that do not provide the author's name and publication date will be excluded as they do not provide all the information required for data extraction. Given that the first social media platforms emerged in the 2000s, publications issued before January 1, 2000, will not be considered. Material not available in full-text version or published only in languages other than English or French will be excluded due to our inability to fully access their content. Publications in the form of peer-reviewed original articles, systematic literature reviews, meta-analyses, and scoping literature reviews will be included as the review process ensures the validity of these types of evidence-based publications. Textbooks, books, dissertations, theses, and reports will also be included as they are also typically reviewed. Quantitative, qualitative, and mixed methods studies will be considered to take into account the various aspects of our research concepts. Primary sources will be excluded if already incorporated into an included evidence synthesis unless

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the data they contain are not reported in the evidence synthesis. Opinion pieces, media articles, written or video commentaries, editorials, press releases, speeches, letters to the editor, conference proceedings and data papers will not be considered as they may not have been reviewed or be evidence-based.

The number of publications selected at each stage will be reported in a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram [31]. Excluded publications and the reasons for exclusion at the full-text round of screening will be reported in the final review.

Considering the broad nature of scoping reviews, it is possible that research, screening, and selection may lead to the identification of new research terms or concepts, or new sources of data [30]. The methodology may need to be adapted accordingly. In that eventuality, any adjustments made will be noted, justified, and reported in the final review.

Charting the Data From the Included Studies

Data relevant to answering our research questions will be extracted from the selected publications. An Excel data extraction form will be used to chart the following main items from each publication: title of publication, year of publication, themes, actors and sources of climate change-related misinformation reported, and conclusion (key messages). Also, extracting information on the geographic area referenced will make it possible to determine whether the publication reports on misinformation in a Canadian context. As there are multiple frameworks for defining and evaluating misinformation, the frameworks used in publications to classify information as misinformation will also be charted. As the extraction form is being iteratively developed specifically for this review, a preliminary version, which is subject to further adjustments, is presented here (Textbox 2). As recommended by Pollock et al [32], a pilot test of the extraction form will be conducted independently by each of the 2 reviewers for 10 of each type of publication included in the review to ensure that the form is accurate and in order to make any required adjustments. Inconsistencies revealed by testing will be discussed and resolved by consensus among the 2 reviewers, consulting a third research team member whenever required. Adjustments made to the extraction form and rationales will be noted and reported in the final review.

Using the tested standardized extraction form, data extraction from each included publication will be performed by a first reviewer. Extraction from each publication included will be reviewed by a second reviewer to validate accuracy and completeness [32]. If the extraction form needs to be updated in an iterative process, these revisions and rationales will also be noted and reported. Discrepancies occurring during data extraction will be discussed and settled by consensus between the 2 reviewers, consulting a third research team member if necessary. Authors of publications may be contacted to obtain and confirm data if needed.

The final version of the extraction form and the list and definitions of items extracted from publications will be presented in the final review. Any data assumptions and simplifications made will also be noted and presented in the final review.

Textbox 2. Preliminary data extraction form.

- Title of publication:
- Type of publication (original article, review, book, thesis, report, etc):
- Author's name:
- Year of publication:
- Geographical area:
- In the case of a study:
  - Aim of study:
  - Study population:
  - Method:
  - Results:
- Climate change–related topics (global warming, greenhouse effect, extreme weather events, natural disasters, etc) covered:
- Social media platforms covered:
- Framework used to define and evaluate misinformation:
- Themes of climate change–related misinformation reported:
- Actors tied to climate change–related misinformation reported:
- Sources of climate change–related misinformation reported:
- Conclusion (key messages):
- Other:

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Collating, Summarizing, and Reporting the Findings

An overview and description of all the included publications and extracted data will be presented in the final review. For each publication, the citations, characteristics, and relevant data will be reported in tabular format.

Charted data will be processed by the research team in order to answer the general and specific research questions. To summarize findings, we will use qualitative methods to regroup data and identify key themes relevant to our research question and generate meaningful insights. The results will be presented using narrative format or visual representations such as maps, diagrams, or tables, ensuring that key findings are reported in a clear and concise manner.

Results

Funding for this project was provided in December 2023. The first step in the methodological approach, the identification of the research questions, was achieved by the research team in January 2024. Accordingly, the literature search strategies for the bibliographic databases were iteratively developed from January to March 2024 for MEDLINE, Embase, and Web of Science by EB and VT and in July 2024 for GreenFILE by EB. The gray literature search strategy was developed in July 2024 by EB and VT.

The MEDLINE, Embase, and Web of Science databases were searched according to final strategies on March 26, 2024, by VT. The first round of selection of publications identified through these databases was achieved in April 2024 by MV and VT. As of July 2024, the second round of selection was being pursued by MV and VT. The search through the GreenFILE database and the gray literature is scheduled for October to December 2024.

The final selection of publications, the charting, collating, and summarizing of data, as well as the reporting of findings is planned for 2025. We intend to publish the findings of this scoping review as a research paper in a dedicated peer-reviewed journal.

Discussion

Expected Outcomes

This protocol will enable us to assess the current state of knowledge about misinformation regarding climate change and related environmental events on social media from an updated perspective, including the latest social media platforms that could not have been covered by earlier reviews [9,21]. This will also enable us to answer our more specific research questions by identifying the themes, actors, and sources of misinformation concerning climate change and related environmental events disseminated on social media and revealing how these trends have changed over time.

Trends could also be identified by collating and summarizing data on climate change and related environmental events according to topics (global warming, greenhouse effect, extreme weather events, natural disasters, etc), time periods, social media platforms, and geographical areas covered by the selected publications. Identifying misinformation trends and variations over time and between platforms will help guide interventions aimed at raising awareness and combating misinformation. For example, findings emerging from this review could steer the development of programs teaching prevention, detection, or correction of the various found forms of misinformation about climate change and related environmental events found circulating recently on specific social media platforms. Findings from this review could also potentially add to knowledge and support further research about other related topics, such as people's perceptions [33,34], mental health conditions [35,36], and behaviors [37-39] linked to climate change. The findings could also produce insights about echo chambers and misinformation networks leading to a better understanding of the argumentation, values, cultural contexts, and beliefs behind the spread of misinformation about climate change and related environmental events on social media. As climate change–related misinformation also circulates offline [7], this review will support a broader understanding of these issues by enriching knowledge through the addition of updated insights about such circulation on social media.

As misinformation is known to undermine actions and support in the fight against climate change [3,6], the potential identification of a particularly Canadian context of themes, actors and sources of climate change-related misinformation on social media could help point toward avenues for future research and guide the planning and implementation of local actions aimed at addressing this issue [9,39,40]. Finally, this scoping review may lead us to report on gaps in the current state of knowledge.

Limitations

This protocol for a scoping review has a few limitations. To streamline our queries among the selected databases, the social media search strategies include keywords specific to platforms targeting only occidental populations and offering content in English or French. Studies on climate change misinformation circulating on other social media, such as the Chinese platform Weibo (Sina Corp) [41], could, however, be identified by our selection of keywords referring to social media in broad terms. Since this scoping review aims to map the overall landscape of research on climate change and related environmental misinformation on social media, study approaches and definitions of misinformation used by the different publications included may vary widely. This could make it difficult to extract data, collate, summarize, and collectively report the findings from the different publications. Following defined data extraction and analysis processes, entailing the use of a detailed standardized data extraction form and spreadsheets, will facilitate the synthesis of findings.

Conclusions

By developing this scoping review protocol, we aim to facilitate our review of the current state of knowledge on misinformation regarding climate change and related environmental events on social media and, more specifically, to identify the themes, actors, and sources of such misinformation. Conducting the review would also allow us to identify a local context for this issue. By enhancing this knowledge base in an updated and

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contextualized manner, we intend to facilitate the targeting of efforts to combat misinformation related to climate change disseminated on social media.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the development of this study protocol.

Authors' Contributions

MV, IGS, and TD were responsible for the funding acquisition. MV, IGS, and TD were in charge of the conceptualization and design of the methodology of this work. MV and VT wrote the original manuscript draft with significant contributions from all authors in the revision stages. EB and VT developed the search strategies. The final version of the manuscript was approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Databases search strategies.
[PDF File (Adobe PDF File), 471 KB - resprot_v13i1e59345_app1.pdf]

Multimedia Appendix 2
Examples of prompts similar to those used for proofreading.
[PDF File (Adobe PDF File), 92 KB - resprot_v13i1e59345_app2.pdf]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

AI-Supported Digital Microscopy Diagnostics in Primary Health Care Laboratories: Protocol for a Scoping Review

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Abstract

Background: Digital microscopy combined with artificial intelligence (AI) is increasingly being implemented in health care, predominantly in advanced laboratory settings. However, AI-supported digital microscopy could be especially advantageous in primary health care settings, since such methods could improve access to diagnostics via automation and lead to a decreased need for experts on site. To our knowledge, no scoping or systematic review had been published on the use of AI-supported digital microscopy within primary health care laboratories when this scoping review was initiated. A scoping review can guide future research by providing insights to help navigate the challenges of implementing these novel methods in primary health care laboratories.

Objective: The objective of this scoping review is to map peer-reviewed studies on AI-supported digital microscopy in primary health care laboratories to generate an overview of the subject.

Methods: A systematic search of the databases PubMed, Web of Science, Embase, and IEEE will be conducted. Only peer-reviewed articles in English will be considered, and no limit on publication year will be applied. The concept inclusion criteria in the scoping review include studies that have applied AI-supported digital microscopy with the aim of achieving a diagnosis on the subject level. In addition, the studies must have been performed in the context of primary health care laboratories, as defined by the criteria of not having a pathologist on site and using simple sample preparations. The study selection and data extraction will be performed by 2 independent researchers, and in the case of disagreements, a third researcher will be involved. The results will be presented in a table developed by the researchers, including information on investigated diseases, sample collection, preparation and digitization, AI model used, and results. Furthermore, the results will be described narratively to provide an overview of the studies included. The proposed methodology is in accordance with the JBI methodology for scoping reviews.

Results: The scoping review was initiated in January 2023, and a protocol was published in the Open Science Framework in January 2024. The protocol was completed in March 2024, and the systematic search will be performed after the protocol has been peer reviewed. The scoping review is expected to be finalized by the end of 2024.

Conclusions: A systematic review of studies on AI-supported digital microscopy in primary health care laboratories is anticipated to identify the diseases where these novel methods could be advantageous, along with the shared challenges encountered and approaches taken to address them.

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KEYWORDS

AI; artificial intelligence; convolutional neural network; deep learning; diagnosis; digital diagnostics; machine learning; pathology; primary health care; whole slide images

Introduction

Background

Artificial intelligence (AI) in the form of machine learning has successfully been applied to image-based diagnostics within several medical fields [1]. Deep learning is a machine learning method that utilizes artificial neural networks that mimic the neurons of the brain and enables computers to learn and represent complex patterns in data. Convolutional neural networks (CNNs) and vision transformers are currently the most commonly used artificial neural networks for image classification and interpretation [2]. A strength of CNNs is their ability to extract features from images, such as edges or textures, which they can then use to identify complex patterns like nuclei, parasite eggs, or other structures [3]. In contrast, vision transformers split images into patches and can identify dependencies and relationships between these patches [2]. Combinations of CNNs, transformers, and other AI models have been used in attempts to leverage the strengths of different architectures [3].

Implementing AI-based diagnostics into the workflow has the potential to automate processes, increase productivity in laboratories, and improve diagnostic accuracy [4]. Multiple AI-based diagnostic systems have been approved by the US Food and Drug Administration (FDA) or corresponding authorities in Europe (notified bodies for CE marking), for example, for cervical cancer screening and prostate cancer diagnostics [4-6]. Most diagnostic systems in use utilize high-end digital imaging instruments, so called whole-slide scanners, and require access to advanced laboratory infrastructure and may, therefore, not be optimal for use in primary health care (PHC) laboratories [4,5]. However, the development of cheaper, portable digital microscope scanners has enabled research on the use of AI-supported diagnostic systems suitable for PHC laboratories [7,8].

The World Health Organization (WHO) has emphasized the importance of providing diagnostics near the patient in PHC settings, to enhance the accuracy and timeliness of diagnoses, improve clinical decision-making, and reduce the risk of diagnostic errors [9,10]. A PHC laboratory, also known as a tier 1 laboratory, can be defined as a laboratory primarily serving outpatients by providing point-of-care tests, performing slide microscopy for simple preparations, and preparing fine needle aspirations and other simple tissue specimens that are later dispatched to a tier 2 laboratory for analysis. The tier 1 laboratories work with a small budget compared to more advanced laboratories and are generally managed by a laboratory technician, supervised by a pathologist from a distance [10].

The implementation of AI-supported diagnostic systems could be particularly advantageous at PHC laboratories. To begin with, since PHC laboratories do not have access to expertise in the form of a pathologist, the application of AI could enable further analyses being performed on site, consequently increasing the availability of diagnostics [10,11]. In addition, a systematic review showed the implementation of AI-supported diagnostics for microscopy increased the effectivity of laboratory personnel [4]. Henceforth, implementation of AI could potentially lower the costs of diagnostics. Furthermore, moving diagnostics from advanced laboratories to PHC laboratories has the potential to enable faster diagnostics.

Studies have investigated the use of AI-supported microscopy in PHC settings in diagnostics for different diseases, such as oral and cervical cancers [7,12]. Furthermore, studies have targeted various parasitic infections, for example, schistosomiasis and infections caused by soil-transmitted helminths [13,14]. Although the targeted diseases differed in these studies, it appears that the researchers faced similar challenges because of the commonalities in the methodologies applied. Challenges observed when comparing these studies include the following: first, the sample preparation method needs to be simple enough to be easily performed in PHC laboratories, while maintaining sufficient sample quality, to enable AI-based analysis of the digitized sample. For example, variance in sample thickness and preparation artifacts can result in poor-quality, whole-slide images, which makes analysis with AI models challenging [8,13]. Second, the sample digitization instrument needs to be cost-efficient and easy to use in a PHC setting (with potentially unstable internet and electricity access, as well as other demanding environmental conditions) [8]. Third, the AI models need to be reliable and feasible to implement in the diagnostic workflow in a way that provides robust and accurate diagnostics. This puts a demand on acquiring training data of sufficient size and variance, as well as using appropriate AI models.

A preliminary search of the databases PubMed and Cochrane was performed to investigate whether any scoping or systematic review had been performed investigating the use of AI-supported digital microscopy in PHC laboratories. A few similar reviews were found. A systematic review of AI diagnostics for oral cancer [15] has some overlap with our proposed review, but because it investigates a single disease, it does not provide an overview of the development of AI-supported digital microscopy in PHC laboratories. A systematic review evaluating the application of AI to whole-slide images of tissue samples stained with hematoxylin and eosin (H&E) was also identified [16]. This article presents the current state of knowledge on AI implementation in pathology in high-end laboratories, highlighting different approaches regarding datasets, preprocessing of images, and different approaches to image analysis. However, to our knowledge, no scoping review has been performed to compile the present knowledge and evidence on AI-supported digital microscopy diagnostics in PHC settings.

A scoping review performed on this subject is of particular value, since multiple challenges exist that needs to be mapped and addressed to successfully implement a diagnostic system with AI-supported digital microscopy in PHC laboratories. Such

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a review can also provide knowledge regarding what approaches have been applied so far and guide future research toward a potential implementation of AI-supported digital microscopy in PHC laboratories.

This scoping review aims to systematically review published studies related to AI-supported digital microscopy in PHC laboratories. The scoping review will specifically address the following questions: (1) In which diseases has AI-based microscopy been applied for diagnostics within PHC laboratories? (2) What methods have been used in acquiring microscopy images to train and analyze AI models for diagnostics? (3) What AI models and training approaches have been applied? and (4) How has the AI-supported diagnostic system performed compared to expert microscopists with regard to diagnostic accuracy?

Review Question

The research question was as follows: What studies have been published on implementing AI-supported digital microscopy in PHC laboratories? What methods have been used, what issues have been faced, and what results have been achieved?

Methods

Study Design

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [17]. A PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist can be found in Multimedia Appendix 1 [18]. A protocol has been published in the Open Science Framework (OSF) [19]. The inclusion and exclusion criteria are presented in Table 1.

Table 1. Table1. Inclusion and exclusion criteria for identified studies.

Study characteristic	Inclusion criteria	Exclusion criteria
Language	• English	• Not English
Study design	• Diagnostic test accuracy studies	• Not diagnostic test accuracy studies
Population	• Humans	• Animals
Concept	• AI[a] techniques applied as a diagnostic tool on microscopy • Final slide-level diagnosis was performed and compared to that from a standard microscopist • Outcome valuable for clinicians	• Studies that applied AI models on images not conventionally analyzed in microscopy • No final slide-level diagnosis
Context	• Performed at a primary health care laboratory (tier 1 laboratory) • No pathologist is needed on site • Simple sample preparations, such as stool sample preparation, or simple tissue preparations, such as fine needle aspirations	• Studies performed in an advanced laboratory setting

[a]AI: artificial intelligence.

Eligibility Criteria

Participants

This scoping review will consider studies on human subjects. No exclusion will be performed based on age, sex, economic status, or nationality.

Concept

The studies to be included in this scoping review will have to fulfill 3 concept criteria. First, the studies need to have been performed on images gathered with an imaging instrument built to automatically capture microscopy sample areas large enough for diagnostic purposes. Further, the imaging instrument used must be operated in a way that does not require human expertise to determine what areas of the slide should be captured. Microscopy was defined as deploying a light source, optical lenses, and a digital camera to acquire a magnified image of a biological sample, generating an image conventionally interpreted by a microscopist.

Second, the studies need to have utilized AI when analyzing the microscopy images. AI was defined as a computer system that is trained to perform a task that typically requires human intelligence. No exclusion of studies will be done based on the architecture of the AI model or the dataset used for training. This analysis of the microscopy images can be performed on site or in a remote cloud environment.

Third, the studies must have compared the AI-supported diagnostic system to a standard diagnostic system. A diagnostic system was defined as all the steps included in the diagnostic process, from sample collection to the acquisition of results. The result needs to be sufficient to reach a diagnosis at the subject level.

Context

The included studies must have been performed in a PHC laboratory setting. To be defined as a PHC laboratory, also known as a tier 1 laboratory, the laboratory should fulfill 2 criteria. First, regarding staffing, the laboratory should be run

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by a laboratory technician, not requiring a pathologist on site. Second, the sample preparations should not exceed the capabilities of a PHC laboratory. Acceptable samples collected include stool, urine, blood, cytology smears, and fine needle aspirations of superficial tissue (eg, from suspected lumps in breasts). The sample staining procedure must be possible to perform manually without advanced laboratory equipment such as a microtome or tissue processor [10]. Different samples that fulfill these criteria include Kato-Katz thick stool smears, blood smears, centrifuged urine samples, Papanicolaou-stained cervical smears, and H&E-stained fine needle cytology smears [10]. Since the context of PHC laboratories is based on human medicine, the exclusion criteria and initial search strategy were changed to exclude veterinary medicine, which was included in the initial protocol published on OSF [19].

Types of Sources

All types of diagnostic test accuracy studies will be included. Because diagnostic test accuracy studies can be both retrospective and prospective, studies using either approach will be included. Additionally, studies using both paired and random designs for reference standards will be included [20]. The included studies must be published in English.

Search Strategy

The search strategy was designed to identify peer-reviewed published articles. An initial limited search of PubMed and Cochrane was undertaken to identify articles on the topic. Search blocks were created for the final search based on terms used in the identified articles. The search blocks were developed to find articles containing the 2 concepts, microscopy and AI, as well as the context specification of being in a PHC setting, with 1 block created for each. A detailed description of the search strategy is presented in Multimedia Appendix 2. The reference lists of all included articles will be reviewed for additional studies and duplicates. In addition, all the articles citing the included articles will be reviewed. The databases to be searched are PubMed, Web of Science, Embase, and IEEE.

Study/Source of Evidence Selection

Following the search, all identified articles will be compiled in a reference management software system (Zotero, version 6.0.20; January 13, 2023; Corporation for Digital Scholarship), and duplicates will be removed. Following a pilot test, titles and abstracts will be screened by 2 independent reviewers for assessment against the inclusion criteria of the review. After the exclusion based on abstracts, the full text of the remaining studies will be assessed in detail against the inclusion criteria by 2 independent reviewers. The reasons for exclusion during the full-text screening will be recorded and reported. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion between the reviewers and an additional researcher. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1) [21].

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for study inclusion.

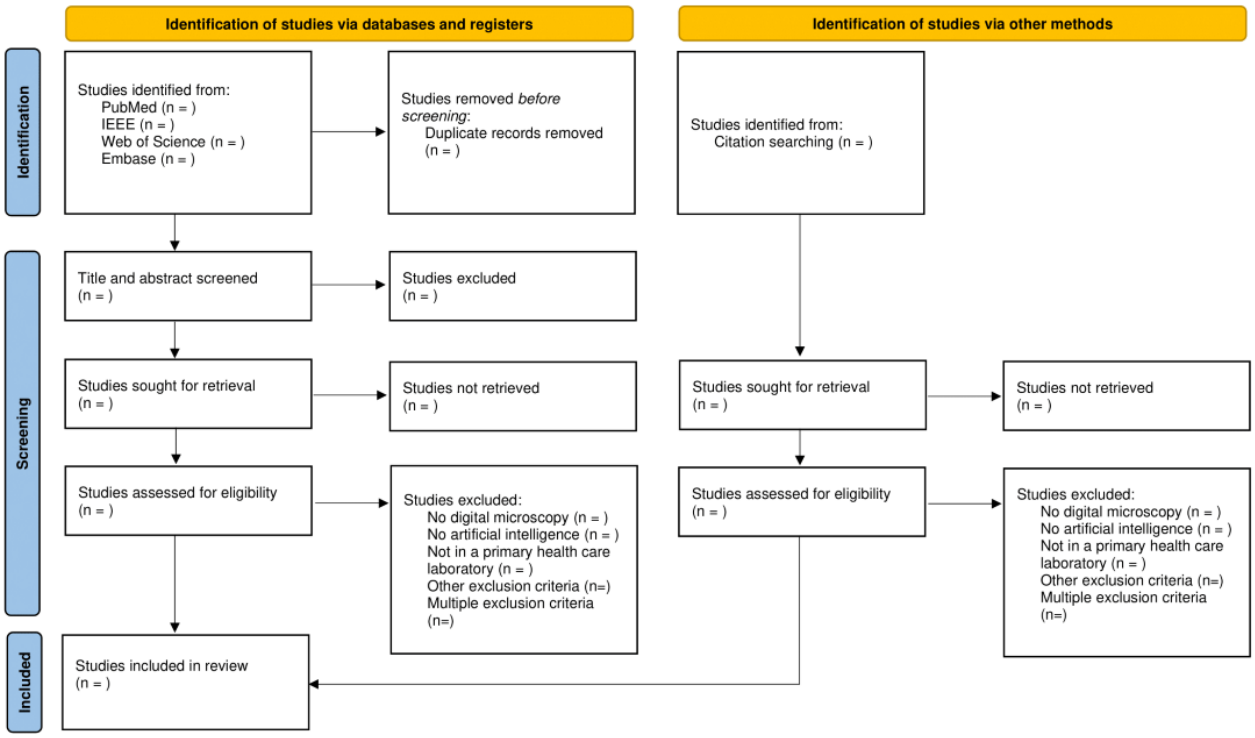

Data Charting and Synthesis

Data will be extracted from studies included in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers, which can be found in Multimedia Appendix 3. Any disagreements that arise will be solved through discussion between the reviewers and an additional researcher. If any uncertainties in the data arise, the corresponding author of the manuscript will be contacted. The findings will be presented narratively and in a table format based on the

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extraction tool developed beforehand by the researchers. The table will have eight columns: (1) the study name, year of publication, and authors; (2) what disease the study investigated; (3) dataset preparation; (4) training procedure and dataset; (5) AI model architecture; (6) QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) risk of bias; (7) validation set, results, and reference standard; and (8) additional comments. The column of dataset preparation will contain sample collection and preparation as well as digitization procedure. The narrative presentation of the results will aim to provide an overview of the results.

Critical Appraisal of Results

To investigate the bias of the included studies, the QUADAS-2 tool will be applied. This tool was developed to assess the risk of bias for primary diagnostic accuracy studies in 4 areas: patient selection, index test, reference standard, and flow and timing [22]. The results will be presented in a table in the *Results* section, and the specific form for each article can be found in Multimedia Appendix 4.

Results

The scoping review was initiated in January 2023, and a protocol was published in the OSF in January 2024. The protocol was completed in March 2024, and the systematic search will be conducted after the protocol has been peer reviewed. The scoping review is expected to be finalized by the end of 2024. The results of the scoping review will be disseminated through publication in a peer-reviewed journal.

Discussion

This scoping review is anticipated to provide an overview of AI-supported digital microscopy in PHC laboratories and present what issues have been faced and measures taken to address them. In turn, the results will guide researchers who are investigating implementations of AI-supported digital microscopy by providing a disease-agnostic overview. A disease-agnostic overview of AI in microscopy has previously been conducted for H&E-stained samples in more advanced laboratories [16]. However, most scoping and systematics reviews investigating AI-supported digital microscopy in diseases that can be diagnosed outside of high-end laboratories have focused on single diseases [15,23]. Therefore, performing a study focusing on AI-supported digital microscopy for various diseases in PHC laboratories might provide novel information.

Our proposed methodology for the scoping review has several strengths. First, only studies that contain complete diagnostic systems will be considered, thus excluding studies investigating single objects (eg, cancer cells or parasite eggs) or studies containing samples gathered in an artificial setting. By doing this, the results presented in this scoping review will be more applicable to real-world settings. Second, by collating the knowledge gathered from studies performed on a multitude of diseases, this scoping review will provide a comprehensive overview of the published literature on implementing AI-supported digital microscopy in PHC laboratories.

This scoping review protocol has some limitations, for example, regarding the definition of PHC laboratories, since laboratory capabilities can vary significantly within PHC settings. To minimize bias, a definition was chosen based on the description of PHC laboratories by Fleming et al [10], excluding studies in laboratories with a pathologist on site and advanced sample preparation. By opting for a broad definition of PHC laboratories, it is anticipated that more studies will be included. This was deemed advantageous as the purpose of the scoping review is to provide an overview of the entire field; however, the settings in which the studies have been performed will probably vary to a greater extent, making comparison between studies increasingly complicated.

It is relevant to map these studies because large-scale implementation of AI-supported digital microscopy in PHC laboratories has not been achieved; however, the possibility of constructing such a system has increased with technical advancements [8,11]. Multiple studies have investigated different ways to implement AI-supported digital microscopy in PHC laboratories [7,12]. A systematic review of studies investigating AI-supported digital microscopy in PHC laboratories could highlight diseases where these novel methods could improve diagnostics, showcase the shared challenges, and present approaches taken to address them.

Acknowledgments

We acknowledge the support of the Karolinska Institute Library for guidance in developing a satisfactory search strategy. Paperpal Preflight [24] was used when writing the manuscript for a grammar check. Additionally, ChatGPT (GPT-4, OpenAI's large-scale language generation model) [25] was used to evaluate sentences for grammatical correctness and coherence. ChatGPT was not used for writing parts of the manuscript. This study is funded by the Erling-Persson Family Foundation. Additionally, it was supported by The Swedish Research Council, Finska Läkaresällskapet r.f., and Medicinska Understödsföreningen Liv och Hälsa r.f. No funder had any role in the study design or decision to submit the paper for publication.

Data Availability

All data generated within this scoping review will be available when the finalized study is published, such as the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) forms and search details.

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Authors' Contributions

JvB conceived and designed the study, wrote the manuscript, and developed the search strategy. JL conceived and designed the study, and assisted in writing the manuscript and developing the search strategy. NL conceived and designed the study, and assisted in writing the manuscript and developing the search strategy. VD conceived and designed the study and assisted in writing the manuscript. AM assisted in designing the study and in writing the manuscript.

Conflicts of Interest

JL reports receiving personal fees from Aiforia Technologies Oy and serving as cofounder and co-owner of Aiforia Technologies Oy outside of the submitted work; in addition, JL reports having a patent for Mobile Microscope pending (WO2017037334A1; the invention is related to the use of fluorescence imaging filters combined with inexpensive plastic lenses; all rights are with the University of Helsinki) and having a patent for a slide holder for an optical microscope pending (WO2015185805A1; related to motorization of regular microscopes). No other disclosures are reported.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 115 KB - resprot_v13i1e58149_app1.pdf]

Multimedia Appendix 2
Search strategy.
[DOCX File , 14 KB - resprot_v13i1e58149_app2.docx]

Multimedia Appendix 3
Results table.
[DOCX File , 14 KB - resprot_v13i1e58149_app3.docx]

Multimedia Appendix 4
QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool.
[DOCX File , 39 KB - resprot_v13i1e58149_app4.docx]

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Abbreviations

AI: artificial intelligence
CNN: convolutional neural network
FDA: Food and Drug Administration
H&E: hematoxylin and eosin
OSF: Open Science Framework
PHC: primary health care
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2
WHO: World Health Organization

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Protocol

Community Health Worker Videoconferencing Interventions for Disease Management and Health Promotion: Protocol for a Scoping Review

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Abstract

Background: Public health interventions delivered by community health workers (CHWs) have been proven effective in improving health outcomes across multiple fields, particularly in populations that are underserved by traditional health care systems. To date, little research is available about how CHW-led interventions could be successfully delivered virtually, despite many other health care services being offered via telehealth.

Objective: This paper details a scoping review protocol that aims to assess the existing literature on CHW-led interventions using videoconferencing technology.

Methods: The scoping review protocol was developed using the Joanna Briggs Institute's guidelines on conduct of scoping reviews. Included papers will describe a direct intervention to manage disease or improve health, delivered by CHWs via videoconferencing. Multiple literature databases and gray literature will be searched. Abstracts and then full texts will be reviewed to determine inclusion by 2 independent reviewers; conflicts at each stage will be resolved by a third reviewer. A data extraction tool will be used by reviewers to independently chart data from included studies; results will be reviewed for accuracy by a second reviewer. Included papers will be analyzed to identify the breadth of the available evidence, including barriers, facilitators, effectiveness, and best practices described in the literature. Data will be summarized in a narrative review.

Results: This study commenced in April 2022, and the study protocol was finalized in November 2022. A preliminary search of the published literature (excluding gray literature) in July 2024 revealed 276 reports after removal of duplicates. The formal literature search will commence in August 2024, with results available by December 2024. We intend to publish results in the academic literature as well as creating a report accessible to nonacademic and community audiences.

Conclusions: This review will illuminate the breadth of the evidence available on CHW videoconferencing interventions, with specific focus on strategies for implementation success and equity of access. and will be of great value to organizations that offer CHW services.

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(JMIR Res Protoc 2024;13:e55160) doi:10.2196/55160

KEYWORDS

community health worker; lay health worker; telehealth; videoconferencing; intervention; digital divide; disease management; health promotion

Introduction

Community health workers (CHWs) are workers who are not health care professionals but are trained to provide certain health interventions in their communities [1,2]. CHWs play pivotal roles in promoting health in a variety of settings and are especially recognized for their usefulness in resource-limited contexts. They are called upon to complete a broad variety of tasks, including providing education, connecting patients to resources, helping individuals overcome barriers to care, providing basic medical treatments, collecting health data, and providing psychosocial support [1,2]. Health interventions led by CHWs have been effective at improving outcomes in several areas including maternal and child health, infectious disease prevention, immunization, and chronic disease management [3]. They have also proved effective at reducing health disparities and improving the health of populations who face difficulties accessing care in traditional health care models [4-9].

CHW programs have long been using mobile health (mHealth) technology, which involves the use of mobile devices and apps to support communication between the CHW and the patient [10-12]. More recently, the growing interest in and demand for telehealth services, in part spurred by the COVID-19 pandemic, have raised the question of whether CHW services could also be adapted to use videoconferencing platforms [13,14]. The use of video presents an intriguing alternative to telephone-based CHW interventions, given that the ability of the patient to see the CHW face-to-face might enhance CHW trustworthiness and rapport [15], which are advantages in the essential CHW task of providing psychosocial support [2].

However, the use of video technology in disadvantaged populations creates a risk of widening the "digital divide," referring to disparities in access to digital technology that are typically associated with socioeconomic factors [16-18]. For example, disadvantaged populations are more likely to encounter barriers such as lack of access to equipment or internet connectivity and low technological literacy, which are further exacerbated by language barriers [19-22]. The barriers to videoconferencing are likely greater than those in accessing other mHealth interventions, due to the increased internet bandwidth and device technology required, as well as the complexity of video apps. Conversely, if successful virtual CHW interventions can be developed, they could have great benefit, including potentially lower costs, reduced time required, and increased participant satisfaction, compared with in-person CHW services. If executed in a way that is sensitive to barriers faced by marginalized populations, they could also potentially increase access for participants who would not avail themselves of in-person CHW services [16,23]. These benefits would be relevant even in the post–COVID-19 era.

We sought to better understand the scope of current evidence regarding CHW videoconferencing interventions to determine how this evidence could be applied toward the development of high-quality CHW telehealth interventions that are sensitive to potential barriers faced by marginalized groups. To our knowledge there are no existing reviews addressing the delivery of videoconferencing interventions specifically by CHWs. We focus on videoconferencing due to the potential advantages of lower costs and time required and increased patient access and satisfaction, and given that several reviews of mHealth CHW interventions exist [10-12]. Therefore, the following research question of this scoping review was developed: What is known about videoconferencing community health worker interventions designed to improve health? Our population of interest is all persons regardless of age, gender, or background, and we will consider interventions studied in any context (including geographic location and language).

Our specific objectives are to determine (1) the kinds of health issues for which CHW videoconferencing interventions have been used, (2) barriers and facilitators to the CHW interventions, (3) any existing indicators of effectiveness of videoconferencing interventions, and (4) any identified best practices for CHW videoconferencing interventions. A scoping review was best suited to this research question because we sought to characterize the scope of evidence available rather than to statistically compare outcomes.

Methods

We developed our protocol based on the guidelines laid out in the Joanna Briggs Institute's guidelines on conduct of scoping reviews [24,25], and our reporting will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [26] and the checklist for reporting items for scoping review protocols developed by Joanna Briggs Institute (Multimedia Appendix 1) [25]. Important protocol updates will be reported in our final scoping review report. A preliminary search of relevant databases was conducted and no current or in-progress systematic or scoping reviews on the topic were identified.

Eligibility Criteria

Papers will be reviewed if they meet each of the three inclusion criteria: (1) the paper describes an intervention designed to directly improve health, (2) the intervention is performed by a CHW, and (3) the intervention includes the use of videoconferencing (see Table 1 for further detail). We defined videoconferencing as a real-time interaction between the CHW and the participant with video and sound [27] (importantly excluding from this definition other forms of telehealth and mHealth, such as app-based, text message, or telephone-only interventions).

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Table 1. Explanation of inclusion criteria for scoping review of community health worker videoconferencing interventions for disease management and health promotion.

Inclusion criteria	Explanation/important exclusions
Describes a program or intervention designed to improve health	This does not include training programs that do not involve delivering services.
Intervention is performed by a CHW[a]	We will not hold to any strict definition of CHW. We will include any abstract that self-defines as community health worker, lay health worker, promotor, etc.
Includes the use of videoconferencing	Videoconferencing is defined as a real-time interaction with video and sound, with the CHW on one end and participant on the other. This does not equal app-based, text-message based, or telephone-only activities that do not include a program or intervention that is designed to improve health and performed by a CHW.

[a]CHW: community health worker.

We adopted the definition of CHW outlined by Ballard et al [1] as "any lay health workers who:

1. Live in the area they serve
2. Are primarily based in the community (as opposed to a health facility)
3. Belong to the formal health system (i.e., are managed by the government or an implementing NGO)
4. Perform tasks related to health care delivery, and
5. Have received organized training but may not have received formal or paraprofessional certification or tertiary education degree" [1].

However, during our preliminary search we noted that the vast majority of papers did not provide enough information to verify whether this definition was met. Therefore, in order to create the most sensitive search strategy, we will include papers that self-define as involving CHWs or workers of other titles analogous to CHWs (Multimedia Appendix 2).

We will consider all sources of evidence for this review, including primary studies, literature reviews, opinions, letters, and guidelines. We will also include gray literature, as many community health interventions may be described on program or government sites and not captured in academic databases.

Exclusion criteria are failure to meet any of the inclusion criteria detailed in Table 1 or insufficient information in full-text review to determine whether each inclusion criterion is met (eg, if we are unable to determine whether there is video during the CHW-participant interactions). No studies will be excluded based on the date of publication, language of text, geographic location, outcome examined, or evidence type.

Search Strategy

A research librarian at the University of Washington (author TJ) was consulted to guide the literature search strategy. Our search was structured around the use of 2 concepts: CHWs and videoconferencing. Based on prior knowledge of the literature and a preliminary literature search, we developed a list of keywords synonymous with each of these concepts. In addition, the list of synonyms for "community health worker" was augmented by consulting the MeSH (Medical Subject Headings)- and Emtree-controlled vocabulary and was expanded using proximity operators for databases in which this was an option. We then developed these lists into a full search strategy (Multimedia Appendix 2). An initial trial of the search string was run on PubMed and determined to successfully capture our target data. A weakness of the search string used was that it did capture papers describing remote training programs for CHWs, which are outside the scope of this review. However, it was determined that the volume of captured studies was low enough that these could be excluded in the abstract-screening stage. The search string was translated to the other databases (Multimedia Appendix 2). The databases PubMed, CINAHL, Embase, Global Health (EBSCO), Web of Science, Global Index Medicus, and the Cochrane Library will be searched for published literature. A gray literature search will be conducted using the following sources: IGO/search from the American Library Association Government Documents Caucus, a general Google search limited to .gov sites and .org sites, NIH RePORTER (which lists ongoing National Institutes of Health–funded projects), the Patient-Centered Outcomes Research Institute (which conducts studies on comparative clinical effectiveness research focusing on outcomes important to patients), Social Work Abstracts (EBSCO), Social Services Abstracts (ProQuest), and Sociological Abstracts (ProQuest). Reference lists of included papers will be reviewed, and additional papers may be added through snowball sampling during the data extraction phase.

Data Management

After all searches have been performed, database search results will be uploaded to Mendeley (Elsevier Ltd) where duplicate papers will be removed. Citations will then be exported to RIS format and imported to Rayyan (Rayyan Sytems, Inc) [28] for screening. In the case of Google searches, results will be reviewed and duplicates removed by hand before uploading to Rayyan.

Study Selection

All papers will undergo review to determine whether they meet inclusion criteria using the Rayyan software. For papers with an abstract, the abstract will first be screened. Papers whose abstracts meet inclusion criteria will progress to the full-text screening. We will also screen the full text of any papers whose abstracts do not include sufficient information to verify that all inclusion criteria are present. Each abstract will be screened by 2 different reviewers, blinded to the result of the other reviewer, and the paper will progress to the full-text screening when both reviewers agree. Conflicts will be resolved by a third-person tiebreaker. Papers that do not have an abstract will automatically be included in the full-text review stage. In preparation for

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abstract screening, a trial run will be conducted in which all reviewers screen the same 20 abstracts and then meet to discuss disagreements and clarify methods.

Full-text review will then be completed, again with 2 reviewers screening each paper in a blinded fashion using Rayyan. Conflicts will be resolved by a third, blinded reviewer. At the full-text review stage, if all inclusion criteria cannot be confirmed, the paper will be excluded. Reasons for exclusion of sources of evidence that do not meet the inclusion criteria at this stage will be recorded and reported in the scoping review.

The results of the search and the study selection process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [26]. In addition, we will also include a list of citations for excluded studies and their reason for exclusion in the final review.

Data Extraction

Data will be extracted from papers included in the scoping review using a data extraction tool developed by the reviewers, with 1 reviewer independently performing the data extraction and a second reviewer verifying the data. The draft data extraction tool (provided in Multimedia Appendix 3) will be pilot-tested on 2 papers by all reviewers prior to proceeding. The tool will be modified and revised as necessary during the process of extracting data. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion.

Data Analysis

The data extraction tool will allow included papers to be distilled into the important points. Our analysis will include both descriptive statistics and a narrative review to summarize findings and draw conclusions. We will describe the number of papers, publication dates, country of origin or language, and what target populations or health issues are addressed in the papers in tabular format. We will then narratively describe our findings relating to the objectives of the review, including patterns in barriers and facilitators to the success of virtual programs, perceived drawbacks and benefits of virtual programs, and a summary of advice or best practices described in the literature. Depending on the number and breadth of papers included, we will consider separate subgroup analyses according to country income level (eg, high and upper-middle income vs low and lower-middle income countries) and type of concern targeted by the CHW intervention (ie, medical disease, mental health, social concerns, etc). As is typical of scoping reviews, we will not assess paper quality during data extraction as our goal is to cover the breadth of evidence available on the research question [24].

Results

This study began in April 2022. The final study protocol was completed in November 2022. A preliminary search of the published literature (excluding gray literature) was performed in July 2024 and revealed 276 reports after removal of duplicates. The formal literature search is expected to commence in August 2024, with results projected to be available in December 2024. We intend to publish a manuscript in the public health literature to describe our conclusions to an academic audience, which should be ready for submission in 2025. We also intend to create a report that is accessible to nonacademic and community audiences detailing our findings.

Discussion

The scoping review described in this protocol aims to elucidate the breadth of evidence available on videoconferencing interventions led by CHWs. We will focus our discussion of the results on effectiveness of studied interventions, how interventions should be delivered, what factors are important in their success or failure, and how to ensure access for underresourced individuals. Our planned subgroup analyses will help compare and contrast various approaches between programs with different target populations and health concerns.

We anticipate that our review will identify a relatively small number of peer-reviewed manuscripts describing the use of videoconferencing by CHWs, but that more examples may exist in the gray literature. Such a finding would reflect the need for additional high-quality studies examining such programs. In addition, we suspect that included studies may be primarily based in high-income countries, which would reflect the increased resources required to access videoconferencing interventions. Such a finding may spur future research on methods to reduce barriers to digital technologies for patients.

Of note, in this study we have focused on videoconferencing interventions delivered by CHWs, in order to explore the nature of these interventions and potentially uncover best practices for their delivery. Programs delivered using videoconferencing technology by nature require access to devices and web-based connectivity, which pose potential barriers for underresourced individuals. CHWs are often called upon to help address health disparities for such individuals [1,2], and videoconferencing interventions (especially if offered to the exclusion of other, more easily accessible modes of delivery) risk exacerbating existing health disparities, a concept known as the “digital divide” [13,29-31]. This review aims to spotlight practices used by CHW videoconferencing interventions to mitigate widening of this divide.

To our knowledge, this will be the first review to focus on the use of videoconferencing during CHW interactions with patients. However, existing literature exploring CHW use of mHealth interventions offers insights that may be applicable to CHW videoconferencing interventions. Specifically, mHealth interventions using apps and mobile devices can improve engagement of both the CHW and the client [10]. However, several challenges in adoption and feasibility of mHealth interventions have been identified, including difficulties with CHWs adopting the technologies (although this could be mitigated by adequate training), technical difficulties with hardware and software, and lack of culturally appropriate design [10,11]. Such challenges could present themselves to an even greater degree in CHW use of videoconferencing, given the fact that videoconferencing technology is potentially more difficult to use and resource-intensive than mHealth applications; our review will help characterize these differences.

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Existing literature investigating the use of videoconferencing by health care providers other than CHWs can also be illuminating. For example, a systematic review of telemedicine programs (including synchronous telephone and videoconferencing) implemented within formal health care systems in US rural or low-income populations concluded that telemedicine is acceptable and feasible to these underresourced groups [32]. Advantages of telemedicine over in-person services included increased efficiency, reduced costs (in some cases), improved access for distant patient populations, and reduced missed appointments. Several potential barriers to implementation were identified, including reduced participant satisfaction with or interest in telehealth in some subpopulations, lack of technical expertise or quality broadband access, low patient digital literacy, and difficulty with establishing rapport remotely [32]. The use of teleconferencing by CHWs in similar populations may present similar advantages and challenges, and our review will add to the literature a greater understanding of these as it relates to the unique roles and capabilities of CHWs.

Our study design has a number of limitations that we have worked to mitigate. One such limitation is that the terms used to describe the concept of a CHW in the health literature are variable, and distinct terms are used to describe individuals with similar roles in different contexts. We have attempted to create a comprehensive, culturally inclusive search strategy to address these limitations. On the other hand, many reports do not explicitly describe the background or functions of individuals identified as CHWs, making it difficult to verify that the terms are used similarly across studies, which may complicate the interpretation of our results. Defining a comprehensive search to target the concept of videoconferencing is similarly challenging, as terms related to telehealth are inconsistently used and have considerable overlap. For example, videoconferencing services could be alternatively described using synonyms such as “virtual,” “remote,” or “teleconferencing,” but these terms are imprecise and also reference a variety of other types of telehealth services. Finally, we will not assess the quality of studies included in our analysis. We feel that this methodologic choice is both consistent with the format of a scoping review and pragmatic due to the inclusion of all study designs as well as gray literature.

In conclusion, this scoping review will characterize the evidence available regarding videoconferencing interventions delivered by CHWs to improve health, with a focus on best practices for implementation success as well as strategies to ensure equitable access. As the digital divide persists between those who have access to digital technology and those who do not, it is imperative that interventions using developing technologies ensure access to services for those who are the most vulnerable. CHWs have multiple strengths in reducing health disparities and promoting health among underresourced populations, and while videoconferencing presents an opportunity to expand their reach, it must not be at the sacrifice of those strengths. This review will provide evidence that will be invaluable to governmental and community-based organizations that offer CHW services, as well as researchers studying the effectiveness of these interventions. Ultimately, our results will enable the development of recommendations to improve likelihood of intervention success, while simultaneously avoiding widening the digital divide.

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Data Availability

All data generated or analyzed during this study will be included in the published paper for the final Scoping Review and its supplementary information files.

Authors' Contributions

MEC conceived of the scoping review, provided content expertise, and led the development of the protocol, and is the guarantor of the review. All authors collaboratively developed the methodology. TJ developed the search strategy. MEC, SF, SP, SE, LM, and AD performed the initial literature review. MEC and SF wrote the first draft of the Scoping Review Protocol, and all authors reviewed, edited, and approved the final version of the Protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Joanna Briggs Institute scoping review protocol reporting checklist.
[PDF File (Adobe PDF File), 213 KB - resprot_v13i1e55160_app1.pdf]

Multimedia Appendix 2

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Search strings.
[PDF File (Adobe PDF File), 253 KB - resprot_v13i1e55160_app2.pdf]

Multimedia Appendix 3
Data extraction table.
[PDF File (Adobe PDF File), 100 KB - resprot_v13i1e55160_app3.pdf]

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Abbreviations

CHW: community health worker
MeSH: Medical Subject Headings
mHealth: mobile health
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Assistive Technology to Support Dementia Management: Protocol for a Scoping Review of Reviews

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Abstract

Background: In Canada, more than 60% of persons living with dementia reside in their own homes, and over 25% rely heavily on their care partners (ie, family members or friends) for assistance with daily activities such as personal hygiene, eating, and walking. Assistive technology (AT) is a key dementia management strategy, helping to maintain health and social support in home and community settings. AT comprises assistive products and services required for safe and effective use. Persons living with dementia and their care partners often require multiple types of AT to maintain their needs, dignity, and autonomy. AT for dementia management is rapidly developing with abundant scientific literature, which can present a challenge to efficiently navigate and extract insights for policy and personal decision-making.

Objective: This scoping review aims to synthesize review-level evidence from published scientific literature on AT to support dementia management for persons living with dementia and their care partners in their homes and communities. Research gaps in knowledge and areas for further investigation into the use and access of AT will be identified. This review will provide an overview of AT types and characteristics and chart the outcomes and conclusions in review-level evidence.

Methods: This review will follow the Joanna Briggs Institute's framework for conducting scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. In total, 6 electronic databases will be searched. Articles will be screened according to the "Population-Concept-Context (PCC)" framework for eligible studies. Population includes persons living with dementia, their care partners, and health care professionals (eg, therapists or others who recommend AT). Concept includes AT and self-help devices of many types. Context includes homes and communities. A data charting template will guide data extraction, charting, and summarization. A descriptive numerical

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summary and an overview of the findings will be presented. Data, such as (1) article information (eg, author and year), (2) article characteristics (eg, review type), (3) AT types and characteristics, (4) setting and population characteristics, and (5) key review outcomes and conclusions, will be extracted.

Results: A total of 10,978 unique citations were identified across the 6 electronic databases. This review is in the full-text screening stage, which is expected to be completed by October 2024.

Conclusions: This review will provide a comprehensive understanding and documentation of the published scientific literature on AT to support dementia management. Findings from this review are expected to provide evidence-based insights on the complexities of AT types, uses, availability, and access. The author group's diverse national and international perspectives may contribute to knowledge exchange and influence standards to improve the daily function, safety, and well-being of persons living with dementia.

Trial Registration: Open Science Framework DKSM9; https://osf.io/dksm9

International Registered Report Identifier (IRRID): PRR1-10.2196/57036

(JMIR Res Protoc 2024;13:e57036) doi:10.2196/57036

KEYWORDS

assistive technology; assistive products; dementia; care partners; caregivers; elderly

Introduction

Background

As the population ages, the number of older adults affected by dementia, most commonly being Alzheimer disease, is expected to triple by 2050 [1]. Age is a significant risk factor for dementia [1]. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (*DSM-5-TR*), dementia, a major neurocognitive disorder, refers to a significant decline over time in one or more cognitive domains ("executive function, complex attention, memory, language, learning perceptual-motor, social cognition") [2]. The degree of dementia severity is determined by its impact on the ability of persons living with dementia to independently carry out activities of daily living [2,3]. In Canada, more than 60% of persons living with dementia reside in their own homes, and over 25% rely heavily on their care partners (ie, family members or friends) for assistance with daily activities such as personal hygiene, eating, and walking [4]. However, care partners face challenges in supporting persons living with dementia due to competing demands (eg, children and jobs), resulting in around two-thirds of care partners experiencing stress and depressive symptoms [5]. To effectively manage dementia at home and cope with symptoms, persons living with dementia and their care partners need diverse strategies and interventions beyond medication alone [1,6-8]. With an aging population, the risks of developing dementia pose a major public health concern. As such, there is heightened interest and urgency for strategies and interventions to maintain health and social support for persons living with dementia and their care partners. Assistive technology (AT) is a key dementia management strategy [9], enabling persons living with dementia to live at home longer [4,10] and contributing to maintained health and social services in home and community settings [11].

Assistive Technology

AT is the umbrella term for the combination of assistive products and the services needed to ensure safe assessment, distribution, and use of assistive products [12,13]. As defined by the International Organization for Standardization (ISO), assistive products (ie, devices, software, equipment, or instruments) maintain or improve a person's functionality and reduce disability [14]. The services associated with AT refer to the "human factors" necessary to fit the product to the person, environment, and task, and include the application of organized knowledge and skills to the provision, use, and assessment of assistive products [12,15,16]. AT is most effective when provided with "early intervention, careful assessment, the correct prescription, and home-based follow-up training in how to use AT" [17]. AT is closely associated with environmental interventions (eg, home modifications), forming a technology chain of supports [18]. There has been rapid development of technological supports for older people and people with disabilities, including for those with functional limitations due to dementia [19]. Persons living with dementia and their care partners often require multiple types of AT to meet their needs and maintain their dignity and autonomy. AT includes products such as a wheelchair, medication reminder, appliance monitor, wayfinding device, and mobile app for navigation assistance [17], involving both access to the product and assessment, trial, training, maintenance, and follow-up services [15].

Rationale

A growing body of research is focused on developing, evaluating, and understanding AT applications for dementia management to promote the well-being of persons living with dementia and alleviate the strain experienced by their care partners [10,11,20-22]. For example, monitoring technologies for persons living with dementia have been found to increase feelings of safety and security, promote their independence, and reduce care partner strain [10,23-27]. Reminder systems have been shown to increase the execution of daily activities such as taking medications, eating and drinking [10,28-31]. AT that target safety in the homes of persons living with dementia have been observed to reduce falls and accidents and decrease care partner strain [32]. Information and communication technologies (eg, mobile devices, apps, and the internet) have been used to support cognitive stimulation and emotional well-being in persons living with dementia and social support and education for care partners [10]. The abundance of diverse and

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broad-ranging published reviews, compounded by the rapid development of technological supports for older people and people with disabilities [19], presents a challenge for researchers, policy makers, persons living with dementia and their care partners, and health care professionals (eg, therapists) who recommend AT for dementia management, to efficiently navigate and extract valuable insights for policy and personal decision-making regarding AT to support dementia management. Therefore, a scoping review of reviews is warranted to comprehensively, systematically, and feasibly map the scientific literature in this field.

Review Objectives

This paper outlines a protocol for a scoping review of reviews that aims to synthesize review-level evidence from published scientific literature on AT to support dementia management for persons living with dementia and their care partners in their own homes and communities. This synthesis will identify research gaps in knowledge and areas for further investigation regarding the use and access of AT by persons living with dementia, their care partners, and health care professionals (eg, therapists) who recommend AT for dementia management. This review will also chart the key outcomes used and conclusions made in review-level evidence.

Methods

Terminology, Definitions, and Classifications

Dementia

While age is a significant risk factor for dementia [1], cognitive decline can also impact younger individuals [2]. The recent versions of the *Diagnostic and Statistical Manual of Mental Disorders* (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [*DSM-5*] and *DSM-5-TR*) criteria have updated the definition to "major neurocognitive disorder," offering a broader perspective [2] of the conditions that fall under the umbrella of major neurocognitive disorder (previously known as dementia). The evolving understanding of dementia in *DSM-5-TR* will guide the screening process, providing this review with more relevant and applicable articles. However, considering the term "dementia" continues to be used in society and medical literature [2,33], it will be used in this review.

Assistive Technology

AT for persons living with dementia has rapidly developed, and the scope of this field is broad, diverse, and extensive in Canada and beyond. Therefore, subjective interpretations may arise when defining, categorizing, or classifying AT for persons living with dementia. There is inconsistency in the terminology used in the literature and geographical regions in relation to AT [34]. The literature often uses vague and interchangeable terms such as AT, products, services, devices, technologies, equipment, aids, and supports. However, the term "assistive products" is now preferred and commonly used internationally, including the World Health Organization's (WHO) [11] and ISO's [14] definitions. In this protocol, we will substitute the term "AT" used in previous literature with "assistive products" when it is clear that only products, not services, are being referenced.

Assistive Products—Classification and Terminology (ISO 9999:2022)

There are several classifications for AT interventions for persons with disabilities, such as the global standardized nomenclature for medical devices (Global Medical Device Nomenclature [GMDN] and Systematized Nomenclature of Medicine [SNOMED]) [35], WHO's International Classification of Functioning, Disability and Health (ICF) [36], and ISO 9999:2022 Assistive Products—Classification and Terminology [14]. Although standards are regularly updated, as in WHO ICF [37], and the definition of disability encompasses (ie, does not exclude) age and progressive conditions such as dementia, there is no focal sublist of classifications focused exclusively on dementia [38]. ISO 9999 is a related member of the WHO Family of International Classifications (FIC) [14], which provides high-quality classifications for relevant health sectors [37]. Therefore, it is most appropriate to use the ISO 9999 taxonomy in categorizing or classifying the types and characteristics of AT encountered in this review, providing this review with precise guidance [39].

ISO 9999 defines 11 classes, subclasses, and divisions of assistive products that are most relevant to optimizing functioning and reducing disability [14] (refer to Table 1 for the 11 classes of assistive products). This approach proves especially valuable when many countries use varying names to refer to the same product category and help specify definitions and identify the conceptual boundaries [40,41] of the AT types and characteristics important to manage dementia at home. This approach also aligns with the work carried out in Australia by one of the coauthors of this review (NL), offering an international perspective.

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Table 1. International Organization for Standardization (ISO) 9999:2022 classes of assistive products.

Code	Title
04	"Assistive products for measuring, stimulating or training physiological and psychological functions"
06	"Orthoses and prostheses"
09	"Assistive products for self-care activities and participation in self-care"
12	"Assistive products for activities and participation relating to personal mobility and transportation"
15	"Assistive products for domestic activities and participation in domestic life"
18	"Furnishings, fixtures and other assistive products for supporting activities in indoor and outdoor human-made environments"
22	"Assistive products for communication and information management"
24	"Assistive products for controlling, carrying, moving and handling objects and devices"
27	"Assistive products for controlling, adapting or measuring elements of physical environments"
28	"Assistive products for work activities and participation in employment"
30	"Assistive products for recreation and leisure"

Scoping Review of Reviews

The protocol design was initially informed by establishing the need for a scoping review of reviews (instead of a scoping review). The information specialists (Maureen Pakosh and EM) from the Department of Library and Information Services at the University Health Network, with the first author (CD), conducted an exploratory literature search on AT to support dementia management. Following this search, CD consulted with the principal investigators (RHW and BC) to clarify and establish the review question, Population-Concept-Context (PCC) framework for eligible studies [42,43], and design of this review. Due to the abundance of diverse and broad-ranging published reviews found in this topic area, a scoping review of reviews was selected to map the scientific literature comprehensively, systematically, and feasibly on AT to support dementia management.

This review will follow the Joanna Briggs Institute (JBI) methodological framework and guidance for conducting scoping reviews [42] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist for reporting results [42,43]. This review will use the PRISMA-ScR sections that are consistent with our review of reviews and justification for areas that are not reported will be presented in the final review article. The main elements of this scoping review framework include (1) review question, (2) search strategy, (3) inclusion and exclusion criteria, (4) sources of evidence selection, (5) data charting, and (6) analysis of the evidence and presentation of results. A consultation process with diverse interest-holder groups to validate and disseminate findings will be included in this review. Guidance for the exploratory review question and broad search for relevant studies will come from the PCC framework for eligible studies [42,43]. As the main objective of this review is to describe the state of the scientific literature, a quality assessment will not be conducted [40,42,44-46].

This scoping review protocol is registered with the Open Science Framework (OSF) [47]. When conducting this review, any protocol amendments will be documented in the OSF and final paper. Once this review is complete, the results will be disseminated through publications and conferences on AT, health care policies, and dementia topics.

Review Question

This scoping review of reviews will be guided by the question, "What AT types and characteristics have been documented in the scientific literature to support dementia management for persons living with dementia and their care partners in their own homes and communities?"

The review question is formulated using the PCC framework for eligible studies [42,43] (Table 2).

Table 2. The Population-Concept-Context (PCC) framework for eligible studies.

Concept	Determinants
Population (P)	• Persons living with dementia • Care partners of persons living with dementia • Health care professionals (eg, therapists) who recommend AT[a] to persons living with dementia and their care partners for dementia management
Concept (C)	• AT types and characteristics to support dementia management
Context (C)	• Persons living with dementia and their care partners in their own homes and communities

[a]AT: assistive technology.

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Search Strategy

The search strategy will include a previous review of relevant literature by the first author (CD), informing the initial list of search terms and strategy. Subject matter experts (AA, AM, BC, HC, and RHW) and 2 information specialists (Maureen Pakosh and EM) will provide additional inputs and revisions. The search strategy, subject headings, and corresponding free-text terms will be informed by the priority assistive products list [13], the ISO 9999 classification and terminology standard for assistive products [14], and My AT Outcomes Framework (MyATOF) [8]. The priority assistive products list was introduced by the WHO as the first stage of implementing a global commitment to improve access to assistive products—the Global Cooperation on Assistive Technology (GATE) [13]. MyATOF is an Australian framework that integrates AT process principles and outcomes research, directing interest-holders in articulating AT usage through 6 dimensions (ie, supports, outcomes, costs, rights, service delivery, and consumer experience) [48].

The search scope will remain broad by using 2 PCC concepts (population and concept) from the PCC framework in Table 2. As this scoping review will not compare AT interventions with other dementia management strategies (eg, medical devices and treatments for dementia) [49], no comparison terms will be incorporated into the search.

The initial iterations of the search included synonyms of AT (eg, self-help devices) and terms related to technology (eg, computers and electronics). However, since AT is a broad concept, additional terms will be generated through review of the above sources and discussion among the research team to ensure comprehensive representation of AT products and functional abilities addressed by AT. In addition to types of products (eg, computers and wheelchairs), terms combining functional activities (eg, eating and drinking) and technology (eg, device, product, and tool) will provide additional sensitivity to the search (Multimedia Appendix 1). Using this strategy limits the need to include all potential products (eg, potato peelers), which would be impractical and unlikely to yield results in the scientific literature.

The search process will be conducted in collaboration with Maureen Pakosh and EM. Maureen Pakosh will develop the initial draft search strategies in 6 electronic databases, including APA PsycINFO (Ovid), CINAHL Ultimate (EBSCOhost), Embase (Ovid), Emcare Nursing (Ovid), Medline ALL (Ovid), and Web of Science Core Collection. Decisions regarding the search terms and the search process will be resolved over multiple iterations of the search strategy through discussion among the research team (AA, AM, AMB, BC, CD, ED, EM, HC, JN, NL, and RHW).

Following additional consultation with diverse interest-holder groups (refer to *Consultation Process* under the *Methods* section), EM will revise the initial MEDLINE search strategy, as necessary. The MEDLINE search strategy will be peer-reviewed by a third rehabilitation information specialist (Jessica Babineau) following PRESS (Peer Review of Electronic Search Strategies) guidelines [50]. A study design filter will be included to limit the results to reviews. No date or language restrictions will be imposed on the search; however, non-English results will be excluded during the title, abstract, and full-text screening stages.

Based on the MEDLINE search strategy, EM will conduct corresponding searches in the 6 electronic databases above. The search will include articles from database inception to July 2023. Bibliographic duplicates will be removed by EM using EndNote 20 (Clarivate) [51] and an adapted Bramer method [52,53]. Deduplicated results will be uploaded into Covidence (Veritas Health Innovation Ltd), a software platform designed for screening and data extraction [54], by CD.

Inclusion and Exclusion Criteria

The screening process will be guided by the PCC inclusion and exclusion criteria (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Population
  - Persons living with dementia (dementia, as a major neurocognitive disorder, is defined as cognitive decline over time in one or more cognitive domains ["executive function, complex attention, memory, language, learning, perceptual-motor, social cognition"] [2] and interference with independence in daily activities such as managing finances or medication [2]. Dementia may be due to a range of subtypes such as "Alzheimer's disease, frontotemporal degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance or medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease" [2].)
  - Care partners (ie, family members or friends) of persons living with dementia
  - Health care professionals (eg, therapists) who recommend assistive technology (AT) to persons living with dementia and their care partners for dementia management
  - Persons living with dementia and care partners of any age, gender, or ethnicity, living in any country or region
- Concept
  - AT, that is, assistive products (devices, software, equipment, or instruments) and associated services that maintain or improve a person's functioning and independence [14]
  - AT that falls under the 11 classes of assistive products classified by International Organization for Standardization (ISO) 9999 [14] (Table 1)
- Context
  - Persons living with dementia living in their own home and community (a home and community is where an individual can live safely, independently, and comfortably [55] as they age, with access to health and social support [56].)

Exclusion criteria

- Population
  - Persons living without dementia
  - Persons living with cognitive decline not due to dementia
  - Persons living with cognitive decline exclusively due to mild cognitive impairment or mild neurocognitive disorder (mild cognitive impairment, or mild neurocognitive disorder, is defined as a modest impairment in several cognitive domains and not interfering with independence in daily activities [2].)
  - Persons living with cognitive decline exclusively due to delirium (delirium is defined as "disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention)" [2], with reduced environmental awareness, over a short period of time [2].)
  - Persons living with cognitive decline exclusively due to another mental disorder such as major depressive disorder, schizophrenia, etc [2]
- Concept
  - AT used for prevention, assessments, monitoring, diagnosis, and treatment will not be included unless the AT is used to help persons living with dementia maintain or improve functioning and independence in their daily lives
- Context
  - Persons living with dementia living exclusively in a shared communal environment (shared communal environments offer 24-hour, 7-day-a-week supervised on-site care, including health care, personal care, meals, laundry, and housekeeping [57]. Among these are long-term care homes and facilities, known within Canada as "nursing homes, personal care facilities, residential continuing care facilities, etc." [55])
  - Hospitals, primary care ambulatory or outpatient clinics and doctor's offices

Types of Evidence Sources

Articles of any type of review methodology (eg, scoping review, systematic review, and narrative review) published in peer-reviewed journals will be included. Therefore, researchers with expertise in both quantitative and qualitative methodologies will contribute to the development of the narrative. Non–peer-reviewed articles, protocols, theses or dissertations, editorials, conference abstracts, gray literature, and non-English articles will be excluded.

Source of Evidence Selection

Title and Abstract Screening

A total of 3 reviewers (CD, ED, and JN) will be involved in the title and abstract screening process. The first author (CD) will independently screen all eligible articles in Covidence [46] to determine their suitability for a full-text review according to the PCC inclusion and exclusion criteria. Subsequently, each secondary reviewer (ED and JN) will screen a subset of articles independently. CD will monitor the level of agreement between

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the reviewers throughout the screening process. Covidence will export the agreement proportion to Microsoft Excel. Designating each article into yes, no, or maybe categories and the reasons for these designations will be recorded in Covidence [54]. Predefined tags in Covidence will be created to ensure ease of recording reasons for exclusion throughout the screening process. The reviewers will meet throughout the process to discuss their decisions and reasons for including or excluding articles. Any discrepancies will be resolved in discussion with the principal investigators (BC and RHW). The JBI recommended procedure for pilot testing will be used for the title and abstract screening stage [42]. CD, in collaboration with the research team, will critically analyze the final sample of articles sent to full-text screening to inform the creation of the data charting template. The data charting template will be developed in Microsoft Excel [58].

Full-Text Screening

In total, 3 reviewers (CD, ED, and JN) will be involved in the full-text screening process. The first author (CD) will independently conduct the screening in Covidence [54] to determine their inclusion in the scoping review. Subsequently, each secondary reviewer (ED and JN) will screen a subset of full-text articles independently. CD will critically analyze the final sample of studies, and all reviewers will be involved in the charting process. At the full-text screening stage, the reviewers may request further details about an article directly from the corresponding author. The number of articles reviewed and included will be outlined in a PRISMA-ScR flow diagram [59], with reasons for exclusion at the full-text level. The reviewers will continue to meet throughout to discuss their decisions and reasons for including or excluding articles. Discussions with the principal investigators (BC and RHW) will occur to resolve any discrepancies. The JBI-recommended procedure for pilot testing will be used for the full-text screening stage [42]. CD, in collaboration with the research team, will critically analyze the final sample of articles sent for data charting to inform the revision of the data charting template if necessary.

Data Charting

Once the articles are fully reviewed, the data will be extracted, charted, and integrated into a comprehensive format (ie, table). The data charting template will be used to capture relevant data from included articles to meet the objectives of this scoping review. An example of the data to be extracted is described in Table 3.

Table 3. Data extraction template.

Type of data	Description of data
Article information	Author, publication year, country, journal name, and location of publication.
Article characteristics	Review type, number of studies included in the review, and reported time period of studies included.
AT[a] types and characteristics	All AT types and characteristics described in the review, and the purpose of AT described for and used by persons living with dementia, their care partners, and health care professionals (eg, therapists) who recommend AT to persons living with dementia and their care partners.
Setting and population characteristics	Country or region, type of home and community setting described where AT is used, available or recommended.
	Age, sex, gender, or ethnicity. Given women's higher risk for dementia [60] and increased likelihood to be care partners [61], participants' sex and gender, and gender-related factors influencing AT use and access, will be collected [60,61].
Key review outcomes and conclusions	Main findings, outcomes, and conclusions drawn from each article.

[a]AT: assistive technology.

The JBI-recommended procedure for pilot testing will be used for data extraction [42]. A total of 3 reviewers (CD, ED, and JN) will independently conduct a pilot test to extract data from at least 3 full-text articles. The pilot test findings will be refined and adjusted through team discussions. The pilot test will continue until reviewers adequately understand the data charting template, context, and process of data extraction.

Following the completion of the pilot test, reviewers will proceed to extract data from all full-text articles using the data charting template. If specific information is unavailable, reviewers may contact the study authors to obtain it. As the review progresses, the reviewers may extract additional information of relevance to address the scoping review objectives and revise the data charting template accordingly [42]. In conducting this scoping review, the focus is on synthesizing and analyzing existing reviews. Therefore, the scope of this review will not include an in-depth analysis of individual primary studies.

Analysis of the Evidence and Presentation of Results

After extracting the data from included full-text articles, the data will be synthesized using descriptive analysis (eg, frequencies, means, and ranges). A descriptive numerical summary and overview of the findings will be presented in tabular format.

Consultation Process

The Project Advisory Committee (PAC), comprising persons living with dementia, care partners, researchers, partner and network organization representatives, and knowledge user partners who have a direct interest in the outcomes of this research [62], will be consulted for their inputs. They will also provide resources to complete this scoping review and assist in knowledge dissemination strategies and activities. The PAC

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convenes every 4 to 6 months. PAC members will also be consulted individually on matters where there is expertise in content, methodology, analyses, and knowledge mobilization and dissemination.

Ethical Considerations

This review does not involve collecting any data from human or animal participants; therefore, research ethics approval is unnecessary.

Results

Across the 6 electronic databases (APA PsycINFO [Ovid], CINAHL Ultimate [EBSCOhost], Embase [Ovid], Emcare Nursing [Ovid], Medline ALL [Ovid; includes PubMed non-MEDLINE records], and Web of Science Core Collection), 21,747 results were retrieved. After deduplication, 10,978 unique citations were retained. A search strategy for MEDLINE is provided in Multimedia Appendix 1. This review is in the full-text screening stage, which is expected to be completed by October 2024.

Discussion

Anticipated Findings

This review will provide a comprehensive understanding and documentation of the published scientific literature on AT to support dementia management. Findings from this review are expected to provide evidence-based insights to diverse groups of interest-holders to facilitate discussions on the complexities of current AT types, uses, availability, and access for persons living with dementia and their care partners. Furthermore, the author group's diverse national and international perspectives may contribute to knowledge exchange and influence standards to improve the daily function, safety, and well-being of persons living with dementia.

Findings from this review will also lay the groundwork for a larger Canadian Institute of Health Research (CIHR)–funded project to examine the creation and economic evaluation of combining different AT into effective bundles or packages [15,63-67] for dementia management in Canada and beyond. This work aligns with national initiatives such as the Canadian Dementia Strategy [68] and global recommendations by the WHO regarding the formulation of a comprehensive "Package of Interventions for Rehabilitation" for health conditions, including dementia [69].

The field of AT for dementia management continues to grow [10,11,19-22], with an abundance of diverse and broad-ranging published reviews focused on developing, evaluating, and understanding AT applications. Despite its considerable impact on the field, there are still challenges to efficiently navigate and extract valuable insights regarding AT for policy and personal decision-making. This scoping review of reviews is therefore warranted to map the scientific literature in this area comprehensively, systematically, and feasibly.

Limitations

This scoping review may have limitations. First, this review does not incorporate searches of gray literature and other non–peer-reviewed academic resources. As the development of AT is rapidly progressing, these advancements may not be documented in the existing scientific literature. In addition, only review articles will be considered for inclusion, and if there are AT interventions reported exclusively in primary reports, they may not be captured in this review. An independent environmental scan will be conducted by members of the research team (CD, BC, JN, and RHW) as a separate review, encompassing various documents and resources not typically accessible through scientific databases. These documents and resources may include organizational websites, policy documents, reports, magazine articles, newsletters, and blogs. Second, the search strategy may miss relevant reviews due to the selected databases lacking coverage of all published literature, inaccuracies in database indexing, and the broad scope of AT and complexity and limitations of terms used [70]. This limitation is addressed by searching multiple bibliographic databases and using a comprehensive set of search terms covering both products and relevant functional abilities. In addition, to mitigate these risks, a hand-search of the reference lists of relevant articles will be considered to identify any further citations that may have been overlooked during the initial electronic database search. However, the reviews may exclude other languages as well. It is also possible that the search strategy may limit the types of AT that appear in the results because the search terms are based on established terminology and categories of AT. Finally, only studies written in English will be included, which may exclude relevant reviews from non–English-speaking countries or regions, limiting our findings' generalizability and applicability.

Although limitations may exist, this scoping review will enable a comprehensive understanding and documentation of the types and characteristics of AT to support dementia management for persons living with dementia and their care partners in their own homes and communities.

Conclusions

The knowledge synthesized from this review may broadly serve as a framework to create greater insights into dementia management using AT [61] among persons living with dementia; their care partners; and various other interest-holders groups, such as health care professionals (eg, therapists) who recommend AT to persons living with dementia and their care partners, policy makers, researchers, partner organizations, and networks. It is also anticipated that the research community may benefit from the generated knowledge from this review to formulate new research inquiries and approaches for larger-scale studies on AT use and access by persons living with dementia and their care partners for dementia management.

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Acknowledgments

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We would also like to thank the Project Advisory Committee (PAC) members for providing feedback on the initial research question, methodology, and the Population-Concept-Context (PCC) framework for eligible studies described in the protocol.

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Authors' Contributions

CD contributed to conceptualization, methodology, writing—original draft, reviewing, and editing. ED contributed to writing—original draft, review, and editing. JN contributed to methodology and writing—original draft, review, and editing. EM, HC, and NL contributed to methodology and writing—review and editing. AA, AM, and AMB contributed to writing—review and editing. BC and RHW contributed to supervision, resources, conceptualization, methodology, writing—original draft, review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search strategy.
[DOCX File , 16 KB - resprot_v13i1e57036_app1.docx]

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Abbreviations

AT: assistive technology
CIHR: Canadian Institute of Health Research
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
FIC: Family of International Classifications
GATE: Global Cooperation on Assistive Technology
GMDN: Global Medical Device Nomenclature
ICF: International Classification of Functioning, Disability and Health
ISO: International Organization for Standardization
JBI: Joanna Briggs Institute
MyATOF: My AT Outcomes Framework
OSF: Open Science Framework
PAC: Project Advisory Committee
PCC: Population-Concept-Context
PRESS: Peer Review of Electronic Search Strategies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SNOMED: Systematized Nomenclature of Medicine
WHO: World Health Organization

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Protocol

Phenotype-Genotype Correlation in Morquio A Syndrome: Protocol for a Meta-Analysis

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Abstract

Background: Mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio A syndrome, is a rare lysosomal storage disease characterized by autosomal recessive inheritance of mutations in the N-acetylgalactosamine-6-sulfatase (*GALNS*) gene. This leads to a deficiency of the GALNS enzyme, causing the accumulation of glycosaminoglycans in tissues. Morquio A syndrome primarily affects the skeletal system and joints but can also impact various organs, resulting in symptoms such as hearing and vision loss, respiratory issues, spinal cord compression, heart diseases, and hepatomegaly. The genotype-phenotype relationship is diverse, with studies highlighting variants associated with classic, nonclassic, or intermediate phenotypes. Understanding these genetic factors is crucial for predicting disease prognosis and tailoring effective treatment strategies for individuals with Morquio A syndrome.

Objective: The aim of this meta-analysis is to comprehend the relationship between the severity of the phenotype and the genotype of patients with MPS IVA, considering factors such as the type of variant and its location in the different domains of the protein.

Methods: This meta-analysis will include articles featuring participants of all genders and age groups who have a molecular diagnosis of MPS IVA and a description of the phenotype. Literature published in English, Spanish, and Portuguese will be considered. Exclusion criteria will encompass studies lacking full-text availability and those involving patients with an MPS IVA diagnosis but without phenotype information. The databases to be searched include PubMed, MEDLINE, ScienceDirect, and Scopus. The screening of literature, paper selection, and data extraction will involve 2 independent reviewers, who will conduct the process blindly. In the event of disagreements between the 2 reviewers at any stage, resolution will be sought through discussion or with the involvement of an additional reviewer. The final selection of manuscripts will be based on consensus. The results of the review will be presented using descriptive statistics, and the information will be organized in either diagrammatic or tabular formats, following the guidelines provided by the Joanna Briggs Institute. Genotype-phenotype relationships will be analyzed using IBM SPSS Statistics, using chi-square tests, Fisher exact tests, and regression analysis to interpret the data.

Results: A literature search conducted in January 2024 produced 760 results. The review is expected to be completed by the end of 2024.

Conclusions: This meta-analysis will gather and analyze information on the phenotype-genotype relationship in patients diagnosed with MPS IVA. The data collection and resulting analyses will make a substantial contribution to understanding the underlying mechanism of the disease, enabling the prediction of the syndrome's progression and severity.

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KEYWORDS

Morquio A syndrome; genotype-phenotype associations; rare diseases; scoping review; Mucopolysaccharidosis type IV; meta-analysis; genotype; GALNS gene; N-acetylgalactosamine-6-sulfatase; pathophysiology; laboratories; mutations

Introduction

Mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio A syndrome, is a rare lysosomal storage disease characterized by autosomal recessive inheritance. It originates from a defect in the N-acetylgalactosamine-6-sulfatase (GALNS) enzyme, resulting from mutations in the *GALNS* gene [1].

The deficiency of the GALNS enzyme leads to the accumulation of glycosaminoglycans, such as chondroitin-6-sulfate and keratan sulfate, in various tissues and organs. This primarily causes symptoms in the skeletal system and joints, but other clinical manifestations can also occur, including hearing and vision loss, respiratory diseases, spinal cord compression, heart diseases, and hepatomegaly [2].

The phenotypic spectrum of the disease is broad, ranging from attenuated forms (nonclassic) with late-onset clinical manifestations and slow progression to severe forms (classic) with early-onset clinical manifestations [1].

The *GALNS* gene is located on chromosome 16 region q24.3 and consists of 14 exons [3]. It encodes 13 transcripts, with *NM_000512.5* as the reference transcript, spanning a length of 2344 base pairs, which codes for a protein with 522 amino acids [4].

The protein resulting from the *GALNS* gene, with UniProt accession number P34059, forms a homodimer, where each monomer in its x-ray crystallographic structure presents 3 domains: an N-terminal domain containing the active site (28-379), a second domain with antiparallel B chains (380-481), and a C-terminal domain (482-510) that complements the active site where a calcium ligand binds. Each monomer contains 2 N-linked glycosylation sites at asparagine 204 and asparagine 423, and 3 disulfide bonds (308-419, 489-518, and 501-507), along with an unpaired cysteine (164) [5].

The genotype-phenotype relationship has garnered increasing interest in predicting disease prognosis based on genetic findings. It requires more in-depth analysis, considering factors such as the type of variant, its location in the protein domain, and its effect on the tertiary structure. For instance, Cárdenas et al [6] found that variants associated with the classic phenotype affected highly conserved protein regions. However, statistically significant results were not obtained due to limitations in sample size [6].

In contrast, Zanetti et al [7] analyzed 314 homozygous individuals, identifying 135 variants. Of these, 103 were associated with a classic phenotype, 19 with a nonclassic phenotype, 2 with an intermediate phenotype, and 11 with conflicts in phenotype classification. Discordance between phenotype classification and patient genotype may be influenced by differences in the age of diagnosis [7].

Tomatsu et al [8] found that among missense variants, the most common variants were associated with a classic phenotype (63 cases) or an attenuated phenotype (30 cases). Eight nonsense mutations and 2 large deletions were linked to severe phenotypes; 16 small deletions were associated with severe phenotypes, with 4 being undefined; 4 insertions were linked to severe phenotypes, with 1 associated with an attenuated phenotype; and 8 splice-site mutations were associated with severe phenotypes, while 1 was linked to an attenuated phenotype [8]. Concurrently, specific variants have been associated with distinct phenotypes, such as c.1156 C>T, present in 6 homozygous individuals with a classic phenotype, and c.761 A>G, associated with an intermediate phenotype in 2 homozygous patients [9].

Although the relationship between specific variants and the severity of MPS IVA has been previously demonstrated, there are certain limitations that could lead to discrepancies in the analyzed data. These limitations include the use of enzyme replacement therapy, variations in the age at which clinical characteristics are evaluated, and the interaction between variants in compound heterozygous patients. Hence, this meta-analysis proposes to determine the relationship between different types of genetic variants in the *GALNS* gene and the severity of the phenotype in patients with MPS IVA.

Methods

This meta-analysis proposal is based on the parameters stipulated by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [10] and the Cochrane Collaboration [11].

Eligibility Criteria

Studies will be included that involve participants of any gender and age, with a molecular diagnosis of MPS IVA, along with a description and/or classification of the clinical phenotype.

Inclusion Criteria

The included studies must meet the following criteria:

- Molecular diagnosis of MPS IVA
- Classification regarding the severity of the phenotype or information on clinical manifestations that enables classification, according to guidelines or protocols endorsed by genetics societies

Exclusion Criteria

The exclusion criteria are as follows:

- Individuals with a diagnosis other than MPS IVA

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- Unavailable full-text articles
- Articles with patients with MPS IVA but without a molecular diagnosis

Types Sources

This meta-analysis will encompass a broad range of study designs, incorporating both experimental and quasi-experimental methodologies. Experimental designs, such as randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies, will be included. Additionally, observational studies, including both prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion.

Furthermore, various observational study designs, such as case series, individual case reports, and descriptive cross-sectional studies, will also be considered for inclusion in this review. Qualitative studies will be considered as well.

Search Strategy

The search strategy has been designed to identify published studies exclusively in Spanish, English, and Portuguese regardless of the publication date. Key terms from article titles and abstracts, as well as index terms, have been used to formulate a comprehensive search strategy for various databases, including MEDLINE, Web of Science, the Cochrane Library, ScienceDirect, PubMed, and Scopus.

The Medical Subject Headings (MeSH) keywords used for the database search are as follows: (GALNS OR “galactosamine-6-sulfatase” OR “Mucopolysaccharidosis IV”) AND (“genetic variants” OR “genetic variations” OR “mutations”) AND (“clinical” OR “phenotype”).

The search will be conducted by a single reviewer, who will perform the search in the specified databases, adhering to the MeSH keywords outlined above.

Study Selection

The identified bibliography will be uploaded to the Covidence platform (Veritas Health Innovation Ltd), duplicates will be removed, and 3 reviewers will screen the literature based on the title and abstract. Subsequently, the full text will be analyzed to verify compliance with the inclusion criteria. Exclusion reasons will be categorized and reported in the systematic review. Any disagreements will be resolved by an additional reviewer or through consensus among the reviewers. The results will be presented in the final systematic review.

Data Extraction

A data extraction instrument was created. A total of 2 researchers will extract the data from each record. Extraction fields include the following: the country where the study was conducted, year of publication, data characterization (physiopathology, diagnostic, epidemiology, management or treatment, and complications), study design, medical history, clinical diagnosis, diagnostic test and results, and clinical interventions. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer.

Data Analysis and Presentation

A descriptive tabulation of the necessary information will be conducted to establish the genotype-phenotype relationship in patients with MPS IVA, encompassing epidemiology, physiopathology, and genetic diagnosis. Data will be analyzed using IBM SPSS Statistics software. The genotype-phenotype association will be assessed using chi-square or Fisher exact tests and/or regression analysis. The entirety of gathered knowledge will be summarized and discussed, taking into consideration the limitations of the review.

Compound heterozygous variants will not be considered in the genotype-phenotype analysis due to the inherent complexity of interactions between these variants. However, they will be individually described and discussed, aiming to establish a precedent for future research and publications in the field.

Furthermore, in the event of discrepancies in the phenotypes of homozygous patients carrying the same variant, the authors of the original publications will be contacted to investigate potential factors that may contribute to this variability, such as age at diagnosis and the use of enzyme replacement therapy. Each finding will be discussed in detail.

Reference Searches

Snowballing or citation tracking criteria will be applied to identify significant articles pertinent to the research topic. This process will involve utilizing the reference list of a paper or citations of a paper by other articles to uncover additional manuscripts relevant to the study’s subject. Once potential new manuscripts and citations are identified, a backward snowballing search will be conducted by scrutinizing the reference list and excluding papers that do not meet the basic inclusion criteria. Subsequently, previously examined papers from the list will be eliminated. If a paper aligns with the inclusion criteria, potential new manuscripts will be pinpointed by reviewing the reference list of the included paper [12]. Subsequently, forward snowballing will be conducted, identifying new papers from the reference list of included papers, utilizing a method like backward snowballing.

Expected Findings

This exploratory review aims to categorize the phenotypic severity of patients with MPS IVA and associate these phenotypes with specific genotypes. By mapping each pathogenic variant onto the GALNS protein structure, the analysis will evaluate how these variants in different domains and regions of the protein influence disease severity. This approach will help identify patterns of pathogenic variants associated with varying levels of clinical severity, providing key insights into how the location and type of variant affect GALNS functionality and the overall severity of MPS IVA. The findings will offer a deeper understanding of genotype-phenotype relationships, with potential to guide future diagnostic and therapeutic approaches.

Results

In January 2024, a comprehensive literature search was conducted in PubMed, MEDLINE, ScienceDirect, and Scopus,

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identifying 752 articles after duplicate removal (Figure 1). The review will be completed by the end of 2024, with all relevant manuscripts managed through Covidence software to streamline the systematic review process.

Figure 1. Flowchart of the literature selection process.

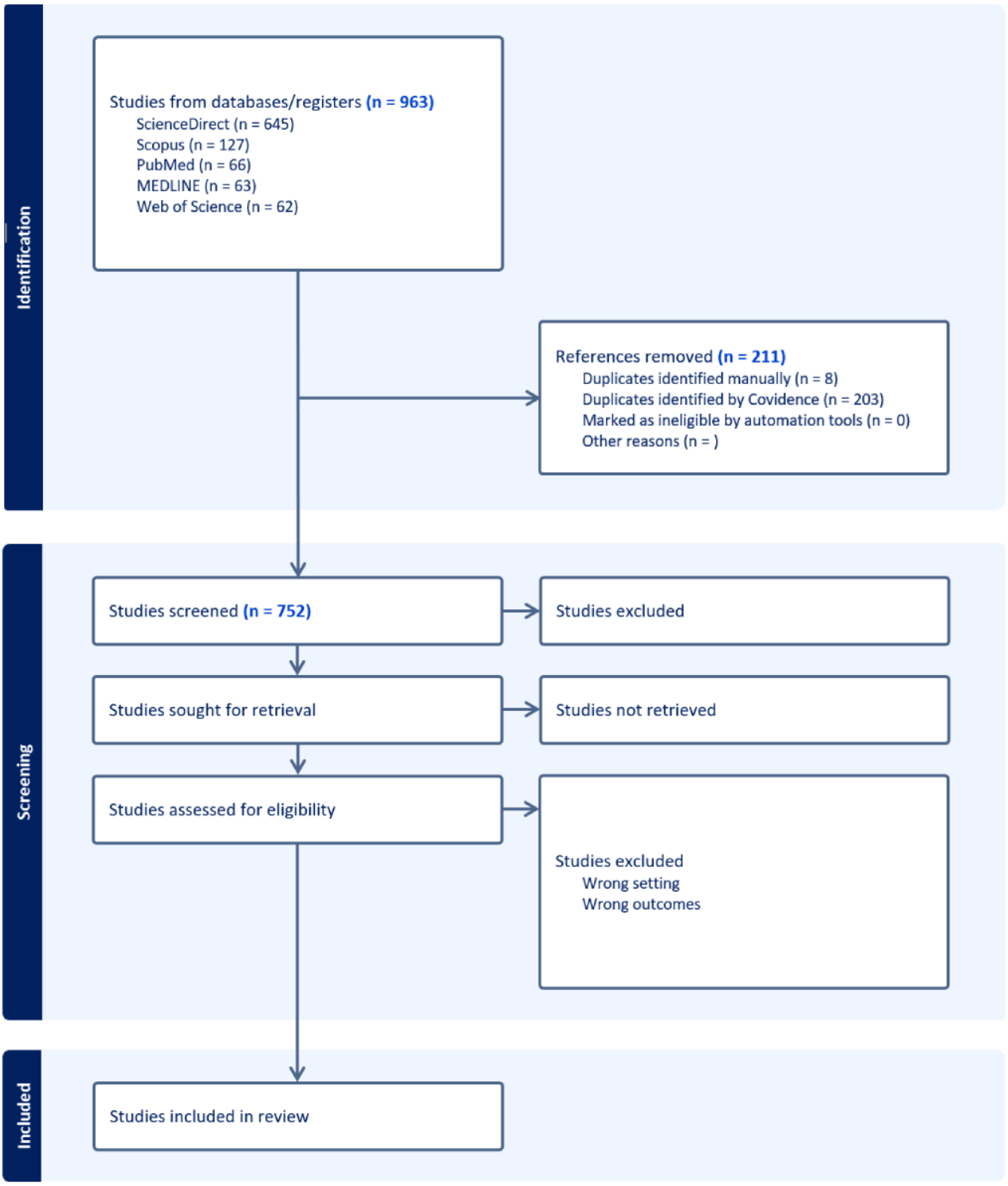

Discussion

Summary of the Main Findings

The meta-analysis is expected to demonstrate the relationship between the type of genetic variation and its location in the GALNS protein and the severity of the phenotype in patients with MPS IVA.

Contrasting Literature

The relationship between *GALNS* variants and their impact on pathophysiology, severity, and treatment opportunities is a well-studied topic. Several investigations have explored the genotype-phenotype relationship, such as the study by Zanetti et al [7], which included 314 patients with 135 different variants. Of these variants, 103 were associated with a severe phenotype,

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19 with a nonsevere phenotype, 2 with an intermediate phenotype, and 11 with conflicting clinical phenotypes. According to the authors, the inconsistency in phenotype-genotype classification could be attributed to the heterogeneity of the disease and the varying ages of the patients at diagnosis [7].

Additionally, studies such as Yi et al [13] found 82 patients with a severe phenotype, 14 with an intermediate phenotype, and 12 with an attenuated phenotype. The classification included both homozygous and compound heterozygous patients and was based on the type of variants and their location in the protein [13].

Furthermore, some identified variants have even led to the identification of new clinical variations that have led to the reporting of new cases, such as the one identified by Ge et al [14] that establishes a relationship between neurogenic bladder and MPS IV.

Among the findings on the correlation between genotype or genetic variations in mutations and the patient's phenotypic presentation, studies such as Tomatsu et al [15] stand out. The authors proposed that some genetic variations in conserved regions directly affect the enzyme's functional capacity and lead to specific phenotypic alterations that require a more in-depth intervention process in patients with MPS IVA [15]. Other studies, such as Jezela-Stanek et al [16], found that phenotype-genotype assessment and correlation have been shown to predict aspects related to anthropometric measurements and associated complications.

On the other hand, this meta-analysis presents several limitations, including variations in phenotype severity that are independent of genotype. For instance, enzyme replacement therapy, designed to mitigate disease progression, may influence the outcomes. Additionally, age differences are a significant factor, particularly in patients diagnosed at early stages, where clinical characteristics may not yet be fully developed. Furthermore, in compound heterozygous patients, it is challenging to establish a precise relationship between genotype and phenotype, as the final characteristics will be affected by the interaction of both variants.

Conclusions

Understanding the relationship between variant types, protein mutation location, and patient phenotypes will enhance our comprehension of which protein sites and types of variants have the greatest impact on the pathophysiology of MPS IVA. This knowledge will not only aid in predicting disease severity in new cases but also facilitate more precise monitoring of disease progression, serving as a marker for complications associated with Morquio A syndrome. These insights will have broader implications for guiding medical interventions, allowing for greater precision and effectiveness in treatment strategies.

Data Availability

All data generated or analyzed during this study are included in the published paper.

Authors' Contributions

Conceptualization – LD-O
Investigation – LD-O and PAD-C
Methodology – LD-O and PAD-C
Writing – original draft – LD-O, PAD-C, DAN-P, WS, JDG-M, and HP
Writing – review & editing – LD-O, PAD-C , DAN-P, WS, JDG-M, and HP

Conflicts of Interest

None declared.

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Abbreviations

GALNS: N-acetylgalactosamine-6-sulfatase
MeSH: Medical Subject Headings
MPS IVA: mucopolysaccharidosis type IVA
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Progress of Implementation of World Health Organization Global Antimicrobial Resistance Surveillance System Recommendations on Priority Pathogen-Antibiotic Sensitivity Testing in Africa: Protocol for a Scoping Review

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Abstract

Background: Antimicrobial resistance (AMR) is a major global public health concern, particularly in low- and middle-income countries where resources and infrastructure for an adequate response are limited. The World Health Organization (WHO) Global Antimicrobial Resistance Surveillance System (GLASS) was introduced in 2016 to address these challenges, outlining recommendations for priority pathogen-antibiotic combinations. Despite this initiative, implementation in Africa remains understudied. This scoping review aims to assess the current state of implementing WHO GLASS recommendations on antimicrobial sensitivity testing (AST) in Africa.

Objective: The primary objective of this study is to determine the current state of implementing the WHO GLASS recommendations on AST for priority pathogen-antimicrobial combinations. The review will further document if the reporting of AST results is according to “susceptible,” “intermediate,” and “resistant” recommendations according to GLASS.

Methods: Following the methodological framework by Arksey and O’Malley, studies published between January 2016 and November 2023 will be included. Search strategies will target electronic databases, including MEDLINE, Scopus, CINAHL, and Embase. Eligible studies will document isolates tested for antimicrobial sensitivity, focusing on WHO-priority specimens and pathogens. Data extraction will focus on key study characteristics, study context, population, and adherence to WHO GLASS recommendations on AST. Descriptive statistics involving summarizing the quantitative data extracted through measures of central tendency and variation will be used. Covidence and Microsoft Excel software will be used. This study will systematically identify, collate, and analyze relevant studies and data sources based on clear inclusion criteria to provide a clear picture of the progress achieved in the implementation of the WHO GLASS recommendations. Areas for further improvement will be documented to inform future efforts to strengthen GLASS implementation for enhanced AMR surveillance in Africa.

Results: The study results are expected in August 2024.

Conclusions: To our knowledge, this scoping review will be the first to comprehensively examine the implementation of WHO GLASS recommendations in Africa, shedding light on the challenges and successes of AMR surveillance in the region. Addressing these issues aims to contribute to global efforts to combat AMR.

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KEYWORDS

antimicrobial resistance; antibiotic sensitivity testing; global antimicrobial resistance surveillance system; GLASS implementation; AMR Surveillance; Africa

Introduction

Drug-resistant infections are a leading cause of morbidity and mortality, with 1.5 million related deaths reported in 2019 [1]. Low- and middle-income countries, such as those in Africa, disproportionately face challenges associated with communicable diseases, yet there is limited data on the epidemiology, impact, and geographical distribution of antimicrobial resistance (AMR) in these regions [2] as comprehensive population-based AMR surveillance poses considerable challenges [3-6]. The 2014 World Health Organization (WHO) report on global surveillance of AMR emphasized the lack of information regarding pathogens that pose significant public health risks [7]. Assessing and monitoring AMR trends globally is limited by a lack of quality data [8].

AMR surveillance systems are fundamental elements of infectious disease management [6] and provide the basis for a deeper comprehension of AMR spread [9]. AMR surveillance data can enhance public health, guide health policy decisions, prompt responses to health crises, offer early alerts about emerging threats, and identify longstanding resistance patterns [6]. In low- and middle-income countries, the capability for surveillance of AMR varies [9], with sub-Saharan Africa and Southeast Asia exhibiting the least developed coverage compared with high-income countries [10-12]. In these low-income areas, such as Africa, AMR surveillance challenges are significant due to weak infrastructure, including the underdeveloped treatment infrastructure, lack of adequately trained human resources and limited funding within health systems, various legal and policy limitations, and other socioeconomic factors (culture and societal factors) [13,14]. Despite the above challenges faced, a number of countries in Africa are implementing the WHO Global Antimicrobial Resistance Surveillance System (GLASS) recommendations on AMR surveillance [15]. This is in addition to other tools like the Global Action Plan and the WHO benchmarks [16].

AMR surveillance is 1 of the 5 strategic objectives of the AMR Global Action Plan [3]. To inform surveillance, the WHO launched the GLASS manual in 2015 [15] to standardize surveillance, including antimicrobial sensitivity testing (AST). The WHO GLASS manual makes several recommendations on AMR surveillance systems. Among these include recommendations on priority specimens and pathogens for AMR surveillance of routine clinical samples [15]. In addition, the WHO has identified priority antibiotics for which monitoring of resistance should be done (Table 1) [15]. To achieve this, the GLASS manual recommends pathogen-antimicrobial combinations on which GLASS gathers data [15].

The antimicrobial substances against which resistance or nonsusceptibility will be monitored were selected because either they are commonly recommended first-line treatment or surrogate substances for resistance in drugs commonly used to treat patients, or the pathogen-antimicrobial combination is of particular concern because of limited treatment options. The recommended priority specimens include blood, urine, feces, and urethral and cervical swabs (Table 2) [15]. The priority specimens were selected because they can be used to isolate pathogens that cause most of the common human infections in the bloodstream, urinary tract, gastrointestinal tract, and genital or reproductive tract. The purpose of using priority specimens and pathogens was to enable systematic capacity building for countries as they set up their national AMR surveillance programs [17]. Despite these recommendations, countries could also report on additional specimens and pathogens if national capacity for surveillance of these organisms exists.

Although the GLASS manual was rolled out in 2016, the extent of its implementation, specifically for priority specimens and pathogen-antibiotic combinations, has not been fully explored, especially in Africa. We aim to review existing literature to fill this knowledge gap and inform current and future practices of AMR surveillance. Specifically, we shall review, summarize, and report on priority specimens, pathogen-antibiotic combinations testing, and reporting in the context of the WHO GLASS manual.

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Table 1. Pathogen-antimicrobial combinations on which the Global Antimicrobial Resistance Surveillance System gathers data.

Pathogen	Antibacterial class	Antibacterial agents that may be used for AST[a,b,c]
Escherichia coli	• Sulphonamides and trimethoprim • Fluoroquinolones • Third-generation cephalosporins • Fourth-generation cephalosporins • Carbapenems • Polymyxins • Penicillins	• Cotrimoxazole • Ciprofloxacin or levofloxacin • Ceftriaxone or cefotaxime and ceftazidime • Cefepime Imipenem, meropenem, ertapenem, or doripenem • Colistin • Ampicillin
Klebsiella pneumoniae	• Sulphonamides and trimethoprim • Fluoroquinolones • Third-generation cephalosporins • Fourth-generation cephalosporins • Carbapenems • Polymyxins	• Cotrimoxazole • Ciprofloxacin or levofloxacin • Ceftriaxone or cefotaxime and ceftazidime • Cefepime • Imipenem, meropenem, ertapenem, or doripenem • Colistin
Acinetobacter baumannii	• Tetracyclines • Aminoglycosides • Carbapenems[d] • Polymyxins	• Tigecycline or minocycline • Gentamicin and amikacin • Imipenem, meropenem, or doripenem • Colistin
Staphylococcus aureus	• Penicillinase-stable beta-lactams	• Cefoxitin[e]
Streptococcus pneumoniae	• Penicillins • Sulphonamides and trimethoprim • Third-generation cephalosporins	• Oxacillin[f] • Penicillin G • Cotrimoxazole • Ceftriaxone or cefotaxime
Salmonella spp.	• Fluoroquinolones • Third-generation cephalosporins • Carbapenemsd	• Ciprofloxacin or levofloxacin • Ceftriaxone or cefotaxime and ceftazidime • Imipenem, meropenem, ertapenem, or doripenem
Shigella spp.	• Fluoroquinolones • Third-generation cephalosporins • Macrolides	• Ciprofloxacin or levofloxacin • Ceftriaxone or cefotaxime and ceftazidime • Azithromycin
Neisseria gonorrhoeae	• Third-generation cephalosporins • Macrolides • Aminocyclitols • Fluoroquinolones • Aminoglycosides	• Cefixime • Ceftriaxone • Azithromycin • Spectinomycin • Ciprofloxacin • Gentamicin

[a]AST: antimicrobial sensitivity testing

[b]The listed substances are priorities for surveillance of resistance in each pathogen, although they may not be first-line options for treatment. One or more of the drugs listed may be tested.

[c]One or more of the drugs listed may be tested in countries. Susceptible, intermediate, resistant, and nominator and denominator data for each shall be reported separately.

[d]Imipenem or meropenem is preferred to represent the group when available.

[e]Cefoxitin is a surrogate for testing susceptibility to oxacillin (methicillin and nafcillin); the antimicrobial sensitivity testing report to clinicians should state susceptibility or resistance to oxacillin.

[f]Oxacillin is a surrogate for testing reduced susceptibility or resistance to penicillin; the antimicrobial sensitivity testing report to clinicians should state reduced susceptibility or resistance to penicillin.

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Table 2. Global Antimicrobial Resistance Surveillance System priority specimens and pathogens for the scoping review.

Priority specimens	Priority pathogens
Bloodstream infections	• *Klebsiella pneumoniae* • *Acinetobacter baumannii* • *Staphylococcus aureus* • *Streptococcus pneumoniae* • *Salmonella spp.*
Urinary tract infections	• *Escherichia coli* • *Klebsiella pneumoniae.*
Acute diarrhea	• *Salmonella spp.* • *Shigella spp.*

Methods

Study Eligibility

The primary objective of this study is to determine the current state of implementing the WHO GLASS recommendations on AST for priority pathogen-antimicrobial combinations. We shall use a scoping review to map concepts around the study topic. The methodological framework proposed by Arksey and O'Malley [18] (6-step scoping review process) will be adopted for this proposed review [18]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance for scoping reviews will be used to report the study findings [19]. We anticipate that the methodologies of the studies will be more diverse, including observational studies, randomized controlled trials, cohort, and mixed methods studies. We will include only published and peer-reviewed articles (Textbox 1).

Textbox 1. Inclusion and exclusion criteria for the different articles to include in the scoping review.

Inclusion criteria

- The inclusion criteria will be based on the Population, Concept, and Context framework as proposed by the Joanna Briggs Institute for scoping reviews as a less restricted alternative to the Population, Intervention, Comparator, and Outcome framework [20]. Original research articles and short reports with primary data will be included.

Exclusion criteria

- Editorials, commentaries, review papers, or any other publication without primary data
- Studies with insufficient data regarding the study question
- Studies not published in English
- Studies published before 2016

Study Population

The scoping review will include studies that document isolates collected and tested for antimicrobial sensitivity in Africa. Only isolates from the WHO priority specimens will be included. All reported isolates will be assessed to determine whether the WHO priority pathogen-antibiotic combinations were tested as per the WHO GLASS manual recommendations. Our secondary objective for this review will be to document whether reporting of AST results is according to "susceptible," "intermediate," and "resistant" recommendations.

Search Strategy

Search strategies will target the following electronic databases: MEDLINE, Scopus, CINAHL, and Embase. Keywords used for the search will include "Antimicrobial Resistance," "Anti-microbial Susceptibility," "AST," "AMR Surveillance," "Diagnostic," "Africa," and specific names of all African countries (Table 3). Finally, screening of reference lists of included documents for relevant articles will be undertaken. Endnote (Clarivate) will be used to manage citations, Covidence will be used to screen abstracts and full texts, and Microsoft Excel will be used for data extraction and charting the H stages of this review.

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Table 3. Sample search terms or concepts that will be searched as keywords and subject headings.

Subject headings	Keywords
MeSH[a] search terms	"Drug resistance" OR "Antimicrobial resistance" OR "Bacterial resistance" OR "Drug Resistance, Bacterial", OR "Microbial Sensitivity Tests OR "Drug Resistance, Microbial" AND
Text word search	"antibiotic resistan*" OR "antibacterial resistan*" OR "antimicrobial resistan*" OR "antimicrobial drug resistan*" OR "antibiotic drug resistan*" OR "antibacterial drug resistan*" OR "bacteraemia" OR "bacteremia" OR "bloodstream inf*" AND
Title and abstract	"angola" OR "benin" OR "botswana" OR burkina faso" OR "burundi" OR "cameroon" OR "cape verde" OR "central african republic" OR "chad" OR "ivory coast" OR "cote d ivoire" OR "congo" OR "comoros" OR "djibouti" OR "Equatorial Guinea" OR "eritrea" OR "ethiopia" OR "gabon" OR "gambia" OR "ghana" OR "guinea" OR "guinea bissau" OR "kenya" OR "leshoto" OR liberia" OR "madagascar" OR "malawi" OR "Mali" OR "mauritania" OR "mozambique" OR "namibia" OR "niger" OR "nigeria" OR "rhodesia" OR "rwanda" OR "sao tome" OR "senegal" OR "seychelles" OR "sierra leone" OR "somalia" OR "south africa" OR "sudan" "swaziland" OR "tanzania" OR "togo" OR "uganda" OR "zambia" OR "zimbabwe" OR "africa"

[a]MeSH: medical subject headings.

Data Extraction, Charting, Synthesis, Analysis, and Presentation of Results

Data Extraction

After searching the primary sources, articles will be exported from Endnote into Covidence for further screening and analysis. Covidence will be used to remove duplicate sources from the initial pool and complete screening at 2 levels. We shall develop a template for data extraction. Key variables to be extracted will include author and year of publication, study title, inclusion criteria, study type, study setting, study population, priority specimen, priority pathogen, pathogens isolated, antimicrobial agent and class used, and reporting in the context of the WHO GLASS manual and significant findings.

The adapted extraction tool will be used in both the initial stages of study screening (to confirm study relevance) and selection and the later phase of data extraction from the selected studies. The customized data extraction tool will be used to collect relevant information on the (1) key study characteristics (eg, publication year, publication type, study design, country, and patient population characteristics), (2) detailed information on the study context and population, and (3) AST of bacterial isolates against the WHO GLASS recommendations.

To ensure systematic and reproducible study selection and data charting processes and to foster high interrater reliability, a calibration exercise will be undertaken. First, the review lead will use a seminal article to ascertain if the extraction instrument is appropriate for its intended use. Once confidence in the tool has been internally established, 2 members of the review team will be involved in the pilot of the extraction tool, using a minimum of 20 abstracts to review titles and abstracts against the inclusion criteria mentioned earlier. We will review the results of the calibration, discuss any discrepancies among reviewers, and make refinements to the extraction tool as identified and required. Reviewers will, at the same time, document reasons for exclusion on the extraction form and progress those articles considered relevant and eligible to the second phase of full-text screening. Confirmed sources for inclusion in the scoping review will then be moved to the final stages of data extraction, charting, and synthesis.

Following the identification and selection of the relevant literature, we will explore within those studies the AST of isolates according to WHO GLASS pathogen-antibiotic combinations. The reviewers will independently chart data in duplicate from each eligible article. Should there be any disagreements among the reviewers, these will be resolved through discussion. The supervising reviewer will resolve any conflicts and provide oversight for the whole process. We aim to provide a descriptive summary of the gaps in the implementation of the WHO GLASS manual, specifically to AST, based on the priority pathogen-antibiotic recommendation. Where relevant, we intend to suggest how the barriers can be addressed to improve AMR surveillance.

Primary Data Synthesis and Analysis

Descriptive statistics involving the analysis and summarizing of the data through measures of variability and central tendency will be used. Where required, stratification by factors like study type (cohort, cross-sectional, trails, and others), study settings (community or community), and others will be undertaken at the analysis stage. This will allow for a more nuanced understanding of the implementation progress and help minimize bias at the analysis stage of the review.

Data Presentation and Dissemination Plan

The data will be provided in well-organized tables and visuals, such as charts, summarizing the quantitative data generated. The data will be published in an international peer-reviewed journal to reach a broad academic and research audience or community. The results will also be presented at conferences.

Risk of Bias Assessment or Quality Appraisal

Consistent with the Joanna Briggs Institute scoping review methodology, as this is a scoping review that aims to map all available knowledge regarding the study topic, we will not perform a risk of bias assessment. We shall appraise articles for quality using the Critical Appraisal Skills Programme (CASP) checklist. Where articles of low quality are included, a comment will be made.

Patient and Public Involvement

Patients will not be directly involved in this study. However, the findings will be published for the wider community and

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policymakers, with the view that they could improve public health and contribute to efforts to control AMR.

Ethical Considerations

No ethical clearance is needed for this study as it will be based on already published articles, and no human participants will be involved directly in the study.

Results

The results of the study are expected in August 2024.

Discussion

Expected Findings

This proposed review is intended to map evidence of the progress in implementing the WHO GLASS recommendations on AST for priority pathogen-antimicrobial combinations [15]. It will inform current and future practices of AMR surveillance, provide ground for further research on GLASS implementation activity research, and inform policy makers on areas of improvement in AMR control activities. Through conducting surveillance of specific pathogens over time, one can detect emerging pathogens and implement timely control, understand epidemiological trends, discover changes in the antimicrobial susceptibility profile of the organisms, monitor and inform treatment guidelines, and facilitate outbreak response [21,22].

Despite the great outcomes and strengths we anticipate from this study, several limitations are still envisaged. The fact that the review is to be conducted with reference to the first WHO GLASS manual 2015, a small scope for pathogens and priority pathogen-antibiotic combinations, will be considered.

Conclusions

AMR surveillance is one of the critical approaches to estimate and fight the burden of antibiotic resistance. This scoping review will be the first to provide information on the progress of implementation of the WHO GLASS initiative in Africa.

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Data Availability

All data generated or analyzed during this study will be included in the published paper and its supplementary information files.

Authors' Contributions

All the authors contributed equally to the development of this study protocol.

Conflicts of Interest

None declared.

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Abbreviations

AMR: antimicrobial resistance
AST: antimicrobial sensitivity testing
CASP: Critical Appraisal Skills Programme
GLASS: Global Antimicrobial Resistance Surveillance System
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance for scoping reviews
WHO: World Health Organization

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Protocol

Barriers and Facilitators Affecting Access to Health Care for People With Syphilis: Protocol for a Scoping Review

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Abstract

Background: Syphilis is a systemic, preventable, and curable infection caused by the bacterium *Treponema pallidum*. Despite being treatable, syphilis continues to have a high incidence, with a resurgence observed even in countries with strong health surveillance systems. This highlights the need to understand the various strategies used globally to improve access to care for individuals with syphilis.

Objective: This scoping review aims to identify and map the barriers and facilitators affecting access to health care for people with syphilis.

Methods: This scoping review will follow the methodology outlined by the Joanna Briggs Institute. The search will be conducted across several databases, including PubMed/MEDLINE, Scopus, Embase, LILACS (Virtual Health Library), and CINAHL (EBSCO). In addition, sources of unpublished studies or gray literature will be explored. Studies focusing on access to health care for individuals with syphilis will be included, regardless of geographic location, country, or language. Two independent reviewers will assess the results, and data will be extracted using a tool specifically developed for this review. The extracted quantitative data will be presented in tables and analyzed using descending hierarchical classification, represented by a class dendrogram. Barriers and facilitators will be categorized into dimensions of access.

Results: Database searching began in October 2024. Full-text screening and review are expected to be completed in December 2024. Data extraction and analysis are expected to be completed by February 2025, and the final report will be completed in March 2025.

Conclusions: The findings of this scoping review, guided by this protocol, will elucidate the main barriers and facilitators that affect access to syphilis treatment. This study may contribute to the practices of health professionals, managers, and the academic community, and provide relevant information for the population.

Trial Registration: Open Science Framework Registries osf.io/kpsab; https://osf.io/kpsab

International Registered Report Identifier (IRRID): PRR1-10.2196/63561

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KEYWORDS

syphilis; acquired syphilis; congenital syphilis; gestational syphilis; Treponema pallidum; health services accessibility; access to health services; scoping review

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Introduction

Syphilis is a systemic, preventable, and curable infection caused by the bacterium *Treponema pallidum*. The main route of transmission is sexual, but it can also be transmitted from mother to fetus during the gestational period [1]. If not treated, syphilis may cause serious complications, such as an increased risk of contracting other sexually transmitted infections, neurological and ocular changes, hearing or balance impairments (or both), death, neonatal death, prematurity, low birth weight, and stillbirths. Syphilis is the second most common cause of stillbirths due to infectious diseases worldwide [2].

Syphilis is one of the most important sexually transmitted infections in the world [3]. Studies estimate that more than 11 million new cases of syphilis occur annually worldwide, with high incidence in Latin America, Africa, and Asia [4]. Furthermore, some countries with good surveillance of sexually transmitted infections, such as the United States, Canada, Australia, and Japan, have reported a resurgence of syphilis after the COVID-19 pandemic [5].

The resurgence and high incidence of syphilis indicate a failure in its control and should be seen as an urgent call for targeted and intense action. Effective control requires sufficient funding, coordinated public policies on prenatal and sexual health care, clear guidelines, campaigns to encourage people to seek care without fear of discrimination, and educational programs. Thus, sustained and effective efforts are needed to control this infection [6]. The limited access to health care caused by social, structural, and economic barriers hinders the early detection and treatment of syphilis, resulting in perpetuated transmission and increased morbidity and mortality [7,8]. It is understood that caring for people with syphilis requires a multifaceted approach that involves collaboration between governments, managers, health professionals, and society [9].

It is necessary to know the different strategies adopted to care for people with syphilis worldwide. Currently, there are studies that point out some barriers or facilitators affecting access to care for people with syphilis; however, they address only a certain service or a classification of syphilis (acquired, gestational, or congenital) in a certain location or country [10-12], justifying this study. In addition, these barriers and facilitators may change over the years and may also be different in different countries, as they have different socioeconomic, cultural, and geographical contexts, as well as varied health systems, which is an additional part of this research.

In May 2024, a preliminary search was conducted in PubMed, Joanna Briggs Institute (JBI) Evidence Synthesis, PROSPERO, and the Open Science Framework. No other planned or ongoing reviews on this topic were identified.

Therefore, this scoping review aims to identify and map the barriers and facilitators affecting access to health care for people with syphilis. The results of this review will provide subsidies for discussions on public health policies aimed at the population with syphilis, the implementation of new projects, and the encouragement of research based on the gaps identified during the research. They will also allow health professionals to make more effective interventions, demonstrating the relevance of this research.

Methods

In line with open science, this protocol is methodologically organized. It allows the entire scientific method to be replicated, thereby mitigating the risk of bias in research [13].

Study Design

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [14], based on the theoretical framework proposed by Arksey and O'Malley [15], and updated by Levac et al [16]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [17] will be used to report the results (Multimedia Appendix 1).

The stages of the scoping review include (1) definition and alignment of the objective with the research question; (2) development and alignment of inclusion criteria; (3) description of the search for evidence, selection and extraction of data, and presentation of evidence; (4) search for evidence; (5) selection of evidence; (6) extraction of evidence; (7) analysis of evidence; (8) presentation of the results; and (9) summary of evidence, conclusions, and implications of findings [14].

Stage 1: Definition and Alignment of the Objective With the Research Question

We used the population, concept, and context mnemonic to assist in forming the research question and developing the study title. Here, we define the population as individuals with syphilis, the concept as access to health care, and the context as the environment of health services globally. Therefore, the question that will guide this study is as follows: What are the barriers and facilitators affecting access to health care for people with syphilis?

Stage 2: Development and Alignment of Inclusion Criteria

Overview

Studies will be included if the full text is available. Studies published in any language will be included. Those in a language other than Portuguese will initially be translated using Google Translate, and the full text will be professionally translated if the study meets the inclusion criteria. This scoping review will consider gray literature, such as theses, dissertations, and government reports. Individual case reports, clinical protocols, conference and event summaries, and journal editorials will be excluded as their usefulness in this review is not anticipated. Considering the mnemonic adopted, the eligible studies are the following.

Population

This review will consider studies that address people with acquired, congenital, or gestational syphilis. Acquired syphilis is conceptualized as a disease transmitted from one person infected with the bacterium *T pallidum* to another during sex (anal, vaginal, or oral) without a condom or by blood

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transfusion. Particularly when it affects a pregnant woman, it is called gestational syphilis [18].

Concept

This study will consider conceptual studies that discuss access to health care. Access has been conceptualized in numerous ways. Here, we have defined access as the opportunity to identify health care needs; seek health care services; reach, obtain, or use health care services; and actually have health needs resolved [19].

Context

The context of interest is health services. Thus, studies conducted in primary care units, outpatient departments, multidisciplinary or specialized clinics (or both), maternity wards, hospitals, and emergency care units will be included. In addition, any geographic scenario and country will be considered.

Stage 3: Description of the Search for Evidence, Selection, Extraction of Data, and Presentation of Evidence

An initial search limited to PubMed and the Virtual Health Library (*Biblioteca Virtual en Salud*; VHL) was conducted to identify the main Medical Subject Headings (MeSH) terms and Health Sciences Descriptors (Descriptors in Health Sciences; *Descritores em Ciências da Saúde* [DeCS]) related to the topic. The search strategy was constructed using controlled health vocabulary, including MeSH, DeCS, and Emtree, to expand results across different databases. Then, a search was conducted to identify synonyms and keywords. The search strategy was expanded and validated by an experienced librarian (AA). Multimedia Appendix 2 shows the complete search strategy built for PubMed/MEDLINE.

The search strategy will be adapted for each database and information source, including PubMed/MEDLINE, Scopus, Embase, LILACS via VHL (in Portuguese, Spanish, and English), and CINAHL (EBSCO). These databases were selected to allow for a more comprehensive search. In addition, sources of unpublished studies or gray literature will be searched, including Google Scholar (limited to the first 100 results), Brazilian Digital Library of Theses and Dissertations, the Catalog of Theses and Dissertations of the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and ProQuest Dissertations and Theses Global.

Reference lists from all included sources will be reviewed to identify any additional relevant studies. If necessary, the authors of the included studies will be consulted by email for any additional information.

Stage 4: Search for Evidence

After the search, all identified quotes will be collected and imported into the free version of Rayyan (Qatar Foundation), where duplicates will be removed and studies will be selected. Two reviewers (RB and RP) will conduct a pilot test to reduce bias, standardize the selection process, and verify compliance with the study protocol. The pilot test will be carried out using a random sample of 25 titles and abstracts, following the eligibility criteria. The team will discuss any discrepancies and change criteria and definitions, if necessary. Screening will begin only after at least 75% agreement [14].

Once the pilot test is complete, the 2 reviewers (RB and RP) will use Rayyan to read the titles and abstracts of all studies identified by the eligibility criteria. If there are disagreements between reviewers during the process, resolution will be reached through consultation with a third reviewer (JC).

Stage 5: Selection of Evidence

After reading the titles and abstracts of all studies, potentially relevant sources will be obtained in full and exported to Google Drive. The full text of selected studies will undergo a detailed assessment against the inclusion criteria by 2 independent reviewers (RB and RP). Reasons for exclusion will be recorded. In case of disagreements between reviewers during the selection process, resolution will be reached by consulting the third reviewer (JC). The study selection process will be reported in the PRISMA-SCR flowchart [20].

Stage 6: Extraction of Evidence

The reviewers developed a draft data extraction form (Table 1), based on suggestions provided in the JBI methodology for scoping reviews [14]. For better data extraction, the framework proposed by Levesque et al [19] outlines 5 dimensions of accessibility: approachability, acceptability, availability and accommodation, affordability, and appropriateness.

Approachability refers to whether individuals with health needs can identify available services, understand their potential impact, and access them. This dimension is influenced by factors such as transparency, information about available treatments and services, outreach activities, health literacy, knowledge about health, and cultural beliefs. Acceptability involves cultural and social factors that determine whether individuals find the aspects of a service (eg, the gender or social group of providers, the associated medical beliefs) appropriate and acceptable [19].

Availability and accommodation pertain to whether health services are physically accessible and available in a timely manner. This includes the existence of adequate facilities, building accessibility, transportation systems, flexible working hours, and the qualifications of health professionals. Affordability relates to the economic capacity of individuals to spend resources and time on necessary services. Factors such as poverty, social isolation, and indebtedness can limit an individual's ability to pay for needed care. Appropriateness concerns the suitability and quality of the services provided, including their integrated and continuous nature [21].

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Table 1. Preliminary data extraction form.

Variable	Standardization
First author and year of publication	• Identify the first author and year of publication of the study
Objective	• Detail the objective of the study
Study design	• Classify according to modality (theoretical, field, and bibliographic), objectives (exploratory, descriptive, and explanatory), and approach (quantitative and qualitative)
Study population	• Detail the population of the study
Data collection procedure	• Describe the type of data collection procedure used in the study
The country where the research was carried out	• Identify the country where the study was conducted
Syphilis classification	• Identify the classification of syphilis covered in the study: congenital syphilis, gestational syphilis, or acquired syphilis
Study location	• Identify in which service or institution the study was carried out (basic health units, outpatient clinics, multidisciplinary or specialized clinics, maternity wards, hospitals, and emergency care units)
Results	• Describe the main barriers and facilitators to access health care for people with syphilis based on the 5 dimensions of accessibility (Approachability, Acceptability, Availability and accommodation, Affordability, and Appropriateness) and 5 corresponding abilities of populations (Ability to perceive, Ability to seek, Ability to reach, Ability to pay, and Ability to engage) [19] • The barriers and facilitators that are explicit in the texts will be extracted

Initially, there will be a pilot test for the use of the extraction tool. Two reviewers (RB and RP) will conduct the test using a sample of 10 papers. The goal is to ensure that important information is completely extracted and that the process is standardized. At this stage, relevant variables that emerged during the test may be included.

Two independent reviewers (RB and RP) will use the form to extract data from all eligible studies. In case of discrepancies between reviewers, a consensus will be reached through discussion with the third reviewer (JC). The authors of the studies will be contacted to obtain missing or additional data, if needed.

Stage 7: Analysis of Evidence

The results will be analyzed quantitatively and qualitatively. Quantitative analysis will use descriptive statistics with absolute and relative frequency. The Thematic Content Analysis method will be used for qualitative analysis. This method uses systematic and objective procedures, consisting of unraveling the “nuclei of meaning” that decompose communication and whose presence or frequency of appearance can signify something relevant to the chosen analytical objective [22]. The IRaMuTeQ software, developed by Pierre Ratinaud, will contribute to the lexical analysis of the textual corpus [23].

Stage 8: Presentation of Results

Results will be presented using a PRISMA-ScR flowchart [20]. The extracted quantitative data will be presented in tables and by the class dendrogram for descending hierarchical classification. This allows the analysis of text segments that present similar vocabulary and vocabulary different from other text segments, simultaneously calculating distances and proximities based on chi-square tests. With these analyses, IRaMuTeQ organizes the words in a dendrogram—which represents the quantity and linguistic composition of classes based on a grouping of terms—from which the absolute frequency of each of them and the aggregate chi-square value are obtained [23].

The barriers and facilitators will be categorized into dimensions of access: (1) Accessibility, (2) Acceptability, (3) Availability and accommodation, (4) Affordability, and (5) Appropriate. From each thematic category, there will be a summary description of the extracted information.

Stage 9: Summary of Evidence, Conclusions, and Implications of Findings

Once the previous steps have been completed, a summary of the evidence will be drawn up to support the conclusion. We will list the gaps in knowledge to guide future research.

Results

The database search began in October 2024, generating 995 articles, of which 306 were duplicates. The next step will be to search the gray literature. Upon completion, there will be screening of titles and abstracts and review of the full text, with completion scheduled for December 2024. Data extraction and analysis should be carried out in January and February 2025, with the expectation that the final report will be ready for shipping by March 2025. The results of this research will be published in open-access and peer-reviewed journals, a testament to our commitment to disseminating knowledge in the scientific community and ensuring the credibility of our findings.

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Discussion

Overview

The scoping review has gained prominence globally in the field of health evidence synthesis [24]. This methodology was chosen for this study because it aims to map the literature in a specific area of interest—in this case, access to health services for people with syphilis on a global scale. The scoping review is particularly useful when reviews on a subject have not yet been published. It allows for the inclusion of a broad range of study designs and aims to identify and synthesize the available evidence [14,15].

We chose to use IRaMuTeQ for data analysis, a free software that enables various types of textual data analysis, from basic lexicography (eg, word frequency calculation) to more complex multivariate analyses, such as descending hierarchical classification and similarity analysis [23]. The software organizes the distribution of vocabulary in an easily understandable and visually clear manner, such as through similitude analysis and word clouds. The advantages of using software for data analysis include improved organization and separation of information, increased process efficiency, easier location of text segments, and faster coding compared with manual methods [25].

A key strength of this scoping review is the experienced research team, who are well versed in the study of syphilis and in applying the scoping review methodology. To ensure a highly sensitive search strategy for this protocol, we collaborated with a librarian affiliated with the researchers institution, which enhanced the comprehensiveness of the search and allowed for greater access to relevant literature. Importantly, the research will not be limited by time or language constraints.

Access to health services has been a subject of analysis since the latter half of the 20th century [26]. Over the years, authors have conceptualized access to health care differently. The Levesque, Harris, and Russell model was chosen for its comprehensive scope. Their conceptual framework, published almost 7 years ago, is still considered relatively new. One key aspect of this model is its portrayal of access as a dynamic process or journey in contrast to the static concept as defined by others. The 5 proposed dimensions are interconnected, offering a multidimensional view of access to health within the context of health systems, thereby shedding light on the complexity of the topic [19,27].

The most common challenges of this model are related to repeated instances, and there may be difficulties in categorizing information into specific dimensions or when responses fall into more than 1 dimension. Another weakness is the inability to consider time-related access elements (waiting time and travel time) [27].

Access to health care for people with syphilis requires ongoing attention from health managers, professionals, and researchers due to the high incidence of the infection in various regions globally. Numerous initiatives have been developed in recent years to combat this epidemic. For instance, in 2016, the World Health Organization launched the Global Health Sector Strategy on Sexually Transmitted Infections 2016-2021, aiming for a 90% reduction in the incidence of *T pallidum* and fewer than 50 cases of congenital syphilis per 100,000 live births in 80% of countries by 2023 [28]. In 2017, the Pan American Health Organization set goals to increase syphilis screening and appropriate treatment coverage in pregnant women to 95% or more, aiming to eliminate vertical transmission of syphilis [29].

Despite these governmental efforts, syphilis remains a persistent public health challenge. Watt et al [30] identified several factors that contribute to low access among young people to sexual and reproductive health services, including a lack of knowledge about available services, cultural and religious barriers, judgmental attitudes of health professionals, and insufficient privacy in health facilities.

Additional barriers to syphilis testing and care include stigma, discrimination, gender-based violence, past negative health care experiences, reluctance to disclose sexual practices, confidentiality concerns, and limited access to health facilities [31,32]. These barriers can be addressed through continuing education for health care teams, which fosters reflection on the work process and recognizes the needs and potential of the service. In-service learning is essential for improving the quality of health care.

Socioeconomic disparities, limitations in government financial transfers for health in specific regions, the concentration of health services in urban areas, and restricted access for populations in rural and riverside areas also hinder care for patients with syphilis. Understanding these barriers and facilitators allows health policy makers and managers to act at local or regional levels, designing policies and programs based on successful experiences identified in the scoping review, with adaptations for the specific context.

As identified through this scoping review, there is a significant knowledge gap regarding the barriers and facilitators to accessing health care for people with syphilis, whether acquired, congenital, or gestational, in a global context.

The scarcity of studies on these topics remains an obstacle to controlling syphilis at the community level. This study aims to explore the breadth of the literature, map current evidence, and identify gaps in knowledge about syphilis worldwide.

Moreover, it is anticipated that the results of this scoping review will be significant in prompting changes at both macropolitical and micropolitical levels, leading to better access to health care services and improved quality of care for people with syphilis.

The study also aims to raise awareness among society and health professionals about the importance of providing welcoming and attentive care for people with syphilis, ensuring that they receive the same rights to quality care as anyone else.

Limitations

The use of descriptors and search terms in only English, Portuguese, and Spanish may limit the study by potentially excluding relevant research published in other languages. In addition, the absence of searches on institutional websites across all countries for gray literature may also be a limitation, although

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this is not expected to significantly impact the development of the scoping review.

Furthermore, the quality and methodological rigor of the included studies will not be assessed, as this is characteristic of a scoping review, which could introduce biases in the synthesis of the results.

Conclusions

This paper presents a scoping review protocol. Upon completion of the study, it will map the barriers and facilitators to health care access for people with syphilis, identify challenges to health care access in various parts of the world, and elucidate potential strategies for improving service delivery in syphilis care.

The full results will be disseminated through scientific conferences and international publications, with the aim of reaching 3 key target audiences: public health policy makers, health care professionals who care for people with syphilis, and researchers focused on this topic.

Ultimately, the study may highlight the need to develop and refine policies that prevent barriers to care from impeding access to health services, particularly in Brazil.

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Authors' Contributions

All authors made substantial contributions to the conception of the manuscript, drafted the paper, or revised it critically for important intellectual content. Furthermore, they granted final approval for the version to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.
[DOC File , 91 KB - resprot_v13i1e63561_app1.doc]

Multimedia Appendix 2
Search terms and results from an initial search conducted in PubMed.
[DOC File , 35 KB - resprot_v13i1e63561_app2.doc]

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Abbreviations

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

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DeCS: Health Sciences Descriptors (Descritores em Ciências da Saúde)
JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
VHL: Virtual Health Library (Biblioteca Virtual en Salud)

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Protocol

Factors Influencing Domestic Human Trafficking in Africa: Protocol for a Scoping Review

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Abstract

Background: Human trafficking is a human rights violation in every region of the world. The African continent is not spared. Every year, millions of people experience significant health and social consequences. International organizations and governments combating human trafficking are hindered by a lack of knowledge about what factors influence domestic (within-country) human trafficking.

Objective: This study aims to conduct a scoping review to collate and synthesize literature on factors influencing domestic trafficking in Africa.

Methods: We will follow Arksey and O'Malley's framework to answer the question about reported influences on domestic human trafficking and their relative weight. The search strategy will explore PubMed, CINAHL, Web of Science, and Scopus. A total of 2 independent researchers will select quantitative, qualitative, or mixed methods studies that examine relationships influencing domestic human trafficking. We will document our results by following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. We will extract a list of all reported relationships between identified factors influencing domestic human trafficking in each study. Based on a discourse analysis approach, we will weigh the strengths of the relationships based on how frequently they are reported across the included studies. We will summarize the findings as fuzzy cognitive maps depicting the relationships reported in the literature. The maps represent the influences between concepts (nodes) linked by arrows (edges) going from each cause to its outcomes. These maps are helpful visual summaries of the factors associated with domestic human trafficking, allowing a comparison with maps to be created by stakeholder groups.

Results: This project received financial support in March 2023. We expect to start the project in March 2024. We recruited 2 research staff members to conduct the scoping review and expect to publish the results in March 2025.

Conclusions: The review will provide a comprehensive understanding of factors influencing domestic human trafficking in Africa. The overlap of human trafficking with other forms of exploitation, the limited literature on domestic human trafficking, and the likely diversity of factors are challenges for the review. We propose strategies to address these challenges.

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KEYWORDS

domestic human trafficking; Africa; scoping review protocol; protocol; human trafficking; trafficking; modern slavery; human rights violation; discourse analysis; exploitation; fuzzy cognitive map

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Introduction

Human trafficking, also known as modern slavery, is a human rights violation. Every year, millions of people experience significant health and social consequences. In 2021, the Global Slavery Index estimated that 50 million people were living in slavery, an increase of 10 million since 2016 [1]. In Africa, 7 million men, women, and children were living in modern slavery, a prevalence of 5.2 people for every 1000 people [2].

"Human trafficking," "Modern slavery," and "Trafficking in person" are umbrella terms to refer to both sex trafficking and forced labor [3,4]. The 2000 United Nations Palermo Protocol defines human trafficking as follows:

> *The recruitment, transportation, transfer, harbouring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation [5].*
>
> *Human trafficking can include but does not require movements of people. People may be considered trafficking victims regardless of whether they were born into a state of servitude, were exploited in their hometown, or were transported to the exploitative situation [3].*
>
> *In domestic human trafficking situations, all stages of the trafficking process, including the recruitment of victims, occur within national borders [6].*

International human trafficking has received more attention compared with domestic human trafficking [7-10], even though most people are trafficked within their home countries; a 2022 United Nations report mentioned that of the people trafficked in sub-Saharan Africa that are detected, 85% are domestically trafficked [11].

Evidence on factors influencing human trafficking in Africa is emerging. A scoping review of domestic and international human trafficking in Ethiopia found that push factors of human trafficking are poverty, gender discriminatory practices, environmental factors, poor governance, demographic factors, famine, war, political instability, and economics. The pull factors are the demand for domestic workers and cheap uncompensated labor [12]. In the same review, sociocultural factors were identified as factors leaving women and children vulnerable to trafficking: early child marriage, lack of access to social services in rural areas, limited access to education (especially for girls), limited parental education, family discord, dissatisfaction with traditional ways of life, the attraction of paid work to support natal families, pregnancy outside of marriage and associated stigma, leaving school at an early age, and large family size [12].

A 2022 mixed methods study among women and girls trafficked in Uganda and Nigeria reported that family poverty, violence, and neglect exposed them to being trafficked nationally and internationally [13]. The participants described traumatic events in their family lives, such as the loss of one or both parents, emotional abuse, physical and sexual violence by caregivers, neglect, sexual exploitation, child labor, witnessing violence, parental alcohol abuse, parental divorce, extreme poverty, and hunger before being trafficked [13]. A 2023 qualitative study among youth trafficked nationally and internationally in Uganda identified poverty and abusive home life, frequently triggered by the death of a caretaker. Limited education, lack of social support, and survival needs pushed people who are trafficked into exploitative situations [14]. The available evidence does not give a clear picture of the specific factors influencing domestic trafficking.

In addition, the antitrafficking responses are not sufficiently aligned with the contexts in which they are implemented [15]. A 2024 systematic review on implementation science research in exit and postexit human trafficking interventions in sub-Saharan Africa reported on how local perspectives on poverty, gender norms, child labor, and family expectations differ from implementer's perspectives (mostly outsiders), which undermined social acceptability and potential effectiveness of anti–human trafficking strategies [15].

While there is emerging evidence on factors associated with human trafficking in Africa, there is a critical need to expand our understanding of factors influencing specifically domestic human trafficking to improve co-design interventions to combat human trafficking [16]. Developing effective evidence-based strategies requires participatory approaches that allow stakeholders to contextualize the available literature and discuss the most effective strategy locally [17]. This scoping review will collate and synthesize the published literature on factors influencing domestic human trafficking in Africa to inform evidence-based policies and guide future research efforts.

Methods

Study Design

This scoping review will follow the Arksey and O'Malley [18] framework for scoping reviews and use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines to report the review [19] (Figure 1 [20] and Multimedia Appendix 1).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart template. For the "Records identified from" section, we will report the number of records identified from each database or register searched (rather than the total number across all databases or registers). For the "Records excluded" section, if automation tools were used, we will indicate how many records were excluded by a human and how many were excluded by automation tools.

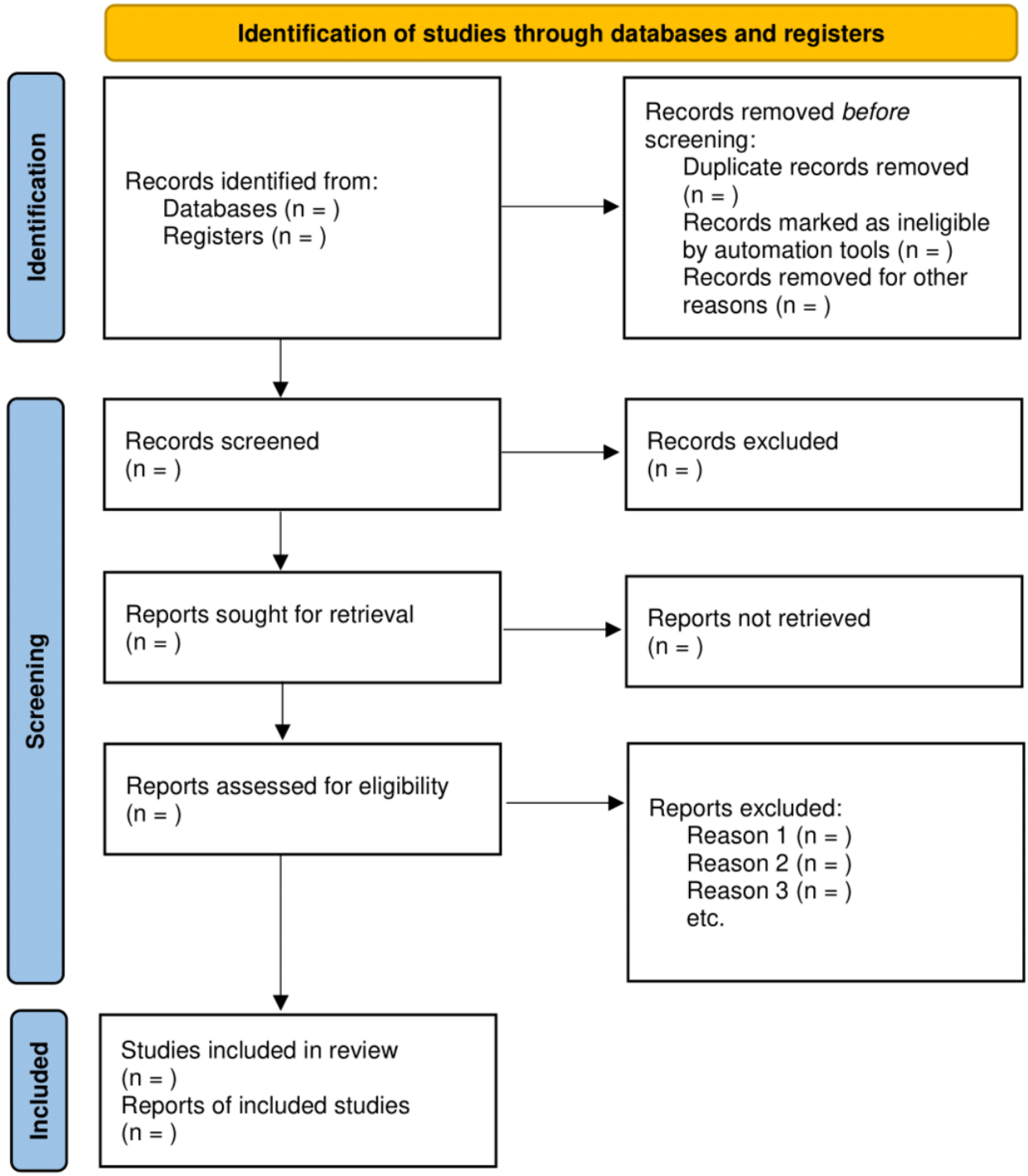

Scoping studies are knowledge syntheses that "aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available and can be undertaken as stand-alone projects, especially where an area is complex or has not been reviewed comprehensively before" [18]. Arksey and O'Malley [18] developed an approach to scoping review based on six stages: (1) identifying a research question; (2) identifying relevant studies; (3) study selection; (4) charting data; (5) summarizing, synthesizing, and reporting the results; and (6) consultation.

Stages

Stage 1: Identification of Research Question

The primary research questions are (1) What factors influence domestic human trafficking in Africa? and (2) Based on the available evidence, what is the relative weight of their influence?

The secondary research questions are (1) What methods have researchers used to identify factors influencing domestic human

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trafficking? and (2) What are the research gaps on factors influencing domestic human trafficking?

Stage 2: Identifying Relevant Studies

With the help of a specialist librarian, we will design a search strategy using Medical Subject Headings terms and Boolean operators ("AND" and "OR"; Multimedia Appendix 2). We will search the electronic databases such as PubMed, CINAHL, Web of Science, and Scopus and manually search the reference lists of included articles.

The review will include peer-reviewed articles on human populations reported in English and French. We will restrict geographical settings to Africa and focus on the last 24 years of publication (2000 to 2024). In 2000, the United Nations Convention against Transnational Organized Crime adopted a protocol to prevent, suppress, and punish trafficking in persons, with a focus on women and children. The protocol defines the crime of trafficking in human beings [5].

This scoping review will focus on domestic human trafficking, as defined in the *Introduction* section:

> *All the stages of the trafficking process occur within a country's borders. There are no international cross-border movements. However, victims can be moved across or within cities or provinces [6].*

This form of trafficking can involve various types of exploitation, including forced labor, sexual exploitation, forced marriage, and other forms of abuse and coercion [3,4].

In this review, we will use the terms human trafficking and modern slavery interchangeably if it refers to "situations of exploitation that a person cannot refuse or leave because of threats, violence, coercion, deception, and/or abuse of power" [3,4].

The strategy for identifying relevant articles has 2 steps. The first is an initial search in MEDLINE and PubMed to analyze text words in titles, abstracts, and index terms. The second step updates the term and runs the search strategies in all databases.

Stage 3: Study Selection

After completing the search and excluding duplicated records, we will export the list of references into Covidence to support the selection process [21]. A total of 2 independent researchers will select the studies. They will screen titles and abstracts against the predetermined inclusion and exclusion criteria to identify potentially relevant papers. A second round will use the full papers to support the selection decision. An independent team member will reconcile differences between the reviewers if they occur.

To be included, a paper must (1) be a peer-reviewed paper; (2) include human participants (women, men, and children) who self-identified or were defined by researchers as having been trafficked or are in a trafficked situation; (3) research takes place in African countries; (4) focus on domestic human trafficking, forced labor (domestic servitude, factory, mine, agriculture, and fishing industries), or sexual exploitation, forced marriage, and forced begging; (5) be an empirical study using qualitative, quantitative, or mixed methods analysis; and (6) report factors influencing domestic human trafficking. By factor, we mean circumstances and situations perceived as a cause of domestic human trafficking. The protocol will not focus on a specific type of participants (survivors, traffickers, etc) or levels (micro, meso, and macro) of factors. We will consider all of them and coherently organize them in charting and synthesizing data stages.

The exclusion criteria are (1) papers about exclusively international human trafficking, which refer to foreigners (often from countries with limited economic resources) who are brought to another country for labor or sex exploitation; (2) protocols; (3) theoretical, conceptual, and discussion papers; (4) commentaries, conference abstracts, letters of correspondence, and editorials; (5) PhD and master's dissertations; (6) papers about animal trafficking; (7) papers about organ trafficking; (8) research that takes place only in Europe, North America, and Asian countries; and (9) papers published before 2000. Scoping review methods do not require an assessment of the quality of evidence [19].

Stage 4: Charting Data

Based on the reading of full texts, 2 independent reviewers will extract the following items into Covidence:

1. Study characteristics (title, year of publication, country, study design, population, and sample size)
2. Type of trafficking (labor, sexual exploitation, domestic servitude, and forced marriage)
3. Scope of the study (national, regional, provincial, districts, municipality, and villages)
4. Settings and units of analysis (nongovernmental organizations, community-based or faith organizations, health services, and schools)
5. Methods to identify and assess factors influencing human trafficking
6. Strategies for participant recruitment
7. Relationships describing associations with domestic human trafficking are described with three elements: (A) factors that influence an outcome, (B) the outcome of the relationship, and (C) a sign to indicate if the relationship is positive or negative
8. Contextual data (eg, law enforcement, legal framework, antitrafficking local policies, statistics of domestic human trafficking, survivor's profiles, and the type of human trafficking more prevalent)

A total of 2 reviewers will pilot the data extraction using a random sample of 5 articles. They will use an Airtable application to chart the data. The pilot will refine the data extraction template and ensure the consistency of the extraction process across reviewers.

Stage 5: Summarize, Synthesize, and Report the Results

Reporting will include tables and charts of the geographic and population distribution of studies, methods used, and findings about the factors influencing domestic trafficking.

We will depict the scoping review findings as a fuzzy cognitive map reflecting the reported factors influencing domestic trafficking. Fuzzy cognitive mapping can combine diverse

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knowledge sources to inform research and actions [22]. The maps depict factors (influences) as nodes linked by weighted arrows (relationships and the strength of their influence) [23,24]. We will identify the reported influences with outcomes for each study and indicate if they are positive (+1) or negative (–1). A relationship is positive if the increment of the origin factor results in the outcome's increment (an increased risk of trafficking). If an increase in the influence results in a decrease in the outcomes, the relationship is negative (a reduction of trafficking). Figure 2 shows hypothetical influences on domestic trafficking to present an example of a fuzzy cognitive map. A direct relationship will have a direct arrow from one concept (factor) to the primary outcome (human trafficking). In Figure 2, famine increases the risk of domestic human trafficking. An indirect relationship will have an arrow from one to more concepts before reaching the outcome. For instance, political instability leads to war, which in turn increases gender discriminatory practices, which in turn leads to an increase in human trafficking. Arrows in dotted lines represent relationships of protective factors associated with human trafficking. For example, more economic opportunities lead to less poverty. More access to school leads to less human trafficking. This technique helps to identify all the direct and indirect relationships influencing an outcome and the nature of the relationships, which are either positive (increase the risk of being trafficked) or negative (decrease the risk of being trafficked).

Figure 2. An example of a fuzzy cognitive map.

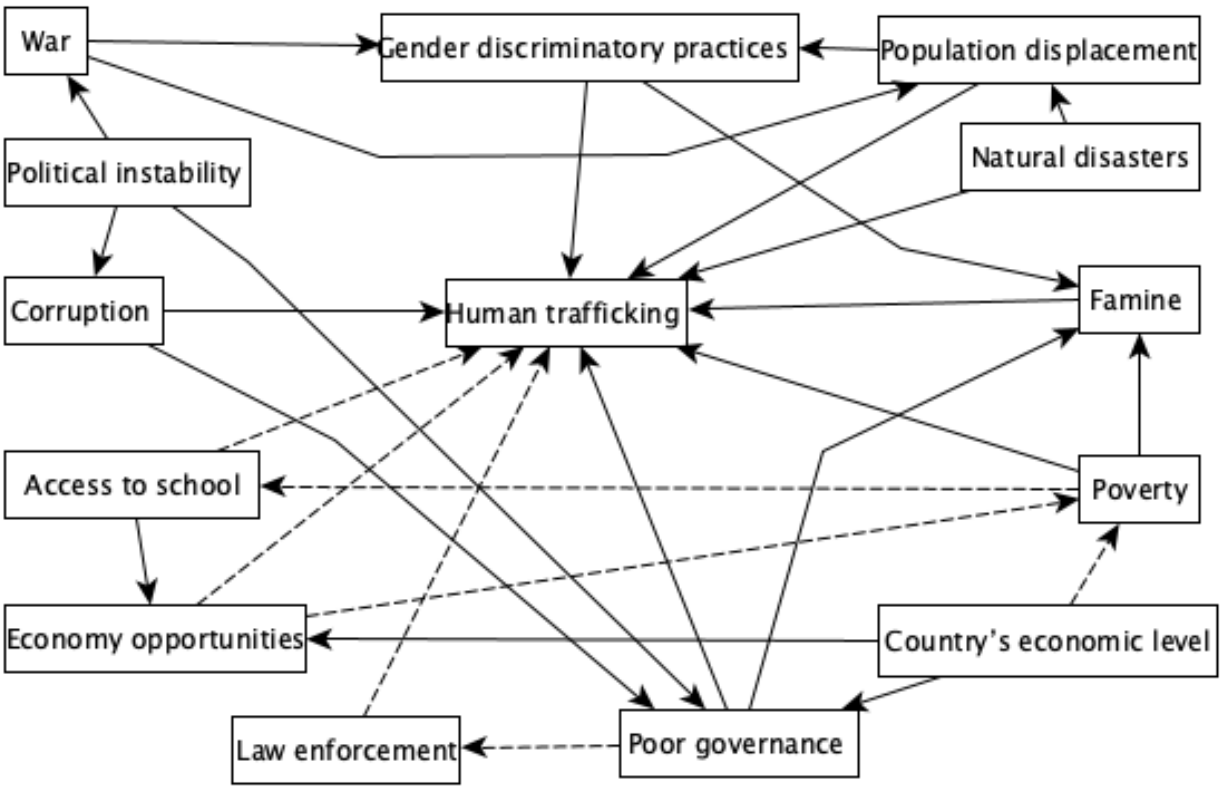

We will calculate fuzzy transitive closure on the collection of relationships from each study, identifying the maximum influence one cause can have on other outcomes through direct and indirect connections [24,25]. Based on a discourse analysis approach, we will weigh the relationships' strengths based on how frequently they are reported across the included studies [26]. A relationship reported by many studies in the literature would have a more substantial weight than a relationship reported in only 1 or 2 studies. We will count the number of times a relationship appears in the literature and divide this number by the maximum frequency. Values closer to 1 will have more weight in the literature, and values closer to 0 will have less weight.

Stage 6: Consultations

This scoping review is a step in a proposed more extensive participatory research project on domestic human trafficking in an African setting. We will use the literature map from this scoping review to compare with the stakeholder maps we plan to create [22]. Engaging stakeholders in the process is essential because it will allow them to consider the available research evidence in the context of their views and support them in making evidence-informed decisions [17].

The stakeholders are domestic human trafficking survivors, community leaders and service providers, and representatives from relevant government ministries and nongovernmental organizations.

We will invite each stakeholder group separately to join a fuzzy cognitive mapping session. With the support of 2 facilitators (facilitator and notetaker), each stakeholder group will draw a map.

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Fuzzy cognitive maps are soft models representing perceived causality about an issue. They describe the factors that stakeholders consider to be the causes of an outcome [22,23].

In this case, stakeholders will identify perceived causal factors influencing domestic human trafficking. During a mapping session, the facilitator writes the outcome (domestic human trafficking) on a magnetic tile of a whiteboard. The facilitator invites participants to mention the causes of the outcome, writing each cause on a tile and placing it on the board. Then, the facilitator asks participants to identify relationships between factors, and the facilitator draws arrows between them. The facilitator invites participants to determine which one is the strongest (weight 5) and which one is the weakest (weight 1) arrow. The participants assign weights to all the other relationships (weights 2-4). When the map is complete, the facilitator takes a picture of the map. We have used this technique successfully in many projects [27-30].

We will digitize the maps with yEd (yWorks GmbH) software that generates, imports, and manages diagrams [31]. We will undertake fuzzy transitive closure to determine all possible indirect relationships between factors as part of a longer causal pathway of connected factors [25]. Social network analysis will identify the digitized maps' most influential perceived causes and critical intermediate outcomes [23]. Stakeholders will compare the map based on the scoping review with their own maps of perceived causes of domestic human trafficking. The scoping review and stakeholder maps will provide the evidential base for deliberative dialogue.

Results

This project received financial support in March 2023. We expect to start this project in March 2024. We recruited 2 research staff to conduct the scoping review. We expect to publish the scoping review results in March 2025.

Discussion

Expected Findings

This scoping review will collate and synthesize the published literature on factors influencing domestic human trafficking in Africa.

The review will highlight the relationships associated with domestic human trafficking, allowing researchers and practitioners to focus on them to design and target their interventions, potentially increasing their effectiveness. The review will determine the most influential "pathways," from potential causes to the outcome of domestic human trafficking. It will identify gaps in the evidence and guide future research.

Human trafficking involves interconnected social, geographic, health, legal, new technologies (artificial intelligence and social media), political, and economic factors. Therefore, the scoping review findings could be relevant to researchers and practitioners from many disciplines.

We expect some challenges in conducting the review. The published literature overlaps the concept of human trafficking with other concepts, such as smuggling and internal migration. Few studies might be conducted on domestic human trafficking. Much domestic human trafficking occurs underground and is unrecognized and underreported. To ensure we effectively capture studies of domestic human trafficking, we will adjust the search strategy based on the text of the initially identified articles. We will document changes to the initial search matrix.

The scoping review may reveal a wide range of relationships reported in the literature, making it difficult to identify the most influential ones. The transitive closure of the fuzzy cognitive maps from the scoping review will help objectively determine the most influential "pathways" from potential causes to the outcome of domestic human trafficking [25,32].

This review will inform the design of evidence-based policies and guide future research efforts.

Conclusions

Research on human trafficking in Africa is growing; this review will collate all the currently available evidence on factors influencing domestic trafficking. It will inform evidence-based policies and guide future research efforts.

Acknowledgments

The authors would like to thank Genevieve Gore, who supported the adjustment of the search strategy. This work was supported by a Canadian Institute Research grant (185767). The financial sponsor did not participate in the review.

Data Availability

Data sharing does not apply to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

LB designed the scoping review protocol. AR-C, LB, and IS developed the search strategy. LB and IS developed the inclusion and exclusion criteria. AD and IS provided expertise in synthesizing the results. NA and AC contributed to the overall approach of the protocol. LB, AC, and NA drafted the manuscript. All authors read, provided feedback on the several drafts, and approved the final manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA flow diagram.
[DOCX File , 60 KB - resprot_v13i1e56392_app1.docx]

Multimedia Appendix 2
Search strategies in electronic databases.
[DOCX File , 15 KB - resprot_v13i1e56392_app2.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Characteristics of Student-Led Clinics in the Allied Health Professions: Protocol for a Scoping Review

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Abstract

Background: Student-led clinics can provide students from allied health professions with the opportunity to gain valuable placement experience as an integral component of their preregistration program, enabling them to develop their competencies, professional skills, and administrative and leadership skills. Student-led clinics have the capacity to help meet the demand for appropriate practice-based learning opportunities, as there is an expectation that all allied health professions students should have high-quality learning experiences, ensuring the future workforce is fit for purpose. An overview of existing student-led clinics will increase our understanding of key characteristics, assisting education providers who may be considering the development of their own clinics. This will include key factors to ensure that this model of practice-based learning meets the needs of service users, students, and education providers.

Objective: This scoping review aims to increase our understanding of the characteristics of student-led clinics by answering the questions (1) what student-led clinics exist in the allied health professions, and (2) what are their characteristics?

Methods: This scoping review has been developed in conjunction with Joanna Briggs Institute methodology. We will consider studies and publications that include student-led clinics as an integral part of the preregistration curriculum for allied health professions students as defined by the Health and Care Professions Council. An extensive search of electronic databases will be conducted, including PubMed, MEDLINE, and CINAHL, among others. Search strategies, including the identified keywords and index terms, will be modified for each included database used. Reference lists of all included evidence will be screened for additional relevant studies. Studies published in English with no date limitations will be included. Relevant sources will be imported into Covidence for screening conducted by 2 reviewers (SR and KB). Data extraction will be conducted by 2 reviewers using a piloted data extraction tool, and data will be charted and tabulated using the Template for Intervention Description and Replication (TIDieR) checklist. Data will be presented with a narrative summary and illustrated by graphs and figures. The scoping review will be reported in conjunction with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews) and the STORIES (Structured Approach to the Reporting In health care education of Evidence Synthesis) statement for health care education evidence synthesis.

Results: An initial limited search was conducted in February 2024. The study will be conducted in 2025. Publication of the results is expected in late 2025.

Conclusions: This scoping review will provide key information regarding the characteristics of student-led clinics and will be of interest to preregistration education programs within the allied health professions who have an interest in exploring opportunities to address placement capacity issues.

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KEYWORDS

student-run clinic; student-facilitated clinic; allied health profession; interprofessional; higher education; university; tertiary education; preregistration; social care environment; practice based learning

Introduction

Background

Practice-based learning is a core component of preregistration allied health programs and provides students with a valuable opportunity to develop the necessary skills and gain experience in health care delivery [1]. Meeting the demand for practice-based learning opportunities within the context of a changing health and social care environment is, however, challenging [1]. Increased student numbers and funding availability have been identified as areas leading to an increased demand for practice-based learning opportunities [2]. Strategies such as exploring different approaches to the traditional models of practice-based learning, for example, hospital-based placements, could help to address practice-based learning capacity issues [3].

There is an expectation that all allied health professions students should have high-quality, practice-based learning opportunities to ensure that the workforce is fit for the future, is able to develop effective partnerships, and have the skills to be able to flourish within a changing health and social care environment [4]. In the United Kingdom, the Health and Care Professions Council (HCPC) standards for preregistration education require practice-based learning to be an integral part of allied health programs and outline the responsibility of education providers to ensure the quality of practice-based learning [5]. The AHP Principles of Practice Based Learning highlight the requirement for students to engage in a diverse range of practice-based learning opportunities in order to reflect current health care provision, support the development of the professions, and shape the workforce of the future [6].

Student-Led Clinics

Student-led clinics are a form of practice-based learning where students take responsibility for the organization and delivery of services under the supervision of staff [7]. They offer an innovative way of meeting demand in relation to providing opportunities for practice-based learning for allied health students, such as occupational therapy students. Student-led clinics are increasing as part of preregistration programs and provide experiential learning opportunities with a focus on clear goals and community services [8]. Student-led clinics present a valuable opportunity for students to participate in health care delivery [9]. The reasons for establishing student-led clinics internationally vary, but their focus could be on the support of underserved populations while addressing the challenges of meeting the demands of increasing student numbers and practice-based learning capacity issues [10]. Physiotherapy student-led clinics have demonstrated that they provide valuable educational opportunities for students while also providing cost-effective services to the public [11]. Student-led clinics can also provide valuable opportunities for interprofessional collaboration as they can be used to facilitate interprofessional learning experiences within a practice context [3]. In student-led clinics, students have the opportunity to develop their competencies and professional skills, as well as administrative and leadership skills, while also being able to take a lead role in the organization of the service being delivered under the supervision of a qualified health professional [7,12-14]. Other benefits of student-led clinics include the opportunity to interact with service users, work with students from other professions, learn about the role of other professions, and the development of clinical skills [7,15]. In addition, student-led clinics can enable students to develop their ability to demonstrate compassion and empathy for underserved populations and an opportunity to engage in experiences that may not normally be available as part of their education [9,16]. Reported benefits of student-led clinics include increased time for assessment and treatment, more holistic and integrated care, and increased access to services [17]. In contrast, the potential barriers to student-led clinics include sustainability from resource, time, and cost perspectives [7]. Other issues to be considered relate to the physical environment, such as space available and time commitments for practice educators [16]. This suggests that there are several factors to consider in the development of a student-led clinic, for example, its objectives, core features such as the patient population, the interprofessional care team, establishing community partnerships, and the use of technology [7,18]. Other factors to consider in the development of a student-led clinic are the structure of the clinic, its place within the curriculum [7], as well as engaging in a process of consultation with university stakeholders to explore the feasibility and accessibility of establishing a student-led clinic [19]. How the development of clinical skills would be measured, the training of educators, and the evaluation of outcomes for service users [7] would also be factors to consider in the development of a student-led clinic within an educational context.

However, limited research is available in relation to the characteristics of student-led clinics to guide their development in order to create effective educational opportunities for allied health students. As research related to student-led clinics is in its infancy [7], this review seeks to explore the characteristics of student-led clinics within the allied health professions in order to map and chart the existing evidence base, identify main concepts, and identify gaps in knowledge in this research area [20]. This will provide an in-depth understanding of the characteristics of student-led clinics within allied health professions, as the review will provide information relating to characteristics, such as types of clinics and students involved, aims of student-led clinics, populations served, and the place of the clinic within the curriculum [7]. This is with the aim of developing an effective solution to practice-based learning capacity issues as well as to inform future research. Exploring the existing evidence base in this area enables the development of student-led clinics to be based on current evidence and for valuable insight to be gained in relation to the purpose and characteristics of student-led clinics.

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Review Questions

This scoping review will focus on reviewing and collating data to provide an outline of the current body of research available in order to address the questions (1) what student-led clinics exist in the allied health professions, and (2) what are their characteristics?

Methods

Study Design

This review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews to ensure a systematic methodology that can be replicated [21]. This scoping review is available as a project on the open science framework [22]. It will be reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews) [20] and the STORIES (Structured Approach to the Reporting In health care education of Evidence Synthesis) statement for health care education evidence synthesis that provides specific guidance for reporting evidence synthesis within the context of health care education. This includes being specific about why a particular method of review was identified, how decisions were made in relation to the inclusion and exclusion criteria, and the process for data extraction [23].

Eligibility Criteria

Participants

This review will focus on preregistration students from allied health professions. Preregistration allied health programs are approved educational programs that lead to eligibility to apply for registration with a regulatory body such as the HCPC within the United Kingdom. A preregistration program can be defined as a pathway into a profession [24]. The allied health professions included will be the 15 professions currently regulated by the HCPC in the United Kingdom. These include art therapists, biomedical scientists, podiatrists, chiropodists, clinical scientists, dietitians, hearing aid dispensers, occupational therapists, operating department practitioners, orthoptists, paramedics, physiotherapists, practitioner psychologists, prosthetists, orthotists, radiographers, and speech and language therapists [5]. In countries other than the United Kingdom, the term allied health may include different professions; however, for the purposes of this review, only allied professions as defined by the HCPC will be included.

Studies will be excluded if they focus on nursing, pharmacy, dentistry, or medical students, as they would not directly address the review question, which focuses on student-led clinics within allied health professions.

Concept

The concept being mapped within this scoping review will be the characteristics of student-led clinics, where students take responsibility for the organization and delivery of services under the supervision of staff [7]. This review will consider studies relating to student-led clinics with any type of service users and will not focus on a particular condition, diagnosis, or service user group. The drivers of student-led clinics can be to facilitate student skill development, provision of clinical placement hours, and social enterprise and altruism [7]. Student-led clinics that have been established with these or similar aims will be included in the review. Specific areas of interest are the characteristics of student-led clinics, such as type and location, duration, aims, type of allied health students, and development activities of the student-led clinic. Studies will be included that focus on a range of methods of delivery of student-led clinics, such as face-to-face, online, or hybrid delivery. As student-led clinics should be led by students [25], studies will be excluded where clinics are run by educators or practitioners, as these would potentially not provide insight into students in a leadership role. Studies will also be excluded whose primary focus is on aspects of student-led clinics, such as evaluating student and service user outcomes, cost-effectiveness, and satisfaction with service provision. Although these areas have been highlighted as being relevant for future research into student-led clinics [7], they are beyond the scope of this review. The Template for Intervention Description and Replication (TIDieR) will be used to extract relevant information from studies in order to present an accepted and methodical description of the characteristics of student-led clinics [26].

Context

The scoping review will consider studies that specifically focus on clinics, regardless of geographical location, that are led by allied health students within a higher education context. This is so that the student-led clinics included in the review will provide a learning experience for students as well as provide services [27]. The review will include studies that focus on student-led clinics that are an integral part of the preregistration curriculum [28]. Studies that focus on student-led clinics within a university context that are a formal part of the education of health professionals [9] will be considered within this scoping review; this will include studies that use student-led clinics at different stages within the curriculum [7]. Student-led clinics that take place in environments outside of a university-based setting (community and hospital settings) will be considered for inclusion as long as they are an integral part of the preregistration curriculum.

Types of Sources

This scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. Text and opinion papers will also be considered for inclusion in this scoping review. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies will also be considered that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. In addition, reference lists of systematic reviews will be considered in order to identify potential studies.

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Review Team

The review is being conducted by a team comprised of experienced academics with an interest in occupational therapy practice-based learning (SR, KB, and KT).

Patient and Public Involvement

This scoping review protocol includes the involvement of KB who is a practice educator and academic.

Search Strategy

The search strategy aims to locate both published and unpublished studies. An initial limited search of MEDLINE, CINAHL, Cochrane Database of Systematic Reviews, PROSPERO (International Prospective Register of Systematic Reviews), and JBI Evidence Synthesis was conducted. There are 3 systematic reviews, a rapid evidence assessment, and a rapid review registered with PROSPERO with a focus on student-led clinics. The systematic review protocols identified focused on different aspects of student-led clinics, such as health interventions for adults with or at risk of chronic disease [29]; patient, client, consumer, and student outcomes of participating in a student-led clinic [30]; and colorectal cancer screening in free clinics [31]. The rapid evidence assessment focuses on the assessment of student-assisted assessment and brief intervention clinics to address gaps in remote and rural health care [32]. The rapid review focuses on the impact and scope of student-led clinics, but with a focus on rehabilitation science and student and service user outcomes [33]. In addition, a scoping review has been published in the last 3 years on the characteristics of student-led groups and clinics, but this relates specifically to physical rehabilitation [7]. As the primary focus of this proposed scoping review will be on the characteristics of student-led clinics, such as the type and location, duration, aims, type of allied health students, and development activities of any student-led clinic, it is not anticipated that these reviews will result in duplication as they either have a specific focus on student and service user outcomes, a particular condition, an aspect of rehabilitation, or an area of practice (remote and rural).

While conducting the initial limited search, the term “student led clinic” was mainly used. However, as studies were available both within the United Kingdom and in a global context, the terms “student run clinic” and “student facilitated clinic” were also included in recognition that different terminology may be used. During the initial search, the inclusion of the term “placement” in addition to search terms relating to student-led clinics, allied health students, and education limited the studies available. The search terms relating to education were therefore expanded to try and ensure that studies relating to student-led clinics as a model of placement were identified. Following the initial limited search, the text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for PubMed, MEDLINE, CINAHL, ERIC, Science Direct, PsycArticles, PsycINFO, TRIP database, and ProQuest Nursing and Allied Health Database, ProQuest One Academic, The Cochrane Library, and JBI Evidence-Based Practice database (Multimedia Appendix 1). The search strategy, which will include all the identified keywords and index terms, will be modified for each included database or information source. The reference list of all the included evidence sources will be screened for any relevant additional studies. Gray literature will also be searched, which will include the allied health professional body websites of the 15 professions currently regulated by the HCPC in the United Kingdom. This will include the Royal College of Occupational Therapists, the Chartered Society of Physiotherapists, and also the Royal College of Podiatry, among others. The professional bodies may also be contacted to source relevant materials relating to student-led clinics as a model of placement. Dissertations will also be searched through the ProQuest One Academic database, which provides access to ProQuest Dissertations and Theses Global. Studies published in English will be included, as the resources for translation are not available, and date limiters will not be used.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into a bibliographic software, or citation management system, and duplicates removed (ProQuest Ref Works). Potentially relevant sources will be retrieved and imported into the Covidence screening and data extraction tool. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers (SR and KB) for assessment against the inclusion criteria for the review. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers (SR and KB). Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer (KT). The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [20].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers using a data extraction tool based on the TIDieR checklist [23,26]. The TIDieR checklist was selected to aid the charting of clinical components, including participants, concepts, context, study methods, and key findings relevant to the review question.

A draft extraction form is provided in Multimedia Appendix 2, which will be piloted and then modified and revised as necessary. There will be 2 reviewers, 1 for extracting and 1 for checking (SR and KB). Initially, both reviewers will independently review a selection of studies for consistency in relation to what is being extracted. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer. If appropriate, authors of papers will be contacted to request missing or additional data, as required. A logical and descriptive summary of the results that align with the questions of the review will be presented.

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Ethical Considerations

As the methodology of the scoping review consists of reviewing and collecting data from publicly accessible material, ethical approval is not required.

Results

The initial scoping search conducted in February 2024 indicated that there was sufficient literature available to answer the research questions. The study will be conducted in 2025, with publication of the results expected in late 2025.

Discussion

The scoping review will provide an outline of the current body of research relating to the characteristics of student-led clinics in the allied health professions that are an integral part of a preregistration curriculum. This scoping review will provide comprehensive information relating to the characteristics of student-led clinics across a range of allied health professions (as recognized by the HCPC), including arts therapists, biomedical scientists, podiatrists, chiropodists, clinical scientists, dietitians, hearing aid dispensers, occupational therapists, operating department practitioners, orthoptists, paramedics, physiotherapists, practitioner psychologists, prosthetists, orthotists, radiographers, and speech and language therapists [5]. The scoping review will also make an important contribution to gain a better understanding of how student-led clinics operate within preregistration programs.

This understanding of student-led clinics will contribute to the development of student-led clinics, gaining insight into their value in addressing placement capacity issues, and identifying gaps in knowledge in this research area and areas of future research [23].

It is important to highlight that there are some limitations in relation to conducting the proposed scoping review. While a comprehensive search strategy has been developed, there is a risk that some data that could have provided additional insights in relation to the characteristics of student-led clinics have been omitted. This risk is reduced by the process of searching gray literature and reference lists of included studies. As the aim of the scoping review is to identify and map evidence in a particular area [34], the studies included in the scoping review will not be critically appraised but will be used to develop insight and understanding in relation to the characteristics of student-led clinics. The reviewers therefore will be unable to comment on the quality of the studies that are included in the scoping review. In addition, the search strategy focuses on studies that have been published in English; therefore, some studies that would have been appropriate for inclusion, but published in other languages, could have been omitted from the scoping review.

The findings of the proposed scoping review will be of particular interest to preregistration education programs within the allied health professions, which have a focus on addressing placement capacity issues.

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Data Availability

All data that are relevant to the study are included within the article or uploaded as Multimedia Appendices 1-2.

Authors' Contributions

The design of the protocol and the drafting of the manuscript were conducted by SR, KT, and KB.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 22 KB - resprot_v13i1e58084_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 23 KB - resprot_v13i1e58084_app2.docx]

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Abbreviations

HCPC: Health and Care Professions Council
JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review
PROSPERO: International Prospective Register of Systematic Reviews
STORIES: Structured Approach to the Reporting In health care education of Evidence Synthesis
TIDieR: Template for Intervention Description and Replication

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Protocol

Wearables and Smartphones for Tracking Modifiable Risk Factors in Metabolic Health: Protocol for a Scoping Review

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Abstract

Background: Metabolic diseases, such as cardiovascular diseases and diabetes, contribute significantly to global mortality and disability. Wearable devices and smartphones are increasingly used to track and manage modifiable risk factors associated with metabolic diseases. However, no established guidelines exist on how to derive meaningful signals from these devices, often hampering cross-study comparisons.

Objective: This study aims to systematically overview the current empirical literature on how wearables and smartphones are used to track modifiable (physiological and lifestyle) risk factors associated with metabolic diseases.

Methods: We will conduct a scoping review to overview how wearable and smartphone-based studies measure modifiable risk factors related to metabolic diseases. We will search 5 databases (Scopus, Web of Science, PubMed, Cochrane Central Register of Controlled Trials, and SPORTDiscus) from 2019 to 2024, with search terms related to wearables, smartphones, and modifiable risk factors associated with metabolic diseases. Eligible studies will use smartphones or wearables (worn on the wrist, finger, arm, hip, and chest) to track physiological or lifestyle factors related to metabolic diseases. We will follow the reporting guideline standards from PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) and the JBI (Joanna Briggs Institute) guidance on scoping review methodology. Two reviewers will independently screen articles for inclusion and extract data using a standardized form. The findings will be synthesized and reported qualitatively and quantitatively.

Results: Data collection is expected to begin in November 2024; data analysis in the first quarter of 2025; and submission to a peer-reviewed journal by the second quarter of 2025. We expect to identify the degree to which wearable and smartphone-based studies track modifiable risk factors collectively (versus in isolation), and the consistency and variation in how modifiable risk factors are measured across existing studies.

Conclusions: Results are expected to inform more standardized guidelines on wearable and smartphone-based measurements, with the goal of aiding cross-study comparison. The final report is planned for submission to a peer-reviewed, indexed journal. This review is among the first to systematically overview the current landscape on how wearables and smartphones measure modifiable risk factors associated with metabolic diseases.

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KEYWORDS

wearable; smartphone; mHealth; metabolic disease; lifestyle; physiological; risk factor; mobile phone

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Introduction

Noncommunicable diseases lead to 41 million deaths per year globally and are estimated to cost, on average, more than US $2 trillion per year [1,2]. A large portion of noncommunicable diseases–related burden is attributed to a growing prevalence of metabolic diseases, namely type 2 diabetes, hypertension, hyperlipidemia, obesity, and, more recently, nonalcoholic fatty liver disease [3,4]. Metabolic diseases are projected to increase significantly, with diabetes prevalence rates expected to double from 529 million in 2021 to 1.3 billion in 2050, and related expenditures projected to surpass US $1054 billion by 2045 [5].

A large body of research has shown that metabolic diseases, for example, type 2 diabetes, are influenced by a complex network of modifiable factors. These include lifestyle factors (ie, nutrition, physical activity, sleep, stress, and substance abuse) and physiological markers (ie, blood sugar, triglycerides, and high-density lipoprotein cholesterol) [6-10]. Following complex systems perspectives, modifiable factors interact [11,12] and together shape disease outcomes over time, with up to 70% of cardiovascular disease cases and mortality attributed to modifiable risk factors [8,9,12].

In parallel, wearables (ie, devices worn on the wrist, finger, arm, and chest) and smartphones are increasingly used to track modifiable risk factors in daily life, with improved precision and accuracy [13]. These digital devices offer key advantages over lab-based measurements, such as continuous and person-specific data collection in (near) real-time. For instance, smartwatches can track physical activity and sleep patterns in the natural environment with minimal burden [14]. Further, mobile apps can detect dietary patterns through image-based food recognition [15] and brief ecologic momentary assessments [16] in free-living conditions. These high-dimensional, longitudinal data enable continuous monitoring and can be used to trigger personalized lifestyle interventions, for example by personalizing recommendations on nutrition, sleep, and physical activity [14,16,17]. By enabling remote monitoring, wearables, and smartphones can potentially improve access to care and reduce the costs of metabolic disease management [18,19] versus standard lab-based clinical approaches [20].

While studies increasingly demonstrate the promise of wearables for tracking, preventing, and managing metabolic diseases [21], several key gaps remain in the newly evolving field of digital metabolic health. Here, we focus on two gaps. First, recent perspectives highlight the importance of tracking multiple, modifiable risk factors in parallel (vs a single risk factor in isolation) for a more comprehensive lens into an individual's metabolic health profile [22]. However, the extent to which existing studies focus on multiple versus risk factors remains unclear. Second, alongside the proliferation of wearables and smartphones, there are concerns regarding data comparability, even when researchers aim to measure the same risk factors [23]. Specifically, there is growing evidence of incommensurability, with researchers employing different operationalizations and measures of the same risk factors (ie, physical inactivity), thus making direct cross-study comparisons challenging. This heterogeneity can make it difficult to directly track between-study effects [20] and present a barrier to building cumulative and generalizable knowledge [24]. Motivated by these gaps, it is essential to examine which modifiable risk factors are measured using wearables and smartphones and how recent work has begun to overview the use of different wearable technologies in cardiometabolic diseases [20] and the role of digital health technologies in metabolic disorders among older adults, more broadly [25]. However, to our knowledge, no studies have specifically focused on the landscape of modifiable risk factors. Thus, we aim to address the two questions, that are (1) Which modifiable risk factors are most often studied in wearable and smartphone-based metabolic health research? and (2) To what extent are measures of modifiable risk factors consistent across studies, particularly in measurement methods?

Gaining a comprehensive understanding of the current landscape of modifiable risk factors, tracked using wearables and smartphones, is crucial to inform more consistent measurement guidelines. Given the broad nature of the inquiry and the emerging status of the field, we deemed a scoping review the most appropriate method for investigating these research questions.

Methods

Overview

We will follow the 2020 JBI methodological guidance for scoping reviews [26,27], developed by the JBI Scoping Review Methodology Group. Accordingly, our scoping review is structured to follow seven stages, which consist of (1) title and research question, (2) identifying inclusion criteria, (3) identifying a search strategy, (4) evidence screening and selection, (5) data extraction, (6) data analysis, and (7) presentation of results. To guarantee adherence to reporting, we will also follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [28].

Stage 1: Title and Research Question

The title was developed based on the PCC (population, concept, and context) mnemonic [26], with a focus on the concept and context, namely wearables and smartphones for modifiable risk factors. The title does not explicitly mention the study population due to our broad inclusion criteria (eg, any adults). Motivated by gaps in previous work [20,29] and a lack of overview in the field, this scoping review aims to systematically describe (1) which modifiable risk factors are most often studied in wearable and smartphone-based metabolic health research, and (2) to what extent are measures of modifiable risk factors consistent across studies in terms of measurement methods.

Stage 2: Inclusion and Exclusion Criteria

Eligible studies will be peer-reviewed, written in English, published in 2019 and after (to reflect the most current literature and build on previous work [30]); and will include a full-text version. Given our research aims, eligible studies will: (1) measure lifestyle and physiological factors relevant to metabolic health, use (2) smartphones or wearables worn on the wrist, finger, arm, and chest, and (3) analyze the generated wearables or smartphone data for outcome assessment related to metabolic

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health. Qualitative studies will be excluded. Building on previous work [30], we will include wearable devices that cost <€500 (US $570) per device hardware, consistent with price cut-offs in previous work [30]. We will include membership-based devices. The study population will include adults aged 18 years and older. We will use institutional journal subscriptions and interlibrary loan services to access studies, and in cases where no full text is available, authors will be contacted with a waiting period of 7 days before study exclusion. Textbox 1 presents the study's inclusion and exclusion criteria.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion Criteria

- Peer-reviewed empirical study
- Published from 2019 to 2024
- The study involves wearables or smartphones for data collection
- The study focuses on modifiable risk factors in metabolic health or disease contexts (a minimum of one factor from Table S1 in Multimedia Appendix 1 is included)

Exclusion Criteria

- The article is not in English
- The publication type is not an original empirical article (ie, conference abstract, commentary, or letters to the editor)
- No quantitative analyses
- Wearable costs≥500€ (US $570)
- Study population age <18 years
- Primary research objectives and analyses do not involve wearable or smartphone-collected data, or the outcome is not related to metabolic health

Stage 3: Search Strategy

Building on the most recent reviews in the wearable, digital health, and metabolic health domains [20,29], we identified key search terms capturing wearables or smartphones and prominent modifiable risk factors associated with metabolic diseases [6]. A full list of key search terms can be found in Table S2 in Multimedia Appendix 1. We will search the following 5 major databases, that are Scopus, Web of Science, PubMed, Cochrane Centralized Register of Controlled Trials, and SportDiscus. Identified studies will be imported into the systematic review tool Rayyan developed by the Qatar Computing Research Institute [31].

Stage 4: Evidence Screening and Selection

Study evidence screening and selection will be performed based on the inclusion and exclusion criteria (see Textbox 1). We will first screen the title and abstract based on the predefined criteria, followed by screening the full text. This process will be conducted by 2 reviewers in parallel, and any discrepancies in study eligibility will be resolved by a third reviewer.

Stage 5: Data Extraction

For each eligible study, we will extract information using a standardized data charting form. In total, 2 reviewers will manually chart the extracted information, and a third reviewer will resolve any discrepancies. The data charting form is presented in Table 1. The data charting form is adapted from prior work [25].

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Table 1. Data charting form.

Charting information	Explanation (if applicable)
Authors	—[a]
Year of publication	—
Country of origin	Where the study was conducted
Population type	Healthy, at-risk, clinically diagnosed
Population demographic	Age or gender or race
Sample size	—
Intervention	Yes or no
If yes, intervention type	—
If yes, duration of intervention	—
Type of wearable	That is a wrist-worn wearable, smartphone, and mobile application.
Modifiable risk factor	That is (a) physiological risk factor, (b) lifestyle risk factor, (c) or both
Modifiable risk factor measure	risk factor type (ie, physical activity)
Unit of measurement	Measure operationalization (ie, step count per day)
Sampling method	That is (a) ecological momentary assessment or self-report; (b) passive sensing.
Measure sampling frequency	—
Overall measurement duration	—
Number of total risk factors	—

[a]Not applicable.

Stages 6 and 7: Data analysis and presentation of results

Following the data charting process outlined in Table 1, the gathered data will be synthesized and summarized in descriptive tables and figures. According to our first research question, we will categorize the modifiable risk factors per each study. Next, we will aggregate the overall prevalence of each modifiable risk factor and the proportion of studies that measure single or multiple modifiable risk factors. Based on our second question, we will describe the measures used to operationalize the most prevalent factors, and we will overview the overlap (vs discrepancies) in measurement, that is, how consistently risk factors are measured across studies. The findings will be summarized and communicated through tables and figures. Relevant findings will be communicated to diverse stakeholders, such as digital metabolic health researchers, healthcare professionals, digital health interest groups, metabolic disease patient organizations, and health insurance providers, through presentations and workshops.

Ethical Considerations

No ethics approval is required for this study as it does not involve conducting trials or collecting primary data.

Results

A structured search strategy was developed to summarize the landscape of modifiable risk factors for metabolic health and their measurements in the context of wearable and smartphone research. As of the submission of this protocol in October 2024, no data collection has begun. Data collection is scheduled to begin in November 2024, with data analysis set to start in the first quarter of 2025. The results are anticipated to be submitted for peer-reviewed publication as a scoping review by the second quarter of 2025 and will be disseminated through publication in relevant journals and presentations at conferences.

Discussion

Anticipated Findings

Prior research [8,29,32] has demonstrated that multiple modifiable risk factors jointly contribute to metabolic disease outcomes. In parallel, a growing number of studies are leveraging wearables and smartphones to track metabolic diseases in daily life (for example, [33,34]). However, it remains unclear whether existing studies examine multiple modifiable risk factors simultaneously or focus on a single factor in isolation. Our results are expected to reveal whether, and the degree to which, studies examine a range of modifiable risk factors in parallel, thereby offering a comprehensive approach, or if they predominantly isolate a single factor, which would suggest a gap in integrating broader determinants of metabolic diseases. Anticipated findings may indicate that certain risk factors, such as physical activity or diet, are more commonly tracked, while others, like stress or sleep, might be underrepresented, thereby revealing potential gaps in the current research focus. Our results could also highlight a strong consistency in the way risk factors are measured (eg, uniform use of validated metrics across studies) or substantial variation in measurement approaches. In the latter case, this inconsistency

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could point to challenges in comparing or integrating findings across different studies, thereby underscoring the need for standardization in risk factor measurement using wearables and smartphones.

The scoping review is expected to extend the existing literature in several ways. First, Lee et al [20], have begun to outline the characteristics of wearable devices to track cardiometabolic outcomes, but have not examined the degree to which studies examine different risk factors collectively, nor the consistency in measurement across studies. Our review aims to fill these gaps by systematically assessing the extent to which different risk factors are measured together (rather than in isolation), and by evaluating the consistency in measurement across studies. Previous reviews have primarily focused on the application of wearables or digital health technologies within the context of a single disease such as obesity or diabetes [23,35-37], or a single risk factor (eg, nutrition, physical activity, or stress) [14,38-41]. In contrast, our scoping review aims to provide a more comprehensive risk-factor perspective in a broader metabolic health framework.

To the best of our knowledge, this protocol is among the first systematic attempts to outline the current landscape of modifiable risk factors in digital metabolic health research, with a particular focus on the consistency of risk factor measurement across studies. We expect this research to contribute to existing knowledge by systematically scoping the variability in wearable and smartphone-based measurements, thus paving the way for improved measurement standards and comparability across studies. This scoping review will have several limitations, such as only including literature restricted in English, and quantitative empirical studies, which may omit more recent qualitative or industry developments. Our results will be specific to body-worn wearables costing up to €500 (US $570), a price point that may still be considered expensive. As such, some wearables included in our analysis may still be financially out of reach for many, reflecting a potential barrier to accessibility. We will also exclude other potentially relevant devices that are not worn on the body such as breath analyzers. Furthermore, there is often no consensus on the definition of metabolic health in the literature [42], which may lead to varied interpretations of metabolic risk factors. However, drawing from previous studies, we have compiled an extensive list of modifiable risk factors, encompassing both lifestyle behaviors and physiological indicators [43-50]. Future research may compare how different risk factors, and measurement approaches, predict metabolic disease outcomes.

Conclusion

Overall, this scoping review aims to synthesize existing research on how wearable and smartphone-based studies track modifiable risk factors in digital metabolic health. This work may potentially motivate the development of measurement reporting standards, thereby improving the consistency and applicability of measurements in digital metabolic health studies.

Authors' Contributions

VB and MJ conceived the idea. VB wrote the first version of the manuscript. TK and MJ provided feedback on the manuscript and revised it. TK and MJ provided methodological guidance.

Conflicts of Interest

VB, TK, and MJ are affiliated with the Centre for Digital Health Interventions, a joint initiative of the Institute for Implementation Science in Health Care, University of Zurich, the Department of Management, Technology, and Economics at Federal Institute of Technology Zurich, and the Institute of Technology Management and School of Medicine at the University of St. Gallen, Centre for Digital Health Interventions is funded in part by Mavie Next, an Austrian health care provider, Christian Social Health Insurance of Switzerland, a Swiss health insurer, and MedTech Innovation partners, a growth equity firm. TK was also a cofounder of Pathmate Technologies, a university spin-off company that creates and delivers digital clinical pathways. However, Mavie Next, Christian Social Health Insurance of Switzerland, MedTech Innovation partners, and Pathmate Technologies were involved in this protocol. All other authors have no conflicting interests.

Multimedia Appendix 1
Search strategy for modifiable risk factors in metabolic health studies.
[DOCX File , 28 KB - resprot_v13i1e59539_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PCC: population, concept, and context

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Evaluation Methods, Indicators, and Outcomes in Learning Health Systems: Protocol for a Jurisdictional Scan

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Abstract

Background: In learning health systems (LHSs), real-time evidence, informatics, patient-provider partnerships and experiences, and organizational culture are combined to conduct "learning cycles" that support improvements in care. Although the concept of LHSs is fairly well established in the literature, evaluation methods, mechanisms, and indicators are less consistently described. Furthermore, LHSs often use "usual care" or "status quo" as a benchmark for comparing new approaches to care, but disentangling usual care from multifarious care modalities found across settings is challenging. There is a need to identify which evaluation methods are used within LHSs, describe how LHS growth and maturity are conceptualized, and determine what tools and measures are being used to evaluate LHSs at the system level.

Objective: This study aimed to (1) identify international examples of LHSs and describe their evaluation approaches, frameworks, indicators, and outcomes; and (2) describe common characteristics, emphases, assumptions, or challenges in establishing counterfactuals in LHSs.

Methods: A jurisdictional scan, which is a method used to explore, understand, and assess how problems have been framed by others in a given field, will be conducted according to modified PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. LHSs will be identified through a search of peer-reviewed and gray literature using Ovid MEDLINE, EBSCO CINAHL, Ovid Embase, Clarivate Web of Science, PubMed non-MEDLINE databases, and the web. We will describe evaluation approaches used both at the LHS learning cycle and system levels. To gain a comprehensive understanding of each LHS, including details specific to evaluation, self-identified LHSs will be included if they are described according to at least 4 of 11 prespecified criteria (core functionalities, analytics, use of evidence, co-design or implementation, evaluation, change management or governance structures, data sharing, knowledge sharing, training or capacity building, equity, and sustainability). Search results will be screened, extracted, and analyzed to inform a descriptive review pertaining to our main objectives. Evaluation methods and approaches, both within learning cycles and at the system level, as well as frameworks, indicators, and target outcomes, will be identified and summarized descriptively. Across evaluations, common challenges, assumptions, contextual factors, and mechanisms will be described.

Results: As of October 2024, the database searches described above yielded 3503 citations after duplicate removal. Full-text screening of 117 articles is complete, and 49 articles are under analysis. Results are expected in early 2025.

Conclusions: This research will characterize the current landscape of LHS evaluation approaches and provide a foundation for developing consistent and scalable metrics of LHS growth, maturity, and success. This work will also serve to identify opportunities for improving the alignment of current evaluation approaches and metrics with population health needs, community priorities, equity, and health system strategic aims.

Trial Registration: Open Science Framework b5u7e; https://osf.io/b5u7e

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KEYWORDS

learning health systems; evaluation; jurisdictional scan; counterfactuals; LHS; health system; real-time evidence; informatics; organizational culture; learning cycles; benchmark; patient care; gaps; health care; inequities; development; implementation; intervention; new approach

Introduction

Evidence-to-practice gaps in health care contribute to inefficient and ineffective care, ballooning costs, poor experiences for patients, frustration and burnout for health care providers, and widening health inequities [1]. In response to these challenges, there is a growing emphasis on the development, implementation, and evaluation of learning health systems (LHSs). LHSs address gaps between knowledge and practice by combining real-time evidence, informatics systems, patient-provider partnerships and experiences, and institutional strategies in learning cycles, which support continuous innovation and improvements in care [2]. Worldwide, various health care organizations have adopted LHS approaches, and while the objectives are often consistent, evaluation methods (both within learning cycles and at the system level) and markers of growth, maturity, and success tend to be more variable and incomprehensively described [3,4]. Evaluation approaches within learning cycles of LHSs, and of LHSs themselves, often depend on factors such as data availability, quality, and sharing restrictions (particularly for routinely collected data to inform baseline measures), context, time, experimental methodology, and knowledge translation [5,6]. This results in variable feasibility, applicability, and relevance across settings and presents a challenge for identifying what a "successful" LHS looks like in practice; determining the overall effectiveness of LHS on patient, provider, population, cost, and equity outcomes; and continuously improving how LHSs operate.

When LHSs conduct cycles of data collection, knowledge synthesis, and practice change [7], they often use "usual care" or "status quo" as the benchmark or counterfactual for comparing new interventions or approaches. However, in the evolving landscape of pragmatic and realist research, teasing apart what is "usual" or what would happen if an event or condition had been different has become a challenging endeavor as a result of the complexity of the system and subsequent interventions. This is particularly a challenge when attempting to disentangle components that contribute to success in new care solutions from the multifarious existing care modalities found across settings [5]. As a result, empirical evidence has occasionally revealed unexpected outcomes when comparing complex care models or approaches to usual care, wherein, for example, the introduction of novel elements, such as health care worker interventions featuring more frequent touchpoints and early health challenge detection, can paradoxically result in adverse outcomes, such as increased hospital admissions [8,9]. Assessing the impact of new care models in an LHS should be assessed holistically, including investigation into not just "what works" but also questions about "for whom, under which circumstances, and why?" [10].

Despite best efforts to share methodological innovations and lessons learned specific to LHSs, a comprehensive scan of existing LHS evaluation approaches is needed. This protocol describes a jurisdictional scan to scope and characterize the evaluation approaches and methodologies in international examples of self-identified LHSs with the following objectives:

1. Identify international examples of LHSs and describe their evaluation approaches, frameworks, indicators, and outcomes
2. Elucidate common characteristics, emphases, assumptions, or challenges described in establishing counterfactuals in LHS research, and describe how these counterfactuals impact the evaluation process

Methods

Overview

Jurisdictional scans are used to explore and understand how problems have been framed by others in a given field and to compare and assess the strengths and weaknesses of each approach [11]. In addition, they aim to produce policy-relevant results by including details of the problem in context, making them useful tools for understanding how a specific initiative has been framed, conducted, or disseminated in other jurisdictions [12]. This approach was selected over others such as a narrative review, which provides a detailed description of a topic but without an emphasis on policy relevance, or a realist review, which seeks to understand contexts and mechanisms associated with intervention outcomes due to its use for performing comparative analyses, identifying practical implementation insights, and highlighting context-specific information. This approach is fitting for LHSs because the concept of an LHS is often interpreted, envisioned, and constructed differently across contexts due to its relative novelty; variety of frameworks available; and context-driven priorities, resources, and leadership [13]. The results of this jurisdictional scan will summarize insights, key learnings, challenges, and implementation considerations with attention to both context-specific factors and generalizability across settings. This jurisdictional scan will use a literature review to identify potentially relevant LHSs.

Theoretical Approach

The LHS Action Framework [13,14] (Figure 1) informs the authors' approach to understanding LHSs. This framework was developed by consolidating existing LHS frameworks in the literature, and it describes how research and health care

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operations are linked and enacted in a comprehensive LHS approach to advance population health and health equity. It was produced to identify capabilities necessary to enact the learning elements required, including key questions and methods, to ensure a systematic approach to learning and achieve equity-centered quadruple aim metrics. The LHS Action Framework has five learning gears: (1) analytics and population insights; (2) evidence synthesis; (3) patient, caregiver, and provider co-design; (4) implementation; and (5) evaluation, and three health system gears representing different care settings, services, and institutions. In this review, the focus is on the evaluation gear while acknowledging the relevance to and impact of the other 4 gears on LHS evaluation.

The Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions [10] will guide the assessment of how each LHS conducts evaluation. LHSs, either at the learning cycle or system level, are complex interventions as they often involve implementing and integrating multiple and diverse components and targeting a range of behaviors among different populations and settings, and require broad and varied expertise and skills [10]. The MRC framework not only guides consideration for whether an intervention achieves its intended outcome but adds relevant context such as value relative to required resources, peripheral intended or unintended impacts, theoretical underpinnings, interactions with the broader environment, and contributions to system change and decision making. This framework is particularly relevant to LHSs as it also focuses on the individuals involved in determining evaluation questions and outcomes and how those individuals are impacted by an intervention, consistent with a core pillar of LHS models that emphasize patient and health care provider perspectives [2,13].

In absence of specific reporting guidance for jurisdictional scans, the authors adapted the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist (Multimedia Appendix 1). An information specialist (AG) with expertise in LHSs and international terminology used to describe them supported the search development and implementation across Ovid MEDLINE, EBSCO CINAHL, Ovid Embase, Clarivate Web of Science, and PubMed non-MEDLINE databases, as well as gray literature and relevant websites (the search strategy is shown in Multimedia Appendix 1). The search strategy was built based on the search by Enticott et al [15] and defines LHSs according to the Institute of Medicine's [16] definition, "a system in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and healthcare." Authors will also leverage professional networks to identify relevant sources of literature in the form of websites, newsletters, or online or print reports.

Figure 1. Learning Health System Action Framework (reproduced from Reid et al [13], which is published under Creative Commons Attribution 4.0 International License [14]).

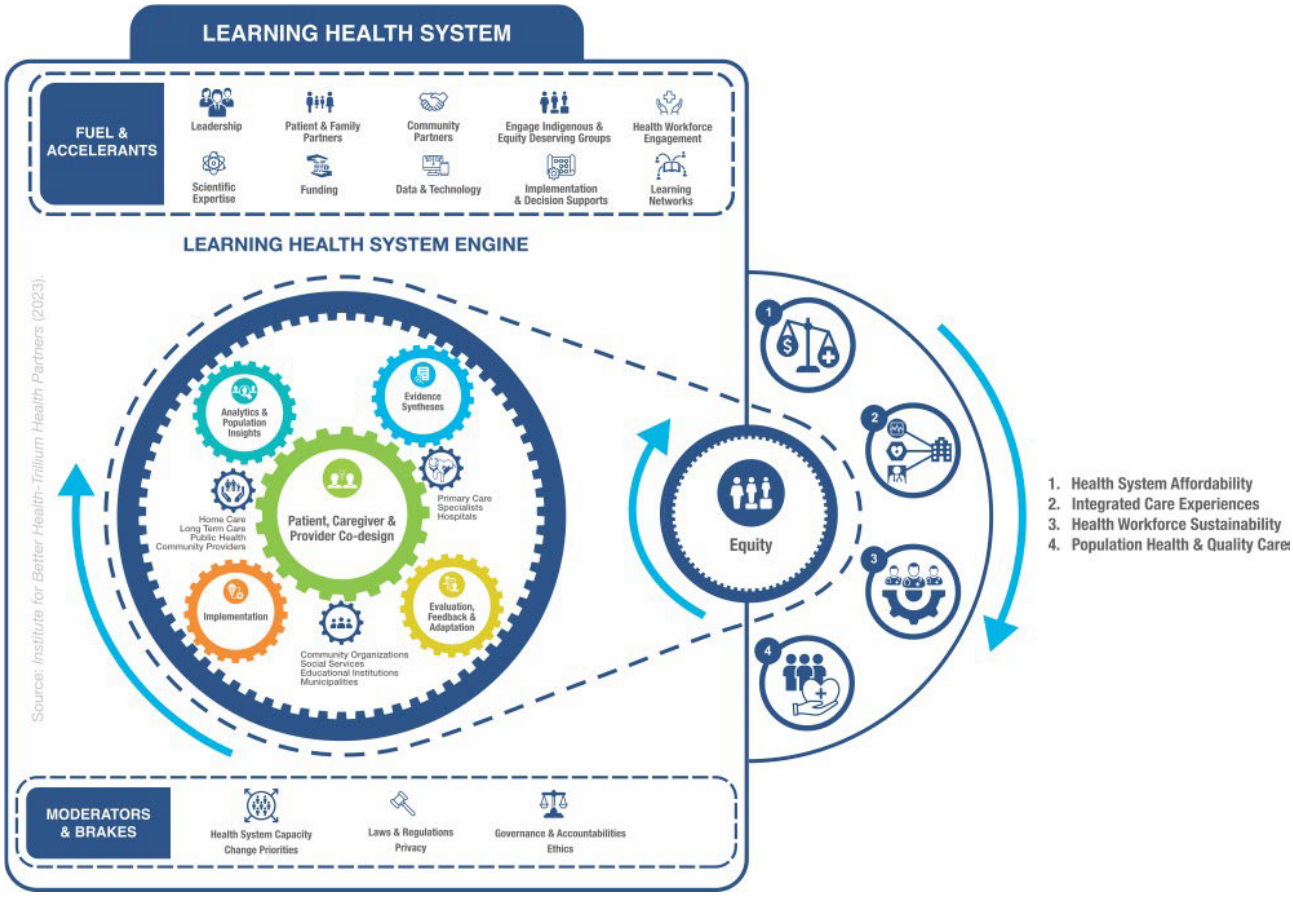

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Eligibility Criteria

LHSs that are self-described as such in peer-reviewed journal articles, reports, and web pages will be considered for inclusion. Authors must self-identify their LHS using at least one of the following descriptors, which were informed by existing literature [17] to ensure international and context-specific terminology for LHS were captured:

1. Learning health[care] system
2. Learning health[care] network
3. Learning collaborative
4. Learning laboratory
5. Community-clinician participatory data health care research
6. Data-driven improvement initiative
7. Practice-based data or research network
8. Circular data-driven health care
9. Rapid LHS

Only literature published after 2007, when LHSs were formally conceptualized [18], and those written in English will be considered. LHSs will only be included when described in sufficient detail according to at least 4 of 11 criteria that describe LHSs, which were informed by the LHS Action Framework and other literature [4,13,19] (core functionalities, analytics, use of evidence, co-design or implementation, evaluation, change management or governance structures, data sharing, knowledge sharing, training or capacity building, equity, and sustainability), to facilitate a fulsome description of the system within the resultant papers. Given that there is a great deal of ambiguity in how LHSs are defined and described, broad inclusion criteria were chosen based on a review of candidate papers, discussions with leaders in this topic, and team knowledge of varied terminology used to describe LHSs across regions and contexts. Therefore, an LHS described only as a research setting, for example, but without further information will not be included. Multiple publications about a single LHS may be combined to pool information about these characteristics if needed; reference lists of each included paper will be reviewed to identify complementary articles. Ideally, each identified LHS will include a description of its evaluation approach either at learning cycle or system levels, but articles that describe LHSs without information about evaluation will still be included to highlight gaps in the literature where they may exist.

A total of 3 independent screeners (SV, CW, and MB) will review all titles and abstracts identified in the literature search in Covidence in duplicate. Authors SV, CW, and MB will resolve any uncertainties and verify the final sample. A data extractor (BP) will independently code each LHS according to the 11 possible constructs listed above, which will then be reviewed by the study team (SV, CW, and MB) to verify accuracy and reach a consensus for inclusion. Team meetings will be held biweekly to review progress, resolve queries, and troubleshoot issues.

Data Extraction

Each included LHS will be described according to the following core evaluation characteristics, where data are available. For a full description of extraction criteria definitions, refer to Table S1 in Multimedia Appendix 1.

- LHS objectives
- At the learning cycle level:
  - Evaluation, feedback, and adaptation approaches, mechanisms, and methods
  - Data sources, including counterfactuals
  - How counterfactuals are established and defined
- At the system level:
  - Evaluation methods
  - Evaluation framework
  - Metrics, indicators, or outcomes of growth, maturity, or success
  - Strategies for routine data collection, quality, and accessibility or sharing
  - Evaluation data sources
- Change management and governance structures
- Contextual factors (eg, system priorities, breadth, and resources; time; and clinical population)
- Data and infrastructure sharing processes
- Personnel involved in evaluation
- Knowledge sharing practices

Additional descriptors, where available, will include:

- LHS name
- Country
- Sector(s) involved (primary care; hospital; specialist care; long-term care; community, population, or public health; industry; and other)
- Patient population(s) served
- Patient population size
- Personnel involved (patients, health care providers, operational staff, leadership, and other)
- Reference to grounding framework or model or theoretical development

Analysis

Data analysis for this review will follow a 2-stage process aimed at addressing our two research objectives, which are (1) to identify international LHS and describe their evaluation approaches, frameworks, indicators, and outcomes, and (2) to determine common facilitators and challenges described in establishing counterfactuals in LHS research. A combination of quantitative (ie, frequency counts) and qualitative (ie, thematic analysis of publication text) methods will be used to summarize findings relevant to each objective. From these findings, we will generate a summary of recommendations for evaluation approaches and future research, aimed at both individual LHS learning cycles and LHSs more broadly. It is anticipated that this analysis process may also yield gaps in the literature, especially on the establishment of counterfactuals in LHS research. Regardless of the comprehensiveness of our findings, we will discuss the implications of what was not reported and provide recommendations of where future work can be focused in order to strengthen the field of LHSs. The data extraction form is shown in Multimedia Appendix 1. All data will be extracted into a spreadsheet through Airtable (Formagrid, Inc) [20] and descriptors will be summarized as appropriate.

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Patient Partnership and Knowledge Translation Plan

Using the Knowledge-to-Action framework by Graham et al [21], authors will develop an active knowledge translation plan by (1) identifying key messages arising from this scan, (2) determining the principal target audience for each of these messages, (3) seeking and involving the most credible messenger for these messages, and (4) launching a knowledge translation strategy that is grounded in the best available evidence. Drawing upon a diverse range of approaches to disseminate the results of this scan, including a virtual symposium that will bring together the key target audience of this research, publishing our results, and presenting findings at local and international scientific conferences, these strategies will ensure that these findings reflect the needs of the end users of this information and facilitate appropriate sharing of outputs. The study authors lead an international LHS collaboration hub and will co-design the next steps, guided by the findings of this work, alongside multidisciplinary health system leaders, patient and community partners, clinicians, and policy makers.

Anticipated Challenges

There may be potential challenges related to this jurisdictional scan. First, the yield of the literature search may be more extensive than anticipated. To overcome this, authors will work closely with the information specialist to ensure that the scope of the scan is manageable but comprehensive. Second, it is anticipated that for many LHSs, it will be challenging to discern or categorize evaluation characteristics solely from what is described and published. Corresponding authors of published literature will be contacted through email to obtain additional details when necessary.

Results

As of October 2024, the database searches described above yielded 3503 citations after duplicate removal. Full-text screening of 117 articles is complete, and 49 articles are under analysis. Results are expected in early 2025.

Discussion

Expected Findings

This jurisdictional scan will serve to map and characterize existing self-identified international LHSs and provide an improved understanding of how these LHSs conduct evaluations both within learning cycles and at the system level. Many LHSs worldwide have not yet reached full maturity or may not have established fulsome evaluation approaches [2,22], which adds complexity to this work but will help identify opportunities for improvement, collaboration, and resource development. Although available literature does report on common LHS objectives and how they are operationalized [4,23], approaches to comprehensive LHS evaluations at the system and learning cycle level have not yet been identified, summarized, and presented. Furthermore, once described, there is a need to understand what constitutes success of adopting an LHS approach, how it is attained and maintained, and what would happen if the LHS had not been implemented. This study will address this research gap.

This jurisdictional scan may have some limitations. While we will use a comprehensive search strategy developed by a research librarian, the reliance on self-report to identify LHSs means that this review may not identify or capture all LHSs and their evaluation approaches, especially as some may be unreported or documented internally within health systems. We also anticipate considerable variation in the approach and scale of LHS evaluations, which may make data synthesis challenging; however, this study is intended to be descriptive and will provide an evidence base that may guide more consistent evaluation approaches in the future.

Conclusions

By describing how LHSs currently conceptualize success and measure impacts on patient, provider, population, cost, and equity outcomes, knowledge generated from this research will contribute to the development of harmonized criteria health system leaders, researchers, and community partners can use to benchmark progress of a maturing LHS and set context-relevant targets for evaluation, growth, and improvement. This work will also serve to identify opportunities for improving the alignment of current evaluation approaches and metrics with population health needs, community priorities, and health system strategic aims. We will leverage a Canadian network of health system leaders, clinicians, researchers, trainees, and patient and community partners to communicate and build upon the findings of this work, which will increase its potential to be used as foundation for building evaluation tools, frameworks, and resources.

Acknowledgments

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Data Availability

No primary data have been generated or analyzed at this stage. All data sources will be properly cited and referenced in the final publication. The datasets analyzed during this scan will be available from the corresponding authors of the original studies. Any supplementary materials or datasets generated during the review process will be made available on study completion with reasonable request.

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Authors' Contributions

SV, MB, and CW conceptualized the study, drafted the manuscript, and will perform article screening to collect data. AG created and implemented the search strategy. BP will extract and analyze data and contributed to drafting the manuscript. All authors approved the final manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist, search strategy, data extraction form, and extraction criteria and definitions.
[DOCX File , 36 KB - resprot_v13i1e57929_app1.docx]

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Abbreviations

LHS: learning health system
MRC: Medical Research Council
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Sustainability of Interprofessional Education: Protocol for a Scoping Review

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Abstract

Background: Interprofessional education (IPE) is an approach that can improve health care quality, contribute to the qualification of health care professionals, and train undergraduate students. Although this strategy has made significant progress in the last decade, integration, sustainability, and institutional growth are still priorities worldwide. Thus, maintaining strategies is essential for their full development and evolution.

Objective: This study aimed to identify discussions about the sustainability of IPE and map its actions or strategies (or both).

Methods: The scoping review will follow the Joanna Briggs Institute methodology. This scoping review protocol follows the *JBI Reviewers' Manual*, with 6 stages: identifying the research question; identifying relevant studies; study selection; data extraction and coding; analysis and interpretation of results; and consultation with stakeholders. Two independent and blind reviewers will evaluate and select studies available in English, Portuguese, and Spanish based on the eligibility criteria. Searches will be conducted on LILACS, Embase, Scopus, PubMed/MEDLINE, ERIC, Web of Science, CINAHL, Google Scholar databases; ProQuest Dissertations & Theses Global, and Brazilian Digital Library of Theses and Dissertations. The main research question is as follows: What have been the sustainability strategies for IPE actions? This scoping review will incorporate studies (empirical or theoretical-reflective) that address strategies or actions (or both) for IPE sustainability. They must present a quantitative, qualitative, or mixed methods approach and be available in full text. Data on strategies or actions for IPE sustainability will be extracted and inserted into a spreadsheet for analysis. Quantitative data will be analyzed using descriptive statistics, while qualitative analysis will identify meanings and patterns through thematic analysis. Thus, the aim is to present the compiled findings in tables and charts.

Results: The database search was conducted on March 22, 2024. In April and May 2024, duplicate studies were excluded. From July to November 2024, study selection will be carried out. In December 2024, data extraction and tabulation will take place, as well as consultation with stakeholders. The aim is to publish the results in scientific journals in January 2025.

Conclusions: This protocol will guide this scoping review to identify discussions on the sustainability of IPE and map its actions or strategies (or both); summarize the definitions and institutions that develop or promote IPE; and present the main recommendations for the area under study. Additionally, possible research gaps can be identified to guide future studies. This review will shed light on existing knowledge gaps and the current state of research, which could provide support for future research, programs, and policy responses to foster collaboration and interprofessional practice and, consequently, improve the quality of user care. This information will be useful in supporting decision-making by government officials, managers, teachers, facilitators, and students in the implementation, maintenance, and development of IPE.

Trial Registration: Open Science Framework 5VNJS; https://osf.io/5vnjs/

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International Registered Report Identifier (IRRID): DERR1-10.2196/60763

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KEYWORDS

college education; health training; interprofessional education; IPE; sustainability; collaborative practice; training of human resources in health; undergraduate medical education; students; student learners; professional development; health care professional training

Introduction

The current social and economic situation is changing the epidemiological and demographic profile worldwide, increasing social inequalities and health care problems. Therefore, changes are needed in health systems and the training of health care professionals [1]. In this context, interprofessional education (IPE) qualifies health care professionals and trains students from several undergraduate programs, evidencing its ability to improve health care [2]. This strategy allows members of more than 1 health profession to interactively learn how to improve interprofessional collaboration or the health and well-being of patients [3]; the latter is one of the most important benefits of IPE [4].

The literature also highlights the benefits of IPE to students, facilitators, and patients of health services. Students benefit from an improved understanding of other health professions, as well as practical learning on how to work in interprofessional teams and maximize patient care and outcomes. For facilitators, IPE provides reflections and learning about their professional practice and highlights the importance of the entire team focusing on the patient care. For patients, IPE improves the quality of care [5]. IPE starts from recognizing that the health-disease process is the expression of life and work (ie, how individuals, families, and social groups are inserted in society) and meeting the needs of the complex health care network, based on collaboration between health care professionals [6].

Global changes, especially after the COVID-19 pandemic, have presented an opportunity to increase innovation in education, health systems, and their interaction. In this sense, education facilitated by information technologies began to be used, offering subsidies for competency-based education and IPE [7]. Although this strategy has made significant progress over the last decade, the Interprofessional Research Global stated that IPE integration, sustainability, and growth at the institutional level are still priorities worldwide [8]. Therefore, maintaining strategies is essential for its full development and evolution.

Thus, this study understands sustainability as strategies, elements, initiatives, or investments (or both) that contribute to and ensure the continuity of IPE at the macro, meso, and micro levels [9,10].

Several barriers affect the performance of IPE, such as the hegemonic trend of uniprofessional training; the management of health services and its influence on the organization of the work process in health in a productive sense (quantity of procedures); the significant turnover of team members; and, primarily, the COVID-19 pandemic, identified as the greatest obstacle to the successful implementation of this interprofessional initiative [9]. Therefore, sustainability for IPE remains a persistent challenge due to the adversities that hinder its progress.

The synthesis of sustainability strategies or actions (or both) for IPE may help managers, teachers, and facilitators in their decision-making at their institutions. The compilation may assist them in maintaining IPE in their practice settings (educational institutions or health services) and developing new sustainability strategies. Furthermore, this scoping review may assist in the development of new research.

Considering the need to synthesize and consolidate sustainability strategies for maintaining IPE and global changes after the pandemic, this scoping review will seek to identify discussions about the sustainability of IPE and map its actions or strategies (or both).

Methods

Overview

The proposed scoping review will be conducted in accordance with the JBI methodology [11] for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [12] for the presentation of the research reports. Also, the review will consider the recommendations by Peters et al [13] to ensure rigor, transparency, and reliability.

A preliminary search was conducted in January 2024, as Joanna Briggs Institute (JBI) recommended [11]. The International Prospective Register of Systematic Reviews, the Cochrane Library, JBI Evidence Synthesis, and the MEDLINE (by PubMed) databases were searched. The search terms used were (“Interprofessional education”) AND (“Sustainability” OR “Sustain” OR “Continuity” OR “Durability” OR “Sustainabilities”); and in the Virtual Health Library (“Interprofessional Education”) AND (“Sustainability” OR “Maintenance” OR “Continuity” OR “Durability”).

A literature review study [14] was identified; the authors evidenced the barriers and facilitators for IPE until December 2012. They highlighted the importance of facilitators for IPE sustainability. However, this review neither focused on sustainability nor followed the JBI recommendations, which are reliable since they ensure transparency and rigor. Thus, this topic requires an update.

Review Question

The research question was formulated using the Population, Concept, and Context mnemonic [15].

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Population

This review will consider studies that explore any IPE initiatives in courses, programs, electives, mandatory subjects, extensive activities, projects developed in communities, hospital training wards, care teams, common activities, online modules in the distance education modality, case discussions, and simulated activities; these interventions must have involved at least 2 health professions [16]. Thus, the population is broad [17].

Concept

This review will consider studies that explore IPE sustainability. Sustainability is defined as the condition or quality of something that can sustain, defend, maintain, or conserve itself [18]. In 2010, the World Health Organization launched the "Framework for Action on Interprofessional Education and Collaborative Practice" [19], which had an influence worldwide. This framework followed the changes in the education of health care professionals. The document provided strategies and ideas that helped policy makers implement IPE and collaborative practice in public policy.

In America, the Pan American Health Organization released a technical cooperation that launched a Regional Network on IPE and strengthened its implementation in national human resources policies for health. Thus, initiatives were needed to ensure IPE sustainability in the academic area, continuing health education practices, and daily teamwork [16]. For instance, Brazil launched an action plan to implement IPE, a promising initiative to ensure IPE sustainability in the country [16]. The plan includes initiatives such as curricular changes and the educational practices of health care professionals using IPE.

Context

This review will consider studies developed in the IPE context, whether an academic, educational, or professional practice, that included curriculum-based or continuing IPE education. No restrictions will be made regarding geographic location, sex, ethnicity, or other demographic components. IPE is a method that emerged to train health care professionals to promote collaboration within and between teams, improving health care quality [20].

In this context, the questions of this scoping review protocol were defined as follows: How is the literature presenting the discussion of IPE sustainability? Has IPE sustainability entered the agendas of teaching-service institutions? What have been the sustainability strategies for IPE actions?

Identification of Relevant Studies

The search strategy will be formulated based on a combination of controlled descriptors (health science descriptors, Medical Subject Headings [MeSH], CINAHL subject headings, and Emtree) and keywords (or both) related to the topic, associated with the Booleans operators "AND" and "OR."

Searches will be conducted in the LILACS, Embase, Scopus, MEDLINE, ERIC, Web of Science, and CINAHL databases. Sources of unpublished studies and gray literature will also be searched in Google Scholar, ProQuest Dissertations & Theses Global, and Brazilian Digital Library of Theses and Dissertations. A manual search will also be conducted in the reference lists of the initially selected studies to find other eligible studies. Furthermore, authors will be contacted by email to request the full text when needed.

An initial limited search was performed on the MEDLINE database to identify studies on the topic. The terms contained in the titles and abstracts of the relevant studies and their index terms were used to develop a comprehensive search strategy for MEDLINE (refer to Multimedia Appendix 1). The search strategy will be adapted for each information source, including all identified keywords and index terms. The reference lists of studies selected for full-text review will be analyzed to identify other eligible studies.

The search strategy will locate primary studies, reviews, and opinion articles. Duplicates, studies, documents whose acquisition is not allowed through university institutional log-in, and those that are out of scope will be excluded, that is, articles that do not respond to the objective of the study.

This scoping review will consider studies available in full text (empirical or theoretical-reflective) that present a quantitative, qualitative, or mixed methods approach. In addition, systematic reviews and opinion articles will be considered for inclusion. Studies published in English, Spanish, and Portuguese will be included. Those in other languages will not be included due to financial and time constraints for translations. The date of publication will not be restricted.

Study Selection

After searching the databases, all identified records will be grouped and imported into Rayyan; duplicates will be removed. Following pilot-testing, 2 independent reviewers will assess titles and abstracts based on the inclusion criteria. Potentially relevant studies will be retrieved in full text, and their citation will be imported from Rayyan. Two independent reviewers will also assess the full text of the citations. Reasons for excluding full-text studies will be reported in the scoping review. A third reviewer will be consulted in case of disagreements between the reviewers at each stage of the study selection. The research results will be fully reported in the final scoping review and presented in a PRISMA flow diagram [21].

Data Extraction and Coding

In a pilot test, 2 independent reviewers will extract data from the studies included using a data extraction tool (Microsoft Excel) developed by the reviewers. The pilot test will be conducted with a random sample of the first 25 studies (title and abstract), which will be organized in alphabetical order using the Rayyan software, to assess the eligibility criteria and agreement among researchers; the agreement must reach at least 75% before proceeding with independent evaluation. The reviewers will later check the extracted data to discuss discrepancies and ensure accuracy. Details about study selection (identification, screening, eligibility, and inclusion) will be presented in a flowchart.

The extracted data will include specific details about the initiatives, courses, programs, or disciplines (population); strategy or action for IPE sustainability (concept); definition that the study uses for IPE (context); characteristics of

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discussions on IPE sustainability; and evidence source details and results. A draft extraction tool will be used (Table 1), which was modified and revised as needed during the data extraction for each included study. Modifications will be detailed in the full scoping review. Any disagreements between reviewers will be resolved by discussion with a third reviewer. Authors will be contacted to request missing or additional data when needed. As scoping reviews do not seek to assess the quality of the selected studies, the risks of bias in the studies will not be assessed.

Table 1. Instrument for data extraction.

Data[a]	Description
Type of production	Study, book chapter, event summary, dissertation, thesis, and others
Research approach	Quantitative, qualitative, or mixed
Publication date	Year of publication
Country where the study was conducted	Where the study was conducted or published
Scientific journal	Journal that published the study
Author qualification	Highest title of the first author
Title	Study title
Objective/purpose	Objective or purpose of the study
Type of study	Type of research described by the authors
Data collection	Methods for data collection
Study population	Name of initiatives, courses, programs, and disciplines
Concept: sustainability	Description of the strategy or action for IPE[b] sustainability
Context: IPE	Describe the concept the article uses for IPE
Development institution	Institution that promoted or developed strategies or actions for the IPE sustainability
Results	Main results of the study
Recommendations	Recommendations that the study can offer for IPE

[a]Adapted from the Joanna Briggs Institute model [11].

[b]IPE: interprofessional education.

Analysis and Interpretation of Results

Quantitative data will be analyzed using descriptive statistics and presented in absolute or relative frequency, such as type of production, research approach, publication date, country where the study was conducted, among others. Meanwhile, qualitative analysis will identify meanings and patterns through thematic analysis, such as mapping the strategies for the sustainability of IPE, through the categorization of data, depending on the findings of the research.

A qualitative and quantitative synthesis and a narrative of the data extracted from the selected studies will be developed to describe the characteristics of the discussions about sustainability and the actions or strategies (or both) of IPE, thus answering the research questions.

The information will be presented in tables, compiling the main results, conclusions, and implications.

Consultation With Stakeholders

It is intended to introduce the preliminary results to 5 stakeholders in the field of IPE in such a way that they can analyze and identify any gaps that may be present. This step will help expand knowledge through new evidence not identified in the review, making it possible to develop strategies and directions for future studies [22].

To this end, the stakeholders will be sent an email with an informed consent, an electronic spreadsheet with the preliminary results, as well as a request for appraisal. Stakeholders will not be identified, and the authors will ask for an appraisal of the results and possible new fields or evidence, such as suggestions for additional articles or data that could be extracted from the studies.

Ethical Considerations

This study will comply with the ethical principles of research with human beings [23]. It was therefore submitted to and approved by the Research Ethics Committee of the Onofre Lopes University Hospital of the Federal University of Rio Grande do Norte, under Protocol 6.483.476.

Results

To this end, this study was registered with the Open Science Framework (OSF) on February 8, 2024. The database search step took place on March 22, 2024. In April and May 2024, the duplicate studies were excluded. In June 2024, the protocol was submitted to the journal. From July to November 2024, the selection of studies will be carried out. In December 2024, data extraction and tabulation will take place, as well as consultation with stakeholders. In January 2025, the review will be submitted to a scientific journal.

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The results of this review will be shared through publications in renowned, peer-reviewed, and open access journals of great importance to public health and education, favoring and expanding the dissemination of knowledge to the scientific community. Any changes to this protocol will be reported appropriately in the record made in the OSF and in the final publication, including dates and justifications.

Discussion

Expected Findings

This protocol will guide this scoping review to identify discussions on the sustainability of IPE and map its actions or strategies (or both). This is similar to what was observed in a study conducted in 2021 [24], which presents enablers for the introduction of collaborative competence in the curriculum using an interprofessional framework. The study points out, based on previously developed experiences, that teamwork along with the definition of clear goals and strategic plans commonly increases the acceptance of team-based approaches among faculty and students. In this process, change management and communication skills are considered fundamental to this formula for success. Thus, awareness and a positive attitude toward the change process among faculty and students, through training on the attitudes, knowledge, and skills necessary to work efficiently with other professionals and provide safe, high-quality patient care, should be regarded as a key step during implementation.

Mapping this information will help decision makers, managers, teachers, facilitators, and students to implement, maintain, and develop IPE. It should be noted that vocational training is currently at a crucial moment for potential changes [7].

In addition, this review will shed light on existing knowledge gaps and the current state of research, which could support future research, programs, and policy responses to foster collaboration and interprofessional practice and, consequently, improve the quality of user care. In this way, the results of this review may support the development and implementation of more robust studies, such as systematic reviews, in addition to assisting in the development of primary studies, using other methodologies, thus expanding the results of studies already developed on IPE.

All the steps of the scoping review favor its transparency and allow it to be methodologically replicated according to the principles of open science, reducing the risk of bias and duplication of data.

It is noteworthy that the results will be disseminated to the academic community through scientific journals, scientific events, and other relevant public health communication channels.

Limitations

This protocol guides the development of the scoping review. Nonetheless, it may not cover all the pertinent literature. Thus, studies indexed in different databases may not be traced in the searches. In addition, the limitation of language to English, Portuguese, and Spanish for the inclusion of studies may not locate some publications. Furthermore, the use of descriptors and search terms in English and Portuguese may also be a limitation for this study. However, the study will present the main results in the area, addressing the proposed objective.

Conclusion

This study protocol introduces the main methodological steps that will be followed, so that the review will synthesize the main strategies and actions for IPE sustainability, the definitions and institutions that develop or foster IPE, as well as the main recommendations for the area under study. This knowledge will enable researchers, managers, teachers, students, and political decision makers to better understand what can be done in terms of implementing, maintaining, and developing IPE.

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Data Availability

The spreadsheet with the consolidated data will be deposited in the Open Science Framework, so that the entire dataset on which the paper's conclusions are based will be available to readers.

Authors' Contributions

NHSO conceived the study idea and wrote the manuscript. All authors contributed to the writing, approved the manuscript, and agreed with the methodology.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for MEDLINE (PubMed). Research conducted in March 2024.

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Abbreviations

IPE: interprofessional education
JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
OSF: Open Science Framework
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

The Use of "Cancer Ratio" in Differentiating Malignant and Tuberculous Pleural Effusions: Protocol for a Prospective Observational Study

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Abstract

Background: Differentiating between tuberculosis and malignancy as the cause of an exudative lymphocyte predominant pleural effusion is difficult due to similarities in the cellular and biochemical characteristics of the pleural fluid in both conditions. Microbiological tests in tubercular pleural effusions have a poor diagnostic yield, and the long turnaround time for results prevents an early diagnosis. The diagnosis of malignant pleural effusion (MPE) is hampered by a variable yield of pleural fluid cytology and closed pleural biopsy and the fact that thoracoscopy may not be readily available or feasible in each patient. A key gap in the existing knowledge is the performance of the serum lactate dehydrogenase to pleural adenosine deaminase ratio (ie, "cancer ratio"; CR) in differentiating between tuberculous and MPE in a high tuberculosis prevalence country like India, although its use has been well established in Western literature. The CR may find a practical application in the community health care settings in low-income countries without ready access to biopsy.

Objective: This study aimed to evaluate the CR as a test to differentiate tubercular and malignant etiology in patients with an exudative lymphocyte predominant pleural effusion. Secondary objectives to be assessed include a comparison of CR to pleural fluid carcinoembryonic antigen in MPE and the association of histologic type of lung carcinoma to the CR positivity.

Methods: This hospital-based, prospective, observational study will include patients admitted with pleural effusion whose pleural fluid reports indicate a lymphocyte-predominant exudate. The ability of the CR to discriminate between tuberculous and MPE will be evaluated as a primary objective of this study. The performance of CR and pleural fluid carcinoembryonic antigen in the diagnosis of MPE will be compared using the receiver operating characteristics and area under the curve for both tests as a secondary objective. The association between a positive CR and histologic type of lung cancer will be analyzed as well.

Results: Data collection began in June 2022. As of March 24, 2024, we have recruited 22 patients. Outcomes of the study are expected at the end of 2024.

Conclusions: The results of this study will provide an objective basis for the use of CR in differentiating between tuberculosis and malignancy as the cause of an exudative lymphocyte predominant pleural effusion.

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KEYWORDS

tuberculosis; pleural; pleural effusion; malignant; biomarkers; tumor; cancer ratio; differential diagnosis; respiratory disease

Introduction

Pleural effusion is a common mode of presentation in patients with both respiratory and systemic diseases. The global incidence of pleural effusion is estimated to be 5/1000 person-years, with 1.5 million new cases diagnosed each year in the United States alone [1]. Previously published studies in India have revealed tuberculosis and malignancy to be common causes of exudative pleural effusion in India [2-5]. The implications of tuberculosis and malignancy being the cause of pleural effusion are strikingly different. The diagnosis of tubercular pleural effusion (TPE) indicates a potentially curable disease. In contrast, a malignant pleural effusion (MPE) is evidence of an advanced stage of malignancy with incurability and a poor prognosis [6].

TPE occurs in approximately 5% of patients with tuberculosis infection. It results from a delayed hypersensitivity reaction to tuberculoproteins present in the pleural space, and hence, microbiological tests on the pleural fluid are generally negative. Acid-fast bacillus stain on the pleural fluid is positive in less than 10% of the samples, whereas pleural fluid culture for mycobacteria is positive in approximately 30%. Liquid culture media, such as the BACTEC-Mycobacteria Growth Indicator Tube–automated mycobacterial detection system, provide higher yields and faster results than conventional solid culture methods [7]. However, these microbiological tests for confirmation of TPE can be time-consuming, and the decision to initiate treatment would need to be taken much before this. Due to the shortcomings associated with the microbiological tests, pleural fluid adenosine deaminase (ADA) has been commonly used as a surrogate biomarker to establish the diagnosis of pleural tuberculosis. ADA is a T lymphocyte enzyme elevated in diseases like tuberculosis, where cellular immunity is stimulated [8]. Almost all patients with TPE have a pleural fluid ADA level above 40 U/L—the most widely accepted cutoff value for the diagnosis of TPE, at which it has a sensitivity and specificity of 92% and 90%, respectively [9]. Using the GeneXpert Mycobacterium tuberculosis/Rifampicin Ultra assay on the pleural fluid sample is not recommended for the diagnosis of TPE, as the sensitivity of this test on the pleural fluid is very low, leading to either a missed or delayed diagnosis [10].

Approximately 15% of all patients with cancer develop MPE [11]. The diagnosis of MPE is made by demonstrating exfoliated malignant cells in the pleural fluid or histopathological evidence of malignancy in the pleural tissue obtained by either a thoracoscopic or a closed pleural biopsy. Pleural fluid cytology has an overall sensitivity of 58.2% (range 20.5%-86%), with the yield depending on factors like the mechanism of effusion, type of primary tumor, number of specimens, and skill of the cytopathologist [12,13]. The diagnostic yield of closed pleural biopsy in MPE ranges from 39% to 75%, which is inferior to cytology since the blind procedure may sometimes yield insufficient or a nonrepresentative sample [8]. Thoracoscopic evaluation and biopsy is the investigation of choice where the initial pleural fluid reports are inconclusive for MPE. However, thoracoscopy is an expensive procedure needing expertise and a thoracic surgery backup, and its availability remains limited in low-income countries. In this context, tumor markers in the pleural fluid have been evaluated as a potential tool for diagnosing MPE. A study evaluating the diagnostic value of tumor markers reported pleural fluid carcinoembryonic antigen (CEA) as having the highest diagnostic accuracy with a sensitivity of 72.2%, a specificity of 92.2%, a positive predictive value of 89.7%, and a negative predictive value of 77.8% [14]. A study involving 1230 patients also revealed pleural fluid CEA (using a cutoff value of 3.7 ng/mL) to be the best diagnostic marker in separating pleural effusions of malignant from benign etiology [15]. Krishnan et al [16], in their study, showed the sensitivity and specificity of pleural fluid CEA in diagnosing MPE to be 93.5% and 73% while using a cutoff value of 2.15 ng/mL. Other studies have shown varying sensitivity and specificity of pleural fluid CEA in MPE diagnosis, which could be attributed to the varying CEA cutoff values in these studies, which ranged from 3 to 50 ng/mL [16-20]. The wide range in the cutoff values and the observation that false positive results for pleural fluid CEA are also seen in parapneumonic effusion, empyema, and TPE have limited the clinical use of this test [21].

Verma et al [22] first described the use of the “cancer ratio” (CR), that is, the serum lactate dehydrogenase (LDH) to pleural adenosine deaminase ratio, to identify MPE and reported a high specificity and sensitivity using a cutoff level >20. LDH is a cytoplasmic enzyme present in tissues involved in anaerobic glycolysis and gluconeogenesis. High LDH levels are seen in myocardial infarction, acute liver failure, hemolytic anemias, myopathies, sepsis, and cancers. The increase in serum LDH in cancers is due to the preferential use of glycolysis for energy in the tumor cells, which is mediated by LDH [23]. A high ADA level in pleural fluid suggests TPE, whereas a low ADA level indicates a high probability of an MPE. It is postulated that combining both markers as a ratio has the potential for use in diagnosing MPE. Both serum LDH and pleural fluid ADA are included in the routine laboratory investigations in patients with pleural effusion, making the CR a simple, point-of-care test without any additional cost to the patient.

The use of CR in the diagnosis of both neutrophil- and lymphocyte-predominant exudative MPE has been established in a previous study [22]. Pooled data from a meta-analysis of 7 studies showed an overall sensitivity of 0.96, a specificity of 0.88, a positive likelihood ratio of 7.70, and a negative likelihood ratio of 0.05. The area under the curve was 0.98, indicating a high overall diagnostic accuracy for CR in the prediction of MPE [24]. Other studies, while validating the use of CR in diagnosing MPE, have suggested measuring “CR plus” (ie, the ratio of CR to the percentage of differential pleural fluid lymphocyte count) to improve the specificity of the CR in differentiating MPE from TPE [25,26].

The etiology of pleural effusion remains unknown in up to 5% to 25% of patients after the initial diagnostic workup. The

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important conditions to consider in patients with recurrent undiagnosed pleural exudates are malignancy and tuberculosis [27]. CR has been reported in the Western literature as a useful test on the pleural fluid sample that could quickly and reliably separate MPE from TPE. This study aims to explore its use in the Indian population with a high prevalence of tuberculosis. Also, there is no literature studying the association of a positive CR with the histologic type of cancer and limited studies comparing the performance of pleural fluid CEA and CR estimations in diagnosing MPE, 2 questions the authors seek to answer through this study.

Methods

The key aspects of the study protocol are summarized below.

Study Design and Setting

This study is designed as a hospital-based, prospective, observational study. This study will be conducted in the teaching hospitals affiliated with Kasturba Medical College, which includes Kasturba Medical College Hospital, Attavar, Mangalore, and Government Wenlock District Hospital, Mangalore, located in the southern state of Karnataka in India.

Study Objectives

Primary Objective

The primary objective was to evaluate the CR as a test to differentiate tubercular and malignant etiology in patients with an exudative lymphocytic pleural effusion.

Secondary Objectives

Secondary objectives were (1) to compare the performance of CR and pleural fluid CEA estimations in diagnosing MPE and (2) to determine the association of histologic types of lung cancers, that is, squamous, small-cell, adenocarcinoma, and large-cell carcinoma, to the CR positivity in MPEs.

Eligibility Criteria

This study will be conducted among patients of both genders, aged 18 years and older, admitted into the teaching hospitals affiliated with Kasturba Medical College over 2 years from 2022 to 2024 for the management of pleural effusion and are planned for a pleural fluid aspiration and analysis. The study inclusion and exclusion criteria are specified in Textbox 1. The variables and the operational definitions used in the study are specified in Textbox 2.

Textbox 1. Inclusion criteria and exclusion criteria.

Inclusion criteria

- Patients admitted with pleural effusion whose pleural fluid reports are suggestive of:
  - An exudative pleural effusion as per the Light [8] criteria, that is, meeting 1 or more of the following criteria:
    - Pleural fluid protein: serum protein >.5
    - Pleural fluid lactate dehydrogenase: serum lactate dehydrogenase >.6
    - Pleural fluid lactate dehydrogenase is more than two-thirds of the normal upper limit for serum
  - Pleural fluid is lymphocyte predominant (>50% lymphocytes in pleural fluid differential cell count)

Exclusion criteria

- Aspirated pleural fluid is a transudate as per the Light [8] criteria
- Aspirated pleural fluid is an exudate having neutrophil predominance (>50% neutrophils in pleural fluid differential cell count)
- Lymphocyte predominant (>50% lymphocytes in pleural fluid differential cell count) exudative pleural effusion of etiologies other than tuberculosis or malignancy

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Textbox 2. Variables and operational definitions.

- A diagnosis of malignant pleural effusion will be considered based on criteria that consist of:
  - Pleural fluid cytology positive for malignant cells, or
  - Pleural biopsy histopathology is suggestive of malignancy
- A diagnosis of tuberculous pleural effusion will be considered based on the following:
  - Pleural fluid acid-fast bacilli positive on Ziehl-Nelsen stain, or
  - Mycobacterial growth on pleural fluid culture, or
  - Pleural fluid GeneXpert Ultra: Mycobacterium tuberculosis and rifampicin resistance detection, (Cepheid) positive for M tuberculosis, or
  - Pleural biopsy specimen reported as tuberculous etiology, or
  - Pleural fluid adenosine deaminase value of >40 U/L with negative malignant cytology in an exudative lymphocyte predominant effusion followed by a decision of the clinician to treat with anti-tuberculous drugs [8]
- A cancer ratio (serum lactate dehydrogenase to pleural adenosine deaminase ratio) at a cutoff level of > 20 will be used for identifying malignant pleural effusion
  - The prespecified threshold of 20 was based on a previous study, which showed a sensitivity of 0.84 and a specificity of 0.92 when using this cutoff [15].
- A pleural fluid carcinoembryonic antigen level of 2.4 ng/mL will be used as a marker to identify a malignant pleural effusion
  - The cutoff level of 2.4 ng/mL was chosen based on a previous study, which showed a sensitivity of 93.5% and specificity of 73% at this threshold [16]

Study Population Recruitment

Patients satisfying the inclusion and exclusion criteria will be chosen using the nonprobability convenience sampling method.

Sample Size Calculation

The sample size was calculated based on the previously published study by ElSharawy et al [26], in which the mean CR in MPE was 52.43 (SD 19.36). Assuming 80% power and accepting a type-I error of 5%, the sample size was calculated to be 28 patients for this study.

The sample size for this study was calculated manually using the formula:

where N is the sample size, z_{α}=1.96 at a 95% CI, s_n is the sensitivity taken as 91% from a previous study [26], L is the precision of 15 %, and P is the expected prevalence of 50%. The precision is kept at 15% so that the calculated sample size (N=28) is feasible enough to be completed in the stipulated study duration of 2 years.

Data Collection

The study investigator will take written informed consent from admitted patients with pleural effusion who satisfy the inclusion and exclusion criteria outlined above. The study investigator will ensure that the aspirated pleural fluid sample is sent for protein, glucose, LDH, ADA, CEA, and pleural fluid differential white cell count analysis and that simultaneously a serum sample is collected for estimation of protein and LDH levels. Microbiological analyses, which include Ziehl-Nelsen stain, Gram stain, ordinary culture, acid-fast bacillus culture of pleural fluid, and pleural fluid cytology, will be done in all the pleural fluid samples. Where available, reports of pleural biopsy, pleural fluid cell block, and pleural fluid GeneXpert Mycobacterium Tuberculosis/Rifampicin Ultra assay will also be used in the final data analysis.

Data extraction will be done manually by the study investigator, and details like clinicodemographic data of study participants, pleural fluid analysis reports, and other relevant investigations will be extracted from medical records using a study proforma developed by the authors as the data extraction tool, from which the results will be analyzed at the end of the study.

Statistical Analysis

The analysis will be done by using the method of descriptive statistics. Statistical package IBM SPSS Statistics for Windows, version 23.0 (IBM Corp) will be used for the analysis. The actual P value will be recorded for all observations, and P<.05 will be considered statistically significant.

The diagnostic performance of CR and pleural fluid CEA as predictors for MPE will be compared using the receiver operating characteristics and the area under the receiver operating characteristics (area under the curve), taking cutoff values of >20 and 2.4 ng/mL, respectively.

A diagnostic 2×2 contingency table will be used to compare the performance of CR (at a cutoff of 20) and CEA (at a cutoff of 2.4 ng/mL) in arriving at the final diagnosis (as per methodology prespecified in the operational definitions).

Ethical Considerations

The protocol is approved by the Institutional Ethics Committee, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India (IEC KMC MLE 02022/179) in May 2022. We will conduct this trial following

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the principles described in the Declaration of Helsinki. Written informed consent will be obtained from all participants before their inclusion in the trial.

Results

Data collection began in June 2022. The expected date for data collection is between June 2022 and June 2024. As of March 24, 2024, we have recruited 22 patients. We anticipate completing the data analysis by August 2024. We expect the results to be published by January 2025.

Discussion

Principal Findings

This study primarily explores the use of CR in differentiating tuberculosis and malignancy as the cause of an exudative lymphocytic pleural effusion in hospitals without access to invasive investigations like thoracoscopy. This ratio is based on serum LDH and pleural fluid ADA measurements, which are simple, inexpensive, and point-of-care tests available at most primary health care centers.

Strengths and Limitations

A significant strength of this study is that the prospective enrollment of patients will ensure that data collection will be complete in all aspects for most patients. This study design is better than a record-based retrospective study, which may not retrieve all parameters of research interest. Also, a single-center study within a stipulated time frame of 2 years ensures uniformity in detection methods and reagent kits used in the measurement of LDH, ADA, and CEA, which ensures the validity of the results. However, there are several limitations that the investigators envisage in this study. First, the study population is restricted to hospitalized patients who might have a higher LDH ratio due to underlying ailments, which could give a false positive CR even in patients without underlying malignancy. Second, the literature review reveals different cutoff values of the CR, with some studies showing an increase with age [28,29], whereas this study uses the most cited single cutoff value for the CR. If such variability is observed in this study, the authors plan to perform subgroup analysis using a logistic regression model to find the association between the confounding variable and the CR. Third, the relatively small sample size of this study may make it difficult to determine the association of histologic types of lung cancer to CR positivity in patients with MPE. Fourth, since lymphocytic exudates other than tuberculosis and malignancy are excluded in this study, we cannot be confident that the results may not also be seen in conditions such as rheumatoid pleuritis, benign asbestos effusion, and so on, which present with lymphocytic effusions.

Future Research

Considering the wide range of cutoffs reported in the literature, further studies will be needed to validate the optimal standardized cutoff for CR in the Indian population. The sample size for a multicenter external validation of the optimum CR cutoff derived in this study is estimated to be 252 based on a precision of 5% and previous power analysis. Also, further research on CR in transudates and nonlymphocytic pleural effusions would be required before the findings of this study could be generalized to all MPEs.

Conclusions

If found to be an accurate diagnostic test for MPE, CR has the potential to be used in community health settings and low-income countries without firsthand access to cytology or biopsy services. In such resource-limited settings, it could be used as a screening test for MPE, so that patients with high CR in their pleural fluid could be subsequently referred to centers where other invasive investigations to confirm an MPE, like a closed pleural biopsy, thoracoscopic biopsy, or image-guided (either computed tomography or ultrasound) biopsy, could be planned.

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Data Availability

The data that will support the findings of this study will be derived from patient medical record data. The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SPC contributed to conceptualization, formal analysis, investigation, methodology, software, visualization, writing-original draft, writing-review and editing. PRA performed conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review and editing. TA handled conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing-original draft, writing-review and editing. AR contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing-original draft, writing-review and editing. HK performed data curation, formal analysis, methodology, software, supervision, validation, writing-review and editing. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflicts of Interest

None declared.

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Abbreviations

ADA: adenosine deaminase
CEA: carcinoembryonic antigen
CR: cancer ratio
LDH: lactate dehydrogenase
MPE: malignant pleural effusion
TPE: tuberculous pleural effusion

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Protocol

Exploring Molecular Genetics Research on Obesity in Malaysia: Protocol for a Scoping Review

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Abstract

Background: Obesity presents a growing challenge to public health, and its intricate association with genetics continues to be a compelling field of study. In countries such as Malaysia, where diverse genetic backgrounds converge, exploring the molecular genetics of obesity is even more imperative.

Objective: This scoping review aimed to explore the literature on molecular genetics of obesity in Malaysia. Specifically, we sought to characterize existing studies, identify the genetic determinants of obesity, and assess their association with obesity predisposition in the population.

Methods: This scoping review followed the methodology of the Joanna Briggs Institute and used the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist as its guiding framework. Searches were conducted using electronic databases such as PubMed, ScienceDirect, and Scopus, filtering for human studies published until March 2024. Eligible studies included peer-reviewed articles on the Malaysian population irrespective of age or sex. This review excluded review articles, book chapters, non–peer-reviewed conference proceedings, gray literature, and preclinical studies, and the reference lists of the retrieved studies were manually examined to ensure thorough inclusion. The articles were subjected to a 2-stage screening process (title/abstract and full text) conducted by 2 reviewers to assess eligibility. Eligible articles were then extracted following a data extraction framework and organized into a charting table. Only studies investigating the genetics of obesity in Malaysian populations were included.

Results: As of March 2024, our extensive search strategy has yielded 572 records. After removing 153 duplicates, 419 records were screened by title and abstract, resulting in 47 selected for full-text review. Of these, 34 were chosen for data extraction and detailed analysis. These studies predominantly involved participants from major ethnic groups (Malay, Chinese, and Indian) recruited from local health centers and university communities. The articles primarily explored the relationship between specific gene variants and obesity or obesity-related health parameters. This ongoing research is expected to be completed with a comprehensive scoping review by April 2025.

Conclusions: This review provides valuable insights into the genetic determinants of obesity in Malaysia, despite limitations such as no quality appraisal being conducted for the included studies and the search strategy being restricted to selected databases, potentially omitting relevant studies. However, this review ensured reliability and reproducibility by adhering to the Joanna Briggs Institute and PRISMA-ScR guidelines. Ultimately, this study advances the understanding of local research and sets the foundation for future molecular genetic studies to improve obesity risk prediction and management in Malaysia's multiethnic population.

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KEYWORDS

genetics; biomarkers; molecular; obesity; Malaysia; scoping review; protocol

Introduction

Obesity presents a substantial public health challenge, exerting a significant global impact on economies and health care systems. The World Obesity Atlas 2023 predicts that over 51% of the global population will become obese or overweight within the next 12 years [1]. In this global crisis, Malaysia, an upper–middle-income country with a diverse population, ranks as the fattest nation in Southeast Asia [2]. Currently, more than half of Malaysian adults are overweight or obese [3], which increases the risk of diabetes, high blood pressure, and hypercholesterolemia [4,5]. These noncommunicable diseases incur an economic toll of approximately RM 8.91 billion (equivalent to US $2.01 billion), derived from productivity losses in the working-age population [6]. Hence, targeted interventions and comprehensive strategies are imperative to address the escalating obesity burden in Malaysia.

Genetic variation across populations significantly contributes to differences in gene expression phenotypes, which can potentially affect the prevalence of obesity. While general healthy eating guidelines can benefit individuals with poor dietary habits, a “one-size-fits-all” approach is often insufficient. Health disparities persist owing to gene-diet interactions, are influenced by genetic ancestry, and significantly affect how different individuals respond to the same dietary recommendations [7,8]. Additionally, individuals’ genetic makeup significantly influences how obesogenic environments contribute to obesity predisposition [9,10]. For instance, the *FTO* gene variant rs9939609 has a significant correlation with BMI in populations of European and African ancestry [11,12] and some Asian populations [13-15] but varies in other Asian populations [16]. Ethnic-specific risk factors have significant relevance in Malaysia, where distinct ethnicities exhibit varying predispositions to obesity, resulting in certain groups having a higher prevalence of body fat [17] and metabolic syndrome [18].

Molecular genetic investigations into obesity are notably scarce despite the significant health burden posed by the conditions in this country. A scoping review revealed a marked surge in obesity research conducted in Malaysia from 2008 to 2017 in response to the unprecedented prevalence of overweight and obesity in the country. However, only 12.3% of studies used experimental methods to investigate potential biomarkers, with genetic studies receiving minimal attention [19]. Moreover, the lack of a systematic compilation of existing research hampers efforts to effectively build upon previous work, exacerbating the challenge of designing new studies to address the research gap. Identifying the genetic determinants linked to obesity is crucial for developing targeted interventions to address the distinct challenges encountered by each group in combating obesity.

While lifestyle modifications for obesity have shown promise in reducing weight and improving cardiometabolic risk factors in the population [20-23], sustaining these changes over the long term remains a significant challenge [24,25]. Studying the genetic factors and metabolic pathways is crucial for the treatment and prevention of obesity. A recent study showed that integrating genomic data into a digital precision weight-loss program greatly enhances model accuracy and intervention effectiveness through personalized coaching based on genetic risk [26]. Additionally, genetic variants linked to abdominal obesity have been found to predict waist circumference regain after weight loss, emphasizing the role of genetics in long-term weight management [27]. Studies such as the OBEGEN study underscore the importance of integrating genetic testing with clinical data to enhance the predictability of weight loss outcomes following bariatric surgery [28]. These findings are corroborated by subsequent research [29,30]. This integrative approach will facilitate the development of personalized and cost-effective treatments for obesity.

Therefore, the primary purpose of this scoping review is to map the existing knowledge and findings and highlight gaps to guide future research. This scoping review aimed to explore published articles on molecular genetic research on obesity in the Malaysian context. We evaluated the published evidence regarding (1) study characteristics, including participant profiles (ie, sex and ethnicity) and aims/objectives; (2) key findings focusing on genetic determinants of obesity; and (3) the degree of association between the markers and obesity predisposition indicated by measures such as minor allele frequency or odds ratio values.

Methods

Study Design

The scoping review adheres to the most recent edition of the Joanna Briggs Institute Manual for Evidence Synthesis [31], using the framework established by Arksey and O’Malley [32] and subsequently enhanced by Levac et al [33]. This framework encompasses five key steps: (1) defining the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) compiling, summarizing, and presenting the findings. This method aims to comprehensively map the scope of research on a given topic, reveal existing knowledge, identify gaps, clarify known and unknown facets [33], and situate findings within policy and practical contexts [34]. The findings adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) reporting guidelines to guarantee transparency and reproducibility [35]. The PRISMA-ScR checklist is provided in Multimedia Appendix 1.

This scoping review was registered in the Open Science Framework database (registration QYZKA) [36]. Citations were organized and duplicates were systematically removed using EndNote (Clarivate Analytics). A preliminary search was performed to identify previously published reviews on this topic. The search conducted on March 1, 2024, encompassed the following databases: MEDLINE (Ovid), Cochrane Library, and PROSPERO, using the keywords: “obesity” AND “genetic”

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AND “Malaysia.” No other systematic or scoping reviews on this topic, either published or registered, were discovered.

Step 1: Identify the Research Question

Following the guidance of Levac et al [33], scoping review questions maintained a broad scope, while ensuring precise definitions of concepts to develop a robust search strategy. In alignment with these principles, the formulation of the research questions investigated in this review arose from discussions and consensus among reviewers. Therefore, the primary research question was as follows: What are the genetic determinants of obesity prevalent in the Malaysian population and how strongly are they related to obesity predisposition? Additionally, we aimed to determine the pathways through which these genetic factors contribute to obesity predisposition.

Step 2: Identify Relevant Studies

The second phase of the scoping review focused on establishing criteria for selecting the research to be incorporated into the review. Despite the broad nature of a scoping review, these criteria guide the search process and aid in identifying relevant sources. The scoping review included peer-reviewed literature from the MEDLINE/PubMed, ScienceDirect, and Scopus electronic databases. The reviewers used an iterative process guided by Levac et al [33] to identify key search phrases. The search strategy shown in Table 1 involves generating subject headings and a list of keywords, incorporating Boolean operators (eg, AND and OR), adjacencies, and truncations. Medical Subject Headings terms were integrated and adjusted across different databases. The search strings for each database were finalized based on this exploratory scoping phase. The detailed search strategy and strings for all databases are provided in Multimedia Appendix 2.

Table 1. Example of search terms and their combinations in PubMed database.

Search number	Query
1	“gene*”[Title/Abstract] OR “polymorphism*”[Title/Abstract] OR “snp”[Title/Abstract] OR “genetic*”[Title/Abstract] OR “protein*”[Title/Abstract] OR “dna”[Title/Abstract] OR “rna”[Title/Abstract] OR “genetic variant”[Title/Abstract] OR “mutation*”[Title/Abstract] OR “variant*”[Title/Abstract] OR “GWAS”[Title/Abstract]
2	“malay*”[Title/Abstract] OR “malaysian chinese”[Title/Abstract] OR “malaysian indian”[Title/Abstract] OR “malaysia”[Title/Abstract]
3	“obes*”[Title/Abstract] OR “overweight”[Title/Abstract] OR “obesity”[Title/Abstract] OR “obes*”[MeSH[a] Terms] OR “obesity”[MeSH Terms] OR “overweight”[MeSH Terms]
4	#1 AND #2 AND #3

[a]MeSH: Medical Subject Headings.

This scoping review encompasses studies involving all ethnicities in Malaysia, including Malay; Chinese; Indian; and non-Malay indigenous groups from Sabah and Sarawak, known as Bumiputera Sabah and Sarawak, as well as other indigenous communities. Articles published in peer-reviewed journals were considered, whereas systematic reviews, meta-analyses, scoping reviews, gray literature, PhD theses, abstracts, book chapters, perspectives, opinions, and commentaries were excluded. In addition, nonreviewed conference proceedings were omitted due to feasibility constraints and limited information.

Following the preliminary search, we refined our search strategy to enhance the identification of eligible studies. First, we expanded the search to include all studies up to March 2024 by removing restrictions on the publication year. This decision was based on the observation that limiting the search to the past 5 years yielded fewer relevant results. We included articles in both English and Malay for comprehensive coverage relevant to the Malaysian context. Furthermore, we incorporated additional keywords related to molecular genetics to improve the sensitivity of our search strategy. The inclusion and exclusion criteria are presented in Table 2.

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Table 2. Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Studies to be assessed	Molecular research on obesity that explores genetic determinants	Nonmolecular obesity study
Literature	Peer-reviewed research paper	Gray literature, PhD theses, abstracts, systematic reviews, meta-analyses, scoping reviews, book chapters, perspectives, opinions, commentaries, and nonreviewed conference proceedings.
Species	Human/clinical studies	Preclinical studies encompass both in vivo and in vitro research
Population	Study conducted among Malaysians (Malay, Chinese, Indian, Bumiputera Sabah and Sarawak and indigenous people), of all ages and sexes	Non-Malaysian population
Language	Articles published in English and Malay	Non-English or non-Malay articles
Publication date	All until March 2024	—[a]

[a]Not applicable.

Step 3: Study Selection

After the search, all identified articles were retrieved from each database and imported into the reference management software EndNote (version X9; Clarivate Analytics) in RIS/nbib file format. The team manually scanned all the included studies to locate other relevant studies. The articles in Endnote were screened for duplication and eliminated before being imported into Microsoft Excel spreadsheets.

Two independent reviewers screened the selected titles and abstracts based on the eligibility outlined in the inclusion and exclusion criteria and assessed whether the content addressed the research questions. The next step consisted of obtaining the full texts of the selected and identified articles and distributing them equally among the team members. Two reviewers independently screened the entire texts of the articles and were required to justify the reasons for their exclusion. Any disagreements among the reviewers during the selection process were resolved through discussion or with the involvement of a third reviewer, until a complete consensus was reached. The scoping review reported and documented the reasons for omitting sources during the full-text evaluation. The search results will be incorporated into the planned scoping review guided by the PRISMA-ScR flow diagram and checklist [25].

Step 4: Extract and Chart the Data

The team initially reviewed several articles to ensure a thorough understanding of the conceptual framework and identified essential data to address the research questions. Subsequently, a data collection form was developed in accordance with the data extraction framework (Table 3) to assess full articles that met the eligibility criteria. Prior to implementation, all reviewers examined and pretested the form to ensure its effectiveness in capturing pertinent information. Data extraction was conducted in duplicate, and 2 reviewers independently extracted data from all eligible articles. Discrepancies between the extracted data were carefully examined to ensure their accuracy and consistency. Based on feedback from team members, the data extraction form was revised before final adoption. The compiled data were organized into a single Microsoft Excel document for validation and coding. Finally, the reviewers agreed upon a standardized data extraction method that encompassed all relevant information.

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Table 3. Data extraction framework.

Main category and subcategory	Description
Bibliographic information	
Authors	—[a]
Title	—
Year of publication	—
Journal name	—
Objectives of the study	
—	Indicate the objectives or aims of the study
Study population	
Target population	Specify if the study (1) targets individuals within a subpopulation or (2) broad population
By BMI	Specify the distribution of the study population by BMI
By gender	Specify if the study focuses on a specific gender, particularly girls, boys, and older people, or indicate the distribution of study participants by gender
By ethnic background	Specify if the study targets certain ethnic groups
By sample size	Indicate the sample size of the study population and each study group (eg, control and treatment if applicable)
Results and key findings	
Main findings	Summary of main findings
Genetic determinants	Identify the genetic factors influencing obesity predisposition, including variants, mutations, and gene expression patterns
Association with obesity	Indicate the degree of genetic association with obesity, including measures such as minor allele frequency (MAF) or odd ratio (OR) (if applicable)
Discussion and conclusion	
Conclusion	Indicate the conclusion stated in the study
Study implications	Implications for practice, policy, or further research
Study limitations	Limitations/challenges of the study or approach as stated by authors

[a]Not applicable.

Step 5: Collate, Summarize, and Report the Results

The proposed scoping review identifies the available information on the human genetics of obesity in the Malaysian context, summarizes the findings, and contextualizes the research questions. The charted evidence will be used to identify knowledge gaps and make recommendations for future research directions and needs in this field. A narrative approach will be used to report the findings, with results presented in aggregate as appropriate, and patterns and trends (if identified) illustrated in visual formats (eg, tables, figures, and charts).

Results

The systematic scoping review protocol was initiated in February 2023. This study was conducted without any external funding. Preliminary data collection commenced in March 2023 and was updated in March 2024, resulting in 572 results from the electronic database searches. Following the removal of duplicates (n=153), 419 records were screened by title and abstract, resulting in 47 records selected for full-text review. Of these, 34 were retained for data extraction and analysis. A PRISMA flow diagram is presented in Multimedia Appendix 3. Most of the studies primarily focused on major ethnic groups, such as Malay, Chinese, or Indian, who were recruited from local health centers and university communities. These studies investigated the association between specific gene variants and obesity or obesity-related health parameters. The final results will be submitted for a systematic scoping review in April 2025.

Discussion

The growing obesity crisis poses significant challenges to public health and the economy, with Malaysia being one of the most affected countries. Half of the adult population is currently overweight or obese, accompanied by an increase in noncommunicable diseases [3]. While environmental factors contribute to this surge, obesity results from a complex interplay between these factors and genetic predispositions, critically influencing individual susceptibility to the “obesogenic” environment.

The scope of this review specifically encompasses human or clinical studies while excluding preclinical investigations such as in vivo or in vitro studies. Prioritizing human or clinical studies on genetic obesity not only enhances our understanding of how genetic factors impact disease risk, treatment responses, and overall well-being but also has practical implications for

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personalized health care [37-39]. Despite the proven success of personalized medicine in guiding the prevention, diagnosis, and treatment of conditions, such as cancer, using genetic and phenotypic information, its implementation in addressing obesity remains limited. Moreover, this review was limited to research conducted in Malaysia, including studies across various ethnic groups and across all segments of the population, including both sexes.

This review synthesizes research from diverse ethnic backgrounds in Malaysia to identify knowledge gaps and prioritize future research questions, shaping the path for future studies. Revealing the trends and characteristics of genetic studies on obesity in Malaysia will guide researchers toward areas that are likely to yield new insights. This streamlined approach has expedited advancements in elucidating the molecular genetic basis of human obesity. Additionally, mapping research in this field can inform policy decisions on obesity and public health, aiding resource allocation and intervention design. The outcomes of this review will be shared through publications and presentations at conferences, enriching the scientific community's understanding of the genetic factors that influence obesity in Malaysia. However, this scoping review has some limitations. First, we did not perform a quality appraisal of the included studies. Furthermore, the search strategy was limited to the selected databases, which may have led to the omission of relevant studies. Despite these limitations, this review adhered to the stringent guidelines of the Joanna Briggs Institute and PRISMA-ScR, ensuring its reliability and reproducibility.

This review aims to comprehensively explore and consolidate the existing literature on the molecular genetics of obesity in Malaysia. The discussion will analyze the findings within the framework of the study attributes and primary outcomes, focusing on genetic determinants and their association with obesity susceptibility. Furthermore, our study seeks to explore the identified genes and their corresponding pathways that influence the progression of obesity using a comprehensive integrative analytical approach. This approach offers a deeper understanding of the protein-protein interaction network, potentially providing valuable insights into the complex biological mechanisms underlying obesity.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SSH conceptualized and designed the study, and facilitated the registration of this scoping review with NIH Malaysia. LAZ managed the protocol registration and drafted the study protocol. LAZ, NAZA, and NAS developed the search strategy and drafted the manuscript for the scoping review protocol, which was then reviewed, edited, and finalized under the supervision of SSH. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 83 KB - resprot_v13i1e60838_app1.pdf]

Multimedia Appendix 2
Detailed search strategies for each database used in the scoping review.
[PDF File (Adobe PDF File), 70 KB - resprot_v13i1e60838_app2.pdf]

Multimedia Appendix 3
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram.
[PDF File (Adobe PDF File), 57 KB - resprot_v13i1e60838_app3.pdf]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Seasonal Malaria Chemoprevention Therapy in Children Up To 9 Years of Age: Protocol for a Cluster-Randomized Trial Study

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Abstract

Background: Seasonal malaria chemoprevention (SMC) is recommended by the World Health Organization for the sub-Sahel region in sub-Saharan Africa for preventing malaria in children 3 months old to younger than 5 years. Since 2016, the Malian National Malaria Control Program has deployed SMC countrywide during its high malaria transmission season at a rate of 4 monthly cycles annually. The standard SMC regimen includes sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ). Resistance against SP is suspected to be rising across West Africa; therefore, assessing the effectiveness of an alternative antimalarial drug for SMC is needed to provide a second-line regimen when it is ultimately needed. It is not well understood whether SMC effectively prevents malaria in children aged 5 years or older.

Objective: The primary goal of the study is to compare 2 SMC regimens (SP-AQ and dihydroartemisinin-piperaquine [DHA-PQ]) in preventing uncomplicated *Plasmodium falciparum* malaria in children 3 months to 9 years old. Secondly, we will assess the possible use of DHA-PQ as an alternative SMC drug in areas where resistance to SP or AQ may increase following intensive use.

Methods: The study design is a 3-arm cluster-randomized design comparing the SP-AQ and DHA-PQ arms in 2 age groups (younger than 5 years and 5-9 years) and a control group for children aged 5-9 years. Standard SMC (SP-AQ) for children younger than 5 years was provided to the control arm, while SMC with SP-AQ was delivered to children aged 3 months to 9 years (arm 2), and SMC with DHA-PQ will be implemented in study arm 3 for children up to 9 years of age. The study was performed in Mali's Koulikoro District, a rural area in southwest Mali with historically high malaria transmission rates. The study's primary outcome is *P falciparum* incidence for 2 SMC regimens in children up to 9 years of age. Should DHA-PQ provide an acceptable alternative to SP-AQ, a plausible second-line prevention option would be available in the event of SP resistance or drug supply shortages. A significant byproduct of this effort included bolstering district health information systems for rapid identification of severe malaria cases.

Results: The study began on July 1, 2019. Through November 2022, a total of 4556 children 3 months old to younger than 5 years were enrolled. Data collection ended in spring 2023, and the findings are expected to be published later in early 2024.

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Conclusions: Routine evaluation of antimalarial drugs is needed to establish appropriate SMC age targets. The study goals here may impact public health policy and provide alternative therapies in the event of drug shortages or resistance.

Trial Registration: ClinicalTrials.gov NCT04149106, https://clinicaltrials.gov/ct2/show/NCT04149106

International Registered Report Identifier (IRRID): DERR1-10.2196/51660

(JMIR Res Protoc 2024;13:e51660) doi:10.2196/51660

KEYWORDS

malaria; seasonal malaria chemoprevention; RCT; randomized; controlled trial; controlled trials; parasite; parasites; mosquito; mosquitoes; vector-borne; malarial; antimalarial; age; Plasmodium falciparum, protocol, cluster-randomized trial; child; children; infant; infants; pediatric; pediatrics; clinical trial; clinical trials; drug; drugs; pharmacy; pharmacology; pharmaceutic; pharmaceutics; pharmaceuticals; pharmaceutical; medication; medications

Introduction

Malaria is endemic to south and central Mali, where over 90% of its approximately 17.6 million population is at risk for infection [1]. The disease primarily burdens rural areas that maintain suitable larval habitats and lack access to adequate health care [1]. Malaria transmission is highly seasonal in Mali (length of the transmission periods varies from 3 to 6 months), with a peak of malaria cases at the end of the rainy season (October through November), though it may be affected by irrigation schemes [2,3]. Deaths due to malaria registered at health centers totaled 1050 in 2017, with 669 (63.7%) occurring among children younger than 5 years. However, these results are likely substantially underreported. For instance, in 2015, health facilities in Mali reported over 2.3 million confirmed malaria cases and 1544 malaria deaths, but actual estimates were 7.5 million and 21,000, respectively [1].

Since 2007, support from the US Presidential Malaria Initiative program and other sponsors resulted in a 50% reduction in Mali's malaria burden. These efforts have been carried out through increased preventive and treatment measures such as long-lasting insecticide-treated mosquito nets (LLINs), indoor residual spraying, artemisinin-based combination therapies (ACTs), and intermittent preventive treatment of pregnant women (IPTp); and more recently, seasonal malaria chemoprevention (SMC). The most widely implemented malaria control interventions are the joint use of LLINs and rapid treatment of malaria cases with ACTs, IPTp, and SMC. Indoor residual spraying was previously implemented on a small scale in several Malian districts but is currently implemented in only a single district in central Mali.

Despite the broad deployment of these interventions, malaria prevalence and incidence rates remain high in Mali according to the routine Malaria Indicators Surveys [4]. Since 2010, the International Centers of Excellence in Malaria Research (ICEMR), in collaboration with Mali's National Malaria Control Program (NMCP), has identified significant constraints to malaria control implementation strategies in Mali, including the upward shift of the prevalence of infection and incidence of disease in children younger than 5 years to children aged 5-9 and 10-14 years [5,6]. These findings are particularly significant as the World Health Organization (WHO) guidelines recommend SMC only for children 3 months old to younger than 5 years. Therefore, the Mali NMCP and its partners have expressed SMC effectiveness and intervention strategies as key research priorities.

While the sulfadoxin and pyrimethamine regimen (SP) remains effective in West Africa, resistance to this regimen has been observed in East African regions where *Plasmodium falciparum* is highly prevalent. SMC is not currently recommended for countries in southern and eastern Africa due to widespread resistance, although there are some locations where transmission patterns suggest potential suitability [7,8]. In western parts of Africa, higher frequencies of the triple dihydrofolate reductase mutants and the quadruple mutant (triple dihydrofolate reductase plus dihydropteroate synthetase 437) associated with significant resistance to SP have been observed in children receiving SMC in both Mali and Senegal [9,10]. Recent studies have also reported SP resistance in several parts of Mali [11,12]. The wide-scale deployment of SMC in sub-Saharan African countries required increased focus on *P falciparum* resistance as well as ongoing assessments of new alternative drug combinations for SMC as this strategy has proven to be effective in reducing the impact on severe malaria and mortality in children 3 months old to younger than 5 years [13]. A recent study in Burkina Faso suggests that higher dosages and extended dosing of dihydroartemisinin-piperaquine (DHA-PQ) to 4 monthly doses (and cover the entire high malaria transmission period) could reduce malaria incidence up to 58% during the peak transmission season [14,15]. DHA-PQ has demonstrated excellent efficacy for chemoprevention and benefits from the long half-life of piperaquine and offers a protective efficacy of 98% against malaria in Thai adults when administered monthly [7]. In Senegalese children, similar monthly malaria incidence was observed among children receiving monthly DHA-PQ vs SP+amodiaquine (AQ) as SMC regimen [8].

A study in Uganda reported a 58% greater protective efficacy for DHA-PQ over SP-AQ based on monthly administration among children younger than 5 years [9]. This study aims to determine whether SMC effectively prevents malaria in children aged 5-9 years. The evidence-based approaches used will guide policy in Mali and other countries in West Africa using SMC.

Methods

Ethical Considerations

The study was approved by the University of Sciences, Techniques and Technologies Ethics Board under the following reference (N°2019/04/CE/FMPOS). The trial will report the

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efficacy of 2 SMC subtypes (SP-AQ and DHA-PQ) for preventing *P falciparum* malaria in children aged 5-9 years in Mali. Should the findings show that SMC is efficacious for children in this age group, it may impact policy SMC delivery in Mali.

Study Site

Mali's Koulikoro District is situated in its southern region, approximately 50 miles (18 km) north of Bamako and 255 miles (410 km) from the Guinea border [11]. The district maintains 21 health zones and 71 community health posts. The current population in the district is 282,570, with approximately 4% of its population <1 year of age and 18% between 1 and 4 years of age. The total number of villages a community health center covers ranges from 8 to 31. The most populous village is Kolebougou, with 34,712 persons; the least populated is Souban Village, with 5085 persons. Ongoing malaria control activities include case management (rapid diagnostic tests and ACTs), IPTp, SMC, and LLIN use. District health centers maintain clinical and laboratory research capacity and full-time staff and clinicians for malaria screening and patient care. The site was chosen for the proposed research because of its diverse range of malaria control interventions, collaborative research agreements with the University of Sciences, Techniques and Technologies of Bamako, Mali (USTTB), high malaria transmission rates, and rural location.

Study Design and Population

The study was as a 3-arm cluster-randomized design, as illustrated in Figure 1.

Figure 1. Study design of a 3-arm cluster-randomized trial on age targets for season malaria chemoprevention. The study was performed from July 2019 to March 2023. AQ: amodiaquine; DHA: dihydroartemisinin; PQ: piperaquine; SP: sulfadoxine-pyrimethamine.

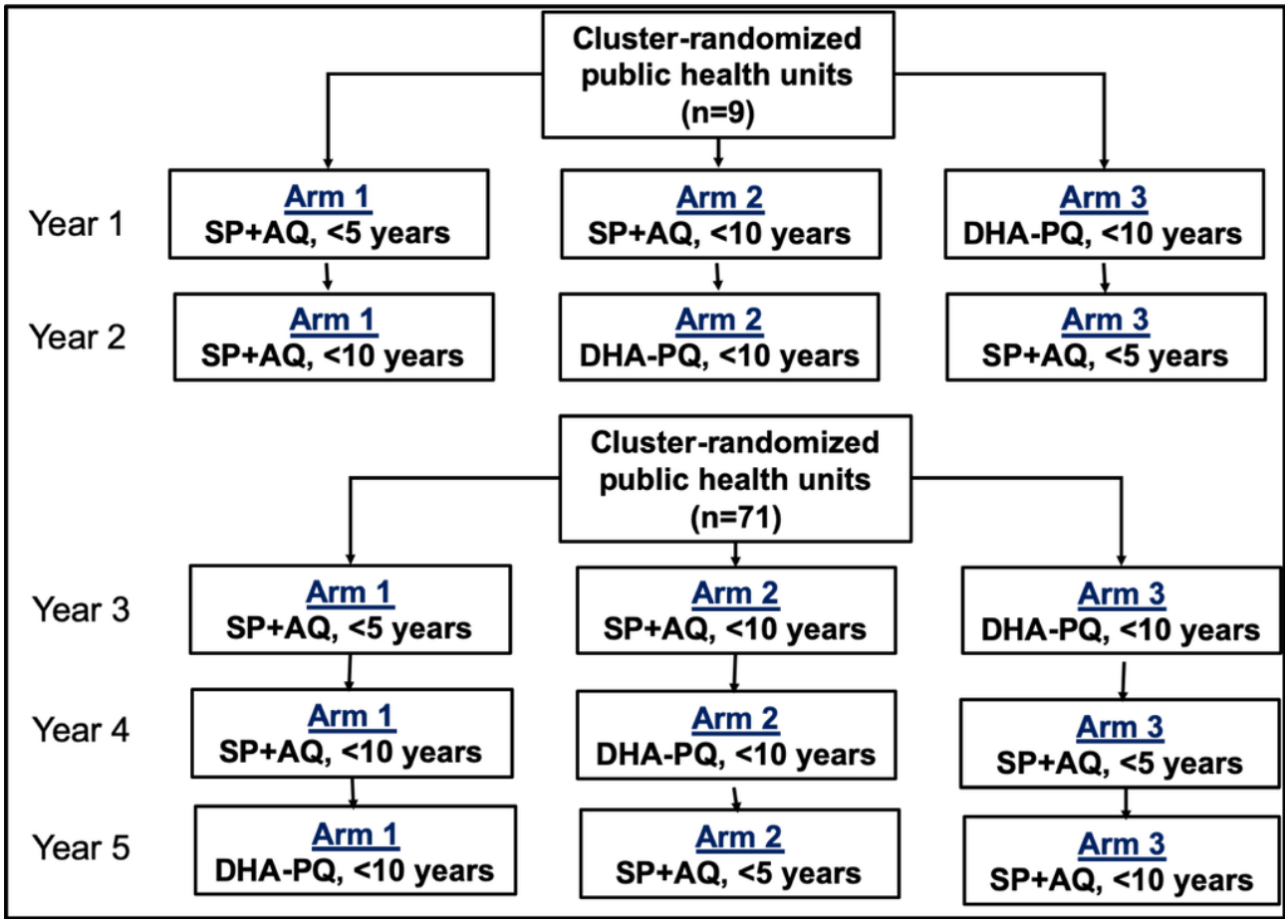

The study population includes children aged 3 months to 9 years in each village. Each study arm includes 3 corresponding public health units (PHUs) that differ with respect to their ecology, proximity to the Niger River, and region in the context of Koulikoro District (northern, central, and southern).

Cluster Selection

A total of 9 villages were randomly selected from Mali's Koulikoro District for participation. The selection strategy focused on 3 aspects: proximity to the Niger River (which lies in the southern part of the region) and the central and northern parts of the sampling region. Within these strata, villages were rank-ordered according to their populations. Random selection was carried out such that villages of high, medium, and low populations were sampled from each of these strata. A total of 3 villages (1 village per stratum with different ranking in terms of population size) were assigned to a single treatment arm (Figure 2).

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Figure 2. Map of the 9 study sites in Mali's Koulikoro District. The 9 study sites are near the central part of Mali's Koulikoro District. Study sites were selected as 3 villages near the Niger River, 3 villages in the northern part of Koulikoro District, and 3 villages in the central part of Koulikoro. AQ: amodiaquine; DHA: dihydroartemisinin; PQ: piperaquine; SP: sulfadoxine-pyrimethamine.

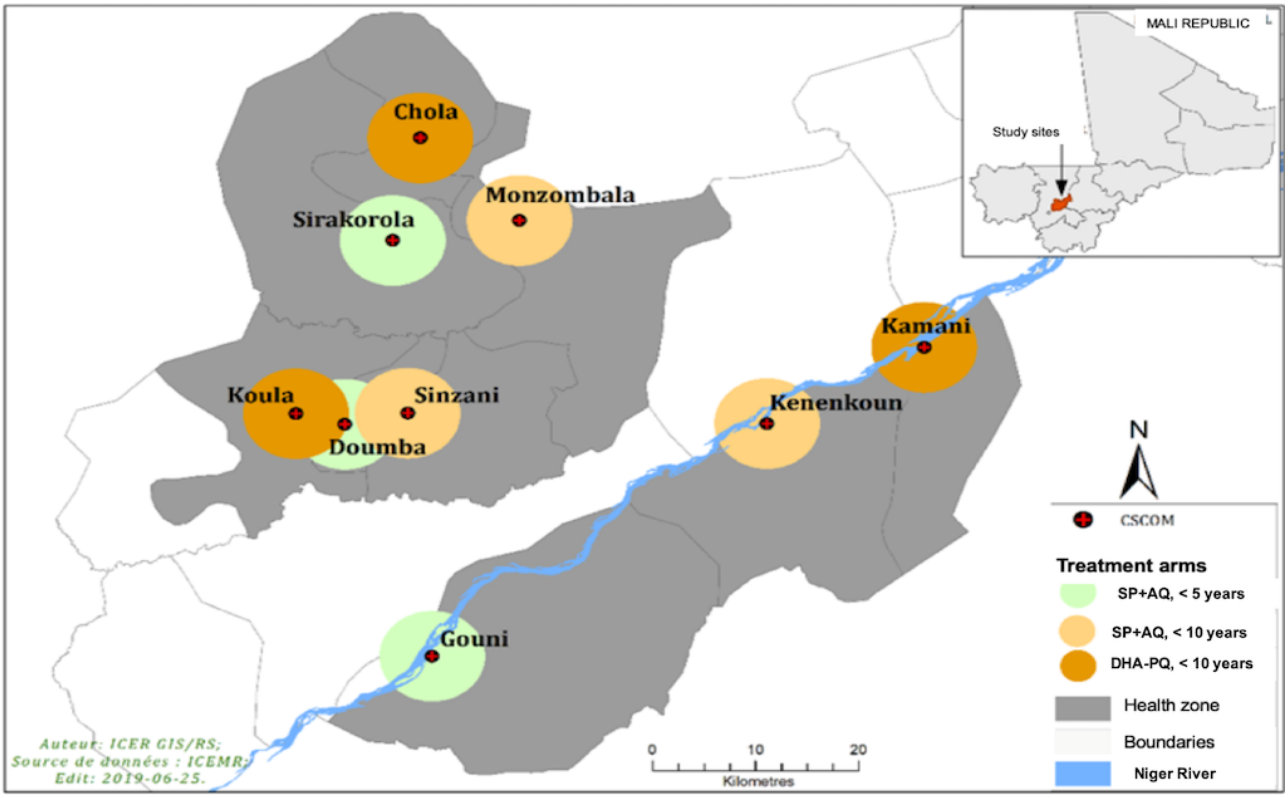

The southernmost villages (Gouni, Kenenkoun, Kamani) are situated near the Niger River, while the remaining villages (Doumba, Sinzani, Koula; and Sirakorola, Monzombala, and Chola) lie in the northern and southern parts of the region above the Niger River, respectively.

Randomization

Probability proportional to population size sampling was used for allocating villages to the study arm. Random treatment assignment was balanced according to population size in each stratum (low, medium, and high), resulting in a 3 by 3 Latin square arrangement (Table 1).

Table 1. Study site classification per sampling region within the Koulikoro District, Mali.

Region	Population size		
	Small	Medium	Large
South	Gouni (A)[a]	Kamani (C)	Kenenkoun (B)
Central	Sinzani (B)	Doumba (A)	Koula (C)
North	Chola (C)	Monzombala (B)	Sirakorola (A)

[a]A, B, and C denote the 3 study arms.

Specifically, PHUs were rank-ordered according to their total populations, and the top 3 PHUs (in terms of their populations) were chosen to represent Koulikoro's southern, central, and northern regions. The PHUs were then randomized to treatment according to the Latin square arrangement shown in Table 1.

Eligibility and Enrollment

Participants were eligible to participate if they were residents of the sampled village, aged 3 months to 9 years of age at enrollment, were asymptomatic of current chronic diseases, and did not have a history of allergies to SP, AQ, or DHA-PQ therapies. Informed, written consent is required for all study participants annually. Consent was administered in oral or written formats and included a full description of voluntary participation, the right to withdraw from the study at any time, and the right to refuse to answer any question or participate in any research component.

Study Outcomes

The primary study outcome is the incidence of severe or uncomplicated *P falciparum* malaria. The population denominator for incidence calculations was derived from the house-to-house enumeration with household member listing. Secondary outcomes were abstracted from censuses and enumeration lists for selected villages, including village-level distributions on populations, age, gender, residential status, and LLIN use. Exhaustive selection was carried out in villages for selected PHUs for those children who met the eligibility criteria

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and for whom consent of parents or tutors for enrollment was obtained. A baseline malaria infection prevalence survey was carried out before the initial SMC campaign. Follow-up surveys at community health centers were also carried out to assess malaria incidence among study participants. Monthly SMC administration and compliance with treatment assessment were captured via reports by caregivers and measurement of AQ metabolite by enzyme-linked immunosorbent assays. Demographic data, including age, sex, and clinical parameters (including temperature, pulse, and respiration rate), were recorded at a community health center visit. Malaria cases were defined as fever or a history of fever within the past 48 hours associated with either positive malaria rapid diagnostic test or a positive blood smear prepared during that visit.

Hypotheses and Rationale

The primary hypotheses were as follows:

1. Malaria incidence in children was at least 10% higher in the 5- to 9-year age group without SP-AQ than in children in the 5- to 9-year age group with SP-AQ.
2. Malaria incidence in children 3 months old to younger than 5 years receiving DHA-PQ was not statistically different from children in the same age group receiving SP-AQ.

Data Collection and Management

Confirmed malaria case incidence data will be collected from public health facilities through electronic data capture. A REDCap (Research Electronic Data Capture; Vanderbilt University) database and mobile app were used for this study, and data synchronization will be performed daily for quality checking complemented with data queries distributed to the centralized data center at USTTB.

A Priori Sample Size and Statistical Power

The power and sample size assessment is based on the ability to detect a clinically significant difference in malaria incidence proportions between the 3 comparison groups in year 1. The minimum clinically meaningful differences between the comparison groups was set at 10%. The sample sizes were calculated assuming a design effect of 2 with a 2-sided type I error set at 0.05 and power set at 80%. The number of required subjects per study arm for detecting at least 10% differences in malaria incidence proportions was 1552 in year 1. This result was inflated by 233 subjects in year 2 to account for new subjects due to increased child ages, yielding 1785 participants per arm total or 5355 participants overall.

Phase 2 (Years 3-5, 2021-2023)

This phase involved expansion to 71 public health posts in years 3-5 (Figure 3). The district-wide data collection plan will build on the efforts for years 1-2 and focus on (1) cluster-randomized health posts to the 3 treatment arms and (2) semiannual community cross-sectional surveys. More specifically, the 71 health posts over the entire district were divided into 4 regions (Table 2).

Figure 3. Map of the selection approach for 71 public health posts in Mali's Koulikoro District.

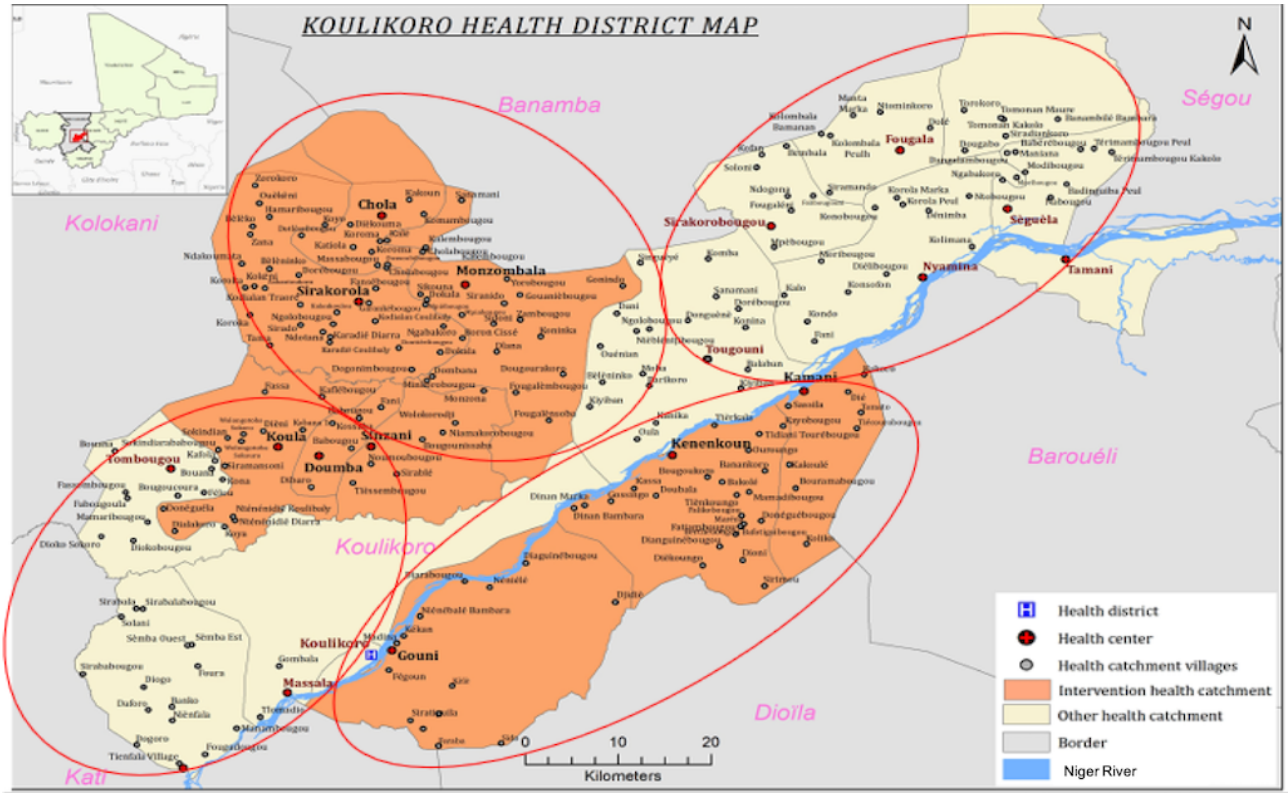

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Table 2. Stratum matched by the year of the study.

Stratum (region), years 3-5 sampling approach	Stratum (region), years 1-2 sampling approach
Northeast	Not done
Northwest	North
Southwest	Central
Southeast	South

Within the stratum, health posts will be randomized to 1 of 3 treatment arms (SP-AQ <5 years, SP-AQ <10 years, and DHA-PQ <10 years). Allocation was proportional to population size based on census populations up to 9 years of age while balancing on population sizes across the 3 study arms. For regions maintaining a total number of health posts that were not divisible by 3, 1 or 2 adjacent health posts were considered as a single unit to ensure divisibility (Figure 3).

The health facilities selected in years 1 and 2 were also be selected in years 3-5 and will leverage the process and training already in place in 9 health centers. Patterns over the entire 5-year study period will be analyzed for these 9 villages. Semiannual cross-sectional household surveys will permit assessment of community-level effects over the entire 5-year period.

Results

The study began on July 1, 2019. Through November 2022, a total of 4556 children were enrolled during the pilot phase (2019-2020) in 9 villages across the Koulikoro Health District. In 2022, preliminary findings have been presented at the American Society of Tropical Medicine Conference [16] and published in the *American Journal of Tropical Medicine and Hygiene* [17]. SP-AQ and DHA-PQ were highly effective in reducing *P falciparum* malaria in children 5-9 years in Koulikoro, Mali, at both the pilot and district-wide study phases. Data collection ended in spring 2023, and the findings are expected to be published later in early 2024. Results will be summarized and reported using both intention-to-treat and per-protocol analyses.

Discussion

This study was designed to assess the effectiveness and efficacy of SP-AQ in children aged up to 9 years and of DHA-PQ as an alternative in the event of drug resistance to AQ or SP in West Africa and, more broadly, across Africa. The trial included 2 SMC regimens to provide a viable alternative therapy in the event of drug resistance or shortages in drug supply. The study enrolled over 5000 subjects in 9 villages in Mali's Koulikoro District. The expanded phase of the study covered the entire Koulikoro District. The initial phase of the study covered 9 villages, which may be considered as a pilot for the larger district-wide trial.

This study provides an opportunity to directly measure the effect of the 2 drugs while extending SMC to older children in response to recent reports showing an age shift in malaria incidence and prevalence among older children. The study site here comprised different ecological settings represented countrywide with differential malaria transmission intensities. For instance, each study arm was composed of a village located along the Niger River where longer transmission seasons have historically occurred, a village located in the central part of Koulikoro District where malaria transmission peaks between July and October, and a village in the southern part of Koulikoro District where malaria transmission season has been historically shorter (August to November) than the other 2 locations. Also, all selected villages maintain community health facilities where malaria case management is done routinely. Additionally, a routine assessment of treatment compliance by measuring amodiaquine metabolite in the veinous blood of children after treatment will be performed for the first time to determine SMC compliance across all 4 dosing periods. While the number of villages was initially restricted to 3 per study arm, all 71 PHUs in Koulikoro will be covered across the 3 study arms should the study meet the go/no go criteria for continued funding.

Particular challenges at the outset of the study planning involved garnering support from regional health administrators about using DHA-PQ instead of SMC and extending SMC use to children aged 5-9 years. Since the inception of Mali's NMCP, a key partner in this effort made apparent the study's rationale in terms of its implications on potential drug resistance with health agents, community leaders, and health workers before the SMC campaign was launched in Mali. Determining the appropriate age target for preventive therapies remains challenging for developing countries like Mali. The age captured during the most recent census was used to estimate the number of children failing in the <5 and 5-9-year age groups, which was usually reported by the participants' parents or guardians. However, approximately 2% of subjects were misclassified during the SMC administration due to erroneous reporting during the census. Therefore, more accurate estimations of participant age (which was used to define the comparison groups) were captured for the study here at baseline.

SMC covers the rainy season that coincidentally occurs during school vacations and agricultural activities in rural Mali. Therefore, a child's movement during that period is often a cause for losses to follow-up as children frequently might travel to Mali's capital city of Bamako from July to September, while others will move with their family to the farms (hamlets) until October when school commences.

We believe that this study provides a somewhat novel study design that will aid researchers in assessing age targets in locations where controlled studies are not feasible.

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Acknowledgments

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Data Availability

Data will be archived on the ClinEpiDB institutional repository [18] to ensure long-term availability, preservation, and access. The data sets generated during this study are available from the corresponding author on reasonable request as well as from the West Africa International Centers of Excellence in Malaria Research (ICEMR) Program Director by e-mail (sdoumbi@icermali.org or sdoumbia@gmail.com)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute of Allergy and Infectious Diseases Special Emphasis Panel Limited Competition: Revision Applications for International Centers of Excellence for Malaria Research (NIH, USA).
[PDF File (Adobe PDF File), 421 KB - resprot_v13i1e51660_app1.pdf]

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Abbreviations

ACT: artemisinin-based combination therapy
AQ: amodiaquine
DHA: dihydroartemisinin
ICEMR: International Centers of Excellence in Malaria Research
IPTp: intermittent preventive treatment of pregnant women
LLIN: long-lasting insecticide-treated mosquito net
NMCP: National Malaria Control Program
PHU: public health unit
PQ: piperaquine
REDCap: Research Electronic Data Capture
SMC: seasonal malaria chemoprevention
SP: sulfadoxine-pyrimethamine
USTTB: University of Sciences, Techniques and Technologies of Bamako, Mali
WHO: World Health Organization

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Protocol

Combining Federated Machine Learning and Qualitative Methods to Investigate Novel Pediatric Asthma Subtypes: Protocol for a Mixed Methods Study

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Abstract

Background: Pediatric asthma is a heterogeneous disease; however, current characterizations of its subtypes are limited. Machine learning (ML) methods are well-suited for identifying subtypes. In particular, deep neural networks can learn patient representations by leveraging longitudinal information captured in electronic health records (EHRs) while considering future outcomes. However, the traditional approach for subtype analysis requires large amounts of EHR data, which may contain protected health information causing potential concerns regarding patient privacy. Federated learning is the key technology to address privacy concerns while preserving the accuracy and performance of ML algorithms. Federated learning could enable multisite development and implementation of ML algorithms to facilitate the translation of artificial intelligence into clinical practice.

Objective: The aim of this study is to develop a research protocol for implementation of federated ML across a large clinical research network to identify and discover pediatric asthma subtypes and their progression over time.

Methods: This mixed methods study uses data and clinicians from the OneFlorida+ clinical research network, which is a large regional network covering linked and longitudinal patient-level real-world data (RWD) of over 20 million patients from Florida, Georgia, and Alabama in the United States. To characterize the subtypes, we will use OneFlorida+ data from 2011 to 2023 and develop a research-grade pediatric asthma computable phenotype and clinical natural language processing pipeline to identify pediatric patients with asthma aged 2-18 years. We will then apply federated learning to characterize pediatric asthma subtypes and their temporal progression. Using the Promoting Action on Research Implementation in Health Services framework, we will conduct focus groups with practicing pediatric asthma clinicians within the OneFlorida+ network to investigate the clinical utility of the subtypes. With a user-centered design, we will create prototypes to visualize the subtypes in the EHR to best assist with the clinical management of children with asthma.

Results: OneFlorida+ data from 2011 to 2023 have been collected for 411,628 patients aged 2-18 years along with 11,156,148 clinical notes. We expect to complete the computable phenotyping within the first year of the project, followed by subtyping during the second and third years, and then will perform the focus groups and establish the user-centered design in the fourth and fifth years of the project.

Conclusions: Pediatric asthma subtypes incorporating RWD from diverse populations could improve patient outcomes by moving the field closer to precision pediatric asthma care. Our privacy-preserving federated learning methodology and qualitative implementation work will address several challenges of applying ML to large, multicenter RWD data.

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International Registered Report Identifier (IRRID): DERR1-10.2196/57981

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KEYWORDS

pediatric asthma; machine learning; federated learning; qualitative research

Introduction

Globally, nearly 22 million children are diagnosed with asthma [1]. In the United States alone, 4.5 million children are living with asthma, and exacerbations from asthma account for an estimated 500,000 emergency department visits and 64,000 hospitalizations annually [2-4]. Care for school-aged children with asthma accounts for US $5.92 billion of US health care spending [5]. Asthma is a chronic respiratory disease characterized by constriction of the lower airways, resulting in wheezing, cough, and shortness of breath [1]. Although asthma can be diagnosed with pulmonary function tests, it is often diagnosed clinically by a physician based on patient history and examination [1].

Pediatric asthma is a heterogeneous disease characterized by a range of etiologies, triggers, clinical manifestations, severities, and treatment responses [6]. Such disease heterogeneity can be classified into subphenotypes or subtypes. However, current pediatric asthma subtypes are primarily confined to allergic versus nonallergic asthma [7]. This simple dichotomous classification does not account for overlapping subtypes, the evolution of subtypes over time as a child grows and develops, differences in severity (especially considering racial and ethnic disparities), or the influence of social determinants of health (SDOH; defined as nonmedical factors that influence health outcomes according to the World Health Organization [8]). It is imperative to improve subtype characterization of pediatric asthma to facilitate more personalized and effective primary and emergency care and reduce the burden of care at both individual and population levels.

Machine learning (ML) methods such as deep neural networks that capture longitudinal information to learn new patient representations, combined with downstream clustering, are well-suited for identifying relevant subtypes [9]. Clustering algorithms for pediatric asthma subtypes would ideally be applied to large data sets containing voluminous electronic health record (EHR) data, including free-text note data, from diverse areas and populations. However, the inclusion of protected health information (PHI) and other sensitive data in EHR free-text notes raises privacy concerns, which requires the deidentification of structured and narrative EHR information. Manual deidentification is time-consuming and cannot be scaled up to large-scale studies, whereas automated deidentification of EHRs using machines cannot completely remove PHI. Federated learning is a subfield of ML that can address these privacy issues by allowing a central server to communicate with local sites to learn a global model, the parameters of which are then sent back to the local sites [10].

In this study, we propose to apply novel, privacy-preserving federated ML methods to identify and model pediatric asthma subtypes and their progression over time [11]. Federated learning is an ML technique that trains a shared global model with a central server while keeping data at the local sites, as opposed to aggregating individual site data together [10]. We will apply federated learning to a large, distributed clinical research network containing nearly 20 million demographically and socioeconomically diverse patients from the southeastern United States (Florida, Georgia, and Alabama). Despite the increasing sophistication of various ML techniques, there remain significant challenges in implementing ML algorithms, decision tools, and other forms of clinical support in frontline health care settings [12]. Therefore, we will also interweave our technical data science methods with qualitative implementation science research to "design for dissemination" [13], and ultimately optimize the translation of our research findings into clinical practice.

Methods

Overview of the Data Source and Study Design

This study uses the OneFlorida+ clinical research network [14], which is a large regional network covering linked and longitudinal patient-level real-world data (RWD) from over 20 million patients from Florida, Georgia, and Alabama in the United States. OneFlorida+ contains detailed patient demographic data, diagnoses, procedures, vital signs, medications, and laboratory results from Medicaid and Medicare claims; vital statistics; and EHRs from 15 clinical partners. Data quality in OneFlorida+ is maintained at each step of the data pipeline, with quality assurance governed by the OneFlorida+ data trust team.

To accomplish our study aims (Figure 1), we will initially develop and optimize a research-grade pediatric asthma computable phenotype (CP) and a clinical natural language processing (NLP) pipeline to accurately extract pediatric asthma–relevant information from EHRs. Subsequently, we will use deep learning models to capture the temporal representation of patients at each local site. Through federated learning, we will collaboratively learn the representation models across different sites and leverage federated clustering to characterize harmonized pediatric asthma subtypes and their progression across the sites in the OneFlorida+ database. We will also integrate focus groups with OneFlorida+ clinical network asthma clinicians to assess the clinical utility of the identified subtypes. Additionally, we will develop initial EHR prototypes for visualizing subtype information and evaluate the utility of these prototypes.

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Figure 1. Overview of the mixed methods study design. CP: computable phenotype; EHR: electronic health record; NLP: natural language processing; RWD: real-world data; SDOH: social determinants of health.

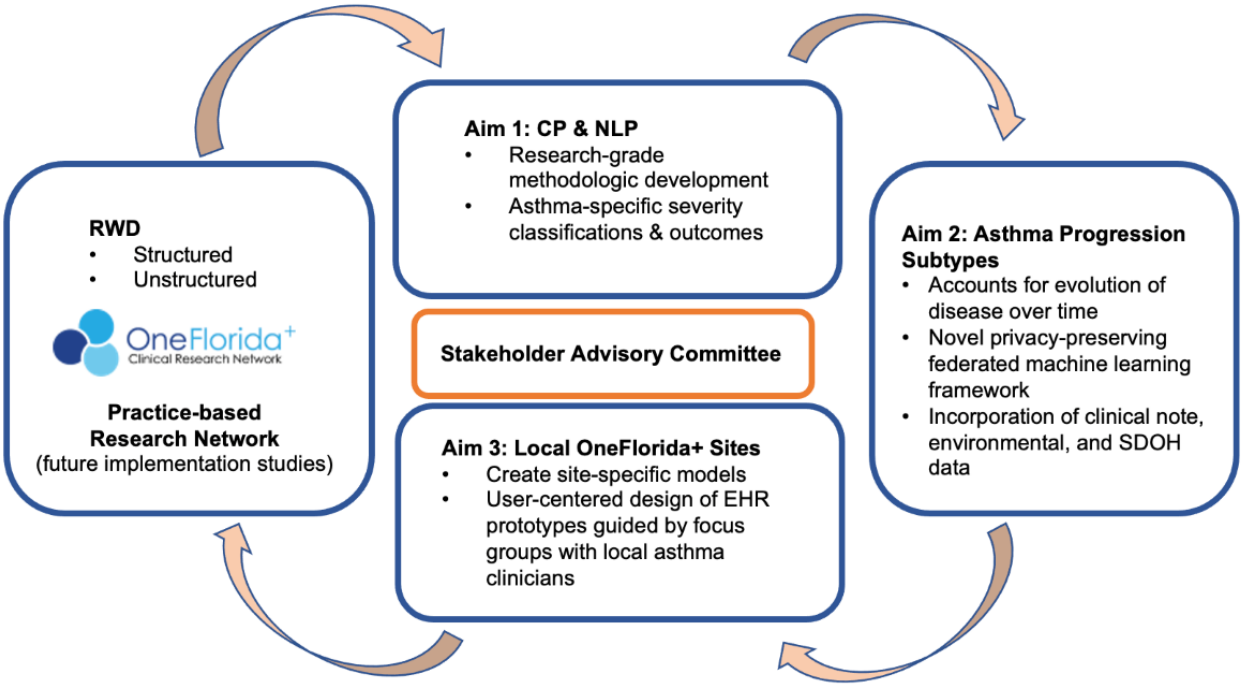

Ethical Considerations

The University of Florida Institutional Review Board (IRB) approved the subtyping study, including the use of both structured and unstructured data with a waiver of informed consent (UF IRB#202002779). For each participating site in this study, data will be securely stored on Health Insurance Portability and Accountability Act–compliant servers approved for the storage of PHI. Access to these files will be restricted to individuals included in the IRB protocol, ensuring compliance with ethical and regulatory standards. Specifically, for the University of Florida site, data will also be stored on HiPerGator for the required computing resources. We will adhere to the established procedures outlined in the "PHI on HiPerGator Process" documentation [15], which includes registering the project through a request in the University of Florida's Integrated Risk Management system and ensuring all project members sign the corresponding agreement form. For the focus group study, we will consent participants and compensate them with US $150 per session.

Stakeholder Advisory Committee

We will initially establish a stakeholder advisory committee to provide guidance on the study design, interpretation of results, and the dissemination and implementation of findings. In addition to the core study team, we will include multiple pediatric asthma stakeholders, including patients and caregivers, in the advisory committee (Textbox 1). The committee will meet twice yearly for the 5-year duration of the study. Meetings will comprise study team presentations on study progress and results. Committee members will be prompted for specific feedback and will also have ample opportunities to provide any input and suggestions to the study team. The number of members, their professional roles, and the guidance requested from the committee were determined according to Patient-Centered Outcomes Research Institute Research Engagement Principles [16].

Textbox 1. Composition of the stakeholder advisory committee.

- Patients and caregivers (n=2 teenage patients and n=2 caregivers)
- School nurses (n=1 elementary school, n=1 middle/high school)
- Clinical providers (n=2 primary care pediatricians, n=1 emergency or intensive care pediatric physician, n=1 allergist, n=1 pediatric pulmonologist)
- Health systems administrator (n=1)
- Public health agency representative (n=1)
- Health care insurance representative (n=1)
- Core study team (n=4)

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Developing a Pediatric Asthma CP

Accurately identifying pediatric patients with asthma from retrospective EHRs is crucial for ensuring the fidelity of the entire project. Although diagnostic criteria for asthma exist, as published by the National Asthma Education and Prevention Program [17], many clinicians rely on combinations of patient history, physical exam findings, and/or diagnostic tests to diagnose asthma in children. Additionally, pediatric asthma can present with varied and subtle symptoms. Therefore, simple inclusion and exclusion criteria based on *International Classification of Diseases* codes may not be sufficiently nuanced or comprehensive to identify all pediatric patients with asthma.

CPs are clinical states determined solely from EHR and/or other data that can be processed by a computer [18]. To date, there has been no widely validated and accepted pediatric asthma CP developed. Existing CPs for identifying pediatric patients with asthma from longitudinal EHR data (eg, CAPriCORN, PheKB, and NLP-PAC [19-21]) have shown variable performance when externally validated. We will refine these existing CPs and, if necessary, develop our own de novo pediatric asthma CP using a variety of structured and unstructured data available in the University of Florida and OneFlorida+ EHRs. If the development of new CPs is required, we will apply ML-based models (eg, transformer-based models). We will use standard CP development methods, including chart review by expert physicians to label charts. According to the methods of Buderer et al [22], given a Type I error of .05 and an acceptable width of the 95% CI of 0.1 with an estimated prevalence of pediatric asthma in the United States of 8.1% [1], for a minimum specificity and sensitivity of 0.9, we will need to manually review at least 427 charts as the minimum sample size. Due to sample size requirements for the NLP pipeline (see below), we will review 500 charts in the qualifying pediatric age range of 2-18 years. We plan to sample the charts from the entire pediatric data set to avoid bias in the development of the CP. We may need to review more charts to have a sufficient number of asthma cases.

Developing a Clinical NLP Pipeline to Categorize Pediatric Patients With Asthma and Their Disease Severity

A key aspect of pediatric asthma research using RWD is appropriately identifying patients with asthma and categorizing them by severity, clinical outcomes, and other characteristics (eg, SDOH). However, relying solely on structured data limits the ability of algorithms to identify and classify pediatric patients with asthma [23]. For example, some symptoms defining asthma severity (eg, nighttime cough, frequency of rescue inhaler usage) may be found only in clinical notes. Therefore, incorporating unstructured data using NLP can enhance the performance of pediatric asthma CPs [24]. We will extract patient characteristics from clinical narratives (ie, clinical concept extraction/named-entity recognition) by systematically examining different NLP models, with a focus on deep learning models (especially transformers such as Bidirectional Encoder Representations from Transformers), which have shown superior performance to other model types [25]. These models scan input words in sequence and determine the optimal labeling based on context features from surrounding words.

To build these models, we will perform a comprehensive literature search for keywords and phrases related to history, symptoms, environmental factors, and SDOH pertinent to pediatric asthma. We will then highlight these keywords and phrases in notes using the web-based annotation system BRAT [26]. The coprincipal investigator, who is a clinician experienced in the treatment of pediatric asthma, will train a team of 5 research coordinators to annotate records. At least 2 annotators will annotate the same 500 notes to develop an annotated gold-standard data set. Any disagreements will be resolved by the clinical coprincipal investigator. We will then split this data set into training and testing data sets, and the corpus will be normalized using a pipeline previously constructed for sentence boundary detection and tokenization [27]. We will apply our large language model GatorTron [28] to handle both negation and abbreviations in a unified model. Model performance (ie, how accurately the model extracted the entities of intent) will be evaluated on the testing data set with the microaveraged precision, recall, and F_1-score using strict and lenient (ie, partial matching of boundary) criteria. The best-performing model will be used to extract relevant pediatric asthma data from clinical notes, which can be incorporated into refining the CPs mentioned above.

Of note, with both CP and NLP pipeline development, the same data can exist in both structured and unstructured forms, which may not have the same value, making data harmonization a key consideration for this project. To select the most reliable and detailed information source, we will carefully review all pediatric asthma variables and CP rules during each project step for redundancy, accuracy, and complimentary/discordant data. For example, a medication prescription can be found in the structured data (eg, inhaled corticosteroid), but the true frequency of its use by the patient may be found in the clinical notes (eg, once daily instead of twice daily). To mitigate redundancy, we will use strategies such as data deduplication [29], feature selection [30], and integrating insights from both structured and unstructured sources [31]. To enhance accuracy and reconcile any discrepancies between data sets, we will use techniques such as data fusion [32] and expert review.

Modeling Pediatric Asthma Subtypes and Their Temporal Progression Pathways With a Patient Representation Learning Model

After identifying pediatric patients with asthma using the most accurate CP, we will model the temporal representation of the asthma severity levels. Toward this end, we will include 2 years of data before and a minimum of 2 years after asthma symptoms first appear, as data prior to an asthma diagnosis allows for the inclusion of antecedent data that may be critical to asthma subtyping. We will define the asthma onset date by the first date in which the patient is classified as a positive case as per the most accurate pediatric asthma CP.

As illustrated in Figure 2, we will aggregate relevant EHR data for each patient into vectors within 3-month blocks (ie, window sizes, although we will consider varying window sizes in this

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project). Each vector corresponds to a particular event type (eg, clinical encounter, diagnosis, procedure, medication, or symptoms) based on discrete structured data and data extracted from clinical notes using NLP. For example, the dimensionality of a diagnosis vector equals the number of distinct diagnosis codes, with each dimension's value representing the frequency of that code appearing in the current 3-month period. We will divide each patient's data into multiple subsequences. We plan to explore a wide range of deep learning methods, including long short-term memory autoencoders (baseline) [33], outcome-oriented transformers [34], and block-recurrent transformers [35], based on our initial review of state-of-the-art models to effectively represent the sequential records of pediatric patients with asthma.

Figure 2. The asthma temporal trajectory in electronic health records.

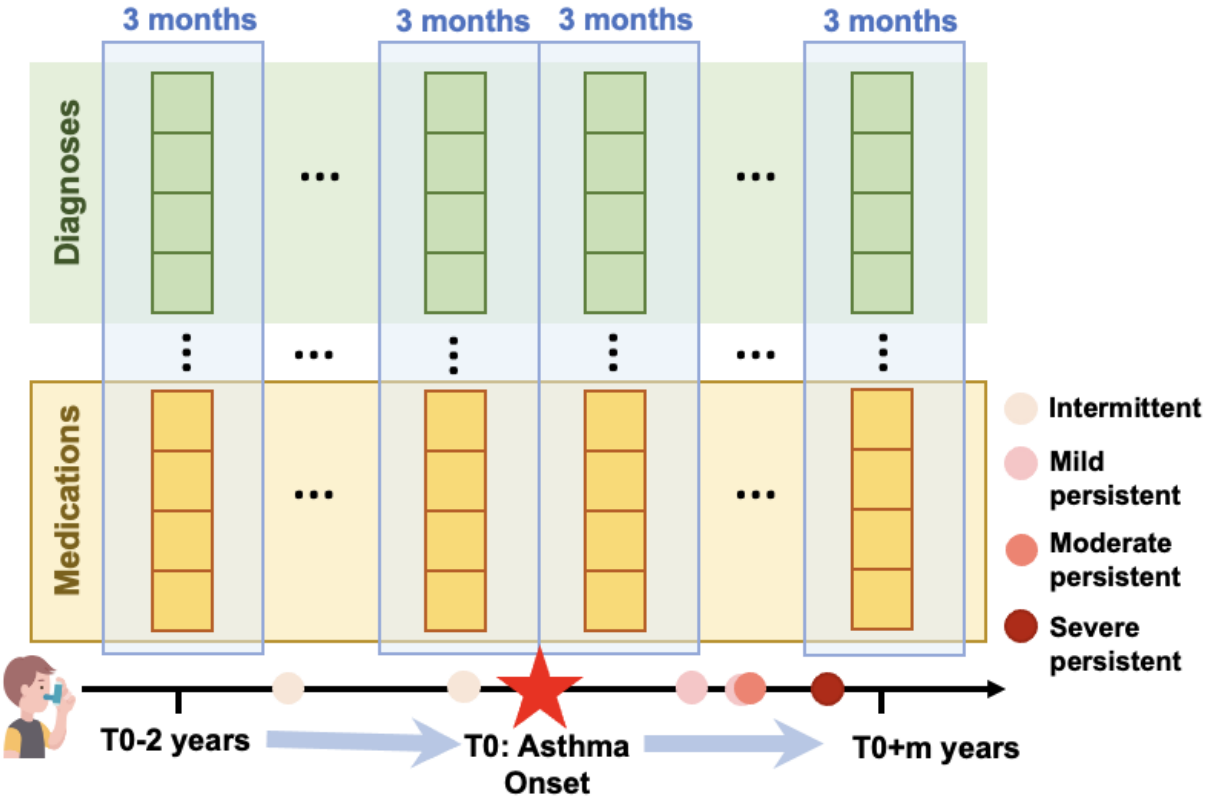

After obtaining temporal representations, we will apply hierarchical agglomerative clustering [36] to determine the clusters of the subsequences (ie, states), as illustrated in Figure 3. Subsequences will be grouped according to the similarity of their progression embedding vectors learned through the previous modeling process. We will select the Ward method for hierarchical agglomerative clustering [36]. Unlike other methods that measure distance directly, the Ward method focuses on analyzing the variance of clusters. It achieves this by iteratively merging the most similar clusters, with the goal of minimizing the increase in the error sum of squares upon cluster combination. By reducing variance within each cluster, the Ward method facilitates the formation of compact and distinct clusters. Once we have established the clusters of subsequences (ie, states), we will determine the states for each patient based on the cluster centers of the corresponding subsequences derived from that patient. The trajectory pattern of the patient is represented by different states that change over time (ie, the progression from one state to another). Each progression subtype will include patients with similar trajectory patterns. For instance, if a patient is divided into four subsequences and three states (eg, A1, A2, A3) are identified using the clustering algorithm [10], the trajectory pattern of that patient would be "A1 to A3 to A1 to A2." Additionally, we will develop predictive models to identify key features that transition patients from one state to another, using different states as labels.

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Figure 3. Identifying asthma progression subtypes. (A) Framework of identifying asthma progression subtypes. (B) System structure of federated clustering. (C) Explanation of progression subtypes.

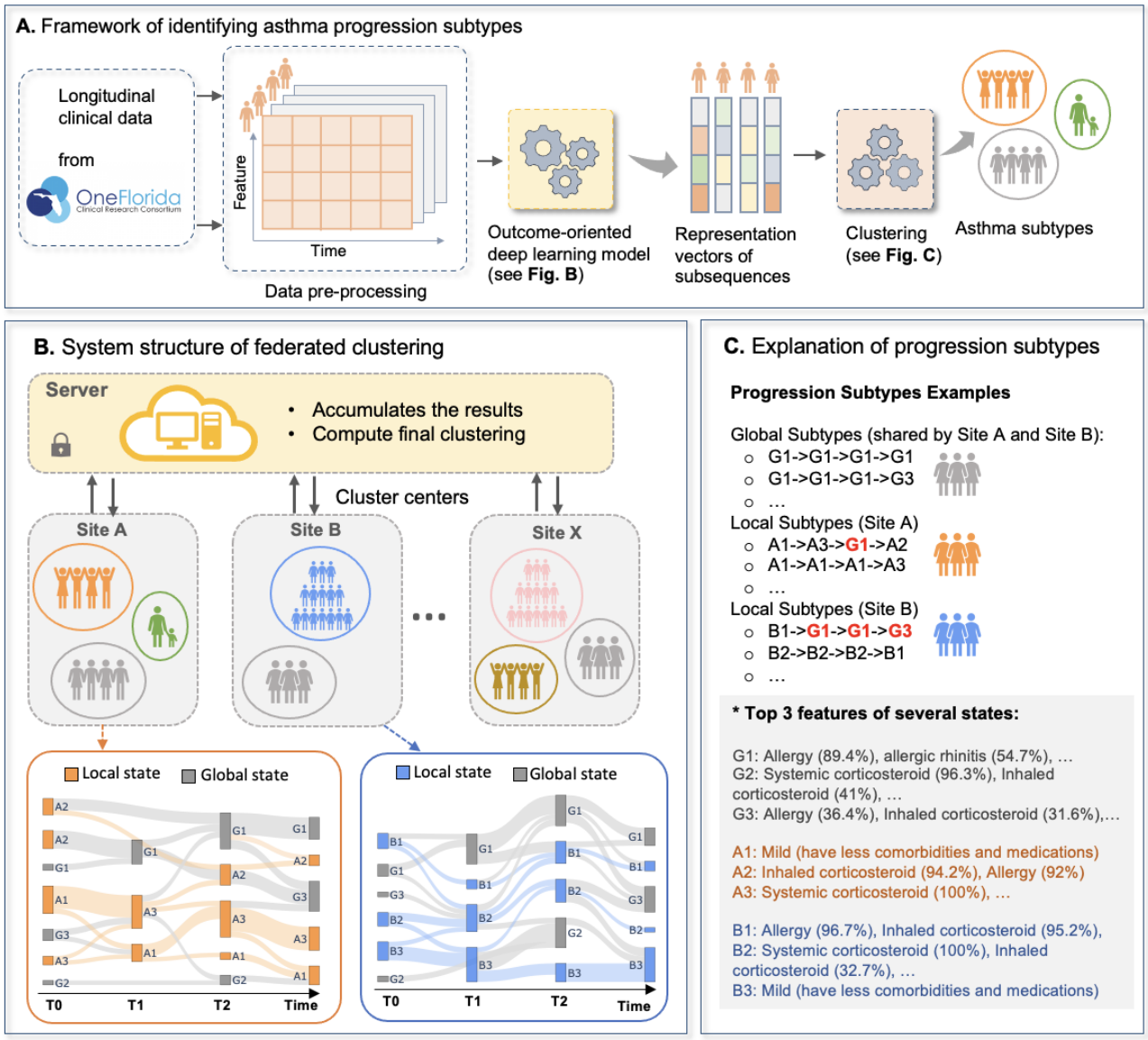

Federated Learning for Identifying Asthma Progression Subtypes Across OneFlorida+ Networks

In the subsection above, we described how we will model pediatric asthma subtypes and their temporal progression pathways using a patient representation learning model within individual local institutions. However, extending this approach to distributed clinical research networks such as OneFlorida+ necessitates careful consideration of privacy issues. Hence, we propose leveraging federated learning, which is a technique that connects fragmented data sources to learn a global model without sharing sensitive patient data across sites [10]. Under this federated learning framework, each OneFlorida+ site periodically communicates the local updates to a central server. The central server then aggregates these updates and sends back the parameters of the updated global model to the sites. This process ensures that patient data remain decentralized and secure while allowing collaborative model training across distributed sites.

In addition, we will use a federated clustering approach to identify OneFlorida+ site–specific subtypes and shared subtypes across all OneFlorida+ sites, accounting for the heterogeneity of patients with asthma across different health care systems. Figure 3B shows examples of site-specific progression subtypes for two theoretical sites (ie, site A and site B). The colorful progressions (ie, orange paths and blue paths at the bottom of Figure 3B) are local site-specific progression subtypes. The grey paths represent shared progression subtypes (ie, created after federated learning clustering identified global states by leveraging other sites' data).

Studying the Utility and Integration of Progression Subtype Data Into Clinical Practice

While asthma severity classifications are currently used as clinical decision support for pediatric asthma clinicians [37], our subtype data are expected to encompass a broader range of features. Prior to integrating our findings into a user-centered design of an EHR-based clinical decision support system, it is essential to know how clinicians will use the novel asthma

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progression subtypes generated by this project, specifically what information is most relevant (eg, subtype characteristics, progression patterns, modifiable risk factors) and how it is used in different practice settings (eg, primary care, subspecialty care, emergency/inpatient care).

Therefore, we have adopted a "design for dissemination" approach [13], and will use the Promoting Action on Research Implementation in Health Services (PARIHS) framework [38] to interweave our quantitative subtyping results with qualitative feedback from pediatric asthma clinicians. We will conduct sequential rounds of focus groups to better understand the clinical utility of this information and plan for its eventual clinical implementation. The first round of focus groups will involve practicing pediatric asthma clinicians from local OneFlorida+ sites, where we will present the progression subtype results (including both site-specific and global model data). We will recruit focus group participants from the spectrum of clinicians who care for children with asthma to understand how progression subtype data are interpreted and used across the continuum of care, including primary care physicians (eg, pediatricians, family medicine practitioners), emergency physicians, pediatric inpatient hospitalists and critical care physicians, pediatric pulmonologists, and allergists, as well as health information technology professionals. For clinician participants, we will recruit MDs, DOs, and other allied health professionals who autonomously see patients and have been in practice at least 2 years.

We will deductively code focus group transcripts using the PARIHS framework, which was selected owing to its ability to systematically explore themes key to the implementation of research into clinical practice (Table 1). Two members of the study team trained in qualitative methods will separately code the transcripts. We will calculate Cohen κ for coder interrater reliability and resolve discrepancies by study team consensus. Using NVivo, we will combine related codes to construct overarching themes and relate those themes to PARIHS elements and subelements (Table 1).

Table 1. Promoting Action on Research Implementation in Health Services (PARIHS) framework and themes [38] to explore in the first round of focus groups.

PARIHS element	Relation to study
Evidence	
Research	Subtype features, number, progressions
Clinical and patient experience	SDOH[a], health disparities, patient age, health literacy
Local data	Site-specific versus global subtype models
Context	
Culture	Clinician, health care system, patient/caregiver, community
Leadership	Health care system and payer attitudes, clinician incentives
Evaluation	Asthma severity classification, patient-centered outcomes
Facilitation	
Purpose	Clinical decisions, risk factor modification
Role	Specialty, clinical setting
Skills and attributes	Specialty, clinical setting, EHR[b] fluency

[a]SDOH: social determinants of health.

[b]EHR: electronic health record.

Based on feedback from the first round of focus groups and our stakeholder advisory committee, we will develop multiple EHR design prototypes, according to a user-centered design, for incorporating pediatric asthma progression subtype data (considering both shared/global subtypes and site-specific subtypes). Subsequently, we will conduct a second round of focus groups with the same participants to present these EHR design prototypes in a high-fidelity manner (ie, demonstration video showing how the system is integrated into the clinicians' EHR with functionality, and, when applicable, a mock-up system where the end users can interact in a simulated EHR environment). During these sessions, we will gather clinicians' feedback on how they would interpret the information and interact with alerts and other functions (when applicable), identify usability issues, and solicit preferences and suggestions for improvement.

Study Limitations and Potential Expansions

While OneFlorida+ is a large sample of pediatric patients with asthma, it does not represent all pediatric patients with asthma, and thus our subtypes may not be generalizable nationwide or worldwide. Missing data is possible, particularly with regard to patient-reported variables. When possible, we will query the free-text data to fill in missing variables. For variables likely to be missing at random, we will use tools such as multiple imputation by chained equations and regression-based imputations [39]. For variables missing not at random, we will consider selection model–based methods, including outcome-dependent sampling for longitudinal outcomes [39]. We will leverage the infrastructure of OneFlorida+ and our study team's existing relationships with clinical partners at each identified site to recruit practicing clinicians for focus groups.

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In the unlikely event that we do not meet our target recruitment for focus group participants, we can expand the focus groups beyond the OneFlorida+ network.

Results

Funding Acquisition and Recruitment

This study obtained funding from the National Institutes of Health/National Heart, Lung, and Blood Institute on September 1, 2023 (1R01HL169277). In September 2024, we began data abstraction. The OneFlorida+ data trust contains approximately 21.29 million patients. Between 2011 and 2023, OneFlorida+ recorded data for 411,628 patients aged 2-18 years and contained 11,156,148 clinical notes.

Current Asthma CPs

As an initial step in developing pediatric asthma CPs, we conducted a rapid review of the published English-language literature for existing CPs for pediatric asthma. The review identified four CPs for pediatric asthma and a fifth for classifying pediatric asthma severity (Table 2).

Table 2. Existing pediatric asthma computable phenotypes (CPs), data composition, and performance metrics.

CP	Structured data	Unstructured data	Performance metrics[a]			
			PPV[b] (%)	NPV[c] (%)	Sensitivity (%)	Specificity (%)
CAPriCORN [40]	Yes	No	90	96	89	96
PheKB [41]	Yes	Yes	67	90	73	87
NLP-PAC [24]	Yes	Yes	89	97	92	96
Problem List [42]	Yes	No	98	N/R[d]	N/R	N/R
Pediatric Asthma Severity[e] [43]	Yes	Yes	N/A[f]	N/A	N/A	N/A

[a]Performance metrics based off original studies.

[b]PPV: positive predictive value.

[c]NPV: negative predictive value.

[d]N/R: not reported.

[e]Performance judged by various components of computable phenotypes and combinations of components agreement with physician expert review of severity as judged by the weighted κ value, which ranged from –0.11 to 0.46.

[f]N/A: not applicable.

Project Timeline

In the first year of the project, we will construct and optimize the pediatric asthma CP and develop a clinical NLP pipeline to better categorize pediatric asthma patients and their disease severity. In the second and third years, we will implement federated learning strategies to model pediatric asthma subtypes and their progression. In the fourth and fifth years, we will engage in focus groups with frontline asthma clinicians to assess the clinical utility of the subtypes, design EHR prototypes for clinicians to visualize subtype information, and conduct another round of focus groups to gather feedback on the EHR prototypes. Our stakeholder advisory committee will convene biannually throughout the project's duration. We expect to publish our subtyping results in year 4 and the focus group and EHR prototype work at the end of year 5.

Discussion

The results of this project will advance both methodologic and clinical science. With regard to technical and methodologic development, the CP and NLP pipeline can assist other pediatric asthma researchers. Our novel privacy-preserving federated learning methodology addresses several challenges associated with analyzing large multicenter RWD and provides a generalizable framework for other clinical research networks. Additionally, the framework of our federated learning methodology could also be applied to the study of subtypes of other chronic, heterogeneous diseases. Clinically, pediatric asthma progression subtypes incorporating RWD can help improve patient outcomes by moving the field closer to precision pediatric asthma care, tailoring medications, addressing potentially preventable risk factors, and preventing exacerbations that risk morbidity and mortality. Importantly, our concomitant qualitative research and stakeholder engagement lays the foundation for efficient and timely implementation of our subtypes into clinical practice.

Acknowledgments

The authors acknowledge Dr Jiang Bian, PhD, for his mentorship and guidance.

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Data Availability

As OneFlorida+ is a data set containing identifying information, we will not make our data publicly available. We will develop tutorials and a manual of operations for the computable phenotype and natural language processing code and tools we will develop in this project. Final code will be made available as open-source software.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Center for Scientific Review Special Emphasis Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 94 KB - resprot_v13i1e57981_app1.pdf]

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Abbreviations

CP: computable phenotype
EHR: electronic health record
IRB: Institutional Review Board
ML: machine learning
NLP: natural language processing
PARIHS: Promoting Action on Research Implementation in Health Services
PHI: protected health information
RWD: real-world data
SDOH: social determinants of health

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Protocol

mHealth-Based Just-in-Time Adaptive Intervention to Improve the Physical Activity Levels of Individuals With Spinal Cord Injury: Protocol for a Randomized Controlled Trial

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Abstract

Background: The lack of regular physical activity (PA) in individuals with spinal cord injury (SCI) in the United States is an ongoing health crisis. Regular PA and exercise-based interventions have been linked with improved outcomes and healthier lifestyles among those with SCI. Providing people with an accurate estimate of their everyday PA level can promote PA. Furthermore, PA tracking can be combined with mobile health technology such as smartphones and smartwatches to provide a just-in-time adaptive intervention (JITAI) for individuals with SCI as they go about everyday life. A JITAI can prompt an individual to set a PA goal or provide feedback about their PA levels.

Objective: The primary aim of this study is to investigate whether minutes of moderate-intensity PA among individuals with SCI can be increased by integrating a JITAI with a web-based PA intervention (WI) program. The WI program is a 14-week web-based PA program widely recommended for individuals with disabilities. A secondary aim is to investigate the benefit of a JITAI on proximal PA, defined as minutes of moderate-intensity PA within 120 minutes of a PA feedback prompt.

Methods: Individuals with SCI (N=196) will be randomized to a WI arm or a WI+JITAI arm. Within the WI+JITAI arm, a microrandomized trial will be used to randomize participants several times a day to different tailored feedback and PA recommendations. Participants will take part in the 24-week study from their home environment in the community. The study has three phases: (1) baseline, (2) WI program with or without JITAI, and (3) PA sustainability. Participants will provide survey-based information at the initial meeting and at the end of weeks 2, 8, 16, and 24. Participants will be asked to wear a smartwatch every day for ≥12 hours for the duration of the study.

Results: Recruitment and enrollment began in May 2023. Data analysis is expected to be completed within 6 months of finishing participant data collection.

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Conclusions: The JITAI has the potential to achieve long-term PA performance by delivering tailored, just-in-time feedback based on the person's actual PA behavior rather than a generic PA recommendation. New insights from this study may guide intervention designers to develop engaging PA interventions for individuals with disability.

Trial Registration: ClinicalTrials.gov NCT05317832; https://clinicaltrials.gov/study/NCT05317832

International Registered Report Identifier (IRRID): DERR1-10.2196/57699

(JMIR Res Protoc 2024;13:e57699) doi:10.2196/57699

KEYWORDS

spinal cord injury; physical activity; just-in-time adaptive intervention; mobile health; randomized controlled trial; microrandomized trial; wearable sensors; ecological momentary assessment; community; mobile phone

Introduction

Background

Physical inactivity is a significant concern among the >300,000 individuals living with spinal cord injury (SCI) in the United States [1], who are at an elevated risk of mortality due to cardiovascular diseases, diabetes, and lung disease [2-4]. Low levels of physical activity (PA) in individuals with SCI have also been associated with secondary health conditions such as pain, fatigue, and depression [5-7]. Research studies have found varying percentages of the population with SCI that perform regular PA [8-10]. On the higher end, Rauch et al [8] found that 48.9% of 485 participants with SCI in Switzerland met World Health Organization recommendations of 2.5 hours per week of moderate-intensity or higher PA, and 18.6% were physically inactive. On the lower end, Tasiemski et al [10] found that only 20% of 985 people with SCI in the United Kingdom performed regular PA of 2 hours per week, and 53.3% reported no regular PA. Furthermore, several other studies have indicated that most individuals with SCI do not perform regular PA [11-13].

Regular PA and exercise interventions in individuals with SCI have been linked with improved cardiorespiratory fitness, quality of life, and functional independence, as well as reduced risk of cardiometabolic disease, depression, and shoulder pain [11,12,14,15]. Although there are significant health and quality-of-life benefits with regular PA, various barriers limit individuals with SCI from performing PA regularly [16]. To address some of these barriers, the National Center on Health, Physical Activity, and Disability (NCHPAD) has developed a free web-based PA program for people with mobility limitations, chronic health conditions, and physical disabilities [17]. Web-based PA programs can lead to an increase in PA level and duration of PA performed by individuals with SCI [18-21]. One of the facilitators that can promote PA during PA intervention programs is to provide people with an accurate estimate of their everyday PA level in the community [18,22-24]. This information can empower individuals with knowledge about their regular PA levels, which in turn can help develop a physically active identity [16].

The PA of individuals with SCI is frequently assessed through samples of individuals who provide self-reports [8-10], which may have recall bias and social acceptability bias. To address these limitations and to better quantify PA and exercise interventions, researchers have validated sensor-based activity monitors in laboratories and community-dwelling environments [22,23,25]. PA tracking can also be combined with mobile health (mHealth) technology to provide a just-in-time adaptive intervention (JITAI) for individuals with SCI as they go about everyday life. A JITAI uses mHealth technology to deliver the intervention at appropriate times and contexts to support individuals' health behaviors [24,26,27]. For example, Klasnja et al [27] used a JITAI to provide a real-time feedback intervention aimed at improving step count in individuals without disabilities. Our team tested a pilot JITAI for its feasibility and acceptability in individuals with SCI [24]. Results from our pilot study indicated that participants wished to have the system provide customized messages to help them further increase their PA levels. These customized messages combined with web-based PA intervention programs have the potential to impact factors such as intent to increase PA, awareness of PA benefits, reminders, and encouragement that are related to increased PA levels in individuals with SCI [11,12,18,28].

Objectives

The overarching goal of this study is to investigate the benefits of combining an mHealth-based JITAI with the NCHPAD's 14-week web-based PA intervention (WI) program for increasing and sustaining moderate-intensity or higher PA levels among individuals with SCI. This protocol outlines the study design for investigating the impact of integrating a JITAI with the WI program via a randomized controlled trial that integrates a 2-arm trial and a microrandomized trial (MRT). Specifically, individuals with SCI (N=196) will be randomized to either a WI program or a WI program combined with the JITAI (WI+JITAI). Within the WI+JITAI arm, an MRT [27,29,30] will be used to microrandomize participants several times a day to various types of feedback and PA recommendations. The primary aim is to investigate the long-term benefits of adding a JITAI to WI. We hypothesize that the integration of a JITAI into WI will produce significantly higher PA levels than those with WI alone. The secondary aim is to investigate the benefit of just-in-time PA feedback on proximal PA. Proximal PA is defined as moderate-intensity PA within 120 minutes of a PA feedback prompt. The exploratory aim will investigate time-invariant moderators such as biological sex and level of injury and time-varying moderators such as prior PA and engagement with the JITAI to help identify subgroups of individuals with SCI who are likely to benefit the most from the integration of a JITAI with WI.

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Methods

Ethical Considerations

The institutional review board at Temple University has reviewed and approved this research study (protocol number 27338). The study will be executed in accordance with the ethical standards for human participants. All participants will provide written informed consent. The consent form will include the purpose of the research study, description of what participation in the study entails, and contact information of the principal investigator and the institutional review board. The consent form will be discussed with all participants by an investigator, and the participant will be offered a chance to consent at the conclusion of this discussion. Should the potential participant wish additional time to consider whether to consent, they will be given as much time as they desire. All participants will receive a copy of the consent form for their records. Verbal discussion will ensure participants understand each consent topic as it is discussed, and participants will be advised that their signature indicates their understanding and consent. It is reinforced throughout the consent form that participants are free to ask questions at any stage of the study, including before, during, or after the consent process. All participants will be informed of their right to withdraw from the study at any time. To maintain confidentiality, records and sensor data will be deidentified by assigning a case number to each participant. The study is registered on ClinicalTrials.gov (NCT05317832).

Research Design

Overview

Participants will take part in the study from their home environment in the community. The study has three phases: (1) baseline (weeks 1 and 2); (2) WI program with or without JITAI (weeks 3-16); and (3) PA sustainability (weeks 17-24). Participants will provide survey-based information at various time points during the 24-week study. Participants will be asked to wear a smartwatch every day for ≥12 hours for the duration of the study. The PA intervention for this study is informed by the capability, opportunity, and motivation (COM-B) model, which highlights that these 3 constructs should be considered when developing a behavioral intervention [31]. To our knowledge, this is the first study to optimize a JITAI that has the potential to boost PA levels using real-time feedback for individuals with SCI.

Behavioral Intervention Model

The proposed intervention approach builds on the COM-B model [31]—an organizing framework for designing behavior change interventions [32-34]. An individual's capability, opportunity, and motivation interact to generate behavior (eg, PA) that in turn influences these 3 constructs (Figure 1) [31]. Capability is the individual's psychological and physical capacity to perform the desired activity, including having the necessary knowledge and skills. Motivation is the individual's internal drive or energy that directs behavior, including conscious or analytic decision-making, as well as habitual processes and emotional responses. Opportunity captures environmental (social and physical) factors external to the individual that facilitate or undermine behavior. The solid arrows in Figure 1 represent potential influence between these constructs [31]. For example, opportunity can enhance (eg, a supportive environment) or inhibit (eg, an adverse environment) motivation and capabilities [31]. It is also possible that enacting a behavior can alter capability, motivation, and opportunity. This framework incorporates context naturally through the "opportunity" construct [31]. For individuals with SCI, the context is characterized by physiological and environmental barriers to participate in PA [16,35] and stigma [36], which can hinder motivation and capability to engage in PA.

Figure 1. The proposed intervention builds on the capability, motivation, and opportunity model—a framework for understanding behavior (adapted from Michie et al [31], which is published under Creative Commons Attribution 2.0 International License [37]). The solid arrows represent potential influence between system components. An individual's capability, motivation, and opportunity interact to generate behavior (eg, physical activity [PA]) that in turn influences these 3 constructs. SCI: spinal cord injury.

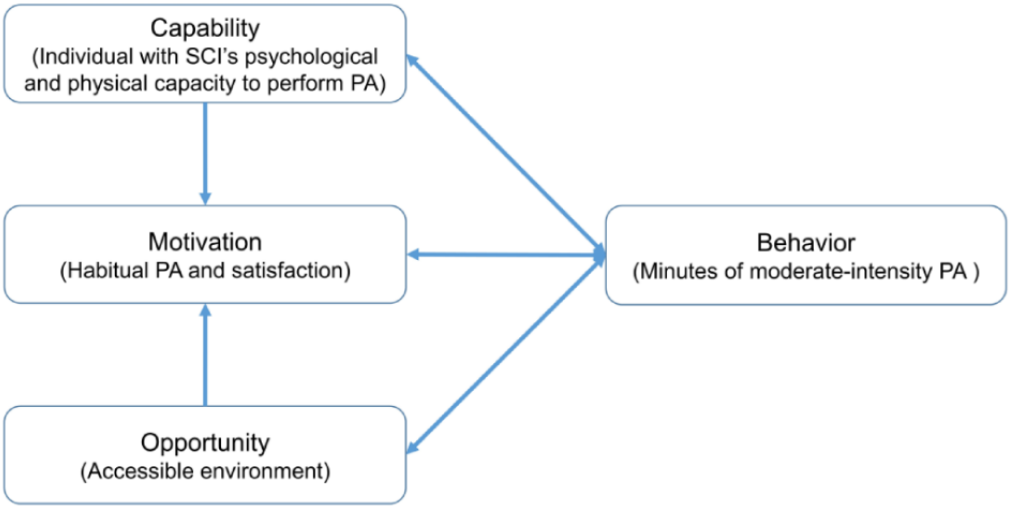

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Conceptual Framework of the JITAI

The framework used for this proposed study (Figure 2) is adapted from Nahum-Shani et al [26], which highlights 4 components including decision points, intervention options, tailoring variables, and decision rules. JITAIs often provide an intervention through a smartphone, wearable activity monitor, or both. The system automatically determines which intervention option, such as prompting an individual to set a goal to perform PA or prompting feedback about PA, could be helpful or especially effective. Engagement with the JITAI, that is, effort invested in the JITAI [38], is critical for intervention effectiveness [26]; therefore, JITAI components should be selected and designed to promote engagement [27].

Figure 2. Conceptual framework of just-in-time adaptive intervention components including decision points, intervention options, tailoring variables, and decision rules for our proposed study (adapted from Nahum-Shani et al [26], which is published under Creative Commons Attribution Noncommercial International License [39]). SCI: spinal cord injury.

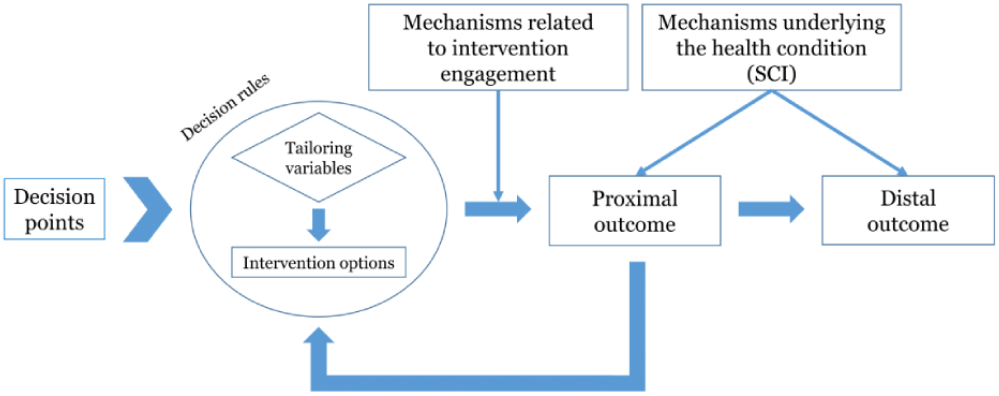

NCHPAD's WI Program

Our proposed JITAI will be offered along with NCHPAD's 14 Weeks to a Healthier You Program [17,40,41], modified to be accessible on a smartphone or tablet. This 14-week WI program was launched in 2011 by NCHPAD with funding from the Centers for Disease Control and Prevention [40]. Since its launch, the program has been used by >45,000 people with various physical disabilities. It is the most widely recommended web-based PA program across various disabilities and state disability programs [42]. The program's uniqueness lies in its ability to offer tailored exercise that matches the participants' functional capabilities. The WI program was developed with guidance from literature and practice in health behavior change and internet-based health promotion programming. In addition, preliminary evaluations by individuals with disabilities were used to update the WI program. Textbox 1 lists motivational resource for each week of the program [41]. The content for all weeks include an introductory video, exercise resources, motivational resources, recipes, and nutrition resources. Customizable features for all weeks include my schedule, initial assessment, badge reward system, my goals, and daily reminder.

Textbox 1. Motivational resources for each week of the National Center on Health, Physical Activity, and Disability's 14-week web-based physical activity program.

Motivational resources

- Week 1: Goal setting
- Week 2: Overcoming barriers
- Week 3: Benefits of activity
- Week 4: Weight management
- Week 5: Self-monitoring
- Week 6: Keep it fun!
- Week 7: Rewarding yourself
- Week 8: Building social support
- Week 9: Stimulus control
- Week 10: Preventing injuries
- Week 11: Self-advocacy in recreation
- Week 12: Activity in daily life
- Week 13: Avoiding overtraining
- Week 14: Keeping it up!

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Integration of JITAI With WI

The integration between the WI and JITAI is designed to blend multiple evidence-based components aimed at prompting capability, motivation, and opportunity for engaging in PA among individuals with SCI (Table 1). Capability will be enhanced by not only providing tailored information and advice for individuals with SCI via the standard WI but also by using self-regulatory techniques, operationalized by setting goals, monitoring progress, and providing timely feedback via the JITAI [24,26,31]. To enhance motivation to engage in PA, the JITAI will reinforce progress by providing just-in-time feedback about the minutes of moderate-intensity PA achieved or remaining to be achieved toward the daily goal. Opportunity will be enhanced by identifying specific types of goals (tailored, standard, or goal not presented) and PA feedback (achieved, to-go, or feedback not presented) that will be most beneficial in promoting daily and proximal PA, respectively. Although the standard goal encourages the individual to perform 20 minutes of moderate-intensity PA for the day based on PA guidelines for adults with SCI [43], a tailored goal is based on average minutes of moderate-intensity PA performed by the individual over the last 7 days. The choice of the last 7 days is based on PA guidelines for adults with SCI [43] and our pilot study [24] in which participants had lower PA for 1 or 2 days during the week. Although the achieved PA feedback message focuses on the PA level the person has accomplished until that moment in the day, the to-go message focuses on the remainder of the PA level the person has to accomplish to meet their designated goal. Prior research has indicated that the gain-framed messages were more likely than loss-framed messages to encourage prevention behaviors such as PA [44]. In this study, we are interested in evaluating whether participants prefer achieved PA message (gained) or to-go message (to gain) to accomplish their goal. In addition, the participants will be reminded to engage with the WI on a regular basis.

Table 1. Evidence-based components of the capability, opportunity, and motivation model targeted by the web-based physical activity intervention (WI) arm and WI+just-in-time adaptive intervention (JITAI) arm.

	WI	WI+JITAI
Capability	• Tailored information and advice • Weekly goal setting • Monitoring weekly progress	• WI: tailored information and advice, weekly goal setting, monitoring weekly progress • JITAI: goal setting for the day, just-in-time tailored PA[a] information
Motivation	• Badges for completing weekly modules on WI • PA progress over the last 7 days	• WI: badges for completing weekly modules on WI; PA progress over the last 7 days • JITAI: PA recommendations during goal setting; just-in-time tailored PA feedback messages; availability of real-time PA information; goal attainment at the end of day
Opportunity	• Daily reminder to complete WI program	• WI: daily reminder to complete WI program • JITAI: just-in-time specific type of feedback to encourage proximal (within 120 min) PA achievement; just-in-time feedback to encourage more distal (daily goal) PA achievement

[a]PA: physical activity.

PA Intervention Components

The PA intervention components include either the WI program or the WI program combined with JITAI for individuals assigned to the WI or WI+JITAI arms, respectively.

WI Program

Participants will access the 14-week WI program and answer questions related to their interests, needs, and abilities (Textbox 1), which will be used to tailor the content (exercises and videos). Participants can monitor the WI program use on their dashboard. From this point forward, program content automatically updates every week to introduce new exercises and a weekly motivational and educational topic. Participants will receive a daily reminder, except for the day off, on the smartwatch to access the WI program (Figure 3). Furthermore, participants will have access to the minutes of moderate-intensity PA performed over the last 7 days on the study smartphone (Figure 4).

Figure 3. Schedule of reminders delivered over a week on a smartwatch. Participants will receive a daily reminder, except for the day off, on the smartwatch to access the web-based physical activity intervention (WI) program.

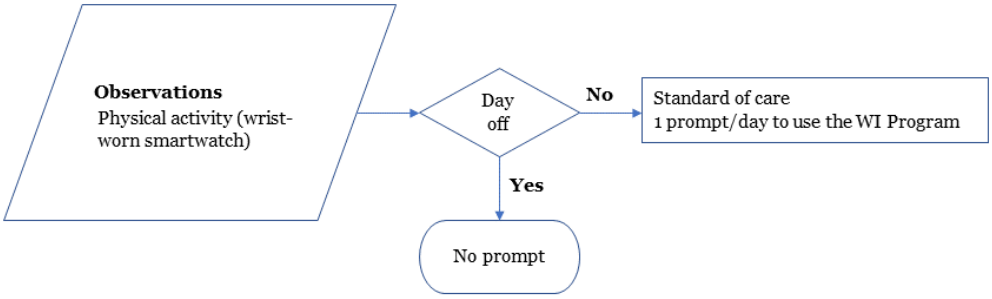

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Figure 4. Example of feedback and reminders of physical activity. Left: participants will have access to physical activity levels performed over the last 7 days on the smartphone. Right: participants will receive a daily reminder, except for the day off, on the smartwatch to access the web-based physical activity intervention program.

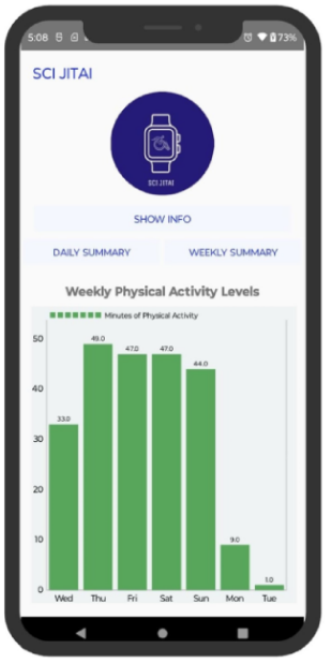

JITAI Components

Participants in the WI+JITAI arm will have access to the JITAI components. In addition to WI program access, participants will receive just-in-time feedback and PA recommendations informed by the guidelines for adults with SCI [43]. Participants will have access to the minutes of moderate-intensity PA performed over the last 7 days on the study phone. In addition, they will have near–real-time access to minutes of moderate-intensity PA performed for the day on their smartwatch.

During the 22-week intervention period, the PA feedback and recommendation messages will be delivered using microrandomization, which involves random selection of intervention options at each possible time of delivery [29,45]. The microrandomizations will assess the proximal benefits of just-in-time interventions (Figures 5 and 6): (1) *PA recommendations* by randomizing the participant with a 33% probability to a standard, tailored, or no goal within 1 to 2 hours of waking up (Figure 7) and (2) *PA feedback prompts* by randomizing the participant with a 50% probability to a JITAI message or no message twice a day (Figure 8). The first and second PA feedback prompts are randomized between 2 and 4 hours after wake-up and 6 to 8 hours after wake-up, respectively. Table 2 shows the type and number of messages participants will receive during the intervention period. Within the *PA feedback prompts*, the participant will be randomized to an achieved or to-go message with a 25% probability per day. The participant can acknowledge seeing the JITAI message by pressing a “Got it” pop-up button that appears on their smartwatch. Furthermore, since the smartwatch’s accelerometer sensor can detect movement-based PA and not the intensity of the strength exercises, participants will respond to a short ecological momentary assessment, presented on their smartwatch at the end of the day to confirm whether they performed exercises (aerobic, strength, or both; Figure 9). The choice of 2 randomizations per day for *feedback prompts* was based on our pilot study [24], in which the participants felt that 5 interruptions per day were reasonable and not distracting. The other 3 interruptions include goal-type message, WI reminder, and a short ecologic momentary assessment at the end of the day.

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Figure 5. Schedule of reminders, just-in-time adaptive intervention (JITAI) messages, and physical activity recommendations delivered on a smartwatch. (A) Study flow over a week: participants will receive a daily reminder, except for the day off, to access the web-based physical activity intervention (WI) program. Participants will be randomized to receive a standard or tailored physical activity goal, or no goal, for 2 of the days each week. (B) Study flow over a day: participants in the intervention group. Participants will be randomized twice during each day to receive or not receive a JITAI feedback prompt. EMA: ecological momentary assessment; R: randomized.

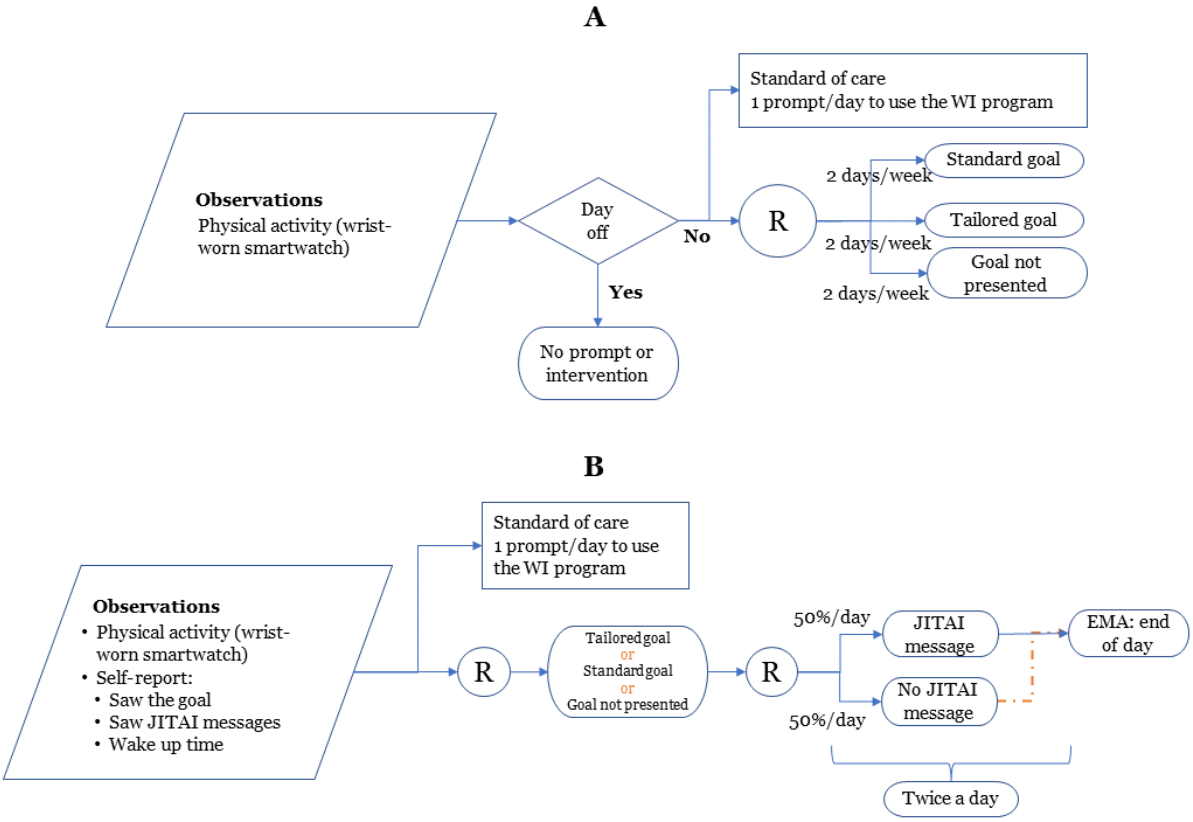

Figure 6. Example of real-time daily feedback on the smartphone (left) and smartwatch (right). The goal for the day in this example is 27 minutes of moderate-intensity physical activity (PA). This is in addition to having access to PA levels performed over the last 7 days on the smartphone.

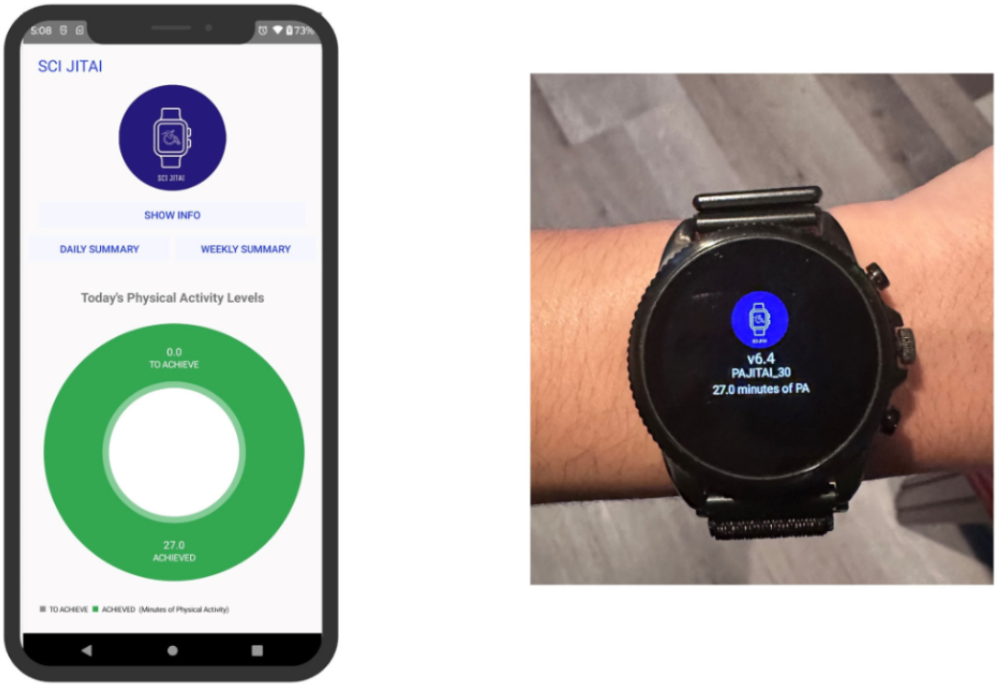

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Figure 7. Participants will be randomized to a standard goal, tailored goal, or no goal condition within 1 to 2 hours of waking up. Top: goal setting—standard goal. Bottom: goal setting—tailored goal. The "Try again" screen will automatically time out back to the goal screen if the user does not press the "Try again" button in 3 seconds. Messages will be reprompted up to 3 times.

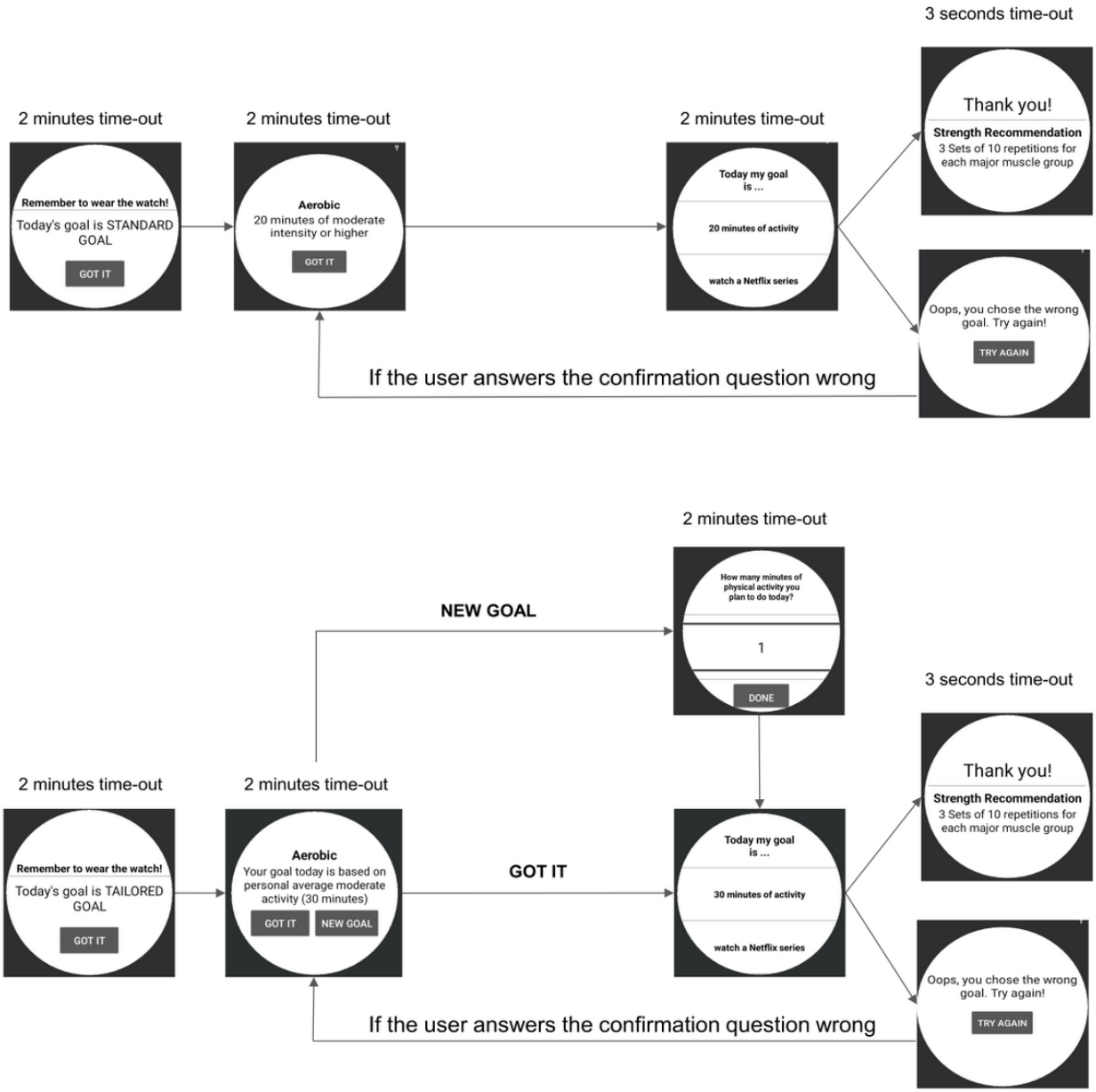

Figure 8. Participants will be randomized to a just-in-time adaptive intervention (JITAI) message or no message twice a day. Left: JITAI message—achieved. Middle: JITAI message—to go. Right: if the user acknowledges the JITAI message, then the user receives a "fortune cookie"–like message on the smartwatch.

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Table 2. The type and average number of messages participants will receive during the physical activity intervention period.

Goal-type message (number of days in a week)	Number of JITAI[a] or no message per goal type (randomized)		Number and type of JITAI messages per goal type (randomized)		Number of ecological momentary assessments per goal type
	JITAI message	No message	JITAI (achieved)	JITAI (to go)	
Standard goal (2)	2	2	1	1	2
Tailored goal (2)	2	2	1	1	2
No goal (2)	2	2	2	0	2
Day off (1)	0	0	0	0	1

[a]JITAI: just-in-time adaptive intervention.

Figure 9. Participants will respond to an end-of-day ecological momentary assessment to confirm whether they performed exercises (aerobic, strength, or both).

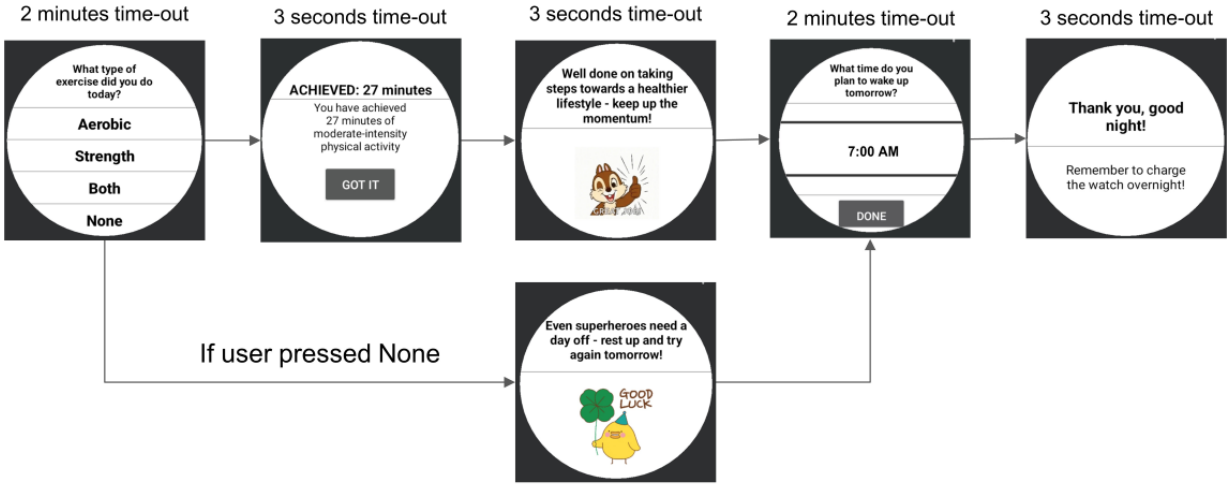

Personalized PA Threshold Identification

A multifaceted approach of using self-reported PA data with sensor data from the smartwatch during the baseline period will help identify personalized PA thresholds. These personalized PA thresholds are then used by the JITAI to determine whether minutes of moderate-intensity PA per day for each participant have been achieved each day for the rest of the study period. Baseline PA data are quantified using a motion summary measure that is computationally feasible on the smartwatch for real-time computation. Area under the curve (AUC) values obtained from high-pass–filtered triaxial accelerometer signals are summed each minute to obtain a single motion measure per minute, which is then further summed throughout the day. The AUC values provide a quantitative and cumulative measure of PA over time because they integrate the intensity of motion activity over time. The choice of a relatively simple measure of PA intensity is due to its low computational demands on the central processing unit, causing a reduced impact on the battery life of the smartwatch. In addition, self-reported PA data are collected through the Physical Activity Recall Assessment for people with SCI, which provides subjective insights from the participants [46]. After the baseline data collection, we will meticulously compare the self-reported PA data with AUC data to determine a new threshold value for each participant (Figure 10) to gain a more comprehensive understanding of their actual PA levels and intensity. The rationale for this process is due to various functional deficits resulting from complete or incomplete SCI at different neurological levels (cervical, thoracic, lumbar, and sacral) [47]. These functional deficits, in turn, lead to large biomechanical variations of upper extremity use during exercise and mobility. Moreover, developing person-specific models that are trained to recognize the types of activities each person with SCI can perform would be burdensome. Our approach of using movement data from a wrist-worn smartwatch allows us to generalize the intervention to persons with SCI without requiring them to come to a laboratory for extensive measurements.

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Figure 10. Flowchart to identify a personalized physical activity (PA) threshold. The new threshold value will allow us to calculate minutes of moderate-intensity PA per day for each participant. AUC: area under the curve; PARA-SCI: Physical Activity Recall Assessment for people with spinal cord injury.

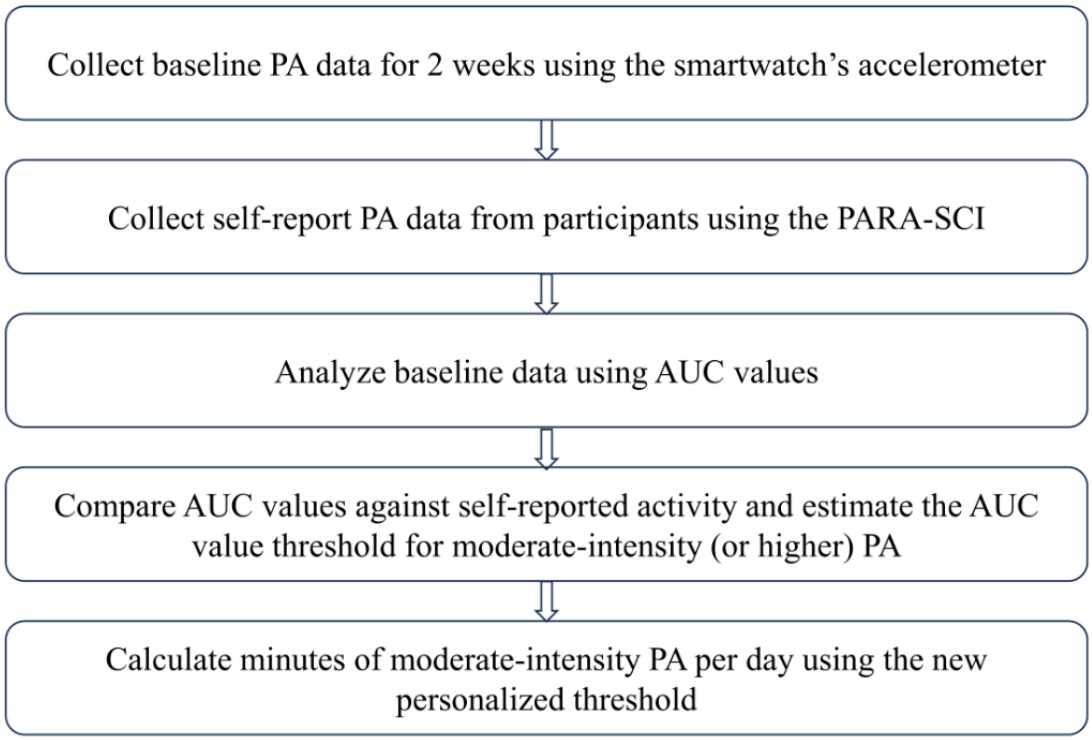

Sample Size Determination

Sample size calculation for the primary aim (a 2-arm randomized controlled trial) indicated that 82 participants are needed per group to detect at least a standardized mean difference of 0.44 [48] (considered small to moderate) in the primary outcome, with 80% power (assuming a 2-sided test with an α level of .05). On the basis of prior research [49,50] and our pilot study [24], we anticipate a 20% dropout rate. Thus, we plan to recruit a total of 196 participants with SCI (98 participants per group). In addition, power analysis for the secondary aim (an MRT) based on 2 randomizations per day indicated that a sample size of 69 is needed to detect a difference between JITAI message and no message on the proximal PA achieved for the WI+JITAI arm [30,51]. We assumed an average proximal treatment effect for message versus no message of 0.10 (considered small) that starts with 0.12 (ie, a small effect) and decreases linearly for the 16 weeks, an α level of .05, and 80% power [30]. We will have sufficient power for the MRT given we plan to recruit 98 individuals for the WI+JITAI arm to ensure that the primary aim is powered.

Recruitment

Our collaborative research team will work with coinvestigators from Magee Rehabilitation Hospital, MossRehab Hospital, Thomas Jefferson University Hospital, and Good Shepherd Rehabilitation Network to recruit participants for this study. We have an established collaboration for the past 6 years. Participants will be recruited through a multipronged approach including (1) the clinicians identifying patients with SCI at their clinics who are eligible for the study and providing them with study flyers, (2) flyers being placed in the common areas of the outpatient clinics, and (3) flyers being distributed through their listserves. In addition, we will send flyers to local and national support groups for individuals with SCI in the United States to increase the visibility of our study.

Eligibility Criteria

Participants will be included if they (1) are aged 18 to 75 years; (2) have a traumatic (neurological level of injury at cervical level 5 and below) or nontraumatic SCI; (3) are ≥6 months after SCI; (4) use a manual or a power wheelchair as their primary means of mobility (>80% of time); (5) show readiness for PA as assessed by the Physical Activity Readiness Questionnaire; (6) can use their upper arms for exercise; (7) can use a smartphone including interacting, recharging, and carrying it with them; and (8) can use a smartwatch including interacting, recharging, and wearing it. Participants will be excluded if they (1) have any secondary complications such as pressure injuries, contractures, and infections that medically restrict their activity in any way; (2) are diagnosed with traumatic brain injury; and (3) have a history of cardiovascular disease.

Screening

Participants who contact us and indicate an interest to participate in the study will be informed about the inclusion and exclusion criteria. Participants will verbally indicate if they meet the criteria. If they meet the criteria, we will schedule a first meeting with them. If they do not qualify, we will not record or store any data.

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Protocol and Assessments

Participant Meetings

All study procedures will be performed at Temple University or in the community. Our team can work with the participants remotely via Health Insurance Portability and Accountability Act–compliant video conference meeting software, such as Zoom (Zoom Video Communications), to obtain study-related information; we will send participants an Android-based smartphone and a smartwatch through postal mail. The research team can also meet with participants for a 30-minute face-to-face meeting if they prefer and are located within the greater Philadelphia region. All precautions will be taken to minimize the risks to participants and the research staff during the face-to-face meeting. Recruiting individuals who wish to remotely participate in the study will help improve the chances of including individuals with SCI who face transportation barriers, boost recruitment, and enhance retention.

The initial meeting will allow individuals with SCI to provide informed consent and answer questions about their demographics, SCI, wheelchair, and health and activity history. From prior research studies, the investigators estimate that the questionnaires will take approximately 60 to 90 minutes to complete (Textbox 2). Participants will also answer questionnaires 4 to 12 indicated in Textbox 2 at the end of weeks 2, 8, 16, and 24.

Textbox 2. Questionnaire answered by the participants at the initial meeting (numbers 1-12) and at the end of weeks 2, 8, 16, and 24 (numbers 4-12).

Questionnaire
1. Demographics (eg, age, biological sex, gender, race, ethnicity, and marital status)
2. Spinal cord injury (SCI) and level of injury (SCI Core Data Set Form, SCI Spinal Column Injury Basic Data Set Form, Non-traumatic SCI Data Sets Version 1.0 Form, and American Spinal Cord Injury Association Impairment Scale)
3. Mobility (Assistive Mobility Devices and Orthoses Form)
4. Pressure injuries (Pressure Ulcer Scale for Healing Tool 3.0), if applicable
5. Pain (International SCI Pain Basic Data Set Version 2.0 Form)
6. Fatigue (Neuro-QOL Item Bank Version 1.0 Fatigue Short Form)
7. Function (Spinal Cord Independence Measure III)
8. Quality of life (Quality of Life Basic Data Set Version 1.0)
9. Physical activity (PA) history (Physical Activity Recall Assessment for people with SCI Survey and Leisure Time Physical Activity Questionnaire for People with SCI Survey)
10. PA behavior (SCI Physical Activity Behavior Survey)
11. Barriers to PA (Barriers to Physical Activity Questionnaire for People with Mobility Impairments)
12. Participants' motivation (Physical Activity and Leisure Motivation Scale)

Allocation and Blinding

After the baseline data collection, participants will be randomly allocated to one of 2 study arms (WI arm or WI+JITAI arm) based on the randomization schedule established by the project biostatistician. Participants will be block randomized on the basis of their level of injury: tetraplegia (higher-level injury) versus other (lower-level injury).

Participants will be masked (single blinding) to the study arm. All participants will receive the same WI program and commercial off-the-shelf technology. Participants in both arms will have access to minutes of moderate-intensity PA performed over the last 7 days, which is designed to motivate them to use the smartwatch in the community. In addition, the participants in the WI+JITAI arm will receive randomized prompts of various types of tailored feedback and PA recommendations over the course of the study.

Participant Testing in the Community

Overview

The research team will conduct a web-based training session for all participants to introduce them to the WI program, and study-related smartphone and smartwatch. Participants will be loaned an Android-based smartphone and smartwatch. Participants will be asked to wear the smartwatch every day for ≥12 hours. Participants are expected to wear the smartwatch for at least 6 days of the week to assist with good quality data collection for the study. They will be asked to charge the smartphone and smartwatch nightly. Participants can leave the smartphone at home. Once smartphone and smartwatch setup is complete, participants will be instructed to continue with their normal daily routine for 2 weeks during baseline data collection. With regard to the WI and WI+JITAI arms, at the end of the study, the research team will send the participants a return postal packet for them to return the study-related smartphone and smartwatch.

WI Program

Participants will access the 14-week WI program. Participants will receive reminders on the smartwatch to access the WI program. Furthermore, the study team will emphasize features such as badges for completing weekly modules to promote engagement with the WI program.

WI Arm

Participants in the WI arm will take part in the WI program mentioned above. They will also have access to the minutes of

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moderate-intensity PA performed over the last 7 days on their study smartphone. After the WI program is completed in week 16, the participants will transition to the PA sustainability phase (weeks 17-24), which will include participants having continued access to the WI program and PA performed over the last 7 days.

WI+JITAI Arm

Participants in the WI+JITAI arm will also take part in the WI program. They will have access to minutes of moderate-intensity PA performed over the last 7 days on their study smartphone, just-in-time feedback, and PA recommendations that are informed by PA guidelines for adults with SCI [43] on their smartwatch, and near–real-time minutes of PA performed over the day on their smartwatch. After the WI program is completed in week 16, the participants will transition to the PA sustainability phase (weeks 17-24), which will include participants having continued access to the WI program and feedback and recommendations on their study smartphone and smartwatch.

Compensation

Participants will receive gift cards for a total value of US $160 for completing the study. The participant incentives are provided upon completion of meetings and data collection. The incentives are divided into US $20 per meeting for the initial and final meetings of the study and US $20 for every 4-week duration of the study for a 24-week study.

Statistical Analysis

Overview

For all aims, descriptive statistics will be obtained to assess distributional assumptions, and any transformations will be applied if needed. In addition, we will examine patterns of missingness and handle this appropriately through either multiple imputation or using models that can appropriately handle missingness (eg, mixed-effects models). We will also examine whether there are any group differences on baseline covariates (eg, pain, fatigue, health, and activity history) despite randomization, and if so, we will statistically control for these variables in our models. All analysis will be performed with an α level of .05.

Primary Aim Analysis

We hypothesize that the integration of WI+JITAI will produce significantly higher PA levels over 14 weeks than the standard WI alone. Exploratory outcomes include long-term PA (measured via sensors and self-report) over 24 weeks (approximately 6 months). To test our hypothesis, we will fit a mixed-effects model in which the group indicator variable is a predictor, and the outcomes are the PA measurements at 2, 8, and 16 weeks. We will include an interaction with time in the model because we hypothesize that although PA levels may increase in both groups, they will increase more in the WI+JITAI group. We will also include a random intercept and slope for time. To evaluate long-term PA, we will include the PA levels at 24 weeks in the model.

Secondary Aim Analysis

Data from the individuals with SCI assigned to the WI+JITAI condition will be used to assess the impact of randomly provided just-in-time PA feedback on proximal PA. The analysis will address the question of whether, on average, the just-in-time PA feedback intervention has a proximal effect on moderate-intensity PA within 120 minutes of the feedback prompt. We will also assess the impact of randomly provided goal-type message for the day on daily PA level achievement. We will use a generalization of regression analysis specifically developed to ensure unbiased estimation of causal effects of time-varying treatments (eg, feedback prompts) in mHealth settings [52,53]. Since the treatment is time-varying, potential time-varying moderators, such as pain or fatigue, and potential control variables, such as PA in the 30 minutes before the randomization decision point, may be outcomes of past treatment. Because our randomization probability is constant over the course of the study, we can use generalized estimating equations in which we include availability as weights with an independence working correlation matrix and sandwich SEs as described in Boruvka et al [52]. We use an independence correlation matrix because causal effect estimates are biased if off-diagonal elements are present [48,54]. These analyses pool time-varying, longitudinal data across all study participants. There are 2 possible intervention options at each decision point (PA feedback or no feedback). Thus, the models will include an indicator variable for PA feedback versus no feedback. In addition, we will include day in the study, as well as the interaction between day and each treatment indicator variable, and potential control variables such as PA in the 30 minutes before the randomization decision point to assess whether the proximal effect varies over the course of the study.

Exploratory Analysis

Moderators will include age, biological sex, race, ethnicity, level of injury, function, mobility, pain, and fatigue. The exploratory analysis aims to identify subgroups of individuals with SCI who are likely to benefit the most from the integration of just-in-time PA feedback and recommendations with WI. We will conduct 2 moderation analyses. First, we will incorporate moderators into our primary aim models to identify subgroups of individuals with SCI who are likely to benefit the most from the integration of just-in-time PA feedback and recommendations with WI. Second, we will address potential time-varying moderators, such as prior PA and engagement with the JITAI, self-reported pain (number and type), and fatigue, which can be incorporated into the model described in the secondary analysis [52]. Engagement with JITAI will be captured by participants' response to the "Got it" pop-up button that appears on the smartwatch when they receive a JITAI message. We will also examine potential time-invariant moderators such as biological sex and SCI level. This analysis will allow us to identify subgroups of individuals who are likely to benefit from particular types of messages (eg, tailored vs standard messages).

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Results

Overview

This study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (Multimedia Appendix 1). Recruitment and enrollment began on May 25, 2023. As of the submission of this manuscript, participant enrollment is ongoing. Since the research study involves no more than minimal risk, there will be no interim analysis, and data and safety monitoring will occur in accordance with guidelines by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the institutional review board of record. Data analysis is expected to be completed within 6 months of ending participant data collection.

Dissemination Policy

We plan to disseminate our findings in the form of interdisciplinary peer-reviewed manuscripts, presentations at local rehabilitation hospitals, and presentations at national and international conferences.

Discussion

Implications

PA interventions paired with mHealth technologies that continuously measure behavior can provide novel insights about PA patterns in the community. Individuals with SCI, although generally stable in the chronic postrehabilitation phase, are at a higher risk than the general population for secondary health conditions due to physiological changes associated with injury and due to sedentary behaviors potentially related to the use of assistive technology such as wheelchairs [50,55]. Accurate, real-time measurement of PA using affordable and convenient wearable monitors will not only enable more research on existing behavior and relationships to health outcomes but also allow insight into innovative JITAIs that may help individuals with SCI become more active in everyday life. To address these needs, we will investigate whether combining a JITAI with a WI program increases and sustains PA levels among individuals with SCI in the community. The JITAI will automatically detect PA levels and provide behavior-sensitive PA recommendations and feedback to increase PA in individuals with SCI. Although existing PA-based programs often require individuals to participate in them several times a week, a JITAI can act as a constant companion that encourages individuals and assists them in attaining their daily and weekly PA goals. The JITAI will operate as people go about their everyday lives in the community; as they do so, the JITAI will provide timely and tailored encouragement, feedback, and PA interventions designed to support sustainable behavior change [24,27].

Regular PA feedback has the potential to make individuals self-aware of their PA levels, which may be effective in a small percentage of individuals who are motivated to increase their PA levels [56]. To achieve long-term PA performance required to support behavior change and maintenance, there is a need to tailor PA feedback and recommendations based on an individual's behaviors and goals. This study will focus on understanding the impact of different messages on promoting proximal PA performance. Furthermore, use of an MRT study design will allow us to assess the effect of the JITAI components on participants' PA levels over time. MRT designs enable us to investigate the causal proximal effects of just-in-time interventions and test time-varying moderators of those effects [29,30]. On the basis of the impact of the type of messages on proximal PA, MRT results will allow us to determine the relative utility of various feedback and PA recommendation strategies.

Anticipated Findings

This project will investigate a state-of-the-art JITAI-enhanced WI program, which is guided by the COM-B model [31], that highlights the importance of capability, motivation, and opportunity for behavior change. JITAIs using mHealth technology can deliver an intervention that feels dynamic and personally responsive and thus more engaging to the individual. In this study, we will test whether PA levels change with WI and JITAI-based PA recommendations and feedback prompts. We will test 3 ways of providing PA recommendations (standard goal, tailored goal, or no goal) and 3 types of feedback prompts (PA achieved, PA to-go, or PA feedback not presented) to determine whether adding the JITAI to the WI may impact PA levels and sustain changes over time. Furthermore, the study design will allow us to identify subgroups of individuals with SCI who are likely to benefit the most from the integration of JITAI with WI. The identification of such subgroups will inform the design, development, and evaluation of JITAIs for future physical rehabilitation intervention studies for individuals with and without disabilities.

Limitations

One of the potential limitations of this study is that our JITAI has been developed for Android-based smartphones, which provide greater flexibility in research and are used by 53.9% of smartphone users in North America [57]. In addition, we are loaning participants study-related devices that are not personal devices. If we can show the efficacy of the JITAI with this randomized clinical trial using Android devices, the approach of using a JITAI to provide a PA intervention could be converted to other operating systems (eg, iPhone with Apple Watch). This step-wise approach is cost-effective and will test the viability of the underlying behavior change approach; future versions of the JITAI that use personal devices may further improve compliance and reduce burden. We will recruit adults with SCI between 18 and 75 years old; this age range includes 89.2% of all those with SCI [2]. Children will not be studied due to their use of different wheelchairs during their development, and because children's responses to and recovery from an SCI differ from those of adults. However, evaluation of JITAI in children with SCI is a potential avenue for future investigations. Another limitation concerns the use of a relatively simple measure of PA intensity. Future work might use more sophisticated, person-specific models trained to recognize the types of activities each person with SCI can perform when obtaining moderate-intensity PA.

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Conclusions

The JITAI has the potential to improve long-term PA performance by delivering tailored just-in-time feedback based on the person's actual PA behavior rather than a generic PA recommendation. New insights from this study may assist intervention developers in creating more engaging PA interventions for individuals with disabilities. Our work could lead to more impactful and sustainable clinical and rehabilitation interventions for this population by demonstrating how the use of affordable, off-the-shelf consumer devices to create a JITAI may enhance existing interventions.

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Data Availability

Data sharing is not applicable to this paper because no data sets were generated or analyzed during development of this study protocol. The deidentified data sets generated during the actual research study will be presented in the main manuscript and as additional supporting files.

Authors' Contributions

DLC, IN-S, MT, RJM, SSI, and SVH contributed substantially to the conception and design of the study and intervention. RLC, LAB, MS-R, MSRL, SAK-H, RJM, and SVH contributed substantially to the recruitment design of the clinical trial. HL and SSI developed and optimized the just-in-time adaptive intervention mHealth application. RLC, HL, CH, SSI, and SVH contributed substantially to the feasibility, testing, and evaluation of the just-in-time adaptive intervention mHealth application and design and development of data pipeline for collecting sensor data from this decentralized clinical trial. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the CMPC - Clinical Management of Patients in Community-based Settings Study Section - National Institutes of Health (NIH), United States.
[PDF File (Adobe PDF File), 131 KB - resprot_v13i1e57699_app1.pdf]

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Abbreviations

AUC: area under the curve
COM-B: capability, opportunity, and motivation model
JITAI: just-in-time adaptive intervention
mHealth: mobile health
MRT: microrandomized trial
NCHPAD: National Center on Health, Physical Activity, and Disability
PA: physical activity
PARA-SCI: Physical Activity Recall Assessment for people with spinal cord injury
SCI: spinal cord injury
WI: web-based physical activity intervention

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Protocol

Mobile App Promoting Resilience in Stress Management for Adolescents and Young Adults With Cancer: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Adolescents and young adults (AYAs) with cancer are at risk of poor psychosocial outcomes. AYAs grew up with the internet and digital technology, and mobile Health (mHealth) psychosocial interventions have the potential to overcome care access barriers.

Objective: This pilot randomized controlled trial (RCT) aimed to establish the feasibility, acceptability, and preliminary efficacy of a fully automated mobile app version of the Promoting Resilience in Stress Management intervention (mPRISM). Promoting Resilience in Stress Management is an evidence-based intervention developed in collaboration with AYAs, based on stress and coping theory, resilience theory, and evidence-based coping strategies. We hypothesized that mPRISM would be feasible, acceptable, and appropriate.

Methods: This is a parallel, 2-arm, single-site pilot RCT with a waitlist control design. The study will recruit 80 AYAs with cancer from a clinic. Eligible AYAs are aged 12 to 25 years, within 12 months of a new cancer diagnosis, receiving chemotherapy or radiation therapy, speak, read, or write in English, and are cognitively able to participate in study procedures. Recruitment by clinical research coordinators will occur remotely by phone, video, or text. Participants will be randomized to psychosocial usual care (UC) alone or UC plus mPRISM for an 8-week intervention period, and will remain unblinded to study condition. Enrolled participants will complete surveys at baseline before randomization, 8 weeks, and 3-month follow-up. Using a waitlist design, the UC arm will receive mPRISM upon completion of 3-month follow-up surveys. Those in the UC arm will complete 2 additional measurement points at immediate posttreatment and 3 months later. The primary outcomes of interest are feasibility, defined as ≥60% enrollment and ≥70% retention (ie, percentage of participants who completed the study), and "feasibility, acceptability, and appropriateness" as defined by cut-off scores ≥4/5 on 3 brief validated implementation outcome measures (feasibility of implementation measure, acceptability of intervention measure [AIM], intervention appropriateness measure [IAM]). We will apply top-box scoring for the implementation measures. Exploratory outcomes of interest include patient-reported health-related quality of life, resilience, distress, anxiety, depression, pain, and sleep. We will conduct an intention-to-treat analysis to compare

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the outcomes of the mPRISM arm versus the control arm with covariate-adjusted regression models. We will summarize individual digital usage metrics using descriptive statistics.

Results: Since September 2023, we have enrolled 20 participants and recruitment is ongoing.

Conclusions: Although our previous work suggests AYAs with cancer are interested in mHealth psychosocial interventions, such interventions have not yet been sufficiently evaluated or implemented among AYA oncology patients. mPRISM may serve as a potential mHealth intervention to fill this gap. In this study, we will test the feasibility, acceptability, and preliminary efficacy of mPRISM. This work will inform future larger-scale RCTs powered for efficacy outcomes.

Trial Registration: ClinicalTrials.gov NCT05842902; https://clinicaltrials.gov/study/NCT05842902

International Registered Report Identifier (IRRID): DERR1-10.2196/57950

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KEYWORDS

adolescents; young adult; cancer; mHealth; psychosocial intervention; stress management; coping; resilience; health-related quality of life; randomized controlled trial; mobile phone

Introduction

Pediatric adolescents and young adults (AYAs), 12-25 years old, with cancer experience unique developmental and psychosocial needs because cancer disrupts typical developmental experiences and life transitions including the pursuit of educational and vocational goals and the establishment of social, personal, and sexual identity [1]. AYAs with cancer experience poor psychosocial outcomes including social isolation, behavioral adjustment problems, depression, anxiety, and stress [2,3]. In addition, quality of life (QoL) and psychosocial outcomes among AYA cancer survivors are inferior to their younger pediatric and older adult counterparts [4]. Such sequelae are further associated with negative long-term survivorship outcomes such as low educational attainment, unemployment, and financial dependence [5]. Elevated psychological distress in AYA cancer survivors is associated with medical costs of US $4415 per year [6].

The Promoting Resilience in Stress Management (PRISM) program is an evidence-based resilience intervention designed for and in collaboration with AYAs [7-13]. PRISM is a brief, manualized, evidence-based intervention delivered one-to-one in person by layperson coaches. PRISM was developed based on iterative research within the AYA and pediatric oncology population, stress and coping theory, resilience theory, and evidence-based cognitive-behavioral and mindfulness interventions [7-13]. Previous studies suggest in-person delivery of PRISM is feasible and valuable to AYA patients and parents [11,12]. In a randomized controlled trial (RCT) of AYAs with cancer, PRISM was associated with improved self-reported resilience, distress, and health-related quality of life (HRQoL), with moderate effect sizes [14,15]. However, despite these promising effects, major barriers limit the dissemination and reach of in-person interventions such as PRISM, including geographic proximity, transportation, limited trained personnel, and treatment costs.

Skills-based psychosocial interventions are increasingly deployed through mobile Health (mHealth) platforms [16,17] and show promise in early research in youth with chronic illnesses [18]. Smartphones have become ubiquitous [19], irrespective of gender, race and ethnicity, and socioeconomic status [20]. The implementation of mHealth-based care delivery has the potential to improve access to evidence-based treatment and reduce health disparities; for example, 73% of families living below the poverty line in the United States have one or more smartphones and digital interventions have been proposed as a feasible means of disseminating health programs in homeless populations [21,22]. Thus, mHealth interventions have the potential to be universally accessible regardless of geographic, financial, and infrastructure constraints. mHealth platforms confer the advantages of appeal (self-pacing, instant availability, anonymity), reach, and cost-effectiveness [23-25]. This may be particularly important for meeting the needs of AYAs, who grew up in the digital age and are accustomed to interacting on smartphones and prefer internet-based self-help [24,26]. Smartphone adoption and internet use have skyrocketed among younger generations, with 95%-96% of teenagers and young adults in the United States owning a smartphone [27,28]. The internet serves as a primary means of physical- and mental health-related information-seeking and communication platforms for AYAs [26,29]. In addition, AYAs are reluctant to seek traditional forms of psychotherapy due to social stigma and discomfort in discussing personal problems and prefer digital interventions [24-26,30].

Despite the promise of mHealth interventions and the appeal to AYAs in particular, psychosocial mHealth interventions focused on improving QoL and psychosocial outcomes have not been evaluated or implemented among AYA oncology patients. This paper describes the protocol of an ongoing pilot RCT of a digitized version of PRISM deployed through a smartphone app (mobile app Promoting Resilience in Stress Management [mPRISM]).

Methods

Study Aims

The primary aim of this study is to evaluate the feasibility and acceptability of a self-guided mHealth resilience intervention (mPRISM) for AYAs with cancer. mPRISM content is based on stress and coping theory, resilience theory, and evidence-based psychosocial interventions. We hypothesize that mPRISM will be feasible as measured by ≥60% enrollment and ≥70% retention of participants to complete the study; and

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feasible, acceptable, and appropriate as measured by 3 brief well-established implementation measures (feasibility of intervention measure [FIM], acceptability of intervention measure [AIM], and intervention appropriateness measure [IAM] scores ≥4/5) [31]. Exploratory aims are to (1) examine preliminary efficacy assessed by validated patient-reported outcome measures at posttreatment and 3-month follow-up and (2) summarize digital usage metrics and engagement patterns under naturalistic conditions to inform future study design and to prepare participant instructions on how to use the app.

Trial Design

This is a parallel, 2-arm, pilot RCT (Figure 1) [32]. Participants (N=80) with cancer will be enrolled and randomized to usual care (UC) or UC plus mPRISM at a single site. Using a waitlist design, mPRISM will be provided to the UC arm at a 3-month follow-up. Participant randomization to the study arm will occur after the completion of baseline surveys and in a 1:1 allocation ratio. As a waitlist design is being used, it is not possible to blind participants to the intervention condition [33]. Study outcomes, however, are completed independently by AYA participants to minimize bias.

Figure 1. Schedule of all study activities. mPRISM: mobile app Promoting Resilience in Stress Management. T: timepoint.

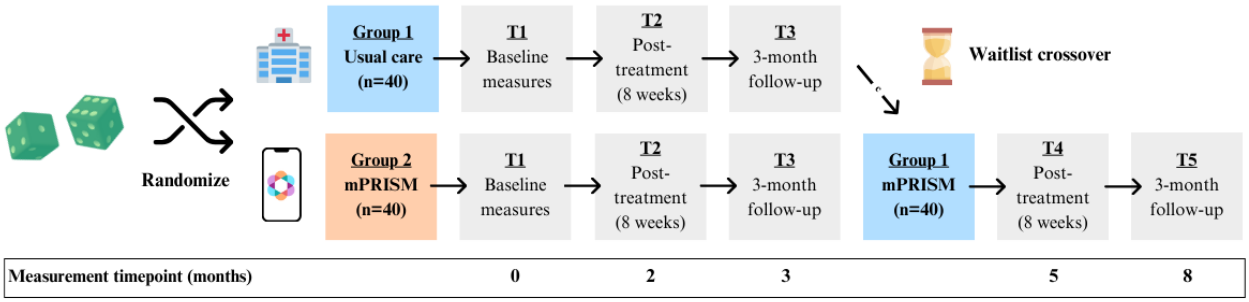

Participants

AYAs are eligible if they are (1) 12-25 years old; (2) within 12 months of diagnosis of new cancer; (3) receiving chemotherapy or radiation therapy at Seattle Children's Hospital; (4) speak, read, or write English; and (5) have no cognitive limitations that would make participation difficult. We will provide iPads (Apple Inc) for the duration of the study for those who do not own a device.

Exclusion criteria include patient refusal to participate or parental refusal to participate for patients <18 years of age, patients who received a diagnosis of malignancy >12 months ago, patients with relapsed or refractory cancer, patients who have not received any chemotherapy or radiation therapy as part of their cancer treatment, cognitively or physically unable to participate, and previous participation in other PRISM-based studies. Clinical research coordinators will identify potential participants and prescreen through clinic rosters and electronic medical records. Recruitment by clinical research coordinators will occur remotely by phone, video, or SMS text messaging (ie, Zoom [Qumu Corp], Microsoft Teams, Webex [Cisco Systems], Skype [Microsoft Corp], email, SMS text messaging, and MyChart message [Epic Systems]).

Intervention Conditions

UC

UC consists of standard nondirected supportive care provided for all patients including an assigned social worker who provides ad hoc services (mental health, financial, and housing support) at the request of the patient or family or medical team throughout cancer treatment. The AYA or their medical team can request referrals to psychology, psychiatry, pain medicine, child life, chaplaincy, palliative care, and art or music therapy.

Usual Care Plus mPRISM

In addition to UC, participants will receive access to mPRISM. PRISM is a brief, evidence-based resilience coaching intervention consisting of 4 scripted sessions delivered 1:1 by layperson coaches with high fidelity [11,14]. Sessions cover 4 core skills that are stress management (deep breathing, relaxation, and mindfulness techniques), goal setting (setting goals that are specific, measurable, actionable, and realistic, and planning around potential obstacles and barriers), cognitive reframing (identifying, challenging, and reframing negative thoughts), and meaning-making (identifying benefits, purpose, and meaning from cancer experience). Content from the in-person PRISM intervention was adapted to a mobile app (mPRISM), retaining core skills of the PRISM program (stress management, goal setting, cognitive reframing, and meaning-making [Figure 2]). Like the in-person PRISM program, mPRISM was co-designed with AYAs and with multiple iterations of stakeholder feedback. mPRISM contains tutorials showcasing audio-visual skills, dynamic skills practice opportunities, tracking systems of self-logged stress and resilience meters, a photo journal to review practiced skills, app notification reminders, and media links to other resources. AYAs randomized to mPRISM will receive a unique download code for the app. AYAs randomized to UC will receive a download code for the app after completion of their 3-month follow-up surveys. Once they receive access to mPRISM, all participants are instructed to use the app for 8 weeks.

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Figure 2. Selected examples of skills and practice materials on the mobile app version of Promoting Resilience in Stress Management. PRISM: Promoting Resilience in Stress Management.

App "buttons"	PRISM skill	Sample exercise	Exercise details	Sample home screen (does not depict real participant)
	Managing stress	"Breathe"	Audio-visual guide to learn and practice "square breathing" techniques.	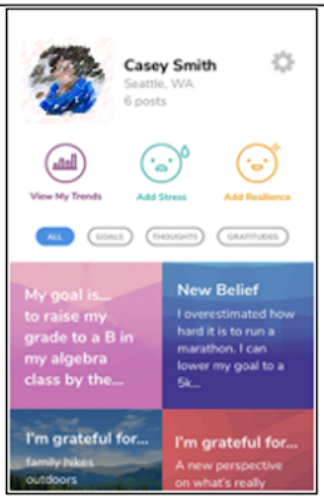
	Goal-setting	"Set a goal"	Log of goals with anticipated steps, timelines, pitfalls, and alternatives.	
	Cognitive reframing	"Catch your thoughts"	Log of recognized and "reframed" thoughts.	
	Meaning-making	"Find the positive"	Log of text or photos in response to "I'm grateful for…"	

Measures

Enrolled AYA participants will complete surveys at baseline before randomization, posttreatment (at 8 weeks), and 3-month follow-up (at 20 weeks). All surveys will be completed electronically by REDCap (Research Electronic Data Capture; Vanderbilt University) SMS text messaging or email survey invitation [34,35]. Survey responses will be scored based on measure scoring guidelines from the measure developers. In a waitlist design, the UC arm will receive mPRISM upon completion of the 3-month follow-up surveys to increase retention and optimize the use of the full sample size for analysis. This second wave of data collection for UC will include 2 additional measurement points at immediate posttreatment and 3 months later. Measure batteries at each timepoint take approximately 15-25 minutes to complete.

Data Storage

Data will be stored within a REDCap database on a secure, internal, HIPAA (Health Insurance Portability and Accountability Act)-compliant, password-protected Seattle Children's server. Electronic consent will be stored in the same password-protected, secure database using the REDCap eConsent framework that securely collects, stores, and archives electronic consent information [34,35]. All electronic access to REDCap is encrypted.

Primary Outcomes: Feasibility, Acceptability, and Appropriateness

Feasibility is defined as ≥60% enrollment and ≥70% retention who complete the study. The FIM, AIM, and IAM are well-validated 4-item implementation science measures with strong reliability and validity [31]. Measures query perceptions of the feasibility, acceptability, and appropriateness of adopting an evidence-based practice. Items are rated on a 5-point Likert scale from "completely disagree" to "completely agree," and total scores range from 1 to 5. Higher scores indicate greater acceptability, appropriateness, and feasibility, respectively. These 3 measures have been used independently and in conjunction. Feasibility, acceptability, and appropriateness cut-off scores are defined as measure scores ≥4 (on a 5-point scale).

Secondary and Exploratory Outcomes

Usability

The System Usability Scale (SUS) is a well-validated 10-item scale to evaluate the perceived usability of digital interventions with strong reliability and adequate validity [36]. Items are rated on a 5-point Likert scale for a total score ranging from 0 to 100, and scores ≥70 constitute adequate usability.

Health-Related Quality of Life

The PedsQL (Pediatric Quality of Life Inventory) 4.0 Generic and 3.0 Cancer Module include 50 items evaluating the HRQoL of AYAs with cancer and have strong reliability and validity [37]. Queries assess physical, emotional, social, and school well-being, plus cancer-related pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. Items are rated on a 5-point Likert scale, and we will use the total scale score. Scores are linearly transformed to a 0 to 100 scale, with higher scores indicating better HRQoL.

Resilience

The Connor-Davidson Resilience Scale (CD-RISC) is a well-validated and widely used 10-item instrument to measure inherent resiliency that has demonstrated strong reliability and validity [38]. Questions revolve around personal

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problem-solving and approaches to adversity. Items are rated on a 5-point Likert scale; scores range from 0 to 40, and higher scores indicate higher resilience.

Distress

The Kessler Psychological Distress Scale (K6) is a 6-item scale that measures the level of psychological distress and has strong reliability and validity [39]. The instrument strongly discriminates between community cases and noncases of the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) psychiatric disorders such as serious emotional distress or serious mental illness. Items are rated on a 5-point Likert scale, scores range from 0 to 24, and higher scores indicate higher distress.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) is a 7-item scale that assesses symptoms of anxiety and depression, respectively, in patients with serious illness [40]. It has been validated in AYAs with chronic illness and cancer survivors and has strong reliability and validity [41,42]. Items are scored 0-3 (subscale range 0-21), with scores ≥8 categorized as borderline abnormal, and ≥11 categorized as abnormal.

Digital Usage Metrics

Individual backend user data for mPRISM are collected in real time using Mixpanel, an event analytics service that tracks user engagement with mobile apps [43].

Data Analysis

Power

The role of rigorous pilot studies such as this study is designed to determine feasibility [44,45]. Although not powered for efficacy, we will examine preliminary efficacy data for meaningful trends in terms of clinical significance with minimal clinically important difference (MCID) defined as half the SD for outcomes [46].

Primary Outcomes

Outcome domains will be assessed with Proctor's framework [47] to determine implementation success (Table 1). Penetration will be assessed by clinic recruitment rates with ≥60% enrollment considered feasible. Uptake will be assessed through retention rates with ≥70% of participants completing the study considered feasible. We will apply top-box scoring [48] for the implementation measures, which is widely used in satisfaction research. Acceptability, appropriateness, and feasibility will be considered high if corresponding top-box scores are 80%.

Table 1. Proctor's domains assessed in data analysis plan.

Domain	Data analysis plan
Penetration	Recruitment rate
Uptake	Retention rate
Feasibility, acceptability, and appropriateness	Top-box scoring of validated implementation measures
Patient outcomes	Regression models of validated function and symptomatology measures

Secondary and Exploratory Outcomes

Data from all participants who complete baseline surveys will be included in intent-to-treat analyses [49]. Before UC crosses over to receive mPRISM, the first phase of the study can be viewed as a parallel 2-armed RCT. Given the first phase parallel group RCT design, we will first compare posttreatment efficacy outcomes between mPRISM and UC using 2-sample independent *t* tests [50]. We will explore a range of effect sizes around what is observed in this pilot trial and assume larger SEs. Exploratory efficacy will be examined using the first phase parallel RCT data with regression models [44,45]. The effect of assessment time and other unbalanced confounders will be assessed as covariates in the models [51]. Potential covariates include age, gender, and diagnosis, which have been shown to influence psychosocial outcomes [52]. Estimation will be based on restricted maximum likelihood and significance based on the Wald *t* test [53]. With regard to digital usage data, we will summarize individual digital usage metrics (eg, number of usage sessions and total duration of use) using descriptive statistics and graphical tools.

Ethical Considerations

All procedures are approved by the Seattle Children's Hospital Institutional Review Board (STUDY00004006). The trial is registered at ClinicalTrials.gov (NCT05842902). All participants will provide informed consent (18-25 years old) or assent with parental consent (12-17 years old). Study participation is completely voluntary and participants are allowed to opt out of the study at any time. Privacy and confidentiality protections will be in accordance with institutional ethical guidelines. Study data are collected on secure, internal, HIPAA-compliant REDCap servers only accessible to the study team [34,35]. The collection of identifiable information is limited to that required to contact participants for study procedures and to report on sample demographics. Participants consented to use of data for study publications and no individually identifiable information will be reported in study publications. Participants will be compensated US $25 in electronic gift cards for completing each survey.

Results

This project was funded in September 2022, and received IRB approval in November 2022. We began study enrollment in September 2023. As of July 2024, we have enrolled 25 participants and recruitment is ongoing. We expect to complete data collection in 2027.

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Discussion

Principal Findings

The World Health Organization states that digital and mHealth technologies have the potential to revolutionize health care and improve access to services [54]. mHealth interventions provide (1) in-the-moment support in patients' day-to-day lives, (2) have been proven to be cost-effective due to reduced personnel and infrastructure requirements [55], and (3) have the ability to reach patients in remote areas and those traditionally underserved. Although there are 325,000 health-related apps available for download as of 2017 and a growth rate of 25% year-to-year [56], there are no evidence-based psychosocial mHealth interventions for AYAs with cancer. This pilot RCT is designed to evaluate the feasibility and acceptability of the mPRISM intervention, a skills-based mobile app adapted from the in-person PRISM program. This ongoing trial takes a critical next step in translating evidence-based interventions to digital platforms, expanding the reach of evidence-based supportive care to the vulnerable populations who need them. We anticipate that mPRISM will be feasible, acceptable, and appropriate. Exploratory patient-reported outcomes will inform sample size for future powered trials. Individual backend user data will explore patterns of engagement with skills modules. We expect findings from this pilot trial to inform the testing of mPRISM in a larger scale multisite hybrid effectiveness-implementation RCT powered for efficacy outcomes.

Limitations

This study has several anticipated challenges. First, this is a single-site pilot trial, which may limit the generalizability of findings. However, the strengths of this single-site study are established relationships with the clinic to ensure project completion and preliminary data for future scale-up initiatives. Second, it is possible that we may have higher attrition rates and lower adherence, which is common in smartphone-based mental health interventions [57]. However, members of our research team have over a decade of experience and background with digital behavioral health interventions in research settings that have demonstrated low attrition and high adherence rates. We will monitor attrition rates on a monthly basis. If attrition is >50%, we will increase the level of study coordinator contact to ensure project completion. This will provide information on potential behavioral nudge strategies to increase engagement and sustainability. Third, we are primarily using remote recruitment methods, which may lead to higher or lower recruitment rates than expected. Fourth, we do not provide instructions to participants on how to engage with mPRISM, although a recommended order of module completion is available on the home screen based on the in-person version of the intervention. Digital usage metrics will inform future study design and the potential development of more structured instructions on how best to engage with mPRISM. Fifth, participants are not blinded to intervention conditions, which is a potential source of bias. Here, we evaluate the additive value of mPRISM to UC which is the standard of care all patients receive. Sixth, this is a feasibility waitlist control trial design, which limits our ability to make causal inferences regarding efficacy. Nonetheless, we will examine exploratory trends of symptom change. Future larger-scale studies will incorporate active treatment comparison conditions (eg, another behavioral health app) and be sufficiently powered for efficacy. In addition, future studies will test and refine implementation strategies in multisite clinical settings and include adaptations for other languages, cultures, and patient groups.

Conclusions

AYAs with cancer are a vulnerable population with unmet psychosocial needs. mHealth initiatives have the unique potential to scale up interventions and overcome structural barriers and unequal access to psychosocial treatment. Although our previous work suggests AYAs with cancer are interested in mHealth psychosocial interventions to improve QoL, resilience, and distress [58,59], such interventions have not yet been sufficiently evaluated or implemented among AYA oncology patients. mPRISM may serve as a potential mHealth intervention to fill this gap. This pilot trial will inform the necessary sample sizes and power of a future larger multisite hybrid effectiveness-implementation trial. Future studies will assess barriers and facilitators to mHealth psychosocial intervention adoption and maintenance, and strategies to increase and maintain mobile app engagement. This pilot study and future studies building on this work aim to expand the reach, adoption, and sustainability of evidence-based mHealth psychosocial interventions. Since the COVID-19 pandemic, digitally deployed supportive care has rapidly evolved and accelerated in research and practice settings [60]. This study has important clinical implications in the use of mHealth for psychosocial symptom self-management, exploring the potential integration of digital tools with psychosocial standard of care practices, and increasing access to care for underresourced groups.

Acknowledgments

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Data Availability

Deidentified human participants' data from this research study will be banked indefinitely. The data sets generated during and analyzed during this study are not publicly available due to research involving minors at a single pediatric oncology treatment center and a geographically specific population but data are available from the corresponding author on reasonable request.

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Conflicts of Interest

DB-Z has financial interests in Merlin and FOCUS technology. He has provided consultation services to Trusst Health, K Health, Boehringer Ingelheim, eQuility, Deep Valley Labs, Butler Hospital, and Otsuka Pharmaceuticals. None of the authors has a financial or other conflict of interest to disclose.

Multimedia Appendix 1
External peer review report.
[PDF File (Adobe PDF File), 125 KB - resprot_v13i1e57950_app1.pdf]

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Abbreviations

AIM: Acceptability of Intervention Measure
AYA: adolescent and young adult
CD-RISC: Connor-Davidson Resilience Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
FIM: Feasibility of Intervention Measure
HADS: Hospital Anxiety and Depression Scale
HIPAA: Health Insurance Portability and Accountability Act
HRQoL: health-related quality of life

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IAM: Intervention Appropriateness Measure
K6: Kessler Psychological Distress Scale
MCID: minimal clinically important difference
mHealth: mobile health
mPRISM: mobile app Promoting Resilience in Stress Management
PedsQL: Pediatric Quality of Life Inventory
PRISM: Promoting Resilience in Stress Management
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SUS: System Usability Scale
UC: usual care

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Protocol

Improving Neurological Health in Aging Via Neuroplasticity-Based Computerized Exercise: Protocol for a Randomized Controlled Trial

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Abstract

Background: Our current understanding of how computerized brain training drives cognitive and functional benefits remains incomplete. This paper describes the protocol for Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise (INHANCE), a randomized controlled trial in healthy older adults designed to evaluate whether brain training improves cholinergic signaling.

Objective: INHANCE evaluates whether 2 computerized training programs alter acetylcholine binding using the vesicular acetylcholine transporter ligand [18F] fluoroethoxybenzovesamicol ([18F] FEOBV) and positron emission tomography (PET).

Methods: In this phase IIb, prospective, double-blind, parallel-arm, active-controlled randomized trial, a minimum of 92 community-dwelling healthy adults aged 65 years and older are randomly assigned to a brain training program designed using the principles of neuroplasticity (BrainHQ by Posit Science) or to an active control program of computer games designed for entertainment (eg, Solitaire). Both programs consist of 30-minute sessions, 7 times per week for 10 weeks (35 total hours), completed remotely at home using either loaned or personal devices. The primary outcome is the change in FEOBV binding in the anterior cingulate cortex, assessed at baseline and posttest. Exploratory cognitive and behavioral outcomes sensitive to acetylcholine are evaluated before, immediately after, and 3 months following the intervention to assess the maintenance of observed effects.

Results: The trial was funded in September 2019. The study received approval from the Western Institutional Review Board in October 2020 with Research Ethics Board of McGill University Health Centre and Health Canada approvals in June 2021. The trial is currently ongoing. The first participant was enrolled in July 2021, enrollment closed when 93 participants were randomized in December 2023, and the trial will conclude in June 2024. The study team will be unblinded to conduct analyses after the final participant exits the study. We expect to publish the results in the fourth quarter of 2024.

Conclusions: There remains a critical need to identify effective and scalable nonpharmaceutical interventions to enhance cognition in older adults. This trial contributes to our understanding of brain training by providing a potential neurochemical explanation of cognitive benefit.

Trial Registration: ClinicalTrials.gov NCT04149457; https://clinicaltrials.gov/ct2/show/NCT04149457

International Registered Report Identifier (IRRID): DERR1-10.2196/59705

(JMIR Res Protoc 2024;13:e59705) doi:10.2196/59705

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KEYWORDS

brain training; cognitive training; healthy aging; neuroplasticity; acetylcholine; FEOBV; randomized controlled trial; aging; ageing; elderly; elder; older adults; older adult; neurological health; cognitive; computerized brain training; computerize; cognition; cognitive decline; Canada

Introduction

Background

Specific forms of computerized brain training demonstrate observable cognitive and functional benefits. The largest brain training trial to date, Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) [1], provides compelling evidence that speed of processing training yields enduring gains that generalize beyond the trained task. This speed training exercise called Double Decision (BrainHQ) has been associated with a 29%-48% reduction in the risk of dementia over a decade-long follow-up, depending on the number of training hours completed [2]. Additional studies Additional studies have reported a range of benefits, including decreased at-fault motor vehicle collisions [3], slowed decline in instrumental activities of daily living [4-8], greater likelihood of improved locus of control [9], improved self-rated health [10], reduced health care payer-related costs [11], decreased onset of age-related depression [12], alleviation of depressive symptoms [13], and a lowered risk of global decline in health-related quality of life [14,15].

Another form of training, called Freeze Frame (BrainHQ), was neuroscientifically designed to engage tonic and phasic attention to naturally upregulate neuromodulatory control and amplify the training benefits of Double Decision [16]. Initial investigations suggest notable improvements in executive function, skill acquisition, spatial and nonspatial attention, and sleep duration and quality [16-20].

The mechanisms underlying the cognitive benefits of brain training are largely unknown, although a few pilot studies, mostly conducted in clinical cohorts, offer intriguing insights. These studies suggest potential improvements in functional connectivity [21,22], improved brain synchronization [23], increased hippocampal activation [24], and improved white matter (WM) insulation between brain regions dedicated to visual and attentional processing [25]. Central to these network-based changes is synaptic plasticity, a fundamental process regulated by key neuromodulatory centers in the brain that oversee the release of neurotransmitters, most notably acetylcholine [26,27].

If age-related cognitive decline is paralleled by the atrophy and diminished signaling of acetylcholine, then it follows that augmenting acetylcholine may hold promise for enhancing cognition. A pilot investigation conducted at McGill University provides initial support for this view: a cohort of 5 healthy older adults engaged in a 6-week training program using Freeze Frame showed a 16%-24% increase in forebrain acetylcholine binding, which mirrored performance on a sustained vigilance assessment. Acetylcholine binding was measured through positron emission tomography (PET) using the radiotracer [18F] fluoroethoxybenzovesamicol ([18F] FEOBV) that binds to vesicular acetylcholine transporter [28]. Previous studies have demonstrated that FEOBV-PET binding patterns are consistent with the known organization of the cholinergic system and that aging is associated with a significant decline of 2.5% in FEOBV binding per decade in the anterior cingulate cortex [29].

This Study

INHANCE is a phase IIb, prospective, double-blind, parallel-arm, active-controlled, randomized trial in healthy adults aged 65 years and older who are randomly assigned to a computerized speed and attention brain training program (BrainHQ) or to an active control of games designed for entertainment (eg, Solitaire).

The objective is to develop a mechanistic understanding of these training programs using FEOBV-PET. Exploratory endpoints include a standard cognitive battery (National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research [NIH EXAMINER]), behavioral assessments sensitive to acetylcholine (heart rate variability and pupillometry), and train-to-task assessments to evaluate target engagement. Both the cognitive and behavioral assessments are conducted at baseline, posttest, and at a no-contact 3-month follow-up to evaluate durability. We hypothesize that participants training on speed and attention will show greater FEOBV binding at posttest versus baseline within the anterior cingulate cortex compared with the active control. We do not consider the active control program to be fully inert and may find that both forms of training improve some (potentially different) indices of cognition performance and behavior.

Methods

Trial Design

Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise (INHANCE) is a double-blind, parallel-arm, active-controlled, randomized clinical trial evaluating the superiority of speed and attention brain training against an active control of computer games.

Recruitment and Eligibility

All participants were recruited near McGill University, Canada, where the FEOBV radiotracer is synthesized and administered.

Recruitment methods included public presentations (TV, radio stations, and conferences), newspapers, word of mouth, and flyers. Flyers were posted in churches, community centers, Facebook groups, local libraries, and at the neurology clinic at the Montreal Neurological Hospital. Flyers described the study and included information regarding inclusion and exclusion criteria as well as the method for contact. They described the opportunity to volunteer for a clinical trial to advance the science and treatment of age-related cognitive decline. Compensation was described in appropriate terms that were not overemphasized relative to the remainder of the text. No

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indication of “free medical treatment” was communicated. All materials used for advertising or recruitment received ethics approval before implementation.

Participants were screened for the following inclusion criteria: (1) potential participants must be 65 years or older at the time of study screening; (2) potential participants should be cognitively healthy and score ≥23 on the Montreal Cognitive Assessment (MoCA) [30]; (3) potential participants must be likely able to complete all primary outcome measures in the judgment of the investigator; (4) potential participants must demonstrate adequate decisional capacity, in the judgment of the investigator, and be capable of making an informed decision regarding their participation in this research study; (5) potential participants must have the visual, auditory, and motor capacity to use the computerized intervention in the judgment of the investigator; (6) potential participants must already have, be willing to obtain, or be willing to travel to locations with internet connectivity to complete intervention activities; and (7) potential participants must be able to communicate in either English or French.

Participants were excluded based on the following criteria: (1) potential participants have an existing diagnosis of major or minor neurocognitive disorder at screening; (2) potential participants answer “yes” to “active suicidal ideation” with “specific plan and intent” on the Columbia-Suicide Severity Rating Scale (C-SSRS) [31] or any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the “suicidal behavior” section if the ideation or behavior occurred within 2 months from participant’s date of consent (as recommended by the US Food and Drug Administration for treatment trials); (3) potential participants are depressed and score >10 on the Geriatric Depression Scale–Short Form (GDS-SF) [32,33]; (4) potential participants have been treated with a computer-based cognitive training program manufactured by Posit Science within 5 years of the date of consent given maintenance effects established in previous work [15]; (5) potential participants are participating in a concurrent clinical trial (involving an investigational pharmaceutical, behavioral treatment, medical device, or other) that, in the judgment of the investigator, could affect the outcome of this study; (6) potential participants are pregnant or breastfeeding due to unknown effects of the FEOBV radioligand in pregnant and nursing individuals; (7) potential participants have claustrophobia or implantation with any medical devices above the waist that may concentrate radio frequency fields or have other medical issues that may frustrate participation in magnetic resonance imaging (MRI) procedures; (8) potential participants have medical illnesses deemed to interfere with participation in study activities or unstable or untreated conditions that may affect cognition, including substance abuse or dependence disorders, drugs that interfere with cholinergic function, ongoing chemotherapy, or other cancer treatment; and (9) potential participants show signs of intoxication due to current substance abuse (including alcohol or illegal drugs).

Randomization

Given the potential importance of demographic variables in response to training, we used a minimization method of adaptive stratified randomization with a 1:1 allocation; the “platinum standard” of randomization methods when stratification is required [34] to minimize the imbalance between the number of participants in each group over factors known to influence performance. We balanced groups based on the distribution of acetylcholine scores and the NIH EXAMINER composite score. Previous research has shown that binding in the anterior cingulate significantly decreases with age while binding in the occipital cortex does not [29]. The acetylcholine score is defined as the ratio of the anterior cingulate to the occipital cortex to mitigate interindividual differences in baseline blinding.

The minimization method addresses the general problem of ensuring stratification across multiple factors in small- or moderate-sized trials. The various imbalances are added together to give the overall imbalance in the study. Group assignment is then made at random with a heavy probability weighting (0.8) in favor of the group that would minimize imbalance. Out of 2, 1 participant (50%) will be assigned to the intervention group, and 1 participant (50%) will be assigned to the active control group.

Participant allocation was performed after the baseline visit (V1) and before the planned first day of program use. Baseline data were fully monitored for each participant, with all queries resolved, because allocation depended on obtaining data for the 2 prognostic variables. See the study flow diagram in Figure 1.

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Figure 1. Study flow diagram. MRI: magnetic resonance imaging; PET: positron emission tomography.

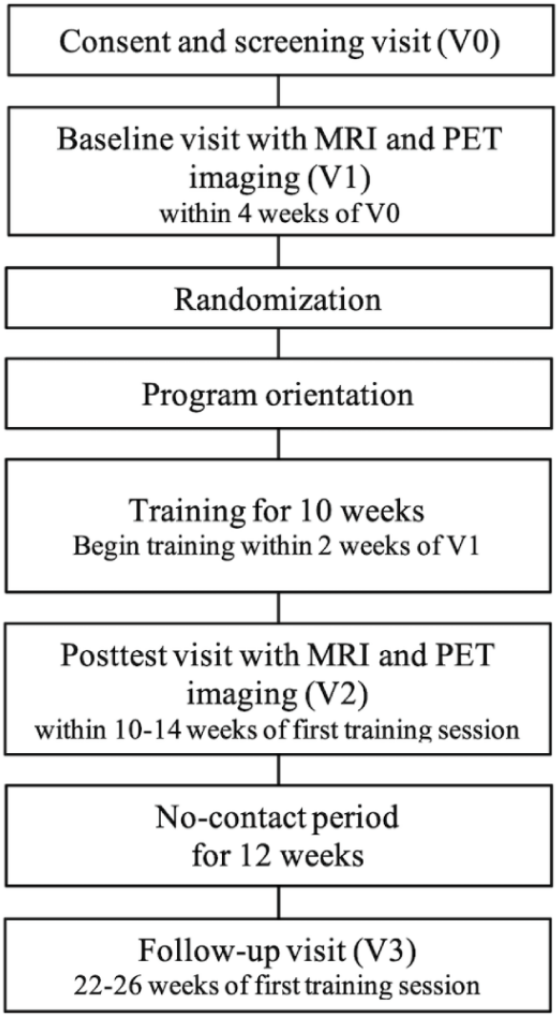

Consent and Screening Visit (V0)

Study staff will discuss study goals, activities, and requirements with the potential participant, complete the informed consent discussion, and if appropriate the potential participant will consent to join the study. Study staff will perform required inclusion and exclusion assessments. This visit will last approximately 1 hour.

Baseline Visit (V1)

If the participants are eligible, the participant will complete the cognitive assessment battery and the pretraining PET and MRI recordings. This visit will last approximately 3 hours and can be split into 2 sessions if needed.

Randomization

The participants will be randomized after the baseline visit and before the planned first day of the training program. Randomization will not take place until the screening and baseline data have been fully reviewed, residual data queries have been resolved, electronic data capture fields have been monitored, and it has been verified that the participant has met eligibility requirements.

Program Orientation

The participants will attend a program orientation session so that study staff may orient them to the training program in person or remotely. The participant will also receive detailed written information on how to perform the training program over the next several weeks. During this period, study staff will conduct weekly check-ins over the phone or email to answer questions and troubleshoot issues.

Intervention Period

The participants will engage in the assigned program for approximately 30 minutes per session, 7 sessions per week, for 10 weeks (approximately 3 months after randomization is complete).

Posttest Visit (V2)

The cognitive assessment battery along with PET and MRI imaging will be completed following the intervention period, approximately 3 months after initial enrollment. The participants will be informed that they will no longer have access to the intervention applications after this visit. This visit will last approximately 3 hours and may be split into 2 sessions if needed.

No-Contact Period

After the posttest visit, the participant will be entered into a follow-up period lasting 3 months with no further program use.

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Study staff may connect with the participant once a month during this time to maintain engagement.

Follow-Up Visit (End of Study, V3)

This assessment visit will be completed approximately 6 months after the initial enrollment. The participants will complete the cognitive assessment battery and will be formally exited from the study following this visit, concluding their participation. This visit will last approximately 1.5 hours.

Blinding

Unblinded study staff will provide support for participants using their assigned programs. Only blinded study staff are authorized to participate in assessment administration, scoring, evaluation, follow-up of study participants after randomization, and baseline data analyses. The principal investigators and site investigator are required to complete a Delegation of Authority Form before the start of the study indicating which activities individual site research team members will be authorized to complete. To prevent unblinding, the following controls occurred at the site level: (1) the cognitive training condition and the active control condition will be identified as "Treatment A" and "Treatment B"; (2) participants will be instructed and reminded not to discuss details related to their training program with site staff, colleagues, friends, or acquaintances; (3) principal investigators will be instructed to not discuss details of either treatment arm with site personnel; (4) the site will be required to minimize the possibility of accidental unblinding of the site staff (eg, unintended viewing of treatment sessions); and (5) signage will be posted in appropriate areas throughout the facility reminding participants to not discuss study details.

[18F] Fluoroethoxybenzovesamicol

PET imaging will be performed with a radioligand, FEOBV [35-38], which will be administered intravenously through a fine-needle catheter inserted into an arm vein. Participants will wait for approximately 180 minutes for FEOBV to distribute across the brain. During this time, they will remain at rest but will be able to use the washroom and walk around if desired. The expected dose for 2 PET scans is estimated at 11-15.4 mSv and does not exceed the nationally accepted limits of 50 mSv per year [37]. FEOBV is undetectable at 20 hours post administration.

Participants will be positioned lying on their backs for the PET imaging session. A transmission study lasting 5 minutes will be performed using a 68 Ge source. Participants will then receive a slow push intravenous injection of 350-400 MBq of FEOBV (which corresponds to 8.05 mSv to 9.2 mSV given that the dose per MBq of FEOBV is 0.023 mSv per MBq). A 60-minute list mode acquisition will be launched at the start of the injection. The PET marker will be produced according to methods described previously [39]. All PET imaging sessions will be supervised by a qualified nuclear medicine physician.

Intervention

The intervention included Double Decision [2,5,40] and Freeze Frame [16,17,20], designed using the principles of neuroplasticity, in a 35-hour training schedule delivered over a 10-week period (approximately 30 minutes per session, 7 sessions per week, for a total of 70 sessions). All training was completed remotely at the participant's home. See Figure 2 for the trial events of both exercises.

Double Decision trains visual speed of processing and selective attention [2,5,40]. In this dual-task exercise, participants discriminate a visual stimulus presented in the center of gaze while simultaneously locating a target in the peripheral visual field. There are 40 unique levels that vary in the discriminability of the central targets, the eccentricity of the peripheral target, the contrast between background and foreground stimuli, and the number of peripheral distractors. The adaptive dimension is display exposure duration (how long the items are on the screen) [41]. As the participant gets trials correct, exposure duration decreases requiring less time to complete the task; conversely, as the participant gets trials incorrect, exposure duration increases to make the task easier. Raw scores are defined as the exposure duration at approximately 80% criterion accuracy in milliseconds. The best possible raw score is 32 milliseconds and the worst possible score is 3162 milliseconds. Analyses will use *z* scores generated using the mean and SD from the intent-to-treat (ITT) population.

Freeze Frame trains 2 well-characterized, intrinsic properties of neuromodulatory control, which are tonic and phasic alertness [16,17,20]. Tonic alertness refers to the ongoing state of intrinsic readiness that fluctuates in the order of minutes to hours and is intimately involved with sustaining attention while providing the cognitive tone necessary for performing more complicated functions such as working memory and executive control. In contrast, phasic alertness is the rapid modulation in alertness due to any briefly engaging event and is vital for operations such as orienting and selective attention. In this continuous performance training exercise, participants must remember a target image presented at the start of the trial after which a continuous stream of targets and foils are interleaved with unequal probability. Users must withhold the prepotent motor response to all targets and respond to only foils. The 40 unique levels vary in the discriminability between targets and foils, the speed at which the images are presented, and the categories of the stimuli presented. The adaptive dimension is target and foil frequency defined as the single target frequency required for users to achieve at least 80% accuracy (n=24/30) in target identification and 80% (n=24/30) in foil identification within each epoch of 30 trials [42]. The adaptivity range is 1-7 corresponding to 40% (12/30 trials), 35% (10-11/30 trials), 30% (9/30 trials), 25% (7-8/30 trials), 20% (6/30 trials), 15% (4-5/30 trials), and 10% (3/30 trials) target frequencies, respectively. Scoring is available as 1-7, overall mean accuracy, and d'prime as a measure of sensitivity. Higher scores indicate better performance. Analyses will use *z* scores generated using the mean and SD from the ITT population.

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Figure 2. Trial events for Double Decision and Freeze Frame.

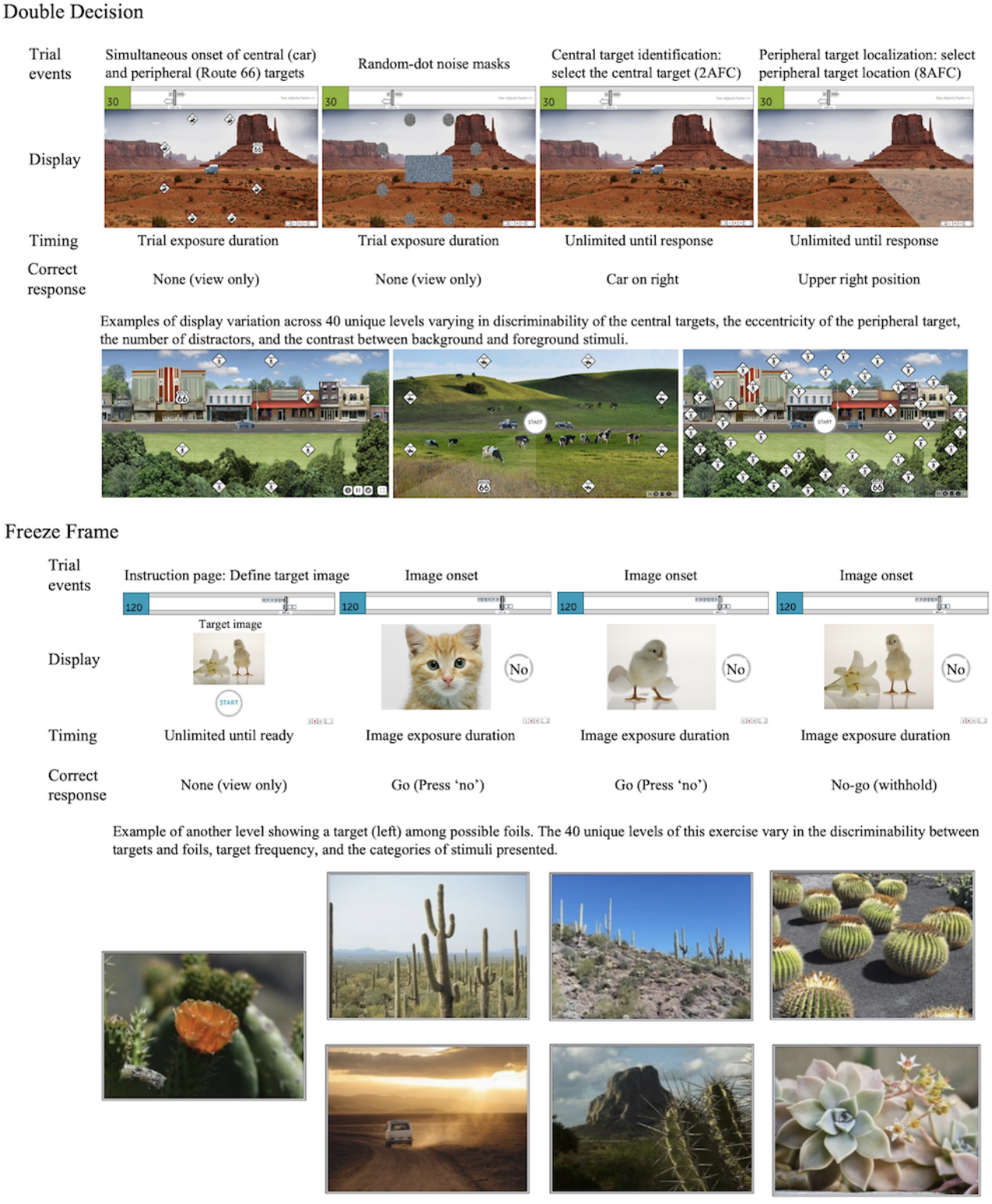

Active Control

The active control includes previously vetted and popular casual video games designed for entertainment for a 35-hour training schedule delivered over a 10-week period (30 minutes per session, 7 sessions per week, for a total of 70 sessions). Games are rated E (for everyone) by the Entertainment Software Rating Board. All training was completed at the participant's home. See Figure 3 for displays of these well-known games.

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Figure 3. Games used in the active control arm include spinoffs of solitaire (left) and Bricks Breaker (right).

We matched the intervention and active control in overall program use intensity, visual modality, staff interaction, and engagement to provide a comparison group that matches the intervention on the aforementioned attributes without the key elements specific to improving neuromodulatory control. The games are designed to be nonspeeded, nonadaptive, and to not actively engage neural systems that underlie aging.

Games will be accessed by participants on the same platform as participants in the intervention to minimize unblinding.

Sample Size

Based on the 0.27 SD seen in anterior cingulate FEOBV binding from our pilot study, detecting a small-moderate effect size (17% increase in binding in anterior cingulate FEOBV binding postintervention) with a power of 0.8 and α *P* value of .05 would require 40 participants in each of the 2 groups (80 total). We assume a 15% attrition rate and will enroll at least 92 participants to achieve 80 completers.

Ethical Considerations

The study has been developed in accordance with the Declaration of Helsinki guidelines and was approved by the Western Institutional Review Board (IRB00000533) and the Research Ethics Board of McGill University Health Centre (2020-6474). The radioligand 18F-FEOBV was approved by Health Canada (control # 252085).

Informed Consent

Prospective participants will undergo a phone screen that includes an overview of study details and a discussion of risks along with questions to assess the inclusion and exclusion criteria. Eligible individuals expressing interest in the study will be invited to the study site to complete the informed consent discussion, followed by a behavioral screening session, health questionnaire, and interview. The informed consent discussion will take place in a private room at the study site. Participants will be provided a copy of the approved consent form detailing the general purposes and procedures of the study. Study staff will provide detailed information about study requirements, offer participants an opportunity to ask questions, and provide clarification before signing the consent. Participants will be encouraged to take time to consider whether they wish to participate in the study and discuss with family before signing the consent. At the participant's request, study staff may be asked to step out of the room to provide privacy for such discussions. To participate in this study, an individual must be judged capable of understanding the nature of the research, risks, and potential benefits. The consent form will clearly state that the participant may withdraw consent and stop participation at any time without judgment or penalty. Potential risks and benefits will be explained by the study staff, and the participants will be asked to sign the consent form. A member of the study staff will also sign the consent form. No study activities will take place before participant consent.

On the consent form, both the treatment and active control programs will be described as "computer-based activities designed to engage cognitive processing," and the goal of the trial will be described as "comparing 2 forms of cognitive remediation." The goal of this description is to ensure that if participants realize that they are engaged in a training experience that differs from other friends or colleagues enrolled in the trial, they will not assume that they are participating in an experimental versus control, thereby maintaining the integrity of the blinded study.

The consenting study team member will inform participants about compensation for their participation in the study. We will provide US $30 (CAD $40) for the baseline visit and PET and MRI imaging (V1), US $10 (CAD $13) for every 10 training sessions completed (maximum of US $70 [CAD $91] for completing all 70 sessions) during the intervention period, US $30 (CAD $40) for completing the posttest visit and PET and MRI imaging (V2) and US $30 (CAD $40) for the end-of-study 3-month follow-up visit (V3). Participants who complete the study in its entirety will be reimbursed US $160 (CAD $211). Payment for assessment visits will occur following the completion of that visit. If a participant must repeat an assessment visit due to administrative assessment or study staff errors, participants may be provided additional compensation for that session. If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and training sessions they have completed.

Participants will either be given a loaner tablet (Lenovo M10 Android 9.0 tablet) to complete their assigned training exercises to help bridge gaps in digital access or be given the option to train on a personal device.

One fully executed copy of the informed consent will be provided directly to the participant, and the original signed form will be retained in a secure manner at the study site and be available for inspection at the study site upon the request of

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representatives of relevant regulatory agencies. The copy of the consent form taken home by the participant will include appropriate telephone and email contact information, including the site investigator and the site's reviewing IRB.

Spouses and partners of participants are not part of INHANCE but, if interested, will receive a complimentary license to the same training program as the participant to reduce the risk of shared training on the same account.

Measures and Data Collection

See Table 1 for all measures and time points.

Table 1. List of study activities and time points used in Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise (INHANCE). Unanticipated adverse device effects were reported as needed. Study exit was reported when the participants exited from the study.

Study activity	Consent and screening visit (V0)[a]	Baseline visit (V1)[b] within 4 weeks of V0	Program orientation and intervention for 10 weeks begin training within 2 weeks of V1	Posttest visit (V2)[c] within 10-14 weeks of the first training session	No-contact period for 12 weeks	Follow-up visit (V3)[d] within 16-22 weeks of the first training session
Informed consent	✓					
Inclusion and exclusion criteria	✓					
Demographics	✓					
Medical history	✓					
Medications	✓					
MoCA[e]	✓					
GDS-SF[f]	✓					
C-SSRS[g], baseline	✓					
MRI[h] and PET[i] imaging		✓		✓		
NIH EXAMINER[j]		✓		✓		✓
Train-to-task assessments with heart rate variability and pupillometry		✓		✓		✓
C-SSRS, since last visit		✓		✓		✓
Medications, since the last visit		✓		✓		✓
Adverse effects		✓		✓		✓
Randomization		✓				
Program Orientation			✓			
Computer training			✓			
Weekly phone check-in			✓			

[a]V0: consent and screening visit.

[b]V1: baseline visit.

[c]V2: posttest visit.

[d]V3: follow-up visit (end of study).

[e]MoCA: Montreal Cognitive Assessment.

[f]GDS-SF: Geriatric Depression Scale–Short Form.

[g]C-SSRS: The Columbia Suicide Severity Rating Scale.

[h]MRI: magnetic resonance imaging.

[i]PET: positron-emission tomography.

[j]NIH EXAMINER: National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research.

Screening

Following informed consent, potential participants will complete a set of structured interviews, neuropsychological assessments, and self-report questionnaires to evaluate their eligibility for the study. The following measures will be administered to participants at screening: (1) A structured clinical interview (20 minutes, in person) will collect key demographic (eg, year of

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birth, age, and education) and medical history information, including medical diagnoses and current medications. (2) The MoCA (10 minutes, in person) will assess global cognitive function. The MoCA tests visuospatial processing, executive functioning, naming, memory, attention, language, abstraction, delayed recall, and orientation to time and place for a total of 30 points, with higher scores indicating better performance [43]. Potential participants must score 23 or above on the MoCA to be eligible for INHANCE. This cutoff maximizes true positives and minimizes false positives (Youden index=0.71) [30]. Those who receive a score lower than 23 are referred to a neurologist for an evaluation of cognitive impairment. (3) The GDS-SF (7 minutes, in person) will assess depression. The GDS-SF is a self-report questionnaire in which participants respond with a yes or no to 15 questions about how they felt over the past week [32,33]. This assessment has good internal consistency (α coefficient of .82) and validity (dimensionality coefficients of .94 across multiple time points) [44,45]. Potential participants must score 9 or less on the GDS-SF to be eligible for INHANCE [45]. Those who receive a score of 10 or higher are referred to a physician for appropriate treatment. The Columbia Suicide Severity Rating Scale (C-SSRS) (10 minutes, in person) will assess suicidal ideation and behavior [31]. The C-SSRS is a questionnaire with high sensitivity and specificity that assesses the severity of ideation, intensity of ideation, suicidal behavior, and lethality [31]. Potential participants who endorse suicidal ideation (question 5 “Active suicidal ideation with specific plan and intent”) or any suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) if the ideation or behavior occurred within 2 months from participant’s date of consent will be referred to a physician for appropriate treatment. In addition, study participants meeting these criteria at any timepoint throughout the study will be asked to complete a final assessment, if appropriate, and then withdraw from the study to be referred for appropriate treatment.

Outcome Measures

Outcome measures will assess the extent to which brain training leads to measurable changes within the cholinergic system, cognition, and behavior in healthy older adults. The primary outcome is acetylcholine binding measured by FEOBV-PET [37,38] at baseline versus posttest. All other outcomes are exploratory and will be measured at baseline, posttest, and at a 3-month follow-up after the training is complete. (1) A structural MRI (20 minutes, in person) will be acquired during the first scanning session to coregister the PET data with each individual’s neuroanatomical brain image. In total, 3-dimensional T1-weighted anatomical MR image volumes covering the entire brain will be acquired on a 3T Siemens Magnetom Prisma (Siemens) scanner with an 8 channels head coil (repetition time=27 ms; echo time=9.20 ms; between 176 and 192 sagittally oriented slices with a slice thickness of 1 mm; acquisition matrix=240×256; field of view=256 mm). (2) The National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (NIH EXAMINER; 20 minutes, in person) will assess cognitive performance [46]. Participants will complete a set of computerized assessments evaluating executive function (Flanker, Set-Shifting, and Anti-Saccades) and performance will be measured using the composite *z* score shown to have good reliability and validity [47]. (3) Behavioral assessments of heart rate variability and pupillometry will assess cholinergic function (15 minutes, in person). Pupillometry acquisition will be carried out using Tobii Pro Glasses 2 (Tobii) and heart rate variability will be acquired using a 4-lead Consensys ECG Development Kit (Shimmer). Both are measured while completing the 2 train-to-task assessments described below. (4) Computerized train-to-task assessments for Double Decision and Freeze Frame (15 minutes, in person) will serve as a positive control for task learning [48]. We expect large improvements in the intervention group on these assessments because they have directly practiced these tasks. The data are relevant because individuals failing to make progress on train-to-task assessments may represent a subpopulation not treatable with this program, and individuals making strong progress may represent a subpopulation particularly amenable to treatment with this program. The 2 assessments in this group are modeled upon a single level from their respective training exercise using a scoring algorithm that waits until the participant achieves asymptotic performance.

Data Management

All study-related data are recorded into a secure, web-based electronic case report form at the study site through the Longitudinal Online Research and Imaging System (LORIS). This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act and Personal Information Protection and Electronic Documents Act standards for confidentiality and privacy [49].

Following consent, each participant will be assigned a standardized Participant Identification Number composed of digits to identify the study and digits to identify the participant. All electronic case report form data entry will be deidentified, using the Participant Identification Number and not the participant’s name, but will include identifying information in the form, such as the date of the assessment administration, age, and potentially other dates associated with the data collected.

PET Image Processing

The SPM12 software [50] is used to perform all data preprocessing according to the following steps: (1) the T1-weighted structural images of all participants are spatially normalized to the MNI-152 standard reference template [51], and segmented into gray matter, WM, and cerebrospinal fluid tissues using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm [52]; (2) the static FEOBV PET images are then coregistered to the participant’s T1, and from there to the MNI-152 template by applying the deformation fields obtained in the first step. A Muller-Gartner partial-volume correction method is used to remove the partial volume effect on the PET images [52]; (3) finally, normalized partial volume effect–corrected FEOBV PET images are spatially smoothed to 8 mm full width at half maximum to remove random noise.

For all spatially normalized FEOBV PET images, the mean standard uptake value ratios are computed in preselected regions

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of interest (ROIs) using a supratentorial WM mask as a reference region to normalize the FEOBV PET images [53]. An anatomical MNI-space atlas (Hammers Atlas) [54] is applied to the PET images to quantify regional differences in FEOBV uptake within preselected ROIs.

Statistical Analysis

The data analysis plan defines a primary ITT population, a single primary outcome measure, a set of exploratory outcome measures, a single primary evaluation time point, an exploratory evaluation time point, a primary statistical analysis methodology, a criterion for statistical significance, and guidance for the interpretation of results.

The primary ITT population is defined as all participants who were randomized and completed the first training session [55]. This includes all randomized participants except those who drop or withdraw post randomization and pretraining.

The primary outcome measure assesses forebrain FEOBV binding in the anterior cingulate cortex at baseline and posttest between the intervention and active control groups. The exploratory outcome measures are FEOBV binding across additional ROIs (posterior anterior cingulate, primary auditory cortex, primary sensorimotor cortex, parietal lobe, frontal lobe, occipital lobe, temporal lobe, global cortex, hippocampus, parahippocampal gyrus, putamen, caudate, striatum, nucleus basalis of Meynert), NIH EXAMINER composite score, Double Decision and Freeze Frame train-to-task assessment scores, heart rate variability, pupillometry, and MRI volumetrics. The 3-month follow-up assessment is an exploratory timepoint.

The primary statistical analysis methodology is a linear mixed model approach. We will first compare intervention and active control groups in the ITT population at baseline using *t* tests or chi-square tests to determine if differences in baseline variables remain after the randomization process. Variables that show a significant α ($P<.05$) will be noted and used as covariates in the model [55]. We will examine the data for each outcome measure using a linear mixed effects model with treatment group and time as fixed factors, and covariates as necessary from the baseline analysis. Missing data will be accounted for using iterative full-information maximum likelihood estimation. Within-group effects for each time point (posttraining, follow-up) will be calculated using data from each group. Between-group effects for each time point will be calculated in the same way, adding an interaction term (training group × time) to estimate the effect of cognitive training on outcome measure change. *P* values and effect sizes will be reported.

To evaluate the efficacy of BrainHQ to upregulate acetylcholine, we will conduct the analysis based on the baseline and posttest data. Finding a significant α of $P<.05$ on the FEOBV primary outcome measure will support the statement that the intervention increases acetylcholine binding.

To evaluate the endurance of cognitive effects following the completion of training (NIH EXAMINER), we will conduct confirmatory analyses based on the posttest and follow-up assessment data to evaluate the endurance of the change (maintenance, decline, or increase). Showing maintenance or improvement between posttest and follow-up will support the statement that a brief intensive training epoch maintains (or improves) cognition after training has ceased.

Additional exploratory analyses will use Pearson or Spearman correlations [56] as relevant and will compare FEOBV binding against the NIH EXAMINER composite score, all exploratory ROIs, the train-to-task assessments, heart rate variability, pupillometry, MoCA performance, demographic variables, and the number of levels trained for the ITT. We will also conduct these analyses for those who completed the minimum effective dose of 10 hours of training or achieved a score on the Double Decision posttest assessment of 400 milliseconds or faster [1,57-59]. We will compare the NIH EXAMINER composite score with the primary and exploratory ROIs, train-to-task assessments, heart rate variability, pupillometry, MRI volumetrics, MoCA, and the number of levels trained for the ITT, and for those who completed the 10-hour minimum and achieved 400 milliseconds or faster on the Double Decision posttest assessment. Responder analyses will evaluate key moderators (age, sex, MoCA, baseline cognitive performance on NIH EXAMINER composite, baseline cognitive performance on the train-to-task assessments, and number of levels completed) to assess who responds most to training. No correction for multiple comparisons will be made for exploratory analyses and all trending relationships ($P<.10$) will be reported.

Results

Overview

The trial was funded in September 2019. The first participant was enrolled in July 2021, enrollment closed when 93 participants were randomized in December 2023, and the trial will conclude in June 2024. The trial is currently ongoing. The study team will be unblinded to conduct analyses after the final participant exits the study. We expect to publish the results in the fourth quarter of 2024.

Dissemination

In accordance with the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (NOT-OD-16-149) and the Clinical Trial Registration and Results Information Submission regulation (42 CFR Part 11), INHANCE was registered on ClinicalTrials.gov within 21 calendar days after the enrollment of the first participant, and the study page has been continuously maintained and meets all reporting and regulatory requirements, and the study registration link was shared on all participant consent forms.

Data from this trial will be broadly shared with the research community and laypersons through the conventional scientific publication process. The final study results will be submitted to a peer-reviewed indexed scientific journal within 2 years after the last participant's final study visit. Following the completion of the a priori data analysis plan, we will make the complete data set available to McGill investigators to conduct further post hoc exploratory analyses. Any relevant results will be submitted to relevant peer-reviewed journals. In 2026, two years after the completion of the trial, the complete raw data

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set will be available in LORIS, a freely available, open-source, and provenance-sharing data archive.

If the intervention shows a positive benefit on the primary outcome measure, then global distribution of an effective, low-risk, highly scalable brain training program will be justified and INHANCE will be commercially available on popular web-based platforms (eg, Chrome, Safari, and Firefox), iOS (Apple Inc) and Android devices across 14 languages (English, French, Spanish, Japanese, German, Hebrew, Italian, Korean, Portuguese, Greek, Dutch, Arabic, Mandarin, and Russian).

Discussion

Brief Summary

The goal of INHANCE is to conduct a double-blind, parallel-arm, active-controlled randomized trial to evaluate the impact of a 10-week computerized brain training program focused on speed and attention versus active control on cholinergic signaling in healthy adults aged 65 years and older, on the path to understanding how brain training enhances cognition. Recruitment for the trial began in July 2021 and concluded in December 2023, with the study set to complete in June 2024. Should the intervention demonstrate an increase in acetylcholine binding at posttest compared with baseline, the trial would identify a core mechanism of action and support the adoption of a simple, cost-effective, and scalable form of computerized training to protect against age-related cognitive decline.

Comparison to Existing Work

Acetylcholine is widely recognized as a crucial neurotransmitter that regulates synaptic plasticity and supports overall brain health. Despite this, in vivo measurement of acetylcholine in humans has been scarce [36,60]. FEOBV-PET provides unique insights into the cholinergic system's effect on cognitive performance, and this current trial is the largest imaging study of this radioligand to date. The trial's findings will enhance our understanding of FEOBV's association with aging and cognitive performance and its sensitivity to behavioral intervention.

Limitations of This Study

Both training programs required a substantial time commitment of 30 minutes per session, 7 days a week for 10 weeks, totaling 35 hours. While missed sessions are anticipated, the frequency and total training hours surpass those in previous studies and meta-analyses of brain training [40,61]. In addition, both interventions require participants to operate an internet-connected device (or be willing to learn), which may limit the generalizability of the recruited sample.

Conclusions

Given the widespread interest and ongoing initiatives to identify nonpharmacological interventions for preventing and treating cognitive decline (eg, World-Wide FINGER trials [62-67]), the aims of the current study are of great importance: to further develop this strategy into a standard tool for managing brain health in our older-age populations. The core strengths of INHANCE include offering an online brain training program that represents a low-risk, nonpharmaceutical approach that complements existing conventional methods for maintaining cognitive health in aging adults. In addition, it facilitates rapid, scalable global access for anyone with an internet-connected device.

Future research should evaluate the use of FEOBV-PET as a diagnostic tool for identifying individuals at risk for cognitive decline, its predictive value in clinical populations, and its relevance as an endpoint in interventional trials. In addition, it should establish the mechanistic foundation for pivotal trials that assess the role of brain training in preventing and treating mild cognitive impairment and dementia.

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Data Availability

The data sets generated and analyzed during this study are available in the LORIS repository 2 years after the completion of the trial [49].

Authors' Contributions

MA and TVV are principal investigators. EDV-S is the site's principal investigator. MA, EDV-S, and TVV were responsible for the concept and the design of the study. MA wrote the first version of the manuscript and ACDFP wrote the PET Image Processing. SJG was the clinical trial manager at Posit Science. MA, EDV-S, ACDFP, and PJT defined the data analyses. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

MA, TVV, and SJG are employees at Posit Science, the company that develops BrainHQ's brain training and assessment programs. They are shareholders of Posit Science stock. EDV-S and ACDFP declare no competing interests.

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Multimedia Appendix 1
Peer-review report by the Center for Scientific Review Special Emphasis Panel - Center for Scientific Review - Small Business: Psycho/Neuropathology Lifespan Development, STEM Education (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 270 KB - resprot_v13i1e59705_app1.pdf]

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Abbreviations

ACTIVE: Advanced Cognitive Training for Independent and Vital Elderly
C-SSRS: Columbia Suicide Severity Rating Scale
DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
FEOBV: 18F-fluoroethoxybenzovesamicol
GDS-SF: Geriatric Depression Scale – Short Form
INHANCE: Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise
ITT: intent-to-treat
LORIS: Longitudinal Online Research and Imaging System
MoCA: Montreal cognitive assessment
MRI: magnetic resonance imaging
NIH EXAMINER: National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research
PET: positron emission tomography
ROI: regions of interest
V0: consent and screening visit
V1: baseline visit
V2: posttest visit
V3: follow-up visit (End of study)
WM: white matter

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Protocol

Protective Assets Reinforced With Integrated Care and Technology (PARITY): Protocol for a Randomized Controlled Trial

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Abstract

Background: Black women are significantly more likely to experience severe maternal morbidity and are 3 times as likely to die from pregnancy-related causes compared to White women. Using a strengths-based wellness approach within an integrated supportive care program provided by a community doula could offer pragmatic solutions for Black maternal disparities. The Protective Assets Reinforced with Integrated Care and Technology (PARITY) program consists of a wellness technology platform, including informational links to wellness content and reinforcing motivational SMS text messages, as well as community-based doula support delivered both in person and through the technology platform to improve Black maternal wellness.

Objective: This pilot randomized controlled trial (RCT) and mixed methods evaluation aims to (1) determine the feasibility and acceptability of the PARITY intervention; (2) investigate the preliminary efficacy of the PARITY intervention on clinical outcomes (maternal blood pressure, gestational weight gain, and cesarean birth); and (3) investigate changes to wellness behavioral outcomes (nutrition, physical activity, sleep, and health care adherence) and empowered strengths (self-efficacy, social support, motivation, resilience, problem-solving, and self-regulation) in the intervention group compared to a control group.

Methods: A 2-arm RCT and mixed methods evaluation will be conducted. Overall, 60 Black pregnant individuals will be randomized in a ratio of 1:1 to either the intervention or informational control group. Participants in the intervention group will receive access to the technology platform over a 12-week period that ends before birth. Intervention participants will be assigned a doula interventionist, who will meet with them 4 times during the intervention. All participants (intervention and control) will receive a referral for a birth doula at no cost, printed materials about having a healthy pregnancy, and community resources. Feasibility and acceptability will be assessed at the end of the program. Measures will be obtained at baseline (20-28 weeks), the 36th week of pregnancy, birth, and 6-12 weeks post partum. Summary statistics and distribution plots will be used to describe measured variables at each time point. A generalized linear mixed model with a shared random component will be used to analyze the effects of PARITY on clinical, wellness behavioral, and empowered strength outcomes, including baseline nutrition, physical activity, and sleep measures as covariates. For significant effects, post hoc contrasts will be adjusted using the Holm method to maintain comparison-wise error at or <.05. Missing data will be addressed using a pattern-mixture model.

Results: The National Institute of Nursing Research funded this pilot RCT. Recruitment, enrollment, and data collection are ongoing, and the estimated study completion date is October 2024.

Conclusions: The expected results of this study will provide the feasibility and preliminary efficacy of the PARITY intervention, to be used in a larger trial with a 12-month PARITY program intervention.

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International Registered Report Identifier (IRRID): DERR1-10.2196/58580

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KEYWORDS

maternal health; health disparities; doula; African American; mobile phone

Introduction

Background

The United States spends more on health care than any other nation in the world yet has the highest maternal morbidity and mortality rates of all high-income nations [1,2]. Severe maternal morbidity, defined by the Centers for Disease Control and Prevention as maternal outcomes that result in significant or life-threatening consequences for a woman's health, has increased by approximately 200% over the past 20 years, while maternal mortality has increased by 37% since 2018 [3-5]. Black women experience higher rates of pregnancy-related complications and are more likely to die from pregnancy or childbirth compared to White women, regardless of comorbid conditions or socioeconomic status [6-9]. This gap has not narrowed in decades, exposing Black families and their communities to profound emotional, social, and economic consequences that ripple for generations [10]. The effects of increased severe maternal morbidity in Black communities are wide ranging and include higher health service use, higher direct medical costs, extended hospital stays, long-term rehabilitation, ongoing chronic health conditions, disability, and earlier death [11-13].

Most studies regarding susceptible maternal populations commence from a deficit-based discourse, which refers to communication that focuses on deficiencies, lacks, or failures, ultimately perpetuating biases and hindering efforts to address disparities [14,15]. To counteract this deficit-based discourse, it is important to examine, include, and emphasize the strengths and protective assets of Black maternal populations [16]. An asset-based or strengths-based approach uses the positives of an individual, such as their knowledge, skills, and community, as the basis to create protective processes in health and well-being [14]. This study is an example of research designed using an asset-based approach [14], intentionally including measures and tools that elucidate the many strengths of Black maternal populations. This research is framed by the concepts of empowerment and wellness, which are principles of the midwifery model of care [17]. The use of a strengths-based approach helps buffer the deficit discourse participants may have internalized through previous interactions with health care services; highlights the assets of participants; and gives them tools for wellness that can be leveraged in confronting, overcoming, and maintaining resilience to risks within their lives.

Community-integrated care is a solution that empowers Black women to be healthy within the context of the neighborhoods and communities in which they live [18]. Community health workers (CHWs) are trusted members of their community who facilitate access to services and improve health care quality by providing community education, social support, and advocacy [19,20]. In our previous work, an intervention using a prenatal technology platform with CHW reinforcement translated to cost savings on health care use averaging US $1079 for intervention participants compared to control participants [21]. Doulas are a type of CHWs who are trained support persons and advocates who work with individuals during the pregnancy continuum and are uniquely situated to help overcome maternal health disparities [22,23]. Doula care has been shown to improve women's experiences; is associated with improved maternal outcomes; and helps mitigate the effects of social determinants of health through better health literacy, social support, and cultural competence [22].

The theory of maternal adaptive capacity is a strength-focused theoretical framework that focuses on the protective assets one may use to achieve or maintain health throughout pregnancy [24]. On the basis of the theory of maternal adaptive capacity and our preliminary work, this randomized controlled trial (RCT) and mixed methods evaluation examines a novel, strengths-based intervention for pregnant Black women [21,24]. This intervention is entitled the Protective Assets Reinforced With Integrated Care and Technology (PARITY) program and consists of a wellness technology platform and community-based doula support. PARITY is a strengths-focused intervention that uses mobile technology and doula support to empower individual women to bolster their existing strengths (protective assets) to navigate the health care system, improve overall wellness behaviors, and improve maternal outcomes.

Objectives

The overall purpose of this PARITY program is to reinforce protective assets through empowering messaging, promote wellness behaviors, and support Black birthing persons. This pilot trial will provide information on the feasibility, acceptability, and preliminary efficacy of the PARITY intervention among Black pregnant women as well as provide critical information on study design, retention, effect sizes, and outcomes assessment.

The objectives of this study are to (1) explore the feasibility and acceptability of the PARITY intervention; (2) investigate the preliminary efficacy of the PARITY intervention on changes to maternal blood pressure (primary), gestational weight gain, and cesarean birth (secondary) and estimate the effect size of the intervention relative to the control group; and (3) investigate changes to wellness behavioral outcomes (nutrition, physical activity, sleep, and health care adherence) and empowered strengths (self-efficacy, social support, motivation, resilience, problem-solving, and self-regulation) in PARITY intervention participants. With the combination of information, guidance,

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and support toward leveraging their innate strengths into actionable wellness, we hypothesize that the PARITY program will improve maternal blood pressure, gestational weight gain, and cesarean birth rate in the intervention group compared with the information-only control group. Further, we expect emphasizing individual strengths and building from them while navigating pregnancy-related health care will improve wellness behaviors and empowered strength variables such as adherence to medical care, including appointment adherence.

Methods

Study Design

This study is a 2-arm prospective RCT and mixed methods evaluation of the PARITY intervention for pregnant Black women. Participants will be randomized to either the information control group (30/60, 50%) or the intervention group (30/60, 50%) in a 1:1 ratio. A sample size of 30 participants per group provides 80% power to detect a significant difference at a .05 level while accounting for attrition [25-27]. Select intervention participants (10/60, 17% to 15/60, 50%) will engage in a qualitative interview at 12 weeks post partum to discuss their experiences, opinions, and suggestions for the intervention. Participants will be enrolled in the study for up to 24 weeks. This time frame will include enrollment, the intervention, and postpartum follow-up assessments. Due to the nature of the intervention, the participants, interventionists, and research assistants will not be blinded. However, standardized training and standard operating procedures, including the use of deidentified self-reported questionnaires administered at baseline and after the intervention period, will reduce the potential for bias due to not blinding.

Study Population

Participants will be included in the study based on the following criteria: (1) self-identify as being of Black race, (2) pregnant with gestational age 20 to 28 weeks at enrollment, (3) ability to read and write in the English language, (4) planning to give birth in a health care facility and receive obstetrical care with a health care record, (5) reside within 20 minutes of the identified metropolitan area, (6) 19 to 51 years of age, and (7) own a smartphone with internet access. Participants will be excluded from the study for the following reasons: (1) current involvement in another intervention study, (2) planned pregnancy termination, or (3) inability to provide informed consent.

Intervention

Overview

The PARITY program is designed to occur throughout the pregnancy continuum (first trimester through 12 months post partum). For the purposes of this study, the PARITY program will be shortened in length and scope to show feasibility for a larger trial. Participants will be enrolled in the study from 20 to 28 weeks' gestation of pregnancy and will complete postintervention surveys at 6 to 12 weeks post partum. All participants (intervention and information control groups) will receive routine care from obstetric providers (not paid for by the study), printed materials about having a healthy pregnancy, printed materials about community resources, and printed materials with a referral to a birth doula if interested (paid for by the study as an incentive).

The PARITY program involves 2 parts. The first is a wellness technology platform that includes a wellness curriculum and reinforcing SMS motivational messages with links to in-depth wellness content. The second is Black community–based doula support, delivered both in-person and through the technology platform.

The mobile technology component of the intervention is a web-based platform hosted by GoMo Health delivered over a 12-week period and will end before birth [28]. The platform includes web pages with various pregnancy-related wellness content. The content is evidence based, tested by GoMo Health, and based on our preliminary research [21,28]. Participants will receive SMS *text* messages from the web platform, and at times these will include hyperlinks. The doula will be able to communicate with participants, reinforce its content, and hold the intervention sessions within this platform [28]. The platform was approved by the University of Nebraska Medical Center Information Technology Services and is compliant with the Health Insurance Portability and Accountability Act. Participants in the intervention group will receive 4 sessions with the doula interventionist within the technology platform and 12 weeks of tailored wellness, strengths, and health care adherence curriculum and SMS text messaging through the platform. There is a comprehensive database to track calls, opened hyperlinks, and participant engagement with the platform.

Components of the Intervention

Strengths

Participants will receive 12 strengths-focused SMS text messages sent through the web-based technology platform. They will also receive 4 wellness messages with hyperlinks to more in-depth educational content within the web platform related to nutrition, physical activity, and sleep. The content of the messages for this study will be tailored to maternal wellness in Black women and informed by focus groups comprising Black community members [29]. In total, participants will receive 24 SMS text messages over 12 weeks. Messages will focus on improving self-perception, reminding women they can make positive changes and be healthy, instilling a sense of optimism for the future, and imparting competence regarding challenges that may be faced throughout pregnancy and beyond. In addition, messages will convey how strengths can provide buffers against adversity and promote resilience to risk. Messages that promote positive feelings, such as gratitude, humor, and hope, will also be reinforced through a strengths-focused framework.

Nutrition

PARITY includes information on nutrition during pregnancy and beyond. Nutritional advice will focus on eating foods in unprocessed forms (eg, fruits, vegetables, and lean meat), preparing food instead of purchasing fast food, mindfulness in eating, and water consumption. These nutritional guidelines are consistent with healthy weight gain and multiple nutritional benefits without prescribing standards that may require excessive

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financial resources or exclude foods that may be culturally important to participants.

Physical Activity

PARITY includes approaches to increase physical activity and reduce sedentary behaviors. The goal is to significantly increase each individual's physical activity level above baseline. Emphasis will be placed on approaches to exercise safely in pregnancy, finding joy in body movement, walking, and easy ways to reduce sedentary behavior in daily life (eg, using the stairs instead of the elevator).

Sleep

The sleep component of the PARITY intervention addresses ways to improve the quality and duration of sleep in pregnancy and beyond. The content will focus on the benefits of sleep to wellness and pregnancy, sleep hygiene, and troubleshooting sleep problems. Strategies, such as relaxation techniques, regularizing the sleep schedule, stimulus control, and adjusting the bedtime will be included. Specific strategies for improving sleep duration and quality during pregnancy related to nighttime waking and nocturia will also be discussed.

Health Care Adherence

Health care adherence content will include general reminders about adhering to the patient's individually prescribed health care plan and reminders of appointments. The content will also include information on how to approach health care providers with questions and concerns and the importance of engaging with the medical system despite current or past negative experiences and resources on accessing care if needed.

Doula Sessions

Each participant will work with a Black community–based doula interventionist who will communicate with them via the PARITY mobile technology platform during the study. The doula interventionist will have certifications as a doula and training in emotional and educational support, pregnancy health, privacy and confidentiality, inspiring change (theories of health), various learning styles, health literacy, and cultural competency. All doula sessions will be conducted by the same doula interventionist, who will be blinded to all outcome data.

The SMS text messaging will be sent in the doula's voice. The doula interventionist will communicate with each participant in 4 live sessions lasting 30 to 60 minutes. These live conversations will include basic instruction and open-ended conversations focused on reinforcing strengths and wellness habits. In addition, these check-ins will promote health care adherence and provide guidance on navigating the health care system. The doula interventionists will assist participants through the strengths-focused framework of maternal adaptive capacity to identify and understand each participant's particular barriers to wellness and health care adherence and to design approaches that increase behavioral change [24]. The doula interventionist will suggest community resources based on the participant's needs.

Qualitative Interviews

The qualitative interview uses the strengths-focused framework of the theory of maternal adaptive capacity to better understand the acceptability of the intervention and its role in emphasizing protective assets in Black pregnant women [24]. A total of 10 to 15 participants from the intervention group will be interviewed at 12 weeks post partum. A semistructured interview guide will be used to gather in-depth qualitative information. The interview guide consists of open-ended questions and additional probes that explore participants' experiences and opinions regarding the various intervention components. The interviewer will have the flexibility to ask additional questions for further clarification and to ensure comprehensive understanding.

Information Control Group

Participants assigned to the information control group will receive routine care from obstetric providers (not paid for by study), printed materials about having a healthy pregnancy, printed materials about community resources, and printed materials with a referral to a birth doula if interested (paid for by the study and offered as an incentive).

Outcomes

The feasibility of a full trial will be monitored throughout the study (eg, the randomization, recruitment, and retention of participants; data collection; and adherence). Additional data will be collected only on intervention participants. These include data on engagement with the PARITY intervention based on the number of hyperlinks clicked, time engaged in the content, and the number of doula sessions completed throughout the 12 weeks. A total of 10 to 15 intervention participants will be asked to complete a qualitative interview to discuss their experiences with the intervention and the acceptability of the technology component, doula component, and strength messaging component at 12 weeks post partum.

Clinical maternal outcomes (maternal blood pressure, gestational weight gain, delivery modality, and exploratory perinatal outcomes) will be measured at 20 weeks, 36 weeks, birth, and 6 weeks post partum and will be collected from the medical record. At baseline (20-28 weeks' gestation), demographics, discrimination, and neighborhood variables will be assessed using self-report questionnaires administered via REDCap (Research Electronic Data Capture; version 14.3.11) [30,31]. At baseline and 6 to 12 weeks post partum, wellness-related behavior outcomes (nutritional intake, physical activity, and sleep quality) and empowered strengths (self-efficacy, social support, problem-solving, motivation, resilience, and self-regulation) will be measured using web-based self-report questionnaires in REDCap. In addition, health care adherence (the number of prenatal appointments) will be evaluated retrospectively using medical records.

Recruitment

Prospective participants (intervention and control) will be recruited at the beginning of their pregnancy up to 28 weeks of gestation about interest and participation in the study. Participants will be recruited via advertisements on social media, fliers, and word of mouth. If an individual is interested in

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participating, they will contact the research team by completing the study screening questionnaire in REDCap or via telephone or email. Study personnel will contact the potential participant via telephone or email and explain the study in detail. Once interest is determined and screening eligibility is met, participants will be invited to sign a consent form and a medical release of information form and complete the baseline assessments at 20 to 28 weeks of pregnancy.

Participant Allocation

Randomization allocation will be guided by the National Cancer Institute Clinical Trial Randomization Tool [32]. This tool generates an allocation scheme using the asymptotic maximal procedure. The following parameter inputs were used in the tool: trial size=60, maximum-tolerated imbalance=3; and arms (ratio 1:1). The output of this randomization allocation tool provides a schedule of randomization.

After signing the informed consent and release of medical record forms, participants will be emailed a secure link to complete the baseline enrollment surveys electronically in REDCap. In addition, each participant will be given the Healthy Pregnancy handout [33], Community Resources handout, and Birth Doula handout, in addition to the standard consent documents. Participants will be randomized according to the randomization schedule based on when they complete the enrollment surveys. Once a participant completes the enrollment surveys, the research coordinator will inform the participant of their group assignment and explain the procedures related to the assigned group.

Individuals randomized to the information control group will be dismissed and informed that they will be contacted by study personnel 6 to 12 weeks post partum to complete the follow-up assessments. Individuals randomized to the intervention group will be contacted by the doula interventionist to schedule their first doula session and be onboarded to the PARITY platform. The interventionist will explain that the participant will receive 3 additional sessions (4 in total) with the doula interventionist in addition to the mobile technology platform where communication can occur with the doula.

During the sessions, the doula interventionist will use the Doula Sessions Manual, which contains a script for each visit. The doula interventionist will track when contact is made with the participant on a form called the Intervention Fidelity Checklist. To ensure the fidelity of the intervention, the doula interventionist's adherence to the intervention protocol will be measured through an audit of the dates and missed visits on the Intervention Fidelity Checklist and monthly review meetings.

All participants will complete postintervention surveys at 6 to 12 weeks post partum. At approximately 12 weeks post partum (or upon the receipt of records), participant medical records will be accessed to extract the pertinent outcome data. A total of 10 to 15 participants in the intervention group will be approached about completing the qualitative portion of the study. Participants will be approached in order based on the study's completion date.

Ethical Considerations

This protocol was approved by the University of Nebraska Medical Center Institutional Review Board (IRB; #0076-23-EP). Participants must sign an informed consent form before participating in the study. The consent process involves a detailed description of the study, describing any participation risks, indicating that participation is voluntary and that the participant has the right to withdraw at any time. Informed consent will be obtained in a private, quiet location to facilitate discussion and thoughtful consideration. Research team members will assess participants' capacity to consent, answer questions, and ensure understanding.

To maintain participant confidentiality, all study data will be deidentified. Each participant will be assigned an identification code for use on all study materials. The link between a participant's name and identification code will be stored only on the consent form, which will be kept in a locked file in the principal investigator's office, separate from other study materials. Data sources include consent forms; medical records; transcribed interviews, handwritten notes; and data entered in REDCap, a secure web-based application for research data management [30,31]. Hard copies of any data will be stored in a locked file accessible only to the investigators or the IRB. All electronic data, including entries in REDCap, will be password protected and encrypted. Medical record data will be encrypted and transmitted through secure firewalls. All transcripts from the qualitative interviews will be deidentified, encrypted, stored in a locked facility, and available for analysis and review only by study staff. Only study personnel, the research sponsor, the IRB, and legally authorized individuals will have access to the research records. Upon study completion, all personal health information will be removed from the database. Study findings will be published in scientific journals or presented at meetings without revealing patient identities.

Participants will receive a US $50 gift card for completing baseline assessments and US $50 for completing follow-up assessments. Participants in the qualitative portion of the study will be compensated with a gift card valued at US $25.

Outcome Measures

At enrollment, participants will sign a medical release of information form allowing the research team to measure data retrospectively from the participant's medical records. To collect the self-report questionnaires for the enrollment and postpartum assessments, each participant will use a unique, secure link to complete the electronic questionnaires in REDCap at baseline after informed consent is signed and at 6 to 12 weeks post partum based on the participant's due date. Reminders from the research team will be sent to participants using various forms of contact (phone and email) to complete the questionnaires as needed.

The following outcome measures will be used to examine the feasibility and acceptability of the PARITY intervention:

1. Feasibility will be assessed through enrollment, attrition, adherence to the intervention, and data collection.

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a. Enrollment rate: enrollment will be measured by the percentage of eligible individuals who agree to participate in the trial.
b. Attrition rate: attrition will be measured by the percentage of eligible individuals who complete the study.
c. Adherence to the intervention: adherence to the intervention will be measured using the Intervention Fidelity Checklist, where the doula interventionist will track when contact is made with participants and the number of doula sessions completed. Engagement with the platform will be tracked through clicks and the time spent on the platform.
d. Data collection: data collection feasibility will be measured through study personnel's sense of ease of use, time required, and missing data.

2. Acceptability of and experiences with the intervention will be assessed using in-depth qualitative information gathered through interviews with intervention participants at 6 to 12 weeks post partum. Interviews will solicit (1) the usefulness of the intervention, (2) ideas to improve the intervention, (3) satisfaction with the intervention, and (4) the utility of innovative technology to deliver the intervention. The qualitative interviews will be audio recorded and transcribed verbatim.

The following outcome measures will be used to examine the preliminary efficacy of the PARITY intervention:

1. Maternal blood pressure (primary) at 20 weeks, 36 weeks, birth, and 6 weeks post partum will be measured retrospectively from the medical record at 12 weeks post partum. The data will be analyzed as a continuous variable using the participant's blood pressure (systolic and diastolic) as well as categorically with the blood pressure classifications of hypertension (>140/90) and severe hypertension (>160/110).
2. Gestational weight gain (secondary), or the amount of weight gained in pounds at 20 weeks, birth, and 6 weeks post partum, will be measured retrospectively from the medical record at 12 weeks post partum.
3. Cesarean birth (secondary) will be assessed from the delivery modality (vaginal, cesarean, or assisted vaginal delivery), measured retrospectively from the medical record at 12 weeks post partum.
4. Perinatal outcomes (exploratory) from birth will be measured retrospectively at 12 weeks post partum via the maternal medical record. The perinatal outcomes that will be measured include preterm delivery; gestational diabetes; birth weight; gestational age at delivery; anesthesia used during labor; labor length; delivery provider type (obstetric physician, family physician, resident physician, or certified nurse midwife); and intrapartum medical diagnoses according to the
International Classification of Diseases, 10th Revision [34], including hypertensive disorders of pregnancy, intrapartum fever, and postpartum hemorrhage. In addition, the Appearance, Pulse, Grimace response, Activity, and Respiration score of the newborn at birth will be measured as a way to summarize the health of the baby [35].

The following outcome measures will be used to investigate changes to wellness behavioral outcomes and empowered strengths:

1. Wellness-related behavioral outcomes:
a. *Nutritional intake* will be measured with the Multifactor Screener, 2000, as used in the Observing Protein and Energy Nutrition Study [36]. This instrument measures approximate intakes of fruits and vegetables and percentage energy from fat and fiber. Respondents will report through a self-administered questionnaire in REDCap how frequently they consume foods in 16 categories and the type of milk consumed. The questionnaire will measure nutrition at baseline and 6 to 12 weeks post partum.
b. *Physical activity* will be measured with the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [37]. The IPAQ-SF consists of 9 items and collects information on the time spent walking, in vigorous and moderate intensity activity, and in sedentary activity over the last 7 days. It is scored by converting the reported time into metabolic equivalent of task (MET) minutes. The MET minutes are then summed to provide an understanding of an individual's physical activity levels, with low levels being <600 MET minutes per week, moderate activity levels being 600 to 2999 MET minutes per week, and high activity levels being ≥3000 MET minutes per week [37]. It will be self-administered in REDCap and takes approximately 10 minutes to complete. The IPAQ-SF is a reliable (α>.80) and valid instrument [37]. Physical activity will be measured at baseline and 6 to 12 weeks post partum.
c. *Sleep quality* will be measured using the Pittsburgh Sleep Quality Index, a reliable (α>.83) and valid self-report questionnaire that assesses sleep quality over a 1-month time interval [38]. The measure consists of 19 individual items, creating 7 component scores that range from 0 to 3 points. The 7 component scores are summed to produce 1 global score that ranges from 0 to 21 points, with 0 indicating no difficulty and 21 indicating severe difficulty across all areas [38]. Sleep quality will be measured through a self-administered survey, which takes about 15 minutes to complete, in REDCap at baseline and 6 to 12 weeks post partum.
d. *Health care adherence* will be measured by the number of health care appointments attended and missed, which will be logged in the medical record. Health care adherence will be measured throughout the pregnancy continuum and collected at 12 weeks post partum retrospectively via the medical record.

2. Empowered strengths:
a. *Self-efficacy* will be measured using the General Self-Efficacy scale [39] administered in REDCap. The General Self-Efficacy scale is a valid and reliable (α>.75-.90) 1D self-report measure that features a 10-item questionnaire assessing the optimistic self-beliefs of individuals to cope with various challenging demands in life [39]. It takes approximately

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5 minutes to complete. The response options are presented along a Likert scale for each item, ranging from 1 (not at all true) to 4 (exactly true). The total score is calculated as the sum of the items, with a higher total score indicating more self-efficacy [39]. Self-efficacy will be measured at baseline and 6 to 12 weeks post partum.

b. *Social support* will be measured using the 10-item Social Provisions Scale [40]. The 10-item Social Provisions Scale is a validated and reliable (α>.80) measure that assesses 5 social provisions: attachment, guidance, social integration, reliable alliance, and reassurance of worth [40]. Each item is rated on a 4-point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree), and the individual item scores are then summed to provide a summary score ranging from 10 to 40 [40]. Higher scores indicate higher levels of social support [41]. Social Support will be measured through a self-administered survey, which takes approximately 5 to 10 minutes to complete, in REDCap at baseline and 6 to 12 weeks post partum.

c. *Motivation* will be measured with the Self-Motivation Inventory (SMI) [42]. The SMI is a 40-item, 5-point Likert scale questionnaire that will be self-administered in REDCap and takes about 15 minutes to complete. The SMI is a valid and reliable (α>.91) instrument measuring self-motivation conceptualized as perseverance independent of external support [42]. Motivation will be measured at baseline and 6 to 12 weeks post partum.

d. *Resilience* will be measured using the 10-item Connor-Davidson Resilience Scale [43]. The 10-item Connor-Davidson Resilience Scale is a valid and reliable (α>.85) unidimensional self-reported scale measuring resilience [43]. Respondents will self-report through a survey in REDCap by rating items on a 5-point Likert scale ranging from 0 (not true at all) to 4 (nearly all of the time). Scores range from 0 to 40, with higher scores representing higher resilience [43]. Resilience will be measured at baseline and 6 to 12 weeks post partum through the survey, which takes about 5 minutes to complete.

e. *Problem-solving* will be measured with the Problem-Solving Inventory (PSI) [44]. The PSI is a valid and reliable (α>.86) self-report instrument that measures how well individuals make decisions and their problem-solving abilities [44]. The PSI includes 32 items using a 6-point Likert scale and takes about 10 minutes to complete. The total score of the questionnaire is the sum of all responses, with lower scores representing lower problem-solving abilities [44]. Problem-solving will be measured through a self-administered survey in REDCap at baseline and 6 to 12 weeks post partum.

f. *Self-regulation* will be measured with the Index of Self-Regulation (ISR) [45]. The ISR is a valid and reliable (α>.87) instrument that measures the level of self-regulation for health behavior change in a 9-item scale [45]. Respondents rate items on a 5-point Likert scale, ranging from 1 (strongly disagree) to 6 (strongly agree), with higher sum scores indicating higher levels of self-regulation for a behavior [46]. Self-regulation will be measured at baseline and 6 to 23 weeks post partum in REDCap through the ISR, which takes about 5 to 10 minutes to complete [46].

3. Other variables that will be assessed are demographics, discrimination, and neighborhood:

a. *Demographics:* an investigator-developed form will measure demographic variables, including income, education, ethnicity, insurance, health provider, relationship status, and pregnancy history, at baseline.

b. *Discrimination:* discrimination will be measured using the Everyday Discrimination Scale [47] through a self-administered survey in REDCap. The Everyday Discrimination Scale is a valid and reliable (α>.74) instrument that measures the frequency of chronic and routine unfair treatment in everyday life [47]. Respondents are asked to report how often they experience unfair treatment in their day-to-day life on a 6-point Likert scale ranging from 1 (never) to 6 (almost every day), with total scores ranging from 10 to 60. Higher scores indicate experiencing discrimination frequently and in a variety of situations [47]. Discrimination will be measured at baseline.

c. *Neighborhood:* neighborhood variables will be assessed using the Neighborhood Collective Efficacy-Community Cohesion and Informal Social Control protocol from the Project on Human Development in Chicago Neighborhoods [48]. This valid and reliable (α=.82) measure includes 10 Likert-style questions that assess trust and expectations among neighbors and is used to determine how the neighborhood environment modifies risky behaviors [48]. It will be self-administered as a survey in REDCap and takes about 10 minutes to complete. The measures consist of 2 subscales, Community Cohesion and Informal Social Control, that include 5 Likert-style items, each ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores indicate greater neighborhood collective efficacy [48]. Neighborhood variables will be measured at baseline.

Data Analysis

Participants will be described using standard summary statistics and distribution plots of measured variables at each point in time. We will estimate the standardized magnitude of each baseline difference and the correlation between each baseline variable and each outcome of interest in the interim and primary end point of early participants to objectively determine baseline variables that will be needed to estimate the unbiased effect of PARITY on each outcome. A shared random component generalized linear mixed model (GLMM) will be used to simultaneously describe and compare the effects of PARITY on clinical outcomes, wellness-related behavioral outcomes, and empowered strength outcomes over the measurement periods [49]. A shared random component model will account for the correlation within participants on any 1 measure and the

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correlation between measures on the same participant at the same time point. The effect of time will be treated as a fixed effect. The time-by-group interaction will be tested; if the interaction *P* value is >.10, it will be dropped from the model. Baseline nutrition, physical activity, and sleep measures will be used as covariates to control for potential differences in the groups and to avoid detecting spurious time-by-treatment interactions due to the random assignment of participants to groups. Demographic or clinical characteristics exhibiting differences between groups at baseline will be investigated as potential covariates in the models. For significant effects, preplanned post hoc contrasts will be computed, and *P* values will be adjusted using the Holm method to maintain comparison-wise error at or <.05 [50]. Unless otherwise specified, the significance level for all tests will be.05.

Missing outcome data caused by loss of follow-up are possibly related to the participant's unobserved outcome measures (nonignorable missingness). The GLMM provides unbiased estimates under missing completely at random and missing at random mechanisms. The data will be reanalyzed using a pattern-mixture model (PMM) to allow for different coefficient changes based on dropout patterns [51]. GLMM and PMM marginal treatment effects will be compared. If the marginal treatment effects differ by >10%, the missingness mechanism will be assumed not at random, and the PMM model marginal estimates will be used to draw conclusions.

Interview data will be analyzed using a thematic analysis approach [52]. The audio recordings will be transcribed verbatim, and the accuracy of the transcripts will be verified by a separate team member who will cross-reference the transcriptions with the audio recordings. Transcripts from interviews will be independently coded in a word processing software by 2 members of the research team. Coding will be completed using an inductive approach to look for specific to more broad patterns across the interview data collected [53]. This will allow for themes and patterns to emerge directly from the data. A list of codes will be recorded and described in a codebook along with the definitions and descriptions of codes and representative quotes from the data so that codes have distinct boundaries. After the data are independently coded, the 2 researchers will discuss the codebook and resolve any discrepancies. The codebook will also help to assess interrater reliability among team members in applying codes to the data [54]. Codes will then be categorized into potential themes by clustering similar codes from participant responses. Audio recordings will be destroyed after transcription has been confirmed. Transcriptions will be destroyed at the end of the study.

Sample Size Calculation for Future Full-Scale RCT

A sample size of 25 participants per group is sufficient to measure the proportional outcomes of recruitment efficiency and attrition for each group separately with an SE ≤0.10, assuming no attrition and worst-case variability (0.25) in each group. Past research suggests that attrition of up to 20% is acceptable and limits bias [26,27]. If there is up to 20% attrition in each group, the SE for each proportional outcome will be ≤0.12.

On the basis of Welch 2-sample 2-tailed *t* test, a minimum sample size of 25 participants per group provides 80% power to measure a difference in mean blood pressure and gestational weight change between the intervention and control groups of 0.81 multiplied by the SD, using a significance level of .05 [25]. If there is up to 20% attrition in each group, a difference of 0.91 multiplied by the SD is detectable with 80% power using a significance level of.05 [25]. We will recruit at least 5 additional participants per group, planning for screen failures or participant withdrawals.

Results

This pilot RCT is funded by the National Institute of Nursing Research. Data collection was initiated in August 2023 and will continue for approximately 2 years. We will report on the outcomes identified above in a peer-reviewed journal. We anticipate that the results of this feasibility RCT will inform a larger RCT with a 12-month version of PARITY.

Discussion

Overview

This pilot RCT and mixed methods evaluation will provide information on the feasibility, acceptability, and preliminary efficacy of the PARITY intervention in Black pregnant women, as well as provide critical information on study design, retention, effect sizes, and outcomes assessment. We anticipate finding improvements in maternal blood pressure, gestational weight gain, and cesarean birth rate in the PARITY program intervention group compared with the information-only control group. In addition, we expect that focusing on strengths and leveraging them during pregnancy will improve wellness behaviors and empowered strength variables, such as adherence to medical care and appointment compliance.

Previous work seeking to understand the mechanisms of Black maternal health disparities have characterized the negative outcomes experienced by Black women as socioeconomic in nature [55,56]. While these factors are associated with maternal morbidity and mortality, Black maternal health disparities cannot be explained entirely by factors such as income, educational level, and health insurance status [7,9]. Further, this narrative is problematic, as it reinforces the stereotype that Black women have low income and are undereducated [57,58]. Indeed, our previous work involving nearly 10,000 nulliparous mothers showed that Black women with higher education and adequate income were more likely to experience maternal morbidity than their counterparts of other racial or ethnic backgrounds who had lower education and income levels [59]. A growing body of evidence suggests that disparities in Black maternal health outcomes are not rooted in biology. Instead, discrimination and bias due to race are driving contributors to the decreased rates of prenatal care, reduced quality of care, and poor health outcomes for childbearing women of color [60-62]. The failure of prior research to ameliorate maternal health disparities may be related to the prevailing deficit-based framework through which maternal health research is designed and disseminated [9].

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Strengths

This research study uses the following strategies to work on overcoming deficit discourse through a strengths orientation: (1) includes a focus on capabilities, strengths, and opportunities; (2) conducts research with and by instead of about the individuals or groups; (3) promotes hope by using language that is person centered and optimistic and leads to positive perceptions; (4) identifies social context and the resources that exist within communities; (5) includes research questions that lead to empowerment; and (6) engages research participants with respect, allowing opportunities in which they offer their expertise about their situation [16].

In addition, current maternal health research rarely focuses on how Black women can become or remain well. Along with health care adherence, wellness includes daily lifestyle habits, such as physical activity, nutrition, sleep, and connectedness, that promote optimal physical and mental health. Our previous work showed that simple wellness-related lifestyle changes, such as physical activity, improved nutrition, and better sleep, were associated with decreased pregnancy complications [52]. Despite being largely ignored in the severe maternal morbidity research literature, wellness strongly impacts maternal outcomes. Daily wellness habits focused on physical activity, nutrition, and sleep are easier for pregnant women to implement compared to complex interventions and have the potential to increase the lifelong health of women and their families. This intervention is designed to work on building strong daily wellness habits and to empower women with the knowledge and tools to make healthy choices.

This research offers a comprehensive, innovative approach to improving maternal wellness by integrating a strengths-based framework, novel technology, and peer-based community support while addressing access to care, quality of care, and each participant's social needs and strengths. This research has the potential to provide pragmatic solutions for Black maternal disparities and shift the narrative about Black women in the research literature. Knowledge gained from this research may inform future research and practices related to community-engaged approaches and interventions.

Challenges and Limitations

Due to the nature of pregnancy and the inexact times during which birth occurs, we expect that participants will receive varying doses of the intervention. This is a limitation of pregnancy-related research and will be accounted for in analyses. In addition, limitations on funding make it so that we cannot translate materials into other languages or provide translators for this feasibility study, limiting the population to English-speaking individuals. The intervention evaluated in this study requires participants to own a smartphone, which also limits the population that can be reached in this study. Finally, several measures obtained at the 4 main data collection time points might burden participants or lend themselves to missing data.

Conclusions

Integrating a unique technology intervention alongside doula support represents a novel approach to maternal health interventions. This research will inform the feasibility of conducting a larger study and other future research involving community-engaged approaches. Moreover, the results hold promise in combating deficit discourse surrounding Black maternal populations, both within academic and clinical settings. By focusing on empowered wellness and leveraging strengths, this intervention aims to reduce maternal health disparities in Black women. The anticipated outcomes of this study will shed light on the effects of the PARITY intervention in addressing these disparities and may illuminate the role of individual protective assets in buffering against maternal health inequities.

Acknowledgments

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Data Availability

All data generated or analyzed during this study will be available in supplementary files or described directly in the main findings paper at the time of publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 159 KB - resprot_v13i1e58580_app1.pdf]

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Abbreviations

CHW: community health worker
GLMM: generalized linear mixed model
IPAQ-SF: International Physical Activity Questionnaire-Short Form
IRB: Institutional Review Board
ISR: Index of Self-Regulation
MET: metabolic equivalent of task
PARITY: Protective Assets Reinforced With Integrated Care and Technology
PMM: pattern-mixture model
PSI: Problem-Solving Inventory
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMI: Self-Motivation Inventory

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Protocol

An Automated Text Messaging Intervention to Reduce Substance Use Self-Stigma (Project RESTART): Protocol for a Feasibility and Acceptability Pilot Study

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Abstract

Background: Stigma is a barrier to treatment and harm reduction seeking in people who use drugs. Most stigma reduction interventions offer psychotherapy or psychoeducation in group-based clinical settings, failing to reach people who are not in treatment. SMS text messaging is an effective and acceptable modality for delivering health information to people who use drugs and may be a suitable conduit for providing information and advice to understand and cope with stigma.

Objective: This paper presents the protocol for a study that aims to determine the feasibility, acceptability, and preliminary effectiveness of a 4-week automated SMS text message intervention to increase stigma resistance and reduce self-stigma in people who use drugs.

Methods: We designed a novel automated SMS text message intervention to address the four personal-level constructs of stigma resistance: (1) not believing stigma and catching and challenging stigmatizing thoughts, (2) empowering oneself through learning about substance use and one's recovery, (3) maintaining one's recovery and proving stigma wrong, and (4) developing a meaningful identity and purpose apart from one's substance use. Theory-based messages were developed and pilot-tested in qualitative elicitation interviews with 22 people who use drugs, resulting in a library of 56 messages. In a single-group, within-subjects, community-based pilot trial, we will enroll 30 participants in the Resisting Stigma and Revaluating Your Thoughts (RESTART) intervention. Participants will receive 2 daily SMS text messages for 4 weeks. Implementation feasibility will be assessed through recruitment, enrollment, retention, and message delivery statistics. User feasibility and acceptability will be assessed at follow-up using 23 survey items informed by the Theoretical Framework of Acceptability. Primary effectiveness outcomes are changes in self-stigma (Substance Abuse Self-Stigma Scale) and stigma resistance (Stigma Resistance Scale) from baseline to follow-up measured via a self-administered survey. Secondary outcomes are changes in hope (Adult Dispositional Hope Scale) and self-esteem (Rosenberg Self-Esteem Scale). Feasibility and acceptability will be assessed with descriptive statistics; effectiveness outcomes will be assessed with paired 2-tailed *t* tests, and group differences will be explored using ANOVA. Overall, 12 participants will also be selected to complete acceptability interviews.

Results: This pilot study was funded by the National Institute on Drug Abuse in April 2023 and received regulatory approval in January 2024 by the University of North Carolina-Chapel Hill Institutional Review Board. Recruitment and enrollment began

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in March 2024. Follow-up visits are expected to conclude by May 2024. Results will be disseminated in relevant peer-reviewed journals.

Conclusions: To the best of our knowledge, this is the first study to address substance use stigma via a self-help SMS text messaging program. Results will add to the nascent literature on stigma reduction in people who use drugs. This protocol may interest researchers who are considering text messaging to address psychosocial needs in hard-to-reach populations.

Trial Registration: ClinicalTrials.gov NCT06281548; https://clinicaltrials.gov/ct2/show/NCT06281548

International Registered Report Identifier (IRRID): DERR1-10.2196/59224

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KEYWORDS

substance use; harm reduction; stigma; self-stigma; stigma resistance; mobile health; mHealth; SMS text messaging; mobile phone

Introduction

Background

Nonmedical use of controlled substances is a leading cause of morbidity and mortality in the United States, with 107,941 reported overdose deaths in 2022 and increasing rates of hepatitis C, endocarditis, and other infectious diseases in people (or person) who use drugs (PWUD) [1-3]. Although evidence-based treatment and harm reduction services are associated with reduced burden of disease [4-10], they remain underused; in the United States, only 6.5% of people with substance use disorders received past-year treatment in 2021 [11]. The role of stigma in the epidemic has come increasingly into focus among policy makers and interventionists [12-16]. Stigma—the social devaluation of PWUD manifesting in stereotypes, prejudice, and discrimination—inhibits help-seeking, promotes substance use as a coping mechanism, and increases the risk of overdose [17-20].

The stigma reduction agenda has, to date, focused overwhelmingly on public stigma—a notoriously slow and challenging target for change—with less research on equipping PWUD to understand and cope with stigmatizing thoughts and experiences [21,22]. Proponents of empowerment approaches (the *self-worth agenda*) suggest that groups considered marginalized should be given resources to understand and challenge their marginalization [13,23,24]. Self-stigma is a salient consequence of public stigma in PWUD. Self-stigma includes self-devaluation (ie, internalized stigma), the fear of encountering public stigma, avoidance of difficult thoughts and experiences, and disengagement from pursuing valued life goals [25]. Self-stigma mediates the association between public stigma and numerous health outcomes, including overdose, making it an important target for intervention [26-31].

A recent systematic review identified 15 intervention trials between 2011 and 2023 with promising evidence of effectiveness in reducing substance use self-stigma [32]. However, almost all studies were in clinical treatment facilities and group settings, ironically failing to reach PWUD who may avoid these settings because of fear of stigma [32].

Noting these gaps, we developed a novel self-help stigma reduction intervention for PWUD in active use premised on the theory of stigma resistance [33]. We chose SMS text messaging as the delivery modality. SMS text message interventions are effective and cost-effective vehicles for addressing substance use and mental health disorders, and PWUD have deemed SMS text messaging an acceptable way to receive health information [34-42]. SMS text messaging also removes some structural barriers (eg, transportation) that would otherwise preclude many PWUD from participating [43].

Objectives

In this paper, we describe the rationale, theoretical framework, and development of a 4-week, automated SMS text message intervention to increase stigma resistance and reduce self-stigma in PWUD. We then describe the protocol for a single-group pilot trial to determine the feasibility, acceptability, and preliminary effectiveness of the intervention. We hypothesize that the intervention will be feasible from the perspective of implementers and PWUD participants; that participants will find the intervention acceptable per our 16-item Theoretical Framework of Acceptability questionnaire; and that participants will experience reductions in self-stigma and improvements in stigma resistance, hope, and self-esteem from baseline to follow-up.

Methods

Ethical Considerations

The protocol was approved by the University of North Carolina-Chapel Hill (UNC) Institutional Review Board in January 2024 (23-2937) and aligns with the principles of the Helsinki Declaration of 1975 (as revised in 2000). Participants will provide written informed consent before beginning any study activities. The informed consent procedure follows the UNC-required consent template, including describing the purpose of the study, procedures to be followed, and risks and benefits of participation. The consent forms use language that is sufficiently simple for laypersons to comprehend. Study staff will be trained to probe for comprehension and to ensure participants understand the voluntariness of their participation. Study records will be stored on password-protected UNC servers; only Institutional Review Board–approved study members will have access. Names are only stored on signed consent forms and will be stored in locked cabinets separately from the data. No identifying data will be published in any

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reports. Total compensation is up to US $75 in gift cards (US $30 for each survey and US $15 for the follow-up interview).

Intervention Overview

Resisting Stigma and Revaluating Your Thoughts (RESTART) is a theory-informed, 4-week automated SMS text message intervention to reduce self-stigma in PWUD (Figure 1). The general approach of RESTART is to equip PWUD with knowledge and skills to understand, cope with, and ultimately resist substance-related stigma. The intervention delivers 2 daily SMS text messages to participants for 4 weeks (56 messages total).

Figure 1. Mock-up of the Resisting Stigma and Revaluating Your Thoughts (RESTART) text messages.

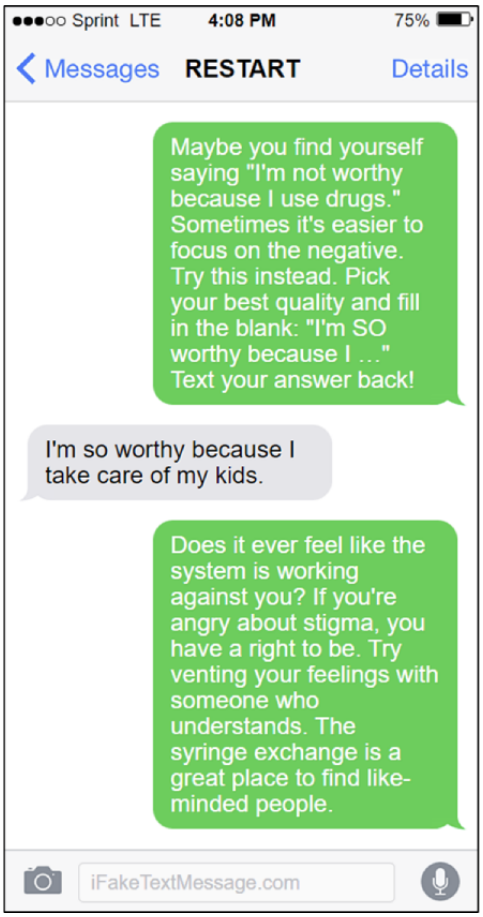

Theoretical Framework

Stigma Resistance

RESTART promotes stigma resistance, a psychosocial process associated with reduced self-stigma and improvements in self-efficacy, hope, self-esteem, mental health, and quality of life [44-48]. Stigma resistance is the active "opposition to the imposition of mental illness stereotypes by others"; high resisters can challenge or deflect stigmatizing attitudes and behaviors and engage in problem-centered rather than avoidant coping styles [46,49,50]. Firmin et al [33] conceptualized stigma resistance strategies at 3 levels: personal (ie, addressing one's stigmatizing thoughts and behaviors), peer (ie, helping others to resist stigma), and public (ie, educating, advocating, and publicly challenging stigma).

RESTART addresses the four components of the personal level of stigma resistance [33]: (1) not believing stigma and catching and challenging stigmatizing thoughts, (2) empowering oneself through learning about substance use and one's recovery, (3) maintaining one's recovery and proving stigma wrong, and (4) developing a meaningful identity and purpose apart from one's substance use. We determined that addressing the peer and public levels of stigma resistance (eg, promoting formal peer service involvement and advocacy) would be infeasible in a short-term messaging intervention, as these would likely require more intensive training and nuanced discussions on disclosure decisions.

Although the constructs of stigma resistance provide a suitable target for change, the theory does not provide guidance on *how* to change attitudes, beliefs, or behaviors [51]. Effective health communication interventions integrate theory from 3 domains: behavior change (which attitudes or beliefs are targeted), information processing (how attention, engagement, and acceptance of messages can be maximized), and message effects (format and content of messages expected to be persuasive and promote change; Table 1) [52].

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Table 1. Theoretical framework for Resisting Stigma and Revaluating Your Thoughts (RESTART).

Theory domain	Applied theories	Role in intervention
Behavior change	Stigma resistance and self-stigma	*Which* attitudes and beliefs are targeted for change?
Information processing	Elaboration likelihood model	*What* mechanisms are needed to promote effortful engagement with the messages?
Message effects	Cognitive restructuring, metacognitive awareness, psychoeducation, cognitive defusion, exemplification, emotional appeals, tailoring, etc	*How* can messages be designed (format or content) to persuade desired cognitive, attitudinal, and emotional outcomes?

Information Processing

Intervention development was informed by the elaboration likelihood model, an information processing theory that is helpful for understanding how individuals engage with persuasive messages and how engagement can lead to enduring attitude change [53]. For messages to influence attitude and behavior change, per the persuasion communication model by McGuire [54], recipients must pay attention to the message, comprehend its meaning, evaluate its content, agree with the message, and store its content in memory for later retrieval [52]. Attributes of the message's source, recipient, context, and content will influence the level of effortful processing (ie, elaboration) by recipients and, ultimately, the message's impact on sustained attitude and behavior change [53,55]. Motivation and the ability to attend to messages can encourage effortful processing [53,56,57]. Examples of strategies informed by the elaboration likelihood model are included in Table 2.

Table 2. Example persuasion strategies informed by the elaboration likelihood model.

Elaboration determinant	Strategy	Activity
Motivation	Increase personal relevance	Reference stereotypes or stigmatizing beliefs that resonate with participants
Ability	Minimize distractions	Send messages at the time of day when participants are least distracted (eg, not at work or driving)
Ability	Use repetition	Reiterate messages in subsequent delivery times or days using similar content but different wording

Message Effects

Message effects were drawn from both the psychotherapeutic and health communication literatures. In a recent systematic review of substance use self-stigma interventions, acceptance and commitment therapy, cognitive behavioral therapy (CBT), and psychoeducation were the most common and efficacious approaches to address self-stigma in clinical encounters [32]. We reviewed acceptance and commitment therapy, CBT, and psychoeducational manuals to identify modalities that could be translated into brief messages. For instance, cognitive restructuring, a component of CBT, suggests identifying and challenging one's distorted thought patterns (such as overgeneralizing or catastrophizing) and reframing these thoughts in more healthy and productive ways [58]. A message using this approach might read as follows:

> *Have you had a bad thought about yourself this week? Let's think of a reason that thought is NOT true. Here's an example: "My family might think I'm selfish. But that's not necessarily true. To be the best I can be, I have to take care of myself first."*

We incorporated multiple approaches from the health communication literature, including exemplification and tailoring, into our messages. Exemplification involves using specific exemplars (such as a celebrity in recovery) that are iconic, relatable, and emotionally arousing instead of generic representations [59]. Tailoring involves designing messages based on the characteristics of individual recipients to enhance personal relevance and increase attention and message processing. A message might address the recipient by name or reference a personal attribute [60,61]. A tailored message might read as follows:

> *Your drug use doesn't define you. You are so much more than that. What other parts of yourself are important to you? What would you want others to know about you? Here's one you shared with us: "I'm proud that I'm back in school."*

Conceptual Model

The message design and content are informed by health communication and psychotherapeutic theories to increase participants' attention to, engagement with, and agreement with the messages (Figure 2). We expect the messages will, in turn, improve participants' stigma resistance by providing information and advice pertaining to its subconstructs, such as challenging stigmatizing thoughts and developing alternative positive identities. Improvements in stigma resistance will give participants the cognitive and behavioral tools to challenge internalized stigma and overcome the fear of enacted stigma [25,44], which will, in turn, improve psychosocial outcomes such as self-esteem and hope [26-30]. Although unmeasured in this pilot study, we expect that reductions in self-stigma from the intervention may attenuate the "why try?" effect and have distal effects on behavioral outcomes such as treatment seeking and harm reduction seeking [18,62-64]. These outcomes could be assessed in future clinical trials if the pilot study demonstrates feasibility, acceptability, and preliminary effectiveness.

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Figure 2. Conceptual model of the intervention. PWUD: people (or person) who use drugs; RESTART: Resisting Stigma and Revaluating Your Thoughts.

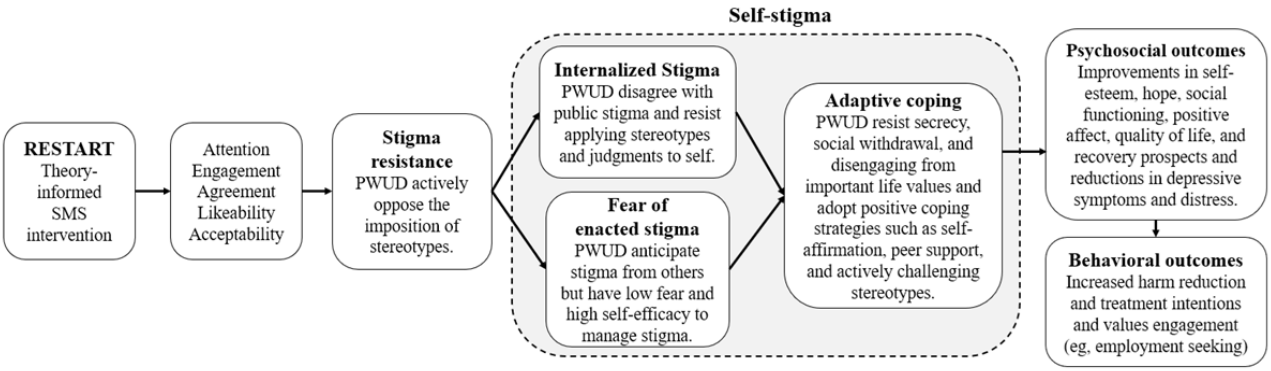

Intervention Development

Phase 1: Initial Message Development

Messages were developed using a modified intervention mapping technique [65]. We designated the 4 personal-level domains of stigma resistance as the "change objectives" of the program. Each message was then mapped onto a stigma resistance domain, a "method of change," (ie, an empirically or theoretically supported approach from the health communication or psychotherapeutic literature), and a commonly held stigma-related belief (to ensure the relevance of the messages' topics).

An initial bank of 20 messages was developed and refined with an expert committee that included a harm reduction practitioner and researchers with expertise in substance use, stigma, clinical psychology, mobile health (mHealth), and health communication.

Phase 2: Intervention Refinement Through Qualitative Elicitation Interviews

We conducted formative qualitative interviews with 22 PWUD to elicit stigmatizing experiences, attitudes, and beliefs; message feedback; and intervention acceptability. Participants were recruited from a syringe service program in Ohio and were eligible if they used illicit drugs in the previous 30 days and owned a mobile phone capable of receiving SMS text messages. Participant ID numbers are included for interview excerpts.

The preliminary 20 messages were tested using concurrent verbal probing on comprehension, liking, relevance, and suggestions for improvement [66]. Each participant reviewed 4 messages. Feedback was iteratively reviewed between interview rounds using the rigorous and accelerated data reduction technique [67], and changes were made for review in subsequent interviews. Overall, each preliminary message was reviewed by 4 to 5 participants. On the basis of participant feedback, messages were simplified to decrease cognitive burden (eg, reducing the reading level or lengthening to clarify content), edited to improve relevance, scaffolded into multiple messages to provide more information, or removed entirely. Several new messages were also created using exemplary in-vivo quotes to raise relevance and credibility, for example:

> *Carrie gets frustrated that people can't see past their drug use. "I don't call you Bill with cancer. I don't call you Sue with glaucoma. So don't call me Carrie the addict." Carrie is not defined by their drug use, and neither are you, [name]. There is so much more to you that makes you... you.*

The evolution of select messages is provided in Table 3.

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Table 3. Examples of message changes from participant feedback.

Original message	Changes	Final message	Exemplifying feedback
"Being an addict isn't a fair label. If you carry Narcan, some people might call you a guardian angel instead."	• Split the message into 2 to increase information and exposure. • Changed label from guardian angel to superhero. • Added in-vivo participant quotes.	• "MORNING: Steve thinks labels like 'junkie' are unfair. He refuses to buy in. It's like his dad taught him, 'It's not what you're called, it's what you answer to.' Can you stand tall and rise above the bullies?" • "EVENING: It helps to come up with different labels! Here's an example: If you carry Narcan, some people might call you a SUPERHERO instead. Does that feel more fair? Be proud of the good you do in the world. Not all heroes wear capes."	• "...maybe I'm your second chance, you know what I mean, I don't know. I just don't feel like an angel or guardian angel." [10.02PA]
"Living with substance use issues is so much harder than most people know. If there's a silver lining, it's that only a determined and resilient person could make it this far."	• Changed 'substance use issues' to 'addiction', which was more salient to participants. • Targeted participant ("only a brave and resilient person like YOU") to increase believability.	• "Addiction is so much harder than most people understand. If there's a silver lining, it's that only a brave and resilient person like YOU could make it this far."	• Participant: "It's the 'only a determined, resilient person can make it this far.' I don't believe that. Because a lot of people just get through because it just happens. I don't know. Divine intervention or just because they rode somebody's coat tail or something." • Interviewer: "What if the wording changed and said something like you had to be determined and resilient to make it this far. Would that feel better?" • Participant: "Yeah. That'd be better." [09.25PB]
"Our thoughts don't always match reality. You can tell yourself you're a pumpkin all day but it won't make it true. Can we question the negative self-talk, too?"	• Because of the high cognitive burden, this message was removed.	• Removed	• Participant: "That one's a bit weird." • Interviewer: "Tell me what you think it means." • Participant: "I have no fucking clue. [LAUGHS] That's gotta be spun. I don't know." [10.11PA]
"What are three things you accomplished this week that make you feel proud? How would others feel about you if they knew what you're capable of?"	• Participants enjoyed working through the message and offered no feedback for changes.	• Unchanged	• Interviewer: "How did it feel to think about it out loud?" • Participant: "Actually, it was pretty good. It just refreshes my memory to something that can help me. As far as, which I take that as a tool right now, because I don't think about it like that, but I just need to remember what I am capable of. That right there will boost my confidence. So that's a good thing." • Interviewer: "Okay. That's great. Anything you'd change about it?" • Participant: "No, definitely not." [10.10PB]

Global feedback on the intervention, its content, and delivery was also solicited. Participants tended to prefer personalized messages rather than those that were generic. They also disliked messages that were too abstract or required a lot of cognitive effort and enjoyed messages that suggested future-oriented activities (eg, goal setting). Importantly, several participants noted that messages encouraging social support (eg, sharing something positive with a loved one) would be difficult for PWUD without supportive relationships. These messages were adjusted to offer alternatives, such as writing in a journal or texting the intervention phone number back.

Participants varied in their preferred message frequency. Some participants preferred less frequent messages ("Probably one in a day, maybe" [09.27PB]), whereas others preferred as many as possible ("I don't care when, how, how many. I would love them." [09.27PA]). Most participants suggested that about 2 or 3 messages per day would be ideal:

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You might send them a message in the morning of, "Good morning, had your coffee this morning?" type of thing. And then some type of, as you go through the day, remember you can start your day over at any time. Don't let it get to you. [...] And at the end of the day, have you done your gratitude list today before you lay down the night? Are you still thankful for what you got? [09.25PA]

Phase 3: Finalizing Message Library

Overview

The message library was finalized in consultation with the expert committee and includes 56 messages (4 introductory messages, 7-17 messages for each of the 4 stigma resistance domains, and 2 concluding messages). Messages will be delivered in a standard order, emphasizing education and affirmation toward the beginning of the 4-week intervention period and more cognitively demanding content (eg, identifying personal values) toward the end. Sample messages mapped to stigma resistance domains, salient beliefs, and theoretical support are provided in Table 4. Example tailoring strategies are provided in Textbox 1. The message text is simplified to a sixth-grade reading level according to the Simple Measure of Gobbledygook readability formula [68].

Table 4. Excerpt from the final message development matrix.

Stigma resistance domain	Salient stigma-related beliefs	Theoretical support	Message
Empowering oneself through learning about substance use and one's recovery	"I judge myself because I think I can do better."	Psychoeducation	"TRUE OR FALSE? If you relapse, your recovery is a failure...FALSE! Did you know relapse is common in other chronic conditions like hypertension and asthma? Returning to use is a normal part of recovery from drug use, too. In fact, most people in long-term recovery have had several "relapses." Even Michael Jordan fell short for six seasons before he won his first championship. Believe in yourself."
Not believing stigma and catching and challenging stigmatizing thoughts	"When people say bad things about me, I believe them."	Cognitive restructuring (cognitive behavioral therapy)	"Have you had a bad thought about yourself this week? Let's think of a reason that thought is NOT true. Here's an example: 'My family might think I'm selfish. But that's not true. To be the best I can be, I have to take care of myself first'."
Maintaining one's recovery and proving stigma wrong	"People think I'm never going to change."	Behavioral activation (cognitive behavioral therapy)	"Haters may say you won't succeed, but we know you will. You are capable of so much. Let's do something small today to prove them wrong. Your theme song for today is [song]. Turn it on and get living!"
Developing a meaningful identity and purpose apart from one's substance use	"I don't have anything important left in life." or "I have nothing to look forward to."	Contact with important values (acceptance and commitment therapy)	"This week, let's think about your PURPOSE in life. "I was put on planet earth to..." It's a hard question, but it's important to think about what keeps us going."

Textbox 1. Example message tailoring strategies.

- Demographic tailoring (gender)
  - "Did you know (26 million men) or (21 million women) are dealing with a substance use disorder? That's more than twice the population of Ohio. There is strength in numbers. If someone treats you like you're different, know that you are not alone in this fight."
- Personalization (stigmatizing label)
  - "OK, here's the exercise. It sounds silly but give it a try. Ready? Say '[word]' out loud. Over and over. Use a goofy voice. For a full minute. When you're done, pay attention. Does '[word]' start to lose its meaning? Sometimes it helps to recognize that words are just words. Are you gonna let others put you down with THIS?"
- Personalization (name)
  - "Here's an exercise. What do you want written on your tombstone? '[Name] was a good friend, a kind soul, and a brave person'. Now you try. Go ahead and write it down. Don't lose sight of what makes you worthy."

Orientation

While stigmatizing experiences (ie, stereotyping and discrimination) were salient in the formative qualitative interviews, 12 (55%) of 22 participants were unfamiliar with the meaning of "stigma." In response, we developed a brief primer on stigma to share during the enrollment phase of the pilot trial.

Preliminary Acceptability

Acceptability of the intervention was high in the formative interviews:

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> *I think it would be great. [...] You could be at the worst moment and something like that come up and it could turn your whole day around, you know, or turn your decision around or, you know, whatever you're going through.* [10.02PB]

> *I think it would be great for real. It shows that people care that don't have to. And that matters. [...] I mean the program itself, to do something like that is awesome. [...] It's the people that care that don't have to.* [09.25PB]

> *Even if this program don't change the world to some of us addicts, it may birth the next program that does.* [10.02PA]

Even participants who admitted coming into the interviews skeptical of the research or unhappy with previous counseling experiences conceded that the program might have value:

> *So honestly, I think it's good. I'll be honest. At first I was like, this is gonna be stupid. All these stupid rehabs around here and shit. I was. I'm for real I was. I feel like, cliche. Like, I mean, that's what I thought before I came and stuff. And then I thought even like, OK, it's going to be cliche. But, you know, not snobby, but like, another... but no, that's very positive. It really is. I have not heard anyone say stuff or do anything like this in [town name].* [10.16PA]

> *I mean, some of it might be corny, but then so what? Some of it's corny, but some of it ain't. You know what I mean? So I don't think that I would look at it like that. [...] I don't feel like it's coming from somebody that's a stranger that's just there for a paycheck. [...] We don't get to hear positive things a lot. [...] We don't say them to ourselves, nor do we get to hear them from others. So I think it's a good idea.* [10.12PA]

Several participants expressed enthusiasm to participate even without compensation, noting the anticipated value of the program to themselves or other PWUD. Though all participants were prompted for concerns, only 1 was offered:

> *I don't think it's a bad idea at all[...] Maybe like the only concern I would have is for like girls who are in relationships with guys[...] Because there's always that, well, who's calling you? Who's texting you?* [10.02PB]

The overwhelmingly positive feedback made us confident to proceed with a pilot trial.

Study Design for the Pilot Trial

Overview

We will assess the feasibility, acceptability, and preliminary effectiveness of RESTART in a pilot trial using a 1-group prepost within-subjects design [69]. All participants will be assigned to the intervention. Preliminary effectiveness measures will be captured at baseline and follow-up via self-report. Demographics will be captured at baseline only. Feasibility and acceptability measures will be captured at follow-up only.

Setting and Participants

The setting for this pilot trial is a rural county in southern Appalachian Ohio designated as economically distressed by the Appalachian Regional Commission [70]. Southern Ohio has been an epicenter of the overdose epidemic for the past 2 decades, with morbidity and mortality rates consistently outpacing the rest of the state and nation [71,72]. High rates of substance use in this region are explained, in part, by high rates of disability from blue-collar jobs, a proliferation of "pill mills" (clinics that prescribe opioids inappropriately for financial gain) early in the epidemic, low evidence-based treatment capacity, and social and economic disadvantage in the region [73-78].

Participants will include 30 PWUD residing in the study county. Previous guidance has indicated that our sample size is an acceptable number for feasibility studies [79-81]. This sample size will allow us to estimate the retention rate to within a 95% CI of +12% or –12% (calculated assuming a retention rate of 85%). The sample size will further allow us to detect moderate effect sizes in the continuous outcomes (Cohen d=0.53) with 80% power (α=.05, 2-tailed) using paired t tests [82].

Eligibility and Recruitment

Prospective participants will be recruited from a local harm reduction program. The program has been active since 2011 and has cultivated a high level of trust with its clients, serving approximately 2000 individuals annually and supporting multiple research studies since its inception. Participants will also be identified through referral by enrolled participants and from contact lists of research participants consenting to recontact from previous studies. To be eligible, participants must be aged at least 18 years; understand English; have reliable daily access to a smartphone with a data plan capable of sending and receiving SMS text messages; reside in the study county with no immediate plans to move; and report past-30 days' use of illicit opioids (eg, heroin and fentanyl), prescription opioids not as prescribed (eg, oxycodone, buprenorphine), methamphetamines, or cocaine. To prevent ineligible individuals from attempting to participate, dummy screening questions will be included to obscure the eligibility criteria, as familiarity with research is high in the community. Participants will be purposively recruited to approximate the gender and racial and ethnic diversity of the study county.

Enrollment

Participants will provide consent and be enrolled in person, and then, they will complete a baseline survey via Computer-Assisted Self-Interview using the Qualtrics survey management system (version March 2024; Qualtrics LLC) [83]. The survey is expected to take 45 to 60 minutes to complete. Participants will then be oriented to the intervention by study staff on study procedures, phone security, handling technical issues, and setting up their phone to receive messages. Study staff will then provide a brief primer on stigma, including its historical background, definition, components (ie, stereotypes, prejudice, and discrimination), forms (eg, public stigma and self-stigma), and consequences (eg, social avoidance). Finally, participants will provide their personalization preferences,

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including message timing, preferred name, and other details that will be incorporated into tailored message templates.

Message Delivery

Participants will receive 2 messages per day (morning and evening) for 28 consecutive days, beginning on the day after enrollment. Messages will be delivered automatically via Twilio (version April 4, 2010; Twilio Inc), a communication platform that uses end-to-end encryption and follows industry-standard security measures. Automation is programmed in Python (version 3.11; Python Software Foundation), a programming language that is compatible with Twilio's application programming interface. Python scripts, message libraries, phone number databases, and other files needed for automation will be stored in AWS Lambda (Amazon Inc), Amazon's serverless computer service for running code. The program will be triggered to run every minute with Amazon EventBridge Scheduler (Amazon Inc).

Follow-Up

Participants will be contacted a few days before their scheduled end date to come in for their follow-up Computer-Assisted Self-Interview survey. The follow-up survey is expected to take approximately 60 minutes to complete. A subsample of participants (12/30, 40%) will also be selected to complete a brief interview covering experiences with and opinions of the program. Interview participants will be randomly selected from those presenting for their follow-up visit.

Measures

Implementation Feasibility

The feasibility of implementing the intervention will be assessed through recruitment, enrollment, retention, and message delivery statistics (Figure 3). We will measure the percentage of contacted individuals who proceed to screening, the percentage of screened individuals who are eligible, the percentage of eligible participants who enroll in the study, the time to reach sample saturation, the dose delivered (ie, percentage of messages successfully sent), and the dose received (ie, percentage of messages successfully delivered to the participant's phone per the carrier network). Read receipts are unavailable for standard SMS text messages delivered through Twilio.

Figure 3. Conceptual model of the feasibility, acceptability, and effectiveness measures. PWUD: people (or person) who use drugs.

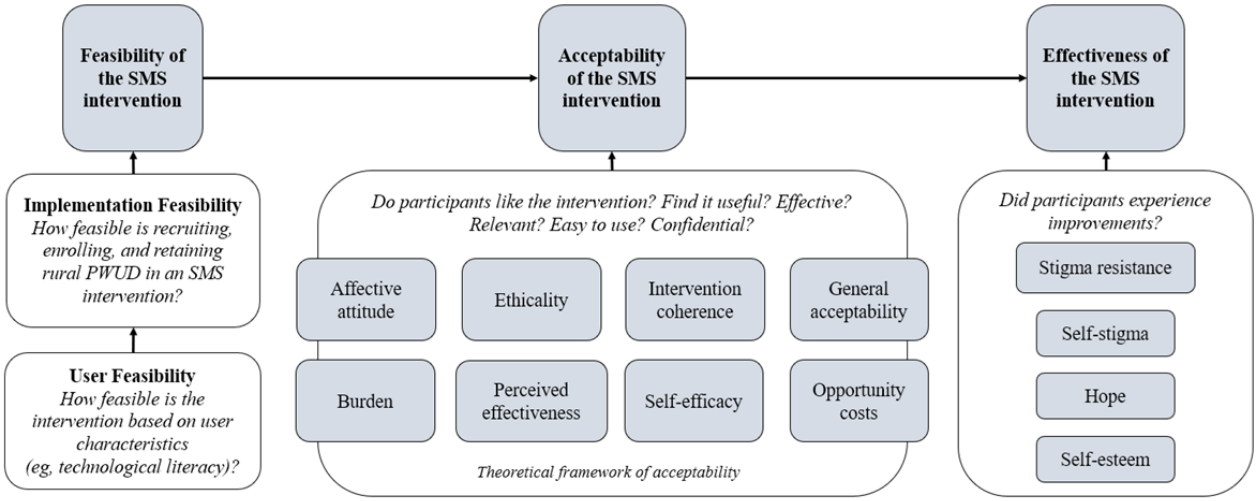

User Feasibility

Intervention feasibility from users' perspectives will be measured at follow-up using three 5-point Likert-type items and 2 binary (yes or no) items adapted from the study by Lian et al [84]:

> *Before the start of this program, how often did you send or receive text messages?*
>
> *Before the start of this program, how comfortable were you with sending or receiving text messages?*
>
> *Between the start of the program and now, did you experience any challenges or changes with your phone (e.g., lost, broken) that prevented you from receiving or reading text messages?*
>
> *Between the start of the program and now, did you experience any challenges or changes with your phone number or phone plan (e.g., changed number, ran out of minutes) that prevented you from receiving or reading text messages?*
>
> *On average, when would you read the text message you received?*

Follow-up interviews will provide additional context by probing how participants engaged with the program, whether technical issues arose, and suggestions to make the program easier to use.

Acceptability

Our literature review availed no standardized measures to assess acceptability in the context of a passive SMS text message intervention. We constructed a novel 18-item Likert-type questionnaire to assess acceptability based on the Theoretical Framework of Acceptability [85] with items adapted from Sekhon et al [86], Lian et al [84], and Knutson et al [87]. Items address the following Theoretical Framework of Acceptability domains: affective attitude (eg, "Overall, how much did you like or dislike the text message program?"), burden (eg, "How

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much effort did it take to engage with the text message program?"), ethicality (eg, "I had concerns about the privacy of my information sent over text message"), intervention coherence (eg, "It is clear to me how the text message program can help me to deal with stigma"), opportunity costs (eg, "Engaging with the text message program interfered with my other priorities"), perceived effectiveness (eg, "Overall, how helpful did you find the program?"), self-efficacy (eg, "How confident did you feel about using the information in the text messages?"), and general acceptability ("How satisfied were you with participating in this study?"). Follow-up interviews will provide additional context by probing on messages and intervention features participants liked or disliked, program concerns, and suggestions for improvement.

Preliminary Effectiveness

Primary effectiveness outcome measures are self-stigma and stigma resistance. Self-stigma will be assessed using the 40-item Substance Abuse Self-Stigma Scale (scale range 40-200; α=.86), which includes 4 subscales: self-devaluation, fear of enacted stigma, stigma avoidance, and values disengagement [25]. Stigma resistance will be assessed with the 20-item Stigma Resistance Scale (scale range 20-100; α=.93; subscales: self-other differentiation, personal identity, personal cognitions, peer stigma resistance, and public stigma resistance) [88]. Secondary effectiveness measures are hope and self-esteem, assessed using the 12-item Adult Dispositional Hope Scale (scale range 8-64; α=.77-.84), which measures agency and pathways to meet one's goals, and the 10-item Rosenberg Self-Esteem Scale (scale range 10-40; α=.77), which measures general self-esteem [89,90]. All scales are summed and scored such that greater scores reflect more favorable outcomes, except for the Substance Abuse Self-Stigma Scale, for which lower scores reflect lower self-stigma. In addition, once per week, participants will be texted a URL to a Qualtrics survey to rate the perceived message effectiveness of the previous week's messages using a single Likert-type item ("How much did each message help you understand how you can cope with stigma?"). Follow-up interviews will provide additional context on changes in knowledge and attitudes during the program.

Analysis

Basic descriptive statistics will be calculated for feasibility, acceptability, and outcome measures. We will present frequency tables for the categorical variables and means, SD, and percentiles (25th, 50th, and 75th) for the continuous variables. For outcome measures, descriptive statistics will be calculated for baseline scores, follow-up scores, and changes in scores.

As this is a feasibility study underpowered for statistical inference, hypothesis testing on the effectiveness outcomes is strictly exploratory. The analysis assumes a null hypothesis of no participant-level change in the outcome measures from baseline to follow-up. Inferential analyses will be conducted on participant-level change in outcome measures from baseline to follow-up using paired *t* tests (or Wilcoxon signed rank tests if response distributions are nonnormal) [69]. We will also examine differences in mean change scores across levels of demographic variables using ANOVA [69]. We will follow an intention-to-treat approach for all outcome measures. Significance levels for analyses will be set at α=.05. We will use R software (version 4.3.0; The R Foundation) for data cleaning, management, and analysis.

Results

Recruitment and enrollment began in March 2024. Follow-up visits concluded in April 2024. Data analyses were completed in July 2024. Findings from this study, regardless of outcomes, will be documented in manuscripts and submitted to relevant peer-reviewed journals. Results will also be reported on ClinicalTrials.gov (NCT06281548).

Discussion

Overview

In this paper, we described the process of developing, implementing, and evaluating a novel automated SMS text message intervention for PWUD. This intervention leverages the theory of stigma resistance with support from the psychotherapeutic and health communication literature to reduce substance use stigma. Messages were designed by researchers with expertise in stigma, substance use, clinical psychology, health communications, and mHealth. Importantly, the intervention received critical input from PWUD on message content, format, tailoring, timing, and frequency. Our study design will allow us to explore multiple quantitative and qualitative facets of feasibility, acceptability, and effectiveness, ultimately informing whether to proceed with a larger clinical trial.

Principal Findings

To the best of our knowledge, this is the first study to address substance use stigma via a self-help SMS text messaging modality. SMS text messaging interventions with promising effectiveness have been implemented to support individuals with mental health conditions, including depression, schizophrenia, eating disorders, and substance use [91]. SMS text messaging is cost-effective and scalable, with fewer technical challenges and equity concerns than mobile apps [92]. Cope Notes is one exemplar that sends automated supportive text messages with evidence for reducing anxiety and depressive symptoms [93]. The creators claim to have 33,766 subscribers across 97 countries as of March 2024 [94]. RESTART provides a test case for extending the potential of SMS text messaging interventions to PWUD, a historically hard-to-reach and hardly reached population [95].

Despite widespread acknowledgment that stigma is a key barrier to harm reduction and treatment use, few studies have intervened on this construct among PWUD in active use [32]. The results of our study will address the current research gap in stigma reduction interventions for PWUD. Our study will further inform whether SMS text messaging is a feasible and acceptable modality for promoting preventive health behaviors in this population.

Limitations and Anticipated Challenges

Our study has several limitations and potential challenges. The modest sample size and quasi-experimental design limit our

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ability to detect effects and make causal inferences. However, the primary aim of the study is to determine the feasibility and acceptability of both the intervention and study design; effectiveness may be further explored in future trials. The intervention was informed by and will be evaluated in PWUD residing in rural southern Ohio, limiting the generalizability of our findings. Retention is a challenge in studies with PWUD, although we have included multiple staggered incentives to minimize this risk [96,97]. Our harm reduction partners have also informed us that many clients frequently change phone numbers or data plans. Participants will be instructed to contact the study team if such technical issues arise, and alternate contact information will be obtained in cases where participants are lost to follow-up. Finally, although not shared by our qualitative participants, privacy and confidentiality may be concerns, particularly given the sensitive nature of the messages. Our communication platform, Twilio, has been used in multiple mHealth studies and uses industry-standard encryption algorithms [98-100]. Participants will also be instructed at enrollment to password protect their phones and provided advice on avoiding inadvertent disclosure.

Conclusions

Almost all federal funding allocated in the United States to date addresses public stigma through mass media campaigns and education programs, although there are questions about the extent to which these approaches move the needle [24,101-104]. Findings from this proposed study will add to the evidence base for self-stigma reduction as a necessary complement to public-facing initiatives in the stigma reduction toolkit [24,32]. Preliminary evidence from our formative qualitative study suggests that RESTART may be an acceptable approach to providing information and advice on self-stigma to PWUD. Our pilot intervention will provide further evidence of acceptability, feasibility, and preliminary effectiveness in anticipation of a scale-up clinical trial. This protocol may be of interest to researchers considering an SMS text messaging modality to address psychosocial needs in hard-to-reach populations such as PWUD.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ALS was responsible for conceptualization, project administration, data acquisition, formal analysis, data interpretation, and writing (original draft). SMN, KEM, NGO, CEP, AGS, WCM, and VFG were responsible for conceptualization, data interpretation, and writing (reviewing and editing).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute on Drug Abuse.
[PDF File (Adobe PDF File), 157 KB - resprot_v13i1e59224_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
mHealth: mobile health
PWUD: people (or person) who use drugs
RESTART: Resisting Stigma and Revaluating Your Thoughts
UNC: University of North Carolina-Chapel Hill

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Protocol

Study of Postacute Sequelae of COVID-19 Using Digital Wearables: Protocol for a Prospective Longitudinal Observational Study

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Abstract

Background: Postacute sequelae of COVID-19 (PASC) remain understudied in nonhospitalized patients. Digital wearables allow for a continuous collection of physiological parameters such as respiratory rate and oxygen saturation that have been predictive of disease trajectories in hospitalized patients.

Objective: This protocol outlines the design and procedures of a prospective, longitudinal, observational study of PASC that aims to identify wearables-collected physiological parameters that are associated with PASC in patients with a positive diagnosis.

Methods: This is a single-arm, prospective, observational study of a cohort of 550 patients, aged 18 to 65 years, male or female, who own a smartphone or a tablet that meets predetermined Bluetooth version and operating system requirements, speak English, and provide documentation of a positive COVID-19 test issued by a health care professional within 5 days before enrollment. The primary end point is long COVID-19, defined as ≥1 symptom at 3 weeks beyond the first symptom onset or positive diagnosis, whichever comes first. The secondary end point is chronic COVID-19, defined as ≥1 symptom at 12 weeks beyond the first symptom onset or positive diagnosis. Participants must be willing and able to consent to participate in the study and adhere to study procedures for 6 months.

Results: The first patient was enrolled in October 2021. The estimated year for publishing the study results is 2025.

Conclusions: This is a fully decentralized study investigating PASC using wearable devices to collect physiological parameters and patient-reported outcomes. The study will shed light on the duration and symptom manifestation of PASC in nonhospitalized patient subgroups and is an exemplar of the use of wearables as population-level monitoring health tools for communicable diseases.

Trial Registration: ClinicalTrials.gov NCT04927442; https://clinicaltrials.gov/study/NCT04927442

International Registered Report Identifier (IRRID): DERR1-10.2196/57382

(JMIR Res Protoc 2024;13:e57382) doi:10.2196/57382

KEYWORDS

postacute sequelae of COVID-19; wearable devices; physiological parameters; prospective observational study; mobile phone

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Introduction

Long-term health consequences have been identified as a core outcome domain for studies of patients with COVID-19 [1]. Dubbed as "long covid" [2] (or post–COVID-19 condition), postacute sequelae of COVID-19 (PASC) have been described on social media and in news media [3,4]. These reports referred to experiences of patients who take longer than normal time to recover or have more than 1 symptom that persists or develops after recovery [5,6]. This prompted calls to investigate the "prevalence, type, duration, and severity of persistent symptoms following resolution of acute SARS-CoV-2 infection, [and] risk factors associated with their development" [7]. Definitions of PASC varied depending on the onset and duration of symptoms, number and clustering of symptoms, patient population, and possibility of alternative explanations [8-11]. Heterogeneity in defining PASC translated into varying prevalence estimates, ranging from 43% to 80% in systematic reviews and meta-analyses of PASC among patients with COVID-19 at ~1+ month after infection [12-15]. Currently, the World Health Organization (WHO) defines PASC as a [16] "condition...in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis."

Patient-reported outcomes (PROs) and clinical evaluations show that patients with COVID-19 exhibit long-term health complications, regardless of initial disease severity [17-21], attributed to several hypothesized biological mechanisms [11,22,23]. These biological mechanisms include persistent viral reservoirs, sustained autoimmune and inflammatory responses, gut microbiome dysbiosis, endothelial dysfunction, and neurological signaling dysfunction [22,23]. PASC symptoms include fatigue, memory loss, and chest and abdominal pain, among 200+ other symptoms that affect multiple organs and systems [12,24-26], whereas emergent conditions include diabetes and hypertension [27,28]. Corroborating evidence shows persistent symptoms in recovered patients of other coronaviruses [29,30] and postviral chronic syndromes (eg, myalgic encephalomyelitis/chronic fatigue syndrome) [31]. Evidence of PASC is based on data primarily from hospitalized patients [18,19,32-35] and minimally from nonhospitalized patients [17,36], who represent ~20% and 80% of patients with COVID-19, respectively [37]. Longitudinal studies of PASC are limited because they have single-time outcome measurements [15], sparsely spaced data collection intervals, or short follow-ups (eg, [32,34,38,39]). Furthermore, studies focus on single symptoms or symptom clusters (eg, [40]), while few report psychological and well-being outcomes (eg, [18,33-35,41]). This raises the need for prospective longitudinal studies of nonhospitalized patients with COVID-19 with extended follow-ups to understand the nature, duration, and multisymptom manifestation of PASC [42,43].

Wearable devices continuously capture physiological parameters, which have been beneficial in detecting COVID-19 and monitoring its acute-phase symptoms [44-59]. These studies show that physiological, sleep, and activity parameters differ in the preinfection versus acute phases of the disease, symptomatic versus asymptomatic patients, and patients with COVID-19 versus healthy people. Physiological parameters collected via wearables parallel clinical indicators (eg, elevated respiratory rate) [60] and self-reported symptoms (eg, shortness of breath) [25] documented in patients and are associated with PASC [61,62]. Wearables-based studies of PASC are scarce and have short follow-ups [63,64]. COVID-19 wearables studies have several limitations including a focus on select parameters (eg, [54,64]); use of custom or specialized devices (eg, [59,65]), which limits their applicability and population-level impact; or recruitment of participants who already own wearable devices (eg, [50,54]), thereby introducing between-device variations in parameter calculations and self-selection biases [66].

This protocol outlines the design, objectives, and procedures of a 6-month decentralized prospective, observational study of PASC in a cohort of 550 nonhospitalized patients with a confirmed positive COVID-19 diagnosis.

Methods

Design

This is a single-arm, prospective, observational study of PASC in a cohort of 550 nonhospitalized patients with a positive COVID-19 diagnosis.

Objective

The study aims to identify physiological parameters collected by wearable devices that are associated with PASC.

End Points

The primary end point is long COVID-19, defined as 1 or more symptom at 3 weeks from date of the first symptom onset or positive diagnosis, whichever comes first. The secondary end point is chronic COVID-19, defined as 1 or more symptom at 12 weeks from symptom onset or positive diagnosis [6,9-11].

Hypothesis

There is an association between physiological parameters collected by wearable devices and patient-reported long or chronic COVID-19.

Population

A total of 550 patients will be recruited based on the demographic composition of the US population (Table 1) [67]. A prospective research volunteer (PRV) must meet all the inclusion criteria to be eligible for enrollment. The inclusion criteria are, first, male or female adults, aged 18 to 65 years. The pediatric population younger than 18 years of age is excluded because it differs from adults who are 18 years or older in infection rates, symptom manifestation, and outcomes [68]. The older than 65 years of age population is excluded because of its high-risk status, which prompted protections to reduce transmission among the older population, especially in nursing homes [69,70]. The second criterion is documentation of a SARS-CoV-19 polymerase chain reaction or antigen or rapid positive test, fewer than or 5 days before enrollment, issued by a public or private health care or COVID-19 testing facility, provider, or practitioner. The third criterion is ownership of or access to a smartphone or tablet, with an existing cellular

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data plan, that is compliant with the following specifications: (1) Android devices with an operating system of 6.0 or newer; Bluetooth 4.2, 5.x, or 6.0; and that implement Bluetooth Low Energy standard; (2) iPhone 6s or 6s plus (Apple) or newer; and (3) iPad mini 4 or newer, iPad 5th generation or newer, iPad Air 2 (second generation or newer), iPad Pro (9.7", 10.5", 11" first generation or newer), or 12.9-inch iPad Pro first generation or newer. The fourth criterion is English language proficiency. Non-English speakers will be unable to use the study mobile app, which is available only in English. The fifth criterion is the ability to understand and willingness to consent to participate. The sixth criterion is stated willingness to comply with all study procedures and availability for study duration. Finally, agreement to adhere to lifestyle considerations throughout the study (eg, wearing the wristband and temperature patch) is needed.

Table 1. Population by sex, race, and ethnicity in the United States, 2019 estimates for 18- to 64-year-old adults and study sample (N=550).

Ethnicity and race	US population, n (%)			Study sample, n (%)[c]		
	Male[a]	Female[a]	Total[b]	Male	Female	Total
Non-Hispanic or Latino						
White	61,422,351 (50.1)	61,189,372 (49.9)	122,611,723 (73)	164 (50.2)	163 (49.8)	327 (73)
Black	13,264,328 (48.1)	14,324,175 (51.9)	27,588,503 (16.4)	36 (48.6)	38 (51.4)	74 (16.4)
American Indian and Alaska Native	1,311,132 (48.8)	1,376,957 (51.2)	2,688,089 (1.6)	3 (42.9)	4 (57.1)	7 (1.6)
Asian	6,788,614 (47.8)	7,418,266 (52.2)	14,206,880 (8.5)	18 (47.4)	20 (52.6)	38 (8.5)
Native Hawaiian and Pacific Islander	376,873 (50)	377,530 (50)	754,403 (0.4)	1 (50)	1 (50)	2 (0.4)
Total	83,163,298 (49.5)	84,686,300 (50.5)	167,849,598 (100)	222 (49.6)	226 (50.4)	448 (81.4)[d]
Hispanic or Latino						
White	17,271,789 (51.1)	16,500,664 (48.9)	33,772,453 (88)	46 (51.7)	43 (48.3)	89 (88)
Black	1,073,954 (48.9)	1,122,733 (51.1)	2,196,687 (5.7)	3 (50)	3 (50)	6 (5.7)
American Indian and Alaska Native	809,646 (52.1)	743,289 (47.9)	1,552,935 (4)	2 (50)	2 (50)	4 (4)
Asian	306,995 (49.7)	311,194 (50.3)	618,189 (1.6)	1 (50)	1 (50)	2 (1.6)
Native Hawaiian and Pacific Islander	116,272 (51.6)	108,954 (48.4)	225,226 (0.6)	1 (100)	N/A[e]	1 (0.6)
Total	19,578,656 (51)	18,786,834 (49)	38,365,490 (100)	53 (52.0)	49 (48.0)	102 (18.6)[d]

[a]"Male" and "Female" cells for US population represent the percentage of each sex out of the total population by race or ethnicity (eg, percentage male individuals out of the total non-Hispanic or Latino White population).

[b]"Total" columns for US population represent the percentage of each race out of the total population by ethnicity (eg, percentage of White individuals out of the total non-Hispanic or Latino population).

[c]Cells for the study sample shown for each racial and ethnic category by sex based on US population aged 18 to 64 years for a sample of 550 patients.

[d]Cells represent total and percentage of the 550 target sample.

[e]N/A: not applicable.

An individual who meets any of the exclusion criteria is not eligible to enroll. The exclusion criteria are (1) residence outside of the US mainland, (2) enrollment in clinical trials on experimental COVID-19 therapeutics at baseline, (3) requirement of hospitalization at enrollment, (4) known history of allergic reaction to adhesives, and (5) inability to consent and unwillingness to comply with study procedures (eg, downloading a mobile app and sharing the data with the research team and providing required data such as close kin contact information).

Recruitment

The Office of Patient Recruitment (OPR) created all recruitment materials and advertised the study in print and on the National Institutes of Health (NIH) Clinical Center television monitors and website [71]. Commercial marketing venues are used depending on recruitment pace and funding availability. Additionally, we partnered with Fulgent Genetics, a company that administers COVID-19 testing in Los Angeles, California. As part of their scheduling for COVID-19 testing, patients who express interest in participating in research studies are asked "would you be interested in sharing information you submitted during this registration process with researchers so they can contact you about studies?"

Only information about patients who have agreed to be contacted is accessed. Outreach activities are engaged in to increase the enrollment of minorities.

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Study Procedures

PRVs contact OPR's recruitment center by phone or email. OPR's staff screens interested PRVs for initial eligibility using yes or no questions. OPR staff shares basic demographic and contact information of eligible PRVs with the study team. PRVs who reach out directly to us or are part of Fulgent Genetics' patient database receive an email and text invitation to enroll in the study, which includes a link to a proactive recruitment survey with yes or no questions like those that OPR uses to determine the initial PRV eligibility. These initial screening questions are about (1) PRV's age; (2) having a confirmed positive COVID-19 test within the past 72 hours, which leaves us 2 additional days to enroll PRVs within the 5-day eligibility window; (3) having an Apple or Android smartphone or tablet with brand and model information; and (4) willingness to comply with study procedures. Initial screening occurs before patients provide an informed consent (IC) to participate in the study.

PRVs who pass the initial screening receive a welcome email inviting them to schedule an enrollment appointment. The email includes a link to an electronic IC, which states that this is a research study and outlines the schedule of activities (Table 2), risks and benefits to patients, and the voluntary and confidential nature of participation. The IC emphasizes that the study wearable devices should not be the basis of any medical decisions. During the appointment, we review the IC with patients who are given opportunities to ask questions and request time to consult with their families or physicians before consenting to participate. Patients who eConsent to participate undergo eligibility verification and are enrolled only if they meet all inclusion criteria and none of the exclusion criteria. Patients who have ≤4 GBs per person on their monthly cellular data plan and limited access to personal Wi-Fi are provided US $60 gift cards to purchase additional GBs from their phone carrier.

Table 2. Schedule of activities.

Procedures	Preenrollment	Enrollment, day 0	Day 1-30	Day 31-60	Day 61-90	Day 91-120	Day 121-150	Day 151-180
Screening	✓							
Informed consent		✓						
Eligibility verification		✓						
Baseline questionnaire		✓						
Physiological data collection (number of days)			30✓	8✓	8✓	8✓	8✓	8✓
Ecological momentary assessments (number of EMAs[a])			30✓	4✓	4✓	4✓	4✓	4✓
Monthly survey (number of surveys)			1✓	1✓	1✓	1✓	1✓	1✓
Adverse outcomes survey (as applicable)			✓	✓	✓	✓	✓	✓
Technical or general support (patient-initiated)			✓	✓	✓	✓	✓	✓

[a]EMA: ecological momentary assessment.

Upon enrollment, patients are assigned a study ID and mobile app log-in credentials, which ensures patients do not use personal identifiable information to create an app account. Using the enrollment date, Research Electronic Data Capture (REDCap; Vanderbilt University) generates calendar dates that correspond to preloaded randomized data collection schedules that map the days on which each patient must perform study activities over 6 months (Table 3). The first day of device wearing starts on the third calendar day post enrollment to allow time for shipping an enrollment kit. During the first month, patients are required to wear a wristband and a temperature patch around the clock and answer a daily 2-question ecological momentary assessment (EMA). For months 2 to 6, patients are required to wear a wristband only for randomly selected 20 pairs of 2 consecutive days, resulting in an additional 40 device-wearing days in total. The schedule has a minimum of 48 hours buffer between 2 consecutive device-wearing periods, an approximately equal representation of weekdays and weekends where each day of the week appears 5 or 6 times during months 2 to 6, and an equal number of device-wearing days each month (ie, 8 days). For each 48-hour device-wearing period, patients answer a 2-question EMA. Patients are encouraged to wear the wristband and temperature patch upon receiving the enrollment kit, to wear the wristband beyond the 8 scheduled days per month during months 2 to 6, and to make up missed device-wearing days.

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Table 3. Sample study schedule[a].

Month and data collection days	Frequency and timing of study activities		
	Device wearing	EMAs[b]	Monthly survey (once)
Month 1 (daily)			On April 2, 2023
Days 1-30	From March 4, 2023, to April 2, 2023	From March 4, 2023, to April 2, 2023	
Month 2 (4 times)			On May 2, 2023
Days 31 and 32	From wake up on April 4, 2023, to wake up on April 6, 2023	On April 6, 2023	
Days 33 and 34	From wake up on April 10, 2023, to wake up on April 12, 2023	On April 12, 2023	
Days 35 and 36	From wake up on April 19, 2023, to wake up on April 21, 2023	On April 21, 2023	
Days 37 and 38	From wake up on April 28, 2023, to wake up on April 30, 2023	On April 30, 2023	
Month 3 (4 times)			On June 1, 2023
Days 39 and 40	From wake up on May 8, 2023, to wake up on May 10, 2023	On May 10, 2023	
Days 41 and 42	From wake up on May 16, 2023, to wake up on May 18, 2023	On May 18, 2023	
Days 43 and 44	From wake up on May 20, 2023, to wake up on May 22, 2023	On May 22, 2023	
Days 45 and 46	From wake up on May 28, 2023, to wake up on May 30, 2023	On May 30, 2023	
Month 4 (4 times)			On July 1, 2023
Days 47 and 48	From wake up on June 4, 2023, to wake up on June 6, 2023	On June 6, 2023	
Days 49 and 50	From wake up on June 9, 2023, to wake up on June 11, 2023	On June 11, 2023	
Days 51 and 52	From wake up on June 14, 2023, to wake up on June 16, 2023	On June 16, 2023	
Days 53 and 54	From wake up on June 28, 2023, to wake up on June 30, 2023	On June 30, 2023	
Month 5 (4 times)			On July 31, 2023
Days 55 and 56	From wake up on July 6, 2023, to wake up on July 8, 2023	On July 8, 2023	
Days 57 and 58	From wake up on July 10, 2023, to wake up on July 12, 2023	On July 12, 2023	
Days 59 and 60	From wake up on July 20, 2023, to wake up on July 22, 2023	On July 22, 2023	
Days 61 and 62	From wake up on July 25, 2023, to wake up on July 27, 2023	On July 27, 2023	
Month 6 (4 times)			On August 18, 2023
Days 63 and 64	From wake up on August 4, 2023, to wake up on August 6, 2023	On August 6, 2023	
Days 65 and 66	From wake up on August 12, 2023, to wake up on August 14, 2023	On August 14, 2023	
Days 67 and 68	From wake up on August 19, 2023, to wake up on August 21, 2023	On August 21, 2023	

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Month and data collection days	Frequency and timing of study activities		
	Device wearing	EMAs[b]	Monthly survey (once)
Days 69 and 70	From wake up on August 24, 2023, to wake up on August 26, 2023	On August 26, 2023	

[a]Schedule is based on an enrollment date of March 1, 2023. Participation in the study is for 6 months with a total of 70 days of digital device wearing. In the first month, patients are required to wear a wristband and temperature patch, then only the wristband in months 2 to 6.

[b]EMA: ecological momentary assessment.

Patients are asked to complete 1 baseline and 6 monthly surveys. The baseline does not expire but patients are encouraged to complete it instantly after their enrollment appointment. Monthly surveys remain open for 12 days. Patients receive their data collection schedule, mobile app log-in credentials, and link to the baseline survey during their enrollment appointment. This allows us to verify that patients are receiving our electronic communications and to review these elements with them. We ship each patient an enrollment kit overnight, which includes (1) a print copy of their data collection schedule and their username for the mobile app account; (2) a wristband, charger, and sweatband; (3) a temperature patch, charger with batteries, and adhesives to secure the patch onto one's body; (4) information sheet with first-time device set up instructions, data sync, and troubleshooting tips; (5) clinical trials informational sheet; and (6) a prepaid return slip with complete address information to ship back any defective devices.

For patients with no incoming wearables data and EMA responses for 3 consecutive days during the first month or 2 consecutive data collection periods during months 2 to 6, we attempt to contact patients to counsel them on the importance of adhering to their assigned study schedule. If we fail to reach a patient, we contact their close kin to complete an adverse events survey. Hospitalized patients are allowed to resume their participation in the study upon discharge and will complete an adverse events survey on their hospital stay. Upon completing the study, patients receive an end-of-study email thanking them and instructing them on how to create a personal mobile app account to continue using their wearable device should they choose to. After data analysis is complete, patients will receive a summary of the main findings.

Study Evaluations

For 6 months, enrolled patients engage in various research activities. First, physiological parameters are passively collected through a wristband, Biostrap EVO Biometric set [72], and a Food and Drug Administration (FDA)-cleared temperature monitor, Vivalink [73]. The wristband is a noninvasive red and infrared optical sensor, which is less sensitive to skin tone variations and perfusion levels, and includes built-in accelerometer and gyroscope sensors that capture 6-axis motion data. Raw biosignals are used to estimate the (1) activity tracking accelerometer data captured continuously at 10 Hertz and converted into step count and activity duration saved in 1-minute increments; (2) arterial pulse volume monitoring using photoplethysmography, a 45-second recording collected at 43 Hertz, which provides derived biometrics including heart rate, heart rate variability with interbeat intervals between successive heartbeats times output, peripheral capillary oxygen saturation as percent oxygen, and respiratory rate; and (3) sleep analysis (eg, sleep duration, sleep onset and wake time, and sleep stages). The wristband technology has been validated previously [74]. The temperature patch collects body temperature captured continuously and reported as an average value each minute given the smartphone is within range. To ensure consistency in patient data, we set the sampling frequency to every 5 minutes and hid the settings option that allows patients to adjust the rate, duration, and intervals between measurements on the mobile app. Patients have instant and continuous access to their data. Second, EMAs capture COVID-19 symptoms and medications [75,76] that are collected in the mobile app (Table 4). Third, a baseline survey captures demographics and social determinants of health [75-77]; technology access [78,79]; COVID-19 symptoms and medications [75,76]; medical information [75,76]; risk and protective factors [78]; and PROs that capture cognitive, mental, and physical health domains [80-89]. Fourth, monthly surveys repeatedly capture data collected at baseline, mainly COVID-19 symptoms and medications [75,76], medical information [75,76], and PROs [80-89]. The first and last monthly surveys capture wearables acceptability data [90-92]. The last survey captures updated data on COVID-19 reinfection, vaccination, and medical care since enrollment in the study. Finally, the adverse outcomes survey captures the occurrence and timing of death or hospitalization, length of hospital stay, and treatment received [75,76].

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Table 4. Study measures.

	Eligibility verification	Baseline survey	Monthly surveys						EMAs[a]	Adverse outcomes survey
			#1	#2	#3	#4	#5	#6		
Inclusion and exclusion questions	✓									
Contact information	✓									
Demographics	✓	✓								
Social determinants of health		✓								
Technology access and acceptability										
Smartphone or tablet access	✓	✓								
Internet or cellular data access	✓	✓								
Wearables acceptability			✓					✓		
COVID-19 information										
COVID-19 testing	✓							✓		
COVID-19 vaccination	✓							✓		
COVID-19 symptoms		✓	✓	✓	✓	✓	✓	✓	✓	
COVID-19 medications		✓	✓	✓	✓	✓	✓	✓	✓	
Medical information										
Concomitant medications		✓								
Pregnancy and menstrual cycle		✓								
Disability		✓								
Existing and new health conditions		✓	✓	✓	✓	✓	✓	✓		
Inpatient or outpatient care		✓	✓	✓	✓	✓	✓	✓		✓
Adverse events								✓		✓
Risk and protective factors										
Body measurements		✓								
Fruit and vegetable intake		✓								
Physical activity		✓								
Tobacco use		✓								
Alcohol consumption		✓								
Marijuana use		✓								
Prescription and illicit drugs use		✓								
Patient-reported outcomes										
General health		✓	✓	✓	✓	✓	✓	✓		
Perceived health change		✓	✓	✓	✓	✓	✓	✓		
EQ-5D-5L health status[b]		✓	✓	✓	✓	✓	✓	✓		
EQ-VAS[c]										
PROMIS[d]-29 profile version 2.1 health-related quality of life[d]		✓	✓	✓	✓	✓	✓	✓		

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	Eligibility verification	Baseline survey	Monthly surveys						EMAs[a]	Adverse outcomes survey
			#1	#2	#3	#4	#5	#6		
PROMIS cognitive function version 2.0 (short form 8a)		✓	✓	✓	✓	✓	✓	✓		
PROMIS dyspnea severity version 1.0 (short form 10a)		✓	✓	✓	✓	✓	✓	✓		

[a]EMA: ecological momentary assessment.

[b]EQ-5D-5L: EurQol 5 domains, 5 levels. Captures 5 health dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

[c]EQ-VAS: EurQol visual analog scale. Captures 7 domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference, in addition to pain intensity.

[d]PROMIS: Patient-reported outcomes measurement information system.

Baseline, monthly, and adverse outcomes surveys are collected using REDCap electronic data capture tools hosted at the National Institute of Diabetes and Digestive and Kidney Diseases [93,94]. REDCap is a secure, web-based platform that serves as the project database and data capture tool. REDCap houses the IC and other study forms (eg, eligibility verification). The Biomedical Translational Research Information System REDCap team of the NIH Clinical Center provided REDCap project administration and consultation.

Compliance and Retention

To maximize compliance with study activities, automatic reminders are sent to all patients. Additional reminders are sent to noncompliant patients. To maximize retention, we review an infographic aimed at increasing patients' research literacy and highlighting the importance of completing research studies during their enrollment appointment [95]. Additionally, whenever there are 50 actively enrolled patients in a given month, protocol-compliant patients who completed their most recent monthly survey and scored ≥75% for device wearing and EMA completion are entered in monthly raffles for a US $100 gift card. Patients keep the wearable devices as a participation incentive.

Statistical Analysis

We assume 20% to 35% event rates for the primary outcome of long COVID-19 and a 10% event rate for the secondary outcome of chronic COVID-19 [17,96].

Power

A nonprobability sample of 550 patients with COVID-19 will be recruited for this study. With 550 participants, we have >85% power to detect a standardized difference (δ/σ) of 0.28, 0.33, and 0.43 in daily continuous physiologic parameters between long or chronic COVID-19 and non–long COVID-19 groups, assuming 35%, 20%, or 10% of participants will have long or chronic COVID-19, respectively, and allowing a 2-sided type I error of 5%. Our analysis will use multiple days of data per participant and will adjust for prognostic baseline factors, thus power will be substantially higher [97].

Analysis Plan

We will use a linear mixed model of daily awake-time and sleep-time (calendar day) values of physiological parameters to determine associations with long and chronic COVID-19, the primary and secondary end points [98]. All valid days will be included for all subjects where a valid day consists of 18 hours of device wearing. Models will include baseline fixed-effect factors for demographic and clinical variables. A term for the COVID-19 status group (ie, non–long COVID-19, long COVID-19, and chronic COVID-19) will be included. All models will have a fixed-effect cubic model for time since testing positive or symptom onset for each COVID-19 status group. Subject-specific random effects (intercept and slope) and a spatial (in time) model will be used for within-subject errors, accounting for correlation between observations within a subject [98]. The cluster robust variance will be used [99,100]. The results of the above model will allow plotting differences between COVID-19 status groups at any time. For formal testing between groups, we will fit models exactly as described, but with only linear time models for each COVID-19 status group. Contrasts between the slope terms will then be used to test if groups have different trends over 6 months. Linear mixed-effect models are robust to missing data based on a missing-at-random assumption [98]. Subgroup analyses will be performed for analyses of both primary and secondary events restricted to patients within demographic characteristics (eg, race and ethnicity).

Data Security

Data from wearables are transferred to iOS or Android mobile phones via Bluetooth and stored in Biostrap cloud servers for data processing to estimate physiological parameters. Patients' personal identifiable information and protected health information are not shared with Biostrap. Data are downloaded weekly to the study server at the National Institute on Minority Health and Health Disparities and a final data transfer will occur at the end of the study.

Ethical Considerations

The protocol was reviewed and approved by the National Institute on Minority Health and Health Disparities's Scientific Review Committee and NIH's Chief Scientific Officer on April 26, 2021. NIH's institutional review board approved the protocol on June 21, 2021 (IRB#: 000315). Amendments were approved on September 23, 2021, and April 20, 2022. Administrative amendments were approved on June 17, 2022, August 24, 2022,

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May 16, 2023, June 30, 2023, and December 8, 2023 (ie, changes to the mailing address and key study personnel). Any adverse events or unanticipated problems are reported to the institutional review board. All patients enrolled in the study provide IC.

Results

The first patient was enrolled on October 11, 2021. We expect to publish the results in 2025.

Discussion

Summary

This protocol is a prospective, longitudinal, observational study of PASC among a cohort of 550 nonhospitalized people with a confirmed positive COVID-19 diagnosis. The study captures intensive longitudinal physiological data collected via digital wearables and PROs for 6 months. The study will shed light on the course of PASC in nonhospitalized patients and represents an example of the use of wearable technology in disease monitoring generally and COVID-19 specifically.

Despite the pandemic emergency state declared officially over [101], research into PASC remains a priority given its health and economic costs [102,103], national initiatives [104,105], continued scientific interest [106,107], and patient advocacy [108-110]. Conservatively, there are 10 to 30 million people who experience PASC, with estimates likely higher if probable and suspected cases are included beyond the 100+ million confirmed COVID-19 cases in the United States [111]. The study will shed light on PASC in patient subgroups given its associations with demographics and risk profiles [34]. This is particularly important because evidence on PASC in racial and ethnic groups is scarce and inconclusive [11,17,40,61,112] despite minority groups disproportionally bearing the burden of COVID-19 infection and adverse outcomes [113]. While COVID-19 wearables-based studies focused mainly on its detection or acute phase, we capture a multitude of PASC digital biomarkers. This will allow us to identify PASC digital phenotypes that aid in its clinical assessment and treatment [114,115]. Furthermore, we can triangulate evidence of PASC from physiological parameters and self-reported patient outcomes [116]. Future studies should determine the clinical use of digital wearables in monitoring nonhospitalized patients with COVID-19 over longer follow-up periods.

Study strengths include its intensive longitudinal data on PROs and physiological parameters, 6-month follow-up, and focus on nonhospitalized patients whose characteristics and disease trajectory differ from hospitalized patients [13,117,118] (compare [12]). We require a positive COVID-19 diagnosis because of PASC-like self-reported symptoms and physiological changes among COVID-19 untested or negative individuals [26,41,46]. This is a decentralized trial, which allows for nationwide recruitment, increased participation of diverse and underrepresented populations in research, and reduced participant burden [119-121].

This study has several limitations. Sample size calculations are based on PASC surveillance data available when the study was launched. These data have since changed based on evolving definitions of PASC [16]. Recruitment started after COVID-19 vaccines were rolled out irrespective of age or underlying medical conditions, which means our sample will include unvaccinated and vaccinated patients. The availability and effectiveness of COVID-19 vaccines and treatments as well as dominant variants throughout recruitment activities may affect study end points [24,39,122,123]. Given limited evidence on the demographic breakdown of patients who endure PASC, our sample reflects the US population by sex and race and ethnicity rather than PASC prevalence in population subgroups [39]. The study mobile app is available only in English. Thus, we exclude non-English speaking patients from participation. Self-selection bias is another limitation whereby participants with certain predispositions (eg, digitally literate) may be inclined to enroll in the study. With a 5-day enrollment window from a positive COVID-19 diagnosis, the initial severity of one's illness can deter PRVs from enrolling. We have no baseline data from patients prior to their positive diagnosis. Given the decentralized nature of the study, its reliance on mobile technologies, and its follow-up duration, certain limitations are expected (eg, data loss due to technical issues or shipping delays, poor compliance, or high attrition) [124-126]. The study wristband is not FDA-approved. Physiological parameters do not capture all PASC symptoms (eg, loss of sense of taste). Accrual is expected to fluctuate with infection rates, which may affect our ability to meet the target sample or prolong recruitment.

This study has wider public health implications pertaining to the role of mobile technologies in digital medicine [114,115,127,128]. Indeed, mobile technologies have been central to public health response to the COVID-19 pandemic [129,130]—from crowdsourcing platforms for contact tracing [131] to symptom reporting [132-134] and sensor data collection [107,135]. Wearables physiological data improve the identification of COVID-19–positive cases above and beyond self-reported symptoms [50], which have been the basis of pilot COVID-19 detection tools [46-48], and show preliminary differentiation between COVID-19 and other respiratory illnesses [136]. Prior to the COVID-19 pandemic, wearables have been piloted for the detection, monitoring, and public surveillance of communicable and noncommunicable diseases, health conditions, and behaviors [137-144]. They enjoy increasing uptake and acceptability, and afford opportunities for unobtrusive and continuous capture of objective data, including awake and sleep-time data, outside of traditional health care settings [114,145]. When integrated with remote monitoring platforms, patient-generated data can support real-time feedback to patients and physicians that is calibrated to a patient's baseline data and has the potential to improve individual-level health outcomes [146,147] (compare [148]). While evidence on wearables and their integration into clinical practice is in its infancy and challenges exist until their potential is fully realized [147,149,150], if widely adopted, wearables can be scaled up as cost-effective tools for population-level disease surveillance, management, and prevention [150].

Conclusions

This protocol outlines a 6-month prospective observational study of PASC in a cohort of 550 nonhospitalized patients with

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a positive COVID-19 diagnosis. The study uses off-the-shelf wearable devices to collect a multitude of physiological parameters to examine their associations with patient-reported PASC. The study exemplifies the potential of wearable technologies in population-level disease monitoring and their wider role in digital medicine.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Disclaimer

Use of commercial products in the study does not imply endorsement of these products. Similarly, authorship does not imply endorsement of any Biostrap USA, LLC or Vivalink products. Biostrap USA, LLC, was paid for the devices used in this study (Biostrap EVO Biometric set and Vivalink temperature monitor) and for the services it provided and has no input on study conceptualization, data analysis, or interpretation. The views expressed in this paper are those of the authors and do not necessarily represent the views of the National Institute on Minority Health and Health Disparities; the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services.

Authors' Contributions

SET conceptualized and supervised the study and drafted the paper. PH built patient database and coordinated efforts with Biostrap USA, LLC. GZ managed patient database. ARD tailored the mobile app for the purposes of this study, implemented automated reminders, compliance checks, and data backup. NM coordinated the study from June 2021 to June 2022. SET, PH, GZ, and NM managed day-to-day tasks. JT devised the analysis plan. TMPW served as the medical advisory investigator for the study. All authors reviewed and approved the paper.

Conflicts of Interest

ARD is employed by Biostrap USA, LLC. All other coauthors declare no conflicts of interest.

Multimedia Appendix 1
Response to scientific review stipulations.
[DOCX File , 134 KB - resprot_v13i1e57382_app1.docx]

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Abbreviations

EMA: ecological momentary assessment
FDA: Food and Drug Administration
IC: informed consent
NIH: National Institutes of Health
OPR: Office of Patient Recruitment
PASC: postacute sequelae of COVID-19
PRO: patient-reported outcome
PRV: prospective research volunteer
REDCap: Research Electronic Data Capture
WHO: World Health Organization

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Protocol

Factorial Trial to Optimize an Internet-Delivered Intervention for Sexual Health After Breast Cancer: Protocol for the WF-2202 Sexual Health and Intimacy Enhancement (SHINE) Trial

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Abstract

Background: Although most survivors of breast cancer report substantial sexual concerns following treatment, few receive support for these concerns. Delivering sexual health care to survivors of breast cancer via the internet could overcome many of the barriers to in-person treatment. Even when delivered remotely, survivor time constraints remain a leading barrier to sexual health intervention uptake.

Objective: Guided by the multiphase optimization strategy methodological framework, the primary objective of this study is to identify the most efficient internet-delivered sexual health intervention package that is expected to provide survivors of breast cancer the greatest benefit with the fewest (and least-intensive) intervention components. This study aims to determine how intervention components work (mediators) and for whom they work best (moderators).

Methods: Partnered, posttreatment adult female survivors of breast cancer (N=320) experiencing at least 1 bothersome sexual symptom (ie, pain with sex, vaginal dryness, low sexual desire, and difficulty with orgasm) related to their breast cancer treatment will be enrolled. Clinic-based recruitment will be conducted via the Wake Forest National Cancer Institute Community Oncology Research Program (NCORP) Research Base. Participants will be randomly assigned to 1 of 16 combinations of four intervention components with two levels each in this factorial trial: (1) psychoeducation about cancer-related sexual morbidity (receive either enhanced vs standard versions); (2) communication skills training for discussing concerns with health care providers (received vs not received); (3) communication skills training for discussing concerns with a partner (received vs not received); and (4) intimacy promotion skills training (received vs not received). Cores will be fully automated and implemented using a robust internet intervention platform with highly engaging elements such as animation, video, and automated email prompts. Survivors will complete web-based assessments at baseline (prerandomization time point) and again at 12 and 24 weeks later. The primary study aim will be achieved through a decision-making process based on systematically evaluating the main and interaction effects of components on sexual distress (Female Sexual Distress Scale–Desire, Arousal, Orgasm) and sexual functioning (Female Sexual Function Index) using a generalized linear model approach to ANOVA with effect coding. Mediation analyses will be conducted through a structural equation modeling approach, and moderation analyses will be conducted by extending the generalized linear model to include interaction effects.

Results: This protocol has been reviewed and approved by the National Cancer Institute Central Institutional Review Board. Data collection is planned to begin in March 2024 and conclude in 2027.

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Conclusions: By identifying the combination of the fewest and least-intensive intervention components likely to provide survivors of breast cancer the greatest sexual health benefit, this study will result in the first internet intervention that is optimized for maximum impact on the undertreated, prevalent, and distressing problem of breast cancer–related sexual morbidity.

Trial Registration: ClinicalTrials.gov NCT06216574; https://clinicaltrials.gov/study/NCT06216574

International Registered Report Identifier (IRRID): PRR1-10.2196/57781

(JMIR Res Protoc 2024;13:e57781) doi:10.2196/57781

KEYWORDS

breast neoplasms; cancer survivorship; clinical trial; communication skills; factorial trial; internet interventions; intimacy; mobile phone; multiphase optimization strategy; sexual distress; sexual functioning; sexual health

Introduction

Background

Breast cancer and its treatment can cause physical (eg, loss of body part and vaginal dryness), psychological (eg, stress and body dissatisfaction), and relational concerns (eg, restricted communication and relational discord) that can lead to problems with sexual distress and dysfunction [1,2]. Therefore, approximately 70% of survivors of breast cancer report clinically relevant symptoms of sexual distress and dysfunction [2-5], which they rank among their most distressing cancer-related problems [6,7]. These sexual concerns are particularly severe among women who were premenopausal at diagnosis, as treatments can induce menopause with more severe symptoms [8-10]; take adjuvant endocrine therapy (AET; tamoxifen or aromatase inhibitors) as it blocks estrogen [11-13]; have comorbid depression and anxiety [14-16]; and have newer relationships or are generally more dissatisfied in their relationship [5,17-19]. Unlike psychological or informational needs that tend to remit naturally, survivors' unmet sexual health needs *increase* over time [20]. Given the prevalence and profound impacts of cancer on sexual health, oncology care standards recommend that all survivors receive information, assessment, and care for sexual symptoms [21,22]. Despite these recommendations, <1 in 3 survivors of breast cancer recall ever discussing sexual health with their cancer care team [23]. Thus, there is an urgent need to develop highly scalable interventions to support survivors' sexual health.

Commonly cited reasons for the lack of comprehensive sexual health care within oncology include limited access to specialty services, provider and patient discomfort in discussing sexual health, and appointment time constraints [24,25]. Delivering fully automated care via the internet can help alleviate these barriers to care by providing evidence-based education and behavioral strategies privately and on demand, anywhere an internet connection exists [26-28]. Comprehensive sexual health interventions have been demonstrated as effective when delivered remotely; however, the substantial time requirements of these multicomponent programs have been a leading barrier to enrolling and retaining survivors in care [28-30]. Maximizing the population-wide impact of sexual health interventions for survivors of breast cancer will require minimizing intervention requirements, without compromising the overall intervention efficacy. More efficient interventions may attract and retain more survivors to benefit from care.

A major gap in the literature regarding the efficacy of individual sexual health components has limited the development of more efficient sexual health treatments for survivors of breast cancer [29]. Because of the complex biopsychosocial nature of sexual health, interventions to improve sexual health after cancer typically include multiple therapeutic components. Leading clinical oncology organizations recommend that women are educated about the effects of cancer on their sexual response cycle, as well as interventions to improve intimacy and relationship concerns [21,31]. Communication skills training is critical to help survivors overcome the barriers of stigma to advocate for their sexual health needs [1]. Because interventions tested in this area to date have tended to test multiple components packaged together and in differing combinations across trials, it has been impossible to differentiate which components work, establish why those components work, or identify for whom different components work best. Addressing these gaps will help promote the development of more efficient, effective, and personalized interventions.

Objectives

The overarching goal of our research is to develop a highly scalable and efficient breast cancer–related sexual health intervention with a strong potential for population-wide impact. Toward that goal, the primary aim of this trial is to identify the combination of the fewest intervention components likely to provide survivors of breast cancer with the greatest sexual health benefit. Intervention components to be tested are (1) level of education about the influence of breast cancer on sexual health, (2) communication skills training for discussing sexual concerns with one's health care team, (3) communication skills training for discussing sexual concerns with one's intimate partner, and (4) intimacy promotion skills training. These components, which address the complex biopsychosocial nature of sexual concerns after breast cancer, were selected based on the research team's prior qualitative and intervention development research [32,33] and are consistent with survivorship care guidelines [21,22]. This aim will be achieved through evaluating the impact of each component, alone and in combination, on survivors' sexual distress and functioning.

This trial will also evaluate the clinical mechanisms of the intervention components and whether different groups of survivors may need different combinations of intervention components. We hypothesize that the intervention components will influence sexual morbidity via mediators selected based on social cognitive theory [34], specifically, through increased

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knowledge about sexual concerns and self-efficacy to discuss them, as well as emotional intimacy with one's partner (see Figure 1 for the trial conceptual model). We also hypothesize that a priori moderators, selected according to clinical and psychosocial characteristics known to influence sexual morbidity in survivors of breast cancer, will influence the components' efficacy. Achieving these research objectives will improve cancer survivorship care by establishing the first internet intervention for breast cancer–related sexual morbidity that has been optimized for maximum impact, as well as clarifying how intervention components work and for whom they work best.

Figure 1. Study conceptual model. AET: adjuvant endocrine therapy.

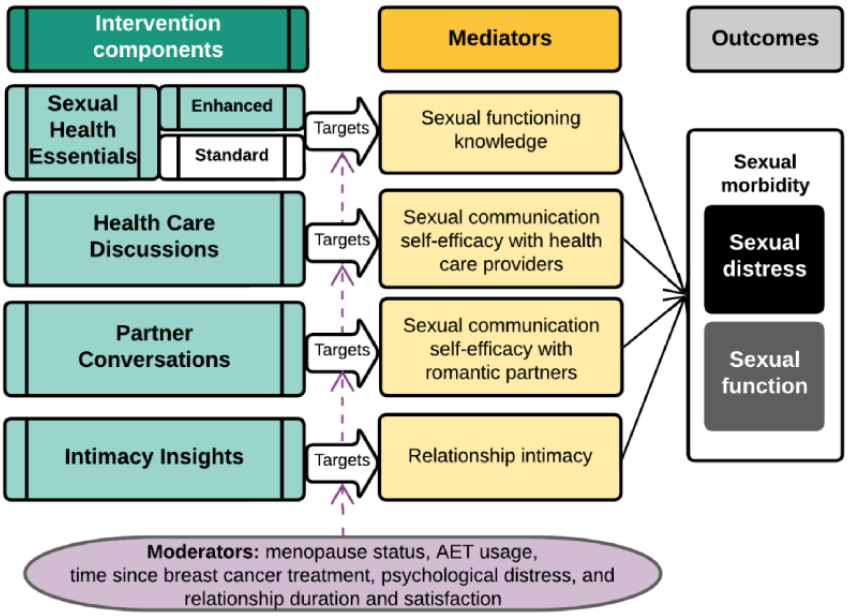

Methods

Ethical Considerations

The study protocol has been reviewed and approved by the National Cancer Institute (NCI) Central Institutional Review Board (CIRB; WF-2202 initially approved on December 1, 2023). Study modifications will be reviewed and approved by the NCI CIRB. Participating study sites and their local institutional review boards will be notified of any modifications. Deidentified data sets used in primary publications will be transferred to the National Clinical Trials Network and NCI Community Oncology Research Program (NCORP) Data Archive in accordance with the agreement between Wake Forest (WF) NCORP Research Base (RB) and NCI. The internet intervention platform hosting the Sexual Health and Intimacy Enhancement (SHINE) intervention is managed by the University of Virginia (UVA) and was designed to support projects that contain protected health information that are subject to compliance with federal and state regulations. Access to data will be in accordance with the Health Care Financing Administration's Internet Security Policy and the Health Insurance Portability and Accountability (HIPAA) Act of 1996. The database servers and web servers are backed up daily and are protected from threats by regular maintenance and the application of hotfix and security patches when released. Security policies are in place with UVA to ensure that access to database repositories and web application server environments is limited. On completion of the trial, summary results will be submitted to ClinicalTrials.gov in accordance with National Institutes of Health (NIH) policies [35]. No participant identifiers will be published.

During the informed consent process, potential participants are informed that this study aims to determine whether an internet-delivered program can help survivors of breast cancer manage cancer-related sexual concerns. Under a waiver of documentation of consent, participants will provide either signed informed consent or verbal informed consent that is documented by the enrolling research staff member. The NCI CIRB–approved informed consent form will be made available open-access with other study materials. Participants will receive a US $50 e-gift card for completing the 12-week assessment and a US $75 e-gift card for completing the 24-week assessment. On request at the end of the 24-week assessment, participants will be provided access to all the SHINE program components through the end of the grant period.

Trial Design

This factorial trial will enroll 320 adult survivors of breast cancer with sexual concerns to test the effects of 4 sexual health intervention components. The primary trial objective is to determine the optimal breast cancer–related sexual health intervention package. The secondary objective is to examine mediators and moderators of intervention component efficacy, and we will also explore survivors' intervention engagement and acceptability. This manuscript reports the protocol for the WF-2202 SHINE trial following recommendations from the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [36,37]; Table 1 provides the World Health Organization trial registration data set. The study protocol was revised following the NIH peer review process (see Multimedia Appendix 1 for reviews).

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Table 1. World Health Organization trial registration data set.

Data category	Information
Primary registry and trial identifying number	• ClinicalTrials.gov identifier: NCT06216574
Date of registration in primary registry	• January 10, 2024
Secondary identifying numbers	• R37CA269776—National Institutes of Health grant; WF[a]-2202—WF NCI[b] Community Oncology Research Program Research Base protocol; • NCI-2023-06866—NCI Clinical Trials Reporting Program registry identifier
Sources of monetary or material support	• NCI (grant UG1CA189824 [multiple principal investigators GJL and KEW] and R37CA269776 [principal investigator KMS]) • The NCI provided a review of the study design. The NCI CIRB[c] serves as the single IRB[d] for this trial. The NCI will review publications before their submission.
Primary sponsor	• University of Virginia • Sponsors (primary and secondary) have no significant role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit the results.
Secondary sponsors	• WF University Health Sciences; Fox Chase Cancer Center
Contact for public queries and scientific queries	• KMS, PhD, Center for Behavioral Health and Technology, UVA, Charlottesville, Virginia (corresponding author)
Public title	• SHINE[e] study
Scientific title	• WF-2202 Optimizing psychosocial intervention for breast cancer–related sexual morbidity
Countries of recruitment	• The United States
Health conditions or problems studied	• Breast cancer; sexual dysfunction

Interventions	• SHINE components (see Multimedia Appendix 2 for intervention details):
	  • Sexual Health Essentials: receive either enhanced or standard versions of the Core
	  • Health Care Discussions: receive the Core or not
	  • Partner Conversations: receive the Core or not
	  • Intimacy Insights: receive the Core or not

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Data category	Information

Inclusion criteria	• Ages eligible for study: ≥18 years
	• Sexes eligible for study: female only
	• Accepts healthy volunteers: no
	• From medical record review:
	  • History of stage 0-III breast cancer diagnosis. History of nonbreast malignancies are permitted.
	  • ≥12 weeks following last primary cancer treatment. For this protocol, primary cancer treatments are defined as chemotherapy, cytotoxic antibody-drug conjugates, checkpoint inhibitors, radiation, and surgical procedures intended to remove malignant tissue. Ongoing AET[f] (eg, tamoxifen, aromatase inhibitors), adjuvant CDK[g] 4/6-inhibitors (eg, abemaciclib), HER2[h]-based monoclonal antibody therapy (eg, trastuzumab, pertuzumab), HER2 targeted tyrosine kinase inhibitors (eg, neratinib), and pending breast reconstructive surgery are allowed.
	  • Aged ≥18 years at the time of study enrollment
	• From self-reported web-based screener
	  • Cisgender female (ie, assigned female at birth, female gender identity)
	  • Currently in an intimate relationship with an individual of any sex and gender identity
	  • Endorse being at least “somewhat” bothered by ≥1 of the following during the last 30 days: (lack of) interest in sexual activity, vaginal dryness, pain during sexual activity, or (lack of) ability to orgasm, as reported on the Patient-Reported Outcomes Measurement Information System SexFS Bother Regarding Sexual Function screener [38]
	  • Endorse that ≥1 of the bothersome sexual symptoms (from above criterion) is related to their breast cancer
	  • Has a working email address (or willing to create one) and receive emails from the study

Exclusion criteria	• From medical record review
	  • Planned cancer treatment for residual, progressive, or recurrent disease within the 24 weeks following enrollment (defined as chemotherapy, cytotoxic antibody-drug conjugates, checkpoint inhibitors, radiation, and surgical procedures intended to remove malignant tissue).
	  • Ongoing AET (eg, tamoxifen, aromatase inhibitors), adjuvant CDK 4/6-inhibitors (eg, abemaciclib), HER2-based monoclonal antibody therapy (eg, trastuzumab, pertuzumab), HER2 targeted tyrosine kinase inhibitors (eg, neratinib), and pending breast reconstructive surgery are allowed.
	• From self-reported web-based screener
	  • Cannot read and comprehend English as indicated by not completing the self-reported screening questionnaire independently
	  • No reliable access to the internet (eg, by home broadband, public network, personal data plan) by computer, tablet, smartphone, etc and is not willing to participate in the tablet lending program for this study
	  • Recent serious mental illness, as defined by reporting an inpatient psychiatric hospitalization within the past 12 months
	  • Currently participating in couple, marital, or sex therapy
	  • Currently pregnant

Study type	• Interventional allocation: randomized • Masking: investigator, outcomes assessor • Assignment: factorial (2^4) • Primary purpose: supportive care

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Data category	Information
Date of first enrollment	• Anticipated in March 2024
Target sample size	• 320
Recruitment status	• Pending (as of manuscript submission)
Primary outcome	• FSDS-DAO[i]: change from baseline to 24-week assessment
Key secondary outcomes	• FSDS-DAO: 12-week assessment • Female Sexual Function Index: 12- and 24-week assessments
Ethics review	• NCI CIRB serves as the single IRB for this trial. Protocol WF-2202 received initial approval as of December 1, 2023. • The study protocol will be reviewed and approved by the local IRB of each participating recruitment site. Participants will receive contact information from the local IRB for inquiries.
Additional SPIRIT[j] information	
Confidentiality	• Data collected through self-report and medical record extraction is collected and maintained through REDCap[k], a HIPAA[l]-compliant web-based data management tool. Participants' data are saved with a unique participant identifier code; personally identifying information is saved separately. SHINE program use data are collected through the research team's HIPAA-compliant internet intervention platform. No participant-identifying information will be shared outside the research team. Data are protected with a certificate of confidentiality
Protocol version	• Version 01.04.2024; issue date: approved February 2, 2024; protocol amendment number: amendment 1; authors: KMS, Julie Turner
Nonapplicable items	• Composition of the coordinating center and trial steering committee; criteria for discontinuing or modifying allocated interventions; procedure for unblinding if needed; interim analyses; additional consent provisions for collection and use of participant data and biological specimens; provisions for posttrial care; assignment of writing committees; plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial or future use

[a]WF: Wake Forest.
[b]NCI: National Cancer Institute.
[c]CIRB: Central Institutional Review Board.
[d]IRB: institutional review board.
[e]SHINE: Sexual Health and Intimacy Enhancement.
[f]AET: adjuvant endocrine therapy.
[g]CDK: cyclin-dependent kinase.
[h]HER2: human epidermal growth factor receptor 2.
[i]FSDS-DAO: Female Sexual Distress Scale–Desire, Arousal, Orgasm.
[j]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.
[k]REDCap: Research Electronic Data Capture.
[l]HIPAA: Health Insurance Portability and Accountability Act.

Our study aims will be achieved via a factorial trial within the optimization phase of the multiphase optimization strategy (MOST) framework. The MOST methodological framework directly addresses our goal of optimizing a multicomponent intervention to improve sexual health after breast cancer [39,40]. In an optimization trial, the effects of intervention components are tested independently and in combination, which allows the identification of an efficient intervention package that only includes components shown to improve survivors' sexual health. Components may also be evaluated to determine whether effects vary systematically across survivors, guiding future treatment tailoring. These insights directly address major research gaps

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regarding how sexual health intervention components work and for which survivors they work best [29].

In this factorial trial, participants will be randomized to 1 of 16 conditions in a factorial design involving 4 intervention components, each with 2 levels (2^4; Figure 2). Participants may continue to receive standard care during the trial. The trial will be conducted via the WF NCORP RB, which has 42 affiliated health system sites, each with its own research infrastructure and dedicated research staff to identify, screen, consent, and enroll survivors for this trial. Only 10% of the affiliated sites are connected with an academic medical center, and 25% of sites are safety-net hospitals, serving patient populations that are commonly neglected in intervention development research [41]. The use of this oncology practice–based research network is important because it will both enhance the generalizability of results to diverse survivors treated in community settings and encourage the eventual translation of the optimized intervention into clinical practice. As required by the NCORP trials, the NCI CIRB serves as the institutional review board of record for this trial.

Figure 2. Study conditions. Pt: participants; SHINE: Sexual Health and Intimacy Enhancement.

Conditions	SHINE intervention components				N pt
	Sexual Health Essentials	Health Care Discussions	Partner Conversations	Intimacy Insights	
1	Enhanced	Yes	Yes	Yes	20
2	Enhanced	Yes	Yes	No	20
3	Enhanced	Yes	No	Yes	20
4	Enhanced	Yes	No	No	20
5	Enhanced	No	Yes	Yes	20
6	Enhanced	No	Yes	No	20
7	Enhanced	No	No	Yes	20
8	Enhanced	No	No	No	20
9	Standard	Yes	Yes	Yes	20
10	Standard	Yes	Yes	No	20
11	Standard	Yes	No	Yes	20
12	Standard	Yes	No	No	20
13	Standard	No	Yes	Yes	20
14	Standard	No	Yes	No	20
15	Standard	No	No	Yes	20
16	Standard	No	No	No	20

Participants

This trial will enroll 320 survivors of breast cancer meeting the following inclusion criteria (see Table 1 for details): (1) history of stage 0 to III breast cancer diagnosis (history of other cancer diagnoses is permitted); (2) ≥12 weeks from last primary cancer treatment (eg, chemotherapy, surgery, or radiation therapy); (3) ≥18 years of age; (4) cisgender female; (5) in an intimate relationship with a person of any sex and gender; (6 and 7) endorse at least 1 bothersome sexual symptom that they attribute to their breast cancer; and (8) willing to receive emails from the study. Survivors will be excluded if they (1) have cancer treatment planned within the study period; (2) cannot read English; (3) do not have reliable internet access (and are not willing to participate in a study tablet loan program); (4) have had a recent episode of serious mental illness; (5) are in current couple, marital, or sex therapy; or (6) are currently pregnant. These eligibility criteria are in keeping with our prior breast cancer–related sexual health intervention research (eg, [42]) and support the evaluation of isolated intervention effects with less risk of contamination or confounding from other interventions or treatments.

Procedures

All study procedures, namely, recruitment, consenting, assessment, and intervention, can be completed remotely (eg, via the internet; see Figure 3 for a schematic of procedures). Potential participants' medical records will be screened by research staff at the participating NCORP sites; this process may be initiated by the staff at the site or by a potentially interested participant contacting the site after learning of the trial via social media, other advertisement, or the NCI Clinical Trials page [43] (Figure 3, steps 0-1). Individuals who meet medical eligibility criteria will be contacted (step 2); those who are interested will complete a self-reported web-based screener regarding the remaining eligibility criteria (step 3). This screener will be completed through REDCap (Research Electronic Data Capture; Vanderbilt University), a HIPAA-compliant, web-based

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survey and research management platform. Individuals not meeting the eligibility criteria will be notified that they are ineligible for the trial, while those who are eligible will be contacted by the NCORP site staff to answer any remaining questions about the trial and obtain informed consent (step 4). Participants who do not have reliable access to the internet via computer, smartphone, or tablet will be offered a cellular data–enabled tablet to use for the full 24-week study period.

Figure 3. Study procedures. NCI: National Cancer Institute; NCORP: National Cancer Institute Community Oncology Research Program.

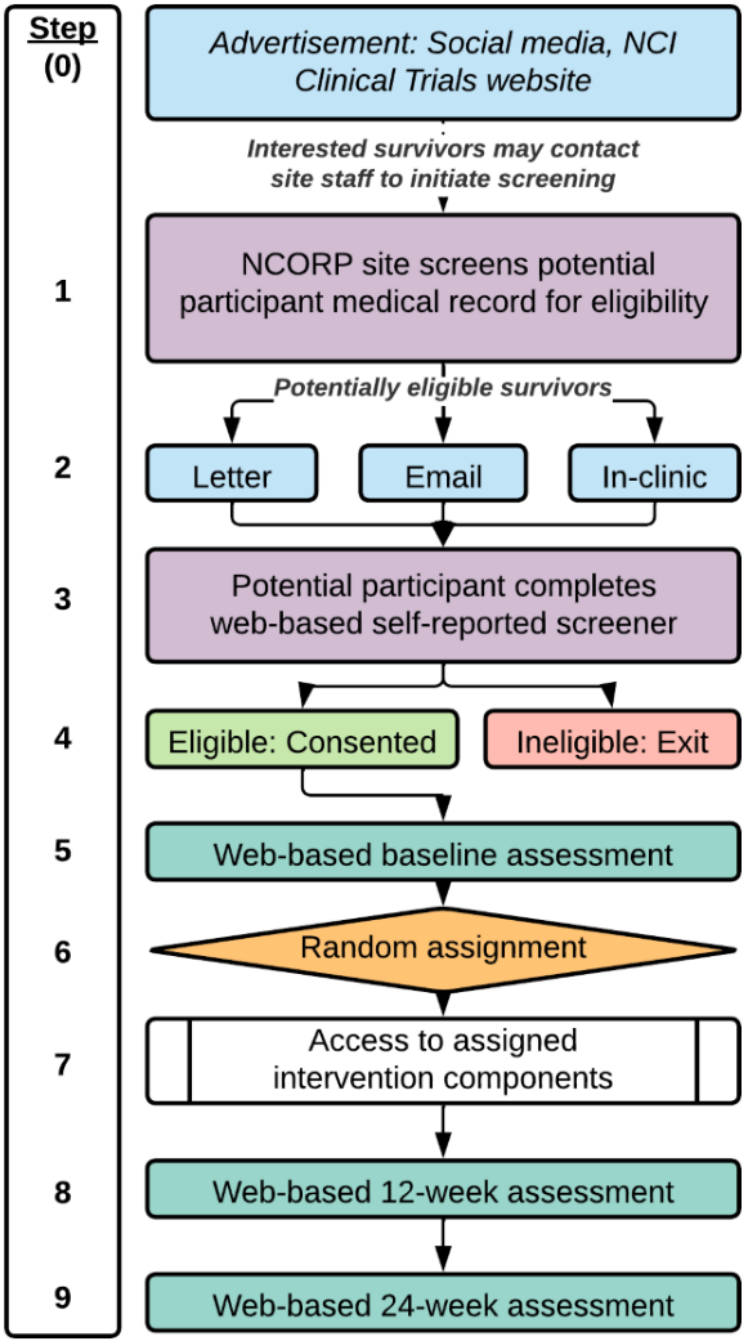

After enrollment, participants will be invited to complete the web-based baseline assessment via REDCap (step 5). On completion of the baseline assessment, participants will be automatically randomized to 1 of the 16 study conditions via REDCap (step 6). Block randomization will be used to help maintain balance across conditions, with varying block sizes of 16, 32, and 48 [44,45]. A participant's randomized condition will not be revealed to the local NCORP study staff; only the

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UVA research coordinator (who implements participants' conditions in the SHINE intervention system) and a WF NCORP RB data manager will have access to participants' randomized condition information. Participants cannot be blinded to their condition. Participants will receive a welcome email directing them to set a password and log into their SHINE program (ie, the set of components assigned to them in their randomized condition; step 7).

After baseline, participants will be asked to complete their SHINE program within the following 12 weeks and to complete follow-up assessments through REDCap at 12 and 24 weeks (steps 8 and 9). A protocol of stepped reminder emails via REDCap and contacts by NCORP site research staff will encourage participants to complete all study assessments.

Intervention

Intervention components are delivered fully automated as a *Core*, or lesson, of content. Components (and component levels) to be tested are (1) education about the influence of breast cancer on sexual health, either with limited information in a static web page format in the Sexual Health Essentials-Standard Core or more comprehensive information through an interactive web program in the Sexual Health Essentials-Enhanced Core; (2) communication skills training for discussing sexual concerns with one's health care team in the Health Care Discussions Core; (3) communication skills training for discussing sexual concerns with one's intimate partner in the Partner Conversations Core; and (4) intimacy promotion skills training in the Intimacy Insights Core. All participants will receive 1 of 2 Sexual Health Essentials Cores (ie, standard [component level=low] or enhanced [component level=high]) given that survivorship care guidelines recommend that all survivors receive education about the influence of cancer treatment on sexual health [21]. For the 3 remaining components, participants will either receive the Core (component level=on) or not receive the Core (component level=off; see Figure 2 for factorial design and Multimedia Appendix 2 for additional Core details).

The Sexual Health Essentials-Enhanced, Health Care Discussions, Partner Conversations, and Intimacy Enhancement Cores each deliver content as stand-alone, web-based programs. These Cores were developed following the Model for Internet Interventions [46] and user-centered design practices to be highly engaging, using interactive elements, audiovisuals, and tailoring. Cores were developed with a team of software engineers and consultants in user interface, user experience, and instructional design. Core content was refined through iterative feedback from survivors of breast cancer. The Sexual Health Essentials-Standard Core provides education via a traditional web page with no tailoring or interactive elements.

Cores take about 20-45 minutes to complete, which participants may do at their convenience and own pace (ie, Cores do not need to be completed in 1 sitting). Participants must complete their Sexual Health Essentials Core (enhanced or standard) before any remaining Cores in their randomized condition are made available. These remaining Cores may be completed in any order. Completed Cores may be revisited and reviewed as often as desired. While technical support is available from the UVA research coordinator, no clinical support will be provided. All Cores were written to an eighth-grade reading level (Flesch-Kincaid Grade Level) [47] or lower.

Participants will access their SHINE program via a password-protected website by computer, tablet, or smartphone. Participants will be monitored by the UVA research coordinator to ensure that they set up a password and can successfully log into the program. The goal of this monitoring is to ensure that the participants can access the intervention. Participants who do not complete their first log-in within a day of receiving the welcome email will receive daily automated reminder emails from the program. If the participant still has not logged in after 3 automated reminder emails, contacts will escalate to reminders by phone call and personal email by the UVA research coordinator and then by the local NCORP site research staff.

There are also automated email prompts to support participant engagement with the SHINE program after participants have successfully logged into the program. Participants who do not initiate Cores within 3 days of initial access will receive a reminder prompt. All participants will receive weekly progress emails regarding their progress through each of their assigned Cores. After participants complete their assigned SHINE program, email prompts will remind them that they may continue to access their SHINE program and review their Cores as desired.

Measures

Overview

Study measures are summarized in Table 2. REDCap surveys require all items to be answered to limit missing data; however, participants may select a "refuse to answer" response for any item. Medical record data on enrolled survivors are collected by participating NCORP site research staff using a standardized medical record data extraction form in REDCap.

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Table 2. Study measures.

Variable or construct	Measurement	Time point (weeks)		
		0 (baseline)	12	24
Screening				
Cancer diagnosis and treatment; age	Medical record extraction			
Sex and gender; relationship status; cancer-related sexual concerns; access to internet and email; serious mental illness; current therapy; and current pregnancy	Self-reported web-based screening questionnaire			
Sample characteristics				
Demographics (eg, race, ethnicity, education, household income, sexual orientation, and partner gender)	Self-reported	✓		
Medical history (eg, diagnosis, treatment type and dates, and other cancer history)	Medical record extraction	✓		✓
Recent sexual experiences, changes in partner status	Patient-Reported Outcomes Measurement Information System sexual functioning screener	✓	✓	✓
Sexual morbidity outcomes				
Sexual distress (primary)	Female Sexual Distress Scale-Desire, Arousal, Orgasm	✓	✓	✓
Sexual functioning (secondary)	Female Sexual Function Index	✓	✓	✓
Mediators				
Sexual functioning knowledge	4-item knowledge perception; 8-item knowledge quiz	✓	✓	✓
Sexual communication self-efficacy with clinicians	2-item confidence to raise and discuss sexual concerns	✓	✓	✓
Sexual communication self-efficacy with partner	Self-Efficacy to Communicate about Sex and Intimacy scale	✓	✓	✓
Emotional intimacy with their partner	Personal Assessment of Intimacy in Relationships—emotional intimacy subscale	✓	✓	✓
Moderators				
Menopause status	Self-reported	✓		
Adjuvant endocrine therapy use	Medical record extraction	✓		
Time since primary breast cancer treatment	Medical record extraction	✓		
Psychological distress	Patient Health Questionnaire-4	✓	✓	✓
Relationship duration	Self-reported	✓		
Relationship satisfaction	Relationship Assessment Scale	✓	✓	✓
Engagement and acceptability				
Engagement	Log-ins, Core completion (recorded by the intervention platform throughout the 24-week study period)			
Satisfaction	Client Satisfaction Questionnaire-8		✓	
Usability	Internet Intervention Utility Questionnaire		✓	

Sexual Morbidity Outcomes

Two outcomes will be evaluated to determine the optimal combination of intervention components: the Female Sexual Distress Scale–Desire, Arousal, Orgasm (FSDS-DAO [48,49]; primary outcome) and the Female Sexual Function Index (FSFI [50-52]; secondary outcome). These measures will be assessed at all 3 time points (ie, baseline, 12-week, and 24-week assessments); the primary evaluation is change between baseline and 24-week assessments.

The FSDS-DAO measures sexual distress among women and will be the primary outcome of the intervention optimization decision-making process. It has established reliability, construct and discriminant validity, and sensitivity to treatment-related changes [48,49]. Participants will rate 15 items on a 5-point Likert scale from 0 (never) to 4 (always). Total sum scores range

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from 0 to 60, with higher scores reflecting greater sexual distress.

The FSFI measures sexual functioning among women. It also has established reliability, construct and discriminant validity, and sensitivity to treatment-related changes [50-52]. Scores will only be evaluated from women who report having sexual activity within the past 4 weeks, as recommended [53]. Participants rate 19 items on a 5- or 6-point Likert scale from 0 (eg, no sexual activity) or 1 (eg, almost never or never) to 5 (eg, almost always or always). To compute a total score, summed scores of each of the 6 domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) are scaled to a maximum score of 6, which are in turn summed for the total score. Total scores range from 2 to 30, with higher scores representing better sexual functioning and a total score of ≤26.0 suggestive of clinically relevant sexual dysfunction.

Mediators

The following a priori mediators will be tested: sexual functioning knowledge (knowledge perception and quiz questions, which were reviewed and revised by survivors of breast cancer); sexual communication self-efficacy with a health care provider (items on confidence to raise and discuss sexual concerns) [33]; sexual communication self-efficacy with partner (Self-efficacy to Communicate about Sex and Intimacy scale [54]); and emotional intimacy with partner (emotional intimacy subscale of the Personal Assessment of Intimacy in Relationships scale [55]). Mediator variables will be assessed at all 3 time points; the primary evaluation is change between baseline and 12-week assessments.

Moderators

The following a priori moderators will be collected or assessed at baseline: menopausal status (self-reported), use of AET (medical record extraction), time since primary breast cancer treatment completion (medical record extraction), psychological distress (Patient Health Questionnaire-4) [56], relationship duration (self-reported), and relationship satisfaction (Relationship Assessment Scale) [57]. Psychological distress and relationship satisfaction will also be measured at 12- and 24-week assessments as exploratory outcomes.

Engagement and Acceptability

Participants' engagement with the SHINE intervention will be characterized by metrics including the number of log-ins and Core completion rates (collected automatically by the SHINE intervention platform). At the 12-week assessment, participants will rate their satisfaction with the SHINE intervention Cores (Client Satisfaction Questionnaire-8) [58] and perceived usability of the Cores (Internet Intervention Utility Questionnaire) [59].

Sample Size and Power Analysis

This factorial trial has been powered to detect a small-to-medium effect size (ie, Cohen *d*=0.30) of intervention components on sexual morbidity outcomes. This represents the smallest effect size that the study team determines would offset the required resources of an intervention component to be delivered to and completed by participants in an optimized intervention. Determined using the MOST R package [60] *FactorialPowerPlan* function (R version 3.6.2; R Foundation for Statistical Computing), 247 survivors of breast cancer would be needed to detect Cohen *d*=0.30 of change in sexual distress from baseline to 24-week assessment (measured by FSDS-DAO) at 80% power with α=.05 for all main effects and interaction effects of the intervention components. In a factorial experimental design with only 2 levels per factor, the power to detect main effects and interaction effects is equal [39,61]. This power analysis assumes a pretest-posttest correlation in sexual distress of *r*=0.65, which is supported by data from the investigators' prior research (Female Sexual Distress Scale pretest-posttest *r*=0.73; N=28) [32] and by Female Sexual Distress Scale validation data (pretest-posttest *r*=0.62; N=318) [49]. The effect size of Cohen *d*=0.30 is reasonable to expect from intervention components, given that prior randomized controlled trials of interventions containing the components demonstrated large effects on sexual distress relative to control (Cohen *d*=0.87 and Cohen *d*=0.59) [28,32]. Conservatively accounting for an estimated 20% attrition (based on the investigators' past trials) [32,42,62] and rounding up to achieve a balanced number of participants per condition, 320 survivors will be randomized in the trial (247/0.80=309 rounded to a total N=320, for n=20 per each of the 16 factorial conditions).

Data Analysis Plan

Overview

In accordance with the NIH requirement, a Data Safety and Monitoring Plan has been established to guide study oversight and ensure the safety of participants and data validity and integrity. Summaries of primary and secondary measures will be reviewed for completeness every 6 months by the WF NCORP RB Data Safety Monitoring Board, along with other key study metrics such as recruitment, retention, patient characteristics, and adverse events. More details about trial oversight and monitoring are available in Multimedia Appendices 3 and 4.

Study methods have been designed to avoid missing data, including efforts to retain participants with incentives and assessment reminder protocols, as well as requiring responses to all items on web-based assessment questionnaires. As it is not possible to entirely avoid missing data, restricted maximum likelihood estimation will be used to address missing data in analyses under a missing at random (MAR) assumption [63-65]. Proposed analyses are robust against MAR data [63,64]. The National Academy of Sciences guidelines for missing data will be followed [64], and the impact of missing data on study conclusions will be explored with sensitivity analyses. Specifically, attrition rates across study conditions will be compared. If a particular condition has a markedly higher dropout rate, baseline covariates that predict attrition will be identified in secondary analyses. Variables determined to predict loss to follow-up will be included in sensitivity analysis models to satisfy the conditions described by Little and Rubin [65] for data to be considered MAR.

Primary analyses will be intention to treat, meaning that the randomized condition assignment will be included in models regardless of whether the participant completes their assigned

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Cores or not. Sensitivity analyses will examine the effects by whether assigned Cores are completed or not. All participants with at least 1 follow-up assessment will be included in analyses. All tests of hypotheses and reported P values will be 2 sided.

Primary Objective Analyses

The primary objective of this study is to identify the most efficient intervention package that is expected to produce the greatest benefit to survivors' sexual health with the fewest (and least-intensive) intervention components. This objective will be achieved using an "all-active components" optimization criterion to guide a decision-making process with systematic data analysis [39]. The main and interaction effects of components will be computed using a generalized linear model (GLM) approach to ANOVA with effect coding to compare the average change in sexual morbidity aggregated across experimental conditions [66].

A model will be conducted for effects on sexual distress, measured by the FSDS-DAO; this model will be prioritized for the intervention optimization decision-making process. First, only components (and component levels) that have a beneficial independent effect (ie, a small-to-moderate positive main effect [Cohen $d \geq 0.3$]) on sexual distress will be provisionally included. Next, these provisional decisions will be reviewed by examining component interaction effects. Components will be considered for addition to the intervention package if they have important (ie, Cohen $d \geq 0.3$) synergistic effects, meaning they amplify the benefit of another component in the package. Components will be considered for removal from the package if they have important (ie, Cohen $d \geq 0.3$) antagonistic effects, meaning they reduce the benefit of another component in the package. Decisions will be informed by computing parsimonious prediction models for outcomes from both the main and interaction effects of the included components [39].

A subsequent model will be conducted for sexual functioning among women reporting sexual activity within the past 4 weeks, measured by the FSFI. Model results will be compared between sexual distress (full population) and sexual functioning (sexually active population only). Components (and component levels) provisionally included based on the sexual distress model findings may be removed if there is a substantial negative effect on sexual function. While discrepant or antagonistic results between the sexual distress and sexual functioning models are possible, they are unlikely, given that FSDS-DAO and FSFI total scores have been found to be highly correlated (r=–0.65 [49]).

Secondary Objective Analyses

Mediation and moderation will be examined separately and will follow the recommendations of prior work [66].

Mediation

An established strategy using structural equation modeling for testing mediation in a factorial experiment will be followed [67]. The mediation effects of components on both sexual distress and sexual functioning will be evaluated within a single model. Mediation hypotheses will be supported if (1) changes in the mediators influence the change in sexual morbidity, (2) intervention components influence the change in the mediators, and (3) changes in the mediators account for the relation between intervention components and changes in sexual morbidity.

In an optimization trial design, mediation analyses are critical both when components produce a positive effect and when there are null findings [68]. If there are null findings of components on primary outcomes, mediation analyses support the next research steps by determining where a breakdown may have occurred. For instance, a hypothesized mediator may influence the outcome, but the component did not adequately influence the mediator. This result would suggest that intervention revisions would be needed to better target the mediator. Mediator analyses are also critical to refining the study's conceptual model.

Moderation

The effect of hypothesized moderators on the effects of intervention components on sexual morbidity will be tested by extending the GLM models from the primary objective analyses to include the interaction effects between intervention components and moderators [66]. Recommendations on centering continuous moderators (ie, time since treatment, psychological distress, and relationship duration and satisfaction) and effect coding categorical moderators (ie, menopausal status and AET use) will be followed [69]. Moderation hypotheses will be supported if the interaction effects are significant ($P<.05$). In addition to the limited set of a priori moderators, other potential moderators (eg, race, ethnicity) may be evaluated for hypothesis generation purposes, adjusting for multiple analyses using false discovery rates. As with mediation analyses, moderation analyses are important regardless of the component effects to understand whether particular groups of survivors differentially benefit from particular components (and combinations of components).

Exploratory Analyses

We will examine survivors' intervention engagement and acceptability. Means and SDs or frequencies, as appropriate, of user engagement metrics will be reported. Whether log-ins differ by components will be tested using the GLM approach as described for the primary objective analyses. The influence of engagement on the change in sexual morbidity outcomes will also be tested by extending GLM models from the primary objective analyses to include the interaction effects between intervention components and engagement. Users' ratings of Core usability and satisfaction will also be reported.

Results

This study is funded by the NCI (UG1CA189824 and R37CA269776; project duration: from January 2023 to December 2027). This trial is registered with ClinicalTrials.gov (NCT06216574). Data collection is planned to begin in March 2024 and conclude in 2027.

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Discussion

Overview

Findings will be used to identify a breast cancer–related sexual health intervention package optimized for maximum impact by providing the greatest expected improvement with the fewest (and least-intensive) intervention components. This will be achieved by evaluating which sexual health intervention components meaningfully improve survivors' sexual health either on their own or in combination with other components. Ensuring that only beneficial components are included in a resulting intervention eliminates unnecessary user effort. Minimizing the time burden to complete the resulting intervention is expected to limit a critical engagement barrier [28,30], permitting more survivors of breast cancer to benefit from this care.

More broadly, the factorial trial design will permit a rigorous evaluation of mechanisms of action for sexual health intervention components and suggest whether certain survivors may need distinct sexual health intervention approaches. These findings from our mediation and moderation analyses will fill a key gap in the literature regarding what specific intervention techniques work and for whom those techniques work best [29]. Furthermore, the results from this optimization trial could accelerate cancer-related sexual health intervention research by demonstrating which therapeutic components may best meet the specific needs, constraints, and characteristics of other target populations [70]. Indeed, the NIH recognizes rigorous testing of the mechanisms of behavioral intervention components as necessary to develop the next generation of more effective and efficient interventions [71].

Comparison With Prior Work

Delivering the optimized and fully automated intervention via the internet promotes its potential impact through greater accessibility, as internet interventions are scalable and overcome many barriers to sexual health care in standard oncology practice. Although prior internet interventions for cancer-related sexual morbidity tested to date have included care delivered by a clinician [28,72-76], delivering such care without the need for clinician involvement would dramatically increase scalability and reduce long-term costs [77]. The fully automated delivery of care also has the advantage of being private, thereby removing the barrier of stigma related to discussing sex and giving women more control over their access to sexual health care after cancer [26,27,30]. Finally, fully automated interventions can be delivered with complete treatment integrity [78], ensuring each survivor using the program has a consistent experience.

Limitations and Future Research

Future research steps are planned to address the limitations of this trial. In this trial, SHINE intervention components are only available in English. To increase the reach of this intervention, future transcreation work with Latina survivors of breast cancer is planned to both translate and culturally adapt the intervention to be appropriate for Spanish-speaking survivors [79-81]. In addition, this intervention only targets survivors of breast cancer and does not have content directed specifically for their partners. Future studies should evaluate whether providing companion educational materials to survivors' partners may enhance intervention outcomes for couples. Finally, as our factorial trial is part of the *optimization phase* of the MOST research framework, a follow-on randomized controlled trial of the optimized intervention package will be needed to test the efficacy of this program.

Conclusions

In summary, this novel optimization trial holds significant potential to address the critically undertreated and distressing breast cancer survivorship concern of sexual morbidity. The factorial trial design will begin to identify which sexual health intervention components work, for whom, and how. These data are directly responsive to calls from leaders in cancer control to advance intervention science through systematically testing intervention components and their mechanisms. By identifying the combination of the fewest and least-intensive intervention components that are likely to provide survivors the greatest benefit, this study will result in the first breast cancer–related sexual health internet intervention optimized for maximum population health impact.

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Data Availability

Deidentified data sets used in primary publications will be transferred to the National Clinical Trials Network and National Cancer Institute Community Oncology Research Program Data Archive in accordance with the agreement between Wake Forest National Cancer Institute Community Oncology Research Program research base and the National Cancer Institute.

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Authors' Contributions

KMS, JBR, EVD, WC, SLS, AHC, SCD, and LMR conceptualized the study; KMS, EVD, and JVG will curate the data; formal analysis will be performed by KMS and EVD; KMS, JBR, EVD, WC, SLS, AHC, SCD, KEW, GJL, and LMR acquired funding; investigation will be led by KMS, EVD, and JVG; methodology was designed by KMS, JBR, EVD, SCD, and LMR; project administration will be overseen by KMS and JVG; resources will be accrued by KMS, JBR, KEW, GJL, and LMR; the study will be supervised by KMS, JBR, EVD, and LMR; writing—original was contributed by KMS, EVD, and JVG, MK, CS; all the authors were responsible for writing—review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
National Institutes of Health grant reviews.
[PDF File (Adobe PDF File), 138 KB - resprot_v13i1e57781_app1.pdf]

Multimedia Appendix 2
Sexual Health and Intimacy Enhancement Intervention details.
[PDF File (Adobe PDF File), 389 KB - resprot_v13i1e57781_app2.pdf]

Multimedia Appendix 3
Sexual Health and Intimacy Enhancement oversight and monitoring details.
[PDF File (Adobe PDF File), 288 KB - resprot_v13i1e57781_app3.pdf]

Multimedia Appendix 4
Data and safety monitoring plan.
[PDF File (Adobe PDF File), 378 KB - resprot_v13i1e57781_app4.pdf]

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Abbreviations

AET: adjuvant endocrine therapy
CIRB: Central Institutional Review Board
FSDS-DAO: Female Sexual Distress Scale–Desire, Arousal, Orgasm
FSFI: Female Sexual Function Index
GLM: generalized linear model
HIPAA: Health Insurance Portability and Accountability
MAR: missing at random
MOST: multiphase optimization strategy
NCI: National Cancer Institute
NCORP: National Cancer Institute Community Oncology Research Program
NIH: National Institutes of Health
RB: Research Base
REDCap: Research Electronic Data Capture
SHINE: Sexual Health and Intimacy Enhancement
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UVA: University of Virginia
WF: Wake Forest

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Protocol

Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE): Protocol for a Nationwide Hybrid Cohort for Transgender Women in the United States

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Abstract

Background: In the United States, transgender women are disproportionately impacted by HIV and prioritized in the national strategy to end the epidemic. Individual, interpersonal, and structural vulnerabilities underlie HIV acquisition among transgender women and fuel syndemic conditions, yet no nationwide cohort monitors their HIV and other health outcomes.

Objective: Our objective is to develop a nationwide cohort to estimate HIV incidence, identify risk factors, and investigate syndemic conditions co-occurring with HIV vulnerability or acquisition among US transgender women. The study is informed by the Syndemics Framework and the Social Ecological Model, positing that stigma-related conditions are synergistically driven by shared multilevel vulnerabilities.

Methods: To address logistical and cost challenges while minimizing technology barriers and research distrust, we aim to establish a novel, hybrid community hub–supported digital cohort (N=3000). The digital cohort is the backbone of the study and

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is enhanced by hubs strategically located across the United States for increased engagement and in-person support. Study participants are English or Spanish speakers, are aged ≥18 years, identify as transgender women or along the transfeminine spectrum, reside in 1 of the 50 states or Puerto Rico, and do not have HIV (laboratory confirmed). Participants are followed for 24 months, with semiannual assessments. These include a questionnaire and laboratory-based HIV testing using self-collected specimens. Using residential zip codes, person-level data will be merged with contextual geolocated data, including population health measures and economic, housing, and other social and structural factors. Analyses will (1) evaluate the contribution of hub support to the digital cohort using descriptive statistics; (2) estimate and characterize syndemic patterns among transgender women using latent class analysis; (3) examine the role of contextual factors in driving syndemics and HIV prevention over time using multilevel regression models; (4) estimate HIV incidence in transgender women and examine the effect of syndemics and contextual factors on HIV incidence using Poisson regression models; and (5) develop dynamic, compartmental models of multilevel combination HIV prevention interventions among transgender women to simulate their impact on HIV incidence through 2030.

Results: Enrollment launched on March 15, 2023, with data collection phases occurring in spring and fall. As of February 24, 2024, a total of 3084 individuals were screened, and 996 (32.3%) met the inclusion criteria and enrolled into the cohort: 2.3% (23/996) enrolled at a hub, and 53.6% (534/996) enrolled through a community hub–supported strategy. Recruitment through purely digital methods contributed 61.5% (1895/3084) of those screened and 42.7% (425/996) of those enrolled in the cohort.

Conclusions: Study findings will inform the development of evidence-based interventions to reduce HIV acquisition and syndemic conditions among US transgender women and advance efforts to end the US HIV epidemic. Methodological findings will also have critical implications for the design of future innovative approaches to HIV research.

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KEYWORDS

transgender women; cohort; United States; HIV; digital methods

Introduction

Background

Transgender women, broadly inclusive of those who identify as transgender women or along the transfeminine spectrum, experience a disproportionately high prevalence of HIV and are prioritized in the Ending the HIV Epidemic (EHE) and National HIV Strategy in the United States [1-3]. Multiple biological, behavioral, and interpersonal vulnerabilities for HIV infection among transgender women are driven and reinforced by structural barriers that limit access to HIV prevention, testing, care, and health services [4]. Transgender women in the United States experience an estimated 14% laboratory-confirmed HIV prevalence [2], although estimates as high as 42% have been reported in recent HIV surveillance, with significant disparities across minoritized racial and ethnic groups [5]. Recent estimates from a cohort of transgender women in Eastern and Southern United States reported an HIV incidence rate of 5.5 per 1000 person-years; there were notable disparities by race and ethnicity, with the incidence rate being as high as 19.3 per 1000 person-years among Black participants [6].

Understanding HIV acquisition among transgender women must be considered in the context of syndemic conditions, that is, "the concentration and deleterious interaction of two or more diseases or other health conditions in a population, especially as a consequence of social inequity and the unjust exercise of power" [7], including the high prevalence of mental health conditions, substance use disorders, and structural and interpersonal violence as a consequence of stigma and discrimination [8-28]. Findings from the National HIV Behavioral Surveillance indicated that among transgender women, more syndemic conditions were associated with increased condomless anal intercourse across racial and ethnic groups, and the prevalence of different syndemic conditions varied by racial and ethnic groups, with excess burden among Black and Latina transgender women [29]. Cross-sectional research has also demonstrated the co-occurring and deleterious interactions of syndemic conditions with HIV vulnerability and with adherence to antiretrovirals for HIV prevention and care [30,31]. Alongside risks, it is vital to identify health-promoting factors and resiliencies that may be leveraged for interventions, including gender affirmation, community involvement, and social support [32-34]. Collectively, this work emphasizes the importance of developing HIV prevention strategies for transgender women that address structural and psychosocial syndemic conditions, support resiliencies, and are tailored for specific demographic groups.

National cohorts are also critical to monitoring epidemic trends and how major events (eg, epidemics, policy changes, and new biomedical interventions) impact HIV and other health conditions, particularly for transgender women who are often misclassified with other populations. While transgender women have contributed extensively to domestic HIV research, most studies in the United States have been cross-sectional or subsumed transgender women within broader risk groups [35-37], limiting scientific inference. Only two cohorts have been implemented among transgender women exclusively in the United States: (1) a facility-based international cohort study of transgender women conducted from 2017 to 2019 that included a site in San Francisco [38] and (2) a multisite, multimodal cohort study conducted from 2018 to 2022 to assess HIV incidence exclusively among transgender women in Eastern and Southern United States (the LITE cohort) [39,40]. Sustained

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cohorts focused on transgender women are needed to monitor epidemic trends unique to transgender women and to assess whether and how national health policies and HIV prevention efforts, including new pre-exposure prophylaxis (PrEP) modalities, impact HIV acquisition in transgender women.

Irrespective of the study population, contemporary HIV cohorts are either facility based or exclusively digital in implementation. Few to none of the cohorts evaluate both models or test hybrid approaches, and most digital cohorts neglect to measure technology access and literacy, missing an opportunity to assess potential biases or test approaches that build on the efficiencies of both models. Results from our prior cohort showed that participants in the site-based mode were more likely to experience individual and structural vulnerabilities (eg, unemployment, sex work, and drug use), whereas participants in the digital mode reported psychosocial and other health vulnerabilities (eg, social isolation, low access to gender-affirming care, and hazardous alcohol use) [6]. Through community engagement, the site-based technology-enhanced model allowed our team to overcome research distrust and permitted follow-up in local communities, revealing incarcerations and deaths that may have been missed in exclusively digital (web-based) cohorts [6]. Mitigating selection bias and the attrition of vulnerable populations is also important for an epidemic underscored by social and health disparities. We aim to explore whether hybrid approaches that leverage the strengths of site-based cohort models can facilitate the engagement and retention of diverse participants in digital HIV cohorts.

Objectives

Our overarching objectives are two-fold: (1) to develop and assess a hybrid community hub–supported digital cohort model, drawing on the unique strengths of site-based and digital cohort methods, for engaging populations facing health, social, and structural contextual disparities, and (2) to evaluate the impact of structural and psychosocial syndemic experiences on HIV incidence among a nationwide cohort of transgender women to inform multilevel HIV prevention strategies.

Our study aims are to (1) determine the efficiency and acceptability of a novel, hub-supported digital cohort of racially and ethnically diverse transgender women aged ≥18 years who are HIV negative; (2) estimate the prevalence and characterize patterns of syndemic experiences among transgender women; (2.1) examine the role of contextual factors (virtual and physical) in driving syndemic experiences over time among transgender women using latent class trajectory analysis; (3) estimate HIV incidence in transgender women, followed every 6 months for at least 24 months to identify tailored approaches for multilevel combination HIV prevention interventions; (3.1) examine the effect of syndemic experiences and contextual factors on HIV incidence among transgender women in the United States; (3.2) characterize the PrEP continuum among transgender women and associations with HIV incidence over time, including the uptake of newly emerging formulations; longitudinal patterns of HIV risk and adherence; and the role of syndemic classes and contextual factors in PrEP uptake, adherence, and retention; and (4) develop dynamic models of multilevel combination HIV prevention interventions and scale-up among transgender women to simulate the impact of evaluated interventions on HIV incidence through 2030, corresponding to the timeline for ending the HIV epidemic outlined in the National HIV strategy.

Methods

Overview

This study is led by principal investigators (PIs) from Johns Hopkins University (PI ALW) and University of Michigan (PI SLR). The study is supported by leading transgender-led, community-based organizations, namely Arianna's Center, Trans Solutions, and the Black Trans Advocacy Coalition, and leading research institutions across the United States, including Johns Hopkins University, Baltimore, Maryland; University of Michigan, Ann Arbor, Michigan; Callen-Lorde, New York City, New York; Emory University and Grady Memorial Hospital, Atlanta, Georgia; University of Miami, Miami, Florida; University of California San Diego, San Diego, California; and Duke University, Durham, North Carolina. Community coinvestigators are essential to the study as they (1) provide input across study design and implementation; (2) serve as bridges to community partners operating in counties outside of hub sites; and (3) support study recruitment, retention, and dissemination across community networks. The coinvestigator research institutions have expertise in HIV epidemiology among key populations, transgender health and clinical care, the management and analysis of longitudinal cohorts, HIV modeling, and sociobehavioral sciences. All study sites are affiliated with or are clinical sites serving transgender women, and all have long established relationships with local organizations and the trans community. A community advisory board (CAB) supports the study team by (1) providing guidance and feedback on research activities and materials; (2) discussing concerns and protection of the community; (3) supporting dissemination efforts within the wider transgender women community; and (4) ensuring the study is conducted in an appropriate and acceptable manner, as well as ensuring the objectives and reporting are beneficial to transgender women.

Conceptual Framework

This proposal is informed by 2 conceptual frameworks, the Syndemics Framework and the Social Ecological Model. Syndemics have been defined as "the concentration and deleterious interaction of two or more diseases or other health conditions in a population, especially as a consequence of social inequity and the unjust exercise of power" [7]. Our conceptualization of social inequity uses an intersectional lens, recognizing that social categories (eg, race, ethnicity, and gender) intersect to affect individual experiences via systems of power and oppression (ie, racism, sexism, and transphobia) [41,42]. For example, among transgender women, pervasive stigma and discriminatory laws compel engagement in sex work for economic survival and gender affirmation while also creating barriers to the provision and uptake of HIV services [32,43,44]. We seek to understand how these and other conditions of social inequity contribute to HIV vulnerability and drive co-occurring, synergistic health conditions. We also seek to identify and understand population strengths and resilience factors (eg, social

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support, community involvement, and gender affirmation) that may mitigate the social inequities that drive HIV syndemics and inform interventions to improve HIV prevention outcomes.

We apply the Syndemics Framework with the Social Ecological Model in recognition that multiple and intersecting levels of risk shape the interaction and distribution of HIV risk among transgender women [45,46]. The Social Ecological Model considers the complex interplay among individual, interpersonal, and structural factors that impact health [47]. We focus on how syndemic conditions at the individual, interpersonal, and structural levels co-occur with the HIV epidemic and may potentiate HIV acquisition risk [48]. The impact of age, race, and ethnicity at the individual level reflects systems of oppression. At the individual level, substance use and mental health disorders reduce the uptake of and adherence to HIV prevention strategies and increase risk for violence [49]. Interpersonal risks include intimate partner violence (IPV), law enforcement interaction, and sex work [50,51]. Employment and health care access, the availability of safe and affordable housing, and exposure to safe environments likely impact health at the structural level.

Recruitment

Our recruitment strategies are built on prior experiences [39,40] and strategies successful in other studies [51-56]. Strategies include community-based recruitment methods (tabling at events, distributing flyers at community organizations, word of mouth, peer referral, etc) as well as web-based methods (app-based advertisements, Google Ads [Google LLC], community listserves, closed social media groups, etc). Given disparities in HIV by race, ethnicity, and geographic location, we ensured diversity by providing recruitment materials in English and Spanish, using diverse images, and implementing geotargeted advertising to southern United States and EHE priority areas.

Study Population

The cohort is composed of English- or Spanish-speaking adults at risk for HIV, aged ≥18 years, assigned male sex at birth who identify as women or along the transfeminine spectrum, and living in the United States or Puerto Rico. Gender identity is verified during enrollment using the 2-step method measuring sex designated at birth (step 1) and current gender identity (step 2) [57,58]. Enrollment in the cohort is restricted to participants with laboratory-confirmed negative HIV test results at enrollment. We do not use stricter inclusion criteria related to sexual risk (eg, PrEP indication), given our prior findings that sexual behaviors are dynamic [59]. An exclusive focus on PrEP-indicated transgender women at baseline misses opportunities to investigate factors that predict changes in sexual behaviors that affect HIV vulnerability. Given documented disparities in the HIV epidemic, our engagement strategy included (1) recruitment efforts using intensive geotargeting to the southern United States; (2) hubs located in EHE priority counties [1]; and (3) a goal to enroll a study population in which at least 50% of participants identify as Black, Indigenous, or Latina.

Cohort participants complete self- or interviewer-administered registration activities, including a preliminary screening to assess eligibility based on age, gender, and self-reported HIV status. Preliminarily eligible participants complete a verification and are then prompted to complete the consent process, which is followed by registration and access to the baseline survey. Completing the initial survey triggers a laboratory order to ship the home specimen collection kit to participants, determined by the participants' specimen collection method preference. Cohort enrollment is defined based on eligible screen, validation, consent, survey completion, and negative laboratory-based HIV test result.

Remote digital surveys are increasingly challenged by fraudulent entries by scammers and bots and duplicate entries [60]. We have built on best practices described by other investigators [35,61-63] and our own experiences to develop a comprehensive method to mitigate the risk of duplicate or fraudulent enrollments. These efforts include 2-step verification procedures, the exclusion of voice over IP (VOIP) phone numbers, real-time checks on duplicate information (phone, email, and IP address), restriction to US and Puerto Rico geographic IP addresses, and blocking banned IPs associated with spam and virus spread. Staff members review baseline survey data (eg, time to survey completion, missingness, and attention filter responses) and conduct phone interviews when fraudulence is suspected to verify that all participants meet preliminary eligibility and are legitimate.

Hub-Supported Digital Cohort Model

A digital cohort platform serves as the backbone of this model wherein candidate participants can enroll and participate remotely from across all areas of the United States and Puerto Rico (Figure 1). Activities are fully technology-enabled, automated, and available in English and Spanish languages, including screening, consent, registration, HIV testing, peer referral, study reminders and notifications (except reactive or indeterminate HIV results), and incentive provision.

The nationwide, digital cohort is enhanced by community hubs strategically located across the United States. Hubs are not primarily responsible for implementing the study protocol or tracking participants but do support community-based recruitment and retention, engage the community via local collaborations, offer staff-administered screening and surveys for participants with low literacy or technology challenges, and support access to clinical services. Hub engagement can occur anywhere along the recruitment-enrollment-retention-referral continuum.

On the basis of prior work [39,40], we anticipate that approximately 65% to 70% of enrolled cohort participants will have fully digital participation, 20% to 25% will be recruited via hubs but will participate in a fully remote mode, and the remaining 5% to 10% of the cohort may require full or periodic in-person support. For those facing participation challenges outside of hub catchment areas, central staff members conduct screening, obtain consent, and administer surveys via phone.

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Figure 1. Conceptualization of hub-supported digital cohort with hubs (red) relative to Ending the HIV Epidemic (EHE) counties and states (dark and light blue).

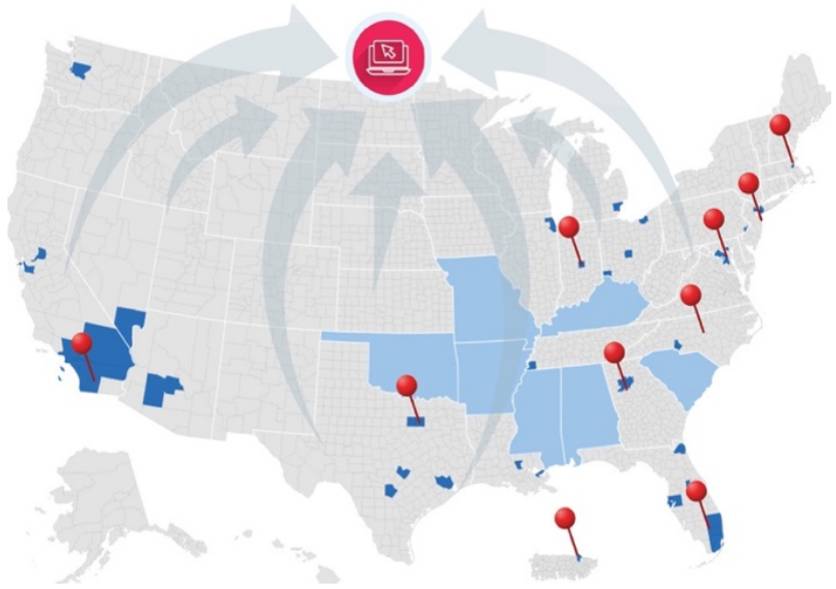

Study Visits

Survey and laboratory data will be collected from cohort participants every 6 months for 24 months via web-based or hub-supported assessments using a web-based system (Figure 2). Participants who experience HIV seroconversion at any point during follow-up will be asked to complete a survey 6 months after confirmatory testing to assess their experiences with engagement in the HIV care continuum.

Study assessments include the completion of a survey questionnaire and HIV testing. Study staff members are available via telephone to support cohort participants with access to the web application. Automated emails and SMS text messages are sent to the participants' device for reminders about upcoming and closing study assessments.

Figure 2. Flow diagram of the Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE) study.

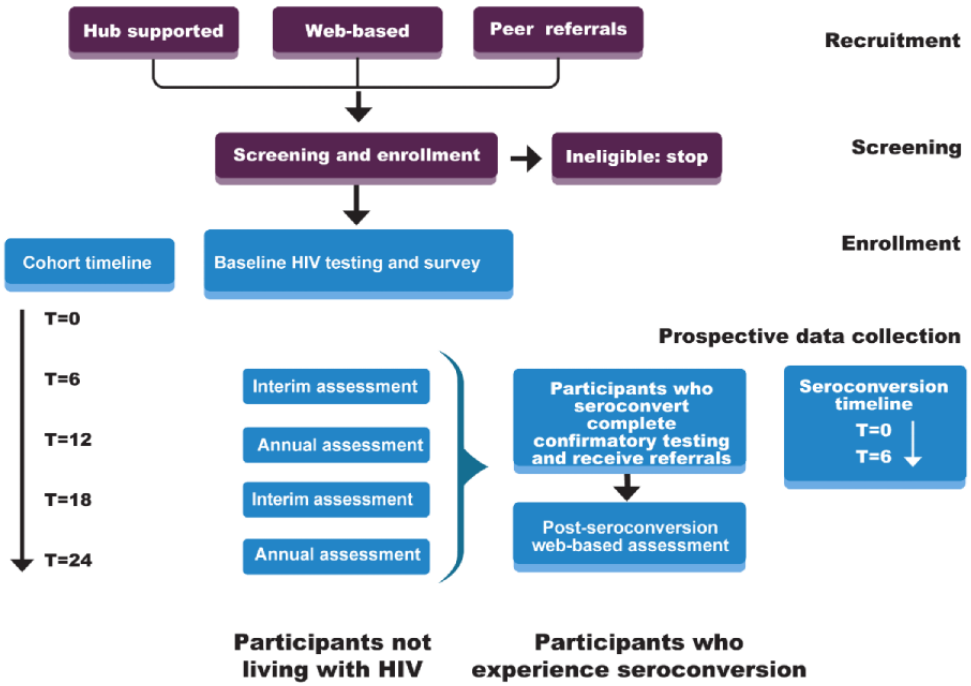

Survey Measures

Survey measures are specific to the visit time point; each calendar year includes 1 fall and 1 spring visit. These calendar-based data collection periods allow for us to measure changes over time as well as conduct cross-sectional analyses for specific time periods. Core measures are repeated at each time point (income, sexual partnerships, mental health, PrEP use, etc), while others are asked either only at baseline (eg, static variables such as date of birth, country of origin, and adverse childhood experiences) or only once at a specific time point.

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Survey measures include, but are not limited to, the following: individual-level measures include self-reported data on demographics, including the zip code of residence, age, race, ethnicity, gender identity, education, income, employment status, health insurance, housing, housing mobility, food insecurity, and history of detention or incarceration; gender affirmation surgery, care, and exogenous hormone use and interruptions, including the age of initiation, based on the US TransPop Survey [64]; sexual health history and the access or uptake of HIV services (including postexposure prophylaxis and PrEP) based on the Centers for Disease Control and Prevention's National HIV Behavioral Surveillance [65]; primary care, mental or behavioral health, and barriers and facilitators to care [15,16,66]; substance use measured through the Alcohol Use Disorder Identification Test-Concise and the Drug Use Identification Test with additional measures for injecting drug use [67,68]; depression symptoms based on the Kessler Psychological Distress Scale and posttraumatic stress disorder (PTSD) symptoms based on the Primary Care PTSD scale [69-71]; and gender euphoria and transgender adaptation and integration assessing adjustment experiences specific to gender identity measured through the Gender Minority Stress and Resilience scale [72,73]. Childhood experiences are measured using the Adverse Childhood Experiences scale and Positive Childhood Experiences scale [74,75].

Interpersonal measures include sexual relationships and behaviors to assess self-reported detailed partner-by-partner sexual behavior information by partner type and HIV status, as well as substance use in the context of HIV acquisition risk, and has been adapted for trans populations to ensure gender-affirmative assessment of sexual risk (S Reisner, unpublished data, June 2017) [76]; and IPV and nonpartner violence victimization, including physical, sexual, and psychological violence and control, and abuse specific to one's transgender experience (trans-specific IPV) [77].

Structural measures include social marginalization and stigma based on the Experiences of Discrimination scale adapted for trans adults in Massachusetts [78] and the US TransPop Survey (reasons for discrimination will be asked, eg, due to race, ethnicity, age, gender identity, or physical disability, in a "select-all-that-apply" format to examine identity and attributional intersectionalities) [64,79]. Social measures include community connectedness and pride using subscales from the Gender Minority Stress and Resilience scale, social support using an abbreviated version of the Medical Outcomes Study Social Support Survey, dignity using a scale developed by Khatib and Armenian [80], flourishing using a scale developed by Diener et al [81]; and experiences and perceptions of state-level stigmatizing and protective laws for transgender populations [73,82-84].

HIV Testing

Biological specimen collection and laboratory-based HIV testing are conducted at every assessment following survey completion. We use self-collected dried blood spots (DBSs) as the primary method for HIV testing; however, based on formative research with LITE participants and feedback from the CAB, we offer several alternative HIV testing strategies to increase acceptability and decrease attrition associated with testing methodology.

The completion of each survey questionnaire automatically triggers the initiation of a laboratory requisition and shipment of a "home kit." The home kit is a small box (ie, fits through all mail slots) that includes detailed, bilingual visual instructions for specimen collection and return mailing to the laboratory, as well as a resource page with information on HIV prevention services and other service options (eg, mental health support). Specimen self-collection materials include 4 lancets, alcohol wipes, adhesive bandage, and Whatman 5-spot DBS specimen card. Participants ship DBS specimens to the study laboratory, where they are tested by a College of American Pathologists–accredited and Clinical Laboratory Improvement Amendments–regulated laboratory using a fourth-generation HIV type 1 antigen/antibody enzyme-linked immunosorbent assay for the qualitative detection of HIV p24 antigen and antibodies to HIV type 1 (groups M and O) and HIV type 2 (sensitivity 100%; specificity 100%; Molecular Testing Labs, unpublished data, December 2020).

Participants who do not feel comfortable completing DBS specimen collection have the option to request oral HIV testing and are mailed an OraSure Oral Fluid Collection Device (OraSure Technologies) within 2 business days. The kits include an insert with study branding, a thank you message, addressed and stamped envelope for shipment to the laboratory, and instructions for oral fluid collection. HIV testing from the oral specimen is done via enzyme immune assay, with positive results being confirmed via western blot. Test performance is estimated to have a sensitivity of 99.6% and specificity of 99.9% [85].

Both DBS and oral fluid specimens are typically processed within 7 business days upon receipt by the laboratory. Notification of nonreactive HIV test results are automatically emailed to the participant. Staff members contact participants with a reactive result within 48 hours of receipt to provide posttest counseling and localized referrals for confirmatory testing and care. Participants near community hubs are linked to affirming services available at the hubs. Staff members call participants with an indeterminate result or rejected specimen to discuss the collection of another specimen or other testing options.

Participants who visit hubs to complete any study activities may also request to have a rapid HIV test completed on site according to local clinical protocols. Staff members enter rapid test results into the study data management system and provide any necessary referrals for confirmatory testing and services.

Participants who report recent testing outside of the study and within 30 days before or during the open study window may submit their HIV test results in lieu of HIV testing through the study. Participants are required to provide a copy of the laboratory report with the date of the laboratory test, laboratory test name, and identification of the participant. The primary purpose of this option is to reduce the research burden for participants who have had recent testing outside of the study.

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Contextual Data

By harmonizing cohort data with contextual, population-based data, our goal is to increase the knowledge base in this field and to parameterize mathematical models to estimate potential impacts of multilevel combination interventions on the HIV epidemic among transgender women. Using participants' self-reported residential zip codes, person-level cohort data will be merged with contextual zip code–, county-, city-, and state-level data, including population health measures and economic, housing, and other social and structural factors (eg, protective laws for transgender populations and digital access; E Dworak, unpublished data, July 2020) [86-88]. Table 1 provides an example of the contextual, population-based data domains and sources that are considered for these analyses and the potential spatial areas where measures of a domain will be operationalized. Measures will be operationalized at a single level or multiple levels of geography depending on availability.

Contextual data will be updated annually or as available throughout the duration of follow-up to reflect the current HIV risk environment for transgender women in the United States. When appropriate, data will be interpolated for years when not available. We will also explore correlation among contextual data measures to determine whether data reduction techniques, such as principal component analysis, are necessary to summarize data measures.

Table 1. Population-based contextual data to be used in the Enhanced Cohort Methods for HIV Research and Epidemiology study.

Domain	Measures and definitions	Spatial area	Sources
Economic	Deprivation, polarization, inequality, and gentrification [20]	ZCTA[a] or county	ACS[b] [89]
Housing	Cost burden, inadequacy, unmet need for housing assistance, and racial and ethnic housing discrimination [3,90,91]	ZCTA or county	ACS [89,92], Picture of Subsidized Households [93], and Housing Mortgage Disclosure Act [90]
Social	Racial and ethnic polarization and segregation, drug-related law enforcement activity, social capital, and violent and hate crime rates	ZCTA or county	ACS [89] and FBI[c] Uniform Crime Reports [91]
Health	HIV incidence, rates of opioid-involved overdose deaths, and density of behavioral health programs	ZCTA or county	AIDSVu [94], CDC WONDER[d], National Directory of Drug and Alcohol Abuse Treatment Programs, and National Directory of Mental Health Treatment Facilities

[a]ZCTA: ZIP Code Tabulation Area.

[b]ACS: American Community Survey.

[c]FBI: Federal Bureau of Investigation.

[d]CDC WONDER: Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.

Study Retention

The use of thorough tracking and retention procedures increases the likelihood that attrition will be random and not systematic. We use tracking and retention procedures proven effective in prior studies. Participants can update email addresses, phone numbers, and physical mailing addresses at any point to ensure contact information is as up to date as possible by logging into the web application. Contact information can also be updated by contacting study staff through email, phone, or text. Assessment reminders are sent to participants through telephone, email, or text once assessment windows open and periodically during the assessment window if the assessment has not been completed. Other strategies to improve retention include regular social events, both web-based and in person, such as study-sponsored yoga classes, cosmetics workshops, and an expungement clinic for marijuana or survival sex charges, as well as study team attendance at local community events.

Our research and community partners have excellent reputations within the community and are known for being nonstigmatizing and ensuring privacy and confidentiality, which assists with retention. We also have an extensive network of transgender-focused organizations and clinical care providers in each of our partnering metropolitan areas who serve as referral centers for health needs. We endeavor to hire study staff members who are transgender women or members of lesbian, gay, bisexual, transgender, and queer communities and who have nursing or public health experience to ensure cultural competence and optimize the acceptability of the study.

Retention is operationally defined as not missing >2 consecutive study assessments. After 1 missed assessment, staff members initiate the retention protocol to individually contact and track participants. Participants who express a desire to prematurely exit the study are asked to complete a participant withdrawal questionnaire (web-based, via phone, or in person) to assess basic characteristics at study exit (eg, HIV status and PrEP use), reason for withdrawal, and whether additional referrals are needed. The study team assesses whether the reason for withdrawal can be addressed and will offer resolution, within the limits of the protocol, to the participant. Aligned with our goals of a welcoming and supporting research environment and scientific rigor, cohort participants who are lost to follow-up or who have previously withdrawn and request to reenter the study will be screened and reassessed for eligibility and, if the timeline allows, administratively considered for re-enrollment.

Sample Size Considerations

The measurement of HIV incidence in transgender women is the primary study outcome. With an enrollment goal of 3000 transgender women and an anticipated 10% loss to follow-up

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per year (as observed in our regional cohort), we estimate an accumulated 5130 person-years of follow-up when participants reach 24 months after enrollment. Given the HIV incidence rate of 5 per 1000 person-years in transgender women in our regional LITE cohort and the dramatic disparities involving a ≥3-fold increase in the rate in subgroups [6], this study has 80% power to detect a 2.6-fold difference in the HIV incidence rate by subgroups (eg, syndemic condition, race, and geography), assuming 2-sided test statistics and 5% type 1 error. In total, 75% of LITE participants reported at least 1 syndemic condition at baseline (eg, substance use, depression, or PTSD per the above criteria) [6]; thus, we expect that 2250 participants will report at least 1 condition, providing sufficient sample for subgroup analysis. Given the evidence of significant recruitment-enrollment cascades in digital cohorts [35,40], we anticipate 7000 individuals will be screened, 5000 will consent, and 3000 will have a negative baseline HIV result for full enrollment into the cohort.

Analytic Plan

Analyses will explore efficiency (number of individuals enrolled and enrollment and retention rates); self-reported acceptability; and potential biases of those recruited, enrolled, and retained. We hypothesize that the hub-supported digital cohort will achieve the sample size and geographic representation goals within the first 24 months of the study. Participants recruited and retained by the hubs will be more racially and ethnically diverse and have lower technology access (neighborhood level and individual level) than those participating through exclusively digital means.

Aim-1 analyses will focus on evaluating the contribution of hub support to the digital cohort. Data visualization techniques will estimate time, cost, and response rates to explore the efficiency of the hub-supported digital cohort as a whole and compare time, cost, and response rates across modes (digital cohort only vs with hub support). Hub support will be identified by proxy links and self-reported exposure to hub activities. Quantitative descriptive analyses will include the comparison of measures of mode acceptability, participant characteristics (eg, demographics, risk behaviors, and HIV status), and contextual data (Table 1) to assess differences in the mode-specific samples that could impact epidemiologic inferences of HIV seroconversion rates. As a sensitivity analysis, we will repeat these analyses restricted to all participants residing in catchment areas around the hub locations. We will incorporate population-based contextual data pertaining to area-level broadband access to assess differences in enrollment and retention by these contextual features as well as personal technology use and access. Differences will be statistically compared across mode (eg, chi-square or Fisher exact test for differences in proportions); we will also use a minimally important "public health" difference. This difference, which is an adaptation of the minimal clinically important difference often used in clinical trials [95,96], is determined by investigators as the minimally meaningful difference that would have an impact on a public health measure, such as HIV prevention uptake. We will use a prespecified difference (eg, –5% and +5%) to incorporate the magnitude into our interpretations of differences, as we anticipate substantial heterogeneity by mode and process measures.

Aim-2 analyses will include latent class analyses of baseline cohort data to identify a set of discrete, mutually exclusive latent classes (syndemic "typologies") of syndemic classes [97]. Latent class membership probabilities γ and item-response probabilities ρ will be estimated by maximum likelihood [97]. Each latent class will be characterized by a unique pattern of individual (eg, mental health and substance use), interpersonal (eg, violence victimization), and structural (eg, unstable housing and incarceration) vulnerabilities comprising syndemic conditions. Measurement invariance across groups will be tested by age, race, ethnicity, and geographic residence. Transgender women will be assigned to a class based on posterior probabilities. Multinomial regression models will estimate statistical predictors of class membership (eg, employment and health care access). HIV acquisition risk, operationalized as a composite variable of behavioral (sexual, injecting, and other behaviors) and risk environments associated with HIV in transgender women [98], will be regressed on latent classes to estimate the risk for one class relative to another (eg, testing associations between syndemic "typologies" and HIV risk) [99]. Model fit will be examined using appropriate indicators (eg, G^2); model selection will be based on information criteria (eg, Akaike information criterion, Bayesian information criterion, consistent Akaike information criterion, and adjusted Bayesian information criterion) and interpretability [97,100,101].

We will examine syndemics over time and model trajectories of change in syndemic classes across follow-up with latent trajectory analyses and latent class growth analyses. We will model time-varying and -nonvarying predictors of changes in class membership, incorporating individual cohort and contextual data. Contextual data described in Table 1 will be incorporated into models to explore prospective impacts on syndemic experiences and differences by participant subgroups. Latent class analyses will use Mplus (Institute for Digital Research and Education).

Tracking and describing differences in attrition by individual, interpersonal, and structural risk factors will be essential to determining the appropriateness of assumptions in incidence and time-to-event analyses. Attrition will be tracked using data visualization techniques, stratifying important metrics over time (such as the number of individuals enrolled and proportion lost to follow-up) by site. Bimonthly, site-specific reports of attrition will be produced for review. We will alert staff to participants who are at risk to trigger a participant-focused retention protocol. Statistical analyses of attrition will include incidence rates and survival analyses to investigate rates of loss to follow-up and death overall among subgroups [102]. Risk ratios will be used to examine individual (eg, demographics and HIV risk behaviors), interpersonal (eg, social factors), and structural predictors of loss to follow-up and death [102].

HIV incidence rates will be estimated as the number of observed HIV seroconversions divided by the number of person-years accumulated; rate ratios and 95% CIs will be estimated using Poisson regression models [6]. Trends by 6-month time intervals will be monitored. HIV incidence rates measured in the entire

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cohort at 12 and 24 months will be estimated. In all trend analyses, a continuous variable for time in the Poisson regression model will test the null hypothesis that there is no difference (ie, no trend) in HIV incidence by 6- or 12-month interval of time since study entry. Assuming a sufficient number of events, a competing risks approach [103] will be used to account for the mortality. We will also visualize the Kaplan-Meier estimates of HIV cumulative incidence with a time-to-event approach that defines the time of origin as study entry and uses log-rank tests for differences, as well as Cox proportional hazards models to estimate hazard ratios and 95% CIs (standard for the competing risk of death) [104]. Analyses will be conducted overall and by subgroup.

Incorporating both cohort survey measures and contextual data, individual, interpersonal, and structural risk factors will be included in the Poisson regression models. To account for the nonindependence of observations within geographic areas, generalized estimating equations with a robust estimation of variances will be used to estimate the association of individual, interpersonal, and structural risk factors with HIV incidence [105]. We will separately model trajectories of HIV risk as a function of changing syndemic classes using latent trajectory analyses and latent class growth analyses.

Differences in PrEP indication and use among transgender women will be assessed at baseline. Perceptions and use of emerging formulations and modalities will be assessed using cross-sectional descriptive analyses of annual surveys at relevant time points. Descriptive statistics (chi-square tests and 2-tailed *t* tests) and log binomial models (or, when these models fail to converge, Poisson regression models with robust variance) will be used to estimate prevalence ratios and 95% CIs. Patterns of PrEP indication and prevention-relevant adherence over time will be estimated using group-based multitrajectory modeling, a data-driven approach for identifying latent longitudinal strata across distinct but related indicators (in separate models and using Nagin model selection criteria) [59,106,107]. We will then use the maximum posterior probability to assign participants into trajectory categories and use multinomial logistic regression models to identify correlates of each trajectory. Identified PrEP indication–adherence classes will be tested for associations with HIV incidence.

Dynamic Compartmental Model

We will develop a dynamic compartmental model of HIV transmission and acquisition in transgender women and their sexual partners by incorporating information obtained through the Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE) cohort, the LITE cohort, and other prior work [108-111]. The model will be used to (1) better understand epidemic dynamics by quantifying the contribution of different individual, interpersonal, and structural determinants to HIV incidence in the context of other syndemic conditions (ie, substance use and mental health); (2) identify optimal PrEP regimen and delivery strategies; and (3) design HIV combination prevention packages to achieve EHE incidence reduction goals by 2030.

The model will disaggregate the population by key determinants of HIV risk and HIV care at the *individual level* (eg, age, race, ethnicity, and syndemic conditions), *interpersonal level (*eg, engagement in sex work and IPV), and *structural level* (health care access and employment). The population will also be disaggregated by HIV status or stage, HIV care status, and PrEP status. HIV transmission will be a function of biological and behavioral risk factors, including the number of partners, sex acts per partner, condom use and sexual positioning by partner type in each group, HIV prevalence and antiretroviral therapy (ART) coverage among partners, and PrEP coverage among susceptible individuals. The influence of individual, interpersonal, and structural determinants on HIV risk will be examined by applying relative risks to sexual behaviors associated with each determinant.

We will focus on 4 regional models: Northeast, South, Midwest, and West United States [112]. Nonetheless, it will be possible to apply the model in all US cities in the cohort by populating a database of city-specific model parameters that will be plugged into the region-specific calibration process. This will enable EHE cities to implement relevant analyses to guide local policy. Modeling will be conducted in collaboration with community coinvestigators and the CAB to ensure relevance and acceptability to the transgender women community.

For model parameterization, sociodemographic and behavioral parameters will be informed by the ENCORE cohort (all 4 regions) and the LITE cohort (northeastern and southern regions). Biological parameters defining HIV progression rates [113,114]; transmission probability for different HIV stages [113,114]; types of sex acts [115,116]; the effectiveness of condoms in preventing transmission during anal sex [117]; and the efficacy of ART and PrEP in preventing transmission [118] and acquisition [119,120], respectively, and in delaying ART HIV progression [121-123] will be obtained from systematic reviews and meta-analyses. Relative risks for the independent effect of each key determinant of HIV risk will be obtained through multivariable statistical models using the ENCORE data.

In each of the 4 regions, we will carry out the following steps:

1. We will estimate the contribution of structural determinants (eg, unemployment and low health care access) to HIV incidence using a population attributable fraction (PAF) approach (by implementing counterfactual scenarios assuming no unemployment and adequate access to health care, respectively, over the past decade, 2013 to 2025). Using the same approach, we will estimate the PAF of IPV, substance use, and mental health disorders (in isolation and in combination) to characterize and quantify syndemic effects on the HIV epidemic. The proportion of new HIV infections averted in each scenario compared to the baseline scenario corresponds to the PAF of each determinant, allowing us to identify priorities for HIV prevention interventions [124,125].
2. We will identify PrEP delivery strategies by comparing a scenario with no PrEP with counterfactual scenarios of PrEP delivery. The status quo for PrEP delivery (Figure 3, line S1) will be based on current patterns of PrEP engagement and coverage. We will estimate the reduction in new HIV infections if PrEP patterns remain at current

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levels in each region from 2025 to 2030. A first counterfactual scenario will assume increased PrEP coverage by a relative 50% (Figure 3, line S2). A second counterfactual scenario will assume strategic PrEP provision based on characteristics identified in aim 4 (Figure 3, line S3). For example, those who engage in sex work might benefit the most from daily oral PrEP, while those experiencing substance use disorders or IPV might achieve better outcomes with long-acting formulations [126-128]. We will compare the number of new infections averted in each scenario to baseline (Figure 3, line S1) to assess the impact of increasing PrEP coverage and more strategic delivery.

3. We will design HIV combination prevention packages to achieve EHE incidence targets by identifying the most effective combination of interventions to achieve a 90% reduction in incidence among transgender women by 2030, compared to 2017 values in each region (Figure 3, line S4). In addition to PrEP scale-up, we will consider interventions to increase employment [129,130], health care access [131], condom use and negotiation skills [132], and mental health and substance use treatment to address epidemic drivers at structural, interpersonal, and individual levels.

Figure 3. Predicted reduction in HIV incidence under different pre-exposure prophylaxis (PrEP) and combination prevention scenarios versus baseline. The black line corresponds to the baseline in the absence of PrEP and additional combination prevention interventions. EHE: Ending the HIV Epidemic.

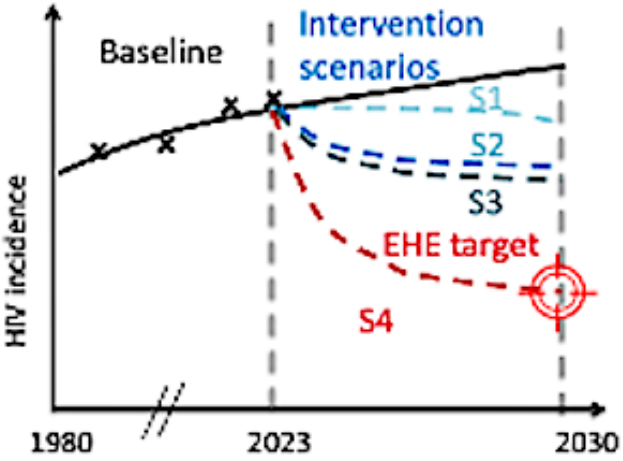

Ethical Considerations

The Johns Hopkins Single Institutional Review Board (IRB00355445) reviewed and approved this study. Johns Hopkins Single Institutional Review Board served as the institutional review board of record for all partner institutions in this multisite study. As a minimal risk study, participants were asked to provide consent in the English or Spanish language using an oral consent form in web-based format prior to initiating research activities. Upon the completion of the survey, participants are provided a US $15 incentive through the modality of their choice. Upon study receipt of participant laboratory results, a US $65 incentive is issued to the participant, for a total of US $80 per visit. Incentives are available through an electronic gift code, which can be redeemed at hundreds of stores on the web, including Walmart, Target, Sephora, Amazon, and other well-known stores, or through a prepaid debit card. The inclusion of a cash-accessible option was critical to the acceptability of the study design by participants, as informed by our prior experiences.

Identifiers were collected from participants for the purposes of shipping specimen collection kits and incentive cards (as applicable) and for study reminders; however, only deidentified data are available for analysis.

Results

Enrollment opened on March 15, 2023, with enrollment and data collection phases occurring from March 15, 2023, to June 30, 2023, and from November 1, 2023, to December 15, 2023, respectively. As of February 24, 2024, before the next opening of enrollment and data collection, a total of 3084 people were screened for participation. Of those screened, 61.19% (n=1887) were considered eligible and consented to participate in the study, 32.98% (n=1017) completed both the survey and HIV testing activities, and 32.3% (n=996) were fully eligible based on final HIV result and enrolled into the cohort. Figure 4 displays the continuum from screening to enrollment with arrows displaying the percentage remaining from the prior step in the continuum. The most significant drop in the continuum occurred at the completion of the HIV test, in which 66.21% (1017/1536) of those who completed the survey went on to complete a remote HIV test, regardless of the testing method.

Among those enrolled in the cohort, 2.3% (23/996) were enrolled directly in a hub, and 53.6% (534/996) were enrolled through a community-engaged, hub-supported strategy. Recruitment through purely digital recruitment methods, including recruitment through web-based advertisements and dating apps, have contributed to 61.45% (1895/3084) of those screened and 42.7% (425/996) of those enrolled in the cohort.

Table 2 displays the screening characteristics of individuals who completed screening and who ultimately enrolled in the cohort as of February 2024. Between screening and enrollment, ≥5-percentage-point declines were observed in the proportions of participants who were aged 18 to 24 years, who identified as non-Hispanic Black, and who resided in Southern United States.

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Figure 4. Enrollment continuum in a nationwide, hub-supported cohort of transgender women.

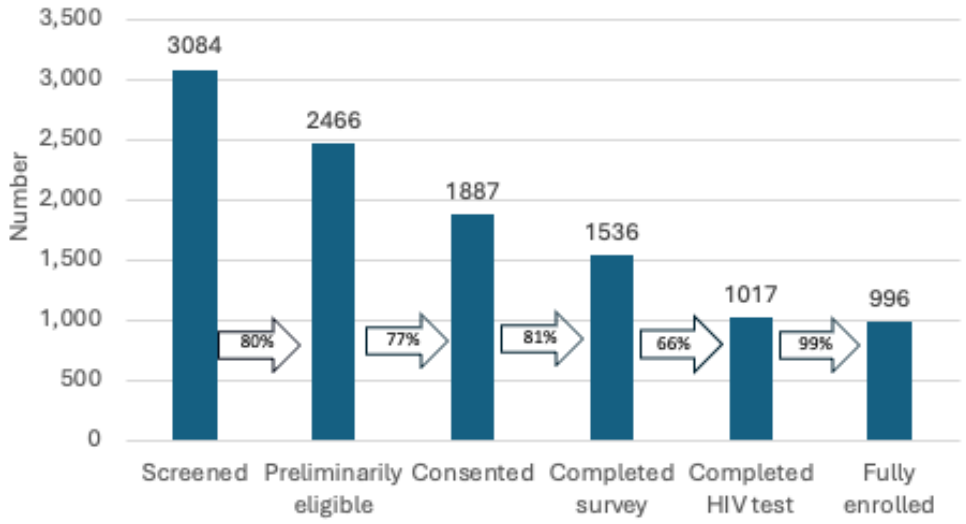

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Table 2. Screening characteristics of individuals screened and enrolled into the nationwide, community hub–supported digital cohort.

Characteristic	Screened (N=3084), n (%)	Enrolled (n=996), n (%)
Age group (y)		
18-24	615 (19.94)	146 (14.66)
25-29	571 (18.51)	201 (20.18)
30-39	1034 (33.53)	367 (36.85)
40-49	452 (14.66)	140 (14.06)
≥50	381 (12.35)	142 (14.26)
Race and ethnic identity		
Hispanic Black	72 (2.33)	13 (1.31)
Hispanic White	165 (5.35)	65 (6.53)
Hispanic and more than 1 or another race	401 (13)	85 (8.53)
Non-Hispanic Black	494 (16.02)	111 (11.14)
Non-Hispanic White	1562 (50.65)	583 (58.53)
Non-Hispanic and more than 1 or another race	230 (7.46)	93 (9.34)
Unknown	160 (5.19)	46 (4.62)
Language		
English	2965 (96.14)	970 (97.39)
Spanish	119 (3.86)	26 (2.61)
US census region		
Midwest	489 (15.86)	187 (18.78)
Northeast	748 (24.25)	297 (29.82)
Puerto Rico	15 (0.49)	7 (0.7)
South	1189 (38.55)	312 (31.33)
West	643 (20.85)	193 (19.38)
Recruitment source		
Community partner	262 (8.5)	63 (6.33)
Former participant	536 (17.38)	338 (33.94)
Hub	297 (9.63)	133 (13.35)
Peer referral	94 (3.05)	37 (3.71)
Web-based advertisements	403 (13.07)	77 (7.73)
Dating app advertisements	1492 (48.38)	348 (34.94)

Discussion

Anticipated Findings

This study will provide important data on multilevel determinants of HIV risk and syndemic patterns among transgender women at the national level, allowing us to contrast by region and state and better understand the impact of syndemics and contextual factors on HIV prevention and the overall epidemic. The study design builds upon successfully used protocols among transgender women by our study team and aims to address gaps in exclusively digital or exclusively facility-based methods, particularly as gap relates to differences in study population and HIV vulnerabilities [6,39]. This protocol innovatively uses digital cohort methodology supported by community-engaged, hub-supported methods with options for in-person activities to ensure thorough support for and the diversity of experiences among research participants.

Specifically, our preliminary findings have shown that recruitment through purely digital recruitment methods contributed to 61.45% (1895/3084) of those screened to date but only 42.7% (425/996) of those ultimately enrolled in the cohort, highlighting that while digital methods reach geographic breadth, they may not be sufficient alone for achieving HIV recruitment goals or for enrolling a participant population generalizable to the US population of transgender women. As this research proceeds, we will explore how the hybrid community-engaged, hub-supported model expands (or not) the diversity of the sample and supports the retention of the cohort.

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Limitations

The costs and management of this hub-supported model are likely to be perceived as a limitation; however, we suspect that this cohort model is cost-effective, as our experience has shown that individuals disproportionately affected by HIV often need support for study participation and other health and social support. While the pooled contribution from participants enrolling or participating through hubs alongside exclusively web-based participants adds strength to the study, pooled results can provide misleading or overly smoothed inferences. Our analytic "best practices" protocol includes the examination of data to understand the magnitude of heterogeneity in estimates [133]. Further, we will use sensitivity analyses to examine the influence of hubs on specific results, such as by omitting subgroups systematically using jackknife methods with unequal partitions [134]. Finally, we do not propose to trial HIV prevention strategies; however, participants will receive geolocated referrals to HIV prevention and other health or social services tailored to their needs. Further, our use of mathematical modeling provides an opportunity to test multiple HIV prevention strategies among transgender women to inform future trials and national and regional HIV prevention efforts.

Conclusions

Study findings will have critical implications for the design of future cohorts, given the disparities underlying HIV epidemics. Our understanding of HIV incidence and risk for HIV among transgender women will be augmented by the inclusion of contextual data, which allows us to examine larger social and structural factors that affect the health and well-being of transgender women and can serve as modifiable factors and intervention targets beyond the individual level. The use of mathematical modeling provides an opportunity to simulate multiple HIV prevention strategies among transgender women to inform future trials and national and regional HIV prevention efforts.

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The authors thank the transgender women who take part in this study. This study would not have been possible without their participation. The authors also acknowledge the work of the community advisory board that provides input across all stages of this research.

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The ENCORE study collaborative team members to be included are as follows: University of Michigan (UM): SLR (multiple principal investigator [PI]); Johns Hopkins University (JHU): ALW (multiple PI), KNA, EC, JC, EH, SL, CP, MS, and CW; Arianna's Center: AL; Black Transgender Advocacy Coalition (BTAC): C Brown; Callen-Lorde Community Health Center: A Radix; Duke University: TP and C Beyrer; Emory University and Grady Hospital: JSS and JSH; Trans Solutions: MM; University of Miami: AJW and AR; and University of California San Diego: AB.

Data Availability

Deidentified individual data and a data dictionary will be made available upon reasonable request after the approval of a proposal and signing of a data use agreement. There is a formal process for external users to request access to Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE) data, which involves review and approval by principal investigators from each study site and the community advisory board. Further details and forms can be obtained by emailing ALW and SLR.

Conflicts of Interest

ALW, TP, and EC receive funding from ViiV Healthcare for their institutions.

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Abbreviations

ART: antiretroviral therapy
CAB: community advisory board
DBS: dried blood spot
EHE: Ending the HIV Epidemic
ENCORE: Enhanced Cohort Methods for HIV Research and Epidemiology
IPV: intimate partner violence
JHU: Johns Hopkins University
PAF: population attributable fraction
PI: principal investigator
PrEP: pre-exposure prophylaxis
PTSD: posttraumatic stress disorder
VOIP: voice over IP

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Protocol

Digitizing Survivorship Care Plans Through the POST-Treatment Health Outcomes of Cancer Survivors (POSTHOC) Mobile App: Protocol for a Phase II Randomized Controlled Trial

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Abstract

Background: Survivorship care plans (SCPs) are provided at the completion of cancer treatment to aid in the transition from active treatment to long-term survivorship. They describe the details of a patient's diagnosis and treatment and offer recommendations for follow-up appointments, referrals, and healthy behaviors. The plans are currently paper-based and become outdated as soon as a patient's health status changes. There is a need to digitize these plans to improve their accessibility, modifiability, and longevity. With current technology, SCPs can be linked to mobile devices and activity trackers so that patients can track health behaviors and compare them to their clinical goals, taking charge of their own health.

Objective: A mobile app, POSTHOC (POST-Treatment Health Outcomes of Cancer Survivors), that digitizes the SCP was developed, with goals of integrating it with wearable technologies and electronic medical records. Herein, we are conducting a randomized controlled trial that evaluates the POSTHOC app versus the traditional SCP on total symptom burden in the early posttreatment period.

Methods: We will recruit 54 patients who have recently completed curative therapy for cancer (any type) in person and remotely. They will be randomized 2:1, POSTHOC:usual care (unblinded). Those randomized to the POSTHOC group will receive their SCP via the app and will choose to focus on nutrition or exercise for the duration of the study based on their individual plan and personal preferences. Those randomized to the control group will get a paper-based plan. At baseline, 6 weeks, and 12 weeks, we will evaluate patient-reported outcomes, including total symptom burden (web-based questionnaire), diet (24-hour Automated Self-Administered [ASA24]), and physical activity (Fitbit Charge 6 [Google LLC]). We will also collect quantitative and qualitative feedback on the usability of the app from those in the POSTHOC arm to improve the app for future implementation studies, with a specific focus on patient-provider communication. For feasibility, we will calculate the percentage of patients who used the

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POSTHOC app at least 3 times per week. We will use linear mixed models to evaluate the effects of the POSTHOC app versus those of usual care on other outcomes at weeks 6 and 12.

Results: This trial is open to accrual in the University of Maryland Medical System as of March 2024, and as of July 3, 2024, a total of 20 participants have consented.

Conclusions: This study is among the first to digitize the SCP in a mobile app and test the effects of a mobile health–delivered behavioral health intervention on symptom burden in cancer survivors. Our results will provide evidence about the effects of health self-management on symptoms. This knowledge will be integral to larger randomized controlled studies, integration with the electronic medical record, and nationwide implementation.

Trial Registration: ClinicalTrials.gov NCT05499663; https://clinicaltrials.gov/ct2/show/NCT05499663

International Registered Report Identifier (IRRID): DERR1-10.2196/59222

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KEYWORDS

mobile health; mHealth; symptoms; clinical trial; posttreatment; oncology; mobile phone

Introduction

Background

As of 2022, more than 18 million Americans had a medical history that included cancer, and the prevalence of cancer is projected to continue to increase [1]. This growth has raised concerns about whether the health care industry is adequately prepared to meet the unique health care needs of cancer survivors. Years after treatment ends, cancer survivors continue to cope with symptoms of the disease and side effects of the treatment, including physical limitations, cognitive sequelae, depression, sleep problems, fatigue, and pain. A survey of demographically diverse cancer survivors in California estimates that the average survivor has 5 comorbidities and that 40% of these conditions arise after treatment ends [2]. As cancer rates rise and treatment continues to improve, the size of the cancer survivor population and survivorship duration will continue to increase [3]. This growth trend necessitates the health care industry to develop new tools to support cancer survivors during the posttreatment period to promote long-term clinical and supportive care outcomes.

The health care community has already taken some actions to address posttreatment challenges. As recommended by the National Academy of Medicine (formally the Institute of Medicine), all cancer survivors should receive a survivorship care plan (SCP) from their oncology clinical care team after their primary treatment ends [4]. The American College of Surgeons Commission on Cancer set SCP guidelines to recommend that survivors receive information regarding future check-ups and tests, education on potential late and long-term effects of the cancer treatment, and recommendations for improving health after treatment [5]. However, current practices for the continued care of survivors are burdensome; are complex; must be continuously updated; and require that survivors, oncologists, and primary care providers coordinate efforts to monitor for recurrence, monitor physical and psychosocial effects of treatment, and promote healthy living [6,7]. Due to this complexity and infrequent communication between survivors and their care team between scheduled check-ups, these practices are not enough to ensure timely symptom identification and adherence to recommendations [8]. Additional tools are needed to supplement the SCP to promote self-management, encourage the achievement or maintenance of healthy lifestyle behaviors, and facilitate the detection of risk for posttreatment complications.

One way to address issues with current SCP practices is through mobile health (mHealth) interventions. mHealth data capabilities have grown significantly due to a greater adoption of smart devices, improved mobile network coverage, and increased focus of American culture on self-monitoring and preventative health [9]. Indeed, interest in mHealth interventions to enhance overall wellness has increased exponentially in the last decade [10], including among patients with cancer [11]. mHealth apps that promote exercise have a variety of functions, including easy visualization of step data from an activity tracker, notifications to promote activity (at set times and in response to sedentary behavior, as detected from participants' activity tracker) [12], a newsfeed, educational information, easy visualization of users' activity compared to their goals or prescriptions, peer-support via 2-way messaging with other participants, and symptom tracking [11,13,14]. mHealth apps to deliver nutrition or healthy eating interventions are less prevalent than those that deliver physical activity interventions, although nutrition-related mHealth interventions among cancer survivors have promoted weight loss with preliminary success [15-17]. In addition to enabling the self-monitoring of physical activity and nutrition, mHealth has advantages for researchers in monitoring ambulatory behaviors and soliciting immediate responses to questions, known as ecological momentary assessment (EMA) [18]. Specifically, EMA provides an unprecedented opportunity to capture changes in symptoms over a single day and model how symptoms can predict lifestyle behaviors later that day or how lifestyle behaviors can acutely affect symptoms [19].

To our knowledge, 4 SCP mobile apps are under development [20-24], addressing requests from patients, clinicians, and organizations. First, Baseman et al [20] evaluated the feasibility and acceptability of SmartSurvivor, a mobile breast cancer survivorship care app, in a pilot study. The goals of the app were to facilitate care coordination; support medical, psychosocial, and practical needs; and improve survivors' long-term health outcomes [20]. Overall, both survivors and

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providers felt that SmartSurvivor was a potentially valuable tool to support long-term SCP objectives [20]. Second, Denzen et al [22] and Preussler et al [21] are designing a web-based survivorship program for recipients of hematopoietic cell transplants called INSPIRE (Internet Survivorship Program with Information and Resources), which includes a mobile app. In focus groups, patients appreciated the comprehensiveness of the information provided, noting that some material was not provided by their providers [21]. They also noted its usefulness in guiding communication with physicians. However, they would have liked to receive more personalized information (eg, on transplant-induced gastrointestinal upset) as well as a means to monitor and track certain aspects of health [21]. Third, Murphy et al [23] are designing a mobile app to deliver the SCP to survivors of childhood cancer. The authors previously tested a portable, credit card–sized passport to improve the survivors' knowledge of diagnosis, treatment, risks, and follow-up care. Patients who received the passport demonstrated improved and sustained knowledge compared to those who did not receive the passport until >4 months later [23]. The authors are following up on these results to develop a survivorship mobile phone app and suggest further study on the strengths and weaknesses of a mobile app approach [23]. Fourth, Stan et al [24] are designing an app-based, eHealth record–integrated interactive care plan for breast cancer survivors. The goals of the app are to make the SCP into an actionable and engaging guide for patients and provide remote monitoring services for primary care providers [24]. The implementation of the app with 23 patients was feasible and created minimal provider burden, but patient engagement was below the feasibility threshold, suggesting that changes may enhance adoption [24]. There are other digital applications and mobile apps designed to aid cancer survivors with self-management, but they do not deliver the SCP [25-27].

Qualitative and feasibility studies have concluded that people who have had a cancer diagnosis find both health-tracking apps and SCP useful [10,15,16,20-22,28,29]. However, despite the high number of trials conducted thus far, the apps did not incorporate wearable devices or health tracking, the studies tended to be small and underpowered to detect changes in physical activity patterns, and the projects incorporated only limited feedback from clinicians.

This Study

This study will fill a significant gap in the literature by being the first study, to our knowledge, to both digitize the SCP in a mobile app integrated with a wearable activity tracker and test the effects of the app on symptom burden in cancer survivors. We hypothesize that (1) the POSTHOC (POST-Treatment Health Outcomes of Cancer Survivors; Charles River Analytics) app is feasible, acceptable, and useful for cancer survivors; (2) the POSTHOC app will reduce cumulative symptom burden reported by patients compared to usual care; and (3) the POSTHOC app will improve health behaviors compared to usual care, as measured by patient-reported physical activity. The results of this study will be built upon to improve the usefulness of the app and integrate it into clinical workflow.

Methods

Ethical Considerations

Ethics approval was obtained from the University of Maryland Greenebaum Comprehensive Cancer Center (UMGCCC) Clinical Research Center (GCCC2280), the University of Maryland School of Nursing Office of Research and Scholarship (HP-00100473), the University of Maryland Baltimore (UMB) Institutional Review Board (HP-00100473), and 4 community oncology practices in the University of Maryland Medical System. This study was registered at ClinicalTrials.gov (NCT05499663). All participants will provide informed consent (see Multimedia Appendices 1 and 2 for more details). Participants are compensated $50 USD for their time to participate in the study and may keep the Fitbit activity tracker.

Because the SCP includes protected health information, we are ensuring the safety of the data using several layers of security. First, the SCP includes minimal protected health information that could be used in a security breach; it does not include name, birthday, address, phone number, email address, or medical record number. Second, the SparkCare platform, which houses the POSTHOC app and the PostgreSQL database, is installed on UMB servers managed using Azure (Microsoft Corp) services, so data are not transferred to or from Charles River Analytics or anywhere other than the participants' personal smartphones. Third, we installed an Internet Information Services (Microsoft Corp) webserver; obtained a public IP address, domain name, and security certificate; and configured a domain name system. The POSTHOC app is not publicly available and can be accessed only via an internal developer link that can be opened only via an invitation (via Test Flight for Apple users).

The POSTHOC app also has a "clinician portal" on a dual authentication–protected website. The clinician portal allows study team members to invite participants, manage participants, assign participants to the POSTHOC or usual care arm, and enter the SCP. Only the study team has access to the study data, although participants may share the data with their provider at their discretion.

Aims, Design, and Setting

Aims

The primary aim is to assess the feasibility, acceptability, and usability of the POSTHOC app among cancer survivors (randomized to the app group: 36/54, 67%). The secondary aim is to obtain a preliminary estimate of the effect of the POSTHOC app versus usual care on cumulative patient-reported symptom burden (approximately 36/54, 67% in the intervention arm and approximately 18/54, 33% in the usual care arm). The tertiary aim is to obtain a preliminary estimate of the effect of the POSTHOC app versus usual care on patient-reported and objectively measured health behaviors (physical activity, diet, and sleep). Exploratory mechanistic aims are to (1) assess cross-sectional associations between health behaviors (physical activity, diet, and sleep) and cumulative symptom burden at baseline; (2) explore associations between changes in health behaviors (physical activity, diet, and sleep) and cumulative

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symptom burden from baseline to 6 weeks and from baseline to 12 weeks; and (3) explore associations between adherence to the intervention and changes in the same measures—symptoms, physical activity, diet, and sleep.

Design and Setting of the Study

This study is a phase II feasibility and preliminary efficacy, parallel-arm, randomized controlled trial conducted via the University of Maryland School of Nursing. Recruitment will occur at the University of Maryland Medical System cancer centers, including the UMGCCC in Baltimore, Maryland; the Cancer Center at University of Maryland (UM) Shore Regional Health in Easton, Maryland; the Cancer Institute at UM St. Joseph Medical Center in Towson, Maryland; the Kaufman Cancer Center at UM Upper Chesapeake Health in Bel Air, Maryland; and the Tate Cancer Center at UM Baltimore Washington Medical Center in Glen Burnie, Maryland. We will recruit 54 cancer survivors at an expected recruitment rate of 3 to 5 participants per month for 12 to 18 months.

Study Procedures

Recruitment, Screening, and Baseline Data Collection

Potential participants will be identified using four methods: (1) screening medical records, (2) direct referral from providers (eg, nurses, nurse navigators, and physicians), (3) flyers, and (4) advertising via standard UMB networks (eg, ResearchMatch). After a potential participant has shown an initial interest in the study, the study team will review eligibility and send the consent form, which includes a detailed discussion of the study activities (see Multimedia Appendix 1 for a copy of the consent form). If the person volunteers to participate, study personnel can obtain informed consent in person or remotely via phone or videoconference and electronic remote consent.

To be eligible for the study, participants must (1) be aged ≥18 years; (2) have had a cancer diagnosis (any type); (3) soon complete treatment or have recently completed treatment (within the past 12 weeks) with chemotherapy, radiotherapy, or surgery with curative intent; (4) have received, plan to receive, or be open to receiving an SCP as per their provider; (5) have access to a device capable of running the POSTHOC app and Fitbit [Google LLC] app (eg, Android [Google LLC] or Apple [Apple, Inc] smartphone) and reliable internet access; (6) be able to read and understand English; and (7) be able to provide written informed consent. Participants must not have planned surgery, radiotherapy, or chemotherapy during the study period (hormonal and biological therapy is allowed). Digital literacy is an implicit *de facto* eligibility criterion.

Participation is voluntary, and all participants are free to withdraw from the study at any time for any reason. For example, if someone becomes ineligible for the study after they consent or if they have recurrence or a surgery planned while they are on study, they will not be withdrawn from the study unless their clinical care team feels that withdrawal is the most appropriate decision.

All study activities can be done remotely, and there is no essential face-to-face interaction between the study team and the participant (Figure 1). After consent, participants receive a Fitbit activity tracker (Charge 6) and orientation to use the tracker and POSTHOC app. The app and clinician portal are available through Charles River Analytics' SparkCare platform. The app is freely downloadable from the Apple Store (Apple Inc) or Google Play (Google LLC). Participants need a personalized invitation from someone on our research team to set up an account in SparkCare and access the POSTHOC app. Our study team will guide the participant through the download and setup of Gmail (if they do not already have an account, which is necessary for Fitbit), Fitbit, and POSTHOC (Figure 2A [30-32]), either in person, over the phone, or via videoconference.

In addition, during baseline, participants will complete an On-Study form that includes questions on demographics and clinical characteristics and baseline questionnaires (approximately 35-50 minutes) via REDCap (Research Electronic Data Capture; version 13.7.4; Vanderbilt University). Participants will wear the activity tracker for 7 days to assess physical activity and sleep. We will also conduct EMAs via the POSTHOC app for these 7 days, during which participants will be prompted to answer 5 questions 4 times per day; the default times will be 9 AM, 12:30 PM, 4 PM, and 7:30 PM but can be adjusted based on the participant's schedule and preferences (ideally begin 1 to 2 hours after waking; Figure 2C). These questions will capture key symptoms, such as distress, fatigue, pain, numbness and tingling, and interference of any symptoms with daily activity, on scales ranging from 0 (symptom not present) to 10 (as bad as you can imagine). Dietary intake data will be collected by a study team member using the Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool (National Cancer Institute) [33]. During the baseline week, all participants will have a "light" version of the POSTHOC app that has only initial data collection features, activity tracking and EMA data collection.

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Figure 1. Study schema. In this randomized controlled trial, participants will first consent and download the POSTHOC (POST-Treatment Health Outcomes of Cancer Survivors) and Fitbit apps. After baseline assessments, they will be randomized and be in the study phase for 12 weeks. Our team will contact all participants at least every 2 weeks, and assessments will occur at weeks 6 and 12. We will then conduct an exit interview to solicit qualitative feedback on the app and the study.

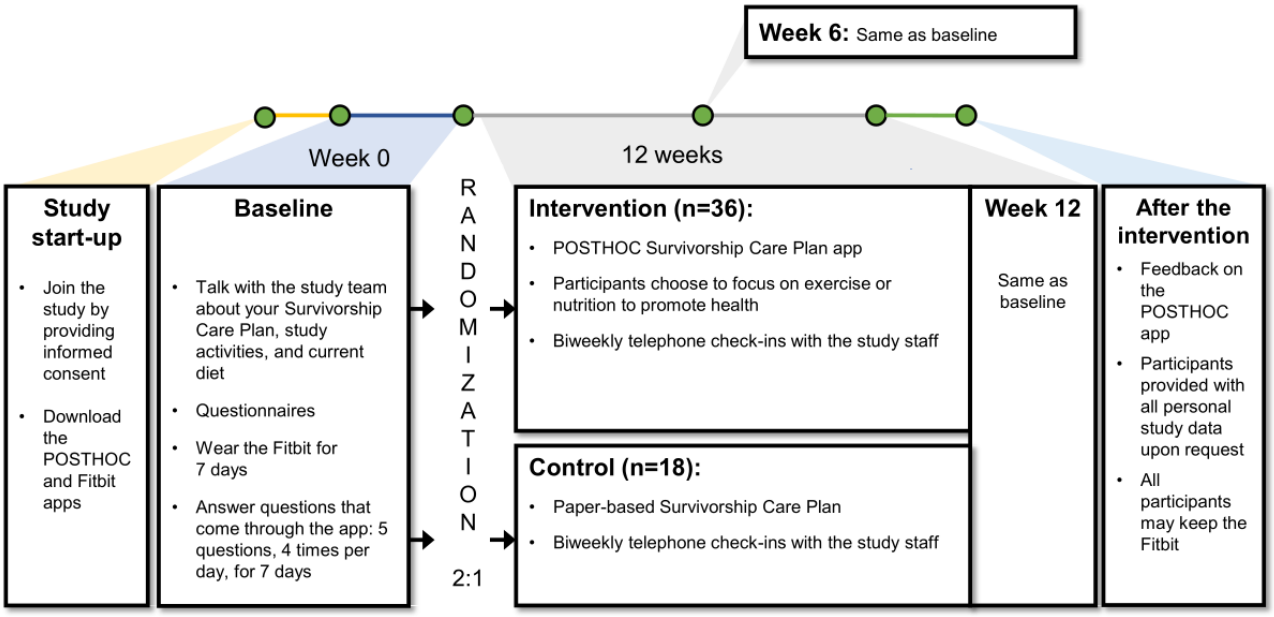

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Figure 2. Screenshots of the POSTHOC (POST-Treatment Health Outcomes of Cancer Survivors) app. (A) The home screen for participants randomized to the POSTHOC arm of the clinical trial. Here, participants see whether they have recorded any symptoms and any dietary data they have entered. Steps, minutes of moderate and vigorous exercise, and sleep data are pulled from the Fitbit app. A green check indicates whether the goal was met for the day. Participants may navigate to the survivorship care plan (SCP; "My Care Plan"), Settings (gear in the top right), Symptoms, and Nutrition from here. (B) The SCP is divided into 6 sections based on the American Society for Clinical Oncology (ASCO) template for SCPs, survivorship guidelines from the National Comprehensive Cancer Network, and the University of Maryland Medical System's SCP template. (C) Ecological momentary assessment (EMA) is administered 4 times per day for 7 days at baseline, week 6, and week 12. While the SCP will be manually entered into the POSTHOC app for this trial, it is an ultimate goal to interface the platform with the medical record so that the plan can be updated as a person's health and goals change.

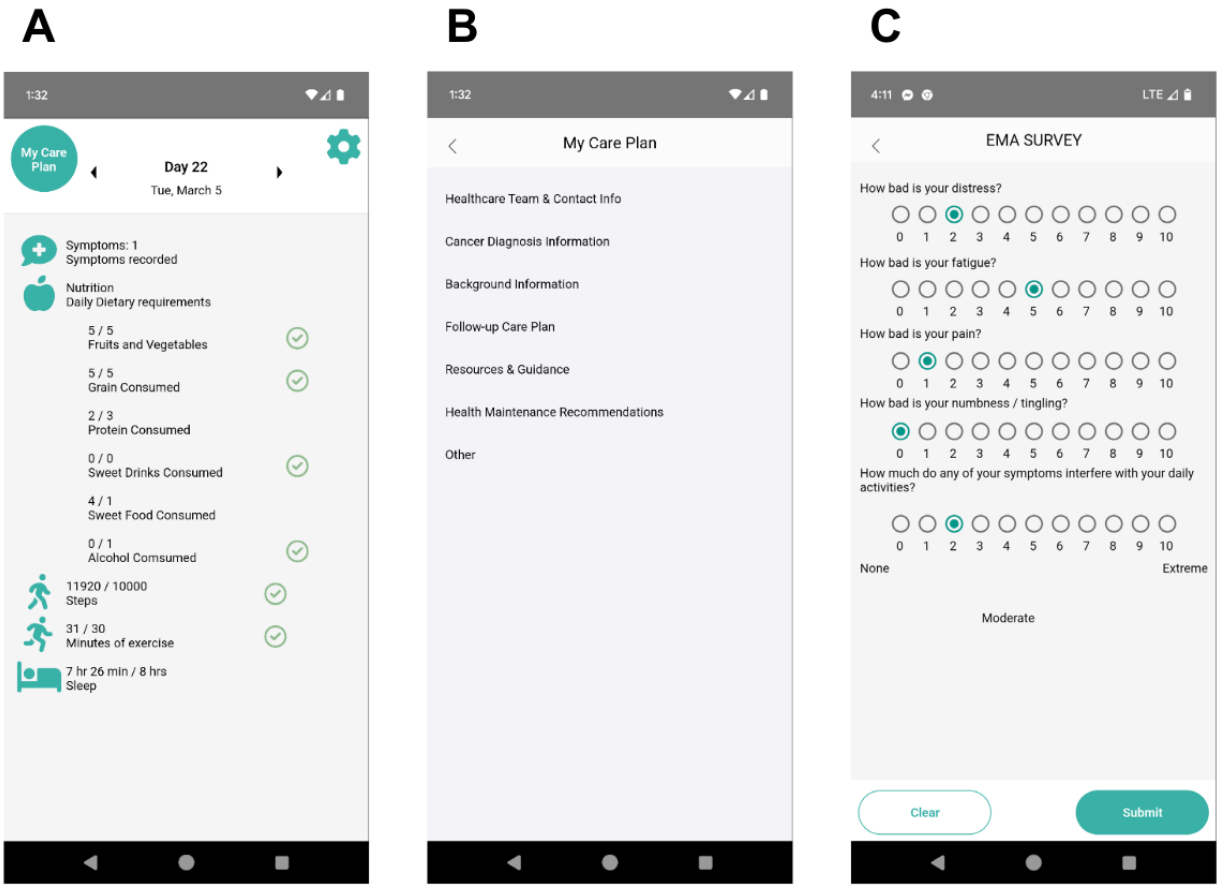

Randomization

We will use a computer-generated table with random blocks of 3 and 6 and stratify based on whether the participant had chemotherapy or not (yes or no) because symptoms and side effects of chemotherapy versus radiation tend to differ. The randomization table was generated by the statistician, SZ, and is stored in the REDCap database; allocation is concealed from the study staff who will be recruiting and randomizing the participants. After baseline data collection, participants will be randomized 2:1 to the POSTHOC app group (~36/54, 67%) versus the control group (18/54, 33%) in REDCap.

Delivery of the Intervention

If a participant is randomized to the intervention arm, a member of the study staff will switch them to the "intervention arm" in the clinician portal, and they will have full access to all the features of the app (Table 1). A trained member of the study team will enter data from the medical record into the SCP in the app (Figure 2B) and go over the SCP with them. The interventionalists will be trained and will use a checklist to ensure fidelity and prevent drift [34]. The participant will have a one-on-one meeting with an interventionalist and choose whether they want to prioritize nutrition or exercise as part of the study.

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Table 1. Comparison of tools available to the intervention and control groups through the POSTHOC[a] app.

Feature	Intervention	Control
Receive the SCP[b]	✓ (in the app)	✓ (on paper)
Ability to enter key symptoms during EMA[c]	✓	✓
Access to Fitbit	✓	✓
Access to the diet-tracking feature	✓	
Access to the comparison between their steps, minutes of moderate and vigorous exercise, dietary intake, and sleep time against the respective SCP guidelines	✓	
Location to log daily symptoms in the app	✓	

[a]POSTHOC: POST-Treatment Health Outcomes of Cancer Survivors.

[b]SCP: survivorship care plan.

[c]EMA: ecological momentary assessment.

Participants who choose to focus on exercise will be encouraged but not required to use their activity tracker during weeks 1 to 5 and 7 to 11 so that they can monitor their daily activity against their goals more easily. Over the course of the 12-week intervention, patients will gradually build up to goals laid out in the American College of Sports Medicine Physical Activity Guidelines for Cancer Survivors [35]. They will start at their baseline step level and increase their daily step goal by 5% to 10% each week (toward 10,000 steps per day, if possible). They will aim to complete 20 to 30 minutes of moderate-intensity aerobic exercise (40%-59% heart rate reserve) per day for a total of at least 150 minutes a week. They will also be encouraged to undergo stretching and resistance training for all major muscle groups 2 times a week, when possible.

Participants who choose to focus on nutrition will be encouraged to answer brief questions at the end of each day regarding their intake of fruits, vegetables, whole grains, and sweets to compare their eating habits to their goals in the POSTHOC app on a daily basis (Table S1 in Multimedia Appendix 2). Entry is possible for previous days if they forget to log. Goals will be based on the SCP guidelines, including working toward or maintaining a healthy BMI and consuming at least 5 servings of fruits and vegetables per day. Their goal will be to increase their adherence score for their nutrition goals, which will be determined through their questionnaire responses and the dietary assessment tool.

In the control arm, participants will keep the "light" version of the POSTHOC app that has minimal data collection features (Table 1). They will be told that they do not need to wear the activity tracker except for weeks 6 and 12. Participants will be provided with a digital (PDF) or paper-based version of the SCP, which they will go over with a trained member of the study team after randomization.

To match expectation effects across the 2 study arms, all participants will be told that we are testing a new app and that we are studying symptoms in early posttreatment survivorship. However, we will avoid the use of terms such as "control group" and "intervention group." We will emphasize the importance of all participants' data because we do not know much about the relationships between healthy lifestyle behaviors (eg, nutrition, physical activity, and sleep) and symptoms in early posttreatment survivorship.

For both arms, a member of the study team will call each participant approximately once every 2 weeks for the 12 weeks to encourage engagement; monitor adverse events; and, as appropriate, get feedback on the usability of the app (Table 2). At 6 and 12 weeks, the baseline assessments will be repeated, including the 35 to 50 minutes of questionnaires, wearing the activity tracker for 7 days, EMA for 7 days, and 24-hour dietary assessment. In total, we expect that participants will spend approximately 6 to 9 hours completing study activities over 14 weeks.

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Table 2. Data collection table.

Assessment or activity	Study goal	Assessment location	Baseline (week 0)	Intervention (weeks 1-12)	Week 6	Week 12	Postintervention (week 13)
Coordinators only							
Clinical Record Form	Demographics and clinical characteristics	REDCap[a]	✓				
Clinical Record Form	Health care utilization	REDCap			✓	✓	
Clinical Record Form	Clinician-reported patient health (ie, ECOG[b] performance status)	REDCap	✓			✓	
Participants							
On Study[c]	Demographics and clinical characteristics	Clinic or home (REDCap[d])	✓				
Acceptability[c] and usability[c] of the POSTHOC[e] app (intervention arm only)	Aim 1	Clinic or home (REDCap[d])			✓	✓	
MDASI[c,f]	Aim 2	Clinic or home (REDCap[d])	✓		✓	✓	
Activity tracker (Fitbit)	Aim 3	Home	✓		✓	✓	
24-hour dietary assessment	Aim 3	Home	✓		✓	✓	
GLTEQ[c,g]	Aim 3	Clinic or home (REDCap[d])	✓		✓	✓	
EMA[h]	Exploratory	Home	✓		✓	✓	
FACIT-F[c,i]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
ISI[c,j]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
CIPN-20[c,k]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
BPI[c,l]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
BFI[c,m]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
DT[c,n]	Exploratory	Clinic or home (REDCap[d])	✓		✓	✓	
HCCQ[c,o]	Exploratory	Clinic or home (REDCap[d])				✓	
Health care Utilization	Exploratory	Clinic or home via phone			✓	✓	
Telephone check-in (intervention and control)	Compliance booster and troubleshooting	Home		Biweekly for 12 weeks			
Exit interview	Exploratory	Clinic or home					✓[p]

[a]REDCap: Research Electronic Data Capture.

[b]ECOG: Eastern Cooperative Oncology Group.

[c]Questionnaire, as administered via a packet of questionnaires.

[d]If a participant prefers, they may complete paper-based versions of these assessments and return them to the study team in person or in a postage-paid envelope.

[e]POSTHOC: POST-Treatment Healthcare Outcomes for Cancer Survivors.

[f]MDASI: Monroe Dunaway Anderson Symptom Inventory.

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[g]GLTEQ: Godin Leisure-Time Questionnaire.

[h]EMA: ecological momentary assessment.

[i]FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue.

[j]ISI: Insomnia Severity Index.

[k]CIPN-20: Chemotherapy-Induced Peripheral Neuropathy–20.

[l]BPI: Brief Pain Inventory-Short Form.

[m]BFI: Brief Fatigue Inventory.

[n]DT: Distress Thermometer.

[o]HCCQ: Health Care Climate Questionnaire.

[p]The exit interview will be conducted earlier than week 13 if the participant withdraws early.

The POSTHOC App

The POSTHOC app was designed by Charles River Analytics specifically for this project (screenshots in Figure 2). It was designed to run on both Android (Google LLC) and iOS (Apple, Inc) devices, which account for >90% of all smartphones in the United States [36]. A dedicated team of developers will make periodic updates to the app and to the backend server to comply with updates released by Android and Apple. The trial opened in March 2024 with version 1.1.11, and as of July 2024, the recent version was 1.1.13. Updates were made to increase the speed at which the app syncs with Fitbit and opens for the user.

The app was designed to (1) store information from the SCP, including information about diagnosis, treatments, and future plans and (2) collect data regarding ongoing health status, as it pertains to the SCP (eg, nutrition, physical activity, sleep habits, and symptoms). Data will be collected through a combination of manual entry and automatic collection by the Fitbit activity tracker that we will provide. All data collected by the POSTHOC app (ie, physical activity, diet, and EMA data) will be stored on a Health Insurance Portability and Accountability Act (HIPAA)–compliant server at UMB.

Outcome Measures

Physical Activity, Diet, and Symptoms

Physical activity and sleep will be measured via a Fitbit Charge 6, which will be given at no cost to the participants. They will be asked to wear the Fitbit for 7 days during weeks 0 (baseline), 6, and 12. Dietary intake will be assessed using the ASA24 Dietary Assessment Tool [33]. The ASA24 Dietary Assessment Tool is a freely available web-based tool used for epidemiologic, interventional, behavioral, or clinical research that enables multiple automatically coded 24-hour dietary recalls. It will be administered by a licensed dietitian or registered nurse in person, via telephone, or via videoconference and takes approximately 30 to 45 minutes.

EMA will be collected via the POSTHOC app 4 times throughout the day for 7 days at weeks 0, 6, and 12. The app will alert the participant to report the severity of 4 common symptoms, namely pain, distress, fatigue, numbness or tingling, and the interference of symptoms with daily activity on a scale of 0 to 10. While research studies have shown success with this type of data collection [37], participants will have the option to "turn off notifications" if they are too burdensome. The POSTHOC app does not have any notifications other than those for the EMAs.

Questionnaires

Questionnaires will be administered via REDCap [38] or on paper, and then the responses will be manually entered into REDCap at weeks 0, 6, and 12 (Textbox 1). There are 15 questionnaires; 13 are self-administered, and 2 are researcher-administered. The On Study form will be completed at baseline only, questionnaires on Health Care Utilization and the Acceptability and Usability of the app will be administered during a routine check-in call at weeks 6 and 12 only, the Health Care Climate Questionnaire will be administered at 12 weeks only, the questionnaire on Acceptability and Usability will be administered to the intervention group only, and the 11 other questionnaires will be completed at baseline, week 6, and week 12 (Table 2). They should take approximately 35 to 40 minutes in total to complete.

Responses to questionnaires (eg, On Study), as well as the Clinical Record Form, will be collected via REDCap and, therefore, will be stored on UMB servers. Charles River Analytics will not have access to any of the data collected in this study.

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Textbox 1. Questionnaires to be administered.

Questionnaires

1. On Study: this form contains questions on demographics; clinical characteristics; and how much participants think the app, exercise, and healthy eating could help reduce any symptoms they are experiencing. This is a custom questionnaire that should take 5 to 10 minutes to complete.
2. MD Anderson Symptom Inventory (MDASI) [39-41]: the 13-item MDASI is a patient-reported multisymptom outcome assessment scale that assesses the severity of symptoms experienced by patients with cancer and how much the symptoms interfere with daily living (eg, walking, activity, working, housework, relations with other people, enjoyment of life, and mood). The assessment takes ≤5 minutes to complete. The Cronbach α reliability ranges from 0.82 to 0.94. The sum of the 13 items will be used as the primary aim herein.
3. Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) [42]: the FACIT-F is a 40-item, validated, self-administered, and commonly used measure of fatigue and quality of life over the last 7 days with 5 subscales, namely physical well-being, social well-being, emotional well-being, functional well-being, and fatigue. A higher score indicates a higher quality of life. The assessment takes 10 to 15 minutes to complete. The Cronbach α reliability is 0.96.
4. Brief Fatigue Inventory (BFI [43]): the BFI is a 10-item, validated, self-administered, and commonly used measure that captures 24-hour fatigue and includes 6 single-item questions regarding how fatigue has interfered with general activity, mood, work, etc. The assessment takes ≤5 minutes to complete. The Cronbach α reliability ranges from 0.82 to 0.97.
5. Brief Pain Inventory–Short Form (BPI-SF) [44]: the BPI is a self-administered, validated measure of pain severity at its least, worst, and average in the last 24 hours from 1 to 10. It enquires about pain right now; medications taken for pain; and how the pain has interfered with general activity, mood, walking, work, relations with other people, sleep, and the enjoyment of life. The assessment takes ≤5 minutes to complete. The Cronbach α reliability ranges from 0.77 to 0.91.
6. Insomnia Severity Index (ISI) [45,46]: the ISI is a validated self-administered 7-item questionnaire that assesses sleep quality based on difficulties falling asleep, staying asleep, and waking up too early; satisfaction with sleep pattern; how noticeable any sleep problem is to others; worry about sleep problems; and interference of sleep problems with daily functioning. The assessment takes ≤5 minutes to complete. The Cronbach α reliability is 0.79.
7. Godin Leisure-Time Exercise Questionnaire (GLTEQ) [47]: the GLTEQ is a 3-item self-administered questionnaire that measures the frequency of strenuous (eg, running, hockey, vigorous swimming, roller-skating, and judo), moderate (eg, fast walking, easy swimming, easy bicycling, volleyball, and badminton), and mild or light (eg, yoga, fishing from the river bank, easy walking, and bowling) leisure-time physical activity performed for periods of ≥15 minutes over a usual week, with resulting scores interpreted as active, moderately active, or insufficiently active or sedentary.
8. Chemotherapy-Induced Peripheral Neuropathy-20 (CIPN-20) [48]: the CIPN-20 is a 20-item self-administered quality-of-life questionnaire to elicit patients' experience of symptoms and functional limitations related to numbness, tingling, and other symptoms of chemotherapy-induced peripheral neuropathy and is recommended by a National Cancer Institute (NCI) task force [49]. The Cronbach α reliability ranges from 0.73 to 0.88.
9. Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) [50]: the FACT-Cog is a 37-item self-assessment scale validated in routine clinical practice to assess chemotherapy-induced cognitive impairment in adults with cancer. The assessment takes 10 to 15 minutes to complete. The Cronbach α reliability ranges from 0.58 to 0.63.
10. Hospital Anxiety and Depression Scale (HADS) [51]: the HADS is a 14-item self-reported questionnaire that comprises 7 questions for depression and 7 questions for anxiety and takes 2 to 5 minutes to complete. The Cronbach α reliability is 0.78 for the anxiety subscale and 0.86 for the depression subscale.
11. Distress Thermometer (DT) [52]: the DT is a common self-reported rapid screening tool that uses a rating scale ranging from 0 (no distress) to 10 (extreme distress) and was developed to assess psychological distress in people affected by cancer. The assessment takes approximately 2 to 3 minutes to complete.
12. Health Care Climate Questionnaire (HCCQ) [53] (modified; 12 weeks only): we modified the HCCQ to probe communication regarding healthy lifestyle behaviors (eg, Your doctor encouraged you to ask questions about healthy lifestyle behaviors). This questionnaire includes 6 questions, each with response options ranging from 1 (strongly disagree) to 5 (strongly agree); the total score ranges from 6 to 30, with 6 indicating the lowest satisfaction with patient-provider communication and 30 indicating the highest satisfaction.
13. Health Care Utilization survey (6 and 12 weeks only): here, we will inquire about any medical appointments (scheduled or unscheduled), hospitalizations, out-of-pocket health care expenses, and whether any of the events were cancer related.
14. Acceptability survey (6 weeks and postintervention interview only): we will ask 6 questions to gather feedback about how much the participant liked the app, what features they enjoy or do not use, and whether they would recommend the app to others.
15. System Usability Scale (SUS) [54,55] (6 weeks and postintervention interview only): the SUS is a simple questionnaire designed to assess the usability of a particular device or product on a Likert scale of 1 (strongly agree with the statement) to 5 (strongly disagree with the statement).

Exit Interview

After the completion of the study (or earlier if a participant withdraws early from the study), a member of the study team will conduct an exit interview to understand the participants' experience of being in the study. We will ask them whether they think the app was helpful for alleviating their symptoms and improving their health behaviors. We will ask them what they liked about the study, what they did not like about it, what features they liked or did not like about the POSTHOC app (for those in the intervention arm), whether they would recommend the study to others, etc. To get more information regarding

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patient-provider communication, we will ask about the number and quality of conversations regarding physical activity and diet between a patient and their provider or providers, as well as questions to understand patients' preferences and expectations in regard to where (eg, clinic or home), when, how often, and with whom (eg, primary care physician or oncologist) patient-provider communication regarding lifestyle behaviors should take place. This semistructured interview will use qualitative methods and will last approximately 30 minutes [56]. It will be audio recorded with explicit permission at the time of the interview and then transcribed for qualitative and mixed methods data analyses.

For qualitative analysis, we will use the qualitative descriptive approach [57]. This approach solicits information from those experiencing the phenomenon under investigation, that is, the use of the POSTHOC app in early posttreatment cancer survivorship. We will analyze data from both the POSTHOC group and the control group, although the control group will not be asked some questions that are specific to the app. Our analysis will involve a deductive approach, where codes will be based on the questions in the exit interview. In addition, we will use a secondary inductive approach to capture themes in the data on which questions were not originally included in the interview guide [58,59]. With an iterative process, at least 2 independent coders will review all the transcripts and use deductive coding in response to questions asked about specific elements of the POSTHOC app, the study, etc, as well as open coding to inductively identify emergent themes. All reviewers will then convene with the study chair to discuss codes and subcodes, standardize them, and then generate a codebook. Coders will examine the transcripts a second time, and then, the team will reconvene and refine the codes as appropriate. Coding will then be completed. The total number of times a code was used, as well as the relative proportion of participants who had a quote that fit into each code, will be quantified and compared, and differences will be reconciled through discussion.

Adherence

We will measure adherence to the intervention, retention, requests for data entry, and adherence to the goals of the intervention in relation to what is laid out in the SCP. Retention will be measured based on how many participants complete week-12 questionnaires; we predict that we will have ≥85% retention. Adherence to the study requests will be monitored as the percentage of data points received version requested, which will be different for those in the POSTHOC arm versus the usual care arm and for those in the nutrition group versus exercise group within the POSTHOC arm. We predict that we will have lower response rates in the groups that are asked to contribute more (ie, in terms of daily nutrition entries). Nutrition adherence will be measured with an adherence score calculated at week 6 and week 12 based on participant responses to brief questions asked at the end of each day regarding their intake of fruits, vegetables, whole grains, and sweets. Their score will be compared to goals in the SCP. For those who choose to emphasize exercise, actual physical activity from Fitbit will be compared to physical activity goals outlined by the SCP.

Medical Records

The Clinical Record Form will be completed by the study staff at baseline. It contains questions on demographics, height, weight, current menopausal status, Karnofsky performance status or Eastern Cooperative Oncology Group performance status, comorbidities (eg, hypertension and diabetes), cancer type, cancer stage, surgical procedures, types and doses of treatments (eg, chemotherapy type and dosing, hormone therapy, and radiotherapy regimen), most recent blood work (eg, hemoglobin, hematocrit, and lymphocytes), other medications, and medical history (eg, prior myocardial infarction).

At weeks 6 and 12, a member of the study team will record Health Care Utilization, including the number of unplanned medical encounters such as emergency department, urgent care, oncologist, and primary care visits over the previous 6 weeks (approximately 1 and a half months). At week 12, we will note the provider-rated Eastern Cooperative Oncology Group status (or equivalent).

Statistical Analysis

Data Handling

We will capture patient-reported data electronically using the POSTHOC app and REDCap [38]. Data from the POSTHOC app will be viewable on the clinician portal and exportable to a CSV file; REDCap data will also be exportable to a CSV file. Study data will be deidentified for analysis. We will audit our database and visually inspect all data (eg, Q-Q plots, boxplots, and scatter plots). These inspections will include histograms of various outcome variables as well as plots of means and fitted regression curves. If distributional assumptions are not met (eg, normality of residuals), we will use transformations or nonparametric methods [60]. We will assess outliers to determine whether they are erroneous. If they are valid, we will conduct sensitivity analyses with and without outliers.

We will facilitate the completion of all measures. The reasons for missing data will be tabulated according to the treatment group (via interview, if possible), and participants who dropped out will be compared with those who completed the study with regard to demographic and disease characteristics. The mechanism of missing data will be assessed to select an appropriate statistical method [61-63]. Specifically, if the data appear to be missing at random, we will use multiple imputation or the maximum likelihood method to obtain unbiased estimates of key statistics. If the data are suspected to be missing not at random, a sensitivity analysis using selection and pattern mixture models will be run to determine the impact on results. If the estimates are similar to the ones obtained from the simpler analysis of only complete cases, we will report the complete-case analysis results.

Sample Size

Power calculations were based on data from a prior single-arm pilot study that we conducted among a similar group of cancer survivors (National Institutes of Health project 75N91019C00026). Results from this analysis of covariance suggested a pre-post correlation of 0.65 [64]. With 2-tailed α=.15 [49], a sample size of 46 (after 15% missing data and a

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2:1 ratio of sample in arms) would provide 80% power to detect a standardized between-arm difference of 0.50, which corresponds to a medium-sized and clinically meaningful effect [65]. Preliminary data generated from another previous study of ours among cancer survivors [66] suggested an SD of cumulative symptom burden from a similar symptom inventory of 17.0. On the basis of the estimated effect size for this study, 0.50, we expect that the average cumulative symptom burden will decrease by 8.5 points more in the POSTHOC group than in the control group from baseline to 12 weeks.

Primary Outcome

The primary outcome is the feasibility of the POSTHOC app, which will be determined by calculating the percentage of patients with cancer in the POSTHOC group that used the app at least 3 times per week. We hypothesize that at least 75% (≥27/36) of patients will view or log data in the app at least 3 times per week at weeks 6 and 12.

Statistical Analysis for Aims

The statistician cannot be blinded due to the 2:1 randomization scheme.

Aim 1 assesses feasibility, acceptability, and usability. For feasibility, we will calculate the percentage of patients who used the POSTHOC app at least 3 times per week, as explained earlier. For acceptability, at weeks 6 and 12, we will estimate the percentage of patients who (1) found the app useful (≥4 on a scale of 1 to 7), (2) would recommend it to others (≥4 on a scale of 1 to 7), and (3) would use the app in the future (at least monthly). For usability, we will calculate summary statistics based on an overall usability score from the System Usability Scale (score range 0-100) [54]. A score of 68 (12.5) is considered average, with >68 points considered “above average” and <68 “below average” [55]; these values are relevant to digital health apps [67]. We will review the qualitative data within the acceptability or usability questionnaires and those collected during interviews to identify general themes related to specific design features that participants liked or that make the app challenging to use or understand.

Aim 2 assesses the effects of the intervention versus control on cumulative symptom burden. Our data from aim 2 will provide estimated effect sizes to inform the sample size of a confirmatory phase III randomized controlled trial, per clinical trial guidelines [68]. Cumulative symptom burden will be calculated as the sum of the individual severity levels from the 13 core symptoms from the MD Anderson Symptom Inventory (total symptom burden ranging from 0 to 130) [39,40]. We will use linear mixed modeling [69] with total symptom burden at week 6 as the primary symptom outcome, study arm (POSTHOC app vs usual care arm) as the main independent variable, and total symptom burden at week 0 as a covariate. In the case of a substantial imbalance in other factors between arms at baseline (eg, age), we might include additional covariates in the model. We chose week 6 as the primary time point because preliminary data from our group show greater benefits of behavioral interventions earlier into the interventions rather than later (IR Kleckner, unpublished data, August 2024; and Kleckner et al [70]). We will use the intent-to-treat principle and include each participant in the arm to which they were assigned, regardless of the use of the app for those assigned to the POSTHOC arm. We will also assess the effects of the intervention versus usual care at week 12 as an exploratory aim.

Aim 3 will evaluate the effects of the intervention on physical activity (steps and time engaged in moderate and vigorous physical activity) and nutrition (ASA24 scores and daily habits). Similar linear mixed models will evaluate the effects of the POSTHOC app versus usual care on other outcomes at week 6 and week 12. To evaluate the longitudinal trajectory of each outcome, we will use repeated measures linear mixed models incorporating the specific outcome at all 3 time points and using a linear contrast to test the effects of study arm.

Exploratory outcome analyses will include a test of mediation and moderation effects of the POSTHOC app by physical activity adherence, sex, age, etc on outcomes [71-73].

Results

This project was funded by the National Cancer Institute in September 2021. Approval from the Institutional Review Board at the UMB was obtained on February 21, 2024, and the trial was opened to accrual on March 1, 2024. As of July 3, 2024, a total of 20 participants have been enrolled. We expect to complete enrollment in fall 2024, complete data collection in winter 2025, and publish the results in winter 2026.

Discussion

Expected and Predicted Results

In regard to our first hypothesis that the POSTHOC app is feasible, acceptable, and useful for cancer survivors, we predict that at least 75% (≥27/36) of participants in the POSTHOC arm will view or log data in the app at least 3 times per week. We also predict that at least 75% (≥27/36) of patients will enjoy using the app (Likert rating of >3 out of 5) and will recommend it to other patients (yes or no) at weeks 6 and 12. We further expect that participants will find the app useful overall but will suggest areas for improvement. In regard to our second hypothesis that POSTHOC will reduce the cumulative symptom burden reported by patients compared to usual care, we predict that the sum of the 13-item MD Anderson Symptom Inventory will be at least 8.5 points lower for patients in the POSTHOC arm than for patients in the usual care arm. Finally, in regard to our third hypothesis that the POSTHOC app will improve health behaviors compared to usual care, we predict that patients in the POSTHOC arm who choose to focus on exercise will complete at least 500 more steps per day than patients in the usual care arm (but hopefully at least 1000 to 2000 steps more per day than controls), based on our prior studies of exercise in patients with cancer [74]. We predict that these extra daily steps will correspond to an extra 10 to 20 minutes per day of moderate physical activity; thus, more patients in the POSTHOC group will meet the American College of Sports Medicine Physical Activity Guidelines for Cancer Survivors [35] than patients in the control group. For participants who choose to focus on nutrition, we predict that they will have a higher adherence to the nutrition goals laid out in their SCP than participants in the

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control group based on data from the 24-hour dietary assessment. We will also explore whether those in the POSTHOC arm who focused on exercise adhered to the nutrition goals laid out in the SCP compared to those in the control arm and compared to those who chose to focus on nutrition.

Integration of This Project Into Prior Literature

The growing population of cancer survivors must cope with symptoms of the disease and side effects of treatment, and current SCPs are not enough to ensure timely symptom identification and adherence to recommendations in the SCPs [8]. They are burdensome, complex, and not easily accessible. Despite increasing interest in mHealth interventions to enhance overall wellness (eg, Fitbit and MyFitnessPal [MyFitnessPal, Inc]) and the development of apps to store the SCP (eg, the studies by Baseman et al [20], Preussler et al [21], and Denzen et al [22]), no platform has capitalized on the potential of mHealth to combine the SCP with healthy behavior monitoring. This protocol describes a randomized controlled trial to evaluate the feasibility, usability, and preliminary efficacy of a new mobile SCP app that interfaces with Fitbit, POSTHOC, versus a traditional paper-based SCP in terms of total symptom burden in the early posttreatment period in addition to its ability to promote healthy lifestyle behaviors and patient-provider communication.

Charles River Analytics completed a phase I project to launch the development of an app called POSTHOC to digitize the SCPs. Specifically, the team conducted targeted interviews with survivors, clinicians, and researchers to understand how providers track symptoms of cancer with their current tools, including the SCP, and what features could be added to the existing tools and workflows to streamline care. Accordingly, the POSTHOC app was designed to go beyond routine plans to deliver an updatable SCP, collect data regarding ongoing health status, and promote healthy lifestyle behaviors. The success of the phase I of the project enabled us to build upon the platform in phase II, which involves the testing of the app in a clinical population regarding feasibility, usability, and preliminary efficacy in reducing symptom burden.

Prior studies with digital SCPs have not used a care plan–specific mobile app, have been underpowered to detect changes in physical activity patterns, or have tended to focus exclusively on exercise interventions rather than nutrition and exercise interventions [20-22,75,76]. If successful, this study will contribute to the user-centered design of a platform for a digital SCP. In addition, it can assist cancer survivors with engaging in healthy behaviors and facilitate communication between the survivor and the person's clinical care team, including their primary care physician. This study will provide evidence about the effects of the self-management of health on health care use, cancer symptoms, and treatment side effects. This knowledge will be integral to later, larger randomized controlled studies; integration with the electronic medical record; and nationwide or worldwide implementation.

Clinical Implications

In the near future, the POSTHOC app could help advance the management of post–cancer treatment symptoms with nutrition and exercise interventions. We foresee 3 key benefits to the integration of the POSTHOC app into the clinical workflow. First, the app will be able to gather personalized health information outside the clinic's walls and provide on-demand, real-time feedback to survivors. A future goal is for the app to be able to interface with medical records to facilitate conversation about health-promoting behaviors between the patient and the clinical care team. These personalized health data permit providers to keep track of emerging symptom patterns and adherence to the SCP and provide support tools as they seek to promote healthy behaviors. Second, the app will provide information and tools to health providers in an easy-to-use format, giving health care professionals unprecedented access to survivor data to guide patient-provider communication and clinical decision-making, including oncologists, primary care physicians, and physical therapists, as we have suggested for treating chemotherapy-induced neuropathy [77]. Finally, the app will securely handle personalized health information to promote accessibility while maintaining interoperability with hospital information technology. This increases provider efficiency while maintaining the focus on survivor needs.

It is the ultimate goal for the POSTHOC app to be available to anyone with an Apple or Android smartphone. While the features of the app would remain the same between real-world and research settings, there would be one main difference in the setup: the research team is currently manually entering the SCP into the app for the participant. In the real world, the clinical care team should not be burdened with entering the SCP into a separate app, but the goal would be for the app to interface with the electronic medical record so that the app can automatically fetch the SCP and continuously update as the user's health status and goals change.

Potential Problems and Solutions

We are prepared to address potential problems that may arise during the implementation of the study. During the recruitment phase, we may have trouble recruiting participants. We will then widen our eligibility criteria and use different advertising strategies, including forming closer relationships with oncologists and advanced practice providers, spending more time with patients in clinics, and advertising among cancer support groups. In the intervention phase, participants may have difficulty understanding the user interface and using the app. We will do our best to provide comprehensive guidelines for use. If necessary, we will offer more opportunities for in-person instructions and weekly tutorials with study team members. In addition, participants may not use the app and answer survey questions regularly. To encourage participants to actively engage with the app whenever possible, we will plan consistent check-ins with study team members. If technical issues arise, a support team from Charles River Analytics get on call to push updates wirelessly and address technological concerns.

Strengths and Limitations

This study has several strengths. First, we expect this study to include a diverse sample of participants and have high generalizability to cancer survivors in the United States. In the UMGCCC catchment area, approximately 30% of people

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identify as Black or African American, compared to 13% of Americans across the United States, and we expect our cohort to reflect our catchment area. Moreover, we will recruit from the cancer center in downtown Baltimore, Maryland, as well as from affiliated community oncology clinics in suburban and rural areas. Second, this study uses EMA and ultrahigh-frequency sampling, with data collected daily during the morning, early afternoon, later afternoon, and evening. The results may offer insights into the interplay of exercise, symptom burden, and circadian effects. They can also be applied to make inferences regarding causality on a small-time scale (ie, throughout the day and day to day). Past studies have either been underpowered to detect daily changes in physical activity or used lower-frequency sampling, asking participants to respond to 1 or 2 daily messages or a set number of prompts within a designated period [75,76]. Third, this study offers both nutrition and physical activity options. Prior studies have tended to focus exclusively on exercise rather than nutrition and exercise interventions and have not offered participants the option to focus on either exercise or nutrition.

This study also has limitations. First, this is a phase II feasibility and preliminary efficacy study (n=54), and the results should be tested for replication and validation before being implemented into guidelines. Nevertheless, we expect that this work will help lay the groundwork for larger studies to test similar hypotheses. Second, this study includes a usual care control instead of an active control. However, in this context, including a usual care control allows for the most direct evaluation of a mHealth-delivered behavioral intervention in comparison to an mHealth diet and activity tracker. Third, this study collects information primarily from patient-reported outcomes, with no clinical assessments of signs (eg, blood-based biomarkers). However, the data collection methods include digital measures of diet, activity, and sleep, which allow for objective assessments of physical health. Fourth, bias may be introduced into this study in that only people who are comfortable enough with technology to beta-test an app will enroll. Those who enroll and are less comfortable with technology might be more likely to remain in the study if they are in the control group than if they are in the POSTHOC group, but dropout rates should not affect our primary outcome (feasibility, acceptability, and usability, analyzing only data from the POSTHOC arm) or symptom data in aim 2. While we might have POSTHOC participants who do not use the app (nonadherence), it will not be possible for control participants to use the app (contamination) because we have control over what features all the participants can see. Nonadherence will lead to more conservative effect size estimates of the effect of the intervention on symptom burden. Our analyses will be a step toward understanding how we can digitize the SCP into a mobile app to help improve outcomes for posttreatment cancer survivors.

Future Work

Future initiatives will work to optimize the reach and usefulness of the POSTHOC app, as well as the design and logistics of clinical trials to test the app's efficacy in alleviating symptom burden. For example, we are working toward allowing the POSTHOC app to interface with the electronic medical record to facilitate conversations about lifestyle behaviors between the patient and the clinical care team. We will also incorporate feedback from participants and clinicians to improve the features of the app to maximize its usability and usefulness for survivors, their caregivers, and their clinical care team.

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Data Availability

The source codes of the POSTHOC (POST-Treatment Healthcare Outcomes for Cancer Survivors) app and SparkCare server are owned by Charles River Analytics and are confidential and proprietary under NIH SBIR 75N91021C00019. Researchers who would like to replicate, build upon, or collaborate on research involving these systems are encouraged to reach out to Charles River Analytics [78]. Deidentified data collected as part of the clinical trial may be shared with a data use agreement with the University of Maryland Baltimore upon reasonable request to the corresponding author, ASK.

Conflicts of Interest

ATW and NMM are employed by Charles River Analytics. All other authors declare no other conflicts of interest.

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Multimedia Appendix 1
Consent form.
[PDF File (Adobe PDF File), 525 KB - resprot_v13i1e59222_app1.pdf]

Multimedia Appendix 2
Supplementary material on the consent process, privacy, confidentiality, and the daily nutrition questions.
[DOCX File , 17 KB - resprot_v13i1e59222_app2.docx]

Multimedia Appendix 3
CONSORT-eHEALTH submission form.
[PDF File (Adobe PDF File), 1205 KB - resprot_v13i1e59222_app3.pdf]

Multimedia Appendix 4
Peer-review from Small Business Innovation Research (SBIR) - National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) Proposals (USA).
[PDF File (Adobe PDF File), 355 KB - resprot_v13i1e59222_app4.pdf]

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Abbreviations

ASA24: Automated Self-Administered 24-hour
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act

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INSPIRE: Internet Survivorship Program with Information and Resources
mHealth: mobile health
POSTHOC: POST-Treatment Health Outcomes of Cancer Survivors
REDCap: Research Electronic Data Capture
SCP: survivorship care plan
UM: University of Maryland
UMB: University of Maryland Baltimore
UMGCCC: University of Maryland Greenebaum Comprehensive Cancer Center

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Protocol

Serious Gaming for Chemotherapy-Induced Nausea and Vomiting in Older Adults With Cancer: Protocol for a Randomized Clinical Trial

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Abstract

Background: Older adults are at high risk for toxicity due to cancer treatment and increased risk for adverse events related to chemotherapy-induced nausea and vomiting (CINV). Unfortunately, older adults report multiple treatment-related symptoms but use few strategies to self-manage these symptoms due to erroneous beliefs related to the effectiveness of commonly taught self-management strategies. We developed a novel serious game, Managing at Home (MAH), to help older adults learn how to effectively self-manage CINV at home.

Objective: This study has 2 aims. Aim 1 is to examine changes in CINV severity, self-management behaviors, functioning, quality of life, cognitive representation, and health care use within the intervention group from baseline (T_1) to completion of the study (T_6). Aim 2 is to determine the efficacy of the MAH intervention by comparing differences in primary outcomes (CINV severity and health care use) and secondary outcomes (self-management behaviors, functioning, and quality of life) between the intervention and control groups at each follow-up visit (T_2-T_6) and completion of the study (T_6).

Methods: This is a longitudinal randomized clinical trial. We will collect data from 500 older adults receiving cancer-related chemotherapy at baseline (T1) and at each treatment cycle until cycle 6 (T6). Participants will be enrolled if they are 60 years or older of age, are newly diagnosed with cancer, being treated with any chemotherapy agent with moderate or high emetic potential, are on a 2-, 3-, or 4-week treatment cycle, are proficient in English, and have a telephone. Previous diagnosis or treatment for cancer, end-stage disease with less than 6 months to live, and uncorrected visual or hearing impairment are exclusion criteria.

Results: This study was funded in September 2022 and received institutional review board approval in October 2022. As of July 2023, the enrollment of participants is ongoing and currently has 130 enrolled participants. Data collection and analysis will be complete in 2027.

Conclusions: This study addresses self-management of CINV in older adults using an innovative serious game. The MAH intervention uses simulation and gaming technology to engage older adults in active learning in order to reframe erroneous perceptions about symptom self-management. If shown to be effective, it can easily be adapted to include other cancer-related symptoms or other chronic illnesses.

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International Registered Report Identifier (IRRID): DERR1-10.2196/64673

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KEYWORDS

chemotherapy-induced nausea and vomiting; aged; serious game; symptom self-management; mobile phone; neoplasms; self-care

Introduction

Background

Older adults (≥65 years) represent about 15% (46 million) of the US population, and the rate is expected to double (90 million) by 2050 [1-3]. They also represent 55% of all cancer diagnoses [2,4]. With an aging population, the number of older adults with cancer will also increase, taxing limited health care resources. Despite advances in antiemetic therapy, older adults diagnosed with cancer experience chemotherapy-induced nausea and vomiting (CINV) [5]. Although older adults are less likely to have CINV symptoms, they are more likely to experience serious consequences (eg, dehydration and renal impairment) than younger adults [6-8] due to the presence of multiple comorbidities, compromised organ function, frailty, and decreased overall functioning [9-11]. CINV occurs in up to 80% of adults receiving chemotherapy [12,13] and can lead to metabolic and nutritional issues (eg, loss of appetite, weight loss, and malnutrition), decrease in self-care and functioning, decline in physical and mental status, and poor quality of life (QOL) [12]. Up to 47% of adults receiving moderate to high emetogenic chemotherapy will experience a hospital admission (HA) related to CINV [14,15] and ~20% will have an unplanned emergency department (ED) visit [16]. The Centers for Medicare and Medicaid Services [17] urge improving care and reducing unplanned ED visits in those receiving cancer treatment. Therefore, interventions are needed to decrease CINV symptoms, improve functioning and QOL among older adults, and reduce health care use due to poor CINV symptom self-management.

Despite clinical guidelines for managing CINV, ~49% of adults with cancer are undertreated for CINV [13,18], and prevention of CINV remains a challenge [5]. Risk factors for undertreatment include the type of chemotherapy, being treated in the outpatient clinic, and out-of-pocket costs for antiemetics [18]. Health care practitioners report that managing breakthrough nausea within the first 5 days after chemotherapy is a common occurrence, while managing delayed CINV is the most challenging [19]. About 32% of practitioners report the need to stop or delay cancer treatment in patients due to CINV [19].

While the above risk factors for CINV are beyond the scope of this study and control of patients with cancer, there are many pharmacologic and nonpharmacologic strategies that older adults can use to prevent or self-manage CINV and minimize negative effects. Older adults diagnosed with cancer experience multiple side effects from chemotherapy treatment, yet do very little to manage those side effects [20,21]. In general, older adults modify their lives to reduce the severity of side effects rather than engaging in active self-management of those side effects [22-25]. Older adults are slower to take action against symptoms than younger adults [26], tend to minimize symptoms and their consequences [27-29], and normalize and interpret symptoms as part of aging, leading them to delay seeking or starting treatment [26,30]. They also delay treatment due to being uncertain about the symptom's severity or seriousness and believing that treatment or management is not possible [28]. Some older adults believe that side effects have to be endured as part of their cancer treatment [31,32]. However, those who believe they can manage their symptoms engage in self-management strategies [33]. Interventions, such as the Managing at Home (MAH)-CINV [34], which specifically address older adults' erroneous symptom beliefs and encourage them to engage in preventative and self-management behaviors may be able to alter their responses to side effects due to cancer treatment [35].

Printed standard patient education material for CINV based on well-known treatment and prevention guidelines (Textbox 1) are routinely provided to new patients and their family members so they can self-manage CINV at home. However, there is very little research related to how older adults self-manage side effects at home during chemotherapy treatment. Prior research by this team shows that without additional educational intervention, only ~25% of older adults who experience nausea actively manage it with medication [21]. Instead, they prefer to modify their activities or use dietary strategies to manage their nausea [21]. However, we found that with additional technology-based education and intervention and a change to their erroneous symptom beliefs, preventative and self-management strategies improve overall with twice as many older adults engaging in CINV prevention activities compared to a control group [34]. Results from our pilot study using the MAH educational intervention indicate that over 55% of participants used hydration as a strategy to prevent CINV [34]. Dietary strategies, taking antiemetics, and relaxation techniques were the top appropriate preventative and self-management strategies used by participants [34]. Although our educational intervention increased the use of these strategies, our sample size was too small to examine the effectiveness of the MAH intervention to improve the CINV symptoms. Therefore, the goal of this project is to examine the effectiveness of the MAH intervention in reducing CINV symptoms among older adults.

At the time that our team developed the MAH intervention, few studies used technology-based platforms to educate older adults. Those who used these platforms focused on Wii Fit games to promote exercise [36], mobile devices to increase physical activity [37], and avatars and touchscreen technology to manage diabetes [38]. However, since then, serious gaming interventions are becoming more popular. Serious gaming is a well-established method designed to support learning and change health-related behavior by engaging individuals in an entertaining experience [39-41]. Serious gaming capitalizes on fun while promoting behavior change [40]. It is also consistent with our goal of changing behavior by changing their beliefs about self-care related to CINV.

Recent research has used serious gaming among older adults to increase self-management knowledge about heart failure [42], detect cognitive impairment [43], provide cognitive task training

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[44], promote active lifestyle [45], provide education about pain management after surgery [46], detect frailty through grip strength [47], and provide training on how to avoid falls [48]. All of these studies have shown that serious gaming is usable, feasible, and acceptable for use in older adults. Our pilot study showed that it is feasible to recruit older adults diagnosed with cancer to participate in our intervention using serious gaming, and the MAH has high acceptability among users [34]. Coupled with the positive impact the MAH had on increasing preventative and self-management behaviors, this novel intervention shows promise in influencing how older adults think about CINV management and engage in self-management behaviors.

Older adults are using more technology on a day-to-day basis and becoming more proficient. A 2020 American Association of Retired Persons report states that older adults are embracing new technology, with over 50% purchasing some sort of technological product in the past year. Over half of the population aged 50 years and older own a smart tablet, and about 77% of older adults own a smartphone [49]. Another 2021 American Association of Retired Persons report states that older adults increased their use of technology during the recent COVID-19 pandemic and have bridged the "digital gap" between them and younger generations. Due to the pandemic and resulting social isolation, older adults, including people aged 70 years and older purchased, and used, more devices such as smartphones, tablets, and wearables [50]. This shows that older adults are embracing technology and are becoming more literate with the technology. This supports the use of our technology-based intervention and data collection strategies.

Textbox 1. Common recommended chemotherapy-induced nausea and vomiting interventions.

Pharmacologic

- Medication
  - Antiemetic therapy as prescribed by the physician

Nonpharmacologic

- Nutrition
  - Eat dry food, small meals, and bland and easy to digest foods
  - Sit up after eating
  - Avoid cooking odors
  - Avoid spicy and greasy foods
- Hydration
  - Drink 8 to 12 cups of liquid per day
  - Drink even if not thirsty
  - Include liquids like soup, ice pops, flavored ices, and gelatin
  - Limit caffeine products
- Complementary
  - Relaxation, yoga, behavioral therapy (distraction and meditation), guided imagery, controlled breathing, environmental changes, and acupuncture or acupressure

Aims and Hypotheses

The goal of this project is to examine the effectiveness of the MAH intervention in reducing CINV severity and health care use and increasing functioning and QOL. We aim to:

- Aim 1: Examine changes in CINV severity, self-management behaviors, functioning, QOL, cognitive representation, and health care use within the intervention group (IG) from baseline (T_1) to completion of the study (T_6).
  - We hypothesize that the IG will report lower levels of CINV severity and health care use and higher levels of self-management, functioning, cognitive change, and QOL from baseline to the completion of the study.
- Aim 2: Determine efficacy of the MAH intervention by comparing differences in primary outcomes (CINV severity and health care use) and secondary outcomes (self-management behaviors, functioning, and QOL) between the IG and control group at each follow-up visit (T_2-T_6) and completion of the study (T_6).
  - We hypothesize that the IG will report lower levels of CINV severity and health care use at T_2-T_6 than the control group.
  - We hypothesize that the IG will report higher levels of self-management behaviors, functioning, and QOL at T_2-T_6 than the control group.

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Methods

Study Design

Using a randomized clinical trial, we will enroll older adults from 2 clinical sites in Florida. Participants will be randomized to either the IG or attention control group (ACG). The IG will receive the MAH at baseline, and the ACG will receive it at the end of the study. Data will be collected over 6 months or 6 chemo cycles (T_2-T_6). Data related to CINV severity, self-management, functioning, QOL, and health care use at baseline and at the 6 time points will be collected from both groups.

Settings

The intervention will be offered at outpatient treatment centers at a community cancer center in Orlando, Florida, and a Comprehensive Cancer Center in Miami, Florida, that provide care to over 6000 adults aged 60 years and older each year. These numbers indicate an ample sampling pool of older adults diagnosed with cancer.

Study Participants

A sample of 500 participants will be enrolled if they meet the following inclusion criteria: ≥60 years of age, newly diagnosed with cancer, treatment with any chemotherapeutic agent of moderate or high emetic potential [51], on a 2-, 3- or 4-week treatment cycle, proficient in English, and have a telephone. Exclusion criteria are previous diagnosis or treatment for cancer, end-stage disease with less than 6 months to live, and visually or hearing impaired without corrective device. Dementia or cognitive impairment is not a concern with this population since they have already been cognitively screened to consent to treatment at each site. These criteria were also successfully used in our pilot study.

Power Analysis and Sample Size

For aim 1, when the outcome of interest is continuous (eg, CINV severity and number of self-management behaviors), a sample of 100 participants, measured continuously throughout the study period between T1 and T6, achieves a power of 0.904 when using a chi-square test from a generalized estimating equation (GEE) analysis to test whether the average slope of the participants differs significantly at a significance level of .05. The residual SD is anticipated to be 1.00. Missing values are assumed to occur completely at random (missing completely at random [MCAR]). These missing value proportions will be combined to form the pairwise observant probabilities using the independent method. The anticipated proportions missing at each measurement time are 0.00, 0.08, 0.16, 0.24, 0.32, and 0.40. The first row of the autocorrelation matrix of the responses within a participant is assumed to be 1.0000, 0.4000, 0.1600, 0.0640, 0.0256, and 0.0102. Other rows follow the same pattern. For aim 1, a total of 254 participants, each scheduled to be measured 6 times, achieves a power of 0.90 when using a 2-sided Wald test from a GEE analysis with a count outcome (eg, QOL) to test whether a $\mu1(1)$ of 0.500 differs from a $\mu2(1)$ of 1.000 at a significance level of .05. $\mu1(0)$ and $\mu2(0)$ are assumed to be 1.000. Missing values are assumed to occur completely at random (MCAR). These missing value proportions will be combined to form the pairwise observant probabilities using the independent method. The anticipated proportions missing at each measurement time are 0.00, 0.08, 0.16, 0.24, 0.32, and 0.40. The first row of the autocorrelation matrix of the responses within a participant is assumed to be 1.000, 0.500, 0.250, 0.125, 0.063, and 0.031. Other rows follow the same pattern.

For aim 1, when the outcome of interest in binomial (eg, resource use), a sample of 357 participants, each scheduled to be measured 6 times, achieves a power of 0.90 when using a 2-sided Wald test from a GEE analysis with the binary outcome to test whether a P1(1) of 0.500 differs from a P2(1) of 0.250 at a significance level of .05. P1(0) and P2(0) are assumed to be 0.500. Missing value (MCARs) proportions will be combined to form the pairwise observant probabilities using the independent method. The anticipated proportions missing at each measurement time are 0.00, 0.08, 0.16, 0.24, 0.32, and 0.40. The first row of the autocorrelation matrix of the responses within a participant is assumed to be 1.000, 0.500, 0.250, 0.125, 0.063, and 0.031. Other rows follow the same pattern.

For aim 2, based on the assumption of a nausea severity mean score of 6.20, range from 2 to 9, an SD of 2.44, and a clinically meaningful difference in mean nausea severity score of 1 between the IG and control group, a sample size of 500 participants (250 per group), measured between 6 and up to 30 times (depending on the outcome variable of interest), achieves 87% power to detect a difference between the (fixed) group means. The ratio of the subject-specific slope variance to σ^2 is 0.100. The correlation between measurements within a participant is 0.100. The test was based on a mixed model regression analysis using a significance level of .05. This power analysis was calculated using PASS 20 (NCSS LLC). Anticipating an attrition rate of ~22%, we will seek to enroll 610 older adults for this study. Attrition to mortality is not expected to be high due to the exclusion criteria for those with less than 6 months to live.

Recruitment, Randomization, and Procedures

Successful recruitment and retention strategies previously established by our team will guide this study [27,34,52-54]. A stratified sampling strategy followed by randomization will be used. This sample will mirror Florida demographics and aim to recruit participants in the following percentages: female (51%), male (49%), Black (16%), Hispanic (26.4%), White (77%), and other races (7%). At both clinical sites, a research assistant will screen all new patients for eligibility using their respective electronic medical record systems. Eligible patients will be approached by the research assistant at their first chemotherapy appointment and asked to participate. In our pilot study, this timing acted as a distraction for patients while they waited for chemotherapy to start and did not interfere with treatment, nursing care, or education. In addition, prior to treatment, all patients have received standard written education regarding treatment effects and will expect CINV as a possible effect of treatment; therefore, being approached about the study is not expected to elicit anxiety. Informed consent will be obtained in a private area of the clinic open to the research assistant, and a copy of the consent form will be given to the participant.

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Once informed consent is obtained, baseline measures will be completed, and participants will be randomized (IG and ACG) to either group by choosing an envelope with a group assignment. If they are randomized to the IG, the intervention will begin immediately. Regardless, participants in each group will receive standard care (1) on admission to the cancer center (receipt of standard written educational materials that patients are instructed to bring to each appointment), (2) at a treatment planning visit in the clinic (receipt of specific handouts regarding treatment and potential side effects, and (3) at time of treatment (verbal review of chemotherapy and symptom handouts by treatment center or chemotherapy nurses). Retention of all participants will be enhanced with (1) weekly follow-up telephone calls and (2) ACG offered MAH at the end of the study.

Intervention

The intervention consists of three parts: (1) the MAH serious game, (2) self-care discussion with the research assistant, and (3) follow-up.

Part 1: The MAH Serious Game

The game will be administered and supervised by the research assistant. Participants will play the game on an iPad at the outpatient treatment center prior to their first chemotherapy treatment. Headphones can be used to ensure privacy and limit distraction. During the game, players make decisions for the avatar based on common CINV management practices (eg, taking medication, dietary strategies, and staying hydrated; Textbox 1), which cause the avatar to become nauseated or be nausea-free.

Part 2: Self-Care Discussion With the Research Assistant

At the end of the game, the research assistant will answer any questions the participant has and make clarification when needed. In the event, if a participant's avatar has a negative outcome (ie, severe nausea), self-management behaviors will be corrected by the research assistant. In our pilot study, these discussions varied between none and 1 or 2 questions from participants. Based on our pilot data, we estimate that 10% (n=25) of players needed a more in-depth discussion to correct self-management behaviors. In this study, we will document the types of questions asked and the content of these discussions to improve the internal validity of the intervention. We will also document the involvement of caregivers in the intervention, if it occurs.

Part 3: Follow-Up

Participants will be allowed to play the game as many times as they choose during that chemotherapy visit or at subsequent visits in order to practice making decisions and visualizing consequences and outcomes. Once the participant is discharged home, the graduate research assistant (GRA), blinded to the treatment group, will call participants weekly to see how they are doing and remind them to respond to data collection texts or use paper or pencil forms. To reduce bias, a scripted interview form will be used, and no "teaching" will occur. Calls will only be to check in with the participants and remind them to collect data. If participants ask questions about managing CINV and other symptoms, the GRA will instruct them to contact their oncology team for additional management. In addition, participants will be asked to follow cancer center procedures and call their oncologist if they are having problems or have questions.

Treatment Fidelity and Monitoring

The MAH will be presented and delivered by research assistants who have been trained in the game and CINV symptom management strategies. The research assistant will answer questions during the decision discussion based on common self-management options (Textbox 1). A checklist for each interaction with the participant will guide each encounter. Minor interruptions (<10 minutes) to gameplay will be recorded, and participants will resume gameplay where they left off. Technology malfunctions (eg, frozen screen) will be recorded, and participants will be asked to start MAH over again using a new iPad.

End Points

The study will continue until one of the following end points is met: (1) completion of the study, (2) no longer receiving chemotherapy treatment, or (3) unreasonable delays in treatment.

Control Group

Participants in the control group will receive (1) standard care, (2) follow-up phone calls from the GRA to remind them to reply to data collection texts, and (3) the opportunity to play MAH at the end of the study. To reduce bias, a scripted interview form will be used, and no "teaching" will occur. Calls will only be to check in with the participants and remind them to collect data. If participants ask questions about managing CINV and other symptoms, the GRA will instruct them to contact their clinic nurse for additional management. In addition, participants will be asked to follow cancer center procedures and call their oncologist if they are having problems or have questions. Contamination between groups is not expected since participants are likely scheduled for chemotherapy at different times and receiving treatment in different areas of the treatment center.

Outcome Measures

Primary Outcome Measures

Health Care Resource Use

Health care resource use is defined as any unplanned ED admission or HA and will be recorded via participant report using a dichotomous(Y/N) variable at each follow-up phone contact, text, and treatment visit. Follow-up questions about the reason for the admission, length of time for admission, and treatment will also be asked. The report will be verified by medical record review whenever possible.

CINV Severity

CINV severity will be collected on the web using texted links to surveys and will include the presence and severity of CINV (0-10 Likert scale). Participants without a smartphone will be provided the paper and pencil Symptom Management Checklist (SMC; see Data Collection section) to record this data.

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Secondary Outcome Measures

Self-Management Behaviors

CINV prevention and self-management actions, effectiveness of actions (0-10 Likert scale), and amount of hydration will be recorded using the SMC that was used in the pilot study to measure CINV severity and prevention and self-management behaviors. Participants will be asked to record their highest level of nausea each day and preventative self-management actions for CINV and hydration. When experiencing CINV, the participant will use the SMC to record (1) CINV severity (0-10 Likert scale) prior to self-management, (2) the type of self-management strategies used, and (3) the strategies perceived helpfulness in reducing nausea (0-10 Likert scale). All self-management strategies are coded (eg, "MED"=taking antiemetic and "DIS"=using distraction), and the participants will fill in the strategy code they are using on the form. Participants with a smartphone will complete this form electronically, and those without a smartphone will use the paper or pen version, which will be collected by the research assistant at each chemotherapy cycle visit.

Symptom Severity

Part I of the Symptom Representation Questionnaire [55] has a 24-item self-report measure that will be used to identify the presence and severity of common treatment-related symptoms (0- to 10-point Likert scale), including nausea and vomiting. This measure asks respondents to think about their symptoms over the past week.

Cognitive Representation

Part II of the Symptom Representation Questionnaire [55] has an additional 15 questions to assess cognitive representation (identity, cause, timeline, consequences, and cure or control) or beliefs about specific symptoms (0-4 agreement scale). This measure includes subscales for symptom cause (2 questions), timeline (3 questions), cure or control (3 questions), and consequence (6 questions). Only the cognitive representation of nausea will be evaluated. Original reliability statistics for this instrument were fair (Cronbach α=0.63-0.88 for the subscales) [55], and our pilot showed a Cronbach α of 0.64. The cognitive representation questions will be modified at baseline to assess participants' beliefs about potential CINV consequences and their ability to be controlled or cured. These data will be collected again at the end of the study.

Health-Related QOL

The European Organization for Research and Treatment of Cancer-30 [56] will measure QOL at each treatment cycle. This frequency is consistent with other studies that have measured QOL in older adults over time [57,58]. This well-known scale includes 5 functional scales, 3 symptom scales, and 6 single items using a 4-point Likert scale (1=not at all to 4=very much), and 2 global health or QOL items using a 7-point Likert scale (1=very poor to 7=excellent). Higher scores on the functional and health or QOL scale indicate better functioning, while higher scores on the symptom-related scales and items indicate higher symptoms. The tool was previously shown to be reliable in studies with older adults (Cronbach α=0.89) [56] and had a Cronbach α of 0.80 in our pilot study.

Additional Measures

Sociodemographic Characteristics

Sociodemographic characteristics include age, gender, race or ethnicity, comorbidity information, education level, and income level. These characteristics will be measured at T_1 (baseline).

Experiential Characteristics

Experiential characteristics include cancer diagnosis and stage, chemotherapy regimen with antiemetics, additional treatments (eg, radiation therapy), discharge antiemetic prescriptions, fluids during treatment, changes to the treatment plan (ie, delays in treatment, chemotherapy dose reductions, and changes in chemotherapy), and number of times game is played. All cancer information will be collected from the patient's electronic medical record by the research assistant.

Data Collection

Once enrolled in the study (T_1—baseline), research assistants will electronically record information about the participants' diagnosis and treatment plan collected from medical records. Participants in both groups will complete baseline questionnaires electronically on an iPad given to them by the research assistant. The research assistant will demonstrate how to complete the electronic questionnaire and assist with any questions or issues that may occur during data collection. The research assistant will also meet with participants at subsequent treatment cycles (T_2-T_6) to have them fill out the electronic questionnaires on the iPad. Assistance will be given as needed.

Between treatment cycles, we will collect information about CINV severity, self-management behaviors, and any ED visit or HA from all participants. Participants with smartphones will be asked to respond to SMS text messages that will provide a link to the SMC, where they will electronically record information about their CINV severity, self-management behaviors, and any ED visit or HA. Participants will receive SMS text messages daily for the first week after treatment and then every 3 days until their next cycle of chemotherapy. This pattern will repeat at each treatment cycle. Current research supports the use of SMS text messaging since it is estimated that ~77% of older adults use smartphones. In total, 81% of adults ages 60 to 69 years report use of smartphones [49], and 79% of those ages 70-74 years report use of smartphones [59]. Research assistants will provide a tutorial on how to use the electronic links and enter data prior to the end of the first appointment. Participants without smartphones will be given a paper and pencil version of the SMC. They will be asked to record data on their daily CINV severity, self-management behaviors, and any ED visit or HA. The paper and pencil method of data collection was successfully used in the pilot study with ~75% of participants at least tracking fluids and ~64% tracking self-management behaviors over time [34]. All participants will be contacted weekly by a GRA, blinded to their treatment group, to assess how they are doing, answer any study-related questions, and encourage participants to reply to the texts or complete the paper and pencil data collection. The GRA will not manage the care of participants while they are in the study, instead, they will refer participants to their oncology team if

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they have questions or concerns about treatment-related side effects they are experiencing.

Data Management and Integrity

All data will be stored using REDCap (Research Electronic Data Capture; Vanderbilt University) [60], a secure web application database, which will be accessed by a secure web connection with authentication and data logging. Due to the multisite feature of this study, 2 separate REDCap systems will be set up on the University of Miami and University of Central Florida servers separately, but they will share the same structure so that the data could be communicated and analyzed in a consistent way. For surveys that will be filled out by participants electronically, a secured and unique link will be sent via email or text so that the data can be captured accurately. A unique identifier associated with each participant will also be incorporated into the surveys so that the survey responses could be easily identified and rechecked by research staff. Research assistants will also use this identifier when they enter data from the electronic medical record and from their checklists. For any paper and pen surveys, the project director or research assistants will review all data for completeness and appropriate entries before it is entered into the study database.

At the beginning of the data entry process, a minimum of 1 in every 10 participant records will be checked against the original record for data errors. Records for review will be randomly chosen by the data manager. As the study progresses, the frequency of monitoring will be based on the results of the previous data review. If the error rate is unacceptable, then the monitoring will increase until the error rate is acceptable (less than 5% of all data). In consultation with the principal investigator (VL), the data manager will develop reports that will help in the coordination and management of the project and also allow project staff to monitor the quality of the data and the progress of the study. The data files will be backed up daily during the data entry process and once a month when data collection is complete by the data manager. All data files will be housed on the university servers, which are backed up every 24 hours, and copies will be stored off-site for additional security. Access to the database will be password-protected and limited to the investigators, research personnel, project director, and data manager. Furthermore, the user rights will be assigned appropriately by the project manager or data manager to ensure data security and privacy.

Data Analysis

Overview

Prior to the testing of hypotheses and modeling of outcome data, a detailed descriptive analysis of all data collected will be performed, involving the summarization of data and the use of exploratory data analytic techniques. This preliminary exploration of the data will be used to (1) verify randomization by assessing the comparability of groups on key descriptors at baseline, (2) describe univariate and bivariate sample distributions of the data, (3) ascertain the interrelationships between variables, and (4) check for the violation of assumptions necessary for parametric statistical techniques. Specifically, appropriate statistics describing the location (eg, means and percentiles) and dispersion (eg, SDs and ranges) of the distributions of each continuous type variable will be computed for the total sample and over time (when applicable). Frequency counts and percentages will be calculated for categorical variables. Normality will be assessed graphically (eg, histograms and normal probability plots) and inferentially (eg, skewness and kurtosis divided by their SE and Shapiro and Wilk *W* statistic). Levene test for equality of variances will be used to test the assumptions for all analyses using parametric statistics to compare means. If the necessary statistical assumptions are severely violated whereby compromising the validity of the proposed statistical procedure, data transformations or alternate statistically robust approaches, such as analogous nonparametric approaches, will be used.

Aim 1

Aim 1 examines changes in CINV severity, self-management behaviors, functioning, QOL, cognitive representation, and health care use within the IG from baseline (T_1) to completion of the study (T_6). We hypothesize that the IG will report lower levels of CINV severity and health care use and higher levels of self-management, functioning, cognitive change, and QOL from baseline to the completion of the study.

Changes in primary and secondary outcomes from T1 to T6 will be assessed using linear (CINV severity, self-management behaviors, cognitive representation, and functioning), binary (resource use), and ordinal (QOL) regressions, as appropriate, within a GEE framework. All models will control for the effects of 7 demographic (age, gender, race or ethnicity, comorbidity, education level, income level, and insurance status) and 5 experiential (cancer type, emetic potential, treatment frequency, intake of IV fluids between treatment cycles, and number of home antiemetics) variables. GEE models are well suited for this type of repeated measures design, as they account for within-subject correlations between repeated measurements over time in a longitudinal design. Furthermore, GEE models are not restricted by any distributional assumptions including the assumptions of normality required by most other approaches to longitudinal analysis such as repeated measures ANOVA. Finally, GEE models provide robust parameter and SE estimates even if the working correlation structure for the data is misspaced [61]. The analysis will be 2-tailed and conducted with SAS (version 9.4; SAS Institute Inc).

Aim 2

Aim 2 determines the efficacy of the MAH intervention by comparing differences in primary outcomes (CINV severity and health care use) and secondary outcomes (self-management behaviors, functioning, and QOL) between the IG and control group at each follow-up visit (T_2-T_6) and completion of the study (T_6). We hypothesize that the IG will report lower levels of CINV severity and health care use at T_2-T_6 than the control group. We hypothesize that the IG will report higher levels of self-management behaviors, functioning, and QOL at T_2-T_6 than the control group.

The effect of the intervention on primary and secondary outcomes at each follow-up visit and at the completion of the study will be assessed using generalized linear mixed models

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(GLMMs). GLMMs are an extension of general linear models allowing the study of within- and between-subjects repeated measures variations over time. GLMMs can also be used to fit normal and nonnormal response variables, as it is the case in this study. The interaction of time and treatment will be assessed by using an interaction term in the longitudinal models. All models will control for the effects of demographic and experiential variables listed in aim 1. The analysis will be 2-tailed and conducted with SAS (version 9.4).

Ethical Considerations

This study was approved by the institutional review board (IRB) at the University of Central Florida on October 7, 2022 (STUDY00003948). This IRB also serves as a single IRB. Written informed consent will be obtained prior to any data collection and randomization. Study data will be deidentified and stored on password-protected servers that will be accessible only to the study team. Individual participants will not be identified in any presentation or publication materials. Participants are compensated with a US $75.00 gift card at the end of their participation in the study.

Results

This study was funded in September 2022 and received IRB approval in October 2022. As of July 2023, the enrollment of participants is ongoing and currently has 130 enrolled participants. Data collection and analysis will be complete in 2027.

Discussion

Preliminary Findings

Our MAH intervention is focused on changing older adults' perceptions about managing CINV and helping them to learn to use more self-management strategies at home to avoid unplanned HA and ED admission. Our goal is to examine the effectiveness of the MAH intervention in reducing CINV severity and health care use while increasing functioning and QOL.

Our pilot study (n=80) showed small effect sizes and no significant difference between the IG and control group for the main outcome variables of nausea, vomiting, QOL, or health care use. However, the IG reported being more engaged in self-care behaviors to prevent nausea compared to the control group. The IG reported using twice the number of self-management strategies to prevent nausea compared to the control group (1486 vs 768), while the control group reported using twice the number of self-management strategies to manage CINV (1311 vs 681) once they had it [31]. The pilot study also demonstrated the interventions' feasibility and also showed the game was easy to play and useful in helping them manage CINV at home [31]. These results support that the MAH intervention may have shifted prior beliefs related to the timing of symptom self-management at home and increased the belief that engaging in self-management was beneficial.

Future Implications

This study addresses a common and serious side effect of chemotherapy that often leads to severe toxicity and unplanned HA and ED admission in older adults with cancer. It also supports using new technologies, such as serious games, as an educational tool for older adults. If effective, this program can be expanded to include scenarios for multiple symptoms that are typically experienced simultaneously by people under treatment for cancer. In addition, the intervention can be culturally adapted for multiple populations.

Limitations, Potential Challenges, and Alternatives

Recruitment and Retention

Although recruitment and retention of older adults in a clinical trial may be challenging, this study will use successful procedures developed in the pilot study. Diverse recruitment will be enhanced by the addition of the Sylvester Comprehensive Cancer Center, which is located in Miami, Florida, where over 60% (approximately 276,173 people) of the population is Hispanic. Retention will be enhanced through the availability of the MAH intervention at the end of the study for the ACG and follow-up phone calls for both groups.

Respondent Burden

Data will be collected electronically at each time point while the participants are at the cancer centers receiving treatment and is expected to take 15-20 minutes at T_1 and no longer than 5 minutes at subsequent visits (T_2-T_6). In addition, SMS text messages or daily pen or pencil forms will be used to collect data between treatment visits and will consist of only 7 questions. Texts will be reduced from every day in the first week after treatment to every third day to reduce the burden on participants.

Lack of Technology

Older adults who do not own a smartphone will be able to provide symptom management data in a paper or pen format, which was successful in the pilot study.

Conclusions

Older adults are at risk for severe cancer treatment–related side effects and often neglect to engage in symptom prevention or self-management behaviors, which can lead to unplanned ED admission and HAs for treatment. Finding new and innovative ways, like the MAH intervention, to educate older adults about symptom management is critical. The significance of the proposed intervention lies in its ability to allow older adults to practice making decisions about CINV self-care, visualize the consequences of self-management decisions, and reframe their beliefs (cognitive representation) about symptom self-management. MAH is poised to reduce health care costs by decreasing the use of resources (unplanned ED admission or HAs) for CINV due to poor symptom self-management. This research aligns with the National Institute of Nursing Research [62] priority of symptom reduction through self-management and the Centers for Medicare and Medicaid Services [17] priority of improving care and reducing unplanned ED visits in those receiving cancer treatment.

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Acknowledgments

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Data Availability

The datasets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

VL, JC, PIG, and AA contributed to the study conceptualization, design, and data analysis plan. VL wrote the original draft, and JC, PIG, and AA contributed to revisions of the original draft. All authors have agreed on the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACG: attention control group
CINV: chemotherapy-induced nausea and vomiting
ED: emergency department
GEE: generalized estimating equation
GLMM: generalized linear mixed model
GRA: graduate research assistant
HA: hospital admission
IG: intervention group
IRB: institutional review board
MAH: Managing at Home
MCAR: missing completely at random
QOL: quality of life
REDCap: Research Electronic Data Capture
SMC: Symptom Management Checklist

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Protocol

Assessing a Couples-Based, Digital HIV Serostatus-Neutral Intervention (Para Ti, Para Mí, Para Nosotros) for Adult Cisgender Sexual Minority Male Couples in Lima, Peru: Protocol for a 6-Month Pilot Randomized Controlled Trial

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Abstract

Background: HIV disproportionately affects sexual minority men (SMM; eg, gay, bisexual, and other men who have sex with men) in Lima, Peru; epidemiological data estimate that 32% to 39% of new HIV infections occur among adult cisgender SMM within primary partnerships (ie, male couples). Most HIV prevention-care research in Lima, Peru, has focused on SMM as individuals and not couples. To help address this critical gap in prevention care, we developed Para Ti, Para Mí, Para Nosotros (P3): a couples-based, digital HIV serostatus-neutral intervention (DHI) for adult cisgender SMM couples in Lima, Peru. The P3 DHI is designed to facilitate couples with skill-building, communication, decision-making, and working together to form and adhere to a detailed prevention care plan that aligns with their explicit sexual agreement. The P3 DHI is theoretically informed, self-guided, directed, sequential, and fully automated.

Objective: This pilot randomized controlled trial (RCT) aims to examine the preliminary effects of P3 on couples' formation and adherence to a detailed prevention care plan containing evidence-based strategies that also aligns with their explicit sexual agreement over time. In addition, the feasibility of enrollment and retention and couples' acceptability of P3 will be assessed.

Methods: The research implements a prospective, 6-month pilot RCT with a 3-month delayed control condition. After baseline, 60 enrolled SMM couples will be randomized to 1 of 2 conditions. Couples randomized to the unmatched, delayed control condition will receive access to the P3 DHI to use during the last 3 months of the trial after the 3-month assessment. Couples randomized to the immediate intervention condition will immediately receive access to the P3 DHI for 6 months. Study assessments will occur at baseline and months 3 and 6. Descriptive, comparative, qualitative, and longitudinal analyses using generalized linear mixed-effect, multilevel, and actor-partner interdependence models will be conducted to address the specific aims.

Results: The 6-month pilot RCT is ongoing. Recruitment, enrollment, and data collection began in January 2023 and ended in April 2024. A total of 74 adult cisgender SMM couples met all inclusion criteria, provided consent, and were enrolled in the pilot RCT. Retention was 92% (68/74) at month 6. Data are currently being analyzed to address the 3 specific aims regarding feasibility, acceptability, and preliminary efficacy.

Conclusions: Findings from this research will reveal whether couples deemed the P3 DHI to be acceptable. Findings will also highlight the preliminary efficacy of the P3 DHI on couples managing their vulnerability to HIV and other sexually transmitted

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infections (STIs) over time via alignment of their prevention-care plan and sexual agreement. Trial findings will help shape the future direction of the P3 DHI while addressing the existing gap in prevention and care services for couples in the local context.

Trial Registration: ClinicalTrials.gov NCT05873855; https://clinicaltrials.gov/study/NCT05873855

International Registered Report Identifier (IRRID): DERR1-10.2196/63106

(JMIR Res Protoc 2024;13:e63106) doi:10.2196/63106

KEYWORDS

digital health intervention; HIV prevention care; sexually transmitted infection; cisgender, sexual minority male couples; randomized controlled trial; Peru; mobile phone

Introduction

Background

Peru, similar to much of Latin America, has a concentrated HIV epidemic, where cisgender, sexual minority men (SMM; ie, gay, bisexual, and other men who have sex with men) are the primary population affected by HIV. While estimates vary across studies, most studies estimate 10% of HIV prevalence [1,2]; recent incidence estimates continue to be high, estimating an incidence rate of >6 cases per 100 person-years [3]. While there have been fewer studies focusing on sexually transmitted infections (STIs), existing studies point to a similar epidemic pattern [4,5]. Furthermore, epidemiological estimates indicate that between 32% and 39% of new HIV infections among adult cisgender SMM occur within primary partnerships (ie, among male couples) [6].

Although couples have been considered an important population for HIV prevention, no interventions focusing on couples have been tested or implemented in Peru. In this context, same-sex couples (eg, sexual and gender minorities) remain unacknowledged by Peruvian law and exist within a context of limited social and societal support [7]. In addition, while the health system provides both antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP), couples have not been integrated into considerations of treatment as prevention or PrEP provision, apart from pregnant women with a partner who is living with HIV. In short, HIV prevention care efforts in Peru have exclusively been limited to individual-level measures.

To attain the goal of expanding services beyond the individual level, we conducted pilot work to better understand the needs and interests of cisgender SMM couples in dyadic approaches to HIV or STI prevention care. Our pilot work included an acceptability project with 42 adult cisgender SMM couples who used a former couples-based, eHealth HIV and STI prevention intervention [8] and provided feedback about their experience of using it and how they would like to have it adapted and improved to best meet their relationship and prevention care needs. Findings from this pilot work have previously been described in detail [9-11]. These findings highlighted that the couples' acceptability of the intervention was high. In addition, couples' recommendations to improve the intervention centered on three main areas: (1) revamping it to be serostatus neutral, (2) ensuring that it addresses acceptance and ways to improve relations with their own and partner's family as well as ways to strengthen the relationship with their partner, and 3) ensuring that it is accessible for use on different web-connected devices to increase reach and availability. Documented evidence from the literature [6] and the aforementioned pilot work represented the completion of the assessment and decision stages of the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing) model [12] that led to the decision to adapt the former couples-based eHealth HIV and STI prevention intervention. The remaining stages of the ADAPT-ITT model were followed to adapt the intervention into its current form, which is a couples-based, digital HIV serostatus neutral intervention (DHI) called Para Ti, Para Mí, Para Nosotros (P3).

This paper describes the protocol for a 6-month pilot randomized controlled trial (RCT) of the P3 DHI for adult cisgender SMM couples in Lima, Peru. The P3 DHI is designed to facilitate and enhance skills-building of communication and decision-making as well as to encourage relationship partners to work together toward their shared health and relationship goals, with an emphasis on sexual health, HIV and STI prevention care, and relationship dynamics.

P3 Structure and Organization

The P3 DHI is a secure web app compliant with the Health Insurance Portability and Accountability Act. It can be used across a variety of different web-connected devices, ranging from smartphones to desktop computers. Two types of end users may access and use the P3 DHI: (1) both members of the couple and (2) administrators such as researchers and organizational staff. All users must create an account to access and use nonpublic components of the P3 DHI web app (eg, intervention and administrative portal). The publicly available and accessible components of the P3 DHI include information about the study trial, access to the eligibility screener, e-consent, contact information verification process, and partner study invite system.

The P3 DHI hosts the couples-based, HIV serostatus–neutral intervention that can be hidden or activated, depending on the study design of the trial and randomization assignment of the couple. The P3 DHI also provides participants with access to assessments that automatically populate over time (ie, closer to the due date) and link directly with Qualtrics (Qualtrics International Inc). Furthermore, the P3 DHI incorporates and uses an automated message reminder system. Participants receive up to 5 different types of SMS text messages. One type of SMS text message is instructional, such as for verifying contact information, for creating a study account to access the DHI, and other similar tasks. Another type of SMS text message serves as a reminder for participants to complete their assessments by a certain due date. An additional SMS text

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message type provides prompts for partners of the couple to start the intervention, whereas another type of SMS text message provides prompts of encouragement to finish the intervention once started. The final type of SMS text message serves the purpose of informing 1 partner that the other partner has caught up to them in the module. All SMS text message types are automated and sent based on predetermined dates or using actions and inactions.

Theoretical Foundation of P3

The P3 DHI is theoretically guided by the Couples Interdependence Theory for Health Behavior Change (CIT-HBC; Figure 1) [13,14]. CIT-HBC accounts for the potential ways partners interact and influence their own and one another's outcomes and behaviors within the context of their relationship. CIT-HBC provides a useful framework to better understand and encourage health behavior change while considering both partners' needs and the needs of their relationship (ie, following a couple-based approach). The aim of CIT-HBC is to encourage both the partners to initiate and maintain behaviors that enhance their health (eg, their uptake of and adherence to using evidence-based HIV and STI prevention care strategies over time). CIT-HBC considers how communal coping and transformation of motivation affect the outcomes and behaviors among couples to inform health behavior change. Transformation of motivation accounts for changes in partners' behavior from a primarily individual-focused motivation to one that is more prorelationship, considering the health needs of both partners and their health-enhancing behaviors [13,14], which is represented via a shift from an individualistic viewpoint to a more shared view of we. Communal coping refers to partners holding a shared assessment of a health threat and a vision of shared action about managing their behaviors and related efforts [13,14] and what both partners will do together to manage their HIV or STI vulnerability. Couple's interdependence and communal coping approaches have previously been used to understand how health behavior change occurs, including health-enhancing and health-compromising behaviors related to HIV among adult cisgender SMM couples. For example, CIT-HBC is the foundation for couples HIV testing and counseling [15,16]. Regarding measurement for initiating and sustaining health behavior change, CIT-HBC accounts for how partners interact to influence one another's outcomes through the actor-partner interdependence model (APIM) [17]. APIM permits measurement of actor effects (ie, how a partner influences his own behavior) and partner effects (ie, how each member of the couple influences his partner's behaviors, independent of their own behaviors).

Figure 1. Conceptual model of Couples Interdependence Theory for Health Behavior Change (adapted from Lewis et al [13]).

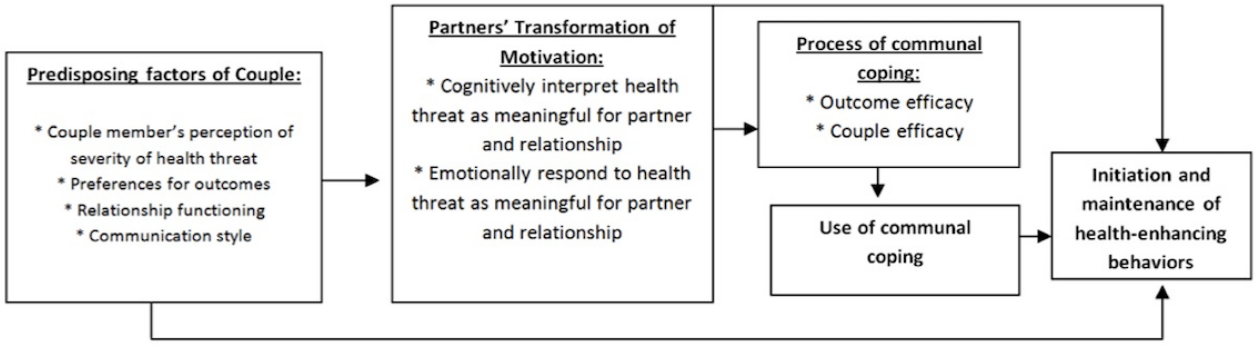

P3 Intervention

The couples-based intervention within the P3 DHI is organized into 5 modules. Each module focuses on a core topic with relevant content and related activities, including quizzes, videos, and infographics. Module 1 focuses on communication and decision-making. Module 2 is about HIV and STI prevention care and sexual pleasure. Module 3 centers on sexual agreements. Module 4 is about relationship strengthening, social support, and goal setting. Module 5 focuses on physical activity. All modules reinforce relevancy to sexual health and prevention care. A variety of behavioral change techniques [18] are embedded within each module, including goal setting (behavior), problem solving, action planning, review of behavioral goal, social support (unspecific), social support (practical), information about health consequences, demonstration of the behavior through videos and credible sources, and tailoring and personalization. Drawing from our formative work that led to this pilot RCT protocol, this research refined a previously developed behavioral change technique called dyadic comparison. Dyadic comparison reveals similarities and differences between couple partners to help further their understanding about sexual health and related topics by facilitating communication, decision-making, and goal setting for themselves and their relationship.

P3 User Interface and User Experience

The participant or client user interface of the P3 DHI, that is, what partners and couples experience while using the program, is directed, sequential, and fully automated (ie, without human involvement). Specifically, both the partners must complete module 1 before they can proceed to module 2; they must complete module 2 before accessing module 3, and so forth. Once a module is complete, both the partners may revisit any section of it, including reviewing their responses to the activities and retaking the module. Each module is also organized into subsections that are referred to individually and as a couple, denoted by symbols with instructional text to inform and remind the user of who is involved in each subsection. Estimated time approximations to complete a module and its subsections are also provided at the start of each module (eg, part A: 5 minutes). An estimated time of 15 to 20 minutes is needed to complete a

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module, excluding any conversation time that would occur between the partners. Figure 2 provides an example screenshot of the P3 DHI.

Figure 2. Para Ti, Para Mí, Para Nosotros (P3) web app landing page to access the eligibility screener and the intervention via an "iniciar session.".

In addition to a secure SMS text messaging system to communicate with participants, the P3 DHI also contains an administrative and clinical portal for researchers and staff. The administrative portal serves as a one-stop shop to store, organize, and monitor data associated with the trial. Along with its other features, the portal contains a dashboard and participant tracking system. The dashboard provides a global overview of all study participants and couples' engagement with the study, ranging from data associated with eligibility and enrollment rates and information on assessment and module completions. The dashboard also offers researchers and staff the ability to download data about participants' and couples' experiences with regard to using the intervention modules within the P3 DHI. Finally, as each couple progresses through the trial, the participant tracking system provides descriptive details including due and completion dates of assessments as well as when and which modules are completed.

Both the dashboard and participant tracking system are interactive such that all numbers displayed in the dashboard provide the administrative user the ability to learn more about which specific participants or couples are linked to a particular characteristic in the dashboard (eg, number of enrolled couples in the immediate intervention arm). In addition, each participant and couple are assigned a unique ID. Selecting and clicking on the unique ID in the administrative portal leads to a web page providing information about the couple, their assessments (eg, due date and completion date), their module use (date of completion relative to assessment timeline for trial), links to their screener responses, when and which SMS text message reminders they have received, contact information, and HIV and STI testing details, including results. Figures 3 and 4 provide screenshot examples of the administrative portal.

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Figure 3. The participant snapshot within the dashboard of the Para Ti, Para Mí, Para Nosotros (P3) administrative portal that provides the number of couples who have met all eligibility criteria (ie, accepted), registered by creating a study profile, and completed the baseline assessment for enrollment.

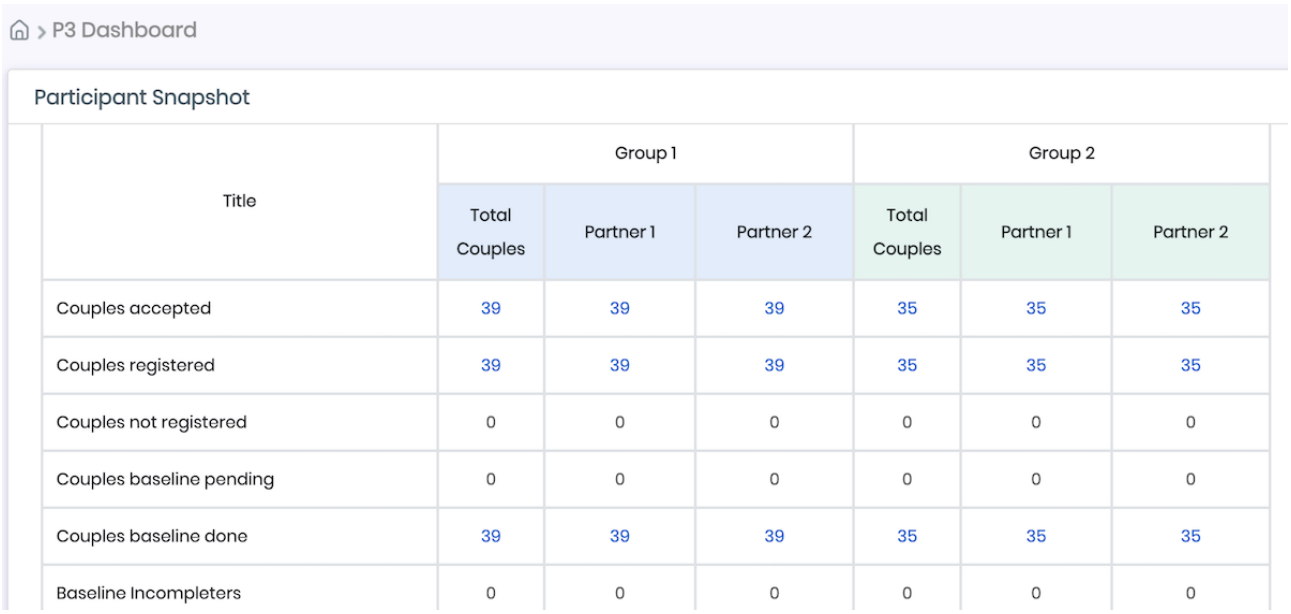

Title	Group 1			Group 2		
	Total Couples	Partner 1	Partner 2	Total Couples	Partner 1	Partner 2
Couples accepted	39	39	39	35	35	35
Couples registered	39	39	39	35	35	35
Couples not registered	0	0	0	0	0	0
Couples baseline pending	0	0	0	0	0	0
Couples baseline done	39	39	39	35	35	35
Baseline Incompleters	0	0	0	0	0	0

Figure 4. A screenshot of the participant tracking within the Para Ti, Para Mí, Para Nosotros (P3) administrative portal showing the progress of each participant during the pilot randomized controlled trial.

Group	Status	Screener	Baseline	M1	M2	M3	M4	M5	3M	M1	M2	M3	M4	M5	6M	Exit Interview
G1	Study Completed	26/09/2023	D - 11/10/2023 C - 05/10/2023	⊗	⊗	⊗	⊗	⊗	D - 07/01/2024 C - 02/01/2024	-	-	-	-	-	D - 06/04/2024 C - 01/04/2024	09/04/2024
G1	Study Completed	18/09/2023	D - 11/10/2023 C - 05/10/2023	⊗	⊗	⊗	⊗	⊗	D - 07/01/2024 C - 06/01/2024	-	-	-	-	-	D - 06/04/2024 C - 28/03/2024	09/04/2024
G2	Study Completed	16/02/2023	D - 28/02/2023 C - 21/02/2023	-	-	-	-	-	D - 27/05/2023 C - 17/05/2023	⊗	⊗	⊗	⊗	⊗	D - 25/08/2023 C - 15/08/2023	06/09/2023
G2	Study Completed	16/02/2023	D - 28/02/2023 C - 21/02/2023	-	-	-	-	-	D - 27/05/2023 C - 30/05/2023	⊗	⊗	⊗	⊗	⊗	D - 25/08/2023 C - 28/08/2023	06/09/2023

Our formative work with the population, including the use of a community advisory board and human-centered design methods [19-22], informed the overall structure, organizational layout, and user interface and user experience of the alpha and current beta version of the P3 DHI. The beta version of the P3 DHI will be evaluated using a 6-month long pilot RCT.

Specific Aims

There are 3 specific aims for this pilot RCT with adult cisgender SMM couples in Lima, Peru:

- To assess the feasibility of retaining 60 eligible couples who consented to participate in a 6-month pilot RCT, through quantitative measurement of enrollment, retention, and attrition rates plus reason(s) for attrition.
- To describe the acceptability of P3 using mixed methods [23] from 3 data sources: at final follow-up, the partners' responses to the Health Information Usability Evaluation Scale [24] and other survey items (eg, 3 things liked best or least about P3 and features for improvement) will be captured, along with the additional details they will share about their experiences during the individual-level, qualitative exit interview. Partners' paradata will also be descriptively analyzed to describe the patterns of use, such as completion rates, time, and reuse.
- To examine the preliminary efficacy of the P3 DHI on couples through the following measures:
  - Formation and adherence to an HIV and STI prevention care plan containing evidence-based strategies (eg, using ART for undetectable=untransmissible [U=U], PrEP, and routine testing)
  - Formation and adherence to a detailed sexual agreement
  - Relationship functioning (eg, mutual constructive communication, self-efficacy of decision-making, and working together)
  - Self-reported and biomarker-confirmed indicators of vulnerability vis-à-vis sexual behaviors (eg, condomless anal sex [CAS]) and HIV and STIs

To accomplish the above specific aims, data will be collected from both the partners of the couple during the trial; analytic comparisons will be made between the 2 intervention trial conditions. The purpose of this paper is to describe the protocol that will be used to conduct a 6-month pilot RCT of the P3 DHI with adult cisgender SMM couples in Lima, Peru.

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Methods

Trial Study Design

The study design for the P3 DHI is a 6-month pilot RCT with an unmatched delayed control condition of 3 months. The pilot RCT for the P3 DHI is registered on ClinicalTrials.gov (NCT05873855). Assessments will occur every 3 months after the baseline assessment (at 3 and 6 months). Participants (ie, couples) will initially be blinded to which randomized condition they receive for the pilot RCT. Most study participation activities, including recruitment, eligibility screening, consent, enrollment, assessments, intervention, and exit interviews will occur on Zoom (Zoom Video Communications). During the pilot trial, participants will also undergo in-person HIV and STI testing at a local community-based organization at baseline and month 6. The planned sample size for enrollment is 60 adult cisgender SMM couples. The planned sample size will be balanced by dyad HIV serostatus and stratified by trial arm (ie, 10 seroconcordant negative, 10 serodiscordant, and 10 seroconcordant positive couples per arm). Florida International University (FIU) and Universidad Peruana Cayetano Heredia's respective institutional review boards have approved the study protocol and all associated study activities.

Recruitment

Active and passive recruitment strategies will be used to recruit the sample. These strategies include (1) placement of targeted advertisements on social media platforms (eg, Facebook and Instagram [Meta Platforms, Inc], Scuff [Perry Street Software, Inc], and Grindr [Grindr, Inc]); (2) emailing informational flyers to sexual and gender minority communities and HIV and STI service organizations; and (3) referrals from health providers, peers, or relationship partners. All interested participants will be referred to the project website to learn more about the study, complete the brief eligibility screener, provide e-consent, and submit their own and their partners' contact information (WhatsApp number). Both partners of each couple must complete the eligibility screener, provide e-consent, and enter accurate and complete contact information to be considered for eligibility.

Inclusion and Exclusion Criteria

Overview

This pilot RCT study will use a 3-level approach to determine eligibility. Level 1 will determine an individual's eligibility based on their responses to the screener (ie, individual level). Level 2 will determine a couple's eligibility using data from both the participants who indicate that they are in a relationship with one another (ie, couple level). Embedded electronic algorithms within the eligibility screener will automatically determine whether individuals meet the criteria for level 1 eligibility and whether couples meet the criteria for level 2 eligibility, provided that both partners complete the screener, consent, and all contact information. Level 3 will only occur if the inclusion criteria for levels 1 and 2 are met. Unlike the previous levels, the study staff will apply level 3 eligibility criteria during a Zoom study onboarding meeting by asking both partners of the couple to verify some of their responses to the eligibility screener.

Level 1: Individual Eligibility

Each individual participant within an adult cisgender SMM couple must meet the following individual-level eligibility criteria for the P3 pilot RCT: (1) currently identifies as male and was assigned male at birth (ie, cisgender); (2) be aged ≥18 years; (3) has access to a web-connected device (eg, smartphone, laptop, tablet, or computer); (4) lives in and plans to live in Lima, Peru, for the next 6 months; (5) reports being in a relationship with another cisgender, SMM partner and defines their partner as *someone they feel emotionally or romantically committed to above all others, such as a partner, husband, boyfriend, etc*.; (6) reports being in their relationship for a minimum of 3 months; (7) reports having had CAS with their relationship partner within the previous 3 months; (8) one of the relationship partners reports having had CAS with a casual sex partner in the same timeframe; (9) reports to having no history (ie, within prior 3 months and ever) of intimate partner violence; (10) reports not being coerced by their partner (or others) to participate in the study and related activities; (11) reports feeling safe in the current relationship to participate in the study and related activities; and (12) indicates willingness to test for HIV and other STIs at a local community–based organization at baseline and at 6 months after baseline.

Except for level 1 eligibility criterion number 8, individuals who do not meet all other above-mentioned criteria, will be deemed ineligible, thanked for their interest in the study, and provided a list of HIV and STI prevention resources and other health and relationship-oriented resources that are available in Lima, Peru. Individuals who meet all other criteria (other than number 8) will be prompted to complete an e-consent and enter complete contact information of themselves and their partner. Then, partner 2 will receive a study invite via WhatsApp, which will provide them with access to the eligibility screener and e-consent (if applicable). Level 2 eligibility criteria will automatically be evaluated once both partners complete the eligibility screener.

Level 2: Couple-Level Eligibility for Relationship Verification

Web-based relationship verification and validation techniques, which entails a series of questions that compares both the partners' responses about their relationship (eg, partners' birth month, tattoo, cohabitation, and pet ownership) will be used [25,26], Relationship verification is based on both partners' responses to 7 screener items that are automatically evaluated against predetermined decision rules. The 7 items that will be used include age, birth month, relationship status, relationship length, cohabitation, owning pets, and having tattoos. Couples with both partners who provide answers that crossmatch to at least 5 of the 7 questions will be deemed as passing the relationship verification criteria. Couples who do not pass the relationship verification process will not be allowed to participate in the study even if they meet the eligibility criteria of level 1. The relationship verification process of level 2 is in place to help ensure that web-based data will be collected from participants who are in a relationship with one another. Couples

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who do not pass level 2 eligibility will be thanked for their interest in the study and provided a list of HIV and STI prevention care resources and other health and relationship-oriented resources available in Lima. Couples who meet level 2 eligibility criteria will be invited to attend a brief onboarding Zoom meeting with a staff member of the study.

Level 3: Study Onboarding Zoom Meeting

Couples who meet all eligible criteria, provide e-consent, enter complete and accurate contact information, and pass the requirements for *relationship verification and data validation* will be invited to partake in a 10 to 15-minute onboarding Zoom meeting. During the meeting, the study staff will assess the couples' verification and interest in participating, discuss study expectations and timelines, answer questions, and decide whether to admit the couple into the study. Once admitted, each partner of the couple will be asked to create their own profile on the P3 DHI using their own web-connected device. Their profile will give them access to the baseline assessment followed by whichever intervention group they are randomly assigned to for the pilot RCT.

Web-Based Fraud Deterrent and Data Validity Safeguards

A variety of fraud deterrents will be embedded and programmed into the eligibility screener to help deter the infiltration of "bots" and fraudulent data entries. Specifically, the eligibility screener will only allow entries from Peru-based IP addresses; no more than 3 screener entries may originate from the same IP address. Start and stop times of completed screener entries will also be monitored and evaluated against a predetermined minimum time for completion. Once an electronically screened individual is deemed eligible for level 1 criteria and has provided e-consent, they will be required to validate their WhatsApp number by entering a 4-digit code sent to their WhatsApp number and entering that specific code in the DHI web system.

Data validity safeguards will also be used to determine whether responses come from 2 unique individuals in a relationship and not from 1 person pretending to be 2 people (ie, fraudulent responses). The eligibility screener date and completion times of couples who pass levels 1 and 2 of the eligibility criteria will also be examined in conjunction with corresponding IP addresses for these entries. Back-to-back screener entries (ie, the start time of the new entry closely following the stop time of the previous entry) and entries specifically from the same IP address will be flagged for review by examining other eligibility criteria and contact information. Overall, each couple must pass the first 2 validation criteria and have no more than 3 screener entries between them. The investigative team uses these relationship verification and data validation test processes to identify true couples in previous and ongoing web-based studies involving couples.

Ethical Considerations

The FIU and Universidad Peruana Cayetano Heredia Institutional Review Board approved all study-related activities for the 6-month pilot RCT of the P3 DHI (IRB-22-0496, IRB 201101). The project will have a certificate of confidentiality in place as a requirement of the funding agency. The e-consent form will inform participants of confidentiality guidelines and standards. No identifying data will be collected before informed consent is received from the participants; each partner will be required to individually provide consent electronically. The participants will be informed to complete the eligibility screener in a location they deem to be private. If a participant decides to withdraw from the study after providing consent and identifying data (eg, name, email address, and WhatsApp number), then any identifying data associated with the participant will be deleted. In addition, the participants will be instructed to participate in the individual, qualitative exit interview via Zoom or in person at Epicentro in a private setting or a room; the study staff will also be hosting these interviews in a private setting, either on a computer or using a digital recorder. Finally, all correspondence with the participants will be devoid of any indication of the content, purpose, or target population of the study; the participants will be encouraged to delete correspondence (eg, WhatsApp messages) as soon as the participant decides they no longer need the contained information.

Regarding confidentiality and data management practices, neither partner will have access to the other partner's test results or data from assessments or interviews. Each study participant will be required to create and use a username and unique passcode to gain access and use the P3 DHI. Furthermore, the participants will be automatically logged out of the P3 DHI after a period of inactivity. All data will be coded by a unique individual study number, and personal identifier records will be kept in password-protected files on password-protected computers. HIV and STI test results will be coded using the participant ID; this ID will not have any potential identifying information and will only be accessible to study staff. All recorded videos on Zoom will only occur on the study staff's secure laptop (password protected and in password-protected files). Similarly, all recorded audio files will only be available on the study staff's designated digital recorder. From this recorder, the audio will then be immediately uploaded to the study staff's secure laptop (password protected files). Records will be kept confidential to the level allowed by law, and only the staff assigned to the study will have access to nonanonymous records. Information provided by the study participants will not be released to outside sources unless legally required or written consent is provided by the study participant.

All eligibility screener, consent, and intervention use (ie, paradata) data will be collected and blockchain encrypted via the P3 DHI secure web app hosted on a secure server (Azure; Microsoft Corp). Quantitative baseline and follow-up assessment data will be collected and managed using Qualtrics, an electronic survey data-capturing tool at FIU. Qualtrics is a secure, web-based survey application that is compliant with the Health Insurance Portability and Accountability Act. All Qualtrics servers are backed up daily and monitored for hardware failures. At the end of the trial, all data for the study will be stored on OneDrive, which will only be accessible to the study team through an SSL-encrypted connection that backs FIU's firewall system.

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Randomization

An allocated randomization block of 2:2, via an embedded algorithm within the P3 DHI, will be used to randomly assign couples to one of the following 2 intervention conditions following the baseline assessment: (1) an immediate intervention condition where couples will be able to use the P3 DHI for 6 months or (2) a 3-month delayed intervention condition where couples will be able to use the P3 DHI for the last 3 months of the trial. For ethical reasons, a delayed control condition was chosen for the trial study to provide all couples with access to the intervention while also permitting the ability to compare outcome differences between trial arms for the first 3 months of the pilot RCT. In sum, all couples in the pilot RCT will have access to use the P3 DHI for a minimum of 3 months, which will enable data pooling of the entire couple sample (N=60; ie, first 3 months for the immediate intervention condition plus the last 3 months with the delayed intervention condition). The study design will also enable the examination of long-term effects of the P3 DHI (ie, effects after 6 months of use) on outcomes and their use of the P3 DHI among couples randomized to the immediate intervention condition (n=30). Randomization will be blinded to couples but not to the study staff (administrators).

Pilot RCT Baseline and Follow-Up Measures

Items about evaluation will only be assessed during follow-ups after the participants receive the intervention. All other measures, items, and scales will be assessed at each time point throughout the trial, including baseline. In addition to screening for inclusion, the eligibility screener will capture a variety of demographic information from each participant including age, race, sex at birth, gender identity, sexual identity, highest education attainment, current employment status, has a primary health care provider, relationship type, relationship length, couple cohabitation, and couple HIV serostatus. Other demographic information will be captured at each data collection time point (ie, at baseline, months 3 and 6) to assess participant's current living arrangement, type of health insurance, affordability to pay for health care or medication costs when needed in the past 3 months, as well as whether participants were in a situation that required them to reduce a meal size or skip a meal because of not having enough money for food in the past 3 months (social determinants of health). Skip patterns will be used accordingly for baseline and follow-up assessments at months 3 and 6. Multimedia Appendix 1 [24,27-49] provides a brief description of all other items and scales that will be assessed at each time point and how they relate to the constructs of CIT-HBC [13,14].

Beyond the General Anxiety Disorder 2-item, 5 other items will be used to capture aspects about anxiety and worry specifically related to sex and being in a relationship. The items include the following: "Do you ever feel like you are walking on eggshells around your partner? (Yes, No, I don't remember)"; "In thinking about the past 3 months, how much did you worry or feel anxious about having sex with your partner? (0=never to 4=always)"; "To what extent did this anxiety stop you from enjoying sex with your partner? (0=not at all to 2=a lot)"; "In thinking about the past 3 months, how much did you worry or feel anxious about having sex with others, not including your partner? (0=never to 4=always)"; and "To what extent did this anxiety stop you from enjoying sex with others, not including your partner? (0=not at all to 2=a lot)." Skip patterns will be used for the above set of items such that some items may not be displayed depending on the participant's response to the previous item.

Furthermore, some scales will be modified based on feedback from the Community Advisory Board and to help reduce time burden for participants. For instance, single global items from validated scales (eg, Dyadic Trust Scale [34] and Investment Model short form [36]) may alternatively be used to capture interpersonal trust, relationship commitment, and relationship satisfaction instead of the complete scale.

In addition to self-reports of partners using strategies over time, we will ask each participant to test for HIV and STIs at baseline and at 6 months post baseline by going to a local community-based organization. Biological data for new diagnoses of HIV, chlamydia, gonorrhea, and syphilis will be collected. For those previously diagnosed with syphilis, the rapid plasma reagin test will be processed to examine antibodies to syphilis. HIV will be assessed using a rapid test, with a rapid test from another manufacturer used as a confirmatory test if the first is positive. GeneXpert polymerase chain reaction testing will be used to diagnose chlamydia and gonorrhea infections.

Relationship Dissolution

It is possible that some couples may end their relationship during the eligibility and enrollment process (before enrollment) or sometimes after trial enrollment (eg, between 3 and 6 months after baseline). Couples who self-report that their relationship had ended (through a follow-up assessment or by contacting the study team directly) while participating in the 6-month pilot RCT will not be permitted to continue participating in the study as a couple or as a participant. Couples who end their relationship between assessments will be asked to complete one more assessment, capturing information on any influence they perceive the study to have had on the end of their relationship before being administratively removed from the trial. In an assessment, couples who self-report that their relationship had ended will be administratively removed from the trial afterward. To prevent contamination of the intervention, neither partner of couples who have broken up will be permitted to rejoin the study if or when they enter a new relationship, even if all eligibility criteria are met. We will check this by cross-checking the contact details of all partners in our contact database to ensure that prior participants are not reenrolled.

Incentives

Each participant will receive an incentive (ie, cash) for their time associated with the study activities at set time points during the pilot trial: baseline 50 Peruvian Soles (US $14) for baseline and 55 Peruvian soles (US $15) for month 3 and month 6, respectively.

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Analytic Plan

Overview

For aim 1, we will define and measure feasibility as the ability to recruit, screen for eligibility, enroll, and retain couples in the 6-month pilot RCT over time. Our preliminary work [9-11] demonstrated our ability to recruit, screen for eligibility, and enroll eligible adult cisgender SMM couples in Lima, Peru. We will extend this work for the proposed project to assess feasibility with a larger sample of couples with a focus on retention for the 6-month pilot RCT. As such, some examples of the research questions we seek to answer through this specific aim are as follows: (1) Is it feasible to retain >90% of the couples in the 6-month pilot RCT? (2) Is it feasible to retain >90% of the couples who have both partners complete all 3 quantitative assessments (baseline, month 3, and month 6)? and (3) Is it feasible to have >90% of couples with both partners completing their individual-level, exit interview at 6 months? In line with common research practices (which can help inform a larger RCT), we will evaluate which recruitment strategies (eg, targeted advertisements placed on Facebook or Instagram vs in-person recruitment by research staff) led to the highest proportion of interested individuals starting or completing the eligibility screener as well as couple eligibility and consent. Through our established protocols (ie, standard operating procedures), the study will track and quantitatively describe the reasons why individuals and couples were ineligible, track enrollment rates among consented and eligible couples, assess retention among enrolled couples during the pilot RCT by arm, and which retention practices appealed to participants. The research will also track the reasons for attrition. A detailed CONSORT (Consolidated Standards of Reporting Trials) diagram will be produced at the conclusion of the pilot RCT. We will also quantitatively calculate the proportions of how many participants provided permission and documentation (paper or through the web portal) about their use of prevention strategies during the pilot RCT. We will apply the data obtained from the eligibility screeners to use descriptive statistics at the individual and couple levels and explore whether differences exist based on the couples' HIV serostatus.

For aim 2, acceptability of P3 will be defined through participant and couples' use of it (ie, paradata) as well as their attitudes from their experiences of using it over time (ie, quantitative and qualitative dyadic data). For each couple, the research will measure acceptability using and analyzing 3 types of data from both of the relationship partners: (1) quantitative measures will include the Health Information Technology Usability Evaluation scale [24], perceived effect of using P3 on a couples' relationship [49], and self-reports of the number of intervention modules completed; (2) a qualitative, individual exit interview will be conducted to provide context and supplement partners' responses to their quantitative measures as well as their top 3 likes, top 3 dislikes, and recommendations to enhance P3; and (3) paradata from the couples' use of the intervention over time (eg, module completion and time to complete each module).

Quantitative Measures

All statistical analyses will be performed with SAS (SAS Institute) or Stata (version 14.2; StataCorp) with modeling using PROC MIXED or GLIMIMIX. We will generate descriptive statistics to calculate means, SDs, counts, and proportions at the individual and couple levels for the Health Information Technology Usability Evaluation scale [24] (mean and SD) and other evaluation items and by dyad HIV serostatus group. The study will also explore, univariately, whether differences exist by couples' HIV serostatus for these quantitative measures by applying ANOVA and chi-square tests for couple-level continuous and categorical independent variables, respectively.

Qualitative Measures

The study will conduct content analysis [50,51] of the qualitative dyadic data collected through the exit interviews at the final follow-up in the pilot trial. Specifically, we will conduct summative content analysis [50,51] of P3 to generate counts and proportions of how many couples had one or both partners mention keywords, topics, or activities, by trial arm, and by couple HIV status. We will also conduct conventional content analysis [50,51] of the qualitative dyadic data to generate coding categories from the transcripts, which may illuminate broader themes of what participants or couples liked and used in P3. Emergent themes may include the use of infographics in educational content about different topics covered, answering questions in the activities to receive tailored recommendations, or watching videos. At least 3 research team members will read all transcripts, take notes, and identify overarching themes. The team will then meet to discuss the overarching themes before rereading and coding the transcripts for these themes, starting with summative content analysis [50,51] to generate counts of keywords before repeating the process for conventional content analysis [50,51]. During subsequent meetings, the team will compare and discuss their coding and will make adjustments as needed before creating the codebook. The codebook will describe the themes and their corresponding definitions. Each team member will then use the codebook to code the transcripts once again. This process will be applied for all transcripts; then, each team member will review one another's coding of the transcripts to ensure that consistency will be achieved for the themes identified (ie, interrater reliability >0.90). All coding will be done using a web-based management tool, such as Dedoose (9.2.012 Mac; Sociocultural Research Consultants LLC). In the end, a sum count of each individual-level response per theme will be calculated to describe the proportion of endorsement within and between couples for the entire sample, by arm, and by couple HIV serostatus resulting in tables to visualize these endorsements. Representative quotes will also be identified for use to disseminate findings in peer-reviewed outlets (eg, manuscripts and conferences).

Paradata From Use of the P3 Intervention

This research will generate descriptive statistics to calculate means, SDs, counts (with ranges), and proportions at the individual and couple levels from the dyadic paradata collected. Firstly, this study will calculate the number of couples who completed all 5 modules in the intervention (vs 4, 3, 2, 1, and none). The researchers will also calculate how much time the participants and couples took to complete each module (eg, module 1=10 minutes) and the total time taken to complete all 5 modules. Next, we will descriptively analyze couples'

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responses to the various questions and activities embedded within each of the modules. For all the abovementioned analyses, we will explore whether differences exist by trial arm (eg, n=30 who immediately received the intervention vs n=30 in the delayed control group) and by couples' HIV serostatus using comparative analyses.

Mixed Methods

This research will use an embedded mixed methods design [23] because both quantitative and qualitative dyadic data about the acceptability of the intervention will be collected. In this case, a qualitative strand has been added within a primarily quantitative-focused design (trial assessments and paradata) to enhance our understanding of what participants and couples liked and disliked about the intervention and to provide context about why they appreciated certain features, and, if applicable, what things they wished the intervention had but did not. Put simply, this research will review the findings obtained from analysis of the quantitative data and paradata along with the findings from the qualitative analyses to provide a more comprehensive picture about participants' and couples' use and thoughts of P3 relative to their relationships and managing their vulnerability to HIV and other STIs.

Aim 3: Preliminary Efficacy of the Intervention

Using the 6-month pilot RCT, this research will examine the preliminary efficacy of the intervention on couples: (A) formation and adherence to an HIV and STI prevention care plan containing evidence-based strategies (eg, ART for U=U, PrEP, and routine testing); (B) formation and adherence to a detailed sexual agreement, (C) relationship functioning (eg, mutual constructive communication and self-efficacy of decision-making and working together), and (D) self-reported and biomarker-confirmed indicators of vulnerability vis-à-vis sexual behaviors (eg, CAS) and HIV and STIs. The pilot RCT will have an allocation ratio of 1:1 and block randomization with a block size of 2, with blocks defined by dyad serostatus. Outcomes A and B will be dichotomous, outcome C will be continuous based on a bounded Likert scales, whereas outcome D will be a count variable based on STI incidence, HIV incidence, and CAS.

Preliminary efficacy will be assessed by considering changes in couples' outcomes A to D over time. For the immediate intervention arm, the differences in outcomes A to D will be observed between receipt of the intervention and subsequent follow-up assessments at 3 months and 6 months (n=30). For the waitlist arm, the differences in outcomes A to D will be observed between receipt of the intervention after the 3-month assessment and subsequent follow-up assessment at month 6 (n=30). As such, this study will be able to pool and combine data from the 30 couples from the immediate intervention arm with data from the 30 couples from the waitlist arm to observe changes in outcomes (ie, from A-D) over a 3-month time period (N=60). Furthermore, through this study, we will also be able to observe changes in couples' outcomes (ie, from A-D) for a longer period of time (6 months) for the immediate intervention arm (n=30). Comparisons in couples' outcomes A to D by trial arm (immediate arm vs waitlist arm) will occur between baseline and month 3. In summary, the design we chose for the proposed 6-month pilot RCT is advantageous for 3 reasons: (1) it will allow us to compare differences between immediate intervention and delayed intervention arms for 3 months; (2) it will allow us to make comparisons within the delayed arm from no intervention before to intervention after (months 3 to 6) the assessment; and (3) it will facilitate generating additional intervention data that can be pooled from the immediate and delayed intervention arms to obtain more robust estimates of intervention effect size to more accurately estimate sample size and power for an efficacy RCT in the future.

Primary Analyses

For outcomes A to D, descriptive statistics will be used to characterize the sample at each time point during the trial (baseline, month 3, and month 6), and by trial arm and couples' HIV serostatus. Descriptive statistics will also be used to summarize cohort characteristics, relationship functioning variables, and sexual behaviors by the trial arm and by couples' HIV serostatus. For couples, dyadic data will be calculated if there are no missing values from either partner. For continuous variables, couple-level mean variables will be generated by taking the averaged value from both partners' scores. For within-dyad variables, couple-level differences will be generated by taking the absolute difference between each of the partner's scores. Categorical dyadic variables will be generated based on whether both partners had the same or different answers. Two-sample 2-tailed *t* tests and chi-square tests will be used to evaluate differences between the immediate intervention arm and delayed intervention control arm for couple-level continuous and categorical independent variables, respectively, to further characterize the sample of couples in the trial.

An intention-to-treat (full analysis) approach will be used to determine the comparison between groups based on the initial randomization and using outcomes for all randomized individuals. The primary analysis will be to compare the proportions of couples with outcomes A, B, and D in the immediate intervention versus the proportions of couples with similar outcomes in the delayed control arm using a chi-square test with one degree of freedom in a univariate analysis from the corresponding contingency table. The efficacy rate will also be presented as the ratio between binomial proportions with CIs estimated through conventional methods used for the couple-level measurement.

Longitudinal analyses will also be conducted [52-54], specifically for outcome C, relationship functioning variables, to explore changes over time and whether these changes differ by arm and by couples' HIV serostatus. Specifically, generalized linear mixed-effects models (GLMMs) with SAS PROC GLIMMIX will be used to analyze the longitudinal data for outcome C from all 3 time points: baseline, 3 months, and 6 months after randomization. The analysis will fit a GLMM with fixed effects for time, a term for the pilot arm (immediate intervention vs delayed), and an arm-by-time interaction term. The GLMM will include random effects for the intercept and couple cluster (to account for within-couple correlation over time). Model fitting statistics will be used to determine the suitability of more parsimonious (eg, autoregressive) correlation structures and nonlinear effects for time. From the fitted

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GLMMs, the primary hypothesis will be examined by testing whether the coefficient of the group-by-time interaction term (the difference in slopes between immediate intervention vs delayed) is different from 0. The primary analysis will be performed at the couple level, with exploratory analyses performed at the individual level. For individual-level analyses, all models will use similar GLMMs with random effects to account for the intracluster correlation of couple members. We will also explore outcomes (A-D) at the individual level (n=120) by looking at each participant's changes over time as secondary analyses of interest using multilevel models.

Intention to Treat

An intention to treat approach [55-57] will be used to include all enrolled participants in the analysis. Any individuals or couples lost to follow-up will be assigned an adverse outcome (for outcomes A, B, and D) to be able to include them in the analysis. For outcome C, those lost to follow-up will have to be excluded as the outcome is continuous and there is no cutoff to determine an adverse outcome. This follows an intention-to-treat analysis plan where all randomized individuals are included in the final analysis independent of their participation after baseline assessment, which will also help ensure that the benefit of randomization to balance confounders is retained.

Relationship Dissolution

The approximate date and primary reasons for the relationship ending, including whether the reasoning is linked to study participation or intervention use, will be captured through the quantitative follow-up assessment or when the research staff contact participants, each month, to ensure that their contact information is current. To avoid intervention contamination and outcomes, couples who break up (ie, whose relationship has ended) during the pilot RCT will not be permitted to rejoin the study with a new partner. After completion of the pilot RCT, we will conduct a sensitivity analysis to quantitatively explore whether couples who break up comparatively differ from those who did not break up during the pilot RCT. Partners or couples' data will still be used in the intention-to-treat analysis plan via the last observation carried forward method [55,57]. On the basis of the principal investigator's prior intervention work with couples, we do not anticipate >5% of couples breaking up during the pilot trial. In the study by Mitchell [8] and another study involving couples [58], <5% of couples had ended their relationship while in the study, and none had reported their reasons as being associated with the study participation. In addition, the length of time that couples will wait before receiving the intervention is 3 months, which may further decrease the possibility of their relationship ending before receiving the intervention. For the reasons mentioned, we expect that the impact of couple dissolution will be minimal in creating systematically different samples between trial arms. However, we cannot predict the rate of relationship dissolution and will adjust analyses accordingly to account for any differences between trial arms and differences over time if observed.

Power, Sample Size, and Effect Size Estimations

All power calculations were performed with PASS 2020 [59]. For the couple-level analyses, with 60 couples randomized to 2 arms (30 couples in each), for outcome C, we will have 80% power to detect a difference of 0.75 SDs of the mean relationship functioning measure (large effect [60]) using a linear model. For the dichotomous outcomes A and B, we will have 80% power to detect an absolute difference of 35% between the intervention and delayed conditions using a chi-square test. Our power increases for the outcomes analyzed at the individual level, where the correlation between individuals within a dyad must be considered (ie, the interdependence of individuals nested within dyads). For the incidence rate of outcome D assuming Poisson distribution, 30 couples in each arm will have 80% power to detect a difference of 50% rate reduction in STI rate (including HIV) between the intervention and delayed conditions at 6 months assuming a within-pair coefficient of variation between clusters at 0.25 and the intraclass correlation coefficient as high as 0.1 (even higher ICCs do not reduce rate reduction measure in a significant or meaningful way magnitude wise). For all analyses, the α level was set at .05 with 95% CI. This is a feasibility and acceptability trial that is only powered to detect large effects; however, if effect sizes are lower than hypothesized, we will use that information to properly power a large-scale RCT.

Missing Data

Reminders and incentives will be used to maximize participation in the follow-ups. For the primary outcome measures, any missing data due to attrition would be handled as mentioned in the Intention to Treat section. In addition, missing data mechanisms [61-63] will be examined by comparing differences between the dropouts and the observed data. We will perform 25 conditional model-based multiple imputations within group using SAS PROC MI, and will aggregate the results into an overall group, time, and group-by-time interaction with SAS PROC MIANALYZE to provide unbiased intervention effects and their variances. This will also be advantageous if there is a differential dropout for the delayed condition due to wait time. To ensure the validity of the imputed data, 4 parallel models will be performed as a sensitivity analysis on (1) imputed data, (2) completers-only data, (3) assuming adverse outcome for those missing, and (4) applying GLMMs that have the advantage of handling incomplete unbalanced repeated-measures data by incorporating population average and subject-level trajectories, and in turn providing unbiased estimates of parameter of interests. If necessary, post hoc power analyses will be performed using the bootstrap method to calculate the observed power for the detected effect size.

Exploratory Secondary Analysis: APIM

To analyze for actor-partner effects using the APIM framework, we will arrange the data in a pairwise format following recommendations provided by Kenny et al [17]. Actor and partner effects will then be estimated using the generalized estimated equations algorithm described by Loeys et al [64], which accounts for the correlation between individuals within a couple using a robust variance estimate. The Wald test based on robust variance of the generalized estimated equations models

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performs quite well in testing actor and partner effects when the number of dyads is >50 [65]. Several models will be examined for significant actor-partner effects about cisgender SMM couples' outcomes of A and B. For each outcome, 2 actor-partner models will be constructed to test the impact of demographics and common relationship characteristics (model 1) separately from the impact of the average absolute change in relationship functioning variables (eg, couple mean and within-dyad difference) over time (model 2). Trial arm assignment will be controlled in each actor-partner model as a potential confounder. The parameter estimates produced from these models will be used to detect the actor-partner effects. To make the interpretation of the actor-partner effects more intuitive, we will convert the coefficients and 95% confidence limits to adjusted relative risk ratio and corresponding 95% confidence limits for presentation. Two-sided *P* values <.05 will be considered statistically significant. We will also consider analyzing joint and mutual joint effects based on time availability.

Results

This 6-month pilot RCT is ongoing. Recruitment, enrollment, and data collection began in January 2023 and ended in April 2024. A total of 74 adult cisgender SMM couples met all inclusion criteria, provided consent, and were enrolled in the pilot RCT. Retention was 92% (68/74) at month 6. Data are currently being analyzed to address the 3 specific aims. Findings will be disseminated through peer-reviewed journals and conference presentations.

Discussion

Principal Findings

This protocol describes the methods that will be used to conduct a 6-month pilot RCT to assess the feasibility, acceptability, and preliminary efficacy of P3, a couples-based DHI. Regarding feasibility, the enrolled sample exceeded the targeted sample size of 60 adult cisgender SMM couples by 23% (74/60), indicating a clear interest in this type of intervention and potential future public health service for the local population in Lima, Peru. Future findings from the trial will reveal details pertaining to which recruitment strategies worked best to reach the intended audience, how well the enrollment procedures worked, and the proportion of couples who were retained at the end of the 6-month pilot RCT along with reasons for attrition.

Findings relevant to the acceptability of P3 will be showcased using various data sources, all indicating whether couples deemed P3 to be acceptable as a couples-based DHI for meeting their prevention-care and relationship needs. Acceptability-related findings will also help describe potential areas to refine and improve P3.

It is anticipated that results from the pilot RCT will reveal the preliminary efficacy of the P3 DHI on couples' formation and adherence to an HIV and STI prevention-care plan containing evidence-based strategies (eg, routine testing, PrEP, and ART for U=U), formation and adherence to a detailed sexual agreement, and their perceptions that their prevention-care plan and sexual agreement were in alignment. In addition, preliminary efficacy results will highlight whether couples' relationship functioning, including mutual constructive communication and self-efficacy in working and making decisions together about their sexual health, improved over time. Finally, preliminary efficacy results will describe changes regarding partners' and couples' vulnerability to HIV and other STIs over time by analyzing self-reports of sexual behaviors (eg, CAS) and biomarker confirmation of test results.

Conclusions

The protocol details the methods of how the 6-month pilot RCT will be conducted and the expected findings from it. The ultimate goal of this line of research is to complement and expand HIV and STI prevention-care services by offering an effective couples-based DHI for adult cisgender SMM couples in Lima, Peru. Couples-based HIV serostatus neutral programs currently do not exist, despite the public health need for such research [6]. The anticipated next step of this research will include conducting a fully powered RCT to establish the efficacy of the P3 DHI. In addition, future research is needed to better understand the real-world barriers and facilitators of implementation and dissemination to sustainably offer P3 DHI within the realm of existing HIV- and STI- related services. As such, the next study would include conducting a hybrid type 1 trial [66,67] along with integrating the findings and lessons learned from this pilot trial.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Brief description of scale or items relative to couples interdependence theory for health behavior change construct.
[DOCX File , 23 KB - resprot_v13i1e63106_app1.docx]

Multimedia Appendix 2
Peer review report from HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 148 KB - resprot_v13i1e63106_app2.pdf]

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Abbreviations

ADAPT-ITT: Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing
APIM: actor-partner interdependence model
ART: antiretroviral therapy
CAS: condomless anal sex
CIT-HBC: Couples Interdependence Theory for health behavior change
CONSORT: Consolidated Standards of Reporting Trials
DHI: digital HIV serostatus-neutral intervention
FIU: Florida International University
GLMM: generalized linear mixed-effects model
P3: Para Ti, Para Mí, Para Nosotros
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SMM: sexual minority men
STI: sexually transmitted infection
U=U: undetectable=untransmissible
UPCH: Universidad Peruana Cayetano Heredia

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Protocol

Home-Based Digital Exercise Training Program to Improve Physical Function of Older Sepsis Survivors: Protocol of the HEAL Sepsis Randomized Clinical Trial

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Abstract

Background: While sepsis, an exaggerated response to infection, can affect people of all age groups, it is more prevalent in middle-aged and older adults. Older adults suffer worse short-term and long-term outcomes than younger patients. Older sepsis survivors are commonly discharged to long-term acute care facilities, where they often die within 1 year. Those who return home from the hospital lose the momentum of physical function improvement after early inpatient rehabilitation, and often face exacerbation of comorbidities and decline in physical function. Additionally, patients who are discharged home often live at distant locations and are not able to commute to rehabilitation centers due to their poor health status. Therefore, remotely delivered exercise interventions tailored to this population hold promise to improve physical function safely and effectively after sepsis. However, this type of intervention has yet to be tested in this population.

Objective: This study aims to assess the safety, feasibility, and ease of recruitment and retention of participants for a remotely delivered physical activity intervention for improving physical function in middle-aged and older sepsis survivors.

Methods: The proposed intervention will be delivered through a digital health platform that comprises a patient-facing mobile app and a 12-week physical activity program specifically designed for middle-aged and older sepsis survivors with poor health status who may face challenges participating in traditional out-patient or community-based exercise interventions. This study is ongoing and plans to enroll 40 sepsis survivors aged 55 years and older who will be randomized to either a remotely delivered exercise intervention group or a control group (electronic health diary). Both groups will use a tablet containing the Health in Motion app (Blue Marble Health). The intervention group will receive a clinician-designed personalized avatar-guided home exercise program and reminders while the control group will self-report daily activities using the in-app health diary feature.

Results: This study is the first to use a home-based, remotely monitored 12-week exercise program to improve physical function in sepsis survivors. This study will evaluate the safety, feasibility, and efficacy, providing the necessary knowledge to design and calculate power for future larger trials.

Conclusions: This study will provide important information for planning a future randomized clinical trial to test the efficacy of a remotely delivered exercise intervention in this high-risk population.

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Trial Registration: ClinicalTrials.gov NCT05568511; https://clinicaltrials.gov/study/NCT05568511
International Registered Report Identifier (IRRID): DERR1-10.2196/60270

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KEYWORDS

sepsis; physical function; exercise; rehabilitation; remotely delivered; aging

Introduction

Sepsis, an exaggerated response to an infection, affects all age groups [1]. However, adults aged 55 years and older are more commonly affected [2]. Despite reduced mortality, many sepsis survivors become critically ill with lasting low-grade multiple organ failure and systemic inflammation [3,4]. Older sepsis survivors are more likely to be discharged from the hospital to long-term acute care or skilled nursing facilities, and many require rehospitalization or die within 1 year [3]. Those who return home, often develop new or face exacerbation of preexisting comorbidities as well as a decline in physical function due to the lack of continuous physical function-enhancing interventions such as physical therapy (PT) or occupational therapy (OT) [1]. Postsepsis chronic systemic inflammation appears to perpetuate a decline in physical function in older adults by sustained muscle wasting leading to difficulties performing daily activities [1,4-6].

While early hospital-based PT and OT aim to improve physical function, patients often do not have access to structured interventions once discharged [7]. Thus, sedentary, home-bound sepsis survivors may be at high risk for stagnation or even worsening physical function, despite initial improvements in physical function gained during early rehabilitation. Therefore, there is a need for postdischarge exercise interventions customized to older sepsis survivors aimed at improving and sustaining their physical function at home. Aside from traditional home-based PT or OT available to a few individuals, a feasible home-based approach to improve the physical function of older sepsis survivors does not exist.

Current mobile health apps can deliver structured home-based exercise programs to reach daily activity goals. These mobile platforms can capture the most important outcomes, including physical function measures and adherence to exercise, entirely remotely via the mobile app. Data from assessments, exercise adherence, and response to exercise can be remotely monitored by the clinician at the clinical site who can remotely adjust the home exercise program to ensure the patient is performing the appropriate exercise dose and intensity. This unique approach can address the important issues of improving physical function in older sepsis survivors with poor health status, low physical function, and living in remote locations who are unlikely to participate in clinic-based exercise intervention programs. The goal of this paper is to describe a study protocol, that will test the feasibility and safety of a personalized 12-week digital, home-based, remotely monitored exercise intervention, compared to a control group who self-reports activities and does not receive exercise progression, in middle-aged and older sepsis survivors (Figure 1).

Figure 1. Conceptual model. V1: visit 1; V2: visit 2, V3: visit 3; V4; visit 4; V5: visit 5.

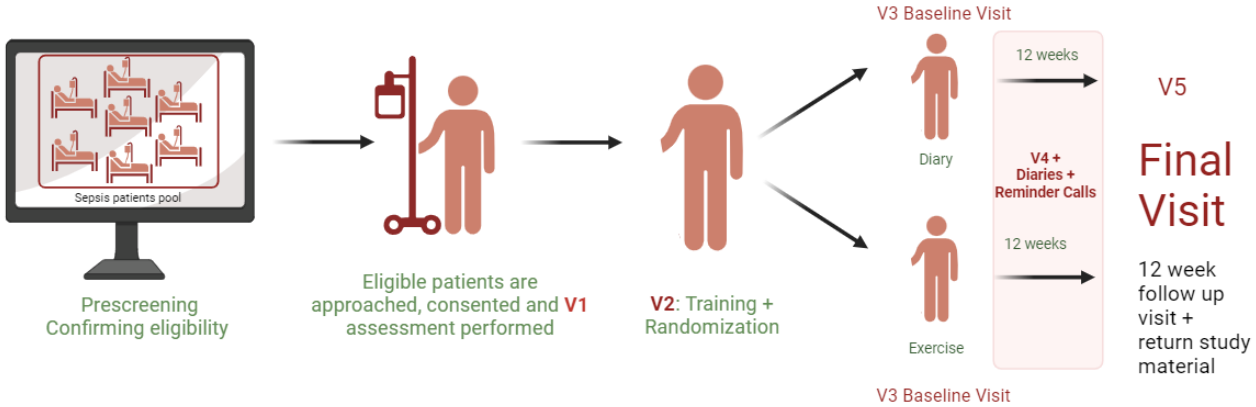

Methods

Study Design

To our knowledge, this will be the first single-blind, randomized clinical trial to evaluate the feasibility, safety, and efficacy of a 12-week remotely delivered intervention that administers avatar-guided exercise training with remote therapeutic monitoring to enhance physical function in middle-aged and older sepsis survivors. The study was registered with the database ClinicalTrials.gov (NCT05568511). The primary goals of this study are to test the safety and feasibility of this therapeutic intervention model. Safety is measured by the total number of adverse events occurring during the study period (primary) and the rate of adverse events per participant. The Health in Motion app (Blue Marble Health) allows for participants to report adverse experiences as well as illnesses, falls, and hospital visits. The participants will be encouraged to report all potential adverse events, and hospital records will be monitored regularly by study staff. Feasibility will be

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measured by adherence rates, completion rates, evaluation of reasons for withdrawal or noncompletion, and the number and nature of reports regarding technical difficulties that participants encounter while using the app. Efficacy will be measured by the mean change in the 30 second sit to stand test (30SSTS), the 4 stage balance test (4SBT), and timed up and go test (TUG) as measures of physical performance (secondary outcomes). The EQ-5D-5L will be used to capture self-reported health-related quality of life.

Participants

This study will enroll 40 sepsis survivors aged 55 years and older with in-hospital short performance physical battery (SPPB) scores≤10 who will be discharged from the hospital and have access to Wi-Fi at home as the app requires it for proper use. Sepsis survivors who (1) will be discharged to a long-term facility, (2) will be involved in a structured rehabilitation program, (3) are unable to perform lower or upper body exercise, (4) have severe cardiac disease (New York Health Association class III or IV), (5) are significantly immunocompromised, (6) have been diagnosed with significant cognitive impairment, (7) have progressive degenerative neurological disease, (8) have severe pulmonary disease that requires steroid therapy or the use of supplemental oxygen, (9) are participating in another interventional study, or (10) are pregnant will be excluded. An overview of inclusion and exclusion criteria is provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Able to perform lower- and upper-body movements
- Sepsis survivor
- Aged 55 years and older
- Short performance physical battery (SPPB)≤10
- Being discharged to home from the hospital after surviving sepsis
- Willingness to be randomized to either treatment or control group
- Willingness to use the devices and technology in the study
- Willingness to participate in all study procedures

Exclusion criteria

- Failure to provide informed consent
- Pregnant
- Discharge to a long-term facility
- Involvement in a structured rehabilitation program
- Inability to perform lower or upper-body exercises (eg, being in wheelchair)
- Severe cardiac disease, including New York Health Association class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina
- Diagnosed significant cognitive impairment, including known dementia diagnosis
- Organ transplant recipient on immunosuppressive agents
- HIV or AIDS with CD4+ T-lymphocytes count <200
- Severe immunocompromised state (eg, participant has neutropenia receiving cytotoxic chemotherapy with absolute neutrophil count <500/ul or expected to decline to <500/uL within the next 3 days)
- Progressive, degenerative neurologic disease (eg, Parkinson disease), multiple sclerosis
- Severe pulmonary disease, requiring either steroid pills or injections or the use of supplemental oxygen
- Simultaneous participation in another intervention trial
- No internet access in primary place of living

Recruitment

This study is ongoing. The study suggested timeline is from May 1, 2023, to April 30, 2025. Table 1 provides a breakdown of data to be collected at each visit.

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Table 1. Data collection summary by study visit.

Study phase	Hospital or home[a]	Hospital or home[a]	Home-based assessments		
Time-point description	Screening visit[a] (V1)	Check-in visit[a] (V2)	Baseline visit[a] (V3)	Follow-up visit[a] (V4)	12-week follow-up visit (V5)
Week	–8 to 0 weeks	–2 to 0 weeks	0 week	1 to 12 weeks	12 weeks (V5: –3 to + 7 days)
Method of the visits	In-person	In-person	Zoom call	Weekly call	Zoom call
Consent, review of inclusion or exclusion criteria	✓[a]				
Demographic and contact information	✓[a]				
Medical history review	✓[a]				
Medication inventory	✓[a]		✓		✓
Release of medical records authorizations form	✓[a]				
Depression questionnaire using CES-D[b]	✓[a]				
Short physical performance battery test	✓[a]				
Pregnancy test		✓		✓[c]	
Randomization		✓			
Distribute TheraBand		✓			
Distribute or collect tablets and pre-addressed return package		✓			✓
Update of medical history			✓		✓
MOCA/BLIND[d]			✓		✓
Quality of life questionnaire—EQ-5D-5L version (via app)			✓		✓
Timed up and go (via app)			✓		✓
30 second sit to stand test (via app)					
4 stage balance test (via app)					
Collection of adverse experiences	✓[a]		✓	✓	✓
ECOG[e]/WHO[f]/Zubrod Scale			✓		✓

[a]Screening visit (V1) and check-in visit (V2) may be scheduled on the same day for those patients recruited after hospital discharge.

[b]CES-D: Center for Epidemiologic Studies Depression Scale.

[c]We will send urine pregnancy tests every month for participants to complete at home. Pregnancy status will also be reassessed during the weekly calls.

[d]MOCA/Blind: Montreal Cognitive Assessment.

[e]ECOG: Eastern Cooperative Oncology Group.

[f]WHO: World Health Organization.

Participant Prescreening in the Electronic Health Records

Participants will be recruited at the University of Florida Health Shands Hospital in Gainesville, Florida, United States. Recruitment will start by reviewing admitted patient lists in the EPIC electronic health record (EHR) system (Epic Systems Corp). Participants must meet study criteria as well as qualify as septic using sepsis 3 criteria (sequential organ failure assessment score ≥2 compared to baseline with identified source of infection) [8]. All hospitalized patients with sepsis will be managed via the evidence-based management protocol that emphasizes early antibiotic administration, fluid resuscitation, and hemodynamic monitoring and support, consistent with current Surviving Sepsis Campaign guidelines [9,10]. Patients who screen positive for sepsis and are being treated by the standard-of-care sepsis protocol will be candidates for this study. Prescreening enables more patients to undergo screening since staff clinicians are unable to screen potential participants as part of their typical work duty.

In addition to the EPIC EHR review, clinical staff members, including physicians who serve as co-investigators or nurse coordinators, might recognize potential patients under their care

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and request the study team to assess their eligibility more thoroughly.

Confirmation of Eligibility

Once the clinical prescreening is complete, the study team physicians (also employed at the University of Florida Health Shands Hospital) or study staff (if a nonphysician clinical staff identified the potential participant) will confirm eligibility via a chart review.

Approaching Participants in the Hospital

Study staff will inform the clinical staff as to the potential participant's eligibility and will request the clinical staff to approach the patient to gauge the patient's interest in participating in the study. Once the patient expresses interest, the clinical staff will inform the study staff who will introduce the study to the patient more formally. If the study staff cannot speak with the patient directly to assess their study interest, either because of the patient's location or time constraints, the study staff will ask a member of the patient's clinical team, nurse or physician, to inquire about the patient's interest in participating in the study. Patients will not be approached by the research coordinator until a member of their clinical staff has made initial contact and confirmation of their interest has been received by a member of the study team. If potential participants would like to learn more about the study but do not want to be approached by the study staff, they will be offered the study flyer that contains more information about the study and the study coordinators' contact information and will be asked to contact the study coordinator if interested.

Research coordinators will approach the patients within 7 days before discharge or up to 3 days after discharge, for those patients who were discharged after business hours. The coordinator will consent the appropriate candidates and then further confirm their eligibility. Consent will be sought by coordinators, all of whom are familiar with institutional logistics and infrastructure and are experienced in the nuances of enrollment and informed consent for this challenging patient population. Coordinators will also monitor the clinical trajectory daily in the EPIC EHR and look for notes related to patient discharge planning. Consecutive patients meeting the criteria will be enrolled daily between 7 AM and 10 PM.

Visit 1

Following the participants' consent, they will undergo additional assessments to establish their eligibility, which will take place during visit 1 (also referred to as V1). Participants' medical history and medication inventory will be reviewed for safety and to further confirm eligibility. Participants will also be asked to complete the SPPB which is an in-person physical function test comprising a 4-meter walk, repeated chair stands, and 3 increasingly difficult standing balance tests [11,12]. Participants scoring >10 points on the SPPB will be excluded from the study. Participants will also be screened for depression using the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire. If participants score≥16 on the CES-D, their clinical care team will be notified to provide them with appropriate care [13]. These participants will also be encouraged to discuss the results with their primary care physician. We will also collect demographic information as well as have participants sign a medical records release form. If the participant does not wish to schedule visit 2 (V2) at the end of visit 1, study staff will schedule a time to contact the participant per their request. Coordinators will leave their contact information with the participant.

Demographics, Medical History, and Medication Inventory

Participants will be asked to provide demographic information including birth date, address, phone number, sex at birth, gender, and ethnic background. Coordinators will use a case report form approved by the institutional review board to collect this information. Medical history will be assessed during prescreening but will be confirmed with the participant at V1 using a questionnaire. Participants will be asked a series of questions about their medical history to which they can answer "yes," "no," "I don't know," or "decline to answer." Medication inventory will also be collected. Initially, outpatient medications will be assessed using the patient's medical records, confirmed during V1, and will be confirmed with the patient.

Visit 2

A second in-person home or hospital visit, V2, will be scheduled with each participant to explain all aspects of the study.

Participants will be randomized to either an intervention or a standard care control group immediately prior to this visit. All participants will be provided with tablets preloaded with both the Health in Motion and the Zoom apps. Before the visit, the study staff will ensure that all study devices are functional. The tablet will be Wi-Fi enabled for connection with a home internet network. Participants will receive in-person training and paper instructions on how to use and navigate Zoom call, tablet, and the Health in Motion app. The Zoom app will be used to connect with research study staff during the remote assessment visits. The participant will demonstrate understanding by reviewing the explained process with the study staff. Female participants who are aged 55 to 62 years with undetermined childbearing status per their medical records will be required to complete a urine pregnancy test during V2. Additionally, study coordinators will use information gleaned from conversations with the participant and their family members as well as a review of medical records to assess the participant's ability to complete activities of daily living (ADL). In addition, we will use the Eastern Cooperative Oncology Group score, also called the Zubrod score (ECOG/Zubrod), to subjectively score their baseline abilities to complete ADL prior to hospitalization. Participants will also be given a prepaid or preaddressed box with packing supplies to mail any relevant study material back to the study team. In addition, participants randomized to the intervention group will receive rubber resistance bands (THERABAND) to add resistance to exercises as they progress.

Remote Assessment Visits

Remote assessments will take place after the home visit and after –3 to +7 days of completion of the 12-week intervention phase. These visits are identified as baseline or V3 and 12-week follow-up or V5, respectively. Assessments will be conducted over Zoom by blinded study staff. Study staff will ensure the

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participant is performing the assessments properly and will visually monitor the safety of the participant. Assessments include a combination of physical function tests (TUG, 30STST, and 4SBT) and self-reported questionnaires (EQ-5D-5L, The Montreal Cognitive Assessment [MOCA-Blind], and ECOG/Zubrod).

Physical Function Assessments

Physical assessments include TUG [14], 30SSTS [15,16], and 4SBT [17] which are the primary efficacy outcomes for this study. These assessments are administered remotely through the Health in Motion app. The physical function tests will be completed at V3 and V5.

The TUG test [14] measures the time taken to stand from a seated position, walk 3 meters (about 10 feet), turn around, walk back, and sit down. This test measures fall risk, mobility, frailty, and lower extremity function. Two trials are completed and the faster of the 2 trials is the final score.

The 30SSTS [15,16] measures the number of times the participant can stand up from a seated position in 30 seconds. This test measures endurance and leg strength. The score is the total completed number of stands.

The 4SBT [17] measures an individual's fall risk via their ability to hold static balance positions. This test consists of 4 stages of static balance positions, each progressively more difficult to maintain. Stage 1 is standing with feet touching side to side, stage 2 positions the feet in a semitandem position, stage 3 is full tandem, and stage 4 requires the individual to balance on 1 leg. In order to progress to the next stage, the static balance position must be maintained for 10 seconds without moving their feet or needing support. The total number of seconds a participant is able to hold the position for each stage becomes their score for a max score of 40. If a participant is not able to complete a stage, the test stops at this point and all subsequent stages are scored 0.

Self-Reported Questionnaires

At the initial screening visit (visit 3 [V3]) and the 12-week follow-up (visit 5 [V5]), a blinded study coordinator will administer questionnaires to evaluate participants' cognitive function (MoCA/BLIND), quality of life (EQ-5D-5L), and self-perceived physical limitations (ECOG/Zubrod).

CES-D is a 20-item assessment tool that evaluates an individual's depression symptoms by using commonly used self-statements that mirror their mental state. Participants will report the frequency with which they identify with these self-statements, such as "I felt hopeful about the future," over the past week. Ratings are assigned on a 4-point Likert scale, ranging from 0=rarely or none of the time (0-1 days) to 3=most or all the time (5-7 days).

The MoCA/BLIND questionnaire serves as a screening tool for identifying cognitive impairment by evaluating various domains, including short-term memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to time and place. The MoCA-BLIND is an abbreviated telephone version that has no visual elements, scored out of 12 [18].

The EQ-5D-5L assessment will be administered using the Health in Motion app. It consists of inquiries about mobility, self-care, pain, usual activities, and psychological well-being, each with 5 response options (1=no problem, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=unable). A summary index, with a maximum score of 1 will be generated from these 5 items using the US conversion table. The maximum score of 1 represents an optimal health state. Higher scores on individual indices reflect greater frequency and severity of issues.

Scored Questionnaires

Unblinded coordinators will use the ECOG/Zubrod scale during V2, V3, and V5 to characterize the patient's level of functioning in terms of performing ADLs and physical ability. The ECOG/Zubrod scale consists of 5 categories numbered 0-5 with 0 being fully independent with no limitations, 4 being completely disabled (bed-bound, wheelchair-bound) and unable to perform self-care, and 5 as dead. The score is established by a study coordinator in the most unbiased manner through interviews conducted with both patients and their family members as well as chart reviews.

Exercise Intervention

After the baseline visit, participants in the intervention group will be asked to begin the personalized exercise training program. This will consist of 12 weeks (5 days per week) of a guided exercise intervention program. Each session will consist of a 5-minute warm-up, followed by a 20-minute combination of aerobic and resistance or bodyweight exercises, stretching, and balance activities, and a 5-minute cooldown. In the early weeks of intervention, participants are mainly assigned 20-30 balance, stretching, and mobility activities with about one-third of exercises consisting of light strengthening activities including side-stepping, body weight rowing, and arm presses. There is equal emphasis on upper and lower body exercises and movement. As the intervention progresses throughout the 12 weeks, up to approximately 40 total exercises are assigned, with the goal of about half being more advanced strengthening exercises such as heel raises, chair push-ups, chest presses, and bicep curls using THERABANDs. Aerobic exercise mainly consists of walking, with progressively longer intervals assigned throughout the intervention.

According to the American College of Sports Medicine/American Heart Association guidelines, the intensity of exercise will be monitored using 10-point category-ratio scale, similar to the Borg scale, in which a score of 0=no physical exertion at all and 10=the extreme intensity of activity) [19,20]. Participants will be instructed to exercise at a self-perceived exertion level of approximately 3-4 and will be prompted to report their exertion level in the app throughout their daily exercise sessions. Coordinators will monitor their perceived exertion level and will adjust the intensity depending on participants' progress and self-exertion score. The intensity of the resistance exercises will be increased with either the addition of the THERABANDs, an increase in the number of repetitions, and the elimination or reduction of a support mechanism for balance purposes.

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Reminder Calls, Compliance, and Adherence

For reminder calls, all participants will receive regular phone calls to check on their health status, reminding them to charge the tablets, and to capture reports of adverse events. For the intervention group, participants will be contacted daily (5 days/week) for the first 2 weeks of the intervention. After 2 weeks for the intervention group and for the entire duration of the study for the control group, participants will be contacted weekly. We will reassess their childbearing status during the weekly calls, if applicable. If a participant reports that they could potentially be pregnant, they will be sent the urine pregnancy test via mail promptly to confirm their pregnancy status.

Compliance, for this study, is defined as the number of days exercising for 30 minutes per week; exercising 5 times/week for at least 30 minutes reflecting a 100% compliance.

Adherence, for this study, is defined as the number of days in which exercise was attempted or completed; logging into the app 5 times/week reflecting 100% adherence regardless of exercise time.

Compliance and adherence to their training schedule will be emphasized to the intervention group and they will be evaluated for any barriers if they miss 2 consecutive days or more of the exercise. Compliance and adherence will be monitored throughout the study duration remotely using the app's administrative dashboard. Participants may experience complications that may impact compliance and adherence to the exercise program. Common causes of poor compliance and adherence include vacations, spousal care, fatigue, fluctuations in motivation, perceived lack of benefit, physical discomfort, and adverse health experiences.

Health Diary Entries

Participants in the control group will document their daily activities using the health diary feature available in the Health in Motion app. If any participant feels unsafe performing a test or their daily intervention program (if in the intervention group), they may skip the activity and input their reason within the textbox feature in the in-app diary.

Safety

Several procedures will be adopted to ensure participant safety. Trained study personnel will explain potential adverse events and risks related to the study activities will be explained to the participants during the informed consent process by our trained study personnel. The study's purpose and methods will also be explained in simple, easy-to-understand language. They will be encouraged to read the informed consent and ask questions. Adverse events will be collected and monitored by research staff during weekly calls and scheduled assessments. Participants will be encouraged to report the occurrence of adverse events in their in-app health diary within 48 hours of the occurrence. Participants will have access to study personnel 24 hours per day, 7 days a week to report serious adverse events or concerns regarding safety. They will be given the phone number of both the principal investigator and the lead research coordinator for urgent matters. Coordinators will also record adverse events that occur during functional assessments. The principal investigator and the study physician will review the reported adverse events to ensure the participants are safe to continue participating in the study. In consultation with the study physicians, a participant may be asked to seek medical attention or to schedule an in-person or telemedicine visit with the study physician.

Participants in the intervention group (group 1) will take part in warm-up and cooldown exercises to minimize discomfort and injury. Exercises will begin with low intensity and will gradually increase depending on the participant's progress and reported exertion level in prior sessions. During V2 (in-home or hospital), participants will be advised to move slowly when attempting to rise from a seated or lying position as they are at risk of experiencing orthostatic hypotension. Further, participants will be instructed to stop the guided exercise when they feel pain, tightness, or pressure in the chest, significant shortness of breath, feeling faint, lightheaded, or dizzy, or significant other symptoms or medical problems. They will be instructed to report the event into the Health in Motion app and report it to the coordinator either immediately or in the next weekly call. The number of safety and adverse events will be tabulated as a primary safety outcome. At the end of the study, we will assess the safety of the proposed interventions by assaying the number of adverse events and serious adverse events reported in the exercise versus the control group.

Female participants aged 55 to 62 years will also complete urine pregnancy tests at home every month during the intervention period.

Statistical Analyses

For qualitative measures, we will assess if the intervention is feasible, meaning relevant to this population and sustainable, by assessing participant feedback regarding the practicality of using this program, time commitment expectations, and ease of using the app among a diverse population in terms of age, sex, race, socioeconomic status, and baseline mobility. Safety will be evaluated by keeping in close contact with participants and asking them to report any discomfort, injury, or safety concerns.

The primary efficacy analysis will follow an "intent-to-treat" model [21]. For quantitative measures, differences in mean outcome measures and effect sizes between intervention groups will be calculated. Baseline characteristics of participants who do and do not have follow-up measures will be compared for missing data analysis. The relatively small sample size may imbalance prerandomization covariates [22]. Thus, caution will be taken in the interpretation of hypothesis tests.

Ethical Considerations

Human Subject Ethical Review Approvals or Exemptions

Per institutional guidelines, this study has been reviewed and approved by the University of Florida's institutional review board, under the project number IRB202200027. This study will operate under a partial Health Insurance Portability and Accountability Act waiver, allowing limited access to participant medical records only as deemed necessary by appropriately

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trained study staff. Study staff will minimize access to protected health information to what is absolutely necessary to determine candidacy for the study.

Informed Consent

During the informed consent process, participants are informed of their right to opt out of the study at any time with no penalties. For secondary analyses using existing data, we do not require additional consent. Study data are deidentified at the analysis phase, for additional scenarios where informed consent may not be required.

Privacy and Confidentiality

Each participant is given a unique identifier (HS0X with X being enrollment order in ascending order). The participant's name is collected and kept in their binder, but data when input to REDCap (Vanderbilt University) are deidentified. Binders are kept under double-lock conditions. After the closure of the study, identifying information will be removed from the participant's binder.

Compensation Details

Participant payment outlines are discussed in the informed consent process including all potential payments they can be eligible for should they complete the study, payment schedule, and method of payment. Participants are paid US $50 during their baseline Zoom visit, US $50 at 4 weeks, US $50 at 8 weeks, and US $150 once they have completed the 12-week follow-up visit and returned the tablet via mail. If a participant has to travel to complete a screening visit within 72 hours of enrollment, they will be compensated an additional US $10. There are no other exceptions for the rate of payment, as long as a participant continues to comply with study guidelines they are compensated as stated.

Results

Previous research studies suggest that physical activity interventions prevent mobility disability in rather healthy older adults [1,18,23]. However, older sepsis survivors are frailer, more sedentary, and lower-functioning, and are more likely to struggle to travel to exercise or rehabilitation facilities to receive supervised exercise training programs than older adults of the same age [7,24]. To our knowledge, this will be the first home-based therapeutic approach with remote therapeutic monitoring, to improve the physical function of older sepsis survivors using a 12-week exercise program delivered via a digital health platform. The goal of this study is to evaluate the safety and feasibility of this remotely delivered exercise program. Additionally, it will assess the efficacy of the intervention and provide descriptive estimates of effects, and nominal estimation of the mean changes in physical function. Evaluating feasibility through this study will also help to the assess ease of recruitment and retainment of participants, adherence to study intervention protocol, and safety by assessing the percentage of serious adverse events reported. These data will be used to estimate the power needed for a larger randomized clinical trial. As of August 2024, 15 eligible patients have been enrolled in the study. Screening and recruitment are still ongoing and are estimated to be completed by January 2025.

Discussion

The study design is built upon the work of similar studies but with a few novel features. Several studies have shown that mainly home-based exercise programs delivered over several weeks with progressively more difficult exercises are efficacious at improving physical function in older adults with [3,25,26] and without chronic illness [18,27]. Many of these studies are home based but are not remotely or digitally delivered like our study. We anticipate that this will enhance the program's accessibility for individuals facing geographical barriers or transportation challenges, residing in remote regions, or those for whom physical intervention programs have not been recommended by their health care providers.

Furthermore, drawing from comparable research on home-based exercise regimens for older adults and individuals recovering from critical illness, our exercise program advances participants through increasingly challenging exercises. However, we have added a novel component with the ability to adjust exercise difficulty based on perceived exertion rating scales. In fact, this was identified as a limitation from a study closely resembling ours [2].

The participants are another unique aspect of our study. We are unaware of any home-based exercise program studies whose population solely consists of patients hospitalized for sepsis. This builds upon existing literature which has shown that in-hospital rehabilitation is associated with less physical disability once released from the hospital [20,28]. Often, these patients do not continue the momentum of exercise at home. It must be noted that there is also a need for sepsis-specific studies, as compared to patients hospitalized for other reasons because those hospitalized for sepsis have higher rates of physical disability when discharged [29-31].

Another notable limitation of previous studies is the lack of baseline data, which made it difficult to identify individuals who would benefit the most from rehabilitation after critical illness [2,3]. This challenge is addressed in our study design. Baseline data are measured using several methods that have been validated by experts [4-6,24] for comparison at follow-up evaluation. We will also prevent patients who may be physically fit and will not receive extra benefits from this study by excluding those who score less than 10 on the SPPB at the screening encounter.

In addition to many novel features, there are some notable strengths to our study design. To mitigate anticipated issues with adherence, our team will be in regular contact with participants and will ask specific questions to facilitate identifying and intervening on issues before they arise. Additionally, our team will use a feature on the Blue Marble Health app that allows for monitoring of compliance with daily exercise. A social problem-solving approach will be used to identify and address compliance issues. To mitigate potential dropout, all study procedures will be conducted remotely or are designed to be convenient for participants. V2 will occur while the patient is in the hospital, or the study staff will travel to the participants' homes to provide them with study materials and instructions for use. Otherwise, the entire program including

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assessments and check-ins is delivered remotely. Additionally, our team meets weekly to discuss concerns and strategies to proactively address problems.

As for the study limitations, first, enrollment of participants in the critical care hospital setting will be challenging. This population is often too ill to participate in an exercise intervention program, and many are referred to outpatient rehabilitation or nursing facilities where they will receive PT or OT. Another pertinent limitation is the lack of true baseline data regarding the prior level of function. Study staff will review participants' medical records and collateral may be obtained from friends and family but ultimately all information is subjective. Finally, although we will be able to monitor how much time is spent on each exercise and how many repetitions are completed, there is no definitive way to confirm if the exercises are being performed correctly or at the intensity required to improve physical function, which presents a limitation for monitoring the participants' true exercise participation.

Collectively, the concepts, methodology, and interventions involved in this study are novel to the field of critical care medicine, geriatrics, and rehabilitation. As sepsis is often associated with high rates of morbidity and mortality, understanding how to minimize these effects through rehabilitation is critical to older individuals' long-term health outcomes and quality of life. If our program is found to be safe, efficacious, and feasible for use in older sepsis survivors, we hope to further assess viability of this program in improving physical function outcomes using a larger sample size.

Acknowledgments

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Authors' Contributions

RTM is the principal investigator of the study. RSZ, MKO, and NE were involved in writing this manuscript. RSZ, MKO, LLH, and YL are research coordinators for the study. PAE, NB, and JSD are the physicians of the study. SF is the chief operating officer of Blue Marble Health. PAE, FWG, CL, SDA, and BS are coinvestigators on the study.

Conflicts of Interest

SF is the co-founder and CEO of Blue Marble Health, the developer of the software Platform used in this study.

Multimedia Appendix 1
Peer review report from the Aging Systems and Geriatrics (ASG) Study Section - Brain Disorders and Clinical Neuroscience Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 80 KB - resprot_v13i1e60270_app1.pdf]

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Abbreviations

30SSTS: 30 second sit to stand test
4SBT: 4 stage balance test
ADL: activities of daily living
CES-D: Center for Epidemiologic Studies Depression Scale
ECOG: Eastern Cooperative Oncology Group
EHR: electronic health record
MOCA/Blind: Montreal Cognitive Assessment
OT: occupational therapy
PT: physical therapy
SPPB: short physical performance battery
TUG: timed up and go test
V1: visit 1
V2: visit 2
V3: visit 3
V5: visit 5

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Protocol

Development and Testing of a Mobile App for Management of Gestational Diabetes in Nepal: Protocol for a User-Centered Design Study and Exploratory Randomized Controlled Trial

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Abstract

Background: The prevalence of gestational diabetes mellitus (GDM) is increasing, particularly in low- and middle-income countries (LMICs) like Nepal. GDM self-management, including intensive dietary and lifestyle modifications and blood glucose monitoring, is critical to maintain glycemic control and prevent adverse outcomes. However, in resource-limited settings, several barriers hinder optimal self-management. Mobile health (mHealth) technology holds promise as a strategy to augment GDM treatment by promoting healthy behaviors and supporting self-management, but this approach has not yet been tested in any LMIC.

Objective: This report describes the protocol to develop a culturally tailored mHealth app that supports self-management and treatment of GDM (GDM–Dhulikhel Hospital [GDM-DH] app, phase 1) and test its usability and preliminary efficacy (phase 2) among patients with GDM in a periurban hospital setting in Nepal.

Methods: The study will be conducted at Dhulikhel Hospital in Dhulikhel, Nepal. In the development phase (phase 1), a prototype of the GDM-DH app will be developed based on expert reviews and a user-centered design approach. To understand facilitators and barriers to GDM self-management and to gather feedback on the prototype, focus groups and in-depth interviews will be conducted with patients with GDM (n=12), health care providers (n=5), and family members (n=3), with plans to recruit further if saturation is not achieved. Feedback will be used to build a minimum viable product, which will undergo user testing with 18 patients with GDM using a think-aloud protocol. The final GDM-DH app will be developed based on user feedback and following an iterative product design and user testing process. In the randomized controlled trial phase (phase 2), newly diagnosed patients with GDM (n=120) will be recruited and randomized to either standard care alone or standard care plus the GDM-DH app from 24-30 weeks gestation until delivery. In this proof-of-concept trial, feasibility outcomes will be app usage, self-monitoring

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adherence, and app usability and acceptability. Exploratory treatment outcomes will be maternal glycemic control at 6 weeks post partum, birth weight, and rates of labor induction and cesarean delivery. Qualitative data obtained from phase 1 will be analyzed using thematic analysis. In phase 2, independent 2-tailed *t* tests or chi-square analyses will examine differences in outcomes between the 2 treatment conditions.

Results: As of July 2024, we have completed phase 1. Phase 2 is underway. The first participant was enrolled in October 2021, with 99 participants enrolled as of July 2024. We anticipate completing recruitment by December 2024 and disseminating findings by December 2025.

Conclusions: App-based lifestyle interventions for GDM management are not common in LMICs, where GDM prevalence is rapidly increasing. This proof-of-concept trial will provide valuable insights into the potential of leveraging mHealth app–based platforms for GDM self-management in LMICs.

Trial Registration: ClinicalTrials.gov NCT04198857; https://clinicaltrials.gov/study/NCT04198857

International Registered Report Identifier (IRRID): DERR1-10.2196/59423

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KEYWORDS

gestational diabetes mellitus; mobile health; mHealth; self-management; pregnancy; maternal and child health; South Asia; Nepal; low- and middle-income country; mobile phone

Introduction

Background

Gestational diabetes mellitus (GDM), characterized by hyperglycemia that develops during pregnancy, is one of the most common and increasingly prevalent pregnancy complications [1,2]. The International Diabetes Federation estimated that approximately 14% of pregnancies worldwide were affected by GDM in 2021 [2]. A significant proportion of these cases occur in low- and middle-income countries (LMICs), where over 90% of type 2 diabetes (T2D) cases in adults are also reported [3]. In Nepal, a low-income country in South Asia, the national prevalence of GDM is not documented, but regional estimates are high, ranging from 6.6% to over 20% [4-6].

GDM is associated with increased risks of adverse maternal and fetal outcomes, including preeclampsia, birth injuries, labor complications, cesarean delivery, and large for gestational-age babies [7-9]. Although GDM usually resolves after delivery, women with GDM are more likely to develop T2D in the future compared to women with normoglycemic pregnancies [10,11], and fetal exposure to maternal hyperglycemia may predispose offspring to obesity and T2D [12,13]. GDM is also a significant economic burden, with estimated costs from GDM and its downstream consequences ranging from £147 (US $196) million to US $1.6 billion in high-income countries [14,15].

Adequate management of GDM, including diet and lifestyle modifications and frequent self-monitoring of blood glucose, reduces maternal and neonatal complications [16,17]. However, in resource-limited settings like Nepal, GDM management constitutes a significant burden on both patients and the health care system [18,19]. Scalable and cost-effective strategies are thus needed to manage the growing burden of GDM and its consequences in low-resource countries such as Nepal. Barriers to the management of GDM in Nepal exist at multiple levels, including those at the individual (eg, health literacy, lack of knowledge or self-efficacy, and time constraints), interpersonal (eg, cultural practices and family influence on prenatal care decisions) [20-22], and health systems or structural (eg, access to health care, resources, transportation, availability of clinicians, and time for counseling) level [18,23-26]. Mobile health (mHealth) technology provides opportunities to address these multilevel barriers by enhancing self-efficacy and knowledge, promoting self-management behaviors relating to GDM, and facilitating communication between patients and their health care team [27,28]. Evidence from high-income countries shows that mHealth interventions for GDM can improve patient satisfaction and reduce costs [29,30], while achieving better or similar maternal glycemic levels and pregnancy outcomes compared to standard care alone [31]. Nepal has high rates of mobile service penetration among people who are pregnant [32], and prior studies in LMICs support the use of mHealth technology during pregnancy for health promotion, appointment reminders, and improved nutritional status [33-36].

Despite the evidence supporting the use of mHealth technology to improve the self-management of GDM, digital tools for GDM have not been designed to address the unique needs of people who are pregnant and living in LMICs. Innovative and culturally tailored approaches are needed to optimize self-management of GDM in low-resource settings like Nepal [37]. The aim of this paper is to describe the protocol to develop and test the usability, acceptability, and preliminary efficacy of a user-centered, culturally tailored mHealth platform (GDM–Dhulikhel Hospital [GDM-DH] app + web portal) designed to support self-management and treatment of GDM among patients in a periurban hospital setting in Nepal.

Objective and Hypothesis

In the first phase of the study, our objective is to develop an app prototype for the GDM-DH platform, gather user feedback on the proposed GDM-DH platform, and identify barriers and facilitators to its uptake. In the second phase, we will evaluate the preliminary efficacy of the GDM-DH platform alongside standard care, compared to standard care alone, on perinatal health outcomes, including maternal blood glucose levels, birth weight, and neonatal hypoglycemia. We hypothesize that the GDM-DH platform will show good usability and preliminary efficacy for improving perinatal health outcomes.

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Methods

Study Overview

The study consists of two phases: (1) the design and development of the GDM-DH app platform and (2) a proof-of-concept randomized controlled trial (RCT) to assess its usability, acceptability, and preliminary efficacy (Figure 1). This study will be conducted at Dhulikhel Hospital, a community-based, flagship university hospital of Kathmandu University in Nepal. Dhulikhel Hospital has a catchment population of 1.9 million people and delivers approximately 3000 babies annually [38]. This trial is registered on ClinicalTrials.gov (NCT04198857).

Figure 1. Overview of the study design. GDM-DH: gestational diabetes mellitus-Dhulikhel Hospital.

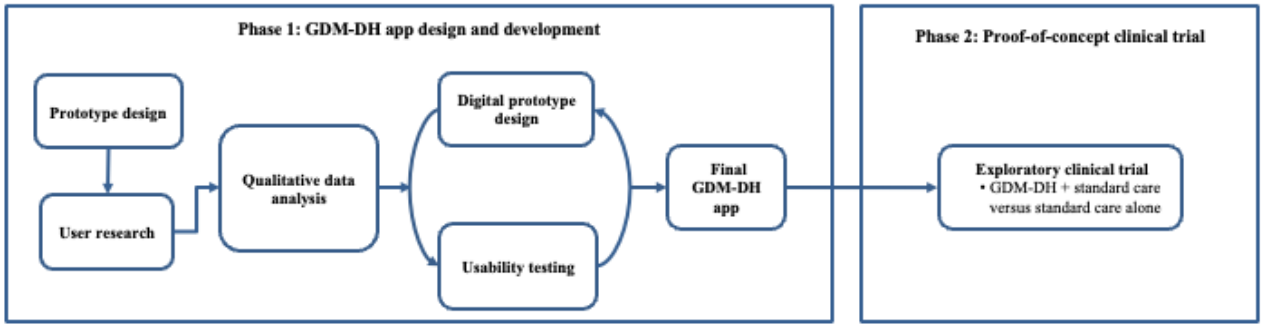

Ethical Considerations

Institutional approval for this study was granted by Rutgers University Newark Health Sciences institutional review board (Pro2019001883 [phase 1] and Pro2019002841 [phase 2]) and the ethical review board of the Nepal Health Research Council (registration 735/2019). All potential human participants will receive an explanation of the study at screening, including study rationale, procedures, and appointment schedules. Eligible participants will receive a detailed description of the study, including possible risks and benefits, measures to protect privacy, and the right to terminate involvement in the study at any time. Signed written informed consent will be obtained from each participant by a trained research assistant at Dhulikhel Hospital. Enrollment procedures will occur in a private room. To maintain participant confidentiality, documents and forms with identifying information will be stored separately in a locked filing cabinet and in a secure password-protected Box folder (Box Inc), a Health Insurance Portability and Accountability Act (HIPAA)–compliant file storage service. Only select study staff will have access to these files. In phase 1 of the study, participants, including women with GDM and their spouses, will receive a mobile recharge card worth Nepalese rupees 500 (approximately US $3.77) to compensate for their time in the interview, focus group, or usability testing. In phase 2, participants will be compensated with a US $10 prepaid internet data package.

Phase 1: GDM-DH App Design and Development

The goal of the GDM-DH app is to assist patients in the self-management of GDM by improving their efficacy in adhering to the recommended diet and physical activity regimens and facilitating desired clinical and social support. The app will also help clinicians by providing easily digestible visual displays of patient data and behaviors, which will in turn aid in their clinical decision-making and counseling.

We will take a user-centered approach to design and develop the GDM-DH app that matches the needs and technological sophistication of the target users. As outlined in Figure 1, we will form a multidisciplinary team of experts to design an app prototype, followed by a qualitative or requirement-gathering phase to collect user feedback on the app prototype features and functions. After incorporating and revising the app prototype, we will build a minimum viable product (MVP) and subsequently conduct usability testing. The final GDM-DH app will be developed following an iterative process of product design and user testing. Each step of the app design and development is detailed in the upcoming sections.

Phase 1A: Prototype Design

As part of the formative phase of the app development, we will first develop a prototype of the GDM-DH app, in collaboration with a multidisciplinary team including experts in GDM, mHealth, and behavior and implementation sciences, as well as health care providers at Dhulikhel Hospital. The content modules and features to be included in the app will be selected based on literature review, relevant theory-based behavioral strategies, and discussion with subject matter experts. The primary educational content will be information on GDM and associated risk factors and health outcomes, clinical and lifestyle management of GDM, dietary and physical activity recommendations for women with GDM, and the benefits of a healthy diet and active lifestyle during pregnancy. Other components will be guided by Bandura's [39] Social Cognitive Theory (SCT), which postulates that behavior change is guided by several cognitive and social factors, including perceived self-efficacy, social support, outcome expectancies, and perceived barriers and facilitators to the behavior change [40]. Consistent with the SCT framework, we will include features that support self-management of GDM by (1) providing health education; (2) helping patients identify and set target health goals (for diet, physical activity, and glucose levels); (3) enhancing their self-efficacy to meet target goals; and (4) facilitating desired support from family members.

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Key Domains of the GDM-DH App

Self-Management of GDM

The app will provide basic educational information about GDM and the importance of managing GDM for optimal maternal and infant health. The app will also include culturally tailored dietary and physical activity recommendations with relevant recipes and example meal plans. The core component of the app will allow participants to record and self-monitor their blood glucose levels, blood pressure, carbohydrate intake, physical activity, and gestational weight gain. To assist with estimating the carbohydrate intake of meals, the app will include typical portion-size images of common carbohydrate food sources in a staple Nepalese diet. Weight, blood pressure, and blood glucose levels can be manually entered by users either biweekly after clinic testing or daily if they have equipment at home.

Based on the user input data, the GDM-DH app will automatically generate tailored feedback and help users monitor their progress toward target health goals. The app will compare carbohydrate intake, physical activity, gestational weight gain, blood glucose, and blood pressure levels to existing evidence-based guidelines [41-45] via a feedback engine and will generate visual display charts. These charts will summarize diet, physical activity, gestational weight gain, blood glucose, and blood pressure patterns, allowing participants to monitor their alignment and progress toward target goals.

The GDM-DH app will enhance self-efficacy to adhere to recommendations and meet target goals with a variety of multimedia modules (eg, video lessons) that provide appropriate strategies and practice opportunities to problem-solve around barriers to health behaviors. These modules will consider specific cultural, social, and physical environmental challenges that patients with GDM face in adopting a healthy diet and lifestyle.

Facilitation of Health Exchange Between Patients and Providers

Providers will have access to a web-based administrative portal that syncs with the patient-facing GDM-DH app and allows them to register a new patient, as well as enter, update, or review clinical and other patient-related information (eg, glucose values, blood pressure, weight, diet entries, clinic history, and notes). This portal is intended to streamline the providers' workflow, as they can quickly look at patient data visualizations to understand patient behaviors and progress and guide their treatment and counseling accordingly.

Family Member Support

The GDM-DH app will also facilitate involvement from family members or friends, who strongly influence prenatal care–related decisions and dietary behaviors in Nepal [20-22]. Via a social network "follow" feature, patients will be able to list 1 or more family members or friends as contacts in the app and give that contact permission to view their logged data and progress summary. This feature will be added to the GDM-DH app to garner social support and offer a source of accountability, motivation, and shared experience.

Phase 1B: Qualitative User Research

The objective of this qualitative phase is to gather user feedback on the GDM-DH app prototype and understand the perceived facilitators and barriers to GDM self-management. We will recruit patients diagnosed with GDM within the past year from Dhulikhel Hospital to participate in a focus group or semistructured in-depth interview [46]. Eligible patients will be pregnant women who (1) receive antenatal care at Dhulikhel Hospital, (2) receive a GDM diagnosis (within the preceding year), (3) own a smartphone, and (4) can understand and read Nepali. Patients with learning difficulties or vision or hearing impairments will be excluded. Patients with a confirmed GDM diagnosis will be recruited into the study with the help of a senior obstetrician-gynecologist (OB-GYN; coinvestigator in the study) and other staff in the OB-GYN Department at Dhulikhel Hospital. We will recruit 12 women with GDM but plan to recruit further if data saturation is not achieved [47-49]. We will also conduct key informant interviews with clinicians from Dhulikhel Hospital (n=5) and family members of patients with GDM (n=3) to collect feedback on the GDM-DH prototype. Eligibility criteria for family members include being a spouse or direct relative of a patient with GDM who was diagnosed with GDM within the past year at Dhulikhel Hospital. All participants will provide written informed consent.

Before the focus group or in-depth interview, current and previously diagnosed patients with GDM will complete a structured questionnaire assessing sociodemographics and pregnancy-related information. The focus group and in-depth interviews will be developed in Nepali with a set of questions and probes to thoroughly understand the perceived social, cultural, and environmental facilitators and barriers to GDM management, including participants' views, opinions, and knowledge about GDM management, perceived self-efficacy, and strategies to enhance adherence to lifestyle modifications [50]. We will also collect feedback on the GDM-DH app prototype, including (1) the app dashboard, layout, and navigation; (2) the usefulness of app features; (3) the burden of data entry; (4) the usefulness of educational modules covered; (5) clarity of graphs and data visualizations; and (6) additional features and content. The focus group or interview guide will be developed in consultation with the study team with a study investigator (AS) who has prior experience conducting qualitative studies in this population taking the lead. A trained research coordinator will administer the focus group and in-depth interviews at Dhulikhel Hospital.

Given the clinical applications and setting of our study, the qualitative arm of this research takes a pragmatic worldview. In analyzing the qualitative data, our goal will be to generate practical and actionable insights that can directly inform and improve the GDM-DH platform with the ultimate goal of improving patient outcomes. The focus group and in-depth interview will be audio recorded and transcribed before analysis. Qualitative data will be uploaded onto the NVivo 12 software (Lumivero) for data management and analysis. We will follow Braun and Clarke's [51] 6-phase approach to thematic analysis, including (1) familiarizing with the data, (2) generating initial codes that will be compiled into a codebook, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes,

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and (6) producing the final report [51]. Our analysis will use both inductive and deductive approaches. First, we will develop deductive themes based on our interview guide. Next, we will read the transcripts to identify text related to the deductive themes and define new inductive themes that emerge from the data. A codebook will be developed by revisiting the text within the identified themes, defining codes, and reorganizing or grouping those not aligning with existing themes into new ones. A second research analyst will use this codebook to independently code the transcripts. After coding is completed, the 2 research assistants will compare the coding schemes and resolve any discrepancies through mutual agreement, with assistance from the study investigator. A third research analyst will calculate the intercoder reliability, achieving a level of 80%. Multiple investigators will review the data and provide insights based on their content knowledge and expertise.

Phase 1C: Usability Testing

Incorporating and revising the app prototype based on qualitative user research, we will build the MVP, the simplest possible version of the GDM-DH app, which will retain its most important features and functionalities. The MVP of the GDM-DH app will undergo usability testing with patients with GDM via think-aloud protocol [52]. The eligibility criteria to recruit patients with GDM for usability testing will be the same as the criteria used for phase 1B—qualitative user research. We will use a convenience sampling strategy to recruit 18 participants for the usability testing [53]. All patients will be required to provide written informed consent.

Individual one-on-one usability testing sessions will be conducted in a private space and overseen by 2 facilitators; 1 facilitator will lead the session while a designated note-taker will record users' verbalizations. Usability testing will consist of a 2-step think-aloud protocol in which the participants will be asked to verbalize their thoughts as they navigate and complete various specified tasks (eg, profile setup, diet entry, review weight visualizations, and open video lesson) on the GDM-DH app [54]. Participants will also be asked to rate the difficulty of completing each task on a 5-point scale ranging from "very easy" to "difficult." At the end of the usability testing session, participants will complete the System Usability Scale (SUS, scored 0-100), a reliable and widely used 10-item 5-point Likert scale questionnaire for global assessment of systems usability [54]. After the usability testing, we will ask open-ended questions to collect feedback on the app, such as how to improve upon the features and functions of the app. The final version of the GDM-DH app will be developed following an iterative process of product design and user testing and will be used in the proof-of-concept RCT in the second phase of the study.

Phase 2: Proof-of-Concept RCT

The objective of the RCT is to answer the research question—in women with GDM, does augmenting standard care with the GDM-DH platform, compared to standard care alone, show preliminary efficacy in improving clinical perinatal outcomes, including maternal blood glucose levels, birth weight, and neonatal hypoglycemia?

Participant Eligibility and Recruitment

Patients who are newly diagnosed with GDM will be recruited from the Obstetric Outpatient Department at Dhulikhel Hospital. Patients who are pregnant and receiving antenatal care at the Obstetric Outpatient Department undergo routine screening for GDM at 24 to 28 weeks of gestation and are diagnosed using the Carpenter-Coustan criteria [55]. Eligible patients must (1) receive GDM diagnosis based on Carpenter-Coustan criteria [55], (2) be aged 18 years or older, (3) be ≤30 weeks gestational age, (4) receive antenatal care at Dhulikhel Hospital, (5) own an Android smartphone, (6) have internet connectivity at home, and (7) understand and read Nepali. Patients with learning difficulties or vision or hearing impairments will be excluded.

Enrollment and Randomization

We will enroll 120 newly diagnosed patients with GDM from the Obstetric Outpatient Department at Dhulikhel Hospital between 24 and 30 weeks gestational age (baseline). At baseline, all participants will be briefed about the study and asked to provide written informed consent to agree to participate in the study. All participants will then complete a structured questionnaire to assess sociodemographics, prepregnancy weight, and lifestyle factors, such as smoking and alcohol use. Next, participants will be randomly assigned in a 1:1 fashion to 1 of the 2 treatment conditions—either GDM-DH app intervention + standard care or standard care only, for up to 16 weeks, starting from baseline until delivery (Figure 2). Random permuted blocks of sizes 4 or 6 will be used using a statistical software in order to prevent treatment imbalance and ensure that participants are allocated to each group equally. The allocation sequence will be concealed from the research assistant and research nurse using sequentially numbered opaque sealed envelopes. Due to the nature of the study, clinicians and participants will not be blinded to the group allocation.

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Figure 2. Overview of study design of phase 2 (proof-of-concept clinical trial) and measurement time points. Measures in blue are collected in both study groups, while measures in red are only collected in the intervention group. GDM: gestational diabetes mellitus; GDM-DH: gestational diabetes mellitus-Dhulikhel Hospital; MAUQ: mHealth App Usability Questionnaire; SUS: System Usability Scale.

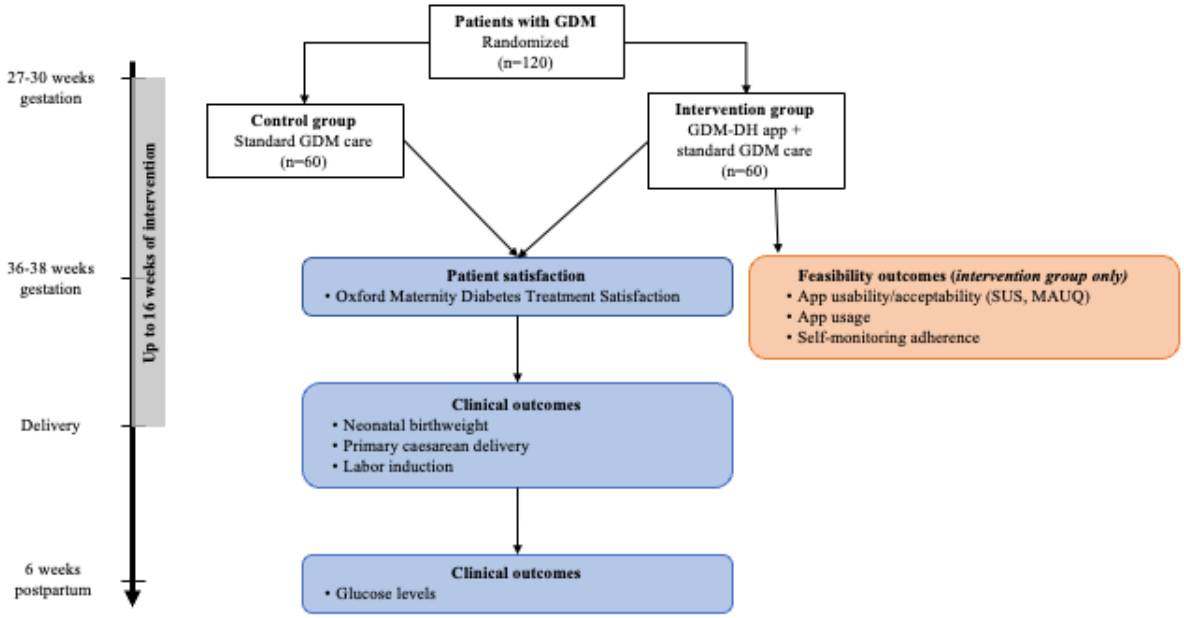

Standard Care

Standard care for patients with GDM at Dhulikhel Hospital entails a counseling session with an OB-GYN physician, which covers basic disease information, dietary and physical activity recommendations for GDM management, target blood glucose levels before and after meals, and the course of treatment. The primary treatment for GDM includes modifications to diet and physical activity. Participants consult a dietitian and a physical therapist to develop a diet and physical activity plan based on prepregnancy weight and GDM disease severity. In addition to setting carbohydrate goals, major dietary recommendations include eating small meals throughout the day, lowering sugar and refined carbohydrate intake, and increasing the intake of vegetables and whole grains. Patients are provided with leaflets and brochures in addition to verbal information about managing GDM with diet and physical activity. As per the standard care protocol, patients with GDM are asked to visit the Obstetric Outpatient Department for glucose testing every 2 weeks, and after each testing, blood glucose levels are recorded in paper booklets assigned to each patient. If feasible, patients are also encouraged to buy a glucometer and perform daily blood glucose testing at home. The OB-GYN physicians monitor the blood glucose levels across testing and, if needed, may prescribe oral hypoglycemic medications or insulin to the patient over the course of treatment.

Study Intervention

In addition to standard care, participants in the intervention group will use the GDM-DH app to support self-management behaviors. At baseline, participants in the intervention group will have the GDM-DH app downloaded onto their mobile phones and receive a detailed orientation on its use from a trained research coordinator. Participants will be instructed to input their carbohydrate intake at meals, gestational weight gain, blood glucose levels, and blood pressure into the GDM-DH app, and the GDM-DH app will track the daily number of steps taken by the user. The GDM-DH app will automatically generate feedback through visual charts to help users understand how their health data relate to recommendations. Users can use this information to set goals and self-manage their GDM. The GDM-DH app will also send in-app notifications and reminders to input data and attend prenatal care appointments. During standard care prenatal visits, clinicians will review data from the app via a web portal to inform treatment decisions and recommendations. Approved family members can also be added to the app and can track patient progress.

Outcome Measures

Perinatal Health Outcomes

Exploratory maternal and neonatal health outcomes will be measured at delivery and 6 weeks post partum (Table 1). Primary exploratory treatment outcomes will be maternal glycemic control measures at 6 weeks post partum, neonatal birth weight, and rates of labor induction and cesarean delivery. As secondary exploratory treatment outcomes, we will also look at gestational weight gain, glucose levels above the glycemic targets and rates of insulin therapy, neonatal hypoglycemia, and admittance to the neonatal intensive care unit (NICU).

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Table 1. Study outcomes and covariates for phase 2, proof-of-concept randomized controlled trial.

Outcome variable	Data source	Collection timepoint			
		Baseline	36-38 weeks gestation	Delivery	6-weeks post partum
Maternal outcomes					
Fasting and 2-hour blood glucose	Medical record	✓			✓
Gestational weight gain	Medical record			✓	
Glucose readings during gestation	GDM-DH[a] app and medical record (intervention group); medical record (standard care group)			✓	
Initiation of insulin therapy	Medical record			✓	
Induction of labor	Medical record			✓	
Cesarean delivery	Medical record			✓	
Neonatal outcomes					
Birth weight	Medical record			✓	
Apgar score	Medical record			✓	
NICU[b] admission	Medical record			✓	
Neonatal hypoglycemia	Medical record			✓	
Usability and acceptability outcomes					
Oxford Maternity Diabetes Treatment Satisfaction Questionnaire [56]	Survey (self-report)		✓		
Variables measured in the intervention group only					
App usage	GDM-DH app				
Time spent on the app					✓
Self-monitoring compliance (observed vs expected number of entries)	GDM-DH app				
Carbohydrate intake					✓
Blood glucose entries					
Blood pressure entries					
Weight entries					
mHealth[c] App Usability Questionnaire [57]	Survey (self-report)		✓		
System Usability Scale [54]	Survey (self-report)		✓		
Covariates					
Sociodemographics	Survey (self-report)	✓			
Prepregnancy weight	Survey (self-report)	✓			

[a]GDM-DH: gestational diabetes mellitus-Dhulikhel Hospital.

[b]NICU: neonatal intensive care unit.

[c]mHealth: mobile health.

At 6 weeks (±5 days) post partum, all participants will undergo a standard 75 g oral glucose tolerance test. Fasting and 2-hour glucose levels will be measured in the hospital laboratory using standard laboratory methods, and we will abstract these measures from the medical record. Blood glucose measures from the routine screening for GDM at 24 to 28 weeks of gestation will also be abstracted from the medical record. Additional maternal outcome variables will be collected at delivery. Induction of labor (yes or no), cesarean delivery (yes or no), and initiation of insulin therapy (yes or no) will be abstracted from the medical records. Gestational weight gain measures will be abstracted from the medical record and calculated by subtracting the measured weight at or before 12 weeks gestation from the measured weight at delivery. Maternal gestational glucose readings will be extracted from the app and medical record (for the intervention group) or the medical record (standard care group), and the proportions and frequency of glucose levels above the glycemic targets (≤5.5 mmol/L preprandial and ≤6.6 mmol/L at 2 hours postprandial) will be calculated. Neonatal outcome measures will also be collected

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at delivery. Prior to discharge (<24 hours after delivery), neonatal birth weight will be abstracted from the medical record. Neonatal Apgar score, NICU admission (yes or no), and neonatal hypoglycemia (yes or no) will be abstracted from the medical record.

Usability and Acceptability

At 36 to 38 weeks gestation, we will use the Oxford Maternity Diabetes Treatment Satisfaction Questionnaire, a validated 9-item 7-point Likert scale questionnaire (+3= strongly agree to –3= strongly disagree; possible scores 0-27) that can be completed in under 5 minutes, to assess general satisfaction and acceptability of GDM care [56]. Good acceptability will be considered predominantly (>80%) neutral or positive scores on all 9 items. The questionnaire will also include space for free text responses, where participants will be encouraged to provide additional feedback or suggestions.

For participants randomized to the study intervention group, we will collect additional measures. Questionnaires, which can be completed in under 5 minutes, will be administered by a trained research assistant at 36 to 38 weeks gestation to assess app usability and acceptability. The SUS will be used to assess perceived app usability, with a score of 68 (out of 100) demonstrating good usability [54]. Usability will also be assessed through a secondary mHealth App Usability Questionnaire (MAUQ) [57]. The MAUQ is a 7-point, 21-item survey designed to assess patient feedback on mHealth apps and has been previously validated. The MAUQ comprises of 3 subscales—ease of use and satisfaction (8 items, questions 1-8); system information arrangement (6 items, questions 9-14); and usefulness (7 items, questions 15-21), with responses to questions ranging on a 7-point scale from 1 (strongly agree) to 7 (strongly disagree). Lower scores indicate superior performance or a more positive user experience compared to higher scores. In addition to app usability and acceptability, we will collect data about app usage and self-monitoring frequency (eg, the actual number of app entries or expected app entries multiplied by 100 for carbohydrate intake or blood glucose). These data will be collected post partum from the GDM-DH app.

Sample Size Estimation and Considerations

Treatment-related change in glycemic control is of primary interest to this study, and we will be adequately powered to examine whether mean change in fasting and 2-hour blood glucose levels from 24 to 28 weeks gestation (collected at enrollment) to 6 weeks post partum differed significantly by the treatment condition. Power analyses were estimated based on repeated measures ANOVA with in-between interaction using G*Power (version 3.1.9.2; Heinrich Heine University Düsseldorf). For an estimated medium effect size of 0.25 (partial eta squared =0.06), an α error level of .05, a nonsphericity correction of 1, and to test 2 groups with 2 repeated measurements with a correlation of 0.5, a sample size of 34 is required to achieve the power of 80%. We will recruit an additional 86 patients (total n=120) to account for possible attrition and to test other hypotheses with exploratory clinical outcomes. Prior RCTs evaluating mHealth solutions for GDM management detected significant differences in treatment arms with similar or smaller sample sizes [58-60]. In 2017, the number of live births in Dhulikhel Hospital was 2983. Using a conservative incidence rate of 5%, the expected number of newly diagnosed patients with GDM per month is 12. Anticipating a conservative recruitment rate of 50%, we expect it will take 20 months to recruit 120 patients with GDM for the study.

Statistical Analysis

Data analysis will be done using SAS (version 9.4; SAS Institute). Maternal and infant characteristics will be described overall and by treatment condition using descriptive statistics (mean, SDs for continuous variables or frequencies for categorical variables). Independent 2-tailed *t* tests or chi-square analyses will examine differences in birth weight or rates of labor induction or cesarean delivery, respectively, between the 2 treatment conditions [61,62]. Usability and acceptability measures reported by the study intervention group will be summarized using descriptive statistics. A repeated measures ANOVA will be used to investigate whether fasting and 2-hour blood glucose levels differed across the 2 timepoints (within effect), and more importantly, whether the mean changes in fasting and 2-hour blood glucose levels over time (24 to 28 weeks gestation to 6 weeks post partum) differed by the 2 treatment conditions (interaction effect) [63]. Two separate models will be tested for fasting and 2-hour blood glucose levels, respectively. Assumptions of sphericity will be evaluated using Mauchly's [64] test statistic for all models. A *P* value of <.05 will be considered statistically significant for all analyses.

Results

As of July 2024, we have completed phase 1 of the study. Phase 2 is underway. The first participant was enrolled in the RCT in October 2021, with 99 participants enrolled as of July 2024. We anticipate completing recruitment by December 2024 and disseminating the findings by December 2025.

Discussion

Principal Findings

This protocol describes the study methodology to develop a user-centered and culturally tailored GDM-DH platform and to determine the usability, acceptability, and preliminary efficacy of the platform among patients with GDM in a university hospital setting in Nepal. The GDM-DH platform will be designed to support patients with GDM in adopting optimal self-management behaviors and assist providers with timely and informed clinical decision-making. We anticipate that the platform will show good usability and acceptability, as well as demonstrate preliminary efficacy for improving perinatal health outcomes, including maternal glycemic control measures at 6 weeks post partum, neonatal birth weight, and rates of labor induction and cesarean delivery. To our knowledge, this will be the first RCT evaluating an intervention that leverages mHealth for GDM treatment and management in an LMIC setting.

Prior research conducted in high-income countries demonstrates that mHealth interventions for GDM, including smartphone

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apps and web-based tools, promote self-management behaviors, improve glycemic control, and reduce the risks of adverse perinatal outcomes [65-67]. However, existing app-based interventions for GDM management primarily focus on remote glucose monitoring with manual feedback from health care providers [58,59,68,69], which is resource-intensive and burdensome for both providers and participants, thus limiting the potential for widespread dissemination and impact in resource-limited settings. Our platform addresses these challenges by providing automated feedback, which may help to overcome resource limitations and reduce provider burden. While personalized and culturally tailored digital tools are beneficial for enhancing GDM self-management and improving perinatal health [66], few app designs are culturally responsive [70]. The GDM-DH platform improves upon existing mobile interventions for GDM by integrating cultural practices and family influence on prenatal care, offering social support and culturally tailored dietary and physical activity recommendations, and providing automatically generated personalized feedback to optimize GDM management without the need for significant human resources.

Research and Practice Implications

The GDM-DH app has the potential to significantly improve standard GDM care in Nepal by supporting self-management practices, facilitating informed clinical decision-making, and potentially enhancing clinical outcomes. If our GDM-DH platform proves successful, our findings will be highly relevant to the broader South Asian population and will guide the future development, testing, and optimization of tailored mHealth GDM interventions for other patient groups with low technological sophistication and unique cultural needs. Additionally, the methodologies and lessons learned from designing and implementing the GDM-DH app may inform similar mHealth initiatives in other LMICs.

Strengths

This study has several strengths and innovative aspects, including the user-centered and culturally tailored design based on behavioral theory, a lifestyle-based self-management approach using technology to minimize user burden, family member involvement, clinician input, and potential to augment prenatal care in a resource-limited setting. The potential for the GDM-DH app to augment prenatal care in resource-limited settings may be particularly significant for countries like Nepal, given the increasing rates of T2D and its comorbidities that consume health care resources [71,72]. Moreover, adequate treatment and management of GDM are critical to disrupting the cycle of intergenerational obesity and diabetes [73], and mHealth may serve as a valuable early-stage intervention strategy to curb the burgeoning T2D epidemic in Nepal and other LMICs.

Limitations

There are also limitations to the GDM-DH app and study protocol. To minimize user burden, the app collects and provides feedback only on carbohydrate intake, so other aspects of diet (eg, energy intake and fat intake) are not collected. However, the Nepalese diet is characterized by frequent consumption of carbohydrate-rich food sources [74], and carbohydrate intake is a crucial component of GDM self-management [41]. Similarly, the app only records steps taken and does not collect any information about additional aspects of physical activity. Despite this limitation, we expect to capture the majority of physical activity as walking is the most commonly reported exercise during pregnancy [75]. Manual entry of diet, blood glucose, blood pressure, and weight may impact user engagement, as it is time and effort-consuming. However, manual entry may allow participants to be more aware of their behaviors and associated physiological effects, thereby enhancing self-efficacy [40]. Since the app was designed to address the cultural barriers and technological literacy of pregnant women in Nepal, findings may not be generalizable to other women with GDM. If the app is efficacious, a similar process to adapt and culturally tailor the app to other settings and populations may be followed. Finally, this study may not be adequately powered to test secondary clinical outcomes (eg, NICU admission). However, we will be able to explore the trends and treatment differences in secondary outcomes, enabling us to power a larger study.

Future Directions and Dissemination

In a future study, we will conduct a type 1 or type 2 effectiveness-implementation trial to test the clinical and cost-effectiveness of the GDM-DH platform in improving GDM treatment outcomes. We will make every effort to keep the technologies (GDM-DH platform) developed as a result of this research project, if any, widely available and accessible to the research community.

Conclusions

With increasing rates of GDM, particularly in resource-limited settings, there is a heightened interest in developing innovative approaches to augment the treatment and management of this common pregnancy complication. App-based lifestyle interventions for GDM management are not common, especially in LMICs where GDM prevalence is rapidly increasing. This protocol describes the study methodology for developing and testing an mHealth platform designed to manage and treat GDM in Nepal. This proof-of-concept trial will garner important information about leveraging mobile technology for GDM management in LMICs and holds important public health relevance for the broader South Asian population.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 187 KB - resprot_v13i1e59423_app1.pdf]

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Abbreviations

GDM: gestational diabetes mellitus
GDM-DH: gestational diabetes mellitus–Dhulikhel Hospital
HIPAA: Health Insurance Portability and Accountability Act
LMIC: low- and middle-income country
MAUQ: Mobile Health App Usability Questionnaire
mHealth: mobile health
MVP: minimum viable product
NICU: neonatal intensive care unit
OB-GYN: obstetrician-gynecologist
RCT: randomized controlled trial
SCT: Social Cognitive Theory
SUS: System Usability Scale
T2D: type 2 diabetes

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Protocol

Integrated Online-to-Offline Model of Care for HIV Prevention and Treatment Among Men Who Have Sex With Men in Malaysia: Protocol for an Intervention Development and a Multiphase Trial

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Abstract

Background: HIV continues to have a disproportionate impact on specific populations in Malaysia, particularly men who have sex with men (MSM). HIV self-testing (HIVST) is a strategy that has been shown to scale up HIV testing rates. However, it faces shortcomings because of concerns about self-efficacy, result interpretation, and lack of counseling and linkage to care. This underscores the need for an innovative approach that integrates HIVST with timely counseling, expert guidance, and referrals to enhance engagement in relevant HIV prevention or treatment.

Objective: This study aims to describe the protocol used in developing and testing a web-based platform (ie, CINTAI) providing an HIVST kit and real-time e-counseling to support online-to-offline linkage to HIV care services for MSM in Malaysia.

Methods: The methods are reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines. In phase I, we will adapt existing HIVST web-based platforms to create a new online-to-offline HIVST and counseling platform called “CINTAI” for Malaysian MSM. In phase II, we will use a type 1 hybrid implementation trial design to determine the feasibility, acceptability, and preliminary efficacy of “CINTAI” compared with treatment as usual among Malaysian MSM, with assessments conducted over 6 months. Multilevel implementation factors will also be collected to guide future adoption and scale-up. We will enroll 78 MSM in the pilot randomized controlled trial. Baseline characteristics will be tested for homogeneity between groups using appropriate statistical tests. A generalized linear mixed model with random subject effects will account for within-subject correlation. Treatment assignment, time, interaction, and confounders will be included. The proportion of MSM tested for HIV over 6 months and other outcomes (pre-exposure prophylaxis for HIV or antiretroviral therapy linkage, HIV risk behaviors, and chemsex harm reduction) will be compared using linear contrasts.

Results: We completed phase I of the proposed study in April 2024 and started phase II in May 2024, with 15 participants recruited (7 in the CINTAI and 8 in the treatment-as-usual groups). On the basis of a series of formative works completed during phase I, we developed a fully functional, web-based platform that provides a digital platform for MSM in Malaysia to order HIVST kits for free and to receive HIV counseling, followed by offline linkage to HIV prevention services (if HIV negative) or HIV treatment services (if HIV positive).

Conclusions: Despite being at high risk for HIV transmission, MSM in Malaysia have alarmingly low testing and linkage to HIV care services, prompting the need for innovative approaches to support HIV prevention efforts. If found to be feasible and

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acceptable, CINTAI can be easily adapted for a range of health outcomes and health care delivery services for MSM, including adaptation to other low- and middle-income countries.

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KEYWORDS

HIV; HIV testing; pre-exposure prophylaxis; antiretroviral therapy; CINTAI; men who have sex with men; online-to-offline model; eHealth

Introduction

As opposed to overall declining HIV trends globally, its incidence is rising among certain vulnerable subpopulations, such as sexual and gender minority groups, and in some regions of the world, particularly in Southeast Asia [1-3]. Men who have sex with men (MSM) are one such example and constitute a disproportionate fraction of people living with HIV [1,3]. In Malaysia, a country in the Asia-Pacific region, the HIV epidemic has transitioned to MSM and led to climbing mortality rates within the past decade [4,5]. Several contributing factors have exacerbated the HIV epidemic in Malaysia among MSM. Malaysian MSM are at a disproportionate risk for comorbid substance use and psychiatric disorders, which also fuel transmission, including depression and amphetamine-type stimulant use, which has led, in recent years, to an increase in sexualized drug use ("chemsex") in this subgroup, further compounding risky behaviors such as condomless sex and multiple sexual partners [6-10]. Therefore, there is a greater urgency for routine HIV testing to expedite prevention, early diagnosis, and treatment.

Although HIV testing guidelines indicate that MSM with high-risk sexual behaviors (eg, condomless receptive anal sex and multiple anal sex partners) are recommended to receive testing every 3-6 months [11], HIV testing rates among MSM in Malaysia remain alarmingly low according to recent studies, with 33.8% of them never having tested for HIV in the past and only around 30% having tested for HIV in the past 6 months [12]. Low HIV testing uptake and linkage to care in this subgroup can be explained by several factors, including the criminalization of same-sex sexual activity and ensuing stigmatization around HIV, compounded by fears around disclosing sexuality and prevailing distrust of health care professionals, which render access to care more complex and suboptimal [13-16].

eHealth, defined as the use of information and communication technologies in health care delivery, dismantles social access barriers to care and, therefore, has the potential to improve accessibility to services among stigmatized populations, especially in Malaysia [17-20]. The stigma- and discrimination-conducive setting in Malaysia renders Malaysian MSM prime potential beneficiaries of such a strategy, coupled with their widespread use of web technologies for sexual health [21]. As such, Malaysian MSM who are reluctant to "come out" may find it a more accessible and less stigmatizing method of obtaining resources and care.

HIV self-testing (HIVST) is an effective strategy to maximize confidentiality while avoiding conventional HIV testing facilities. However, its use in Malaysia remains low (25.2%) due to a lack of self-efficacy for HIVST, concerns about misinterpreting results, and missed opportunities for counseling and linkage to care [22]. The median out-of-pocket health expenditure for patients with HIV/AIDS in Malaysia was RM 1080 (US $254.48) per year, representing 14.7% of patients' median income [23]. This indicates the need for an innovative approach meant to complement HIVST with access to timely HIV knowledge and expertise from clinicians, as well as guidance on using and interpreting the result and recommended referrals or next steps.

To fill this gap, we aim to develop a web-based HIVST kit delivery platform (ie, CINTAI; "love" in Bahasa Malaysia) designed for MSM in Malaysia that provides free and anonymous HIVST kits as well as real-time e-counseling for HIVST (eHIVST) integrated with online-to-offline (O2O) linkage to HIV and other harm reduction support services. Guided by implementation science and a commitment to health equity, the study seeks to generate robust ideas on the feasibility and acceptability of this intervention for potential adaptation in other low- and middle-income countries. This paper aims to describe the protocol that will be used in the development and pilot testing of "CINTAI" to improve HIV testing and linkage to HIV prevention and treatment services among MSM in Malaysia. The implementation of web-based interventions like CINTAI will significantly increase the rates of HIV testing and linkage to HIV prevention and treatment services among MSM in Malaysia compared with the current standard of care.

Methods

Multiphase Study Design

The methods are reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines [24]. This study will be conducted in 2 phases. In phase I (development phase), we will adapt existing HIVST web-based platforms to create a new O2O HIVST and counseling platform called "CINTAI" for Malaysian MSM. In phase II (testing phase), we will use a type 1 hybrid implementation trial design to determine the feasibility, acceptability, and preliminary efficacy of the CINTAI platform. Additionally, we will assess multilevel implementation factors using the Consolidated Framework for Implementation Research (CFIR) to guide future adoption and scale-up of the CINTAI platform.

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Theoretical Framework

The Behavioral Model for Vulnerable Populations will guide intervention development and implementation [25]. This model indicates that health behavior can be explained in terms of predisposing factors (eg, characteristics of the individuals or community that influence health service use), enabling factors (eg, personal, family, and community resources), and need factors (eg, perceived and evaluated health status). This was chosen as the model for this study because it incorporates specific vulnerabilities and competing needs that lead to significant barriers to obtaining health care among Malaysian MSM, and it has been used in a wide variety of geographical contexts and patient populations.

Phase I: Development of the CINTAI Platform

Overview

We will adapt and refine the existing platforms (ie, Jom-Test and Adam's Love) using the modified Intervention Mapping for Adaptation framework to develop the CINTAI platform for optimal use among Malaysian MSM. The modified Intervention Mapping for Adaptation model comprises the sequential steps listed below. The study procedural phases are described in Figure 1.

Figure 1. Description of study procedural phases. UI: user interface.

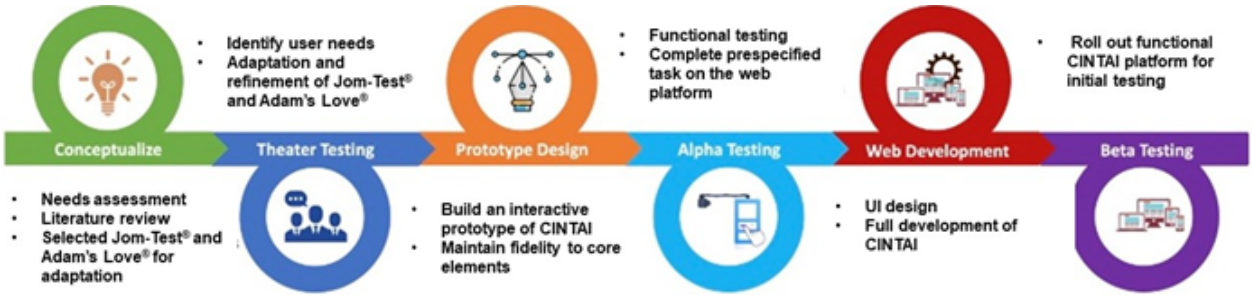

Jom-Test and Adam's Love

Adam's Love is a web-based O2O HIV service delivery platform designed to improve HIV testing and pre-exposure prophylaxis for HIV (PrEP) uptake among MSM in Thailand. Its key features included risk assessment, real-time e-counseling (instant messaging, SMS text messaging, and audio or video call), an online site- and service-specific booking system, and a real-time monitoring feature to track and monitor individuals' progress. It has demonstrated success in engaging hard-to-reach Thai MSM in e-counseling, assessing risks in real time, and effectively linking them online to relevant clinical services using its novel O2O model [26]. Jom-Test, on the other hand, is a web-based HIVST platform developed to promote HIV testing by providing free and anonymous HIVST kits to MSM [27].

Phase IA: Theater Testing

Participants and Recruitment

We will conduct focus group discussions (FGDs) with MSM and stakeholders to adapt, expand, and refine the content and functionalities of Jom-Test and Adam's Love to create an interactive prototype of the CINTAI platform. We aim to conduct 6 FGDs with 6-7 MSM per group and 3 FGDs with 6-7 stakeholders per group to theater test the existing platform to develop an interactive prototype of CINTAI. We will continue to recruit participants until saturation is achieved. Eligibility criteria for MSM will include identifying as MSM (HIV negative, HIV positive, or HIV status unknown) and being 18 years of age or older. Clinical stakeholders will include counselors, nongovernmental organization and clinic staff, and physicians who provide HIV-related services to MSM in Malaysia. MSM living with HIV are included in the eligibility criteria to learn their unique perspectives in navigating through the Malaysian health system and accessing HIV treatment services. We will recruit MSM participants using posts and social media advertisements, geospatial dating apps (eg, Grindr and Hornet), peer referrals, and announcements in MSM-led or serving community organizations.

Theater Testing Procedures

Participants will first be screened using an online questionnaire to assess their eligibility. We will then conduct the FGDs in person using 2 semistructured interview guides (for MSM or clinical stakeholders). FGDs will be audio recorded and transcribed for later analysis. If the in-person FGD does not provide sufficient and meaningful information or if many potential participants are reluctant to participate in an in-person session, we will offer an option to participate in a remote FGD session using videoconferencing technology.

Session Content

The FGDs among MSM will broadly explore the 3 domains of the Behavioral Model for Vulnerable Populations framework [25] related to the target population, including *predisposing factors* (demographic, substance use, and mental health), *enabling resources* (income, transportation, available clinical and support services, and discrimination in the health care setting), and *need factors* (perceived health status). Sessions for both MSM and clinical stakeholders will involve feedback regarding how the digital platform could improve HIV testing frequency and linkage to prevention and treatment services. Sessions will also foster discussion by addressing limitations found in existing platforms, including additional features unique to the Malaysian context, such as e-counseling with O2O service delivery and integration of low-threshold harm reduction services.

Phase IB: Alpha Testing

In this step, the results from the theater testing phase will be used to refine and improve the content and functions of the existing platforms and tailor them to the Malaysian MSM. This

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will lead to the development of an interactive prototype of CINTAI.

Participants and Recruitment

Screening and enrollment of MSM (n=5; HIV negative or HIV status unknown only) and clinical stakeholders (n=5) will be identical to methods used for the theater testing.

Procedures

Individual one-on-one "thinking aloud" sessions [28] will occur between the participant and a facilitator. Each session will be video recorded to capture the participant's experience with the "CINTAI" prototype. Participants will be asked to complete specific tasks, including profile setup, risk assessment, HIVST kit and PartyPack [29] ordering, scheduling of e-counseling sessions for HIV testing or chemsex, and finding PrEP providers using the locator feature, all while narrating their thoughts. After this is completed, participants will fill out a questionnaire assessing platform testing–related experiences as well as their experience completing the given tasks using the prototype. Open-ended questions will be used to assess the ease and experience of use, recommended modifications, and overall feasibility. Clinical stakeholders will provide specific feedback regarding the clarity, usefulness, and format of the visual summary of user data.

Analysis

Recorded sessions will be transcribed, and facilitator notes will be compiled to examine and identify usability problems. Verbal indicators of usability problems from participants, such as doubt, task difficulty, incomprehensibility, or annoyance, will be scanned, and the total number of problems will be collated. A distinction will be made according to how issues surfaced in the data: observation of behavioral data, verbalization by the participants, or both. Based on these results, recommendations for further modifications will be synthesized to prepare for the beta version (phase IC).

Expected Elements of the CINTAI Platform (Beta Version)

Elements of "CINTAI" will minimally include features already present in Jom-Test (eg, ordering of an HIVST kit and written instructions for using HIVST) and Adam's Love (eg, e-counseling support via instant messaging, SMS text messaging, or video or audio call; online booking system; and risk calculator tool), as well as the following additional components: a monitoring dashboard, geocoded location options for HIV testing, HIV prevention and treatment clinics and chemsex-related services, and peer navigation-style assistance, to increase user engagement and provide a seamless handoff to clinical services. Additionally, the platform will incorporate screening of engagement in chemsex as well as real-time e-counseling on chemsex harm reduction strategies, including referrals to suitable care and support services. The platform will also include a chemsex harm reduction kit called the "PartyPack." The PartyPack is a feasible and acceptable HIV and sexually transmitted infection prevention tool previously used among MSM in Thailand [29,30] and will be incorporated in "CINTAI" as an optional "add-on" that users can request. The PartyPack is a small box containing condoms, personal lubricant, and a QR code that, when scanned through a smartphone, links users to chemsex harm reduction resources on the "CINTAI" platform. This will ensure that individuals who intend to engage in chemsex have access to the information and tools necessary to lower their health risks in a nonjudgmental environment. Features of the "CINTAI" platform are depicted in Figure 2.

Figure 2. Features in the CINTAI digital platform. HIVST: HIV self-testing; O2O: online-to-offline; PrEP: pre-exposure prophylaxis for HIV.

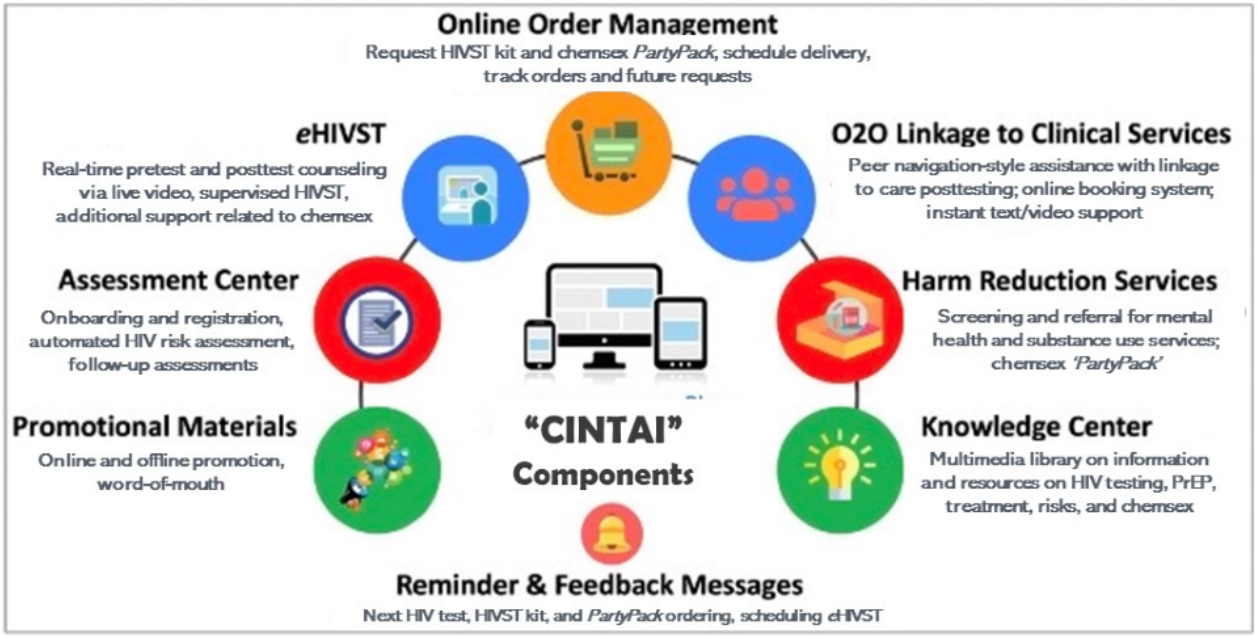

Phase IC: Beta Testing

Beta testing is conducted to identify any remaining bugs or usability issues of the newly developed platform in a "real world" setting. This period will last 2 months and will be conducted to finalize the software's design, functionality, and usability.

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Participants and Recruitment

Recruitment and screening of participants will be identical to prior phases of the project. A sample size of 10 participants was chosen based on recommendations for initial beta testing of a new technology [31]. Eligible participants will be at least 18 years old; HIV negative or of unknown HIV status; cisgender men; identify as MSM; and have access to a smartphone, computer, or internet-enabled tablet [31].

Procedures

Participants will be asked to complete a pre-use survey that will collect sociodemographic characteristics as well as information about perceived barriers to HIV testing access, and linkage to HIV prevention and treatment for services uptake. After completing the survey, participants will attend the CINTAI onboarding tutorial and access the platform using a single-use registration access code. Participants will be asked to use the CINTAI platform for 60 days and encouraged to use all its components. On day 60, participants will be asked to complete a post-use survey using the Systems Usability Scale (SUS), which will take around 20-30 minutes [32]. To evaluate engagement and interest, web analytics will be collected, including the number of log-ins, the duration of each session, pages visited, and features used on the CINTAI platform. Lastly, audio-recorded, exit, one-on-one interview sessions will be conducted to explore participant feedback on the functionality of the platform, including the errors encountered, and their motivation to use CINTAI to inform further refinement of the platform. One-to-one interviews can last from 30 to 60 minutes, depending on the participants' nature.

Analysis

The score of the SUS usability tool [32] ranges from 0 to 100, and a cutoff of 50 is the industry standard for acceptance usability [33], but we will be using a score of ≥70 as being minimally acceptable. Differences in pre- or postuse surveys will be analyzed using 2-tailed *t* tests or Wilcoxon rank-sum tests to evaluate changes in HIV testing and subsequent linkage to clinical services. The reliability of the scale will be measured by calculating Cronbach α. Qualitative data will be analyzed using the same approach as theater testing FGDs.

Phase II: Testing of the CINTAI Platform

Overview

We will conduct a hybrid type 1 implementation science trial [34] that involves an assessment of the feasibility, acceptability, and preliminary efficacy of the CINTAI platform, while simultaneously assessing contextual implementation factors to guide its future adoption and scale-up. The hybrid type 1 efficacy trial provides a heuristic to assess implementation factors during (not after) the efficacy study. A summary of phase II study activities and measures is shown in Table 1.

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Table 1. Study activity and measures (phase II).

Study activity	Timeline			
	Prebaseline	Baseline	3 months	6 months
Enrollment				
Eligibility screen	✓			
Informed consent		✓		
Randomization		✓		
Interventions				
Website onboarding		✓		
Access to the website				
CINTAI group		✓	✓	✓
TAU[a] group		✓	✓	✓
Assessments				
Focus groups		✓	✓	✓
Feasibility and acceptability				
Feasibility of screening[b]			✓	✓
HIVST[c] management[d]			✓	✓
eHIVST[e] utilization[f]			✓	✓
Usability[g]			✓	✓
Web analytics			✓	✓
Preliminary efficacy				
HIV testing			✓	✓
Linkage to PrEP[h] or ART[i]			✓	✓
Engagement in HIV risky behavior			✓	✓
Uptake of harm reduction services[j]			✓	✓
Payment		✓	✓	✓

[a]TAU: treatment as usual.

[b]Feasibility of screening, recruitment, randomization, retention, and fidelity to study protocol.

[c]HIVST: HIV self-testing.

[d]HIVST kit and PartyPack distribution data retrieved from the HIVST management dashboard.

[e]eHIVST: e-counseling for HIVST.

[f]Use of eHIVST and chemsex-related services (screening and e-counseling).

[g]Subjective usability of CINTAI using the System Usability Scale.

[h]PrEP: pre-exposure prophylaxis for HIV.

[i]ART: antiretroviral therapy.

[j]Uptake of chemsex-related harm reduction services: mental health counselors, psychiatrists, and needle exchange programs.

Phase IIA: Pilot Trial of the CINTAI Platform

Study Design

We will conduct a prospective randomized controlled trial to evaluate the CINTAI platform versus treatment as usual (TAU) among MSM in Malaysia for primary (ie, feasibility and acceptability) and secondary (ie, preliminary efficacy) outcomes over 6 months of observation, with assessments at 3 and 6 months. We will enroll 78 participants who will be randomized (1:1) to receive either CINTAI or TAU to ensure a balance between study arms [35,36] (Figure 3).

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Figure 3. Study design of the CINTAI trial (phase IIA). eHIVST: e-counseling for HIV self-testing; HIVST: HIV self-testing kits; O2O: online-to-offline; TAU: treatment as usual.

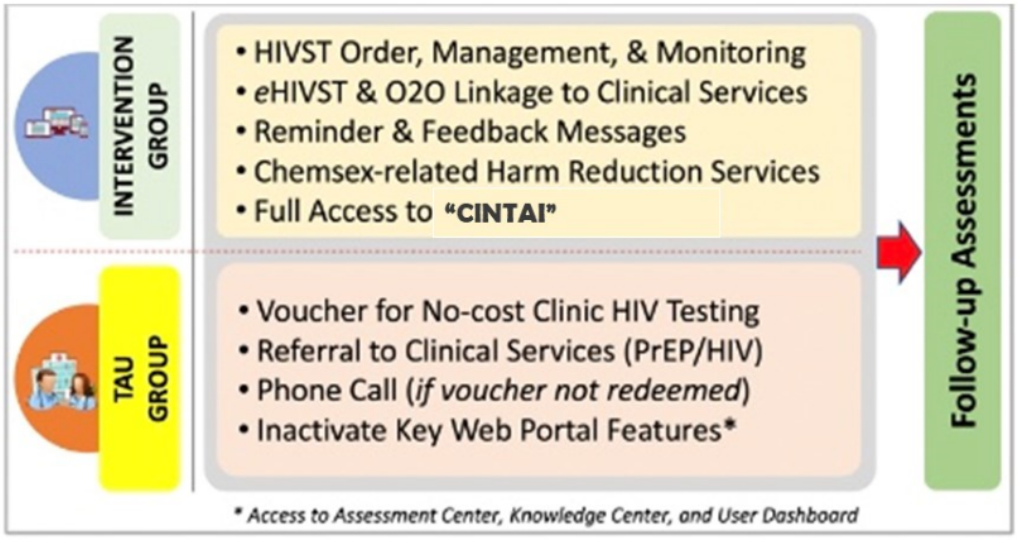

Participants, Recruitment, and Procedures

Eligibility criteria and recruitment measures will be identical to procedures used for the beta testing period (phase IC). Potential participants will fill out a web-based screening form to assess eligibility. Eligible participants will receive a call from researchers where they will be informed about the study and guided through consent procedures. Participants will then complete a baseline assessment and be randomized to CINTAI or TAU. Once randomization is complete, participants will be introduced to the staff members and study procedures.

Participants in the CINTAI group will be given access to all features, including an assessment center, online registration, risk calculator, HIVST kit order, management and monitoring, automated reminders, real-time e-counseling, chemsex-related harm reduction services, chat functions, and a knowledge center. These participants will follow a predetermined pathway to accessing services such as HIVST kit ordering, e-counseling, and subsequent O2O linkage to HIV clinical services. The TAU group participants will be given access to the CINTAI platform, with major intervention features being deactivated. The TAU group participants can only access the assessment center, knowledge center, and a voucher for no-cost community-based HIV testing. Participants in both groups will be followed for 6 months, with assessments at 3 and 6 months, which will take around 20-30 minutes to complete.

Primary Outcomes

Feasibility will be measured using metrics for the number of individuals screened, enrolled, and randomized. Retention will be monitored using web analytics showing the frequency and length of "CINTAI" use. Acceptability will be measured using the SUS usability tool (mentioned above; mean score of ≥70 for minimum acceptability) [32,37], HIVST kit and PartyPack [29] distribution, use of O2O e-counseling, and analysis of qualitative data from FGDs. In the previous study, the Cronbach α value of SUS was 0.95 [38].

Secondary Outcome

Preliminary efficacy will be assessed through several constructs. First, counselors will document the completion of HIV testing at the defined intervals (months 3 and 6) in the study database. To assess possible testing events occurring outside the study, participants will be asked whether they received any additional HIV testing as well as extract testing events via medical records. Second, posttest linkage to PrEP (HIV–) or antiretroviral therapy (ART; HIV+) will be measured, including the date of the first clinic visit, time to ART or PrEP initiation, and all clinic visit dates for the first 6 months of follow-up (to measure retention in care; self-report and extract from medical records).

Analytical Plan

Baseline characteristics will be tested for homogeneity between both groups using the 2-tailed *t* test or the Wilcoxon rank sum test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. Between-group differences will be adjusted for in the model. A generalized linear mixed model [39] with random subject effects will be built to account for the correlation in repeated measurements that occur within subjects. Treatment assignment, time, the interaction between time and treatment assignment, and any other confounders will be included as covariates. The proportion of MSM who have tested for HIV over the 6-month study period will be estimated and compared using linear contrasts. Similar analyses will be conducted for other outcomes (linkage to PrEP or ART, engagement in HIV risk behaviors, and uptake of chemsex-related harm reduction services).

Sample Size

Power analyses conducted in R using the power package (R Foundation for Statistical Computing) for single-level generalized linear models [40] suggest 80% power to detect a statistically significant (P<.05) medium effect size (Cohen d=0.15) with 64 participants. An additional 14 participants (approximately 20% of the sample size) will be recruited to account for potential attrition, for a total of 78 participants or 39 participants per study condition.

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Phase IIB: Explore Multilevel Implementation Factors

The CFIR will be used to gather multilevel implementation factors for future adoption. CFIR provides a structured menu of constructs associated with effective implementation and can be used flexibly at any phase [41,42]. It consists of 5 domains with 39 underlying constructs [41]. As recommended [41], we have identified 11 constructs relevant to our trial (Table 2).

Table 2. CFIR[a] constructs to explore multilevel implementation factors.

Domains	Constructs	Sample questionnaires
Intervention	• Relative advantage • Adaptability • Design quality and packaging	• How does CINTAI compare with other alternatives? • What changes will be needed for CINTAI to work effectively? • What is your perception of the O2O[b] model of service delivery?
Internal context	• Structural characteristics • Readiness for implementation	• What kinds of infrastructure changes will be needed to accommodate the program? • What level of endorsement or support have you seen or heard from leaders?
External context	• Patient needs and resources	• What barriers will the users face while using CINTAI?
Participants	• Knowledge and beliefs • Self-efficacy	• Do you have any feelings of anticipation? Stress? Enthusiasm? Why? • How confident do you think your colleagues feel about using CINTAI?
Process	• Planning • Engaging	• What have you done (or what do you plan to do) to implement CINTAI? • What steps have been taken to encourage people to use CINTAI?

[a]CFIR: Consolidated Framework for Implementation Research.

[b]O2O: online-to-offline.

We will conduct FGDs with the CINTAI group participants (n=20) and clinical stakeholders (eg, clinicians and administrative staff from nongovernmental organizations, clinics, and hospitals; n=15), where we will measure implementation and process measures, existing and potential barriers and facilitators, as well as identify available resources and key community partners. Screening, enrollment, and FGD procedures will be identical to the procedures used for alpha testing. Participants will be asked questions related to the multilevel implementation factors based on the sample guide available elsewhere [43] (Table 2) but tailored for the Malaysian context. Results are expected to provide insights into the feasibility and acceptability of the platform, including barriers to and facilitators of implementation, and will be used to improve the future adoption and implementation of the CINTAI platform nationwide and in other low- and middle-income countries.

Ethical Considerations

The institutional review board at the University of Connecticut approved this study's protocol (H22-0075), with an institutional reliance agreement with the University of Malaya. All staff notes, audiotapes, participant information, and transcripts will be kept in a separate locked cabinet within the offices in Centre of Excellence for Research in AIDS (CERiA) and destroyed once uploaded to the University of Connecticut's secure server, which is HIPAA (Health Insurance Portability and Accountability Act) compliant. After explaining the details of the study, such as aims, possible risks, and benefits, the research assistants will obtain informed consent from participants. All participants will be reminded that their refusal to participate in no way will negatively affect their relationship with any of the participating agencies or clinics and their ability to continue medical services from area clinics in the future. The principal investigator and all research staff will make every effort to protect the privacy and confidentiality of the participant information. In Phase II, participants will receive 40 RM (approximately US $9.31) at three assessment time points (baseline, 3 months, and 6 months) for their time and effort in participating in the study.

Results

The implementation of theater testing, alpha testing, and beta testing will result in tangible improvements in the functionality, engagement, and user satisfaction of "CINTAI." The linkage between site users and their clinical providers will also become more seamless. We completed phase I of the proposed study in April 2024. We started phase II in May 2024, with 15 participants recruited (7 in the CINTAI and 8 in the treatment as usual groups) as of September 2024. We anticipate that participant recruitment and data collection will be completed in early to mid-2025. On the basis of a series of formative works completed during this phase, we have developed a fully functional, Malaysia's first comprehensive, online HIVST platform with integrated counseling, that is, the CINTAI website. The term "CINTAI" derives from the local language, signifying "Love." CINTAI provides a digital platform for MSM in Malaysia to facilitate their engagement in HIV prevention in a fast and convenient manner. It offers HIV prevention (ie, HIV testing) and other support services (eg, referral to mental health services). We have also developed a web-based "CINTAI Clinic Dashboard," which provides role-based access to research staff to facilitate patient care for CINTAI users.

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Discussion

Principal Findings

MSM are among the most at-risk groups for HIV transmission, yet HIV testing and PrEP usage have remained low in Malaysia. The objective of this study is to develop and test a contextual web-based platform for Malaysian MSM with features of HIVST, real-time e-counseling, and O2O linkage to HIV prevention and treatment.

The CINTAI platform will help break different individual, social, and structural barriers by (1) delivering relevant information and resources to MSM during the critical "window" of testing; (2) educating MSM about HIV risk behaviors, strategies for risk reduction, and supporting for linkage to HIV prevention, treatment, and harm reduction services in the community; (3) empowering MSM by enabling e-counselors to develop strategies for posttest linkage to offline services; (4) decreasing long clinic wait times and reducing the number of clinical visits; and (5) collaborating with local stakeholders to facilitate linkage between eHIVST and subsequent offline clinical services (prevention, treatment, and chemsex-related harm reduction services).

We anticipate that the CINTAI platform will be an optimal intervention in diverse settings, which will be determined later after exploring multilevel implementation factors for future adoptions. If successful, the CINTAI platform will be among the first intervention packages for MSM clients, clinicians, and the overall health system to improve the uptake of HIV prevention and testing in Malaysia.

Conclusions

Suboptimal access to care among MSM in Malaysia has left them at increased risk for HIV and comorbid substance use and psychiatric disorders. The CINTAI platform has the potential to improve access to HIVST, prevention and treatment, and harm reduction services in this subgroup, providing a seamless route to these services for those at risk. If CINTAI is found to be feasible and acceptable, it can be continuously adapted and improved with the goal of reducing HIV incidence and bolstering access to HIV care among MSM in Malaysia.

Acknowledgments

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Conflicts of Interest

RS is an Associate Editor for *JMIR mHealth and uHealth*.

Multimedia Appendix 1
Peer-review report by HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (HIBI) - Risk, Prevention and Health Behavior Integrated Review - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 242 KB - resprot_v13i1e60962_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
CERiA: Centre of Excellence for Research in AIDS
CFIR: Consolidated Framework for Implementation Research
eHIVST: e-counseling for HIV self-testing
FGD: focus group discussion
HIPAA: Health Insurance Portability and Accountability Act
HIVST: HIV self-testing
MSM: men who have sex with men
O2O: online-to-offline
PrEP: pre-exposure prophylaxis for HIV
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUS: Systems Usability Scale
TAU: treatment as usual

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Protocol

The CHALO! 2.0 mHealth-Based Multilevel Intervention to Promote HIV Testing and Linkage-to-Care Among Men Who Have Sex with Men in Mumbai, India: Protocol for a Randomized Controlled Trial

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Abstract

Background: Current programs to engage marginalized populations such as gay and bisexual individuals and other men who have sex with men (MSM) in HIV prevention interventions do not often reach all MSM who may benefit from them. To reduce the global burden of HIV, far-reaching strategies are needed to engage MSM in HIV prevention and treatment. Globally, including low- and middle-income countries, MSM are now widely using internet-based social and mobile technologies (SMTs; eg, dating apps, social media, and WhatsApp [Meta]), which provides an unprecedented opportunity to engage unreached and underserved groups, such as MSM for HIV prevention and care.

Objective: This study aimed to assess the effectiveness of a multilevel mobile health (mHealth)–based intervention to improve HIV testing uptake and status neutral linkage-to-care among sexually active MSM reached through internet-based platforms in Mumbai, India.

Methods: In this randomized controlled trial, we will determine whether CHALO! 2.0 (a theory-based multilevel intervention delivered in part through WhatsApp) results in increased HIV testing and linkage-to-care (prevention or treatment). This study is being conducted among 1000 sexually active MSM who are unaware of their HIV status (never tested or tested >6 months ago) and are recruited through SMTs in Mumbai, India. We will conduct a 12-week, 3-arm randomized trial comparing CHALO! 2.0 to 2 control conditions—an attention-matched SMT-based control (also including a digital coupon for free HIV testing) and a digital coupon–only control. The primary outcomes will be HIV testing and status neutral linkage-to-care by 6 months post enrollment. Participants will be followed up for a total of 18 months to evaluate the long-term impact.

Results: The study was funded in 2020, with recruitment having started in April 2022 due to delays from the COVID-19 pandemic. Baseline survey data collection began in April 2022, with follow-up surveys starting in July 2022. As of April 2022, we enrolled 1004 participants in the study. The completion of follow-up data collection is expected in January 2025, with results to be published thereafter.

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Conclusions: While global health agencies have called for internet-based interventions to engage populations vulnerable to HIV who are not being reached, few proven effective and scalable models exist and none is in India, which has one of the world's largest HIV epidemics. This study will address this gap by testing a multicomponent mHealth intervention to reach and engage MSM at high priority for HIV interventions and link them to HIV testing and prevention or treatment.

Trial Registration: ClinicalTrials.gov NCT04814654; https://clinicaltrials.gov/study/NCT04814654. Clinical Trial Registry of India CTRI/2021/03/032280

International Registered Report Identifier (IRRID): DERR1-10.2196/59873

(JMIR Res Protoc 2024;13:e59873) doi:10.2196/59873

KEYWORDS

Keywords: digital health; HIV prevention; social media; stigma; gay; men who have sex with men; MSM

Introduction

Background

HIV remains a significant public health issue, with an estimated 39 million individuals living with HIV in 2021 and new diagnoses continuing to be concentrated among key populations globally including gay, bisexual, and other men who have sex with men (MSM) [1]. India has the third largest population of people living with HIV globally, with it disproportionately affecting MSM. In India, MSM have an estimated national HIV prevalence of 3.78% compared with 0.21% among the overall population in 2021 [2] and are designated a key priority population for HIV interventions by India's National AIDS Control Program. To end the HIV epidemic, one of the initial steps includes HIV testing and enabling linkage to treatment (which is free for all in India) or prevention. However, HIV testing remains suboptimal among Indian MSM as it does globally. Previous studies, that recruited Indian MSM through in-person approaches, report that 18%-49% of MSM have never been HIV-tested [3,4]. In recent studies reaching Indian MSM online, a substantial proportion (23%-47%) had never undergone HIV testing [5,6], and in 1 large study, approximately 75% of sexually active MSM were unaware of their current HIV status (ie, were never HIV-tested or were last tested more than 12 months before) [7].

HIV testing interventions and strategies for MSM are often limited in their reach and impact, in part due to the social stigma associated with both same-sex behaviors and HIV. Both globally and in India, MSM often face barriers in accessing accurate information about HIV and services tailored to their needs [8-11]. Coupled with community-level stigma, a lack of knowledge and support for accessing sexual health care reduces awareness of needing and motivation for HIV testing and subsequent care. However, a key challenge faced by outreach programs is how to engage individuals who fear being seen at MSM-identified spaces due to the stigma associated with attending an LGBTQ (lesbian, gay, bisexual, transgender, and queer or questioning) or HIV center (eg, general voluntary testing or counseling centers) or other logistical challenges. Traditional interventions that rely on an in-person outreach model may not address barriers that prevent individuals from seeking care and may also fail to reach MSM who do not frequent physical meeting venues, do not identify as a sexual minority, or are unlikely to go to LBGTQ- or HIV-affiliated settings [5-7,12-14]. Innovative strategies are thus needed to overcome stigma and ensure equitable and accessible services to meet the UNAIDS (Joint United Nations Programme on HIV/AIDS) 95-95-95 goals, that is, 95% of people living with HIV know their HIV status, 95% of those diagnosed receiving sustained antiretroviral therapy, and 95% of those receiving therapy achieving viral suppression by 2030 [8].

Evidence suggests that mass media HIV awareness campaigns, information provision, linkage to support services, stigma reduction, and reducing structural barriers may all improve HIV testing rates and subsequent linkage-to-care [15,16] mobile health (mHealth)–based interventions leveraging social media and other internet-based communication technologies (SMTs) such as WhatsApp [Meta] provides opportunities to both reach and engage MSM into health services at scale, although little evidence from India currently exists. SMT use has rapidly increased in both India and globally. There has been a rapid growth in India's digital population with 600 million active internet users in the past decade, and approximately 487.5 million active WhatsApp users, making WhatsApp a critical communication tool in India [17]. This growth has been followed by an increasing use of SMTs by MSM and other groups to socialize and seek sexual, romantic, or transactional partners [18]. Thus, leveraging SMTs presents an unprecedented opportunity to reach and engage Indian MSM in HIV prevention, linkage to health care, and provide access to support services [13].

Current evidence suggest that internet-based interventions can influence offline health behaviors [8,13,15,19-21] including HIV testing. However, there are limited data assessing the potential of SMTs to increase HIV testing among MSM in India or South Asia aside from small pilot studies [7,16,18,19,21-23]. Previous research among Indian MSM suggest that interventions using SMTs are feasible and acceptable [5,14]. However, there are limited data on its effectiveness for increasing HIV testing in India or other South Asian countries. One pilot study among Indian MSM used SMTs to deliver HIV-testing and prevention-related messages to MSM recruited through social media, finding high feasibility, acceptability, and a significant rise in self-reported HIV testing (from 31.5% to 43.8%) and an increased intention to test (from 44.6% to 65.4%) over 12 weeks [7]. However, it did not objectively assess HIV testing, address structural barriers to testing access, or assess linkage to care (important elements to inform widespread scale-up). Because changing health behaviors, especially for stigmatized conditions could be a slow process, evaluating outcomes over a longer

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duration of time is warranted to inform HIV-related outreach strategies, although some data exist globally and to our knowledge, none in India.

Aims

First, to determine whether CHALO! 2.0 increases HIV testing compared with control conditions and to identify factors associated with HIV testing.

Second, to determine whether CHALO! 2.0 increases linkage-to-care (both HIV prevention through counseling and use of pre-exposure prophylaxis [PrEP] and HIV treatment with antiretrovirals) and to identify factors associated with linkage to care.

Objectives

The objective of this study is to test CHALO! 2.0 (a WhatsApp-based multilevel intervention) in a randomized control trial to help answer the following questions: (1) Is CHALO 2.0 efficacious for increasing actual (not self-reported) HIV testing, compared with an attention-matched control (AMC)? (2) Does CHALO! 2.0 results in durable increases in repeat HIV testing? (3) Does CHALO! 2.0 improve linkage to both prevention and treatment? (4) If offered multiple free testing choices (at MSM community organizations, through private laboratories, or self-testing) without a behavioral intervention, do MSM obtain HIV tests and link to care, or is an active SMT behavioral intervention needed to increase uptake?

Our hypothesis is that CHALO! 2.0, a community-developed, theoretically grounded, SMT-based intervention, will reach and engage Indian MSM, enhance motivation and skills to obtain HIV testing and care, and overcome structural barriers compared with either attention-matched or digital coupon–only (DCO) control arms. The rationale is that determining the efficacy of a rapidly scalable SMT-based intervention is needed to facilitate widespread adoption. Even a modestly effective SMT-based intervention reaching thousands of MSM can dramatically and significantly impact the epidemic by increasing HIV status awareness and linkage-to-care and thus reducing new infections.

Methods

Trial Design

This study is a 3-armed, randomized controlled trial among 1000 MSM, recruited through SMTs and unaware of their HIV status. Eligible participants are randomized 1:1:1 to 3 arms: (1) CHALO 2.0: an HIV-focused multimedia messaging arm to deliver information, motivation, and skills to access testing and care; (2) an AMC focused on general health messaging; and (3) a no message control arm. Participants in all arms receive digital coupons for choices of free HIV testing and access to virtual peer outreach workers for linkage to care support. Active messaging occurs twice per week for 12 weeks with follow-up assessments and outcome measurement through 18 months post enrollment. This design allows all participants to receive intervention components, consistent with ethical and accepted practice.

Study Setting

The study is being implemented in Mumbai and Thane, Maharashtra, India, by The Humsafar Trust (HST) in collaboration with academic partners. Established as one of India's first LGBTQ+ (lesbian, gay, bisexual, transgender, queer or questioning, plus [others]) community–based organizations, HST implements a variety of HIV-related prevention, support, and treatment programs across India and has a long history of academic research partnerships including its own Federal Wide Assurance registered institutional review board (IRB) [7,24].

Mumbai is a mega-metropolitan city in Maharashtra state with a population of 21.67 million in 2024 [25]. Thane is the most populous district in the state of Maharashtra, situated contiguously with Mumbai, with individuals commuting to and from both locations for work, school, residence, and socialization. Recent reports from India's National AIDS Control Organization (NACO) show that Maharashtra is estimated to have the highest new HIV infections and an HIV prevalence of 1.2% in Mumbai and 0.46% in Thane (compared with 0.21% nationally in 2021), with new diagnosis concentrated among key populations including MSM [2].

Inclusion and Exclusion Criteria

Inclusion criteria for this study are (1) age of ≥18 years; (2) live or work in the Mumbai metropolitan area, including Thane; (3) are fluent in Hindi or English, (4) male sex at birth; (5) report having anal sex with men in the past 1 year; (6) report either that they have never tested for HIV, are unaware of their HIV test results, or are HIV-negative with their last HIV test >6 months ago and have had anal sex since last test; (7) able to provide and verify their WhatsApp mobile number; and (8) have not participated in a previous HIV research study (by self-report). The exclusion criteria include being unwilling to consent to the study, failing to verify the provided WhatsApp number, or not completing the baseline survey. Sexual orientation or expression was not part of the eligibility criteria. This study did not include transgender men, as it focused on cisgender MSM and not transgender men. As a quality control measure, individuals who provided duplicate digital payment ID (Google Pay, Paytm, or UPI [Unified Payments Interface] ID) or submitted the survey in less than 3 minutes will be excluded from the analyses.

Theoretical Frameworks for CHALO! 2.0

CHALO! 2.0 is developed as a multicomponent multilevel intervention, grounded in the socio-ecological model (SEM) [26,27] and the information-motivation-behavioral skills (IMB) frameworks for behavior change [28-31] (Figure 1). The SEM demonstrates the need to target factors at various levels of influence to support behavior change, while the IMB model focuses on information, motivation, and behavioral skills as determinants for HIV testing and linkage-to-care. CHALO! 2.0 intervention components were designed to target these domains as shown in Figure 1.

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Figure 1. CHALO! 2.0 conceptual model based on information-motivation-behavioral and socio-ecological model (SEM) frameworks. IMB: information-motivation-behavioral. MSM: men who have sex with men.

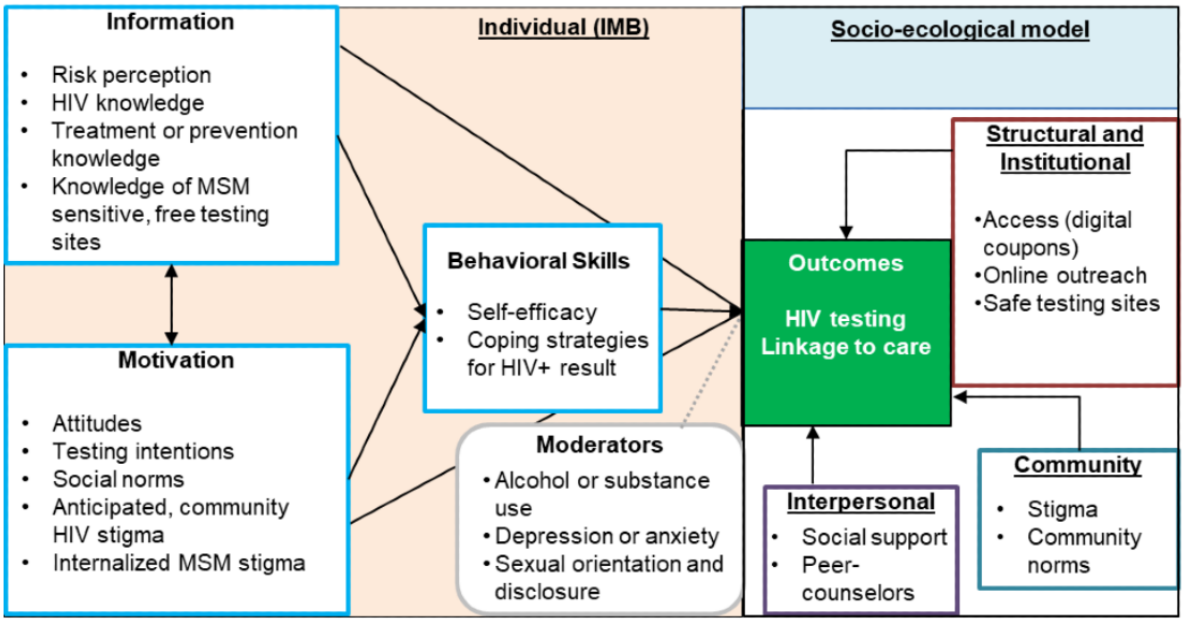

The CHALO! 2.0 Intervention

Participants randomized to this arm receive a 12-week intervention comprising digital media messages sent twice weekly (24 unique messages) through HST's verified WhatsApp business account (Figure 2). These messages are focused on topics related to HIV, HIV testing, and HIV prevention (including PrEP) and treatment specifically tailored for Indian MSM. The messages target information, motivation, and behavioral skills as well as community norms, stigma related to HIV, and same-sex attraction using a combination of text messages, infographics, and brief videos (eg, 1 minute in length).

The content of the messages served to provide the following:

1. Information: dissemination of HIV knowledge, logistical details about testing and care, and information about PrEP and postexposure prophylaxis (PEP).

2. Motivation: inclusion of brief video clips aimed at creating social norms for HIV testing.

3. Behavioral skills: presentation of video clips demonstrating how to request and obtain an HIV test at HST or a private laboratory using digital coupons, and guidance on ordering and using the HIV self-test kit.

4. Interaction: access to peer outreach and health care workers through WhatsApp messages and audio calls for resolving any queries and testing or linkage support.

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Figure 2. Participant flow and components under each study arm. HST: The Humsafar Trust.

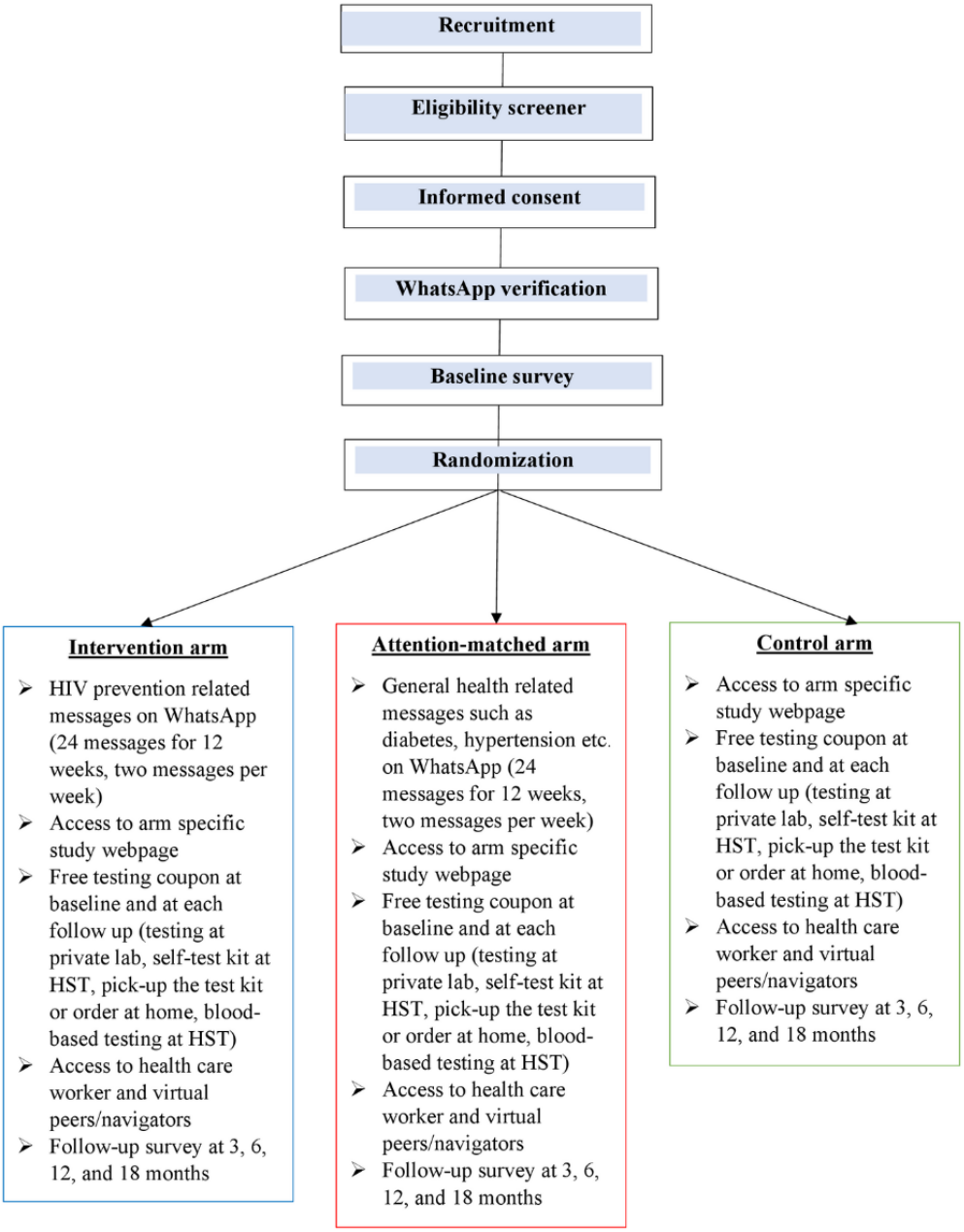

Intervention Content Development

We used a collaborative process with a multidisciplinary team to develop and refine all intervention components and study procedures over 5 months, similar to the CHALO pilot [13]. The team consisted of 14 individuals—3 community-based HIV researchers, a community advisory board (CAB), peer outreach workers, and HIV testing staff members. The intervention content underwent development and refinement through a series of 4 consultations with the community and peer outreach staff at HST. The workshops were led by 2 study team members (JC and SR) with expertise in group facilitation to identify the most important barriers and facilitators to HIV testing and preventive services, develop messages, and establish the sequence and scheduling of the messages or themes. A total of 14 MSM with diverse lived experiences participated in the workshops (eg, community-based organization clients, peer outreach workers, and HIV testing counselors). We used user-centered design and open-space technology processes to conduct the workshops, similar to the pilot study [13]. The open-space technique is a process that is used across disciplines to help ensure the inclusion of diverse viewpoints and has been used to facilitate the identification of challenges or barriers to a task or behavior (eg, HIV testing) and the identification of potential solutions to overcome them [32]. The workshop participants also identified top health priorities within the MSM community, apart from HIV, to be included in the AMC arm. The outcomes from the community consultations were then discussed with the CAB and the overall study team to finalize intervention messaging, sequence, and frequency of the messages. We leveraged videoconferencing tools to facilitate workshops (eg, breakout rooms and polling tools to reach consensus), considering COVID-19 restrictions on in-person meetings.

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Attention-Matched Control Arm

Participants randomized to the AMC arm receive informational messages disseminated twice a week for 12 weeks through the same WhatsApp Business account used for the intervention. These messages include both text and infographics. While the message delivery schedule aligns with the CHALO! 2.0 arm, the content in the AMC arm differs significantly. It focuses on addressing the top health priorities identified by participants in the community consultation, such as diabetes, hypertension, obesity, nutrition, stress management, and hair and skin care, among others. The messaging content for the AMC arm was finalized with guidance from the study team and the CAB.

Digital Coupon–Only Control

Participants randomized to this arm receive only a welcome message with no health-related content.

Common Components Across All Trial Arms

Personalized Digital Coupon for Free HIV Testing

All participants, regardless of their assigned arm, receive a personalized digital coupon after enrollment. The coupon comprises a code linked to their study ID. The digital coupon code is associated with participants' mobile numbers at the back end, enabling the study team to reach out if preventive or treatment services are required. Each coupon is redeemable once during the study period. The participants will receive the study coupon at baseline and at each follow-up.

Choice of HIV Testing Strategy

Participants are offered digital coupons for free testing and can select from three testing modalities, such as (1) standard counselor-based finger-prick rapid testing at HST (3 sites across Mumbai); (2) self-testing using rapid oral swabs (Orasure, Inc), which can be used at any of the HST's 3 sites, picked-up by participants or delivered through a local courier to participant's preferred location; and (3) a fourth generation HIV antibody/antigen test at a private laboratory with locations across Mumbai and Thane. Participants walking in to test (either blood-based or oral swab kit) are provided with face-to-face pre-and posttest counseling by the counselor and health care workers (HCWs). Participants opting for tests using the self-test kit or at a private laboratory can watch the pre- and posttest counseling and "how to use the kit" video on the study web pages.

Informational Web Page

Each participant receives an arm-specific link to an identical informational web page, detailing testing sites, the contact information of online peer counselors, and MSM-specific health services provided by HST. This page hosts pre- and posttest counseling videos in case testing using the self-test kit at a preferred location or at a private laboratory and offers contact details for online peer counselors and HCWs.

Virtual Peer Outreach Workers

All participants have access to virtual peer outreach workers through WhatsApp to address inquiries related to testing facilities or self-test kit ordering or use, and linkage to services. The virtual peers also connect the participants with the HCWs.

Linkage-to-Care

Specific protocols are implemented for HIV-positive results, including linkage and monitoring. Participants are offered linkage to care services, regardless of their test result, and those testing positive are further provided with automated messages on positive living.

Recruitment Strategies and Enrollment

The recruitment process involves various strategies such as outreach on MSM dating apps, advertisements by community-based Instagram (Meta) influencers, paid advertisements on Grindr (Grindr Inc), and the snowball technique. All advertisements contain a study link that directs potential participants to a landing page with more information about the study and an eligibility screener. Eligible participants proceed to an informed consent page on the Health Machine (Avegen), a web-based survey platform created for the study. After consenting, participants verify their WhatsApp number through a link sent from the study's WhatsApp account and then proceed to the baseline survey followed by randomization as shown in Figure 2.

Randomization and Blinding

Participants are randomized in a 1:1:1 ratio to the 3 arms—CHALO! 2.0 (intervention), AMC, and digital coupon (coupon-only)—using a random blocked design with a fixed block size of 6. Stratification is based on previous HIV testing history, that is, never tested or not tested in over 6 months. Allocation to the arms is automated through a system developed by the technology partner, reducing bias in allocation and analysis. To minimize bias, double blinding is used. Participants remain unaware of their assigned arm and receive automated messages for surveys. Staff collecting HIV testing and linkage-to-care data remain blinded. HST's online peer counselors and navigators are unaware of the study hypothesis to maintain blinding.

Online Study Assessments

Online surveys in Hindi and English collect self-reported data on sexual behaviors, previous HIV testing, HIV knowledge (transmission, treatment, and prevention), self-efficacy for HIV testing and care, stigma, and covariates as detailed in Table 1. Surveys also help assess potential contamination between the study arms. Participants receive automated baseline and then follow-up surveys at 3, 6, 12, and 18 months after enrollment. Participants receive WhatsApp reminders 3 and 7 days after the survey link is triggered. Nonresponses within 7 days of the baseline survey lead to baseline archiving. Follow-up surveys allow 1 month for completion.

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Table 1. Domains assessed at baseline and follow-up surveys.

Survey section	Baseline	3 months	6 months	12 months	18 months
Section 1: HIV testing access or preferences and PrEP[a] or PEP[b] use [5,7,33-35]					
HIV testing, HIV testing access	✓	✓	✓	✓	✓
Preferences for HIV testing, self-testing acceptability	✓	✓	✓	✓	✓
Intention to test in next 3 months	✓	✓	✓	✓	—[c]
Decisional balance for HIV testing—pros and cons	✓	—	—	—	—
HIV prevention knowledge, HIV testing knowledge	✓	✓	✓	✓	✓
HIV testing and coping self-efficacy	✓	✓	—	✓	—
PrEP decision balance (benefit and stigma)	✓	✓	✓	✓	—
HIV risk perception	✓	✓	✓	✓	✓
History of health care provider–diagnosed STIs[d]	✓	✓	✓	—	—
Section 2: Behaviors [5,7,36]					
Relationships, sexual and behaviors	✓	✓	✓	✓	✓
Condom use	✓	✓	✓	✓	✓
Alcohol use	✓	✓	✓	—	—
Substance use	✓	✓	✓	✓	✓
Section 3: Social support, resilience, and resources [37,38]					
HIV and sexual health social support	✓	✓	✓	✓	—
Gay or LGBTQ[e] community attachment	✓	—	—	✓	—
Connectedness to LGBTQ social media	✓	✓	✓	✓	✓
Section 4: Stigma and mental health [39,40]					
Anticipated HIV stigma for testing	✓	—	—	—	—
Internalized homonegativity	✓	✓	✓	—	✓
Depression, anxiety	✓	✓	✓	✓	—
Section 5: Identity and outness [7]					
Sexual identity, outness	✓	✓	✓	✓	✓
Education, income, living status	✓	—	✓	✓	✓
Previous use of HST[f], allied sites	✓	—	—	—	—
Online or virtual HIV and sexual health support	✓	—	—	—	—

[a]PrEP: pre-exposure prophylaxis.

[b]PEP: postexposure prophylaxis.

[c]Not applicable.

[d]STI: sexually transmitted infection.

[e]LGBTQ: lesbian, gay, bisexual, transgender, and queer or questioning.

[f]HST: The Humsafar Trust.

Tracking and Retention

Participants are sent automated reminders on WhatsApp alongside their individual survey link for scheduled surveys at 3, 6, 12, and 18 months. If surveys are not completed, peer outreach workers attempt to contact participants up to 3 times by WhatsApp messages and phone calls.

Outcomes

For HIV Testing

Primary: Verified receipt of an HIV test within 6 months post randomization.

Secondary: Frequency of HIV testing within 18 months, receipt of verified HIV tests within 12 and 18 months, and self-reported HIV tests within 6 months.

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For Linkage to Care

Primary: Linkage-to-prevention (yes or no) comprising counseling or PrEP use.

Secondary: HIV treatment linkage, antiretroviral therapy initiation for HIV-positive persons, sexual behavior indicators, all self-reported through baseline and follow-up assessments.

Exploratory Outcomes

The exploratory outcomes include the use of alcohol or other substances, the use of PEP, testing or treatment for any sexually transmitted infections, and the type of care site access for testing and treatment (HST community-based organization vs other health care facilities).

Study arm-specific outcomes such as HIV knowledge, stigma measures, risk perception, self-efficacy, social support, intention to get an HIV test, and SMT engagement.

Sources of Data

Survey Data

Self-reported data at Baseline and at subsequent follow-up surveys.

Testing Data

Use of the unique coupons at different testing sites, verified by peer counselors or laboratory technicians, recording dates, times, and locations of usage. The test results, whether from a self-test at home or pickup or testing at the private laboratory are shared by the participants, which are verified against the test report uploaded by the laboratory onto their secure portal with access to the data manager. Counselor-based testing is verified at HST by cross-referencing phone numbers with the clinic database. Self-test participants receive incentives for sharing pictures of the test kit dial.

Linkage to Care

HCWs oversee linkage to treatment clinics and primary care or PrEP access, providing information to the data manager.

Messaging Data

WhatsApp Business Analytics data shared by WhatsApp provide details on whether the messages are being sent, delivered, and read by the study participants. The online peer counselor interactions are monitored at the back end through a messaging platform. The web page visits and engagement with content are assessed by studying website visits using Google Analytics and analytics from the YouTube (Google) channel. Considering the limitation of attributing data to unique individuals due to technological constraints.

Exit Interviews

To provide insights into why CHALO! 2.0 may or may not work to increase HIV testing and linkage-to-care and obtain data to inform potential scale-up, we will perform phone-based exit interviews with 5-10 randomly selected participants from each of the following groups, who are never HIV tested, tested only once, tested multiple times, linked to HIV treatment, linked to HIV prevention care (eg, PrEP and counseling), and not linked to care. After obtaining verbal consent, we will record the interviews, transcribe, and explore the interview data using thematic analysis.

Statistical Analysis Plan

All primary analyses will be intention-to-treat, including participants who are lost to follow-up. In secondary analyses, we will conduct per-protocol analyses to ascertain outcomes among participants who viewed messages, identify exposure levels ("intervention dose") that may be associated with outcomes, and compare models stratified by testing history. We will conduct additional exploratory analyses on a per-protocol basis to assess factors such as SMT engagement, usability, and interaction with intervention "dose."

Aim 1 analyses will compare the proportion of HIV testing at 6 months between CHALO! 2.0 (n_1=300) and control participants (n_2=300) using chi-square tests. We will also compare CHALO! 2.0 participants with DCO participants using chi-square tests. Although this is a randomized trial, to account for possible confounders we will also perform logistic regression [41] with HIV testing at 6 months as the dichotomous outcome and intervention arm as the primary predictor, adjusting for the covariates. In secondary analyses, we will repeat these analyses with HIV testing at 12 months and 18 months as outcomes. We will also compare the cumulative frequency of HIV tests at 18 months between CHALO! 2.0 participants (n_1=266) versus AMC (n_2=266) or DCO (n_2=266) using Poisson tests. We will account for possible confounders using Poisson regression [41], with frequency of HIV testing as the outcome and intervention arm as the primary predictor, adjusting for confounders.

Aim 2 analyses will compare rates of linkage-to-prevention (ie, counseling and PrEP initiation) at 12 months for HIV-negative participants between study arms using chi-square tests and will also perform logistic regression with linkage-to-prevention as the outcome, study arm as the primary predictor, and adjusting for covariates. For secondary and exploratory outcomes, we will use ANOVA for continuous variables and chi-square tests for categorical outcomes. Exploratory analyses will report initial HIV-testing strategies and assess associations with participant characteristics. Secondary and exploratory outcomes will be analyzed using appropriate statistical tests (ANOVA or chi-square) as needed.

Sample Size

For aim 1, with a total of 1000 participants, we expect at least 900 participants at 6 months, and 800 participants at 12 months. This will provide a total of n=300 per arm at 6 months, and 266 participants per arm at 12 months. Based on findings from online intervention studies of HIV testing showing 1.7-2.2 increases in odds of testing in intervention versus control conditions (across low- and high-income countries and heterogeneous online interventions) [42-45], we estimate the proportion of HIV testing at 6 months to be 70% (210/300) for CHALO! 2.0 versus 35% (105/300) for AMC and 30% (90/300) for DCO. With the expected sample, the study's 2 main effects (CHALO! 2.0 vs AMC and CHALO! 2.0 vs DCO) have >99% power (Table 2). We also provide power estimates based on a wider range of parameters in Table 3, showing that we have sufficient power to detect between-group differences in the primary

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outcome with even smaller effect sizes. Power was calculated using PASS software V15.0 (NCSS), with all analyses conducted with a 2-tailed α of .025, resulting in a family-wise error rate of at most 0.05 for the primary outcome.

For aim 2, we anticipate that there will be no higher than 7% prevalence of undiagnosed HIV. Combined with expected HIV testing rates by 12 months of at least 75%, 45%, and 35% [46,47] in the 3 arms, we anticipate the available sample size of participants without HIV for aim 2 to be CHALO! 2.0 (n_1=247), AMC (n_2=139), and DCO (n_2=108). Based on HST's current linkage-to-care rates for HIV-negative individuals (30%) [48], we expect the rate of linkage-to-prevention care at 12 months to be 30% for CHALO! versus 15% for AMC vs 5% for DCO. The study's 2 main effects (CHALO! vs AMC and CHALO! 2.0 vs DCO) have >90% and >99% power, respectively (Table 3). We also provide power estimates for smaller effect sizes. The power was calculated using PASS software V15.0., with a 2-tailed α of .025, resulting in a family-wise error rate of at most 0.05 for the aim 2 primary outcome.

Table 2. HIV testing proportion at 6 months.

Power[a]	Intervention (CHALO! 2.0; n_1=300)	Attention–Matched Control (n_2=300)	Digital coupon–only (n_2=300)
>99%	0.5-0.75	0.2-0.5	0.15-0.45
>93%	0.5-0.6	0.35-0.45	0.35-0.45
>59%	0.5-0.60	0.4-0.5	0.4
>15%	0.5	0.45	0.45

[a]Power is for intervention compared with each control separately.

Table 3. Proportion linked to HIV prevention by 12 months.

Power[a]	Intervention arm (n_1=247)	Attention-matched control (n_2=139)	Digital coupon–only (n_2=108)
>99%	0.15-0.4	0.05-0.1	0.03-0.1
>98%	0.3-0.4	0.1-0.2	0.3-0.1
>90%	0.3	0.15	0.1-0.15
>70%	0.2	0.1	0.08
>49%	0.3	0.2	0.2
>21%	0.15	0.1	0.1

[a]Power is for intervention compared to each control separately.

Ethical Considerations

This study has been approved by the IRBs of HST (India) (HST-IRB-42/4-11/2023) and Albert Einstein College of Medicine (United States) (2018-9471) and cleared by the Health Ministry Screening Committee of India.

Incentives

Participants receive digital cash incentives for completing research surveys as follows: baseline, INR 300 (US $3.60); 3 months, INR 500 (US $6.01); 6 months, INR 550 (US $6.61); 12 months, INR 600 (US $7.21); and 18 months, INR 1000 (US $12.01). Participants can choose their preferred mode for digital payments (eg, PayTM, GPay, and UPI) which are widely used by all socioeconomic classes in India.

Data Management and Security

Data analyses and reporting will be conducted only using deidentified data so that no participant is identifiable, and data will be reported in aggregate. To deliver incentives, participants are asked to provide the mobile numbers linked to the digital payment app (requirement for enrollment and to pay incentives). However, no names or other identifiable information, such as address or locality, are collected. All participant responses are kept confidential. Data collected for the project are downloaded onto secure servers and stored in password-protected, encrypted files.

The study uses a secure survey platform for data collection, using Transport Layer Security encryption to safeguard transmitted data. The survey platform ensures data integrity and confidentiality by adhering to rigorous security measures including FISMA (Federal Information Security Management Act) [49], Federal Information Processing Standards (FIPS) Publication 200 [50], and HITECH (Health Information Technology for Economic and Clinical Health Act) guidelines [51]. Access to the complete dataset is limited to the principal investigator (VVP) and essential study personnel. User-specific access levels and monitoring capabilities are in place to identify any unusual activities within the system. WhatsApp, with its end-to-end encryption, ensures secure communication between the study team and participants. Our technology consultants provide ongoing advice on data security. Study participants are also informed about recorded communications during the consent process.

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Adverse Events

Possible adverse events include potential breaches of confidentiality leading to embarrassment or disclosure of sexual orientation or participation in an HIV prevention program. Other possible adverse events could include distress if receiving a positive sexually transmitted infection or HIV test result, and negative interactions with nonstudy personnel at care sites not under the purview of HST or the study (eg, private laboratories or non-HST clinics). To mitigate these risks, we continually monitor data security and work only with deidentified data (except when needing to contact participants). Adverse events are monitored during study assessments and participant interactions, with immediate intervention following HST protocols and reporting to the IRB as necessary.

Data Safety and Monitoring Board

The study also has a Data Safety and Monitoring Board, which performs biannual safety checks and yearly efficacy analyses. If prespecified significant differences in HIV testing or care linkage are observed, the study arm that does not show benefit may be stopped with the individuals being rerandomized to the other 2 arms.

Results

The study was funded in 2020, with recruitment starting in April 2022 due to delays from the COVID-19 pandemic. Baseline survey data collection began in April 2022, with follow-up surveys starting in July 2022. As of April 2022, we enrolled 1004 participants in the study. The completion of follow-up data collection is expected in January 2025, with results to be published thereafter.

Discussion

Principal Findings

This study aims to assess the effectiveness of a social media–based HIV prevention intervention to increase HIV testing among MSM reached through internet-based platforms in Mumbai, India. This trial uses multiple social media platforms to reach, engage, and deliver digital content to influence HIV testing and linkage-to-care among MSM in India. Globally and in India, unknown HIV status remains a critical barrier to ending the HIV epidemic. Existing interventions to increase HIV testing and facilitate linkage-to-care in India have had limited success in reaching MSM who do not visit MSM-associated physical venues. In addition, existing interventions that rely on physical venue-based outreach may not adapt to the shifting patterns of socialization and partner seeking from offline to digital venues. Consequently, alternative outreach and engagement models, such as CHALO! 2.0, are necessary to engage MSM unreached by current HIV testing and care programs.

If successful, CHALO! 2.0 has the potential to overcome several multilevel barriers to HIV testing and status-neutral linkage to care for Indian MSM. It may efficiently reach MSM online, overcome barriers to engagement, and facilitate linkage to multiple HIV testing and care options that are consistent with individual preferences and meet individual needs [52-55]. We anticipate findings from this study will advance our understanding of how an SMT-mediated multilevel intervention can influence care outcomes for stigmatized conditions such as HIV in low- and middle-income country settings. We also expect that the study design will help determine the extent to which an HIV-focused educational intervention may be needed to increase HIV testing and care uptake relative to control conditions.

Strengths and Limitations

The CHALO! 2.0 intervention has several key strengths. First, it leverages WhatsApp, a widely-used social media and messaging platform to engage Indian MSM and overcome challenges to adopting new technology or apps—a barrier faced by many eHealth interventions. Second, CHALO! 2.0 intervention components are theoretically grounded in multiple behavior change frameworks, thereby increasing its likelihood of success for increasing HIV testing and linkage-to-care. Next, CHALO! 2.0 offers tailored and community-developed digital content addressing the unique needs of Indian MSM, fostering a more comprehensive approach. Finally, providing access to a range of free HIV testing and care options including self-testing and bypassing in-person counseling for testing may help promote privacy and comfort and overcome anticipated stigma—an important barrier to HIV testing engagement.

This study also has limitations to consider. First, the study findings may not generalize to Indian MSM not reachable online, for whom face-to-face interventions currently exist. Next, the study's dependence on digital technology may pose challenges for individuals with low digital literacy, potentially hindering their engagement or comprehension of the information provided. Finally, the study design relies on the ability to read and write to successfully enroll into the study; therefore, different strategies and study designs are needed to engage individuals with low literacy.

Conclusion

Global health agencies have called for digital health interventions to engage populations who are vulnerable to HIV but are not being reached, yet few impactful and scalable models exist for low- and middle-income countries. In India, with one of the world's largest MSM HIV epidemics, no such eHealth interventions have been rigorously designed—a gap this study will help fill. This study has the potential to provide actionable information to diverse stakeholders, including whether or not CHALO! 2.0 is effective relative to the control conditions and insights about virtually reaching and engaging Indian MSM. This study addresses key evidence gaps by testing an innovative, scalable, mHealth-based intervention model to engage MSM in India at a high priority for HIV-related interventions. Finally, it has the potential to provide policy-relevant information for government and service organizations to design and implement similar mHealth-based interventions to address HIV.

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Acknowledgments

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Data Availability

The datasets generated and analyzed during the current study will be made available after study completion and publication of primary findings from the corresponding author on reasonable request with appropriate ethical approvals and data use agreements.

Authors' Contributions

VVP, SR, AD, SG, and JA contributed to the conceptualization. VVP, SR, AD, SG, JA, RSK, KHM, VC, and JC performed the methodology. VVP, SR, AD, and JC handled the investigation and project administration. VC, AD, SR, VVP, JA, and SG acquired resources and funding. RSK contributed to the statistical expertise in trial design and formal analyses. All authors reviewed, edited, and approved the manuscript before submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report for the Chalo! 2.0 protocol.
[PDF File (Adobe PDF File), 520 KB - resprot_v13i1e59873_app1.pdf]

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Abbreviations

AMC: attention-matched control
CAB: community advisory board
DCO: digital coupon–only
FIPS: Federal Information Processing Standards
FISMA: Federal Information Security Management Act
HCW: health care worker
HITECH: Health Information Technology for Economic and Clinical Health Act
HST: The Humsafar Trust
IMB: information-motivation-behavioral skills
IRB: institutional review board
LGBTQ: lesbian, gay, bisexual, transgender, and queer or questioning
LGBTQ+: lesbian, gay, bisexual, transgender, queer or questioning, plus (others)
mHealth: mobile health
MSM: men who have sex with men
NACO: National AIDS Control Organization
PEP: postexposure prophylaxis
PrEP: pre-exposure prophylaxis
SEM: socio-ecological model
SMT: social media technology
UNAIDS: Joint United Nations Programme on HIV/AIDS
UPI: Unified Payments Interface

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Protocol

A Video-Based Communication Intervention for Fecal Ostomy Surgery (CI-oSurg): Protocol for Open Pilot Testing to Improve Intervention Acceptability and Feasibility

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Abstract

Background: Approximately 100,000 patients undergo fecal ostomy operations annually across the United States. This patient population experiences high surgical complication rates and poor biopsychosocial outcomes. Surgical teams are not trained to address the psychosocial needs that often arise during recovery after fecal ostomy surgery.

Objective: This study aims to refine and establish the acceptability and usability of the Communication Intervention for fecal ostomy Surgery (CI-oSurg), a web-based communication intervention aimed at reducing distress among patients recovering from ostomy surgery.

Methods: We describe the proposed study design, methodology, and training protocol. We will conduct an open pilot (n=24 patients and n=8 clinicians) of video-based training to first identify the level and types of distress patients are experiencing. Next, patients will view web videos that address frequent challenges faced by ostomy patients, considering practical management and emotional and adaptation concerns. Qualitative one-to-one semistructured interviews will be conducted with participants to explore the acceptability and feasibility of the program and refine the intervention and study procedures.

Results: This study has been approved by the Mass General Brigham Institutional Review Board. Study funding has been obtained, and recruitment is planned for the fall of 2024.

Conclusions: Through this study, we will refine CI-oSurg, a web-based communication intervention focused on reducing distress after ostomy surgery, to improve intervention acceptability and usability. These improvements will allow us to establish the usability and acceptability of the intervention before efficacy testing to determine the ability of this intervention to reduce distress after fecal ostomy surgery.

Trial Registration: ClinicalTrials.gov NCT06320002; https://clinicaltrials.gov/study/NCT06320002

International Registered Report Identifier (IRRID): PRR1-10.2196/60575

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KEYWORDS

fecal ostomy; distress; open pilot; fecal ostomy surgeryl CI-oSurg; intervention acceptability; biopsychosocial outcomes; psychosocial support; ostomy care

Introduction

Approximately 100,000 patients undergo fecal ostomy operations annually across the United States [1]. This patient population experiences high surgical complication rates (up to 37%), including surgical site infections, dehydration, and hospital readmissions [2]. Patients undergoing fecal ostomy surgery have poor biopsychosocial outcomes, including decreased quality of life and caregiver burden [3-7]. Surgical teams are not trained to address the psychosocial needs that often arise during recovery after fecal ostomy surgery.

Current colorectal surgery guidelines support the use of interventions to improve biopsychosocial outcomes after ostomy surgery based on expert opinion [8]. Despite these recommendations, a study by Follick et al [9] highlights the lack of adequate ostomy support, with 46% of ostomates reporting that they needed more information than was provided in the time after surgery, with 40% indicating that their spouse needed additional information as well. Furthermore, 45% indicated that more information would have helped them deal more effectively with the emotional effects of their ostomy. Despite this need for more and better information, enhanced recovery after surgery interventions, and the focus of hospital systems on increased throughput, the time spent in the hospital setting is decreased. This limits the time for education of patients and care partners. There is a lack of evidence-based interventions to address distress in the postoperative period for fecal ostomy patients.

The overall goal of our work is to improve biopsychosocial outcomes of patients recovering from fecal ostomy surgery. This study protocol is part of a larger research program to develop, refine, and establish the efficacy of Communication Intervention for fecal ostomy Surgery (CI-oSurg), a video-based communication intervention to support patients and surgical teams during recovery from fecal ostomy surgery. This study aims to elicit and systematically evaluate key stakeholder perspectives on the acceptability and usability of a video-based communication intervention for fecal ostomy surgery, including content and procedures (eg, recruitment and screening methods, eligibility, timing of the intervention, and intervention delivery). Our hypothesis is that iterative improvements to the intervention (ie, CI-oSurg) will improve the acceptability and usability of the intervention before efficacy testing.

Methods

Study Design

In this study, we will perform open pilot testing of the CI-oSurg intervention with 8 surgical team clinicians (ie, surgeons who perform fecal ostomy operations, inpatient surgical nurses, outpatient surgical advanced practice practitioners, and ostomy nurses) and 24 fecal ostomy patients at a single academic surgical clinic until acceptability is improved [10,11]. Clinicians and patients will use the communication intervention to augment routine surgical care communication, see Figure 1.

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Figure 1. Concept model for improving communication after surgery. CI-oSurg: Communication Intervention for fecal ostomy Surgery; HRQoL: health-related quality of life.

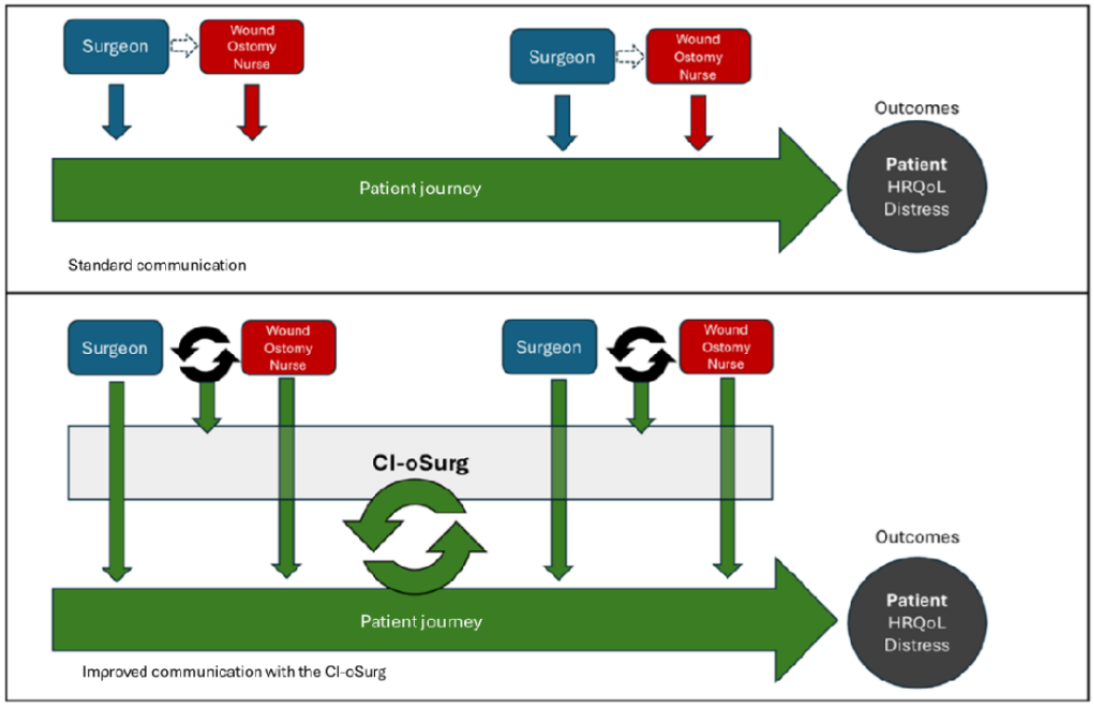

The intervention prototype was developed based on qualitative interviews with patients recovering from elective ostomy surgery and focus groups of clinicians experienced in the care of this surgical patient population. The intervention includes a modified version of the National Comprehensive Cancer Network Distress Management Tool [12] and video support materials. The modified distress tool includes a description of distress: an unpleasant experience of a mental, physical, social, or spiritual nature that can affect the way one thinks, feels, or acts. Next, a single distress thermometer question is asked to report the patient's level of distress on a scale of 0 (no distress) to 10 (extreme distress). Finally, patients complete a problem list to identify concerns they experienced over the past week across domains of physical, emotional, social, practical, and spiritual or religious concerns. After completing this modified distress tool, patients are provided a list of support videos that address the most frequent areas of concern of patients recovering from ostomy surgery (more details in Figure 2). After exposure to the intervention, participants will complete cognitive interviews to provide feedback on the intervention content and protocol to improve acceptability and usability in the surgical setting, as well as a brief survey within 30 days of their operation.

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Figure 2. Overview for patients of the Communication Intervention for fecal ostomy Surgery (CI-oSurg) prototype.

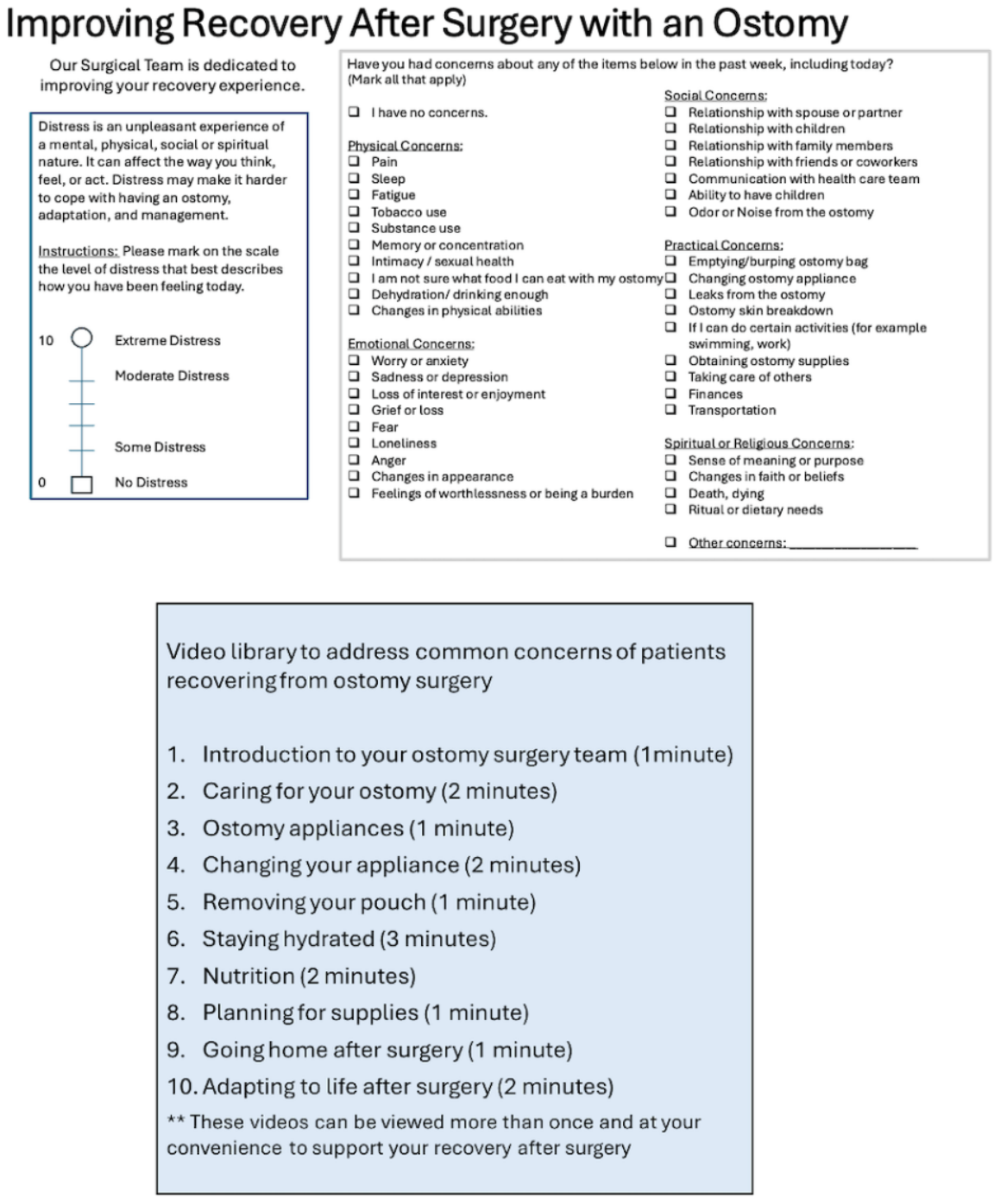

Recruitment, Screening, and Setting

We will recruit adult patients (aged 18 years or older) scheduled for elective surgery with a fecal ostomy from the outpatient surgical clinic at a single tertiary academic medical center. We will perform purposeful sampling to ensure that half of the patients are aged 65 years or older to understand the acceptability and usability of the intervention across the aging continuum. The potential participants will be identified by the surgical team and research assistant through medical chart review. The research assistant will then complete screening and consent procedures before enrollment. Eligible participants will be (1) fluent in English, (2) willing and able to participate in a live interview or survey, and (3) undergoing elective fecal ostomy surgery. Exclusion criteria include severe cognitive impairment (eg, advanced dementia, stroke, serious mental illness, or altered mental status due to septic shock), causing an inability to perform teach-back for consent, and ensuring meaningful participation in study interviews [13].

We will recruit 8 adult clinicians who participate in the care of patients with a fecal ostomy. Potential participants will be recruited from the same single tertiary academic medical center through surgical team meetings and email. Potential participants will include surgeons who perform fecal ostomy operations, inpatient surgical nurses, outpatient surgical advanced practice practitioners, and ostomy nurses. The research assistant will complete screening and consent procedures before enrollment. Clinician participants will review the CI-oSurg intervention and

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training module, a 30-minute in-person didactic session with role-play to ensure an understanding of the intervention and study purpose.

The intervention will be provided on general and gastrointestinal surgical inpatient floors at a Boston tertiary care hospital where a high volume of colorectal surgery is performed. These surgical inpatient floors are staffed by nurses experienced in caring for patients with fecal ostomies who have access to onsite ostomy nursing staff during weekdays.

Study Intervention

Participating clinicians will be trained in the CI-oSurg intervention and protocol using the CI-oSurg training module. The training module will consist of a 30-minute in-person didactic session with role-play of intervention components. This will occur in the inpatient surgical floor conference room to provide participants with a convenient and familiar setting where they will execute the intervention. We will provide flexible scheduling and reschedule sessions as needed to increase clinician recruitment. During this module, participants will learn the potential benefits of psychological support for patients recovering from ostomy surgery and address the distress patients often experience during the recovery process. Participants will view the intervention, including intervention video content.

In total, 24 consenting patient participants will complete the CI-oSurg intervention assessment and management video series 1-3 days after fecal ostomy surgery while admitted to the hospital. The intervention content and protocol will be refined iteratively with each group of 4 to 6 participants based on qualitative feedback from the interviews. For example, participants will be asked if the content addresses concerns using understandable terms and images and if they would like to repeat the intervention in the hospital or at home through a web-based platform on a personal tablet or device. Patients might request changes to the images of the video content, the size of the font, or the speed of audio recordings.

Using a semistructured interview guide, participants will then undergo an approximately 30-minute in-person cognitive interview before discharge from the hospital and within 2 weeks of surgery. Interview guide content is designed to gather feedback on the proposed CI-oSurg content and protocol. Specifically, this study is designed to gather participants' perspectives on the following: (1) acceptability of the CI-oSurg content components, (2) acceptability of clinician training sessions, (3) useability of the intervention with the surgical team and existing clinical staff, and (4) proposed recruitment procedures for a future clinical trial.

Study Procedures

To improve the credibility of results, interviews will be performed by trained qualitative researchers, audio recorded, and transcribed. Rapid data analysis will be performed to allow changes to be quickly made to the intervention to improve acceptability and feasibility in the busy inpatient surgical setting before in-depth coding and analysis. Final study data will undergo in-depth coding and analysis to ensure the credibility of findings, with double coding of at least 20% of interviews to ensure consistency. A hybrid inductive-deductive approach [14] will be used for qualitative coding, and a modified framework method for thematic synthesis in the final analysis [15-17]. Our team will use an iterative refinement of the CI-oSurg intervention and protocol based on ongoing data collection and rapid data analysis, consistent with previous studies [18].

Data Collection

Data from all participants will be collected using REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at Massachusetts General Hospital (MGH) and a HIPAA (Health Insurance Portability and Accountability Act)-approved electronic data capture system [19]. Demographic data will be obtained upon study enrollment (ie, age, sex, race and ethnicity, education, and occupation). In addition, the World Health Organization Brief Quality of Life Evaluation [20] and Hospital Anxiety and Depression Scale [21] data will be collected from patient participants 1 month after the surgery date to evaluate retention for future clinical trial planning. Assessment responses from the intervention will be collected by the research assistant as part of the CI-oSurg intervention. The Client Satisfaction Questionnaire [22] will be administered within 1 month of intervention use. In addition, we will conduct qualitative interviews with patients and clinicians. Interviews will be 1:1 and will last approximately 30 minutes to allow adequate time for discussion. The interview will follow a semistructured interview guide with open-ended prompts and questions surrounding domains including (1) perceptions of fecal ostomy care after surgery, (2) feedback on the CI-oSurg intervention procedures and content, and (3) ways of maximizing acceptability and feasibility of use. The interviewer will follow the guide with further probes to develop a comprehensive understanding of the participants' perspectives (more details in Multimedia Appendix 1).

Interviews will be audio-recorded and performed by a trained research assistant with expertise in qualitative research methods. Recordings will be transcribed and reviewed with rapid data analysis using a template developed by the research team. The template will be used to inform formal coding and intervention refinement with observations within key interview domains, critical participant statements, and other important observations. The research team will work to generate information on clinical team perspectives regarding the acceptability and usability of the intervention procedures and content.

Data Analysis

Audio recordings will be transcribed and deidentified. Evaluation of deidentified data using rapid analysis will be performed in Microsoft Excel to allow rapid updates to the intervention based on participant feedback. A hybrid deductive-inductive approach to qualitative data analysis will be used, guided by a modified framework method [14-17]. Our deductive approach will be based on our interview guide, rapid analysis template (more details in Multimedia Appendix 2), and codebook domains. These are influenced by our previous research on patient perspectives on challenges faced by patients undergoing fecal ostomy surgery and the findings from our clinician focus groups for prototype development. For example, we will include prompts in the interview guide that assess the

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perspectives of patients and clinicians in evaluating social support and adapting to life after surgery.

Transcripts will undergo rapid data analysis with summarizing data matrices to determine real-time data saturation before conducting more extensive qualitative analyses [23]. Rapid data analysis bypasses the process of in-depth coding and organizes data immediately following qualitative interviews based on interview script templates [24]. Rapid analysis will be used to enact changes to the CI-oSurg intervention and protocol until thematic saturation is reached, with 32 participants anticipated based on past studies and practical considerations [25]. Discrepancies in coding or analysis will be resolved through discussions with the larger research team to ensure consistency and accuracy.

Ethical Considerations

This study was approved by the Mass General Brigham Hospital Institutional Review Board (2023P003564). Informed consent will be obtained verbally during enrollment and during qualitative interviews. Participant data will be deidentified and stored securely on HIPAA-compliant servers. Participants will not receive compensation for participation.

Results

The study has been approved by the Mass General Brigham Institutional Review Board and registered with ClinicalTrials.gov. Study funding was obtained in the summer of 2022. Open pilot recruitment is expected to begin in fall 2024. Completion is anticipated by winter 2024, with plans for dissemination of study findings at national surgical meetings in the spring of 2025, with peer-reviewed publications to follow.

Discussion

Findings from this study will improve the acceptability and usability of a web-based communication intervention for fecal ostomy surgery to address challenges leading to distress during fecal ostomy surgery recovery. Recovery after fecal ostomy surgery requires practical management changes (ie, changing an ostomy appliance and monitoring output) as well as emotional adaptation to life with an ostomy. This novel intervention leverages existing technology and resources in surgical clinics to provide scalable, psychologically informed care aimed at improving the biopsychosocial outcomes of patients recovering from fecal ostomy surgery.

Current colorectal surgery guidelines support the use of interventions to improve biopsychosocial outcomes after ostomy surgery based on expert opinion [26]. Communication interventions have been used in some surgical practices (ie, oncology) to identify distress [27,28]. However, these interventions are not currently used in benign surgical settings, and management strategies to address ostomy patient needs are lacking. The intervention refined in this study will evaluate the level of distress, identify the potential needs of patients recovering from ostomy surgery, and provide management steps. By addressing common concerns identified by patients and clinicians interviewed by our team during prototype development, we hypothesize that the intervention will reduce postoperative patient distress during future efficacy testing.

The intervention under development in this study, CI-oSurg, is novel because current surgical care models limit the integration of psychologically informed care. While psychiatrists are involved in the care of select surgical patient populations (preoperative bariatric surgery screening), there is a lack of psychological support for patients facing and recovering from fecal ostomy surgery. Providing individual counseling to all fecal ostomy patients is unlikely to be feasible due to resource constraints [29]. However, screening for distress, anxiety, and depression before and after ostomy surgery is a key first step in identifying the needs of this high-risk surgical population [9,30,31]. The use of a distress screen in this communication intervention with a problem list to compartmentalize challenges will provide surgical teams with a better understanding of specific, individualized interventions needed to support patients during recovery after ostomy surgery.

In this study, we will ensure the recruitment of older adults facing fecal ostomy surgery to understand the unique needs of this growing patient population. Older adults undergoing fecal ostomy surgery have poor biopsychosocial outcomes, including a high rate of permanent ostomy formation, poor quality of life, and high levels of caregiver burden [3-7,31-34]. A study by Bosshardt [35] reports high rates of mortality and permanent ostomy among patients aged 70 years or older. Among aging adults, poor outcomes can be linked to geriatric conditions. For example, arthritis or sensory impairments can impact patients' ability to perform practical management tasks required for independent ostomy care, and polypharmacy and neurocognitive impairment contribute to dehydration. If older adults note new challenges, such as medication management for dehydration, we will refine the intervention to address these needs before finalizing prototype content. This focus on older adult ostomy patients will provide key insights to improve the care of this growing surgical population [36].

During this open pilot phase, certain barriers may arise to using this intervention in the busy inpatient surgical setting. This study will identify and address barriers to intervention acceptability, such as clinicians' limited time or unfamiliarity with distress screening strategies before efficacy testing [37,38]. In addition, the usability of certain intervention components might need to be modified (ie, using hospital-provided tablets vs personal devices). Using a human-centered design approach to obtain information on these potential barriers is a critical step in intervention development to optimize the intervention acceptability before efficacy testing.

This study should be considered in light of important limitations. The web-based intervention content is only in English; therefore, lack of English fluency is an exclusion criterion. Future work will need to be performed to develop and evaluate the acceptability and usability of a culturally adapted intervention in diverse populations considering different languages and ethnic groups. Next, the study will be performed at a single institution in the northeastern United States. Clinicians practicing in different hospital settings might find unique challenges when

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using interventions with different clinical demands or patient populations.

Conclusion

Through this open pilot study, we will refine CI-oSurg, a web-based communication intervention focused on addressing the biopsychosocial needs of patients recovering from ostomy surgery. Current colorectal surgery guidelines support the use of interventions to improve outcomes after ostomy surgery; however, there is a paucity of evidence-based interventions to address the needs of this population. This study is the next step in establishing the usability and acceptability of the CI-oSurg intervention. Future efficacy testing will provide surgical teams with an evidence-based, scalable communication intervention that addresses the biopsychosocial needs of this large surgical patient population.

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Data Availability

The data sets generated during and/or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

CEC contributed to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, and writing of the original draft, as well as editing. AR contributed to the conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and writing of the original draft, as well as editing. MB contributed to the conceptualization, investigation, methodology, supervision, validation, visualization, and review and editing of the manuscript. ZC contributed to the conceptualization, investigation, methodology, supervision, validation, visualization, and review and editing of the manuscript. AMV contributed to the conceptualization, investigation, methodology, supervision, validation, visualization, and review and editing of the manuscript. CSR contributed to the conceptualization, funding acquisition, investigation, methodology, supervision, validation, visualization, and review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Semistructured interview guides.
[DOCX File , 16 KB - resprot_v13i1e60575_app1.docx]

Multimedia Appendix 2
Rapid analysis template.
[DOCX File , 14 KB - resprot_v13i1e60575_app2.docx]

Multimedia Appendix 3
Peer-review report by the Career Development for Clinicians/Health Professionals Study Section - National Institute on Aging Initial Review Group - Career Development for Clinicians and Health Professional Awards (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 1310 KB - resprot_v13i1e60575_app3.pdf]

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Abbreviations

CI-oSurg: Communication Intervention for fecal ostomy Surgery
HIPAA: Health Insurance Portability and Accountability Act
MGH: Massachusetts General Hospital
REDCap: Research Electronic Data Capture

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Protocol

A Mindfulness-Based Lifestyle Intervention for Dementia Risk Reduction: Protocol for the My Healthy Brain Feasibility Randomized Controlled Trial

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Abstract

Background: Lifestyle behavior change and mindfulness have direct and synergistic effects on cognitive functioning and may prevent Alzheimer disease and Alzheimer disease–related dementias (AD/ADRD). We are iteratively developing and testing My Healthy Brain (MHB), the first mindfulness-based lifestyle group program targeting AD/ADRD risk factors in older adults with subjective cognitive decline. Our pilot studies (National Institutes of Health [NIH] stage 1A) have shown that MHB is feasible, acceptable, and associated with improvement in lifestyle behavior and cognitive outcomes.

Objective: We will compare the feasibility of MHB versus an education control (health enhancement program [HEP]) in 50 older adults (aged ≥60 y) with subjective cognitive decline and AD/ADRD risk factors. In an NIH stage 1B randomized controlled trial (RCT), we will evaluate feasibility benchmarks, improvements in cognitive and lifestyle outcomes, and engagement of hypothesized mechanisms.

Methods: We are recruiting through clinics, flyers, web-based research platforms, and community partnerships. Participants are randomized to MHB or the HEP, both delivered in telehealth groups over 8 weeks. MHB participants learn behavior modification and mindfulness skills to achieve individualized lifestyle goals. HEP participants receive lifestyle education and group support. Assessments are repeated after the intervention and at a 6-month follow-up. Our primary outcomes are feasibility, acceptability,

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appropriateness, credibility, satisfaction, and fidelity benchmarks. The secondary outcomes are cognitive function and lifestyle (physical activity, sleep, nutrition, alcohol and tobacco use, and mental and social activity) behaviors. Data analyses will include the proportion of MHB and HEP participants who meet each benchmark (primary outcome) and paired samples 2-tailed *t* tests, Cohen *d* effect sizes, and the minimal clinically important difference for each measure (secondary outcomes).

Results: Recruitment began in January 2024. We received 225 inquiries. Of these 225 individuals, 40 (17.8%) were eligible. Of the 40 eligible participants, 21 (52.5%) were enrolled in 2 group cohorts, 17 (42.5%) were on hold for future group cohorts, and 2 (5%) withdrew before enrollment. All participants have completed before the intervention assessments. All cohort 1 participants (9/21, 43%) have completed either MHB or the HEP (≥6 of 8 sessions) and after the intervention assessments. The intervention for cohort 2 (12/21, 57%) is ongoing. Adherence rates for the Garmin Vivosmart 5 (128/147, 87.1% weeks) and daily surveys (105/122, 86.1% weeks) are high. No enrolled participants have dropped out. Enrollment is projected to be completed by December 2024.

Conclusions: The RCT will inform the development of a larger efficacy RCT (NIH stage 2) of MHB versus the HEP in a more diverse sample of older adults, testing mechanisms of improvements through theoretically driven mediators and moderators. The integration of mindfulness with lifestyle behavior change in MHB has the potential to be an effective and sustainable approach for increasing the uptake of AD/ADRD risk reduction strategies among older adults.

Trial Registration: ClinicalTrials.gov NCT05934136; https://www.clinicaltrials.gov/study/NCT05934136

International Registered Report Identifier (IRRID): DERR1-10.2196/64149

(JMIR Res Protoc 2024;13:e64149) doi:10.2196/64149

KEYWORDS

lifestyle; cognitive decline; brain health; mindfulness; mind-body therapies; telemedicine; digital health; randomized clinical trial

Introduction

Background

Alzheimer disease and Alzheimer disease–related dementias (AD/ADRD) are debilitating neurodegenerative disorders that impair cognitive and daily functioning [1]. An estimated 50 million people are living with AD/ADRD worldwide, with 10 million new cases occurring annually [2-4]. AD/ADRD places an immense burden on individuals, families, and health care systems. The economic toll of family and unpaid caregiving for AD/ADRD was US $346.6 billion in 2023 [5]. In the early stages of AD/ADRD, approximately half of adults aged ≥65 years perceive subjective cognitive decline (SCD) [6,7] in memory or other cognitive domains before neurodegeneration can be detected through cognitive testing [8,9]. SCD is associated with a greater likelihood of underlying AD/ADRD biomarker pathology and increased risk for future cognitive decline and AD/ADRD [10-13]. This preclinical stage is a critical window to engage older adults in preventive interventions that aim to modify AD/ADRD risk factors.

Growing research indicates that multiple lifestyle behaviors are important for AD/ADRD prevention [14-21]. In 2020, the Lancet Commission on Dementia identified 12 modifiable risk factors accounting for 40% of AD/ADRD cases worldwide: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, a history of head injury, and exposure to air pollution [22]. The commission also highlighted the need for further research on additional lifestyle risk factors such as poor sleep [23-25], diet [23,26], and mental activity [27,28], which may influence AD/ADRD risk but have shown mixed findings [29]. Multidomain trials targeting modifiable lifestyle risk factors identified in the *Lancet* report have demonstrated the potential to improve cognition among older adults with early cognitive decline [30,31]. However, not all multidomain trials have reported positive results [32-34]. Trials have also failed to modify behaviors [33], or they have inconsistently reported lifestyle outcomes [30]. Complex and time-intensive intervention designs hindered participant adherence [35,36] and limit future implementation. Additional research is needed to develop more effective and practical interventions that promote sustained engagement and adherence to AD/ADRD prevention strategies among older adults.

Mindfulness practices may help address challenges in modifying lifestyle behaviors and offer direct brain health benefits. Mindfulness is commonly defined as the practice of nonjudgmental awareness of the present moment [37]. Mindful self-regulation theory suggests that mindfulness involves several self-regulation processes (eg, emotion regulation, cognitive control, and self-monitoring) that enhance one's ability to cope with urges (eg, overeating or avoiding exercise) and make healthier lifestyle choices [38-40]. Mindfulness practice is positively associated with measures of enhanced brain structure [41-43] and cognitive function [41,44-48]. In addition, mindfulness is associated with reductions in psychological symptoms, such as depression, anxiety, and attitudes and worries regarding AD/ADRD [49-52], which are independent risk factors for AD/ADRD [53-56] and an inactive lifestyle [57]. Mindfulness is feasible and acceptable for older adults, including individuals with SCD [38,52,58]. Prior research suggests that cognitive benefits associated with mindfulness can be observed with brief practice [59-61], suggesting that mindfulness is amenable to time-limited interventions. Despite these advantages, mindfulness has been overlooked in behavior modification AD/ADRD prevention interventions.

Our interdisciplinary team has developed the first group mindfulness-based lifestyle intervention (My Healthy Brain [MHB]) that aims to modify early risk for AD/ADRD. We

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conducted a series of preliminary studies to develop MHB following the National Institutes of Health (NIH) Stage Model [62], an iterative framework for guiding behavioral intervention development and testing, from pilot studies to implementation and dissemination (Figure 1). First, our systematic review and meta-analysis (we analyzed 79 studies with 9233 participants) found moderate- to high-quality evidence that mindfulness-based interventions were associated with significant improvements in multiple lifestyle behaviors linked to brain health, including sleep, physical activity, alcohol use, and tobacco cessation [63]. Second, we conducted iterative studies of older adults with AD/ADRD risk factors to determine the best delivery modality and strategies to incorporate mindfulness into lifestyle behaviors. Preliminary studies included (1) an in-person clinical pilot (N=24) [64], (2) a telehealth group case series (N=7) [65], and (3) a mixed methods study to adapt the program via qualitative focus groups (N=11) and conduct a feasibility pilot with exit interviews (N=10) [66]. MHB met benchmarks set a priori for feasibility, credibility, satisfaction, and safety (there were no adverse events). We observed preliminary improvements (moderate to large effects) in subjective and objective measures of cognitive function, physical activity, sleep, and proposed mechanisms. Exit interviews confirmed the satisfaction with mindfulness and feasibility with technologies to support behavior change (monitoring steps via an activity watch) and remote delivery (Zoom; Zoom Video Communications, Inc). Finally, we conducted a qualitative study with health care professionals caring for older patients (N=26) to address barriers to implementing study procedures (eg, recruitment, enrollment, and retention) and maximizing diversity to prepare for the first feasibility randomized controlled trial (RCT) of MHB [67].

Figure 1. Iterative development of My Healthy Brain (MHB) following the National Institutes of Health Stage Model. The current feasibility randomized controlled trial (RCT; starred box) will inform an efficacy RCT (dashed box). HEP: health enhancement program.

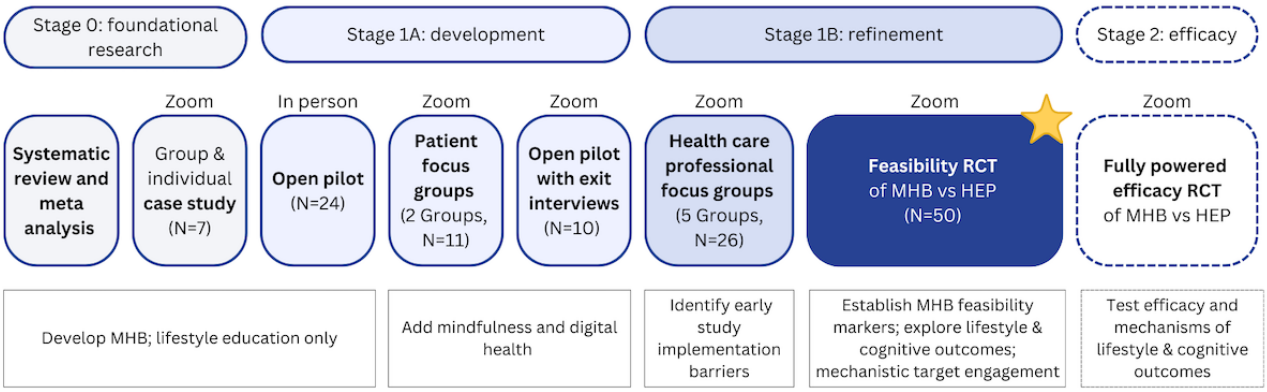

Objectives

Building upon our preliminary studies, we report on the improved protocol and initial launch of the first feasibility RCT of MHB (NIH stage 1B). We are enrolling 50 older adults (aged ≥60 y) with SCD and modifiable AD/ADRD lifestyle risk factors. Participants are randomized to MHB or a time- and attention-matched education control (health enhancement program [HEP]) [68,69], both delivered in telehealth groups over 8 weeks. The primary aim is to assess the feasibility, acceptability, appropriateness, credibility, satisfaction, and fidelity of MHB against established Go–No-Go benchmarks [64,70-74]. The secondary aim is to investigate preliminary improvements in cognitive and lifestyle outcomes and engagement in proposed mechanisms. The results will inform the first efficacy RCT of MHB and mechanistic testing of cognitive and lifestyle outcomes.

Methods

Overview

We are conducting a virtual, single-blind, feasibility RCT of the MHB intervention versus the HEP [68,69] education control (N=50). Our study is consistent with the research objectives and activities specified in stage 1B of the NIH Stage Model [62]. NIH stage 1 focuses on intervention development, testing, refinement, and modification. NIH stage 1B activities emphasize the refinement of intervention and training materials, feasibility and pilot testing, and early attention to implementation. As such, our study is designed to confirm the feasibility of MHB and assess engagement in intervention outcomes and hypothesized mechanisms before conducting a fully powered efficacy RCT [75-77]. All procedures described herein are conducted fully remotely, allowing for both local and national recruitment. We followed the National Council on Aging guidelines for using technology with older adults [78] and our established digital health trials [66,70,74,79-92]. Figure 2 presents the study flow.

We preregistered our RCT on ClinicalTrials.gov (NCT05934136) before enrolling the first participant.

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Figure 2. Study flow and timeline. Color key: yellow=recruitment, green=assessment, and blue=programs. BRANCH: Boston Remote Assessment for Neurocognitive Health; Garmin: Garmin Vivosmart 5 watch; HEP: health enhancement program; MHB: My Healthy Brain; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SCD: subjective cognitive decline.

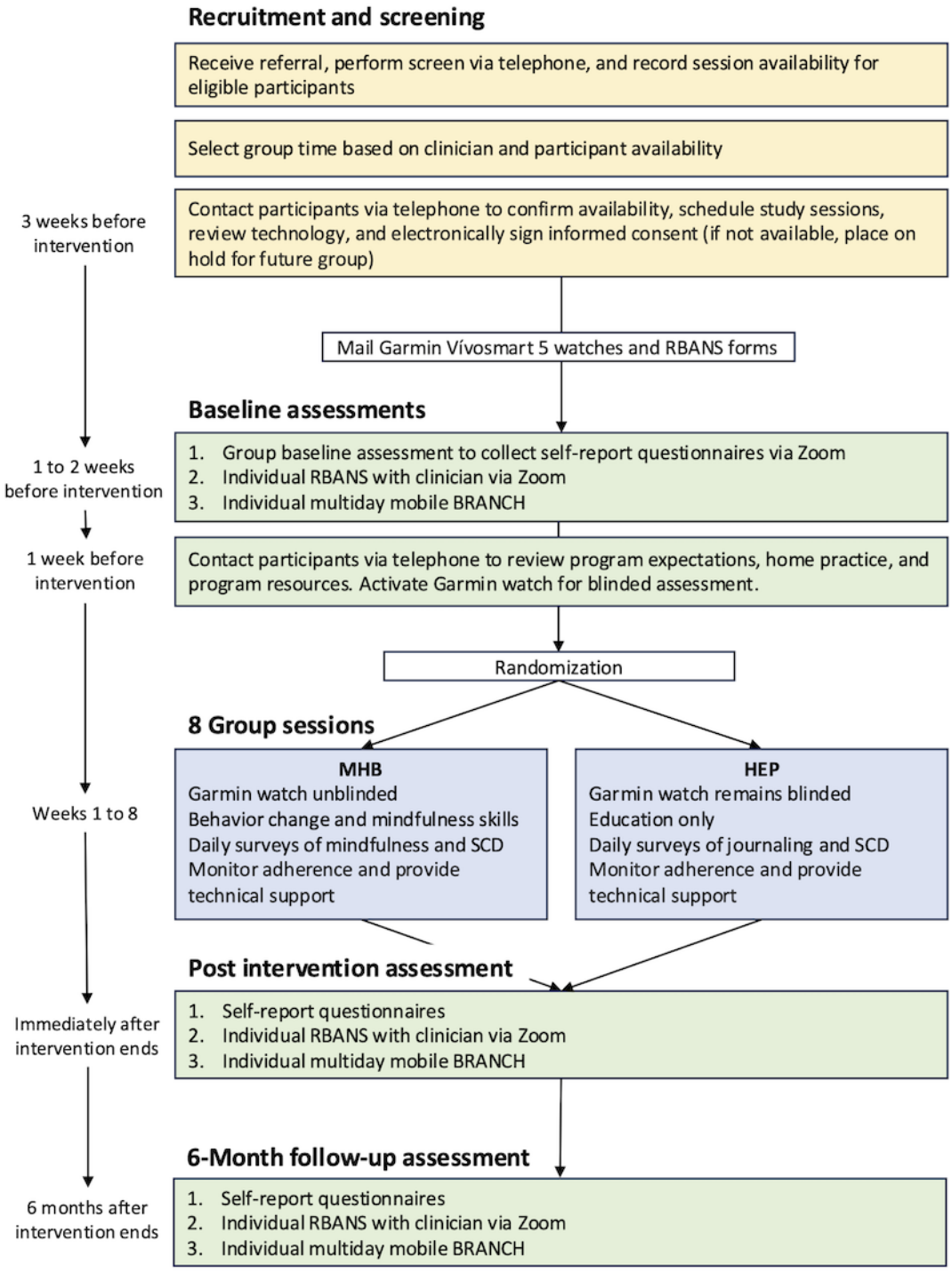

Ethical Considerations

The Mass General Brigham (MGB) institutional review board (IRB) approved all study procedures (2023P001770). All participants review and sign written informed consent with a clinical research assistant (RA) before completing study procedures. Consent informs participants that, with any group-based intervention, there may be confidentiality and privacy risks. To minimize these risks, we discuss the importance of confidentiality at the start of each group; request that participants attend the session from a private location; and all data are deidentified, maintained in a secured location, and only accessed by IRB-approved members of the research team. Participants are compensated up to US $220: US $30 for before the intervention assessments, US $60 for after the intervention assessments, US $90 for 6-month follow-up assessments, with an additional US $40 for 7 out of 7 valid days of Garmin Vivosmart 5 wear during the before the intervention assessment period. This compensation strategy is meant to optimize participant engagement and motivation for 6-month follow-up assessments.

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Participants

Participants are older adults (aged ≥60) who are at early risk for AD/ADRD as determined by the presence of SCD [8], have no cognitive impairment (Telephone Interview for Cognitive Status score >30) [93], and have modifiable AD/ADRD risk factors (Cardiovascular Risk Factors, Aging, and Incidence of Dementia [CAIDE] score ≥6) [94,95]. Textbox 1 shows our full inclusion and exclusion criteria and rationales, which we have refined through our previous pilot studies [64-66]. These eligibility criteria were informed by similar lifestyle AD/ADRD prevention trials [30,31,35] and behavioral interventions for older adults [74,81,83,92,96].

Textbox 1. Study inclusion and exclusion criteria with rationales.

Inclusion criteria and brief rationales

1. Aged ≥60 years: study population
2. Subjective cognitive decline (SCD; eg, forgetting information, getting lost, and repeating oneself): SCD Initiative criteria [8]
3. Cardiovascular Risk Factors, Aging, and Incidence of Dementia score ≥6 [94,95]: modifiable Alzheimer disease and Alzheimer disease–related dementias (AD/ADRD) risk factors [30,35]
4. Telephone Interview for Cognitive Status score >30 [93]: absence of AD/ADRD that would prevent meaningful engagement
5. Functional Assessment Questionnaire score <9 [97,98]: functional independence and ability to participate meaningfully
6. English fluency and literacy: data validity (all measures are validated for use in English) and delivery modality
7. Ability and willingness to participate via live video in group session: delivery modality
8. No self-reported safety issues with initiating lifestyle changes during the study: safety of participants and validity

Exclusion criteria and brief rationales

1. Mild cognitive impairment, AD/ADRD, or other neurodegenerative disease: study confound (intervention targets early AD/ADRD risk; ability to participate meaningfully)
2. Psychotropic medication (eg, antidepressant) change in <3 months: study confound
3. Psychosis, uncontrolled bipolar disorder, or uncontrolled substance dependence or abuse: study confound (safety of participants; treatment confound; can affect participants' answers)
4. Current self-report of suicidal ideation: participant safety
5. Serious medical illness expected to worsen in 6 months (eg, cancer): study confound (serious medical illness may act as a third variable)
6. Use of an activity watch to track physical activity or sleep in <3 months and unwillingness to stop using it for the duration of the program: treatment confound
7. Mindfulness practice lasting >45 minutes per week or cognitive behavioral therapy in <3 months: treatment confound
8. Self-reported step count >5000 per day or ≥30 minutes of exercise per day: study population (intervention targets increased activity among sedentary older adults)

Recruitment and Enrollment

Our recruitment strategy incorporates a combination of hospital partnerships, community outreach, and internet-based recruitment methods. Through our preliminary studies, we developed partnerships with several MGB clinics that are directly involved in the care of older patients with SCD. The clinics represent expertise in geriatrics, geriatric psychiatry, neurology, neuropsychology, memory care, and integrative medicine. To promote the study within our hospital, we have engaged clinic leadership, presented in team meetings, and distributed our IRB-approved flyer to providers and clinic waiting areas. The flyer contains study contact information and a QR code to an eligibility self-screener. In addition, patients can contact the study through a hospital web-based recruitment platform (MGB Rally). We aim to maximize the inclusion of older adults from diverse and underserved backgrounds to address disparities in AD/ADRD [99,100] and underrepresentation in prevention clinical trials [101,102]. First, we have proactively formed collaborations with MGB clinics that serve more diverse patients. Second, we have engaged community organizations and Councils on Aging (commonly known as "senior centers") in Massachusetts. Community outreach consists of engaging community leadership, disseminating recruitment materials, and conducting public events (eg, networking nights and educational talks). We are specifically targeting outreach to underresourced communities of older adults in Massachusetts who face significant health disparities and heightened risk factors for AD/ADRD [103]. Third, we have consulted with our center's Community Engagement Core on evidence-based recruitment strategies [104]. Fourth and last, we have expanded our outreach nationally via social media platforms, web-based study postings (eg, ClinicalTrials.gov and Alzheimers.gov), and articles and presentations developed for public audiences.

Screening and Enrollment

The RA logs all referral information in a standardized REDCap (Research Electronic Data Capture; Vanderbilt University) [105] database. Participants have the option to complete an initial screening survey independently or by telephone with the RA. The RA contacts all potentially eligible participants to answer

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questions about the study, collect availability for groups, and assess technology access and readiness. Individuals who do not meet study criteria are offered resource sheets developed for older adults with SCD. The principal investigator (RAM) reviews all eligibility decisions and consults with the multidisciplinary study team if needed. After group times have been set, the RA meets with participants individually over Zoom to schedule the before the intervention assessments, review study technology, and obtain electronic informed consent via REDCap. The RA uses secure email to send confirmation and Zoom links for the before the intervention assessments.

Assessments

Overview

Tables 1 and 2 detail the assessments and the frequency of data collection. All assessment data are stored in a REDCap database. An RA blinded to randomization reviews all measures for missing data, errors, or invalid responses.

Table 1. Primary outcomes.

Construct and measure	Scoring	Criteria	Time point
Feasibility			
Recruitment and enrollment	Percentage of individuals who participate and enroll from the total contacted	≥70%=good, ≥80%=excellent	Before the intervention
Outcome assessments	Percentage of participants with no missing outcome assessment data	≥70%=good, ≥80%=excellent	Before the intervention, after the intervention, and at 6-month follow-up
Garmin Vivosmart 5 watch	Percentage of participants who wore the watch at least 5 out of 7 days per week [106,107] for at least 10 hours a day [71]	≥70%=good, ≥80%=excellent	After the intervention
Daily surveys	Percentage of participants who completed at least 5 out of 7 daily surveys during the program	≥70%=good, ≥80%=excellent	After the intervention
Acceptability			
Satisfaction	Client Satisfaction Questionnaire [108] assesses patient satisfaction with the program; percentage of participants with scores (minimum=3, maximum=12) above the scale's midpoint	≥70%=good, ≥80%=excellent	After the intervention
Program attendance	Percentage of participants who attend ≥6 out of 8 sessions	≥70%=good, ≥80%=excellent	After the intervention
Perceived improvements	Modified Patient Global Impression of Change [109] asks participants about perceived improvements in cognitive function, lifestyle, and emotional well-being outcomes; percentage of participants who report improvement in each outcome domain (ranging from 1=*very much worse* to 7=*very much improved*)	≥70%=good, ≥80%=excellent	After the intervention and at 6-month follow-up
Appropriateness			
Credibility and expectancy	Credibility and Expectancy Questionnaire [110] assesses participant perceptions of the treatment as believable, convincing, and logical; percentage of participants with scores (minimum=3, maximum=27) above the scale's midpoint	≥70%=good, ≥80%=excellent	Before the intervention
Fidelity			
Therapist fidelity	Percentage of sessions in which the study clinician completed an audio recording, progress note, and checklist with 100% of the content delivered (confirmed by blinded RA independently coding a random 10% of audio-recorded sessions)	≥75%=good, 90%=excellent	Study completion
Study procedures	Fidelity of staff to the study procedures as calculated by the frequency of protocol deviations	<5 deviations=good, 0 deviations=excellent	Study completion
Patient safety	Number of self-reported adverse events	Mild in ≤10% of participants=good, none=excellent	Study completion

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Table 2. Study measures and constructs. Demographic and clinical characteristics are assessed before the intervention. All other measures are assessed before the intervention, after the intervention, and at 6-month follow-up.

Measure and description	Scoring	Psychometric evidence
Demographic characteristics		
Age, gender, biological sex, race, ethnicity, education, income, occupation, marital status, living situation, and languages spoken	—[a]	—
Clinical characteristics		
Mental health history, medical history, height, weight, Lifestyle for Brain Health (LIBRA) score [111-116], SCD[b] diagnosis, medications and supplements taken for memory	—	—
Cognitive function		
Cognitive Function Index [117], a 14-item measure assessing self-report of SCD across daily functions	1 (*yes*) to 0 (*no*) cognitive changes compared to 1 year ago; higher total scores (minimum=0, maximum=14) indicate greater SCD complaints	Adequate internal consistency and validity for older adults [118-120]
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [121], a comprehensive assessment that includes measures of visual, verbal, and numeric associative memory properties and provides a measure of global cognition	Higher *z* and index scores (minimum=0, maximum=160) indicate greater global and domain-specific cognitive functioning	Clinically valid [121] and high internal reliability among older adults [122]
Physical activity		
PROMIS[c] Physical Function [123], an 8-item self-report of daily physical functioning	5-point scale ranging from 1=*unable to do* to 5=*without any difficulty*; higher T-scores indicate greater physical function and lower disability	Acceptable construct validity for older adults, sensitive to change during intervention studies, and excellent internal reliability [123,124]
Godin Leisure-Time Exercise Questionnaire [125], a 3-item self-report of the frequency of engagement in light, moderate, and vigorous physical activity	Number of times per week engaged in activity; higher scores indicate greater frequency of physical activity for each intensity level	Good construct validity [126] and relatively reliable [127]
Change in step count, measured via the Garmin Vivosmart 5 [128] (change in average step count during the 7 days preceding before the intervention assessment, throughout the intervention period, and 7 days at 6-month follow-up)	Higher step count totals indicate greater physical activity levels (walking)	Low actigraphy-measured step count is correlated with AD/ADRD[d] risk and cognitive decline [129]; MCID[e]=600 to 1100 steps [130]
Sleep		
Pittsburgh Sleep Quality Index [131], a 9-item self-report of sleep patterns and overall quality	Combination of 4-point scale ranging from 1=*not during the past month, very good* to 4=≥*3 times per week, very bad* and open responses; total scores range from 0 to 21, with a score of ≥5 indicating clinically significant sleep disturbance	Prior research supports the Pittsburgh Sleep Quality Index in older adults; high test-retest reliability, fair internal reliability [132], and good validity [133]
Change in total sleep time, measured in minutes via the Garmin Vivosmart 5 [128] (change in total sleep time during the 7 days preceding before the intervention assessment, throughout the intervention period, and 7 days at 6-month follow-up)	Higher total minutes indicate greater sleep time	Poor actigraphy-measured sleep is correlated with AD/ADRD risk and cognitive decline [134]; MCID=40-minute increase [135]
Mediterranean diet		
Mediterranean Eating Pattern for Americans Screener [131,136], a 16-item self-report of adherence to Mediterranean dietary recommendations	Participants earn 1 point for each food within the recommended serving size (range=0-16); higher total scores (minimum=0, maximum=21) indicate greater adherence to the Mediterranean diet	Poor internal reliability [131,136]; however, brief self-reports of the Mediterranean diet are limited
Alcohol and tobacco use		
PROMIS Alcohol Use [137], a 7-item self-report of at-risk drinking	5-point scale ranging from 1=*never* to 5=*almost always*; higher T-scores indicate greater problematic alcohol use	High convergent validity [137] and modest test-retest reliability [138]

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Measure and description	Scoring	Psychometric evidence
CDC[f] Behavioral Risk Factor Surveillance System questionnaire concerning tobacco use [139], a 2-item self-report of tobacco use history and current frequency of use of 6 common tobacco products	5-point scale ranging from 1=*less than once a month* to 5=*daily or almost daily*; higher scores indicate greater tobacco use	—
Social functioning		
PROMIS Loneliness [140], a 5-item self-report of perceived loneliness	5-point scale ranging from 1=*never* to 5=*always*; higher T-scores indicate greater perceived loneliness	Good internal and test-retest reliability [141]
Social Engagement and Activities Questionnaire [142], a 10-item self-report of general and social-group activities	6-point scale ranging from 1=*not at all* to 6=*every day*; higher total scores (minimum=0, maximum=50) indicate greater participation in socially engaging activities	High convergent validity for older adults [142]
PROMIS Satisfaction with Social Roles and Activities [143], an 8-item self-report of satisfaction with ability to perform social activities and meet social needs	5-point scale ranging from 1=*not at all* to 5=*very much*; higher T-scores indicate greater satisfaction with social roles and activities	High reliability and acceptable item-total correlations [144]
Mental activity		
Memory Compensation Questionnaire [145], a 44-item measure assessing the use of cognitive compensatory strategies for actual or perceived memory loss; the external and internal subscales (12 items) relevant to the MHB[g] program are extracted	5-point scale ranging from 1=*never* to 5=*always*; higher total scores (minimum=0, maximum=65) indicate greater use of external and internal memory compensation strategies	Good internal validity among older adults [145]
Measure of cognitive activities (adapted from Geda et al [146]), a 10-item self-report measure that assesses the extent to which an individual engaged in mentally stimulating and social activities over the past week	5-point scale ranging from 1=*never* to 5=*every day*; higher total scores (minimum=0, maximum=10) indicate greater participation in cognitively stimulating activities	Good test-retest reliability [147] and adequate construct validity [148]
Depression and anxiety		
PROMIS Depression [149], a 4-item measure assessing negative mood, views of self, engagement in daily living, and social components	5-point scale for depressive symptoms ranging from 1=*never* to 5=*always*; higher T-scores indicate greater depression	High reliability estimates among diverse older adults and clinically valid [150,151]
PROMIS Anxiety [149], a 4-item measure assessing fear, worry, hyperarousal, and somatic symptoms	5-point scale for anxiety symptoms ranging from 1=*never* to 5=*always*; higher T-scores indicate greater anxiety	High reliability estimates among diverse older adults [150] and strong validity [152]
Mindfulness		
Applied Mindfulness Process Scale [153], a 15-item instrument that measures the frequency of mindfulness practice	5-point scale ranging from 1=*never* to 5=*almost always*; higher total scores (minimum=0, maximum=60) indicate greater use of daily mindfulness activities	Strong internal consistency reliability and item-total reliability [153]
Self-regulation		
Emotion Regulation Questionnaire [154], a 10-item self-report of emotion regulation strategies, both in how emotions are felt and expressed	7-point scale ranging from 1=*strongly disagree* to 7=*strongly agree*; higher total scores (range 10-70) indicate greater tendency to regulate emotions using cognitive reappraisal and expressive suppression strategies	Fair internal reliability among older adults [155] and strong validity [156]
Cognitive Control and Flexibility Questionnaire [157], an 18-item self-report of control over unwanted experiences	4-point scale ranging from 1=*seldom or never* to 4=*almost always*; higher total scores (minimum=13, maximum=52) indicate greater daily use of cognitive control and flexibility	Excellent internal consistency and good construct validity in a community sample [157]
Attitudes to change AD/ADRD behaviors		
Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction scale [158], a 27-item self-report of attitudes to change behaviors to prevent AD/ADRD	5-point Likert scale ranging from 1=*strongly disagree* to 5=*strongly agree*; higher total scores (minimum=27, maximum=135) indicate greater motivation to alter lifestyle factors and health behaviors to reduce risk of dementia	Moderate to high internal reliability and test-retest reliability in a sample of older adults without dementia [158]
Exploratory assessments		

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Measure and description	Scoring	Psychometric evidence
Multiday Boston Remote Assessment for Neurocognitive Health [159], a 7-day, mobile, self-administered assessment measuring paired associative learning based on everyday objects (signs, groceries, and faces)	Digit-Signs Test (correct number of street sign–number pairings identified), Groceries Prices Test (correct number of grocery-price pairings identified), Face-Name Test (average of correct responses from 2 face-name pairings: first letter name recall and full name recall); higher scores on learning curve (scored over 7 days) indicate better performance (minimum=0, maximum=1)	Good test-retest reliability of the learning curves and excellent reliability between participants' 2 composite learning curves [160]
Daily surveys of mindfulness practice (MHB), journaling (HEP[h]), and SCD symptoms (both groups)	Daily mindfulness completed (*yes* or *no*), skills practiced (categorical: all that apply), and time spent practicing these skills (total minutes) in MHB; minutes spent journaling in the HEP [161]; SCD symptoms measured using an 11-point Likert scale ranging from 0=*bad: my thinking is very difficult or slow* to 10=*good: my thinking is sharp and quick* [162,163]	—

[a]Not applicable.

[b]SCD: subjective cognitive decline.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

[d]AD/ADRD: Alzheimer disease and Alzheimer disease–related dementias.

[e]MCID: minimal clinically important difference.

[f]CDC: Centers for Disease Control and Prevention.

[g]MHB: My Healthy Brain.

[h]HEP: health enhancement program.

Benchmarks

Consistent with NIH stage 1B [62] and pilot study guidelines [76,77], our primary outcomes are a priori markers for feasibility, acceptability, appropriateness, credibility, satisfaction, and fidelity. We set Go–No-Go benchmarks based on similar pilot studies of technology-enabled behavioral interventions for older adult populations [64,70-74].

Self-Reported Outcomes

Our selection of self-reported outcomes was guided by our conceptual model (refer to the MHB Intervention subsection), our stage 1 preliminary studies [64-66], and similar lifestyle trials [30,31]. Self-reported outcomes are collected before the intervention, after the intervention, and at the 6-month follow-up during a 60-minute Zoom session. Participants receive a secure link to the self-reported outcomes survey via email from the RA. To aid focus, the RA mutes all participants in the group Zoom session. Participants can use the Zoom hand-raise function or temporarily unmute themselves to seek technical support or ask questions. This system has been used to remotely collect self-reported outcomes for multiple trials of older adults with cognitive impairment [74,83].

Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a comprehensive assessment battery of multidomain cognitive performance [121]. We replaced the Montreal Cognitive Assessment used in our preliminary studies with the RBANS to improve sensitivity to preclinical cognitive changes among older adults with SCD [164-166]. Additional advantages of the RBANS include (1) a total of 4 forms available for repeated assessments to reduce practice effects [167], (2) a comprehensive assessment of 12 subtests in 20 to 30 minutes, (3) strong psychometric properties [168], (4) established telepractice guidelines [169], and (5) administration protocols developed by our team based on similar virtual trials [83].

Trained clinicians administer the RBANS to individual participants via Zoom following a standardized protocol informed by telepractice guidelines [169]. Participants are mailed all testing materials (eg, figure drawing and coding sheets) in advance. Before testing, clinicians ensure that the participants' environment is optimal (quiet, private, no distractions, writing surface, adequate lighting, etc), internet connection is stable, and audio and video are clear. Participants without access to a large-screen device are provided an iPad to ensure clear visibility of the testing stimuli. Participants mail back their written materials for scoring using a prepaid envelope.

Garmin Vivosmart 5 Watch

We selected the Garmin Vivosmart 5 to replace the ActiGraph GT9X. Our preliminary studies revealed that the ActiGraph GT9X is cost prohibitive and frequently had technical support issues that resulted in interrupted data collection and study operations. Additional participant and scientific advantages of the Garmin Vivosmart 5 include (1) its commercial availability and user-friendly design, which promote future scalability; (2) the ability to conduct blinded assessments at study end points by selecting watch faces that do not display step count data; and (3) its reliability and validity for passive monitoring of physical activity and sleep among older adults [170-174]. Our testing showed that step counts measured using the Garmin

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Vivosmart 5 were internally consistent and produced similar estimates to another widely used device (Fitbit).

The Garmin Vivosmart 5 serves 2 purposes in the RCT. First, in conjunction with the Garmin Connect app, it provides self-monitoring tools (eg, real-time step counting and "move" notifications) to promote engagement in physical activity and sleep [171]. Second, it provides objective, continuous, and passive data to capture within-person changes [175,176] in these lifestyle behaviors during the intervention [177,178]. Wearable devices are both feasible and acceptable for older adults and provide valid measurements of physical activity and sleep [179].

The Garmin Vivosmart 5 is mailed to participants 1 to 2 weeks before the intervention phase, and they set up the watch with the RA during an individual Zoom session. The RA pairs the watch with the participant's mobile phone and reviews basic instructions (how to wear, charge, and sync). Participants are instructed to wear the Garmin Vivosmart 5 on their nondominant hand for 24 hours per day (except when briefly removing it for charging) to track steps and sleep. The watch is waterproof and can last up to 7 days per charge. Participants sync their data using the Garmin Connect app daily and charge the watch regularly. The RA turns off self-monitoring features (step count and sleep notifications) for blinded before the intervention assessments in both MHB and HEP groups. After the before the intervention assessments are complete, the RA turns on the self-monitoring features in the MHB group only because activity reinforcement is a core component of the technology-enhanced intervention.

Garmin Vivosmart 5 adherence is defined as ≥10 hours of valid wear time based on prior research [180-183]. Wear time is calculated in relation to heart rate by Fitabase [184]. The RA monitors Fitabase and contacts participants after 48 hours of Garmin Vivosmart 5 nonadherence to provide technical support. We estimate a truncated average 7-day step count and sleep data for each participant, measured by the Garmin Vivosmart 5 before the intervention, after the intervention, and at the 6-month follow-up, using an established protocol [71,92,96]. We exclude nonadherent or invalid days of wear as well as the highest and lowest values to reduce the influence of outliers. A minimum of 3 valid days of wear at each time point is required to calculate the averages. Sleep metrics include total hours asleep and sleep efficiency (the ratio of time asleep to time spent in bed) using guidelines for older adults [185]. We visually inspect sleep-wake patterns during the day to exclude naps from the sleep calculations [186].

Exploratory Assessments

Multiday Boston Remote Assessment for Neurocognitive Health

We are exploring the feasibility of integrating daily mobile cognitive functioning assessments via the Boston Remote Assessment for Neurocognitive Health (BRANCH) platform [160,187,188]. The multiday paradigm using BRANCH can be self-administered without researcher supervision using any web-enabled device (mobile phone, tablet device, or computer). Similar to RBANS assessments, we provide an iPad for participants who do not own a web-enabled device to complete the multiday BRANCH tests. Participants complete 1 BRANCH test per day for 7 days during the 3 main assessment periods; they complete a unique version at each time point (before the intervention, after the intervention, and the 6-month follow-up). Participants complete a brief sequence of three visual associative memory tasks involving everyday objects: (1) Digit-Signs Test (correct number of street sign–number pairings identified), (2) Groceries Prices Test (correct number of grocery-price pairings identified), and (3) Face-Name Test (average of correct responses from 2 face-name pairings: first letter name recall and full name recall). Multiday learning curves to capture the speed and learning of BRANCH stimuli will be computed for each task [160]. Participants are instructed to take the multiday BRANCH tests in a quiet, distraction-free environment. Participants indicate a preferred time to complete the assessment once per day. They receive automated and secure SMS text messages or email reminders with a link to access the test. The administration of the multiday BRANCH tests takes approximately 12 minutes per day. The multiday BRANCH tests have demonstrated strong feasibility, reliability, validity, and sensitivity to subtle changes in learning and memory in preclinical AD/ADRD [160,189].

Daily Surveys

Participants receive daily surveys to indicate adherence and SCD symptoms during the intervention phase. Daily surveys are sent from Twilio (Twilio Inc), a messaging platform with REDCap integration. Participants can receive the surveys via telephone calls, SMS text messages, or secure email according to personal preference. Daily surveys for MHB participants include (1) logging mindfulness practice (*yes* or *no*), (2) program mindfulness skills practiced (all that apply), and (3) total time (in minutes) spent practicing these skills. Similar to other mindfulness RCTs [161], HEP participants are asked to report daily minutes spent journaling to control for the time and attention devoted to the active skills in MHB. Participants in both groups will provide a global rating of perceived SCD (*What is your level of cognitive functioning right now?*) on an 11-point Likert scale ranging from 0=*bad: my thinking is very difficult or slow* to 10=*good: my thinking is sharp and quick* [162,163]. Participants may opt out of messages for the daily surveys and switch to a paper-and-pencil log.

Randomization

One week before the first session of MHB or the HEP, the RA randomizes participants to receive either 8 weeks of the MHB intervention or the HEP education control. Randomization follows a 1:1 ratio using permuted blocks of size 4. To maintain blinding of group assignments, participants are informed that they can participate in 1 of 2 programs: MHB 1 (active intervention [MHB]) or MHB 2 (control [HEP]). To reduce contamination, we ask participants not to share specific information discussed in the group (eg, skills learned and topics discussed) with anyone for the duration of the study. All participants will receive both electronic and paper copies of their assigned treatment manual.

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Treatment Arms

MHB Intervention

The iterative development of MHB has followed the NIH Stage Model [62] and Science of Behavior Change [190] frameworks. The objective of MHB is to increase the uptake and maintenance of lifestyle behavior modification to reduce the risk of AD/ADRD and cognitive decline among older adults, fostering long-term brain health and well-being (Figure 3). This objective aligns with the Scaffolding Theory of Aging and Cognition [191], which posits that lifestyle behaviors enhance "neural compensatory scaffolding," thereby preserving brain structure, function, and cognition with aging. MHB targets *modifiable* lifestyle behaviors identified in our meta-analysis [63], relevant literature on modifiable AD/ADRD risk factors [22,192,193], and similar multidomain lifestyle interventions [30,31]. Modifiable lifestyle behaviors include physical activity, adherence to a Mediterranean diet, sleep quality, alcohol use, tobacco cessation, social functioning, and mental activity. MHB does not target other AD/ADRD risk factors that are not modifiable through a group-based behavioral intervention (eg, a history of head injury or exposure to air pollution [22]).

The intervention design and procedures were informed by MHB preliminary studies [64-66] and a similar virtual program for older adults with early cognitive decline [74,81,83,92,194]. MHB is delivered via 90-minute Zoom meetings in small groups of 5 to 10 older adults with early AD/ADRD risk (refer to Textbox 1 for the eligibility criteria). The MHB program is led by a clinical health psychologist with aging expertise and a supervised clinical psychology doctoral trainee. All sessions provide education on AD/ADRD risk factors and teach evidence-based behavior modification skills grounded in cognitive behavioral therapy [195] and mindful self-regulation theory [38-40]. Guided by qualitative work with older adults [71,96], we adapted all program skills to account for challenges related to SCD symptoms and aging (eg, forgetfulness, mobility issues, and loneliness). Textbox 2 contains a full list of topics for each MHB session. Participants receive a copy of the manual along with access to the program website, which includes educational videos, recordings of mindfulness skills, and additional resources.

In the first session, the group leader provides an overview of the program, sets expectations for participation (eg, attendance, home practice, and appropriate group behavior), defines key terms (eg, dementia, brain health, and mindfulness), and allows group members to introduce themselves. The remainder of the first session and all subsequent sessions follow the same agenda: review previous material (10% of session time), problem-solve adherence barriers (10%), discuss progress toward participants' goals (10%), provide education on AD/ADRD risk factors (30%), and practice and apply behavior modification and mindfulness skills (40%). Group members are encouraged to collaboratively support each other by sharing strategies for coping with SCD symptoms and achieving lifestyle goals. MHB group participants wear the Garmin Vivosmart 5 to increase their daily step count gradually and safely following a quota-based pacing protocol (10% increase each week if step goal is achieved) [83]. At the end of each session, participants set an individualized specific, measurable, achievable, relevant, and timely (SMART) lifestyle behavioral goal [196]. During the week between MHB sessions, participants execute their SMART goal and practice mindfulness (5-10 min/d).

Figure 3. Conceptual model of My Healthy Brain (MHB). AD/ADRD: Alzheimer disease and Alzheimer disease–related dementias.

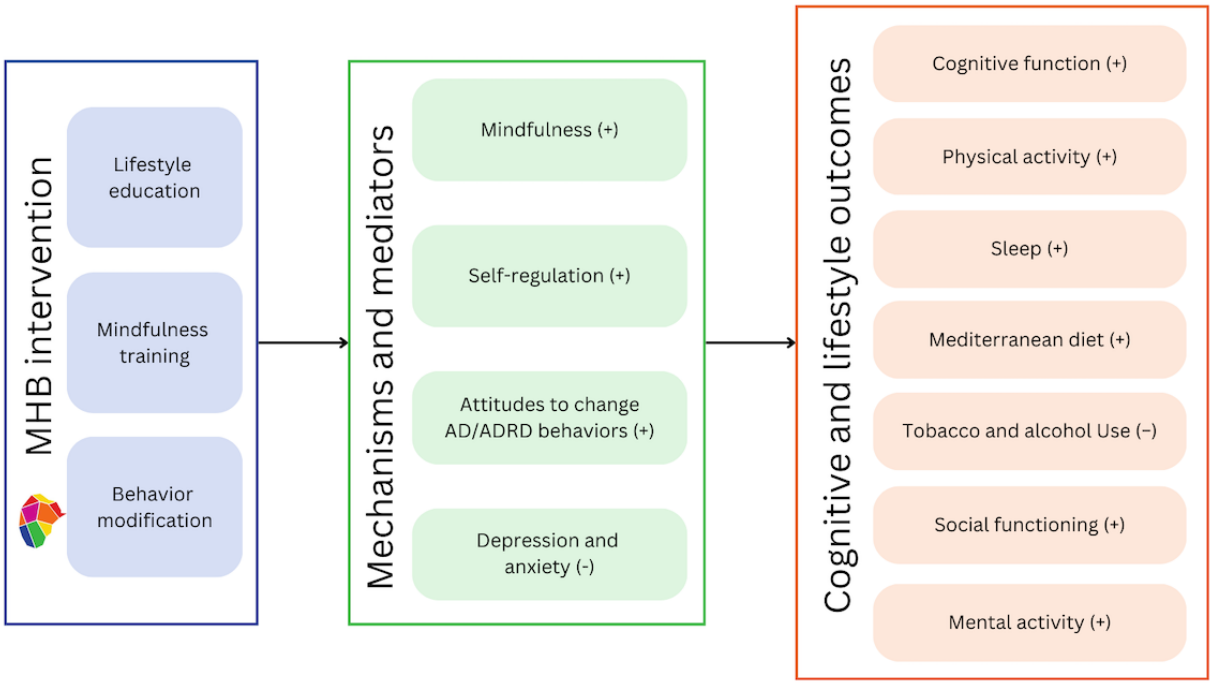

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Textbox 2. Session outline for My Healthy Brain (MHB) and the health enhancement program (HEP).

MHB sessions and content

- Session 1: Brain health and mindfulness
  - Education: define brain health, bust common myths about brain health, identify protective lifestyle factors, and understand the benefits of mindfulness
  - Mindfulness: practice "mindful awareness of breath" meditation
  - Behavioral: reflect on motivations for participating, assess current brain health habits, and set lifestyle goals for the program
- Session 2: Physical activity and walking
  - Education: understand the importance of physical activity (walking) for brain health, and use a wearable device (Garmin Vivosmart 5 watch) to monitor and reinforce my daily step count
  - Mindfulness: pay attention nonjudgmentally by practicing "body scan" meditation
  - Behavioral: set realistic and achievable walking goals (quota-based pacing), and link activities to enjoyment and purpose
- Session 3: Quality sleep
  - Education: understand the importance of sleep for brain health, and use a wearable device (Garmin Vivosmart 5 watch) to monitor sleep (total time and efficiency)
  - Mindfulness: learn how mindful responding can lead to healthier lifestyle choices through the "mindful STOP (stop, take a breath, observe, and proceed)" meditation
  - Behavioral: use behavioral sleep hygiene strategies and problem-solve barriers to getting quality sleep
- Session 4: Mediterranean and Mediterranean–Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet
  - Education: understand the importance of the Mediterranean or MIND diet for brain health
  - Mindfulness: bring mindfulness to my daily experiences through "mindful eating" meditation
  - Behavioral: notice hunger and fullness urges to reduce overeating, and track dietary changes using a MIND diet log
- Session 5: Mental activity and cognitive reserve
  - Education: understand the importance of being mentally active for brain health, and identify cognitive strengths and weaknesses
  - Mindfulness: learn the brain health benefits of mindfulness and practice "bringing awareness to unwanted experiences" meditation
  - Behavioral: develop compensatory strategies for memory-related problems (MRPs), and get mentally active to build cognitive reserve
- Session 6: Social activity and brain health
  - Education: understand the importance of social activities for brain health and the risks of loneliness
  - Mindfulness: practice mindful communication to improve my relationships, openness, and compassion to myself and others; and practice "love and kindness" meditation
  - Behavioral: brainstorm ways to become more socially active, and create shared activity plans to reduce loneliness
- Session 7: Mindfulness of unhealthy urges
  - Education: understand the impacts of alcohol, tobacco, and substance use on brain health, identify urges that become unhealthy habits
  - Mindfulness: practice tolerating urges with the "urge surfing" meditation
  - Behavioral: break unhealthy habits by identifying environments and stressors that derail lifestyle goals
- Session 8: Maintaining a brain-healthy life
  - Education: understand how to sustain a healthy lifestyle and prepare for the end of MHB
  - Mindfulness: review how to integrate mindfulness into daily life and practice "mountain" meditation
  - Behavioral: evaluate progress in the program and develop a plan to main acquired skills

HEP sessions and content

- Session 1: Program overview and MRPs
  - Program goals, understand MRPs, how stress and MRPs are connected, and the impact of stress

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- Session 2: The connection between MRPs and physical wellness
  - Understand the connection between MRPs and physical wellness
- Session 3: Sleep and wellness—connection with MRPs
  - Healthy sleeping strategies and cognitive and physical health
- Session 4: Exercise and wellness—connection with MRPs
  - Physical exercise, maintaining healthy weight, and tips for getting active
- Session 5: Nutrition—connection with MRPs
  - Basic nutrition, unique needs and tips for older adults, and portion size
- Session 6: Substance use, supplements, and medications—connection with MRPs
  - The impact of tobacco and alcohol use on brain health and aging, guidance on over-the-counter memory supplements, and medication management
- Session 7: Social support and loneliness—connection with MRPs
  - The impact of social isolation on brain health, types of social support, and physician support
- Session 8: Program review
  - Overview of program content

HEP Control

The HEP is a time- and attention-matched education control [68,69]. The HEP has been used in similar RCTs, including those involving older adults with SCD [74,81,83,92,197-201]. This active control accounts for the effect of time spent as well as feedback and support from group members and the study clinician. Participants receive lifestyle education consistent with public health recommendations and standards for health promotion (eg, physical activity, sleep, and the Mediterranean diet; Textbox 2). Participants do not learn the mindfulness or behavior modification skills unique to MHB. To control for the time and attention devoted to MHB skills, HEP participants are instructed to journal for 5 to 10 minutes per day. HEP participants wear the Garmin Vivosmart 5 but do not monitor steps and sleep or set goals (ie, these features are disabled in the Garmin Connect app).

Data Analyses

Power Analysis

Consistent with the NIH Stage Model [62] and guidelines for feasibility pilot studies [76,77], the pilot RCT trial is primarily focused on feasibility benchmarks and *not* efficacy testing. With a sample size of 50 participants and assuming conservatively that the 10 feasibility criteria are independent, the study will have >80% power to confirm all benchmarks if at least 82% of the participants meet the specified benchmark for each criterion. The proposed sample size is consistent with prior similar pilot trials [83].

Primary Analyses (Feasibility)

Statistical analyses will be performed in R (version 4.2.1; R Foundation for Statistical Computing) using RStudio (Posit Software, PBC) [202,203]. We will calculate frequencies and proportions to assess a priori feasibility Go–No-Go benchmarks for the feasibility, acceptability, appropriateness, credibility, satisfaction, and fidelity of the programs [64,70-74]. If these benchmarks are not met, revisions will be necessary before an efficacy trial. We will report benchmarks separately for the MHB intervention and HEP control groups.

Exploratory Analyses

Consistent with the Science of Behavior Change framework [189], we will test preliminary improvements and explore mechanisms to guide intervention refinements before efficacy testing. For each measure, we will report descriptive statistics, paired samples 2-tailed *t* tests, and Cohen *d* effect sizes (small=0.2, medium=0.5, and large=0.8) [204] with 95% CIs and minimal clinically important difference where available. We will analyze the MHB and HEP groups separately. We will explore associations between hypothesized mechanisms and outcomes to gauge the evidence of engagement in the targets of the MHB intervention. Finally, we will examine adherence and person-specific patterns of intensive longitudinal data (Garmin Vivosmart 5, multiday BRANCH tests, and daily surveys) during the RCT.

Results

Overview

This study was funded by a National Institute on Aging Mentored Patient-Oriented Research Career Development Award (K23; 1 K23 AG075257-01; September 2022). The study was approved by the IRB in October 2023. We began recruitment in January 2024. As of June 1, 2024, a total of 225 individuals had inquired about the study via self-referral or referral from a clinician or community partner. We made initial contact and conducted screenings with 213 (94.7%) of the 225

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individuals; 25.6% (40/156) met the eligibility criteria. Of the 40 eligible participants, 21 (52.5%) were enrolled in 2 group cohorts, 17 (42.5%) were on hold for future group cohorts, and 2 (5%) withdrew before enrollment. Primary reasons for ineligibility included low AD/ADRD risk (CAIDE score <6; 54/116, 46.6%), active lifestyle (>5000 average steps per day and ≥30 minutes of exercise per day; 26/116, 22.4%), no self-reported SCD (18/116, 15.5%), age <60 years (16/116, 13.8%), regular mindfulness practice (8/116, 6.9%), and clinically significant cognitive impairment (Telephone Interview for Cognitive Status score <31 out of a maximum possible 41 points; 5/116, 4.3%).

All 21 enrolled participants were randomized to MHB (n=11, 52%) or the HEP (n=10, 48%) across 2 group cohorts (cohort 1: n=9, 43%; cohort 2: n=12, 57%). All participants completed before the intervention assessments. No participants have dropped out after enrollment. All participants in our first cohort completed ≥6 out of 8 sessions of either MHB or the HEP (including minimal makeup sessions) and after the intervention assessments (9/9, 100%). One participant requested to skip the HEP session on substance use due to a traumatic family history. The intervention for our second cohort (12/21, 57%) is ongoing (5 out of 8 sessions completed; 100% attendance with minimal makeup sessions). Across both cohorts, adherence rates are high for the Garmin Vivosmart 5 (128/147, 87.1% total weeks) and daily surveys (105/122, 86.1% total weeks). We plan to complete enrollment by December 2024 and data analyses by December 2025.

Demographics

Sample characteristics for enrolled cohorts 1 and 2 are presented in Table 3.

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Table 3. Demographics of enrolled and scheduled My Healthy Brain study participants (n=21).

Characteristics	Values
Age (y), mean (SD; range)	72 (7.71; 60-88)
Sex, n (%)	
Female	16 (76)
Male	5 (24)
Chose not to answer	0 (0)
Gender, n (%)	
Women	16 (76)
Men	5 (24)
Nonbinary	0 (0)
Chose not to answer	0 (0)
Ethnicity, n (%)	
Hispanic or Latinx	1 (5)
Not Hispanic or Latinx	19 (91)
Chose not to answer	1 (5)
Race, n (%)	
Asian or Asian American	1 (5)
Black or African American	1 (5)
White	17 (81)
Multiracial	0 (0)
Chose not to answer	2 (10)
Marital status, n (%)	
Single, never married	2 (11)
Married	9 (43)
Living with significant other	0 (0)
Separated or divorced	5 (24)
Widowed	5 (24)
Chose not to answer	0 (0)
Living status, n (%)	
Live alone	7 (33)
Live alone with spouse or partner	9 (43)
Live alone with 1 other friend or roommate	2 (10)
Live with caregiver	0 (0)
Live with group (private residence)	2 (10)
Live in a group home	1 (5)
Other	0 (0)
Chose not to answer	0 (0)
Education, n (%)	
Completed high school or GED[a] (12 y)	1 (5)
Some college or associate's degree (<16 y)	2 (10)
Completed 4 years of college (16 y)	8 (38)
Graduate or professional degree (>16 y)	10 (48)
Chose not to answer	0 (0)

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Characteristics	Values
Employment status, n (%)	
Employed full time	5 (24)
Employed part time	4 (19)
Retired	12 (57)
Other	0 (0)
Chose not to answer	0 (0)
Income (US $), n (%)	
<10,000	1 (5)
10,000 to <15,000	0 (0)
15,000 to <20,000	0 (0)
20,000 to <25,000	3 (14)
25,000 to <35,000	1 (5)
35,000 to <50,000	3 (14)
50,000 to <75,000	6 (29)
75,000 to <100,000	3 (14)
≥100,000	4 (19)
Chose not to answer	0 (0)

[a]GED: General Educational Development.

Discussion

Summary

SCD represents a critical opportunity for early intervention to modify risk factors for AD/ADRD. MHB addresses this gap by offering a novel group mindfulness-based lifestyle program tailored to older adults with SCD. Single-arm open pilot studies (NIH stage 1A) have demonstrated the feasibility and acceptability of MHB, indicating its potential to bypass challenges to lifestyle behavior modification and improve cognitive outcomes among older adults. These preliminary studies also revealed barriers to participation that must be addressed during the design and execution of the first RCT of MHB before conducting fully powered trials or implementing the program in clinical care.

The primary aim of this feasibility RCT is to establish the feasibility, acceptability, appropriateness, credibility, satisfaction, and fidelity of the MHB intervention compared to the HEP active control (NIH stage 1B). Our secondary aim is to explore preliminary signals of improvement in outcomes and hypothesized mechanisms (Table 1 and Figure 3). Testing these aims and our ability to randomize participants to MHB versus the HEP will serve as a “dress rehearsal” for a subsequent efficacy RCT. In addition, this RCT will provide valuable insights into the feasibility of integrating multiple digital health technologies into a lifestyle trial for older adults with SCD. If feasible, the novel integration of passive activity sensors, repeated mobile cognitive assessments, and daily surveys offer a comprehensive framework for monitoring adherence and understanding individual responses to lifestyle interventions and the mechanisms of action. This is notable because the pathways by which lifestyle interventions may improve cognitive outcomes and prevent AD/ADRD among older adults with SCD are poorly understood.

We have made several changes to our study protocol (Multimedia Appendix 1) guided by our qualitative studies [67]. Using implementation science frameworks [205-207] and the socioecological model [208], the protocol changes and strategies aim to maximize RCT outcomes, increase sample diversity within our RCT, and reduce barriers to AD/ADRD prevention efforts [209-212]. Initial observations suggest that our protocol changes and strategies have been effective. We have observed a high volume of inquiries, indicating that our outreach efforts have been successful and that older adults are interested in participating in the study. Participant adherence to both programs is notably high, with positive engagement in the mindfulness and behavior change skills taught in MHB. Preliminary Garmin Vivosmart 5 and daily survey adherence data are also promising but must be confirmed upon study completion. Providing individualized support and devices at no cost has enabled us to include and retain older adults with limited technological access or proficiency [209,210,213]. To date, the enrolled participants predominantly represent White, well-educated women. In our next group cohorts, we will prioritize the inclusion of racial and ethnic minoritized older adults to address their underrepresentation in prevention RCTs and their increased risk of AD/ADRD [101,102]. We are conducting broader outreach, including both professional and community groups, to further increase awareness and diverse participation [214,215]. The feasibility RCT will provide initial information on our ability to engage older adult communities in AD/ADRD prevention research.

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Limitations

Despite the protocol improvements, several limitations remain and are outlined in the following subsections (additional limitations may arise during the execution of our trial).

Sample Diversity

While we have increased the diversity of our recruitment sources through community outreach, it is difficult to enroll racial and ethnic minoritized older adults. It takes time to build trust in community partnerships and address barriers to participation in clinical trials rooted in social determinants of health [216]. In addition, our interventions are currently only available in English, which greatly limits our ability to include many older adults in our community who speak Spanish or other languages. To address disparities in AD/ADRD prevention, future studies will incorporate principles of community-based participatory research and set benchmarks for enrolling minoritized older adults.

Digital Health Divide

We have designed a more digitally inclusive virtual RCT by providing devices and individualized technological support. However, the RCT fails to serve older adults who are disinterested in virtual interventions, lack broadband internet access, or experience other challenges with technology (eg, visual or hearing impairments).

Identification of Early AD/ADRD Risk

We aim to identify older adults with the earliest preclinical AD/ADRD, determined by the presence of cardiovascular risk factors (CAIDE scores) and rigorous criteria for SCD [8], similar to other lifestyle trials [30,31,35]. However, SCD presents as unspecific symptoms and can be attributed to normal cognitive aging, psychiatric disorders (eg, depression and anxiety), sleep disturbances, and other conditions rather than neurodegeneration [8]. The development of meaningful cognitive markers is increasingly important in interventions aiming to modify early risk of AD/ADRD, such as MHB.

Conclusions

The MHB feasibility RCT represents a significant step toward developing practical, evidence-based interventions for early AD/ADRD prevention. By addressing key benchmarks and engagement in intervention targets, this study lays the groundwork for larger trials aimed at validating the potential long-term benefits of mindfulness-based lifestyle programs in reducing dementia risk. Following the NIH Stage Model, the next phase of intervention development will evaluate MHB versus the HEP in a larger RCT and more diverse sample (NIH stage 2). We will rigorously test the superiority of MHB versus the HEP in enhancing cognitive and lifestyle outcomes among older adults with SCD and modifiable AD/ADRD risk factors. If successful, MHB could provide an effective and scalable intervention for reducing AD/ADRD risk, leveraging digital health technology to promote sustained behavior change and brain health.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RAM was responsible for conceptualization, funding acquisition, methodology, investigation, writing the original draft, and reviewing and editing the manuscript. MEL was responsible for project administration, investigation, writing the original draft, and reviewing and editing the manuscript. JEC was responsible for project administration and reviewing and editing the manuscript. CSR was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript. OIO was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript. BBH was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript. JAB was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript. SJB was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript. The My Healthy Brain team was responsible for project administration, investigation, and reviewing and editing the manuscript. AMV was responsible for funding acquisition, methodology, supervision, and reviewing and editing the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of protocol changes and strategies to enhance randomized controlled trial outcomes.
[DOCX File , 17 KB - resprot_v13i1e64149_app1.docx]

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Abbreviations

AD/ADRD: Alzheimer disease and Alzheimer disease–related dementias
BRANCH: Boston Remote Assessment for Neurocognitive Health
CAIDE: Cardiovascular Risk Factors, Aging, and Incidence of Dementia
HEP: health enhancement program
IRB: institutional review board
MGB: Mass General Brigham
MHB: My Healthy Brain
NIH: National Institutes of Health
RA: research assistant
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCD: subjective cognitive decline
SMART: specific, measurable, achievable, relevant, and timely

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Protocol

Efficacy of a Mobile App–Based Behavioral Intervention (DRIVEN) to Help Individuals With Unemployment-Related Emotional Distress Return to Work: Protocol for a Randomized Controlled Trial

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Abstract

Background: Employment plays an important role in the maintenance of mental and physical health. Losing a job creates emotional distress, which can, in turn, interfere with effective job seeking. Thus, a program for job seekers that provides support for both the logistics of job seeking as well as emotional distress may help people find employment and improve emotional well-being.

Objective: This study aims to test the efficacy of the 6-week intervention for job seekers in a randomized controlled trial.

Methods: This is a parallel-assignment randomized control trial comparing a 6-week return-to-work intervention versus job seeking as usual for a stratified sample of job seekers (n=150). The intervention will be delivered through a mobile phone app and scheduled video counseling sessions with a job coach. Assessments will be taken weekly during the intervention as well as 8 and 16 weeks later. The intervention and control group procedures will be administered remotely, allowing the study to take place in several regions of the United States. Eligible participants will be adults aged 18 to 65 years, currently unemployed, and actively searching for work. Participants will be recruited from 7 major metropolitan areas in the United States using online advertisements on Craigslist. The primary outcome measure is the Job Search Behavior Scale, which has 2 subscales, preparatory job search behavior and active job search behavior. Employment status will also be assessed throughout the trial. A mixed-model regression analysis will be used to compare job searching behavior in the intervention group versus the control group. A time-to-event analysis (ie, survival analysis) will be used to compare employment status in the 2 experimental groups. Secondary outcomes will also be evaluated, including job search self-efficacy and mental health-related outcomes such as anxiety and depression.

Results: This study started on August 7, 2023, and as of June 2024, we have enrolled 140 participants. Enrollment began in August 2023 and will conclude by October 2024. Half of the participants (75/150, 50%) will be assigned to the intervention arm while the other half (75/150, 50%) will be assigned to the control arm, job seeking as usual.

Conclusions: The findings from this study will determine the efficacy of a mobile app–based intervention that uses both job training and psychological techniques on job seeking and employment outcomes. This first trial of Distress Return-to-Work Intervention (DRIVEN) will provide important information about blended support techniques for unemployed individuals,

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determine the usefulness of mobile apps to address large-scale mental health outcomes, and improve our understanding of the relationship between depression and unemployment status.

Trial Registration: ClinicalTrials.gov NCT06026280; https://clinicaltrials.gov/study/NCT06026280

International Registered Report Identifier (IRRID): DERR1-10.2196/62715

(JMIR Res Protoc 2024;13:e62715) doi:10.2196/62715

KEYWORDS

unemployment; wellness; depression; job stress; job distress; career coaching; coaching; mhealth; ehealth; job-seeking; mobile app; behavioral intervention;

Introduction

Background

As of July 2024, roughly 4.3% (13 million adults) of the US population were unemployed, and states have accrued in interest alone over US $519 million for unemployment funds [1,2]. Employment is a known social determinant of health and a critical part of daily life, providing income, social connections, and a sense of meaning and purpose [3,4]. In the United States, employment is also how many citizens purchase health insurance and by extension have access to health care [5]. Although employment plays a significant role in individuals' lives, economies often fluctuate in their ability to provide sustainable employment opportunities for job seekers. This was highlighted by the COVID-19 pandemic that resulted in high levels of job loss and furloughs. However, even in the context of a strong overall economy and the current historically low levels of unemployment [2], job seekers can experience emotional distress that interferes with a job search [6]. Unemployment jeopardizes financial and social stability, which in turn can increase the risk for, and exacerbate the severity of, emotional disorders such as major depressive disorder (MDD) [7]. In addition, depression is associated with decreased drive and motivation [8,9], which can interfere with job seeking. This situation prolongs financial hardship, creating more emotional distress and even increasing risk of suicide [10-13].

One perspective is that by reducing the severity of MDD or emotional distress in the context of other disorders, occupational impairment would improve. However, an alternative perspective is that occupational impairment is an important target that may warrant its own intervention, just as there are interventions that exist specifically for insomnia and anhedonia [14-17]. Psychological interventions that aim to improve motivation, positive emotions, and cognitive flexibility are likely to be critical components of a job seeking intervention for individuals, especially those with elevated emotional distress. Improving motivation, positive behaviors, and mastery are specific goals of behavioral activation interventions [18,19] and may support effective job seeking as well. Similarly, given the changing landscape of employment, improving cognitive flexibility through cognitive restructuring techniques [20,21] can help job seekers adapt expectations and reduce rigidity about the types of jobs to apply for, their suitability for particular jobs, "upskilling" (ie, gaining new skills necessary for your field), and "reskilling" (ie, gaining new skills necessary for a new field) [22].

Currently, job seeking and career counseling interventions alone may not improve emotional support or improve employment outcomes [23]. Similarly, individual placement services appear to increase competitive employment but may not meaningfully improve emotional distress [24,25]. Importantly, some combined psychological intervention strategies with job seeking or career counseling have been shown to be efficacious in empirical studies [26]. These studies highlight the evidence base and scientific premise for an intervention that combines these 2 approaches. For example, in a randomized control trial (RCT) comparing job seekers who received job search assistance to job seekers who received job search assistance and cognitive behavior therapy (CBT), the authors found that the CBT group reported better affective state improvement and higher rates of employment than the control group [27]. Improving cognitive flexibility is a key component of many approaches to psychotherapy that can readily be adapted for job seekers, even in the absence of a diagnosed disorder [28-32]. Similarly, RCTs from industrial and organizational psychology have shown that job seeking programs that promote skill development and motivation increase the likelihood that individuals find and maintain employment [33,34]. Over the last 30 years, few studies have rigorously evaluated intervention programs that blend psychological treatments with job seeking skills for unemployed individuals [26,35-37]. These interventions slightly improved long-term employment rates compared with controls, but more research is needed in larger studies to support the findings [26].

Purpose

To date, few studies have evaluated the effectiveness of combining psychological interventions with job seeking skills for individuals experiencing unemployment-related emotional distress. Thus, the aim of this study is to develop and empirically test the efficacy of a blended intervention to reduce emotional distress and increase job seeking behavior, with the goal of helping people return to work. This project is an RCT (up to N=150) funded by a Fast Track Small Business Technology Transfer grant from the National Institute for Mental Health (R42MH127971). Based on previous literature, we hypothesize individuals randomized to the intervention, hereafter referred to as Distress Return-to-Work Intervention (DRIVEN), will report (1) more job seeking behaviors, (2) higher employment rates, (3) improved depression scores, and (4) other improved health-related outcomes during a 6-week program and during 2- and 4-month follow-up after participating in DRIVEN when compared with the control individuals. We also hypothesize that improvement in depression will predict greater subsequent

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job seeking, and job seeking behavior will also predict improved depressive symptoms.

Trial Design

We will test the efficacy of DRIVEN in a 2-arm parallel assignment RCT of up to 150 job seekers by comparing DRIVEN to a control condition consisting of self-guided job seeking. We will determine whether individuals in DRIVEN exhibit more job seeking behavior, job search self-efficacy, improved in Inventory of Depression and Anxiety Symptoms (IDAS-II) [38], improved related health domains (measured by the Patient Reported Outcomes Measurement Information System [PROMIS]) [39], and higher rates of employment than those in the control condition. We will also use autoregressive modeling to determine the directional relationship between improvements in depression and greater job seeking. Overall, the aim of this study is to determine if the use of DRIVEN improves job search behavior among unemployed individuals with emotional distress.

Methods

Inclusion and Exclusion Criteria

Eligible participants will need to meet the following criteria: 18-65 years of age, currently unemployed and actively searching for work, previously employed full-time (35 hours per week or more) for at least 1 year before unemployment, received an individual highest salary of US $100,000 or less, own an iPhone (Apple Inc) or Android smartphone, able to provide informed consent, have a minimum depression score according to the PROMIS depression 8a scale (T score of 45 or a raw score of > 9) [39], and able to communicate in English (verbal and written; refer to Textbox 1). Unemployment is defined as working less than 8 hours a week. For participant selection, we will seek to enroll a diverse sample for a high level of generalizability. We also want the sample to reflect the level of psychological treatment provided by DRIVEN and the population it was designed for. Thus, we will exclude participants if they are experiencing current moderate or severe alcohol or substance use disorders, suicidal planning, or active suicidal ideation or are currently employed, retired, or a full-time or part-time student. Participants with current manic or psychotic symptoms will also be excluded. We will not exclude pregnant women.

Textbox 1. Participant eligibility criteria.

Inclusion criteria:

- 18-65 years of age
- Currently unemployed and actively searching for work
- Before unemployment, were employed full-time (35 hours per week or more) for at least 1 year
- Before unemployment, received an individual highest salary of US $100,000 or less
- Owns an iPhone or Android Phone
- Willing and able to provide informed consent
- Has a minimum depression score according to the PROMIS 8a depression scale
- Able to communicate in English (verbal and written)

Exclusion criteria:

- Current moderate or severe alcohol or substance use disorders
- Current symptoms of mania or psychosis
- Currently employed, retired, or a full or part-time student

Sample Size

Up to 150 participants will be recruited for the RCT. The sample size was determined based on the study design, proposed statistical analysis plan, anticipated effect size, and participants lost to follow-up. Specific information about sample size selection can be found in the statistical analysis plan (Multimedia Appendix 1). Participants will be randomized into 1 of 2 groups: DRIVEN versus control. We will stratify randomization by gender. Other demographics, such as age, race, and ethnicity, will be monitored to ensure a diverse sample.

Recruitment Methods and Study Setting

Participants will be recruited from 7 major metropolitan areas in the United States using online advertisements on Craigslist. These cities include New York, Los Angeles, Chicago, Houston, Jacksonville, Philadelphia, and Phoenix. These cities were selected because of their high population densities and collective geographical diversity.

Consent

Informed consent will occur remotely and electronically through REDCap (Research Electronic Data Capture; Vanderbilt University). A study team member will call the participants to guide them through the process and answer any questions. They

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will explain the research, duration of participation, and description of procedures and measures to be obtained as well as any potential risks or benefits related to study procedures. They will also explain how the confidentiality of their records will be maintained and will provide contact information of research staff who can answer questions or concerns. Participants will also receive information regarding the voluntary nature of their participation, that refusal to participate will not affect their clinical care, and that they may discontinue participation at any time. Consenting participants will receive a copy of the consent materials for their records.

Recruitment and Randomization Procedure

Interested participants will fill out an eligibility survey screener provided from the online advertisement. If eligible based on the screener, a research assistant will call and verify the participant's eligibility, provide informed consent, and administer the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*; SCID) [40] to assess exclusionary conditions and to help characterize the sample, and then randomize the participant to one of the study arms (DRIVEN or control). The SCID is a semistructured clinical interview that assesses *DSM-5* disorders. Our condensed version of the SCID assesses for MDD, alcohol, and substance use disorders; several anxiety disorders; and obsessive-compulsive disorder. It takes approximately an hour and a half to complete. Randomization tables for the trial were created using the *blockrand* package of R (R Core Team), stratifying based on gender [41].

Interventions

DRIVEN Overview

DRIVEN is a behavioral intervention that integrates strategies from CBT (eg, behavioral activation techniques to improve positive affect and drive) with job seeking and career counseling (eg, interview coaching, customizing job applications). DRIVEN includes exercises, videos, and 3 coaching sessions (done with a live coach by video), to help develop and refine job search skills (Table 1). DRIVEN is a 6-week program largely delivered through a smartphone app, a common approach used in employment and mental health research [42-44]. Each job coaching session lasts 1 hour and includes a review of participants' exercises and homework from the previous week, progress review on goals, and a discussion of the next steps in the program.

DRIVEN was developed by the academic team and the small business partner, Inspiration at Work. Development was also informed by an advisory board of experts on employment, depression, behavioral and digital interventions, as well as the job seeking end users and community partners. DRIVEN went through 2 rounds of user testing to address design defects and improve product clarity before this trial.

Table 1. Distress Return-to-Work Intervention (DRIVEN) content and coaching focus by program week. DRIVEN is a 6-week program consisting of in-app exercises and three scheduled coaching sessions on weeks 2, 4, and 6.

Week	DRIVEN app content focus and goals	Coaching session focus
1	Become familiar with the DRIVEN program and what to expect. Learn about flexible thinking and how positive thoughts and actions influence emotions.	—[a]
2	Learn to recognize the symptoms of stress and combat them using our core strategies of thinking flexibly and taking action.	Welcome, rapport-building, and recap of a flexible thinking exercise and content from week 1.
3	Better understand and build their own skills based on what employers are looking for and the types of jobs that best fit into their lives.	—
4	Understand internet-based applications including cover letters and resumes	Discuss how to recognize stress and use flexible thinking and taking action to address it. Coaches will also discuss employer-preferred skills and identify ideal jobs for the candidate.
5	Networking and interviewing	—
6	Recap core strategies of thinking flexibly and taking action, and put them into practice after the intervention concludes.	Review the components of an internet-based application. Discuss ways to meet people who could provide work opportunities for them.

[a]Not applicable.

DRIVEN Coach Selection, Training, and Supervision

DRIVEN career coaches will be recruited from major global career coaching associations (International Coaching Federation, etc) and will require at least 5 years of professional coaching experience. Eligible candidates will have completed a National Board for Health and Wellness Coaching–approved training program, run at least 50 health and wellness coaching sessions, and have at least an associate's degree. The position of DRIVEN coach will not be publicly posted. Rather, coaches will be personally referred by a corporate human resources leader who has worked with them extensively and then will be interviewed by AL before receiving an offer. During coach selection, AL will select 4 coaches for this study and prioritize racial and ethnic diversity to maximize the generalizability of our results. With this goal combination in mind, the principal investigator (PI) of the business entity, AL, will conduct video interviews with final candidates before onboarding and training the selected 4.

DRIVEN coaches will receive 2 hours of internet-based video training in CBT from authors and PIs SAS and JWG. They will also spend 6 to 8 hours reviewing the DRIVEN program and its materials in their entirety through self-study. Each coach will receive a comprehensive coaching manual, which details

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the goals and agenda for each participant's coaching session. Finally, coaches will receive live demo instructions on how to use the DRIVEN coach's portal, an internet-based platform on which they can view their coaching appointments, make changes, and review participant exercises.

Coaches will be assigned 7 cohorts of participants ranging from 1-4 participants over the course of the study. Coaches will work with 1 or 2 cohorts at the same time. Cohort numbers will be tracked in REDCap and through payments.

The 4 DRIVEN coaches will be supervised closely by author AL. Supervision included weekly check-ins through email and phone calls during the study period. These discussions will focus on the general tone of the coaching sessions, participant experiences, and any challenges about the process.

Coaches will also be able to reach out to AL directly with questions about the intervention or how to address participant concerns. Once finished with their last cohort, coaches will complete a written synopsis of participant progress and record their own reflections on the program's effectiveness in general.

Control: Self-Guided Job Seeking

Participants in the control condition will receive weekly emails with articles about how to find employment (eg, articles on LinkedIn giving job seeking advice). Topics for the self-guided arm include how to search for a job on the internet, refining your job search, resume writing, cover letter and application packages, practicing interviews, and networking. Participants in this arm will not be sent any of the new materials created for DRIVEN.

Outcomes

This project will collect four outcomes through questionnaires: (1) job seeking behaviors and job search self-efficacy, (2) employment outcomes, (3) depression scores, and (4) other health-related outcomes. Participants will complete REDCap questionnaires at baseline, each week during the intervention period, and at 8 and 16 weeks after the intervention is complete. A complete table of the outcomes and their collection over time can be found in Table 2.

Table 2. Outcome measures and capture frequency during the study period.

Measure	Intervention period							Follow-up	
	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 14	Wk 22
Job seeking behaviors and job search self-efficacy									
1. Job Search Behavior Scale [45]	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Job Search Self Efficacy Scale [46]	✓			✓			✓	✓	✓
Employment									
3. Employment Status Questionnaire		✓	✓	✓	✓	✓	✓	✓	✓
Depression scores									
4. PROMIS[a] Depression 8a[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓
5. IDAS II[c] - Social Anxiety [38]	✓			✓			✓	✓	✓
PROMIS									
6. PROMIS Positive Affect 15a	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. PROMIS Meaning and Purpose 8a	✓						✓	✓	✓
8. Participant Global Impression of Change [47]							✓	✓	✓
Additional measures									
9. Cognitive-Behavioral Avoidance Scale [48]	✓					✓	✓	✓	✓
10 .Behavioral Activation for Depression Scale [49]	✓					✓	✓	✓	✓
11. Cognitive Flexibility Inventory [50]	✓					✓	✓	✓	✓
12. System Usability Scale [51] (DRIVEN[d] participants only)		✓					✓		
13. Treatment Assessment Questionnaire								✓	✓
14. Credibility and Expectancy Questionnaire [52]	✓								

[a]PROMIS: patient-reported outcome measure information system.

[b]All PROMIS measures are available online at the HealthMeasures website.

[c]IDAS II: Inventory of Depression and Anxiety Symptoms.

[d]DRIVEN: Distress Return-to-Work Intervention.

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Job Seeking Behaviors and Job Search Self-Efficacy

Job seeking behaviors will be measured using a variant of Blau's [45] Job Search Behavior measures. These include the number of times participants engaged in 10 different job seeking activities. This measure consists of two subscales: (1) preparatory job seeking behaviors (5 items) and (2) active job seeking behaviors (5 items). Items are scored on a 1 to 5 scale from "0 times" to "6 or more times." Subscales are scored by adding up the responses to the items in each subscale. The questionnaire can be completed in under 2 minutes. Job search self-efficacy will be measured using the instrument by Saks et al [46], which captures a participants' confidence level engaging in 20 job search-related activities. This measure consists of two subscales: (1) self-efficacy related to job search behaviors (10 items) and (2) self-efficacy related to job search outcomes (10 items). Items are scored on a 1 to 5 scale from "not at all confident" to "totally confident." Subscales are scored by adding up the responses to the items in each subscale. The questionnaire can be completed in under 3 minutes. Job seeking behaviors will be captured weekly from baseline to 6 weeks, and then again at the 8- and 16-week follow-ups. Job search self-efficacy will be collected at baseline, week 3, and week 6 during the intervention and at 8 and 16 weeks after the intervention is complete.

Employment Outcomes

Employment information includes questions about employment status, number of hours worked, annual salary, hourly or salary status, how the job was obtained, and perceived benefit from this study on their job search. Employment measures will be collected weekly from baseline to 6 weeks, and then again at 8 and 16 weeks after the intervention is complete.

Depression Scores

To measure depression scores, we will use the PROMIS depression 8a item short form [39]. This is an 8-item questionnaire with items that are scored on a 1 to 5 scale from "never" to "always." The measure is scored by calculating T-scores and SE of the item responses through an autoscoring algorithm in REDCap. The questionnaire can be completed in about a minute. PROMIS depression scores will be captured weekly from baseline to 6 weeks, and then again at the 8- and 16-week follow-ups. All PROMIS measures are available from the United States Department of Health and Human Services at the HealthMeasures website.

Secondary Measures

We will also use the PROMIS positive affect 15a short form, PROMIS meaning and purpose 8a short form, IDAS-II [38], and Participant Global Impression of Change score [47] to measure secondary participant mental health outcomes. PROMIS positive affect is a 15-item measure designed to capture positive affect or mood. Items are scored on a 1 to 5 scale from "not at all" to "very much." The measure is scored by calculating T-scores and SE of the item responses through an auto-scoring algorithm in REDCap. The questionnaire can be completed in about 2 minutes. PROMIS positive affect measures will be collected weekly from baseline to 6 weeks, and then again at the 8- and 16-week follow-ups.

PROMIS meaning and purpose is an 8-item measure designed to capture how meaningful and purposeful a participant views their life. The first 3 items are scored on a 1 to 5 scale from "strongly disagree" to "strongly agree." The other 5 items are scored on a 1 to 5 scale from "not at all" to "very much." The measure is scored by calculating T-scores and SE of the item responses through an auto-scoring algorithm in REDCap. The questionnaire can be completed in about a minute. PROMIS meaning and purpose will be collected at baseline and week 6 during the intervention and at 8 and 16 weeks after the intervention is complete.

To capture the expression of symptoms related to social anxiety, we will administer the social anxiety subscale (6 items) of the IDAS-II. Items are scored on a 1 to 5 scale from "not at all" to "extremely." The subscales are scored by adding up the responses to its items. The measure can be completed in under a minute. The IDAS-II will be collected at baseline, week 3, and week 6 during the intervention and at 8 and 16 weeks after the intervention is complete. The Participant Global Impression of Change scale is a 1-item measure assessing overall perceived change in the participant's mental health since the beginning of the course of treatment in the study. The item is scored on a 1 to 5 scale from "much better" to "much worse." The measure can be completed in under a minute. The Participant Global Impression of Change will be collected at week 6 during the intervention and at 8 and 16 weeks after the intervention is complete. Additional measures will include the Cognitive-Behavioral Avoidance Scale [48], Behavioral Activation for Depression Scale [49], Cognitive Flexibility Inventory [50], System Usability Scale [51], Treatment Assessment, and Credibility & Expectancy Questionnaire [52] (Table 2).

Allocation for RCTs

A randomization list, stratified by gender, was created using the *blockrand* package of R [41], which uses randomly varying block sizes and then equally allocates participants to groups within the block. Block sizes were 2, 4, 6, and 8. A seed was set for reproducibility. The randomization list was uploaded to REDCap and then used for sequential participants, within the gender, being randomized. After randomization, participants are onboarded to their respective arms of the study.

Data Management and Monitoring

All data for this study will be collected and managed in REDCap. The study team will review these data at regular meetings, including the demographic composition of the sample, missing data, and other descriptive statistics. The study has a data safety monitoring board composed of a licensed psychologist and 2 statisticians.

Plans for Managing Harms

This study may uncover suicidality during the course of the study, especially through the baseline SCID. To identify and manage participants who may be at risk of taking their own life, we created a participant protection plan. PIs and authors, SAS and JWG, both licensed clinical psychologists with many years of experience treating mood and anxiety disorders, will conduct training sessions with research team staff. This training will

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consist of reading assignments and didactic discussion on how to address any suicidality on the part of the participants. All staff will be expected to demonstrate competence in handling suicidality before beginning work on the study. All staff will be trained on a standard protocol for assessing suicidality and taking appropriate action. Any instance of suicidality (ie, suicidal ideation or greater) will be followed up using the Columbia-Suicide Severity Rating Scale [53]. In the unlikely event that a person is at immediate risk for lethal self-harm, emergency services will be contacted. These incidents will be reported to the institutional review board as needed and discussed among the research team for ongoing improvement of our study procedures.

When the study is completed, all participants will be given a referral list in case they wish to follow up for further job searching support. Moreover, the participants will be invited to contact the study team with questions about follow-up care, which is a method that we have successfully used in past studies.

The collection of possibly identifiable participant data introduces risk to participants. To address these concerns, we will deidentify participants, assign subject identification numbers, and store all data on password-protected and encrypted servers.

Statistical Methods

We expect that participants in DRIVEN will exhibit more favorable trajectories over time (ie, be more likely to secure a job, engage in more job seeking behavior, and experience less depression) than those in the control condition. All statistical results will be supplemented with graphical analyses. If needed, robust and nonparametric approaches will be used. Exploratory models will test whether any variables moderate the trajectory of outcomes. A full description of the statistical approach is included in Multimedia Appendicex 1.

Primary Outcome Analysis

The 2 subscales of the Job Search Behavior Scale [36] will be used as primary outcomes: preparatory job search behavior and active job search behavior. The primary outcomes for this RCT will be evaluated with mixed models implemented in the *nlme* and related R packages. Because R and related packages are frequently updated, we will include the version numbers of these packages and software when the results are published. A random intercept will be included in the model, combined with a random effect for the baseline. Time will be measured in days from baseline and added to the model as a continuous variable. We will also include a quadratic effect of time (ie, time squared) to account for possible nonlinear relationships. A model that includes the main effect of treatment (coded as 0 or 1) as well as an interaction with treatment and time will serve as a full model, which will be compared with a reduced model that omits any treatment effects. Although we will evaluate statistical significance at an α level of .05, we will also inspect and report effect sizes and CIs for model parameters. All assessment periods from baseline to 16-week follow-up will be included in the model.

Secondary Outcomes Analysis

This RCT will also compare employment status (securing a job) for participants who received DRIVEN and those in the control condition, consisting of self-guided job seeking. Securing a job will be analyzed using time-to-event (also known as, survival) analysis using the proportional hazards assumption. Continuous outcomes will be assessed using mixed models with the *nlme* R package. We will evaluate reductions in depressive symptoms as measured by the PROMIS depression 8a item short form. We will include participants using the intent-to-treat criterion, in which all randomized participants are included in the analysis.

Autoregressive Analyses

We will determine the directional effects between depression and job seeking. Specifically, we will determine whether reductions in depressive symptoms lead to greater subsequent job seeking behavior or whether job seeking behavior leads to greater subsequent reductions in depression. This will be tested by examining whether levels of depression in 1 week (time t–1) explain variance in job seeking behavior the subsequent week (time t), or vice versa. We will use the *lavaan* and other packages of R to determine whether higher depression for 1 week predicts greater job seeking the subsequent week. These models will also test the opposite directional effect, as well as exploratory analyses of other variables (eg, positive affect; job seeking self-efficacy). Finally, to test whether the associations differ between treatment arms, fixed effects dummy codes for groups will be added to the models.

Ethical Considerations

This research protocol will be submitted for approval to Advarra (Pro00062697), an independent institutional review board. All research personnel are trained and certified in research and HIPAA (Health Insurance Portability and Accountability Act) regulations. Eligible individuals will be informed about the risks of participation including the risk of data breach, the future use of their data, and steps taken by the research team to minimize the likelihood of harm. Data will be deidentified and assigned a participant number and stored on password-protected servers adhering to Northwestern University's data security policies. Participants will also receive compensation information including the total amount, the timeline for delivery, and the method for receipt. Participants will be eligible to receive a total of US $350 if all outcome surveys are completed. Payments will be distributed as surveys are completed through a digital card.

Results

This project received funding from the National Institutes of Health And started on August 7, 2023. As of June 2024, we have enrolled 140 participants. The RCT began in August 2023, and all data collection will be completed by October 2024. Once the analyses are completed, the results will be reported to ClinicalTrials.gov.

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Discussion

Principal Findings

We anticipate participants who receive DRIVEN will report more job search behaviors on each subscale of the Job Search Behavior questionnaire—both preparatory and active job search behaviors. We anticipate that participants who receive DRIVEN will have better employment rates and improved depression scores, compared with participants in the control condition. If these hypotheses are supported, it suggests that by addressing the mental health needs of job seekers and providing practical job search support, unemployment rates can be reduced for the betterment of the individual job seeker and the workforce at large.

We also expect that in a cross-lagged panel model, lower depression scores will predict higher levels of job seeking behaviors. Similarly, higher levels of job seeking behaviors will predict lower depression scores.

Limitations

This study is primarily limited by the selection process. These results may not be generalizable to adults beyond the study population such as those older than 65 years or individuals with substance use disorders, psychosis, or mania. In addition, the sample is representative of individuals who seek employment through Craigslist. As with RCT designs, we also anticipate a loss to follow-up. We are also potentially limited by the fact that participants were financially compensated to complete the clinical assessments, which could artificially inflate their motivational scores. Further, we acknowledge a potential bias from participants since blinding is difficult in eHealth trials. In addition, results may be biased if the user experiences any usability issues interacting with the DRIVEN mobile app. This limitation may require validation or additional monitoring of user experience with these tools to improve the confidence of our results. To mitigate this concern, we will capture participant characteristics associated with digital interaction or usability challenges such as age, education, gender, technology literacy, socioeconomic status, and limiting participation to users with smart devices.

Strengths and Future Directions

Given the interconnectedness of mental health and employment, programs such as DRIVEN are important for individuals seeking work, as well as for society at large especially in times of high unemployment. Depending on the findings from this study, DRIVEN may be a tool prime for commercialization and adaptation for specific populations and settings. To expand the reach of DRIVEN, it could be implemented in health systems and in high-volume specialties such as primary care and emergency medicine. DRIVEN may also serve as a tool for addressing a major interdependent pillar of social determinants of health. Policy makers at the regional, state, and federal levels may want to invest in interventions like DRIVEN that can reduce unemployment rates and promote income and housing stability, social connectedness, meaning, and even access to health insurance. By addressing the upstream factors that shape the quality of an individual's life, we may be able to improve the lives of Americans and reduce future diseases and their financial burden. Further, policies to support individual employment may reduce community-related public health concerns such as crime and violence [54].

Conclusion

Unemployment continues to be a challenging social determinant of health to address and has received additional attention in light of the recent COVID-19 pandemic [55], especially given its association with depression and suicide risk [8,12,56]. Several studies have evaluated interventions to improve employment with vocational services [23], individual placement and support [24], and by trying to improve an individuals' health [26]. Among interventions trying to address an individuals' health, interventions that used therapeutic and job search support were most promising [26]. Thus, the purpose of this study was to develop and test the efficacy of a combined intervention approach (CBT and job search training) for unemployed individuals with depression.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be available through ClinicalTrials.gov when the principal findings are published.

Authors' Contributions

JWG, SAS, and AL lead the conceptualization and funding acquisition of this project along with the expertise of AKG for intervention development. MLS and SL lead recruitment, data curation, and compensation. KRA supported software conceptualization and development. ECD wrote the original draft. JWG, SAS, AL, AKG, MLS, SL, MM, and KRA provided feedback and edits on several revisions of the manuscript and gave final approval before submission. No artificial intelligence was used to support any portion of the manuscript creation.

Conflicts of Interest

ECD, MLS, SL, MM, and KRA have no conflicts to report. AL owns an equity interest in Inspiration at Work and is one of the recipients of the National Institutes of Health (NIH) Small Business Technology Transfer (STTR) grant. JWG and his lab at the University of Chicago receive funding from NIH. Along with the research team, JWG is one of the principal investigators of this study and thus has received research funding from National Institute of Mental Health for this work. Not related to this manuscript, JWG earns income treating patients as a clinical psychologist, and in the past has received remuneration for other academic work (eg, speaking engagements, grant reviewing), as well as compensation for research consulting. He has received funding from the National Eczema Association, Pfizer, and internal research grants, not related to this project. AKG and SAS also receive funding from the NIH. SAS is also a principal investigator on the project.

Multimedia Appendix 1
Statistical analysis plan.
[DOCX File , 37 KB - resprot_v13i1e62715_app1.docx]

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Abbreviations

CBT: cognitive behavioral therapy
DRIVEN: Distress Return-to-Work Intervention
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HIPAA: Health Insurance Portability and Accountability Act
IDAS-II: Inventory of Depression and Anxiety Symptoms
MDD: major depressive disorder
PI: principal investigator
PROMIS: patient-reported outcome measure information system
RCT: randomized control trial
REDCap: Research Electronic Data Capture
SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

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Protocol

Sleep Treatment Education Program for Cancer Survivors: Protocol for an Efficacy Trial

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Abstract

Background: Cancer survivors are at increased risk for chronic insomnia, even years after treatment completion. As insomnia is associated with a variety of long-term health consequences, access to insomnia treatment is critically important for the survivor population. Cognitive behavioral therapy for insomnia (CBTI) is the recommended first-line treatment for insomnia but remains largely unavailable to survivors. Treatment barriers include geographic limitations, a shortage of trained providers, and demanding treatment regimens. Designed with these limitations in mind, the Sleep Treatment Education Program (STEP-1) delivers components of CBTI in a low-intensity educational intervention delivered online.

Objective: This is a phase II pilot randomized controlled trial. The primary aims are to test the efficacy of STEP-1 to improve (1) insomnia symptoms and (2) mood in cancer survivors compared to a control condition. The secondary aims will (1) explore participant factors associated with clinically significant response, (2) evaluate acceptability of the control intervention, (3) explore feasibility of delivering individualized coaching sessions for participants who do not have a significant response to STEP-1, and (4) describe participants' satisfaction with STEP-1 and suggestions for improvement.

Methods: This 2-arm randomized controlled trial enrolled 70 off-treatment cancer survivors aged 40-89 years with clinically significant insomnia. Participants are randomized to receive either the STEP-1 intervention or control condition (relaxation education); interventions are delivered in one-on-one, synchronous, virtual videoconference sessions by trained interventionists. The STEP-1 intervention presents educational information on the development of insomnia after cancer and offers suggestions for improving insomnia symptoms based on the CBTI elements of sleep hygiene, stimulus control, and cognitive restructuring. With the interventionist, participants review the suggestions and develop a personalized sleep action plan for implementation. The relaxation education session provides information on the potential benefits of relaxation and how to independently access online relaxation exercises. The Insomnia Severity Index is used to measure insomnia symptoms, and the Profile of Mood States Short Form is used to measure mood at baseline and 4 and 8 weeks after intervention. The primary end point is change in the Insomnia Severity Index score at 8 weeks, and the secondary end point is change in mood symptoms (Profile of Mood States Short Form) at 8 weeks.

Results: This trial was funded in July 2022. Enrollment and data collection began in February 2023 and concluded in October 2024, with 70 participants enrolled. The analysis will begin in fall 2024, and the results are expected in winter 2025.

Conclusions: Trial results will determine if STEP-1 effects go beyond those that could be attributed to placebo and other nonspecific treatment factors. Should results support the efficacy of STEP-1 to improve mood and insomnia symptoms, we anticipate developing efficacy and implementation trials of STEP-1 in larger and more diverse samples.

Trial Registration: ClinicalTrials.gov NCT05519982; https://clinicaltrials.gov/study/NCT05519982

International Registered Report Identifier (IRRID): DERR1-10.2196/60762

(JMIR Res Protoc 2024;13:e60762) doi:10.2196/60762

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KEYWORDS

insomnia; mood; cancer survivors; online interventions; protocol; cognitive behavioral therapy; CBT; cognitive behavioral therapy for insomnia; CBTI; digital health; sleep disorders; sleep treatment education program; STEP-1

Introduction

Intensive treatments that improve cancer outcomes place survivors at high risk for developing medical and psychosocial late effects [1-5]. While insomnia may typically be considered a minor symptom in the larger cancer context, it frequently develops into a debilitating chronic condition related to significant health problems. In the general population, indirect economic costs of untreated insomnia exceed US $100 billion in the United States per year, primarily from diminished workplace performance, increased use of health care, and increased accident risk [6,7]. As many as 1 in 4 cancer survivors experience clinically significant insomnia even 10 years after cancer treatment has ended [8,9]. If untreated, insomnia is associated with heart disease, obesity, hypertension, diabetes, depression, and anxiety [4,10-18]. Survivors are already vulnerable to many of these same health conditions due to their cancer treatment history; therefore, in order to maintain their overall health, access to effective insomnia treatment is critically important.

Cognitive behavioral therapy for insomnia (CBTI) is a well-established and empirically supported treatment. A systematic review found that CBTI given to cancer survivors "provides significant, lasting improvement" [19]. Even compared to pharmacotherapy, multiple randomized trials have demonstrated that it is the most effective long-term insomnia treatment [20-22].

Despite compelling evidence, growing populations of cancer survivors who need it find this treatment largely unavailable [23]. Fewer than one-third of the most well-resourced cancer centers in the United States provide CBTI for patients or survivors [24]. To make effective insomnia treatment available to survivors, existing barriers must be resolved, including the shortage of trained CBTI providers and the need for more efficient and less burdensome treatments than standard CBTI, which have limited uptake and dropout rates of 20% to 40% [25-28].

To address these challenges and deliver effective insomnia treatment to cancer survivors, we have developed the Sleep Treatment Education Program (STEP-1). The STEP-1 intervention includes (1) core CBTI components, (2) answers to survivors' frequently asked questions about sleep and CBTI, and (3) a written sleep action plan to promote adherence.

The STEP-1 intervention is brief, low cost, and low intensity and targets survivors' specific needs and experiences. Delivered in a single virtual videoconference session, STEP-1 does not require travel to a specialized site for insomnia treatment and is available for survivors to access anywhere. STEP-1 provides guided behavioral planning to help survivors make informed choices to manage their insomnia. This self-management approach aims to support survivors' autonomy and avoid a prescriptive stance [29]. In a single-arm pilot study, STEP-1 was found to significantly reduce insomnia symptoms in cancer survivors [30]. As the next step in this line of work, the efficacy of the STEP-1 intervention will be evaluated in a larger sample and compared to a control intervention in the randomized controlled trial described here.

The primary aims of the study are (1) to determine the efficacy of STEP-1 to reduce insomnia and (2) to improve mood symptoms in survivors compared to a control condition. Specifically, we hypothesize that insomnia symptoms (primary outcome) and mood (secondary outcome) will improve significantly in STEP-1 participants relative to control condition participants (primary aim). Secondary aims are (1) to explore participant and program adherence factors associated with clinically significant response to STEP-1, (2) to evaluate the acceptability of the control intervention, (3) to explore the feasibility of delivering individualized coaching sessions for participants who do not have a significant response to the STEP-1 intervention, and (4) to describe participants' satisfaction with STEP-1 and their suggestions for improving the intervention.

Methods

Study Design

The STEP-1 intervention is being evaluated in a pilot randomized clinical trial, guided by the Obesity-Related Behavioral Intervention Trials (ORBIT) model [31]. Although originally developed by obesity researchers, the ORBIT model has been adapted for the development and early testing of behavioral interventions of all kinds [31-33]. Participants are randomized (1:1) to receive either (1) the STEP-1 intervention or (2) relaxation education (enhanced usual care control condition). STEP-1 and relaxation education are each delivered in a single online session via synchronous videoconference. Outcomes are assessed at baseline and again 4 and 8 weeks postbaseline. Participants will be recruited from treatment centers, advocacy groups, and social media and will complete all study activities remotely online. Of note, a modified version of STEP-1 adapted to address the needs of young adult survivors is currently being evaluated in a separate trial using similar methods [34].

Participants

Participants will be 70 off-treatment survivors aged 40-89 years. To be eligible for enrollment, participants were diagnosed with cancer (excluding nonmelanoma skin cancer) at least 1 year prior, have received no cancer therapy (excluding chemoprevention) in the past 4 months, and have no additional cancer therapy planned. Participants must be able to read and write in English, have access to the internet on a daily basis, and have significant insomnia as evidenced by an Insomnia Severity Index (ISI) score greater than or equal to 12 [35]. Survivors who have specific health conditions, medications, or past insomnia treatments that may affect their sleep or response

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to STEP-1 are excluded; for participant inclusion and exclusion criteria, see Table 1.

Table 1. Study inclusion and exclusion criteria.

Category and criteria	Rationale
Inclusion criteria	
General	
• Age 40-89 years • Able to read and write in English	Enroll off-treatment survivors able to participate in the intervention currently available only in English.
Health issues	
• History of a cancer diagnosis (except nonmelanoma skin cancer) ≥1 year prior • No active cancer therapy (excluding chemoprevention) in the past 4 months, and no further therapy planned	Enroll off-treatment survivors able to participate in the intervention currently available only in English.
Internet access	
• Regular access to the internet on a daily basis	To ensure participants have adequate ability to complete online study.
Sleep problems	
• Significant insomnia, as evidenced by an Insomnia Severity Index score ≥12	To test this intervention in individuals with clinically significant insomnia.
Exclusion criteria	
General	
• Any impairment (eg, sensory and cognitive) that interferes with the ability to complete all study measures independently	Exclude individuals not able to independently complete the study procedures.
Health issues	
• Report ever being diagnosed with bipolar disorder • Report ever being diagnosed with a seizure disorder or have experienced a seizure in the past 12 months	Exclude individuals for whom behavioral treatment for insomnia may require modification due to medical conditions [36,37].
Sleep problems	
• Intention to adjust (decrease or increase) the use of any prescribed or over-the-counter medications taken to decrease insomnia during the study period • Survivors who report being diagnosed with sleep apnea who are not receiving recommended medical treatment • Survivors who report suspected sleep apnea who have not completed an evaluation by a sleep specialist • Survivors who report their usual bedtime is not between 5 PM and 5 AM • Employment that involves irregular sleep patterns, such as shift work or frequent long-distance travel across time zones, or employment in a position that could impact public safety	Exclude individuals whose sleep symptoms may require significant modifications in behavioral treatment for their insomnia [38,39].
Prior insomnia treatment	
• Prior participation in a research study, which provided an educational or behavioral intervention for insomnia. • Prior participation in a behavioral treatment or patient education program for insomnia delivered at the study site. • Participation in behavioral or educational interventions for insomnia in the 2 years prior to enrollment (including synchronous and asynchronous online insomnia programs).	Enroll only participants naïve to the insomnia educational programs and behavioral treatments.

Recruitment

All procedures and materials for recruitment are designed to allow survivors to self-refer to the study. These materials include a study information sheet (Multimedia Appendix 1), outreach letters and emails, informational postcards, and brief study descriptions suitable for patient-facing materials distributed by patient support and advocacy groups. For survivors interested

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in learning more about the study, all materials include phone, email, and web contact information. Examples, including a brief informational video, can be seen on the study website: StepForSleep.com.

Several methods are used for distribution of these materials to potentially eligible survivors. At our cancer center, study information postcards have been placed in waiting areas. Around the hospital, study information appears on patient-facing screens (eg, in the cafeteria and waiting areas). The study team meets with clinical providers who are informed of the study and given recruitment information and materials to share with patients. Several clinical teams have collaborated with the study team to send recruitment information directly to their potentially eligible patients. Additionally, center programs that serve supportive care needs are also asked to include study information in their newsletters, emails, or social media posts. Following similar procedures, study information and materials have been shared with providers at several other cancer centers and with patient support and advocacy groups (regionally and nationally) for distribution to their patients or members. These informational materials are also posted on research portals and selected social media sites (eg, Facebook; Instagram; Reddit; and X, formerly known as Twitter).

Procedures

Screening and Scheduling

Survivors interested in STEP-1 first contact the study team via email or phone call. Any preliminary questions about the study are answered, and survivors are provided with the study information sheet (Multimedia Appendix 1), which includes details on the study procedures and aims. Survivors who are interested in participating are scheduled for screening via videoconference. The screening meeting is conducted by a research assistant (BLB, KGM, EMM, and IDD) who answers any additional questions survivors may ask about the study and administers the eligibility screening. Eligible survivors are invited to schedule a STEP-1 intervention session, and ineligible survivors are provided with a resource guide [40] for finding help with insomnia or other sleep issues. Any questions or concerns in this process are referred to the study's principal investigator (CJR) for clarification and final determination of eligibility.

Intervention Session

The intervention session is delivered in a single, synchronous, one-on-one videoconference session. Eligible participants complete the institutional review board (IRB) approved online consent procedure and a baseline survey before being randomized to receive the control condition or STEP-1 intervention (Figure 1). Following the intervention, participants are scheduled for follow-up contact.

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Figure 1. Participant flow diagram. ISI: Insomnia Severity Index; STEP-1: Sleep Treatment Education Program.

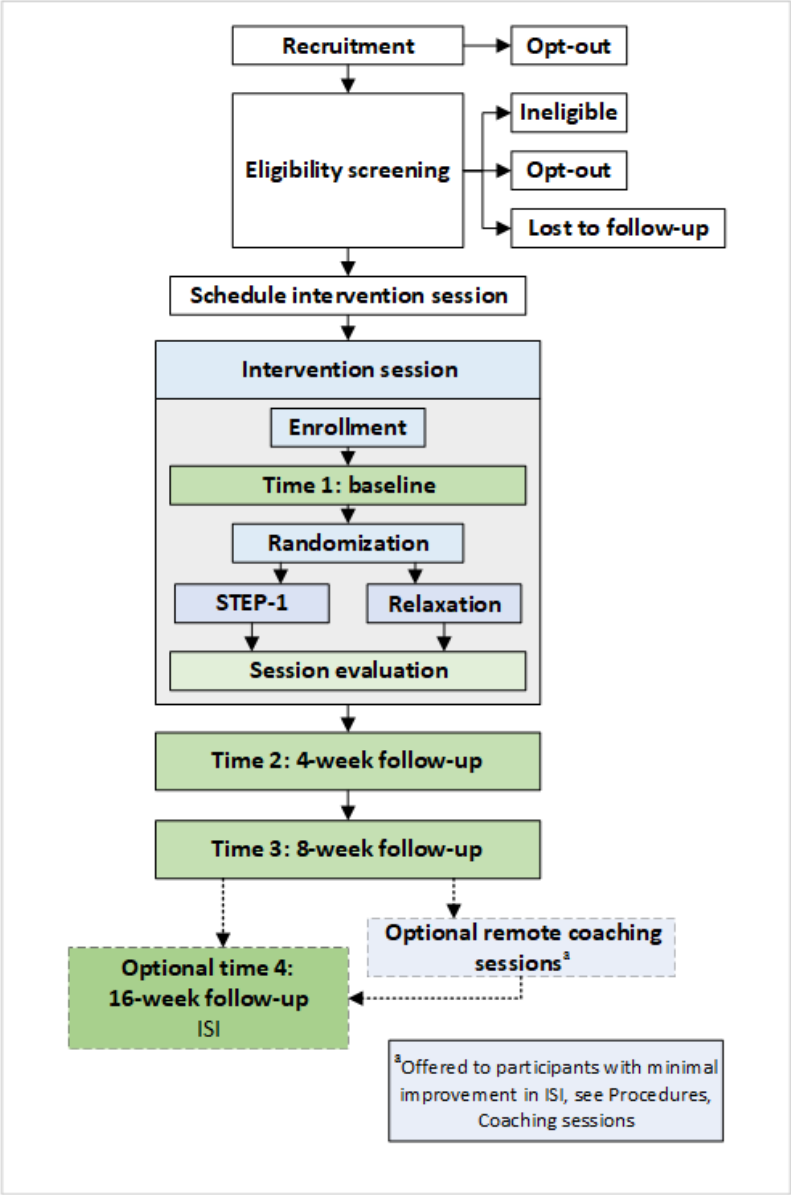

Baseline Survey

Consented participants complete a baseline survey directly in the web-based Qualtrics survey platform [41]. Participants enter data directly into Qualtrics with study staff offering technical support as needed but not collecting data directly from participants.

Randomization

After the baseline survey is complete, participants are randomized using Sealed Envelope [42], a commercially available digital application for randomizing patients in clinical trials. Participants are randomized (1:1) to either (1) STEP-1 or (2) an enhanced usual care control condition (relaxation education). The study arms are balanced by age group; randomization, with a block size of 4, is stratified by those between 40 and 64 years versus 65 and 89 years. Once randomized, participants are informed and immediately receive their assigned intervention session via videoconference.

STEP-1 Intervention Delivery

STEP-1 is delivered in individual sessions by trained interventionists during a single 75-minute synchronous videoconference session using HIPAA (Health Insurance Portability and Accountability Act) compliant technology [43-45]. Interventionists deliver STEP-1 using a slide deck of 42 slides and following a structured outline, with copies of session materials (eg, presentation slides and sleep action plan template) provided to participants by email. During the session, the participant can see and hear the presenter, view the presentation slides, and ask questions in real time. After introducing educational information based on Spielman's model of insomnia [46] and the association of insomnia with cancer, the interventionist presents suggestions for improving survivors' sleep based on CBTI components of sleep hygiene, stimulus control, and cognitive restructuring [19,27,47-49]. For ease of comprehension, this material is presented in 4 sections: addressing lifestyle issues (eg, limiting alcohol and stimulants), sleep environment (eg, avoiding bed for nonsleep activities), sleep timing (eg, setting a regular wakeup time), and managing

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expectations and challenges (eg, sleep worry and physical symptoms), with the underlying rationale and potential benefit for each suggestion provided. After each of the 4 sections, the participant is asked to review the suggestions presented and complete their sleep action plan template, with the interventionist supporting them to record their current sleep practices and behavioral changes they intend to make. Action plans of this kind are commonly used in behavioral self-management interventions [29] and have been shown valuable in promoting successful behavior change [50,51]. Information about how the COVID-19 pandemic may exacerbate sleep problems and what aspects of STEP-1 can address this has been noted briefly in the introduction and "managing expectations and challenges" sections. In summarizing the session, the interventionist offers examples of STEP-1 suggestions, as they might be implemented over the course of a single day with a discussion of potential challenges and strategies to manage them.

Relaxation Education (Control Condition) Delivery

The relaxation education is delivered in a single one-on-one synchronous videoconference session. This session lasts 60 minutes and is delivered by a study team member using a slide deck of 23 slides and following a structured outline. A copy of the presentation slides and a curated resource sheet of web-based videos are provided to each control group participant by email. The presentation begins with a brief description of how relaxation may be of benefit for insomnia. Participants are introduced to a variety of common relaxation exercises (eg, progressive muscle relaxation, paced breathing, and guided imagery) and given information about how to access relaxation exercises independently during the study period. Specifically, they are provided access to a free app and given a list of videos available on the web. During the session, participants are given the opportunity to practice accessing relaxation exercises on the app and recommended videos on the web with study staff providing technical support as needed. Participants who do not have a mobile device compatible with the app are loaned a device for the study period. To close the session, the presenter makes suggestions to the participants on how to integrate these exercises into their routines to reduce stress and improve sleep independently. Self-guided online relaxation intervention was selected for the control condition, as 90% of American people use the internet [52], and the internet is very often used by cancer survivors for health information [53]. Delivering this education session in a way that closely follows the structure and methods used in the STEP-1 session allows for control for attention and other nonspecific factors while also addressing ethical and practical problems associated with waitlist or no-treatment controls [54].

Follow-Up

After completing their assigned interventions, participants in both conditions are scheduled for their 4-week follow-up call (Figure 1) and are asked about their preference (eg, phone, email, and mail) for reminders.

Baseline Session Evaluation

All participants are asked to complete a satisfaction form evaluating their experience with the intervention session upon its conclusion. Participants receive a link to a questionnaire on which they report on ease of use and acceptability, satisfaction, and credibility of the session. Participants are encouraged to complete it while still in the intervention session but have the option to complete it later. Participants receive a US $10 gift card upon completion of this evaluation.

Postintervention Follow-Up: Outcome Data Collection

Study staff contact participants by telephone at previously scheduled times, 4 and 8 weeks postbaseline. Participants are asked to enter follow-up data directly into Qualtrics and are provided with technical assistance if needed. If participants cannot complete the full assessment at the scheduled time due to time constraints, they are asked to complete the 7-item ISI (primary outcome measure) verbally, and their responses are collected; they are then asked to complete the full questionnaire at their earliest convenience. Participants receive email reminders in advance of each phone call. At the 4-week call, participants schedule a phone call for the 8-week assessment. Upon completion of the 4- and 8-week assessments, participants receive a US $25 gift card. At the time of their 8-week follow-up phone call, participants are asked if they would be willing to complete an optional additional ISI assessment 2 months later; participants who agree receive an email with a Qualtrics link for this assessment. The link is sent again a week later for nonresponders, but participants receive no additional reminders and do not receive an incentive for this final optional assessment.

Coaching Sessions

Coaching sessions have been demonstrated as an effective enhancement to behavioral interventions for cancer survivors and other populations [55-59]. Including them in this trial will allow for collecting data on their potential utility for enhancing the STEP-1 intervention. Participants randomized to the STEP-1 condition who did not have a ≥6-point decrease in their ISI score [60] at 8-week follow-up are offered the option to continue on the study for 4 weeks. During this time, participants will receive 2 individualized coaching sessions to explore the feasibility of delivering individualized coaching sessions. The optimal timing for the first coaching session is within 7 days after the 8-week follow-up, and the second session should be 7 days after the first. However, they may be scheduled any time within 23 days after the 8-week follow-up with at least 5 days between coaching sessions. Paraprofessional coaches trained and supervised by psychologists with CBTI expertise deliver the coaching sessions remotely by following a structured outline adapted from the principal investigator's (CJR) insomnia study for young adult cancer survivors [34]. During 30-minute coaching sessions, participants review progress and challenges in following their sleep action plan. Coaches offer support and encouragement and may refer participants to the on-hand materials to help answer questions and reinforce program goals and suggestions.

Following principles of symptom self-management [59,61-64], coaching sessions are not prescriptive but promote survivors' self-management skills (eg, goal-setting and problem-solving)

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to implement their sleep action plan. At the end of the 4-week period, participants complete a questionnaire assessing acceptability and satisfaction with the coaching sessions and complete the ISI and sleep change measure. Participants will receive a US $25 gift card upon completion of this questionnaire. Administrative data on coaching sessions missed, interrupted, or rescheduled as well as session duration will be collected.

Intervention Training and Supervision

STEP-1 Intervention

Study interventionists have graduate-level training in social work, psychology, or related disciplines but no prior training in behavioral sleep medicine. Interventionists begin training by familiarizing themselves with the STEP-1 protocol and participant-facing materials and reviewing them with the principal investigator (CJR). Trainees are asked to closely review the STEP-1 presentation slides and the structured outline detailing how each slide should be presented to participants before reviewing audiotaped, videotaped, and transcribed STEP-1 sessions. When possible, and with the consent of a participant, trainees attend at least 1 live intervention session to observe STEP-1 administration. Following the session, the interventionist answers any questions the trainee might have and demonstrates postsession procedures. As a next step, trainees deliver the STEP-1 intervention in mock intervention sessions with confederates playing the role of a study participant; an experienced interventionist acts as the confederate in at least 1 mock session. These mock sessions are recorded and transcribed before being reviewed for fidelity by the principal investigator (CJR). The principal investigator (CJR) approves interventionists to conduct STEP-1 sessions with study participants after they demonstrate fidelity to the structured outline for each slide of the STEP-1 presentation. Additionally, to maintain fidelity over time and reduce deviation between interventionists, interventionists record and transcribe an intervention session (recording only themselves and not the participant) after every 5 to 10 participants; these transcriptions are scored for fidelity and discussed with the principal investigator (CJR).

Self-Guided Relaxation Education

Interventionists begin training on the relaxation education intervention by familiarizing themselves with the patient-facing materials. They closely review the presentation slides and structured outline detailing how each slide should be presented. These materials are then discussed with the principal investigator (CJR) and other study team members as a group. As in STEP-1 training, when possible, trainees attend at least 1 live intervention session (with participant consent). The trainee observes session administration, and the interventionist answers any questions the trainee might have and demonstrates postsession procedures. As this condition introduces a self-management resource-based intervention, interventionist training focuses on taking the proper steps to explain the intervention, assisting participants in accessing the online materials, and supporting them in independently selecting exercises they wish to try. Control session interventionists are approved to conduct the relaxation education sessions with study participants after demonstrating reliability following the structured outline for each slide of the presentation in a recorded mock interview reviewed by the principal investigator (CJR).

Coaching

Paraprofessionals are trained as STEP-1 coaches using a coaching session outline and semistructured script. Coach trainees listen to a minimum of 3 live coaching sessions conducted by an experienced coach. The trainee and experienced coach discuss the flow of the coaching script and participants' reports of sleep action plan challenges and successes. Trainees then conduct 2 audiotaped mock coaching sessions with an experienced coach or psychologist with CBTI experience acting as a participant and receive feedback on the content of the sessions. Finally, trainees conduct at least 2 live sessions with study participants accompanied in the session by an experienced coach serving as a session coleader. Upon review of these training procedures, the principal investigator (CJR) approves coaches to conduct coaching sessions with study participants.

Measures

Outcome measures for this trial are the ISI [65] (primary) measuring the change in insomnia symptoms and the Profile of Mood States Short Form [66] (POMS-SF; secondary) measuring the change in mood symptoms. The 7-item ISI is the most commonly used measure in insomnia research and has been validated in cancer populations [67]. It has demonstrated adequate internal consistency and is sensitive to detect changes in perceived sleep difficulties with treatment. The POMS-SF is a commonly used measure of psychological distress that has been validated in cancer populations [68]. It is a 35-item measure that assesses the mood states of participants and provides multiple scales including an overall Total Mood Disturbance score used here.

Additional information to describe participants' sleep was collected using the Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form [69], the Consensus Sleep Diary-Morning [70], and the Morningness-Eveningness Questionnaire [71]. The 8-item Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form evaluates sleep disturbances and their impact on overall sleep quality; items include specific sleep problems (eg, restless sleep) as well as satisfaction with sleep quality and amount of sleep. Nine items from the Consensus Sleep Diary-Morning are used to assess daily sleep quality and sleep latency; items include time of attempts to fall asleep, number and duration of awakenings, time of final awakening, final rise time, and perceived sleep quality. Five items from the Morningness-Eveningness Questionnaire asking about preferred times for sleep, waking, and physical and mental activities are used to evaluate chronotype.

To describe participants' demographic characteristics, medical history, current health, and program adherence, several additional measures are used. Demographic information (eg, gender and education), medical information (eg, cancer history and chronic conditions), and insomnia history (eg, insomnia duration, burden, and past treatments) are collected by a direct patient report on a baseline survey developed for this study. The survey also includes 1 physical health item from the Short

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Form Health Survey [72] asking respondents to rate their overall health, as well as a Pain Thermometer asking participants to rate their current pain on a 1-10 scale [73]. The sleep action report gathers information on changes made in sleep behaviors during the study period, including both changes suggested or recommended in the intervention sessions as well as those not included in the study interventions (eg, change in sleep medications and starting a nonstudy behavioral intervention).

Finally, several participant report measures will be used to capture participant experience and satisfaction with the intervention. Ease of use and acceptability of the online videoconference format will be assessed using 14 checklist items adapted from the Telehealth Usability Questionnaire [74], intervention credibility will be assessed using the 6-item credibility or expectancy questionnaire [75], and satisfaction with the interventions (STEP-1 and relaxation education) will be assessed with checklist items adapted from principal investigator's previous survivorship education trials [30]. At the 8-week postintervention time point, participants will complete a brief questionnaire to provide feedback about the intervention and how it could be improved. Participants who receive the coaching sessions will also complete a brief coaching satisfaction evaluation after the second coaching phone call. Details of all measures and time points are included in Table 2.

Table 2. Study measures.

Measure	Baseline	4-Week follow-up	8-Week follow-up	Coaching session #2	16-Week follow-up (optional)
Insomnia Severity Index	✓	✓	✓	✓	✓
Profile of Mood States Short Form	✓	✓	✓		
PROMIS[a] Sleep Disturbance Short Form	✓		✓		
Consensus Sleep Diary			✓		
Morningness-Eveningness Questionnaire	✓				
Demographic information	✓				
Medical information	✓				
Single item from the Short Form Health Survey	✓	✓	✓		
Pain Thermometer	✓	✓	✓		
Sleep action report (behavioral) or relaxation action report (control)		✓	✓	✓	
Nonstudy sleep treatment change		✓	✓	✓	
Sleep action plan (behavioral)	✓				
Intervention session evaluation	✓				
Telehealth Usability Questionnaire	✓				
Credibility questionnaire	✓				
STEP-1[b] satisfaction evaluation			✓		
Coaching evaluation				✓	

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]STEP-1: Sleep Treatment Education Program.

Statistical Analysis

Primary and Secondary Aims

This is a randomized 2-arm trial comparing the STEP-1 intervention (experimental arm) to a self-guided relaxation education intervention (control arm). The primary end point is a change in ISI score from baseline to 8 weeks postintervention. The secondary end point is a change in mood symptoms on the POMS-SF at 8 weeks postintervention. Change scores will be treated as continuous variables. A repeated measures ANOVA [76] will be used to determine if the STEP-1 intervention significantly reduces insomnia symptoms (ISI scores) and improves mood symptoms (POMS-SF scores) compared to a control condition. ISI and POMS-SF scores will be treated as dependent variables using 2-way ANOVA [76] procedures (α=.05) with 1 between-subjects factor (group; STEP-1 vs control), 1 within-subjects factor (time), and an interaction term (group×time). A clinically significant response to the STEP-1 intervention will be defined as a reduction of ISI scores ≥6 points at 8 weeks. Cohen *d* [77] will be used to quantify within-group effect sizes, and Hedges *g* [78] adjustment will estimate between-group effect sizes. ISI and POMS-SF collected at 4 weeks postintervention will be analyzed using similar methods. Secondary aims will be analyzed using descriptive statistics (secondary aims 2, 3, and 4), logistic regression (secondary aim 1), and 2-tailed *t* tests and chi-square analyses (secondary aim 2) [76].

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Sample Size and Statistical Power for Primary End Point

To meet the primary aims, we require 60 participants with evaluable data but will enroll 70 as a hedge against attrition. As is common for most CBTI interventions [79], STEP-1 has demonstrated large effects of $d \geq 1.00$ in our pilot-testing [30]. Using this effect size as a reference, the study is conservatively powered to detect an effect size of 0.6 (primary aim). With a sample size of 60 (30 per arm), the study will have 90% power to detect an effect of this size (2-sided test with $\alpha=.05$). In the event that the sample size is reduced to 50 (25 per arm), the study will retain >80% power to detect an effect of this size (2-sided test with $\alpha=.05$).

Missing Data

The primary analysis will be an intention-to-treat analysis of randomized subjects. We anticipate minimal missing data (<10%) based on experience using similar data collection methods. If needed, we will use multiple imputation to account for missing data. Baseline sleep and mood variables will be included as potential factors in the imputation model. Sensitivity analysis will impute missing change scores with values sampled from an estimated distribution of change scores from the control group participants.

Ethical Considerations

Prior to study activation and participant enrollment, the study protocol was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (protocol 20-516) and registered on ClinicalTrials.gov (NCT05519982). Prior to enrollment in this minimal-risk study, potential participants complete a consent process approved by the Dana-Farber Cancer Institute's IRB. Before enrolling, potential participants receive the STEP-1 study information sheet, containing all the elements of informed consent. At the beginning of the intervention session, the interventionist reviews the study information sheet and answers any questions the potential participant may have. Additionally, survivors last screened for eligibility more than 2 weeks prior are rescreened for eligibility. Finally, eligible individuals who wish to enroll in the study are asked to provide consent using an online consent process in use at the Dana-Farber Cancer Institute. Participants receive online gift cards to compensate them for the completion of all postsession questionnaires. The value of the gift cards ranges from US $10 to US $25 in accordance with time required to complete the questionnaires. The maximum compensation for any individual participant who completes all postsurvey questionnaires is US $85 in gift cards. All data are securely stored using HIPAA-compliant servers and software approved for the use of protected health information. Additionally, data are deidentified upon collection and stored under a study identification number.

Results

This trial was funded by the National Cancer Society in July 2022, and the protocol described here was approved in January 2023. Enrollment and data collection began in February 2023; a total of 70 participants were enrolled as of September 2024. Final data collection concluded in October 2024. We anticipate that data analysis will begin in fall 2024, and results are expected in winter 2025.

Discussion

Principal Findings

This study is the first randomized controlled trial to test the hypothesis that the STEP-1 intervention significantly reduces insomnia in cancer survivors (aim 1). By comparing change in symptoms in the STEP-1 participants compared to those in the control condition, the trial will help determine if STEP-1 effects go beyond those that could be attributed to placebo and other nonspecific treatment factors. With additional measures and more extended follow-up than in the previous pilot, this trial will also provide more information about how durable STEP-1 effects may be and if improvement is seen in mood symptoms as well as insomnia (aim 2). In addition, exploratory analyses of participant characteristics will focus on identifying subgroups of cancer survivors most likely to benefit from STEP-1 and evaluate the suitability of the relaxation education control condition for the cancer survivor population (secondary aims 1 and 2). Finally, by testing the utility of individualized coaching sessions and eliciting participant suggestions to improve STEP-1, study results will inform future directions for further optimizing the intervention (aims 3 and 4).

Comparison to Prior Work

Despite numerous clinical trials supporting its effectiveness [23,25-28], CBTI remains woefully underused by cancer survivors due to barriers to access and demands of the treatment itself [19-22,80-82]. To address limited access and adherence to standard CBTI, STEP-1 was designed as a low-intensity behavioral intervention presenting established elements of CBTI in a single online educational format. STEP-1 was adapted from a single-session sleep education intervention previously developed as part of a stepped-care insomnia intervention for survivors [83]. Consistent with the ORBIT model for the development of behavioral interventions [31-33], pretesting with cancer survivors (phase I) guided refinements of STEP-1, and a subsequent single-arm pilot (phase IIa) supported its potential to reduce insomnia in cancer survivors [30]. Though it is informed by CBTI concepts and methods as a single-session educational intervention delivered by nonsleep specialists, STEP-1 represents a significant departure from standard CBTI, which typically requires 5 or more treatment sessions delivered by mental health specialists. Results of this controlled trial are now needed to justify and inform further development and testing of the novel approach taken by STEP-1. Specifically, the results of the current trial will inform the design of these new trials by guiding the selection of participants, control groups, and measures and further optimization of the intervention.

Strengths and Limitations

Conceptualized within the ORBIT model, this early phase trial (IIb) is not intended to conclusively evaluate the efficacy of STEP-1 but rather to confirm the appropriateness of conducting a future (phase III) effectiveness trial and to inform its design. As such, the current trial design has several notable limitations.

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Because the primary end point of the study is at 8-week follow-up, it will not shed light on the longer-term effects of the intervention. Similarly, with a modest size sample of English-speaking participants, there will be limited data on how demographic, cultural, and other participant variables moderate the effects of the intervention. Despite these limitations, by including a larger sample, a control condition, and a longer follow-up period, trial data will provide new and clinically relevant information essential to evaluating the efficacy of STEP-1 and the low-intensity self-management approach to insomnia intervention more generally.

Conclusions

It is well accepted that behavioral treatment significantly reduces insomnia symptoms and should be the first-line treatment for most patients [84,85]. Unfortunately, it is also widely accepted that due to treatment barriers and challenges, most cancer survivors with insomnia never receive this evidence-based care [23,24]. This trial aims to provide cancer survivors access to effective behavioral insomnia treatment by developing and testing a brief, low-intensity intervention that addresses their needs and interests and can be delivered to them wherever they have internet access. If found effective, this approach has the potential to greatly improve access to care for the growing population of survivors whose health and quality of life are negatively impacted by insomnia.

Acknowledgments

This study is funded by the National Cancer Institute (R21CA267857; CJR).

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CJR led the funding acquisition, methodology, and supervision of this study. CJR, ESZ, and CM-N contributed to the conceptualization of this study. CM-N and BLB conducted the project’s administration. BLB, ALM, KGM, EMM, and IDD carried out the investigation and data curation. BLB and CJR contributed to the original draft of this paper. All authors contributed to the review and editing of this paper. All authors approved this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study information sheet.
[PDF File (Adobe PDF File), 72 KB - resprot_v13i1e60762_app1.pdf]

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Abbreviations

CBTI: cognitive behavioral therapy for insomnia
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISI: Insomnia Severity Index
ORBIT: Obesity-Related Behavioral Intervention Trials
POMS-SF: Profile of Mood States Short Form
STEP-1: Sleep Treatment Education Program

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Protocol

A Web-Based Mind-Body Intervention to Improve Resilience Among Patients With Nontraumatic Painful Upper-Extremity Conditions and Comorbid Risky Substance Use: Protocol for a Mixed Methods Study

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Abstract

Background: Nontraumatic painful upper-extremity conditions (NPUCs) are largely age-related degenerations that affect the majority of adults. Most patients with NPUCs do not seek medical care and adjust on their own. Among those who do seek care, approximately 20% report risky substance use, defined as a consumption pattern that increases the risk of harm to physical or psychosocial health. In the context of NPUC, risky substance use is associated with more intense pain, emotional distress, disability, and opioid or other substance misuse (ie, cross-tolerance). Consequently, risky substance use is a significant modifiable risk factor for the progression and maintenance of chronic pain-related disability and comorbid psychopathology among patients with NPUCs.

Objective: This study aims to develop, adapt, and test the feasibility of the Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use (Web-TIRELESS), a novel, asynchronous, and web-based mind-body intervention aimed at modifying maladaptive pain-coping behaviors in patients with NPUC and comorbid risky substance use. This study illustrates the proposed study design, methodology, and intervention content.

Methods: In aim 1, we will conduct live video qualitative interviews (n=20) with care-seeking adult patients with NPUC and comorbid risky substance use to inform the development and refinement of Web-TIRELESS and study procedures. In aim 2, we propose an open pilot study (n=12) of Web-TIRELESS with exit interviews and pre- and postintervention assessments to evaluate the feasibility, credibility, and acceptability of Web-TIRELESS and refine study procedures. Aim 3 consists of a pilot feasibility randomized controlled trial of Web-TIRELESS versus minimally enhanced usual care (n=50), both of which follow a web-based modality, to demonstrate the feasibility of recruitment procedures and data collection, as well as the feasibility, credibility, and acceptability of Web-TIRELESS and the control condition (adherence, retention, fidelity, and satisfaction), following prespecified benchmarks.

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Results: Patient interviews (aim 1) concluded in May 2024 and qualitative analysis is expected to be completed in September 2024. Completion of aim 2 (data collection and analysis) is expected by June 2025. The completion of aim 3 and other study-related operations is anticipated by June 2027.

Conclusions: We will develop and test Web-TIRELESS, the first asynchronous mind-body intervention specifically adapted to enhance resilience in response to chronic pain among individuals with NPUCs and comorbid risky substance use. Results from this 3-aim study (feasibility, acceptability, and satisfaction of Web-TIRELESS) will be leveraged to inform a future efficacy randomized controlled trial of Web-TIRELESS versus the minimally enhanced usual care.

Trial Registration: ClinicalTrials.gov NCT06366633; https://clinicaltrials.gov/study/NCT06366633

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KEYWORDS

chronic pain; upper-extremity conditions; psychiatry; mindfulness; mind-body; substance use; web-based intervention development

Introduction

Background

Nontraumatic painful upper-extremity conditions (NPUCs) are highly prevalent in the adult population and are typically age-related degenerations that become chronically painful [1-3]. The most common NPUC diagnoses include trigger joints; tendinopathy; and arthritis of the shoulder, elbow, and hand [4]. Most patients with NPUCs do not seek treatment and instead find ways to independently adapt [5,6]. Of those who do seek care from a medical provider, many choose not to pursue treatment upon reassurance from their provider and learning that most interventions are palliative (eg, joint injections and pain medications) rather than disease modifying [4,7]. For patients who commit to medical treatment, outcomes can vary widely, leading to inconsistent results, and the emotional and financial costs involved are significant [4,7,8]. Therefore, it is essential to develop evidence-based interventions that address the unique needs of patients who seek care for their NPUCs.

Risky substance use, defined as patterns of use that increase one's risk of physical or psychological harm, is a maladaptive behavioral pain response exhibited in up to 20% of care-seeking patients with NPUC [9]. Comorbid risky substance use is associated with worse treatment outcomes [9-11], greater pain severity, disability, psychological distress, and the development and progression of chronic pain [10,12,13]. The established reciprocal model of pain and substance use can explain the development and maintenance of pain and disability in patients with NPUC and comorbid risky substance use patterns [14]. This model posits that risky substance use affects pain regulation via both peripheral (ie, tissue damage) and central (ie, aberrant pain processing) mechanisms, escalating the allostatic load on pain neurocircuitry and abstinence-induced hyperalgesia (Figure 1). This process can trigger maladaptive cognitive and behavioral responses such as pain catastrophizing, pain-related fear, and activity avoidance, which in turn can amplify the reported intensity of pain, increase disability, and exacerbate emotional distress (ie, fear-avoidance-driven cycle of pain exacerbation) [15]. According to the reciprocal model of pain and substance use, NPUC and risky substance use mutually reinforce each other via their shared transdiagnostic mechanisms of pain catastrophizing, pain-related fear, and avoidance [14,16-19]. This mechanism creates a vicious cycle that intensifies chronic pain, increases substance use, exacerbates disability, and heightens emotional distress (Figure 1) [14,20]. Therefore, it is crucial to target the underlying mechanisms driving the reciprocal relationship between pain and substance use in order to enhance treatment outcomes for this patient population.

Figure 1. Reciprocal model of pain and substance use with adaptations from the fear-avoidance model of pain.

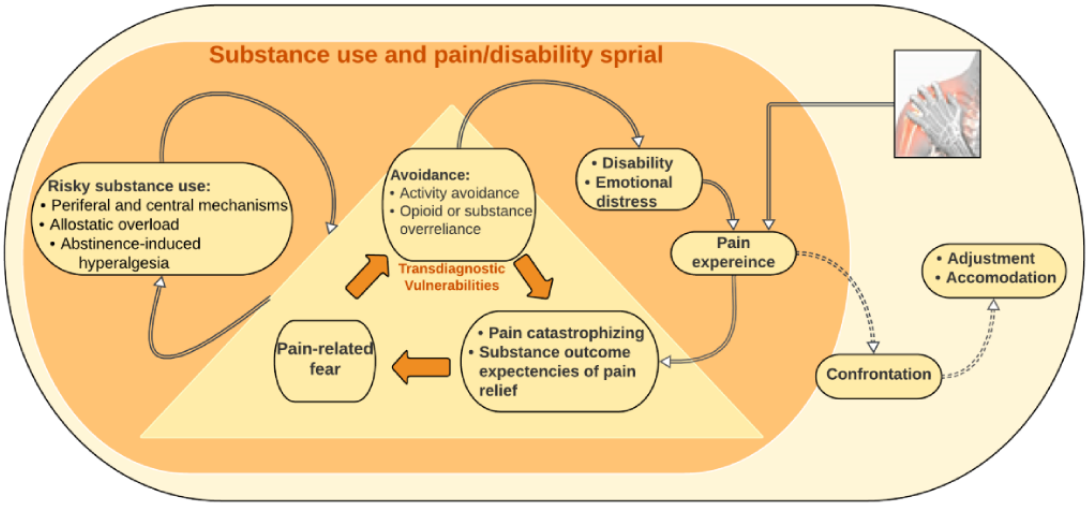

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Despite compelling evidence highlighting the detrimental impact of risky substance use on patient outcomes and health care costs, there are currently no evidence-based interventions tailored to the specific treatment needs of care-seeking patients with NPUC and comorbid risky substance use. Within the context of upper-extremity orthopedic practices, providers frequently fail to address the threat to treatment outcomes posed by patterns of risky substance use. Moreover, patients with NPUC may also minimize or fail to disclose their substance use, either to obtain prescription pain medication or due to the perceived stigma surrounding substance use [21]. These deficiencies pose a substantial public health concern, considering the strong correlation between risky substance use and heightened mortality, multimorbidity, and associated health care expenses [22,23]. It is therefore critical to develop feasible, acceptable, and effective interventions that address maladaptive pain-related regulatory behaviors and processes in patients seeking care for NPUC who have comorbid risky substance use.

Mind-body interventions show promise in effectively addressing risky substance use, chronic pain, and associated disability. They target the transdiagnostic mechanisms contributing to both conditions [5,24-27], demonstrating effectiveness in reducing pain disability and intensity [25,26], substance use urges [27], and related distress [24-26]. These interventions are increasingly appealing to orthopedic care-seeking patients as they bypass the discomfort related to stigma when pursuing treatments for substance use and mental health issues [28]. Notably, asynchronous web-based platforms are particularly well-suited for delivering mind-body treatments to patients with comorbid nonphysical symptom chronicities (NPUCs) and risky substance use [29]. These programs hold promise because they (1) address concerns related to stigma by allowing for anonymity [28]; (2) are low cost [30,31]; (3) offer accessible long-term symptom management for NPUC [32]; (4) circumvent barriers to quality care such as limited availability of skilled providers, transportation, and commitment to a particular day or time [32]; and (5) may increase self-efficacy by supporting patients' ownership over the management of their health condition [33].

Objectives

This study outlines the protocol for developing and testing the feasibility of the Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use (Web-TIRELESS), a web-based mind-body intervention designed for patients with NPUC and comorbid risky substance use (Figure 2). We aim to adapt the Toolkit for Optimal Recovery after Orthopedic Injury (TOR)—our team's previously developed brief, live-video, mind-body preventive treatment for chronic pain among at-risk individuals with acute orthopedic injuries [34]—for the unique needs of our target population and evaluate its feasibility, acceptability, and credibility. We propose a mixed methods approach to iteratively refine Web-TIRELESS across three study aims (Figure 3).

- Qualitative live video interviews: Conduct up to 20 qualitative live video interviews with adult patients with comorbid risky substance use seeking orthopedic care for NPUC to identify this population's treatment needs and preferences. These insights will inform the development of Web-TIRELESS and study procedures.
- Open pilot study: Implement an open pilot study with 12 participants (10 completers), including exit interviews and pre- and postintervention assessments, to evaluate the feasibility, credibility, and acceptability of Web-TIRELESS and study procedures.
- Pilot feasibility randomized controlled trial (RCT): Conduct a pilot feasibility RCT comparing Web-TIRELESS to web-based minimally enhanced usual care (Web-MEUC) with 50 participants (40 completers). This trial aims to demonstrate the feasibility of recruitment and data collection, as well as the feasibility, credibility, and acceptability of both the Web-TIRELESS and control conditions (adherence, retention, fidelity, and satisfaction). We hypothesize that the finalized Web-TIRELESS will be feasible; acceptable from a patient perspective; and have the potential to effectively and efficiently decrease disability, pain, risky substance use, and related distress among care-seeking patients with NPUC and comorbid risky substance use. This paper describes the study protocol and methodology.

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Figure 2. Conceptual model of Web-TIRELESS. Web-TIRELESS: Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use.

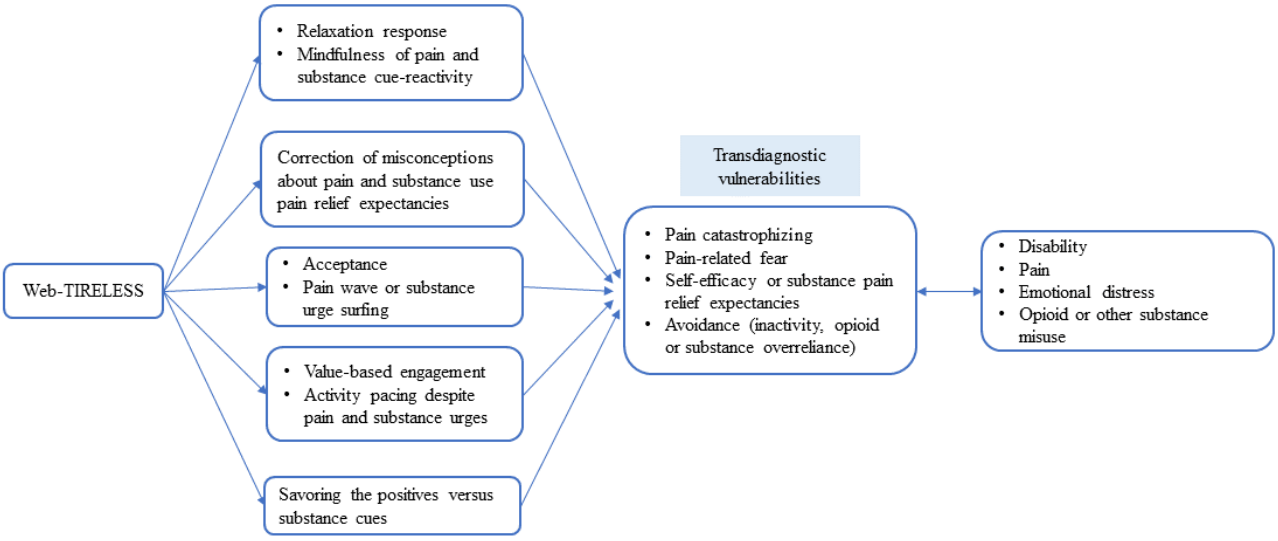

Figure 3. Study schema of Web-TIRELESS. RCT: randomized controlled trial; WEB-TIRELESS: Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use.

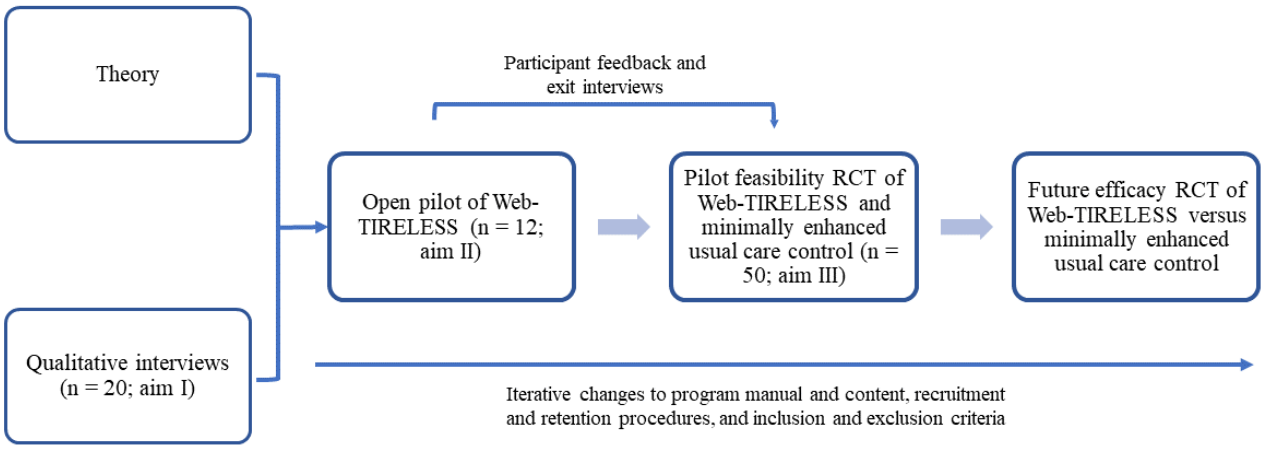

Methods

Study Design

The design and methodology of this study are in alignment with the Science of Behavioral Change framework [35] and the National Center for Complementary and Integrative Health (NCCIH) guidelines for intervention development [36]. Therefore, our primary outcomes will be the feasibility, credibility, and acceptability of Web-TIRELESS, rather than efficacy. The secondary outcomes are pain intensity, disability, pain catastrophizing, and avoidance. See Multimedia Appendix 1 for peer review of this research proposal by the NCCIH.

Ethical Considerations

The Massachusetts General Brigham (MGB) institutional review board (IRB) approved all the study procedures for aims 1 and 2 (2021P001630; 2024P000713).

Inclusion and Exclusion Criteria

Study inclusion criteria for all study phases are as follows: (1) care-seeking patient of the Massachusetts General Hospital Orthopedic Hand and Arm Center; (2) aged 18 years and older; (3) diagnosed with NPUC (eg, arthritis or trigger finger); (4) pain score>4 on the Numerical Rating Scale [37]; (5) risky substance use (score of >10 and <27 for alcohol, or >3 and <27 for cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids, tobacco, or E-cigarettes on the Alcohol, Smoking and Substance Involvement Screening Test [ASSIST]) [38]; (6) owns a device with internet access; (7) English fluency; and (8) able and willing to participate.

Exclusion criteria for all study phases are as follows: (1) participation in mind-body or specialized substance abuse treatment in the past 3 months; (2) practice of mindfulness more than 45 min/wk in the past 3 months; (3) changes to psychotropic medication (eg, antidepressants) within the last 3 months; (4) serious untreated mental illness (eg, schizophrenia); (5) current suicidal ideations; (6) pregnancy; (7) secondary gains (eg, pending disability claim); (8) moderate to severe cognitive impairment (≥4 on the Short Portable Mental Status Questionnaire) [39]; and (9) lifetime history of surgery for the presented NPUC (aim 1) or history of surgery for the presented NPUC within the last 6 months (aims 2 and 3).

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Recruitment and Sampling

All patients will be recruited and enrolled out of the Orthopedic Hand and Arm Service at Massachusetts General Hospital's main campus. Study staff will review the medical records of patients with upcoming appointments, identify prospective participants, and inform clinic staff of their potential eligibility. On the day of their medical appointment, study staff will approach patients in person during their clinic visit to assess study eligibility and interest. Only patients confirmed by clinic staff or medical charts to have a nontraumatic condition will be considered for enrollment. To avoid interfering with clinic flow, informed consent forms (aims 2 and 3 only) will be sent and signed electronically via REDCap (Research Electronic Data Capture; Vanderbilt University), a secure web-based survey platform hosted by MGB.

Procedures

Aim 1 (Development Phase)—Qualitative Interviews

The MGB-IRB approved all study procedures and determined that this phase of the study was exempt from written informed consent. First, we will develop a semistructured qualitative interview script that assesses the target population's specific treatment experiences and needs, as well as their perceptions of Web-TIRELESS. Additionally, we will develop a Web-TIRELESS prototype to be showcased to participants for feedback. Up to 20 interviews will be conducted with eligible patients via live video. All interviews will be guided by the semistructured script and facilitated by a trained member of the study staff. Specifically, the interview topics include (1) perception of effects of the NPUC and risky substance use on function; (2) pain management and substance use cessation skills training needs; (3) difficult situations or challenging experiences; (4) perception of the Web-TIRELESS prototype; (5) barriers and facilitators to participation and adherence, including comfort and confidence working with web-based platforms, physical barriers such as difficulty typing or using mouse, and strategies to address this (eg, education, voice activation); and (6) ideal recruitment and retention strategies. Participants will be provided with information on core program content, skills, and format for their perceptions and feedback.

Interested eligible patients will provide informed verbal consent to participate and can receive assistance with operating the videoconferencing software (ie, Zoom [Zoom Video Communications]) as necessary. All qualitative interviews will be audio recorded with the patient's permission, transcribed, and analyzed using Dedoose version 9.0.90 (SocioCultural Research Consultants). Data from the interviews will be used to further develop and refine Web-TIRELESS.

Aim 2 (Development Phase)— Open Pilot Study

We will conduct an open pilot of Web-TIRELESS followed by exit interviews with up to 12 patients. Participants will complete survey assessments at baseline and postintervention and encouraged to practice and log their use of program skills regularly. This information will provide evidence of the degree to which participants are engaged with the program platform and content. Each of the 4 Web-TIRELESS sessions will be between 30 and 45 minutes long. The exit interviews will take approximately 30 minutes and will follow similar procedures to aim 1 (eg, audio recorded and transcribed). A semistructured interview script will be developed to assess participants' perceptions of the program skills, methodology, feasibility, acceptability, and satisfaction. Results from the open pilot and exit interviews will be used to further refine the study procedures and Web-TIRELESS program. The *Data Analysis* section provides a detailed description of the analysis plan.

Aim 3 (Intervention Phase)—Feasibility RCT

Following written informed consent and the baseline assessment, up to 50 participants will be randomly assigned via permuted blocks using a sequence developed by a statistician to either the active (Web-TIRELESS) or control (Web-MEUC) program on a 1:1 ratio. Both interventions will be web based, and participants will be blinded to the study conditions. All patients will also complete survey assessments at baseline, posttest (ie, after completing the 4-week active or control intervention), and 6-month follow-up via the secure REDCap system.

Program Structure and Modification

Web-TIRELESS (Intervention)

The original TOR follows a 1-on-1, live-video modality and is composed of 4 manualized 45-minute weekly sessions with a clinician. TOR aims to teach mind-body skills that elicit the relaxation response (eg, body scan, deep breathing), mindfulness, cognitive-behavioral strategies (eg, reframing), activity pacing, and acceptance and commitment skills (eg, acceptance) [34]. In the process of adapting TOR, we will remove the irrelevant skills, revise the language to focus on upper extremity conditions, and add new modules relevant to resilience in the face of chronic pain and substance use (see Table 1 for the proposed Web-TIRELESS content). The Web-TIRELESS content may be subject to minor changes following the integration of participant feedback. The modality of Web-TIRLESS will differ from TOR in that all sessions will be on-demand 30 to 45-minute web-based videos. Each Web-TIRELESS session will consist of short (1-5 minutes) educational, exercise, and home practice goal-setting videos. Participants will be instructed to complete 1 session per week on a day and time of their choosing. While participants are given guidance on how to leverage Web-TIRELESS as a resource, session frequency and overall engagement with the program will be determined by each individual. The end of each session includes a "prescription for resilience," which provides specific home practice assignments for the following week (eg, "Practice deep breathing at least once this week"). Following the completion of each session, participants must pass a knowledge check (ie, a 5-minute web-based quiz) before proceeding to the next session. In between sessions, participants are encouraged via text message reminders to practice and log their use of the Web-TIRELESS program skills independently. Home practice materials will include audio and video clips from the most recent session that guide the independent practice of program skills. The overall duration of the program will vary per participant but is expected to take 3-5 weeks to complete.

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Table 1. Proposed adaptations for the Web-TIRELESS[a] intervention.

Session	Original toolkit (TOR[b])	Adapted content for NPUC[c] and web-based delivery (Web-TIRELESS)
__[d]	—	• Introductory information session on the Web-TIRELESS program (eg, how to use it, where to get support).

1	• Treatment rationale
	• Physical, emotional, and cognitive factors that impact recovery after injury
	• Debunk myths about pain
	• Set goals for recovery
	• Relaxation strategies
	• Set homework
		• Education
		  • Treatment rationale for targeting pain or disability and promoting resilience or adaptation
		  • Education on the spiral of pain, disability, and substance use and its risk factors
		  • Debunk pain misconceptions and substance use outcome expectancies of pain relief
		  • Introduce relaxation response strategies for managing pain and substance use urges
		• Skills
		  • Goal setting for managing pain and substance use
		  • Scripted breathing and body scan practices
		  • Establish goals for home practice
		• Exercise
		  • 2-minute diaphragmatic breathing
		• 5-minute web-based quiz

2	• Review homework
	• Discuss biopsychosocial model and mind-body links for pain
	• Develop the patient's unique recovery path.
	• Mindfulness skills for habituating to pain
	• Set homework
		• Review (following 5 minutes of scripted breathing practice)
		  • Home practice; tips for problem-solving barriers to practice.
		  • Prompts for reflection
		• Education
		  • "pain spiral" and "coping path"
		  • Provide education on biopsychosocial model and mind-body links for NPUC or substance use.
		  • Psychoeducation on urge lifecycle and dynamics and ways to fight against impulses.
		• Skills
		  • Develop personalized pain or coping path and substance use cessation.
		  • Pain or substance urge wave surfing exercise focusing on the transitory nature of episodes.
		  • Mindfulness skills for habituating to NPUC and substance use urge time-course (mindful STOP[e]; mindful breathing)
		  • Home practice goal setting
		• Exercise
		  • 5-Minute "Substance Use Urge Surfing" video to facilitate substance use impulse control.
		• 5-minute web-based quiz

3	• Review homework
	• Review personal recovery path
	• Mindfulness of pain
	• Challenge unhelpful thoughts about pain to speed up recovery
	• Learn behaviors to speed up recovery (activity pacing)
	• Set homework
		• Review (following 5 minutes of scripted breathing practice)
		  • Home practice; tips for problem-solving barriers to practice.
		  • Prompts for reflection
		• Education
		  • Mindfulness of pain and substance use urges.
		  • Psychoeducation on negative automatic thoughts ("unhelpful thoughts about pain, and substance-related expectancies: pain catastrophizing, fear and avoidance") and cognitive reframing
		  • Physical activity pacing and setting activity goals
		  • Psychoeducation on positive affective responses to natural reward versus substance cues ("Savoring the positives").
		• Skills
		  • Observer exercise for pain and substance use urges
		  • Challenge unhelpful thoughts (ie, cognitive reframing)
		  • Savoring the positive technique to increase resiliency
		  • Home practice goal setting
		• Exercise
		  • 5-minute "Observer Exercise" video to facilitate self-identity beyond pain and substance use.
		• 5-minute web-based quiz

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Session	Original toolkit (TOR[b])	Adapted content for NPUC[c] and web-based delivery (Web-TIRELESS)

4	• Review homework
	• Acceptance strategies
	• Review all toolkit skills
	• Review challenges with toolkit
	• Plan for continued coping
		• Review (following 5 minutes of scripted breathing practice)
		  • Home practice; tips for problem-solving barriers to practice
		  • Prompts for reflection
		• Education
		  • Acceptance strategies for pain, substance urge, and related distress.
		  • Reframing versus acceptance for pain and substance urges.
		  • Tips for staying on the coping path and implementing skills in the future (eg, pain communication, social support seeking, sleep hygiene, recognizing high-risk substance use situations like pain flare-ups).
		  • Referral information
		• Skills
		  • Acceptance-based exercises (eg, diffusion, self as context, and self-compassion strategies).
		  • Review all program skills
		• Exercise
		  • 2-minute “Ladder Metaphor” video to help patients plan for possible barriers to resilience in the future (ie, relapse prevention).
		• 5-minute web-based quiz

[a]WEB-TIRELESS: Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use.

[b]TOR: Toolkit for Optimal Recovery after Orthopedic Injury.

[c]NPUC: nontraumatic painful upper-extremity condition.

[d]Not applicable.

[e]STOP: Stop, Take a breath, Observe with curiosity, Proceed mindfully.

Web-MEUC (Control)

The Web-MEUC will be an educational digital web-based pamphlet (accessible for the duration of follow-up) containing brief information related to the intervention topics. This includes the trajectory of pain and adaptation in NPUC, the role of relaxation strategies to manage pain, the impact of maladaptive coping behaviors such as substance use, and the importance of cessation and returning to engagement in activities of daily living. Web-MEUC will not include any skills (ie, active ingredients).

Measures

Sociodemographic Characteristics (Baseline Only)

To better understand our sample, we will collect the following sociodemographic information at baseline: age; sex; gender identity; race; ethnicity; education level; marital status; and employment status.

Clinical Variables (Baseline Only)

We will collect data on NPUC, date of diagnosis, symptom trajectory, and treatment history.

Involvement of Substance Use (Eligibility Screening Only)

To assess the severity of risky substance use, we will use the World Health Organization’s ASSIST [38]. Each substance type (ie, alcohol, tobacco, cannabis, stimulants, inhalants, sedatives, hallucinogens, and opioids) is scored separately on the ASSIST, with scores on each ranging from 0 to 40. Higher scores indicate more problematic substance use for the respective substance type.

Primary Outcomes

In accordance with the Science of Behavioral Change framework [35] and NCCIH guidelines for intervention development [36], primary outcomes for this 3-aim study include a priori feasibility, credibility, fidelity, and credibility benchmarks (Table 2).

- Feasibility of recruitment: The proportion of eligible patients that agree to participate.
- Treatment credibility (baseline only): The proportion of participants that score above the midline on the Credibility and Expectancy Questionnaire [40]. The Credibility and Expectancy Questionnaire will be administered to assess the degree to which one believes the intervention will effectively manage one’s upper extremity pain condition, substance use, and related worries. Some items are scored on an 11-point 0%-100% scale while others are scored on a 1-9 Linkert scale. Higher scores represent higher credibility and expectancy.
- Feasibility of assessments: The proportion of participants that complete survey assessment with no measure fully missing.
- Acceptability of treatment: The proportion of participants that complete 3 of 4 program sessions.
- Feasibility of homework adherence: The proportion of participants that practice and report using 1 or more skills on 3 d/wk.
- Treatment satisfaction (postintervention time point only): The proportion of participants that score above the midline on the Client Satisfaction Questionnaire [41]. The Client Satisfaction Questionnaire is a 3-item questionnaire that measures on a scale of 1 to 4 the degree to which the participant is satisfied with the program and its ability to

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meet their needs. Higher scores represent greater satisfaction.

- Acceptability of web-based delivery (postintervention time point only): The proportion of participants that score above the midline on the User Experience Scale [42]. The User Experience Scale assesses how well patients like the web-based program content and delivery. Total scores range from 22 to 110 with higher scores indicating greater satisfaction with the platform.

Table 2. A priori feasibility benchmarks.

Outcome	Acceptable	Excellent
Credibility and expectancy	70% and more of participants with score over the midpoint on the Credibility and Expectancy Scale	75% and more of participants with score over the midpoint on the Credibility and Expectancy Scale
Acceptability of treatment (satisfaction)	70% and more of participants with scores over the midline on the Client Satisfaction Scale	75% or more of participants with scores over the midline on the Client Satisfaction Scale
Acceptability of web-based delivery (satisfaction)	70% and more of participants with scores over the midline on the User Experience Scale	75% and more of participants with scores over the midline on the User Experience Scale
Feasibility of recruitment	70% and more eligible patients approached agree to participate	80% and more of eligible patients approached agree to participate
Acceptability of treatment (attendance)	70% and more of participants attend 3 out of 4 sessions	80% and more of participants attend 3 out of 4 sessions
Adherence to homework	70% and more of participants practice at least 1 skill on 3 days/week	80% and more of participants practice at least 1 skill on 3 days/week
Feasibility of assessments	70% and more of participants complete all assessments (with no measures missing)	90% and more of participants complete all assessments (with no measures missing)
Adverse events	Minimal	None

Secondary Outcomes

Participants in the open pilot and feasibility RCT will complete the surveys described later at baseline, postintervention (ie, after fully completing active or control intervention), and a 6-month follow-up (feasibility RCT only) unless otherwise stated.

Pain Severity

The Graded Chronic Pain Scale [43] will be used to assess pain severity and pain-related disability. Total scores range from 0 to 10 with higher scores indicating worse pain severity.

Pain Intensity

The Numerical Rating Scale [37] will assess the intensity of pain at rest and with activity on a 10-point Likert scale (eg, from 0=no pain to 10=worst possible pain).

Disability

The 30-item Disabilities of the Arm, Shoulder, and Hand [44] will quantify the severity of disability as it relates to NPUC. Higher scores indicate greater disability.

Pain Catastrophizing

The Pain Catastrophizing Scale [45] will be administered to assess participants' proclivity for magnification, helplessness, and rumination of pain. Scores range from 0 to 52 with higher scores indicating greater pain catastrophizing.

Pain Anxiety

We will use the Pain Anxiety Symptoms Scale–Short Form [46] to assess fear and anxiety related to pain. Scores range from 0 to 100 with higher scores indicating greater pain-related fear and anxiety.

Hypervigilance

The Pain Vigilance and Awareness Questionnaire [47] will measure participants' preoccupation with or attention to pain. Scores range from 16 to 96 with higher scores indicating greater pain vigilance.

Fear Avoidance

We will assess fear avoidance using the Brief Experiential Avoidance Questionnaire [48] which quantifies tendencies to avoid unpleasant internal experiences. Scores range from 15 to 90 with higher scores indicating greater avoidance behaviors.

Opioid Misuse

Participants will complete the Current Opioid Misuse Measure [49], which assesses the risk for aberrant medication-related behavior in persons with chronic pain. Scores range from 0 to 68 with higher scores indicating greater risk for opioid misuse.

Substance Use

The Timeline Follow Back [50] will be self-administered by patients following the completion of each Web-TIRELESS session and leveraged as a motivational interviewing technique. The Timeline Follow assesses daily estimates of alcohol, cannabis, cigarette, and other substance use during the past week (0 to 7 days prior). Higher scores indicate more severe substance use.

Anxiety

To assess symptoms of anxiety, we will use the 8-item Patient-Reported Outcomes Measurement Information System Emotional Distress–Anxiety 8b version 1.0 [51]. Scores of this measure range from 8 to 40 with higher scores indicating greater anxiety symptom severity.

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Depression

The Patient-Reported Outcomes Measurement Information System Emotional Distress–Depression 8b version 1.0 [51] is an 8-item measure that will be used to assess symptoms of depression. Scores range from 8 to 40 with higher scores indicating greater depression symptom severity.

Self-Report Measures

Patients will be required to fill out a series of questionnaires online through the secure REDCap system. The completion of these questionnaires is expected to take approximately 30 minutes. To enhance data completeness, patients will be prompted to address any missed items at the end of the session. Additionally, a blinded research assistant, who is not involved in the recruitment process, will review each completed questionnaire to confirm that responses are not randomly made or uniformly affirmative.

Data Analysis

Aim 1: Qualitative Interviews

Analyses will be guided by the framework method [52,53] and follow a deductive-inductive approach with predetermined themes [54] while allowing for inductive flexibility where themes or codes come from data [52,55]. Prior to initiating the qualitative coding, we will develop a preliminary codebook with predetermined themes [54], which will be subject to changes as distinct patterns in the data emerge throughout coding [52,55]. Qualitative data (ie, deidentified interview transcripts) will be analyzed using Dedoose version 9.0.90 (SocioCultural Research Consultants). Qualitative coding will be completed by the principal investigator and reliability coding will be done by a trained research assistant. To ensure scientific rigor, we will assess the reliability (κ) of the application of codes to qualitative responses with the ultimate goal of establishing adequate interrater reliability (κ>.80). Discrepancies in the application of codes will be resolved through discussion until agreement is sufficiently reached.

Aim 2: Open Pilot Study

We will use a mixed methods approach [56] to analyze the quantitative survey data and qualitative exit interview data. For quantitative analysis, we will focus on descriptive statistics with estimated variance for each measure, and within-group pre-post paired 2-tailed *t* tests (with Cohen *d* effect sizes). This will allow us to assess the preliminary efficacy of Web-TIRELESS. We will also execute exploratory correlations to test the processes (eg, within-group changes in risky substance use and pain or disability) [57-59]. Frequency and proportions will also be used to assess the feasibility of recruitment, retention, and treatment credibility or satisfaction (Table 2). Qualitative data derived from exit interviews will be analyzed using the procedures outlined in aim 1. Finally, we will use the embedded approach for mixed methods [56] to integrate the qualitative and quantitative data and interpret the results to refine the Web-TIRELESS before the feasibility RCT.

Aim 3: Feasibility RCT

We will use the same analysis techniques to assess feasibility, acceptability, credibility, and satisfaction as in aim 2. Drop-outs will be counted as not meeting applicable feasibility criteria. Benchmarks that need to be met before an efficacy trial (Table 2) will be reported separately for each intervention [60]. If these criteria are not met, we will make the necessary revisions to ensure that they are fulfilled.

Treatment Fidelity

For aims 1 and 2, fidelity to the web-based program material will be assessed using a user experience software (eg, Google Analytics [Google]) that monitors engagement with the web-based treatments (access to and time spent on each web page, log-in and use of material, and completion of web-based quizzes).

Power Analysis

This trial is primarily focused on feasibility and not efficacy, meaning that power analysis of group differences or significant pre-post changes in outcome measures is inappropriate. Furthermore, power analysis is not appropriate for qualitative analysis. However, saturation of themes is expected for the qualitative interviews with up to 20 patients [61]. With a sample size of 50 in aim 3 and assuming conservatively that the 7 feasibility criteria evaluated are independent, the study will have more than 80% power to confirm all feasibility criteria if the expected rate of each criterion is at least 83%.

Results

This study is funded by the National Institutes of Health (1K23AT012364-01). Aim 1 was approved by the MGB-IRB (P# 2021P001630) in January 2023, qualitative interviews concluded in May 2024, and completion of aim-1 data analysis is expected in December 2024. MGB-IRB protocol approval was garnered for aim 2 (P# 2024P000713) in May 2024 and recruitment started in October 2024. Completion of aim-2 data analysis is projected for June 2025. Aim-3 IRB approval and initiation of participant recruitment is anticipated by July 2025. Data collection and analysis (aim 3) are expected to conclude in January 2027. Overall completion of aim 3 and other study-related operations is anticipated by June 2027.

Discussion

Significance

Risky substance use is common among care-seeking patients with NPUC, with prevalence rates of up to 1 in 5. It serves as a significant modifiable risk factor for the progression and maintenance of chronic pain, opioid and other substance use disorders, disability, and distress [9,10,12-14]. Identifying patients with NPUC and comorbid risky substance use and enrolling them in an asynchronous, web-based mind-body program may be an effective and efficient approach to reducing pain and disability while preventing prolonged and costly care for this population. In this paper, we illustrate the methodology and study procedures for developing, adapting, and establishing the feasibility of Web-TIRELESS, a novel program aimed at enhancing resilience and fostering adaptive coping strategies for chronic pain, substance use, and related distress among care-seeking patients with NPUC and comorbid risky substance

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use. Informed by the reciprocal model of pain and substance use [14] as well as the fear-avoidance model of pain [15,62], Web-TIRELESS proposes an integrated approach. This approach harnesses a range of mind-body skills (eg, mindfulness, deep breathing, savoring the positives), cognitive behavioral strategies (eg, reframing), acceptance and commitment skills (eg, substance use urge surfing, value-based goal setting). These components are strategically designed to target transdiagnostic factors relevant to NPUC and the comorbidity of risky substance use.

The results of this 3-aim trial will offer crucial insights to prepare for a fully powered efficacy RCT comparing Web-TIRELESS with a Web-MEUC control. This design and methodology align with the Science of Behavioral Change framework [35] and NCCIH recommendations for intervention development, which posit that iterative refinement and establishment of feasibility best ensure the scientific rigor of subsequent efficacy trials [36]. Designing and developing behavioral interventions and study procedures that preemptively identify prospective patients, cater to the specific needs of the target population, and establish the power to detect change is vital to safeguard against the common consequences of testing efficacy before feasibility. Importantly, this methodical process elucidates valuable firsthand information from the target population (eg, treatment needs, preferences, perceptions, and barriers to treatment), which may inform the development of other treatments or interventions tailored to this population. If our proposed model of care proves effective, it could be extended to other patient populations with nontraumatic painful conditions, such as those affecting the knee, hip, ankle, or spine, who present with similar treatment challenges.

Limitations

The primary limitation of this study includes its limited scope. Given that the primary outcomes of each study aim are centered around feasibility, we cannot make claims of program efficacy until a future efficacy trial. Additionally, because the program is currently being developed for English speakers only, the generalizability of our results across diverse ethnolinguistic groups will be unknown. Finally, due to our sample consisting of only patients with NPUCs, it is unclear if the effects will be comparable across other patient populations with nontraumatic painful conditions and risky substance use.

Conclusions

In summary, this study aims to develop, adapt, and establish the feasibility of Web-TIRELESS, the first asynchronous mind-body intervention specifically tailored to aid in coping with chronic upper-extremity pain among individuals with NPUCs and comorbid risky substance use. By iteratively refining and adapting the intervention based on feedback from qualitative patient interviews, we aim to increase the likelihood of establishing program efficacy in future trials. The results from this study will inform a future efficacy RCT of Web-TIRELESS versus a Web-MEUC control group. Future studies should also explore the extent to which Web-TIRELESS can be applied to comparable patient groups experiencing both risky substance use and nontraumatic painful conditions.

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Data Availability

Upon trial completion, the datasets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NL, AMV, and JB are credited for producing the “original draft” of this manuscript. DR, AMV, JB, CSM, ARB, NCC, and RG developed the “methodology” for the proposed research presented within this manuscript. NL, JWD, LGS, DR, AMV, and JB participated in the “conceptualization” of the proposed research and thus, the manuscript itself. NL, JB, CSM, ARB, NCC, and RG have assisted with project administration. NCC, AMV, and JB contributed to the “validation” of this study and the corresponding manuscript. JB is responsible for the “funding acquisition,” “project supervision,” and “software” development. All authors participated in the “revising review and editing” of this manuscript.

Conflicts of Interest

CM received an honorarium unrelated to this research for his role as teaching faculty at AO North America. AB is a consultant for Stryker, Synthes, and Trimed. All authors’ institutions received NIH funding.

Multimedia Appendix 1
Peer review report from the National Center for Complementary and Integrative Health Special Emphasis Panel (ZAT1 JM (13)) - NCCIH Training and Education Review Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 136 KB - resprot_v13i1e64547_app1.pdf]

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Abbreviations

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
IRB: institutional review board
MGB: Massachusetts General Brigham
NCCIH: National Center for Complementary and Integrative Health
NPUC: nontraumatic painful upper-extremity condition
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
Web-MEUC: web-based minimally enhanced usual care
Web-TIRELESS: Web-Based Toolkit for Resilient Life Beyond Pain and Substance Use

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Protocol

Comparing Synchronous and Asynchronous Remotely Delivered Lifestyle Interventions: Protocol for a Randomized Noninferiority Trial

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Abstract

Background: Remotely delivered lifestyle interventions have emerged to increase the reach and accessibility of traditional interventions that involve numerous in-person visits. Remote interventions can be delivered synchronously via videoconference software or phone or asynchronously via online platforms. Asynchronously delivered interventions are convenient and flexible in that they allow people to participate at any time and as such, they may be more sustainable. Evidence for asynchronous interventions is needed given their potential for convenience and sustainability, which may have implications for weight loss maintenance.

Objective: This is a randomized noninferiority trial comparing 2 remotely delivered lifestyle interventions: one that is delivered synchronously via videoconference meetings and one that is delivered asynchronously through private Facebook (Meta) groups. We hypothesize that the percent weight loss difference between conditions at 6 and 12 months will be less than 2% and that the asynchronous condition will cost less to deliver per pound lost. We also hypothesize that engagement will be higher in the asynchronous condition at 12, 18, and 24 months and that the asynchronous condition will have greater weight loss at 24 months.

Methods: We will randomize 328 participants with overweight or obesity to a remotely delivered lifestyle intervention that is delivered either synchronously or asynchronously. Delivery of the synchronous lifestyle intervention will be via videoconference group sessions, whereas the delivery of the asynchronous lifestyle intervention will be via private Facebook groups. The lifestyle intervention in both conditions is based on the Diabetes Prevention Program. The intervention goals are to lose 5%-10% of baseline weight and to work toward 300 minutes per week of moderate intensity physical activity. The core intervention will last for 12 months and be led by counselors in each group. This will be followed by a 12-month maintenance phase to be led by participant volunteers from each group. Participant engagement and weight loss maintenance will be assessed during this phase. The primary outcome is mean percent weight loss at 6 and 12 months. The noninferiority margin for differences in weight loss between conditions is 2% at both 6 and 12 months. We will model percent weight loss at 6 and 12 months using general linear regression models with the intent-to-treat sample. Secondary outcomes include engagement, collective efficacy, cost, and weight loss at 18 and 24 months.

Results: The funding period began on August 17, 2023, and the study was approved by the University of Connecticut Institutional Review Board on August 17, 2023. Participant recruitment will begin December 2024 and the intervention will begin February 2024.

Conclusions: If hypotheses are confirmed, this work will provide evidence that asynchronously delivered remote interventions are as efficacious as synchronously delivered ones and more sustainable such that people will engage in them longer and retain more weight loss for less cost.

Trial Registration: ClinicalTrials.gov NCT06393725; https://tinyurl.com/4kzzwkc9

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International Registered Report Identifier (IRRID): PRR1-10.2196/65323

(JMIR Res Protoc 2024;13:e65323) doi:10.2196/65323

KEYWORDS

obesity; lifestyle intervention; digital health; weight loss maintenance; engagement; mobile phone

Introduction

Obesity, a significant risk factor for type 2 diabetes, affects 39% of US adults [1,2]. Lifestyle interventions such as the Diabetes Prevention Program (DPP) have shown strong efficacy for producing weight loss, but they have many barriers to participation and are not sustainable long term even though obesity is a chronic condition [3]. Technology allows us to provide lifestyle interventions to patients with fewer barriers and possibly greater sustainability. Technology-delivered interventions utilize online platforms, videoconferencing, or mobile apps to deliver counseling, peer support, and multimedia content to patients. They allow people to participate from anywhere they can access the internet. Technology-delivered lifestyle interventions have been done synchronously via online meetings or asynchronously via messaging on apps or other platforms [4]. The literature lends few insights as to the comparative efficacy of different technology-based modalities for the delivery of lifestyle interventions.

A systematic review of 21 technology-delivered lifestyle interventions based on the DPP revealed a mean percent weight loss at 15 months of about –3.98% and those with moderate to high methodological quality produced about –3.40% [4]. Notably, technology-delivered interventions that included human counseling produced greater weight loss than fully automated programs. Only 3 trials compared digital to in-person lifestyle interventions. In one of those trials, investigators had to pivot from in-person visits to videoconferencing visits during the pandemic and found that weight loss did not differ by modality [5]. However, participants were not randomized to the conditions. In another trial, investigators randomized 43 participants to in-person or videoconference lifestyle interventions and found no weight loss differences between groups, but they were not powered to establish noninferiority [6]. A third trial that was powered for noninferiority compared in-person to an asynchronous technology-delivered intervention and found that the in-person intervention resulted in significantly more weight loss at 6 months, but not at 12 months [7]. A gap in the literature is how asynchronous delivery compares with synchronous delivery when both interventions are delivered via technology. Asynchronous lifestyle interventions, by not requiring that participants be available to attend regularly scheduled meetings, offer a convenient alternative to synchronous interventions delivered via videoconference.

Asynchronous interventions allow counselors and participants to engage individually through messaging or in groups via discussion threads. One randomized trial tested the efficacy of an asynchronous lifestyle intervention delivered via a commercial mobile app (Noom) that involved asynchronous messaging with coaches and a group of peers. Intervention participants lost a significantly higher percentage of weight than those in a no-treatment control group at 6 months (mean=–3.69% vs –0.15%) and 12 months (mean=–2.54% vs 0.33%) [8]. Several pilot trials have established the feasibility and acceptability of asynchronous technology-delivered lifestyle interventions [9-14], including one trial of rural adults that compared the feasibility of an asynchronous lifestyle intervention delivered via Facebook to a synchronous version delivered via videoconferencing [10]. It found high rates of retention, satisfaction, and dietary self-monitoring compliance in both groups with no differences between groups. Weight loss at 6 months was not different between groups but this trial was not powered for noninferiority. No fully powered weight loss trials have compared an asynchronous technology-delivered lifestyle intervention to a synchronous one. However, a randomized trial of adults with depression compared an asynchronous technology-delivered depression therapy to a synchronous video teletherapy condition [15]. In the asynchronous condition, participants could send messages to their therapist at any time and receive daily replies. In the synchronous condition, participants met with their therapist once weekly for a 45-minute video teletherapy session. Noninferiority was established for the asynchronous condition in depression, anxiety, and functioning outcomes and participants found this modality highly acceptable. More research is needed to establish the efficacy of asynchronous technology-delivered lifestyle interventions given that many people with obesity may not be able to participate in programs that require attendance at scheduled meetings either in person or remotely.

Since the dawn of email, SMS text messaging, and social media, asynchronous communication has become ubiquitous in everyday life. A survey of 1300 US adults found that 77% said the feature they use most on their smartphone is texting, 64% said social media, 48% said email, and only 32% said phone calls [16]. Social media use, which is comprised of asynchronous exchanges, is prevalent in the United States. The Pew Internet Research Survey reported that 72% of US adults have at least one social media account [17]. On average, social media users spend 147 minutes a day (~2.5 hours) on social media sites [18]. Because so much human communication is asynchronous, research is needed to explore how to deliver health care services through asynchronous communication technologies. Rather than inventing a new asynchronous technology to deliver a lifestyle intervention, we have been using commercial social media platforms as a means to “meet people where they are” given how much time people spend on these sites [13]. This sidesteps the expense of developing a novel platform and trying to get people to log into and use it, especially when their attention is absorbed by popular social media platforms.

An advantage of asynchronous interventions delivered via social media platforms is the potential for sustainability, which, in this

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context, we define as the length of time the intervention group remains intact. To the extent that the group remains intact, members can continue to receive support and access resources. A major problem with synchronous lifestyle interventions, whether delivered in-person or via technology, is that the intervention group disbands when the intervention is over, thus participants lose the support and resources the group provided. Unsurprisingly, weight regain is routinely observed in the period following lifestyle interventions [19]. Asynchronous lifestyle interventions delivered on commercial social media platforms like Facebook may be more sustainable because staying in the group requires no effort on the part of participants and the intervention content is still available to them as long as they remain in the group. Participants already use Facebook multiple times a day and will continue to after the program, which means the space created on Facebook can continue to be used by participants long after the program ends. In one pilot feasibility trial of a lifestyle intervention conducted in private Facebook groups, participants were randomized to a group of 40 participants or a group of 94 participants and after the 3-month intervention, the counselors exited both Facebook groups, but the groups remained open for 1 year and were each led by a participant volunteer [13]. Engagement in the large group continued through month 8 and then dropped off, whereas in the small group, engagement ceased after month 3. Furthermore, the larger group (n=94) produced nearly 5-fold greater engagement than the small group, which was much larger than the proportional difference in group size. The findings reveal that asynchronous groups will continue to engage after an intervention ends, even in the absence of an interventionist, and larger groups appear to engage more and for a longer time than smaller groups. Research is needed to examine if greater group engagement following an asynchronous lifestyle intervention is accompanied by greater weight loss maintenance.

The current study is a noninferiority randomized controlled trial testing whether weight loss following a yearlong asynchronous lifestyle intervention conducted in a private Facebook group is noninferior to that of a synchronous lifestyle intervention conducted via videoconference meetings. Due to the ease of engaging in asynchronous groups, we hypothesize that the asynchronous group will have greater engagement than the synchronous group, which requires participants to attend meetings to engage with the intervention. We also hypothesize that the asynchronous condition will cost less per pound lost to deliver. After the 1-year intervention, the counselors in each group will turn group leadership over to a participant volunteer for the subsequent year. We hypothesize that the asynchronous group will engage more and for a longer period of time than the synchronous group and thus retain more weight loss at 18 and 24 months. The conceptual foundation for this hypothesis lies in Bandura's concept of collective efficacy, which is when members of a group feel connected to their group and believe that the group shares their goals and abilities [20]. In groups with high collective efficacy, group members are empowered to work collectively to solve problems and this facilitates greater success toward goals among the group as a whole. We hypothesize that members in the asynchronous condition, by virtue of having more opportunities to engage (ie, 24/7) will experience higher collective efficacy than the synchronous condition where interactions are restricted to 22 group meetings. Furthermore, we hypothesize that the asynchronous condition will have greater engagement in the postintervention period because it is easier to engage there than it will be in the synchronous condition where engagement will depend on (1) how reliably the volunteer group leader arranges regular videoconference meetings and (2) the availability of group members to attend those meetings. In the asynchronous condition, engaging in the postintervention period entails very little effort and is not as heavily reliant on the volunteer group leader, since any member can post at any time. We suspect collective efficacy may decline in the synchronous condition during the postintervention period due to these participation barriers. We will measure collective efficacy to test our hypothesis that the asynchronous condition will have greater collective efficacy by the end of the 1-year program and the 1-year peer-led maintenance phase than the synchronous condition.

Methods

Study Design

The proposed design is a randomized controlled noninferiority trial. We will randomize 328 adults who are overweight or obese to either an asynchronous or synchronous condition. Participants in the asynchronous condition will receive lifestyle counseling via a private group on Facebook. Participants in the synchronous condition will receive a lifestyle intervention via videoconference group meetings. Two waves of 164 participants will each be randomized into two groups of 82 participants. Content in both conditions is based on the DPP Lifestyle Intervention [21]. Measurements will be taken at baseline, 6, 12, 18, and 24 months. Percent weight change at 6 and 12 months is the primary end point. Secondary end points include engagement, collective efficacy, cost, and sustainability, defined as engagement in the year-long postintervention period.

Study Population

To be eligible, participants must be between the ages of 18 and 65 years, have a BMI between 27 and 45 kg/m^2, have Bluetooth or Wi-Fi connectivity at home (for scale), go on Facebook at least 5 days per week over the past 2 weeks, and own a smartphone. Participants must not be pregnant, lactating, or have plans to during the study period; have bipolar disorder, substance abuse, psychosis, bulimia, binge eating disorder, or severe depression; have had bariatric surgery or plans to during the study; taking medication that affects weight, lost ≥5% of weight in past 6 months, participated in another weight loss program or plans to during the study; have chronic pain or a medical condition that interferes with the ability to exercise; have type 1 diabetes; be unable to walk one-fourth of a mile unaided without stopping; or use nicotine via cigarettes or vaping on a weekly basis.

Recruitment

Participants will be recruited via Research Match [22] and ads posted in university listserves, social media, and Craigslist throughout the United States. To attract men who are typically underrepresented in weight loss trials [23], we will use targeted

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ads as well as recruit on Reddit, where 74% of users are male. To attract racial and ethnic minorities who are typically underrepresented in weight loss trials, we will use targeted ads. We aim to recruit a sample that is 30% (98/328) minorities and 50% (164/328) male. Participants clicking on the recruitment ad will complete electronic consent and a screening survey.

Onboarding Webinar

Interested candidates who are eligible will complete an online baseline survey and attend a 1-hour study webinar where study staff members will use a Methods-Motivational Interviewing approach to help participants understand the scientific rationale of the trial design, research questions, and methods [24]. This provides participants with a comprehensive understanding of the commitment entailed in trial enrollment. This helps set clear expectations for participants (eg, transparency about the length of assessments), explain the scientific rationale for procedures (eg, randomization and impact of dropouts on conclusions), diffuse ambivalence about research participation using motivational interviewing, increase research literacy, build trust, and make explicit commitments to self and trial. We will also ask participants at this time to not engage with one another outside of the study, including by phone, email, social media, in person, and so on. We will explain the scientific rationale for this request as well as the importance of respecting each other's privacy by not reaching out to other study participants in ways that participants have not consented to. Upon completion, participants will be mailed a Wi-Fi scale and given log-in info for the scale so we can record weight for assessments. Participants will receive US $40 for completing the baseline assessment.

Randomization

After participants complete the orientation webinar and set up their scale, they will be randomized 1:1 to the two conditions in randomly permuted blocks of size 4 and 6 using the ralloc program in Stata (StataCorp) [25]. We will stratify randomization by sex and baseline BMI (27-34 and 35-45 kg/m^2).

Intervention Conditions

Asynchronous Lifestyle Intervention

Two interventionists will each run a group in each condition to balance the conditions by the interventionist. The DPP lifestyle intervention will be delivered in a counselor-led Facebook group with twice daily preprogrammed posts as in our previous studies [12,23,26,27]. All Facebook groups will be on the "private" setting, which means only group members can see the group and its content. Each week's content is based on the corresponding module of the DPP. The DPP assigns participants the goals of (1) calorie tracking to achieve a calorie goal based on the amount needed to lose 1-2 pounds per week, (2) developing a heart-healthy diet, (3) engaging in 300 minutes per week of moderate intensity exercise, and (4) engaging in strength training twice or more a week. On Mondays, the counselor posts 2 goals for the group to work on that week including one diet goal (eg, reduce added sugar) and one exercise goal (eg, add 15 minutes of moderate intensity exercise on 3 days) to help participants progress toward the overall program targets. On Fridays, the counselor posts a weigh-in post asking participants to reply with their weight change in pounds for the week. This ensures participants are weighing themselves weekly and allows an opportunity for problem solving for those not losing weight. Goal accountability happens each Sunday when the counselor posts asking participants to report how they did on the weekly goals. In between these recurring posts are posts that reflect the DPP module for the week. Many posts contain links to a Pinterest page where we house myriad recipes, meal plans, and workouts tailored to a wide range of dietary preferences (eg, vegetarian) and cultural influences (eg, African American and Latinx). We also include images in our posts that represent individuals from diverse backgrounds by gender, race and ethnicity, marital status, and sexual orientation. Finally, participants can send their counselor private messages.

Asynchronous Peer-Led Maintenance Phase

At the end of the 12-month intervention, counselors will query their groups for 2 volunteer moderators to take over the leadership role of each group for the next 12 months. In a previous pilot trial, we were successful in getting volunteer moderators at first request in both groups [13]. In that trial, we did not give volunteers specific guidance on what to post or how to run the group, and we discovered that under those conditions, volunteer moderators continued the weigh-ins but otherwise relied on group members to post in the group. This time we plan to give the volunteer moderators a library of 182 posts (based on the DPP protocol) that they can draw from to start conversations. The library will include goal-setting posts, weigh-in posts, problem-solving posts, goal accountability posts, and additional content that emphasizes lessons learned from the DPP. We will also arrange a 30-minute orientation call with each volunteer moderator to discuss the posts, give them guidance on how to moderate a Facebook group, send them a 19-minute video produced by Facebook on how to run a Facebook group (including guidance on privacy), advise them to post daily and encourage group members to post updates about their progress and ask the group their questions, and finally, we will advise them on how to secure a replacement moderator if and when they no longer want to moderate the group. Moderators may use the library as they wish and post whatever they or the group prefers. The counselors will exit the group when the maintenance phase commences. Study staff members will remain in the group but will not post or engage unless any activity occurs that could indicate a breach of confidentiality or any other type of harm. Neither occurred in our previous pilot. Participants will be informed that study staff members will extract engagement data from the group during this phase.

Synchronous Remote Lifestyle Intervention

The DPP lifestyle intervention will be delivered by a counselor in weekly videoconference sessions. The 16-session Core of the DPP Lifestyle Intervention will be delivered over 6 months (90 mins/meeting) followed by monthly meetings for 6 months (22 meetings total) [21].

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Synchronous Peer-Led Maintenance Phase

At the end of the intervention period, the counselors will query their groups for 2 volunteer moderators to take over the leadership role of each group for the next 12 months. The leadership role entails hosting the videoconference sessions. We will give the group leaders access to a videoconference account so they may host sessions without a cost. As in the asynchronous condition, we will provide the group leaders with additional content from the DPP to use in the groups if they so choose. We will also arrange a 30-minute orientation call with each volunteer group leader to discuss the content, give them guidance on how to lead a group, and advise them on how to secure a replacement group leader if and when they no longer want to lead the group. Group leaders may use the content we provide as they wish or run the group in whatever way they and the group prefer. The counselor will not attend the group meetings; however, a study staff member will attend to record attendance and run the transcription software, but they will not engage unless any activity occurs that could indicate a breach of confidentiality or any other type of harm. Participants will be informed that study staff members will save the chat data and use transcription software to record the group conversation during this phase so that this data can be used for research purposes.

Follow-Up Assessments

At 6, 12, 18, and 24 months after baseline, weight data will be collected from Wi-Fi scales and participants will complete online surveys. Compensation is US $40 at 6 months, US $50 at 12 months, US $40 at 18 months, and US $50 at 24 months. Participants who complete all of the follow-ups will receive a bonus of US $50.

Measures

Weight

Weight will be gathered from the Wi-Fi scales we provide to participants as in our previous research [28]. In the event that Wi-Fi is not working, participants will be asked to send a photo of their weight on the scale. Participants will be advised to weigh themselves in the morning, without clothing, before eating and after voiding. We will download weight data from participants' scales at each time point. We will calculate absolute weight change in pounds and percent weight change.

Engagement

Because the nature of engagement in each condition is different, the metric by which we will compare conditions will be word count, defined as total spoken or typed words. In the asynchronous condition, we will manually extract engagement data from Facebook, including posts, replies, reactions (eg, like, love, angry, and haha), poll votes, and private messages to the counselor. Engagement data will be extracted during the intervention phase and the peer-led maintenance phase. The total word count will include the total word count from replies and posts. For Facebook reactions (eg, hitting a like button), the word used will be the type of reaction button used (like, love, laugh, anger, sad, and care). For poll votes, the words included will be those in the option they voted for in the poll. Facebook puts a 24-character limit for each answer option in a poll and every effort will be made to balance the word count across poll options. Each participant's engagement will be exported into a separate file, and then Pennebaker's word counting software (Linguistic Inquiry and Word Count, LIWC-22), which has been validated for research purposes [29], will be used to determine the total words typed in the group by each participant and the proportion of words that reflect 4 dimensions of language (analytical thinking, clout, authenticity, and emotional tone). Analytical thinking refers to the degree to which the language used is formal and logical and reflects hierarchical thinking patterns. Language that is low in analytical thinking is more intuitive, personal, friendly, and warm. Clout refers to the language that expresses social status, confidence, or leadership. Authenticity refers to language that is honest, spontaneous, and lacking in social inhibition, and it is characteristic of conversations between close ties or friends. Finally, emotional tone reflects the number of positive emotion words (positive tone) and negative emotion words (negative tone) used.

In the synchronous condition, we will use Webex videoconference software to record and transcribe the group meetings. Then a research staff member will compare the transcript to the video for accuracy and make edits to the transcript accordingly. Because participants might use the chat to ask questions or make comments, we will also save the chats so this data can be included in the word count for each participant. Each participant's words spoken and typed will be exported into a separate file and analyzed with LIWC-22 as well.

Collective Efficacy

Participants will complete the Online Collective Efficacy Scale, a 35-item validated scale designed to assess the degree to which members of an online group feel they are active contributors to a high-functioning group [30]. This measure has three subscales, which are (1) social presence, (2) engagement, and (3) collaboration and augmentation.

Cost

We will systematically track costs associated with the delivery of both intervention conditions, capturing information on the costs that would be required to implement each intervention in practice (ie, outside a research context) [31]. Intervention costs will be distinguished from costs associated with research and development (eg, recruitment). We will create an accounting system that captures administrative and intervention time for both conditions. We will use cost-capture templates to evaluate staff members' time. National salary data will be used to calculate costs including administration (eg, staff members' time to schedule intervention posts) and intervention delivery (eg, counselor time) costs.

Counselor time will be measured in each condition so that cost can be calculated. In the asynchronous condition, counselors will be given a study phone to use exclusively for counseling and will create a unique Facebook account for the study and only use it for their designated group. The time a user spends on Facebook each day can be found in settings under "Your Time on Facebook" [32]. Counselors will be asked to enter the

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minutes spent each day into a Research Electronic Database Capture (REDCap, Vanderbilt University) database each week. In the synchronous condition, counselors will enter the minutes spent preparing for and conducting the group meetings in a REDCap database each week.

Contamination

At 1 year and 2 years, survey items will assess whether participants engaged with each other outside of their assigned intervention modality, including in person, phone, email, social media, videoconference, or otherwise. They will be asked how many participants they engaged with through these alternative means and how many contacts they had. We will also assess if they engaged in any form of online or in-person weight loss programs so that this can be controlled for in the analyses.

Sample Size Estimation

We powered this trial to detect noninferiority for the primary outcome, percent weight loss at 6 and 12 months. We determined the sample size using methods developed for noninferiority trials [33]. In this noninferiority trial, the null hypothesis is that the asynchronous condition is inferior to the synchronous condition and the alternate hypothesis is that the asynchronous condition is noninferior to the synchronous condition. "Not inferior to" is defined by the noninferiority margin, δ. Here, we set δ=2%, based on a clinically meaningful difference in mean weight loss between the two conditions. Thus, adequate power for clinical noninferiority requires a sample size such that there is a better than 90% probability that the lower limit of the CI lies above –δ, if the true effect size is zero or above. We will use an SD of 5.5% based on our previous trial [7]. With α=.05, and δ=2%, we have 90% power to conclude that the asynchronous condition is not inferior to the synchronous condition with 131 participants per arm. Assuming 20% attrition, we will enroll 328 participants (164 per arm). Weight loss maintenance will be tested in a longitudinal design, assuming 5 time points (including pretest, 6, 12, 18, and 24 months) clustered within individuals. From the conservative perspective of the inferiority effect size, δ=2%, SD 5.5%, with α=.05, and intraclass correlation coefficient (ICC) 0.6, this trial will have power of 97.6% to yield a statistically significant result with a sample size of 328 participants.

For engagement, we have 80% power to detect differences of ≥0.26 SDs in engagement (word count) between conditions. With 164 participants available per arm (N=328) and α=.05, we have 90% power to detect differences in mean cost per participant of 0.36 SD. For example, if the SD for cost is US $100, then we have 94% power to detect differences in mean cost per participant of US $35. In our previous noninferiority trial comparing a synchronous in-person lifestyle intervention to an asynchronous remote lifestyle intervention, the difference in cost per participant was US $82.66 [7]. We suspect the difference will be less in this trial because travel costs contributed to the difference in our previous trial which used an in-person condition.

In terms of engagement during the Peer Led Maintenance Phase, we have 80% power to detect differences of ≥0.79 SDs in engagement (word count) between conditions.

Analytic Plan

Reporting and data analyses of this trial will follow the recommendations laid out in the study by Piaggio et al [34]. We will use an intention-to-treat approach, meaning all randomized participants will be included in the model in their originally randomized conditions. We will evaluate the comparability of baseline characteristics by condition. If groups differ on any variables, those variables will be used as covariates in the primary analyses. Other preliminary analyses will include assessing patterns of missing data, dropout rates, distributional properties of dependent measures, and correlations among outcome measures. Attrition in weight loss studies may not be random [35,36]. We will perform a series of sensitivity analyses to understand the extent of potential bias by assuming the subjects who dropped out are missing completely at random (ie, independent of the outcome), are responders to the intervention, or are nonresponders to the intervention. We will have quality checks to make sure our missing data is minimal but if we have more than 5% data missing, we will use multiple imputations [37,38].

We will model percent weight loss at 6 and 12 months using a general or generalized (depending on outcome distribution characteristics) linear regression model framework, with percent weight loss as the dependent variable and intervention condition as the independent variable, and include any unbalanced participants' characteristics as covariates. This model will provide a statistical test of the intervention effect and the estimated coefficient, and the estimated CI will provide the estimate of the intervention effect. Our analytic approach aims to test whether the asynchronous condition is not appreciably worse than (ie, not inferior to) the synchronous condition by our a priori inferiority margin of 2%. The effect size reveals clinical noninferiority of the asynchronous condition if the CI lies completely above the noninferiority margin (2%). Weight loss maintenance at 18 and 24 months will be analyzed using the same approach described for aim 1, and we will examine if the CI lies completely above 0 to test if the asynchronous condition has greater weight loss.

For engagement data, we will compare conditions on word count and proportion of the 4 language dimensions (analytical thinking, clout, authenticity, and emotional tone) at 6 months, 1, and 2 years using the same statistical model as described for the primary outcome and test if the resulting CI contains 0. We will graphically explore distributional assumptions and adapt the analyses, if necessary, fitting the most appropriate distribution. We hypothesize that the mean word count per participant will be higher in the asynchronous condition at 1 year and 2 years. Exploratory analyses will compare conditions on the 4 language dimensions at 1 and 2 years as well. Intervention and participant costs per participant will be computed and average costs will be compared across conditions. As Ritzwoller et al [31] recommends, we will perform sensitivity analyses to estimate the range of intervention costs after varying the inputs. We will estimate a range of costs based on varying assumptions. We will compare conditions on total program costs per participant and total program costs per pound lost. Assuming a normal distribution of total costs per participant, we will first compute *t* tests comparing the average cost per

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participant across treatment conditions. We will test the null hypothesis of no difference between groups using a 2-sided test and α=.05. If the total cost per participant is not normally distributed, a nonparametric approach using the Mann-Whitney test for median comparisons will be used. If participant characteristics are found to differ according to treatment allocation, general or generalized multivariable methods will be used to adjust for the potential confounding effects of these characteristics. Assuming a normal distribution of total costs per participant, multivariable general linear regression models will be used. If not normal, generalized linear models will be used. We hypothesize that the asynchronous condition will cost less per participant (and less per pound lost) than the synchronous condition.

Ethical Considerations

This trial was approved by the University of Connecticut Human Subjects Institutional Review Board (H23-0383) and is registered on ClinicalTrials.gov (NCT06393725). Possible risks of participating in this trial include exercise-related injury, accidental exposure of personal information, discomfort with study procedures, or an unpleasant interaction with another group member in the group-based intervention. The exercise part of the intervention emphasizes moderate intensity physical activity to reduce the likelihood of discomfort, pain, or injury. The intervention provides guidance on how to do exercises safely to avoid pain or injury. Participants reporting discomfort will be advised to contact their primary care doctor. By excluding people who cannot walk unaided for one-fourth of a mile and those with chronic pain or a medical condition that inhibits their ability to exercise, we reduce the risk of injury. To avoid accidental exposure of personal information, tracking data will be stored electronically in REDCap, a network secure data entry program, and in the UConn-supported R drive which is secure. Only those who have institutional review board approval to work on the study will have access to the R drive and REDCap database for this study. Participants will be informed that they may withdraw from the study at any time if they feel discomfort with any of the study procedures or if they do not want to answer a question on a survey, they can skip it. Participants will be asked to report to their assigned counselor if any comments or conversations in the group make them uncomfortable so that steps can be taken to prevent a recurrence.

Results

Recruitment will occur from October 2024 to July 2025. Data collection will end on June 2027 and be followed by data analyses. Results will be reported on ClinicalTrials.gov and in a published manuscript.

Discussion

Significance of the Study

Obesity affects over 85 million adults in the United States [39]. The workforce needed to make traditional clinic or community-based lifestyle interventions available to all who need them simply does not exist. Intervention approaches that have few barriers to participation and are scalable, sustainable, and low-cost are greatly needed. The rapid shift to telehealth during the COVID-19 pandemic has increased the demand for remote care among the public and health care systems, and necessity has given patients and providers opportunities to learn telehealth skills. The pandemic has also led to a broadening of telehealth reimbursement policies and many of those policies have become permanent [40]. However, reimbursement is limited to synchronous telehealth care (eg, video and calls). Expansion of reimbursement policy to asynchronous care will require evidence for efficacy. Such evidence has been accumulating for behavioral treatments for depression [15,41-43] but is greatly needed for obesity as well. Given how much communication habits have shifted to asynchronous forms (eg, text, email, and social media) in recent years, it is time to examine asynchronous approaches to behavioral interventions. The urgency to produce evidence for innovative telehealth solutions has never been higher and the rapid uptake of telehealth resulting from the pandemic presents opportunities for growth and innovation. Our goal is to produce evidence for an asynchronous lifestyle intervention that is scalable and sustainable.

Limitations

This study has several limitations. First, lifestyle interventions typically attract predominantly white and female samples [23], which means the literature this study was based on may not be generalizable to more diverse samples. We will use a targeted recruitment approach to attract men and minority populations to prevent this issue. Second, people who are not Facebook users will be excluded, which may also affect the generalizability of the results. Facebook is the most popular social media platform that 68% of US adults report using [44]. The rationale for using Facebook to deliver a lifestyle intervention is to bring content to them on a platform they already use. Studies should explore whether nonusers would be amenable to receiving a lifestyle intervention on Facebook and the barriers that exist for those who prefer not to use Facebook for this purpose. Third, weight data will be collected through digital scales that we ship to participants which prevents us from being physically present when they weigh themselves and ensuring they weigh themselves unclothed and after voiding as instructed. To prevent errant values, we contact participants who lose or gain >5 pounds in a single week or gain ≥5% of their baseline weight at a follow-up visit to verify accuracy and identify the cause if known. By conducting the trial remotely, we can recruit more diverse samples without geographical limitations.

Conclusions

This work has a high potential for impact in that it could establish evidence that an asynchronous lifestyle intervention that can treat >80 patients at a time is noninferior to a synchronous remote lifestyle intervention in weight loss at both 6 months and 1 year, but superior in sustainability and possibly weight loss maintenance, while also being lower in cost per pound lost. This work will produce a library of 2 years of asynchronous lifestyle intervention content that is suitable for delivery via online platforms and training materials for interventionists and support staff members. This could be used

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by clinics, large employers, or insurers who could then conduct programs for their target populations. Given the vast ecosystem of patient communities on Facebook, in a future hybrid effectiveness-implementation trial, we plan to partner with leaders of large patient-led Facebook groups to offer this programming to interested members in separate private groups.

Acknowledgments

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Data Availability

The datasets generated will be available at the NIDDK Central Repository. Data will be available within 1 year after the award ends and be available for 10 years. We will include the DOI in relevant publications.

Authors' Contributions

SP conceived of the research question and methodology, has supervision responsibilities, and drafted and edited the manuscript. RX drafted the analytic plan and sample size estimation and will conduct statistical analyses and data visualization. RB, CI, JG, and DF reviewed and edited the manuscript. DF and RB have project administration, investigation, and supervision responsibilities. RB has data curation responsibilities. All authors read and approved of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Lifestyle Change and Behavioral Health Study Section (LCBH) - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 127 KB - resprot_v13i1e65323_app1.pdf]

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Abbreviations

DPP: Diabetes Prevention Program
ICC: intraclass correlation coefficient
LIWC-22: Linguistic Inquiry and Word Count
REDCap: Research Electronic Data Capture

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Protocol

Prehabilitation Exercise Training to Target Improved Muscle Strength in Pretransplant Patients Diagnosed With Multiple Myeloma: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Muscle mass and strength are severely compromised in patients diagnosed with multiple myeloma, such that the risk of poor overall survival increases as the prevalence of low muscle mass, also known as sarcopenia, increases. Additionally, at the time of autologous stem cell transplant (ASCT), 51% of patients experience low muscle mass and strength, which can prolong hospitalization and lead to increased risk of obesity, insulin resistance, lowered physical function, and poor quality of life.

Objective: The PROTECT (Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation) trial will examine the preliminary effects of digitally supervised prehabilitative aerobic and resistance exercise on muscle strength in patients with multiple myeloma scheduled for ASCT.

Methods: This prospective, 2-armed single-center randomized controlled trial will recruit 30 patients with multiple myeloma, aged 18 years and older, planning to receive ASCT. Individuals will be assigned to either the exercise or the waitlist control group. The 8-week exercise intervention is home-based and digitally supervised by a clinical exercise trainer. The frequency of the exercise intervention is 3 times per week consisting of aerobic exercise on a cycle ergometer and resistance exercises, which are individually tailored based on patient health status. The waitlist control group maintains normal daily activities of living and is offered the intervention within 6 months from ASCT. The primary outcome is lower limb muscle strength, measured using the 10-repetition maximum leg press or extensor strength. Additional outcomes include physical and cardiorespiratory function, patient-reported outcomes, cardiometabolic health outcomes, and clinical outcomes.

Results: The trial was funded in the fall of 2022 and recruitment began in June 2023. As of August 2024, a total of 3 participants have consented and been randomized (n=1, exercise group; n=2, waitlist control group). Trial completion and start of data analysis is expected in July 2025 with expected results to be published in early winter of 2026.

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Conclusions: We expect exercise to improve lower limb muscle strength and overall health outcomes compared to the waitlist control group. Results will contribute foundational knowledge needed to conduct larger-phase clinical trials testing the clinical benefits of prehabilitation exercise in this patient population. This study will provide insight into a prehabilitative exercise intervention designed to support patient prognosis.

Trial Registration: ClinicalTrials.gov NCT05706766; https://clinicaltrials.gov/study/NCT05706766

International Registered Report Identifier (IRRID): DERR1-10.2196/64905

(JMIR Res Protoc 2024;13:e64905) doi:10.2196/64905

KEYWORDS

multiple myeloma; stem cell transplantation; exercise training; aerobic exercise; resistance exercise; preoperative exercise; muscle strength; physical fitness

Introduction

Background

Across diseases with transplant-eligible patients, multiple myeloma diagnoses make up 35% of autologous stem cell transplants (ASCT) [1,2]. Due to advancements in this routine noncurative therapy that replaces diseased bone marrow with healthy blood stem cells, life expectancy has been extended by an estimated 5-10 years in patients with multiple myeloma [3]. However, patients with multiple myeloma who receive ASCT often experience physical deconditioning prior to ASCT [4], which leads to a reduced ability in activities of daily function [5] that may contribute to loss of muscle mass and strength. Lowered skeletal muscle mass, a characteristic of sarcopenia, prior to ASCT is correlated with postoperative complications [6]. Patients receiving ASCT, who can experience sarcopenia or sarcopenic obesity at the time of transplant, have an increased risk of worsened overall survival [7].

Patients with multiple myeloma who participate in the ~150 minutes of exercise, as recommended by the American College of Sports Medicine [8,9], experience better clinical outcomes including revised myeloma comorbidity index scores, treatment tolerance, length of hospital stay, remission status, overall survival, and progression-free survival compared to age-matched inactive patients [10]. Physical fitness outcomes, such as muscle strength and cardiovascular fitness, along with quality of life and fatigue, are improved in patients with multiple myeloma who undergo aerobic and resistance exercise training [11]. Previous trials have shown progressive aerobic and resistance exercise training as safe with no adverse events [12], particularly when implemented post-ASCT in patients with multiple myeloma [11,13]. Moreover, preliminary feasibility data indicates challenges with in-person attendance during the pre-ASCT phase and presents the opportunity to study a digitally supervised prehabilitation model to support already suppressed activity levels in this population [14]. With the intent to optimize muscle strength and physical fitness, precise exercise prescription (ie, intensity, duration, and frequency) is currently unclear, given the different exercise program modalities used in patients with multiple myeloma over the past 2 decades [12,13,15-20].

Objectives

The goal of this randomized controlled trial, "Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation: The PROTECT (Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation) trial (Figure 1)," is to assess the impact of digitally supervised, individually tailored prehabilitative aerobic and resistance exercise in patients with multiple myeloma undergoing ASCT (Figure 1) on lower limb muscle strength (primary objective) in the exercise group compared to the waitlist control group. The secondary and tertiary objectives will examine physical capacity (physical function and cardiorespiratory fitness) and patient-reported outcomes (fatigue and quality of life), cardiometabolic health outcomes (biomarkers and body composition), along with posttransplant clinical outcomes including Hematopoietic Cell Transplantation-Comorbidity Index, length of hospital stay, readmission rates, and treatment-related adverse events. Finally, due to the nonprofound changes given the limited intervention period, the exploratory objective is to evaluate the exercise intervention completed post-ASCT on muscle strength, physical capacity, patient-reported outcomes, and cardiometabolic health outcomes. We hypothesize that prehabilitative aerobic and resistance exercise will improve lower limb muscle strength prior to receiving ASCT and 30 days posttransplant in the exercise group compared to the waitlist control group.

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Figure 1. Conceptual framework of the PROTECT Trial. ASCT: autologous stem cell transplant; PROTECT: Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation.

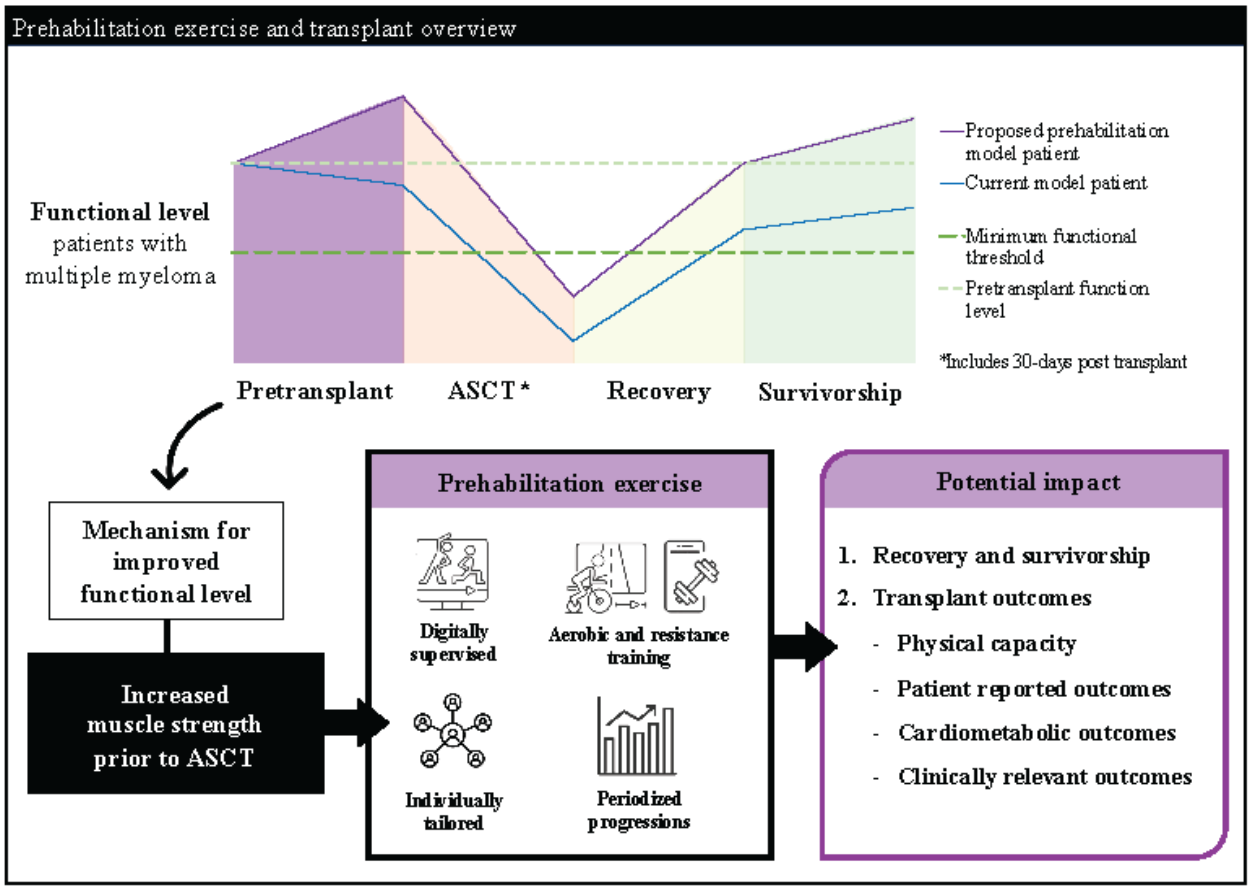

Methods

Study Design

The PROTECT trial is a prospective, single-center, two-arm randomized controlled trial conducted at the Dana-Farber Cancer Institute (Boston, Massachusetts). Patients with multiple myeloma scheduled to receive ASCT are randomly assigned to one of two groups: exercise group or waitlist control group. The study schema and timeline (Figure 2) involve an 8-week intervention with a 30-day posttransplant follow-up. This study protocol is in accordance with the Consolidated Standards of Reporting Trials guidelines [21].

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Figure 2. Study outline for the PROTECT Trial. ASCT: autologous stem cell transplant; PROTECT: Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation.

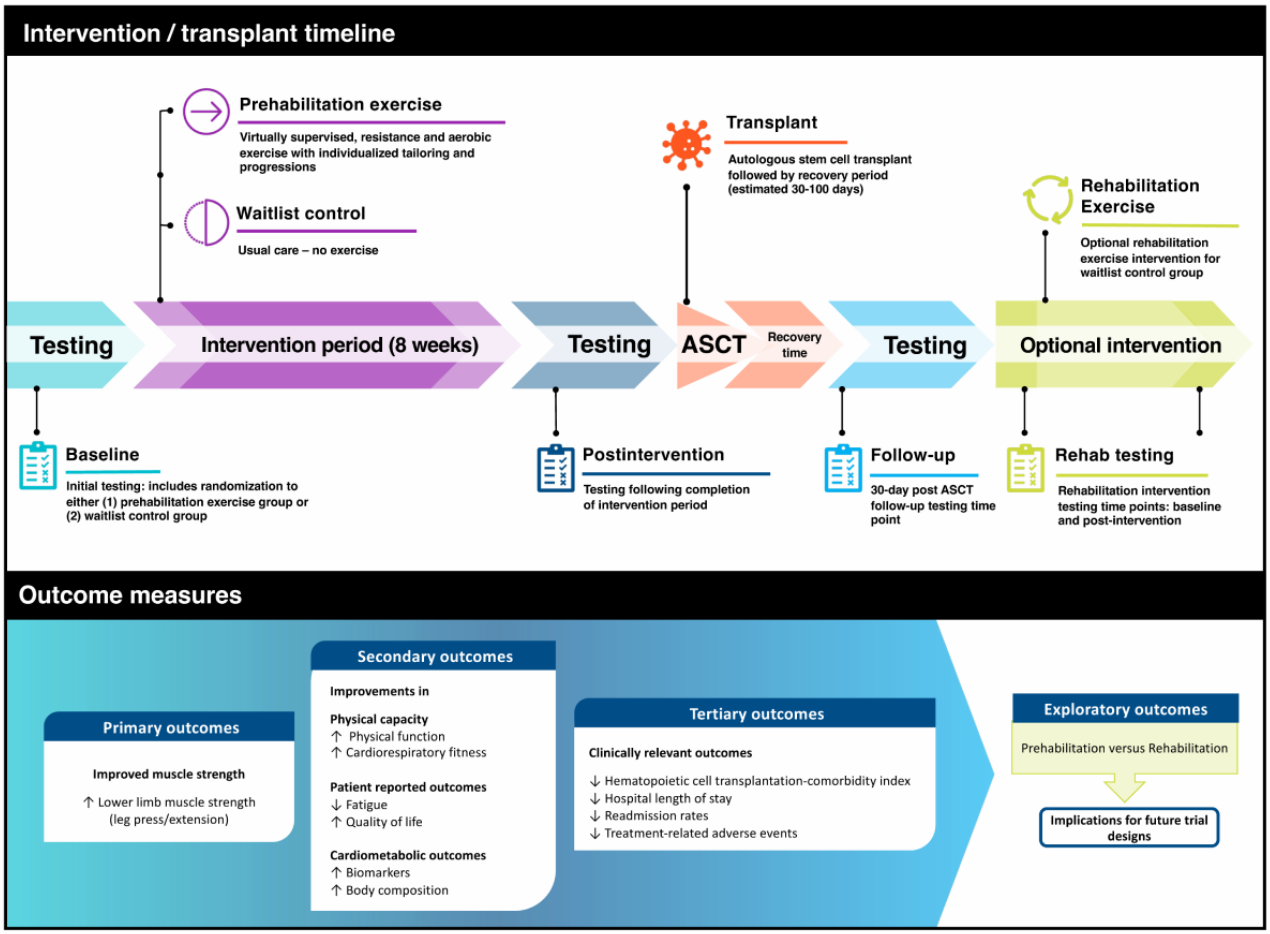

Participants and Recruitment

This trial includes patients diagnosed with multiple myeloma who are scheduled to receive ASCT with the full inclusion and exclusion criteria depicted in Textbox 1. Potential participants will be identified at the Dana-Farber Cancer Institute through various recruitment strategies including screening hematologic oncology clinic lists, and use of patient advertisements in waiting areas. A study coordinator contacts the patients' treating providers or oncologists to request permission to contact potential participants who are identified through patient lists. Further screening of potentially eligible participants is conducted by study staff in person or by phone to confirm remaining eligibilities, which includes the use of the Godin Leisure-Time Exercise Questionnaire [22] to assess physical activity history and using questions similar to the Physical Activity Readiness Questionnaire to assess patient's health status [23]. Patients interested in participating are scheduled for a digital or in-person visit to review the protocol and sign informed consent, with the option to sign consent electronically.

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Textbox 1. Inclusion and exclusion criteria of the PROTECT Trial.

Inclusion criteria

- Aged 18 years and older.
- All patients will have a diagnosis of multiple myeloma, referral to the Dana-Farber Cancer Institute transplant team, and assigned to the autologous transplantation waiting list for a first transplant.
- Planning to receive autologous stem cell transplant after 6 weeks with or without concurrent neoadjuvant treatments at Dana-Farber Cancer Institute.
- Medical clearance to perform moderate to vigorous intensity aerobic and resistance exercise intervention and fitness testing by their treating physician or a certified clinical exercise physiologist.
- Speak English.
- Currently participating in less than or equal to 60 minutes of structured moderate to vigorous intensity exercise per week.
- Willing to travel to Dana-Farber Cancer Institute for necessary data collection.
- Ability to understand and the willingness to sign a written informed consent document.
- The effects of exercise on the developing fetus are unknown. For this reason, women of child-bearing potential must agree to undergo a pregnancy test and to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for 6 months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating in the trial, she should inform her treating physician immediately.

Exclusion criteria

- History of unstable angina, abnormal resting electrocardiogram or unstable angina, or a heart attack in the previous month to allow safe completion of the cardiopulmonary exercise test or VO_2 (maximum rate of oxygen consumption) peak test.
- Patients with known spinal instability, spinal cord compression or neurological deficits, or contraindications that preclude exercise.
- Those who have had recent (within 6 weeks) spinal surgery or other intervention surgery or pathological fractures.
- Those deemed unsuitable to partake by the transplant or study team.
- Patients at high risk of impending pathologic fracture of a weight-bearing bone (including spine, hip or femur, and humerus) as determined by a physician.
- Unable or unwilling to undertake an exercise program on a regular basis.
- Pre-existing musculoskeletal or cardiorespiratory disease, or metabolic diseases that could exacerbate with exercise, in addition to other conditions deemed unsafe by physician.
- Patients with other active malignancies requiring active therapy.
- Participate in more than 60 minutes of structured moderate to vigorous intensity exercise per week.
- Unable to travel to Dana-Farber Cancer Institute for necessary data collection.
- Participants, who in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

Ethical Considerations

Approval of the trial protocol was obtained from the institutional review board at the Dana-Farber Cancer Institute (22-403) and registered at ClinicalTrials.gov (NCT05706766). All participants review and sign an informed consent document that includes the option to opt-out at any point during the trial. Per Dana-Farber Cancer Institute policy, all patient identification information is deidentified. Participants are provided compensation (US $25) for each testing visit completed in the form of a cash spending card.

Randomization and Blinding

Participants are randomly assigned to either the exercise group or the waitlist control group in a 1:1 ratio following the completion of baseline assessments. Prior to the trial start, the study biostatistician prepared the randomization schema and provided the randomization allocation to staff through a web-based application (REDCap [Research Electronic Data Capture]; Vanderbilt University) [24] to blind study investigators to the randomization process. The nature of the exercise intervention prevents blinding the study participants, interventionists, and outcome assessors. However, study investigators adhere to a set protocol to standardize outcome assessments and avoid bias.

Prehabilitative Aerobic and Resistance Exercise Intervention

Overview

The exercise group receives a prehabilitative, home-based, digitally supervised multimodal (aerobic and resistance) 8-week exercise program led by a clinical exercise trainer. The program consists of 24 sessions that are conducted three times per week for eight weeks, with each session approximating 60-90 minutes. Blood pressure will be assessed with an automatic blood pressure cuff prior to the start of each session and heart rate (HR) will be monitored using a real-time HR monitor (ie, Fitbit

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watch), both devices are provided to the participant. Each session includes a 5-minute warm-up of low-intensity aerobic exercise, prescribed as 57%-64% of HR maximum [25], and a cool-down stretching period with 3-4 static stretches that target major muscle groups, held for 30 seconds each. The aerobic intensity and resistance load for each exercise are determined through one-repetition maximum (1RM) and peak oxygen consumption, respectively, during baseline testing. A qualified exercise trainer will individually tailor training, with gradual progression based on current exercise guidelines and principles during the digitally supervised sessions [26].

Upon completion of baseline testing, patients randomized to the exercise group are provided an introductory session in-person for exercise familiarization delivered by a clinical exercise trainer that will include an overview of the exercise program and coach a reduced sample exercise session to ensure activation of target muscle groups in each exercise. The intervention systematically progressed (Table 1) from low intensity and gradually increased to high intensity over the 8-week duration based on patient health status and ability. Enrolled patients will be provided, at no cost, a Wi-Fi–enabled tablet for digital delivery of training, a stationary bike, and sets of adjustable resistance bands. Each session will include 5 resistance exercises with 1 core exercise, and up to 20 minutes of aerobic cycling.

Table 1. Progression model for the prehabilitative aerobic and resistance exercise intervention.

Intervention time point	Resistance exercise progression[a]			Aerobic exercise progression	
Intervention timepoint	Intensity (%1RM[b])	Sets	Repetitions	Intensity (% HR^{c}_{max})	Duration (minutes)
1	50	2	12-15	60	15
2	55	3	12-15	60	15
3	60	3	12-15	65	15
4	60	3	12-15	65	15
5	65	3	10-12	70	20
6	65	3	10-12	70	20
7	70	3	8-10	75	20
8	70	3	8-10	75	20

[a]Resistance exercises: up to 3 upper body, 3 lower body, and 1 core exercises will be selected. Depending on the daily needs of the participant and bone lesion site, alternative exercises may be prescribed at the discretion of the exercise trainer.

[b]1RM: one-repetition maximum.

[c]HR: heart rate.

Resistance Exercise

Resistance exercise will target upper and lower body muscle groups with each exercise performed as 2-3 sets of 8-15 repetitions at intensities 50%-75% 1RM. Resistance exercise training will be performed using body weight and progressed with elastic resistance bands of various strengths in accordance with individual patient health. Resistance training will start at 50% of the participant's 1RM and increase in intensity every two weeks by 5% or 10% until the goal of 70% 1RM is reached. The number of repetitions will increase in order for participants to perform 3 sets of 8-10 repetitions by week 8. Rest periods of ~60 seconds will be counted between each set of resistance exercises. The clinical exercise trainer will make adjustments for patients who progress beyond the estimated weights from the 10RM testing or are unable to meet the prescribed intensities.

Aerobic Exercise

Prescribed aerobic exercise will target cardiovascular health and lower limb strength through 15- to 20-minute training bouts consisting of a 60%-75% HR maximum. Digitally supervised sessions are tailored by clinical exercise trainers using gradual progressions based on current exercise guidelines and principles [26]. Aerobic exercise will begin at 60% HR maximum and progress in an alternating fashion in either intensity or duration, by 5% or 5-minute increments, respectively, each week. Appropriate exercise intensity will be maintained using a HR monitor during each session.

Measures During Exercise Sessions

At the start of each training session, the clinical exercise trainer will use the Therapy-Related Symptom Checklist to assess and identify participant-reported symptom occurrence and severity in each exercise session [27]. The clinical exercise trainer will record participants verbal responses, at the start and end of each session, to the Exercise-Induced Feeling Inventory, which assesses an individual's feeling state postexercise and is also used for the assessment of self-motivation to adhere to an exercise regimen [28].

Waitlist Control

The waitlist control group will receive usual care during the initial visit that includes counseling about the details of the surgery and anticipated recovery. Participants in the waitlist control group will be offered the PROTECT intervention and exercise resources within 6 months of the end of the study period (after the 30-day post-ASCT follow-up time point), based on the desired participant start date.

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Outcome Measures

Overview

The outcomes are assessed at baseline, postintervention, and 30-day posttransplant follow-up. All measures are performed by trained study personnel at the Dana-Farber Cancer Institute. Postintervention assessment (week 10; visit 27) includes a reassessment of baseline measures. The 30-day post-ASCT follow-up (week 14-15; visit 28) consists of a reassessment of baseline measures (not including dual-energy x-ray absorptiometry [DEXA]) in addition to Hematopoietic Cell Transplantation-Comorbidity Index, length of hospital stay, readmission rates, and treatment-related adverse events. If the intervention is selected following the ASCT recovery period, the waitlist control group testing (visits 29-54) includes assessment of baseline measures (not including DEXA) pre- and postintervention (visits 29 and 54, respectively).

Primary Outcomes—Lower Limb Muscle Strength

Percent change in lower limb muscle strength is the primary outcome. The 1RM value will be estimated from 10RM muscle strength tests on the leg press or leg extension. The test selected is dependent on the bone lesion site and the participant's health status. Additional strength testing using approximately 5 resistance band exercises individually selected for participants based on health status; 1RM values will be calculated and reported using validated equations [29,30]. Alternative strength exercises will be used to ensure participants' safety as needed for both testing and training periods. Following a warm-up, 3-5 attempts will be given to reach the final 10RM load with a 2-minute rest period between attempts.

Secondary Outcomes

Physical Capacity

Physical capacity, in this study, is comprised of physical function measures (a total of five) and cardiorespiratory fitness.

Physical function is assessed by the Short Physical Performance Battery, a validated measure that includes 3 sections [31]. This includes the following three lower extremity measures, all held for 10 seconds or when the participant steps out of position, (1) timed balance is assessed through the side-by-side stand, semitandem stand, and tandem stand. (2) Gait speed is assessed through the time recorded over a 4-meter distance and participants are allowed two attempts. (3) Chair stand is performed through a single chair stand and five repeated chair stands in quick succession that are timed to completion.

Physical function is also assessed through the Margaria Stair Climb, Timed Up-and-Go test, Sit-to-Stand test, and handgrip strength. The Margaria Stair Climb measures functional power using a stair climb test that has been successfully performed and correlated with lower-extremity power and mobility performance in older adults [32]. Participants ascend a flight of 10 stairs one step at a time as quickly as possible without hand support and the average time from the third to the ninth stair, out of 3 trials, is calculated to the nearest 0.01 second. The Timed Up-and-Go test assesses mobility and has been shown to predict immediate fall risk better than static balance tests or isometric muscle strength [33]. Participants begin seated in a chair with hands on the armrests and are asked to rise, walk to a line on the floor 3 meters from the chair, turn around, and return to the same seated position as quickly and safely as possible. Scores are taken as the average time of three trials to complete the task. The Sit to Stand test includes participants rising to a full standing position and sitting back down repeatedly for 30 seconds, the total number of repetitions is recorded. Finally, grip strength is measured using a hand-held dynamometer on the participant's dominant hand, where they grip the handle of the dynamometer with one hand with as much pressure as possible for three seconds.

Cardiorespiratory fitness (functional aerobic capacity) is assessed as VO_{2peak} (peak aerobic capacity) during exercise exertion testing on a stationary bike, where participants complete a maximal cycling protocol that comprises a 10W increase in workload every one minute, starting at 40W and concludes when the participant is unable to physically cycle.

Criteria for VO_{2peak} must meet two of the three following criteria: (1) participant reports the reason for stopping the test is due to dyspnea or muscular (leg) fatigue or a similar description indicating volitional fatigue or exhaustion as evaluated by the qualified exercise physiologist; (2) respiratory exchange ratio≥1.10; and (3) rating of perceived exertion (RPE)≥7 on the 0-10 Borg scale. During the test, gas exchange is measured by a metabolic cart (TrueOne 2400, ParvoMedic Inc, Salt Lake City, Utah) and VO_{2max} is determined as the highest oxygen value obtained at maximal exertion. HR (Polar USA, Lake Success, New York) and RPE (Borg CR10 scale) [34] are recorded during the test. If maximal testing is not permitted or unable to be performed, participants may complete the YMCA submaximal cycling protocol to measure estimated maximal aerobic capacity and maximal power output. The initial workload will be set at 150 kg/min and includes three-minute intervals. The predicted maximum workload and oxygen uptake will be determined using the plotted points of the HR versus workload (kg/m/min) and the participant's estimated HR max (220-age) [35].

Participant Reported Outcomes

Various aspects of psychosocial outcomes are assessed using validated questionnaires, including the PROMIS Cancer Fatigue Short Form to assess fatigue [36,37], the Vulnerable Elders Survey-13 to predict functional decline and mortality [38,39], and the Clinical Frailty Scale, to evaluate, evaluates comorbidity, function, and cognition [40]. The Functional Assessment of Cancer Therapy–Multiple Myeloma is a 41-item measure for quality of life in patients with multiple myeloma [41]. The Functional Assessment of Cancer Therapy-Bone Pain assesses bone pain and its effect on the quality of life and changes in response to treatment [42]. The Brief Pain Inventory short version is a 2-factor questionnaire to assess location and pain severity using a visual diagram and has been validated in patients with cancer [43,44]. The Hospital Anxiety and Depression Scale is a self-rated scale to assess psychological distress [45]. Finally, sleep quality will be assessed using the Pittsburg Sleep Quality Index, which contains 19 questions evaluating 7 domains of sleep- subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep

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disturbances, use of sleep medication, and daytime dysfunction [46,47].

Cardiometabolic Outcomes

Fasting (12-hour fast) blood is drawn from the antecubital vein (~30 cc) by a trained phlebotomist. For each sample, a total of six 10 mL tubes will be collected, three ethylenediaminetetraacetic acid and three Serum tubes, along with one additional lavender-topped tube (whole blood in ethylenediaminetetraacetic acid), for a total of 62 mL of blood drawn at each testing timepoint. Samples are centrifuged and then aliquoted and stored at –80 °C for future measures. Blood samples will be transported to Brigham Research Assay Core near the study end for batch-testing analysis of glucose, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, insulin, insulin resistance (Homeostatic Model Assessment for Insulin Resistance), triglycerides, and glycosylated hemoglobin. Future measures will include the analysis of additional biomarkers.

Lean mass, fat mass, and body fat % are obtained from the whole-body DEXA scan (completed only at baseline and postintervention testing timepoints). Premenopausal participants complete a pregnancy test (urine sample) prior to the body composition assessment to ensure the participant is not pregnant. BMI in kg/m^2 will be calculated from height and weight. A constant tension tape measure is used to obtain waist circumference defined as the distance around the waist using the umbilicus as the reference point. A constant tension tape measure is used to obtain hip circumference defined as the distance around the widest girth of the buttocks using the greater trochanter as a landmark. Body composition is assessed via bioelectrical impedance using a validated device (Tanita 780, Arlington Heights, Illinois). The device will estimate body fat using an algorithm based on age, sex, height, and body weight.

Tertiary Outcomes—Posttransplant Clinical Outcomes

Posttransplant clinical outcomes are assessed through a review of patient medical records and include the Hematopoietic Cell Transplantation-Comorbidity Index, length of hospital stay, readmission rates, and treatment-related adverse events.

Exploratory Outcomes

The treatment trajectory for patients with multiple myeloma incorporates prehabilitation and rehabilitation, though when a patient experiences the most benefit is unclear, as they occur at different stages of the treatment trajectory. Therefore, a self-controlled single-group analysis will be done on the participants from the waitlist control who elect the exercise program post-ASCT to assess how an 8-week exercise intervention completed post-ASCT affects muscle strength, physical capacity, patient-reported outcomes, and cardiometabolic health outcomes.

Adverse Events

Participants are evaluated for potential adverse events (eg, pain, muscle soreness, nausea, and bone pain) during each exercise session in the study period. Phone numbers for study staff are provided to report potential intervention-related adverse events. The National Cancer Institute Common Terminology Criteria for Adverse Events V5 is used to assess participants and documented by the study staff at each exercise session. Study progress and injuries are reported upon during weekly meetings through in-person updates, phone calls, or weekly email updates. Adverse events, both serious and nonserious, and deaths encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention sessions, are followed to resolution, or until the principal investigator determines the participant as stable or the event as irreversible, or the participant is lost to follow-up.

Sample Size

We anticipate recruiting 1-2 participants per month, based on the accrual rates (3 to 4 participants per month) of previous exercise intervention studies [48]. A total of 30 eligible participants will be entered into this study and randomly assigned to the intervention and the control groups in a 1:1 ratio (15 per group). The sample size is based on general recommendations (24 to 50) for pilot studies in general [49-51] and this study provides 80% power to detect the effect size of Cohen d=1.15 (taking account of 10% dropout) at .05 two-sided α level.

Statistical Analysis

The primary analysis is a mean difference in percent change from baseline (week 0, preintervention), between the intervention and the control groups in lower leg muscle strength over 2 time points: pretransplant (week 9, postintervention), and posttransplant (week 14-15, 30-day post-ASCT follow-up). Linear mixed-effects models are used to compare the between-group differences at postintervention and follow-up after adjusting for baseline value of the outcome and covariates, where the intervention indicator and time are included as fixed effects and participants are included as random effects. From previous studies, the estimated standard deviation of change in muscle strength (measured through leg press) from baseline to pretransplant is 16.8 kg. Thus, this study will detect a between-group mean difference of 19.3 kg with 80% power. The primary analyses will be based on the intention-to-treat principle including all randomized participants. The same analyses will also be performed with the per-protocol population.

To test hypotheses related to differences in physical capacity, patient-reported outcomes, and cardiometabolic health outcomes across groups at study completion, standard statistical techniques are used to assess within-group differences among each end point (ie, 2-tailed t test or Wilcoxon signed rank test, proportions, and corresponding 95% exact CI, etc) and between-group differences (ie, 2-tailed t tests, two-sample Wilcoxon tests, generalized linear mixed-effects model for longitudinal measurements, and so on). As an exploratory analysis to assess group differences, each clinical outcome as continuous variables (ie, length of hospital stay and the number of comorbidities) and categorical variables (ie, hospital readmission) is analyzed using 2-sample t tests for continuous variables and Fisher exact test will be used for analyzing categorical variables. An exploratory analysis to assess differences in the postintervention self-elected exercise for the waitlist control group will be assessed for end points of aim 1-2

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using paired *t* tests and Cohen d is calculated to determine the effect size.

Results

The trial was funded in 2022 (DFCI McGraw/Patterson Research Fund from the Division of Population Sciences at the DFCI)). As of October 2024, a total of 3 participants have consented and been randomized (n=1, exercise group; n=2, waitlist control group). Trial completion and start of data analysis is expected in July 2025 with expected results to be published in early winter of 2026.

Discussion

Expected Findings

The primary purpose of the PROTECT Trial is to investigate if an 8-week digitally supervised prehabilitative exercise intervention improves lower limb muscle strength in patients with multiple myeloma. The PROTECT Trial provides a comprehensive assessment of physical capacity, patient-reported health outcomes, and cardiometabolic health as secondary outcomes, and evaluates patient posttransplant outcomes as tertiary outcomes. Furthermore, we will examine the effects of the patient's self-elected exercise intervention following the ASCT recovery period to explore the benefits of prehabilitative versus rehabilitative exercise.

Outcomes from the PROTECT Trial will provide vital information on muscle strength development using a prehabilitative exercise modality in a patient population with low health status. Various exercise modalities targeting muscle strength have been assessed across cancers, with the most highly studied in breast, prostate, and colorectal cancers, and few interventions implemented within patients with multiple myeloma.

The goal of the proposed exercise intervention in the PROTECT Trial is to improve muscular strength in patients with multiple myeloma, a population more advanced in age (ie, 31.2% aged 65-74 years) [52]. The development of sarcopenia, as a result of disease-related physical inactivity due to immobility or disability (ie, fatigue in response to induction therapy, bone pain as a result of lesions due to disease progression) [53], is associated with post-ASCT complications in patients with multiple myeloma [7] and is indicated by decreased muscle strength [54]. Additionally, inflammation contributes to muscle wasting and may result from tumor cells releasing cytokines, though the biological mechanism of exercise and the inflammatory response is presently unclear in multiple myeloma [55,56]. Chronic low-grade inflammation, common in older adults (inflammaging), may also contribute to decreases in muscle mass, strength, and function (sarcopenia) through multiple pathways, primarily, mTORC1-mediated protein synthesis, metabolism, and mitochondrial biogenesis [56,57].

Proposed mechanisms for counteracting sarcopenia include reducing inflammation, promoting exercise-induced muscle hypertrophy, and decreasing fat infiltration following exercise (sarcopenic obesity) [58-60]. In fact, exercise training attenuates protein degradation signaling pathways and stimulates muscle protein synthesis, with overall anti-inflammatory and antioxidative effects that can mitigate both the sarcopenic effects and cancer-induced muscle wasting that occur [61,62]. In older adults specifically, muscle mass and function are improved with exercise, which increases the expression of insulin-like growth factor 1 and the subsequent increase of muscle protein synthesis [63]. Improved muscular function and strength following aerobic and resistance exercise interventions have been demonstrated in healthy adults and hematologic oncology populations [12,15,64]. Taking these processes and clinical populations into account, we hypothesize the proposed prehabilitative aerobic and resistance exercise intervention will target muscle protein synthesis to improve muscle strength in patients with multiple myeloma scheduled for ASCT.

Current evidence suggests muscle hypertrophy occurs with an estimated number of 18 resistance training sessions, performed over 6-10 weeks [65], which will be captured in the eight-week training period of the proposed exercise intervention. Effective resistance training oriented for hypertrophy consists of mechanical tension and metabolic stress [66] and promotes muscle protein synthesis in relation to muscle protein degradation [67]. The combination of increased muscle protein synthesis, decreased muscle protein degradation, and overall motor learning are supportive of pathways at the molecular level that lead to increased muscle mass, increased muscle force production, and overall physical strength [67]. Furthermore, resistance exercise has been implicated in stimulating the mTORC1 pathway (master growth regulator that senses and integrates diverse nutritional and environmental cues including growth factors, energy levels, cellular stress, and amino acids), which may improve mitochondrial function, increase muscle mass, and improve metabolic health, all in support of the development of muscular strength [62]. Hence, applying said principles of exercise to patients with multiple myeloma supports the primary outcome measure, improving muscular strength, of the PROTECT Trial.

Mechanisms for improvements in physical capacity, cardiometabolic health outcomes, and patient-reported outcomes along with posttransplant clinical outcomes, are described below. Exercise, particularly resistance training as noted above, stimulates muscle protein synthesis, leading to increased muscle mass and strength. However, resistance training also has the potential to improve endurance by enhancing mitochondrial function and improving motor control by neuronal growth. Cardiovascular adaptations increase oxygen transport capacity, cardiovascular health, and metabolic regulation, mitigating the risk of chronic diseases of aging. Additionally, exercise provides mental health benefits, reducing stress and enhancing cognitive function, potentially prolonging longevity and enhancing quality of life, particularly in patients with cancer undergoing pre- and posttransplant therapy.

Prehabilitative exercise, or exercise prior to medical treatment, has been successfully deployed in presurgical candidates and other tumor sites, yet there is a paucity of evidence on the effect of prehabilitation in patients receiving transplant; IMPROVE-BMT is an ongoing investigation to address this topic [68]. A recent study shows that a multimodal intervention program with partially supervised exercise training combined

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with nutritional support prior to transplant is feasible and safe. Patients showed improvements in fat-free muscle mass, physical performance, and health-related quality of life [69]. Additional research is needed to assess outcomes that support quality of life, overall survival, and relevant clinical outcomes along with the challenges of delivering the exercise in hospital and outpatient settings. Importantly, recent investigations indicate the acceptability and feasibility of delivering exercise prehabilitation, in person and digitally within the ASCT pathway in myeloma, but warrant further investigation on the combined effects and at the level of personalized or individualized therapy [70].

The prehabilitation intervention investigated in this study represents a novel approach to addressing the limited evidence on the benefits of prehabilitation. Prehabilitation, broadly recognized for its potential to enhance physical and psychological resilience, holds promise in optimizing outcomes for patients with cancer. Specifically, its application in the context of multiple myeloma remains understudied. The exploratory aims intend to examine the comparative effectiveness of rehabilitation versus prehabilitation, providing valuable insights into their respective contributions to patient well-being in this clinical setting.

The design of this trial includes digitally supervised, individually tailored prehabilitative exercise intervention that is progressed over the course of 8 weeks. Digital supervision allows for participants who are immunocompromised to safely complete the exercise at home and reduces the need to travel to and from the study site, outside of testing visits that are coordinated with ongoing treatment plans. Each program is designed to progress each week at 5% increments based on baseline strength and cardiorespiratory measures. The individually tailored aspect provides flexibility for patients who experience treatment-related symptoms or are able to easily manage the prescribed exercise.

Strengths and Limitations

Strengths of this study design include a rigorously designed exercise intervention, taking into account exercise tolerance, bone pain, development of bone lesions, and limited mobility, and is individually tailored and supervised by a qualified exercise trainer. This approach supports gradual increases in load and volume over the training period and enhances program adherence. The training is conducted digitally, allowing individuals who cannot travel to the research site three times per week to participate and provides scheduling flexibility.

Limitations of this study design include a limited sample size, digital delivery, and short duration of exercise. Training is conducted remotely via a video communication platform Zoom (Zoom Video Communications, Inc), which may restrict the assessment of the full range of motion and utilization of alternative techniques to ensure the correct execution of each movement. Additionally, digital training limits the ability to assess the participant's state through breathing and facial expressions, potentially impacting the reported RPE and the ability to monitor progression accurately.

Conclusions

The PROTECT Trial will contribute to understanding the role of prehabilitative exercise, in a digitally supervised setting, on muscular strength outcomes in patients with multiple myeloma who receive ASCT. Findings from this trial will provide information on patient health outcomes following transplant including overall functional capacity. Understanding the limitations to exercise within this population may help develop future larger-scale exercise interventions in the prehabilitative and rehabilitative spaces that support patients with multiple myeloma from the time of diagnosis into survivorship.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

CMD-C and AJN conceptualized the study idea. CMD-C, AJN, and RLW developed the methodology. CMD-C and AJN are responsible for funding acquisition of the trial. All authors contributed to manuscript writing, revision, and final approval.

Conflicts of Interest

None declared.

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Table 4: number of HCTs performed in the United States and reported to CIBMTR—by disease and donor type, 2015-2019 health resources and services administration: healthcare systems bureau. Healthcare Systems Bureau. 2021. URL: https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report [accessed 2021-04-15]
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Abbreviations

ASCT: autologous stem cell transplant
DEXA: dual-energy x-ray absorptiometry
HR: heart rate
PROTECT: Prehabilitation Exercise Training in Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation
REDCap: Research Electronic Data Capture
RM: repetition maximum
RPE: rating of perceived exertion

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Protocol

Surveillance of Food and Waterborne Pathogens in North-East India: Protocol for a Laboratory-Based Sentinel Surveillance Study

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Abstract

Background: Food safety is a global concern, which is often underestimated owing to challenges in investigating foodborne diseases. These challenges arise from the increased globalization of the food trade, advancements in agricultural practices, and shifts in environmental factors. In North-East India, common diarrheal outbreaks from fermented foods pose significant health risks. Despite these challenges, systematic data on foodborne pathogens is lacking in India, highlighting a crucial gap in understanding food safety issues.

Objective: The aim of this research protocol is to establish an integrated surveillance system to identify enteric pathogens circulating within humans, food animals, and the environment through a health approach in North-East India, and to conduct outbreak investigations.

Methods: The Indian Council of Medical Research (ICMR) initiated a surveillance study across all 8 North-East states in India, employing a centralized digital database for data collation. The project aims to enhance the infrastructure for microbial culture, antibiotic sensitivity testing, and molecular epidemiological studies. The study involves laboratory-based surveillance of foodborne pathogens in market foods, hospitalized diarrheal patients, poultry and animal farms, slaughterhouses, butcher shops, and diarrheal outbreaks. A standardized case report form ensures consistent data collection of age, sex, signs, symptoms, and admission dates for diarrheal cases. Stool and rectal swabs will undergo testing for pathogen identification and antimicrobial resistance. Similarly, samples of market foods, food animals, and the environment will be collected. Outbreaks confirmed by the Integrated Disease Surveillance Project (IDSP) will be thoroughly investigated following standardized guidelines.

Results: In phase I, 5 surveillance centers were established across 4 states (ie, Assam [Dibrugarh and Guwahati], Tripura, Sikkim, and Arunachal Pradesh) in 2020. Following an interim phase I data assessment and the successful establishment of a streamlined system for data procurement, investigation, recording, and analysis, along with the implementation of regular training and monitoring programs, phase II expansion was initiated in 2023-24. This includes the addition of 7 more centers (including 3 veterinary centers) in the remaining 4 states (ie, Manipur, Meghalaya, Mizoram, and Nagaland), eventually covering the entire North-Eastern Region of India.

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Conclusions: Food and waterborne diseases are a constant public health problem in many countries. Key challenges to the enhancement of food safety policy include the paucity of systematic data and awareness. With this background, ICMR's initiative is the first systematic surveillance study in the country to adopt a single health approach. Data obtained from this project will help to understand the risk of acquiring food and waterborne pathogens, their transmission pathways, and antimicrobial resistance patterns. The scientific evidence generated through this project will be helpful in formulating and strengthening food safety policy and in initiating government programs to protect the health of the nation.

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KEYWORDS

foodborne diseases; enteric pathogens; surveillance; food safety; outbreak; antimicrobial resistance; public health

Introduction

Background

Food and waterborne diseases and outbreaks are emerging as a greater global health burden, analogous to malaria, HIV/AIDS, or tuberculosis. The globalization of the food trade, changing agriculture and animal farming practices, and rapid shifts in environmental factors have created conditions favorable for the emergence, re-emergence, and spread of food and waterborne pathogens, compounding the challenge of effectively responding to foodborne threats to public health [1].

More than 200 different infections are spread through contaminated food and water, ranging from diarrhea to cancer [2]. The World Health Organization (WHO) has estimated that 2 million deaths occur every year due to consumption of contaminated food or water and that almost 30% of foodborne infection–associated mortality cases occur among children younger than 5 years [1]. The reported incidence of foodborne diseases represents less than 1% to 10% of the actual number [3], as most patients with mild symptoms do not seek medical care, causing cases to go unreported [4].

The developing world is at a higher risk of foodborne diseases. South East Asia has the second highest burden of foodborne diseases after Africa. Moreover, the WHO has reported a high burden of diarrheal and invasive enteric diseases in the Indian region, which is nearly double the global average and 20 times higher than that in Europe [5]. The Ministry of Health and Family Welfare (MoHFW), Government of India has reported that food poisoning is one of the most common outbreaks reported apart from acute diarrheal disease. It was also noted that the incidence of acute diarrheal disease and contamination of food is high in places where food is cooked in bulk such as canteens, hotels, and wedding venues [6]. The coherent regulatory strategy adopted to reduce foodborne illness in India includes monitoring and surveillance programs for the assessment of biological risk and residues of various contaminants in food products through the Food Safety and Standards Authority of India (FSSAI) established under the Food Safety and Standards Act, 2006, and surveillance through the Integrated Disease Surveillance Project (IDSP) implemented by the National Centre for Disease Control (NCDC). India has a large unorganized food sector (roadside vendors, *dhabas*, food carts, street stalls, etc) that provides inexpensive food to the economically weaker sections. The hygiene and sanitary practices of street food vendors are a matter of grave concern [7]. Government schemes, such as *Clean Street Food Hubs*, *Clean and Fresh Fruit and Vegetable Markets*, and *Eat Right Campus* for schools, colleges, workplaces, and other campuses, for creating awareness around mindful eating have been successfully established in 2023 on a Pan-India basis. The Swachh Bharat Mission, which involves a sanitation initiative for open defecation-free status, has improved the overall situation regarding diarrheal diseases in India. However, there is a crucial need for systematic data to inform policy decisions and prevent the transmission of pathogens among humans, food, animals, and the environment.

A wide range of pathogenic microorganisms are capable of infecting food products before consumption [8,9]. The WHO has prioritized 22 enteric foodborne pathogens for assessing the burden of foodborne illness [7]. These infections are attributed to specific foods, such as chicken, precooked meat, fish, dairy products, fermented foods, fruits, and vegetables [1]. Food-producing animals (eg, cattle, chickens, pigs, turkeys, etc) are also major reservoirs for pathogens such as *Campylobacter* species, non-Typhi serotypes of *Salmonella enterica*, Shiga toxin–producing *Escherichia coli*, and *Listeria monocytogenes* [10]. Further, many pathogens that are commonly associated with food can also be transmitted indirectly through the environment, animals, or infected or carrier people [11]. However, without data on the major foodborne pathogens circulating in each region and their ability to cause foodborne diseases and outbreaks, it is difficult to make strong food safety guidelines.

The North-Eastern Region (NER) of India shares international borders with China, Bangladesh, Bhutan, Nepal, and Myanmar. The food habits and cultures of each state are different and influenced by the neighboring countries. The preferred diet of the North-Eastern population in India is mainly raw, boiled, fermented, smoked, grilled, and roasted food. The preparation of these traditional foods often lacks appropriate sanitary practices and involves uncontrolled natural fermentation, which can transmit pathogens from food to humans. Additionally, an irregular electricity supply may support the proliferation of pathogens due to temperature fluctuations that affect stored meats and other food items [12]. Although intermittent outbreaks due to the consumption of traditional and fermented foods in the NER are commonly reported, detailed scientific investigations or interventions are limited [13]. This is mainly attributed to insufficient laboratory support; limited

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collaboration with the NCDC, state health authorities, and community leaders; and inadequate support for researchers, outbreak investigations, training of field workers, and funding.

As the first step toward bridging this knowledge gap, the Indian Council of Medical Research (ICMR), New Delhi, undertook an initiative to conduct sentinel surveillance of foodborne pathogens through a strong laboratory network in the 8 states of North-East India. Here, we present the methodology that has been adapted to initiate the ICMR Foodborne Pathogen Surveillance and Research Network (ICMR-FoodNet), covering the entire NER of India in phases I and II. The successful deployment of this program in all states of the NER will serve as a strong foundation for extending the network to other states within the country. Phase II expansion holds the potential to strengthen the impact of ICMR-FoodNet on a national scale, thus enhancing the overall food safety landscape in India.

Aims and Objectives

The overall aim is to identify food and waterborne pathogens to determine the risk factors that contribute to sporadic diarrheal outbreaks through population-based studies while examining the importance of different risks associated with food safety and hygiene practices as contributors to infections in the NER of India. The specific objectives are given in Textbox 1.

Textbox 1. Objectives for the foodborne pathogen surveillance.

Primary objectives

- To identify the major circulating pathogens in humans, the food chain (food items and animal-sourced food), and the environment, causing food and waterborne diseases through market, hospital, animal husbandry, and community-based sentinel surveillance and outbreak investigations
- To document regional and seasonal variations in diarrheal diseases caused by food and waterborne pathogens
- To identify sources and pathogens causing outbreaks of food and waterborne diseases through systematic investigation of public health response
- To document genotyping and antimicrobial susceptibility patterns of identified bacterial pathogens

Secondary objectives

- To develop capacity for bacterial culture, antimicrobial susceptibility testing, molecular testing, metagenomics, and outbreak investigations at North-East institutes for food and waterborne pathogens
- To determine clonality using molecular tools to trace the spread of infections

Methods

Study Design

Laboratory-based multicentric sentinel surveillance is used to collect prospective data from markets (market surveillance); hospitals (hospital surveillance); and poultry farms, animal farms, slaughterhouses, and butcher shops (animal husbandry surveillance) and assess the outbreak situation through 12 ICMR-FoodNet centers.

Study Setting

ICMR initiated a foodborne pathogen survey and research network (ICMR-FoodNet) in North-East India in 2020. In phase I, 5 sites were initiated in 4 states (Assam [Dibrugarh and Guwahati], Sikkim, Arunachal Pradesh, and Tripura). Based on the interim data of phase I, the ICMR-FoodNet is being expanded to the remaining 4 NER states (ie, Meghalaya, Manipur, Mizoram, and Nagaland) with 4 medical and 3 veterinary centers to cover the entire NER.

As shown in Figure 1, the ICMR-FoodNet centers include (1) ICMR-Regional Medical Research Centre (RMRC) Dibrugarh, Assam; (2) Guwahati Medical College and Hospital (GMCH), Guwahati, Assam; (3) Bakin Pertin General Hospital & Training Centre (BPGH&TC), Pasighat, Arunachal Pradesh; (4) Agartala Government Medical College (AGMC), Agartala, Tripura; (5) Sikkim Manipal Institute of Medical Sciences (SMIMS), Gangtok, Sikkim; (6) North Eastern Indira Gandhi Regional Institute of Health & Medical Science (NEIGRIHMS), Shillong, Meghalaya; (7) State Disease Diagnostic Laboratory, (SDDL), Shillong, Meghalaya; (8) College of Veterinary Science and Animal Husbandry (CoVSAH), Central Agricultural University (CAU), Aizawl, Mizoram; (9) Zoram Medical College (ZMC), Mizoram; (10) Institute of Bioresources and Sustainable Development (IBSD), Imphal, Manipur; (11) CoVSAH, CAU, Nagaland; and (12) Christian Institute of Health Sciences and Research (CIHSR), Dimapur, Nagaland. These centers have helped to develop a comprehensive laboratory network in the NER. ICMR-National Institute for Research in Bacterial Infections (NIRBI) and Centre for Development of Advanced Computing (C-DAC), Kolkata act as external quality assurance/training and data management centers, respectively.

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Figure 1. Geographical map of ICMR-FoodNet centers and partner sites. AGMC: Agartala Government Medical College; BPGH: Bakin Pertin General Hospital; CAU: Central Agricultural University; C-DAC: Centre for Development of Advanced Computing; CIHSR: Christian Institute of Health Sciences and Research; CoVSAH: College of Veterinary Science and Animal Husbandry; EQC: external quality control; FoodNet: Foodborne Pathogen Surveillance and Research Network; GMCH: Guwahati Medical College and Hospital; IBSD: Institute of Bioresources and Sustainable Development; ICMR: Indian Council of Medical Research; NEIGRIHMS: North Eastern Indira Gandhi Regional Institute of Health & Medical Science; NIE: National Institute of Epidemiology; NIRBI: National Institute for Research in Bacterial Infections; RMRC: Regional Medical Research Centre; SDDL: State Disease Diagnostic Laboratory; SMIMS: Sikkim Manipal Institute of Medical Sciences.

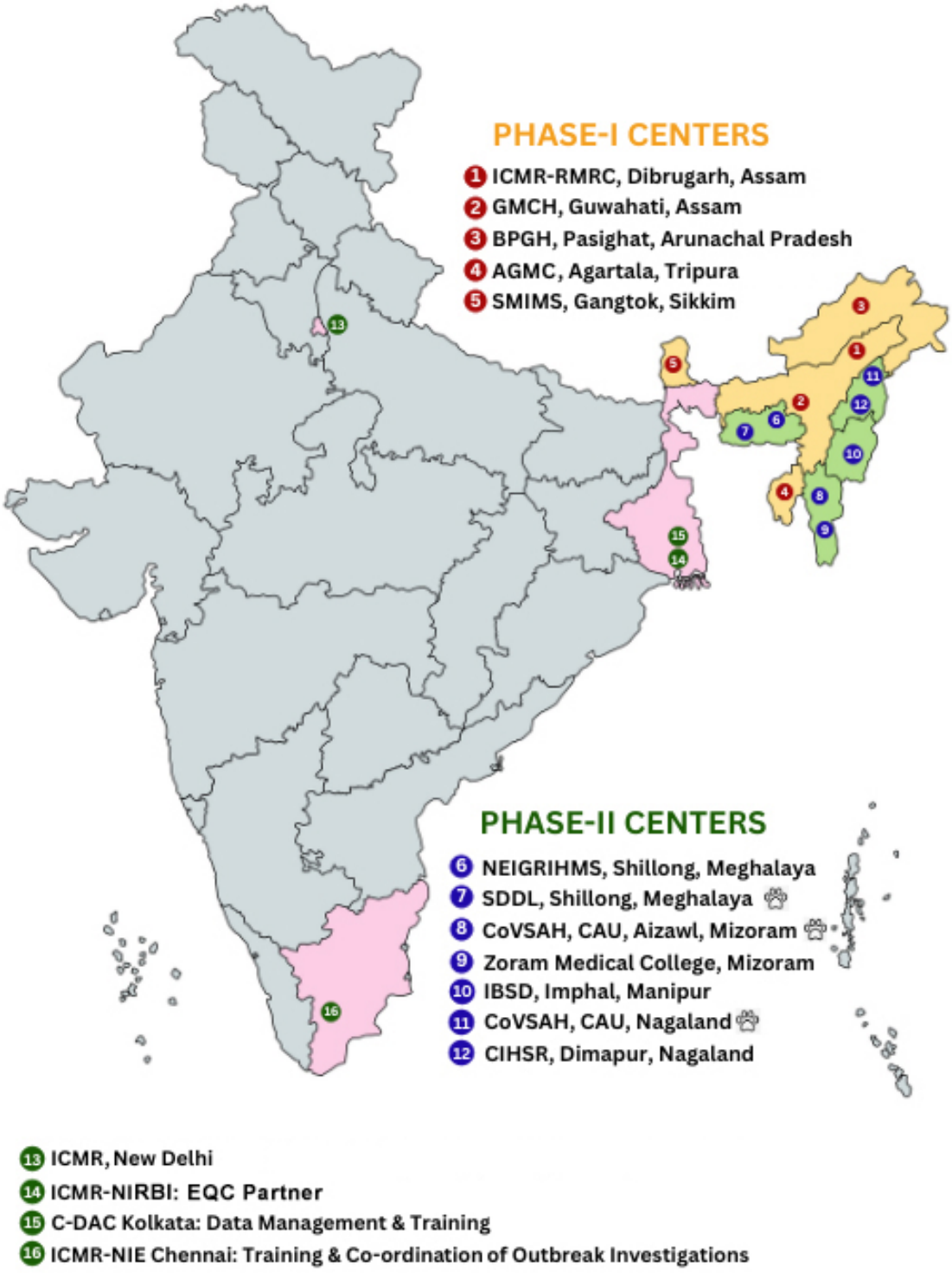

The network provides advanced diagnostic services for all enteric pathogens, conducts laboratory training to develop skilled personnel, and investigates outbreaks and antimicrobial resistance (AMR).

Duration

The duration of each phase is 5 years, including the identification of sites or institutions, laboratory and data entry training, and pilot studies.

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Case Definition

Case definitions adapted for this project are according to the guidelines of the IDSP, MoHFW, Government of India [14].

The term *foodborne disease*, including foodborne intoxication and foodborne infection, covers illnesses acquired through the consumption of contaminated food [15]. *Diarrhea* is defined as the passage of three or more loose watery stools in the past 24 hours (with or without vomiting) [16]. *Foodborne disease outbreaks* are defined as the occurrence of two or more cases of a similar illness resulting from ingestion of a common food or the observed number of cases of a particular disease exceeding the expected number. These can be confirmed (when at least one causal agent is identified) or suspected (based on clinical and epidemiological information). Although most cases are sporadic, these diseases draw attention to themselves due to outbreaks, and a thorough investigation can help in identifying control measures [15].

Ethical Considerations

Approval

This protocol has received ethics approval from the ICMR-Central Ethics Committee on Human Research (ICMR-CECHR) (reference number: CECHR 003/2023). Additionally, approval has been obtained from the following institutional ethics committees: ICMR- RMRC, Dibrugarh, Assam (RMRC/Dib/IEC (Human)/2019-20/1883); GMCH, Guwahati, Assam (MC/190/2007/PI-11/Oct-2019/19); BPGH&TC, Pasighat, Arunachal Pradesh (IIP/IEC/07/2019); AGMC, Agartala, Tripura (4(6-11)-AGMC/Medical Education/Ethics Com./2018/27980); SMIMS, Gangtok, Sikkim (SMIMS/IEC/2019-116); NEIGRIHMS, Shillong, Meghalaya (NEIGR/IEC/M11/F33/2023); CoVSAH & CAU, Aizawl, Mizoram (CVSC/CAU/IAEC/22-23/P-2); ZMC, Mizoram (F.20016/1/18-ZMC/IEC/107); IBSD, Imphal, Manipur (IEC-02/2023-002); CoVSAH & CAU, Nagaland (1476/Go/Re/SL/11/CPCSEA); and CIHSR, Dimapur, Nagaland (027/2023-24/IEC-CIHSR). Memorandums of agreement have been signed between the ICMR and all FoodNet centers for shared principles, objectives, and responsibilities.

Consent

Written informed consent for hospital surveillance will be obtained from each patient among patients aged ≥18 years, from a parent or guardian among patients aged ≤10 years, and from a parent or guardian with additional assent among patients aged 11-17 years. Additionally, informed consent will be obtained from each food or animal handler for animal husbandry and market surveillance. Consent will also be obtained for the storage of clinically relevant enteric bacterial strains, stool sample collection, and the use of participant data for future studies.

Privacy and Confidentiality

All information and data obtained from the medical records of the patients for this project will be considered confidential. The digital documentation of the clinical data will take place in an anonymized fashion. Nonidentifiable data (eg, name and date of birth) will be entered into the database. There will be no pseudonyms, which would make a retrospective reidentification of the patient possible. All data and results will be stored for at least 10 years after the publication of the results.

Compensation Details

No compensation will be provided to participants in this surveillance.

Standard Operating Procedure

The procedures of sample collection, transport, isolation, and identification of bacteria and viruses for the diagnosis of foodborne infections and their antimicrobial susceptibility testing have been detailed in the standard operating procedure presented in Multimedia Appendix 1.

Setting of Data Collection

To cover a state comprehensively, 4 districts from each state will be chosen, covering East, West, North, and South zones, and within each district, 1 local market, 1 hospital, 1 poultry farm, 1 animal farm, 1 slaughterhouse, and 1 butcher area, covering both rural and urban areas, will be identified for sample collection. The shops in the market will be chosen randomly during each visit for food sample collection (twice a week) by the research teams. This sentinel surveillance is designed to be ongoing for at least 5 years. The sampling will be carried out throughout the year to monitor trends and detect outbreaks early.

Food handlers directly involved in preparing or handling suspected food items will be interviewed. Similarly, samples from diarrheal cases will be collected from health care facilities (primary health centers and community health centers or district hospitals having provision for the admission of patients) in each district and will be visited twice a week for clinical data and sample collection.

Outbreak investigations will be conducted based on “alerts” or “signals” from the community or IDSP. The NCDC-recommended 10-step approach for outbreak investigations will be followed to generate data [17]. The FoodNet team along with the state IDSP team will work together to investigate the outbreak.

Sample Size

The sample size has been calculated based on the data collected and sample positivity in the first 3 months.

Market Surveillance

A total of 75 food samples, including cooked food items (n=30), uncooked food items (n=40), and traditional state-specific food items (n=5), will be collected from each state every month. Additionally, 20 samples from food handlers will be collected from each state every month.

Hospital Surveillance

Depending on the number of cases, about 20 diarrheal stool samples will be collected from each district every month.

Animal Husbandry Surveillance

A total of 20 samples from dead and slaughtered animals, and 60 animal food products will be collected from each state. Additionally, 20 samples from animal feed and fodder, and 20

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samples from animal handlers and butchers will be collected from each state every month.

Outbreak Investigations

In large outbreaks, clinical samples will be collected from at least 15% to 20% of all cases manifesting illness (cases) and from an appropriate number of exposed but not ill people (controls). In smaller outbreaks, clinical samples will be collected from as many cases as practicable.

Five environmental samples, including water samples and surface swabs, will be collected monthly from hospitals, markets, butcher houses, and poultry farms. Additionally, during all outbreak investigations, communal water sources, along with the water and surfaces used in suspected settings, will be sampled.

Sample Collection

For market surveillance, food items will be collected from restaurants, street food vendors, vegetable and fruit sellers, etc. They are broadly categorized as (1) cooked or processed food items (5 subcategories), (2) uncooked food items (6 subcategories), and (3) state-specific or traditional food items (Textbox 2). Swab samples from working surfaces used for cutting or chopping food items and refrigerator surfaces in shops will also be collected.

Textbox 2. Market surveillance: food item categorization.

Cooked food (restaurant/street food/mid-day meal)

- Meat/fish/seafood (nonveg)
- Rice/flour/pulses
- Vegetables
- Milk products and sweets (processed)
- Refrigerated

Uncooked food

- Raw/dried meat
- Raw/dry fish
- Raw milk
- Whole or cut fruits and vegetables
- Frozen fruits and vegetables
- Dough

State-specific food items (ethnic/traditional food items)

- No soybean/legumes/cereal
- Fermented vegetables/bamboo/pickle
- Meat/fish/seafood (nonveg)
- Edible insects
- Leafy vegetables
- Beverages (milk/tea/alcohol)

For hospital surveillance, samples of stool, rectal swabs, and vomit will be collected from confirmed diarrheal disease patients who present to the hospitals. For animal husbandry surveillance, feces, rectal or cloacal swabs, and intestinal content from carcasses will be collected from poultry or animal farms, slaughterhouses, and butcher areas. Animal-sourced food samples (meat, milk, and eggs) will be collected. Moreover, animal feed and fodder samples will be collected. Furthermore, hand swab, nail bed swab, and nasal swab samples will be collected from suspected carriers (food and animal handlers).

Environmental samples, such as water from a stream or local pond, will be collected. Moreover, water used for cooking or drinking, food processing, hand washing, cleaning, and washing of utensils from market food shops and restaurants; farm water used for drinking and farm activities; and wash water of animal food products from poultry or animal farms and slaughterhouses will be collected.

Three types of samples will be collected for outbreak investigations: (1) clinical samples from patients (stool, rectal swabs, and vomit) and suspected carriers (nasal swabs, nail bed swabs, and rectal swabs); (2) suspected food samples (common foods consumed at events and gatherings, leading to an outbreak); and (3) environmental samples, such as water extracted from a communal source used by the community (eg, a nearby stream, pond, bore well, or tube well).

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Laboratory Investigations

A list of enteric pathogens to be screened from samples collected in market, hospital, and animal husbandry surveillance and outbreak investigations is presented in Table 1.

Culture and sensitivity testing will be performed along with identification by biochemical and serological tests. Polymerase chain reaction (PCR) assays will be performed for bacterial confirmation and detection of virulence genes. Stool samples will be tested by microscopy for the detection of parasites. Viral diagnostic kits (Vitassay qPCR, Spain) will be used during outbreak investigations for the detection of rotavirus, adenovirus, astrovirus, and norovirus. The work plan for the sample collection and data analysis is illustrated in Figure 2.

Table 1. List of pathogens to be screened from samples collected in market, hospital, and animal husbandry surveillance and outbreak investigations.

Sample type/source	Pathogens to be screened	Laboratory examination
Raw milk (locally produced and supplied), ice cream, and dry milk powder	*Listeria monocytogenes*, *Yersinia enterocolitica*, *Campylobacter* spp, diarrheagenic *Escherichia coli*[a], *Staphylococcus aureus*, *Salmonella* spp, *Shigella* spp, *Brucella* spp, *Mycobacterium bovis*, hepatitis A virus (HAV), hepatitis E virus (HEV), and norovirus	Culture, biochemical tests, serotyping, PCR[b] assays, and rapid diagnostic kits for HAV, HEV, and norovirus
Raw pork, beef, mutton, poultry meat, and bush meat	Diarrheagenic *Escherichia coli*[a], *Staphylococcus aureus*, *Salmonella* spp, *Shigella* spp, *Yersinia enterocolitica*, *Clostridium perfringens*, *Listeria monocytogenes*, *Campylobacter* spp, *Clostridioides difficile*, *Brucella* spp, *Leptospira* spp, *Mycobacterium bovis*, parasite ova and cyst, HAV, HEV, and norovirus	*Culture, biochemical tests, serotyping, PCR assays, a nd rapid diagnostic kits for HAV, HEV, and norovirus*
Fish (raw fish or tinned fish)	Pathogenic *Vibrio parahaemolyticus*, *Vibrio cholerae* serogroups O1 and O139, diarrheagenic *Escherichia coli*[a], *Salmonella* spp, *Staphylococcus aureus*, *Listeria monocytogenes*, *Clostridium botulinum*, *Clostridium perfringens*, *Campylobacter* spp, HAV, HEV, and norovirus	Culture, biochemical tests, serotyping, PCR assays, and rapid diagnostic kits for HAV, HEV, and norovirus
Raw vegetables	*Salmonella* spp, *Shigella* spp, diarrheagenic *Escherichia coli*[a], *Vibrio cholerae* serogroups O1 and O139, *Salmonella* spp, *Listeria monocytogenes*, helminth ova and cyst, HAV, HEV, and norovirus	Microscopy, culture, biochemical tests, serotyping, PCR assays, helminth ova and cyst examination, and rapid diagnostic kits for HAV, HEV, and norovirus
Environment (water)	Diarrheagenic *Escherichia coli*[a], *Staphylococcus aureus*, *Salmonella* spp, *Shigella* spp, *Yersinia enterocolitica*, *Clostridium perfringens*, *Listeria monocytogenes*, *Campylobacter* spp, *Vibrio cholerae* serogroups O1 and O139, *Staphylococcus aureus*, *Leptospira* spp, parasite ova and cyst, HAV, HEV, and norovirus	Microscopy, culture, biochemical tests, serotyping, PCR assays, parasite ova and cyst examination, and rapid diagnostic kits for HAV, HEV, and norovirus
Environment food (cooked rice as targeted sampling); Equipment (slicers, grinders, cutting boards, knives, and storage containers)	Diarrheagenic *Escherichia coli*[a], *Staphylococcus aureus*, *Salmonella* spp, *Shigella* spp, *Yersinia enterocolitica*, *Clostridium perfringens*, *Listeria monocytogenes*,*Campylobacterspp*,*Vibrio cholerae* serogroups O1 and O139, pathogenic *Vibrio parahaemolyticus*, parasite ova and cyst, HAV, HEV, and norovirus	Microscopy, culture, biochemical tests, serotyping, PCR assays, and rapid diagnostic kits for HAV, HEV, and norovirus
Food items of suspected hepatitis patients	HAV, HEV, and norovirus	RT-PCR for HAV, HEV, and norovirus
Human (case) stool and vomitus; Human (control) stool	Diarrheagenic *Escherichia coli*[a], *Salmonella* spp, *Shigella* spp, *Yersinia enterocolitica*, *Campylobacter* spp, *Vibrio cholerae* serogroups O1 and O139, pathogenic *Vibrio parahaemolyticus*, parasite ova and cyst, HAV, HEV, and norovirus	Microscopy, culture, biochemical tests, serotyping, PCR assays, parasite ova and cyst examination, and rapid diagnostic kits for HAV, HEV, and norovirus
Food handler (during outbreak) skin swabs, nasal swabs, etc	Diarrheagenic *Escherichia coli*[a]	Culture, biochemical tests, serotyping, and PCR assays
Animal tissues	*Leptospira* spp	Microscopy, culture, biochemical tests, serology, and PCR assays

[a]The pathotypes include enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), Shiga toxin–producing *E. coli* (STEC), and diffusely adherent *E. coli* (DAEC).

[b]PCR: polymerase chain reaction.

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Figure 2. Flowchart of the work plan for sample collection and data analysis. AMR: antimicrobial resistance; OBI: outbreak investigation; PCR: polymerase chain reaction.

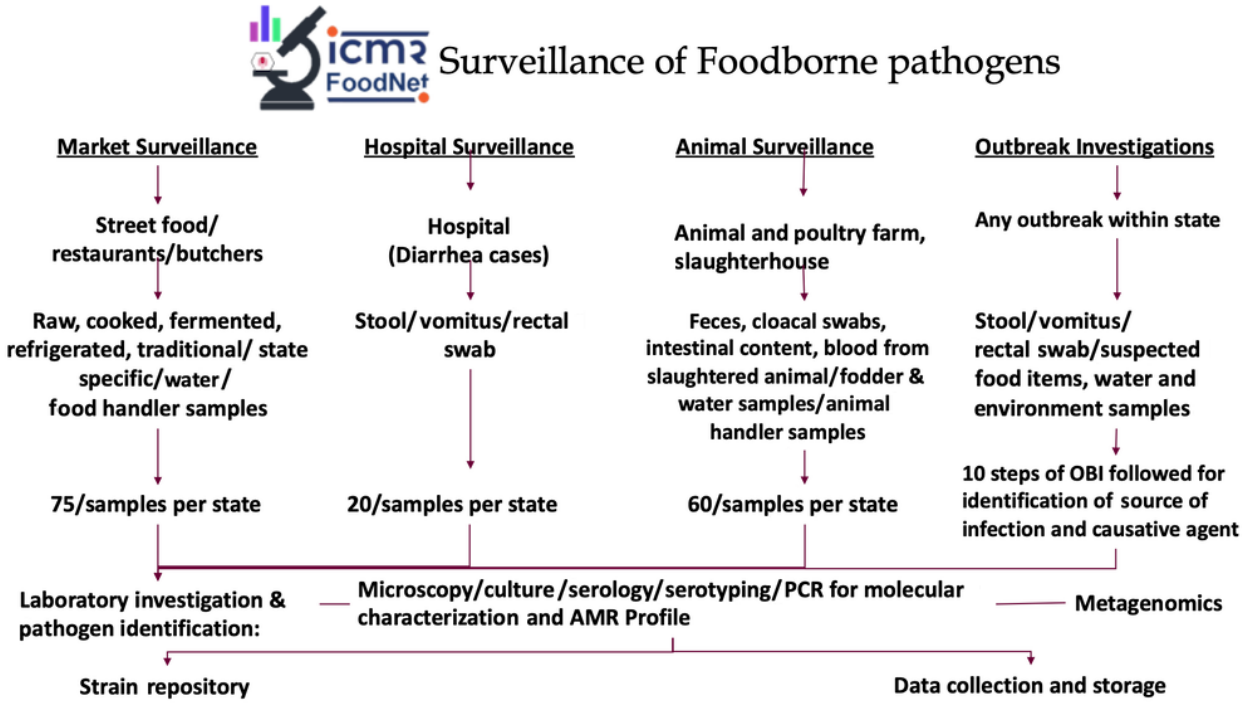

Metagenomics Sample Analysis

Testing will be performed for (1) diarrheal stool samples in which at least one pathogen has been identified by culture or PCR, (2) healthy stool samples as controls from the same population, and (3) suspected food samples for outbreak or food poisoning and samples in which no pathogen was identified. DNA will be extracted from stool samples, and barcoded 16S rRNA gene amplification will be performed, followed by multiplexing of samples for amplicon sequencing.

Quality Assurance

All identified bacterial strains will be preserved in Brain Heart Infusion (BHI)-Glycerol mix at –80 °C and transferred to ICMR-RMRC, Dibrugarh and ICMR-NIRBI, Kolkata for further confirmation, quality control, and genotyping.

Strain Repository

A pathogen repository has been established at RMRC, Dibrugarh and NIRBI, Kolkata in phase I, to preserve fully characterized enteric pathogens for the maintenance and sharing of these pathogens for future research. The same arrangement will be continued in phase II.

Data Management

A centralized, secured role-based web platform [18] has been designed and will be used by data collectors, lab technicians, and researchers for real-time data collection from hospitals, markets, animal farms, and outbreak locations. The data repository has been securely hosted on a cloud server. An electronic case report form (eCRF) has been designed with a drop-down menu to minimize data entry errors, and for additional security, the double data entry method will be followed. An ICMR-FoodNet mobile app has also been developed for data collection. The ICMR-FoodNet app will be maintained on a secure web server at C-DAC, Kolkata and ICMR, New Delhi. The study centers will register online to initiate the work. Site-based login credentials with access control will be used for data entry, data monitoring, and data download. Data validation will be performed by the principal investigator of the respective center. Data on patient age, sex, signs, symptoms, date of admission, date of discharge or death, diagnostic tests, identified pathogen, treatment history, outcome, etc will be recorded in the hospital eCRF record.

Data Analysis

Descriptive analysis of the data will be performed by generating means and proportions. Bivariate and multivariate analyses will be undertaken. Further, analysis of the data will be performed based on a data analysis plan developed by the expert committee and requirements of the state health department.

Dissemination of Data

All centers will conduct networking workshops to sensitize the stakeholders, IDSP officials, and state health officials about the project and induct them into the network. This includes timely dissemination of foodborne disease surveillance data for effective prevention. The involvement of local health agencies in reporting and disseminating information within communities will be emphasized. ICMR-FoodNet will collaborate with IDSP for outbreak investigations, and the resulting recommendations will be shared with state health officials for appropriate action. Communication strategies, such as newsletters, talks, and press releases, will be used to ensure the effective dissemination of information. Additionally, electronic dissemination methods through the ICMR-FoodNet website will be used for efficient data sharing in phase II.

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Project Management

ICMR, New Delhi functions as the coordinating site for planning, funding, and all logistic support. Around 10 eminent scientists (including chairpersons and co-chairpersons) with field expertise have been identified to formulate a project steering committee. These experts will review the task force proposals, suggest changes if any, and recommend for funding. In this project, ICMR-NIRBI, Kolkata is the external quality assurance service (EQAS) and laboratory training site, ICMR-National Institute of Epidemiology (NIE), Chennai is the outbreak investigation training site, and C-DAC, Kolkata is the data management site.

The project at each site will be overseen by an experienced microbiologist serving as the principal investigator, along with epidemiologists, social scientists (co-principal investigators), and a dedicated scientific research team. Regular visits by core committee members, monthly meetings with mentors, half-yearly reviews by the technical review committee, and centralized real-time data monitoring are the important measures implemented to ensure effective management and performance monitoring at each site. These strategies are essential for addressing issues promptly, ensuring data quality, and sustaining the surveillance system effectively.

Results

This surveillance project has been systematically implemented in 2 phases. Five centers were established across 4 states in 2020 in phase I. Data collection began in October 2020 at all 5 study sites, after approval from the ethics committee. The ICMR-FoodNet surveillance system for monitoring foodborne diseases has successfully integrated with key organizations like the IDSP and FSSAI, which are the 2 prime organizations working on foodborne diseases in India under the MoHFW, Government of India. A secured FoodNet Digital platform has been developed for real-time data collection, role-based user dashboards, and a comprehensive e-Lab module [18]. Training sessions have been organized to instruct the project staff in laboratory techniques, data entry and recording, outbreak investigation and reporting, and metagenomic analysis. Following an interim data assessment and the successful establishment of a streamlined system for data procurement, investigation, recording, and analysis, along with the implementation of regular training and monitoring programs in phase I, phase II of the surveillance network was taken up.

The detailed process of developing the ICMR-FoodNet network through 8 systematic steps and the encountered challenges have been previously outlined [19] (Figure 3).

Figure 3. Strategic implementation and Gantt chart timeline overview of the ICMR-FoodNet surveillance project: A multiphase approach for enteric pathogen surveillance in North-East India. FoodNet: Foodborne Pathogen Surveillance and Research Network; ICMR: Indian Council of Medical Research; SOP: standard operating procedure.

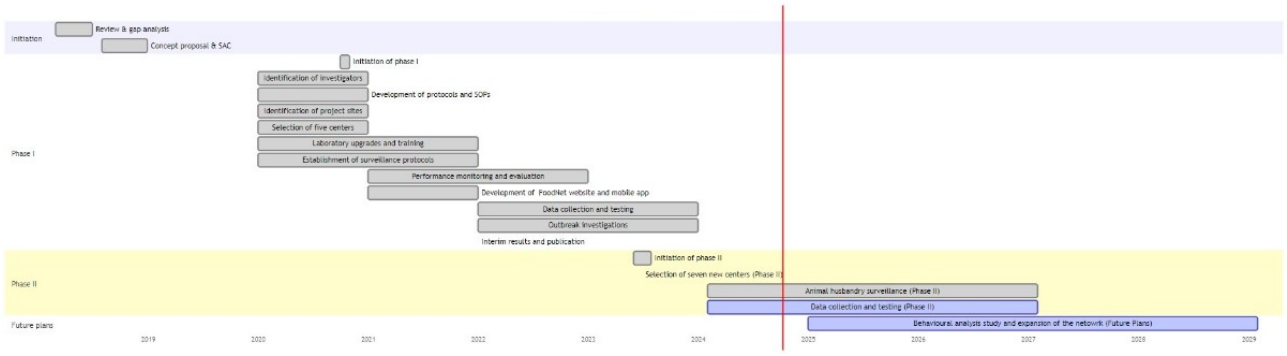

Phase II of the ICMR-FoodNet, initiated in January 2024, aims to expand the surveillance network to Manipur, Meghalaya, Mizoram, and Nagaland by establishing 7 new centers. From January to June 2024, the focus will be on upgrading laboratories for culture, antibiotic sensitivity testing, and molecular studies, alongside training staff in pathogen isolation, identification, and metagenomics. Starting in June 2024 and continuing through December 2027, systematic surveillance and data collection will involve food, clinical, animal, and environmental samples from designated districts. A key component is the animal surveillance module, monitoring poultry farms, animal farms, and slaughterhouses, with samples from animals, handlers, and the environment. Special attention will be given to enteric pathogen profiles in ethnic and traditional foods. Throughout this phase, foodborne and waterborne disease outbreaks will be systematically investigated, and the findings will be promptly reported to state health authorities for swift remedial actions. Continuous quality assurance and monitoring will be ensured through regular visits, meetings, and evaluations, supported by external quality assurance programs and centralized data monitoring. Ongoing data analysis using artificial intelligence and machine learning techniques will help identify trends and sources of foodborne illnesses, with a pathogen repository maintained for future research. By July 2027, further expansion to major metro cities and other states will be planned based on insights and funding, aiming for comprehensive national coverage. This phase will enhance existing infrastructure, integrate a comprehensive animal surveillance module, and focus on detailed data collection of enteric pathogens in ethnic foods, which will improve food safety and inform targeted public health interventions across North-East India.

Discussion

Impact of the ICMR-FoodNet Program

India encounters numerous challenges in safeguarding food safety, particularly in resource-limited states or areas of North-East India. Factors, such as culturally diverse populations,

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low economic development, inadequate sanitation, evolving dynamics in human-animal-environment interactions, and the emergence of AMR, collectively contribute to the prevalence of foodborne illnesses and outbreaks. Despite some prior fragmented studies in India, the real burden of foodborne illness remains significantly underreported and undetermined. The ICMR-FoodNet surveillance initiative is the first systematic study with a standardized methodology, targeting specific pathogens. It aims to generate dynamic region-specific data for monitoring common and emerging foodborne pathogens. This effort will contribute to updating Indian food safety and management protocols. Figure 4 illustrates the surveillance modes and outcomes of the ICMR-FoodNet program.

Figure 4. The modes of surveillance and outcomes of the ICMR-FoodNet program. FoodNet: Foodborne Pathogen Surveillance and Research Network; ICMR: Indian Council of Medical Research.

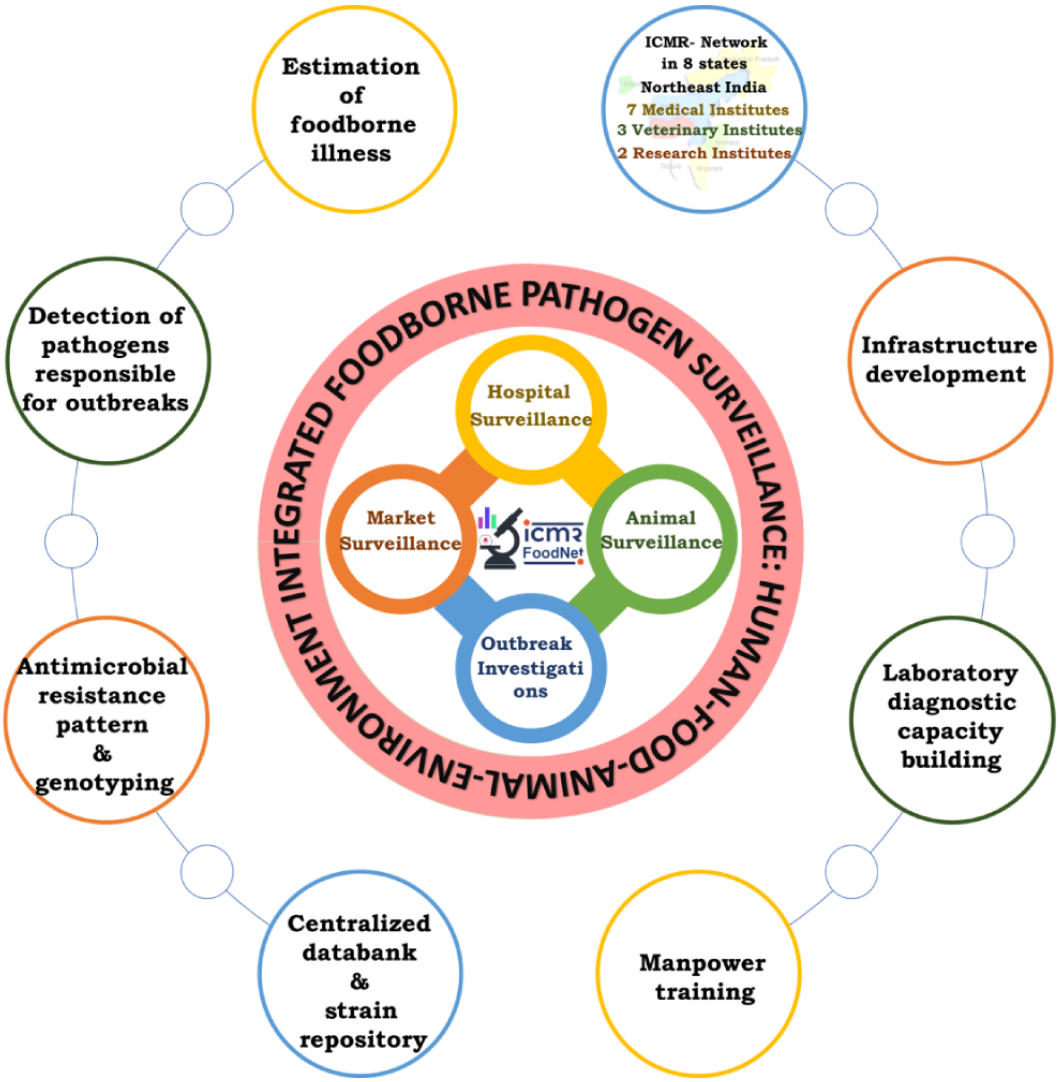

Laboratory-based surveillance provides crucial support in the timely reporting and monitoring of foodborne illnesses and outbreaks, essentially contributing to a well-informed public health response strategy [20,21]. Laboratory data play a vital role in understanding the source of the infection and implementing effective hygiene measures, especially for viral pathogens like norovirus, transmitted through both food and human contact, or rotavirus, which is known to cause high mortality among Indian children [22]. Recent surveillance of foodborne disease outbreaks in India reported 14.5% deaths in Assam, with only 6.4% outbreaks over 10 years, and concurrently, several states and union territories reported very few outbreaks in 10 years [23]. This emphasizes the importance of an improvement in surveillance and reporting, coverage of a large number of specimen tests during outbreaks and unified laboratory standards [24], generation of robust data and data analysis, constant monitoring by committees, and a higher priority for diseases of other vertical programs [25].

The initiative includes the enhancement of state-level laboratories to function as cutting-edge diagnostic facilities for foodborne pathogens. Through routine training programs, skilled manpower is generated, along with the establishment of standardized protocols for pathogen isolation and characterization. A robust laboratory network with internal and external quality assurance systems in place can be a valuable asset to the disease surveillance program. This project not only involves the collection of epidemiological data related to food hygiene and the prevalence of foodborne illnesses and outbreaks, but also strengthens the high-quality laboratory data on causative pathogens and their seasonal and regional trends. There is a

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significant shortage of manpower (particularly the ratio of food safety officers to the population) and a lack of sufficient resources, such as food testing laboratories, as noted by the IDSP. Integrating the ICMR-FoodNet with state health and national programs, especially during outbreak situations, will bolster the public health response in the region.

Despite the identified benefits of genomic surveillance of pathogens causing tuberculosis, malaria, HIV, SARS-CoV-2 infection, etc, the genomic information of enteric pathogens is comparatively low [21]. In order to enhance the methods of detecting and characterizing foodborne pathogens, profiling the virulence and pathogenicity attributes, monitoring AMR, tracking the source, and determining the causative pathogen during outbreak investigations, metagenomic studies will be undertaken in this project. All these aspects will focus on clinical and suspected food samples from outbreaks for characterizing known and unknown pathogens beyond the species or subspecies level (subtyping) in order to determine clonal relationships and trace the spread of infection in outbreak events. The development and validation of metagenome-based diagnosis could hold great potential for facilitating reliable and robust epidemiological investigations of enteric infections and disease surveillance, as culture-based techniques and PCR-based techniques have inherent technical limitations [26,27].

Many factors could be involved in food contamination, including those from the environment and human-related animal handling (slaughtering and processing practices, storage procedures, etc) [28]. Major foodborne pathogens, such as *Salmonella* and *Campylobacter*, originate from animals, are prevalent in farm environments, and are introduced into the food supply systems. Additionally, the indiscriminate use of antibiotics in livestock and agriculture has increased the rapid emergence of AMR pathogens and their transmission [29]. The ICMR-FoodNet integrated surveillance systems of human-food-animal-environment interactions will help understand multiple pathways of foodborne pathogen transmission and identify and address contamination risks in each stage of the food production chain [30]. Data analysis of the 3 main sectors (human, food, and animal) would allow a better understanding of risks across the food chain and source attribution, and facilitate a comprehensive estimation of the spread of AMR. This will help to formulate clinical management policy involving appropriate (eg, regarding AMR in humans) antimicrobial use policy in food-producing animals and horticulture [29,30] in alignment with the National Action Plan for containment of Antimicrobial Resistance (NAP-AMR) that was launched on April 19, 2017, by the NCDC and MoHFW, Government of India.

This project can bridge reporting gaps and initiate systematic collaborative outbreak investigations with IDSP and FSSAI officials. This effort will not only reduce the foodborne outbreak-associated losses in economic terms and human lives, but also enhance the robustness of the existing surveillance system and help national authorities to develop national plans and policies.

While this surveillance project aims to understand foodborne pathogen transmission and AMR in North-East India, several limitations must be acknowledged. The challenging geography and limited infrastructure of the NER of India, including difficult terrain, heavy monsoons, limited transportation, power shortages, and political unrest, can be a significant hurdle. Additionally, sociocultural diversity and language barriers may affect the uniformity of data collection. Owing to diverse farming practices and environmental conditions, the animal surveillance module may not capture all sources of enteric pathogens. The continuous nature of sentinel surveillance requires sustained funding and resources, which can fluctuate, impacting consistency. Recruiting and retaining skilled personnel, especially experienced bacteriologists, can further complicate efforts. Despite these challenges, the project's structured approach aims to mitigate these issues and provide valuable insights into food safety and public health interventions.

Future Plans

Future plans include a comprehensive situational analysis and behavioral assessment, particularly focusing on hygiene practices among food handlers, both at commercial and household levels. Furthermore, a study of mycotoxins in ethnic food samples has been planned. Consolidated data on mycotoxins will help to revise the food safety policy of the country. This network could be expanded to 4 major metro cities in India (ie, Delhi, Mumbai, Chennai, and Kolkata) to initiate nationwide coverage based on experiences from phases I and II and the availability of funds from ICMR/DHR, MoHFW. With accumulated data, proper risk analysis, including risk assessment, risk management, and risk communication, can be performed to estimate the burden of foodborne infections at the state and national levels.

Conclusion

The ICMR-FoodNet program is of national importance as it covers 3 important aspects. The first aspect involves infrastructure development and capacity building of technical manpower in North-East India. The second aspect involves research to estimate the incidence of foodborne pathogens and AMR, and foodborne outbreak investigations for mitigating the risks associated with foodborne pathogens and reducing the incidence of foodborne infections. This project is aimed to provide data similar to the global estimated burden of foodborne illness. The third aspect involves the possible integration of the findings into national policy reforms in food safety in order to develop a well-aligned public health outbreak response.

Acknowledgments

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Data Availability

All data underlying the results are available as part of the article, and no additional source data are required. The datasets used or analyzed during the study will be made available from the corresponding author upon reasonable request.

Authors' Contributions

MD conceptualized and developed the outline for the protocol and revised the manuscript. VA prepared the manuscript. SD provided the graphics for the manuscript. TR, AKO, PS, DG, KGD, TM, IS, TD, and SCH provided critical feedback and helped shape the manuscript. All authors have read and agreed to the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard operating procedures for the Indian Council of Medical Research Foodborne Pathogen Surveillance and Research Network (North-East India).
[PDF File (Adobe PDF File), 4338 KB - resprot_v13i1e56469_app1.pdf]

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Abbreviations

AGMC: Agartala Government Medical College
AMR: antimicrobial resistance
BPGH&TC: Bakin Pertin General Hospital & Training Centre
CAU: Central Agricultural University
C-DAC: Centre for Development of Advanced Computing
CECHR: Central Ethics Committee on Human Research
CIHSR: Christian Institute of Health Sciences and Research
CoVSAH: College of Veterinary Science and Animal Husbandry
eCRF: electronic case report form
FoodNet: Foodborne Pathogen Surveillance and Research Network
FSSAI: Food Safety and Standards Authority of India
GMCH: Guwahati Medical College and Hospital
IBSD: Institute of Bioresources and Sustainable Development
ICMR: Indian Council of Medical Research
IDSP: Integrated Disease Surveillance Project
MoHFW: Ministry of Health and Family Welfare
NCDC: National Centre for Disease Control
NEIGRIHMS: North Eastern Indira Gandhi Regional Institute of Health & Medical Science
NER: North-Eastern Region
NIRBI: National Institute for Research in Bacterial Infections
PCR: polymerase chain reaction
RMRC: Regional Medical Research Centre

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SMIMS: Sikkim Manipal Institute of Medical Sciences
WHO: World Health Organization
ZMC: Zoram Medical College

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